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THESIS

INDOLE RING FORMATION USING A SEQUENTIAL SONOGASHIRA COUPLING AND CACCHI REACTIONS: SYNTHETIC STUDIES TOWARD FLUVASTATIN PRECURSORS

THANYA RUKKIJAKAN

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Fluvastatin, a member of the drug class of statins, is a medically important molecule used in the treatment of hypercholesterolemia and cardiovascular disease. Here, we report the study toward the construction of the indole unit of fluvastatin using a one-pot, sequential Sonogashira and Cacchi reactions. The substituents on the aryl moiety as well as the nitrogen atom were varied in order to assess the effects of these groups toward the yield of the reaction. It was found that the reactions provide low to moderate yield of the desired indole product. Moreover, two by products formed during this multi-step process were identified to be the arylalkyne and the cyclized product with no substituent on the 3 position of indole ring. The results support the nature of palladium-catalyzed reaction, which is highly sensitive to solvent, base, and also the nature of the substrate.

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Thanya Rukkijakan
April, 2012

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LIST OF ABBREVIATIONS

Ac	Acetyl
AFA	Aspergillus fumigates
CF	Cystic fibrosis
DHP	Dihydropyran
DMF	Dimethylformamide
HCV	Hepatitis C Virus
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
IL-8	Interleukin-8
LDL	Low-density lipoprotein
LPS	Pseudomonas aeruginosa
RNA	Ribonucleic acid
TBSCl	*t*-Butyldimethylsilyl chloride
TFA	Tetrahydrofuran
TFAA	Trifluoroacetic anhydride
Ts	Tosyl
TsCl	4-methylbenzenesulfonyl chloride
TsOH	*p*-Toluenesulfonic acid

INDOLE RING FORMATION USING A SEQUENTIAL SONOGASHIRA COUPLING AND CACCHI REACTIONS: SYNTHETIC STUDIES TOWARD FLUVASTATIN PRECURSORS

INTRODUCTION

Fluvastatin is a synthetic drug, which inhibits the activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and effectively blocks cholesterol biosynthesis in hepatocyte cell (Parker et al., 1990). Other biological activities including anti-viral and anti-inflamatory were also reported (Bader, 2010; Bader et al., 2008; Jouneau et al., 2011). Therefore, the synthesis of Fluvastatin and its derivatives is of great interest despite the fact that some synthetic routes have already been reported (Repič et al., 2001; Zacharia et al., 2010). In this work, the construction of a key intermediate, hydroxyl-methylindole (4), using the one-pot, regiospecific consecutive Sonogashira and Cacchi reactions was investigated. A general condition for this multi-step transformation is illustrated in Figure 1.

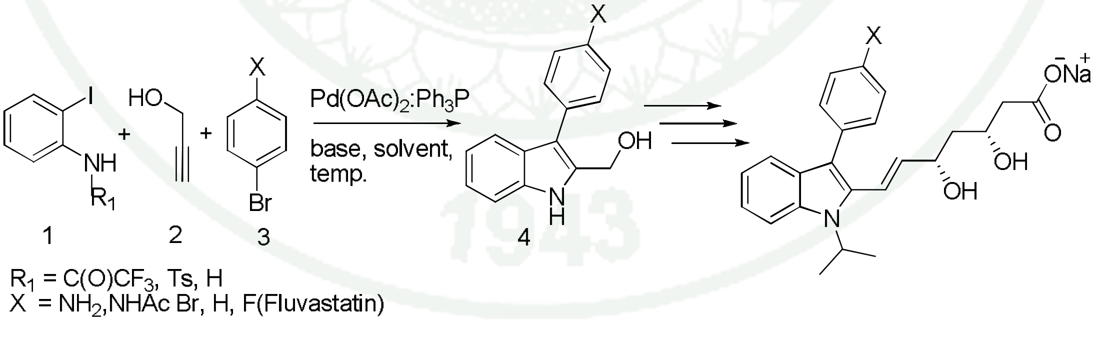


Figure 1 The synthetic condition for hydroxyl-methylindole (4), the key intermediate for the synthesis of fluvastatin and its derivatives

The substituted indole nucleaus is a prominent structural found in natural products and synthesis compounds. Recently, a large number of indole-containing compounds have revealed remarkable pharmacological activities (John Faulkner, 1999; Lounasmaa and Tolvanen, 2000; Preobrazhenskaya et al., 1972). The functionalization and synthesis of indoles had been objective research for decades. Many classic method of indole synthesis are now available, such as Fisher indole synthesis, the Gassman synthesis of indoles from *N*-haloanilines, the Madelung cyclization of *N*-acyl-o-toluidines, the Bischler indole synthesis, the Batcho-Leimgruber synthesis of indoles from o-nitrotoluenes and dimethylformamide acetals, and the reductive cyclization of *o*-nitrobenzyl ketones (Sundberg, 1996). The functionalization of indoles at C-2, C-3, N-atom and aromatic ring were developed for novel drugs with increased potency (Lindquist, Ersoy and Somfai, 2006; Mun, Ham and Jeong, 2004).The regiospecific formation of indoles with substituents at C2, C3 positions is quite a challenge for classical methods.

For the century, palladium-catalyzed reactions are generally applicable of functionalities and synthesis to heterocyclic molecule. The palladium catalyzed synthesis can be applied to fine chemicals, agrochemical and pharmaceutical intermediates, and active ingredients in fewer steps and with less waste than classical methods (Cacchi and Fabrizi, 2011). Many synthesis methods for indole synthesis using palladium catalyst were developed for the construction of regiospecific substituted indole and increased product yield. In 2006, Lu and co-worker reported the one-pot regioselective protocol for a construction of 2,3-disubstituted indole using trifluoro acetylanilide (5), phenylacetalene (6), and substituted bormobenzene (ArBr) (Lu et al., 2006). This one-pot reaction consists of three sequential steps and the outcome of the reaction highly depends on palladium catalysts and arylhalides used in the reaction (Marsden and Haley, 2008). The first step is the formation of *o*-alkynylaniline (7) by Copper-free Sonogashira coupling reaction (Ljungdahl, Bennur, Dallas, Emtenäs and Mårtensson, 2008; Ren, Zhang, Zhu and Zhou, 2007). This intermediate subsequently undergoes cyclization via Cacchi reactions (Cacchi, Fabrizi and Pace, 1998; Y. Chen et al., 2009) and reductive elimination (Step 2). Finally, deprotection of trifluoroacetyl group produces the desired product (8) with a small amount of the side product (9). (Figure 2)

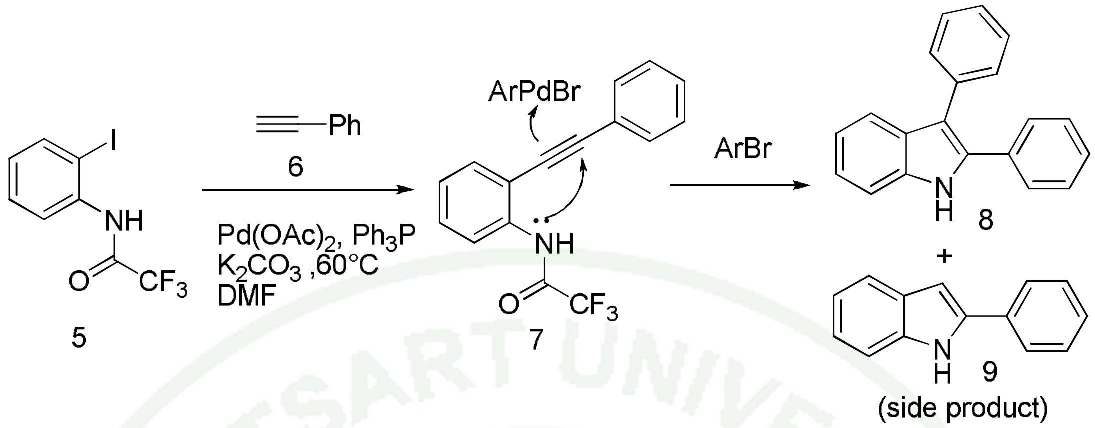


Figure 2 The one pot regiospecific synthesis of 2, 3-disubstituted indole via consecutive Sonogashira and Cacchi reactions (Lu et al., 2006)

The proposed reaction mechanism for one pot regiospecific synthesis of 2, 3-disubstituted indole via consecutive Sonogashira and Cacchi reactions was reported based on copper free Sonogashira coupling (Ljungdahl et al., 2008) and Cacchi reation (Antonio, Sandro and Fabio, 1992). The mechanism comprises the following steps. a) Oxidative addition of Pd^0L_x (I) with *o*-iodoaniline via Sonogashira coupling reaction (orange cycle) provide Pd^{II} complex (II) because oxidative addition of Pd^0 complex with aryl-iodine is reactive than aryl-bromide (Jutand, 2003). b) Ligand dissociation followed by complexation with acetaline leads to Pd^{II} complex (III). c) Deprotonation of Pd^{II} complex (III) to provide intermediate compound (IV). d) Isomerization followed by reductive elimination of the intermediate (IV) to provide *o*-alkynylaniline (7) as Sonogashira product intermediate and Pd^0L_x (I) (Kenkichi, 1991). e). Oxidative addition of Pd^0L_x (I) with aryl bromide via Cacchi reaction (blue cycle) leads to Pd^{II} complex (V). f) Ligand dissociation followed by complexation with *o*-alkynylaniline (7) leads to Pd^{II} complex (VI). g) Ligand dissociation followed by cyclization via aminopalladation to provide Pd^{II} complex (VII) and HBr (Antonio et al., 1992). h) Isomerization followed by reductive elimination of Pd^{II} complex (VII) to provide intermediate product (VIII) and Pd^0L_x (I) r) Hydrolysis of intermediate product (VIII) to give 2,3-diphenyl indole as target product (8). In the other hand the side product (9) can occur by cyclization of Sonogashira product intermediate (7) followed by hydrolysis of indole intermediate (IX). (Figure 3)

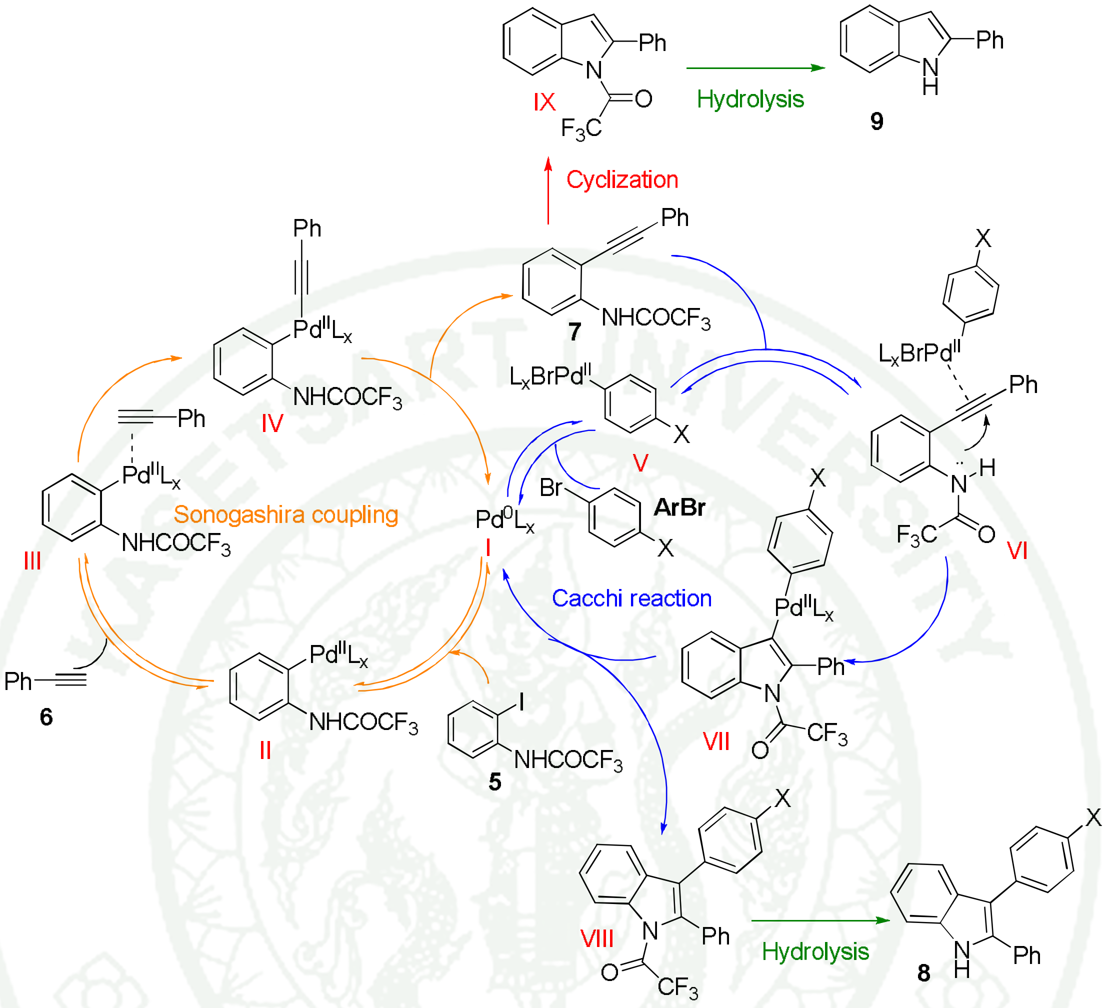


Figure 3 The proposed mechanism of one-pot, regiospecific synthesis of 2,3-disubstituted indoles via consecutive Sonogashira and Cacchi Reactions

We are particularly interested in applying the one-pot sequential Sonogashira and Cacchi reaction to the synthesis of Fluvastatin and its derivatives due to its versatility and an ability to simultaneously introduce substituents at 2 and 3 position of an indole ring regiospecifically. In our study, the previously reported arylacetylene reactant was replaced by propargyl alcohol. The hydroxyl group from reacting alcohol will facilitate the chain extension in the later synthetic steps. The effect of hydroxyl group (with and without protecting groups) on an alkyne was evaluated. Variations of bases as well as different protecting group of *N*-*o*-iodoaniline (1) were also investigated toward the generation of the key intermediate (4).

OBJECTIVES

1. To study and optimize reaction condition for the synthesis of 2-methoxy-3-aryl-indoles via regiospecific, one-pot, three-component coupling based on Cacchi´s protocol.

2. To utilize the condition found from 1. in the preparation of fluvastatin and its derivatives.

LITERATURE REVIEW

1. Biogical activity of Fluvastatin

Fluvastatin is a member of drug class of statin and the first synthestic HMG-CoA reductase racemate inhibitor to be approved for the treatment of hypercholesterolemia. This statin was developed by Novartis and it is marketed under many tread name such as Lescol®, Canef® and, Vastin® (Pfefferkorn, 2006). Fluvastatin competitively inhibits hydroxyl-methylglutaryl-coenzyme A (HMG-CoA) reductase in hepatic cell (Parker et al., 1990). HMG-CoA reductase is an enzyme converting HMG-CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis (Figure 4). The results are decrease in hepatic cholesterol levels, which stimulates the synthesis of LDL receptors and increases hepatic uptake of LDL cholesterol. Finally, the level of plasma total and LDL cholesterol are decrease (Larsen and Schmidt, 2008; Stancu and Sima, 2001).

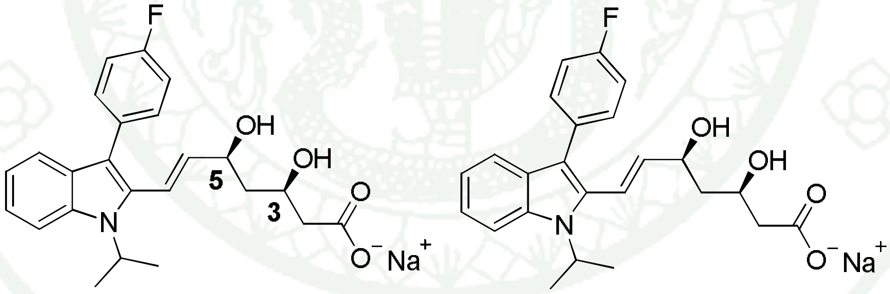


Figure 1 Structure of (+) and (-) fluvastatin sodium (IUPAC name 7-(3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl)-3,5-dihydroxy-6-heptenoic acid)

Other biological activities of fluvastatin have been reported such as antiviral and anti-inflammatory. Fluvastatin shows strong antiviral activity against HCV (Hepatitis C Virus) in clinical studies with 80 mg a day or less, 11/22 (50%) patients responded by lowering HCV RNA. (Bader et al., 2008). The anti-inflammatory property of this statin was evaluated by reduction of Interleukin-8 (IL-8) level via incubated whole blood from cystic fibrosis (CF) patients with Pseudomonas aeruginosa (LPS) or Aspergillus fumigates (AFA) antigens. Fluvastatin shows significant reduction of IL-8 level from whole blood CF patients. However, its inhibitory effect from healthy subjects was decreased or absent. Moreover, the inhibition effect by fluvastatin on CF systemic inflammation may reveal the important therapeutic potential of statins in pathological conditions. This statin associated with the over-production of pro-inflammatory cytokines and chemokines as observed during the manifestation of CF. The anti-inflammatory effect could be related to the modulation of the prenylation of signalling proteins in the cholesterol biosynthesis pathway (Jouneau et al., 2011).

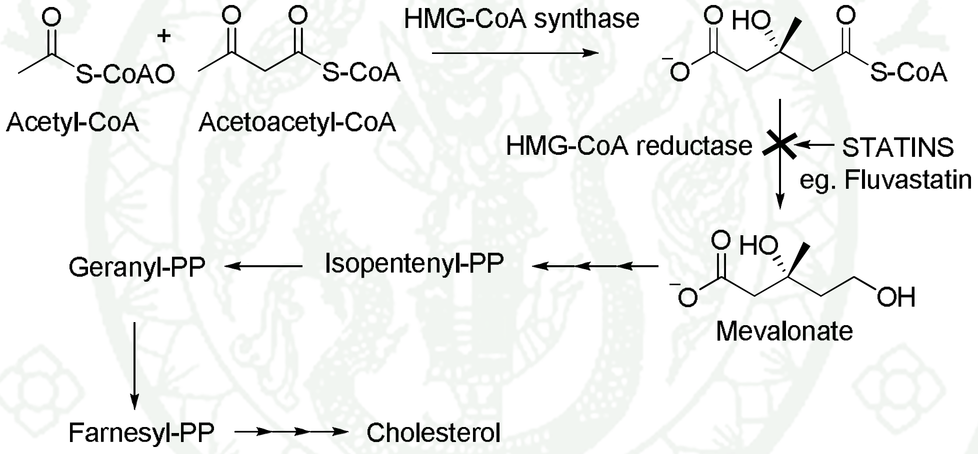


Figure 4 Effect of satin drug on the mevalonate pathway (Bonetti et al., 2003)

2. Total synthesis of Fluvastatin

The early reported synthesis of fluvastatin template, *N*-methyl analog of fluvastatin (17), was conducted via Fischer indole synthesis (Kathawala, 1988, 1994). Total synthesis of *N*-methyl fluvastatin analog started from coupling between ethyl acetoaccetate and *p*-fluorobenzyl bromide (10) (Figure 4). The indole formation between kentone (11) and phenyl diazonium gave indole (12) via Fisher indole synthesis. The methylation at nitrogen of indole (12) by methyl iodide gave *N*-methyl indole (13), which was reduced with diisobutylaluminum hydride to give the primary alcohol (14). Oxidation of primary alcohol (14) with manganese dioxide gave aldehyde (15). The side chain was extended to conjugated aldehyde (16) via transmetallation of tri-*n*-butylstannylvinyl and *n*-butyllithium. Aldol condensation between conjugated aldehyde (16) with methyl acetoacetate, followed by reduction of resulting product (17) gave diol (18). Saponification of diol (10) via sodiumhydroxy, followed by acidification, and heated to form lactone (19) with 15% yield via recrystallization. (Figure 5)

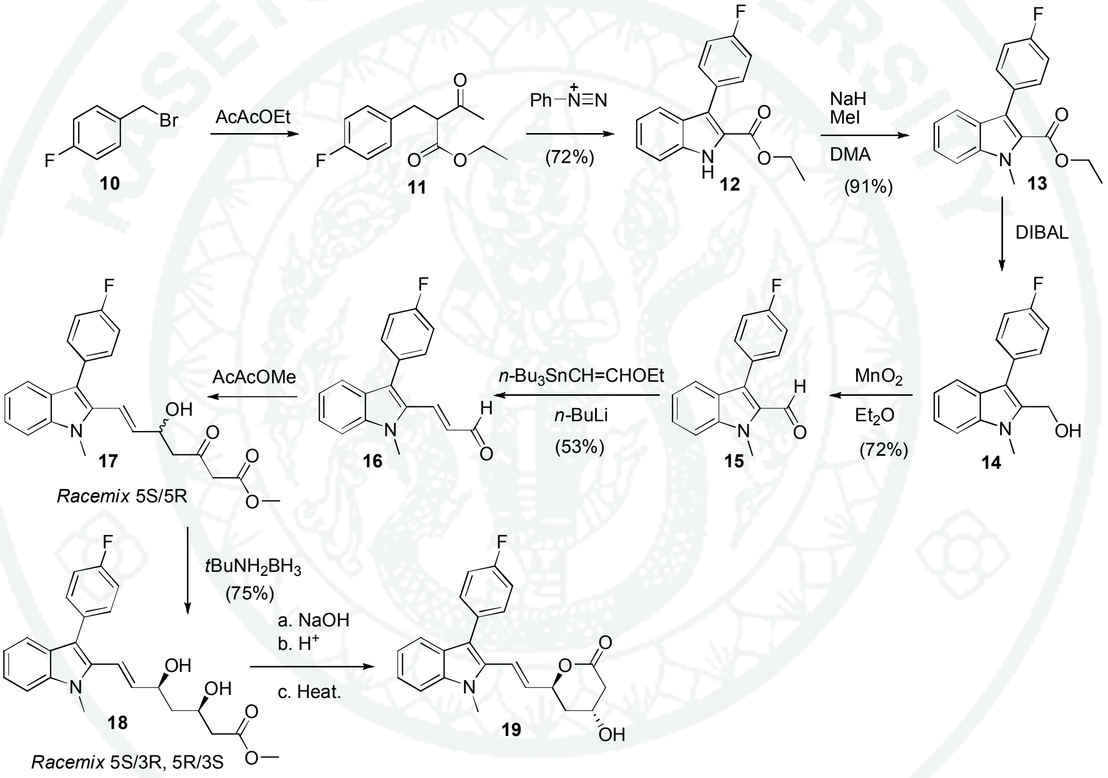


Figure 5 Total synthesis of *N*-methyl fluvasatin analog by Kathawala group (Kathawala, 1988, 1994)

The earyl synthesis of fluvastatin template was important for structure and bioactivity studies. The second total synthesis was developed for commercial process (Repič et al., 2001). The second process sought to shorten reaction sequence, improve yield, increase selectivity of the reaction, and eliminate toxic reagent (such as tri-*n*-butylstannylvinylethoxide). (Figure 6)

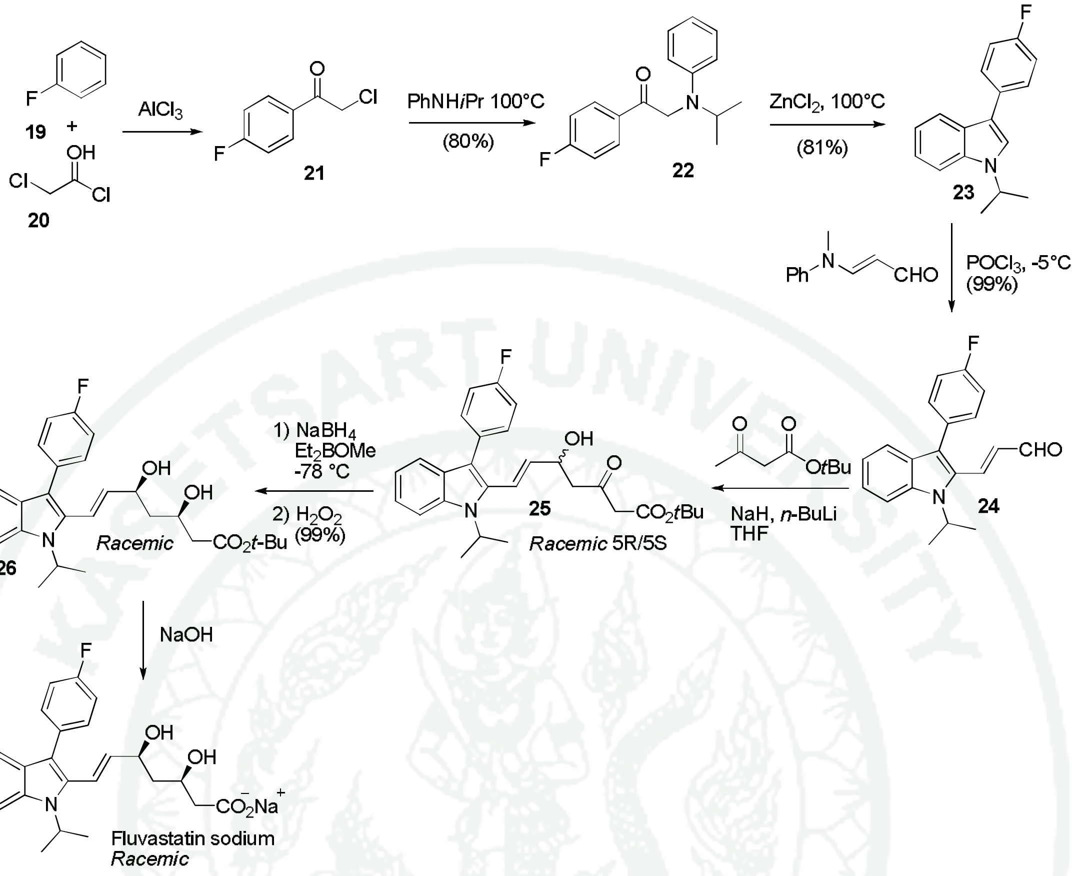


Figure 6 Total synthesis of fluvasatin in commercial proccess (Repič et al., 2001)

The commercial synthetic route of fluvastatin started with Friedel-Crafts acylation of flurobenzene (19) at *para* position with chloroacetyl chloride (20) in the presence of $AlCl_3$ to provide α- chloroketone (21). Substitution at alpha position α chloroketone (21) with *N-isopropyl* aniline generated tertiary anime (23), which was cyclized to indole (24) via Fishler indole synthesis in presence of $ZnCl_2$ (Walkup andLinder, 1985). Installation of the dihydoxylheptanoic acid fragment began with Vilsmeier-Haack formylation reaction. Form this formylation, 3-(*N*-methyl-*N*-pheylamino)accrolein was first treated with $POCl_3$ to generate an iminium salt, which was reacted with indole (23) to form enal (24) (Lee, Amedio, Underwood, Prasad and Repic, 1992). The strategy of this formylation was superior to the earlier route because it facilitated installation of desired enal moiety in a single step as opposed to the four-step sequence in the earlier synthesis (Figure 4). Moreover, synthetic step using toxic reagent such as *tri-n*-butylstanylvinylethoxide was eliminated. The side-chain was installed via generation of dianion of *t*-butylacetoacetate, followed by substitution to enal (24) gave β-hydroxy ketone (25) as racemic mixture (5R/5S). The resulting *t*-butyl ester on the side-chain prevented the formation to lactone (19), when compare with methyl ester of the earlier route. For this reason, the purification of current route proceeded smoother than the earlier route. Stereocontrolled reduction of reacemic β-hydroxy ketoeseter (25) via chelation controlled *syn*-reduction with NaBH$_4$ and Et$_2$BOMe provided diol (26) as a racemic mixture of *syn*-1,3-diols (3S, 5R)/(3R, 5S) (K. M. Chen et al., 1987). Finally, Sponification of *t*-butyl ester (26) with aqueous NaOH gave racemic fluvastatin as sodium salt. (Figure 6)

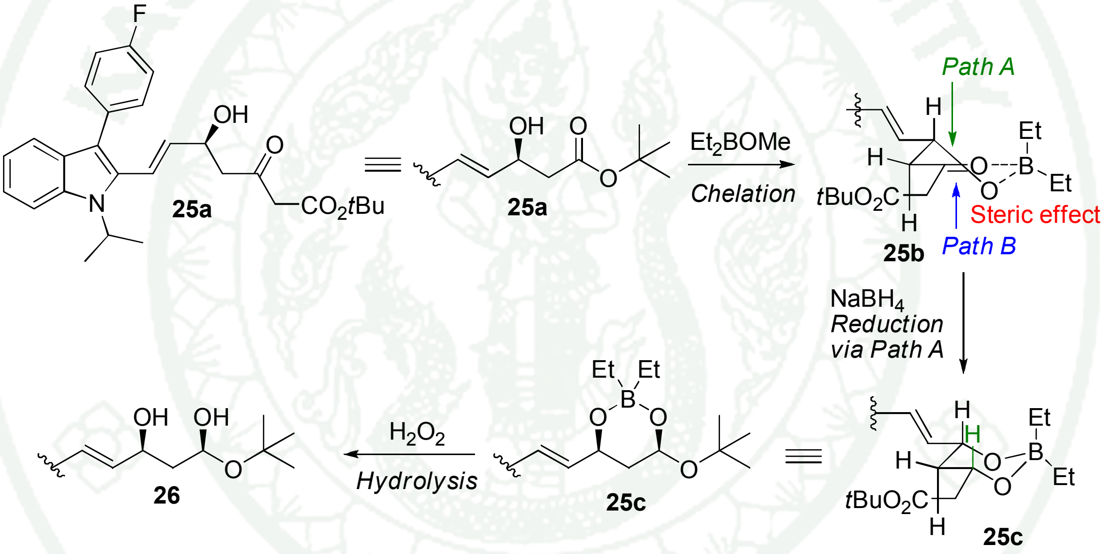


Figure 7 Transition state of stereoselective *syn*-reduction of β-hydroxy ketoester (25) (K. M. Chen et al., 1987; Pfefferkorn, 2006)

This stereoselective *syn* reduction of β-hydroxy ketone (25) for second route (K. M. Chen et al., 1987) generated four stereoisomer from reduction step. The proposed transition state of stereoselective reduction was shown in Figure 7. The chelation of Et$_2$BOMe with β-hydroxy ketone (25) formed the cyclic boronate chelate (25b), which shown in a chair-like conformation. The reducing agent (NaBH$_4$) was preferred to react at less hindered *Path A* of cyclic boronate chelate (25b), and then the cyclic boronate (25c) was obtained. Hydrolysis of cyclic boronate (25c) using hydrogen peroxide gave desired *syn*-1,3-diol product (26) (K. M. Chen et al., 1987).

The enantioselective total synthesis of (+)- and (-)-fluvastatin was reported in 2010 (Zacharia et al., 2010). The advantage of current route was stereocontrol of 1,3 diol with high enantioselectivity. The key step was the coupling of enal (24) with diketene in the presence of Ti(O-*i*-Pr)$_4$ and a chiral Schiff base ligand. The generation of (+)- or (-)-fluvastatin cloud be control by Schiff base. Stereoselective reductions of the resultant keto moiety of β-hydroxy ketoesters provided the desired 1,3-diol with highly enantiomeric excess, which were subsequently recrystallized and saponified to afford (+)- and (-)-fluvastatin. (Figure 7)

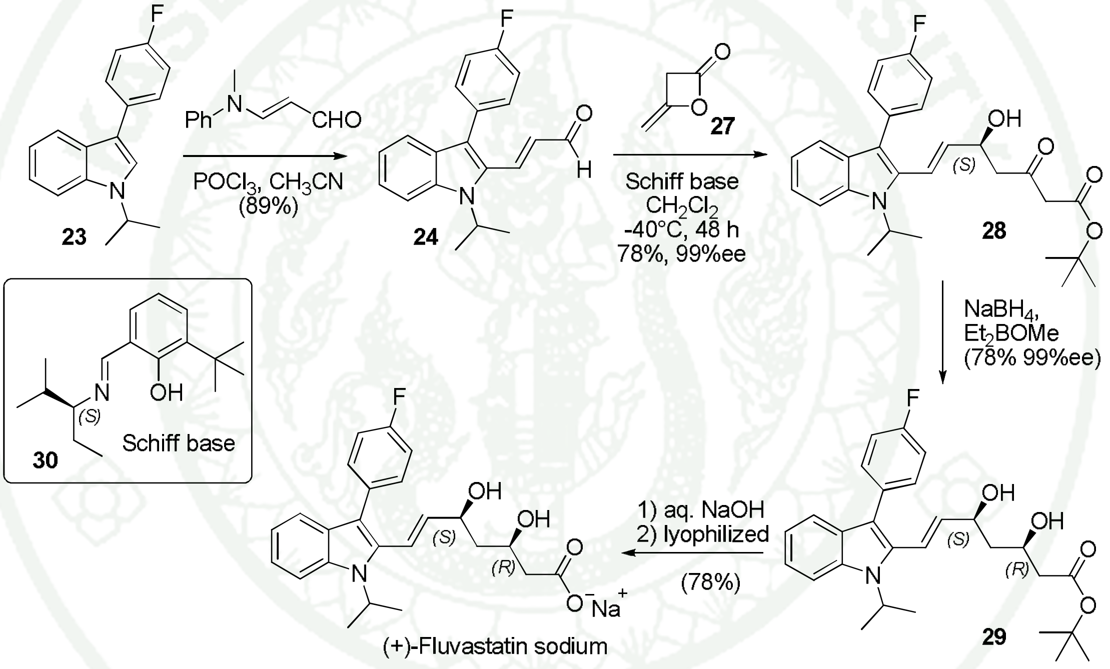


Figure 8 Total synthesis of (+)-fluvastatin via highly enantioselective synthesis and selective reduction *syn* isomer (Zacharia et al., 2010)

The synthesis of fluvastatin began via Vilsmeier-Haack formylation with indole (23) in the presence of POCl$_3$. The Installation of side chain via coupling reaction between enal (24) and diketene (27) in the presence of Ti(O-*i*-Pr)$_4$ and a chiral Schiff base ligand.(30) provide β-hydroxy keto esters (28) with high yield and enantiomeric excess. On the other hand, coupling reaction using other enantiomer of Schiff base ligand (30) gave β-hydroxy keto esters (28) with *R*- configuration, then the configuration of β-hydroxy keto esters product was control via stereoinduction from chiral structure of Schiff base ligands. The enantioselectivity was affected by the amount of Schiff base ligand, which can be explained by invoking the concept of ligand-accelerated catalysis. In other words, the reaction without Schiff base ligand proceeded comparatively slower than those when small quantities of the ligand were used. Subsequently, the diastereoselective reduction of β-hydroxy keto esters (28) provided *syn*-1,3-diol (29) using $NaBH_4$ and Et_2BOMe (K. M. Chen et al., 1987), and formed *anti*-1,3-diol via Evan method using $Me_4NHB(OAc)_3$ (Evans, Chapman and Carreira, 1988). The isopropyl ester (29) was saponified using aqueous NaOH and lyophilized to provide fluvastatin sodium in good yield. This efficient synthesis of each of the four stereoisomers of fluvastatin has been established (Figure 8).

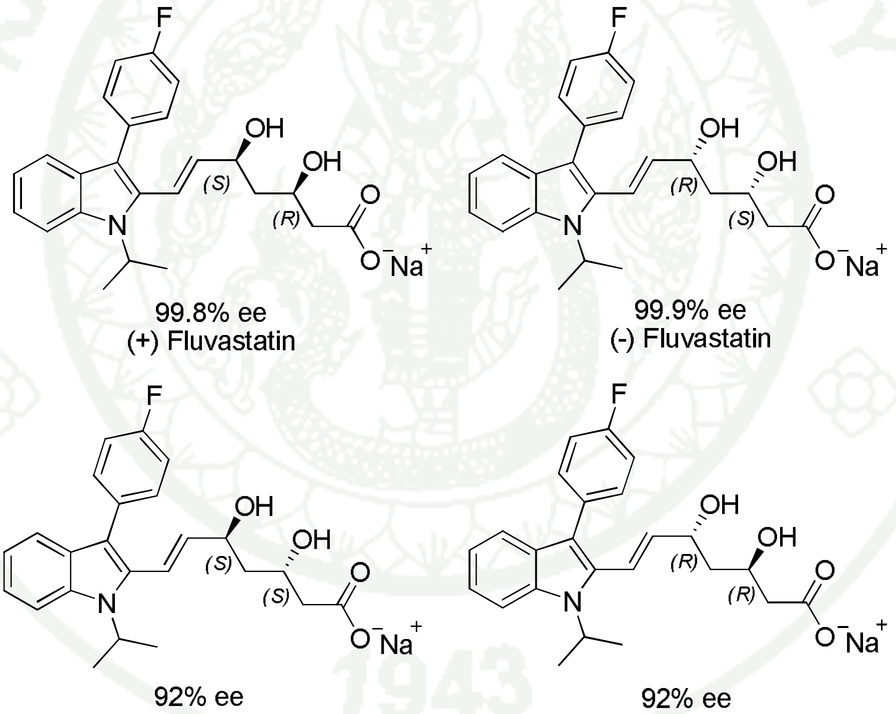


Figure 9 Structure of four stereoisomers fluvastatin was prepare via highly enantioselective synthesis and selective reduction (Zacharia et al., 2010)

3. Indole synthesis

Cyclization of *o*-alkynylanilines via aminopalladation-reductive elimination by Pd(II) salts is an effective method for the synthesis of 2,3-substituted indoles. This compound can be generated from *o*-alkynyltrifluoroacetanilides and R_1X (Figure 9). Cacchi and co-workers have investigated and developed methodology for 2,3 substituted indole synthesis (Cacchi andFabrizi, 2011). Their observations include the following: a) the acidity of the N-H bond plays a major role in this cyclization reaction. Most probably, the effect of the trifluoroacetyl group on the cyclization step promotes the intramolecular nucleophilic attack by proton removal in the transition state leading to the cyclization (Cacchi et al., 1998; Sashida and Kawamukai, 1999). b) The organopalladium complexes appear to be less effective than palladium dichloride in activating the C-C triple bond toward intramolecular nucleophilic attack. c) The trifluoroacetyl group was removed during the reaction or the workup. d) Carbonate bases were found to be better bases than Et_3N. f) The reaction tolerates a variety of functional groups, including aldehyde, ketone, ester, nitro, and nitrile groups. Substituents close to the oxidative addition site do not hamper the reaction. g) The alkyne component of *o*-alkynyltrifluoroacetanilide consists of alkyl, vinyl, electron-withdrawing, and electron-donating substituents to give high yield of 2,3-subsituted indole product.

In 2006, Lu et al. reported one-Pot, regiospecific synthesis of 2,3-disubstituted indoles via Consecutive Sonogashira and Cacchi reaction (Figure 10). The optimal conditions for this one-pot process of *N*-protected *o*-iodoaniline with, aryl acetylene and bromobenzne include the following: (a) The use of trifluoroacetyl as the protecting group of the nitrogen, (b) The use of K_2CO_3 as base and DMF as solvent, and (c) reaction temperature of 60 °C. The yield of 2,3-disubsituted indole products from this methodology is very high (80-90%) and varies upon the position and type of

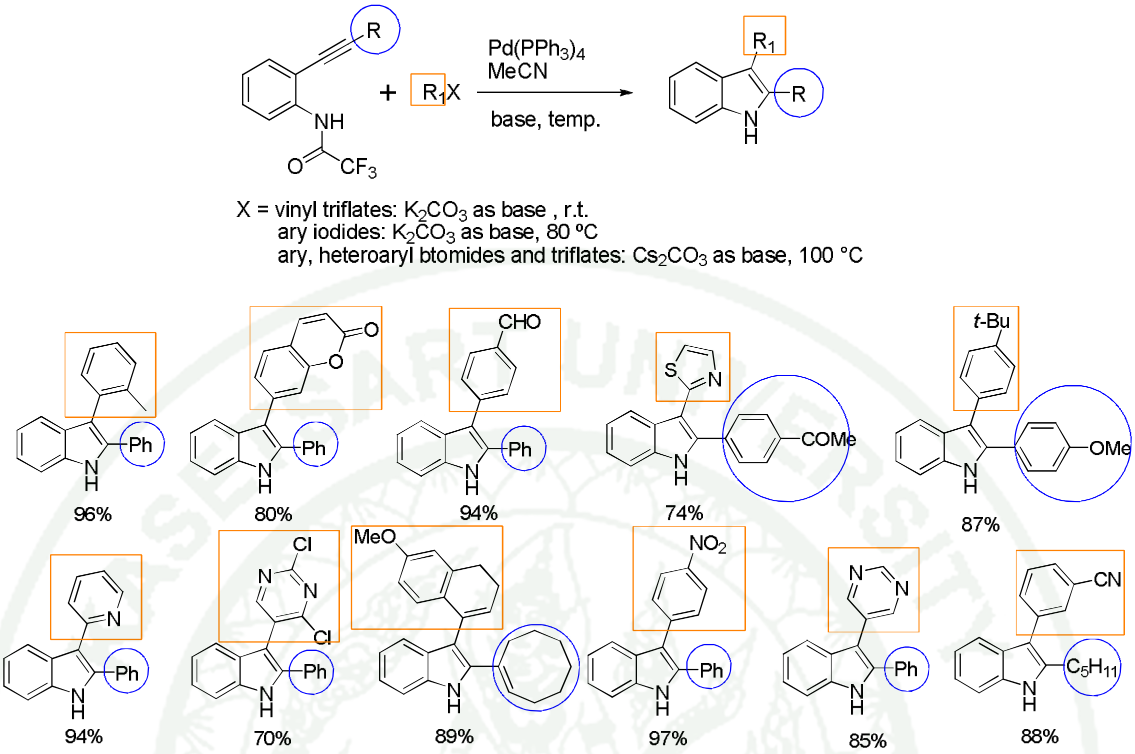


Figure 10 Cyclization of o-alkynylanilines via aminopalladation-reductive elimination by Pd(II) with salts alkynyltrifluoroacetanilides (alkynes component in blue cycle) and R_1X (group such as an aryl, heteroaryl, and vinyl halides or triflates, allyl esters, alkyl halides, and alkynyl bromides in orange square) (Cacchi, 2011 #24)

functional group on the substituted bromobenzene. From this methodology, the copper free Sonogashira coupling and the Cacchi reaction (aminopalladation) are able to take place under the same condition. However, cyclization of *o*-alkynylanilines (30) to 2-substituted indoles (32) can be affected by the occurrence of the non-Pd(II) catalyzed nucleophilic cyclization during after the Sonogashira coupling stage. They also found that CuI is able to catalyze this cyclization, and then they proceeded to screen conditions without CuI.

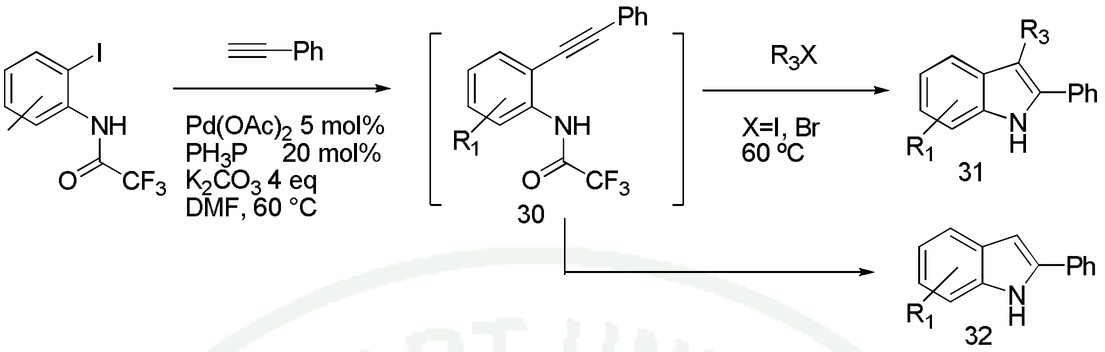


Figure 11 Regiospecific synthesis of 2,3-disubstituted indoles via Consecutive Sonogashira and Cacchi reactions

In 2009, Larock and co-worker reported an efficient, microwave-assisted, one-pot synthesis of indoles under Sonogashira conditions (Figure 11). The reaction consists of two steps under standard Sonogashira coupling between an *N,N*-dimethyl-2-iodoaniline and terminal alkyne, followed by the addition of acetonitrile and an aryl iodide to provide 2,3-disubsited indole. The Sonogashira coupling took place smoothly in Et_3N at room temperature. The cyclization step required higher temperature (about 60 ˚C) and longer reaction time (about 12 hours). Then, they accelerated the rate of one-pot coupling reaction and cyclization process by microwave irradiation. Both of the reactions were completed in less than an hour with percent yields comparable upon structure and electronic property of aryl iodide and alkyne.

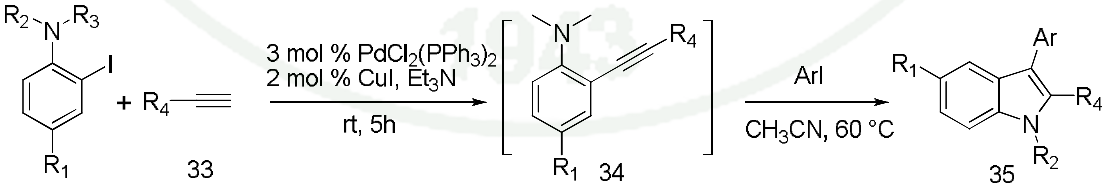


Figure 12 An efficient, microwave-assisted, one-pot synthesis of indoles under Sonogashira Conditions. (Y. Chen et al., 2009)

The observations from this methodology include the following: a) Sonogashira coupling and cyclization takes place smoothly with electron-rich aryl acetylenes. The coupling reaction with aryl acetylene containing an electron-deficient group or more steric bulkiness groups takes longer and gives lower yield, b) Couplings with aliphatic acetylenes can occur smoothly with moderated yield. c) A free hydroxyl group in the alkyne is not well accommodated by this coupling process. d) No significant electronic effect has been observed in either the 2-iodoanilines or the aryl iodides. f) Besides *N,N*-dialkyl-2-iodoanilines, 2-iodo-trifluoroacetanilides can be used as a precursor in the current microwave-irradiated process with moderated yield, but in cyclization step, higher temperature (100 ˚C) and addition of Cs_2CO_3 base is necessary for the success of this chemical transformation.

MATERIALS AND METHODS

Materials

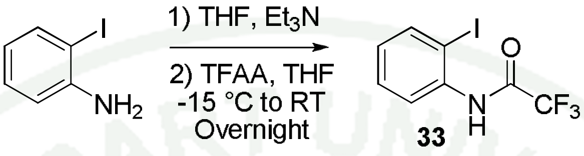
^{1}H-NMR (400 MHz), ^{13}C-NMR (100 MHz) were recorded on a VARIAN$^{\text{UNITY}}$ INOVA 400 MHz NMR spectrometer. Chemical shifts (δ) were reported in parts per million Spectra were acquired in $CDCl_3$ unless otherwise stated. The peak due to residual $CDCl_3$ (7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C) was used as internal reference.

Mass spectra (MS) were recorded on a Variance, Agilent 1100 series by direct inlet ESI mode.

All solvents and chemicals used were reagent grade procured commercially. Analytical TLC was performed on Merck pre-coated silica gel $60F_{254}$ plates. The products were purified by flask column chromatography using Merck silica gel 60 (0.040-0.063 mm).

Methods

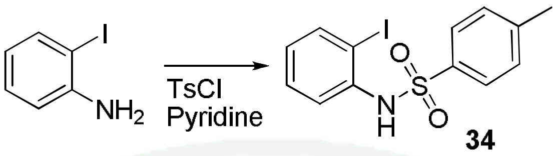
Preparation of the *N*-trifluoroacetyl-2-iodoanilines (33)



These compounds were prepared according to a procedure reported by Kabalka and co-workers (Kabalka, Wang and Pagni, 2001). To a solution of the corresponding 2-iodoaniline (3 g., 13.7 mmol) and triethylamine (Et_3N) (2.29 mL,15.07 mmol) in THF (35 mL) at -15 ˚C was slowly added trifluoroacetic anhydride (TFAA) (2.3 mL, 16.43 mmol) in 20 mL of THF. The resulting mixture was stirred for 1 h and then allowed to warm to room temperature and stirred overnight. The reaction mixture was then poured into a separatory funnel containing water (250 mL) and extracted with ethyl acetate (4x100 mL). The organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel with 5% ethyl acetate/hexanes.

N-Trifluoroacetyl-2-iodoaniline (33) : white solid : Yield 95% ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dt, J = 8.5, 1.4 Hz, 1H), 8.29 (s, 1H), 8.22 (dd, J = 8.2, 1.5 Hz, 1H), 7.85 (dd, J = 8.0, 1.4 Hz, 1H), 6.99 (dt, J = 7.7, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 135.7, 129.6, 127.9, 122.1, 117.1, 114.2, 90.2

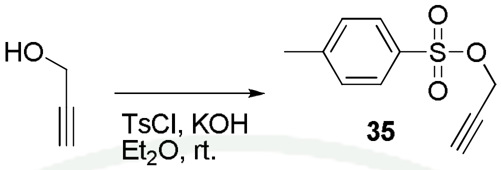
Preparation of *N*-(2-Iodophenyl)-4-methylbenzenesulfonamide (34)



These compounds were prepared according to a procedure reported by Bressy and co-worker (Bressy, Alberico and Lautens, 2005).To a solution of 2-iodoaniline (1.00 g, 4.57 mmol) in pyridine (10 mL) was added in one portion *p*-toluenesulfonyl chloride (914 mg, 4.79 mmol, 1.05 equiv). The reaction was stirred at rt for 1.5 h then quenched with water (10 mL). The solution was extracted with CH_2Cl_2 (3 times) and the combined organic extracts were washed with a 10% aqueous $CuSO_4$ (2 times), dried with anhydrous $MgSO_4$, filtered and concentrated. The crude mixture was purified by flash chromatography using 25% EtOAc/hexanes as eluent to yield **34** (1.62 g, 95%) as white solid.

N-(2-Iodophenyl)-4-methylbenzenesulfonamide (34) : white solid : Yield : 95% ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-161 (m, 4H), 7.30 (dt, J = 8.0, 1.5 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 6.82 (ddd, J = 8.0, 7.4, 1.6 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 139.0, 137.4, 135.8, 129.6, 129.4, 127.4, 126.8, 122.4, 92.3, 21.5; MS (ESI) *m/z* 395.9 $[M+Na]^+$

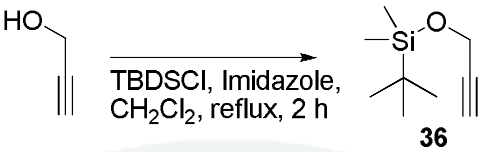
Preparation 2-propyn-1-ol-4-methylbenezene sulfonate (35)



These compounds were prepared according to a procedure reported by Srinivasan and co-worker (Srinivasan, Uttamchandani and Yao, 2006). Propargyl alcohol **33** (5.6 g, 100 mmol) and *p*-toluenesulfonyl chloride (22.8 g, 120 mmol) were dissolved in anhydrous diethyl ether (100 mL) and cooled to -5 °C. Powered KOH (28 g, 500 mmol) was added in 10 portions and stirred for an hour at -5 °C. The reaction was stirred further at room temperature for 4 h, after which the mixture was poured into cold water (50 mL). The layers were separated and the aqueous layer was extracted with ether (2 x 50 mL) and brine (1 x 50 mL). The combined ether extract was dried over anhydrous Na_2SO_4, filtered and dried *in vacuo* to afford a pure dark brownish syrupy liquid.

Prop-2-ynyl 4-methylbenzenesulfonate (35): dark brown syrupy liquid: Yield 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.6 Hz, 2H), 4.66 (d, J = 2.5 Hz, 2H), 2.48 (t, J = 2.5 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 132.6, 129.8, 127.9, 77.3, 75.2, 57.277, 21.5.

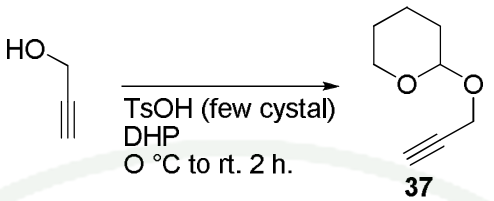
Preparation of *tert*-butyldimethyl(prop-2-ynyloxy)silane (36)



These compounds were prepared according to a procedure reported by Perreault and co-worker (Perreault and Spino, 2006). Propargyl alcohol (10.0 g, 178 mmol) was dissolved in dichloromethane (500 mL). Imidazole (30.4 g, 446 mmol) and *tert*-butyldimethylsilyl chloride (32.3 g, 214 mmol) were added at rt. The reaction mixture was stirred at room temperature for 30 minutes and quenched with water. The phases were separated and the aqueous phase was extracted twice with dichloromethane. The organic layers were combined, washed once with water, washed once with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give a colourless liquid. The crude product **9** (30.1 g, 99%) was used without purification in the next step.

tert-butyldimethyl(prop-2-ynyloxy)silane (36): colorless oil: Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 (d, J = 2.4 Hz, 2H), 2.37 (t, J = 2.4 Hz, 1H), 0.90 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 82.3, 72.8, 51.4, 25.6, 18.2, 5.3.

Preparation of 2-(prop-2-ynyloxy)tetrahydro-2H-pyran (37)

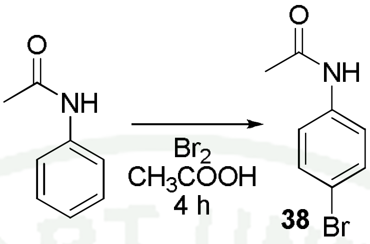


37

These compounds were prepared according to a procedure reported by Inkster and co-worker (Inkster et al., 2005). Neat dihydropyran (11.2 mol) was placed in a round bottomed flask and cooled to 0 ˚C. A small crystal of TsOH catalyst was added; when the crystal was nearly dissolved, propargyl alcohol (11.2 mol) was added and the solution was left to stir for 2 h. The reaction was quenched with 10% $NaHCO_3$ solution (20 mL), diluted with ether (90 mL), and washed twice with 10% $NaHCO_3$ (20 mL). The aqueous portion was back-extracted and the organic layers combined, washed once with brine (10 mL), dried over Na_2SO_4, and purified by flash-chromatography on a silica column (1:1 hexane/ether).

2-(prop-2-ynyloxy)tetrahydro-2H-pyran (37): colorless oil: Yield 76%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.79 (t, J = 3.39 Hz, 1H), 4.23 (dq, J = 16, 2.4 Hz, 2H), 3.81 (ddd, J = 11.5, 9.2, 3.2 Hz, 1H), 2.39 (dt, J = 2.4, 0.4 Hz, 1H), 1.44-1.68 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 96.6, 79.6, 73.8, 61.8, 53.8, 30.1, 25.2, 18.8.

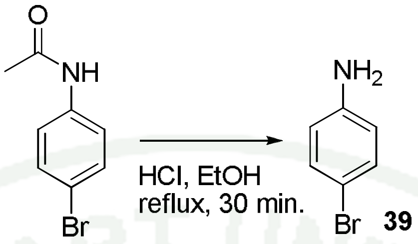
Preparation of *N*-(4-bromophenyl)acetamide (38)



To the solution of acetaniline (5.0036 g, 37 mmol) in CH_2CO_2H (50 mL), was added a solution of bromine (, 48.7 mmol) in CH_2CO_2H (10 mL) for 40 min.. When the addition of bromine was competed, the reaction was stirring for 3 hours. Addition of 375 mL cold water, then the product was collected by vacuum filtration and the wash the pale yellow solid four times with cold water. The product was recrystallize by 95% ethanol/water providing white crystal (6.356 g ,80.2%).

N-(4-bromophenyl)acetamide (38): white crystal: Yeild 80.2%; Mp. 168-169 ^{o}C ^{1}H NMR (400 MHz, DMSO d_6) δ 10.46 (s, 2H), 7.53 (dd, J = 6.8, 2.1 Hz, 2H), 7.44 (dd, J = 7.2, 2.0 Hz, 2H) 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 132.0, 121.5, 117.0, 24.6

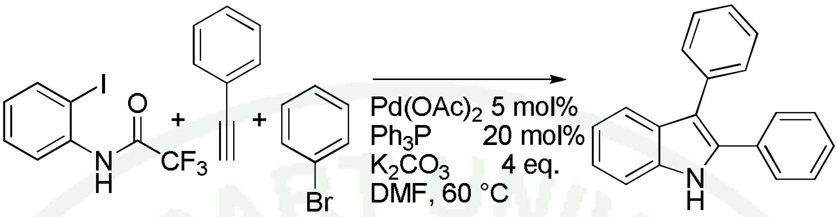
Preparation of 4-bromoaniline (39)



The 4-bromoaneline (2 g, 9.34 mmol) was dissolved in 95% ethanol (5 mL), then the solution was stirring at 70 °C until substrate was dissolve. The conc. HCl (2.4 mL) was added in small portion, then the reaction was refluxed for 30 min.. The reaction solvent was poured into ice-cold water (16 mL) and neutralized to pH 8-9. The white solid was collected by vacuum filtration. the product was recrystallize using 50:50 methanol/water, and the pale yellowe solid was obtain (1.45, 86%)

4-bromoaniline (39): pale yellowe solid: Yeild 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, J = 6.0, 2.2 Hz, 2H), 7.23 (dd J = 3.2, 2.1 Hz 2H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 131.8, 116.5, 109.9

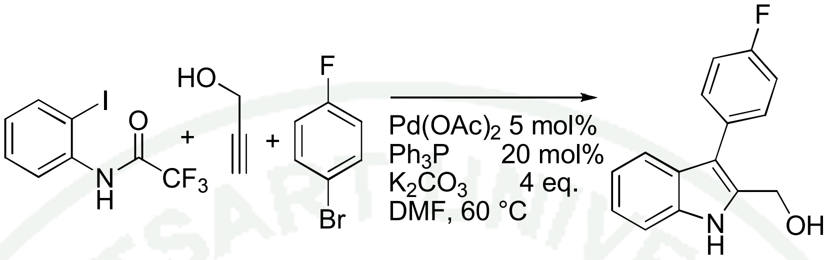
General protocol for the one-pot regiospecific indole synthesis via consecutive Sonogashira and Cacchi reaction with phenylacetaline



The two-neck round bottomed flask equipped with a stir bar was charged with *N*-protected *o*- iodoaniline (0.95 mmol, 1 equiv), bromobenzene (1.425 mmol, 1.5 equiv), $Pd(OAc)_2$ (0.047 mmol, 0.05 equiv), Ph_3P (0.188 mmol, 0.20 equiv), and K_2CO_3 (1.14 mmol, 1.2 equiv) and K_2CO_3 (3.8 mmol, 4 equiv). The reaction flask was evacuated and filled with nitrogen before a spared solution of phenyl acetaline (1.14 mmol, 1.2 equiv) in anhydrous DMF (6.7 mL) were added via syringe. The resulting mixture was stirred and heated to 60 ˚C for 4-24 hours. The mixture was quenched with water, and the aqueous solution was extracted with EtOAc three times. The organic solution was washed with brine and dried over Na_2SO_4. The products were evaporated and purified by flash column chromatography (EtOAc/hexane).

2,3-diphenyl-1H-indole (40) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (1 H, s), 7.66 (1 H, dd, J = 7.8, 1.1 Hz), 7.44-7.19 (12 H, m), 7.13 (1 H, ddd, J = 8.0, 7.0, 1.1 Hz) ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9, 135.0, 134.0, 132.7, 130.1, 128.7, 128.6, 128.5, 128.1, 127.6, 126.2, 122.6, 120.4, 119.7, 115.0, 110.9 MS (ESI), *m/z* 270.2 $[M+H]^+$

General protocol for the one-pot regiospecific indole synthesis via consecutive Sonogashira and Cacchi reactions



The two-neck round bottomed flask equipped with a stir bar was charged with *N*-protected *o*- iodoaniline (0.95 mmol, 1 equiv), *para*-substituted bromobenzene (1,4-dibromobenzene) (1.425 mmol, 1.5 equiv), $Pd(OAc)_2$ (0.047 mmol, 0.05 equiv), Ph_3P (0.188 mmol, 0.20 equiv), and K_2CO_3 (1.14 mmol, 1.2 equiv) for inorganic base condition. The reaction flask was evacuated and filled with nitrogen before a spared solution of propargyl alcohol (1.14 mmol, 1.2 equiv) and liquid *para*-substituted bromobenzene (bromobenzene and 1-bromo-4-fluorobenzene) in anhydrous DMF (6.7 mL) were added via syringe. For the organic base condition, Et_3N was added in the last step. The resulting mixture was stirred and heated to 60 ˚C for 4-24 hours. The mixture was quenched with water, and the aqueous solution was extracted with EtOAc three times. The organic solution was washed with brine and dried over Na_2SO_4. The products were evaporated and purified by flash column chromatography (EtOAc/hexane).

2,2,2-trifluoro-*N*-(2-(3-hydroxyprop-1-ynyl)phenyl) acetamide (41): white powder; m.p. 107-108 ˚C: ^1H NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.32 (d, J = 8.34 Hz, 1H), 7.47 (dd, J = 7.7, 1.5 Hz, 1H), 7.41 (dt, J = 8.6, 8.3, 1.5 Hz, 1H),7.18 (dt, J = 7.6, 1.1 Hz, 1H), 4.58 (d, J = 6.2 Hz, 1H), 1.92 (t, J = 6.2 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$): δ 136.3, 132.0, 130.1, 125.5, 119.8, 117.1, 14.2, 112.8, 96.0, 79.6, 51.4. MS (ESI) *m/z* 266.1 $[M+Na]^+$.

2,2,2-trifluoro-*N*-(2-(3-(tetrahydro-2H-pyran-2-yloxy)prop-1-ynyl)phenyl) acetamide (41a) yellow oil: ^1H NMR (400 MHz, $CDCl_3$); δ 8.78 (s, 1H), 8.34 (d, J =

8.3 Hz, 1H), 7.48 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.17 (dt, *J* = 7.7, 1.1 Hz, 1H), 4.87 (t, *J* = 3.3 Hz, 1H), 4.55 (q, *J* = 16.0 Hz, 2H), 3.92-3.84 (m, 1H), 3.61-3.53 (m, 1H), 1.90-1.50 (m, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 154.7, 136.5 , 132.0, 130.0, 126.3, 125.4, 120.4, 119.7, 112.9, 97.3 , 94.3, 79.7, 62.0, 54.5, 30.2, 25.3; MS (ESI) *m/z* 349.3 [M+Na]$^+$.

(1H-indol-2-yl)methanol (42) red oil: ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.38 (s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.19 (dd, *J* = 11.2, 4.0 Hz, 1H), 7.11 (dt, *J* = 7.4, 0.7 Hz, 1H), 6.40 (s, 1H), 4.78 (s, 2H), 2.12 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 137.5, 136.3, 128.0, 122.1, 120.6, 119.9, 111.0, 100.5, 58.5.

2-((tetrahydro-2H-pyran-2-yloxy)methyl)-1H-indole (42a) red brown oil: ^{1}H NMR (400 MHz, CDCl$_3$); δ 8.54 (s, 1H), 7.59 (dd, *J* = 7.8, 0.4 Hz, 1H), 7.36 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.18 (ddd, *J* = 8.2, 1.4, 0.9 Hz, 1H), 7.10 (ddd, *J* = 7.8, 1.7, 0.9 Hz, 1H), 6.45 (dd, *J* = 1.3, 0.7 Hz, 1H), 4.82 (dd, *J* = 38.6, 12.9 Hz, 2H), 4.72 (dd, *J* = 4.8, 2.8 Hz, 1H), 4.00-3.93 (m, 1H), 3.63-3.55 (m, 1H), 1.20-1.72 (m, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 136.4, 135.2, 125.2, 121.9,120.5, 119.7, 110.8, 101.6, 98.4, 62.9, 62.8, 46.2, 30.6, 25.3; MS (ESI) *m/z* 254.9 [M+Na]$^+$.

2-((*tert*-butyldimethylsilyloxy)methyl)-1H-indole (42b) red oil: ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.28 (s, 1H), 7.57 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.37 (dd, *J* = 8.1, 0.5 Hz, 1H), 7.17 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.09 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 6.32 (dd, *J* = 2.0, 0.9 Hz, 1H), 4.89 (s, 2H), 0.95 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 136.1, 135.89, 123.4, 121.6,120.4, 119.7, 110.8, 98.8, 59.2, 25.9, 18.4, 5.30; MS (ESI) *m/z* 262.4 [M+H]$^+$.

(3-(4-bromophenyl)-1-tosyl-1H-indol-2-yl)methanol (43) light yellow powder: ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.16 (td, *J* = 8.4, 0.9 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.48 (ddd, *J* = 7.9, 1.3, 0.7 Hz, 1H), 7.40-7.35 (m, 3H), 7.28-7.23 (m, 3H), 4.82 (d, *J* = 7.2 Hz, 2H), 3.33 (t, *J* = 7.4 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 145.3, 136.0, 135.6, 135.6, 131.9, 131.6, 131.0, 130.0, 128.8, 126.5, 125.7, 124.3, 124.0, 122.1, 120.2, 114.5, 55.7, 21.6; MS (ESI) *m/z* 479.9 $[M+Na]^+$.

N-(2-(3-hydroxyprop-1-ynyl)phenyl)4-methyl-benzenesulfonamide (44) yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.25-7.19 (m, 2H), 7.08-7.04 (m, , 1H), 4.48 (d, *J* = 5.6 Hz, 2H), 2.37 (s, 3H), 1.83 (t, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 136.5, 136.0, 133.1, 131.6, 129.6, 129.3, 127.2, 125.3, 121.6, 88.3, 84.6, 51.6, 21.5; MS (ESI) *m/z* 324.3 $[M+Na]^+$.

(1-tosyl-1H-indol-2-yl)methanol (45) dark yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.22 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H), 7.15 (dt, *J* = 7.6, 7.3, 1.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.57 (s, 1H),4.83 (d, *J* = 7.3 Hz, 2 H,), 3.04 (t, *J* = 7.3 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 136.3, 128.0, 122.1, 120.6, 119.9, 111.0, 100.5, 58.5; MS (ESI) *m/z* 324.2 $[M+Na]^+$.

3-(4-bromophenyl)prop-2-yn-1-ol (46) white brown solid, m.p. 78-80 °C : ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 4.47 (s, 2H), 2.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.1, 131.6, 122.8, 121.4, 88.3, 84.6, 51.5.

(3-(4-fluorophenyl)-1-tosyl-1H-indol-2-yl)methanol (47) yellow oil: ^{1}H (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.52-7.46 (m, 3H), 7.37 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.29-7.22 (m, 3H), 7.18 (t, *J* = 8.7 Hz, 2H), 4.82 (d, *J* = 7.0 Hz, 1H), 3.35 (t, *J* = 7.2 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.2, 136.0, 135.6, 135.5, 131.8, 131.7, 130.0, 126.5, 125.7, 124.5, 123.9, 120.3, 115.8, 115.6, 114.5, 55.7, 21.6; MS (ESI) *m/z* 418.1 $[M+Na]^+$.

(3-phenyl-1-tosyl-1H-indol-2-yl)methanol (48) orange oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.34-7.27 (m, 3H), 7.21-7.16 (m, 1H), 4.73 (d, *J* =

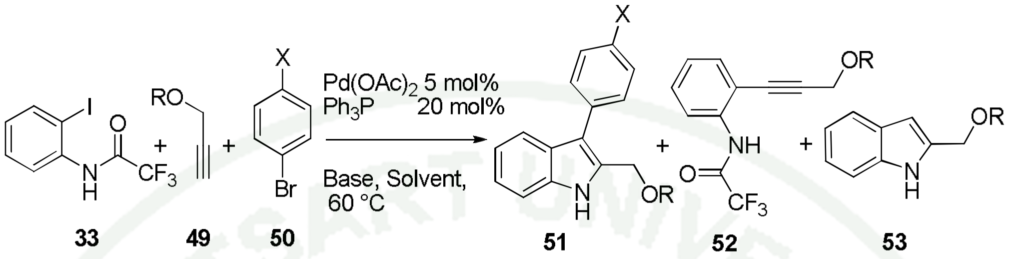
7.4 Hz, 2H), 3.23 (t, J = 7.5 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 136.1, 135.67, 135.5, 132.1, 130.1, 130.0, 129.0, 128.7, 128.0, 126.5, 125.6, 123.8, 120.5, 114.5, 55.8, 29.7, 21.6; MS (ESI) m/z 400.1 $[M+Na]^+$.

RESULTS AND DISCUSSIONS

The key intermediate hydroxyindole (**4**) and its derivatives were synthesized via consecutive Sonogashira and Cacchi reactions from trifluoro-acetylanilide (3**3**), protected propargly alcohol (**49**), and para-substituted bromobenzene (**50**). The reaction was carried out in DMF at 60 ˚C for 24 hours. We were surprised to learn that, under the condition previously reported, the desired product (**51**) cannot be detected (Table 1). Then, several attempts were made in order to optimize the reaction condition. We chose to evaluate the use of organic versus inorganic bases by using triethylamine (Et_3N) and potassium carbonate (K_2CO_3) as candidates for organic and inorganic bases, respectively. The Sonogashira intermediate (**41**) and the side product (**42**) were formed under the conditions utilizing triethylamine as a base (Table 1 entry 2, 4). On the other hand, the use of inorganic base such as potassium carbonate did not provide the product of our interest and also provided little or no side products (Table 1 entry 1, 3). When 1,4-dibromobenzene was used instead of a bromobenzene, variation in side product formation was observed. The effect of protecting group on propargyl alcohol (49) was also evaluated. Although the amount of side products formed was different in each case, none of these conditions provided our desired hydroxyindole (**51**). (Table 1 entry 6-8)

Once the nitrogen protecting group of choice was evaluated to be a tosyl group, the effect of solvent and base was re-evaluated. To our surprise, the inorganic base gives a better yield of the desired product. This result is contrary to our previous screening (Table 1 entry 1, 2). Switching the DMF to acetonitrile as solvent did not significantly improve the reaction (Table 3 entry 1, 3), but rather promoted the Sonogashira coupling between propargyl alcohol and 1,4-dibromobenzene. The stoichiometric ratio between palladium metal and triphenylphosphine ligand was changed from 1:4 to 1:2 (Table 3 entry 1, 4). However, no significant improvement for the formation of our desired product was observed.

Table 1 The product distribution from the sequential Sonogashira and Cacchi reactions under different reaction conditions

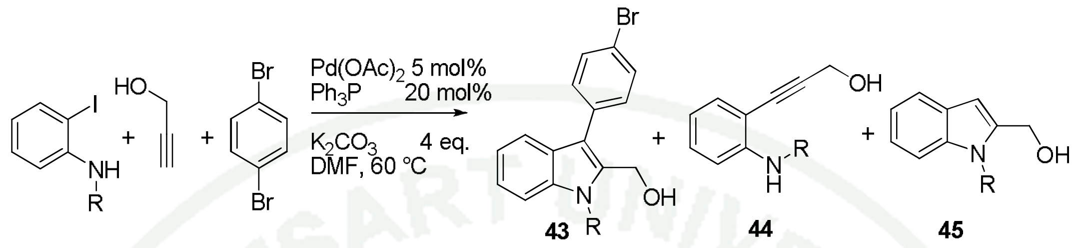


Entry	R	X	Base	Solvent	% yield		
					51	**41**	**42**
1	-OH	H	K_2CO_3	DMF	-	-	-
2	-OH	H	Et_3N	DMF	-	>1	8
3	-OH	Br	K_2CO_3	DMF	-	-	12
4	-OH	Br	Et_3N	DMF	-	56	8
5	-OH	Br	Et_3N	ACN	-	10	7
6	-OTHP[a]	Br	Et_3N	DMF	-	25[d]	35[e]
7	-OTBS[b]	Br	Et_3N	DMF	-	-	20[f]
8	-OTs[c]	Br	Et_3N	DMF	-	-	-

[a] Compound **37**, [b] Compound **36**, [c] Compound **35**, [d] Compound **41a**, [e] Compound **42a**, [f] Compound **42b**

Finally, we chose to evaluate the electronic effect of the *para*-substituent on arylbromide on the sequential Sonogashira and Cacchi reactions. It is worth mentioning that the fluoro substituent was found in fluvastatin at the *para*-position on the aromatic ring. The results indicated that the electron-donating group at the *para*-position of arylbromide did not promote the formation of the desired product (Table 4 entry 4,5). On the other hand, halogens, which served as our candidates for an electron-withdrawing group, provided low percent yields of the desired product (Table 4 entry 1, 2).

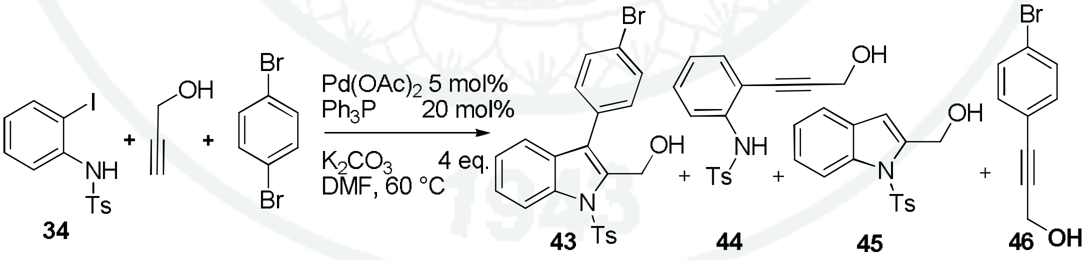
Table 2 The effect of *N*-protection on the sequential Sonogashira and Cacchi reactions



Entry	R	Time	% yield		
			43	44	45
1	H-	24 h.	-	-	5[a]
2	$CF_3(O)C$-	24 h.	-	-	12[a]
3	Ts-	4 h	28	-	45

[a] Compound 42 (R=H

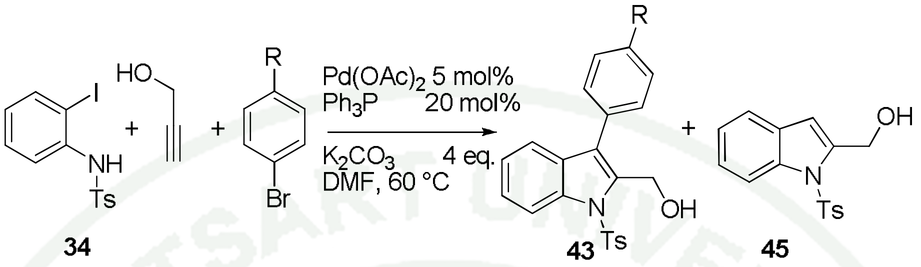
Table 3 The evaluation of different conditions of solvent, base and ratio catalyst to the regioselective consecutive indole synthesis with *N*-(2-iodophenyl)-4-methylbenzene-sulfonamide (**34**)



Entry	Solvent	Base & condition	% yield			
			43	44	45	46
1	DMF	K_2CO_3	28	-	45	-
2	DMF	Et_3N	7	5	41	-
3	CH_3CN	K_2CO_3	5	-	38	8
4[a]	DMF	K_2CO_3	7	-	41	-

[a] ratio of $Pd(OAc)_2$:Ph_3P is 1:2

Table 4 The effect of different substituents at the *para* position of arylbromide on the sequential Sonogashira and Cacchi reactions



Entry	R	% yield	
		43	**45**
1	Br	28%	45%
2	F	10%[a]	30%
3	H	5%[b]	20%
4	NHAc	-	43%
5	NH_2	-	53%

[a] Compound **47**, [b] Compound **48**

The inductive effect of *para*-substituted bromo-benzene affects the oxidative addition between bromo-benzene and palladium complex before pyrrole ring formation via the Cacchi reaction.

CONCLUSION

The sequential Sonogashira and Cacchi reaction were applied to the construction of the key intermediate for fluvastatin synthesis. However, this palladium-catalyzed process strongly depends on the nature of reactants, solvent, and base employed in the reaction. The best screened condition only provides 28% of the key intermediate, 2-hydroxymethyl-3-phenylindole. Alternative methods for the generation of 2-hydroxymethyl-3-phenylindole intermediate are now being investigated.

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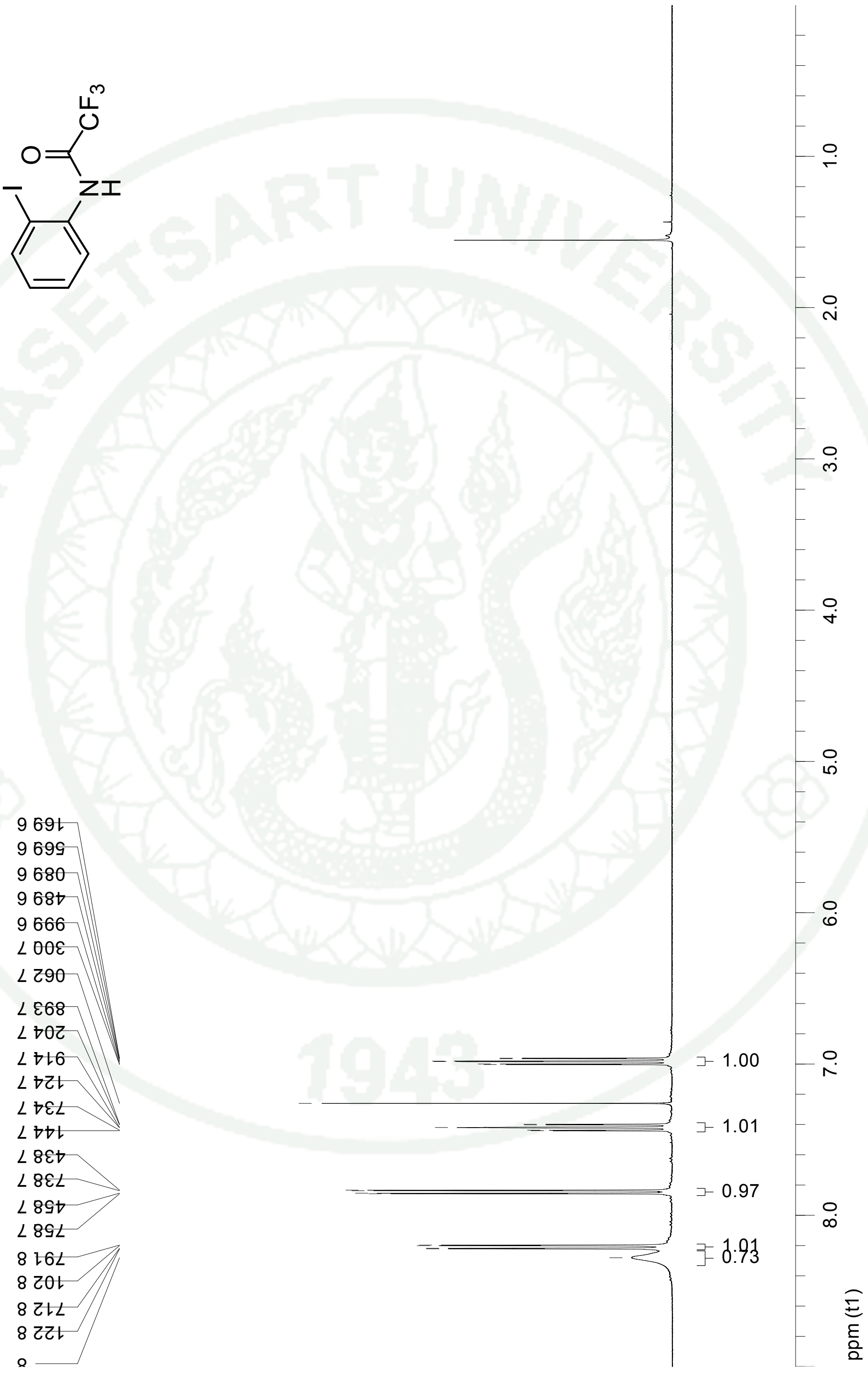
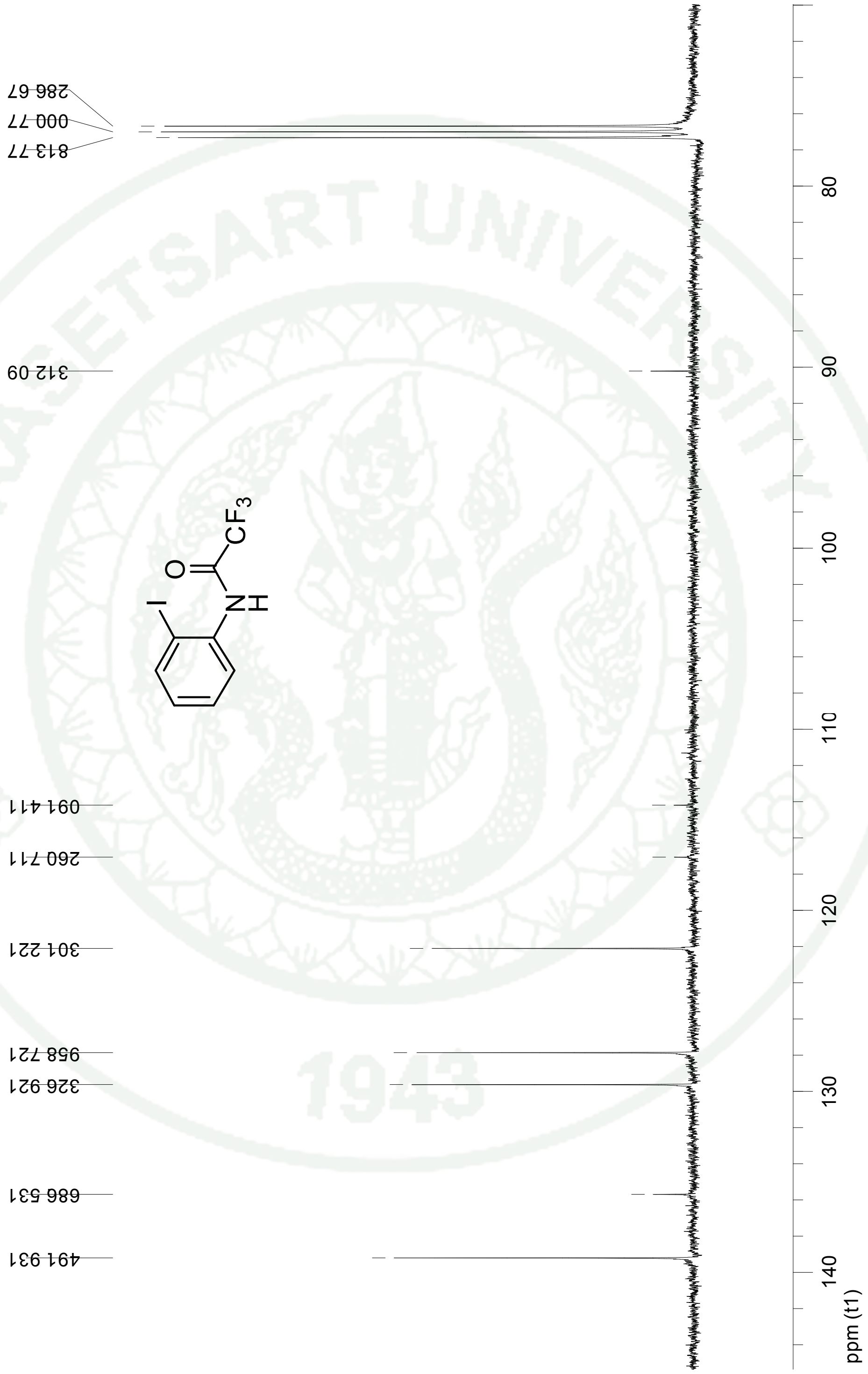
APPENDIX

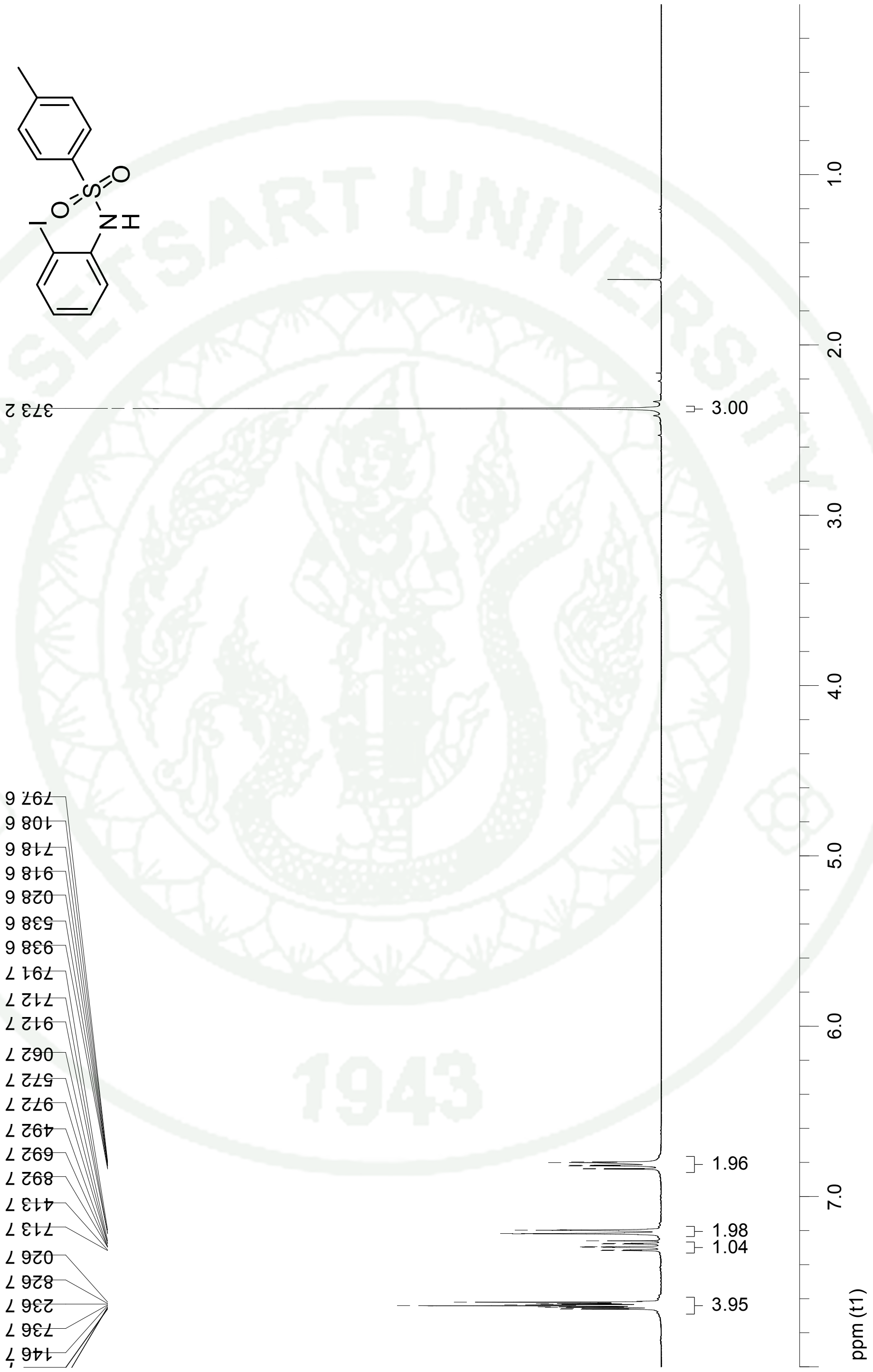
^{1}H NMR of *N*-trifluoroacetyl-2-iodoanilines (33) in $CDCl_3$



^{13}C NMR of *N*-trifluoroacetyl-2-iodoanilines (33) in CDCl$_3$



^{1}H NMR of *N*-(2-Iodophenyl)-4-methylbenzenesulfonamide (34) in $CDCl_3$



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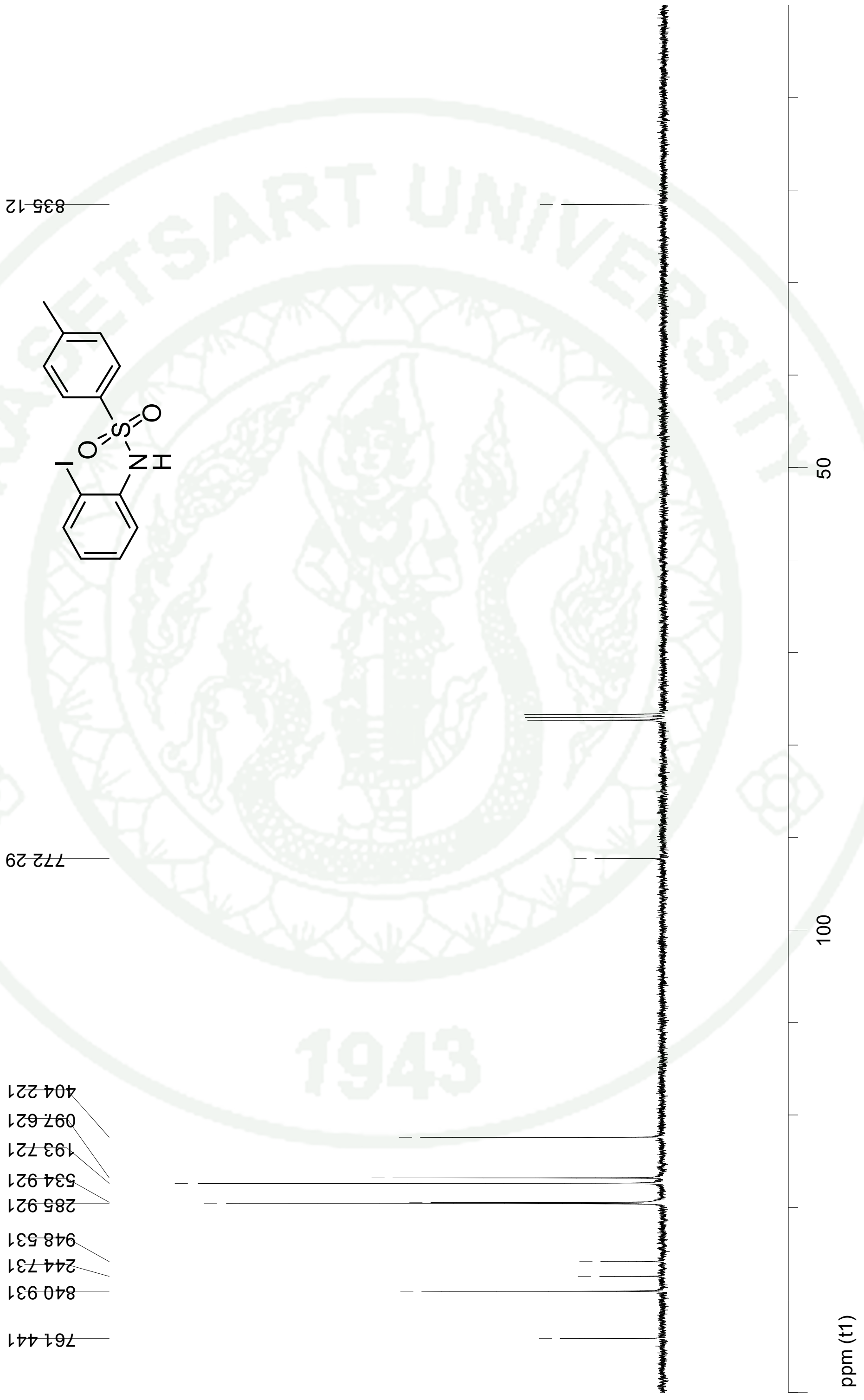
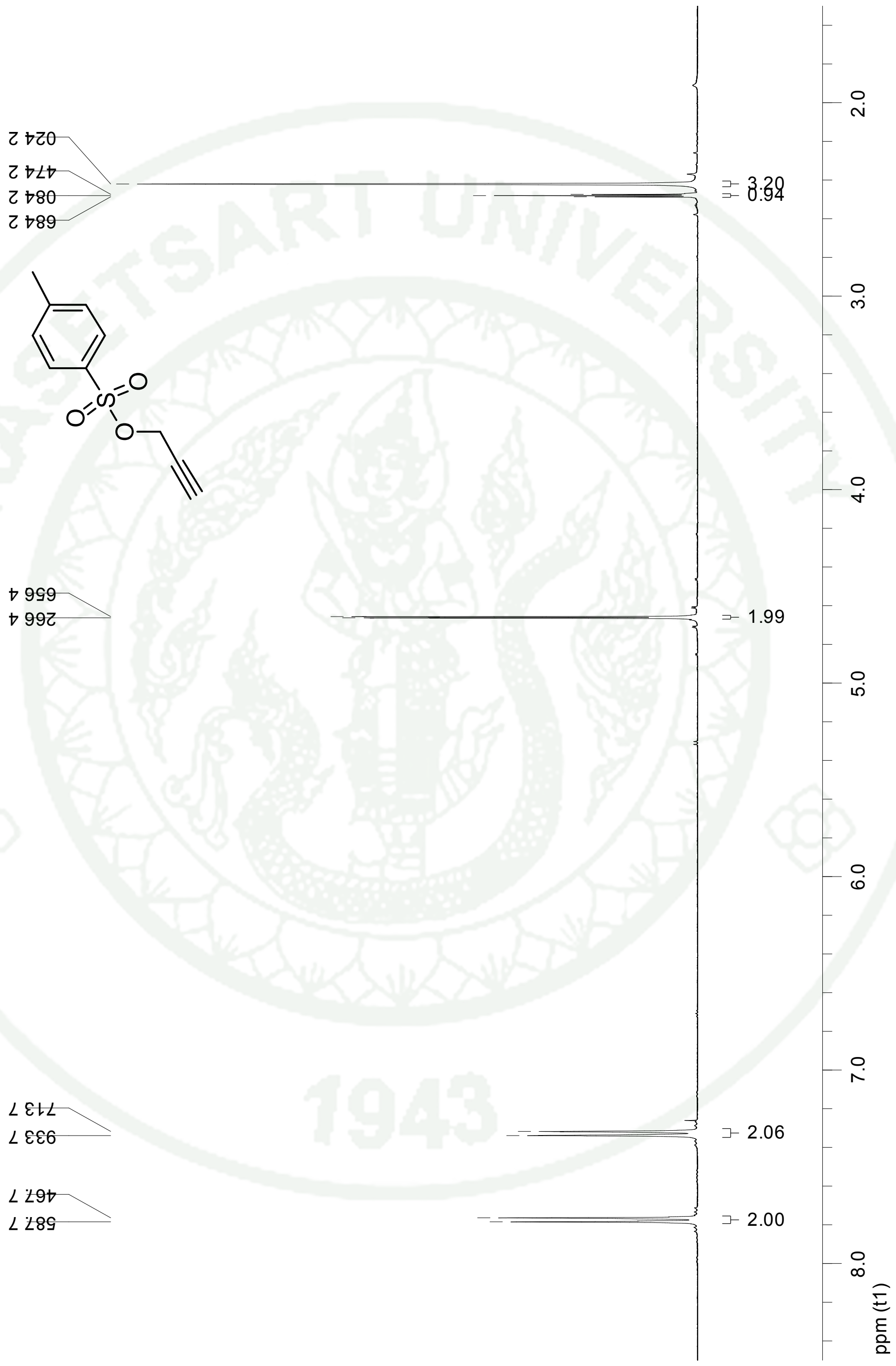


^{1}H NMR of 2-propyn-1-ol-4-methylbenezene sulfonate (35) in $CDCl_3$



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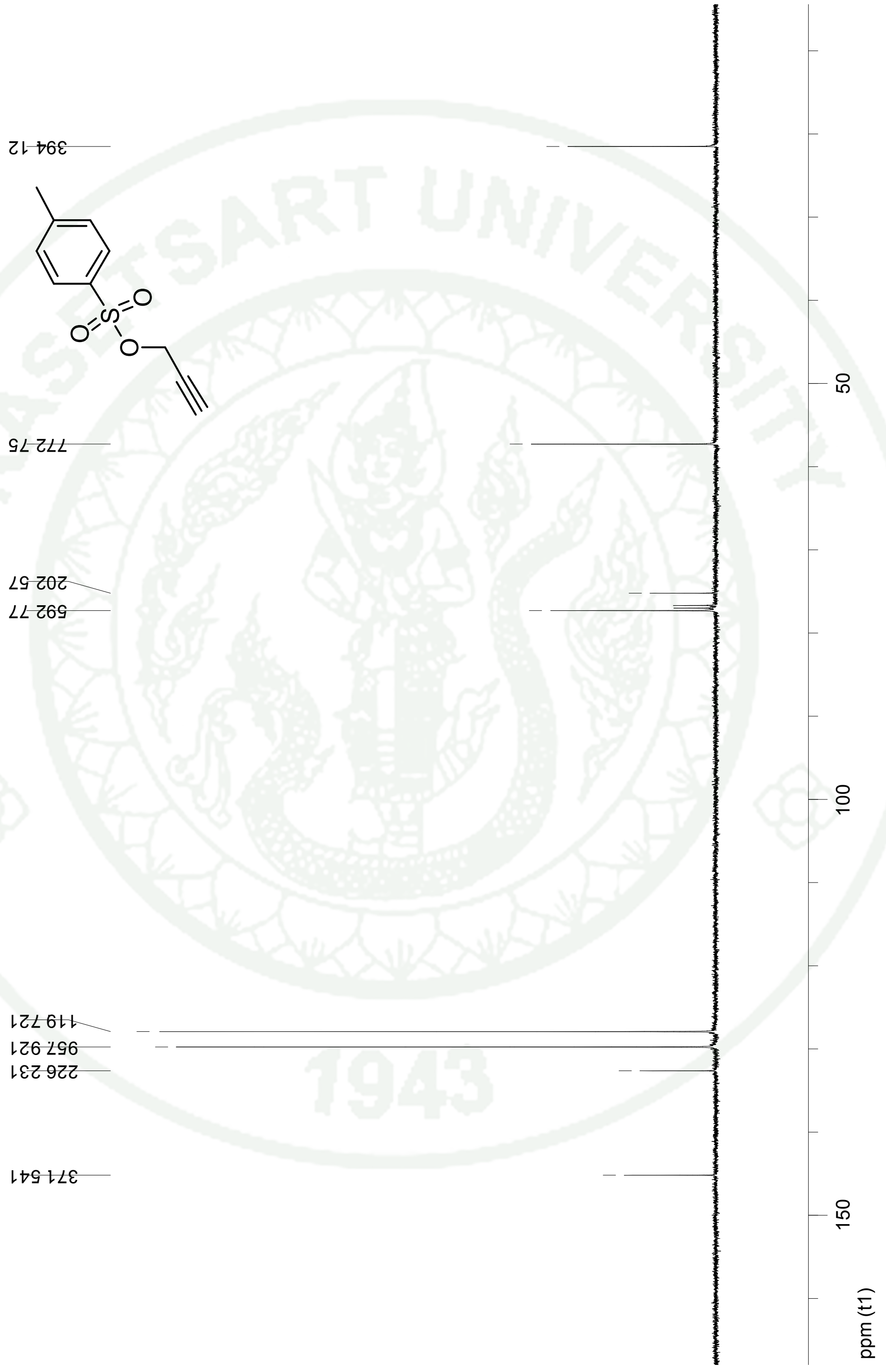
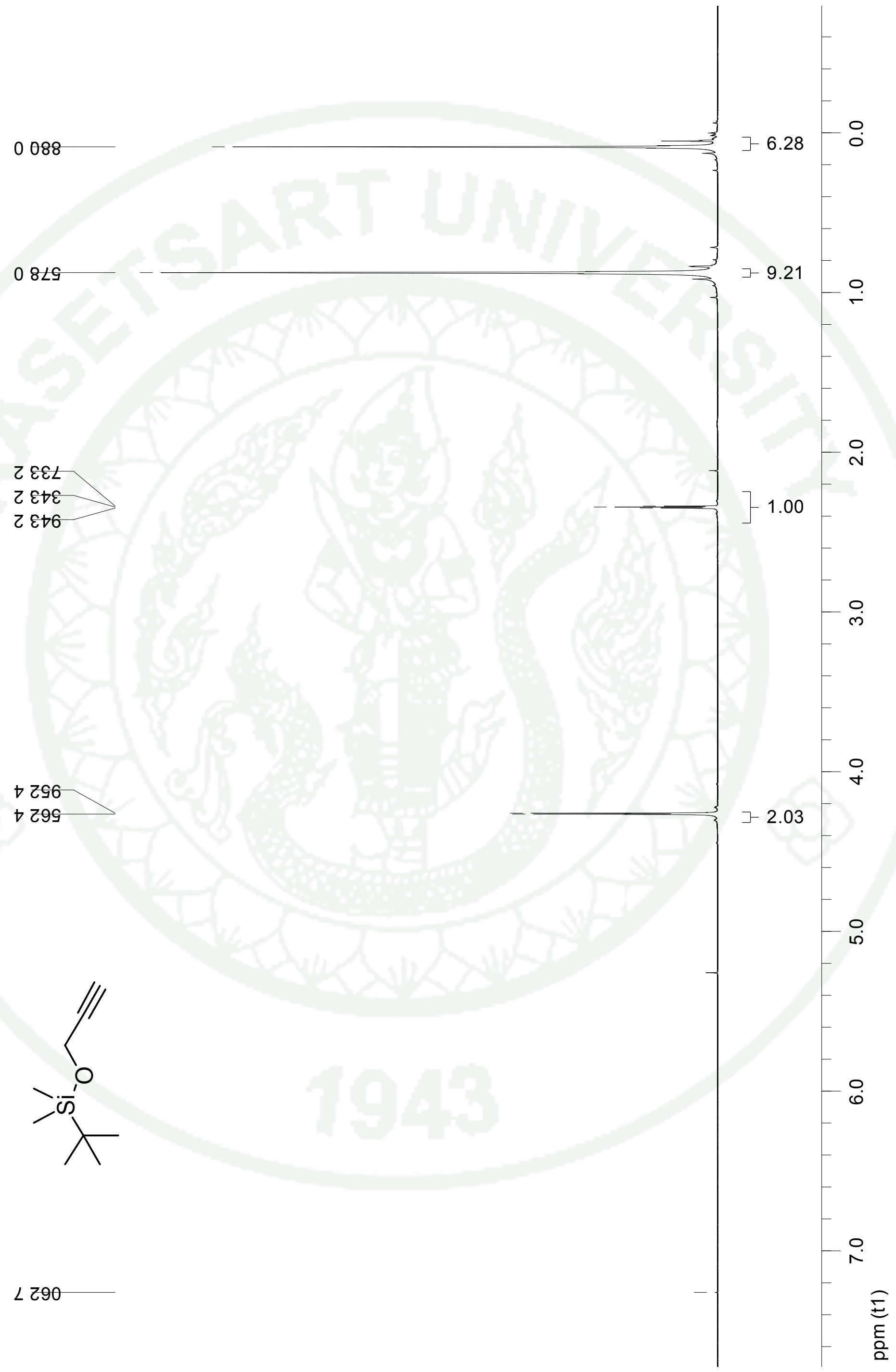


^{1}H NMR of *tert*-butyldimethyl(prop-2-ynyloxy)silane (36) in $CDCl_3$



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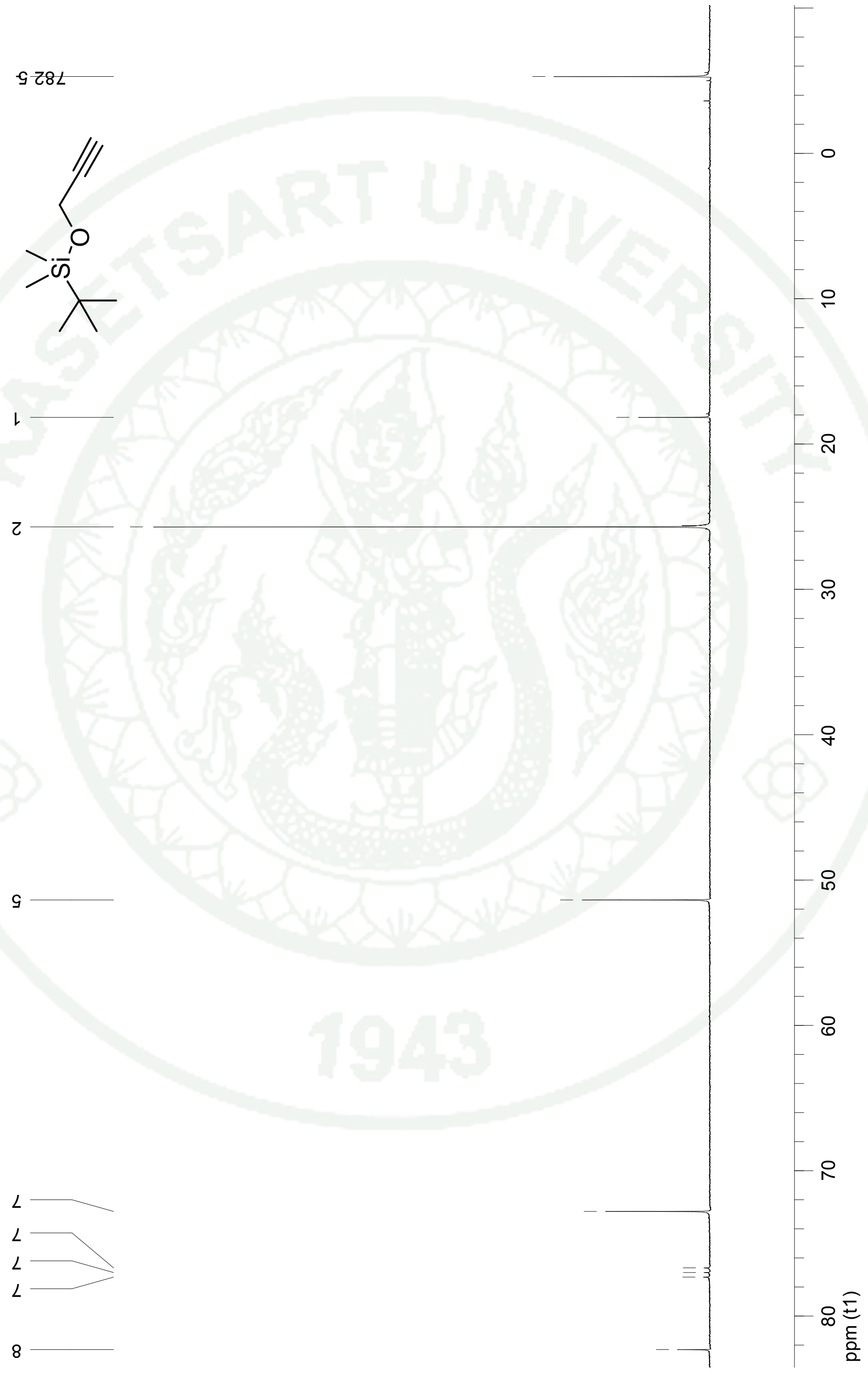
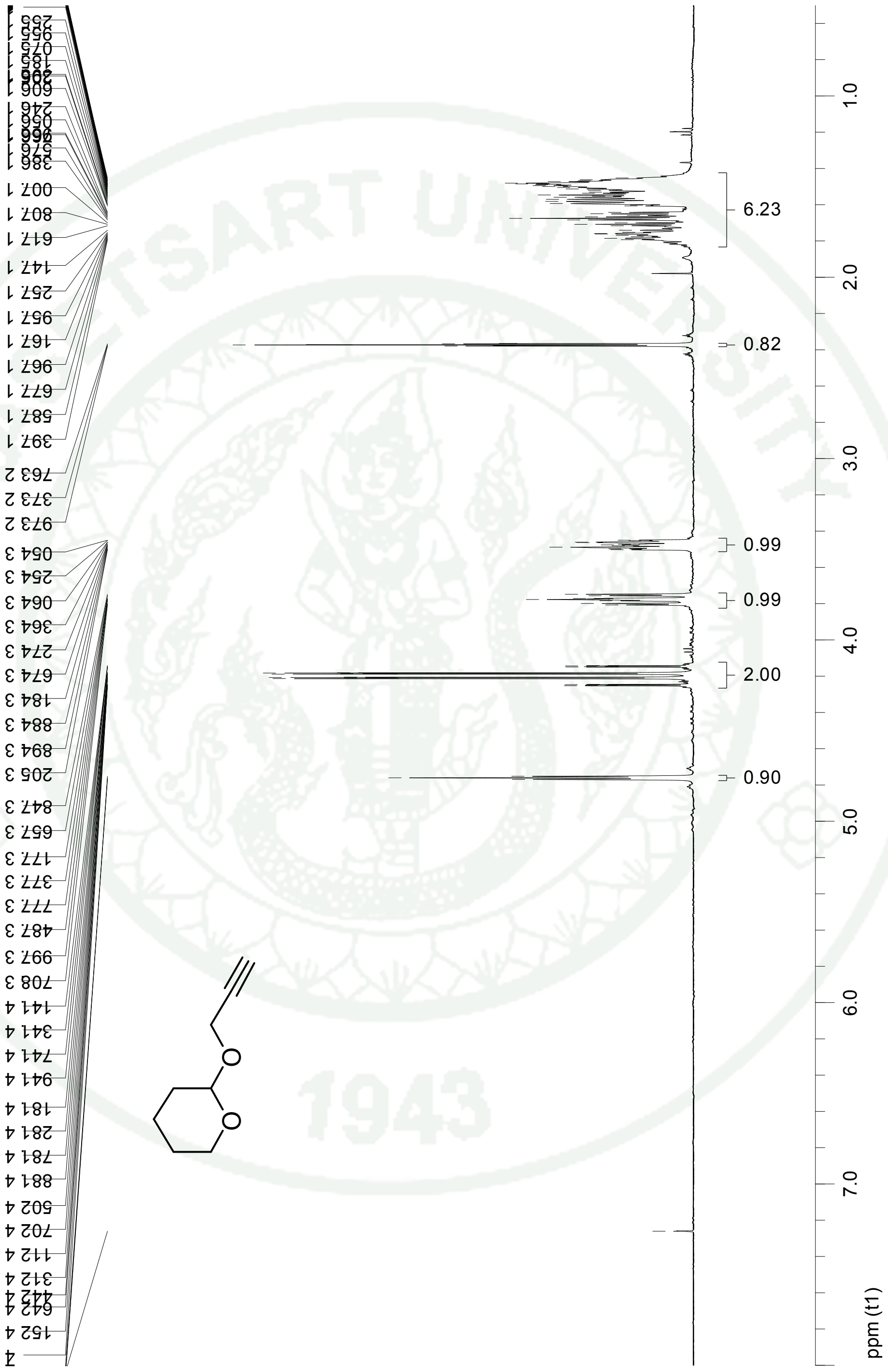


^{1}H NMR of 2-(prop-2-ynyloxy)tetrahydro-2H-pyran (37) in CDCl$_3$



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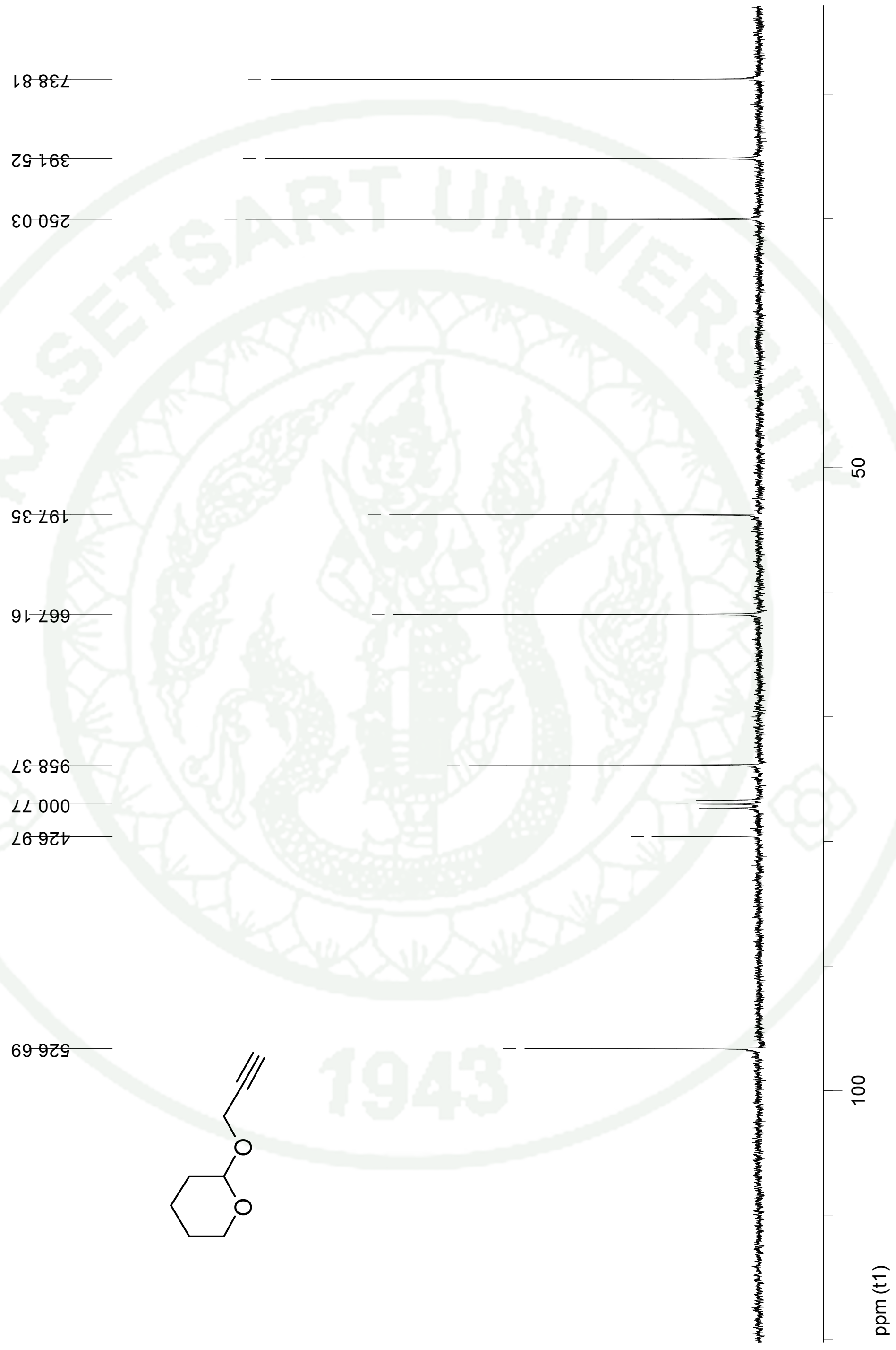
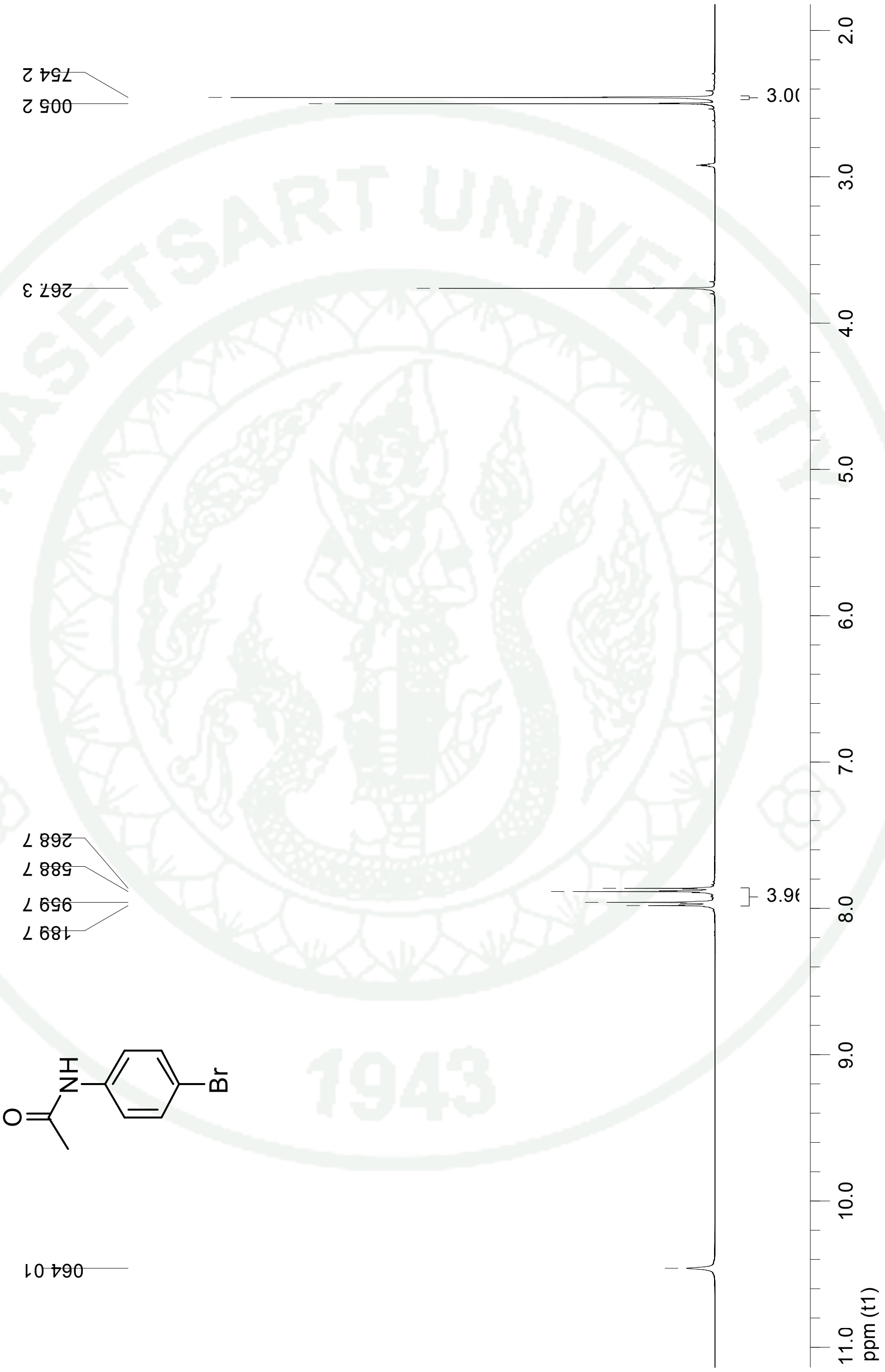


^{1}H NMR of *N*-(4-bromophenyl)acetamide (38) in DMSO-d6



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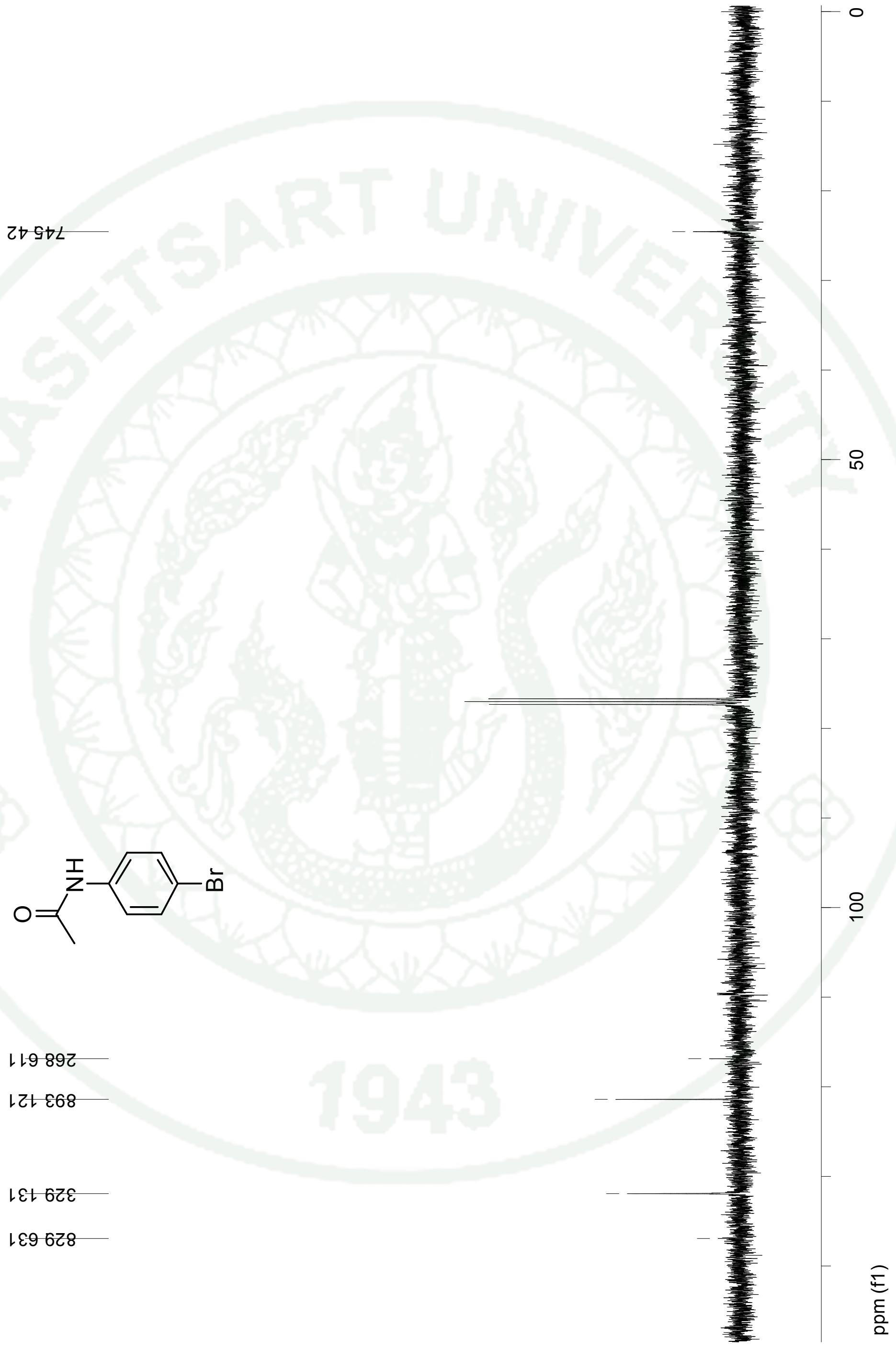
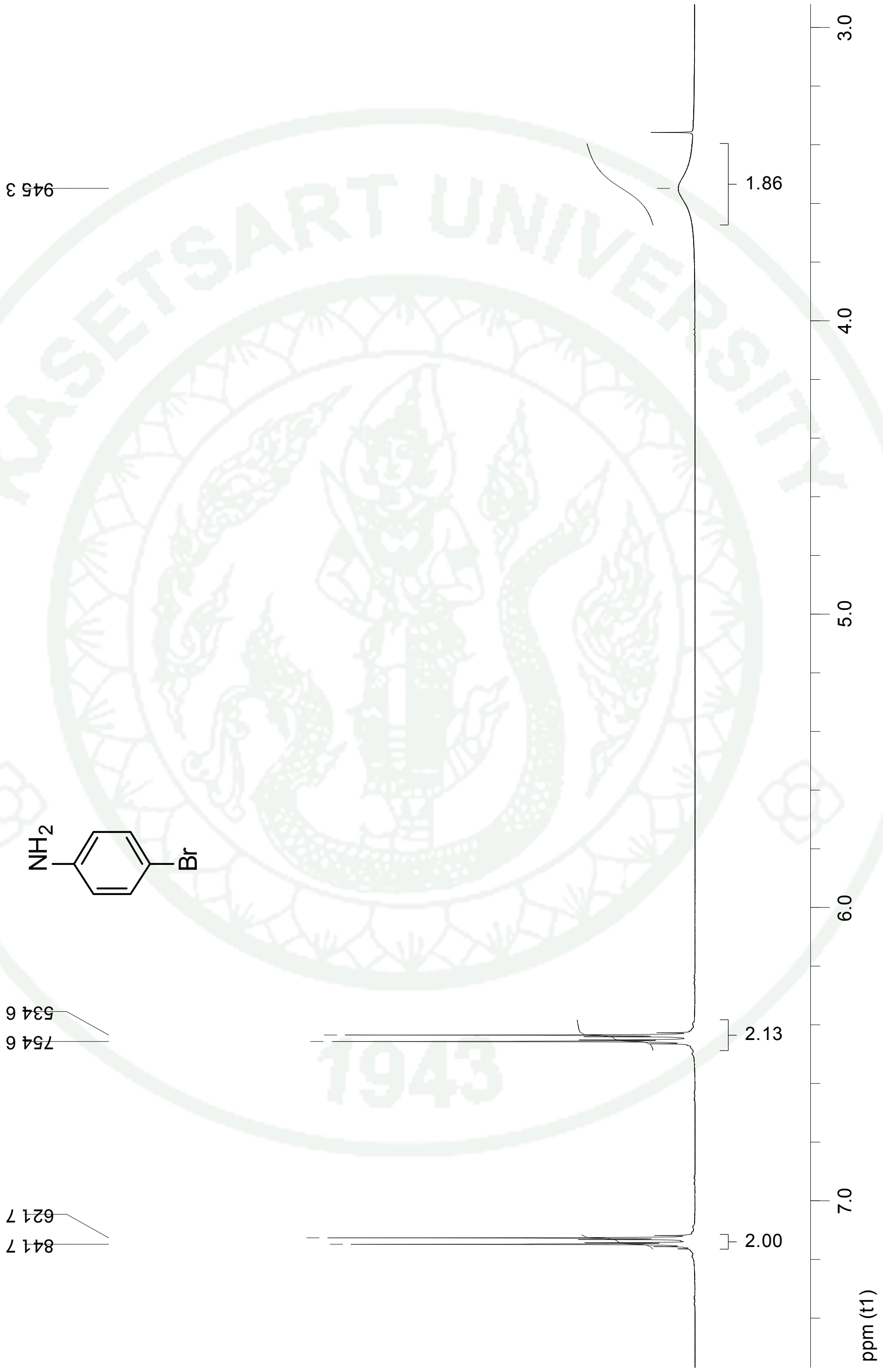


^{1}H NMR of 4-bromoaniline (39) in $CDCl_3$



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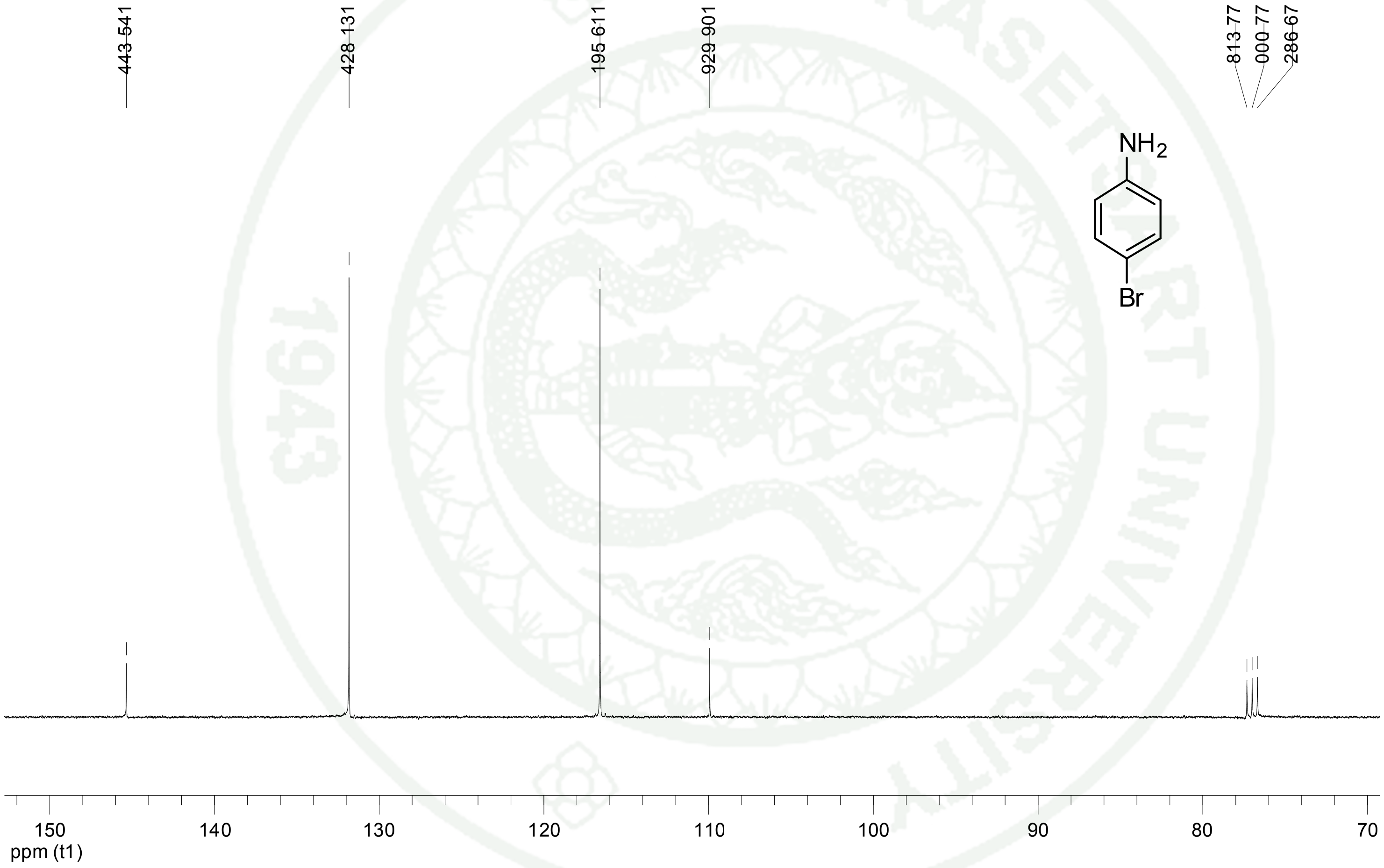
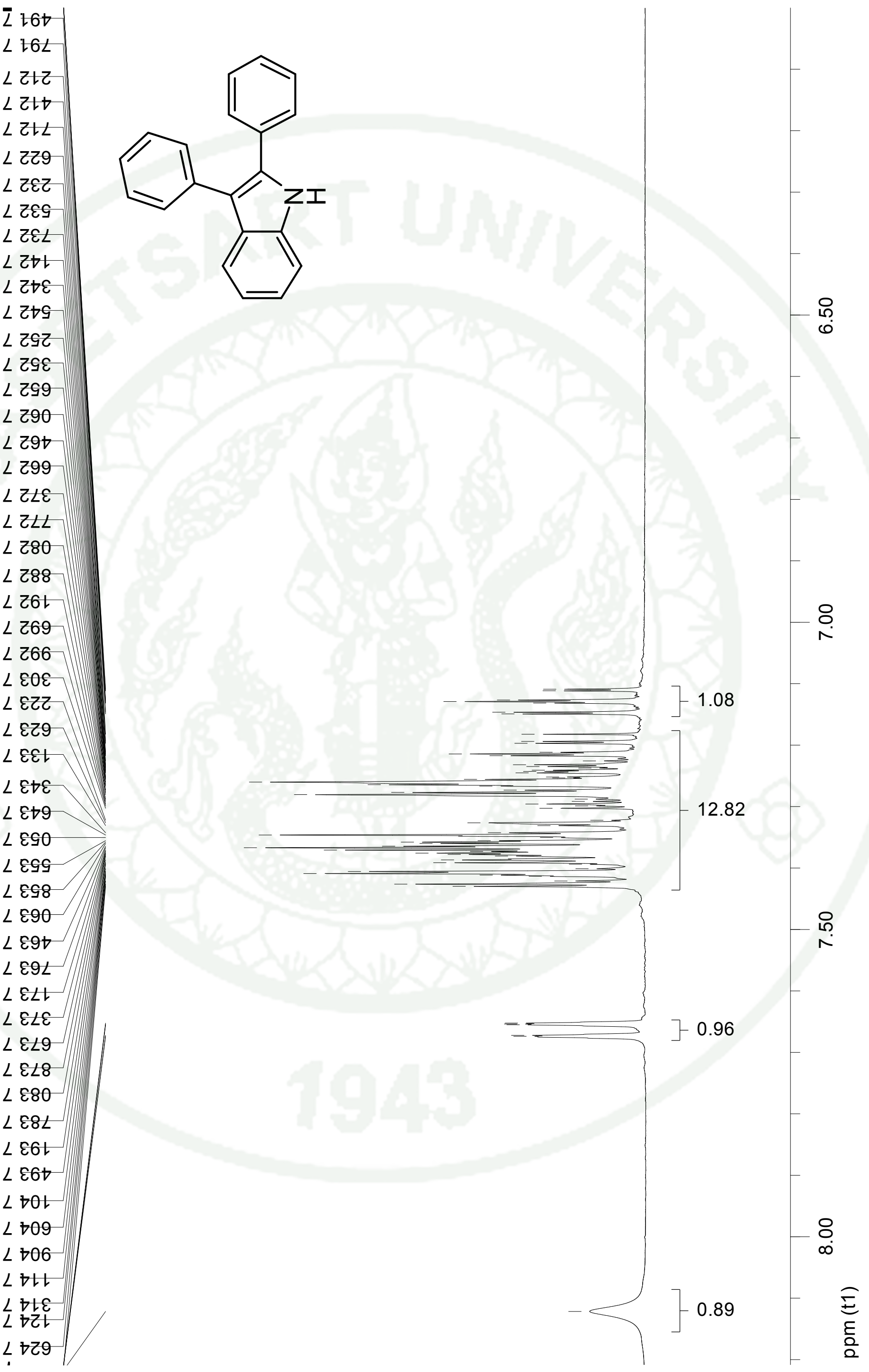


^{1}H NMR of 2,3-diphenyl-1H-indole (40) in $CDCl_3$



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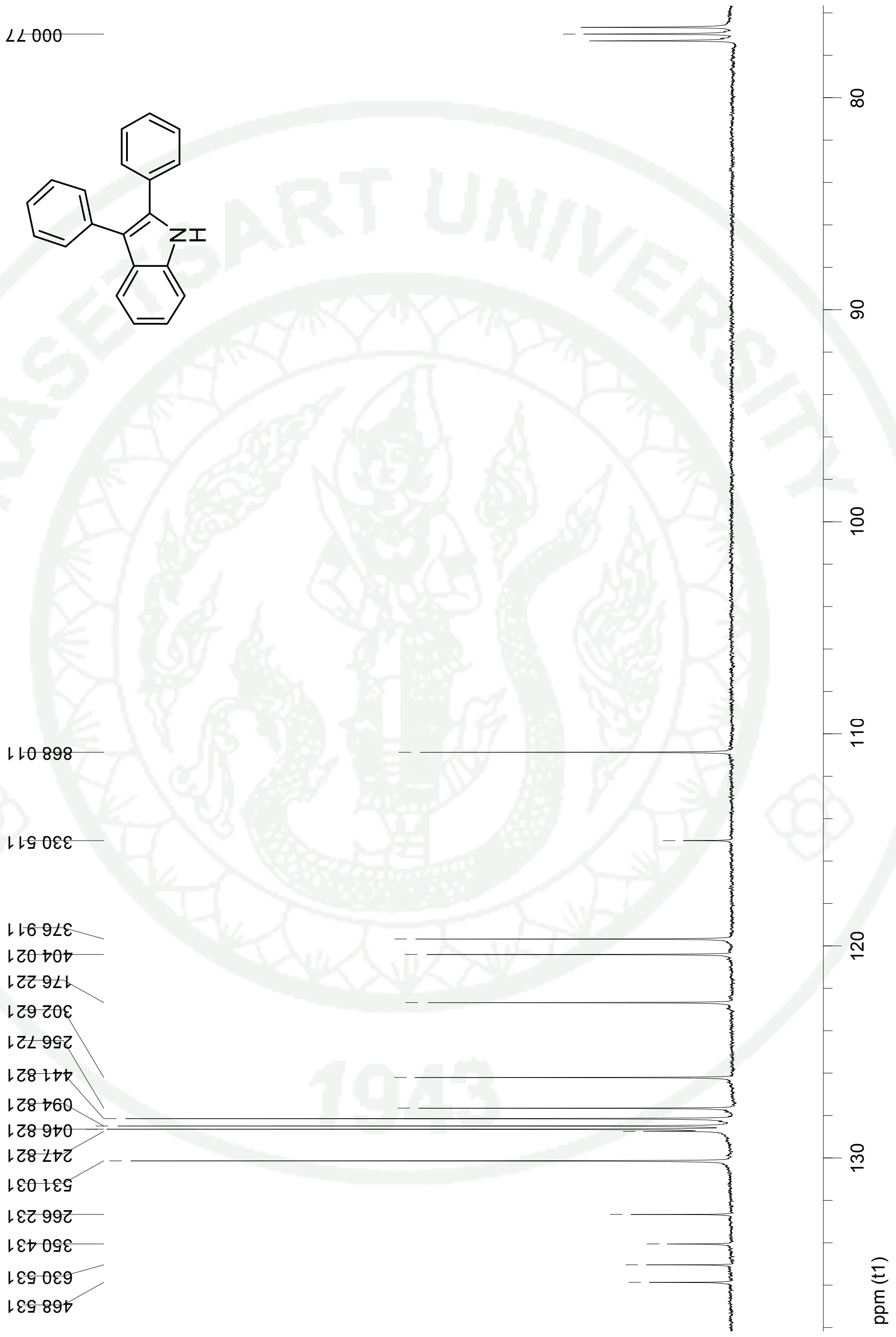
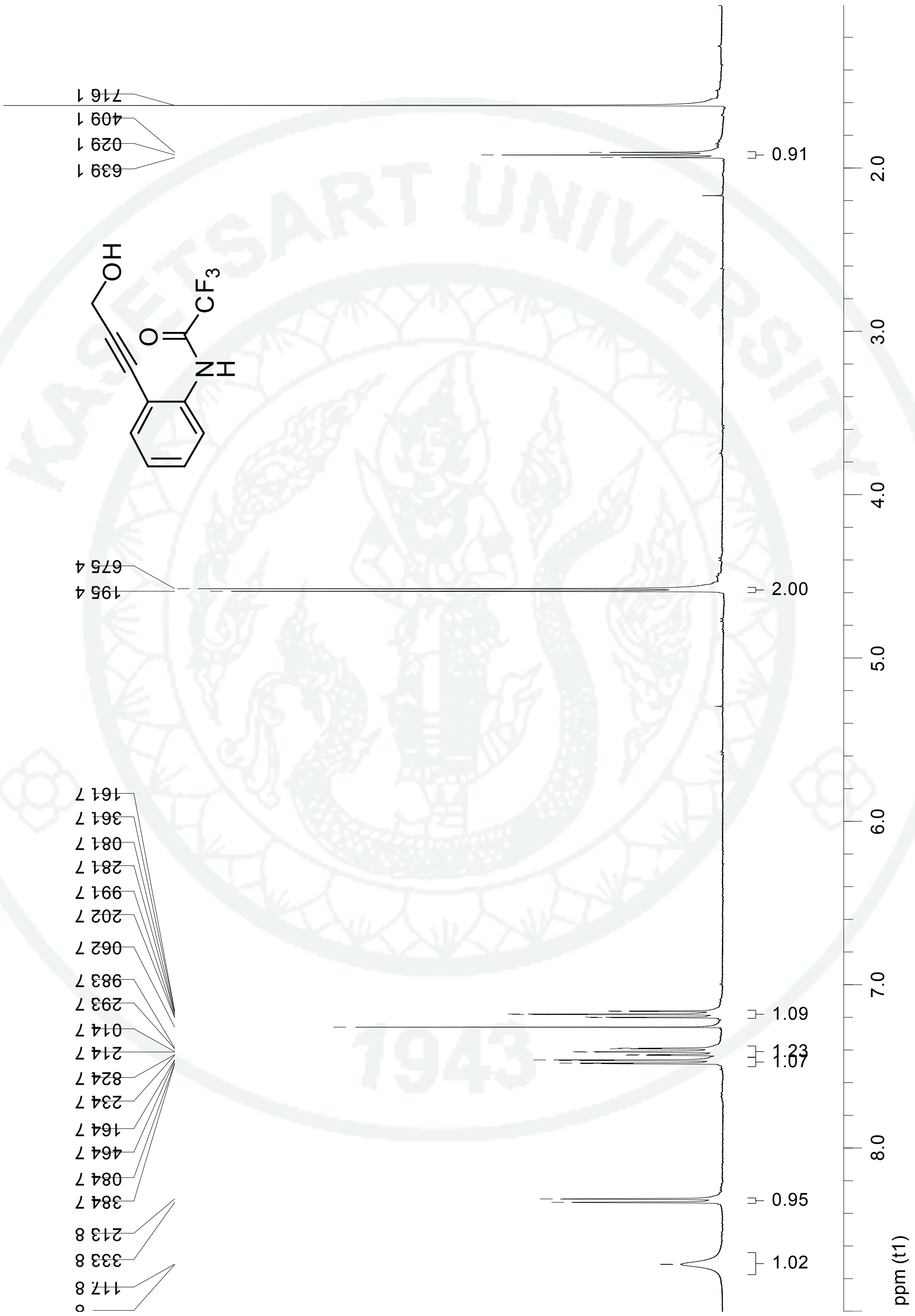


^{1}H NMR of 2,2,2-trifluoro-N-(2-(3-hydroxyprop-1-ynyl)phenyl) acetamide (41) in $CDCl_3$



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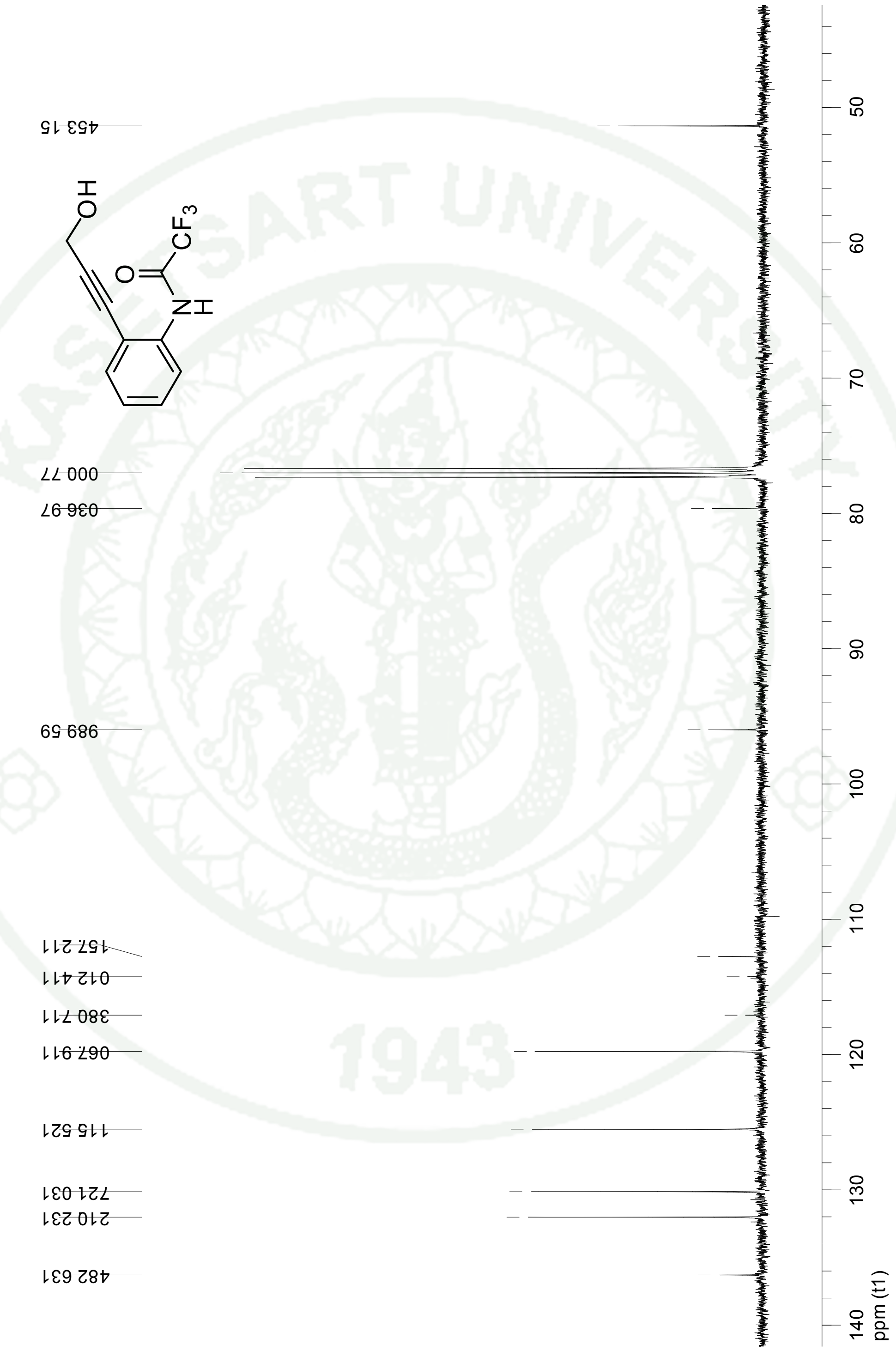
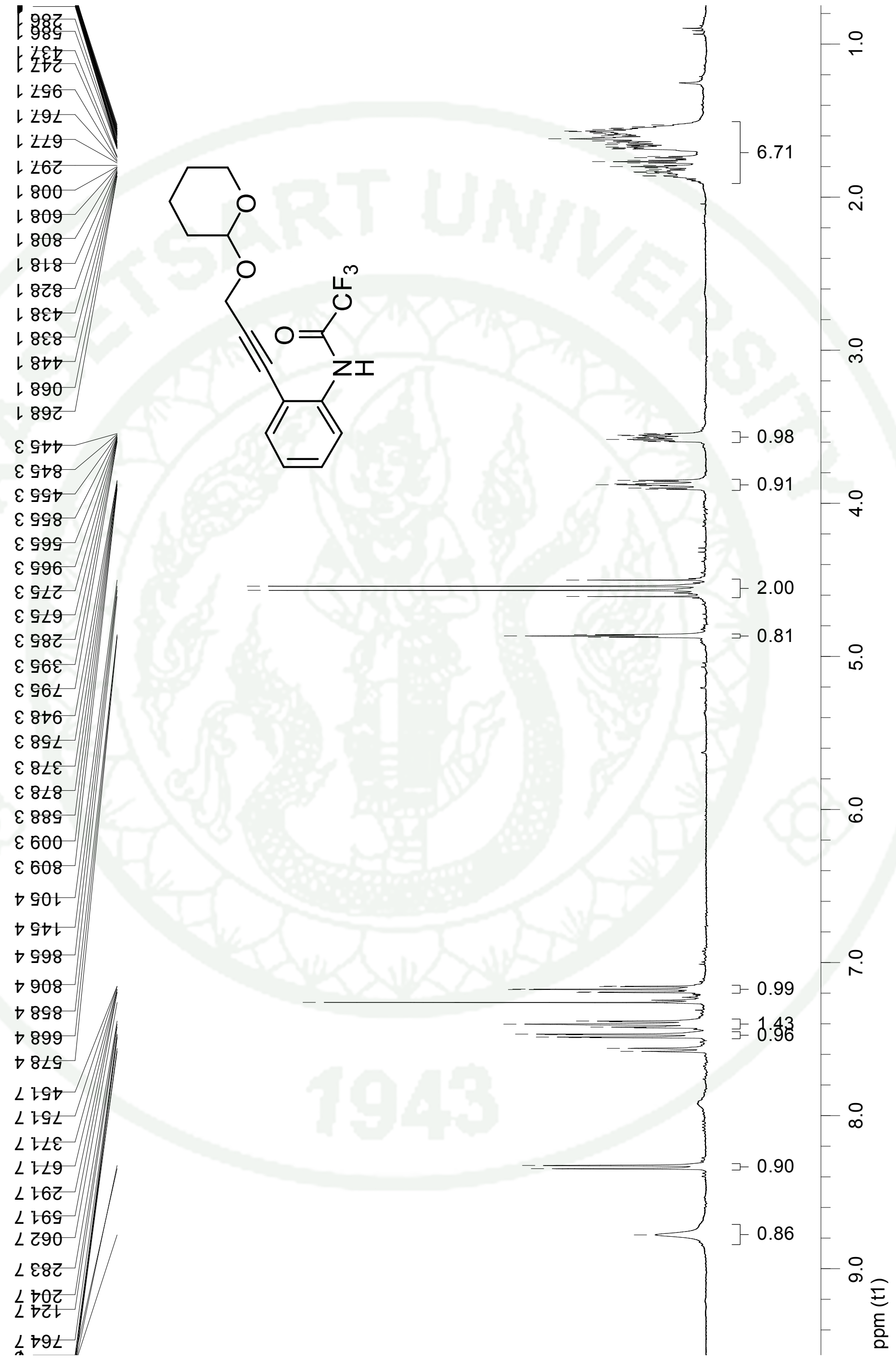


^{1}H NMR of 2,2,2-trifluoro-N-(2-(3-(tetrahydro-2H-pyran-2-yloxy)prop-1-ynyl)phenyl)acetamide (41a) in $CDCl_3$



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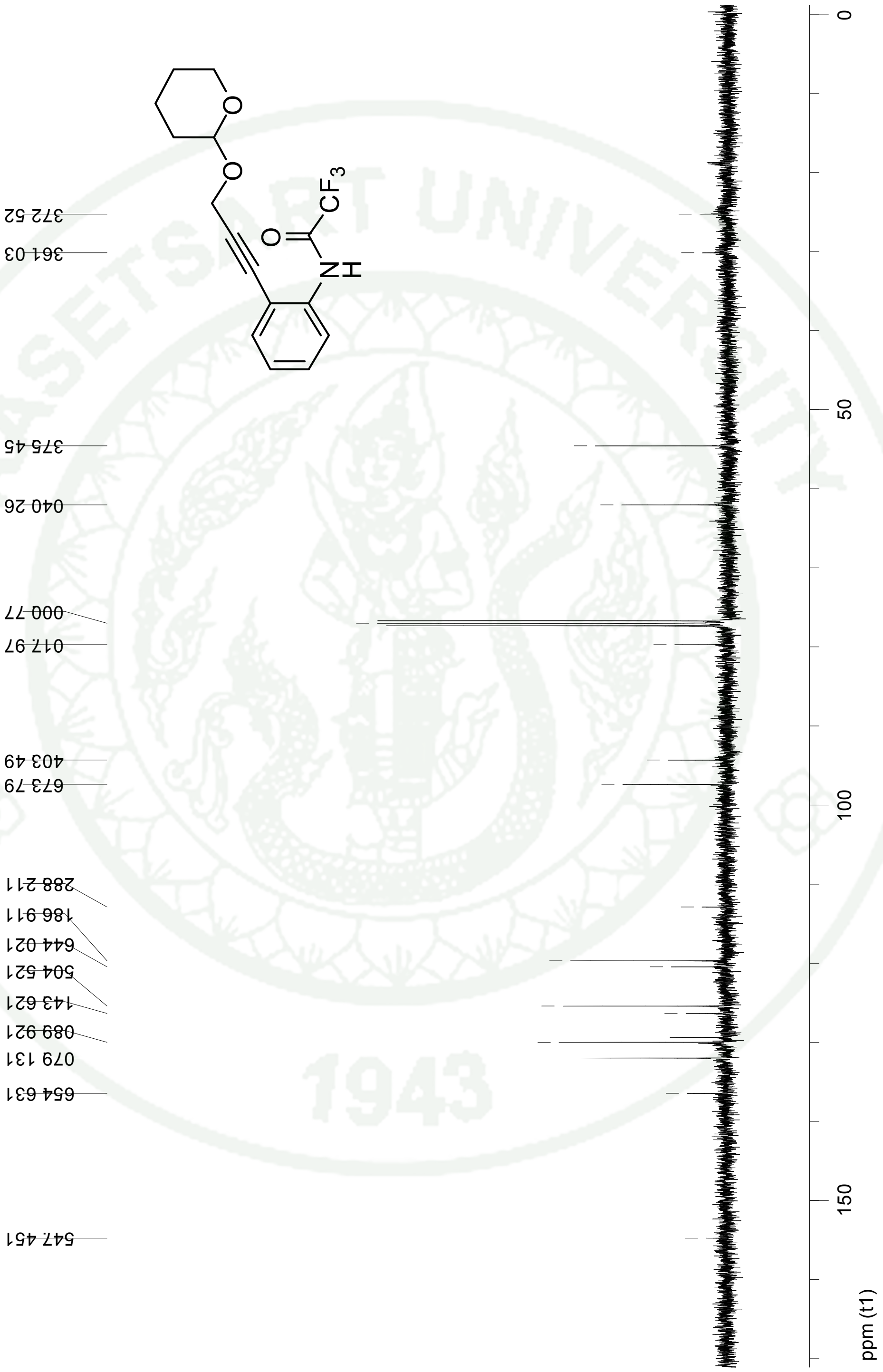
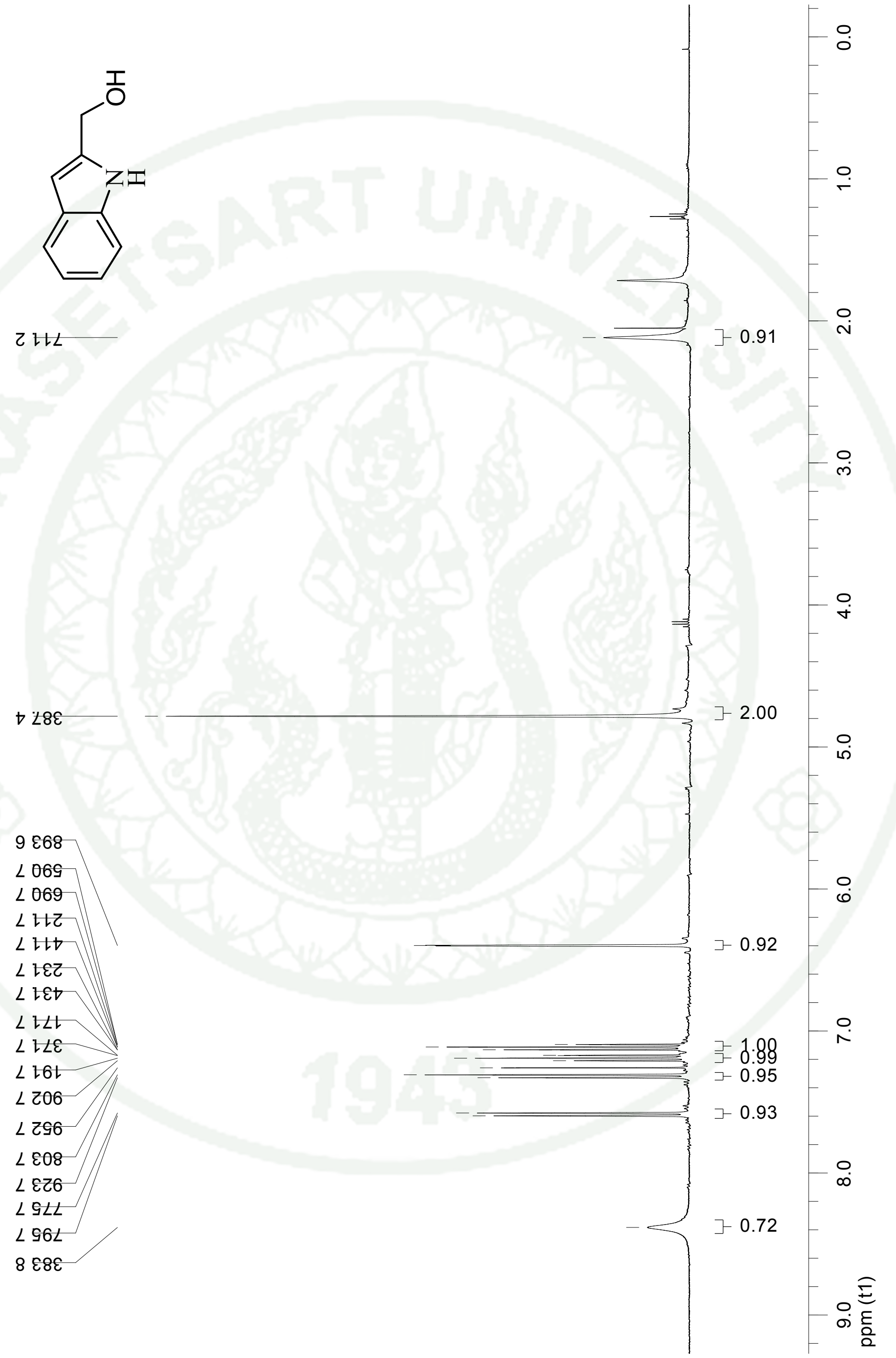


^{1}H NMR of (1H-indol-2-yl)methanol (42) in $CDCl_3$



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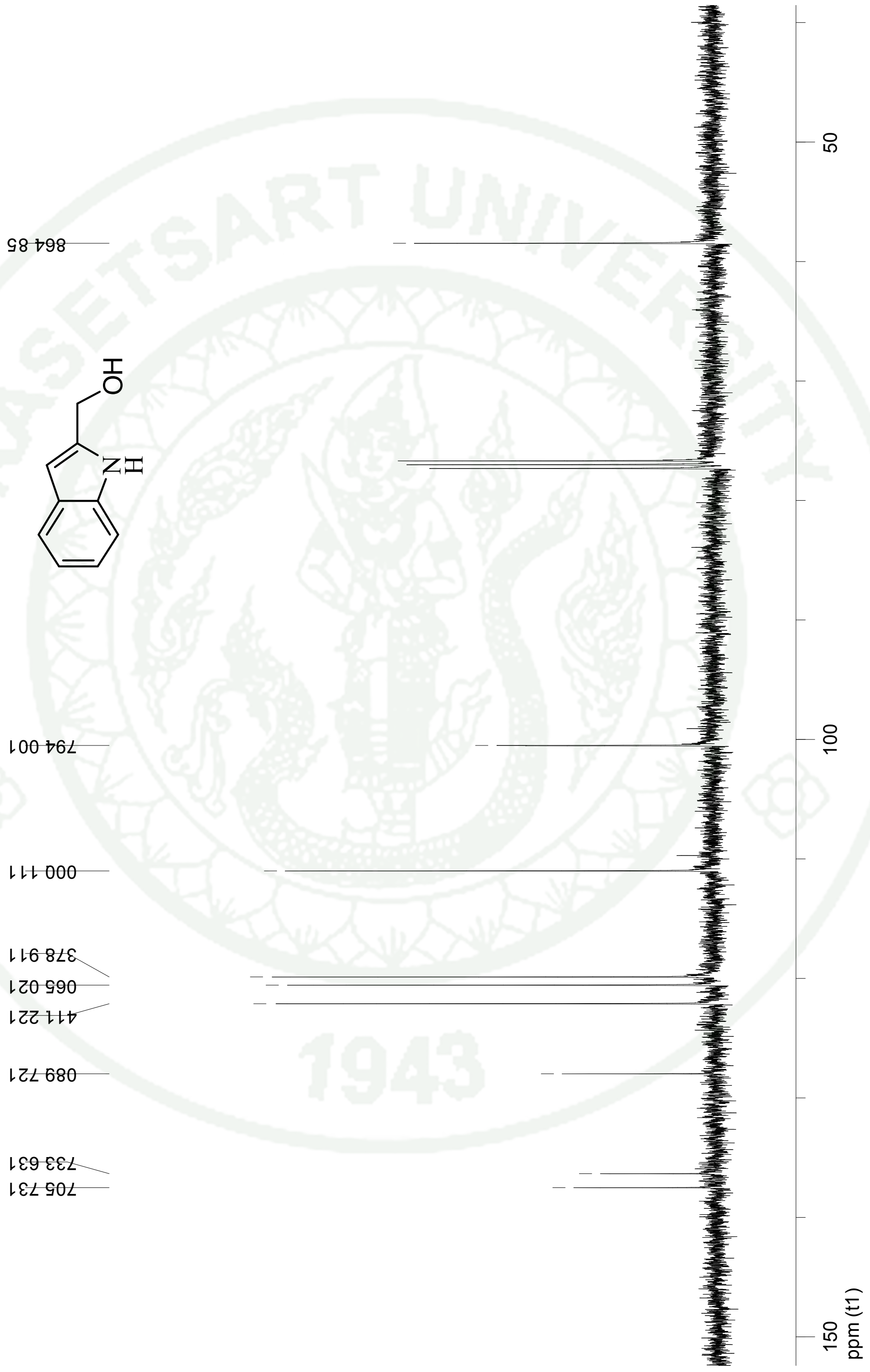

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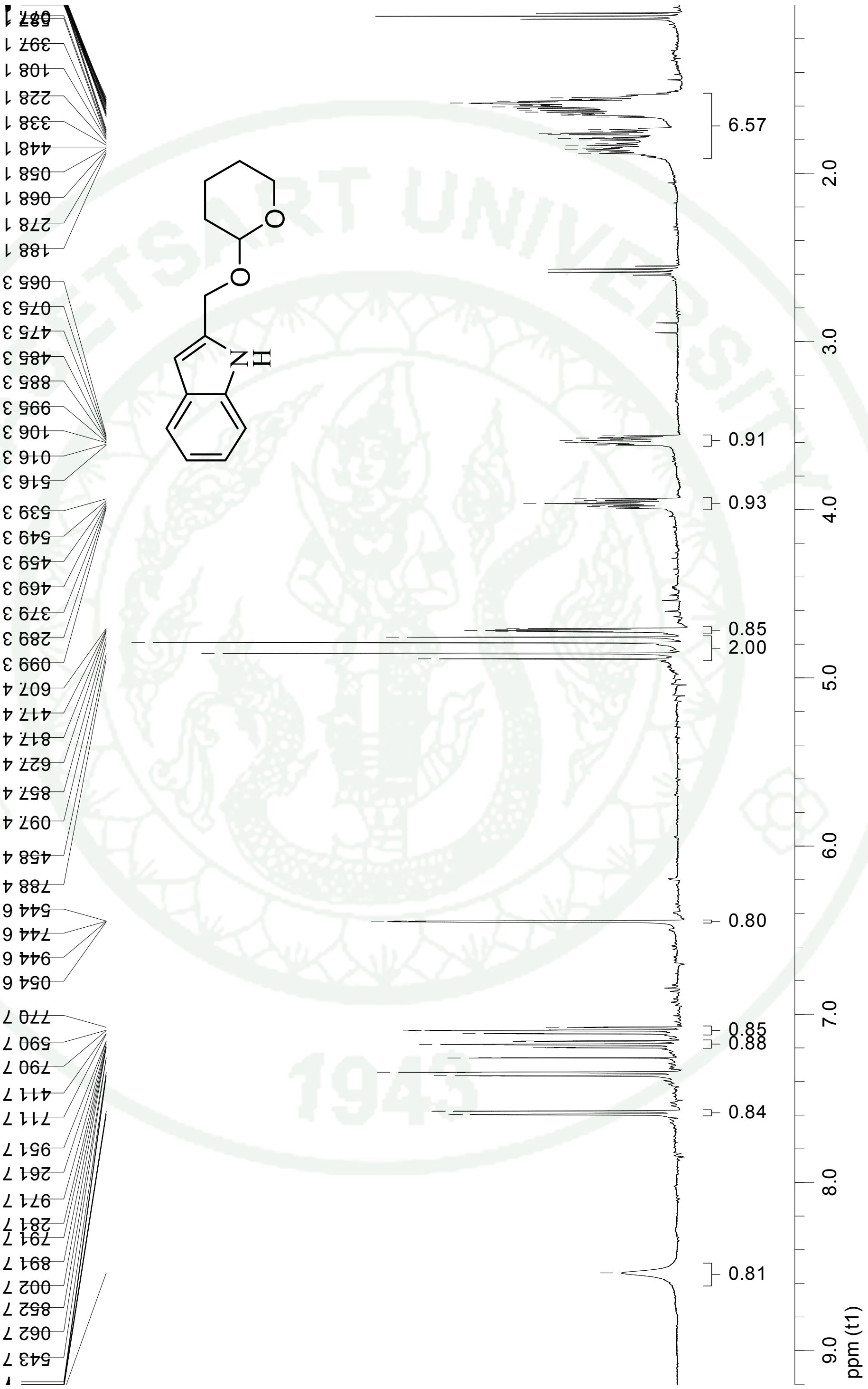

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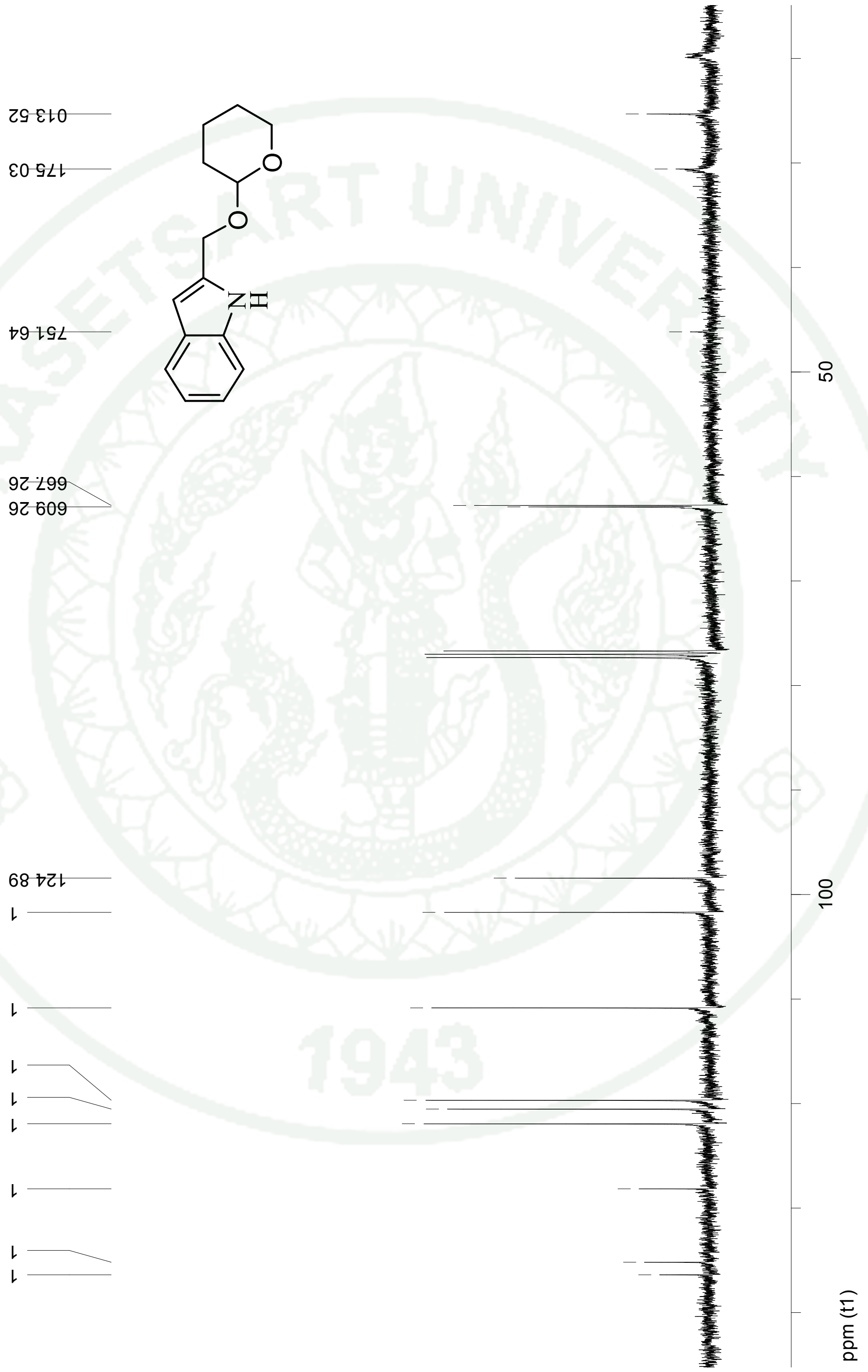
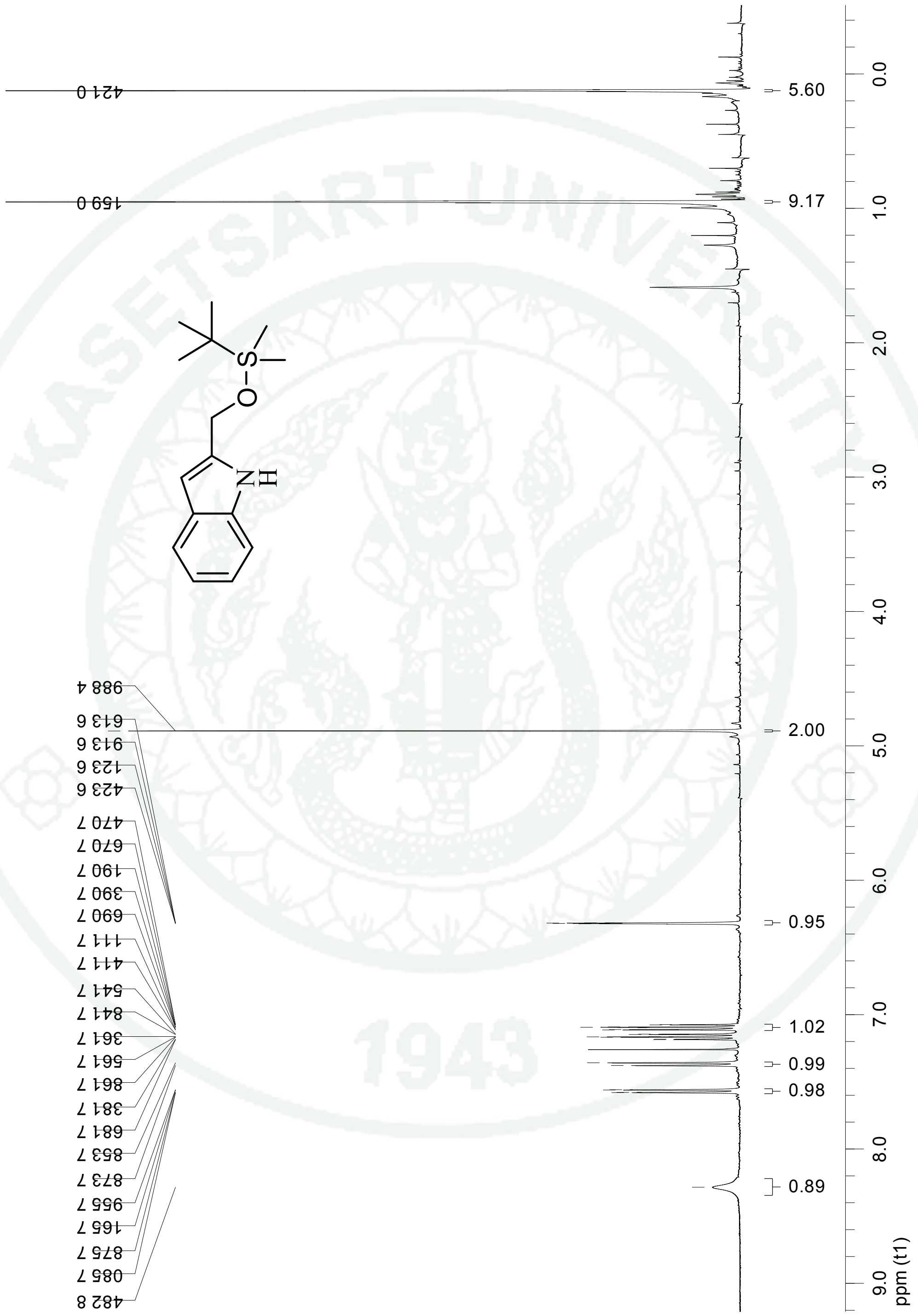


^{1}H NMR of 2-((*tert*-butyldimethylsilyloxy)methyl)-1H-indole (42b) in $CDCl_3$



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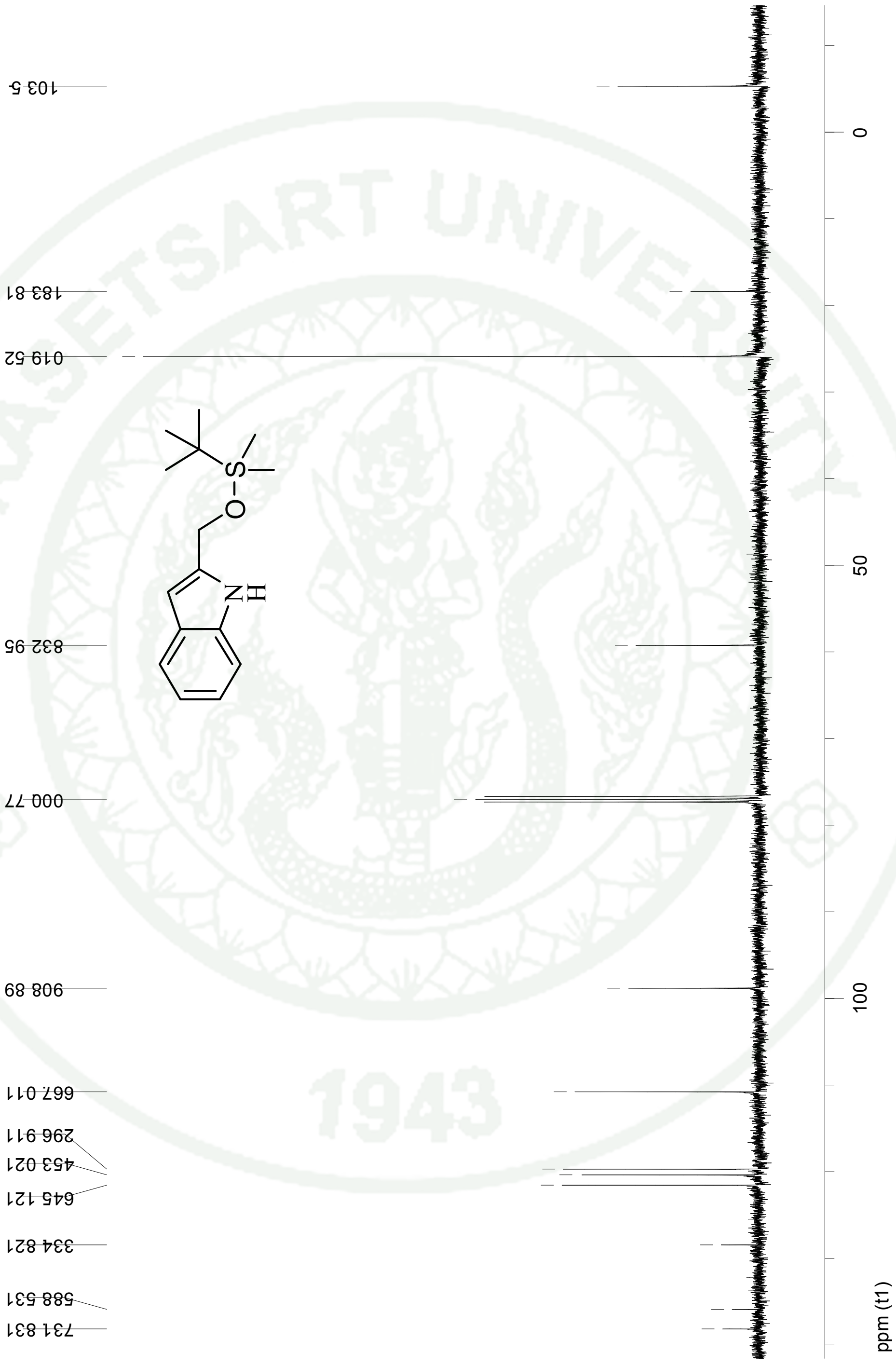
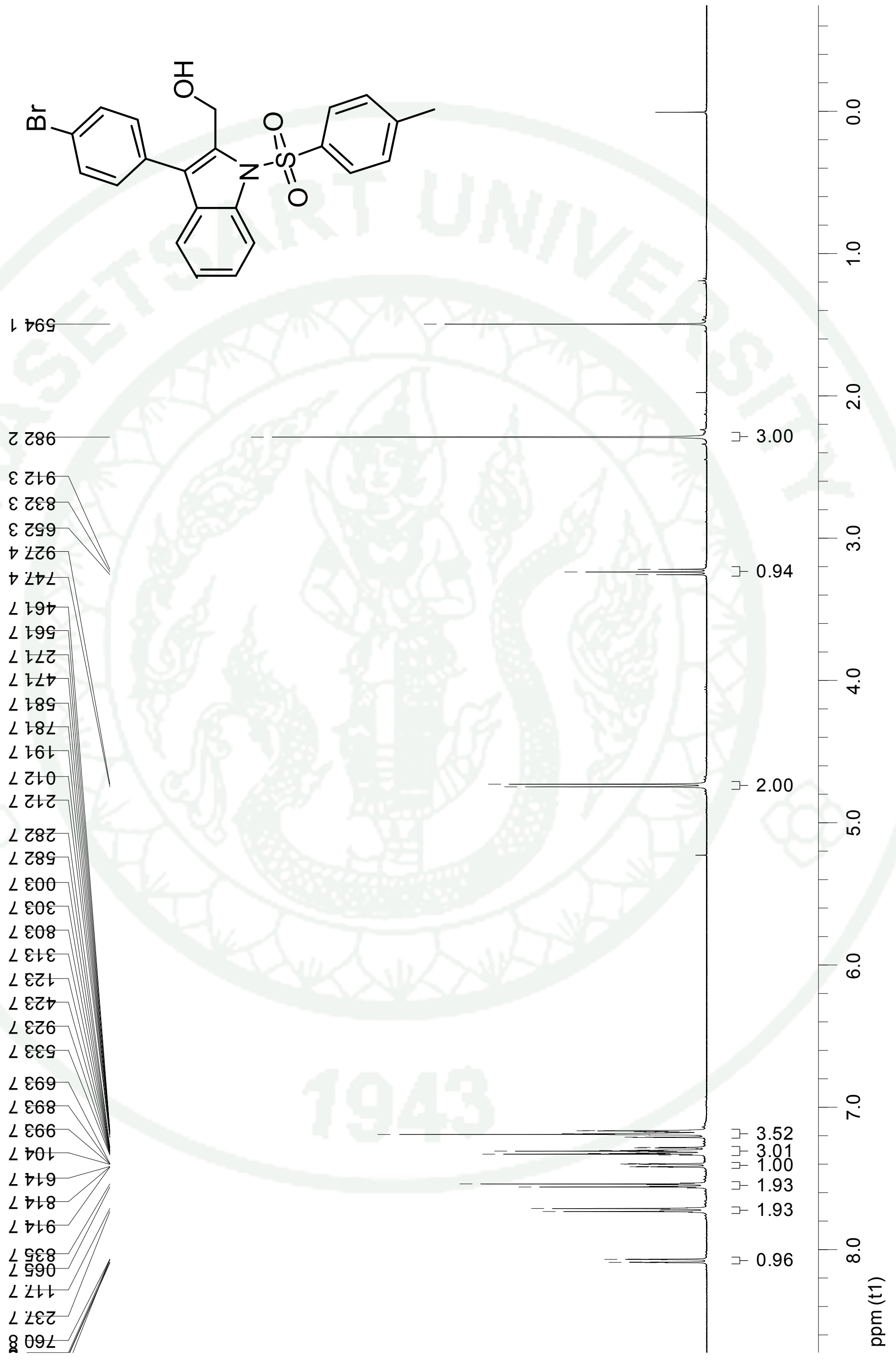


^{1}H NMR of (3-(4-bromophenyl)-1-tosyl-1H-indol-2-yl)methanol (43) in $CDCl_3$



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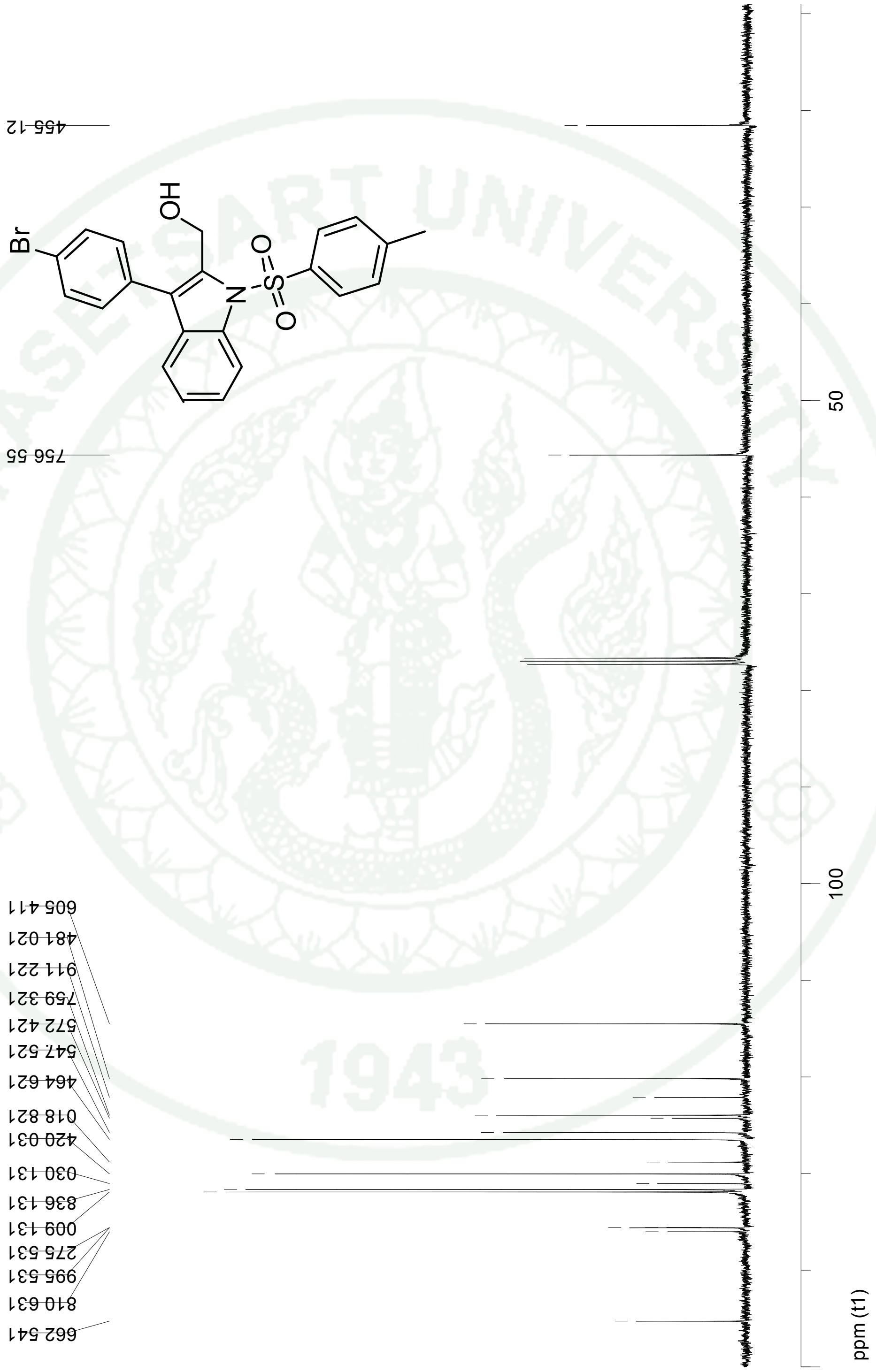

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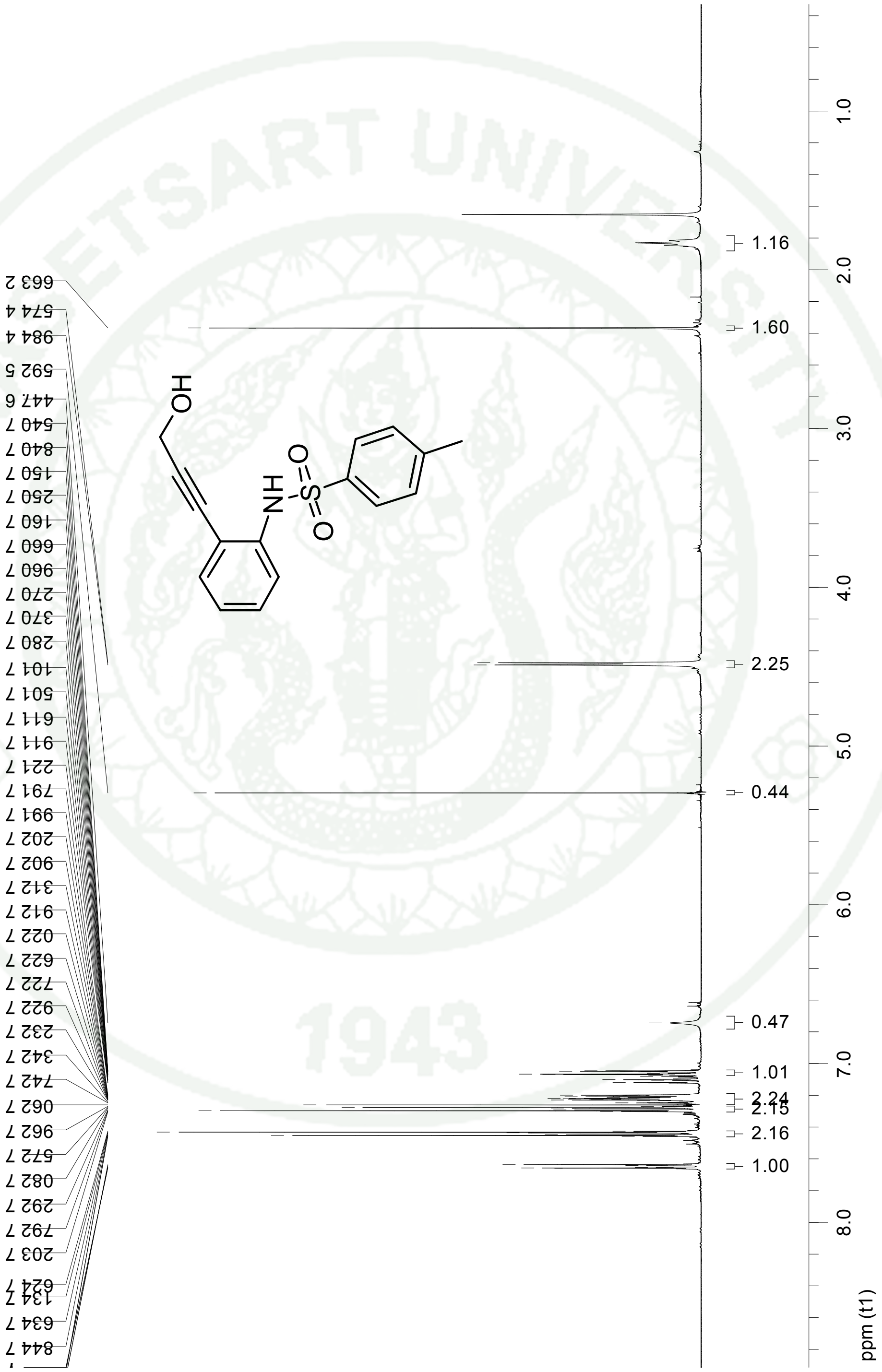

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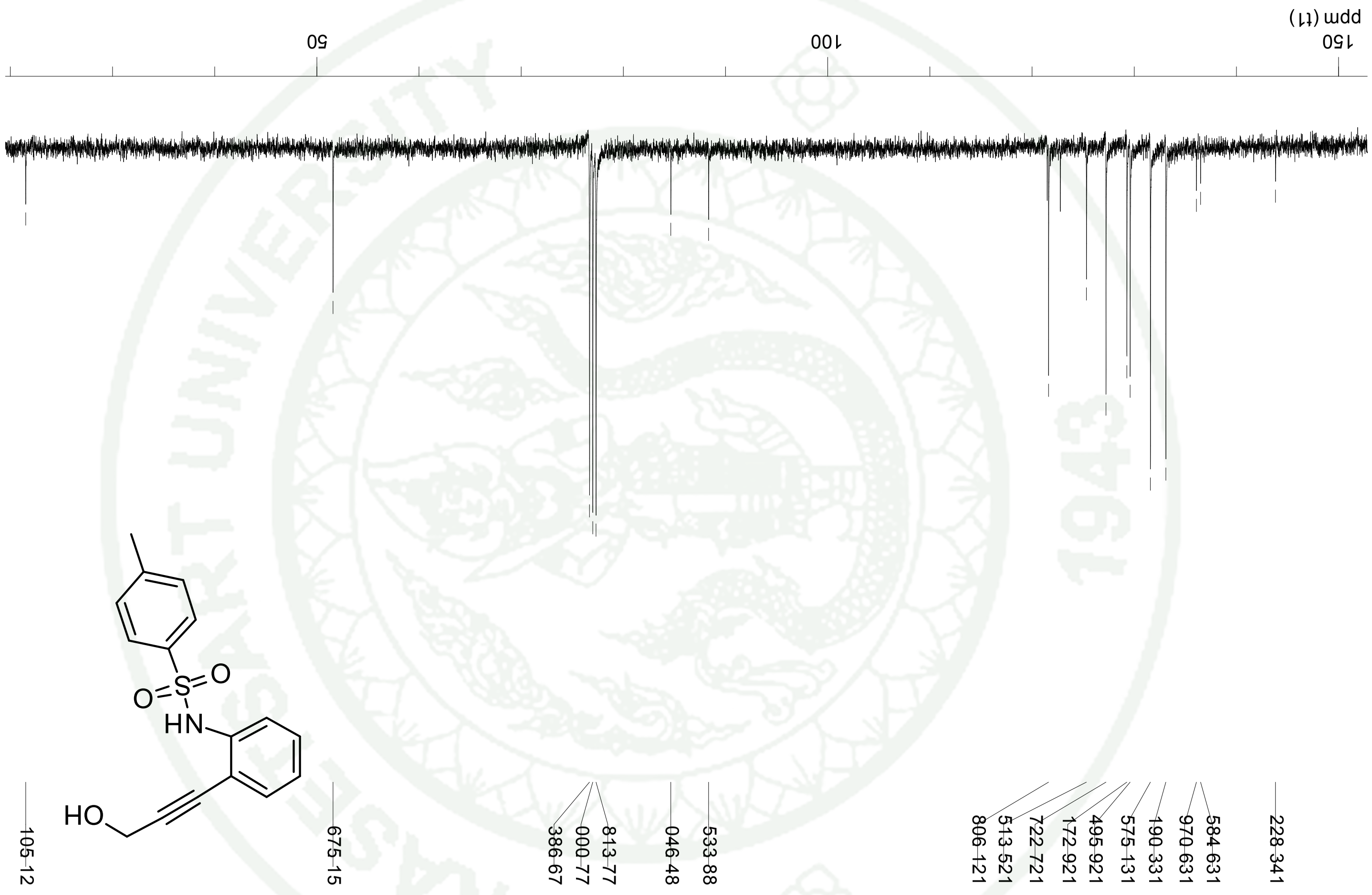

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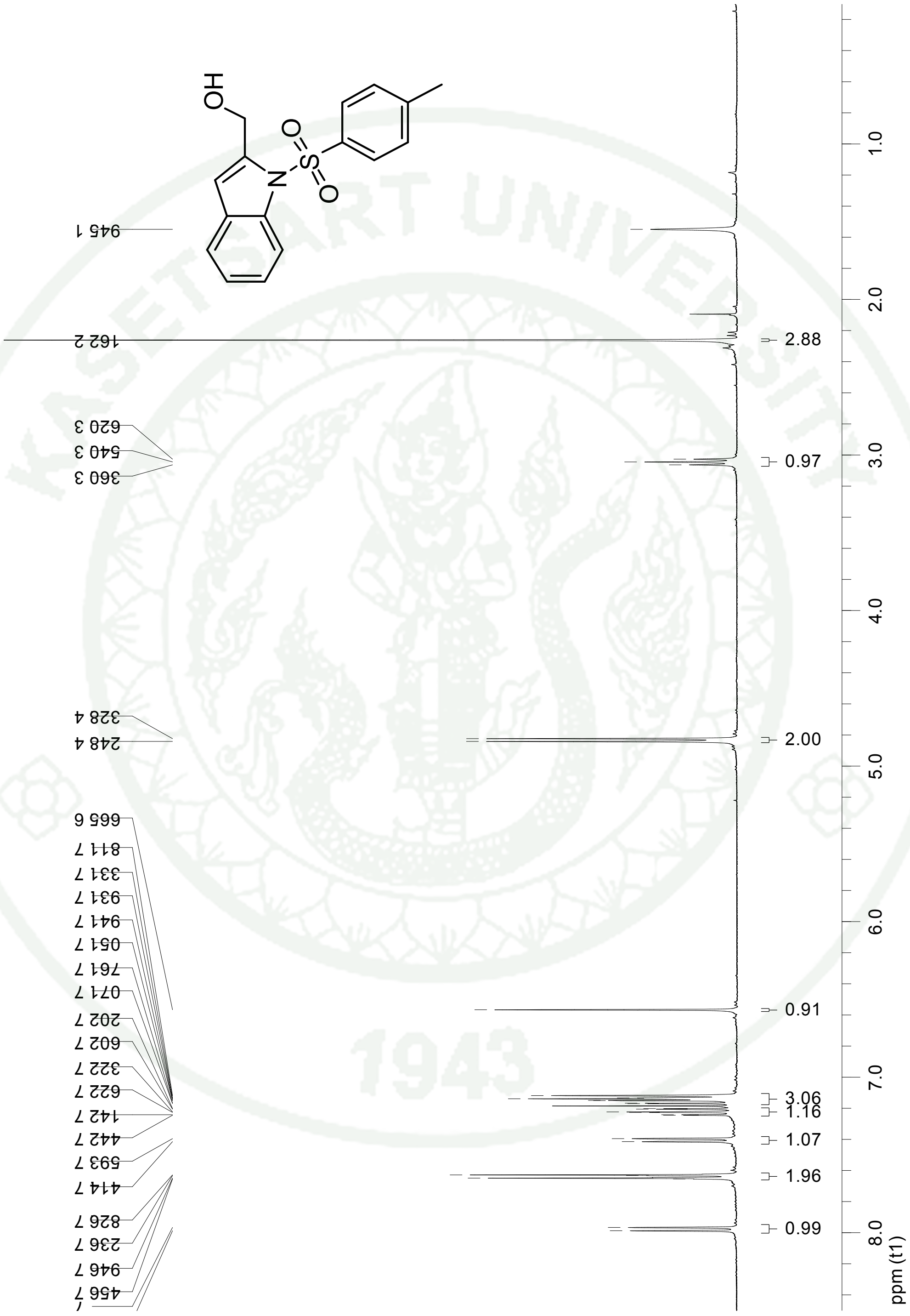
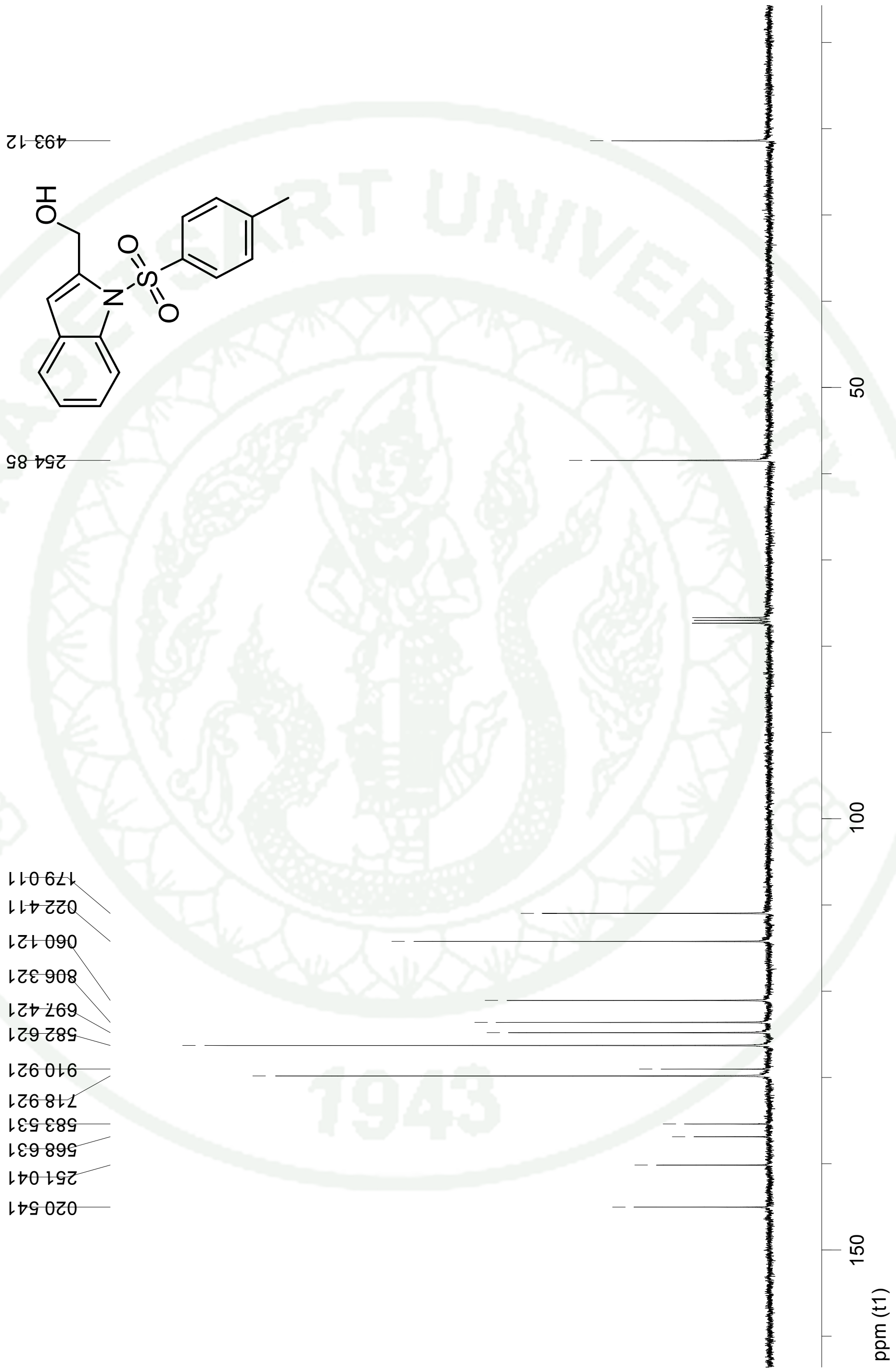
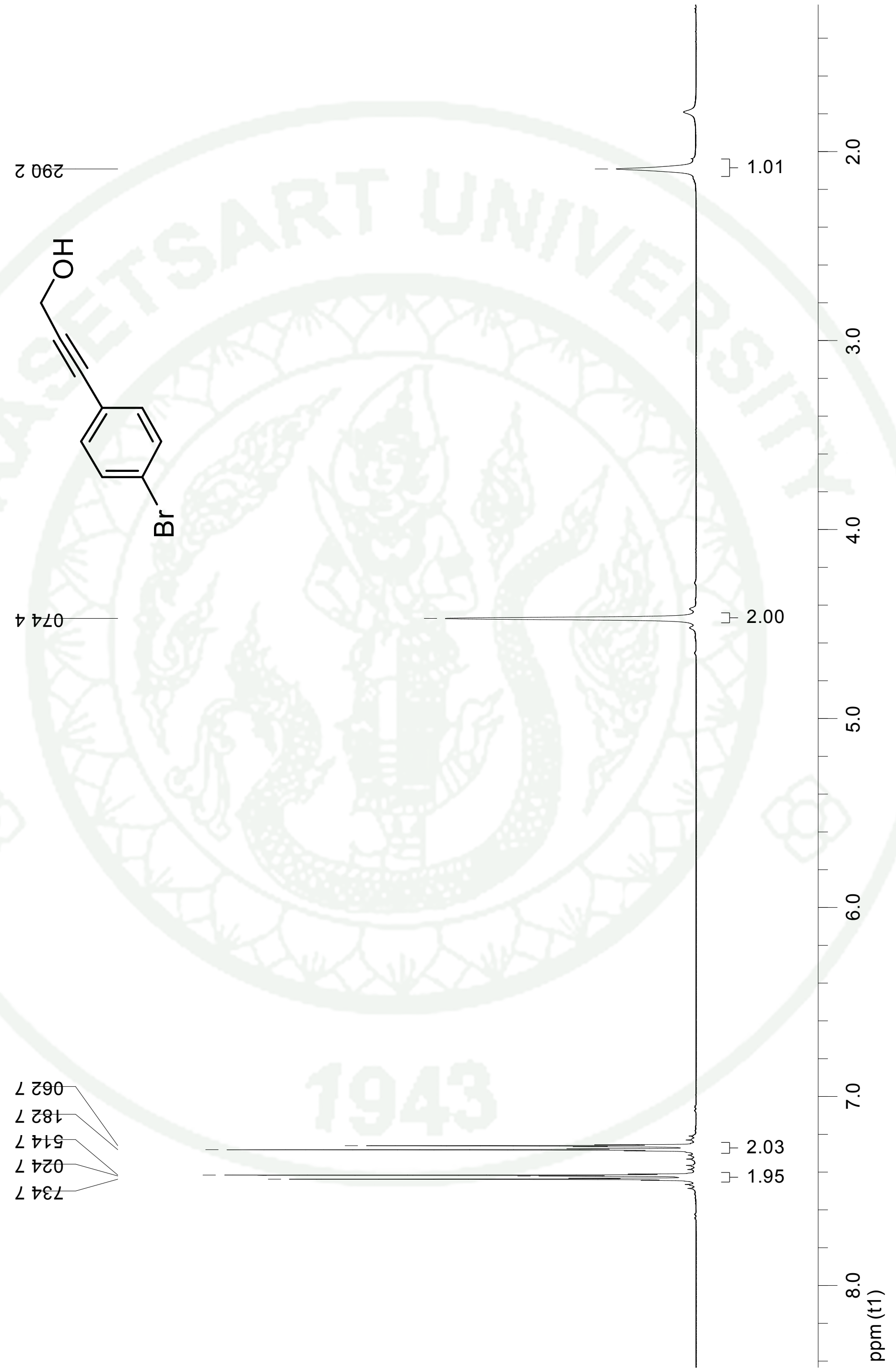


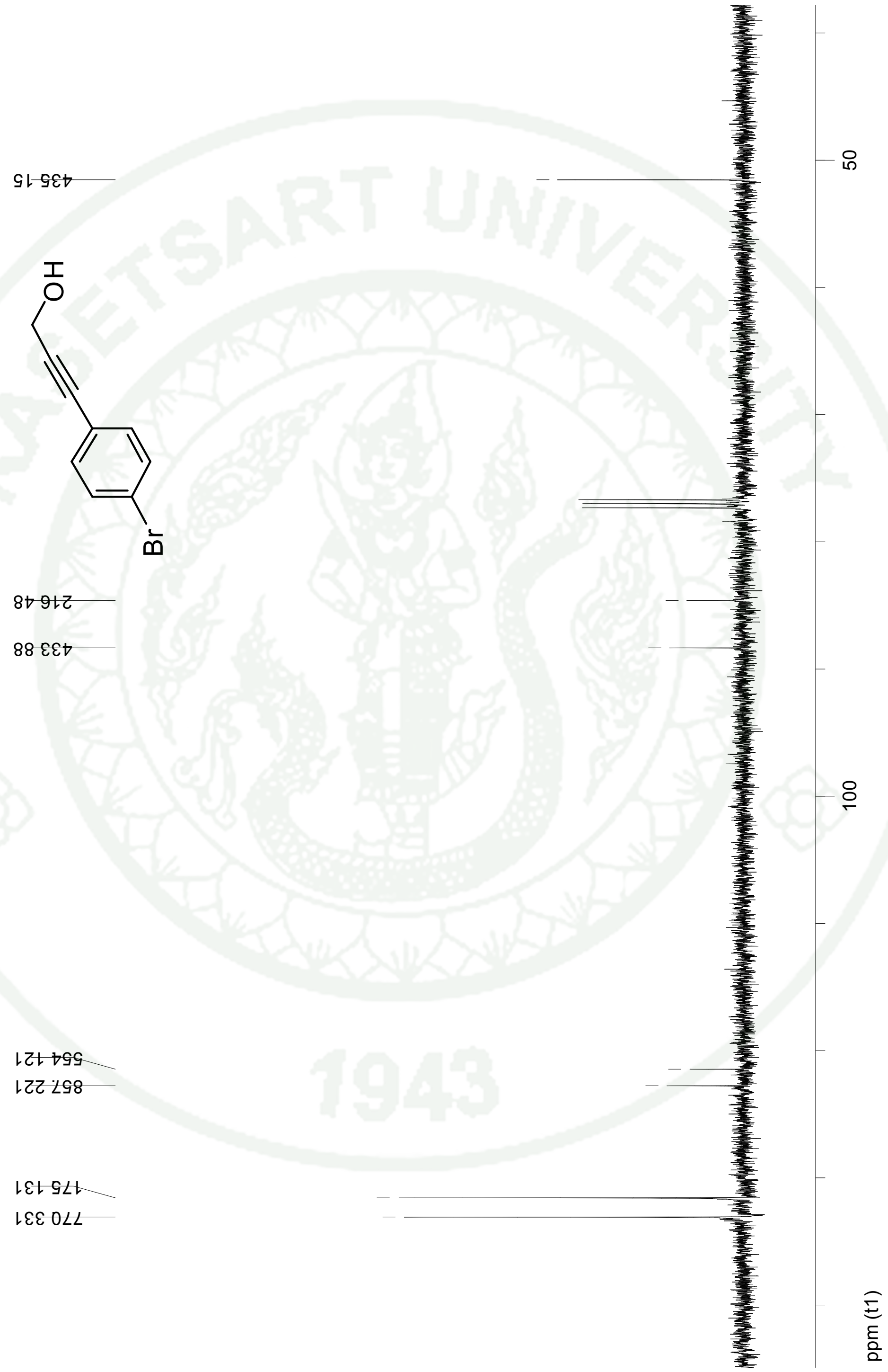
^{13}C NMR of (1-tosyl-1H-indol-2-yl)methanol (45) in $CDCl_3$



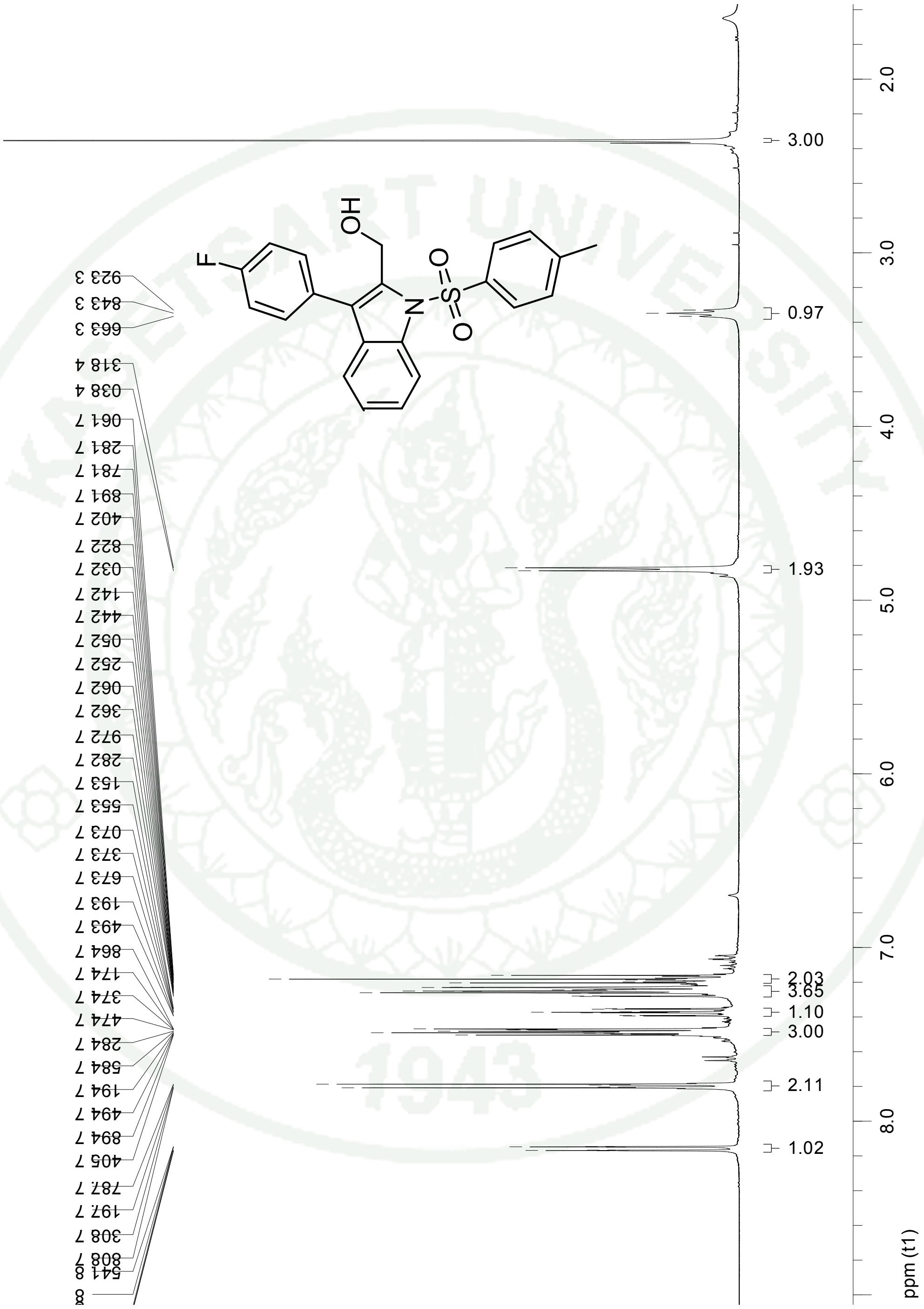
^{1}H NMR of 3-(4-bromophenyl)prop-2-yn-1-ol (46) in $CDCl_3$



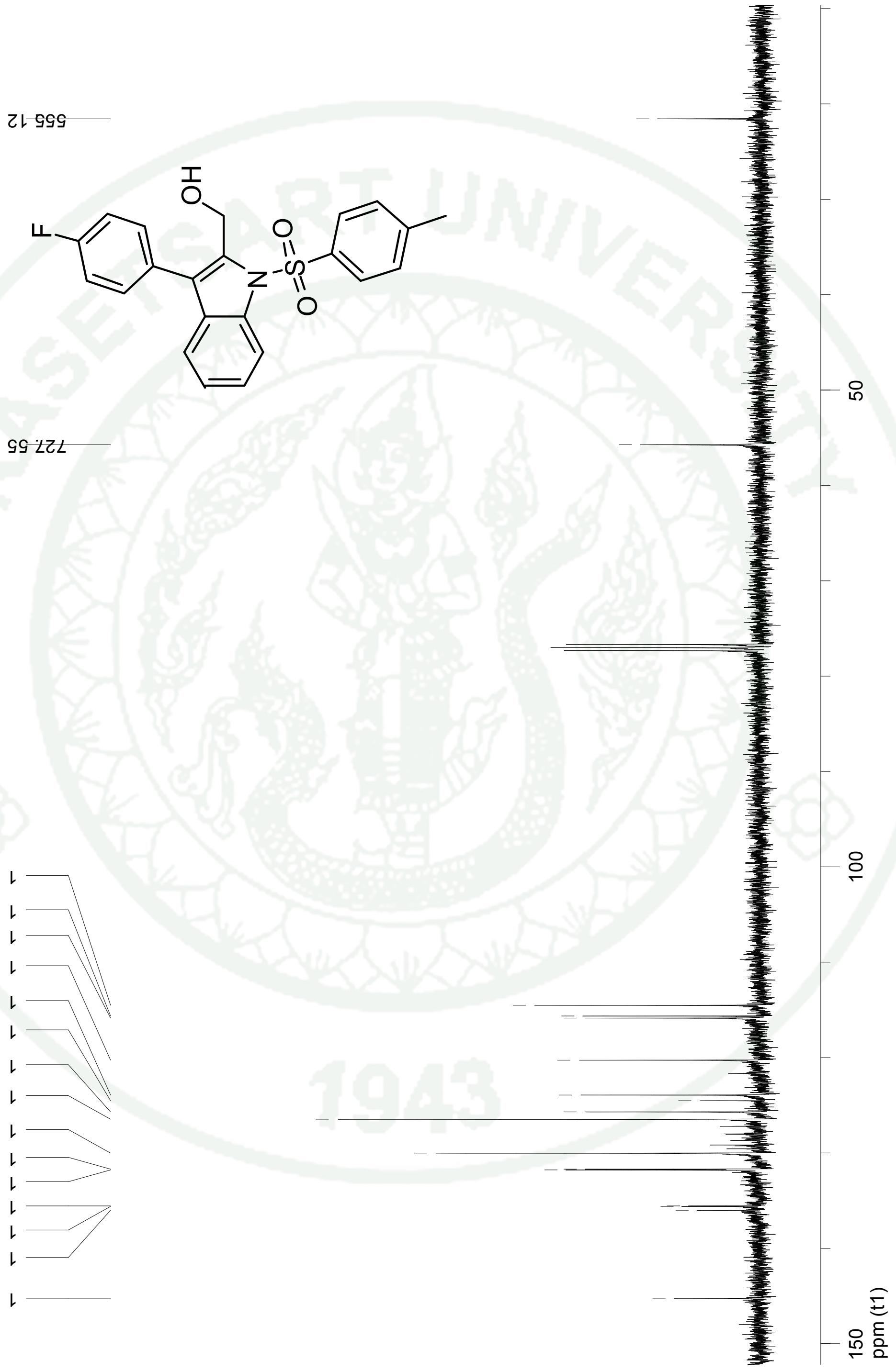
^{13}C NMR of 3-(4-bromophenyl)prop-2-yn-1-ol (46) in CDCl$_3$



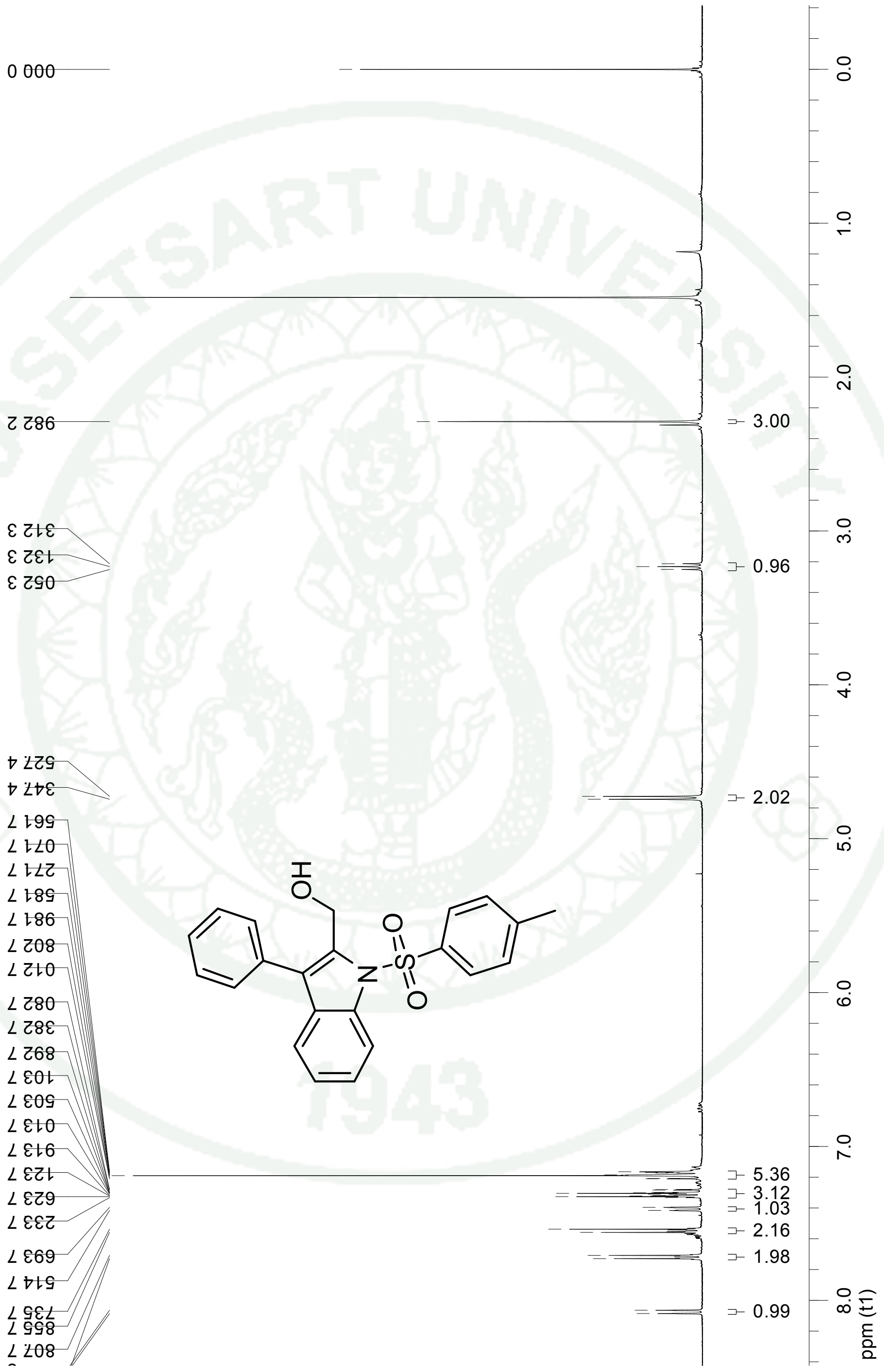
^{1}H NMR of (3-(4-fluorophenyl)-1-tosyl-1H-indol-2-yl)methanol (47) in $CDCl_3$



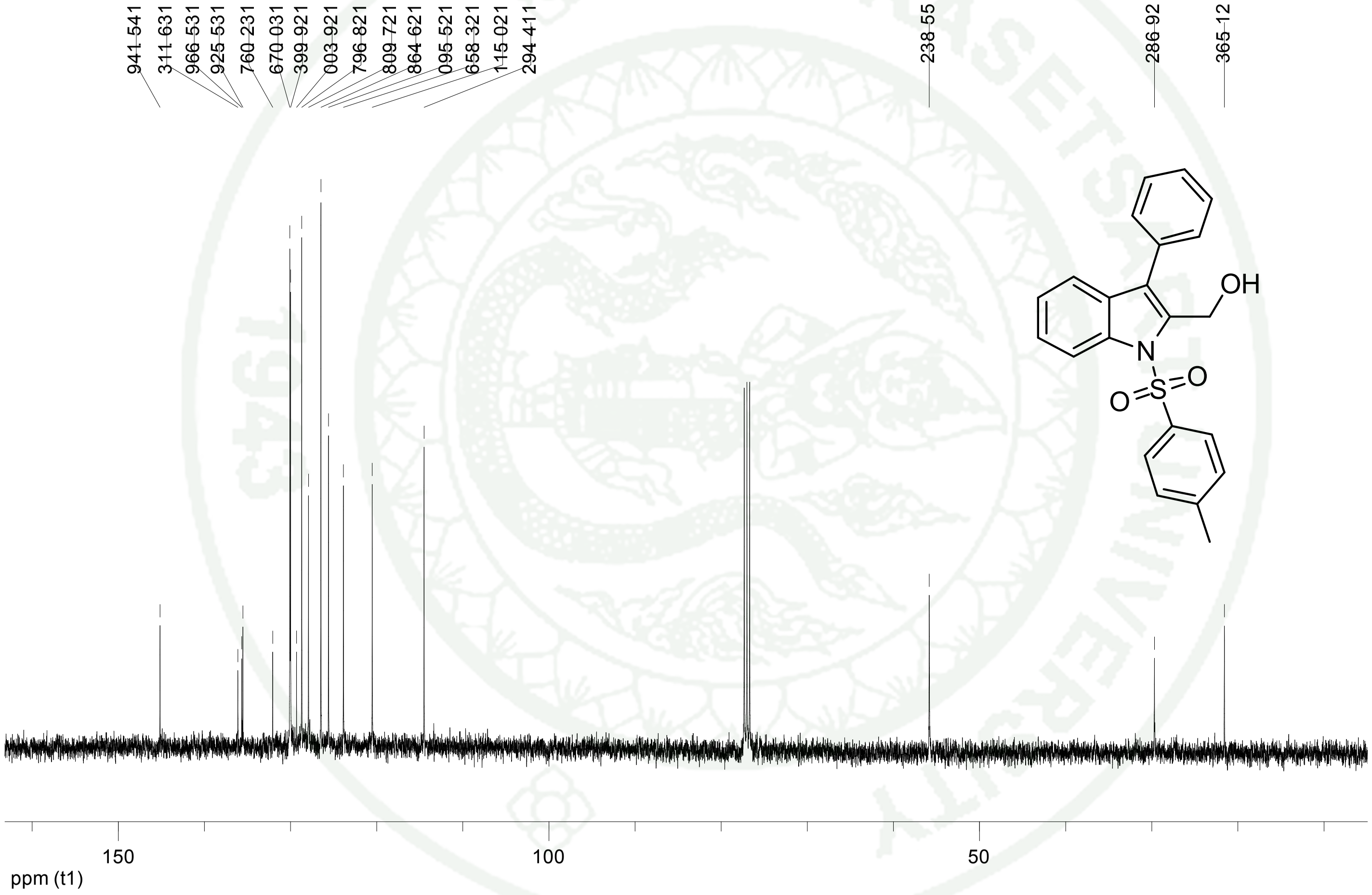
^{13}C NMR of (3-(4-fluorophenyl)-1-tosyl-1H-indol-2-yl)methanol (47) in $CDCl_3$



^{1}H NMR of (3-phenyl-1-tosyl-1H-indol-2-yl)methanol (48) in $CDCl_3$



^{13}C NMR of (3-phenyl-1-tosyl-1H-indol-2-yl)methanol (48) in CDCl$_3$



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