SYNTHETIC DEVELOPMENT FOR C-H DIRECT ACYLATION OF 1-SUBSTITUTED PHTHALAZINES

BY

RUNGSIMA HADSARUNG

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
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ENTITLED

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was approved as partial fulfillment of the requirements for the degree of Master of Science (Chemistry)

on December 8th, 2022

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ABSTRACT

An efficient and simple method for the regiospecific acylation of 1–substituted phthalazines is described in the presence of *tert*–butyl peroxybenzoate (TBPB) as an oxidant and $AlCl_3$ as an additive in dichloroethane (DCE) at 110 ˚C. The reaction involves a coupling reaction between 1–substituted phthalazines with aldehydes or alcohols as an acylating agent through an oxidative cross–dehydrogenative coupling (CDC). This strategy provides an alternative method for the acylation of electron–deficient heteroarenes. To illustrate the applicability of the acylated products, the new route for the synthesis of other functional groups for this class of compound was presented by using a simple chemical reaction that allowed further investigation of their potential biological activities.

Keywords: Acyls, Aldehydes, cross–dehydrogenative coupling (CDC), Heterocyclic compounds, Phthalazines

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I would like to thank the following people for all their support and help with this research. I would not have been able to succeed in my master's degree without them. First, I would like to thank my advisor Dr.Duangduan Chaiyaveij of the department of chemistry at Thammasat University and Dr.Jutatip Boonsombat at Chulabhorn Research Institute. They provided guidance, support, encouragement, and overall insights into this field throughout this project. Second, I appreciate Chulabhorn Research Institute for all lab facilities, and CRI staffs for IR and MS spectroscopic data. Third, I would also like to thank to the Faculty of Science and Technology, Thammasat University for financial support, all lab facilities as well as TU staff for NMR spectroscopic data.

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Rungsima Hadsarung

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LIST OF ABBREVIATIONS

Symbols/Abbreviations	Terms
acac	Acetylacetone
Aliquat 336	Tricaprylylmethylammonium chloride
Ar	Aromatic ring
[Bmim]BF_4	1-Butyl-3-methylimidazolium tetrafluoroborate
Bn	Benzyl group
BPO	Benzoyl peroxide
CDC	Cross-dehydrogenative coupling
conc. HCl	Concentrated hydrochloric acid
$Cu(OTf)_2$	Copper(II) triflate
CFL	Compact Fluorescent Lamp
Cy	Cyclohexyl group
DTBP	*Di-tert*-butyl peroxide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMSO	Dimethyl sulfoxide
DMF	Dimethylformamide
Et	Ethyl group
EtOAC	Ethyl acetate
g	Gram
Hz	Hertz
IL	Ionic liquid
i–Pr	Isopropyl group
i–Bu	Isobutyl group
mCPBA	meta-Chloroperoxybenzoic acid
mp	Melting point
Me	Methyl group

MHz	Megahertz
mg	Milligram
mA	Milliampere
NCS	*N*-Chlorosuccinimide
OMe	Methoxy group
OTf	Trifluoromethylsulfonyl group (triflate group)
PCC	Pyridinium chlorochromate
Ph	Phenyl group
Pr	Propyl group
rt	Room Temperature
TBAB	Tetrabutylammonium bromide
TBPB	*tert*-butyl peroxybenzoate
TBHP	*tert*-butyl hydroperoxide
TMS	Tetramethylsilane
TFA	Trifluoroacetic acid
$TMSN_3$	Trimethylsilyl azide
TLC	Thin-layer chromatography
Temp	Temperature
δ	Chemical shift (ppm)

CHAPTER 1
INTRODUCTION

1.1 Phthalazine compounds and the acylation of nitrogenous heterocycles

Phthalazines or 2,3-Benzodiazine are the bicyclic nitrogen-containing heterocyclic compounds. The core structure is similar to naphthalene, but there are nitrogen atoms at 2–and 3–positions on the aromatic ring. Phthalazines play an essential role in organic chemistry and medicinal researches. They are often used as intermediates for synthesis of other compounds and showed great potential for various biological activities such as anti–convulsant, anti–inflammatory, antitubercular, antihypertensive, analgesics, antifungal, antibacterial, anticancer, and vasorelaxant activities.(Gaurav et al., 2010; J, 2019) These potentials result in the use of phthalazine scaffold as an component for designing and developing novel drugs and bioactive compounds. The example of the phthalazine derivatives as commercial drugs are included: MY−5445 as a phosphodiesterase type 5 inhibitor (PDE5 inhibitor); Vatalanib as a small molecule protein kinase inhibitor to treat cancer; Hydralazine as a molecule used for the treatment of high blood pressure and heart failure; Budralazine as a vasodilator; Olaparib as a medicine for the treatment of advance ovarian cancer in adult, and Azelastine as a molecule used to treat hay fever and allergic conjunctivitis (Figure 1).

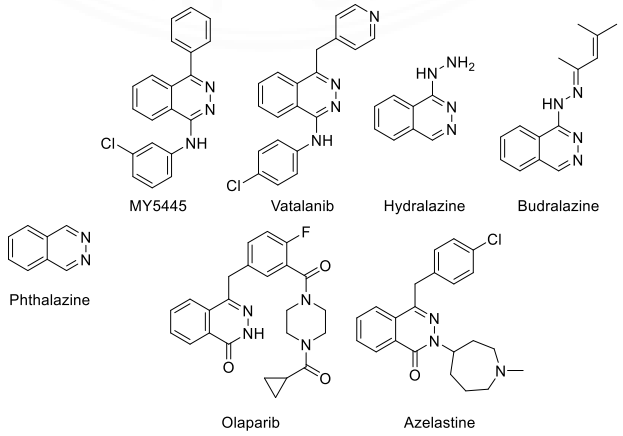


Figure 1. The chemical structure of phthalazine and their commercial drugs

The acylated heteroarenes have gained more attention from medicinal chemistry and biochemistry since these compounds are present in various biologically active natural products and synthetic drugs (Figure 2).(Ali, Behera, Guin, & Patel, 2015; Chen et al., 2015)

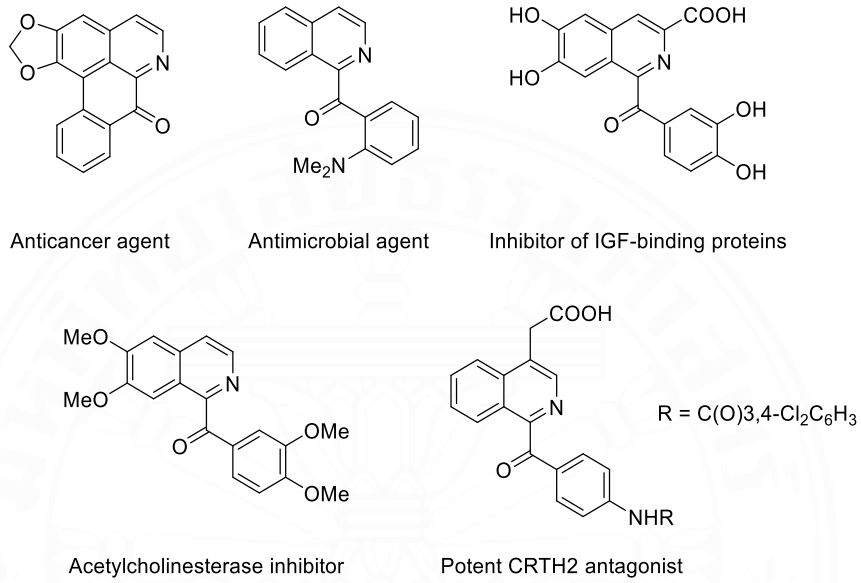
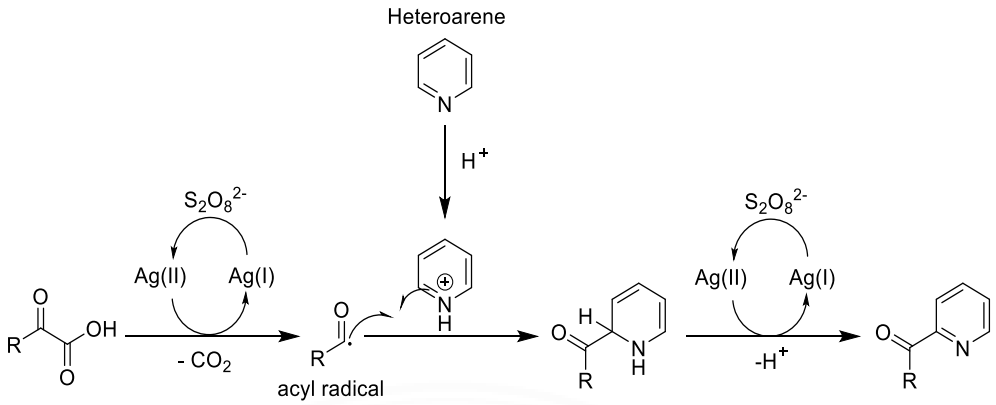


Figure 2. Bio–active of acylated *N*–heterocycle compounds

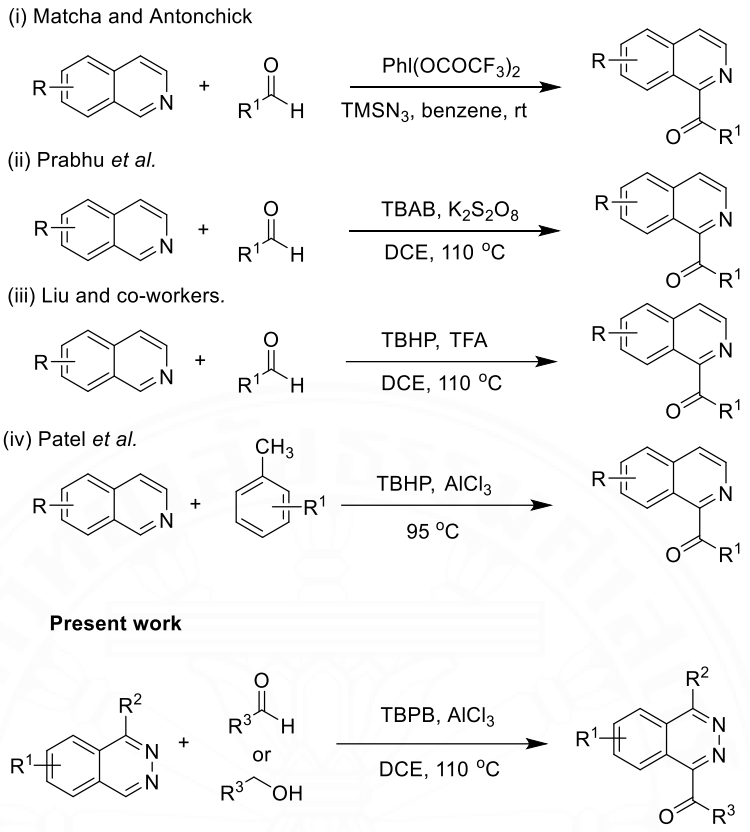
In the past few years, many researchers have attempted to develop methods for the direct acylation of heteroaromatic compounds under atom economic and shorter route conditions instead of the traditional synthetic strategies possessing multiple steps. Among the novel methods, the Minisci reaction is the most commonly used.(Matcha & Antonchick, 2013) The mechanism of the Minisci acylation reaction consists of the generation of an acyl radical from acyl radical sources at the initial step.(Wang & Zeng, 2019) Aldehydes and α–keto acids are widely used to serve as acyl radical precursors in this reaction. Then the protonated *N*-heteroarene is attached by acyl radical, followed by deprotonation and further oxidation, respectively (Scheme 1).(Wang & Zeng, 2019) However, this reaction has some drawbacks such as harsh reaction conditions, low site selectivity, incomplete conversion of the substrate to the corresponding product, limited substrate scope, and the use of metals in large amount.(Matcha & Antonchick, 2013)



Scheme 1. Classical Minisci acylation of heteroarene under oxidative conditions (Fontana, Minisci, Nogueira Barbosa, & Vismara, 1991)

Recently, the mild and metal–free reaction conditions for the acylation of *N*–heterocycles have been reported by Matcha and Antonchick.(Matcha & Antonchick, 2013) They presented a metal–free CDC of *N*–heterocycles with aldehydes using hypervalent iodine reagents ($PhI(OCOCF_3)_2$) and $TMSN_3$. Prabhu *et al*. reported the acylation of isoquinolines, quinolines, and quinoxaline with aldehydes using TBAB and $K_2S_2O_8$.(Siddaraju, Lamani, & Prabhu, 2014) Liu and co–workers employed TBHP/TFA and aldehydes in dichloroethane for the oxidative CDC of *N*–heterocycles under metal–free conditions.(Chen et al., 2015) In the same year, Patel *et al*. carried out the regiospecific benzoylation of *N*–heterocycles with methylbenzenes in the presence of the oxidant TBHP and the catalyst $AlCl_3$.(Ali et al., 2015) In these reports, they demonstrated that oxidant and acidic additives are essential in the acylation reactions of electron deficient-heterocycle (Scheme 2).

Nevertheless, most of the previously reported for the acylation of *N*–heterocycles, there are barely studied using the phthalazine compounds as the starting material. In continuation of our work in developing a method for the synthesis of phthalazine derivatives and biologically active compounds(Hadsarung et al., 2022), herein we describe the acylation of 1–substituted phthalazines under mild, simple, and cost-effective conditions. We envisaged that the direct acylation of phthalazines will expand the scope of the acylation of electron–deficient nitrogen heteroarenes and could generate novel bioactive compounds.



Scheme 2. Literature reports and our approaches for the direct acylation of 1–substituted phthalazines

1.2 Objectives

To synthesize acyl derivatives of phthalazine compounds using a simple operational procedure.

To develop an efficient, mild, and simple method for the regiospecific acylation of phthalazine derivatives.

To present the alternative route and expand the scope for acylation of electron–deficient *N*–heterocycles.

1.3 Scope of research

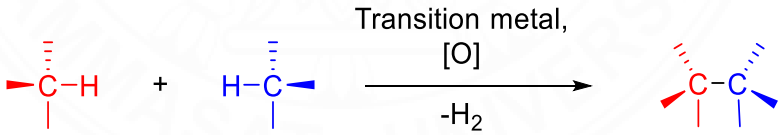
We presented the direct acylation of phthalazine derivatives with aldehydes and alcohols under optimized reaction conditions. First of all, we

investigated to find the appropriate reaction conditions using several oxidants, temperatures, Lewis acidic additives, and solvents. After that, we explored the scope of aldehydes, alcohols, and 1–substituted phthalazines which performed as the acyl sources and substrates respectively, in the reaction under the optimized conditions. Finally, we attempted to functionalize the acylated products using general chemical reactions to show the applicability of these products.

CHAPTER 2
REVIEW OF LITERATURE

2.1 Cross-dehydrogenative coupling (CDC)

Cross-dehydrogenative coupling abbreviated as CDC is the synthetic route to generate C–C bonds directly from two nonfunctionalized C–H bonds under oxidative conditions (Scheme 3).(Matcha & Antonchick, 2013) The reactions involve the elimination of an equivalent of H_2 (g) and generally, oxidants are always used in these reactions.(Lakshman & Vuram, 2017) Such CDC reactions have been applied in the formation of sp^3–sp^3, sp^3–sp^2, sp^3–sp, sp^2–sp^2, sp^2–sp (Sonogashira type), and sp–sp (Glaser coupling) bond.(Lakshman & Vuram, 2017) The prefunctionalization of substrates at the initial step is not required in this transformation, thus reducing the number of steps toward desired products and more efficient methods. However, there is a limitation including low reactivity and selectivity because of the use of high bond dissociation energy and the ubiquity of C–H bonds in compounds.(Matcha & Antonchick, 2013) Therefore, the development of efficient CDC reactions is sought in organic synthesis.



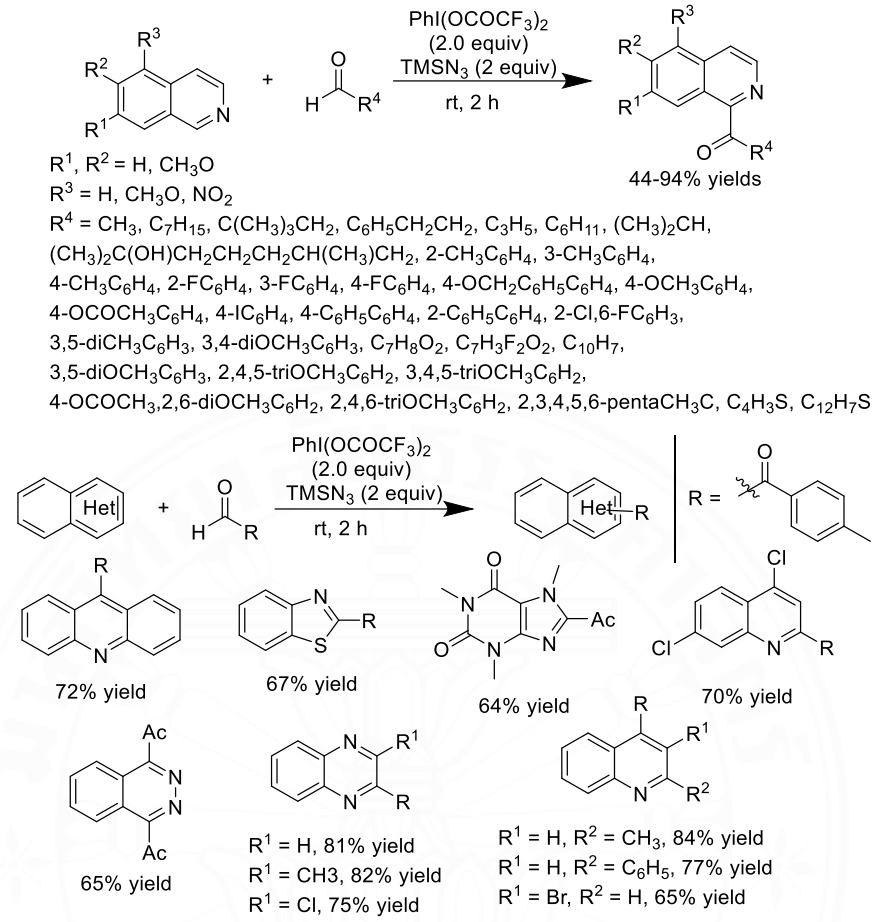
Scheme 3. The general pattern for cross–dehydrogenative coupling (CDC)

Nowadays, several research groups published the employment of the cross–dehydrogenative coupling (CDC) reactions for the acylation of *N*–heterocycles with the different coupling partners. Examples of these studies appeared below.

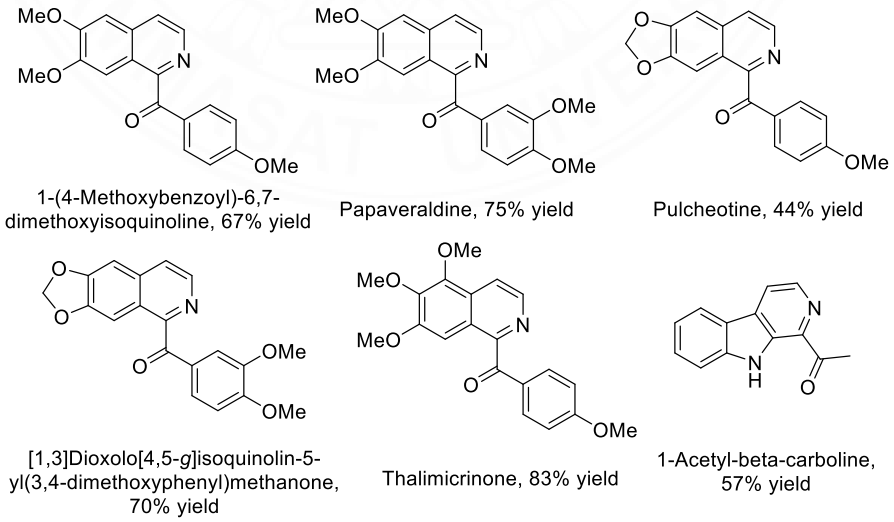
2.1.1 Cross–dehydrogenative coupling of *N*–heterocycles with aldehydes

Aldehydes are regarded as an important functional group as a precursor for CDC reactions. The cleavage and functionalization of C–H bonds of aldehyde led to the synthesis of various compounds. There are several studies on the acylation of nitrogenous heterocyclic compounds that widely employed aldehydes as acyl radical sources in these couplings.

In 2013, Matcha and Antonchick, the preliminary group presented cross–dehydrogenative coupling of heterocycles with aldehydes under metal–free reaction conditions.(Matcha & Antonchick, 2013) They synthesized the acylated heterocycles using hypervalent iodine (PhI ($OCOCF_3$)$_2$) as an oxidant and $TMSN_3$ as an additive in benzene solvent at ambient temperature for 2 hours. This cross–coupling reaction worked well with broad aldehydes including aliphatic, aromatic, and heteroaromatic aldehydes as well as the different heterocycles like isoquinolines, quinolines, quinaxalines, acridine, benzothiazole, and caffeine. The reaction gave the corresponding products in good yields both in small– and large–scale reactions. In addition, several natural alkaloid products were synthesized using this one-step transformation. However, the use of hypervalent iodine reagents is difficult to handle and benzene is a carcinogen reagent (Scheme 4, 5).(Matcha & Antonchick, 2013)

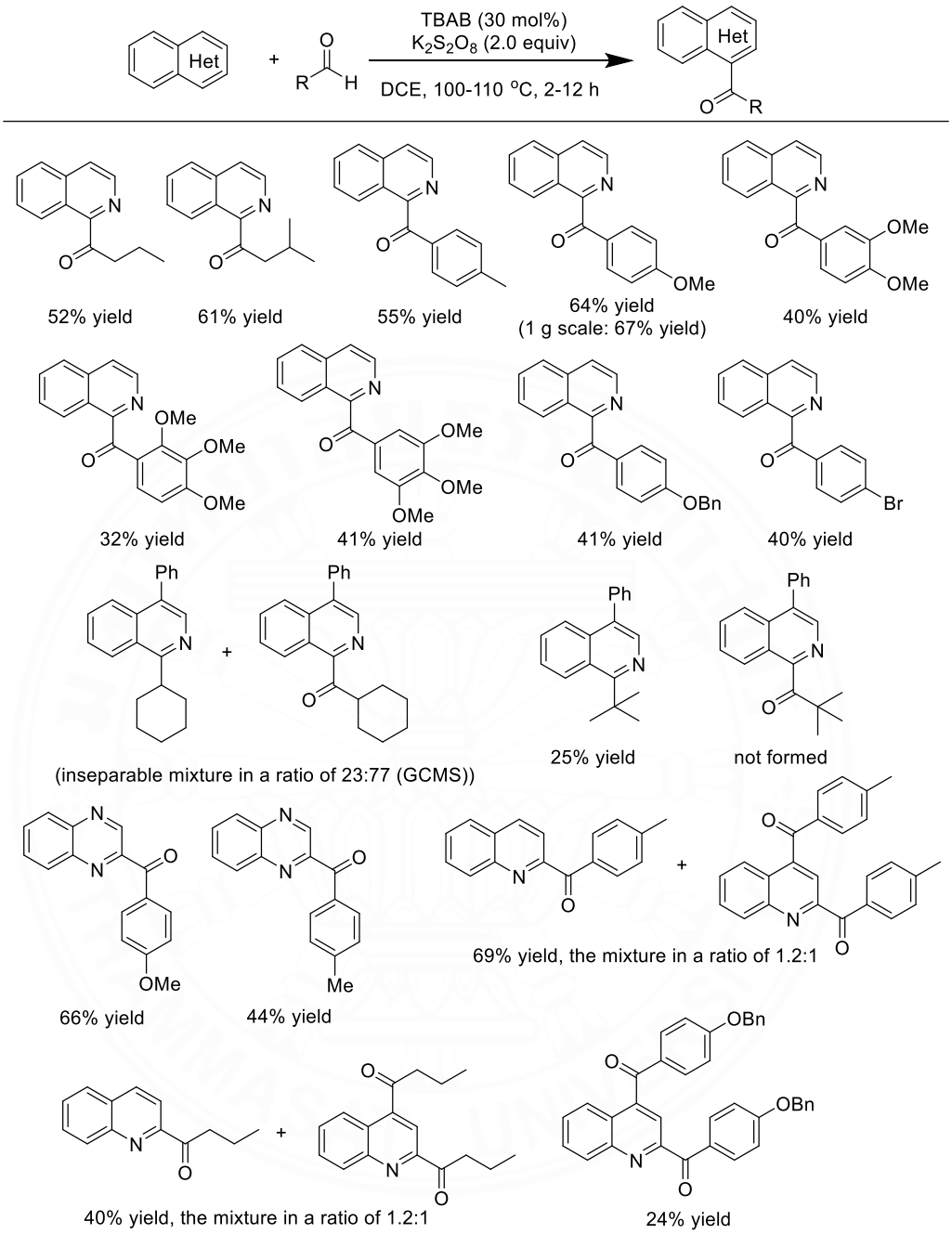


Scheme 4. The CDC reaction of heterocycles with various aldehydes by Matcha group

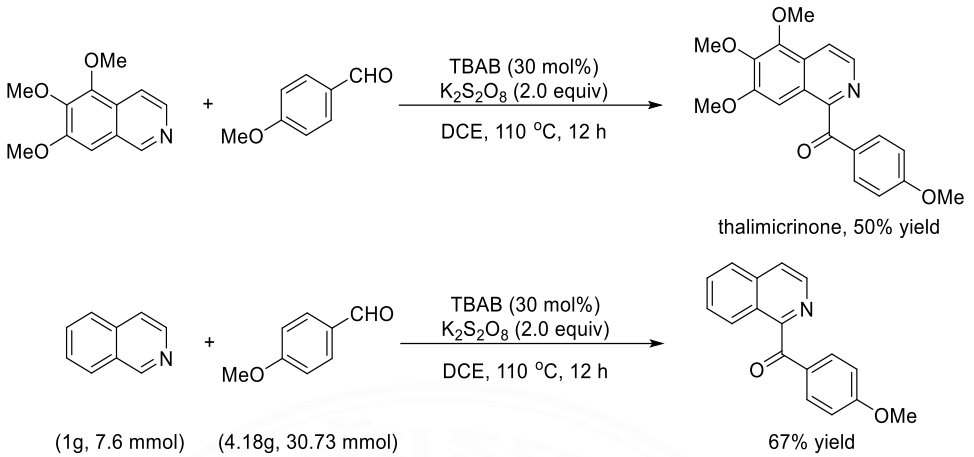


Scheme 5. The application of Matcha group's CDC method for the synthesis of natural alkaloids products

In 2014, Siddaraju and co–workers reported the intermolecular acylation of isoquinoline, quinoline, and quinoxaline derivatives with aldehydes in the presence of the substoichiometric amounts of TBAB and $K_2S_2O_8$ as an oxidant through cross dehydrogenative coupling (CDC).(Siddaraju et al., 2014) This coupling reaction was preferred with electron-rich and less sterically hindered aldehydes. The moderate to poor yields were obtained when reacted with aldehydes possessed electron-poor and more sterically hindered substituents. For example, the reaction of isoquinoline with 4–bromobenzaldehyde and 2,3,4–trimethoxybenzaldehyde furnished the corresponding coupled product in 40 and 32% yields, respectively. In contrast, with the reaction of isoquinoline with 4–methoxybenzaldehyde and 3–methylbutanal, it was found that the reaction gave the acylated products in good yield (64 and 61% yields). Moreover, the formation of products was also determined by the stability of acyl radicals and alkyl radicals that were generated in the reaction. For example, the reaction of 4–phenylisoquinoline with pivalaldehyde which is tertiary aldehyde gave only an alkylated product because the tertiary alkyl radical is more stable than acyl radical in this case. This CDC strategy also underwent well in a scaling–up experiment and was applied to synthesize isoquinoline-derived natural products such as thalimicrinone (Scheme 6,7).(Siddaraju et al., 2014)

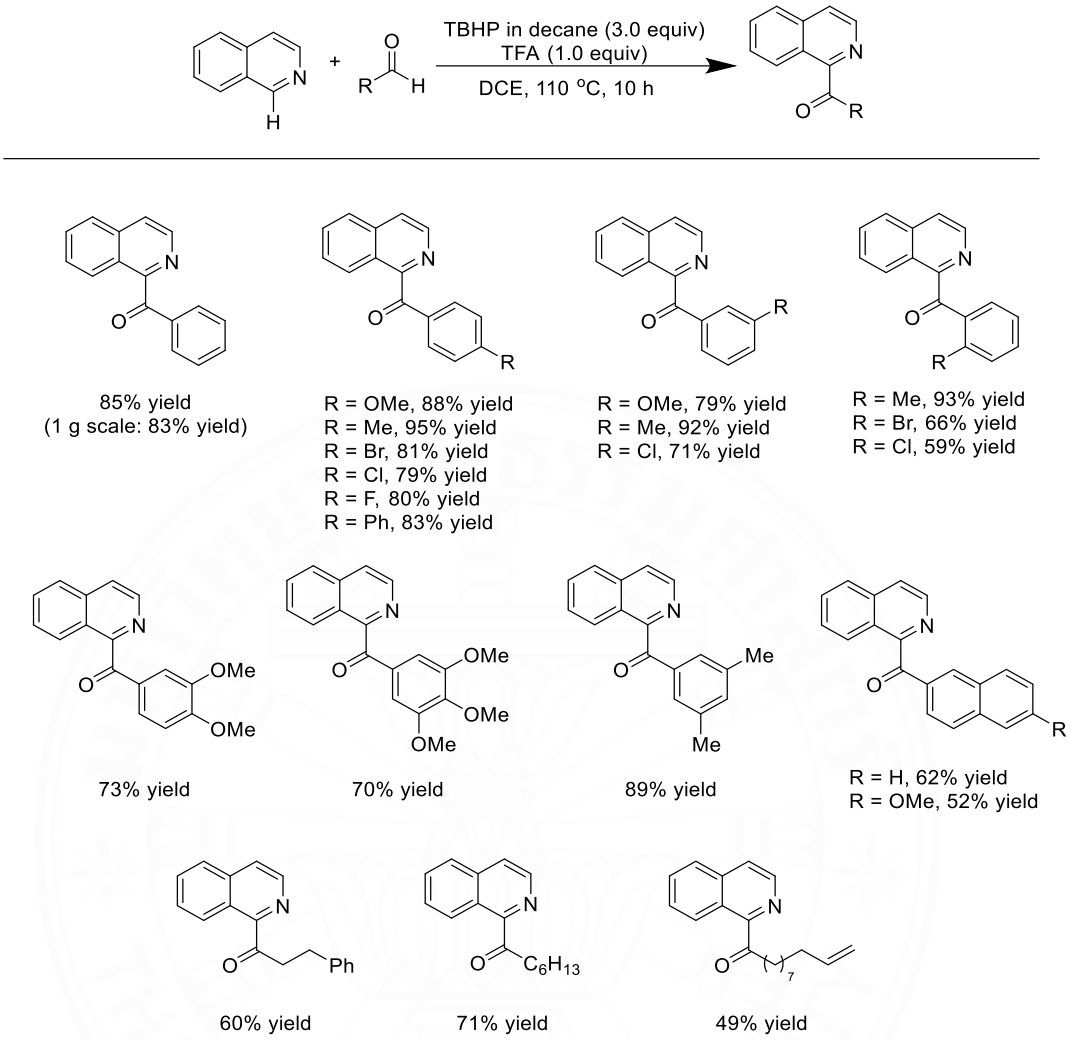


Scheme 6. The acylation of isoquinolines, quinolines, and quinoxalines with aldehydes using TBAB and $K_2S_2O_8$



Scheme 7. The synthesis of thalimicrinone and CDC on a large scale using TBAB and $K_2S_2O_8$

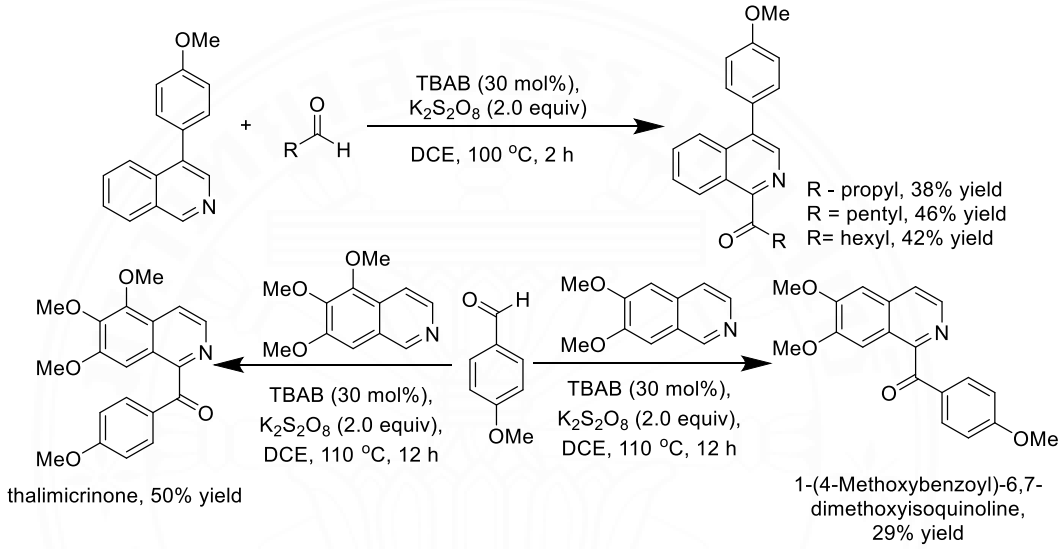
In 2015, Chen and co–workers developed a metal-free oxidative CDC of *N*–heterocycles with diverse aldehydes mediated by TBHP/TFA.(Chen et al., 2015) They found that the reaction did not proceed in the absence of acidic additives, presumable this observation related to the low electrophilicity of the *N*–heterocycles towards the aldehydes in nature. Adding suitable acidic additives might enhance the electrophilicity of the *N*–heterocycles resulting in the higher reactivity of this coupling reaction. Thus, the acidic additives were crucial in the reactivity of this oxidative CDC reaction (Scheme 8).(Chen et al., 2015)



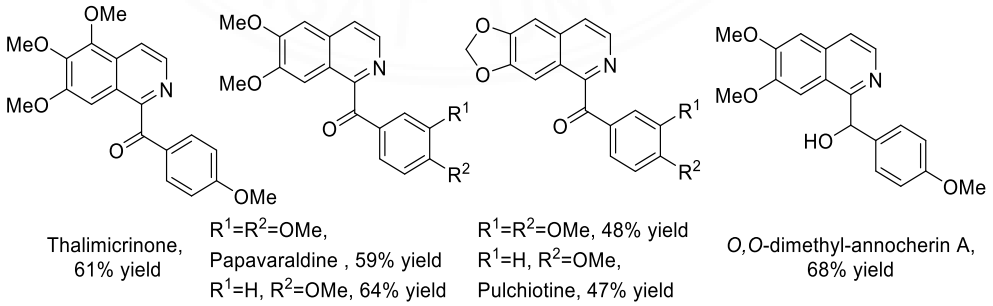
Scheme 8. The oxidative cross–dehydrogenative coupling of isoquinolines with aldehydes in the presence of TBHP/TFA

Siddaraju and Prabhu continuously developed the acylation of heteroarenes. They have reported the acylation of heteroarenes in the presence of TBAB and $K_2S_2O_8$.(Siddaraju et al., 2014) This method was used to synthesize isoquinoline–derived natural products in low to moderate yield and the coupling reaction of a few aliphatic aldehydes such as butanal, hexanal, and heptanal also led to the desired product in low yields (Scheme 9).(Siddaraju et al., 2014) To improve the method, a more efficient strategy was proposed for synthesizing acylated heteroarenes using NCS and TBHP under metal–free conditions in 2016.(Siddaraju & Prabhu, 2016) The use of NCS and TBHP expanded the utility and applicability of the

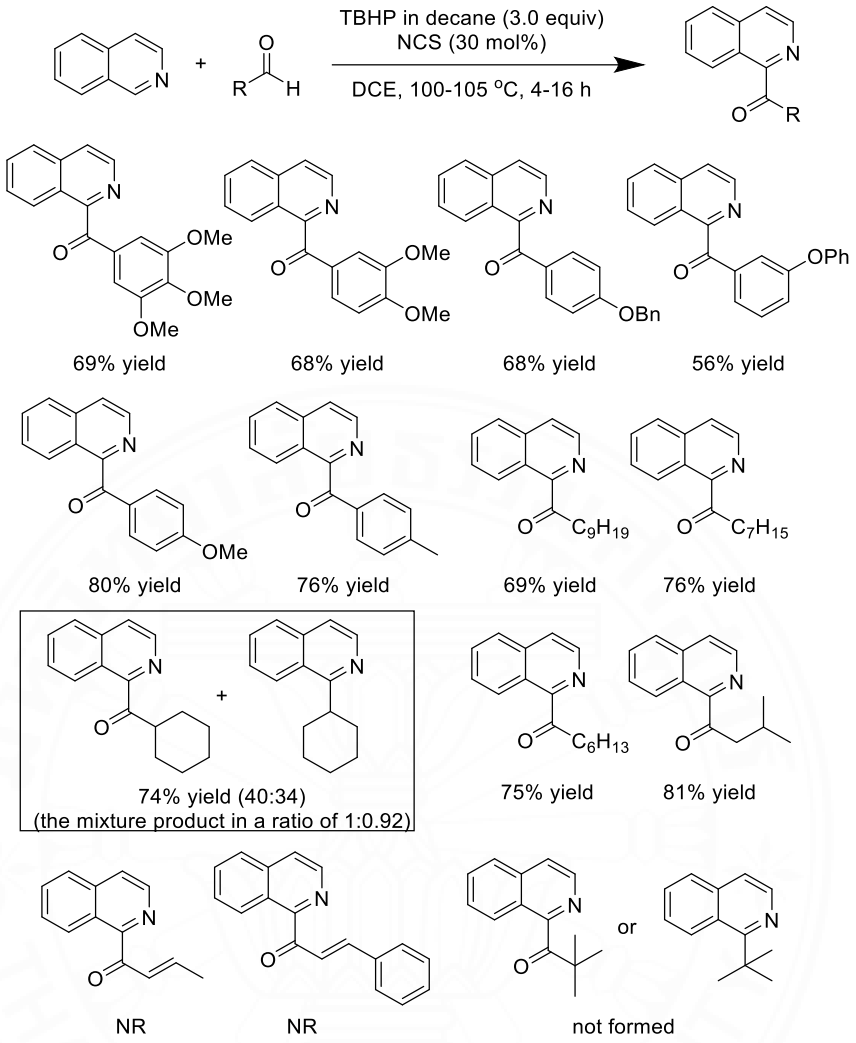
acylation method. This methodology was applied in synthesizing diverse natural products and biologically active compounds including thalimicrinone, papaveraldine, pulchiotine, and *o, o*–dimethyl-annocherin A in 61, 59, 47, and 68% yield, respectively. Moreover, the coupling with aliphatic aldehydes such as decanal, octanal, heptanal, and 3–methylbutanal proceeded well and produced their acylated products in good yields (69–81% yields) (Scheme 10,11).(Siddaraju & Prabhu, 2016)



Scheme 9. The reaction of isoquinoline with aliphatic aldehydes and the synthesis of isoquinoline–derived natural products in the previous report of the Prabhu group



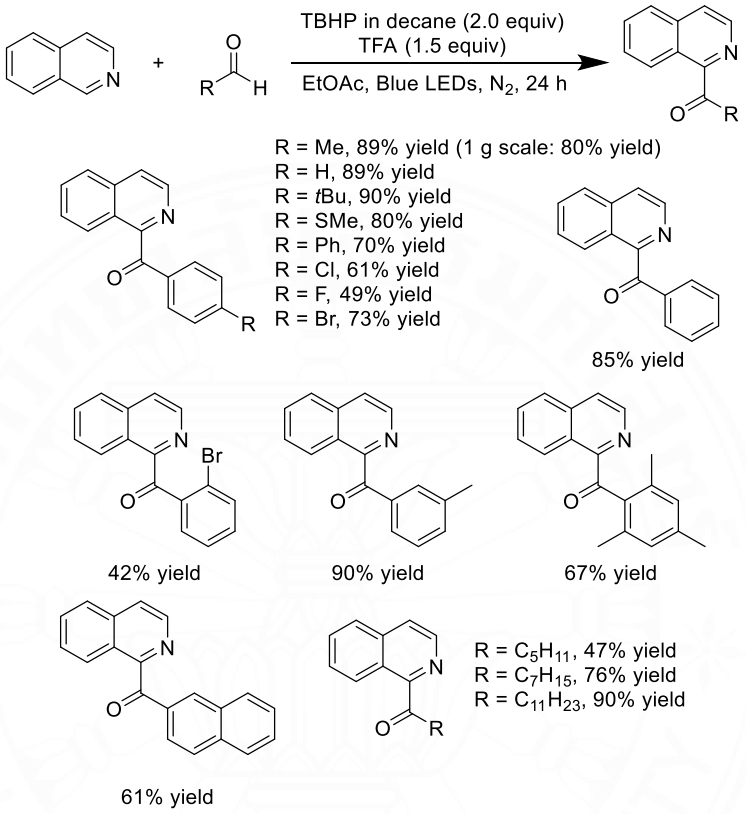
Scheme 10. The application of CDC reaction in the presence of NCS and TBHP for the synthesis of diverse natural products and biologically active compounds



Scheme 11. The intermolecular acylation of isoquinoline with aldehydes using NCS and TBHP

In 2018, Lei *et al.* displayed the visible–light photoredox catalysis without any external photocatalyst for the oxidative acylation of *N*–heterocyclic aromatic compounds with aldehydes.(L. Zhang, Zhang, Li, Wang, & Lei, 2018) The photochemical reaction basically requires the use of an external photocatalyst such as ruthenium and iridium complexes as well as organic dyes because most organic compounds cannot absorb the light in the visible–light spectrum. This reaction was carried out in the presence of TBHP as an oxidant and TFA as an additive under the irradiation of visible–light (blue LEDs), delivering acylated products with aliphatic and aromatic aldehydes in good efficiencies. This CDC process possibly proceeded

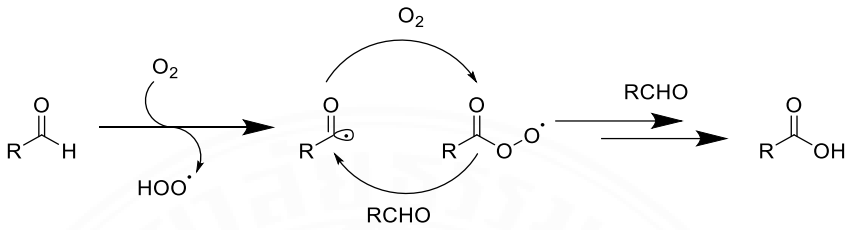
through the formation of a complex of *N*–heterocycles, TFA, and TBHP. Moreover, this strategy was also applicable for a large–scale reaction (Scheme 12).(L. Zhang et al., 2018)



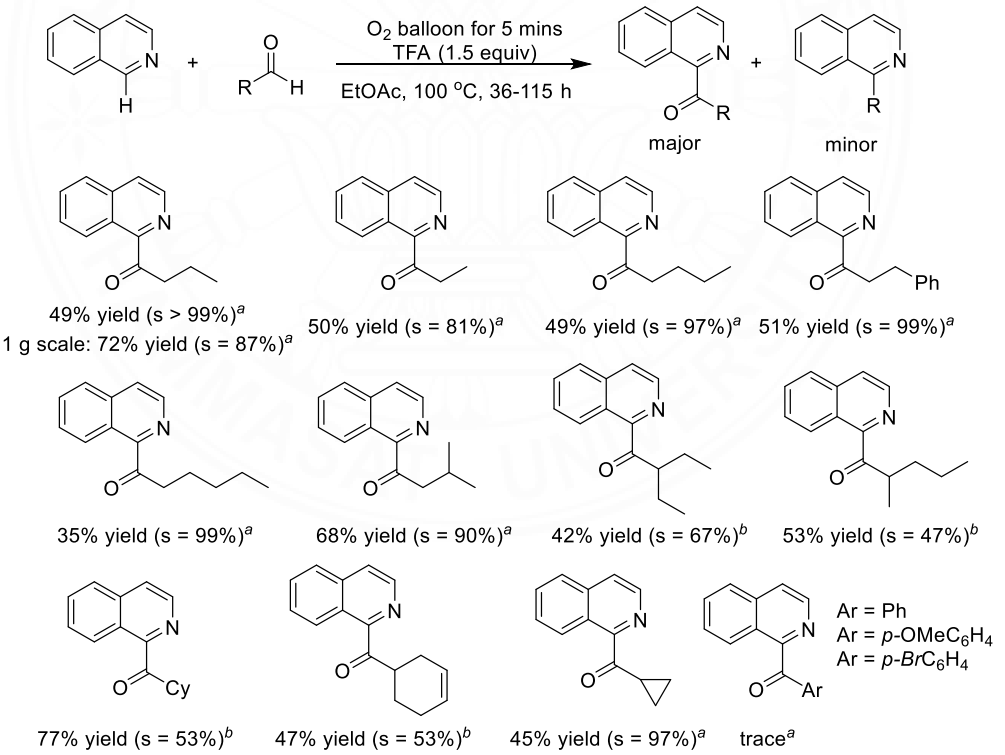
Scheme 12. The oxidative acylation of heteroarenes with aldehydes using visible–light photoredox catalysis

In 2019, Guin, Paul, and Bhakat described the application of auto-oxidation of aldehydes for the development of radical C(sp^2)–H acylation of nitrogen heterocycles.(Paul, Bhakat, & Guin, 2019) This usage led to reducing the use of toxic reagents and the overall cost of the reaction. They focused on the generation of acyl radical *via* homolytic activation of aldehyde under the O_2 atmosphere. The auto–oxidation of aldehyde to carboxylic acid in the presence of excess molecular oxygen forms peracyl radical, which abstracts hydrogen atom of aldehyde to generate the resulting acyl radical and peracid in the reaction. The peracid as a by–product finally decomposes to the corresponding carboxylic acid (Scheme 13). The aerobic C–H

acylation process performed well with different linear aldehydes, delivering the expected products in good yields with high selectivity. On the contrary, with aromatic aldehydes, the reaction afforded only a trace amount of the desired acylated products, presumably caused by an inefficient auto-oxidant of this reaction (Scheme 14).(Paul et al., 2019)



Scheme 13. The aerobic oxidation of the aldehyde to a carboxylic acid with excess molecular oxygen

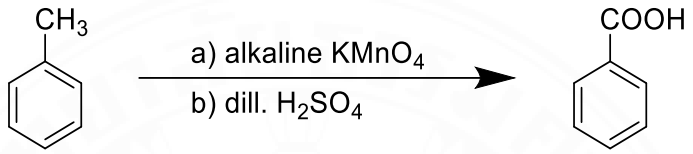


a = Isolated yields of the acylated products are given; structure of major product is drawn; selectivity (s) between acylated and alkylated products determined by GC-mass analysis of the crude reaction mixture.
b = Combined yields of acylated and alkylated products are given.

Scheme 14. The C–H acylation of isoquinoline and different aldehydes through aerobic oxidation of aldehydes

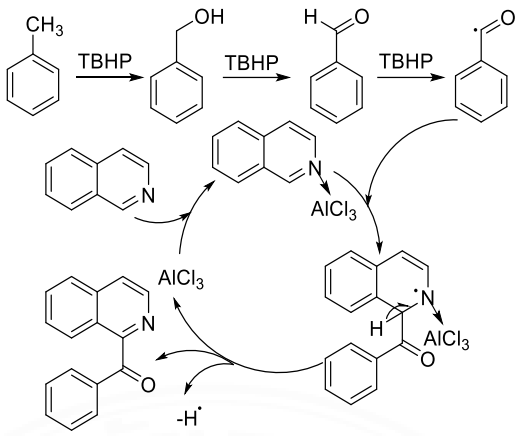
2.1.2 Cross-dehydrogenative coupling of *N*─heterocycles with methylbenzenes

Methylbenzene, also known as toluene, is an aromatic hydrocarbon possessing a methyl group (Me) attached to a benzene ring. It can be oxidized to the corresponding carboxylic acid by treatment with potassium permanganate ($KMnO_4$) since there is a hydrogen atom at the benzylic position (Scheme 15).(Clark, 2020)

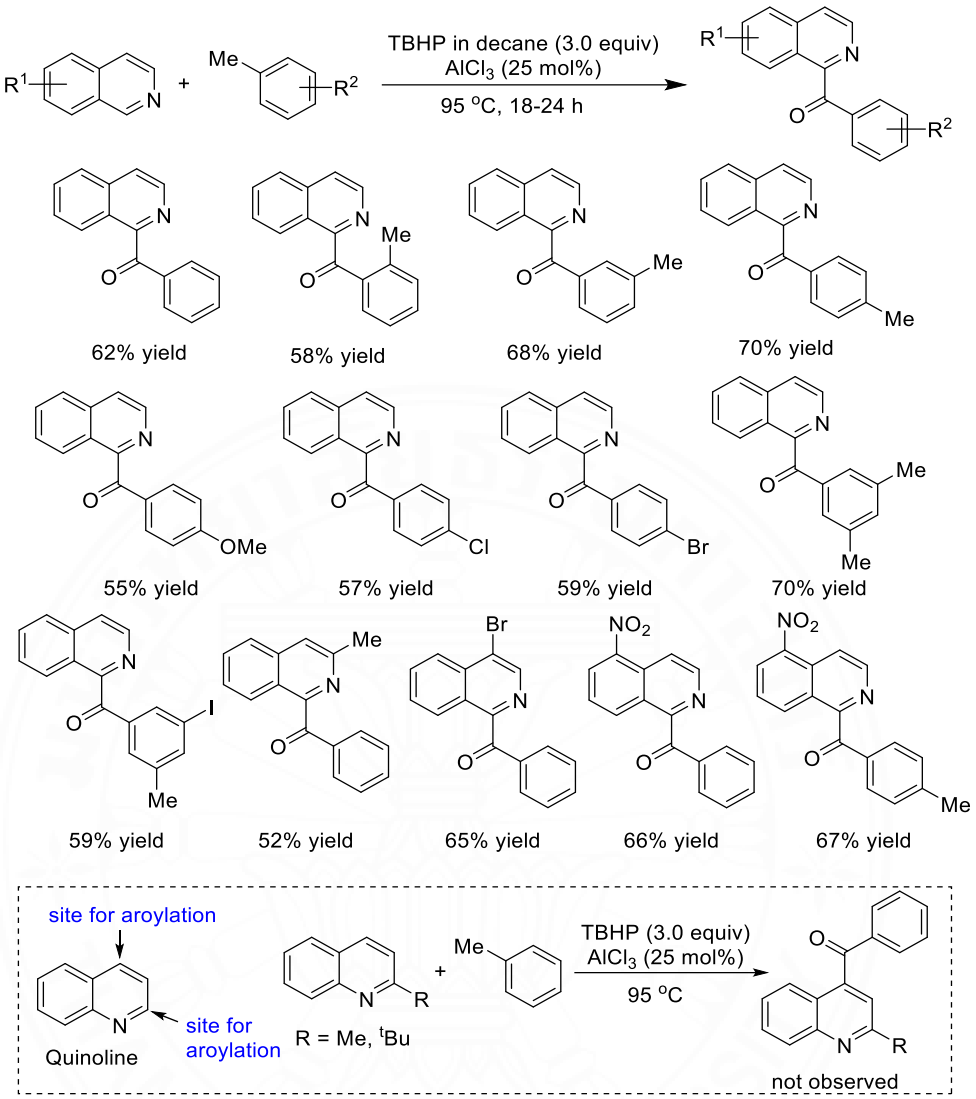


Scheme 15. The oxidation of methylbenzene to a carboxylic acid with $KMnO_4$

In 2015, Ali and co–workers attempted to develop the CDC protocols for the direct acylation of *N*–heterocycles using methylbenzenes as the alternative acyl radical source under metal-free oxidative conditions.(Ali et al., 2015) The reaction was performed in the presence of an oxidant and acidic additives. The formation of an acyl radical from methylbenzenes arose from the oxidation by the oxidant, whereby the TBHP in decane solution was the best choice. Methylbenzene was oxidized sequentially to benzyl alcohol and benzaldehyde without over oxidation to benzoic acid. The C–H bond cleavage of aldehydes produced the acyl radical, which reacted with the coordinated *N*–atom heterocycles and further rearomatized to give the desired acylated products (Scheme 16). The addition of acidic additive promoted the attack of nucleophilic acyl radical onto the α–C of *N*–heterocycles. The *N*–atom is protonated with acidic additive making α–C to nitrogen more electrophilic than the other positions, which facilitates the facile attack of acyl radical in regiospecific manner. The Lewis acid ($AlCl_3$) was employed in this coupling reaction since it activated only one position in the case of *N*–heterocycles possessing various proportions for the nucleophilic radical addition (Scheme 17).(Ali et al., 2015)



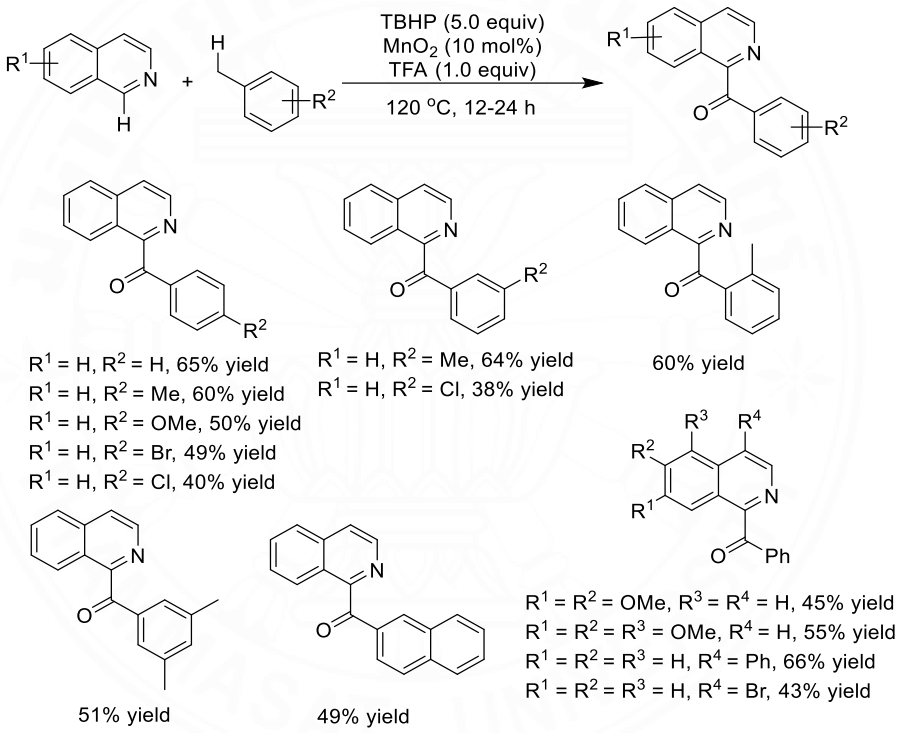
Scheme 16. Proposed acylation mechanism of isoquinoline using TBHP and $AlCl_3$



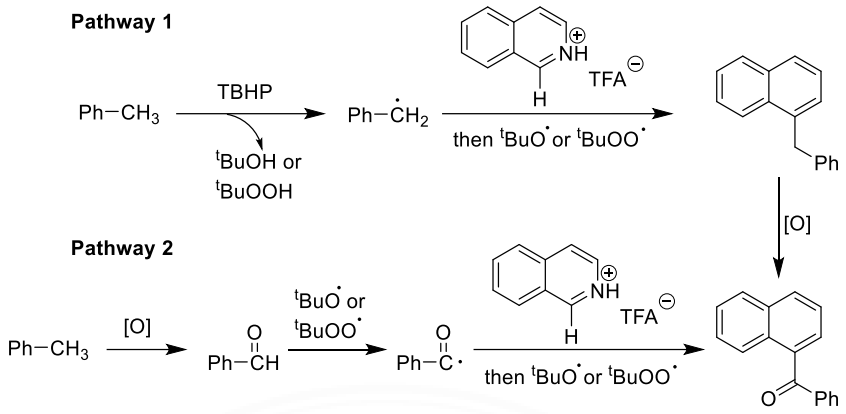
Scheme 17. Regiospecific benzoylation of *N*–heterocycles with methylbenzenes in the presence of TBHP and $AlCl_3$

Wan, Lou, and Lin presented the utilization of methyl arenes as coupling partners for the benzoylation of isoquinolines *via* oxidative cross–dehydrogenative coupling in the same year (Scheme 18).(Wan, Lou, & Liu, 2015) The preactivating factor in coupling partners is unnecessary for this benzoylation. The reaction was carried out in the mixture of TFA, TBHP, and a catalytic amount of MnO_2. Two possible mechanisms were proposed for this reaction because the benzylated product was detected together with the desired benzoylated product by ^{1}H–NMR under these conditions. The first pathway related to the benzylation of the

isoquinolines and methylbenzene, which afforded the corresponding benzylated product. The resulting benzylated was eventually oxidized to the benzoylated isoquinolines. The second pathway involved oxidation of methylbenzene to the benzaldehyde, followed by the formation of acyl radicals produced by H–atom abstraction of the aldehyde by *tert*–butoxy radicals or *tert*–butyl peroxy radicals in the reaction medium. The benzoyl radicals underwent coupling with the protonated *N*–atom isoquinolines, furnishing the target benzoylated products (Scheme 19).(Wan et al., 2015)



Scheme 18. The synthesis of C_1–benzoyl isoquinoline with methyl arene using the combination of TBHP, MnO_2, and TFA



Scheme 19. Proposed mechanism for the CDC reaction of isoquinoline and methyl arene with TBHP, TFA, and a catalytic amount of MnO_2

2.1.3 Cross-dehydrogenative coupling of *N*–heterocycles with benzyl alcohols

Alcohol is an organic compound that consists of at least one of the hydroxyl functional groups (−OH) in the structure. It is classified into 3 types depending on the number of substituents on the C–atom that attaches with the OH group. The types of alcohol include primary (1°), secondary (2°), and tertiary (3°) alcohol (Figure 3). Primary alcohols can be oxidized to a sequential aldehyde and carboxylic acid subject to the reaction conditions. Secondary alcohols can be oxidized to ketone because there is only one H–atom at α–C. Lastly, tertiary alcohols are alcohol possess three substituent groups without H–atom attached to α–C, thus their oxidation is not observed in this group. (Scheme 20).("Oxidation of Alcohols,")

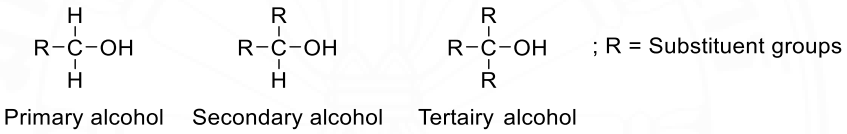
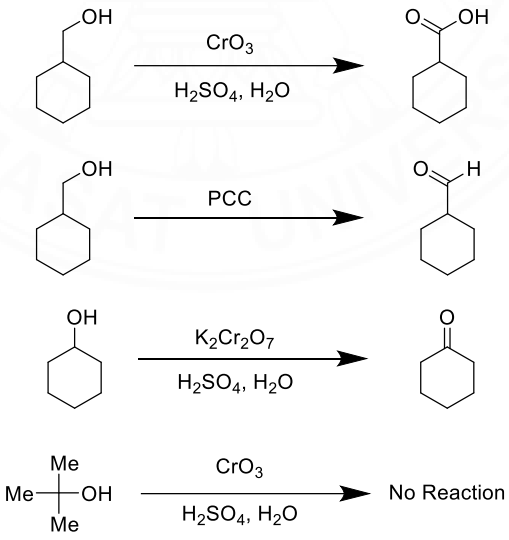
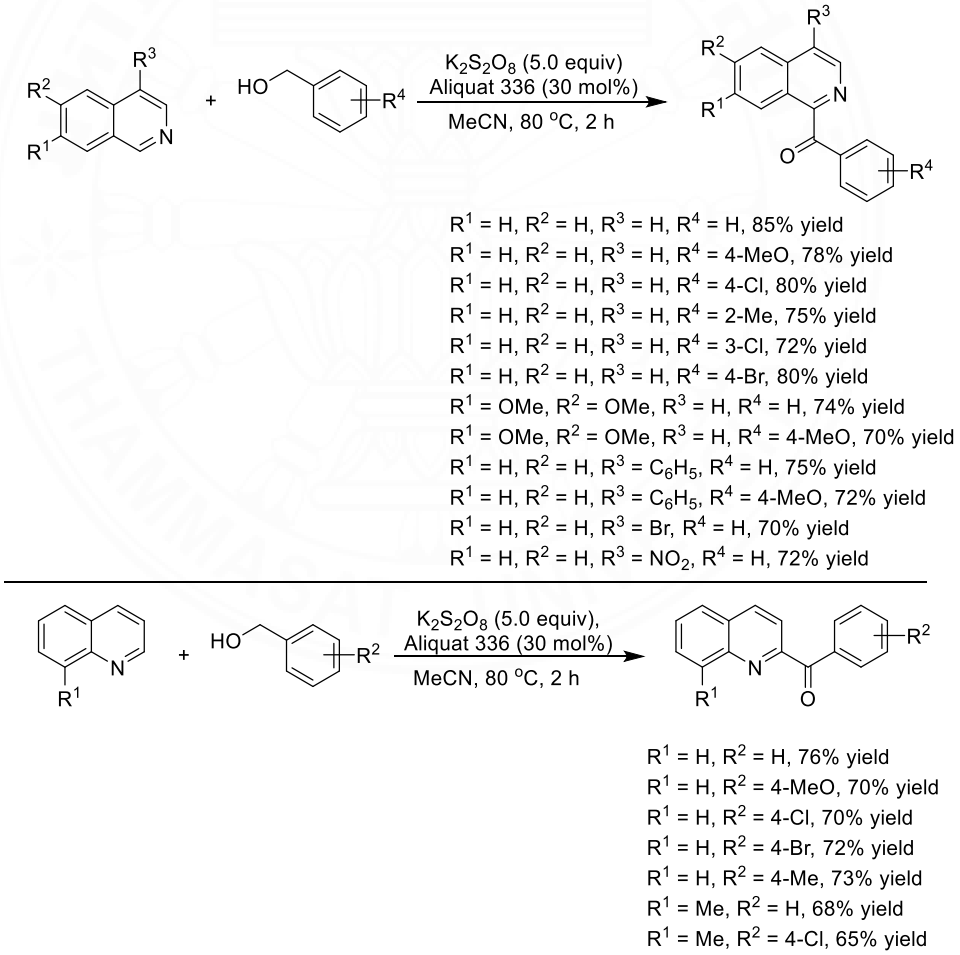


Figure 3. Structure and classification of alcohol



Scheme 20. The oxidation of primary–, secondary–, and tertiary alcohol

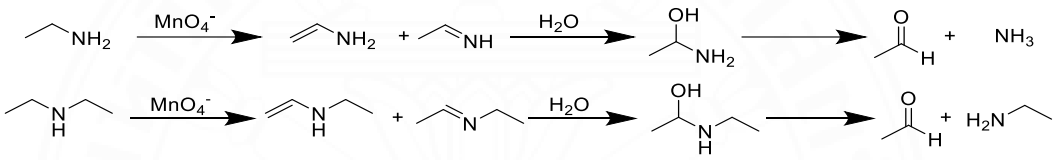
The several published reports for the direct C–H functionalization of isoquinolines and quinolines, commonly used aldehydes and methylarenes as coupling partners whereas arylmethanols have no report.(Adib, Pashazadeh, Rajai-Daryasarei, Kabiri, & Gohari, 2016) Adib *et al*. saw the possibility for the application of arylmethanols in the reaction. In 2016, the oxidative acylation of quinolines and isoquinolines with arylmethanols under transition–metal–free was submitted by their group. The reaction progressed under the existence of the $K_2S_2O_8$ as an oxidant and Aliquat 336 as a transfer agent. Both the oxidant and additive were essential for the promotion of this reaction. Isoquinolines and quinolines successfully coupled with arylmethanols under the optimized conditions within 2 hours, delivering the products in good yields (Scheme 21).(Adib et al., 2016)



Scheme 21. Oxidative cross–dehydrogenative coupling of isoquinolines and quinolines with arylmethanols using $K_2S_2O_8$ and Aliquat 336

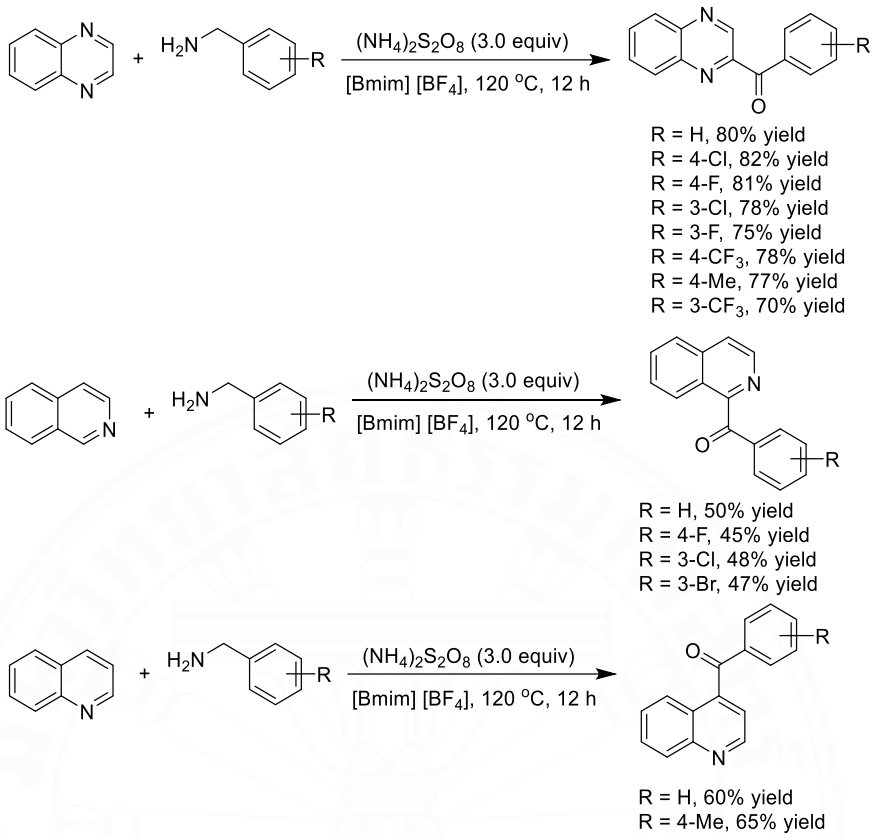
2.1.4 Cross–dehydrogenative coupling of *N*–heterocycles with benzylamines

Benzylamine is an organic compound that is classified into a family of amine groups. The structure consists of the benzyl group connected to the amino functional group. There is chemical formula as $C_6H_5CH_2NH_2$. The amines containing H–atom on α–C to nitrogen can be converted to the aldehydes or ketones by the oxidative hydrolysis process.(Rawalay & Shechter, 1967) The primary and secondary amines are rapidly oxidized to imines and enamines, respectively which are hydrolyzed to the corresponding carbonyl compounds (Scheme 22).



Scheme 22. The oxidative hydrolysis of amines by neutral permanganate in aqueous *t*–butyl alcohol

Sharma, Abdullaha, and Bharate demonstrated the novel and efficient method for C–sp^2 CDC coupling of *N*–heterocycles with benzylamines, which has never been reported.(Sharma, Abdullaha, & Bharate, 2017) The benzoylation of *N*–heterocycles from benzylamines occurred through $(NH_4)_2S_2O_8$ catalyzed benzoyl radical formation in 1–butyl–3–methylimidazolium tetrafluoroborate [Bmim]BF_4. This method required the use of neither a metal catalyst nor a ligand. The 1–butyl–3–methylimidazolium tetrafluoroborate ([Bmim]BF_4) is the representative ionic liquid (IL). The advantages of ILs include nonvolatility, nonflammability, and recyclability. Quinoxalines, isoquinolines, and quinolines with substituted benzylamines participated well in this CDC reaction, giving the highly regiospecific benzoylated products in moderate to good yields. The benzoylation of quinoxalines generated specifically the C_2–benzoylated product while isoquinolines formed only a C_1–benzoylation product, and quinolines gave the only corresponding C_4–acylated product (Scheme 23).(Sharma et al., 2017)



Scheme 23. The C–sp^2 CDC coupling of quinoxalines, isoquinolines, and quinolines with benzylamines using $(NH_4)_2S_2O_8$ and [Bmim]BF_4

2.2 Decarboxylative cross-coupling

Decarboxylative cross–coupling is the efficient method for the formation of the C–C and C–X (X = N, P, S) bond from the C–COOH bond through the loss of CO_2 (Scheme 24).(Guo, Wang, & Duan, 2016) This strategy was applied to delivering of carbonyl compound. α–Keto acids or α–oxocarboxylic acids are usually used as acylating agent because of the structural diversity of α–keto acids. They are carboxylic acids that contain a keto group in α–position (Figure 4). Furthermore, using α–keto acids as an acyl–transfer reagent is a more environmentally friendly method because the reaction produces only CO_2 as a byproduct.(Penteado et al., 2019) To date, numerous efficient decarboxylative cross–coupling have been presented in the published report as an example below.

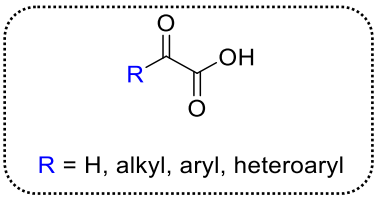
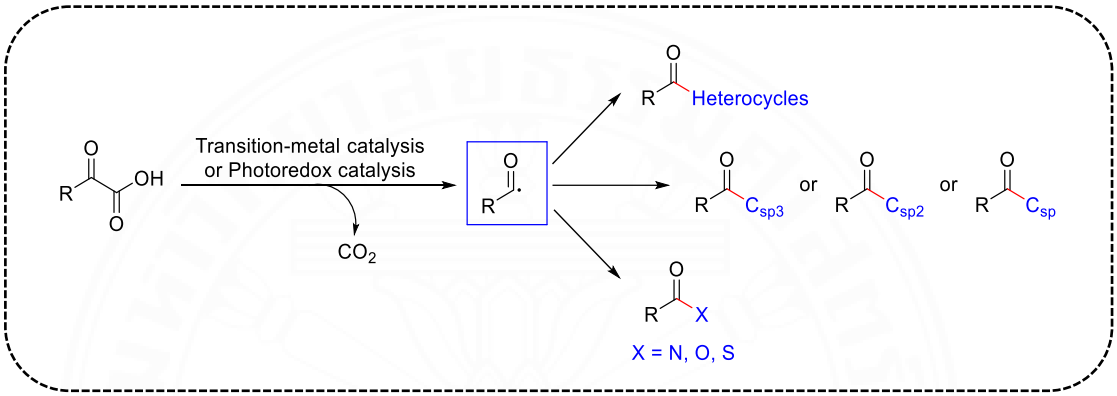


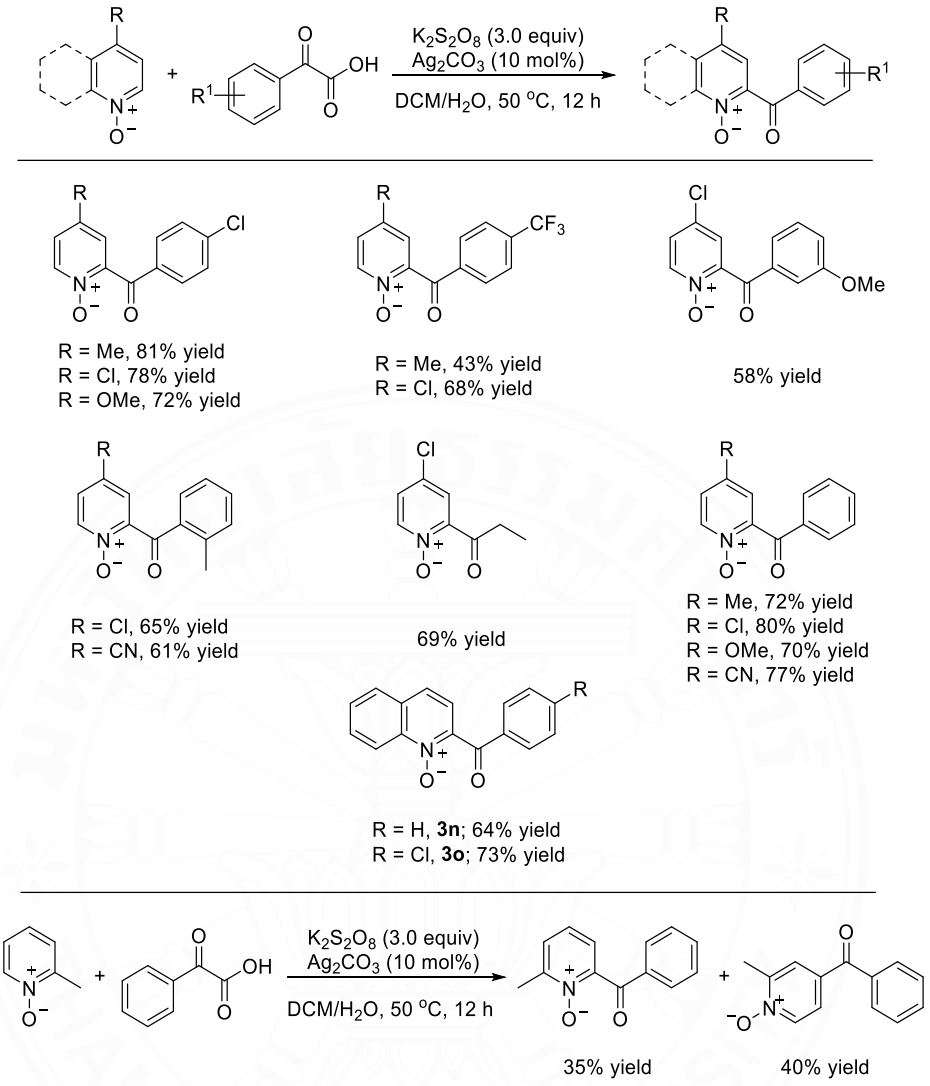
Figure 4. General structure of α–keto acids



Scheme 24. The general procedure for decarboxylative cross–coupling of α–keto acids(Guo et al., 2016)

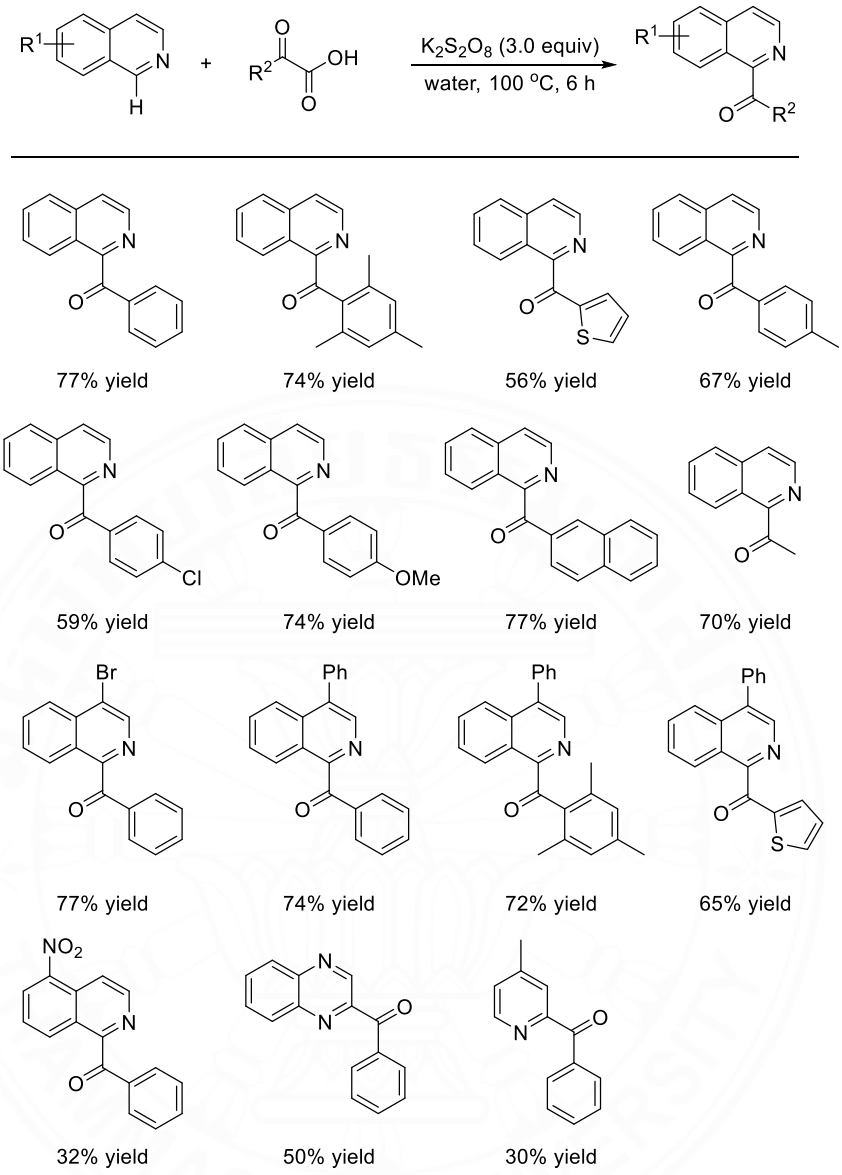
2.2.1 The formation of new Csp^2–Csp^2 bonds in a one-pot reaction

In 2014, Muthusubramanian *et al*. developed an efficient decarboxylative acylation of pyridine–*N*–oxides, allowing the acylated heteroarene *N*–oxides in high yield which was difficult to synthesize using the conventional methods.(Suresh, Kumaran, Senthilkumar, & Muthusubramanian, 2014) Pyridine–*N*–oxides reacted with α-oxocarboxylic acids in the presence of silver catalyst and $K_2S_2O_8$ as an oxidant at 50 °C. Interestingly, the regioselectivity of the acylated pyridine product depended on the position of the substituents on the pyridine ring. The single acylated products (C_2–acylation products) were obtained when 4–substituted pyridine–*N*–oxides were applied as the substrate (Scheme 25).(Suresh et al., 2014)



Scheme 25. Silver–catalyzed decarboxylative acylation of various aryl–*N*–oxides with α–oxocarboxylic acids

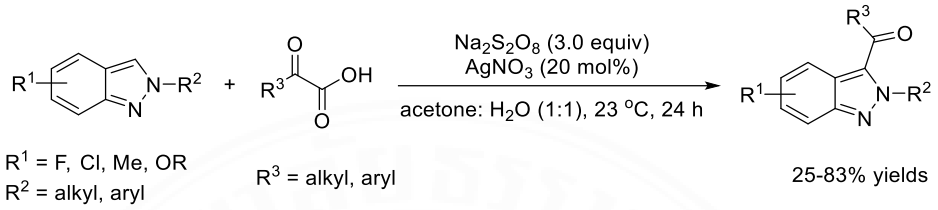
In 2017, Singh and Chaubey developed the regioselective acylation of isoquinolines using α–keto acids under mild and green conditions.(Chaubey & Singh, 2017) The greener approach was performed using $K_2S_2O_8$ as an oxidant in water without using transition metal catalyst and additive. The reaction generated the mono C_1–acylated substituted isoquinolines in good yield with easy purified products (Scheme 26).(Chaubey & Singh, 2017)



Scheme 26. Decarboxylative acylation of isoquinolines, quinoxaline, and picoline using α–keto acids under metal–free in water

In 2018, Kyungsoo Oh and co-workers presented the first direct acylation of *2H*–indazoles.(Bogonda, Kim, & Oh, 2018) The synthesis of 3–acyl–*2H*–indazoles through the direct acylation of *2H*–indazoles has not been achieved before and the formation of this moiety limited to the use of other methods including the cycloaddition of arynes with diazocarbonyl compounds, and the C–H addition and cyclization of azobenzenes using Rh(II)–catalyzed. With the lack of the methods,

Kyungsoo Oh groups developed and suggested the Ag–catalyzed decarboxylative cross-coupling for the direct acyl radical addition of α–keto acids to *2H*–indazoles under mild reaction conditions. The structural variation of 3–acyl–*2H*–indazoles was obtained in 25–83% yields (Scheme 27).(Bogonda et al., 2018)



Scheme 27. The direct acylation methods for *2H*–indazoles with α–keto acids using $AgNO_3$–catalyzed decarboxylative cross–coupling under an ambient temperature reaction

The acyl–substituted pyrazines, especially 2–acylpyrazine show interesting biological activities, such as anti–tumor agent and anti–trypanosomatid agent that are sought in medicinal chemistry (Figure. 5). In general, the synthetic acyl pyrazine compounds required the pre-functionalization process (Scheme 28). Zhao and co-workers proposed the regioselective silver–catalyzed decarboxylative coupling reaction of pyrazines with α–oxocarboxylic acids, allowing the excellent product quality.(Li, Lai, Wu, Zhao, & Zhang, 2018). This protocol generated the C_2–acylated pyrazine products in concise synthetic procedure (Scheme 29).(Li et al., 2018)

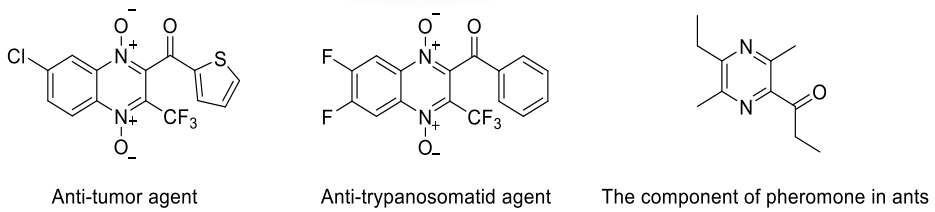
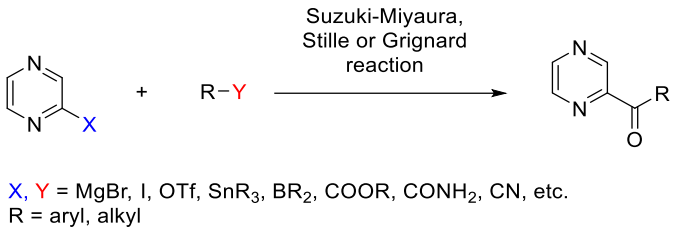
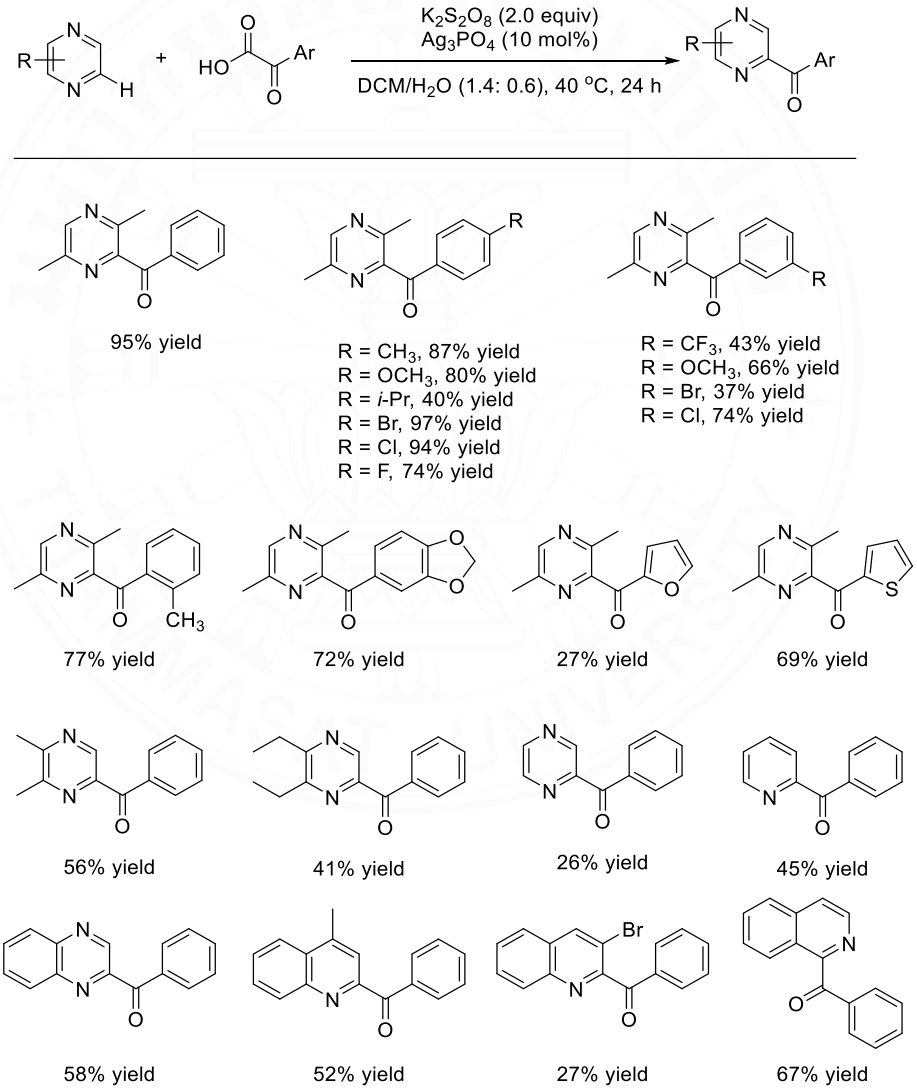


Figure 5. Examples of the bioactive acylated pyrazine derivatives

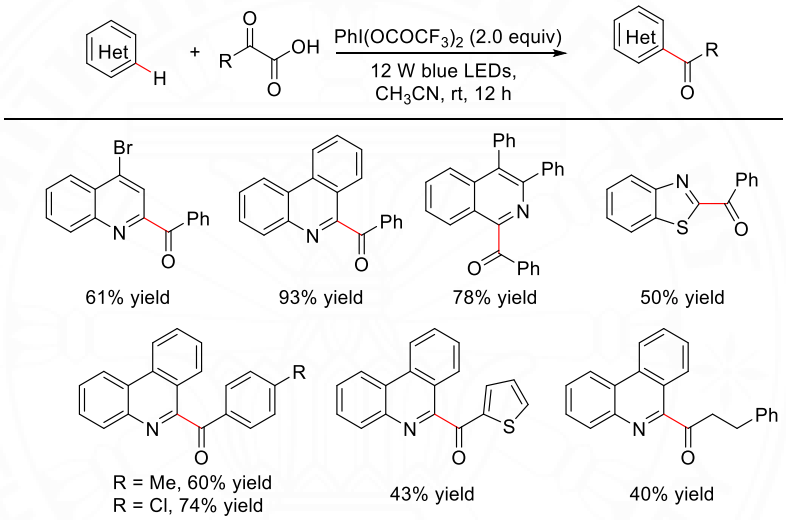


Scheme 28. Pre–functionalized pyrazine for the synthesis of acylated product using classical methods



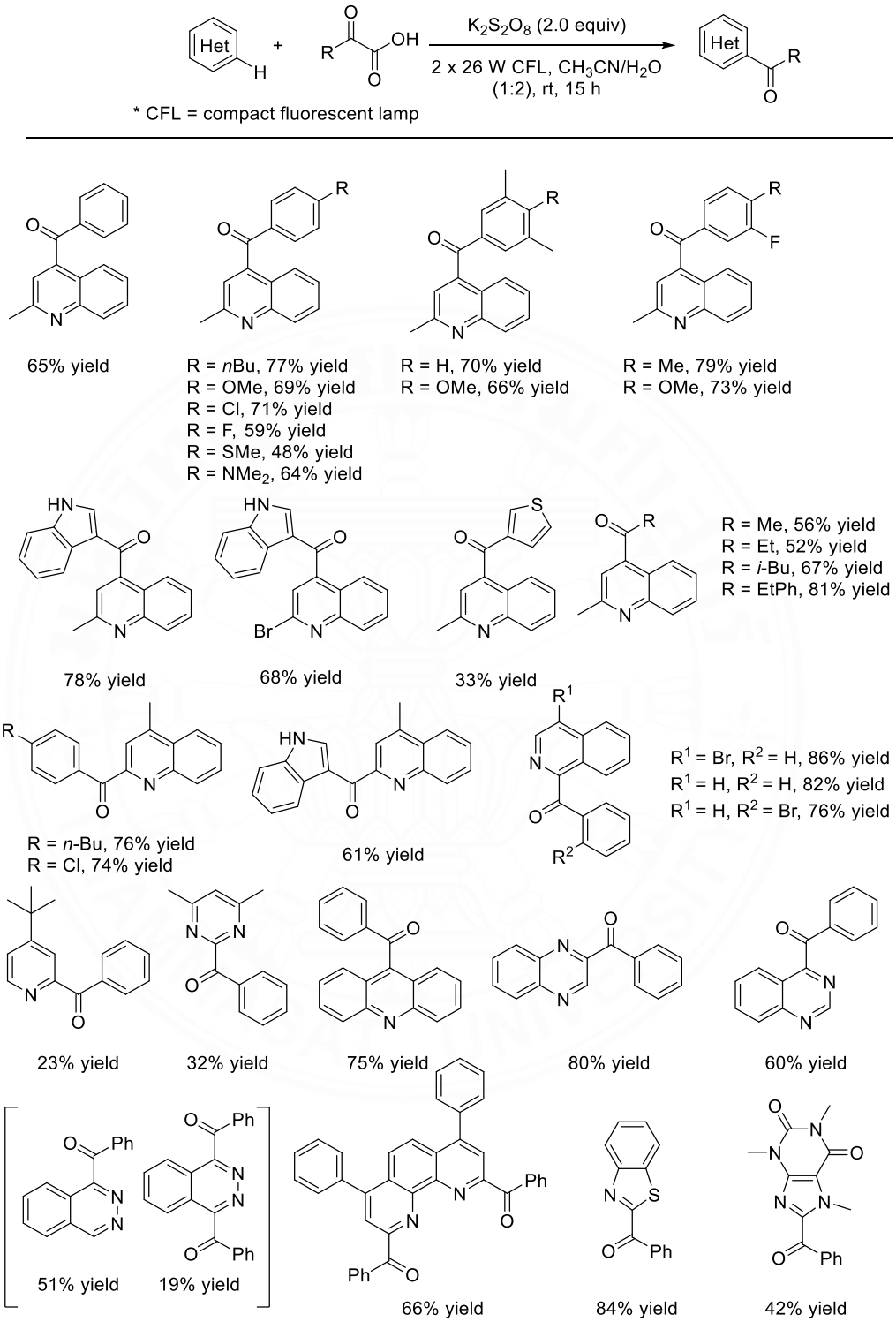
Scheme 29. The silver–catalyzed regioselective C_2–acylation of pyrazine derivatives with α–oxocarboxylic acids

Zhang *et al*. disclosed the direct C–H acylation of *N*–heterocycles with carboxylic acids through visible–light irradiation decarboxylative coupling without photoredox catalysis.(X.-Y. Zhang, Weng, Liang, Yang, & Zhang, 2018) This mild protocol allowed easy access to the couple *N*–heterocycles with a variety of carboxylic acids consisting of aryl-substituted α–oxocarboxylates and heteroaryl–substituted α–oxocarboxylate in good yield. Moreover, the reaction could be applied to gram–scale synthesis that provided a comparable product yield to small–scale reactions (Scheme 30).(X.-Y. Zhang et al., 2018)

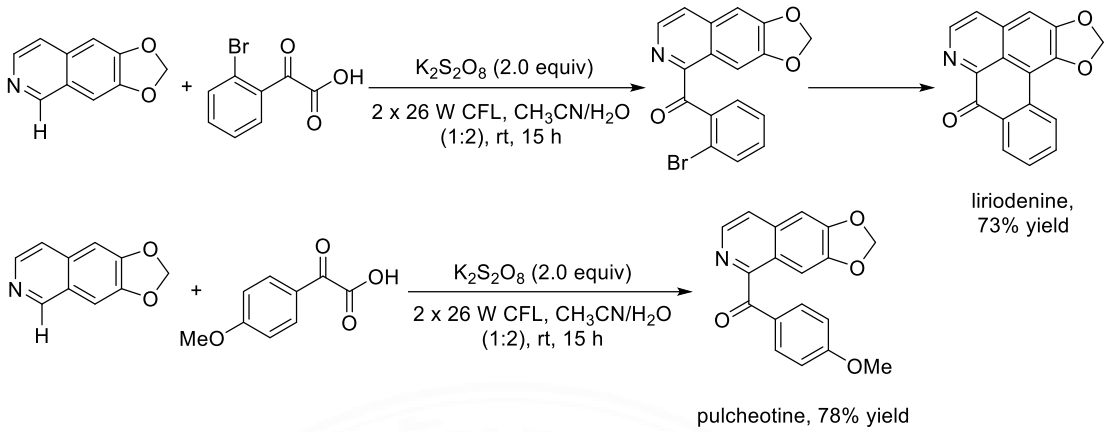


Scheme 30. Visible–light irradiation decarboxylative coupling reaction of *N*–heterocycles with carboxylic acids

Guillemard *et al*. explored visible-light photoinduced acylation of *N*–heterocycles in the absence of any photosensitizer under a mild synthetic method.(Guillemard, Colobert-Leuenberger, & Wencel-Delord, 2018) Photosensitizer such as expensive Ru– and Ir–based complexes or organic dyes generally required in the photocatalytic transformations owing to the fact that most of organic molecules are incapable of absorbing visible–light. The reaction was successfully coupled with a broad range of α–keto acids and *N*–heteroaromatics. In addition, isoquinoline alkaloids pulcheotine and liriodenine could also were synthesized by this protocol (Scheme 31,32).(Guillemard et al., 2018)

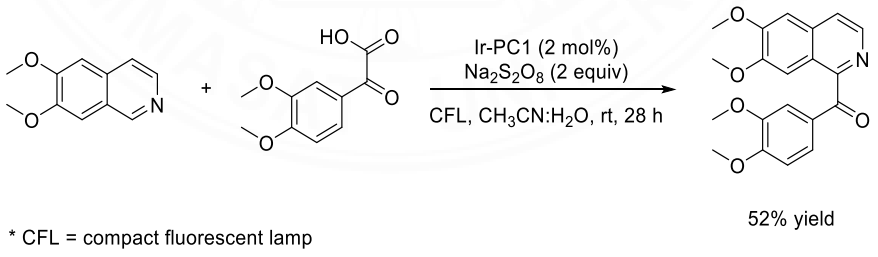


Scheme 31. A photoinduced acylation of an array of *N*–heteroaromatics with α–keto acids

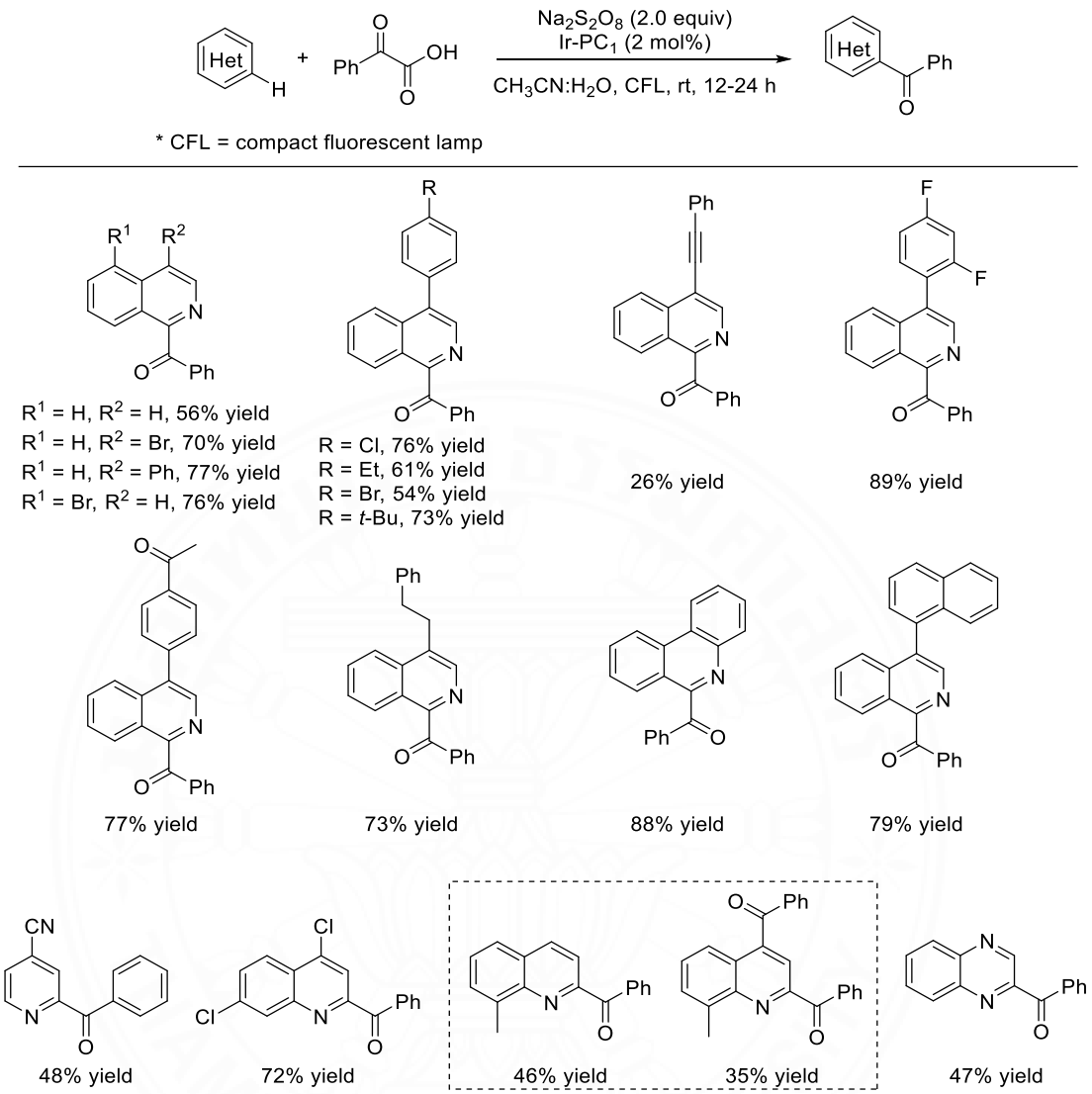


Scheme 32. The synthesis of isoquinoline alkaloids through visible–light acylation of *N*–heterocycles

In 2019, Prabhu and Manna developed the direct decarboxylative acylation of isoquinolines, quinolones, phenanthridines, and pyridines *via* visible–light mediated using phenylglyoxalic acid as an efficient acyl radical source.(Manna & Prabhu, 2019) The acylated *N*–heterocycle compounds were synthesized using a compact fluorescent lamp (CFL) light irradiation, $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (Ir-PC1) as a photocatalyst and $Na_2S_2O_8$ as an oxidant. This mild method could be subjected to a variety of *N*–heterocycles to phenylglyoxalic acid and applied to synthesize a acetylcholinesterase inhibitor (Scheme 33,34).(Manna & Prabhu, 2019)

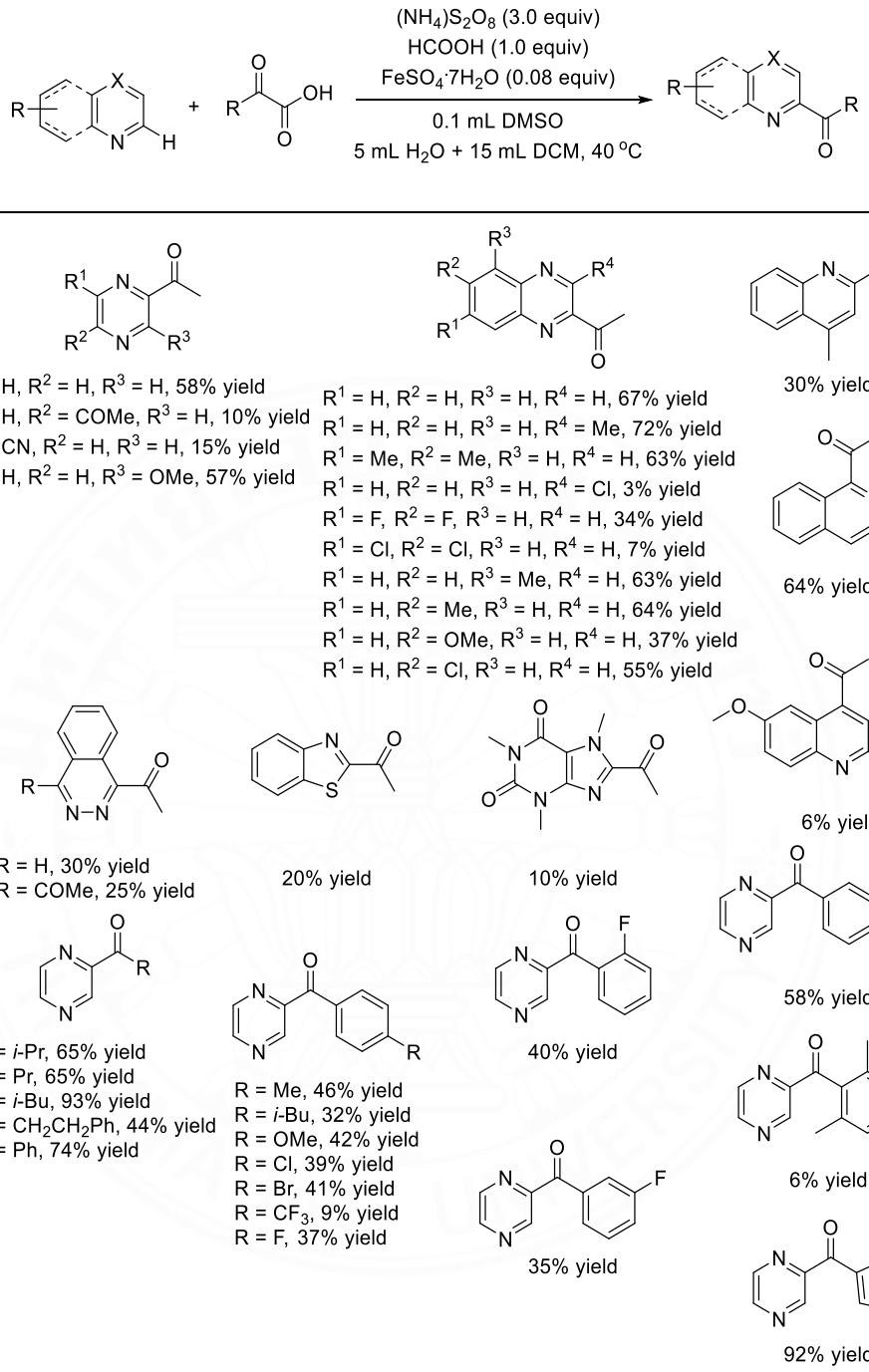


Scheme 33. The synthesis of acetylcholinesterase inhibitor through by the visible-light mediated decarboxylative acylation of isoquinoline



Scheme 34. The decarboxylative acylation of heterocyclic compounds with phenylglyoxalic acids under the irradiation of CFL–light

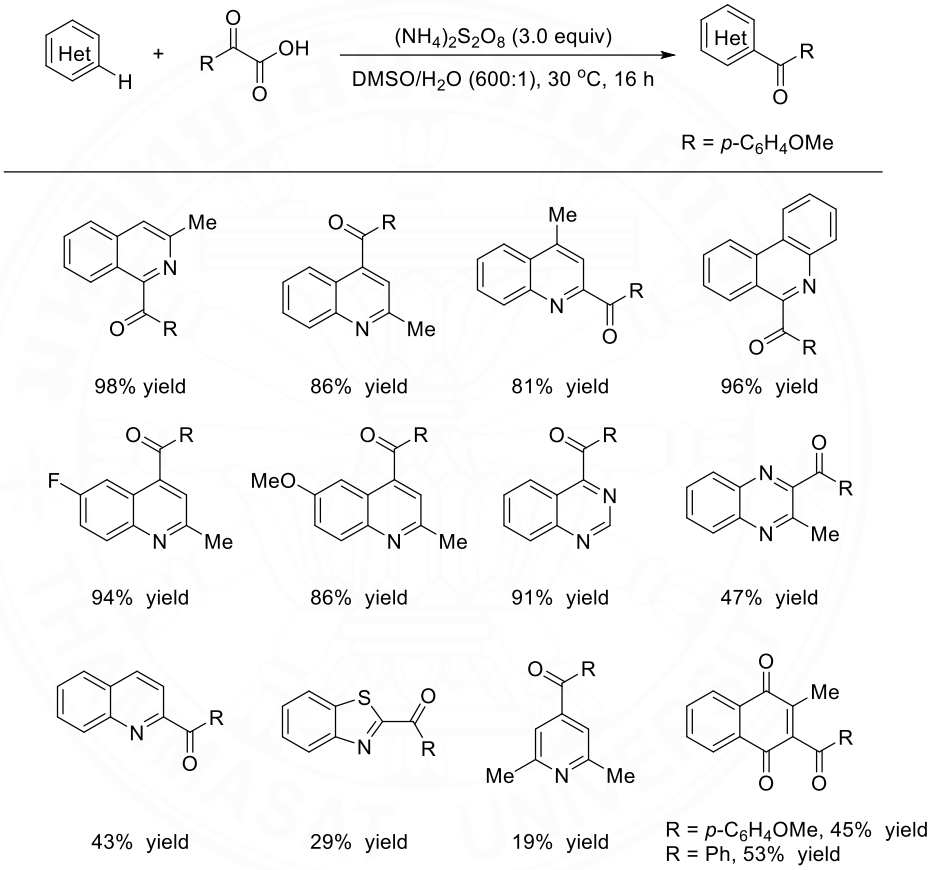
Wang and Zeng presented an efficient intermolecular decarboxylative acylation of *N*–heterocycles with α–keto acids *via* iron–catalyzed Minisci reaction.(Wang & Zeng, 2019) The non–noble metal Fe(II) was applied as a catalyst instead of noble transition metal such as Ru, Pd, and Ag salts that generally used in the Minisci acylation of *N*–heteroarenes. This methodology worked well with aliphatic or aromatic α–keto acids and a wide range of *N*–heteroarene substrates under low temperature condition (Scheme 35).(Wang & Zeng, 2019)



Scheme 35. Iron–catalyzed decarboxylative cross–coupling of *N*–heteroarenes with α–keto acids

Westwood and co-workers reported Minisci direct C–H acylation of basic heterocycles and α–keto acids using only $(NH_4)_2S_2O_8$ reagent without the use of

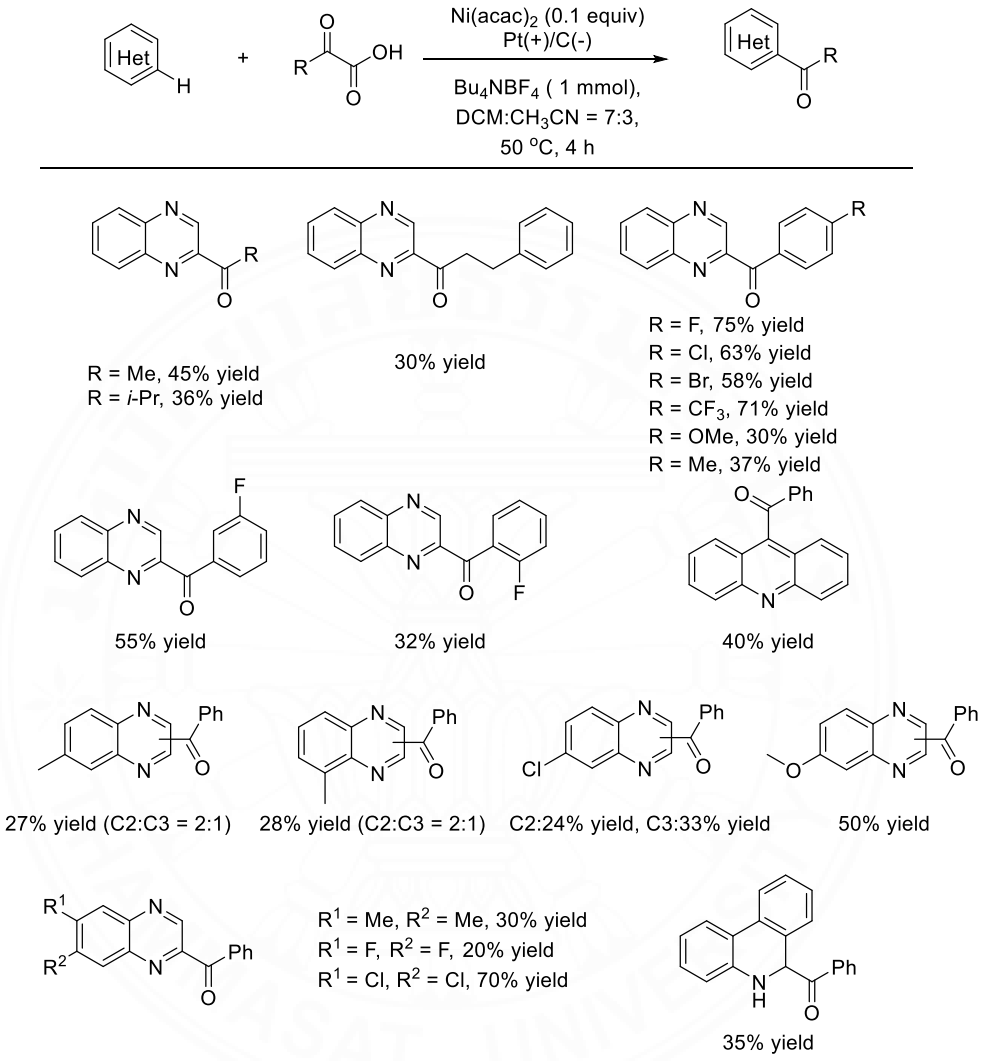
any additives, including metal catalyst, photocatalyst, or light activation.(Westwood, Lamb, Sutherland, & Lee, 2019) The acylated products in good to excellent yields were formed under mild and environmentally friendly conditions. Moreover, the utility of $(NH_4)_2S_2O_8$ was more cost–effective than hypervalent iodine oxidants, and any excess amounts were easily eliminated by washing with water (Scheme 36).(Westwood et al., 2019)



Scheme 36. Minisci–type direct C–H acylation of heterocycles and α–keto acids using $(NH_4)_2S_2O_8$ under mild reaction conditions

In 2020, Ding, Xu, and Zeng developed the Minisci acylation of aromatic electron-deficient heterocycles with α–Keto acids using nickel–catalyzed electrochemical.(Ding, Xu, & Zeng, 2020) The reaction was performed using a platinum net as the anode and a graphite plate as the cathode at a constant current of 5 mA cm^{-2} with $Ni(acac)_2$ as the redox catalyst and Bu_4NBF_4 as the supporting

electrolyte. This coupling avoided the use of an expensive metal catalyst such as silver–based catalysts (Scheme 37).(Ding et al., 2020)



Scheme 37. Decarboxylative cross–coupling of *N*–heteroarenes with α–Keto acids by nickel catalyzed electrochemical

CHAPTER 3
RESEARCH METHODOLOGY

3.1 General

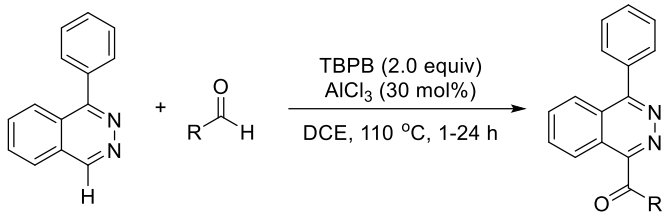
Commercial grade reagents and solvents were used as received from the supplier except where indicated otherwise. Ethyl acetate (EtOAc) and hexane were purified by distillation. Thin layer chromatography was performed on Merck precoated silica gel 60 F254 plates. Silica gel 60 (Silicycle, 70–230 mesh) was used for column chromatography and silica gel 60 PF254 (Merck) was used for preparative thin layer chromatography.

^{1}H and ^{13}C–NMR spectra were recorded in $CDCl_3$ using a Bruker AVANCE 400 NMR spectrometer. ^{1}H–NMR and ^{13}C–NMR chemical shifts (δ) were reported in units of part per million (ppm) relative to tetramethylsilane (TMS) as internal standard at δ equal to zero ppm. Coupling constants (*J*) were reported in Hertz (Hz). For the fine-structure interpretation, the abbreviations of the signals are as follows:

s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, q = quartet, quin = quintet, sep = septet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets

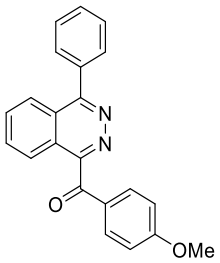
Infrared spectra were recorded on a PerkinElmer Spectrum One Spectrophotometer using a universal attenuated total reflectance (ATR) technique and were reported in cm^{-1}. HRESIMS analyses were determined using a Bruker Daltonics MicroTOF$_{LC}$ mass spectrometer.

3.2 General procedure for the acylation of 1-phenylphthalazine (1a)



Procedure A for the synthesis of compound **3a**–**3aa:** (4-Methoxyphenyl)(4-phenylphthalazin-1-yl)methanone (**3a**). A solution of 1-phenylphthalazine **1a** (50 mg, 0.24 mmol), $AlCl_3$ (9.70 mg, 0.07 mmol), 4-Methoxybenzaldehyde **2a** (0.06 mL, 0.48 mmol), and *tert*-butyl peroxybenzoate (TBPB) (0.10 mL, 0.48 mmol) in dichloroethane (DCE) (1 mL) in sealed tube was stirred at 110 ^{o}C (monitoring the reaction by TLC). The resulting solution was extracted with a saturated sodium bicarbonate solution, CH_2Cl_2, and brine, and dried over anhydrous $MgSO_4$. The combined organic layers were evaporated under reduce pressure. The residue was purified by column chromatography using 20–30% EtOAc/hexane as an eluent to yield the title compound **3a** as a yellow solid (71 mg, 86%).

Procedure B for the synthesis of compound **3a–3ab**: 3-Methyl-1-(4-phenylphthalazin-1-yl)butan-1-one (**3ab**). A solution of 1-phenylphthalazine **1a** (50 mg, 0.24 mmol), $AlCl_3$ (9.70 mg, 0.07 mmol), Isoamyl alcohol **4d** (0.05 mL, 0.48 mmol), and *tert*-butyl peroxybenzoate (TBPB) (0.10 mL, 0.48 mmol) in dichloroethane (DCE) (1 mL) in sealed tube was stirred at 110 $^{\circ}$C (monitoring the reaction by TLC). The resulting solution was extracted with a saturated sodium bicarbonate solution, CH_2Cl_2, and brine, and dried over anhydrous $MgSO_4$. The combined organic layers were evaporated under reduce pressure. The residue was purified by column chromatography using 3–5% EtOAc/hexane as an eluent to yield the title compound **3ab** as a yellow solid (15 mg, 21%).



(4-Methoxyphenyl)(4-phenylphthalazin-1-yl)methanone (3a)

Yield: 86% (71 mg); yellow solid; mp = 165–167 °C.

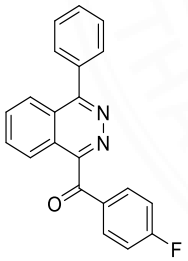
TLC: R_f = 0.40 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3055, 2935, 2842, 1652, 1597, 1574, 1510, 1424, 1386, 1319, 1245, 1167, 1021, and 843 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 3.89 (s, 3H), 6.55–7.05 (m, 2H), 7.57–7.63 (m, 1H), 7.80–7.84 (m, 2H), 7.86–7.93 (m, 2H), 8.10–8.14 (m, 2H), 8.15–8.19 (m, 2H), and 8.21–8.26 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.4, 164.4, 160.6, 155.6, 135.8, 133.5(x2), 132.6, 130.2(x3), 129.6, 129.1, 128.5(x2), 126.6, 125.8, 125.5, 125.3, 113.8(x2), and 55.5.

HRMS Calcd for $[(C_{22}H_{16}N_2O_2)+Na]^+$: 363.1104. Found: 363.1100.



(4-Fluorophenyl)(4-phenylphthalazin-1-yl)methanone (3b)

Yield: 35% (28 mg); yellow oil.

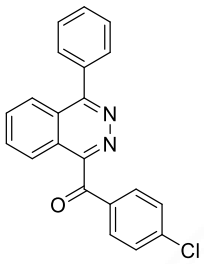
TLC: R_f = 0.90 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3066, 2925, 2854, 1667, 1595, 1385, 1236, 969, 785, and 700 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.19 (t, 2H, J = 8.5 Hz), 7.56–7.67 (m, 3H), 7.77–7.86 (m, 2H), 7.89–7.99 (m, 2H), 8.16–8.24 (m, 3H), and 8.32 (dd, 1H, J = 7.9 and 1.6 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.5, 166.5 (255 Hz), 161.1, 154.8, 135.9, 134.1 (9 Hz), 133.1, 132.96, 132.8 (3 Hz), 130.4(x2), 129.98, 128.8(x2), 127.0, 126.1, 125.6, 125.55, and 115.9 (22 Hz).

HRMS Calcd for $[(C_{21}H_{13}FN_2O)+Na]^+$: 351.0904. Found: 351.0909.



(4-Chlorophenyl)(4-phenylphthalazin-1-yl)methanone (3c)

Yield: 21% (18 mg); yellow solid; mp = 132–133 ˚C.

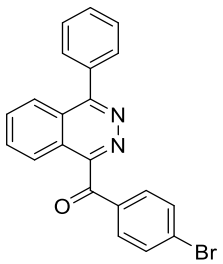
TLC: R_f = 0.79 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3060, 2925, 2854, 1667, 1586, 1522, 1486, 1446, 1386, 1326, 1235, 1175, 1091, 968, 869, 784, 752, 699, and 669 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.49 (d, 2H, J = 8.5 Hz), 7.58–7.65 (m, 3H), 7.79–7.86 (m, 2H), 7.89–7.99 (m, 2H), 8.11 (d, 2H, J = 8.5 Hz), 8.21 (br d, 1H, J = 8.8 Hz), and 8.33 (br d, 1H, J = 8.9 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.9, 161.2, 154.6, 140.9, 135.9, 134.8, 133.2, 133.0, 132.7(x2), 130.4(x2), 130.0, 129.0(x2), 128.8(x2), 127.0, 126.1, 125.6, and 125.5.

HRMS Calcd for $[(C_{21}H_{13}ClN_2O)+Na]^+$: 367.0609. Found: 367.0611.



(4-Bromophenyl)(4-phenylphthalazin-1-yl)methanone (3d)

Yield: 32% (30 mg); yellow solid; mp = 126–128 ˚C.

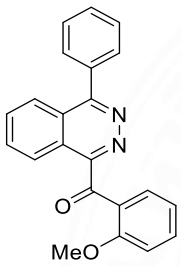
TLC: R_f = 0.67 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3059, 2924, 2853, 1667, 1583, 1566, 1483, 1384, 1238, 868, 783, and 699 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.59–7.64 (m, 3H), 7.64–7.69 (m, 2H), 7.79–7.85 (m, 2H), 7.90–7.98 (m, 2H), 8.01–8.05 (m, 2H), 8.18–8.24 (m, 1H), and 8.31–8.37 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 192.1, 161.2, 154.6, 135.9, 135.2, 133.2, 133.0(x2), 132.8, 132.0(x2), 130.4(x2), 130.0, 129.8, 128.8(x2), 127.1, 126.2, 125.6, and 125.5.

HRMS Calcd for $[(C_{21}H_{13}BrN_2O)+H]^+$: 389.0284. Found: 389.0287.



(2-Methoxyphenyl)(4-phenylphthalazin-1-yl)methanone (3h)

Yield: 59% (49 mg); yellow solid; mp = 156–158 °C.

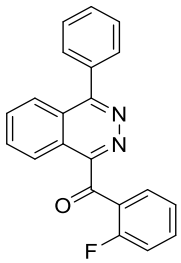
TLC: R_f = 0.40 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3071, 3011, 2979, 2926, 2841, 1663, 1596, 1485, 1382, 1244, 1012, 760, and 705 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 3.45 (s, 3H), 6.94 (d, 1H, J = 8.0 Hz), 7.12 (td, 1H, J = 7.6 and 0.9 Hz), 7.53–7.62 (m, 4H), 7.79–7.82 (m, 2H), 7.87–7.97 (m, 3H), 8.16–8.20 (m, 1H), and 8.40–8.44 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 194.8, 160.6, 159.7, 156.8, 136.2, 134.9, 132.8, 132.4, 131.5, 130.4(x2), 129.8, 128.7(x2), 128.1, 126.7, 125.9, 125.8, 124.8, 121.1, 112.3, and 55.9.

HRMS Calcd for $[(C_{22}H_{16}N_2O_2)+H]^+$: 341.1285. Found: 341.1291.



(2-Fluorophenyl)(4-phenylphthalazin-1-yl)methanone (3i)

Yield: 20% (16 mg); yellow oil.

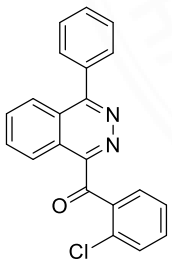
TLC: R_f = 0.55 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3063, 2924, 2854, 1729, 1673, 1609, 1483, 1456, 1383, 1275, 1232, 753, and 699 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.09–7.15 (m, 1H), 7.33 (td, 1H, J = 7.6 and 1.0 Hz), 7.56–7.64 (m, 4H), 7.79–7.85 (m, 2H), 7.90–8.02 (m, 3H), 8.21 (d, 1H, J = 7.7 Hz), and 8.56 (d, 1H, J = 8.2 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 192.4, 162.1 (^1J = 256 Hz), 161.3, 154.8, 136.0, 135.2 (^3J = 9 Hz), 133.3, 132.8, 131.77, 131.76, 130.5(x2), 129.9, 128.7(x2), 127.0, 126.1, 125.5, 125.0, 124.5 (^4J = 3 Hz), and 116.7 (^2J = 22 Hz).

HRMS Calcd for $[(C_{21}H_{13}FN_2O)+Na]^+$: 351.0904. Found: 351.0908.



(2-Chlorophenyl)(4-phenylphthalazin-1-yl)methanone (3j)

Yield: 29% (24 mg); yellow oil.

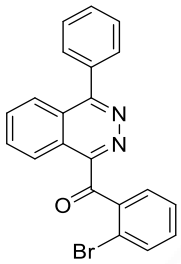
TLC: R_f = 0.80 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3444, 3061, 2956, 2925, 2855, 1681, 1386, 1270, 1228, 1083, 969, 875, 747, and 700 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.39–7.51 (m, 3H), 7.56–7.62 (m, 3H), 7.77 (dd, 1H, J = 7.6 and 1.7 Hz), 7.79–7.85 (m, 2H), 7.94 (t, 1H, J = 8.0 Hz), 8.03 (t, 1H, J = 8.2 Hz), 8.22 (d, 1H, J = 8.4 Hz), and 8.79 (d, 1H, J = 8.3 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 195.6, 161.4, 153.9, 138.7, 135.9, 133.5, 132.8, 132.6, 131.2, 130.5(x2), 130.2, 130.0(x2), 128.7(x2), 127.03, 127.0, 126.1, 125.7, and 125.4.

HRMS Calcd for $[(C_{21}H_{13}ClN_2O)+Na]^+$: 367.0609. Found: 367.0612.



(2-Bromophenyl)(4-phenylphthalazin-1-yl)methanone (3k)

Yield: 21% (20 mg); pale yellow solid; mp = 146–148 °C.

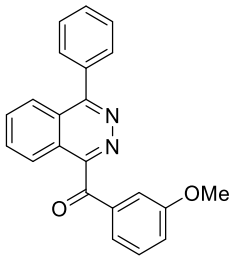
TLC: R_f = 0.76 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3060, 2925, 2853, 1682, 1386, 1268, 1228, 1077, 968, 763, 744, and 699 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.39 (td, 1H, *J* = 7.6 and 1.5 Hz), 7.48 (t, 1H, *J* = 7.5 Hz), 7.55–7.65 (m, 4H), 7.72 (dd, 1H, *J* = 7.6 and 1.4 Hz), 7.78–7.86 (m, 2H), 7.94 (t, 1H, *J* = 7.4 Hz), 8.04 (t, 1H, *J* = 7.4 Hz), 8.22 (d, 1H, *J* = 8.4 Hz), and 8.85 (d, 1H, *J* = 8.4 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 196.3, 161.4, 153.5, 140.8, 135.9, 133.5, 133.3, 132.8, 132.5, 131.2, 130.6(x2), 130.0, 128.7(x2), 127.5, 127.0, 126.1, 125.8, 125.7, and 120.9.

HRMS Calcd for $[(C_{21}H_{13}BrN_2O)+Na]^+$: 413.0085. Found: 413.0084.



(3-Methoxyphenyl)(4-phenylphthalazin-1-yl)methanone (3l)

Yield: 55% (45 mg); yellow solid; mp = 162–164 °C.

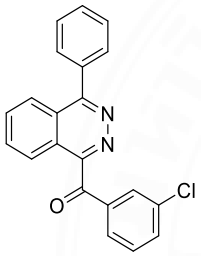
TLC: R_f = 0.57 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3062, 2939, 2837, 1668, 1580, 1485, 1384, 1326, 1263, 1211, 779, 749, and 700 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 3.88 (s, 3H), 7.20 (dd, 1H, J = 8.2 and 2.6 Hz), 7.39 (t, 1H, J = 7.9 Hz), 7.56–7.65 (m, 4H), 7.69–7.73 (m, 1H), 7.79–7.85 (m, 2H), 7.88–7.95 (m, 2H), and 8.16–8.27 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 193.1, 160.9, 159.9, 155.5, 137.6, 136.0, 133.0, 132.9, 130.4(x2), 129.9, 129.7, 128.8(x2), 126.9, 126.0, 125.54, 125.52, 124.7, 121.2, 114.5, and 55.7.

HRMS Calcd for $[(C_{22}H_{16}N_2O_2)+Na]^+$: 363.1104. Found: 363.1104.



(3-Chlorophenyl)(4-phenylphthalazin-1-yl)methanone (3m)

Yield: 14% (12 mg,); pale yellow solid; mp = 192–194 ˚C.

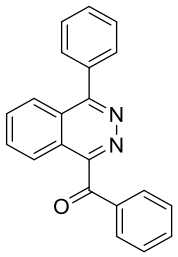
TLC: R_f = 0.81 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3063, 2925, 2849, 1670, 1568, 1386, 1324, 1230, 1076, 973, 896, 782, and 699 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.46 (t, 1H, J = 7.9 Hz), 7.58–7.67 (m, 4H), 7.80–7.87 (m, 2H), 7.95 (m, 2H), 8.03 (d, 1H, J = 7.8 Hz), 8.13 (s, 1H), 8.22 (d, 1H, J = 7.7 Hz), and 8.35 (d, 1H, J = 8.1 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.9, 161.3, 154.4, 138.0, 135.9, 135.0, 134.1, 133.2, 133.0, 131.1, 130.5(x2), 130.1, 130.0, 129.5, 128.8(x2), 127.1, 126.2, 125.6, and 125.5.

HRMS Calcd for $[(C_{21}H_{13}ClN_2O)+Na]^+$: 367.0609. Found: 367.0610.



Phenyl(4-phenylphthalazin-1-yl)methanone (3o)

Yield: 96% (72 mg); yellow solid; mp = 130–131 ˚C.

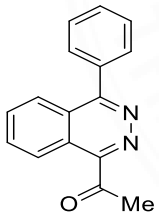
TLC: R_f = 0.63 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3060, 2923, 2852, 2337, 1666, 1596, 1578, 1522, 1487, 1447, 1384, 1327, 1235, 1179, 1075, 1027, 1000, 968, 868, 798, 777, 762, 717, and 699 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.49–7.53 (m, 2H), 7.59–7.67 (m, 4H), 7.81–7.84 (m, 2H), 7.88–7.95 (m, 2H), 8.12–8.14 (m, 2H), 8.18–8.21 (m, 1H), and 8.26–8.29 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 193.0, 160.8, 155.1, 136.2, 135.8, 134.1, 132.8, 132.7, 131.1(x2), 130.2(x2), 129.7, 128.6(x2), 128.5(x2), 126.8, 125.9, and 125.4(x2).

HRMS Calcd for $[(C_{21}H_{14}N_2O)+H]^+$: 311.1179. Found: 311.1177.



1-(4-Phenylphthalazin-1-yl)ethan-1-one (3p)

Yield: 56% (34 mg); brown solid; mp = 151–153 ˚C.

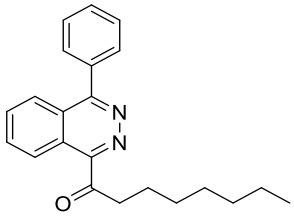
TLC: R_f = 0.57 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3060, 2926, 1697, 1385, 1350, 1312, 1208, 1185, 1133, 964, 778, 764, and 700 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 3.01 (s, 3H), 7.55–7.62 (m, 3H), 7.75–7.80 (m, 2H), 7.88 (ddd, 1H, J = 8.3, 7.1, and 1.2 Hz), 7.98 (ddd, 1H, J = 8.4, 7.0, and 1.3 Hz), 8.14 (d, 1H, J = 8.3 Hz), and 9.05 (d, 1H, J = 8.4 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 201.7, 162.1, 151.6, 135.8, 133.8, 132.6, 130.4(x2), 130.1, 128.8(x2), 126.9, 126.3, 126.2, 124.9, and 28.9.

HRMS Calcd for $[(C_{16}H_{12}N_2O)+Na]^+$: 271.0842. Found: 271.0851.



1-(4-Phenylphthalazin-1-yl)octan-1-one (3q)

Yield: 86% (69 mg); yellow solid; mp = 77–78 ˚C.

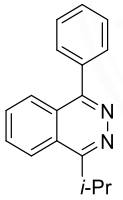
TLC: R_f = 0.77 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3057, 2956, 2920, 2855, 1695, 1389, 974, 913, 788, 762, and 703 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 0.88 (m, 3H), 1.21–1.50 (m, 8H), 1.84 (quin, 2H, *J* = 7.4 Hz), 3.49 (dd, 2H, *J* = 14.9 and 7.3 Hz), 7.56–7.62 (m, 3H), 7.75–7.82 (m, 2H), 7.87 (ddd, 1H, *J* = 8.3, 7.1, and 1.2 Hz), 7.97 (ddd, 1H, *J* = 8.3, 7.1, and 1.2 Hz), 8.14 (d, 1H, *J* = 8.2 Hz), and 8.94 (d, 1H, *J* = 8.4 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 204.1, 161.9, 152.1, 136.0, 133.5, 132.5, 130.4(x2), 130.0, 128.7(x2), 126.8, 126.2, 126.1, 124.9, 40.8, 31.9, 29.4, 29.3, 24.3, 22.8, and 14.2.

HRMS Calcd for $[(C_{22}H_{24}N_2O)+Na]^+$: 355.1781. Found: 355.1783.



1-Isopropyl-4-phenylphthalazine (3r)

Yield: 67% (45 mg); yellow solid; mp = 110–111 ˚C.

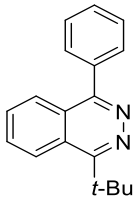
TLC: R_f = 0.44 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3061, 2966, 2929, 2871, 1383, 1181, 1030, 780, 762, 700, and 666 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 1.59 (d, 6H, *J* = 6.8 Hz), 3.95 (sep, 1H, *J* = 6.8 Hz), 7.50–7.59 (m, 3H), 7.73–7.78 (m, 2H), 7.81 (ddd, 1H, *J* = 8.3, 7.1, and 1.2 Hz), 7.90 (ddd, 1H, *J* = 8.2, 7.1, and 1.1 Hz), 8.09 (d, 1H, *J* = 8.1 Hz), and 8.24 (d, 1H, *J* = 7.4 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 163.1, 158.8, 136.8, 131.8, 131.5, 130.3(x2), 129.2, 128.5(x2), 127.2, 125.52, 125.50, 123.9, 30.6, and 22.2(x2).

HRMS Calcd for $[(C_{17}H_{16}N_2)+Na]^+$: 271.1210. Found: 271.1210.



2,2-Dimethyl-1-(4-phenylphthalazin-1-yl)propan-1-one (3s)

Yield: 74% (52 mg); yellow solid; mp = 100–102 ˚C.

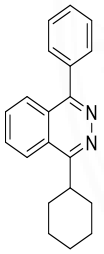
TLC: R_f = 0.70 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3059, 2970, 2929, 2873, 1520, 1446, 1385, 1367, 780, and 700 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 1.76 (s, 9H), 7.51–7.57 (m, 3H), 7.71–7.76 (m, 2H), 7.77–7.80 (m, 1H), 7.86 (ddd, 1H, *J* = 8.4, 7.0, and 1.4 Hz), 8.10 (dd, 1H, *J* = 8.3 and 0.8 Hz), and 8.55 (d, 1H, *J* = 8.5 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 164.1, 159.2, 136.6, 130.9, 130.85, 130.3(x2), 129.2, 128.5(x2), 127.8, 126.5, 126.3, 125.3, 39.3, and 31.1(x3).

HRMS Calcd for $[(C_{18}H_{18}N_2)+Na]^+$: 285.1362. Found: 285.1364.



1-Cyclohexyl-4-phenylphthalazine (3t)

Yield: 42% (32 mg); yellow oil.

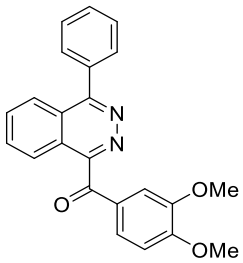
TLC: R_f = 0.63 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3060, 2925, 2852, 1527, 1447, 1383, 998, 780, 756, 699, and 662 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 1.19–1.64 (m, 4H), 1.79–2.15 (m, 6H), 3.55 (tt, 1H, *J* = 14.7 and 3.5 Hz), 7.48–7.60 (m, 3H), 7.72–7.77 (m, 2H), 7.79 (ddd, 1H, *J* = 8.3, 7.0, and 1.2 Hz), 7.89 (ddd, 1H, *J* = 8.3, 7.0, and 1.2 Hz), 8.08 (br d, 1H, *J* = 8.3 Hz), and 8.23 (d, 1H, *J* = 8.4 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 162.7, 158.7, 136.8, 131.8, 131.5, 130.3(x2), 129.2, 128.6(x2), 127.2, 125.6, 125.5, 123.9, 40.8, 32.5(x2), 27.0(x2), and 26.4.

HRMS Calcd for $[(C_{20}H_{20}N_2)+Na]^+$: 311.1519. Found: 311.1517.



(3,4-Dimethoxyphenyl)(4-phenylphthalazin-1-yl)methanone (3u)

Yield: 46% (41 mg); yellow solid; mp = 181–182 ˚C.

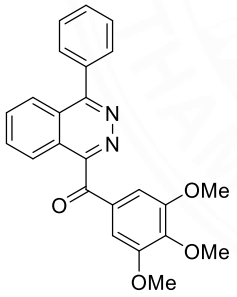
TLC: R_f = 0.36 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3057, 2935, 2840, 1654, 1591, 1583, 1511, 1421, 1383, 1263, 1214, 1174, 1137, 1019, 754, and 700 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 3.95 (s, 3H), 3.99 (s, 3H), 6.87 (d, 1H, J = 8.5 Hz), 7.57–7.64 (m, 4H), 7.79–7.85 (m, 3H), 7.86–7.94 (m, 2H), and 8.14–8.24 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.7, 160.8, 155.8, 154.6, 149.4, 136.0, 132.9(x2), 130.4(x2), 129.9, 129.5, 128.8(x2), 127.9, 126.9, 126.0, 125.7, 125.6, 111.7, 110.2, 56.4, and 56.3.

HRMS Calcd for $[(C_{23}H_{18}N_2O_3)+H]^+$: 371.1390. Found: 371.1391.



(4-Phenylphthalazin-1-yl)(3,4,5-trimethoxyphenyl)methanone (3v)

Yield: 38% (37 mg); pale yellow solid; mp = 177–178 ˚C.

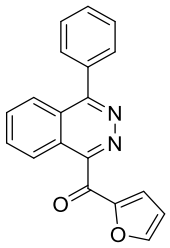
TLC: R_f = 0.44 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 2927, 2854, 1727, 1662, 1580, 1501, 1462, 1415, 1384, 1333, 1207, 1125, 1001, 753, and 701 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 3.87 (d, 6H, J = 7.9 Hz), 3.96 (s, 3H), 7.42 (s, 2H), 7.57–7.64 (m, 3H), 7.80–7.85 (m, 2H), 7.89–7.96 (m, 2H), and 8.18–8.28 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.9, 160.9, 155.5, 153.2(x2), 144.0, 135.9, 133.0, 132.9, 131.3, 130.4(x2), 130.0, 128.8(x2), 126.9, 126.1, 125.7, 125.67, 108.9(x2), 61.2, and 56.5(x2).

HRMS Calcd for $[(C_{24}H_{20}N_2O_4)+H]^+$: 401.1496. Found: 401.1500.



Furan-2-yl(4-phenylphthalazin-1-yl)methanone (3w)

Yield: 16% (12 mg); brown solid; mp = 134–135 °C.

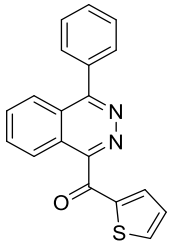
TLC: R_f = 0.40 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3120, 3061, 2925, 2854, 1727, 1652, 1561, 1462, 1386, 1271, 1021, 765, and 700 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 6.65 (dd, 1H, J = 3.6 and 1.7 Hz), 7.59–7.63 (m, 3H), 7.66 (dd, 1H, J = 3.6 and 0.7 Hz), 7.79–7.84 (m, 3H), 7.92 (ddd, 1H, J = 8.3, 7.1, and 1.3 Hz), 7.98 (ddd, 1H, J = 8.4, 7.1, and 1.4 Hz), 8.17–8.21 (m, 1H), and 8.62–8.66 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 179.7, 161.5, 153.5, 152.1, 148.9, 135.9, 133.3, 132.9, 130.4(x2), 130.0, 128.8(x2), 127.0, 126.2, 125.8, 125.5, 125.1, and 113.0.

HRMS Calcd for $[(C_{19}H_{12}N_2O_2)+H]^+$: 301.0972. Found: 301.0970.



(4-Phenylphthalazin-1-yl)(thiophen-2-yl)methanone (3x)

Yield: 37% (28 mg); yellow solid; mp = 130–132 °C.

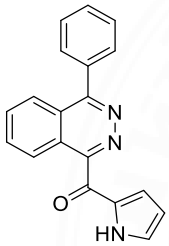
TLC: R_f = 0.61 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3063, 2924, 1639, 1409, 1385, 1348, 1241, 1066, 1037, 960, 800, 729, and 698 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.21 (dd, 1H, J = 4.9 and 3.9 Hz), 7.57–7.65 (m, 3H), 7.79–7.85 (m, 3H), 7.91 (ddd, 1H, J = 8.3, 7.0, and 1.3 Hz), 7.97 (ddd, 1H, J = 8.3, 7.0, and 1.3 Hz), 8.14 (dd, 1H, J = 3.9 and 1.2 Hz), 8.18 (dd, 1H, J = 7.7 and 0.6 Hz), and 8.67 (d, 1H, J = 8.4 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 184.7, 161.5, 153.7, 142.3, 137.6, 137.0, 135.9, 133.2, 132.8, 130.4(x2), 130.0, 128.8(x2), 128.4, 126.9, 126.2, 125.9, and 125.4.

HRMS Calcd for $[(C_{19}H_{12}N_2OS)+Na]^+$: 339.0562. Found: 339.0562.



(4-phenylphthalazin-1-yl)(1H-pyrrol-2-yl)methanone (3y)

Yield: 32% (23 mg,); pale yellow solid; mp = 158–159 °C.

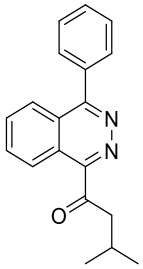
TLC: R_f = 0.37 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3281, 3065, 2924, 2854, 1743, 1619, 1543, 1412, 1369, 1109, 752, and 699 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 6.39 (dt, 1H, J = 4.0 and 2.4 Hz), 7.15–7.20 (m, 1H), 7.30–7.37 (m, 1H), 7.57–7.65 (m, 3H), 7.77–7.84 (m, 2H), 7.90 (ddd, 1H, J = 8.3, 7.1, and 1.3 Hz), 7.93–8.00 (m, 1H), 8.14–8.19 (m, 1H), 8.80 (br s, 1H), and 10.62 (br s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 180.2, 161.3, 154.3, 135.9, 133.1, 132.8, 132.3, 130.4(x2), 130.0, 128.8(x2), 126.8, 126.6, 126.4, 126.3, 125.8, 121.7, and 111.9.

HRMS Calcd for $[(C_{19}H_{13}N_3O)+Na]^+$: 322.0951. Found: 322.0953.



3-Methyl-1-(4-phenylphthalazin-1-yl)butan-1-one (3ab)

Yield: 21% (15 mg); yellow solid; mp = 125–126 °C.

TLC: R_f = 0.69 (elution solvent: EtOAc:hexane = 40:60).

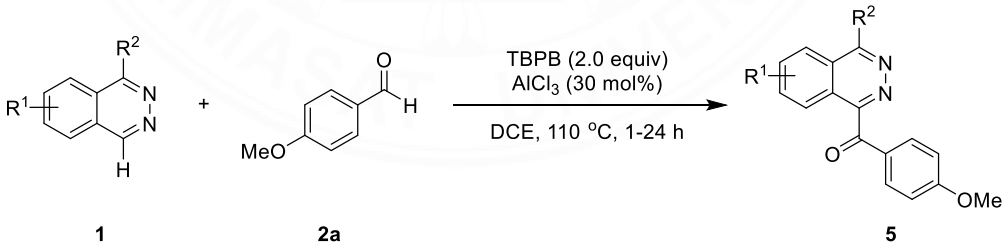
IR (neat) ν_{max} 3056, 2958, 2930, 2872, 1691, 1560, 1521, 1470, 1446, 1387, 1310, 784, 763, and 702 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 1.06 (d, 6H, *J* = 6.7 Hz), 2.41 (sep, 1H, *J* = 6.8 Hz), 3.37 (d, 2H, *J* = 7.0 Hz), 7.57–7.62 (m, 3H), 7.76–7.81 (m, 2H), 7.88 (ddd, 1H, *J* = 8.3, 7.0, and 1.3 Hz), 7.97 (ddd, 1H, *J* = 8.4, 7.0, and 1.3 Hz), 8.15 (ddd, 1H, *J* = 8.3, 1.2, and 0.7 Hz), and 8.94 (ddd, 1H, *J* = 8.4, 1.2, and 0.8 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 203.8, 161.9, 152.3, 136.0, 133.5, 132.5, 130.4(x2), 130.0, 128.8(x2), 126.9, 126.2, 126.1, 124.9, 49.5, 25.3, and 22.9 (x2).

HRMS Calcd for $[(C_{19}H_{18}N_2O)+H]^+$: 291.1492. Found: 291.1502.

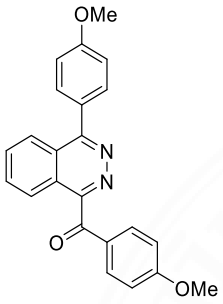
3.3 General procedure for the acylation of 1-substituted phthalazines (1) with 4-anisaldehyde (2a)



1 **2a** **5**

Procedure C for the synthesis of compound **5aa**–**5oa**: (4-Methoxyphenyl)(4-(4-methoxyphenyl)phthalazin-1-yl)methanone (**5aa**). A solution of 1-substituted phthalazines **1** (50 mg, 0.21 mmol), $AlCl_3$ (8.50 mg, 0.06 mmol), 4-Methoxybenzaldehyde **2a** (0.05 mL, 0.42 mmol), and *tert*-butyl peroxybenzoate (TBPB) (0.08 mL, 0.42 mmol) in dichloroethane (DCE) (0.85 mL) in sealed tube was stirred at 110 °C (monitoring the reaction by TLC). The resulting solution was

extracted with a saturated sodium bicarbonate solution, CH_2Cl_2, brine and dried over anhydrous $MgSO_4$. The combined organic layers were evaporated under reduce pressure. The residue was purified by column chromatography using 15–20% EtOAc/hexane as an eluent to yield the title compound **5aa** as a yellow solid (51 mg, 65%).



(4-Methoxyphenyl)(4-(4-methoxyphenyl)phthalazin-1-yl)methanone (5aa)

Yield: 65% (51 mg); yellow solid; mp = 179–180 ˚C.

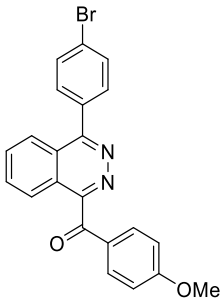
TLC: R_f = 0.67 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 2956, 2923, 2853, 1649, 1598, 1511, 1386, 1246, 1171, 1026, and 780 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 3.90 (s, 3H), 3.93 (s, 3H), 6.98 (d, 2H, J = 8.9 Hz), 7.13 (d, 2H, J = 8.6 Hz), 7.81 (d, 2H, J = 8.6 Hz), 7.87–7.93 (m, 2H), 8.12 (d, 2H, J = 8.9 Hz), and 8.21–8.27 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.6, 164.6, 161.2, 160.4, 155.4, 133.8(x2), 132.8, 132.7, 132.0(x2), 129.5, 128.3, 127.0, 126.1, 125.8, 125.7, 114.3(x2), 114.0(x2), 55.8, and 55.6.

HRMS Calcd for $[(C_{23}H_{18}N_2O_3)+H]^+$: 371.1390. Found: 371.1396.



(4-(4-Bromophenyl)phthalazin-1-yl)(4-methoxyphenyl)methanone (5ba)

Yield: 52% (38 mg); yellow solid; mp = 187–189 ˚C.

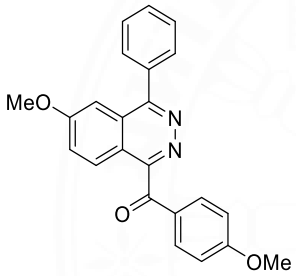
TLC: R_f = 0.67 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3066, 2926, 2841, 1658, 1596, 1573, 1510, 1423, 1382, 1325, 1246, 1170, 968, and 844 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 3.89 (s, 3H), 6.95–7.01 (m, 2H), 7.69–7.77 (m, 4H), 7.89–7.94 (m, 2H), 8.07–8.15 (m, 3H), and 8.21–8.27 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$ δ_C 191.4, 164.7, 159.8, 155.9, 134.9, 133.7(x2), 133.0(x2), 132.0(x2), 131.9(x2), 129.3, 126.4, 125.9, 125.8, 125.5, 124.5, 114.1(x2), and 55.7.

HRMS Calcd for $[(C_{22}H_{15}BrN_2O_2)+H]^+$: 419.0390. Found: 419.0390.



(6-Methoxy-4-phenylphthalazin-1-yl)(4-methoxyphenyl)methanone (5da)

Yield: 42% (33 mg); yellow oil.

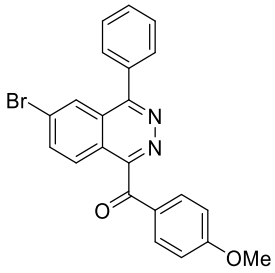
TLC: R_f = 0.60 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3058, 3008, 2924, 2853, 1716, 1658, 1596, 1489, 1403, 1246, 1170, 1140, and 702 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 3.86 (s, 3H), 3.88 (s, 3H), 6.97 (d, 2H, J = 8.8 Hz), 7.41 (d, 1H, J = 2.3 Hz), 7.48 (dd, 1H, J = 9.1 and 2.4 Hz), 7.56–7.64 (m, 3H), 7.80–7.86 (m, 2H), 8.11 (d, 2H, J = 8.8 Hz), and 8.16 (d, 1H, J = 9.1 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.7, 164.6, 162.5, 160.1, 155.1, 136.3, 133.7(x2), 130.0(x2), 129.7, 129.4, 128.8(x2), 128.3, 127.8, 124.6, 121.0, 114.0(x2), 105.1, 55.9, and 55.7.

HRMS Calcd for $[(C_{23}H_{18}N_2O_3)+H]^+$: 371.1390. Found: 371.1392.



(6-Bromo-4-phenylphthalazin-1-yl)(4-methoxyphenyl)methanone (5ea)

Yield: 47% (35 mg); pale yellow solid; mp = 196–197 ˚C.

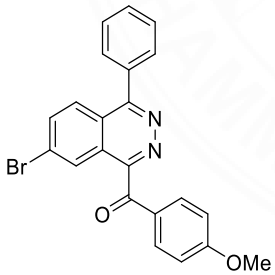
TLC: R_f = 0.67 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3081, 2924, 2843, 1654, 1601, 1574, 1510, 1392, 1319, 1244, 1177, 764, and 695 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 3.90 (s, 3H), 6.99 (d, 2H, J = 8.9 Hz), 7.60–7.67 (m, 3H), 7.77–7.87 (m, 2H), 7.99 (dd, 1H, J = 8.9 and 1.9 Hz), 8.09–8.26 (m, 3H), and 8.31 (d, 1H, J = 1.7 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.0, 164.8, 159.8, 155.3, 136.4, 135.4, 133.8(x2), 130.3(x2), 130.2, 129.1, 129.0(x2), 127.8, 127.6, 127.2, 125.9, 124.1, 114.1(x2), and 55.8.

HRMS Calcd for $[(C_{22}H_{15}BrN_2O_2)+Na]^+$: 441.0209. Found: 441.0205.



(7-Bromo-4-phenylphthalazin-1-yl)(4-methoxyphenyl)methanone (5fa)

Yield: 60% (44 mg); yellow solid; mp = 158–160 ˚C.

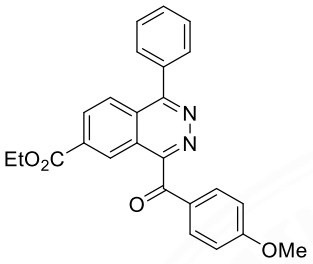
TLC: R_f = 0.59 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3060, 2929, 2842, 1652, 1594, 1572, 1510, 1445, 1384, 1316, 1241, 1170, 841, and 700 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 3.91 (s, 3H), 6.97–7.02 (m, 2H), 7.58–7.63 (m, 3H), 7.77–7.82 (m, 2H), 7.97 (dd, 1H, J = 8.9 and 1.9 Hz), 8.05 (dd, 1H, J = 8.9 and 0.4 Hz), 8.11–8.16 (m, 2H), and 8.45–8.47 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.0, 164.8, 160.6, 154.3, 136.4, 135.6, 133.9(x2), 130.3(x2), 130.1, 129.1, 128.9(x2), 128.7, 128.3, 127.9, 126.7, 124.6, 114.1(x2), and 55.8.

HRMS Calcd for $[(C_{22}H_{15}BrN_2O_2)+H]^+$: 419.0390. Found: 419.0395.



Ethyl 4-(4-methoxybenzoyl)-1-phenylphthalazine-6-carboxylate (5ga)

Yield: 48% (36 mg); yellow solid; mp = 153–155 °C.

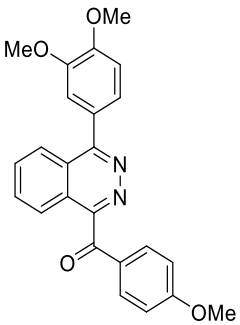
TLC: R_f = 0.53 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3061, 2927, 2852, 1721, 1658, 1596, 1572, 1510, 1445, 1424, 1376, 1285, 1258, 1231, 1170, 1109, 1023, and 701 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 1.42 (t, 3H, J = 7.1 Hz), 3.91 (s, 3H), 4.45 (q, 2H, J = 7.1 Hz), 6.98–7.03 (m, 2H), 7.60–7.65 (m, 3H), 7.80–7.86 (m, 2H), 8.12–8.18 (m, 2H), 8.25 (d, 1H, J = 8.7 Hz), 8.48 (dd, 1H, J = 8.7, and 1.6 Hz), and 8.90–8.93 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.0, 165.1, 164.8, 160.8, 156.1, 135.6, 134.3, 133.9(x2), 132.5, 130.4(x2), 130.2, 129.2, 128.9(x2), 128.0, 127.8, 127.3, 125.3, 114.1(x2), 62.2, 55.8, and 14.4.

HRMS Calcd for $[(C_{25}H_{20}N_2O_4)+H]^+$: 413.1496. Found: 413.1496.



(4-(3,4-Dimethoxyphenyl)phthalazin-1-yl)(4-methoxyphenyl)methanone (5ia)

Yield: 46% (35 mg); pale yellow solid; mp = 146–148 °C.

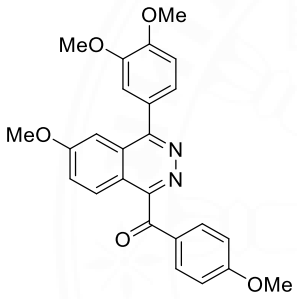
TLC: R_f = 0.71 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3067, 2956, 2924, 2853, 1717, 1656, 1596, 1516, 1418, 1322, 1257, 1234, 1167, 1140, 1024, 900, and 763 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 3.90 (s, 3H), 3.99 (s, 3H), 4.00 (s, 3H), 6.98 (d, 2H, *J* = 8.8 Hz), 7.08 (d, 1H, *J* = 8.2 Hz), 7.38 (dd, 1H, *J* = 8.2 and 1.7 Hz), 7.48 (d, 1H, *J* = 1.6 Hz), 7.88–7.94 (m, 2H), 8.12 (d, 2H, *J* = 8.8 Hz), and 8.22–8.31 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.5, 164.7, 160.3, 155.5, 150.8, 149.5, 133.8(x2), 132.9, 132.8, 129.4, 128.4, 127.1, 126.1, 125.84, 125.81, 123.7, 114.1(x2), 113.6, 111.0, 56.3, 56.2, and 55.8.

HRMS Calcd for $[(C_{24}H_{20}N_2O_4)+H]^+$: 401.1496. Found: 401.1501.



(4-(3,4-Dimethoxyphenyl)-6-methoxyphthalazin-1-yl)(4-methoxyphenyl)methanone (5ja)

Yield: 33% (24 mg); yellow solid; mp = 191–193 °C.

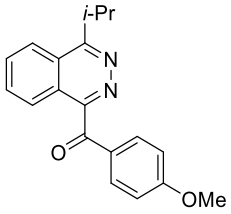
TLC: R_f = 0.26 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3003, 2928, 2842, 1598, 1257, 1226, 1170, 1139, 1025, 901, and 769 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 3.89 (s, 3H), 3.90 (s, 3H), 3.98 (s, 3H), 4.01 (s, 3H), 6.97 (br d, 2H, *J* = 7.0 Hz), 7.08 (d, 1H, *J* = 8.3 Hz), 7.40 (dd, 1H, *J* = 8.2 and 1.9 Hz), 7.44–7.53 (m, 3H), 8.11 (br d, 2H, *J* = 7.0 Hz), and 8.17 (d, 1H, *J* = 9.0 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.8, 164.6, 162.5, 159.7, 154.8, 150.5, 149.5, 133.7(x2), 129.5, 129.0, 128.3, 127.8, 124.6, 123.0, 121.2, 114.0(x2), 113.3, 111.1, 105.2, 56.3, 56.2, 55.9, and 55.7.

HRMS Calcd for $[(C_{25}H_{22}N_2O_5)+Na]^+$: 453.1419. Found: 453.1419.



(4-Isopropylphthalazin-1-yl)(4-methoxyphenyl)methanone (5ka)

Yield: 61% (55 mg); yellow oil.

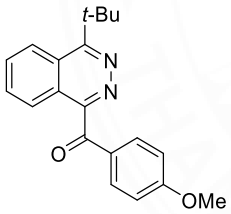
TLC: R_f = 0.57 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3073, 2969, 2931, 2872, 2843, 1659, 1595, 1573, 1510, 1423, 1316, 1241, 1169, 1026, 899, and 780 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 1.57 (s, 3H), 1.59 (s, 3H), 3.87 (s, 3H), 3.97 (hept, 1H, J = 6.8 Hz), 6.93–6.97 (m, 2H), 7.82–7.87 (m, 1H), 7.90–7.95 (m, 1H), 8.05–8.10 (m, 2H), 8.17 (d, 1H, J = 8.2 Hz), 8.25 (d, 1H, J = 8.4 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.8, 165.2, 164.5, 155.6, 133.7(x2), 132.6, 132.3, 129.4, 126.2, 125.5, 125.0, 124.0, 113.9(x2), 55.7, 30.9, 22.1(x2).

HRMS Calcd for $[(C_{19}H_{18}N_2O_2)+H]^+$: 307.1441. Found: 307.1444.



(4-(*Tert*-butyl)phthalazin-1-yl)(4-methoxyphenyl)methanone (5la)

Yield: 61% (53 mg); yellow oil.

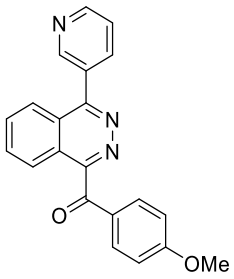
TLC: R_f = 0.58 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3073, 2969, 2929, 2874, 1660, 1595, 1573, 1510, 1461, 1424, 1315, 1246, 1169, 1024, 890, and 779 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 1.74 (s, 9H), 3.85 (s, 3H), 6.91–6.96 (m, 2H), 7.77–7.83 (m, 1H), 7.85–7.91 (m, 1H), 8.02–8.07 (m, 2H), 8.13 (dd, 1H, J = 8.2 and 0.7 Hz), and 8.55 (d, 1H, J = 8.6 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 192.0, 166.0, 164.5, 156.2, 133.5(x2), 131.6, 131.5, 129.3, 126.6, 126.4, 125.8, 125.3, 113.9(x2), 55.7, 39.6, and 31.0(x3).

HRMS Calcd for $[(C_{20}H_{20}N_2O_2)+H]^+$: 321.1598. Found: 321.1602.



(4-Methoxyphenyl)(4-(pyridin-3-yl)phthalazin-1-yl)methanone (5ma)

Yield: 52% (43 mg); pale yellow solid; mp = decomposed.

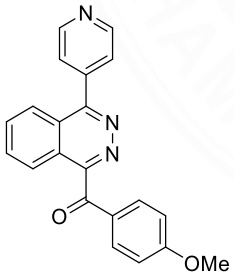
TLC: R_f = 0.15 (elution solvent: EtOAc:hexane = 60:40).

IR (neat) ν_{max} 3371, 3075, 2925, 2845, 1650, 1598, 1574, 1425, 1387, 1321, 1249, 1185, 1018, and 710 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 3.88 (s, 3H), 6.95–7.00 (m, 2H), 7.57 (dd, 1H, *J* = 7.8 and 4.9 Hz), 7.91–7.96 (m, 2H), 8.06–8.14 (m, 3H), 8.19 (dt, 1H, *J* = 7.8 and 1.9 Hz), 8.22–8.27 (m, 1H), 8.83 (dd, 1H, *J* = 4.9 and 1.5 Hz), and 9.06 (d, 1H, *J* = 1.8 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.2, 164.8, 158.1, 156.2, 150.8, 150.6, 137.8, 133.7(x2), 133.4, 133.3, 132.1, 129.2, 126.03, 126.0, 125.98, 125.5, 123.8, 114.1(x2), and 55.7.

HRMS Calcd for $[(C_{21}H_{15}N_3O_2)+H]^+$: 342.1237. Found: 342.1238.



(4-Methoxyphenyl)(4-(pyridin-4-yl)phthalazin-1-yl)methanone (5na)

Yield: 42% (34 mg); pale yellow solid; mp = decomposed.

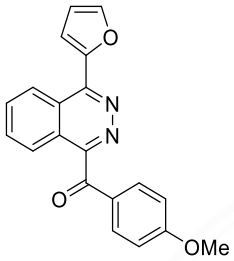
TLC: R_f = 0.21 (elution solvent: EtOAc:hexane = 60:40).

IR (neat) ν_{max} 3385, 3075, 2923, 2845, 1650, 1597, 1574, 1415, 1390, 1320, 1247, 1184, 1018, 842, and 801 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 3.89 (s, 3H), 6.98 (d, 2H, *J* = 8.7 Hz), 7.75 (d, 2H, *J* = 5.2 Hz), 7.92–7.98 (m, 2H), 8.09 (d, 3H, *J* = 8.9 Hz), 8.26 (dd, 1H, *J* = 8.7 and 4.7 Hz), and 8.88 (d, 2H, *J* = 5.1 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.1, 164.8, 158.6, 156.6, 150.3(x2), 143.8, 133.7(x2), 133.4, 133.37, 129.1, 126.1, 125.9, 125.6, 125.4, 124.8(x2), 114.1(x2), and 55.8.

HRMS Calcd for $[(C_{21}H_{15}N_3O_2)+H]^+$: 342.1237. Found: 342.1242.



(4-(Furan-2-yl)phthalazin-1-yl)(4-methoxyphenyl)methanone (5oa)

Yield: 21% (18 mg); pale yellow solid; mp = 184–185 ˚C.

TLC: R_f = 0.44 (elution solvent: EtOAc:hexane = 40:60).

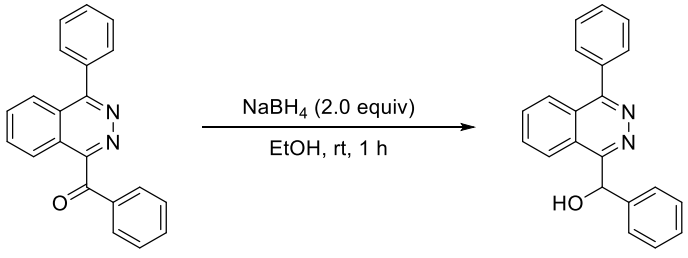
IR (neat) ν_{max} 3138, 2925, 2843, 1598, 1255, 1219, 1173, and 910 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 3.89 (s, 3H), 6.72 (d, 1H, *J* = 1.0 Hz), 6.97 (d, 2H, *J* = 8.4 Hz), 7.59 (d, 1H, *J* = 3.3 Hz), 7.83 (s, 1H), 7.91 (t, 1H, *J* = 7.3 Hz), 7.99 (t, 1H, *J* = 7.4 Hz), 8.09 (d, 2H, *J* = 8.4 Hz), 8.23 (d, 1H, *J* = 8.3 Hz), and 8.99 (d, 1H, *J* = 8.4 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.5, 164.6, 155.2, 152.2, 150.0, 145.5, 133.7(x2), 133.1, 133.0, 129.5, 126.5, 125.83, 125.76, 124.4, 115.0, 114.0(x2), 112.6, and 55.7.

HRMS Calcd for $[(C_{20}H_{14}N_2O_3)+Na]^+$: 353.0897. Found: 353.0897.

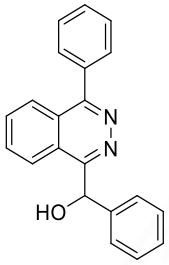
3.4 The procedure for the synthesis of phenyl(4–phenylphthalazin–1–yl) methanol (6) by the reduction with $NaBH_4$



3o **6**

Procedure: Phenyl(4–phenylphthalazin–1–yl) methanol (**6**). A solution containing (20 mg, 0.06 mmol) of compound **3o** and (4.90 mg, 0.13 mmol) of sodium

borohydride ($NaBH_4$) in ethanol (0.30 mL) was stirred at room temperature for 1 h. The resulting reaction was diluted with water and extracted with CH_2Cl_2, brine, dried over anhydrous $MgSO_4$, and concentrated under vacumn. The crude product was further purified by column chromatography using 30−40% EtOAc/hexane as an eluent to yield the title compound **6** as a yellow solid (13 mg, 65%).



Yield: 65% (13 mg); yellow oil.

TLC: R_f = 0.29 (elution solvent: EtOAc:hexane = 40:60).

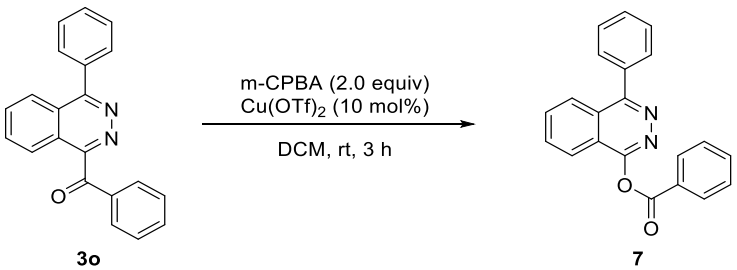
IR (neat) ν_{max} 3212, 3060, 2924, 2854, 1668, 1600, 1492, 1447, 1385, 724, and 698 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 6.05 (br s, 1H), 6.50 (s, 1H), 7.25–7.30 (m, 1H), 7.31–7.37 (m, 2H), 7.46–7.50 (m, 2H), 7.56–7.62 (m, 3H), 7.73–7.85 (m, 4H), 8.01–8.06 (m, 1H), and 8.07–8.15 (m, 1H).

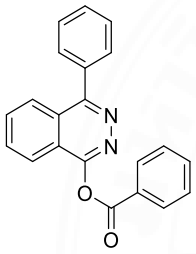
^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 161.0, 157.2, 142.2, 132.5, 131.3, 130.4, 130.3(x2), 129.8, 129.0(x2), 128.79, 128.75(x2), 128.7, 128.4, 127.8(x2), 127.4, 124.4, and 73.0.

HRMS Calcd for $[(C_{21}H_{16}N_2O)+Na]^+$: 335.1155. Found: 335.1158.

3.5 The procedure for the synthesis of 4–phenylphthalazin–1–yl benzoate 7 by Baeyer–Villiger oxidation (Duc & Nguyet, 2019)



Procedure: 4–Phenylphthalazin–1–yl benzoate (**7**). A mixture of compound **3o** (50 mg, 0.16 mmol), m–CPBA (55.67 mg, 0.32 mmol), copper (II) triflate (5.83 mg, 0.02 mmol) in DCM (0.64 mL) was stirred at room temperature for 3 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2 and filtered to remove the excess amount of $Cu(OTf)_2$. After that the filtrate was washed with a saturated sodium bicarbonate solution, brine, and dried over anhydrous $MgSO_4$. The combined organic layers were evaporated under reduce pressure. The residue was purified by column chromatography using 1% EtOAc/DCM as an eluent to yield the title compound **7** as a yellow solid (18 mg, 34%).(Duc & Nguyet, 2019)



Yield: 34% (18 mg); yellow solid; mp = 193–195 ˚C.

TLC: R_f = 0.30 (elution solvent: EtOAc:hexane = 40:60).

IR (neat) ν_{max} 3061, 2925, 2854, 1673, 1596, 1533, 1445, 1352, 1319, 1289, 1233, 719, and 699 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.50–7.57 (m, 3H), 7.58–7.64 (m, 5H), 7.65–7.70 (m, 2H), 7.73 (ddd, 1H, J = 8.2, 7.1, and 1.1 Hz), 8.02 (d, 1H, J = 8.3 Hz), and 8.07 (d, 2H, J = 7.3 Hz).

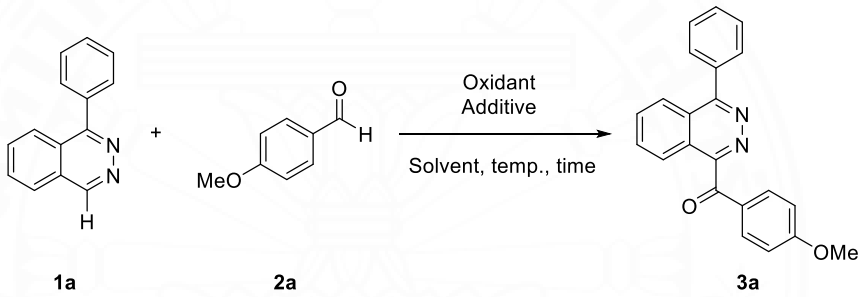
^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 189.7, 157.5, 138.9, 135.2, 135.0, 134.1, 133.9, 131.0(x2), 130.2(x3), 129.7, 129.4, 129.2(x2), 129.0(x2), 126.2, 125.1, and 119.4.

HRMS Calcd for $[(C_{21}H_{14}N_2O_2)+H]^+$: 327.1128. Found: 327.1136.

CHAPTER 4
RESULTS AND DISCUSSION

4.1 Optimization conditions

In optimization studies, 1–phenyl phthalazine (**1a**) and 4–anisaldehyde (**2a**) were used as model substrates. Many factors affected the synthesis of C_1–acylated 4-substituted phthalazines. Therefore, the reaction was examined under several oxidants, temperatures, Lewis acid additives, and solvents in order to investigate the optimal reaction conditions.



Scheme 38. The acylation of 1–phenyl phthalazine (**1a**) with 4–anisaldehyde (**2a**)

4.1.1 The oxidant screening studies

Initially, the oxidant screenings were performed in the presence of 30 mol% of $AlCl_3$ and 2 equivalent of **2a** in 1 mL of 1,2–dichloroethane (DCE) at 110 °C under a sealed tube. When used 2 equivalent of Oxone, 35% H_2O_2 in H_2O, $NaClO_2$, $K_2S_2O_8$, or $Na_2S_2O_8$ as an oxidant, the reaction did not complete after reacting for up to 24 hours albeit gave the desired product in low to moderate yields (entries 1–5, Table 1). To our delight, when using DTBP, 5 M TBHP in decane, 70% aq. TBHP or TBPB as an oxidant (entries 6–9, Table 1) the reaction did complete. Moreover, with 5 M TBHP in decane, 70% aq. TBHP or TBPB, the reaction completed in a short period of time (1–2 hours) (entry 7–9, Table 1), and the use of TBPB provided the highest yield of **3a** (entry 9, Table 1). Therefore, TBPB was used as an oxidant in this acylation. To ascertain the role of the oxidants, no reaction was observed in the absence of oxidant and the precursor **1a** also decomposed (entry 10,

Table 1). This result indicated the essential role of the oxidant for the acylation of phthalazine derivatives.

Table 1.

Oxidant screenings for the acylation of 1–phenyl phthalazines (**1a**)[a]

Entry	**2a** (equiv)	Oxidant (equiv)	Additive (mol %)	Solvent	Temp. (°C)	Time (h)	**1a**[b] (%)	**3a**[c] (%)
1	2	Oxone (2)	$AlCl_3$ (30)	DCE	110	24	49	8
2	2	35% H_2O_2 in H_2O (2)	$AlCl_3$ (30)	DCE	110	24	61	5
3	2	$NaClO_2$ (2)	$AlCl_3$ (30)	DCE	110	24	29	20
4	2	$K_2S_2O_8$ (2)	$AlCl_3$ (30)	DCE	110	24	30	42
5	2	$Na_2S_2O_8$ (2)	$AlCl_3$ (30)	DCE	110	24	45	53
6	2	DTBP (2)	$AlCl_3$ (30)	DCE	110	24	0	46
7	2	$TBHP^{dec}$ (2)	$AlCl_3$ (30)	DCE	110	2	0	53
8	2	$TBHP^{aq}$ (2)	$AlCl_3$ (30)	DCE	110	2	0	77
9	2	TBPB (2)	$AlCl_3$ (30)	DCE	110	1	0	86
10	2	-	$AlCl_3$ (30)	DCE	110	24	0[d]	0

[a]Reaction conditions: **1a** (0.24 mmol), **2a** (0.48 mmol), additive (0.07 mmol), oxidant (0.48 mmol) in solvent (1 mL) under sealed tube. [b] %recovery. [c]Isolated yield. [d]**1a** decomposed.

4.1.2 The reaction temperature screening studies

To examine the effect of temperature, the reactions were conducted at rt, 50 °C, and 80 °C, respectively. The reaction did not proceed at rt and 50 °C (entry 2–3, Table 2). The starting material was recovered in a comparable yield at the initial point. At 80 °C, the reaction could generate the desired product in a 53 % yield (entry 4, Table 2), but the reaction did not complete (entry 4, Table 2). The reaction temperature is one of the important factors because it helped to generate the acyl radical from acyl radical sources. However, if the use of temperature is very high, the

reaction might produce the alkyl radical from decarbonylation of the acyl radical.(Paul et al., 2019) These results demonstrated that 110 ˚C is the appropriate temperature for this reaction.

Table 2.
Temperature reaction screenings for the acylation of 1–phenyl phthalazine (**1a**)[a]

Entry	**2a** (equiv)	Oxidant (equiv)	Additive (mol %)	Solvent	Temp. (˚C)	Time (h)	**1a**[b] (%)	**3a**[c] (%)
1	2	TBPB (2)	$AlCl_3$ (30)	DCE	110	1	0	86
2	2	TBPB (2)	$AlCl_3$ (30)	DCE	rt	24	98	0
3	2	TBPB (2)	$AlCl_3$ (30)	DCE	50	24	85	0
4	2	TBPB (2)	$AlCl_3$ (30)	DCE	80	24	41	53

[a]Reaction conditions: **1a** (0.24 mmol), **2a** (0.48 mmol), additive (0.07 mmol), oxidant (0.48 mmol) in solvent (1 mL) under sealed tube. [b]%recovery. [c]Isolated yield.

4.1.3 The acidic additive screening studies

The acidic additives are another significant constituent for the acylation of *N*–heterocycles. The previous report presented the use of acid as additives to activate nitrogenous heterocycles base in the reaction.(Ali et al., 2015; Chen et al., 2015; Paul et al., 2019; Wan et al., 2015; Wang & Zeng, 2019; L. Zhang et al., 2018) Patel and co–workers indicated Lewis acids are good choices to serve as additives since they generated the regiospecific acylation, especially for *N*–heterocycles possessing the suitable positions more than one position toward acyl radical addition.(Ali et al., 2015) The reaction was initiated in the presence of $AlCl_3$, which represented Lewis acids as an additive. Product **3a** was obtained in an excellent yield of 86% (entry 1, Table 3). To improve the yield, other Lewis acids were used instead of $AlCl_3$. Unfortunately, the yield from these acids as $SnCl_2$ (26%), $InCl_3$ (51%), $ZnCl_2$ (55%) and CsCl (59%) were inferior to $AlCl_3$ (86%) (entries 2–5 vs entry 1, Table 3). Furthermore, the use of $Cu(OTf)_2$, CuCl, $CuCl_2$, $CoCl_2$, and $FeCl_3$ as additives failed to promote the reaction under similar reaction conditions (entries 6-10, Table 3). Interestingly, the reaction was also carried out without using the additives (entry 11, Table 3) and the obtained yield of product **3a** is almost similar to

the use of some Lewis acids. However, the yield dropped when compared with the use of $AlCl_3$ from 86% to 52% (entry 1 vs entry 11, Table 3). These observations suggested that Lewis additives is not indispensable for the proceed of the reaction, nevertheless; the selecting of the appropriate Lewis acid additives led to the formation of the acylated product in a much higher yield. To check the definite role of $AlCl_3$ or Brønsted–Lowry acid (HCl) for activating *N*–atom. The acid (HCl) was probably generated in the reaction medium because the reaction system proceeds under a non-inert atmosphere and used the non–degassed solvents. This doubt was proved by using conc. HCl instead of $AlCl_3$ in equal equivalent amount. The corresponding acylated product was obtained in 54% equally with the absence of Lewis additives (entry 12 vs entry 11, Table 3). This result ascertains the exact role of $AlCl_3$ in this transformation.

Table 3.

Lewis acidic additive screenings for the acylation of 1–phenyl phthalazine (**1a**)[a]

Entry	**2a** (equiv)	Oxidant (equiv)	Additive (mol %)	Solvent	Temp. (°C)	Time (h)	**1a**[b] (%)	**3a**[c] (%)
1	2	TBPB (2)	$AlCl_3$ (30)	DCE	110	1	0	86
2	2	TBPB (2)	$SnCl_2$ (30)	DCE	110	5	0	26
3	2	TBPB (2)	$InCl_3$ (30)	DCE	110	2	0	51
4	2	TBPB (2)	$ZnCl_2$ (30)	DCE	110	6	0	55
5	2	TBPB (2)	CsCl (30)	DCE	110	4	0	59
6	2	TBPB (2)	$Cu(OTf)_2$ (30)	DCE	110	6	23	0
7	2	TBPB (2)	CuCl (30)	DCE	110	7	0[d]	0
8	2	TBPB (2)	$CuCl_2$ (30)	DCE	110	24	0[d]	0
9	2	TBPB (2)	$CoCl_2$ (30)	DCE	110	24	0[d]	0
10	2	TBPB (2)	$FeCl_3$ (30)	DCE	110	24	0[d]	0
11	2	TBPB (2)	–	DCE	110	6	0	52
12	2	TBPB (2)	Conc. HCl (30)	DCE	110	1	0	54

[a]Reaction conditions: **1a** (0.24 mmol), **2a** (0.48 mmol), additive (0.07 mmol), oxidant (0.48 mmol) in solvent (1 mL) under sealed tube. [b]%recovery. [c]Isolated yield. [d]**1a** decomposed.

4.1.4 The solvent screening studies

To study the effect of solvent on the reaction, the reactions were proceeded using a variety of solvents both non-polar and polar instead of DCE. The reactions carried out in toluene, DMF, DMSO, MeCN, MeOH, and H_2O were insufficient performance. Most of the reactions did not complete after 24 hours and the use of DMF led to decomposition of **1a**. Nevertheless, they gave the compound **3a** in low to moderate yield (entries 2–7, Table 4). The solvent screening studies demonstrated that DCE is the best solvent since DCE could transform **1a** to completely product **3a** under a shorter time and higher yield than the other solvents (entry 1, Table 4).

Table 4.

The solvent screenings for the acylation of 1–phenyl phthalazine (**1a**)[a]

Entry	**2a** (equiv)	Oxidant (equiv)	Additive (mol %)	Solvent	Temp. (°C)	Time (h)	**1a**[b] (%)	**3a**[c] (%)
1	2	TBPB (2)	$AlCl_3$ (30)	DCE	110	1	0	86
2	2	TBPB (2)	$AlCl_3$ (30)	Toluene	110	24	5	45
3	2	TBPB (2)	$AlCl_3$ (30)	DMF	110	24	0[d]	12
4	2	TBPB (2)	$AlCl_3$ (30)	DMSO	110	24	68	13
5	2	TBPB (2)	$AlCl_3$ (30)	MeCN	110	24	12	71
6	2	TBPB (2)	$AlCl_3$ (30)	MeOH	110	24	17	14
7	2	TBPB (2)	$AlCl_3$ (30)	Water	110	24	45	28

[a]Reaction conditions: **1a** (0.24 mmol), **2a** (0.48 mmol), additive (0.07 mmol), oxidant (0.48 mmol) in solvent (1 mL) under sealed tube. [b]%recovery. [c]Isolated yield. [d]**1a** decomposed.

4.1.5 Optimization studies with varying amounts of the aldehyde 2a, oxidant, and Lewis acidic additive

The reaction was initially carried out using 2 equivalents of **2a**, 2 equivalent of oxidant, and 30 mol% of additives to ascertain optimal reaction conditions. In this case, the highest yield of acylated **3a** was observed in 86% (entry 1,

Table 5). To optimize the amount of the reagent, we adjusted the composition of the reaction. When the quantity of **2a** was reduced to 1.5 and 1 equivalent, the yield decreased obviously by about 30% of the highest yield (entries 2–3, Table 5). Furthermore, the formation of the corresponding acylated product in a modest yield of 66% and the coupling reacted more sluggishly (5 hours) were observed in the performing the reaction employed oxidant only 1 equivalent (entry 4, Table 5). In addition, the amount of the obtained product **3a** dropped around 25 and 50% compared to the best yield when $AlCl_3$ loading was decreased to 20 and 10 mol%, respectively (entries 5–6, Table 5). This result indicated the amount of $AlCl_3$ in the reaction affected the better yield of the acylated products. Therefore, the equivalent of $AlCl_3$ was increased to 40 mol%, but the yield of **3a** decreased which was an unexpected result (entry 7, Table 5). The optimal amount of $AlCl_3$ is 30 mol%.

Table 5.

The various amounts of the reagents used for the acylation of 1–phenyl phthalazine (**1a**)[a]

Entry	**2a** (equiv)	Oxidant (equiv)	Additive (mol %)	Solvent	Temp. (°C)	Time (h)	**1a**[b] (%)	**3a**[c] (%)
1	2	TBPB (2)	$AlCl_3$ (30)	DCE	110	1	0	86
2	1.5	TBPB (2)	$AlCl_3$ (30)	DCE	110	1	0	60
3	1	TBPB (2)	$AlCl_3$ (30)	DCE	110	1	0	60
4	2	TBPB (1)	$AlCl_3$ (30)	DCE	110	5	0	66
5	2	TBPB (2)	$AlCl_3$ (20)	DCE	110	1	0	63
6	2	TBPB (2)	$AlCl_3$ (10)	DCE	110	1	0	46
7	2	TBPB (2)	$AlCl_3$ (40)	DCE	110	1	0	64

[a]Reaction conditions: **1a** (0.24 mmol), **2a** (0.48 mmol), additive (0.07 mmol), oxidant (0.48 mmol) in solvent (1 mL) under sealed tube. [b]%recovery. [c]Isolated yield.

From these screening studies, the optimal conditions were established using aldehyde (2 equiv), $AlCl_3$ (30 mol%), and TBPB (2 equiv) in DCE at 110 ˚C (entry 9, Table 1).

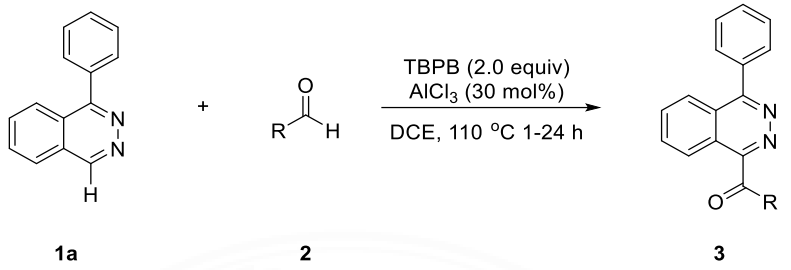
4.2 The scope of aldehydes for acylation of 1–substituted phthalazines

After an investigation of the optimal reaction conditions, we examined the scope of aldehyde substrates in this coupling reaction. The reaction was explored using 1–phenyl phthalazine (**1a**) reacted with aliphatic, aromatic aldehydes possessing both electron–donating as well as electron–withdrawing groups in various positions (*ortho*, *meta*, and *para* positions) and heteroaromatic aldehydes under the optimized reaction conditions (Table 6). It is noteworthy that the aromatic aldehydes with an electron-donating group gave a better yield conversion than aromatic aldehydes with an electron-withdrawing group. 1–phenylphthalazine (**1a**) reacted with 4–methoxy benzaldehyde, 2-methoxy benzaldehyde, and 3-methoxy benzaldehyde gave the corresponding acylated product **3a, 3h, and 3l** in moderate to high yield (55–86%, Table 6). Conversely, the reaction proceeded with aromatic aldehydes bearing an electron-withdrawing halogen (F, Cl, and Br) group at an identical position afforded the desired acylated compounds **3b, 3c**, **3d**, **3i**, **3j**, **3k**, and **3m** in 14–35% yields (Table 6). This observation demonstrated the electronic effect on acyl radical source affected this transformation. We expected that the electron-rich aldehydes were more reactive than benzaldehyde (**2a, 2h, and 2l** vs **2o**) with our results. Surprisingly, the benzaldehyde (**2o**) provided product **3o** in excellent yield (96%, Table 6) more than electron-rich aldehydes. This may be a result of the decreasing catalytic activity of $AlCl_3$ because some portion of $AlCl_3$ might coordinate with the methoxy group on the aromatic aldehydes.(Ali et al., 2015) In addition, the location of the substituent on the aromatic ring of aldehyde also influenced the obtained yield of the acylated product and the reaction time for this coupling. The aromatic aldehyde with electron-donating OMe group at *para* position (**2a**) gave a better yield than *ortho*– or *meta*–positions (**2h and 2l**) and especially, the OMe at *ortho* position took a long reaction time than other positions (4 hours vs 1 hour). These results could be related to the steric effects

on the aldehyde structure. Moreover, polymethoxy-substituted benzaldehydes (**2u and 2v**), which are a common scaffold for bioactive natural products(Chen et al., 2015) was also well tolerable with this acylation. However, a slightly lower yields were obtained (**3u**; 46% and **3v**; 38%, Table 6), presumably because of the effect of the steric hindrance and less efficiently catalytic activity. Moreover, the reaction proceeded with aliphatic aldehydes such as acetaldehyde **2p**, octanal **2q**, isobutyraldehyde **2r**, pivaldehyde **2s**, and cyclohexanecarboxaldehyde **2t**. 1–phenylphthalazine (**1a**) underwent well with acetaldehyde **2p** and octanal **2q** to furnish the coupled product **3p** and **3q** within a short reaction time (1–2 hours) in 56 and 86% yields (Table 6). Unfortunately, the decarbonylation of acyl radical was observed in the reaction of **1a** with the secondary and tertiary aldehydes, such as isobutyraldehyde **2r**, pivaldehyde **2s**, and cyclohexanecarboxaldehyde **2t** under optimal reaction conditions. The reaction formed the corresponding alkylated products **3r** (67%), **3s** (74%), and **3t** (42%) (Table 6), whereas the acylated products were not observed. These observations pointed out that the formation of the desired products depends on the stability of acyl radical and alkyl radical.(Siddaraju et al., 2014) The acylation of 1–substituted phthalazines with aromatic aldehydes generated only the acylated products because the benzoyl radical is more stable than the phenyl radical. While the aliphatic aldehydes were an acyl source, the reaction gave both alkylated and acylated products, followed by the structure of the aldehydes that formed the corresponding free radicals. The alkyl radical of acetaldehyde **2p** and heptanal **2q** was a primary radical, which is less stable than acyl radicals, so the acylated products **3p** and **3q** were obtained. In contrast with isobutyraldehyde **2r**, pivaldehyde **2s**, and cyclohexanecarboxaldehyde **2t**, the corresponding alkyl radicals were secondary and tertiary radicals, which were more stable than acyl radicals. Thus, the alkylated products were formed by the elimination of the carbonyl group of the acyl radicals. Finally, the heteroaromatic aldehydes like furfural (**2w**), thiophene-2-carboxaldehyde (**2x**), and pyrrole carboxaldehyde (**2y**) underwent a coupling reaction with **1a**, furnishing the acylated products **3w**, **3x**, and **3y** in 16, 37, and 32% yields, respectively (Table 6).

Table 6.

The C–H direct acylation of 1–phenylphthalazine (**1a**) with aldehydes[a,b]



1a **2** **3**

R = OMe **3a**, 1 h, 86%; F **3b**, 1 h, 35%; Cl **3c**, 3 h, 21%; Br **3d**, 1 h, 32%; OH **3e**, 24 h, 0%[c]; NO_2 **3f**, 24 h, 0%[c]; NMe_2 **3g**, 7 h, 0%[c]

R = OMe **3h**, 3 h, 59%; F **3i**, 7 h, 20%; Cl **3j**, 3 h, 29%; Br **3k**, 5 h, 21%

R = OMe **3l**, 1 h, 55%; Cl **3m**, 5 h, 14%; OH **3n**, 24 h, 0%[c]

3o, 1 h, 96%

R = Me **3p**, 1 h, 56%; *n*-heptyl **3q**, 2 h, 86%

not formed formed

R = *i*-Pr **3r**, 1 h, 67%; *t*-Bu **3s**, 1 h, 74%; cyclohexyl **3t**, 1 h, 42%

3u, 6 h, 46%

3v, 7 h, 38%

R = **3w**, 24 h, 16%; **3x**, 4 h, 37%; **3y**, 3 h, 32%; **3z**, 7 h, 0%[c]; **3aa**, 5 h, 0%[c]

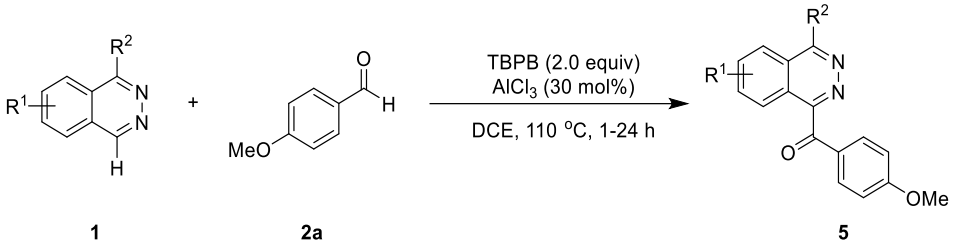
[a]Reaction conditions: **1a** (0.24 mmol), aldehydes **2** (0.48 mmol), $AlCl_3$ (0.07 mmol), TBPB (0.48 mmol) in DCE (1 mL) at 110 °C under sealed tube for 1–24 h. [b]Isolated yield. [c]The product was not synthesized, and the starting material decomposed after the reaction time of 5–24 h.

4.3 The scope of 1–substituted phthalazines for the acylation

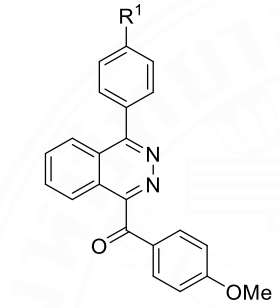
The substrate scope of 1-substituted phthalazines was widely studied with 4-anisaldehyde **2a** in the coupling reaction. 1–Phenylphthalazine bearing electron–donating moiety, such as methoxy and electron-withdrawing moieties, such as bromo and ester at the different positions of the aromatic ring, all smoothly reacted with **2a** to form the corresponding product **5aa**–**5ja** in moderate to good yields (33–65%, Table 7). The reaction was also tolerated with the 1–isopropyl– and 1–(*tert*–butyl) phthalazine afforded acylated product **5ka** and **5la** in 61% yield (Table 7). Similarly, the protocol was applicable to heteroaryl substituent phthalazine such as pyridine and furan which can furnish the coupled products **5ma**, **5na**, and **5oa** in 52, 42, and 21% yield, respectively (Table 7). These observations suggested that this acylation reaction was proceeded well with a variety of 1–substituted phthalazines substrate (Table 7) which demonstrated the efficiency of this C–H direct acylation developed method.

Table 7.

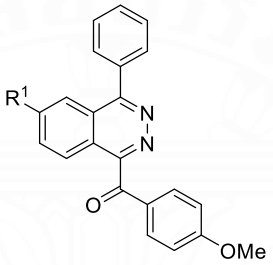
The acylation of 1–substituted phthalazines with 4–anisaldehyde (**2a**) [a,b]



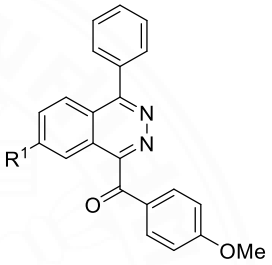
1 **2a** **5**



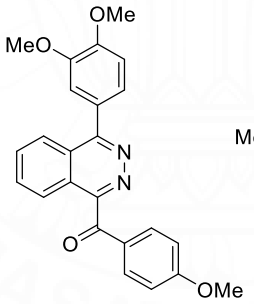
R^1 = OMe **5aa**, 1 h, 65%; Br **5ba**, 5 h, 52%; NO_2 **5ca**, 24 h, 0%[c]



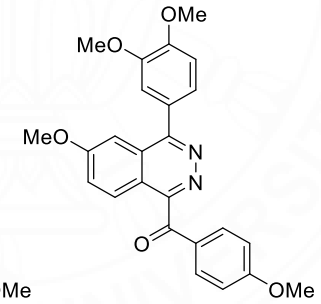
R^1 = OMe **5da**, 5 h, 42%; Br **5ea**, 3 h, 47%



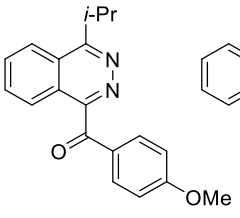
R^1 = Br **5fa**, 1 h, 60%; CO_2Et **5ga**, 3 h, 48%; NO_2 **5ha**, 7 h, 0%[c]



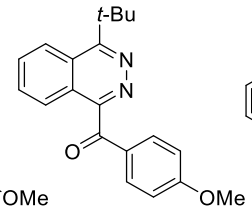
5ia, 2 h, 46%



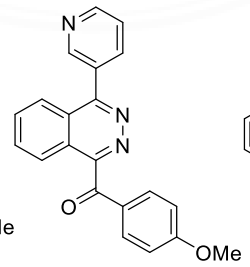
5ja, 5 h, 33%



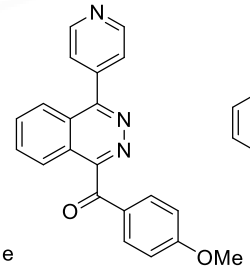
5ka, 1 h, 61%



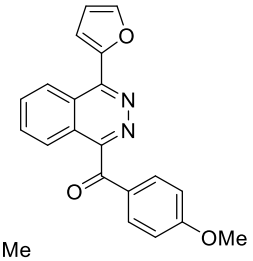
5la, 1 h, 61%



5ma, 7 h, 52%



5na, 7 h, 42%



5oa, 1 h, 21%

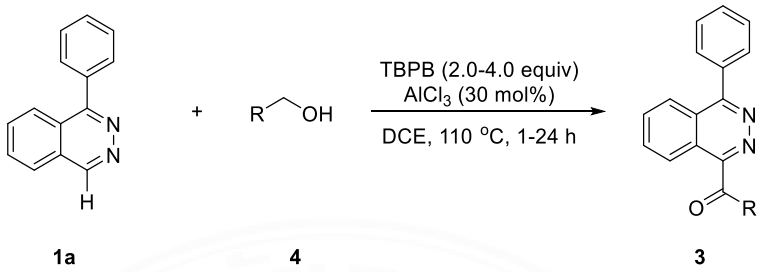
[a]Reaction conditions: **1a** (0.24 mmol), aldehydes **2** (0.48 mmol), $AlCl_3$ (0.07 mmol), TBPB (0.48 mmol) in DCE (1 mL) at 110 °C under sealed tube for 1–24 h. [b]Isolated yield. [c]The product was not synthesized, and the starting material decomposed after the reaction time of 7–24 h.

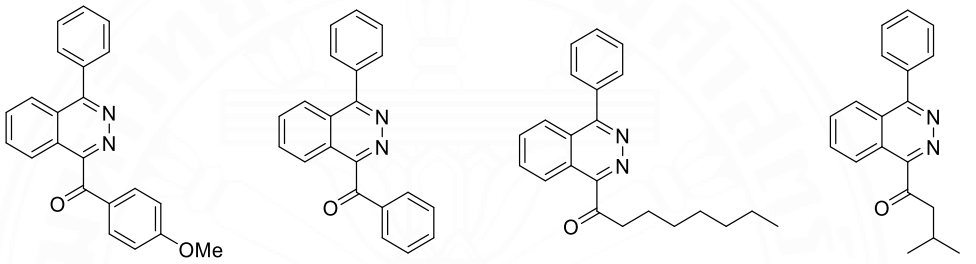
4.4 The scope of primary alcohol for acylation of 1–substituted phthalazines

To expand the scope of the acylation of 1–substituted phthalazines, we attempted to coupling of these compounds with the other source of an acyl radical by using primary alcohol as the acyl source. In theory, primary alcohol can be oxidized to the corresponding aldehydes under oxidative conditions. Therefore, we expected that primary alcohol could be used instead of aldehyde in terms of acyl source and gave the acylated product in a similar trend. At the beginning, the reaction was studied using 1–phenyl phthalazine (**1a**) coupled with 4–methoxybenzyl alcohol (**4a**) and benzyl alcohol (**4b**) because in the previous experiment the corresponding aldehydes gave the high yield of the acylated product. Unfortunately, reaction **1a** with **4a** and **4b** provided the desired product **3a** and **3o** in low yield (25 and 14%, Table 8) and took a long reaction time of 4 and 24 hours, respectively under optimized conditions. As a result, we decided to increase the equivalent of oxidant (TBPB) from 2 to 4 because the amount of oxidant might be insufficient in this transformation. The yield of **3a** and **3o** obtained a slight increase in yields (25 and 14% to 30 and 50%, respectively, Table 8). Adding the amount of oxidant (TBPB) did not result in an improvement in the product yield. Similarly, the reaction underwent with aliphatic alcohols (1–octanol **4c** and isobutanol **4d**), furnishing the acylated product **3q** and **3ab** in low yield (12 and 21% yields, Table 8). This optimized conditions might not be suited for the acylation of 1-substituted phthalazines with alcohols.

Table 8.

The C–H direct acylation of 1–phenylphthalazine (**1a**) with alcohols[a,b]



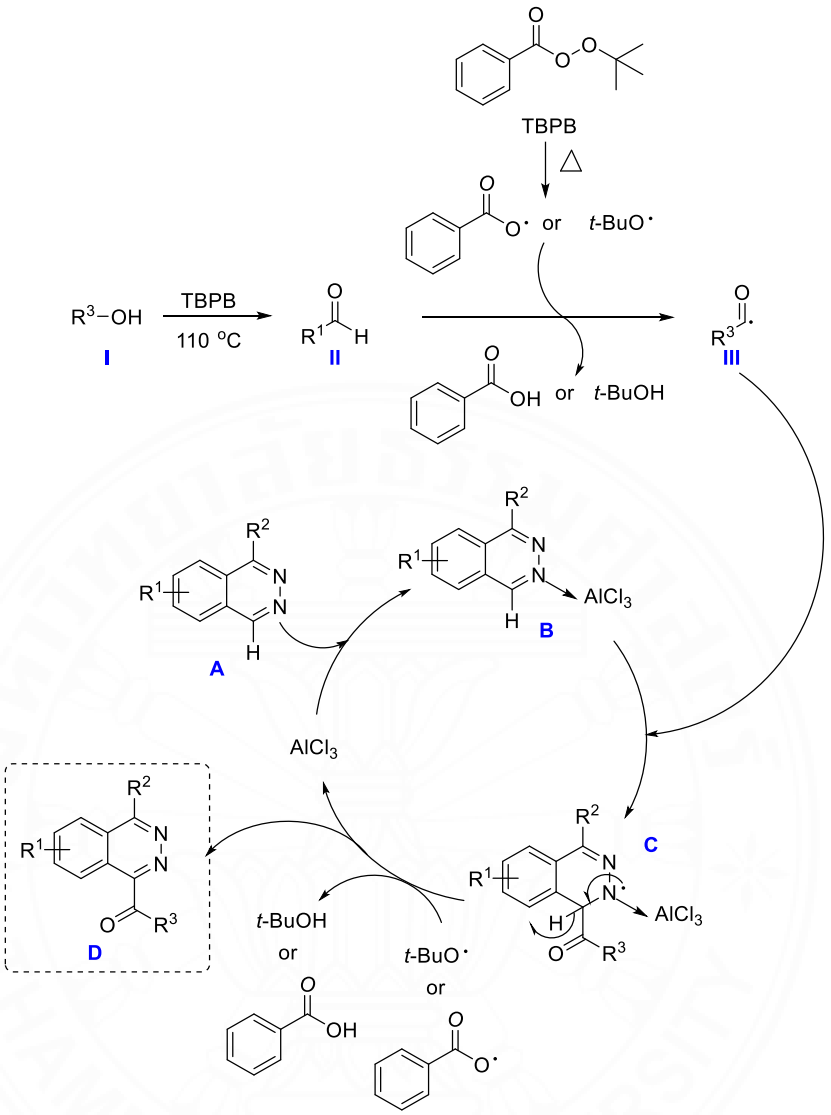


3a, 4 h, 25%[c] 1 h, 30%[d] | **3o**, 7 h, 14%[c] 1 h, 50%[d] | **3q**, 24 h, 12%[c] | **3ab**, 24 h, 21%[c]

[a]Reaction conditions: **1a** (0.24 mmol), alcohol **4** (0.48 mmol), $AlCl_3$ (0.07 mmol) in DCE (1 mL) at 110 °C under sealed tube for 1–24 h. [b]Isolated yield. [c]The reaction underwent in the presence of TBPB (0.48 mmol). [d]The reaction underwent in the presence of TBPB (0.97 mmol).

4.5 Proposed reaction mechanism

On the basis of the experimental results and the precedence in the literature (Ali et al., 2015; Matcha & Antonchick, 2013), we propose a plausible mechanism for the direct acylation of 1–substituted phthalazines (Scheme 39). In the presence of TBPB at 110 °C, Alcohol (**I**) is oxidized to the corresponding aldehyde (**II**), which generates an acyl radical (**III**) by the cleavage of α–hydrogen in aldehydes. 1–substituted phthalazines (**A**) can be coordinated with $AlCl_3$ to form an intermediate **B** that improves the electrophilicity of the C_1 position of **A,** resulting in the facile addition of radical **III** onto **B,** providing radical **C.** An acyl radical **III** is nucleophilic in the medium. Finally, the intermediate **C** rearomatizes by *tert*–butoxyl radical or benzoyl radical to provide the desired acylated product **D**.

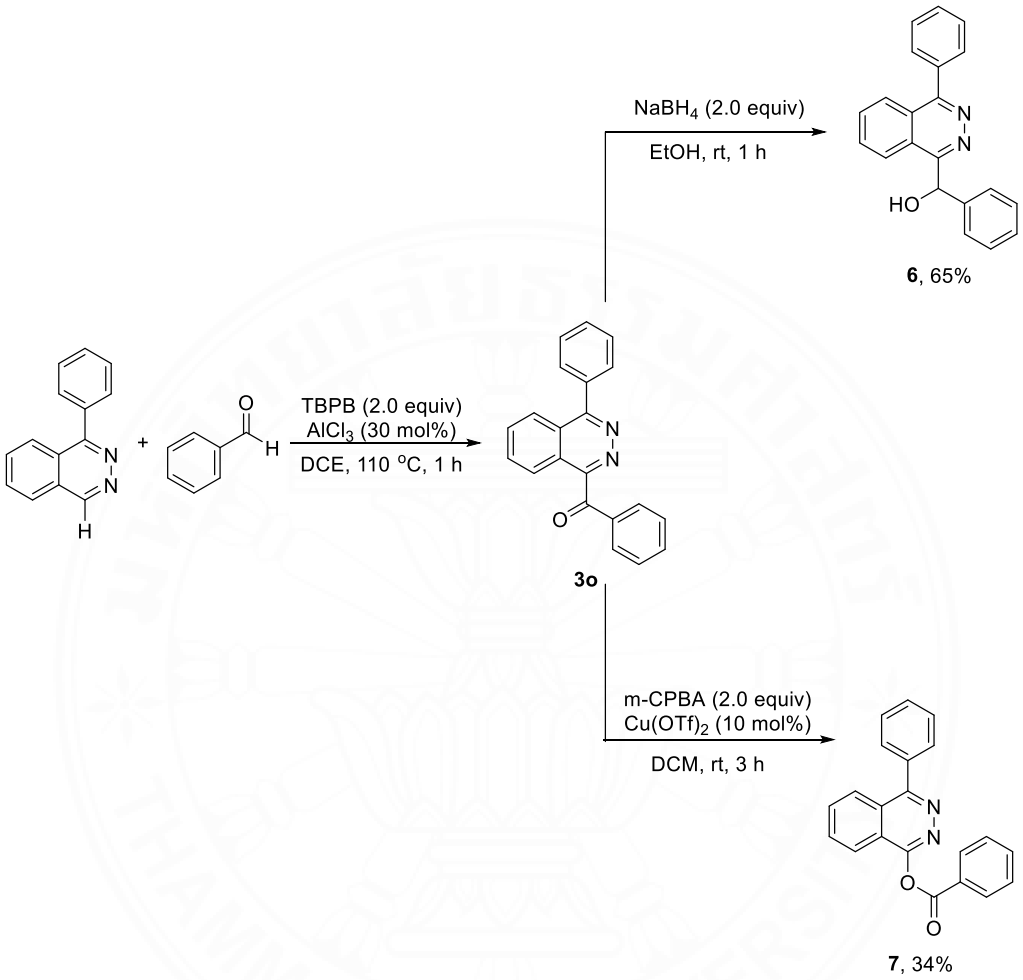


Scheme 39. Proposed mechanism for the direct acylation of 1–substituted phthalazines

4.6 Modification of the acylated products

The synthetic utility of this direct C–H acylation process was next explored using 4–acylated 1–substituted phthalazine **3o** as a model substrate. As can be seen in Scheme 40, the target was focused on the functionalization of the carbonyl functional group on the acylated product through simple chemical reactions, affording the desired product with a one–step reaction. The acylated product **3o** was transformed to the alcohol **6** using the general reduction of ketone with $NaBH_4$. The

ester **7** was synthesized by Baeyer Villger oxidation of ketone **3o**. The acylated product allowed facile access to various functional groups, and the corresponding products were established in moderate to good yields.



Scheme **40**. The modification of the acylated products

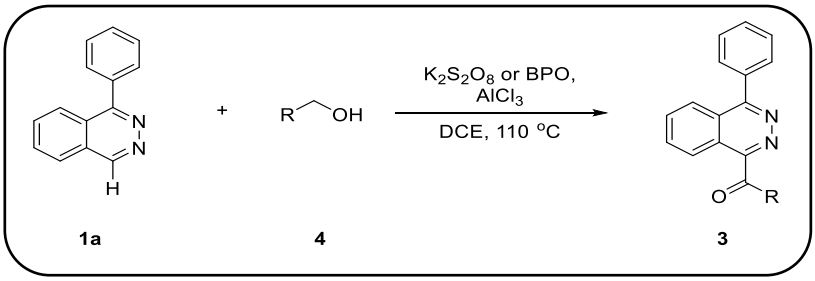
CHAPTER 5
CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

In conclusion, the C–H direct acylation of electron-deficient *N*-heterocycles has been developed. The reaction was performed in the presence of Lewis acid $AlCl_3$ as an additive and TBPB as an oxidant. This acylation was illustrated by the use of 1–substituted phthalazines as the substrates with a broad range of aldehydes and alcohols as the acylating agent. This method offered a facile synthesis of a variety of structurally diverse C_1–acyl substituted phthalazine derivatives in good efficiency. Nevertheless, this protocol suffered from the qualification of the use of alcohols as the coupling agent which allowed the corresponding product in low yield. The application of this methodology has been demonstrated to be useful as it can provide various derivatives with a wide variety of functional groups, suited for further biological activity study.

5.2 The future works

In future work, there are limitations to the use of alcohol as the acyl radical source. The reaction furnished the acylated product in low yield and took a long reaction time. This observation is probably related to the inappropriate oxidant, which is used to oxidize primary alcohols to the corresponding aldehydes. We will attempt to apply the other oxidants in the reaction. Examples of the oxidants that successfully used in direct C-H acylation of *N*-heterocycles with arylmethanols were included $K_2S_2O_8$ and BPO (Adib et al., 2016).



REFERENCES

Adib, M., Pashazadeh, R., Rajai-Daryasarei, S., Kabiri, R., & Gohari, S. (2016). Transition-Metal-Free Acylation of Quinolines and Isoquinolines with Arylmethanols via Oxidative Cross-Dehydrogenative Coupling Reactions. *Synlett, 27*. doi:10.1055/s-0035-1562135

Ali, W., Behera, A., Guin, S., & Patel, B. K. (2015). Regiospecific Benzoylation of Electron-Deficient N-Heterocycles with Methylbenzenes *via* a Minisci-Type Reaction. *The Journal of Organic Chemistry, 80*(11), 5625-5632. doi:10.1021/acs.joc.5b00501

Bogonda, G., Kim, H. Y., & Oh, K. (2018). Direct Acyl Radical Addition to 2H-Indazoles Using Ag-Catalyzed Decarboxylative Cross-Coupling of α-Keto Acids. *Organic Letters, 20*(9), 2711-2715. doi:10.1021/acs.orglett.8b00920

Chaubey, N. R., & Singh, K. N. (2017). Metal-free decarboxylative acylation of isoquinolines using α-keto acids in water. *Tetrahedron Letters, 58*(24), 2347-2350. doi:https://doi.org/10.1016/j.tetlet.2017.04.098

Chen, J., Wan, M., Hua, J., Sun, Y., Lv, Z., Li, W., & Liu, L. (2015). TBHP/TFA mediated oxidative cross-dehydrogenative coupling of N-heterocycles with aldehydes. *Organic & Biomolecular Chemistry, 13*(47), 11561-11566. doi:10.1039/C5OB01763G

Clark, J. (2020, Sep 13,2020). Other Reactions of Benzene and Methylbenzene. Retrieved from https://chem.libretexts.org/@go/page/3980

Ding, H., Xu, K., & Zeng, C.-C. (2020). Nickel-catalyzed electrochemical Minisci acylation of aromatic *N*-heterocycles with α-keto acids *via* ligand-to-metal electron transfer pathway. *Journal of Catalysis, 381*, 38-43. doi:https://doi.org/10.1016/j.jcat.2019.10.030

Duc, D., & Nguyet, N. (2019). Copper triflate catalyzed Baeyer-Villiger oxidation of ketones. *Vietnam Journal of Science and Technology, 57*, 76. doi:10.15625/2525-2518/57/1/12589

Fontana, F., Minisci, F., Nogueira Barbosa, M. C., & Vismara, E. (1991). Homolytic acylation of protonated pyridines and pyrazines with alpha.-keto acids: the

problem of monoacylation. *The Journal of Organic Chemistry, 56*(8), 2866-2869. doi:10.1021/jo00008a050

Gaurav, A., Meda, M., Panda, P., Singh, R., Singh, S., Yadav, A., Singh, U. (2010). Pharmacological action and SAR of Phthalazine derivatives-A Review. *International Journal of Chemical and Analytical Science, 1*.

Guillemard, L., Colobert-Leuenberger, F., & Wencel-Delord, J. (2018). Visible-Light-Triggered, Metal- and Photocatalyst-Free Acylation of *N*-Heterocycles. *Advanced Synthesis and Catalysis, 360*(21), 4184-4190. doi:10.1002/adsc.201800692

Guo, L.-N., Wang, H., & Duan, X.-H. (2016). Recent advances in catalytic decarboxylative acylation reactions via a radical process. *Organic & Biomolecular Chemistry, 14*(31), 7380-7391. doi:10.1039/C6OB01113F

Hadsarung, R., Thongnest, S., Oekchuae, S., Chaiyaveij, D., Boonsombat, J., & Ruchirawat, S. (2022). Facile synthesis of 1-substituted 4-H phthalazine, a versatile scaffold for chemically diverse phthalazines. *Tetrahedron, 121*, 132920. doi:https://doi.org/10.1016/j.tet.2022.132920

J, A. (2019). A Concise Review on Phthlazine Derivatives and its Biological Activities. *Journal of Pharmaceutical Science and Research, 11(7)*, 2526-2532.

Lakshman, M. K., & Vuram, P. K. (2017). Cross-dehydrogenative coupling and oxidative-amination reactions of ethers and alcohols with aromatics and heteroaromatics. *Chemical Science, 8*(9), 5845-5888. doi:10.1039/C7SC01045A

Li, Y., Lai, M., Wu, Z., Zhao, M., & Zhang, M. (2018). Synthesis of 2-Acyl-Substituted Pyrazine Derivatives through Silver-Catalyzed Decarboxylative Coupling Reactions. *ChemistrySelect, 3*, 5588-5592. doi:10.1002/slct.201800496

Manna, S., & Prabhu, K. R. (2019). Visible-Light-Mediated Direct Decarboxylative Acylation of Electron-Deficient Heteroarenes Using α-Ketoacids. *The Journal of Organic Chemistry, 84*(9), 5067-5077. doi:10.1021/acs.joc.9b00004

Matcha, K., & Antonchick, A. P. (2013). Metal-Free Cross-Dehydrogenative Coupling of Heterocycles with Aldehydes. *Angewandte Chemie International Edition, 52*(7), 2082-2086. doi:https://doi.org/10.1002/anie.201208851

Oxidation of Alcohols. (Jan 26, 2022). Retrieved from https://chem.libretexts.org/@go/page/36351

Paul, S., Bhakat, M., & Guin, J. (2019). Radical C−H Acylation of Nitrogen Heterocycles Induced by an Aerobic Oxidation of Aldehydes. *Chemistry – An Asian Journal, 14*(18), 3154-3160. doi:https://doi.org/10.1002/asia.201900857

Penteado, F., Lopes, E. F., Alves, D., Perin, G., Jacob, R. G., & Lenardão, E. J. (2019). α-Keto Acids: Acylating Agents in Organic Synthesis. *Chemical Reviews, 119*(12), 7113-7278. doi:10.1021/acs.chemrev.8b00782

Rawalay, S. S., & Shechter, H. (1967). Oxidation of primary, secondary, and tertiary amines with neutral permanganate. Simple method for degrading amines to aldehydes and ketones. *The Journal of Organic Chemistry, 32*(10), 3129-3131. doi:10.1021/jo01285a042

Sharma, R., Abdullaha, M., & Bharate, S. B. (2017). Oxidant-Controlled C-sp2/sp3–H Cross-Dehydrogenative Coupling of *N*-Heterocycles with Benzylamines. *The Journal of Organic Chemistry, 82*(18), 9786-9793. doi:10.1021/acs.joc.7b00856

Siddaraju, Y., Lamani, M., & Prabhu, K. R. (2014). A Transition Metal-Free Minisci Reaction: Acylation of Isoquinolines, Quinolines, and Quinoxaline. *The Journal of Organic Chemistry, 79*(9), 3856-3865. doi:10.1021/jo500294z

Siddaraju, Y., & Prabhu, K. R. (2016). Transition metal-free Minisci reaction promoted by NCS, and TBHP: acylation of heteroarenes. *Tetrahedron, 72*(7), 959-967. doi:https://doi.org/10.1016/j.tet.2015.12.065

Suresh, R., Kumaran, R. S., Senthilkumar, V., & Muthusubramanian, S. (2014). Silver catalyzed decarboxylative acylation of pyridine-*N*-oxides using α-oxocarboxylic acids. *RSC Advances, 4*(60), 31685-31688. doi:10.1039/C4RA05777E

Wan, M., Lou, H., & Liu, L. (2015). C1-Benzyl and benzoyl isoquinoline synthesis through direct oxidative cross-dehydrogenative coupling with methyl arenes. *Chemical Communications, 51*(73), 13953-13956. doi:10.1039/C5CC04791A

Wang, X.-Z., & Zeng, C.-C. (2019). Iron-catalyzed Minisci acylation of *N*-heteroarenes with α-keto acids. *Tetrahedron, 75*(10), 1425-1430. doi:https://doi.org/10.1016/j.tet.2019.01.060

Westwood, M. T., Lamb, C. J. C., Sutherland, D. R., & Lee, A.-L. (2019). Metal-, Photocatalyst-, and Light-Free Direct C–H Acylation and Carbamoylation of Heterocycles. *Organic Letters, 21*(17), 7119-7123. doi:10.1021/acs.orglett.9b02679

Zhang, L., Zhang, G., Li, Y., Wang, S., & Lei, A. (2018). The synergistic effect of self-assembly and visible-light induced the oxidative C–H acylation of *N*-heterocyclic aromatic compounds with aldehydes. *Chemical Communications, 54*(45), 5744-5747. doi:10.1039/C8CC02342E

Zhang, X.-Y., Weng, W.-Z., Liang, H., Yang, H., & Zhang, B. (2018). Visible-Light-Initiated, Photocatalyst-Free Decarboxylative Coupling of Carboxylic Acids with *N*-Heterocycles. *Organic Letters, 20*(15), 4686-4690. doi:10.1021/acs.orglett.8b02016

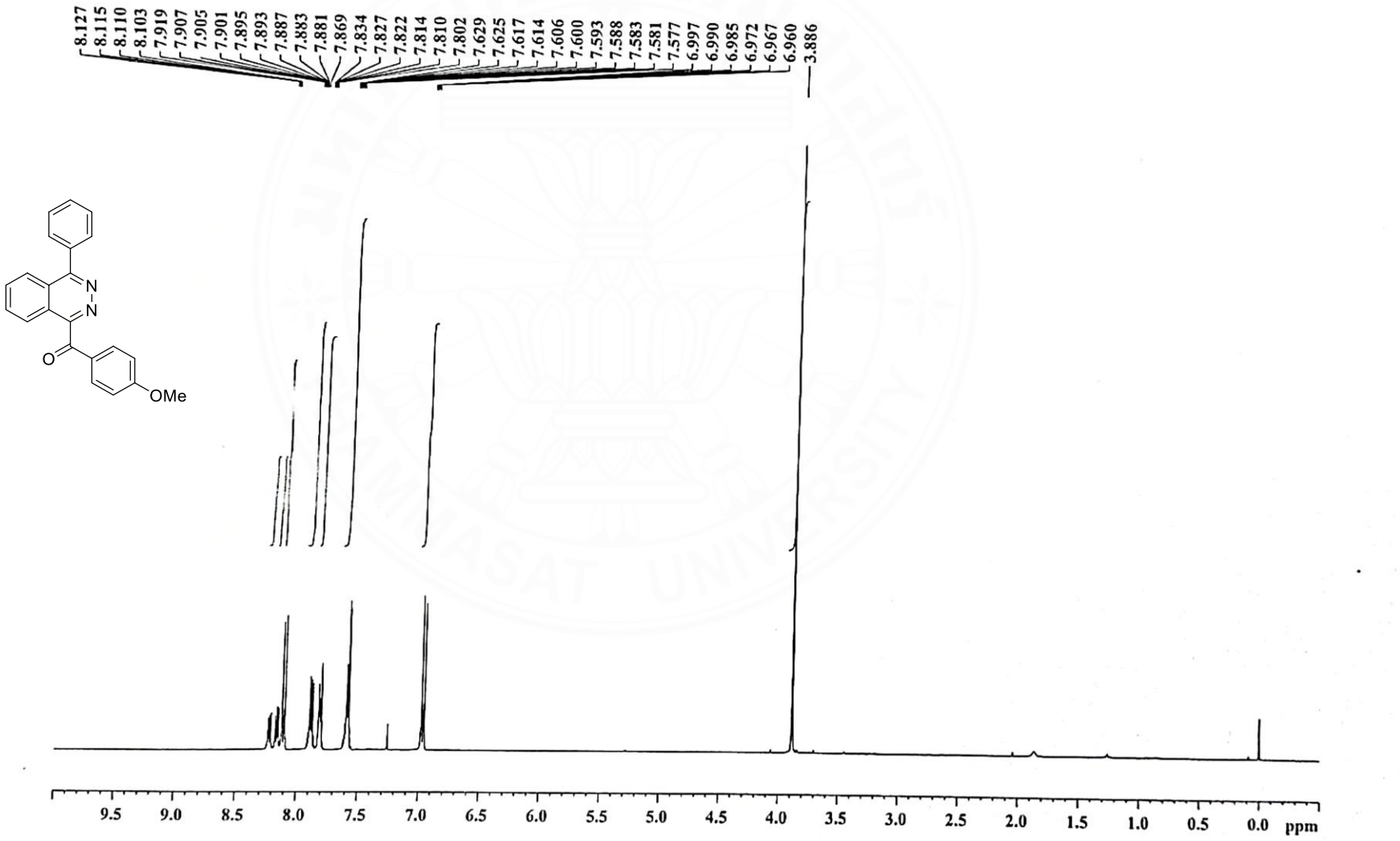
APPENDIX

APPENDIX

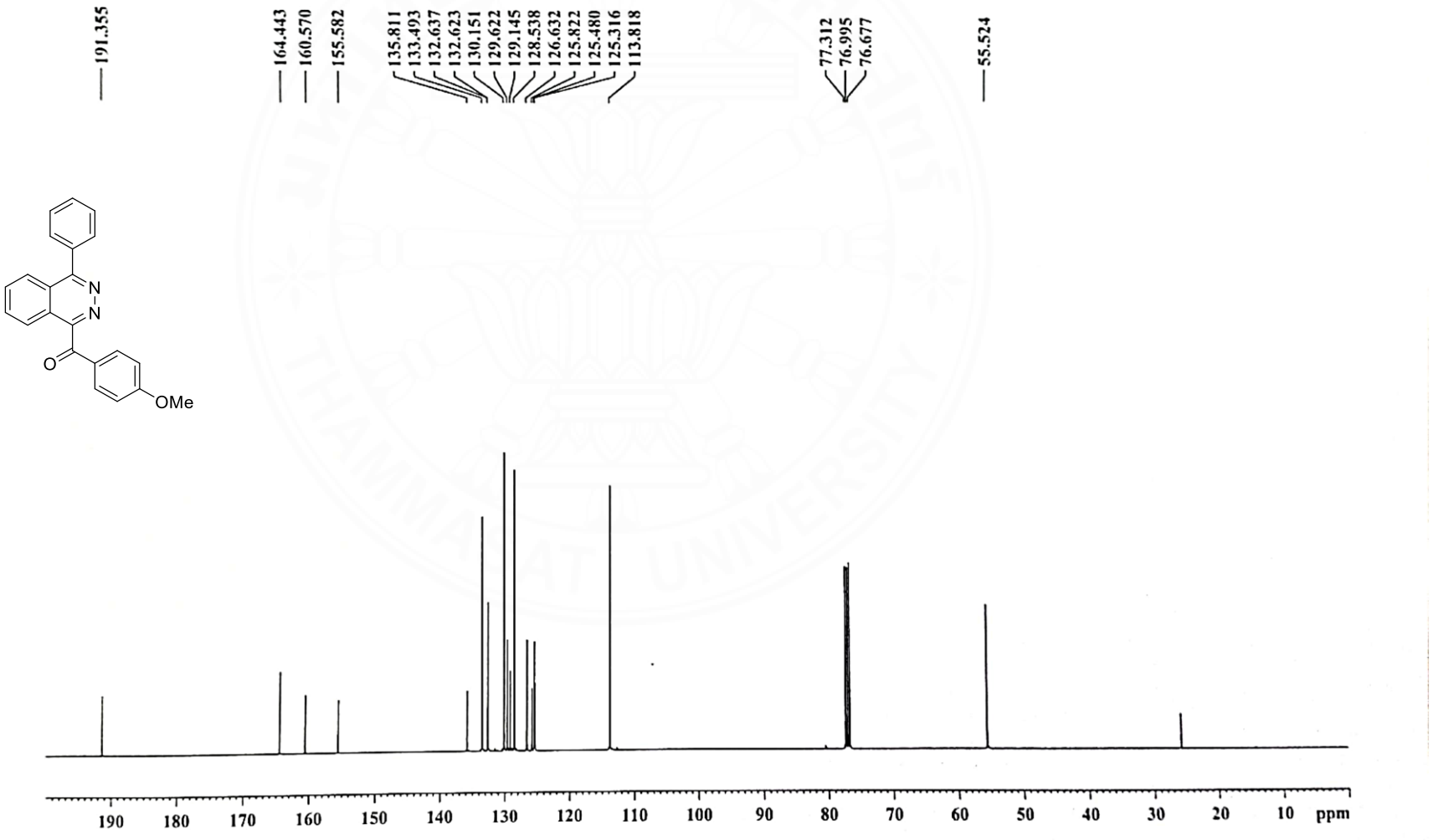
Supplementary Information

NMR spectra

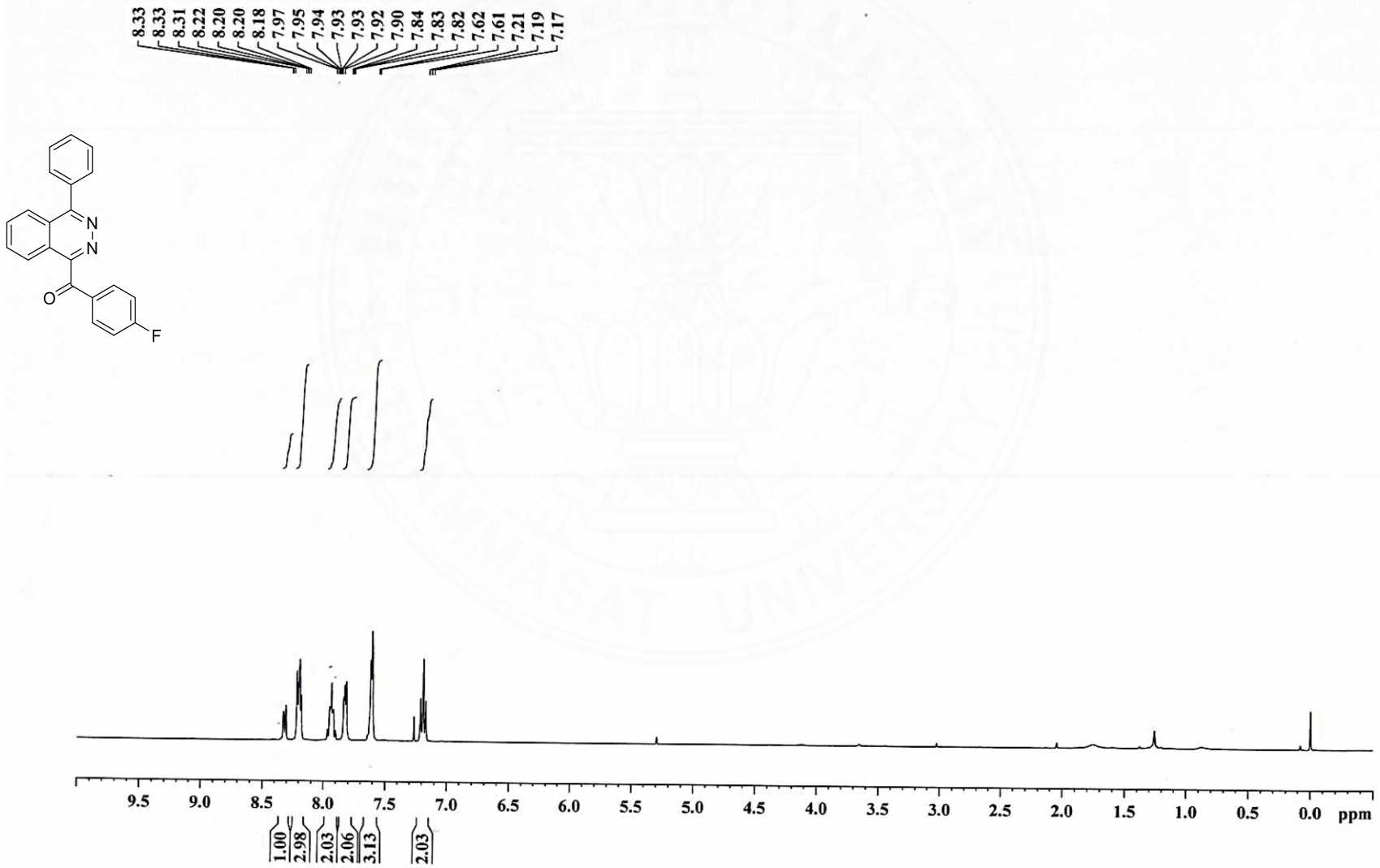
^{1}H-NMR of compound **3a** (400 MHz, $CDCl_3$)



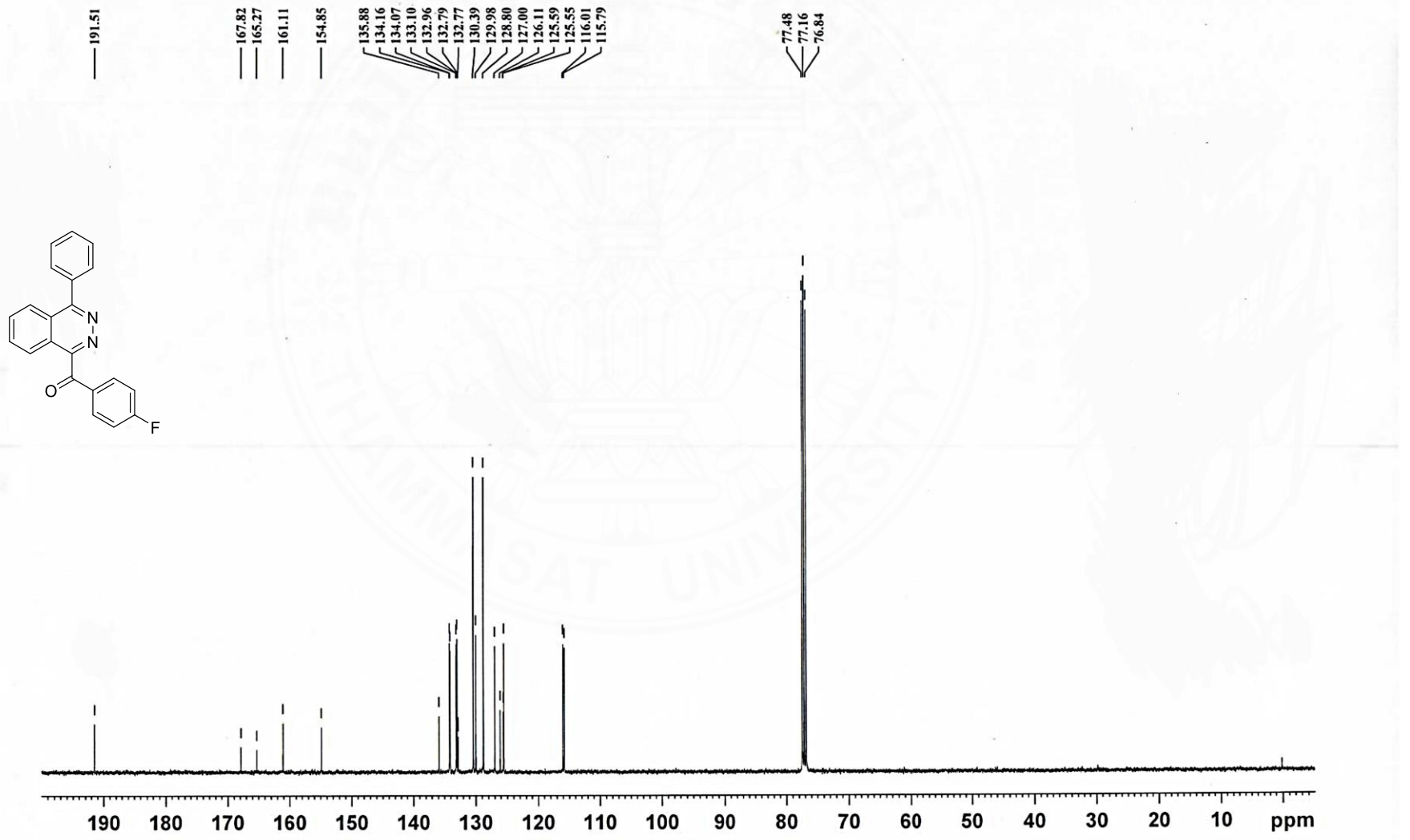
^{13}C-NMR of compound **3a** (100 MHz, $CDCl_3$)



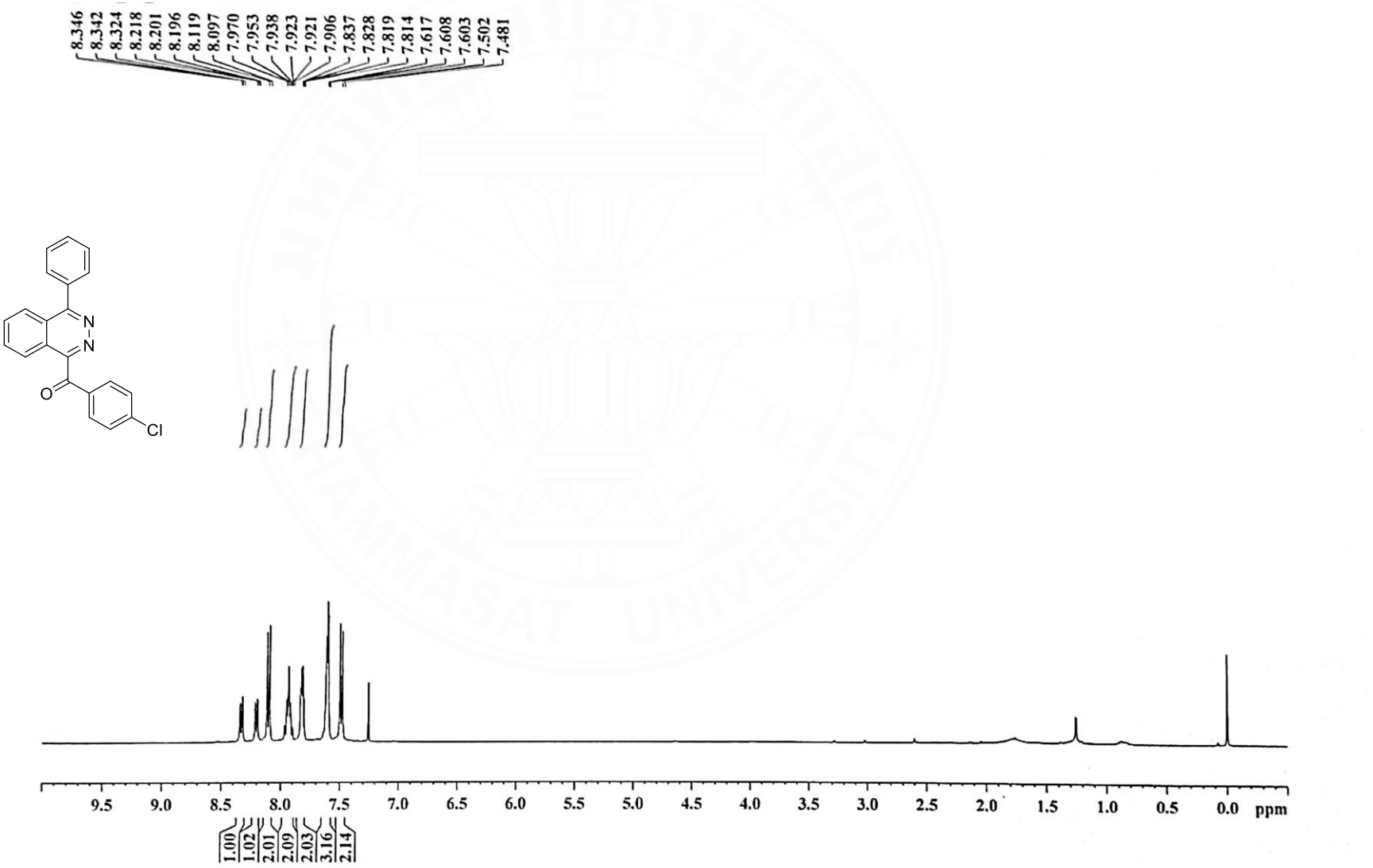
^{1}H-NMR of compound **3b** (400 MHz, $CDCl_3$)



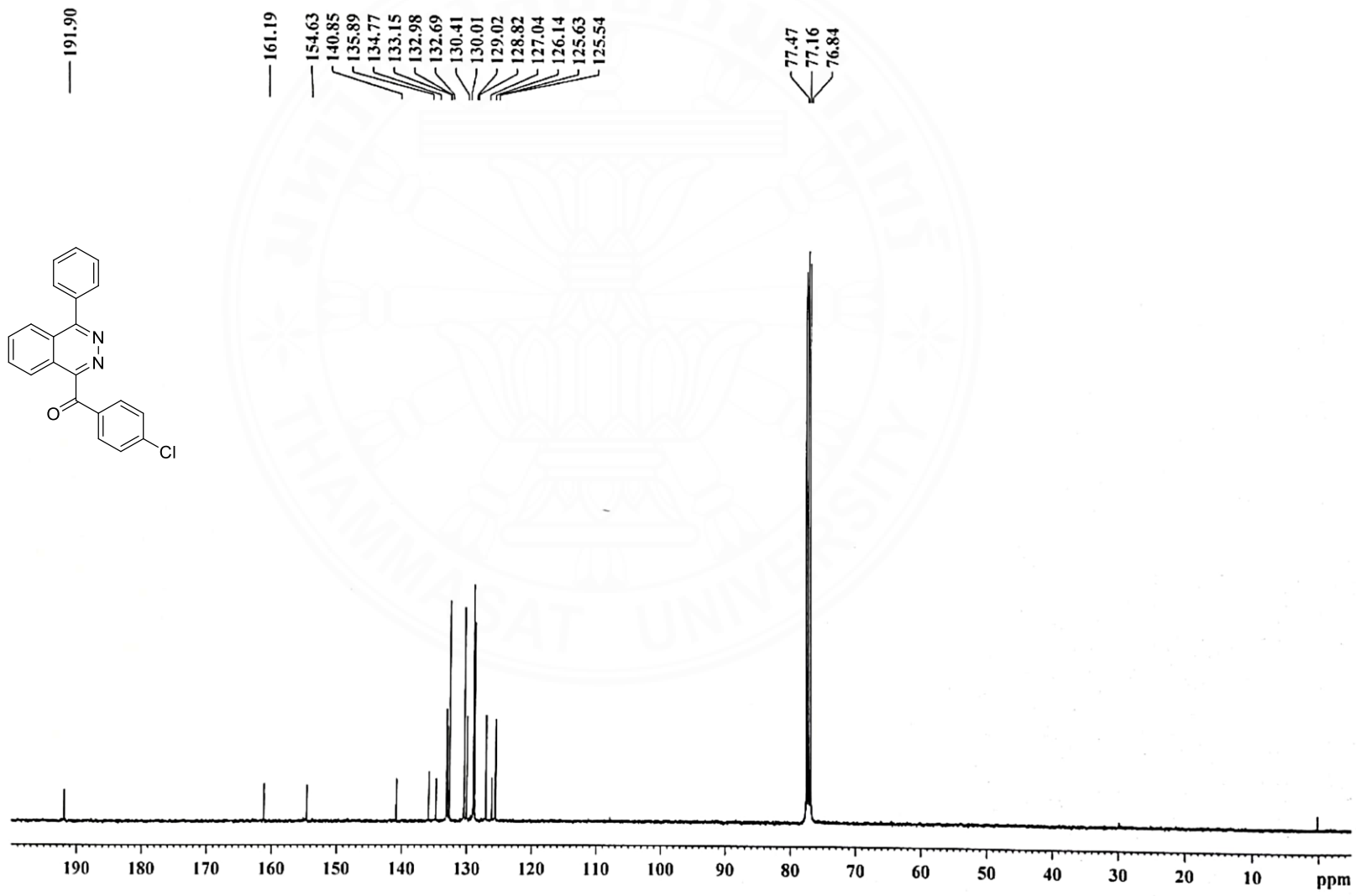
^{13}C-NMR of compound **3b** (100 MHz, $CDCl_3$)



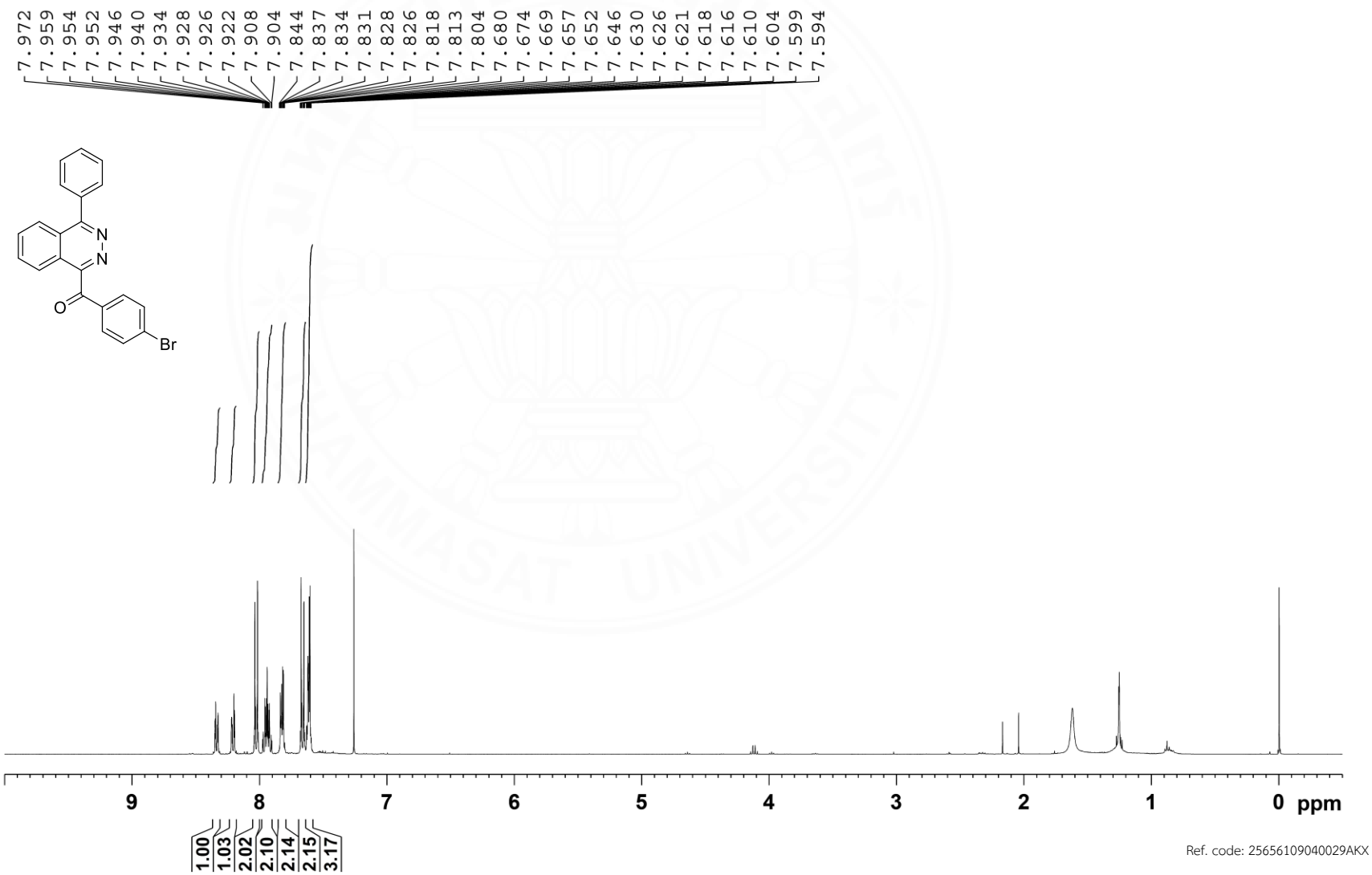
^{1}H-NMR of compound **3c** (400 MHz, $CDCl_3$)



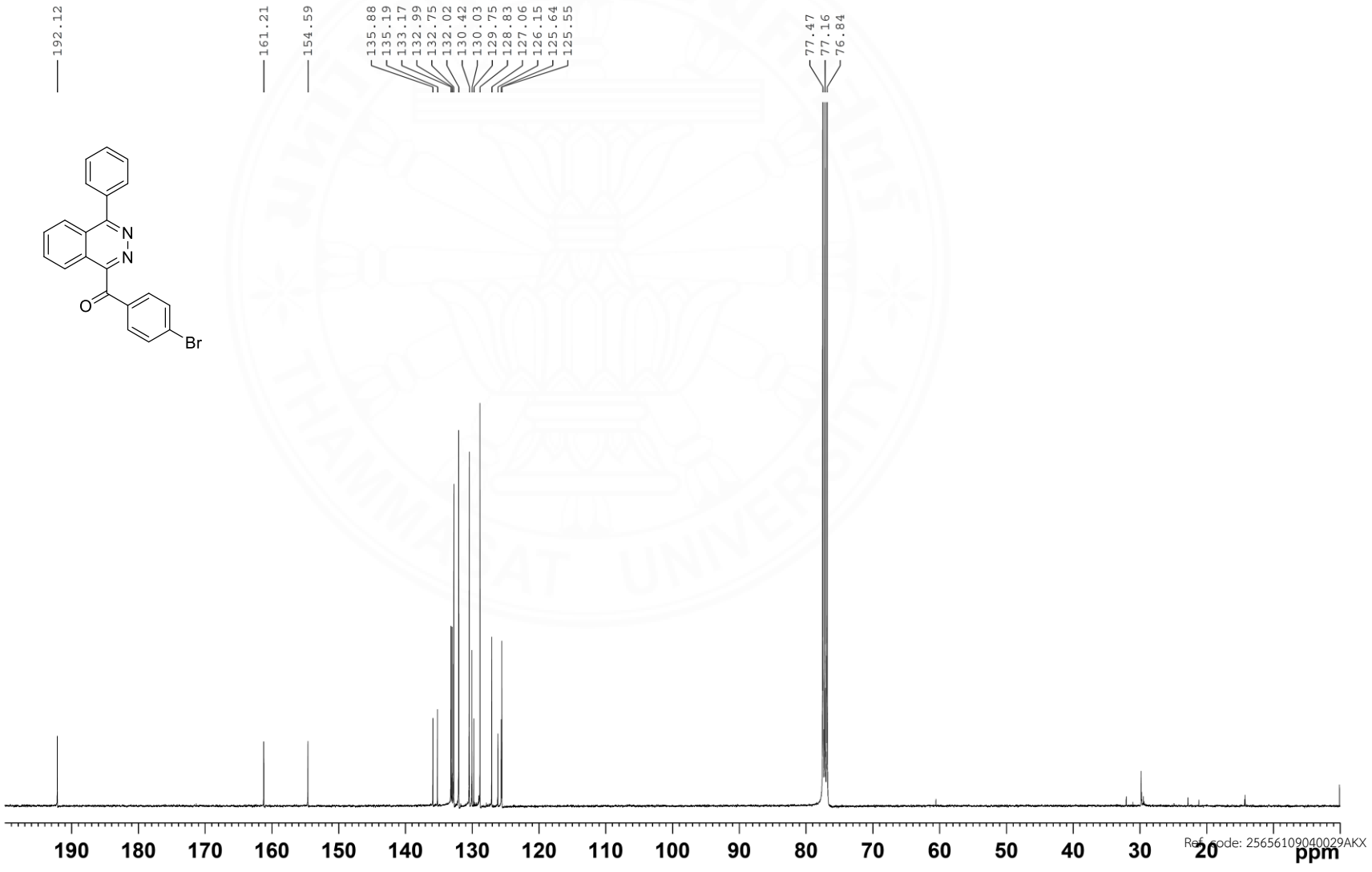
^{13}C-NMR of compound **3c** (100 MHz, $CDCl_3$)



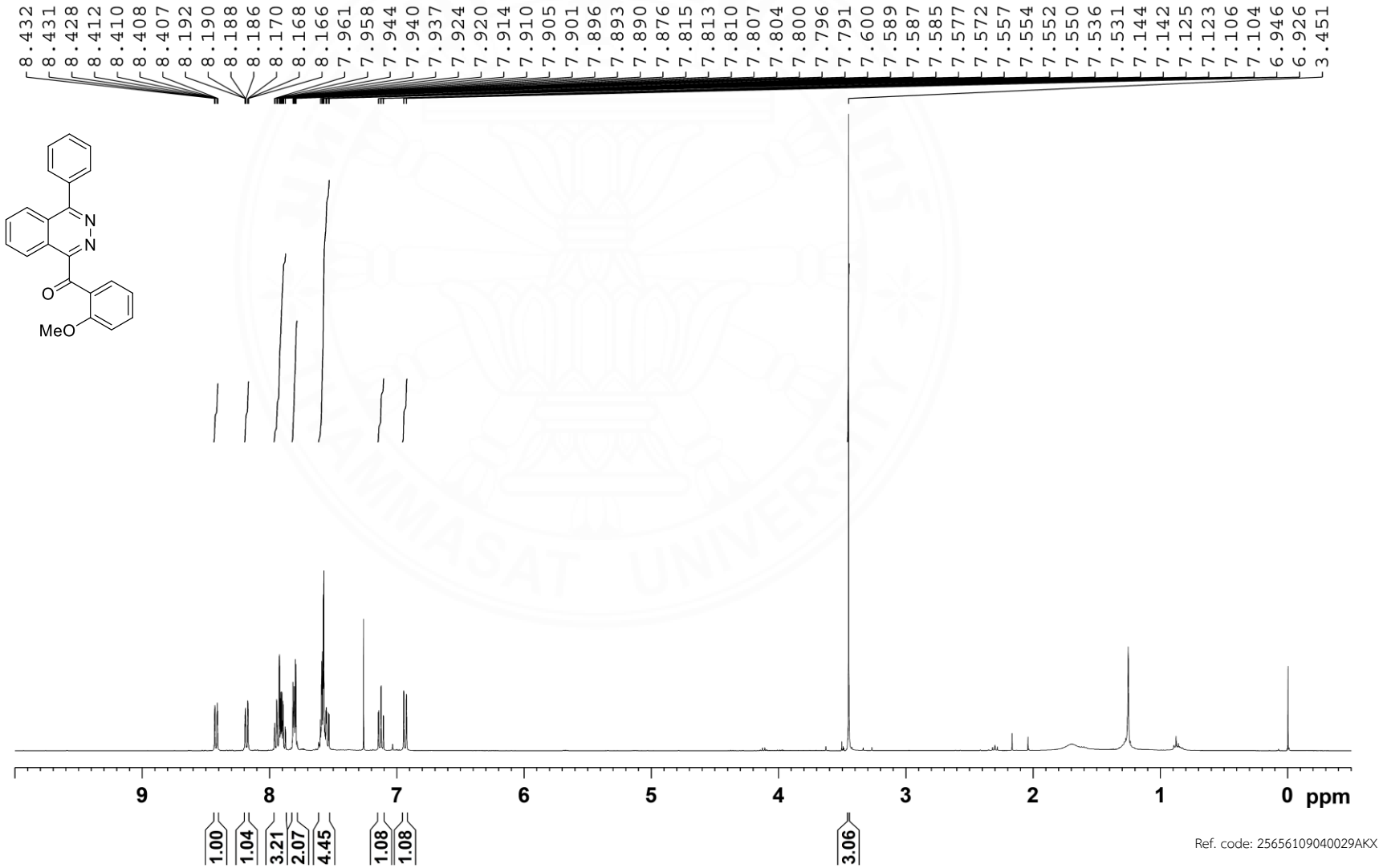
^{1}H-NMR of compound **3d** (400 MHz, $CDCl_3$)



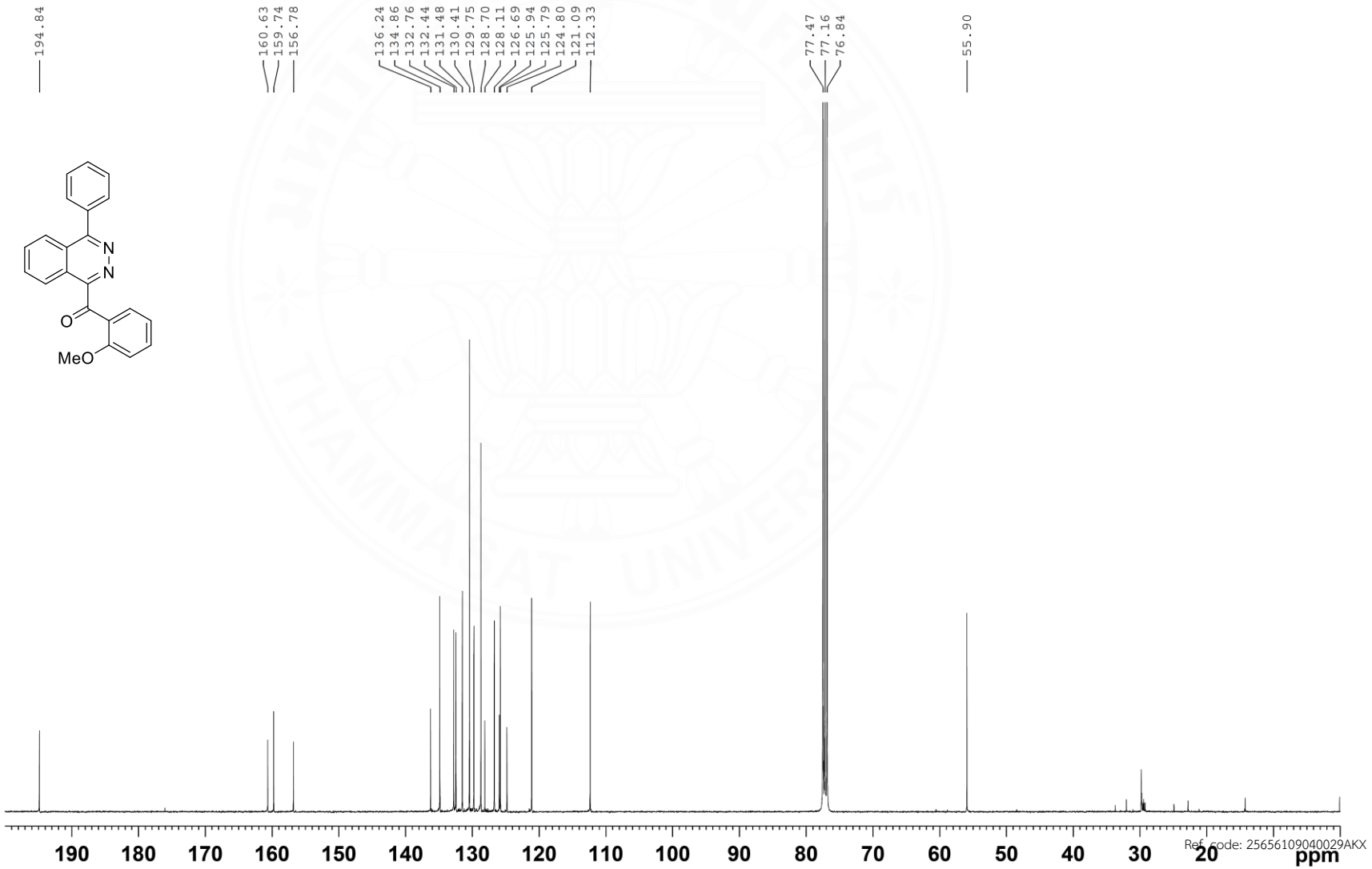
^{13}C-NMR of compound **3d** (100 MHz, $CDCl_3$)



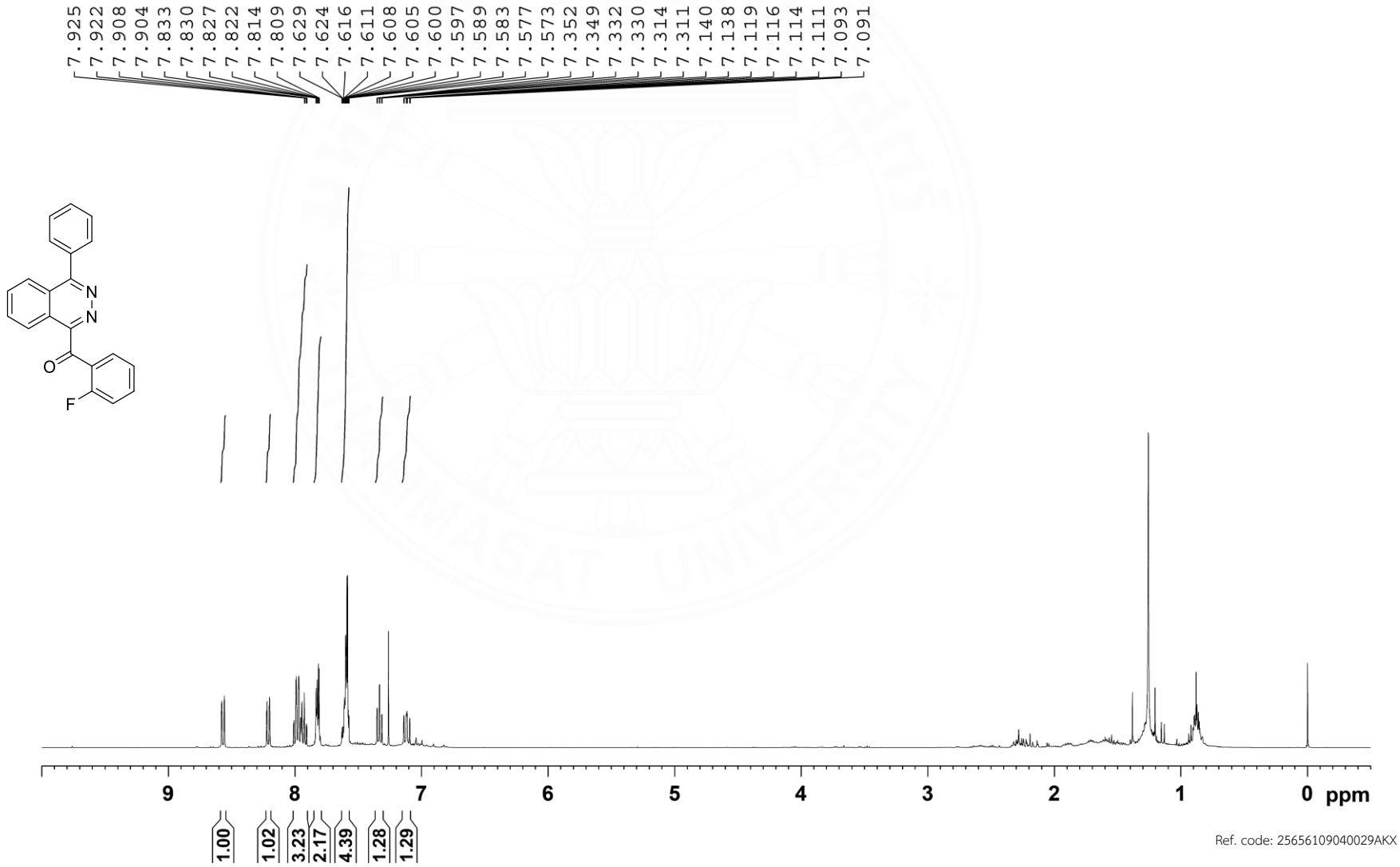
^{1}H-NMR of compound **3h** (400 MHz, $CDCl_3$)



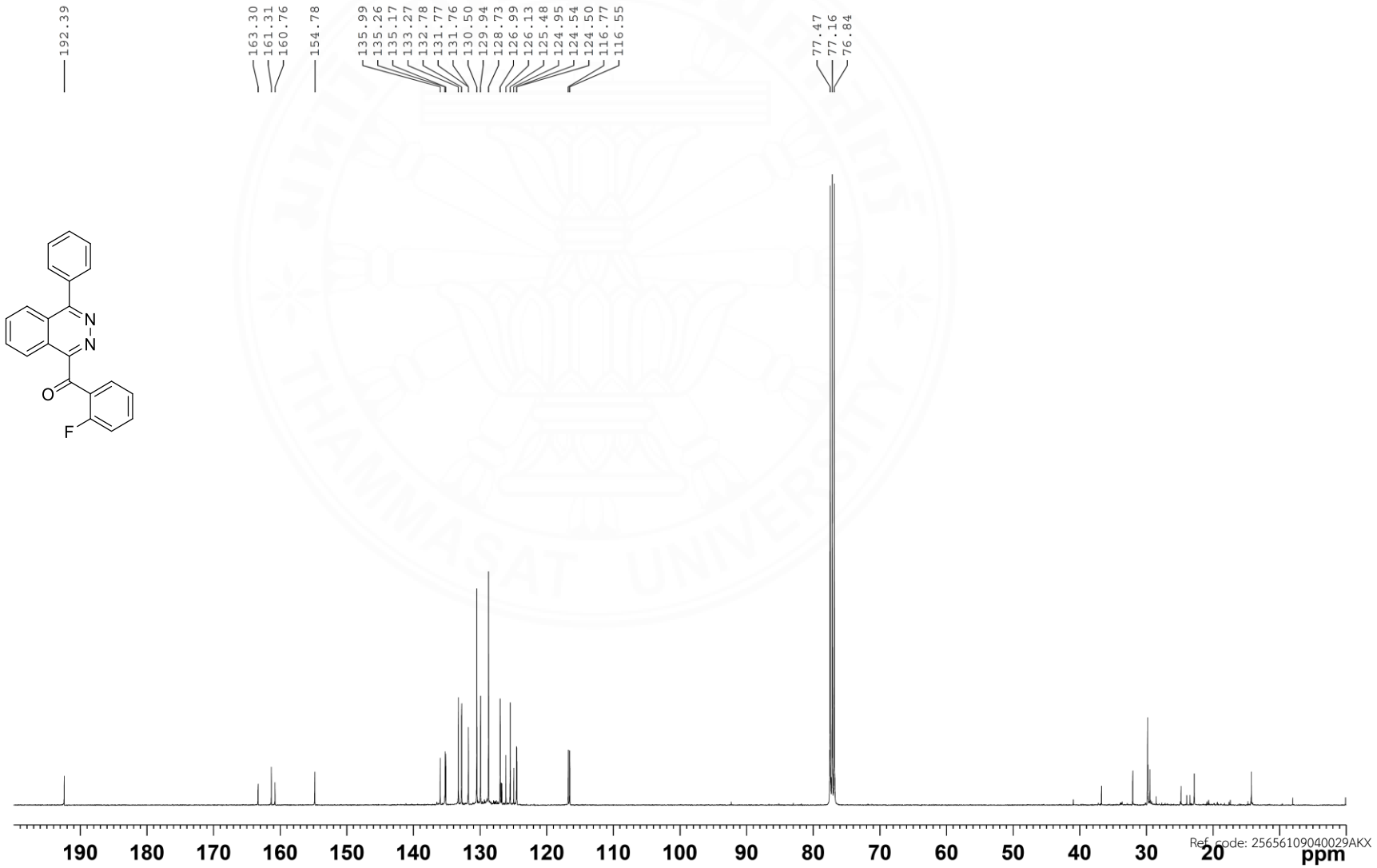
^{13}C-NMR of compound **3h** (100 MHz, $CDCl_3$)



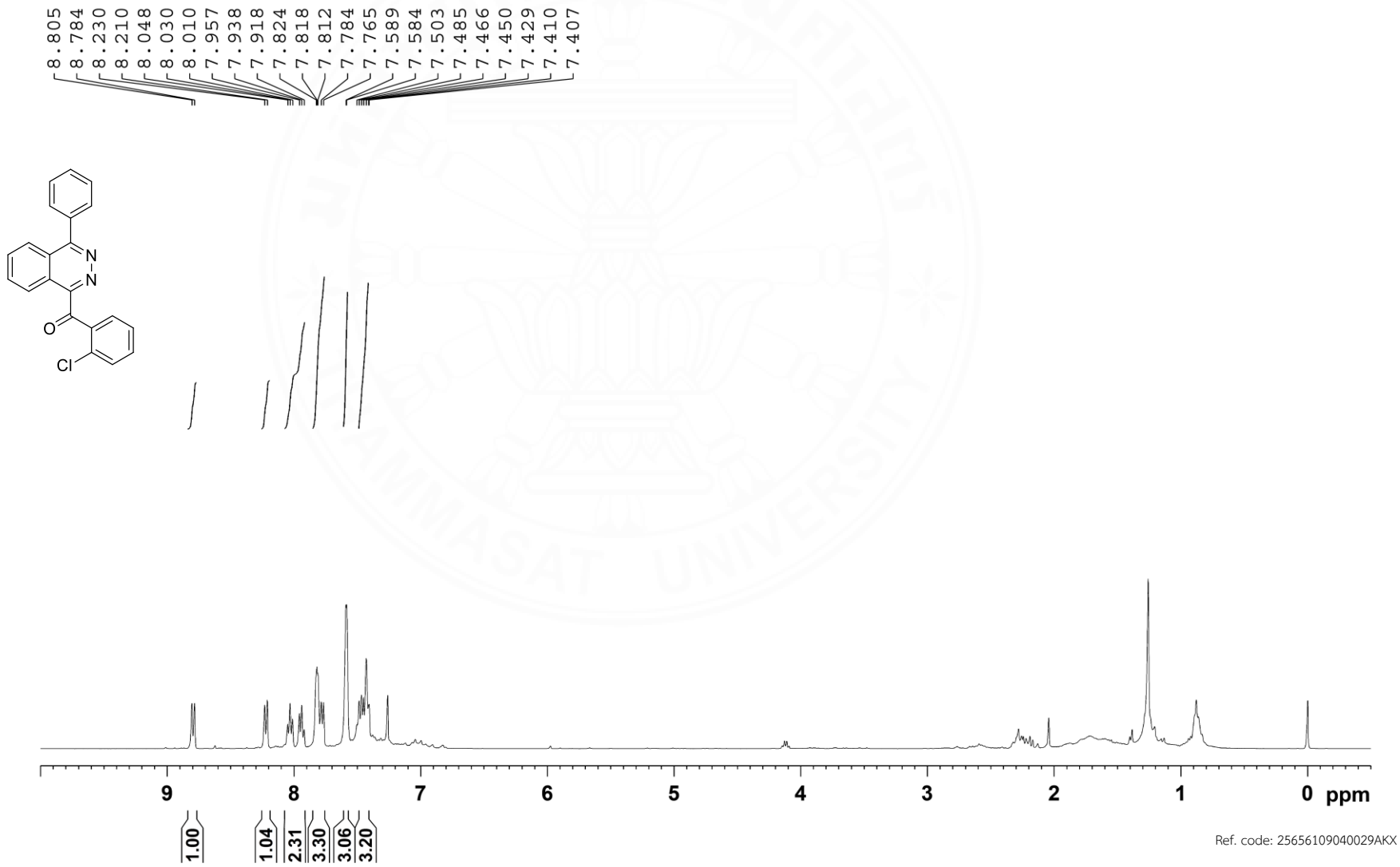
^{1}H-NMR of compound **3i** (400 MHz, $CDCl_3$)



^{13}C-NMR of compound **3i** (400 MHz, $CDCl_3$)



^{1}H-NMR of compound **3j** (400 MHz, $CDCl_3$)



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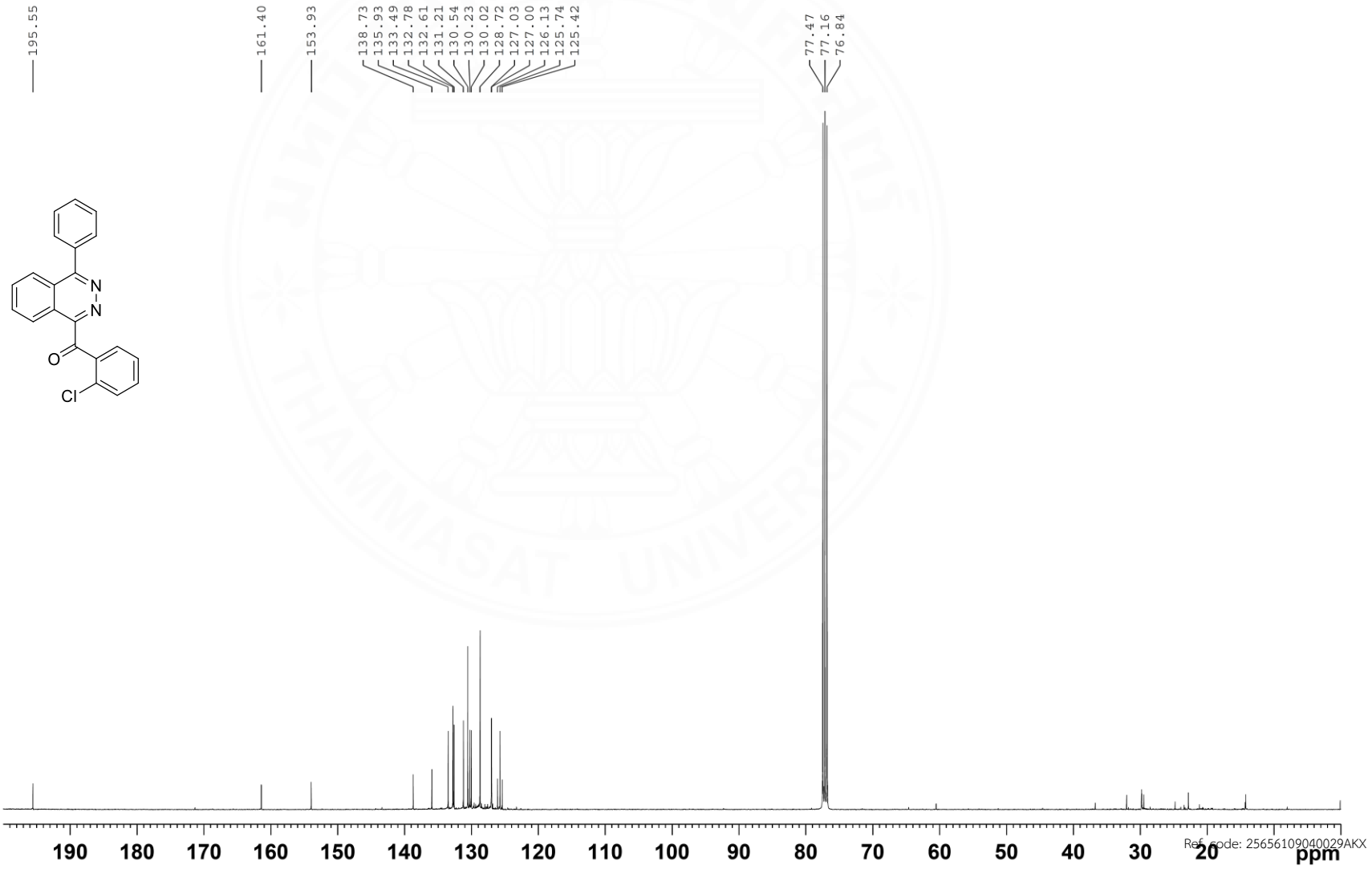
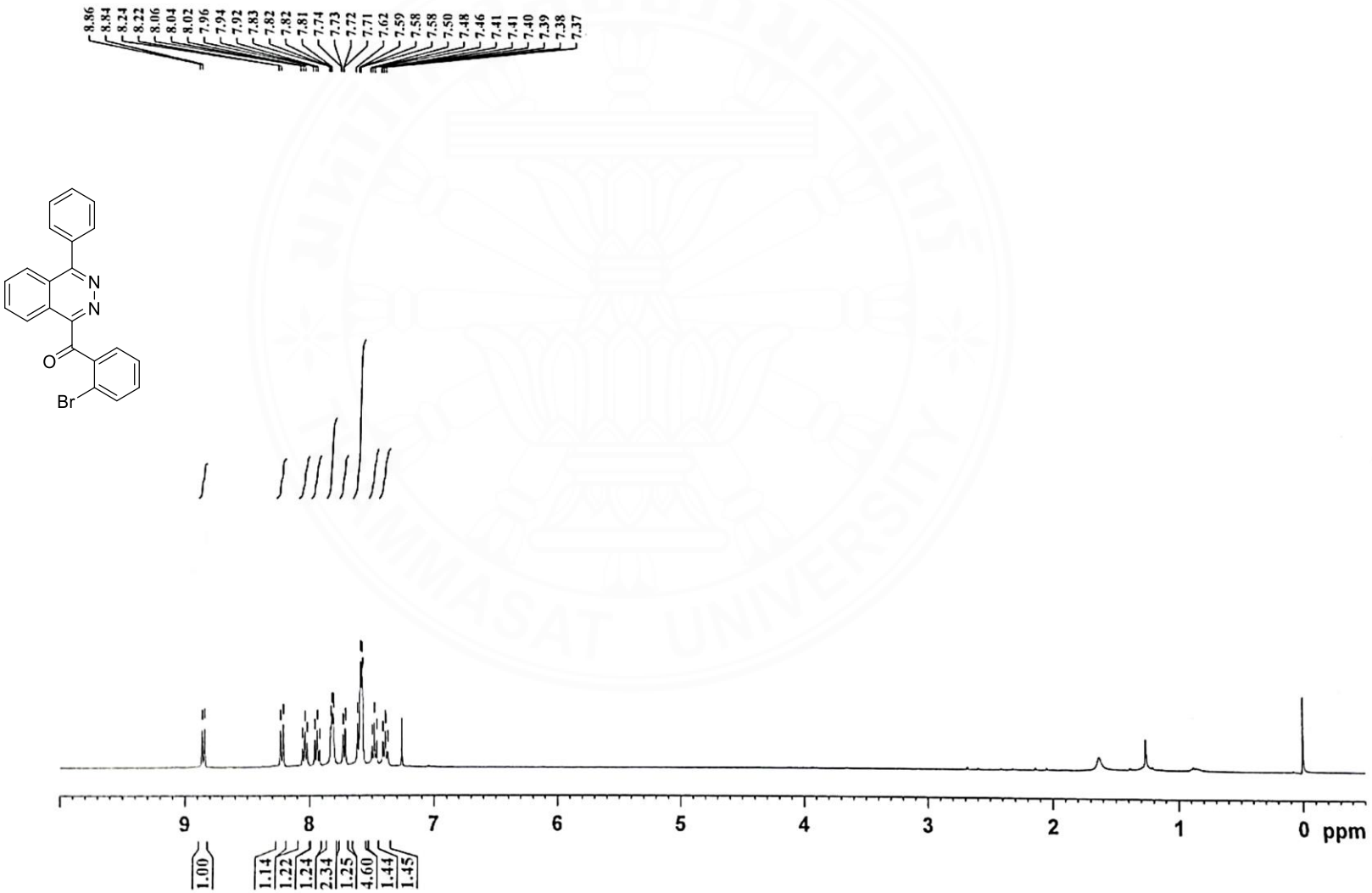
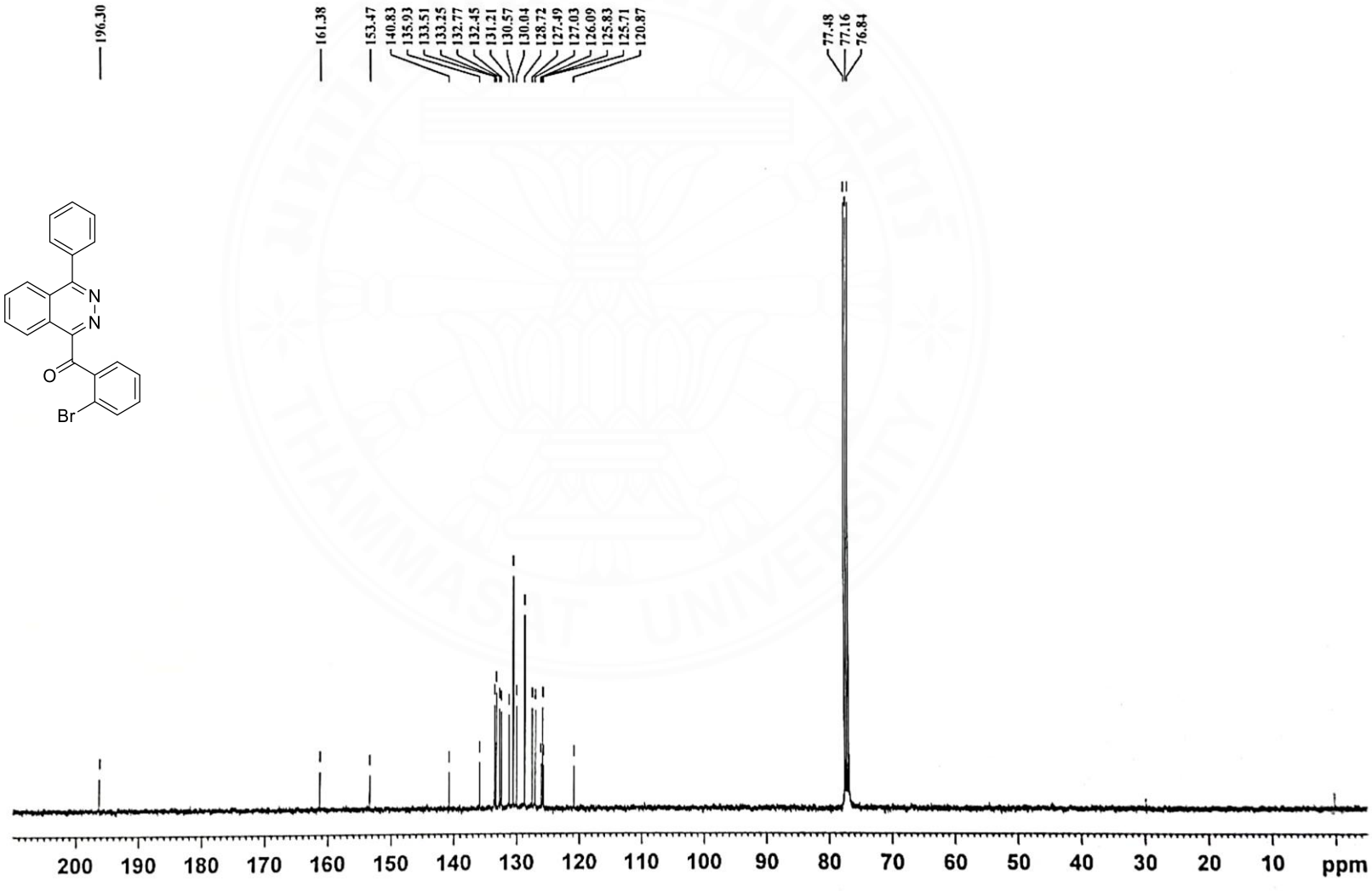


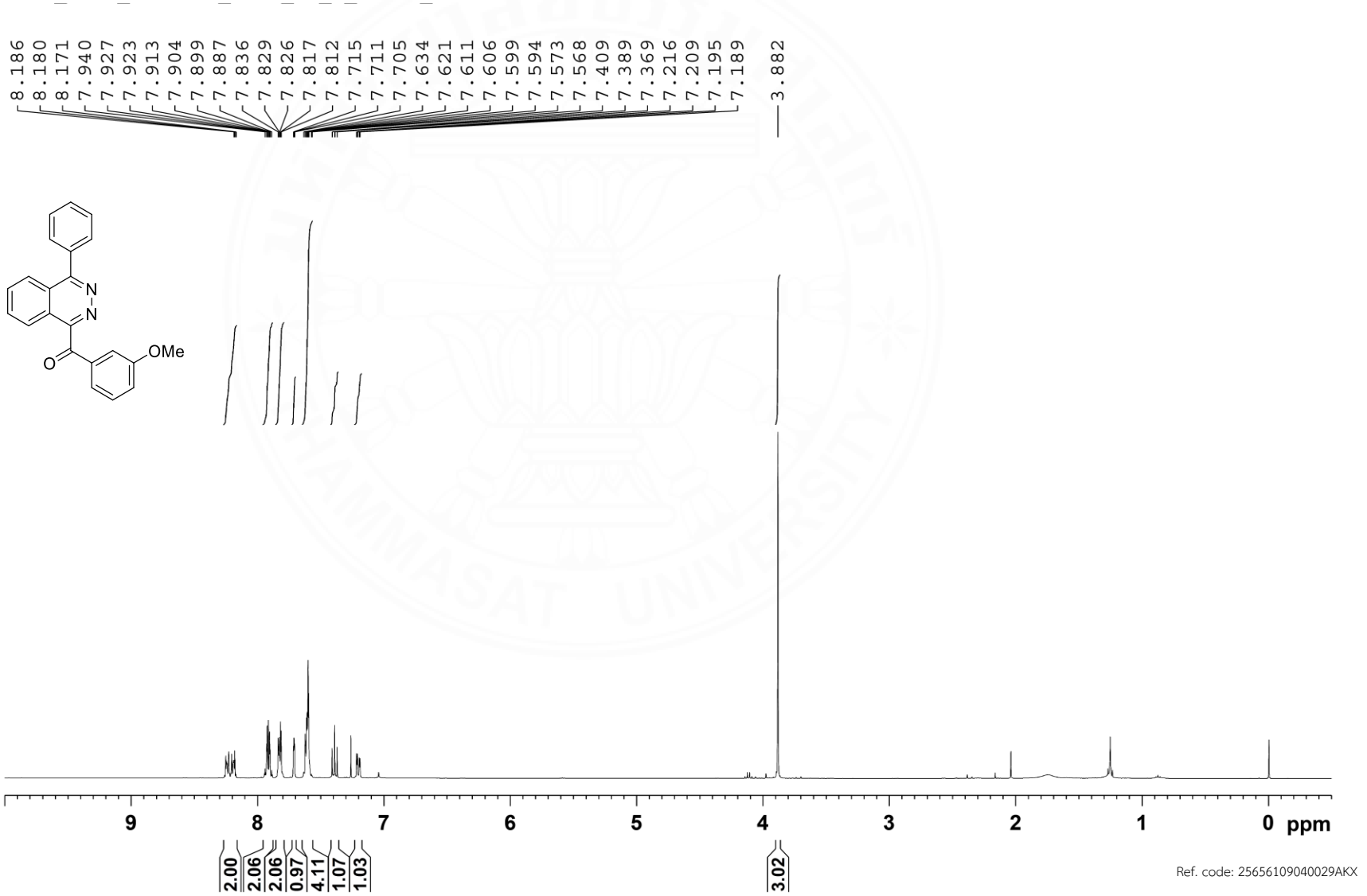
^{1}H-NMR of compound **3k** (400 MHz, $CDCl_3$)



^{13}C-NMR of compound **3k** (100 MHz, $CDCl_3$)



^{1}H-NMR of compound **3l** (400 MHz, $CDCl_3$)



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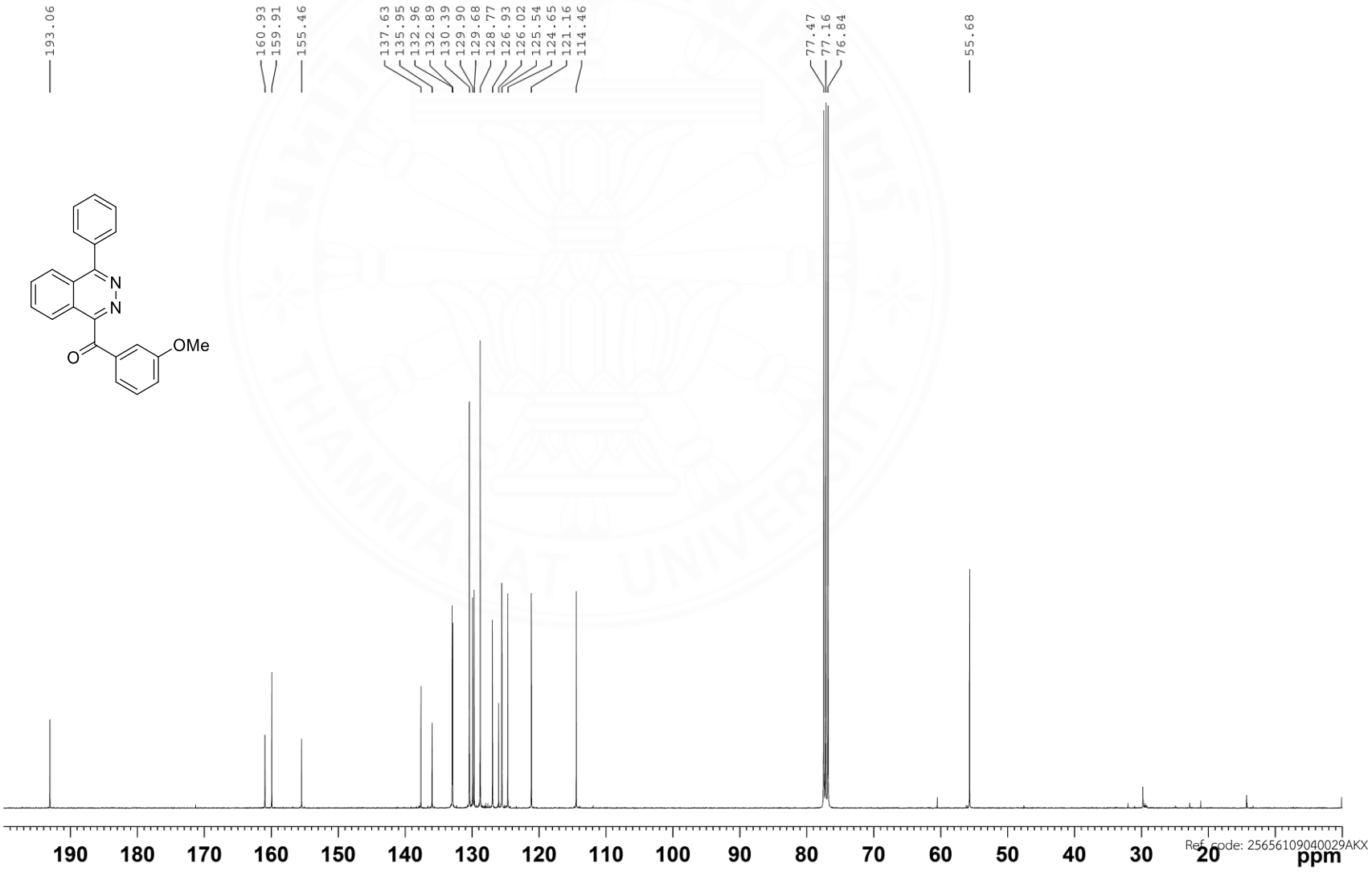
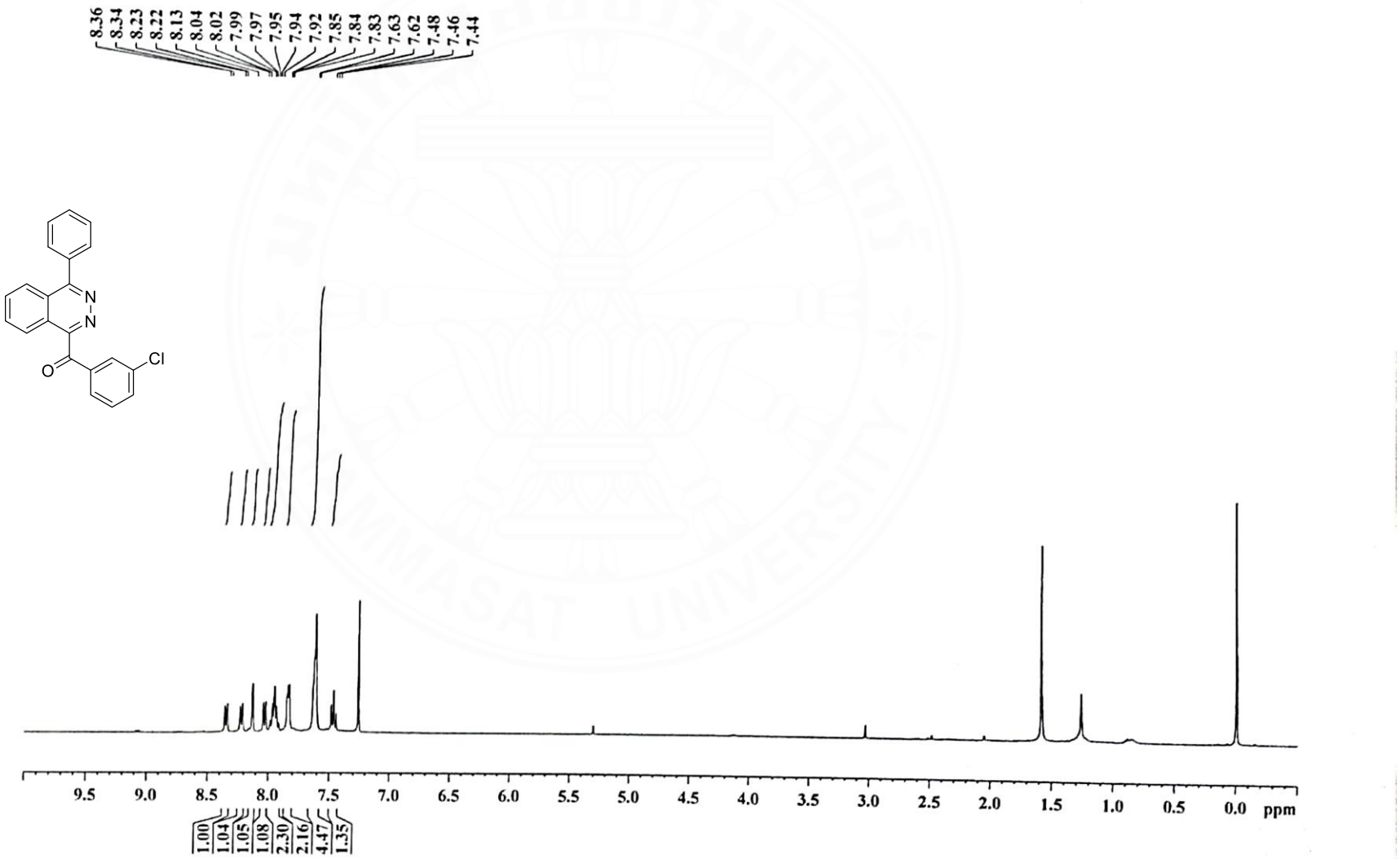
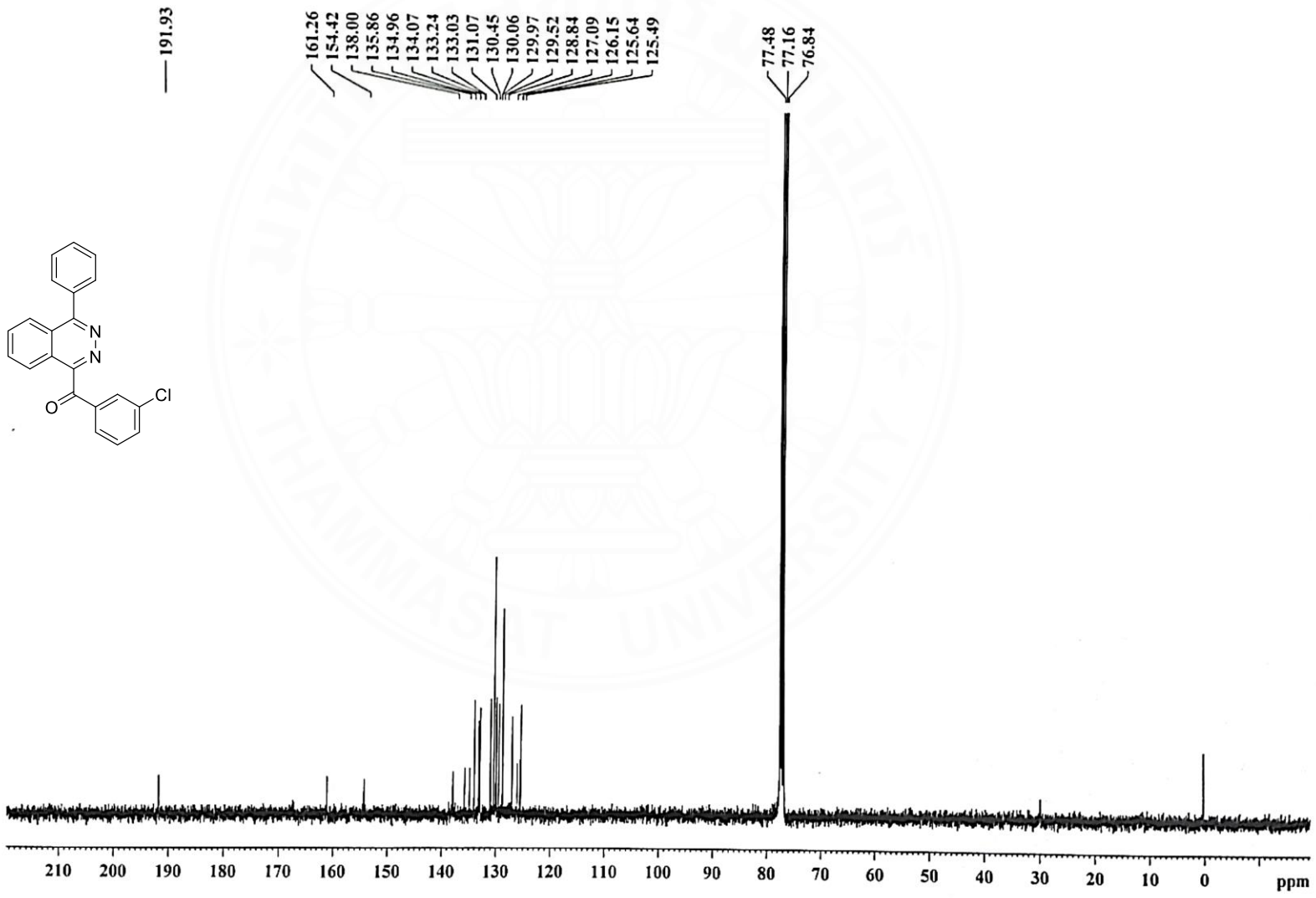


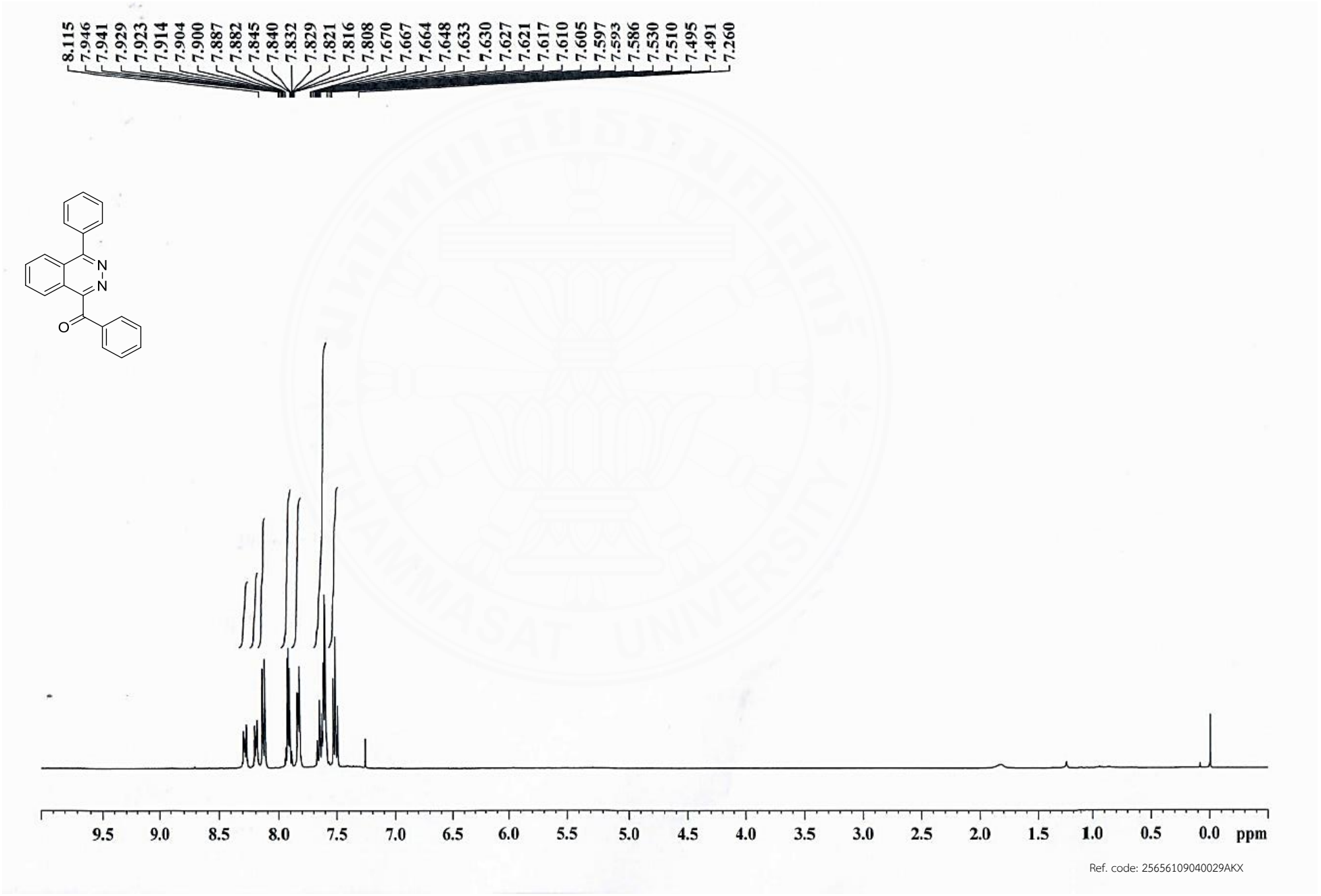
^{1}H-NMR of compound **3m** (400 MHz, $CDCl_3$)



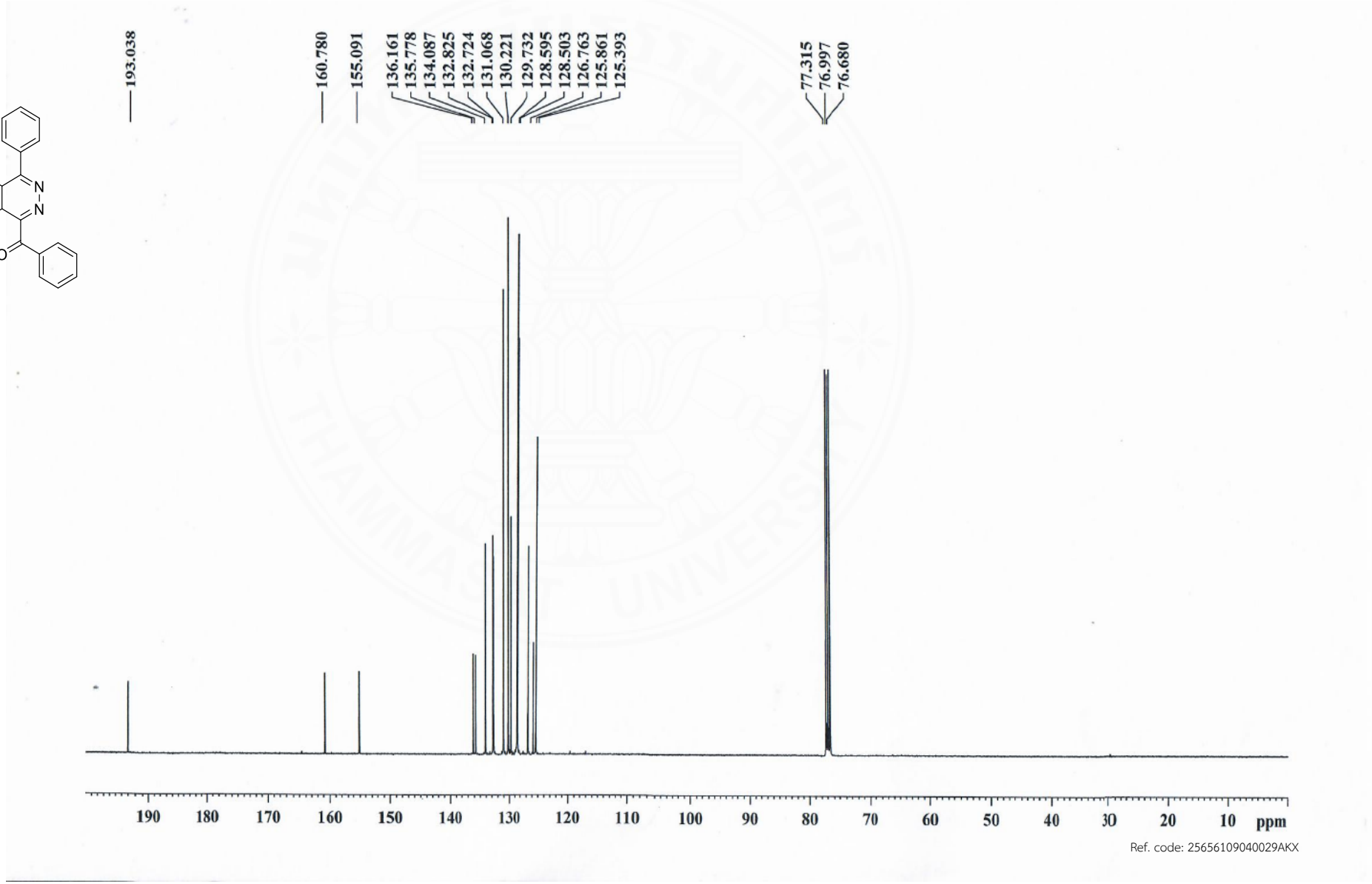
^{13}C-NMR of compound **3m** (100 MHz, $CDCl_3$)



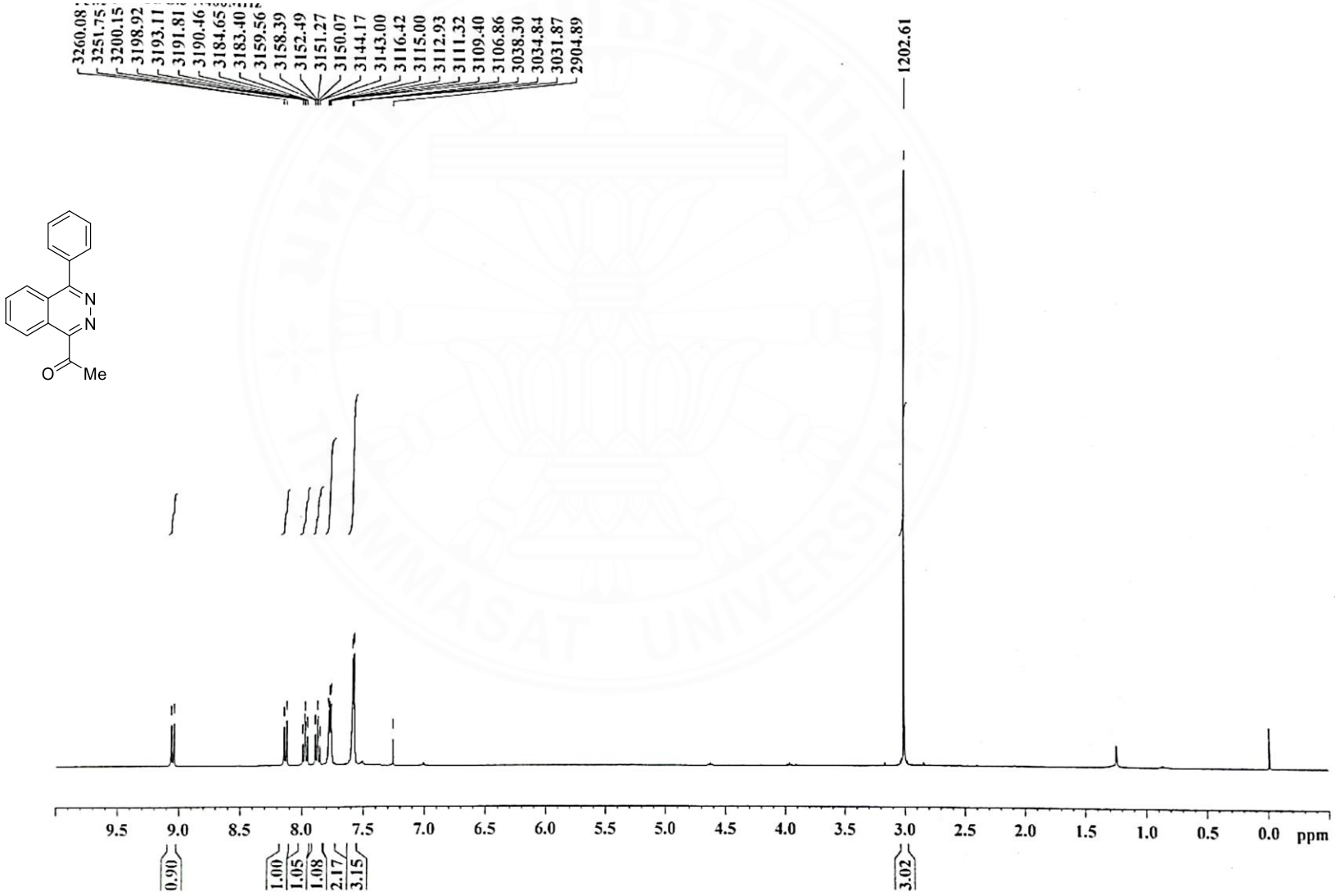
^{1}H-NMR of compound **3o** (400 MHz, $CDCl_3$)



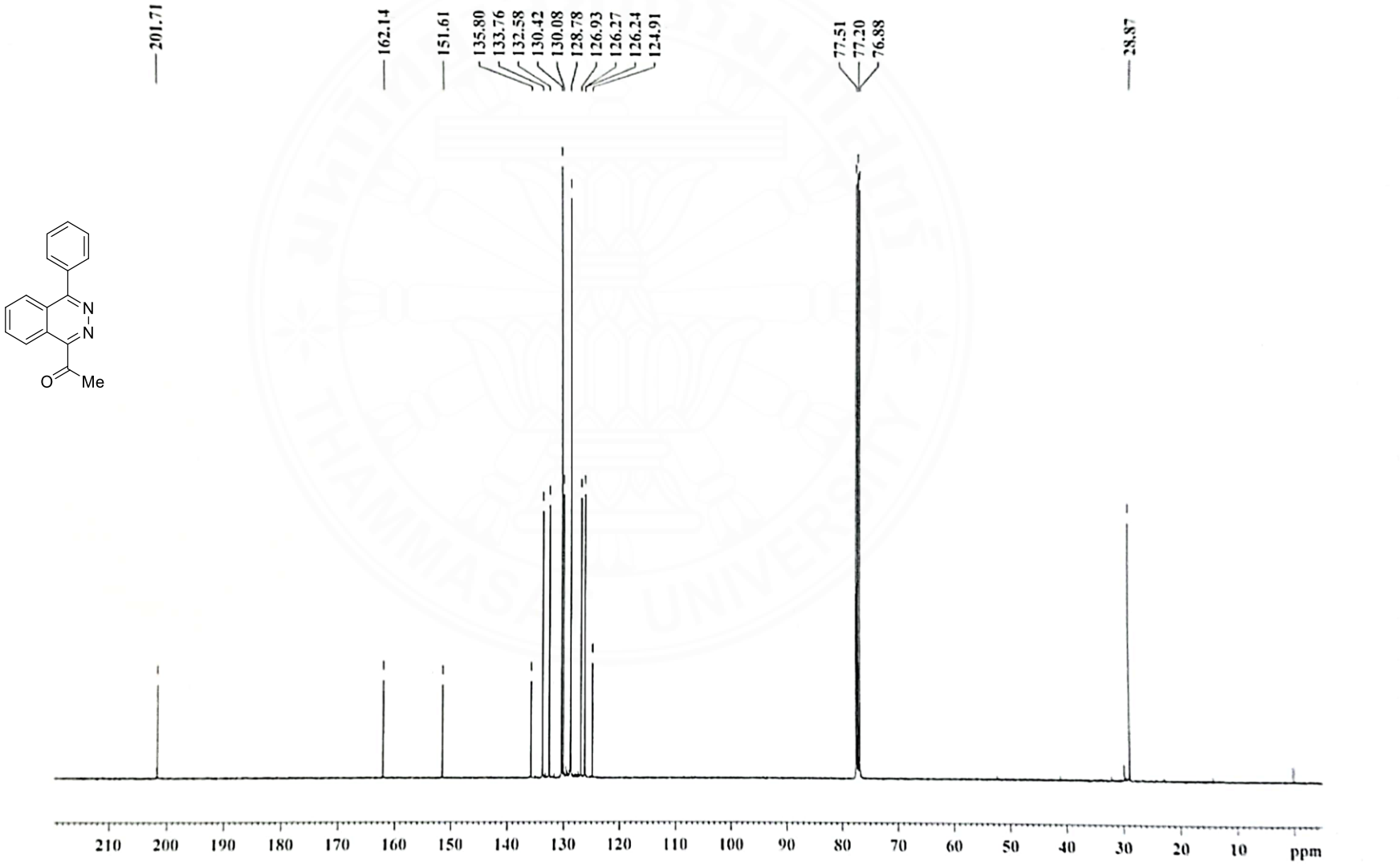
^{13}C-NMR of compound **3o** (100 MHz, $CDCl_3$)



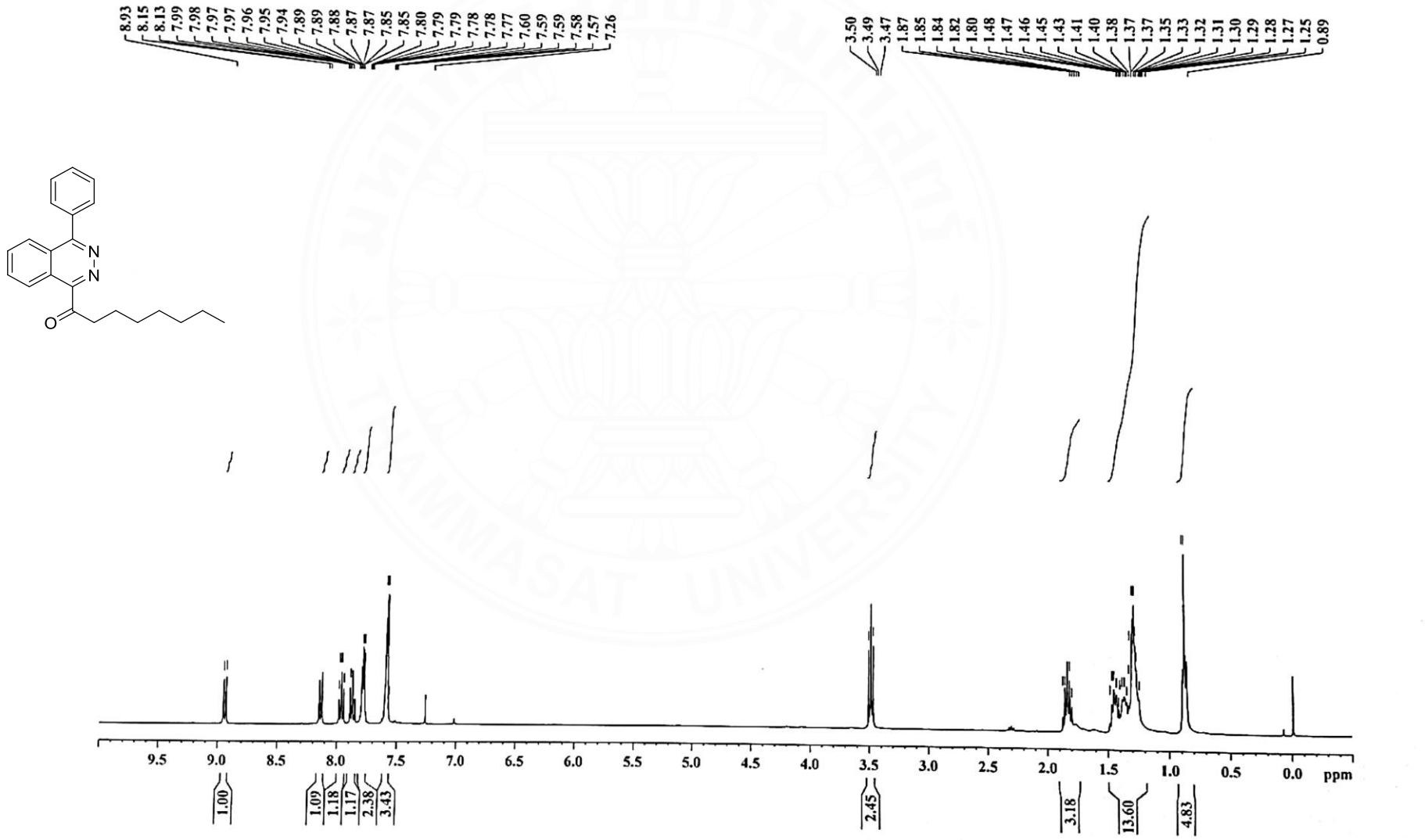
^{1}H-NMR of compound **3p** (400 MHz, $CDCl_3$)



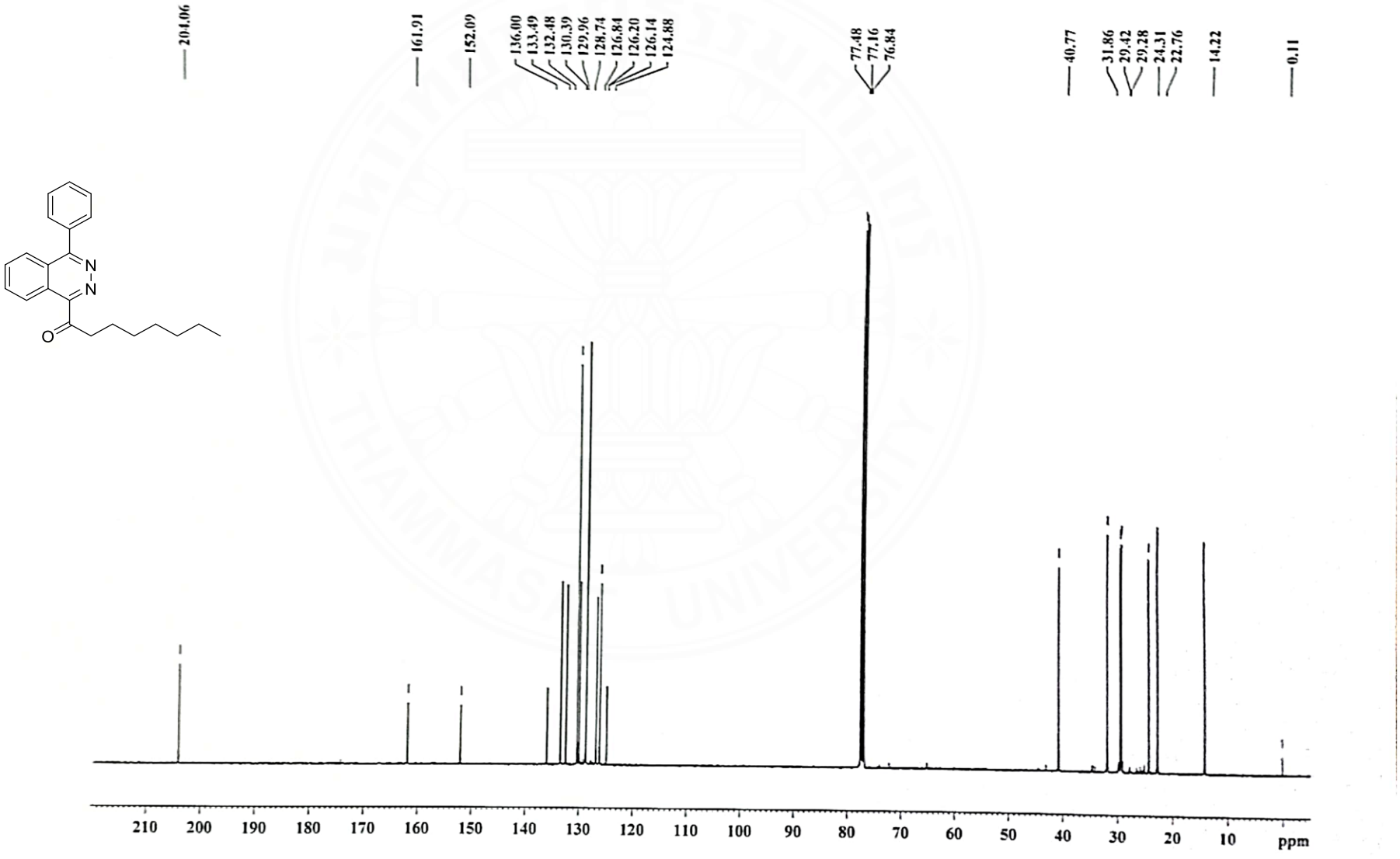
^{13}C-NMR of compound **3p** (100 MHz, $CDCl_3$)



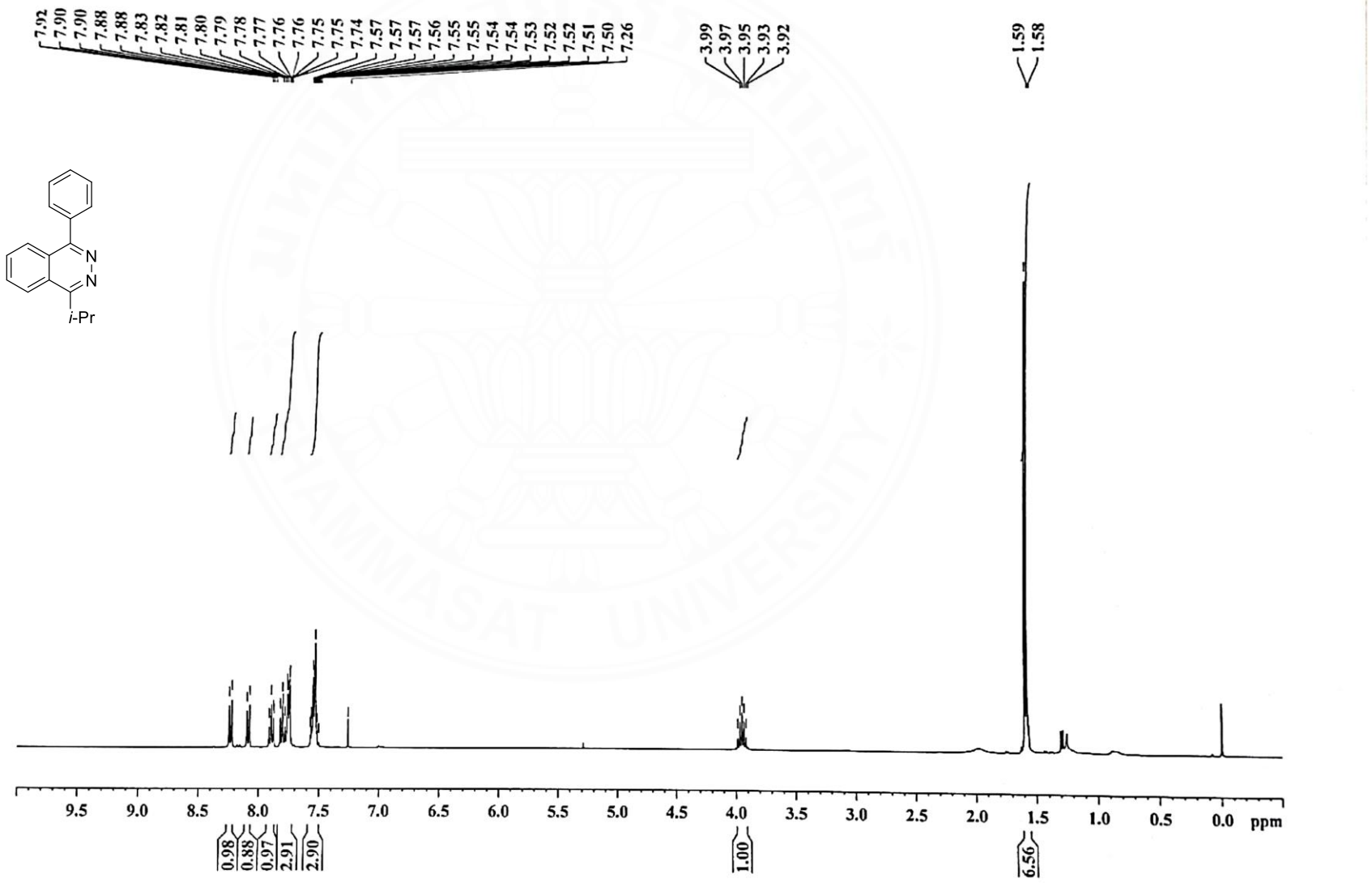
^{1}H-NMR of compound **3q** (400 MHz, $CDCl_3$)



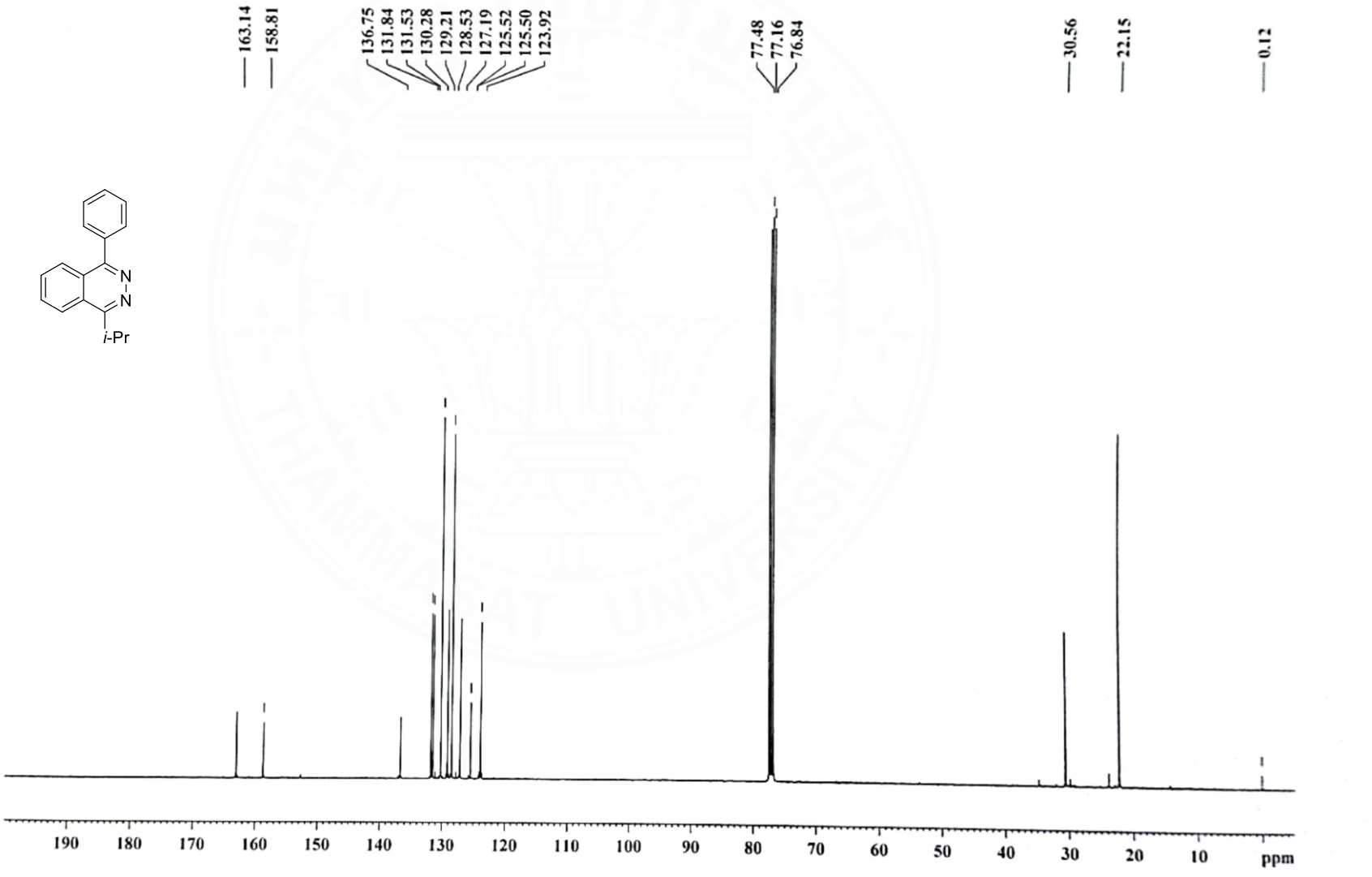
^{13}C-NMR of compound **3q** (100 MHz, $CDCl_3$)



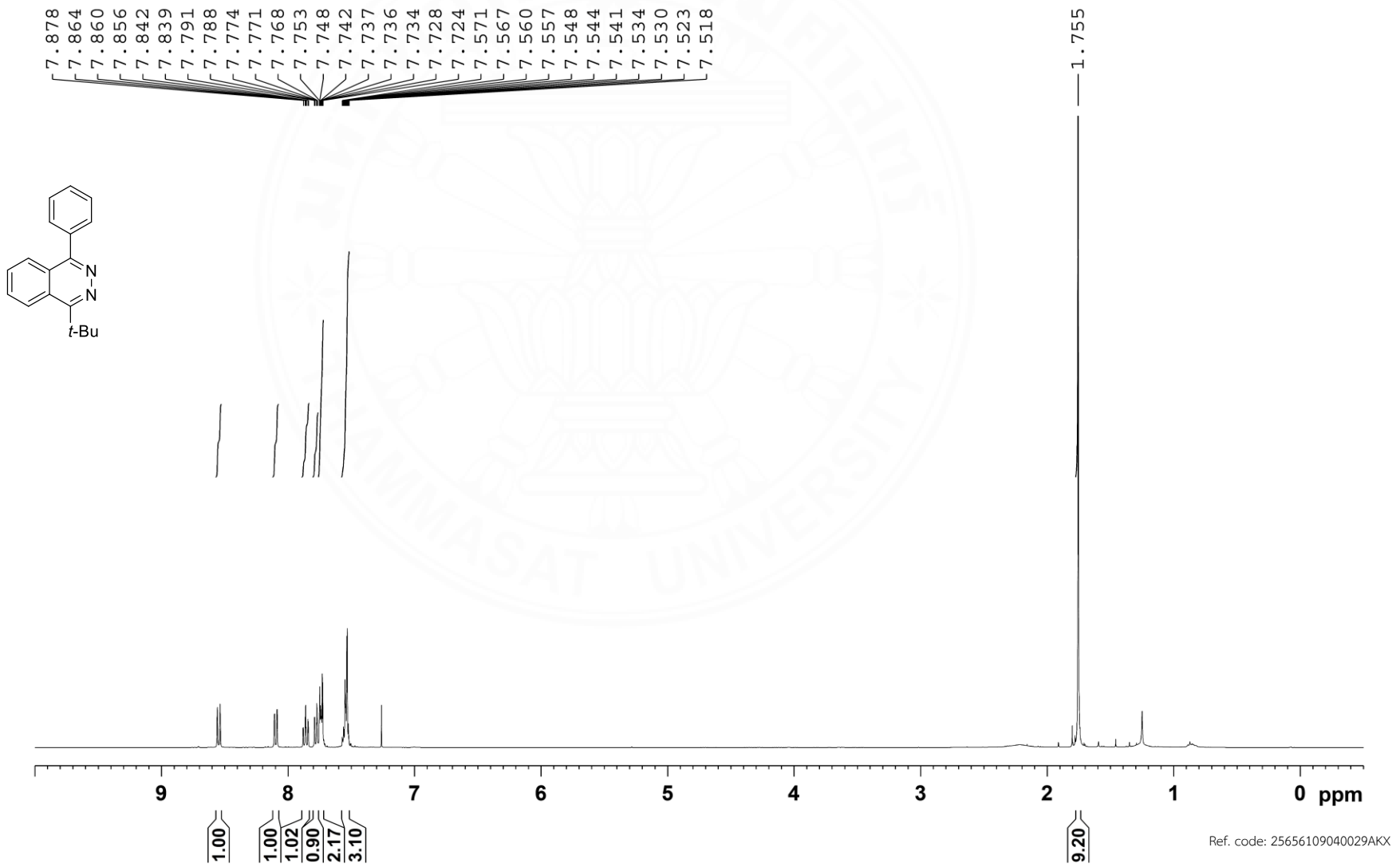
^{1}H-NMR of compound **3r** (400 MHz, $CDCl_3$)



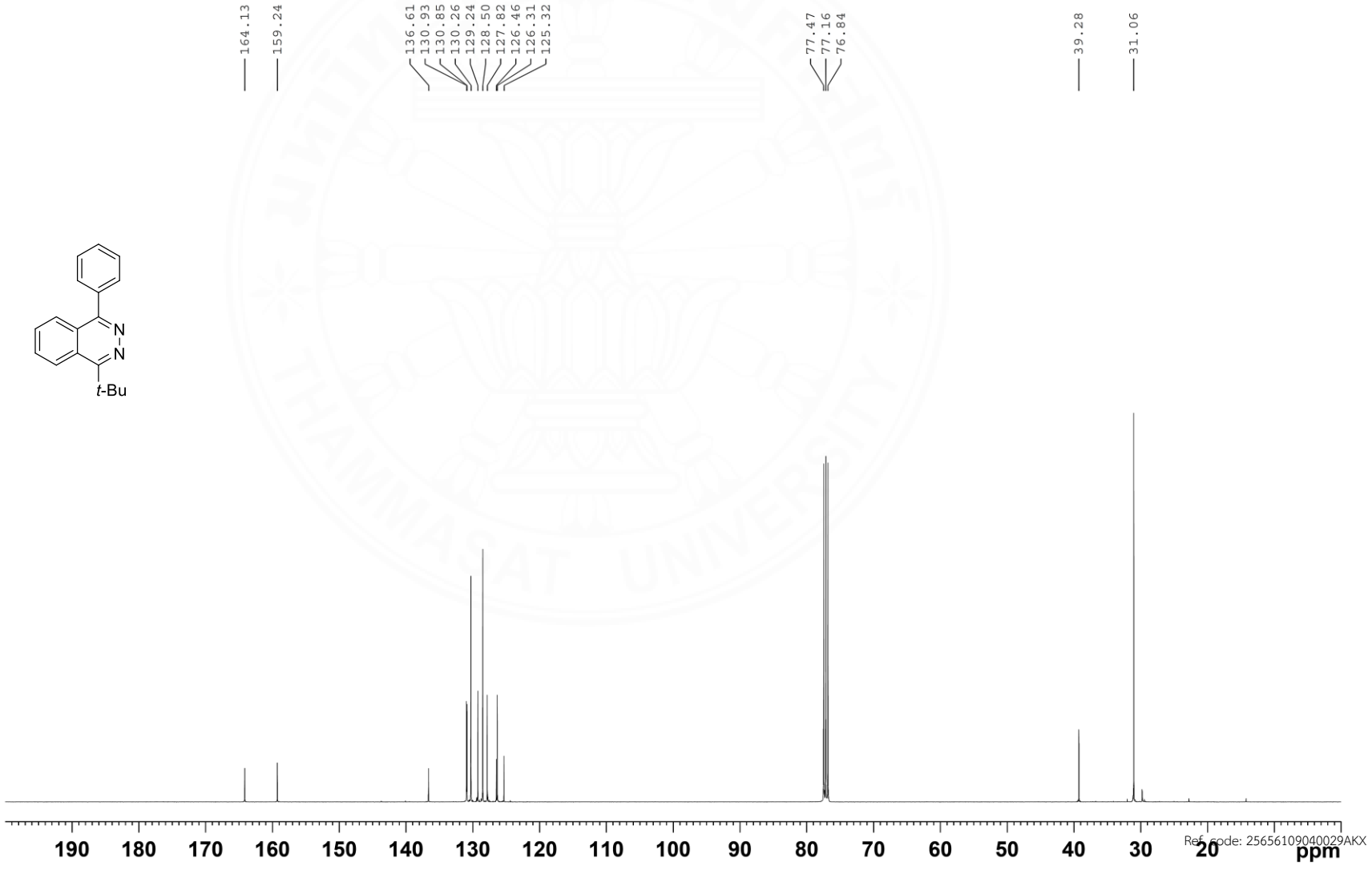
^{13}C-NMR of compound **3r** (100 MHz, $CDCl_3$)



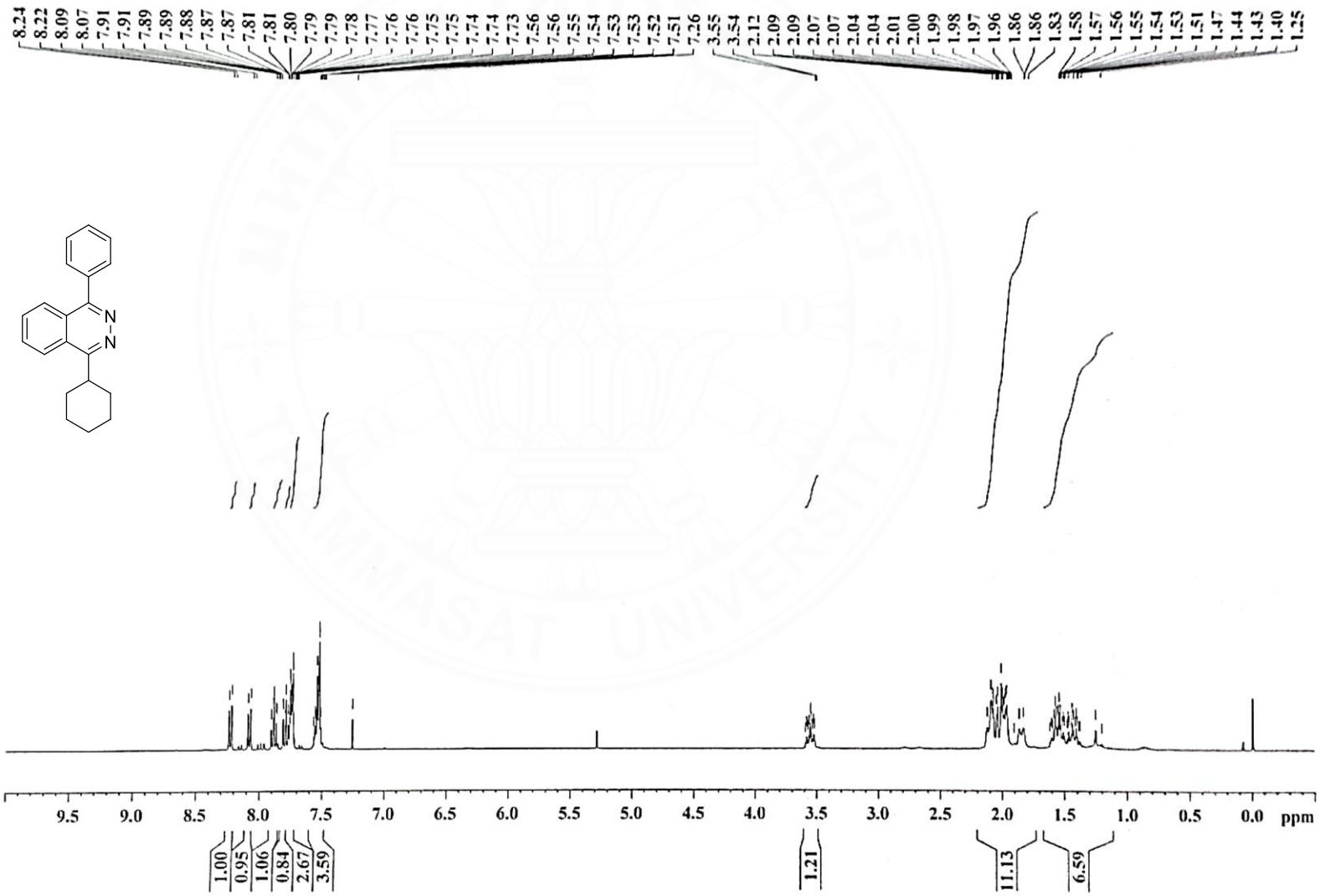
^{1}H-NMR of compound **3s** (400 MHz, $CDCl_3$)



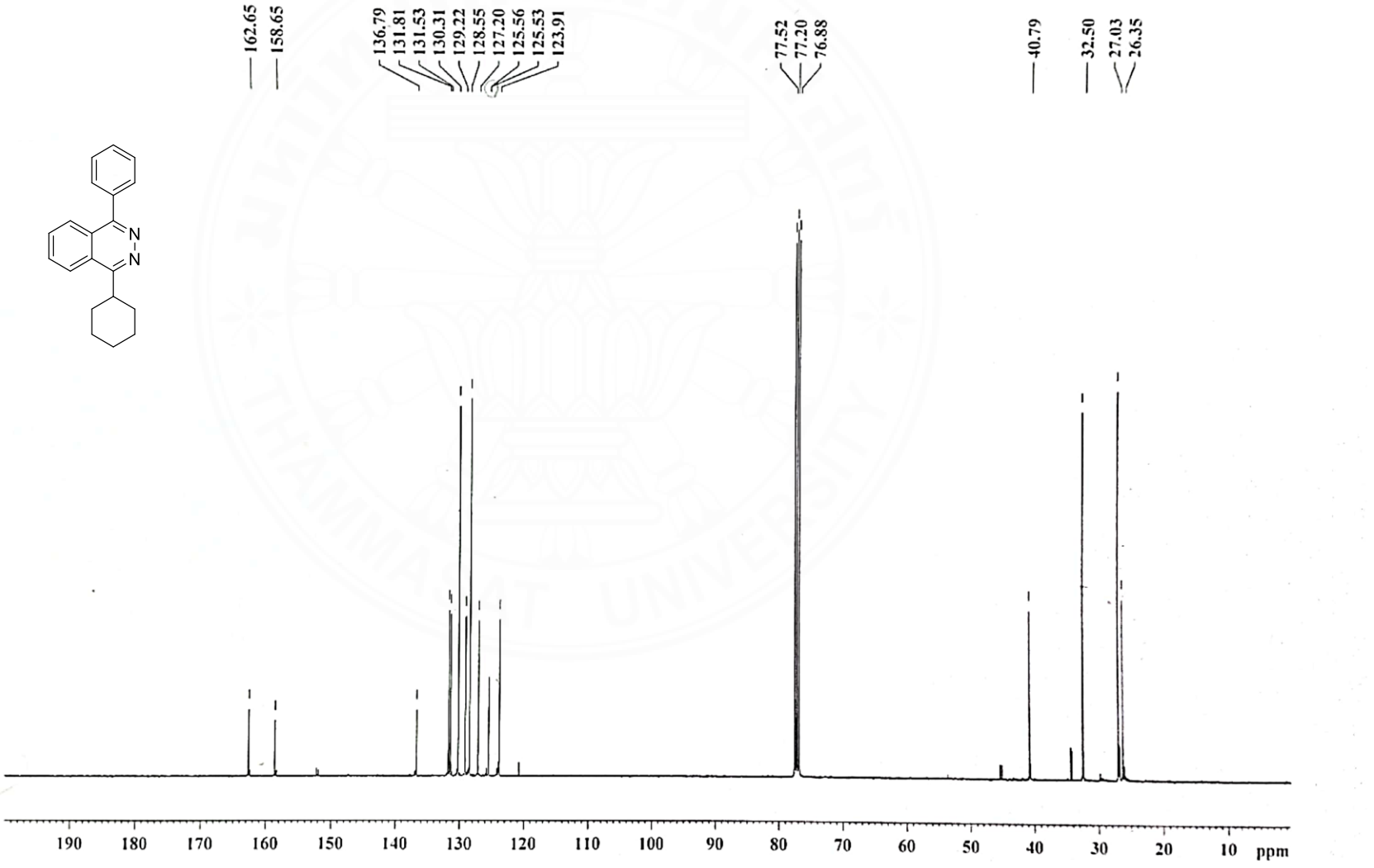
^{13}C-NMR of compound **3s** (100 MHz, $CDCl_3$)



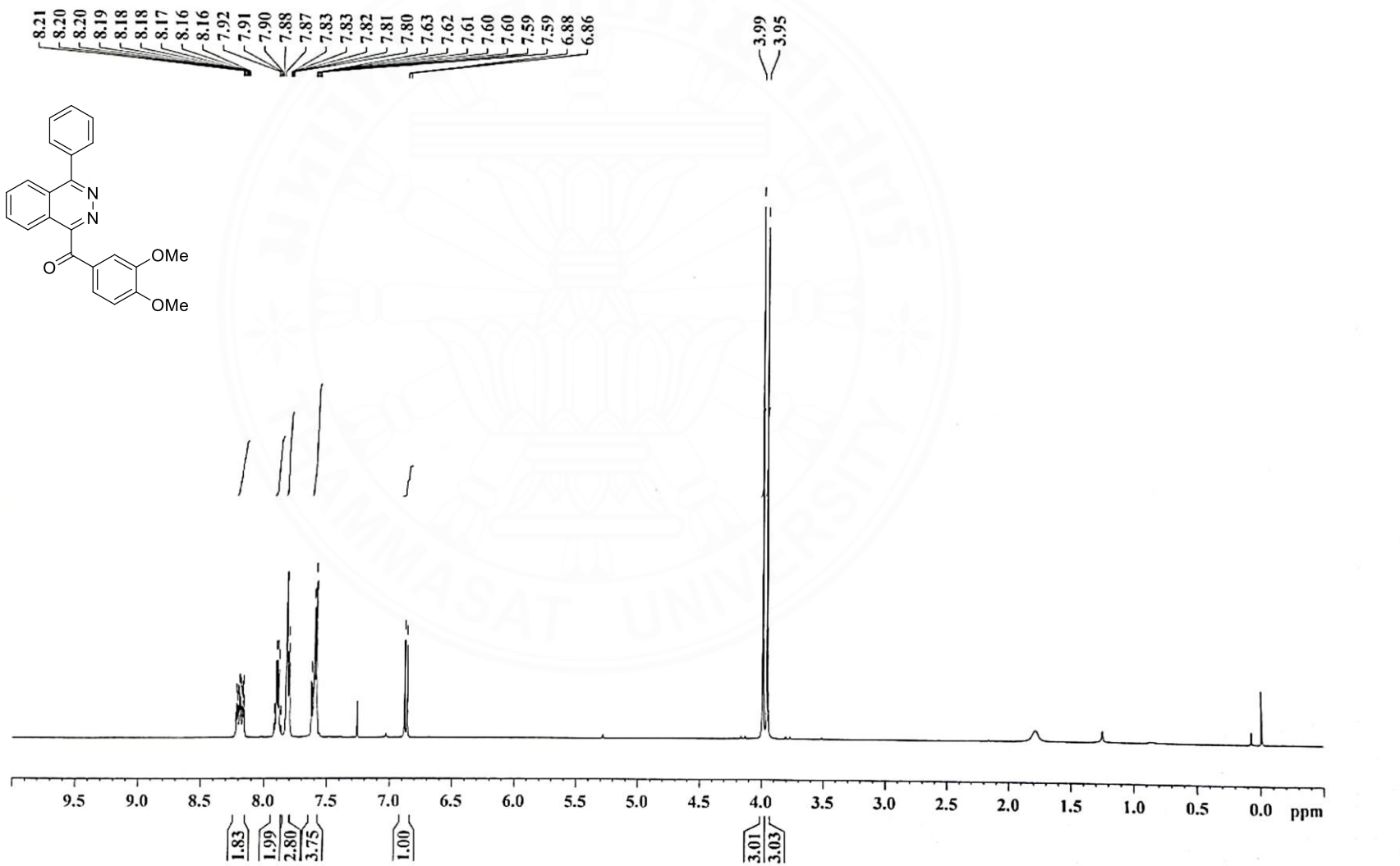
^{1}H-NMR of compound **3t** (400 MHz, $CDCl_3$)



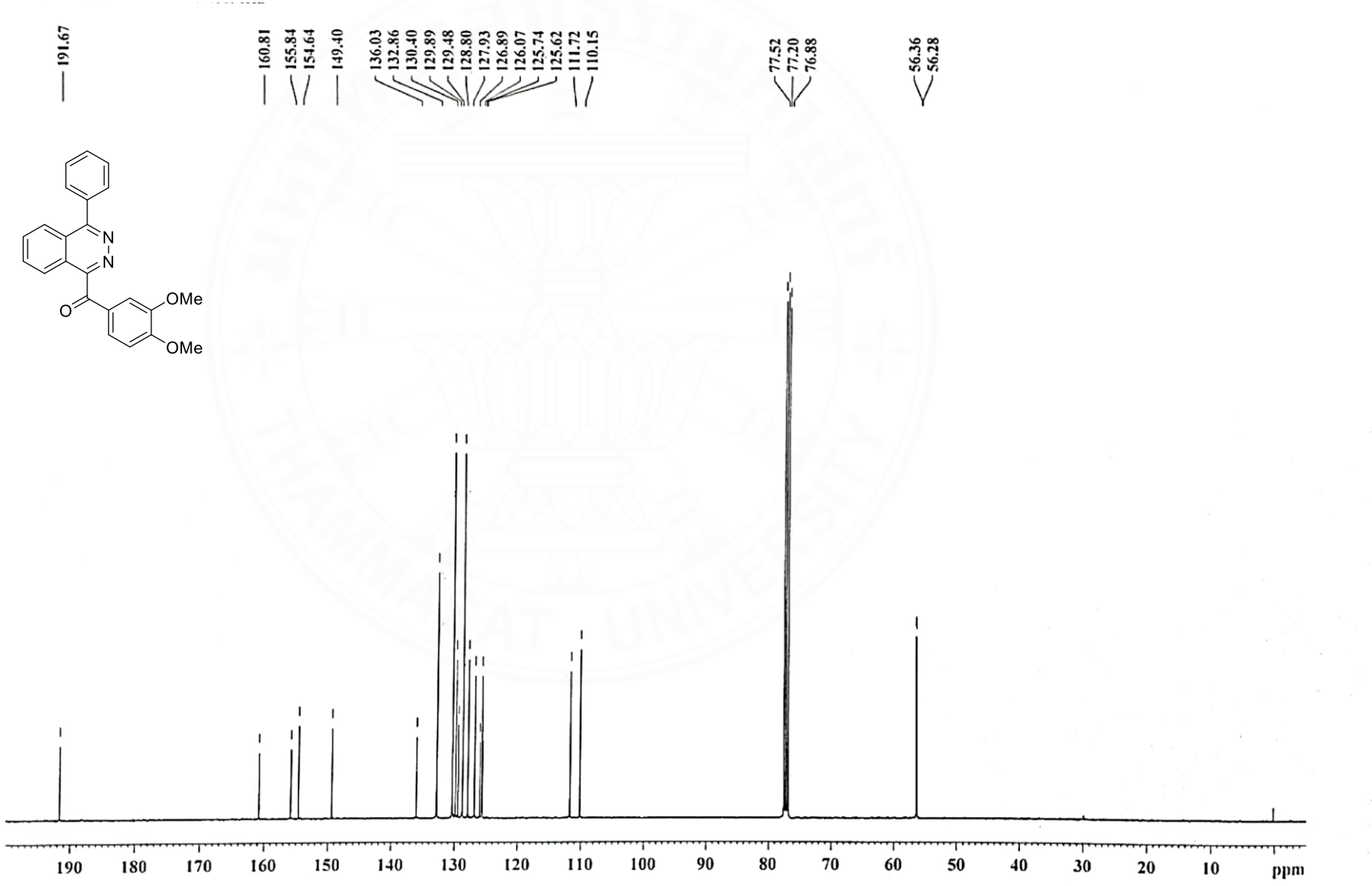
^{13}C-NMR of compound **3t** (100 MHz, $CDCl_3$)



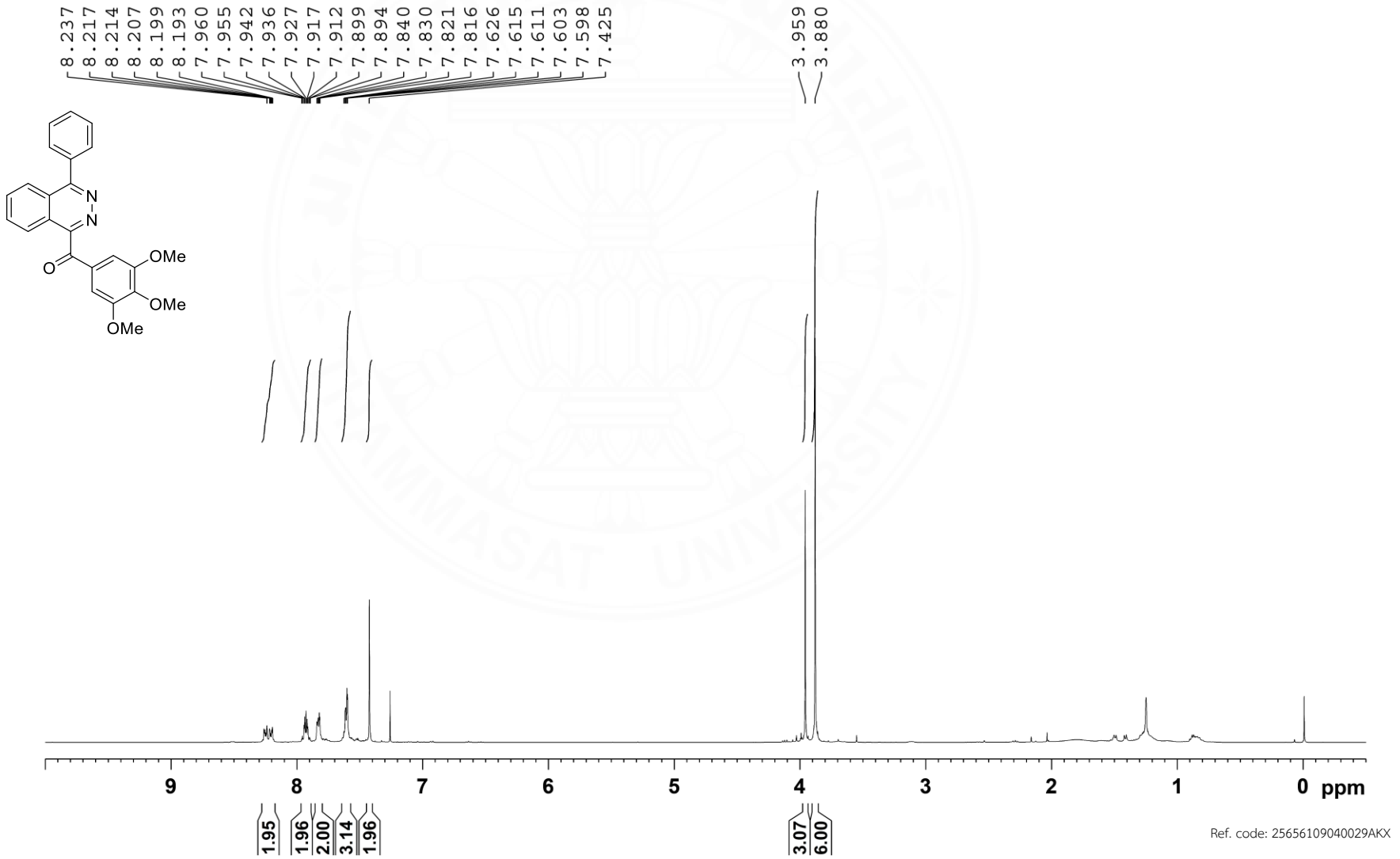
^{1}H-NMR of compound **3u** (400 MHz, $CDCl_3$)



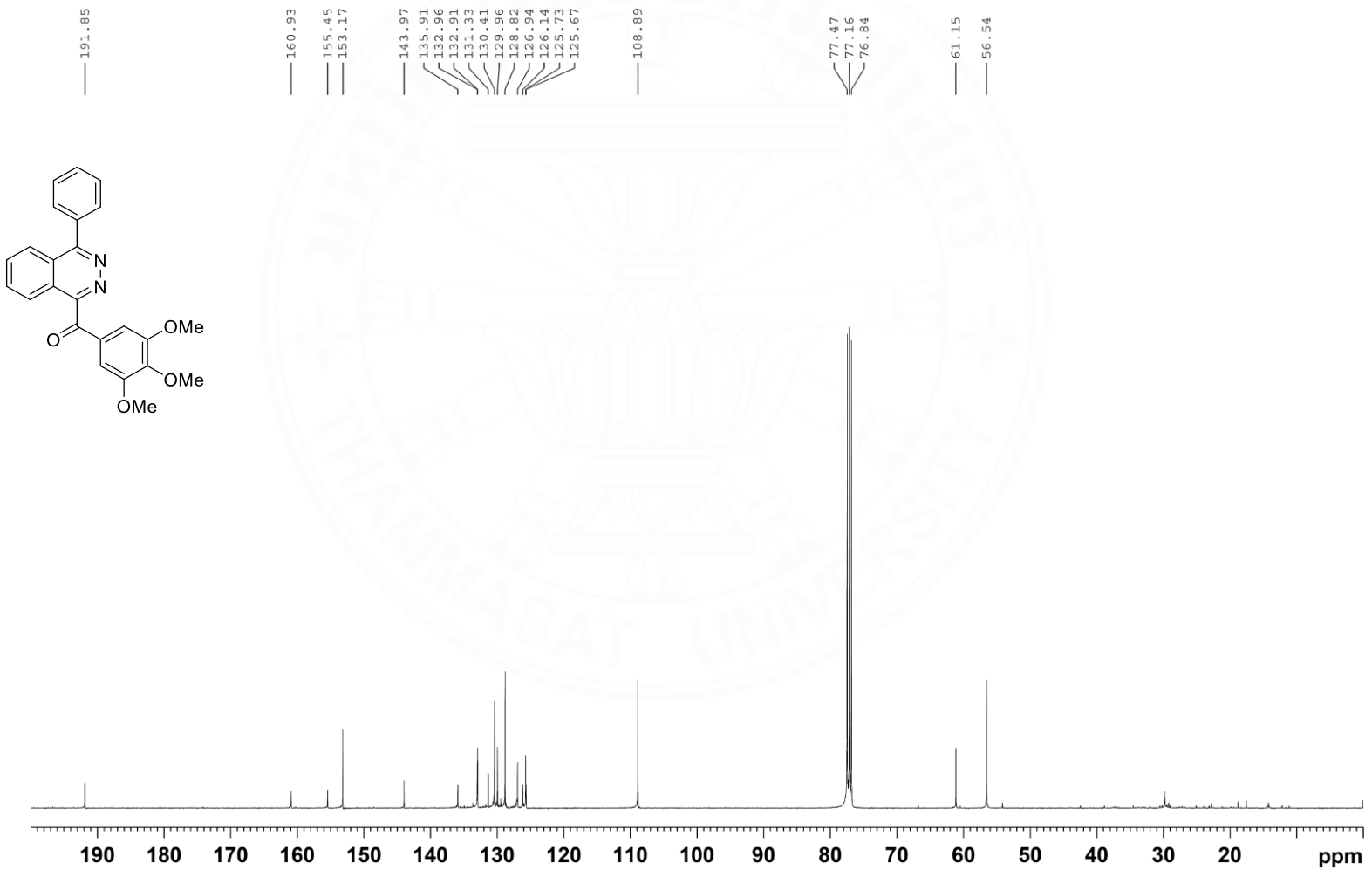
^{13}C-NMR of compound **3u** (100 MHz, $CDCl_3$)



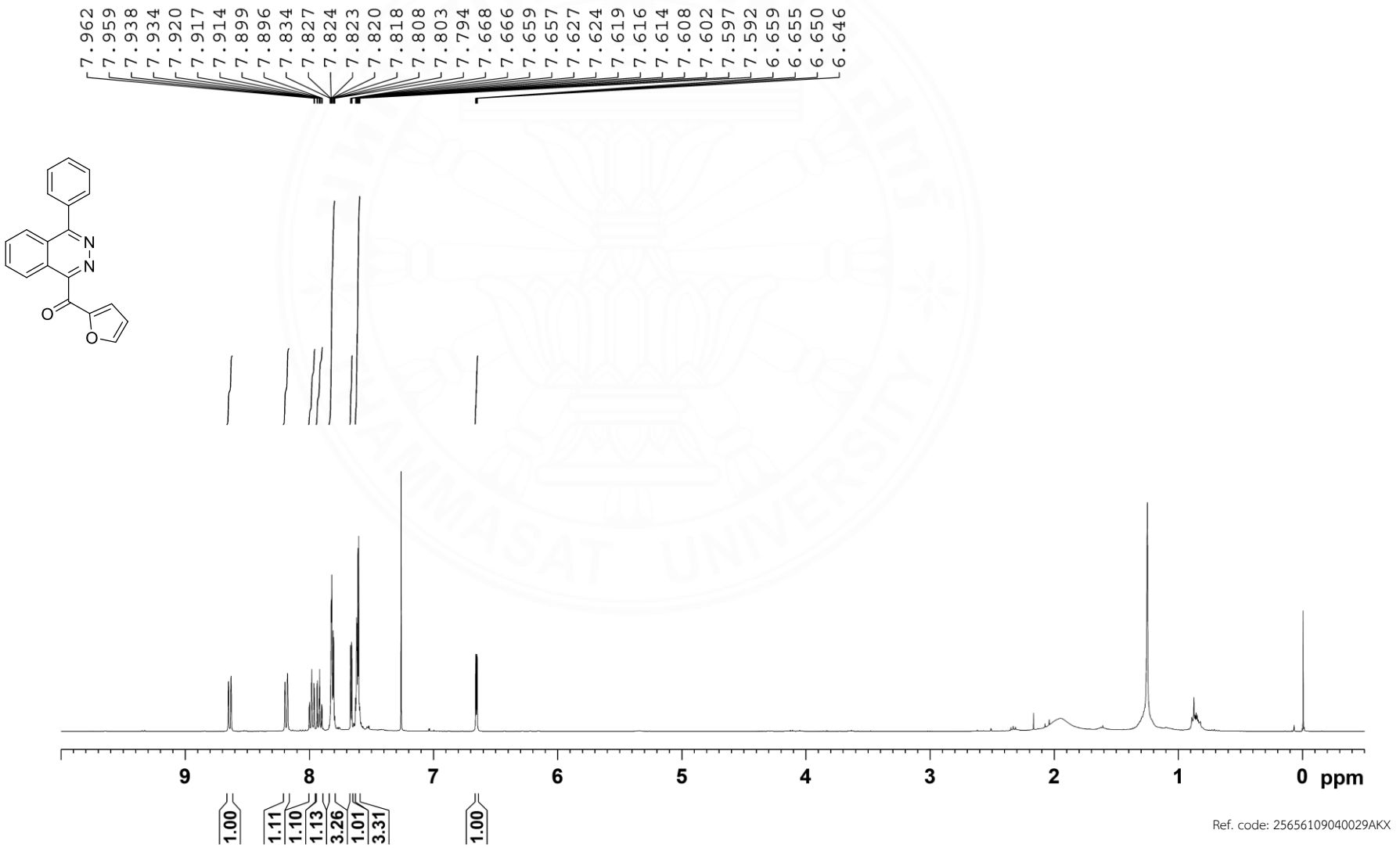
^{1}H-NMR of compound **3v** (400 MHz, $CDCl_3$)



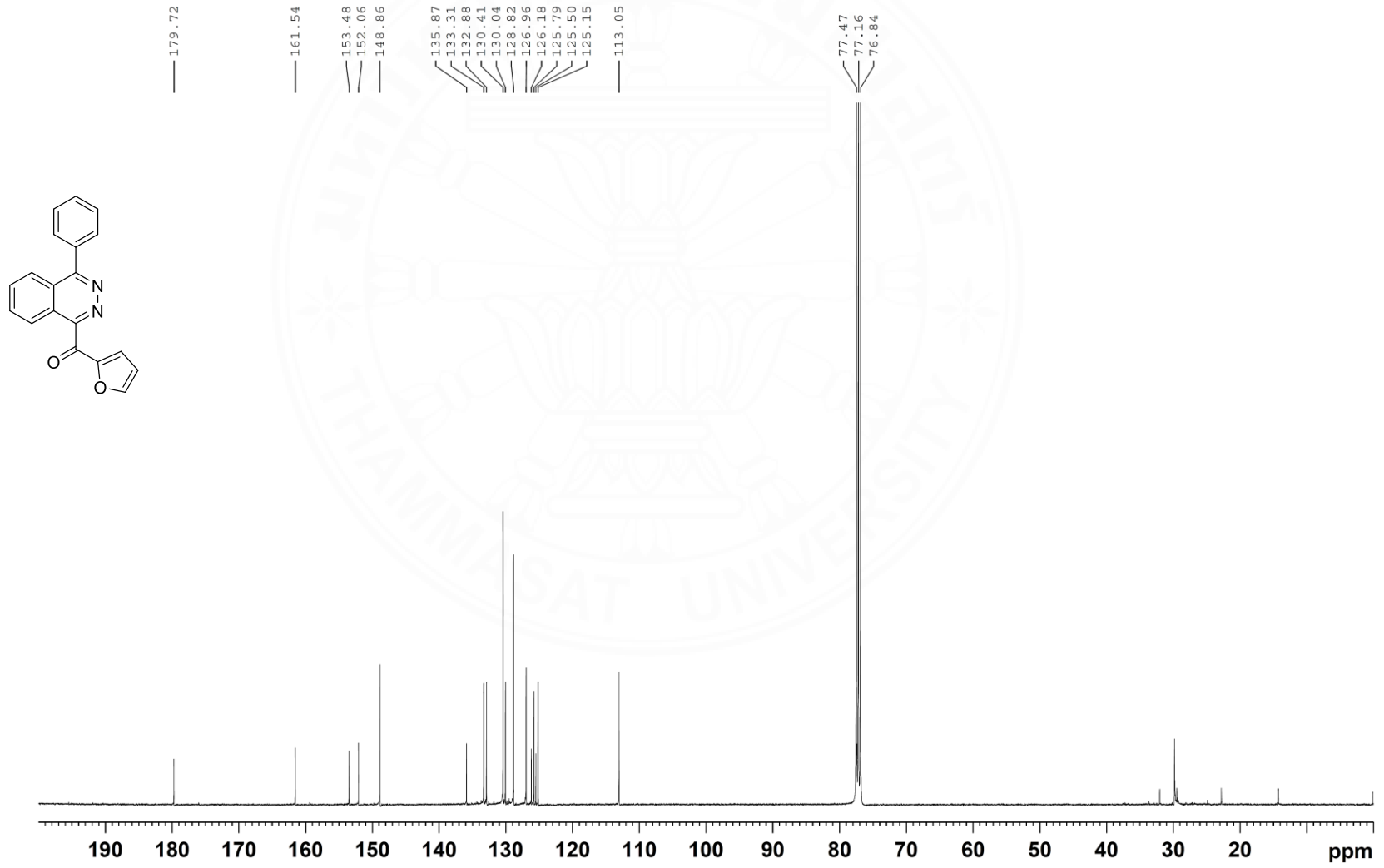
^{13}C-NMR of compound **3v** (100 MHz, $CDCl_3$)



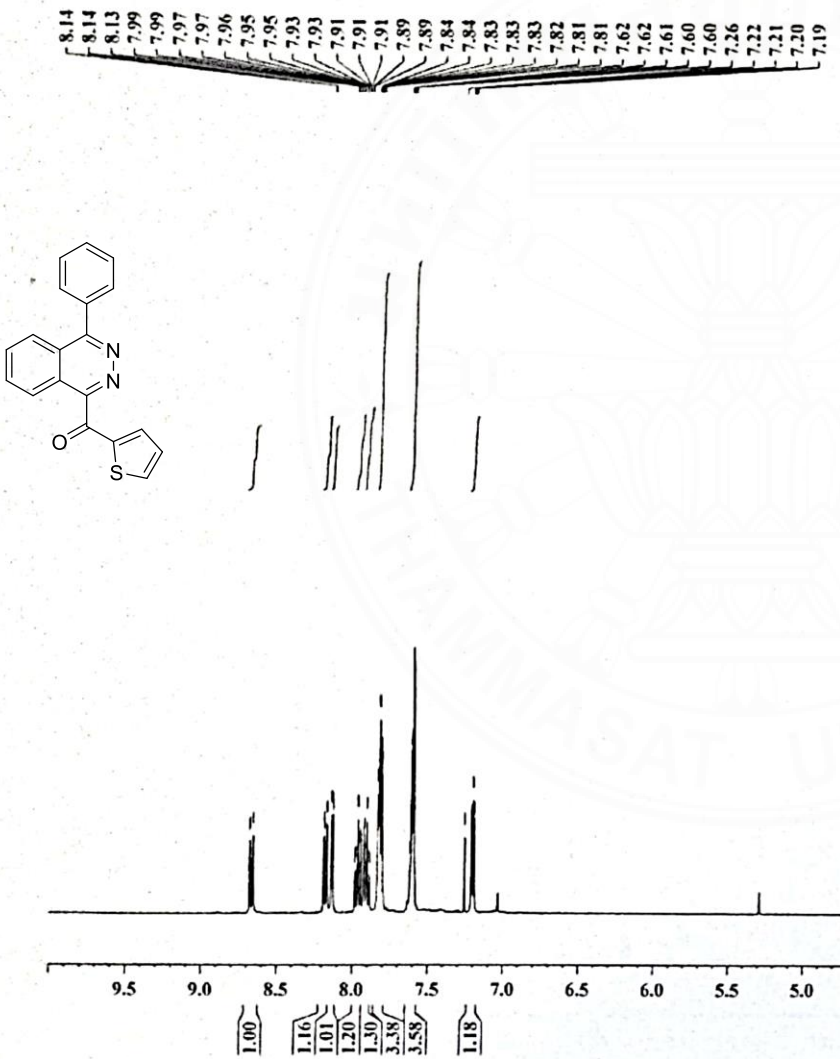
^{1}H-NMR of compound **3w** (400 MHz, $CDCl_3$)



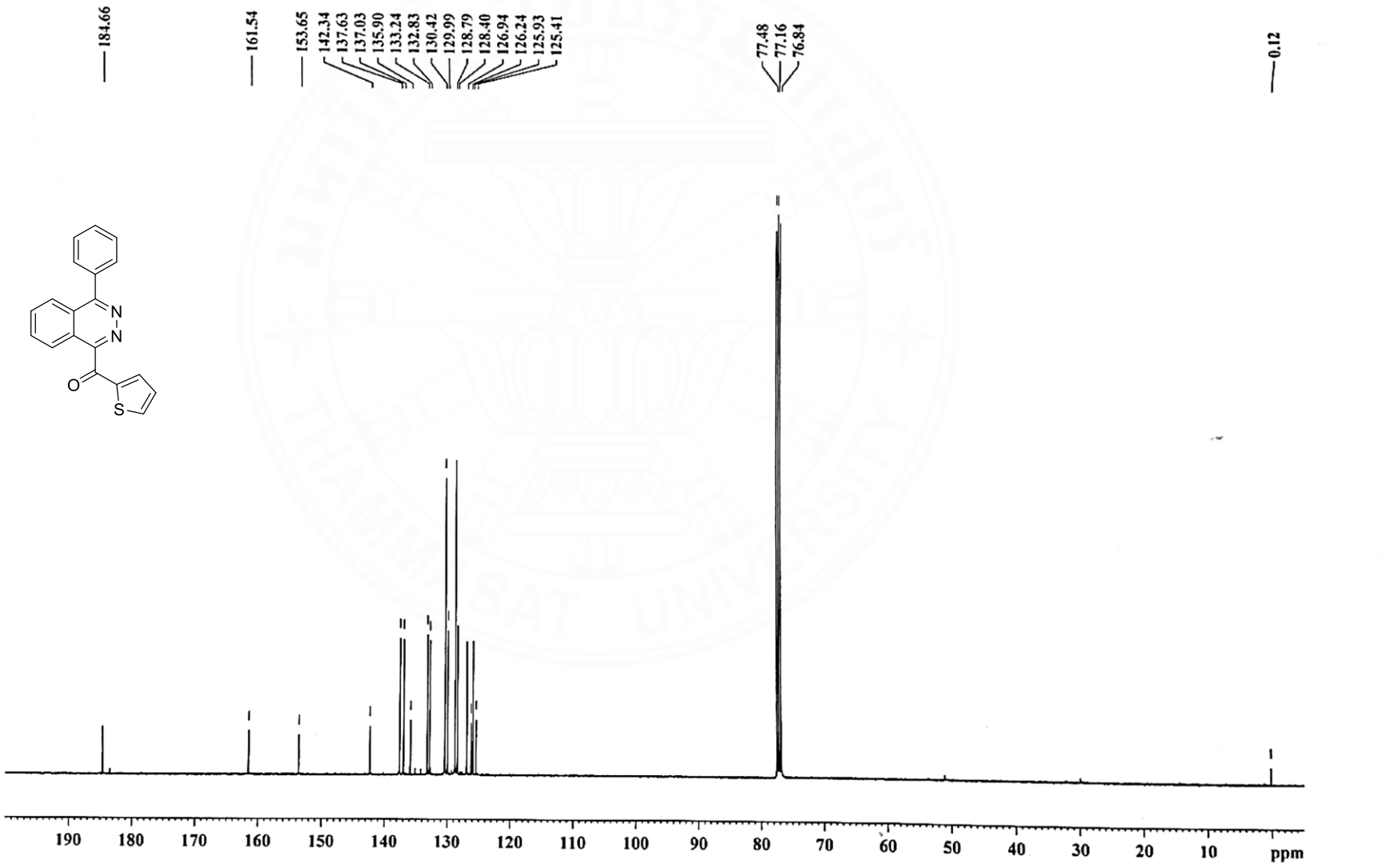
^{13}C-NMR of compound **3w** (100 MHz, $CDCl_3$)



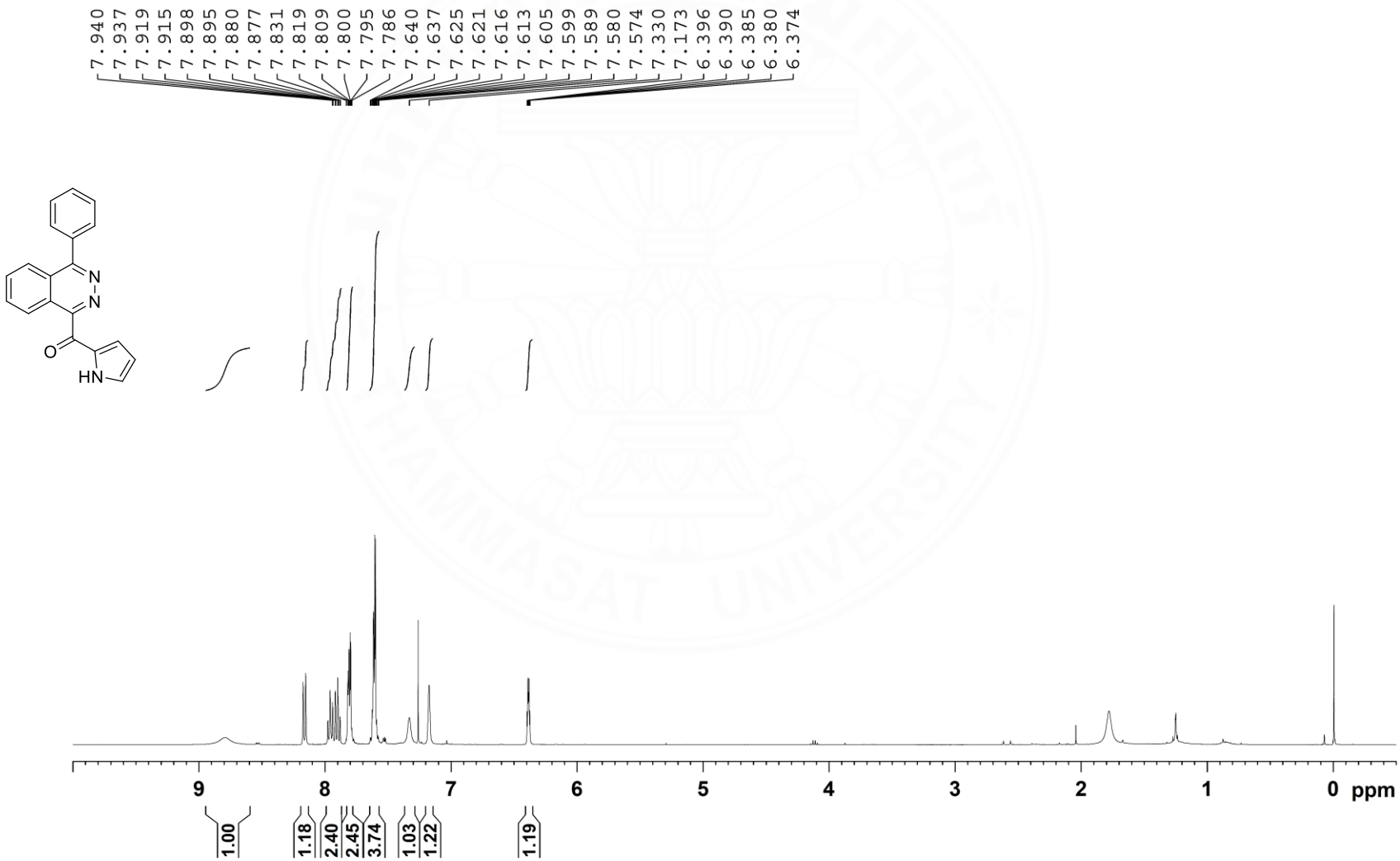
^{1}H-NMR of compound **3x** (400 MHz, $CDCl_3$)



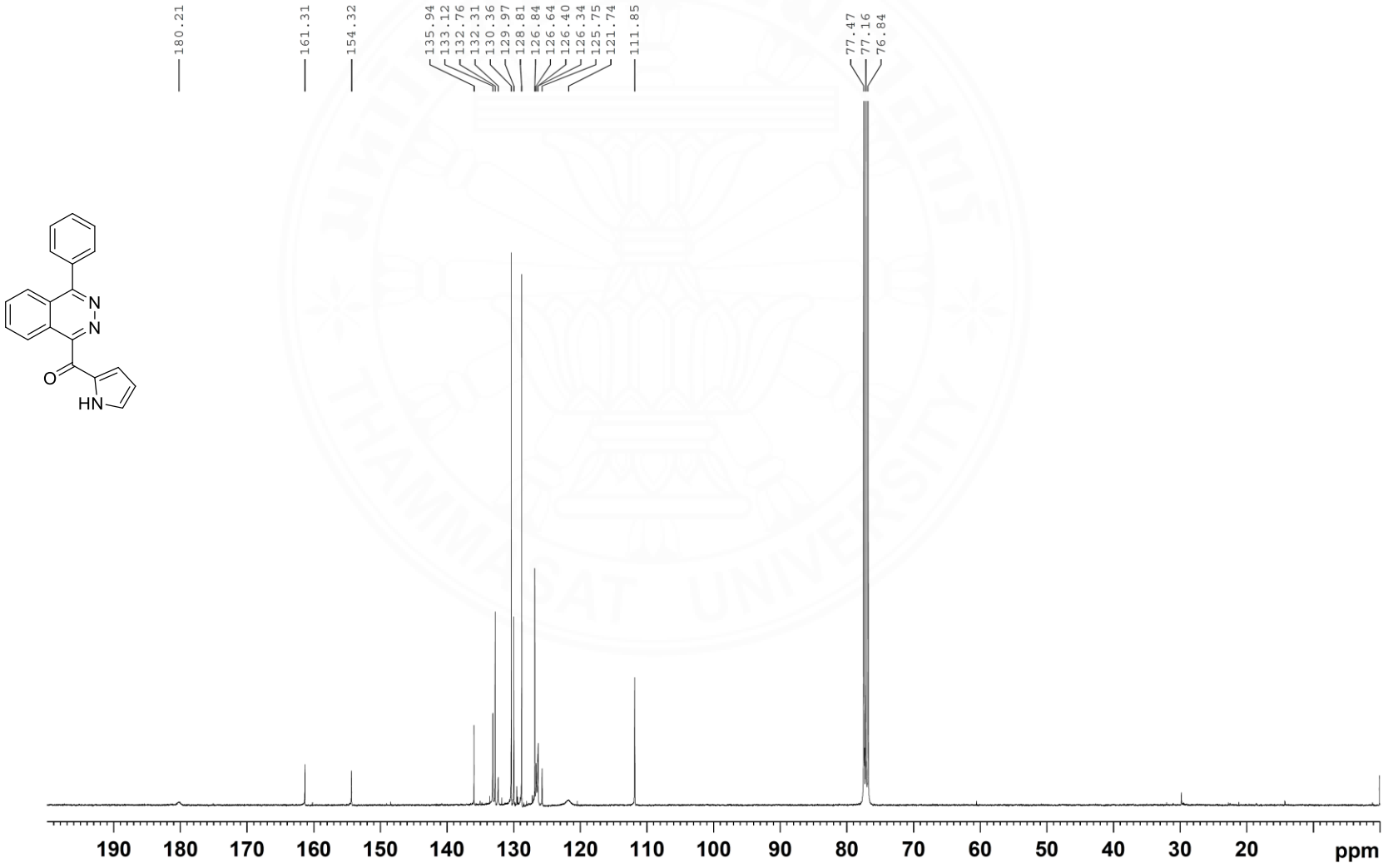
^{13}C-NMR of compound **3x** (100 MHz, $CDCl_3$)



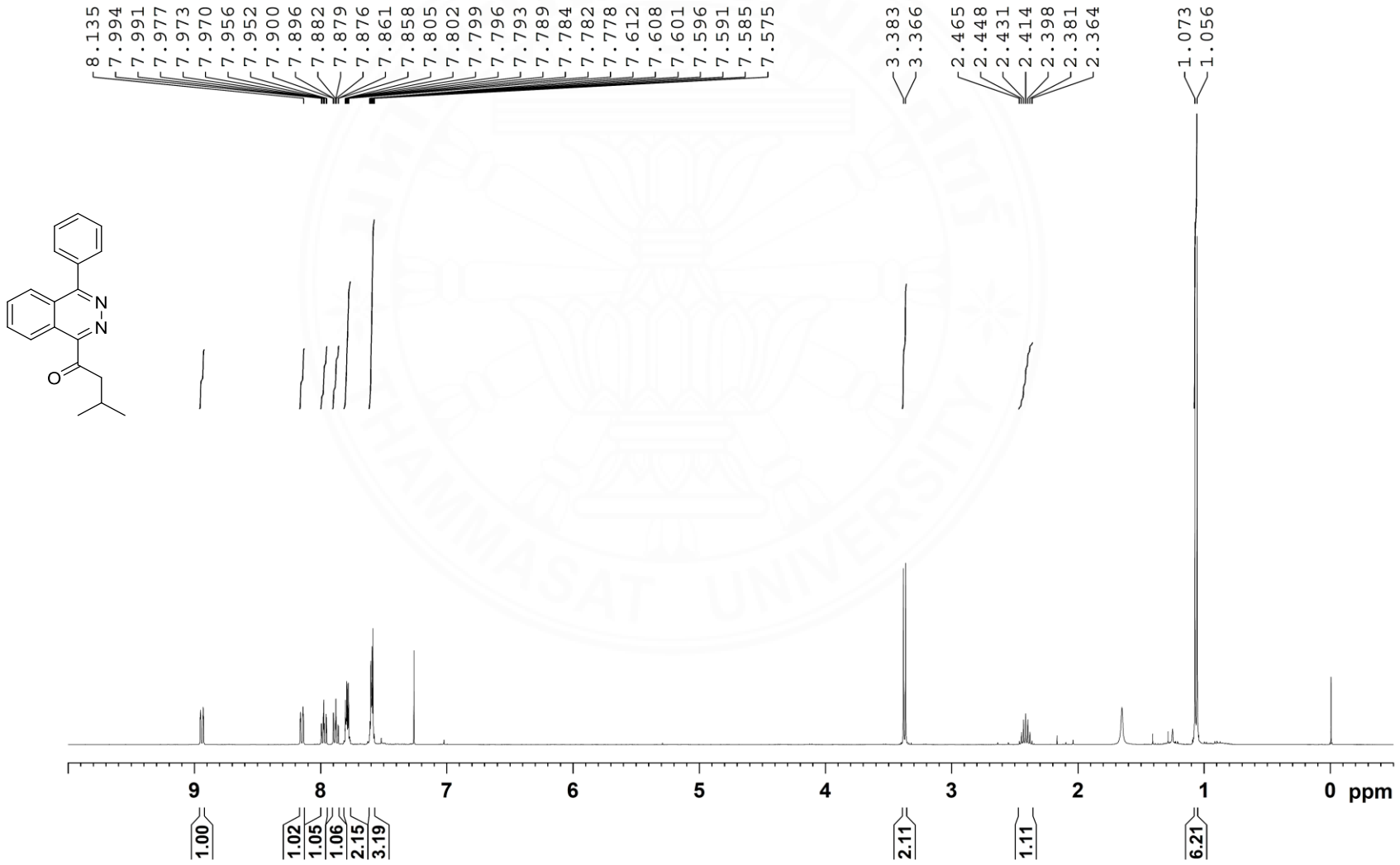
^{1}H-NMR of compound **3y** (400 MHz, $CDCl_3$)



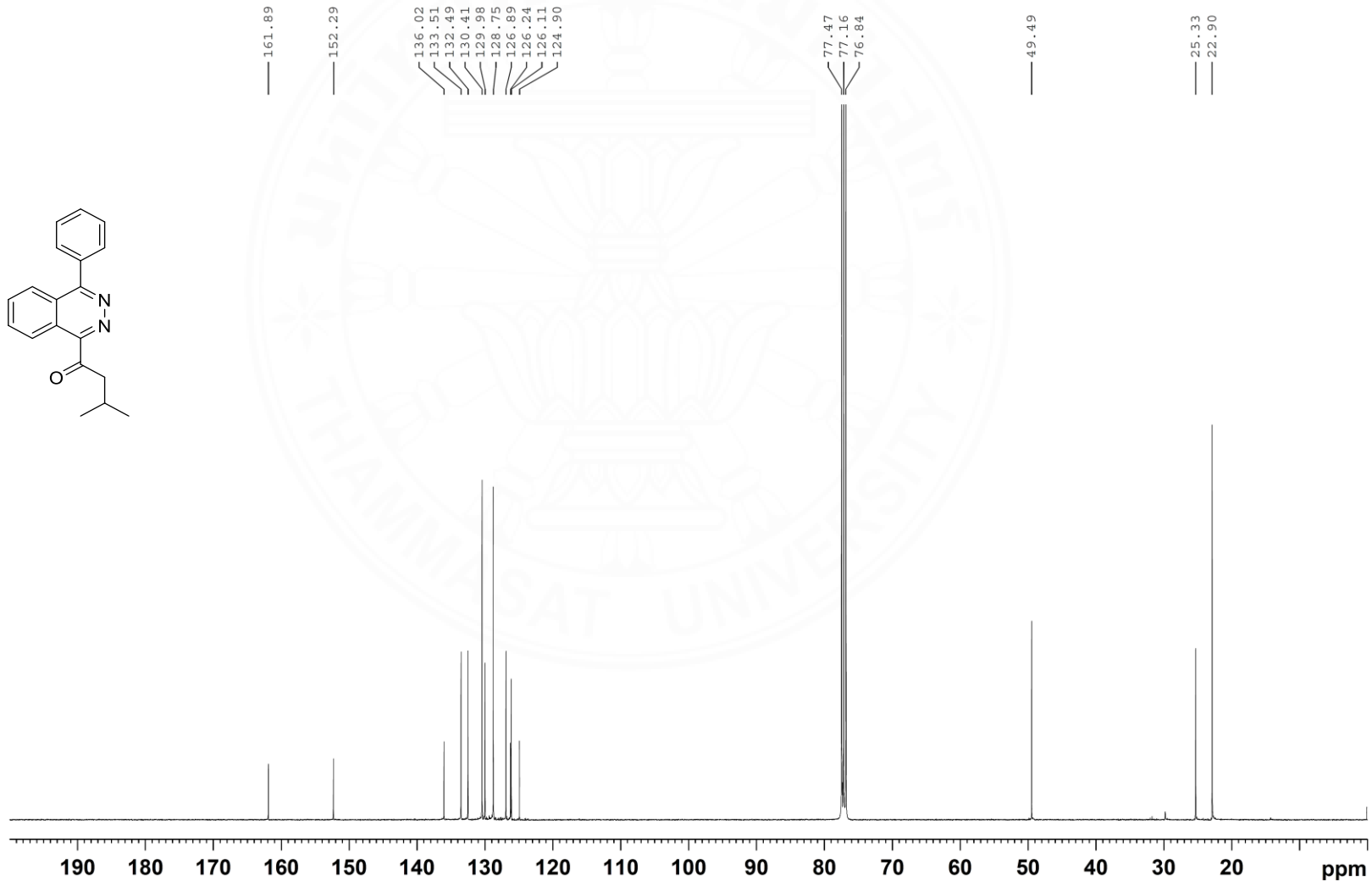
^{13}C-NMR of compound **3y** (100 MHz, $CDCl_3$)



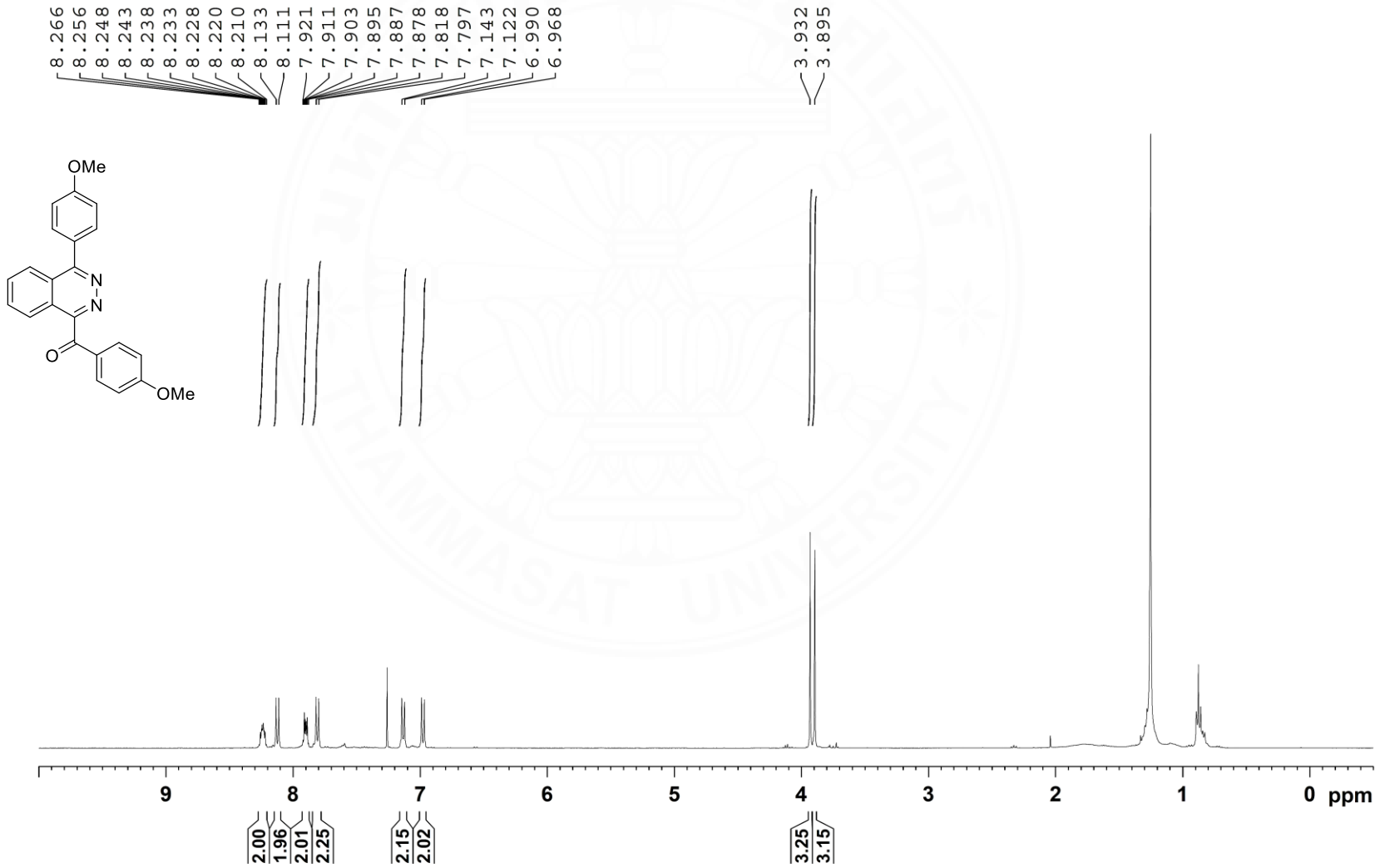
^{1}H-NMR of compound **3ab** (400 MHz, $CDCl_3$)



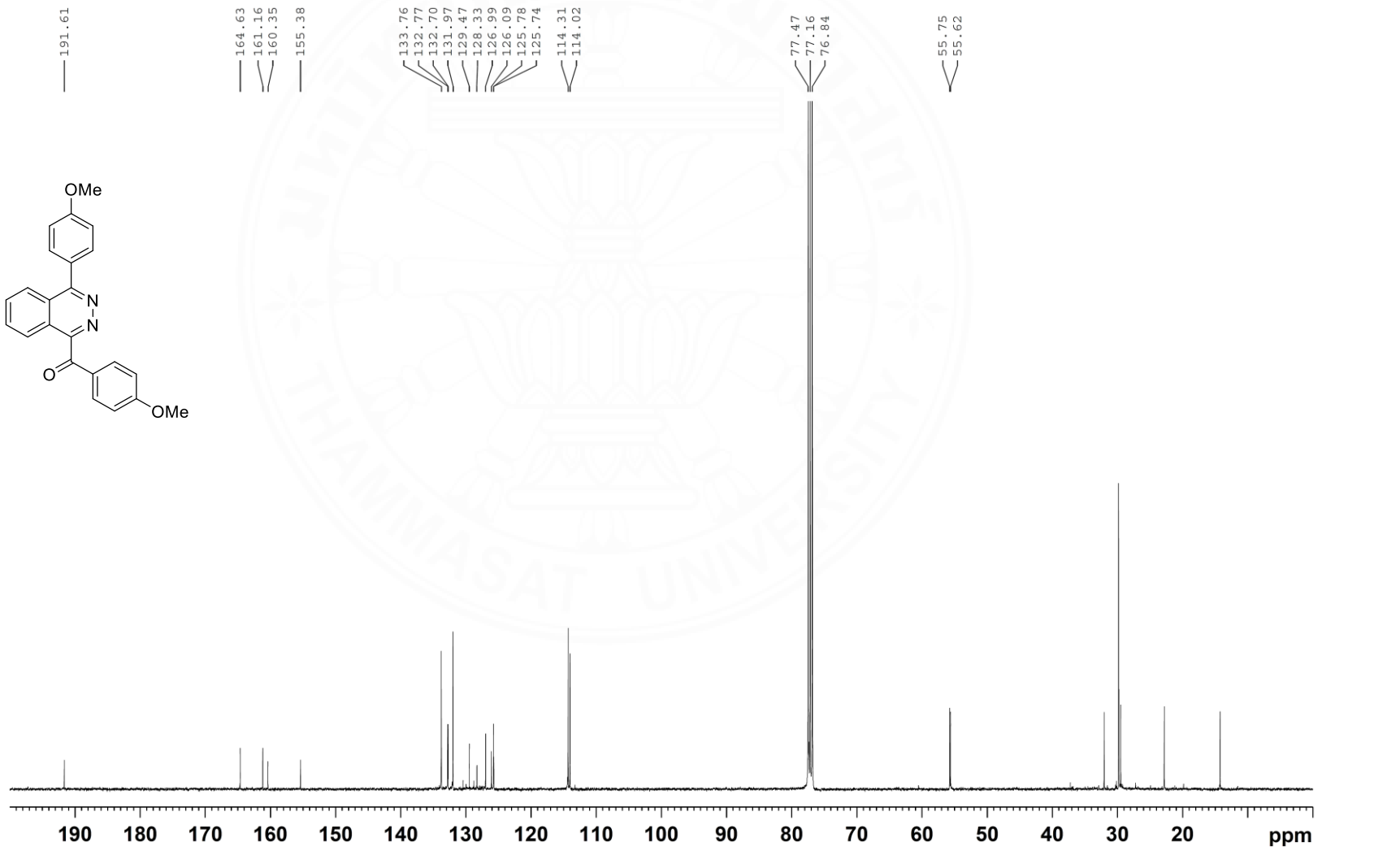
^{13}C-NMR of compound **3ab** (100 MHz, $CDCl_3$)



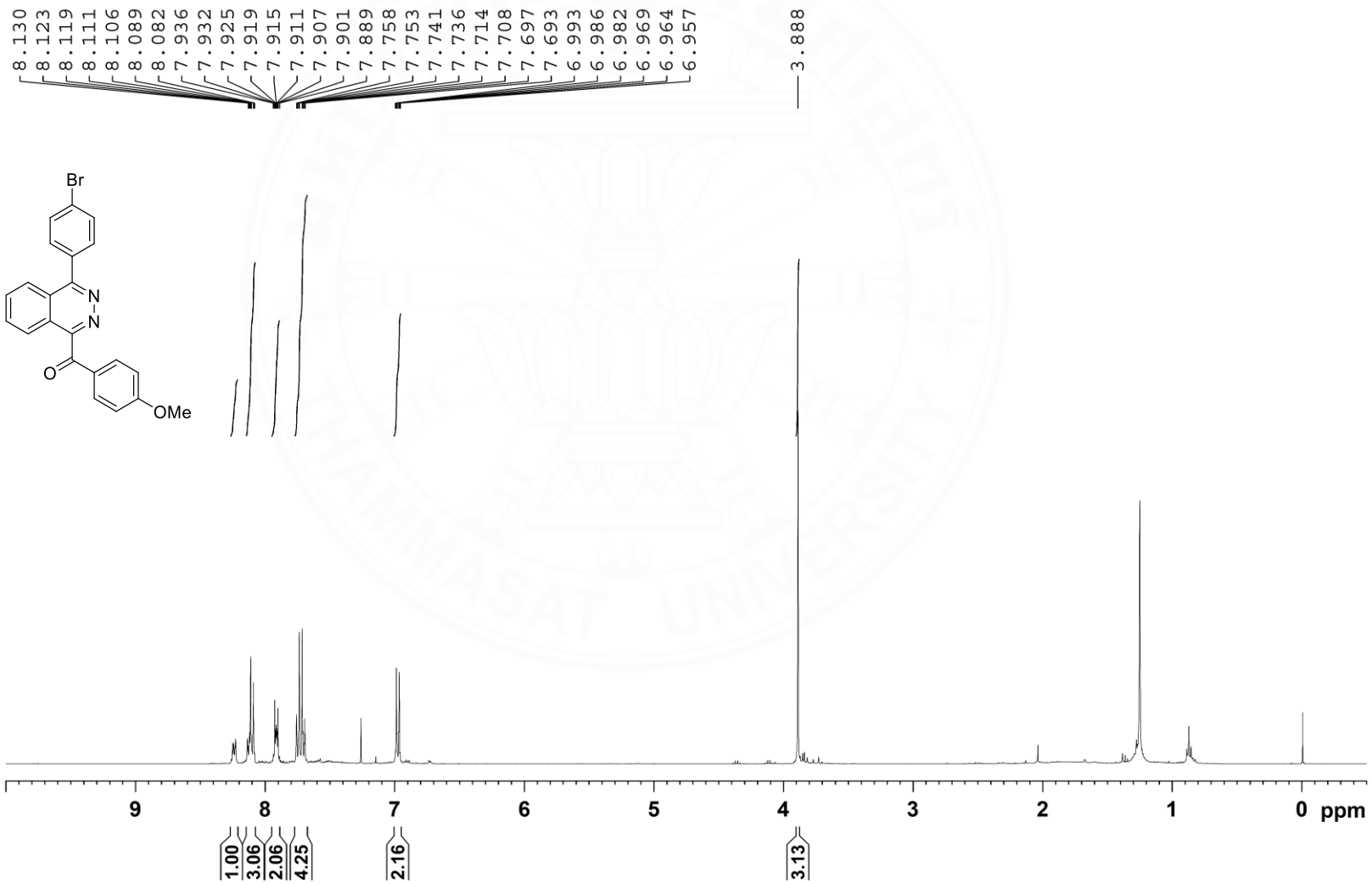
^{1}H-NMR of compound **5aa** (400 MHz, $CDCl_3$)



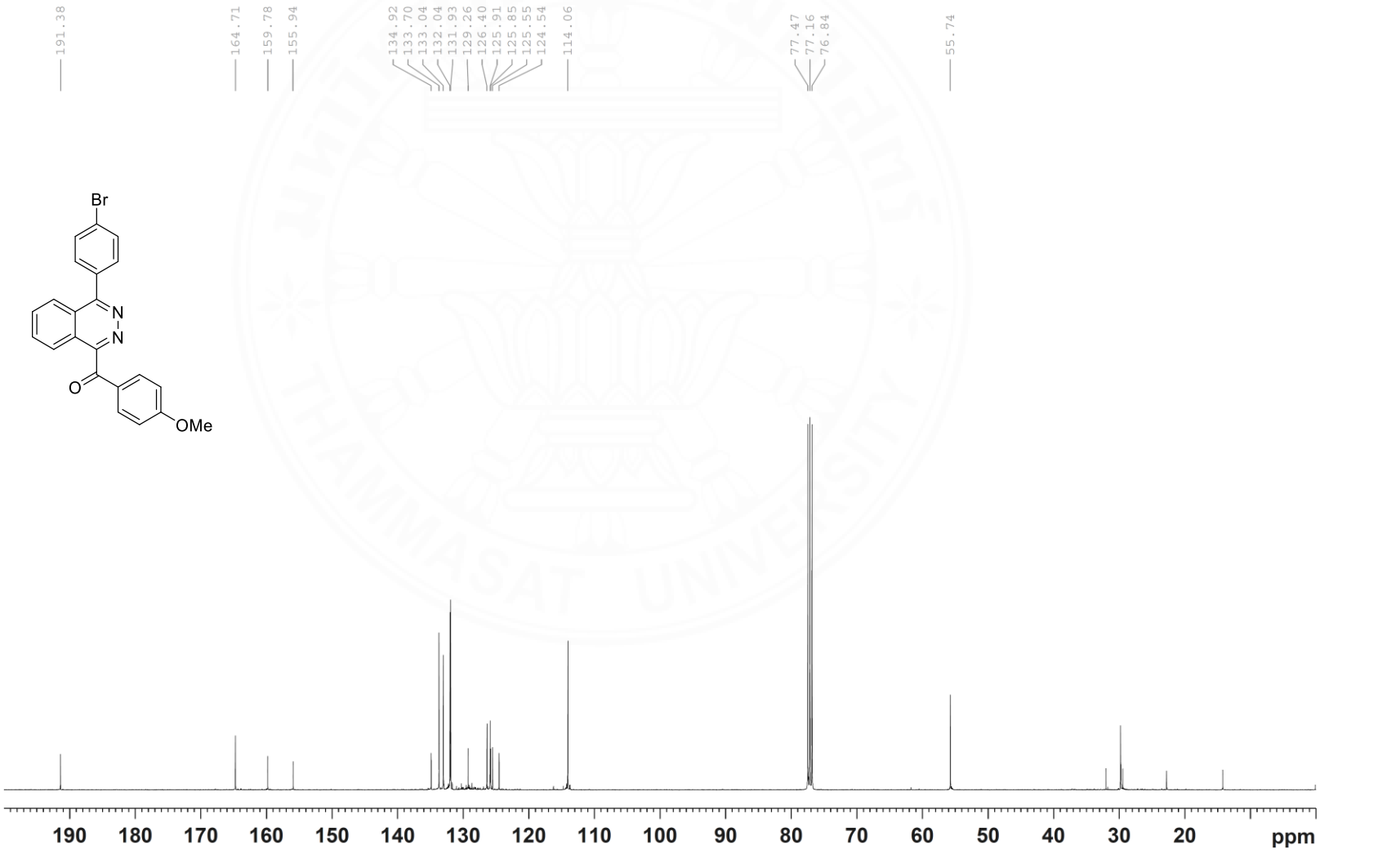
^{13}C-NMR of compound **5aa** (100 MHz, $CDCl_3$)



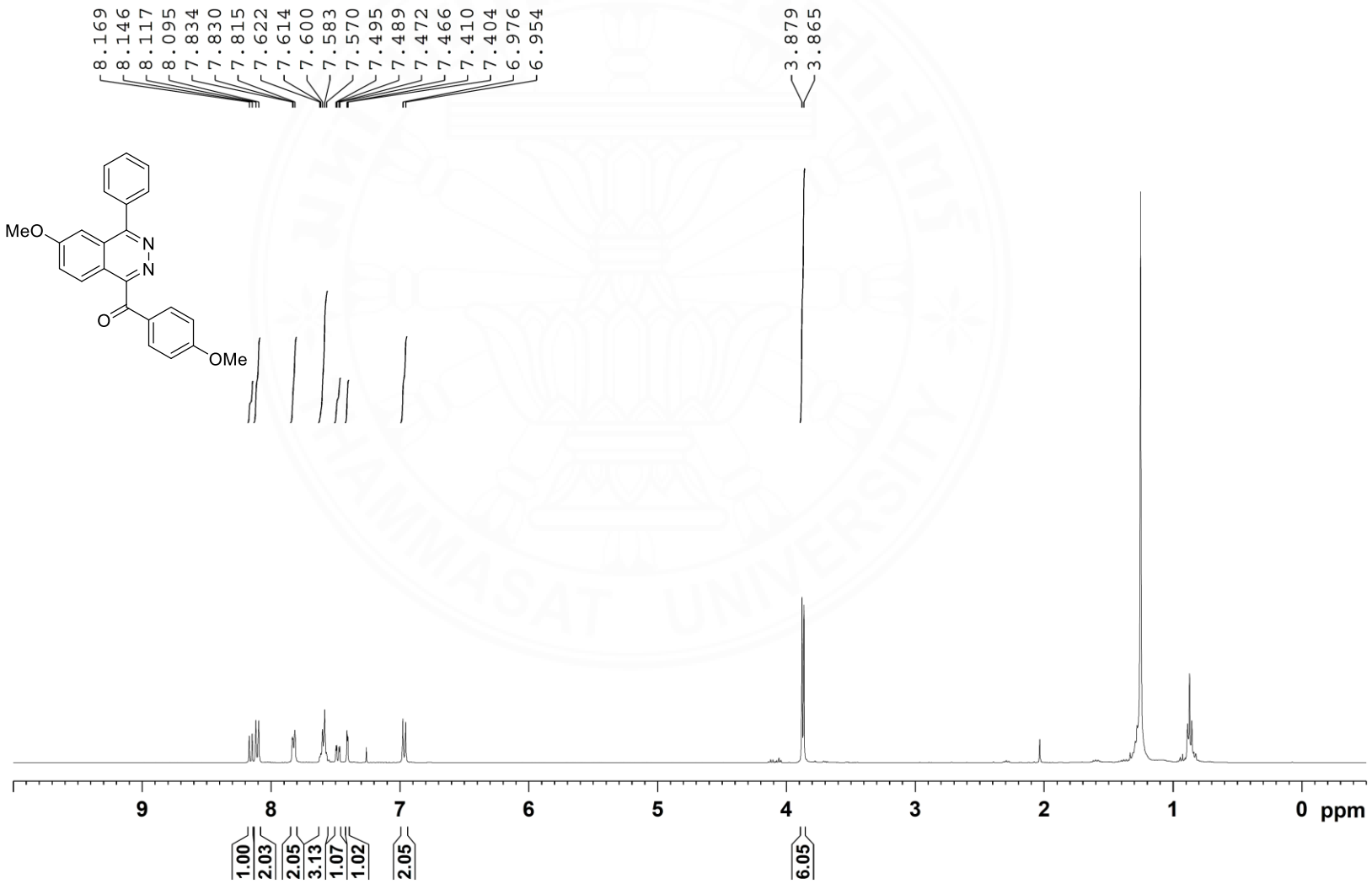
^{1}H-NMR of compound **5ba** (400 MHz, $CDCl_3$)



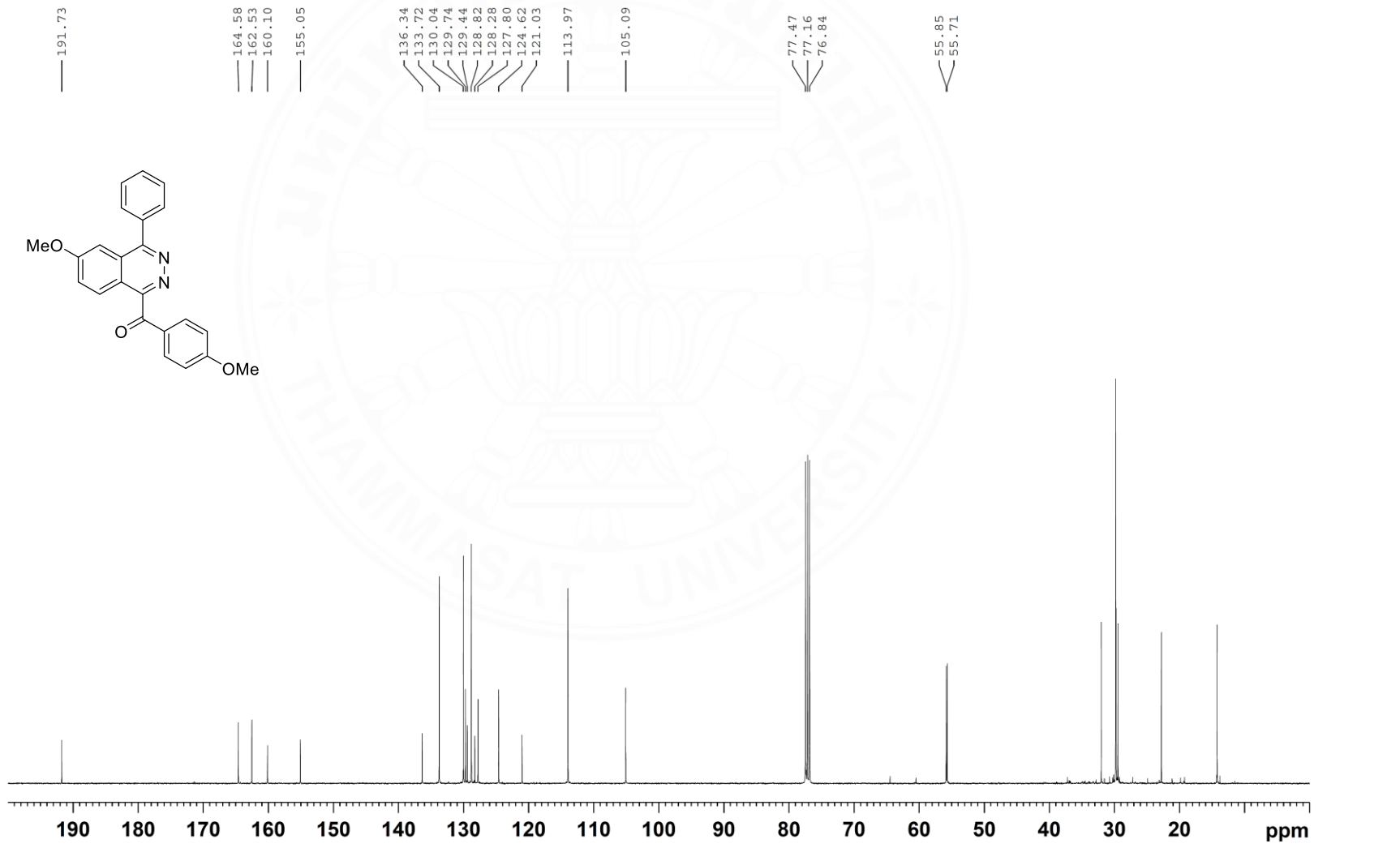
^{13}C-NMR of compound **5ba** (100 MHz, $CDCl_3$)



^{1}H-NMR of compound **5da** (400 MHz, $CDCl_3$)

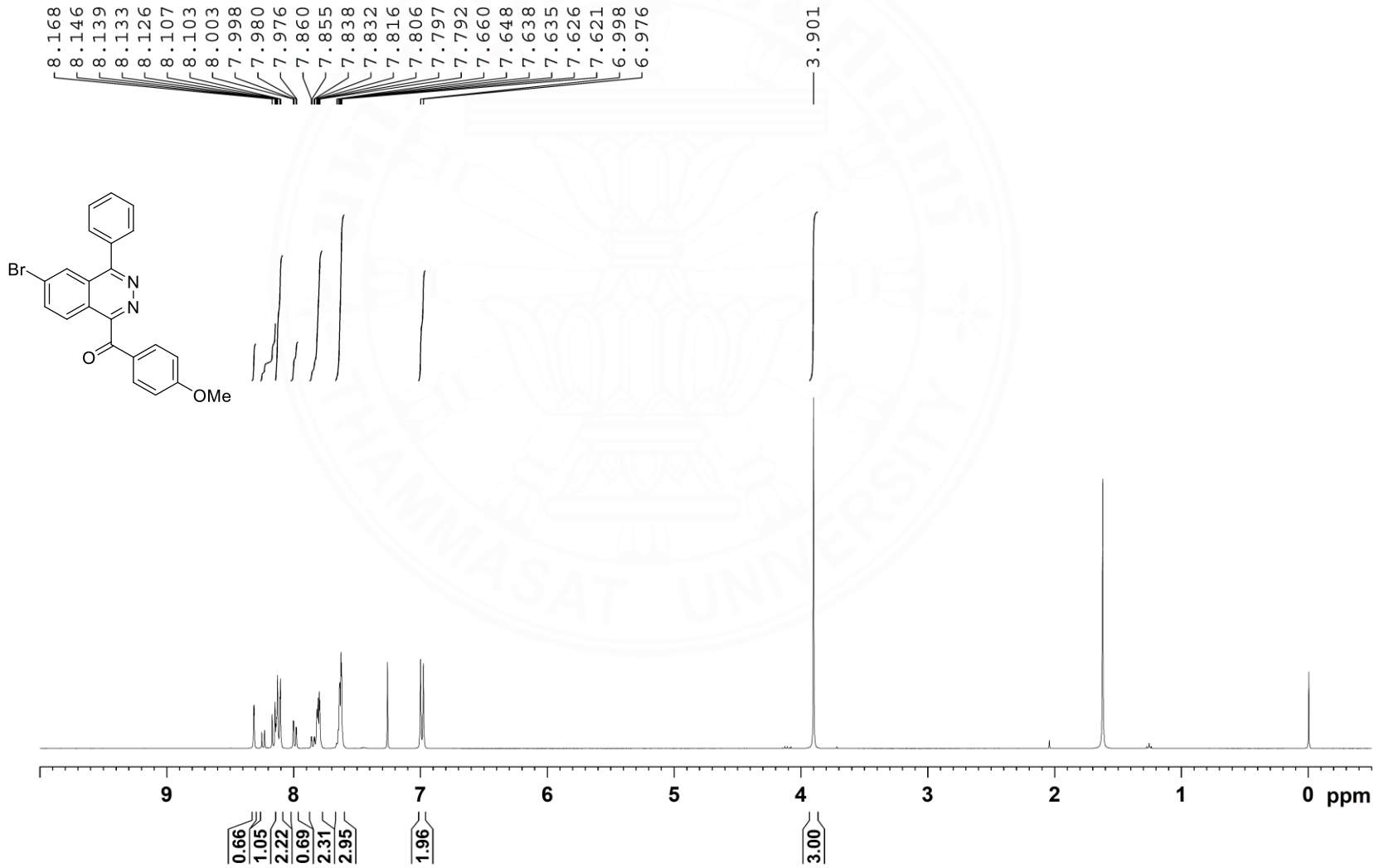


^{13}C-NMR of compound **5da** (100 MHz, $CDCl_3$)

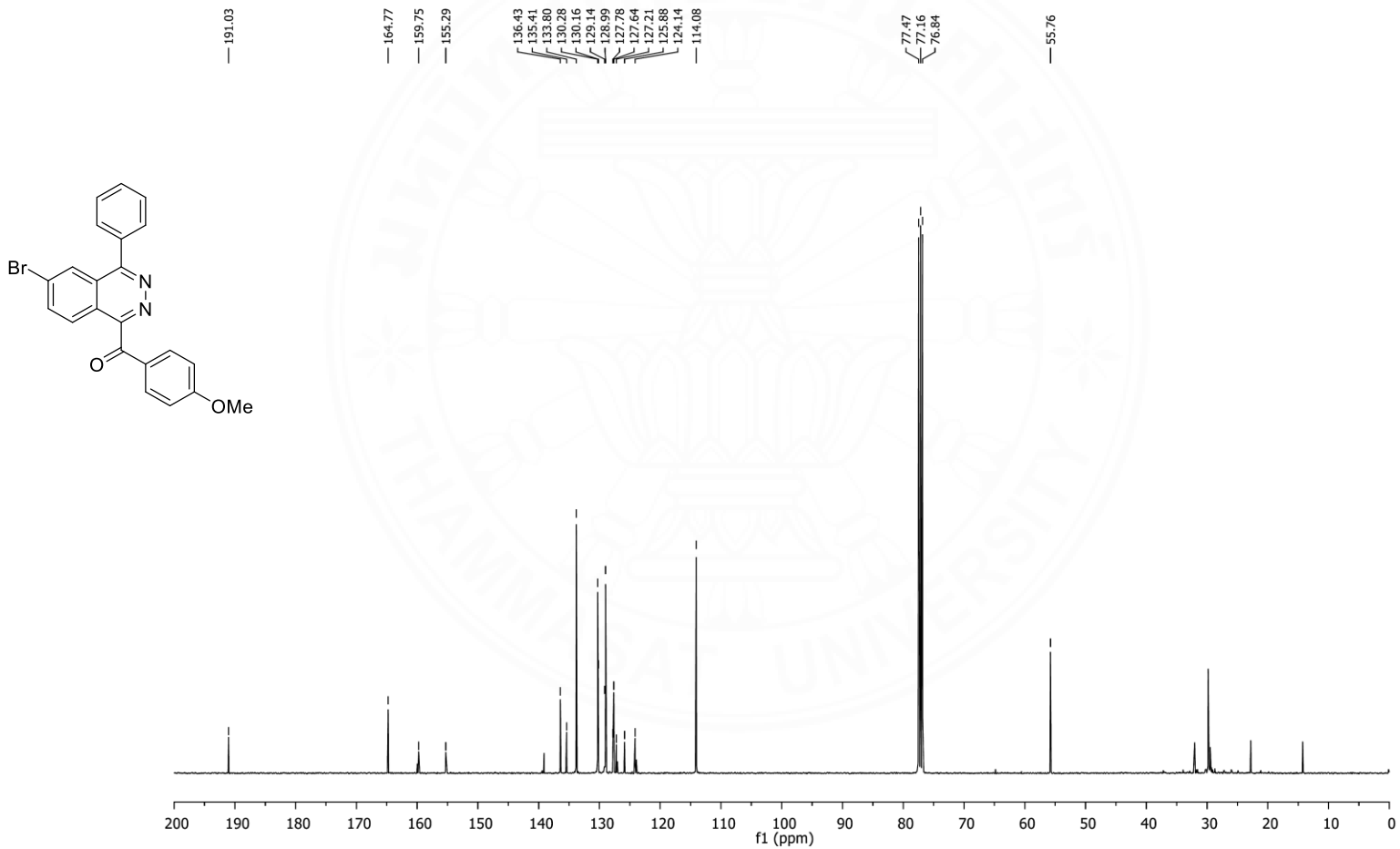


Ref. code: 25656109040029AKX

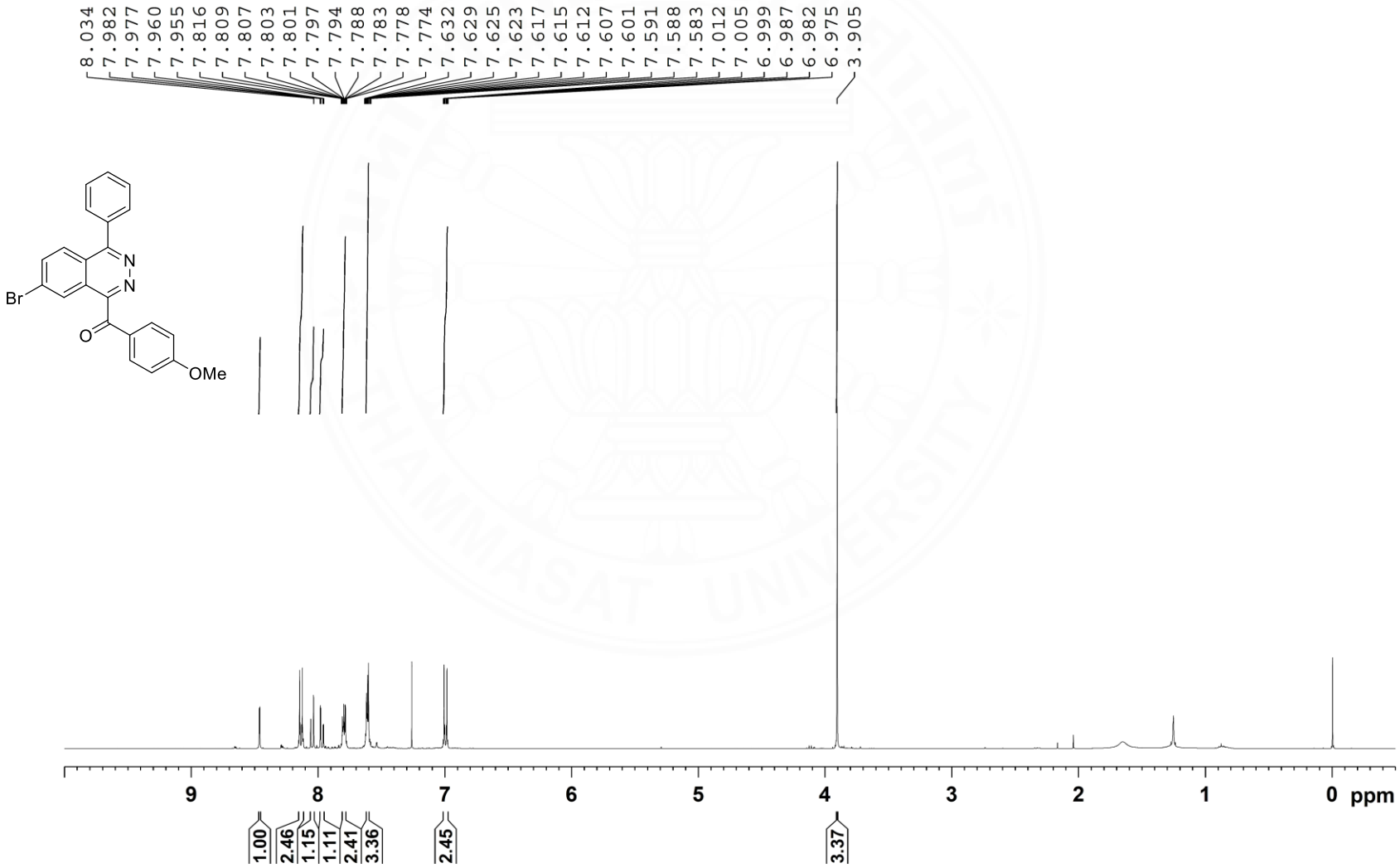
^{1}H-NMR of compound **5ea** (400 MHz, $CDCl_3$)



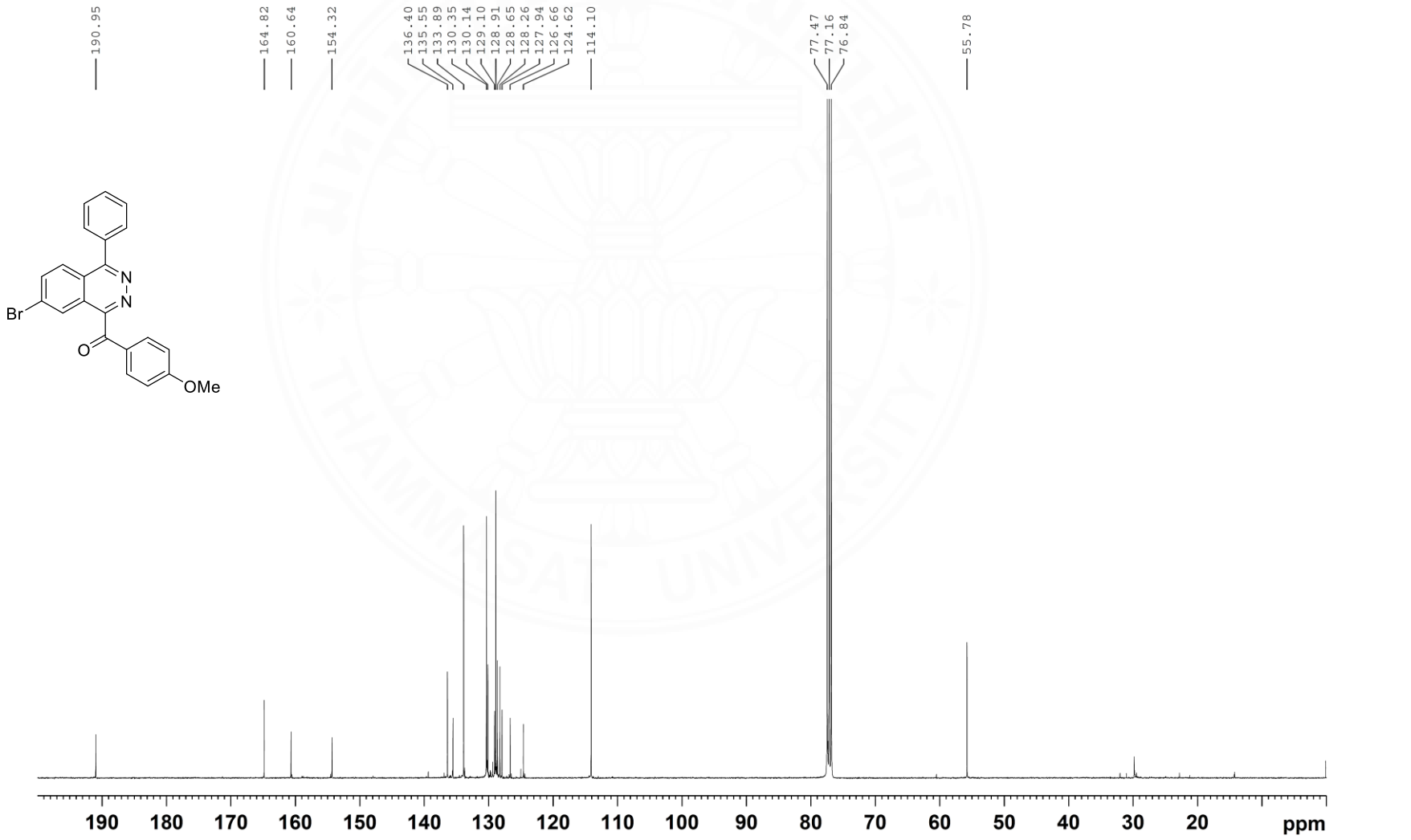
^{13}C-NMR of compound **5ea** (100 MHz, $CDCl_3$)



^{1}H-NMR of compound **5fa** (400 MHz, $CDCl_3$)

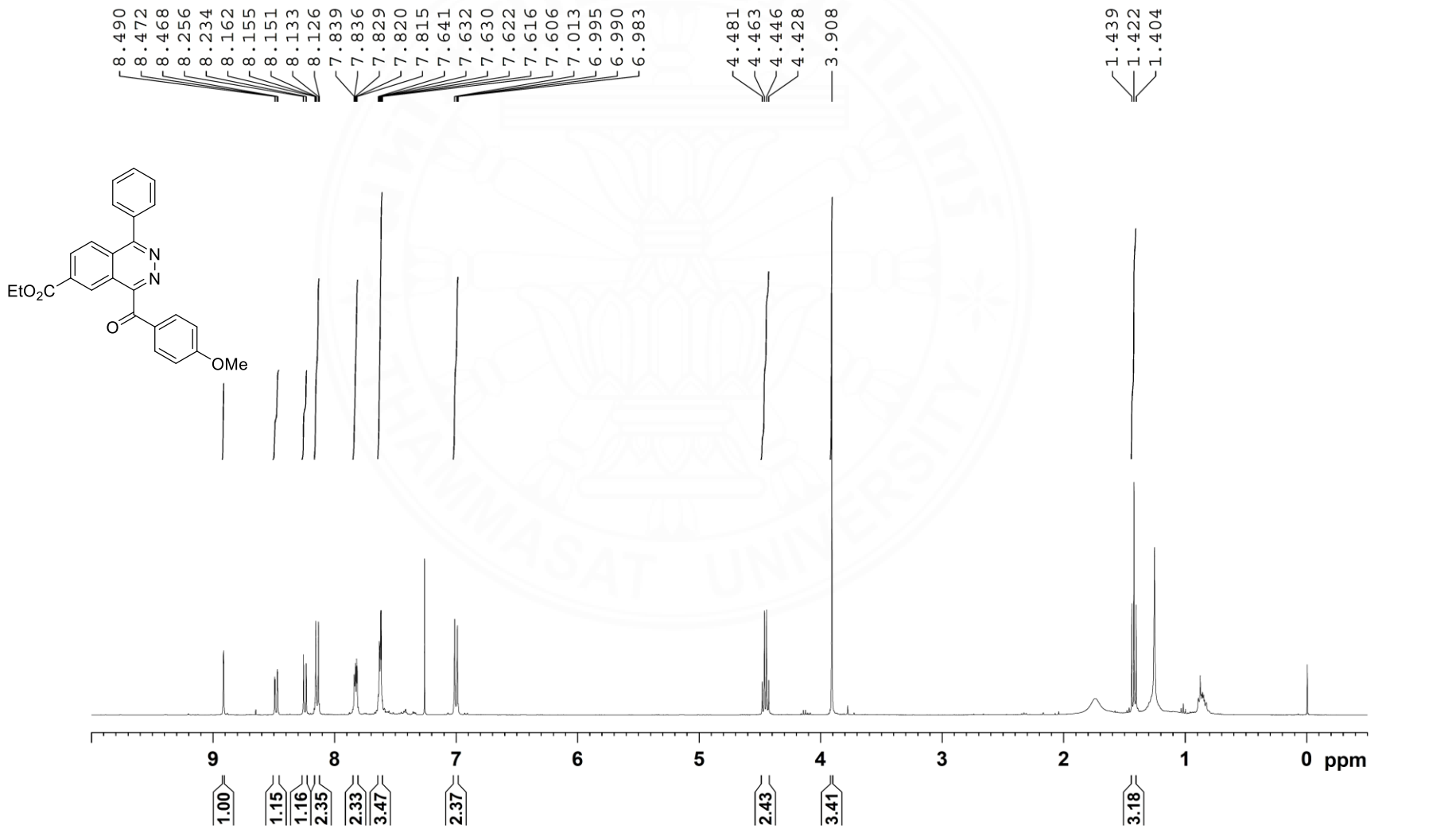


^{13}C-NMR of compound **5fa** (100 MHz, $CDCl_3$)

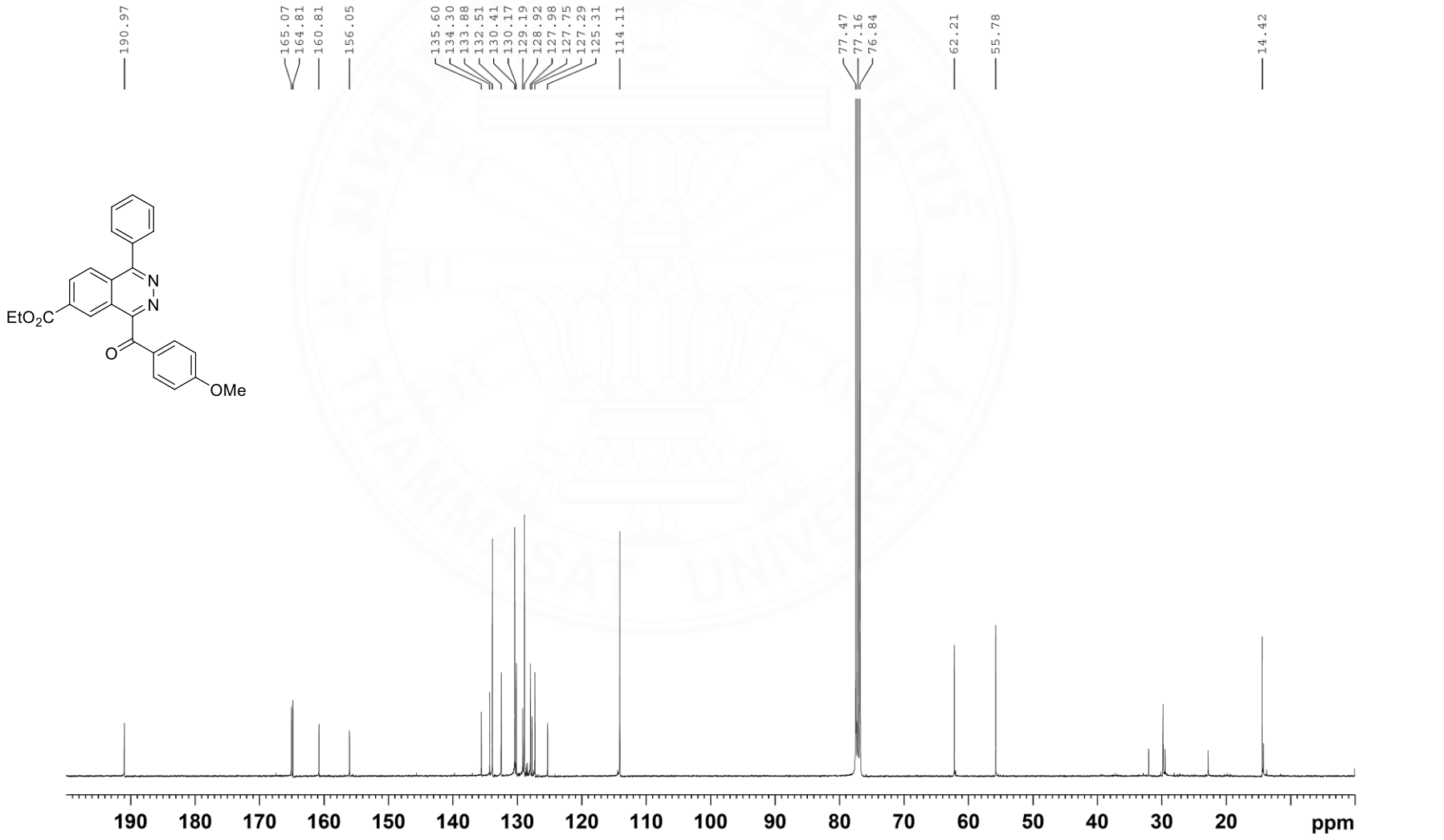


Ref. code: 25656109040029AKX

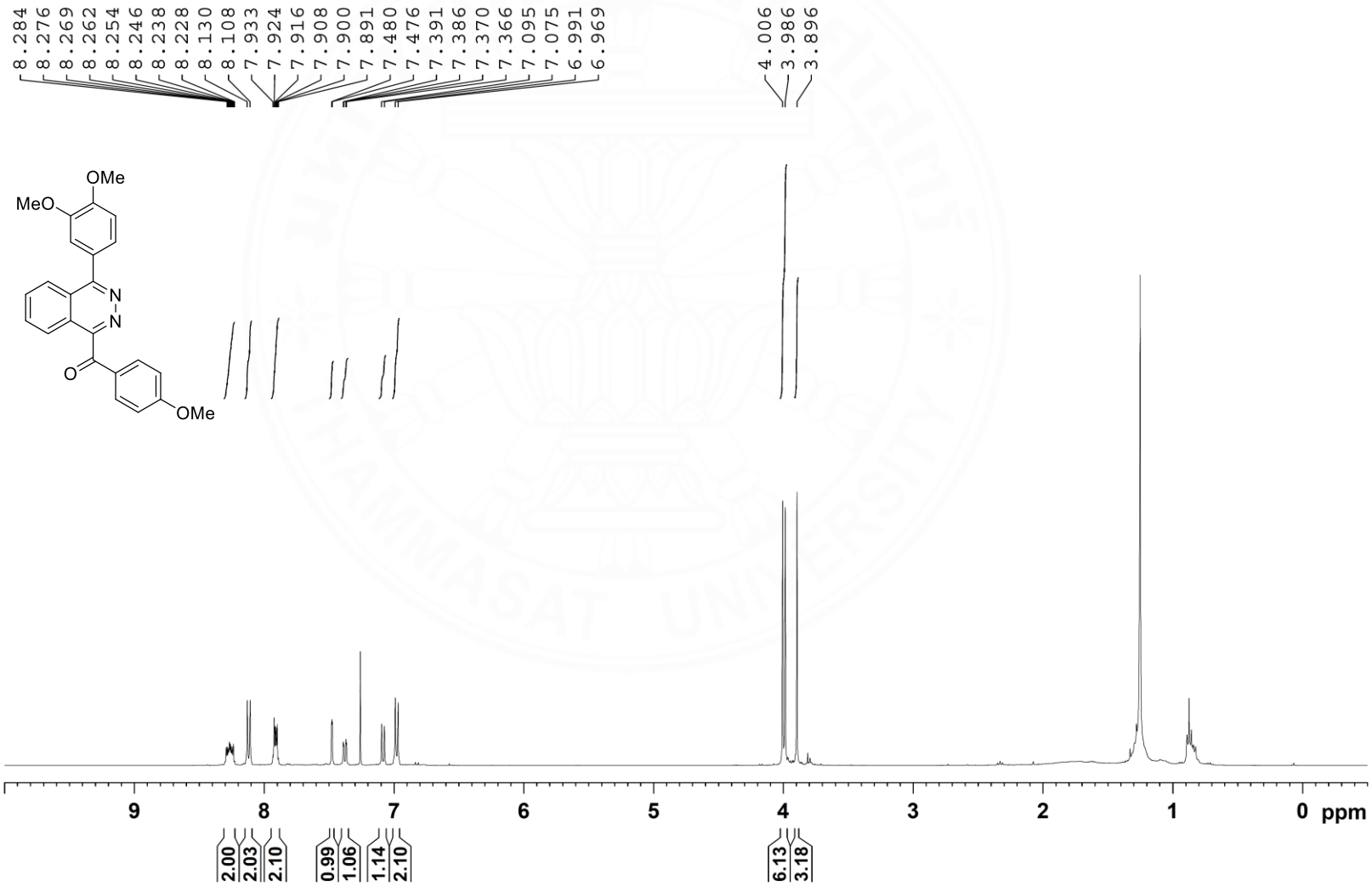
^{1}H-NMR of compound **5ga** (400 MHz, $CDCl_3$)



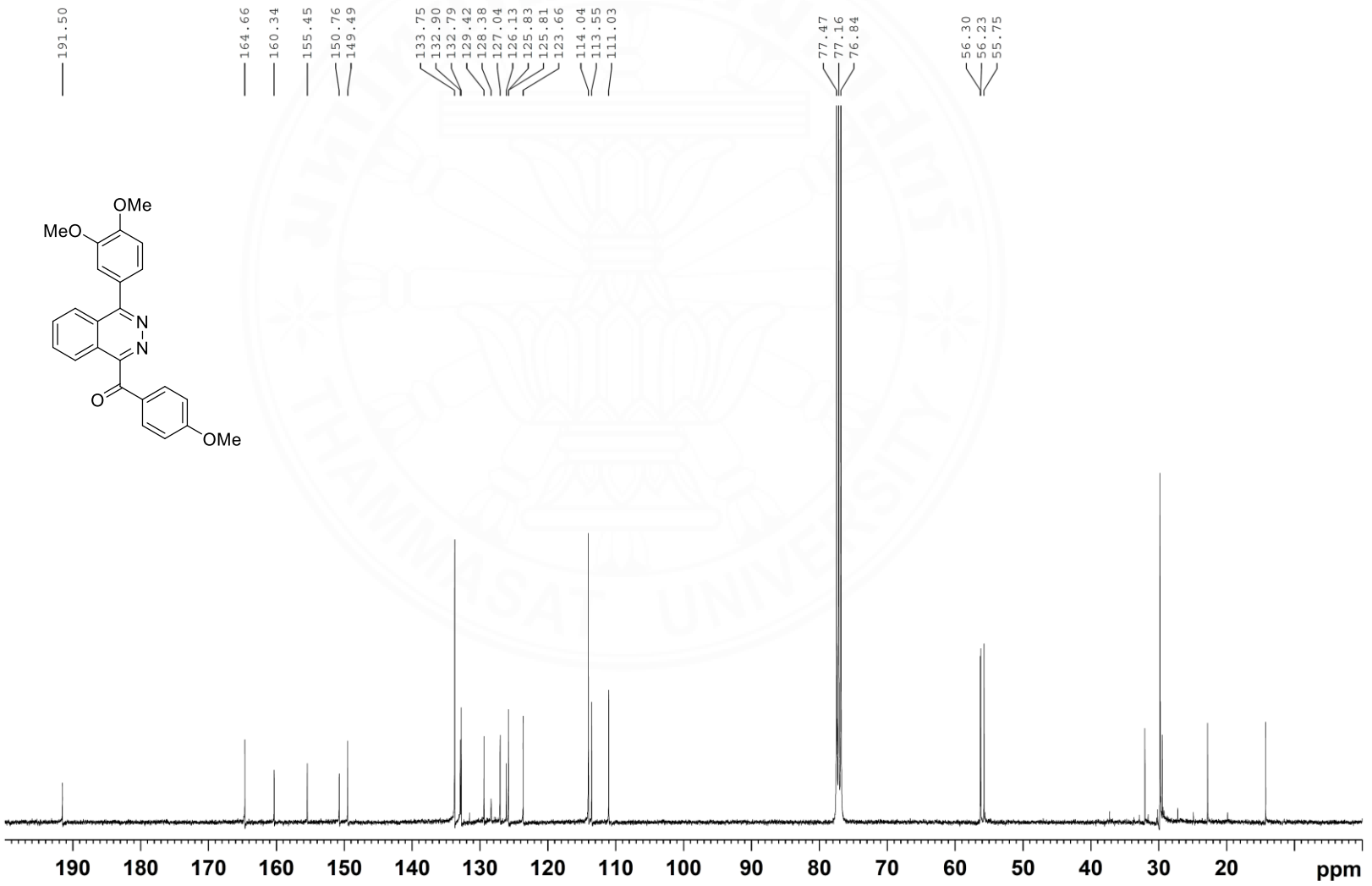
^{13}C-NMR of compound **5ga** (100 MHz, $CDCl_3$)



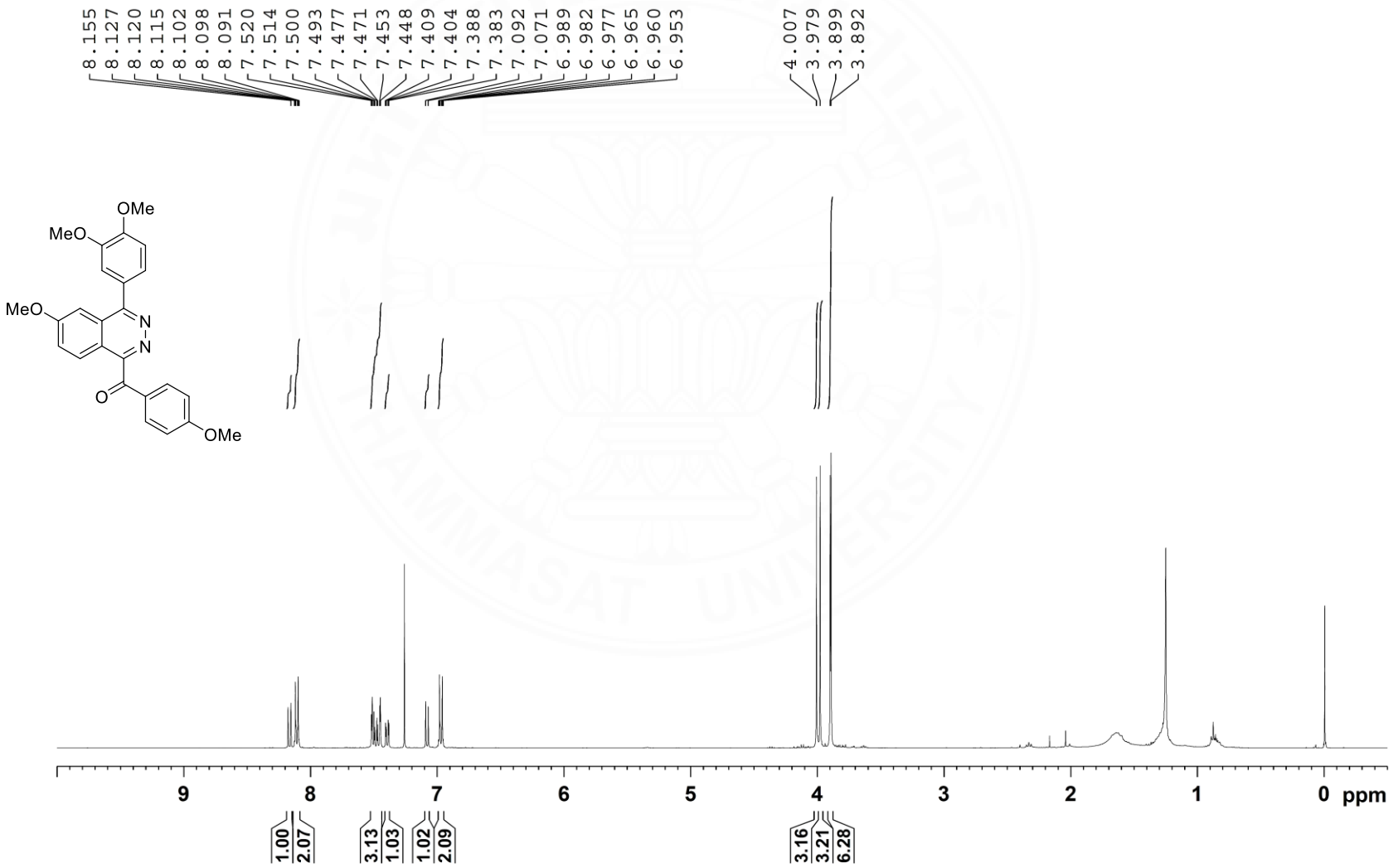
^{1}H-NMR of compound **5ia** (400 MHz, $CDCl_3$)



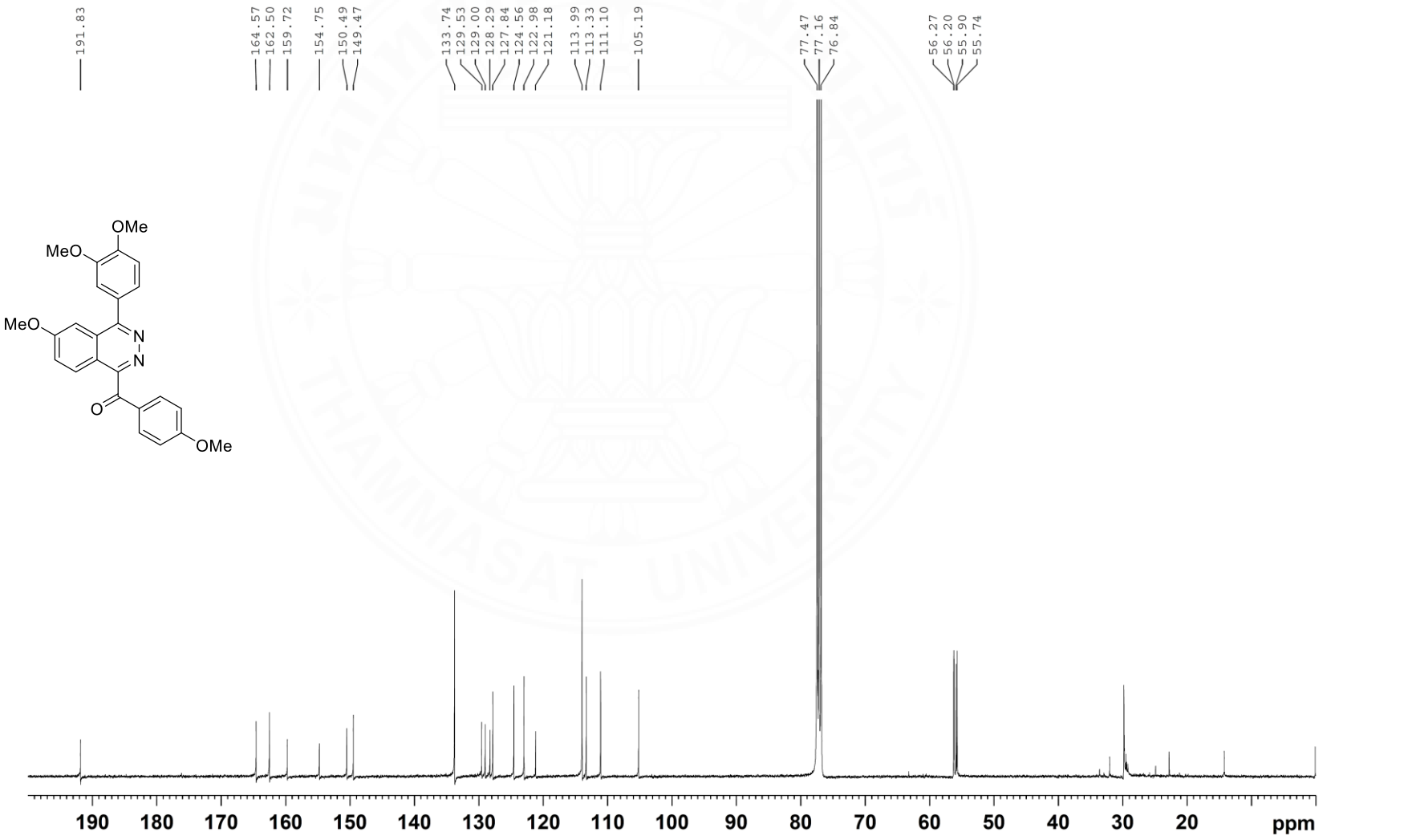
^{13}C-NMR of compound **5ia** (100 MHz, $CDCl_3$)



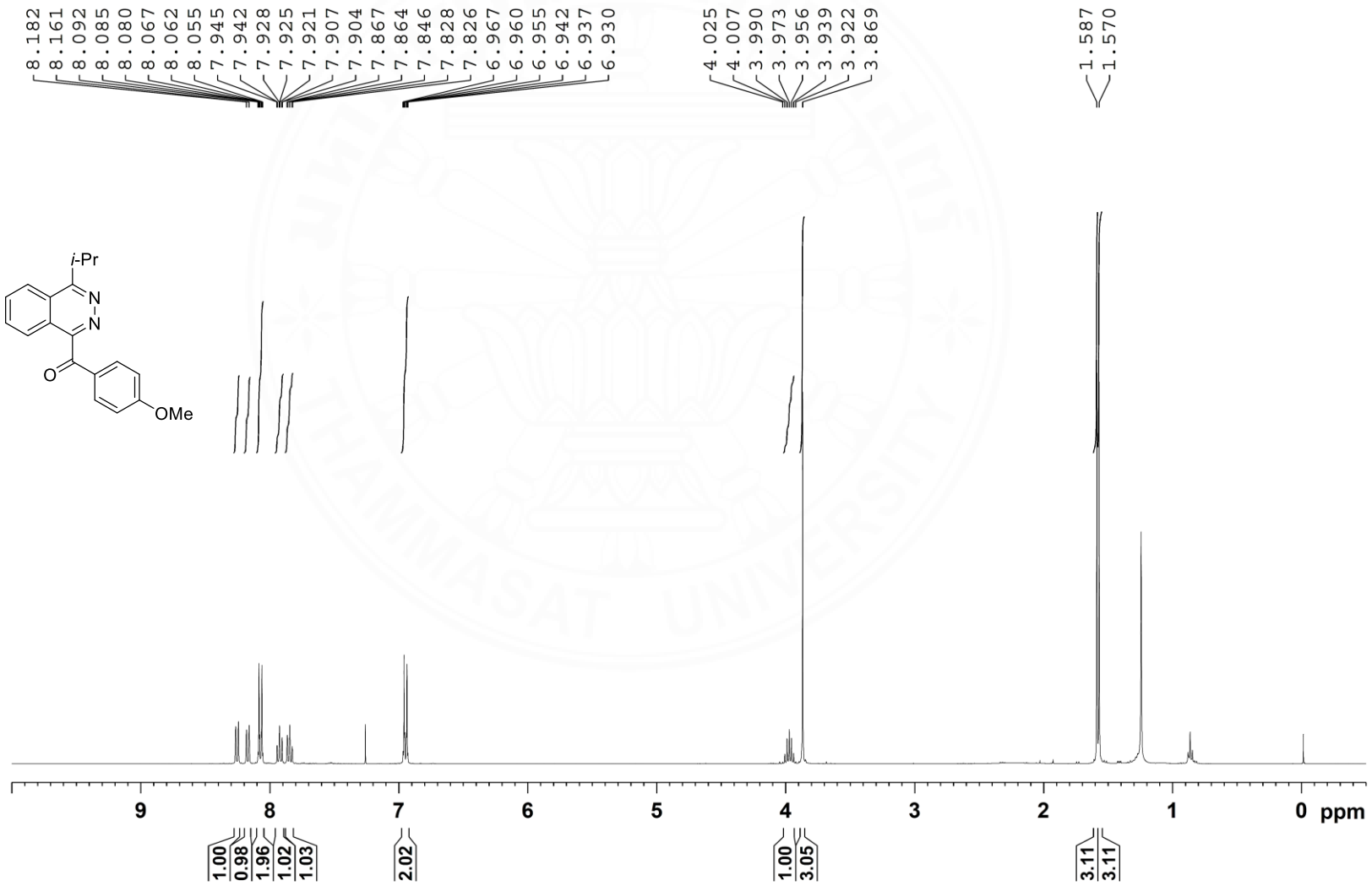
^{1}H-NMR of compound **5ja** (400 MHz, $CDCl_3$)



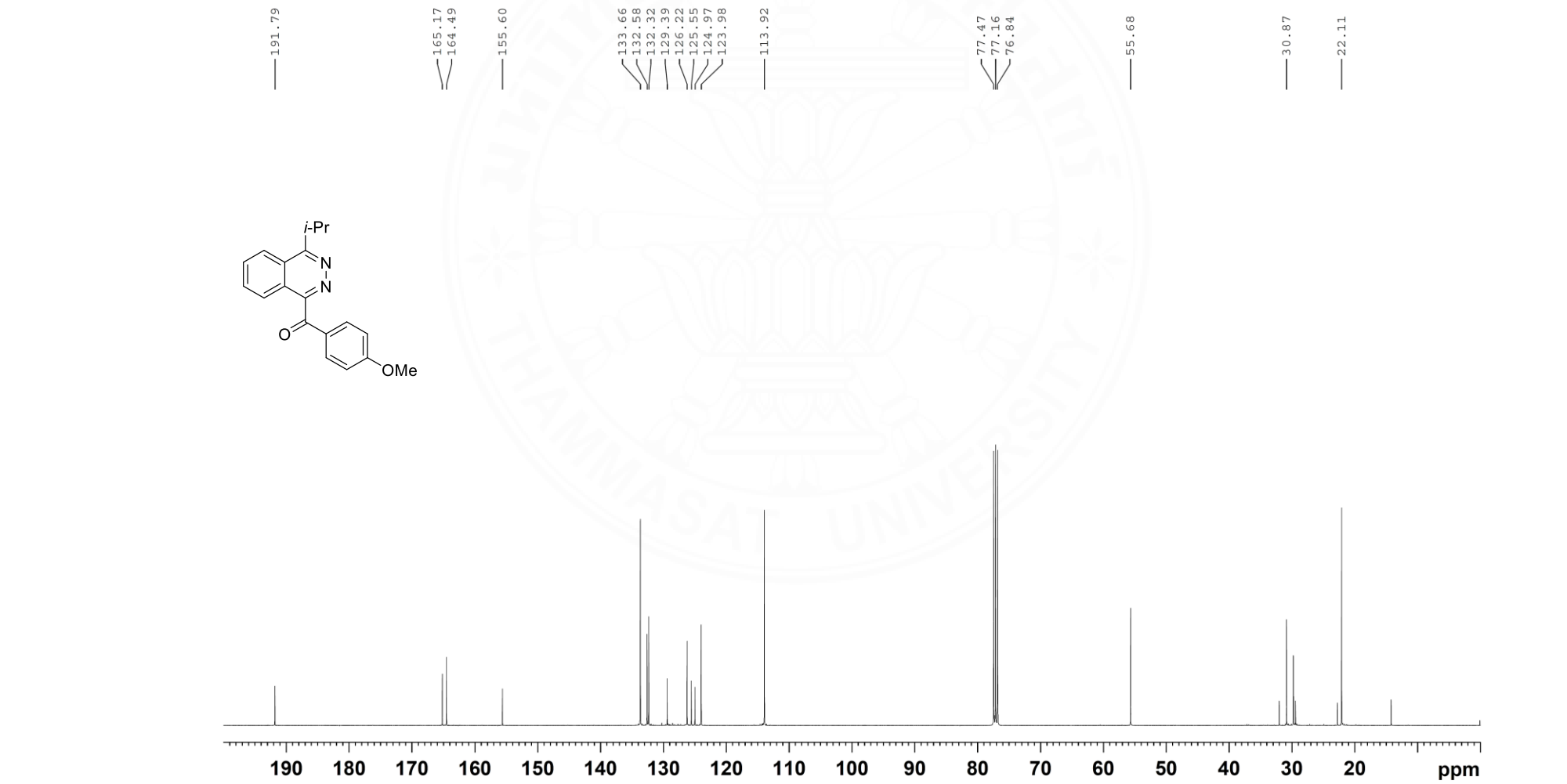
^{13}C-NMR of compound **5ja** (100 MHz, $CDCl_3$)



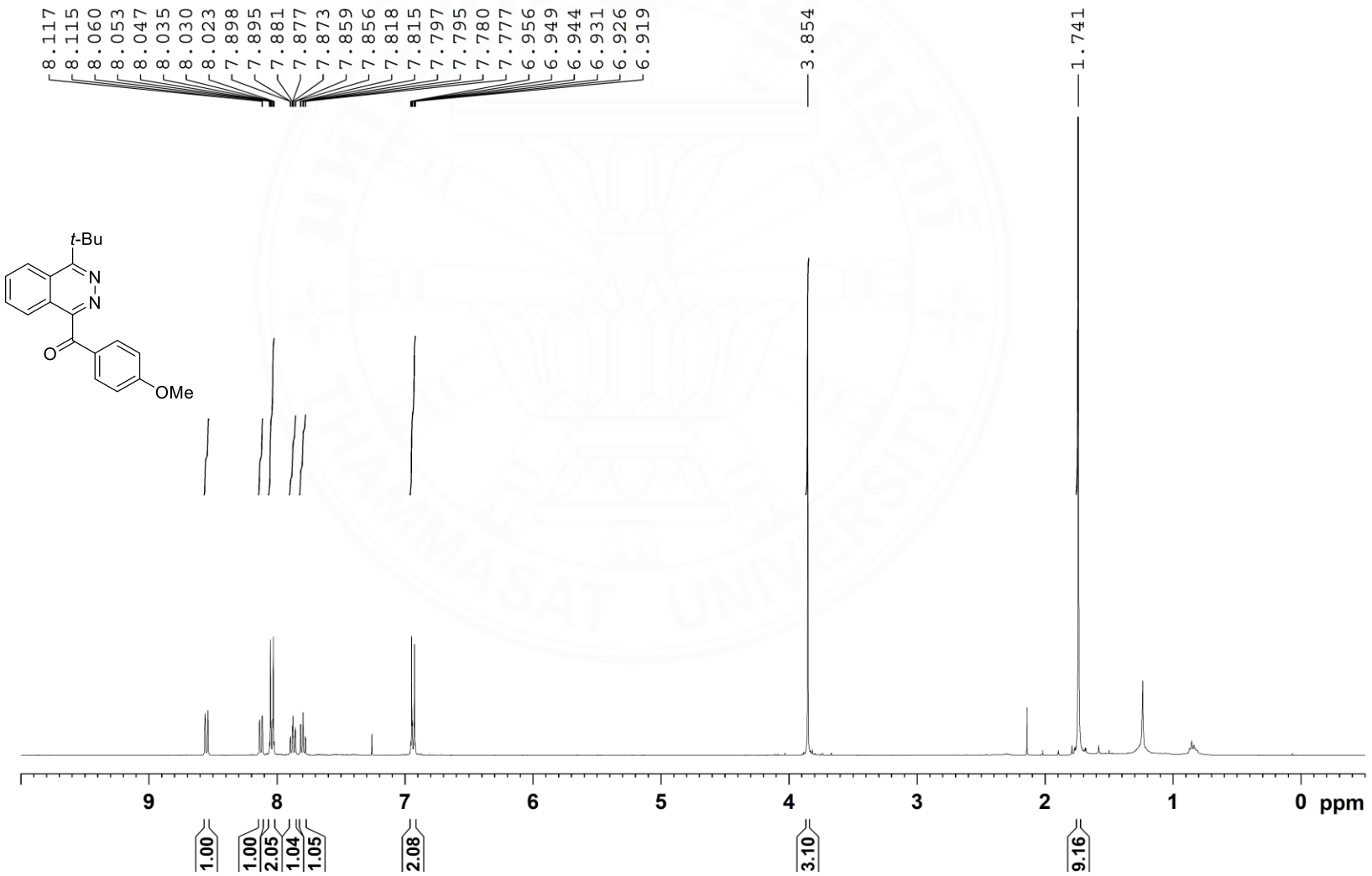
^{1}H-NMR of compound **5ka** (400 MHz, $CDCl_3$)



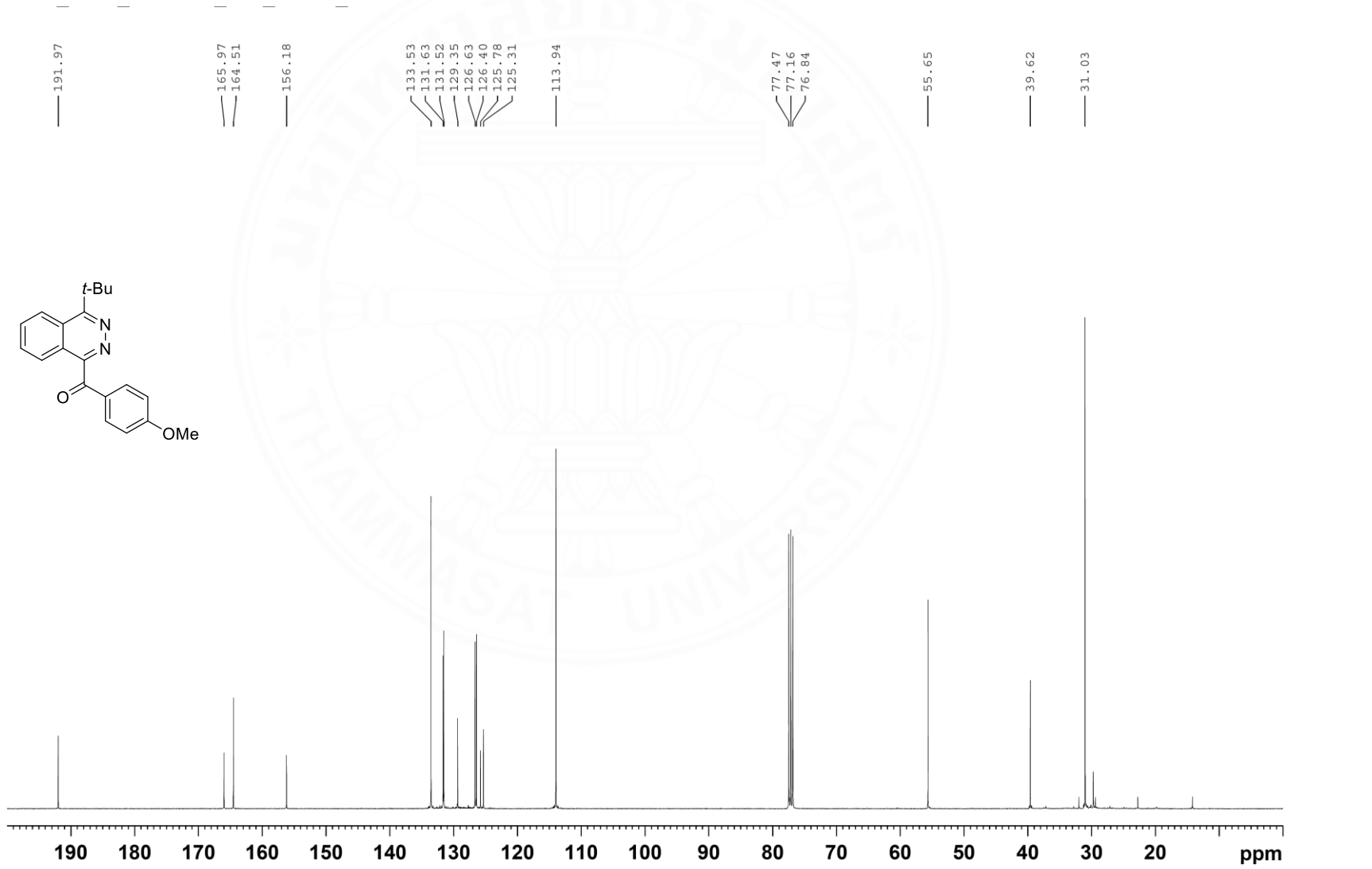
^{13}C-NMR of compound **5ka** (100 MHz, $CDCl_3$)



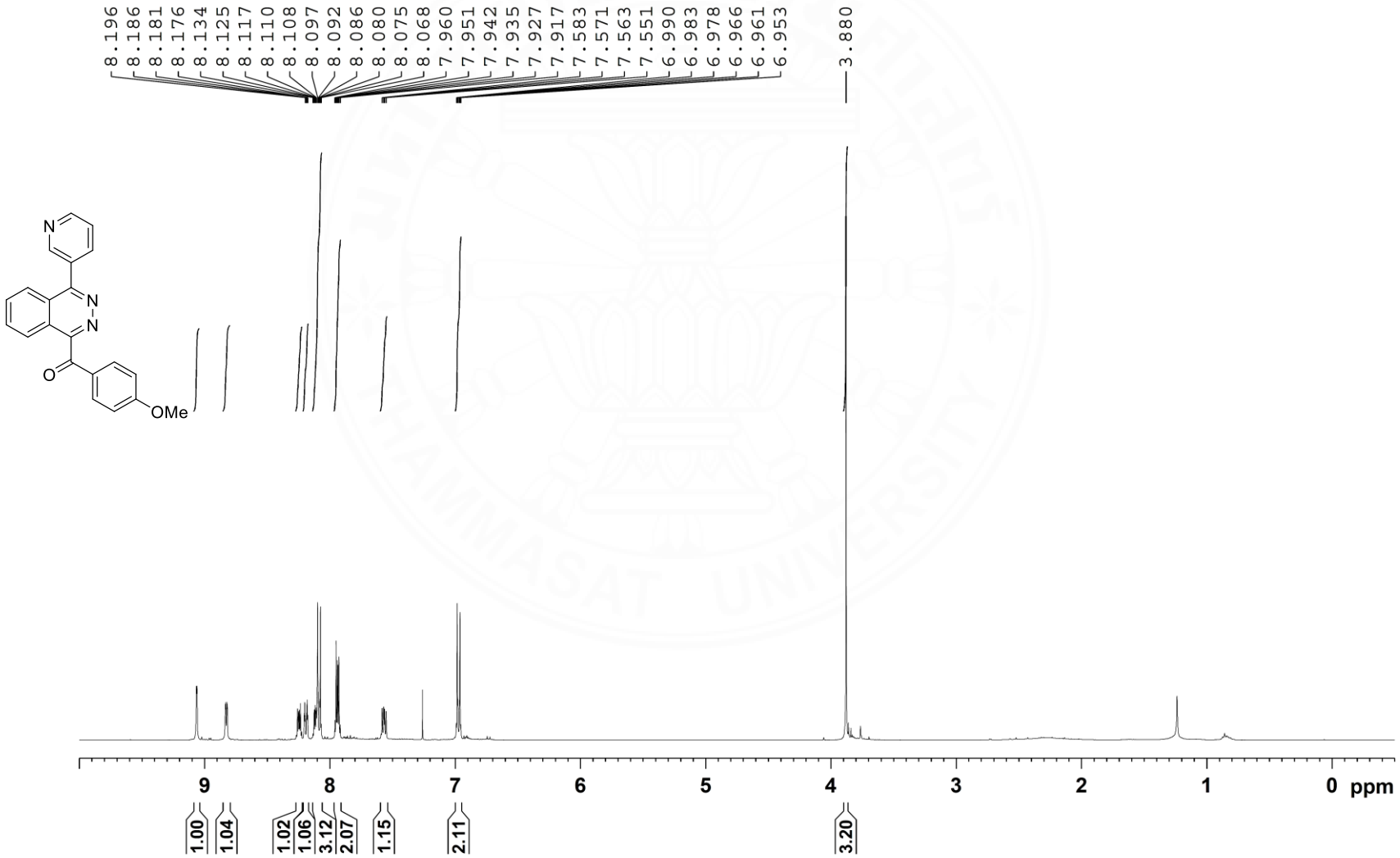
^{1}H-NMR of compound **5la** (400 MHz, $CDCl_3$)



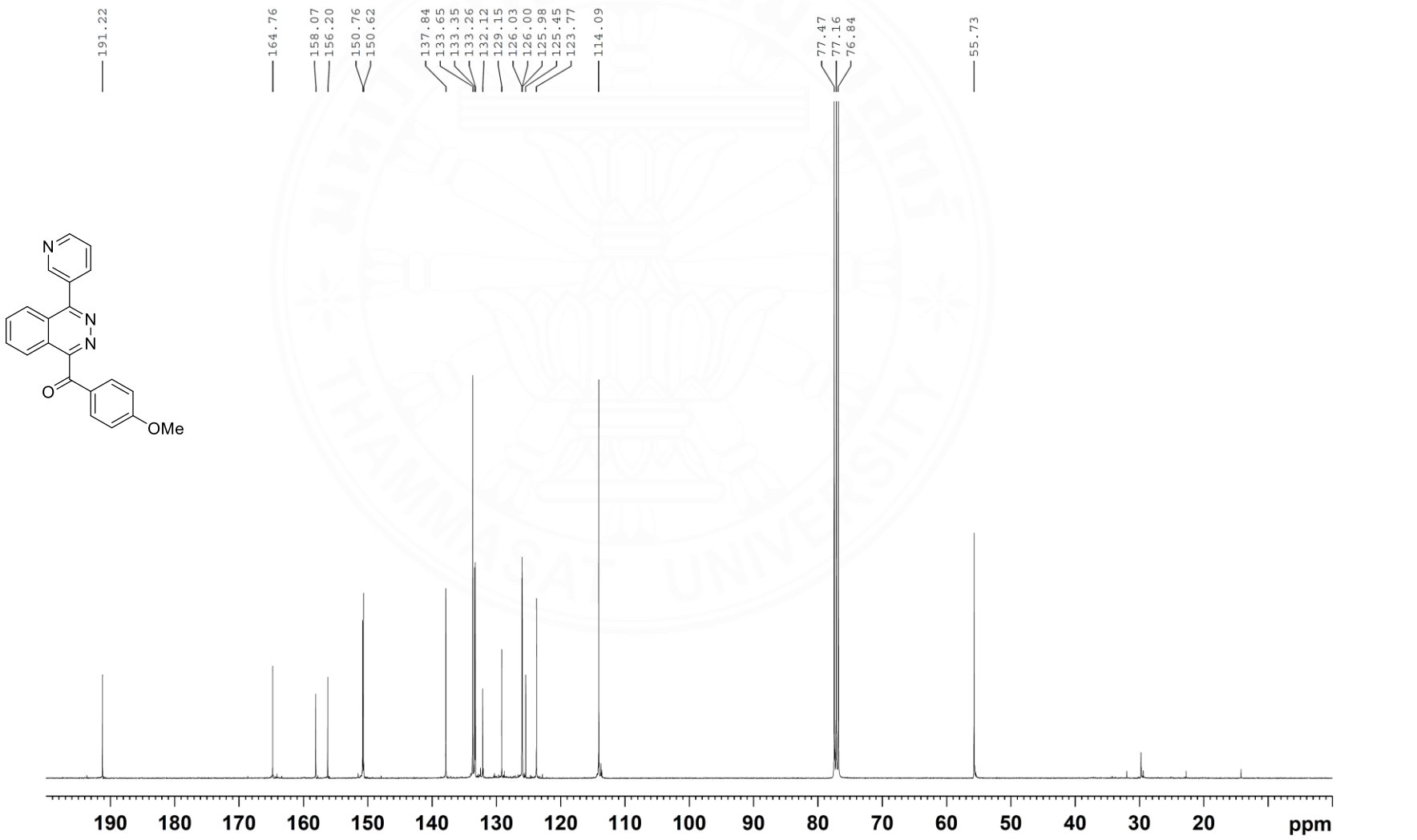
^{13}C-NMR of compound **5la** (100 MHz, $CDCl_3$)



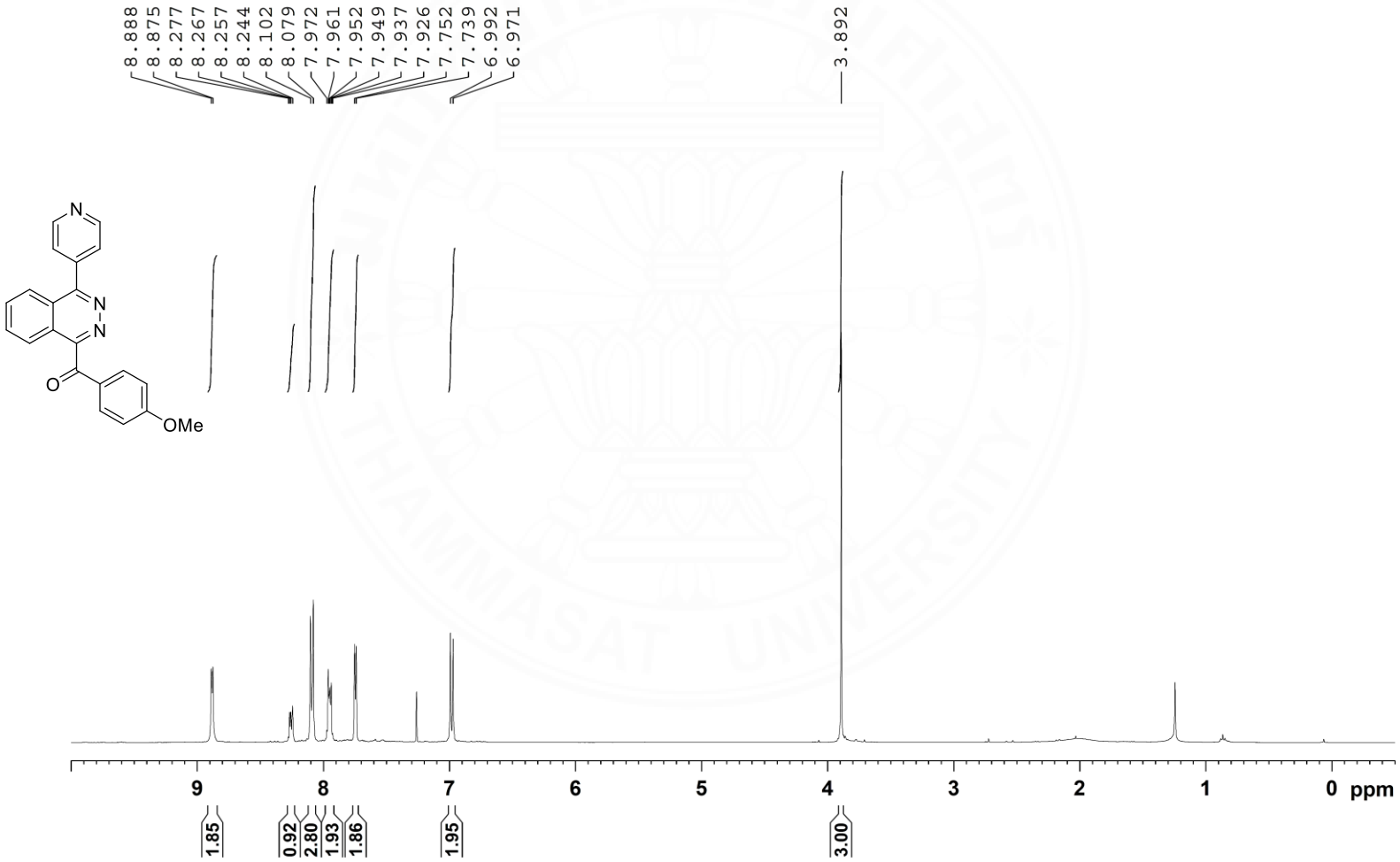
^{1}H-NMR of compound **5ma** (400 MHz, $CDCl_3$)



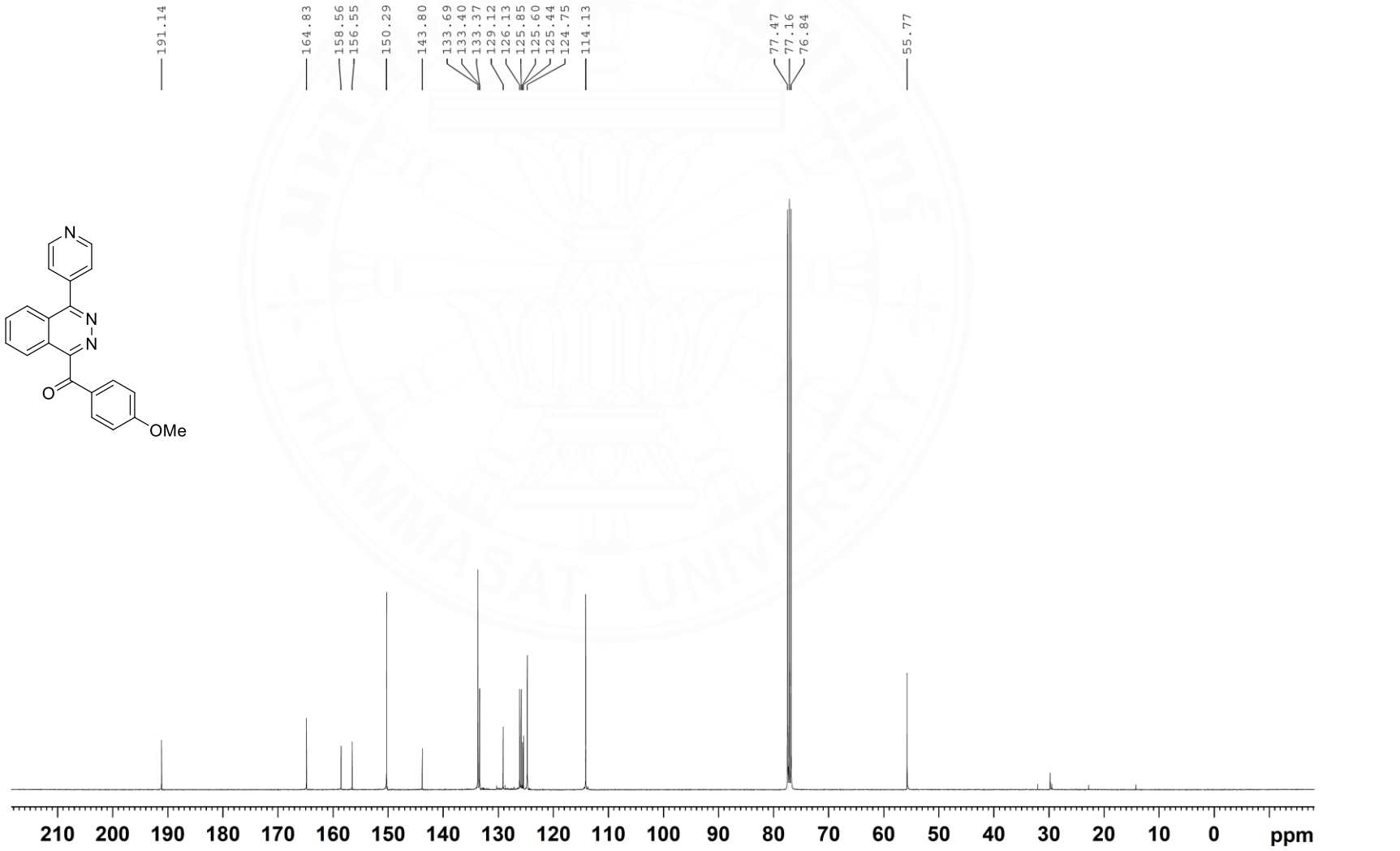
^{13}C-NMR of compound **5ma** (100 MHz, $CDCl_3$)



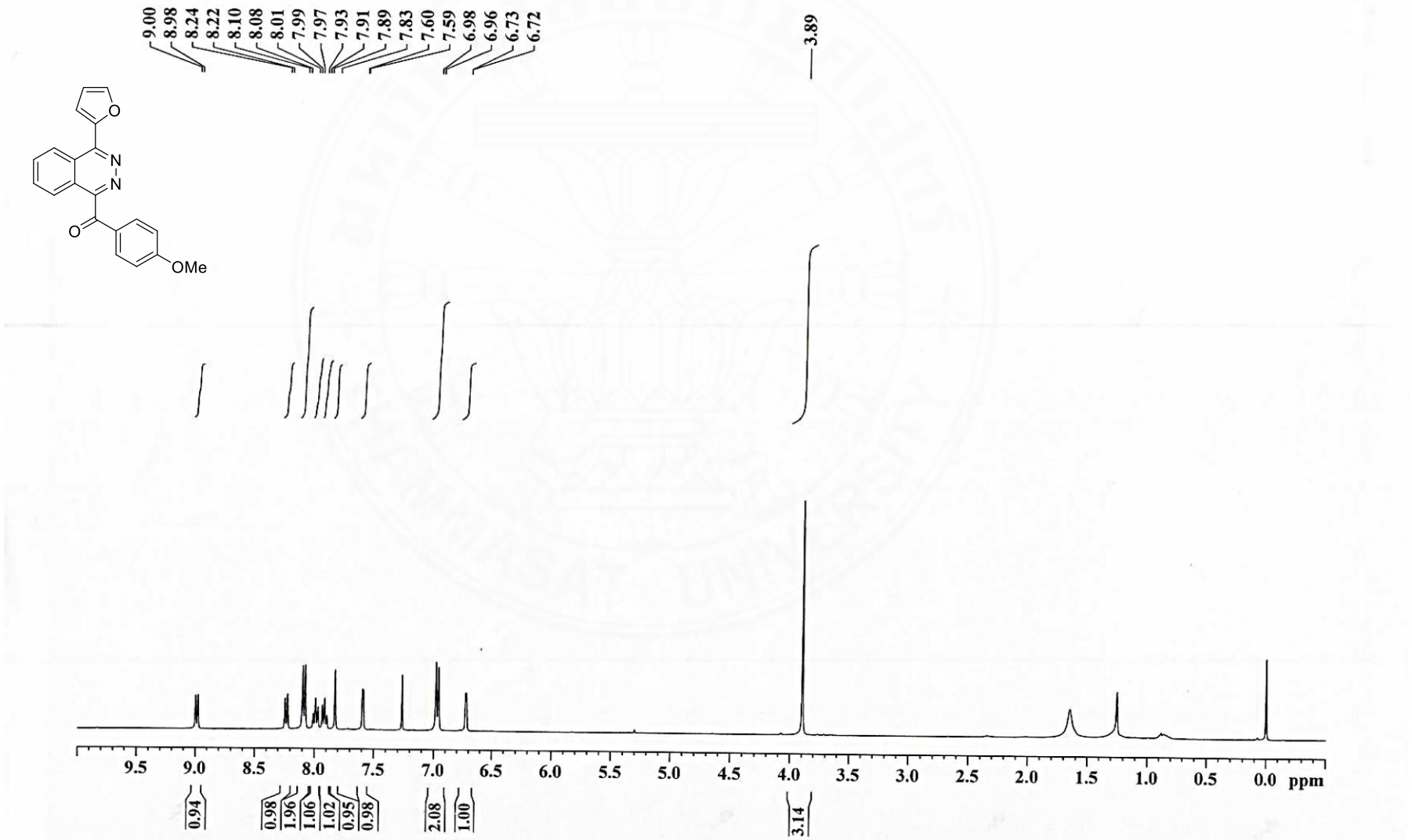
^{1}H-NMR of compound **5na** (400 MHz, $CDCl_3$)



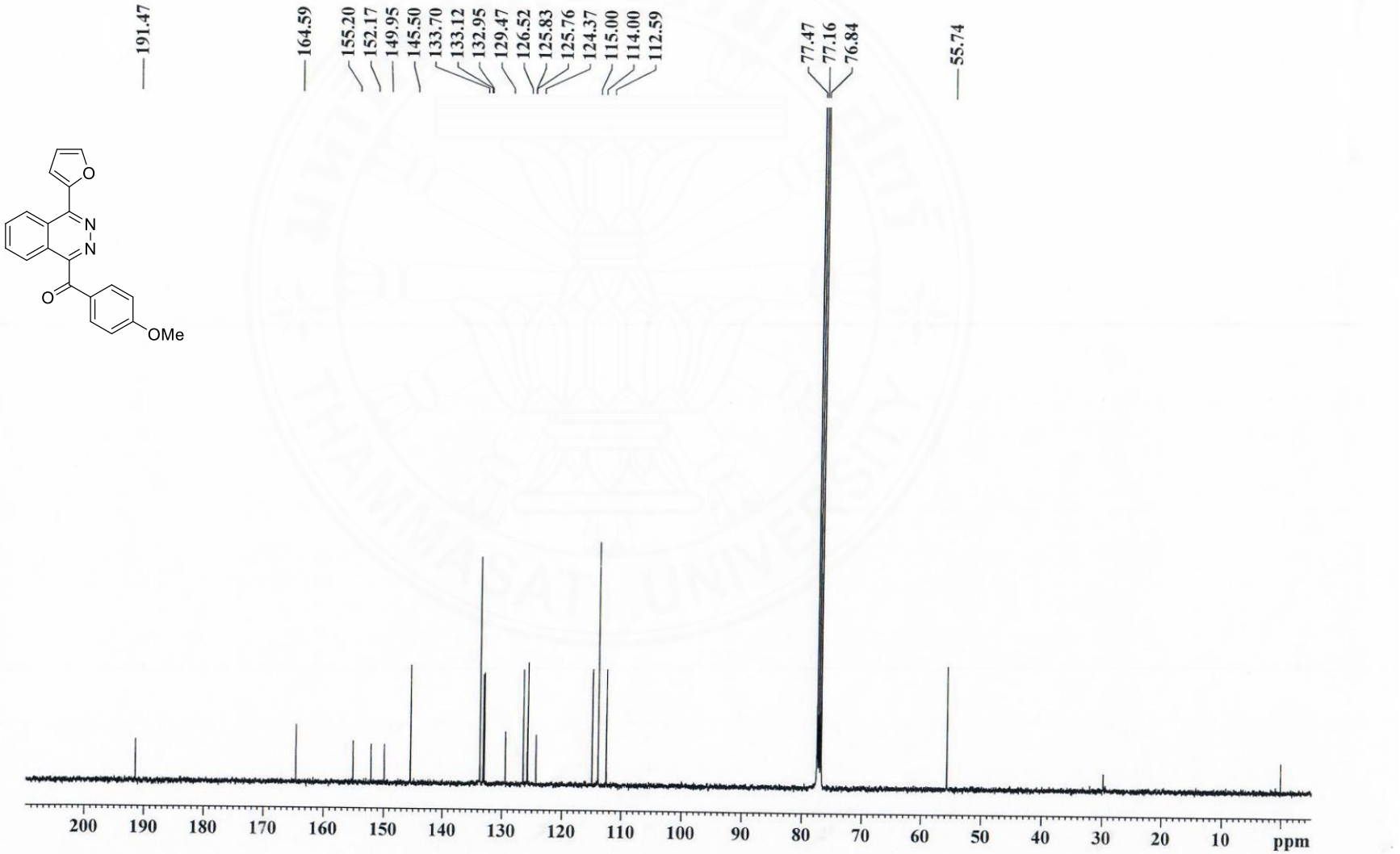
^{13}C-NMR of compound **5na** (100 MHz, $CDCl_3$)



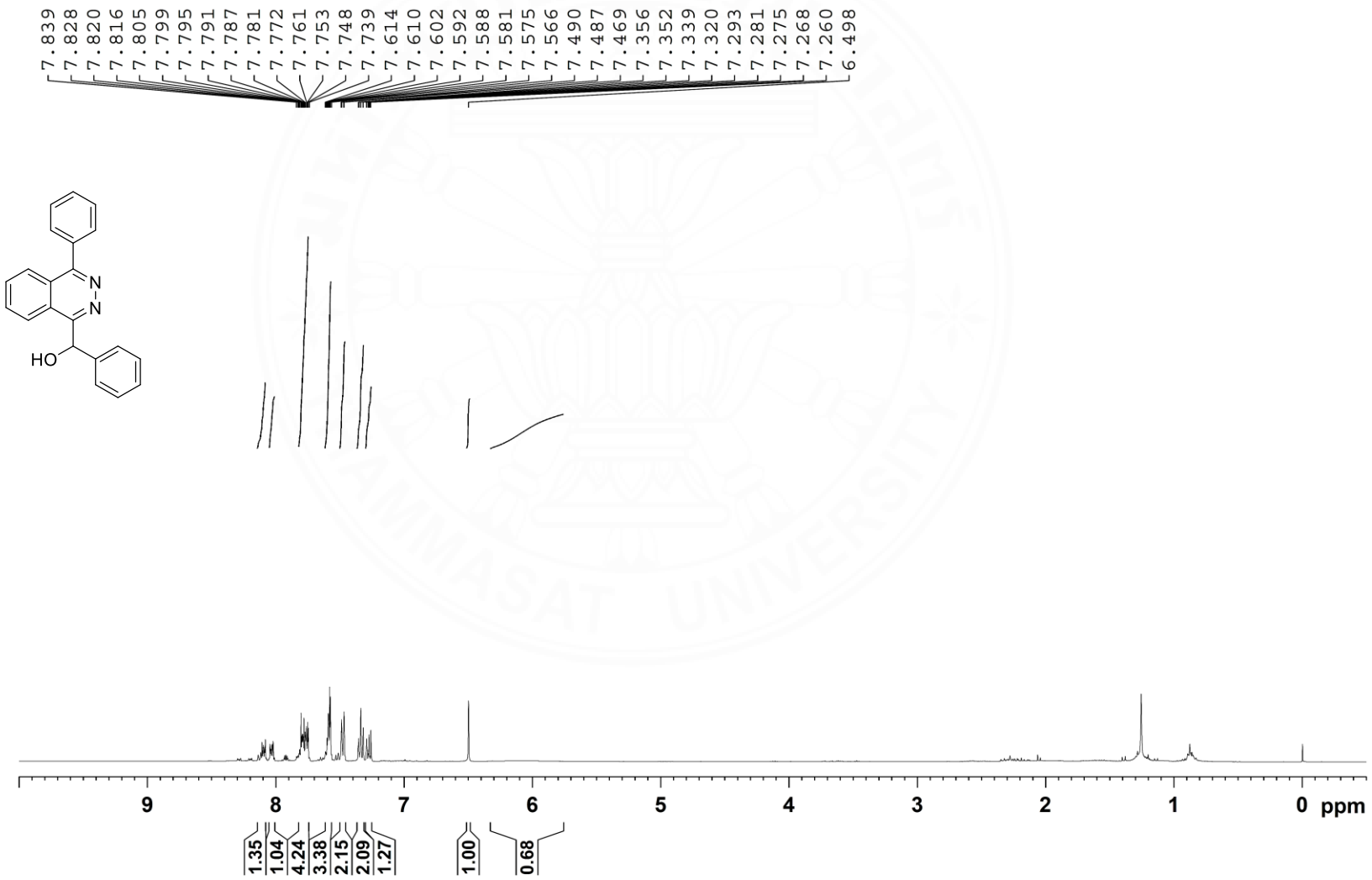
^{1}H-NMR of compound **5oa** (400 MHz, $CDCl_3$)



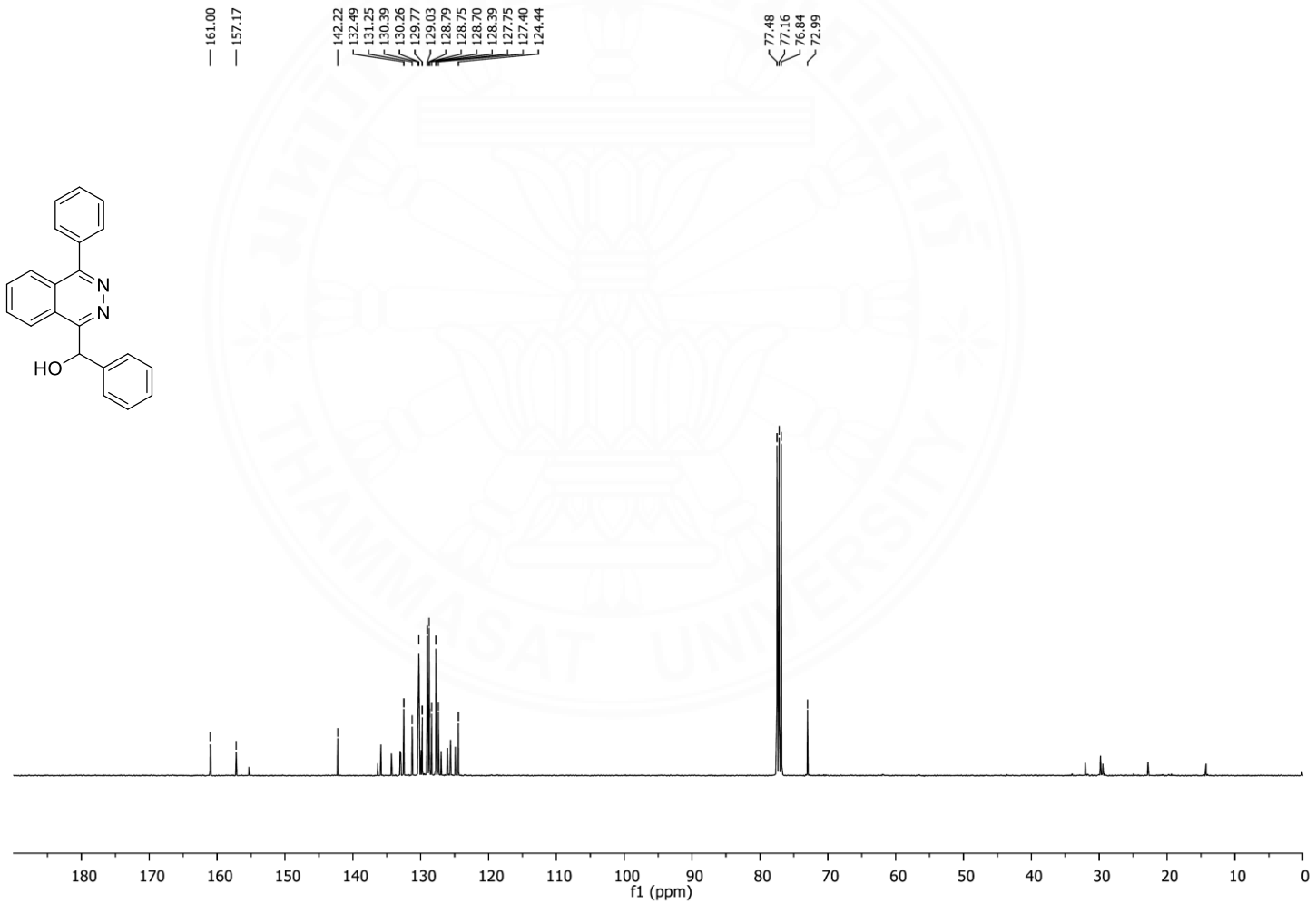
^{13}C-NMR of compound **5oa** (100 MHz, $CDCl_3$)



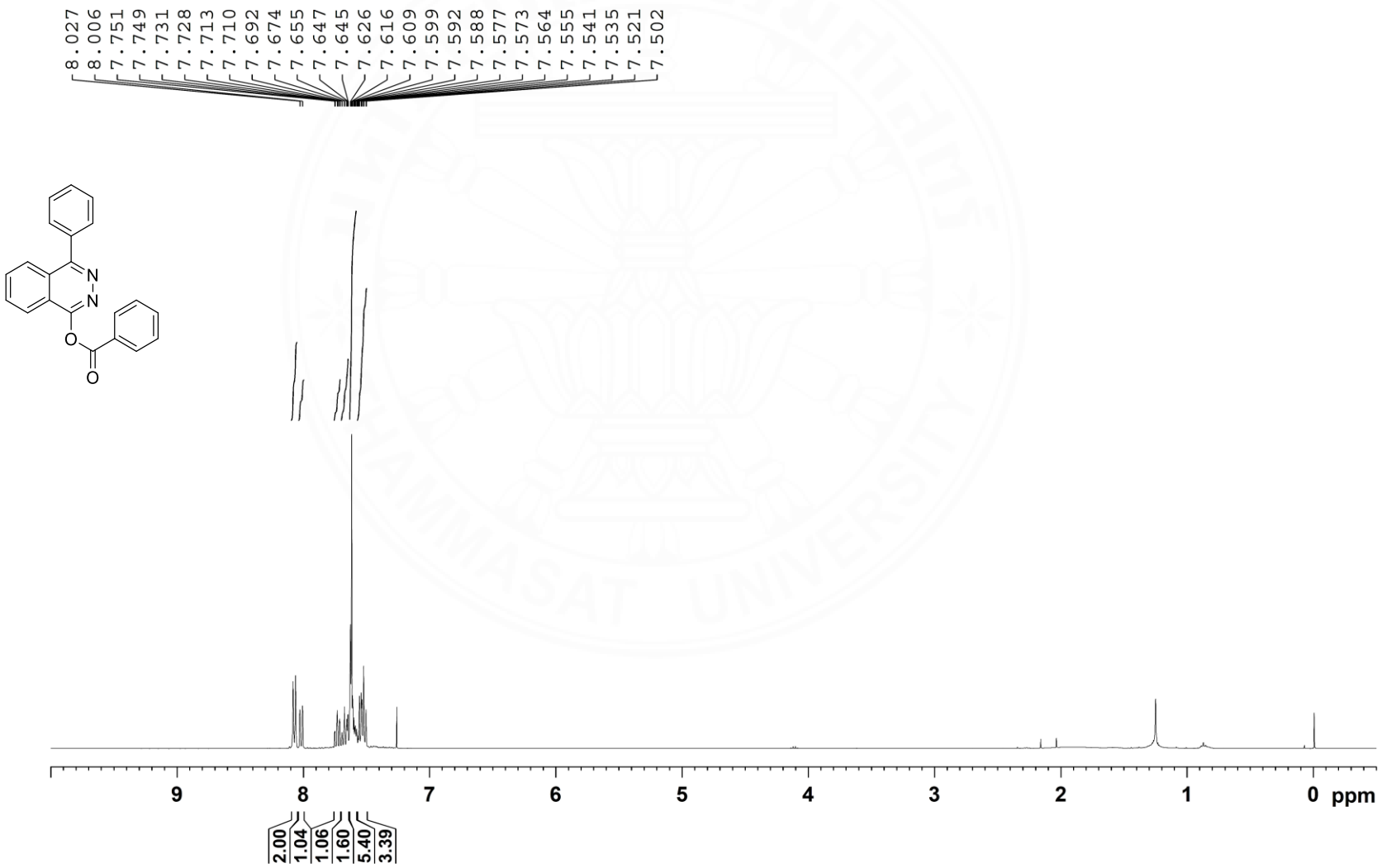
^{1}H-NMR of compound **6** (400 MHz, $CDCl_3$)



^{13}C-NMR of compound **6 (**100 MHz, $CDCl_3$)



^{1}H-NMR of compound **7** (400 MHz, $CDCl_3$)



^{13}C-NMR of compound **7 (**100 MHz, $CDCl_3$)