PART I: SYNTHESIS OF NAPHTHOQUINONE ESTER DERIVATIVES WITH ANTICANCER AND ANTIMALARIAL ACTIVITIES

INTRODUCTION

Anticancer Activity

Cancer causes 7 million deaths every year and more than 11 million people are diagnosed with cancer every year. Cancer is a disease characterized by uncontrolled division of cells and the ability of these cells to invade other tissues, either by direct growth into adjacent tissue through invasion or by implantation into distant sites by metastasis. Metastasis is defined as the stage in which cancer cells are transported and relocated through the blood stream or lymphatic system. Cancer may affect people of all ages and is one of the leading causes of death in developed countries.

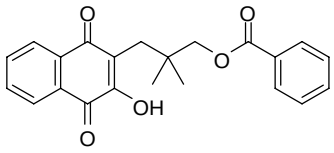
Most cancers can be treated and some cured, depending on the specific type, location and stage. Once diagnosed, cancer is usually treated with a combination of surgery, chemotherapy and radiotherapy. As research develops, treatments are becoming more specific for the type of cancer pathology. Drugs that target specific cancers already exist for several cancers. If untreated, cancers usually cause illness and death.

Rhinacanthus nasutus (L.) Kurz belongs to the Acanthaceae family, which is widely distributed in Southeast Asia, South China, India and Thailand. In Thailand, it is called “Thong Phun Chang”. The leaves and stems of this plant are often used to cure cutaneous eruptions due to ringworm, eczema, pulmonary tuberculosis and neurodermatitis and as an aphrodisiac and aplexiphamic. (Kernan *et al*., 1996) In Taiwan, it is used as a folk medicine for treatment of hepatitis, diabetes, hypertension and skin disease. (Wu *et al*., 1998; Rojanapo *et al*., 1990) In addition, it is used as

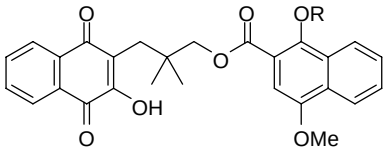
Thai folk medicines for the treatment of cancer, hepatitis and skin diseases such as athlete foot.

Various compounds isolated from *R. nasutus* were reported such as flavonoids, steroids, triterpenes, lignans, coumarins, anthraquinones, quinones and naphthoquinones. Especially, some of the napthoquinones were reported to possess biological activities such as anticancer (Kongkathip *et al*., 2003, 2004), antiplatelet (Wu et al., 1998), antifungal (Kodama *et al*., 1993; Kuwahara *et al*., 1991), antiviral (Sendl *et al*., 1996), anti-inflammatory, antiallergic (Lien *et al*., 2002), and antimalarial activities (Fieser *et al*., 1984; Dalgliesh *et al*., 1949; Porter *et al*., 1972; Likhitwitayawuid *et al*., 1997).

In 2003, our group reported the synthesis of 1,2-naphthoquinone and 1,4-naphthoquinone derivatives which showed cytotoxicity against cancer cell lines (KB, HeLa and $HepG_2$). (Kongkathip *et al*., 2003) A year later, our group also synthesized rhinacanthin-M (**1**), rhinacanthin-N (**2**), rhinacanthin-Q (**3**) and thirty-nine novel naphthoquinone ester derivatives, most of which showed anticancer activity. (Kongkathip *et al*., 2004)



Rhinacanthin-M, **1**



Rhinacanthin-N, **2** , R=H
Rhinacanthin-Q, **3** , R=Me

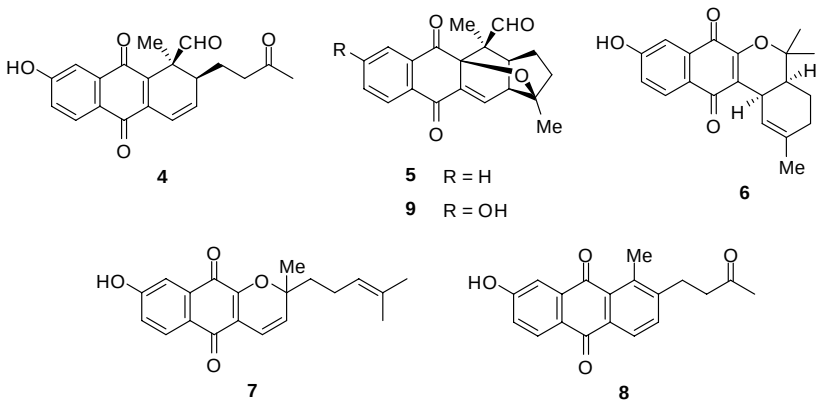
Antimalarial Activity

Malaria affects more than 2400 million people, over 40% of the world's population, in more than 100 countries in the tropics from South America to the Indian peninsula. Every year 300 million to 500 million people suffer from this disease. About 1.5 million to 3 million people in the world die of malaria every year.

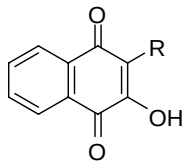
Malaria is an infectious disease caused by the parasite Plasmodia. There are four identified species of this parasite causing human malaria, namely, *Plasmodium vivax*, *P. falciparum*, *P. ovale* and *P. malariae*. The parasite is transmitted by the female anopheles mosquito. Occasionally, transmission occurs by blood transfusion, organ transplantation, needle-sharing, or congenitally from mother to fetus. Malaria is a disease that can be treated in just 48 hours, yet it can cause fatal complications if the diagnosis and treatment are delayed.

P. falciparum is the most important of the malaria plasmodium species. It causes morbidity and deaths and is also influenced by other infectious diseases like measles and also by malnutrition. Vector control has proven futile, so the main combat technique is through drug treatment, but this has so far not been a successful story because of the complexity of the parasite's life cycle, both in man and in the mosquito vector. Immunization would have been the next line of combat, but allelic diversity and antigenic variation makes it difficult to develop a suitable vaccine.

Naphthoquinone derivatives isolated from the plants and fungi did not show only anticancer activity but these compounds also showed antimalarial activity, antifungal and antibacterial. (Kodama *et al*., 1993; Kittakoop *et al*., 1999; Onegi *et al*., 2002) For examples, four naphthoquinones (sterekunthals A (**4**) and B (**5**), pyranokunthones A (**6**) and B (**7**)) and one anthraquinone (anthrakunthone, **8**) together with a known naphthoquinone, pinnatal (**9**), were isolated from the root barks of *Stereospermum kunthianum*. (Onegi *et al*., 2002)



Moreover, synthetic naphthoquinone derivatives have been reported to show various biological activities as well. For example, Fieser has synthesized antimalarial 1,4-naphthoquinones from benzoquinone including 3-alkyl or aryl derivatives of 2-hydroxy-1,4-naphthoquinone (**10**). (Fieser, 1948; Fieser *et al.*, 1984)

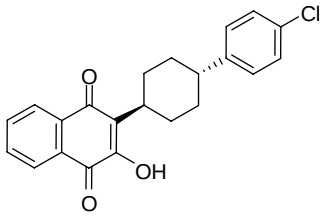


R = alkyl or aryl

10

In 1969, Prescott synthesized and tested 64 amine derivatives of 1,4-naphthoquinone for antimalarial activity against *Plasmodium berghei* infection in mice. Two compounds, bis[2-chloro-1,4-naphthoquinone-3,3'-sulfonylbis(p-phenyl enimine)] and N^4-(2-chloro-1,4-dihydro-1,4-dioxo-2-naphthyl)sulfanilamide exhibited potent antimalarial activity.

In 1998, Williams and Clark reported the synthesis of atovaquone (**11**), 3-hydroxy-1,4-naphthoquinone derivative. This compound was approved and marketed as a prescription drug for the treatment of *Pneumocystis carinii* pneumonia (PCP) and it also showed potent antimalarial activity.



Atovaquone, **11**

In the same year, Marra and co-workers reported the use of atovaquone-proguanil for treatment and prophylaxis of acute, uncomplicated malaria caused by *Plasmodium falciparum* in clinical trials. (Marra *et al*., 2003)

So, it would be interesting to evaluate the anticancer and antimalarial activity and structure-activity relationships (SARs) of the synthesized naphthoquinone ester derivatives. These data will be very useful for future clinical studies and for the drug development.

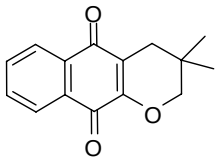
LITRATURE REVIEWS

Naphthoquinone derivatives were isolated from some plants and fungi and they showed a variety of bioactivity. Moreover, some natural naphthoquinones and their derivatives were synthesized and evaluated for the biological activity such as anticancer and antimalarial activities.

Isolation and biological activity of naphthoquinone derivatives

In 1990, Rojanapo and co-workers studied the mutagenicity and antimutagenicity of Thai medicinal plants such as *Acanthus ebracteatus* Vahl, *Plumbago indica* Linn, and *Rhinacanthus nasutus*. The results revealed that various fractions extracted with petroleum ether, hexane and chloroform inhibited the mutagenicity of aflatoxin B_1 and are indirect mutagens.

3,4-Dihydro-3,3-dimethyl-2H-naphtho[2,3-b]pyran-5,10-dione (**12**), a naphthopyran derivative, was isolated from the leaves and stems of *Rhinacanthus nasutus* (Acanthaceae) by Kodama *et al*. in 1993. It showed strongly antifungal activity against *Pyricularia oryzae*, the pathogen of rice blast disease with inhibitory value of 82.3% at 100 ppm.



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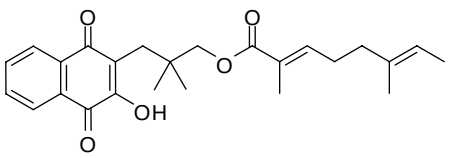
In 1996, Sendl and co-workers reported the isolation of two naphthoquinones, rhinacanthin-C (**13**) and rhinacanthin-D (**14**) from *Rhinacanthus nasutus*. These compounds exhibited inhibitory activity against cytomegalovirus (CMV) with EC_{50} values of 0.02 and 0.22 μg/mL, respectively.



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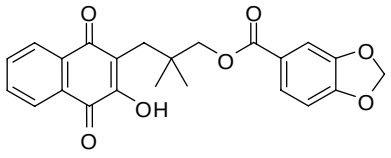

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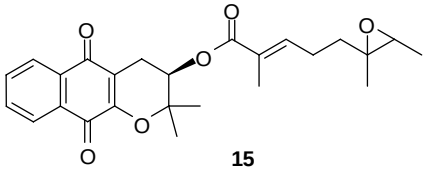
In 1998, Wu *et al*. isolated two dimethyldihydropyranonaphthoquinone esters (**15** and **16**) and eight 2-hydroxy-1,4-naphthoquinone esters (**17**-**24**) from the roots of *Rhinacanthus nasutus*.



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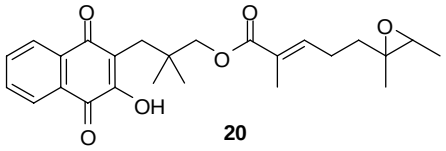

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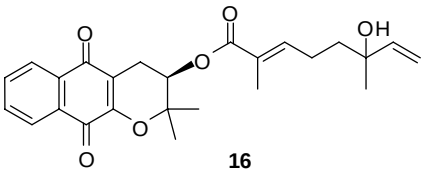

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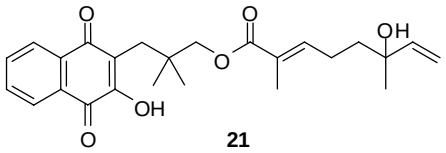

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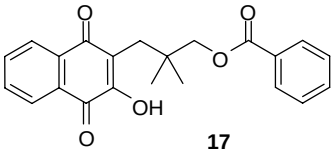

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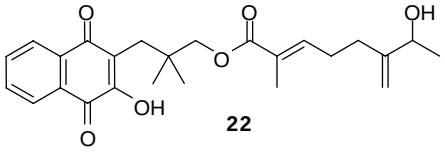

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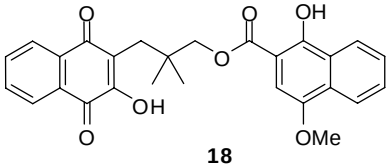

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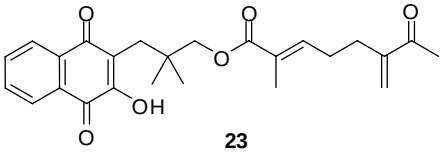

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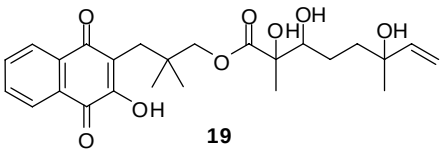

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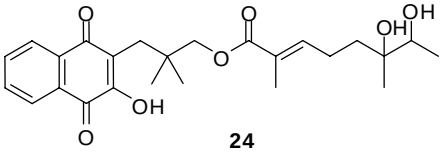

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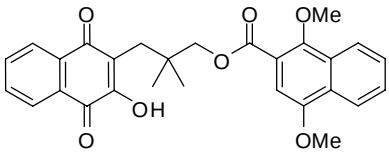
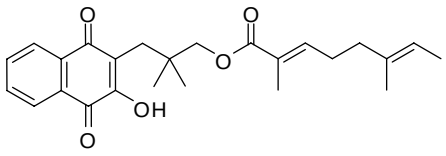
In the same year, Wu and co-workers reported further investigation of the roots of *Rhinacanthus nasutus* which afforded rhinacanthin Q (**3**) together with twenty-four known compounds that they reported previously. Most compounds showed significant cytotoxicity against P-388, A-549, HT-29 and HL-60 cell lines.

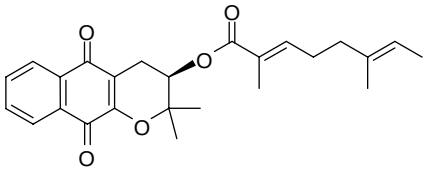
Rhinacanthin Q (**3**), C (**13**) and B (**25**) also showed 72-100% inhibition of rabbit platelet aggregation induced by collagen (10 μg/mL). Only rhinacanthin A (**26**) exhibited antiplatelet aggregation induced by platelet activation factor (2 ng/mL).



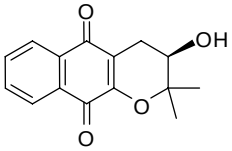
Rhinacanthin Q, **3**



Rhinacanthin C, **13**

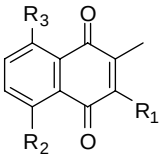


Rhinacanthin B, **25**

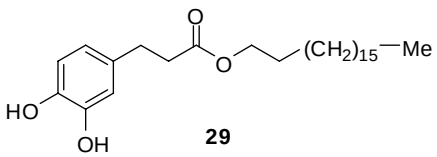


Rhinacanthin A, **26**

In 1998, Likhitwitayawuid *et al* reported isolation of plumbagin (**27**), 2-methylnaphthazarin (**28**), octadecyl caffeate (**29**), isoshinanolone (**30**) and droserone (**31**) from the roots of *Nepenthes thorelii* and the synthesis of some of their derivatives. These compounds were evaluated for antimalarial activity against *Plasmodium falciparum* and some of them showed strong activity especially **27** (IC_{50} = 0.27 μM).



	R1	R2	R3
27	H	OH	H
28	H	OH	OH
31	OH	OH	H
33	H	OMe	H
34	OH	OMe	H
35	OAc	OMe	H
36	OMe	OMe	H
38	Cl	OMe	H



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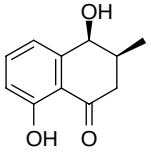

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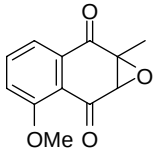

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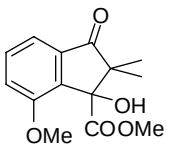

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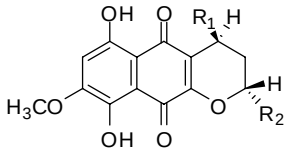
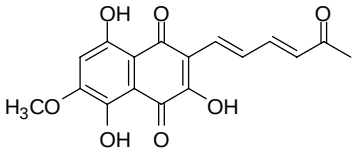
Six bioactive naphthoquinone derivatives, erythrostominone (**39**), deoxyerythrostominone (**40**), 4-O-methyl erythrostominone (**41**), epierythrostominol (**42**), deoxyerythrostominol (**43**) and 3,5,8-trihydroxy-6-methoxy-2-(5-oxohexa-1,3-dienyl)-1,4-naphthoquinone (**44**), were isolated from the insect pathogenic fungus *Cordyceps unilateralis* BCC1869 by Kittakoop and co-workers in 1999. These compounds showed moderate to strong antimalarial activity.





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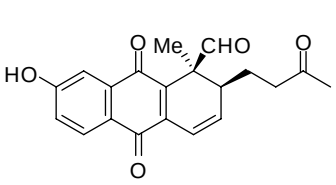
	R1	R2
39	OH	
40	H	
41	OMe	
42	OH	
43	H	

In the same year, Guerra *et al*. reported the interceptive effect of lapachol in rats. The results showed that pregnant Wistar rats were unaffected but there was 100% fetal/embryo mortality, indicating of a strong interceptive effect of lapachol in rats. (Guerra *et al*., 1999)

In 2002, Onegi *et al*. reported the isolation of four novel naphthoquinones (sterekunthals A (**4**) and B (**5**), pyranokunthones A (**6**) and B (**7**)) and one novel anthraquinone (anthrakunthone, **8**) together with a known naphthoquinone pinnatal (**9**) from the root barks of *Stereospermum kunthianum*. These compounds were tested for antiplasmodial activity and toxicity against the endothelial cell line ECV-304. It was found that most of them exhibited moderate to strong antiplasmodial activity and toxicity against ECV-304 cell line.



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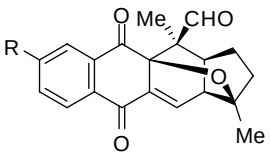
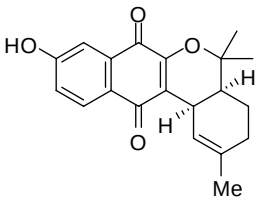


5 R = H

9 R = OH



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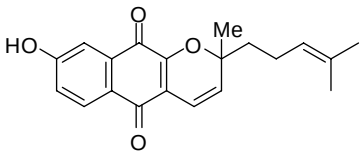

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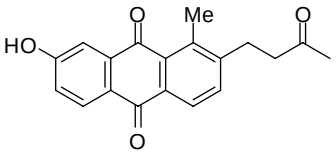
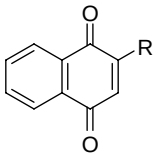


8

Synthesis of naphthoquinone derivatives

In 1948, Fieser synthesized 2-hydroxy-1,4-naphthoquinone by the Diels-Alder reaction of benzoquinone and butadiene. (Fieser, 1948) Thirty-six year later, his group also synthesized 3-alkyl or aryl derivatives of 2-hydroxy-1,4-naphthoquinone (**45**). (Fieser *et al*., 1984)



R = H, cyclohexyl, C_6H_5

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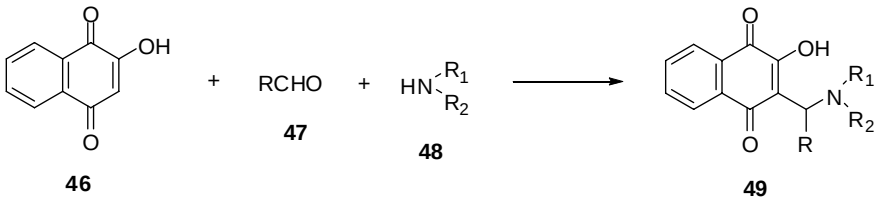
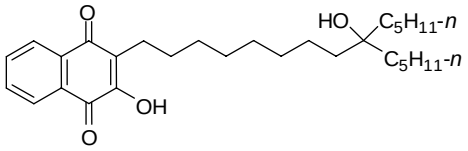
The synthesis of Mannich bases (**49**) of lawsone (**46**) was reported by Dalgliesh (**Scheme 1**) but they showed no significant antimalarial activity. (Dalgliesh, 1949)



46 + RCHO **47** + **48** → **49**

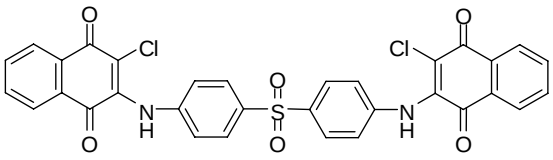
Scheme 1

In 1950, Fawaz and Fieser reported a new synthesis of lapinone (**50**) and found that nine patients with primary vivax malaria were promptly relieved of fever and parasites when they were treated with 2 g of lapinone per day for four days in an initial clinical trial conducted at the American University, Beirut, Lebanon. Two patients had relapsed two and three weeks after treatment, one was free of symptoms for ten months and then either relapsed or was reinfected, and the other six were without relapse for periods of thirteen to fifteen months after treatment.



Lapinone **(50)**

In 1969, Prescott synthesized and tested 64 amine derivatives of 1,4-naphthoquinone for antimalarial activity against *Plasmodium berghei* infection in mice. Two compounds, bis[2-chloro-1,4-naphthoquinone-3,3'-sulfonylbis(p-phenylenimine)] (**51**) and N^4-(2-chloro-1,4-dihydro-1,4-dioxo-3-naphthyl) sulfanilamide (**52**) exhibited potent antimalarial activity.



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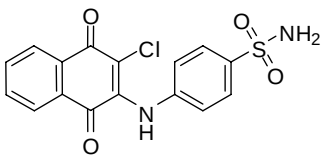
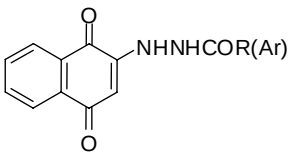


52

In the same year, Dudley and co-workers reported the synthesis of 2-acylhydrazino-1,4-naphthoquinone derivatives (**53**) and related compounds from lawsone. (Dudley *et al*., 1969) Later, Dudley and Chiang synthesized dehydro-α-lapachone (**55**) and dehydro-β-lapachone (**56**) from isolapachol (**54**) by treatment with DDQ. (Dudley and Chiang, 1969)



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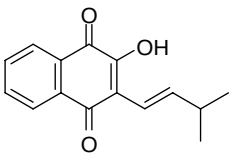

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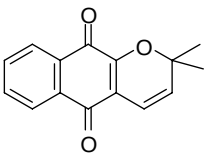

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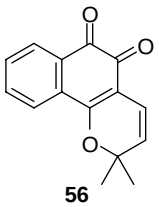
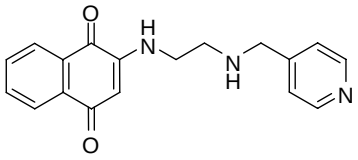


56

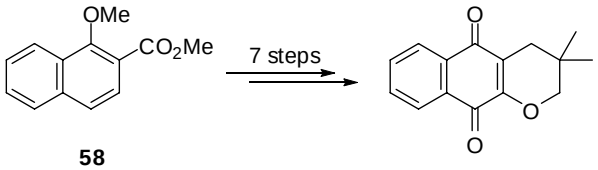
In 1972, Porter *et al*. reported the preparation of eight new 2-alkylamino-1,4-naphthoquinones as potential inhibitors of the biosynthesis and/or function of coenzyme Q_8 in the metabolism of *Plasmodium* and as potential antimalarial activity against *Plasmodium berghei* in the mouse. It was found that **57** showed definite activity (T-C = 3.1 at 640 mg/kg) in the *in vivo* antimalarial test but was too quickly metabolised.



57

In 1973, Martin *et al.* studied about the relationship between physical properties and antimalarial activity of 1,4-naphthoquinones. Due to the naphthoquinones probably exert their antimalarial activity by competing with coenzyme Q to disrupt mitochondrial electron transport, this mechanism of action they expected that the inactive molecules showed differ from the active ones in oxidation-reduction properties. They found that the requirement of reduction for a quinone to be an antimalarial is consistent with postulated mode of action and the active antimalarial compounds are active inhibitors of electron transport.

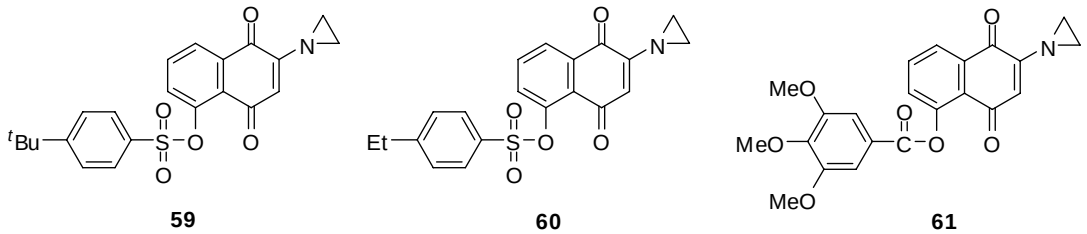
In 1991, Kuwahara *et al*. synthesized an antifungal naphthopyran derivative (**12**), isolated from *Rhinacanthus nasutus*, from methyl 1-methoxy-2-naphthoate (**58**) in 7 steps (**Scheme 2**).



58 **12**

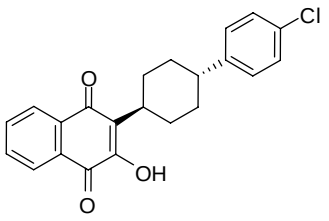
Scheme 2

In the same year, Lin *et al.* synthesized a series of 2-aziridinyl- and 2,3-bis(aziridinyl)-1,4-naphthoquinonyl sulfonate and acylate derivatives and evaluated their antimalarial activity against *Plasmodium falciparum*, Vietnam Smith strain. They found that 2- aziridinyl-1,4-naphthoquinon-5-yl-*p*-tert-butylbenzenesulfonate (**59**), p-ethylbenzenesulfonate (**60**) and 3',4',5'-trimethoxybenzoyl ester (**61**) exhibited potent antimalarial activity with IC_{50} values of 2.4×10^{-8}, 9.6×10^{-8} and 16×10^{-7} M, respectively.

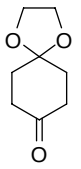


59 **60** **61**

In 1998, Williams and Clark described a route for preparation of atovaquone (**11**), a drug for the treatment of *Pneumocystis carinii* pneumonia (PCP) which is a common parasitic lung infection, from 1,4-cyclohexanedione-*mono*-ethylene ketal (**62**) via a key intermediate, trans-1,4-disubstituted cyclohexane (**63**). This method is a concise route which promises generality for the construction of related naphthoquinones.



Atovaquone, **11**



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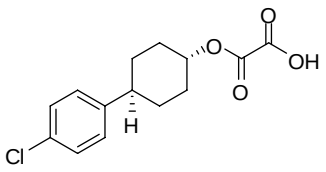
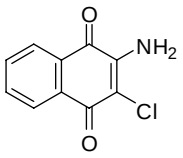


63

In 2001, Kapadia and his co-workers investigated eighteen compounds including several synthetic and natural naphthoquinones as potent antimalarial agents against *Plasmodium falciparum*. They found that 2-amino-3-chloro-1,4-naphthoquinone (**64**) is the most potent against the W2 clone with an IC_{50} value of 0.18 μM which is more potent than chloroquine (**65**) (IC_{50} = 0.23 μM). Moreover, 2-amino-1,4-naphthoquinone and 4-amino-1,2-naphthoquinone analogs showed promising antimalarial activity whereas 2-hydroxy-1,4-naphthoquinone and dimeric quinine were less active.



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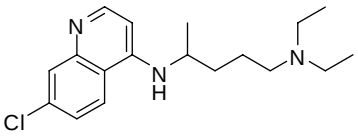
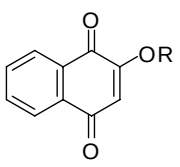


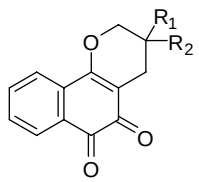
65

Lien and co-workers prepared 2-alkoxy 1,4-naphthoquinone derivatives (**66**-**70**) as antiplatelet, anti-inflammatory and antiallergic agents in 2002. Some of these compounds especially 2-propoxy-1,4-naphthoquinone (**66**) and 2-butoxy-1,4-naphthoquinone (**68**) exhibited potent inhibitory effect on neutrophil superoxide anion formation. (Lien *et al*., 2002)

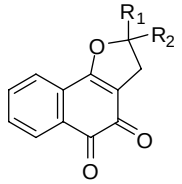


66 R = $-(CH_2)_2CH_3$
67 R = $-CH(CH_3)_2$
68 R = $-(CH_2)_3CH_3$
69 R = $-(CH_2)_4CH_3$
70 R = -Benzyl

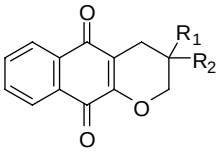
In 2003, Kongkathip *et al*. reported the synthesis and evaluation of the cytotoxicity against cancer cell lines (KB, HeLa and $HepG_2$) and Vero cells of 1,2-naphthoquinone (**71**-**77**) and 1,4-naphthoquinone derivatives (**12** and **78**-**82**).



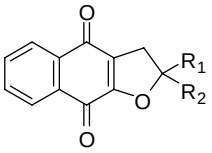
71, R_1 =CH_3, R_2 =CH_3
72, R_1 =H, R_2 =H
73, R_1 =CH_3, R_2 =H
74, R_1 =OH, R_2 =H



75, R_1 =CH_3, R_2 =CH_3
76, R_1 =CH_3, R_2 =H
77, R_1 =H, R_2 =H

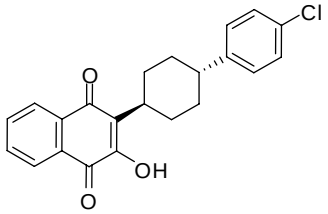


12, R_1 =CH_3, R_2 =CH_3
78, R_1 =H, R_2 =H
79, R_1 =CH_3, R_2 =H

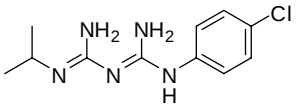


80, R_1 =CH_3, R_2 =CH_3
81, R_1 =CH_3, R_2 =H
82, R_1 =H, R_2 =H

In the same year, Marra *et al*. studied atovaquone-proguanil for treatment of acute, uncomplicated malaria caused by *Plasmodium falciparum* in 8 clinical trials and for prophylaxis of malaria in 6 clinical trials. They found that the treatment with atovaquone-proguanil led to a higher or equally effective cure rate than the comparator antimalarial agents and it was well tolerated in these clinical trials. (Marra *et al*., 2003)

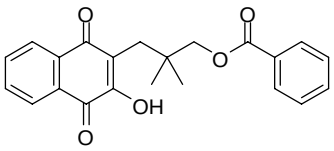


Atovaquone, **11**

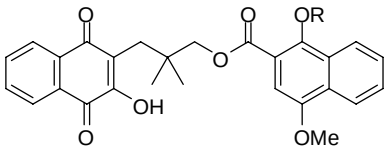


Proguanil, **83**

A year later (2004), Kongkathip and co-workers have reported the synthesis and anticancer activity testing against KB, HeLa and $HepG_2$ cell lines of rhinacanthin-M (**1**), rhinacanthin-N (**2**), rhinacanthin-Q (**3**) and thirty-nine novel naphthoquinone ester derivatives together with computer modeling to study the mode of action of some of the compounds. (**Schemes 3**, **4** and **5**) (Kongkathip *et al*., 2004)

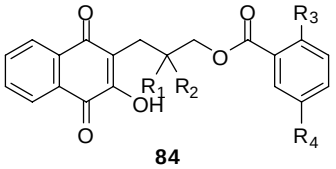


Rhinacanthin-M, **1**



Rhinacanthin-N, **2** , R=H

Rhinacanthin-Q, **3** , R=Me



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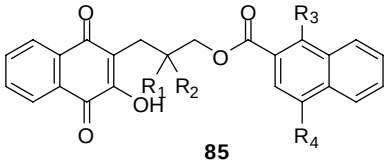

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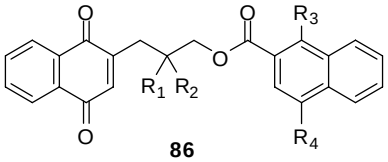

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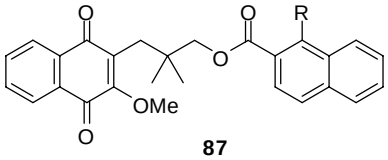

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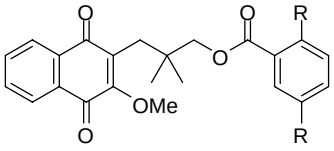
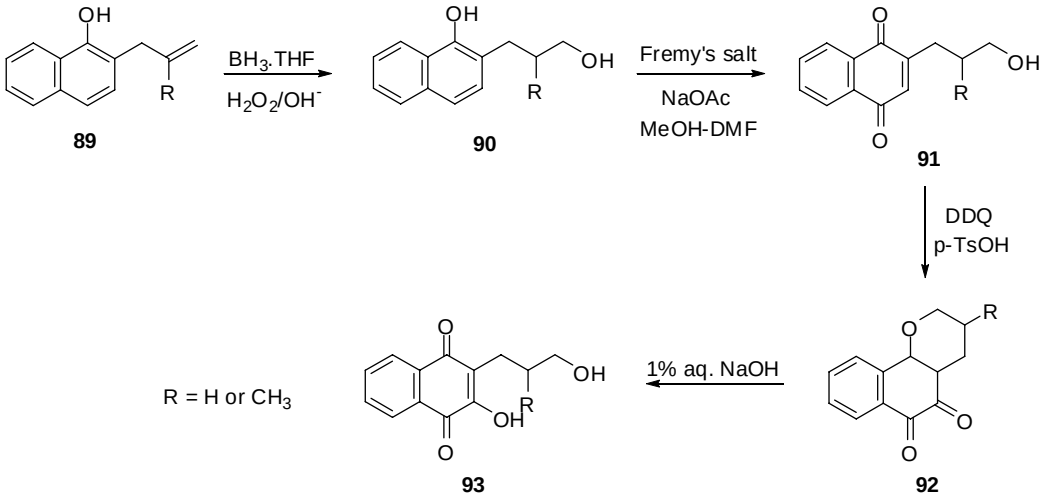


88

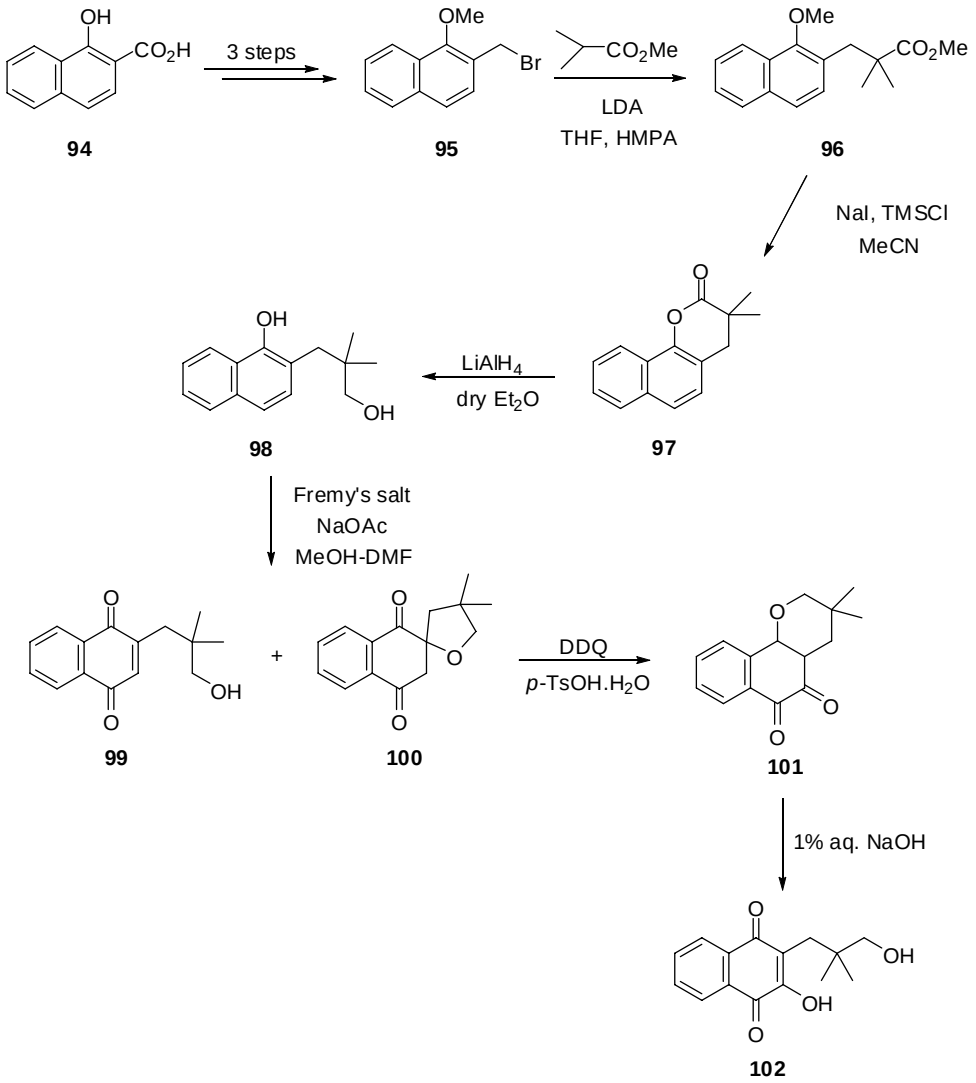
R = H or OH or OCH_3

R_1, R_2 = H or CH_3

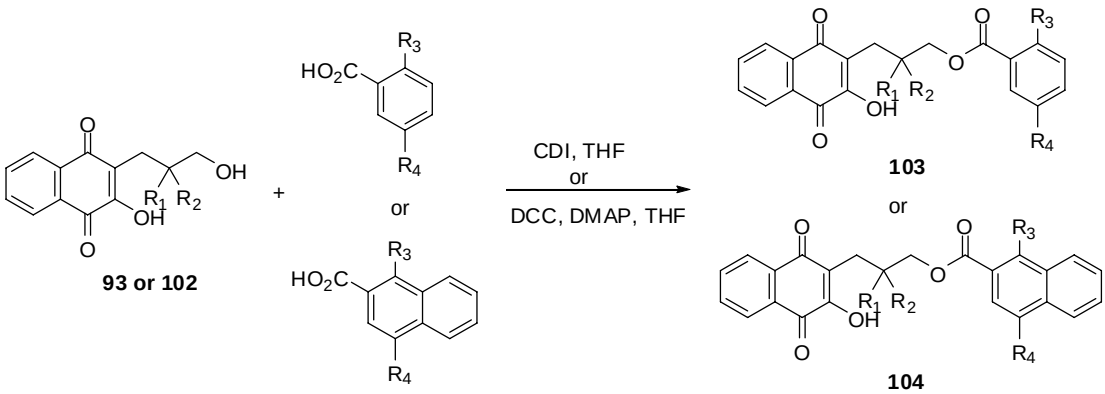
R_3, R_4 = H or OH or OCH_3



Scheme 3



Scheme 4

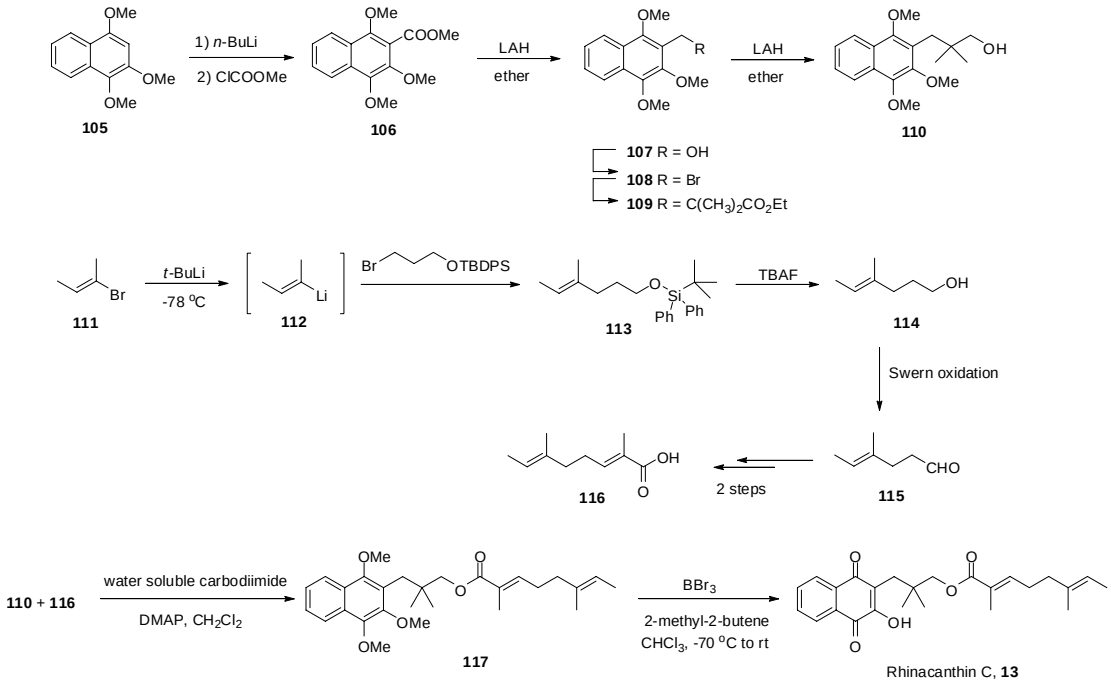


R_1, R_2 = H or CH_3

R_3, R_4 = H or OH or OCH_3

Scheme 5

In the same year, Gotoh *et al*. studied the antiproliferative activity of the ethanol extract of the roots and aqueous extract of the leaves of *Rhinacanthus nasutus* which were assessed *in vitro* and *in vivo* using HeLa, Hvr100-6, PC-3 and T24 cell lines. The said authors also synthesized rhinacanthin C (**13**) from 1,2,4-trimethoxy naphthalene in order to study its inhibitory activity (**Scheme 6**). (Gotoh *et al*., 2004)

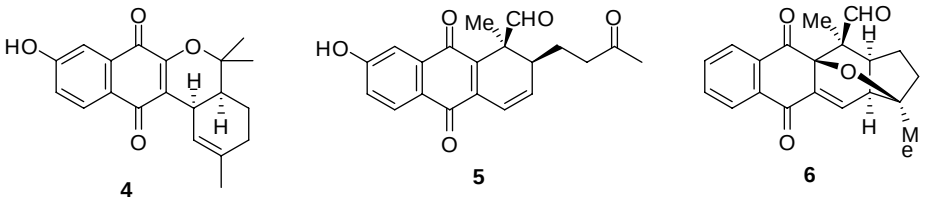


Scheme 6

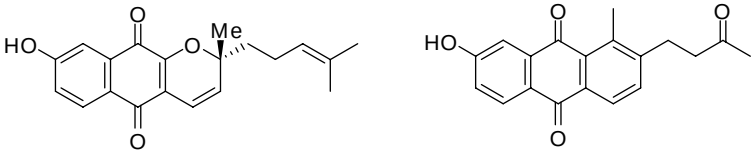
Dos Santos and co-workers also studied quantitative structure-activity relationships of aziridinyl-1,4-naphthoquinone and their antimalarial activity using the MP3 method. They found that 2- and 2,3-aziridinyl-1,4-naphthoquinone antimalarial agents share specific molecular electronic properties related to the ability of some groups in donating or withdrawing electrons of the aromatic ring which affected the Gibbs free energy (ΔG^o) for the redox process. (Dos Santos *et al*., 2004)

In 2005, Malerich *et al*. described the total synthesis of antimalarial naphthoquinone natural products isolated from the Bignoniaceae family such as sterekunthals A (**4**) and B (**5**), pyranokunthones A (**6**) and B (**7**), anthrakunthone (**8**),

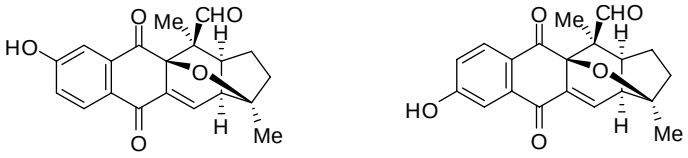
pinnatal (**9**) and isopinnatal (**118**). These compounds were prepared along the lines of a biosynthetic involving pericyclic reactions.



4 **5** **6**

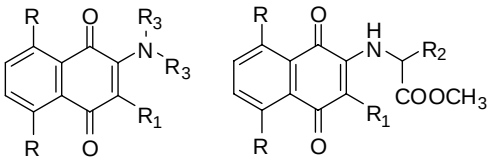


7 **8**



9 **118**

In the same year, Tandon and co-workers synthesized and evaluated the antifungal and antibacterial activities of novel (L)-α-amino acid methyl ester, heteroalkyl and aryl substituted 1,4-naphthoquinone derivatives. (Tandon *et al*., 2005)



119 **120**

MATERIALS AND METHODS

Materials

Instrumentations

Melting points (m.p.) were determined on a Fisher John apparatus and MEI-TEMP capillary melting point apparatus at the Department of Chemistry, Kasetsart University and are incorrected.

The infrared (IR) spectra were recorded on a Perkin-Elmer 2000 Fourier transform infrared spectrophotometer at the Department of Chemistry, Faculty of Science, Kasetsart University.

Mass spectra (MS) were obtained on the GCMS-QP-5050A at Kasetsart Agricultural and Agro Industrial Product Improvement Institute (KAPI) and on AGILENT 1100 series LC/MSB TRAP at the Faculty of Science, Kasetsart University.

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 400 MHz on a VARIAN ^{UNITY} INOVA 400 MHz spectrometer at the Department of Chemistry, Kasetsart University. Chemical shifts (δ) are given in parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard. Coupling constants (J) are given in Hertz (Hz). Unless otherwise specified deuterochloroform ($CDCl_3$) was used as a solvent. The following abbreviations are used: s = singlet, d = doublet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, br s = broad singlet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet, qd = quartet of doublet, ddd = doublet of doublet of doublet.

High resolution mass spectral data (HRMS) were measured at EPSRC National Mass Spectrometry Service Centre, Department of Chemistry, University of Wales Swansea, UK and by LCP Micromass at the National Science and Technology Development Agency (NSTDA), Bangkok, THAILAND.

Elemental analyses were performed by the LECO CHNS-932 at the Faculty of Science, Kasetsart University. Optical rotation were recorded on an AA 1000 Polarimeter at the School of Chemistry, University of Leeds, United Kingdom.

Chromatographic systems

Thin-layer chromatography (TLC) on aluminum sheets with silica gel 60 F_{254} was used routinely for monitoring reaction progress. The chromatograms were visualized under ultraviolet light (254 nm).

Flash column chromatography was performed on silica gel (230-400 mesh, Merck 9385) according to the method of Still (1978).

Chemical reagents

All reagents and solvents were used as received from Merck, Fluka and Aldrich Chemical. Unless otherwise noted in the case of anhydrous conditions, purifications were accomplished according to the standard procedure outlined in Vogel's Text Book of Practical Organic Chemistry (1989).

Dry reagents

Acetone was dried over Type 4A molecular sieves for 24 hours.

Benzene was dried over sodium wire for 24 hours.

Dichloromethane was dried over anhydrous calcium chloride for 24 hours then distilled from calcium hydride and stored over Type 3A molecular sieves.

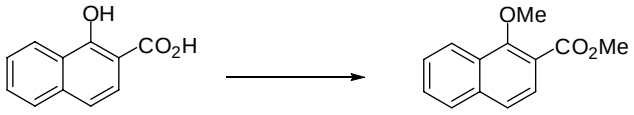
Diethyl ether and tetrahydrofuran (THF) were dried over sodium metal and benzophenone under nitrogen atmosphere until the dark blue or purple colour persisted. The anhydrous ether was distilled immediately before use.

Dimethylformamide (DMF) was dried over Type 3A molecular sieve for 72 hours, followed by distillation under reduced pressure and stored over Type 3A molecular seives

Methods

Chemistry

Methyl 1-methoxynaphthalene-2-carboxylate (121) (Kongkathip *et al*., 2004)



94 **121**

A mixture of 1-hydroxy-2-naphthoic acid (**94**)(11.3 g, 0.06 mol), potassium carbonate (24.8 g, 0.18 mol), and iodomethane (15 mL, 0.24 mol) was dissolved in acetone (200 mL) and then stirred under reflux for 15 hours. The reaction mixture was cooled to room temperature, filtered and washed with acetone. The filtrate was concentrated in vacuo, then dichloromethane was added, washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 3% ethyl acetate-hexane to afford the desired product (**121**)(12.46 g, 96%) as a colourless oil.

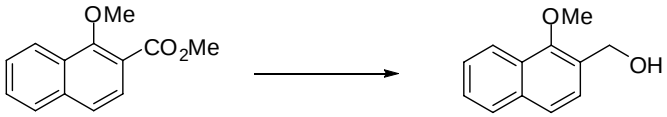
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.98 (s, 3H, CO_2CH_3), 4.07 (s, 3H, OCH_3), 7.57 (m, 2H, ArH), 7.61 (d, *J*=8.7 Hz, 1H, ArH), 7.84 (m, 1H, ArH), 7.86 (d, *J*=8.7 Hz, 1H, ArH), 8.28 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 52.87 (CH_3), 64.02 (CH_3), 119.81 (C), 124.25 (2×C), 127.15 (CH), 127.28 (CH), 128.49 (CH), 128.94 (CH), 129.19 (C), 137.40 (C), 158.91 (C), 167.32 (C=O).

FTIR (neat, cm^{-1}): 2948 (CH, CH_3), 1723 (C=O), 1442, 1340 (C=C), 1240, 1135 (C-O).

MS (EI), *m/z* (% relative intensity): 216 (M^+, 95), 185 (100), 127 (57), 114 (74).

(1-Methoxynaphthalen-2-yl)methanol (122) (Kongkathip *et al*., 2004)



121 **122**

A solution of ester **121** (6.2 g, 0.03 mol) in dry diethyl ether (20 mL) was added dropwise to a stirred and ice-cooled suspension of lithium aluminium hydride (3.3 g, 0.09 mol) in dry diethyl ether (100 mL). After stirring for 2 hours at room temperature, the reaction mixture was quenched with ethyl acetate and water, then extracted with diethyl ether (3×100 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 10% ethyl acetate-hexane to yield the desired product **122** (88%) as a colourless amorphous powder; m.p. 70-71 °C (Kongkathip *et al*., 2003, m.p. 70-71 ºC).

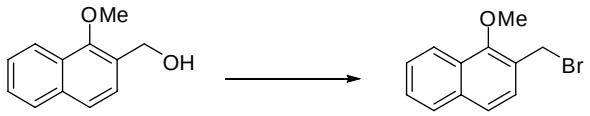
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.22 (br s, 1H, OH), 4.00 (s, 3H, OCH_3), 4.90 (s, 2H, OCH_2), 7.50 (m, 3H, ArH), 7.63 (d, *J*=8.4 Hz, 1H, ArH), 7.84 (dd, *J*=7.5 and 1.3 Hz, 1H, ArH), 8.10 (dd, *J*=7.9 and 0.9 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 61.43 (CH_3), 63.29 (CH_2), 122.69 (CH), 125.06 (CH), 126.81 (CH), 127.29 (CH), 128.45 (C), 128.73 (CH), 129.63 (C), 135.37 (C), 154.35 (C).

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

MS (EI), *m/z* (% relative intensity): 188 (M^+, 71), 156 (39), 127 (100), 115 (72).

2-(Bromomethyl)-1-methoxynaphthalene (95) (Kongkathip *et al*., 2004)



122 **95**

Phosphorus tribromide (1M in dichloromethane, 6.4 mL, 6.4 mmol) was added dropwise to a stirred solution of alcohol **122** (0.6 g, 3.2 mmol) in dry dichloromethane (10 mL). After stirring for 6 hours at room temperature, water was added, then the mixture was neutralised with saturated sodium hydrogen carbonate and extracted with dichloromethane (3×30 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The bromide **95** was obtained as a colourless solid (0.81 g, quantitative yield), m.p. 65-66 °C (Kongkathip *et al*., 2003, m.p. 65-66 °C).

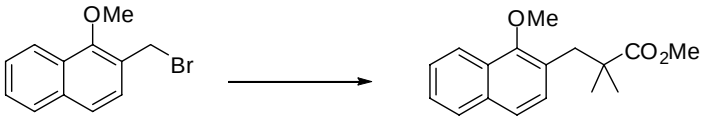
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.00 (s, 3H, OCH_3), 4.70 (s, 2H, CH_2Br), 7.41 (d, *J*=8.4 Hz, 1H, ArH), 7.47 (m, 2H, ArH), 7.57 (d, *J*=8.4 Hz, 1H, ArH), 7.78 (m, 1H, ArH), 8.07 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 29.06 (CH_2), 63.13 (CH_3), 123.13 (CH), 125.41 (CH), 127.03 (CH), 127.46 (CH), 128.51 (C), 128.56 (CH, C), 128.82 (CH), 135.76 (C), 155.02 (C).

FTIR (KBr, cm^{-1}): 2940 (CH_2, CH_3), 1570, 1444, 1366 (C=C), 1211, 1078 (C-O).

MS (EI), *m/z* (% relative intensity): 252 ($[M+1]^+$, 7), 250 (7), 171 (100), 128 (86).

Methyl 2-((1-methoxynaphthalen-2-yl)methyl)-2-methylpropanoate (96)



95 **96**

1M n-Buthyl lithium (7.8 mL, 7.8 mmol) was added dropwise to a stirred solution of diisopropylamine (0.56 mL, 4 mmol) in dry tetrahydrofuran (THF) (5 mL) at 0 °C under nitrogen atmosphere. After stirring for 20 minutes, methyl isobutyrate (0.34 mL, 2.94 mmol) was slowly added at –78 °C to the reaction mixture and stirring was continued for 30 minutes. A solution of bromide **95** (0.49 g, 1.96 mmol) and hexamethylphosphoramide (HMPA) (0.7 mL) in dry THF (2 mL) was added dropwise to the reaction mixture at the same temperature. After stirring for 2 hours at –78 °C, the reaction mixture was quenched with saturated ammonium chloride solution and then extracted with diethyl ether (3×50 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with 5% ethyl acetate-hexane to give the desired product (**96**)(0.47 g, 89%) as a colourless solid; m.p. 99-100°C (Kongkathip *et al.*, 2003, m.p. 99-100 °C).

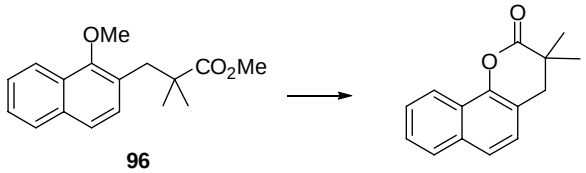
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.20 (s, 6H, 2×CH_3), 3.08 (s, 2H, CH_2), 3.70 (s, 3H, CO_2CH_3), 3.90 (s, 3H, OCH_3), 7.18 (d, *J*=8.4 Hz, 1H, ArH), 7.40-7.55 (m, 3H, ArH), 7.80 (d, *J*=7.8 Hz, 1H, ArH), 8.05 (d, *J*=7.8 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.02 (2×CH_3), 38.90 (CH_2), 42.92 (C), 50.79 (CH_3), 60.63 (CH_3), 121.25 (CH), 122.43 (CH), 124.61 (CH), 124.77 (CH), 125.40 (C), 126.89 (C), 126.92 (CH), 128.29 (CH), 133.16 (C), 153.57 (C), 177.28 (C=O).

FTIR (KBr, cm^{-1}): 2965 (CH_2, CH_3), 1733 (C=O), 1571, 1469, 1371, 1322 (C=C), 1193, 1119 (C-O).

MS (EI), *m/z* (% relative intensity): 272 (M^+, 17), 171 (100), 128 (34), 115 (26).

3,4-Dihydro-3,3-dimethylbenzo[h]chromen-2-one (97)



96 **97**

A mixture of compound **96** (0.8 g, 2.9 mmol) and powdered aluminium chloride (0.78 g, 5.8 mmol) in dry redistilled chlorobenzene (20 mL) was refluxed for 4 hours. The solution was cooled to room temperature and poured into 10% hydrochloric acid (60 mL), then extracted with diethyl ether (3×30 mL). The combined organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Then chlorobenzene was removed by distillation under reduced pressure. The resulting residue was purified by flash column chromatography, eluting with 2% ethyl acetate-hexane to afford the desired product **97** (0.54 g, 83%) as a colourless amorphous powder; m.p. 123-124 °C (Kongkathip *et al.*, 2003, m.p. 123-124 °C).

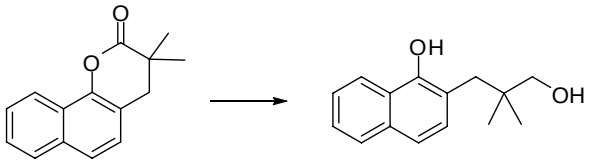
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.30 (s, 6H, 2×CH_3), 2.90 (s, 2H, CH_2), 7.17 (d, *J*=8.3 Hz, 1H, ArH), 7.46 (m, 2H, ArH), 7.53 (d, *J*=8.3 Hz, 1H, ArH), 7.76 (m, 1H, ArH), 8.18 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.46 (2×CH_3), 37.77 (C), 39.37 (CH_2), 117.06 (C), 121.71 (CH), 123.88 (C), 124.51 (CH), 126.47 (CH), 126.98 (CH), 127.07 (CH), 128.20 (CH), 134.07 (C), 146.77 (C), 174.26 (C=O).

FTIR (KBr, cm^{-1}): 2974 (CH_2, CH_3), 1759 (C=O), 1600, 1383 (C=C), 1241, 1174, 1111 (C-O).

MS (EI), *m/z* (% relative intensity): 226 (M^+, 61), 198 (65), 183 (100), 128 (57).

2-(3-Hydroxy-2,2-dimethylpropyl)-1-hydroxy naphthalene (98)



97 **98**

A solution of lactone **97** (0.2 g, 0.88 mmol) in dry tetrahydrofuran (2 mL) was added dropwise to a stirred and ice-cooled suspension of lithium aluminium hydride (0.07 g,1.8 mmol) in dry tetrahydrofuran (2 mL). After stirring for 2 hours at room temperature, the reaction mixture was quenched with ethyl acetate and water, then extracted with diethyl ether (3×20 mL). The combined organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with 3% ethyl acetate-hexane to give the desired product **98** (0.15 g, 71%) as a colourless amorphous powder; m.p. 118-119°C (Kongkathip *et al.*, 2003, m.p. 118-119 °C).

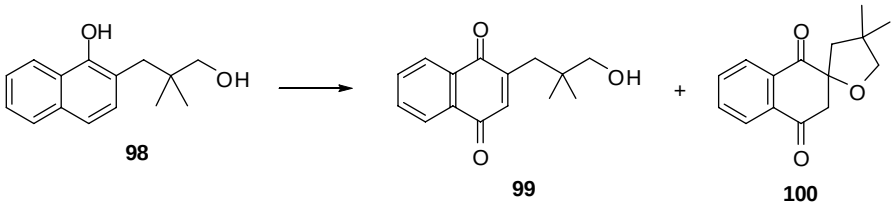
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.04 (s, 6H, 2×CH_3), 2.45 (br s, 1H, OH), 2.77 (s, 2H, CH_2), 3.25 (s, 2H, CH_2O), 7.16 (d, *J*=8.4 Hz, 1H, ArH), 7.34 (d, *J*=8.4 Hz, 1H, ArH), 7.46 (m, 2H, ArH), 7.76 (m, 1H, ArH), 8.30 (m, 1H, ArH), 8.53 (br s, 1H, OH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.83 (2×CH_3), 37.28 (C), 39.05 (CH_2), 69.84 (CH_2), 118.24 (C), 119.62 (CH), 123.11(CH), 125.58 (CH), 126.10 (C), 126.31 (CH), 127.85 (CH), 131.45 (CH), 134.30 (C), 151.52 (C).

FTIR (KBr, cm^{-1}): 3363 (OH), 2955 (CH_2, CH_3), 1572, 1473, 1386 (C=C), 1079, 1033 (C-O).

MS (EI), *m/z* (% relative intensity): 230 (M^+, 28), 183 (16), 157 (100), 128 (76).

2-(3-Hydroxy-2,2-dimethyl propyl)-1,4-naphthoquinone (99) and 1,4-naphthoquinone-2-spiro-2'-(4',4'-dimethyltetrahydrofuran) (100)



A solution of Fremy's salt (1.2 g, 4.4 mmol) in water (30 mL) and 1M aqueous sodium acetate solution (1 mL) was added to a stirred solution of compound **98** (0.14 g, 0.6 mmol) in methanol-dimethylformamide (MeOH-DMF)(3:1)(10 mL). After stirring for 14 hours at room temperature, the reaction mixture was extracted with diethyl ether (3×20 mL). The combined organic phase was washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo to afford the mixture of the desired product **99** and product **100**. The mixture was then seperated by flash column chromatography using 1% ethyl acetate-hexane as an

eluent to give compound **99** (76%) as a yellow solid and compound **100** as a yellow oil in 16% yield. (Kongkathip *et al.*, 2004)

Compound 99; m.p. 81-82 °C (Kongkathip *et al.*, 2004, m.p. 81-82 °C).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.90 (s, 6H, 2×CH_3), 2.50 (s, 2H, CH_2Ar), 3.10 (s, 2H, OCH_2), 6.76 (s, 1H, CH=C), 7.69 (m, 2H, ArH), 8.01 (m, 1H, ArH), 8.05 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.52 (2×CH_3), 37.72 (CH_2), 38.23 (C), 70.27 (CH_2), 126.75(CH), 127.67(CH), 132.63(C), 132.76(C), 134.39(CH), 134.68(CH), 138.98 (CH), 149.47 (C), 185.26 (C=O), 187.34 (C=O).

FTIR (KBr, cm^{-1}): 3420 (OH), 2955 (CH_2, CH_3), 1663 (C=O), 1589, 1466, 1328, 1298 (C=C), 1263, 1041 (C-O).

MS (EI), *m/z* (% relative intensity): 244 (M^+, 8), 214 (40), 172 (100), 144 (47), 115 (80).

Compound 100

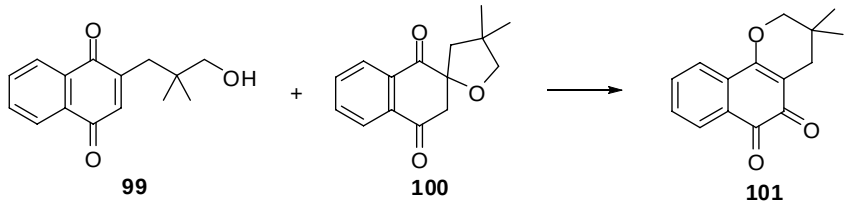
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.10 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.60 and 2.40 (2×d, J_{AB}=13 Hz, 2×1H, CH_2), 3.20 and 3.30 (2×d, J_{AB}=16 Hz, 2×1H, CH_2O), 3.60 and 3.70 (2×d, J_{AB}=8.5 Hz, 2×1H, CH_2CO), 7.76 (m, 2H, ArH), 8.06 (m, 1H, ArH), 8.12 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.18 (CH_3), 28.38 (CH_3), 41.43 (C), 47.13 (CH_2), 51.75 (CH_2), 81.34 (CH_2), 86.79 (C), 127.17 (CH), 128.44 (CH), 134.68 (CH), 134.96 (C), 135.01(CH), 135.79 (C), 194.59 (C=O), 195.63 (C=O).

FTIR (nujol, cm^{-1}): 1700 (C=O), 1600, 1300(C=C), 1053 (C-O).

MS (EI), *m/z* (% relative intensity): 244 (M^+, 67), 201 (57), 146 (67), 104 (83), 76 (100).

3,4-Dihydro-3,3-dimethyl-2H-benzo[h]chromene-5,6-dione (101)



99 **100** **101**

A mixture of compound **99** and **100** (0.15 g, 0.6 mmol), dichlorodicyanobenzoquinone (DDQ) (0.17 g, 0.7 mmol) and p-toluenesulfonic acid monohydrate (0.02 g, 0.06 mmol) in dry benzene (3 mL) was stirred under reflux for 30 minutes. The reaction mixture was cooled to room temperature, filtered, then washed with dichloromethane and concentrated in vacuo. The residue was filtered through aluminium oxide and washed with 50% ethyl acetate-hexane to afford the crude residue which was purified by flash column chromatography eluting with 2% ethyl acetate-hexane to provide the desired product **101** (0.12 g, 81%) as an orange amorphous powder; m.p. 151-152 °C. (Kongkathip *et al.*, 2004, m.p. 151-152 °C)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.00 (s, 6H, 2×CH_3), 2.30 (s, 2H, CH_2), 3.90 (s, 2H, CH_2O), 7.45 (td, *J*=7.6 and 1.2 Hz, 1H, ArH), 7.59 (td, *J*=7.6 and 1.4 Hz, 1H, ArH), 7.76 (dd, *J*=7.8 and 1.2 Hz, 1H, ArH) and 8.01(dd, *J*=7.6 and 1.4 Hz, 1H, ArH).

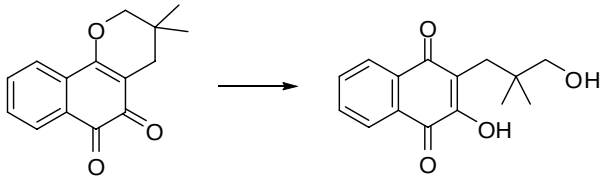
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.47 (2×CH_3), 28.64 (C), 32.59 (CH_2), 77.82 (CH_2), 113.92 (C), 124.80 (CH), 129.37 (CH), 130.49 (C), 131.41 (CH), 132.54 (C), 135.57 (CH), 162.68 (C), 179.66 (C=O), 180.26 (C=O).

FTIR (KBr, cm^{-1}): 2955, 2907 (CH_2, CH_3), 1696, 1640 (C=O), 1599, 1563, 1479, 1295 (C=C), 1228, 1090 (C-O).

MS (EI), *m/z* (% relative intensity): 242 (M^+, 4), 214 (21), 159 (50), 76 (37), 56 (100).

Anal. calcd for $C_{15}H_{14}O_3$: C 74.36, H 5.82. Found: C 74.19, H 5.86.

2-Hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (102)



101 **102**

The solution of compound **101** (0.5 g, 2.1 mmol) in 1% aqueous sodium hydroxide solution (12 mL, 3.1 mmol) was refluxed for 2 hours. Then the reaction mixture was cooled to room temperature and acidified with acetic acid, extracted with dichloromethane (3×50 mL). The combined organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was recrystallized from hexane-dichloromethane to give the desired product **102** (0.45 g, 84%) as a yellow amorphous powder; m.p. 144-145 °C (Kongkathip *et al.*, 2004, m.p. 144-145 °C).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.00 (s, 6H, 2×CH_3), 2.60 (s, 2H, CH_2), 3.10 (s, 2H, CH_2O), 3.70 (br s, 1H, OH), 7.74 (td, *J*=7.5 and 1.4 Hz, 1H, ArH), 7.76 (br s, 1H, OH), 7.80 (td, *J*=7.5 and 1.4 Hz, 1H, ArH), 8.12 (dd, *J*=7.5 and 0.96 Hz, 1H, ArH) and 8.16 (dd, *J*=7.5 and 0.96 Hz, 1H, ArH).

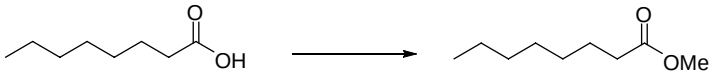
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.87 (2×CH_3), 31.26 (CH_2), 39.19 (C), 70.47 (CH_2), 122.56 (C), 126.94 (CH), 127.84 (CH), 130.11 (C), 133.36 (C), 133.90 (CH), 135.69 (CH), 155.84 (C), 181.54 (C=O), 187.04 (C=O).

FTIR (KBr, cm^{-1}): 3420 (OH), 2970, 2871 (CH_2, CH_3), 1674, 1627 (C=O), 1356, 1272 (C=C), 1216, 1044 (C-O).

MS (EI), *m/z* (% relative intensity): 260 (M+, 2), 230 (77), 188 (100), 160 (35), 77 (76).

Synthesis of 2-methyloctanoic acid (133)

Methyl octanoate 131



130 **131**

A mixture of octanoic acid (**130**)(5.49 mL, 34.7 mmol) and potassium carbonate (7.176 g, 52.0 mmol) was stirred in acetone (40 mL). Methyl iodide (4.32 mL, 69.3 mmol) was added dropwise and the mixture was refluxed for 4 h. The reaction mixture was then filtered and filtrate was evaporated to remove the acetone. After that the residue was dissolved with dichloromethane, washed with water and dried over anhydrous sodium sulfate. The crude residue was purified by flash column chromatography eluting with 1% EtOAc: Hexane to afford the desired product **131** (4.24 g, 77%) as colorless oil.

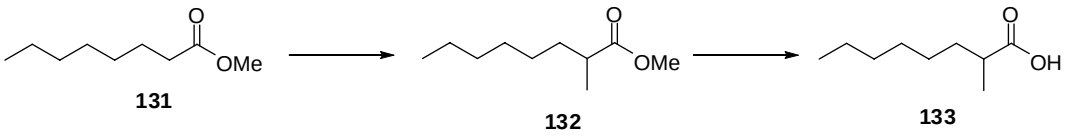
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88 (t, *J*=7.2 Hz, 3H, CH_3CH_2), 1.20-1.04 (m, 8H, $(CH_2)4$), 1.62 (m, 2H, CH_2CH2CO), 2.31 (t, *J*=7.6 Hz, 2H, CH_2CO), 3.67 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.23 (CH_3), 22.78 (CH_2), 25.16 (CH_2), 29.11 (CH_2), 29.31 (CH_2), 31.85 (CH_2), 34.31 (CH_2), 51.60 (OCH_3), 174.35 (C=O).

FTIR (KBr, cm^{-1}): 2947, 2928, 2857 (CH_2, CH_3), 1743 (C=O), 1168 (C-O).

MS (EI), *m/z* (% relative intensity): 159 ($[M+1]^+$, 8), 158 (M+, 23), 157 ($[M-1]^+$, 100), 128 (49).

2-Methyloctanoic acid (133)



1.38 M *n*-Buthyl lithium (9.2 mL, 12.6 mmol) was added dropwise to a stirred solution of diisopropylamine (1.78 mL, 12.6 mmol) in dry tetrahydrofuran (THF) (10 mL) at 0°C under nitrogen. After stirring for 20 minutes, methyl octanoate **131** (1 g, 6.3 mmol) was slowly added at –78°C to the reaction mixture and stirring was continued for 30 minutes. A solution of methyl iodide (0.49 g, 1.96 mmol) and hexamethylphosphoramide (HMPA) (2.2 mL) in dry THF (5 mL) was added dropwise to the reaction mixture at the same temperature. After stirring for 2 hours at –78°C, the reaction mixture was quenched with saturated ammonium chloride solution and then extracted with diethyl ether (3×50 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude residue of the ester product **132.**

The crude residue of the methyl ester **132** was further hydrolysed by stirring with potassium hydroxide (1.41 g, 25.2 mmol) in 50% EtOH: H_2O (20 mL) for 3 h. The solution was cooled to room temperature, acidified with concentrated hydrochloric acid to pH 1 and then extracted with dichloromethane (3×50 mL). The combined organic layers were washed with brine and water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude residue. The crude residue was purified by flash column chromatography eluting with 3% EtOAc: hexane to afford the desired product **133** (a racemic mixture) (528.2 mg, 53%) as colorless oil.

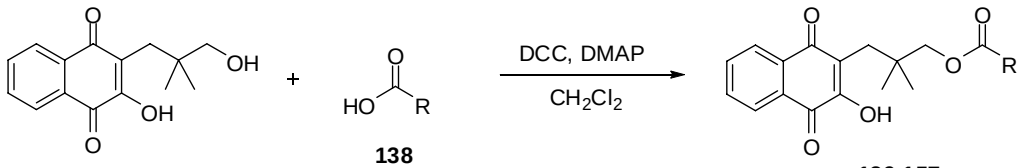
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.89 (t, J=6.8 Hz, 3H, CH_3CH_2), 1.18 (d, J=7.2 Hz, 3H, CH_3CH), 1.24-1.36 (m, 8H, $(CH_2)_8$), 1.38-1.50 (m, 1H, $CHHCHCO$), 1.63-1.74 (m, 1H, $CHHCHCO$), 2.41-2.51 (sext, J=7.2 Hz, 1H, CHCO).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.04 (CH_3), 16.82 (CH_3), 22.59 (CH_2), 27.09 (CH_2), 29.17 (CH_2), 31.67 (CH_2), 33.55 (CH_2), 39.35 (CH_2), 183.15 (C=O).

FTIR (KBr, cm^{-1}): 3434 (OH), 2952, 2929, 2858 (CH_2, CH_3), 1707 (C=O), 1288, 1237 (C-O).

MS (EI), *m/z* (% relative intensity): 159 ($[M+1]^+$, 100), 128 (67), 103 (32), 95 (43).

Synthesis of Naphthoquinone ester derivatives

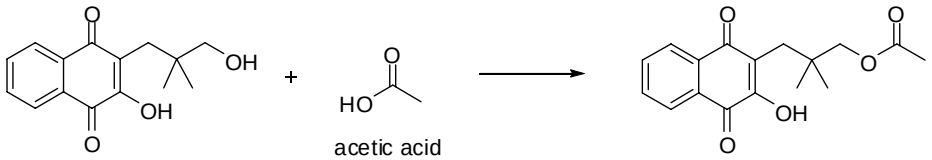


General procedure:

A solution of naphthoquinone alcohol **102** (1 mmol) in dry dichloromethane (2 mL) was added to a stirred solution of carboxylic acid (1.3 mmol) and 4-dimethylaminopyridine (DMAP)(0.3 mmol) in dry dichloromethane. The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 1,3-dicyclohexylcarbodiimide (DCC)(1.3 mmol) in dry dichloromethane was added to the reaction mixture. After stirring continuously overnight at room temperature, the precipitate of dicyclohexylurea was filtered off and the organic solution was washed with saturated ammonium chloride solution and water, then dried over anhydrous

sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl acetate (139)



102 **139**

Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (40 mg, 0.154 mmol), acetic acid (11.4 μL, 0.200 mmol), DCC (41.3 mg, 0.200 mmol), DMAP (5.6 mg, 0.046 mmol) in dry dichloromethane (5 mL) at room temperature over 14 h. The crude residue was purified by flash column chromatography eluting with 5% ethyl acetate-hexane to provide the desired product **139** (41.2 mg, 89%) as a yellow oil which crystallized from hexane–dichloromethane as yellow needles, m.p. 113.5-114.5 ^{o}C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.92 (s, 6H, 2×CH_3), 1.95 (s, 3H, $COCH_3$), 2.6 1 (s, 2H, CH_2Ar), 3.77 (s, 2H, OCH_2), 7.40 (s, 1H, OH), 7.62 (td, *J*=7.6 and 1.4 Hz, 1H, ArH), 7.69 (td, *J*=7.6 and 1.4 Hz, 1H, ArH), 8.02 (dd, *J*=7.6 and 1.4 Hz, 1H, ArH), 8.05 (dd, *J*=7.6 and 1.4 Hz, 1H, ArH).

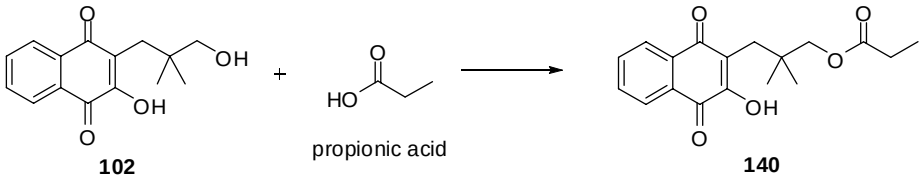
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.87 (CH_2), 25.02 (2×CH_3), 31.88 (CH_3), 36.71 (C), 72.76 (CH_2), 121.68 (C), 126.10 (CH), 127.01 (CH), 129.33 (C), 132.93 (CH, C), 134.97 (CH), 154.21 (C), 171.22 (C=O), 181.21 (C=O), 184.85 (C=O).

FTIR (KBr, cm^{-1}): 3229 (OH), 2964, 2925, 2873 (CH_2, CH_3), 1716, 1670, 1641 (C=O), 1591, 1459, 1274, 1252 (C=C), 1214, 1037 (C-O).

MS (EI), *m/z* (% relative intensity): 301 ($[M-H]^+$, 5), 229 (75), 211 (100), 187 (40), 159 (24), 128 (10), 115 (5).

Anal. calcd for $C_{17}H_{18}O_5$: C 67.54, H 6.00. Found: C 67.43, H 6.27.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl propionate (140)



102 **140**

Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (50 mg, 0.192 mmol), propionic acid (18.7 μL, 0.250 mmol), DCC (51.6 mg, 0.991 mmol), DMAP (7.1 mg, 0.058 mmol) in dry dichloromethane (7 mL) at room temperature over 20 h. The crude residue was purified by flash column chromatography eluting with 2% ethyl acetate-hexane to provide the desired product **140** (43.8 mg, 90%) as a yellow oil which crystallized from hexane–dichloromethane as yellow needles, m.p. 89-90 ^oC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.91 (s, 6H, 2×CH_3), 1.13 (t, *J*=7.6 Hz, 3H, CH_2-*CH_3*), 2.31 (q, *J*=7.6 Hz, 2H, *CH_2*-CH_3), 2.69 (s, 2H, CH_2Ar), 3.86 (s, 2H, OCH_2), 7.43 (s, 1H, OH), 7.70 (td, *J*=7.6 and 1.2 Hz, 1H, ArH), 7.77 (td, *J*=7.6 and 1.2 Hz, 1H, ArH), 8.10 (dd, *J*=7.6 and 1.2 Hz, 1H, ArH), 8.13 (dd, *J*=7.6 and 1.2 Hz, 1H, ArH).

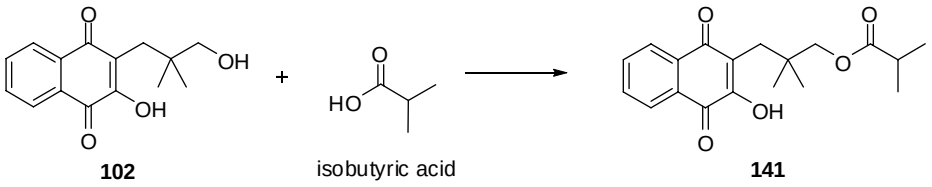
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 9.17 (CH_3), 25.03 (2×CH_3), 27.64 (CH_2), 31.89 (CH_2), 36.83 (C), 72.54 (CH_2), 121.70 (C), 126.10 (CH), 127.00 (CH), 129.33 (C), 132.92 (CH, C), 134.96 (CH), 154.20 (C), 174.48 (C=O), 181.21 (C=O), 184.85 (C=O).

FTIR (KBr, cm^{-1}): 3323 (OH), 2985, 2953, 2925 (CH_2, CH_3), 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.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl isobutyrate (141)



Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (50 mg, 0.192 mmol), isobutyric acid (23.3 μL, 0.250 mmol), DCC (51.6 mg, 0.250 mmol), DMAP (7.1 mg, 0.058 mmol) in dry dichloromethane (7 mL) at room temperature over 20 h. The crude residue was purified by flash column chromatography eluting with 3% ethyl acetate-hexane to provide the desired product **141** (54.6 mg, 86%) as a yellow oil which crystallized from hexane–dichloromethane as yellow needles, m.p. 70.5-71.5 ^oC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.99 (s, 6H, 2×CH_3), 1.17 (d, *J*=7.0 Hz, 6H, *$(CH_3)_2$*-CH), 2.54 (sept, *J*= 7.0 Hz, 1H, $(CH_3)_2$*CH*), 2.69 (s, 2H, CH_2Ar), 3.85 (s, 2H, OCH_2), 7.44 (s, 1H, OH), 7.70 (td, *J*=7.5 and 1.2 Hz, 1H, ArH), 7.77 (td, *J*=7.5 and 1.2 Hz, 1H, ArH), 8.10 (dd, *J*=7.5 and 1.2 Hz, 1H, ArH), 8.13 (dd, *J*=7.5 and 1.2 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.96 (2×CH_3), 24.97 (2×CH_3), 31.84 (CH_2), 34.16 (CH), 36.94 (C), 72.40 (CH_2), 121.65 (C), 126.07 (CH), 126.98 (CH), 129.33

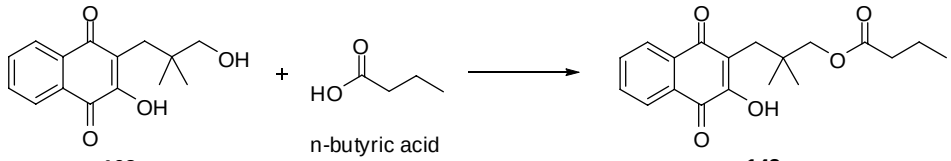
(C), 132.90 (CH, C), 134.92 (CH), 154,27 (C), 177.03 (C=O), 181.20 (C=O), 184.83 (C=O).

FTIR (KBr, cm^{-1}): 3362 (OH), 2969, 2932, 2873 (CH_2, CH_3), 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.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl butyrate (142)



Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (40 mg, 0.154 mmol), n-butyric acid (18.4 µL, 0.200 mmol), DCC (41.3 mg, 0.991 mmol), DMAP (5.6 mg, 0.046 mmol) in dry dichloromethane (5 mL) at room temperature over 18 h. The crude residue was purified by flash column chromatography eluting with 7% ethyl acetate-hexane to provide the desired product **142** (42.2 mg, 87%) as a yellow oil which crystallized from hexane–dichloromethane as yellow needles, m.p. 66-67 ^oC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.85 (t, *J*=7.4 Hz, 3H, *CH_3*-CH_2), 0.92 (s, 6H, 2×CH_3), 1.56 (m, 2H, CH_3-*CH_2*-CH_2), 2.18 (t, *J*=7.4 Hz, 2H, CH_2-*CH_2*-COO), 2.61 (s, 2H, CH_2Ar), 3.79 (s, 2H, OCH_2), 7.37 (s, 1H, OH), 7.62 (td, *J*=7.6 and 1.4 Hz, 1H, ArH), 7.69 (td, *J*=7.6 and 1.4 Hz, 1H, ArH), 8.02 (m, 1H, ArH), 8.05 (m, 1H, ArH).

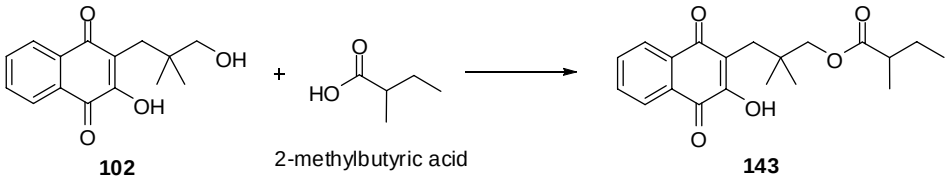
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.69 (CH_3), 18.45 (CH_2), 25.05 (2×CH_3), 31.95 (CH_2), 36.30 (CH_2), 36.83 (C), 72.51 (CH_2), 121.73 (C), 126.10 (CH), 127.02 (CH), 129.34 (C), 132.92 (CH, C), 134.97 (CH), 154.19 (C), 173.70 (C=O), 181.23 (C=O), 184.85 (C=O).

FTIR (KBr, cm^{-1}): 3378 (OH), 2968, 2932, 2873 (CH_2, CH_3), 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.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl 2-methyl butanoate (143)



Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (40 mg, 0.154 mmol), 2-methylbutyric acid (a racemic mixture) (22.0 µL, 0.200 mmol), DCC (41.3 mg, 0.991 mmol), DMAP (5.6 mg, 0.046 mmol) in dry dichloromethane (5 mL) at room temperature over 17 h. The crude residue was purified by flash column chromatography eluting with 4% ethyl acetate-hexane to provide the desired product **143** (a racemic mixture) (42.8 mg, 81%) as a yellow gum.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.89 (t, *J*=7.2 Hz, 3H, *CH_3*CH_2), 0.99 (s, 6H, 2×CH_3), 1.14 (d, *J*=7.0 Hz, 3H, *CH_3*CH(CO)), 1.46 (m, 1H, *CH_2*CH_3), 1.70 (m, 1H, *CH_2*CH_3), 2.35 (sext, *J*=7.0 Hz, 1H, CH_3*CH*(CO)), 2.69 (s, 2H, CH_2Ar), 3.87 (s, 2H,

OCH_2), 7.45 (s, 1H, OH), 7.70 (td, *J*=7.5 and 1.2 Hz, 1H, ArH), 7.77 (td, *J*=7.5 and 1.2 Hz, 1H, ArH), 8.10 (ddd, *J*=7.5, 1.2 and 0.6 Hz, 1H, ArH), 8.13 (ddd, *J*=7.5, 1.2 and 0.6 Hz, 1H, ArH).

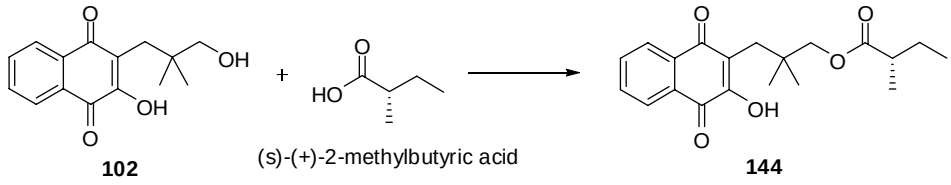
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.25 (CH_3), 17.18 (CH_3), 25.64 ($2\times CH_3$), 27.32 (CH_2), 32.60 (CH_2), 37.58 (C), 41.90 (CH), 73.07 (CH_2), 122.34 (C), 126.73 (CH), 127.67 (CH), 129.99 (C), 133.55 (CH, C), 135.59 (CH), 154.86 (C), 177.26 (C=O), 181.86 (C=O), 185.47 (C=O).

FTIR (KBr, cm^{-1}): 3371 (OH), 2967, 2932, 2873 (CH_2, CH_3), 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.

(S)-3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl 2-methylbutanoate (144)



102 (s)-(+)-2-methylbutyric acid **144**

Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (40 mg, 0.154 mmol), (*S*)-(+)-2-methylbutyric acid (22.0 μL, 0.200 mmol), DCC (41.3 mg, 0.200 mmol), DMAP (5.6 mg, 0.046 mmol) in dry dichloromethane (5 mL) at room temperature over 14h. The crude residue was purified by flash column chromatography eluting with 3% ethyl acetate-hexane to provide the desired product **144** (40.0 mg, 76%) as a yellow gum.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.89 (t, J=7.2 Hz, 3H, CH_3CH_2), 0.99 (s, 6H, 2×CH_3), 1.14 (d, J=7.4 Hz, 3H, $CH_3CH(CO)$), 1.46 (m, 1H, CH_2CH_3), 1.67 (m, 1H, CH_2CH_3), 2.35 (sext, J=7.4 Hz, 1H, $CH_3CH(CO)$), 2.69 (s, 2H, CH_2Ar), 3.87 (s, 2H, OCH_2), 7.44 (s, 1H, OH), 7.70 (td, J=7.6 and 1.6 Hz, 1H, ArH), 7.78 (td, J=7.6 and 1.6 Hz, 1H, ArH), 8.10 (m, 1H, ArH), 8.13 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 11.61 (CH_3), 16.54 (CH_3), 25.00 (CH_3), 25.02 (CH_3), 26.68 (CH_2), 31.94 (CH_2), 36.94 (C), 41.26 (CH), 72.44 (CH_2), 121.70 (C), 126.09 (CH), 127.02 (CH), 129.35 (C), 132.92 (CH, C), 134.95 (CH), 154.24 (C), 176.66 (C=O), 181.23 (C=O), 184.84 (C=O).

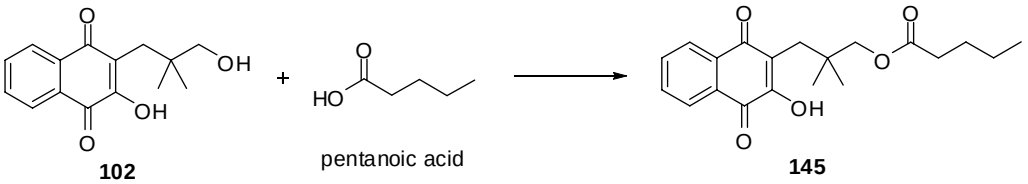
FTIR (KBr, cm^{-1}): 3371 (OH), 2968, 2932, 2873 (CH_2, CH_3), 1731, 1664, 1650 (C=O), 1595, 1462, 1370, 1274 (C=C), 1217, 1049 (C-O).

MS (EI), *m/z* (% relative intensity): 344 (M+, 4), 243 (42), 225 (32), 187 (100), 159 (62).

Optical rotation: $[\alpha]_D^{26}$ = +4.3 (*c* 0.6, $CHCl_3$).

Anal. calcd for $C_{20}H_{24}O_5$: C 69.07, H 7.02. Found: C 69.47, H 7.22.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl pentanoate (145)



102 **145**

Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (50 mg, 0.192 mmol), pentanoic acid

(27.0 μL, 0.250 mmol), DCC (51.6 mg, 0.250 mmol), DMAP (7.1 mg, 0.058 mmol) in dry dichloromethane (7 mL) at room temperature over 20h. The crude residue was purified by flash column chromatography eluting with 4% ethyl acetate-hexane to provide the desired product **145** (30.0 mg, 45%) as a yellow gum which crystallized from hexane–dichloromethane as yellow needles, m.p. 51-52 ^{o}C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88 (t, *J*=7.3 Hz, 3H, CH_3CH_2), 0.99 (s, 6H, 2×CH_3), 1.32 (m, 2H, $CH_3CH_2CH_2$), 1.58 (m, 2H, $CH_2CH_2CH_2$), 2.27 (t, *J*=7.6 Hz, 2H, $COCH_2CH_2$), 2.68 (s, 2H, CH_2Ar), 3.85 (s, 2H, OCH_2), 7.44 (s, 1H, OH), 7.67 (td, *J*=7.6 and 1.4 Hz, 1H, ArH), 7.69 (td, *J*=7.6 and 1.4 Hz, 1H, ArH), 8.09 (dd, *J*=7.6 and 1.4 Hz, 1H, ArH), 8.13 (dd, *J*=7.6 and 1.4 Hz, 1H, ArH).

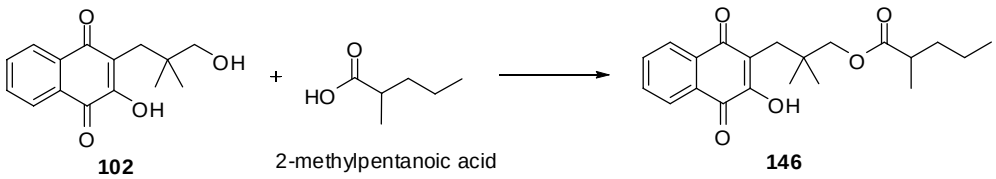
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.66 (CH_3), 22.26 (CH_2), 25.05 (2×CH_3), 27.03 (CH_2), 31.98 (CH_2), 34.11 (CH_2), 36.83 (C), 72.53 (CH_2), 121.74 (C), 126.09 (CH), 127.01 (CH), 129.33 (C), 132.92 (C), 132.95 (CH), 134.96 (CH), 154.17 (C), 173.85 (C=O), 181.22 (C=O), 184.84 (C=O).

FTIR (KBr, cm^{-1}): 3373 (OH), 2957, 2925, 2865 (CH_2, CH_3), 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.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl 2-methylpentanoate (146)



Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (40 mg, 0.154 mmol), 2-methylpentanoic acid (a racemic mixture) (25.0 μL, 0.200 mmol), DCC (41.3 mg, 0.200 mmol), DMAP (5.6 mg, 0.046 mmol) in dry dichloromethane (5 mL) at room temperature over 16h. The crude residue was purified by flash column chromatography eluting with 3% ethyl acetate-hexane to provide the desired product **146** (a racemic mixture) (42.4 mg, 77%) as a yellow gum which crystallized from hexane–dichloromethane as yellow needles, m.p. 57-58 ^{o}C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88 (t, J=7.2 Hz, 3H, $CH_3CH_2CH_2$), 0.99 (s, 6H, 2×CH_3), 1.14 (d, J=7.2 Hz, 3H, $CH_3CH(CO)$), 1.24-1.42 (m, 3H, $CHHCH_2CH_3$), 1.65 (m, 1H, $CHHCH_2CH_3$), 2.43 (sext, J=7.2 Hz, 1H, $CH_3CH(CO)$), 2.69 (s, 2H, CH_2Ar), 3.86 (s, 2H, OCH_2), 7.45 (br s, 1H, OH), 7.70 (td, J=7.6 and 1.2 Hz, 1H, ArH), 7.77 (td, J=7.6 and 1.2 Hz, 1H, ArH), 8.10 (dd, J=7.6 and 1.2 Hz, 1H, ArH), 8.14 (dd, J=7.6 and 1.2 Hz, 1H, ArH).

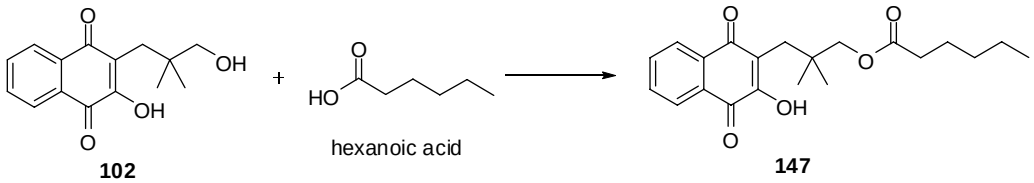
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.55 (CH_3), 17.64 (CH_3), 21.00 (CH_2), 25.64 (CH_3), 25.66 (CH_3), 32.62 (CH_2), 36.50 (CH_2), 37.58 (C), 40.12 (CH), 73.10 (CH_2), 122.34 (C), 126.73 (CH), 127.66 (CH), 130.00 (C), 133.55 (CH, C), 135.59 (CH), 154.90 (C), 177.45 (C=O), 181.88 (C=O), 185.47 (C=O).

FTIR (KBr, cm^{-1}): 3381 (OH), 2959, 2932, 2863 (CH_2, CH_3), 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.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl hexanoate (147)



Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (50 mg, 0.192 mmol), hexanoic acid (32.0 μL, 0.250 mmol), DCC (51.6 mg, 0.250 mmol), DMAP (7.1 mg, 0.058 mmol) in dry dichloromethane (7 mL) at room temperature over 20h. The crude residue was purified by flash column chromatography eluting with 3% ethyl acetate-hexane to provide the desired product **147** (51.0 mg, 74%) as a yellow gum which crystallized from hexane–dichloromethane as yellow needles, m.p. 54.5-55.5 ^{o}C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.89 (t, J=6.7 Hz, 3H, CH_3CH_2), 1.00 (s, 6H, 2×CH_3), 1.28 (m, 4H, $CH_3(CH_2)_2CH_2$), 1.51 (quin, J=7.5, 2H, $CH_2CH_2CH_2CO$), 2.27 (t, 2H, J=7.5 Hz, CH_2CH_2CO), 2.69 (s, 2H, CH_2Ar), 3.87 (s, 2H, OCH_2), 7.62 (br s, 1H, OH), 7.69 (td, J=7.6 and 1.4 Hz, 1H, ArH), 7.77 (td, J=7.6 and 1.4 Hz, 1H, ArH), 8.08 (dd, J=7.6 and 1.4 Hz, 1H, ArH), 8.12 (dd, J=7.6 and 1.4 Hz, 1H, ArH).

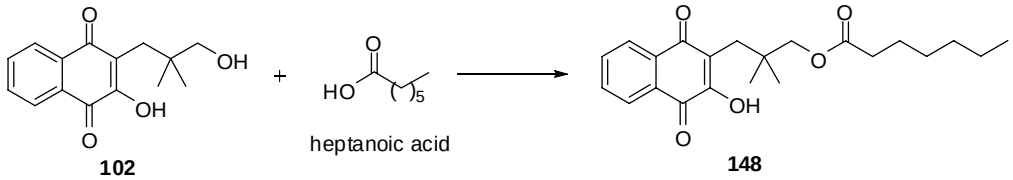
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.53 (CH_3), 22.90 (CH_2), 25.27 (CH_2), 25.68 (2×CH_3), 31.92 (CH_2), 32.59 (CH_2), 34.97 (CH_2), 37.45 (C), 73.17 (CH_2), 122.36 (C), 126.70 (CH), 127.60 (CH), 129.98 (C), 133.53 (CH, C), 135.55 (CH), 154.91 (C), 174.56 (C=O), 181.83 (C=O), 185.48 (C=O).

FTIR (KBr, cm^{-1}): 3366 (OH), 2940, 2865 (CH_2, CH_3), 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.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl heptanoate (148)



102 **148**

Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (50 mg, 0.192 mmol), heptanoic acid (35.0 μL, 0.250 mmol), DCC (51.6 mg, 0.250 mmol), DMAP (7.1 mg, 0.058 mmol) in dry dichloromethane (7 mL) at room temperature over 20h. The crude residue was purified by flash column chromatography eluting with 3% ethyl acetate-hexane to provide the desired product **148** (59.0 mg, 83%) as a yellow gum which crystallized from hexane–dichloromethane as yellow needles, m.p. 57.5-58.5 ^oC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88 (t, *J*=6.9 Hz, 3H, CH_3CH_2), 1.00 (s, 6H, 2×CH_3), 1.28 (m, 6H, $CH_3(CH_2)_3CH_2$), 1.60 (quin, *J*=7.4 Hz, 2H, $CH_2CH_2CH_2CO$), 2.28 (t, 2H, *J*=7.4 Hz, CH_2CH_2CO), 2.69 (s, 2H, CH_2Ar), 3.87 (s, 2H, OCH_2), 7.58 (br s, 1H, OH), 7.70 (td, *J*=7.6 and 1.1 Hz, 1H, ArH), 7.78 (td, *J*=7.6 and 1.1 Hz, 1H, ArH), 8.10 (dd, 1H, *J*=7.6 and 1.1 Hz, ArH), 8.13 (dd, 1H, *J*=7.6 and 1.1 Hz, ArH).

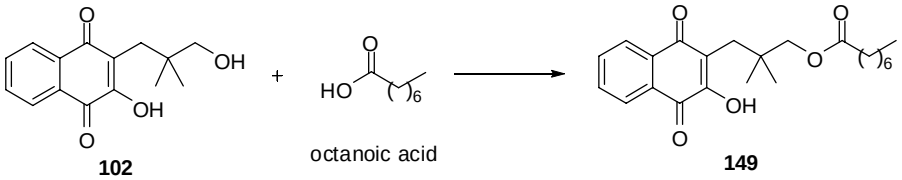
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.65 (CH_3), 23.11 (CH_2), 25.56 (CH_2), 25.69 (2×CH_3), 29.46 (CH_2), 32.05 (CH_2), 32.60 (CH_2), 35.03 (CH_2), 37.46 (C), 73.16 (CH_2), 122.37 (C), 126.72 (CH), 127.62 (CH), 129.98 (C), 133.54 (CH, C), 135.57 (CH), 154.87 (C), 174.55 (C=O), 181.84 (C=O), 185.48 (C=O).

FTIR (KBr, cm^{-1}): 3370 (OH), 2928, 2858 (CH_2, CH_3), 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.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl octanoate (149)



Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (40 mg, 0.154 mmol), octanoic acid (32.0 μL, 0.200 mmol), DCC (41.3 mg, 0.200 mmol), DMAP (5.6 mg, 0.046 mmol) in dry dichloromethane (5 mL) at room temperature over 20h. The crude residue was purified by flash column chromatography eluting with 5% ethyl acetate-hexane to provide the desired product **149** (57.0 mg, 96%) as a yellow gum which crystallized from hexane–dichloromethane as yellow needles, m.p. 56-57 ^oC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.87 (t, *J*=6.9 Hz, 3H, CH_3CH_2), 0.99 (s, 6H, 2×CH_3), 1.27 (br s, 8H, $CH_3(CH_2)_4CH_2$), 1.59 (m, 2H, $CH_2CH_2CH_2CO$), 2.26 (t, *J*=7.6 Hz, 2H, CH_2CH_2CO), 2.68 (s, 2H, CH_2Ar), 3.85 (s, 2H, OCH_2), 7.44 (s, 1H, OH), 7.69 (td, *J*=7.6 and 1.4 Hz, 1H, ArH), 7.76 (td, *J*=7.6 and 1.4 Hz, 1H, ArH), 8.09 (dd, *J*=7.6 and 1.4 Hz, 1H, ArH), 8.12 (dd, *J*=7.6 and 1.4 Hz, 1H, ArH).

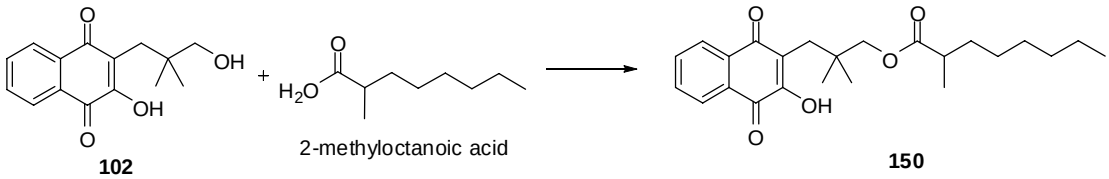
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.02 (CH_3), 22.56 (CH_2), 24.96 (CH_2), 25.04 (2×CH_3), 28.88 (CH_2), 29.11 (CH_2), 31.65 (CH_2), 31.98 (CH_2), 34.38 (CH_2), 36.82 (C), 72.52 (CH_2), 121.73 (C), 126.07 (CH), 126.98 (CH), 129.33 (C), 132.89 (CH), 132.94 (C), 134.93 (CH), 154.18 (C), 173.87 (C=O), 181.20 (C=O), 184.81 (C=O).

FTIR (KBr, cm^{-1}): 3366 (OH), 2924, 2865 (CH_2, CH_3), 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.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl 2-methyloctanoate (150)



Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (35 mg, 0.135 mmol), 2-methyloctanoic acid (a racemic mixture) (27.9 mg, 0.176 mmol), DCC (36.3 mg, 0.176 mmol), DMAP (5.0 mg, 0.041 mmol) in dry dichloromethane (4.5 mL) at room temperature over 20h. The crude residue was purified by flash column chromatography eluting with 4% ethyl acetate-hexane to provide the desired product **150** (45.3 mg, 84%) as a yellow gum.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.86 (t, *J*=6.8 Hz, 3H, $CH_3CH_2CH_2$), 0.99 (s, 6H, 2×CH_3), 1.13 (d, *J*=7.0 Hz, 3H, $CH_3CH(CO)$), 1.25 (m, 6H, $CH_2(CH_2)_3CH3$), 1.37 (m, 2H, $CH_3CH(CO)CH_2CH_2CH_2$), 1.64 (m, 2H, $CH_3CH(CO)CH_2CH_2CH_2$), 2.40 (sext, *J*=7.0 Hz, 1H, $CH_3CH(CO)CH_2$), 2.68 (s, 2H, CH_2Ar), 3.85 (s, 2H, OCH_2),

7.69 (td, *J*=7.6 and 1.2 Hz, 1H, ArH), 7.76 (td, *J*=7.6 and 1.2 Hz, 1H, ArH), 8.09 (m, 1H, ArH), 8.12 (m, 1H, ArH).

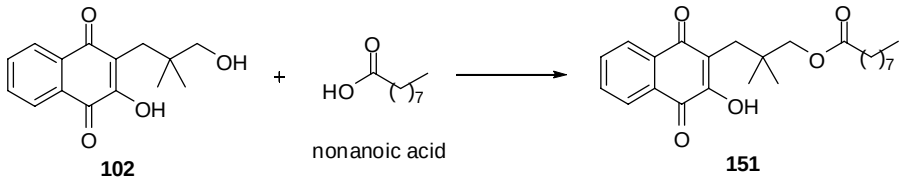
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.70 (CH_3), 17.69 (CH_3), 23.23 (CH_2), 25.64 (CH_3), 25.68 (CH_3), 27.82 (CH_2), 29.81 (CH_2), 32.34 (CH_2), 32.61 (CH_2), 34.38 (CH_2), 37.58 (C), 40.37 (CH), 73.09 (CH_2), 122.33 (C), 126.74 (CH), 127.66 (CH), 129.99 (C), 133.57 (CH, C), 135.60 (CH), 154.90 (C), 177.50 (C=O), 181.86 (C=O), 185.49 (C=O).

FTIR (KBr, cm^{-1}): 3389 (OH), 2959, 2930, 2856 (CH_2, CH_3), 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.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl nonanoate (151)



Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (50 mg, 0.192 mmol), nonanoic acid (40.0 µL, 0.250 mmol), DCC (51.6 mg, 0.250 mmol), DMAP (7.1 mg, 0.058 mmol) in dry dichloromethane (7 mL) at room temperature over 20h. The crude residue was purified by flash column chromatography eluting with 3% ethyl acetate-hexane to

provide the desired product **151** (56.0 mg, 73%) as a yellow gum which crystallized from hexane–dichloromethane as yellow needles, m.p. 52.5-53.5 ^{o}C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.90 (t, *J*=6.7 Hz, 3H, CH_3CH_2), 1.02 (s, 6H, 2×CH_3), 1.28 (m, 10H, CH_3*(*CH_2*)*$_5$$CH_2$, 1.62 (m, 2H, CH_2*CH_2*CH_2CO), 2.29 (t, *J*=7.5 Hz, 2H, CH_2*CH_2*CO), 2.71 (s, 2H, CH_2Ar), 3.87 (s, 2H, OCH_2), 7.47 (s, 1H, OH), 7.73 (t, *J*=7.6 Hz, 1H, ArH), 7.80 (t, *J*=7.6 Hz, 1H, ArH), 8.03 (d, *J*=7.6 Hz, 1H, ArH), 8.06 (d, *J*=7.6 Hz, 1H, ArH).

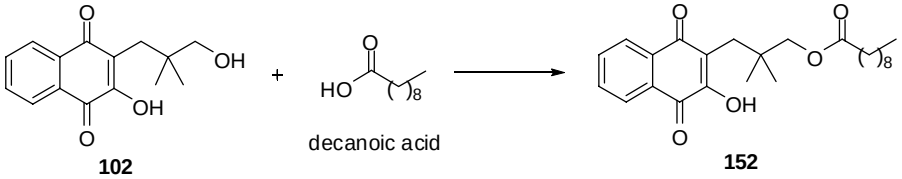
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.71 (CH_3), 23.25 (CH_2), 25.60 (CH_2), 25.68 (2×CH_3), 29.75 (CH_2), 29.79 (CH_2), 29.82 (CH_2), 32.42 (CH_2), 32.60 (CH_2), 35.03 (CH_2), 37.45 (C), 73.16 (CH_2), 122.37 (C), 126,71(CH), 127.61 (CH), 129.98 (C), 133.54 (CH, C), 135.56 (CH), 154.89 (C), 174.55 (C=O), 181.83 (C=O), 185.48 (C=O).

FTIR (KBr, cm^{-1}): 3366 (OH), 2923, 2850 (CH_2, CH_3), 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.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl decanoate (152)



Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (50 mg, 0.192 mmol), decanoic acid (43.1 µL, 0.250 mmol), DCC (51.6 mg, 0.250 mmol), DMAP (7.1 mg, 0.058 mmol) in dry dichloromethane (7 mL) at room temperature over 20h. The crude residue was purified by flash column chromatography eluting with 3% ethyl acetate-hexane to provide the desired product **152** (57.0 mg, 72%) as a yellow gum which crystallized from hexane–dichloromethane as yellow needles, m.p. 61-62 ^{o}C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.91 (t, *J*=6.8 Hz, 3H, CH_3CH_2), 1.02 (s, 6H, 2×CH_3), 1.28 (m, 12H, $CH_3(CH_2)_6CH_2$), 1.62 (m, 2H, $CH_2CH_2CH_2CO$), 2.29 (t, *J*=7.6 Hz, 2H, CH_2CH_2CO), 2.71 (s, 2H, CH_2Ar), 3.88 (s, 2H, OCH_2), 7.46 (s, 1H, OH), 7.73 (td, *J*=7.6 and 1.2 Hz, 1H, ArH), 7.80 (td, *J*=7.6 and 1.2 Hz, 1H, ArH), 8.12 (d, *J*=7.6 Hz, 1H, ArH), 8.15 (d, *J*=7.6 Hz, 1H, ArH).

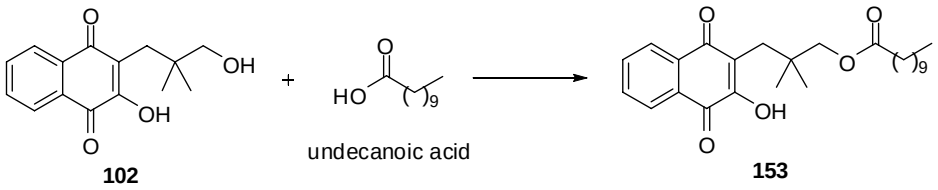
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.72 (CH_3), 23.28 (CH_2), 25.62 (CH_2), 25.69 (2×CH_3), 29.80 (CH_2), 29.88 (2×CH_2), 30.05 (CH_2), 32.47 (CH_2), 32.61 (CH_2), 35.03 (CH_2), 37.47 (C), 73.16 (CH_2), 122.37 (C), 126.72 (CH), 127.63 (CH), 129.97 (C), 133.55 (CH, C), 135.58 (CH), 154.83 (C), 174.54 (C=O), 181.84 (C=O), 185.47 (C=O).

FTIR (KBr, cm^{-1}): 3364 (OH), 2921, 2850 (CH_2, CH_3), 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.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl undecanoate (153)



102 **153**

Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (50 mg, 0.192 mmol), undecanoic acid (52.0 μL, 0.250 mmol), DCC (51.6 mg, 0.250 mmol), DMAP (7.1 mg, 0.058 mmol) in dry dichloromethane (7 mL) at room temperature over 20h. The crude residue was purified by flash column chromatography eluting with 3% ethyl acetate-hexane to provide the desired product **153** (68.0 mg, 83%) as a yellow gum which crystallized from hexane–dichloromethane as yellow needles, m.p. 64.5-65.5 ^{o}C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.90 (t, J=6.8 Hz, 3H, CH_3CH_2), 1.01 (s, 6H, 2×CH_3), 1.28 (m, 14H, $CH_3(CH_2)_7CH_2$), 1.62 (m, 2H, $CH_2CH_2CH_2CO$), 2.29 (t, J=7.6 Hz, 2H, CH_2CH_2CO), 2.71 (s, 2H, CH_2Ar), 3.88 (s, 2H, OCH_2), 7.46 (s, 1H, OH), 7.73 (td, J=7.6 and 1.1 Hz, 1H, ArH), 7.80 (td, J=7.6 and 1.1 Hz, 1H, ArH), 8.12 (dd, J=7.6 and 1.1 Hz, 1H, ArH), 8.15 (dd, J=7.6 and 1.1 Hz, 1H, ArH).

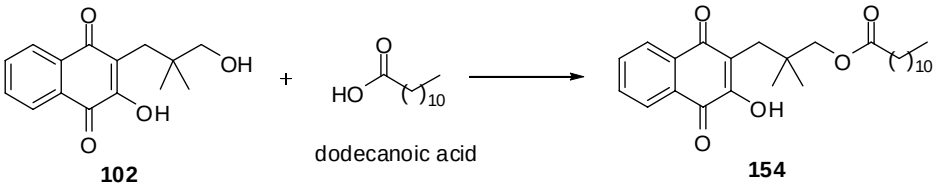
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.08 (CH_3), 22.66 (CH_2), 24.99 (CH_2), 25.06 (2×CH_3), 29.17 (CH_2), 29.24 (CH_2), 29.29 (CH_2), 29.46 (CH_2), 29.54 (CH_2), 31.87 (CH_2), 32.00 (CH_2), 34.40 (CH_2), 36.84 (C), 72.53 (CH_2), 121.74 (C), 126.10 (CH), 127.01 (CH), 129.34 (C), 132.92 (CH), 132.96 (C), 134.96 (CH), 154.16 (C), 173.87 (C=O), 181.22 (C=O), 184.82 (C=O).

FTIR (KBr, cm^{-1}): 3365 (OH), 2917, 2850 (CH_2, CH_3), 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.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl dodecanoate (154)



102 **154**

Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (50 mg, 0.192 mmol), dodecanoic acid (50.1 mg, 0.250 mmol), DCC (51.6 mg, 0.250 mmol), DMAP (7.1 mg, 0.058 mmol) in dry dichloromethane (7 mL) at room temperature over 20h. The crude residue was purified by flash column chromatography eluting with 3% ethyl acetate-hexane to provide the desired product **154** (67.0 mg, 79%) as a yellow gum which crystallized from hexane–dichloromethane as yellow needles, m.p. 68-69 ^oC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.91 (t, J=6.8 Hz, 3H, CH_3CH_2), 1.02 (s, 6H, 2×CH_3), 1.28 (m, 16H, $CH_3(CH_2)_8CH_2$), 1.61 (m, 2H, $CH_2CH_2CH_2CO$), 2.29 (t, J=7.6 Hz, 2H,CH_2CH_2CO), 2.71 (s, 2H, CH_2Ar), 3.88 (s, 2H, OCH_2), 7.46 (s, 1H, OH), 7.73 (td, J=7.6 and 1.3 Hz, 1H, ArH), 7.80 (td, J=7.6 and 1.3 Hz, 1H, ArH), 8.13 (dd, J=7.6 and 1.3 Hz, 1H, ArH), 8.16 (dd, J=7.6 and 1.3 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.73 (CH_3), 23.30 (CH_2), 25.62 (CH_2), 25.69 (2×CH_3), 29.81 (CH_2), 29.88 (CH_2), 29.95 (CH_2), 30.10 (CH_2), 30.22 (2×CH_2), 32.53 (CH_2), 32.61 (CH_2), 35.04 (CH_2), 37.47 (C), 73.16 (CH_2), 122.37 (C), 126.72 (CH),

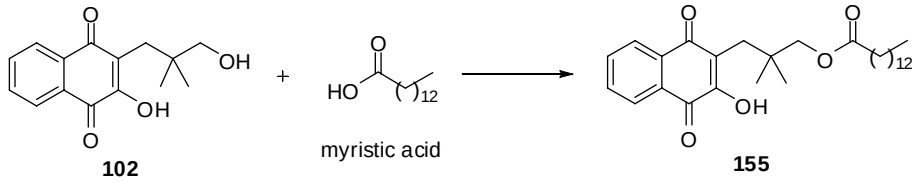
127.64 (CH), 129.97 (C), 133.55 (CH), 133.57 (C), 135.58 (CH), 154.83 (C), 174.53 (C=O), 181.84 (C=O), 185.47 (C=O).

FTIR (KBr, cm^{-1}): 3365 (OH), 2920, 2850 (CH_2, CH_3), 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.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl tetradecanoate (155)



Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (40 mg, 0.154 mmol), myristic acid (45.65 mg, 0.200 mmol), DCC (41.3 mg, 0.200 mmol), DMAP (5.6 mg, 0.046 mmol) in dry dichloromethane (5 mL) at room temperature over 14h. The crude residue was purified by flash column chromatography eluting with 4% ethyl acetate-hexane to provide the desired product **155** (58.2 mg, 80%) as a yellow gum which crystallized from hexane–dichloromethane as yellow needles, m.p. 79-80 ^oC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88 (t, J=6.8 Hz, 3H, CH_3CH_2), 0.99 (s, 6H, 2×CH_3), 1.25 (m, 20H, $CH_3(CH_2)_{10}CH_2$), 1.59 (m, 2H, $CH_2CH_2CH_2CO$), 2.26 (t, 2H, J=7.6 Hz, CH_2CH_2CO), 2.68 (s, 2H, CH_2Ar), 3.86 (s, 2H, OCH_2), 7.44 (s, 1H, OH),

7.70 (td, *J*=7.6 and 1.2 Hz, 1H, ArH), 7.77 (td, *J*=7.6 and 1.2 Hz, 1H, ArH), 8.10 (dd, *J*=7.6 and 1.2 Hz, 1H, ArH), 8.13 (dd, *J*=7.6 and 1.2 Hz, 1H, ArH).

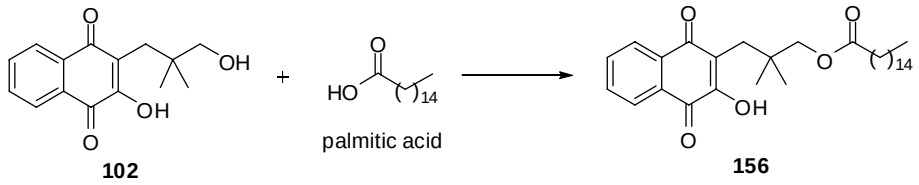
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.72 (CH_3), 23.30 (CH_2), 25.63 (CH_2), 25.70 ($2\times CH_3$), 29.81 (CH_2), 29.88 (CH_2), 29.97 (CH_2), 30.10 (CH_2), 30.23 (CH_2), 30.27 ($3\times CH_2$), 32.54 (CH_2), 32.64 (CH_2), 35.04 (CH_2), 37.48 (C), 73.17 (CH_2), 122.40 (C), 126.73 (CH), 127.66 (CH), 129.99 (C), 133.54 (CH), 133.62 (C), 135.59 (CH), 154.81 (C), 174.50 (C=O), 181.86 (C=O), 185.46 (C=O).

FTIR (KBr, cm^{-1}): 3364 (OH), 2918, 2850 (CH_2, CH_3), 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.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl palmitate (156)



Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (40 mg, 0.154 mmol), palmitic acid (51.26 mg, 0.200 mmol), DCC (41.3 mg, 0.200 mmol), DMAP (5.6 mg, 0.046 mmol) in dry dichloromethane (5 mL) at room temperature over 14h. The crude residue was purified by flash column chromatography eluting with 4% ethyl acetate-hexane to

provide the desired product **156** (58.7 mg, 77%) as a yellow gum which crystallized from hexane–dichloromethane as yellow needles, m.p. 76-77 ^{o}C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88 (t, J=6.8 Hz, 3H, CH_3CH_2), 0.99 (s, 6H, 2×CH_3), 1.25 (br s, 24H, $CH_3(CH_2)_{12}CH_2$), 1.59 (m, 2H, $CH_2CH_2CH_2CO$), 2.26 (t, 2H, J=7.6 Hz, CH_2CH_2CO), 2.68 (s, 2H, CH_2Ar), 3.86 (s, 2H, OCH_2), 7.45 (s, 1H, OH), 7.70 (td, J=7.6 and 1.2 Hz, 1H, ArH), 7.77 (td, J=7.6 and 1.2 Hz, 1H, ArH), 8.10 (dd, J=7.6 and 1.2 Hz, 1H, ArH), 8.13 (dd, J=7.6 and 1.2 Hz, 1H, ArH).

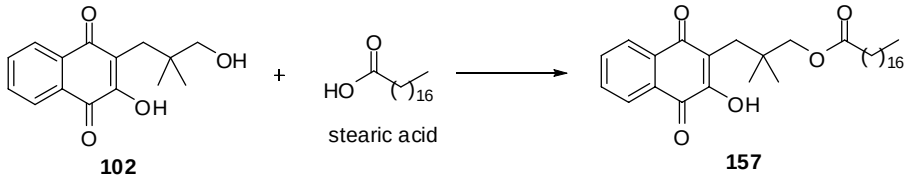
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.72 (CH_3), 23.31 (CH_2), 25.63 (CH_2), 25.70 (2×CH_3), 29.82 (CH_2), 29.88 (CH_2), 29.97 (CH_2), 30.11 (CH_2), 30.28 (3×CH_2), 30.31 (3×CH_2), 32.54 (CH_2), 32.64 (CH_2), 35.04 (CH_2), 37.48 (C), 73.17 (CH_2), 122.40 (C), 126.73 (CH), 127.65 (CH), 130.00 (C), 133.54 (CH), 133.62 (C), 135.58 (CH), 154.81 (C), 174.50 (C=O), 181.86 (C=O), 185.46 (C=O).

FTIR (KBr, cm^{-1}): 3363 (OH), 2917, 2849 (CH_2, CH_3), 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.

3-(1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl stearate (157)



Prepared by the general procedure from 2-hydroxy-3-(3-hydroxy-2,2-dimethylpropyl)-1,4-naphthoquinone (**102**) (40 mg, 0.154 mmol), stearic acid (56.87 mg, 0.200 mmol), DCC (41.3 mg, 0.200 mmol), DMAP (5.6 mg, 0.046 mmol) in dry dichloromethane (5 mL) at room temperature over 14h. The crude residue was purified by flash column chromatography eluting with 4% ethyl acetate-hexane to provide the desired product **157** (60.2 mg, 74%) as a yellow gum which crystallized from hexane–dichloromethane as yellow needles, m.p. 82-83 ^{o}C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88 (t, *J*=6.8 Hz, 3H, CH_3CH_2), 0.99 (s, 6H, 2×CH_3), 1.25 (br s, 28H, $CH_3(CH_2)_{14}CH_2$), 1.59 (m, 2H, $CH_2CH_2CH_2CO$), 2.26 (t, 2H, *J*=7.2 Hz, CH_2CH_2CO), 2.68 (s, 2H, CH_2Ar), 3.86 (s, 2H, OCH_2), 7.44 (s, 1H, OH), 7.70 (td, *J*=7.6 and 1.2 Hz, 1H, ArH), 7.77 (td, *J*=7.6 and 1.2 Hz, 1H, ArH), 8.10 (dd, *J*=7.6 and 1.2 Hz, 1H, ArH), 8.13 (dd, *J*=7.6 and 1.2 Hz, 1H, ArH).

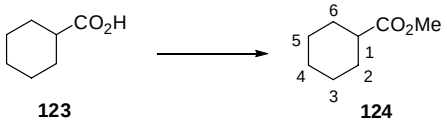
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.72 (CH_3), 23.31 (CH_2), 25.63 (CH_2), 25.70 (2×CH_3), 29.82 (CH_2), 29.88 (CH_2), 29.98 (CH_2), 30.11 (CH_2), 30.31 (8×CH_2), 32.55 (CH_2), 32.64 (CH_2), 35.04 (CH_2), 37.48 (C), 73.17 (CH_2), 122.40 (C), 126.73 (CH), 127.65 (CH), 130.00 (C), 133.54 (CH), 133.62 (C), 135.59 (CH), 154.81 (C), 174.49 (C=O), 181.86 (C=O), 185.46 (C=O).

FTIR (KBr, cm^{-1}): 3363 (OH), 2917, 2849 (CH_2, CH_3), 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.

Methyl cyclohexanecarboxylate (124) (Kongkathip *et al*., 2004)



123 **124**

A mixture of cyclohexylcarboxylic acid (**123**)(6.20 mL, 50.0 mmol) and potassium carbonate (10.35 g, 75.0 mmol) was stirred in acetone (60 mL). Methyl iodide (6.23 mL, 100.0 mmol) was added dropwise and the mixture was refluxed for 6 h. The reaction mixture was then filtered and filtrate was evaporated to remove the acetone. After that the residue was dissolved with dichloromethane, washed with water and dried over anhydrous sodium sulfate. The crude residue was purified by flash column chromatography eluting with 1% EtOAc: hexane to afford the desired product **124** (6.32 g, 89%) as a colorless oil.

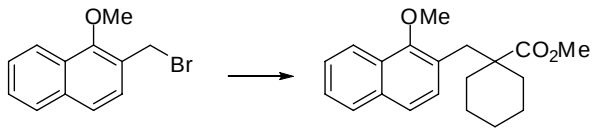
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.10-1.40 (m, 5H, CH_2-3, CH_2-5, CH-4), 1.56 (m, 1H, CH-4), 1.65 (m, 2H, C*H*H-2, C*H*H-6), 1.80 (m, 2H, CH*H*-2, *C*H*H*-6), 2.23, (tt, *J*=11.3 and 3.7 Hz, 1H, $(CH_2)(CH_2)$C*H*-$COOCH_3$), 3.58 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.65 (2×CH_2), 25.96 (CH_2), 29.23 (2×CH_2), 43.32 (CH), 51.62 (CH_3), 176.79 (C=O).

FTIR (KBr, cm^{-1}): 2932, 2850 (CH_2, CH_3), 1735 (C=O), 1168 (C-O).

MS (EI), *m/z* (% relative intensity): 143 ($[M+1]^+$, 42), 111 (18), 93 (98), 83 (78), 81 (100).

Methyl 1-((1-methoxynaphthalen-2-yl)methyl)cyclohexanecarboxylate (125)



95 **125**

1M n-Buthyl lithium (2.4 mL, 2.4 mmol) was added dropwise to a stirred solution of diisopropylamine (0.34 mL, 2.4 mmol) in dry tetrahydrofuran (THF) (5 mL) at 0°C under nitrogen. After stirring for 20 minutes, cyclohexanecarboxylic acid methylester (0.26 mL, 1.8 mmol) was slowly added at –78°C to the reaction mixture

and stirring was continued for 30 minutes. A solution of bromide **95** (0.3 g, 1.2 mmol) and hexamethylphosphoramide (HMPA) (0.4 mL) in dry THF (2 mL) was added dropwise to the reaction mixture at the same temperature. After stirring for 2 hours at –78°C, the reaction mixture was quenched with saturated ammonium chloride solution and then extracted with diethyl ether (3×30 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 1% ethyl acetate-hexane to yield the desired product **125** (0.32 g, 87%) as a colourless solid; m.p. 74-75 ºC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.15-1.40 (m, 4H, 2×CH_2), 1.58-1.67 (m, 4H, 2×CH_3), 2.75 (m, 2H, CH_2), 3.02 (s, 2H, CH_2Ar), 3.68 (s, 3H, CO_2CH_3), 3.90 (s, 3H, OCH_3), 7.16 (d, *J*=8.4 Hz, 1H, ArH), 7.50 (m, 2H, ArH), 7.55 (d, *J*=8.4 Hz, 1H, ArH), 7.84 (dd, *J*=8.4 and 0.7 Hz, 1H, ArH), 8.10 (dd, *J*=8.4 and 0.7 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.14 (2×CH_2), 26.38 (CH_2), 34.92 (2×CH_2), 41.82 (CH_2), 49.70 (C), 52.13 (CH_3), 62.26 (CH_3), 122.90 (CH), 123.88 (CH), 126.23 (CH), 126.40 (C, CH), 128.51 (C), 128.58 (CH), 130.12 (CH), 134.85 (C), 155.20 (C), 177.34 (C=O).

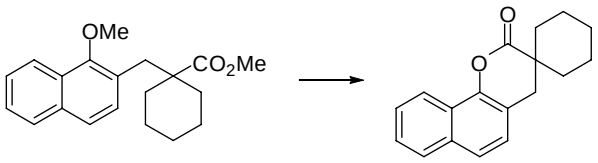
FTIR (KBr, cm^{-1}): 2946, 2925, 2850 (CH_2, CH_3), 1727 (C=O), 1451, 1367 (C=C), 1197, 1130, 1081 (C-O).

MS (EI), *m/z* (% relative intensity): 312 (M^+, 22), 171 (100), 157 (3), 156 (15), 141 (14).

HRMS: calcd for $C_{20}H_{24}O_3$ [M+Na] 335.1623, found 335.1618.

Anal. Calcd. for $C_{20}H_{24}O_3$: C,76.89; H, 7.74. Found: C, 76.96, H, 7.85.

3,4-Dihydro-2-spirocyclohexylbenzo[h]chromen-2-one (126)



125 **126**

A mixture of compound **125** (1.0 g, 3.2 mmol) and aluminium chloride (1.28 g, 9.6 mmol) in dry chlorobenzene (35 mL) was refluxed for 3 hours. The solution was cooled to room temperature and poured into 10% hydrochloric acid (35 mL), then extracted with diethyl ether (3×30 mL). The combined organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Then chlorobenzene was removed by distillation under reduced pressure. The resulting residue was purified by flash column chromatography, eluting with 5% v/v CH_2Cl_2: hexane to afford the desired product **126** (0.69 g, 81%) as a colourless amorphous powder; m.p. 106-107 ºC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.40-1.90 (m, 10H, $(CH_2)_5$), 2.98 (s, 2H, CH_2Ar), 7.17 (d, *J*=8.7 Hz, 1H, ArH), 7.39-7.48 (m, 2H, ArH), 7.51 (d, *J*=8.7 Hz, 1H, ArH), 7.74 (m, 1H, ArH), 8.16 (m, 1H, ArH).

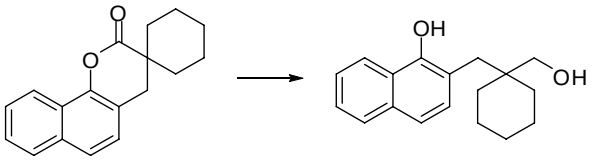
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.46 (2×CH_2), 25.66 (CH_2), 32.42 (2×CH_2), 34.99 (C), 40.15 (CH_2), 115.87 (C), 121.09 (CH), 123.07 (C), 123.69 (CH), 125.92 (CH), 126.25 (CH), 126.33 (CH), 127.51 (CH), 133.42 (C), 145.99 (C), 173.06 (C=O).

FTIR (KBr, cm^{-1}): 2939, 2843 (CH_2), 1753 (C=O), 1444, 1379 (C=C), 1244, 1112, 1086 (C-O).

MS (EI), *m/z* (% relative intensity): 267 ($[M+1]^+$, 100), 238 (23), 169 (26), 157 (13).

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.81, H, 6.86.

2-((1-(Hydroxymethyl)cyclohexyl)methyl)naphthalen-1-ol (127)



126 **127**

A solution of lactone **126** (0.69 mg, 2.59 mmol) in dry diethyl ether (5 mL) was added dropwise to a stirred and ice-cooled suspension of lithium aluminium hydride (0.20 g, 5.18 mmol) in dry diethyl ether (10 mL). After stirring for 3 hours at room temperature, the reaction mixture was quenched with ethyl acetate and water, then extracted with diethyl ether (3×20 mL). The combined organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 5% ethyl acetate-hexane to give the product **127** (0.63 g, 89%) as a colourless amorphous powder; m.p. 126-127 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.30-1.65 (m, 10H, $(CH_2)_5$), 2.78 (s, 2H, CH_2Ar), 3.31 (s, 2H, CH_2OH), 7.11 (d, J=8.4 Hz, 1H, ArH), 7.26 (d, J=8.4 Hz, 1H, ArH), 7.38 (m, 2H, ArH), 7.69 (m, 1H, ArH), 8.25 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.64 (2×CH_2), 26.47 (CH_2), 33.16 (2×CH_2), 35.50 (CH_2), 38.81 (C), 67.43 (CH_2), 117.22 (C), 118.84 (CH), 122.52 (CH), 124.85 (CH), 125.54 (C), 125.59 (CH), 127.12 (CH), 130.45 (CH), 133.62 (C), 151.20 (C).

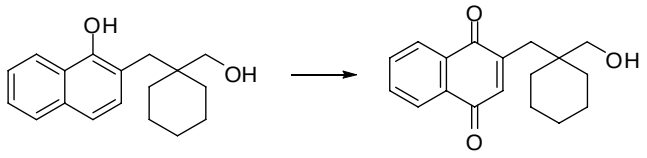
FTIR (KBr, cm^{-1}): 3413 (OH), 3047 (CH-aromatic), 2922, 2856 (CH_2, CH_3), 1570, 1457, 1376, 1273 (C=C), 1072, 1015 (C-O).

MS (EI), *m/z* (% relative intensity): 270 (M^+, 11), 253 (26), 239 (5), 169 (3), 157 (100), 129 (22).

HRMS: calcd for $C_{18}H_{22}O_2$ [M+H] 271.1698, found 271.1699.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.00, H, 8.20.

2-((1-(Hydroxymethyl)cyclohexyl)methyl)naphthalene-1,4-dione (128)



127 **128**

A solution of Fremy's salt (3.47 g, 12.94 mmol) in water (129 mL) was added to a stirred solution of naphthol **127** (0.50 g, 1.85 mmol) in methanol-dimethylformamide (3:1)(32 mL) followed by addition of 1M aqueous sodium acetate solution (3.7 mL). After stirring for 5 hours at room temperature, the reaction mixture was extracted with diethyl ether (3×20 mL). The combined organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography using 10% ethyl acetate-hexane to provide the quinone **128** (0.46 g, 87%) as a pale yellow powder; m.p. 136-137 °C.

^{1}H NMR (Acetone-d_6, 400 MHz) δ: 1.20-1.60 (m, 10H, $(CH_2)_5$), 2.65 (d, *J*=0.8 Hz, 2H, *CH*$_2$C=CH), 3.37 (d, *J*=5.3 Hz, 2H, *CH*$_2$OH), 3.64 (t, *J*=5.3 Hz, 1H, *C*H$_2$O*H*), 6.89 (t, *J*=0.8 Hz, 1H, CH$_2$C=*CH*CO), 7.82 (d, *J*=3.3 Hz, 1H, ArH), 7.83 (d, *J*=3.3 Hz, 1H, ArH), 8.00 (m, 1H, ArH), 8.07 (m, 1H, ArH).

^{13}C NMR (Acetone-d_6, 100 MHz) δ: 22.16 (2×CH_2), 26.82 (CH_2), 31.71 (CH_2), 33.41 (2×CH_2), 36.06 (C), 66.30 (CH_2), 126.14 (CH), 126.77 (C), 127.15

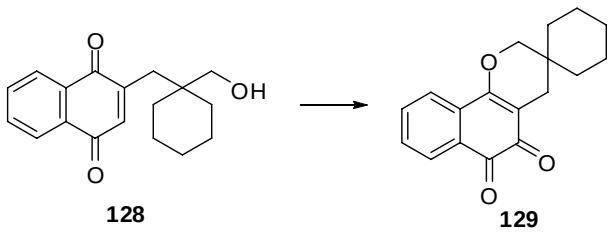
(CH), 133.44 (C), 134.26 (CH), 134.32 (CH), 137.59 (CH), 150.29 (C), 185.03 (C=O), 187.87 (C=O).

FTIR (KBr, cm^{-1}): 3225 (OH), 2922, 2856 (CH_2), 1659, 1627 (C=O), 1590, 1450, 1332, 1310 (C=C), 1021 (C-O).

MS (EI), *m/z* (% relative intensity): 285 ($[M+1]^+$, 100), 253 (53), 239 (7), 173 (24), 157 (19), 129 (3).

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.18, H, 7.33.

3,4-Dihydro-3,3-spirocyclohexyl-2H-naphtho[1,2-b]pyran-5,6-dione (129)



128 **129**

A mixture of quinone **128** (1.64 g, 5.77 mmol), dichlorodicyanobenzoquinone (DDQ) (1.92 g, 6.92 mmol) and *p*-toluenesulfonic acid monohydrate (0.11 g, 0.58 mmol) in dry benzene (40 mL) was stirred under refluxed for 1 hour. The reaction mixture was cooled to room temperature and filtered, then washed with dichloromethane and concentrated in vacuo. The residue was filtered through aluminium oxide to remove DDQ and purified by flash column chromatography using 4% ethyl acetate-hexane to give the desired product **129** (1.36 g, 84%) as an orange amorphous powder; m.p. 131-132 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.30-1.60 (m, 10H, $(CH_2)_5$), 2.41 (s, 2H, CH_2Ar), 4.07 (s, 2H, CH_2O), 7.51 (td, *J*=7.8 and 1.3 Hz, 1H, ArH), 7.64 (td, *J*=7.8 and 1.3 Hz, 1H, ArH), 7.79 (dd, *J*=7.8 and 0.9 Hz, 1H, ArH), 8.08 (dd, *J*=7.8 and 0.9 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.28 (2×CH_2), 26.17 (CH_2), 28.98 (C), 30.72 (CH_2), 33.22 (2×CH_2), 76.15 (CH_2), 113.03(C), 124.08 (CH), 128.68 (CH), 129.88 (C), 130.68 (CH), 131.92 (C), 134.82 (CH), 162.32 (C), 179.09 (C=O), 179.68 (C=O).

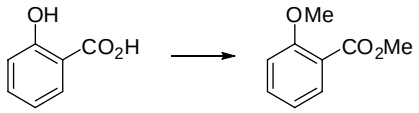
FTIR (KBr, cm^{-1}): 2923, 2848 (CH_2), 1697, 1642 (C=O), 1598, 1568, 1452, 1373, (C=C), 1174, 1085 (C-O).

MS (EI), *m/z* (% relative intensity): 283 ($[M+1]^+$, 100), 265 (5).

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.24, H, 6.62.

Synthesis of 2-methoxybenzoic acid (136) from salicylic acid (134)

Methyl 2-methoxybenzoate (135) (Kongkathip *et al*., 2004)



134 **135**

A mixture of salicylic acid (**134**)(1.0 g, 7.24 mol), potassium carbonate (3.0 g, 21.72 mol), acetone (20 mL) and iodomethane (4.1 mL, 28.96 mol) was stirred and refluxed for 8 hours. Then the reaction mixture was cooled to room temperature, filtered and washed with acetone. The filtrate was concentrated in vacuo, then dichloromethane was added, washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 2% ethyl acetate-hexane to afford the product **135** (1.127 g, 94%) as a colourless oil.

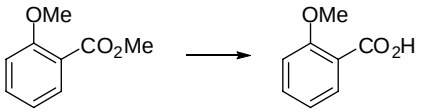
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, CO_2CH_3), 6.99 (m, 2H, ArH), 7.48 (m, 1H, ArH), 7.81 (dd, *J*=7.9 and 1.9 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 52.61 (CH_3), 56.56 (CH_3), 112.60 (CH), 120.72 (C, CH), 132.25 (CH), 134.15 (CH), 159.70 (C), 167.32 (C=O).

FTIR (neat, cm^{-1}): 2951 (CH_3), 1728 (C=O), 1600, 1437, 1304 (C=C), 1253, 1087 (C-O).

MS (EI), *m/z* (% relative intensity): 166 (M^+, 20), 135 (100), 105 (26), 77 (73).

2-Methoxybenzoic acid (136) (Kongkathip *et al*., 2004)



135 **136**

A solution of potassium hydroxide (959.2 mg, 17.13 mmol) in 50% aqeous ethanol (5 mL) was added to a solution of methyl 2-methoxybenzoate (**135**)(711.0 mg, 4.28 mmol) in 50% aqeous ethanol (10 mL). The mixture was stirred under reflux for 3 hours. The solution was cooled to room temperature, acidified with concentrated hydrochloric acid to pH 1 and then extracted with dichloromethane (3×25 mL). The combined organic layers were washed with brine and water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a white solid. The solid was recrystallized with dichloromethane-hexane to afford the desired product **136** as a colorless powder (645.0 mg, 99%), m.p. 91-92 °C.

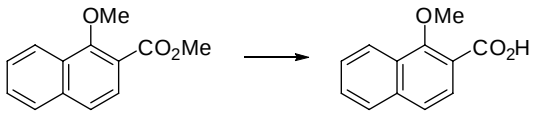
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.10 (s, 3H, OCH_3), 7.08 (d, *J*=8.4 Hz, 1H, ArH), 7.16 (m, 1H, ArH), 7.60 (m, 1H, ArH), 8.20 (dd, *J*=7.8 and 1.8 Hz, 1H, ArH), 10.85 (br s, 1H, OH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 57.30 (CH_3), 112.33 (CH), 118.20 (C), 122.75 (CH), 134.34 (CH), 135.75 (CH), 158.77 (C), 166.37 (C=O).

FTIR (KBr, cm^{-1}): 3013 (OH), 1690 (C=O), 1597, 1465 (C=C), 1258, 1168 (C-O).

MS (EI), *m/z* (% relative intensity): 152 (M^+, 28), 135 (18), 105 (100), 77 (84).

1-Methoxynaphthalene-2-carboxylic acid (137) (Kongkathip *et al*., 2004)



121 **137**

A solution of potassium hydroxide (517.9 mg, 9.25 mmol) in 50% aqeous ethanol (4 mL) was added to a solution of methyl 1-methoxynaphthalene-2-carboxylate (**121**)(500.0 mg, 2.31 mmol) in 50% aqeous ethanol (10 mL). The mixture was stirred under reflux for 3 hours. The solution was cooled to room temperature, acidified with concentrated hydrochloric acid to pH 1 and then extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine and water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a white solid. The solid was recrystallized with dichloromethane-hexane to afford the desired product (**137**) as a colorless powder (645.0 mg, 99%), 126-127 °C.

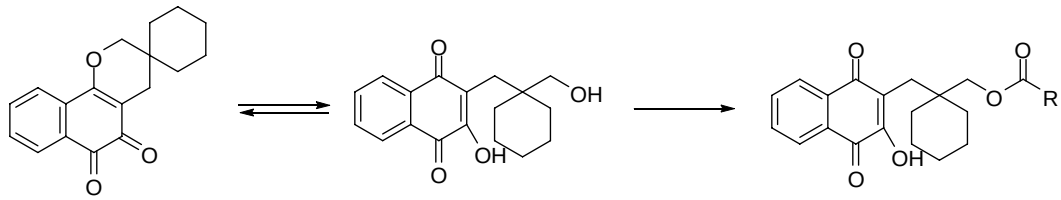
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.20 (s, 3H, OCH_3), 7.66 (m, 2H, ArH), 7.74 (d, *J*=8.7 Hz, 1H, ArH), 7.93 (m, 1H, ArH), 8.11 (d, *J*=8.7 Hz, 1H, ArH), 8.23 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 64.80 (CH_3), 118.43 (C), 123.94 (CH), 125.38 (CH), 127.54 (CH), 127.64 (CH), 128.07 (C), 128.91 (CH), 129.62 (CH), 138.17 (C), 158.98 (C), 169.04 (C=O).

FTIR (KBr, cm^{-1}): 2942 (CH_3), 1694 (C=O), 1442, 1288 (C=C), 1085 (C-O).

MS (EI), *m/z* (% relative intensity): 202 (M^+, 48), 129 (100), 115 (88), 77 (89), 63 (90).

Synthesis of Naphthoquinone ester derivatives



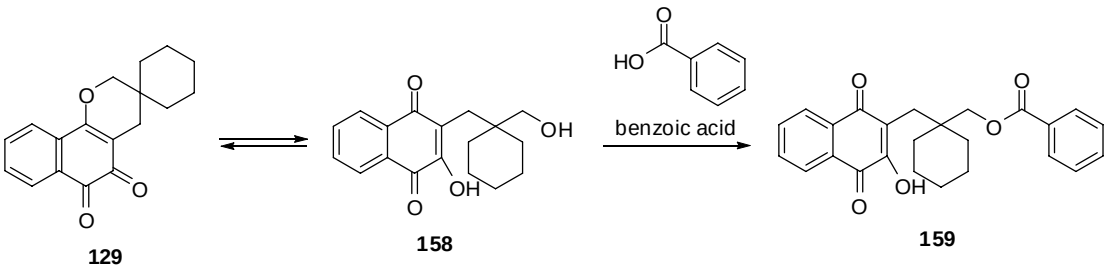
General procedure:

The solution of compound **129** (0.354 mmol) in 1% aqueous sodium hydroxide solution (0.531 mmol) was refluxed for 1 hour. After completion of the reaction, the reaction mixture was cooled to room temperature and neutralized with acetic acid to pH 7, then extracted with dichloromethane (3×15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, then filtered and concentrated in vacuo. After concentration, the intermediate **158** was obtained together with a small amount of the cyclized product **129** (monitoring by TLC).

A solution of carbodiimidazole (CDI)(0.53 mmol) in dry THF (5 mL) was added to a stirred solution of carboxylic acid (0.43 mmol) in THF (2 mL) at room temperature. After 3 hours, a solution of the mixture of compound **129** and naphthoquinone alcohol intermediate **158** in THF (2 mL) was added and then the mixture was stirred at room temperature for 45 hours. The reaction mixture was quenced with saturated ammonium chloride and extracted with dichloromethane (3×15 mL). The combined organic layers were washed with brine and water, dried

over anhydrous sodium sulfate, filtered and the fitrate was concentrated in vacuo. The residue was purified by flash column chromatography.

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclohexyl)methyl benzoate (159)



Compound **159** was synthesized by following the general procedure: 3,4-dihydro-3,3-spirocyclohexyl-2H-naphtho[1,2-b]pyran-5,6-dione (**129**) (100 mg, 0.354 mmol), 1% aqueous sodium hydroxide solution (2.12 mL, 0.531 mmol), benzoic acid (64.9 mg, 0.531 mmol) and CDI (86.1 mg, 0.513 mmol) in dry THF (7 mL) was used following the procedure. The reaction mixture was stirred at room temperature for 15h. The crude residue was purified by flash column chromatography eluting with 3% ethyl acetate-hexane to provide the desired product **159** (18.9 mg, 22% yield for 2 steps) as a yellow gum and cyclized product **129** (16.6 mg). The desired product precipitated from hexane–dichloromethane as a yellow amorphous solid, m.p. 117-118 ^{o}C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.40-1.65 (m, 10H, $(CH_2)_5$), 2.83 (s, 2H, CH_2Ar), 4.24 (s, 2H, OCH_2), 7.42 (s, 1H, OH), 7.44 (m, 1H, ArH), 7.64 (m, 2H, ArH), 7.70 (m, 2H, ArH), 7.90 (d, J=7.6 Hz, 2H, ArH), 8.00 (m, 2H, ArH).

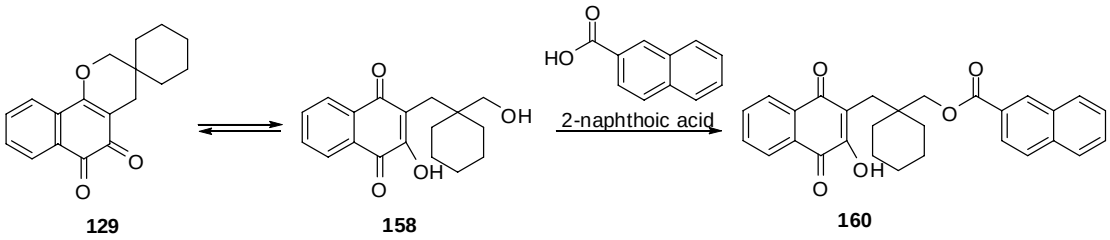
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.72 (2×CH_2), 26.01 (CH_2), 31.76 (CH_2), 33.50 (2×CH_2), 39.42 (C), 69.40 (CH_2), 122.15 (C), 125.93 (CH), 126.97 (CH), 128.12 (2×CH), 129.27 (C), 129.34 (2×CH), 130.37 (C), 132.59 (CH), 132.75 (CH), 133.04 (C), 134.82 (CH), 154.17 (C), 166.52 (C=O), 181.09 (C=O), 185.05 (C=O).

FTIR (neat, cm^{-1}): 3371 (OH), 3067 (CH-aromatic), 2928, 2852 (CH_2), 1715, 1664, 1650 (C=O), 1594, 1451, 1371, 1274 (C=C), 1116, 1025 (C-O).

MS (EI), *m/z* (% relative intensity): 404 (M^+, 100), 296 (22), 284 (76), 257 (42), 175 (9).

Anal. Calcd. for $C_{25}H_{24}O_5$: C, 74.24; H, 5.98. Found: C, 74.44, H, 6.01.

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclohexyl)methyl 2-naphthoate (160)



Compound **160** was synthesized by following the general procedure: 3,4-dihydro-3,3-spirocyclohexyl-2H-naphtho[1,2-b]pyran-5,6-dione (**129**) (100 mg, 0.354 mmol), 1% aqueous sodium hydroxide solution (2.12 mL, 0.531 mmol), 2-naphthoic acid (73.2 mg, 0.425 mmol) and CDI (86.1 mg, 0.513 mmol) in dry THF (6 mL) was used following the procedure. The reaction mixture was stirred at room temperature for 45h. The crude residue was purified by flash column chromatography eluting with 1% ethyl acetate-hexane to provide the desired product **160** (56.0 mg, 43% yield for 2 steps) as yellow gum and cyclized product **129** (19.0 mg). The desired product precipitated from hexane–dichloromethane as a yellow amorphous solid, m.p. 179-180 ^oC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.40-1.70 (m, 10H, $(CH_2)_5$), 2.86 (s, 2H, CH_2Ar), 4.30 (s, 2H, OCH_2), 7.41 (dt, *J*=7.6 and 1.2 Hz, 1H, ArH), 7.42 (s, 1H, OH), 7.48 (m, 1H, ArH), 7.56 (m, 1H, ArH), 7.69 (d, *J*=8.8 Hz, 1H, ArH), 7.73 (d, *J*=8.0

Hz, 1H, ArH), 7.80 (d, *J*=8.4 Hz, 1H, ArH), 7.85 (dd, *J*=7.6 and 1.2 Hz, 2H, ArH), 7.91 (m, 2H, ArH), 8.37 (s, 1H, ArH).

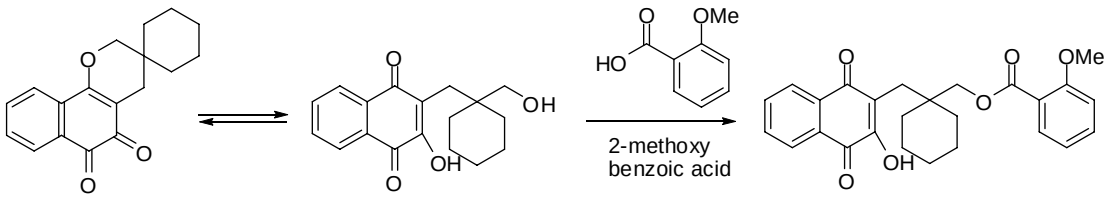
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.06 (2×CH_2), 26.38 (CH_2), 32.34 (CH_2), 33.98 (2×CH_2), 39.77 (C), 70.12 (CH_2), 122.61 (C), 125.35 (CH), 126.14 (CH), 126.74 (CH), 127.09 (CH), 127.85 (C), 127.93 (CH), 128.24 (CH), 128.37 (CH), 129.41 (C), 129.58 (CH), 131.01 (CH), 132.55 (C), 132.79 (CH), 133.22 (C), 134.94 (CH), 135.60, 154.41 (C), 166.99 (C=O), 181.41 (C=O), 185.43 (C=O).

FTIR (neat, cm^{-1}): 3383 (OH), 3055 (CH-aromatic), 2931, 2848 (CH_2), 1713, 1651 (C=O), 1594, 1458, 1374, 1275 (C=C), 1196, 1024 (C-O).

MS (EI), *m/z* (% relative intensity): 454 (M^+, 12), 297 (10), 283 (100), 265 (38).

Anal. Calcd. for $C_{29}H_{26}O_5$: C, 76.63; H, 5.77. Found: C, 76.30, H, 5.90.

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclohexyl)methyl 2-methoxybenzoate (161)



129 **158** **161**

Compound **161** was synthesized by following the general procedure: 3,4-dihydro-3,3-spirocyclohexyl-2H-naphtho[1,2-b]pyran-5,6-dione (**129**) (140 mg, 0.496 mmol), 1% aqueous sodium hydroxide solution (2.98 mL, 0.744 mmol), 2-methoxybenzoic acid (90.6 mg, 0.595 mmol) and CDI (126.7 mg, 0.744 mmol) in dry THF (8 mL) was used following the general procedure. The reaction mixture was stirred at room temperature for 48h. The crude residue was purified by flash column

chromatography eluting with 1% ethyl acetate-hexane to provide the desired product **161** (109.0 mg, 69% yield for 2 steps) as a yellow gum and cyclized product **129** (37.0 mg).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25-1.60 (m, 10H, $(CH_2)_5$), 2.73 (s, 2H, CH_2Ar), 3.73 (s, 3H, OCH_3), 4.13 (s, 2H, OCH_2), 6.74 (m, 2H, ArH), 7.26 (m, 1H, ArH), 7.35 (s, 1H, OH), 7.55 (m, 2H, ArH), 7.65 (dd, *J*=8.0 and 1.8 Hz, 1H, ArH), 7.91 (m, 2H, ArH).

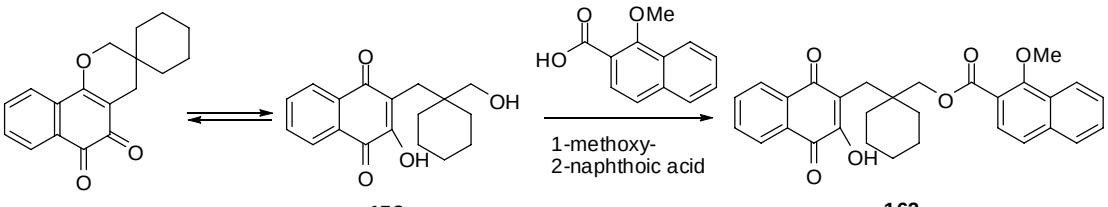
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.74 ($2\times CH_2$), 26.04 (CH_2), 31.72 (CH_2), 33.42 ($2\times CH_2$), 39.41 (C), 55.70 (CH_3), 69.34 (CH_2), 111.77 (CH), 119.90 (CH), 120.09 (C), 122.34 (C), 125.81 (CH), 126.88 (CH), 129.26 (C), 131.71 (CH), 132.64 (CH), 133.01 (C), 133.26 (CH), 134.64 (CH), 154.07 (C), 159.00 (C), 166.22 (C=O), 181.08 (C=O), 185.08 (C=O).

FTIR (neat, cm^{-1}): 3365 (OH), 3062 (CH-aromatic), 2929, 2863 (CH_2), 1716, 1660, 1648 (C=O), 1598, 1460, 1372, 1252 (C=C), 1084, 1024 (C-O).

MS (EI), *m/z* (% relative intensity): 433 ($[M-1]^+$, 7), 297 (12), 265 (8).

Anal. Calcd. for $C_{26}H_{26}O_6$: C, 71.87; H, 6.03. Found: C, 71.75, H, 5.84.

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclohexyl)methyl 1-methoxynaphthalene-2-carboxylate (162)



129 **158** **162**

Compound **162** was synthesized by following the general procedure: 3,4-dihydro-3,3-spirocyclohexyl-2H-naphtho[1,2-b]pyran-5,6-dione (**129**) (140 mg, 0.496 mmol), 1% aqueous sodium hydroxide solution (2.98 mL, 0.744 mmol), 1-methoxy-2-naphthoic acid (120.3 mg, 0.595 mmol) and CDI (120.7 mg, 0.744 mmol) in dry THF (8 mL) was used following the general procedure. The reaction mixture was stirred at room temperature for 48h. The crude residue was purified by flash column chromatography eluting with 1% ethyl acetate-hexane to provide the desired product **162** (67.0 mg, 33% yield for 2 steps) as yellow gum and cyclized product **129** (21.0 mg). The desired product precipitated from hexane–dichloromethane as a yellow amorphous solid, m.p. 124-125 ^{o}C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25-1.67 (m, 10H, $(CH_2)_5$), 2.73 (s, 2H, CH_2Ar), 3.89 (s, 3H, OCH_3), 4.22 (s, 2H, OCH_2), 7.18 (td, *J*=7.6 and 1.2 Hz, 1H, ArH), 7.29 (d, *J*=8.7 Hz, 1H, ArH), 7.30 (td, *J*=7.6 and 1.2 Hz, 1H, ArH), 7.37 (s, 1H, OH), 7.45 (m, 2H, ArH), 7.63 (d, *J*=8.7 Hz, 1H, ArH), 7.67 (d, *J*=7.6 Hz, 2H, ArH), 7.75 (dd, *J*=8.7 and 1.2 Hz, 1H, ArH), 8.02 (d, *J*=8.2 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.75 (2×CH_2), 26.08 (CH_2), 32.01 (CH_2), 33.69 (2×CH_2), 39.39 (C), 63.39 (CH_3), 70.02 (CH_2), 119.36 (C), 122.25 (C), 123.31 (CH), 123.57 (CH), 125.54 (CH), 126.23 (CH), 126.48 (CH), 126.55 (CH), 127.64 (CH), 128.07 (CH), 128.31 (C), 129.04 (C), 132.07 (CH), 132.81 (CH), 134.24 (CH), 136.57 (C), 153.89 (C), 157.92 (C), 166.08 (C=O), 181.13 (C=O), 185.17 (C=O).

FTIR (KBr, cm^{-1}): 3355 (OH), 2970, 2922, 2857 (CH_2), 1709, 1647 (C=O), 1589, 1451, 1371, 1271 (C=C), 1125, 1000 (C-O).

MS (EI), *m/z* (% relative intensity): 484 (M^+, 32), 433 ($[M-1]^+$,100), 297 (12), 283 (71), 265 (7).

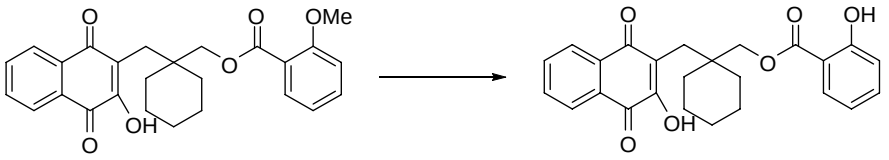
Anal. Calcd. for $C_{30}H_{28}O_6$: C, 79.96; H, 8.20. Found: C, 80.00, H, 8.20.

Demethylation of phenyl and naphthyl methyl ether

General procedure:

1 M Boron tribromide (BBr_3) in dichloromethane (0.115 mmol) was added dropwise to a stirred solution of the methyl ether **161** or **162** (0.115 mmol) in dry dichloromethane (2.5 mL) at 0 ºC and the solution was stirred for 30 minutes at the same temperature. Then water was added and extracted with dichloromethane (3×10 mL). The organic phases were separated, combined, washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford the crude product.

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclohexyl)methyl 2-hydroxybenzoate (163)



Compound **163** was synthesized by following the general procedure: a mixture of methyl ether **161** (50.0 mg, 0.115 mmol) and 1 M BBr_3 (115.0 µL, 0.115 mmol) in dry CH_2Cl_2 (2.5 mL) was stirred at 0 ^oC for 30 minutes. The crude residue was purified by flash column chromatography eluting with 4 % ethyl acetate-hexane. The yellow oil was obtained in 87% yield (42.0 mg), which precipitated from hexane-dichloromethane as a yellow amorphous solid, m.p. 99-100 ^oC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.30-1.70 (m, 10H, $(CH_2)_5$), 2.74 (s, 2H, CH_2Ar), 4.12 (s, 2H, OCH_2), 6.51 (m, 1H, ArH), 6.82 (m, 1H, ArH), 7.24 (m, 1H, ArH), 7.37 (br s, 1H, OH-quinone), 7.55 (m, 3H, ArH), 7.93 (m, 2H, ArH), 10.68 (s, 1H, OH-phenol).

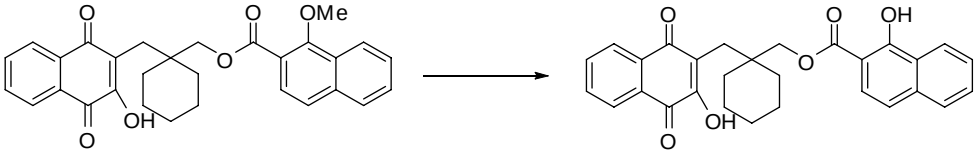
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.65 (2×CH_2), 25.96 (CH_2), 31.67 (CH_2), 33.45 (2×CH_2), 39.30 (C), 69.76 (CH_2), 112.53 (C), 117.43 (CH), 118.84 (CH), 121.84 (C), 125.98 (CH), 126.93 (CH), 129.23 (C), 129.55 (CH), 132.83 (CH), 132.98 (C), 134.92 (CH), 135.34 (C), 154.21 (C), 161.39 (C), 170.01 (C=O), 181.05 (C=O), 185.06 (C=O).

FTIR (KBr, cm^{-1}): 3329 (OH), 2920, 2851 (CH_2), 1675, 1659, 1615 (C=O), 1591, 1487, 1338, 1212 (C=C), 1156, 1090 (C-O).

MS (EI), *m/z* (% relative intensity): 419 ($[M-1]^+$, 2), 297 (3), 283 (100), 265 (11).

Anal. Calcd. for $C_{30}H_{28}O_6$: C, 79.96; H, 8.20. Found: C, 80.00, H, 8.20.

(1-((1,4-Dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)cyclohexyl)methyl 1-hydroxynaphthalene-2-carboxylate (164)



162 **164**

Compound **164** was synthesized by following the general procedure: a mixture of methyl ether **162** (30.0 mg, 0.062 mmol) and 1 M BBr_3 (62.0 μL, 0.062 mmol) in dry CH_2Cl_2 (1.5 mL) was stirred at 0 ^oC for 30 minutes. The crude residue was purified by flash column chromatography eluting with 3% ethyl acetate-hexane. The yellow oil was obtained in 68% yield (19.8 mg), which precipitated from hexane-dichloromethane as a yellow amorphous solid, m.p. 103-104 ^oC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.40-1.70 (m, 10H, $(CH_2)_5$), 2.68 (s, 2H, CH_2Ar), 4.22 (s, 2H, CH_2O), 6.87 (m, 1H, Ar), 7.36 (s, 1H, OH-quinone), 7.34-7.44

(m, 3H, ArH), 7.43 (d, *J*=8.8 Hz, 1H, ArH), 7.49 (m, 1H, ArH), 7.58 (m, 1H, ArH), 7.85 (m, 2H, ArH), 8.27 (m, 1H, ArH), 11.84 (s, 1H, OH-naphthol).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.71 (2×CH_2), 26.01 (CH_2), 31.76 (CH_2), 33.59 (2×CH_2), 39.38 (C), 69.91 (CH_2), 105.79 (C), 118.30 (CH), 121.95 (C), 123.77 (CH), 123.95 (CH), 124.64 (C), 125.61 (CH), 125.82 (CH), 126.79 (CH), 127.32 (CH), 129.17(C), 129.20 (CH), 132.60 (CH), 132.91(C), 134.63 (CH), 136.97 (C), 154.13 (C), 160.55 (C), 170.82 (C=O), 181.08 (C=O), 185.07 (C=O).

FTIR (KBr, cm^{-1}): 3277 (OH), 2923, 2850 (CH_2), 1668, 1638 (C=O), 1595, 1459, 1394, 1351, 1270 (C=C), 1164, 1089 (C-O).

MS (EI), *m/z* (% relative intensity): 470 (M^+, 32), 415 (100).

Anal. Calcd. for $C_{29}H_{26}O_6$: C, 74.03; H, 5.57. Found: C, 74.08, H, 5.45.

Biological Activities

Cytotoxicity assay by the MTT colorimetric method (Skehan *et al.*, 1990)

Compound **139-157** and **159-164** dissolved in dimethyl sulfoxide (DMSO) were subjected to cytotoxic evaluation against KB (human epidermoid carcinoma), HeLa (human cervical carcinoma) and MCF-7 (human breast carcinoma) cell lines employing the colorimetric method. Adriamycin was used as the reference drug which exhibits cytotoxicity against KB, HeLa and MCF-7 cell lines.

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (Sigma Chemical Co.) was dissolved in saline to make a concentration of 5 mg/mL as a stock solution. Cancer cells (3×10^3 cells) suspended in 100 μg/well of MEM medium containing 10% fetal calf serum (FCS, Gibco BRL, Life Technologies, NY) were seeded onto a 96-well culture plate (Coster, Corning Incorporated, NY 14831). After

24h of preincubation at 37 ^{o}C in a humidified atmosphere of 5% CO_2/95% air to allow cell attachment, various concentrations of test solution (10 µL/well) as listed in Tables16 and 17 were added and then incubated for 48h under the above conditions. At the end of the incubation, 10 µL of tetrazolium reagent was added to each well and then incubated at 37 ^{o}C for 4h. The supernatant was decanted, and DMSO (100 µL/well) was added to allow Formosan solubilization. The optical density (OD) of each well was detected by a Microplate reader (Bio-Rad, Benchmark Microplate reader) at 550 nm and for correction at 595 nm. Each determination represents the mean of six replicates. The 50% inhibition concentration (IC_{50}) was determined by curve fitting.

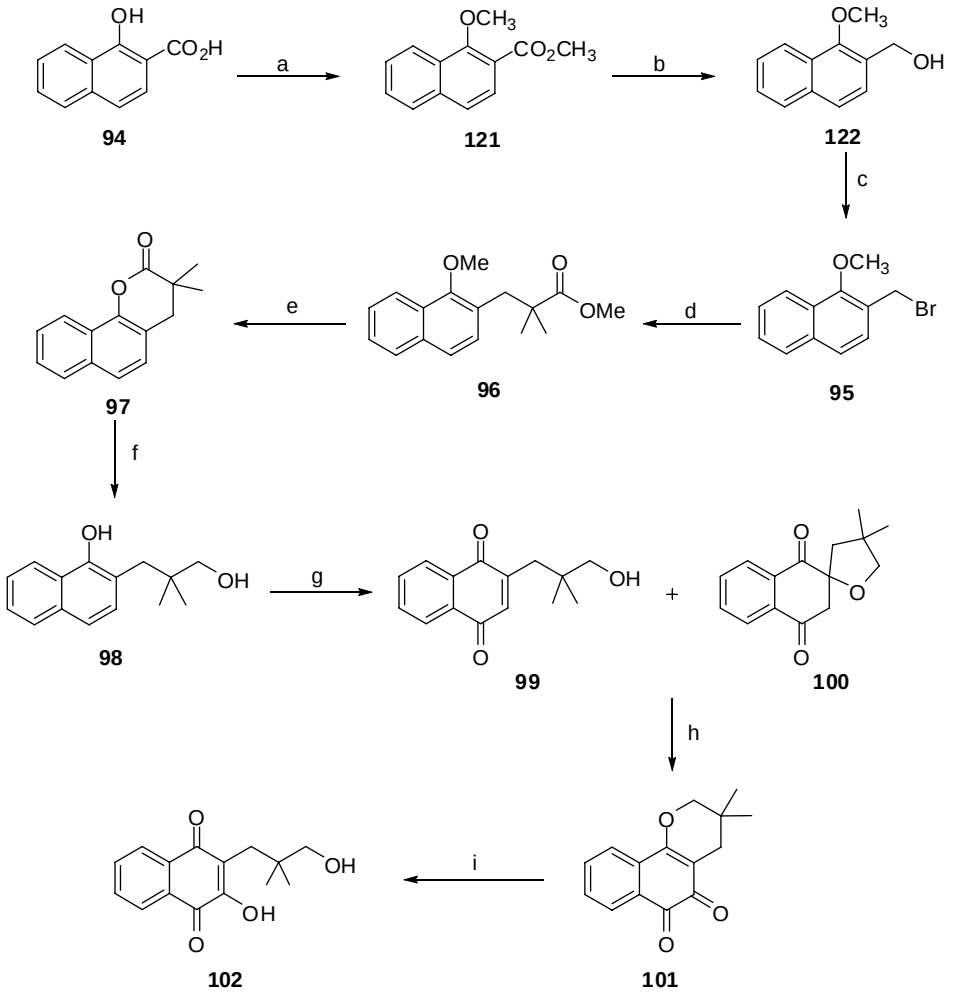
Antimalarial activity assay

Continuous in vitro cultures of the asexual erythrocytic stage of *Plasmodium falciparum* (K1, multidrug resistant stain) were maintained. Quantitative assessment of antimalarial activity in vitro was determined using the microculture radioisotope technique based upon the method described by Desjardins.(Desjardins *et al*., 1979) Inhibited concentration (IC_{50}) represents the concentration that cause 50% inhibition in parasite growth as indicated by the in vitro uptake of [^{3}H]hypoxanthine by *P. falciparum*.

RESULTS

1. Synthesis of naphthoquinone alcohol

Naphthoquinone alcohol, 2-hydroxy-3-(3′-hydroxy-2′,2′-dimethylpropyl) naphthalene-1,4-dione (**102**), was synthesized from 1-hydroxy-2-naphthoic acid (**94**) in nine steps with the overall yield of 26% as shown in **Scheme 7**.



Scheme 7

Reagents and conditions:

a) MeI, K_2CO_3, acetone, reflux, 12h, 96%.

b) $LiAlH_4$, dry ether, rt., 2h, 88%.

c) PBr_3, dry CH_2Cl_2, rt., 6h, quantitative yield.

d) LDA, methyl isobutylate, HMPA, dry THF, -78 °C, 2h, 89%.

e) $AlCl_3$, chlorobenzene, reflux, 4h, 83%.

f) $LiAlH_4$, dry ether, rt., 2h, 71%.

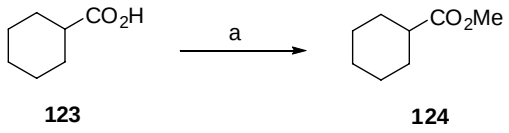
g) Fremy's salt ($NO(SO_3K)_2$), 1M NaOAc, MeOH-DMF (3 :1), rt., 12h, **99** (76%), **100** (16%).

h) DDQ, *p*-TsOH.H_2O, benzene, reflux, 20 min, 81%.

i) 1% aq. NaOH, reflux, 2h, 84%.

2. Synthesis of methyl cyclohexanecarboxylate

Methyl cyclohexanecarboxylate (**124**) was synthesized by methylation of cyclohexanecarboxylic acid (**123**) in 89% yield as shown in **Scheme 8**.



123 **124**

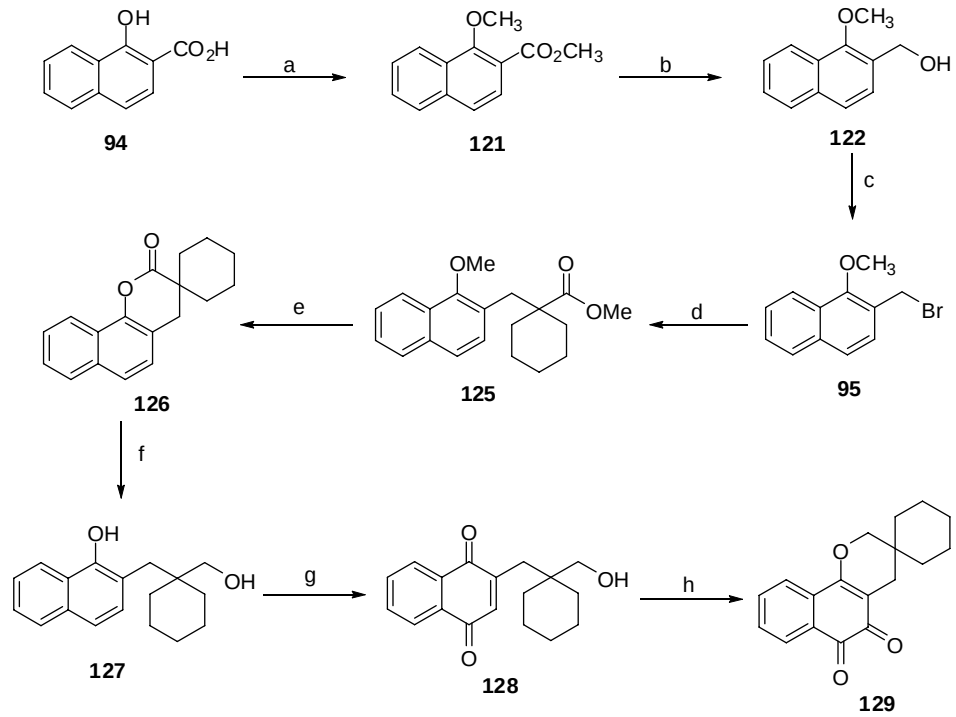
Scheme 8

Reagents and conditions:

a) MeI, K_2CO_3, acetone, reflux, 6h, 89%.

3. Synthesis of rhinacanthone derivative

In the same manner as the synthesis of 2-hydroxy-3-(3′-hydroxy-2′,2′-dimethylpropyl)naphthalene-1,4-dione (**102**), 3,4-dihydro-3,3-spirocyclohexyl-2H-naphtho[1,2-b]pyran-5,6-dione (**129**) was prepared from 1-hydroxy-2-naphthoic acid (**94**) with the overall yield of 39% as shown in **Scheme 9**.



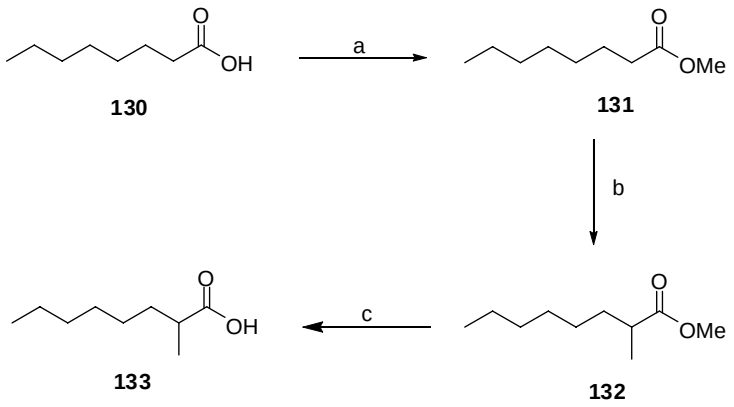
Scheme 9

Reagents and conditions:

a) MeI, K_2CO_3, acetone, reflux, 12h, 96%.
b) $LiAlH_4$, dry ether, rt., 2h, 88%.
c) PBr_3, dry CH_2Cl_2, rt., 6h, quantitative yield.
d) LDA, methyl cyclohexylcarboxylate, HMPA, dry THF, -78 °C, 2h, 87%.
e) $AlCl_3$, chlorobenzene, reflux, 4h, 81%.
f) $LiAlH_4$, dry ether, rt., 2h, 89%.
g) Fremy's salt ($NO(SO_3K)_2$, 1M NaOAc, MeOH-DMF (3 :1), rt, 12h, 87%.
h) DDQ, *p*-TsOH.H2O, benzene, reflux, 20 min, 84%.

4. Synthesis of 2-methyl octanoic acid (133)

2-Methyl octanoic acid (**133**) was derived from octanoic acid (**130**) by a three-step sequence involving methylation to ester, α-methylation of the ester and then hydrolysis. The process is shown in **Scheme 10**.



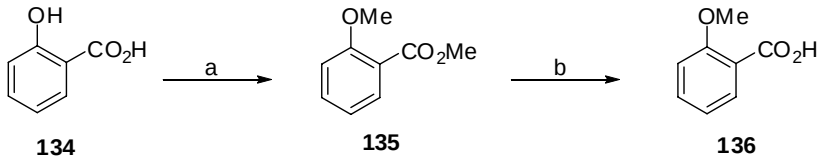
Scheme 10

Reagents and conditions:

a) MeI, K_2CO_3, acetone, reflux, 4h, 77%.
b) LDA, methyl cyclohexylcarboxylate, HMPA, dry THF, -78 °C, 2h.
c) 50% aq. EtOH-KOH, reflux, 3h, 53% for 2 steps.

5. Synthesis of benzoic acid and naphthoic acid derivatives

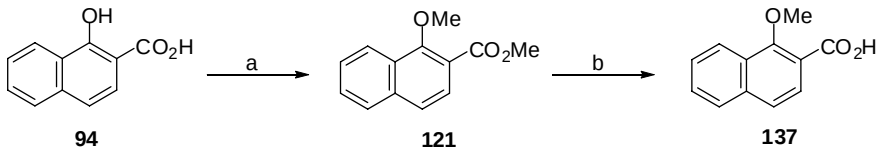
2-Methoxy benzoic acid (**136**) and 1-methoxy-naphthalene-2-carboxylic acid (**137**) were obtained in 2 steps by methylation and hydrolysis with overall yield of 93% and 95%, respectively as shown in **Scheme 11** and **12**.



Scheme 11

Reagents and conditions:

a) MeI, K_2CO_3, acetone, reflux, 6h, 94%.
b) 50% aq. EtOH-KOH, reflux, 3h, 99%.



94 **121** **137**

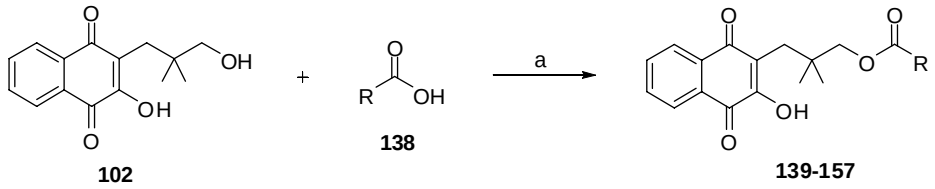
Scheme 12

Reagents and conditions:

a) MeI, K_2CO_3, acetone, reflux, 6h, 96%.
b) 50% aq. EtOH-KOH, reflux, 3h, 99%.

6. Synthesis of naphthoquinone ester derivatives

The synthesis of naphthoquinone aliphatic esters (**139-157**) were accomplished in moderate to excellent yield from esterification of the naphthoquinone alcohol **102** with various aliphatic carboxylic acids (**138**) in the presence of dicyclohexyl carbodiimide (DCC) together with 4-dimethylaminopyridine (DMAP) in dry dichloromethane as shown in **Scheme 13** and **Table 1**.



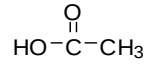
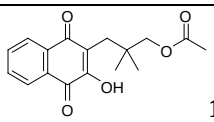
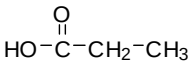
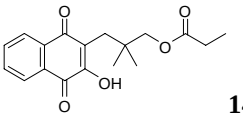
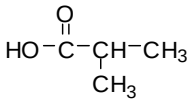
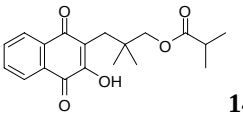
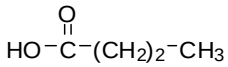
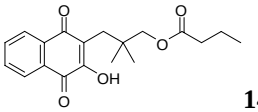
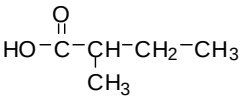
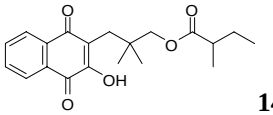
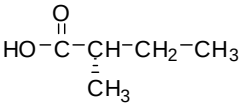
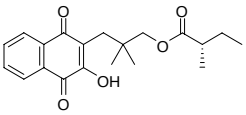
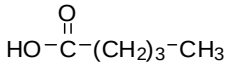
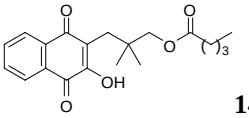
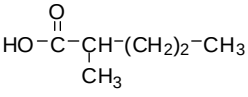
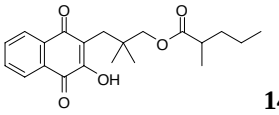
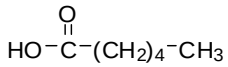
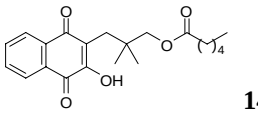
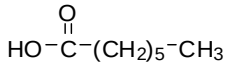
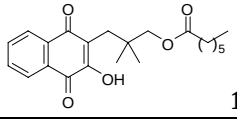
102 **138** **139-157**

Scheme 13

Reagents and conditions:

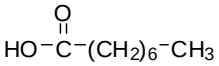
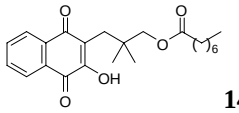
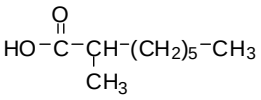
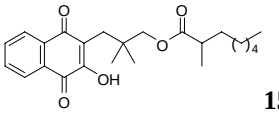
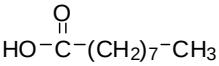
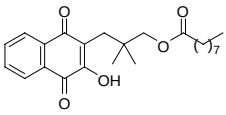
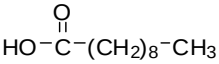
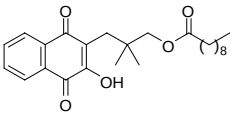
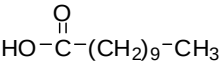
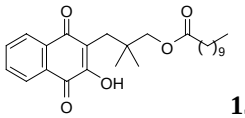
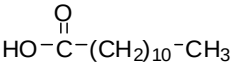
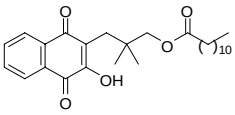
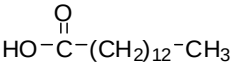
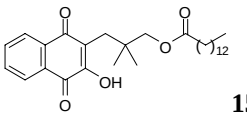
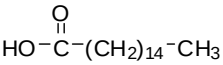
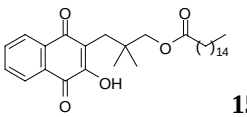
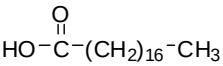
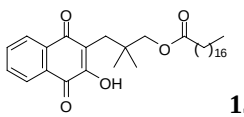
a) Aliphatic carboxylic acids, DMAP, DCC, dry CH_2Cl_2, rt, 12-14h.

Table 1. Synthesis of naphthoquinone aliphatic esters (**139-157**) from naphthoquinone alcohol **102** and various aliphatic carboxylic acids using DCC and DMAP as coupling reagents (**Scheme 13**).

Entry	Carboxylic acid	Product	Yield (%)[1]
1		 **139**	89
2		 **140**	90
3		 **141**	86
4		 **142**	87
5		 **143**	81
6		 **144**	76
7		 **145**	45
8		 **146**	77
9		 **147**	77
10		 **148**	83

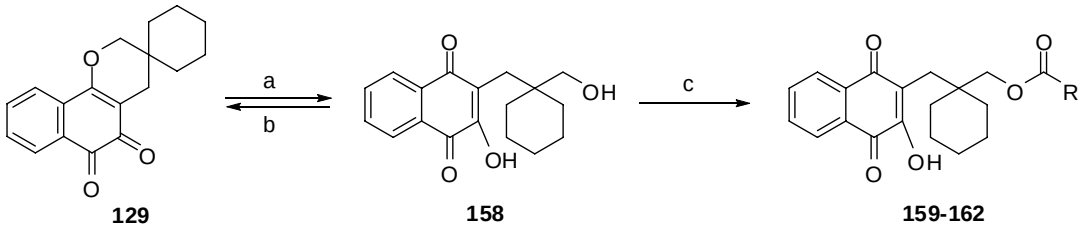
[1]Isolated yield

Table 1. (Continued)

Entry	Carboxylic acid	Product	Yield (%)[1]
11		 **149**	92
12		 **150**	84
13		 **151**	73
14		 **152**	72
15		 **153**	83
16		 **154**	79
17		 **155**	80
18		 **156**	77
19		 **157**	74

[1]Isolated yield

The syntheses of 2'-cyclohexylpropyl naphthoquinone esters (**159-162**) were achieved by basic hydrolysis of the rhinacanthone derivative (**129**) and then esterification of the naphthoquinone alcohol intermediate (**158**) with various aromatic carboxylic acids in the presence of 1,1'-carbodiimidazole (CDI) as shown in **Scheme 14** and **Table 2**.

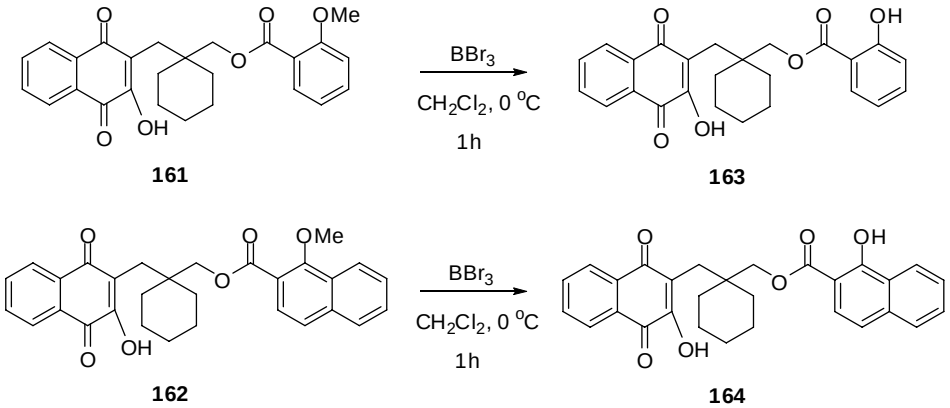


Scheme 14

Reagents and conditions:

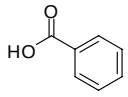
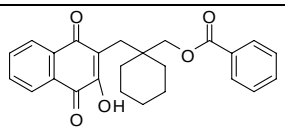
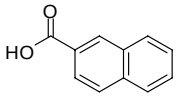
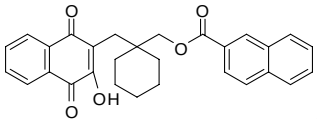
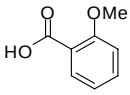
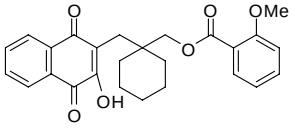
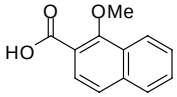
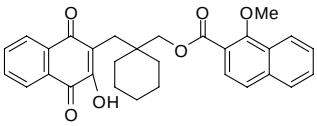
a) 1% aq. NaOH, reflux, 1h.
b) Room temperature.
c) Aromatic carboxylic acids, CDI, dry THF, rt., 12-14h.

Demethylation of the methyl aryl ethers of the ester moieties was accomplished in good yield when treatment with boron tribromide in dichloromethane at 0 ^{o}C as shown in **Scheme 15** and **Table 3**.



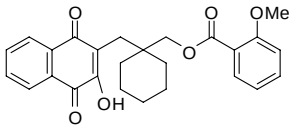
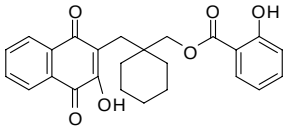
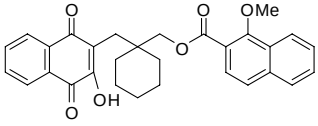
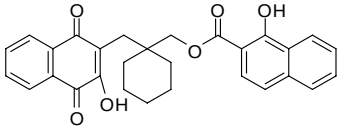
Scheme 15

Table 2. Synthesis of naphthoquinone esters (**159-162**) from naphthoquinone alcohol **158** and various aromatic carboxylic acids using CDI as coupling reagent. (see **Scheme 14**)

Entry	Carboxylic acid	Product	Yield (%)[1]
1		 **159**	22
2		 **160**	43
3		 **161**	69
4		 **162**	33

[1]Isolated yield for two steps

Table 3. Synthesis of naphthoquinone ester (**163-164**) by demethylation of methyl ether with boron tribromide.

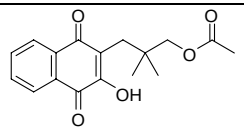
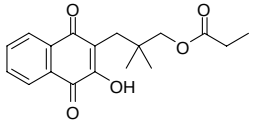
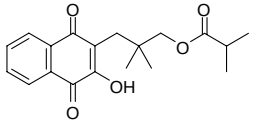
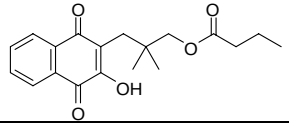
Entry	Methyl aryl ether	Product	Yield (%)[1]
1	 **161**	 **163**	87
2	 **162**	 **164**	68

[1]Isolated yield

Biological Activities

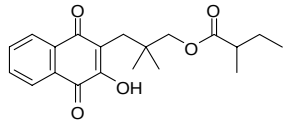
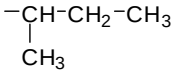
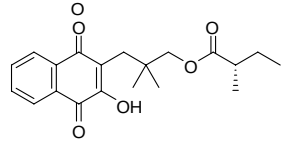
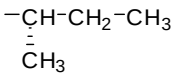
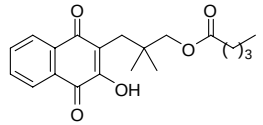
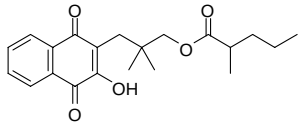
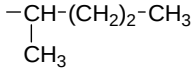
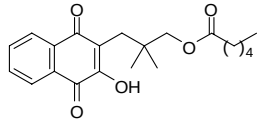
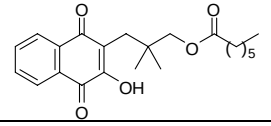
Anticancer activity was tested by Miss Pongpun Siripong and Miss Janthana Yahaufai of the National Cancer Institute of Thailand as shown in **Tables 4** and **5**. Antimalarial activity was tested at the BIOTEC as shown in **Tables 6**.

Table 4. Cytotoxic activities of napthoquinone ester derivatives against Human Carcinoma Cell Lines (KB, HeLa and MCF-7) and normal Vero Cell Lines.

Compound	Structure	Acid (R-)	Cancer cell lines, IC_{50} (μM)[1]			Vero cell line, IC_{50} (μM)[1]
			KB	HeLa	MCF-7	
139		$-CH_3$	220.63±8.60	>330.78	253.7±8.53	138.92±22.13
140		$-CH_2-CH_3$	84.40±12.01	62.27±1.64	281.97±145.09	60.06±7.74
141		$-CH(CH_3)_2$	14.38±1.82	19.67±1.36	177.98±20.92	123.10±50.52
142		$-(CH_2)_2-CH_3$	42.98±6.36	59.93±1.24	143.77±18.52	73.16±14.89

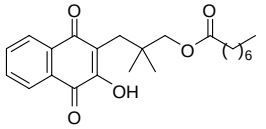
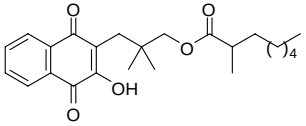
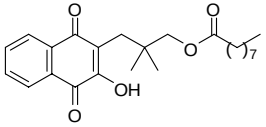
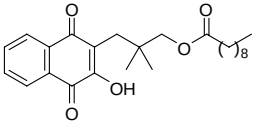
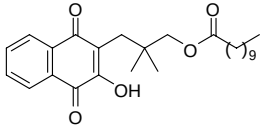
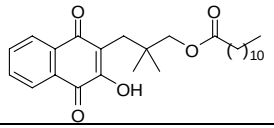
[1]The results are the mean of six replicate determinations ± SD.

Table 4. (Continued)

Compound	Structure	Acid (R-)	Cancer cell lines, IC_{50} (μM)[1]			Vero cell line, IC_{50} (μM)[1]
			KB	HeLa	MCF-7	
143			4.65±0.38	3.83±1.19	140.82±5.72	0.87±0.02
144			5.66±0.15	5.66±0.15	99.68±4.38	0.57±0.02
145			27.79±7.43	31.45±3.86	152.44±6.56	7.84±0.67
146			1.76±0.22	4.66±0.22	128.90±4.58	0.12±0.03
147			41.01±3.35	52.45±2.73	98.21±10.60	169.07±15.60
148			14.42±2.42	27.92±8.24	71.96±5.91	99.34±7.36

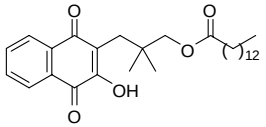
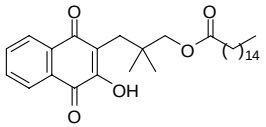
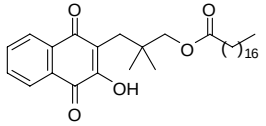
[1]The results are the mean of six replicate determinations ± SD.

Table 4. (Continued)

Compound	Structure	Acid (R-)	Cancer cell lines, IC_{50} (μM)[1]			Vero cell line, IC_{50} (μM)[1]
			KB	HeLa	MCF-7	
149		$-(CH_2)_6-CH_3$	38.29±2.07	31.83±7.45	165.08±6.47	>258.75
150		$-CH(CH_3)-(CH_2)_5-CH_3$	16.78±1.73	3.40±1.15	131.08±15.29	0.45±0.02
151		$-(CH_2)_7-CH_3$	38.70±1.25	22.77±7.52	38.70±1.37	149.81±13.73
152		$-(CH_2)_8-CH_3$	55.48±23.16	30.15±7.60	101.80±19.54	202.64±36.16
153		$-(CH_2)_9-CH_3$	54.83±28.00	7.23±2.64	167.30±5.13	>233.34
154		$-(CH_2)_{10}-CH_3$	35.70±5.20	203.35±31.86	178.95±4.52	248.54±101.67

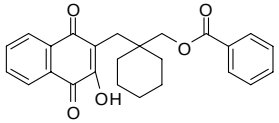
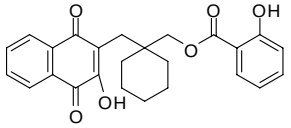
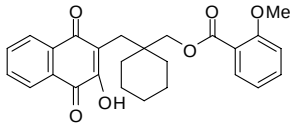
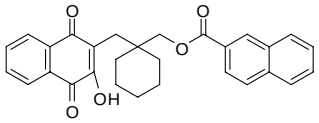
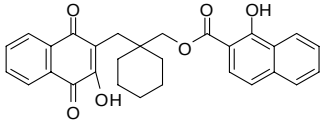
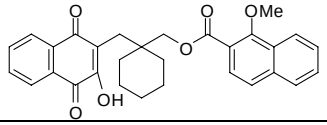
[1]The results are the mean of six replicate determinations ± SD.

Table 4. (Continued)

Compound	Structure	Acid (R-)	Cancer cell lines, IC_{50} (μM)[1]			Vero cell line, IC_{50} (μM)[1]
			KB	HeLa	MCF-7	
155		$-(CH_2)_{12}-CH_3$	51.36±5.61	29.21±7.16	109.79±8.67	58.43±5.82
156		$-(CH_2)_{14}-CH_3$	27.07±2.77	37.60±1.93	121.32±4.35	4.41±2.77
157		$-(CH_2)_{16}-CH_3$	76.66±4.56	129.72±1.56	>189.84	15.51±1.56
Adriamycin[2]	-	-	0.033	0.33	0.003	23.94

[1]The results are the mean of six replicate determinations ± SD.
[2]Used as reference.

Table 5. Cytotoxic activities of napthoquinone ester derivatives against Human Carcinoma Cell Lines (KB, HeLa and MCF-7) and Vero Cell Lines.

Compound	Structure	Cancer cell lines, IC_{50} (μM)[1]			Vero cell line, IC_{50} (μM)[1]
		KB	HeLa	MCF-7	
159		11.45±2.18	17.93±2.67	57.68±5.98	3.51±0.57
163		9.56±0.10	11.42±0.14	35.27±0.98	72.54±2.00
161		11.76±0.46	14.91±0.99	34.92±4.21	98.58±6.08
160		9.42±0.88	15.58±2.24	26.40±10.05	3.89±0.64
164		13.81±0.11	10.63±1.79	29.75±2.34	51.01±5.70
162		11.35±0.06	10.22±0.17	28.21±4.46	58.14±7.31

[1]The results are the mean of six replicate determinations ± SD.
[2]Used as reference.

Table 6. *In vitro* antimalarial activity of naphthoquinone ester derivatives (**139-157**) against *Plasmodium falciparum*, K1 Strain.

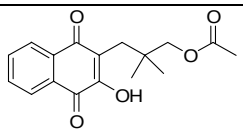
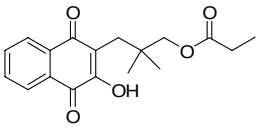
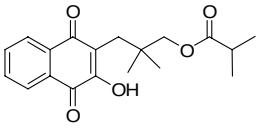
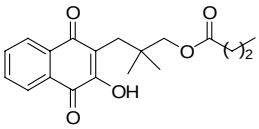
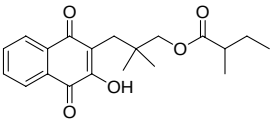
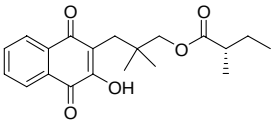
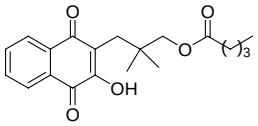
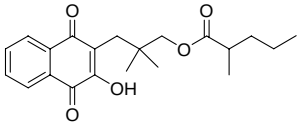
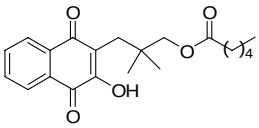
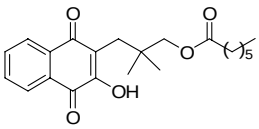
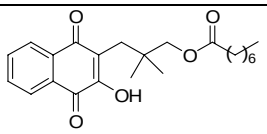
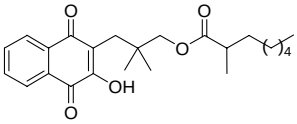
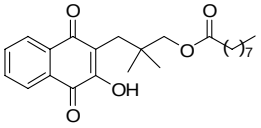
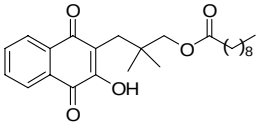
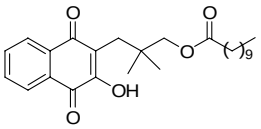
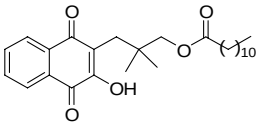
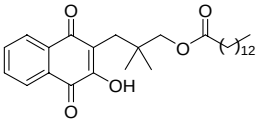
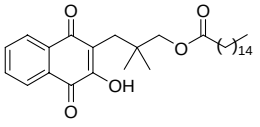
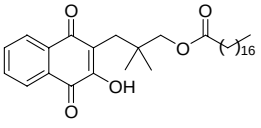
Compound	Structure	Acid (R-)	Antimalarial activity, IC_{50} (μM)
139		$-CH_3$	10.92
140		$-CH_2-CH_3$	4.10
141		$-CH(CH_3)_2$	0.91
142		$-(CH_2)_2-CH_3$	0.91
143		$-CH(CH_3)-CH_2-CH_3$	0.22
144		$-CH(CH_3)-CH_2-CH_3$	0.11
145		$-(CH_2)_3-CH_3$	0.58
146		$-CH(CH_3)-(CH_2)_2-CH_3$	0.12
147		$-(CH_2)_4-CH_3$	1.12
148		$-(CH_2)_5-CH_3$	0.81

Table 6. (Continued)

Compound	Structure	Acid (R-)	Antimalarial activity, IC_{50} (μM)
149		$-(CH_2)_6-CH_3$	0.13
150		$-CH(CH_3)-(CH_2)_5-CH_3$	0.11
151		$-(CH_2)_7-CH_3$	0.50
152		$-(CH_2)_8-CH_3$	0.72
153		$-(CH_2)_9-CH_3$	0.70
154		$-(CH_2)_{10}-CH_3$	0.90
155		$-(CH_2)_{12}-CH_3$	0.032
156		$-(CH_2)_{14}-CH_3$	0.030
157		$-(CH_2)_{16}-CH_3$	0.133
Dihydroar-temisinine[1]	-	-	0.0035

[1]Used as reference.

DISCUSSION

The naphthoquinone ester derivative is a group of natural products found in many medicinal plants. One of these plants is *Rhinacanthus nasutus* and most of compounds found in this plant are rhinacanthin derivatives which are naphthoquinone aromatic and aliphatic esters. These naphthoquinone esters were found to show a variety of biological activity *i.e.* antibacterial, anticancer and antimalarial activities. In the present time, naphthoquinone derivative such as atovaquone (**11**), contains 3-hydroxy-1,4-naphthoquinone core structure, has been used as an antimalarial drug with high activity against multidrug-resistant *Plasmodium falciparum*. It is used in combination with other antimalarial drug such as atovaquone-proguanil and atovaquone-doxycycline. There have also been reported that natural naphthoquinone aliphatic/aromatic ester exhibited cytotoxic activity. (Wu *et al*., 1998) Recently, our group reported the synthesis of rhinacanthin and related naphthoquinone aromatic esters with 2'-dimethyl substituents and found that most of them exhibited cytotoxicity against the cancer cell lines KB, HeLa and $HepG_2$. (Kongkathip *et al*., 2004) Interestingly, all natural naphthoquinone aliphatic esters contain α-methyl group *i.e.* rhinacanthin-C, rhinacanthin-G, rhinacanthin-H and rhinacanthin-K and these compounds showed anticancer activity. Hence, it is very interesting to synthesize naphthoquinone aromatic ester derivatives with cyclohexyl substituents at 2'-position which impart rigidity to the structure for evaluation of anticancer activity, and naphthoquinone aliphatic esters (straight chain and containing of α-methyl group in the ester side chain) for evaluation of anticancer and antimalarial activities and also for studying their structure-activity relationships.

Herein, the synthesis of naphthoquinone ester derivatives is reported. These compounds were obtained by esterification of naphthoquinone alcohols (**102** and **158**) with various aliphatic carboxylic acids or aromatic carboxylic acids. The retrosynthetic analysis of these naphthoquinone esters is shown in **Figure 1**.

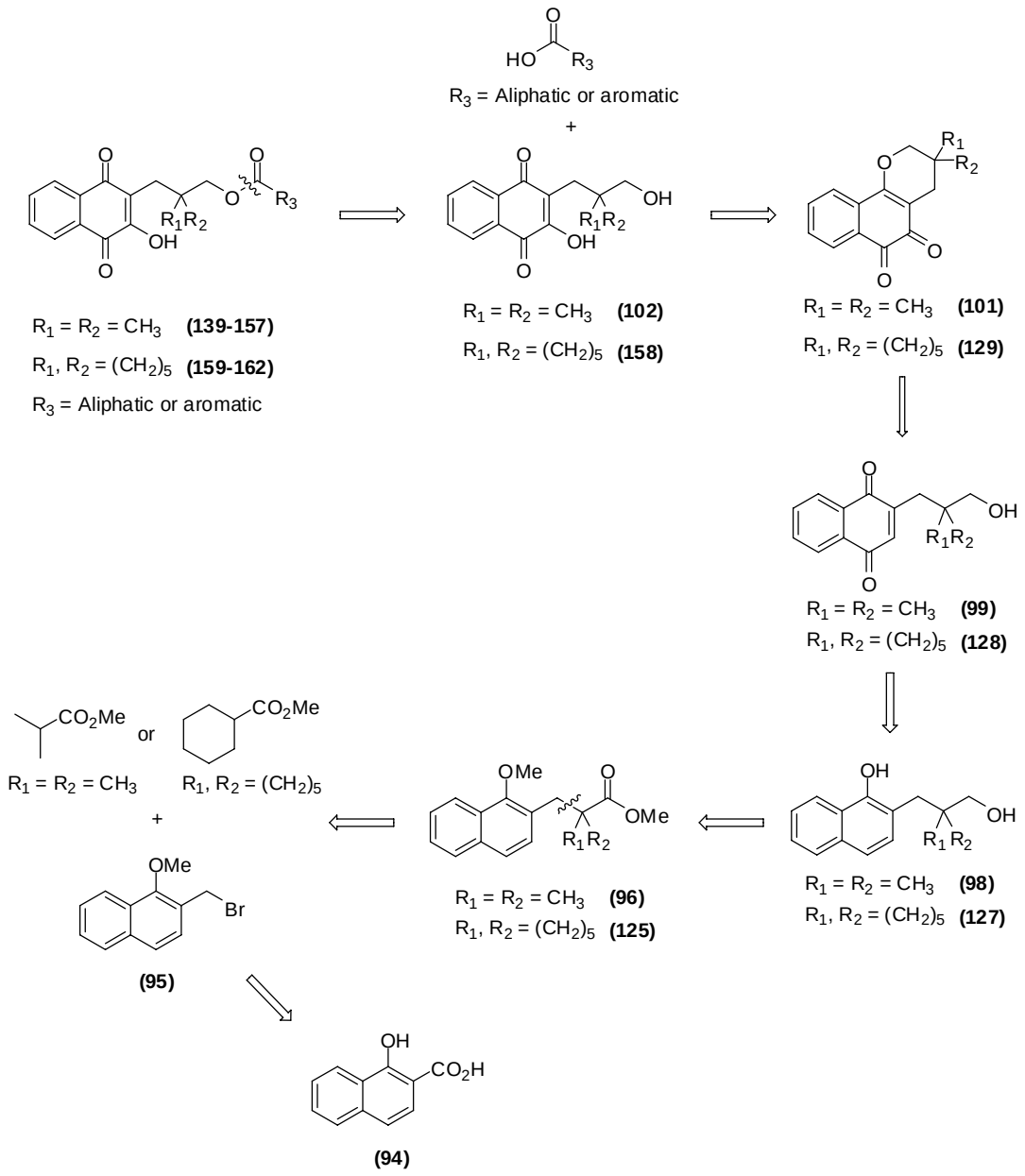
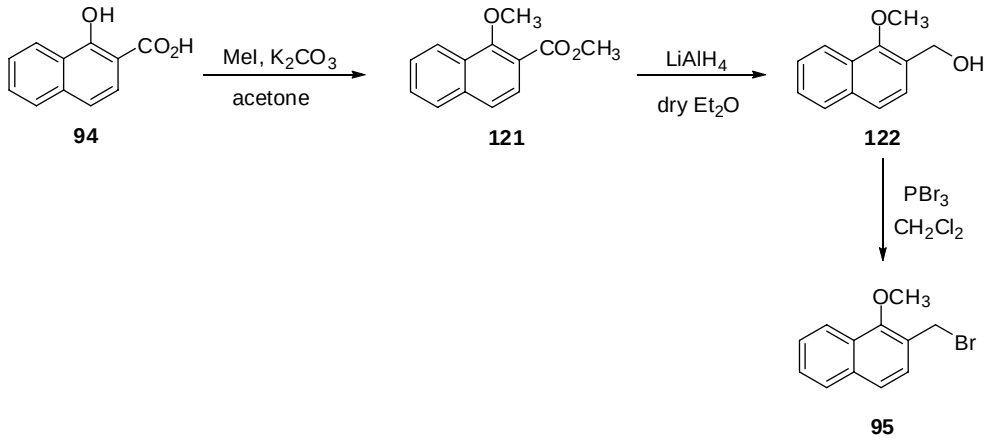


Figure 1. Retrosynthetic analysis of naphthoquinone ester derivatives

Naphthoquinone alcohols (**102** and **158**) could be produced in nine steps with excellent yield of each step. Dimethyl and cyclohexyl substituents at the 2'-position of these naphthoquinone alcohols could be obtained from the alkylation reaction of bromide **95** with methyl isobutyrate and methyl cyclohexanecarboxylate, respectively. Bromide **95** could be synthesized starting from 1-hydroxy-2-naphthoic acid (**94**) via

sequential methylation, reduction and bromination (**Scheme 16**) as reported in the literature (Kongkathip *et al*., 2003).

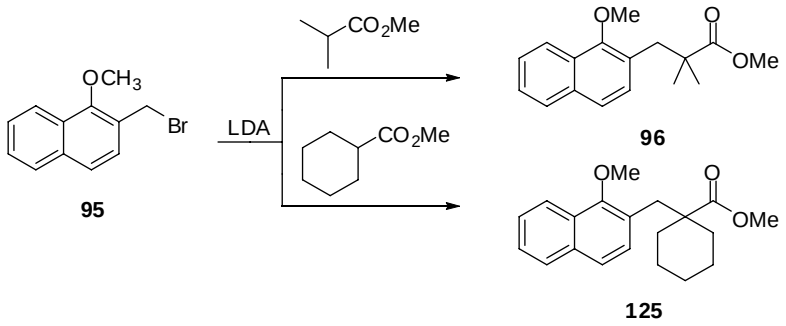


94 **121** **122** **95**

Scheme 16

1-Hydroxy-2-naphthoic acid (**94**) was methylated by using methyl iodide (MeI) and potassium carbonate (K_2CO_3) in acetone under reflux to give methyl ester (**121**) in 96% yield. The ^{1}H NMR (400 MHz) spectrum of this compound in $CDCl_3$ revealed the characteristic peaks of methyl ester and methyl ether protons as two singlets at δ 3.98 and 4.07 ppm, respectively. Its IR spectrum showed the absorption band at 7213 cm^{-1} suggesting the C=O stretching of the ester moiety. The mass spectrum (EI) of this compound, exhibiting a molecular ion peak at *m/z* 216, confirmed the structure. Reduction of methyl ester (**121**) with lithium aluminium hydride ($LiAlH_4$) afforded alcohol **122** in 88% yield. The ^{1}H NMR (400 MHz) spectrum of this compound in $CDCl_3$ showed a broad singlet at δ 2.22 ppm which was assigned to a hydroxyl proton and a singlet signal at δ 4.90 ppm confirmed the methylene proton adjacent to the hydroxyl group. The FTIR spectrum showed a broad absorption band at 3196 cm^{-1}, implying free hydroxyl stretching. The molecular ion peak at *m/z* 188 corresponded to the structure of compound **122**. This alcohol (**122**) was then converted to the bromide product (**95**) by treatment with 1M phosphorus tribromide (PBr_3) in dry dichloromethane. The ^{1}H NMR (400 MHz) spectrum of this compound in $CDCl_3$ exhibited a characteristic peak as a singlet at δ 4.70 ppm of the methylene proton, connected to the bromide. The absence of the IR absorption at 3196 cm^{-1} is an indication of the loss of hydroxyl group in the molecule. The EI mass

spectrum showed a ratio of 1:1 of two molecular ion peaks of two isotopes to confirm the presence of bromide in the molecule. Without purification, bromide **95** was used for the alkylation reaction with methyl isobutyrate or methyl cyclohexanecarboxylate in the presence of lithium diisopropylamide (LDA) to provide the corresponding products (**96** and **125**, respectively) bearing dimethyl and cyclohexyl substituents at the 2'-position of the propyl side chain in 89% and 87%, respectively (**Scheme 17**).



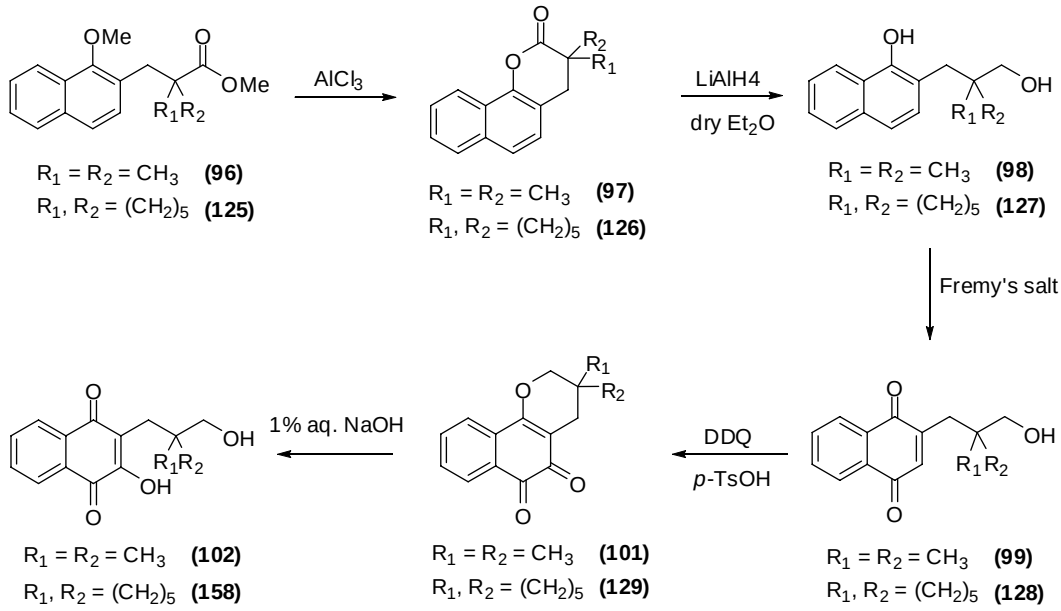
Scheme 17

The ^{1}H NMR (400 MHz) spectrum in $CDCl_3$ of methyl 2-((1-methoxynaphthalen-2-yl)methyl)-2-methylpropanoate (**96**) showed the characteristic peaks as two singlets of methyl ester proton at δ 3.98 ppm and methyl ether proton and 4.07 ppm. A singlet signal at δ 1.20 ppm was assigned to the dimethyl groups of the side chain. The methylene proton appeared at δ 3.08 ppm as a singlet. The IR spectrum of this compound showed the absorption band of C=O stretching of ester at 1733 cm^{-1} and the C-O stretching band at 1119 cm^{-1}. The EI mass spectrum showed by the molecular ion peak at *m/z* 272 confirmed this molecule.

The ^{1}H NMR (400 MHz) spectrum in $CDCl_3$ of methyl 1-((1-methoxynaphthalen-2-yl)methyl)cyclohexanecarboxylate (**125**) exhibited two singlets at δ 3.68 and 3.90 ppm, characteristic of methyl ester and methyl ether protons, respectively. Multiplet signals in the region of δ 1.75-2.75 ppm were assigned to ten protons of the cyclohexyl unit. The methylene proton adjacent to the naphthalene ring showed the characteristic peak at δ 3.02 ppm as a singlet. A group of signals in the aromatic region were assigned to six naphthalene protons. The IR spectrum of

compound **125** showed C=O stretching band of ester at 1727 cm^{-1} and C-O stretching band at 1081 cm^{-1}. The EI mass spectrum showed by the molecular ion peak at *m/z* 312 confirmed this molecule.

These two compounds were used to synthesize the corresponding naphthoquinone alcohols (**102** and **158**) by the same method as shown in **Scheme 18**.



Scheme 18

In **Scheme 18**, the alkylated product **96** was treated with aluminium chloride ($AlCl_3$) in chlorobenzene under reflux to give lactones **97** in 83% yield while **125** gave **126** in 81% yield. The ^1H NMR (400 MHz) spectrum of compound **97** in $CDCl_3$ did not show two singlets in the region of δ 4.00 ppm, indicating that the molecule had no methyl ester. The singlet signal at δ 2.90 ppm is a characteristic of the methylene proton and two methyl protons showed one singlet at δ 1.30 ppm. The IR spectrum of this compound showed the absorption bands at 1759 and 1111 cm^{-1}, implying C=O stretching and C-O stretching of the lactone ring. The EI mass spectrum exhibited the molecular ion peak at *m/z* 226 which confirmed this molecule.

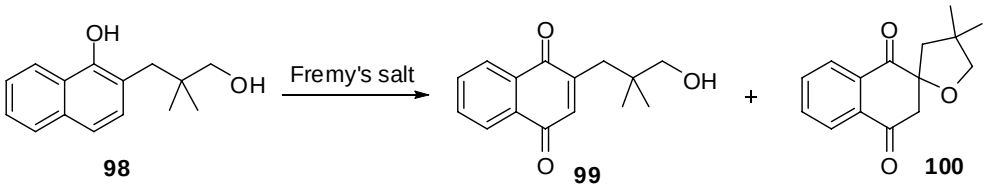
The ^{1}H NMR (400 MHz) spectrum in $CDCl_3$ of 3,4-dihydro-2-spirocyclohexylbenzo[h]chromen-2-one (**126**) showed a singlet signal at δ 2.98 ppm, suggesting a characteristic of the methylene proton. Multiplet signals in the region of δ 1.40-1.90 ppm were assigned to ten protons of the cyclohexyl unit. The IR absorption at 1753 and 1086 cm^{-1} indicated C=O and C-O stretching of lactone ring. The EI mass spectrum showed the peak at *m/z* 267 ($[M+1]^+$, 100% relative intensity), confirmed this molecule.

Reduction of lactones **97** and **126** using lithium aluminium hydride ($LiAlH_4$) yielded naphthol derivatives (**98** and **127**, respectively) in good yield. The ^{1}H NMR (400 MHz) spectrum of naphthol **98** in $CDCl_3$ showed two singlets at δ 2.77 and 3.25 ppm which were assigned to the methylene proton adjacent to the naphthalene ring and the methylene proton connected to the hydroxyl group, respectively. Two methyl protons showed one singlet at δ 1.04 ppm and a broad singlet at δ 2.45 ppm was a characteristic of the hydroxyl proton. The IR spectrum of this compound showed the absorption band at 3363 cm^{-1}, suggesting OH stretching of hydroxyl groups. The EI mass spectrum exhibited by the molecular ion peak at *m/z* 230 confirmed this molecule.

The ^{1}H NMR (400 MHz) spectrum in $CDCl_3$ of 2-((1-(hydroxymethyl) cyclohexyl)methyl)naphthalen-1-ol (**127**) showed two singlet signals at δ 2.78 and 3.31 ppm, suggesting the characteristics of the methylene proton adjacent to the naphthalene ring and the methylene proton connected to the hydroxyl group, respectively. Moreover, multiplet signals in the region of δ 1.30-1.65 ppm were assigned to ten protons of cyclohexyl unit. For the IR spectrum, a presence of a broad absorption band at 3413 cm^{-1} indicated that the molecule is comprised of hydroxyl group. The EI mass spectrum showed the molecular ion peak at *m/z* 270, confirmed this molecule.

Oxidation of naphthols **98** and **127** with Fremy's salt and 1M sodium acetate (NaOAc) in a mixture solvent of 3:1 ratio of methanol-dimethyl formamide (DMF)

provided 1,4-naphthoquinone derivatives (**99** and **128**). In the reaction of naphthol **98**, 1,4-naphthoquinone-2-spiro-2'-(4',4'-dimethyltetrahydrofuran) (**100**) was obtained together with the desired product, 2-(3-hydroxy-2,2-dimethyl propyl)-1,4-naphthoquinone (**99**) in 16% and 76%, respectively (**Scheme 19**).



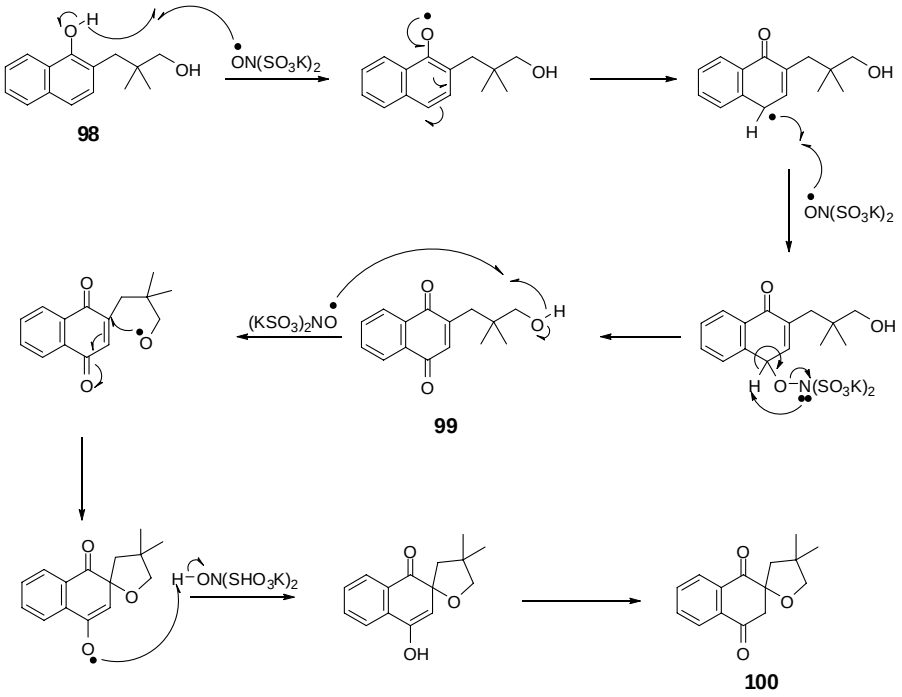
Scheme 19

The ^{1}H NMR (400 MHz) spectrum of compound **99** in $CDCl_3$ showed a singlet signal at δ 6.76 ppm which were assigned to the proton on the quinone ring. One singlet at δ 0.90 ppm was a characteristic of two methyl protons in the side chain. Two singlet signals at δ 2.50 and 3.10 ppm were assigned to the methylene proton adjacent to the naphthoquinone ring and to the methylene proton connected to the hydroxyl group, respectively. The IR spectrum of this compound showed the absorption band at 3420 cm^{-1}, suggesting OH stretching of hydroxyl groups. The C=O stretching of quinone and the C-O stretching of the alcohol side chain appeared at 1663 and 1041 cm^{-1}, respectively. The EI mass spectrum showed by the molecular ion peak at *m/z* 244 confirmed this molecule.

The ^{1}H NMR (400 MHz) spectrum in $CDCl_3$ of 1,4-naphthoquinone-2-spiro-2'-(4',4'-dimethyltetrahydrofuran) (**100**) showed two singlet signals at δ 1.10 and 1.20 ppm which were assigned to two methyl protons on the pyran ring. One singlet at δ 0.90 ppm was a characteristic of two methyl protons in the side chain. Two singlet signals at δ 2.50 and 3.10 ppm which were assigned to the methylene proton adjacent to the naphthoquinone ring and the methylene proton connecting to the hydroxyl group, respectively. The IR spectrum of this compound showed the absorption band of C=O stretching of the quinone at 1700 cm^{-1} and C-O stretching of the alcohol side

chain at 1053 cm^{-1}. The EI mass spectrum showed by the molecular ion peak at *m/z* 244 confirmed this molecule.

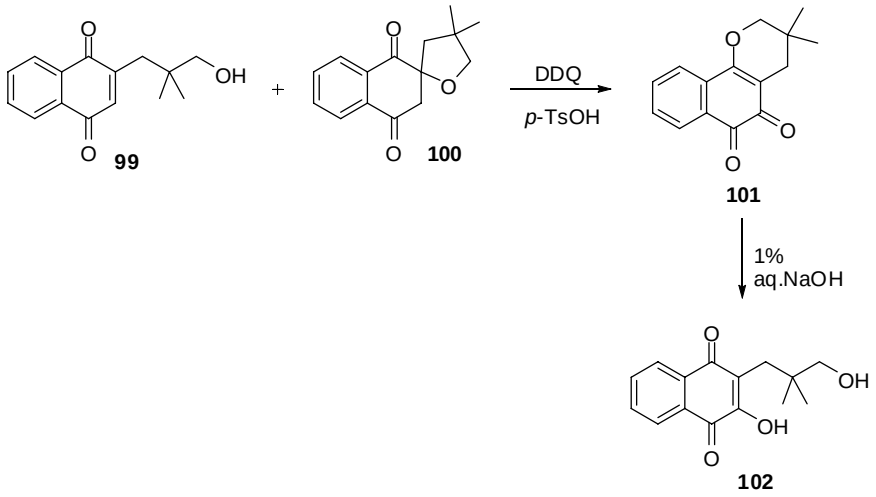
The mechanism of the oxidation of naphthol derivative (**98**) by Fremy's salt yielded the mixture of 2-(3-hydroxy-2,2-dimethyl propyl)-1,4-naphthoquinone (**99**) and 1,4-naphthoquinone-2-spiro-2'-(4',4'-dimethyltetrahydrofuran) (**100**) as shown in **Scheme 20**.



Scheme 20

The mixture products (**99** and **100**) could be converted to rhinacanthone (**101**) in 92% yield by treatment with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and *p*-toluenesulfonic acid (*p*-TsOH) in dry benzene as shown in **Scheme 21**. The ^{1}H NMR (400 MHz) spectrum of rhinacanthone (**101**) in $CDCl_3$ showed two singlet signals at δ 2.30 and 3.90 ppm were assigned to two methylene protons of the pyran ring: δ 2.30 ppm for one methylene proton adjacent to 1,2-naphthoquinone ring and δ 3.90 ppm for the one connected to the oxygen. One singlet at δ 1.00 ppm was a characteristic of two methyl protons in the side chain. The IR spectrum of this compound showed the

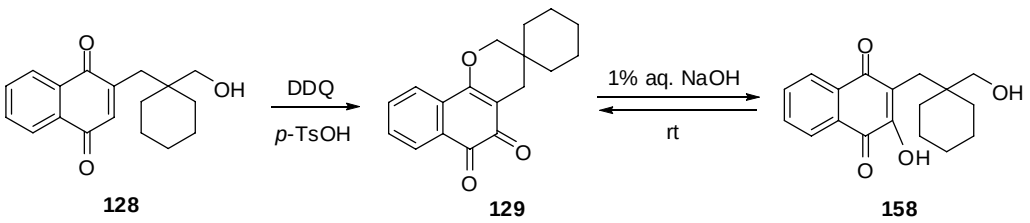
absorption band of C=O stretching at 1696 and 1640 cm^{-1} and C-O stretching at 1090 cm^{-1}. The EI mass spectrum showed by the molecular ion peak at *m/z* 242 confirmed this molecule. Basic hydrolysis of rhinacanthone with 1% aqueous sodium hydroxide (NaOH) under reflux for 2 hours afforded the desired naphthoquinone alcohol (**102**) in 84% yield.



Scheme 21

For the oxidation step using Fremy's salt of 2-((1-(hydroxymethyl) cyclohexyl)methyl)naphthalen-1-ol (**127**), only 1,4-naphthoquinone **128** was obtained in 87% yield. The ^1H NMR (400 MHz) spectrum of this product in acetone-d_6 showed a triplet signal at δ 6.89 ppm with J= 0.8 Hz which were assigned to the proton on the quinone ring. Multiplet signal in the region of δ 1.20-1.60 ppm was a characteristic of ten methylene protons of the cyclohexyl moiety. A doublet signal at δ 2.65 ppm was assigned to the methylene proton adjacent to the naphthoquinone ring. It is coupled to the proton of the quinone ring with J= 0.8 Hz. The methylene proton connected to the hydroxyl group showed a characteristic peak at δ 3.37 ppm. The IR spectrum of this compound showed the absorption band at 3225 cm^{-1}, suggesting OH stretching of the hydroxyl group. The C=O stretching of quinone appeared at 1659 and 1627 cm^{-1} and C-O stretching of the alcohol side chain appeared at 1021 cm^{-1}. The EI mass spectrum showed by the base peak at *m/z* 285 ($[M+1]^+$, 100% relative intensity) confirmed this molecule.

Naphthoquinone **128** was then treated with DDQ and *p*-TsOH in dry benzene to give the rhinacanthone derivative (**129**) in 84% yield (**Scheme 22**). The ^{1}H NMR (400 MHz) spectrum of rhinacanthone derivative (**129**) in $CDCl_3$ showed two singlet signals at δ 2.41 and 4.07 ppm which were assigned to two methylene protons of the pyran ring: δ 2.41 ppm for one methylene proton adjacent to 1,2-naphthoquinone ring and δ 4.07 ppm for that connected to oxygen. Multiplet signal in the region of δ 1.30-1.60 ppm was a characteristic of ten methylene protons of the cyclohexyl moiety. The IR spectrum of this compound showed the absorption band of C=O stretching of quinone at 1697 and 1642 cm^{-1} and C-O stretching at 1085 cm^{-1}. The EI mass spectrum showed by the molecular ion peak at *m/z* 283 as the base peak ($[M+1]^+$, 100% relative intensity) confirmed this molecule.



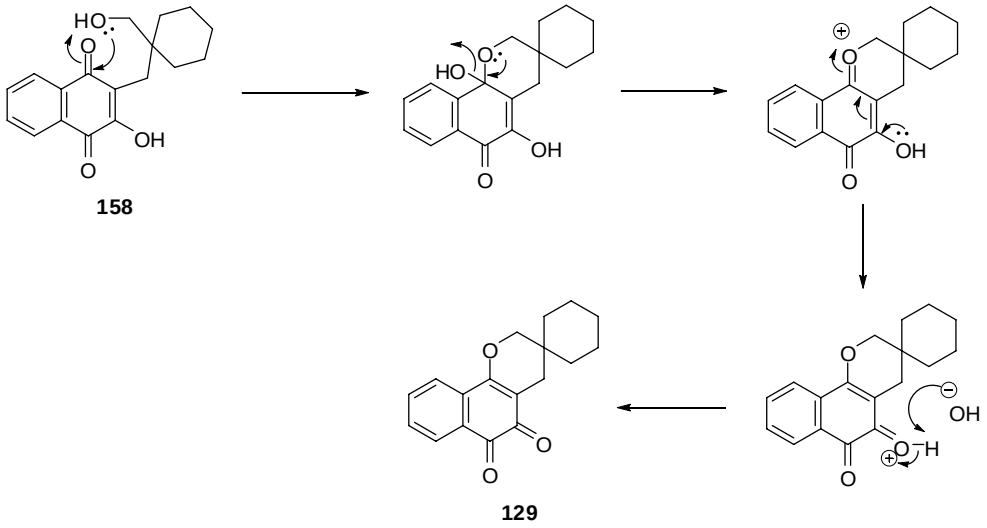
128 **129** **158**

Scheme 22

Basic hydrolysis of this rhinacanthone derivative has been done by using 1% aqueous NaOH under reflux for 1 hour, the desired naphthoquinone alcohol (**158**) was completely obtained which was monitored by thin-layer chromatography (TLC). After work-up with acetic acid to pH 7, the reaction mixture was repeatedly extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to provide the crude product. It was found that some of the desired crude naphthoquinone alcohol was cyclized to the starting material, rhinacanthone derivative (**129**). When the crude product was left at room temperature, rhinacanthone **129** was completely obtained.

Because of the rigidity and strain imparted by the cyclohexyl group to the molecule. The hydroxyl group of the side chain approached close to the carbonyl

group at the 1-position of the naphthoquinone ring and the cyclic form quite arose easily. So, naphthoquinone alcohol **158** should be freshly prepared for the esterification in next step. The reverse cyclization of the naphthoquinone alcohol intermediate (**158**) to the rhinacanthone derivative (**129**) is carried out assigned in **Scheme 23**.

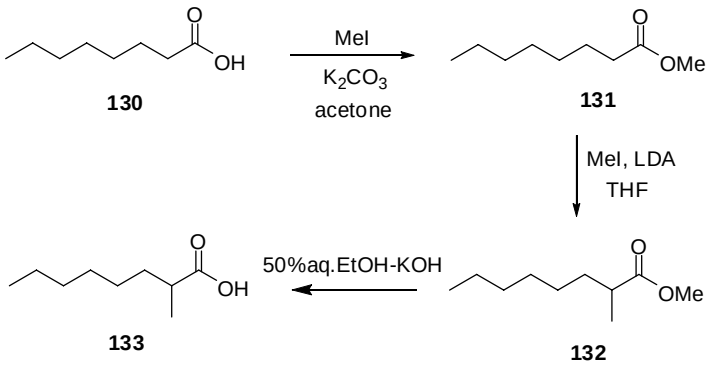


Scheme 23

The condensation between naphthoquinone alcohol (**102**) and a variety of aliphatic carboxylic acids (acetic acid, propionic acid, isobutyric acid, butyric acid, 2-methylbutyric acid, (*s*)-(+)-2-methylbutyric acid, pentanoic acid, 2-methylpentanoic acid, hexanoic acid, heptanoic acid, octanoic acid, 2-methyloctanoic acid, nonanoic acid, decanoic acid, undecanoic acid, dodecanoic acid, myristic acid, palmitic acid and stearic acid) could be accomplished by treatment with dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in dry dichloromethane at room temperature.

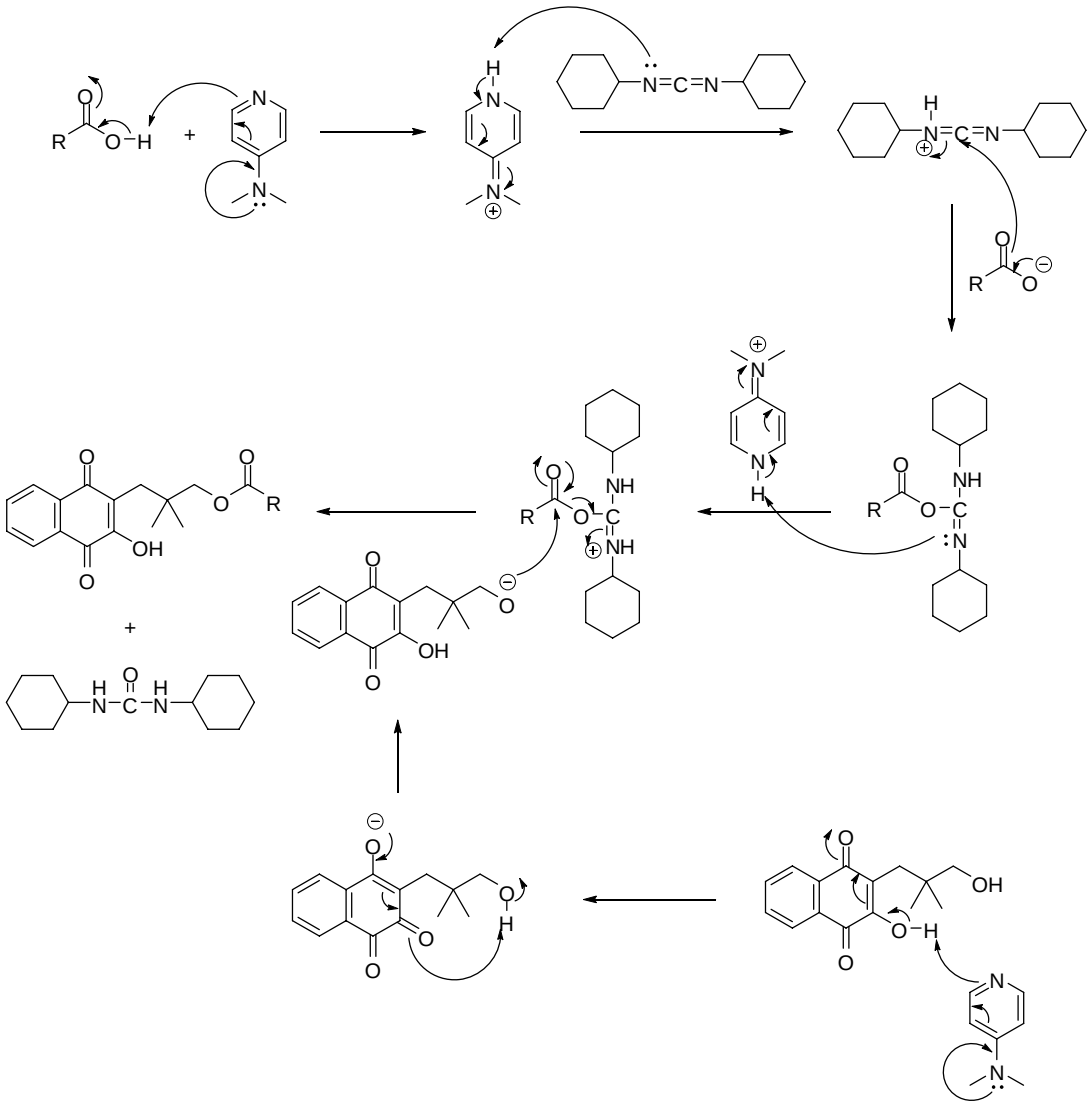
Most of the carboxylic acids are commercially available, except of 2-methyloctanoic acid (**133**) which it could be prepared starting from octanoic acid (**130**) by methylation using methyl iodide (MeI) and potassium carbonate (K_2CO_3) in acetone under reflux for 4 hours to afford the methyl ester product (**131**) in 77% yield (**Scheme 24**). The ^{1}H NMR (400 MHz) spectrum of this methyl ester (**131**) in $CDCl_3$

showed a singlet signal at δ 3.67 ppm which was a characteristic peak of methyl ester group. Triplet signal at δ 0.88 ppm was assigned to the methyl proton of the chain. Another triplet at δ 2.31 ppm was assigned to the methylene proton next to carbonyl group. The IR spectrum of this compound showed the absorption band of C=O stretching of the ester moiety at 1743 cm^{-1} and C-O stretching at 1168 cm^{-1}. The EI mass spectrum showed by the molecular ion peak at *m/z* 158 confirmed this molecule. Methylation at α-position of this ester was accomplished by treatment with methyl iodide in the presence of LDA and hexamethylphosphoramide (HMPA) in dry THF to yield the crude product (**132**). This crude product was further hydrolysed by stirring with potassium hydroxide (KOH) in 50% aqueous EtOH for 3 hours to give the desired product **133** in 53% yield for two steps. The ^{1}H NMR (400 MHz) spectrum of this carboxylic acid (**133**) in $CDCl_3$ showed a hextet signal at δ 2.46 ppm which was a characteristic peak of α-methine proton, coupled to the methyl proton and β-methylene proton with J = 7.2 Hz. A triplet signal at δ 0.89 ppm was assigned to the methyl proton of the chain. The IR spectrum of this compound showed a broad band at 3300-3600 cm^{-1} which was a characteristic of O-H stretching. The absorption of C=O stretching of the acid moiety appeared at 1743 cm^{-1} and C-O stretching appeared at 1168 cm^{-1}. The EI mass spectrum showed by the base peak ([M+1]+, 100% relative intensity) at *m/z* 159 confirmed this molecule.



Scheme 24

The corresponding naphthoquinone esters (**139-157**) from the condensation were obtained in the range of 45-92% yield. The mechanism of this condensation is shown in **Scheme 25**.



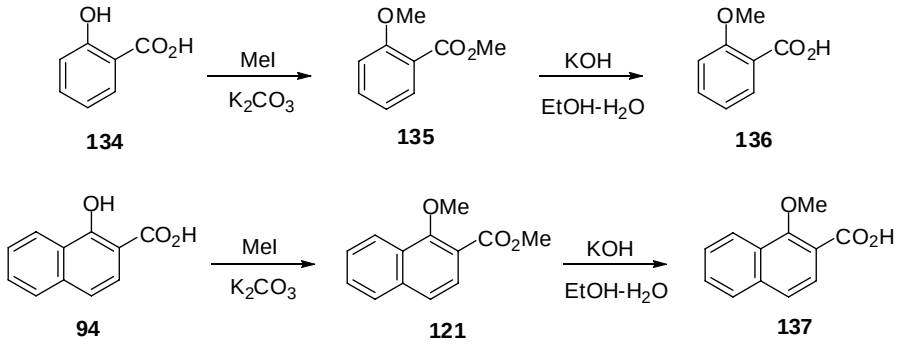
Scheme 25

The ^{1}H NMR (400 MHz) spectrum of naphthoquinone aliphatic esters (**139-157**) in $CDCl_3$ showed a characteristic peak as a singlet signal of the dimethyl protons at C-2' in the region of δ 0.91-1.02 ppm. Singlet signal in the region of δ 2.61-2.71 ppm was assigned to the methylene proton adjacent to the naphthoquinone ring. Another singlet in the region of δ 3.77-3.88 ppm was assigned to the methylene proton next to the oxygen of the ester moiety. The hydroxyl proton at C-3 of the

naphthoquinone ring showed singlet in a region of δ 7.37-7.62 ppm and four aromatic protons showed the characteristic peaks in the region of 7.62-8.16 ppm. Additionally, aliphatic protons of the ester side chain showed characteristic peaks in the region of 0.86-2.40 ppm. The IR spectrum of these naphthoquinone aliphatice esters showed the absorption band of O-H stretching at 3363-3389 cm^{-1}. The C=O stretching of the naphthoquinone group showed the absorption band at 1644-1667 cm^{-1}. The C=O stretching of the ester moiety revealed the absorption band at 1722-1739 cm^{-1} and the C-O stretching appeared at 1048-1210 cm^{-1}.

For the synthesis of naphthoquinone ester derivatives bearing 2'-cyclohexyl substituent, a variety of aromatic carboxylic acids (benzoic acid, 2-naphthoic acid, 2-methoxybenzoic acid and 1-methoxynaphthalene-2-carboxylic acid) was chosen and some of them (2-methoxybenzoic acid (**136**) and 1-methoxynaphthalene-2-carboxylic acid (**137**)) were prepared in several steps. 2-Methoxybenzoic acid (**136**) and 1-methoxynaphthalene-2-carboxylic acid (**137**) could be prepared in the same manner by methylation of 2-hydroxybenzoic acid (**134**) and 1-hydroxy-2-naphthoic acid (**94**), respectively, using MeI and K_2CO_3 in acetone under reflux for 6 hours to yield methyl ester products **135** in 94% yield and **121** in 96% yield (**Scheme 26**). The resulting products were then hydrolyzed under reflux using KOH in 50% EtOH-H_2O to provide the desired products **136** and **137** in 99% yield. The ^{1}H NMR (400 MHz) spectrum of 2-methoxybenzoic acid (**136**) in $CDCl_3$ showed two singlet signals at δ 4.10 and 10.85 ppm which were characteristic peaks of the methoxy proton and hydroxyl proton of carboxylic acid, respectively. Four aromatic protons showed characteristic peaks in the region of δ 7.08-8.20 ppm. The IR spectrum of this compound showed a broad band at 3250-3350 cm^{-1} which was a characteristic of O-H stretching. The absorption of C=O stretching of the carboxyl group appeared at 1690 cm^{-1} and C-O stretching appeared at 1168 cm^{-1}. The EI mass spectrum showed by the molecular ion peak at *m/z* 152 confirmed this molecule. The ^{1}H NMR (400 MHz) spectrum of 1-methoxy-2-naphthoic acid (**137**) in $CDCl_3$ showed a singlet signal at δ 4.20 ppm which is the characteristic peak of the methoxy proton. Six aromatic protons showed characteristic peaks in the region of δ 7.66-8.23 ppm. The IR spectrum of this compound showed

absorption band at 3250-3350 cm^{-1} which was characteristic of O-H stretching. The absorption of C=O stretching of the carboxyl group appeared at 1694 cm^{-1} and C-O stretching appeared at 1085 cm^{-1}. The EI mass spectrum showed by the molecular ion peak at *m/z* 202 confirmed this molecule.

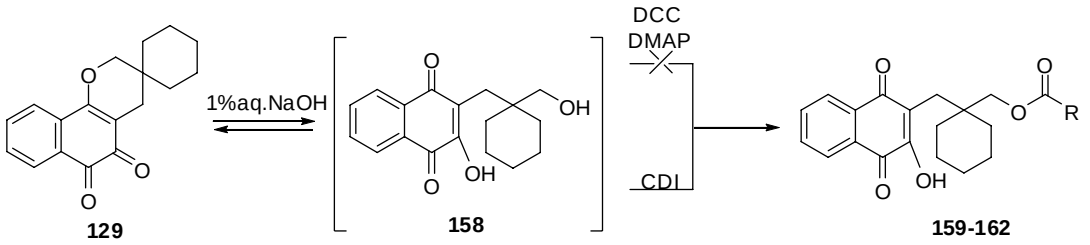


Scheme 26

For the synthesis of naphthoquinone aromatic esters bearing 2'-cyclohexyl substituent (**159-162**), 2'-cyclohexyl substituted rhinacanthone derivative (**129**) was transformed to the naphthoquinone alcohol intermediate (**158**) by basic hydrolysis using 1% aqueous sodium hydroxide under reflux for 1 hour. After the reaction was worked up, this intermediate without purification was used to react with various aromatic carboxylic acids (benzoic acid, 2-naphthoic acid, 2-methoxybenzoic acid and 1-methoxynaphthalene-2-carboxylic acid) in the presence of DCC and DMAP in dry dichloromethane for the condensation. Unfortunately, the desired naphthoquinone ester products were not obtained. So, the condensing agent was changed to carbodiimidazole (CDI) and the reaction mixture was stirred in dry tetrahydrofuran (THF) at room temperature. The desired naphthoquinone ester derivatives (**159-162**) were obtained in 2 steps sequence in the range of 22-78% yield (**Scheme 27**).

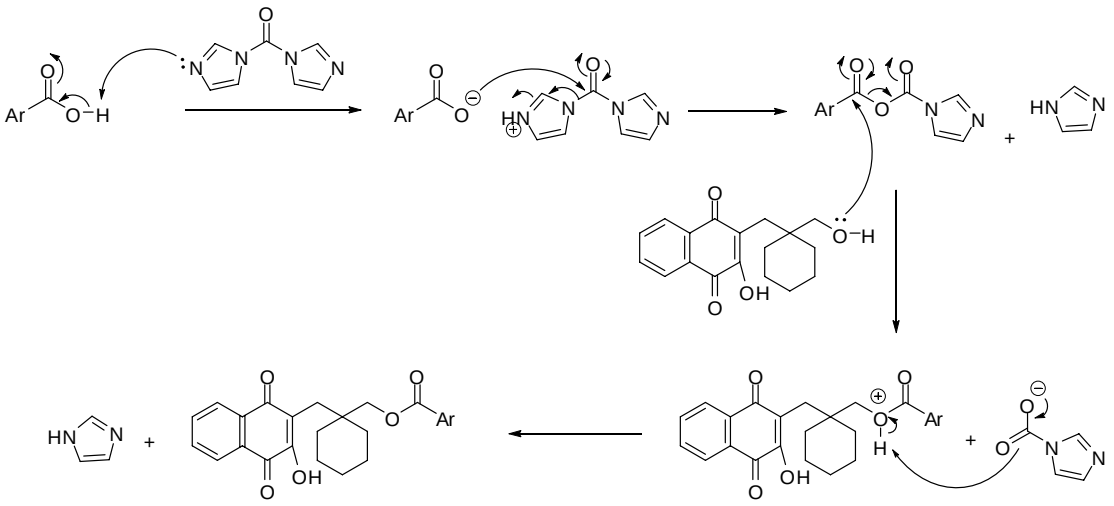
The ^{1}H NMR (400 MHz) spectrum of naphthoquinone aromatic esters (**159-162**) in $CDCl_3$ showed a characteristic peak of the methylene proton adjacent to the naphthoquinone ring in the region of δ 2.73-2.86 ppm as a singlet signal. The other

singlet signal in the region of δ 4.13-4.22 ppm was assigned to the methylene proton next to oxygen of the ester moiety. The hydroxyl proton on naphthoquinone ring showed singlet in the region of δ 7.35-7.42 ppm. Additionally, ten cyclohexyl protons showed the characteristic peaks in the region of 1.25-1.70 ppm. The IR spectrum of these naphthoquinone aliphatic esters showed the absorption band of O-H stretching at 3365-3383 cm^{-1}. The C=O stretching of the naphthoquinone group showed the absorption band at 1648-1660 cm^{-1}. The C=O stretching of the ester moiety revealed the absorption band at 1709-1716 cm^{-1} and C-O stretching at 1025-1196 cm^{-1}.



Scheme 27

The mechanism of the coupling reaction using CDI is shown in **Scheme 28**.



Scheme 28

Afterwards the methyl ether of naphthoquinone esters **161** and **162** was removed using boron tribromide (BBr_3) in dry dichloromethane at 0 ºC to provide naphthoquinone esters **163** in 68% yield and **164** in 87% yield. (**Scheme 15**, page 83) Their ^{1}H NMR (400 MHz) spectra in $CDCl_3$ showed no singlet signal at δ 3.73 and 3.98 ppm which were characteristics of methoxy proton.

Kongkathip's group has reported the synthesis of naphthoquinone aromatic esters bearing dimethyl substituents at the 2′-position and they found that most of them showed potent cytotoxicity against the human cancer cell lines (KB, HeLa and $HepG_2$). (Kongkathip *et al*., 2004) Furthermore, the same authors found that the synthetic naphthoquinone esters containing dimethyl substituents at the 2′-position of the ester moiety showed more potent activity than those with monomethyl and without methyl substituent. So, it is interesting to study the structure-activity relationships (SARs) of naphthoquinone aromatic esters with various substituents at the 2′-position.

Moreover, some naphthoquinone aliphatic esters, such as rhinacanthin-C (**13**), -G (**20**), -H (**21**) and –K (**24**), isolated from *Rhinacanthus nasutus*, showed anticancer activity. For example, rhinacanthin-C has been reported to inhibit cancer cell lines with IC_{50} values of 6.26 μg/mL (KB), 0.26 μg/mL (P-388), 0.68 μg/mL (HT-29) and 26.2 μM (HeLa) and antiproliferative activity with an IC_{50} value of 11.2 μM. (Wu *et al*., 1998 and Gotoh, *et al*. 2004) These natural naphthoquinone aliphatic esters contain methyl substituent at the α-position of the ester moiety. Thus, to study the structure-activity relationships (SARs), synthesis of other naphthoquinone aliphatic esters as well as those with α-methyl substituent is needed.

There are many reports describing naphthoquinone derivatives with antimalarial activity. (Fieser, 1948; Dalgiesh, 1949; Fawaz and Fieser, 1950; Prescott, 1969; Dudley *et al*., 1969; Porter *et al*., 1972; Likhitwitayawuid *et al*., 1998; Kittakoop *et al*., 1999 and Onegi *et al*. 2002) Atovaquone (**11**), containing 3-hydroxy-1,4-naphthoquinone in the structure, has been reported as an antimalarial

drug. (Korsinczky *et al*., 2000, Butcher *et al*., 2003 , Marra *et al*. and Wiesner *et al*., 2003). So, it is very interesting to evaluate our synthetic naphthoquinone esters for their antimalarial activity.

Therefore, these synthetic naphthoquinone aliphatic esters and naphthoquinone aromatic esters were tested for cytotoxicity against the human cancer cell lines: KB (human epidermoid carcinoma), HeLa (human cervical carcinoma) and MCF-7 (human breast cancer) as well as against the normal Vero cell lines (normal kidney cell of the African green monkey), employing the MTT colorimetric method (Skehan *et al*., 1990), with adriamycin (doxorubicin) as a reference drug. The results are shown in **Tables 4** and **5** (pages 85-89). The synthetic naphthoquinone aliphatic esters were also tested for antimalarial activity, results of which are shown in **Table 6** (pages 90-91). It was found that all naphthoquinone aliphatic esters showed very potent antimalarial activity and only a few of them exhibited moderate to strong cytotoxicity against human cancer cell lines.

Naphthoquinone aliphatic esters with α-methyl substituent on the ester part (**141**, **143**, **144**, **146** and **150**) showed more potent cytotoxicity than the naphthoquinone esters without α-methyl group with the same number of straight chain carbons. Interestingly, most of these naphthoquinone aliphatic esters showed no toxicity to Vero cells (IC_{50} > 50 μM).

Table 4 showed that the naphthoquinone ester **141** was moderately active against KB and HeLa cell lines with the IC_{50} values of 14.38±1.82 and 19.67±1.36 μM, respectively whereas naphthoquinones **143**, **144** and **146** showed strong activity against KB cell line with IC_{50} values of 4.65±0.38, 5.66±0.15 and 1.76±0.22 μM, respectively and against HeLa cell line with IC_{50} values of 3.83±1.19, 5.66±0.15 and 4.66±0.22 μM, respectively. Moreover, compound **150** exhibited moderate cytotoxicity against KB cell line with an IC_{50} value of 16.78±1.73 μM and strong activity against HeLa cell line with an IC_{50} value of 3.40±1.15 μM. Having number of straight chain carbons, naphthoquinone esters with α-methyl substituent on the

ester moiety (**141**, **143**, **144**, **146** and **147**) are compared with those of the straight chain (**140**, **142**, **145** and **149**), were more active. In addition, naphthoquinone **148** was moderately active against KB cell line with an IC_{50} value of 14.42±2.42 μM and naphthoquinone **153** was strongly active against HeLa cell line with an IC_{50} value of 7.23±2.64 μM.

Table 5 showed that naphthoquinone aromatic esters (**159-164**) exhibited moderate cytotoxicity against KB and HeLa cell lines with IC_{50} values in the range of 4.02±0.04 μM to 6.50±0.05 μM and 4.80±0.06 μM to 7.25±1.08 μM, respectively. This indicates that substituens at the 2-position of benzoate and 1-position of naphthanoate has no significance to the activity. Furthermore, the naphthoquinone aromatic esters showed more potent anticancer activity than the aliphatic esters.

The results from the antimalarial testing showed that all naphthoquinone aliphatic esters had potent antimalarial activity with IC_{50} values in the range of 0.03-10.92 μM. Naphthoquinone aliphatic esters with shorter straight side chain were less active than that with longer straight side chain (between one to seven carbons) (**139**, **140**, **142**, **145** and **149**). When the side chain contained eight to eleven carbons (**151-154**) less activity was shown. Surprisingly, naphthoquinone esters with side chains containing 13 carbons (**155**) and 15 carbons (**156**) exhibited very potent antimalarial activity with IC_{50} values of 0.032 and 0.030 μM, respectively. And interestingly, when the ester moiety has a methyl substituent at the α-position (naphthoquinone esters **141**, **143**, **144**, **146** and **150**) the compounds showed more potent activity than those with straight chain with IC_{50} values in the range of 0.11-0.91 μM. In comparison to the racemic mixture (**143**) with *S*-configuration of **143** (**144**), the *S*-configuration naphthoquinone **144** showed more potent antimalarial activity (IC_{50} = 0.11 μM) than the racemic mixture (IC_{50} = 0.22 μM).

CONCLUSION

The syntheses of nineteen novel naphthoquinone aliphatic esters (**139-157**) were achieved in ten steps from 1-hydroxy-2-naphthoic acid and aliphatic carboxylic acids with the overall yields in the range of 10-21%. The key step of these syntheses is the alkylation with methyl isobutyrate and methyl cyclohexanecarboxylate, and the esterification of naphthoquinone alcohol and various aliphatic/aromatic carboxylic acids in the presence of DCC/DMAP or CDI as coupling agent. The alkylation using methyl isobutyrate generated naphthoquinone alcohol (**102**) bearing dimethyl substituents at the C2'-position of the propyl side chain. This naphthoquinone alcohol was then condensed with various aliphatic carboxylic acids (acetic acid, propionic acid, isobutyric acid, butyric acid, 2-methylbutyric acid (a racemic mixture), (*S*)-(+)-2-methylbutyric acid, pentanoic acid, 2-methylpentanoic acid (a racemic mixture), hexanoic acid, heptanoic acid, octanoic acid, 2-methyloctanoic acid (a racemic mixture), nonanoic acid, decanoic acid, undecanoic acid, dodecanoic acid, myristic acid, palmitic acid and stearic acid) in the presence of DCC/DMAP to provide the desired naphthoquinone aliphatic esters (**139-157**).

In the same manner, four novel naphthoquinone aromatic esters (**159-162**) were synthesized from 1-hydroxy-2-naphthoic acid and aromatic carboxylic acids in ten steps with overall yields in the range of 9-27%. Alkylation using methyl cyclohexancarboxylate generated naphthoquinone alcohol (**158**) bearing cyclohexyl substituent at the C2'-position of the propyl side chain. Esterification between the naphthoquinone alcohol intermediate (**158**) and various aromatic carboxylic acids using CDI as condensing agent gave naphthoquinone aromatic esters (**159-162**). The naphthoquinone aromatic esters **161** and **162** were demethylated by using BBr_3 to give good yield of naphthoquinone esters **163** and **164**.

The nineteen naphthoquinone aliphatic esters (**139-157**) and six naphthoquinone aromatic esters (**159-164**) were evaluated for the cytotoxic activity against human cancer cell lines (KB, HeLa and MCF-7) as well as the Vero cell lines.

Only a few of naphthoquinone aliphatic esters exhibited moderate to strong cytotoxicity against the human cancer cell lines. Naphthoquinone aliphatic esters with α-methyl substituent on the ester part (**141**, **143**, **144**, **146** and **150**) showed more potent cytotoxicity than those without α-methyl group with the same number of straight chain carbons. So, the methyl at α-position of the ester moiety enhances cytotoxic activity. The racemic mixture (**143**) and *S*-enantiomer (**144**) did not show significant difference in the cytotoxicity. The naphthoquinone aromatic esters (**159-164**) exhibited moderate anticancer activity and the methoxy substituent at 2-position of benzoate and 1-position of naphthanoate has no significance to the activity. Furthermore, the naphthoquinone aromatic esters showed more potent anticancer activity than the aliphatic esters. And most of these naphthoquinone aliphatic esters were not toxic to normal Vero cells (IC_{50} > 50 μM).

Interestingly, naphthoquinone aliphatic esters **139-157** showed very potent antimalarial activity with IC_{50} values in the range of 0.03-10.92 μM. The number of carbons in the straight side chain affects to the activity. Naphthoquinone aliphatic esters with longer chain were more active than those of shorter chains between one carbon to seven carbons chain (**139**, **140**, **142**, **145** and **149**) while the side chain containing eight to eleven carbons (**151-154**) showed no significance in the activity. Naphthoquinone aliphatic esters with the side chain of 13 carbons and 15 carbons (**155** and **158**) are the most active. When the ester moiety has a methyl substituent at the α-position, naphthoquinone esters (**141**, **143**, **144**, **146** and **150**) showed more potent activity than the straight-chain-containing esters. Thus, α-methyl of ester moiety plays more important role in the antimalarial activity. In addition, *S*-enantiomer (**144**) is more effective than the racemic mixture (**143**).

LITERATURE CITED

Butcher, G.A. and R.E. Sinden. 2003. Persistence of Atovaquone in Human Sera Following Treatment: Inhibition of *Plasmodium falciparum* Development *in Vivo* and *in Vitro*. **Am. J. Trop. Med. Hyg.** 68: 111-114.

Dalgliesh, C.E. 1949. Naphthoquinone Antimalarials. Mannich Bases Derived from Lawsone. **J. Am. Chem. Soc.** 71: 1697-1702.

Desjardins, R.E.; C.J. Canfield, J.D. Haynes and J. D. Chulay. 1979. Quantitative Assessment of Antimalarial Activity in vitro by a Semiautomated Microdilution Technique. **Antimicrob. Agents Chemother.** 16: 710-718.

Dos Santos, E.V.M., J.W.de M. Carneiro and V.F. Ferreira. 2004. Quantitative Structure-Activity Relationship in Aziridinyl-1,4-Naphthoquinone Antimalarials: Study of Theoretical Correlations by the PM3 Method. **Bioorg. Med. Chem.** 12: 87-93.

Dudley, K.H., H.W. Miller, P.W. Schneider and R.L. McKee. 1969. Potential Naphthoquinone Antimalarials. 2-Acylhydrazino-1,4-naphthoquinones and Related Compounds. **J. Org. Chem.** 34: 2750-2755.

Dudley, K.H. and R.W. Chiang. 1969. Naphthoquinones. On the Oxidative Cyclization of Isolapachol to Dehydro-α-lapachone and Prototypal Studies Related to the Synthesis of Lapachol and Its Derivatives. **J. Org. Chem.** 34(1): 120-126.

Fawaz, G. and L.F. Fieser. 1950. Naphthoquinone Antimalarial. XXIV. A New Synthesis of Lapinone. **J. Am. Chem. Soc.** 72: 996-1000.

Fieser, F. 1948. Naphthoquinone Antimalarial. III. Diene Synthesis of 1,4-Naphthoquinones. **J. Am. Chem. Soc.** 70: 3165-3174.

Fieser, L.F., E. Berliner, F.J. Bondhus, F.C. Chang, W.G. Dauben, M.G. Ettlinger, G. Fawaz, M. Fields, C. Heidelberger, H. Heymann, W.R. Vaughan, A.G. Wilson, E. Wilson, M.-I. Wu, M.T. Leffler, K.E. Hamlin, E.J. Matson, E.E. Moore, M.B. Moore and H.E. Zaugg. 1984. Naphthoquinone Antimalarials. IV-XI. Synthesis. **J. Am. Chem. Soc.** 70: 3174-3215.

Gotoh, A., T. Sakaeda, T. Kimura, T. Shirakawa, Y. Wada, A. Wada, T. Kimachi, Y. Takemoto, A. Ilda, S. Iwakawa, M. Hirai, H. Tomita, N. Okamura, T. Nakamura and K. Okumura. 2004. Antiproliferative Activity of *Rhinacanthus nasutus* (L.) Kurz Extracts and the Active Moiety, Rhinacanthin C. **Biol. Pharm. Bull.** 27(7): 1070-1074.

Guerra, M.O., A.S.B. Mazoni, M.A.F. Brandao and V.M. Peters. 1999. Interceptive Effect of Lapachol in Rats. **Contraception** 60: 305-307.

Kapadia, G.J., M.A. Azuine, V. Balasubramanian and R. Sridhar. 2001. Aminonaphthoquinones-A Novel Class of Compounds with Potent Antimalarial Activity against *Plasmodium falciparum*. **Pharmacol. Res.** 43: 363-367.

Kittakoop, P., J. Punya, P. Kongsaeree, Y. Lertwerawat, A. Jintasirikul, M. Tanticharoen and Y. Thebtaranonth. 1999. Bioactive naphthoquinones from Cordyceps unilateralis. **Phytochemistry** 52: 453-457.

Kodama, O., H. Ichikawa and T. Akatsuka. 1993. Isolation and Identification of an Antifungal Naphthopyran Derivative from *Rhinacanthus nasutus*. **J. Nat. Prod.** 56(2): 292-294.

Kongkathip, N., B. Kongkathip, P. Siripong, C. Sangma, S. Luangkamin, M. Niyomdecha, S. Pattanapa, S. Piyaviriyagul and P. Kongsaeree. 2003. Potent Antitumor Activity of Synthetic 1,2-Naphthoquinones and 1,4-Naphthoquinones. **Bioorg. Med. Chem.** 11: 3179-3191.

Kongkathip, N., S. Luangkamin, B. Kongkathip, C. Sangma, R. Grigg, P. Kongsaeree, S. Prabpai, N. Pradidphol, S. Piyaviriyagul and P. Siripong. 2004. Synthesis of Novel Rhinacanthins and Related Anticancer Naphthoquinone Esters. **J. Med. Chem.** 47(18): 4427-4438.

Korsinczky, M., N. Chen, B. Kotecka, A. Saul, K. Rieckmann and Q. Cheng. 2000. Mutations in *Plasmodium falciparum* Cytochrome *b* that are Associated with Atovaquone Resistance are Located at a Putative Drug-Binding Site. **Antimicrob. Agents Chemother.** 44: 2100-2108.

Kuwahara, S., A. Nemoto and A. Hiramatsu. 1991. Synthesis of an Antifungal Naphthopyran Derivative Isolated from *Rhinacanthus nasutus* (Acanthaceae). **Agric. Biol. Chem.** 55(11): 2909-2911.

Lien, J.-C., L.-J. Huang, C.-M. Teng, J.-P. Wang and S.-C. Kuo. 2002. Synthesis of 2-Alkoxy 1,4-Naphthoquinone Derivatives as Antiplatelet, Antiinflammatory, and Antiallergic Agents. **Chem. Pharm. Bull.** 50(5): 672-674.

Likhitwitayawuid, K., R. Kaewamatawong, N. Ruangrungsi and J. Krungkrai. 1998. Antimalarial Naphthoquinones from *Nepenthes thorelli*. **Planta Med.** 64: 237-241.

Lin, T.-S., L.-Y. Zhu, S.-P. Xu, A.A. Divo and A.C. Sartorelli. 1991. Synthesis and Antimalarial Activity of 2-Aziridinyl- and 2,3-Bis(aziridinyl)-1,4-naphthoquinonyl Sulfonate and Acylate Derivatives. **J. Med. Chem.** 34: 1634-1639.

Malerich, J.P., T.J. Maimone, G.I. Elliott and D. Trauner, 2005. Biomimetic Synthesis of Antimalarial Naphthoquinones. **J. Am. Chem. Soc.** 127: 6276-6283.

Marra, F., J.R. Salzman and M.H.H. Ensom. 2003. Atovaquone-Proguanil for Prophyaxis and Treatment of Malaria. **Ann. Phamacother**. 37: 1266-1275.

Martin, Y.C., T.M. Bustard and K.R. Lynn. 1973. Relationship between Physical Properties and Antimalarial Activities of 1,4-Naphthoquinones. **J. Med. Chem.** 16: 1089-1093.

Onegi, B., C. Kraft, I. Kohler, M. Freund, K. Jenett-Siems, K. Siems, G. Beyer, M.F. Melzig, U. Bienzle and E. Eich. 2002. Antiplasmodial Activity of Naphthoquinones and One Anthraquinone from *Stereospermum kunthianum*. **Phytochemistry** 60: 39-44.

Porter, T.H., F.S. Skelton, C.M. Bowman and K. Folkers. 1972. Synthesis of New 2-Alkylamino-1,4-naphthoquinones as Inhibitors of Coenzyme Q and as Antimalarials. **J. Med. Chem.** 15(5): 504-506.

Prescott, B. 1969. Potential Antimalarial Agents. Derivatives of 2-Chloro-1,4-naphthoquinone. **J. Med. Chem.** 12: 181-182.

Rojanapo, W., A. Tepsuwan and P. Siripong. 1990. Mutagenicity and Antimutagenicity of Thai Medicinal Plants. **Basic Life Sci.** 52: 447-452.

Sendl, A., J.L. Chen, S.D. Jolad, C. Stoddart, E. Rozhon and M. Kernan. 1996. Two New Naphthoquinones with Antiviral Activity from *Rhinacanthus nasutus*. **J. Nat. Prod.** 59: 808-811.

Skehan, P., R. Storeng, D. Scudiero, A. Monko, J. McMahon, D. Vistica, J.T. Warren, H. Bokesch, S. Kenney and M.R. Boyd. 1990. New Colorimetric Cytotoxicity Assay for Anticancer-Drug Screening. **J. Natl. Cancer. Inst.** 82: 1107-1112.

Tandon, V.K., D.B. Yadav, R.V. Singh, A.K. Chaturvedi and P.K. Shukla. 2005. Synthesis and Biological Evaluation of Novel (L)-α-Amino Acid Methyl Ester, Heteroalkyl, and Aryl Substituted 1,4-Naphthoquinone Derivatives as Antifungal and Antibacterial Agents. **Bioorg. Med. Chem. Lett.** 15: 5324-5328.

Vogel, A.I. 1989. Vogel's Textbook of Practical Organic Chemistry. 5th ed., Longman Group UK Ltd., England. 1600 p.

Wiesner, J., R. Ortmann, H. Jomaa and M. Schlitzer. 2003. New Antimalarial Drugs. **Angew. Chem. Int. Ed.** 42: 5274-5293.

Williams, D.R. and M.P. Clark. 1998. Synthesis of Atovaquone. **Tetrahedron Lett.** 39: 7629-7632.

Wu, T.-S., H.-C. Hsu, P.-L. Wu, C.-M. Teng and Y.-C. Wu. 1998. Rhinacanthin-Q, a Naphthoquinone from *Rhinacanthus nasutus* and Its Biological Activity. **Phytochemistry.** 49(7): 2001-2003.

Wu, T.-S., H.-C. Hsu, P.-L. Wu, Y.-L. Leu, Y.-Y. Chan., C.-Y. Chern, M.-Y. Yeh and H.-J. Tien. 1998. Naphthoquinone Esters from the Root of *Rhinacanthus nasutus*. **Chem. Pharm. Bull.** 46(3): 413-418.