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TITLE: Efficient Synthesis of Anti-influenza, Tamiflu®, Novel Anticancer and Antimalarial Naphthoquinone Amides, Antimalarial *N-O* Heterocycles and Other Bioactive Heterocycles

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THESIS

EFFICIENT SYNTHESIS OF ANTI-INFLUENZA, TAMIFLU®, NOVEL ANTICANCER AND ANTIMALARIAL NAPHTHOQUINONE AMIDES, ANTIMALARIAL *N-O* HETEROCYCLES AND OTHER BIOACTIVE HETEROCYCLES

SUNISA AKKARASAMIYO

A Thesis Submitted in Partial Fulfillment of
the Requirements for the Degree of
Doctor of Philosophy (Chemistry)
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Sunisa Akkarasamiyo 2014: Efficient Synthesis of Anti-influenza, Tamiflu®, Novel Anticancer and Antimalarial Naphthoquinone Amides, Antimalarial *N-O* Heterocycles and Other Bioactive Heterocycles. Doctor of Philosophy (Chemistry), Major Field: Chemistry, Department of Chemistry.
Thesis Advisor: Professor Ngampong Kongkathip, Ph.D. 362 pages.

Tamiflu® (Oseltamivir phosphate) is a potent neuraminidase inhibitor that is used for the treatment of influenza A (H5N1 and H1N1) infection. The total synthesis of Tamiflu® was accomplished in 20 steps with 1.9 % overall yield started from very cheap and abundant starting material, D-glucose. The synthesis represents a new and efficient modified Bernet-Vasella-Barbier reaction of 5-iodo-3-amino-1,2-*O*-isopropylidine furanoside to generate the corresponding diene. Ring closing metathesis was employed to construct the cyclohexene carboxylate core structure. Introduction of the amino function to perform S_N2 substitution with NaN_3 followed by azide reduction. Pentyl ether moiety was introduced through aziridine opening with 3-pentanol.

Rhinacanthins are naphthoquinone ester derivatives which were isolated from Thai herb, *Rhinacanthus nasutus*. In Thailand, *R. nasutus* is used for treatment of cancer. Synthesis of rhinacanthins and derivatives, novel naphthoquinone aromatic and aliphatic esters and naphthoquinone aromatic amides, and their anticancer and antimalarial evaluations were reported by our group. Therefore, novel naphthoquinone aliphatic amides were synthesized to compare their biological activities with those of aromatic amides and the esters. Fourteen novel naphthoquinone aliphatic amides were synthesized in nine steps with 9-25% overall yield from 1-hydroxy-2-naphthoic acid. They were evaluated for their anticancer activity against KB and NCI-H187 cell lines, antimalarial activity against *Plasmodium faciparum*, cytotoxicity to normal Vero cells and studies for the structure activity relationship. Interestingly, all compounds showed anticancer activity with IC_{50} value in the range of 4.83 to 101.86 μM. Four naphthoquinone aliphatic amides with long aliphatic chain length (C9-C18) showed antimalarial activity with IC_{50} values of 0.76 to 10.62 μM.

Malaria is a serious health problem in tropical and sub-tropical zones. Artemisinin and its derivatives are currently effective drugs for the treatment of malaria patients. The structure of artemisinin contains an unusual peroxide bridge (O-O) which is believed that it is responsible for the drug's mechanism of action. The heterocyclic spiro-compounds based on spiroacenapthenones and spirooxindole that contain an N-O bond instead of the O-O bond (peroxide) in artemisinin were synthesized to evaluate antimalarial and anticancer activities. Their compounds were obtained in two steps from 1,3-dipolar cycloaddition of azomethine ylides followed by oxidative Meisenheimer rearrangement. One of triple *N-O* heterocyclic compounds showed inhibition against *Plasmodium faciparum* malaria with a good activity (IC_{50} = 1.04 μM). Seven *N-O* heterocyclic compounds showed anticancer activity with IC_{50} values of 24.45 to 120.78 μM.

Palladium catalysed cascade reaction of allene is very useful for synthesis of biologically active complex structures. We also presented the regio and stereoselective catalytic synthesis of *Z,Z*-bisallylamines, isoquinoline and isoquinolinone from combination of complex allenes, containing purine and quinazolinone cores, with aryl/heteroaryl iodides and ammonium tartrate as a novel ammonium surrogate.

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Student's signature Thesis Advisor's signature

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Sunisa Akkarasamiyo

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LIST OF ABBREVIATIONS

μM	=	Micromolar
Ac	=	Acetyl
aq.	=	aqueous
Ar	=	Aryl (substituted aromatic ring)
Bn	=	Benzyl
Boc	=	*tert*-Butylcarbonyl
br	=	broad signal
BSA	=	Benzene sulfonic acid
CDI	=	Carbonyl diimidazole
cm^{-1}	=	Reciprocal centimeter (wave number)
d	=	Doublet
dba	=	Dibenzylideneacetone
DBU	=	1, 8-Diazabicyclo[5.4.0]undec-7-ene
DCC	=	Dicyclohexylcarbodiimide
dd	=	Doublet of doublets
ddd	=	Doublet of doublet of doublets
DMAP	=	4-Dimethylaminopyridine
DMF	=	*N*, *N*-Dimethylformamide
DMSO	=	Dimethylsulfoxide
DMTMM	=	4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
dt	=	Doublet of triplets
ESI	=	Electrospray ionization
Et	=	Ethyl
EtOAc	=	Ethyl acetate
FTIR	=	Fourier transform infrared spectroscopy
g	=	Gram
h	=	Hour
HRMS	=	High resolution mass spectroscopy

LIST OF ABBREVIATIONS (Continued)

HWE	=	Horner–Wadsworth–Emmons reaction
Hz	=	Hertz
IC_{50}	=	Half maximal inhibitory concentration
In	=	Indium
J	=	Coupling constant
LDA	=	Lithium diisopropylamide
m	=	Multiplet (denotes complex pattern)
m.p.	=	Melting point
m/z	=	A value of mass divided by charge
m-CPBA	=	meta-Chloroperoxybenzoic acid
Me	=	Methyl
min	=	Minute
mL	=	Milliliters
Ms	=	Methanesulfonyl
NMR	=	Nuclear magnetic resonance
NOE	=	Nuclear Overhauser Effect
Pd	=	Palladium
PDC	=	Pyridinium dichromate
Ph	=	Phenyl
q	=	Quartet
RCM	=	Ring closing metathesis
R_f	=	Retention factor in chromatography
t	=	Triplet
TBABr	=	Tetrabutylammonium bromide
TBAF	=	Tetrabutylammonium fluoride
TBHP	=	*tert*-Butyl hydroperoxide
TCCA	=	Trichloroisocyanuric acid
td	=	Triplet of doublets
TEMPO	=	2,2,6,6-Tetramethyl-1-piperidinyloxy free radical

LIST OF ABBREVIATIONS (Continued)

TEOF	=	Triethyl orthoformate
TEOF	=	Triethylorthoformate
Tf	=	Trifluoromethanesulfonate
TFA	=	Trifluoroacetic acid
TFP	=	Tri(2-furyl)phosphine
THF	=	Tetrahydrofuran
TLC	=	Thin-layer chromatography
TOF	=	Time of flight (Mass spectrometry)
Ts	=	*p*-Toluenesulfonyl
Zn	=	Zinc
δ	=	Chemical shift (ppm)
υ_{max}	=	Maximum absorption frequency

EFFICIENT SYNTHESIS OF ANTI-INFLUENZA, TAMIFLU®, NOVEL ANTICANCER AND ANTIMALARIAL NAPHTHOQUINONE AMIDES, ANTIMALARIAL *N-O* HETEROCYCLES AND OTHER BIOACTIVE HETEROCYCLES

INTRODUCTION

1. Influenza and anti-influenza drugs, Oseltamivir phosphate

Influenza or flu is an infectious respiratory illness which is caused by influenza viruses. It is a serious public health problem that causes illnesses and deaths. During the past, 1918 Spanish flu, 1957 Asian flu and 1968 Hong Kong flu pandemics caused millions of death.

Vaccination is a preventing method for influenza. People will need to shot specific vaccine flu every year because of virus will mutate from season to season. Each year WHO will forecast which type of an influenza virus will be spreading. But the time required to produce vaccine is so long, 6-8 months and can only be stockpiled for 18 months. In addition, it should be administered at least 4 weeks before contacting with the virus. Thus preventing by vaccination would be failed to combat an influenza pandemic. Anti-influenza drug can also be used as an alternative method for combating influenza. At present, two classes of anti-influenza drugs are available, the M2 channel inhibitor and neuraminidase (NA) inhibitor.

Amantadine hydrochloride (1) and rimantadine hydrochloride (2) (Figure 2) were the first two M2 channel inhibitor antiviral drugs approved for the treatment of influenza A. But their use has been limited due to their severe central nervous system (CNS) side effects, the rapid emergence of resistance in viral strains, and the lack of efficacy against influenza B virus (Magano, 2009).

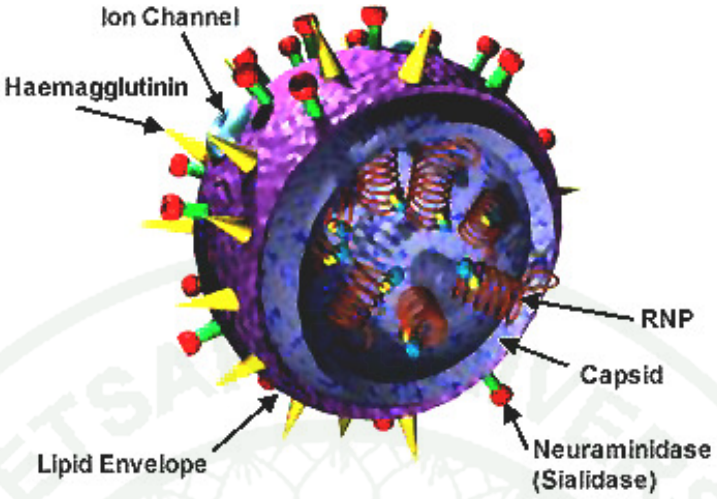


Figure 1 Influenza virus.

Source: National Institutes of Health (2006)

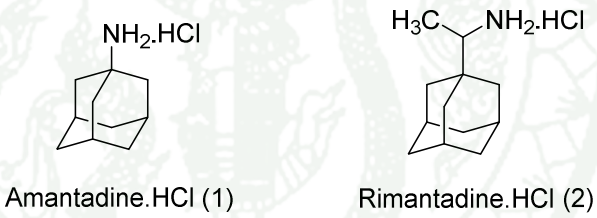


Figure 2 Structures of M2 channel inhibitor drugs.

Zanamivir (6) (Relenza®), oral inhalation drugs, is the first drug in the NA inhibitors class which was discovered in 1989 by Biota scientists in conjunction with Australia's Commonwealth Scientific and Industrial Research Organization (CSIRO) and the Victorian College of Pharmacy at Monash University. The molecule was licensed to GlaxoSmithKline in 1990 for clinical development and approved by the FDA for commercialization in the United States in 1999. The drug was designed by employing the application of structure-based drug design based on the structure of 2-deoxy-2,3-dehydro-*N*-acetylneuraminic acid (9) (DANA) (Meindl, *et al.*, 1974; Palese, *et al.*, 1974), a putative transition state analogue of oxocarbonium intermediate (5), as well as the X-ray crystal structure of NA–sialic acid complex

(Figure 3) (Varghese, *et al*., 1983; Colman, *et al*, 1983) led to the more potent anti-influenza drug by replacing the hydroxyl group at the C-4 position of the ring with more basic amino group (Magano, 2009). As a consequence, oseltamivir phosphate (8), peramivir (10) and other NA inhibitors were also discovered (Figure 4).

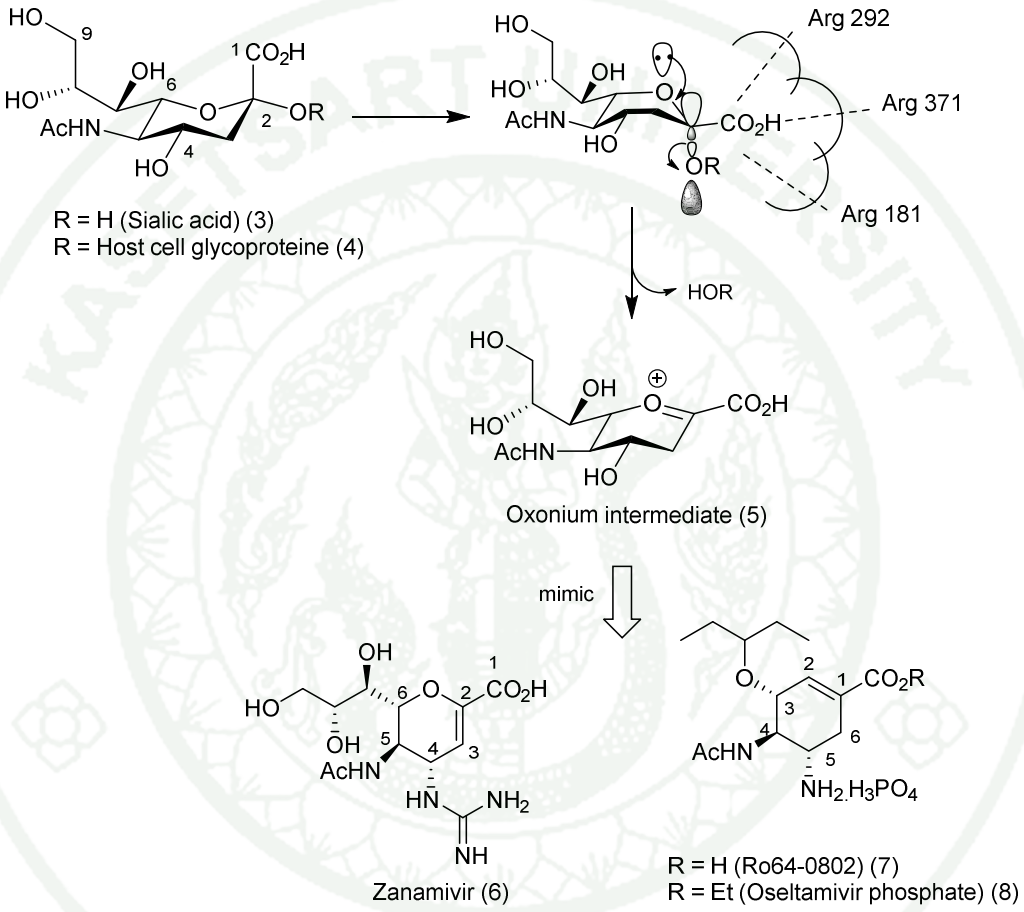


Figure 3 A hydrolysis step of sialic acid by neuraminidase (NA) and design of NA inhibitors.

Source: Shibasaki (2008)

Oseltamivir phosphate (8) is the first orally active neuraminidase inhibitor which was subsequently developed by Gilead Sciences (Kim, *et al.,* 1997) and currently marketed by Hoffmann–La Roche (Federspiel *et al.,* 1999). It is administered as the prodrug oseltamivir phosphate and converted to active oseltamivir

carboxylate by hepatic esterases. Oseltamivir is active against all the neuraminidase subtypes that have been tested so far *in vitro*. Therefore, the drug can be employed to treat seasonal influenza and avian flu.

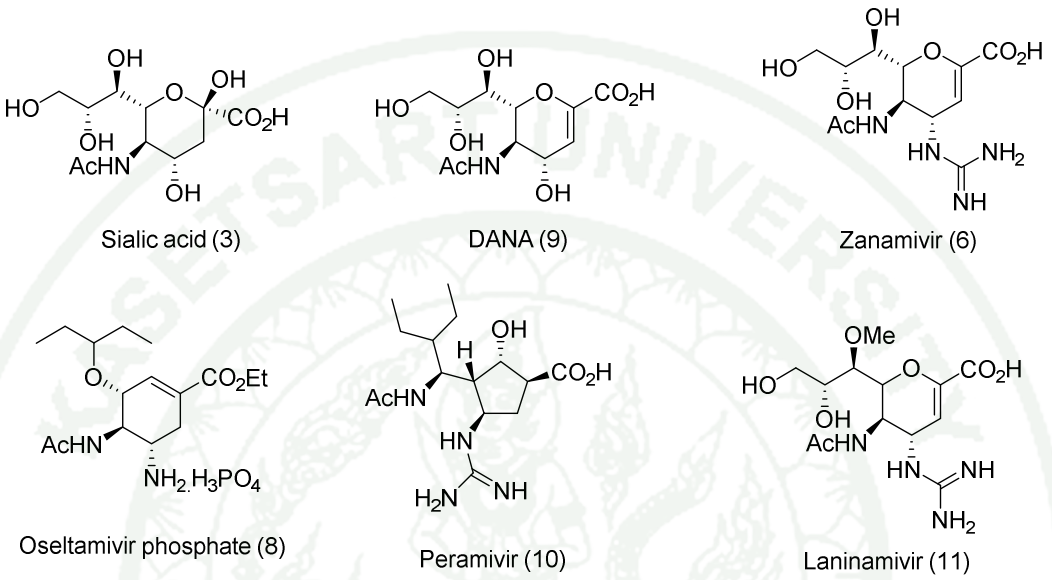


Figure 4 Structures of neuraminidase inhibitors.

Since 1999, Hoffmann-La Roche Company has synthesized oseltamivir phosphate (8) or Tamiflu® as a trade name. The synthesis started from (–)-shikimic acid (132) obtained from Chinese star anise, the seeds of the sweetgum fruit and glucose fermentation using *E.coli.* However, their synthetic methodology has some drawback such as the limited availability of the (–)-shikimic acid (132) which is a starting material and hazardous azide (Federspiel *et al.,* 1999). The development of a practical synthesis of oseltamivir that can provide the high quantity of product and employing a cheap commercial available substrate as well as a safety process are highly challenging. Thus, many synthetic strategies have also been reported by various research groups. Our group (Kongkathip's group) is interested in the benefit of chiral pool monosaccharide therefore my research objective is to synthesize oseltamivir phosphate (Tamiflu®) starting from a cheap and commercially available D-glucose (18). Our retrosynthetic analysis is shown in Figure 5. And synthesis of

Tamiflu® from (–)-shikimic acid (132) with azide free reaction methodology is investigated.

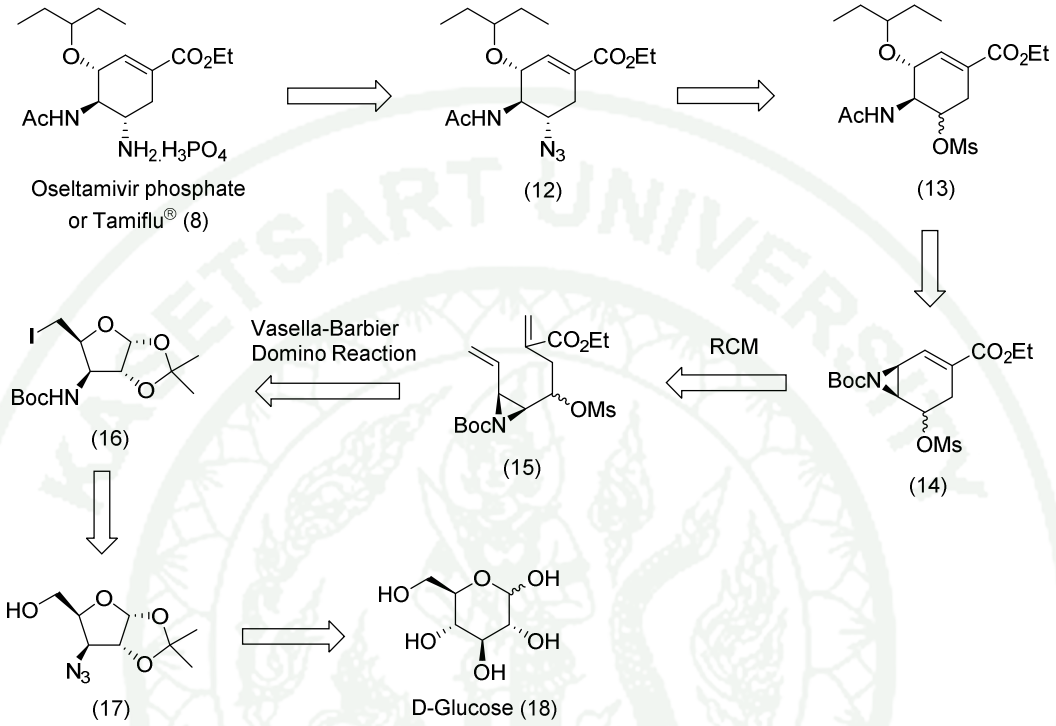


Figure 5 Our retrosynthetic analysis of Tamiflu's synthesis.

2. Cancer and anticancer drugs

Cancer is a large group of diseases which mutation in gene delivered to abnormal cells activity. In 2012, people in worldwide died from cancer around 8.2 million. It is expected that annual cancer cases will rise from 14 million in 2012 to 22 within the next two decades (World Health Organization, 2014). The main types of cancer are lung, stomach, liver, colorectal, breast and cervical. In Thailand, breath and cervical cancers are two major types of cancer in women; lung and liver cancers are two major types in men.

The gene's mutation results from DNA (deoxyribonucleic acid) damage. DNA damage might be induced by UV light, X-rays, chemicals, tobacco, viruses, and parasites. Changing lifestyle to minimize exposure to carcinogens should be a good

way for preventing cancer. Some cancer would be prevented by vaccination such as liver and cervical cancers. At present, there are many methods to treat cancer such as surgery, radiation, chemotherapy, immunotherapy, stem cell therapy or targeted therapy depending on type, location and stage of them. Chemotherapy is one of major methods for treatment of cancer by using drugs to treat cancer cells, but all drugs can also destroy normal growth cells such as bone marrow cells, epidermal cells and hair follicle cells. Thus, some of the side effects are usually found such as neutropenia, anemia, thrombocytopenia, hair loss, oral ulcers etc. Moreover drugs resistant are also found. The ideal cancer chemotherapy drugs are "they should selectively kill cancer cells without undesirable side effect". Examples of cancer chemotherapy drugs according to their mechanism are shown in Figure 6 and Figure 7.

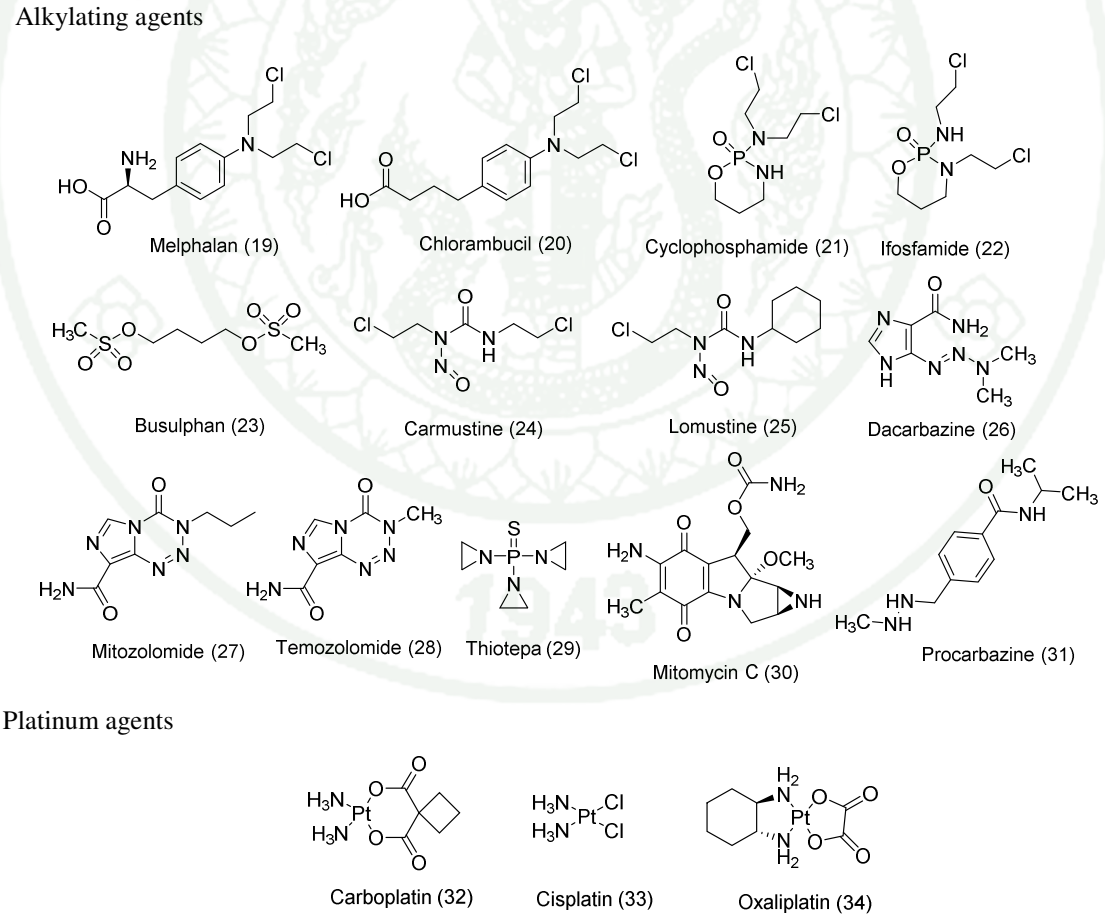
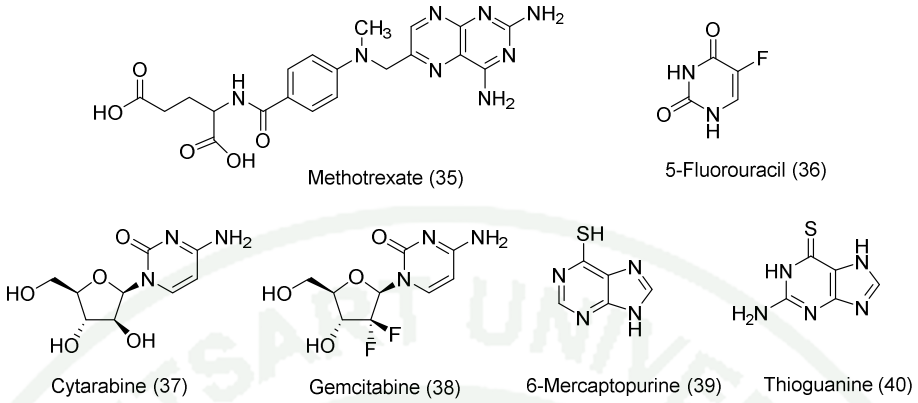
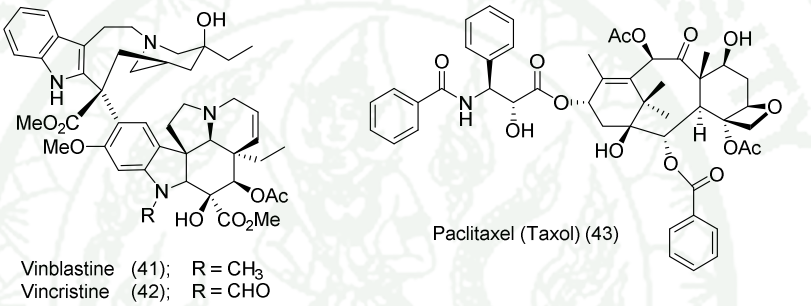


Figure 6 Examples of anticancer drugs.

Antimetabolites



Spindle poisons



Topoisomerase inhibitors

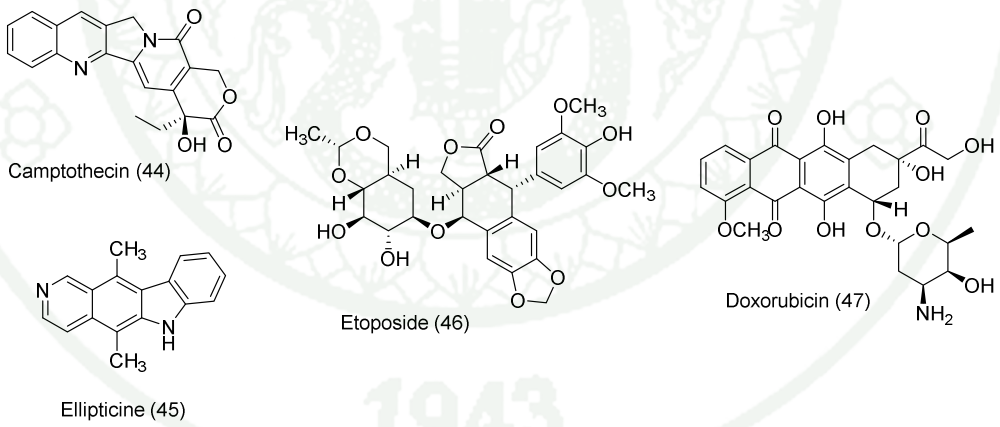


Figure 7 Examples of anticancer drugs.

3. Malaria and Antimalarial drugs

Malaria is a serious health problem in certain regions of sub-Saharan Africa, South East Asia and South American. It was considered as one of the world's biggest killers. Africa is the most affected continent, about 90% of all malaria deaths occurred

there. In Thailand, malaria distributes only hilly and forested areas. Most cases are found around the borders especially Thai – Myanmar and Thai – Cambodia borders.

Malaria infection in human is caused by four species of *Plasmodium* parasite, which are *P.flaciparum*, *P.vivax*, *P.ovale* and *P.malariae.* Most case of malaria and deaths are caused by *P.flaciparum.* The *Plasmodium* parasites are transmitted from human to human via mosquito (female anopheles). The malaria life cycle involves 3 cycles into 2 hosts which are *sporogonic cycle* in mosquito, *exoerythrocytic cycle* and *erythrocytic cycle* in human (Figure 8).

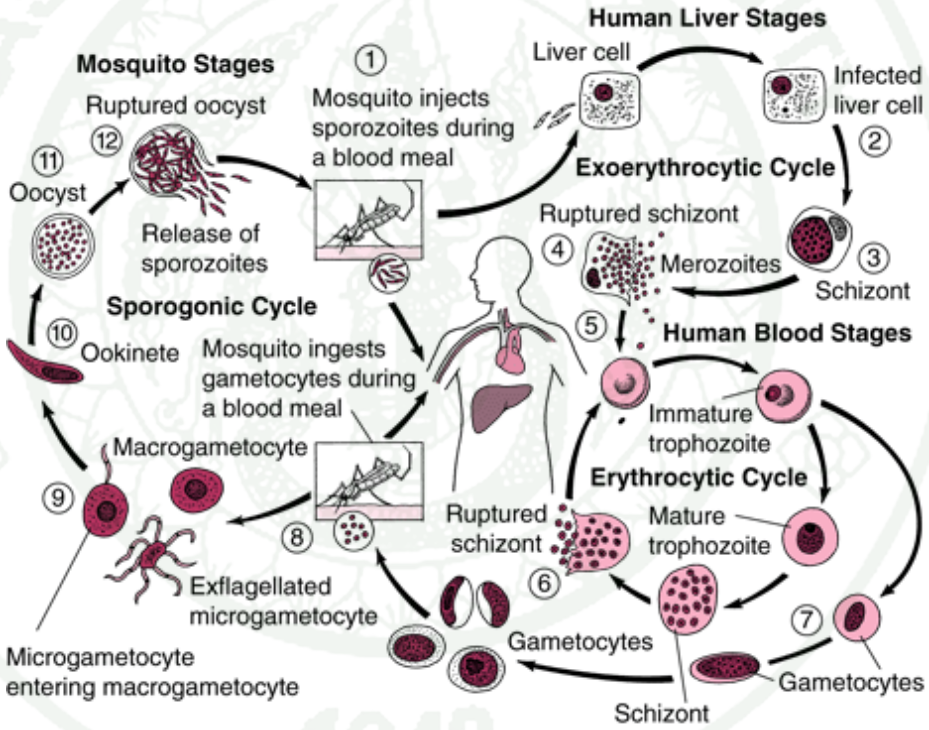


Figure 8 *Plasmodium* life cycles in human and mosquito states.

Source: Pearson (2014)

During the malaria parasite's life cycle in the host erythrocytes, malaria parasites will degrade hemoglobin to release globin protein as nutrients. On the other hand, the free heme by-product is a toxic substrate for the parasite, thus the parasites will detoxify by polymerization of free heme into non-toxic hemozoin (malaria

pigment). This unique mechanism of heme detoxification is a high-priority target for antiparasitic drugs.

Currently, there is no effective malaria vaccine because the development of suitable vaccine is difficultly made by the relatively complex life cycle of malaria parasites. Antimalarial drugs also play an important part, however many drugs resistance has widely spread. Thus, development of new effective antimalarial drugs is always needed because we never know when malaria parasites will become resistant to the currently available drugs. Examples of antimalarial drugs are presented in Figure 9.

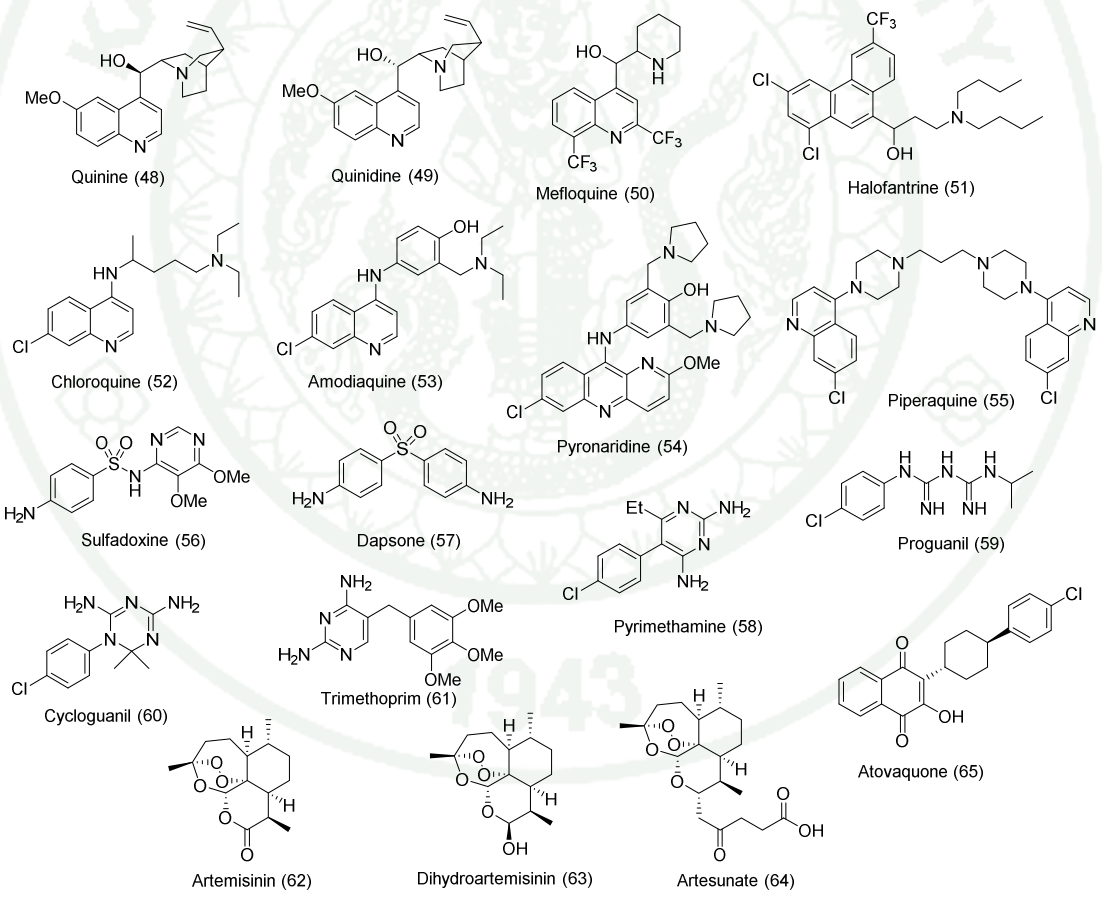


Figure 9 Examples of antimalarial drugs.

Artemisinin (62), a natural sesquiterpene trioxane lactone extracted from the Chinese herb *Artemisia annua* has been used by Chinese herbalists for more than a thousand years in the treatment of many illnesses, such as skin diseases and malaria. It is the currently effective antimalarial drug which is highly active against both chloroquine sensitive and chloroquine-resistant strains of *Plasmodium falciparum*. However, some resistant has been detected but the current malaria treatment still relied on artemisinin-based combination therapies. The molecular targets of artemisinin and peroxide derivative are still under debate. However, there is evidence to suggest that its activity depends on the presence of the endoperoxide and an iron is the primary activator. The iron activator might be in the free Fe^{2+} form, heme form or both (O'Neill, *et al.*, 2010; Fügi, *et al.*, 2010). In addition to acting as an antimalarial agent, artemisinin has also shown cytotoxicity to tumor cells in micromolar range (Woerdenbag, *et al.,* 1993). Furthermore, semi-synthetic analogues such as sodium artesunate showed more potent activity in the low micromolar range. It believed that the mechanism of action depends on endoperoxide and higher iron (II) concentration of cancer cell to mediate radicals species like antimalarial mechanism (Beekman, *et al.,* 1998). However, molecular targets of artemisinin to cancer cell are also still debated. Even through artemisinin-based combination therapies (ACTs) are the best antimalarial drugs available now but increased tolerance to artemisinin in *Plasmodium falciparum* was often found. Thus, drugs development and investigation for obtaining new drugs are necessary for malaria control.

4. Rhinacanthins and related naphthoquinones

Rhinacanthus nasutus Kurz (Acanthaceae) or Thong pan chang (Thai name), Thai traditional herb which has been used for treatment of cancer. It is used as a folk medicine for treatment of hepatitis, diabetes mellitus, hypertension, and skin diseases. This plant is well known as the source of flavonoids, steroids, triterpenoids, anthraquinones, lignans and naphthoquinones (Bukke, *et al.,* 2011). The active components for anticancer activity are rhinacanthins (A-D, G-Q) (67-81) and rhinacanthone (66), naphthoquinone derivatives (Figure 11) (Wu, *et al*., 1998).

However, those anticancer naphthoquinones were obtained in very small amount from plant so it is not enough for studying biological activities and mode of action.

Figure 10 *Rhinacanthus nasutus* Kurz, or Thong pan chang.

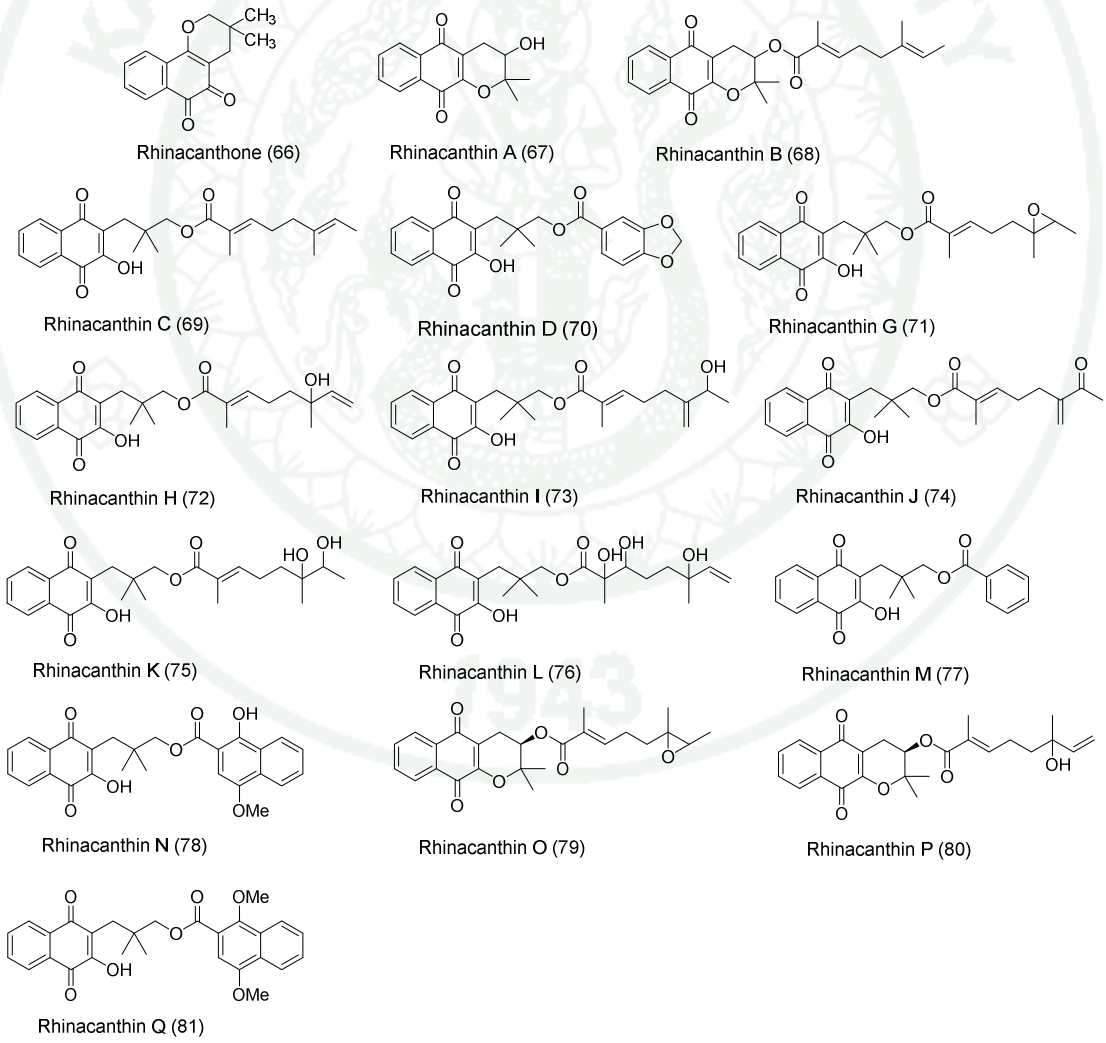


Figure 11 Rhinacanthone and Rhinacanthins from *Rhinacanthus nasutus.*

Because of the interesting biological activity of natural occurring naphthoquinone especially anticancer, our group has synthesized and modified the structure for better activity of compounds which are rhinacanthone (66), pyrano-1,2-naphthoquinones (82), furano-1,2-naphthoquinones (83), pyrano-1,4-naphthoquinones (84) and furano-1,4-naphthoquinone (85) derivatives (Figure 12). These compounds showed cytotoxicity against KB (oral human epidermoid carcinoma), HeLa (human cervical carcinoma) and $HepG_2$ (human hepatocellular carcinoma) cancer cell lines (Kongkathip *et al.,* 2003).

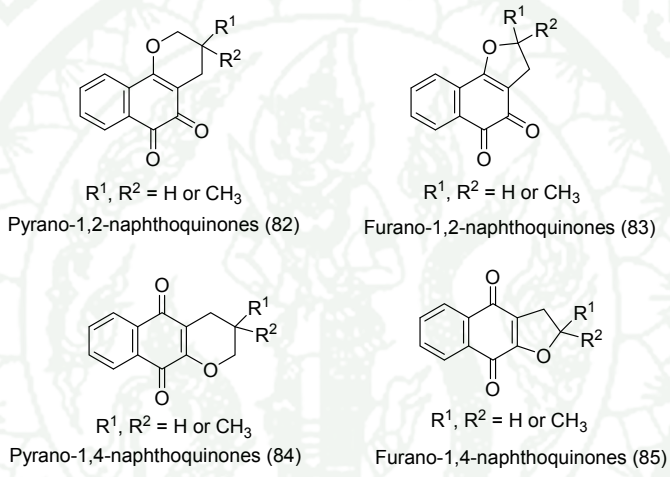


Figure 12 The synthetic 1,2- and 1,4-naphthoquinones.

In 2004, our group (Kongkathip's group) reported synthesis of rhinacanthin M (77), rhinacanthin N (78), rhinacanthin Q (81) and 39 related naphthoquinone esters (Figure 13) together with their cytotoxicities against human carcinoma cell lines, KB, HeLa, and $HepG_2$ cell lines and found that some compounds showed very strong anticancer activity and a little harm to the normal Vero cells (Kongkathip *et al.,* 2004). Study on mode of action of the naphthoquinone esters indicated that rhinacanthin N and rhinacanthin Q inhibit Topo II enzyme as well as doxorubicin (47) anticancer drug.

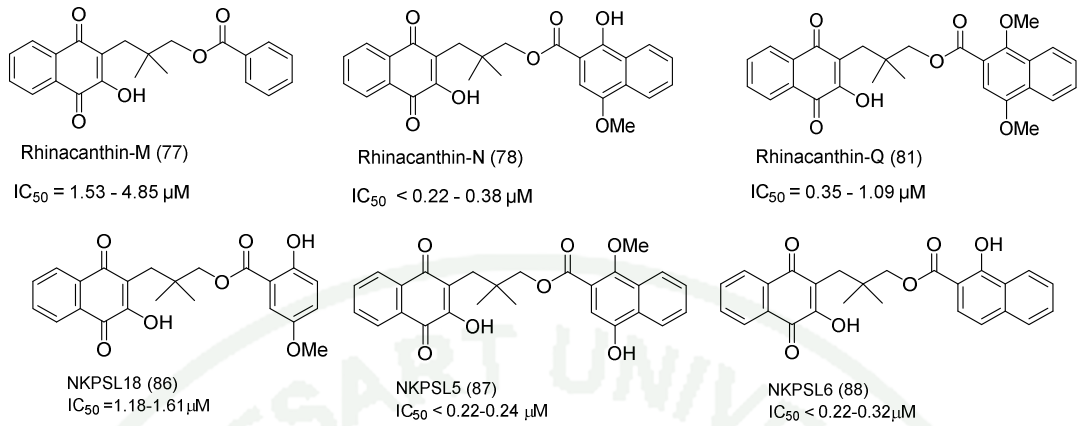


Figure 13 Examples of the synthetic naphthoquinone aromatic esters against KB, HeLa and HepG2 cell lines.

In 2010, our group reported synthesis and anticancer evaluation of naphthoquinone aromatic esters with cyclopentyl and cyclohexyl substutuents for the structure activity relationships study. It was found that the C-2 hydroxy group, 2,2-dimethyl substituents of the propyl chain and aromatic ester moiety affected the anticancer activity (Figure 14). Compound (89) (IC_{50} <0.22 μM) showed better anticancer activity than (93) (IC_{50} 0.66 μM), (94) (IC_{50} 11.35 μM), (90) (IC_{50} 33.66 μM), (91) (IC_{50} 65.48 μM) (Kongkathip *et al.,* 2010).

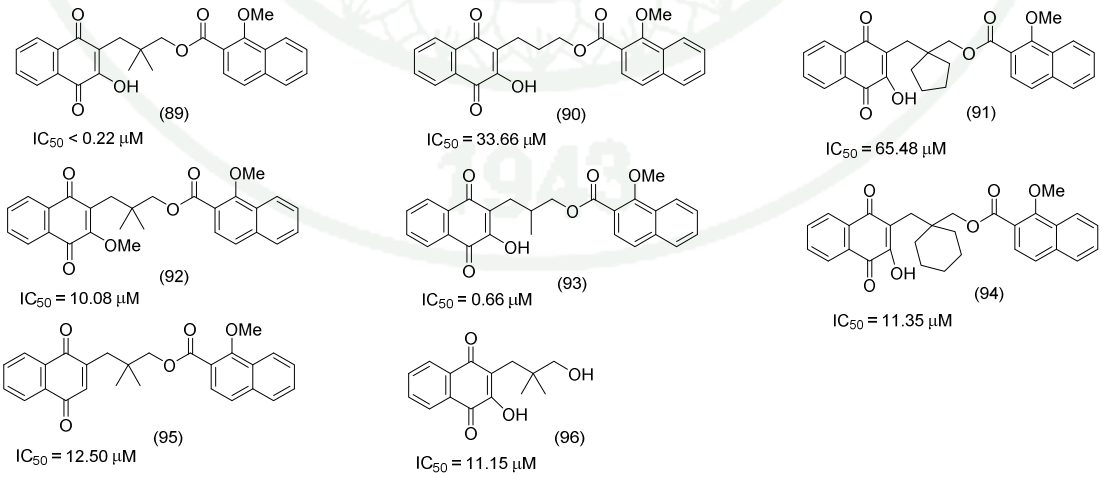


Figure 14 Anticancer activity of the synthetic naphthoquinone aromatic esters with different substituents on the propyl chain against KB cell lines.

Based on the structures of naturally occurring anticancer rhinacanthin C (69), rhinacanthin G (71), rhinacanthin H (72) and rhinacanthin K (75), naphthoquinone aliphatic esters were also synthesized and evaluated for anticancer activity. Naphthoquinone aliphatic esters with α-methyl substituent on the ester part (98) and (99) showed more potent cytotoxicity than those without α-methyl group (97) with the same number of straight chain carbons. The racemic mixture of the α-methyl substituent (98) and pure *S*-enantiomer (99) did not show significant difference in the cytotoxicity (Hasitapan, 2006).

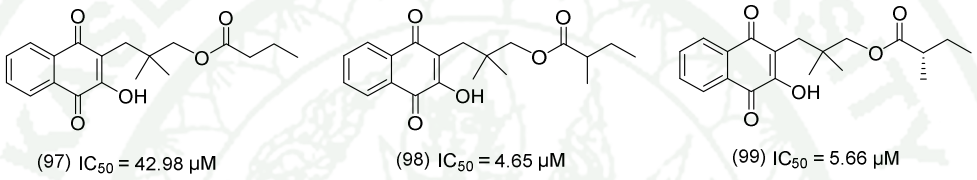


Figure 15 Examples of anticancer naphthoquinone aliphatic esters .

Naphthoquinone aliphatic esters were also evaluated for antimalarial activity (Figure 16). They showed an excellent antimalarial activity against *Plasmodium falciparum* which targets at cytochrome bc_1 complex and most of them are non-toxic to normal Vero cell. For the structure activity relationship study, the compounds with α-methyl substituent on the ester part (98) and (99) showed more potent cytotoxicity than β-methyl (100), α-ethyl (101) substituent and linear chain (97) (Kongkathip *et al.,* 2010).

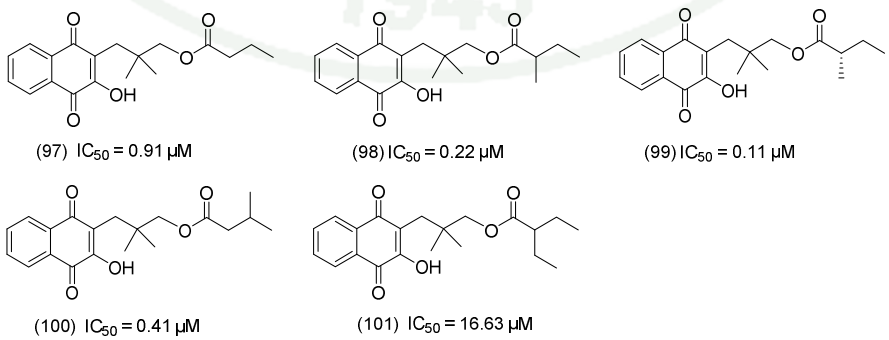


Figure 16 Examples of antimalarial naphthoquinone aliphatic esters.

Naphthoquinone ester with C-2´ dimethyl substituents on the propyl chain (102) showed more potent antimalarial activity than cyclohexyl (104) or without substituents group (103) (Figure 17).

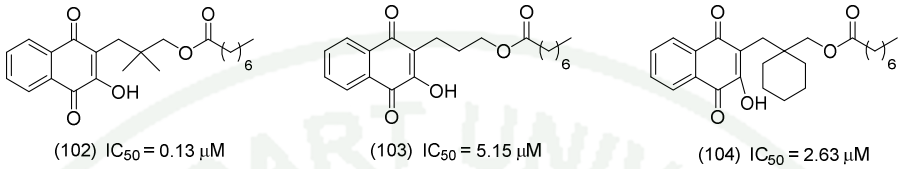


Figure 17 Structure and anticancer activity of synthetic naphthoquinone aliphatic esters with difference substituents on the propyl chain.

There are two naphthoquinones aliphatic ester (105) (C_{14} chain length) and (106) (C_{16} chain length) which showed the greatest antimalarial activity against *Plasmodium falciparum* parasite (Figure 18).

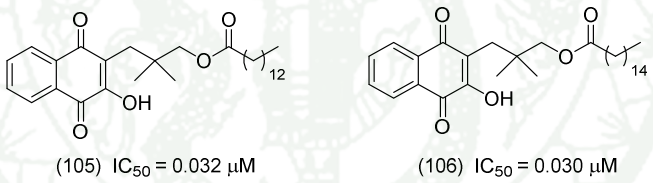


Figure 18 Our synthetic naphthoquinones with the greatest antimalarial activity.

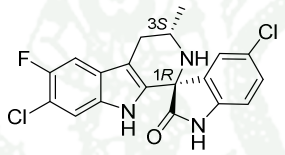
From the results of anticancer and antimalarial evaluation of naphthoquinone aliphatic and aromatic esters, it would be said that the important functional parts of our synthetic naphthoquinones are C-2 hydroxy group of the 1,4-naphthoquinones ring, C-2´ dimethyl substituents on the propyl chain, α-methyl substituent of aliphatic chain, the chain length of aliphatic acids and the ester moiety.

In 2012, our group further investigated synthesis of sixteen novel naphthoquinone aromatic amides and evaluation for anticancer activity against KB, NCI-H187, and MCF-7 cell lines (Kongkathip *et al.,* 2012). Most of naphthoquinone aromatic amides showed weaker toxicity than the previous naphthoquinone aromatic

esters. Study on mode of action of the naphthoquinone aromatic amides found that topoisomerase II enzyme is the molecular target for anticancer activity as well as rhinacanthin N (78) and rhinacanthin Q (81), naphthoquinone aromatic ester.

It is still worthwhile to further synthesize novel naphthoquinone aliphatic amides, as well as to evaluate their anticancer and antimalarial activities in comparison with those of the aromatic, aliphatic esters and aromatic amides, and to compare them with those of the naphthoquinone ester and amide series. Thus my research objective is synthesis of novel naphthoquinone aliphatic amides and their evaluation for anticancer and antimalarial activities.

5. NITD 609, the spiroindolone



NITD 609 (107)

Figure 19 Spiroindolone, NITD 609.

The spiroindolone, NITD 609 (107) is the drug candidate for malaria treatment which was discovered by Yeung and co-worker in 2010 (Yeung, *et al.,* 2010). Structure-activity relationships study (SARs) of racemic spiroazepineindole which was identified from a phenotypic screen on wild type *Plasmodium falciparum* with an in vitro IC_{50} of 90 nM delivered to NITD 609 with IC_{50} values around 1 nM. An incorporation assay with radiolabeled methionine and cysteine revealed that NITD 609, in contrast to other antimalarials, blocked protein synthesis in *P. falciparum* parasites within 1 h of exposure, suggesting a distinct mode of action. The P-type ATPase *Pf*ATP4 had been implicated based on drug resistance studies, but the exact mechanism of action of NITD 609 remains unknown. NITD 609 has excellent oral bioavailability and was curative in the *P. berghei* mouse model at a single dose of 100 mg/kg (Rottmann *et al.,* 2010; van Pelt-Koops, *et al*, 2012). The compound displays a

promising early safety profile and no cardiotoxicity or genotoxicity liabilities. At present, NITD 609 has entered Phase IIa clinical trial studies for malaria treatment (Mäser, P. *et al*., 2012).

From the discovery of NITD 609, potent antimalarial activity and effect of peroxide bridge that contained in artemisinin structure to malarial parasites and cancer cells we were interested to design and synthesize *N-O* heterocyclic spirooxindole compounds (108-109) (Figure 20) and screening for antimalarial and anticancer activities (instead O-O with N-O, average bond energy, N-O =222 kJ/mol, O-O = 142 kJ/mol) (chemwiki, 2012).

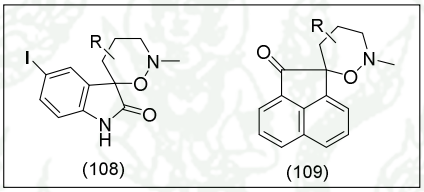


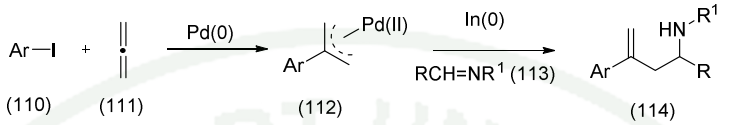
Figure 20 Our designed *N-O* heterocyclic spiro compounds.

6. Palladium catalyzed cascade reactions of allenes

Cascade reactions have become a fascinating branch of organic chemistry. They can be considered under the banner of "green chemistry" because they combine multiple reactions in one step and form molecular complexity without workup and isolation of multiple intermediates. Cascades also result a single waste stream making them environmental friendly. Transition metal catalysed cascades are a powerful tool for generating molecular complexity via both carbon–carbon and carbon–heteroatom bond formation in a regio and stereoselective fashion by using a catalytic amount of mediator.

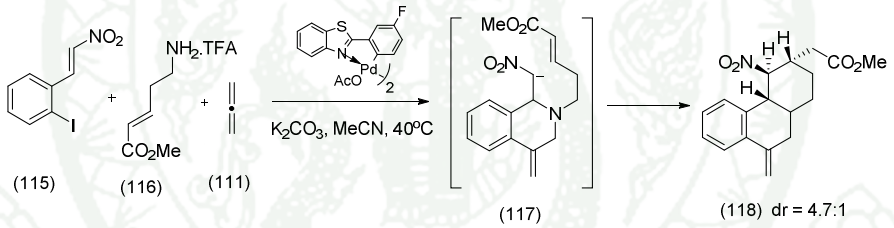
Our group (Grigg's group) has made an extensive study of various types of palladium catalysed cascade reactions of allenes. For examples, in 2002, three component palladium–indium mediated diastereoselective cascade allylation of

imines (113) with allenes (111) and aryl iodides (110) was reported (Scheme 1). This cascade reaction allows much greater levels of molecular diversity and complexity than classical Barbier-type allylations.



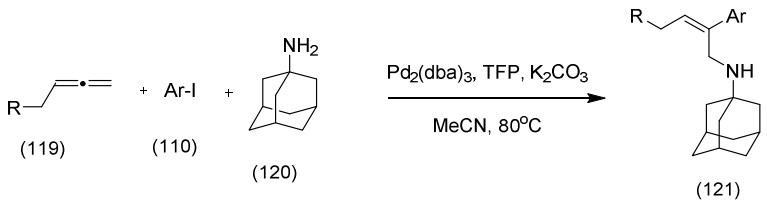
Scheme 1

In 2007, palladium catalysed cascade allene insertion–nucleophile incorporation–Michael addition was reported (Grigg *et al.,* 2007). This cascade sequence successfully forms four bonds, three stereocenters and two rings in moderate yield (Scheme 2).

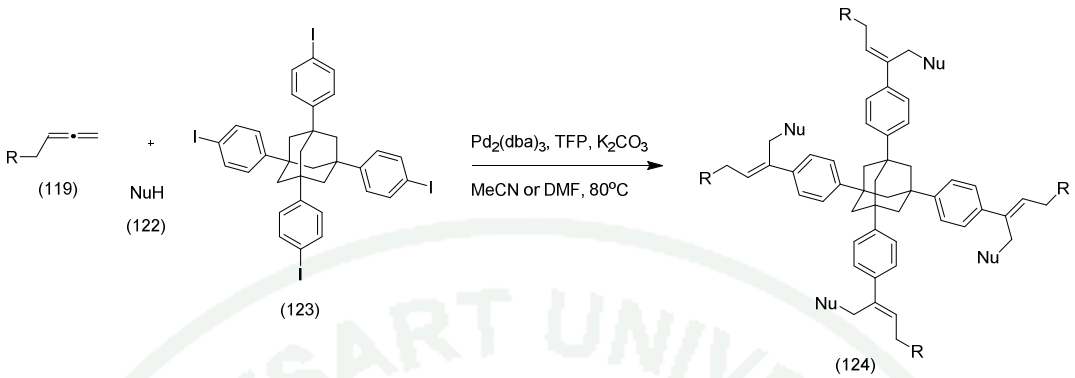


Scheme 2

In 2012, three- and nine-component Pd(0) catalysed cascade reactions of biochemical interested allenes, aryl iodides and N-nucleophiles with concomitant installation of trisubstituted Z-alkenes were also reported (Scheme 3-4) (Grigg *et al.,* 2012).

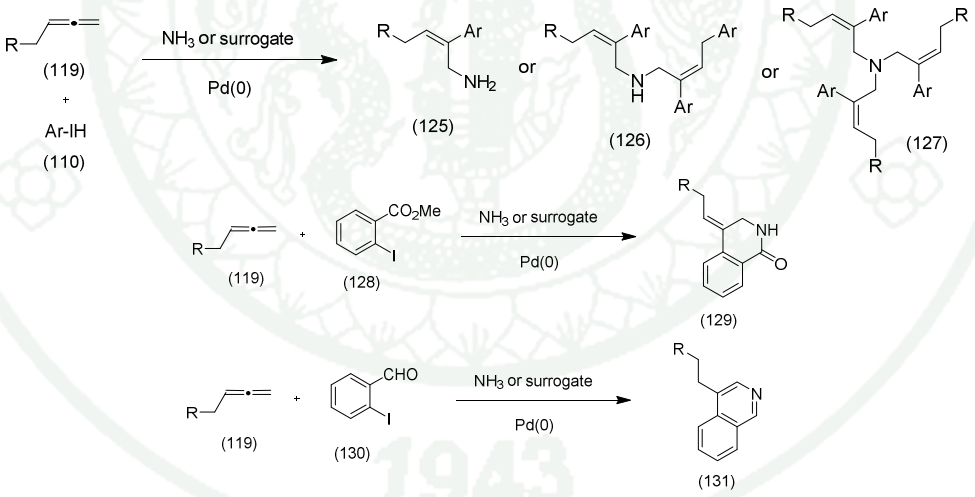


Scheme 3



Scheme 4

Our next interests are replacing amino nucleophile by ammonia or its surrogate to generate trisubstituted *Z*-allylamine (125-127) and extend the scope to synthesize isoquinoline (129) and isoquinolinone (131) (Scheme 5).



Scheme 5 Our interestd in cascade synthesis.

OBJECTIVES

1. To synthesize an anti-avian influenza drug, oseltamivir phosphate (Tamiflu®).

2. To synthesize naphthoquinone aliphatic amides and evaluation for their anticancer and antimalarial activities as well as cytotoxicity to normal Vero cell.

3. To synthesize *N*-*O* heterocyclic compounds and evaluation for their anticancer and antimalarial activities as well as cytotoxicity to normal Vero cell.

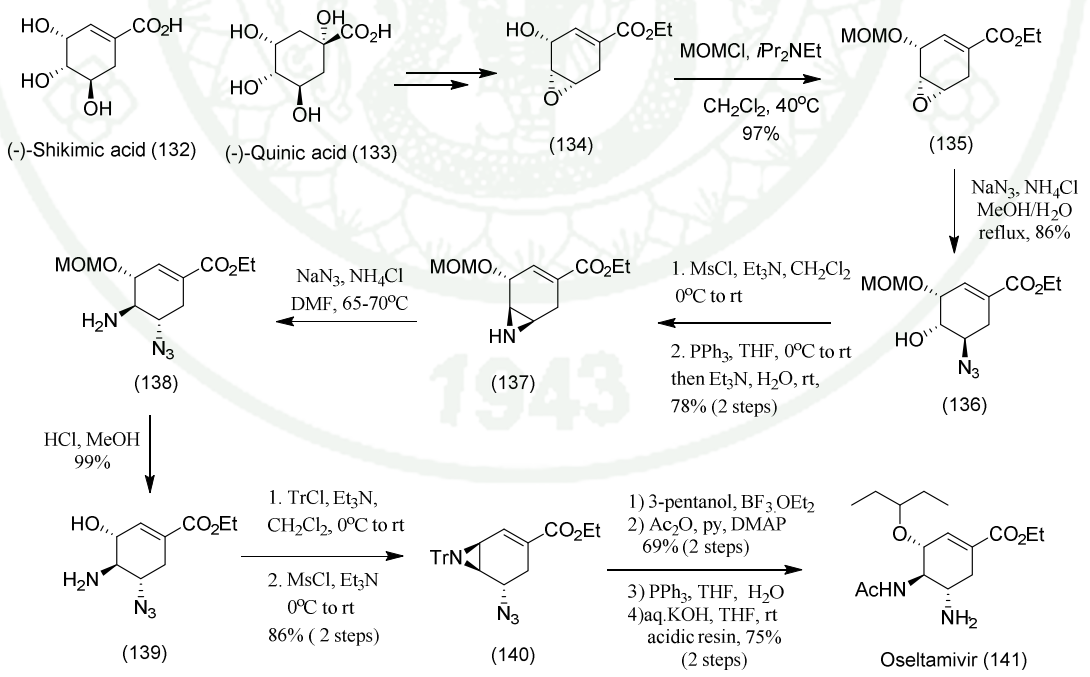
4. To study three component cascade reactions of substituted allenes with ammonia nucleophiles which targeted at the synthesis of bis-allylamines, isoquinolines and isoquinolinones.

LITERATURE REVIEW

Synthesis of oseltamivir phosphate (Tamiflu®)

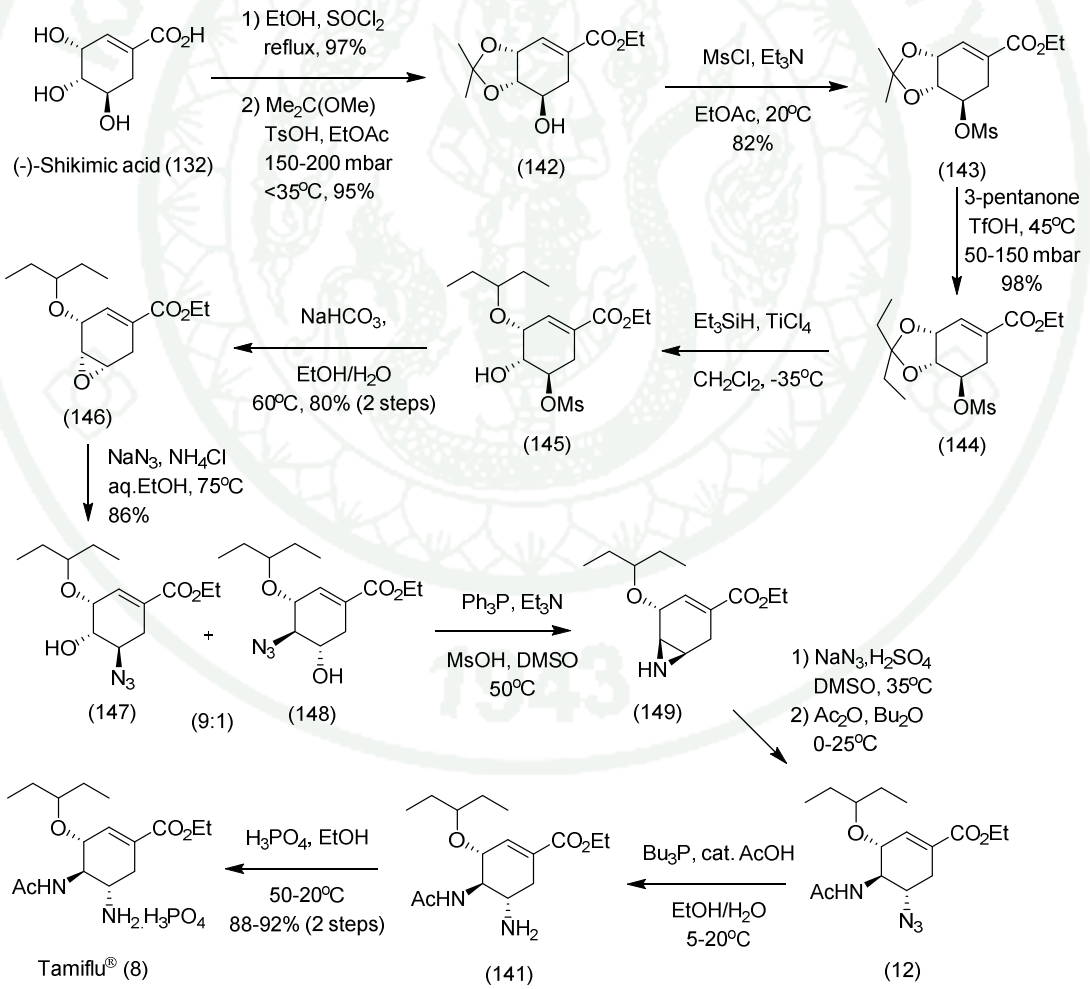
1. Synthesis of Tamiflu® from (–)-shikimic acid (132) and (–)-quinic acid (133)

Oseltamivir (141) is an anti-influenza drug which was discovered at Gilead Sciences and patented in 1995. The structure of oseltamivir (141) are consisted of three important parts which are cyclohexene carboxylate core structure, 3-pentyl ether at C-3 position and two amino group as 4β-acetamide and 5α-amino. The first synthesis of oseltamivir used a natural product, (–)-shikimic acid (132) and (–)-quinic acid (133), as the starting material (Scheme 6). Gilead Sciences synthesis introduced the amino functional groups by opening of epoxide (135) and aziridine (137) with sodium azide and introduced 3-pentyl ether via opening of aziridine (140) with 3-pentanol in the presence of boron trifluoride etherate (Kim *et al.,* 1997).



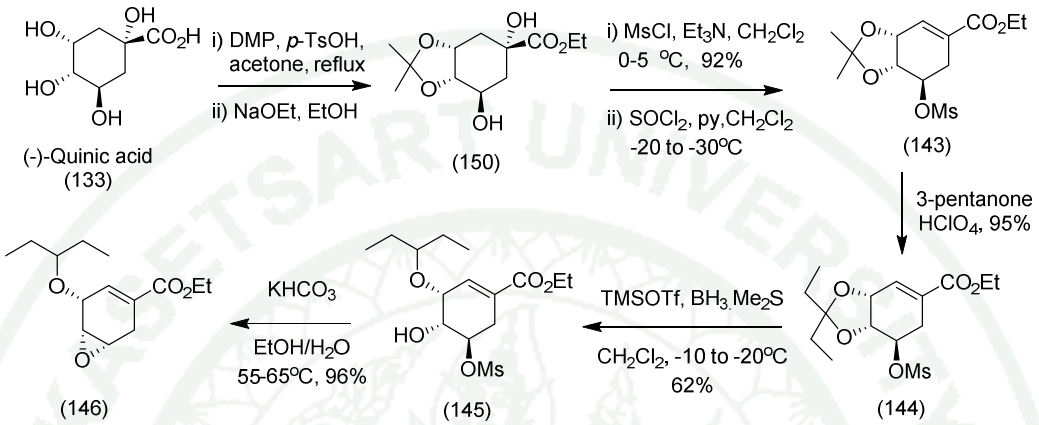
Scheme 6 Gilead Sciences's synthesis of oseltamivir.

In 1996, Gilead Sciences collaborated with F. Hoffmann-La Roche Company to sign for co-development of the drug. In 1999, the oseltamivir (141) was commercially launched as the phosphoric acid salt, under the trade name Tamiflu® (8). For industrial synthesis of Tamiflu®, (–)-shikimic acid (132) was selected to be a starting material due to its oxidation states of all the carbons are the same as in Tamiflu®. Roche's synthesis is characterized by early introduction of the 3-pentyloxy moiety at C-3 by regioselective reductive ring opening of pentylidine acetal (144). Amino functional groups were also introduced by ring opening of epoxide (146) and aziridine (149) by azide (Scheme 7). The Tamiflu® (8) was obtained in 11 steps with 66% yield (Federspiel *et al.,* 1999).



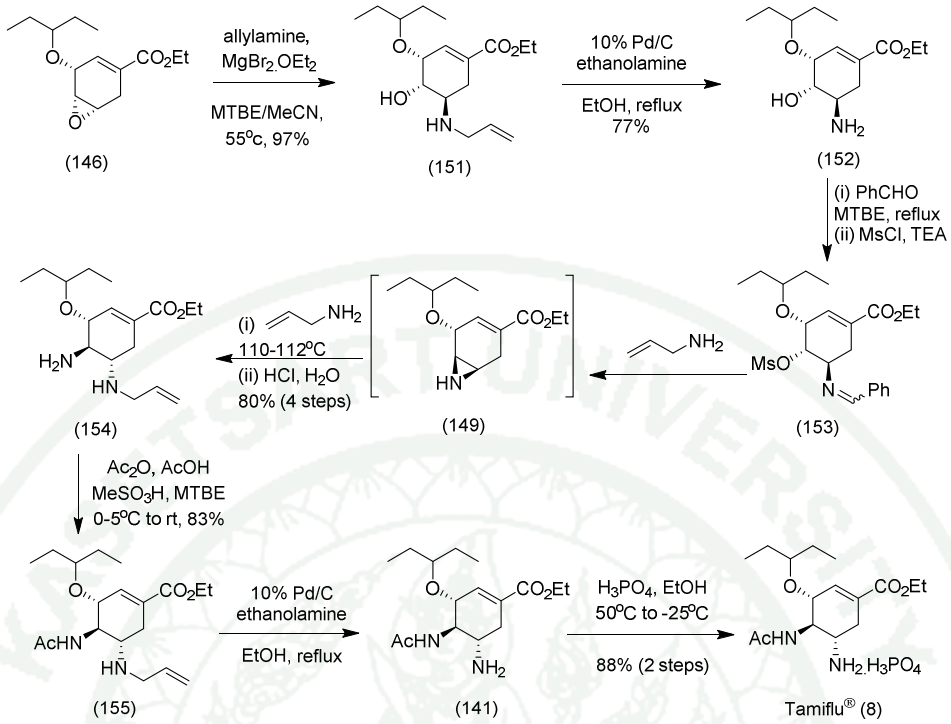
Scheme 7 F. Hoffmann-La Roche's synthesis of oseltamivir phosphate, Tamiflu®.

Due to the high cost and low availability of (–)-shikimic acid (132), (–)-quinic acid (133) was an alternative starting material for synthesis of epoxide (146) (Scheme 8) (Federspiel *et al.,* 1999).



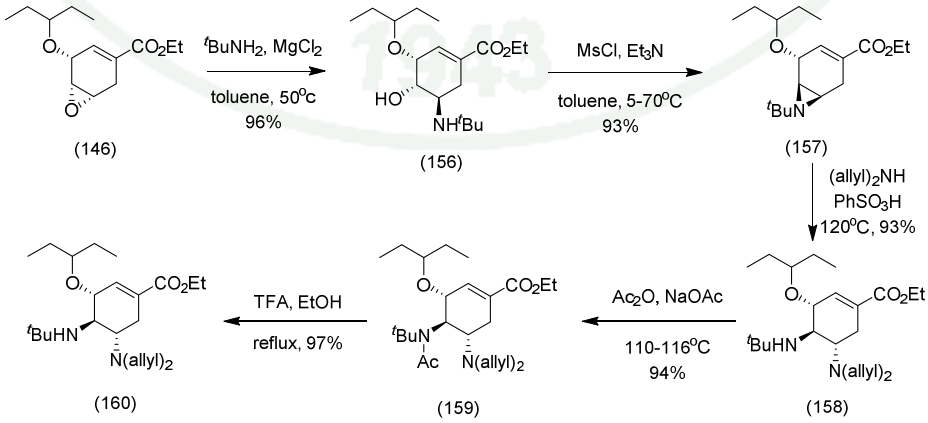
Scheme 8

Because of the hazard and potential explore of azide in the large scale synthesis, the first azide free synthesis of Tamiflu® was developed and published in 2001 by F. Hoffmann-La Roche Company (Scheme 9). In this synthesis, allyl amine was utilized as a nitrogen nucleophile instead of sodium azide in the previous route (Scheme 7) (Karpf *et al.,* 2001).

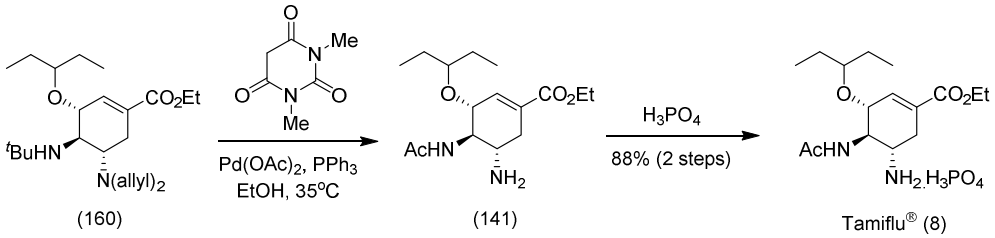


Scheme 9

A second-generation process for azide free synthesis of Tamiflu® has been developed by Roche Colorado Corporation. Their synthesis also started from epoxide (146) but differed in using *tert*-butylamine-magnesium chloride complex and diallyl amine as a nitrogen nucleophile for opening of epoxide and aziridine ring (Schemes 10 and 11). (Harrington *et al.,* 2004)

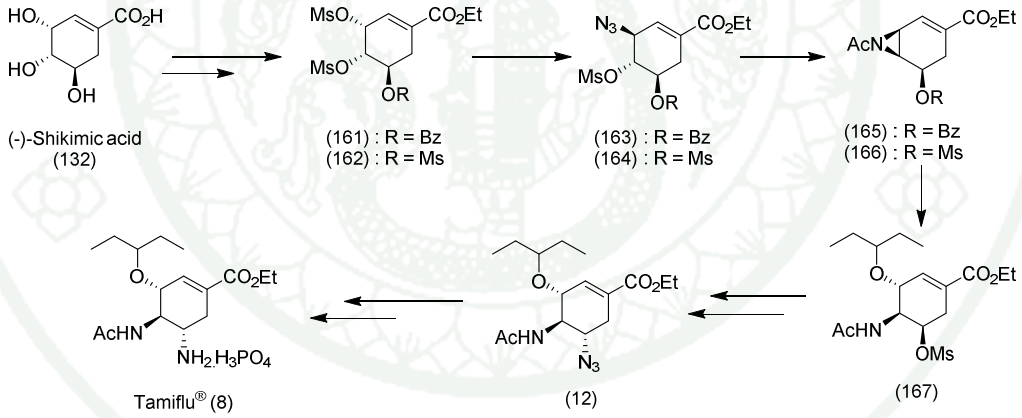


Scheme 10 Roche Colorado's synthesis of Tamiflu® *via* azide free strategy.



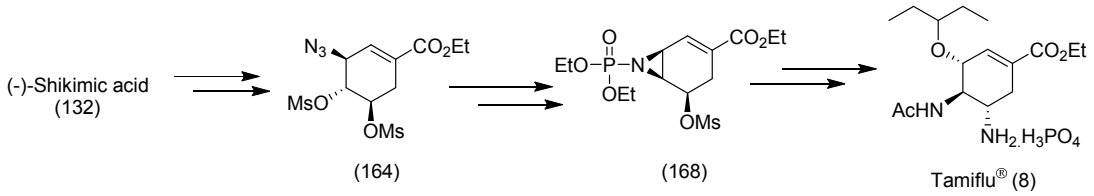
Scheme 11

In 2009, Shi and co-workers reported synthesis of Tamiflu® through benzoyl dimesylate (161) and trimesylate (162) which was transformed to Tamiflu® (8) by following key reactions. i) Regio- and stereoselective substitution of the allylic *O*-mesylate, ii) aziridine formation with triphenyl phosphine, iii) regio- and stereoselective azirine ring opening at the allylic position with 3-pentanol and Lewis acid (Scheme 12) (Shi and Nia, 2009) (Shi *et al*., 2009).



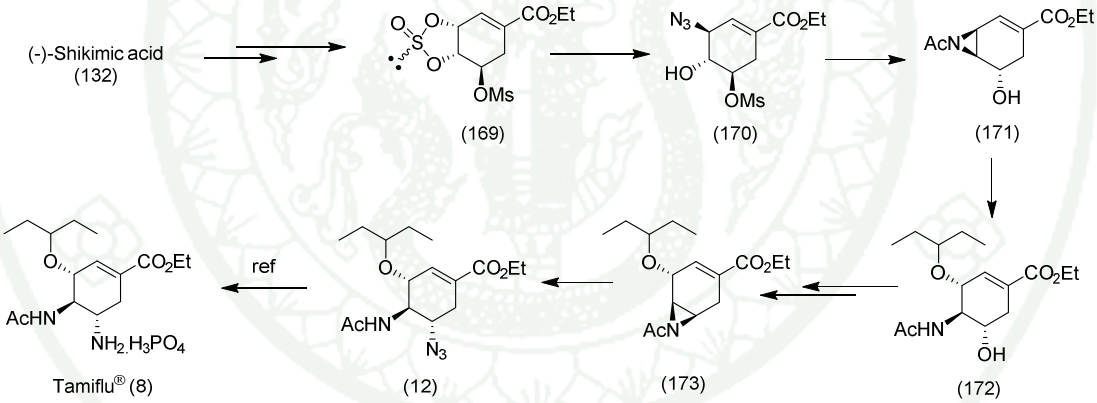
Scheme 12

In the same year, F. Hoffmann-La Roche Company reported efficient route to Tamiflu® via *O*-trimesylation of ethyl shikimate. Their synthesis differed from Shi's synthesis in using of a new protocal involving triethyl phosphite to transform azido mesylate (164) to aziridine under water-free condition (Scheme 13) (Karpf *et a*l., 2009). Later, in 2013, Kalashnikov and co-worker reported facile synthesis of Tamiflu® through Roche's *O*-trimesylate route (Kalashnikov *et al*., 2013).



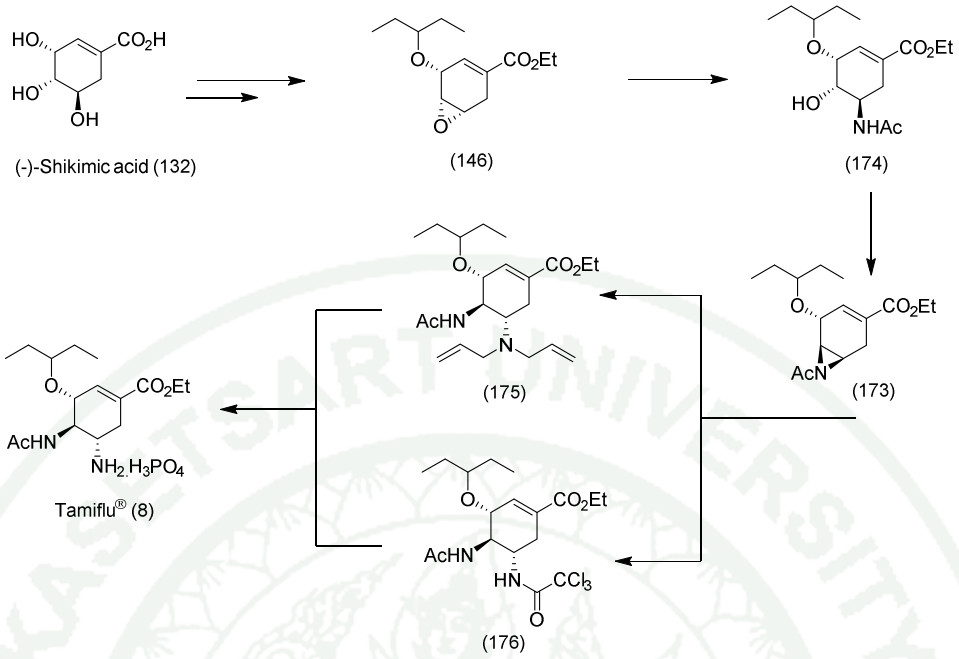
Scheme 13

In 2012, Shi and co-workers reported another synthesis of Tamiflu® through allylic azide (170) which was prepared from cyclic sulfite (169). Tandem aziridine formation and C-5 stereoconversion of azido mesylate (170) using triphenyl phosphine gave aziridine (171) in good yield. 3-Pentyl ether and second amino group was introduced through aziridine ring opening with 3-pentanol and sodium azide, respectively (Scheme 14) (Shi *et al.,* 2012).



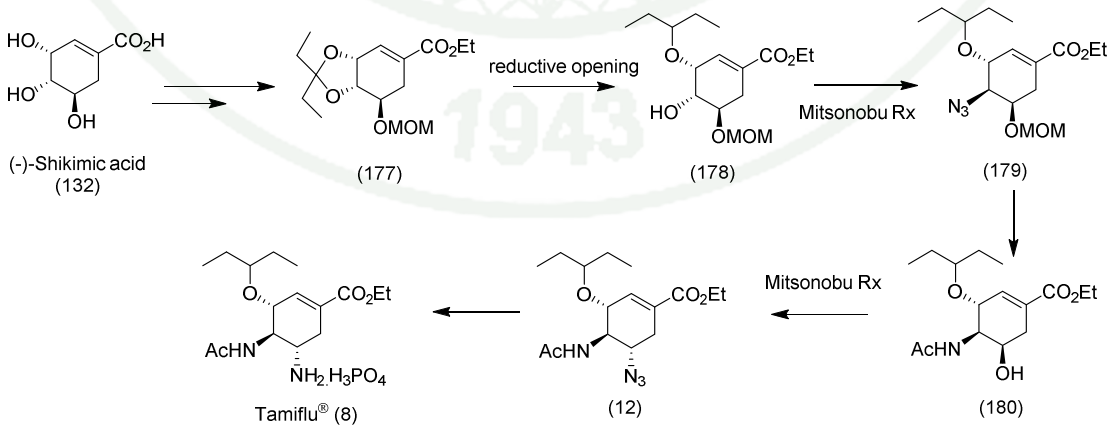
Scheme 14

In 2013, Shi and co-workers also reported synthesis of Tamiflu® from Roche's epoxide (146) via azide free strategy. Tamiflu® was obtained via i) $BF_3.Et_2O$ catalyzed epoxide-opening with acetonitrile to give amino alcohol (174). ii) Aziridine opening with diallylamine and isopropyl 2,2,2-trichloroacetimidate gave (175) and (176), respectively (Scheme 15) (Shi *et al.,* 2013).



Scheme 15

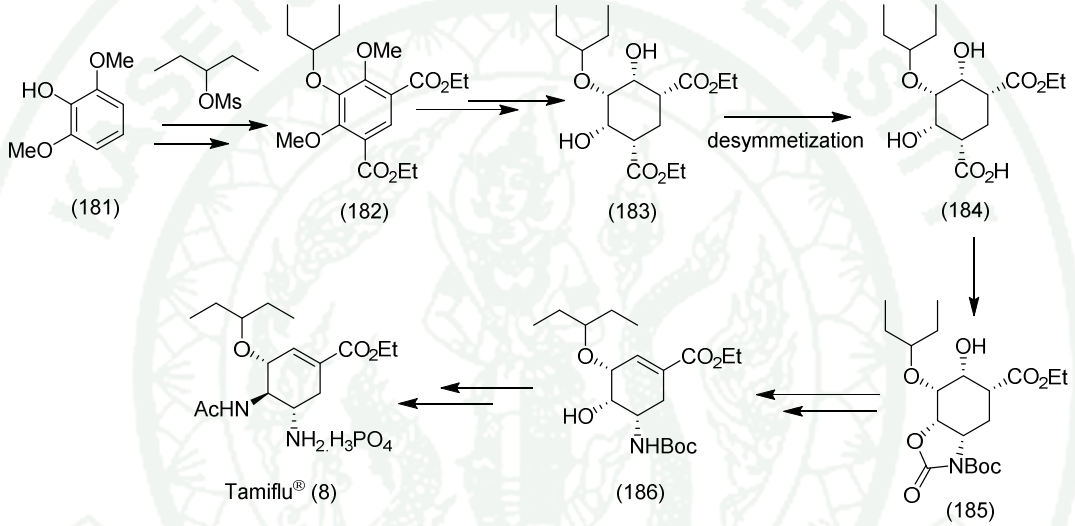
In 2012, Kim and co-workers reported synthesis of Tamiflu® (8) from (–)-shikimic acid (132) by early introduction of the 3-pentyl ether via regioselective reductive ring opening of pentylidine ketal (177). Two amino groups were introduced through an azide Mitsunobu reaction of a (178) and (180) (Scheme 16) (Kim *et al.*, 2012).



Scheme 16

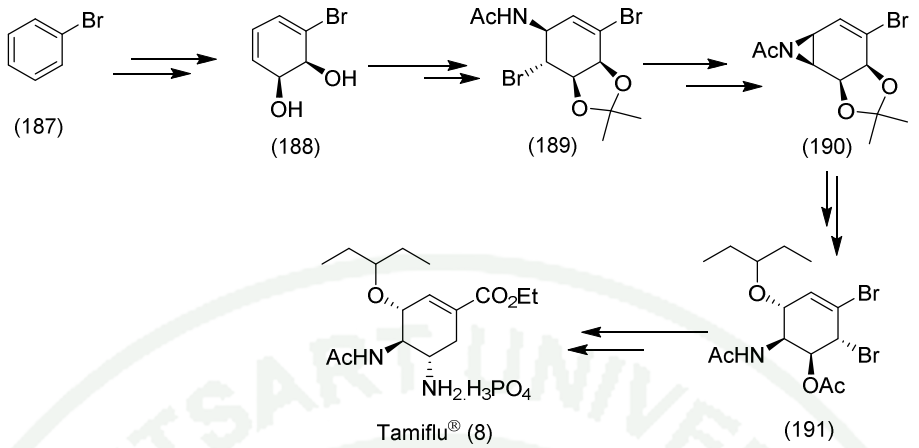
2. Synthesis of Tamiflu® from aromatic compounds

Zutter and co-workers at F. Hoffmann-La Roche Company reported synthesis of Tamiflu® from 2,6-dimethoxyphenol (181). The main features of this approach comprise the *cis*-hydrogenation of (182) and then desymmetrization of the resultant all-*cis*-*meso*diesters (183). Amino function was introduced through Curtius rearrangement and azide substitution (Scheme 17) (Zutter *et al*., 2008).



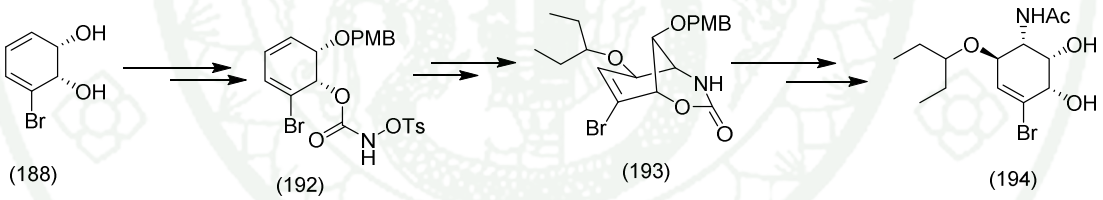
Scheme 17

In 2008, Fang and co-worker reported synthesis of Tamiflu® using the readily available starting material bromoarene *cis*-1,2-dihydrodiol (188), which can be obtained from the microbial oxidation of bromobenzene (187). The first amino group was introduced via $SnBr_4$-catalyzed bromoacetamidation reaction of acetonide of (188) with *N*-bromoacetamide (NBA). The second amino group was introduced via azide substitution (Scheme 18) (Fang *et al.,* 2008).



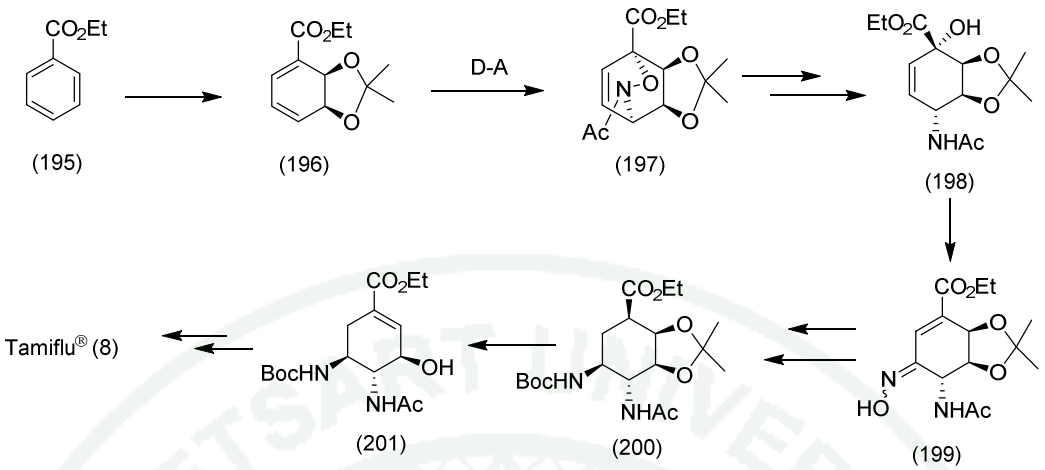
Scheme 18

Banwell and co-workers reported synthesis of Fang's intermediate (194) from bromoarene *cis*-1,2-dihydrodiol (188) through intermediate (193) which was obtained via aziridine formation and opening with 3-pentanol (Scheme 19) (Banwell *et al*., 2008).



Scheme 19

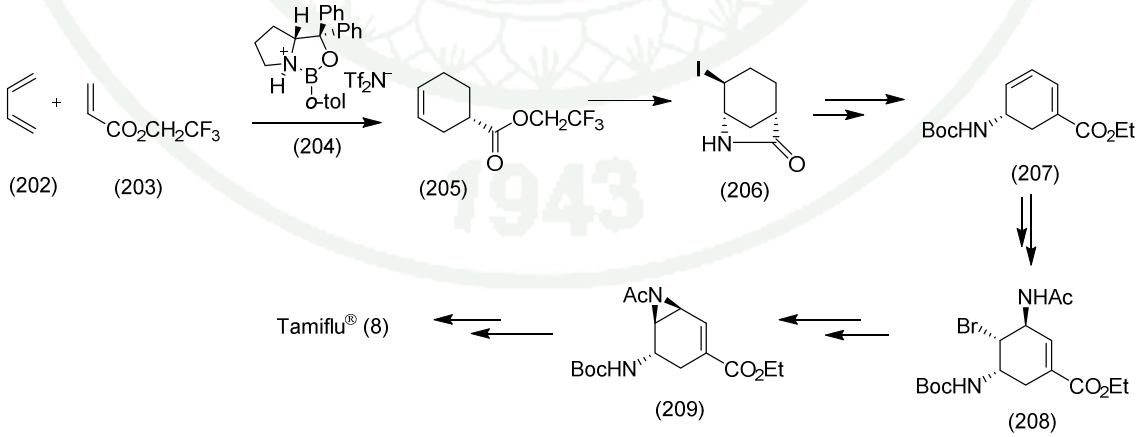
In 2010, Hudlicky and co-workers reported an azide-free synthesis of Tamiflu® from ethyl benzoate (195) which was converted to *cis*-dihydroxycyclohexadiene (196) by enzymatic transformation. The key steps for amino introduction were Diels–Alder cycloaddition of (196) and acyl nitroso compound to give oxazine (197) and oxime (199) formation-reduction (Scheme 20) (Hudlicky *et al.,* 2010).



Scheme 20

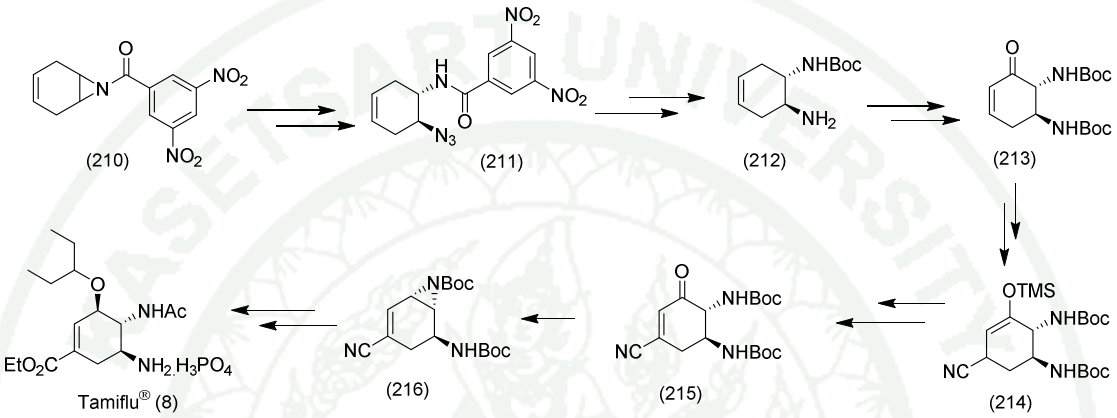
3. Synthesis of Tamiflu® from cyclohexene and cyclohexadiene

Corey and co-workers reported synthesis of Tamiflu® using asymmetric Diels-Alder cycloaddition of diene (202) and dienophile (203) to construct cyclohexene core. Amino functional groups were installed using ammonia and proceed through iodolactamization to give (206) and bromoacetamidation reaction of (207) using *N*-bromoacetamide (Scheme 21) (Corey *et al.,* 2006).



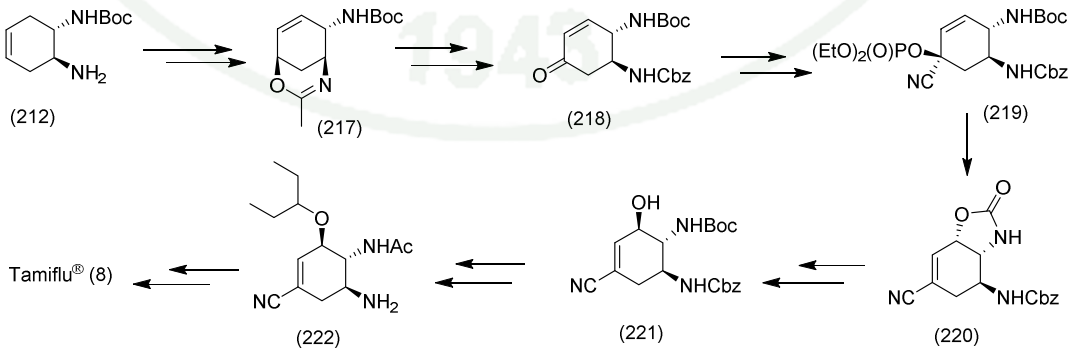
Scheme 21

Shibasaki and co-workers reported synthesis of Tamiflu® (8) using catalytic enantioselective desymmetrization of *meso*-aziridines with $TMSN_3$ to give enantiopure (212) which was converted to (214) by the allylic oxidation and the Ni-catalyzed cyanide conjugate addition. Keto nitrile (215) formation, reduction, aziridine formation gave intermediate (216) (Scheme 22) (Shibasaki *et al*., 2006).



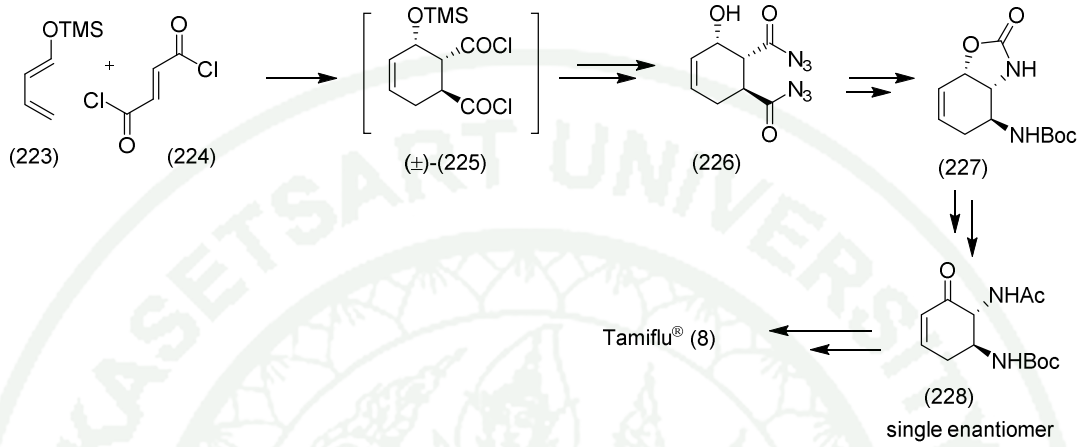
Scheme 22

The second generation of shibasaki's synthesis employed the catalytic enantioselective desymmetrization of meso-aziridines with $TMSN_3$ as an initial step. The allylic oxygen functionality required for 3-pentyl ether formation was introduced by rearrangement of an allylic phosphate followed by substitution with a hydroxyl group (Scheme 23) (Shibasaki *et al.,* 2007).



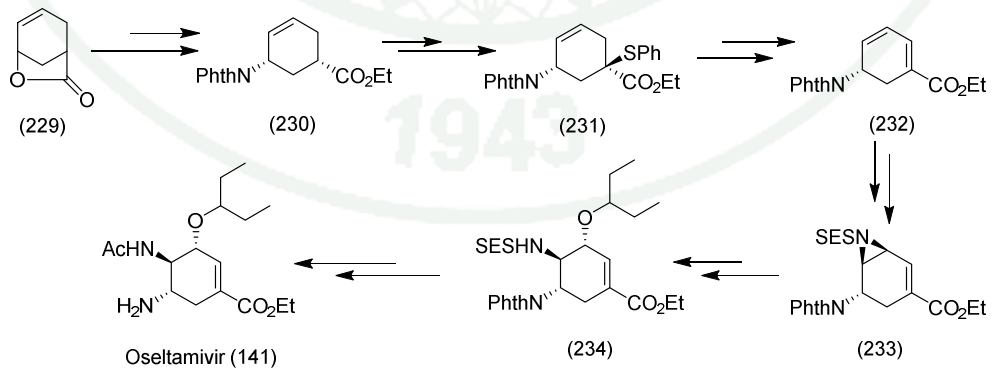
Scheme 23

Third generation of Shibasaki's used Diels–Alder reaction and Curtius rearrangement as key steps to synthesize intermediate (228) (Scheme 24) (Shibasaki *et al*., 2007).



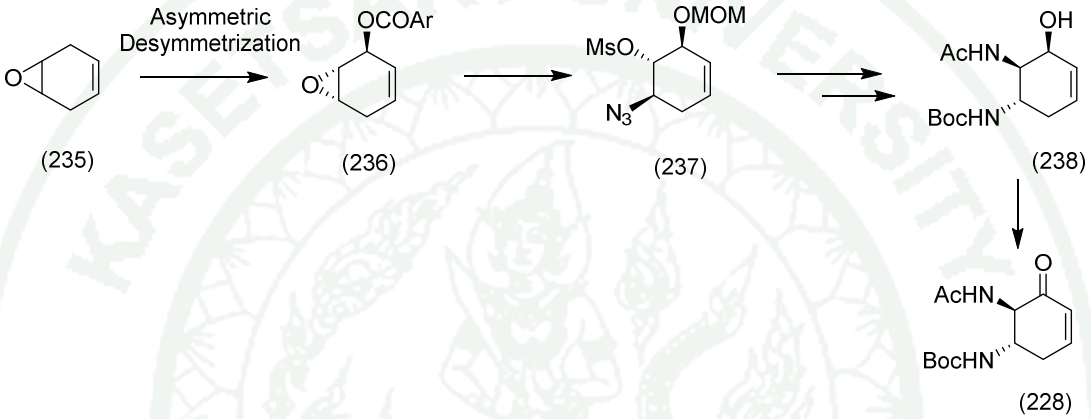
Scheme 24

Trost and co-workers reported synthesis of oseltamivir (141) via palladium-catalyzed deracemizing of racemic-lactone with a nitrogen nucleophile as well as an unprecedented Rh-catalyzed chemo-, regio-, and stereoselective direct aziridination reaction on an electron-deficient conjugated diene system delivered to aziridine intermediate (233) (Scheme 25) (Trost *et al.,* 2008).



Scheme 25

Hayashi and co-workers reported synthesis ketone (228), Shibasaki's third generation intermediate through catalytic asymmetric desymmetrization of 1,2-epoxycyclohex-4-ene (235) using Kharasch-Sosnovsky allylic oxidation to give enantiopure epoxide (236). Azide opening of the epoxide ring, aziridine formation, aziridine opening and oxidation of alcohol afforded intermediate (228) (Scheme 26) (Hayashi *et al*., 2011).

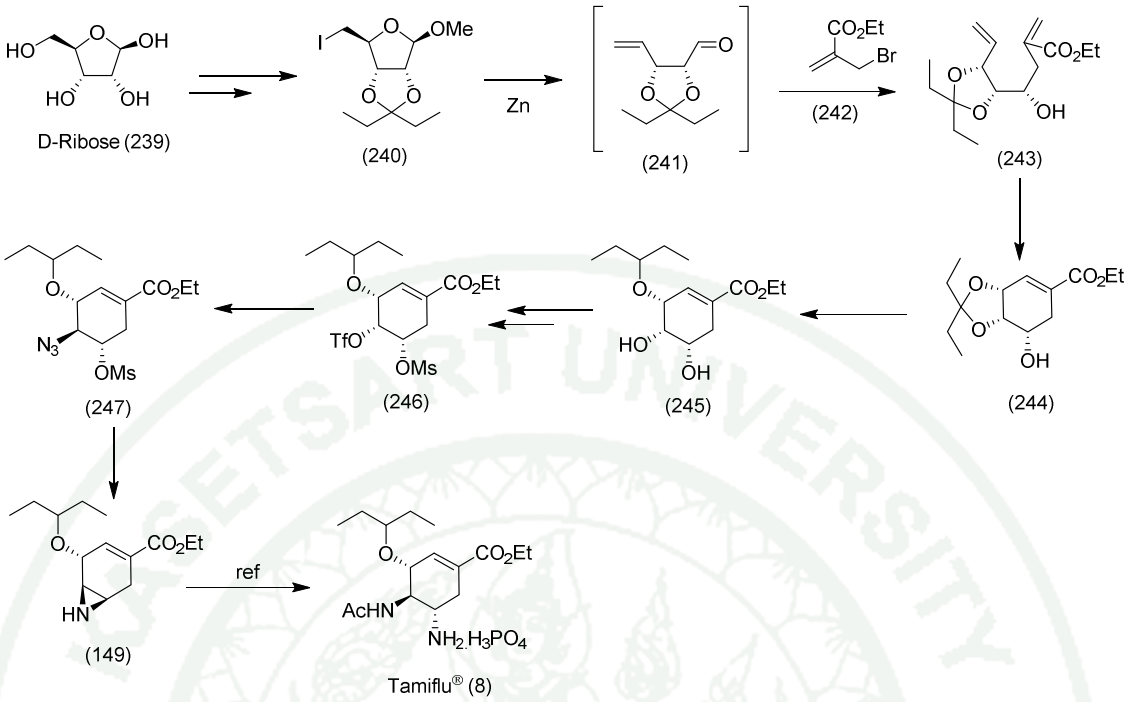


Scheme 26

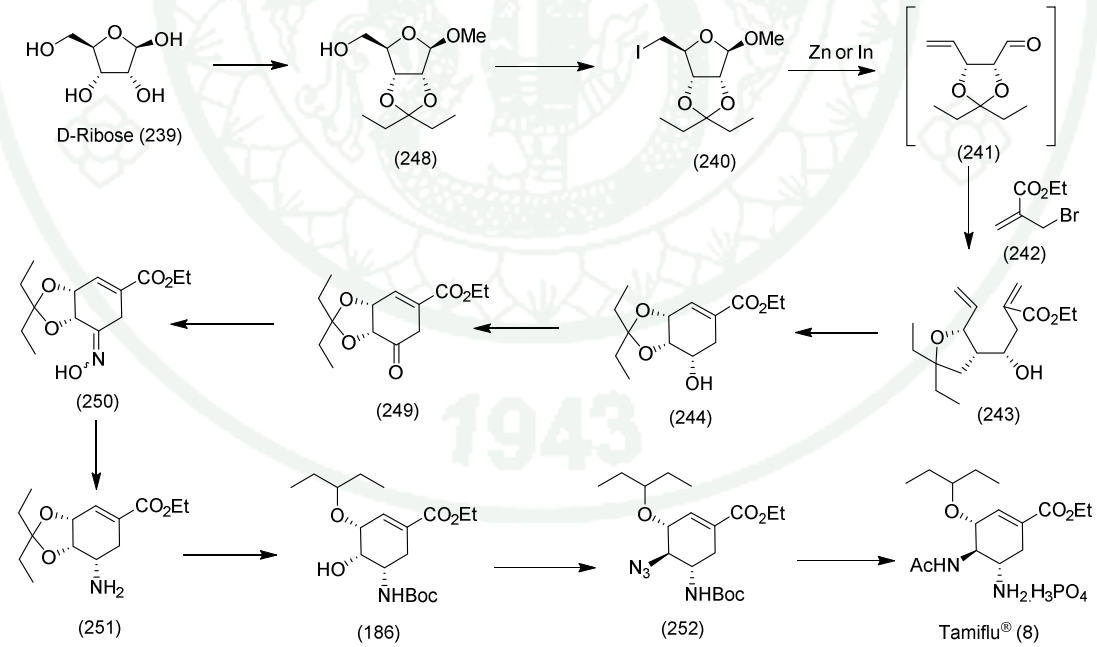
4. Synthesis of Tamiflu® from monosaccharides

4.1 Synthesis of Tamiflu® from D-ribose

The synthesis of Tamiflu® from D-ribose (239) was published by Chen's group and Kongkathip's group (our group) in 2010. The key features of the synthesis include the formation of *epi*-shikimate (244) from D-ribose by metal-mediated domino reaction and ring-closing olefin metathesis (RCM). The penthyl ether moiety was introduced through selective pentylidine ketal formation and then either regioselective reductive ring opening of pentylidine alcohol (244) (Scheme 27)(Chen *et al*. 2010) or pentylidine amino (251) which was obtained from oxime (250) formation and then reduction to give (251) (Scheme 28) (Kongkathip *et al.,* 2010).



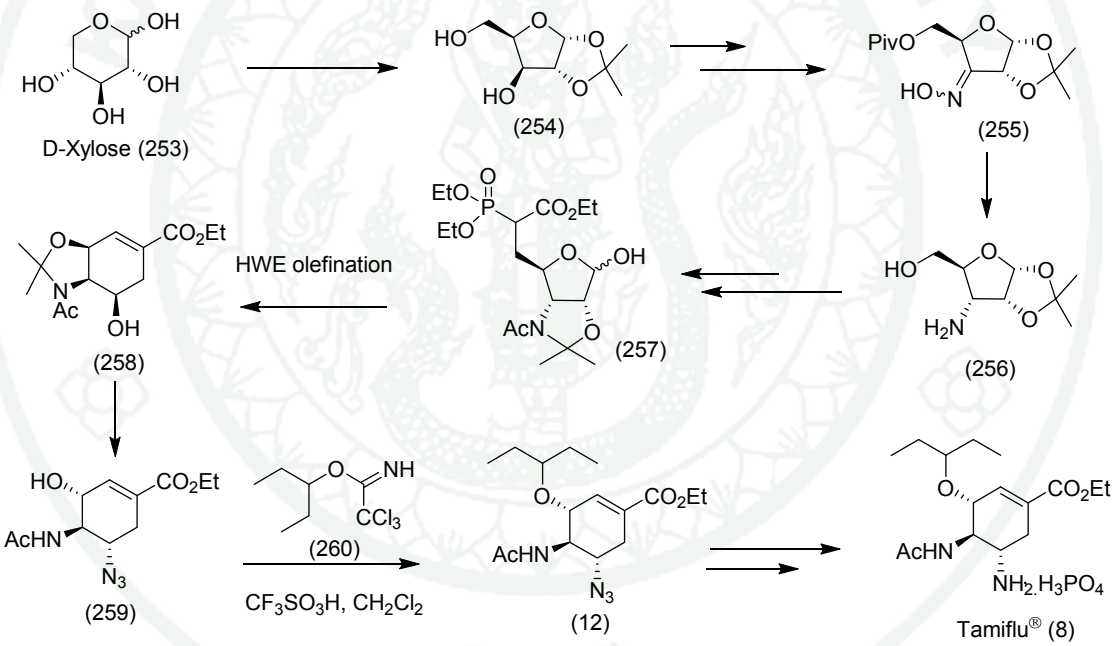
Scheme 27 Chen's formal synthesis of Tamiflu® from D-ribose.



Scheme 28 Kongkathip's synthesis of Tamiflu® from D-ribose.

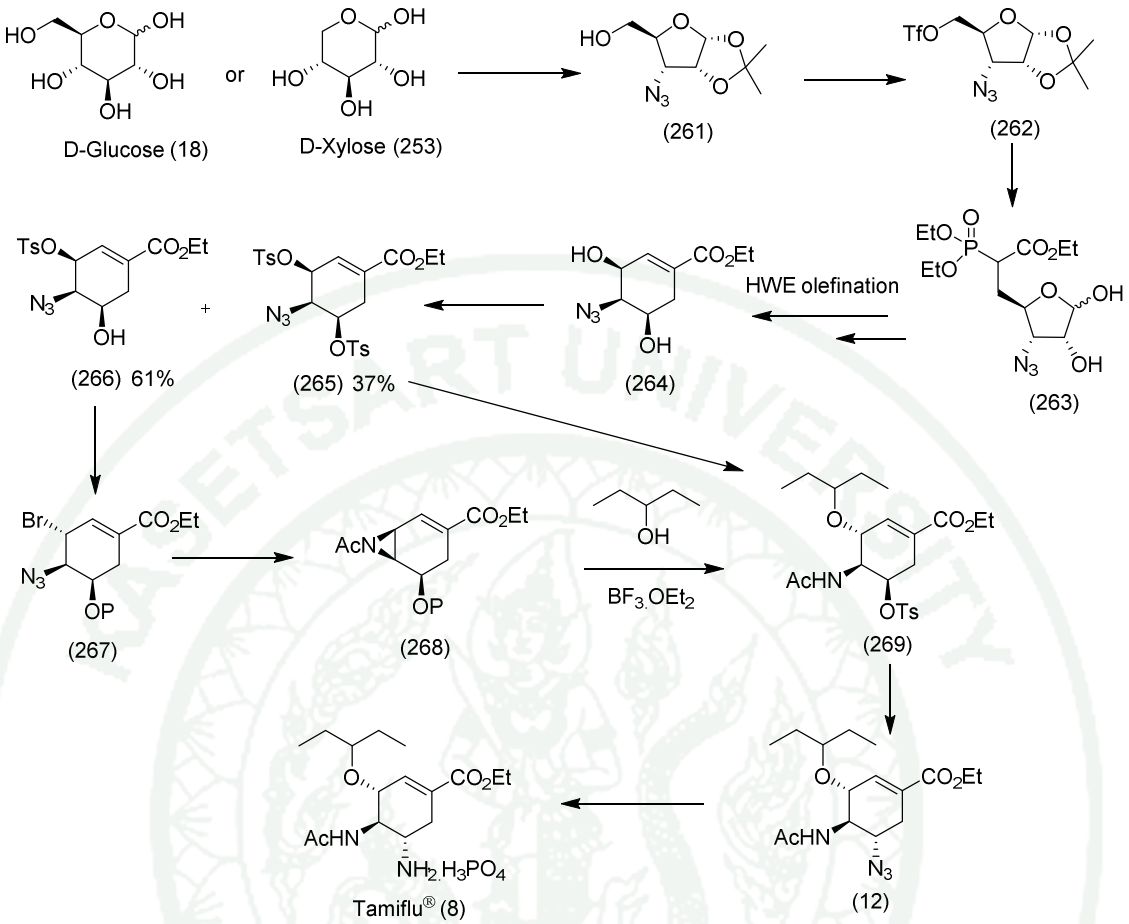
4.2 Synthesis of Tamiflu® from D-glucose and D-xylose

The synthesis of Tamiflu® from D-xylose (253) was published by Fang's group in 2007 by using the Horner–Wadsworth–Emmons reaction (HWE reaction) to construct cyclohexene carboxylate core. β-Acetamide functional group at C-4 position of Tamiflu® was installed *via* oxime (255) formation, reduction and then acetylation. The α-amino group was installed through azide substitution of alcohol (258) by using diphenylphosphoryl azide under Mitsunobu's condition. The pentyl ether moiety was introduced using trichloroazetimidate (260). Their Tamiflu® was obtained in 16 steps with 14% overall yield (Scheme 29) (Fang *et al.,* 2007).



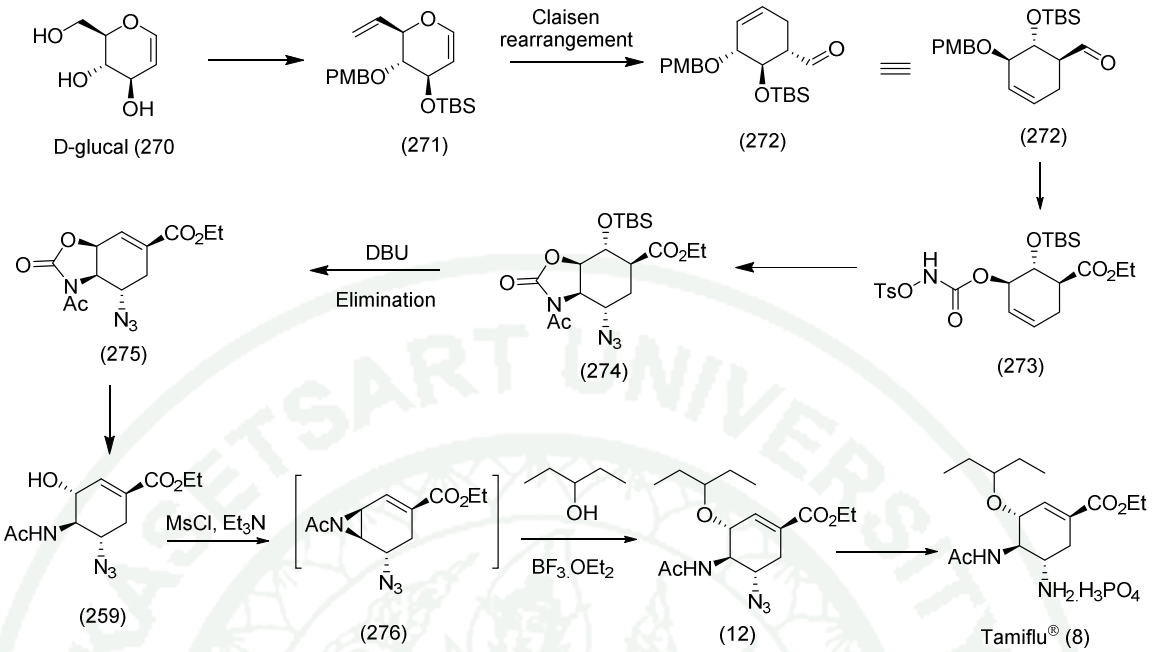
Scheme 29 Fang's synthesis of Tamiflu® from D-xylose.

The synthesis of Tamiflu® from D-xylose (253) and D-glucose (18) were patented by Radatus's group in 2007. The Horner–Wadsworth–Emmons reaction was employed to constructed cyclohexene carboxylate core structure. Amino functional group was introdeced *via* azide substitution reaction and the pentyl ether moiety was installed through aziridin ring opening with 3-pentanol in the presence of boron trifluoride etherate (Scheme 30) (Radatus *et al.,* 2007).



Scheme 30 Radatus's synthesis of Tamiflu® from D-xylose and D-glucose .

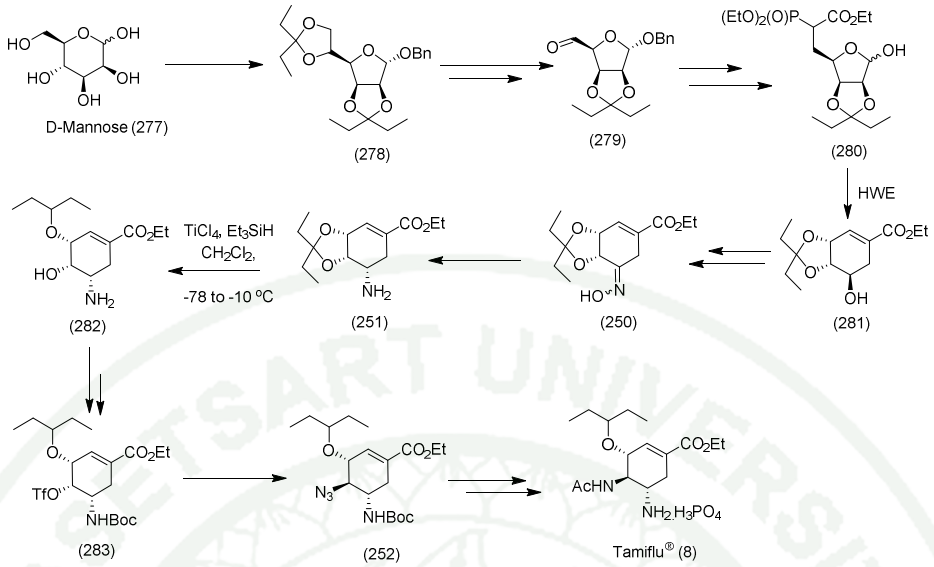
The synthesis of Tamiflu® from D-glucal (270) which can prepare from D-glucose (18) was published by Liu group in 2010. The key features of the synthesis include the formation of cyclohexene carboxylate by 3,3-sigmathopic rearrangement (Claisen rearrangement) of the functionalized glucal (271) and then elimination of silyl ether converted (274) to ethyl cyclohexene carboxylate (275), Tamiflu® core structure. The two amino groups were introduced to the ring via formation of *O*-tosyl carbamate (273) followed by intramolecular aziridine formation and then the second nitrogen functionality was successfully installed via aziridine opening with $TMSN_3$ to give intermediate (274). The pentyl ether was installed by opening of aziridine (276) with 3-pentanol. Their Tamiflu® was obtained in 22 steps with 26 % overall yield (Scheme 31) (Liu *et al.,* 2010).



Scheme 31 Liu's synthesis of Tamiflu® from D-glucal.

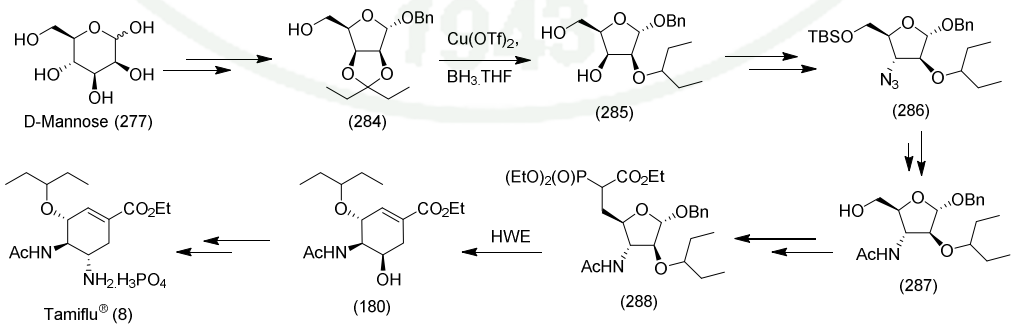
4.3 Synthesis of Tamiflu® from D-mannose

The synthesis of Tamiflu® from D-mannose (277) was published by Kongkathip's group in 2012 in two approaches using the Horner–Wadsworth–Emmons reaction (HWE reaction) to construct the cyclohexene core structure. In the first approach, D-mannose (277) was transformed to ethyl shikimate (281) and the functionalization via installation of 5α-amino functional group through oxime (250) formation and reduction. Reductive ring opening of amino pentylidine ketal (251) was employed to introduce 3-pentyl ether. The 4β-acetamide was installed *via* azide substitution of triflate (283) and then reduction of the corresponding azide with thioacetic acid. Tamiflu® was obtained in 11 steps with 29 % overall yield (Scheme 32) (Kongkathip *et al.,* 2012).



Scheme 32 Kongkathip's synthesis of Tamiflu® from D-mannose.

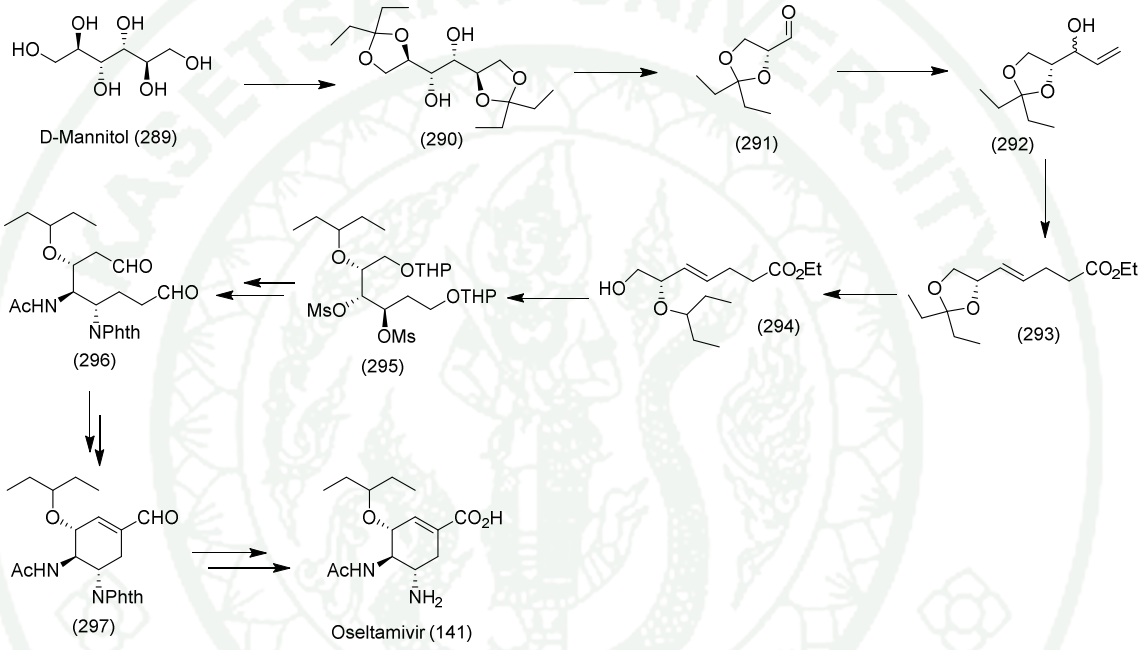
In the second approach, D-mannose (277) was functionalize via introduction of penthyl ether moiety through formation of pentylidine furanoside (284), regioselective reductive ring opening of pentylidine ketal (284) using combination of $Cu(OTf)_2$ and BH_3.THF to give (285). Amino functional groups were introduced *via* azide substitution and reduction. Horner–Wadsworth–Emmons cyclization of phosphonate ester (288) gave intermediate (180) which was converted to Tamiflu® by azide substitution, reduction and phosphate salts formation. Tamiflu® from this approach was obtained in 13 steps with 5 % overall yield (Scheme 33) (Kongkathip *et al.,* 2012).



Scheme 33 Kongkathip's second generation synthesis of Tamiflu® from D-mannose.

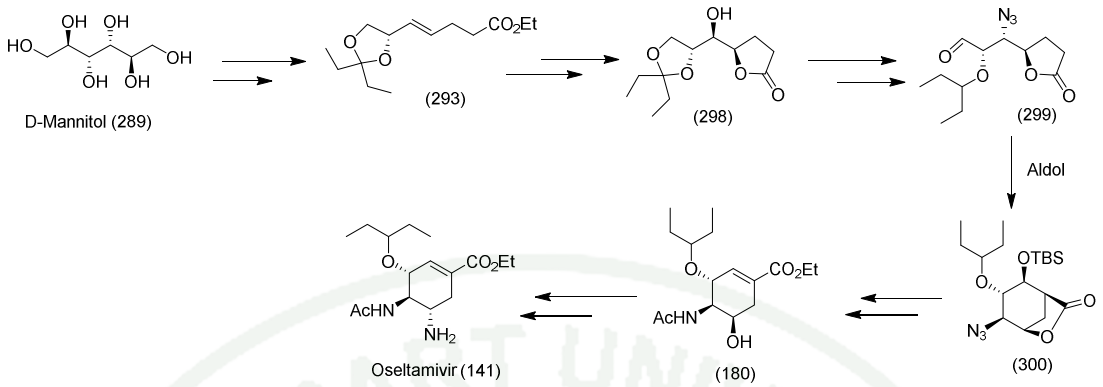
4.4 Synthesis of Tamiflu® from D-mannitol (289)

In 2009, Mandai's and co-workers reported synthesis of oseltamivir free base (141) from D-mannitol (289) using intramolecular aldol condensation of dialdehyde with 3-pentyl ether (296) in construction of cyclohexene (297) (Scheme 34) (Mandai *et al.,* 2009).



Scheme 34

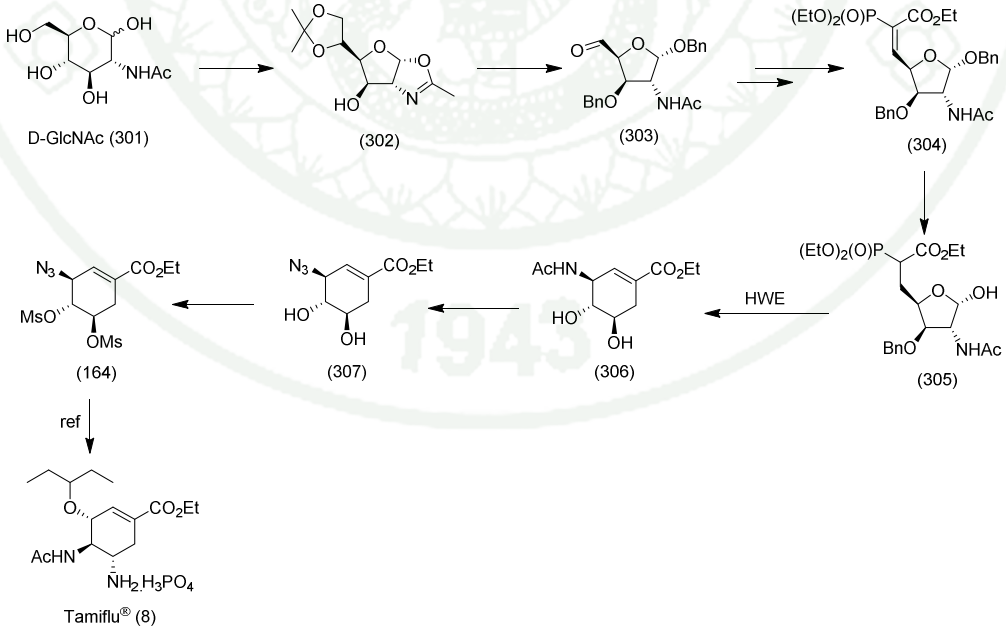
In 2010, synthesis of oseltamivir free base (141) from D-mannitol (289) was published by Ko's group. The key features of the synthesis include the formation of cyclohexene carboxylate (180), Tamiflu ® core structure by cyclization of (299) under Mukaiyama aldol reaction and then elimination of silyl ether. The pentyl ether was first installed via regioselective reductive ring opening of (298). Stereoselective asymmetric dihydroxylation was used to introduce stereochemistry at C4 and C5. The two amino groups were introduced via azide substitution. Their Tamiflu® was obtained in 16 steps with 7 % overall yield (Scheme 35) (Ko *et al.,* 2010).



Scheme 35

4.5 Synthesis of Tamiflu® from D-glucosamine

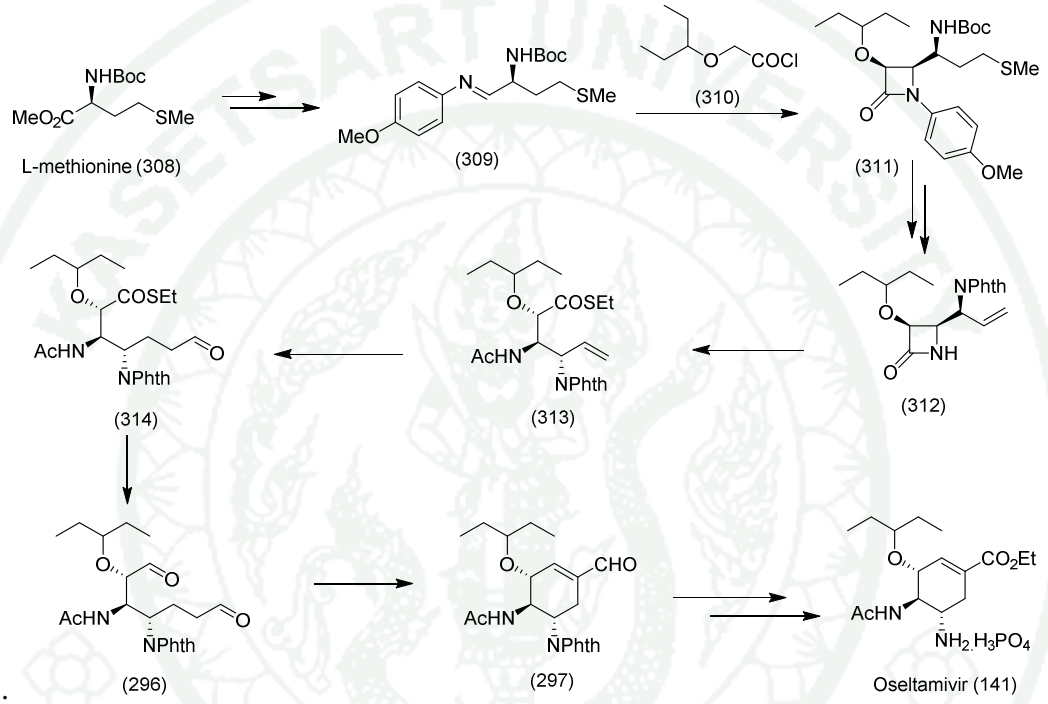
The formal synthesis of Tamiflu® from *N*-acetyl-D-glucosamine (301) was published by Fang and co-workers in 2013. The 3-azido-4,5-di-mesylate intermediate (164) was synthesized in 11 steps from D-glucosimine (301) (Scheme 36) (Fang *et al.*, 2013).



Scheme 36 Fang's formal synthesis of Tamiflu® from *N*-acethyl- D-glucosamine.

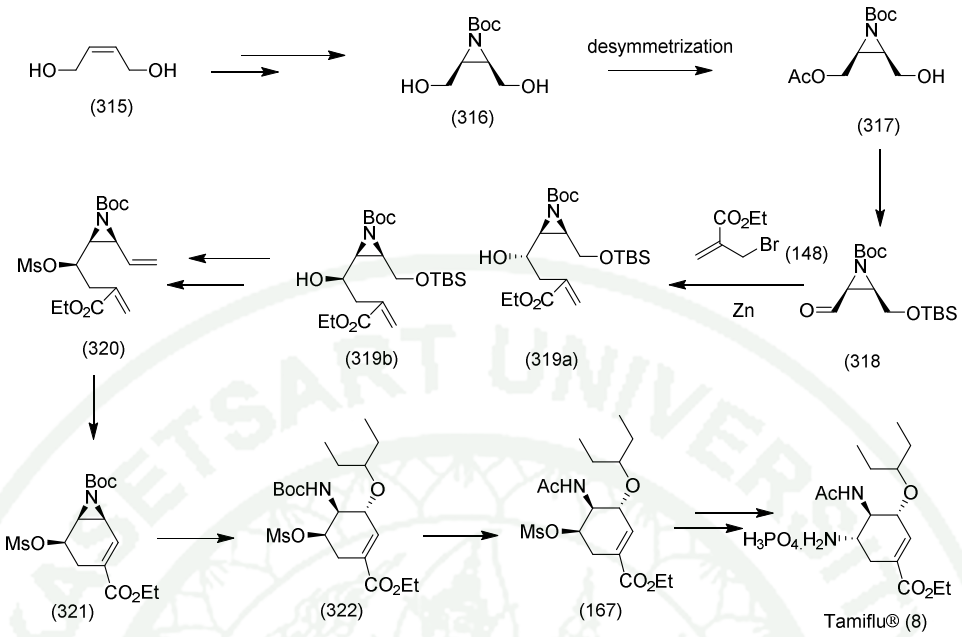
5. Synthesis of Tamiflu® from other starting material

Mandai and co-workers reported enantioselective synthesis of Tamiflu® from L-methionine (308), in which Staudinger reaction was utilized for the alignment of three contiguous stereogenic centers of Tamiflu® (Scheme 37) (Mandai *et al.,* 2007).



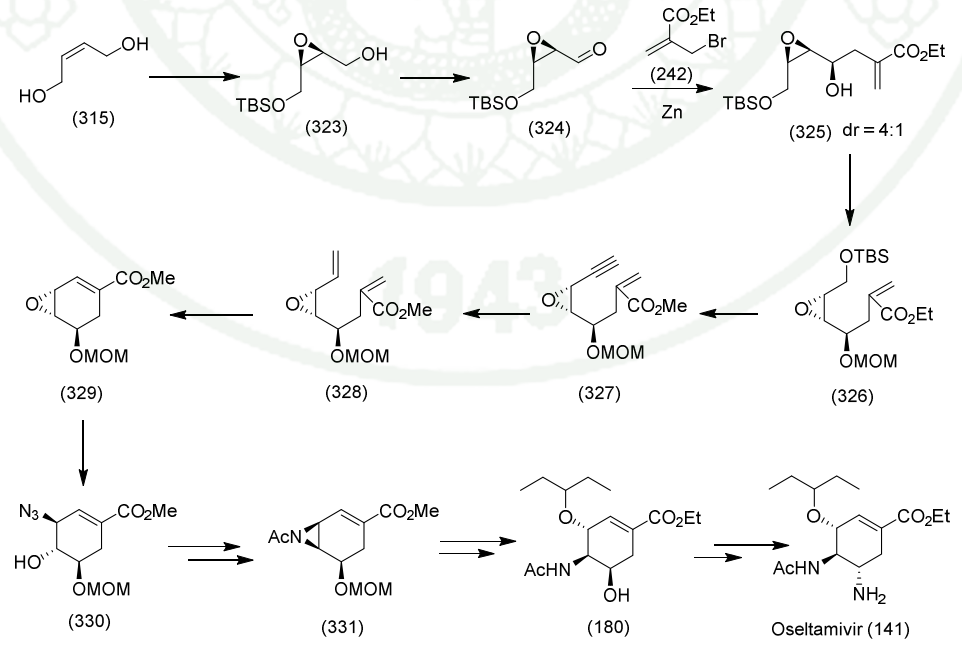
Scheme 37

Kang and co-workers reported synthesis of Tamiflu® using enzymatic desymmetrization of aziridine (316), alkylation of aziridine aldehyde (318) and ring closing metathesis as a key steps (Scheme 38) (Kang *et al.,* 2012).



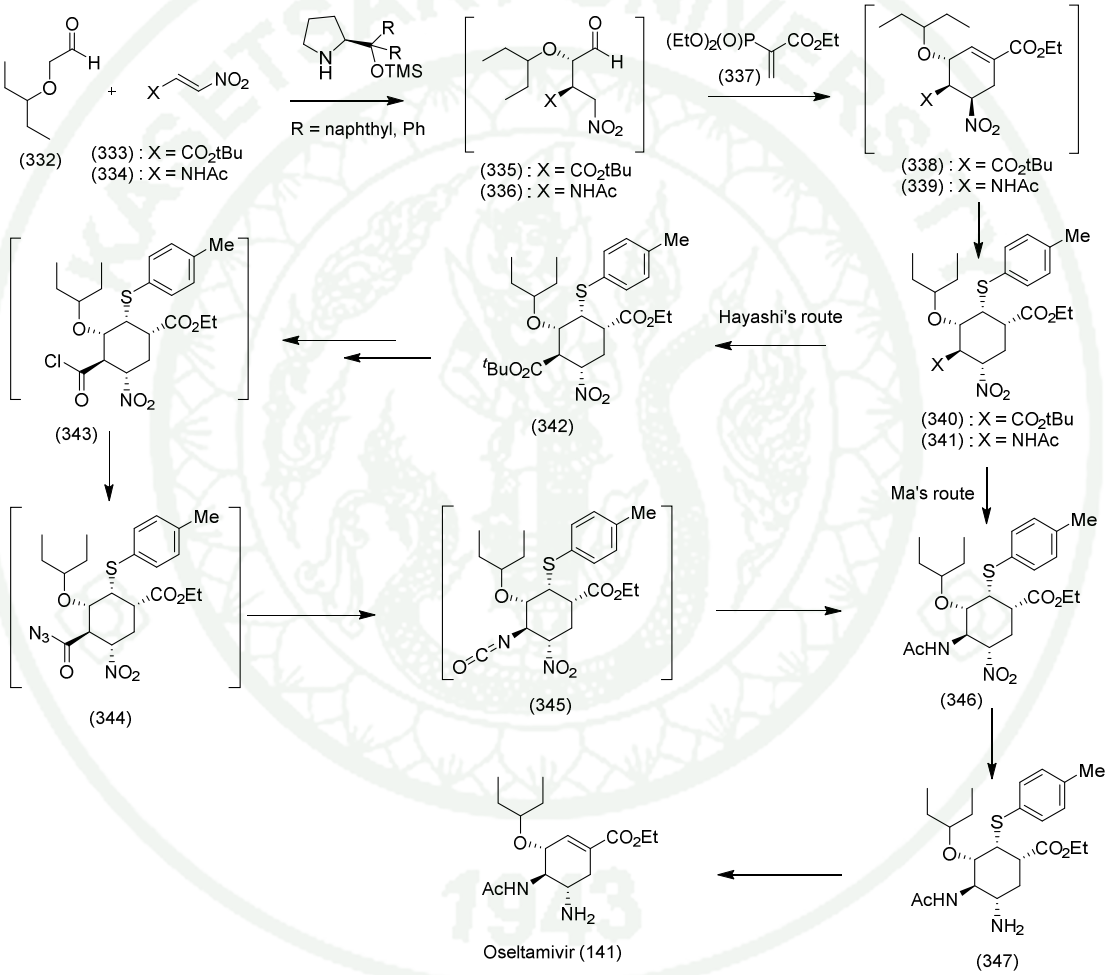
Scheme 38

Sudalai and co-workers reported synthesis of Tamiflu® through alkylation of epoxy aldehyde (324) with acrylate (242) and ring closing metathesis of epoxy diene (328) (Scheme 39) (Sudalai *et al.,* 2012).



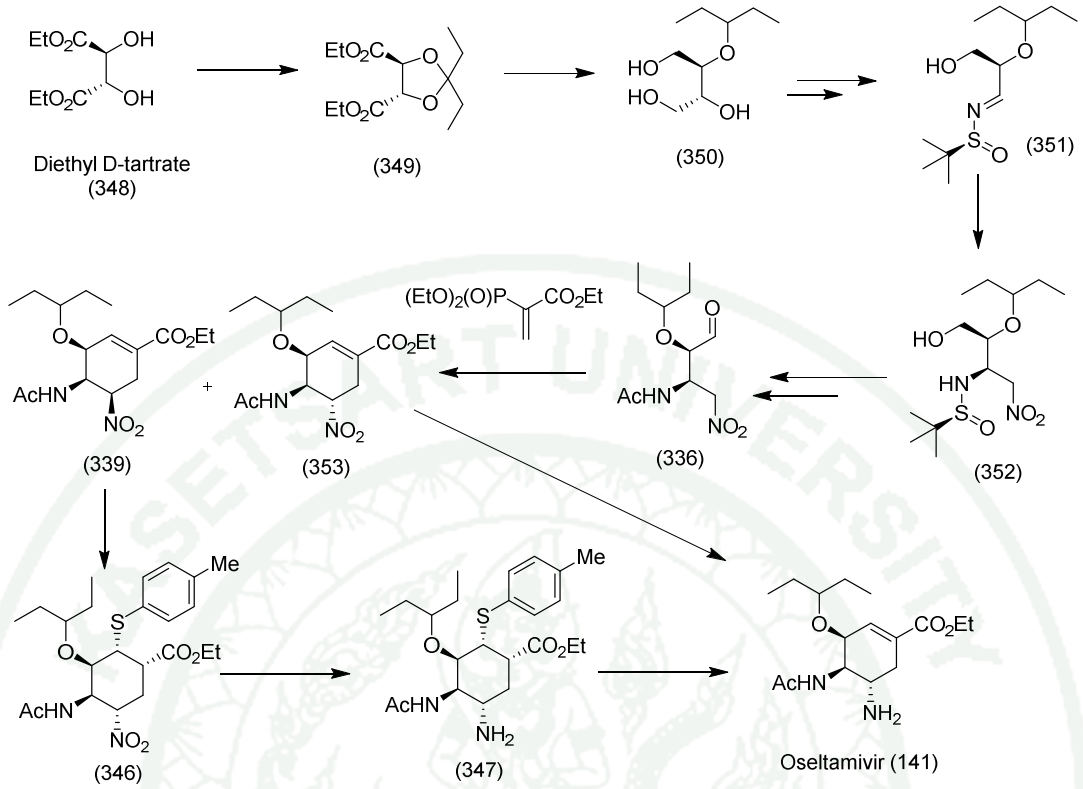
Scheme 39

Hayashi and Ma employed one-pot sequences synthesis of Tamiflu®. Michael reaction of pentan-3-yloxyacetaldehyde (332) and *trans*-nitroalkene (333) and (334), catalyzed by organocatalyst to give (335) and (336) without purification and Michael-HWE of (335) and (336) afforded cyclohexene (338) and (339) with control of five consecutive stereogenic centers (Scheme 40) (Hayashi *et al*., 2009; Hayashi *et al*., 2010; Hayashi *et al*.,2013; Ma *et al*., 2010).



Scheme 40

Lu and co-workers reported synthesis of Tamiflu® from diethyl D-tartrate (348) employing domino nitro-Michel/ Horner–Wadsworth–Emmons reaction (HWE) as a key step (Scheme 41) (Lu *et al.,* 2010).

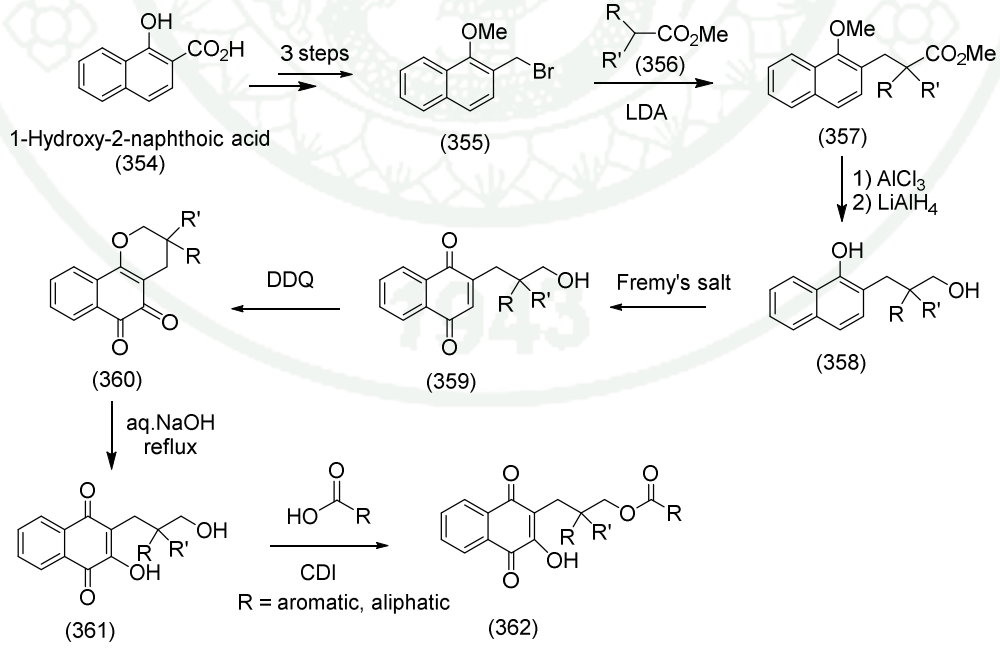


Scheme 41

Synthesis of 2-hydroxy-3-substituted 1,4-naphthoquinones

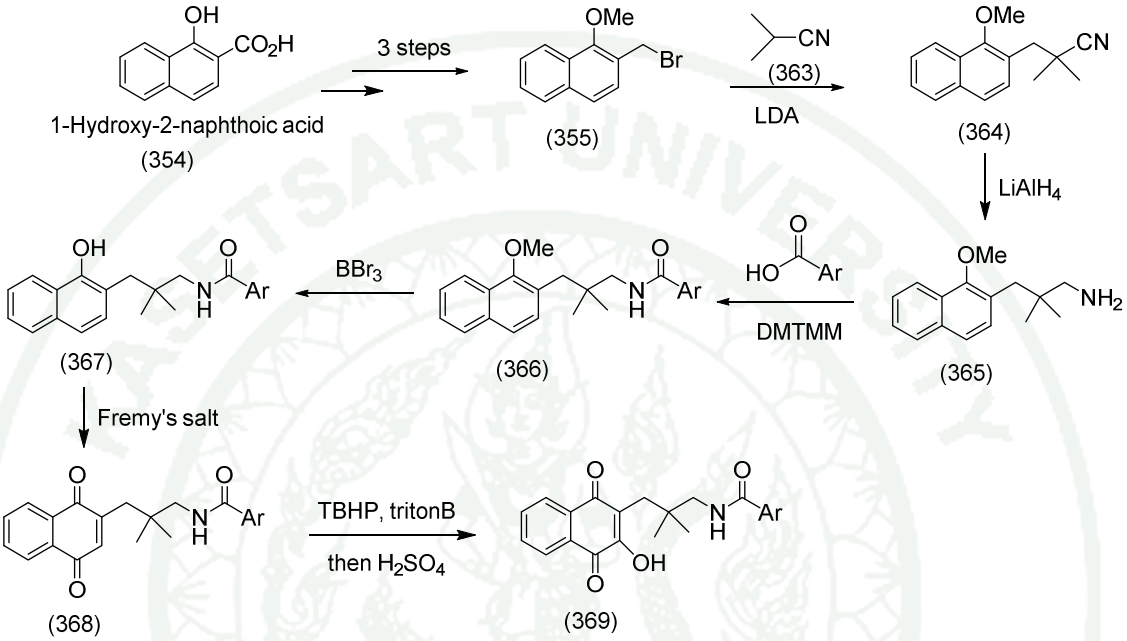
1. Synthesis of 2-hydroxy-3-substituted-1,4-naphthoquinone from benzene/ naphthalene

Kongkathip and co-workers (our group) have extensive studied on naphthoquinone compounds, 2-hydroxy-1,4-naphthoquinone esters (362) were synthesized from 1-hydroxy-2-naphthoic acid (354). The alkyl substitutent was introduced by alkylation of naphthyl bromide with (356) in the presence of lithium diisopropylamide. The quinone ring was constructed via oxidation of naphthol (358) by fremy's salts then the 2-hydroxy functional group was installed via oxidation of 1,4-naphthoquinone (359) with DDQ to generate pyrano-1,2-naphthoquinone (360) which was hydrolyzed with aq.NaOH to give 2-hydroxy-3-substituted-1,4-naphthoquinones (361). Coupling of 2-hydroxy-1,4-naphthoquinone alcohol (361) with various carboxylic acids (aromatic and aliphatic) using carbonyldiimidazole (CDI) gave the naphthoquinone ester (362) in excellent yield (Scheme 42) (Kongkathip *et al.,* 2004; Kongkathip *et al.,* 2010).



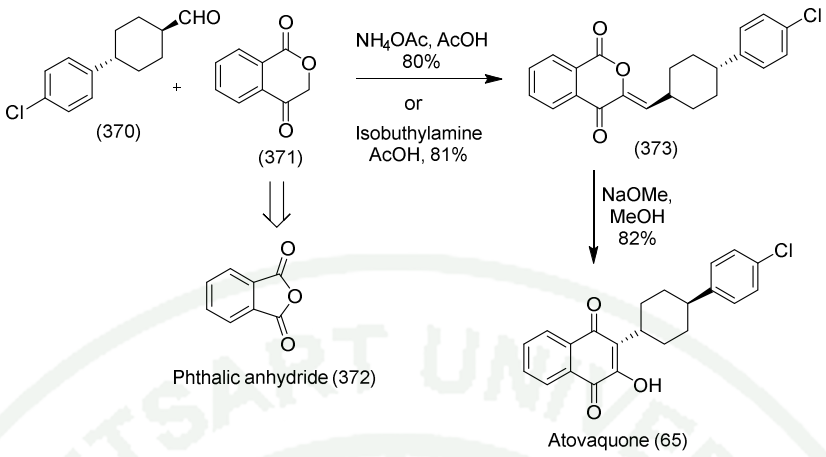
Scheme 42 Synthesis of 2-hydroxy-1,4-naphthoquinone esters.

We also synthesized 2-hydroxy-1,4-naphthoquinone aromatic amides (369) from 1-hydroxy-2-naphthoic acid (354) using key steps as shown in Scheme 43 (Kongkathip *et al.,* 2012).



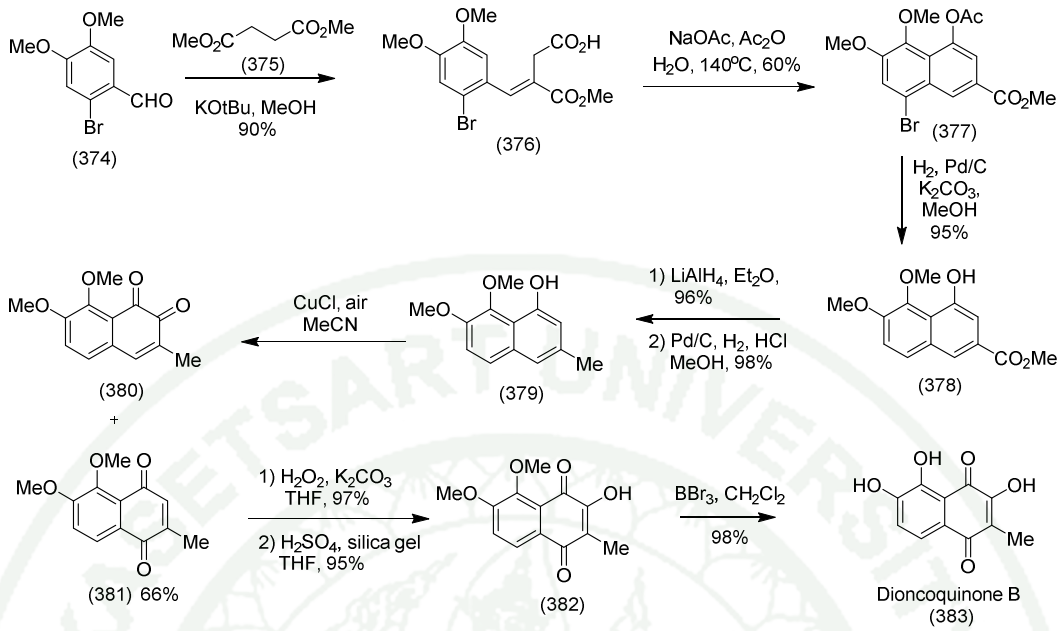
Scheme 43 Synthesis of 2-hydroxy-1,4-naphthoquinone aromatic amides.

Leach and co-workers reported a more sustainable manufacturing route to atovaquone (65) which is a simple method, use of cheap raw materials and gave a high yield product. The synthesis commences with condensation of 1,4-isochromandione (371) obtained from phthalic anhydride (372) with 4-(4-chlorophenyl)cyclohexane-carboxaldehyde (370) gave conjugated ketone (373) which was rearranged to atovaquone (65) by treatment with sodium methoxide (Scheme 44) (Leach *et al*., 2012).



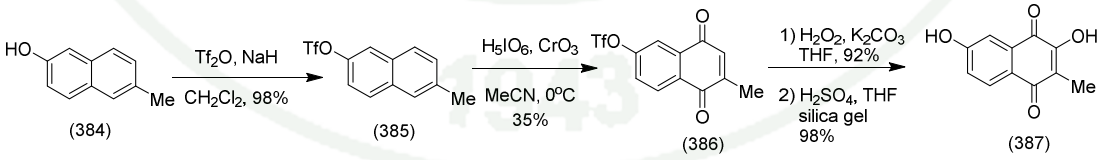
Scheme 44 Synthesis of Atovaquone.

In 2011, Bringmanna and co-workers reported synthesis and anticancer evaluation of dioncoquinones B-C and related naphthoquinones. The highly substituted naphthoquinone compounds were synthesized employing Stobbe condensation of bromo veratrum aldehyde (374) with dimethyl succinate (375) resulted acid ester (376) which was cyclized in acetic anhydride in the presence of sodium acetate to produce naphthalene (377). Air oxidation of naphthol (379) in the presence of CuCl afforded 1,4-naphthoquinone (381) in a 66% yield, accompanied by the respective 1,2-naphthoquinone (380) (ratio 6.5:1). The required 2-hydroxy functionality of the target molecule was introduced by epoxidation of the 2,3-double bond followed by ring opening of the resulting epoxy/diketone to give 2-hydroxy-1,4-naphthoquinone (382) (Scheme 45) (Bringmanna *et al.,* 2011).



Scheme 45 Total synthesis of dioncoquinone B.

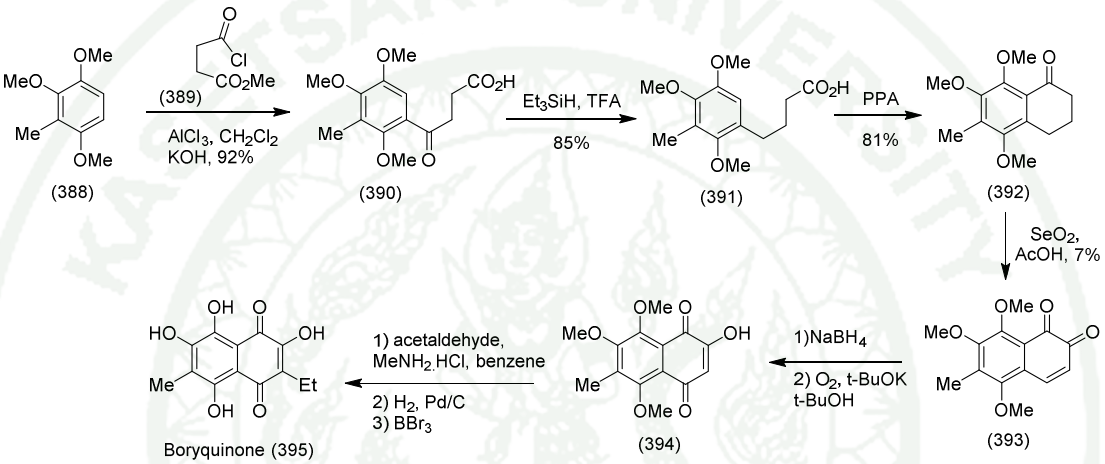
Dioncoquinone B derivative (387) can be synthesized from naphthol (384) through triflate formation followed by selective oxidation of (385) using periodic acid and chromium trioxide to give 1,4-naphthoquinone (386). Epoxidation of the 1,4-naphthoquinone by H_2O_2 with concomitant cleavage of the triflate ester, followed by epoxide ring opening, produced dihydroxynaphthoquinone (387) in excellent yield (Scheme 46) (Bringmanna *et al.,* 2011).



Scheme 46 Synthesis of dioncoquinone B derivatives.

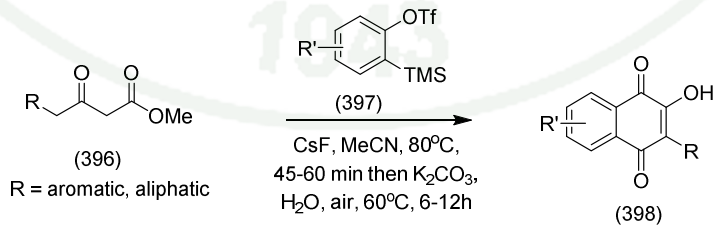
Pettus and co-workers reported syntheses of boryquinone from 3-methyl-1,2,4-trimethoxybenzene (388) through Friedel–Crafts acylation with succinic acid chloride (389) and intramolecular cyclization to generate α-tetralone (392). Oxidation of the α-tetralone (392) with selenium dioxide gave 1,2-naphthoquinone (393) which

was reduced with sodium borohydride and subsequent oxidation in the presence of potassium *tert*-butoxide and oxygen resulted in 2-hydroxy-1,4-naphthoquinone (394). The naphthoquinone compound (394) underwent Mannich reaction with acetaldehyde and methylamine hydrochloride and subsequent hydrogenation of the resulting vinyl residue to afford the corresponding naphthoquinone, Boryquinone (395) (Scheme 47) (Pettus *et al.,* 2009).



Scheme 47 Synthesis of Boryquinone.

In 2009, Stoltz and co-workers reported synthesis of 2-hydroxy-1,4-naphthoquinones via one-pot aryne acyl-alkylation/condensation of β-ketoesters (Scheme 48) (Stoltz *et al.,* 2009).

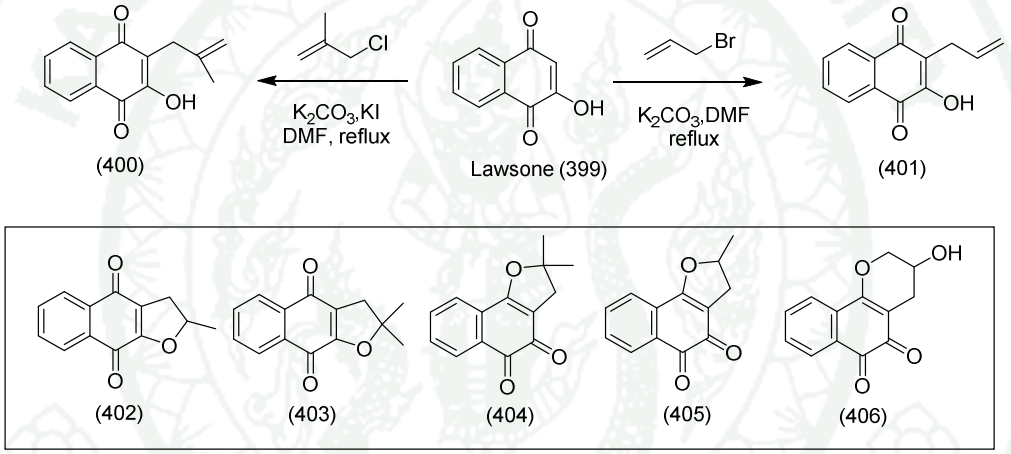


Scheme 48 One-pot synthesis of 2-hydroxy-1,4-naphthoquinones.

2. Synthesis of 2-hydroxy-3-substituted 1, 4-naphthoquinones from lawsone

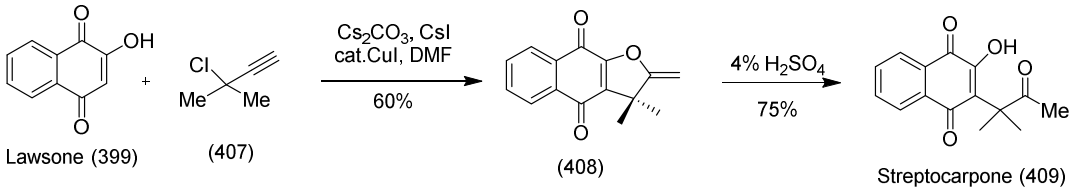
2.1 *via* Alkylation reaction

Our group, Kongkasthip's group reported synthesis of rhinacanthone derivatives with antitumor activity by empolying alkylation of lawsone (399) with allyl halide to give 2-hydroxy-3-substituted-1,4-naphthoquinones (400) and (401) (Scheme 49) (Kongkathip *et al.,* 2003). Compound (400) and (401) was the intermediate for synthesis of (402-406) which showed very strong anticancer activity.



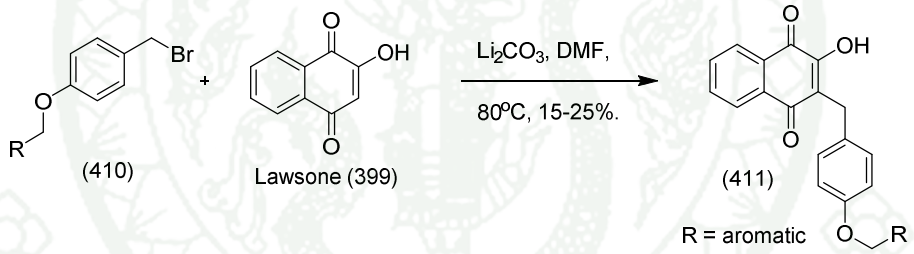
Scheme 49 Synthesis of 2-hydroxy-3-substituted-1,4-naphthoquinones.

Perez and co-workers reported synthesis of streptocarpone (409) from lawsone (399). Their reaction proceed *via* a one-pot, copper catalyzed regioselective propargylation of lawsone (399) with tertiary propargylic halides (407) followed by cyclization by the nucleophilic oxygen at C-2 on the activated alkyne to form the exocyclic enol furanonaphthoquinone (408). The intermediate (408) was transformed to streptocarpone (409) by treated with hot aqueous sulfuric acid (Scheme 50) (Perez *et al.,* 2007).



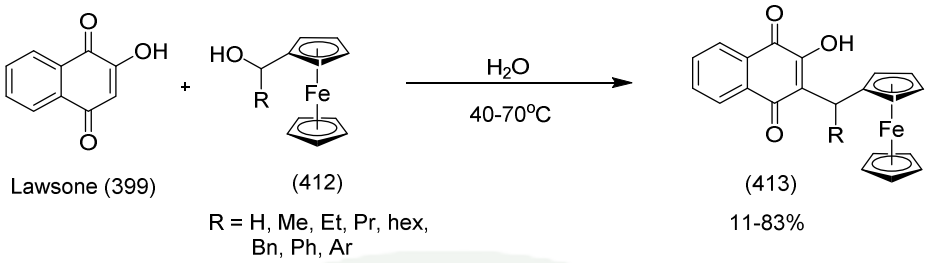
Scheme 50 Synthesis of streptocarpone.

Sundriyal and co-workers reported computer-aided design and synthesis of 2-hyroxy-1,4-naphthoquinone as PPARγ agonists. Eight compounds were synthesized via alkylation of benzyl bromide derivatives (410) with lawsone (399) in 15-25% yield. The isomeric *O*-alkylated product was also formed. Four synthesized compounds were found to bind to the murine PPARγ with IC_{50} ranging from 0.2 to 56.2 μM (Scheme 51) (Sundriyal *et al.,* 2008).



Scheme 51 Synthesis of 2-hydroxy-1,4-naphthoquinone.

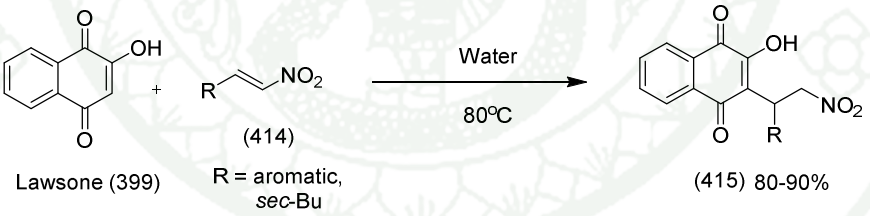
Lamoureux and co-workers reported synthesis of ferrocene-naphthoquinones as antiplasmodial agents. 3-Ferrocenylmethyl-2-hydroxy-1,4-naphthoquinones (413) were synthesized via coupling between lawsone (399) and ferrocenemethanol derivatives (412). This procedure can be carried out "on-water" at moderate temperatures without auxiliaries or catalysts to give the product in moderate to high yields (Scheme 52) (Lamoureux *et al.,* 2013).



Scheme 52 Synthesis of ferrocene-naphthoquinones.

2.2 *via* Michael addition

Yao and co-workers reported Michael addition of lawsone (399) and various nitroolefins (414) under catalyst-free employing 'on water' condition, 2-hydroxy-3-nitroalkenyl naphthoquinones (415) were obtained in excellent yield. The mechanism for the formation of the desired product can be explained on the basis of dual activation of nitroalkene and 2-hydroxy-1,4-naphthoquinones via hydrogen bonding (Scheme 53) (Yao *et al.,* 2009).



Scheme 53

Organocatalytic Michael addition of lawsone (399) and various *di*- and *tri*-substituted nitroolefins (416) has also been reported by several groups. Various organocatalysts (Figure 21) were employed such as sugar thiourea (418) (Reddy *et al.,* 2013), rosin-derived indane amine thiourea (419) (Reddy and Swain *et al.,* 2013), thiophosphorodiamides (420) (Wang *et al.,* 2011), BINOL–quinine–squaramides (421) (Zhou *et al.,* 2014), binaphthyl-derived (422) (Kim *et al.,* 2012), thiourea (423) (Du *et al.,* 2008) and PS-supported squaramide (424) (Peric *et al.,* 2013).

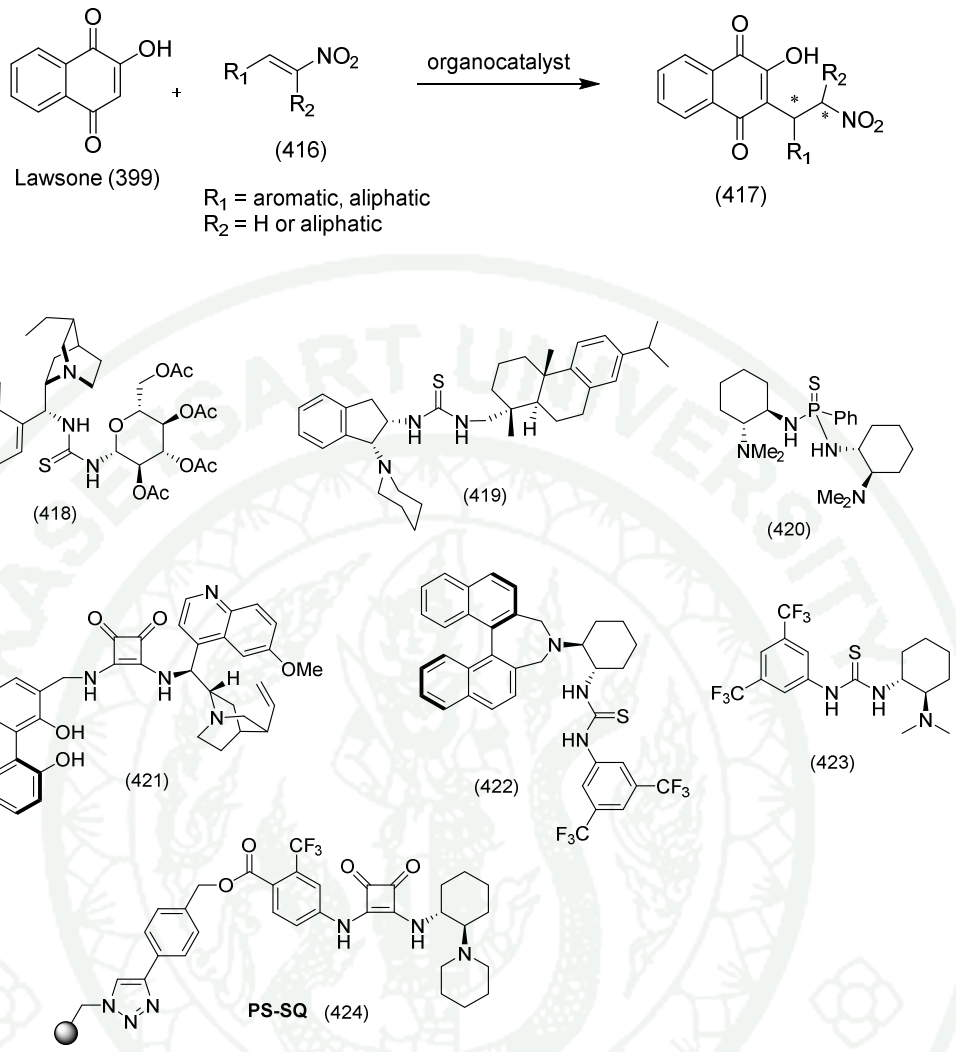
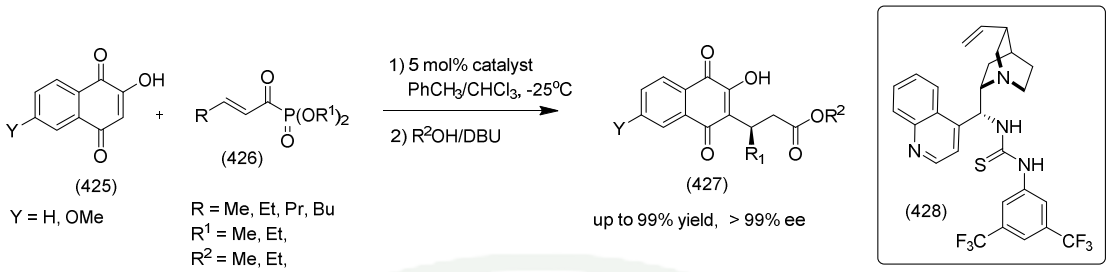


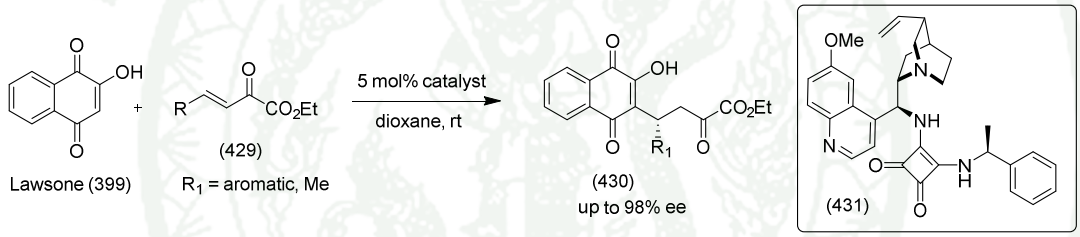
Figure 21 Examples of organocalysts for asymmetric Michael addition of lawsone to nitroolefins.

Wang and co-workers reported using cinchonine-based thiourea (428) as catalyst in enantioselective Michael addition reactions of lawsone (399) and its derivatives (425) with β,γ-unsaturated α-keto-phosphonates (426) (Scheme 54) (Wang *et al.,* 2011).



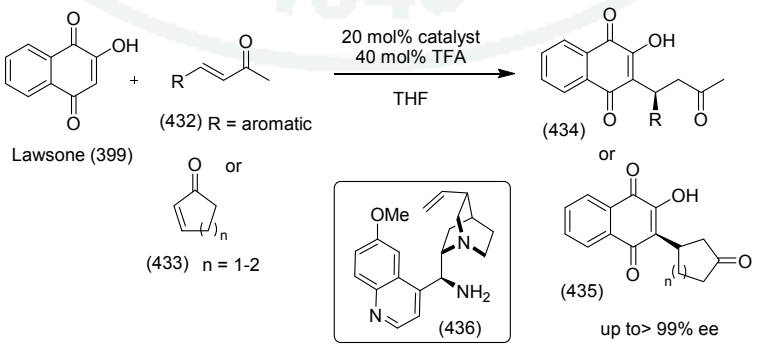
Scheme 54

Xu and co-workers reported highly enantioselective organocatalytic Michael addition of lawsone (399) and β,γ-unsaturated α-oxo esters (429) catalyzed by cinchona-derived squaramide (431) (Scheme 55) (Xu *et al.,* 2010).



Scheme 55

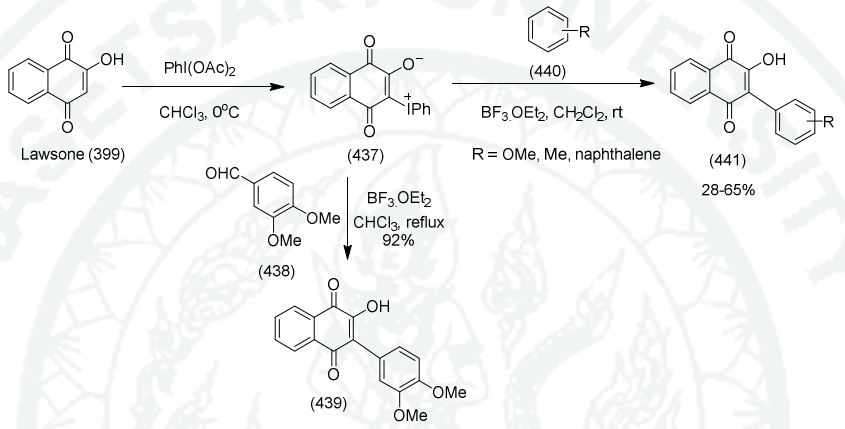
They also reported primary amine presented organocatalyzed Michael addition of naphthoquinone with various α,β-unsaturated ketones (Scheme 56) (Xu *et al.,* 2011).



Scheme 56

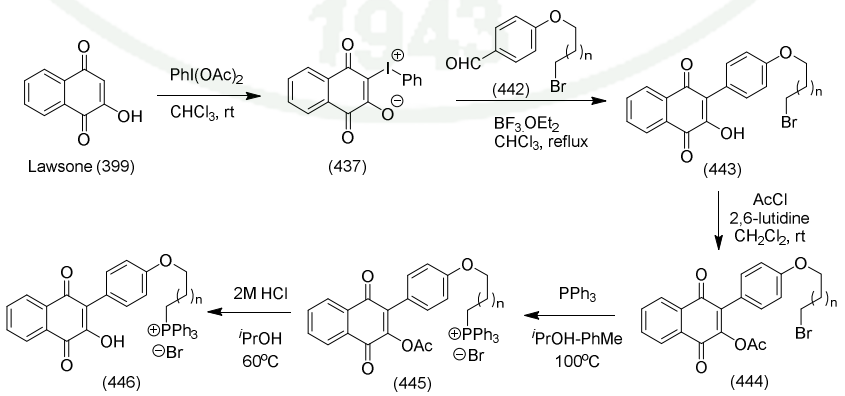
2.3 *via* Iodonium ylide route

Spyroudis and co-workers reported development of arylation reaction of lawsone (399) using BF_3-mediated coupling of phenyliodonium ylide (437) with activated electron rich arenes (440) and aromatic aldehydes (438) (Scheme 57) (Spyroudis *et al.,* 2010).



Scheme 57

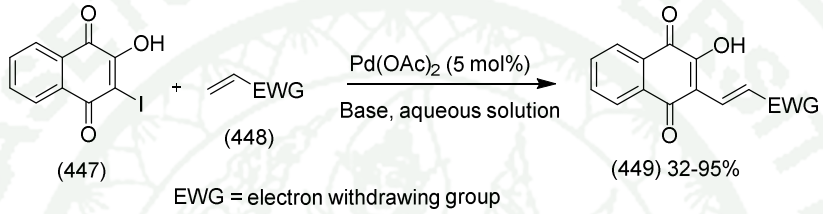
Long and co-workers used Spyroudis's methodology to synthesize 1,4-naphthoquinone cations (446) as antiplasmodial agents. These compounds showed antimalarial activity against *P. falciparum* W2 with IC_{50} values in the range of 17.4–49.5 nM (Scheme 58) (Lo ng *et al*., 2012).



Scheme 58 Synthesis of antiplasmodial agents 1,4-naphthoquinone cations.

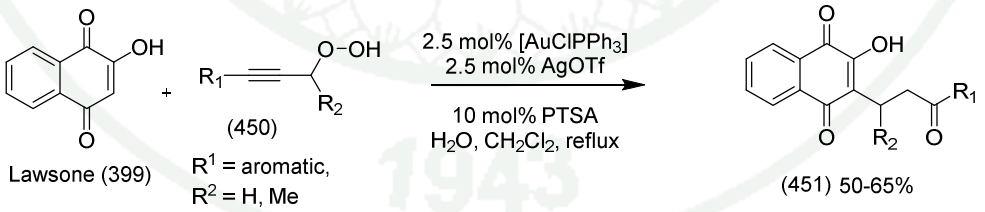
2.4 *via* Metal catalyzed coupling reaction

Perez and co-workers reported an efficient Heck coupling of 2-hydroxy-3-iodo-1,4-naphthoquinone (447) with a series of electron-deficient alkenes (448) in aqueous solution. The method is characterized by simple conditions and facile work-up to isolate the products (449) in good to excellent yields (Scheme 59) (Perez *et al*., 2007).



Scheme 59 Heck coupling of iodolawsone.

Alcaide and co-workers reported gold-catalyzed reactions of primary and secondary propargylic hydroperoxides (450) with a variety of nucleophiles including alcohols, phenols, lawsone and indoles allow the direct and efficient synthesis of β-functionalized ketones (Scheme 60) (Alcaide *et al.,* 2013).

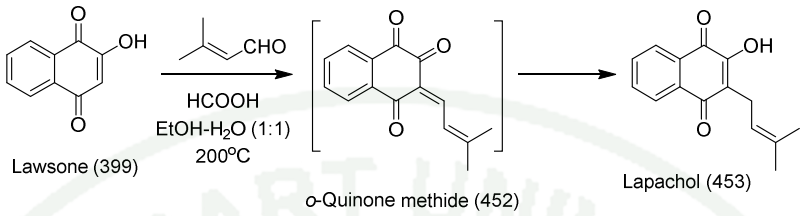


Scheme 60 Gold-catalyzed reaction of propargylic hydroperoxides with lawsone.

2.5 via Nucleophilic addition of *o*-quinone methide

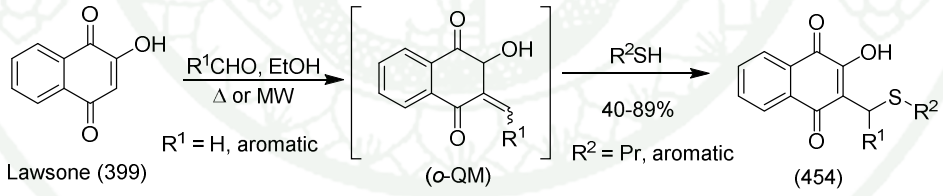
Ferreira and co-workers have reported a new method to prepare lapachol (453) by employing one-pot methodology *C*-alkylation of lawsone (399) to generate

o-quinone methide (452) followed by reduction with formic acid in water (Scheme 61) (Ferreira *et al.,* 2011).



Scheme 61 One-pot synthesis of lapachol.

Garcia and co-workers reported synthesis of 36 antimalarial 2-hydroxy-3-phenylsulfanylmethyl-1,4-naphthoquinones (454) (Scheme 62) via three-component reaction explored the *in situ* the generation of *o*-quinone methides (*o*-QM) via the Knoevenagel condensation between lawsone (399) and the appropriate aldehyde followed by nucleophilic addition of a thiol. The reactions were evaluated under both conventional heating and microwave irradiation to give the products in moderate to high yields (Garcia *et al.,* 2013).

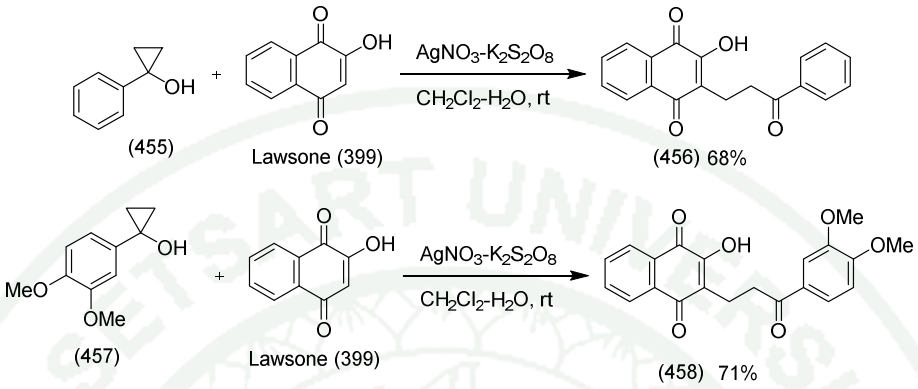


Scheme 62 Preparation of 3-sulfanylmethyl-1,4-naphthoquinones.

2.6 *via* Radical strategy

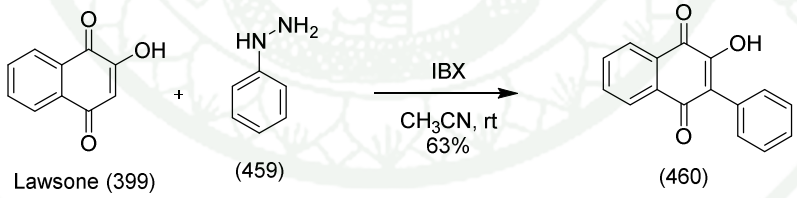
Ilangovan and co-workers reported a convenient method for the preparation of diverse γ-carbonyl quinones by C-H activation of quinone using cyclopropanols derivative (455) and (457) under oxidant system of $AgNO_3/K_2S_2O_8$ to generate β-keto radicals which were successfully added to quinone. Examples of reactions with hydroxynaphthoquinone are shown in Scheme 63. The reactivity of β-

keto radicals is rapid, and hence a protection and deprotection strategy is not generally required (Ilangovan *et al.,* 2013).



Scheme 63 Synthesis of substituted 2-hydroxy-1,4-naphthoquinone.

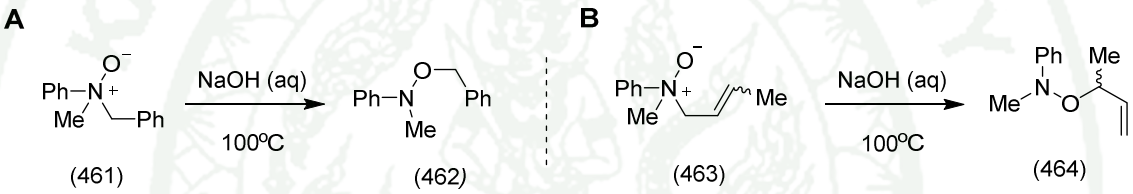
Akamanchi and co-workers reported oxidative arylation of naphthoquinones through aryl radical generated by oxidation of phenylhydraine (459) via *o*-iodobenzoic acid (IBX). The 2-hydroxy-3-substituted-1,4-naphthoquinone (460) was obtained in 63% yield (Scheme 64) (Akamanchi *et al.,* 2014).



Scheme 64 Oxidative arylation of 1,4-naphthoquinones.

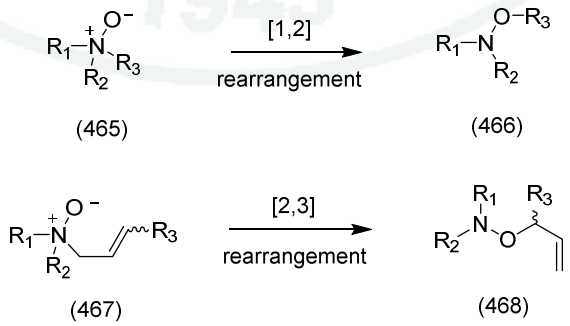
[1,2]-Meisenheimer rearrangement

In 1919, Jakob Meisenheimer reported the rearrangement of *N*-benzyl-*N*-methyl aniline-*N*-oxide (461) in an aqueous sodium hydroxide solution to afford *O*-benzyl-*N*-methyl-*N*-phenyl hydroxylamine (462) (Scheme 65a). Later, Cope and co-workers found that isomerization of *N*-crotyl-*N*-methyl aniline *N*-oxide (463) occurred with the inversion of the allylic system to give *N*-methyl-*O*-(1-methyl-allyl)-*N*-phenylhydroxylamine (464) (Scheme 65b). Therefore rearrangement of tertiary amine *N*-oxide to the hydroxylamine is called Meisenheimer rearrangement (Meisenheimer, 1919; Cope *et al*., 1944; Laszlo, 2005).



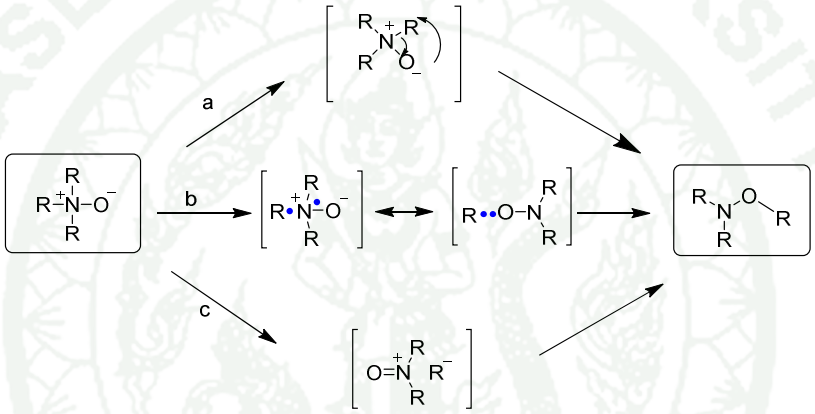
Scheme 65

Meisenheimer rearrangement is consisted of two types of transferation: the first type is [1, 2] rearrangement of tertiary amine *N*-oxides (465) to hydroxylamines (466) and the second type is [2, 3] rearrangement of allylic tertiary amine-*N*-oxides (467) to *O*-allylhydroxylamines (468) (Scheme 66).



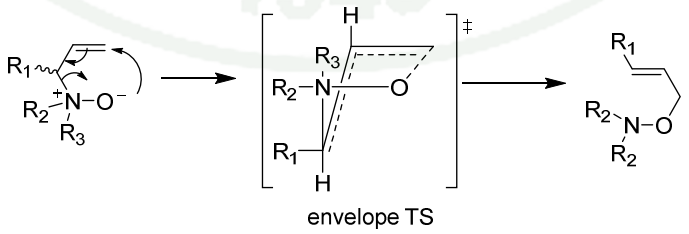
Scheme 66

The mechanism of [1, 2] meisenheimer rearrangement has not been clearly established. Three possible pathways have been proposed (Scheme 67) (Zhang, 2011): i) A concerted sigmatropic rearrangement (Scheme 67a), ii) radical pathway (Scheme 67b) and iii) ionic mechanism (Scheme 67c). It has been thoroughly examined both experimentally and using density functional theory (DFT) calculation. "It is now well-established that this reaction goes through a diradical species, produced via the homolytic cleavage of the C–N bond, that further recombines to form the C–O bond" (Couty, *et al.,* 2012).



Scheme 67

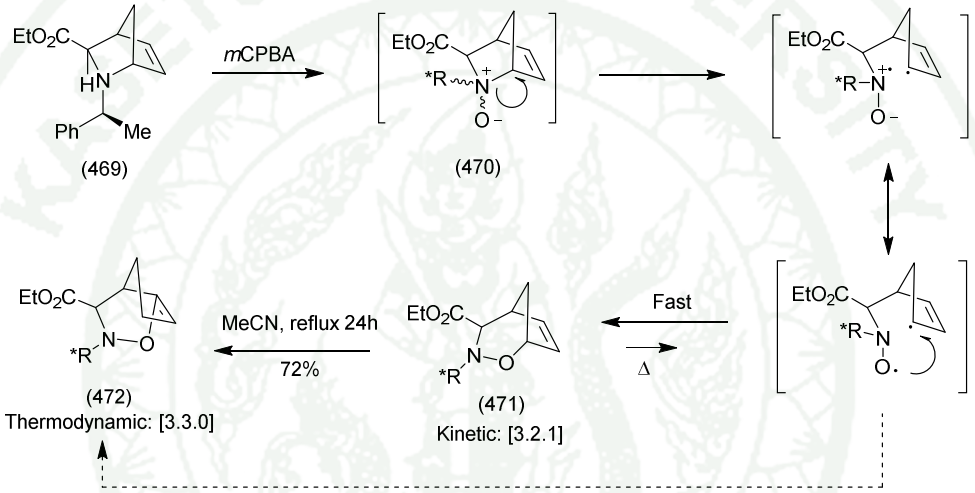
The mechanism of [2,3] Meisenheimer rearrangement is clearly as a concerted sigmatropic rearrangement through five membered enveloped transition state (Scheme 68).



Scheme 68

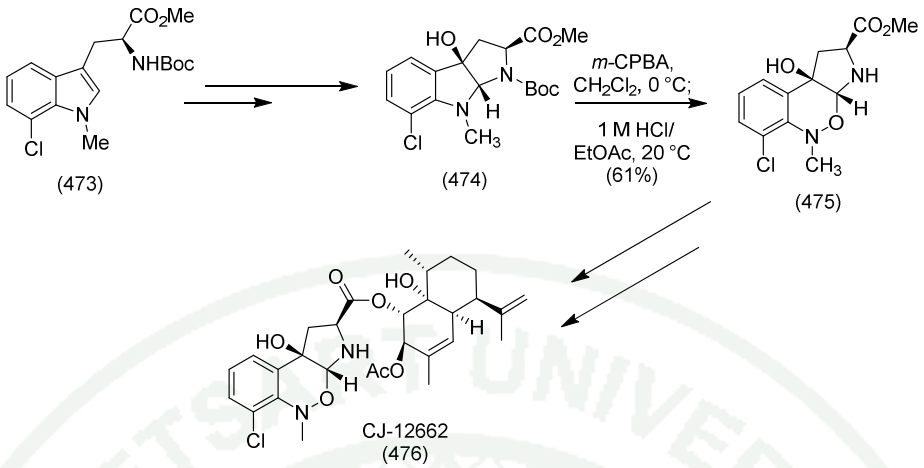
[1, 2]-Meisenheimer rearrangement

Bailey and co-workers reported unusual oxidative rearrangement of amine (469) with *m*-CPBA to give *N*-oxide (470) which rearranged to hydroxylamine (471). Hydroxylamine (471) was heated in acetonitrile led to more thermodynamically stable *O*-allyl hydroxylamine (472). The possible mechanism was proposed based on heterolytic bond cleavage (Scheme 69) (Bailey *et al*., 2000).



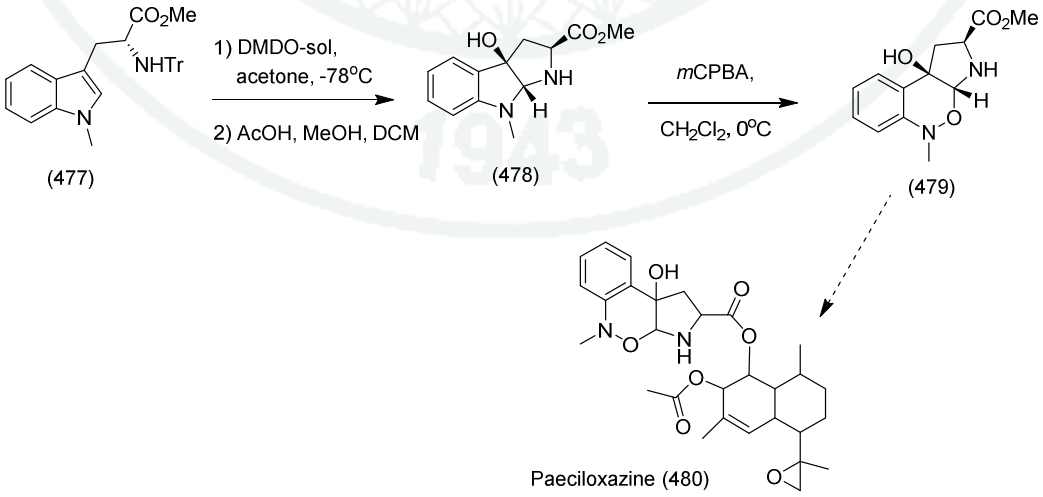
Scheme 69

In 2004, Barrett and co-workers reported synthesis of an unusual terpenoid pyrrolobenzoxazine natural product, CJ-12662 (476). The pyrrolobenzoxazine core structure (475) was constructed via dye-sensitized photooxygenation of a tryptophan derivative (473) to give 3-hydroxy pyrroloindoline (474). Oxidation of amine (474) with *m*-CPBA followed by careful treatment of the corresponding *N*-Boc-*N*-oxide (475) under acidic conditions afforded pyrrolobenzoxazine core structure (Scheme 70) (Barret *et al*., 2004).



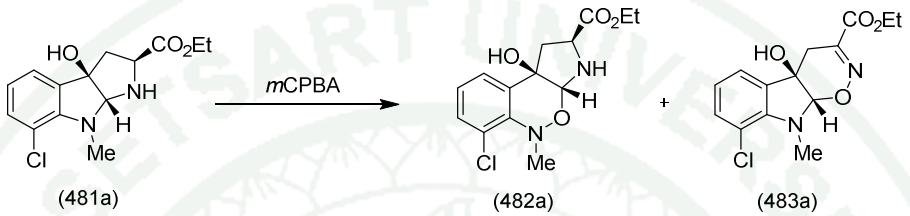
Scheme 70

In the same year, Baldwin and co-workers reported synthesis of the pyrrolobenzoxazine core of paeciloxazine by employing two diastereoselective oxidation reactions. The first oxidation step, the double bond of the indole ring (477) is diastereoselectively epoxidized and then opened by the amino group resulting in the pyrroloindoline moiety to give compound (478). The second oxidation step, more basic tertiary anilinic nitrogen of (478) is oxidized resulting in an *N*-oxide which undergoes Meisenheimer rearrangement to form the resulting pyrrolobenzoxazine derivative (479) (Scheme 71) (Baldwin *et al.,* 2004).



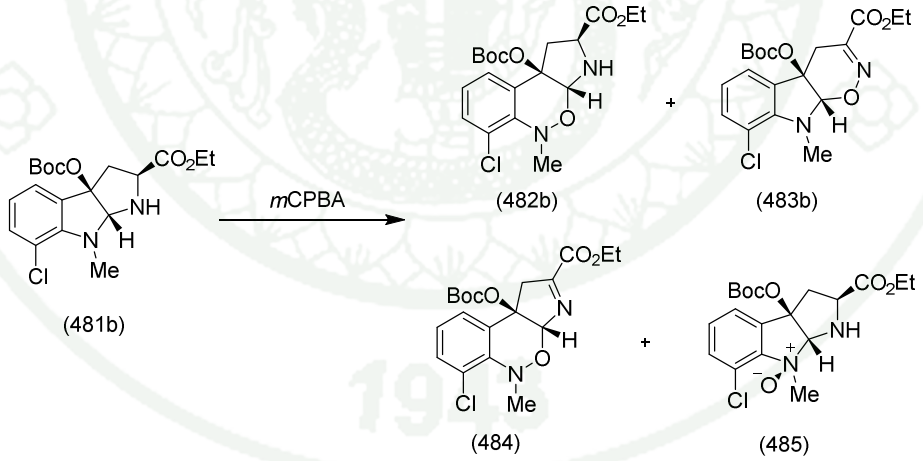
Scheme 71

In 2011, Ghosez and co-workers reported study of the oxidation and Meisenheimer rearrangement of 3-hydroxy-7-chloropyrroloindoles to pyrrolobenzoxazine (Ghosez *et al.,* 2011). The oxidation of 3-hydroxy-7-chloropyrroloindoles (481a) with *m*-CPBA yielded a mixture of Meisenheimer rearranged products (482a) and (483a) (Scheme 72).



Scheme 72

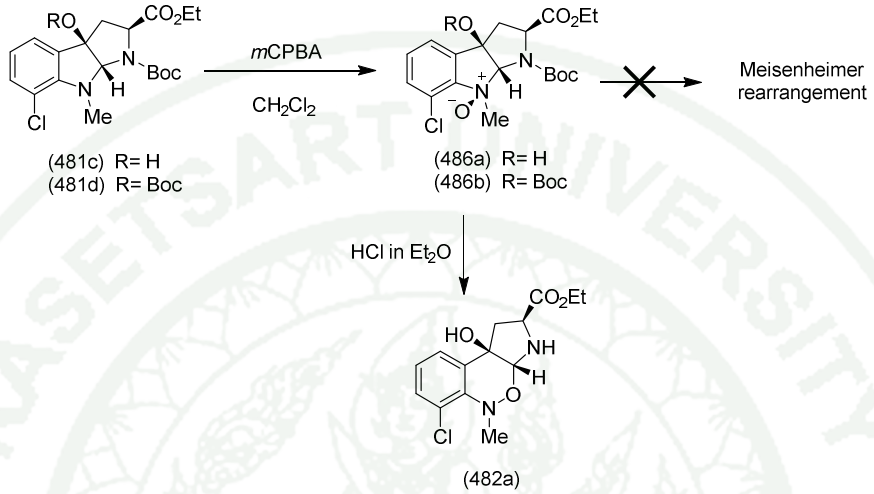
Oxidation of 3-*O*-Boc -7-chloropyrroloindoles (481b) with *m*-CPBA yielded a mixture of Meisenheimer rearranged products (Scheme 73) which a favour (482b).



Scheme 73

The oxidation of the Boc-protected compounds (481c) and (481d) were also examined (Scheme 74), which led to the formation of *N*-oxides (486a) and (486b). None of those *N*-oxides gave the corresponding Meisenheimer rearrangement products upon heating. However, treatment of both (486a) and (486b) with HCl to

cleave the Boc protecting group led to the pyrrolobenzoxazine derivative which was identical to the product (482a) obtained from the Meisenheimer rearrangement of (481a) (Scheme 72)



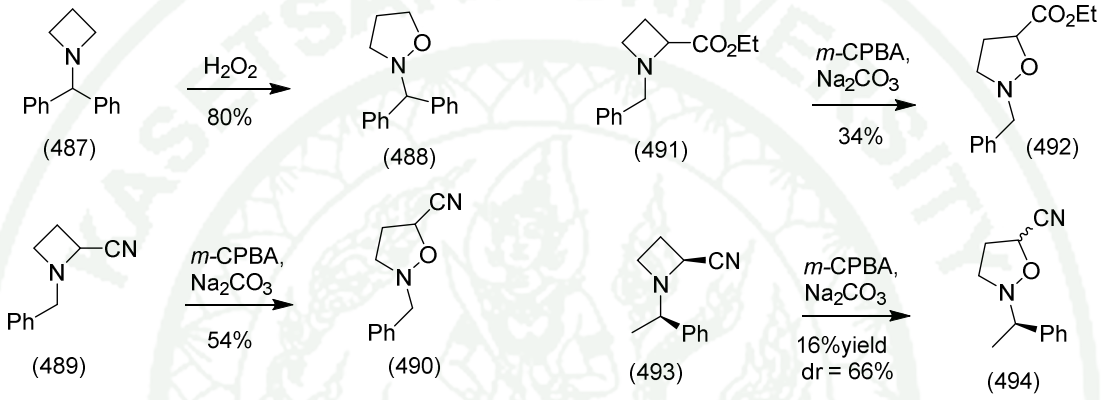
Scheme 74

In the same year (2011), Zhang published density functional theory (DFT) studies on Meisenheimer rearrangement. Both [1,2]- and [2,3]-Meisenheimer rearrangements have been investigated. The results found that when allylic group is involved in tertiary amine *N*-oxide, the concerted [2,3]-allylic shift is most favorable. On the other hand, in [1,2]-Meisenheimer rearrangement, calculations indicate that methyl, ethyl, isopropyl, benzyl and 3-homoadamantyl transfer all favor the radical mechanism, which is in good agreement with the experiments; while phenyl transfer prefers the concerted mechanism. Meanwhile, oxidation will facilitate the functional group transfer (Zhang, 2011).

In 2012, Couty and co-workers reported rearrangement of various functionalized azetidine *N*-oxides to isoxazolidines and mechanistic insights into [1,2] Meisenheimer rearrangement (Couty *et al.,* 2012). Oxidation of azetidine with hydrogen peroxide or *m*-CPBA gave the *N*-oxide which underwent a rapid [1,2] Meisenheimer rearrangement to give the corresponding isoxazolidines (Schemes 75

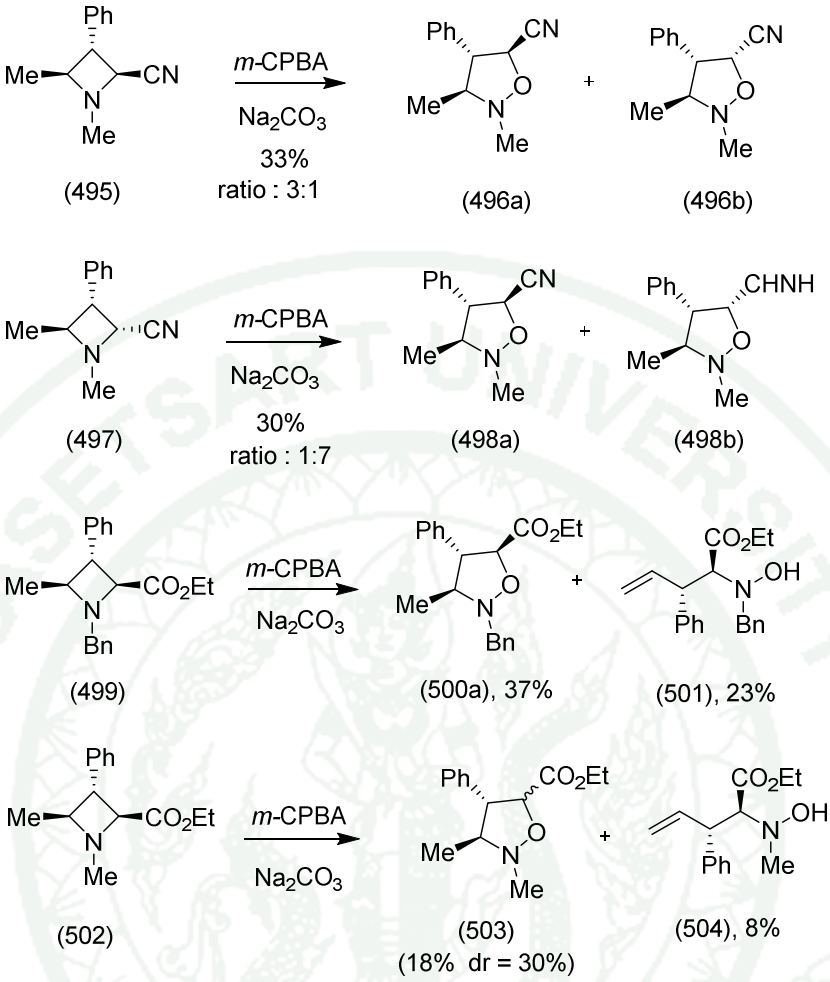
and 76), but the isolated yield are usually low due to incomplete oxidation of starting material and competing oxidation of the produced isoxazolidines led to polar nitrones.

From their experiment, the ring cleavage is regioselective when an ester or nitrile is present at C-2, which is in agreement with the stabilization of the intermediate α-cyano or α-ethoxycarbonyl intermediate radical (Scheme 75).



Scheme 75

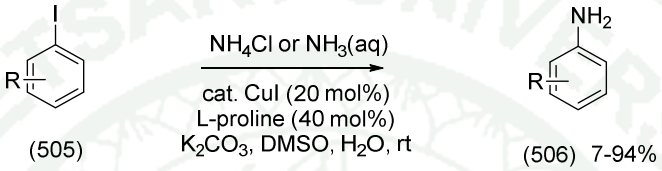
The configuration of the migrating carbon stereocenter is retained only in one case, starting from *N*-benzyl azetidine (499). Starting from *N*-Me azetidines (495), (497) and (502), up to 25% of epimerization is observed, but the ratio of epimers depends on the configuration in the starting material. Thus, they can conclude that the stereospecificity of the reaction depends on several parameters, such as the nature of the intermediate carbon radical, and the nature of the substituents on the azetidine ring (Schemes 76).



Scheme 76

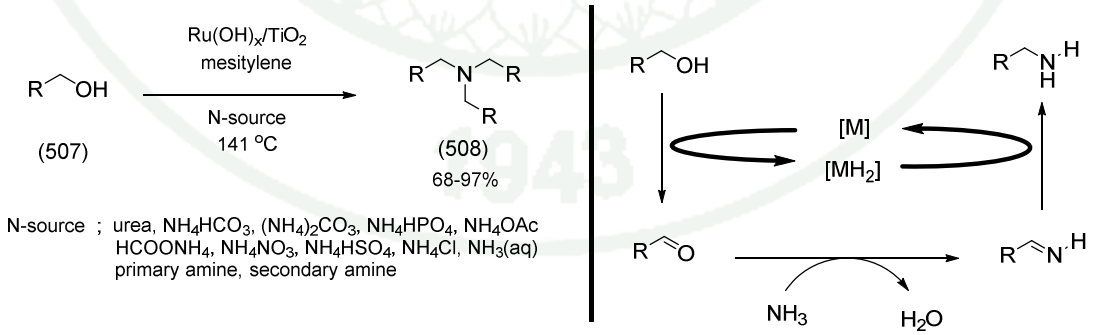
Metal catalyzed reaction of ammonia and its equivalent

In 2008, Chang and co-workers reported copper catalysed *N*-arylation of aryl iodides (505) with ammonia solution or an inexpensive ammonium chloride to provide anilines (506) in low to high yields depending on aryl iodide the starting material (Scheme 77) (Chang, *et al.*, 2008).



Scheme 77

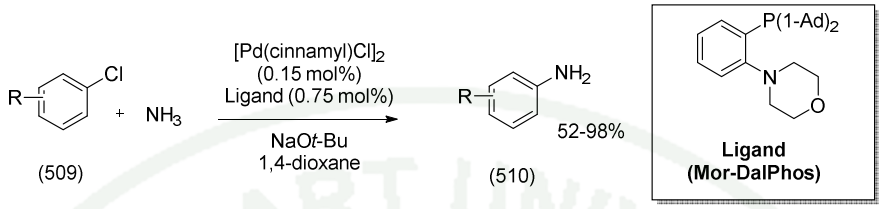
Mizuno and co-workers reported *N*-alkylation of ammonia (or its surrogate) and amine with alcohols (507) using a "borrowing hydrogen strategy" in the presence of an inexpensive supported ruthenium hydroxide catalyst to give amine (508) in excellent yield (Scheme 78) (Mizuno, *et al.,* 2010). This borrowing hydrogen strategy was first introduced independently by the groups of Grigg (Grigg *et al.,* 1981) and Watanabe (Watanabe *et al.,* 1981) in 1981.



Scheme 78

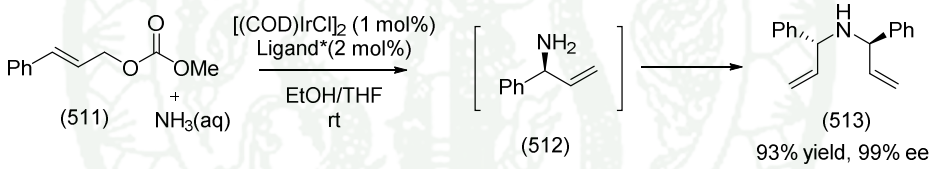
Stradiotto and co-workers have developed an air-stable P, N-ligand (Mor-DalPhos) for palladium-catalyzed ammonia cross-coupling reactions of aryl chlorides

(509) with ammonia. *N*-unprotected aniline (510) was obtained in moderate to excellent yield (Scheme 79) (Stradiotto *et al.,* 2010).



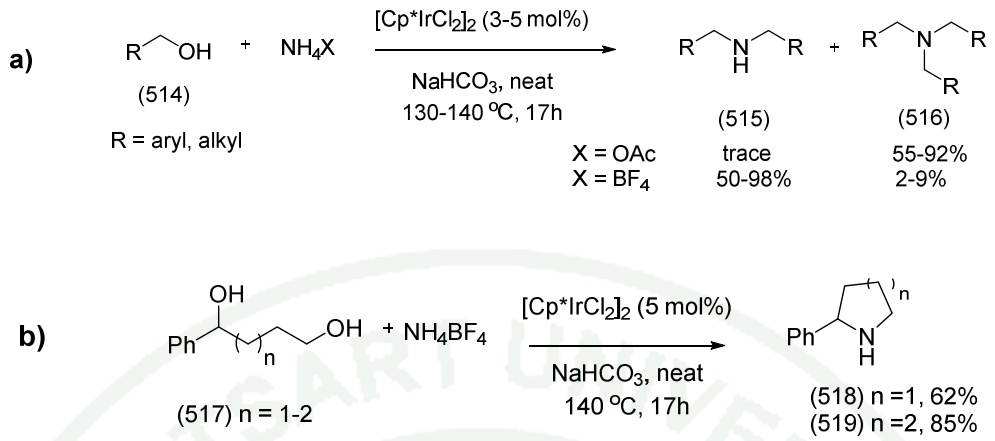
Scheme 79

Hartwig and co-workers have achieved enantioselective allylation of ammonia using an iridium complex catalyst to form diallylamine product (513) in excellent yield and enantiomeric excess (Scheme 80) (Hartwig *et al*., 2007).



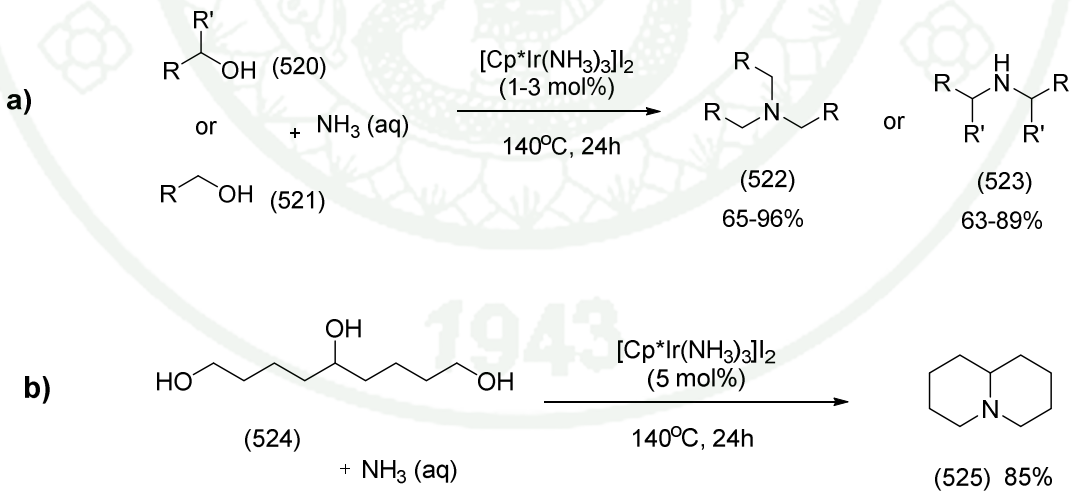
Scheme 80

Yamaguchi and co-workers have developed a new atom-economic catalytic system for the selective synthesis of secondary and tertiary amines (515-516) by iridium catalyzed multi-alkylation of ammonium salts with alcohols without any solvent (Scheme 81a). Furthermore, they also reported an efficient one-pot synthesis of cyclic amines (518-519) from ammonium tetrafluoroborate and diols (517) using this catalyst (Scheme 81b) (Yamaguchi, *et al.,* 2008).



Scheme 81

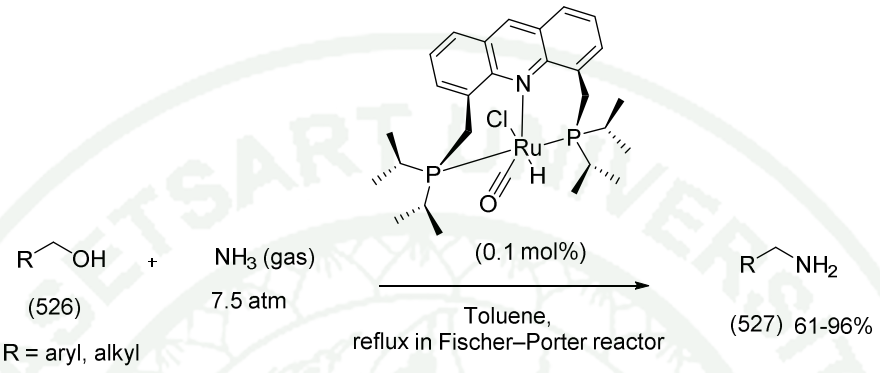
In 2010, Yamaguchi further reported a water-soluble and air stable $Cp^*Ir(NH_3)_3[X]_2$ (X= Br or I) catalyst for the synthesis of amines in aqueous ammonia. A variety of tertiary and secondary amines (522-523) were obtained in good yield (Scheme 82a). A one-flask synthesis of quinolizidine (525) starting with a triol (524) was also demonstrated (Scheme 82b) (Yamaguchi, *el al.,* 2010).



Scheme 82

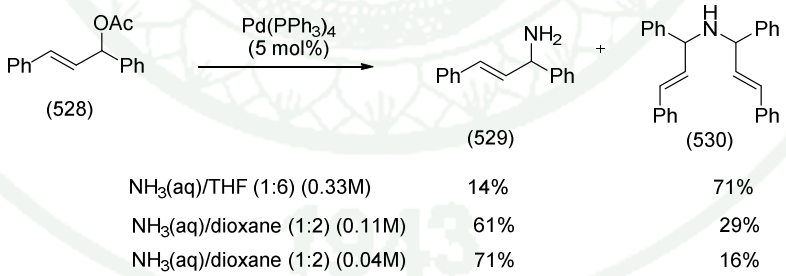
Milstein and co-workers reported using ruthenium pincer complex catalysed selective synthesis of primary amines (527) directly from alcohols (526) and

ammonia. The primary amine product was obtained in good yield both in small and large scale (Scheme 83) (Milstein *et al.,* 2008). The mechanism was proposed through borrowing hydrogen strategy.



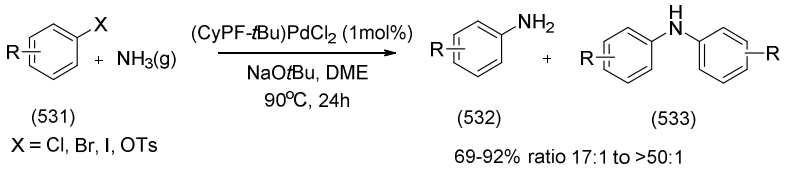
Scheme 83

Kobayashi and co-workers developed a palladium catalyzed allylic amination using aqueous ammonia for selective preparation of primary and secondary amines (529-530). It is noteworthy that the use of aqueous ammonia is essential and that ammonia gas did not react at all (Scheme 84) (Kobayashi *et al.,* 2009).



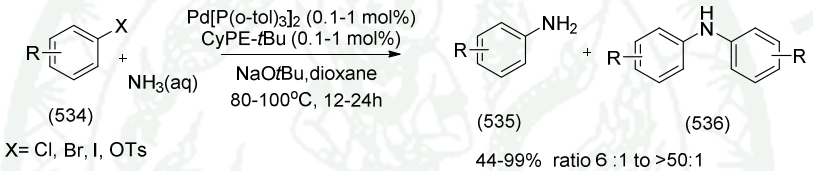
Scheme 84

In 2006, Hartwig and co-workers reported the synthesis of substituted anilines (532) using a palladium-catalyzed coupling reaction of ammonia gas or lithium amide with aryl halides (531) in the presence of sodium *tert*-butoxide. The substituted aniline product (532) was obtained in good yield with a small amount of *N,N*-diarylamine (533) (Scheme 85) (Hartwig *et al.,* 2006).



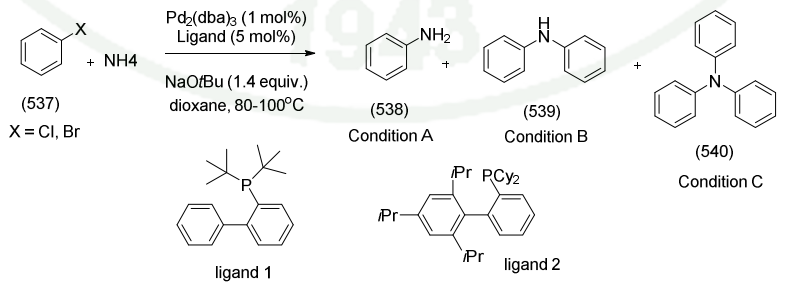
Scheme 85

In 2009, Hartwig also reported the palladium-catalyzed coupling reaction of ammonia with aryl halides (534) or tosylates using an aqueous solution of 0.5 *M* ammonia in dioxane. Unprotected aniline product (535) was obtained in good yield along with *N,N*-diarylamine (536) (Scheme 86) (Hartwig *et al.,* 2009).



Scheme 86

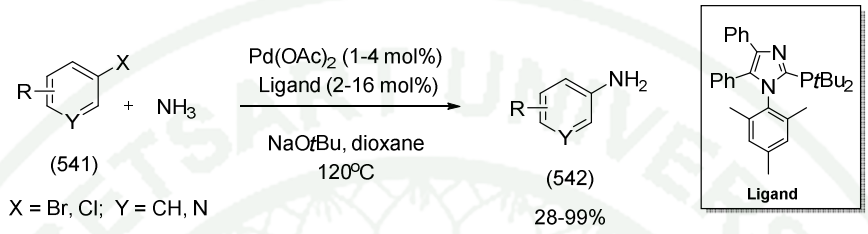
Buchwald and co-workers have developed reaction conditions for the palladium catalyzed coupling of ammonia with aryl halides (537) which allow the selective synthesis of either anilines or di- or triarylamines (539-540) (Scheme 87) (Buchwald *et al.,* 2007).



Conditions A: ligand 1, NH_3(5 equiv); 0.042 M 1,4-dioxane; 80 °C.
Conditions B: ligand 2, NH_3 (3 equiv); 0.0625 M, 1,4-dioxane; 80°C.
Conditions C: ligand 2, NH_3 (0.75 equiv); 0.66 M, 1,4-dioxane; 100 °C

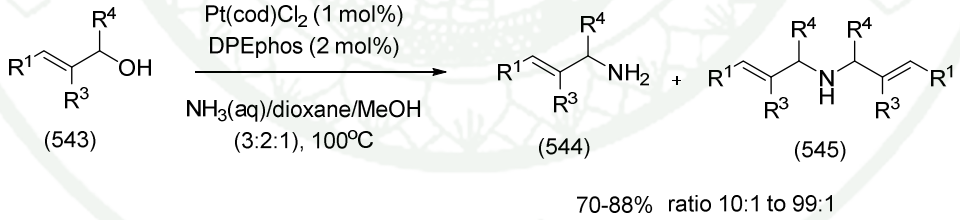
Scheme 87

Beller and co-workers have developed palladium/phosphine catalyzed selective monoarylation of ammonia with different aryl bromides and chlorides. The active catalyst is formed in situ from $Pd(OAc)_2$ and an air- and moisture stable phosphine (Scheme 88) (Beller *et al.,* 2009).



Scheme 88

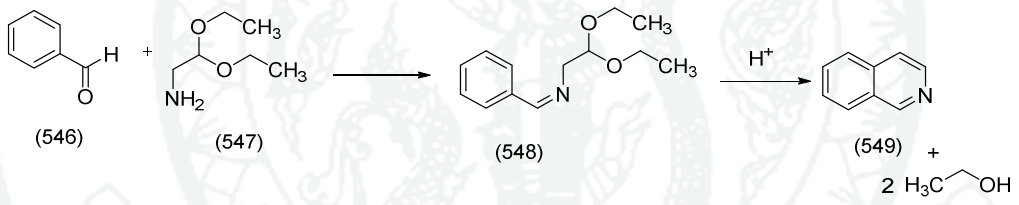
In 2012, Mashima and co-workers reported the first direct catalytic amination of allylic alcohols with aqueous ammonia using a Pt/DPEphos catalyst system without the prior activation of the allylic alcohol. In this protocol, a variety of primary allylamines (544) were directly synthesized from the corresponding allylic alcohols (543) with high monoallylation selectivity (Scheme 89) (Mashima *et al.,* 2012).



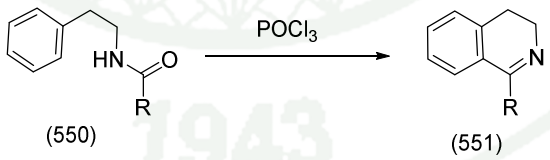
Scheme 89

Metal catalyzed isoquinoline synthesis

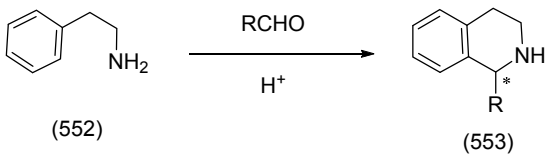
New synthesis of isoquinoline heterocycles is continued to be of interest due to the presence of the isoquinoline ring system in numerous naturally occurring alkaloids as well as in drug candidates possessing interesting biological activities. The classical methods such as Bischler-Napieralski reaction, Pomeranz-Fritsch reaction and Pictet-Spengler reaction have been frequently employed in the total synthesis of isoquinoline alkaloids, but they are all quite limited synthetically as all of these methods are based on electrophilic cyclizations of a α–phenylethylamine to form the nitrogen-containing ring and suffer the disadvantage of employing strong acids in their ring closure steps. Furthermore, the Bischler-Napieralski and Pictet-Spengler reactions require dehydrogenations of dihydro- and tetrahydroisoquinolines, respectively.



Scheme 90 Pomeranz-Fritsch reaction



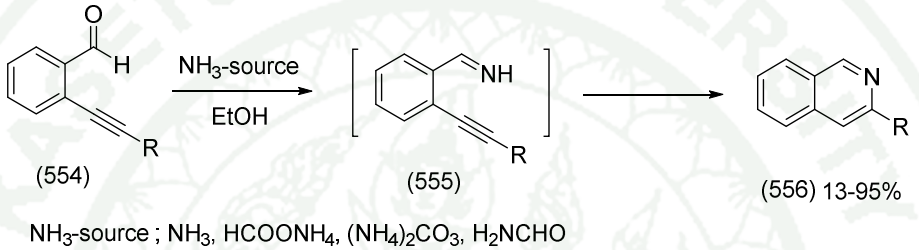
Scheme 91 Bischler-Napieralski reaction



Scheme 92 Pictet-Spengler reaction

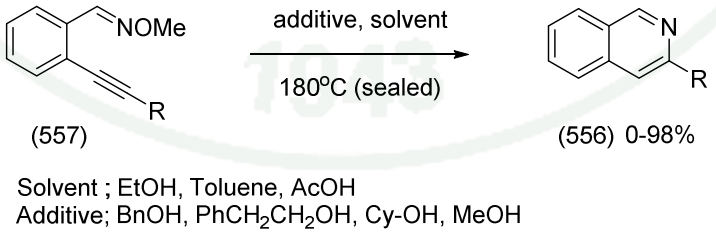
In recent years, the transition metal catalyzed synthesis of isoquinolines has received the most attention.

Sakamoto and co-workers studied the cyclization of 2-alkynyl benzaldehyde (554) with ammonia or its equivalent. The 3-substituted isoquinoline products (556) were presumed to arise via the corresponding imine intermediate (555) (Scheme 93) (Sakamoto *et al.,* 2000).



Scheme 93

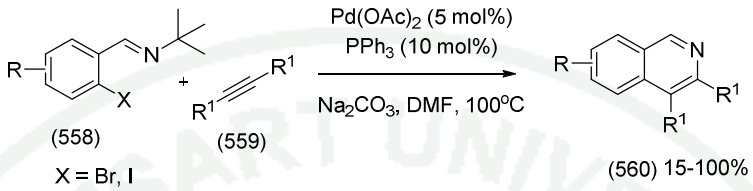
However, these imines (555) are generally unstable, and they chose the corresponding oxime (557) as substrate to elucidate the course of the cyclization. They found that the cyclization of 2-alkynyl benzaldehyde oxime (557) gave the corresponding isoquinoline (556) and that the mechanism was an ionic process (Scheme 94) (Sakamoto *et al.,* 2000).



Scheme 94

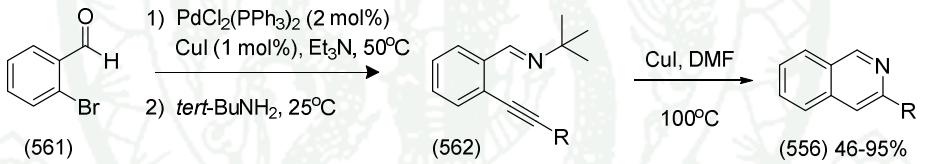
In 2001, Larock and co-workers reported the palladium catalyzed iminoannulation of an internal alkyne to give a substituted isoquinoline. They found

that the iminoannulation failed with methyl, isopropyl, allyl and benzyl imine of 2-iodobenzaldehyde but the *tert*-butylimine (558) gave moderate to good yields of isoquinoline (560) (Scheme 95) (Larock *et al.,* 2001).



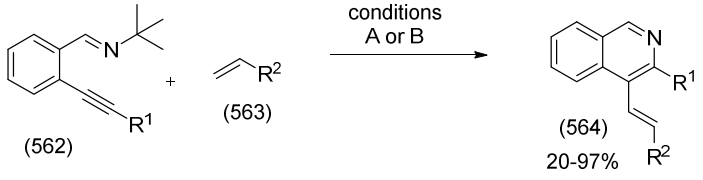
Scheme 95

Further work by Larock showed that copper catalyzed cyclization of the imino alkyne delivered isoquinolines in moderate to excellent yield (Scheme 96) (Roesch, Larock *et al.,* 2001).



Scheme 96

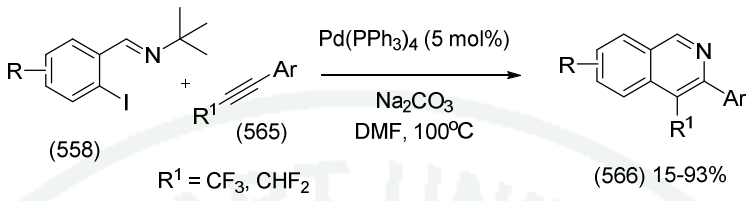
In 2002, Larock reported a tandem palladium catalyzed iminoannulation-Heck reaction to construct 3, 4-disubstituted isoquinolines (564) (Scheme 97) (Larock *et al.*, 2002).



A : $PdBr_2$ (10 mol%), $Cu(OAc)_2$ (2 equiv.), NaOAc, DMSO, 70°C
B : $PdBr_2$ (10 mol%), $CuCl_2$ (10 mol%), $NaHCO_3$, DMSO, O_2, 70°C

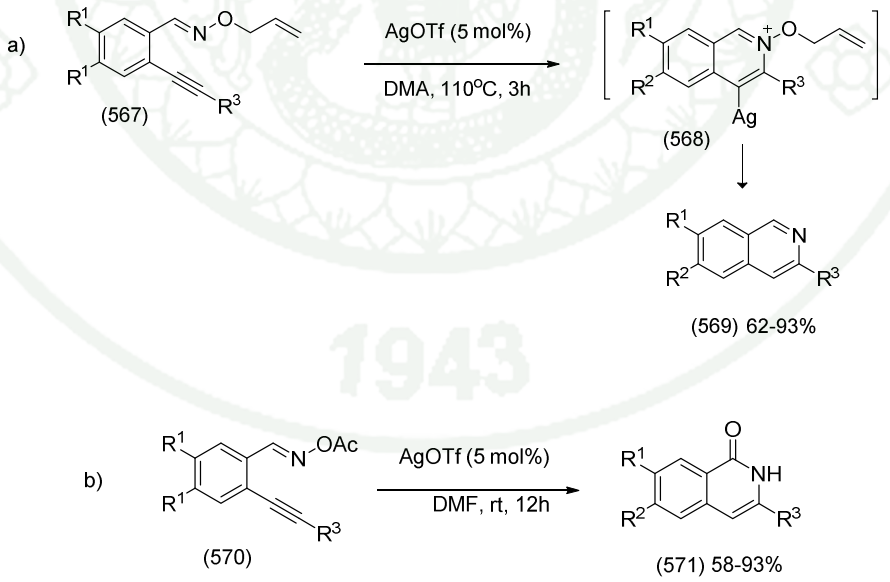
Scheme 97

In 2005, Konno and co-workers extended Larock's work to fluoro alkynes (565) (Scheme 98) (Konno *et al.,* 2005).



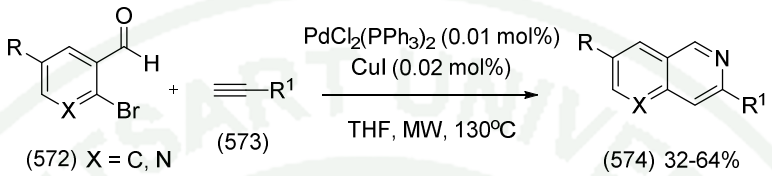
Scheme 98

Zhang and co-workers reported that AgOTf was an effective cyclization catalyst for the reaction of *ortho*-alkynyl aryl aldehyde oxime derivatives (567). Isoquinolines (569) were obtained from the corresponding *O*-methyl, *O*-allyl and *O*-benzyl oxime in good to excellent yield (Scheme 99a). On the other hand cyclization of oxime-OAc (570) gave isoquinolinone (571) in moderate to excellent yield (Scheme 99b) (Zhang *et al.,* 2009).



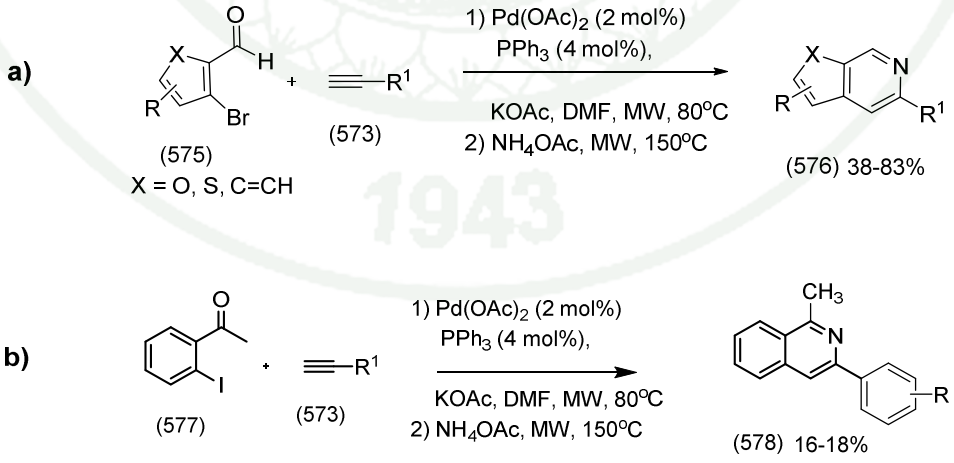
Scheme 99

Abbiati and co-workers synthesed isoquinolines (574) via microwave assisted palladium catalyzed cascade reaction of 2-bromo benzaldehyde (572) with a mono alkyne in the presence of aqueous ammonia. The corresponding isoquinoline was obtained in moderate yield (Scheme 100) (Abbiati *et al.,* 2010).



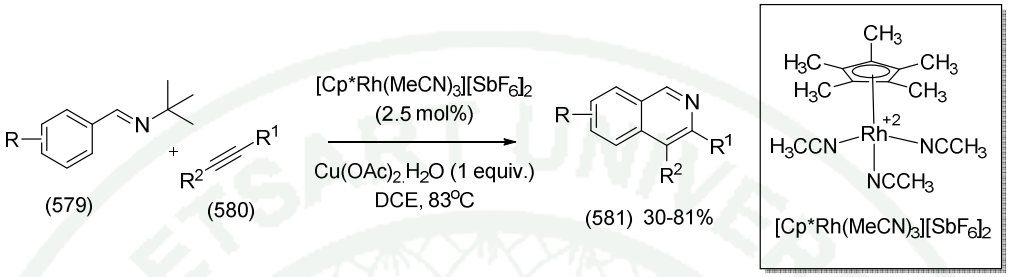
Scheme 100

Chen and co-workers reported the microwave assisted 3-component one pot synthesis of isoquinolines, furopyridines and thienopyridines (576) by palladium catalyzed annulations reaction of 2-bromoaryl aldehydes with terminal alkynes and ammonium acetate. The products were obtained in moderate to excellent yield (Scheme 101a). They also expanded the protocol to 2´-bromoarylketones (577) to access 1-substituted isoquinolines (578) but only low yield of the product was obtained (Scheme 101b) (Chen *et al.,* 2012).



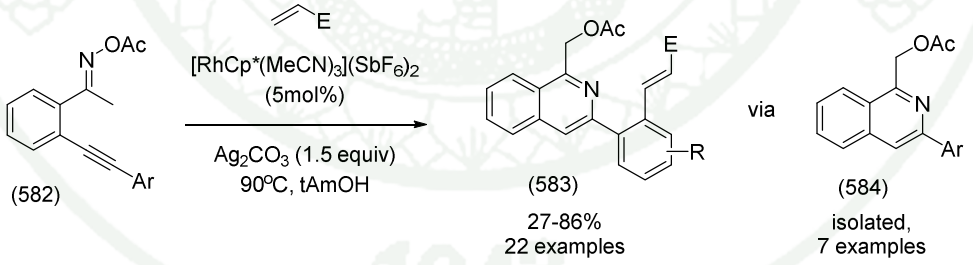
Scheme 101

In 2009, Fagnou and co-workers reported Rh(III) catalyzed protocol for the synthesized of substituted isoquinolines (581) *via* reaction of benzalimine (579) and internal alkynes. Their methodology did not require a halo-substituted on benzalimine (Scheme 102) (Fagnou *et al.,* 2009).



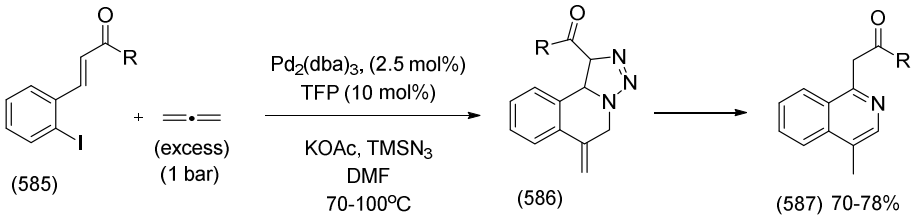
Scheme 102

Li and co-workers have achieved rhodium (III)-catalyzed oxidative coupling between olefins and aryl alkynes bearing an *N*-OAc imine functionality (582). This reaction produced isoquinolines (583) bearing an *ortho*-olefinated 3-aryl group as a result of C-N and C-C coupling. This protocol allows the synthesis of functionalized isoquinolines under simple conditions (Scheme 103) (Li *et al.*, 2012).



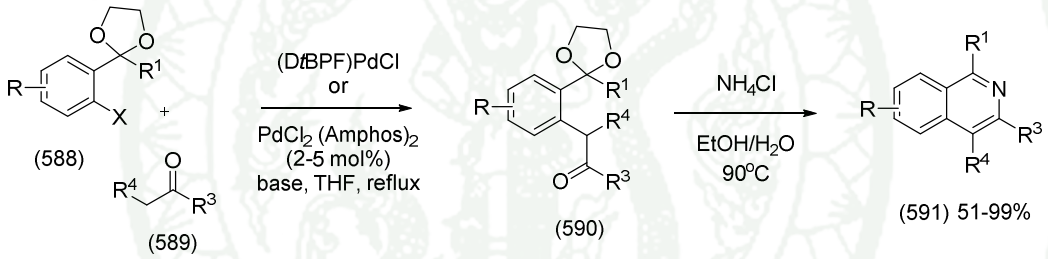
Scheme 103

Grigg and co-workers constructed a 3-component palladium catalyzed allene/azide capture /intramolecular 1,3-dipolar cycloaddition cascade to furnish triazoles (586) which fragment and aromatize to isoquinoline (587). Their protocol is a different cascade strategy to obtain the corresponding isoquinoline (Scheme 104) (Grigg *et al.*, 2005).



Scheme 104

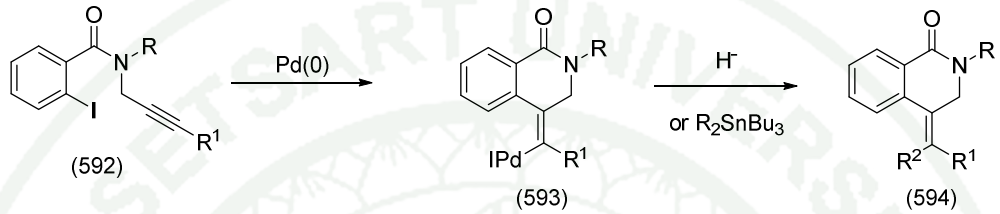
Donohoe and co-workers recently presented the synthesis of highly substituted isoquinolines via a palladium catalyzed α-arylation of ketones followed by cyclization to afforded isoquinolines (591) in excellent yield (Scheme 105) (Donohoe *et al.*, 2012).



Scheme 105

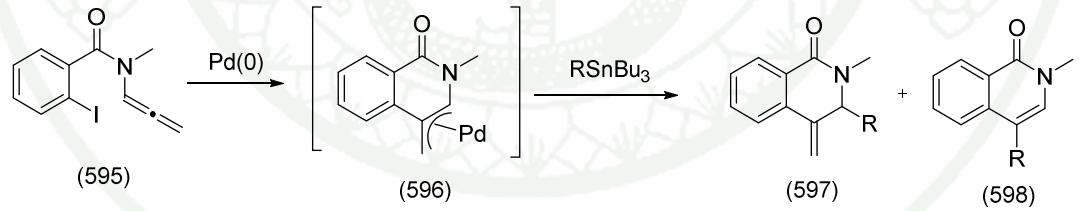
Metal catalyzed 4-alkene-3,4-dihydroisoquinolinone synthesis

Grigg and co-workers reported palladium catalyzed 6-exo-dig cyclization of 2-iodobenzamide acetylide (592) followed by capture of palladium (II) species with hydride ion or organotin (IV) reagents (Scheme 106) (Grigg *et al.*, 1996).



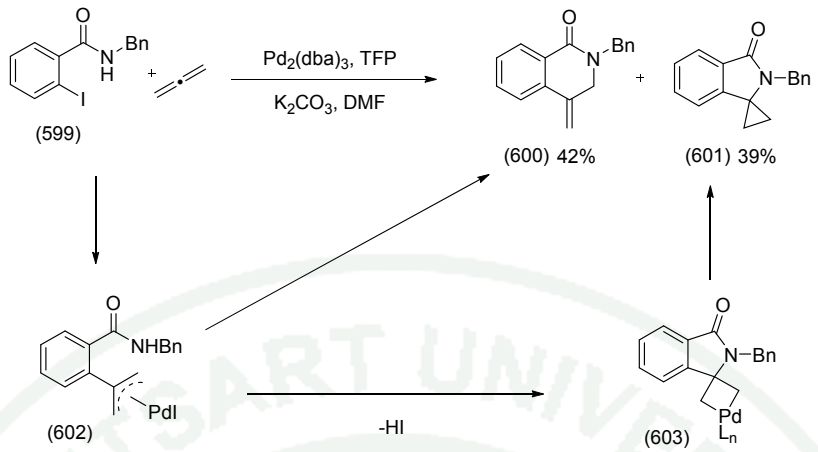
Scheme 106

Reaction of 2-iodobenzamide allene (595) using organotin (IV) reagents capture π-allyl palladium complex was also reported by Grigg group in 2000. Isoquinolinone (598) and dihydroisoquinolinone (597) were obtained in 60-70% nearly 1:1 ratio (Scheme 107) (Grigg *et al*., 2000).



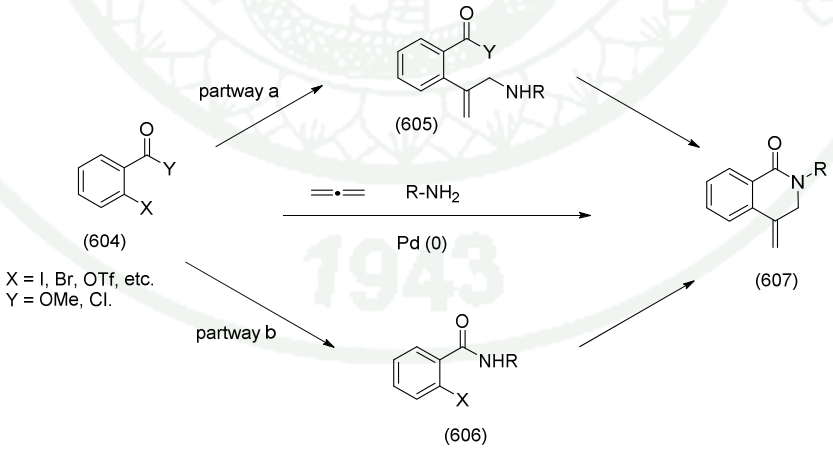
Scheme 107

In 2001 Grigg reported palladium coupling reaction of *ortho*-iodobenzamides (599) with allene to form dihydroisoquinolinone (600) and cyclopropanes (601) which is believed to proceed via an intermediate palladacyclobutane (603) (Scheme 108) (Grigg *et al.,* 2001).



Scheme 108

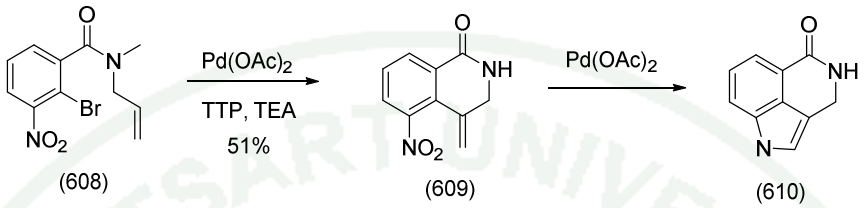
In 2002, They continue reported a novel palladium-catalysed three-component cascade process of 2-iodobenzoyl chloride or methyl 2-iodobenzoate, allene and primary aliphatic or aromatic amines to furnished *N*-substituted 4 methylene-3,4-dihydro-1(2*H*)-isoquinolin-1-ones (607) in good yield. They have evidence for reaction of methyl 2-iodobenzoate proceeding via partway **a** whereas 2-iodobenzoyl chloride follows pathway **b** (Scheme 109) (Grigg *et al.*, 2002).



Scheme 109

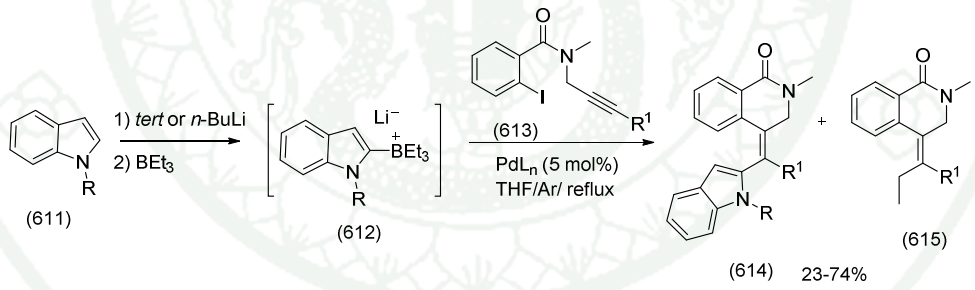
Söderberg and co-workers reported a route to 3,4-fused indoles (610) via two consecutive palladium-catalyzed which included an intramolecular Heck reaction

followed by a reductive *N*-heteroannulation. 5-nitro-4-methylene-3,4-dihydroisoquinolin-1(2*H*)-one one intermediate (609) was obtained in 51% yield (Scheme 110) (Söderberg *et al.,* 2005).



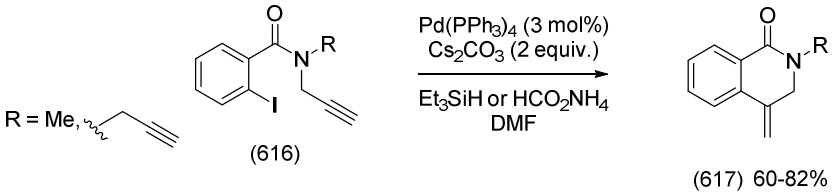
Scheme 110

Ishikura and co-workers reported palladium-catalyzed tandem cyclization-cross-coupling reaction of acetylide 2-iodobenzamide (613) using indolylborate (612) as a transfer agent delivered to 3,4-dihydro-isoquinolinone (614-615) (Scheme 111) (Ishikura *et al*., 2006).



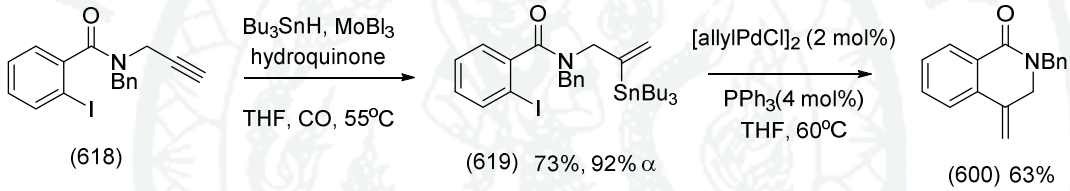
Scheme 111

In 2003, 4-methylene-3,4-dihydro-isoquinolinone (617) were synthesized via palladium-catalyzed cycloreductions of haloene-ynes in the presence of triethylsilane or ammonium formate. This methodology was described by Oh and co-worker (Scheme 112) (Oh *et al.,* 2003).



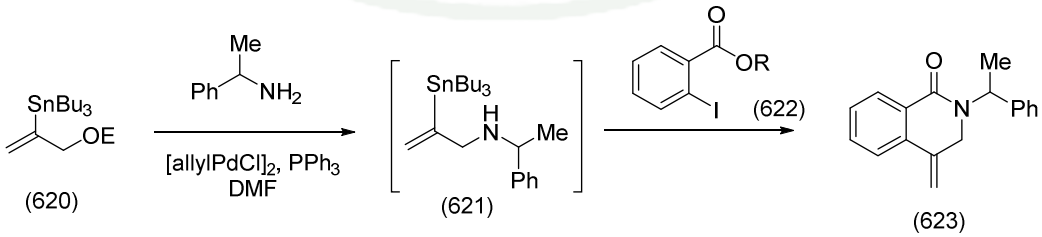
Scheme 112

Mo-catalyzed hydrostannations of propagyl 2-iodobenzamide (618) provided α-stannylated allylic amides (619) which underwent an intramolecular Stille cyclization, giving rise to4-methylene -3,4-dihydro-isoquinolinone (600) in good yield (Scheme 113) (Kazmaier *et al.*, 2009).



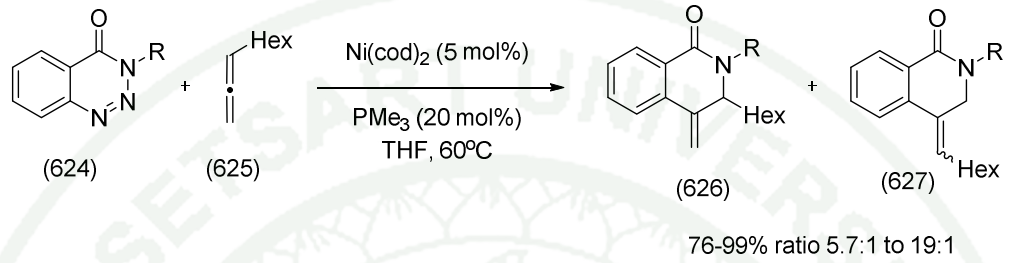
Scheme 113

Kazmaier and co-workers have shown transforming of stannylated allyl carbonates (620) to stannylated allylamines (621) which can be further modified *via* Stille couplings delivered to a wide range of substituted and functionalized allylamines. 4-methylene-3,4-dihydro-isoquinolinone (623) was obtained from this procedure in a good yield (Scheme 114) (Kazmaier *et al.,* 2011).



Scheme 114

Murakami and co-workers reported synthesis of substituted 3,4-dihydroisoquinolin-1(2*H*)-ones (626-627) using denitrogenative annulation reaction of 1,2,3-benzotriazin-4(3*H*)-ones (624) with allenes to provide product in excellent yield with regioselectivity (Scheme 115) (Murakami *et al.*, 2010).



Scheme 115

MATERIALS AND METHODS

Materials

Instrumentation

The following analytical methods were used throughout this work, unless otherwise indicated.

Proton nuclear magnetic resonance (^{1}H-NMR) spectra and carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on a VARIAN^{UTITY} INOVA 400 MHz NMR spectrometer at the Department of Chemistry, Faculty of Science, Kasetsart University, Bruker DPX300 spectrometer at the School of Chemistry, University of Leeds, Bruker AVANCE 300 spectrometer at the Department of Chemistry, Faculty of Science, Silpakorn University and Bruker 300 spectrometer at the Department of Chemistry, Faculty of Science, Chulalongkorn University. Chemical shifts were recorded as δ values in ppm. Coupling constants (*J*) are given in Hz, and multiplicity is defined as follows: br = broad, s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, td = triplet of doublet, q = quartet, quint = quintet, m = multiplet.

Optical rotations were measured using a JASCO P-2000 polarimeter at the Government Pharmaceutical Organization and a JASCO P-1010 polarimeter at the Department of Chemistry, Faculty of Science, Silpakorn University.

Infrared (IR) spectra were recorded in the range 4000-400 cm^{-1} on a Perkin-Elmer 2000 FT-IR spectrophotometer at the Department of Chemistry, Faculty of Science, Kasetsart University or a Perkin-Elmer Spectrum FT-IR spectrometer at the School of Chemistry, University of Leeds. Samples were analyzed as neat liquid, KBr disks or using a golden gate apparatus.

High resolution mass spectrometry was recorded on Q-TOF2 spectrometer at PERCH Mass Spectrometry Research Laboratory, Department of Chemistry, Faculty of Science, Chiang Mai University, Bruker micrOTOF spectrometer at University of Leeds and Bruker micrOTOF-QIII spectrometer at Department of Chemistry, Faculty of Science, Kasetsart University.

Chromatographic system

Analytical thin-layer chromatography (TLC) was conducted on aluminum-backed 0.2 mm thick silica gel 60 F254 plates (Merck) and the chromatograms were visualized under a 254 nm UV lam.p.and/or by spraying with a solution of vanillin (3% in EtOH with 3% sulfuric acid) or solution of $KMnO_4$ in 5% NaOH followed by heating.

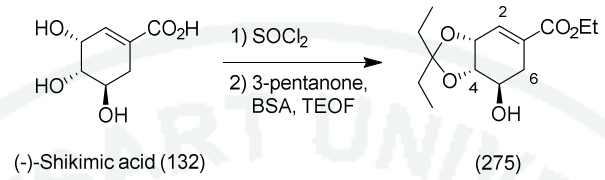
Flash column chromatography was carried out using Merck Geduran® Si 60, silica gel (40-63 μm) and SiliaFlash F60 silica gel (40-63 μm, 60Å).

Chemical reagents

Starting materials sourced from commercial suppliers were used as received unless otherwise stated. Analytical grade solvents and reagents used for synthesis were obtained from commercial source and used directly without further purification unless noted. Dry tetrahydrofuran (THF) was freshly distilled under nitrogen atmosphere from sodium with benzophenone as an indicator. Dichloromethane (CH_2Cl_2) was dried over anhydrous calcium chloride and distilled from calcium hydride immediately prior to use.

Methods

Ethyl 3,4-*O*-isopentylidene-5-hydroxy shikimate (275)



(-)-Shikimic acid (132) (275)

To a solution of (-)-shikimic acid (132) (10.14 g, 58.77 mmol) in EtOH (45 mL) was slowly added $SOCl_2$ (2.1 mL, 28.74 mmol). This solution was refluxed for 3h. After cooling, the solvent was evaporated to dryness. The crude shikimate ester (628) was dissolved in 3-pentanone (30.4 mL, 287.35 mmol) at 0 ^{o}C. Triethyl ortho formate (11.5 mL, 69.9 mmol) was added followed by a solution of benzene sulfonic acid (0.54 g, 2.91 mmol) in pentanone (1 mL). The reaction mixture was stirred at room temperature for 5 h Et_3N (0.5 mL, 3.50 mmol) was added. The solution was extracted with CH_2Cl_2 (3x100 mL). The combined organic layer were dried with anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 2:1) to give hydroxy ketal (275) as a viscous oil (12.38 g, 79 % 2 steps) .

FTIR (film), ν_{max}, cm^{-1}: 3459 (OH), 2976, 2940, 2883 (CH), 1714 (C=O), 1655 (C=C)

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 6.90 (t, *J* = 1.4 Hz, 1H, H-2), 4.74 (m, 1H, H-3), 4.19 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.10 (t, *J* = 6.8 Hz, 1H, H-4), 3.90 (td, *J* = 4.6, 7.7 Hz, 1H, H-5), 2.80 (br s, 1H, OH), 2.73 (dd, *J* = 4.6, 17.4 Hz, 1H, H-6), 2.23 (ddt, *J* = 1.7, 8.0, 17.4 Hz, 1H, H-6), 1.69-1.58 (m, 4H, 2x(CH_2CH_3)), 1.28 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 0.90 (t, *J* = 7.41 Hz, 3H, CH_2CH_3), 0.86 (t, *J* = 7.4 Hz, 3H, CH_2CH_3)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 166.2 (C=O), 134.1 (C-2), 130.2 (C-1), 113.5 (C), 77.7 (C-4), 72.2 (C-3), 68.7 (C-5), 29.6 (CH_2CH_3), 29.3 ($CO_2CH_2CH_3$), 29.0 (C-6), 14.1 ($CO_2CH_2CH_3$), 8.5 (CH_2CH_3), 7.83 (CH_2CH_3)

HRMS (ESI^+) *m/z* : $C_{14}H_{23}O_5$ $[M+H]^+$, calcd 271.1545, found 271.1548

Ethyl 3,4-*O*-isopentylidene-5-oxo shikimate (249)

(275) (249)

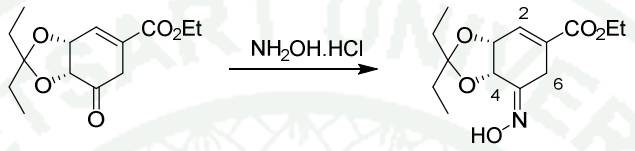
To a cooled suspension of trichloroisocyanuric acid (5.19 g, 22.34 mmol) in CH_2Cl_2 (54 mL) was added TEMPO (87.26 mg, 0.56 mmol) followed by solution of ethyl 3,4-*O*-isopentylidene-5-hydroxy shikimate (275) (3.02 g,11.17 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 45 min. After this time, the reaction mixture was filtered through celite and concentrated under reduced pressure. The crude ketone was used in the next step without further purification (for spectroscopic data: The crude ketone (249) was purified by flash column chromatography (silica gel, hexane:EtOAc 4:1) to give the pure cyclohexenenone ester (249) as a colourless oil.

FTIR (film), ν_{max}, cm^{-1}: 2976, 2942, 2883 (C-H), 1720 (C=O), 1659 (C=C)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.89-6.83 (m, 1H, H-2), 5.01-4.95 (m, 1H, H-3), 4.38 (d, *J* = 6.5 Hz, 1H, H-4), 4.18 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.28 (dt, *J* = 19.5, 1.8 Hz, 1H, H-6), 3.09 (d, *J* = 19.5 Hz, 1H, H-6), 1.61-1.51 (m, 4H, 2x (CH_2CH_3)), 1.25 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 0.85 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 0.81 (t, *J* =7.5 Hz, 3H, CH_2CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 203.2 (C=O), 165.0 (C=O), 133.7 (C-2), 129.1 (C-1), 115.5 (C), 77.4 (C-4), 75.9 (C-3), 61.4 ($CO_2\mathit{CH_2}CH_3$), 36.5 (C-6), 29.9 ($\mathit{CH_2}CH_3$), 29.2 ($\mathit{CH_2}CH_3$), 14.0 ($CO_2CH_2\mathit{CH_3}$), 8.2 ($CH_2\mathit{CH_3}$), 8.0 ($CH_2\mathit{CH_3}$)

Ethyl 3,4-O-isopentylidene-5-hydroxylamine shikimate (250)



(249) (250)

To the crude ketone (249) (7.41 mmol) in EtOH (14 mL) was added hydroxylamine hydrochloride (1.43 g, 14.81 mmol) followed by pyridine (14 mL). The reaction mixture was stirred at room temperature for 2 h. The solution was poured into water and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude oxime was purified by (silica gel, hexane:EtOAc, 4:1) to give the pure oxime (250) as a yellow oil (1.55 g, 71%, 2 steps).

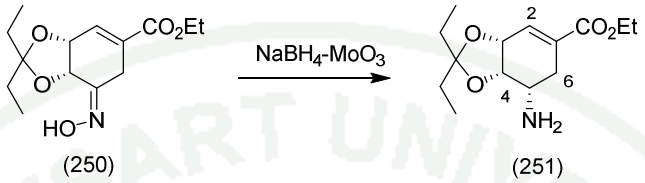
FTIR (film), ν_{max}, cm^{-1}: 3382 (OH), 2976, 2940, 2883 (CH), 1716 (C=O), 1661 (C=C)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 9.68 (s, 1H, OH), 6.74-6.71 (m, 1H, H-2), 4.80-4.76 (m, 1H, H-3), 4.61 (d, *J* = 5.4 Hz, 1H, H-4), 4.18 (q, *J* = 7.2 Hz, 2H, $CO_2\mathit{CH_2}CH_3$), 3.73 (d, *J* = 21.6 Hz, 1H, H-6), 2.89 (dt, *J* = 21.6, 2.4 Hz, 1H, H-6), 1.60 (q, *J* = 7.5 Hz, 2H, $\mathit{CH_2}CH_3$), 1.54 (q, *J* = 7.5 Hz, 2H, $\mathit{CH_2}CH_3$), 1.24 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2\mathit{CH_3}$), 0.85 (t, *J* = 7.5 Hz, 3H, $CH_2\mathit{CH_3}$), 0.77 (t, *J* = 7.5 Hz, 3H, $CH_2\mathit{CH_3}$)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 166.1 (C=O), 152.5 (C-5), 135.6 (C-2), 126.8 (C-1), 114.3 (C-7), 73.5 (C-3), 73.4 (C-4), 61.1 ($CO_2\mathit{CH_2}CH_3$), 30.3 ($\mathit{CH_2}CH_3$), 29.5 ($\mathit{CH_2}CH_3$), 20.8 (C-6), 14.0 ($CO_2CH_2\mathit{CH_3}$), 8.1 ($CH_2\mathit{CH_3}$), 8.0 ($CH_2\mathit{CH_3}$)

HRMS (ESI^+) *m/z* : $C_{14}H_{22}NO_5$ $[M+H]^+$, calcd 284.1498, found 284.1498

Ethyl 3,4-*O*-isopentylidene-5*α*-amino shikimate (251)



(250) (251)

To a mixture of the oxime (250) (511 mg, 1.73 mmol) and MoO_3 (344 mg, 2.39 mmol) in MeOH (17 mL) was added $NaBH_4$ (654 mg, 17.3 mmol) portionwise. An exothermic reaction occurred with vigorous gas. The reaction mixture was stirred at room temperature for 30 min or the reaction was completed (monitor byTLC). To the reaction mixture was added brine and the precipitate was filtered off. The filtrate was extracted with EtOAc (3x10mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give amino pentylidine acetal (251) as a yellow brown oil (448 mg, 92 %).

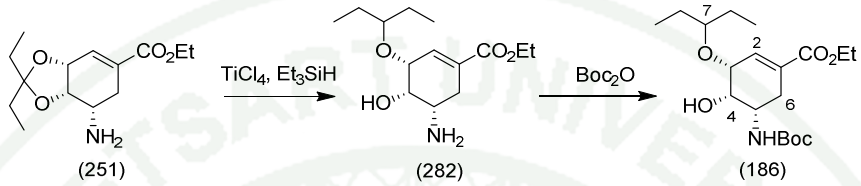
FTIR (film), ν_{max}, cm^{-1}: 3364, 3299 (NH), 2974, 2940, 2881 (CH), 1718 (C=O), 1651 (C=C)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.66 (t, *J* = 3.2 Hz, 1H, H-2), 4.68-4.63 (m, 1H, H-3), 4.26 (dd, *J* = 2.4, 5.6 Hz, 1H, H-4), 4.14 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 2.93 (ddd, *J* = 10.7, 5.2, 2.4 Hz, 1H, H-5), 2.51 (dd, *J* = 5.2, 16.3 Hz, 1H, H-6), 2.13 (ddt, *J* = 16.3, 10.7, 2.4 Hz, 1H, H-6), 1.59 (dq, *J* = 7.5, 3.2 Hz, 2H, CH_2CH_3), 1.50 (q, *J* = 7.5 Hz, 2H, CH_2CH_3), 1.23 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 0.85 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 0.75 (t, *J* = 7.5 Hz, 3H, CH_2CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 166.5 (C=O), 134.9 (C-2), 130.5 (C-1), 113.1 (C), 76.6 (C-3), 73.1 (C-4), 60.8 ($CO_2CH_2CH_3$), 49.3 (C-5), 30.0 (C-6), 29.5 (CH_2CH_3), 28.7 (C-9), 14.1 ($CO_2CH_2CH_3$), 8.4 (CH_2CH_3), 7.9 (CH_2CH_3)

HRMS (ESI$^+$) *m/z* : $C_{14}H_{24}NO_4$ $[M+H]^+$, calcd 270.1705, found 270.1705

Ethyl (3*R*,4*S*,5*S*)-5-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (186)



To a solution of the amino pentylidine ketal (251) (2.00g, 7.12 mmol), in CH_2Cl_2 (20mL) at -78 ^oC was added Et_3SiH (1.5 mL, 9.26 mmol). A solution of $TiCl_4$ (0.97 mL, 8.54 mmol) was added dropwise. The reaction mixture was warmed to -10 ^oC and stirred at this temperature for 6 h. $TiCl_4$ (0.23mL, 2.14 mmol) was added and stirred for 1 h. 10%NH_4OH (5mL) was added and the suspension was filtered. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x50mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude amino alcohol (282) was used in the next step without further purification.

To a solution of crude amino alcohol (282) (7.12 mmol) in MeOH (30mL) was added Boc_2O (2.33g, 10.7mmol) and stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 1:4) to give *N*-Boc amino alcohol (186) as a light yellow solid (2.72 g, 66%, 2 steps).

FTIR (film), ν_{max}, cm^{-1}: 3546 (NH), 3357 (OH), 2973(CH), 1714 (C=O), 1505 (C=C)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.65 (s, 1H, H-2), 5.16 (d, *J* = 8.1 Hz, 1H, NH), 4.18 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.14-4.10 (br, 1H, H-3), 4.03-3.99 (br, 1H, H-4), 3.85 (q, *J* = 5.7 Hz, 1H, H-5), 3.40 (p, *J* = 5.7 Hz, 1H, H-7), 2.57 (dd, *J* =

5.7, 11.8 Hz, 1H, H-6), 2.51 (br s, 1H, OH), 2.36-2.25 (m, 1H, H-6), 1.60-1.49 (m, 4H, 2x(CH_2CH_3)), 1.43 (s, 9H, C(CH_3)$_3$), 1.27 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 0.91 (t, J = 7.4 Hz, 6H, 2x(CH_2CH_3))

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 166.1 (C=O), 155.4 (C=O), 135.6 (C-2), 130.5 (C-1), 81.6 (C-7), 79.5 ($\underline{C}(CH_3)_3$), 73.7 ($CO_2CH_2CH_3$), 68.0 (C-4), 60.8 (C-3), 48.6 (C-5), 28.3(C($\underline{CH_3}$)$_3$), 27.0 (C-6), 26.2 (CH_2CH_3), 26.0 (CH_2CH_3), 14.1 ($CO_2CH_2CH_3$), 9.6 (CH_2CH_3), 9.3 (CH_2CH_3)

HRMS (ESI$^+$) *m/z* : $C_{19}H_{33}NO_6Na$ [M+Na], calcd 394.2206, Found 394.2206

1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (629)

D-Glucose (18) (629)

To a suspension of D-glucose monohydrate (18) (1.00 g, 5.05 mmol) in acetone (10mL) was added trimethyl orthoformate (1.33 mL, 12.12 mmol) followed by solution of benzenesulfonic acid (94mg, 0.51 mmol) in acetone (1mL). The reaction mixture was stirred at room temperature under nitrogen atmosphere for 6 h and neutralized with triethylamine (0.85ml, 0.61mmol). The solution was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.The crude product was crystallized in hexane to give the desired product (629) (1.06 g, 80%) as a white needle, m.p.107-108 ºC (lit. m.p. 109-110 ºC; Ferreira *et al*, 2010), $[\alpha]_D^{25}$ -12.1 (*c* 0.43, CH_2Cl_2) (lit. $[\alpha]_D^{22}$ -12.7 ($CHCl_3$); Collins , 1965).

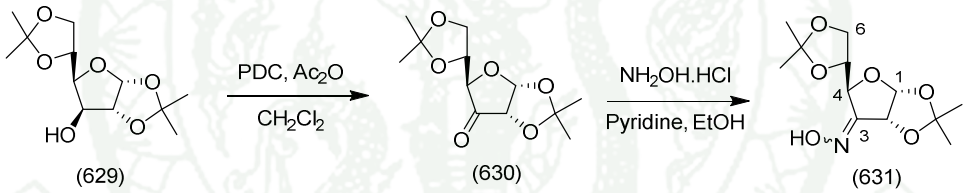
FTIR (film), ν_{max}, cm^{-1}: 3431 (OH), 2985, 2951, 2872 (CH)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.89 (d, *J* = 3.6 Hz, 1H, H-1), 4.48 (d, *J* = 3.6 Hz, 1H, H-2), 4.26 (d, *J* = 2.8 Hz, 1H, H-5), 4.30 (ddd, *J* = 5.3, 6.1, 7.8 Hz, H-3), 4.12 (dd, *J* = 6.1, 8.6 Hz, 1H, H-6), 4.02 (dd, *J* = 2.8, 7.8 Hz, 1H, H-4). 3.95 (dd, *J* = 5.3, 8.6 Hz, 1H, H-6), 2.77 (d, *J* = 3.9 Hz, 1H, OH), 1.49 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 111.8 (C), 109.6 (C), 105.2 (C-1), 85.1 (C-2), 81.2 (C-3), 75.0 (C-4), 73.3 (C-5), 67.6 (C-6), 26.8 (CH_3), 26.7 (CH_3), 26.1 (CH_3), 25.1 (CH_3)

HRMS (ESI^+) *m/z* : $C_{12}H_{20}O_6Na$ [M+Na], calcd 283.1158, found 283.1158

3-Hydroxylamine-l,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (631)



To a mixture of pyridinium dichromate (3.34 g, 11.53 mmol) and acetic anhydride (5.45 mL, 57.69 mmol) in dry CH_2Cl_2 (90 mL) was added solution of alcohol (629) (5.00 g, 19.23 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was heated under reflux for 3 h and cooled to room temperature. After the solvent was removed under vacuum the residue was diluted with EtOAc. The precipitate was filtered through a shot silica gel column and eluted with ethyl acetate. The filtrate was concentrated under reduced pressure to give the crude ketone (630) as a colourless amorphous solid which was used in the next step without further purification.

To a solution of ketone (630) (19.23 mmol) in anhydrous pyridine (20 mL) and ethanol (20 mL) was added hydroxylamine hydrochloride (5.79 g, 57.69mmol) and stirred at 60 ^{o}C for 6 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in EtOAc. The organic layer was washed with

water, and the aqueous layer was extracted with EtOAc (3×100mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residual was purified by flash column chromatography (silica gel, hexane: EtOAc 3:1) to afford the corresponding oxime (631) (3.29 g, 63%) as a mixture of *syn/anti* isomers. Recrystallization with hexane/CH_2Cl_2 gave a colourless plate, m.p. 106-107 ºC (lit. m.p. 106–109 ºC; Wightman *et al*., 2000), $[\alpha]_D^{23}$ +186.9 (*c* 2.20, $CHCl_3$) (lit. $[\alpha]_D^{25}$ +193.8- (*c* 0.98, $CHCl_3$; Wightman *et al*, 2000).

FTIR (film), ν_{max}, cm^{-1}: 3283 (OH), 2992, 2939, 2895 (CH)

HRMS (ESI^+) *m/z* : $C_{12}H_{19}NO_6Na$ [M+Na], calcd 296.1110, found 296.1102

***Z*-isomer of (631) : Major isomer**

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.96 (s, 1H, OH), 5.93 (d, *J* = 4.5 Hz, 1H, H-1), 5.25 (dd, *J* = 1.3, 4.5 Hz, 1H, H-2), 4.73 (dd, *J* = 1.3, 4.8 Hz, 1H, H-4), 4.27 (dt, *J* = 4.8, 6.4 Hz, 1H, H-5), 4.05-3.93 (m, 2H, H-6), 1.48 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.32 (s, 3H, CH_3)

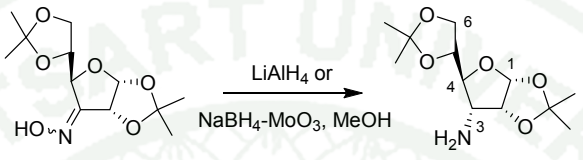
^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 157.6 (C-3), 113.7 (C), 110.2 (C), 104.7 (C-1), 77.3 (CH), 76.6 (CH), 74.2 (CH), 65.4 (C-6), 27.5 (CH_3), 27.2 (CH_3), 26.2 (CH_3), 25.1 (CH_3)

***E*-isomer of (631) : Minor isomer**

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.95 (s,1H, OH), 5.98 (d, *J* = 4.6 Hz,1H, H-1), 5.22 (dd, *J* = 1.4, 2.2 Hz, 1H, H-4), 4.99 (dd, *J* = 4.6, 1.3 Hz, 1H, H-2), 4.47 (dt, *J* = 2.2, 6.8 Hz, 1H, H-5), 4.05-3.93 (m, 1H, H-6), 1.41 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.30 (s, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 158.2 (C-3), 114.0 (C), 109.8 (C), 104.5 (C-1), 78.9 (C-2), 77.6 (C-4), 77.3 (C-5), 64.8 (C-6), 27.5 (CH_3), 27.3 (CH_3), 26.0 (CH_3), 25.2 (CH_3)

3-Amino-3-deoxy-l,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (632)



Procedure A:

To an ice-cooled solution of oxime (631) (80 mg, 0.29 mmol) in dry THF (1.6 mL) was added lithium aluminum hydride (33.4 mg, 0.88 mmol). The mixture was refluxed at 60 °C under nitrogen atmosphere for 30 min. The reaction was quenched with saturated aq. $NaHCO_3$ at 0°C and extracted with Et_2O (3x5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to affored amine (632) (30 mg, 39 %) as a colourless amorphous. Recrystallization with hexane/ CH_2Cl_2 gave a light yellow cubic of the amino furanose, m.p.86-88 ºC (lit. m.p. 88-90 ºC; Onodera *et al*., 1968), $[\alpha]_D^{27}$ +43.0 (*c* 0.85, $CHCl_3$) (lit. $[\alpha]_D^{28}$ +41.3 (*c* 1.2, $CHCl_3$); Onodera *et al*., 1968)

FTIR (film), ν_{max}, cm^{-1}: 3395, 3322 (NH), 2991, 2946, 2862 (CH)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.57 (d, *J* = 3.7 Hz, 1H, H-1), 4.37 (dd, *J* = 3.7, 4.8 Hz, 1H, H-2), 3.95 (q, *J* = 5.7 Hz, 2H, H-6), 3.90 (dd, *J* = 6.3, 8.3 Hz, 1H, H-5), 3.82 (dd, *J* = 5.7, 8.3 Hz, 1H, H-6), 3.44 (dd, *J* = 6.3, 9.1 Hz, 1H, H-4), 2.95 (dd, *J* = 4.8, 9.1 Hz, 1H, H-3), 1.37 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.16 (s, 3H, CH_3)

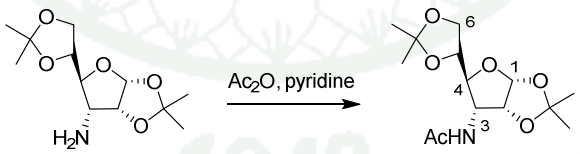
^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 111.7 (C), 109.6 (C), 103.7 (C-1), 81.1 (C-4), 80.8 (C-2), 76.7 (C-5), 66.6 (C-6), 57.8 (C-3), 26.3 (CH_3), 26.2 (CH_3), 25.9 (CH_3), 24.8 (CH_3)

HRMS (ESI^+) *m/z* : $C_{12}H_{21}NO_5Na$ [M+Na], calcd 282.1317, found 282.1325

Procedure B:

To a mixture of oxime (631) (2.03 g, 7.44 mmol) and MoO_3 (1.48 g, 10.26 mmol) in MeOH (70 mL) was added $NaBH_4$ (1.40 g, 37.18 mmol) portionwise. An exothermic reaction occurred with vigorous gas. The reaction mixture was stirred at room temperature for 30 min or when reaction was completed (monitor by TLC). Saturated aq.NaCl was added, the precipitate was filtered off. The filtrate was extracted with EtOAc (3x100mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, MeOH:CH_2Cl_2, 3:97) to give the amino furanose (632) as a light yellow amorphous solid (1.48 g, 77%).

3-Acetamido-3-deoxy-l,2:5,6-di-*O*-isopropylidene-α- D-allofuranose (633)



(632) (633)

To a solution of amino furanose (632) (2.22 g, 8.57 mmol) in pyridine (9.7 mL) was added acetic anhydride (5.0 mL). The reaction mixture was stirred at room temperature for 3 h and quenched with MeOH (5.0 mL). The trace Ac_2O was removed by coevaporated with toluene (30 mL). The crude product was purified by flash column chromatography (silica gel, MeOH:CH_2Cl_2, 2:98) to give acetamido furanose (633) as a white solid (2.20 g, 96 %). Recrystallization with hexane/CH_2Cl_2 gave a white needle of the acetamido furanose, m.p.125-126 ºC (lit. mp128-129 ºC; Onodera

et al., 1968), $[\alpha]_D^{27}$ +58.2 (*c* 7.0, $CHCl_3$) (lit. $[\alpha]_D^{28}$ +71.8 (*c* 0.8, $CHCl_3$); Onodera *et al*., 1968.)

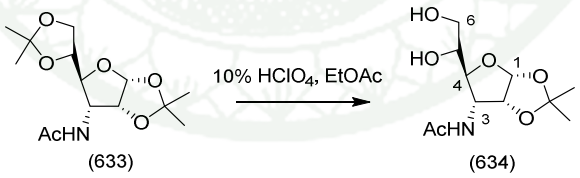
FTIR (film), ν_{max}, cm^{-1}: 3333 (NH), 2989, 2949, 2896 (CH), 1675 (C=O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.84 (d, *J* = 8.4 Hz,1H, NH), 5.78 (d, *J* = 3.8 Hz,1H, H-1), 4.56 (dd, *J* = 3.8, 4.6 Hz,1H, H-2), 4.19-4.12 (m, 2H, H-3, H-5), 4.04 (dd, *J* = 6.6, 8.2 Hz, 1H, H-6), 3.89 (dd, *J* = 6.2, 8.2 Hz, 1H, H-6), 3.84 (dd, *J* = 4.3, 9.6 Hz, 1H, H-4), 1.98 (s, 3H, C(O)*CH$_3$*), 1.51 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.29 (s, 6H, 2xCH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 169.8 (C=O), 111.1 (C), 109.4 (C), 104.0 (C-1), 78.8 (C-4), 78.4 (C-2), 75.4 (C-5), 64.9 (C-6), 53.1 (C-3), 26.4 (CH_3), 26.2 (CH_3), 26.1 (2) (2xCH_3), 23.0 (C(O)*CH$_3$*)

HRMS (ESI^+) *m/z* : $C_{14}H_{23}NO_6Na$ [M+Na], calcd 324.1423, found 324.1425

3-Acetamido-3-deoxy-1,2-*O*-isopropylidene-α- D-allofuranose (634)



(633) (634)

To a solution of acetamido furanose (633) (93 mg, 0.311 mmol) in EtOAc (5 mL) was added 10% $HClO_4$ (0.1 mL). The reaction mixture was stirred at room temperature for 20 min and neutralized with NH_4OH, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, MeOH:CH_2Cl_2, 5:95) to give acetamido-diol (634) as a white solid (76 mg, 89 %). Recrystallization with EtOAc gave a white cubic of the acetamido-diol, m.p.156-158 ºC (lit. 154-155; Ando *et al*., 1970), $[\alpha]_D^{28}$ +23.0 (*c* 0.60, MeOH) (lit. $[\alpha]_D^{23}$ +158.3 (*c* 1.08, MeOH); Ando *et al*., 1970).

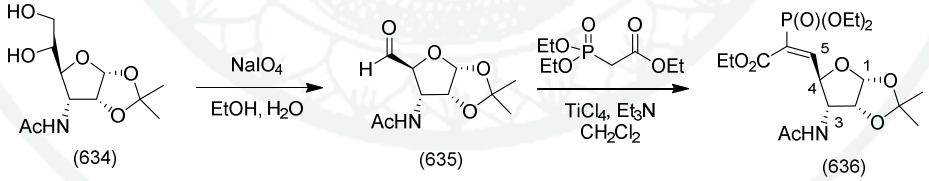
FTIR (film), ν_{max}, cm^{-1}: 3526 (NH), 3319 (OH), 2980, 2915, 2887 (CH), 1653 (C=O)

^{1}H-NMR ($CDCl_3$+CD_3OD, 400 MHz) δ: 5.81 (d, *J* = 3.7 Hz, 1H, H-1), 4.66 (dd, *J* = 3.82, 1.08 Hz, 1H, H-2), 4.30 (td, *J* = 1.0, 5.0, 9.3 Hz, 1H, H-3), 3.91 (dd, *J* = 5.0, 9.3 Hz, 1H, H-4), 3.79 (dd, *J* = 4.8, 10.9 Hz, 1H, H-5), 3.65 (dd, *J* = 4.2, 11.5 Hz, 1H, H-6), 3.57 (dd, *J* = 6.6, 11.5 Hz, 1H, H-6), 2.03 (s, 3H, C(O)*CH*$_3$), 1.44 (s, 3H, CH_3), 1.27 (s, 3H, CH_3)

^{13}C-NMR ($CDCl_3$+CD_3OD, 100 MHz) δ: 172.3 (C=O), 122.8 (C), 104.2 (C-1), 79.5 (C-2), 79.1 (C-4), 72.3 (C-5), 63.1 (C-6), 53.2 (C-3), 26. 5 (CH_3), 26.3 (CH_3), 22.6 (C(O)*CH*$_3$)

HRMS (ESI^+) *m/z* : $C_{11}H_{19}NO_6Na$ [M+Na], calcd 284.1110, found 284.1111

Ethyl (2*E*)-3-[(3a*R*,5*R*,6*R*,6a*R*)-6-acetamido-2,2-dimethyltetrahydrofuro[2,3-*d*] [1,3] dioxol -5-yl]-2-(diethoxyphosphoryl)acrylate (636)



To a solution of the diol (634) (420 mg, 1.54 mmol) in EtOH (15 mL) at 0^{o}C was slowly added a solution of $NaIO_4$ (395 mg, 1.85 mmol) in water (5 mL). The reaction mixture was further stirred at 0^{o}C for 30 min and diluted with EtOH (10 mL) and filtered to remove precipitate. The excess $NaIO_4$ was destroyed by addition of ethylene glycol (3 mL), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, MeOH:CH_2Cl_2, 3:97) to give the aldehyde (635) (300 mg, 80%) as the colourless oil which was immediately used in the next step.

To a solution of triethyl phosphonoacetate (0.40 mL, 1.85 mmol) in CH_2Cl_2 (6 mL) at 0°C was added $TiCl_4$ (0.40 mL, 3.69 mmol) followed by a solution of Et_3N (0.70 mL, 4.92 mmol) in CH_2Cl_2 (6 mL) dropwise. The reaction mixture was further stirred at 0°C for 30 min then a solution of the aldehyde (635) (300 mg, 1.23 mmol) in CH_2Cl_2 (6 mL) was added to the reaction mixture and further stirred for 2 h at 0 °C. Water (30 mL) was added and the solution was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were washed with saturated aq.$NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, MeOH:CH_2Cl_2, 3:97) to give the acrylate (636) (320 mg, 77 %) as a colourless oil, $[\alpha]_D^{25}$ +6.53 (*c* 1.92, $CHCl_3$).

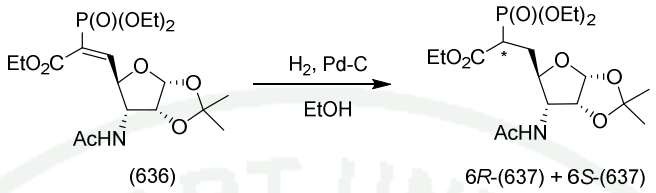
FTIR (film), ν_{max}, cm^{-1}: 3446(NH), 2986 (CH), 1723, 1663 (C=O), 1019 (P=O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.95 (dd, *J* = 8.1, 22.4 Hz, 1H, H-5), 6.41 (d, *J* = 7.6 Hz, 1H, NH), 5.80 (d, *J* = 3.6 Hz,1H, H-1), 5.02 (ddd, *J* = 2.5, 8.2, 10.4 Hz, 1H, H-4), 4.70 (t, *J* = 3.6 Hz, 1H, H-2), 4.27-4.18 (m, 2H, $CO_2CH_2CH_3$), 4.17-3.98 (m, 5H, H-3+P(O)(OCH_2CH_3)$_2$), 1.92 (s, 3H, C(O)CH_3), 1.50 (s, 3H, CH_3), 1.35-1.28 (m, 12H, CH_3)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 170.1 (C=O), 164.6, 164.4 (C=O, J_{C-P} = 12Hz), 153.3, 153.2 (C-5, J_{C-P} = 6Hz), 129.1, 126.7 (C-6, J_{C-P} = 160 Hz), 112.5 (C), 104.3 (C-1), 78.4 (C-2), 74.8, 74.6 (C-4, J_{C-P} = 18 Hz), 62.7, 62.5 ($CO_2CH_2CH_3$, J_{C-P} = 11 Hz), 62.6 (P(O)OCH_2CH_3), 61. (P(O)OCH_2CH_3), 56.4 (C-3), 26.3 (CH_3), 26.0 (CH_3), 22.7 ($CH_3C(O)$), 16.0 (CH_3), 15.9 (CH_3),13.8 (CH_3)

HRMS (ESI^+) *m/z* : $C_{18}H_{30}NNaO_9P$ [M+Na], calcd 458.1556, found 458.1241

Ethyl 3-[(3a*R*, 5*R*, 6*R*, 6a*R*)-6-acetamido-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3] dioxol-5-yl]-2- (diethoxyphosphoryl)propanoate (637)



(636) 6*R*-(637) + 6*S*-(637)

To a solution of the acrylate (636) (300 mg) in EtOH (50 mL) was added palladium on activated carbon (30 mg, 10% w/w) and the resulting suspension was stirred under a hydrogen atmosphere for 1 h (a balloon of hydrogen gas was equipped to the reaction flask, ca. 1 atm). The mixture was then filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, MeOH:CH_2Cl_2, 3:97) to give two inseparable of diastereomer of propanoate (637) (270 mg,89%) as a colourless oil.

FTIR (film), ν_{max}, cm^{-1}: 3252 (NH), 2985, 2937 (CH), 1731, 1712 (C=O), 1054, 1023 (P-O)

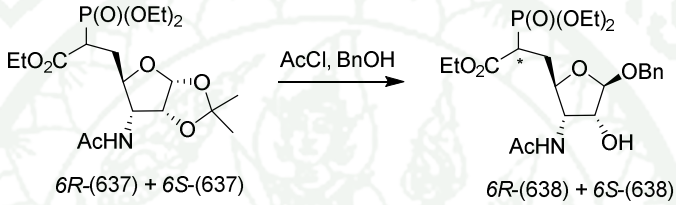
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.89 (d, 1H, *J* = 9.6 Hz, NH), 5.80 (d, 1H, *J* = 8.9 Hz, NH), 5.74 (d, 1H, *J* = 4.0 Hz, H-1), 5.72 (d, 1H, *J* = 4.0 Hz, H-1), 4.55-4.50 (m, 2H, 2xH-2), 4.18-4.00 (m, 14H, H-3, 2x$CO_2CH_2CH_3$, 4xP(O)OCH_2CH_3), 3.84 (ddd, 1H, *J* = 5.0, 9.5, 8.7 Hz, H-4), 3.68 (dt, 1H, *J* = 9.5, 2.8 Hz, H-4), 3.23(ddd, 1H, *J* = 3.2, 11.8, 23.8 Hz, H-6), 3.08 (ddd, 1H, *J* = 6.4, 7.7, 22.5 Hz, H-6), 2.29 (m, 1H, H-5), 2.16 (m, 2H, 2xH-5), 1.97 (s, 3H, C(O)CH_3), 1.96 (s, 3H, C(O)CH_3), 1.93-192 (m, 1H, H-5), 1.56-1.18 (m, 30H, 2x$CO_2CH_2CH_3$, 4xP(O)OCH_2CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 170(2) (2xCO), 168.9 (2) (CO, J_{C-P} = 6 Hz), 168.8 (2) (CO, J_{C-P} = 5 Hz), 112.3 (C), 112.2 (C), 103.9 (2) (2x C-1), 79.1 (C-2), 79.0 (C-2), 77.7, 77.6 (C-2, J_{C-P} = 11 Hz), 76.7, 76.5 (C-2, J_{C-P} = 11 Hz), 62.9-62.7 (6) ($CO_2CH_2CH_3$, P(O)OCH_2CH_3), 61.4 (2) ($CO_2CH_2CH_3$, P(O)OCH_2CH_3), 55.6 (C-3), 55.2 (C-3), 43.3, 42.0 (C-6, J_{C-P} = 130 Hz), 41.5, 41.2 (C-6, J_{C-P} = 131 Hz), 29.9 (2)

(C-5, $J_{C\text{-}P}$ = 5 Hz), 29.4, 29.3 (C-5, $J_{C\text{-}P}$ = 4 Hz), 26.5 (2) (CH_3), 26.3 (2) (CH_3), 23.3 (2xCH_3CO), 16.4-16.2 (4) (2xCH_3), 14.1 (CH_3), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{18}H_{32}NO_9NaP$ [M+Na], calcd 460.1712, found 460.1713

Ethyl 3-[(2*R*, 3*S*, 4*R*, 5*S*)-3-acetamido-5-(benzyloxy)-4-hydroxytetrahydrofuran-2-yl]-2-(diethoxyphosphoryl)propanoate (638)



6R-(637) + *6S*-(637) *6R*-(638) + *6S*-(638)

To a solution of acetamido furopropanoate (637) (427 mg, 1.27 mmol) in BnOH (2.5 mL) at 0ºC was slowly added acetyl chloride (0.1 mL, 1.52 mmol). The reaction mixture was stirred at room temperature for 3 h, and then a NH_4OH (2 mL) was added to neutralize the reaction. The reaction mixture was evaporated and the residue was purified by flash column chromatography (silica gel, gradient hexane:EtOAc, 2:1 and then MeOH:CH_2Cl_2, 5:95) to give inseparable of diastereomer of the product (638) (309 mg, 68%) as a colourless oil.

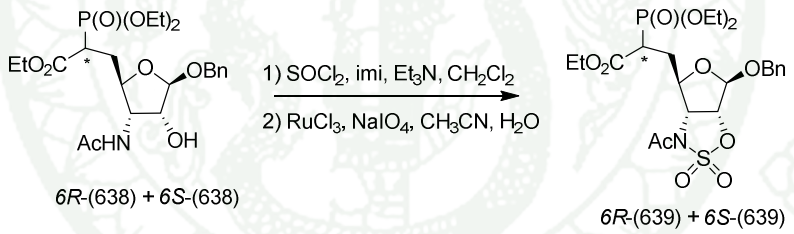
FTIR (film), ν_{max}, cm^{-1}: 3418 (NH), 2984, 2935 (CH), 1732 (C=O), 1661, 1651 (C=C), 1028 (P-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.34–7.19 (m, 10H, ArH), 6.77 (d, 1H, *J* = 8.5 Hz, NH), 6.66 (d, *J* = 8.0 Hz, 1H, NH), 4.94 (s, 1H, H-1), 4.91 (s, 1H, H-1), 4.69 (d, 1H, *J* = 11.9 Hz, H-2), 4.69 (d, 1H. *J* = 11.6 Hz, H-2), 4.45-4.35 (m, 3H, H-3, CH_2Ph), 4.28–4.07 (m, 15H, H-3, CH_2Ph, 2x$CO_2CH_2CH_3$, 4xP(O)OCH_2CH_3), 3.99–3.98 (m, 2H, 2xH-4), 3.37 (ddd, 1H, *J* = 3.8, 14.5, 19.7 Hz, H-6), 3.22 (dt, *J* = 6.4, 22.7 Hz, 1H, H-6), 2.48-1.95 (m, 4H, 2xH-5), 1.97 (s, 3H, C(O)CH_3), 1.95 (s, 3H, C(O)CH_3), 1.33–1.19 (m, 18H, 2x$CO_2CH_2CH_3$, 4xP(O)OCH_2CH_3))

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 170.9 (CO), 170.8 (CO), 168.7, 168.6 (CO, $J_{C\text{-}P}$ = 5 Hz), 168.5, 168.4 (CO, $J_{C\text{-}P}$ = 5 Hz), 137.2 (2) (2xAr), 128.2 (ArH), 128.1 (2xArH), 128.0 (2xArH), 127.7 (ArH), 127.6 (2xArH), 127.5 (ArH), 127.4 (ArH), 106.4 (C-1), 106.3 (C-1), 80.7, 80.5 (C-4, $J_{C\text{-}P}$ = 13 Hz), 79.3, 79.1 (C-4, $J_{C\text{-}P}$ = 14 Hz), 74.5 (2xC-2), 68.5 (CH_2Ph), 68.4 (CH_2Ph), 63.0-62.5 (4xOCH_2), 61.4 (OCH_2), 61.2 (OCH_2), 55.4 (C-3), 55.1 (C-3), 43.3, 41.6 (C-6, $J_{C\text{-}P}$ = 130 Hz), 43.1, 41.3 (C-6, $J_{C\text{-}P}$ = 130 Hz), 32.8 (2xC-5), 22.7 (2x(CO)*CH_3*), 16.0 (2xCH_3),15.9 (2xCH_3), 13.7 (2xCH_3)

HRMS (ESI^+) *m/z* : $C_{22}H_{34}NO_9NaP$ [M+Na], calcd 510.1869, found 510.1869

Ethyl 3-[(3a*R*,4*R*,6a*R*)-3-acetyl-6-(benzyloxy)-2,2-dioxidotetrahydro-3*H*-furo[3,4-*d*][1,2,3]oxathiazol-4-yl]-2-(diethoxyphosphoryl)propanoate (639)



To a solution of the acetamido hydroxyl propanoate (638) (254 mg, 0.71 mmol), Et_3N (0.30 mL, 2.12 mmol) and imidazole (192 mg, 2.82 mmol) in dry CH_2Cl_2 (9 mL) at 0 ^oC was added a solution of $SOCl_2$ (0.06 mL, 0.85 mmol) in dry CH_2Cl_2 (4 mL) dropwise over 10 min. The mixture was stirred at 0 ^oC for 1 h and then poured into water (10 mL) and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the cyclic sulfamidite which was used in next step without purification.

To a solution of the cyclic sulfamidite (0.71 mmol) in MeCN (7 mL) at 0 ^oC was added a solution of $RuCl_3$ (2 mg, 0.01 mol %) and $NaIO_4$ (226 mg, 1.06 mmol) in

water (5 mL) and stirred at 0 ^{o}C for 1 h. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were washed with saturated aq.$NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, MeOH:CH_2Cl_2, 2:98) to give the cyclic sulfamidate (639) (168 mg, 43%) as a colourless oil.

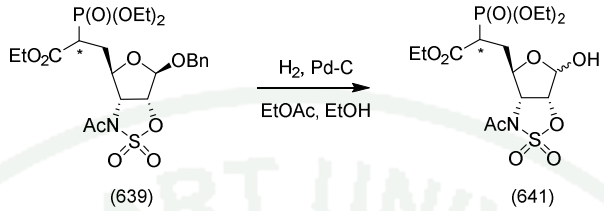
FTIR (film), ν_{max}, cm^{-1}: 2983, 2930 (CH), 1731 (C=O), 1376, 1191 (SO_2), 1059, 1025 (P-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.39-7.22 (m, 10H, ArH), 5.33 (s, 2H, 2xH-1), 5.14 (d, *J* = 6.3 Hz, 2H, 2xH-2), 4.82-4.74 (m, 4H, 2xH-3, CH_2Ph), 4.50 (m, 2H, CH_2Ph), 4.43 (ddd, *J* =2.7, 6.0, 8.5 Hz, 1H, H-4), 4.31-4.05 (m, 13H, H-4, 2xCO_2*CH_2*CH_3, 4xP(O)O*CH_2*CH_3), 3.41-3.29 (m, 2H, 2xH-6), 2.72-2.13 (m, 4H, 2x H-5), 2.43 (s, 6H, 2xC(O)*CH_3*), 1.35-1.23 (m, 18H, 2xCO_2CH_2*CH_3*, 4xP(O) OCH_2*CH_3*)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 168.7 (CO), 168.0 (CO), 166.5 (CO), 166.5 (CO), 135.8 (Ar), 135.8 (Ar), 128.6 (2) (2xArH), 128.5 (2) (2xArH), 128.3 (ArH), 128.2 (3) (3xArH), 128.1 (2) (2xArH), 103.7 (2) ((2xC-1), $J_{C\text{-}P}$ = 8 Hz), 86.0, 85.9 (C-4, $J_{C\text{-}P}$ = 12 Hz), 85.2, 85.1 (C-4, $J_{C\text{-}P}$ = 12 Hz), 84.3, 84.1 (C-2, $J_{C\text{-}P}$ = 14 Hz), 69.9 (CH_2Ph), 69.8 (CH_2Ph), 63.3 (C-3), 63.1 (C-3), 63.0-62.8 (CO_2*CH_2*CH_3, P(O)O*CH_2*CH_3), 61.7 (CO_2*CH_2*CH_3, P(O)O*CH_2*CH_3), 61. 6 (CO_2*CH_2*CH_3, P(O)O*CH_2*CH_3), 43.0, 41.7 (C-6, $J_{C\text{-}P}$ = 130 Hz), 42.8, 41.5 (C-6, $J_{C\text{-}P}$ = 130 Hz), 33.1, (C-5), 32.8 (C-5), 21.7 (2x$(CO)CH_3$), 16.3 (2) (4xCH_3), 16.2 (2xCH_3)

HRMS (ESI^{+}) *m/z* : $C_{22}H_{32}NO_{11}NaPS$ [M+Na], calcd 572.1331, found 572.1332

Ethyl 3-[(3a*R*,4*R*,6a*R*)-3-acetyl-6-hydroxy-2,2-dioxidotetrahydro-3*H*-furo[3,4-*d*][1,2,3]oxathiazol-4-yl]-2-(diethoxyphosphoryl)propanoate (641)



(639) (641)

To a suspension of palladium on activated carbon (20 mg, 40% w/w) in EtOH (2 mL) was stirred under a hydrogen atmosphere for 1 h (a balloon of hydrogen gas was equipped to the reaction flask, ca. 1 atm). A solution of (639) (50 mg) in EtOAc (2 mL) was added to the reaction mixture and stirred under a hydrogen atmosphere for 6 h. The mixture was then filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, MeOH:CH_2Cl_2, 3:97) to give an inseparable of diastereomer of the product (641) (30 mg,72%) as a colourless oil.

FTIR (film), ν_{max}, cm^{-1}: 3252 (OH), 2985, 2937 (CH), 1731, 1712 (C=O), 1374, 1191 (SO_2), 1054, 1023 (P-O)

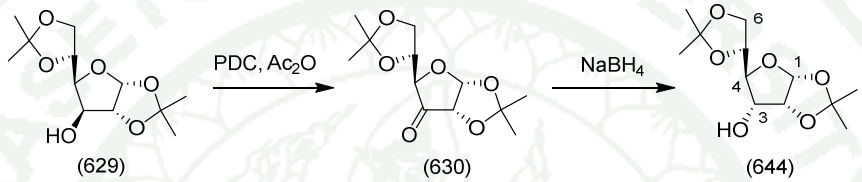
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.62 (s, 1H, H-1), 5,57 (s, 1H, H-1), 5.11 (d, *J* = 4.2 Hz, 1H, H-2), 5.10 (d, *J* = 4.2 Hz, 1H, H-2), 4.77 (quint, *J* = 3.1 Hz, 2H,2xH-3), 4.34-4.27 (m, 1H, H-4), 4.26-4.08 (m, 13H, H-4, $CO_2CH_2CH_3$, P(O)OCH_2CH_3), 3.36 (ddd, *J* = 3.7, 9.5, 24.8 Hz, 1H, H-6), 3.20 (ddd, *J* = 4.6, 9.3, 24.2 Hz, 1H, H-6), 2.67-2.27 (m, 4H, 2xH-5), 4.45 (s, 3H, C(O)CH_3), 4.44 (s, 3H, C(O)CH_3), 1.36-1.25 (m, 18H, $CO_2CH_2CH_3$, P(O)OCH_2CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 168.0 (CO), 167.9 (CO), 166.7 (CO), 166.6 (CO), 99.8 (2xC-1), 86.1, 85.91 (C-4, $J_{C\text{-}P}$ = 13 Hz), 84.8 (C-2), 84.5 (C-2), 84.4, 84.2 (C-4, $J_{C\text{-}P}$ = 13 Hz), 63.7-63.1 ($CO_2CH_2CH_3$, P(O)OCH_2CH_3), 62.1 ($CO_2CH_2CH_3$, P(O)OCH_2CH_3), 61.6 ($CO_2CH_2CH_3$, P(O)OCH_2CH_3), 42.4, 40.7 (2xC-6, $J_{C\text{-}P}$ = 130

Hz), 33.2, 33.1 (C-5, $J_{C\text{-}P}$ = 3 Hz), 32.9, 32.8 (C-5, $J_{C\text{-}P}$ = 3 Hz), 21.7 (2xCH_3CO), 16.2(3) (3xCH_3), 16.1 (CH_3), 13.9 (2) (2xCH_3)

HRMS (ESI^+) *m/z* : $C_{15}H_{26}NO_{11}NaPS$ [M+Na], calcd 482.0862, found 482.0865

1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranose (644)



To a mixture of pyridinium dichromate (9.04 g, 24.04 mmol) and acetic anhydride (9.09 mL, 96.15 mmol) in CH_2Cl_2 (90 mL) was added a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (629) (5.00 g, 19.23 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was heated under reflux for 3 h and cooled to room temperature. The reaction mixture was diluted with ethyl acetate. The precipitate was filtered through a shot silica gel column and eluted with ethyl acetate. The filtrate was concentrated under reduced pressure to give the crude ketone (630) as a colourless amorphous solid which was used in the next step without further purification.

To a solution of ketone (630) (4.37 g, 16.94 mmol) in 56% EtOH (20 mL) was added dropwise a solution of $NaBH_4$ (807 m g, 21.34 mmol) in H_2O (22 mL). After 2 h, the solvent was removed by evaporation. The residue was purified by Flash column chromatography (silica gel, hexane:EtOAc, 2:1) to give the α-allofuranose (644) (3.01 g, 68%) as a colourless amorphous which was recrystallized from hexane to give a colourless plate of the α-allofuranose, m.p.72-73 ºC (lit. 75-77 ºC; Ferreira *et al*, 2010), $[\alpha]_D^{25}$ +27.7 (*c* 0.52, MeOH) (lit. $[\alpha]_D^{22}$ +38 ($CHCl_3$); Collins, 1965).

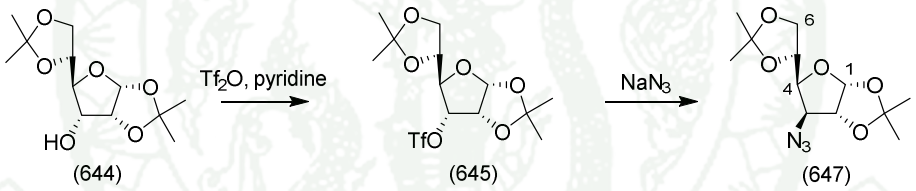
FTIR (film), ν_{max}, cm^{-1}: 3488 (O-H), 2988, 2935, 2896 (C-H), 1216, 1067, 1018 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.76 (d, *J* = 3.8 Hz, 1H, H-1), 4.56 (dd, *J* = 3.8, 5.2 Hz, 1H, H-2), 4.25 (td, *J* = 4.6, 6.6 Hz, 1H, H-5), 4.02 (dd, *J* = 6.6, 8.4 Hz, 1H, H-6), 3.99 (dd, *J* = 5.2, 8.4 Hz, 1H, H-3), 3.96 (dd, *J* = 6.6, 8.4 Hz, 1H, H-6), 3.77 (dd, *J* = 4.7, 8.4 Hz, 1H, H-4), 2.59 (d, *J* = 8.2 Hz, 1H, OH), 1.56 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.36 (s, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 112.7 (C), 109.7 (C), 103.8 (C-1), 79.6 (C-2), 79.0 (C-5), 75.5 (C-3), 72.4 (C-4), 65.6 (C-6), 26.5 (CH_3), 26.4 (CH_3), 26.2 (CH_3), 25.2 (CH_3)

HRMS (ESI^+) *m/z* : $C_{12}H_{20}O_6Na$ [M+Na], calcd 283.1158, found 283.1156

3-Azido-3-deoxy-1,2:5,6-diisopropylidene-α- D-glucofuranose (647)



Procedure1

To a solution of α-allofuranose (644) (2.90 g, 11.15 mmol) in CH_2Cl_2 (30 mL) at 0 ºC under nitrogen was added pyridine (2.69 mL, 33.45 mmol) followed by trifluoromethane-sulfonic anhydride (2.25 mL, 13.38 mmol). The mixture was stirred for 30 min at 0ºC, water was added to the solution, and the mixture was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the triflate (645) which was used in the next step without purification.

To a solution of the crude triflate (645) (11.15 mmol) in DMF (18 mL) was added sodium azide (3.26 g, 50.17 mmol) stirred at rt for 15 h. Water was added to the solution, and the mixture was extracted with ethyl acetate (3x70 mL). The

combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 8:1) to give the azido furanose (647) (2.70 g, 85%) as a colourless oil, $[\alpha]_D^{25}$ –37.1 (*c* 0.92, CH_2Cl_2) (lit. $[\alpha]_D^{22}$ −36 (*c* 0.65, $CHCl_3$); Manta *et al.*, 2012).

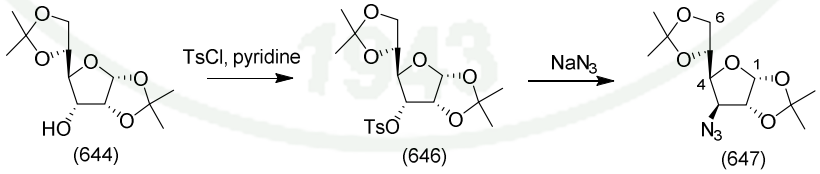
FTIR (film), ν_{max}, cm^{-1}: 2988, 2886 (C-H), 2103(N=N=N), 1216, 1075, 1021 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.83 (d, *J* = 3.6 Hz, 1H, H-1), 4.60 (d, *J* = 3.6 Hz, 1H, H-2), 4.25-4.19 (m, 1H, H-5), 4.12 (ddd, *J* = 1.0, 6.0, 8.7 Hz, 1H, H-6), 4.09-4.05 (m, 2H, H-3, H-6), 3.96 (ddd, *J* = 1.0, 4.8, 8.7 Hz, 1H, H-4), 1.49 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.30 (s, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 112.1 (C), 109.4 (C), 104.9 (CH), 83.2 (CH), 80.3 (CH), 72.9 (CH), 67.5 (CH), 66.2 (CH), 26.7 (CH_3), 26.5 (CH_3), 26.1 (CH_3), 25.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{12}H_{19}N_3O_5Na$ [M+Na], calcd 308.1222, found 308.1219

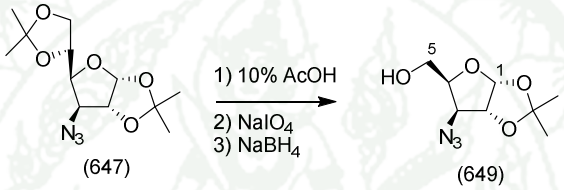
Procedure 2



To a solution of α-allofuranose (644) (3.61 g, 13.88 mmol) in pyridine (36 mL) was added *p*-toluenesulfonyl chloride (7.49 g, 39.27 mmol) and stirred at 65 ºC for 5 h. The reaction mixture was cooled to room temperature, then water was added and the precipitrate of the corresponding tosylate (646) was filtered off.

To a solution of the crude tosylate (646) (13.88 mmol) in DMF (50 mL) was added sodium azide (4.51 g, 69.40 mmol) and then stirred under reflux for 24 h. Water was added to the reaction mixture, and then the mixture was extracted with EtOAc (3x80 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 6:1) to give the azido furanose (647) (2.46 g, 62%) as a colourless oil.

3-Azido-3-deoxy-1,2-*O*-isopropylidene-α- D-xylofuranose (649)



To a solution of the azido furanose (647) (400 mg, 1.40 mmol) in 75% AcOH (4.5 mL) was stirred at 55 °C for 1 h. The reaction mixture was co-evaporated with toluene to remove AcOH. The residue was dissolved in EtOH (4.5 mL) at 0°C then a solution of $NaIO_4$ (360 mg, 1.68 mmol) in H_2O (2.3 mL) was added dropwise to the reaction mixture. After 20 min, $NaBH_4$ (150 mg, 4.20 mmol) was added and the reaction mixture was stirred at 0°C for 1 h. The reaction mixture was filtered, and the filtrate was evaporated. The residue was purified by flash column chromatography (silica gel, hexane: EtOAc, 1:1) to give the azido alcohol (649) (258 mg, 86%) as a colourless oil, $[\alpha]_D^{27}$ –50.0 (*c* 6.5, $CHCl_3$) (lit. $[\alpha]_D^{20}$ –44 (*c* 3.87, $CHCl_3$); Horenstein *et al*., 1997).

FTIR (film), ν_{max}, cm^{-1}: 3540, (O-H), 2987 (C-H), 2100(N=N=N), 1286, 1087, 1018 (C-O)

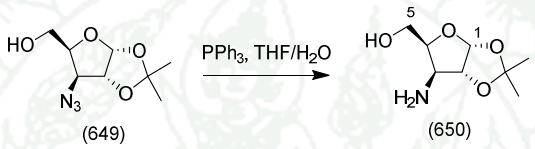
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.89 (d, *J* = 3.7 Hz, 1H, H-1), 4.64 (d, *J* = 3.7 Hz, 1H, H-2), 4.32 (td, *J* = 3.3, 5.6 Hz, 1H, H-4), 3.99 (d, *J* = 3.3 Hz, 1H, H-3), 3.87

(dd, *J* = 6.3, 11.6 Hz, 1H, H-5), 3.78 (dd, *J* = 5.6, 11.6 Hz, 1H, H-5), 1.48 (s, 3H, CH_3), 1.30 (s, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 112.1 (CH), 104.5 (C), 83.4 (CH), 79.5 (CH), 65.8 (CH), 60.3 (CH_2), 26.3 (CH_3), 26.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_8H_{13}N_3O_4Na$ [M+Na], calcd 238.0804, found 238.0805

3-Amino-3-deoxy-1,2-*O*-isopropylidene-α- D-xylofuranose (650)



(649) (650)

To **a** solution of the azido furanose (649) (967 mg, 4.50 mmol) in a mixture of THF:water (4:1) (25 mL) was added triphenylphosphine (2.36 g, 8.96 mmol) and stirred at room temperature for 15 h. Then, the solvent was removed by evaporation and the residue was purified by flash column chromatography (silica gel, MeOH:CH_2Cl_2, 10: 90) to give the amino furanose (650) (841mg, 99%) as a colourless oil, $[\alpha]_D^{25}$ –2.28 (*c* 1.99, $CHCl_3$).

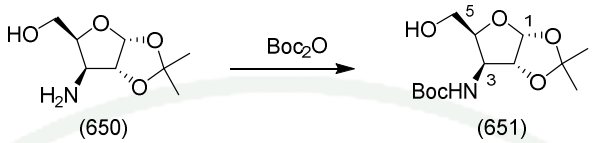
FTIR (film), ν_{max}, cm^{-1}: 3465 (OH), 3373 (NH), 2987, 2937 (C-H), 1217 (C-N), 1071 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.89 (d, *J* = 3.6 Hz, 1H, H-1), 4.36 (d, *J* = 3.6 Hz, 1H, H-2), 4.20 (dt, *J* = 5.3, 3.6 Hz, 1H, H-4), 3.91-3.79 (m, 2H, H-5), 3.45 (d, *J* = 3.6 Hz, 1H, H-3), 1.47 (s, 3H, CH_3), 1.27 (s, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 111.4 (C), 104.2 (C-1), 86.5 (C-2), 79.5 (C-4), 59.9 (C-5), 57.3 (C-3), 26.4 (CH_3), 26.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_8H_{16}NO_4$ $[M+H]^+$, calcd 190.1079, found 190.1081

3-*tert*-Butoxycarbonylamino-3-deoxy-1,2-*O*-isopropylidene-α- D-xylofuranose (651)



(650) (651)

To a solution of the amino furanose (650) (643 mg, 3.42 mmol) in MeOH (7 mL) was added Boc_2O (1.49 mg, 6.84 mmol) and stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 4:1) to give the *N*-Boc amino furanose (651) as a colourless amorphous (816 mg**,** 83%), m.p.155-157 ºC, $[\alpha]_D^{25}$ +5.1 (*c* 3.41, $CHCl_3$).

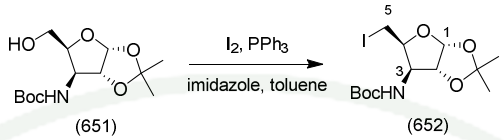
FTIR (film), ν_{max}, cm^{-1}: 3429 (OH), 3297 (NH), 2984 (C-H), 1708 (C=O), 1062 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.84 (d, *J* = 3.7 Hz, 1H, H-1), 5.55 (d, *J* = 6.4 Hz, 1H, NH), 4.54 (d, *J* = 3.7 Hz, 1H, H-2), 4.30-4.24 (m, 1H, H-3), 4.15-4.09 (m, 1H, H-4), 3.85-3.76 (m, 1H, H-5), 1.49 (s, 3H, CH_3), 1.43 (s, 9H, C(CH_3)$_3$), 1.28 (s, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 156.2 (C=O), 112.0 (C), 104.3 (C-1), 84.7 (C-2), 80.3 (C-4), 78.1 (*C*(CH_3)$_3$), 59.9 (C-5), 57.9 (C-3), 28.3 (C(CH_3)$_3$), 26.6 (CH_3), 26.2 (CH_3)

HRMS (ESI^+) *m/z* : $C_{13}H_{23}NO_6Na$ [M+Na], calcd 312.1423, found 312.1424

3-*tert*-Butyl carbamate-3-deoxy-1,2-*O*-isopropylidene-5-iodo-5-deoxy-α-D-xylofuranose (652)



(651) (652)

To a solution of the hydroxyl furanose (651) (1.98 g, 6.86 mmol) in toluene (32 mL) and acetonitrile (7 mL) was added imidazole (1.40 g, 20.57 mmol) and triphenylphosphine (4.42 g, 16.49 mmol) and then iodine (4.18 g, 16.49 mmol). The reaction mixture was refluxed for 3h and cooled to room temperature. The reaction mixture was diluted with ethyl acetate (100 mL) and the organic layer was washed with 10% sodium thiosulphate solution (3x100 mL), water (150 mL) and brine (150 mL). The organic layer were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane: EtOAc, 2:1) to give the iodo furanose (652) (1.48 mg, 64%) as a colourless amorphous solid which was recrystallized from hexane to give the colourless needle of the iodo furanose, m.p. 114-115 ºC, $[\alpha]_D^{26}$ –20.8 (*c* 2.30, $CHCl_3$).

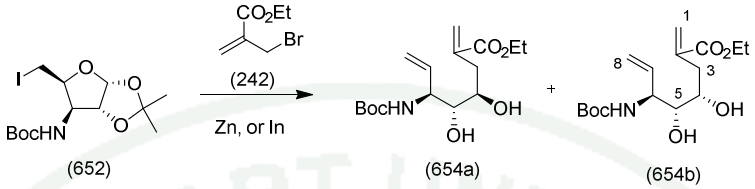
FTIR (film), ν_{max}, cm^{-1}: 3432, (N-H), 2983, 2930 (C-H), 1714(C=O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.85 (d, *J* = 3.6 Hz, 1H, H-1), 4.54 (d, *J* = 3.6 Hz, 1H, H-2), 4.44 (br, 1H, H-3), 4.32 (d, *J* = 9.1 Hz, 1H, H-5), 3.24 (t, *J* = 9.1 Hz, 1H, H-4), 3.10 (dd, *J* = 8.0, 10.1 Hz, 1H, H-5), 1.51 (s, 3H, CH_3), 1.45 (s, 9H, $C(CH_3)_3$), 1.28 (s, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 154.8 (C=O), 112.1 (C), 104.5 (C-1), 84.8 (C-2), 80.3 (C-4), 79.2 ($C(CH_3)_3$), 57.4 (C-3), 28.2 ($C(CH_3)_3$), 26.5 (CH_3), 26.1 (CH_3), -1.8 (C-5)

HRMS (ESI^+) *m/z*: $C_{13}H_{22}NO_5NaI$ [M+Na], calcd 422.0440, found 422.0443

tert-Butyl (3*S*,4*R*)-7-(ethoxycarbonyl)-4,5-dihydroxyocta-1,7-dien-3-ylcarbamate (654)



Procedure A:

To a solution of the iodide furanose (652) (738 mg, 1.85 mmol) in 2:1 THF: H_2O (60 mL) was added activated zinc powder (1.78 g, 27.78 mmol) and 10% acetic acid (1 mL). The mixture was sonicated at 40°C for 30 min and then ethyl 2-(bromomethyl) acrylate (242) (0.52 mL, 3.7 mmol) was added dropwise to the reaction mixture. The sonication was continued for an additional 30 min and the reaction mixture was then filtered. The filtrate was extracted with CH_2Cl_2 (3x70mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 2:1) to give the diene (654a) (260 mg, 43%) and (654b) (238 mg, 39%) as colourless oil.

Procedure B:

To a solution of the iodide furanose (652) (610 mg, 1.52 mmol) in 2:1 THF: H_2O (60 mL) was added activated zinc powder (978 mg, 15.28 mmol) and 10% acetic acid (2 mL). The mixture was sonicated at 40°C for 1h and then zinc powder was filtered off. The filtrate was added indium powder (877 mg, 7.64 mmol) and ethyl 2-(bromomethyl) acrylate (242) (0.64 mL, 4.59 mmol). The sonication was continued for an additional 3 h and the reaction mixture was then filtered. The filtrate was extracted with CH_2Cl_2 (3x70mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude

product was purified by flash column chromatography (silica gel, hexane:EtOAc, 2:1) to give the diene (654a) (294 mg, 58%) and (654b) (119 mg, 24%) as colourless oil.

Ethyl (4*R*, 5*R*, 6*S*)-6-[(tert-butoxycarbonyl)amino]-4,5-dihydroxy-2-methylidene oct-7-enoate (654a)

$[\alpha]_D^{26}$ +8.3 (*c* 0.39, $CHCl_3$)

FTIR (film), ν_{max}, cm^{-1}: 3403 br, (N-H, OH), 2980 (C-H), 1701 (C=O), 1522 (C=C)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.21 (d, *J* = 1.4 Hz, 1H, H-1), 5.79 (ddd, *J* = 5.9, 6.5, 17.1 Hz, 1H, H-7), 5.69 (d, *J* = 0.9 Hz, 1H, H-1), 5.22 (dt, *J* = 1.2, 17.1 Hz, 1H, H-8), 5.15 (dt, *J* = 1.1, 10.4 H, 1H, H-8), 4.23 (br, 1H, H-6), 4.17 (qd, *J* = 1.1, 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.72 (td, *J* = 4.8, 8.6 Hz, 1H, H-4), 3.39 (t, *J* = 4.8 Hz, 1H, H-5), 2.59 (dd, *J* = 2.6, 14.2 Hz, 1H, H-3), 2.47 (dd, *J* = 8.6, 14.2 Hz, 1H, H-3), 1.39 (s, 9H, $C(CH_3)_3$), 1.29 (s, 3H, $CO_2CH_2CH_3$)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 167.9 (C=O), 156.1 (C=O), 136.9 (C=C), 136.3(C-2), 128.0 (C=C), 116.2 (C=C), 79.6 ($C(CH_3)_3$), 75.4 (C-5), 71.6 (C-4), 70.6 (C-6), 61.0 ($CO_2CH_2CH_3$), 54.5, (C-6), 36.3 (C-3), 28.2 ($C(CH_3)_3$), 14.0 ($CO_2CH_2CH_3$)

HRMS (ESI^+) *m/z* : $C_{16}H_{27}NNaO_6$ [M+Na], calcd 352.1731, found 352.1742

Ethyl (4*S*, 5*R*, 6*S*)-6-[(tert-butoxycarbonyl)amino]-4,5-dihydroxy-2-methylidene oct-7-enoate (654b)

$[\alpha]_D^{26}$ +111 (*c* 0.05, $CHCl_3$)

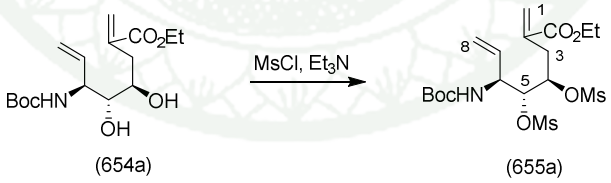
FTIR (film), ν_{max}, cm^{-1}: 3431 br, (N-H, OH), 2981 (C-H), 1690 (C=O), 1507 (C=C)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.23 (d, *J* = 1.5 Hz, 1H, H-1), 5.85 (ddd, *J* = 5.2, 10.5, 17.4 Hz, 1H, H-7), 5.74 (s, 1H, H-1), 5.22 (dt, *J* = 1.3, 17.4 Hz, 1H, H-8), 5.16 (dt, *J* = 1.3, 10.5 Hz, 1H, H-8), 4.47 (br, 1H, H-6), 4.17 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.52 (br, 1H, H-4), 3.35 (dd, *J* = 2.0, 8.8 Hz, 1H, H-5), 2.74 (dd, *J* = 3.0, 14.5 Hz, 1H, H-3), 2.45 (dd, *J* = 7.6, 14.5 Hz, 1H, H-3), 1.39 (s, 9H, $C(CH_3)_3$), 1.25 (s, 3H, $CO_2CH_2CH_3$)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 168.3 (C=O), 157.0 (C=O), 136.7 (C=C), 136.3 (C-2), 128.2 (C=C), 115.9 (C=C), 79.9 ($C(CH_3)_3$), 75.7 (C-5), 69.9 (C-4), 60.9 ($CO_2CH_2CH_3$), 53.2 (C-6), 35.0 (C-3), 28.1 ($C(CH_3)_3$), 13.9 ($CO_2CH_2CH_3$)

HRMS (ESI^+) *m/z* : $C_{16}H_{27}NNaO_6$ [M+Na] calcd 352.1731, found 352.1739

Ethyl (4*R*, 5*R*, 6*S*)-6-[(*tert*-butoxycarbonyl)amino]-2-methylidene-4,5 bis[(methyl sulfonyl)oxy]oct-7-enoate (655a)



(654a) (655a)

To a solution of the diol (654a) (133 mg, 0.40 mmol) in CH_2Cl_2 (2 mL) at 0ºC was added and Et_3N (0.17 mL, 1.21 mmol) followed by methanesulfonyl chloride (0.1 mL, 1.21 mmol). The reaction mixture was stirred at 0ºC for 1 h then water was added to the solution, and the mixture was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 1:1) to give the mesylate (655a) (126mg, 65%) as a colourless oil, $[\alpha]_D^{26}$ –29.4 (*c* 0.75, $CHCl_3$).

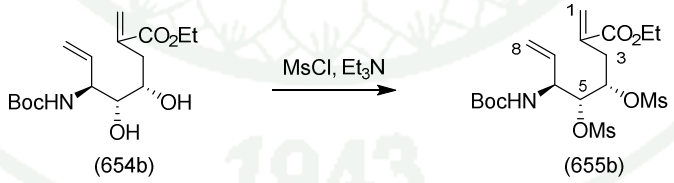
FTIR (film), ν_{max}, cm^{-1}: 3415, (N-H), 2981 (C-H), 1709 (C=O), 1358, 1336 1175 (SO_2)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.35 (s, 1H, H-1), 5.93-5.38 (m, 1H, H-7), 5.83 (s, 1H, H-1), 5.34 (d, *J* = 16.6 Hz, 1H, H-8), 5.31 (dt, *J* = 10.3 Hz, 1H, H-8), 5.12 (td, *J* = 6.9, 5.0 Hz, 1H, H-4), 4.99 (d, *J* = 8.6 Hz, 1H, H-6), 4.74 (d, *J* = 5.0 Hz, 1H, H-5), 4.20 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.12 (s, 3H, SO_2CH_3), 3.04 (s, 3H, SO_2CH_3), 2.92 (dd, *J* = 5.2, 14.5 Hz, 1H, H-3), 2.78 (dd, *J* = 6.9 14.5 Hz, 1H, H-3), 1.43 (s, 9H, $C(CH_3)_3$), 1.28 (s, 3H, $CO_2CH_2CH_3$)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 166.3 (C=O), 155.0 (C=O), 134.3 (C-2), 134.1 (C=C), 130.5 (C=C), 118.2 (C=C), 81.2 ($C(CH_3)_3$), 80.4 (C-5), 76.8 (C-4), 61.2 ($CO_2CH_2CH_3$), 52.4 (C-6), 39.1 (SO_2CH_3), 38.8 (SO_2CH_3), 34.4 (C-3), 28.2 ($C(CH_3)_3$), 14.0 ($CO_2CH_2CH_3$)

HRMS (ESI^+) *m/z* : $C_{18}H_{32}NO_{10}S_2$ [M+H], calcd 486.1462, found 486.1461

Ethyl (4*S*, 5*R*, 6*S*)-6-[(*tert*-butoxycarbonyl)amino]-2-methylidene-4,5-bis[(methyl sulfonyl)oxy]oct-7-enoate (655b)



(654b) (655b)

To a solution of the diol (654b) (240mg, 0.729 mmol) in CH_2Cl_2 (5 mL) at 0ºC was added and Et_3N (0.3 mL, 2.19 mmol) followed by methanesulfonyl chloride (0.2 mL, 2.19 mmol). The reaction mixture was stirred at 0ºC for 1 h then water was added to the solution, and the mixture was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column

chromatography (silica gel, hexane:EtOAc, 1:1) to give the mesylate (655b) (300 mg, 60%) as a colourless oil, $[\alpha]_D^{26}$ +38.2 (*c* 0.21, $CHCl_3$).

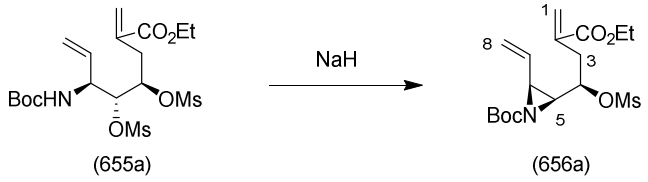
FTIR (film), ν_{max}, cm^{-1}: 3432, (N-H), 2989 (C-H), 1701, 1646 (C=O), 1355, 1177 (SO_2)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.33 (d, *J* = 0.9 Hz, 1H, H-1), 5.86 (ddd, *J* = 6.3, 10.4, 17.2 Hz, 1H, H-7), 5.77 (s, 1H, H-1), 5.42 (d, *J* = 17.2 Hz, 1H, H-8), 5.35 (dt, *J* = 1.1, 10.4 Hz, 1H, H-8), 5.13 (ddd, *J* = 3.2, 2.5, 9.8 Hz, 1H, H-4), 5.01 (d, *J* = 9.4 Hz, 1H, NH), 4.89 (dd, *J* = 2.2, 7.0 Hz, 1H, H-6), 4.55 (br, 1H, H-5), 4.17 (qd, *J* = 1.7, 7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.13 (s, 3H, SO_2CH_3), 2.98 (s, 3H, SO_2CH_3), 2.87 (dd, *J* = 3.2, 14.3, 1H, H-3), 2.71 (dd, *J* = 10.1 14.3 Hz, 1H, H-3), 1.43 (s, 9H, $C(CH_3)_3$), 1.29 (s, 3H, $CO_2CH_2CH_3$)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 166.1 (C=O), 155.0 (C=O), 134.5 (C-2), 133.0 (C=C), 130.0 (C=C), 119.3 (C=C), 81.5 ($C(CH_3)_3$), 80.2 (C-5), 78.4 (C-4), 61.2 ($CO_2CH_2CH_3$), 52.4(C-6), 38.9 (SO_2CH_3), 38.5 (SO_2CH_3), 32.6 (C-3), 28.2 ($C(CH_3)_3$), 14.1 ($CO_2CH_2CH_3$)

HRMS (ESI^+) *m/z* : $C_{18}H_{31}NNaO_{10}S_2$ [M+Na], calcd 508.1282, found 508.1283

***(4R, 5S, 6S)*-2-Carboethoxy-4-methanesylfonyloxy-5,6-*tert*-butyl aziridine carboxylate-1,7-octadiene (656a)**



(655a) (656a)

To a solution of the dimesylate (655a) (198 mg, 0.408 mmol) in a mixed solvent of CH_2Cl_2 (40 mL) and DMSO (5.5 mL) was added sodium hydride (60% in

oil) (33 mg, 0.816 mmol). The reaction mixture was stirred at room temperature for 1h then water was added, and the mixture was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 4:1) to give the vinyl aziridine (656a) (70 mg, 44%) as a colourless oil, $[\alpha]_D^{27}$ +20.8 (*c* 0.31, $CHCl_3$) (lit. $[\alpha]_D^{20}$ +25.1 (*c* 1.33, $CHCl_3$); Kang *et al.,* 2012).

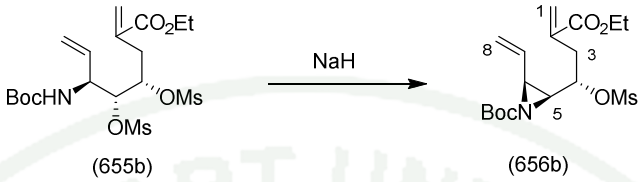
FTIR (film), ν_{max}, cm^{-1}: 3422, (N-H), 2920 (C-H), 1706 (C=O), 1366, 1175 (SO_2)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.33 (d, *J* = 1.2 Hz, 1H, H-1), 5.84 (ddd, *J* = 5.9, 10.4, 16.9 Hz, 1H, H-7), 5.78 (d, *J* = 0.9 Hz, 1H, H-1), 5.39 (ddd, *J* = 1.1, 1.5, 17.0 Hz, 1H, H-8), 5.49 (ddd, *J* = 0.7, 1.5, 10.4 Hz, 1H, H-8), 4.66 (ddd, *J* = 3.6, 7.9, 9.4 Hz, 1H, H-4), 4.26-4.17 (m, 2H, $CO_2CH_2CH_3$), 3.14 (tt, *J* = 5.8, 0.8 Hz, 1H, H-6), 3.04 (ddd, *J* = 0.9, 3.7, 14.7 Hz, 1H, H-3), 2.93 (s, 3H, SO_2CH_3), 2.77 (dd, *J* = 5.8, 7.9 Hz, 1H, H-5), 2.76 (ddd, *J* = 0.6, 9.5, 14.7 Hz, 1H, H-3), 1.47 (s, 9H, $C(CH_3)_3$), 1.30 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 166.3 (C=O), 161.2 (C=O), 135.1 (C-2), 131.1 (C=C), 129.2 (C=C), 120.3 (C=C), 81.0 ($C(CH_3)_3$),76.6 (C-4), 61.0 ($CO_2CH_2CH_3$), 44.6 (C-5), 43.6 (C-6), 38.6 (SO_2CH_3), 36.8 (C-3), 27.9 ($C(CH_3)_3$), 14.2 ($CO_2CH_2CH_3$)

HRMS (ESI^+) *m/z* : $C_{17}H_{27}NNaO_7S$ [M+Na], calcd 412.1400, found 412.1419

***(4R, 5S, 6S)*-2-Carboethoxy-4-methanesylfonyloxy-5,6-*tert*-butyl aziridine carboxylate-1,7-octadiene (656b)**



(655b) (656b)

To a solution of the dimesylate (655b) (208 mg, 0.429 mmol) in a mixed solvent of CH_2Cl_2 (43 mL) and DMSO (5.7 mL) was added sodium hydride (60% in oil) (35 mg, 0.858 mmol). The reaction mixture was stirred at room temperature for 1h then water was added, and the mixture was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 4:1) to give the vinyl aziridine (656b) (148 mg, 88%) as a colourless oil, $[\alpha]_D^{25}$ +28.7 (c 1.03, CHCl3).

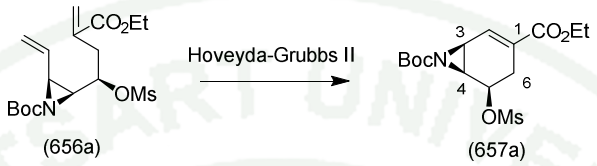
FTIR (film), ν_{max}, cm^{-1}: 3438, (N-H), 2980 (C-H), 1720 (C=O), 1366, 1176 (SO_2)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.33 (d, *J* = 1.1 Hz, 1H, H-1), 5.75 (d, *J* = 0.9 Hz, 1H, H-1), 5.69 (ddd, *J* = 6.6, 10.3, 17.0 Hz, 1H, H-7), 5.50 (dt, *J* = 0.9, 17.0 Hz, 1H, H-8), 5.37 (d, *J* = 10.3 Hz, 1H, H-8), 4.52 (td, *J* = 4.5, 8.9 Hz, 1H, H-4), 4.19 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.14-3.11 (overlap with SO_2CH_3, 1H, H-6), 3.12 (s, 3H, SO_2CH_3), 2.73 (dd, *J* = 6.6, 9.3 Hz, 1H, H-5), 2.71 (ddd, *J* = 0.9, 4.5, 13.8 Hz, 1H, H-3), 2.60 (dd, *J* = 8.6, 14.0 Hz, 1H, H-3), 1.43 (s, 9H, $C(CH_3)_3$), 1.28 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 166.1 (C=O), 160.9 (C=O), 134.1 (C-2), 130.8 (C=C), 129.9 (C=C), 121.0 (C=C), 82.2 ($C(CH_3)_3$), 80.8 (C-4), 60.9 ($CO_2CH_2CH_3$) 45.1 (C-5), 42.9 (C-6), 39.0 (SO_2CH_3), 36.1 (C-3), 27.8 ($C(CH_3)_3$), 14.1 ($CO_2CH_2CH_3$)

HRMS (ESI$^+$) *m/z* : $C_{17}H_{27}NNaO_7S$ [M+Na], calcd 412.1400, found 412.1407

Ethyl (*3R, 4S, 5R*)-3, 4-(*tert*-butyl azidine carboxylate)-5-(methylsulfonyloxy)-cyclohex-1-enecarboxylate (657a)



To a solution of the vinyl aziridine (656a) (30 mg, 0.062 mmol) in dry CH_2Cl_2 (6 mL) was added Hoveyda-Grubbs catalyst (second generation) (4 mg, 0.0062 mmol). The reaction mixture was stirred at 40 °C for 16 h then the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane:EtOAc, 4:1) to give the desired aziridine cyclohexene (657a) (11 mg, 49 %) as a colourless oil, $[\alpha]_D^{26}$ –10.2 (*c* 0.25, $CHCl_3$) (lit. $[\alpha]_D^{22}$ –8.29 (*c* 1.62, $CHCl_3$); Kang *et al.,* 2012).

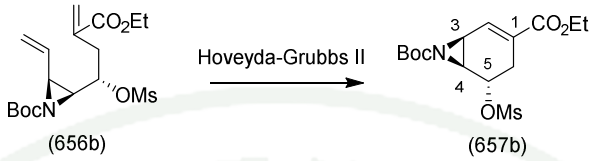
FTIR (film), ν_{max}, cm^{-1}: 3394, (N-H), 2923 (C-H), 1716 (C=O), 1367, 1175 (SO_2)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.10 (dd, *J* = 3.4, 4.6 Hz, 1H, H-2), 5.00 (ddd, *J* = 2.3, 6.6, 10.1 Hz, H1H, -5), 4.20 (dq, *J* = 0.7, 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.37 (dt, *J* = 2.0, 6.6 Hz, 1H, H-4), 3.18 (s, 3H, SO_2CH_3), 3.11 (dd, *J* = 4.6, 6.3 Hz, 1H, H-3), 3.05 (ddd, *J* = 1.8, 6.6, 16.4 Hz, 1H, H-6), 2.40 (ddd, *J* = 3.4, 10.2, 16.4 Hz, 1H, H-6), 1.46 (s, 9H, $C(CH_3)_3$), 1.29 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 164.9 (C=O), 160.5 (C=O), 132.6 (C-1), 131.3 (C-2), 82.6 ($C(CH_3)_3$), 75.2 (C-5), 61.2 ($CO_2CH_2CH_3$), 40.8 (C-4), 39.4 (SO_2CH_3), 36.1 (C-3), 27.8 ($C(CH_3)_3$), 26.6 (C-*6*), 14.2 ($CO_2CH_2CH_3$)

HRMS (ESI$^+$) *m/z* : $C_{15}H_{23}NNaO_7S$ [M+Na] calcd 384.1087, found 384.1087

Ethyl (*3R, 4S, 5S*)-3, 4-(*tert*-butyl azidine carboxylate)-5-(methylsulfonyloxy)-cyclohex-1-enecarboxylate (657b)



(656b) (657b)

To a solution of the vinyl aziridine (656b) (127 mg, 0.262 mmol) in dry CH_2Cl_2 (26 mL) was added Hoveyda-Grubbs catalyst (second generation) (17 mg, 0.026 mmol).The reaction mixture was stirred at 40 °C for 16 h then the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane:EtOAc, 4:1) to give the desired aziridine cyclohexene (657b) (56 mg, 60%) as a colourless oil, $[\alpha]_D^{25}$ +52.2 (*c* 0.17, $CHCl_3$).

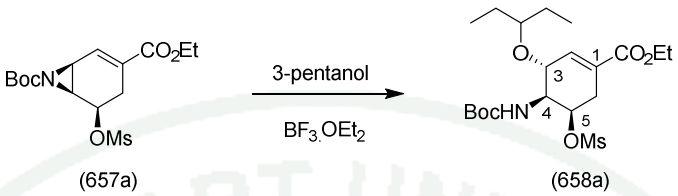
FTIR (film), ν_{max}, cm^{-1}: 3369, (N-H), 2923 (C-H), 1716 (C=O), 1364, 1176 (SO_2)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.19 (dd, *J* = 3.3, 4.7 Hz, 1H, H-1), 5.46 (quint, *J* = 2.4 Hz, 1H, H-5), 4.19 (dq, *J* = 7.1, 1.0 Hz, 2H, $CO_2CH_2CH_3$), 3.28 (dt, *J* = 2.3, 5.8 Hz, 1H, H-4), 3.10 (dd, *J* = 4.9, 5.6 Hz, 1H, H-3), 3.02 (dt, *J* = 2.1, 17.9 Hz, 1H, H-6), 3.01(s, 3H, SO_2CH_3), 2.39 (ddd, *J* = 3.3, 4.5, 17.9 Hz, 1H, H-6), 1.43 (s, 9H, $C(CH_3)_3$), 1.27 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 165.5 (C=O), 160.1 (C=O), 133.4 (C-2), 128.8 (C-1), 82.7 ($C(CH_3)_3$), 72.2 (C-5), 61.1 ($CO_2CH_2CH_3$), 40.1 (C-4), 38.7 (SO_2CH_3), 33.3 (C-3), 27.8 ($C(CH_3)_3$), 26.9 (C-6), 14.2 ($CO_2CH_2CH_3$)

HRMS (ESI^+) *m/z* : $C_{15}H_{23}NNaO_7S$ [M+Na] calcd 384.1087, found 384.1103

Ethyl (3*R*, 4*S*, 5*R*)-4-[(*tert*-butoxycarbonyl)amino]-5-[(methylsulfonyl)oxy]-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (658a)



(657a) (658a)

To a solution of the aziridine cyclohexene (657a) (17 mg, 0.047 mmol) in 3-pentanol (1.2 mL) at −10 °C was added $BF_3 \cdot OEt_2$ (9 µL, 0.070 mmol) in 3-pentanol (0.5 mL). The reaction mixture was stirred for 2 h at −10 °C then the mixture was diluted with EtOAc (10 mL) and 20% aq. K_2CO_3 (5 mL). The organic phase was separated and washed with water (5 mL) and brine (5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 4:1) to give the desired product (658a) (20 mg, 95 %) which was recrystallized from hexane/CH_2Cl_2 to give a colourless needle of the desired product, m.p. 160-161 ºC (lit. m.p. 157-158.5 ºC; Kang *et al*., 2012), $[\alpha]_D^{26}$ −166.7 (*c* 0.07, $CHCl_3$) (lit. $[\alpha]_D^{19}$ −75.4 (*c* 1.52, $CHCl_3$); Kang *et al*., 2012).

FTIR (film), ν_{max}, cm^{-1}: 3364, (N-H), 2929 (C-H), 1721, 1682 (C=O), 1345, 1172 (SO_2)

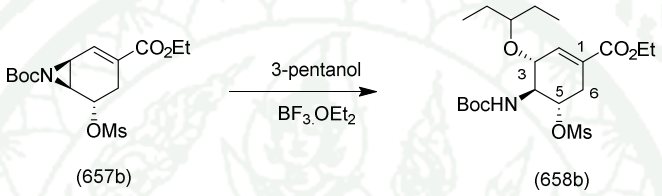
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.85 (dt, *J* = 1.5, 2.9 Hz, 1H, H-2), 5.22 (br s, 1H, H-5), 4.76 (d, *J* = 7.4 Hz, 1H, NH), 4.22 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.05-4.00 (m, 1H, H-4), 4.00-3.94 (m, 1H, H-3), 3.40 (quint, *J* = 5.8 Hz, 1H, H-7), 3.04 (s, 3H, SO_2CH_3), 2.86-2.68 (m, 2H, H-6), 1.59−1.48 (m, 4H, 2x(CH_2CH_3)), 1.44 (s, 9H, $C(CH_3)_3$), 1.29 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 0.92 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 0.91 (t, *J* = 7.2 Hz, 3H, CH_2CH_3)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 165.6 (C=O), 155.4 (C=O), 136.5 (C-2), 127.8 (C-1), 82.4 (2) ($CH(CH_2CH_3)_2$, $C(CH_3)_3$), 80.2 (C-3), 72.8 (C-5), 61.1 ($CO_2CH_2CH_3$),

52.8 (C-4), 38.4 (SO_2CH_3), 29.3 (CH_2CH_3), 28.3 (CH_2CH_3), 26.3 ($C(CH_3)_3$), 26.0 (C-6), 14.1 ($CO_2CH_2CH_3$), 9.6 (CH_2CH_3), 9.3 (CH_2CH_3)

HRMS (ESI^+) *m/z* : $C_{20}H_{35}NNaO_8S$ [M+Na], calcd 472.1976, found 472.1997

Ethyl (3*R*,4*S*,5*S*)-4-[(*tert*-butoxycarbonyl)amino]-5-[(methylsulfonyl)oxy]-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (658b)



(657b) (658b)

To a solution of the aziridine cyclohexene (657b) (45 mg, 0.124 mmol) in 3-pentanol (4 mL) at −10 °C was added $BF_3{\cdot}OEt_2$ (24 μL, 0.187 mmol) in 3-pentanol (1.5 mL). The reaction mixture was stirred for 2 h at −10 °C then the mixture was diluted with EtOAc (10 mL) and 20% aq. K_2CO_3 (10 mL). The organic phase was separated and washed with water (5 mL) and brine (5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 4:1) to give the desired product (658b) (51 mg, 91%) as a white solid, m.p. 117-119 ºC, $[\alpha]_D^{25}$ +140.5 (*c* 0.05, $CHCl_3$).

FTIR (film), ν_{max}, cm^{-1}: 3344, (N-H), 2920 (C-H), 1719, 1683 (C=O), 1363, 1179 (SO_2)

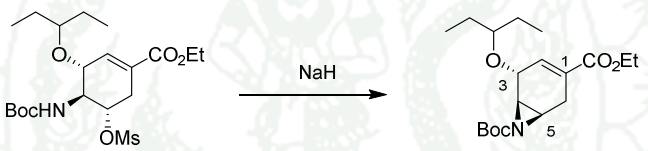
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.75 (t, *J* = 1.8 Hz, 1H, H-2), 5.07-4.97 (m, 1H, NH), 4.93 (d, *J* = 7.7 Hz, 1H, H-5), 4.39 (d, *J* = 7.4 Hz, 1H, H-4), 4.19 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.54-3.24 (m, 1H, H-3), 3.29-3.21 (m, 1H, H-7), 3.13-3.04 (m, 1H, H-6), 3.03 (s, 3H, SO_2CH_3), 2.53 (ddt, *J* = 3.1, 9.8, 17.5 Hz, 2H, H-6), 1.53−1.45

(m, 4H, 2x(CH_2CH_3)), 1.41 (s, 9H, C(CH_3)$_3$), 1.26 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 0.89 (t, J = 7.3 Hz, 3H, CH_2CH_3), 0.88 (t, J = 7.3 Hz, 3H, CH_2CH_3)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 165.5 (C=O), 155.4 (C=O), 138.0 (C-2), 127.2 (C-1), 82.6 (2) (*C*H(CH_2CH_3)$_2$, *C*(CH_3)$_3$), 76.1 (C-3), 74.0 (C-5), 61.1 ($CO_2CH_2CH_3$), 56.6 (C-4), 38.3 (SO_2CH_3), 31.8 (CH_2CH_3), 28.3 (CH_2CH_3), 26.3 (C(CH_3)$_3$), 25.7 (C-6), 14.2 ($CO_2CH_2CH_3$), 9.5 (CH_2CH_3), 9.3 (CH_2CH_3)

HRMS (ESI$^+$) *m/z* : $C_{20}H_{36}NO_8S$ [M+H], calcd 450.2156, found 450.2156

Ethyl (3*R*, 4*R*, 5*R*)-4, 5-(*tert*-butyl aziridine carboxylate)-3-(pentane-3-yloxy)-cyclohex-1-ene-1-carboxylate (659)



(658b) (659)

To a solution of the mesylate (658b) (44mg, 0.098 mmol) in a mixed solvent of CH_2Cl_2 (6 mL) and DMSO (0.2 mL) was added sodium hydride (60% in oil) (8 mg, 0.196 mmol). The reaction mixture was stirred at room temperature for 30 min then water was added, and the mixture was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 8:1) to give the aziridine (659) (30 mg, 87%) as a colourless oil, $[\alpha]_D^{26}$ –28.0 (*c* 0.43, $CHCl_3$).

FTIR (film), ν_{max}, cm^{-1}: 3375, (N-H), 2929 (C-H), 1719 (C=O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.78 (br s, 1H, H-2), 4.39 (br s, 1H, NH), 4.18 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.42 (quint, J = 5.9 Hz, 1H, H-7), 2.94 (br d, J = 19.2 Hz, 1H, H-4), 2.88-2.78 (m, 2H, H-6), 2.60 (br d, J = 19.2 Hz, 1H, H-5),

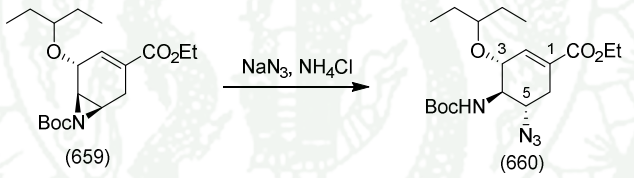
1.61−1.48 (m, 4H, 2x(CH_2CH_3)), 1.43 (s, 9H, C$(CH_3)_3$), 1.26 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 0.96 (t, J = 7.2 Hz, 3H, CH_2CH_3), 0.89 (t, J = 7.2 Hz, 3H, CH_2CH_3)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 166.5 (C=O), 161.6 (C=O), 133.1 (C-2), 127.8 (C-1), 82.5 ($C(CH_3)_3$), 81.4 ($CH(CH_2CH_3)_2$), 68.6 (C-3), 60.8 ($CO_2CH_2CH_3$), 37.5 (C-4), 35.8 (C-5), 27.8 (2x(CH_2CH_3)), 26.6 (C$(CH_3)_3$), 23.5 (C-6), 14.2 ($CO_2CH_2CH_3$), 9.9 (CH_2CH_3), 9.5 (CH_2CH_3)

HRMS (ESI^+) *m/z* : $C_{19}H_{31}NNaO_5$ [M+Na], calcd 376.2094, found 376.2100

Ethyl (*3R, 4R, 5S*)-4-(*tert*-butoxycarbonyl)-5-azido-3-(1-ethylpropoxy)-cyclohex-1-ene-1-carboxylate (660)

Procedure 1



To a solution of the aziridine (659) (5 mg, 0.014 mmol) in anhydrous DMF (2 mL) was added sodium azide (16 mg, 0.21mmol) and ammonium chloride (3 mg, 0.05 mmol). The reaction mixture was heated and stirred at 90 °C for 6 h. Then the reaction was cooled down to room temperature, EtOAc (10 mL) and water (5 mL) were added. The organic phase was separated and washed with water (5 mL). The organic layers was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 8:1) to give the azide (660) (5 mg, 89 %) as a white solid, m.p. 127-128 $[\alpha]_D^{26}$ –35.0 (*c* 0.86, $CHCl_3$).

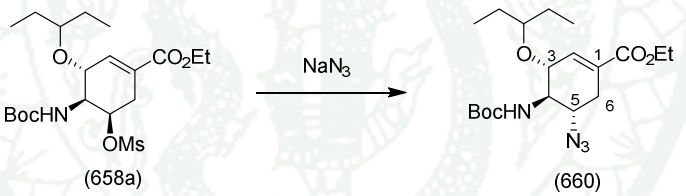
FTIR (film), ν_{max}, cm^{-1}: 3341, (N-H), 2978 (C-H), 2103(N=N=N), 1719, 1687 (C=O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.77 (d *J* = 2.2 Hz, 1H, H-2), 4.91 (br s, 1H, H-3), 4.48 (br s, 1H, H-4), 4.20 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.34 (quint, *J* = 5.7 Hz, 1H, H-7), 3.12 (br s, 1H, H-5), 2.83 (dd, *J* = 5.7, 17.7 Hz, 1H, H-6), 2.20 (br s, 1H, H-6), 1.56–1.47 (m, 4H, 2x(CH_2CH_3)), 1.45 (s, 9H, C$(CH_3)_3$), 1.26 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 0.91 (t, *J* = 7.3 Hz, 6H, 2x(CH_2CH_3))

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 165.7 (C=O), 155.2 (C=O), 138.1 (C-2), 127.9 (C-1), 82.1 ($CH(CH_2CH_3)_2$), 79.6 ($C(CH_3)_3$), 73.5 (C-3), 60.8 ($CO_2CH_2CH_3$), 58.1 (C-5), 57.5 (C-4), 30.6 (C-6), 28.2 (C$(CH_3)_3$), 26.1 (CH_2CH_3), 25.5 (CH_2CH_3), 14.0 ($CO_2CH_2CH_3$), 9.5 (CH_2CH_3), 9.2 (CH_2CH_3)

HRMS (ESI^+) *m/z* : $C_{19}H_{32}N_4O_5Na$ [M+Na], calcd 419.2265, found 419.2276

Procedure 2



(658a) (660)

To a solution of the mesylate (658a) (12 mg, 0.026 mmol) in a mixed solvent of DMF (2 mL) and water (0.4 mL) was added sodium azide (14 mg, 0.214mmol). The reaction mixture was heated and stirred at 90 °C for 8 h. Then the reaction was cooled down to room temperature, EtOAc (10 mL) and water (5 mL) were added. The organic phase was separated and washed with water (5 mL). The organic layers was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 8:1) to give the azide (660) (7 mg, 68 %) as a white solid.

Ethyl (*3R,4R,5S*)-4-(acetamido)-5-azido-3-(1-ethylpropoxy)-cyclohex-1-ene-1-carboxylate (12)

(660) (12)

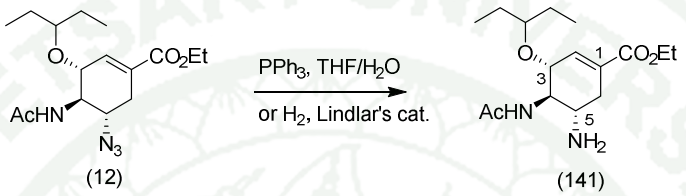
To a solution of the *N*-Boc azido (660) (82 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) at 0ºC was added trifluoro acetic acid (0.32 mL, 4.14 mmol). The reaction mixture was warmed to room temperature and stirred for 4h. Saturated aq.$NaHCO_3$ was added to neutralize the mixture and then extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in pyridine (0.23 mL), acetic anhydride was then added. The reaction mixture was stirred at room temperature for 1 h and quenched with MeOH (0.23 mL). The trace Ac_2O was removed by coevaporattion with toluene (10 mL). The crude product was purified by flash column chromatography (silica gel, hexane:EtOAc, 2:1) to give *N*-Ac azido (12) (55 mg, 78 %) which was recrystallized from hexane/CH_2Cl_2 to give a colourless needle, m.p. 137-139 ºC (lit.138-139ºC; Kang *et al*., 2012), $[\alpha]_D^{23}$ –33.1 (*c* 0.40, $CHCl_3$) (lit. $[\alpha]_D^{21}$ –44.7 (*c* 0.83, $CHCl_3$); Kang *et al*., 2012).

FTIR (film), ν_{max}, cm^{-1}: 3278, (N-H), 2967 (C-H), 2101(N=N=N), 1719, 1656 (C=O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.76 (d, *J* = 2.3 Hz, 1H, H-2), 6.28 (d, *J* = 6.9 Hz, 1H, NH), 4.50 (d, *J* = 8.8 Hz, 1H, H-4), 4.19 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.19-4.13 (m, 1H, H-3), 3.40 (td, *J* = 8.1, 10.4 Hz, 1H, H-5), 3.31 (quint, *J* = 5.7 Hz, 1H, H-7), 2.83 (dd, *J* = 5..7, 17.6 Hz, 1H, H-6), 2.21 (ddt, *J* = 2.9, 10.4, 17.6 Hz, 1H, H-6), 2.01 (s, 3H, C(O)CH_3), 1.55-1.43 (m, 4H, CH_2CH_3), 1.27 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 0.92-0.84 (m, 6H, *2x*(CH_2CH_3))

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 171.2 (C=O), 165.7 (C=O), 138.0 (C-2), 128.0 (C-1), 82.0 (*CH*(CH_2CH_3)$_2$), 73.7 (C-3), 61.0 (CO_2*CH*$_2$$CH_3$), 58.0 (2) (C-4, C-5), 30.4 (C-6), 26.2 (CH_2), 25.5 (CH_2), 23.4 (C(O)*CH*$_3$), 14.1 ($CO_2CH_2CH_3$), 9.5 (CH_3), 9.2 (CH_3)

Oseltamivir free base (141)



Procedure A:

To a solution of the azido acetamide (12) (19 mg, 0.056 mmol) in 4:1 THF:water (1 mL) was added triphenyl phosphine (23 mg, 0.084 mmol) at room temperature. The reaction mixture was refluxed for 3 h and cooled to room temperature. Solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, CH_2Cl_2:MeOH, 4:1) to give the oseltamivir (141) (13 mg,74%) as a colourless oil.

Procedure 2:

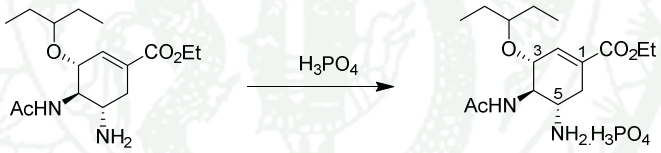
To a solution of azido acetamide (12) (55 mg) in EtOH (10 mL) was treated with Lindlar's catalyst (55 mg) and the resulting suspension was stirred under atmosphere of hydrogen gas for 10 h. The mixture was then filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2:MeOH, 4:1) to give the oseltamivir (141) (45 mg,88%) as a colourless oil, $[\alpha]_D^{23}$ –41.7 (*c* 0.92, $CHCl_3$) (lit. $[\alpha]_D^{25}$ –55.8 (*c* 2.05, $CHCl_3$); Mandai *et al.,* 2009).

FTIR (film), ν_{max}, cm^{-1}: 3412, (N-H), 2966 (C-H), 1714, 1651 (C=O), 1559 (C=C)

^{1}H-NMR ($CDCl_3$, 400 MHz) 6.74 (s, 1H, H-2), 6.69 (d, *J* = 8.4 Hz, 1H, NH), 4.22-4.12 (m, 3H, H-3, $CO_2CH_2CH_3$), 3.65 (td, *J* = 8.9, 10.0 Hz, 1H, H-4), 3.39-3.24 (m, 2H, H-5, H-7), 2.78 (dd, *J* = 5.0, 18.2 Hz, 1H, H-6), 2.28-2.16 (m, 1H, H-6), 2.01 (s, 3H, C(O)CH_3), 1.53-1.42 (m, 4H, CH_2CH_3), 1.26 (t, *J* = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 0.87 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 0.85 (t, *J* = 7.3 Hz, 3H, CH_2CH_3)

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 171.8 (C=O), 166.1 (C=O), 138.0 (C-2), 128.8 (C-1), 81.9 ($CH(CH_2CH_3)_2$), 74.9 (C-3), 60.9 ($CO_2CH_2CH_3$), 57.2 (C-4), 49.2 (C-5), 32.4 (C-6), 26.1 (CH_2), 25.6 (CH_2), 23.6 (C(O)CH_3), 14.1 ($CO_2CH_2CH_3$), 9.5 (CH_3), 9.2 (CH_3)

Oseltamivir Phosphate (Tamiflu®) (8)



Oseltamivir free base (141) — Oseltamivir phosphate Tamiflu® (8)

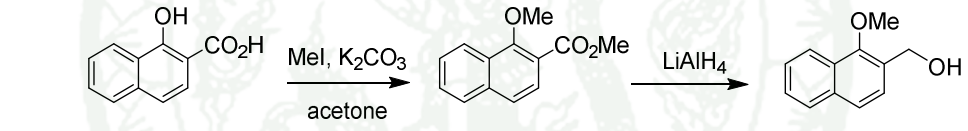
To a solution of the oseltamivir free base (141) (10 mg) in ethanol (1 mL) and added a hot (60 °C) solution of phosphoric acid (3 mg) in ethanol (1mL). The reaction mixture was heated and stirred at 60 °C for 3h. After cooling to 0°C, the precipitates were collected by filtration and rinsed with cold acetone (2×1 mL) to afford oseltamivir phosphate (8) (Tamiflu®) (9 mg, 70%) as a white crystal. m.p. 203-204 °C (lit. 202–203 °C; Kang *et al*., 2012), $[\alpha]_D^{23}$ –31.7 (*c* 0.22, H_2O) (lit. $[\alpha]_D^{29}$ –30.8 (*c* 0.70, H_2O); Kang *et al*., 2012).

FTIR (KBr), ν_{max}, cm^{-1}: 3422, (N-H), 3233 (NH_3^+), 2874 (C-H), 1719, 1629 (C=O), 1553 (C=C), 1355, 1177 (SO_2)

^{1}H-NMR (D_2O, 400 MHz) δ: 6.88 (s,1H, H-2), 4.35 (d, *J* = 8.8 Hz, 1H, H-3), 4.28 (q, *J* = 7.3 Hz, 2H, $CO_2CH_2CH_3$), 4.08 (dd, *J* = 9.2, 11.7 Hz, 1H, H-4), 3.62 (td, *J* = 5.7, 10.5 Hz, 1H, H-5), 3.58 (quint, *J* = 7.5 Hz, 1H, $CH(CH_2CH_3)_2$), 2.99 (dd, *J* = 5.6, 17.5 Hz, 1H, H-6), 2.55 (dt, *J* = 10.5, 17.5 Hz, 1H, H-6), 2.11 (s, 3H, C(O)CH_3), 1.65-1.45 (m, 4H, $CH(CH_2CH_3)_2$), 1.31 (t, *J* = 7.3 Hz, 3H, $CO_2CH_2CH_3$), 0.91 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 0.87 (t, *J* = 7.4 Hz, 3H, CH_2CH_3)

^{13}C-NMR (D_2O, 75 MHz) δ: 175.2 (C=O), 167.4 (C=O), 137.9 (C-2), 127.6 (C-1), 84.3 ($CH(CH_2CH_3)_2$), 75.0 ($CO_2CH_2CH_3$), 62.3 (C-3), 52.6 (C-4), 49.1 (C-5), 28.1 (C-6), 25.4 (CH_2CH_3), 25.0 (CH_2CH_3), 22.3 (C(O)CH_3), 13.2 ($CO_2CH_2CH_3$), 8.5 (CH_2CH_3), 8.4 (CH_2CH_3)

(1-Methoxynaphthalen-2-yl)methanol (662)



1-Hydroxy-2-naphthoic acid (354) (661) (662)

A mixture of 1-hydroxy-2-naphthoic acid (354) (2.00 g, 10.63 mmol), K_2CO_3 (5.87 g, 42.51 mmol) and methyl iodide (2.7 mL, 42.51 mmol) in acetone (43 mL) was stirred and heated at 70 ^{o}C in Schlenk tube for 24 h. The reaction was cooled to room temperature and then K_2CO_3 was filtered out. The filtrate was concentrated under reduced pressure to give the desired methyl ester (661) as a brown oil. The crude ester was used in the next step without purification.

To a solution of the methyl ester (661) (5.38 g, 24.94 mmol) in dry THF (70 mL) at 0^{o}C was added lithium aluminum hydride (1.89 g, 49.88 mmol). The reaction mixture was warmed to room temperature and stirred under nitrogen atmosphere for 2 h. Then the mixture was quenched with saturated aq.$NaHCO_3$ at 0 ^{o}C and extracted with ethyl acetate (3x100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude

alcohol was purified by flash column chromatography (silica gel, hexane:EtOAc: 10:1) to give the pure alcohol (662) as a colourless amorphous solid (4.36 g, 94%), m.p.70-71 ºC (lit. 70–71 °C; Kongkathip *et al*., 2003).

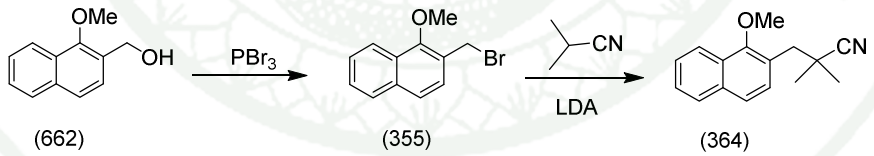
FTIR (KBr), ν_{max}, cm^{-1}: 3196 (OH), 1570, 1503, 1448 (C=C), 1233, 1053 (C-O);

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.08 (dd, *J* = 7.8, 0.9 Hz, 1H, ArH), 7.81 (dd, *J* = 7.1, 1.8 Hz, 1H, ArH), 7.58 (d, *J* = 8.5 Hz, 1H, ArH), 7.52-7.44 (m, 3H, ArH), 4.86 (s, 2H, OCH_2Ar), 3.92 (s, 3H, OCH_3), 2.72 (br s, 1H, OH)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 153.8 (Ar), 134.9 (Ar), 129.3(Ar), 128.3 (ArH), 128. 0 (Ar), 126.9 (ArH), 126.4 (ArH), 126.3 (ArH), 124.6 (ArH), 122.3 (ArH), 62.8 (CH_2), 60.8 (OCH_3)

HRMS (ESI^+) *m/z* : $C_{12}H_{12}NNaO_2$ [M+Na], calcd 211.0735, found 211.0742

Methyl 2-((1-methoxynaphthalen-2-yl) methyl)-2-methylpropanenitrile (364)



(662) (355) (364)

To a solution of the alcohol (662) (1.00 g, 5.38 mmol) in dry CH_2Cl_2 (8.0 mL) was slowly added phosphorous tribromide (1 *M* in CH_2Cl_2, 10.7 mL, 10.75 mmol). The reaction mixture was stirred at room temperature under nitrogen atmosphere for 6 h. Water was added, then the mixture was neutralized with saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 2-(bromomethyl)-1-methoxynaphthalene (355) as light brown amorphous solid. The crude bromide was used in the next step without purification.

To a cool solution of isobutyronitrile (2.1 mL, 23.28 mmol) in dry THF (23 mL) at -78°C was added lithium diisopropylamide (2 *M* in THF/*n*-heptane, 11.6 mL, 23.28 mmol). The reaction mixture was stirred at this temperature for 1 h under nitrogen atmosphere. A solution of bromide (355) (1.93g, 7.76 mmol) in dry THF (9.3 mL) and HMPA (2.9 mL) was added dropwise and stirred at -78°C for 1 h. The reaction mixture was quenched with saturated aq. NH_4Cl and then extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude alkylation product was purified by flash column chromatography (silica gel, hexane:EtOAc, 10:1) to give the desired nitrile (364) as a colourless amorphous solid (4.36 g, 73%), mp 61-62 ºC (lit. 60-61 °C; Kongkathip *et al*., 2012).

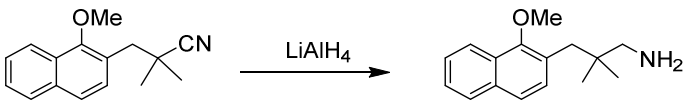
FTIR (KBr), ν_{max}, cm^{-1}: 3048, 2979, 2845 (CH), 2232 (CN), 1596, 1572, (C=C), 1233 (C-O);

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.11-8.07 (m, 1H, ArH), 7.87-7.82 (m, 1H, ArH), 7.63 (d, *J* = 8.5 Hz, 1H, ArH), 7.55-7.46 (m, 3H, ArH), 3.90 (s, 3H, OCH_3), 3.06 (s, 2H, CH_2Ar), 1.40 (s, 6H, 2×CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 154.6 (Ar), 134.4 (Ar), 128.7 (ArH), 128.0 (ArH), 127.6 (Ar), 125.9 (2×ArH), 125.1 (Ar), 124.2 (CN), 123.9 (ArH), 122.2 (ArH), 61.8 (OCH_3), 39.6 (CH_2), 33.6 (C), 26.4 (2×CH_3)

HRMS (ESI^+) *m/z* : $C_{16}H_{18}NO$ $[M+H]^+$, calcd 240.1388, found 240.1388

3-(1-Methoxynaphthalen-2-yl)-2,2-dimethylpropan-1- amine (365)



(364) (365)

To a suspension of lithium aluminum hydride (632 mg, 16.65 mmol) in dry THF (30 mL) at 0°C was slowly added a solution of nitrile (364) (1.97g, 8.33 mmol) in dry THF (5 mL). The reaction mixture was warmed to room temperature and stirred under nitrogen atmosphere for 1 h. The reaction was quenched with saturated aq.$NaHCO_3$ at 0°C and extracted with ethyl acetate (3x100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, MeOH:CH_2Cl_2, 1:10) to give the desired amine (365) as a colourless gum (1.82g, 90%).

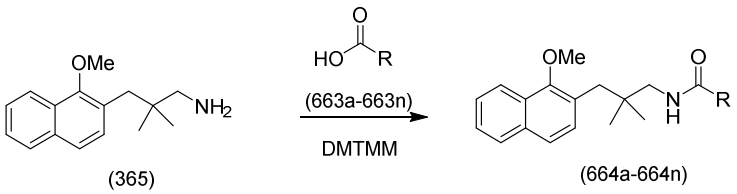
FTIR (KBr), ν_{max}, cm^{-1}: 3341 (NH), 3052, 2957 (CH), 1571(C=C), 1265 (CN), 1233, 1081 (C-O);

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.03-7.98 (m, 1H, ArH), 7.77-7.73 (m, 1H, ArH), 7.46 (d, *J* = 8.4 Hz, 1H, ArH), 7.44-7.35 (m, 2H, ArH), 7.20 (d, *J* = 8.4 Hz, 1H, ArH), 3.83 (s, 3H, OCH_3), 2.65 (s, 2H, CH_2Ar), 2.36 (s, 2H, CH_2N), 0.87 (s, 6H, 2×CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 154.3 (Ar), 134.0 (Ar), 130.5 (ArH), 127.9 (ArH), 127.8 (Ar), 127.5 (Ar), 125.7 (ArH), 125.4 (ArH), 123.1 (ArH), 122.2 (ArH), 61.7 (OCH_3), 52.2 (CH_2N), 38.8 (CH_2), 37.2 (C), 25.4 (2×CH_3)

HRMS (ESI^+) *m/z* : $C_{16}H_{21}NO$ $[M+H]^+$, calcd 244.1701, found 244.1700

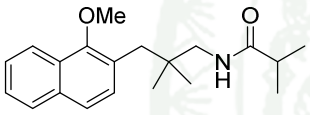
***N*-[3-(1-methoxy-2-naphthyl)-2,2-dimethylpropyl] amide (664a-664n)**



General procedure

To a mixture of amine (365) (1 mmol) and carboxylic acids (663a-663n) (1.1 mmol) in MeOH (10 mL) was added 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (1.1 mmol). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, and then the residue was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give *N*-[3-(1-methoxy-2-naphthyl)-2,2-dimethylpropyl]amide (664a-664n).

***N*-[3-(1-Methoxy-2-naphthyl)-2,2-dimethylpropyl]-2-methylpropanamide (664a)**



(664a)

Flash column chromatography, eluting with 4:1 hexane:EtOAc afforded the amide (664a) (81%) as a colourless oil.

FTIR (film), ν_{max}, cm^{-1}: 3323 (NH), 2964, 2933, 2871 (CH), 1651 (C=O), 1598, 1547 (C=C), 1262 (C-N), 1232 (C-O)

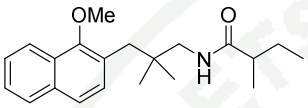
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.99 (dd, *J* = 8.4, 0.7 Hz, 1H, ArH), 7.76 (dd, *J* = 8.4, 0.7 Hz, 1H, ArH), 7.49 (d, *J* = 8.4 Hz, 1H, ArH), 7.51 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.45 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH),7.19 (d, 1H, *J* = 8.5 Hz, ArH), 6.72 (t, *J* = 5.5 Hz, 1H, NH), 3.88 (s, 3H, OCH_3), 2.78 (d, *J* = 6.6 Hz, 2H, CH_2N), 2.61 (s, 2H, CH_2Ar), 2.34 (heptet, *J* = 6.9 Hz, 1H, CH), 1.12 (d, *J* = 6.9 Hz, 6H, 2×CH_3) 0.92 (s, 6H, 2×CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 176.8 (C=O), 153.4 (Ar), 133.9 (Ar), 130.0 (ArH), 127.9 (ArH), 127.4 (Ar), 126.8 (Ar), 125.9 (ArH), 125.6 (ArH), 123.6 (ArH),

121.8 (ArH), 61.9 (OCH_3), 46.5 (CH_2), 39.0 (CH_2), 37.1 (CH), 35.9 (C), 26.0 ($2\times CH_3$), 19.6 ($2\times CH_3$)

HRMS (ESI^+) *m/z* : $C_{20}H_{28}NO_2$ $[M+H]^+$, calcd 314.2120, found 314.2128

***N*-[3-(1-Methoxy-2-naphthyl)-2,2-dimethylpropyl]-2-methylbutanamide (664b)**



(664b)

Flash column chromatography, eluting with 4:1 hexane:EtOAc afforded the amide (664b) (81%) as a colourless oil.

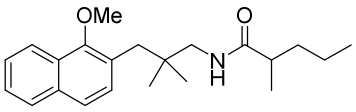
FTIR (film), ν_{max}, cm^{-1}: 3329 (NH), 2963, 2933, 2873 (CH), 1655 (C=O), 1598, 1545 (C=C), 1262 (C-N), 1232 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.06 (dd, *J* = 8.4, 0.7 Hz, 1H, ArH), 7.82 (dd, *J* = 8.4, 0.7 Hz, 1H, ArH), 7.55 (d, *J* = 8.4 Hz, 1H, ArH), 7.49 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.44 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.26 (d, 1H, *J* = 8.4 Hz, ArH), 6.82 (t, *J* = 5.6 Hz, 1H, NH), 3.74 (s, 3H, OCH_3), 2.87 (m, 2H, CH_2N), 2.68 (dd, *J* = 13.4, 3.5 Hz, 2H, CH_2Ar), 2.15 (sixtet, *J* = 6.9 Hz 1H, CH), 1.75-1.63 (m, 1H, CH_2), 1.50-1.39 (m, 1H, CH_2), 1.16 (d, *J* = 6.9 Hz, 3H, CH_3), 1.00 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.93 (t, *J* = 7.3 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 176.4 (C=O), 153.6 (Ar), 134.1 (Ar), 130.2 (ArH), 128.0 (ArH), 127.5 (Ar), 127.0 (Ar), 126.1 (ArH), 125.7 (ArH), 123.8 (ArH), 121.9 (ArH), 62.0 (OCH_3), 46.8 (CH_2), 43.8 (CH), 39.2 (CH_2), 37.2 (C), 27.4 (CH_2), 26.3 (CH_3), 26.2 (CH_3), 17.7 (CH_3), 12.1 (CH_3)

HRMS (ESI^+) *m/z* : $C_{21}H_{30}NO_2$ $[M+H]^+$, calcd 328.2277, found328.2285

***N*-[3-(1-Methoxy-2-naphthyl)-2,2-dimethylpropyl]-2-methylpentanamide (664c)**



(664c)

Flash column chromatography, eluting with 4:1 hexane:EtOAc afforded the amide (664c) (89%) as a colourless oil.

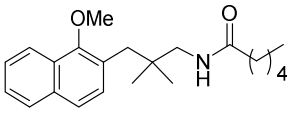
FTIR (film), ν_{max}, cm^{-1}: 3335 (NH), 2961, 2932, 2872 (CH), 1655 (C=O), 1598, 1545 (C=C), 1264 (C-N), 1233, 1081 (C-O);

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.05 (d, *J* = 8.4 Hz, 1H, ArH), 7.81 (d, *J* = 8.4 Hz, 1H, ArH), 7.55 (d, *J* = 8.5 Hz, 1H, ArH), 7.49 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.44 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.26 (d, 1H, *J* = 8.5 Hz, ArH), 6.78 (t, *J* = 5.2 Hz, 1H, NH), 3.94 (s, 3H, OCH_3), 2.91-2.77 (m, 2H, CH_2N), 2.68 (d, *J* = 13.4, 2.6 Hz, 2H, CH_2Ar), 2.25 (sixtet, *J* = 6.8 Hz, 1H, CH), 1.68-1.56 (m, 1H, CH_2), 1.39-1.26 (m, 1+2H, CH_2), 1.15 (d, *J* = 6.8 Hz, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 0.91 (t, *J* = 7.1 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 176.5 (C=O), 153.5 (Ar), 134.0 (Ar), 130.1 (ArH), 128.0 (ArH), 127.5 (Ar), 127.0 (Ar), 126.0 (ArH), 125.7 (ArH), 123.7 (ArH), 121.8 (ArH), 62.0 (OCH_3), 46.7 (CH_2), 41.9 (CH), 39.2 (CH_2), 37.1 (C), 36.1 (CH_2), 26.3 (CH_3), 26.2 (CH_3), 20.7 (CH_2), 18.0 (CH_3), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{22}H_{31}NNaO_2$ [M+Na], calcd 364.2252, found 364.2235

***N*-[3-(1-Methoxy-2-naphthyl)-2,2-dimethylpropyl]hexanamide (664d)**



(664d)

Flash column chromatography, eluting with 4:1 hexane:EtOAc afforded the amide (664d) (90%) as a colourless oil.

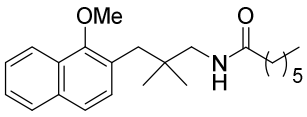
FTIR (film), ν_{max}, cm^{-1}: 3317 (NH), 2958, 2870 (CH), 1649 (C=O), 1598, 1547 (C=C), 1263 (C-N), 1233, 1082 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.06 (d, *J* = 8.3 Hz, 1H, ArH), 7.82 (d, *J* = 8.3 Hz, 1H, ArH), 7.55 (d, *J* = 8.5 Hz, 1H, ArH), 7.50 (td, *J* = 8.3, 1.2 Hz, 1H, ArH), 7.44 (td, *J* = 8.3, 1.2 Hz, 1H, ArH), 7.25 (d, 1H, *J* = 8.5 Hz, ArH), 6.73 (t, *J* = 5.1 Hz, 1H, NH), 3.93 (s, 3H, OCH_3), 2.86 (d, *J* = 6.7 Hz, 2H, CH_2N), 2.68 (s, 2H, CH_2Ar), 2.21 (t, *J* = 7.3 Hz, 3H, CH_2CO), 1.66 (quintet, *J* = 7.3 Hz, 2H, CH_2), 1.35-1.30 (m, 4H, 2×CH_2), 0.99 (s, 6H, 2×CH_3), 0.90 (t, *J* = 7.0 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 173.1 (C=O), 153.5 (Ar), 134.1 (Ar), 130.1 (ArH), 128.0 (ArH), 127.5 (Ar), 126.9 (Ar), 126.0 (ArH), 125.7 (ArH), 123.7 (ArH), 121.9 (ArH), 62.0 (OCH_3), 46.9 (CH_2), 39.2 (CH_2), 37.3 (C), 37.1 (CH_2), 31.5 (CH_2), 26.2 (2×CH_3), 25.6 (CH_2), 22.4 (CH_2), 13.9 (CH_3)

HRMS (ESI^+) *m/z* : $C_{22}H_{31}NNaO_2$ [M+Na], calcd 364.2252, found 364.2257

***N*-[3-(1-Methoxy-2-naphthyl)-2,2-dimethylpropyl]heptanamide (664e)**



(664e)

Flash column chromatography, eluting with 4:1 hexane:EtOAc afforded the amide (664e) (95%) as a colourless oil.

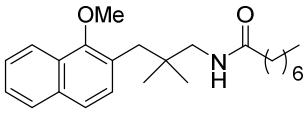
FTIR (film), ν_{max}, cm^{-1}: 3352 (NH), 2956, 2930 (CH), 1650 (C=O), 1612, 1556 (C=C), 1260 (C-N), 1234, 1082 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.04 (d, *J*= 8.3 Hz, 1H, ArH), 7.80 (d, *J* = 8.3 Hz, 1H, ArH), 7.54 (d, *J* = 8.5 Hz, 1H, ArH), 7.49 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.44 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.24 (d, 1H, *J* = 8.5 Hz, ArH), 6.93 (t, *J* = 5.1 Hz, 1H, NH), 3.93 (s, 3H, OCH_3), 2.85 (d, *J* = 6.7 Hz, 2H, CH_2N), 2.67 (s, 2H, CH_2Ar), 2.23 (t, *J* = 7.4 Hz, 2H, CH_2CO), 1.61 (quintet, *J* = 7.4 Hz, 2H, CH_2), 1.37-1.21 (m, 6H, 3×CH_2), 0.98(s, 6H, 2×CH_3), 0.87 (t, *J* = 7.0 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 173.7 (C=O), 153.4 (Ar), 134.0 (Ar), 130.0 (ArH), 128.0 (ArH), 127.4 (Ar), 126.8 (Ar), 126.0 (ArH), 125.7 (ArH), 123.8 (ArH), 121.8 (ArH), 61.9 (OCH_3), 46.9 (CH_2), 39.2 (CH_2), 37.3 (C), 37.2 (CH_2), 31.5 (CH_2), 28.7 (CH_2), 26.1 (2×CH_3), 25.9 (CH_2), 22.4 (CH_2), 13.9 (CH_3)

HRMS (ESI^+) *m/z* : $C_{23}H_{33}NNaO_2$ [M+Na], calcd 378.2409, found 378.2392

***N*-[3-(1-Methoxy-2-naphthyl)-2,2-dimethylpropyl]octanamide (664f)**



(664f)

Flash column chromatography, eluting with 4:1 hexane:EtOAc afforded the amide (664f) (99%) as a colourless oil.

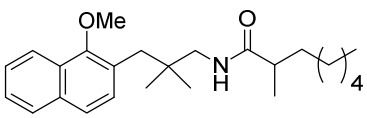
FTIR (film), ν_{max}, cm^{-1}: 3353 (NH), 2928, 2856 (CH), 1651 (C=O), 1598, 1547 (C=C), 1262 (C-N), 1232, 1082 (C-O);

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.04 (d, *J* = 8.3 Hz, 1H, ArH), 7.80 (d, *J* = 8.3 Hz, 1H, ArH), 7.54 (d, *J* = 8.5 Hz, 1H, ArH), 7.49 (td, *J* = 8.2, 1.3 Hz, 1H, ArH), 7.44 (td, *J* = 8.2, 1.3 Hz, 1H, ArH), 7.24 (d, 1H, *J* = 8.5 Hz, ArH), 6.92 (t, *J* = 5.1 Hz, 1H, NH), 3.93 (s, 3H, OCH_3), 2.86 (d, *J* = 6.6 Hz, 2H, CH_2N), 2.67 (s, 2H, CH_2Ar), 2.23 (t, *J* = 7.4 Hz, 2H, CH_2CO), 1.61 (quintet, *J* = 7.4 Hz, 2H, CH_2), 1.36-1.19 (m, 8H, 4×CH_2), 0.98 (s, 6H, 2×CH_3), 0.85 (t, *J* = 7.3 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 173.7 (C=O), 153.4 (Ar), 134.0 (Ar), 130.0 (ArH), 128.0 (ArH), 127.4 (Ar), 126.8 (Ar), 126.0 (ArH), 125.7 (ArH), 123.8 (ArH), 121.8 (ArH), 61.9 (OCH_3), 46.9 (CH_2), 39.2 (CH_2), 37.2 (C), 31.6 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 26.1 (2×CH_3), 25.9 (CH_2), 22.5 (CH_2), 13.9 (CH_3)

HRMS (ESI^+) *m/z* : $C_{24}H_{36}NO_2$ $[M+H]^+$, calcd 370.2746, found 370.2749

***N*-[3-(1-Methoxy-2-naphthyl)-2,2-dimethylpropyl]-2-methyloctanamide (664g)**



(664g)

Flash column chromatography, eluting with 4:1 hexane:EtOAc afforded the amide (664g) (77%) as a colourless oil.

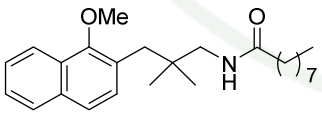
FTIR (film), ν_{max}, cm^{-1}: 3317 (NH), 2958, 2928, 2855 (CH), 1649 (C=O), 1547 (C=C), 1259 (C-N), 1233, 1082 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.00 (d, *J* = 8.3 Hz, 1H, ArH), 7.77 (d, *J* = 8.3 Hz, 1H, ArH), 7.50 (d, *J* = 8.5 Hz, 1H, ArH), 7.45 (td, *J* = 8.2, 1.3 Hz, 1H, ArH), 7.40 (td, *J* = 8.2, 1.3 Hz, 1H, ArH), 7.21 (d, *J* = 8.5 Hz, 1H, ArH), 6.73 (t, *J* = 6.3 Hz, 1H, NH), 3.89 (s, 3H, OCH_3), 2.89-2.74 (m, 2H, CH_2N), 2.63 (dd, *J* = 13.4, 1.6 Hz, 2H, CH_2Ar), 2.16 (sixtet, *J* = 6.5 Hz, 1H, CH), 1.65-1.54 (m, 1H, CH_2), 1.38-1.16 (m, 1+8H, CH_2), 1.11 (d, *J* = 7.0 Hz, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 0.82 (t, *J* = 6.5 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 176.4 (C=O), 153.5 (Ar), 134.0 (Ar), 130.1(ArH), 128.0 (ArH), 127.5 (Ar), 127.0 (Ar), 126.0 (ArH), 125.7 (ArH), 123.7 (ArH), 121.8 (ArH), 61.9 (OCH_3), 46.7 (CH_2), 42.1 (CH), 39.2 (CH_2), 37.1 (C), 34.4 (CH_2), 31.8 (CH_2), 27.2 (2×CH_2), 26.2 (2×CH_3), 22.5 (CH_2), 18.0 (CH_3), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{25}H_{38}NO_2$ $[M+H]^+$, calcd 384.2903, found 384.2903

***N*-[3-(1-Methoxy-2-naphthyl)-2,2-dimethylpropyl]nonanamide (664h)**



(664h)

Flash column chromatography, eluting with 4:1 hexane:EtOAc afforded the amide (664h) (94%) as a colourless oil.

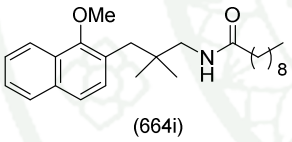
FTIR (film), ν_{max}, cm^{-1}: 3311 (NH), 2955, 2926, 2854 (CH), 1646 (C=O), 1598, 1548 (C=C), 1260 (C-N), 1233, 1082 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.05 (d, *J* = 8.3 Hz, 1H, ArH), 7.81 (d, *J* = 8.3 Hz, 1H, ArH), 7.55 (d, *J* = 8.5 Hz, 1H, ArH), 7.50 (ddd, *J* = 9.3, 8.2, 1.3 Hz, 1H, ArH), 7.44 (ddd, *J* = 9.3, 8.2, 1.3 Hz, 1H, ArH), 7.25 (d, 1H, *J* = 8.5 Hz, ArH), 6.80 (t, *J* = 5.9 Hz, 1H, NH), 3.94 (s, 3H, OCH_3), 2.86 (d, *J* = 6.6 Hz, 2H, CH_2N), 2.68 (s, 2H, CH_2Ar), 2.21 (t, *J* = 7.4 Hz, 2H, CH_2CO), 1.61 (quintet, *J* = 7.3 Hz, 2H, CH_2), 1.37-1.24 (m, 10H, 5×CH_2), 0.99 (s, 6H, 2×CH_3), 0.88 (t, *J* = 7.3 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 173.1 (C=O), 153.6 (Ar), 134.1 (Ar), 130.2 (ArH), 128.0 (ArH), 127.5 (Ar), 127.0 (Ar), 126.1 (ArH), 125.7 (ArH), 123.8 (ArH), 121.9 (ArH), 62.0 (OCH_3), 46.9 (CH_2), 39.2 (CH_2), 37.4 (C), 37.1 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.2 (2×CH_3), 26.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3)

HRMS (ESI^+) *m/z* : $C_{25}H_{38}NO_2$ $[M+H]^+$, calcd 384.2903, found 384.2923

***N*-[3-(1-Methoxy-2-naphthyl)-2,2-dimethylpropyl]decanamide (664i)**



(664i)

Flash column chromatography, eluting with 4:1 hexane:EtOAc afforded the amide (664i) (98%) as a colourless oil.

FTIR (film), ν_{max}, cm^{-1}: 3320 (NH), 2926, 2854 (CH), 1655 (C=O), 1598, 1542 (C=C), 1264 (C-N), 1232, 1081 (C-O)

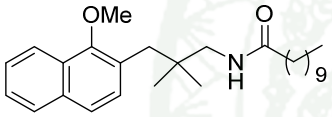
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.06 (dd, *J* = 8.3, 0.7 Hz, 1H, ArH), 7.82 (d, *J* = 8.3 Hz, 1H, ArH), 7.55 (d, *J* = 8.5 Hz, 1H, ArH), 7.50 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.45 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.26 (d, 1H, *J* = 8.5 Hz, ArH), 6.80 (t, *J* = 5.9 Hz, 1H, NH), 3.94 (s, 3H, OCH_3), 2.86 (d, *J* = 6.6 Hz, 2H, CH_2N),

2.68 (s, 2H, CH_2Ar), 2.21 (t, *J* = 7.4 Hz, 2H, CH_2CO), 1.64 (quintet, *J* = 7.4 Hz, 2H, CH_2), 1.37-1.21 (m, 12H, 6×CH_2), 0.99 (s, 6H, 2×CH_3), 0.87 (t, *J* = 6.8 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 173.1 (C=O), 153.5 (Ar), 134.1 (Ar), 130.1 (ArH), 128.0 (ArH), 127.5 (Ar), 127.0 (Ar), 126.0 (ArH), 125.7 (ArH), 123.7 (ArH), 121.9 (ArH), 62.0 (OCH_3), 46.9 (CH_2), 39.2 (CH_2), 37.3 (C), 37.1 (CH_2), 31.8 (CH_2), 29.5 (CH_2), 29.4 (2×CH_2), 29.2 (CH_2), 26.2 (2×CH_3), 26.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3)

HRMS (ESI^+) *m/z* : $C_{26}H_{40}NO_2$ $[M+H]^+$, calcd 398.3059, found 398.3063

***N*-[3-(1-Methoxy-2-naphthyl)-2,2-dimethylpropyl]undecanamide (664j)**



(664j)

Flash column chromatography, eluting with 4:1 hexane:EtOAc afforded the amide (664j) (91%) as a colourless oil.

FTIR (film), ν_{max}, cm^{-1}: 3316 (NH), 2925, 2854 (CH), 1650 (C=O), 1598, 1551 (C=C), 1262 (C-N), 1232, 1082 (C-O)

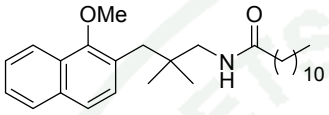
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.07 (d, *J* = 8.3 Hz, 1H, ArH), 7.83 (d, *J* = 8.3 Hz, 1H, ArH), 7.57 (d, *J* = 8.5 Hz, 1H, ArH), 7.52 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.46 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.27 (d, 1H, *J* = 8.5 Hz, ArH), 6.80 (t, *J* = 5.9 Hz, 1H, NH), 3.98 (s, 3H, OCH_3), 2.88 (d, *J* = 6.6 Hz, 2H, CH_2N), 2.69 (s, 2H, CH_2Ar), 2.22 (t, *J* = 7.8 Hz, 2H, CH_2CO), 1.66 (quintet, *J* = 7.8 Hz, 2H, CH_2), 1.39-1.21 (m, 14H, 7xCH_2), 1.00 (s, 6H, 2xCH_3), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 173.0 (C=O), 153.5 (Ar), 134.0 (Ar), 130.1 (ArH), 128.0 (ArH), 127.5 (Ar), 127.0 (Ar), 126.0 (ArH), 125.7 (ArH), 123.7 (ArH),

121.8 (ArH), 62.0 (OCH_3), 46.8 (CH_2), 39.2 (CH_2), 37.3 (C), 37.1 (CH_2), 31.8 (CH_2), 29.5 (2) (CH_2), 29.3 (2) (CH_2), 26.2 (2×CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{27}H_{42}NO_2$ $[M+H]^+$, calcd 412.3216, found 412.3229

***N*-[3-(1-Methoxy-2-naphthyl)-2,2-dimethylpropyl]dodecanamide (664k)**



(664k)

Flash column chromatography, eluting with 4:1 hexane:EtOAc afforded the amide (664k) (89%) as a colourless oil.

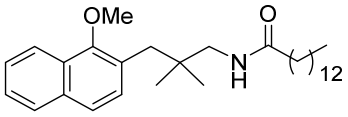
FTIR (film), ν_{max}, cm^{-1}: 3312 (NH), 2955, 2924, 2853 (CH), 1646 (C=O), 1598, 1551 (C=C), 1262 (C-N), 1233, 1082 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.07 (d, *J* = 8.3 Hz, 1H, ArH), 7.83 (d, *J* = 8.3 Hz, 1H, ArH), 7.57 (d, *J* = 8.5 Hz, 1H, ArH), 7.52 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.46 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.27 (d, 1H, *J* = 8.5 Hz, ArH), 6.79 (t, *J* = 6.2 Hz, 1H, NH), 3.96 (s, 3H, OCH_3), 2.87 (d, *J* = 6.6 Hz, 2H, CH_2N), 2.69 (s, 2H, CH_2Ar), 2.22 (t, *J* = 7.4 Hz, 2H, CH_2CO), 1.66 (quintet, *J* = 7.4 Hz, 2H, CH_2), 1.38-1.24 (m, 16H, 8×CH_2), 1.00 (s, 6H, 2×CH_3), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 173.1 (C=O), 153.5 (Ar), 134.1 (Ar), 130.1 (ArH), 128.0 (ArH), 127.5 (Ar), 127.0 (Ar), 126.0 (ArH), 125.7 (ArH), 123.7 (ArH), 121.9 (ArH), 62.0 (OCH_3), 46.9 (CH_2), 39.2 (CH_2), 37.4 (C), 37.1 (CH_2), 31.9 (CH_2), 29.6 (2×CH_2), 29.5 (CH_2), 29.4 (2×CH_2), 29.3 (CH_2), 26.2 (2×CH_3), 26.0 (CH_2), 22.6 (CH_2), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{28}H_{43}NNaO_2$ [M+Na], calcd 448.3191, found 448.3209

***N*-[3-(1-Methoxy-2-naphthyl)-2,2-dimethylpropyl]tetradecanamide (664l)**



(664l)

Flash column chromatography, eluting with 4:1 hexane:EtOAc afforded the amide (664l) (90%) as a white amorphous solid.

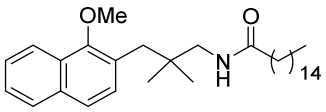
FTIR (film), ν_{max}, cm^{-1}: 3317 (NH), 2925, 2853 (CH), 1648 (C=O), 1598, 1546 (C=C), 1263 (C-N), 1232, 1082 (C-O);

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.07 (d, *J* = 8.3 Hz, 1H, ArH), 7.83 (d, *J* = 8.3 Hz, 1H, ArH), 7.57 (d, *J* = 8.5 Hz, 1H, ArH), 7.52 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.46 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.27 (d, 1H, *J* = 8.5 Hz, ArH), 6.79 (t, *J* = 6.6 Hz, 1H, NH), 3.95 (s, 3H, OCH_3), 2.87 (d, *J* = 6.6 Hz, 2H, CH_2N), 2.69 (s, 2H, CH_2Ar), 2.22 (t, *J* = 7.9 Hz, 2H, CH_2CO), 1.65 (quintet, *J* = 7.9 Hz, 2H, CH_2), 1.38-1.21 (m, 20H, 10×CH_2), 1.00 (s, 6H, 2×CH_3), 0.88 (t, *J* = 6.6 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 173.1(C=O), 153.5 (Ar), 134.0 (Ar), 130.1 (ArH), 128.0 (ArH), 127.5 (Ar), 126.1 (2) (Ar, ArH), 125.7 (ArH), 123.7 (ArH), 121.9 (ArH), 62.0 (OCH_3), 46.8 (CH_2), 39.2 (CH_2), 37.3 (C), 37.1 (CH_2), 31.9 (CH_2), 29.7 (6×CH_2), 29.5 (CH_2), 29.4 (2×CH_2), 29.3 (CH_2), 26.2 (2×CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{30}H_{48}NO_2$ $[M+H]^+$, calcd 454.3685, found 454.3681

***N*-[3-(1-Methoxy-2-naphthyl)-2,2-dimethylpropyl]hexadecanamide (664m)**



(664m)

Flash column chromatography, eluting with 4:1 hexane:EtOAc afforded the amide (664m) (97%) as a white amorphous solid.

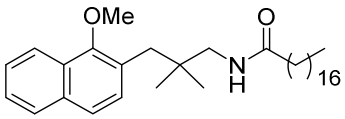
FTIR (film), ν_{max}, cm^{-1}: 3306 (NH), 2922, 2851(CH), 1642 (C=O), 1551 (C=C), 1264 (C-N), 1232, 1082 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.01 (d, *J* = 8.3 Hz, 1H, ArH), 7.78 (d, *J* = 8.3 Hz, 1H, ArH), 7.51 (d, *J* = 8.5 Hz, 1H, ArH), 7.49 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.44 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.22 (d, 1H, *J* = 8.5 Hz, ArH), 6.75 (t, *J* = 6.2 Hz, 1H, NH), 4.00 (s, 3H, OCH_3), 2.82 (d, *J* = 6.5 Hz, 2H, CH_2N), 2.63 (s, 2H, CH_2Ar), 2.16 (t, *J* = 7.4 Hz, 2H, CH_2CO), 1.60 (quintet, *J* = 7.4 Hz, 2H, CH_2), 1.32-1.10 (m, 24H, 12×CH_2), 0.95 (s, 6H, 2×CH_3), 0.82 (t, *J* = 6.1 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 173.1 (C=O), 153.5 (Ar), 134.1 (Ar), 130.2 (ArH), 128.0 (ArH), 127.5 (Ar), 127.0 (Ar), 126.0 (ArH), 125.7 (ArH), 123.8 (ArH), 121.9 (ArH), 62.1 (OCH_3), 46.9 (CH_2), 39.2 (CH_2), 37.4 (C), 37.1 (CH_2), 31.9 (CH_2), 29.7 (4×CH_2), 29.6 (3×CH_2), 29.5 (CH_2), 29.4 (2×CH_2), 29.3 (CH_2), 26.2 (2×CH_3), 26.0 (CH_2), 22.7 (CH_2), 14.1 (CH_3)

HRMS (ESI^+) *m/z* : $C_{32}H_{52}NO_2$ $[M+H]^+$, calcd 482.3998, found 482.3999

***N*-[3-(1-Methoxy-2-naphthyl)-2,2-dimethylpropyl]octadecanamide (664n)**



(664n)

Flash column chromatography, eluting with 4:1 hexane:EtOAc afforded the amide (664n) (70%) as a white amorphous solid.

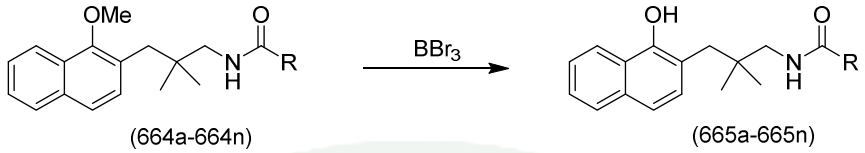
FTIR (film), ν_{max}, cm^{-1}: 3303 (NH), 2921, 2851 (CH), 1665 (C=O), 1598, 1547 (C=C), 1262 (C-N), 1232, 1081 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.07 (d, *J* = 8.3 Hz, 1H, ArH), 7.84 (d, *J* = 8.3 Hz, 1H, ArH), 7.57 (d, *J* = 8.5 Hz, 1H, ArH), 7.49 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.44 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H, ArH), 7.26 (d, 1H, *J* = 8.5 Hz, ArH), 6.96 (t, *J* = 6.2 Hz, 1H, NH), 3.95 (s, 3H, OCH_3), 2.86 (d, *J* = 6.5 Hz, 2H, CH_2N), 2.68 (s, 2H, CH_2Ar), 2.27 (t, *J* = 7.4 Hz, 2H, CH_2CO), 1.66 (quintet, *J* = 7.4 Hz, 2H, CH_2), 1.39-1.17 (m, 28H, 14×CH_2), 0.99 (s, 6H, 2×CH_3), 0.82 (t, *J* = 6.1 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 173.1 (C=O), 153.5 (Ar), 134.1 (Ar), 130.2 (ArH), 128.1 (ArH), 127.5 (Ar), 127.0 (Ar), 126.1 (ArH), 125.8 (ArH), 123.8 (ArH), 121.9 (ArH), 62.1 (OCH_3), 46.8 (CH_2), 39.2 (CH_2), 37.5 (C), 37.2 (CH_2), 31.9 (CH_2), 29.7 (7×CH_2), 29.6 (2×CH_2), 29.5 (CH_2), 29.4 (2×CH_2), 26.3 (2×CH_3), 26.0 (CH_2), 22.7 (CH_2), 14.2 (CH_3)

HRMS (ESI^+) *m/z* : $C_{34}H_{56}NO_2$ $[M+H]^+$ calcd 510.4311, found 510.4325

_N_-[3-(1-Hydroxy-2-naphthyl)-2,2-dimethylpropyl] amide (665)



(664a-664n) (665a-665n)

General Prodecure

To a solution of *N*-[3-(1-methoxy-2-naphthyl)-2,2-dimethylpropyl] amide (664a-664n) (1 mmol) in dry CH_2Cl_2 (50 mL) at 0^oC was slowly added BBr_3 (2 mmol). The reaction mixture was warmed to room temperature and stirred under nitrogen atmosphere for 3 h. Water was added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give *N*-[3-(1-hydroxy-2-naphthyl)-2,2-dimethylpropyl] amide (665a-665n). The crude product was used in the next step without further purification.

_N_-[3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] amide (666a-666n)

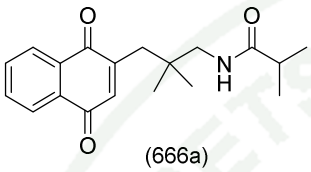
(665a-665n) (666a-666n)

General procedure:

To a solution of *N*-[3-(1-hydroxy-2-naphthyl)-2,2-dimethylpropyl] amide (665a-665n) (1 mmol) in MeOH (10 mL) and DMF (30 mL) was added NaOAc (1M, 10 mL) followed by Fremy's salt (6 mmol) in water (20 mL). After stirring at room temperature for 12 h, the reaction mixture was extracted with diethyl ether. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column

chromatography (silica gel, ethyl acetate: hexane, 1:2) to give the *N*-[3-(1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] amide (666a-666n).

_N_-[3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]-2-methyl propanamide (666a)



(666a)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (666a) (82%) as a yellow amorphous solid.

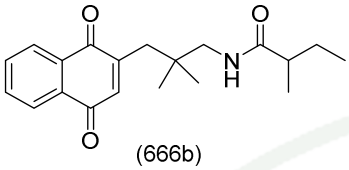
FTIR (film), ν_{max}, cm^{-1}: 3409 (NH), 2967, 2931, 2873 (CH), 1656, 1633 (C=O), 1594, 1537 (C=C), 1271 (C-N)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.06-8.02 (m, 1H, ArH), 8.01-7.99 (m, 1H, ArH), 7.70-7.67 (m, 2H, ArH), 6.80 (s, 1H, ArH), 6.58 (t, *J* = 6.4 Hz, 1H, NH), 2.90 (d, *J* = 6.4 Hz, 2H, CH_2N), 2.45 (s, 2H, CH_2Ar), 2.43 (heptet, *J* = 6.8 Hz, 1H, CH), 1.22 (d, *J* = 6.8 Hz, 6H, 2×CH_3), 0.93 (s, 6H, 2×CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.5 (C=O), 184.4 (C=O), 177.1 (C=O), 148.2 (Ar), 138.7 (ArH), 134.1 (ArH), 133.8 (ArH), 131.9 (2×Ar), 127.0 (ArH), 126.1 (ArH), 46.7 (CH_2), 37.9 (CH), 37.0 (CH_2), 36.0 (C), 25.8 (2×CH_3), 19.8 (2×CH_3)

HRMS (ESI^+) *m/z* : $C_{19}H_{23}NNaO_3$ [M+Na], calcd 336.1576, found 336.1561

***N*-[3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]-2-methyl butanamide (666b)**



(666b)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (666b) (87%) as a yellow amorphous solid.

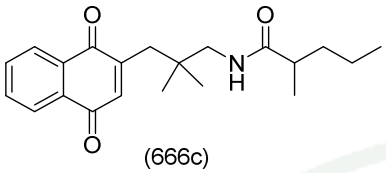
FTIR (film), ν_{max}, cm^{-1}: 3393 (N-H), 2966, 2932, 2874 (C=C-H), 1662 (C=O), 1595, 1541 (C=C), 1267 (C-N)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.07-8.03 (m, 1H, ArH), 8.03-7.99 (m, 1H, ArH), 7.72-7.68 (m, 2H, ArH), 6.78 (s, 1H, ArH), 6.52 (t, *J* = 6.0 Hz, 1H, NH), 2.94 (m, 2H, CH_2N), 2.43 (s, 2H, CH_2Ar), 2.22 (sixtet, *J* = 6.8 Hz, 1H, CH), 1.76-7.63 (m, 1H, CH_2), 1.51-1.39 (m, 1H, CH_2), 1.19 (d, *J* = 6.8 Hz, 2H, CH_3), 0.94-0.90 (ovalapping, 9H, 3×CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.3 (C=O), 184.4 (C=O), 167.6 (C=O), 148.2 (Ar), 138.6 (ArH), 134.0 (ArH), 133.7 (ArH), 132.0 (Ar), 131.9 (Ar), 126.9 (ArH), 126.1 (ArH), 46.7 (CH_2), 43.6 (CH), 37.9 (CH_2), 36.9 (C), 27.3 (CH_2), 26.0 (CH_3), 25.0 (CH_3), 17.5 (CH_3), 12.7 (CH_3)

HRMS (ESI^+) *m/z* : $C_{20}H_{26}NO_3$ $[M+H]^+$, calcd 328.1913, found 328.1920

***N*-[3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]-2-methyl pentanamide (666c)**



(666c)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (666c) (85%) as a yellow amorphous solid.

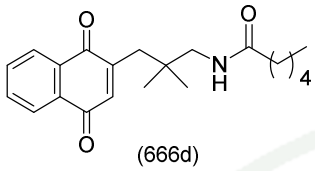
FTIR (film), ν_{max}, cm^{-1}: 3409 (NH), 2967, 2931, 2873 (CH), 1656, 1633 (C=O), 1594, 1537 (C=C), 1271 (C-N)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.05-8.02 (m, 1H, ArH), 8.03-7.98 (m, 1H, ArH), 7.70-7.67 (m, 2H, ArH), 6.77 (s, 1H, ArH), 6.50 (t, *J* = 6.3 Hz, 1H, NH), 2.88 (d, *J* = 6.4 Hz, 2H, CH_2N), 2.41 (s, 2H, CH_2Ar), 2.32-2.22 (m, 1H, CH), 1.69-1.59 (m, 1H, CH_2), 1.41-1.26 (m, 1+2H, CH_2), 1.14 (d, *J* = 7.1 Hz, 3H, CH_3), 0.89 (s, 6H, 2xCH_3), 0.87 (t, *J* = 7.4 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.4 (C=O), 184.4 (C=O), 176.8 (C=O), 148.2 (Ar), 138.6 (ArH), 134.0 (ArH), 133.7 (ArH), 132.0 (Ar), 131.9 (Ar), 126.9 (ArH), 126.1 (ArH), 46.8 (CH_2), 41.7 (CH), 37.8 (CH_2), 36.9 (CH_2), 36.0 (C), 26.0 (2×CH_3), 20.6 (CH_2), 17.9 (CH_3), 13.7 (CH_3)

HRMS (ESI^+) *m/z* : $C_{21}H_{28}NO_3$ $[M+H]^+$, calcd 342.2069, found 342.2077

***N*-[3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]hexanamide (666d)**



(666d)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (666d) (83%) as a yellow amorphous solid.

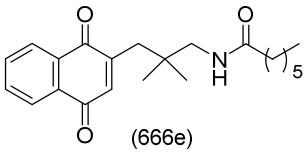
FTIR (film), ν_{max}, cm^{-1}: 3315 (NH), 2961, 2931, 2872 (CH), 1661, 1614 (C=O), 1594, 1535 (C=C), 1273 (C-N);

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.09-8.05 (m, 1H, ArH), 8.05-8.02 (m, 1H, ArH), 7.74-7.70 (m, 2H, ArH), 6.81 (s, 1H, ArH), 6.55 (t, *J* = 6.4 Hz, 1H, NH), 2.93 (d, *J* = 6.4 Hz, 2H, CH_2N), 2.45 (s, 2H, CH_2Ar), 2.26 (t, *J* = 7.8 Hz, 2H, CH_2CO), 1.70 (m, 2H, CH_2), 1.38-1.17 (m, 4H, 2×CH_2), 0.90 (s, 6H, 2×CH_3), 0.81 (t, *J* = 6.6 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.4 (C=O), 184.5 (C=O), 173.4 (C=O), 148.3 (Ar), 138.7 (ArH), 134.1 (ArH), 133.8 (ArH), 132.1 (Ar), 132.0 (Ar), 127.0 (ArH), 126.2 (ArH), 47.1 (CH_2), 38.0 (C), 37.1 (CH_2), 37.0 (CH_2), 31.5 (CH_2), 25.8 (2×CH_3), 25.6 (CH_2), 22.4 (CH_2), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{21}H_{28}NO_3$ $[M+H]^+$, calcd 342.2069, found 342.2064

***N*-[3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]heptanamide (666e)**


(666e)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (666e) (60%) as a yellow amorphous solid.

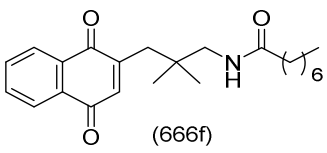
FTIR (film), ν_{max}, cm^{-1}: 3404 (NH), 2959, 2929, 2859 (CH), 1661, 1614 (C=O), 1594, 1535 (C=C), 1271 (C-N)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.10-8.07 (m, 1H, ArH), 8.07-8.04 (m, 1H, ArH), 7.75-7.72 (m, 2H, ArH), 6.82 (s, 1H, ArH), 6.51 (t, *J* = 6.3 Hz, 1H, NH), 2.93 (d, *J* = 6.3 Hz, 2H, CH_2N), 2.47 (s, 2H, CH_2Ar), 2.28 (t, *J* = 7.8 Hz, 2H, CH_2CO), 1.69 (quintet, *J* = 7.8 Hz, 2H, CH_2), 1.40-1.28 (m, 6H, 3×CH_2), 0.95 (s, 6H, 2×CH_3), 0.88 (t, *J* = 6.6 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.5 (C=O), 184.5 (C=O), 173.4 (C=O), 148.3 (Ar), 138.7 (ArH), 134.1 (ArH), 133.8 (ArH), 132.1 (Ar), 132.0 (Ar), 127.0 (ArH), 126.2 (ArH), 47.0 (CH_2), 38.0 (C), 37.2 (CH_2), 36.9 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 25.9 (2×CH_3), 25.8 (CH_2), 22.6 (CH_2), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{22}H_{30}NO_3$ $[M+H]^+$, calcd 356.2226, found 356.2218

***N*-[3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]octanamide (666f)**


(666f)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (666f) (91%) as a yellow amorphous solid.

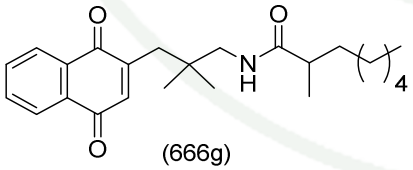
FTIR (film), ν_{max}, cm^{-1}: 3315 (NH), 2969, 2873 (CH), 1664, 1613 (C=O), 1594 (C=C), 1265 (C-N)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.07-8.03 (m, 1H, ArH), 8.02-7.99 (m, 1H, ArH), 7.72-7.68 (m, 2H, ArH), 6.79 (s, 1H, ArH), 6.58 (t, *J* = 6.3 Hz, 1H, NH), 2.91 (d, *J* = 6.3 Hz, 2H, CH_2N), 2.44 (s, 2H, CH_2Ar), 2.24 (t, *J* = 7.4 Hz, 2H, CH_2CO), 1.66 (quintet, *J* = 7.4 Hz, 2H, CH_2), 1.37-1.19 (m, 8H, 4×CH_2), 0.91 (s, 6H, 2×CH_3), 0.83 (t, *J* = 6.7 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.2 (C=O), 184.3 (C=O), 173.3 (C=O), 148.2 (Ar), 138.5 (ArH), 133.9 (ArH), 133.6 (ArH), 132.0 (Ar), 131.8 (Ar), 126.8 (ArH), 126.0 (ArH), 47.1 (CH_2), 37.8 (C), 37.0 (CH_2), 36.8 (CH_2), 31.6 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 25.8 (2×CH_3), 25.7 (CH_2), 22.5 (CH_2), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{23}H_{31}NNaO_3$ [M+Na], calcd 392.2202, found 392.2199

***N*-[3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]-2-methyl octanamide (666g)**



(666g)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (666g) (94%) as a yellow amorphous solid.

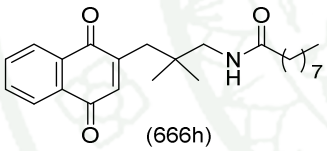
FTIR (film), ν_{max}, cm^{-1}: 3405 (NH), 2930, 2857 (CH), 1650, 1614 (C=O), 1594, 1537 (C=C), 1266 (C-N)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.05-8.02 (m, 1H, ArH), 8.01-7.98 (m, 1H, ArH), 7.69-7.66 (m, 2H, ArH), 6.77 (s, 1H, ArH), 6.47 (t, *J* = 6.4 Hz, 1H, NH), 2.87 (d, *J* = 6.4 Hz, 2H, CH_2N), 2.41 (s, 2H, CH_2Ar), 2.26 (sixtet, *J* =6.7 Hz, 1H, CH), 1.70-1.59 (m, 1H, CH_2), 1.43-1.32 (m, 1H, CH_2), 1.32-1.17 (m, 8H, 4×CH_2), 1.14 (d, *J* = 6.7 Hz, 3H, CH_3), 0.90 (s, 6H, 2×CH_3), 0.80 (t, *J* = 7.0 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.4 (C=O), 184.4 (C=O), 176.8 (C=O), 148.2 (Ar), 138.7 (ArH), 134.0 (ArH), 133.7 (ArH), 132.1(Ar), 131.9 (Ar), 126.9 (ArH), 126.1 (ArH), 46.8 (CH_2), 42.0 (CH), 37.9 (CH_2), 37.0 (CH_2), 34.4 (C), 31.7 (CH_2), 29.3 (CH_2), 27.5 (CH_2), 25.9 (CH_3), 25.8 (CH_3), 22.6 (CH_2), 18.1(CH_3), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{24}H_{34}NO_3$ $[M+H]^+$, calcd 384.2539, found 384.2556

***N*-[3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]nonanamide (666h)**



(666h)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (666h) (92%) as a yellow amorphous solid.

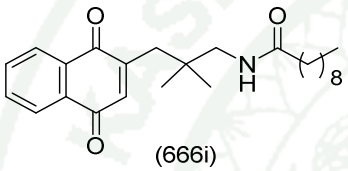
FTIR (film), ν_{max}, cm^{-1}: 3397 (NH), 2956, 2926, 2855 (CH), 1664, 1614 (C=O), 1594, 1542 (C=C), 1272 (C-N)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.03-8.00 (m, 1H, ArH), 8.00-7.97 (m, 1H, ArH), 7.69-7.65 (m, 2H, ArH), 6.76 (s, 1H, ArH), 6.45 (t, *J* = 6.5 Hz, 1H, NH), 2.87 (d, *J* = 6.5 Hz, 2H, CH_2N), 2.40 (s, 2H, CH_2Ar), 2.21 (t, *J* = 7.7 Hz, 2H, CH_2CO), 1.63 (quintet, *J* = 7.7 Hz, 2H, CH_2), 1.35-1.16 (m, 10H, 5×CH_2), 0.88 (s, 6H, 2×CH_3), 0.79 (t, *J* = 7.1 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.4 (C=O), 184.4 (C=O), 173.3 (C=O), 148.2 (Ar), 138.6 (ArH), 134.0 (ArH), 133.7 (ArH), 132.1 (Ar), 131.9 (Ar), 126.9 (ArH), 126.1 (ArH), 47.0 (CH_2), 37.9 (C), 37.1 (CH_2), 36.9 (CH_2), 31.8 (CH_2), 29.3 (2×CH_2), 29.1 (CH_2), 25.9 (2×CH_3), 25.8 (CH_2), 22.6 (CH_2), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{24}H_{34}NO_3$ $[M+H]^+$, calcd 384.2539, found 384.2520

***N*-[3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]decanamide (666i)**



(666i)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (666i) (85%) as a yellow amorphous solid.

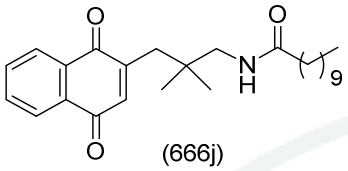
FTIR (film), ν_{max}, cm^{-1}: 2921, 2854 (CH), 1667, 1650, 1614, (C=O), 1594, 1538 (C=C), 1271 (C-N)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.04-8.00 (m, 1H, ArH), 8.00-7.97 (m, 1H, ArH), 7.69-7.66 (m, 2H, ArH), 6.76 (s, 1H, ArH), 6.45 (t, *J* = 6.6 Hz, 1H, NH), 2.87 (d, *J* = 6.6 Hz, 2H, CH_2N), 2.40 (s, 2H, CH_2Ar), 2.21 (t, *J* = 7.7 Hz, 2H, CH_2CO), 1.62 (quintet, *J* = 7.7 Hz, 2H, CH_2), 1.34-1.11(m, 12H, 6×CH_2), 0.88 (s, 6H, 2×CH_3), 0.79 (t, *J* = 7.9 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.4 (C=O), 184.4 (C=O), 173.3 (C=O), 148.2 (Ar), 138.6 (ArH), 134.0 (ArH), 133.7 (ArH), 132.0 (Ar), 131.9 (Ar), 126.9 (ArH), 126.1 (ArH), 47.0 (CH_2), 37.9 (C), 37.1 (CH_2), 36.9 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.3 (2×CH_2), 29.2 (CH_2), 25.9 (2×CH_3), 25.8 (CH_2), 22.6 (CH_2), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{25}H_{36}NO_3$ $[M+H]^+$, calcd 398.2695, found 398.2704

***N*-[3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]undecanamide (666j)**



(666j)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (666j) (91%) as a yellow amorphous solid.

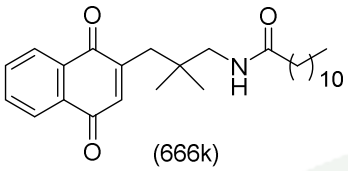
FTIR (film), ν_{max}, cm^{-1}: 3404 (NH), 2927, 2854 (CH), 1663 (C=O), 1595, 1528 (C=C), 1265 (C-N);

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.04-8.00 (m, 1H, ArH), 8.00-7.96 (m, 1H, ArH), 7.70-7.65 (m, 2H, ArH), 6.76 (s, 1H, ARH), 6.61 (br, 1H, NH), 2.89 (d, *J* = 6.4 Hz, 2H, CH_2N), 2.42 (s, 2H, CH_2Ar), 2.22 (t, *J* = 7.7 Hz, 2H, CH_2CO), 1.63 (quintet, *J* = 7.7 Hz, 2H, CH_2), 1.34-1.11(m, 14H, 7×CH_2), 0.89 (s, 6H, 2×CH_3), 0.78 (t, *J* = 7.0 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.2 (C=O), 184.3 (C=O), 173.3 (C=O), 148.2 (Ar), 138.5 (ArH), 133.9 (ArH), 133.6 (ArH), 131.9 (Ar), 131.8 (Ar), 126.8 (ArH), 126.0 (ArH), 47.0 (CH_2), 37.7 (C), 36.9 (CH_2), 36.7 (CH_2), 31.7 (2×CH_2), 29.3 (2×CH_2), 29.2 (CH_2), 29.1 (CH_2), 25.8 (2×CH_3), 25.4 (CH_2), 22.5 (CH_2), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{26}H_{37}NNaO_3$ [M+Na], calcd 434.2671, found 434.2691

***N*-[3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]dodecanamide (666k)**



(666k)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (666k) (93%) as a yellow amorphous solid.

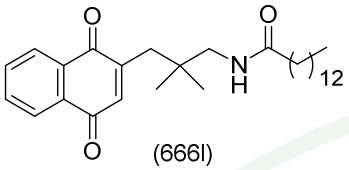
FTIR (film), ν_{max}, cm^{-1}: 3402 (NH), 2926, 2854 (CH), 1663 (C=O), 1595, 1533 (C=C), 1265 (C-N)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.00-7.96 (m, 1H, ArH), 7.96-7.91 (m, 1H, ArH), 7.66-7.61 (m, 2H, ArH), 6.73 (s, 1H, ArH), 6.66 (br, 1H, NH), 2.88 (d, *J* = 6.5 Hz, 2H, CH_2N), 2.39 (s, 2H, CH_2Ar), 2.19 (t, *J* = 7.7 Hz, 2H, CH_2CO), 1.60 (quintet, *J* = 7.7 Hz, 2H, CH_2), 1.33-1.07 (m, 14H, 7×CH_2), 0.85 (s, 6H, 2×CH_3), 0.75 (t, *J* = 6.7 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.0 (C=O), 184.2 (C=O), 173.3 (C=O), 148.1 (Ar), 138.3 (ArH), 133.8 (ArH), 133.5 (ArH), 131.8 (Ar), 131.7 (Ar), 126.7 (ArH), 125.8 (ArH), 47.0 (CH_2), 37.6 (C), 36.8 (CH_2), 36.6 (CH_2), 31.6 (CH_2), 29.4 (3×CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 25.7 (2×CH_3), 25.3 (CH_2), 22.4 (CH_2), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{27}H_{39}NNaO_3$ [M+Na], calcd 448.2828, found 448.2827

***N*-[3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]tetradecan-amide (666l)**



(666l)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (666l) (84%) as a yellow amorphous solid.

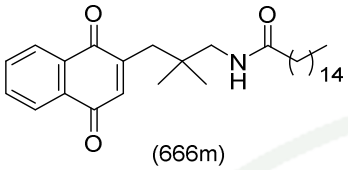
FTIR (film), ν_{max}, cm^{-1}: 3413 (N-H), 2926, 2854 (CH), 1664, 1613 (C=O), 1594, 1523 (C=C), 1265 (C-N)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.08-8.05 (m, 1H, ArH), 8.05-8.01 (m, 1H, ArH), 7.73-7.69 (m, 2H, ArH), 6.80 (s, 1H, ArH), 6.52 (t, *J* = 6.6 Hz, 1H, NH), 2.92 (d, *J* = 6.6 Hz, 2H, CH_2N), 2.45 (s, 2H, CH_2Ar), 2.26 (t, *J* = 7.4 Hz, 2H, CH_2CO), 1.67 (quintet, *J* = 7.4 Hz, 2H, CH_2), 1.39-1.15 (m, 20H, 10×CH_2), 0.93 (s, 6H, 2×CH_3), 0.83 (t, *J* = 6.9 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.5 (C=O), 184.4 (C=O), 173.3 (C=O), 148.2 (Ar), 138.6 (ArH), 134.0 (ArH), 133.7 (ArH), 132.1 (Ar), 131.9 (Ar), 126.9 (ArH), 126.1 (Ar), 47.0 (CH_2), 37.9 (C), 37.1 (CH_2), 36.9 (CH_2), 31.1 (CH_2), 29.6 (4×CH_2), 29.5 (3×CH_2), 29.2 (CH_2), 25.8 (2×CH_3), 25.6 (CH_2), 22.5 (CH_2), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{29}H_{43}NNaO_3$ [M+Na], calcd 476.3141, found 476.3141

***N*-[3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]hexadecan-amide (666m)**



(666m)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (666m) (81%) as a yellow amorphous solid.

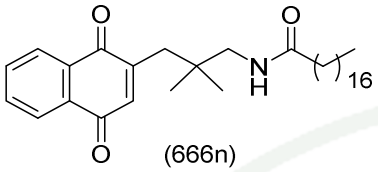
FTIR (film), ν_{max}, cm^{-1}: 3410 (NH), 2917, 2849 (CH), 1661, 1613 (C=O), 1593, 1557 (C=C), 1270 (C-N)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.04-8.00 (m, 1H, ArH), 8.00-7.97 (m, 1H, ArH), 7.69-7.65 (m, 2H, ArH), 6.76 (s, 1H, ArH), 6.46 (t, *J* = 6.4 Hz, 1H, NH), 2.87 (d, *J* = 6.4 Hz, 2H, CH_2N), 2.40 (s, 2H, CH_2Ar), 2.21 (t, *J* = 7.4 Hz, 2H, CH_2CO), 1.63 (quintet, *J* = 7.4 Hz, 2H, CH_2), 1.35-1.10 (m, 24H, 12×CH_2), 0.88 (s, 6H, 2×CH_3), 0.79 (t, *J* = 6.7 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.4 (C=O), 184.4 (C=O), 173.3 (C=O), 148.2 (Ar), 138.7 (ArH), 134.0 (ArH), 133.7 (ArH), 132.1 (Ar), 131.9 (Ar), 126.9 (ArH), 126.1 (ArH), 47.0 (CH_2), 37.9 (C), 37.2 (CH_2), 36.9 (CH_2), 31.9 (CH_2), 29.6 (6×CH_2), 29.5 (CH_2), 29.4 (2×CH_2), 29.3 (CH_2), 25.9 (2×CH_3), 25.8 (CH_2), 22.6 (CH_2), 14.1 (CH_3)

HRMS (ESI^+) *m/z* : $C_{31}H_{47}NNaO_3$ [M+Na], calcd 504.3454, found 504.3434

***N*-[3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]octadecan-amide (666n)**



(666n)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (666n) (98%) as a yellow amorphous solid.

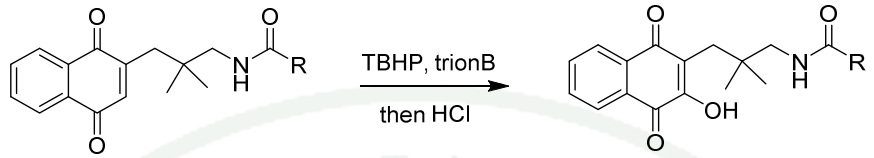
FTIR (film), ν_{max}, cm^{-1}: 3314 (NH), 2926, 2853 (C=C), 1663, 1613 (C=O), 1594, 1522 (C=C), 1265 (C-N)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.02-7.99 (m, 1H, ArH), 7.98-7.92 (m, 1H, ArH), 7.67-7.64 (m, 2H, ArH), 6.74 (s, 1H, ArH), 6.42 (t, *J* = 6.5 Hz, 1H, NH), 2.85 (d, *J* = 6.5 Hz, 2H, CH_2N), 2.39 (s, 2H, CH_2Ar), 2.20 (t, *J* = 7.4 Hz, 2H, CH_2CO), 1.61 (quintet, *J* = 7.4 Hz, 2H, CH_2), 1.33-1.12 (m, 28H, 14×CH_2), 0.87 (s, 6H, 2×CH_3), 0.78 (t, *J* = 6.5 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.5 (C=O), 184.4 (C=O), 173.3 (C=O), 148.2 (Ar), 138.7 (ArH), 134.0 (ArH), 133.7 (ArH), 132.0 (Ar), 131.9 (Ar), 126.9 (ArH), 126.1 (ArH), 47.0 (CH_2), 37.9 (C), 37.2 (CH_2), 36.9 (CH_2), 31.9 (CH_2), 29.7 (6×CH_2), 29.6 (2×CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (2×CH_2), 25.9 (2×CH_3), 25.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3)

HRMS (ESI^+) *m/z* : $C_{33}H_{52}NO_3$ $[M+H]^+$, calcd 510.3947, found 510.3940

***N*-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] amide (667)**

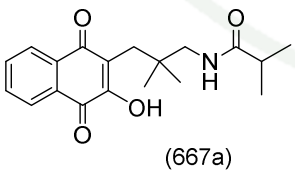


(666a-666n) (667a-667n)

General procedure:

To a solution of *N*-[3-(1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] amide (666a-666n) (1 mmol) in THF (13 mL), was added TBHP (12 mmol) followed by tritonB (3 mmol) until the solution turned red. The reaction mixture was stirred at room temperature for 20 min and then 10% HCl was added until the solution turned yellow. The mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, ethyl acetate: hexane, 1:2) to give *N*-[3-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] amide (667a-667n).

***N*-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]-2-methylpropanamide (667a)**



(667a)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (667a) (9%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals of (667a), m.p.127-129 °C.

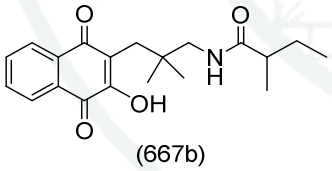
FTIR (KBr), ν_{max}, cm^{-1}: 3291 (NH), 2968, 2930 (CH), 1668, 1641, 1624 (C=O), 1595, 1577 (C=C), 1272 (C-N), 1216 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.11 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 8.08 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.76 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.69 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 6.92 (t, *J* = 6.7 Hz, 1H, NH), 2.91 (d, *J* = 6.7 Hz, 2H, CH_2N), 2.53 (s, 2H, CH_2Ar), 2.50 (heptet, *J* = 6.9 Hz, 1H, CH), 1.24 (d, *J* = 6.9 Hz, 6H, 2×CH_3), 0.95 (s, 6H, 2×CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.0 (C=O), 180.9 (C=O), 177.2 (C=O), 155.0 (Ar), 135.1 (ArH), 133.3 (ArH), 132.8 (Ar), 129.3 (Ar), 127.1 (ArH), 126.3 (ArH), 121.6 (Ar), 46.8 (CH_2), 38.2 (C), 36.1 (CH), 31.9 (CH_2), 26.2 (2×CH_3), 19.8 (2×CH_3)

HRMS (ESI^+) *m/z* : $C_{19}H_{23}NNaO_4$ [M+Na], calcd 352.1519, found 352.1517

***N*-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]-2-methylbutanamide (667b)**



(667b)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (667b) (11%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals of (667b), m.p.120-121 °C.

FTIR (KBr), ν_{max}, cm^{-1}: 3294 (NH), 2967, 2920, 2873 (CH), 1668, 1641, 1623 (C=O), 1596, 1566 (C=C), 1272 (C-N), 1215 (C-O);

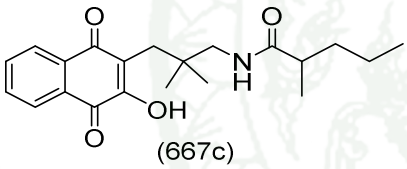
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.10 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 8.07 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.75 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.68 (td, *J* = 7.6, 1.4

Hz, 1H, ArH), 6.95 (t, *J* = 6.7 Hz, 1H, NH), 2.99-2.87 (m, 2H, CH_2N), 2.52 (s, 2H, CH_2Ar), 2.32-2.22 (m, 1H, CH), 1.80-1.68 (m, 1H, CH_2), 1.56-1.43, (m, 1H, CH_2), 1.21 (d, *J* = 6.9 Hz, 3H, CH_3), 0.95-0.94 (overlapping, 9H, 3xCH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.0 (C=O), 180.9 (C=O), 176.9 (C=O), 155.1 (Ar), 135.1 (ArH), 133.2 (ArH), 132.7 (Ar), 129.3 (Ar), 127.1 (ArH), 126.3 (ArH), 121.5 (Ar), 47.0 (CH_2), 43.6 (CH), 38.1 (C), 31.8 (CH_2), 27.3 (CH_2), 26.2 (2×CH_3), 17.6 (CH_3), 12.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{20}H_{25}NNaO_4$ [M+Na], calcd 366.1676, found 366.1692

***N*-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]-2-methyl pentanamide (667c)**



(667c)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (667c) (21%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals of (667c), m.p.145-147 °C.

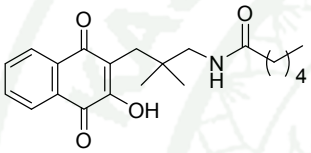
FTIR (KBr), ν_{max}, cm^{-1}: 3295 (NH), 2963, 2930, 2871 (CH), 1669, 1642, 1623 (C=O), 1596, 1566 (C=C), 1271 (C-N), 1215 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.06 (ddd, *J* = 7.6, 1.4, 0.4 Hz, 1H, ArH), 8.03 (ddd, *J* = 7.6, 1.4, 0.4 Hz, 1H, ArH), 7.71 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.64 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 6.84 (t, *J* = 6.7 Hz, 1H, NH), 2.93-2,82 (m, 2H, CH_2N), 2.48 (s, 2H, CH_2Ar), 2.33-2.25 (m, 1H, CH), 1.70-1.63 (m, 1H, CH_2), 1.39-3.28 (m, 1H+2H, CH_2), 1.16 (d, *J* = 6.9 Hz, 3H, CH_3), 0.90 (s, 6H, 2×CH_3), 0.87 (t, *J* = 7.3 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.0 (C=O), 180.9 (C=O), 176.8 (C=O), 155.1 (Ar), 135.0 (ArH), 133.2 (ArH), 132.8 (Ar), 129.4 (Ar), 127.1 (ArH), 126.3 (ArH), 121.6 (Ar), 46.9 (CH_2), 41.8 (CH), 38.1 (C), 36.5 (CH_2), 31.8 (CH_2), 26.1 (2×CH_3), 20.7 (CH_2), 18.0 (CH_3), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{21}H_{27}NNaO_4$ [M+Na], calcd 380.1832, found 380.1836

***N*-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] hexanamide (667d)**



(667d)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (667d) (22%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals of (667d), m.p.79-80 °C.

FTIR (KBr), ν_{max}, cm^{-1}: 3357 (NH), 2960, 2924, 2855 (CH), 1673, 1660, 1632 (C=O), 1594, 1578, 1550 (C=C), 1273 (C-N), 1216 (C-O)

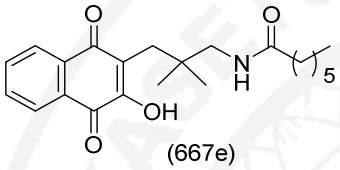
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.07 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 8.04 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.72 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.65 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.53 (s, 1H, OH), 6.79 (t, *J* = 6.8 Hz, 1H, NH), 2.87 (d, *J* = 6.8 Hz, 2H, CH_2N), 2.48 (s, 2H, CH_2Ar), 2.24 (t, *J* = 7.5 Hz, 2H, CH_2CO), 1.66 (quintet, *J* = 7.5 Hz, 2H, CH_2), 1.35-1.27 (m, 4H, 2×CH_2), 0.91 (s, 6H, 2×CH_3), 0.86 (t, *J* = 6.5 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.0 (C=O), 180.9 (C=O), 173.4 (C=O), 155.0 (Ar), 135.1 (ArH), 133.2 (ArH), 132.8 (Ar), 129.3 (Ar), 127.1 (ArH), 126.3

(ArH), 121.6 (Ar), 47.1 (CH_2), 38.1 (C), 37.2 (CH_2), 31.9 (CH_2), 31.6 (CH_2), 26.2 ($2\times CH_3$), 25.6 (CH_2), 22.4 (CH_2), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{21}H_{27}NNaO_4$ [M+Na], calcd 380.1832, found 380.1850

***N*-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] heptanamide (667e)**



(667e)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (667e) (10%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals of (667e), m.p. 85-86 °C.

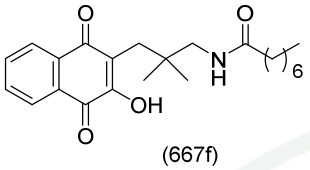
FTIR (KBr), ν_{max}, cm^{-1}: 3358 (NH), 2928, 2870 (CH), 1673, 1632 (C=O), 1594, 1578, 1549 (C=C), 1274 (C-N), 1216 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.16 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 8.13 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.81 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.74 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.63 (s, 1H, OH), 6.87 (t, *J* = 6.8 Hz, 1H, NH), 2.96 (d, *J* = 6.8 Hz, 2H, CH_2N), 2.57 (s, 2H, CH_2Ar), 2.32 (t, *J* = 7.8 Hz, 2H, CH_2CO), 1.74 (quintet, *J* = 7.8 Hz, 2H, CH_2), 1.47-1.31 (m, 6H, $3\times CH_2$), 0.99 (s, 6H, $2\times CH_3$), 0.92 (t, *J* = 6.8 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.0 (C=O), 180.9 (C=O), 173.3 (C=O), 155.0 (Ar), 135.1 (ArH), 133.2 (ArH), 132.8 (Ar), 129.3 (Ar), 127.1 (ArH), 126.3 (ArH), 121.6 (Ar), 47.1 (CH_2), 38.1 (C), 37.3 (CH_2), 31.9 (CH_2), 31.6 (CH_2), 29.4 (CH_2), 26.2 ($2\times CH_3$), 25.9 (CH_2), 22.5 (CH_2), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{22}H_{29}NNaO_4$ [M+Na], calcd 394.1989, found 394.2008

***N*-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] octanamide (667f)**



(667f)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (667f) (13%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals of (667f), m.p. 113-114°C.

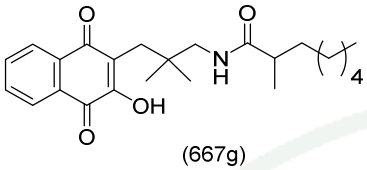
FTIR (KBr), ν_{max}, cm^{-1}: 3355 (NH), 2957, 2925, 2853(CH), 1671, 1632 (C=O), 1594, 1578, 1551(C=C), 1274 (C-N), 1216 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.09 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 8.06 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.74 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.67 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 6.85 (t, *J* = 6.3 Hz, 1H, NH), 2.92 (d, *J* = 6.3 Hz, 2H, CH_2N), 2.53 (s, 2H, CH_2Ar), 2.27 (t, *J* = 7.7 Hz, 2H, CH_2CO), 1.70 (quintet, *J* = 7.7 Hz, 2H, CH_2), 1.40-1.21 (m, 8H, 4×CH_2), 0.95 (s, 6H, 2×CH_3), 0.86 (t, *J* = 6.9 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.0 (C=O), 180.9 (C=O), 173.4 (C=O), 155.1 (Ar), 135.1 (ArH), 133.2 (ArH), 132.8 (Ar), 129.4 (Ar), 127.1 (ArH), 126.3 (ArH), 121.6 (Ar), 47.1 (CH_2), 38.0 (C), 37.3 (CH_2), 31.9 (CH_2), 31.7 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 26.2 (2×CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{23}H_{31}NNaO_4$ [M+Na], calcd 408.2145, found 408.2152

***N*-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]-2-methyl octanamide (667g)**



(667g)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (667g) (19%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals of (667g), m.p. 102-104 °C.

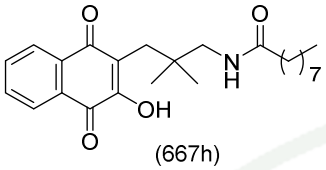
FTIR (KBr), ν_{max}, cm^{-1}: 3295 (NH), 2965, 2922, 2855 (CH), 1668, 1642, 1623 (C=O), 1597, 1560 (C=C), 1271(C-N), 1214 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.12 (dd, *J* = 7.8, 1.4 Hz, 1H, ArH), 8.09 (dd, *J* = 7.8, 1.4 Hz, 1H, ArH), 7.77 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.70 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.58 (s, 1H, OH), 6.86 (t, *J* = 6.6 Hz, 1H, NH), 2.94 (dd, *J* = 6.6, 4.5 Hz, 2H, CH_2N), 2.54 (s, 2H, CH_2Ar), 2.39-2.30 (m, 1H, CH), 1.79-1.67 (m, 1H, CH_2), 1.37-1.22 (m, 1H+8H, CH_2), 1.21 (d, *J* = 6.4 Hz, 3H, CH_3), 0.96 (s, 6H, 2×CH_3), 0.86 (t, *J* = 7.3 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.0 (C=O), 180.9 (C=O), 178.8 (C=O), 155.0 (Ar), 135.1 (ArH), 133.3 (ArH), 132.9 (Ar), 129.3 (Ar), 127.2 (ArH), 126.3 (ArH), 121.6 (Ar), 47.0 (CH_2), 42.1 (CH), 38.2 (C), 34.5 (CH_2), 31.9 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 27.6 (CH_2), 26.3 (CH_3), 26.2 (CH_3), 22.6 (CH_2), 18.1 (CH_3), 14.1 (CH_3)

HRMS (ESI^+) *m/z* : $C_{24}H_{33}NNaO_4$ [M+Na], calcd 422.2302, found 422.2321

***N*-*[*3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] nonanamide (667h)**



(667h)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (667h) (25%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals of (667h), m.p. 111-113 °C.

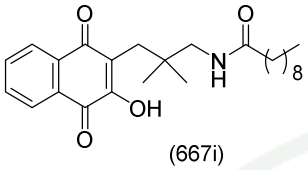
FTIR (KBr), ν_{max}, cm^{-1}: 3357 (NH), 2959**,** 2923, 2853 (CH), 1665, 1633 (C=O), 1594, 1578, 1550 (C=C), 1273 (C-N), 1215 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.11 (dd, *J* = 7.6, 1.1 Hz, 1H, ArH), 8.08 (dd, *J* = 7.6, 1.1 Hz, 1H, ArH), 7.76 (td, *J* = 7.6, 1.3 Hz, 1H, ArH), 7.69 (td, *J* = 7.6, 1.3 Hz, 1H, ArH), 6.90 (t, *J* = 6.3 Hz, 1H, NH), 2.93 (d, *J* = 6.3 Hz, 2H, CH_2N), 2.54 (s, 2H, CH_2Ar), 2.30 (t, *J* = 7.7 Hz, 2H, CH_2CO), 1.71 (quintet, *J* = 7.7 Hz, 2H, CH_2), 1.40-1.24 (m, 10H, 5×CH_2), 0.96 (s, 6H, 2×CH_3), 0.86 (t, *J* = 7.0 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.0 (C=O), 180.9 (C=O), 173.4 (C=O), 155.1 (Ar), 135.0 (ArH), 133.2 (ArH), 132.8 (Ar), 129.4 (Ar), 127.1 (ArH), 126.3 (ArH), 121.6 (Ar), 47.1 (CH_2), 38.0 (C), 37.3 (CH_2), 31.8 (2×CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.2 (2×CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{24}H_{33}NNaO_4$ [M+Na], calcd 422.2302, found 422.2320

***N*-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] decanamide (667i)**



(667i)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (667i) (17%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals of (667i), m.p. 107-108 °C.

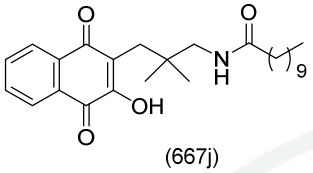
FTIR (KBr), ν_{max}, cm^{-1}: 3358 (NH), 2921, 2853 (CH), 1664, 1631 (C=O), 1594, 1578, 1551(C=C), 1273 (C-N), 1216 (C-O)

^{1}H-NMR ($CDCl_3$, 300MHz) δ: 8.16 (dd, *J* = 7.6, 1.1 Hz, 1H, ArH), 8.13 (dd, *J* = 7.6, 1.1 Hz, 1H, ArH), 7.81 (td, *J* = 7.6, 1.6 Hz, 1H, ArH), 7.74 (td, *J* = 7.6, 1.6 Hz, 1H, ArH), 6.88 (t, *J* = 6.8 Hz, 1H, NH), 2.96 (d, *J* = 6.8 Hz, 2H, CH_2N), 2.57 (s, 2H, CH_2Ar), 2.32 (t, *J* = 7.8 Hz, 2H, CH_2CO), 1.74 (quintet, *J* = 7.8 Hz, 2H, CH_2), 1.44-1.24 (m, 12H, 6×CH_2), 0.99 (s, 6H, 2×CH_3), 0.89 (t, *J* = 7.1 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.0 (C=O), 180.9 (C=O), 173.5 (C=O), 155.1 (Ar), 135.0 (ArH), 133.2 (ArH), 132.8 (Ar), 129.4 (Ar), 127.1 (ArH), 126.3 (ArH), 121.5 (Ar), 47.0 (CH_2), 38.0 (C), 37.2 (CH_2), 31.8 (CH_2), 29.6 (2×CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.2 (2×CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.1 (CH_3)

HRMS (ESI^+) *m/z* : $C_{25}H_{36}NO_4$ $[M+H]^+$, calcd 414.2644, found 414.2628

***N*-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] undecanamide (667j)**



(667j)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (667j) (14%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals of (667j), m.p. 93-94 °C.

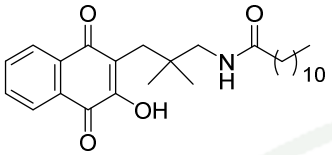
FTIR (KBr), ν_{max}, cm^{-1}: 3361 (NH), 2921, 2853 (CH), 1665, 1632 (C=O), 1594, 1578, 1550 (C=C), 1273 (C-N), 1215 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.10 (dd, *J* = 7.6, 1.1 Hz, 1H, ArH), 8.07 (dd, *J* = 7.6, 1.1 Hz, 1H, ArH), 7.75 (td, *J* = 7.6, 1.1 Hz, 1H, ArH), 7.68 (td, *J* = 7.6, 1.1 Hz, 1H, ArH), 6.89 (t, *J* = 6.3 Hz, 1H, NH), 2.92 (d, *J* = 6.3 Hz, 2H, CH_2N), 2.53 (s, 2H, CH_2Ar), 2.29 (t, *J* = 7.7 Hz, 2H, CH_2CO), 1.69 (quintet, *J* = 7.7 Hz, 2H, CH_2), 1.40-1.19 (m, 14H, 7×CH_2), 0.95 (s, 6H, 2×CH_3), 0.84 (t, *J* = 6.3 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.0 (C=O), 180.9 (C=O), 173.5 (C=O), 155.1 (Ar), 135.0 (ArH), 133.2 (ArH), 132.8 (Ar), 129.4 (Ar), 127.1 (ArH), 126.3 (ArH), 121.5 (Ar), 47.0 (CH_2), 38.0 (C), 37.2 (CH_2), 31.8 (2×CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (2×CH_2), 29.3 (CH_2), 26.2 (2×CH_3), 25.9(CH_2), 22.6 (CH_2), 14.1 (CH_3)

HRMS (ESI^+) *m/z* : $C_{26}H_{37}NNaO_4$ [M+Na], calcd 450.2615, found 450.2618

***N*-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] dodecanamide (667k)**



(667k)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (667k) (14%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals of (667k), m.p. 97-98 °C.

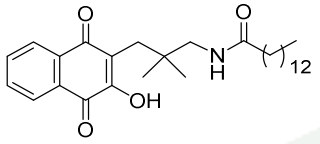
FTIR (KBr), ν_{max}, cm^{-1}: 3355 (NH), 2917, 2853 (CH), 1673, 1662, 1633 (C=O), 1594, 1578, 1551 (C=C), 1273 (C-N), 1216 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.09 (d, *J* = 7.6 Hz, 1H, ArH), 8.06 (d, *J* = 7.6 Hz, 1H, ArH), 7.73 (td, *J* = 7.6, 1.1 Hz, 1H, ArH), 7.67 (td, *J* = 7.6, 1.1 Hz, 1H, ArH), 6.89 (t, *J* = 6.6 Hz, 1H, NH), 2.92 (d, *J* = 6.6 Hz, 2H, CH_2N), 2.52 (s, 2H, CH_2Ar), 2.28 (t, *J* = 7.4 Hz, 2H, CH_2CO), 1.68 (quintet, *J* = 7.4 Hz, 2H, CH_2), 1.40-1.15 (m, 16H, 8×CH_2), 0.94 (s, 6H, 2×CH_3), 0.83 (t, *J* = 6.7 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.0 (C=O), 180.9 (C=O), 173.5 (C=O), 155.3 (Ar), 135.0 (ArH), 133.2 (ArH), 132.7 (Ar), 129.4 (Ar), 127.0 (ArH), 126.2 (ArH), 121.6 (Ar), 47.1 (CH_2), 38.0 (C), 37.2 (CH_2), 31.8 (CH_2), 29.6 (2×CH_2), 29.5 (CH_2), 29.4 (3×CH_2), 29.3 (CH_2), 26.2 (2×CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.1 (CH_3)

HRMS (ESI^+) *m/z* : $C_{27}H_{39}NNaO_4$ [M+Na], calcd 464.2771, found 464.2775

***N*-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] tetradecanamide (667l)**



(667l)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (667l) (12%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals of (667l), m.p. 94-95 °C.

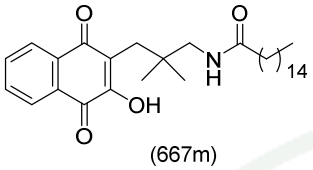
FTIR (KBr), ν_{max}, cm^{-1}: 3354 (NH), 2918, 2851 (CH), 1673, 1661, 1631 (C=O), 1594, 1578, 1552 (C=C), 1273 (C-N), 1216 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.13 (ddd, *J* = 7.6, 1.4, 0.4 Hz, 1H, ArH), 8.10 (ddd, *J* = 7.6, 1.4, 0.4 Hz, 1H, ArH), 7.77 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.71 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 6.86 (t, *J* = 6.5 Hz, 1H, NH), 2.94 (d, *J* = 6.5 Hz, 2H, CH_2N), 2.55 (s, 2H, CH_2Ar), 2.30 (t, *J* = 7.5 Hz, 2H, CH_2CO), 1.71 (quintet, *J* = 7.5Hz, 2H, CH_2), 1.43-1.17 (m, 20H, 10×CH_2), 0.96 (s, 6H, 2×CH_3), 0.87 (t, *J* = 6.5 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.0 (C=O), 180.9 (C=O), 173.4 (C=O), 155.0 (Ar), 135.1 (ArH), 133.2 (ArH), 132.8 (Ar), 129.4 (Ar), 127.1 (ArH), 126.3 (ArH), 121.6 (Ar), 47.1 (CH_2), 38.1 (C), 37.3 (CH_2), 31.9 (CH_2), 29.7 (2×CH_2), 29.6 (2×CH_2), 29.5 (CH_2), 29.4 (3×CH_2), 29.3 (CH_2), 26.4 (2×CH_3), 25.9 (CH_2), 22.7 (CH_2), 14.1(CH_3)

HRMS (ESI^+) *m/z* : $C_{29}H_{43}NNaO_4$ [M+Na], calcd 492.3084, found 492.3072

***N*-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] hexadecanamide (667m)**



(667m)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (667m) (19%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals of (667m), m.p. 94-95 °C.

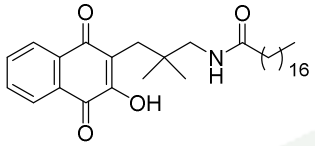
FTIR (KBr), ν_{max}, cm^{-1}: 3355 (NH), 2918, 2850(CH), 1673, 1662, 1631(C=O), 1594, 1578, 1551(C=C), 1273 (C-N), 1216 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.11 (ddd, *J* = 7.6, 1.3, 0.4 Hz, 1H, ArH), 8.03 (ddd, *J* = 7.6, 1.3, 0.4 Hz, 1H, ArH), 7.76 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.69 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 6.89 (t, *J* = 6.4 Hz, 1H, NH), 2.93 (d, *J* = 6.4 Hz, 2H, CH_2N), 2.54 (s, 2H, CH_2Ar), 2.30 (t, *J* = 7.7 Hz, 2H, CH_2CO), 1.71 (quintet, *J* = 7.7 Hz, 2H, CH_2), 1.42-1.21 (m, 24H, 12×CH_2), 0.96 (s, 6H, 2×CH_3), 0.86 (t, *J* = 6.7 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.0 (C=O), 180.9 (C=O), 173.4 (C=O), 155.1 (Ar), 135.0 (ArH), 133.2 (ArH), 132.8 (Ar), 129.4 (Ar), 127.1 (ArH), 126.3 (ArH), 121.5 (Ar), 47.1 (CH_2), 38.0 (C), 37.3 (CH_2), 31.9 (2×CH_2), 29.7 (3×CH_2), 29.6 (3×CH_2), 29.5 (CH_2), 29.4 (2×CH_2), 29.3 (CH_2), 26.2 (2×CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3)

HRMS (ESI^+) *m/z* : $C_{31}H_{47}NNaO_4$ [M+Na], calcd 520.3397, found 520.3393

***N*-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] octadecanamide (667n)**



(667n)

Flash column chromatography, eluting with 2:1 hexane:EtOAc afforded the product (667n) (25%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals of (667n), m.p. 95-96 °C.

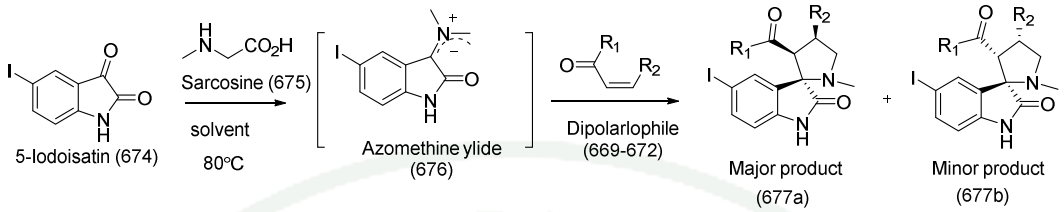
FTIR (KBr), ν_{max}, cm^{-1}: 3317 (NH), 2918, 2849 (CH), 1671, 1645 (C=O), 1594, 1579, 1554 (C=C), 1274 (C-N), 1214 (C-O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.06 (ddd, *J* = 7.6, 1.4, 0.4 Hz, 1H, ArH), 8.04 (ddd, *J* = 7.6, 1.4, 0.4 Hz, 1H, ArH), 7.71 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.65 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 6.84 (t, *J* = 6.7 Hz, 1H, NH), 2.88 (d, *J* = 6.7 Hz, 2H, CH_2N), 2.49 (s, 2H, CH_2Ar), 2.25 (t, *J* = 7.7 Hz, 2H, CH_2CO), 1.66 (quintet, *J* =7.7 Hz, 2H, CH_2), 1.37-1.11 (m, 28H, 14×CH_2), 0.91 (s, 6H, 2×CH_3), 0.81 (t, *J* = 6.7 Hz, 3H, CH_3)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 186.0 (C=O), 180.9 (C=O), 173.5 (C=O), 155.1 (Ar), 135.1 (ArH), 133.2 (ArH), 132.8 (Ar), 129.4 (Ar), 127.1 (ArH), 126.3 (ArH), 121.5 (Ar), 47.1 (CH_2), 38.1 (C), 37.3 (CH_2), 31.9 (2×CH_2), 29.7 (8×CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.2 (2×CH_3), 26.0 (CH_2), 22.7 (CH_2), 14.1 (CH_3)

HRMS (ESI^+) *m/z* : $C_{33}H_{51}NNaO_4$ [M+Na], calcd 548.3710, found 548.3700

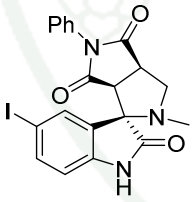
Spirooxindole pyrrolidine compounds



General procedure:

A mixture of 5-iodoisatin (674) (1 mmol), sarcosine (675) (1 mmol) and dipolarlophile (669-672) (1 mmol) in acetonitrile or EtOH (10 mL) was stirred and heated at 80 °C. When the reaction was completed (monitored by TLC or ^{1}H-NMR of reaction mixture) the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel).

(3*R*,3a'*R*,6a'*S*)-5-Iodo-2'-methyl-5'-phenyl-3a',6a'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',6'(1*H*,3'*H*,5'*H*)-trione (678a)



(678a)

1,3-Dipolar cycloaddition of 5-iodoisatin (674), sarcosine (675) and *N*-phenylmaleimide (669) in acetonitrile gave pure major product (678a) as a precipitate from the reaction mixture 36% then the filtrate was evaporated under reduced pressure and purified by flash column chromatography (silica gel, hexane:EtOAc, 2:1) to give more major product (678a) 13% and minor product (678b) 26%.

Major product (678a): Crystallization in EtOH gave a colourless crystal m.p.295-296 °C; R_f : 0.08 (1:1 hexane: EtOAc)

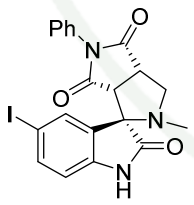
FTIR (solid), ν_{max}, cm^{-1}: 3306 (N-H), 2929 (C=C-H), 2867(C=C-H), 1771(C=O), 1722(C=O), 1694 (C=O), 1619(C=C), 1595 (C=C), 1123 (C-N), 599 (C-I)

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 10.77 (s, 1H, NH), 7.60 (dd, *J* = 1.7, 6.6 Hz, 1H, ArH), 7.54 (tt, *J* = 1.5, 7.7 Hz, 2H, PhH), 7.46, (tt, *J* = 7.3, 1.9 Hz, 1H, PhH,), 7.30 (m, 1H, PhH), 7.15 (d, *J* = 1.7 Hz, 1H, ArH), 6.14 (d, *J* = 8.1 Hz, 1H, ArH), 3.77 (t, *J* = 7.5 Hz, 1H, C*H*CH_2), 3.61-3.53 (m, *J* = 7.7, 1.6 Hz, 2H, CCH+CH_2), 3.37 (d, *J* = 9.1 Hz, 1H, NCH_2), 2.02 (s, 3H, NCH_3)

^{13}C-NMR (75 MHz, DMSO-d_6) δ: 180.0 (C=O), 177.1 (C=O), 177.0 (C=O), 142.5 (Ar), 138.0 (ArH), 133.9 (ArH), 132.2 (Ph), 129.1 (PhH), 128.6 (PhH), 128.1 (Ar), 126.6 (PhH), 112.3 (ArH), 84.3 (ArI), 71.9 (C), 54.2 (NCH_2), 52.3 (C*CH*), 44.8 (*CH*CH_2), 34.3 (NCH_3)

HRMS (ESI^+) *m/z* : $C_{20}H_{17}IN_3O_3$ $[M+H]^+$ 474.0309 found 474.0294

(3*R*,3a'*S*,6a'*R*)-5-Iodo-2'-methyl-5'-phenyl-3a',6a'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',6'(1*H*,3'*H*,5'*H*)-trione (678b)



(678b)

Minor product (678b): Crystallization in EtOH gave a colourless crystal of the (678b), m.p. 269-271°C.

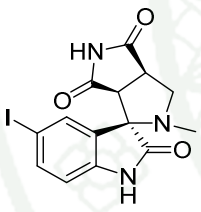
FTIR (solid), ν_{max}, cm^{-1}: 3100 (N-H), 2849 (C=C-H), 1778 (C=O), 1739 (C=O), 1704 (C=O), 1610 (C=C), 1596 (C=C), 1120 (C-N), 627 (C-I)

^{1}H-NMR (300MHz, DMSO-d_6) δ: 10.73 (s, 1H, NH), 7.71 (d, *J* = 1.7 Hz, 1H, ArH), 7.63 (dd, *J* = 1.7, 8.0 Hz, 1H, ArH,), 7.53-7.39 (m, 3H, PhH), 7.25-7.19 (m, 2H, PhH), 6.71 (d, *J* = 8.0 Hz, 1H, ArH,), 3.92-3.86 (m, 2H, CH), 3.54-3.44 (m, 1H, NCH_2), 3.39-3.31 (m, 1H, NCH_2), 1.99 (s, 3H, NCH_3)

^{13}C-NMR (75MHz, DMSO-d_6) δ: 177.1 (C=O), 176.0 (C=O), 174.8 (C=O), 142.4 (Ar), 138.2 (ArH), 132.9 (ArH), 132.3 (Ph), 130.7 (Ar), 128.9 (PhH), 128.4 (PhH), 127.0 (PhH), 112.3 (ArH), 85.3 (ArI), 72.4 (C), 53.7(2)(CH_2, CH), 43.6 (CH), 34.2 (CH_3)

HRMS (ESI^+) *m/z* : $C_{20}H_{16}IN_3O_3Na$ [M+Na], calcd 496.0129, found 496.0133

(3*R*,3a'*R*,6a'*S*)-5-Iodo-2'-methyl-3a',6a'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',6'(1*H*,3'*H*,5'*H*)-trione (679)



(679)

1,3-Dipolar cycloaddition of 5-iodoisatin (674), sarcosine (675) and maleimide (670) in acetonitrile or EtOH gave the cycloadduct as a precipitrate in the reaction mixture. The precipitate was filtered to give the desired product (679) 75%. Crystallization in EtOH gave a colourless crystal of the (679), m.p. 310-311 °C.

FTIR (solid), ν_{max}, cm^{-1}: 3188 (N-H), 2981 (C=C-H), 2893 (C=C-H), 1774(C=O), 1717(C=O), 1614(C=C), 1472 (C=C), 1197 (C-N), 1063 (C-N,), 591 (C-I)

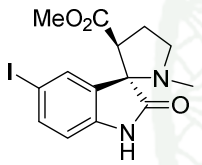
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 11.57 (s, 1H, NH,), 10.70 (s, 1H, NH), 7.58 (dd, *J* =1.7, 6.4 Hz, 1H, ArH), 7.06 (d, *J* = 1.7 Hz, 1H, ArH), 6.70 (d, *J* = 8.0

Hz, 1H, ArH), 3.50 (t, *J* = 7.8 Hz, 1H, CH), 3.44 (t, *J* = 8.6 Hz, 1H, NCH_2), 3.33 (d, *J* = 7.8 Hz, 1H, CH), 3.20 (d, *J* = 8.6 Hz, 1H, NCH_2), 1.95 (s, 3H, NCH_3)

^{13}C-NMR (75MHz, DMSO-d_6) δ: 180.3 (C=O), 177.2 (C=O), 176.4 (C=O), 142.4 (Ar), 138.0 (ArH), 134.0 (ArH), 128.0 (Ar), 112.0 (ArH), 84.3 (ArI), 71.5 (C), 53.8 (NCH_2), 52.9 (CH), 45.5 (CH), 34.3 (NCH_3)

HRMS (TOF EI$^+$) *m/z* : $C_{14}H_{12}IN_3O_3$ $[M+H]^+$, calcd 396.9926, found 396.9925

Methyl(3*R*,3'*S*)-5-iodo-1'-methyl-2-oxo-1,2-dihydrospiro[indole-3,2'-pyrrolidine] -3'-carboxylate (680a)



(680a)

Flash column chromatography eluting with 1:1 hexane:EtOAc afforded the major product (680a) (80.7%) as a colourless amorphous solid, crystallization in $CHCl_3$: hexane to give snow white crystal of the (680a), m.p. 171-172 °C.

FTIR (film), ν_{max}, cm^{-1}: 3242(NH), 2949(C=C-H), 3847(C=C-H), 1732(C=O), 1613(C=C), 1471(C=C), 1123(C-N), 1176(C-N), 627(C-I)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.99 (s, 1H, NH), 7.56 (dd, *J* = 8.2, 1.6 Hz, 1H, ArH), 7.41 (s, 1H, ArH), 6.75 (d, *J* = 8.2 Hz, 1H, ArH), 3.63 (t, *J* = 9.2 Hz, 1H, C*H*CO_2CH_3), 3.39 (dd, *J* = 7.6, 8.1 Hz, 1H, NCH_2), 3.32 (s, 1H, CO_2*CH_3*), 3.09(dt, *J* = 4.6, 9.2 Hz, 1H, CH_2N), 2.69-2.55 (m, 1H, CH_2), 2.47-2.33 (m, 1H, CH_2), 2.13 (s, 3H, NCH_3)

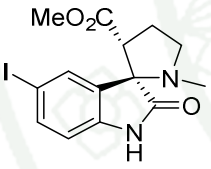
^{13}C-NMR (75MHz, $CDCl_3$) δ: 179.4 (N-C=O), 171.2 (O-C=O), 141.1 (Ar), 138.2 (ArH), 133.7 (ArH), 129.3 (Ar), 112.4 (ArH), 85.1 (ArI), 73.6 (C), 53.2 (NCH_2), 52.5 (CH), 51.8 (OCH_3), 35.4 (NCH_3), 25.1 (CH_2)

HRMS (ESI^+) *m/z* : $C_{14}H_{16}IN_2O_3$ $[M+H]^+$, calcd 387.0200, found 387.0209

Table 1 NOE experiment of compound (680a) in $CDCl_3$.

Irradiated	**Ar-H**	**CH_2(a)** **2.58**	**CH_2(b)** **2.37**	**CH**	**NCH_2(a)** **3.09**
Ar-H (6)	-100	2.27	-	-	2.95
CH	-	-	4.91	–99.56	-

Methyl(3*R*,3'*R*)-5-iodo-1'-methyl-2-oxo-1,2-dihydrospiro[indole-3,2'-pyrrolidine] -3'-carboxylate (680b)



(680b)

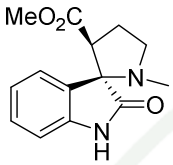
Minor product (680b) 7% yield as a colourless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.97 (s, 1H, NH), 7.56 (dd, *J* = 1.8, 8.0 Hz, 1H, ArH), 7.54 (d, *J* = 1.8 Hz, 1H, ArH), 6.64 (d, *J* = 8.0 Hz, 1H, ArH), 3.57 (s, 3H, CO_2CH_3), 3.49 (dd, *J* = 1.2, 9.4 Hz, 1H, CH), 3.30-3.22 (m, 2H, NCH_2), 2.67-2.53 (m, 1H, CH_2), 2.49-2.36 (m, 1H, CH_2), 2.10 (s, 3H, NCH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 177.3 (N-C=O), 171.6 (O-C=O), 141.2 (Ar), 138.0 (ArH), 132.7 (ArH), 128.6 (Ar), 111.7 (ArH), 85.2 (ArI), 72.3 (C), 53.1 (CH), 52.0 (OCH_3), 51.8 (NCH_2), 35.0 (NCH_3), 24.8 (CH_2)

HRMS (ESI$^+$) *m/z* : $C_{14}H_{16}IN_2O_3$ $[M+H]^+$, calcd 387.0200, found 387.0202

Methyl (3*R*,3'*S*)-1'-methyl-2-oxo-1,2-dihydrospiro[indole-3,2'-pyrrolidine]-3'-carboxylate (681)



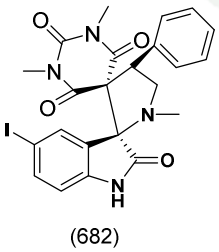
(681)

Minor product (681) 3% yield as a colourless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.23 (dt, *J* = 1.3, 7.7 Hz, 1H, ArH), 7.12 (dd, *J* = 0.5, 7.4 Hz 1H, ArH), 7.00 (dt, *J* = 1.0, 7.6 Hz, 1H, ArH,), 6.87 (dd, *J* = 0.7, 7.7 Hz, 1H, ArH), 3.60 (dd, *J* = 9.5, 18.8 Hz, 1H, CH), 3.42-3.32 (m, 1H, NCH_2), 3.23 (s, 3H, CO_2CH_3), 3.09 (dt, *J* = 4.8, 9.1 Hz, 1H, NCH_2), 2.69-2.54 (m, 1H, CH_2), 2.43-2.30 (m, 1H, CH_2), 2.11 (s, 3H, NCH_3)

HRMS (ESI$^+$) *m/z* : $C_{14}H_{17}N_2O_3$ $[M+H]^+$, calcd 261.1234, found 261.1241

(3*S*,4'*R*)-5-Iodo-1',1'',3''-trimethyl-4'-phenyl-2''*H*-dispiro[indole-3,2'-pyrrolidine-3',5''-pyrimidine]-2,2'',4'',6''(1*H*,1''*H*,3''*H*)-tetrone (682)



(682)

Flash column chromatography eluting with 2:1 hexane:EtOAc afforded the desired product (682) in (34%, dr =18:1) as a colourless amorphous solid, m.p. 165-166 °C.

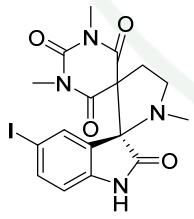
FTIR (film), ν_{max}, cm^{-1}: 3294 (N-H), 3030 (C=C-H), 2953 (C=C-H), 2867 (C=C-H), 1726 (C=O), 1685 (C=O), 1612 (C=C), 1464 (C=C), 1182 (C-N), 1124 (C-N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.06 (s, 1H, NH), 7.58 (dd, *J* =1.8, 8.1 Hz, 1H, ArH), 7.39 (d, *J* =1.7 Hz, 1H, ArH), 7.33-7.20 (m, 5H, PhH), 6.75 (d, *J* = 8.1 Hz, 1H, ArH), 5.40 (dd, *J* = 1.3, 8.8 Hz, 1H, C*H*Ph), 4.20 (t, *J* = 8.5 Hz, 1H, CH_2N), 3.70 (dd, *J* = 2.0, 8.5Hz, 1H, CH_2N), 3.10 (s, 3H, $C(O)NCH_3$), 3.08 (s, 3H, $C(O)NCH_3$), 2.30 (s, 3H, NCH_3)

^{13}C-NMR (75MHz, $CDCl_3$) δ: 176.28 (N-C=O), 166.71 (C=O), 164.41 (C=O), 149.87 (N-C(O)-N), 141.69 (Ar), 139.81 (ArH), 136.24 (Ph), 133.79 (ArH), 128.93 (PhH), 128.46 (PhH), 127.45 (PhH), 125.86 (Ar), 112.45 (ArH), 84.88 (ArI), 81.04 (C), 68.27 (C), 56.28 (NCH_2), 44.67 (CH), 35.80 (NCH_3), 29.36 (NCH_3), 28.40 (NCH_3)

HRMS (ESI^+) *m/z* : $C_{23}H_{22}IN_4O_4$ $[M+H]^+$, calcd 545.0680, found 545.0681

(3*S*)-5-Iodo-1',1'',3''-trimethyl-2''*H*-dispiro[indole-3,2'-pyrrolidine-3',5''-pyrimidine]-2,2'',4'',6''(1*H*,1''*H*,3''*H*)-tetrone (683)



(683)

Minor product (683); Crystallization in MeOH gave colourless crystal of the (683), m.p. 196-197 °C

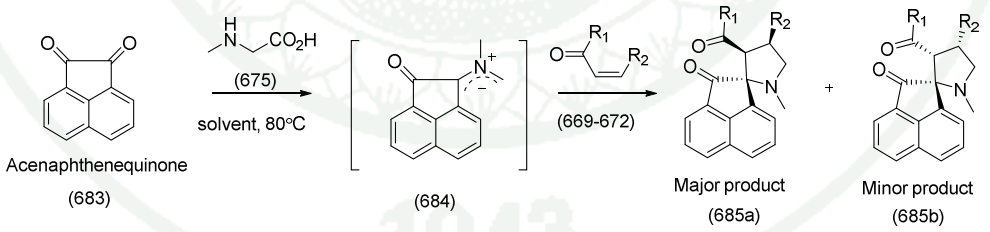
FTIR (solid), ν_{max}, cm^{-1}: 3324 (N-H), 2920 (C=C-H), 2856 (C=C-H), 1754 (C=O), 1726 (C=O), 1704, (C=O), 1693 (C=O), 1616 (C=C), 1471 (C=C), 1123 (C-N), 1065 (C-N)

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 10.57 (s, 1H, NH), 7.75 (ddd, *J* =0.8, 0.9, 8.1 Hz, 1H, ArH), 7.03 (d, *J* =1.5 Hz, 1H, ArH), 6.61 (dd, *J* = 8.2, 0.7 Hz, 1H, ArH), 3.27 (octet, *J* = 4.9, 2.9 Hz, 2H, NCH_2), 3.00-2.92 (m, 1H, CH_2), 2.91 (s, 3H, $C(O)NCH_3$), 2.87 (s, 3H, $C(O)NCH_3$), 2.38 (sextet, *J* = 4.5, 5.2 Hz, 1H, CH_2), 2.30 (s, 3H, NCH_3)

^{13}C-NMR (75 MHz, DMSO-d_6) δ: 174.1 (N-C=O),167.41 (C=O), 166.44 (C=O), 150.41 (N-C(O)-N), 142.62 (Ar), 138.85 (ArH), 133.04 (ArH), 125.96 (Ar), 111.96 (ArH), 83.97 (C), 64.54 (C), 51.70 (NCH_2), 34.98 (NCH_3), 28.75 (NCH_3), 27.98 (NCH_3), 25.96 (CH_2)

HRMS (ESI^+) *m/z* : $C_{17}H_{18}IN_4O_4$ $[M+H]^+$, calcd 469.0367, found 469.0376

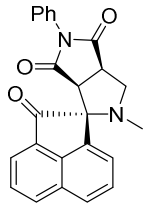
Spiroacenathene pyrrolidine compounds



General procedure:

A mixture of acenaphthoquinone (683) (1 mmol), sarcosine (675) (1 mmol) and dipolarlophile (669-672) (1 mmol) in EtOH (10 mL) was stirred and heated at 80 °C. When the reaction was completed (monitor by TLC or ^{1}H-NMR of the reaction mixture) the solvent was removed under reduced pressure and the crude reaction was purified by flash column chromatography (silica gel) to give the cycloadduct.

(1*R*,3a'*R*,6a'*S*)-2'-Methyl-5'-phenyl-3a',6a'-dihydro-2*H*,2'*H*-spiro[acenaphthyl-ene -1,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',6'(3'*H*,5'*H*)-trione (686a)



(686a)

Flash column chromatography eluting with 2:1 hexane:EtOAc afforded the major product (686a) (65%) as a yellow amorphous solid, m.p. 162-163 °C

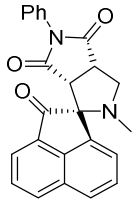
FTIR (film) ν_{max}, cm^{-1}: 3019 (C=C-H), 2950 (C=C-H), 2863 (C=C-H), 1714 (C=O), 1603 (C=C), 1500 (C=C), 1194 (C-N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.14 (d, *J* = 8.1Hz, 1H, ArH), 7.91 (d, *J* = 7.0 Hz, 1H, ArH), 7.90 (d, *J* = 8.3 Hz, 1H, ArH), 7.73 (dd, *J* = 7.1, 8.1 Hz, 1H, ArH), 7.64 (dd, *J* = 7.1, 8.3 Hz, 1H, ArH), 7.53-7.46 (m, 2H, PhH), 7.44-7.33 (m, 4H, ArH), 3.92 (dd, *J* = 7.7, 9.4 Hz, 1H, CH_2), 3.78 (dt, *J* = 1.2, 8.2 Hz, 1H, CH_2*CH*), 3.66 (dd, *J* = 1.0, 9.4 Hz, 1H, CH_2), 3.61 (d, *J* = 8.2 Hz, 1H, CCH), 2.05 (s, 3H, CH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 207.6 (C=O), 178.2 (N-C=O), 174.6 (N-C=O), 142.9 (Ar), 134.8 (Ar), 132.5 (ArH), 132.0 (Ar), 130.6 (Ar), 130.4 (Ar), 129.3 (ArH), 128.7 (ArH), 128.5 (ArH), 128.3 (ArH), 126.4 (ArH), 125.8 (ArH), 123.1 (ArH), 121.4 (ArH), 76.5 (C), 55.6 (CH_2),52.0 (CCH), 44.9 (CH_2*CH*), 34.8 (CH_3)

HRMS (ESI^+) *m/z* : $C_{24}H_{19}N_2O_3$ $[M+H]^+$, calcd 383.1390, found 383.1344

(1*R*,3a'*S*,6a'*R*)-2'-Ethyl-5'-phenyl-3a',6a'-dihydro-2*H*,2'*H*-spiro[acenaphthylene -1,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',6'(3'*H*,5'*H*)-trione (686b)



(686b)

Minor product (686b) 32% as a yellow amorphous solid, m.p. 192-194 °C

FTIR (film) ν_{max}, cm^{-1}: 3019 (C=C-H), 2944 (C=C-H), 2849 (C=C-H), 1711 (C=O), 1598 (C=C), 1498 (C=C), 1196 (C-N)

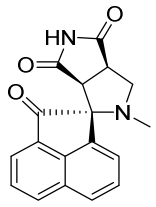
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.13 (d, *J* = 8.2 Hz, 1H, ArH,), 7.92 (d, *J* = 8.2 Hz, 1H, ArH), 7.90 (d, *J* = 7.0 Hz, 1H, ArH), 7.75-7.67 (m, 2H, ArH), 7.61 (d, *J* = 7.0 Hz, 1H, ArH), 7.50-7.42 (m, 2H, ArH), 7.41-7.33 (m, 3H, ArH), 3.93-3.75 (m, 3H), 3.70-3.62 (m, 1H), 2.03 (s, 3H, NCH_3)

^{1}H-NMR (300 MHz, C_6D_6) δ: 7.81-7.74 (m, 3H, ArH), 7.61 (dd, *J* = 0.6, 8.2 Hz, 1H, ArH,), 7.57 (dd, *J* = 0.8, 8.2 Hz, 1H, ArH,), 7.44 (dd, *J* = 6.9, 8.0 Hz, 1H, ArH), 7.38 (dd, *J* = 0.9, 6.9 Hz, 1H, ArH), 7.27-7.20 (m, 2H, ArH), 7.17 (dd, *J* = 7.0, 8.2 Hz, 1H, ArH), 7.08 (tt, *J* = 1.1, 7.6 Hz, 1H, ArH), 3.88 (dd, *J* = 5.3, 8.9Hz, 1H, CH_2), 3.45 (d, *J* = 9.2 Hz, 1H, CCH), 3.35 (t, *J* = 8.9 Hz, 1H, CH_2*CH*,), 3.26 (ddd, *J* = 5.4, 8.8 Hz, 1H, CH_2), 1.84 (s, 3H, CH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 205.5 (C=O), 177.0 (N-C=O), 175.0 (N-C=O), 142.4 (Ar), 138.2 (Ar), 132.3 (ArH), 131.9 (Ar), 131.7 (Ar), 130.7 (Ar), 129.2 (PhH), 128.7 (ArH), 128.5 (ArH), 126.9 (PhH), 125.8 (ArH), 121.5 (ArH), 120.6 (ArH), 76.8 (C), 55.6 (CH_2), 55.0 (CCH), 44.5 (CH_2*CH*), 34.8 (CH_3)

HRMS (ESI^+) *m/z* : $C_{24}H_{19}N_2O_3$ $[M+H]^+$, calcd 383.1390, found 383.1379.

(1*R*,3a'*R*,6a'*S*)-2'-Methyl-3a',6a'-dihydro-2*H*,2'*H*-spiro[acenaphthylene-1,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',6'(3'*H*,5'*H*)-trione (687a)



(687a)

Flash column chromatography eluting with gradient 2:1 and the 1:1 hexane:EtOAc afforded the major product (687a) (75%) as a yellow amorphous solid, m.p. 223-224 °C

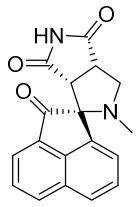
FTIR (film) ν_{max}, cm^{-1}: 3021, 3217 (NH), 3068 (C=C-H), 2954 (C=C-H), 2855 (C=C-H), 1744 (C=O), 1716 (C=O), 1604 (C=C), 1474 (C=C), 1191 (C-N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.99 (s, 1H, NH), 8.15 (d, *J* = 8.2 Hz, 1H, ArH), 7.92 (t, *J* = 8.2, 6.9 Hz, 2H, ArH), 7.75 (dd, *J* = 7.2, 7.9 Hz, 1H, ArH), 7.67 (dd, *J* = 7.2, 8.2Hz, 1H, ArH), 7.41 (d, *J* = 6.9 Hz, 1H, ArH), 3.83 (dd, *J* = 7.9, 9.4 Hz, 1H, NCH_2), 3.65 (dt, *J* = 0.8, 7.9 Hz, 1H, CH_2*CH*), 3.55 (d, *J* = 9.8 Hz, 1H, NCH_2), 3.46 (d, *J* = 8.2 Hz, 1H, CCH), 2.04 (s, 3H, CH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 207.6 (C=O), 179.4 (N-C=O), 175.8 (N-C=O), 142.8 (Ar), 134.6 (Ar), 132.5 (ArH), 130.5 (Ar), 130.2 (Ar), 128.5 (ArH), 128.2 (ArH), 125.8 (ArH), 123.0 (ArH), 121.3 (ArH), 76.0 (C), 55.0 (NCH_2), 53.0 (C*CH*),46.1 (CH_2*CH*), 34.7 (CH_3)

HRMS (ESI^+) *m/z* : $C_{18}H_{15}N_2O_3$ $[M+H]^+$, calcd 307.1077, found. 307.1075

(1*R*,3a'*S*,6a'*R*)-2'-Methyl-3a',6a'-dihydro-2*H*,2'*H*-spiro[acenaphthylene-1,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',6'(3'*H*,5'*H*)-trione (687b)



(687b)

Minor product (687b): 10% as a yellow amorphous solid, m.p. 225-226 °C.

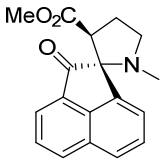
FTIR (film) ν_{max}, cm^{-1}: 3401 (NH), 2928 (C=C-H), 2848 (C=C-H), 2801 (C=C-H), 1731 (C=O), 1715 (C=O), 1602 (C=C), 1523 (C=C), 1422(C=C), 1148 (C-N)

^{1}H-NMR (300 MHz, pyridine-d_5) δ: 8.11 (d, *J* = 8.2 Hz, 1H, ArH), 7.97-7.91 (m, 2H, ArH), 7.77-7.61 (m, 3H, ArH), 4.17 (d, *J* = 8.9 Hz, 1H, CCH), 4.11-4.02 (m, 1H, CH_2CH), 3.98 (dd, *J* = 5.0, 9.3 Hz, 1H, CH_2), 3.67 (dd, *J* = 9.2, 8.4 Hz, 1H, CH_2), 1.99 (s, 3H, CH_3)

^{13}C-NMR (75 MHz, pyridine-d_5) δ: 207.6 (C=O), 182.1 (N-C=O), 179.8 (N-C=O), 143.9 (Ar), 141.2 (Ar), 134.1 (Ar), 134.0 (ArH), 132.7 (Ar), 130.9 (ArH), 130.4 (ArH), 127.4 (ArH), 122.9 (ArH), 122.8 (ArH), 78.56 (C), 59.44 (C*CH*), 57.45 (NCH_2), 48.2 (CH_2CH), 36.4 (CH_3)

HRMS (ESI^+) *m/z* : $C_{18}H_{15}N_2O_3$ $[M+H]^+$, calcd 307.1077, found. 307.1077

Methyl (1*R*,3'*S*)-1'-methyl-2-oxo-2*H*-spiro[acenaphthylene-1,2'-pyrrolidine]-3'-carboxylate (688a)



(688a)

Flash column chromatography eluting with 4:1 hexane:EtOAc afforded the major product (688a) (87%) as a yellow amorphous, and then it was crystallized with Et_2O to give yellow crystal of the (688a), m.p. 60-62 °C.

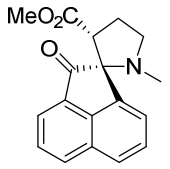
FTIR (film) ν_{max}, cm^{-1}: 3020(C=C-H), 2949(C=C-H), 2846(C=C-H), 2792(C=C-H), 1733(C=O), 1622(C=C), 1603(C=C), 1493(C=C), 1216(C-N), 1172(C-N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.13 (d, *J* = 8.2 Hz, 1H, ArH), 7.99 (d, *J* =7.0 Hz, 1H, ArH), 7.87 (d, *J* = 8.4 Hz, 1H, ArH), 7.74 (dd, *J* = 0.8, 7.7 Hz, 1H, ArH), 7.62 (dd, *J* = 1.4, 7.7 Hz, 1H, ArH), 7.43 (d, *J* = 7.0 Hz, 1H, ArH), 3.70 (t, *J* = 9.2 Hz, 1H, CH), 3.52-3.43 (m, 1H, CH_2N), 3.19 (sixtet, *J* = 4.9 Hz, 1H, CH_2N,), 2.89 (s, 3H, CO_2CH_3), 2.80-2.65 (m, 1H, CH_2), 2.51-2.38 (m, 1H, CH_2), 2.00 (s, 3H, NCH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 206.1 (C=O), 171.8 (-O-C=O), 142.2 (Ar), 136.3 (Ar), 132.3 (Ar), 131.9 (ArH), 130.4 (Ar), 128.2 (ArH), 128.0 (ArH), 125.1 (ArH), 122.0 (ArH), 121.3 (ArH), 76.9 (C), 53.9 (CH_2N), 52.6 (CH), 51.1 (OCH_3), 35.7 (NCH_3), 25.2 (CH_2)

HRMS (ESI^+) *m/z* : $C_{18}H_{18}NO_3$ $[M+H]^+$, calcd 296.1281, found 296.1284

Methyl (1*R*,3'*R*)-1'-methyl-2-oxo-2*H*-spiro[acenaphthylene-1,2'-pyrrolidine]-3'-carboxylate (688b)



(688b)

Minor product (688b) 8.6% as a yellow gum.

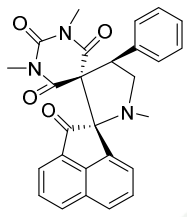
FTIR (film) ν_{max}, cm^{-1}: 2952 (C=C-H), 2849 (C=C-H), 1736 (C=O), 1717 (C=C), 1606 (C=C), 1214 (C-N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.09 (d, *J* = 8.2 Hz, 1H, ArH), 7.89 (d, *J* = 3.6 Hz, 1H, ArH), 7.86 (dd, *J* = 0.6, 1.2 Hz, 1H, ArH), 7.72 (dd, *J* = 0.8, 7.7 Hz, 1H, ArH), 7.68 (dd, *J* =1.4, 7.7 Hz, 1H, ArH), 7.57 (d, *J* = 6.9 Hz, 1H, ArH), 3.70 (dd, *J* = 9.2, 1.2 Hz, 1H, CH), 3.47-3.32 (m, 2H, CH_2N), 2.34 (s, 3H, CO_2CH_3), 2.79-2.66 (m, 1H, CH_2), 2.59-2.45 (m, 1H, CH_2), 2.00 (s, 3H, NCH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 207.4 (C=O), 172.1 (O-C=O), 142.6 (Ar), 139.01 (Ar), 132.8 (Ar), 131.3 (ArH), 130.4 (Ar), 128.6 (ArH), 128.2 (ArH), 125.1 (ArH), 120.0 (ArH), 119.8 (ArH), 75.8 (C), 53.7 (CH_2N), 52.9 (CH), 51.6 (OCH_3), 35.1 (NCH_3), 25.6 (CH_2)

HRMS (ESI^+) *m/z* : $C_{18}H_{18}NO_3$ $[M+H]^+$, calcd 296.1281, found 296.1289

(1*S*,4'*R*)-1',1'',3''-Trimethyl-4'-phenyl-2*H*,2''*H*-dispiro[acenaphthylene-1,2'-pyrrolidine-3',5''-pyrimidine]-2,2'',4'',6''(1''*H*,3''*H*)-tetrone (689)



(689)

Flash column chromatography eluting with 4:1 hexane:EtOAc afforded the desired product (689) (74%, dr= 22:1) as a yellow amorphous, and then it was crystallized with $CHCl_3$:hexane to give yellow crystal of (689), m.p. 160-162 °C.

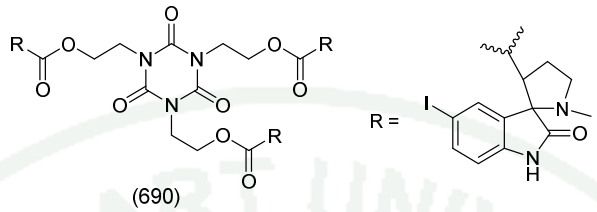
FTIR (film) ν_{max}, cm^{-1}: 3027 (C=C-H), 2952 (C=C-H), 2865 (C=C-H), 1723 (C=O), 1682 (C=O), 1603 (C=C), 1494 (C=C), 1215 (C-N), 1130 (C-N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.09 (d, *J* = 8.3 Hz, 1H, ArH), 7.93 (d, *J* = 4.7 Hz, 1H, ArH), 7.90 (d, *J* = 6.4 Hz, 1H, ArH), 7.74 (dd, *J* = 1.0, 7.1 Hz, 1H, ArH), 7.62 (dd, *J* = 1.2, 7.1 Hz, 1H, ArH), 7.39 (d, *J* = 7.0 Hz, 1H, ArH), 7.37-7.32 (m, 2H, PhH), 7.29-7.19 (m, 3H, PhH), 5.39 (dd, *J* = 1.3, 8.7 Hz, 1H, CHPh), 4.29 (t, *J* = 8.6 Hz, 1H, CH_2N), 3.88 (dd, *J* = 1.9, 8.6 Hz, 1H, CH_2N), 3.00 (s, 3H, NCH_3), 2.41 (s, 3H, NCH_3), 2.34 (s, 3H, NCH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 202.8 (C=O), 167.0 (N-C=O), 164.7 (N-C=O), 149.7 (N-C(O)-N), 141.8 (Ar), 136.5 (Ph), 133.5 (Ar), 131.6 (ArH), 130.7 (Ar), 133.3 (Ar), 129.0 (PhH), 128.5 (ArH), 128.4 (PhH), 128.0 (ArH), 127.4 (PhH), 126.6 (ArH), 121.4 (ArH), 121.3 (ArH), 84.0 (C), 69.2 (C), 56.7 (NCH_2), 46.0 (CHPh), 35.6 (NCH_3), 28.4 ($C(O)NCH_3$), 28.23 ($C(O)NCH_3$)

HRMS (ESI^+) *m/z* : calcd 454.1761 found 454.1775.

2,4,6-Trioxo-1,3,5-triazinane-1,3,5-triyl)triethane-2,1-diyl tri[5-iodo-1'-methyl-2-oxo-1,2-dihydrospiro[indole-3,2'-pyrrolidine] -3'-carboxylate] (690)



(690)

Flash column chromatography eluting with 90:5:5 $CHCl_3$: MeOH: NH_4OH afforded the cycloadduct in 68% as a mixture of isomers. The major product (unsymmetrical) as a brown amorphous foam.

FTIR (film) ν_{max}, cm^{-1}: 3225 (NH), 3015 (C=C-H), 2972 (C=C-H), 2849 (C=C-H), 1731 (C=O), 1698(C=O), 1612 (C=C), 1469 (C=C), 1213 (C-N), 1176 (C-N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 11.02 (s, NH), 8.98 (s, NH), 7.59 (dd, *J* = 1.7, 8.2 Hz, ArH), 7.50 (dd, *J* = 1.7, 8.2 Hz, ArH) 7.40 (d, *J* = 1.6 Hz, ArH), 7.38 (d, *J* = 1.6Hz, ArH), 6.80 (d, *J* = 8.2 Hz, ArH), 6.65 (d, *J* = 8.2 Hz, ArH), 4..06-3.90 (m, OCH_2 +NCH_2), 3.90-3.75 (m, NCH_2 + NCH_2), 3.64 (t, *J* = 9.3 Hz, CH), 3.50 (t, *J* = 9.3 Hz, CH), 3.46-3.25 (m, CO_2CH_2+NCH_2), 3.11-2.98 (m, NCH_2), 2.68-2.27 (m, CH_2), 2.15 (s, NCH_3), 2.08 (s, NCH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 179.6, 177.8 (O-C(O)), 170.6, 170.5 (N-C(O)C), 148.6, 147.7 (N-C(O)-N), 141.6, 141.1 (Ar), 138.5, 138.0 (ArH), 133.9, 133.8 (ArH), 129.5, 129.0 (Ar),112.2, 112.0 (ArH), 84.9, 84.8 (ArI), 74.2, 73.0 (C), 63.6, 61.4 (CO_2CH_2), 53.6, 53.1 (NCH_2), 52.6, 52.5 (CH), 41.5, 41.1 (NCH_2), 35.7, 35.4 (NCH_3), 25.1, 24.2 (CH_2)

HRMS (ESI^+) *m/z*: $C_{48}H_{48}I_3N_9NaO_{12}$ [M+Na], calcd 1346.0449, found 1346.0494

Minor product (symmetrical) as a brown amorphous foam.

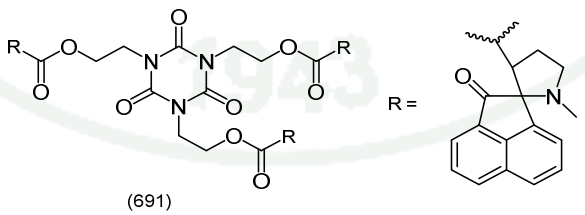
FTIR (film) ν_{max}, cm^{-1}: 3234 (NH), 2969 (C=C-H), 2848 (C=C-H), 3020 (C=C-H), 1731 (C=O), 1693(C=O), 1614(C=C), 1454(C=C), 1219(C-N), 1165(C-N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 10.45 (s, 1H, NH), 7.57 (dd, *J* = 8.2, 1.7 Hz, 1H, ArH), 7.38 (d, *J* = 1.5 Hz, 1H, ArH), 6.79 (d, *J* = 8.27 Hz, 1H, ArH), 4.05-3.94 (m, 1H, OCH_2), 3.91-3.76 (m, 2H, NCH_2), 3.59 (t, *J* = 9.7 Hz, 1H, CH), 3.43-3.27 (m, 2H, CO_2CH_2+NCH_2), 3.04 (dt, *J* = 5.5, 3.6 Hz, 1H, NCH_2), 2.64-2.49 (m, 1H, CH_2), 2.40-2.26 (m, 1H, CH_2), 2.13 (s, 3H, NCH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 179.2 (O-(C)), 170.6 (N-C(O)), 148.3 (N-C(O)-N), 141.5 (Ar), 138.3 (ArH 4), 133.8 (ArH 6), 129.2 (Ar), 112.2 (ArH 3), 84.8 (ArI), 73.9 (Q), 62.9 (OCH_2), 53.5 (NCH_2), 52.5 (CH), 41.4 (NCH_2), 35.6 (NCH_3), 24.5 (CH_2)

HRMS (ESI^+) *m/z* : $C_{48}H_{48}I_3N_9NaO_{12}$ [M+Na], calcd 1346.0449, found 1346.0475

2,4,6-Trioxo-1,3,5-triazinane-1,3,5-triyl)triethane-2,1-diyl tri[1'-methyl-2*H*-spiro [acenaphthylene-1,2'-pyrrolidin]-2-one] (691)



(691)

Flash column chromatography eluting with gradient (1:1) and (1:2) hexane:EtOAc afforded the major product (691) (symmetrical) (42%) as a yellow amorphous foam.

FTIR (film) ν_{max}, cm^{-1}: 3020 (C=C-H), 2969 (C=C-H), 2848 (C=C-H), 1730 (C=O), 1697(C=O), 1603 (C=C), 1459 (C=C), 1217 (C-N), 1171 (C-N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.11 (d, *J* = 8.4 Hz, 1H, ArH), 7,89 (m, 1H, ArH), 7.86 (d, *J* = 8.4 Hz, 1H, ArH), 7.69 (dt, *J* = 7.1, 2.1, 1.1 Hz, 1H, ArH), 7.61 (dd, *J* = 1.2, 6.7Hz, 1H, ArH), 7.41 (d, *J* = 6.8 Hz, 1H, ArH), 3.75-3.66 (m, 1H, CO_2CH_2), 3.61 (t, *J* = 8.8 Hz, 1H, CH), 3.44 (q, *J* = 8.3 Hz, 1H, NCH_2), 3.39-3.23 (m, 2H, $C(O)NCH_2$), 3.17 (sextet, *J* = 4.9 Hz, 1H, NCH_2), 3.12-3.00 (m, 1H, CO_2CH_2), 2.72-2.57 (m, 1H, CH_2), 2.47-2.33 (m, 1H, CH_2), 1.98 (s, 1H, NCH_3), 1.97 (s, 1H, NCH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 205.8 (C=O), 171.0 (N-C=O), 147.8 (Ar), 142.1 (Ar), 136.2 (Ar), 132.1 (Ar), 132.0 (ArH), 130.4 (Ar), 128.3 (ArH), 128.0 (ArH), 125.2 (ArH),121.9 (ArH), 121.2 (ArH), 76.7(C), 60.2 (CH_2), 53.8 (CH_2), 52.4 (CH), 40.6 (CH_2), 35.6 (CH_3), 25.2 (CH_2)

HRMS (ESI^+) *m/z* : $C_{60}H_{55}N_6O_{12}$ $[M+H]^+$, calcd 1051.3872, found 1051.3879

Minor product (unsymmetrical) 17% as a yellow amorphous foam.

FTIR (film) ν_{max}, cm^{-1}: 3020 (C=C-H), 2967 (C=C-H), 2847 (C=C-H), 1730 (C=O), 1697(C=O), 1604 (C=C), 1461 (C=C), 1215 (C-N), 1168 (C-N)

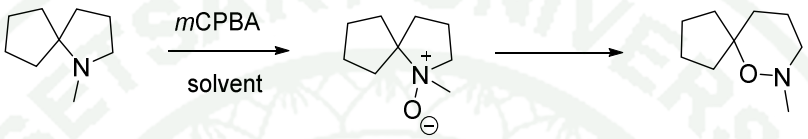
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.11, 8.02 (d, *J* = 8.1Hz, ArH,), 7.93-7.55 (m, ArH), 7.49, 7.41 (d, *J* = 6.8 Hz, ArH), 4.16-4.04 (m, CO_2CH_2), 3.83-3.55 (m), 3.50-3.38 (m), 3.38-3.23 (m), 3.23-3.00 (m), 2.75-2.50 (m), 2.50-2.31 (m), 1.98 (s, NCH_3),1.94 (s, NCH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 207.4, 205.8 (C=O), 171.4, 171.0(2) (O-C=O), 148.0, 147.9, 147.8(2) (Ar), 142.5, 142.1 (Ar), 139.0, 136.3 (Ar), 132.7**,** 132.2 (Ar), 132.0, 131.2 (ArH), 130.4, 130.3 (Ar), 128.5, 128.3 (ArH), 128.2, 128.0 (ArH), 125.2, 125.0 (ArH), 122.0, 121.2 (2) (ArH), 119.9,119.8 (2), 119.7 (ArH), 76.7, 75.5

(C), 60.7, 60.2 (CH_2), 53.83, 52.8 (CH_2), 53.5, 52.4(2) (CH), 41.4, 40.6 (CH_2), 35.7, 35.0 (CH_3), 25.3**,** 25.2(2) (CH_2)

HRMS (ESI^+) *m/z* : $C_{60}H_{55}N_6O_{12}$ $[M+H]^+$, calcd 1051.3872, found 1051.3884

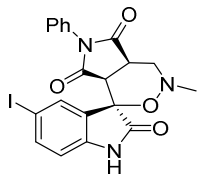
***N-O* Heterocycles spirooxindole**



General procedure:

A solution of *m*-CPBA (1.05 mmol) in CH_2Cl_2 (17 mL) was added dropwise to a solution of spiropyrrolidine (1mmol) in CH_2Cl_2 (8.5 mL) at 0^oC. The solution was allowed to warm to room temperature with stirring until the reaction completed. The reaction mixture was washed with potassium carbonate solution and then water. The organic layer was dried over anhydrous $MgSO_4$, concentrated *in vaccuo* and crystallization or purification by flash column chromatography (silica gel) to give the *N-O* hetreocycles.

(3*R*,4a'*R*,7a'*S*)-5-Iodo-3'-methyl-6'-phenyl-4a',7a'-dihydro-3'*H*-spiro[indole-3,1'-pyrrolo[3,4-*d*][1,2]oxazine]-2,5',7'(1*H*,4'*H*,6'*H*)-trione (692a)



(692a)

Flash column chromatography eluting with 2:1 hexane:EtOAc gave (692a) (87.0%) as a colourless amorphous. Crystallization in acetonitrile to gave colourless crystal of the (692a), m.p. 218-219 °C

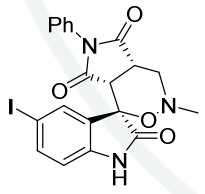
FTIR (solid) ν_{max}, cm^{-1}: 1725(C=O), 1706(C=O), 1612(C=C), 1495(C=C), 1439(C=C), 1198(C-N)

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 11.00 (s, 1H, NH), 7.69 (d, *J* =1.6 Hz, 1H, ArH), 7.64 (dd, *J* = 1.8, 8.2 Hz, 1H, ArH), 7.47-7.38 (m, 3H, PhH), 6.94-6.88 (m, 2H, PhH), 6.72 (d, *J* = 8.2 Hz, 1H, ArH), 3.80 (dd, *J* = 5.4, 9.1 Hz, 1H, CH_2CH), 3.69 (d, *J* = 12.7 Hz, 1H, CH_2), 3.61 (d, *J* = 8.8 Hz, 1H, CCH), 2.90 (dd, *J* = 5.6, 12.8 Hz, 1H, CH_2), 2.54 (s, 3H, NCH_3)

^{13}C-NMR (75 MHz, DMSO-d_6) δ: 176.2 (N-C=O), 172.3 (C=O), 172.0 (C=O), 141.0 (Ar), 137.6 (ArH), 134.2 (ArH), 130.3 (Ph), 128.2 (Ar), 127.7 (PhH), 127.3 (PhH), 125.3 (PhH), 111.5 (ArH), 83.5 (ArI), 78.6 (C), 53.7 (CH_2), 49.9 (NCH_3), 44.6 (*C*H), 40.7 (CH_2*C*H)

HRMS (ESI^+) *m/z*: $C_{20}H_{16}IN_3NaO_4$ [M+Na], calcd 512.0078, Found 512.0059

(3*R*,4a'*S*,7a'*R*)-5-Iodo-3'-methyl-6'-phenyl-4a',7a'-dihydro-3'*H*-spiro[indole-3,1'-pyrrolo[3,4-*d*][1,2]oxazine]-2,5',7'(1*H*,4'*H*,6'*H*)-trione (692b)



(692b)

(692b): colourless amorphous solid, m.p. 168-169 °C.

FTIR (film) ν_{max}, cm^{-1}: 3273(NH), 3016(C=C-H), 1738(C=O), 1615(C=C), 1478(C=C), 1206(C-N), 1181(C-N)

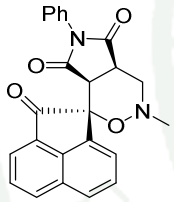
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.51 (s, 1H, NH), 7.57 (d, *J* = 1.4 Hz, 1H, ArH), 7.40 (dd, *J* = 1.6, 8.2 Hz, 1H, ArH), 7.36-7.25 (m, 5H, PhH), 6.32 (d, *J* = 8.2

Hz, 1H, ArH), 3.68 (d, *J* = 12.2 Hz, 1H, CH_2), 3.47 (d, *J* = 9.6 Hz, 1H, CCH), 3.25 (dd, *J* = 6.1, 8.9 Hz, 1H, CH_2CH), 2.81 (dd, *J* = 5.9, 12.6 Hz, 1H, CH_2), 2.55 (s, 3H, NCH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 176.8 (C=O), 174.9 (C=O), 173.5 (C=O), 141.3 (N-C(O)-N), 139.7 (ArH), 133.2 (ArH), 131.7 (Ar), 130.4 (Ar), 129.2 (PhH), 128.9 (PhH), 126.6 (PhH), 112.9 (ArH), 85.2 (ArI), 78.7 (C), 51.9 (CH_2), 46.3 (CH_3), 40.9 (CH), 39.1 (CH)

HRMS (ESI^+) *m/z*: $C_{20}H_{16}IN_3NaO_4$ [M+Na], calcd 512.0078, Found 512.0088

(1*R*,4a'*R*,7a'*S*)-3'-Methyl-6'-phenyl-4a',7a'-dihydro-2*H*,3'*H*-spiro[acenaphthylene-1,1'-pyrrolo[3,4-*d*][1,2]oxazine]-2,5',7'(4'*H*,6'*H*)-trione (693a)



(693a)

Crystallization in MeOH gave a colourless crystal of the (693a) (75%), m.p. 216-218 °C.

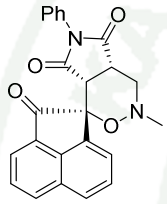
FTIR (film) ν_{max}, cm^{-1}: 2956 (C=C-H), 2917 (C=C-H), 2897 (C=C-H), 1715 (C=O), 1601 (C=C), 1177 (C-N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.15 (dd, *J* = 0.5, 8.1Hz, 1H, ArH), 8.08 (dd, *J* = 0.6, 7.1 Hz, 1H, ArH), 7.93 (dd, *J* = 0.4, 8.4 Hz, 1H, ArH), 7.87 (dd, *J* = 0.6, 7.1 Hz, 1H, ArH), 7.75 (dd, *J* = 7.1, 8.1 Hz, 1H, ArH), 7.56 (dd, *J* = 7.1, 8.4 Hz, 1H, ArH), 7.34-7.25 (m, 3H, PhH), 7.80-7.74 (m, 2H, PhH), 4.02 (d, *J* = 9.0 Hz, 1H, CCH), 3.89 (dd, *J* = 0.7, 12.5 Hz, 1H, CH_2), 3.50 (ddd, *J* = 1.0, 5.7, 9.0 Hz, 1H, CH_2CH), 3.18 (dd, *J* = 5.7, 12.5 Hz, 1H, CH_2), 2.61 (s, 3H, CH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 197.9 (C=O), 177.1 (N-C=O), 173.3 (N-C=O), 143.0 (Ar), 135.6 (Ar), 132.7 (ArH), 131.3 (Ar), 130.8 (Ar), 130.6 (Ar), 128.0 (PhH), 128.4 (ArH), 128.3 (ArH), 128.1 (ArH), 126.4 (ArH), 125.7 (PhH), 124.6 (ArH), 123.3 (ArH), 83.9 (C), 51.4 (CH_2), 45.9 (CH_3), 42.2 (C*C*H), 39.8 (CH_2*C*H)

HRMS (ESI^+) *m/z*: $C_{24}H_{19}N_2O_4$ $[M+H]^+$, calcd 399.1339, found 399.1337

(1*R*,4a'*S*,7a'*R*)-3'-Methyl-6'-phenyl-4a',7a'-dihydro-2*H*,3'*H*-spiro[acenaphthylene -1,1'-pyrrolo[3,4-*d*][1,2]oxazine]-2,5',7'(4'*H*,6'*H*)-trione (693b)



(693b)

Crystallization in MeOH gave a colourless crystal of (693b) (65%), m.p. 185-187 °C.

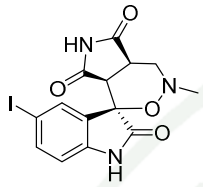
FTIR (film) ν_{max}, cm^{-1}: 3017 (C=C-H), 2962 (C=C-H), 2882 (C=C-H), 1714 (C=O), 1786 (C=O), 1606 (C=C), 1598 (C=C), 1500 (C=C), 1195 (C-N), 1180 (C-N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 8.0 Hz, 1H, ArH,), 7.95-7.88 (m, 2H, ArH), 7.71-7.65 (m, 3H, ArH), 7.47-7.31 (m, 5H, ArH), 3.95 (d, *J* = 9.6 Hz, 1H, CCH), 3.82 (d, *J* = 12.3 Hz, 1H, CH_2), 3.48-3.39 (m, 1H, C*H*CH_2), 2.99 (dd, *J* = 6.1, 12.5 Hz, 1H, CH_2), 2.57 (s, 3H, NCH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 197.4 (C=O), 176.8 (N-C=O), 174.8 (N-C=O), 142.0 (Ar), 137.7 (Ar), 132.0 (Ar), 131.5 (ArH), 131.2 (Ar), 130.7 (Ar), 129.1 (PhH), 128.7 (ArH), 128.6(2) (ArH), 126.8 (PhH), 126.7 (ArH), 122.7 (Ar), 120.9 (Ar), 82.2 (C), 52.3 (CH_2), 46.3 (CH_3), 40.6 (C*C*H), 39.5 (CH_2*C*H)

HRMS (ESI^+) *m/z*: $C_{24}H_{18}N_2NaO_4$ [M +Na], calcd 421.1159, found 421.1166

(3*R*,4a'*R*,7a'*S*)-5-Iodo-3'-methyl-4a',7a'-dihydro-3'*H*-spiro[indole-3,1'-pyrrolo [3,4-*d*][1,2]oxazine]-2,5',7'(1*H*,4'*H*,6'*H*)-trione (694)



(694)

A solution of *m*-CPBA (2 mmol) in MeOH (17 mL) was added dropwise to a solution of spiropyrrolidine (679) (1mmol) in MeOH (8.5 mL) at 0°C. The stirred solution was allowed to warm to room temperature with stirring for 24h. The solvent was removed under reduced pressure then DMSO was added (5 mL). The reaction mixture was heated at 60°C with stirring for 1h. Water was added and extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, concentrated *in vaccuo* and purification by flash column chromatography (silica gel, hexane:EtOAc, 2:1) to give the desired product (694) 62% as a colourless amorphous solid, m.p. 206-208 °C.

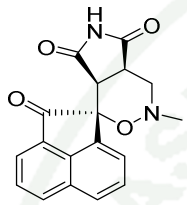
FTIR (solid) ν_{max}, cm^{-1}: 1790(C=O), 1725(C=O), 1703(C=O), 1611(C=C), 1462 (C=C), 1432 (C=C)

^{1}H-NMR (300 MHz, pyridine-d_6) δ: 8.42 (d, *J* =1.6 Hz, 1H, ArH), 7.60 (dd, *J* = 1.8, 8.1 Hz, 1H, ArH), 6.77 (d, *J* = 8.1 Hz, 1H, ArH), 4.26 (d, *J* = 8.9 Hz, 1H, CCH), 3.86 (d, *J* = 12.6 Hz, 1H, CH_2), 3.7 (ddd, *J* = 0.9, 3.4, 5.4 Hz, 1H, CH_2CH), 2.92 (dd, *J* = 5.7, 12.6 Hz, 1H, CH_2), 2.46 (s, 3H, NCH_3)

^{13}C-NMR (75 MHz, pyridine-d_6) δ: 181.2 (N-C=O), 177.6 (C=O), 174.6 (C=O), 144.2 (Ar), 139.6 (ArH), 137.2 (ArH), 131.6 (Ar), 113.2 (ArH), 85.2 (5), 81.6 (C), 52.3 (CH_2), 46.5 (NCH_3), 44.8 (C*C*H), 41.3 (CH_2*C*H)

HRMS (ESI$^+$) *m/z*: $C_{28}H_{24}I_2N_6$ Na O_8 [2M +Na], calcd 848.9637, found 848.9626

(1*R*,4a'*R*,7a'*S*)-3'-Methyl-4a',7a'-dihydro-2*H*,3'*H*-spiro[acenaphthylene-1,1'-pyrrolo[3,4-*d*][1,2]oxazine]-2,5',7'(4'*H*,6'*H*)-trione (695)



(695)

Crystallization in MeOH give colourless crystal of (695) (89%), m.p. 158-160 °C.

FTIR (film) ν_{max}, cm^{-1}: 3401 (N-H), 2923 (C=C-H), 2902 (C=C-H), 1734 (C=O), 1601 (C=C), 1522(C=C), 1130 (C-N)

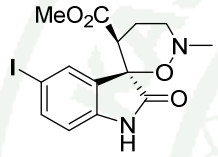
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.14 (dd, *J* = 8.1, 0.4 Hz, 1H, ArH), 8.05 (dd, *J* = 7.0, 0.5 Hz, 1H, ArH), 7.90 (d, *J* = 8.0 Hz, 1H, ArH), 7.80 (d, *J* = 7.0, 0.5 Hz, 1H, ArH), 7.74 (dd, *J* = 7.1, 8.0 Hz ,1H, ArH), 7.54 (dd, *J* = 7.1, 8.2 Hz, 1H, ArH), 3.88 (d, *J* = 8.9 Hz, 1H, CCH), 3.73 (dd, *J* = 12.3, 0.6 Hz, 1H, CH_2), 3.35 (ddd, *J* = 0.7, 5.8, 8.9 Hz, 1H, CH_2CH), 3.07 (dd, *J* = 5.8, 12.5 Hz, 1H, CH_2), 2.56 (s, 3H, CH_3)

^{1}H-NMR (300 MHz, pyridine-d_5) δ: 8.18 (d, *J* = 6.9 Hz, 1H, ArH), 8.07 (d, *J* = 7.1 Hz, 1H, ArH,), 8.00 (d, *J* = 8.2 Hz, 1H, ArH), 7.80 (d, *J* =8.4 Hz, 1H, ArH), 7.57 (dd, *J* = 7.1, 8.0 Hz 1H, ArH), 7.44 (dd, *J* = 7.1, 8.2 Hz, 1H, ArH), 4.33 (d, *J* = 8.9 Hz, 1H, CCH), 3.98 (d, *J* = 12.5 Hz, 1H, CH_2), 3.80 (ddd, *J* = 0.7, 5.8, 8.9 Hz, 1H, CH_2CH), 3.02 (dd, *J* = 5.8, 12.5 Hz, 1H, CH_2), 2.48 (s, 3H, CH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 200.4 (C=O), 182.7 (N-C=O), 179.2 (N-C=O), 145.1 (Ar), 139.1 (Ar), 134.8 (ArH), 132.9 (Ar), 132.7 (Ar), 130.1(2) (ArH), 128.0 (ArH), 126.6 (ArH), 124.5 (ArH), 86.0 (C), 53.7 (CH_2), 47.7 (CH_3), (45.7), (C*C*H), 42.8 (CH_2*C*H)

HRMS (ESI^+) *m/z* : $C_{18}H_{15}N_2O_4$ $[M+H]^+$, calcd 323.1026, found 323.1017

Methyl (3*R*,5'*S*)-5-iodo-2'-methyl-2-oxo-1,2-dihydrospiro[indole-3,6'-[1,2]oxazinane] -5'-carboxylate (696)



(696)

Crystallization in $CHCl_3$ gave colourless crystal of (696) (83%), m.p. 174-175 °C.

FTIR (film) ν_{max}, cm^{-1}: 3247 (N-H), 3014 (C=C-H), 2953 (C=C-H), 2847 (C=C-H), 1732 (C=O), 1612 (C=C), 1469 (C=C), 1436 (C=C), 1215 (C-N), 1233 (C-N), 755 (C-I)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.39 (s, 1H, NH), 8.02 (d, *J* = 1.9 Hz, 1H, ArH), 7.58 (dd, *J* = 1.7, 8.2 Hz, 1H, ArH), 6.70 (d, *J* = 8.2 Hz, 1H, ArH), 3.43 (s, 3H, CO_2CH_3), 3.29 (dd, *J* = 5.4, 13.2 Hz, 1H, CH), 3.17 (dq, *J* = 2.1, 12.0 Hz, 1H, NCH_2), 2.83 (td, *J* = 2.8, 12.2 Hz, 1H, NCH_2), 2.56 (s, 3H, NCH_3), 2.56 (dq, *J* = 4.7, 12.9 Hz, 1H, CH_2), 2.28-2.16 (m, 1H, CH_2)

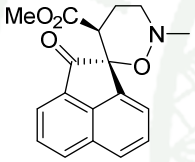
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 174.4 (N-C=O), 170.5 (O-C=O), 141.4 (Ar), 138.5 (ArH), 136.3 (ArH), 130.1 (ArN), 112.1 (ArH), 84.8 (ArI), 80.5 (C), 55.8 (NCH_2),51.9 (OCH_3), 46.4 (NCH_3), 43.8 (CH), 22.9 (CH_2)

HRMS (ESI^+) *m/z*: $C_{14}H_{16}IN_2O$ $[M+H]^+$, calcd 403.0149, found 403.0156

Table 2 NOE experiment of compound (696) in $CDCl_3$.

Irradiated	**Ar-H**	**CH_2(a)**	**CH_2(b)**	**CH**	**NCH_2**
		2.56	**2.28**		**2.86**
Ar-H (6)	–100	5.17	–1.19	-	-
CH	-	-	3.22	–100	1.96

Methyl (1*R*,5'*S*)-2'-methyl-2-oxo-2*H*-spiro[acenaphthylene-1,6'-[1,2]oxazinane]-5'-carboxylate (697)



(697)

Crystallization in Et_2O gave colourless crystal of (697) (98%), m.p. 133-135 °C.

FTIR (film) ν_{max}, cm^{-1}: 3017(C=C-H), 2945(C=C-H),, 2874(C=C-H),, 2787(C=C-H), 1733(C=O), 1603(C=C), 1434 (C=C), 1216(C-N), 1194(C-N)

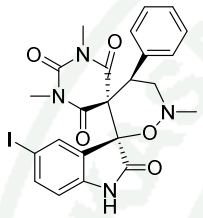
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.10 (dd, *J* = 0.5, 8.1 Hz, 1H, ArH), 8.03 (dd, *J* = 0.4, 7.0 Hz, 1H, ArH), 8.02 (dd, *J* = 0.6, 6.9 Hz, 1H, ArH), 7.89 (dd, *J* = 0.4, 8.3 Hz, 1H, ArH), 7.72 (dd, *J* = 1.1, 7.6 Hz, 1H, ArH), 7.62 (dd, *J* = 1.4, 7.7 Hz, 1H, ArH), 3.51 (dd, *J* = 5.4, 10.2 Hz, 1H, CH), 3.25 (dq, *J* = 2.5, 11.8 Hz, 1H, CH_2N), 2.97 (s, 3H, CO_2CH_3), 2.90 (dd, *J* = 2.8, 10.6 Hz, 1H, CH_2N), 2.56 (ddd, *J* = 4.5, 12.8, 13.5 Hz, 1H, CH_2), 2.56 (s, 3H, NCH_3), 2.27 (dp, *J* = 2.6, 13.7 Hz, 1H, CH_2)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 198.7 (C=O), 170.9 (O-C=O), 142.4 (Ar), 136.7 (Ar), 131.7 (ArH), 131.6 (Ar), 130.6 (Ar), 128.2 (ArH), 127.8 (ArH), 125.6

(ArH), 124.6 (ArH), 122.0 (ArH), 83.82 (C), 56.3 (NCH_2), 51.2 (OCH_3), 46.5 (NCH_3), 44.1 (CH), 23.5 (CH_2)

HRMS (ESI^+) *m/z*: $C_{18}H_{18}NO_4$ $[M+H]^+$, calcd 312.1230, found 312.1239

(3*S*,4'*R*)-5-Iodo-1'',2',3''-trimethyl-4'-phenyl-2''*H*-dispiro[indole-3,6'-[1,2]oxazinane-5',5''-pyrimidine]-2,2'',4'',6''(1*H*,1''*H*,3''*H*)-tetrone (698)



(698)

m-CPBA in CH_2Cl_2 (20 mL) was washed with phosphate buffer (2x40 mL) (50 mL 0.1*M* KH_2PO_4 and 41 mL of 0.1*M* NaOH) to remove carboxylic acid. The organic layer was dried ($MgSO_4$) then concentrated in vacuo to afford the pure *m*-CPBA . A solution of *m*-CPBA (1.05 mmol) in $CHCl_3$ (17 mL) was added dropwise to a solution of spiropyrrolidine (682) (1mmol) in $CHCl_3$ (8.5 mL) at room temperatureand stirred for 2h. The reaction mixture was washed with potassium carbonate solution and then water. The organic layer was dried over anhydrous $MgSO_4$, concentrated *in vacuo*. Flash column chromatography eluting with 1:1 hexane:EtOAc afforded the major product (698) (10%) as a brown amorphous solid, m.p. 187-188 °C.

FTIR (film) ν_{max}, cm^{-1}: 3233(N-H), 1737(C=O), 1682(C=O), 1613(C=C), 1467(C=C), 1440(C=C), 1217(C-N), 1187(C-N)

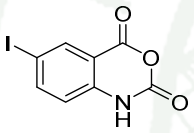
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.58 (s, 1H, NH), 7.55 (dd, *J* = 1.7, 8.2 Hz, 1H, ArH), 7.38 (d, *J* = 1.6 Hz, 1H, ArH), 7.27-7.22 (m, 3H, PhH), 7.15-7.08 (m, 2H, PhH), 6.70 (d, *J* = 8.2 Hz, 1H, ArH), 5.02 (dd, *J* = 3.7, 12.1 Hz, 1H, *CH*Ph), 4.05 (t, *J*

= 12.1 Hz, 1H, CH_2), 3.25 (dd, *J* = 3.9, 12.0 Hz, 1H, CH_2), 3.15 (s, 3H, NCH_3), 2.89 (s, 3H, NCH_3), 2.87 (s, 3H, NCH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 171.9 (C=O), 167.5 (C=O), 165.7 (C=O), 149.4 (N-C(O)-N), 141.2 (Ar), 140.1 (ArH), 136.0 (Ar), 134.3 (ArH), 128.7 (PhH), 128.6 (PhH), 128.6 (PhH), 126.7 (Ar), 112.4 (ArH), 84.4 (ArI), 80.5 (C), 59.1 (C), 55.8 (CH_2), 46.8 (NCH_3), 43.8 (CHPh), 28.7 (NCH_3), 28.2 (NCH_3)

HRMS (ESI^+) *m/z*: $C_{23}H_{22}N_4O_5$ $[M+H]^+$, calcd 561.0629, found 561.0645

6-Iodo-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (732)



(732)

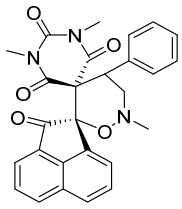
Minor product (732) as a red amorphous solid, m.p. 234-237 °C.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 11.82 (s, 1H, NH), 8.12 (d, *J* = 1.9 Hz, 1H, ArH), 8.01 (ddd, *J* = 8.6, 2.0, 0.8 Hz, 1H, ArH), 6.95 (d, *J* = 8.6 Hz, 1H, ArH)

^{13}C-NMR (75 MHz, DMSO-d_6) δ: 158.7 (C=O), 146.7 (C=O), 144.8 (ArH 4), 140.91 (Ar), 136.39 (ArH 6), 117.55 (ArH 3), 112.63 (Ar), 86.04(ArI)

HRMS (ESI^+) *m/z*: $C_8H_4INNaO_3$ [M+Na], calcd 311.9128, found 311.9121

(1*S*)-1'',2',3''-Trimethyl-4'-phenyl-2*H*,2''*H*-dispiro[acenaphthylene-1,6'-[1,2]oxazinane-5',5''-pyrimidine]-2,2'',4'',6''(1''*H*,3''*H*)-tetrone (699)



(699)

Flash column chromatography eluting with 4:1 hexane:EtOAc afforded the desired product (699) (70%) as a yellow amorphous, and then it was crystallized with $CHCl_3$: hexane to give a yellow crystal of (699), m.p. 188-190 °C.

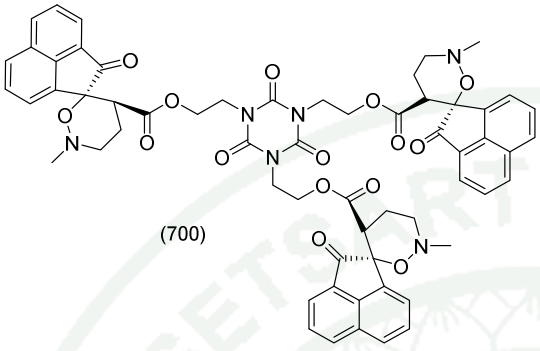
FTIR (film) ν_{max}, cm^{-1}: 3016(C=C-H), 1732(C=O), 1688(C=O), 1602(C=C), 1436(C=C), 1217(C-N), 1083(C-N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.07 (d, *J* = 7.0 Hz, 1H, ArH), 8.04 (dd, *J* = 0.5, 8.2 Hz, 1H, ArH), 7.88 (d, *J* = 8.3 Hz, 1H, ArH), 7.57 (dd, *J* = 1.1, 7.0 Hz, 1H, ArH), 7.54 (dd, *J* = 0.9, 8.3 Hz, 1H, ArH), 7.42 (d, *J* = 7.1 Hz, 1H, ArH), 7.30-7.24 (m, 3H, PhH), 7.17-7.11 (m, 2H, PhH), 5.18 (dd, *J* = 3.7, 12.1 Hz, 1H, C*H*Ph), 4.08 (t, *J* = 12.1 Hz, 1H, CH_2N), 3.29 (dd, *J* = 3.8, 12.1 Hz, 1H, CH_2N), 3.15 (s, 3H, NCH_3), 2.88 (s, 3H, NCH_3), 2.35 (s, 3H, NCH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 194.6 (C=O), 168.3 (N-C=O), 165.9 (N-C=O), 149.5 (N-C(O)-N), 140.7 (Ar), 136.2 (Ph), 134.9 (Ar), 131.9 (Ar), 130.7 (ArH), 130.5 (Ar), 128.8(2) (PhH, ArH), 128.3(2) (PhH, ArH), 127.1 (ArH), 122.4 (ArH), 122.3 (ArH), 83.0 (C), 60.0 (C), 55.9 (NCH_2), 46.8 (NCH_3), 45.1 (PhCH), 28.3 (NCH_3), 28.2 (NCH_3)

HRMS (ESI^+) *m/z*: $C_{27}H_{24}N_3O_5$ $[M+H]^+$, calcd 470.1710, found 470.1720

(2,4,6-Trioxo-1,3,5-triazinane-1,3,5-triyl)triethane-2,1-diyl tris(2'-methyl-2-oxo-2*H*-spiro[acenaphthylene-1,6'-[1,2]oxazinane]-5'-carboxylate (700)



(700)

Flash column chromatography eluting with 1:1 hexane:EtOAc afforded the major product (700) (98%) as a colourless amorphous foam.

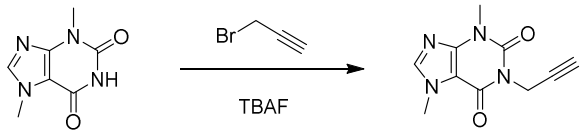
FTIR (film) ν_{max}, cm^{-1}: 3019 (C=C-H), 296 1(C=C-H), 2874 (C=C-H), 2842 (C=C-H), 1732 (C=O), 1695 (C=O), 1604 (C=C), 1462 (C=C), 1206 (C-N), 1186 (C-N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.07 (d, *J* = 8.2 Hz, 1H, ArH), 7.99 (d, *J* = 7.0 Hz, 1H, ArH), 7.87 (d, *J* = 8.3 Hz, 1H, ArH), 7.86 (d, *J* = 6.9 Hz, 1H, ArH), 7.67-7.56 (m, 2H, ArH), 3.77 (m, 1H, $C(O)NCH_2$), 3.71-3.49 (m, 1H, CO_2CH_2), 3.42 (dd, *J* = 12.8, 5.1 Hz, 1H, CH), 3.38-3.28 (m, 1H, $C(O)NCH_2$), 8.18 (dm, *J* = 11.0 Hz, 1H, NCH_2), 2.85 (t, *J* = 12.0 Hz, 1H, NCH_2), 52.6 (dq, *J* = 13.1, 4.1 Hz, 1H, NCH_2), 2.53 (s, 1H, NCH_3), 2.21 (dm, *J* = 13.7 Hz, 1H, CH_2)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 198.3 (C=O), 170.1 (2) (N-C=O), 148.2 (Ar), 142.5 (Ar), 136.8 (Ar), 131.9 (ArH), 131.5 (Ar), 128.2 (ArH), 127.8 (ArH), 125.7 (ArH), 124.6 (ArH), 121.8(2) (ArH), 83.6 (Q), 60.4 ($C(O)N\underline{C}H_2$), 56.3 (NCH_2), 46.5 (NCH_3), 43.9 (CH), 41.0 (NCH2), 23.5 (CH_2)

HRMS (ESI^+) *m/z*: $C_{60}H_{54}N_6NaO_{15}$ [M+Na], calcd 1121.3539, found 1121.3545

3,7-Dimethyl-1-(prop-2-yn-1-yl)-3,7-dihydro-1H-purine-2,6-dione (702)



(701) (702)

A solution of propargyl bromide in toluene (80% solution, 3.3 mL, 30 mmol) was added to a suspension of theobromine (701) (2.7 g, 15 mmol) and tetra-*n*-butylammonium fluoride (1 *M* solution in THF, 30 ml) in THF (90 ml) and stirred at room temperature for 16 h. The mixture was concentrated *in vacuo*, the residue was dissolved in CH_2Cl_2 and then washed with water. The organic layer was dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. Crystallization of the residue from MeOH yielded the product (702) (2.85 g, 87%) as the colourless needles, m.p. 190-191 °C, R_f 0.19 (5% MeOH/CH_2Cl_2).

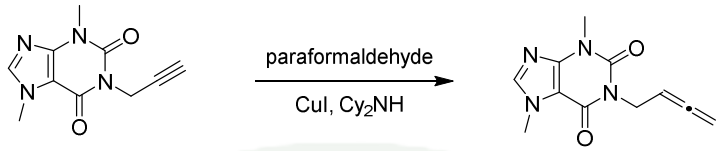
FTIR (film), ν_{max}, cm^{-1}: 1703, 1654 (C=O), 1619, 1595 (C=C), 1123 (C-N)

^{1}H-NMR ($CDCl_3$, 300MHz) δ: 7.56 (s, 1H, N=C*H*), 4.79 (d, *J* = 2.4 Hz, 2H, NCH_2), 4.01 (s, 3H, NCH_3), 3.60 (s, 3H, NCH_3), 2.20 (t, *J* = 2.4 Hz, 1H, C≡CH)

^{13}C-NMR (CDCl3, 75MHz) δ: 154.3 (C=O), 150.8 (C=O), 149.1 (C), 141.8 (N=CH), 107.5 (C), 78.7 (*C*≡CH), 70.5 (C≡*C*H), 33.7 (NCH_3), 30.4 (NCH_2), 29.8 (NCH_3)

HRMS (ESI^+) *m/z*: $C_{10}H_{10}N_4NaO_2$ [M+Na], calcd 241.0696, found 241.0691

1-(Buta-2,3-dien-1-yl)-3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione (703)



(702) (703)

A mixture of *N*-alkynyl purine (702) (2.19g, 10 mmol), dicyclohexylamine (3.59 mL, 18.08 mmol), paraformaldehyde (0.75g, 25 mmol) and CuI (0.95 g, 5 mmol) in dioxane (45 mL) was stirred under reflux for 3h. The reaction mixture was cooled to room temperature and then solvent was removed under reduced pressure. The residue was dissolved in chloroform and washed with 10% NH_4OH (3x100 mL) then water (2x100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. Crystallization of the residue from MeOH yielded the product (703) (1.82 g, 78%) as a colourless powder, m.p. 122-124 °C, R_f 0.19 (5% MeOH/CH_2Cl_2).

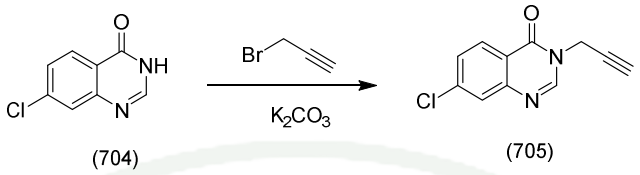
FTIR (film), ν_{max}, cm^{-1}: 1957 (C=C=C), 1703, 1654 (C=O), 1600, 1547 (C=C)

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.53 (s, 1H, N=CH), 5.31 (p, *J* = 6.5 Hz, 1H, *CH*=C=CH_2), 4.80 (dt, *J* = 2.8, 6.6 Hz, 2H, NCH_2), 4.63 (dt, *J* = 2.9, 6.1 Hz, 2H, CH=C=*CH_2*), 4.00 (s, 3H, NCH_3), 3.58 (s, 3H, NCH_3)

^{13}C-NMR (CDCl3, 75MHz) δ: 208.9 (CH=*C*=CH_2), 154.9 (C=O), 151.2 (C=O), 148.8 (C=C), 141.5 (N=*C*H), 107.6 (C=C), 86.3 (*CH*=C=CH_2), 39.5 (NCH_2), 33.6 (NCH_3), 29.7 (NCH_3)

HRMS (ESI^+) *m/z*: $C_{11}H_{12}N_4NaO_2$ [M+Na], calcd 255.08512, found 255.0844

7-Chloro-3-(prop-2-yn-1-yl)quinazolin-4(3H)-one (705)



(704) (705)

A solution of propargyl bromide in toluene (80% solution, 6.6 mL, 60 mmol) was added to a suspension of 7-chloro-4-hydroxy quinazoline (704) (5.4 g, 30 mmol) and potassium carbonate (16.4 g, 120 mmol) in acetone (75 ml) and the mixture was stirred at room temperature for 20 h. Potassium carbonate was filtered out, the filtrate was evaporated to remove acetone. The residue was dissolved in CH_2Cl_2 and washed with water. The organic phase was dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. Crystallization of the residue from MeOH yielded the product (705) (5.8 g, 88%) as the colourless needles, m.p. 140-142 °C, R_f 0.28 (1:1 hexane:EtOAc).

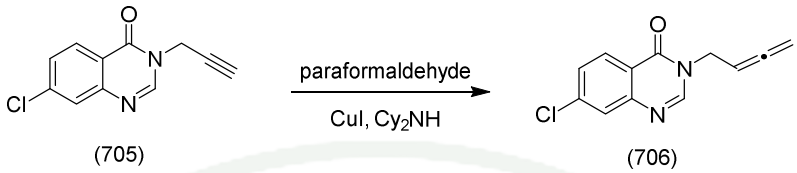
FTIR (film), ν_{max}, cm^{-1}: 1669 (C=O), 1603 (C=C)

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.32 (s, 1H, N=CH), 8.23 (d, *J* = 8.6 Hz, 1H, ArH), 7.71 (d, *J* = 2.0 Hz, 1H, ArH), 7.46 (dd, *J* = 2.0, 8.6 Hz, 1H, ArH), 4.81 (d, *J* = 2.6 Hz, 2H, NCH_2), 2.54 (t, *J* = 2.6 Hz, 1H, C≡CH)

^{13}C-NMR (CDCl3, 75 MHz) δ: 159.8 (C=O), 148.9 (C), 146.2 (N=CH), 140.8 (C), 128.2(2) (CH), 127.2 (CH), 120.2 (C), 76.1 (*C*≡CH), 75.5 (C≡*C*H), 35.3 (NCH_2)

HRMS (ESI^+) *m/z*: $C_{11}H_8ClN_2O$ $[M+H]^+$, calcd 219.0320, found 219.0313

3-(Buta-2,3-dien-1-yl)-7-chloroquinazolin-4(3H)-one (706)



(705) (706)

A mixture of alkyne (705) (770 mg, 3.5 mmol), dicyclohexylamine (1.2 mL, 6.4 mmol), para-formaldehyde (265 mg, 8.8 mmol) and CuI (335 mg, 1.8 mmol) in dioxane (16 mL) was stirred under reflux for 3h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in chloroform and washed with 10% NH_4OH (3x60 mL) then water (2x60 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography (silica gel, hexane:EtOAc, 1:1) and then crystallization with hexane/chlorofrom yielded the product (706) (590 mg, 72%) as a light brown rod crystal, m.p. 60-62 °C, R_f 0.28 (1:1 hexane:EtOAc).

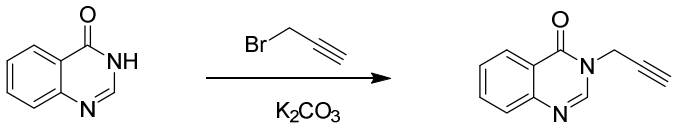
FTIR (film), ν_{max}, cm^{-1}: 3066 (C=C-H), 1957(C=C=C), 1673 (C=O), 1603 (C=C)

^{1}H-NMR ($CDCl_3$, 300MHz) δ: 8.23 (d, *J* = 8.6 Hz, 1H, ArH), 8.07 (s, 1H, N=CH), 7.70 (d, *J* = 2.0 Hz, 1H, ArH), 7.46 (dd, *J* = 2.0, 8.6 Hz, 1H, ArH), 5.42 (p, *J* = 6.3 Hz, 1H, *CH*=C=CH_2), 4.88 (dt, *J* = 2.9, 6.6 Hz, 2H, CH=C=*CH_2*), 4.60 (dt, *J* = 2.9, 6.1 Hz, 2H, NCH_2)

^{13}C-NMR (CDCl3, 75MHz) δ: 209.0 (CH=*C*=CH_2), 160.1 (C=O), 149.0 (C), 147.4 (N=CH), 140.5 (C), 128.3 (CH), 127.9 (CH), 127.1 (CH), 120.5 (ArCl), 86.5 (*CH*=C=CH_2), 78.4 (CH=C=*CH_2*), 44.5 (NCH_2)

HRMS (ESI^+) *m/z*: $C_{12}H_{10}ClN_2O$ $[M+H]^+$, calcd 233.0476, found 233.0467

3-(Prop-2-yn-1-yl)quinazolin-4(3H)-one (708)



(707) (708)

A solution of propargyl bromide in toluene (80% solution, 0.45 mL, 4 mmol) was added to a suspension of 4-hydroxy quinazoline (707) (292 mg, 2 mmol) and potassium carbonate (1.1 g, 8 mmol) in acetone (5 ml) and the mixture was stirred at room temperature for 20 h. The solution was then filtered and the filtrate evaporated to remove acetone. The residue was dissolved in CH_2Cl_2 and washed with water. The organic phase was dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. Crystallisation of the residue from hexane-CH_2Cl_2 yielded the product (708) (302 mg, 82%) as light yellow needles, m.p. 107-109 ºC, R_f 0.21 (1:1 hexane:EtOAc).

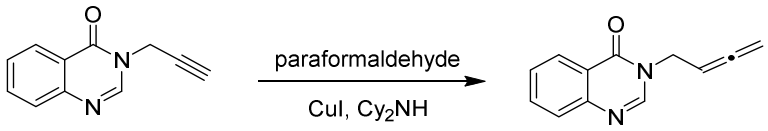
FTIR (film), ν_{max}, cm^{-1}: 1668 (C=O), 1607 (C=C)

^{1}H-NMR ($CDCl_3$, 300MHz) δ: 8.33 (dm, 1H, ArH), 8.31 (s, 1H, N=CH_2), 7.82-7.71 (m, 2H, ArH), 7.53 (dd, *J* = 1.5, 6.8, 8.2 Hz, 1H, ArH), 4.83 (d, *J* = 2.6 Hz, 2H, NCH_2), 2.50 (t, *J* = 2.6 Hz, 1H, C≡CH)

^{13}C-NMR (CDCl3, 75MHz) δ: 160.4 (C=O), 147.9 (C), 145.0 (N=CH), 134.6 (CH), 127.6 (2) (CH), 126.8 (CH), 121.8 (C), 76.4 (*C*≡CH), 75.2 (C≡*C*H), 35.2 (NCH_2)

HRMS (ESI^+) *m/z*: $C_{11}H_9N_2O$ $[M+H]^+$, calcd 185.0709, found 185.0717

3-(Buta-2,3-dien-1-yl)quinazolin-4(3H)-one (709)



(708) (709)

A mixture of (708) (1.63 g, 8.84 mmol), dicyclohexylamine (3.2 mL, 15.92 mmol), paraformaldehyde (0.66 g, 22.1 mmol) and CuI (0.84 g, 4.42mmol) in dioxane (40 mL) was stirred under reflux for 3h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in chloroform and washed with 10% NH_4OH (3x100 mL) then water (2x100mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography (silica gel, hexane:EtOAc 1:1) and then crystallization from hexane/chlorofrom yielded the desired product (709) (1.86g, 68%) as a light brown flat, m.p. 66-67 °C; R_f 0.21 (1:1 hexane:EtOAc).

FTIR (film), ν_{max}, cm^{-1}: 3053 (C=C-H), 1956 (C=C=C), 1677 (C=O), 1611 (C=C)

^{1}H-NMR ($CDCl_3$, 300MHz) δ: 8.32 (dm, 1H ArH), 8.06 (s, 1H, N=CH), 7.80-7.69 (m, 2H, ArH), 7.52 (ddd, *J* = 1.5, 6.8, 8.2 Hz, 1H, ArH), 5.43 (p, *J* = 6.4 Hz, 1H, *CH*=C=CH_2), 4.88 (dt, *J* = 3.0, 6.6 Hz, 2H, CH=C=*CH_2*), 4.62 (dt, *J* = 3.0, 6.2 Hz, 2H, NCH_2)

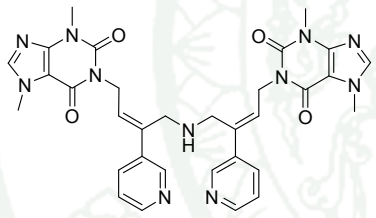
^{13}C-NMR ($CDCl_3$, 75MHz) δ: 208.9 (CH=*C*=CH_2), 160.7 (C=O), 148.0 (C), 146.3 (N=CH), 134.2 (CH), 127.5 (CH), 127.3 (CH), 126.7 (CH), 122.0 (C), 86.6 (*CH*=C=CH_2), 78.2 (CH=C=*CH_2*), 44.5 (NCH_2)

HRMS (ESI^+) *m/z*: $C_{12}H_{11}N_2O$ $[M+H]^+$, calcd 199.0866, found 199.0868

General procedure for casecade synthesis of bis-allylamines (711-713)

A mixture of allene (0.5 mmol), aryliodide (0.6 mmol), ammonium tartrate (1.5-3 mmol), Pd_2dba_3 (2.5 mol%), TFP (0.1 mol%) and potassium carbonate (1 mmol) in 5:1 v/v dioxane:DMF (12 mL) was heated and stirred at 100°C until the reaction complete (monitor by TLC). The reaction mixture was then cooled to room temperature and the solvent evaporated. CH_2Cl_2 was then added and the solution extracted with 30% NH_4OH then water. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography, silica gel.

1,1'-{Iminobis[(2*Z*)-3-(pyridin-3-yl)but-2-ene-4,1-diyl]}bis(3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione) (711a)



(711a)

Flash chromatography gradient eluting with 95:5 $CHCl_3$:MeOH and then 90:5:5 ($CHCl_3$: MeOH: NH_4OH) gave the the colourless amorphous product (711a) (80%), m.p. 148-149 °C, R_f : 0.26 (20% MeOH/$CHCl_3$).

FTIR (film), ν_{max}, cm^{-1}: 3312 (N-H), 3113, 3051, 2949 (C=C-H), 1704, 1666 (C=O), 1604 (C=C), 1550 (C=N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.70 (d, *J* =1.7 Hz, 1H, ArH), 8.44 (dd, *J* = 4.7, 1.3 Hz, 1H, ArH), 7.76 (dt, *J* = 8.0, 1.8 Hz, 1H, ArH), 7.53 (s, 1H, N=CH), 7.15 (dd, *J* = 8.0, 4.8 Hz, 1H, ArH), 5.92 (t, *J* = 7.0 Hz, 1H, C=CH), 4.90 (d, *J* = 7.0 Hz, 2H, NCH_2), 3.98 (s, 3H, NCH_3), 3.94 (s, 2H, CH_2NH), 3.60 (s, 3H, NCH_3)

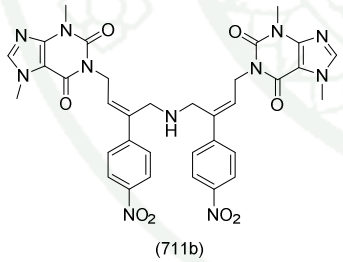
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 155.0 (C=O), 151.3 (C=O), 148.9 (C), 148.3 (ArH), 147.8 (ArH), 141.6 (N=CH), 138.7 (C), 137.1 (C), 133.9 (ArH), 126.6 (C=*C*H), 123.0 (ArH), 107.6 (C), 48.0 ($NHCH_2$), 39.5 (NCH_2), 33.6 (NCH_3), 29.8 (NCH_3)

HRMS (ESI^+) *m/z*: $C_{32}H_{34}N_{11}O_4$ $[M+H]^+$, calcd 636.2790, found 636.2780

Table 3 NOE experiment of compound (711a) in $CDCl_3$.

Irradiated	CH_2N	C=CH	CH_2NH	Pyridine-H (8.70 ppm)	Pyridine-H (7.76 ppm)
CH_2N	–100	5.20	3.54	-	-
C=CH	3.25	–100	-	6.62	3.79
CH_2NH	3.66	-	–100	3.12	3.19

1,1'-{Iminobis[(2*Z*)-3-(4-nitrophenyl)but-2-ene-4,1-diyl]}bis(3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione) (711b)



(711b)

Flash chromatography gradient eluting with 95:5 and then 90:10 $CHCl_3$:MeOH gave the the colourless amorphous product (711b) (82%), m.p. 228-230 °C, R_f : 0.16 (5% MeOH/CH_2Cl_2).

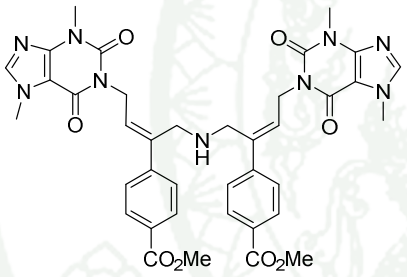
FTIR (solid), ν_{max}, cm^{-1}: 3122 (C=C-H), 1702, 1655 (C=O), 1591 (C=C), 1342 (nitro)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.10 (d, *J* = 8.8 Hz, 2H, ArH), 7.65 (d, *J* = 8.8 Hz, 2H, ArH), 7.53 (s, 1H, N=CH), 6.00 (t, *J* = 6.8 Hz, 1H, C=CH), 4.89 (d, *J* = 6.8 Hz, 2H, NCH_2), 3.97 (s, 3H, NCH_3), 3.94 (s, 2H, C*H*$_2$NH), 3.57 (s, 3H, NCH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 155.0 (C=O), 151.4 (C=O), 149.0 (C), 148.2 (C), 146.9 (C), 141.7 (N=CH), 139.7 (C), 128.7 (CH), 127.2 (CH), 123.5 (2xArH), 107.6 (C), 48.2 ($NHCH_2$), 39.6 (NCH_2), 33.6 (NCH_3), 29.8 (NCH_3)

HRMS (ESI^+) *m/z*: $C_{34}H_{34}N_{11}O_8$ $[M+H]^+$, calcd 724.2586, found 724.2588

Dimethyl 4,4'-{iminobis[(2Z)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)but-2-ene-1,2-diyl]}dibenzoate (711c)



(711c)

Flash chromatography eluting with 95:5 $CHCl_3$:MeOH gave the the the colourless amorphous product (711c) (80%), m.p. 212-214 °C, R_f : 0.30 (10% MeOH/ CH_2Cl_2).

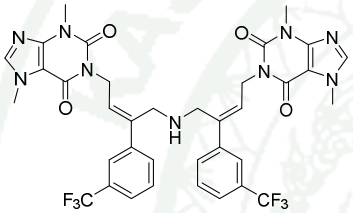
FTIR (film), ν_{max}, cm^{-1}: 1703, 1658 (C=O), 1605 (C=C), 1549 (C=N), 1280 (C-O)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.89 (d, *J* = 8.5 Hz, 2H, ArH), 7.52 (s, 1H, N=CH), 7.51 (d, *J* = 8.5 Hz, 2H, ArH), 5.96 (t, *J* = 7.0 Hz, 1H, C=CH), 4.88 (d, *J* = 7.0 Hz, 2H, NCH_2), 3.97 (s, 3H, NCH_3), 3.95 (s, 2H, C*H*$_2$NH), 3.89 (s, 3H, CO_2Me), 3.57 (s, 3H, NCH_3)

^{13}C-NMR (75MHz, $CDCl_3$) δ: 166.9 (C=O), 154.9 (C=O), 151.3 (C=O), 148.9 (C), 146.0 (C), 141.6 (N=CH), 140.7 (C), 129.5 (2xArH), 128.6 (C), 126.9 (C=*C*H), 126.4 (2xArH), 107.6 (C), 52.0 (OCH_3), 47.9 ($NHCH_2$), 39.6 (NCH_2), 33.6 (NCH_3), 29.7 (NCH_3)

HRMS (ESI^+) *m/z*: $C_{38}H_{40}N_9O_8$ $[M+H]^+$, calcd 750.2994, found 750.3029

1,1'-(Iminobis{(2Z)-3-[3-(trifluoromethyl)phenyl]but-2-ene-4,1-diyl})bis(3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione) (711d)



(711d)

Flash column chromatography eluting with 95:5 $CHCl_3$:MeOH gave the the colourless amorphous product (711d) (63%), m.p. 193-195 °C, R_f : 0.32 (10% MeOH/ CH_2Cl_2).

FTIR (film), ν_{max}, cm^{-1}: 3524 (N-H), 3113, 2955 (C=C-H), 1704, 1659 (C=O), 1604 (C=C), 1550 (C=N), 1123, 1334 (C-F)

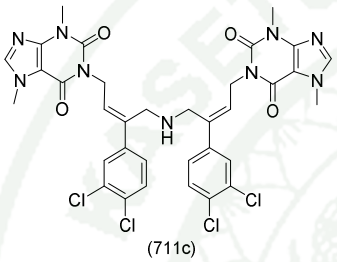
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.76 (s, 1H, ArH), 7.65 (d, *J* = 7.7 Hz, 1H, ArH), 7.51 (s, 1H, N=CH), 7.44 (d, *J* = 7.7 Hz, 1H, ArH), 7.33 (t, *J* = 7.7 Hz, 1H, ArH), 5.91 (t, *J* = 7.1 Hz, 1H, C=CH), 4.89 (d, *J* = 7.1 Hz, 2H, NCH_2), 3.96 (s, 3H, NCH_3), 3.95 (s, 2H, CH_2NH), 3.56 (s, 3H, NCH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 155.0 (C=O), 151.4 (C=O), 148.9 (C), 142.3 (C), 141.6 (N=CH), 140.3 (C), 130.4 (q, J_{C-F} = 31.9 Hz, Ar), 129.8 (ArH), 128.6 (ArH), 126.5 (C=*C*H), 126.0-122.4 (d, *J* =272.8 Hz, ArH), 123.8 (q, *J* = 3.7 Hz,

ArH), 123.2 (q, *J* = 3.9 Hz, ArH), 107.6 (C), 48.3 (CH_2NH), 39.6 (CH_2N), 33. 6 (CH_3N), 29.7 (CH_3N)

HRMS (ESI^+) *m/z*: $C_{36}H_{34}F_6N_9O_4$ $[M+H]^+$, calcd 770.2632, found 770.2657

1,1'-{Iminobis[(2Z)-3-(3,4-dichlorophenyl)but-2-ene-4,1-diyl]}bis(3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione) (711c)



(711c)

Flash chromatography eluting with 97:3 $CHCl_3$:MeOH gave the the the colourless amorphous product (711e) (81%), m.p. 128-130 °C, R_f : 0.32 (10% MeOH/ CH_2Cl_2).

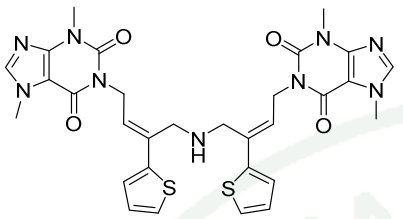
FTIR (film), ν_{max}, cm^{-1}: 3505 (N-H), 3115, 3054, 2949 (C=C-H), 1704, 1666 (C=O), 1604 (C=C), 1549 (C=N), 763, 737 (C-Cl)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.60 (t, *J* = 1.0 Hz, 1H, ArH), 7.53 (s, 1H, N=CH), 7.31 (d, *J* = 1.0 Hz, 2H, ArH), 5.89 (d, *J* = 7.0 Hz, 2H, C=CH), 4.87 (d, *J* = 7.0 Hz, 2H, NCH_2), 3.98 (s, 3H, NCH_3), 3.89 (s, 2H, CH_2NH) , 3.58 (s, 3H, NCH_3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 154.9 (C=O), 151.3 (C=O), 148.9 (C), 141.6 (2) (N=CH, C), 139.4 (C), 132.2 (C), 131.0 (C), 130.0 (CH), 128.5 (CH), 126.5 (C=CH), 125.8 (CH), 107.6 (C), 48.0 (CH_2NH), 39.5 (NCH_2), 33.6 (NCH_3), 29.8 (NCH_3)

HRMS (ESI^+) *m/z*: $C_{34}H_{32}{}^{35}Cl_4N_9O_4$ $[M+H]^+$, calcd 770.1326, found 770.1315

1,1'-{Iminobis[(2E)-3-(2-thienyl)but-2-ene-4,1-diyl]}bis(3,7-dimethyl-3,7-dihydro -1H-purine-2,6-dione) (711f)



(711f)

Flash chromatography eluting with gradient 95:5 $CHCl_3$:MeOH and then 93: 5:2 ($CHCl_3$:MeOH:NH_4OH) gave the the the colourless amorphous product (711f) (66%), m.p. 200-203 °C, R_f : 0.26 (10% MeOH/CH_2Cl_2).

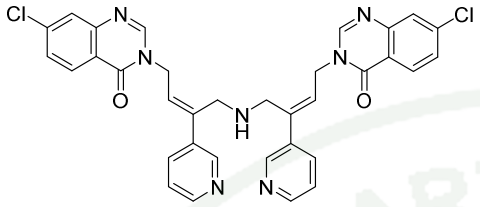
FTIR (film), ν_{max}, cm^{-1}: 1703, 1659 (C=O), 1604 (C=C), 1549 (C=N), 734 (C-S)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.50 (s, 1H, N=CH), 7.15 (dd, *J* = 3.6, 0.7 Hz, 2H, 2 x ArH), 7.10 (dd, *J* = 5.1 ,0.7 Hz, 2H, 2 x ArH), 6.90 (dd, *J* = 5.1, 3.6 Hz, 2H, 2 x ArH), 6.03 (t, *J* = 7.3 Hz, 2H, 2 x C=CH), 4.90 (d, *J* = 7.3 Hz, 4H, 2 x NCH_2), 3.98 (s, 4H, 2 x *CH_2*NH), 3.96 (s, 6H, 2 x NCH_3), 3.56 (s, 6H, 2 x NCH_3) 2.18 (s, 1H, NH)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 155.0 (C=O), 151.3 (C=O), 148.8 (C), 145.1 (C), 141.5 (N=CH), 135.6 (C), 127.3 (CH), 124.2 (CH), 124.1 (CH), 123.0 (C=*C*H), 107.7 (C), 48.4 (CH_2NH), 39.5 (CH_2N), 33.6 (CH_3N), 29.7 (CH_3N)

HRMS (ESI^+) *m/z*: $C_{30}H_{32}N_9O_4S_2$ $[M+H]^+$, calcd 646.2013, found 646.2036

3,3'-{Iminobis[(2Z)-3-(pyridin-3-yl)but-2-ene-4,1-diyl]}bis(7-chloroquinazolin-4(3H)-one (712a)



(712a)

Flash chromatography eluting with gradient 95:5 and then 90:10 $CHCl_3$:MeOH gave the the the colourless amorphous product (712a) (52%), m.p. 210-212 °C, R_f : 0.14 (10% MeOH/$CHCl_3$).

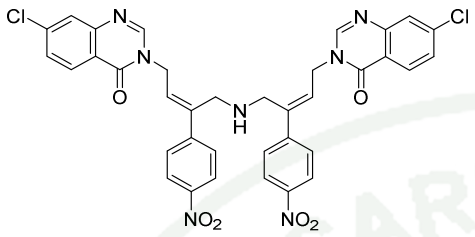
FTIR (solid), ν_{max}, cm^{-1}: 3298 (N-H), 3066, 2928, 2851 (C=C-H), 1682 (C=O), 1604 (C=C), 1556 (C=N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.67 (d, *J* = 1.9 Hz, 2H, 2×ArH), 8.49 (dd, *J* = 4.8, 1.5 Hz, 2H, 2×ArH), 8.19 (d, *J* = 7.9 Hz, 2H, 2×ArH), 8.17 (s, 2H, 2×N=CH), 7.70 (td, *J* = 8.1, 1.8 Hz, 2H, 2×ArH), 7.68 (d, *J* = 1.9 Hz, 2H, 2×ArH), 7.44 (dd, *J* = 8.6, 2.0 Hz, 2H, 2×ArH), 7.20 (ddd, *J* = 7.9, 4.8, 0.5 Hz, 2H, 2×ArH), 5.91 (t, *J* = 7.2 Hz, 2H, 2×C=CH), 4.86 (d, *J* = 7.2, 4H, 2×CH_2N), 3.92 (s, 4H, 2×C*H*$_2$NH), 2.11 (br s, 1H, NH)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 160.4 (C=O), 149.1 (ArH), 149.0 (C), 147.7 (ArH), 147.3 (N=CH), 140.6 (C), 140.3 (C), 136.2 (C), 133.8 (ArH), 128.2 (ArH), 128.1 (ArH), 127.1 (ArH), 125.5 (C=*C*H), 123.2 (ArH), 120.5 (C), 48.2 (CH_2NH), 44.6 (CH_2N)

HRMS (ESI^+) *m/z*: $C_{34}H_{28}Cl_2N_7O_2$ $[M+H]^+$, calcd 636.1676, found 636.1682

3,3'-{Iminobis[(2Z)-3-(4-nitrophenyl)but-2-ene-4,1-diyl]}bis(7-chloroquinazolin-4(3H)-one) (712b)



(712b)

Flash chromatography eluting with 95:5 $CHCl_3$:MeOH gave the the the colourless amorphous product (712b) (58%), m.p. 165-167 °C, R_f : 0.28 (5% MeOH/CH_2Cl_2).

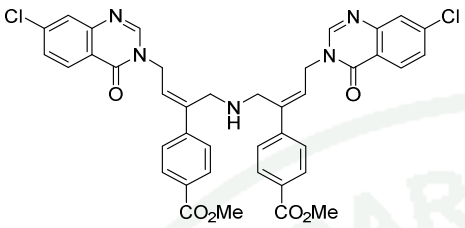
FTIR (solid), ν_{max}, cm^{-1}: 3301 (N-H), 3073, 2925, 2852 (C=C-H), 1667 (C=O), 1601 (C=C), 1346 (NO_2)

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.48 (s, 1H, N=CH), 8.11-8.04 (m, 3H, ArH), 7.74–7.68 (m, 3H, ArH), 7.54 (dd, *J* = 8.6, 2.2 Hz, 1H, ArH), 6.20 (t, *J* = 6.7 Hz, 1H, C=CH), 4.87 (d, *J* = 6.7 Hz, 2H, CH_2N), 3.86 (s, 2H, C*H*$_2$NH)

^{13}C-NMR (75 MHz, DMSO-d_6) δ: 159.6 (C=O), 149.2 (N=CH), 149.0 (C), 147.4 (C), 146.2 (C), 139.4 (C), 138.9 (C), 128.7 (CH), 128.0 (CH), 127.5 (CH), 127.2 (CH), 126.2 (CH), 123.2 (CH), 120.4 (C), 46.8 (CH_2NH), 44.3 (CH_2N)

HRMS (ESI^+) *m/z*: $C_{36}H_{28}Cl_2N_7O_6$ $[M+H]^+$, calcd 724.1473, found 724.1483

Dimethyl 4,4'-{iminobis[(2Z)-4-(7-chloro-4-oxoquinazolin-3(4H)-yl)but-2-ene-1,2-diyl]} dibenzoate (712c)



(712c)

Flash chromatography eluting with 95:5 $CHCl_3$:MeOH gave the the the colourless amorphous product (712c) (60%), m.p. 194-196 °C, R_f : 0.33 (10% MeOH/$CHCl_3$).

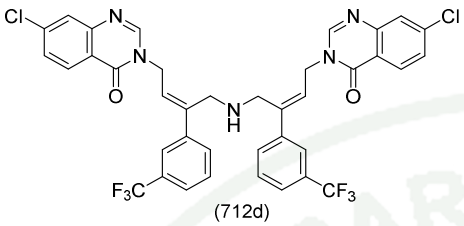
FTIR (solid), ν_{max}, cm^{-1}: 3298 (N-H), 3030, 2953, 2857 (C=C-H), 1707, 1663 (C=O), 1603 (C=C), 1553 (C=N), 1288 (C-O)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.20 (d, *J* = 8.6 Hz, 2H, 2×ArH), 8.14 (s, 2H, 2×N=CH), 7.92 (d, *J* = 8.6 Hz, 4H, 4×ArH), 7.68 (d, *J* = 1.9 Hz, 2H, 2×ArH), 7.47–7.39 (m, 6H, 6×ArH), 5.95 (t, *J* = 7.1 Hz, 2H, 2×ArH), 4.82 (d, *J* = 7.1 Hz, 4H, 2×CH_2N), 3.90 (s, 4H, 2×*CH_2*NH), 3.88 (s, 6H, 2×CO_2Me), 1.78 (br s, 1H, NH)

^{13}C-NMR (75MHz, $CDCl_3$) δ: 166.6 (C=O), 160.4 (C=O), 149.0 (C), 147.3 (N=CH), 144.9 (C), 142.4 (C), 140.6 (C), 129.8 (CH), 129.5 (C), 128.2 (CH), 128.0 (CH), 127.1 (CH), 126.4 (CH), 125.7 (CH), 120.5 (C), 52.2 (OCH_3), 47.9 (NCH_2), 44.5 ($NHCH_2$)

HRMS (ESI^+) *m/z* : $C_{40}H_{34}Cl_2N_5O_6$ $[M+H]^+$, calcd 750.1881, found 750.1917

3,3'-{Iminobis[(2Z)-3-[3-(trifluoromethyl)phenyl]but-2-ene-4,1-diyl]}bis(7-chloroquinazolin-4(3H)-one) (712d)



(712d)

Flash chromatography eluting with 95:5 $CHCl_3$:MeOH gave the the the colourless amorphous product (712d) (40%), m.p. 171-172 °C, R_f : 0.32 (10% MeOH/$CHCl_3$).

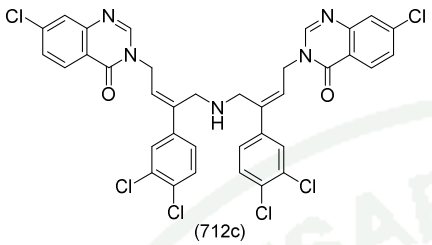
FTIR (solid), ν_{max}, cm^{-1}: 3302 (N-H), 3068, 2849 (C=C-H), 1660 (C=O), 1602 (C=C), 1555 (C=N), 1341 (C-N), 1100 (C-F)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.19 (d, *J* = 8.5 Hz, 1H, ArH), 8.17 (s, 1H, N=CH), 7.69 (s, 1H, ArH), 7.68 (s, 1H, ArH), 7.58 (d, *J* = 7.7 Hz, 1H, ArH), 7.50 (d, *J* = 7.7 Hz, 1H, ArH), 7.44 (dd, *J* = 8.6, 2.0 Hz, 2H, ArH), 7.40 (t, *J* = 7.7 Hz, 1H, ArH), 5.92 (t, *J* = 7.2 Hz, 1H, C=CH), 4.86 (d, *J* = 7.2 Hz, 2H, CH_2N), 3.93 (s, 2H, C*H*$_2$NH)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 160.4 (C=O), 149.0 (C), 147.3 (N=CH), 142.0 (C), 141.5 (C), 140.6 (C), 130.8 (q, J_{C-F}=33.8, C), 129.7 (CH), 129.0 (CH), 128.2 (CH), 128.1 (CH), 127.1 (CH), 125.7-122.2 (d, J_{C-F} = 272.6, CH), 124.6 (q, *J* = 3.6 Hz, CH), 123.2 (q, *J* = 3.8 Hz, CH), 120.5 (C), 48.4 (CH_2NH), 44.6 (CH_2N)

HRMS (ESI^+) *m/z*: $C_{38}H_{28}Cl_2F_6N_5O_2$ $[M+H]^+$, calcd 770.1519, found 770.1515

3,3'-{Iminobis[(2Z)-3-(3,4-dichlorophenyl)but-2-ene-4,1-diyl]}bis(7-chloroquinazolin-4(3H)-one) (712c)


(712c)

Flash chromatography eluting with 95:5 $CHCl_3$:MeOH gave the the the colourless amorphous product (712c) (67%), m.p. 150-151 °C, R_f : 0.56 (10% MeOH/CH_2Cl_2).

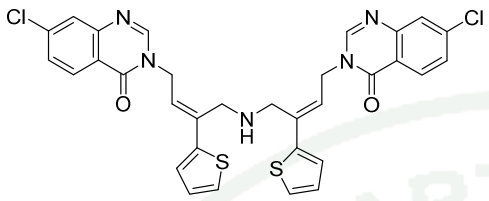
FTIR (solid), ν_{max}, cm^{-1}: 3299 (N-H), 3068, 2855 (C=C-H), 1659 (C=O), 1603 (C=C), 1553 (C=N), 783 (C-Cl)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.19 (d, *J* = 8.6 Hz, 2H, 2×ArH), 8.17 (s, 1H, N=CH), 7.68 (d, *J* = 2.0 Hz, 2H, 2×ArH), 7.52 (d, *J* = 2.0 Hz, 2H, 2×ArH), 7.44 (dd, *J* = 8.6, 2.0 Hz, 2H, 2×ArH), 7.33 (d, *J* = 8.4 Hz, 2H, 2×ArH), 7.22 (dd, *J* = 8.4, 2.0 Hz, 2H, 2×ArH), 5.88 (t, *J* = 7.1 Hz, 2H, 2×C=CH), 4.84 (d, *J* = 7.1 Hz, 4H, 2×CH_2N), 3.85 (s, 4H, 2×*CH_2*NH), 1.91 (br s, 1H, NH)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 160.4 (C=O), 149.0 (C), 147.3 (N=CH), 141.1 (C), 140.7 (C), 140.5 (C), 132.6 (C), 132.0 (C), 130.4 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.1 (CH), 125.7 (CH), 125.3 (CH), 120.5 (C), 48.1 (CH_2NH), 44.6 (CH_2N)

HRMS (ESI^+) *m/z*: $C_{36}H_{26}{}^{35}Cl_6N_5O_2$ $[M+H]^+$, calcd 770.0212, found 770.0239

3,3'-{Iminobis[(2Z)-3-(2-thienyl)but-2-ene-4,1-diyl]}bis(7-chloroquinazolin-4(3H)-one) (712f)



(712f)

Flash chromatography eluting with 98:2 $CHCl_3$:MeOH gave the the the colourless amorphous product (712f) (48%), m.p. 186-188 °C, R_f : 0.42 (10% MeOH/$CHCl_3$).

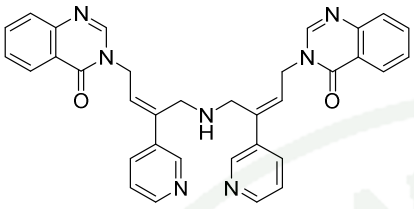
FTIR (solid), ν_{max}, cm^{-1}: 3304 (N-H), 3077, 2851 (C=C-H), 1662 (C=O), 1602 (C=C)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.20 (d, *J* = 8.6 Hz, 2H, 2×ArH), 8.19 (s, 2H, 2×N=CH), 7.67 (d, *J* = 1.9 Hz, 2H, 2×ArH), 7.43 (dd, *J* = 8.6, 2.0 Hz, 2H, 2×ArH), 7.17 (dd, *J* = 5.1, 1.0 Hz, 2H, 2×ArH), 7.12 (dd, *J* = 3.6, 1.0 Hz, 2H, 2×ArH), 6.95 (dd, *J* = 5.1, 3.7 Hz, 2H, 2×ArH), 6.04 (t, *J* = 7.3 Hz, 2H, 2×C=CH), 4.85 (d, *J* = 7.3 Hz, 4H, 2×CH_2N), 3.92 (s, 4H, 2×C*H*$_2$NH), 1.86 (br s, 1H, NH)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 160.4 (C=O), 149.1 (C), 147.5 (N=CH), 143.9 (C), 140.5 (C), 136.7 (C), 128.2 (CH), 128.0 (CH), 127.6 (CH), 127.1 (CH), 125.2 (CH), 124.5 (CH), 122.1 (CH), 120.6 (C), 48.3 ($NHCH_2$), 44.2 (NCH_2)

HRMS (ESI^+) *m/z*: $C_{32}H_{26}Cl_2N_5O_2S_2$ $[M+H]^+$, calcd 646.0899, found 646.0901

3,3'-{Iminobis[(2Z)-3-(pyridin-3-yl)but-2-ene-4,1-diyl]}diquinazolin-4(3H)-one (713a)



(713a)

Precipitation from MeOH gave the the colourless solid product (713a) (56%), m.p. 168-170 °C, R_f : 0.08 (10% MeOH/$CHCl_3$).

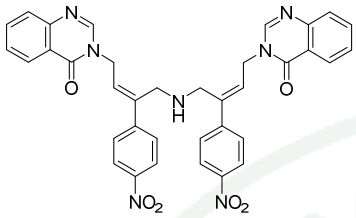
FTIR (solid), ν_{max}, cm^{-1}: 3294 (N-H), 3053, 2854 (C=C-H), 1673 (C=O), 1609 (C=C), 1562 (C=N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.67 (d, *J* = 1.8 Hz, 2H, 2×ArH), 8.48 (dd, *J* = 4.8, 1.6 Hz, 2H, 2×ArH), 8.29 (ddd, *J* = 8.0, 1.5, 0.5 Hz, 2H, 2×ArH), 8.20 (s, 2H, 2×N=CH), 7.79-7.67 (m, 6H, 6×ArH), 7.50 (ddd, *J* = 8.0, 6.8, 1.5 Hz, 2H, 2×ArH), 7.20 (ddd, *J* = 8.0, 4.8, 0.7 Hz, 2H, 2×ArH), 5.92 (t, *J* = 7.2 Hz, 2H, 2×C=CH) , 4.88 (d, *J* = 7.2 Hz, 4H, 2×CH_2N), 3.93 (s, 4H, 2×*CH_2*NH), 2.02 (br s, 1H, NH)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 161.0 (C=O), 148.9 (CH), 148.0 (C), 147.6 (CH), 146.1 (N=CH), 140.0 (C), 136.6 (C), 134.4 (CH), 133.9 (CH), 127.5 (2) (CH), 126.7 (CH), 125.9 (CH), 123.2 (CH), 122.1 (C), 48.1 (CH_2NH), 44.5 (CH_2N)

HRMS (ESI^+) *m/z*: $C_{34}H_{30}N_7O_2$ $[M+H]^+$, calcd 568.2455, found 568.2465

3,3'-{Iminobis[(2Z)-3-(4-nitrophenyl)but-2-ene-4,1-diyl]}diquinazolin-4(3H)-one (713b)


(713b)

Precipitation from MeOH gave a the the colourless solid product (713b) (57%), m.p. 190-192 °C, R_f : 0.42 (10% MeOH/$CHCl_3$).

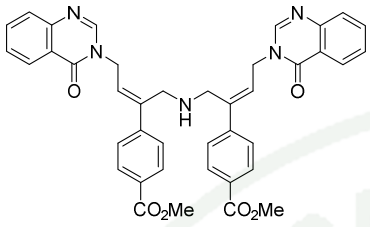
FTIR (solid), ν_{max}, cm^{-1}: 3298 (N-H), 3080, 2927, 2849 (C=C-H), 1672 (C=O), 1609 (C=C), 1350 (NO_2)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.26 (dd, *J* = 8.0, 1.1 Hz, 2H, 2×ArH), 8.17–8.10 (m, 4H, 4×ArH), 8.14 (s, 2H, 2×N=CH), 7.81–7.67 (m, 4H, 4×ArH), 7.63–7.57 (m, 4H, 4×ArH), 7.51 (ddd, *J* = 8.1, 7.0, 1.4 Hz, 2H, 2×ArH), 6.01 (t, *J* = 7.2 Hz, 2H, 2×C=CH), 4.90 (d, *J* = 7.2 Hz, 4H, 2×NCH_2), 3.96 (s, 4H, 2×*CH_2*NH), 1.60 (br s, 1H, NH)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 161.0 (C=O), 148.0 (C), 147.3 (2) (C), 145.9 (N=CH), 141.3 (C), 134.5 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 126.6 (CH), 123.7 (CH), 122.0 (C), 48.5 ($NHCH_2$), 44.6 (NCH_2)

HRMS (ESI^+) *m/z*: $C_{36}H_{30}N_7O_6$ $[M+H]^+$, calcd 656.2252, found 656.2272

Dimethyl 4,4'-{iminobis[(2Z)-4-(4-oxoquinazolin-3(4H)-yl)but-2-ene-1,2-diyl]} dibenzoate (713c)



(713c)

Flash chromatography eluting with 95:5 $CHCl_3$:MeOH gave the the the colourless amorphous product (713c) (57%), m.p. 207-209 °C, R_f : 0.31 (10% MeOH/$CHCl_3$).

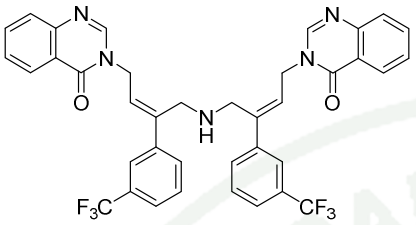
FTIR (film), ν_{max}, cm^{-1}: 3311 (N-H), 3076, 2950, 2860 (C=C-H), 1727, 1659 (C=O), 1607 (C=C), 1278 (C-O)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.28 (dd, *J* = 8.1, 1.0 Hz, 4H, 4×ArH), 8.15 (s, 2H, 2×N=CH), 7.92 (d, *J* = 8.6 Hz, 4H, 4×ArH), 7.78–7.67 (m, 4H, 4×ArH), 7.49 (ddd, *J* = 8.1, 6.9, 1.5 Hz, 2H, 2×ArH), 7.42 (d, *J* = 8.6 Hz, 4H, 4×ArH), 5.96 (t, *J* = 7.1 Hz, 2H, 2×C=CH), 4.85 (d, *J* = 7.1 Hz, 4H, 2×CH_2N), 3.92 (s, 4H, 2×*CH_2*NH), 3.87 (s, 6H, 2×CO_2Me), 1.70 (br s, 1H, NH)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.6 (C=O), 161.0 (C=O), 148.1 (C), 146.2 (N=CH), 145.0 (C), 142.2 (C), 134.3 (CH), 129.8 (CH), 129.4 (C), 127.5 (CH), 127.4 (CH), 126.7 (CH), 126.4 (CH), 126.1 (CH), 122.1 (C), 52.1 (OCH_3), 47.9 ($NHCH_2$), 44.4 (NCH_2)

HRMS (ESI^+) *m/z*: $C_{40}H_{36}N_5O_6$ $[M+H]^+$, calcd 682.2660, found 682.2647

3,3'-{Iminobis[(2Z)-3[3-(trifluoromethyl)phenyl)]but-2-ene-4,1-diyl]}diquinazolin-4(3H)-one (713d)



(713d)

Flash chromatography eluting with 95:5 $CHCl_3$:MeOH gave the the the colourless amorphous product (713d) (65%), m.p. 140-142 °C, R_f : 0.25 (10% MeOH/$CHCl_3$).

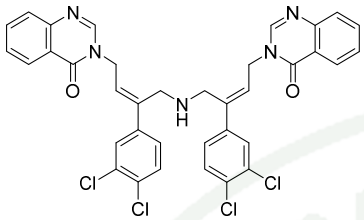
FTIR (solid), ν_{max}, cm^{-1}: 3308 (N-H), 1664 (C=O), 1336 (C-N), 1122 (C-F)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.28 (dd, *J* = 8.0, 1.0 Hz, 2H, 2×ArH), 8.18 (s, 2H, 2×N=CH), 7.78–7.66 (m, 6H, 6×ArH), 7.58 (d, *J* = 7.8 Hz, 2H, 2×ArH), 7.52–7.45 (m, 4H, 4×ArH), 7.38 (t, *J* = 7.8 Hz, 2H, 2×ArH), 5.94 (t, *J* =7.1 Hz, 2H, 2×C=CH), 4.89 (d, *J* = 7.1 Hz, 4H, 2×CH_2N), 3.95 (s, 4H, 2×*CH_2*NH), 2.00 (br s, 1H, NH)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 161.0 (C=O), 148.1 (C), 146.2 (N=CH), 141.7 (C), 141.5 (C), 134.4 (CH), 130.8 (q, *J* = 31.5 Hz, Ar), 129.7 (CH), 129.0 (CH), 127.5 (CH), 127.4 (CH), 126.7 (CH), 125.8 (CH), 124.5(q, *J* = 3.8 Hz, ArH), 123.2(q, *J* =3.7Hz, ArH), 122.2-118.6 (d, *J* =272.1 Hz, Ar), 48.4 (CH_2NH), 44.6 (CH_2N)

HRMS (ESI^+) *m/z*: $C_{38}H_{30}F_6N_5O_2$ $[M+H]^+$, calcd 702.2298, found 702.2330

3,3'-{Iminobis[(2Z)-3-(3,4-dichlorophenyl)but-2-ene-4,1-diyl]}diquinazolin-4(3H)-one (713e)


(713e)

Flash chromatography eluting with 95:5 $CHCl_3$:MeOH gave the the the colourless amorphous product (713e) (65%), m.p. 180-182 °C, R_f : 0.49 (10% MeOH/CH_2Cl_2).

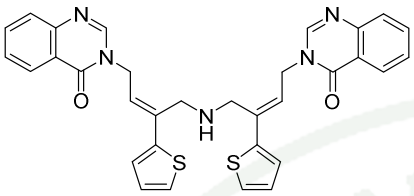
FTIR (solid), ν_{max}, cm^{-1}: 3309 (N-H), 3078, 2933, 2861 (C=C-H), 1667 (C=O), 1606 (C=C), 1563 (C=N), 771 (C-Cl)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.28 (dd, *J* = 8.1, 1.0 Hz, 2H, 2×ArH), 8.17 (s, 2H, 2×N=CH), 7.79–7.67 (m, 4H, 4×ArH), 7.53 (d, *J* = 1.9 Hz, 2H, 2×ArH), 7.50 (ddd, *J* = 8.1, 7.0, 1.5 Hz, 2H, 2×ArH), 7.33 (d, *J* = 8.4 Hz, 2H, 2×ArH), 7.22 (dd, *J* = 8.4, 2.1 Hz, 2H, 2×ArH), 5.90 (t, *J* = 7.1 Hz, 2H, 2×C=CH), 4.87 (d, *J* = 7.1 Hz, 4H, 2×CH_2N), 3.87 (s, 4H, 2×C*H*$_2$NH), 1.93 (br s, 1H, NH)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 161.0 (C=O), 148.1 (C), 146.1 (N=CH), 140.9 (C), 140.7 (C), 134.4 (CH), 132.6 (C), 131.9 (C), 130.3 (CH), 128.5 (CH), 127.6 (CH), 127.5 (CH), 126.7 (CH), 125.7 (CH), 125.6 (CH), 122.1 (C), 48.1 (CH_2NH), 44.5 (CH_2N);

HRMS (ESI^+) *m/z*: $C_{36}H_{28}{}^{35}Cl_4N_5O_2$ $[M+H]^+$, calcd 702.0992, found 702.0979

3,3'-{Iminobis[(2E)-3-(2-thienyl)but-2-ene-4,1-diyl]}diquinazolin-4(3H)-one (713f)



(713f)

Precipitation from MeOH gave the the colourless solid product (713f) (65%), m.p. 144-147 °C, R_f : 0.42 (10% MeOH/CH_2Cl_2).

FTIR (film), ν_{max}, cm^{-1}: 1669 (C=O), 1608 (C=C), 773, 754 (C-S)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.29 (dd, *J* = 8.1, 1.0 Hz, 2H, 2×ArH), 8.18 (s, 2H, 2×N=CH), 7.77-7.67 (m, 2H, 2×ArH), 7.48 (ddd, *J* = 8.1, 6.8, 1.6 Hz, 2H, 2×ArH), 7.16 (dd, *J* = 5.1, 1.0 Hz, 2H, 2×ArH), 7.12 (dd, *J* = 3.6, 1.0 Hz, 2H, 2×ArH), 6.94 (dd, *J* = 5.1, 3.6 Hz, 2H, 2×ArH), 6.06 (t, *J* = 7.3 Hz, 2H, 2×C=CH), 4.87 (d, *J* = 7.3 Hz, 4H, 2×NCH_2), 3.93 (s, 4H, 2×CH_2NH), 1.98 (br s, 1H, NH)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 161.0 (C=O), 148.1 (C), 146.4 (N=CH), 144.0 (C), 136.4 (C), 134.3 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 126.7 (CH), 125.1 (CH), 124.5 (CH), 122.5 (CH), 122.1 (C), 48.3 ($NHCH_2$), 44.2 (NCH_2)

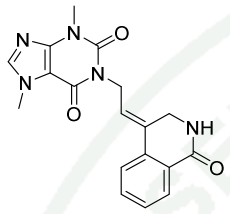
HRMS (ESI^+) *m/z*: $C_{32}H_{28}N_5O_2S_2$ $[M+H]^+$, calcd 578.1679, found 578.1689

General procedure for casecade synthesis of isoquinolinone

A mixture of allene (1 mmol), methyl 2-iodobenzoate (714) (1.2 mmol), ammonium tartrate (6 mmol), Pd_2dba_3 (2.5 mol%), TFP (0.1 mol%) and potassium carbonate (1 mmol) in 5:1 v/v dioxane:DMF (24 mL) was heated and stirred at 100°C until the reaction complete (monitor by TLC). The reaction mixture was then cooled

to room temperature and the solvent evaporated. The residue was purified by flash column chromatography, silica gel.

3,7-Dimethyl-1-[(2*Z*)-2-(1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)ethyl]-3,7-dihydro-1H-purine-2,6-dione (715a)



(715a)

From general procedure, the residue was washed with MeOH gave the the the colourless amorphous product (715a) (67%), m.p. 242-244 °C, R_f: 0.34 (10% MeOH/CH_2Cl_2).

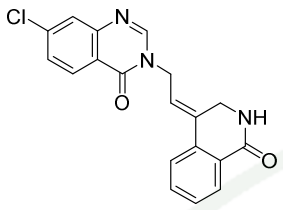
FTIR (solid), ν_{max}, cm^{-1}: 3054, 2987 (C=C-H), 1701, 1655 (C=O), 1421 (C=C), 1605 (C=N)

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 8.91 (s, 1H, NH), 8.04 (d, *J* = 8.0 Hz, 1H, ArH), 7.90 (s, 1H, N=CH), 7.61-7.55 (m, 2H, ArH), 7.48-7.41 (m, 1H, ArH), 6.19 (t, *J* = 7.6 Hz, 1H, C=CH), 4.80 (d, *J* = 7.6 Hz, 2H, CH_2N), 4.67 (s, 2H, CH_2NH), 4.05 (s, 3H, CH_3N), 3.59 (s, 3H, CH_3N)

^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 167.6 (C=O), 154.5 (C=O), 151.1 (C=O), 147.2 (C), 141.4 (HC=N), 136.9 (C), 134.1 (CH), 130.5 (C), 129.1 (CH), 128.3 (CH), 124.6 (C), 123.6 (CH), 122.5 (H*C*=C), 107.7 (C), 41.6 (CH_2NH), 38.8 (CH_2N), 34.3 (CH_3N), 30.4 (CH_3N)

HRMS (ESI^+) *m/z*: $C_{18}H_{17}N_5NaO_3$ [M+Na], calcd 374.1224, found 374.1238

7-Chloro-3-[(2Z)-2-(1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)ethyl]quinazolin-4(3H)-one (716a)



(716a)

Flash chromatography eluting with gradient 98:2 and 95:5 CH_2Cl_2:MeOH gave the the the colourless amorphous product (716a) (65%) m.p. 204-205 °C, R_f : 0.19 (5% MeOH/CH_2Cl_2).

FTIR (solid), ν_{max}, cm^{-1}: 3045 (C=C-H), 1676 (C=O), 1421 (C=C), 1604 (C=N), 738 (C-Cl)

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.53 (s, 1H, N=CH), 8.21 (s, 1H, ArH), 8.14 (d, 1H, *J* = 8.6 Hz, ArH), 7.92 (dd, *J* = 7.6, 1.3 Hz, 1H, ArH), 7.76 (d, *J* = 2.0 Hz, 1H, ArH), 7.67 (d, *J* = 7.7 Hz, 1H, ArH), 7.57 (dd, *J* = 8.6, 2.0 Hz, 1H, ArH), 7.51 (td, *J* = 7.4, 1.3 Hz, 1H, ArH), 7.41 (td, *J* = 7.3, 0.8 Hz, 1H, ArH), 6.28 (t, *J* = 6.7 Hz, 1H, C=CH), 4.82 (d, *J* = 6.7 Hz, 2H, CH_2N), 4.38 (s, 2H, CH_2NH)

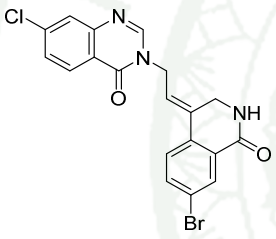
^{13}C-NMR (75 MHz, DMSO-d_6) δ: 163.0 (C=O), 159.6 (C=O), 149.3 (HC=N), 149.0 (Ar), 138.9 (Ar), 135.9 (Ar), 132.1 (ArH), 130.9 (Ar), 128.4 (ArH), 128.1 (ArH), 127.3 (2) (ArH), 126.3 (ArH), 123.4 (ArH), 121.8 (*HC*=C), 120.5 (C),43.8 (CH_2N), 40.8 (CH_2NH)

HRMS (ESI^+) *m/z*: $C_{19}H_{14}ClN_3NaO_2$ [M+Na], calcd 374.0667, found 374.0672

Table 4 NOE experiment of compound (716a) in DMSO-d_6.

Irradiated	CH_2N	C=CH	CH_2NH	N=CH (8.53 ppm)	Ar-H (8.14 ppm)	Ar-H (7.67 ppm)
CH_2N	–100	3.50	4.30	8.45	-	-
C=CH	2.80	–100	-	1.89	-	12.29
CH_2NH	2.45	-	-100	-	3.49	-

3-[(2*Z*)-2-(7-Bromo-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)ethyl]-7-chloro-quinazolin-4(3H)-one (716b)



(716b)

Flash chromatography eluting with gradient 97:3 and then 95:5 $CHCl_3$:MeOH gave the the the colourless amorphous product (716b) (61%), m.p. 244-246 °C, R_f 0.30 : (10% MeOH/CH_2Cl_2).

FTIR (solid), ν_{max}, cm^{-1}: 3201 (N-H), 3033 (C=C-H), 1685, 1654 (C=O), 1603 (C=N), 1466 (C=C), 760 (C-Cl)

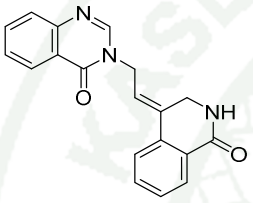
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.52 (s, 1H, N=CH), 8.38 (br s, 1H, NH), 8.15 (d, *J* = 8.4 Hz, 1H, ArH), 7.88 (d, *J* =1.5 Hz, 1H, ArH), 7.77 (d, *J* = 1.4 Hz, 1H, ArH), 7.73-7.56 (m, 3H, ArH), 6.34 (t, *J* = 6.6 Hz, 1H, C=CH), 4.80 (d, *J* = 6.6 Hz, 2H, CH_2N), 4.38 (s, 2H, CH_2NH)

^{13}C-NMR (75 MHz, DMSO-d_6) δ: 161.7 (C=O), 159.6 (C=O), 149.3 (N=CH), 149.1 (Ar), 138.9 (Ar), 135.1 (Ar), 134.8 (ArH), 129.6 (ArH), 129.1 (Ar), 128.1

(ArH), 127.3 (ArH), 126.3 (ArH), 125.9 (ArH), 122.9 (C=CH), 121.5 (C), 120.5 (C), 43.8 (CH_2N), 40.7 (CH_2NH)

HRMS (ESI^+) *m/z*: $C_{19}H_{13}BrClN_3O_2$ [M+Na], calcd 451.9772, found 451.9790

3-[(2*Z*)-2-(1-Oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)ethyl]quinazolin-4(3H)-one (717a)



(717a)

Flash chromatography eluting with gradient 95:5 and then 90:10 CH_2Cl_2:MeOH gave the the colourless amorphous product (717a) (63%), m.p. 229-232 °C, R_f : 0.26 (10% MeOH/CH_2Cl_2).

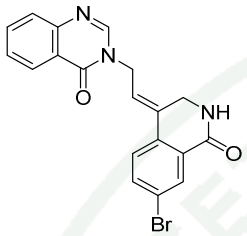
FTIR (film), ν_{max}, cm^{-1}: 3621 (N-H), 3054, 2986, 2954 (C=C-H), 1665, 1611 (C=O), 1421 (C=C)

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.49 (s, 1H, ArH), 8.22 (s, 1H, NH), 8.17 (d, *J* = 7.9 Hz, 1H, ArH), 7.92 (d, *J* = 7.6 Hz, 1H, ArH), 7.84 (t, *J* = 7.6 Hz, 1H, ArH), 7.70 (d, *J* = 6.9 Hz, 1H, ArH), 7.68 (d, *J* = 6.7 Hz, 1H, ArH), 7.56 (t, *J* = 7.9 Hz, 1H, ArH), 7.50 (t, *J* = 7.3 Hz, 1H, ArH), 7.42 (t, *J* = 7.3 Hz, 1H, ArH), 6.29 (t, *J* = 6.7 Hz, 1H, C=CH), 4.83 (d, *J* = 6.8 Hz, 1H, CH_2N), 4.38 (s, 1H, CH_2NH)

^{13}C-NMR (75 MHz, DMSO-d_6) δ: 163.0 (C=O), 160.1 (C=O), 148.0 (C), 147.9 (N=CH), 136.0 (Ar), 134.3 (ArH), 132.1 (ArH), 130.8 (Ar), 128.4 (ArH), 127.3 (2) (ArH, Ar), 127.2 (ArH), 127.1 (ArH), 126.0 (ArH), 123.4 (ArH), 122.0 (C=CH), 121.6 (C), 43.6 (CH_2N), 40.8 (CH_2NH)

HRMS (ESI$^+$) *m/z*: $C_{19}H_{15}N_3NaO_2$ [M+Na], calcd 340.1056, found 340.1061

3-[(2*Z*)-2-(7-Bromo-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)ethyl]quinazolin-4(3H)-one (717b)



(717b)

Flash chromatography eluting with gradient 97:3 and then 95:5 $CHCl_3$:MeOH gave the the colourless amorphous product (717b) (64%), m.p. 202-204 °C, R_f 0.27 : (10% MeOH/CH_2Cl_2).

FTIR (solid), ν_{max}, cm^{-1}: 3209 (N-H), 3080, 3021 (C=C-H), 1681 (C=O), 1607 (C=N), 1473 (C=C), 760 (C-Br)

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.47 (s, 1H, N=CH), 8.38 (s, 1H, NH), 8.16 (dd, *J* = 8.0, 0.9 Hz, 1H, ArH), 7.99 (d, *J* = 1.9 Hz, 1H, ArH), 7.84 (td, *J* = 8.5, 1.5 Hz, 1H, ArH), 7.73-7.65 (m, 3H, ArH), 7.55 (td, *J* = 7.5, 0.8 Hz, 1H, ArH), 6.35 (t, *J* = 6.7 Hz, 1H, C=CH), 4.81 (d, *J* = 6.7 Hz, 2H, CH_2N), 4.39 (s, 2H, CH_2NH)

^{13}C-NMR (75 MHz, DMSO-d_6) δ: 161.7 (C=O), 160.1 (C=O), 147.9 (Ar), 147.8 (N=CH), 135.1 (Ar), 134.8 (ArH), 134.3 (ArH), 129.7 (ArH), 129.6 (Ar), 129.1 (Ar), 127.2 (ArH), 127.0 (ArH), 126.0 (2) (ArH), 123.1 (C=CH), 121.6 (C), 121.5 (C), 43.7 (CH_2NH), 40.7 (CH_2N)

HRMS (ESI$^+$) *m/z*: $C_{19}H_{15}BrN_3O_2$ [M+H]$^+$, calcd 396.0342, found 396.0358

General procedure for casecade synthesis of isoquinoline

Procedure A:

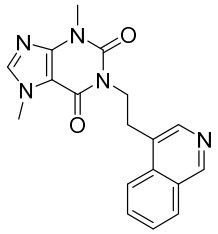
A mixture of allene (0.5 mmol), 2-iodobenzaldehyde (718) (0.6 mmol), ammonium tartrate (1.5-3 mmol), Pd_2dba_3 (2.5 mol%), TFP (0.1 mol%) and potassium carbonate (1 mmol) in 5:1 v/v dioxane:DMF (12 mL) was heated and stirred at 100°C under reflux condenser until the reaction complete (monitor by TLC). The reaction mixture was then cooled to room temperature and the solvent evaporated. $CH_2Cl_2$was then added and the solution extracted with 30% NH_4OH then water. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography, silica gel.

*Procedure B**

A mixture of allene, 2-iodobenzaldehyde (718); ammonium citrate, Pd_2dba_3, TFP and potassium carbonate in 2:1 v/v EtOH/water (12 mL/mmol) was heated and stirred at 100°C in sealed tube until the reaction complete (monitor by TLC). The reaction mixture was cooled to room temperature then sat.K_2CO_3 was added. Organic layer was separated then aqueous phase was extracted with CH_2Cl_2 (x 2). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography, silica gel.

*See amount of starting material and reagent in Table 23.

1-[2-(Isoquinolin-4-yl)ethyl]-3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione (719)



(719)

From general procedure A, Flash chromatography eluting with gradient 97:3 and then 95:5 $CHCl_3$:MeOH gave light brown amorphous solid of (719) (63%), m.p. 206-208 ºC, R_f : 0.33(10% MeOH/CH_2Cl_2).

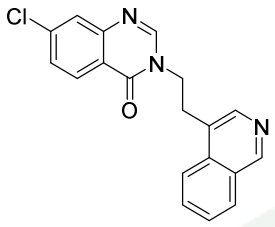
FTIR (film), ν_{max}, cm^{-1}: 3054, 2986 (C=C-H), 1705, 1655 (C=O), 1552 (C=N)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.17 (s, 1H, ArCH=N), 8.50 (s, 1H, NCH), 8.47 (d, *J* = 8.3 Hz, 1H, ArH), 8.00 (d, *J* = 8.0 Hz, 1H, ArH), 7.85 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H, ArH), 7.64 (ddd, *J* = 8.0, 7.0, 0.9 Hz, 1H, ArH), 7.55 (s, 1H, N=CH), 4.33 (m AA'BB', 2H, CH_2N), 4.03 (s, 3H, NCH_3), 3.64 (s, 3H, CH_3N), 3.36 (m AA'BB', 2H, CH_2)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 155.1 (C=O), 152.0 (ArH), 151.5 (Ar), 148.9 (Ar), 143.5 (Ar), 141.6 (Ar), 135.0 (Ar), 130.8 (ArH), 128.1 (ArH), 127.0 (ArH), 123.3 (ArH), 107.7 (Ar), 42.0 (CH_2N), 33.7 (NCH_3), 29.8 (NCH_3), 28.9 (CH_2)

HRMS (ESI^+) *m/z*: $C_{18}H_{18}N_5O_2$ $[M+H]^+$, calcd 336.1455, found 336.1461

7-Chloro-3-[2-(isoquinolin-4-yl)ethyl]quinazolin-4(3H)-one (720)



(720)

From general procedure A, Flash chromatography eluting with gradient 97:3 and then 95:5 $CHCl_3$:MeOH gave the the colourless amorphous solid of (720), m.p. 190-192 °C, R_f : 0.51 (10% MeOH/CH_2Cl_2).

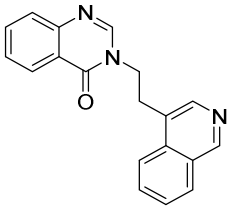
FTIR (solid), ν_{max}, cm^{-1}: 2955(C=C-H), 1661 (C=O), 1598 (C=N), 1554, 1462 (C=C), 785 (C-Cl)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.17 (s, 1H, ArCH=N), 8.35 (s, 1H, NCH), 8.29 (d, *J* = 8.5 Hz, 1H, ArH), 8.22 (d, *J* = 8.4 Hz, 1H, ArH), 8.01 (d, *J* = 8.0 Hz, 1H, ArH), 7.78 (t, *J* = 8.0 Hz, 1H, ArH), 7.71 (s, 1H, N=CH), 7.68-7.60 (m, 2H, ArH), 7.48 (dd, *J* = 8.4, 1.7 Hz, 1H, ArH), 4.31 (t, *J* = 7.4 Hz, 2H, CH_2N), 3.53 (t, *J* = 7.4 Hz, 2H, CH_2)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 160.7 (C=O), 152.6 (ArH), 149.0 (Ar), 147.2 (ArH), 143.5 (ArH), 140.6 (Ar), 134.6 (Ar), 131.1 (ArH), 128.6 (ArH), 128.4 (Ar), 128.1 (ArH), 128.0 (ArH), 127.4 (ArH), 127.1 (ArH), 126.7 (Ar), 122.5 (ArH), 120.5 (Ar), 48.2 (CH_2), 29.5 (CH_2)

HRMS (ESI^+) *m/z*: $C_{19}H_{15}ClN_3O$ $[M+H]^+$, calcd 336.0898, found 336.0907

3-[2-(Isoquinolin-4-yl)ethyl]quinazolin-4(3H)-one (721)



(721)

From general procedure A, Flash chromatography eluting with gradient 97:3 and then 95:5 $CHCl_3$:MeOH gave the colourless amorphous solid of (721) (40%), m.p. 208-210 °C, R_f : 0.33 (10% MeOH/CH_2Cl_2).

FTIR (solid), ν_{max}, cm^{-1}: 3054, 2986 (C=C-H), 1672 (C=O), 1610 (C=N), 1421 (C=C)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.18 (s, 1H, ArCH=N), 8.38 (dd, *J* = 7.9, 1.3 Hz, 1H, ArH), 8.37 (s, 1H, NCH), 8.27 (d, *J* = 8.5 Hz, 1H, ArH), 8.00 (d, *J* = 8.1 Hz, 1H, ArH), 7.82-7.73 (m, 2H, ArH), 7.75 (s, 1H, N=CH), 7.67 (dd, *J* = 7.7, 0.7 Hz, 1H, ArH), 7.63(ddd, *J* = 8.0, 7.0, 0.9 Hz, 1H, ArH), 7.54 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H, ArH), 4.32 (m AA´BB´, 2H, CH_2N), 3.53 (m AA´BB´, 2H, CH_2)

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 161.3 (C=O), 152.5 (N=CH), 148.1 (Ar), 146.1 (ArH), 143.5 (ArH), 134.6 (Ar), 134.4 (ArH), 131.1 (ArH), 128.5(2) (ArH, Ar), 127.6 (ArH), 127.5 (ArH), 127.4 (ArH), 126.8 (Ar), 126.5 (ArH), 122.6 (ArH), 122.0 (Ar), 48.2 (CH_2N), 29.6 (CH_2)

HRMS (ESI^+) *m/z*: $C_{19}H_{16}N_3O$ $[M+H]^+$, calcd 302.1288, found 302.1279

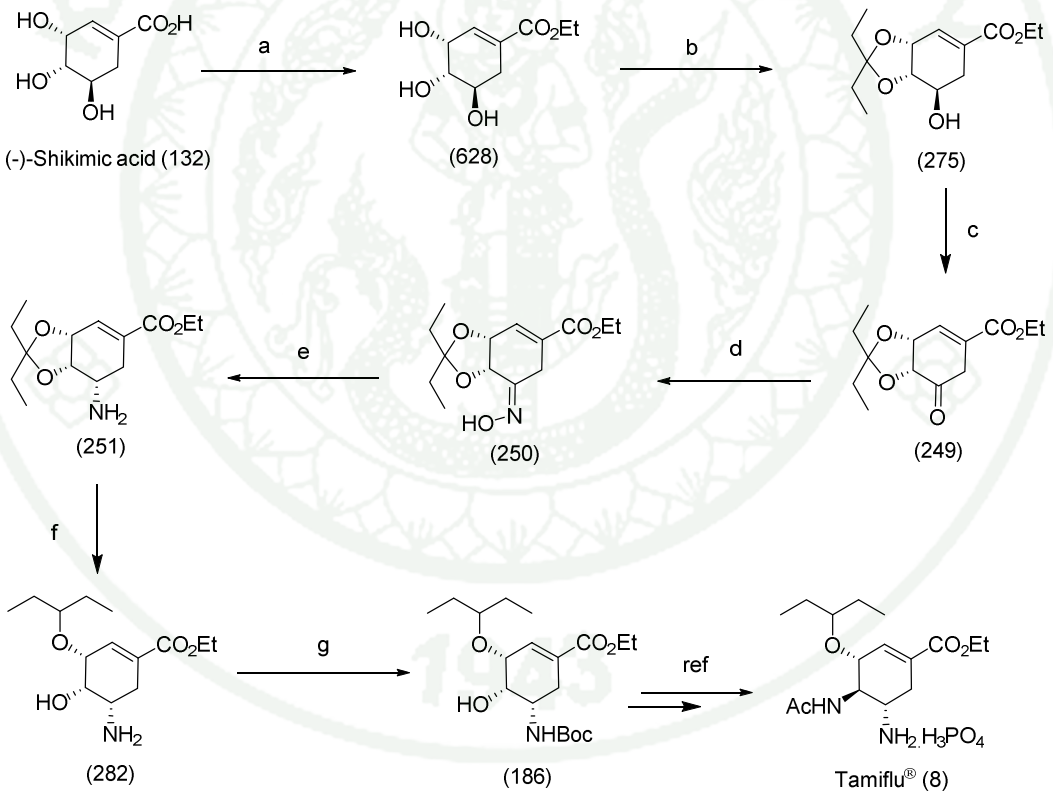
RESULTS AND DISCUSSION

Results

1. Synthesis of Tamiflu®

1.1 Synthesis of Tamiflu® from (–)-shikimic acid (132)

Amino alcohol intermediat (186) was synthesized from (–)-shilimic acid (132) via azide free strategy as shown in Scheme 116



Scheme 116

Reagents and conditions:

a) $SOCl_2$, EtOH, reflux, 3h

b) 3-pentanone, TEOF, BSA, rt, 5h then Et_3N, 79%, 2 steps

c) TEMPO, TCCA, CH_2Cl_2, rt, 30 min

d) $NH_2OH.HCl$, EtOH, pyridine, rt, 2h, 70%, 2 steps

e) $NaBH_4$, MoO_3, MeOH, 30 min, 93%

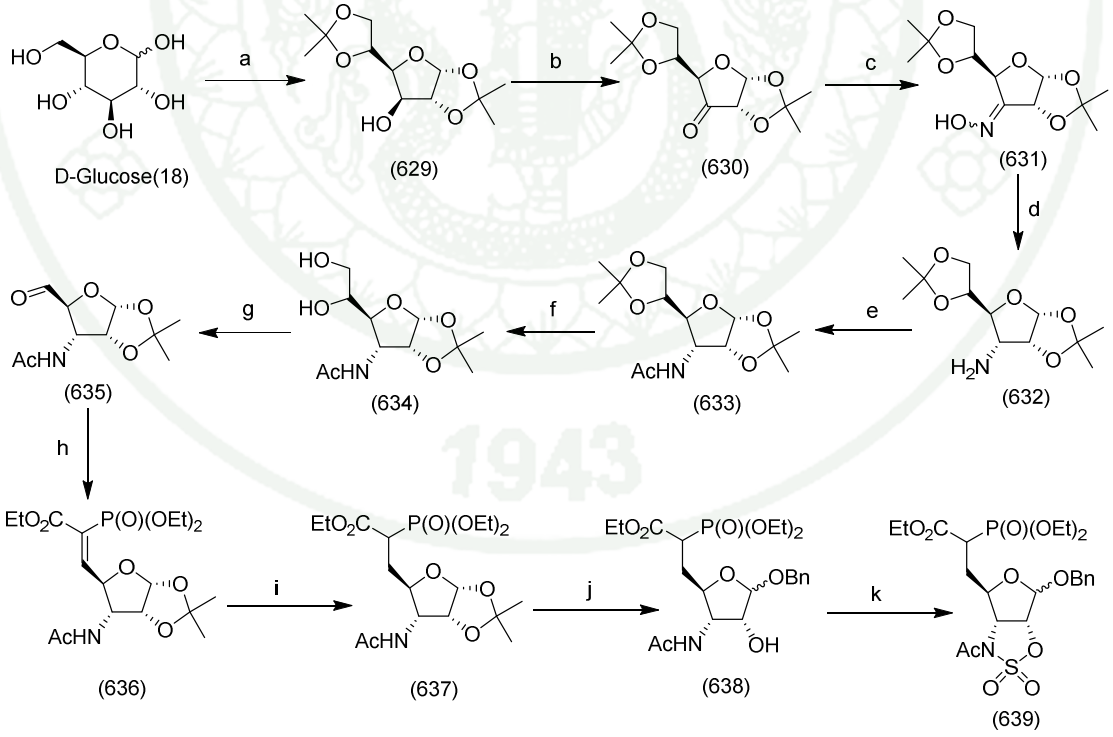
f) $TiCl_4$, Et_3SiH, CH_2Cl_2, -78ºC to -10ºC, 7h,

g) Boc_2O, MeOH, rt, 3h, 69%, 2 steps

1.2 Attempts to synthesize Tamiflu® (8) from D-glucose (18) via HWE olefination and cyclic sulfamidate approach

1.2.1 Synthesis of cyclic sulfamidate (639) from D-glucose (18).

The cyclic sulfamidate (639) was synthesized from D-glucose (18) as shown in Scheme 117



Scheme 117

Reagents and conditions:

a) Acetone, TEOF, BSA, rt, then Et_3N, 24 h, 80%

b) Ac_2O, PDC, CH_2Cl_2, 60 ºC, 3 h

c) $NH_2OH.HCl$, pyridine, reflux, 6 h, 60% (2 steps)

d) $LiAlH_4$, THF, reflux, 30 min, 39% or $NaBH_4$-MoO_3, MeOH, rt, 77%

e) Ac_2O, pyridine, rt, 3h, 92%

f) 10%$HClO_4$, EtOAc, rt, 30 min, 89% or 75%AcOH, 60 ºC, 1 h

g) $NaIO_4$, EtOH, H_2O, 0 ºC, 1 h, 90%

h) Triethylphosphonoacetate, $TiCl_4$, Et_3N, CH_2Cl_2, 0 ºC, 3h, 77%

i) H_2, 5% Pd-C, EtOH, 1 h, 89%

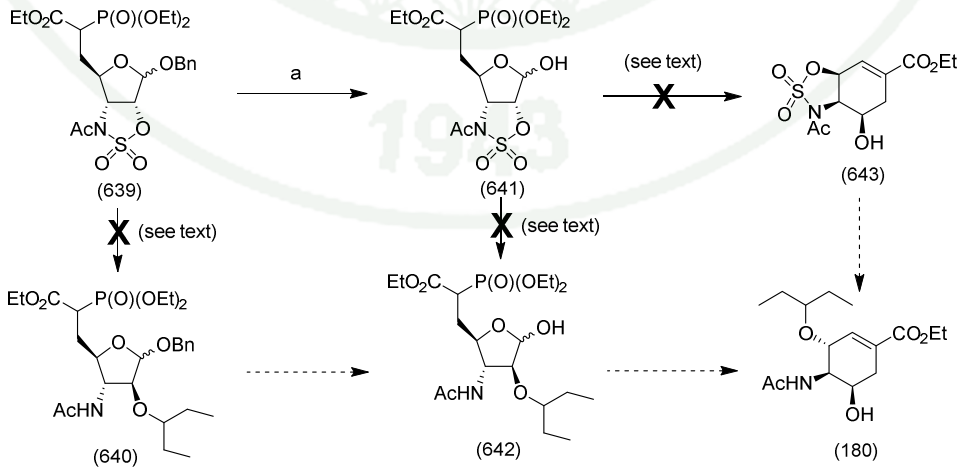
j) AcCl, BnOH, 0 ºC to rt, 3 h, 68 %

k) $SOCl_2$, imidazole, Et_3N, CH_2Cl_2, 0 ºC, 1 h

l) $RuCl_3$, $NaIO_4$, CH_3CN, H_2O, 0 ºC, 1 h, 70%, 2 steps

1.2.2 Attempts to synthesize Tamiflu intermediates from cyclic sulfamidate (639)

Tamiflu intermediate (180) was attempted to synthesize using various approach from cyclic sulfamidate (639) as shown in Scheme 118



Scheme 118

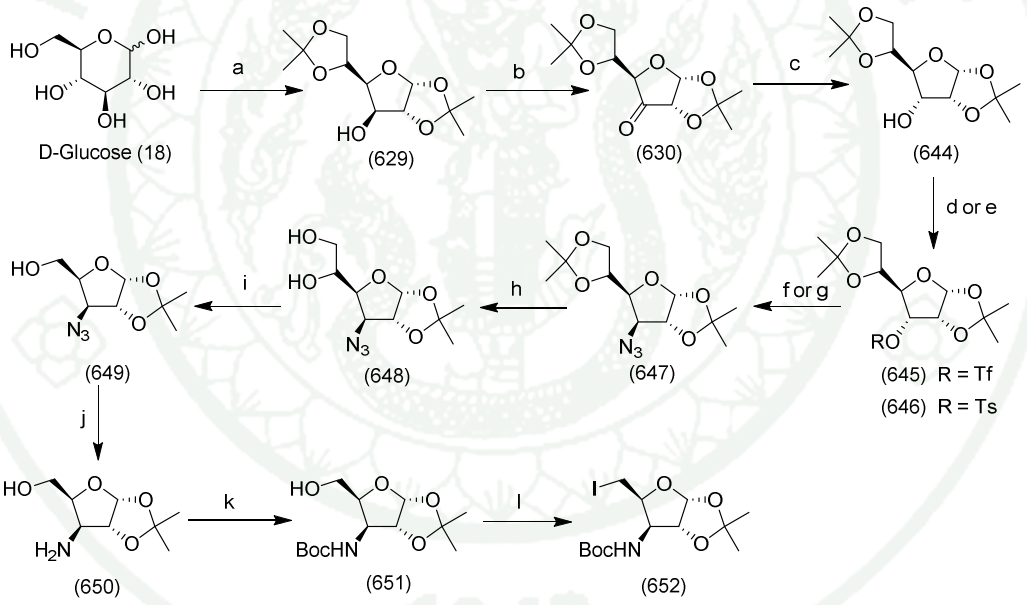
Reagents and conditions:

a) H_2, 10% Pd-C, EtOH, EtOAc, 6 h, 72%

1.3 Synthesis of Tamiflu® from D-glucose (18) *via* Zn mediated domino approach

1.3.1 Synthesis of 5-iodo-furanoside (652) from D-glucose (18)

5-Iodo-furanoside (652) was successfully synthesized from D-glucose (18) as shown in Scheme 119



Scheme 119

Reagents and conditions:

a) Acetone, TEOF, BSA, rt, then Et_3N, 24 h, 80%

b) Ac_2O, PDC, CH_2Cl_2, 60 ºC, 3 h

c) $NaBH_4$, EtOH, H_2O, rt, 2 h, 68% (2 steps)

d) Tf_2O, pyridine, CH_2Cl_2, 0 ºC, 1 h

e) TsCl, pyridine, 50 ºC, 2 h

f) NaN_3, DMF, rt, 24 h, 85%

g) NaN_3, DMF, reflux, 24 h, 62%

h) 75%AcOH, 60 ºC, 1 h

i) $NaIO_4$, EtOH, H_2O, 0 ºC, 1 h, then $NaBH_4$, 1 h, 86%

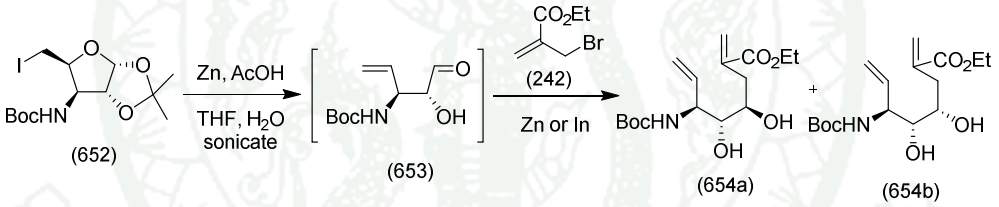
j) PPh_3, THF, H_2O, rt, 16 h, 99%

k) Boc_2O, MeOH, rt, 3 h, 83%

l) I_2, PPh_3, imidazole, toluene, CH_3CN, reflux, 5 h, 64%

1.3.2 Metal mediate domino reaction of 5-iodo-furanoside (652)

Metal mediate domino reaction of 5-iodo-furanoside (652) was examined as shown in Scheme 120



Scheme 120

Table 5 Zinc mediated reductive ring opening -alkylation of 5-iodo-furanoside (652).

Entry	Reagents and conditions	166a (%)[c]	166b (%)[c]
1	(i) Zn, AcOH, THF:H_2O (2:1), sonicate, 40ºC, 1 h then (ii) (242), sonicate, 40 ºC, 1 h	43	39
2	(i) Zn[a], AcOH, THF:H_2O (2:1), sonicate, 40ºC, 1 h then (ii) In[b], (242), sonicate, 40 ºC, 3 h	58	24

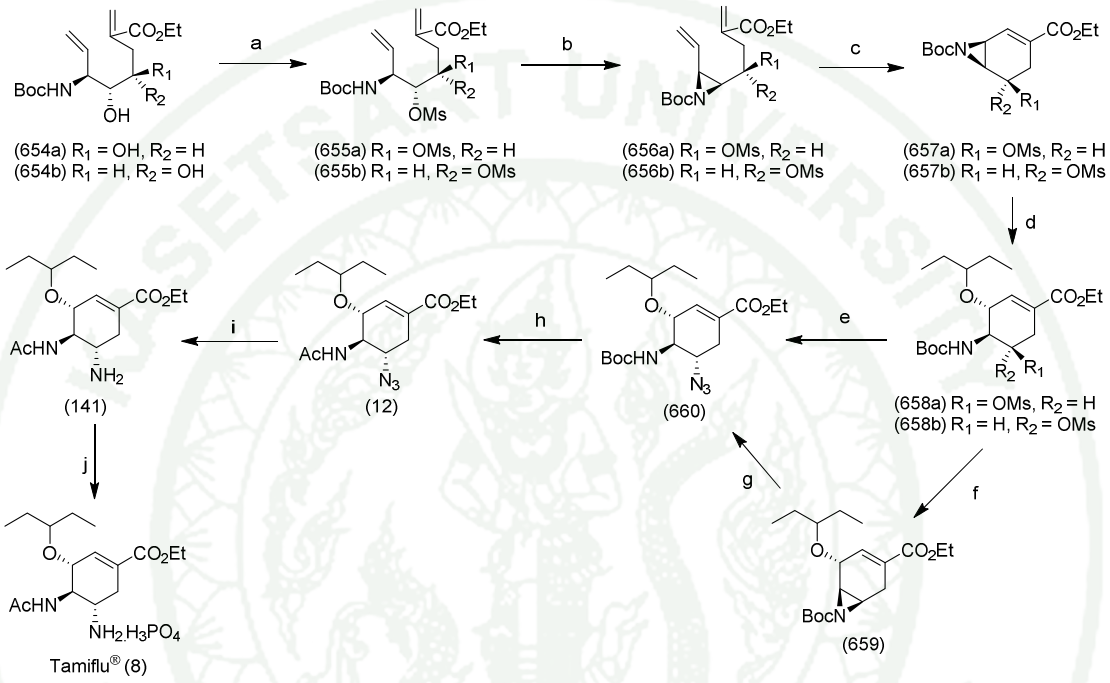
[a] Replaced activated zinc with indium powder result no reaction.

[b] Zinc was removed by filter and the filtrate was then treated with indium powder.

[c] Isolated yield

1.3.3 Synthesis of Tamiflu® from diol intermediate (654)

(*4R, 5R*)-Diol intermediate (654a) and (*4S, 5R)*-diol intermediate (654b) were transformed to Tamiflu® (8) in 8-9 steps as shown in Scheme 121.



Scheme 121

Reagents and conditions:

a) MsCl, Et_3N, CH_2Cl_2, 0 ºC, 3 h, 65% from (654a), 60% from (654b)

b) NaH, CH_2Cl_2, DMSO, rt, 1 h, 44% from (655a), 88% from (655b)

c) Hoveda-Grubbs II, CH_2Cl_2, 0 ºC, 16 h, 49% from (656a), 60% from (656b)

d) 3-pentanol, $BF_3.OEt_2$, –10 ºC, 2 h, 95% from (657a), 91% from (657b)

e) NaN_3, DMF, H_2O, 90 ºC, 8 h, 68%

f) NaH, CH_2Cl_2, DMSO, rt, 30 min, 87%

g) NaN_3, NH_4Cl, DMF, 90 ºC, 6 h, 89%

h) (i) TFA, CH_2Cl_2, 0 ºC to rt, 4 h (ii) Ac_2O, pyridine, rt, 1 h, 78%

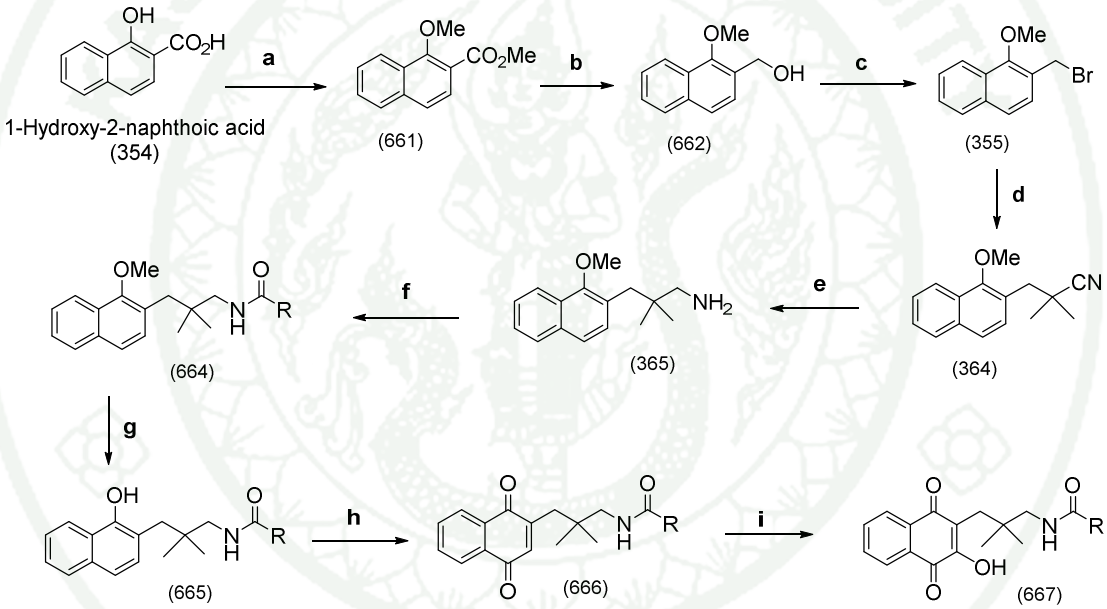
i) PPh_3, THF/H_2O (4:1), refluxed, 3 h, 74%

j) H_3PO_4, EtOH, 60 ºC, 3 h, 70%

2. Synthesis of naphthoquinone aliphatic amides with their anticancer and antimalarial activities evaluation

2.1 Synthesis of naphthoquinone aliphatic amides

Naphthoquinone aliphatic amides (667) were synthesized from 1-hydroxy -2-naphthoic acid (354) in nine steps as described in Scheme 122.



Scheme 122

Reagents and conditions:

a) MeI, K_2CO_3, acetone, reflux, 24 h

b) $LiAlH_4$, THF, 0 ºC to rt, 2 h, 94%, 2 steps

c) PBr_3, CH_2Cl_2, rt, 6 h

d) Isobutyronitrile, LDA, HMPA, THF, –78 ºC, 1 h, 73%, 2 steps

e) $LiAlH_4$, THF, 0 ºC to rt, 1 h, 90%

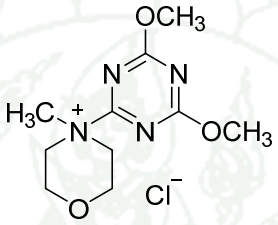
f) Carboxylic acid (663a-663n), DMTMM, MeOH, rt, 30 min, 70-99%

g) BBr_3, CH_2Cl_2, 0 ºC to rt, 3 h, 60-100%

h) Fremy's salt, DMF-MeOH (3:1), water, NaOAc, rt, 12 h, 81-98%

i) TBHP, triton, THF, 20 min, then 10% HCl, 8-30%

Preparation of amides (664a-664n) were achieved in excellent yield by coupling of amine (365) with various carboxylic acides (663a-663n) using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (668) (Figure 22) as condensing agent. The results were shown in Table 6.



DMTMM (668)

Figure 22 Structure of DMTMM.

Table 6 Amide (664) formation using DMTMM (668) as condensing agent.

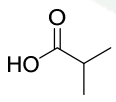
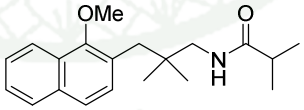
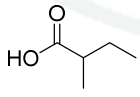
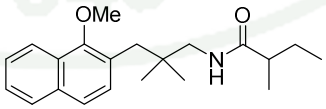
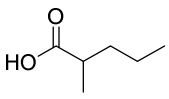
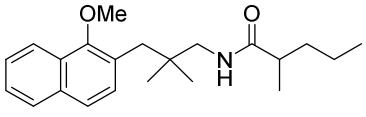
Entry	Carboxylic acid	Product	%Yield
1	 (663a)	 (664a)	81
2	 (663b)	 (664b)	81
3	 (663c)	 (664c)	89

Table 6 (Continued)

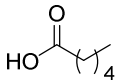
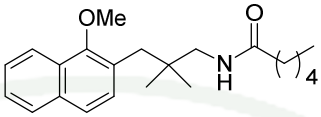
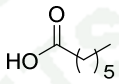
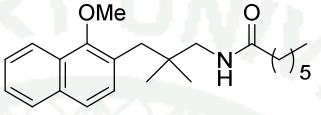
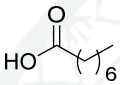
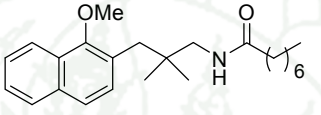
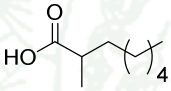
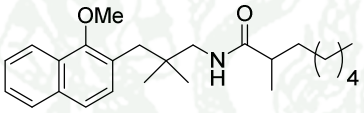
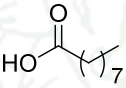
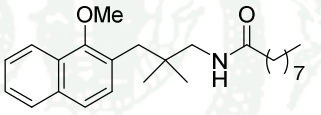
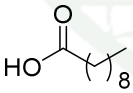
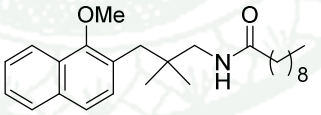
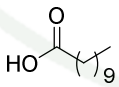
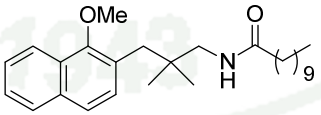
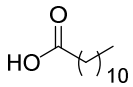
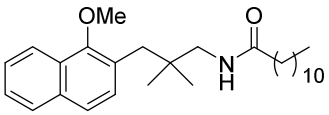
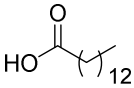
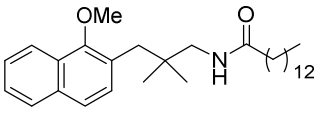
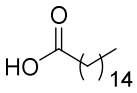
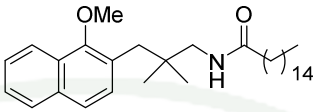
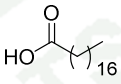
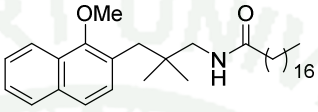
Entry	Carboxylic acid	Product	%Yield
4	 (663d)	 (664d)	90
5	 (663e)	 (664e)	95
6	 (663f)	 (664f)	99
7	 (663g)	 (664g)	77
8	 (663h)	 (664h)	94
9	 (663i)	 (664i)	98
10	 (663j)	 (664j)	91
11	 (663k)	 (664k)	89
12	 (663l)	 (664l)	90

Table 6 (Continued)

Entry	Carboxylic acid	Product	%Yield
13	 (663m)	 (664m)	97
14	 (663n)	 (664n)	70

1-Hydroxy naphthalenes (665a-665n) were prepared via demethylation of 1-methoxy naphthalenes (664a-664n) using boron tribromide (BBr_3) in high yield (Table 7).

Table 7 Demethylation of 1-methoxynaphthalene (664a-664n) using BBr_3.

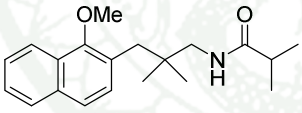
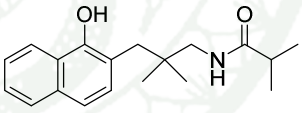
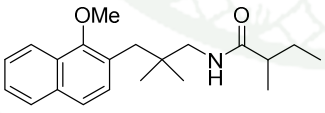
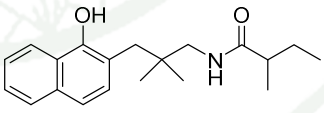
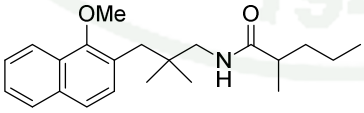
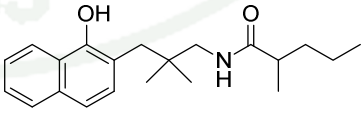
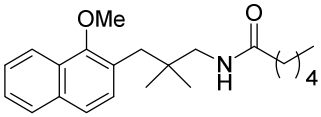
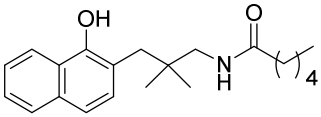
Entry	Reactant	Product	%Yield
1	 (664a)	 (665a)	63
2	 (664b)	 (665b)	80
3	 (664c)	 (665c)	100
4	 (664d)	 (665d)	93

Table 7 (Continued)

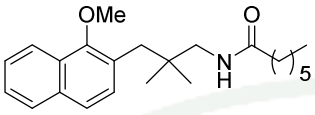
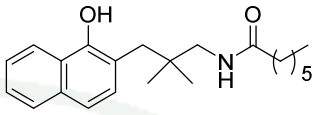
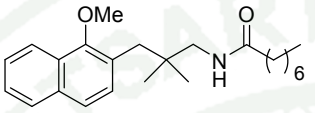
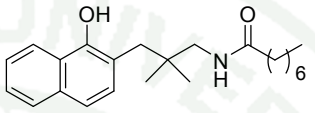
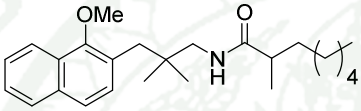
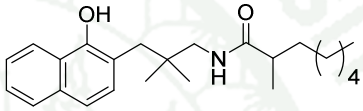
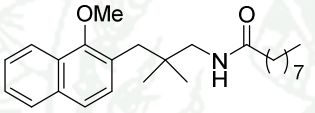
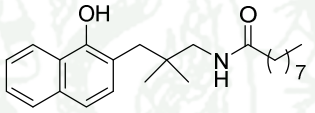
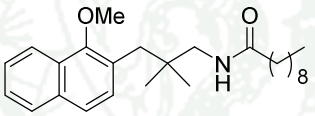
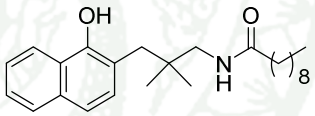
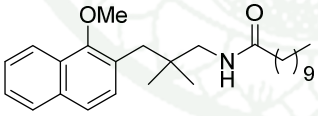
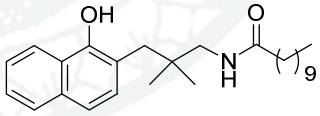
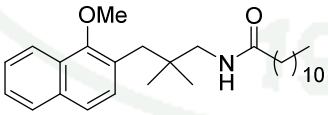
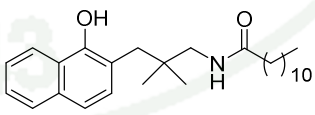
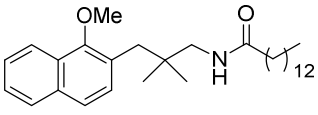
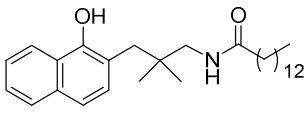
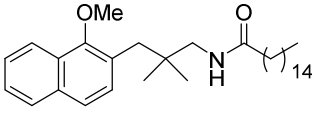
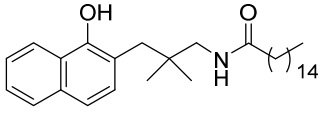
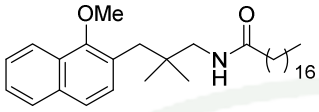
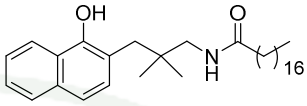
Entry	Reactant	Product	%Yield
5	 (664e)	 (665e)	65
6	 (664f)	 (665f)	60
7	 (664g)	 (665g)	96
8	 (664h)	 (665h)	97
9	 (664i)	 (665i)	93
10	 (664j)	 (665j)	94
11	 (664k)	 (665k)	91
12	 (664l)	 (665l)	93
13	 (664m)	 (665m)	98

Table 7 (Continued)

Entry	Reactant	Product	%Yield
14	 (664n)	 (665n)	100

Oxidation of 1-hydroxy naphthalenes (665a-665n) by Fremy's salt gave the naphthoquinones (666a-666n) in excellent yield as shown in Table 8

Table 8 Oxidation of 1-hydroxynaphthalenes (665a-665n) to 1,4-naphthaquinones (666a-666n) using Fremy's salt.

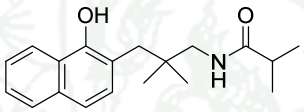
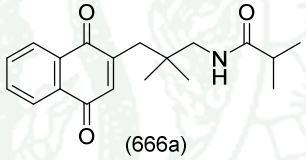
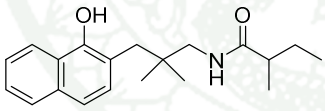
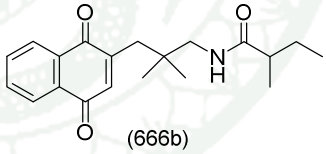
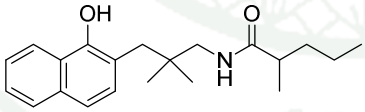
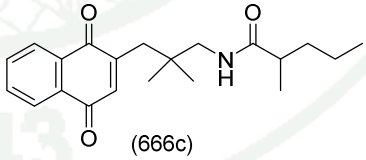
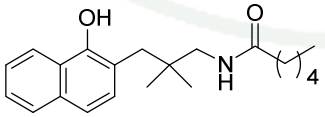
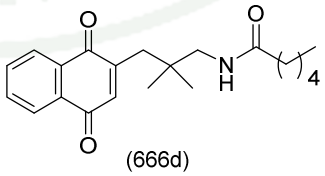
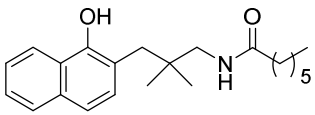
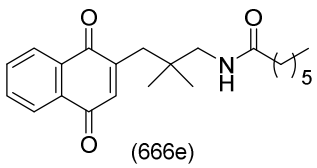
Entry	Reactant	Product	%Yield
1	 (665a)	 (666a)	82
2	 (665b)	 (666b)	87
3	 (665c)	 (666c)	85
4	 (665d)	 (666d)	83
5	 (665e)	 (666e)	60

Table 8 (Continued)

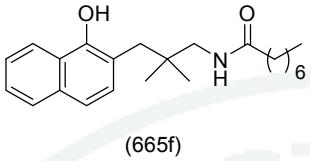
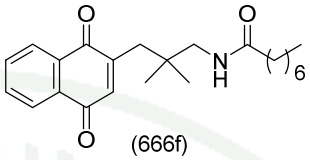
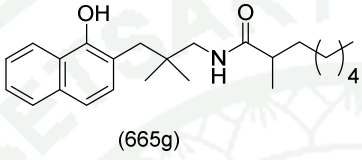
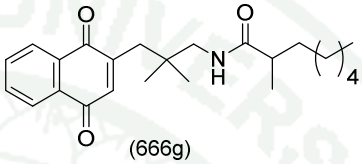
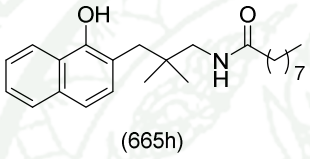
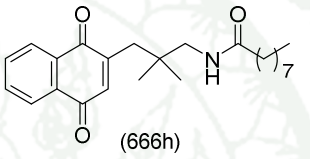
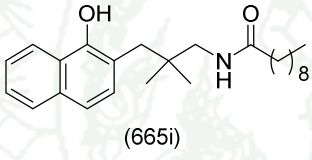
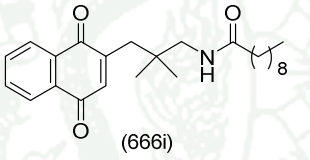
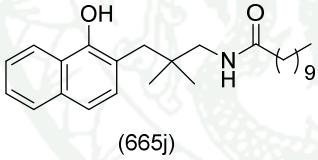
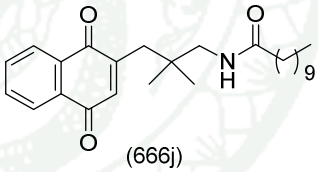
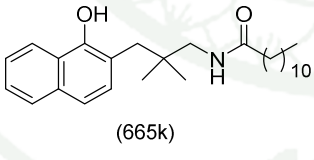
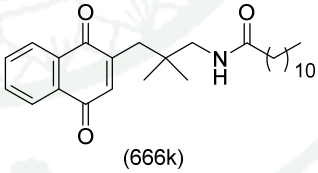
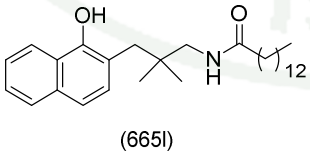
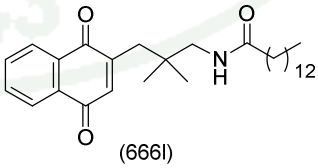
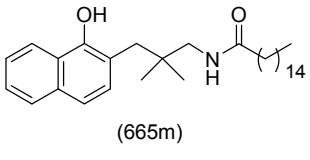
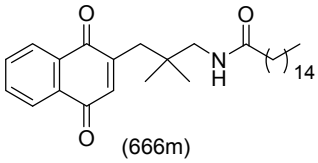
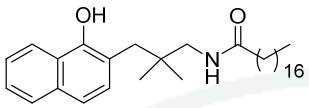
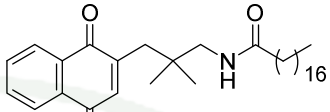
Entry	Reactant	Product	%Yield
6	 (665f)	 (666f)	91
7	 (665g)	 (666g)	94
8	 (665h)	 (666h)	92
9	 (665i)	 (666i)	85
10	 (665j)	 (666j)	91
11	 (665k)	 (666k)	93
12	 (665l)	 (666l)	84
13	 (665m)	 (666m)	81

Table 8 (Continued)

Entry	Reactant	Product	%Yield
14	 (665n)	 (666n)	98

The target 2-hydroxy 1,4-naphthoquinone amides (667a-667n) were completed by hydroxylation of 1,4-naphthoquinone amides (666a-666n) using *tert*-butylhydroperoxide (TBHP), triton B in THF. The results are shown in Table 9

Table 9 Hydroxylation of naphthoquiones (666a-666n) using TBHP, tritonB in THF.

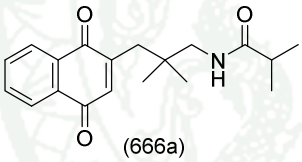
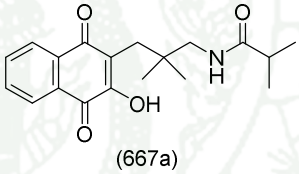
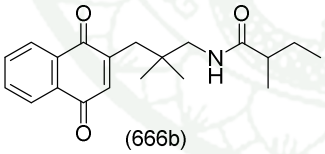
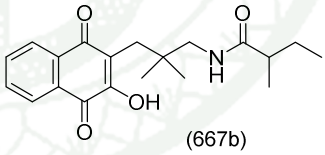
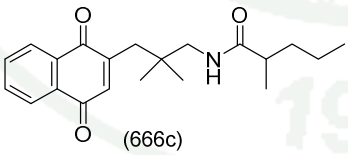
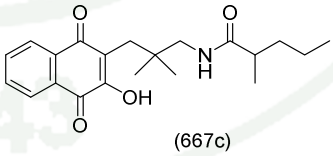
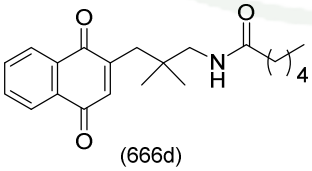
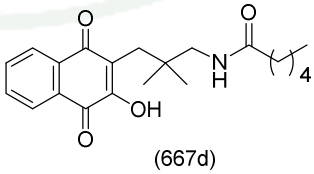
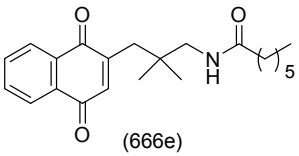
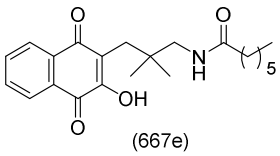
Entry	Reactant	Product	%Yield
1	 (666a)	 (667a)	33
2	 (666b)	 (667b)	31
3	 (666c)	 (667c)	45
4	 (666d)	 (667d)	52
5	 (666e)	 (667e)	43

Table 9 (Continued)

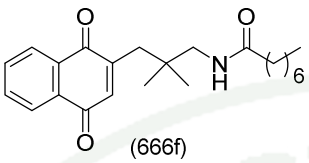
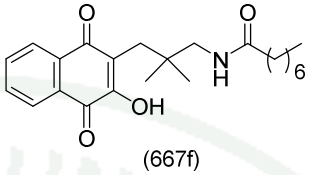
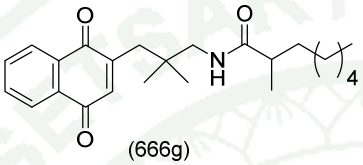
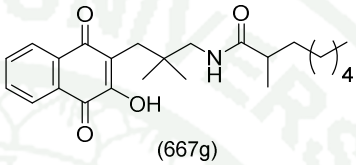
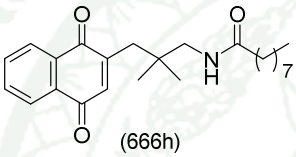
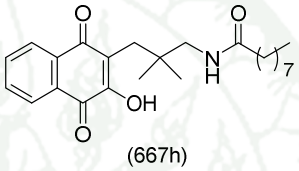
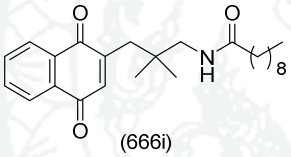
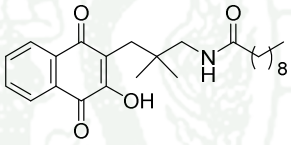
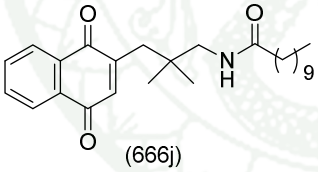
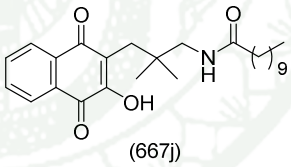
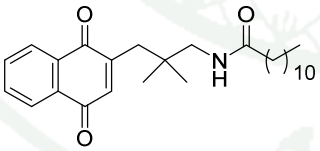
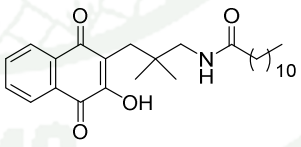
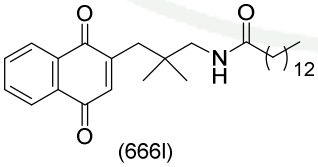
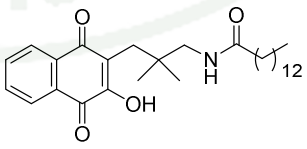
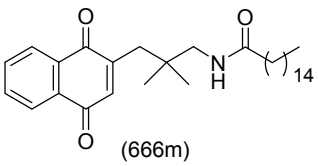
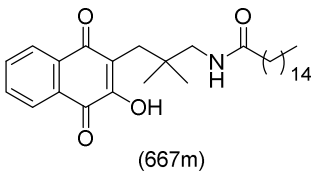
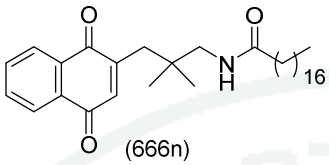
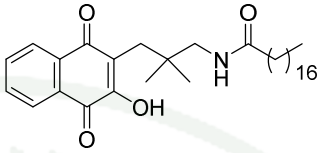
Entry	Reactant	Product	%Yield
6	 (666f)	 (667f)	40
7	 (666g)	 (667g)	44
8	 (666h)	 (667h)	49
9	 (666i)	 (667i)	35
10	 (666j)	 (667j)	30
11	 (666k)	 (667k)	29
12	 (666l)	 (667l)	27
13	 (666m)	 (667m)	61

Table 9 (Continued)

Entry	Reactant	Product	%Yield
14	 (666n)	 (667n)	59

2.2 Biological Activities evaluation of the synthetic naphthoquinone amides

Fourteen naphthoquinone aliphatic amides (667a-667n) were submitted to bioassay laboratory of BIOTEC for evaluation of anticancer activity against human cancer cell lines, KB (Oral cavity cancer), NCI-H187 (Small cell lung cancer), MCF7 (breast cancer) using REsazurin Microplate assay (REMA), antimalarial activity against *Plasmodium falciparum* K1 strain using Microculture Radioisotope Technique and cytotoxicity to normal Vero cell (African green monkey kidney) using Green Fluorescent Protein (GFP)-based assay. The results are summarized in Table 10 and Table 11.

Table 10 Cytotoxicities of naphthoquinone aliphatic amides (667a-667n) against human carcinoma cell lines (KB, MCF7 and NCI-H187) and Vero cell lines.

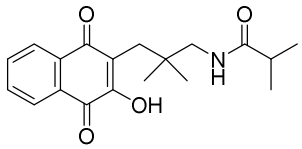
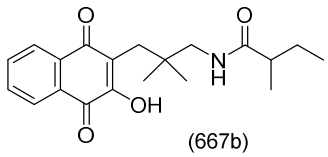
Compound	Cancer cell lines IC_{50} (µM)[a]			Vero cell IC_{50} (µM)
	KB-cell	MCF7 cell	NCI-H187-cell	
 (667a)	94.63	80.33	89.62	Non-cytotoxic
 (667b)	101.86	31.04	89.36	Non-cytotoxic

Table 10 (Continued)

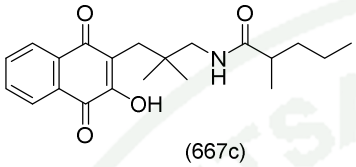
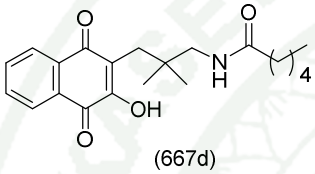
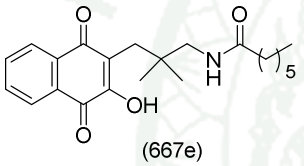
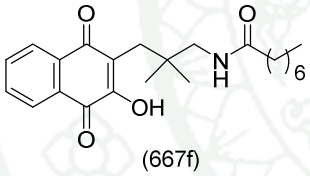
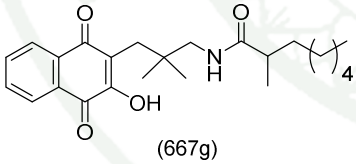
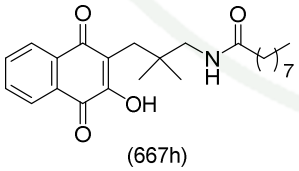
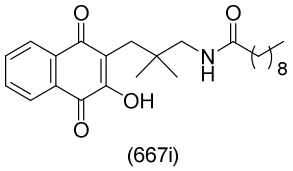
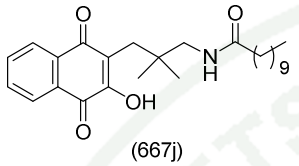
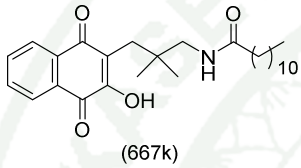
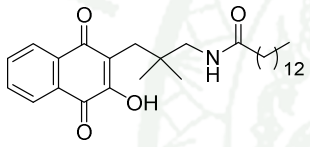
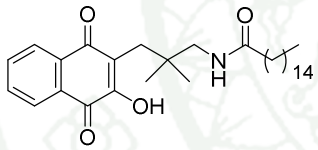
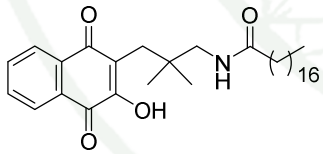
Compound	Cancer cell lines IC_{50} (µM)[a]			Vero cell IC_{50} (µM)
	KB-cell	MCF7 cell	NCI-H187-cell	
 (667c)	47.08	36.37	51.31	48.09
 (667d)	40.23	x	31.42	46.58
 (667e)	28.21	x	18.95	24.82
 (667f)	24.64	x	19.95	18.42
 (667g)	23.73	x	17.42	15.54
 (667h)	19.65	34.49	14.64	16.67
 (667i)	18.50	13.35	13.83	15.04

Table 10 (Continued)

Compound	Cancer cell lines IC_{50} (µM)[a]			Vero cell IC_{50} (µM)
	KB-cell	MCF7 cell	NCI-H187-cell	
 (667j)	17.63	41.91	7.32	14.92
 (667k)	12.82	46.83	8.22	13.86
 (667l)	25.10	inactive	17.35	9.81
 (667m)	5.12	37.55	13.82	5.60
 (667n)	6.35[b]	13.56[b]	4.83[b]	5.76[b]
Ellipticine (45)[c]	2.85	-	2.176	4.18
Doxorubicin (47)[c]	0.966	15.51	0.125	-

[a] Data are typical values from six replicate experiments.

[b] Partially soluble in 100% DMSO.

[c] Used as references.

Table 11 *In vitro* antimalarial activity of naphthoquinone aliphatic amides (667a-667n) against *Plasmodium falciparum*, K1 strain.

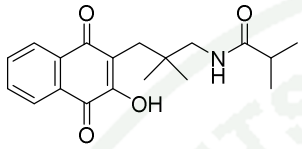
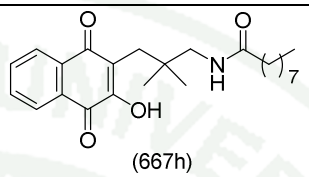
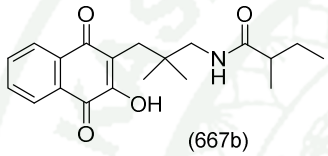
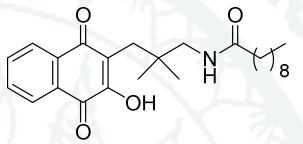
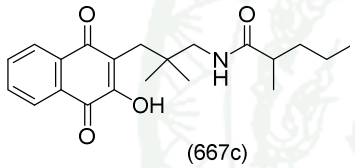
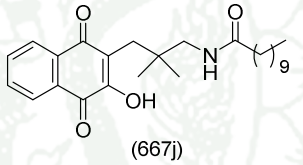
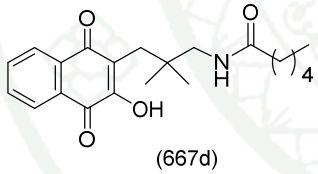
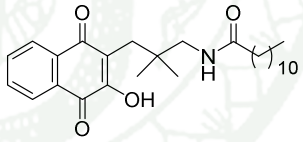
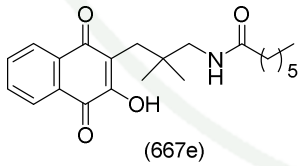
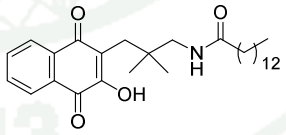
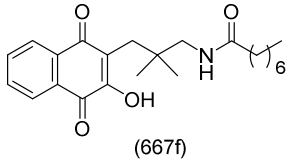
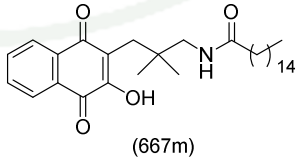
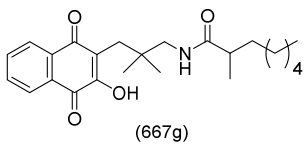
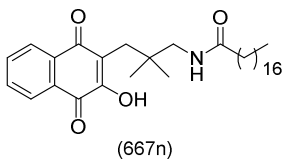
Compound	Antimalarial IC_{50} (µM)[a]	Compound	Antimalarial IC_{50} (µM)[a]
 (667a)	inactive	 (667h)	inactive
 (667b)	inactive	 (667i)	inactive
 (667c)	inactive	 (667j)	12.46
 (667d)	inactive	 (667k)	10.62
 (667e)	inactive	 (667l)	1.02
 (667f)	inactive	 (667m)	2.81
 (667g)	inactive	 (667n)	0.76[b]

Table 11 (Continued)

Compound	Antimalarial IC_{50} (μM)[a]	Compound	Antimalarial IC_{50} (μM)[a]
Dihydroartemisinine (63)[c]	0.00225	Mefloquine (50)[c]	0.0300

[a] Data are typical values from six replicate experiments.

[b] Partially soluble in 100% DMSO.

[c] Used as references.

3. Synthesis of *N,O*-hetreocycles with their anticancer and antimalarial activities evaluation

3.1 Synthesis of spirooxindole pyrrolidines compounds

Spirooxindole pyrrolidines (677) were synthesized via 1,3-dipolar cycloaddition of azomethine ylides (676), generated in situ from 5-iodoisatin (674) and sarcosine (675), with various dipolarophiles (669-672) (Figure 23). The results of the cycloaddition reactions are summarized in Table 12.

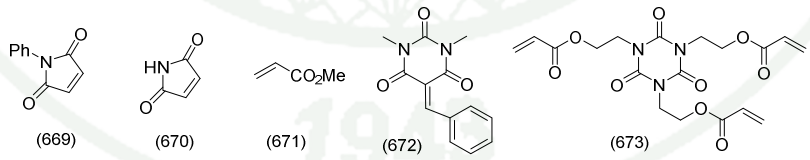
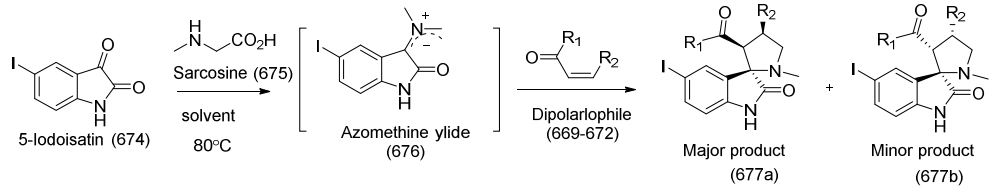


Figure 23 Our interested dipolarophils for 1,3-dipolar cycloaddition.



Scheme 123

Table 12 1,3-Dipolar cycloaddition reactions of azomethine ylide (686) with various dipolarlophiles[a].

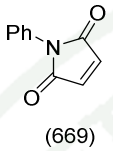
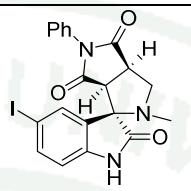
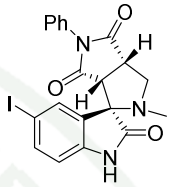
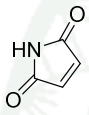
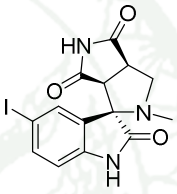
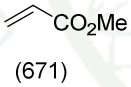
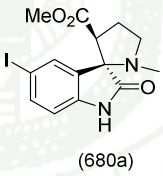
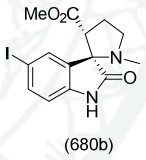
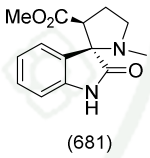
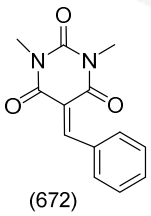
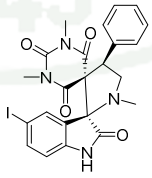
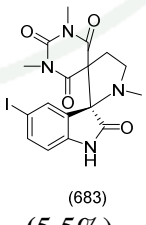
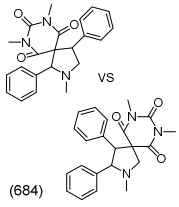
Entry	Dipolarophile	Solvent	Time (h)	Product		
1	 (669)	CH_3CN	20	 (678a) (50%)	 (678b) (25%)	
2	(669)	EtOH	3	(678a) (71%)	(678b) (27%)	
3	 (670)	CH_3CN	23	 (679) (75%)		
4	(670)	EtOH	2.5	(679) (88%)		
5	 (671)	CH_3CN	24	 (680a) (80.7%)	 (680b) (7%)	 (681) (3%)
6	(671)	EtOH	2.5h	(680a) (92%)	(680b) (1.6%)	(681)(4%)
7	 (672)	CH_3CN	8	 (682) (34%, dr=18:1)	 (683) (5.5%)	 (684)

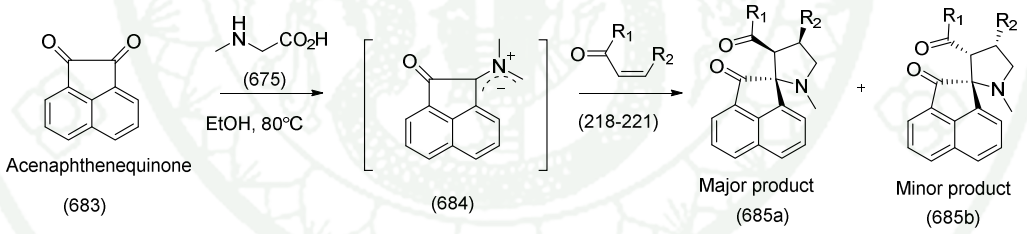
Table 12 (Continued)

Entry	Dipolarophile	Solvent	Time (h)	Product
8	(672)	toluene	24	No reaction
9	(672)	EtOH	2	(682) (73%,dr=22:1)

[a] Reaction was carried out at 80 ºC

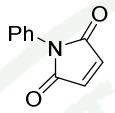
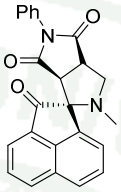
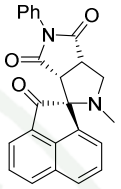
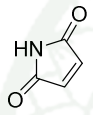
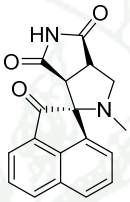
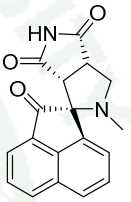
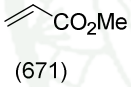
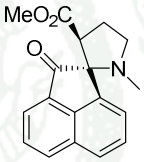
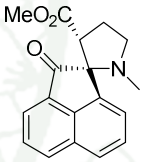
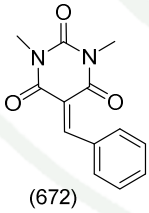
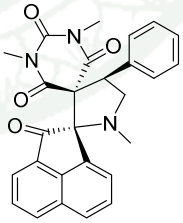
3.2. Synthesis of spiroacenaphthenonyl pyrrolidine compounds

Spiroacenaphthenonyl pyrrolidines (685) were constructed via 1,3-dipolar cycloaddition of azomethine ylide (684), generated in situ from acenaphthenone (683) and sarcosine (675), with various dipolarophiles (669-672). The results of the cycloaddition reactions are summarized in Table 13.



Scheme 124

Table 13 1,3-Dipolar cycloaddition reactions of azomethine ylide (684) with various dipolarlophiles[a].

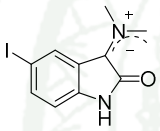
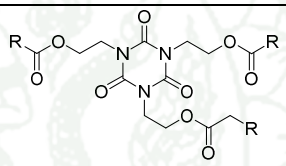
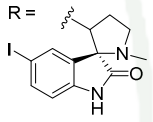
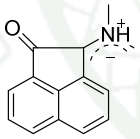
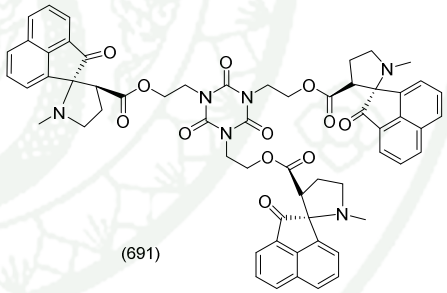
Entry	Dipolarophile	Solvent	Time (h)	Product
1	 (669)	EtOH	2.5	 (686a) 65%  (686b) 32%
2	 (670)	EtOH	2	 (687a) 75%  (687b) 10%
3	 (671)	EtOH	22	 (688a) (87%)  (688b) (8.6%)
4	 (672)	EtOH	1	 (689) (74%,dr= 22:1)

[a] Reaction was carried out at 80 ºC

3.3 Seven component 1,3-dipolar cycloaddition reaction of azomethine ylide with triple dipolarophile

Triple spiropyrrolidines (690) and (691) were constructed via 1,3-dipolar cycloaddition of azomethine ylide (676) and (684) with triple dipolarophile (673). The results of the cycloaddition reactions are summarized in Table 14.

Table 14 Seven component 1,3-dipolar cycloaddition of azomethine ylide with triple dipolarlophiles (673)[a].

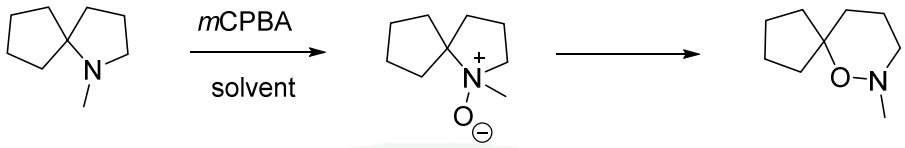
Entry	Azomethine ylide	Solvent	Time (h)	Product
1	 (676)	CH_3CN	48	 Mixture (690) 
2	 (684)	CH_3CN	22	 (691) 48%

[a] Reaction was carried out at 80 ºC

3.4 Meisenheimer rearrangement of the synthetic spiropyrrolidine.

N-O heterocyclic spirooxindole and *N-O* heterocycles spiroacenaphthenone were synthesized via 1,2-Meisenheimer rearrangement of spirooxindole pyrrolidines and spiroacenaphthenonyl pyrrolidine. The results of the 1,2-Meisenheimer rearrangement are shown in Table 15.

Table 15 Meisenheimer rearrangement of spiropyrrolidines.



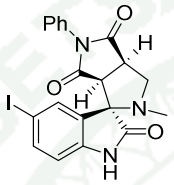
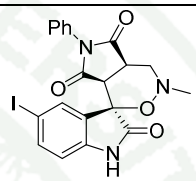
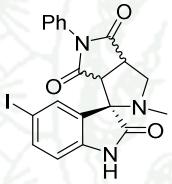
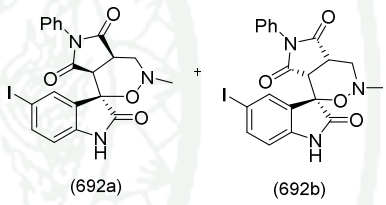
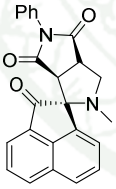
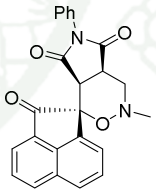
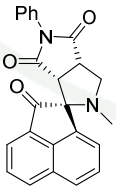
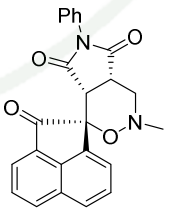
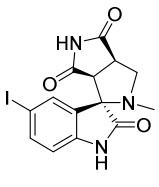
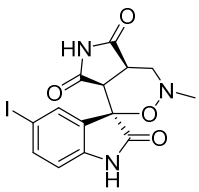
Entry	Starting material	Condition	Product
1	 (678a)	1) *m*CPBA, MeOH 0 ºC to rt 4h, 2) CH_3CN, reflux, 1 h	 (692a) 87%
2	 (687a)+(687b) (1:1)	1) *m*CPBA, MeOH 0 ºC to rt 4h, 2) CH_3CN, reflux, 1 h	 (692a) (692b) 91% (1:1)
3	 (686a)	1) *m*CPBA, CH_2Cl_2 0 ºC to rt 4h, 2) CH_3CN, reflux, 2 h	 (693a) 75%
4	 (686b)	1) *m*CPBA, CH_2Cl_2 0 ºC to rt 4h, 2) CH_3CN, reflux, 2 h	 (693b) 65%
5	 (679)	1) *m*CPBA, MeOH 0 ºC to rt 24 h, 2) DMSO, 60 ºC, 1 h	 (694) 62%

Table 15 (Continued)

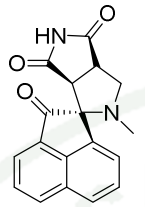
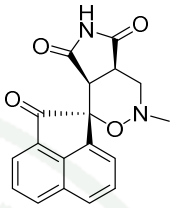
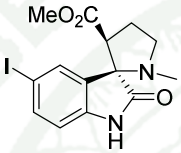
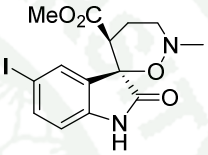
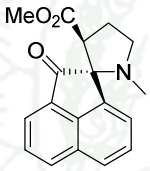
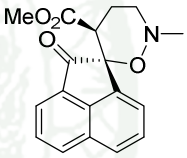
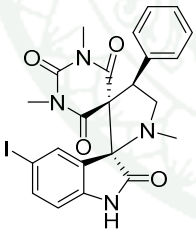
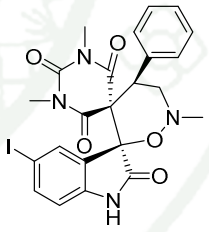
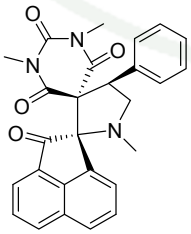
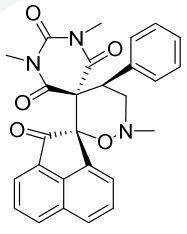
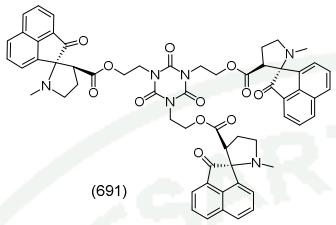
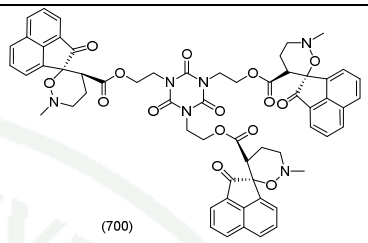
Entry	Starting material	Condition	Product
6	 (687a)	1) *m*CPBA, CH_2Cl_2 0 ºC to rt 1h, 2) CH_3CN, reflux, 1 h	 (695) 89%
7	 (680a)	*m*CPBA, CH_2Cl_2 0 ºC to rt, 3 h	 (696) 83%
8	 (688a)	*m*CPBA, CH_2Cl_2 0 ºC to rt, 6 h	 (697) 98%
9	 (682)	*m*CPBA(2 eq), $CHCl_3$, rt, min	 (698) 10% (20% brsm)
10	 (689) 74%(dr = 22:1)	*m*CPBA, CH_2Cl_2 0ºC to rt, 3h	 (699) 70% (dr = 1:11)

Table 15 (Continued)

Entry	Starting material	Condition	Product
11	 (691)	*m*CPBA, CH_2Cl_2 0 ºC to rt, 26 h	 (700) 98%

3.5 Biological activity of the synthetic *N-O* heterocyclic spiro compounds

N-O heterocyclic spiro compounds (692-700) were submitted to bioassay lolaboratory of BIOTEC, Thailand for evaluation of anticancer against human cancer cell line, KB (Oral cavity cancer) using REsazurin Microplate assay (REMA), anti malarial activities against *Plasmodium falciparum* K1 strain using Microculture Radioisotope Technique and cytotoxicity to normal Vero cell (African green monkey kidney) using Green Fluorescent Protein (GFP)-based assay. The results are summarized in Table 16

Table 16 Antimalarial Activity, Cytotoxicity against KB-cell lines and Vero cells of *N-O* heterocyclic spiro compounds (692-700).

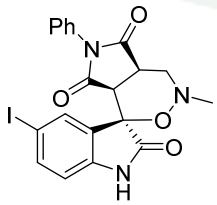
Entry	Compound	Antimalarial (µM)[a]	Anticancer (µM)[a]	Vero cell (µM)[a]
1	 (692a)	Inactive	39.96	Non-cytotoxic

Table 16 (Continued)

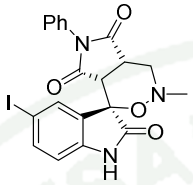
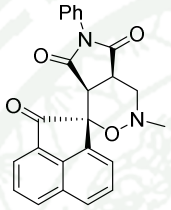
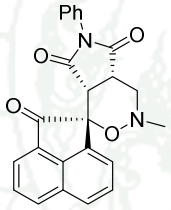
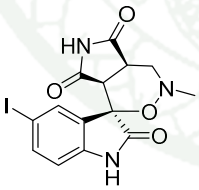
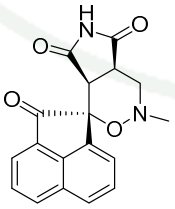
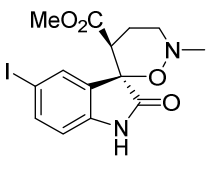
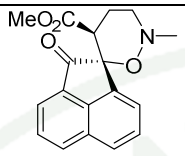
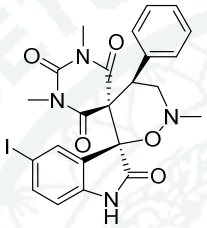
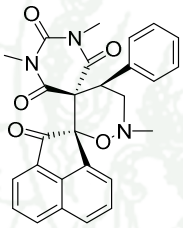
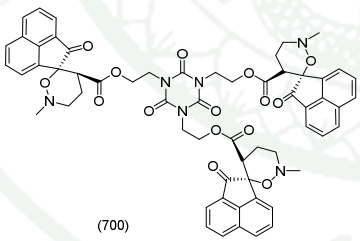
Entry	Compound	Antimalarial (μM)[a]	Anticancer (μM)[a]	Vero cell (μM)[a]
2	 (692b)	Inactive	Inactive	Non-cytotoxic
3	 (693a)	Inactive	120.78	Non-cytotoxic
4	 (693b)	Inactive	118.44	Non-cytotoxic
5	 (694)	Inactive	Inactive	Non-cytotoxic
6	 (695)	Inactive	64.13	Non-cytotoxic
7	 (696)	Inactive	Inactive	Non-cytotoxic

Table 16 (Continued)

Entry	Compound	Antimalarial (μM)[a]	Anticancer (μM)[a]	Vero cell (μM)[a]
8	 (697)	Inactive	35.91	Non-cytotoxic
9	 (698)	Inactive	24.45	18.63 mg/mL
10	 (699)	Inactive	25.69	Non-cytotoxic
11	 (700)	1.04	inactive	Non-cytotoxic
12	Dihydroartemisinine (63)[b]	0.00116	-	-
13	Ellipticine (45)[b]	-	1.76	4.59
14	Doxorubicin (47)[b]	-	0.55	-

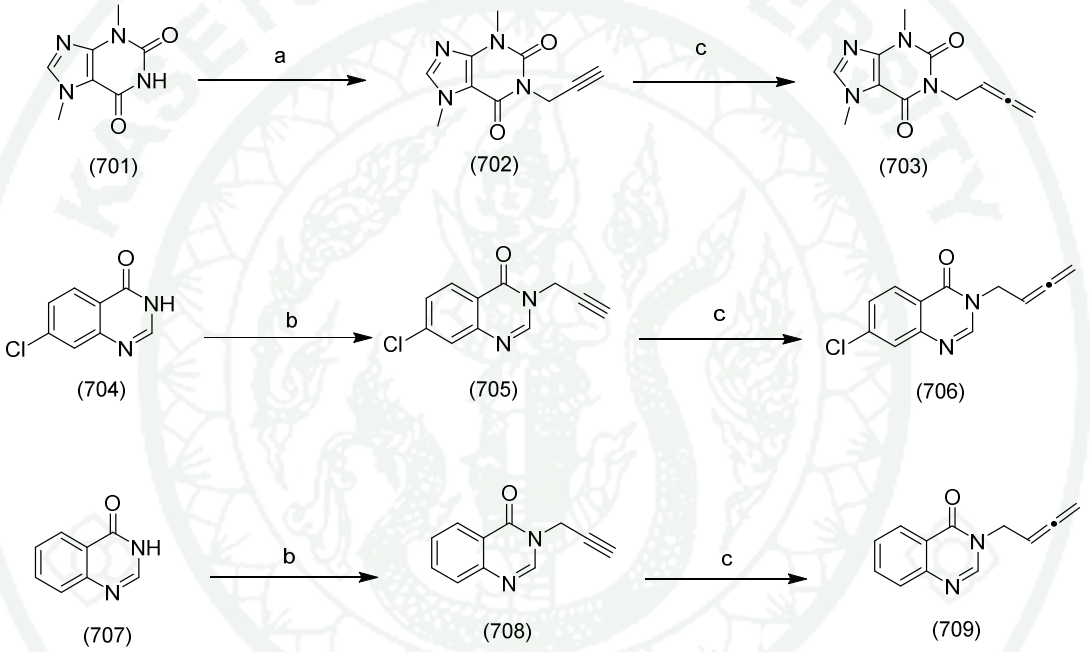
[a] Data are typical values from six replicate experiments.

[b] Used as references

4. Palladium catalysed cascade reaction of allene

4.1 Synthesis of allenes

The allene starting materials in our cascade reaction were synthesized via a two step process from theobromine (701), chloro4-quinazolinone (704) and 4-quinazolinone (707) as shown in Scheme 125.



Scheme 125

Reagents and conditions:

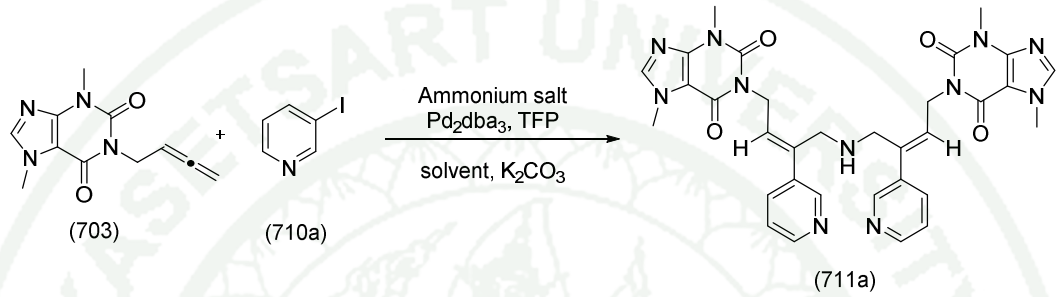
a) Propargyl bromide, TBAF, THF, rt, 16 h, 87%

b) Propargyl bromide, K_2CO_3, acetone, rt, 20 h, 88% for (705), 82% for (708)

c) Paraformaldehyde, CuI, Cy_2NH, 1,4-dioxane, reflux, 3 h, 78% for (703), 82% for (706), 68% for (709)

4.2 Five-component palladium-catalysed cascade reaction of allene

The results of investigation optimization conditions for palladium catalyzed cascade synthesis of complex bis-allylamines (711) from purine allene (703) are shown in Table 17.



Scheme 126

Table 17 Optimization of reaction conditions for palladium catalyzed cascade synthesis of complex bis-allylamines[a].

Entry	Ammonium Salt (equiv)	Solvent	K_2CO_3 (equiv.)	Time (h)	Yield (%)
1	Carbonate (6)	DMF/H_2O (2:1)	-	3	55
2	Carbonate (6)	Toluene	-	24	no reaction
3	Carbonate (6)	Dioxane	-	24	trace
4	Carbonate (6)	Dioxane/DMF(5:1)	2	24	63
5	Carbonate (6)	Dioxane/DMF(5:1)	-	24	57
6	NH_4OH	DMF	-	3	55
7	Tartrate (6)	DMF	-	18	*E/Z*mixture

Table 17 (Continued)

Entry	Ammonium Salt (equiv)	Solvent	K_2CO_3 (equiv.)	Time (h)	Yield (%)
8	Tartrate (6)	DMF/H_2O(2:1)	-	3	*E*/*Z*mixture
9	Tartrate (6)	Dioxane	-	20	trace
10	Tartrate (6)	Dioxane	2	24	b
11	Tartrate (3)	Dioxane/DMF(5:1)	-	22	trace
12	Tartrate (6)	Dioxane/DMF(5:1)	2	22	80
13	Tartrate (3)	Dioxane/DMF(5:1)	2	22	77
14	Tartrate (3)	Dioxane/water(5:1)	2	40	75
15	Citrate (6)	Dioxane/DMF(5:1)	2	23	77

[a] allene (1 mmol), aryl iodide (1.2 mmol), Pd_2dba_3 (2.5 mol%), TFP (10 mol%), 100 °C (for tartrate and citrate), 80 °C (for carbonate),

[b] Reaction incomplete at 24 h.

The reaction condition in entries 12 and 13 were selected to make more examples of bis-allylamines with various allenes (Scheme 108) and various aryl iodides (Figure 24) using dibasic ammonium tartrate as the ammonia source.

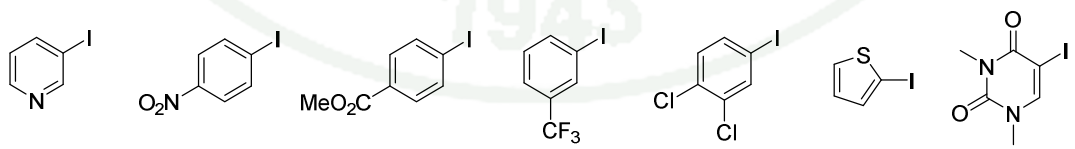
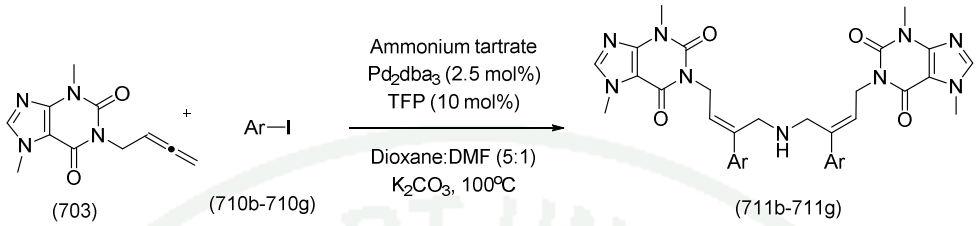


Figure 24 Our interested aryl iodides.

In case of theobromine allene (703), (*Z,Z*)-bis-allylamines (711a-711f) were produced in good to excellent yield (63-82%) (Table 18).



Scheme 127

Table 18 Catalytic casecade synthesis of complex bis-allylamine (711b-711g).

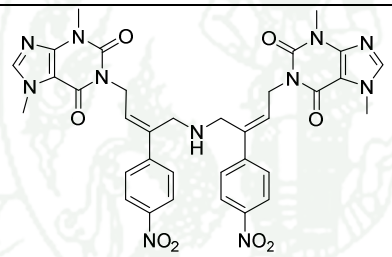
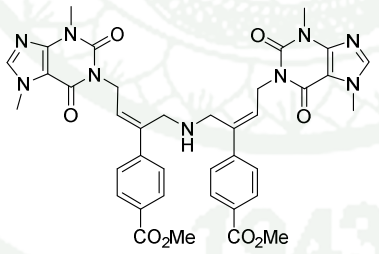
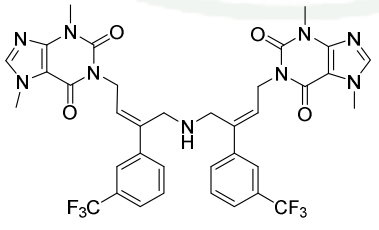
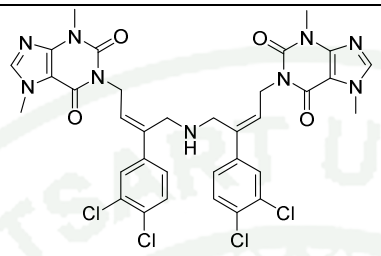
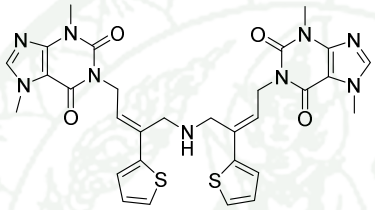
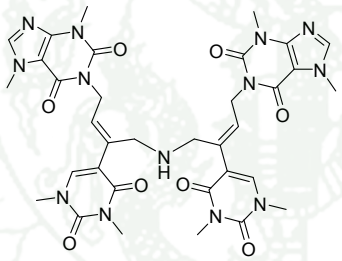
Entry	Product	Time (h)	Yield (%)
1	 (711b)	6	82
2	 (711c)	18	80
3	 (711d)	23	63

Table 18 (Continued)

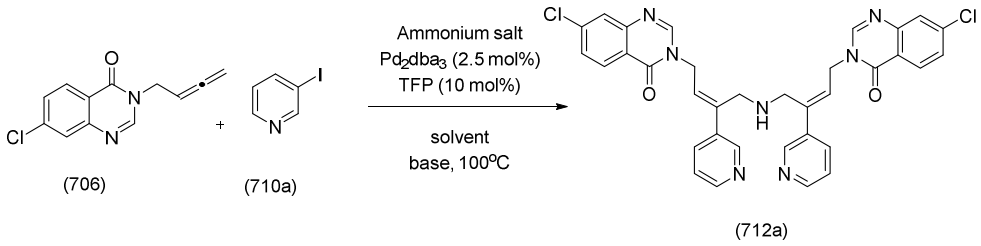
Entry	Product	Time (h)	Yield (%)
4	 (711e)	12	81
5	 (711f)	23[b]	66 79%(borsm)[b]
6	 (711g)	4	90[c] as a mixture of *E/Z* isomer

[a] allene (1 mmol), aryl iodide (1.2 mmol), Pd_2dba_3 (2.5 mol%), TFP (10 mol%), ammonium tartrate (6 mmol), dioxane:DMF (5:1)(24 mL)100 °C

[b] based on recovered starting material;

[c] 3 equiv. ammonium tartrate was used.

Optimization of reaction conditions for palladium catalyzed cascade synthesis of complex bis-allylamines using and chloro-substituted quinazolinone allenes (706) are shown in (Table 19).



Scheme 128

Table 19 Optimization of reaction conditions for palladium catalyzed cascade synthesis of complex bis-allylamines[a].

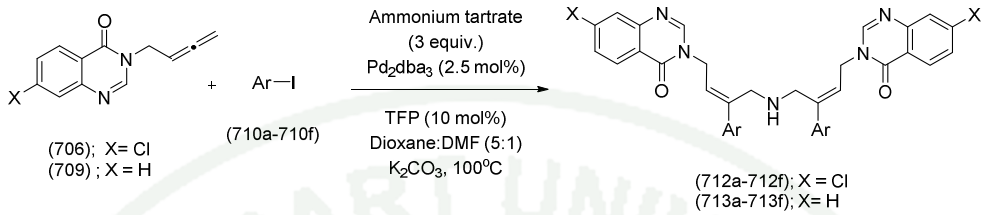
Entry	Solvent	Ammonium salt	Base (equiv.)	Time (h)	Yield (%)	Ratio[b] *(ZZ/EZ)*
1	Dioxane/DMF(5:)	Tartrate (3)	K_2CO_3 (2)	8	69%	3:1
2	Dioxane	Tartrate (3)	Ag_2CO_3(2)	19	Complex mixture	-
3	Dioxane/DMF(5:1)	Tartrate (3)	Cs_2CO_3(2)	24	18%	3.8:1
4	Dioxane/DMF(5:1)	Tartrate (3)	K_2CO_3(2)	2.5	-	5:1
5	Dioxane/DMF(5:1)	Tartrate (3)	K_2CO_3(2)	5	-	5:1
7	Dioxane/water(2:1)	Carbonate (6)	-	19	-	3.2:1
8	DMF/Water (2:1)	Carbonate (6)	-	5	43%	3:1

[a] allene (1 mmol), aryl iodide (1.2 mmol), Pd_2dba_3 (2.5 mol%), TFP (10 mol%), dioxane:DMF (5:1)(24 mL)100 °C

[b] The ratio was obtained from ^{1}H-NMR integration

Even though the reaction of the chloro-quinazolone allene (706) gave a mixture of *E/Z* isomer, it was possible to isolate pure (*Z,Z*) bis-allylamine (712a) in more than 50% yield by precipitation of the *E/Z* mixture in methanol. The pure *Z,Z*-isomer precipitated from the solution. More examples of bis-allylamine from

quinazolone allene (706) and (709) are shown in Table 20. The yields of *Z,Z*- isomer range from 40-67%.



Scheme 129

Table 20 Catalytic cascade synthesis of complex bis-allylamine (712) and (713).

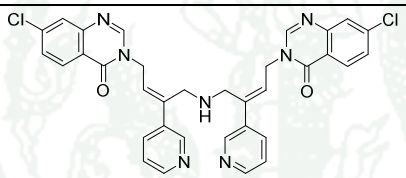
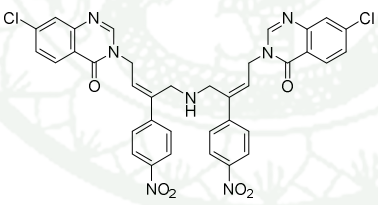
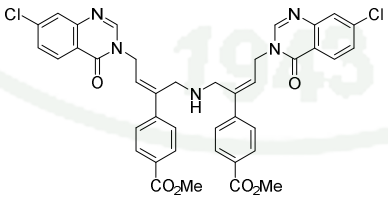
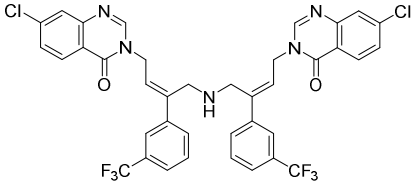
Entry	Product	Time (h)	Yield (%)
1	 (712a)	8	52
2	 (712b)	3	58
3	 (712c)	7	60
4	 (712d)	7	40

Table 20 (Continued)

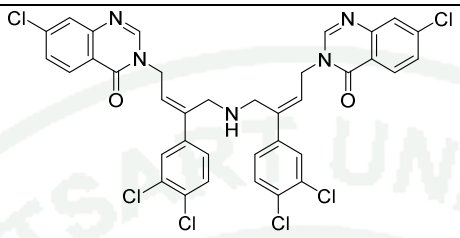
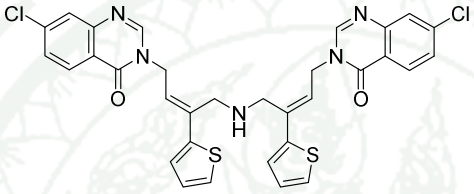
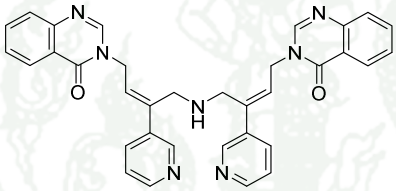
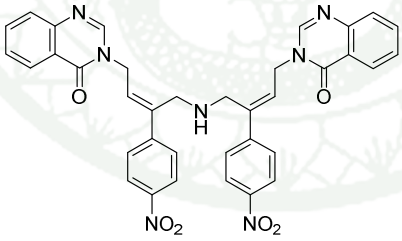
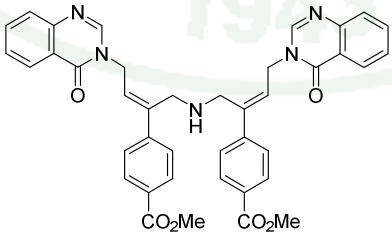
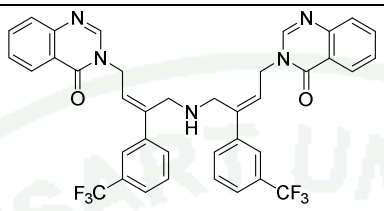
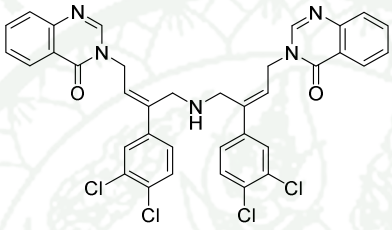
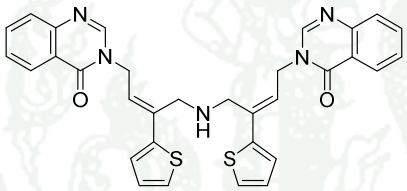
Entry	Product	Time (h)	Yield (%)
5	 (712e)	5	67
6	 (712f)	10	48
7	 (713a)	4.5	56
8	 (713b)	3	57
9	 (713c)	6	57

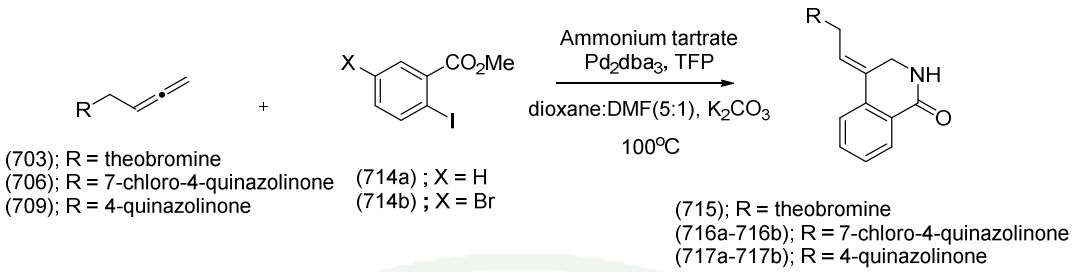
Table 20 (Continued)

Entry	Product	Time (h)	Yield (%)
10	 (713d)	5	65
11	 (713e)	3.5	65
12	 (713f)	6	65

[a] allene (1 mmol), aryl iodide (1.2 mmol), Pd_2dba_3 (2.5 mol%), TFP (10 mol%), ammonium tartrate (6 mmol), K_2CO_3 (2 mmol), (5:1) dioxane:DMF (24 mL)100 °C

4.3 Palladium catalyzed cascade synthesis of complex 3,4-dihydroiso-quinolinone

Our standard condition for selective synthesis of bis-*Z,Z*- allylamines (Table 17, entries 11 and 12) could also be applied for synthesis of 3,4-dihydroisoquinolinone (715-717) (Table 21).



Scheme 130

Table 21 Palladium catalyzed cascade synthesis of complex 3,4-dihydroisoquinolinone[a].

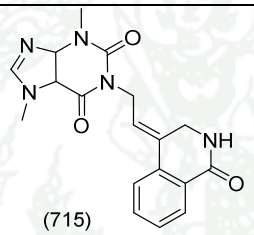
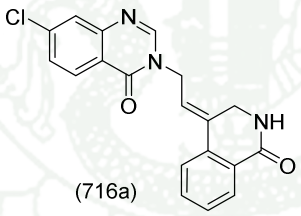
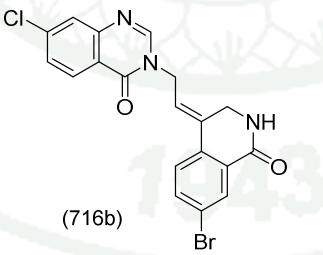
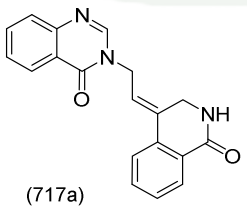
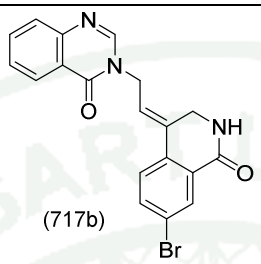
Entry	Product	Time (h)	Yield (%)
1	 (715)	31	71[b]
2		31	67
3	 (716a)	28	65
4	 (716b)	18	61
5	 (717a)	22	63

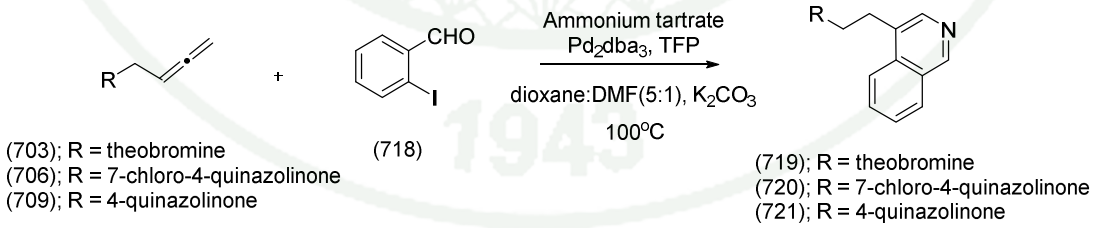
Table 21 (Continued)

Entry	Product	Time (h)	Yield (%)
6	 (717b)	16	64

[a] allene (1 mmol), aryl iodide (1.2 mmol), Pd_2dba_3 (2.5 mol%), TFP (10 mol%), ammonium tartrate (6 mmol), K_2CO_3 (2mmol), dioxane:DMF (5:1)(24 mL)100 °C; [b] aryl iodide (2 mmol)

4.4 Palladium catalyzed cascade synthesis of complex isoquinoline

We were able to generate isoquinolines (719-720) by using our standard condition in 40-68% yield depending on the allene starting material. In the case of quinazolinone allenes (706) and (709), the isoquinoline products (720-721) were obtained in 40-43% yield. Theobromine allene (703) gave a superior result (63-68%).



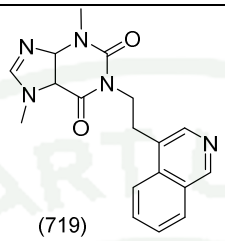
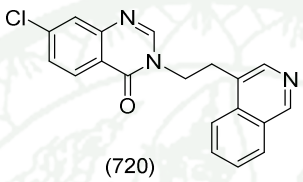
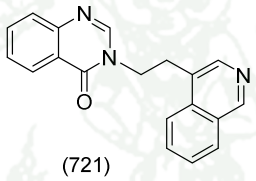
(703); R = theobromine
(706); R = 7-chloro-4-quinazolinone
(709); R = 4-quinazolinone

(718)

(719); R = theobromine
(720); R = 7-chloro-4-quinazolinone
(721); R = 4-quinazolinone

Scheme 131

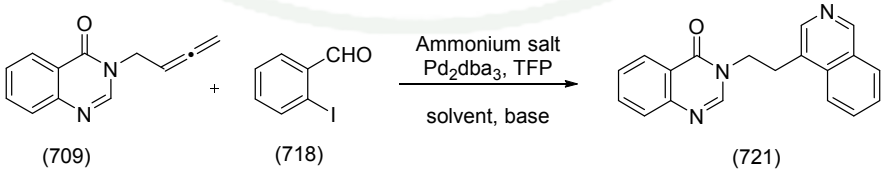
Table 22 Palladium catalyzed cascade synthesis of complex isoquinolines[a].

Entry	Products	Time (h)	Yield(%)
1	 (719)	23	68[b]
2		23	63
3	 (720)	24	43
4	 (721)	26	40

[a] allene (1 mmol), 2-iodobenzaldehyde (1.2 mmol), Pd_2dba_3 (2.5 mol%), TFP (10 mol%), ammonium tartrate (6 mmol), K_2CO_3 (2 mmol), dioxane:DMF (5:1)(24 mL)100 °C

[b] 2-iodobenzaldehyde (2 mmol).

Attempts to improve the quinalolinone-isoquinoline yield are shown in Table 23.



(709) (718) (721)

Scheme 132

Table 23 Optimization of reaction conditions for palladium catalyzed cascade synthesis of isoquinoline[a].

Entry	Ammonium Salt (equiv)	Base (equiv)	Solvent	Time (h)	Yield (%)
1	Tartrate (6)	K_2CO_3(2)	Dioxane:DMF(5:1)	26	40
2	Tartrate (10)	K_2CO_3(2)	Dioxane:DMF (5:1)	21	40
3	Tartrate (10)	K_2CO_3(2)	Dioxane:DMF(5:1)[e]	20	52
4	Tartrate (10)	K_2CO_3(2)	Dioxane:EtOH:H_2O(2:1:1)[e]	22	60
5	Tartrate (6)	K_2CO_3(2)	Dioxane:EtOH:H_2O(2:1:1)[e]	24	58
6	Citrate (6)	K_2CO_3(2)	Dioxane:EtOH:H_2O(2:1:1)[e]	19	61
7	Citrate (6)	-	Dioxane:EtOH:H_2O(2:1:1)[e]	9	45
8	Citrate (6)+ Ascorbic(0.5)	K_2CO_3(2)	Dioxane:EtOH:H_2O(2:1:1)[e]	9	45
9	Citrate (6)	K_2CO_3(2)	EtOH:H_2O(2:1)[e]	9	60
12	Tartrate (6)	K_2CO_3(2)	Dioxane:H_2O(5:1)[e]	23	Complex mixture
10	Citrate (6)	-	EtOH	12	47
11	Citrate (6)	K_2CO_3(2)	EtOH	12	Complex mixture
13	Carbonate(6)	K_2CO_3(2)	EtOH:H_2O(2:1)[e]	15	Complex mixture
14	Acetate (6)	K_2CO_3(2)	EtOH:H_2O(2:1)[e]	15	29
15	Citrate (6)	K_2CO_3(2)	EtOH:H_2O(2:1)[e]	9	62[b]
16	Citrate (6)	K_2CO_3(2)	EtOH:H_2O(2:1)[e]	9	67[c]
17	Citrate (6)	-	EtOH:H_2O(2:1)[e]	5	63[c]
18	Citrate (6)	K_2CO_3(2)	EtOH:H_2O(2:1)[e]	3	64[c,d]

[a] allene (0.25 mmol), 2-iodobenzaldehyde (0.3 mmol), Pd_2dba_3 (2.5 mol%), TFP (10 mol%), 100 °C; [b] Allene 1.2 eq, aryl iodide 1 eq. ; [c] Allene 1.5 eq, aryl iodide 1 eq. [d] 5 mol% Pd_2dba_3; [e] Reaction was performed in sealed tube.

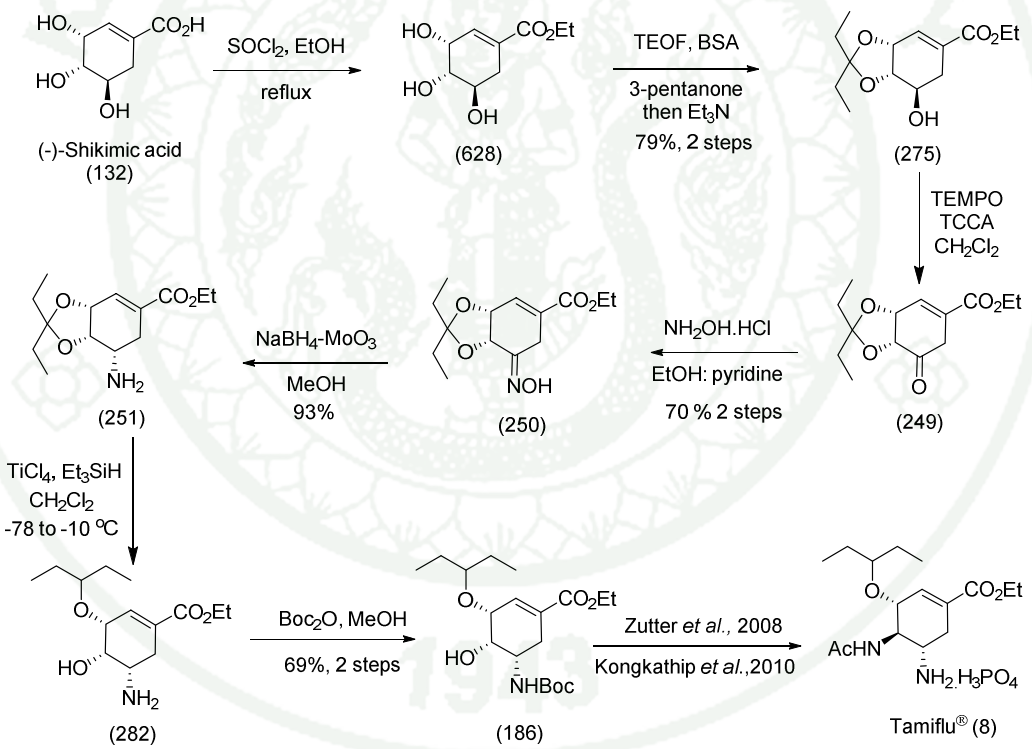
Discussion

1. Synthesis of Tamiflu®

Herein we reported the synthesis of Tamiflu® (8) from (–)-shikimic acid (132) and inexpensive D-glucose (18) as shown below.

1.1 Synthesis of Tamiflu® (8) from (–)-shikimic acid (132)

In this section we reported the synthesis of Tamiflu® intermediate (186) and attempted to convert into Tamiflu® via azide free strategy.

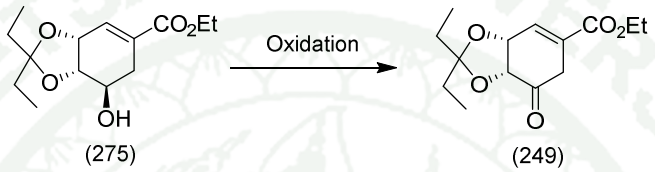


Scheme 133

Boc protected amino alcohol (186) was synthesized in seven steps from (–) -shikimic acid (132). Reaction of (–)-shikimic acid (132) with thionyl chloride in EtOH gave ethyl shikimate (628) which was protected as pentylidine ketal (275) by using 3-pentanone in the presence of triethyl orthoformate (TEOF) and benzene

sulfonic acid (BSA). Oxidation of alcohol (275) to the ketone (249) was challenging; various oxidation conditions with alcohol (275) were failed (Table 24). Only combination of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and trichloroisocyanuric acid (TCCA) in CH_2Cl_2 (entry 4) was a suitable condition for oxidizing the corresponding alcohol (275) to ketone (249).

Table 24 Investigation reaction condition for oxidation of alcohol (275).



(275) (249)

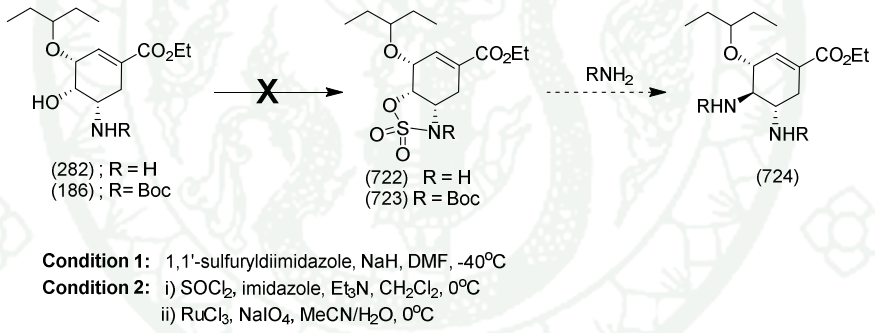
Entry	Oxidation Condition	Result
1	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC	Complex mixture
2	PDC, CH_2Cl_2, rt	No reaction
3	PDC, 3Å molecular sieve, CH_2Cl_2, rt	No reaction
4	TEMPO, TCCA, CH_2Cl_2, 0 ^oC to rt	73%
5	TEMPO, TCCA, NaI, 15%$NaHCO_3$, acetone, 0 ^oC to rt	No reaction
6	TEMPO, TCCA, NaI, CH_2Cl_2, 0 ^oC to rt	Reaction did not complete after 2h
7	TEMPO, Oxone, TBABr, CH_2Cl_2, rt	No reaction
8	TEMPO, Oxone, TBABr, toluene, rt	No reaction
9	TEMPO, 4%NaOCl, TBABr, KBr, sat.$NaHCO_3$, CH_2Cl_2, 0 ^oC	Complex mixture

The 5α-NH_2 group was introduced by reductive amination of ketone (249) which included oxime (250) formation using $NH_2OH.HCl$ in pyridine:EtOH and reduction of the oxime (250) with $NaBH_4$-MoO_3 to give amine (251) in excellent yield. Other reducing agents for oxime reduction were also tried; combination of $NaBH_4$ with $NiCl_2$ gave the complex mixture whereas using BH_3.THF resulted no reaction. The stereochemistry of amine (251) was confirmed by NOESY NMR experiment. Reductive ring opening of amino pentylidine ketal (251) using $TiCl_4$ in

the presence of Et_3SiH at –78 ºC to –10 ºC afforded the high polar and water soluble amino alcohol (282) which was a trouble in purification step. Thus, the amino hydroxyl (282) was protected as *N*-Boc before subjecting to silica gel column chromatography for purification to give Boc protected amino alcohol (186) in high yield.

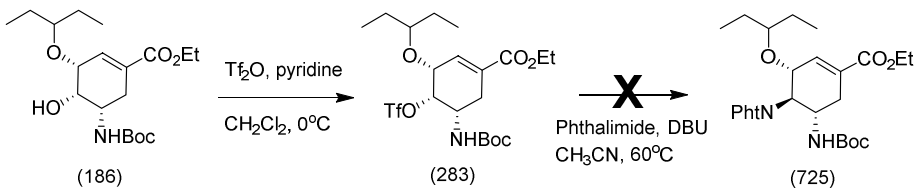
Our attempt to synthesize Tamiflu® (8) via azide free strategy is shown in Scheme 134 and 135.

The nucleophilic displacement of cyclic sulfamidate was our interested strategy for introduction of the second amino group into Tamiflu's molecule. However, preparation of the cyclic sulfamidate (722) and (723) from amino alcohol (282) and (186) under conditions showed in Scheme 134 were unsuccessful.



Scheme 134

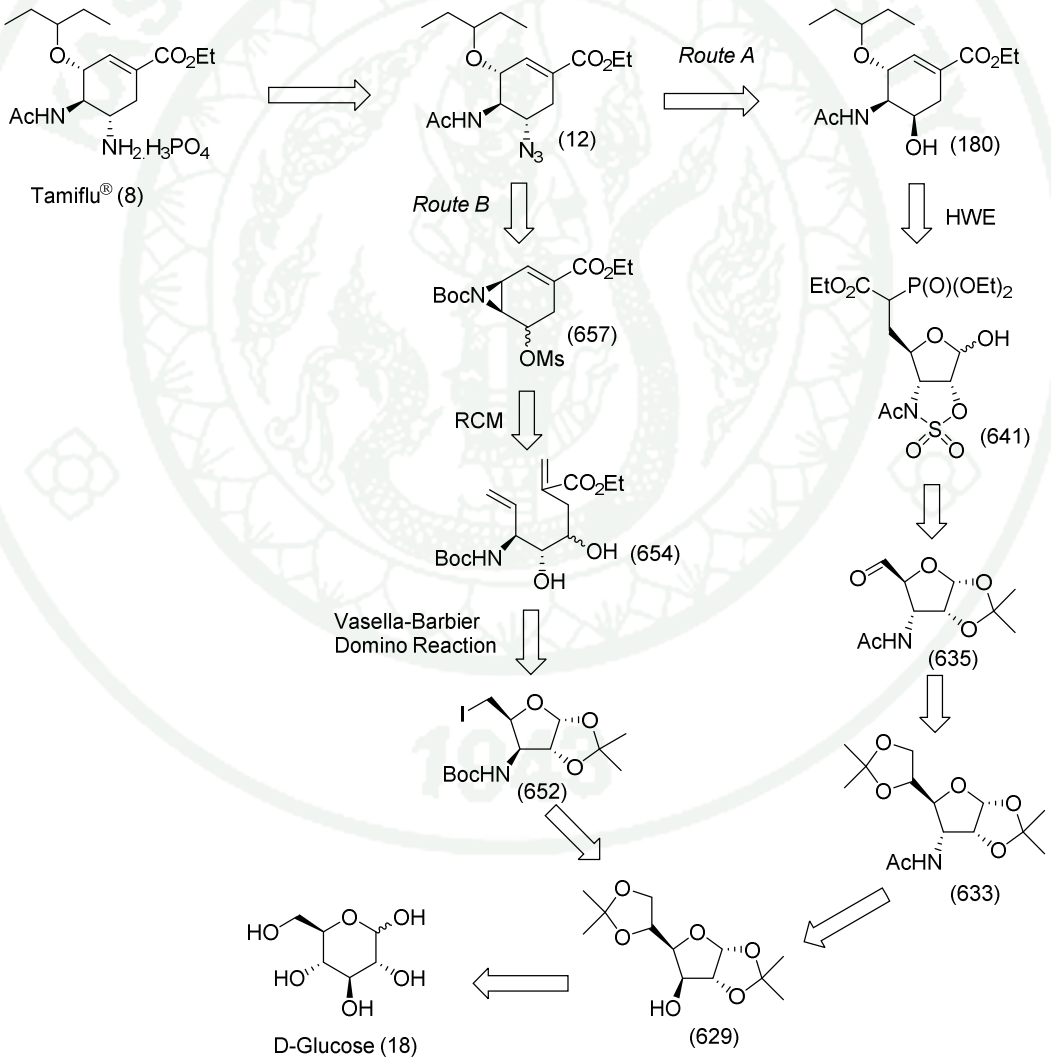
Nucleophilic displacement of the triflate (283) by phthalimide was also failed, no reaction was observed (Scheme 135).



Scheme 135

1.2 Synthesis of Tamiflu® (8) from D-glucose (18)

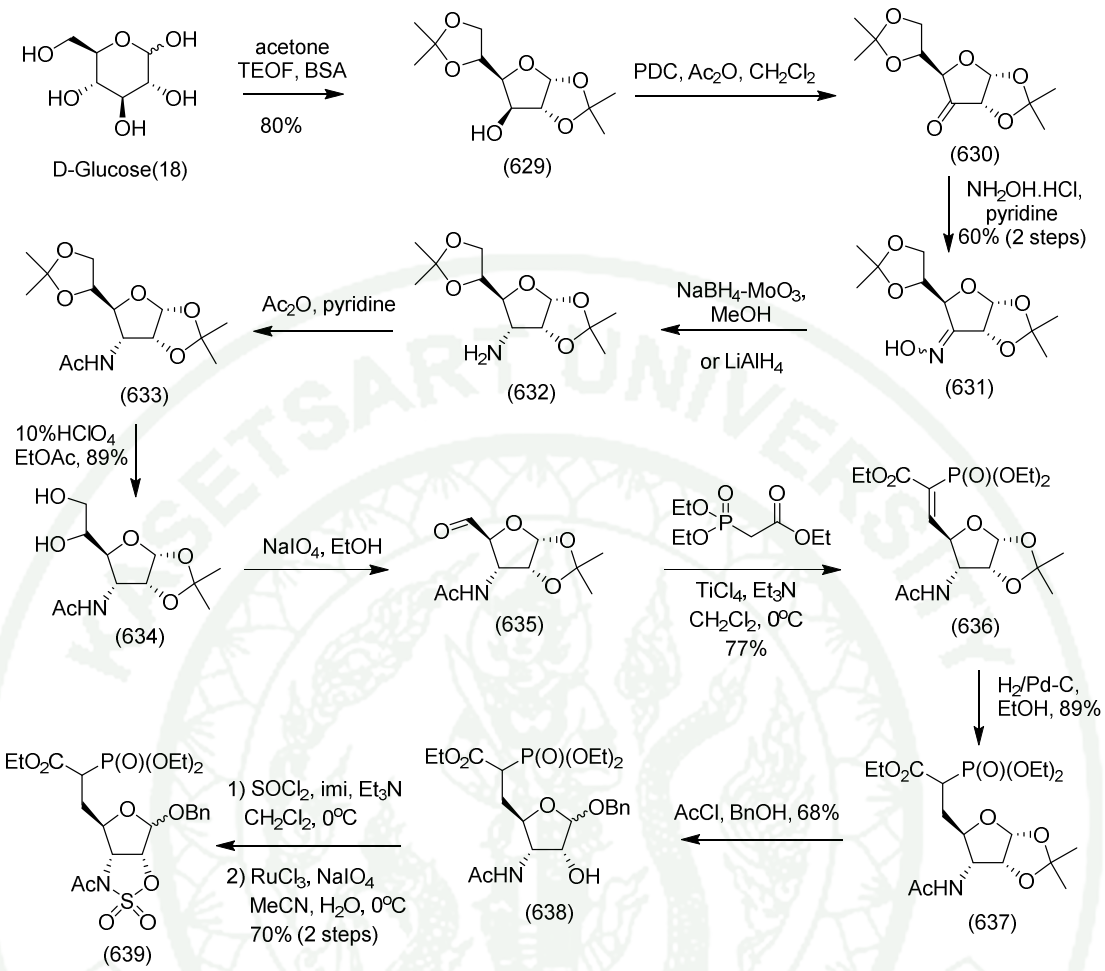
Herein we report the synthesis of Tamiflu® (8) from D-glucose (18) by two independence approaches; the first approach employed Horner-Wadsworth-Emmons (HWE) olefination to construct the cyclohexene carboxylate and installation of 3-pentyl ether through nucleophilic substitution of cyclic sulfamidate. The second approach employed ring closing metathesis (RCM) to construct the cyclohexene carboxylate and introduction of 3-pentyl ether through aziridine. Our retrosynthetic analysis was shown in Scheme 136



Scheme 136

1.2.1 Synthesis of Tamiflu® (8) from D-glucose (18) via HWE strategy

The synthesis was started from protection of D-glucose (18) as diacetal with acetone in the presence of triethyl orthoformate (TEOF) and benzene sulfonic acid (BSA) to give 1,2:5,6-diisopropylidene glucose (629) in 80% yield (a gram scale). Installation of the α-acetamido group was achieved in four-step sequence involving oxidation of secondary alcohol (629) to ketone (630), formation of oxime (631), reduction of (631) to amine (632) and then acetylation to give acetamide (633) in good yield. Selective hydrolysis of 5,6 isopropylidene acetal (633) using 10% perchloric acid or 75% acetic acid generated the diol product (634), which underwent oxidative cleavage upon treatment with $NaIO_4$ to afford aldehyde intermediate (635). Aldol condensation of aldehyde (635) with triethyl phosphonoacetate in the presence of $TiCl_4$ and Et_3N yielded *E*-olefin (636) in 77% and *Z*-olefin in a trace amount. Hydrogenation of the olefin (636) using palladium catalyst on activated carbon under hydrogen atmosphere gave (637) as two inseparable diastereomers. Hydrolysis of 1,2 isopropylidine acetal (637) using hydrogen chloride gas generated in situ from acetyl chloride in benzyl alcohol gave the amino alcohol (638) in 68% to favour the β-anomer. Cyclic sulfamidate (639) was synthesized in good yield by treatment of amino alcohol (638) with thionyl chloride in the presence of imidazole and triethylamine and subsequent oxidation with $RuCl_3$-$NaIO_4$ (Scheme 137).

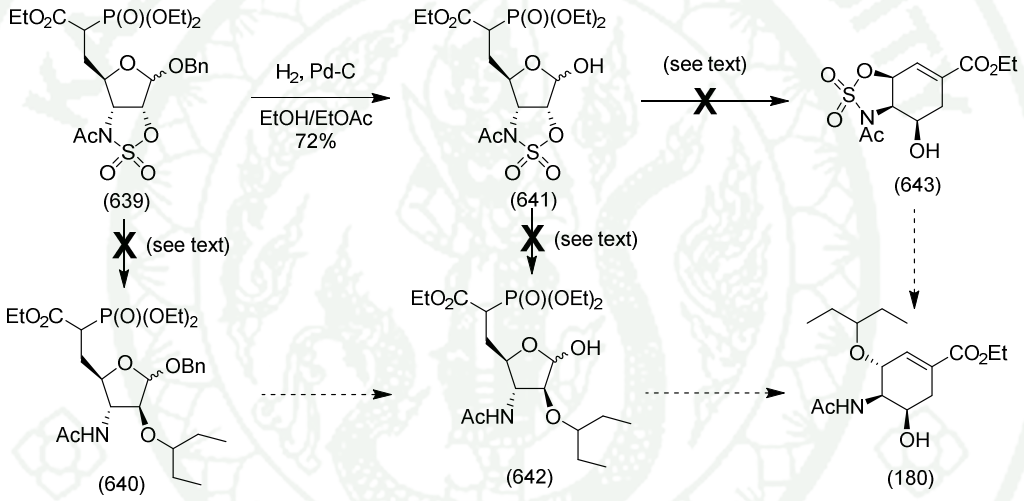


Scheme 137

Cyclic sulfamidate (639) was attempted to transform to Tamiflu's intermediate (180) by several strategies (Scheme138). Introduction of 3-pentyl ether to C-2 position of furanoside by treatment of cyclic sulfamidate (639) with 3-pentanol in the presence of LDA only gave a deacetylated product. Reaction of the cyclic sulfamidate (639) with boiling 3-pentanol in the presence of acid or Lewis acid such as *p*-TsOH and $BF_3.OEt_2$ gave no reaction. Innertion of cyclic sulfamidate opening by 3-pentanol might be due to weak of positive charge at C-2 position (Peregrina *et al.,* 2009) or steric hindrance of an anomeric benzyl ether. Thus benzyl protecting group at anomeric position was removed by hydrogenolysis using palladium catalyst on activated carbon under hydrogen atmosphere to give hemiacetal (641). However,

treatment of the sulfamidate hemiacetal (641) with $Cu(OTf)_2$ in 3-pentanol only gave a complexed mixture.

From the unsuccessful introduction of 3-pentyl ether in this stage, we decided to construct cyclohexene core structure via HWE-olefination first and installation of 3-pentyl ether at the more reactive allylic position later. Unfortunately, an HWE olefination of (641) using DBU in acetonitrile or THF with/without NaI gave the unidentified polar compound which was decomposed in silica gel column. Changing base from DBU to NaH in THF also gave the same result.



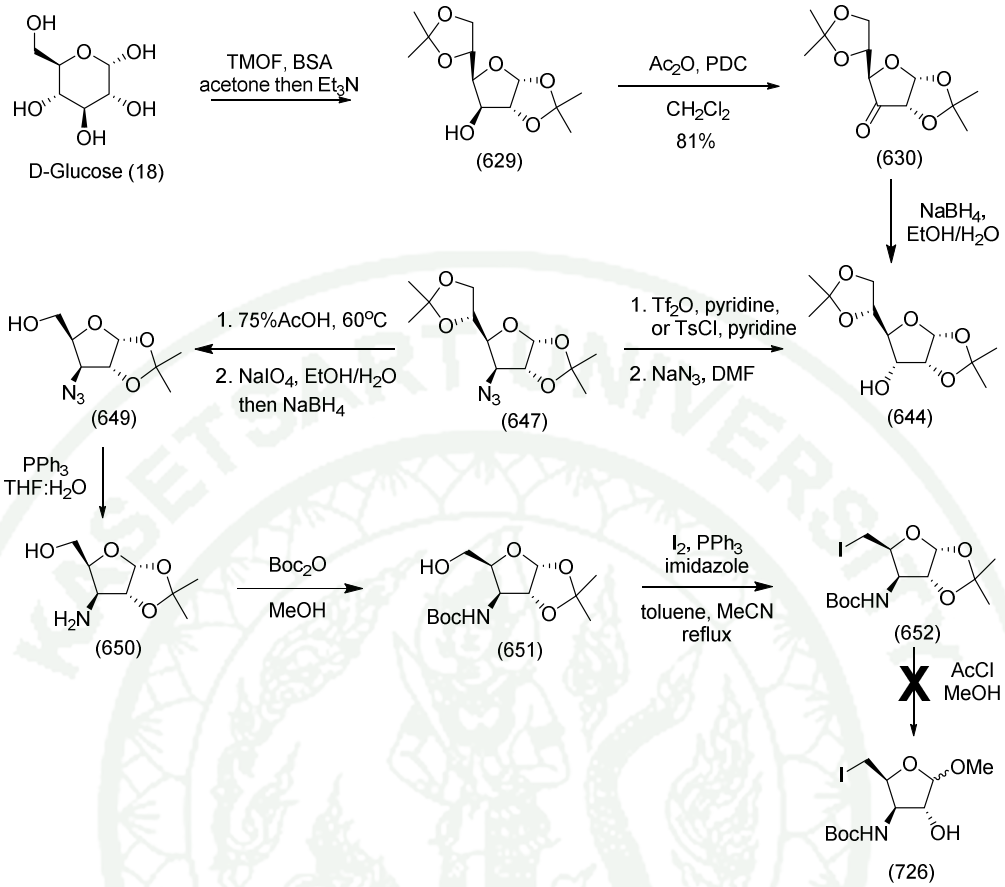
Scheme 138

1.2.1 Synthesis of Tamiflu® (8) from D-glucose (18) via RCM strategy

In this approach, 3-pentyl ether would be installed through aziridine ring opening with 3-pentanol. Cyclohexene carboxylate core structure (657) could be constructed via ring closing metathesis of diene (654) which was obtained from domino reaction of 5-iodo furanoside (652) via retrosynthetic route as shown in Scheme 136 (route B).

5-Iodoaminofuranoside (652) was synthesized in nine steps from D-glucose (18) by modified method described by Ohrui and co-workers (Scheme 139). Reduction of ketone (630) with $NaBH_4$ in ethanol provided 3α-hydroxy intermediate (644) in moderated yield. Activation of hydroxyl group as a triflate or tosylate and then azide displacement yielded β-azido furanoside (647). Selective hydrolysis of 5,6 isopropylidene acetal (647) using 75% acetic acid generated the diol product, followed by oxidative cleavage using $NaIO_4$ and reduction of the corresponding aldehyde with $NaBH_4$ gave azido alcohol (649) in good yield. Staudinger reduction of azide (649) using triphenylphosphine (PPh_3) in THF:H_2O gave amino alcohol (650) in high yield (Diéguez *et al.,* 2009). Selective protection of amino group in the presence of primary alcohol using Boc_2O in methanol afforded carbamate (651). Iodination of alcohol (651) using a combination of iodine, triphenylphosphine and imidazole gave 5-iodo furanoside (652) in 64% yield.

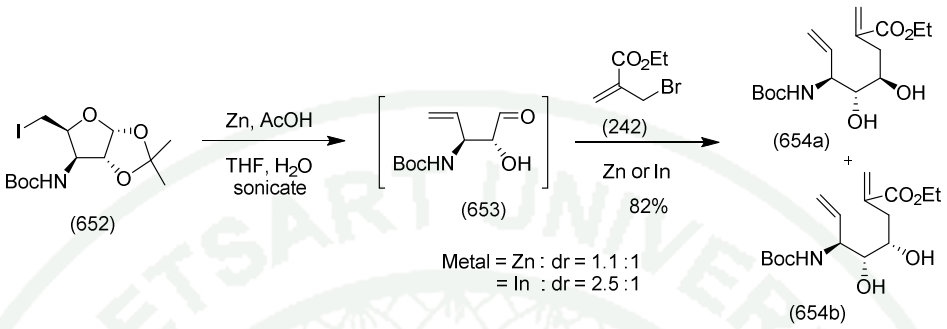
It has been reported that zinc mediated ring opening (Vasella-Bernett reaction) of 5-deoxy-5-iodo-D-xylofuranoside bearing different protecting group at C-2 and C-3 position was difficult to proceed (Portella *et al.,* 2010). Therefore it is necessary to convert 5-iodo-1,2-*O*-isopropylidenefuranoside to the corresponding methyl furanoside before the reaction was performed (Portella *et al.,* 2007). Unfortunately, conversion of 5-iodo-3-amino-1,2-isopropylidine *xylo*furanoside (652) to methyl 5-deoxy-5-iodo xylofuranoside (726) was unsuccessful. Only a high polar compound was obtained.



Scheme 139

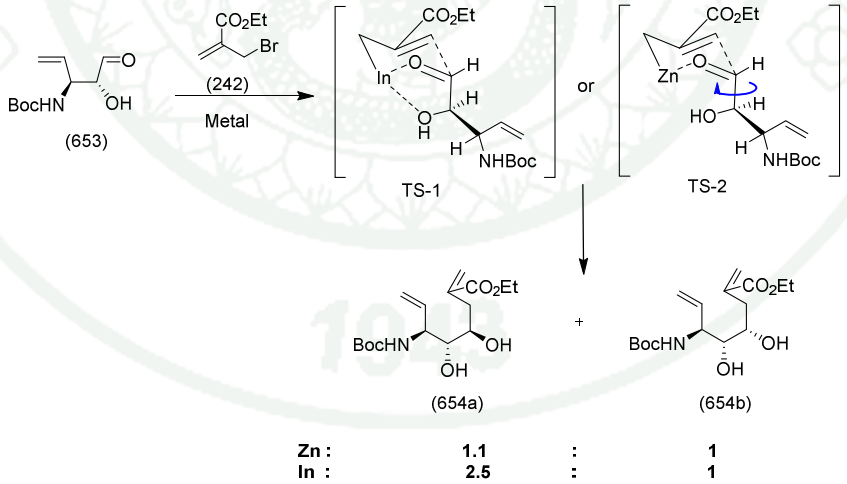
However, we have discovered a new and efficient methodology for domino reductive ring opening–allylation of 5-deoxy-5-iodo-3-amino-3-deoxy-1,2-isopropylidine xylofuranoside (652).The reaction of (652) with activated zinc in the presence of 10% acetic acid in mixed solvent THF:H_2O (2:1) under sonication (Scheme 140) generated the corresponding aldehyde intermediate (653), then in situ treated with ethyl-2-(bromomethyl) acrylate (242) delivered the diene (654a) and (654b) in 82% as diastereomer (dr =1.1:1) which was separated by silica gel column chromatography. It was found that the diasteromeric ratio was slightly improved by replacement of activated zinc with indium powder in the allylation step (dr = 2.5:1, 82%). It has been reported in the literature that indium would not promote the fragmentation of iodide (Madsen *et al.,* 2005). The stereochemistry outcome of (654a) and (654b) was assigned after formation of cyclohexene (657a) and (657b) by

comparison its NMR data to the compound that reported in the literature (Hang *et al*., 2012).



Scheme 140

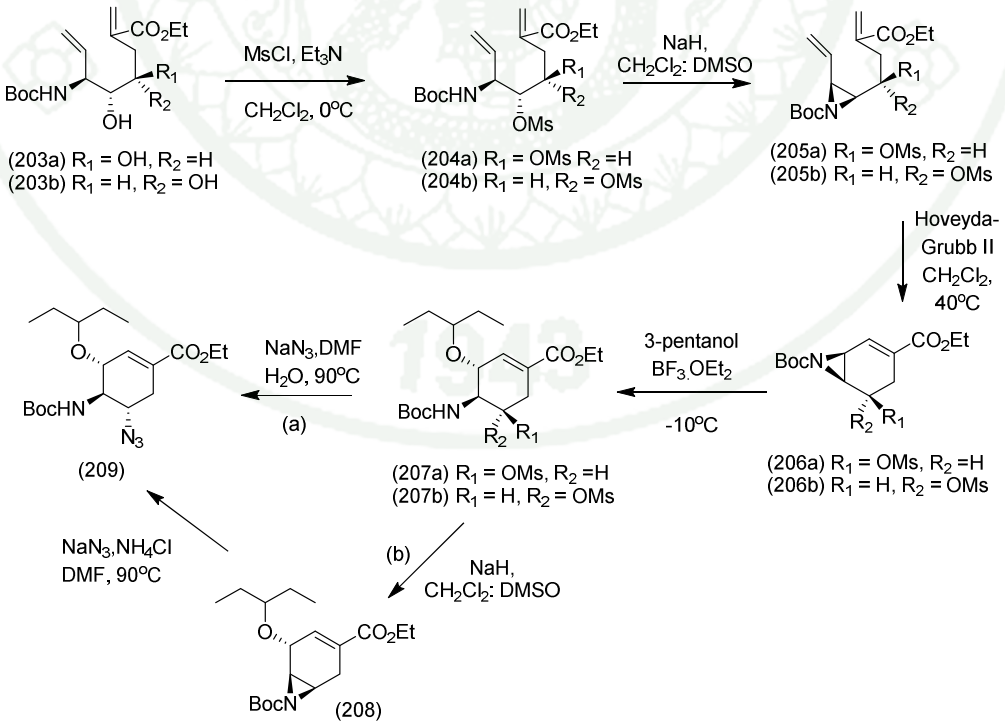
The improvement of stereoselectivity of the reaction with indium catalyses has been explained by α-chelation of indium metal to carbonyl aldehyde and adjacent hetero atom, led to nucleophile attack of the the metal allyl on the least sterically hindered face (Scheme 141).



Scheme 141

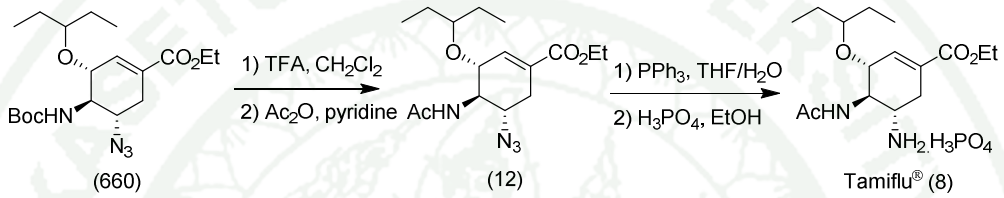
Both diene (654a) and (654b) were transformed to Tamiflu® (8) in 8 and 9 steps via the following reactions (Scheme 142). Mesylation of diol (654a) and (654b) using mesyl chloride, Et_3N in CH_2Cl_2 in 0 ºC gave dimesylate (655a) and (655b) in

60% and 65% yield, respectively. Aziridine formation of (655a) and (655b) using sodium hydride in a mixture of solvents, CH_2Cl_2: DMSO (9:1) delivered to the desired aziridine in high yield of (656b) (88%) and moderate yield of (656a) (44%). The result of low aziridine yield (656a) caused by formation of side product which was unstable on silica gel column chromatography. Ring closing metathesis of the aziridine diene (656a) and (656b) using 2nd Hoveda-Grubbs catalyst afforded the aziridine cyclohexene (657a) and (657b) in 49% and 60% yield, respectively along with recovered starting material. The aziridine cyclohexene (657a) and (657b) was then treated with $BF_3.OEt_2$ in 3-pentanol at –10 ºC led to a highly regio- and stereoselective ring-opening to provide (658a) and (658b) in 95% and 91% yield, respectively. The mesylate (658a) was converted to azide (660) via azide replacement of OMs group. On the other hand, the mesylate (658b) was converted to azide (660) through aziridine (659) by treatment with sodium hydride in CH_2Cl_2:DMSO to give the desired aziridine (659) in high yield (87%). The obtained aziridine was then subjected to ring-opening reactions with sodium azide in the presence of ammonium chloride to yield azide (660) in 89% yield.



Scheme 142

The synthesis was completed by conversion *N*-Boc of (660) to *N*-Ac and then reduction of the azido to amino group (Scheme 143). Thus treatment of (660) with TFA and then acetylated with acetic anhydride gave (12) in 78% yield. Reduction of azido group of (12) using triphynylphosphine or hydrogenation with Lindlar's catalyst gave oseltamivir free base in high yield. Treatment of oseltamivir free base with phosphoric acid in hot ethanol gave oseltamivir phosphate (Tamiflu®) (8) in good yield (Scheme 143).



Scheme 143

2. Synthesis of naphthoquinone aliphatic amides

2.1 Synthesis

Rhinacanthins are naphthoquinone ester derivatives which were isolated from *Rhinacanthus nasutus* is called "Thong Phun Chang" in Thailand. The leaves and stems of this plant are often used to cure cutaneous eruption due to ring worm, eczema, pulmonary, tuberculosis and neurodermatitis and as an aphrodisiac and aplexiphamic. In Taiwan, it was used as a folk medicine for treatment of hepatitis, diabetes mellitus, hypertension, and skin diseases. And also in Thailand, the roots and leaves of *R. nasutus* are used for treatment of cancer. The active components for anticancer activity are rhinacanthone (66) and fifteen rhinacanthins (A-D, G-Q) (67-81) (Figure 11, intoduction).

Our group has previously reported synthesis of rhinacanthin M, N, Q and related naphthoquinone aromatic esters with anticancer activity (Kongkathip *et al*., 2004). We found that naphthoquinone aromatic esters contained C-3 hydroxy group and 2´, 2´-dimethyl substitutents at propyl chain showed significant cytotoxicities to

cancer cells (Kongkathip *et al*., 2004; Kongkathip *et al*., 2010). Because of broad spectrum of biological activities of amide compounds, naphthoquinone aromatic amides were also synthesized to evaluate anticancer activity (Kongkathip *et al*., 2012). Even though most of the aromatic amides showed weaker cytotoxicities to cancer cells than the aromatic esters but it showed lesser cytoxicity to normal Vero cells than the ester ones. Study on mechanism of action of naphthoquinone aromatic esters and amides found that Topoisomerase II is a molecular target of them (Kongkathip *et al*., 2004; Kongkathip *et al*., 2012).

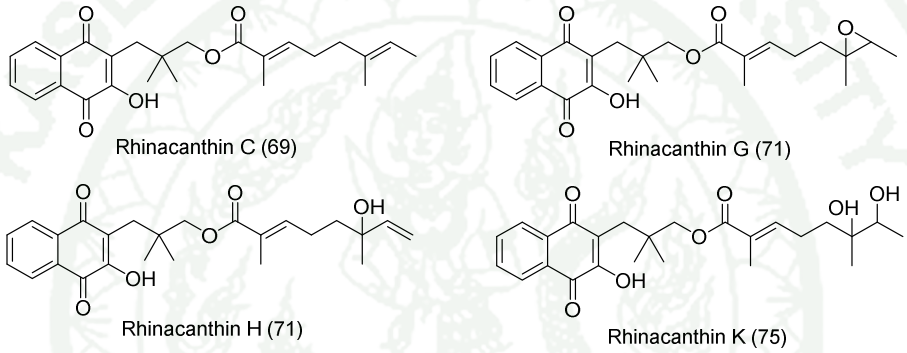


Figure 25 Structures of rhinacanthin-C, -G,-H, and –K.

Naphthoquinone aliphatic esters were also synthesized based on the structure of anticancer rhinacanthin C, G, H and K (Figure 25) and evaluated for anticancer (Hasitapan, 2006) and antimalarial activities (Kongkathip *et al*., 2010). Most of synthetic rhinacanthins and naphthoquinone aromatic esters exhibited great anticancer activity whereas the synthetic naphthoquinone aliphatic esters displayed highly potent antimalarial activity against *Plasmodium falciparum* (IC_{50} 0.03-16.63 μM). Interestingly, two naphthoquinone aliphatic esters (102) and (105) (Figure 26) showed a great antimalarial activity and were not toxic to normal Vero cells. Study on mechanism of action of these two selected naphthoquinone aliphatic esters found that both compounds selectively inhibited *P.falciparum* 3D7cyt bc_1 as well as atovaquone (65) (1,4-naphthoquinone antimalarial drug) and no inhibition on rat cyt bc_1 (Kongkathip *et al.,* 2010).

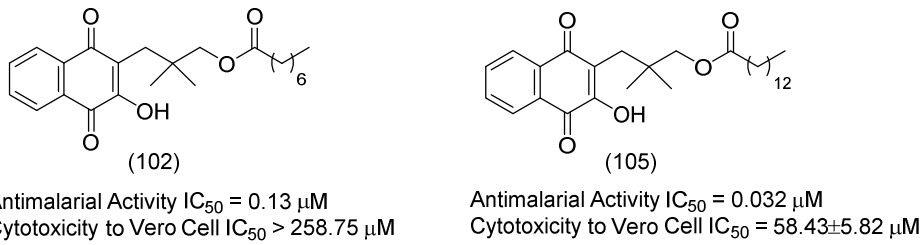
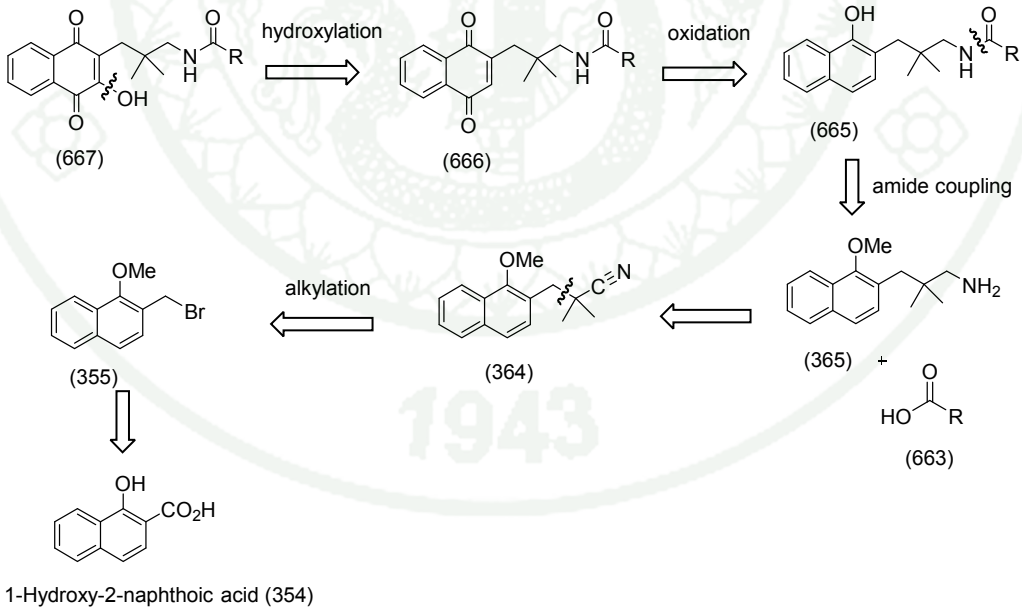


Figure 26 Structures of two naphthoquinone aliphatic esters which inhibited *Plasmodium falciparum* without toxicity to normal Vero cells.

From this evidence, we are interested to synthesize naphthoquinone aliphatic amides analogue to compare its anticancer and antimalarial activities with the aliphatic esters and those of aromatic series.

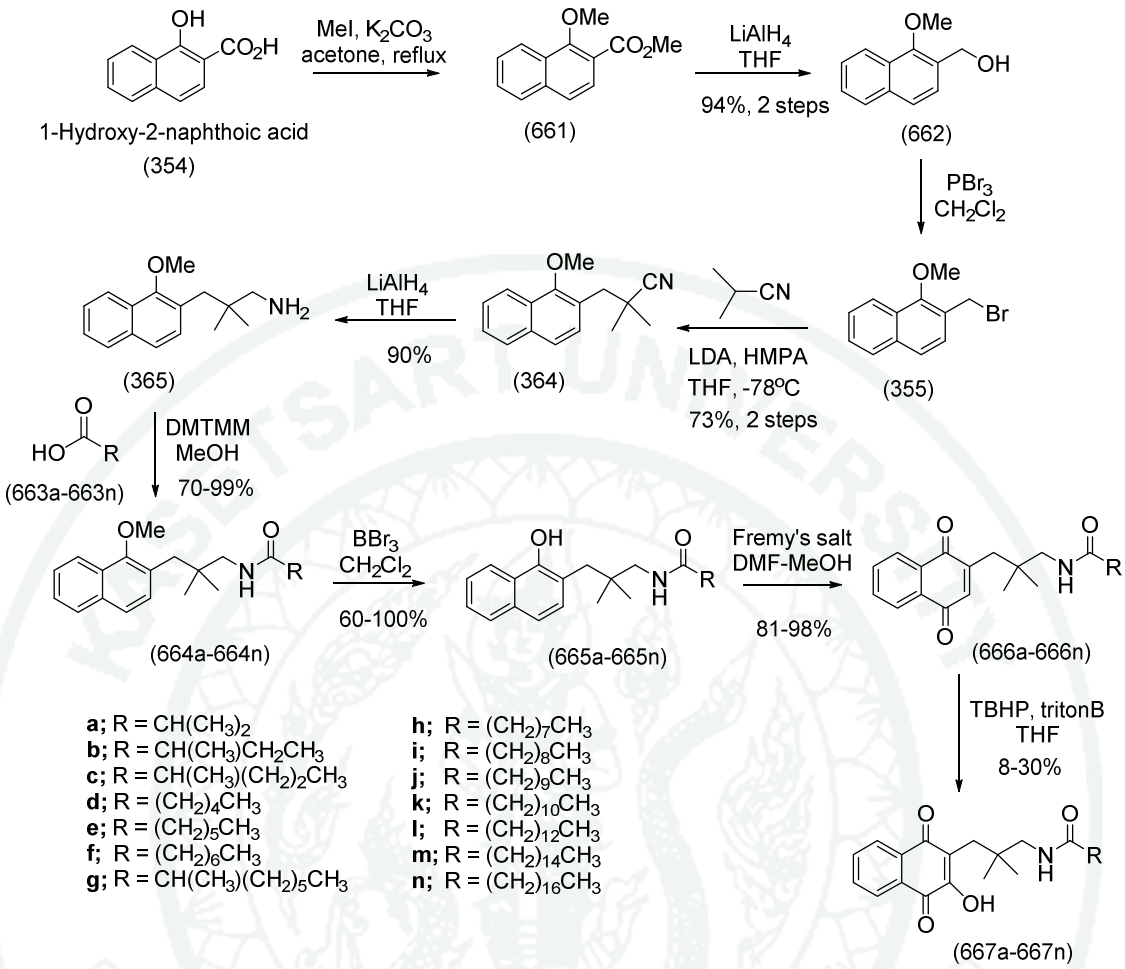
Naphthoquinone aliphatic amides were successfully synthesized based on the disconnection as shown in Scheme 144.



Scheme 144 Retrosynthetic analysis of naphoquinone aliphatic amides.

Naphthoquinone aliphatic amides were synthesized by following the method as described in synthesis of naphthoquinone aromatic amides (Kongkathip *et al*.,

2012). Fourteen naphthoquinone aliphatic amides (667a-667n) were produced in nine steps from 1-hydroxy-2-naphthoic acid (354) (Scheme 145) via the following reactions, starting from methylation of 1-hydroxy-2-naphthoic acid (354) with MeI in the presence of K_2CO_3 under reflux in acetone to give methyl ester (661) in excellent yield. Reduction of ester (661) using lithium aluminium hydride ($LiAlH_4$) in THF generated alcohol (662) in 94% for 2 steps. Bromination of the resulting alcohol with PBr_3 in CH_2Cl_2 afforded bromide intermediate (355) which was alkylated with isobutyronitrile in the presence of lithium diisopropylamide (LDA) yielded nitrile (364) in 73%. Reduction of the nitrile (364) with $LiAlH_4$ delivered to amine (365) in 90% yield. Amide (664a-664n) formation was obtained from coupling of amine (365) with various aliphatic carboxylic acids (663a-663n) (C_3-C_{18})**.** It was found that DMTMM (668) **(**4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride) is the best coupling agent. DCC and CDI were tried but the resulting amides were obtained in very low yield (Pradidphol, 2012). Demethylation of (664a-664n) with BBr_3 afforded naphthol amide (665a-665n) in 60-100%. Oxidation of naphthol amide (665a-665n) with Fremy's salt yielded naphthoquinone amide (666a-666n) in 81-98%. Hydroxylation of naphthoquinone amide (666a-666n) using *tert*-butylhydroperoxide (TBHP) in the presence of tritonB delivered to target molecule, naphthoquinone amide (667a-667n) in 27-61%. Based on our previous work (Kongkathip *et al*, 2012), it was found that hydroxylation step of naphthoquinone aromatic amides gave a superior yield (54 - 95%) than those of aliphatic amides (27-61%). This may be accounted for the easier hydrolysis of the aliphatic amide than the aromatic amide (less electrophilicity) by the base.



Scheme 145 Synthesis of naphthoquinone aliphatic amides.

2.2 Biological activity evaluation of the naphthoquinones (667a-667n)

Fourteen novel synthetic naphthoquinone aliphatic amides (667a-667n) were submitted to bioassay lolaboratory of BIOTEC for evaluation of their cytotoxicity against human cancer cell lines KB (oral cavity cancer), NCI-H187 (Small cell lung cancer) and MCF7 (breast cancer) by the REsazurin Microplate Assay (REMA) (Brien *et al.,* 2000), antimalarial activities against *Plasmodium falciparum* by the Microculture Radioisotope Technique (Bradford, 1976) and normal Vero cell lines by Green Fluorescent Protein (GFP)-based assay (Hunt *et al.,* 1999) (Table 6 and 7).

The results founded that naphthoquinone aliphatic amides with longer aliphatic chain (carbon 7 to 18 atoms) showed more potent cytotoxicity against cancer cell lines (KB, NCI-H187 and MCF7) than the shorter ones. For anticancer activity against oral cavity cancer (KB cancer cell lines), naphthoquinone compounds (667m) (C_{16}) and (667n) (C_{18}) showed the greatest activity with IC_{50} values of 5.12 and 6.35 μM respectively. Anticancer activity against lung cancer (NCI-H187 cancer cell lines), naphthoquinone aliphatic amides (667n) (C_{18}) showed the best activity with IC_{50} value of 4.83 μM. They were also evaluated for inhibition against breast cancer (MCF7 cancer cell lines) and it was found that naphthoquinone (667i) (C_{10}) showed the strong inhibition against breast cancer (MCF7 cancer cell line) with IC_{50} value of 13.35 μM.

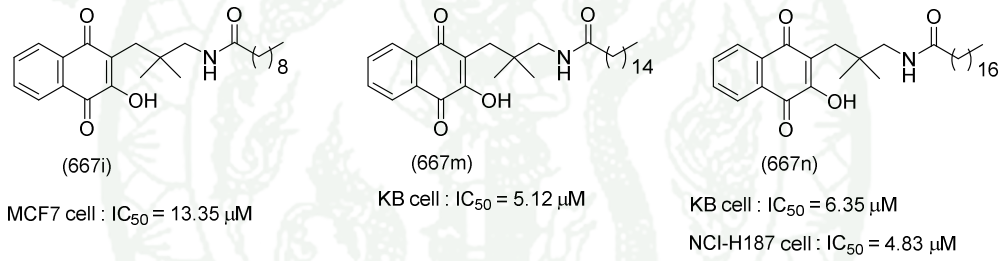
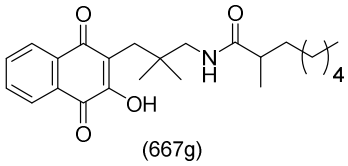
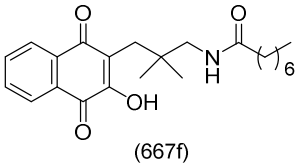


Figure 27 The best inhibition of cancer cells of our synthetic naphthoquinone aliphatic amides.

Naphthoquinone aliphatic amides with α-methyl substituent at aliphatic chain showed the same results as the compound without the α-methyl substituent which is contrast with those of the aliphatic ester series.



(667g)

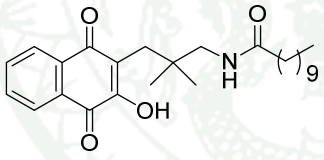


(667f)

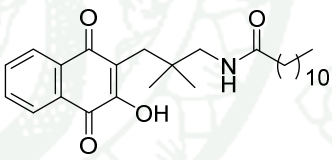
KB	IC_{50} = 23.73 μM	IC_{50} = 24.64 μM
NCI-H187	IC_{50} = 17.42 μM	IC_{50} = 19.95 μM
Vero cell	IC_{50} = 15.54 μM	IC_{50} = 18.42 μM

Figure 28 Cytotoxicity of naphthoquinone aliphatic amides with α-methyl substituent at aliphatic chain versus the compound without α-methyl substituent.

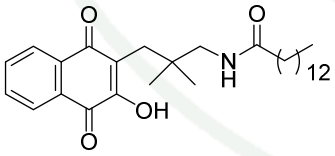
The results from the antimalarial testing showed that naphthoquinone aliphatic amides with 11 to 18 carbon atoms of straight chain exhibited potent antimalarial acitivity with IC_{50} values of 0.76 to 12.46 μM. The longer straight chain showed more potent activity than the shorter one.



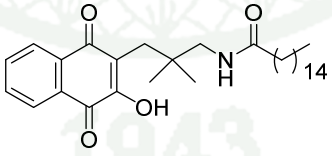
(667j): IC_{50} = 12.46 μM



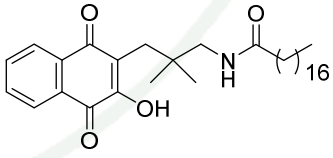
(667k): IC_{50} = 10.62 μM



(667l) : IC_{50} = 1.02 μM



(667m): IC_{50} = 2.81 μM



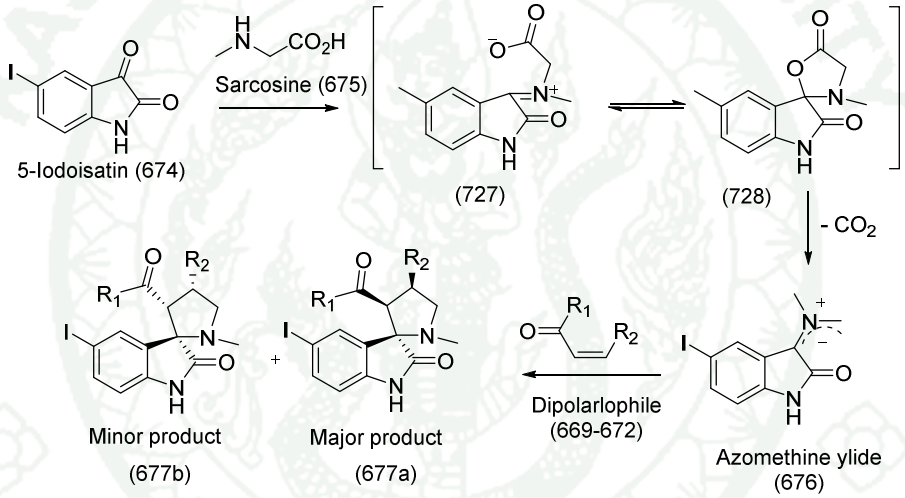
(667n) : IC_{50} = 0.76 μM

Figure 29 Structures of the antimalarial naphthoquinone aliphatic amides.

3. Synthesis of *N,O*-heterocycles

3.1 Synthesis of spirooxindole pyrrolidines compounds

Spirooxindole pyrrolidines have been synthesized via 1,3-dipolar cycloaddition of azomethine ylides (676), generated in situ from 5-iodoisatin (674) and sarcosine (675), through a decarboxylation route. Regioselective 1,3-dipolar cycloaddition with various dipolarlophiles (669-672) gave the *endo*-cycloadduct as a major isomer (Scheme 146).



Scheme 146

The regioselectivity in the product formation was explained by considering secondary orbital interaction (SOI) of the carbonyl of azomethine ylide with carbonyl of dipolarlophile (Figure 30).

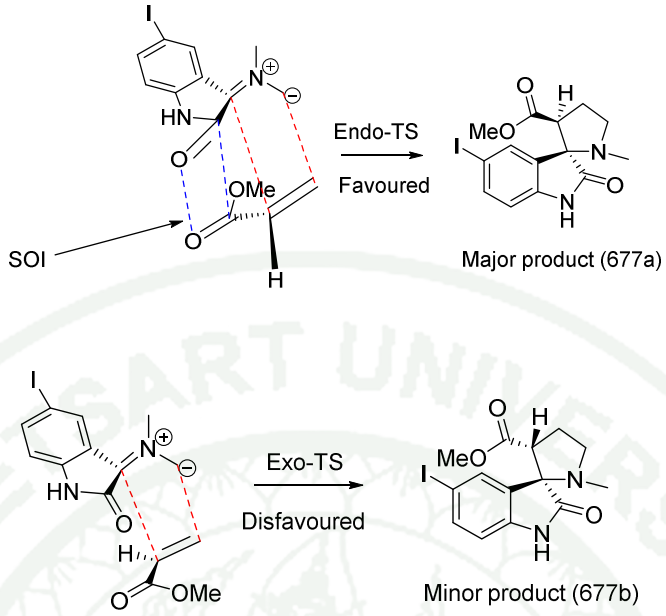


Figure 30 Transition state of 1,3-dipolar cycloaddition of azomethine ylide.

The results of the cycloaddition reactions are summarized in Table 12. Initially, all of the reactions were performed in acetonitrile at 80ºC. Conversion of 5-iodoisatin (674), starting material to the product could be indicated by disappearance of 5-iodoisatin which observed by the reaction colour (red to light orange or colourless).

1,3-Dipolar cycloaddition reaction with symmetrical dipolarlophiles, maleimide (670) and *N*-phenylmaleimide (669) gave the desired product precipitate from the reaction mixture. However, the two reactions showed difference results (Table 12, entries 1 and 2). Maleimide (670) gave the 1,3-cycloadduct (679) *endo* favored as a single diastereomer whereas *N*-phenylmaleimide (669) gave a ~2:1 mixture of (678a) and (678b) (indicated by NMR) of *endo : exo* favored. The latter result might be explained by an interaction between the positively charged nitrogen atoms of azomethine ylide with the phenyl group of *N*-phenyl maleimide (Figure 31) versus the *endo* transition state. The pure major isomer (678a) precipitated when the reaction was carried out in acetonitrile whereas (678b) precipitated in cool acetonitrile.

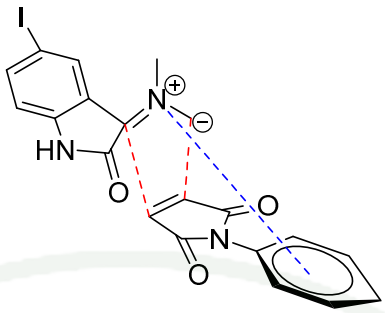


Figure 31 *exo*-transition state.

1,3-Dipolar cycloaddition reaction with the unsymmetrical dipolarlophile, methyl acrylate (671) afforded a 27:2.3:1 mixture of cycloadducts (680a), (680b) and (681) (Table 12, entry 5). Under these reaction conditions, the minor isomer (681) had lost the iodide substituent. The deiodination may arise from formation of a small amount of Pd(II)H either due to traces of water in the solvent or by insertion into the isatin N-H bond. However, the iodide is not lost in the maleimide, *N*-phenylmaleimide and barbiturate reactions (Table 12, entries 1-4 and 7-9). It would seem to be related to the methyl acrylate and may therefore be due to a Baylis-Hillman type reaction.

Double spiro compound (682a) was obtained from 1,3-dipolar cycloaddition reaction of dipolarlophile (672) which was synthesized from condensation of *N,N*-dimethyl barbituric acid with benzaldehyde in water. (Deb *et al.,* 2005) Initially, when the reaction was carried out in acetonitrile for 8h, the desired cycloadduct (682) was obtained in low yield (34%, dr= 18:1) and side product (683), was formed due to a loss of the phenyl group. The cycloaddition of an azomethine ylide, generated from benzaldehyde and sarcosine, to give the compound (684) (approx 30%), was also observed. However the compound (684) proved unstable to silica chromatography and was not further studied. Surprisingly, when the reaction mixture was left at 80 °C for 24h the desired product (682) was not observed. The desired cycloadduct (682) was obtained in a good yield (73%, dr = 22:1) when the reaction was carried out in boiling ethanol for 2h. We found that 5-iodoisatin (674) and sarcosine (675) have a greater solubility in ethanol than in acetonitrile allowing a short reaction time without

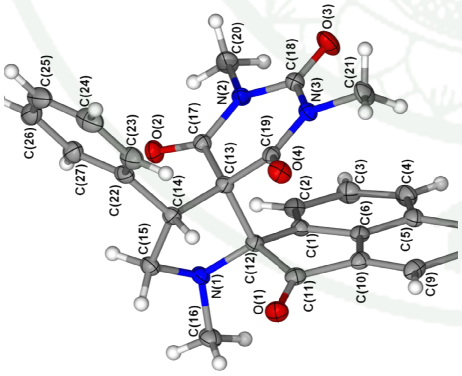
side products. Thus the 1,3-dipolar cycloaddition of azomethine ylides (676) was repeated in ethanol to give the superior results, shorter reaction time and higher yield, than the reaction in acetonitrile.

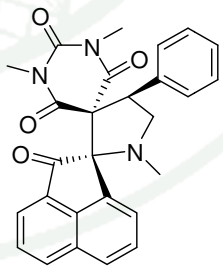
3.2 Synthesis of spiroacenaphthenonyl pyrrolidine compounds

Spiroacenaphthenonyl pyrrolidine compounds were constructed in the same manner with spirooxindole pyrrolidines when 5-iodisatin (674) was replaced with acenaphthenenone (683) and the reactions were performed in ethanol at 80 ºC (optimal conditions). The results of the cycloaddition reactions are summarized in Table 13. The reaction also showed a similar behavior with 1,3-dipolar cycloaddition of azomethine ylide from 5-iodoisatin but the reaction of methyl acrylate (671), dipolarlophile in ethanol used a long reaction time as the reaction of acetonitrile.

3.3 Confirmation of regioselectivity

The stereochemistry of (689) was established by an X-ray crystal structure (Figure 32).





(689)

Figure 32 X-ray crystal structure showed relative stereochemistry of (689).

3.4 Seven component 1,3-dipolar cycloaddition reaction of azomethine ylide with a triple dipolarlophile (673)

We next tamed our attention to achieving an unusual seven component 1,3-dipolar cycloaddition reaction of azomethine ylide with a triple dipolarlophile, tris[2-(acryloyloxy)ethyl]isocyanurate (673) (Table 14). This was enthusiastically investigated because the product of the novel reaction would display multivalent interactions with increased interaction with biological system (Ungaro *et al*., 2007).

The tris dipolarlophile (673) underwent 1,3-dipolar cycloaddition of azomethine ylides (676) and (684) to form triple cycloadducts in a good yield. Such triple cycloadditions can give rise to multiple possible diastereoisomers. From TLC plate observations, more than six spots due to spirooxindole cycloadduct (690) were observed. We have isolated and confirmed the structures of some triple cycloadducts by NMR spectroscopy and high resolution mass spectroscopy but the relative configuration has not yet been confirmed. In case of spiroacenaphthenone, four spots were observed on TLC plate and the major product, a symmetrical product (691) was obtained in 48% yield.

3.5 Synthesis of *N*-*O* heterocycle spiro compounds

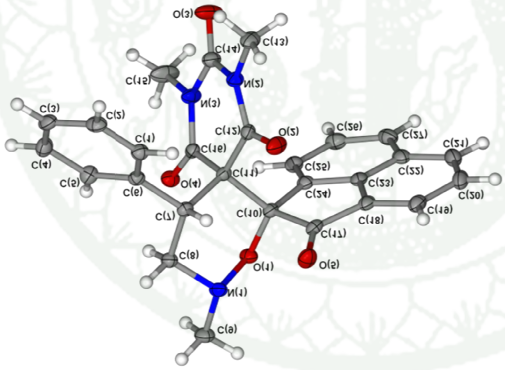
With the spiropyrrolidine compounds in hand, we studied their conversion to *N*-*O* heterocycles via 1,2-Meisenheimer rearrangement.

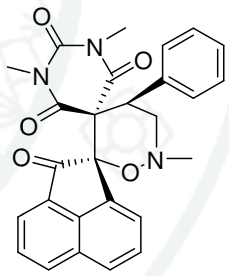
Oxidation of the obtained spiropyrrolidine cycloadducts with *m*-chloroperbenzoic acid (*m*-CPBA) initiated the 1,2-Meisenheimer rearrangement, regio- and stereoselectively, in excellent yield except (698) which unstable under reaction condition (Table 15).

In the case of spiropyrrolidine cycloadducts (678-679) and (686-687) obtained from maleimide (670) and *N*-phenylmaleimide (669), treatment of the substrate with *m*-chloroperbenzoic acid in CH_2Cl_2 or methanol afforded the stable *N*-oxide which

was performed 1,2-Meisenheimer rearrangement by heating in acetonitrile for 1-2 h (Table 15, entries1-2 and 5). Observation of the stable *N*-oxides could be explained by formation of hydrogen bonding between *N*-oxide oxygen with NH hydrogen of maleimide or *N*-Ph hydrogen of *N*-phenylmaleimide (O'Neil *et al.,* 1998). Reaction of (678) in CH_2Cl_2 gave a longer reaction time (16h) than methanol (4h) (Table 11, entries 1-2) whereas (679) (Table 11, entry 5) resulted in no reaction in CH_2Cl_2. The reaction has been conducted in methanol for 24h to generate *N*-oxide. Unfortunately, the *N*-oxide did not undergo rearrangement when refluxed in acetonitrile which appeared to be due to lack of solubility of the compound in the solvent. We found that heating the *N*-oxide in DMSO at 60 ^{o}C gave 1,2-Meisenheimer rearrangement of this compound (694).

The structure and selectivity of the 1,2-Meisenheimer product was confirmed by X-ray crystallography of (699) (Figure 33).



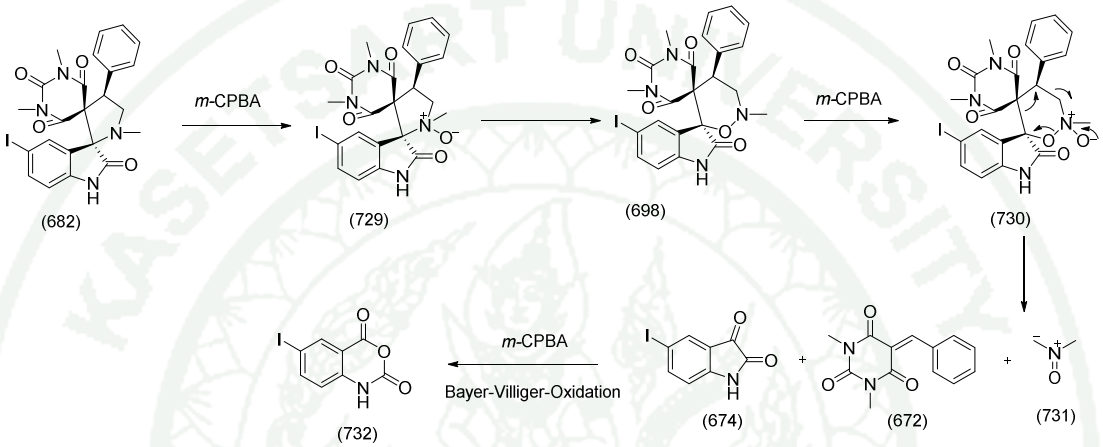


(699)

Figure 33 X-ray crystal structure of (699).

In case of double spiro *N-O* heterocycle (682) which was obtained in low yield (Table 15, entry 9) when *m*-CPBA was used without pre-treatment with phosphate buffer to remove *m*-chlorobenzoic acid the undesired product (732) and the unreacted starting material (682) were isolated instead of the desired product (698). Treatment of 5 mole equivalent of *m*-CPBA in the presence of 5 mole equivalent potassium carbonate delivered to only undesired product (732). The desired product (698) was formed in 10% yield with 80% recovered starting material using 2 mole equivalent of

pure *m*-CPBA in chloroform at room temperature. We assumed that the Meisenheimer product (698) would be oxidized again by *m*-CPBA to *N*-oxide (730) followed by ring opening to generate 5-iodoisatin (674) which was oxidized with another molecule of *m*-CPBA through Bayer-Villiger oxidition to obtain isatoic anhydride (732) (Scheme 147).



Scheme 147

3.6 Biological activity

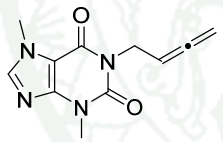
The synthetic *N-O* heterocyclic spiro compounds (692-700) have been screened for antimalaria and anticancer activities. The results are shown in Table 16. The triple *N-O* heterocyclic spiro compound (700) has shown a good antimalarial activity with IC_{50} 1.04 μM. Unfortunately, *N-O* heterocyclic spiro compounds (692-699) have not shown antimalarial activity. Antimalarial activity of the triple *N-O* heterocyclic spiro compound (700) would influence from multivalent interactions of the compound to biological targets at *Plasmodium* parasite. Seven *N-O* heterocyclic spiro compounds (692a), (693a), (693b), (695), (697), (698) and (699) have shown inhibition against human oral cavity cancer cell line (KB cell line) with IC_{50} 24.45-120.78 μM. The most active compound are double spiro compound (698) and (699) (IC_{50} = 24.45 and 25.69 μM). When we compare core structure, spiroacenaphthenone (695) and (697) exhibit inhibition against KB cell line with IC_{50} 64.13μM and 35.91μM, respectively but spirooxindole (694) and (696) are inactive. Relative

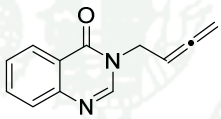
stereochemistry is important for spirooxindole with *N*-phenyl imide (692) because *anti* carbonyl (692a) is active anticancer with IC_{50} = 39.96 μM but *syn* carbonyl (692b) is inactive. On the other hand, the relative stereochemistry does not play major role for spiroacenaphthenone with *N*-phenyl imide (693) (IC_{50} = 120.78 and 118.44 μM for (693a) and (693b), respectively).

4. Palladium catalyzed cascade reaction of allenes

4.1 Synthesis of allenes

Three biologically active significant core allenes such as purine and 4-quinazolinone have been synthesized for our cascade reaction via a two step process which included *N*- propagylation with propagyl bromide in the presence of base and yielded the propargylic in excellent yield. The second step of which was a modified Crabbé reaction of propargylic substrates.


(703)


(706)

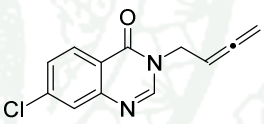
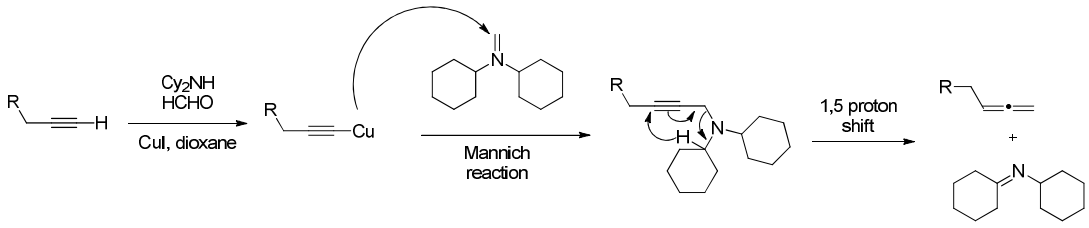

(709)

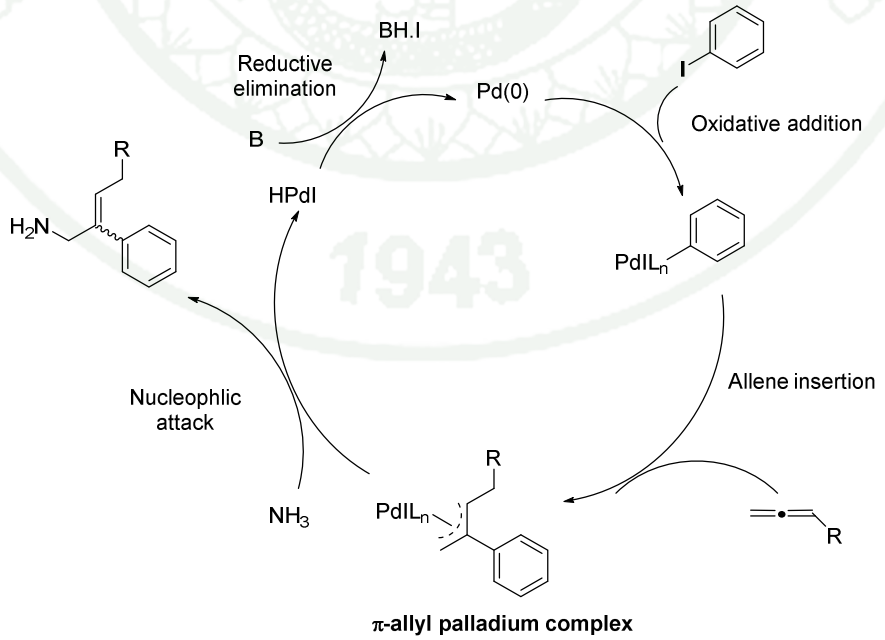
Figure 34 Allenes.

The Crabbé reaction is reaction for the synthesis of allenes from alkynes employing diisopropylamine, paraformaldehyde and copper bromide in dioxane (Crabbé *et al.,* 1979). However, in many cases the reaction provides the products in low yields. In 2009, Ma and co-workers reported a modified Crabbé reaction using CuI and dicyclohexylamine instead of diisopropylamine and copper bromide to give terminal allenes in higher yields (Ma *et al.,* 2009). Mechanism of allene formation was shown in Scheme 148.

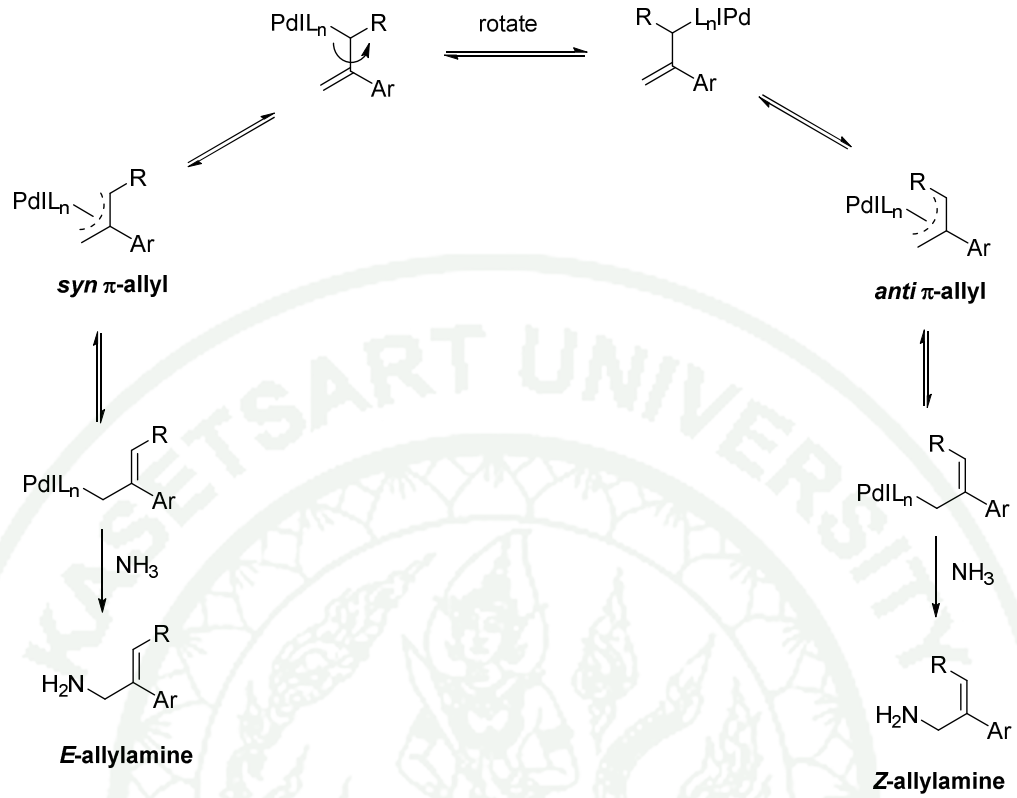


Scheme 148

Palladium catalysed cascade reactions of allenes with aryl iodides in the presence of an ammonia nucleophile could deliver an allylamine product. The mechanism of the cascade reaction involves oxidative addition of Pd(0) to an aryl iodide to form an aryl palladium (II) complex which coordinates to allene and adds regioselectively to the terminal double bond to deliver an intermediate π-allyl palladium (II) complex. Nucleophiles attack at least substituted carbon of the *syn*- and *anti*-palladium π-allyl complexes which can interconvert through rearrangement to the σ-allyl complexes to furnish the product as a mixture of *E/Z* isomers (Scheme 149). However it is possible to obtain a single isomer from this type of cascade process depending on reaction conditions.



Scheme 149



Scheme 150

Previous work in the MIDAS Centre at the University of Leed found that the solvent affects the stereochemistry of the allylamine product. In polar solvents such as formamide the *syn*-allylpalladium (II) species would appear to be more stable than the *anti*-allylpalladium (II) species suggesting high solvent polarity favours *E*-isomer selectivity. On the other hand low polarity solvent such as toluene and dioxane are important for *Z*-isomer selectivity (Scheme 150).

Theobromine allene (703) and 3-iodopyridine (710a) were used as models for optimization (Table 17). The ammonia surrogate used in our cascade synthesis are ammonium carbonate, ammonium tartrate, ammonium citrate and a 30% ammonia solution.

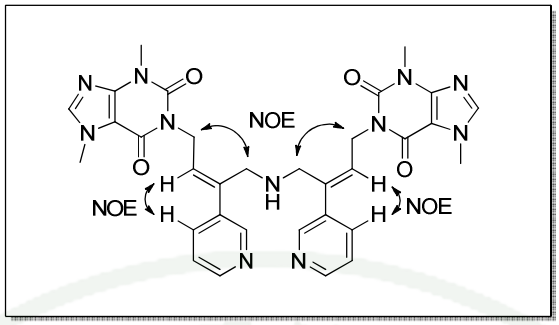
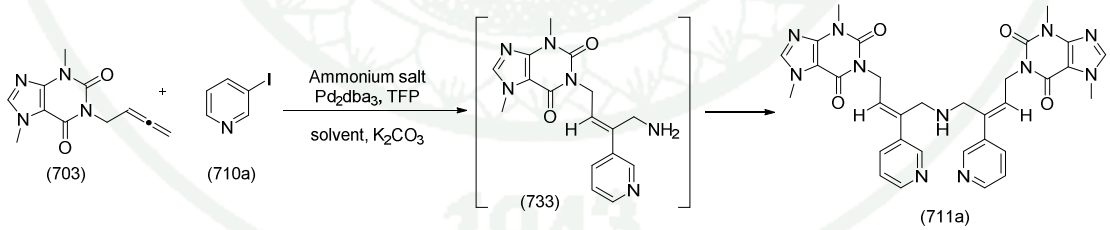


Figure 35 NOE correlation of (711a).

My research work started from repeating entry 1 (Table 17) which was investigated by Elghareeb E. Elboray, a member of the MIDAS Centre at the University of Leeds. Ammonium carbonate was used as an initial ammonia source and the reaction was run in DMF/H_2O (2:1) without base for 3h. The desired (*Z,Z*)-bis-allylamine was obtained in 55% yield. The stereochemistry was confirmed by NOE experiments (Figure 35). The cascade reaction gave exclusively the bis-allylamine product (711a) indicating the allylamine product (733) is more reactive than ammonia (Scheme 151). The tris-allylamine was not observed which might be due to steric hindrance.



Scheme 151

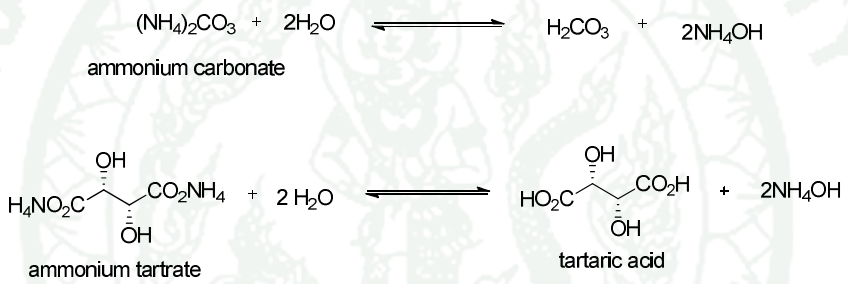
Replacing ammonium carbonate with 30% aqueous ammonium hydroxide solution gave the same result (Table 17, entries 1 and 6). Reaction with ammonium tartrate in DMF/H_2O resulted in an *E/Z* isomer mixture (Table 17, entry 8) which complicated attempts to separate and calculate the ratio. The reaction in DMF only also gave an *E/Z* mixture after a long reaction time (18 h) (Table 17, entry 7).

From the above results indicating reaction in polar solvents gave an *E/Z* isomer mixture we expected that the reaction in lower or non-polar solvents such as toluene and dioxane would give the *Z*-selective allylamine. Unfortunately, the reaction did not proceed in toluene or dioxane (Table 17, entries 2, 3 and 9). When K_2CO_3 was added to the reaction in dioxan the reaction was incomplete after 24 h. Dimethyl formamide (DMF) was added to try and speed the reaction up (Table 17, entries 4, 5, 11, 12, 13 and 15). The desired product was then obtained in up to 80% yield and the reaction was complete within 23 h.

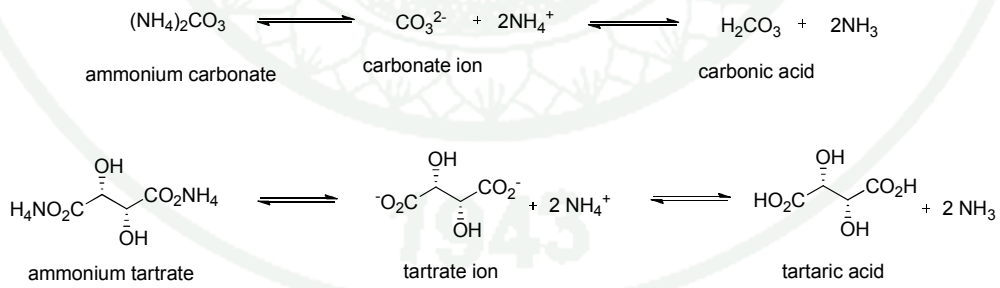
Interestingly, in the ammonium carbonate reaction, the desired product was easily soluble in chloroform but in tartrate and citrate reactions, the desired product did not dissolve in chloroform and the melting points were also different (carbonate reaction = 148-149 °C, tartrate reaction = 238-240 ° C). We assume that differentiation of physical properties is caused by protonation of bis-allylamine by stronger acids, tartaric acid (pK_a = 2.95, 4.25) or citric acid (pK_a = 3.09, 4.75, 5.41) versus mild carbonic acid (pK_a = 6.37, 10.33) which did not protonate the allylamine product. This hypothesis was supported by shaking the protonated product with ammonium hydroxide to obtain a non-protonated product which dissolved in chloroform. The advantage of the ammonium tartrate reaction is the easier workup and purification steps because the tartrate salt and K_2CO_3 did not dissolve in a mixture of dioxane/DMF. Removal of the solid from tartrate reaction by filtration and evaporation the protonated of (*Z,Z*)-bis-allylamine which when washed with chloroform delivered a pure (*Z,Z*)-bis-allylamine product form without chromatography. On the other hand, reaction in a mixture of dioxane/water (Table 17, entry 14) resulted in a homogeneous phase, with all the components were soluble in the solvent requiring extraction and chromatography work up and purification steps.

Surprisingly, reactions of both ammonium carbonate and ammonium tartrate in a mixture of DMF/water without K_2CO_3 were completed in a short time (3h) but a mixture of *E/Z* isomers was found (Table 17, entries 1 and 8). Normally in Heck type reactions, base is important for the reductive elimination step because it helps to reduced Pd (II) (H-PdL_n-I) to Pd (0) in the catalytic cycle (Scheme 149). In our

reaction, when water was added into the reaction of both ammonium tartrate and ammonium carbonate, ammonium hydroxide was generated in situ (Scheme 152) thus additional external bases are not necessary. Cascade reaction of ammonium carbonate in the presence or absence of K_2CO_3 in dioxane/DMF resulted bis-allylamine (Table17, entries 4 and 5). But the reaction of ammonium tartrate in the presence and absence of K_2CO_3 in dioxane/DMF gave different result (Table 17, entries 11 and 12). This observation could be explained by the nature of the anion, carbonate anion is basic enough to deprotonated but tartrate anion lacks sufficient basicity (Scheme 153). Thus cascade reactions of ammonium tartrate need K_2CO_3 to help in the reductive elimination step.



Scheme 152



Scheme 153

When the amount of dibasic ammonium tartrate was reduced from 6 equivalents to 3 equivalents the reaction was completed in the same time with essentially the same yield (Table 17, entries 12 and 13). Tribasic ammonium citrate differed from dibasic ammonium tartrate, six equivalents of ammonium citrate result

in a 77% yield of bis-allylamine after 23h but three equivalents of ammonium citrate required 30 h reaction time for the same yield.

We selected the condition in entries 11 and 12 to make more examples of bis-allylamines with various allenes (Figure 34) and aryl iodides (Figure 24) using dibasic ammonium tartrate as the ammonia source and the aryliodides in Figure 24. In case of theobromine allene (703), six (*Z,Z*)-bis-allylamines were produced in good to excellent yields (63-82%) (Table18). However when *N,N*-dimethyl 5-iodouracil (710g) was used, the bis-allyamine (711g) was obtained in excellent yield (90%) but as an *E/Z* isomeric mixture which was difficult to separate and calculate the ratio. This might be due to coordination of the C=O of the uracil group to the π–allyl which could stabilizes both *syn*- and *anti*-π-allyl complexes and delivers a mixture of *E/Z* isomers.

In case of quinazolinone allenes (706), our standard condition (Table 17, entries 11-12) gave bis-allylamine (712a) in 69% yield as a mixture of *ZZ/EZ* isomer in a 3:1 ratio (Table 19, entry 1). We tried to improve the *E/Z* isomeric ratio by using the chloro-substituted quinazolinone allene (706) and 3-iodopyridine (710a) as substrates but were unable to get only the *Z*-isomer (Table 19, entries 2-8). Even though the reaction of the chloro-quinazolone allene (706) gave a mixture of *E/Z* isomer, it was possible to isolate pure (*Z,Z*) bis-allylamine in more than 50% yield by precipitation of the *E/Z* mixture in methanol. The pure *Z,Z* isomer precipitated from the solution. Twelve examples of bis-allylamine (712-713) from quinazolone allenes (706) and (709) were synthesized as showed in Table 20. The yields of *Z,Z*- isomer were ranging from 40-67%.

4.3 Cascade synthesis of complex 3,4-dihydroisoquinolinone and isoquinoline

Our standard condition for selective synthesis of bis-*Z,Z*- allylamines (711-713) (Table 17, entries 11and 12) could also be applied to 3,4-dihydroisoquinolinone syntheses (Table 21). Palladium catalysed cascade reaction of the allenes (703) (706) and (709), methyl 2-iodobenzoate (714) and ammonium

tartrate afforded dihydroisoquinolinones (715-717) in 61-71% yield as a single isomer. The stereochemistry was confirmed by NOE studies on (716a) (Figure 36).

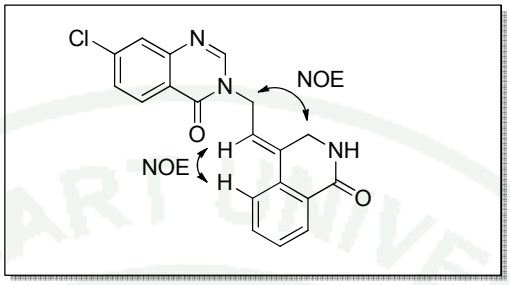
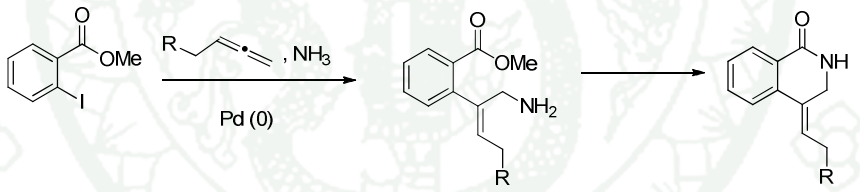


Figure 36 NOE correlation of (716a).

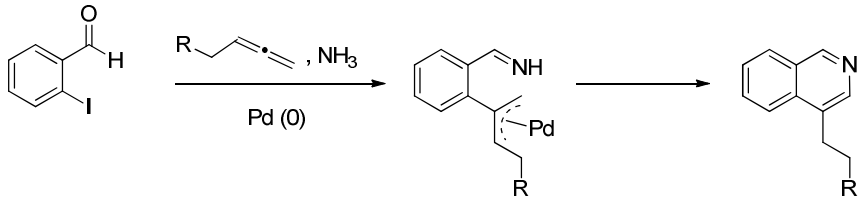
According to previous work (Scheme 109, literature review), the mechanism of the cascade reaction could proceed through an allylamine ester which undergoes intramolecular cyclisation to form dihydroisoquinolinone (Scheme 154).



Scheme 154

4.4 Cascade synthesis of complex isoquinoline

Cascade synthesis of complex isoquinoline (719-721) could be perform by replacing methyl-2-iodobenzoate (714) with 2-iodobenzaldehyde (718). The mechanism should be proceed through imine intermediate attach π-allyl palladium complex followed by isomerization to give isoquinoline (Scheme 155).



Scheme 155

Using our standard conditions (Table17, entry 11) we were able to generate isoquinolines (719-721) in 40-68% depending on the allene starting materials. In the case of quinazolinone allenes (706) and (709), the isoquinoline products (720-721) were obtained in 40-43% yield. Theobromine allene (703) gave a superior result (63-68%)(Table22, entries 3 and 4).

Attempts to improve the quinalolinone-isoquinoline (yield are shown in Table 19) by increasing the amount of ammonium tartrate (from 6 to 10 eq.) did not affect the yield of desired product (Table 23, entry 2), but when the reaction was perform in a sealed tube the yield increased to 52% (Table23, entry 3). Reaction of ammonium tartrate or citrate in a three solvent system, (2:1:1) dioxane:EtOH:H_2O gave improved results. The amount of ammonium salts did not affect the yield (Table 23, entries 4-6) but tribasic ammonium citrate gave the fastest reaction (Table 23, entry 6). In case of three solvent systems, pressure has an effect. When the reaction was heated under reflux no reaction was observed. When K_2CO_3 was removed from the reaction lower yield was obtained (Table 23, entry 7). We found that citrate reactions in a mixture of ethanol/water showed better results. Excess of the allene (Table23, entries 15-18) gave a higher yield than excess of 2-iodobenzaldehyde (Table 23, entry 9). Increase catalyst loading did not affect the yield but result a shorter reaction time (Table 23, entries 16 and 18).

CONCLUSIONS

1. Synthesis of Tamiflu®

We have accomplished an efficient synthesis of Tamiflu® from cheap and abundant, D-glucose in 19 steps with 0.76 % overall yield (through the (*4R, 5R)*-dihydroxyl diene intermediate) and 20 steps with 1.88 % overall yield (through (*4S, 5R*)-dihydroxyl diene intermediate). The key features included a new and efficient zinc mediated Bernett-Vasila-Barbier domino reaction of 5-deoxy-5-iodo-3-amino-3-deoxy-1,2-*O*-isopropylidine *xylo*furanose which was obtained from D-glucose to generate the corresponding diene. Ring closing olefin metathesis was employed to construct cyclohexene carboxylate core structure. 3-Pentyl ether was introduced via regio- and stereospecific ring opening of aziridine with 3-pentanol.

Moreover we have synthesized Tamiflu® intermediate using (–)-shikimic acid, possessing cyclohexene carboxylic acid skeleton in Tamiflu®. The main feature of the synthesis are introduction of 5α-amino group of Tamiflu® through azide free strategy, oxidation-reductive amination of 3,4-pentylidine ethyl shikimate to give the 5α-amino 3,4-pentylidine and regioselective reductive ring opening of the 5α -amino pentylidine finally provided 3-pentyloxy-4-hydroxy-5-amino ethyl shikimate.

2. Synthesis of naphthoquinone amides

Fifteen novel naphthoquinone aliphatic amides were synthesized in nine steps from commercially available 1-hydroxy-2-naphthoic acid with 9-25% overall yields. The key steps of this synthesis are alkylation of naphthyl bromide (355) with isobutylonitrile to install 2,2-dimethyl substituent as well as amino groups, amide formation using DMTMM as a condensing agent, oxidation of 1-hydroxynaphthalene to 1,4-naphthoquinone using Fremy's salt and hydroxylation reaction using TBHP, tritonB to install hydroxyl group to the naphthoquinone.

The synthetic naphthoquinone aliphatic amides were evaluated for cytotoxicity against human cancer cell lines, KB, NCI-H187 and MCF7 as well as against the Vero normal cell lines. From the result of their cytotoxicity test in correlation with their structures, naphthoquinone aliphatic amides with the shorter aliphatic chain length (C_3-C_6) showed lower anticancer activities than the longer ones (C_{11}-C_{18}) and the α-methyl substituent at aliphatic chain did not affect the anticancer activity. Naphthoquinone aliphatic amides showed cytotoxicity against KB, NCI-H187 and MCF-7 cancer cell lines with IC_{50} values of 5.12-101.86 μM, 4.8-89.62μM and 13.35-80.33μM, respectively. The anticancer activity of our synthetic naphthoquinone was performed by inhibition of the DNA TopoisomeraseII.

In comparison with naphthoquinone aliphatic esters (Hasitaphan, 2006), Naphthoquinone aliphatic amides with the chain length longer than 7-carbon atoms showed stronger anticancer activity than aliphatic esters whereas the amides with shorter aliphatic chain (less than 7-carbon atoms) showed less anticancer activity when compare to the esters ones. In conclusion, naphthoquinone aliphatic amides and esters showed stronger anticancer activity against KB cancer cell lines than the aromatic amides but weaker than the aromatic esters.

Fifteen naphthoquinone aliphatic amides were also tested for antimalarial activity against *Plasmodium falciparum*, K1 strain. The results revealed that naphthoquinone aliphatic amides with long aliphatic chain (C_{11}-C_{18}) and naphthoquinone aliphatic amide with C-7 and α-methyl substituent exhibited potent antimalarial activity with IC_{50} value ranging from 0.76-12.46 μM.

But in comparison with naphthoquinone aliphatic esters, naphthoquinone aliphatic amides revealed a less potent antimalarial activity in comparison to the esters (IC_{50} value 0.030-1.12 μM).

3. Synthesis of *N,O*-heterocycles

We have successful synthesized eleven *N-O* hetercyclic spiro compounds using 1,3-dipolar cycloaddition of azomethine ylide through decarboxylation route followed by 1,2-Meisenheimer rearrangement in a good yield, except compound (698) which was decomposed when treated with *m*-CPBA.

All synthetic *N-O* hetercyclic spiro compounds were screened for their antimalarial and anticancer activities. The only triple *N-O* heterocyclic (700) showed very good antimalarial activity (IC_{50} = 1.04 μM) and non-toxic to normal Vero cell. This is a good sign to develop for antimalarial drugs candidate in the future.

Seven *N-O* heterocyclic spiro compounds have shown moderate to weak cytotoxicity against KB cell lines (IC_{50} 24.45 to 120.78 μM) and mostly non-toxic to normal Vero cell.

4. Palladium catalyzed caccade reaction of allene

We have successfully synthesized eighteen examples of bis-(*Z,Z*) allylamines via a palladium calalysed three component cascade reaction of allenes, aryl halide and ammonia nucleophiles (ammonium tartrate or ammonium citrate) in moderate to high yield (40-82%).This methodology has been extended to the synthesis of five examples of 3,4-dihydroisoquinolone and three examples of isoquinolines in moderate yield (40-71%).

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APPENDIX

LIST OF APPENDIX CONTENTS

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An efficient synthesis of oseltamivir phosphate (Tamiflu) via a metal-mediated domino reaction and ring-closing metathesis

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ABSTRACT

An efficient synthesis of the influenza neuraminidase inhibitor prodrug oseltamivir phosphate (Tamiflu) from cheap, commercially available D-ribose is described. The main features of this approach comprise a metal (Zn, In)-mediated domino reaction and ring-closing olefin metathesis (RCM) of the resultant functionalized dienes to produce the Tamiflu skeleton. The synthesis described in this Letter represents a new and efficient transformation of a shikimic acid derivative into a 1,2-diamino compound which involved oxidation of an alcohol followed by reductive amination, regioselective ring opening of an amino pentylidene ketal and stereospecific nucleophilic replacement of a triflate with an azide.

Oseltamivir phosphate (Tamiflu, **1**) (Fig. 1) is used as an orally active drug for the treatment and the prevention of infections due to influenza viruses. Tamiflu is hydrolyzed by an esterase enzyme to the corresponding carboxylic acid, which is a potent inhibitor of neuraminidases A and B.[1] Recently, this compound was found to be active against the swine flu virus (H1N1 human flu) which has become a global influenza pandemic.[2] Many nations now have plans to stock a significant amount of this compound in case of a possible influenza outbreak. As a result, concerns have been raised about the capacity of the existing production process to meet world demand. These arise because the current manufacturing process uses (−)-shikimic acid as the starting compound which is not always readily available in consistently pure form.[3] Consequently, there has been intense effort from the chemical community in developing alternative approaches which start from cheap and readily available substrates.[4] The recent disclosure, by Chen and co-workers, of the synthesis of the title compound from the readily available and inexpensive D-ribose[5] prompts us to report our own efforts in the area.

As shown by our retrosynthetic analysis (Fig. 1), we envisioned installation of the cyclohexene ester core of Tamiflu via ring-closing metathesis of a diene generated by metal-mediated reductive elimination of an iodoribose derivative and in situ alkylation of an aldehyde intermediate by a metal allyl reagent. This diene can then be converted into the cyclohexene ester by ring-closing olefin metathesis (RCM).

The synthesis started from D-ribose with protection of the *syn*-1,2-dihydroxy group as the 3-pentylidene ketal **2** by reaction with 3-pentanone in methanolic saturated HCl solution and trimethyl orthoformate [$HC(OMe)_3$]. The alcohol **2** was then converted into the iodoribose derivative **3** in 79% yield by treatment with PPh_3 and iodine in the presence of imidazole (Scheme 1).[6]

We next examined the Bernet–Vasella domino reaction[7] of iodoribose derivative **3** in the presence of Zn and ethyl 2-(bromomethyl)acrylate. Activated zinc dust in THF under sonication conditions proved to be very reliable and consistently gave full conversion and a very high yield of the desired diene **4**. However, the reaction proceeded slowly in THF alone. The reactivity could be enhanced by addition of H_2O as a co-solvent.

The reaction of **3** with Zn in THF/H_2O (2:1) gave the desired diene **4** along with lactone **5** resulting from cyclization of hydroxy

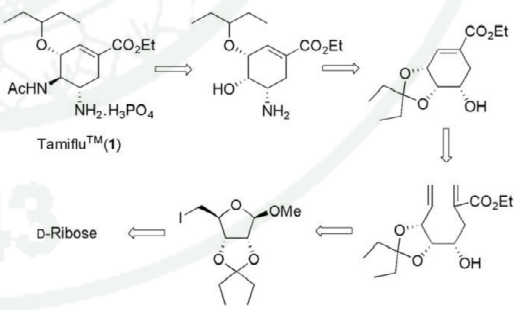

Figure 1. Retrosynthetic analysis of oseltamivir phosphate (**1**) from D-ribose via a 1,2-amino hydroxy intermediate.

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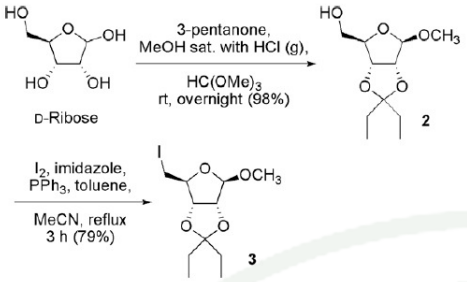
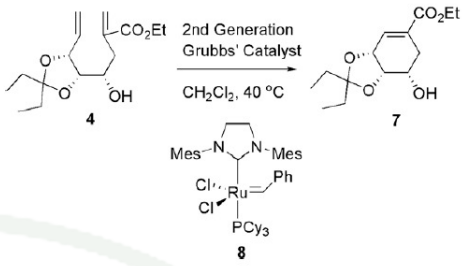


Scheme 1. Preparation of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (**3**).

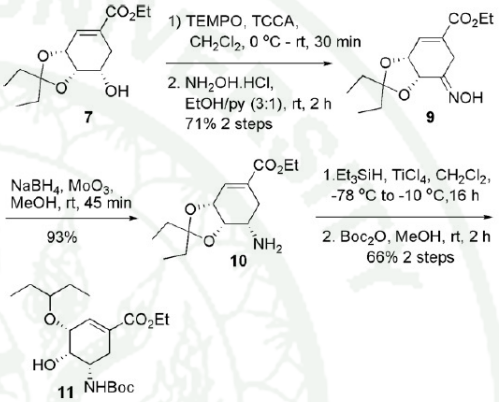


Scheme 2. Ring-closing metathesis (RCM) of diene **4**.

ester **4** (Table 1, entry 1). Besides zinc, the reaction with indium was also investigated. This reaction proceeded significantly slower than with zinc under the same conditions to give the desired diene and a substantial amount of the alkylated by-product **6** (entry 2). However the amount of by-product **6** could be reduced and the yield of **4** was improved significantly to 70% by the addition of acetic acid (0.01 equiv) and sonication until the intermediate aldehyde was formed (monitoring by TLC) before the introduction of ethyl 2-(bromomethyl)acrylate (entry 3).

Using the second-generation Grubbs' catalyst (**8**), the diene **4** underwent ring-closing metathesis to provide 5-*epi*-shikimic acid derivative **7** in 60% yield (Scheme 2). The ^{1}H and ^{13}C NMR spectra of **7** were in agreement with those reported by Chen and co-workers,[5] and hence the stereochemistry of **4** could be assigned (see Supplementary data). Moreover, we did not detect the other isomeric shikimic acid derivative during the RCM reaction, and thus compound **4** is a single stereoisomer.

Our strategy for the transformation of 5-*epi*-shikimic acid derivative **7** into the 1,2-diamino derivative was different from reports in the literature.[3a–d,8] The secondary hydroxy group of **7** was converted into an amino group by oxidation with TEMPO and trichloroisocyanuric acid (TCCA) to provide the corresponding ketone, followed by oxime formation and then reduction of the oxime with $NaBH_4$ catalyzed by MoO_3 to give 5-amino ketal **10**. Regioselective reductive ring opening of the 5-amino ketal was best performed employing a highly selective protocol (Et_3SiH and $TiCl_4$ in CH_2Cl_2 at −78 °C to −10 °C) as reported by scientists at Roche in their shikimic acid route.[3b] However, the hydroxy amino product was difficult to separate by column chromatography. Protection of the amino group with Boc anhydride made chromatographic separation of the protected product **11** much easier (Scheme 3).

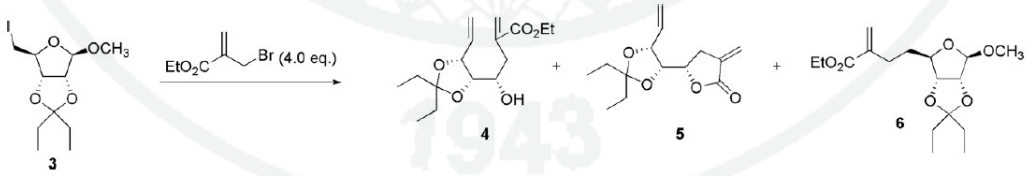


Scheme 3. Synthesis of amino alcohol **11**.

It is interesting to note that when the amino group of ketal **10** was *N*-Boc protected (**10a**), cleavage of the ketal group under the same reaction conditions gave the other regioisomer **11a** (Scheme 4).

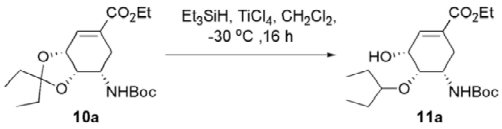
To transform the hydroxy amino compound **11** into the 1,2-diamino carboxylate **13**, the hydroxy group was activated as the triflate which was used in the next step without purification due to its instability (Scheme 5). The triflate underwent S_N2 displacement with sodium azide in acetone/water (9:1) to provide the azido amine **12** in good yield. The azide group of **12** was transformed directly into an acetamide by treatment with thioacetic acid and 2,6-

Table 1
Zinc- and indium-mediated elimination–allylation of **3**

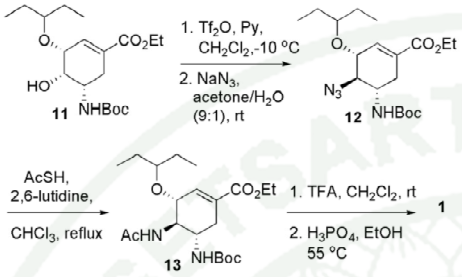


Entry	Metal	Reagents	Yield of **4**[b] (%)	Yield of **5**[b] (%)	Yield of **6**[b] (%)
1	Zn	THF/H_2O (2:1), sonicate, 50 °C, 3 h	71	22	—
2	In	THF/H_2O (2:1), sonicate, 50 °C, 3 h	45	—	30
3	In	THF/H_2O (2:1), AcOH sonicate, 50 °C, 1 h [a]	70	—	7

[a] AcOH (0.01 equiv) was added, the mixture was sonicated until the aldehyde intermediate formed (monitoring by TLC) then ethyl 2-(bromomethyl)acrylate was added and the reaction was sonicated for another 2 h.
[b] Isolated yield.



Scheme 4. Reductive opening of pentylidene ketal **10a**.



Scheme 5. Completion of the synthesis of oseltamivir phosphate (**1**).

lutidine in chloroform at reflux to afford **13** (44% yield, three steps from **11**).[9] Finally, the Boc protecting group of **13** was removed with TFA in CH_2Cl_2 to form an amine, which was directly exposed to 1.2 equiv of phosphoric acid in EtOH at 55 °C to afford oseltamivir phosphate (**1**) in 75% yield (two steps).

In summary, we have accomplished an efficient synthesis of oseltamivir phosphate in 14 steps and 5% overall yield, using cheap and abundant D-ribose as the starting material. The key features of the synthesis include the formation of an *epi*-shikimic acid ester by combining a metal-mediated domino reaction with ring-closing olefin metathesis (RCM). Moreover, transformation of the *epi*-shikimic acid derivative into a 1,2-diamino compound represents a new and efficient synthetic route for the synthesis of Tamiflu which has the potential to be developed as an industrial process in the future.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.044.

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Original article

Synthesis of novel naphthoquinone aliphatic amides and esters and their anticancer evaluation

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ABSTRACT

Fourteen new naphthoquinone aliphatic amides and seventeen naphthoquinone aliphatic esters were synthesized in nine to ten steps from 1-hydroxy-2-naphthoic acid with 9–25% overall yield for the amides, and 16–21% overall yield for the esters. The key step of the amide synthesis is a coupling reaction between amine and various aliphatic acids using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) as a coupling agent while for the ester synthesis, DCC/DMAP or CDI was used as the coupling reagent between aliphatic acids and naphthoquinone alcohol. Both naphthoquinone amides and esters were evaluated for their anticancer activity against KB cells. It was found that naphthoquinone aliphatic amides showed stronger anticancer activity than those of the esters when the chains are longer than 7-carbon atoms. The optimum chain of amides is expected to be 16-carbon atoms. In addition, naphthoquinone aliphatic esters with α-methyl on the ester moiety possessed much stronger anticancer activity than the straight chains. Decatenation assay revealed that naphthoquinone amide with 16-carbon atoms chain at 15 μM and 20 μM can completely inhibit hTopoIIα activity while at 10 μM the enzyme activity was moderately inhibited. Molecular docking result also showed the same trend as the cytotoxicity and decatenation assay.

1. Introduction

Rhinacanthins (1,4-naphthoquinone) and Rhinacanthone (1,2-naphthoquinone) isolated from *Rhinacanthus nasutus* (Thai name: Thong Pan Chang) (Acanthaceae) showed biological activities [1–5], especially anticancer activity. Studies on apoptosis mechanism of rhinacanthins and rhinacanthone were investigated [5]. Because of very interesting anticancer activity of rhinacanthins and rhinacanthone, we have synthesized rhinacanthins [6], rhinacanthone, 1,2-pyrano, 1,4-pyrano and furanonaphthoquinones [7], naphthoquinone aromatic and aliphatic esters [6,8] and naphthoquinone 2′-cyclopentyl and 2′-cyclohexyl esters [9]. Most of them exhibited anticancer activity especially naphthoquinone aromatic esters, whereas some aliphatic esters showed very good antimalarial activity with lesser or no toxicity against Vero cells [8]. In addition, it was found that 2′,2′-dimethyl substituents on the propyl chain showed more potent activity than those of other 2′,2′-substituents [9]. This was the reason why novel naphthoquinone aromatic amides with 2′,2′-dimethyl groups were synthesized and evaluated for anticancer activity [10]. Although it was revealed that naphthoquinone aromatic amides exhibited less anticancer activity than those of aromatic esters with 2′,2′-dimethyl substituents [8], it is still worthwhile to further synthesize novel naphthoquinone aliphatic amides, as well as to evaluate their anticancer activity in comparison with those of the aromatic amides and the aliphatic esters, and to compare them with those of the naphthoquinone ester and amide series.

Therefore this paper describes the synthesis of fourteen novel naphthoquinone aliphatic amides and seventeen naphthoquinone aliphatic esters starting from commercially available 1-hydroxy-2-naphthoic acid in nine to ten steps. All thirty-one synthetic aliphatic amides and esters were tested for cytotoxicity against KB cells and normal Vero cells in comparison with the aromatic ones. According to our previous work on naphthoquinone esters and amides [6,10], the compound exhibited the TopoII inhibition activity in corresponding with β-lapachone (1,2-naphthoquinone) and related naphthoquinones [11]. Therefore, in this paper, the decatenation assay for human Topoisomerase IIα and molecular

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docking analysis of some selected naphthoquinone compounds were also carried out.

2. Results and discussion

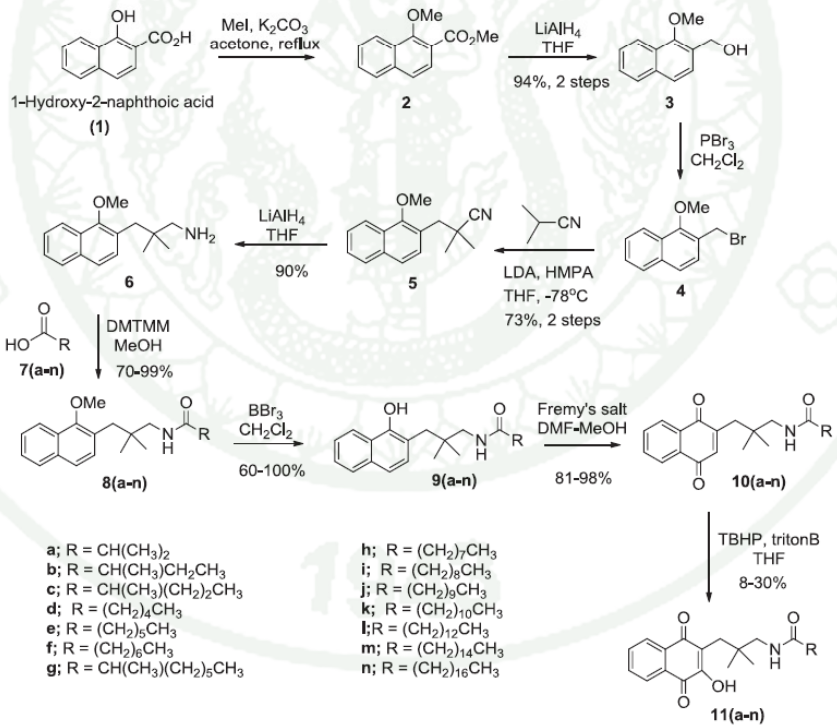
2.1. Synthesis

A series of naphthoquinone aliphatic amides was synthesized and investigated for their anticancer activity. Methylation of 1-hydroxy-2-naphthoic acid (**1**) followed by reduction, bromination, alkylation and then reduction provided amine **6** [10]. Coupling reactions between **6** and various aliphatic acids **7a–n** were done using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) in methanol to give various amides **8a–n** with good to excellent yields (70–99% yield). Then demethylation using boron tribromide gave naphthol amides **9a–n** with various acyl groups in moderate to quantitative yield. The target naphthoquinone aliphatic amides **11a–n** (Scheme 1), were obtained by oxidation of **9a–n** with Fremy's salt followed by hydroxylation with *tert*-butyl hydroperoxide (TBHP). It was found that the hydroxylation step of naphthoquinone aliphatic amides gave lower yields than those of aromatic amides [10]. This may be accounted for by the easier hydrolysis of the aliphatic amide group than the aromatic amide group (less electrophilicity) under basic condition. In comparison to the aliphatic amides, seventeen naphthoquinone aliphatic esters were also synthesized by the same method as used in our previous report [8] (Scheme 2) and their anticancer activity was also determined.

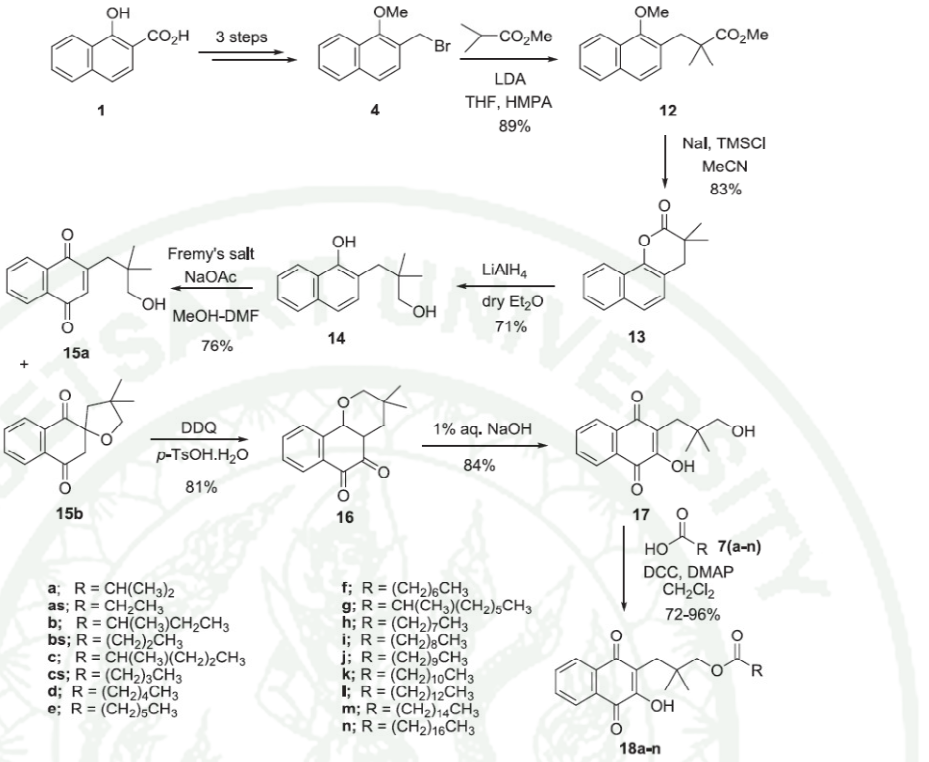
2.2. Biological activity

Fourteen novel synthetic naphthoquinone aliphatic amides and seventeen naphthoquinone aliphatic esters were evaluated for their cytotoxicity against human cancer cell lines KB (oral cavity cancer) by the REsazurin Microplate Assay (REMA) [12] and normal Vero cell lines by green fluorescent protein (GFP)-based assay [13]. The results are shown in Tables 1 and 2.

Tables 1 and 2 demonstrate anticancer activity against KB cells of naphthoquinone aliphatic amides and esters, respectively. The results showed that chain lengths of amide and ester moieties affected the anticancer activities. It can be seen that when the chain lengths are between 3- to 7-carbon atoms, the ester series (**18a–e**, IC_{50} = 1.76–41.01 μM) inhibited KB cells stronger than the amide series (**11a–e**, IC_{50} = 28.21–101.86 μM). With the exception of amide **11d** and ester **18d** which showed similar results (IC_{50} values of 40.23 and 41.01 μM, respectively). With respect to the aliphatic amides, in contrast to those with shorter chain lengths, the longer chain aliphatic amides with more than 7-carbon atoms showed more potent anticancer activities. For example, amide **11f** (IC_{50} = 24.64 μM) with an 8-carbon atoms showed stronger activity than ester **18f** (IC_{50} = 38.29 μM) and amides **11m** (16-carbon atoms) and **11n** (18-carbon atoms) exhibited very strong activity with IC_{50} values of 5.12 and 6.35 μM, respectively, whereas esters **18m** (16-carbon atoms) and **18n** (18-carbon atoms) showed much lesser anticancer activities. However, it is interesting to note that these two esters (**18m** and **18n**) showed very good antimalarial activity, which has been described in our previous paper [8].



Scheme 1. Synthesis of naphthoquinone aliphatic amides **11a–n**.



Scheme 2. Synthesis of naphthoquinone aliphatic esters **18a–n**.

Regarding to the results, amides having 16- and 18-carbon atoms chains could be the optimal chain length for the anticancer activity.

Interestingly, the esters containing α-methyl on the chain inhibited cancer cells stronger than those of the ones without α-methyl group whereas no difference of the amide series was detected. In the same manner, most of naturally occurring naphthoquinone aliphatic esters containing α-methyl isolated from *R. nasutus* such as rhinacanthin-C, G, H, and K (Fig. 1) showed potent anticancer activities [3]. Therefore, it would be very useful for further comparison with and without α-methyl group on the aliphatic chain of the ester series.

Table 2 shows that naphthoquinone aliphatic esters with α-methyl on the chain (**18a**, **18b**, **18c** and **18g**, IC_{50} = 14.38, 4.65, 1.76, 16.78 μM, respectively) exhibited more potent cytotoxicity than the naphthoquinone esters without α-methyl group given with the same chain lengths (**18as**, **18bs**, **18cs** and **18f**, IC_{50} = 84.40, 42.98, 27.79, 38.29 μM, respectively).

According to our findings, it is evident that naphthoquinone aliphatic amides showed stronger anticancer activity than the aromatic amides [10] and aliphatic esters. In order to gain further understanding on structure–activity relationship (SAR), some naphthoquinone aliphatic amides and esters (i.e. **11c**, **11m**, **18c** and **18m**) were selected for the evaluation of human Topoisomerase IIα (hTopoIIα) inhibition and for molecular docking analysis.

2.3. Human Topoisomerase IIα inhibitory activity

The decatenation assay was used to determine the inhibitory activity of novel naphthoquinone aromatic amides and esters versus hTopoIIα. Enzyme hTopoIIα catalyzes the ATP-dependent decatenation of long-chain, catenated DNA molecules into free relaxed and supercoiled forms [14]. Fig. 2 shows hTopoIIα inhibitory activity against four selected compounds (**11c**, **11m**, **18c** and **18m**) at final concentration of 50 μM. It can be clearly seen that compound **11m**, which is a naphthoquinone aliphatic amide with 16-carbon atoms side chain long, exhibited strong hTopoIIα inhibitory activity while compound **18m**, a naphthoquinone aliphatic ester with 16-carbon atoms side chain long, can moderately inhibit the hTopoIIα activity. This result correlated well with the cytotoxicity test in that aliphatic amides with long carbon side chains showed better cytotoxicity compared to the aliphatic esters. In contrast to the naphthoquinone aliphatic ester or amide containing a long side chain, those with shorter side chains, such as compounds **11c** and **18c**, displayed low hTopoIIα inhibitory activity. However, by comparing between the naphthoquinone aliphatic ester and amide with short side chains, the naphthoquinone aliphatic ester can inhibit hTopoIIα activity better than the naphthoquinone aliphatic amide. Therefore, the trend of hTopoIIα inhibition activity is altered when the aliphatic side chain grows. Taken together, it can be concluded that with the short side chain, the naphthoquinone aliphatic ester is a better hTopoIIα inhibitor

Table 1
Cytotoxicity of the synthetic naphthoquinone aliphatic amides **11a–n** against KB cells and normal Vero cells.

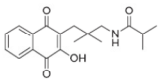
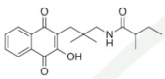
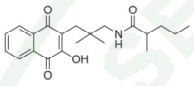
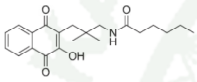
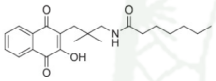
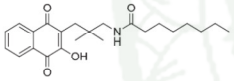
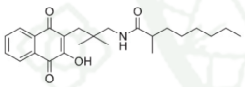
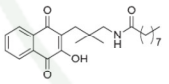
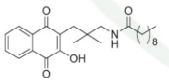
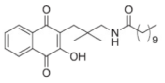
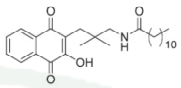
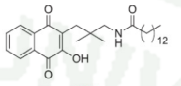
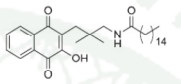
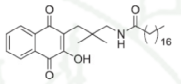
Compounds	IC_{50} (μM)[a]	
	Anticancer (KB cells)	Cytotoxicity to primary cells (Vero cells)
 **11a**	94.63	Non-cytotoxic
 **11b**	101.86	Non-cytotoxic
 **11c**	47.08	48.09
 **11d**	40.23	46.58
 **11e**	28.21	24.82
 **11f**	24.64	18.42
 **11g**	23.73	15.54
 **11h**	19.65	16.67
 **11i**	18.50	15.04
 **11j**	17.63	14.92

Table 1 (*continued*)

Compounds	IC_{50} (μM)[a]	
	Anticancer (KB cells)	Cytotoxicity to primary cells (Vero cells)
 **11k**	12.82	13.86
 **11l**	25.10	9.81
 **11m**	5.12	5.60
 **11n**	6.35[b]	5.76[b]
Doxorubicin[c]	0.96	23.94

KB, human epidermoid carcinoma.
[a] Data are typical values from six replicate experiments.
[b] Partially soluble in 100% DMSO.
[c] Used as a reference.

Table 2
Cytotoxicity of the synthetic naphthoquinone aliphatic esters **18a–n** against KB cells and normal Vero cells.

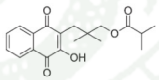
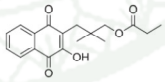
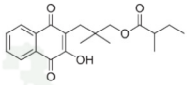
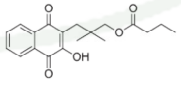
Compounds	IC_{50} (μM)[a]	
	Anticancer (KB cells)	Cytotoxicity to primary cells (Vero cells)
 **18a**	14.38	123.10
 **18as**	84.40	60.06
 **18b**	4.65	0.87
 **18bs**	42.98	73.16

Table 2 (*continued*)

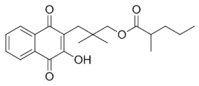
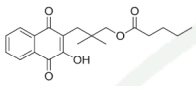
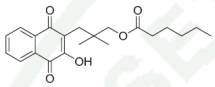
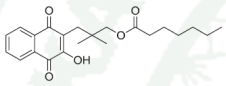
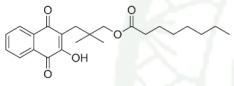
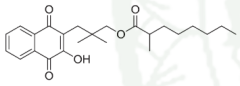
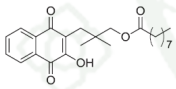
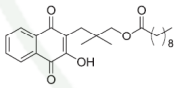
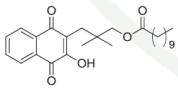
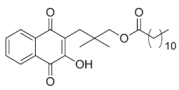
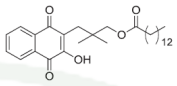
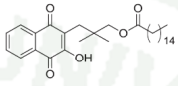
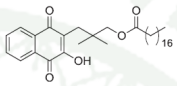
Compounds	IC_{50} (μM)[a]	
	Anticancer (KB cells)	Cytotoxicity to primary cells (Vero cells)
 **18c**	1.76	0.12
 **18cs**	27.79	7.84
 **18d**	41.01	169.07
 **18e**	14.42	99.34
 **18f**	38.29	>258.75
 **18g**	16.78	0.45
 **18h**	38.70	149.81
 **18i**	55.48	202.64
 **18j**	54.83	>233.34
 **18k**	35.70	248.54

Table 2 (*continued*)

Compounds	IC_{50} (μM)[a]	
	Anticancer (KB cells)	Cytotoxicity to primary cells (Vero cells)
 **18l**	51.36	58.43
 **18m**	27.07	4.41
 **18n**	76.66	15.51
Doxorubicin[b]	0.96	23.94

KB, human epidermoid carcinoma.
[a] Data are typical values from six replicate experiments.
[b] Used as a reference.

than the naphthoquinone aliphatic amide. However, when the side chain is extended, the naphthoquinone aliphatic amide becomes a potent hTopoIIα inhibitor.

To gain better understanding in structure–activity relationship, compound **11m** was further evaluated for hTopoIIα inhibitory activity at lower concentrations (5, 10, 15 and 20 μM) as shown in Fig. 3. The compound can completely inhibit hTopoIIα activity at final concentrations of 15 μM and 20 μM while moderately reducing hTopoIIα activity at final concentration of 10 μM. However, the compound did not show any hTopoIIα inhibitory activity at final concentration of 5 μM compared to doxorubicin at the same concentration. In comparison with our previous naphthoquinone aromatic amides [10], it can be clearly seen that naphthoquinone aliphatic amide **11m** is a better hTopoIIα inhibitor than naphthoquinone aromatic amides. Therefore, molecular docking of some selected naphthoquinone aliphatic amides and esters was performed in order to obtain an insight into the binding of the compounds to DNA binding domain of hTopoIIα.

2.4. Molecular docking analysis

According to our previous work [6,10], naphthoquinone aromatic amides and esters were found to bind at the DNA binding domain of hTopoIIα. The different spatial arrangement between naphthoquinone aromatic amides containing phenyl and naphthyl groups was observed while for naphthoquinone aromatic esters the quinone ring was found lying on the right-hand side and the propyl chain pointing down. With difference in structural rigidity between naphthoquinone aromatic amides/esters and the aliphatic ones, molecular docking analysis of hTopoIIα with selected naphthoquinone aromatic amides and esters was then carried out.

According to Fig. 4, in compounds **11c** and **18c**, the carbonyl groups of the amide and ester form hydrogen bonds with R804 located near the active site Y805. The distance between hydrogen bond donor and acceptor for compound **11c** is slightly longer than compound **18c**, indicating a weaker hydrogen bonding interaction. The amino acid R804 is conserved among TopoII family and the

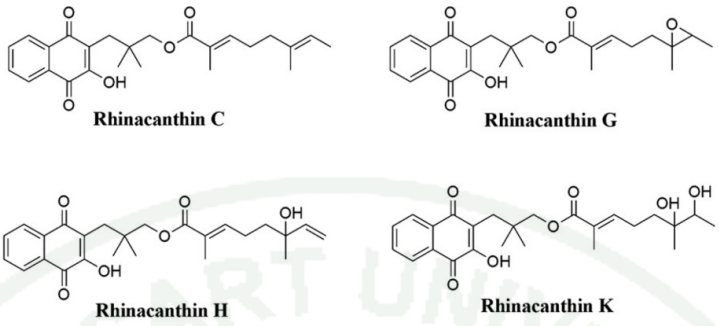


Fig. 1. Structures of rhinacanthin-C, -G,-H, and -K.

R804A mutation decreased decatenation and DNA cleavage activity about 5 and 10 folds, respectively [15]. Unlike compounds **11c** and **18c**, compounds **11m** and **18m** bound to hTopoIIα with slightly different orientation. Compound **11m** forms hydrogen bond with K798 while no hydrogen bonding is observed in compound **18m** which may relate to the weaker hTopoIIα inhibition compared to compound **11m**. Residues K798 and R804 are solvent-accessible positively-charged residues located at a loop near DNA recognition helix α4 of the HTH motif [16]. Collectively, our docking result correlated well with that of cytotoxicity assay and hTopoIIα inhibitory activity in that naphthoquinone aliphatic amide with longer chain is a better inhibitor than the ester while with the shorter chain length, the naphthoquinone aliphatic ester is a more potent inhibitor than the amide.

3. Conclusion

Fourteen new naphthoquinone amides and seventeen naphthoquinone aliphatic esters were synthesized and evaluated for anticancer activity. Naphthoquinone aliphatic amides were synthesized from 1-hydroxy-2-naphthoic acid in 9 steps whereas naphthoquinone aliphatic esters were synthesized as described in the previous report [8]. Naphthoquinone aliphatic amides with the shorter length of aliphatic chain (3- to 7-carbon atoms) demonstrated less anticancer activity than those of aliphatic ones with the longer chains than 7-carbon atoms. Naphthoquinone aliphatic amides with the chain length, longer than 7-carbon atoms showed stronger anticancer activity than aliphatic esters containing linear chains of the same number of carbons. The optimum aliphatic chain of amides, 16- and 18-carbon atoms, displayed very good anticancer activity. In comparison with the aromatic amides, the aliphatic amides showed stronger activity. However, among these, naphthoquinone aromatic esters [6] showed the strongest activity. For the ester series, α-methyl substituent of the aliphatic chain had a pronounced effect on anticancer activity than those without α-methyl group. The decatenation assay revealed that naphthoquinone amide **11m** can inhibit hTopoIIα activity at 10 μM, which was much better than previously reported naphthoquinone aromatic amides. Therefore, further development of this compound can lead to a potent hTopoIIα inhibitor.

4. Experimental section

4.1. Chemistry

The starting material, 1-hydroxy-2-naphthoic acid, was purchased from FLUKA. All reagents were obtained from FLUKA, MERCK, ACROSS and ALDRICH. Solvents were dried by distillation from the appropriate drying reagents immediately prior to use. Tetrahydrofuran and ether were distilled from sodium and benzophenone under nitrogen atmosphere. Dichloromethane was distilled from calcium hydride under nitrogen. Dimethylformamide was distilled under reduced pressure and stored over Type 3 Å molecular sieves. Moisture- and air-sensitive reactions were carried out under an atmosphere of nitrogen. Analytical thin-layer chromatography (TLC) was conducted using Merck TLC aluminum sheet (silica gel 60 F_{254}). Compounds were visualized by ultraviolet light and/or by heating the plate after dipping in a 1% solution of vanillin

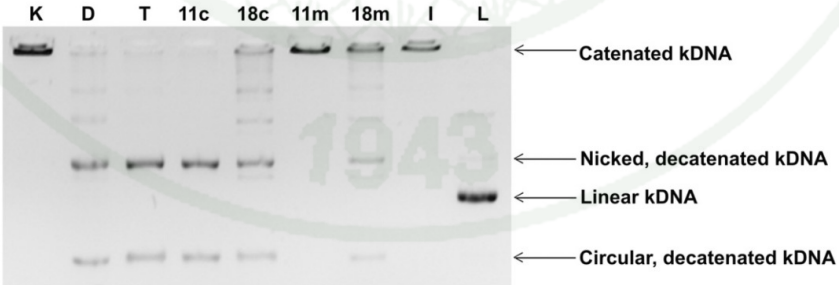


Fig. 2. Topoisomerase IIα inhibitory activity of naphthoquinone aliphatic amides (**11c**, **11m**) and naphthoquinone aliphatic esters (**18c**, **18m**). The compounds were examined in final concentration of 50 μM. Lanes K: kDNA only, lane D: decatenated kDNA only, lane T: kDNA + hTopoIIα, lanes **11c**, **18c**, **11m** and **18m**: kDNA + hTopoIIα + compounds **11c**, **18c**, **11m** and **18m**, respectively, lane I: kDNA + hTopoIIα + 50 μM doxorubicin and lane L: linearized kDNA marker. Catenated kDNA does not migrate out of the loading wells.

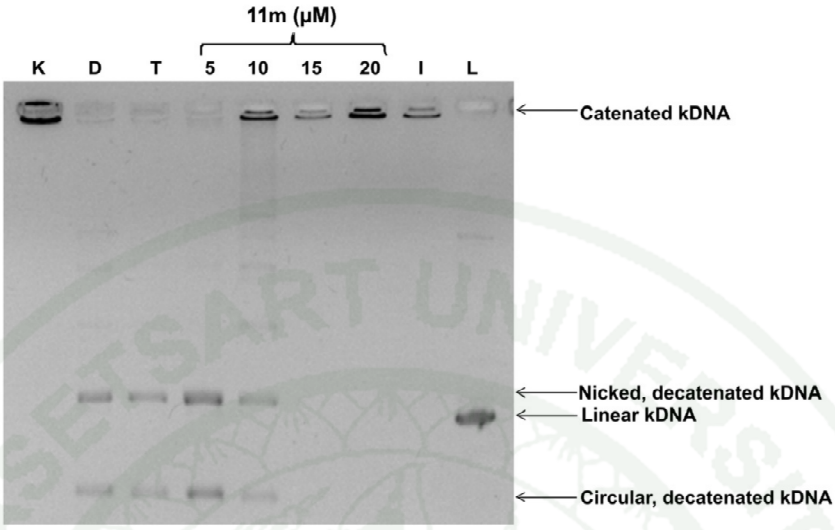


Fig. 3. Topoisomerase IIα inhibitory activity of compound **11m** at various concentrations. The compound was examined in final concentration of 5, 10, 15 and 20 μM, respectively, as designated. Lanes K: kDNA only, lane D: decatenated kDNA only, lane T: kDNA + hTopoIIα, Lane 5, 10, 15, and 20: kDNA + hTopoIIα + compounds **11m** at 5, 10, 15 and 20 μM, respectively, lane I: kDNA + hTopoIIα + 5 μM doxorubicin and lane L: linearized kDNA marker. Catenated kDNA does not migrate out of the loading wells.

in 0.1 M sulfuric acid in ethanol. Flash column chromatography was performed on silica gel (230–400 mesh, Merck 9385). Infrared (IR) spectra were recorded on a Perkin–Elmer 2000 Fourier transform infrared spectrophotometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using a Bruker AVANCE 300 MHz spectrometer and VARIAN^{UNITY} INOVA 400 MHz spectrometer. Amine **6** and naphthoquinone aliphatic esters **18a**–**n** were prepared as described in previous reports [8,10].

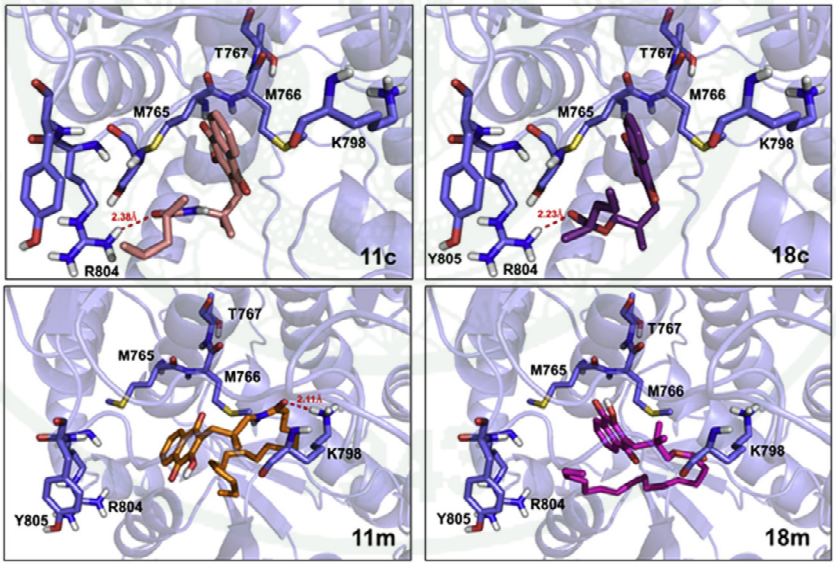


Fig. 4. H-bond interaction observed in DNA-binding domain of hTopoIIα. The amino acids of hTopoIIα are depicted in stick representation and colored by the atom type (carbon, blue slate; oxygen, red; hydrogen, white and nitrogen, blue). The dotted red lines represent the hydrogen bonding interaction. Compounds **11c**, **18c**, **11m** and **18m** are shown in stick and colored by the atom type (carbon, salmon, deep purple, orange, magenta respectively; oxygen, red; hydrogen, white and nitrogen, blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.2. Synthetic procedures

4.2.1. General procedure for amide coupling

To a mixture of amine **6** (1 mmol) and carboxylic acids **7a–n** (1.1 mmol) in methanol (10 mL) was added 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (1.1 mmol). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, and then the residue was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give *N*-[3-(1-methoxy-2-naphthyl)-2,2-dimethylpropyl]amide (**8a–n**). All spectroscopic data of compounds **8a–n** are shown in the Supplementary data.

4.2.2. General procedure for demethylation reaction of N-[3-(1-methoxy-2-naphthyl)-2,2-dimethylpropyl] amide (8a–n)

To a solution of *N*-[3-(1-methoxy-2-naphthyl)-2,2-dimethylpropyl] amide (**8a–n**) (1 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C was slowly added BBr_3 (2 mmol). The reaction mixture was warmed to room temperature and stirred under nitrogen atmosphere for 3 h. Water was added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give *N*-[3-(1-hydroxy-2-naphthyl)-2,2-dimethylpropyl] amide (**9a–n**). The crude product was used in the next step without further purification.

4.2.3. General procedure for Fremy's salt oxidation reaction of N-[3-(1-hydroxy-2-naphthyl)-2,2-dimethylpropyl] amide (9a–n)

To a solution of *N*-[3-(1-hydroxy-2-naphthyl)-2,2-dimethylpropyl] amide (**9a–n**) (1 mmol) in MeOH (10 mL) and DMF (30 mL) was added NaOAc (1 M, 10 mL) followed by Fremy's salt (6 mmol) in water (20 mL). After stirring at room temperature for 12 h, the reaction mixture was extracted with diethyl ether. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, ethyl acetate:hexane, 1:2) to give the *N*-[3-(1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] amide (**10a–n**). All spectroscopic data of compounds **10a–n** are shown in the Supplementary data.

4.2.4. General procedure for hydroxylation reaction of N-[3-(1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] amide (10a–n)

To a solution of *N*-[3-(1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] amide (**10a–n**) (1 mmol) in THF (13 mL), was added TBHP (12 mmol) followed by triton B (3 mmol) until the solution turned red. The reaction mixture was stirred at room temperature for 20 min and then 10% HCl was added until the solution turned yellow. The mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, ethyl acetate:hexane, 1:2) to give *N*-[3-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] amide (**11a–n**).

4.2.4.1. N-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]-2-methylpropanamide (11a).

Flash column chromatography, eluting with 2:1 hexane:ethyl acetate afforded the product **11a** (9%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals, mp 127–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 8.08 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.76 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.69 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 6.92 (t, *J* = 6.7 Hz, 1H, NH), 2.91 (d, *J* = 6.7 Hz, 2H, CH_2N), 2.53 (s, 2H, CH_2Ar), 2.50 (heptet, *J* = 6.9 Hz, 1H, CH), 1.24 (d, *J* = 6.9 Hz, 6H, 2× CH_3), 0.95 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0 (C=O), 180.9 (C=O), 177.2 (C=O), 155.0 (Ar), 135.1 (ArH), 133.3 (ArH), 132.8 (Ar), 129.3 (Ar), 127.1 (ArH), 126.3 (ArH), 121.6 (Ar), 46.8 (CH_2), 38.2 (C), 36.1 (CH), 31.9 (CH_2), 26.2 (2× CH_3), 19.8 (2× CH_3); IR (KBr) = 3291 (NH), 2968, 2930 (CH), 1668, 1641, 1624 (C=O), 1595, 1577 (C=C), 1272 (C–N), 1216 (C–O); HRMS (ESI^+): *m*/*z* [M + Na] calcd for $C_{19}H_{23}NNaO_4$: 352.1519, found: 352.1517.

4.2.4.2. N-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]-2-methylbutanamide (11b).

Flash column chromatography, eluting with 2:1 hexane:ethyl acetate afforded the product **11b** (11%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals, mp 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 8.07 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.75 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.68 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 6.95 (t, *J* = 6.7 Hz, 1H, NH), 2.99–2.87 (m, 2H, CH_2N), 2.52 (s, 2H, CH_2Ar), 2.32–2.22 (m, 1H, CH), 1.80–1.68 (m, 1H, CH_2), 1.56–1.43, (m, 1H, CH_2), 1.21 (d, *J* = 6.9 Hz, 3H, CH_3), 0.95–0.94 (overlapping, 9H, 3× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0 (C=O), 180.9 (C=O), 176.9 (C=O), 155.1 (Ar), 135.1 (ArH), 133.2 (ArH), 132.7 (Ar), 129.3 (Ar), 127.1 (ArH), 126.3 (ArH), 121.5 (Ar), 47.0 (CH_2), 43.6 (CH), 38.1 (C), 31.8 (CH_2), 27.3 (CH_2), 26.2 (2× CH_3), 17.6 (CH_3), 12.0 (CH_3); IR (KBr) = 3294 (NH), 2967, 2920, 2873 (CH), 1668, 1641, 1623 (C=O), 1596, 1566 (C=C), 1272 (C–N), 1215 (C–O); HRMS (ESI^+): *m*/*z* [M + Na] calcd for $C_{20}H_{25}NNaO_4$: 366.1676, found: 366.1692.

4.2.4.3. N-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]-2-methyl pentanamide (11c).

Flash column chromatography, eluting with 2:1 hexane:ethyl acetate afforded the product **11c** (21%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals, mp 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (ddd, *J* = 7.6, 1.4, 0.4 Hz, 1H, ArH), 8.03 (ddd, *J* = 7.6, 1.4, 0.4 Hz, 1H, ArH), 7.71 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.64 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 6.84 (t, *J* = 6.7 Hz, 1H, NH), 2.93–2.82 (m, 2H, CH_2N), 2.48 (s, 2H, CH_2Ar), 2.33–2.25 (m, 1H, CH), 1.70–1.63 (m, 1H, CH_2), 1.39–3.28 (m, 1H + 2H, CH_2), 1.16 (d, *J* = 6.9 Hz, 3H, CH_3), 0.90 (s, 6H, 2× CH_3), 0.87 (t, *J* = 7.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0 (C=O), 180.9 (C=O), 176.8 (C=O), 155.1 (Ar), 135.0 (ArH), 133.2 (ArH), 132.8 (Ar), 129.4 (Ar), 127.1 (ArH), 126.3 (ArH), 121.6 (Ar), 46.9 (CH_2), 41.8 (CH), 38.1 (C), 36.5 (CH_2), 31.8 (CH_2), 26.1 (2× CH_3), 20.7 (CH_2), 18.0 (CH_3), 14.0 (CH_3); IR (KBr) = 3295 (NH), 2963, 2930, 2871 (CH), 1669, 1642, 1623 (C=O), 1596, 1566 (C=C), 1271 (C–N), 1215 (C–O); HRMS (ESI^+): *m*/*z* [M + Na] calcd for $C_{21}H_{27}NNaO_4$: 380.1832, found: 380.1836.

4.2.4.4. N-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] hexanamide (11d).

Flash column chromatography, eluting with 2:1 hexane:ethyl acetate afforded the product **11d** (22%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals, mp 79–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 8.04 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.72 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.65 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.53 (s, 1H, OH), 6.79 (t, *J* = 6.8 Hz, 1H, NH), 2.87 (d, *J* = 6.8 Hz, 2H, CH_2N), 2.48 (s, 2H, CH_2Ar), 2.24 (t, *J* = 7.5 Hz, 2H, CH_2CO), 1.66 (quintet, *J* = 7.5 Hz, 2H, CH_2), 1.35–1.27 (m, 4H, 2× CH_2), 0.91 (s, 6H, 2× CH_3), 0.86 (t, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0 (C=O), 180.9 (C=O), 173.4 (C=O), 155.0 (Ar), 135.1 (ArH), 133.2 (ArH), 132.8 (Ar), 129.3 (Ar), 127.1 (ArH), 126.3 (ArH), 121.6 (Ar), 47.1 (CH_2), 38.1 (C), 37.2 (CH_2), 31.9 (CH_2), 31.6 (CH_2), 26.2 (2× CH_3), 25.6 (CH_2), 22.4 (CH_2), 14.0 (CH_3); IR (KBr) = 3357 (NH), 2960, 2924, 2855 (CH), 1673, 1660, 1632 (C=O), 1594, 1578, 1550 (C=C), 1273 (C–N), 1216 (C–O); HRMS (ESI^+): *m*/*z* [M + Na] calcd for $C_{21}H_{27}NNaO_4$: 380.1832 found 380.1850.

*4.2.4.5. N-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] heptanamide (**11e**).* Flash column chromatography, eluting with 2:1 hexane:ethyl acetate afforded the product **11e** (10%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals, mp 85–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (dd, J = 7.6, 1.4 Hz, 1H, ArH), 8.13 (dd, J = 7.6, 1.4 Hz, 1H, ArH), 7.81 (td, J = 7.6, 1.4 Hz, 1H, ArH), 7.74 (td, J = 7.6, 1.4 Hz, 1H, ArH), 7.63 (s, 1H, OH), 6.87 (t, J = 6.8 Hz, 1H, NH), 2.96 (d, J = 6.8 Hz, 2H, CH_2N), 2.57 (s, 2H, CH_2Ar), 2.32 (t, J = 7.8 Hz, 2H, CH_2CO), 1.74 (quintet, J = 7.8 Hz, 2H, CH_2), 1.47–1.31 (m, 6H, 3× CH_2), 0.99 (s, 6H, 2× CH_3), 0.92 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0 (C=O), 180.9 (C=O), 173.3 (C=O), 155.0 (Ar), 135.1 (ArH), 133.2 (ArH), 132.8 (Ar), 129.3 (Ar), 127.1 (ArH), 126.3 (ArH), 121.6 (Ar), 47.1 (CH_2), 38.1 (C), 37.3 (CH_2), 31.9 (CH_2), 31.6 (CH_2), 29.4 (CH_2), 26.2 (2× CH_3), 25.9 (CH_2), 22.5 (CH_2), 14.0 (CH_3); IR (KBr) = 3358 (NH), 2928, 2870 (CH), 1673, 1632 (C=O), 1594, 1578, 1549 (C=C), 1274 (C–N), 1216 (C–O); HRMS (ESI^+): m/z [M + Na] calcd for $C_{22}H_{29}NNaO_4$: 394.1989, found: 394.2008.

*4.2.4.6. N-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl] octanamide (**11f**).* Flash column chromatography, eluting with 2:1 hexane:ethyl acetate afforded the product **11f** (13%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals, mp 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (dd, J = 7.6, 1.4 Hz, 1H, ArH), 8.06 (dd, J = 7.6, 1.4 Hz, 1H, ArH), 7.74 (td, J = 7.6, 1.4 Hz, 1H, ArH), 7.67 (td, J = 7.6, 1.4 Hz, 1H, ArH), 6.85 (t, J = 6.3 Hz, 1H, NH), 2.92 (d, J = 6.3 Hz, 2H, CH_2N), 2.53 (s, 2H, CH_2Ar), 2.27 (t, J = 7.7 Hz, 2H, CH_2CO), 1.70 (quintet, J = 7.7 Hz, 2H, CH_2), 1.40–1.21 (m, 8H, 4× CH_2), 0.95 (s, 6H, 2× CH_3), 0.86 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0 (C=O), 180.9 (C=O), 173.4 (C=O), 155.1 (Ar), 135.1 (ArH), 133.2 (ArH), 132.8 (Ar), 129.4 (Ar), 127.1 (ArH), 126.3 (ArH), 121.6 (Ar), 47.1 (CH_2), 38.0 (C), 37.3 (CH_2), 31.9 (CH_2), 31.7 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 26.2 (2× CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3); IR (KBr) = 3355 (NH), 2957, 2925, 2853 (CH), 1671, 1632 (C=O), 1594, 1578, 1551 (C=C), 1274 (C–N), 1216 (C–O); HRMS (ESI^+): m/z [M + Na] calcd for $C_{23}H_{31}NNaO_4$: 408.2145, found: 408.2152.

*4.2.4.7. N-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]-2-methyl octanamide (**11g**).* Flash column chromatography, eluting with 2:1 hexane:ethyl acetate afforded the product **11g** (19%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals, mp 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, J = 7.8, 1.4 Hz, 1H, ArH), 8.09 (dd, J = 7.8, 1.4 Hz, 1H, ArH), 7.77 (td, J = 7.6, 1.4 Hz, 1H, ArH), 7.70 (td, J = 7.6, 1.4 Hz, 1H, ArH), 7.58 (s, 1H, OH), 6.86 (t, J = 6.6 Hz, 1H, NH), 2.94 (dd, J = 6.6, 4.5 Hz, 2H, CH_2N), 2.54 (s, 2H, CH_2Ar), 2.39–2.30 (m, 1H, CH), 1.79–1.67 (m, 1H, CH_2), 1.37–1.22 (m, 1H + 8H, CH_2), 1.21 (d, J = 6.4 Hz, 3H, CH_3), 0.96 (s, 6H, 2× CH_3), 0.86 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0 (C=O), 180.9 (C=O), 178.8 (C=O), 155.0 (Ar), 135.1 (ArH), 133.3 (ArH), 132.9 (Ar), 129.3 (Ar), 127.2 (ArH), 126.3 (ArH), 121.6 (Ar), 47.0 (CH_2), 42.1 (CH), 38.2 (C), 34.5 (CH_2), 31.9 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 27.6 (CH_2), 26.3 (CH_3), 26.2 (CH_3), 22.6 (CH_2), 18.1 (CH_3), 14.1 (CH_3); IR (KBr) = 3295 (NH), 2965, 2922, 2855 (CH), 1668, 1642, 1623 (C=O), 1597, 1560 (C=C), 1271 (C–N), 1214 (C–O); HRMS (ESI^+): m/z [M + Na] calcd for $C_{24}H_{33}NNaO_4$: 422.2302, found 422.2321.

*4.2.4.8. N-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]nonanamide (**11h**).* Flash column chromatography, eluting with 2:1 hexane:ethyl acetate afforded the product **11h** (25%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals, mp 111–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (dd, J = 7.6, 1.1 Hz, 1H, ArH), 8.08 (dd, J = 7.6, 1.1 Hz, 1H, ArH), 7.76 (td, J = 7.6, 1.3 Hz, 1H, ArH), 7.69 (td, J = 7.6, 1.3 Hz, 1H, ArH), 6.90 (t, J = 6.3 Hz, 1H, NH), 2.93 (d, J = 6.3 Hz, 2H, CH_2N), 2.54 (s, 2H, CH_2Ar), 2.30 (t, J = 7.7 Hz, 2H, CH_2CO), 1.71 (quintet, J = 7.7 Hz, 2H, CH_2), 1.40–1.24 (m, 10H, 5× CH_2), 0.96 (s, 6H, 2× CH_3), 0.86 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz $CDCl_3$): δ = 186.0 (C=O), 180.9 (C=O), 173.4 (C=O), 155.1 (Ar), 135.0 (ArH), 133.2 (ArH), 132.8 (Ar), 129.4 (Ar), 127.1 (ArH), 126.3 (ArH), 121.6 (Ar), 47.1 (CH_2), 38.0 (C), 37.3 (CH_2), 31.8 (2× CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.2 (2× CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3); IR (KBr) = 3357 (NH), 2959, 2923, 2853 (CH), 1665, 1633 (C=O), 1594, 1578, 1550 (C=C), 1273 (C–N), 1215 (C–O); HRMS (ESI^+): m/z [M + Na] calcd for $C_{24}H_{33}NNaO_4$: 422.2302, found: 422.2320.

*4.2.4.9. N-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]decanamide (**11i**).* Flash column chromatography, eluting with 2:1 hexane:ethyl acetate afforded the product **11i** (17%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals, mp 107–108 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (dd, J = 7.6, 1.1 Hz, 1H, ArH), 8.13 (dd, J = 7.6, 1.1 Hz, 1H, ArH), 7.81 (td, J = 7.6, 1.6 Hz, 1H, ArH), 7.74 (td, J = 7.6, 1.6 Hz, 1H, ArH), 6.88 (t, J = 6.8 Hz, 1H, NH), 2.96 (d, J = 6.8 Hz, 2H, CH_2N), 2.57 (s, 2H, CH_2Ar), 2.32 (t, J = 7.8 Hz, 2H, CH_2CO), 1.74 (quintet, J = 7.8 Hz, 2H, CH_2), 1.44–1.24 (m, 12H, 6× CH_2), 0.99 (s, 6H, 2× CH_3), 0.89 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0 (C=O), 180.9 (C=O), 173.5 (C=O), 155.1 (Ar), 135.0 (ArH), 133.2 (ArH), 132.8 (Ar), 129.4 (Ar), 127.1 (ArH), 126.3 (ArH), 121.5 (Ar), 47.0 (CH_2), 38.0 (C), 37.2 (CH_2), 31.8 (CH_2), 29.6 (2× CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.2 (2× CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.1 (CH_3); IR (KBr) = 3358 (NH), 2921, 2853 (CH), 1664, 1631 (C=O), 1594, 1578, 1551 (C=C), 1273 (C–N), 1216 (C–O): HRMS (ESI^+): m/z [M + H]$^+$ calcd for $C_{25}H_{36}NO_4$: 414.2644, found 414.2628.

*4.2.4.10. N-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]undecanamide (**11j**).* Flash column chromatography, eluting with 2:1 hexane:ethyl acetate afforded the product **11j** (14%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals, mp 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, J = 7.6, 1.1 Hz, 1H, ArH), 8.07 (dd, J = 7.6, 1.1 Hz, 1H, ArH), 7.75 (td, J = 7.6, 1.1 Hz, 1H, ArH), 7.68 (td, J = 7.6, 1.1 Hz, 1H, ArH), 6.89 (t, J = 6.3 Hz, 1H, NH), 2.92 (d, J = 6.3 Hz, 2H, CH_2N), 2.53 (s, 2H, CH_2Ar), 2.29 (t, J = 7.7 Hz, 2H, CH_2CO), 1.69 (quintet, J = 7.7 Hz, 2H, CH_2), 1.40–1.19 (m, 14H, 7× CH_2), 0.95 (s, 6H, 2× CH_3), 0.84 (t, J = 6.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0 (C=O), 180.9 (C=O), 173.5 (C=O), 155.1 (Ar), 135.0 (ArH), 133.2 (ArH), 132.8 (Ar), 129.4 (Ar), 127.1 (ArH), 126.3 (ArH), 121.5 (Ar), 47.0 (CH_2), 38.0 (C), 37.2 (CH_2), 31.8 (2× CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (2× CH_2), 29.3 (CH_2), 26.2 (2× CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.1 (CH_3); IR (KBr) = 3361 (NH), 2921, 2853 (CH), 1665, 1632 (C=O), 1594, 1578, 1550 (C=C), 1273 (C–N), 1215 (C–O); HRMS (ESI^+): m/z [M + Na] calcd for $C_{26}H_{37}NNaO_4$: 450.2615, found: 450.2618.

*4.2.4.11. N-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]dodecanamide (**11k**).* Flash column chromatography, eluting with 2:1 hexane:ethyl acetate afforded the product **11k** (14%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals, mp 97–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 7.6 Hz, 1H, ArH), 8.06 (d, J = 7.6 Hz, 1H, ArH), 7.73 (td, J = 7.6, 1.1 Hz, 1H, ArH), 7.67 (td, J = 7.6, 1.1 Hz, 1H, ArH), 6.89 (t, J = 6.6 Hz, 1H, NH), 2.92 (d, J = 6.6 Hz, 2H, CH_2N), 2.52 (s, 2H, CH_2Ar), 2.28 (t, J = 7.4 Hz, 2H, CH_2CO), 1.68 (quintet, J = 7.4 Hz, 2H, CH_2), 1.40–1.15 (m, 16H, 8× CH_2), 0.94 (s, 6H, 2× CH_3), 0.83 (t, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 186.0 (C=O), 180.9 (C=O), 173.5 (C=O), 155.3 (Ar), 135.0 (ArH), 133.2 (ArH), 132.7 (Ar), 129.4 (Ar), 127.0 (ArH), 126.2 (ArH), 121.6 (Ar), 47.1 (CH_2), 38.0 (C), 37.2 (CH_2), 31.8 (CH_2), 29.6 (2× CH_2), 29.5 (CH_2), 29.4 (3× CH_2), 29.3 (CH_2), 26.2 (2× CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.1 (CH_3); IR (KBr) = 3355 (NH), 2917, 2853 (CH), 1673, 1662, 1633 (C=O), 1594, 1578, 1551 (C=C), 1273 (C–N), 1216 (C–O); HRMS (ESI^+): *m/z* [M + Na] calcd for $C_{27}H_{39}NNaO_4$: 464.2771, found: 464.2775.

*4.2.4.12. N-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]tetradecanamide (**11l**).* Flash column chromatography, eluting with 2:1 hexane:ethyl acetate afforded the product **11l** (12%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals, mp 94–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (ddd, *J* = 7.6, 1.4, 0.4 Hz, 1H, ArH), 8.10 (ddd, *J* = 7.6, 1.4, 0.4 Hz, 1H, ArH), 7.77 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.71 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 6.86 (t, *J* = 6.5 Hz, 1H, NH), 2.94 (d, *J* = 6.5 Hz, 2H, CH_2N), 2.55 (s, 2H, CH_2Ar), 2.30 (t, *J* = 7.5 Hz, 2H, CH_2CO), 1.71 (quintet, *J* = 7.5 Hz, 2H, CH_2), 1.43–1.17 (m, 20H, 10× CH_2), 0.96 (s, 6H, 2× CH_3), 0.87 (t, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0 (C=O), 180.9 (C=O), 173.4 (C=O), 155.0 (Ar), 135.1 (ArH), 133.2 (ArH), 132.8 (Ar), 129.4 (Ar), 127.1 (ArH), 126.3 (ArH), 121.6 (Ar), 47.1 (CH_2), 38.1 (C), 37.3 (CH_2), 31.9 (CH_2), 29.7 (2× CH_2), 29.6 (2× CH_2) 29.5 (CH_2), 29.4 (3× CH_2), 29.3 (CH_2), 26.4 (2× CH_3), 25.9 (CH_2), 22.7 (CH_2), 14.1 (CH_3); IR (KBr) = 3354 (NH), 2918, 2851 (CH), 1673, 1661, 1631 (C=O), 1594, 1578, 1552 (C=C), 1273 (C–N), 1216 (C–O); HRMS (ESI^+): *m/z* [M + Na] calcd for $C_{29}H_{43}NNaO_4$: 492.3084, found: 492.3072.

*4.2.4.13. N-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]hexadecanamide (**11m**).* Flash column chromatography, eluting with 2:1 hexane:ethyl acetate afforded the product **11m** (19%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals, mp 94–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (ddd, *J* = 7.6, 1.3, 0.4 Hz, 1H, ArH), 8.03 (ddd, *J* = 7.6, 1.3, 0.4 Hz, 1H, ArH), 7.76 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.69 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 6.89 (t, *J* = 6.4 Hz, 1H, NH), 2.93 (d, *J* = 6.4 Hz, 2H, CH_2N), 2.54 (s, 2H, CH_2Ar), 2.30 (t, *J* = 7.7 Hz, 2H, CH_2CO), 1.71 (quintet, *J* = 7.7 Hz, 2H, CH_2), 1.42–1.21 (m, 24H, 12× CH_2), 0.96 (s, 6H, 2× CH_3), 0.86 (t, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0 (C=O), 180.9 (C=O), 173.4 (C=O), 155.1 (Ar), 135.0 (ArH), 133.2 (ArH), 132.8 (Ar), 129.4 (Ar), 127.1 (ArH), 126.3 (ArH), 121.5 (Ar), 47.1 (CH_2), 38.0 (C), 37.3 (CH_2), 31.9 (2× CH_2), 29.7 (3× CH_2), 29.6 (3× CH_2), 29.5 (CH_2), 29.4 (2× CH_2), 29.3 (CH_2), 26.2 (2× CH_3), 25.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3); IR (KBr) = 3355 (NH), 2918, 2850 (CH), 1673, 1662, 1631 (C=O), 1594, 1578, 1551 (C=C), 1273 (C–N), 1216 (C–O); HRMS (ESI^+): *m/z* [M + Na] calcd for $C_{31}H_{47}NNaO_4$: 520.3397, found: 520.3393.

*4.2.4.14. N-[3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl]octadecanamide (**11n**).* Flash column chromatography, eluting with 2:1 hexane:ethyl acetate afforded the product **11n** (25%) as a yellow amorphous solid, which was recrystallized from hexane to give yellow crystals, mp 95–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (ddd, *J* = 7.6, 1.4, 0.4 Hz, 1H, ArH), 8.04 (ddd, *J* = 7.6, 1.4, 0.4 Hz, 1H, ArH), 7.71 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.65 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 6.84 (t, *J* = 6.7 Hz, 1H, NH), 2.88 (d, *J* = 6.7 Hz, 2H, CH_2N), 2.49 (s, 2H, CH_2Ar), 2.25 (t, *J* = 7.7 Hz, 2H, CH_2CO), 1.66 (quintet, *J* = 7.7 Hz, 2H, CH_2), 1.37–1.11 (m, 28H, 14× CH_2), 0.91 (s, 6H, 2× CH_3), 0.81 (t, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0 (C=O), 180.9 (C=O), 173.5 (C=O), 155.1 (Ar), 135.1 (ArH), 133.2 (ArH), 132.8 (Ar), 129.4 (Ar), 127.1 (ArH), 126.3 (ArH), 121.5 (Ar), 47.1 (CH_2), 38.1 (C), 37.3 (CH_2), 31.9 (2× CH_2), 29.7 (8× CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.2 (2× CH_3), 26.0 (CH_2), 22.7 (CH_2), 14.1 (CH_3); IR (KBr) = 3317 (NH), 2918, 2849 (CH), 1671, 1645 (C=O), 1594, 1579, 1554 (C=C), 1274 (C–N), 1214 (C–O); HRMS (ESI^+): *m/z* [M + Na] calcd for $C_{33}H_{51}NNaO_4$: 548.3710, found: 548.3700.

*4.2.5. Compounds **12**–**17** were prepared as described in the previous report [6,7]*

Their spectral data are shown in Supplementary data.

*4.2.6. General procedure for coupling of naphthoquinone alcohol **17** with fatty acids to naphthoquinone esters **18a**–**n** [8]*

To a solution of carboxylic acid (1.3 mmol) and 4-dimethylaminopyridine (DMAP) (0.3 mmol) in dry dichloromethane (10 mL) was added naphthoquinone alcohol **17** (1 mmol) in dry dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 5 min when a solution of 1,3-dicyclohexylcarbodiimide (DCC) (1.3 mmol) in dry dichloromethane (15 mL) was added. Stirring was continued overnight at room temperature. The precipitate of dicyclohexylurea was filtered off and the filtrate washed with saturated ammonium chloride solution then water. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel) to give the target product, naphthoquinone aliphatic esters.

*4.2.6.1. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl-2-methyl propanoate (**18a**).* Flash column chromatography, eluting with 30:1 hexane:ethyl acetate afforded the product **18a** (86%) as a yellow gum, which was recrystallized from hexane–dichloromethane to give yellow crystals, mp 70.5–71.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 7.5, 1.2 Hz, 1H, ArH), 8.10 (dd, *J* = 7.5, 1.2 Hz, 1H, ArH), 7.77 (td, *J* = 7.5, 1.2 Hz, 1H, ArH), 7.70 (td, *J* = 7.5, 1.2 Hz, 1H, ArH), 7.44 (s, 1H, OH), 3.85 (s, 2H, OCH_2), 2.69 (s, 2H, CH_2Ar), 2.54 (heptet, *J* = 7.0 Hz, 1H, CH), 1.17 (d, *J* = 7.0 Hz, 6H, 2× CH_3), 0.99 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.8 (C=O), 181.2 (C=O), 177.0 (C=O), 154.3 (Ar), 134.9 (ArH), 132.9 (ArH, Ar), 129.3 (Ar), 127.0 (ArH), 126.1 (ArH), 121.6 (Ar), 72.4 (CH_2), 37.0 (C), 34.2 (CH), 31.8 (CH_2), 25.0 (2× CH_3), 19.0 (2× CH_3); IR (KBr) = 3362 (OH), 2969, 2932, 2873 (CH), 1729, 1666, 1644 (C=O), 1594, 1466, 1371, 1275 (C=C), 1216, 1151 (C–O); MS (EI), *m/z* (% relative intensity): 331 ($[M + H]^+$, 21), 243 (74), 187 (100), 159 (45), 145 (33); Anal. Calcd for $C_{19}H_{22}O_5$: C 69.07, H 6.71. Found: C 69.26, H 6.31.

*4.2.6.2. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl propanoate (**18as**).* Flash column chromatography, eluting with 49:1 hexane:ethyl acetate afforded the product **18as** (90%) as a yellow gum, which was recrystallized from hexane–dichloromethane to give yellow crystals, mp 89–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 7.6, 1.2 Hz, 1H, ArH), 8.10 (dd, *J* = 7.6, 1.2 Hz, 1H, ArH), 7.77 (td, *J* = 7.6, 1.2 Hz, 1H, ArH), 7.70 (td, *J* = 7.6, 1.2 Hz, 1H, ArH), 7.43 (s, 1H, OH), 3.86 (s, 2H, OCH_2), 2.69 (s, 2H, CH_2Ar), 2.31 (q, *J* = 7.6 Hz, 2H, CH_2), 1.13 (t, *J* = 7.6 Hz, 3H, CH_3), 0.91 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.8 (C=O), 181.2 (C=O), 174.5 (C=O), 154.2 (Ar), 135.0 (ArH), 132.9 (ArH, Ar), 129.3 (Ar), 127.0 (ArH), 126.1 (ArH), 121.7 (Ar), 72.5 (CH_2), 36.8 (C), 31.9 (CH_2), 27.6 (CH_2), 25.0 (2× CH_3), 9.2 (CH_3); IR (KBr) = 3323 (OH), 2985, 2953, 2925 (CH), 1708, 1668, 1646 (C=O), 1592, 1460, 1368, 1271 (C=C), 1213, 1022 (C–O); MS (EI), *m/z* (% relative intensity): 316 (M^+, 5), 257 (5), 244 (11), 243 (100), 187 (2); Anal. Calcd for $C_{18}H_{20}O_5$: C 68.34, H 6.37. Found: C 68.46, H 6.49.

*4.2.6.3. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl-2-methyl butanoate (**18b**).* Flash column chromatography, eluting with 25:1 hexane:ethyl acetate afforded the product **18b** (81%) as a yellow gum, which was recrystallized from

hexane–dichloromethane to give yellow crystals, mp 70.5–71.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (ddd, J = 7.5, 1.2, 0.6 Hz, 1H, ArH), 8.10 (ddd, J = 7.5, 1.2, 0.6 Hz, 1H, ArH), 7.77 (td, J = 7.5, 1.2 Hz, 1H, ArH), 7.70 (td, J = 7.5, 1.2 Hz, 1H, ArH), 7.45 (s, 1H, OH), 3.87 (s, 2H, OCH_2), 2.69 (s, 2H, CH_2Ar), 2.35 (hextet, J = 7.0 Hz, 1H, CH), 1.73–1.60 (m, 1H, CH_2), 1.52–1.38 (m, 1H, CH_2), 1.14 (d, J = 7.0 Hz, 3H, CH_3), 0.99 (s, 6H, 2× CH_3), 0.89 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.5 (C=O), 181.9 (C=O), 177.3 (C=O), 154.9 (Ar), 135.6 (ArH), 133.6 (ArH, Ar), 130.0 (Ar), 127.7 (ArH), 126.7 (ArH), 122.3 (Ar), 73.1 (CH_2), 41.9 (CH), 37.6 (C), 32.6 (CH_2), 27.3 (CH_2), 25.6 (2× CH_3), 17.2 (CH_3), 12.2 (CH_3); IR (KBr) = 3371 (OH), 2967, 2932, 2873 (CH), 1731, 1667, 1650 (C=O), 1594, 1461, 1368, 1274 (C=C), 1217, 1049 (C–O); MS (EI), m/z (% relative intensity): 344 (M^+, 10), 243 (100), 225 (43), 187 (97), 159 (71); Anal. Calcd for $C_{20}H_{24}O_5$: C 69.75, H 7.02. Found: C 96.64, H 7.20.

*4.2.6.4. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl butanoate (**18bs**).* Flash column chromatography, eluting with 14:1 hexane:ethyl acetate afforded the product **18bs** (87%) as a yellow gum, which was recrystallized from hexane–dichloromethane to give yellow crystals, mp 66–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16–8.04 (m, 1H, ArH), 8.04–8.01 (m, 1H, ArH), 7.69 (td, J = 7.6, 1.4 Hz, 1H, ArH), 7.62 (td, J = 7.6, 1.4 Hz, 1H, ArH), 7.37 (s, 1H, OH), 3.79 (s, 2H, OCH_2), 2.61 (s, 2H, CH_2Ar), 2.18 (t, J = 7.4 Hz, 2H, CH_2), 1.59–1.47 (m, 2H, CH_2), 0.92 (s, 6H, 2× CH_3), 0.85 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.8 (C=O), 181.2 (C=O), 173.7 (C=O), 154.2 (Ar), 135.0 (ArH), 132.9 (ArH, Ar), 129.3 (Ar), 127.0 (ArH), 126.1 (ArH), 121.7 (Ar), 72.5 (CH_2), 36.8 (C), 36.3 (CH_2), 31.9 (CH_2), 25.0 (2× CH_3), 18.4 (CH_2), 13.7 (CH_3); IR (KBr) = 3378 (OH), 2968, 2932, 2873 (CH), 1701, 1667, 1646 (C=O), 1593, 1459, 1367, 1271 (C=C), 1214, 1015 (C–O); MS (EI), m/z (% relative intensity): 330 (M^+, 11), 243 (9), 229 (64), 211 (96), 187 (48), 159 (28), 149 (100); Anal. Calcd for $C_{19}H_{22}O_5$: C 69.07, H 6.71. Found: C 69.47, H 6.69.

*4.2.6.5. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl-2-methyl pentanoate (**18c**).* Flash column chromatography, eluting with 30:1 hexane:ethyl acetate afforded the product **18c** (77%) as a yellow gum, which was recrystallized from hexane–dichloromethane to give yellow crystals, mp 57–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (dd, J = 7.6, 1.2 Hz, 1H, ArH), 8.10 (dd, J = 7.6, 1.2 Hz, 1H, ArH), 7.77 (td, J = 7.6, 1.2 Hz, 1H, ArH), 7.70 (td, J = 7.6, 1.2 Hz, 1H, ArH), 7.45 (br s, 1H, OH), 3.86 (s, 2H, OCH_2), 2.69 (s, 2H, CH_2Ar), 2.43 (hextet, J = 7.2 Hz, 1H, CH), 1.68–1.59 (m, 1H, CH_2), 1.24–1.42 (m, 1H + 2H, CH_2), 1.14 (d, J = 7.2 Hz, 3H, CH_3), 0.99 (s, 6H, 2× CH_3), 0.88 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.5 (C=O), 181.9 (C=O), 177.5 (C=O), 154.9 (Ar), 135.6 (ArH), 133.6 (ArH, Ar), 130.0 (Ar), 127.7 (ArH), 126.7 (ArH), 122.3 (Ar), 73.1 (CH_2), 40.1 (CH), 37.6 (C), 36.5 (CH_2), 32.6 (CH_2), 25.7 (CH_3), 25.6 (CH_3), 21.0 (CH_2), 17.6 (CH_3), 14.6 (CH_3); IR (KBr) = 3381 (OH), 2959, 2932, 2863 (CH), 1730, 1660, 1650 (C=O), 1594, 1456, 1370, 1275 (C=C), 1218, 1048 (C–O); MS (EI), m/z (% relative intensity): 357 ($[M - H]^+$, 29), 243 (100), 225 (46), 187 (99), 159 (69); Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.18, H, 7.42.

*4.2.6.6. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl pentanoate (**18cs**).* Flash column chromatography, eluting with 24:1 hexane:ethyl acetate afforded the product **18cs** (45%) as a yellow gum, which was recrystallized from hexane–dichloromethane to give yellow crystals, mp 51–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dd, J = 7.6, 1.4 Hz, 1H, ArH), 8.09 (dd, J = 7.6, 1.4 Hz, 1H, ArH), 7.69 (td, J = 7.6, 1.4 Hz, 1H, ArH), 7.67 (td, J = 7.6, 1.4 Hz, 1H, ArH), 7.44 (s, 1H, OH), 3.85 (s, 2H, OCH_2), 2.68 (s, 2H, CH_2Ar), 2.27 (t, J = 7.6 Hz, 2H, CH_2), 1.65–1.58 (m, 2H, CH_2), 1.38–1.25 (m, 2H, CH_2), 0.99 (s, 6H, 2× CH_3), 0.88 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.8 (C=O), 181.2 (C=O), 173.8 (C=O), 154.2 (Ar), 135.0 (ArH), 133.0 (ArH), 132.9 (Ar), 129.3 (Ar), 127.0 (ArH), 126.1 (ArH), 121.7 (Ar), 72.5 (CH_2), 36.8 (C), 34.1 (CH_2), 32.0 (CH_2), 27.0 (CH_2), 25.0 (2× CH_3), 22.3 (CH_2), 13.7 (CH_3); IR (KBr) = 3373 (OH), 2957, 2925, 2865 (CH), 1739, 1666, 1647 (C=O), 1596, 1461, 1374, 1275 (C=C), 1217, 1157 (C–O); MS (EI), m/z (% relative intensity): 344 (M^+, 5), 243 (100), 225 (9), 187 (13), 159 (2); Anal. Calcd for $C_{20}H_{24}O_5$: C 69.75, H 7.02. Found: C 69.94, H 7.36.

*4.2.6.7. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl hexanoate (**18d**).* Flash column chromatography, eluting with 30:1 hexane:ethyl acetate afforded the product **18d** (74%) as a yellow gum, which was recrystallized from hexane–dichloromethane to give yellow crystals, mp 54.5–55.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, J = 7.6, 1.4 Hz, 1H, ArH), 8.08 (dd, J = 7.6, 1.4 Hz, 1H, ArH), 7.77 (td, J = 7.6, 1.4 Hz, 1H, ArH), 7.69 (td, J = 7.6, 1.4 Hz, 1H, ArH), 7.62 (br s, 1H, OH), 3.87 (s, 2H, OCH_2), 2.69 (s, 2H, CH_2Ar), 2.27 (t, 2H, J = 7.5 Hz, CH_2), 1.51 (quintet, J = 7.5, 2H, CH_2), 1.31–1.25 (m, 4H, 2× CH_2), 1.00 (s, 6H, 2× CH_3), 0.89 (t, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.5 (C=O), 181.8 (C=O), 174.6 (C=O), 154.9 (Ar), 135.6 (ArH), 133.5 (ArH, Ar), 130.0 (C), 127.6 (ArH), 126.7 (ArH), 122.4 (Ar), 73.2 (CH_2), 37.5 (C), 35.0 (CH_2), 32.6 (CH_2), 31.9 (CH_2), 25.7 (2× CH_3), 25.3 (CH_2), 22.9 (CH_2), 14.5 (CH_3); IR (KBr) = 3366 (OH), 2940, 2865 (CH), 1738, 1644 (C=O), 1372, 1272 (C=C), 1212, 1155 (C–O); MS (EI), m/z (% relative intensity): 358 (M^+, 2), 243 (100), 225 (12), 187 (16), 158 (2), 149 (18); Anal. Calcd for $C_{21}H_{26}O_5$: C 70.37, H 7.31. Found: C 70.49, H 7.57.

*4.2.6.8. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl heptanoate (**18e**).* Flash column chromatography, eluting with 30:1 hexane:ethyl acetate afforded the product **18e** (83%) as a yellow gum, which was recrystallized from hexane–dichloromethane to give yellow crystals, mp 57.5–58.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dd, 1H, J = 7.6, 1.1 Hz, ArH), 8.10 (dd, 1H, J = 7.6, 1.1 Hz, ArH), 7.78 (td, J = 7.6, 1.1 Hz, 1H, ArH), 7.70 (td, J = 7.6, 1.1 Hz, 1H, ArH), 7.58 (br s, 1H, OH), 3.87 (s, 2H, OCH_2), 2.69 (s, 2H, CH_2Ar), 2.28 (t, 2H, J = 7.4 Hz, CH_2), 1.60 (quintet, J = 7.4 Hz, 2H, CH_2), 1.35–1.21 (m, 6H, 3× CH_2), 1.00 (s, 6H, 2× CH_3), 0.88 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.5 (C=O), 181.8 (C=O), 174.6 (C=O), 154.9 (Ar), 135.6 (ArH), 133.5 (ArH, Ar), 130.0 (C), 127.6 (ArH), 126.7 (ArH), 122.4 (Ar), 73.2 (CH_2), 37.5 (C), 35.0 (CH_2), 32.6 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 25.7 (2× CH_3), 25.6 (CH_2), 23.1 (CH_2), 14.6 (CH_3); IR (KBr) = 3370 (OH), 2928, 2858 (CH), 1739, 1644 (C=O), 1374, 1276 (C=C), 1212, 1156 (C–O); MS (EI), m/z (% relative intensity): 372 (M^+, 9), 242 (26), 227 (11), 188 (28), 159 (12), 113 (100); Anal. Calcd for $C_{22}H_{28}O_5$: C 70.94, H 7.58. Found: C 70.68, H 7.85.

*4.2.6.9. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl octanoate (**18f**).* Flash column chromatography, eluting with 20:1 hexane:ethyl acetate afforded the product **18f** (96%) as a yellow gum, which was recrystallized from hexane–dichloromethane to give yellow crystals, mp 56–57 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, J = 7.6, 1.4 Hz, 1H, ArH), 8.09 (dd, J = 7.6, 1.4 Hz, 1H, ArH), 7.76 (td, J = 7.6, 1.4 Hz, 1H, ArH), 7.69 (td, J = 7.6, 1.4 Hz, 1H, ArH), 7.44 (s, 1H, OH), 3.85 (s, 2H, OCH_2), 2.68 (s, 2H, CH_2Ar), 2.26 (t, J = 7.6 Hz, 2H, CH_2), 1.63–1.55 (m, 2H, CH_2), 1.27 (br s, 8H, 4× CH_2), 0.99 (s, 6H, 2× CH_3), 0.87 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.8 (C=O), 181.2 (C=O), 173.9 (C=O), 154.2 (Ar), 134.9 (ArH), 132.9 (Ar), 132.9 (ArH), 129.3 (Ar), 127.0 (ArH), 126.1 (ArH), 121.7 (Ar), 72.5 (CH_2), 36.8 (C), 34.4 (CH_2), 32.0 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.0 (2× CH_3), 24.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3); IR (KBr) = 3366 (OH), 2924, 2865 (CH),

1735, 1666, 1645 (C=O), 1595, 1461, 1376, 1275 (C=C), 1218, 1156 (C–O); MS (EI), *m/z* (% relative intensity): 385 ([M − H]+, 45), 243 (100); Anal. Calcd for $C_{23}H_{30}O_5$: C 71.48, H 7.82. Found: C 71.72, H 7.71.

*4.2.6.10. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl-2-methyl octanoate (**18g**).* Flash column chromatography, eluting with 25:1 hexane:ethyl acetate afforded the product **18g** (84%) as a yellow gum, which was recrystallized from hexane–dichloromethane to give yellow crystals, mp 57.5–58.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.11 (m, 1H, ArH), 8.11–8.05 (m, 1H, ArH), 7.76 (td, *J* = 7.6, 1.2 Hz, 1H, ArH), 7.69 (td, *J* = 7.6, 1.2 Hz, 1H, ArH), 3.85 (s, 2H, OCH_2), 2.68 (s, 2H, CH_2Ar), 2.40 (hextet, *J* = 7.0 Hz, 1H, CH_3), 1.68–1.89 (m, 2H, CH_2), 1.40–1.32 (m, 2H, CH_2), 1.31–1.18 (m, 6H, 3× CH_2), 1.13 (d, *J* = 7.0 Hz, 3H, CH_3), 0.99 (s, 6H, 2× CH_3), 0.86 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.5 (C=O), 181.9 (C=O), 177.5 (C=O), 154.9 (Ar), 135.6 (ArH), 133.6 (ArH, Ar), 130.0 (C), 127.7 (ArH), 126.7 (ArH), 122.3 (Ar), 73.1 (CH_2), 40.4 (CH), 37.6 (C), 34.4 (CH_2), 32.6 (CH_2), 32.3 (CH_2), 29.8 (CH_2), 27.8 (CH_2), 25.7 (CH_3), 25.6 (CH_3), 23.2 (CH_2), 17.7 (CH_3), 14.7 (CH_3); IR (KBr) = 3389 (OH), 2959, 2930, 2856 (CH), 1722, 1650 (C=O), 1461, 1373, 1268 (C=C), 1214, 1049 (C–O); MS (EI), *m/z* (% relative intensity): 400 ([M − H]$^+$, 29), 243 (100), 225 (46), 187 (99), 159 (69); Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.68, H, 8.41.

*4.2.6.11. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl nonanoate (**18h**).* Flash column chromatography, eluting with 30:1 hexane:ethyl acetate afforded the product **18h** (73%) as a yellow gum, which was recrystallized from hexane–dichloromethane to give yellow crystals, mp 52.5–53.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.6 Hz, 1H, ArH), 8.03 (d, *J* = 7.6 Hz, 1H, ArH), 7.80 (t, *J* = 7.6 Hz, 1H, ArH), 7.73 (t, *J* = 7.6 Hz, 1H, ArH), 7.47 (s, 1H, OH), 3.87 (s, 2H, OCH_2), 2.71 (s, 2H, CH_2Ar), 2.29 (t, *J* = 7.5 Hz, 2H, CH_2), 1.62–1.58 (m, 2H, CH_2), 1.28–1.20 (m, 10H, 5× CH_2), 1.02 (s, 6H, 2× CH_3), 0.90 (t, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.5 (C=O), 181.8 (C=O), 174.5 (C=O), 154.9 (Ar), 135.6 (ArH), 133.5 (ArH, Ar), 130.0 (Ar), 127.6 (ArH), 126.7 (ArH), 122.4 (Ar), 73.2 (CH_2), 37.5 (C), 35.0 (CH_2), 32.6 (CH_2), 32.4 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 25.7 (2× CH_3), 25.6 (CH_2), 23.2 (CH_2), 14.7 (CH_3); IR (KBr) = 3366 (OH), 2923, 2850 (CH), 1739, 1644 (C=O), 1462, 1373, 1268 (C=C), 1212, 1155 (C–O); MS (EI), *m/z* (% relative intensity): 400 (M$^+$, 4), 242 (28), 227 (18), 188 (58), 187 (35), 159 (38), 141 (100); Anal. Calcd for $C_{24}H_{32}O_5$: C 71.97, H 8.05. Found: C 71.82, H 8.35.

*4.2.6.12. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl decanoate (**18i**).* Flash column chromatography, eluting with 30:1 hexane:ethyl acetate afforded the product **18i** (72%) as a yellow gum, which was recrystallized from hexane–dichloromethane to give yellow crystals, mp 61–62 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 7.6 Hz, 1H, ArH), 8.12 (d, *J* = 7.6 Hz, 1H, ArH), 7.80 (td, *J* = 7.6, 1.2 Hz, 1H, ArH), 7.73 (td, *J* = 7.6, 1.2 Hz, 1H, ArH), 7.46 (s, 1H, OH), 3.88 (s, 2H, OCH_2), 2.71 (s, 2H, CH_2Ar), 2.29 (t, *J* = 7.6 Hz, 2H, CH_2), 1.69–1.59 (m, 2H, CH_2), 1.32–1.25 (m, 12H, 6× CH_3), 1.02 (s, 6H, 2× CH_3), 0.91 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.5 (C=O), 181.8 (C=O), 174.5 (C=O), 154.8 (Ar), 135.6 (ArH), 133.6 (ArH, Ar), 130.0 (Ar), 127.6 (ArH), 126.7 (ArH), 122.4 (Ar), 73.2 (CH_2), 37.5 (C), 35.0 (CH_2), 32.6 (CH_2), 32.5 (CH_2), 30.0 (CH_2), 29.9 (2× CH_2), 29.8 (CH_2), 25.7 (2× CH_3), 25.6 (CH_2), 23.3 (CH_2), 14.7 (CH_3); IR (KBr) = 3364 (OH), 2921, 2850 (CH), 1734, 1660, 1645 (C=O), 1376, 1277 (C=C), 1216, 1156 (C–O); MS (EI), *m/z* (% relative intensity): 414 (M$^+$, 5), 243 (10), 242 (28), 227 (43), 188 (61), 187 (64), 159 (65), 155 (79), 71 (100); Anal. Calcd for $C_{25}H_{34}O_5$: C 72.43, H 8.27. Found: C 72.21, H 8.16.

*4.2.6.13. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl undecanoate (**18j**).* Flash column chromatography, eluting with 30:1 hexane:ethyl acetate afforded the product **18j** (83%) as a yellow gum, which was recrystallized from hexane–dichloromethane to give yellow crystals, mp 64.5–65.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 7.6, 1.1 Hz, 1H, ArH), 8.12 (dd, *J* = 7.6, 1.1 Hz, 1H, ArH), 7.80 (td, *J* = 7.6, 1.1 Hz, 1H, ArH), 7.73 (td, *J* = 7.6, 1.1 Hz, 1H, ArH), 7.46 (s, 1H, OH), 3.88 (s, 2H, OCH_2), 2.71 (s, 2H, CH_2Ar), 2.29 (t, *J* = 7.6 Hz, 2H, CH_2), 1.70–1.57 (m, 2H, CH_2), 1.39–1.22 (m, 14H, 7× CH_2), 1.01 (s, 6H, 2× CH_3), 0.90 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.8 (C=O), 181.2 (C=O), 173.9 (C=O), 154.2 (Ar), 135.0 (ArH), 133.0 (Ar), 132.9 (ArH), 129.3 (Ar), 127.0 (ArH), 126.1 (ArH), 121.7 (Ar), 72.5 (CH_2), 36.8 (C), 34.4 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 25.1 (2× CH_3), 25.0 (CH_2), 22.7 (CH_2), 14.1 (CH_3); IR (KBr) = 3365 (OH), 2917, 2850 (CH), 1738, 1645 (C=O), 1518, 1462, 1377, 1276 (C=C), 1212, 1157 (C–O); MS (EI), *m/z* (% relative intensity): 428 (M$^+$, 9), 243 (28), 241 (56), 227 (22), 188 (82), 187 (50), 159 (56), 71 (100); Anal. Calcd for $C_{26}H_{36}O_5$: C 72.87, H 8.47. Found: C 72.59, H 8.32.

*4.2.6.14. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl dodecanoate (**18k**).* Flash column chromatography, eluting with 30:1 hexane:ethyl acetate afforded the product **18k** (79%) as a yellow gum, which was recrystallized from hexane–dichloromethane to give yellow crystals, mp 68–69 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (dd, *J* = 7.6, 1.3 Hz, 1H, ArH), 8.13 (dd, *J* = 7.6, 1.3 Hz, 1H, ArH), 7.80 (td, *J* = 7.6, 1.3 Hz, 1H, ArH), 7.73 (td, *J* = 7.6, 1.3 Hz, 1H, ArH), 7.46 (s, 1H, OH), 3.88 (s, 2H, OCH_2), 2.71 (s, 2H, CH_2Ar), 2.29 (t, *J* = 7.6 Hz, 2H, CH_2), 1.69–1.59 (m, 2H, CH_2), 1.35–1.22 (m, 16H, 8× CH_2), 1.02 (s, 6H, 2× CH_3), 0.91 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.5 (C=O), 181.8 (C=O), 174.5 (C=O), 154.8 (Ar), 135.6 (ArH), 133.6 (Ar), 133.5 (ArH), 130.0 (Ar), 127.6 (ArH), 126.7 (ArH), 122.4 (Ar), 73.2 (CH_2), 37.5 (C), 35.0 (CH_2), 32.6 (CH_2), 32.5 (CH_2), 30.2 (2× CH_2), 30.1 (CH_2), 29.9 (2× CH_2), 29.8 (CH_2), 25.7 (2× CH_3), 25.6 (CH_2), 23.3 (CH_2), 14.7 (CH_3); IR (KBr) = 3365 (OH), 2920, 2850 (CH), 1735, 1645 (C=O), 1515, 1462, 1378, 1272 (C=C), 1210, 1153 (C–O); MS (EI), *m/z* (% relative intensity): 442 (M$^+$, 6), 243 (21), 242 (50), 229 (7), 227 (24), 188 (81), 187 (88), 159 (91), 71 (100); Anal. Calcd for $C_{27}H_{38}O_5$: C 73.27, H 8.65. Found: C 73.40, H 8.64.

*4.2.6.15. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl tetradecanoate (**18l**).* Flash column chromatography, eluting with 25:1 hexane:ethyl acetate afforded the product **18l** (80%) as a yellow gum, which was recrystallized from hexane–dichloromethane to give yellow crystals, mp 79–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 7.6, 1.2 Hz, 1H, ArH), 8.10 (dd, *J* = 7.6, 1.2 Hz, 1H, ArH), 7.77 (td, *J* = 7.6, 1.2 Hz, 1H, ArH), 7.70 (td, *J* = 7.6, 1.2 Hz, 1H, ArH), 7.44 (s, 1H, OH), 3.86 (s, 2H, OCH_2), 2.68 (s, 2H, CH_2Ar), 2.26 (t, 2H, *J* = 7.6 Hz, CH_2), 1.63–1.57 (m, 2H, CH_2), 1.33–1.21 (m, 20H, 10× CH_2), 0.99 (s, 6H, 2× CH_3), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.5 (C=O), 181.9 (C=O), 174.5 (C=O), 154.8 (Ar), 135.6 (ArH), 133.6 (Ar), 133.5 (ArH), 130.0 (Ar), 127.7 (ArH), 126.7 (ArH), 122.4 (Ar), 73.2 (CH_2), 37.5 (C), 35.0 (CH_2), 32.6 (CH_2), 32.5 (CH_2), 30.3 (3× CH_2), 30.2 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 25.7 (2× CH_3), 25.6 (CH_2), 23.3 (CH_2), 14.7 (CH_3); IR (KBr) = 3364 (OH), 2918, 2850 (CH), 1733, 1667, 1645 (C=O), 1595, 1472, 1376, 1276 (C=C), 1218, 1155 (C–O); MS (EI), *m/z* (% relative intensity): 470 (M$^+$, 62), 469 (64), 243 (100), 187 (52), 159 (47); Anal. Calcd for $C_{29}H_{42}O_5$: C 74.01, H 8.99. Found: C 74.06, H 8.69.

*4.2.6.16. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl hexadecanoate (**18m**).* Flash column chromatography,

eluting with 25:1 hexane:ethyl acetate afforded the product **18m** (77%) as a yellow gum, which was recrystallized from hexane–dichloromethane to give yellow crystals, mp 76–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dd, J = 7.6, 1.2 Hz, 1H, ArH), 8.10 (dd, J = 7.6, 1.2 Hz, 1H, ArH), 7.77 (td, J = 7.6, 1.2 Hz, 1H, ArH), 7.70 (td, J = 7.6, 1.2 Hz, 1H, ArH), 7.45 (s, 1H, OH), 3.86 (s, 2H, OCH_2), 2.68 (s, 2H, CH_2Ar), 2.26 (t, 2H, J = 7.6 Hz, CH_2), 1.65–1.48 (m, 2H, CH_2), 1.25 (br s, 24H, 12× CH_2), 0.99 (s, 6H, 2× CH_3), 0.88 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.5 (C=O), 181.9 (C=O), 174.5 (C=O), 154.8 (Ar), 135.6 (ArH), 133.6 (Ar), 133.5 (ArH), 130.0 (Ar), 127.6 (ArH), 126.7 (ArH), 122.4 (Ar), 73.2 (CH_2), 37.5 (C), 35.0 (CH_2), 32.6 (CH_2), 32.5 (CH_2), 30.3 (6× CH_2), 30.1 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 25.7 (2× CH_3), 25.6 (CH_2), 23.3 (CH_2), 14.7 (CH_3); IR (KBr) = 3363 (OH), 2917, 2849 (CH), 1733, 1667, 1645 (C=O), 1595, 1471, 1376, 1276 (C=C), 1218, 1154 (C–O); MS (EI), m/z (% relative intensity): 498 (M^+, 31), 497 (69), 243 (100); Anal. Calcd for $C_{31}H_{46}O_5$: C 74.66, H 9.30. Found: C 74.36, H 9.45.

*4.2.6.17. 3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl octadecanoate (**18n**).* Flash column chromatography, eluting with 25:1 hexane:ethyl acetate afforded the product **18n** (74%) as a yellow gum, which was recrystallized from hexane–dichloromethane to give yellow crystals, mp 82–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dd, J = 7.6, 1.2 Hz, 1H, ArH), 8.10 (dd, J = 7.6, 1.2 Hz, 1H, ArH), 7.77 (td, J = 7.6, 1.2 Hz, 1H, ArH), 7.70 (td, J = 7.6, 1.2 Hz, 1H, ArH), 7.44 (s, 1H, OH), 3.86 (s, 2H, OCH_2), 2.68 (s, 2H, CH_2Ar), 2.26 (t, 2H, J = 7.2 Hz, CH_2), 1.68–1.58 (m, 2H, CH_2), 1.25 (br s, 28H, 14× CH_2), 0.99 (s, 6H, 2× CH_3), 0.88 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.5 (C=O), 181.9 (C=O), 174.5 (C=O), 154.8 (Ar), 135.6 (ArH), 133.6 (Ar), 133.5 (ArH), 130.0 (Ar), 127.6 (ArH), 126.7 (ArH), 122.4 (Ar), 73.2 (CH_2), 37.5 (C), 35.0 (CH_2), 32.6 (CH_2), 32.5 (CH_2), 30.3 (8× CH_2), 30.1 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 25.7 (2× CH_3), 25.6 (CH_2), 23.3 (CH_2), 14.7 (CH_3); IR (KBr) = 3363 (OH), 2917, 2849 (CH), 1733, 1667, 1645 (C=O), 1595, 1471, 1376, 1276 (C=C), 1217, 1155 (C–O); MS (EI), m/z (% relative intensity): 526 (M^+, 90), 243 (100), 229 (6), 187 (9); Anal. Calcd for $C_{33}H_{50}O_5$: C 75.25, H 9.57. Found: C 75.08, H 9.69.

4.3. Resazurin microplate assay (REMA) [12]

Novel naphthoquinone aliphatic amides and esters were subjected to cytotoxic evaluation against KB human-cell lines (epidermoid carcinoma of oral cavity, ATCC CCL-17). Cells at a logarithmic growth phase were harvested and diluted to 7×10^4 cells/mL for KB in fresh medium. Successively, 5 mL of a test sample diluted in 0.5% DMSO and 45 mL of cell suspension were added into 384-well plates. The plates were incubated at 37 °C in 5% CO_2 incubator. After the incubation period (3 days for KB), 12.5 mL of 62.5 mg/mL resazurin solution was added to each well, and the plates were then incubated at 37 °C for 4 h. Fluorescence signals were measured using SpectraMax M5 multi-detection microplate reader (Molecular Devices, USA) at the excitation and emission wavelengths of 530 nm and 590 nm, respectively. Does response curves were plotted from 6 concentrations of 2-fold serially diluted test compounds and the 50% inhibition concentration (IC_{50}) was determined by curve fitting using the SOFTMax Pro software (Molecular Devices, USA). Doxorubicin and 0.5% DMSO were used as a positive and a negative control, respectively.

4.4. Green fluorescent protein (GFP)-based assay [13]

The GFP-expressing Vero cell lines were generated in-house by stably transfecting the African green monkey kidney cell lines (Vero, ATCC CCL-81), with pEGFP-N1 plasmid (Clontech). The cell lines were maintained in minimal essential medium supplemented with 10% heat-inactivated fetal bovine serum, 2 mM L-glutamine, 1 mM sodium pyruvate, 1.5 g/L sodium bicarbonate and 0.8 mg/mL geneticin, at 37 °C in a humidified incubator with 5% CO_2. The assay was carried out by adding 45 μL of cell suspension at 3.3×10^4 cells/mL to each well of 384-well plates containing 5 μL of test compounds previously diluted in 0.5% DMSO, and then incubating for 4 days in 37 °C incubator with 5% CO_2. Fluorescence signals were measured by using SpectraMax M5 multi-detection microplate reader (Molecular Devices, USA) in the bottom-reading mode with excitation and emission wavelengths of 485 and 535 nm. Fluorescence signal at day 4 was subtracted with background fluorescence at day 0. IC_{50} values were obtained as previously described in Section 4.3.

4.5. Topoisomerase assay

Human Topoisomerase IIα activity was determined using Topoisomerase II assay kit (TopGEN Inc.). The reaction mixture containing 60 ng of kinetoplast DNA (kDNA) and 2 units of hTopoIIα was incubated with and without naphthoquinone aliphatic amides and esters at 37 °C for 1 h in complete assay buffer (50 mM Tris-Cl pH 8.0, 150 mM NaCl, 10 mM $MgCl_2$, 0.5 mM dithiothreitol, and 2 mM ATP). Doxorubicin was used as a positive control while decatenated and linearized kDNA were used as markers. The reaction in a final volume of 20 μL was stopped by adding stop buffer/gel loading dye (1% Sarkosyl, 0.025% bromophenol blue and 5% glycerol). Reaction products were run on 1% agarose gel in 0.5× TBE buffer with 0.5 μg/mL ethidium bromide included in the gel. Electrophoresis was performed at 50 V for 1.30 h. After electrophoresis, the gel was destained with distilled water for 30 min and photographed over a UV transilluminator using DNr Bio-Imaging system. One unit of Topoisomerase II is defined as the amount of enzyme that decatenates 0.2 μg of kDNA in 30 min at 37 °C.

4.6. Molecular docking studies

Three-dimensional structure of human TopoIIα (hTopoIIα) was modeled by SWISS-MODEL using human TopoIIβ (hTopoIIβ) as a template (PDB: 3qx3A) [17]. Amino acid sequence identity between hTopoIIα and TopoIIβ was 74.1%. The quality of the modeled hTopoIIα was evaluated using the program PROCHECK [18]. The model possesses a good geometry with 87% of all residues in the most favored region and 10.8% in the allowed region of the Ramachandran plot. Naphthoquinone aliphatic amides (**11c** and **11m**) and esters (**18c** and **18m**) structures were built and optimized at the calculation level hf/6-31g with Gaussian 03. Gasteiger charges were added by using Auto Dock4.0 [19]. All hydrogen atoms were added and water molecules were removed from the protein structure. Lamarckian genetic algorithm (LGA) was used in this study with default search parameters being used except for 100 docking runs. The grid size was set to 60 × 60 × 60 points with a grid spacing of 0.375 Å. The structures with relative lower binding free energy and the most cluster members were chosen for the optimum docking conformation. Three-dimensional structures with the best-docked conformation were visualized and analyzed by PyMOL v. 0.99 and Discovery Studio 2.5 (Accelrys, Inc., CA, USA).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2012.12.006.

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Stereoselective Pd(0) catalysed five component cascade synthesis of complex *Z,Z*-bisallylamines†

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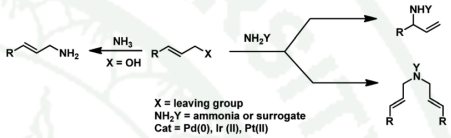
Catalytic 5-component cascade chemistry provides an effective stereo- and regioselective route to novel multi-functional *Z,Z*-bisallylamines. The process, which is capable of considerable further extension, utilises ammonium tartrate as a novel ammonia source which avoids the use of ammonia gas or aqueous ammonia.



Scheme 1 Products arising from allylic aminations.

Both ammonia and non-gaseous ammonia equivalents are well known participants in catalytic cross-coupling amination reactions with aryl/heteroaryl halides.[1a–d] For example NH_4OAc and $(NH_4)_2CO_3$ are well known ammonia sources.[2a–h] Methods employing ammonia include the Cu_2O catalysed reaction of ammonia with aryl/heteroaryl halides to afford primary amines,[3a] and the reaction of aromatic halides with ammonia (80 psi) plus Pd–Josiphos which produces a mixture of mono and di-arylamines in a 17 : 1 to 50 : 1 ratio.[3b] Interestingly Stradiotto *et al.* report aryl tosylates react at room temperature to afford primary amines with their Pd/P–N catalyst system.[3c] The use of Cu^{II} or Pd^0 catalysts can also give rise to indoles under appropriate conditions[4a,b] whilst Cu^{II} catalysts promote amination of aryl halides[5a] and terpinic chlorides[5b] in water. A further sub-set of reactions attracting significant attention are catalytic allylic aminations. Kobayashi and Nagano, employing a $Pd(PPh_3)_4$ catalyst, reported the first successful use of aqueous NH_3 in asymmetric allylic amination.[6a] Hartwig's group[6b–f] and others have employed iridium catalysts with both ammonia and ammonia surrogates. Recently Ghorai *et al.*[7a] reported the allylic substitution of alcohols by an electron deficient ammonia surrogate catalysed by Re_2O_7 and Ohshima *et al.* disclosed the Pt^{II} catalyzed direct amination of allylic alcohols with aqueous ammonia.[7b]

In the Pt^{II} catalyzed amination the use of aqueous ammonia and a triple solvent mixture (H_2O, dioxane, MeOH) are essential for delivering selective monoallylation whilst high concentration of ammonia cause partial deactivation of the catalyst. There are potentially three outcomes of the established allylic amination reactions (Scheme 1). Our interest in this area arose from the potential of replacing the normal 2- and 3-component process, employing allylic substrates with a variable leaving group (Scheme 1), by a 5-component allene cascade. This generates no leaving group and allows a significant increase in molecular complexity for exploiting biochemical space by concomitant installation of variety of aromatic/heteroaromatic substituents. A recent paper by our group reported 3- and 9-component cascades exploiting adamantane as a versatile organic tecton.[8]

We selected ammonium carbonate, tartrate and citrate as ammonium surrogates for our studies. To our knowledge the latter two have not been evaluated as ammonia surrogates. We selected a panel of allenes (Chart 1) based on purine **1**, quinazolinone **2** and **3**, thymidine **4** and uridine **5** cores, chosen to illustrate the significant increase in molecular complexity delivered by the cascade chemistry, together with a panel of aryl/heteroaryl iodides (Chart 1). Initial optimization with **1** and **6a** (Scheme 2, Table 1) using Pd_2dba_3 (tris(dibenzylideneacetone)palladium (0)) and TFP (tri(2-furyl)-phosphine)[9] surveyed toluene, MeCN and dioxane as solvents in the presence of ammonium carbonate at 80 °C. No reaction occurred in toluene and dioxane whilst MeCN gave low yields

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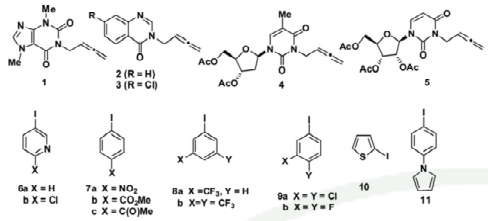
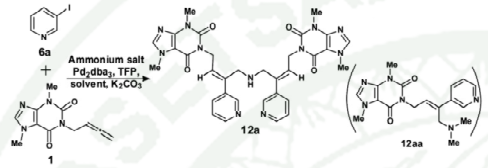


Chart 1 Allene–aryl iodide cascade components.



Scheme 2 Cascade synthesis of complex *Z,Z*-bisallylamine **12a**.

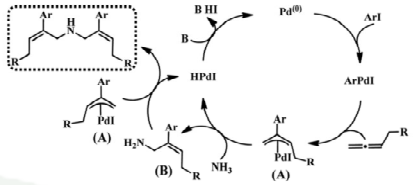
Table 1 Optimization of reaction conditions for cascade synthesis of complex *Z,Z*-bisallylamines[a]

Entry	Ammonium salt (equiv.)	Solvent	Time (h)	Yield (%)
1	Carbonate (6)	DMF–water (2 : 1)	3	58[b]
2	Carbonate (6)	DMF–water (1 : 2)	7	24[b]
3	Carbonate (6)	Dioxane–water (2 : 1)	8	65[c]
4	Tartrate (3)	Dioxane–water (5 : 1)	40	75
5	Carbonate (6)	Dioxane–DMF (5 : 1)	24	63[c]
6	Tartrate (6)	Dioxane–DMF (5 : 1)	22	80
7	Tartrate (3)	Dioxane–DMF (5 : 1)	22	77
8	Citrate (6)	Dioxane–DMF (5 : 1)	23	77
9	Urea (12)	DMF–water (2 : 1)	4	79[d]

[a] Allene (1 mmol), aryl iodide (1.2 mmol), Pd_2dba_3 (2.5 mol%), TFP (10 mol%), K_2CO_3 (2 mmol), 100 °C (for tartrate and citrate), 80 °C (for carbonate and urea). [b] Reaction without K_2CO_3. [c] Reaction with K_2CO_3 or without K_2CO_3 gave the same results. [d] Product **12aa**.

and very slow reactions. Mixed solvents were more effective. Reactions with ammonium carbonate (6 equiv.) in 2 : 1 DMF–water or 1 : 2 DMF–water gave moderate to low yields of **12a** (Table 1, entries 1 and 2). Both ammonium carbonate (6 equiv.) in 2 : 1 dioxane–water and dibasic ammonium tartrate (3 equiv.) in 5 : 1 dioxane–water gave improved yields (Table 1, entries 3 and 4). Ammonium carbonate, tartrate and tribasic ammonium citrate in the presence of K_2CO_3 in 5 : 1 dioxane–DMF furnished good yields of **12a** albeit with longer reaction times (entries 5–8).

Table 1 indicates that when ammonium carbonate was employed the addition of K_2CO_3 was unnecessary due to the lower thermal stability of ammonium carbonate and the faster liberation of ammonia under the reaction conditions (entries 1–3 and 5). In contrast reactions employing ammonium tartrate, which has a high thermal stability compared to ammonium carbonate, required addition of K_2CO_3 to enhance the liberation



Scheme 3 Plausible mechanism for *Z,Z*-bisallylamine synthesis.

of ammonia. Neither the tartrate carboxylate anion or the alcoholic OH groups reacted as nucleophiles under these conditions. The ability of urea to engineer transfer of dimethylamine from DMF to the π-allyl intermediate in the cascade was also briefly explored (Table 1, entry 9) and resulted in the formation of **12aa** (Scheme 2), a protected form of (**B**) (Scheme 3), in 79% yield after 4 h.[7b,10a,b] Our hydroxylamine cascades also deliver protected forms of (**B**).[11] In all other cases the cascade delivered the *Z,Z*-bisallylamine **12a** (see ESI†).

We selected dibasic ammonium tartrate (3–6 mole equivalents) in 5 : 1 dioxane–DMF for an in depth cascade survey (Table 2), generating 30 products in yields ranging from 52–99%. Cascades employing 4-iodonitrobenzene gave, in general, the quickest reactions (Table 2, compounds **12b**, **13a**, **14a** and **15a**, 57–82%), albeit that excess ammonium tartrate was employed to generate products **12b** and **15a.** Reactions employing 3-iodopyridine also worked well (Table 2, compounds **13c**, **14d**, **15f**, **16c** and **16e**, 52–78%) despite the potential for sequestration of the catalyst by the product. 2-Iodothiophene also gave moderate to good yields (Table 2, compounds **12j** and **13f**, 66 and 65%, respectively).

Table 2 5-Component cascade synthesis of complex *Z,Z*-bisallylamines[a]

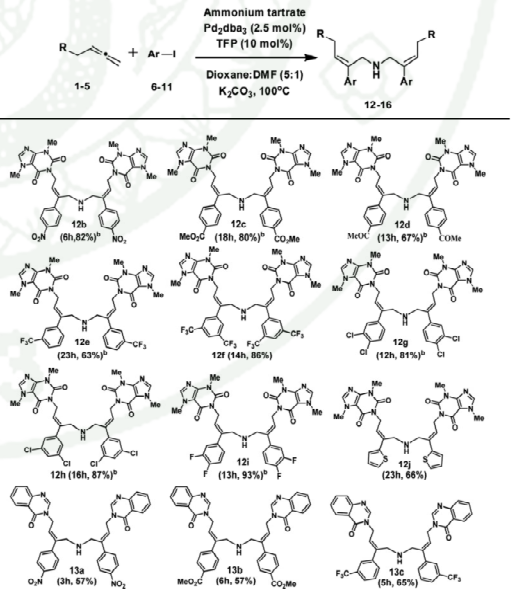
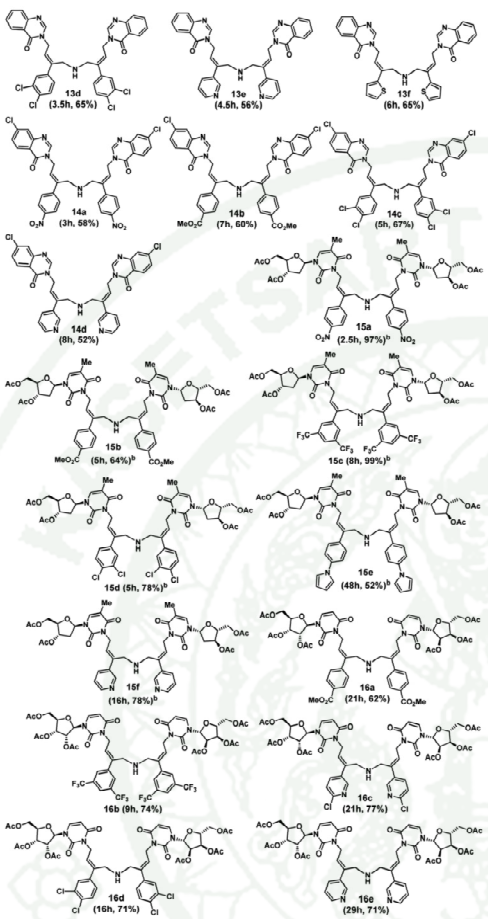


Table 2 (*continued*)



[a] A mixture of allene (1 mmol), aryl iodide (1.2 mmol), Pd_2dba_3 (2.5 mol%), TFP (10 mol%), ammonium tartrate (3 mmol) and K_2CO_3 (2 mmol) in the presence of (5 : 1) dioxane : DMF (24 mL) at 100 °C. [b] Ammonium tartrate (6 equiv.) was used.

A plausible mechanism for the cascade (Scheme 3) starts normally with oxidative addition followed by allene coordination and migratory insertion to furnish the π-allyl complex (**A**) which is attacked by the generated ammonia to afford a mono-allyl amine intermediate (**B**) which attacks the π-complex (**A**) faster than ammonia to give the desired *Z*,*Z*-bisallylamine. The created H–Pd^{II}–I species regenerates Pd^0 *via* reductive elimination in the presence of K_2CO_3. The mechanism requires the intermediate allyl amine (**B**) to be more nucleophilic than ammonia. This has already been commented on by Hartwig[1a,6b,c] for Ir-catalysed allylic amination whilst Kobayashi and Nagano[6a] reported optimization of a Pd-catalysed process for mono-allylic aminations. We note, en passant, that the calculated pK_a's using the ACD/I-Lab web service give pK_a's for the mono-allyl amine conjugate acids of 8.58–9.67 and 9.24 for ammonia.[12]

In summary, we have developed a facile and efficient five component stereoselective cascade synthesis of complex *Z*,*Z*-bisallylamines employing ammonium tartrate as a novel ammonia surrogate. Our protocol displays broad functional group compatibility, effects a substantial increase in molecular complexity and the products offer multivalent tunable probes.

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