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ชื่อโครงการ การสังเคราะห์และศึกษาสมบัติการเป็นตัวเร่งปฏิกิริยาเชิงแสงของสารประกอบเชิงซ้อนทองแดงที่มีอนุพันธ์ของ 8-อะมิโนควิโนลีนเป็นองค์ประกอบ

Synthesis and photocatalyst study of copper complex containing 8-aminoquinoline derivatives

ชื่อนิสิต นายนนทกานต์ ช่วยธานี

ภาควิชา เคมี

ปีการศึกษา 2560

คณะวิทยาศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

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Synthesis and photocatalyst study of copper complex containing 8-aminoquinoline derivatives

By

Mr. Nontakarn Chuaytanee

In Partial Fulfilment for the Degree of Bachelor of Science

Department of Chemistry, Faculty of Science

Chulalongkorn University

Academic Year 2017

Project Title Synthesis and photocatalyst study of copper complex containing 8-aminoquinoline derivatives

By Nontakarn Chuaytanee

Accepted by Department of Chemistry, Faculty of Science, Chulalongkorn University in partial fulfilment of the requirements for the Degree of B achelor of Science

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Quality of the following work is rated: ☑ Excellent ☐ Good ☐ Average

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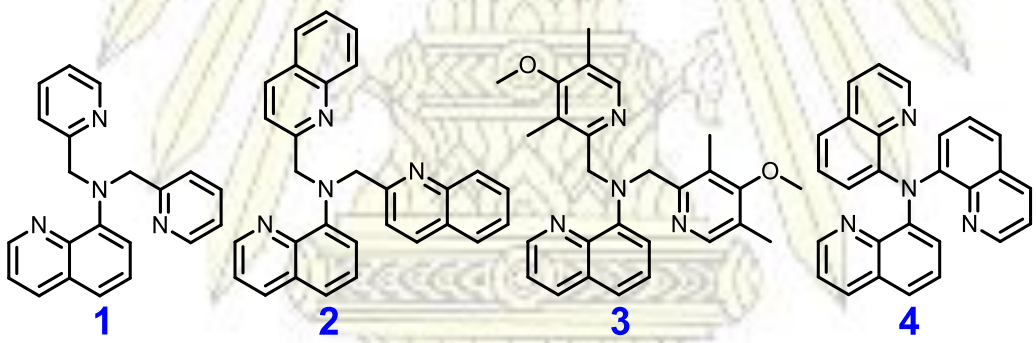
บทคัดย่อ

ปฏิกิริยาอะตอมทรานส์เฟอร์เรดิคัลแอดดิชัน (ATRA) และไซไคลเซชัน (ATRC) ได้รับการยอมรับเป็นหนึ่งในปฏิกิริยาสำหรับการสร้างพันธะระหว่างคาร์บอน-คาร์บอนที่ใช้กันอย่างกว้างขวางในทางเคมีอินทรีย์ ในการพัฒนาตัวเร่งปฏิกิริยาเชิงแสงสำหรับปฏิกิริยานี้ ได้มีการออกแบบ สังเคราะห์ และพิสูจน์ทราบเอกลักษณ์ลิแกนด์ที่คล้ายคลึงกับ tris(pyridin-2-ylmethyl)amine (TPMA) เป็นสารประกอบ **1**-**4** ซึ่งถูกนำมาใช้ศึกษาในการเร่งปฏิกิริยาเชิงแสงระหว่างสไตรีนกับคาร์บอนเตตระคลอไรด์ หรือคลอโรฟอร์ม ผ่านการเกิดสารประกอบเชิงซ้อนกับไอออนทองแดงภายใต้แสงขาว (CFL 32 W) โดยใช้ azobisisobutyronitrile (AIBN) เป็นตัวรีดิวซ์ จากผลการทดลองพบว่าเมื่อผ่านไป 8 ชั่วโมง สารประกอบเชิงซ้อนทองแดงของ TPMA, **1**, **2** และ **4** ให้ร้อยละผลได้มากกว่า 80 ในปฏิกิริยาการเติมคาร์บอนเตตระคลอไรด์บนสไตรีน อย่างไรก็ดี เมื่อเปลี่ยนอัลคิลเฮไลด์เป็นคลอโรฟอร์มซึ่งมีความว่องไวน้อยกว่าพบว่า มีเพียงสารประกอบ **1** เท่านั้นที่ให้ร้อยละผลได้มากกว่า 80 ภายใน 24 ชั่วโมง



ลิแกนด์ที่ได้ออกแบบสำหรับศึกษาปฏิกิริยา ATRA ในงานวิจัยนี้

คำสำคัญ: ตัวเร่งปฏิกิริยาเชิงแสง, 8-อะมิโนควิโลลีน, ปฏิกิริยาการเติมอะตอม ทรานสเฟอร์ เรดิคัล

Project Title Synthesis and photocatalyst study of copper complex containing 8-aminoquinoline derivatives

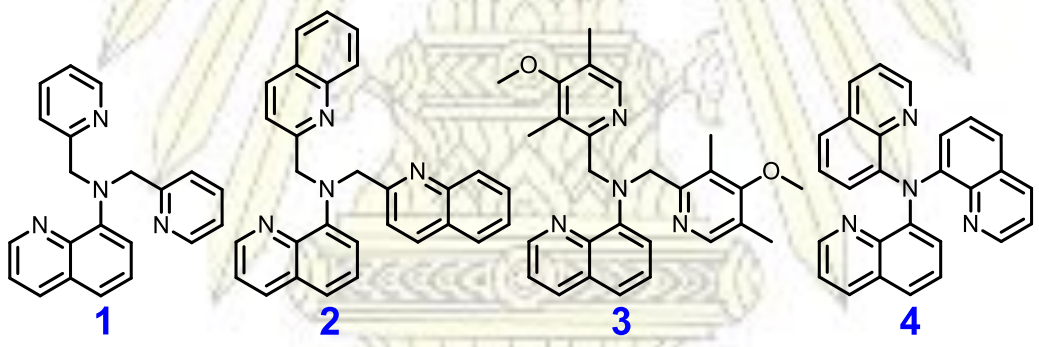
Student name Nontakarn Chuaytanee Student ID: 5733108723

Project Advisor Professor Dr. Mongkol Sukwattanasinitt

Department of Chemistry, Faculty of Science, Chulalongkorn University, Academic Year 2017

ABSTRACT

Atom transfer radical addition (ATRA) and cyclization (ATRC) has been recognized as one of the most worthwhile reactions for carbon-carbon bond formation in organic chemistry. In order to develop an active catalyst for this reaction under visible light, ligands analogous to tris(pyridin-2-ylmethyl)amine (TPMA) were designed, synthesized and characterized (compound **1**-**4**). Their copper complexes were studied in the photocatalyzed ATRA between styrene and carbon tetrachloride or chloroform under irradiation of white light (CFL 32 W) in the presence of azobisisobutyronitrile (AIBN) as a reducing agent. For carbon tetrachloride addition, high yields of styrene adduct was observed with over 80% yield at 8 h when TPMA, **1**, **2** and **4** were used as the ligands. For a less active alkyl halide, chloroform, only ligand **1** gave over 80% yield of the styrene adduct after 24 h.



The designed ligand for ATRA study in this project

KEYWORDS: Photocatalyst, 8-aminoquinoline, Atom transfer radical addition

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Nontakarn Chuaytanee

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LIST OF ABBREVIATIONS

ATRA	Atom transfer radical addition
ATRC	Atom transfer radical cyclization
nm	nanometer
mM	millimolar
μM	micromolar
mmol	millimol
^{1}H NMR	proton nuclear magnetic resonance
^{13}C NMR	carbon-13 nuclear magnetic resonance
MS	Mass spectrometry
ESI	electrospray ionization
m/z	mass per charge
g	gram
mg	milligram
mL	milliliter
μL	microliter
M	molar
s	singlet (NMR)
d	doublet (NMR)
dd	doublet of doublet (NMR)
t	triplet (NMR)
m	multiplet (NMR)
J	coupling constant
Hz	Hertz
MHz	megaHertz
h	hour
s	second
UV	ultraviolet
δ	chemical shift
°C	degree Celsius
% yield	percentage yield

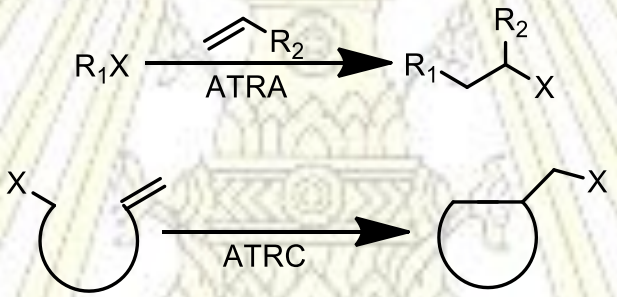
CHAPTER I

INTRODUCTION

1.1 Background and Motivation

1.1.1 Atom transfers radical addition (ATRA) reaction

The center of current challenge for organic synthesis is the improvement of 'Green' reaction especially the reaction that is achievable by green energy source, employment of catalytic process and solvents under mild conditions. Atom-transfer radical addition (ATRA) and cyclization (ATRC) has been recognized as one of the most worthwhile reactions for carbon-carbon bond formation in organic chemistry according to its advantages such as benign conditions, simple set up and minimal byproducts.[1, 2] This type of reactions provides variety of halogenated compounds which can be used for further synthesis of advanced materials, natural products and pharmaceuticals.[3, 4] The development of photo-catalysts used in ATRA and ATRC have been focused on several types of transition metal complexes such as iridium, ruthenium, nickel, iron and copper.[5-7]



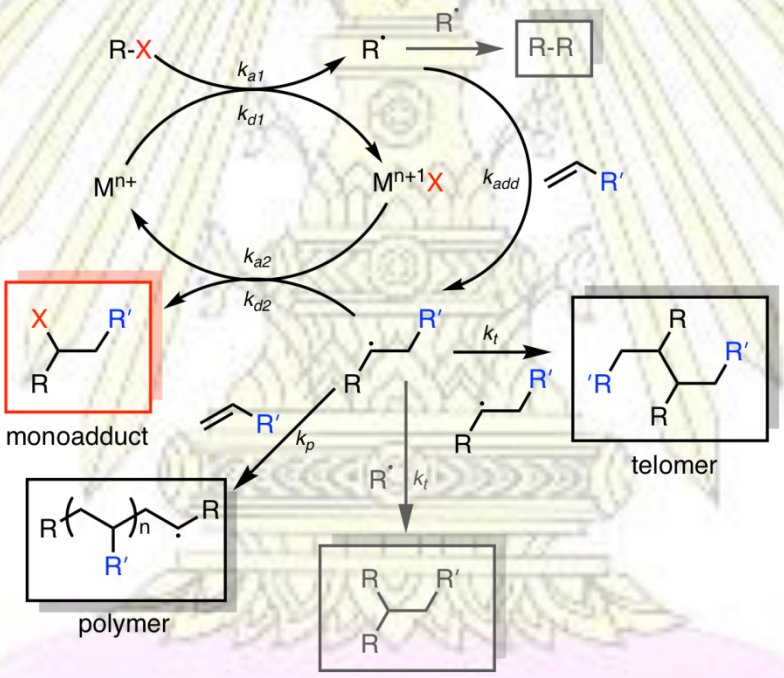
Scheme 1.1 Different types of atom transfer process

Copper complexes become one of the most accessible choices for ATRA due to its lower cost and toxicity. The major study is based on nitrogen-based ligands such as phenanthroline[8], pyridine[9, 10], trispicolylamine[11, 12], and pyrazolylborate[13, 14]. Ones of the most active ligands for copper mediated photoreaction are based on phenanthroline due to its ability to effectively transfer an electron to metal center upon the photoexcitation.[8] In this study, quinoline, a simpler heterocyclic ring, will be explored as a photon absorber for photo-catalyzed ATRA reaction. It will be incorporated into a nitrogen-based ligand such as tris-(2-pyridylmethyl)amine, TPMA. Cu-TPMA complex has been used in conjunction with radical initiator such as AIBN as a reducing agent for thermally catalyzed ATRA reactions.[4, 12] Although their catalytic activity under photo-irradiation has been

observed, the role of light is to photo-activate the reducing agent. The aim of this investigation is to use quinoline to improve the photo-catalytic activity of this type ligand which may potentially avoid the use of radical initiator. A series of 8-aminoquinoline ligands will be synthesized and their copper complexes will be evaluated for photo-catalytic activity in ATRA reactions.

1.1.2 Mechanism of atom transfers radical addition reaction

The commonly accepted mechanism for ATRA had been proposed (Scheme 1.2). The initial step is metal-induced homolytic cleavage of the carbon-halogen bond. This step generates a metal-halide and alkyl radical. The generated alkyl radical then adds to a double bond to afford another alkyl radical intermediate which rapidly abstracts halogen atom from the metal-halide to regenerate the active metal species for the next reaction cycle. [15] The desired addition product is continuously formed. However, the combination or polymerization of the alkyl radicals can lead to competitive products and disturb the catalytic cycles.



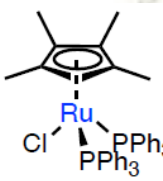
Scheme 1.2 Proposed mechanism for copper catalyzed ATRA

In order to achieve selective ATRA reaction, Matyjaszewski has suggested 3 factors for suspicious concern in this reaction. First, the overall radical concentration in reaction must be low (k_{d1} and k_{d2} >> k_{a1} and k_{a2}) to avoid the radical-radical combination. Second, the product activation must be slower than starting material activation (k_{a1} >> k_{a2}) to prevent further activation of mono-adduct. Third, the oxidation must be faster than propagation (k_{d2} >> k_p) to avoid a polymerization.[2] These criteria implied that the active species of the

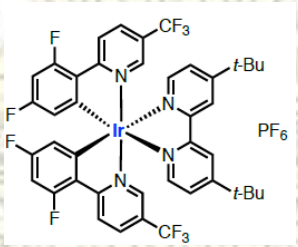
metal catalyst must be present at low concentration at all time but continuously generated in the reaction.

1.2 Literature review

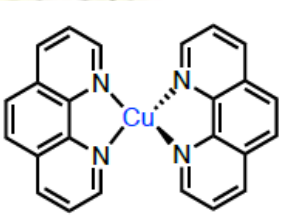
Since the discovery of anti-Markovnikov in addition reaction of hydrogen bromide to unsymmetrical alkenes by peroxide initiators through the radical process in early 1940s, the addition of alkyl halides to olefins in the presence of radical initiators or light were investigated and later well-known as Kharasch reaction. Although the reaction efficiency proceeded under the presence of peroxide or light, the reaction need a highly active and excess of alkyl halide to provide an optimum yield.[16, 17] In 1956, Kochi suggested the termination process of intermediated radical in the presence of metal halides ($CuCl_2$ or $FeCl_2$) through the inner sphere electron transfer mechanism which indicated the significant role of metal salts for addition reaction.[18] This study consistent with the discovery of iron leaching to addition reaction by Minisci's group which can increase the chain transfer constant. They explained that iron could be oxidized by chlorine radical and gave iron(III)chloride as byproduct. A year later Minisci and Vofsi and Asscher first described transition metal catalyzed atom transfer radical addition or TMC-ATRA[19, 20] which is currently studied with various metals such as ruthenium[21], iridium[22], copper[23], iron[24], niobium[25] and nickel[26] (Figure 1.1) under heat, light or ambient temperature. The most common catalysts for ATRA reaction are based on ruthenium and copper of which the conversions between the active and inactive oxidation states are highly reversible.



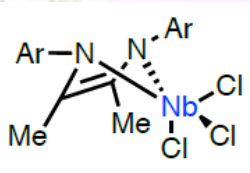
[Cp*RuCl(PPh_3)$_2$]



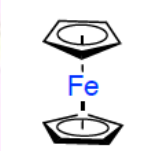
Ir[(dF(CF_3)- ppy)$_2$(dtbbpy)]PF_6



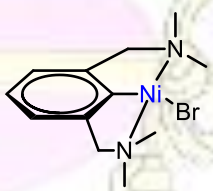
[Cu(Phen)$_2$]



[$NbCl_4$(α- diimine)]



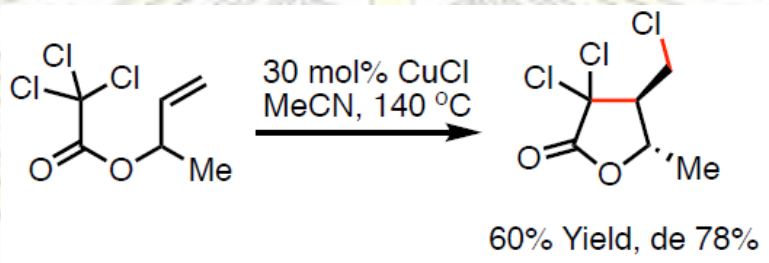
[(C_5H_5)2Fe]



[Ni^{II}{C_6H_3(CH_2NMe_2)$_2$-2,6}Br]

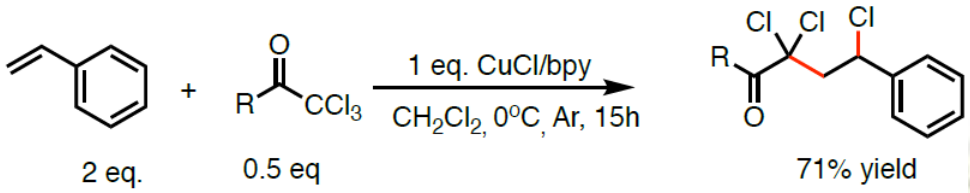
Figure 1.1 Transition metal complexes used as catalysts in ATRA reaction

Copper is one of the most attractive choices for metal center of ATRA catalysts. Copper-mediated intramolecular ATRA or ATRC provided carbon-carbon cyclic compounds which benefit for synthesizing natural products and pharmaceuticals. The pioneer work was found in the synthesis of γ-lactones and γ-lactams by Tsuji's and Clack's group respectively.[27, 28] They suggested that copper(I) chloride efficiently produced cyclic compounds in single pot (Scheme 1.3). Nevertheless, the limitations of these catalyst are the requirement for a large amount of the copper salt. In addition, the requirement of high temperature is unsuitable for intermolecular addition of readily polymerizable alkenes such as methyl methacrylate (MMA), methyl acrylate (MA), styrene, vinyl acetate (VA) and acrylonitrile (AN) due to the competitive polymerization.



Scheme 1.3 Copper catalyzed intramolecular ATRA or ATRC reaction

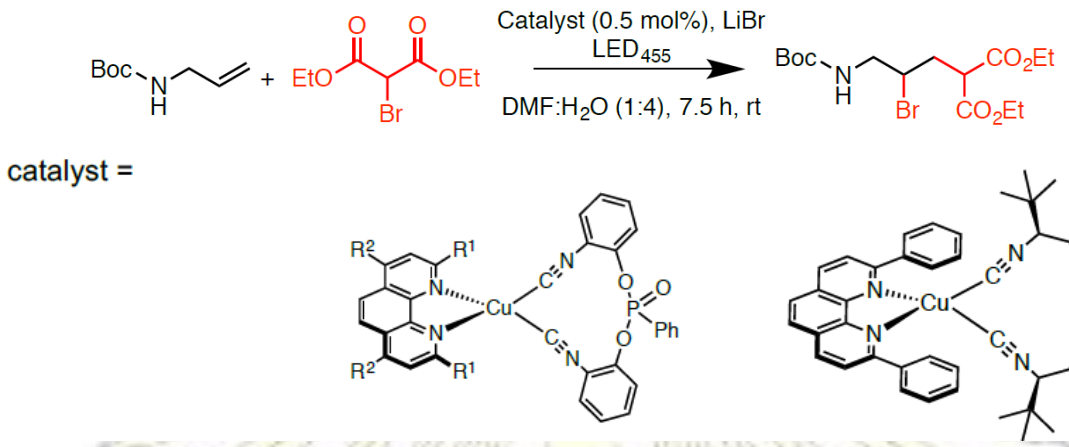
Copper complexes with bipyridine (bpy) is one of primary active catalysts used in ATRA and ATRC reactions. This catalyst showed high activity for catalyzing the addition of chloromethylketones to olefins. In 2006, Yang and co-worker investigated the ATRC reaction of unsaturated α-chloro β-keto esters to obtained a various cyclic compounds in moderate to high yield.[9] Furthermore, a recent study by Hu and co-worker suggested the addition of α,α,α-trichlromethyl ketones to styrene derivatives under low temperature and benign condition in high yield (Scheme 1.4). However, in both studies at least 1 equivalent of copper complex was needed.[10]



Scheme 1.4 ATRA of α-chloro β-keto esters to alkenes by using of CuCl and bipyridine as a catalyst

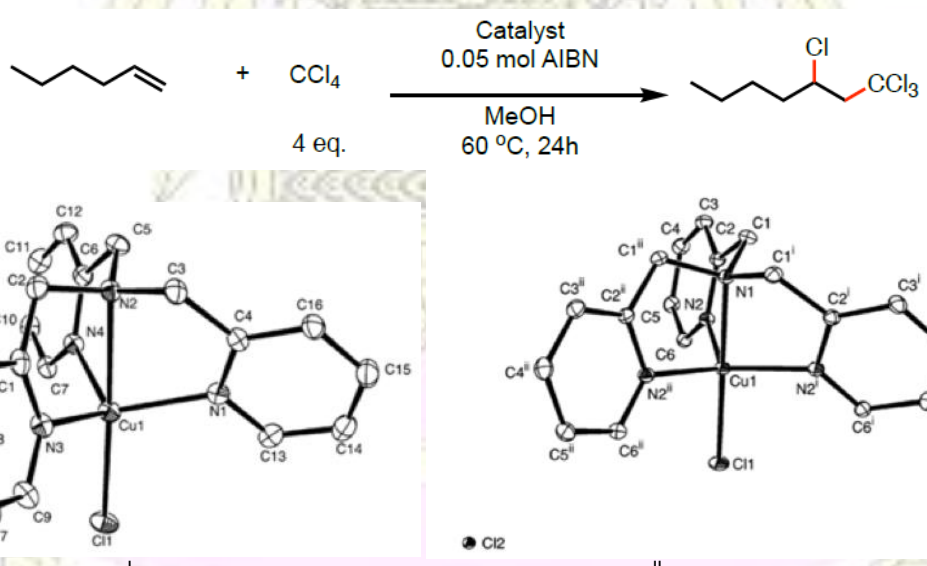
Currently, phenanthroline derivatives are ones of the most active ligands for photo-mediated ATRA reactions due to its ability to harvest energy from UV-visible light and stabilize the generated copper (I) complexes in excited state. These allowed the activation of less active alkylhalides and expansion the scopes of the alkene substrates. The well-known

ligands in this family are bis-phenathroline derivatives. The mixed ligand copper(I) complexes of phenanthroline and wide-bite-angle bidentate phosphine ligand studied by Oliver's group improved both the photophysical properties of the complexes and catalytic activity between the alkyl halides and alkenes (scheme 1.5).[8]



Scheme 1.5 Photo-mediated ATRA reaction studied by Oliver group

Another appealing approach for modern ATRA reaction is the use of activator for regenerating active catalyst. This process was termed as initiators for continuous activator regeneration, ICAR process. In 2007 Tomislav's group reported ICAR-ATRA reaction of CCl_4 and $CHCl_3$ to alkenes by using in-situ $Cu^{I}Cl$ and $Cu^{II}Cl_2$ complexes with tris(2-pyridylmethyl) amine, TPMA as a catalyst in the presence of AIBN as an activator under heating at 60 °C (scheme 1.6). The process produced the addition product in moderated yield by using as low as 0.01 equivalent.



Scheme 1.6 ICAR-ATRA reaction in the presence of AIBN as a reducing agent

Based on the development of new 8-quinoline compounds in our group, we found that the compounds strongly coordinated with copper and their fluorescence signal were quenched. With higher absorptivity at longer wavelength and electron transfer ability of quinoline ring, we designed four nitrogen based ligands for ATRA study. In compound **1**, one of the pyridinylmethyl groups in TPMA was replaced by a quinoline ring. Compound **2** has two pyridine rings in compound **1** replaced by two 2-quinolylmethyl group. This compound is known as effective anticancer drugs but never be used in photo-catalyst area. [29] Compound **3** has two pyridine rings substituted with electron donating methoxy and methyl pycolyl groups. This based on previous studied that tris(methoxy-methyl pycolylamine), TPMA* is more active catalyst for ATRP.[30, 31] Finally, compound **4** was designed by replaced all of the pyridinylmethyl groups in TPMA with three quinoline rings.

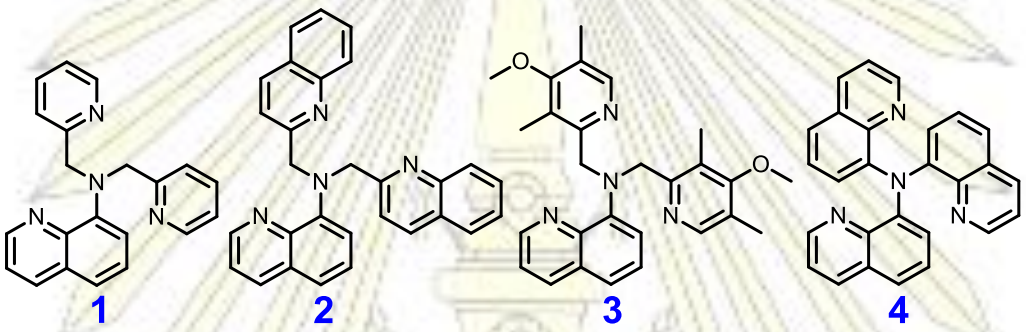


Figure 1.2 The designed ligand for ATRA study in this project

1.3 Objectives

1. To synthesize and characterize a series of ligands and copper complexes containing 8-aminoqionoline derivatives.
2. To study the photo physical property of ligands and complexes.
3. To investigate the photo-catalysis of synthesized complexes for atom transfer radical addition.

CHAPTER II

EXPERIMENTS

2.1 Instruments

1. Balance (AB204-S, Mettler Toledo)
2. Rotary Evaporator (BUCHI Rotavapor R-114)
3. Nuclear Magnetic Resonance Spectrometer (Varian Mercury 400MHz)
4. Mass Spectrometer (micrOTOF-Q II)
5. UV-Visible Spectrophotometer (Agilent Technologies 8453)

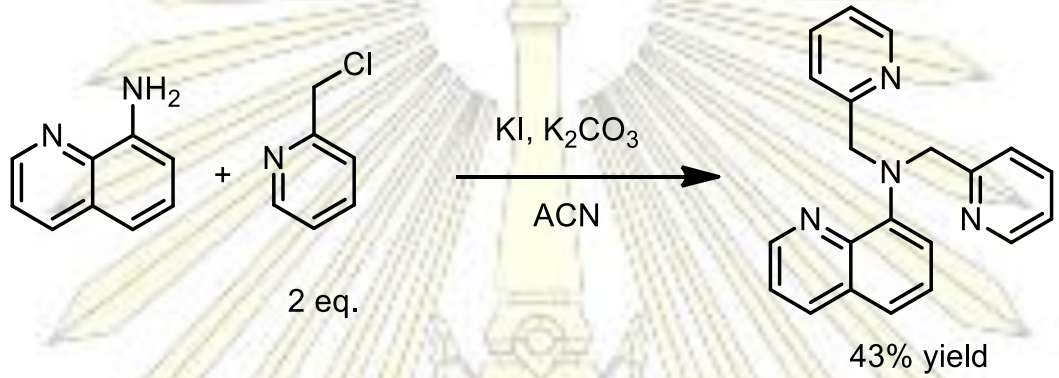
2.2 Chemicals

Chemical name	Abbreviation	Supplier	Grade / purity
8-Aminoquinoline		TCI	98%
2-(chloromethyl)pyridine		TCI	97%
Potassium iodide	KI	Merck	99.5%
Potassium carbonate	K_2CO_3	CARLOERBA	99%
Acetonitrile	ACN	RCI Labscan	AR.
Dichloromethane	DCM	RCI Labscan	CG.
Ethyl acetate	EtOAc	RCI Labscan	CG.
Dimethyl sulfoxide	DMSO	RCI Labscan	AR.
Dimethyl sulfoxide-d_6	DMSO-d_6	CIL	99.9%
2-(chloromethyl)-4-methoxy-3,5-dimethylpyridine		TCI	98%
Methanol	MeOH	RCI Labscan	AR.
Methanol-d_4	MeOH-d_4	CIL	99.8%
Hydrochloric acid	HCl	Merck	AR.
Sodium nitrite	$NaNO_2$	Merck	99%
Sodium hydroxide	NaOH	Merck	99%
Hexane		RCI	CG.
Copper(i) iodide	CuI	Merck	98%
L-proline		Sigma-Aldrich	99%
Tris(pyridin-2-ylmethyl)amine	TPMA	Sigma-Aldrich	98%
Azobisisobutyronitrile	AIBN	Chemieliva	99%
Styrene		Fluka	AR.

Chemical name	Abbreviation	Supplier	Grade / purity
Chloroform	$CHCl_3$	RCI Labscan	99.5%
Carbon tetrachloride	CCl_4	Sigma-Aldrich	
Alumina Oxide 90 active neutral		Merck	
Silica gel 60		Merck	

2.3 Synthesis procedure

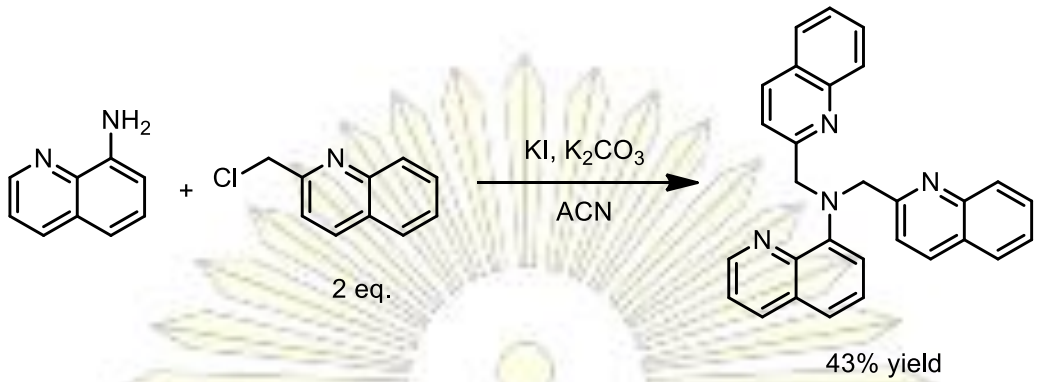
2.3.1 Compound **1**: 8-[bis(2-pyridinylmethyl)amino]quinoline



Scheme 2.1 Synthesis of compound **1**

A mixture of 8-aminoquinoline (0.500 g, 3.468 mmol), 2-(chloromethyl)pyridine (1.4221 g, 8.670 mmol), potassium iodide (0.1726 g, 1.040 mmol) and potassium carbonate (0.5991 g, 4.335 mmol) in a pressure tube was dissolved in acetonitrile (5 mL) and water (3 mL). The solution was stirred at 90 °C for 96 h. After solvent evaporation, the dark brown crude was dissolved in dichloromethane (30 mL) and extracted with water (5 x 30 mL) and dried with anhydrous sodium sulfate. The solvent was evaporated and eluted through an alumina column with 10% ethyl acetate/dichloromethane. After solvent evaporation, the pure product was obtained as a yellow solid. Yield: 0.4963 g, 43%; ^{1}H NMR (400 MHz, DMSO) δ 8.84 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.47 (d, *J* = 4.5 Hz, 2H), 8.27 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.67 (m, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.49 (m, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.30 (m, 1H), 7.20 (m, 2H), 7.04 (d, *J* = 7.6 Hz, 1H), g 4.89 (s, 4H); ^{13}C-NMR (101 MHz, DMSO) δ 159.18, 148.68, 147.48, 146.08, 141.92, 136.49, 136.34, 129.42, 126.37, 121.90, 121.87, 121.08, 120.06, 117.06, 58.67; ESI-MS: calculated for $C_{21}H_{18}N_4Na$: 349.14292, Mass found: 349.15659 $[M+Na]^+$.

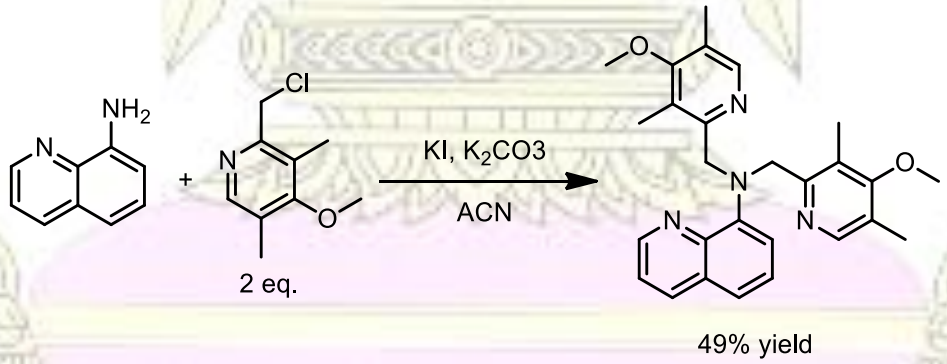
2.3.2 Compound **2**: N,N-bis(quinolin-2-ylmethyl)quinolin-8-amine



Scheme 2.2 Synthesis of compound **2**

This compound was synthesized using a procedure similar to the Compound **1** by starting from 8-aminoquinoline (0.72 g, 5.00 mmol), 2-(chloromethyl)quinoline (2.50 g, 11.70 mmol), potassium iodide (0.66 g, 3.98 mmol) and potassium carbonate (2.00 g, 14.47 mmol). After purification by alumina column chromatography eluted with dichloromethane and solvent evaporation,. The desired product was obtained as a yellow solid. Yield: 1.0323 g, 43%; ^{1}H NMR (400 MHz, DMSO) δ 8.89 (d, *J* = 2.9 Hz, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 8.25 (d, *J* = 8.5 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.87 (m, 4H), 7.71 (t, *J* = 7.5 Hz, 2H), 7.54 (m, 3H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 5.10 (s, 4H); ^{13}C NMR (101 MHz, DMSO) δ 160.29, 147.72, 147.00, 146.20, 142.05, 136.61, 136.30, 129.51, 129.38, 128.43, 127.73, 126.93, 126.40, 126.03, 121.22, 120.38, 120.35, 117.38, 59.52; ESI-MS: calculated for $C_{29}H_{23}N_4$: 427.19227, Mass found: 427.19210 $[M+H]^+$.

2.3.3 Compound **3**: N,N-bis((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)quinolin-8-amine



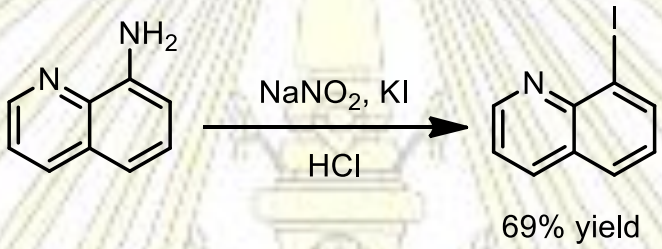
Scheme 2.3 Synthesis of compound **3**

This compound was synthesized using a procedure similar to the Q2P by starting from 8-aminoquinoline (0.72 g, 5.00 mmol), 2-(chloromethyl)-4-methoxy-3,5-dimethylpyridine (2.58 g, 11.62 mmol), potassium iodide (0.66 g, 3.98 mmol) and potassium carbonate (2.00 g, 14.47

mmol). After purification by silica column chromatography eluting with 10% methanol in ethyl acetate and solvent evaporation, the desied product was obtained as a yellow solid. Yield: 1.2707 g, 49%; ^{1}H NMR (400 MHz, DMSO) δ 8.90 (dd, *J* = 4.0, 1.3 Hz, 1H), 8.30 (d, *J* = 8.3 Hz, 1H), 8.10 (s, 1H), 7.58 (s, 1H), 7.56 (s, 1H), 7.50 (dd, *J* = 8.3, 4.0 Hz, 1H), 7.42 (m, 1H), 7.32 (d, *J* = 7.4 Hz, 1H), 4.79 (s, 4H), 3.63 (s, 3H), 3.57 (s, 3H), 2.11 (s, 3H), 1.80 (s, 3H), 1.86 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 176.35, 163.12, 157.00, 148.21, 148.13, 146.93, 143.73, 143.02, 139.77, 136.65, 129.13, 126.39, 124.44, 124.21, 124.06, 123.28, 122.86, 121.32, 121.06, 59.50, 54.73, 50.92, 13.60, 12.74, 11.13, 10.10.; ESI-MS: calculated for $C_{27}H_{31}N_4O_2$: 443.24470, Mass found : 443.24478 $[M+H]^+$.

2.3.4 Compound **4**: tris(8-quinolinyl)amine

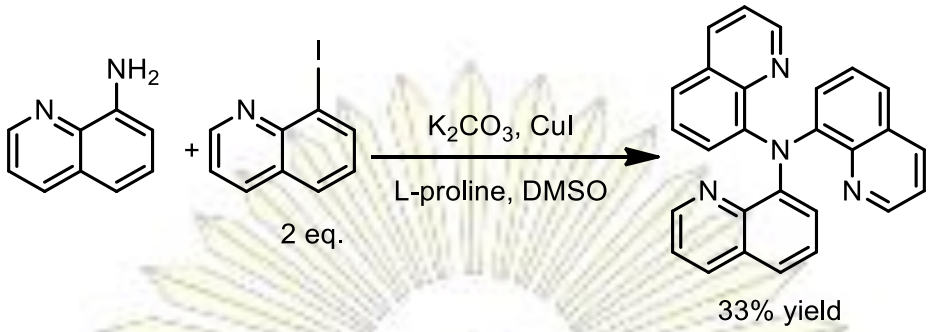
a. Synthesis of 8-iodoquinoline



Scheme 2.4 Synthesis of 8-iodoquinoline

The reaction was setup according to the reported procedure. [32] A mixture of 8-aminoquinoline (1.00 g, 6.94 mmol) in water (3.0 mL) and ice (3.0 g) was gradually added by concentrated hydrochloric acid (3.0 ml) during stirring, which formed a red solution. The solution was chilled in an ice bath and an ice-cool sodium nitrite (0.52 g, 7.54 mmol) in water (3.0 ml) was added to the solution portionwise with stirring. After stirring for 10 minutes the solution of potassium iodide (1.25 g, 7.54 mmol) in water (2.5 mL) was added to the mixture portionwise. Bubbles were formed during the addition and the solution turned to dark brown. After stirring overnight, the solution was heated for 10 minutes. After cooling, black precipitate was filtered out, the filtrate was neutralized by sodium hydroxide until the solution turned basic; the light red oil was noticed at the bottom of the beaker. The dichloromethane (5 x 30 mL) was added to the mixture. After solvent evaporation, the dark crude was obtained. The product was purified by column chromatography on alumina eluting with 10% ethyl acetate in hexane, the yellow oil was received Yield: 1.24 g, 69%; ^{1}H NMR (400 MHz, DMSO) δ 8.98 (d, *J* = 2.2 Hz, 1H), 8.39 (dd, *J* = 12.8, 7.6 Hz, 2H), 8.04 (d, *J* = 7.5 Hz, 1H), 7.62 (dd, *J* = 7.9, 4.1 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H); ESI-MS: calculated for C_9H_7IN: 255.96232, Mass found : 255.96765 $[M+H]^+$.

b. Synthesis of compound **4**



Scheme 2.5 Synthesis of Compound **4**

The reaction was setup according to reported Ullman-type aryl-amination. [33] A mixture of 8-aminoquinoline (0.3494 g, 2.42 mmol), 8-iodoquinoline (1.36 g, 5.33 mmol), potassium carbonate (1.338 g, 9.68 mmol), copper iodide (0.0922 g, 0.484 mmol) and L-proline (0.1115 g, 0.968 mmol) in pressure tube was dissolved in DMSO (4 mL). After that the solution was stirred at 150 ˚C for 96 hours. The dark brown crude was extracted after solvent evaporation with dichloromethane and water for five times and dried with anhydrous sodium sulfate. The product was purified by column chromatography on alumina eluting with 50% hexane in ethyl acetate, After solvent evaporation, the yellow solid was received Yield: 0.3187 g, 33%. ^{1}H NMR (400 MHz, DMSO) δ 8.37 (d, *J* = 3.9 Hz, 1H), 8.27 (d, *J* = 8.2 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.41 – 7.28 (m, 2H), 7.00 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 148.15, 147.70, 142.70, 135.91, 129.28, 126.47, 124.24, 122.73, 120.84. ESI-MS: calculated for $C_{27}H_{19}N_4$: 399.16097, Mass found: 399.16802 $[M+H]^+$.

2.4 Study of photoredox ATRA catalysis

2.4.1 Ligand evaluation

Stock solutions of copper(II) chloride (0.1 M), each ligand (TPMA and **1**-**4**, 0.1 M) and azobisisobutyronitrile (AIBN) were all prepared in methanol-d_4. A reaction was setup by using of styrene and carbontetrachloride as starting materials, AIBN as a reducing agent and the copper-ligand complex generated in-situ as a catalyst in NMR-tube with total volume of 500 µL. The final concentrations of the reactants are presented in Table 2.1. The small magnetic bar was added to each tube. The reaction tubes were purged with argon for 30 s, capped with a rubber stopper and sealed with parafilm. The reaction tubes were placed under white light (CFL 32 W) at ~ 10 cm distance from the bulk, for 24 h. A cooling fan was used to maintain the reaction temperature at 40 ± 2 ˚C. After 24 h the magnetic bar was removed

and the product yield was determined by ^{1}H NMR. The reactions between styrene and chloroform were also studied using the same procedure.

Table 2.1 Concentrations of reagents used in ligand evaluation

Run	Concentration (M)				
	Styrene	CCl_4 or $CHCl_3$	AIBN	$CuCl_2$	Ligand
1-5	1.00	1.50	0.05	0.01	0.01

2.4.2 Study of reagent significance in photoredox catalysis

Reagent significance in photoredox catalysis was studied from the reaction of styrene and chloroform. The presence of AIBN reducing agent, copper complex and light were evaluated against their respective blank control using the same methodology as the previous section. The final concentration of reactants are presented in Table 2.2.

Table 2.2 Concentrations of reagents used in study of reagent significance

Run	Concentration (M)				
	Styrene	Chloroform	AIBN	$CuCl_2$	Compound 1
1	1.00	1.50	0.05	0.01	0.01
2	1.00	1.50	0.00	0.01	0.01
3	1.00	1.50	0.05	0.00	0.01
4	1.00	1.50	0.05	0.01	0.00
5 (Dark)	1.00	1.50	0.05	0.01	0.01

2.5 Photophysical property study

2.5.1 UV-Visible spectroscopy

The stock solution of 1 mM copper(II) chloride and ligands in methanol were prepared. The absorption spectra of all ligands and copper complexes were recorded from methanol solutions (10 μM) in the wavelength range of 230-700 nm at ambient temperature.

2.5.2 Molar absorptivity coefficients (**ε**)

Molar absorptivity coefficients (**ε**) of all ligands and copper complexes in methanol were estimated from UV-vis absorption spectra in the concentrations range of 10-50 μM. The intensities at maximum absorption wavelength of each compound were plotted against the concentration. Each plot is set to be a straight line going through the 0 origin. Molar absorptivity coefficients (**ε**) can be obtained from the slopes of these plots according to the following equation:

$$A = \varepsilon bC$$

*b is the cell path length.

2.6 Metals detection

The stock solutions of ($Ba(NO_3)_2$, $Ca(NO_3)_2$, $Mg(NO_3)_2$, KNO_3, $NaNO_3$, $LiNO_3$, $Cu(NO_3)_2$, $Ni(NO_3)_2$, $Co(NO_3)_2$, $Fe(NO_3)_3$, $Cr(NO_3)_3$, Na_2HAsO_4, $Cd(NO_3)_2$, $AgNO_3$, $Pb(NO_3)_2$, $Al(NO_3)_3$, $Zn(NO_3)_2$, $FeCl_2$, $RuCl_3$, $CuCl_2$, $ZrCl_4$, $Mn(NO_3)_2$ and $PdCl_2$) at 10 mM were prepared in Milli-Q water. The stock solution of 10 mM TPMA and compound **1**-**4** were prepared in dimethylsolfoxide. A pair of the metal ion solution (10 μL) and the compound **1-4** or TPMA solution (10 μL) was individually added to 96-well plate and adjust by adding acetonitrile to obtain the final concentrations of metal ion and ligand of 0.001 M.

Chapter III

Results and discussion

In this study, a series of 8-aminoquinoline derivatives was synthesized and studied as a ligand in Cu-mediated atom transfer radical addition (ATRA) reaction in comparison with TPMA. The structures of the ligands are shown along with TPMA in Figure 3.1. These ligands are designed with the purpose to investigate the effect of replacing the pyridylmethyl group in TPMA with 8-quinolyl groups which should coordinate with Cu(II) ion with similar geometry but different electronic property. Compound **1** has one of the pyridylmethyl groups in TPMA replaced with 8-quinolyl group. Compound **2** has two pyridine rings in compound **1** replaced by two 2-quinolylmethyl group. Compound **3** has two pyridine rings substituted with electron donating methoxy and methyl groups. Compound **4** has all three pyridylmethyl groups in TPMA replaced by 8-quinolyl groups. Compound **1-4** were characterized by ^{1}H-NMR, ^{13}C NMR and MS.

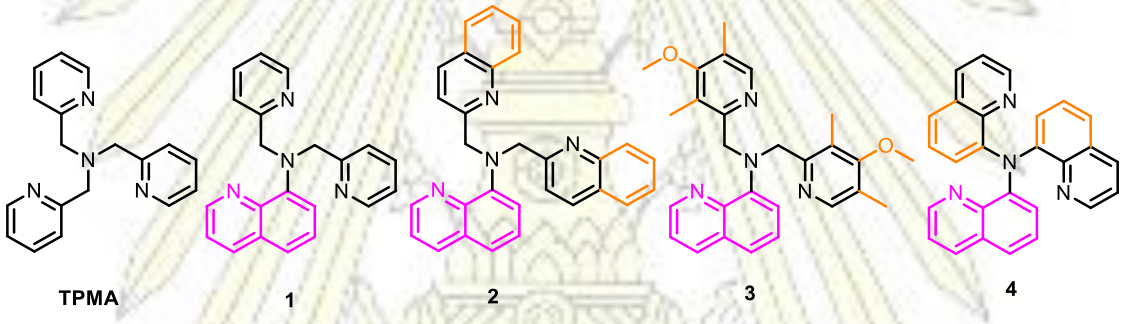
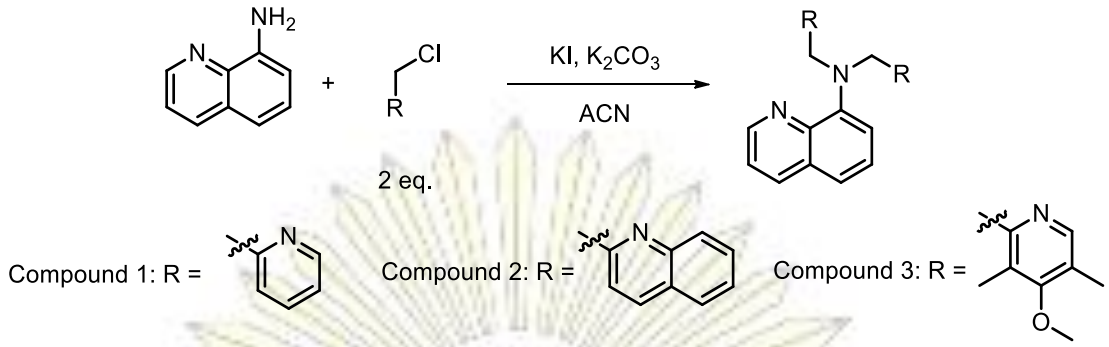


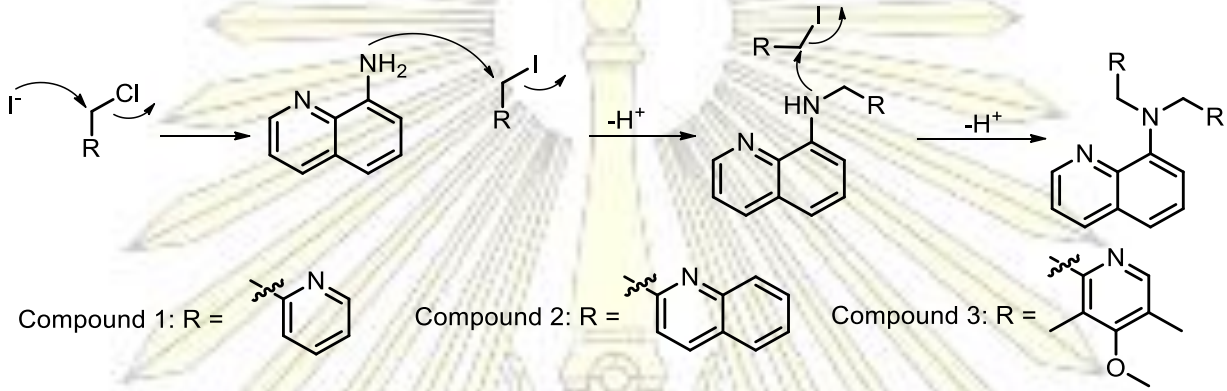
Figure 3.1 Structures of ligands

3.1 Synthesis of ligands

Compounds **1-3** were synthesized from alkylation of 8-aminoquinoline with 2-(chloromethyl)pyridine, 2-(chloromethyl)quinoline and 2-(chloromethyl)-4-methoxy-3,5-dimethylpyridine, respectively with KI as a catalyst and K_2CO_3 as a base (Scheme 3.1). The reactions underwent S_N2 mechanism as shown in Scheme 3.2. The iodide ion acts as a nucleophile attacking alkylchloride to generate the more reactive alkyliodide intermediate which is in turn attacked twice by the amino nucleophile of quinoline to form the products **1-3** in 43%, 43% and 49% yields, respectively.

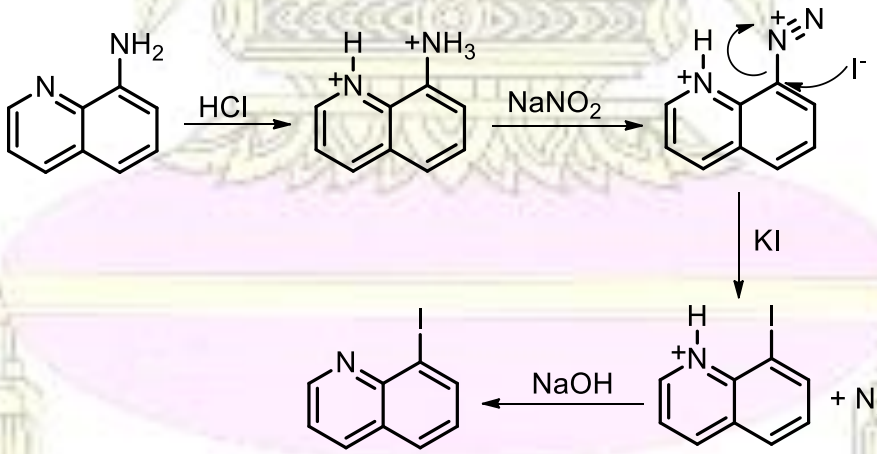


Scheme 3.1 Synthesis of compounds **1-3**



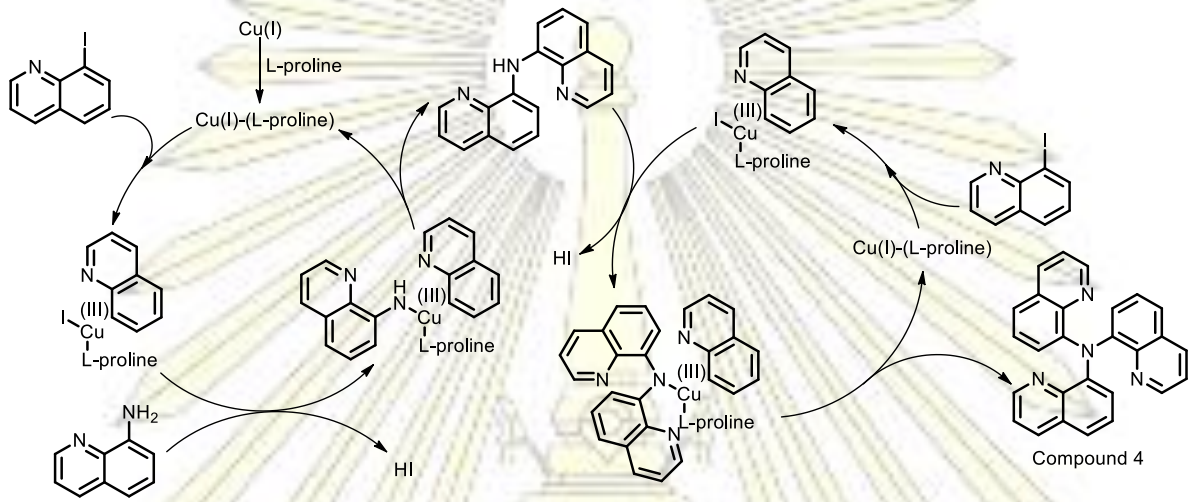
Scheme 3.2 S_N2 mechanism in the synthesis of compounds **1-3**

Compound **4** was synthesized in two steps; In the first step, 8-iodoquinoline was synthesized via the diazotizonium salt generated from 8-aminoquinoline (Scheme 3.3). The protonation by concentrated HCl increased the solubility of 8-aminoquinoline in water that allow a conversion of the amino group to diazonium salt upon addition of sodium nitrite. The diazo group is a strong electron withdrawing group and is a very good leaving group that facilitate the attack by the iodide anion via an S_NAr mechanism.



Scheme 3.3 Reaction mechanism for 8-iodoquinoline synthesis

In the second step, compound **4** was synthesized from Ullman-type aryl-amination reaction between 8-iodoquinoline and 8-aminoquinoline. The mechanism of this reaction is proposed in Scheme 3.4. Starting from Cu(I) complexation, the oxidative addition reaction of Cu(I)-(L-proline) with 8-iodoquinoline generated Cu(III) intermediate. Next, the ligand exchange of iodide ion with 8-aminoquinoline, with an elimination of HI, followed by reductive elimination of diquinolylamine. The reaction cycle is repeated to generate compound **4** in moderate yield. [34]



Scheme 3.4 Mechanism of Ullman-type aryl-amination reaction

3.2 Product characterization

For NMR characterization, ^{1}H NMR spectra of compound **1**-**4** are shown in Figure 3.2. The proton signals of aminoquinoline moiety (a-f) of all compounds showed similar pattern around 7.0-9.0 ppm with some difference in chemical shifts of the individual protons. The proton signals of compound **4** are the most upfield probably due to the anisotropy shielding effect from the ring-current of the quinoline propeller. In compounds **1**-**3**, the signals of methylene groups (g) were found around 4.5-5.0 ppm while the signals of pyridyl and 2-quinolyl groups (h-l) were consistently found around 7.0-8.7 ppm. Interestingly, the signals of methyl and methoxy substituents (x-z and x′-z′) as well as the aromatic protons (h and h′) on the two pyridine rings in compound **3** were separated into two sets found around 1.5-3.7 ppm presumably due to the restricted rotation of the highly steric substituted pyridine rings.

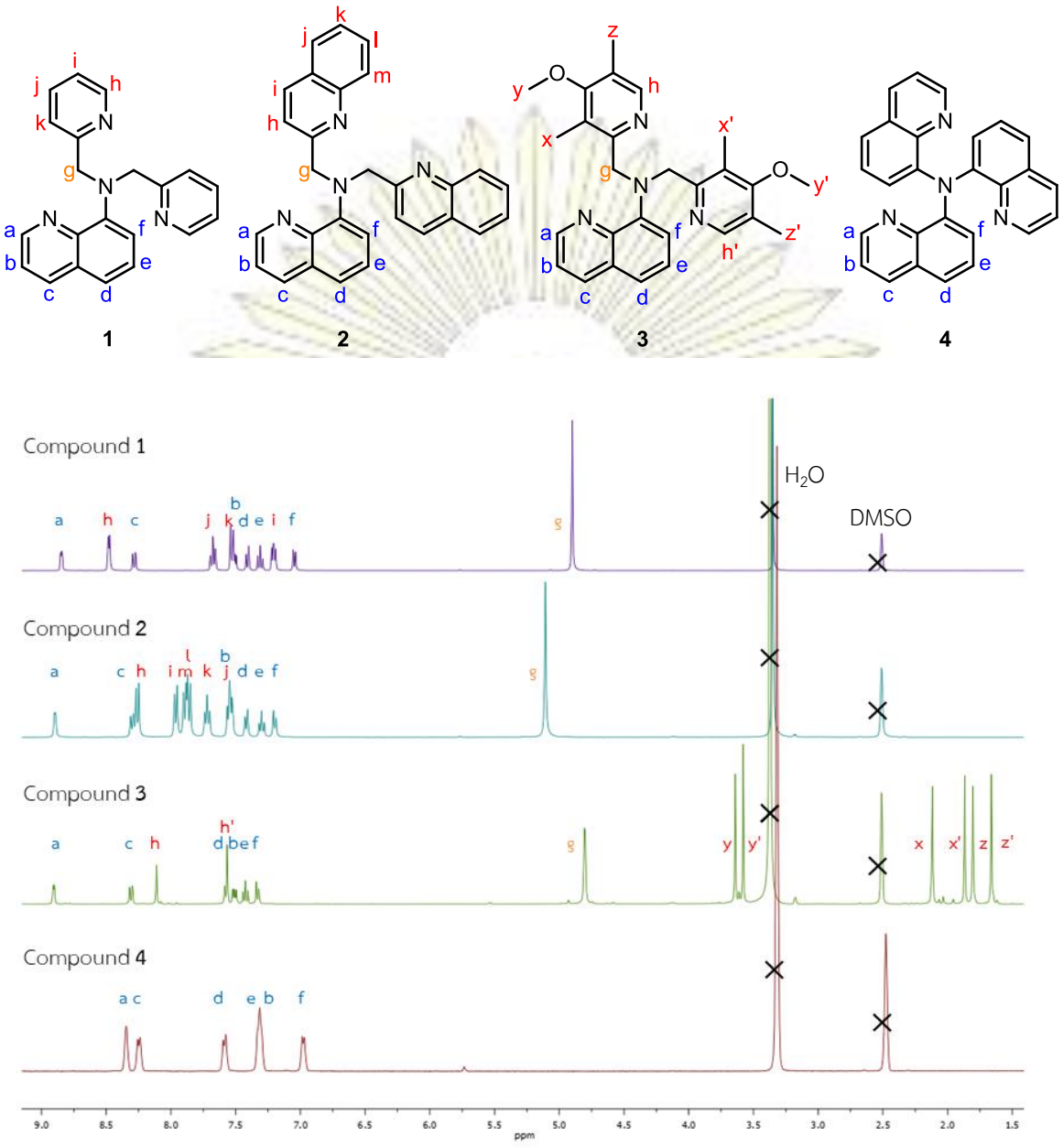
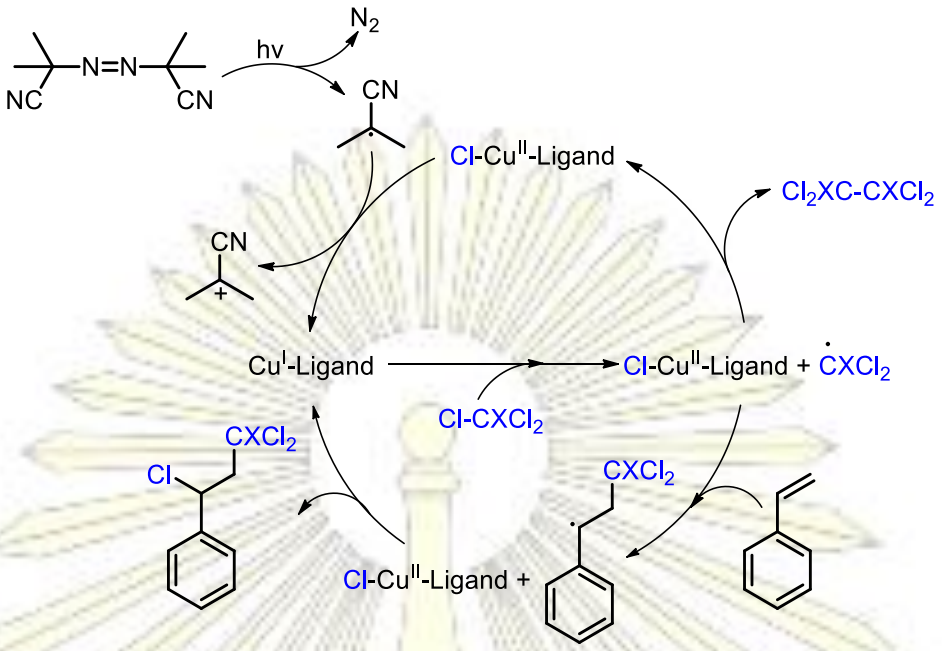


Figure 3.2 ^{1}H NMR characterization of compound **1-4**

3.3 Study of Cu-photocatalyzed ATRA

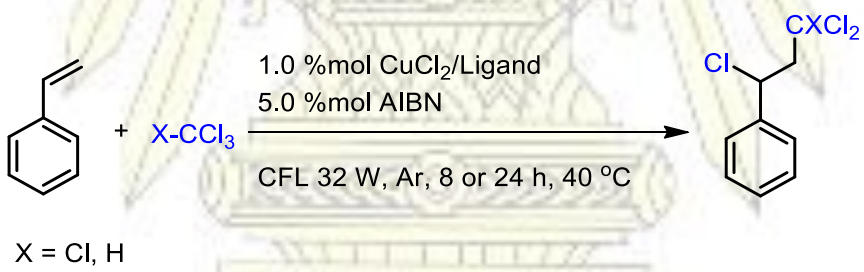
A well accepted mechanism of Cu-photocatalyzed atom transfer radical addition (ATRA) reaction is shown in Scheme 3.5. The initial step is metal induced homolytic cleavage of the carbon-halogen bond. This step generates a metal-halide and alkyl radical. The generated alkyl radical then adds to a double bond to afford another alkyl radical intermediate which rapidly abstracts halogen atom from the metal-halide to regenerate the active metal species for the next reaction cycle. The desired addition product is continuously formed.



Scheme 3.5 Mechanism of Cu-photocatalyzed atom transfer radical addition (ATRA) reaction

3.3.1 Ligand evaluation

The synthesized compounds were evaluated as a potential ligand, in comparison with TPMA, for Cu-photocatalyzed ATRA reaction of styrene with CCl_4 and $CHCl_3$. The addition reactions were conducted under white light with copper(II) complexes generated in-situ and in the presence of AIBN as a reducing agent (Scheme 3.6). The reaction progress was studied by ^{1}H NMR spectra acquired at the reaction time of 8 and 24 hr.



Scheme 3.6 Cu-photocatalyzed ATRA reaction of styrene

The yields of the addition products were determined from the ^{1}H NMR signal integration of the selected proton in the styrene adduct and styrene starting material according to the equation: %yield = 100 × $I_p/(I_p+I_s)$. I_p and I_s are the integrations of the selected proton in the styrene adduct and styrene starting material respectively. From the typical ^{1}H NMR spectrum shown in Figure 3.3, the signals of proton a', b', c', d' and a, b, c were selected for the product and starting material, respectively. The %yields shown in Figure 3.4 are the average from three repetitive reactions.

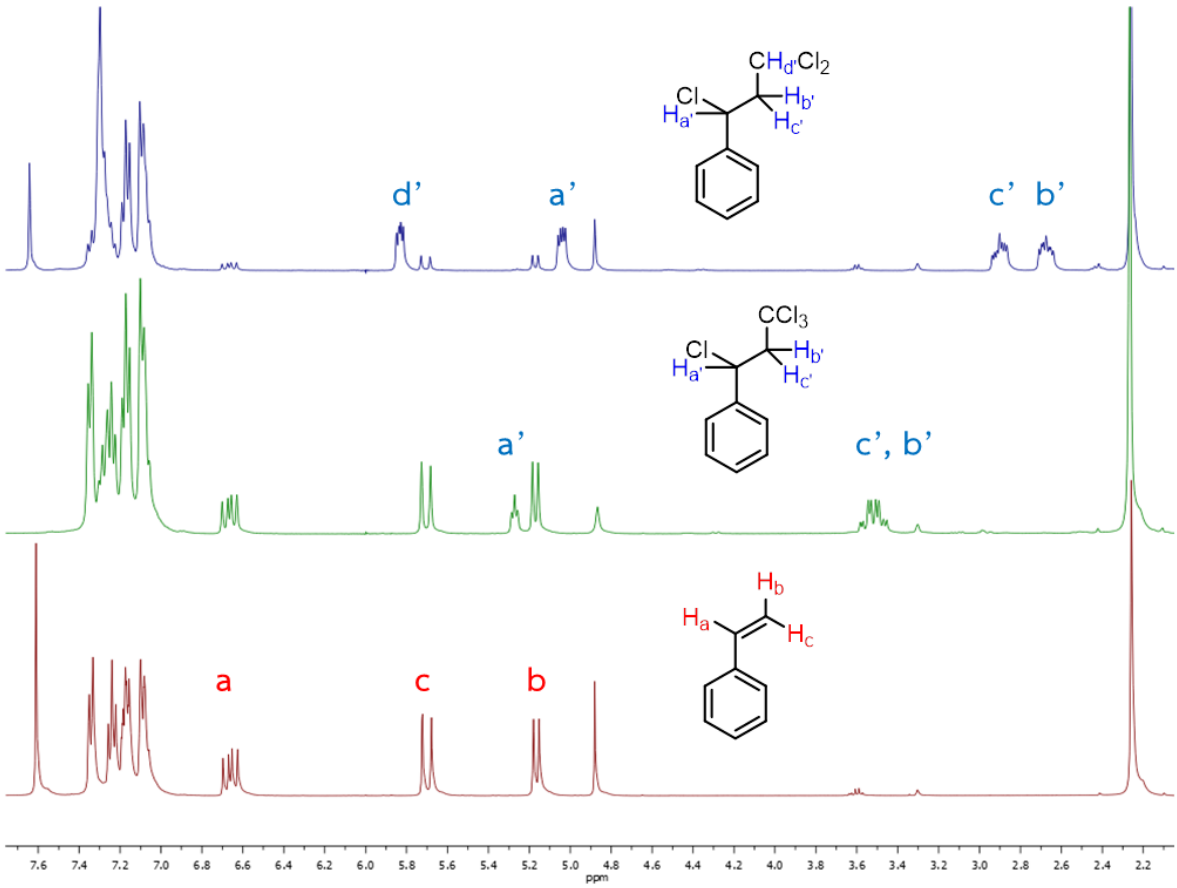


Figure 3.3 ^{1}H NMR spectrum of %yields calculation

For CCl_4, high yields of styrene adduct was observed with over 80% yield at 8 h when TPMA, **1**, **2** and **4** were used as the ligands. With **3** as the ligand, a low yield of only around 35% was observed. This low yield may be attributed to the steric hindrance of the ligands. For a less active alkyl halide, $CHCl_3$, only ligand **1** gave over 80% yield of the styrene adduct after 24 hr. TPMA gave moderate yield of 58% while ligand **2**-**4** gave low yields of less than 30%. These results suggested that the replacement of one pyridylmethlyl group with quinolyl group can enhance the photocatalytic property of the copper complex for ATRA reaction. The explanation for this effect will need further investigation including the structure of copper-ligand complex.

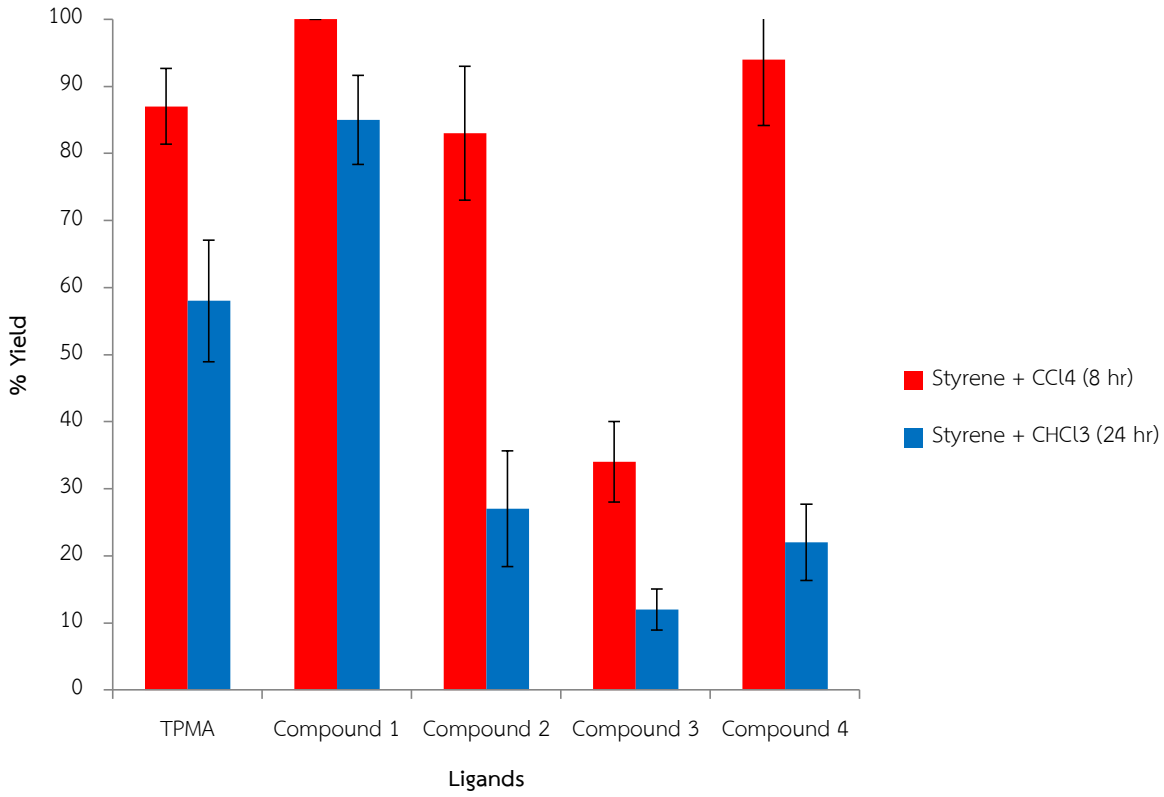
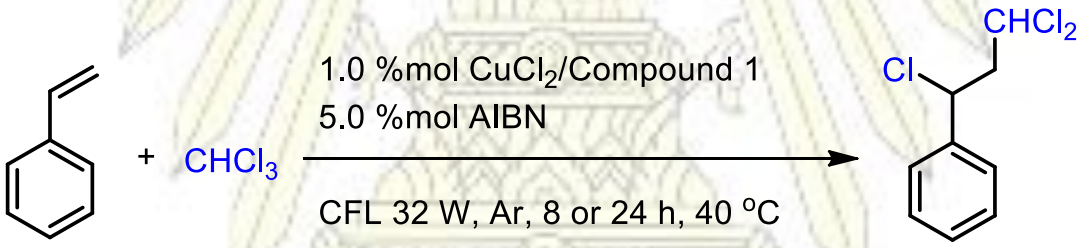


Figure 3.4 Yield of product from Cu-photocatalyzed ATRA of styrene with CCl_4 and $CHCl_3$ using 1.0 % mol of $CuCl_2$-ligand (TPMA and **1-4**) in the presence of 5.0 % mol AIBN.

3.3.2 Study of reagent significance in Cu-photocatalyzed ATRA



Scheme 3.5 Cu-photocatalyzed ATRA reaction used in study of reagent significance

The significance of Cu(II) ion, ligand, AIBN and light in ATRA reaction of styrene with chloroform were studied and the results are shown in Table 3.1. Only Run 1, in which Cu(II) ion, ligand, AIBN and light are present, gave high yield of product of over 88% implied that all of these reagents are important for this ATRA reaction. In the absence of AIBN (Run 2), the reaction gave moderate yield of 54% that confirmed the significance of AIBN. In this reaction, AIBN presumably photo-decomposes to form 2-cyanoprop-2-yl which reduces the initial Cu(II) complex to the active Cu(I) complex. Without AIBN, either the ligand itself or solvent may serve as the reducing agent. If the ligand acts as the reducing agent, it may be deprived from the Cu-complex. In the absence of copper or ligand showed no reaction (Run 3-4). This

indicates the significant role of *in situ* complex as catalyst. In the absence of light (Run 5), the reaction gave low yield of 16% that is probably due to an inefficient decomposition of AIBN to 2-cyanoprop-2-yl at 40 $^{\circ}$C used in this study. This also implied the role of light for excite the copper (I) complex in this reaction.

Table 3.1 Effect of reagents on ATRA reaction of styrene with $CHCl_3$

Run	Concentration (M)			%Yield
	AIBN	$CuCl_2$	Compound 1	
1	0.05	0.01	0.01	88
2	0.00	0.01	0.01	54
3	0.05	0.00	0.01	0
4	0.05	0.01	0.00	0
5 (Dark)	0.05	0.01	0.01	16

3.4 Photophysical property study

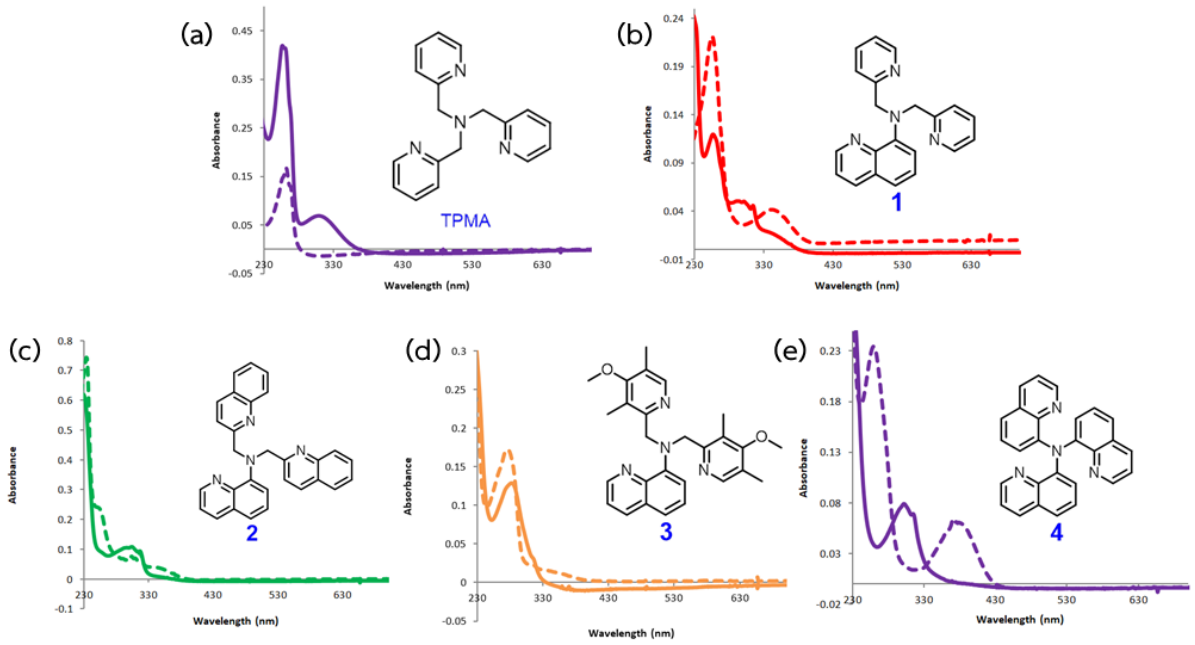


Figure 3.5 (a), (b), (c), (d) and (e) spectra of ligands and copper complexes of 10 μM TPMA, compound **1**-**4** respectively. (▬ ▬ ▬ Ligand, ▬▬▬ Complex)

The normalized electronic absorption spectra of TPMA, compound **1**-**4** and their copper complexes in methanol are shown in Figure 3.5 and their photophysical data are summarized in table 3.2. TPMA showed a single absorption maximum at 262 nm corresponding to the pi-pi* transition of the pyridine ring. The absorption of **1**-**4** showed two

absorption maxima at the wavelength both shorter and longer than 300 nm. The absorption maximum at the shorter wavelength cannot be attributed to the pi-pi* transition of pyridine ring alone as the molar absorptivity of this peak in **1**-**4** is significantly higher than that of TPMA which has three pyridine ring. The fact that very high molar absorptivity of this peak observed for **4**, which has only quinolyl group without pyridine ring, also confirms that this peak is more likely to associate with the pi-pi* transition of the aminoquinoline moiety. The absorption maximum at the longer wavelength may be attributed to either the pi-pi* or n-pi* transition of the aminoquinoline moiety. Further investigation such as quantum calculation may be used to identify the transition associated to this absorption.

The spectra of Cu(II) complexes of all ligands showed an absorption maximum around 300 nm which is probably associated with the metal to ligand charge transfer (MLCT, d_{metal}-pi^*_{ligand} transition). As 1 and 4 the higher catalytic activity than TPMA might due to better the absorption ability of quinoline moieties in its structure. While the molar absorptivity plays less significant.

Table 3.2 Molar absorptivity coefficients (**ε**) of TPMA and compound **1-4** and complexes

	Ligand		Copper complex	
	Wavelength (nm)	Molar absorptivity (**ε**)	Wavelength (nm)	Molar absorptivity (**ε**)
TPMA	262	8,700	257	8,687
			311	1,446
Compound **1**	255	21,407	257	12,765
	341	3,521	314	4,935
Compound **2**	255	22,792	304	10,193
	317	9,022		
Compound **3**	276	17,720	282	13,929
	315	2,459	-	-
Compound **4**	260	23,421	302	8,424
	370	6,656		

3.5 Metal ions sensing study

The photographs of metal ions sensing study of TPMA and **1**-**4** in acetronitrile are shown in Figure 3.6. Compound **1** showed strong green emission with the addition of Cd^{2+}

ion. Compound **2** showed low emission response to all metal ions tested. Compound **3** showed interesting red emission to several metal ions. Compound **4** showed surprisingly strong green emission with Na^{+} ion under the tested condition. These screening results suggested that **1**, **3** and **4** are interesting for further sensitivity and selectivity study and solvent optimization for metal ion sensing applications.

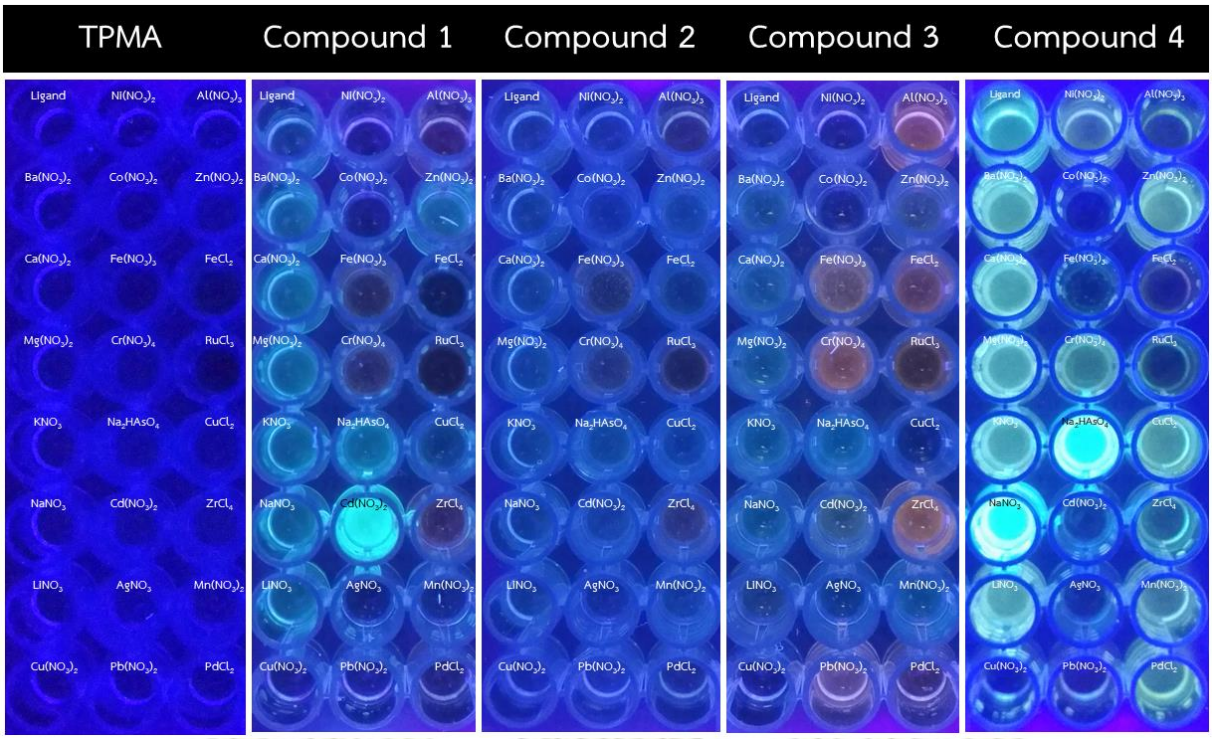


Figure 3.6 Photographs of metal ions sensing study of TPMA and **1-4** in acetronitrile under black light illumination.

CHAPTER IV

CONCLUSION

Four nitrogen based ligand derivatives (compound **1**-**4**) of 8-aminoquinoline were successfully synthesized and characterized. The copper complex with compound **1** obtained highest yield over 80% in photocatalyzed ATRA between styrene and carbontetrachloride or chloroform under irradiation of white light (CFL 32 W) in the presence of azobisisobutyronitrile (AIBN) as a reducing agent. The significance of Cu(II) ion, ligand, AIBN and light were investigated for this reaction. In addition, further investigation of quantum calculation and redox potential measurement might be used to explain catalytic activity of synthesized complexes and design for more active catalyst. Furthermore, compound **1**, **3** and **4** are promising for further study and optimization for metal ion sensing applications.

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APPENDIX

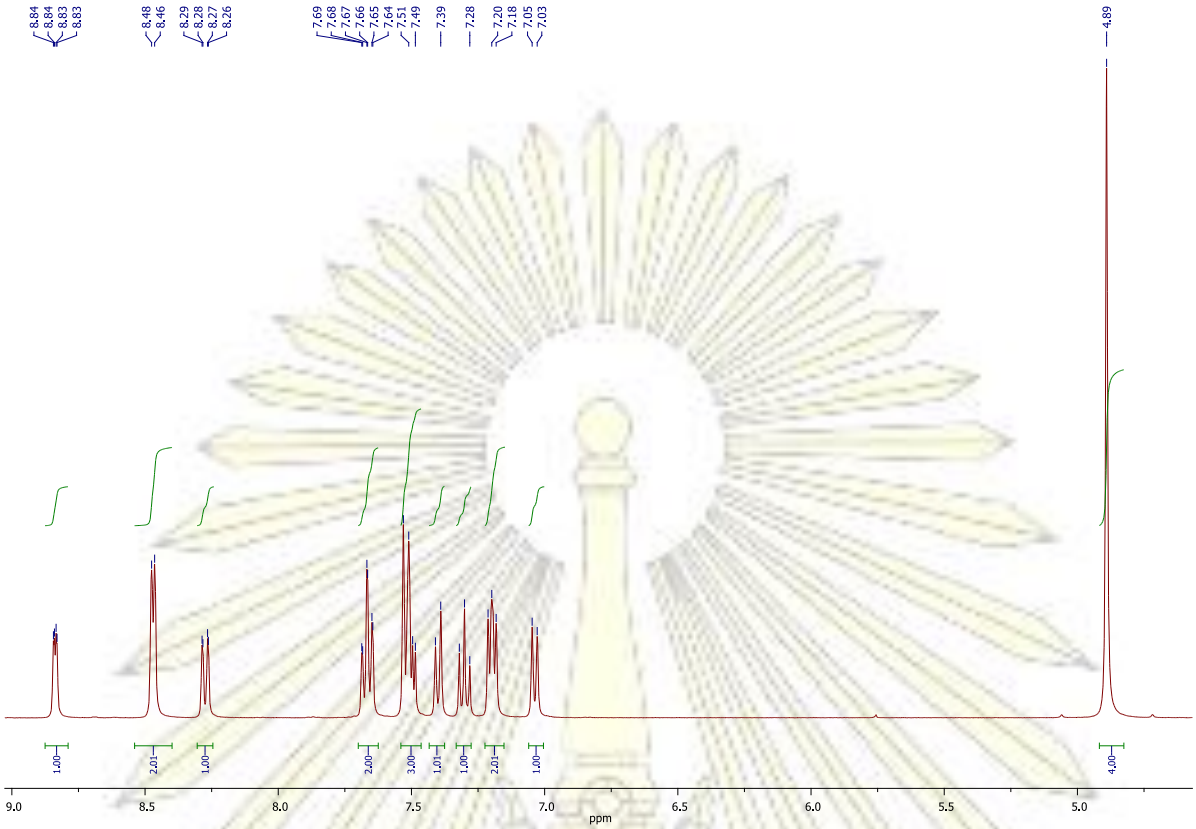

Figure A.1 ^{1}H NMR spectrum (DMSO) of compound **1**

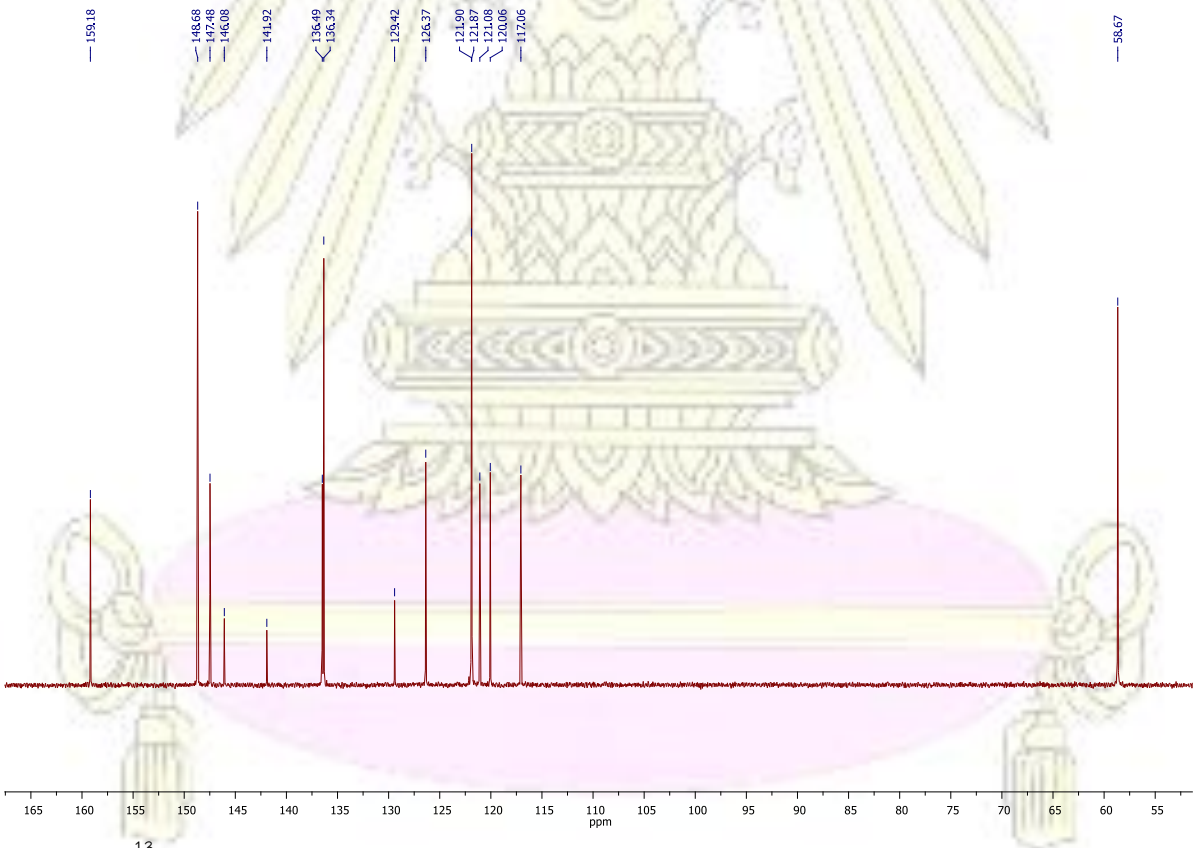

Figure A.2 ^{13}C NMR spectrum (DMSO) of compound **1**

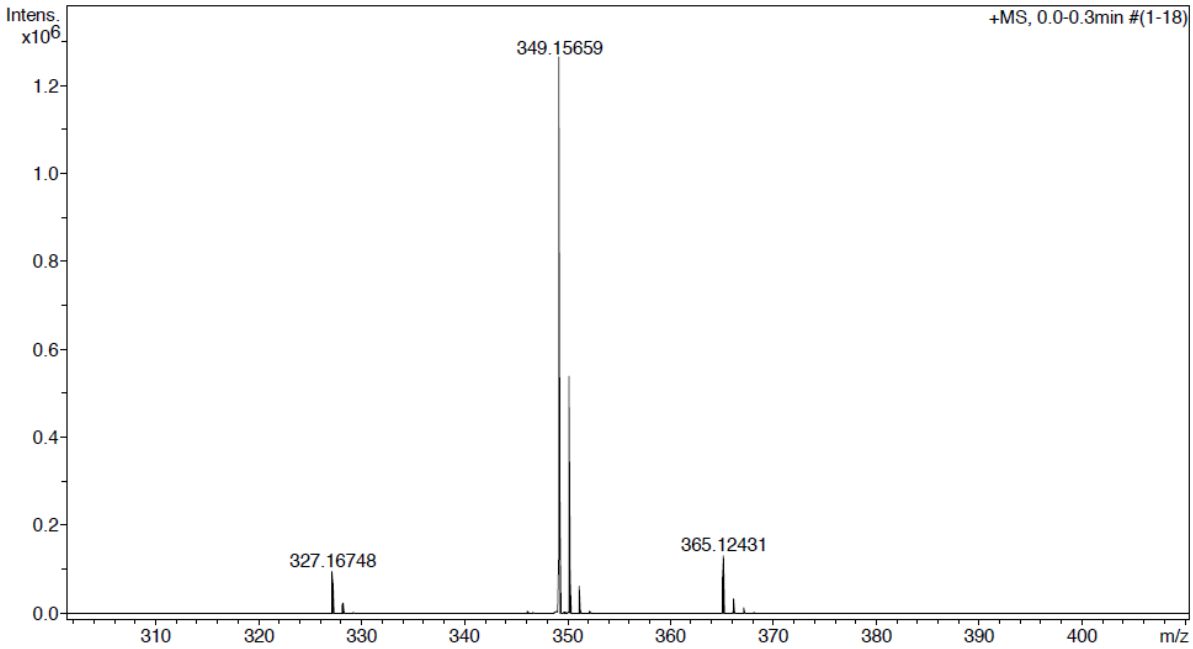

Figure A.3 Mass spectrum of compound **1**

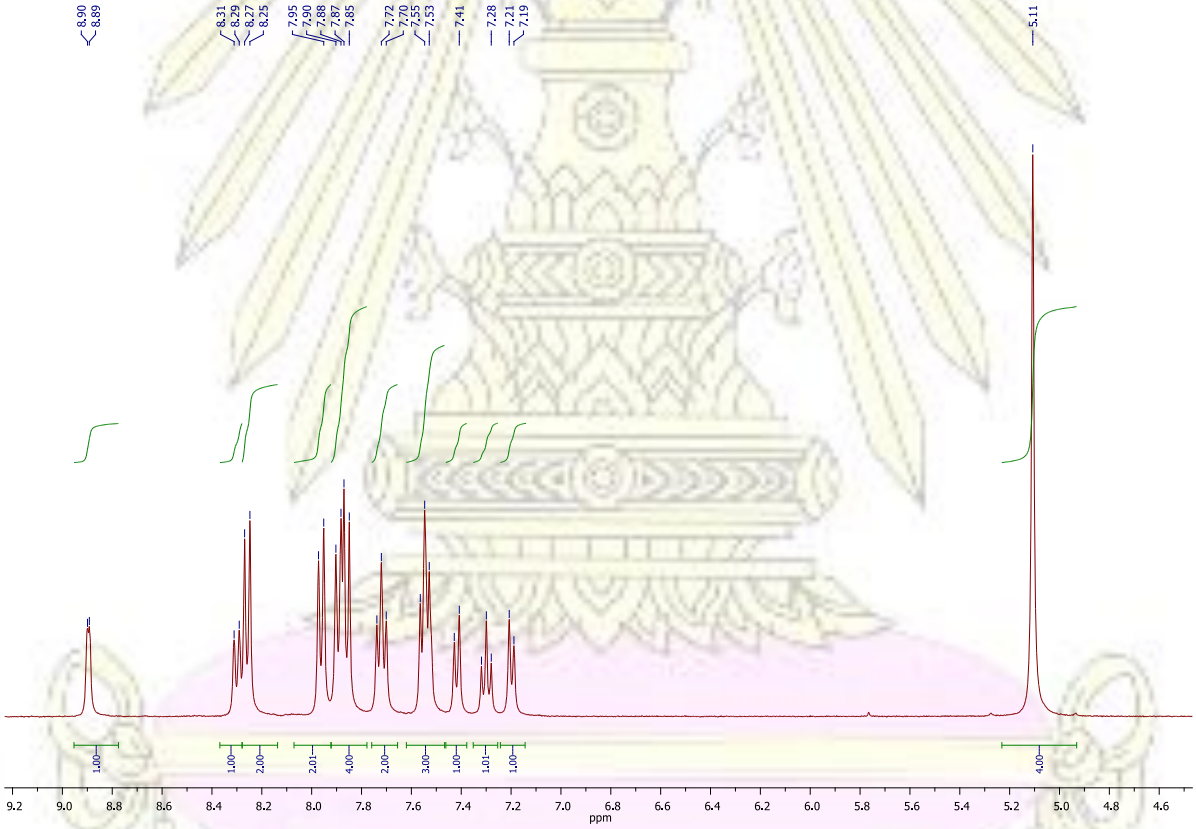

Figure A.4 ^{1}H NMR spectrum (DMSO) of compound **2**

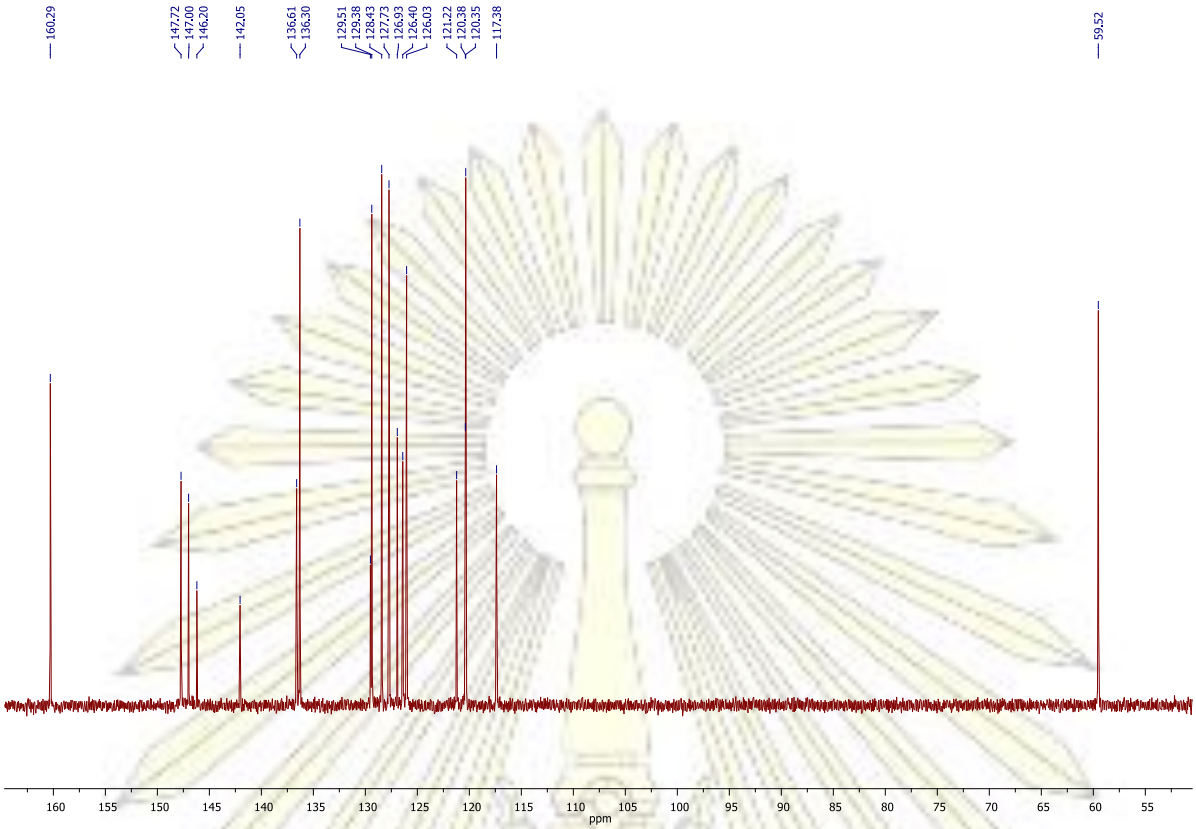

Figure A.5 ^{13}C NMR spectrum (DMSO) of compound **2**

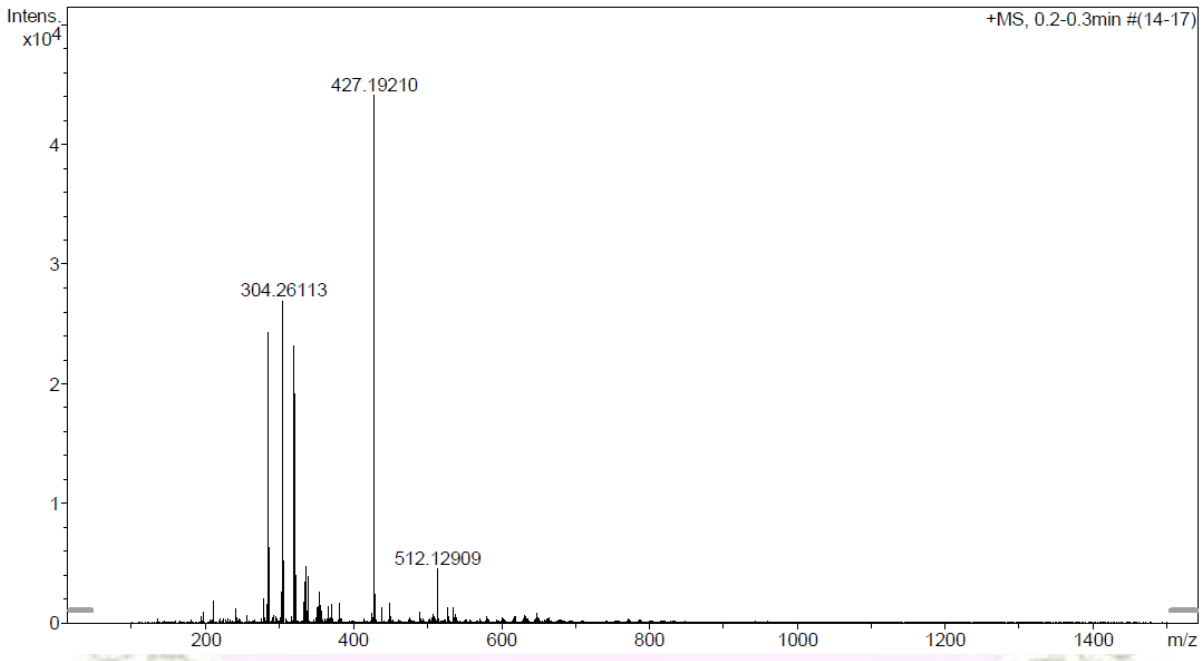

Figure A.6 Mass spectrum of compound **2**

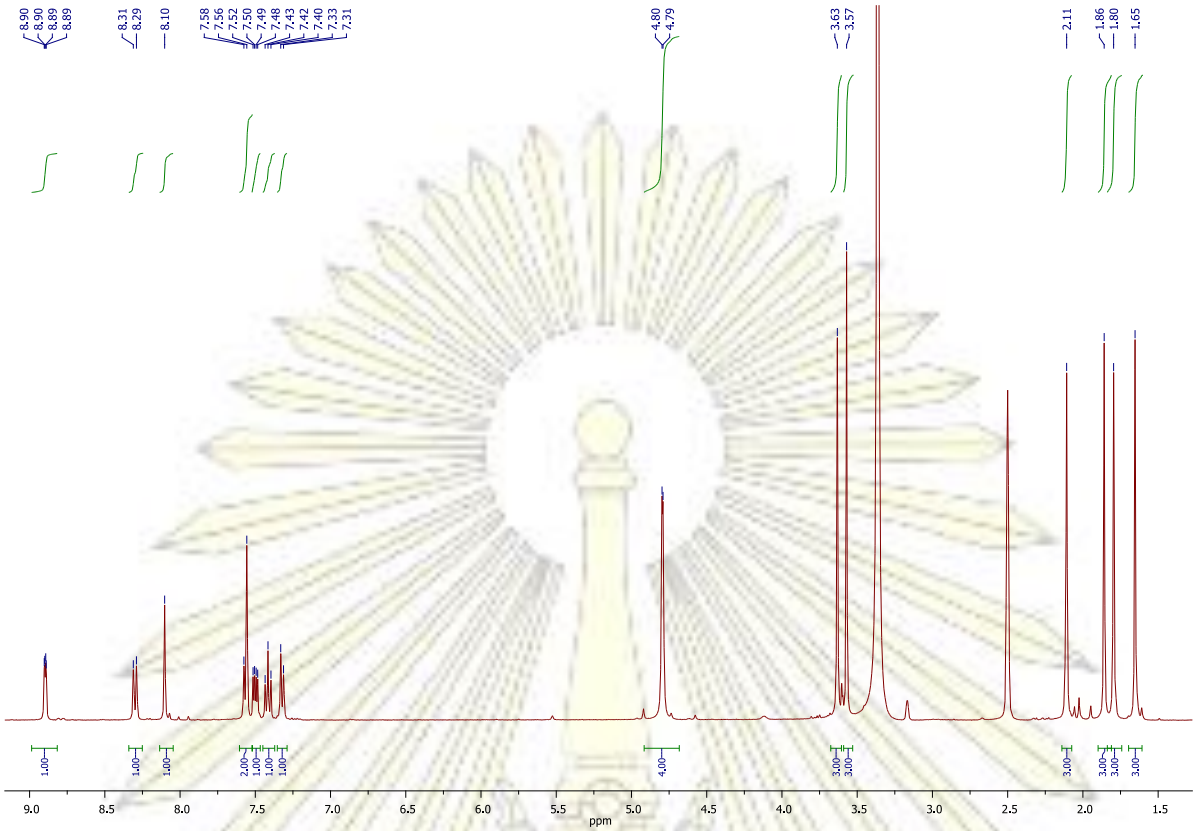

Figure A.7 ^{1}H NMR spectrum (DMSO) of compound **3**

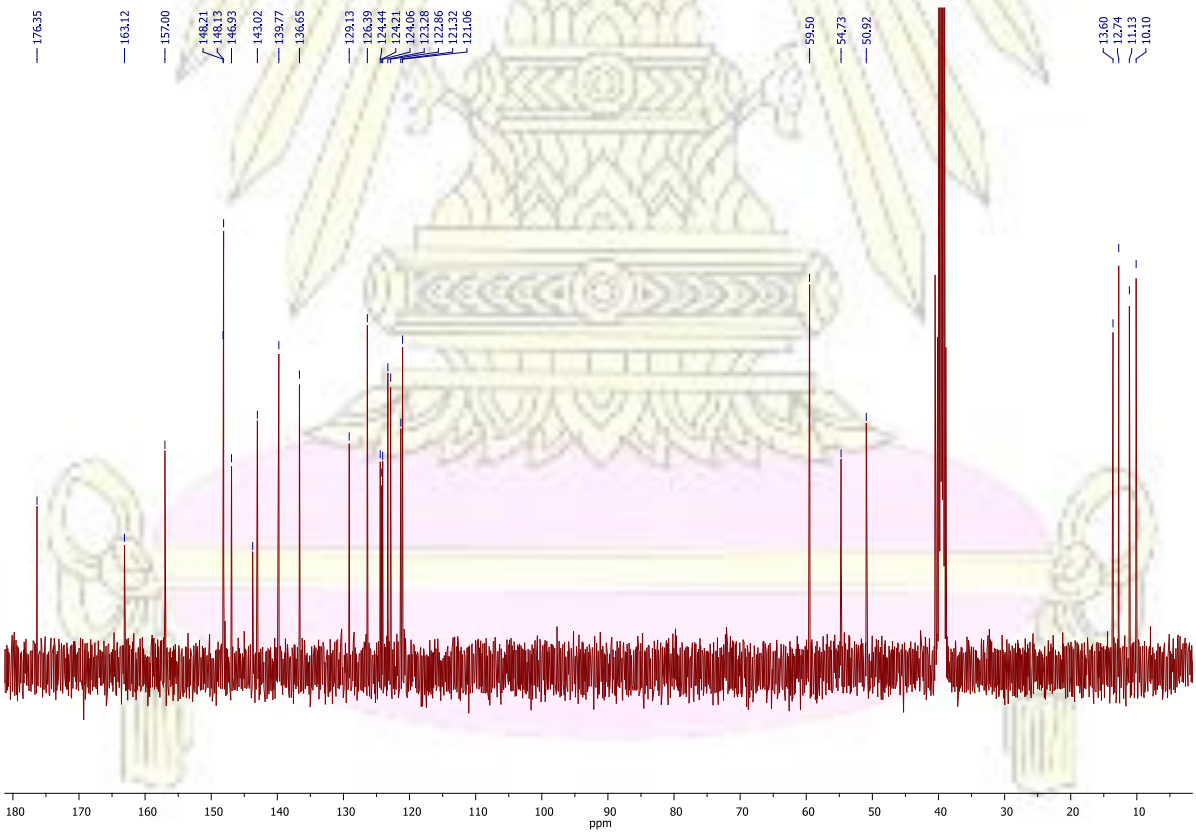

Figure A.8 ^{13}C NMR spectrum (DMSO) of compound **3**

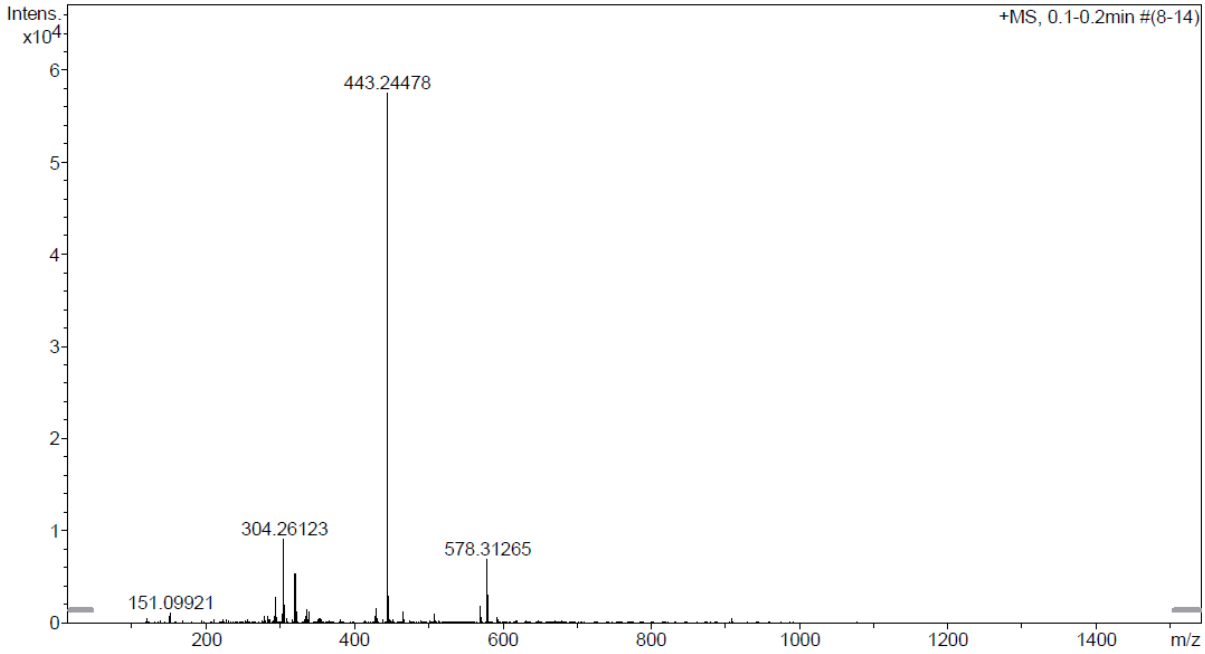

Figure A.9 Mass spectrum of compound **3**

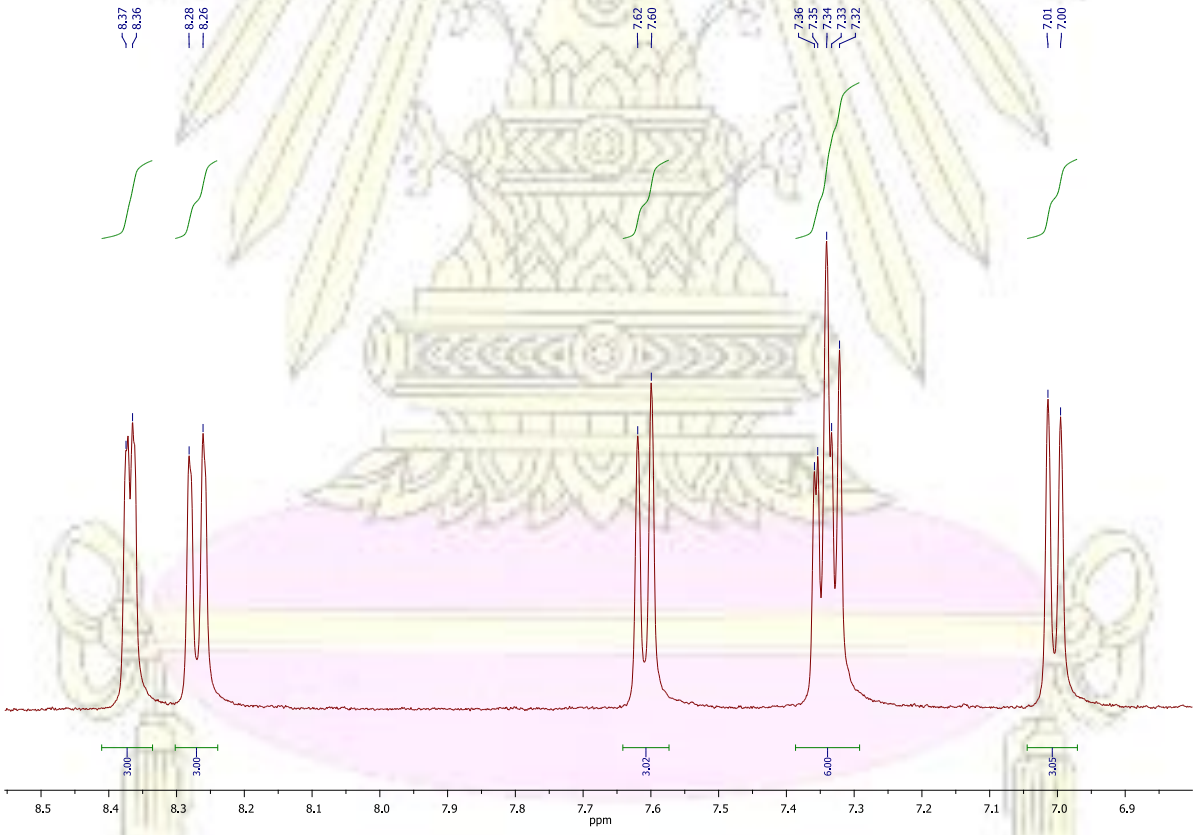

Figure A.10 ^{1}H NMR spectrum (DMSO) of compound **4**

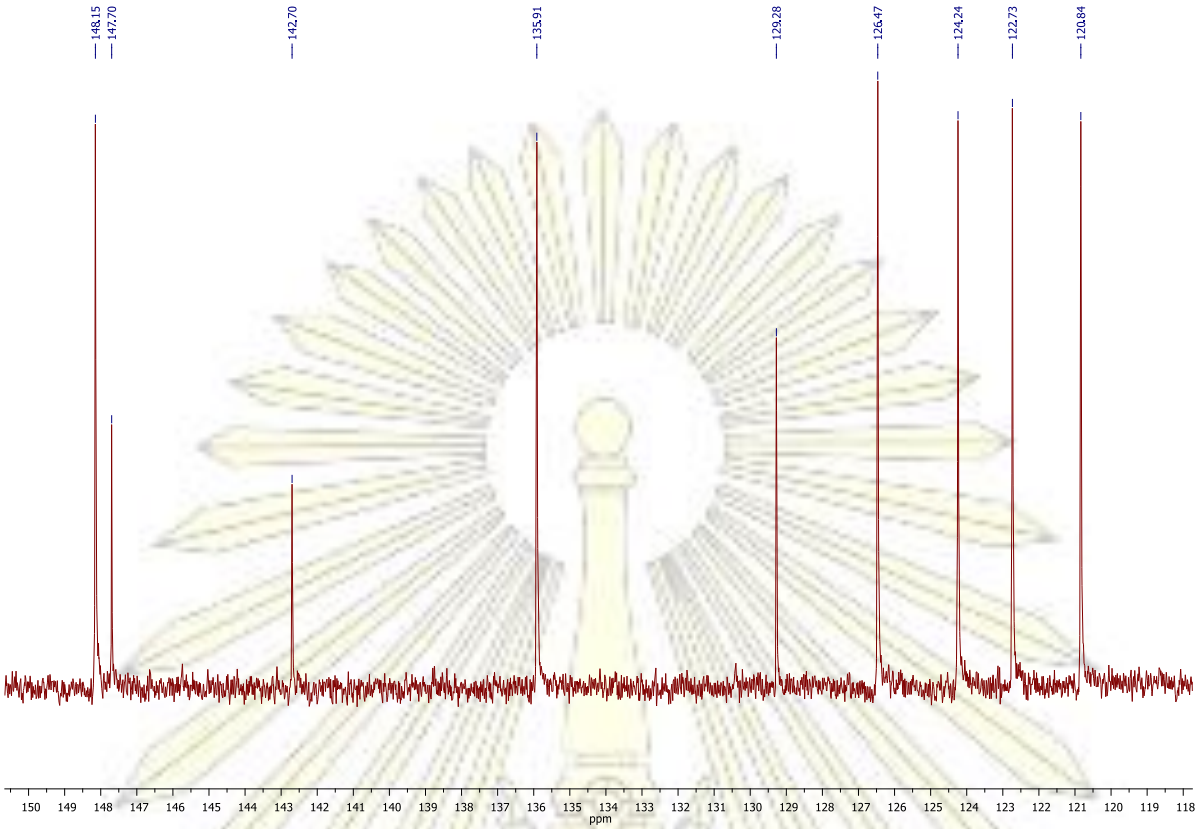

Figure A.11 ^{13}C NMR spectrum (DMSO) of compound **4**

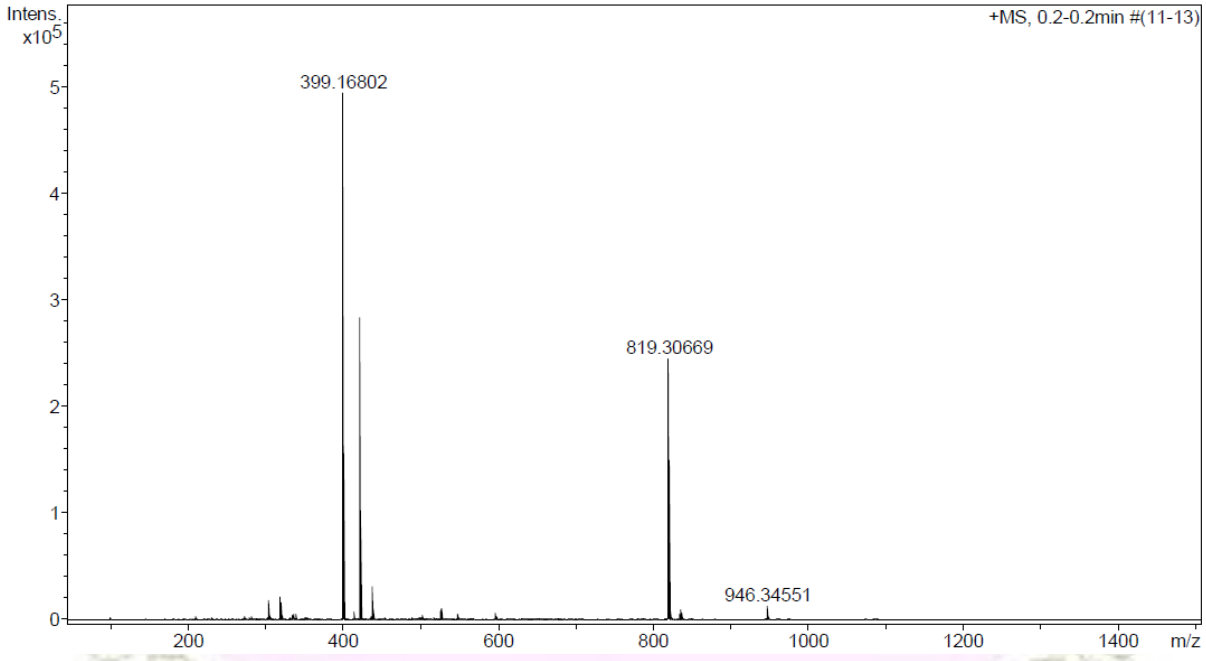

Figure A.12 Mass spectrum of compound **4**

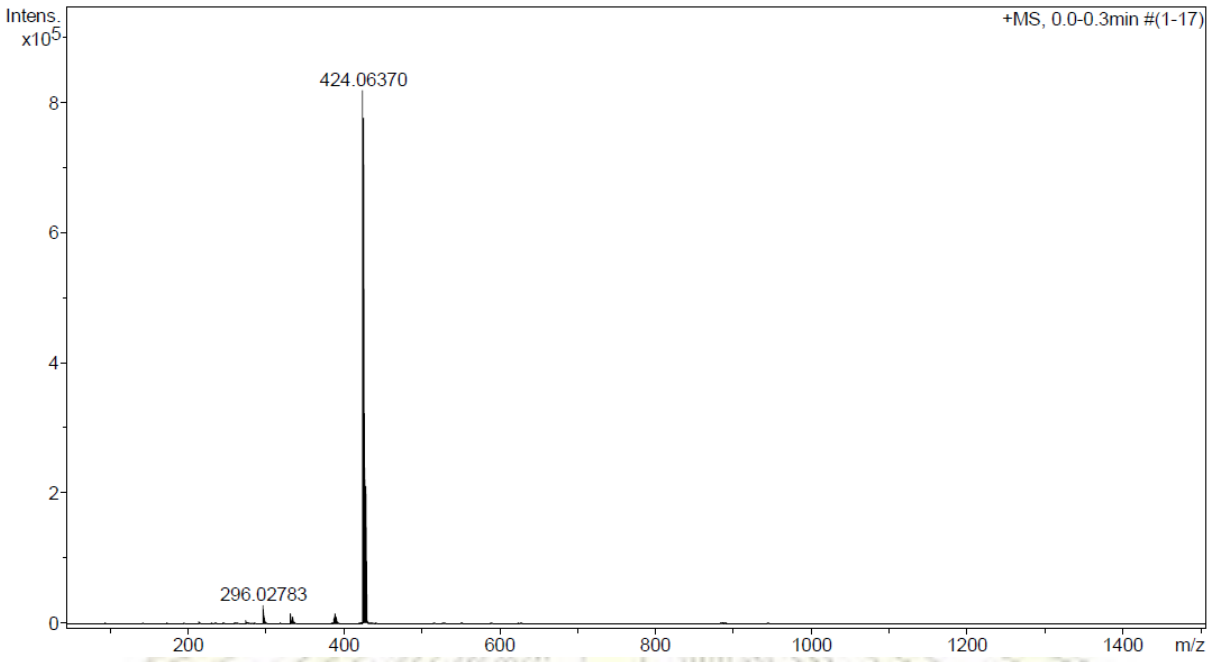

Figure A.13 Mass spectrum of complex **1**

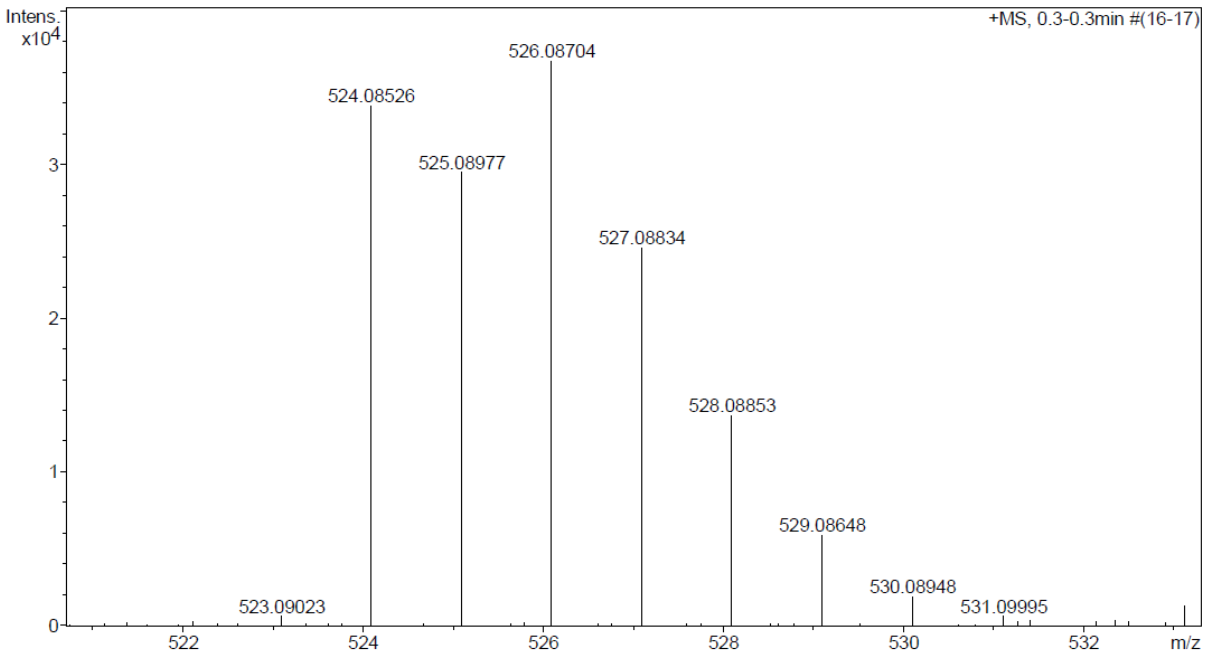

Figure A.14 Mass spectrum of complex **2**

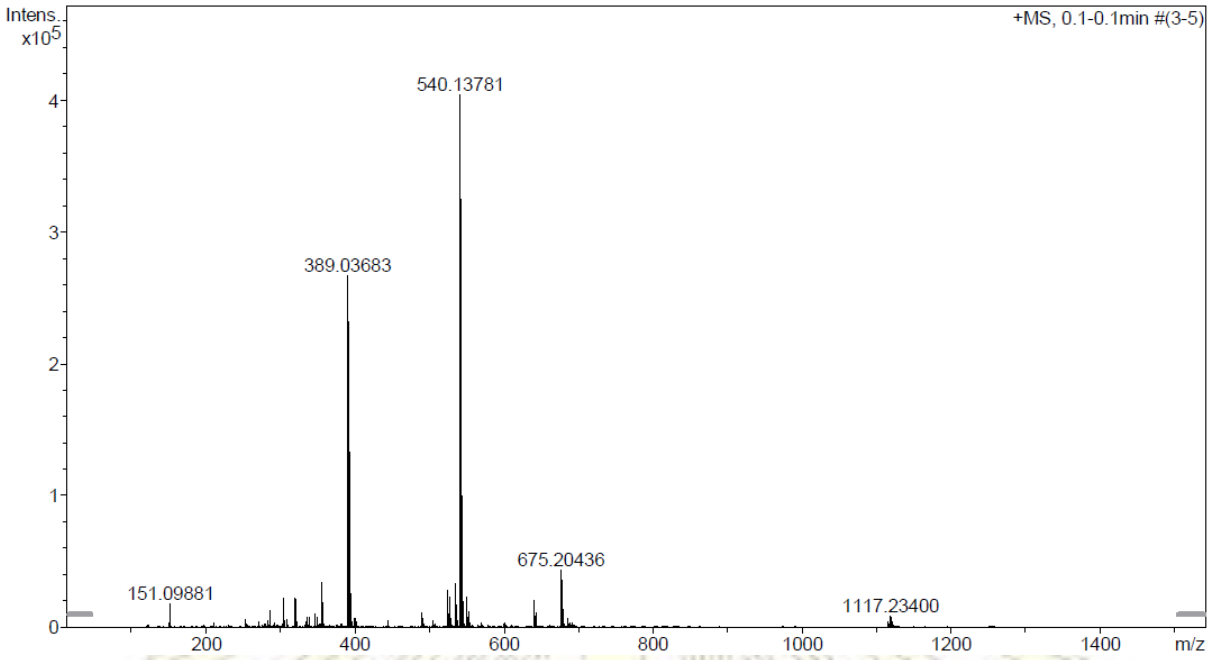

Figure A.15 Mass spectrum of complex **3**

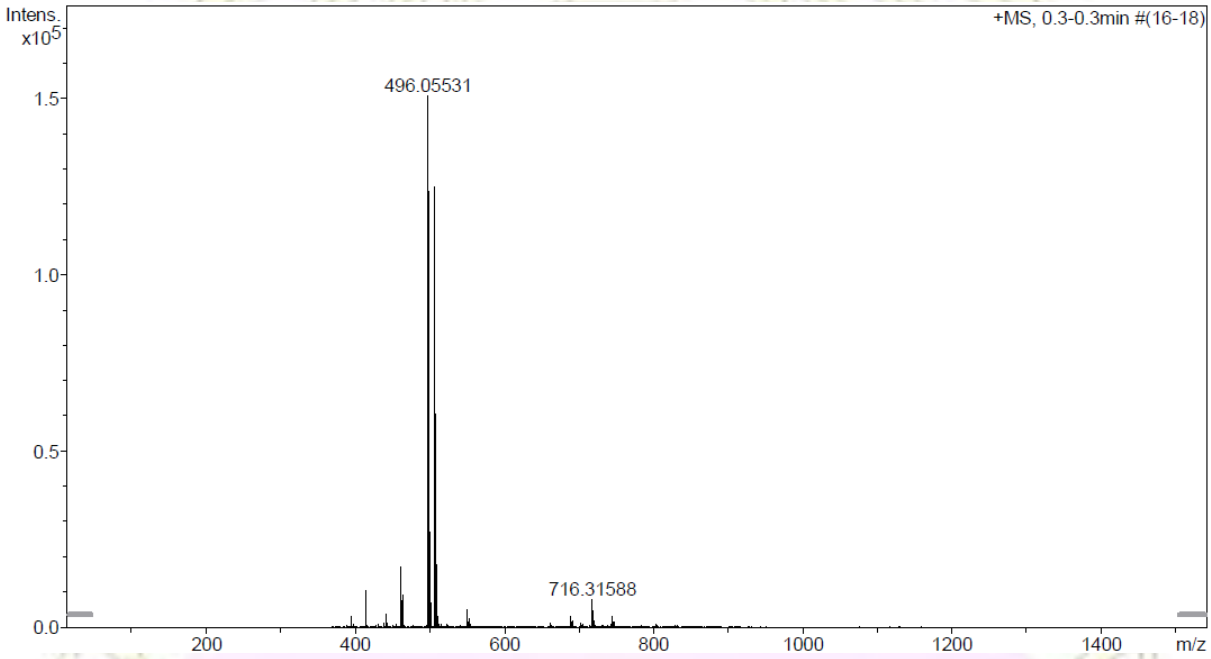

Figure A.16 Mass spectrum of complex **4**

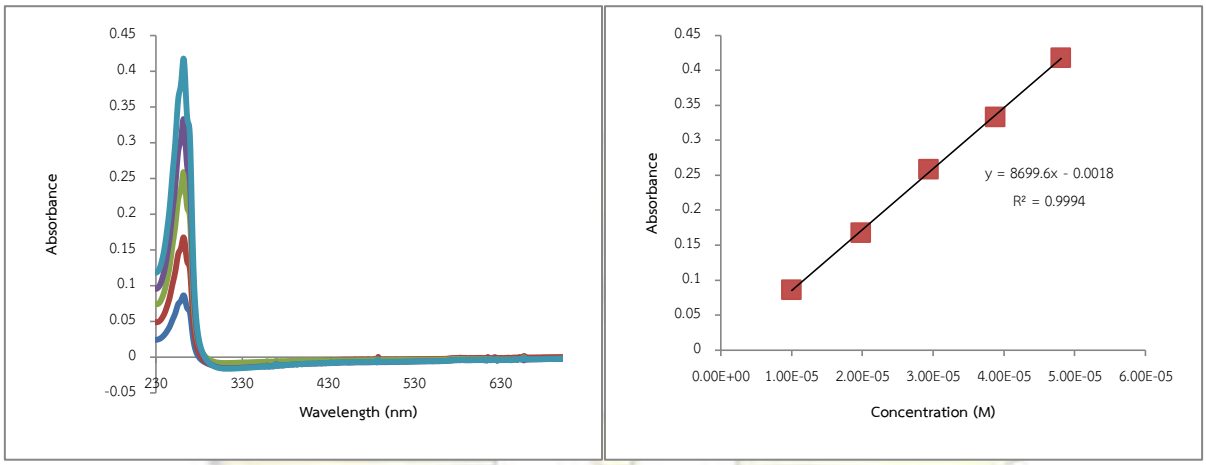

Figure A.17 TPMA (a) UV-vis absorption spectra in the concentrations range of 10-50 μM (b) Molar absorptivity coefficients (**ε**) plot

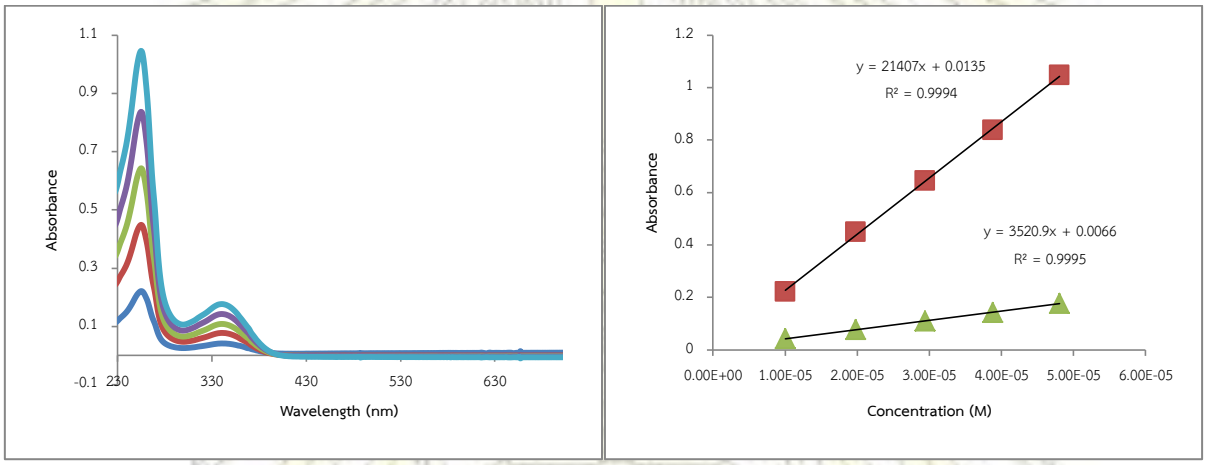

Figure A.18 Compound **1** (a) UV-vis absorption spectra in the concentrations range of 10-50 μM (b) Molar absorptivity coefficients (**ε**) plot

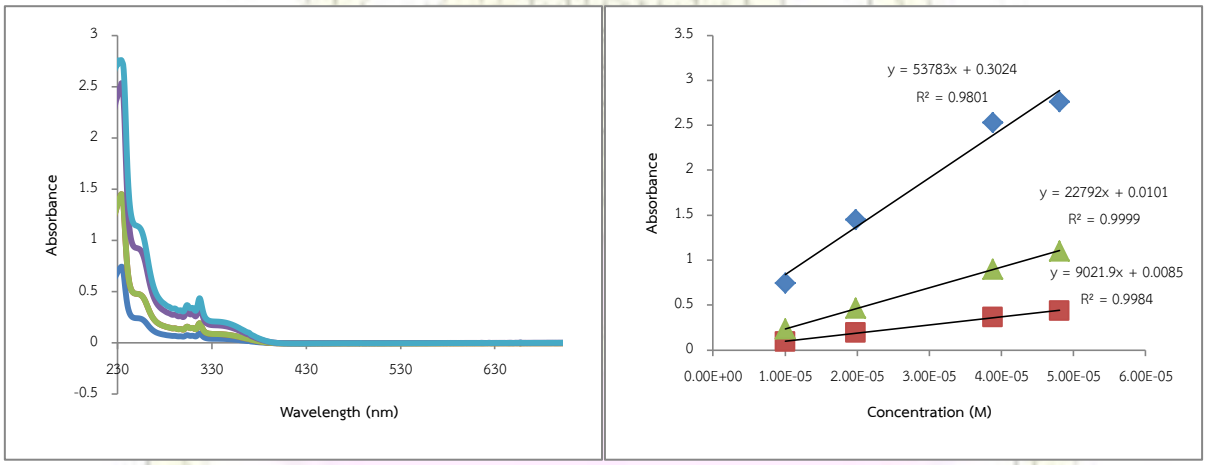

Figure A.19 Compound **2** (a) UV-vis absorption spectra in the concentrations range of 10-50 μM (b) Molar absorptivity coefficients (**ε**) plot

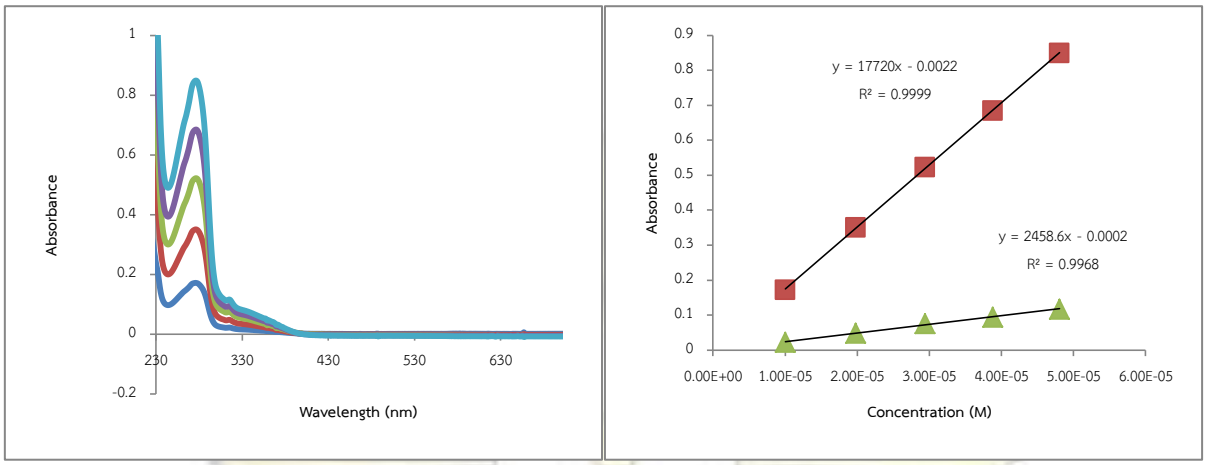

Figure A.20 Compound **3** (a) UV-vis absorption spectra in the concentrations range of 10-50 μM (b) Molar absorptivity coefficients (**ε**) plot

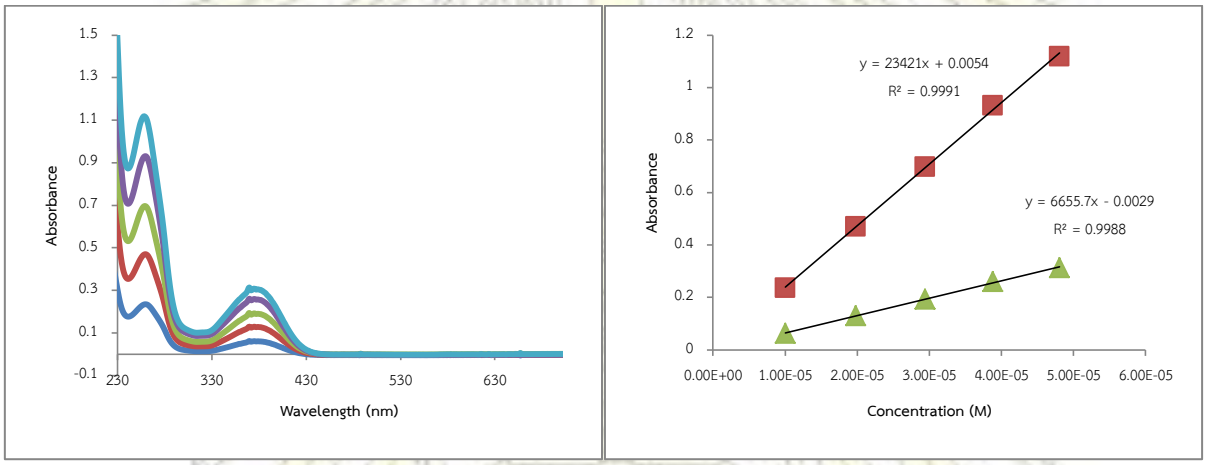

Figure A.21 Compound **4** (a) UV-vis absorption spectra in the concentrations range of 10-50 μM (b) Molar absorptivity coefficients (**ε**) plot

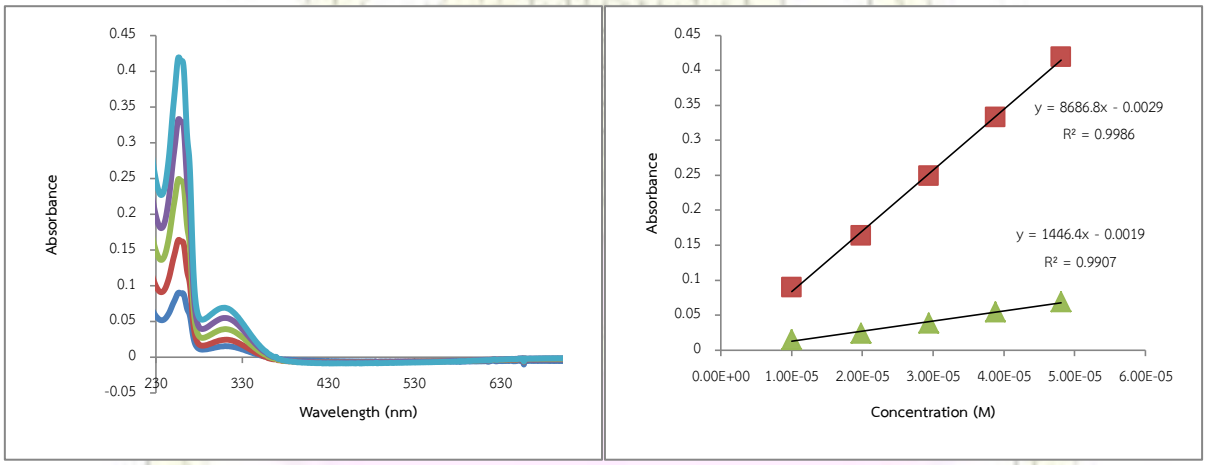

Figure A.22 Complex **TPMA** (a) UV-vis absorption spectra in the concentrations range of 10-50 μM (b) Molar absorptivity coefficients (**ε**) plot

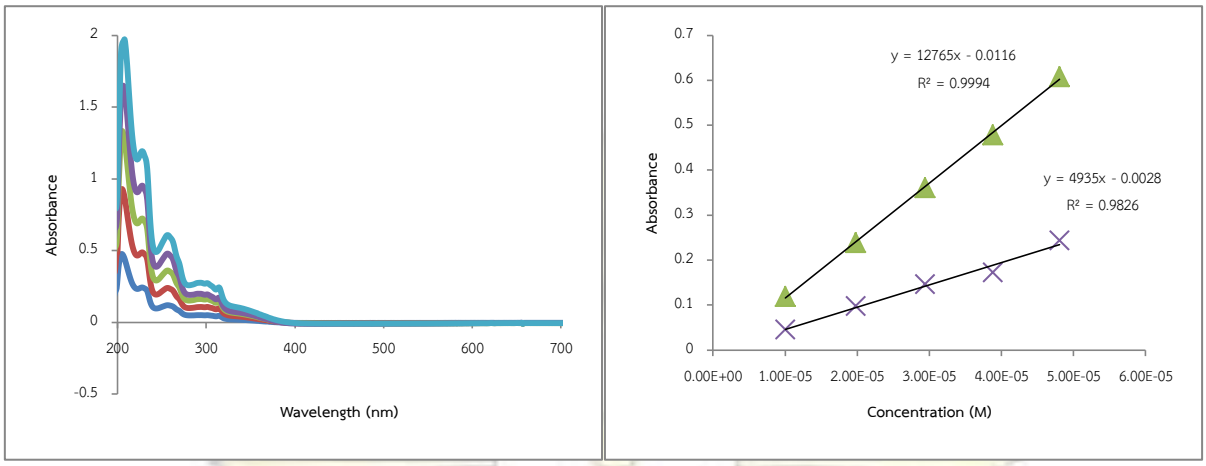

Figure A.23 Complex **1** (a) UV-vis absorption spectra in the concentrations range of 10-50 μM (b) Molar absorptivity coefficients (**ε**) plot

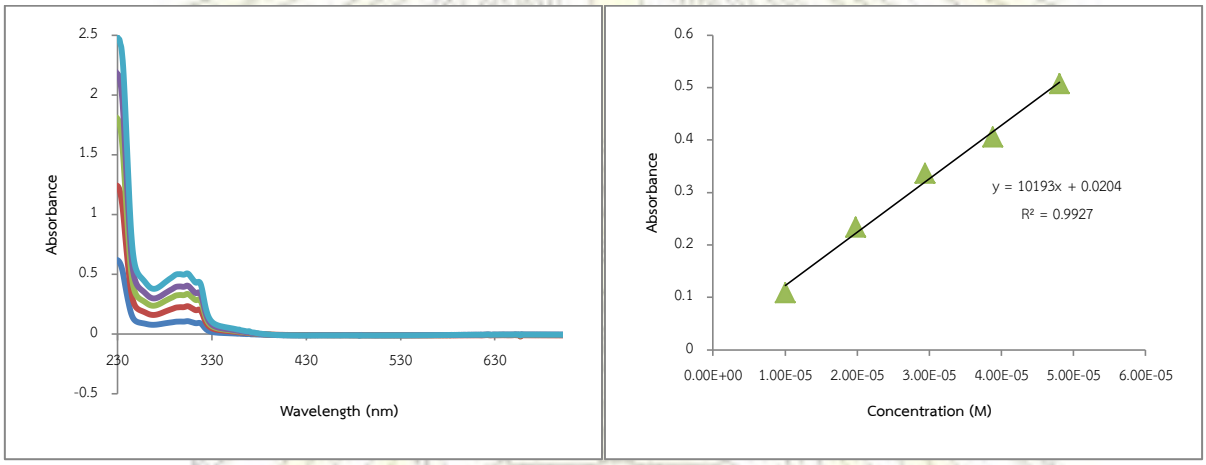

Figure A.24 Complex **2** (a) UV-vis absorption spectra in the concentrations range of 10-50 μM (b) Molar absorptivity coefficients (**ε**) plot

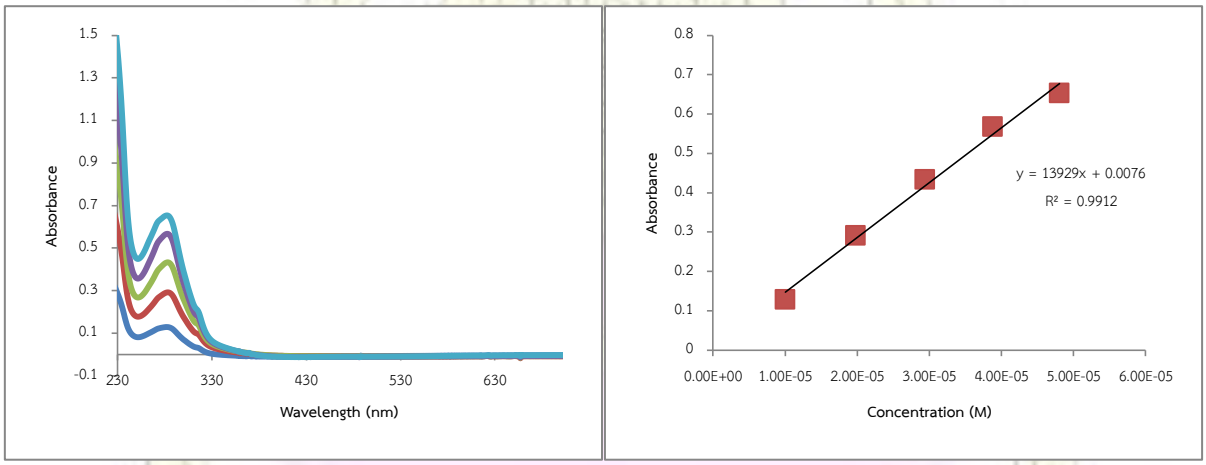

Figure A.25 Complex **3** (a) UV-vis absorption spectra in the concentrations range of 10-50 μM (b) Molar absorptivity coefficients (**ε**) plot

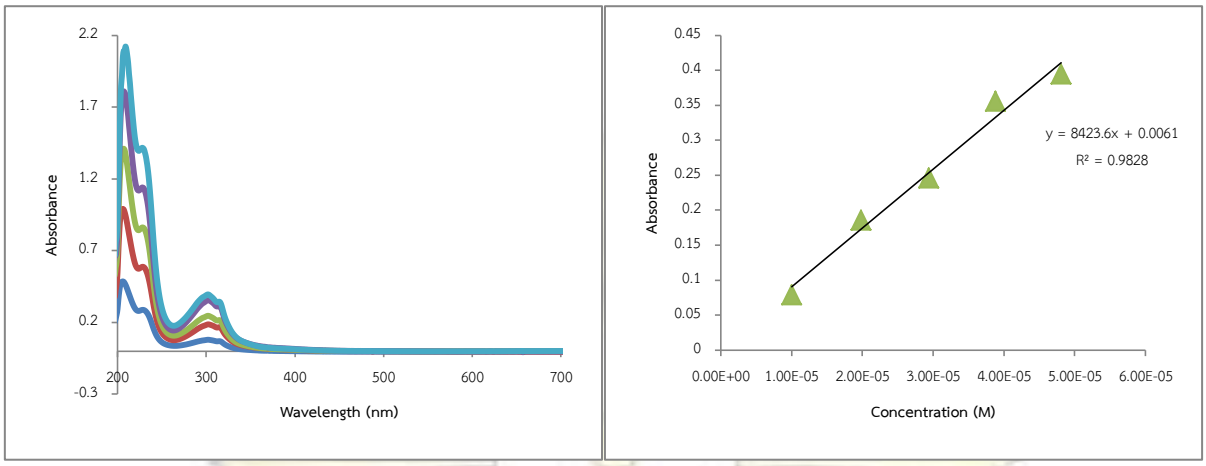

Figure A.26 Complex **4** (a) UV-vis absorption spectra in the concentrations range of 10-50 μM (b) Molar absorptivity coefficients (**ε**) plot

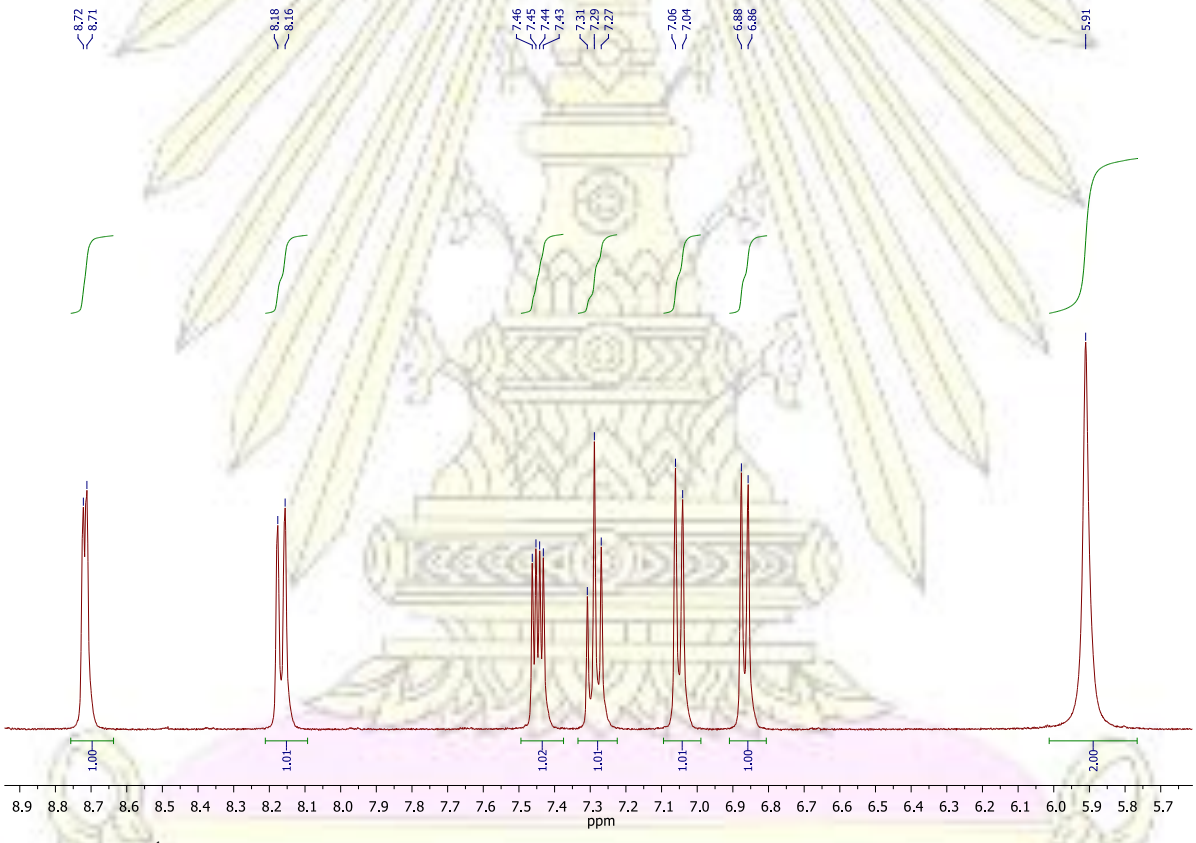

Figure A.27 ^{1}H NMR spectrum (DMSO) of 8-aminoquinoline

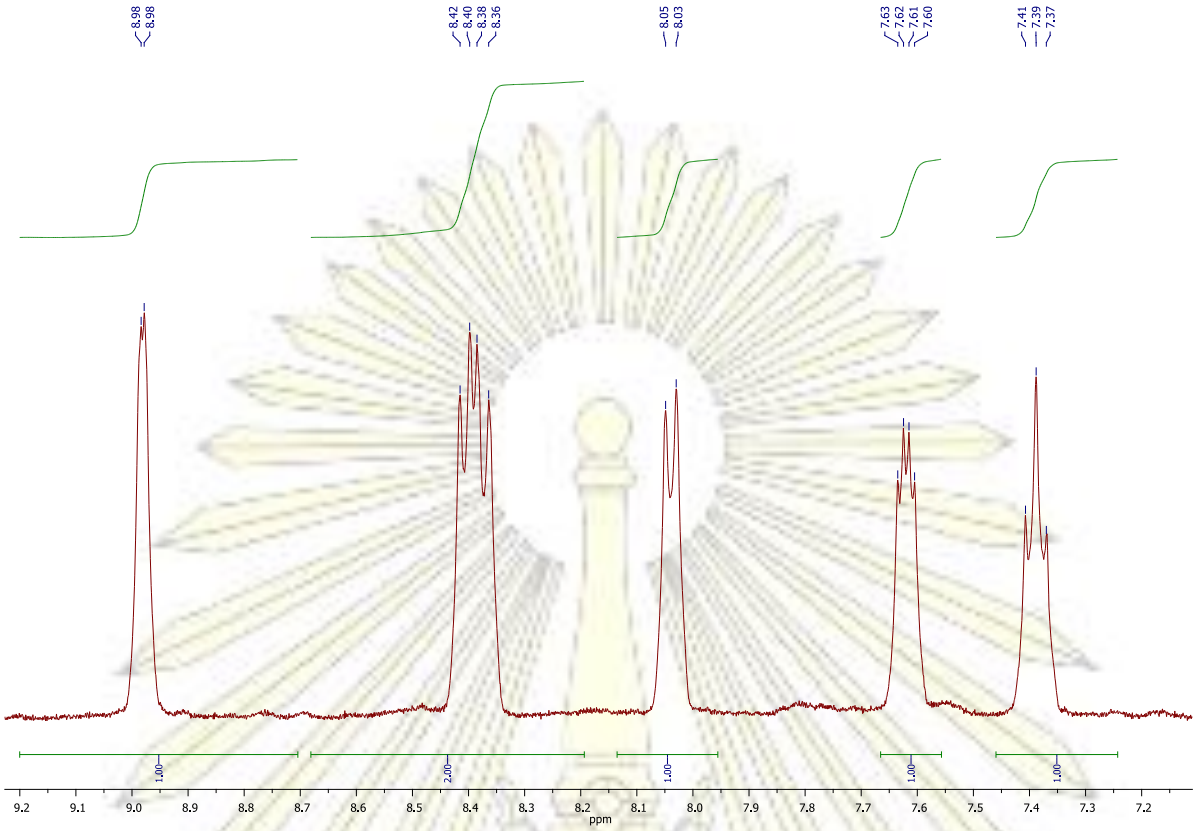

Figure A.28 ^{1}H NMR spectrum (DMSO) of 8-iodoquinoline

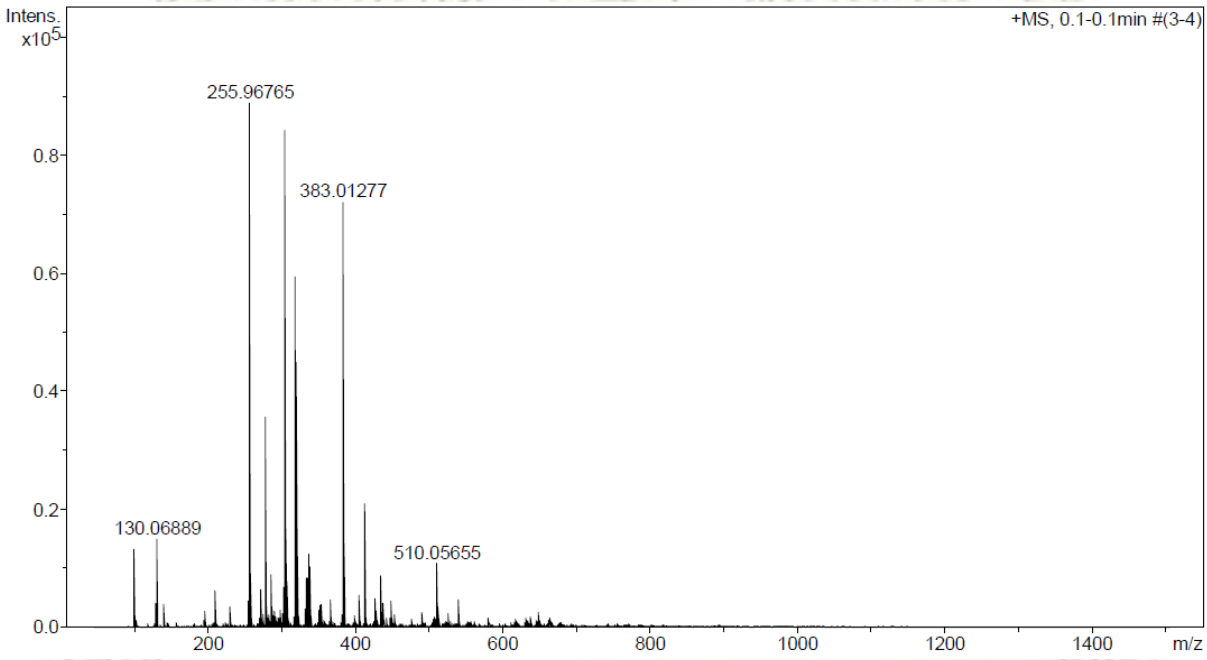

Figure A.29 Mass spectrum of 8-iodoquinoline

VITA

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