National Chiao Tung University
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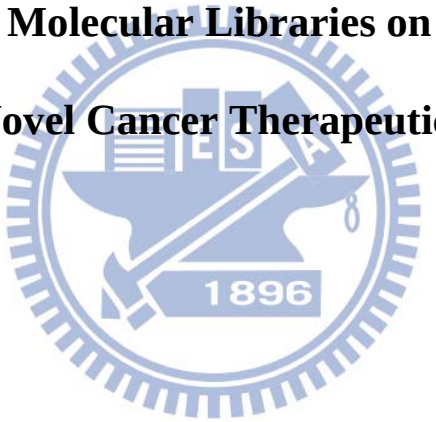
應用化學系博士班
PhD Thesis
博士論文

Studies towards the Synthesis of Fused, Linear and Angular Heterocyclic Small Molecular Libraries on Soluble Support as Novel Cancer Therapeutics



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Studies towards the Synthesis of Fused, Linear and Angular Heterocyclic Small Molecular libraries on Soluble Support as Novel Cancer Therapeutics

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A Thesis

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Department of Applied Chemistry

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ABSTRACT

A novel ionic liquid supported, synthetic protocol has been developed toward the synthesis of tetrahydro-*β*-carboline oxo and thio hydantoin analogs, dihydro-quinazolines and tetrahydro-quinazolines analogue by the use of focused microwave irradiation on ionic liquid support. For the first time we have developed the synthesis of tetrahydro-*β*-carboline oxo and thio hydantoin analogs in environmentally benign media on ionic liquid support.

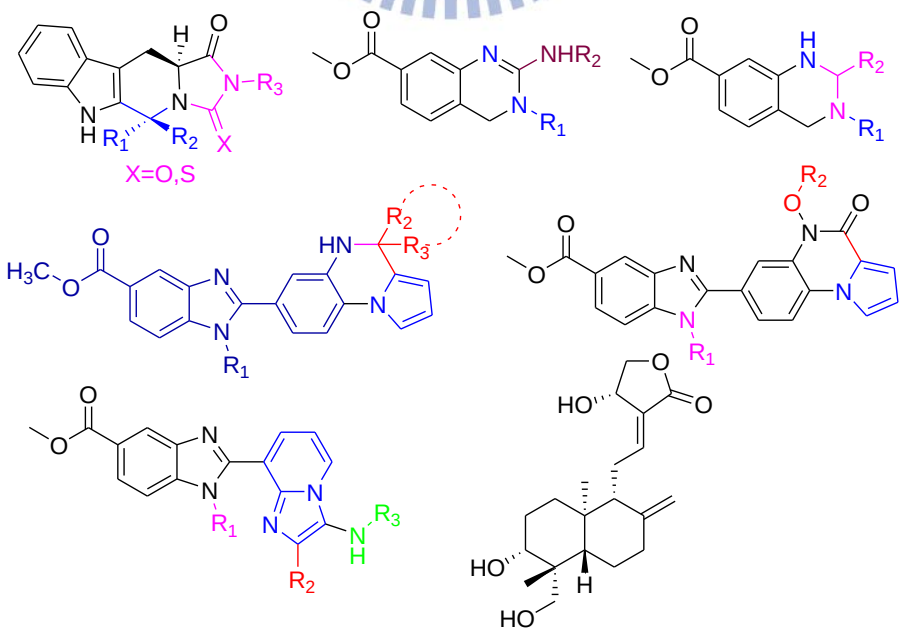
In a study aimed at developing a novel concise approach to the benzimidazole-pyrrolo[1,2-a]quinoxaline and benzimidazole-pyrrolo[1,2-a]quinoxalinone core of medicinal interest, a S_NAr/Pictet-Spengler reaction and partial nitro group reduction/SN_2

reaction has been identified that gives the direct access to the target compound on soluble polymer support under focused microwave irradiation. Pictet-spengler cyclisation, partial nitro group reduction and SN_2 reaction has been identified to developed for the medicinally important core of benzimidazole-pyrrolo[1,2-a]quinoxaline and benzimidazole-pyrrolo[1,2-a]quinoxalinone analogs.

A novel, convergent, and expedient general approach for the synthesis of the benzimidazole-imidazo[1,2-*a*]-pyridine has been described by a Ugi multicomponent reaction in neat condition under focused microwave irradiation.

It has long been recognized that andrographolide and its analogs has anti-inflammatory and anti-cancer agent's properties. Based on different biological properties of andrographolide we have synthesized andrographolide analogs and checked their bioassay.

Generalized representation of synthesized compounds of this dissertation



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DECLARATION

I, Barnali Maiti, declare that the thesis entitled "**Studies towards the Synthesis of Fused, Linear and Angular Heterocyclic Small Molecular libraries on Soluble Support as Novel Cancer Therapeutics"**

I confirm that:

- This work was done wholly or mainly while in candidature for a research degree at this University;
- Where I have consulted the published work of others, this is always clearly attributed;
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;

Date:_____

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Chapter One

Ionic Liquid Supported Synthesis of Hydantoin Fused Tetrahydro-*β*-carbolines in Green Media and Dihydroquinazoline and Tetrahydroquinazolins in Organic Media under Microwave Irradiation

1.0 Introduction

The twenty-first century presents us with numerous interconnected challenges like the relationship between industry and natural system amongst one of them. Industrial measures have conventionally gone hand-in-hand with material processes that cause peril to the health of people and other living beings, both in the immediate present (*e.g*. environment destruction, toxic pollutants,) and in the future (*e.g*. persistent toxicants, climate change) as showin Figure 1.0. Generally, this has been the result of a tendency to neglect the context of industrial operations within the bigger systems of ecology and society.[1-2] As chemists, we should be prepare to tackle this problem. The sciences of chemistry locate to contribute critical tools for redesigning environmental construction. New resources and technologies for industrial and consumer uses are routinely urbanized on the molecular level by chemists.

Figure 1.0 Sources of production of pollutions. *Courtesy*. "*White Paper on Environment Kagawa Prefecture. Kagawa Prefecture Rnvironmental policy Division"*

Simultaneously we should think about toxicity, safety, environmental providence and lifecycle along with function. To develope new substances and technologies we should think about how much it is environment friendly and how much it is cost effective. Also we should learn how to eradicate waste before it is generated, by developing materials that are integrated into material cycles by plan.[3] Green chemistry is now a days highly applicable research areas that have a enormous prospective for beneficial impact in human society since common consumer products increasingly being concerned as health hazards and with global chemical production taking place on the scale of billions of tons per year.[4-5]

1.1. Green Chemistry for Sustainable Development

In this new century, it has been well known that sustainable growth is the keystone of different scientific progress. By converting old technologies into new clean processes and by designing latest products with new eco-compatible processes are the key challenges of chemical sciences. In order to stop problems in the future, green chemistry, is the new direction of chemistry, whose endeavor is to correct everything nearby practices.[6-7] The most important environmental organization, heavy industry and the world of chemistry in broad-spectrum, are developing and following ways focused on particular strategies for pollution avoidance. Green chemistry basically refers to the new sustainability precedence in technological and scientific innovation, on the basis of general rules stressing the need to discard harmful products and processes. Some strategies which can be adopted are

1. Optimisation of balance of global mass in order to reduce waste.

2. Minimisation of power consumption, *e.g*. at ambient temperature and pressure.
3. Use of raw materials taken from renewable resources.
4. Whenever feasible, substitution of old compounds with others which maintain their functional efficiency while reducing their toxic impact on the environment and human health.[8-11]

1.2. Different definition of Green Chemistry

- Green Chemistry is the design of chemical products and processes that reduce or eliminate the use and subsequent generation of hazardous substances in reaction pathway. Green Chemistry relies on a set of 12 principles that can be used to design or re-design molecules, materials and chemical transformations to be safer for human health and the environment.
- The basic philosophy of Green chemistry is that research, techniques and the end results of studies should be as ecologically sound as possible. This field looks at the protection of natural possessions, the environmental impact and the prevention of ecological problems. Moreover, this chemistry is entirely different from environmental chemistry, which is the chemical study of the natural environment.
- Green chemistry, also called sustainable chemistry, that support the design of products and processes which reduce the use and generation of hazardous substances. Green chemistry applies to organic chemistry, inorganic chemistry, biochemistry, analytical chemistry, and even physical chemistry. While green chemistry seems to focus on industrial applications, it does apply to any chemistry choice.

- Green chemistry applies across the life cycle of a chemical product, including its design, manufacture, and use.[12-13]

1.3. The Twelve Principles of Green Chemistry

Prevent Waste

To resist pollution prevention, the chemist is to redesign the chemical transformations in order to minimize the generation of hazardous waste. By preventing waste generation, we can minimize hazards substances associated with waste storage, transportation and treatment.

Maximize Atom Economy

Atom economy is a concept, developed by Prof. B. M. Trost of Stanford University that evaluates the efficiency of a chemical transformation. Similar to a yield calculation, atom economy is a ratio of the total mass of atoms in the desired product to the total mass of atoms in the reactants. In order to minimize waste, we need to redesign efficient chemical transformations which maximize the incorporation of all starting materials used in the process into the final product.

Design less Hazardous Chemical Synthesis

Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess no toxicity to human health and the environment. The goal is to use less hazardous reagents whenever possible and design processes that do not produce hazardous by-products. This principle focuses on choosing reagents that pose the least risk and generate only benign by-products.

Design Safer Chemicals and Products

Chemical products should be designed to affect their desired function while minimizing their toxicity. Toxicity and ecotoxicity are properties of the product. New products can be designed that are inherently safer, while highly effective for the target application. In academic labs this principle should influence the design of synthetic targets and new products.

Use Safer Solvents/Reaction Conditions

The use of auxiliary substances such as solvents, separation agents should be made unnecessary wherever possible when used. Solvent use leads to considerable waste. Reduction of solvent volume or complete elimination of the solvent is often possible. In cases where the solvent is needed, less hazardous replacements should be employed. Purification steps also generate large amounts of solvent and other waste.

Increase Energy Efficiency

Energy requirements of chemical processes should be recognized for their environmental and economic impacts and could be designed for ambient temperature and pressure, so that energy costs associated with extremes in temperature and pressure are minimized.

Use Renewable Feedstocks

Whenever possible, chemical transformations should be designed to utilize raw materials and feedstocks that are renewable. Examples of renewable feedstocks include agricultural products or the wastes of other processes. Examples of depleting feedstocks include raw materials that are mined or generated from fossil fuels (petroleum, natural gas or coal).

Avoid Chemical Derivatives

Use of blocking groups such as protection/deprotection, and temporary modification of physical/chemical processes should be minimized or avoided if possible, because such steps require additional reagents which can generate waste. More selective synthetic transformations will eliminate or reduce the need for protecting groups. In addition, alternative synthetic sequences may eliminate the need to transform functional groups in the presence of other sensitive functionality.

Use Catalysts

As we know that catalytic reagents are superior to stoichiometric reagents which can serve several roles during a transformation. They can enhance the selectivity of a reaction, reduce the temperature of a transformation, enhance the extent of conversion to products and reduce reagent-based waste.

Design for Degradation

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products of hazardless substances and do not persist in the environment.

Analyze in Real-Time to Prevent Pollution

It is always important to monitor the progress of a reaction for completion or to detect the formation of any unwanted by-products. Whenever possible, analytical methodologies should be developed and used to allow monitoring and control to minimize the formation of unnessery by-products.

Minimize the Potential for Accidents

One way to minimize the potential for chemical accidents is to choose reagents and solvents that minimize the potential for explosions, fires and accidental release. So finally, the condesed principles of green chemistry. Twelve principles of green chemistry written in the form of a mnemonic **PRODUCTIVELY** [14-16]

P-Prevent wastes

R-Renewable materials

O-Omit derivatization steps

D-Degradavle chemical products

U-Use safe synthetic methods

C-Catalytic reagents

T-Temperature pressure ambient

I-In-press monitoring

V-Very few auxiliary substances

E-E factor, maximize feed in product.

L-Low toxicity of chemical products

Y-Yes, it is safe.

1.4. Montreal Protocol

The Montreal practice has forced many industries and organizations to reconsider their chemical processes, due to the adverse environmental impact caused by the use of volatile organic solvent, by endowing into a clean technology that reduces waste and by-products from an industrial process to a smallest amount.[17-22]

There appears to be four main alternative strategies

(1) solvent-free synthesis

(2) The use of water as a solvent

(3) The use of supercritical liquids as solvents

(4) The use of ionic liquids as solvents

1.5. Solvent-free synthesis

It has been perceived that evading the use of volatile organic solvents in organic synthesis can reduce the environmental contamination and even be more convenient than using solvent-based synthesis. Since we are living in society, so we should more aware of the environmental impact of human activity, and accordingly of the need to develop cleaner and extra energy-efficient technologies for organic synthesis. It has been recognised that the large-scale use of volatile organic solvents in synthesis has significant implication for environmental pollution. It has also been thought that 'the best solvent when there is no solvent use in the syntheses'. In spite of the power of this announcement, our use and understanding of solvent-free synthesis, especially where solid starting materials are concerned, has stay behind undeveloped in contrast to solvent based methods. As solvent-free synthesis turn into morewidely examined many people are likely to be impressed at the series of reactions, even among solid starting materials. [23a-b]

1.6. Water, the Unique Reaction Medium

1.6.1. Introduction about water

Water which is best solvent worn out by nature for biological chemistry. It is noteworthy that until recently in vitro organic synthesis has mainly avoided water and chemists and industries have been searching for suitable organic solvents, for example, the substitute of the previous commonly used benzene with toluene, etc. Organic chemists have been trained in such a manner that little serious consideration was given to water as a useful reaction solvent. This was perhaps partly the result of a combination of fear of the detrimental effects of hydrolysis and the influence of the ancient alchimia, which teaches that reactants must be in solution to produce a chemical reaction. [24]

1.6.2. Is water the green solvent?

It is well known that ‘‘green’’ solvents refers the goal to minimize the environmental impact resulting from the use of solvents in chemical production, thus recognizing green solvents is a top priority for the organic chemist. Use of no-solvent, i.e. solvent free reactions is another solution, however, this may work for only a few reactions; a lack of reaction medium may lead to overheating of the reaction mixture, in view of the poorly understood heat and mass-transfer issues. Using fluorous and ionic liquids along with aqueous systems and supercritical carbon dioxide, have shaped the main thrust of this progress. Thus, naturally abundant water appears to be a better option because of its non-toxic, non-corrosive and non-flammable nature. Also, water can be contained because of its relatively high vapor pressure as compared to organic solvents, which are favorable traits to render water as a sustainable alternative. [25]

1.6.3. Microwaves chemistry in aqueous medium?

It has been observed that when water is rapidly heated to high temperatures under microwave irradiation, it act like a pseudo-organic solvent. Because of the very high heat capacity of water, precise control of the reaction temperature can be achieved efficiently. MW-enhanced chemistry is based on the efficiency of the interaction of molecules in a reaction mixture with electromagnetic waves generated by a ‘‘microwave dielectric effect’’. This process mainly depends on the specific polarity of molecules. Since water is polar in nature, it has good potential to absorb microwaves and convert them to heat energy, thus accelerating the reactions in an aqueous medium as compared to results obtained using conventional heating. This can be explained by two key mechanisms: dipolar polarization and ionic conduction of water molecules (Figure 1.1). Irradiation of a reaction mixture in an aqueous medium by MW results in the dipole orientation of water molecules and reactants in the electric field. This causes two distinguishing effects: (i) Specific microwave effect: the electrostatic polar effects which produce the dipole–dipole type interaction of the dipolar water molecules and reactants with the electric field component of MW, resulting in energy stabilizations of an electrostatic nature.[26]

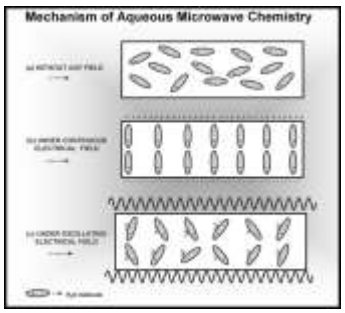


Figure 1.1. Mechanism of Aqueous Microwave Chemistry. *Courtsey. “Polshettiwar, V.; Varma, R. S. Chem. Soc. Rev., 2008, 37, 1546–1557.”*

It is noteworthy to mention that various organic reactions can be conducted in an aqueous medium using MW irradiation, without using any phase-transfer catalyst (PTC). This is because water at higher temperature behaves as a pseudo-organic solvent, as the dielectric constant decreases substantially and an ionic product increases the solvating power towards organic molecules to be similar to that of ethanol or acetone.[27-28]

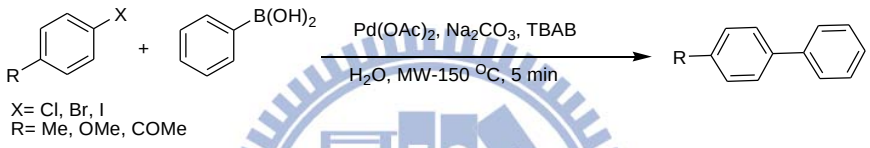
1.6.4. How does aqueous microwave chemistry expedite organic synthesis?

MW-assisted chemistry has blossomed into a useful technique for a variety of applications including drug discovery and organic synthesis. Although MW-assisted reactions in organic solvents have developed rapidly, the focus has now shifted to the more environmentally benign methods, which use greener solvents and supported renewable catalysts. There are many examples of the successful application of MW-assisted chemistry to organic synthesis; these include the use of benign reaction media, solvent-free conditions, and the use of solidsupported and reusable catalysts. To illustrate the advantages of aqueous MW chemistry in rapid and greener organic synthesis, we have reviewed some representative reactions/synthetic pathways developed in recent years in aqueous reaction medium using microwave irradiation.[29-31]

1.6.5. Microwave assisted coupling reactions in water medium

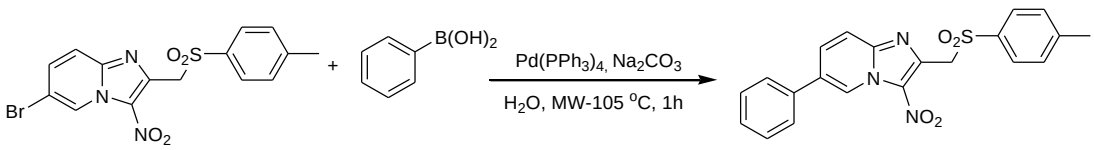
C-C bond forming cross-coupling reactions are one of the most important processes in organic chemistry. The Heck and Suzuki reactions are among the widely used reactions for the formation of carbon–carbon bonds. These reactions are generally catalyzed by

soluble palladium (Pd) complexes with various ligands. However, we have observed that the efficient separation and subsequent recycling of homogeneous transition-metal catalysts remains a scientific challenge and an aspect of economical and ecological relevance. Heterogeneous Pd catalyst systems were found to be highly effective in overcoming some of these issues. However, microwave -assisted coupling reactions in aqueous medium is a fascinating choice of chemists.[32-34] Leadbeater *et. al* have accomplished the Suzuki reactions using various biaryl derivatives from aryl halides and phenylboronic acid in aqueous medium using MW irradiation as shown in Scheme 1.0.[35]



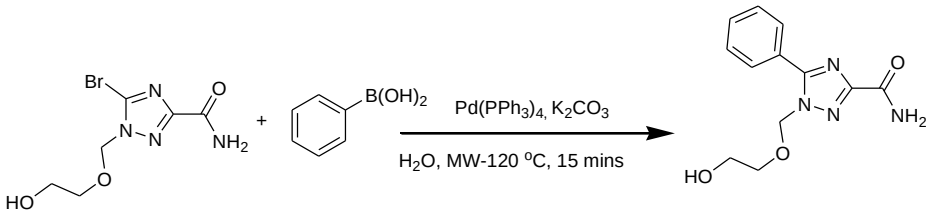
Scheme 1.0 Suzuki cross Coupling reaction in water.

Similarly, Vanelle *et al.* has accomplished an aqueous protocol for Suzuki coupling reaction that involves the reaction of heterocyclic imidazo[1,2-a]pyridines with a range of arylboronic acids under MW irradiation conditions as observed in Scheme 1.1.[36]



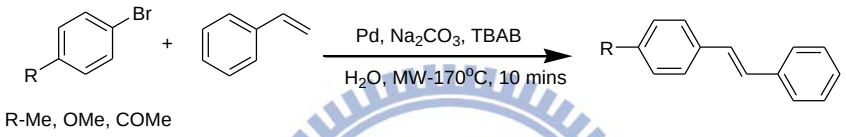
Scheme 1.1. Vanelle *et al* .Suzuki cross coupling reaction in water.

Concurrently, in Scheme 1.2. Zhu *et. al.* have synthesised the 5-Aryltriazole acyclonucleosides with various aromatic groups on the triazole ring via the Suzuki coupling reaction in aqueous solution by MW irradiation. [37]



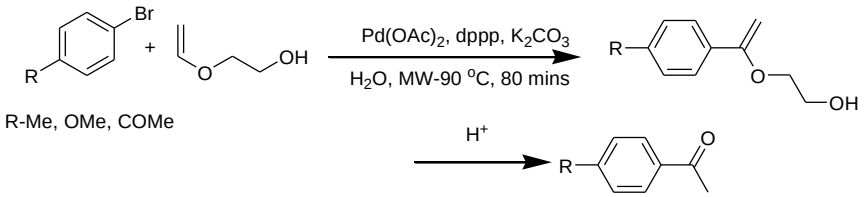
Scheme 1.2. Zhu *et al* .Suzuki cross coupling reaction in water.

With a view to enhance the diversity, Leadbeater *et. al.* has performed the Heck coupling reaction in water using MW heating with Pd-catalyst in Scheme 1.3.[38]



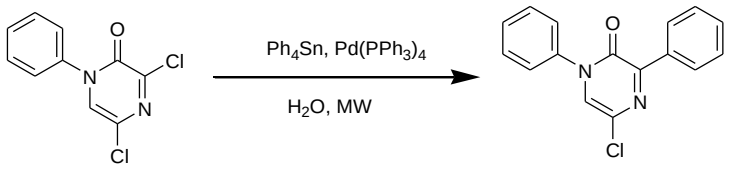
Scheme 1.3. Leadbeater *et al* .Heck cross coupling reaction in water.

Recently, Larhed *et. al.* has reported the highly regio-selective and fast Pd(0)-catalyzed internal R-arylation of ethylene glycol vinyl ether with aryl halides in aqueous medium under microwave irradiation in Scheme 1.4. [39]



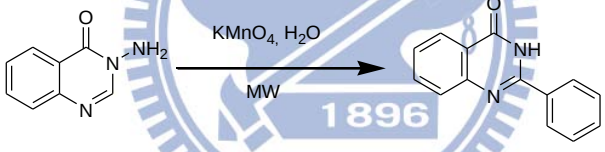
Scheme 1.4. Larhed *et. al.* Heck cross coupling reaction in water.

Similarly, as shown in Scheme 1.5. Eycken *et. al.* has developed the Stille cross coupling reaction between organo-tin compounds and aryl halides in aqueous medium under MW irradiation. [40]



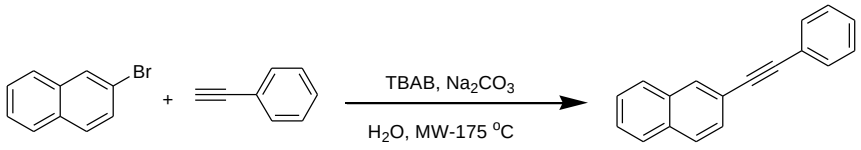
Scheme 1.5. Eycken *et al* . Stille cross coupling reaction in water.

In this report, Arfan *et. al.* has developed the MW-Assisted deamination of aryl 3-amino-4(3*H*)-quinazolinone derivatives in as shown in Scheme 1.6. using potassium permanganate as an oxidant in aqueous medium under microwave irradiation.[41]



Scheme 1.6. Arfan *et al* . Stille cross coupling reaction in water.

Analogously, Eycken *et. al.* has developed the sonogashira cross-coupling reaction as shown in Scheme 1.7. of`terminal acetylenes with aryl or vinyl halides for the creation of carbon–carbon bonds in aqueous medium under MW irradiation. [42]

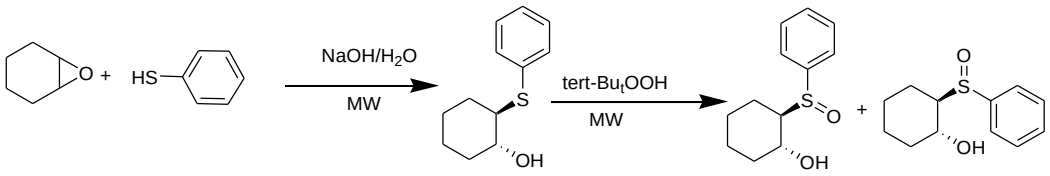


Scheme 1.7. Eycken *et al* . Stille cross coupling reaction in water.

1.7. The use of aqueous microwave chemistry for drug discovery

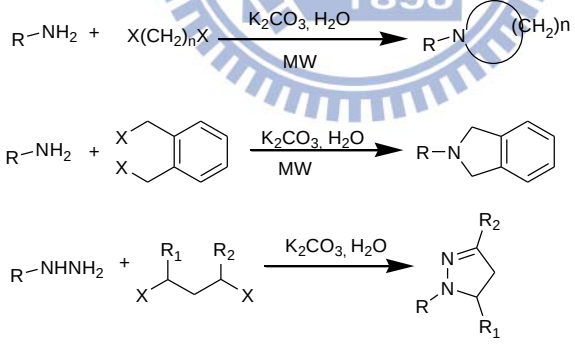
As we know that human life basically depends upon the drug discovery research to fight against various new diseases. However, current protocols for drug discovery are not sustainable with the adverse environmental impact. In drug discovery a variety of techniques such as combinatorial synthesis, parallel synthesis, and automated medicinal chemistry have been developed to increase the pharmaceutically active chemical entities. Although we have observed that most of these techniques are rapid and productive, they generate significant quantities of chemical waste, forcing us to develop new methods with reduced environmental impact. The use of water as a non-toxic reaction medium, together with the microwave heating appears to be promising and enables greener alternatives to thywart this issue. In both lead identification and lead optimization processes, there is a great demands for new small organic molecules. However, the conventional methods of organic synthesis are too slow to satisfy the demand for generation of such compounds. The combinatorial and automated medicinal chemistry have emerged to meet the ever increasing demands of new compounds for drug discovery. The synthetic chemistry community has been under intense pressure to produce, the important substances required by society in a short span of time with an environmentally benign fashion. One of the alternatives is using MW technology. The efficiency of MW flash-heating has resulted in dramatic reductions in reaction times. which is potentially important in traditional medicinal chemistry for the assembly of heterocyclic systems. As we know that Nitrogen heterocycles are abundant in nature and are of great significance to life because theirimportant bio properties. [43-45]

In the Scheme 1.8. Pironti *et. al.* has achieved the synthesis of beta-Hydroxy sulfides and beta-hydroxy sulfoxides by ring-opening of epoxide in aqueous medium.[46]



Scheme 1.8. Pironti *et. al.* used the microwave assisted reaction for beta-Hydroxy sulfides

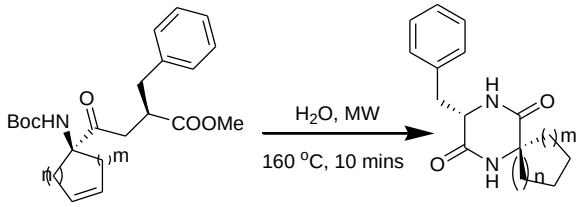
Similarly, Verma *et. al*. has accomplished the efficient synthesis of nitrogen-containing heterocycles, such as substituted azetidines, pyrrolidines, piperidines, azepanes, N substituted 2,3-dihydro-1*H*-isoindoles, 4,5-dihydropyrazoles, pyrazolidines, and 1,2-dihydrophthalazines, in a basic aqueous medium using MW in Scheme 1.9.[47-49]



Scheme 1.9. Verma *et. al*. used the microwave assisted reaction for Heterocyclic analogs

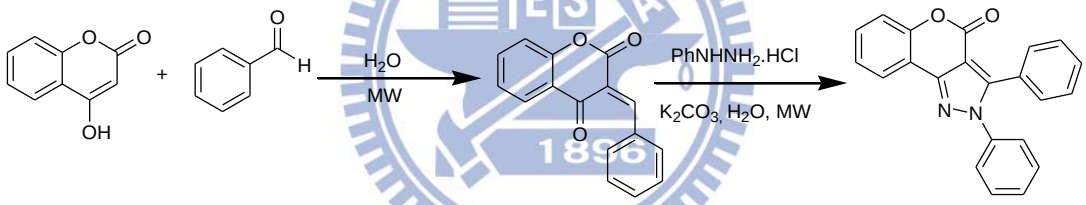
Likewise, Grotli *et. al.* has accomplished an efficient synthesis of spiro-2,5 diketopiperazines (spiro-DKPs) by cyclization of Boc-protected dipeptides containing

spiro-amino acids using MW heating in water in Scheme 1.10. [50]



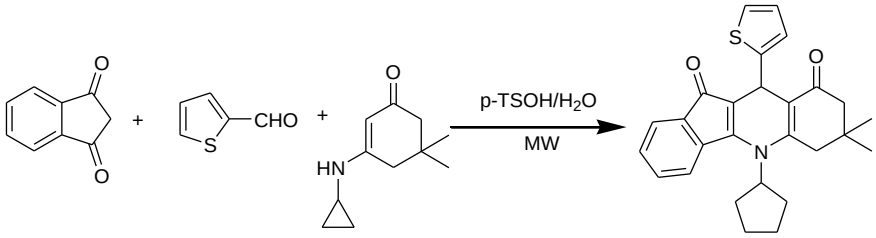
Scheme 1.10. Grotli *et. al.* used the microwave assisted reaction in water for the synthesis of spiro-2,5 diketopiperazines or Heterocyclic analogs.

In Scheme 1.11. Kidwai *et. al.* has accomplished benzopyrano[4,3-c]pyrazoles by heterocondensation reaction between in situ generated 3-arylidene- 2,4-chromanediones and N-substituted hydrazine in water as a solvent under MW irradiation conditions [51]



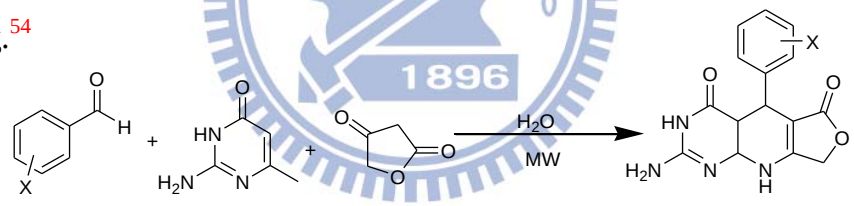
Scheme 1.11. Kidwai *et. al.* accomplished the synthesis of benzopyrano[4,3-c]pyrazoles using the microwave assisted reaction in water.

Similarly, Tu *et. al.* has developed the synthesis of Indenoquinoline derivatives via three-component reaction between aldehydes, 1,3-indanedione and enaminones in aqueous medium in Scheme 1.12. [52]

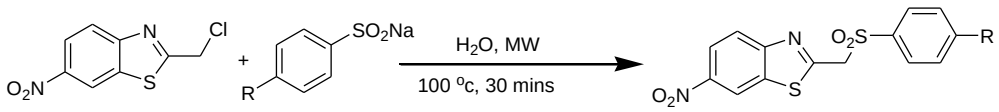


Scheme 1.12. Tu *et. al.* developed the multicomponent synthesis of Indenoquinoline using the microwave assisted reaction in water.

In Scheme 1.13, Zang *et. al.* has accomplished the synthesis of a series of related furo[30,40:5,6]pyrido[2,3-d]pyrimidine derivatives by three-component reactions between an aldehyde, 2,6-diaminopyrimidine-4(3H)-one, and tetronic acid/indane-1,3-dione, without using any catalyst[53] and sulfonyl derivative of benzothiazole was using MW heating.[54]



X=H,4-Cl, 4-br, 4-F, 4-Me
2-Cl, 2NO2



R=H, Me, OMe, F,Cl, Br etc

Scheme 1.13. Zang *et. al.* has accomplished the synthesis bioactive heterocyclic derivatives using microwave irradiation

1.8. Introduction on ionic liquid

It has been established view that the melting points of salts are very high such as sodium chloride melts at 800°C. However, It has been found that there is a group of salts with melting points below 100 °C, are referred to as ionic liquids (ILs). Room-temperature ionic liquids (RTILs) are ILs with melting points at or below ambient temperature. The cationic parts of the majority ionic liquids are organic moieties such as imidazolium, *N*-alkylpyridinium, tetraalkylammonium, and tetraalkylphosphonium ions. The anionic parts preserve organic or inorganic and include such entities as a number of halides, nitrate, acetate, hexafluorophosphate (PF_6), tetrafluoroborate (BF_4), trifluoromethylsulfonate (OTf), and bis(trifluoromethanesulfonyl)imide (NTf_2). Ionic liquids are liquids composed completely of ions as shown in Figure 1.2. . In the past two decades, ionic liquids have been widely used as "green solvents" replacing traditional organic solvents for organic synthesis and catalysis. Research in the field of ionic liquids (ILs) has developed exponentially in recent years. The necessaity to have unconventional solvents that are environmentally friendly, and can serve as effective replacement for conventional organic solvents, has driven extra growth. The ionic liquid has recently received more and more attention as eco-friendly reaction media in organic synthesis. There are innummerable reports have published on the potential use of RTILs as 'neoteric solvents' for various chemical reactions. The use of VOCs poses a risk to those people working in or living close to such processing facilities. In addition VOCs have been greatly concerned in causing changes to the global climate, the formulation of smog as well as being identified as a source of ozone depletion.

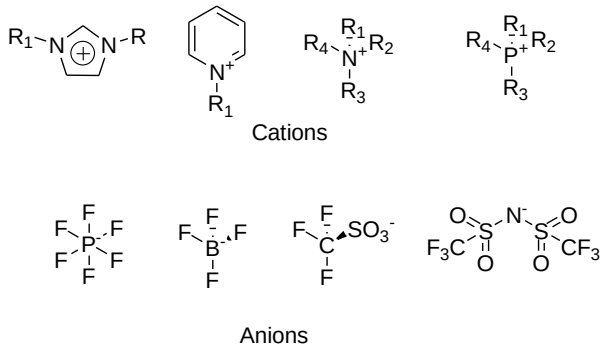


Figure 1.2. Types of cations and anions in ionic liquids

Moreover, ionic liquids possess the following attractive properties

1. They contain a liquid range of 300^{o}C, allowing tremendous kinetic control.

2. They are outstandingly good solvents for a wide range of inorganic, organic and polymeric materials (but, fortunately, they do not dissolve polythene, PTFE or glass): high solubility implies small reactor volumes.

3. They exhibit bronsted, Lewis acidity, as well as super acidity.

4. They have no vapour pressure.

5. Their water sensitivity does not restrict their industrial applications.

6. They are thermally stable up to 200^{o}C.

7. They are relatively cheap, and easy to prepare.

Ionic liquids are emerging as green solvents for chemical processes, because they combine good and tunable solubility properties with negligible vapor pressures and high thermal and chemical stabilities. They are used as reaction media, where they may enhance reaction rates and selectivities.[55]

1.8.1. History of Ionic Liquid:

The original report of a room-temperature ionic liquid appeared in 1914 with an examination by Paul Walden. By the mid 1990s, the basic understanding of the ionic liquids concept was well known in a narrow scientific community, mostly electrochemists, but this area of esoteric curiosity was of little interest, or too focused, for synthetic industrial applications. However there was a proposal that ionic liquids could be used for green chemistry and industrial chemistry. [56]

1.8.2. Designer green solvents:

They are actually designer solvents: either the cation or the anion can be changed, if not at will, then certainly with considerable ease, in order to optimize such phenomena as the relative solubilities of the reactants and products, the reaction kinetics, the liquid range of the solvent, the cost of the solvent, the intrinsic catalytic behaviour of the media, and air-stability of the system. Ionic liquids have the potential to make ideal green solvents as they have negligible vapour pressure and do not evaporate into the atmosphere making them a more environmentally responsible material than traditional organic solvents. They can be recyclable and different combinations of ions make solutions that can dissolve a large range of substances that include coal, plastics, metals and rocks. Ionic liquids are relatively undemanding and inexpensive to manufacture. Ionic liquids can allow easy separation of organic molecules by direct distillation without losing any of the ionic liquid. The liquid range can be as large as 300^{o}C which is higher than that of water and offers the potential for considerable kinetic control of extractive processes.[57-58]

1.8.3. Ionic Liquid for the synthesis of heterocyclic organic compound

The medicinal chemistry community has been under intense pressure to produce drugs required by society in short periods of time, in an environmentally benign fashion. Because of high molecular complexity in drug discovery processes accompanied by time constraints, the primary driver of pharmaceutical green chemistry has become the development of efficient and environmentally benign synthetic protocols. This can be achieved through the proper choice of starting materials, atom economic methodologies with a minimum number of chemical steps, the appropriate use of greener solvents and reagents, and efficient strategies for product isolation and purification. Thus, green chemistry has emerged as a discipline that permitts all aspects of synthetic chemistry. The global need for ionic liquids conventional organic solvents are used in a variety of industrial applications that include the production of pharmaceuticals, the manufacturing of electronic components, the processing of polymers, refrigeration and the synthesis of chemicals which includes Friedel-Crafts reactions, enzyme catalyzed reactions, hydrogenations, benzoylation, Heck reaction, Fischer indole synthesis, etc. RTILs are being looked upon as future commercial solvents. The acidic ionic liquids can act both as catalyst as well as solvent. This dual property of RTIL has turned out to be a boon in itself to carry out a variety of chemical transformations and is aptly given the name 'designer solvent.[59-60]

•Organic chemistry:

•Hydrogenation

•Hydroformylation

•Alkoxycarbonylation

•Cross coupling (Heck, Suzuki, Negishi, Stille)

•Allylic substitution

•Friedel-Crafts alkylation

•Bromination of aromatics/alkynes

•Cyclopropanation

•Synthesis of 2,4,5-triaryl imidazoles

•Synthesis of 3,4-dihydropyrimidin-2(1H)-ones

•Dimer-/Oligomer-/Polymerization

•Chiral solvent for asymmetric synthesis

Despite all those application now a day's ionic liquid are used for the synthesis of new heterocyclic compound. Although there are many publication where ionic liquid was used as a designer green solvent, there are few publication where ionic liquid was used as support. Research in the field where ionic liquid was used as a support is the challenging and one of the hot topics for the medicinal and organic chemist. Supported synthesis is a widely employed technique that has greatly facilitated the synthesis of many compounds and is the critical element behind the explosion in combinatorial synthesis[61]. In order to circumvent the drawback, most recently ionic liquid has emerged as alternative soluble support for carrying out the organic synthesis of biologically relevant compounds. An attractive feature of ionic liquids is that their solubility can be tuned readily. Therefore, phase separation from organic solvent or aqueous phase is allowed depending on the choice of cations and anions. This suggests the possibility of using these small molecular ionic liquids as soluble supports for organic synthesis. Ionic liquid attached substrates are

expected to retain their reactivity, as in solution reactions, and allowed the use of conventional spectroscopic analysis such as NMR during the synthetic process. Figure 1.3. shows the use of ionic liquid as catalyst, solvents, and reagents.

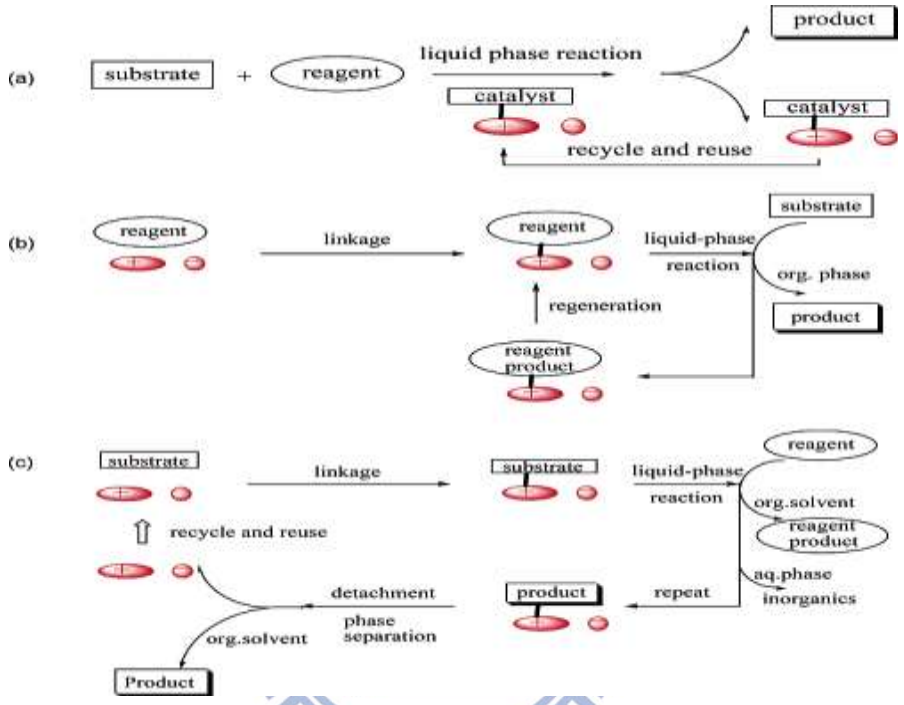


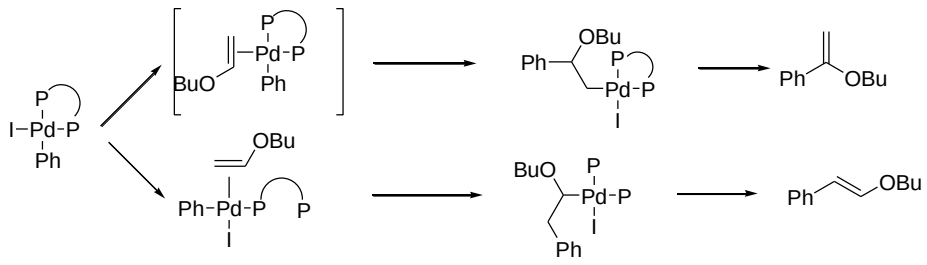
Figure 1.3. Ionic-liquid-supported synthesis: (a) catalyst; (b) reagent; (c) substrate

Courtesy. "Miao, W.; Chan, T. H. Acc.Chem.Res. ***2006,*** *39, 897"*

1.8.4. The use of Ionic-Liquid as catalyst.

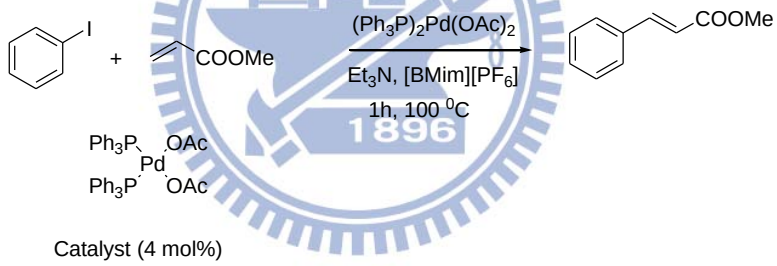
1.8.4.1. Cross coupling Reaction

In 1996, Kaufmann demonstrated the first example in ionic liquid by use of ammonium and phosphonium salts. Under basic conditions, deprotonation and formation of palladium complexes of imidazolium carbenes become facile as shown in Scheme 1.14.[62]



Scheme 1.14. Mechanistic pathway in Cross coupling reaction.

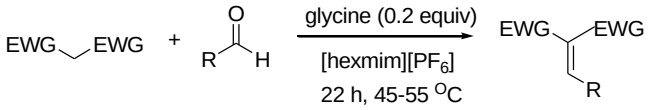
In 1999, Seddon found tri-phasic system – organic: product, ionic liquid: catalyst, aqueous: salt which allows catalyst to be recovered and reused. Similar results for Suzuki, Stille, and Negishi (although yield decreases on recycle experiments for Negishi). In 1999, A. J. Carmichael *et. al.,* showed the palladium catalysed Heck arylation in ionic liquid as a solvent as shown in Scheme 1.15.[63]



Scheme 1.15. Palladium catalysed Heck arylation.

1.8.4.2. Knoevenagel Condensation/Robinson Annulation

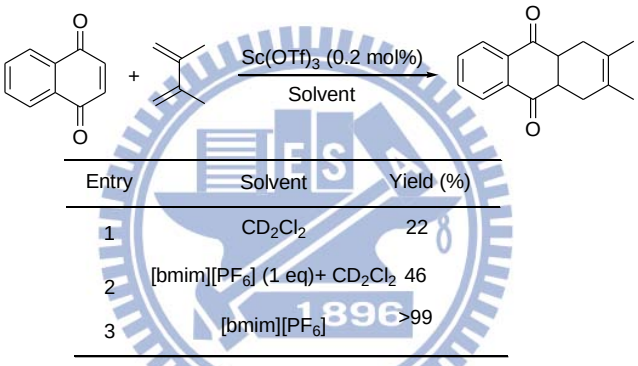
In 2001, Morrison *et. al.* have used the Knoevenagel condensation reactions performed in air without rigorous drying in ionic liquid and the product was extracted with toluene as shown in Scheme 1.16.[64]



Scheme1.16. Knoevenagel Condensation in ionic liquid medium.

1.8.4.3. Diels-Alder Reaction

In 2001, Song *et.al.* have identified that the Diels-Alder reaction can be performed inionic liquid medium. The main advantage was that ionic liquid allows for catalyst recovery, rate acceleration, selectivity enhancement as observed in Scheme 1.17.[65]

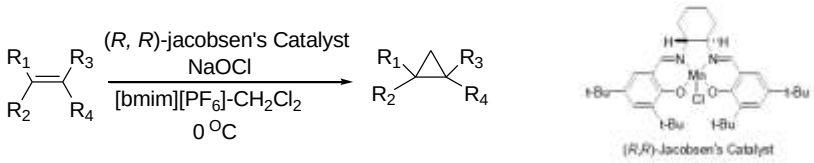


Entry	Solvent	Yield (%)
1	CD_2Cl_2	22
2	[bmim][PF_6] (1 eq)+ CD_2Cl_2	46
3	[bmim][PF_6]	>99

Scheme 1.17. [2+4] Diels-Alder reaction using ionic liquid as a solvent.

1.8.4.4. Olefin Epoxidation

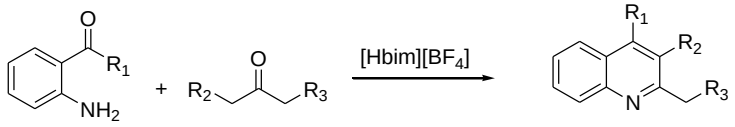
In 2000, Song *et. al.* carried out the olefin epoxidation using (*R*,*R*)-Jacobsen's catalyst immobilized in ionic liquid as shown in Scheme 1.18.[66]



Scheme 1.18. Olefin Epoxidation using ionic liquid as solvent.

1.8.4.5. Friedlander Synthesis

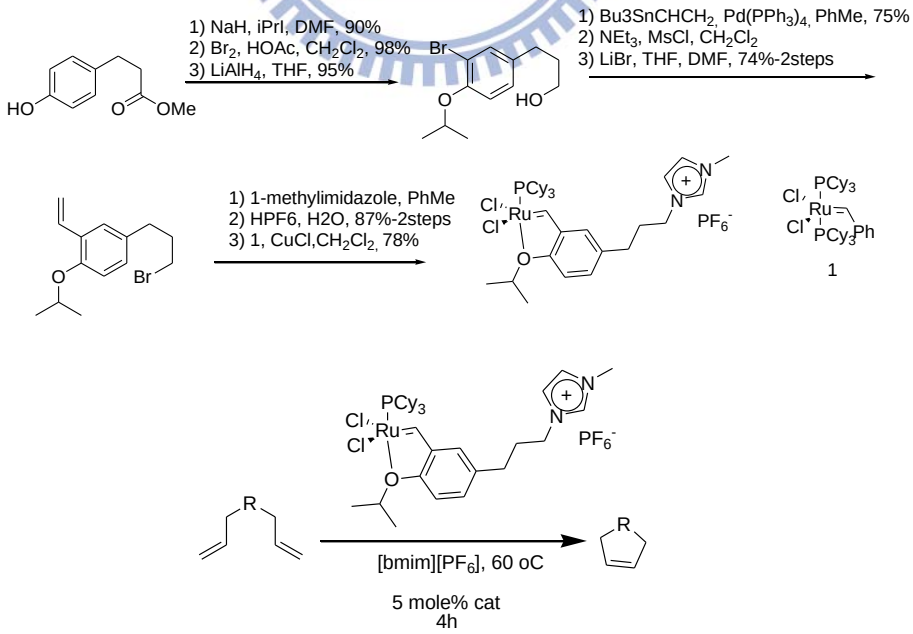
In 2003, Palimkar *et.al.* showed the ionic liquids can be used as reaction medium for the Friedlander quinoline synthesis. Normally this reaction requires common additives such as HCl, H_2SO_4, PTSA, microwave, $ZnCl_2/NEt_3$, and ruthenium or palladium complexes. But using ionic liquids as reaction medium does not require any additives as shown in Scheme 1.19.[67]



Scheme 1.19. Friedlander Synthesis in ionic liquid medium.

1.8.4.6. Ring Closing Metathesis

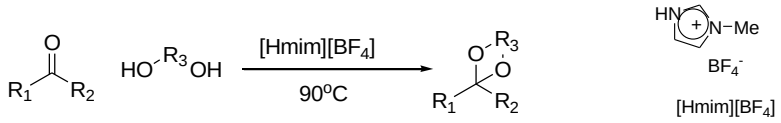
In 2003, Audic *et.al.* have used the ionic liquid in ring ring closing metathesis as shown in Scheme 1.20.[68]



Scheme 1.20. Ring closing metathesis in ionic liquid medium.

1.8.4.7. Diol/Carbonyl Protection

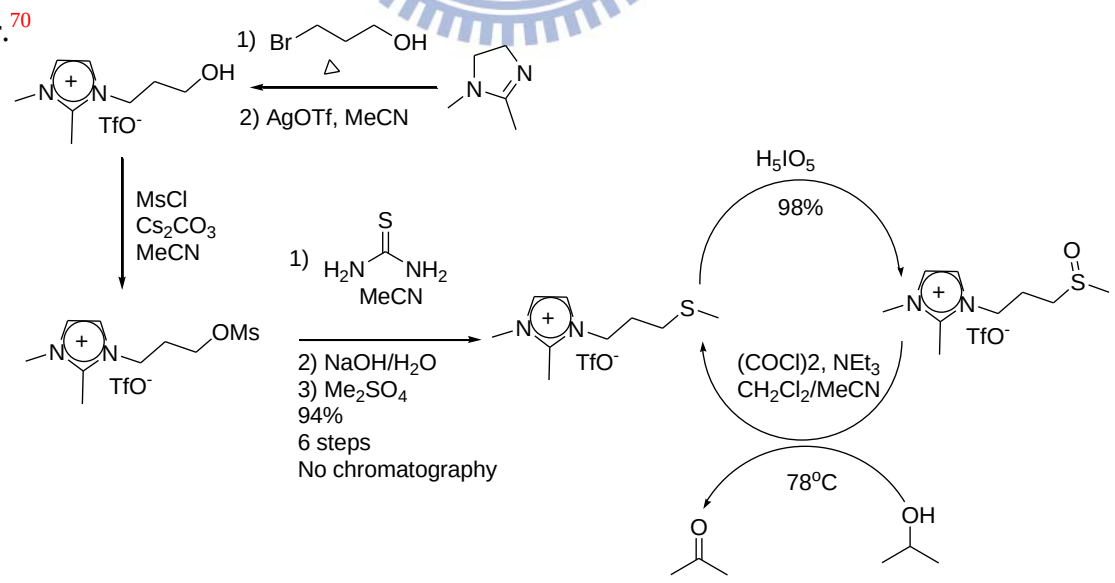
In 2004, He *et. al.* found that carbonyl functionality in organic molecules can be protected using diol in ionic liquid medium as shown in Scheme 1.21[69]



Scheme 1.21. Carbonyl group protection in ionic liquid medium.

1.8.4.8. Swern Oxidation

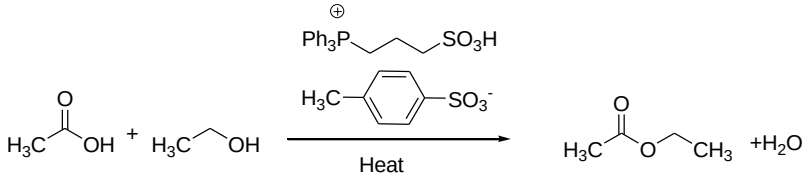
In 2006, Chan *et. al*. have used the ionic liquid as reaction medium for Swern oxidation as shown in Scheme 1.22. The reaction involves the ionic liquid tethered "dimethyl sulfoxide" which can be prepared with no chromatography and no use of volatile (smelly) organosulfur reagents. The Products separated from ionic liquid by phase extraction with ether.[70]



Scheme 1.22. Swern oxidation using ionic liquid tethered dimethyl sulfoxide.

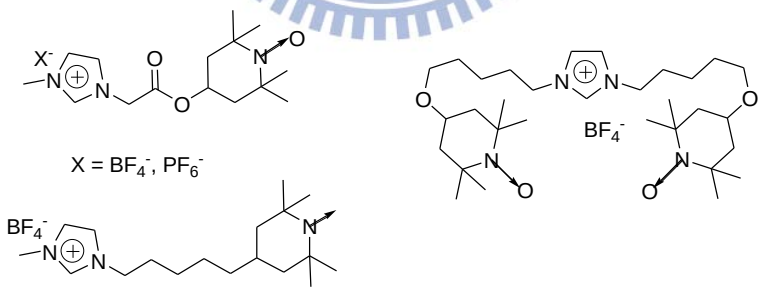
1.8.5. The use of Ionic-Liquid as Supported Catalysis.

Davis was the first to recognize that functionalized ionic liquids can serve not just as reaction media but as catalyst as well in Scheme 1.23. shows the example of the phosphonium salt catalyzes the formation of esters from alcohols and acids, dehydration of alcohols to ethers, and pinacol rearrangement of vicinal diols. [71-72]



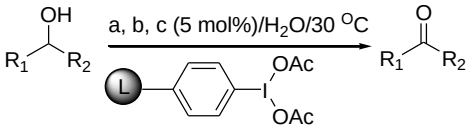
Scheme 1.23. Phosphonium salts catalyses the organic reaction

Ionic liquid supported sulfonic acid can catalyse the esterification of aliphatic acids with olefin and hetero-Michael additions. [73] Gao and Bao [74] reported the IL supported 2,2,6,6-tetramethyl-piperidinyloxy (Scheme 1.24.), free radical TEMPO catalysts for the oxidation of alcohols.



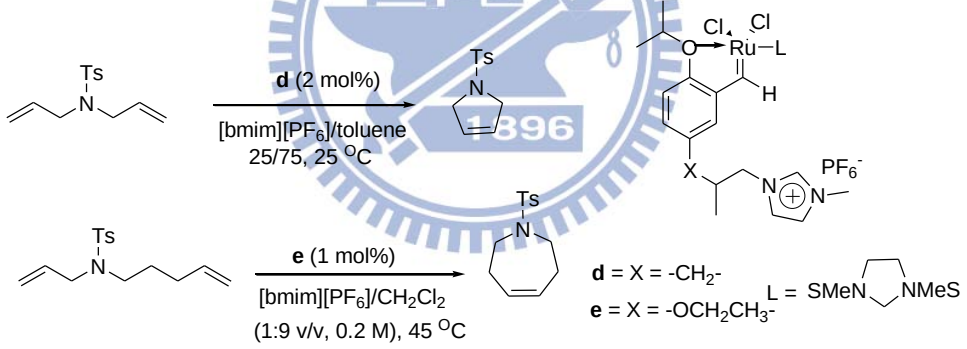
Scheme 1.24. Ionic liquid supported catalyst

All the catalysts showed similar activity to that of free TEMPO and could be reused up to many times without loss of activity in Scheme 1.25.



Scheme 1.25. Catalytic activity of Ionic liquid supported catalyst.

The efficient recycling of IL-supported catalysts suggests that the approach can be useful in metal-catalyzed reactions where the reuse of expensive ligands, metal, or both is critical. In 2003, Guillemine[75] and Yao[76] reported independently the synthesis of IL-supported catalysts for the ring-closing metathesis (RCM) of olefins (Scheme 1.26.). The IL-supported palladium complex was found to catalyze the Heck reactions with good recyclability of up to 10 cycles.[77]

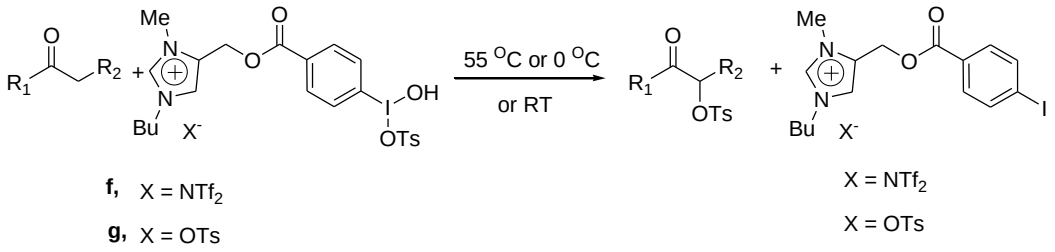


Scheme 1.26. IL-supported catalysts for the ring-closing metathesis (RCM) of olefins.

1.8.6. The use of Ionic-Liquid as Supported Reagents.

Synthetic reagents anchored onto ionic liquids can be separated readily from the reaction mixture by simple phase separation after the desired chemical transformation and then be regenerated and reused. Recently it has been observed that the IL-supported hypervalent

iodine(III) reagents **f** and **g** have been prepared by Handy for the R-tosylation of ketones (Scheme 1.27).[78] The reaction demonstrated the advantage of the tunable separation properties of the ionic liquid support.

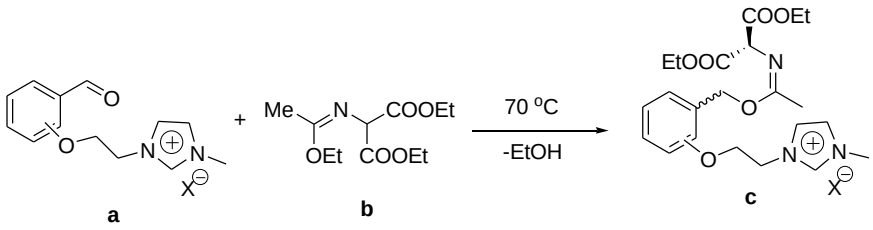


Scheme 1.27. Tosylation of ketones using ionic-liquid as supported reagents

1.8.7. Ionic-Liquid-Supported Synthesis of Small Molecules and Combinatorial Synthesis

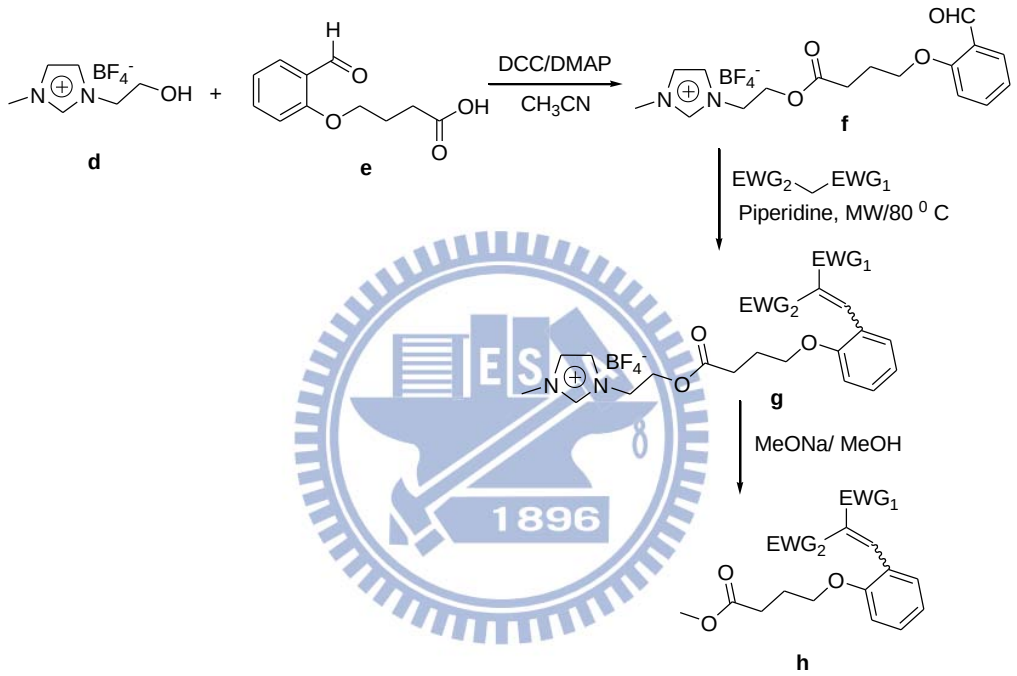
As we all aware of the fact that the supported synthesis is a widely employed technique that has greatly facilitated the synthesis of many compounds and is the critical element behind the explosion in combinatorial synthesis. Traditionally, the supported synthesis has employed a heterogeneous material such as cross linked polystyrene to support one of the reactants. The primary advantage of such a choice is that the supported material, being heterogeneous, can be readily separated by simple filtration from the reaction medium and by-products. At the same time, this heterogeneity limits the types of reactions and reaction conditions that can be employed. Further, using simple polystyrene supports, which are typically functionalized to <10%, the maximum loading is <2 mmol/g. These limitations have led more recently to the development of a variety of 'soluble' supports (e.g. the polyethylene glycol (PEG) supports popularized by Janda). Since the supports are homogeneous in a variety of conventional organic solvents,

reactions can be performed under conventional solution-phase conditions. At the same time, by changing the polarity of the solvent (most frequently by the addition of methanol), the support and supported molecule will precipitate, resulting in facile separation by filtration. While this is a major step forward, there are still limitations to the current supports. In order to circumvent the drawback, most recently ionic liquid has emerged as alternative soluble support for carrying out the organic synthesis of biologically relevant compounds. An attractive feature of ionic liquids is that their solubility can be tuned readily. Therefore, phase separation from organic solvent or aqueous phase is allowed depending on the choice of cations and anions. This suggests the possibility of using these small molecular ionic liquids as soluble supports for organic synthesis. Ionic liquid attached substrates are expected to retain their reactivity, as in solution reactions, and allowed the use of conventional spectroscopic analysis such as NMR during the synthetic process. Bazureau was the first to propose the use of ionic liquid as soluble support for the synthesis of small organic molecules.[79] They observed that the reaction of the IL anchored dipolarophile **a** (*ortho*) with the imidate **b** to give the adduct **c** (Scheme 1.28) was faster than that of the reaction of free 2-ethoxybenzaldehyde with the ionic liquid [emim][NfO](emim)1-ethyl-3-methylimidazolium).[80]



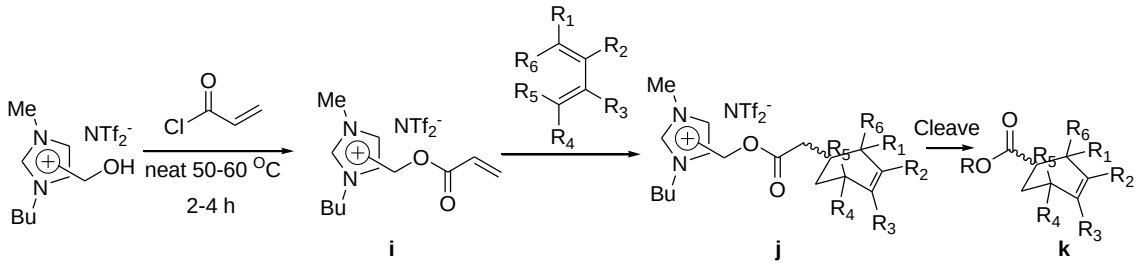
Scheme 1.28. IL supported synthesis of small molecules

They also examined the Knoevenagel and 1,3-dipolar cycloadition reactions with the IL-supported benzaldehyde (Scheme 1.29). Thus, the substituted benzaldehyde was anchored onto the IL support to give **f**. Knoevenagel reaction of substrate under homogeneous conditions gave the products **g** in high yields. Cleavage of the ionic liquid support by basic methanolysis gave the small molecule **h** in good isolated yield.



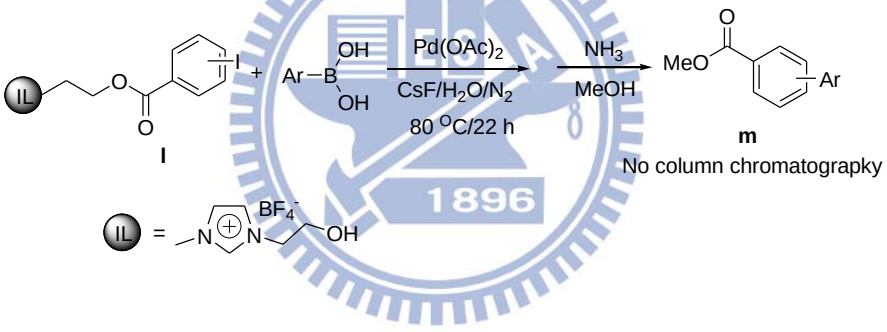
Scheme 1.29. Ionic Liquid supported synthesis of **h**

In an attempt to show the 4+2 cycloaddition reaction on ionic liquid support, Handy and Okello have reacted the acrolyl chloride with ionic liquid to get the IL anchored compound **i**.[81] The ionic liquid support could be recovered in greater than 90% yield and reused as drawn in scheme 1.30.



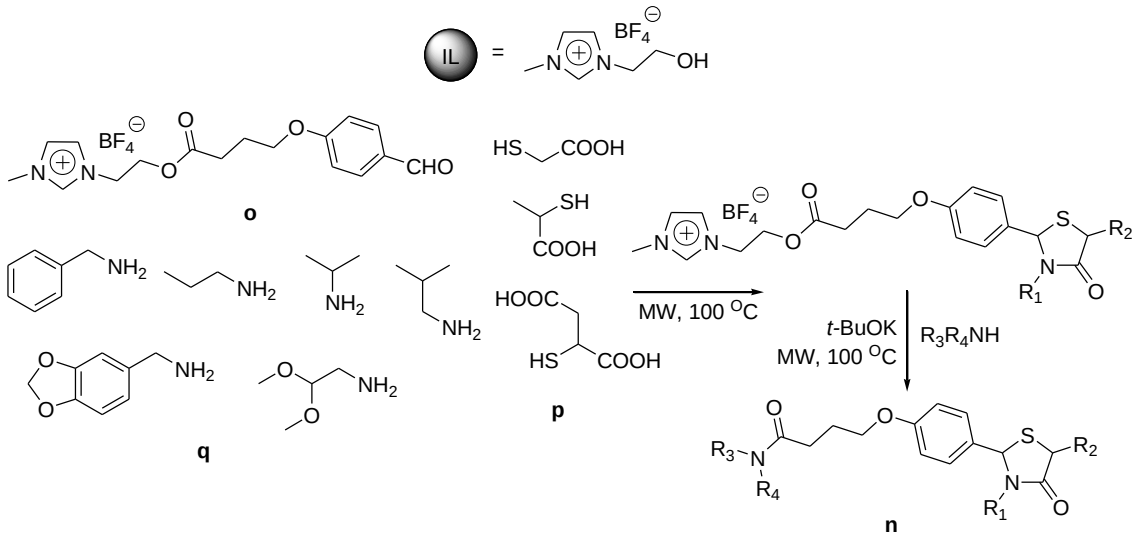
Scheme 1.30. Ionic liquid supported Diels-Alder reaction

In order to demonstrate the advantages of IL-supported synthesis over the conventional solution-phase synthesis, Chen *et. al.* examined a series of Suzuki coupling reactions between boronic acids and the IL-supported iodobenzoates **l** as shown in Scheme 1.31.[81]



Scheme 1.31. Ionic Liquid Supported Suzuki coupling reactions.

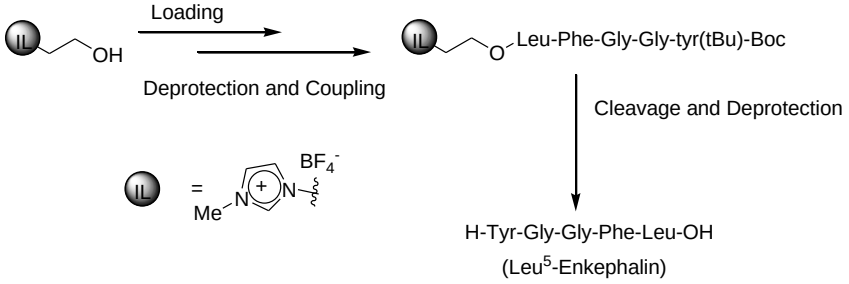
Furthermore it has been observed that the IL-supported strategy for combinatorial synthesis was demonstrated by the preparation of a small library of 4-thiazolidinones **n** (Scheme 1.32).[82]



Scheme 1.32. Ionic Liquid Supported synthesis of small library of 4-thiazolidinones.

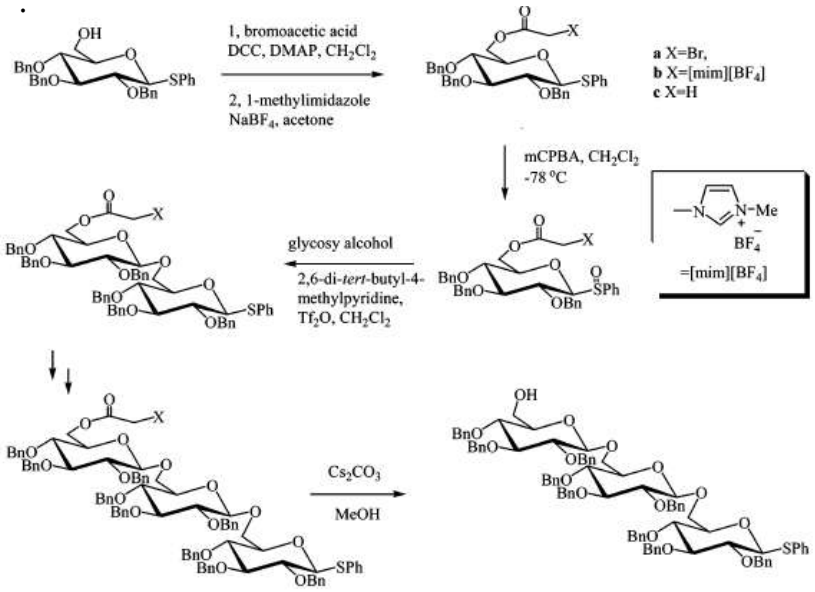
The advantages of using ionic liquid support are as follows: (1) The product isolation is easy because the side products are removed by simple washing with appropriate solvent; (2) in each step, the reaction can be monitored by standard analytical technique; (3) due to the high polarity of the ionic liquid support, microwave irradiation can be easily applied to enhance the reaction; (4) the final product was usually obtained in high purity without flash chromatography.

The same strategy has been tried to apply to the syntheses of important oligomers of biomolecules. Chen *et. al.* have used the synthesis of the bioactive pentapeptide Leu5-enkephalin **r** using ionic liquid support (Scheme 1.33).[84]



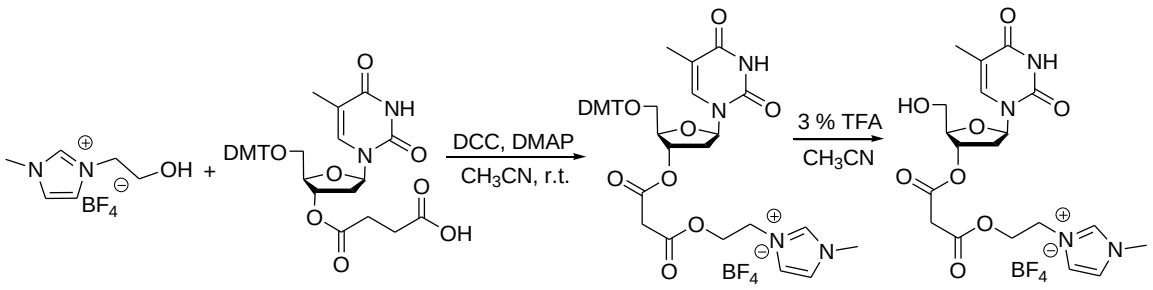
Scheme 1.33. Ionic liquid supported synthesis of Leu5-enkephalin

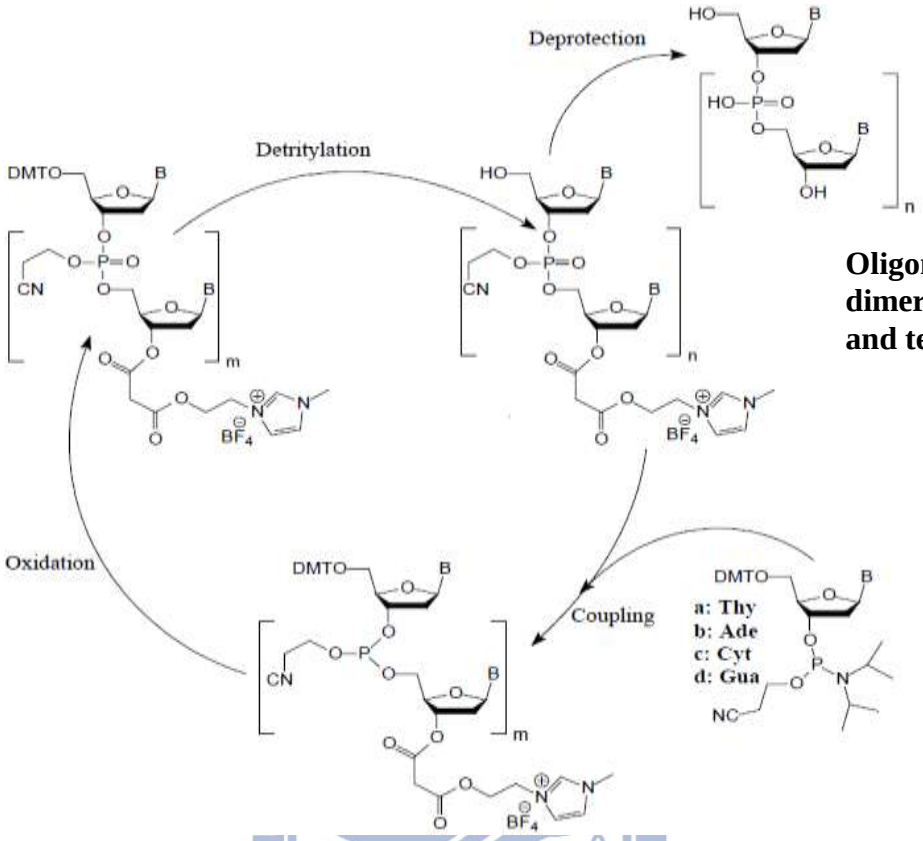
Inspired by this advantage for the success synthesis of oligopeptides in 2006, Chan *et. al*. initiated the, adopted the approach for the synthesis of oligosaccharides as shown in (Scheme 1.34).[85].



Scheme 1.34. Ionic liquid supported synthesis of oligosaccharides.

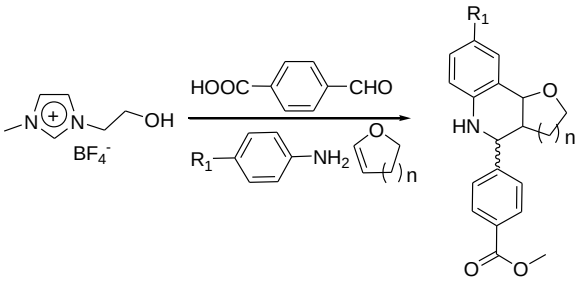
Damha *et.al.*[86] have described the synthesis of oligonucleotides in solution using a soluble ionic liquid as support in Scheme 1.35. Short oligomers of varying base composition were synthesized using this method in high yields and high purity, requiring no chromatography for purification prior to cleavage from the support.





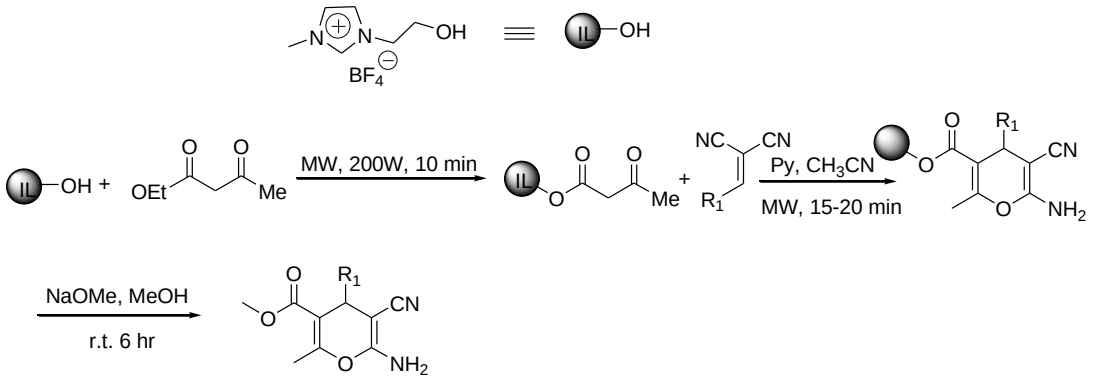
Scheme 1.35. Synthetic cycle of oligonucleotides

In 2007, Li *et.al*. have used the ionic liquid as soluble support for the synthesis of tetrahydropyrano and tetrahydrofuranoquinolines, an important heterocyclic compounds under microwave irradiation as elaborated in Scheme 1.36.[87]



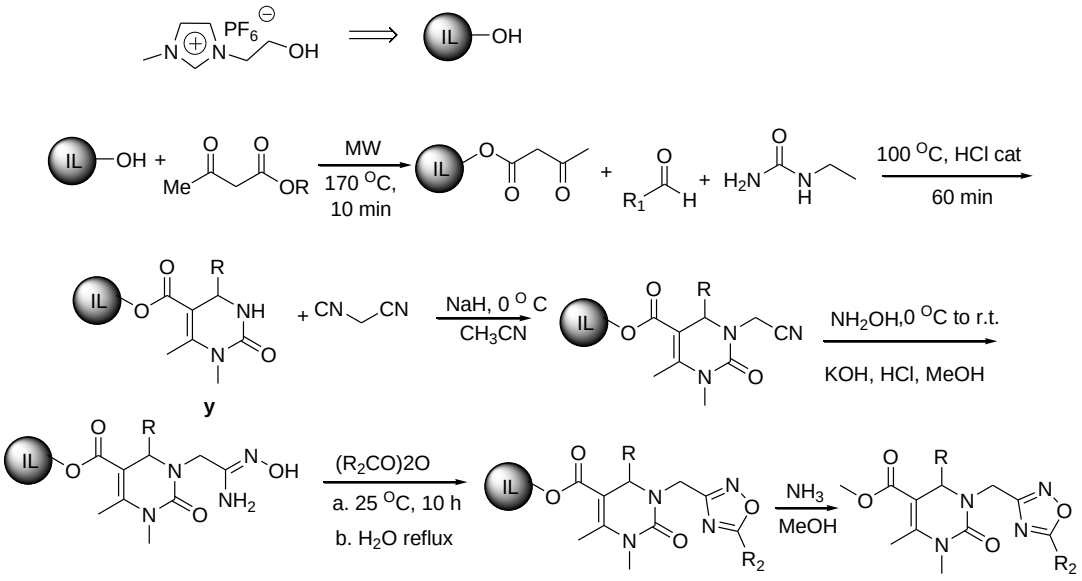
Scheme 1.36. Synthetic cycle of tetrahydropyrano and tetrahydrofuranoquinolines.

Song et al.[88] reported the synthesis of 2-amino-4*H*-pyrans from malononitrile, aryl aldehydes, and 1,3-dicarbonyl compounds using ionic liquids as soluble support as elaborated in Scheme 1.37.



Scheme 1.37. Synthesis of pyran derivatives.

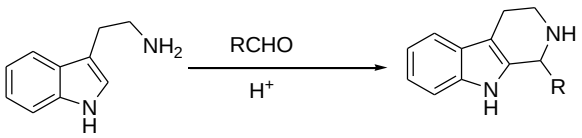
Bazureau *et. al.* executed multicomponent reaction on ionic liquid support to obtain 2 thioxotetrahydropyrimidin4-(1*H*)-ones.[89] The methodology employs microwave irradiation and a matrix of PEG ILPs used for an ionic liquid phase organic synthesis. Continuing their work in this area, Bazureau *et al*.[90] have developed the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) (Scheme 38) with a 1,2,4-oxadiazole group via the three component Biginelli condensation without solvent as drawn in Scheme 1.38.



Scheme 1.38. 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs).

1.9. Pictet-Spengler reaction:

The Pictet–Spengler reaction is a chemical reaction in which a β-arylethylamine such as tryptamine undergoes ring closure reaction after condensation with an aldehyde or ketone. Employing an acidic catalyst under refluxing conditions some reactive compounds give good yields. The Pictet–Spengler reaction can be considered a special case of the mannich reaction as drwan in Scheme 1.39.[91-92]

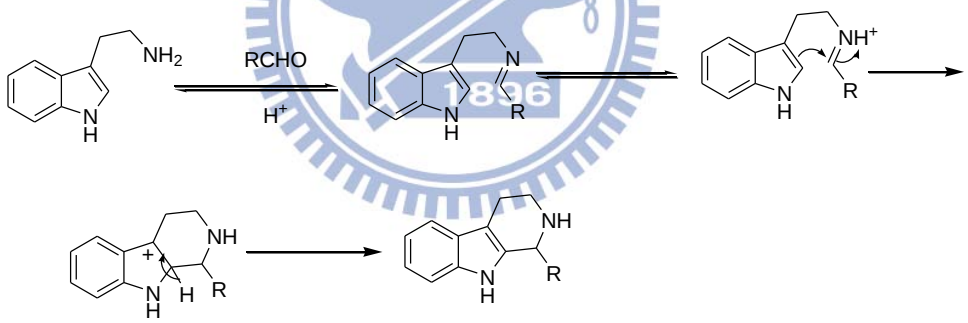


Scheme 1.39. Typical Pictet-Spengler Reaction

The reaction was discovered in 1911 by Ame'Pictet and Theodor Spengler. It has remained an important reaction in the fields of alkaloid and pharmacetical synthesis. The Pictet–Spengler reaction product of tryptophan and aldoses can be identified in foodstuffs such as soy sauce and ketchup. The Pictet–Spengler reaction has been applied to solid phase combinatorial chemistry with great success.[93]

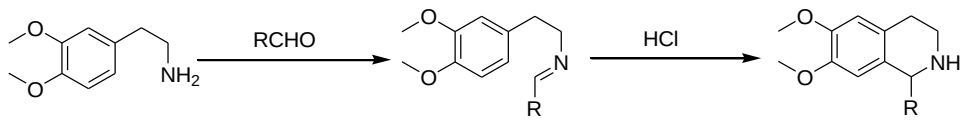
1.9.1. Reaction mechanism

It is the electrophilicity of the imine double bond that is the driving force of the cyclization. The reaction mechanism occurs by initial formation of an iminium ion (**4**) followed by electrophilic substitution at the 2-position. After deprotonation, the desired product is formed. The reaction shown is an example of a 6-endo-trig reaction, which is favoured by Baldwin's ring closure rules as shown in Scheme 1.40. [94]



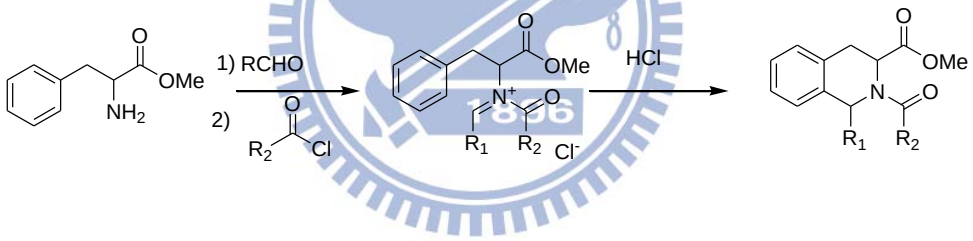
Scheme 1.40. Mechanism of Pictet-Spengler cyclisation

Replacing an indole with a 3,4-dimethoxyphenyl group give the reaction named the Pictet-Spengler tetrahydroisoquinoline synthesis. Reaction conditions are generally harsher than the indole variant, and require refluxing conditions with strong acids like hydrochloric acid, trifluroacetic acid, or superacids as shown in Scheme 1.41. .[95]



Scheme 1.41. Pictet-Spengler Reaction used for the synthesis of Tetrahydroisoquinoline derivative**s**

Sometimes, it has been observed that the instead of catalyzing the Pictet-Spengler cyclization with strong acid, one can acylate the iminium ion forming the intermediate N-acyliminium ion. The N-acyliminium ion is a very powerful eletrophile and most aromatic ring systems will cyclize under mild conditions with good yields as shown in Scheme 1.42.[96]



Scheme 1.42. N-acyliminium ion mediated Pictet-Spengler cyclisation.

1.10. Tetrahydro-*β*-carbolines and its hydantoin derivatives, importance and synthesis.

Tetrahydro-*β*-carbolines (**1A**), a key constituent of most naturally occurring indole alkaloids have received considerable attention to medicinal chemists owing to their important biological activities including anti-aggregation property, in vitro trypanocidal activity, antimalarial and anticonvulsants activity.[97] Recently, it has been found that hydantoin and thio hydantoin derivatives (**1B**) are also possessing several pharmacological properties including dual action for anticonvulsant, antimuscarinic activity, insulinotropic properties, and antifungal activity.[98] However, the ring system **2** as the conceptual derivation of new scaffold, which represents the amalgamation of two important pharmacophores, is much less known (Figure 1.4). The generation of a combined tetracyclic skeleton with tetrahydro-*β*-carboline and hydantoin thus, has a substantial intellectual appeal resembling drug-like molecules. This type of compounds has been documented for the inhibition of cGMP-phosphodiesterase (**2A, 2B**), a chemical messenger in the body that activates the cGMP kinase that results of relaxation of smooth muscle tissue which leads to vasodilation and increased blood flow, a novel antimitotic agent (**2C**), a novel Eg5 inhibitor (**2D**).[99-102] Because of their diverse array of biological activities, these novel drug-like molecules are interesting to explore in early screening (Figure 1.5).

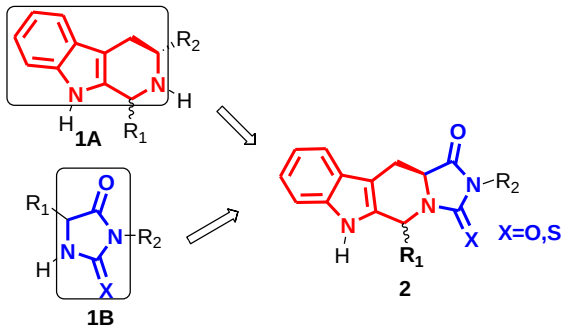


Figure 1.4. Conceptual Derivation of New Scaffold

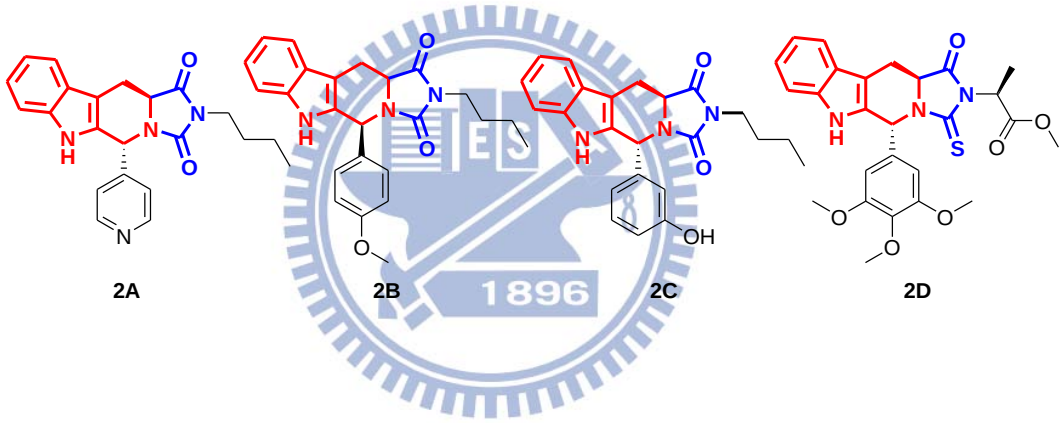
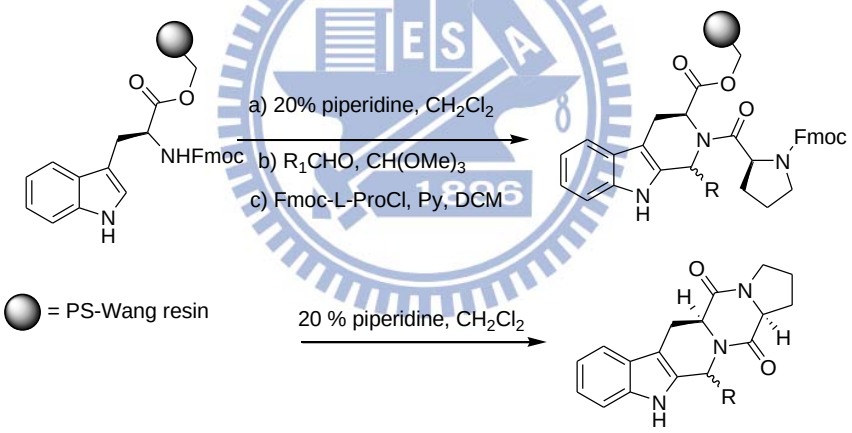


Figure 1.5. Representative Examples of Biological Active Hydantoin Analogs Tethered with Tetrahydro-*β*-Carbolines

The below section briefly reviews methods to the construction of biologically active hydantoin analogs tethered with Tetrahydro-*β*-Carbolines which involves the acid or base catalysed Pictet-Spengler cyclisation of tryptophan metyl ester with aldehydes or ketones

1.11. Chemical methods for synthesizing Hydantoin Analogs Tethered with Tetrahydro-*β*-Carbolines

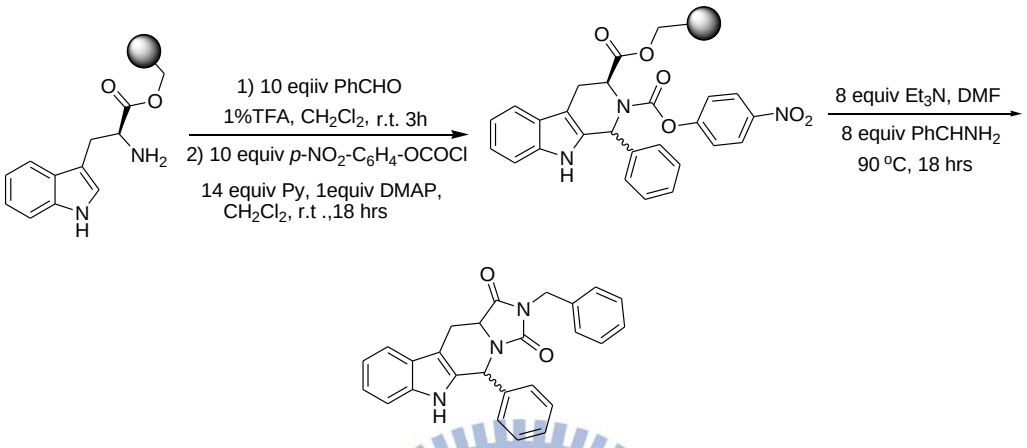
In the year 1999, Ganesan *et. al.* has developed diketo piperazine fused tetrahydro-*β*-carboline by employing L-Tryptophan immobilized loaded on polystyrene-Wang resin. The polymer bound L-tryptophan after Fmoc deprotection was sequentially reacted with an aldehyde and Fmoc-amino acid chloride. This generates a intermediate N-acyliminium species which undergoes Pictet-Spengler condensation to give a mixture of cis and trans tetrahydro-*β*-carbolines. Simultaneously, after Fmoc deprotection, the diketopiperazine ring forms by the traceless fashion as shown in Scheme 1.43.[103]



Scheme 1.43. Traceless synthesis of diketopiprizine fused tetrahydro-*β*-Carbolines on solid phase by Ganesan's *et. al.*

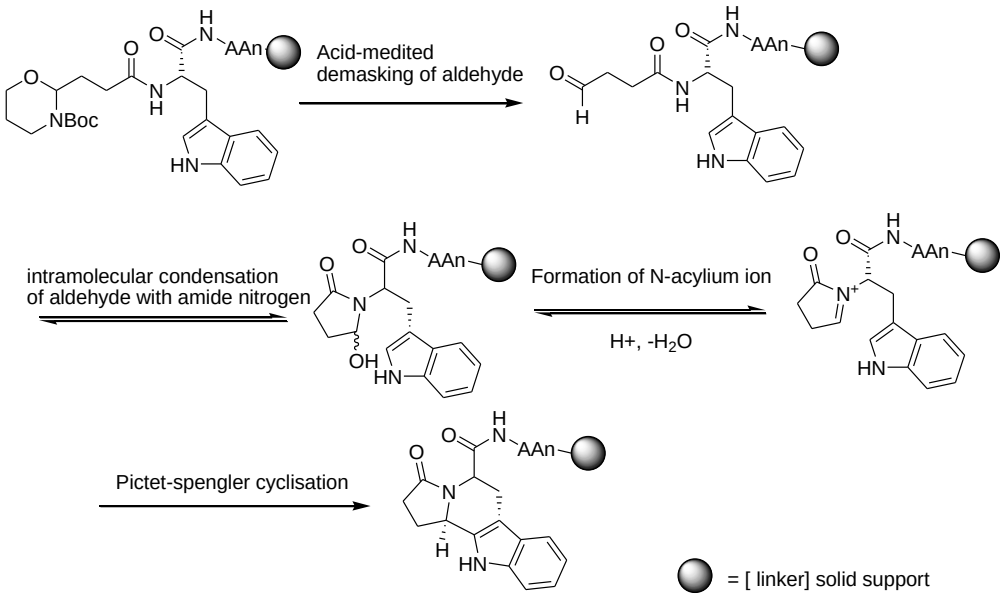
In the year 2002, also for the first time Ganesan *et. al.* has developed hydantoin fused tetrahydro-*β*-carboline on the solid support. The synthetic route consists of a new approach to hydantoins that proceeds via amine addition to an activated carbamate and

instead of using the isocyanate as building blocks as shown in the Scheme 1.44. Similarly, attempted approaches to the solid phase synthesis of hydantoin fused tetrahydroisoquinoline by the isocyanate methods were not materialized. [104]



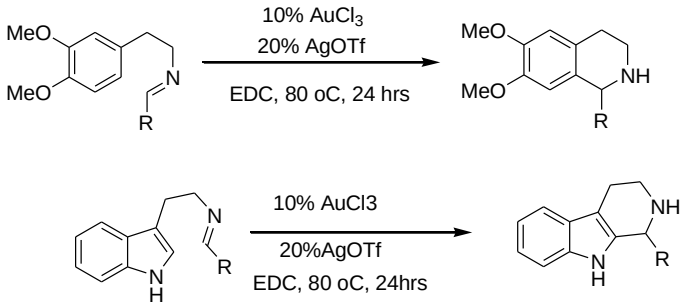
Scheme 1.44. Ganeshan's *et al* method of traceless synthesis of hydantoin fused tetrahydro-*β*-Carbolines on solid phase.

Likewise, in the year 2004, Meldel *et. al.* has developed a novel solid-phase intramolecular Pictet-Spengler reaction. They utilized masked aldehyde protected *N*-Boc-1,3-oxazinanes as building blocks for the generation of solid-supported aldehydes. By exposer to acidic treatment, the protection part of aldehyde functionality is rapidly released and becomes vulnerable to nucleophilic attack from amide nitrogen of the amide backbone, which accounted for the formation of a highly reactive cyclic *N*-acyliminium ion as intermediate. Subsequently, a stereoselective Pictet-Spengler cyclisation took place to provide the target structure as shown in the Scheme 1.45. Finally, the cleavage from the polymer suppots generates the target skeleton.[105]



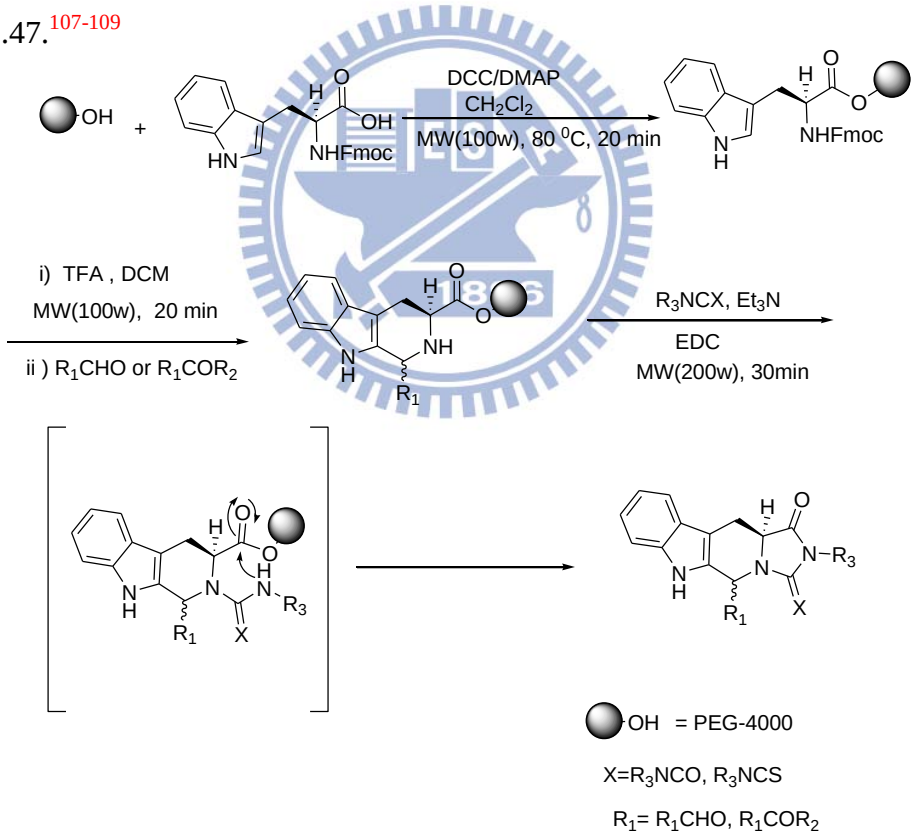
Scheme 1.45. Meldel's method of traceless synthesis of tetrahydro-*β*-Carbolines on solid phase.

In the year 2005, Youn *et. al.* has developed a variety of tetrahydroisoquinoline and tetrahydro-*beta*-carboline ring via mild and efficient $AuCl_3$/AgOTf-catalyzed Pictet-Spengler reactions in moderate to good yields as shown in Scheme 1.46.[106]



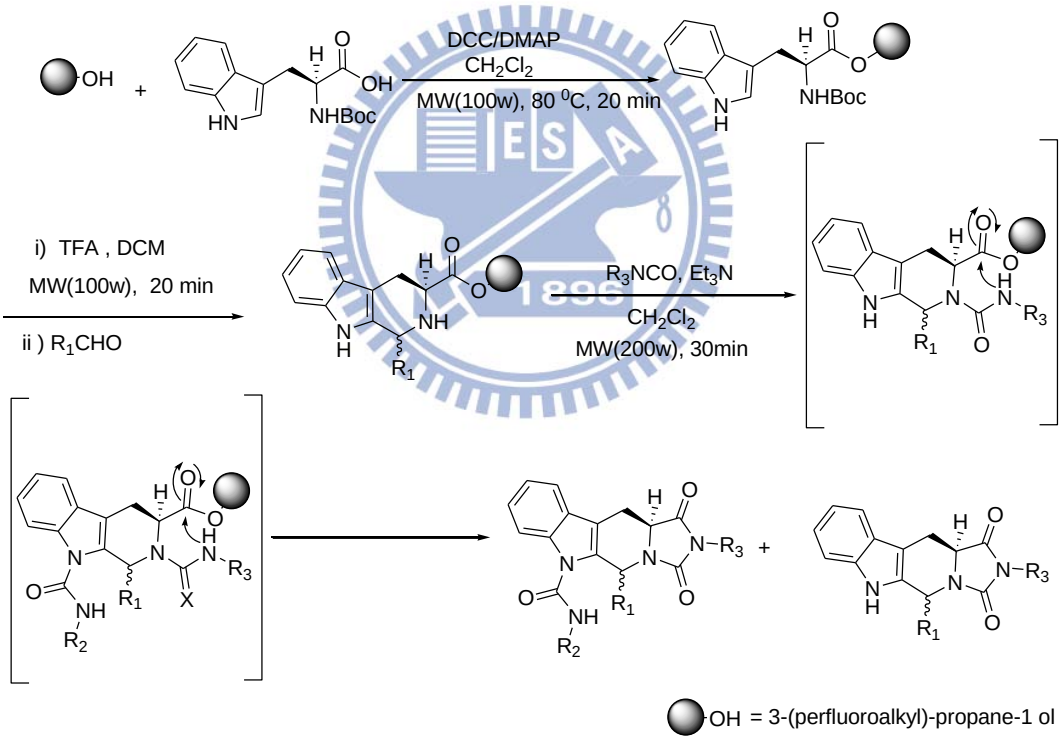
Scheme 1.46. Youn's method for the synthesis of tetrahydro-*β*-Carbolines and isoquinoline.

Subsequently, from the year 2006, our lab has developed pharmacologically interesting tetrahydro-*β*-carboline hydantoins through a four-step traceless synthesis by combinatorial approach. Two-arm PEG was used as a soluble polymer support and reacted with Fmoc or Boc-protected L-tryptophane to generate the polymer bound ester which after Fmoc or Boc deprotection subsequently reacted with aldehyde and ketones at room temperature or microwave irradiartion to generate the tetrahydro-*β*-carboline derivatives. The resulting polymer bound tetrahydro-*β*-carboline intermediates were further reacted with isothiocyanate or isocyanate moiety to undergo the traceless cleavage to generate the hydantoin fused tetrahydro-*β*-carboline as target skeletons as shown in the Scheme 1.47.[107-109]



Scheme 1.47. Suns's *et al* method for the synthesis of hydantoin fused tetrahydro-*β*-Carbolines on Polyethylene glycol as soluble support.

Subsequently in the year 2007, our lab for the first time carried out the the fluorous traceless synthesis of substituted indole alkaloids by attaching the 3-(perfluorooctyl) propanol with Boc protected L-tryptophan. The reaction of perfluoroalkyl (Rfh)-tagged tryptophan esters with various aldehydes underwent Pictet-Spengler reaction to give cis and trans stereoisomers of tetrahydro-*β*-carbolines. The resulting fluorous tagged tetrahydro-*β*-carboline intermediates were further reacted with isocyanate moiety to undergo the traceless cleavage to generate the hydantoin fused tetrahydro-*β*-carboline as target skeletons as shown in the Scheme 1.48.[110]

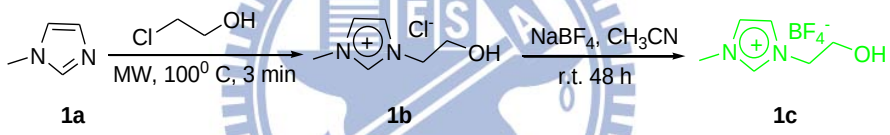


Scheme 1.48. Suns's method for the synthesis of hydantoin fused tetrahydro-*β*-Carbolines on Fluorous tagged as support.

However, all the methods suffer low loading capacity, as well as harsh reaction conditions, and use of toxic organic solvents. The next section describes about the environmentally benign methodology for the target compounds on ionic liquid support.

1.12. Results and Discussions

To attain the target compound on ionic liquid support, First of all we need to synthesize the ionic liquid **1c** from N-methylimidazole and choloroethanol under microwave irradiation using acetonitrile, solvent by anion exchange mechanism as shown in the Scheme 1.49.

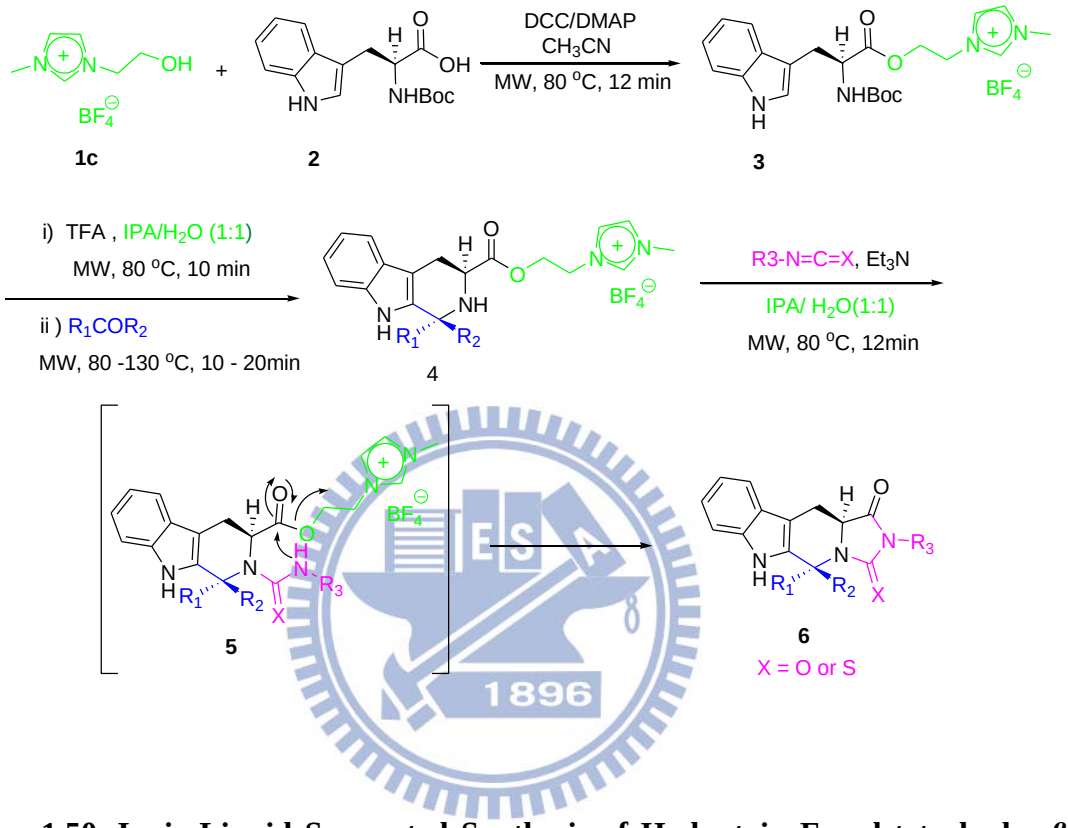


1a **1b** **1c**

Scheme 1.49. **Synthesis of hydroxyl ethyl methyl imidazolium tetrafluoroborate 1c**

After successfil synthesise of ionic liquid **1c**, we turned our attention to the most essential reaction involves the coupling of Boc protected L-tryptophan **2** to hydroxyl ethyl methyl imidazolium tetrafluoroborate **1c** (Scheme 1.50). The ionic liquid was reacted with Boc-Trp-OH **2** in the presence of catalytic amount of 4-dimethylaminopyridine and *N, N'*-dicyclohexylcarbodiimide (DCC) in anhydrous CH_3CN at room temperature for 48 hours to complete coupling of amino acid to ionic liquid tag. For comparison purposes, this coupling reaction was carried out under a set of different conditions, involving a) standard coupling conditions at room temperature for 48 hours; b) thermal heating at

refluxing temperature which required 12 hours to completion; c) microwave irradiation in a closed vessel system under pressure (80 °C, 2 bar) which reduced the coupling time to 12 minutes in Table 1.0.



Scheme 1.50. **Ionic Liquid Supported Synthesis of Hydantoin Fused tetrahydro-*β*-Carbolines.**

After completion of the reaction, the insoluble dicyclohexyl urea (DCU) was filtered off and ionic liquid conjugates **3** were precipitated with slow addition of cold ether which was then filtered to remove the excess un-reacted reagents to obtain the IL-conjugates **3**. Unlike other solid support, the main advantage of using ionic liquid soluble support was its direct monitoring capacity by standard analytical technique such as ^{1}H, ^{13}C NMR and mass spectroscopy. For the first time, we have demonstrated here that the product conversion was quantitative and monitored by regular proton NMR and spectroscopy in

each intermediate step with attached ionic liquid tag. It has been found that protons of -CH_2CH_2OH group of free ionic liquid was appeared in 3.94 ppm in proton NMR spectra A (Figure 1.6.) whereas the same set protons were shifted to 4.48 ppm after attachment to the Boc protected L-tryptophan **2** due to electron withdrawing nature of ester linkage to ionic liquid tag in spectra B. It was then developed for the generation of *β*-carbolines by [5+1] approach, which could again be perceived by the NHBoc deprotection and subsequent Pictet-Spengler cyclisation with carbonyl compounds in aqueous acidic medium.[123-124] It is noteworthy to note that NHBoc deprotection and subsequent cyclisation were carried out in one pot manner using 20 % TFA in H_2O-IPA (1:1) under microwave irradiation (80 °C, 2 bar) for 20-30 minutes.

Table 1.0 Comparison of microwave and conventional heating for the coupling, Pictet- Spengler cyclization and traceless reaction.

Entry	Substrates	Products	Optimized reaction condition		
			Time[a] (h)	Time[b] (h)	Time[c] (h)
1	**2**	**3**	48	12	0.2
2	**3**	**4**	72	18	0.3-0.5
3	**4**	**6**	24	10	0.2

[a] Room Temperature. [b] Reflux conditions. [c]Biotage Initiator

The NHBoc deprotection was achieved in 10 minutes under microwave irradiation, which was further confirmed from the disappearance of *tert*-butyl group around 1.44 ppm in spectra C. The *in-situ* generated amine was subsequently reacted with various carbonyl compounds in the same green media to generate imines which subsequently underwent

intramolecular cyclization to achieve the tetrahydro-*β*-carbolines **4** with ionic liquid tag remained intact. It was introducing the first point of structural diversity after Pictet-Spengler cyclization. When ketones were used in the Pictet-Spengler cyclisation, more harsh reaction condition (130 ^{o}C, 9 bar, 20 min) was required to complete intramolecular cyclization owing to the deactivating nature of the ketone functionality. Moreover, the same set of reaction was finished in 18 hours under refluxing condition. After the reaction was finished, the water and isopropanol was removed from the reaction mixtures under reduced pressure and the residue left was dissolved in CH_3CN and dried over $MgSO_4$, which further precipitated with ether and filtered through fritted funnel to remove un-reacted carbonyl compounds and other side products to obtain the IL-conjugates **4**. The formation of the IL immobilized tetrahydro-*β*-carboline was evident from ^{1}H NMR spectra, which clearly indicates the appearance of NH proton *β*-carboline moiety at 10.4 ppm and two methyl groups absorbance manifested at 2.0 ppm in spectra D. The formation of *cis* and *trans* diastereomers in various ratios of IL bound □-carboline **4** is determined through proton NMR analysis. To create the second diversity point in target structures, the terminal hydantoin moiety is constructed across ionic liquid immobilized β-carbolines by the reaction with various isocyanates and thioisocyanates in environmentally benign solvents under microwave irradiation to form urea intermediate **5**. The nucleophillic addition to proceed here is no need to add any other activating agent. Simultaneous intramolecular cyclization of IL-conjugated urea **5** in water/isopropanol co-solvents followed by cleavage of the ionic liquid support lead to a traceless synthesis of tetracyclic scaffold **6** in high yield and high purity. The cyclization of hydantoin ring and subsequently traceless cleavage of ionic liquid support was performed in one step under

mild basic condition in triethylamine. The reaction was eventually completed in 12 minutes (80 ^{o}C, 2 bar) as compared to that of 10 hours in refluxing condition Table 1. Reaction progress was directly monitored by TLC, which indicated the complete release of the desired compound **6** from the ionic liquid support to confirm the traceless nature of the reaction. The solvents were removed and, the residue left was redissolved in CH_3CN and which was further purified by precipitation in ether to obtain the targeted compounds **6**. The formation was achieved from proton NMR spectra which clearly indicate the nullifying the signal at 10.5 ppm and the disappearance of characteristic signal of ionic liquid tag at 4.8-4.7 ppm (-C*H*$_2$C*H*$_2$-).

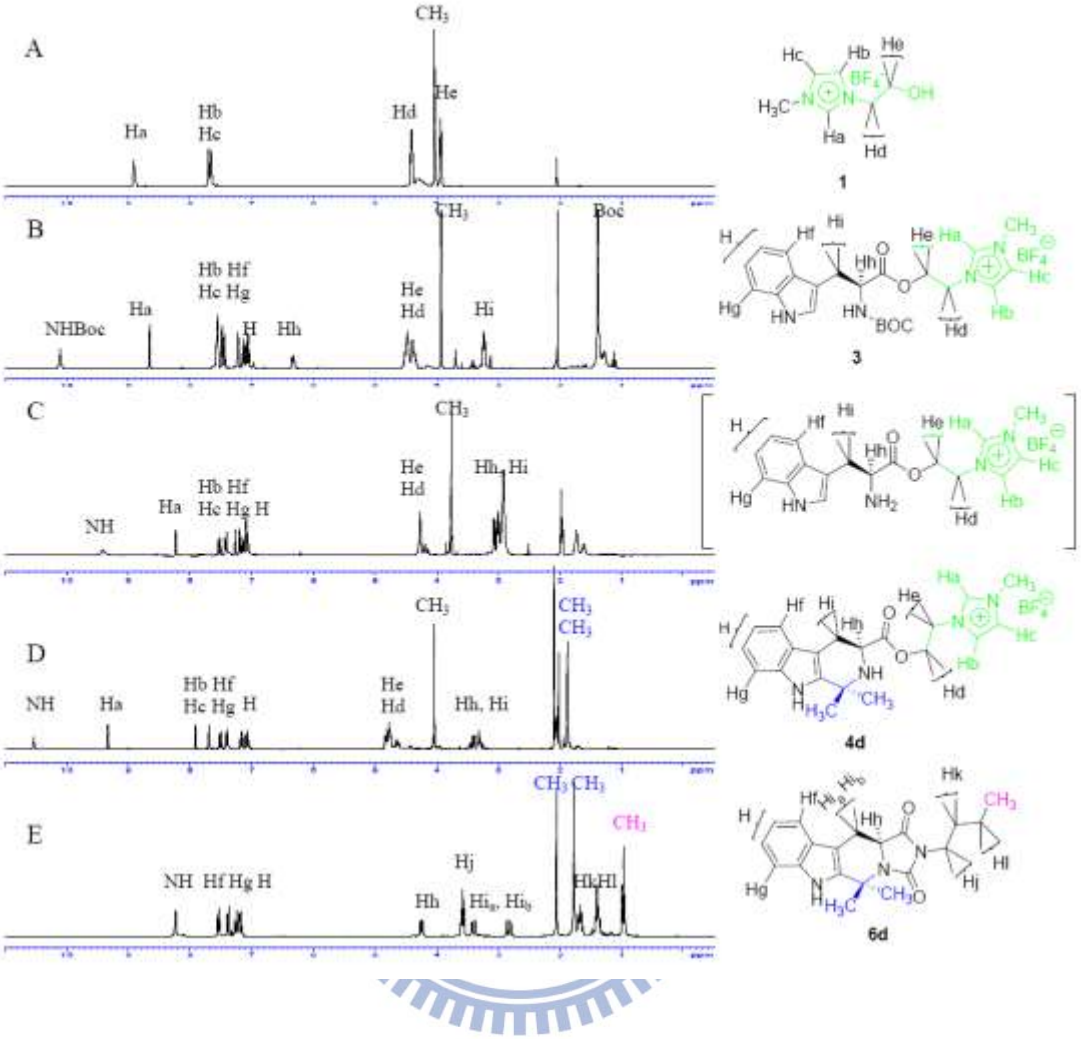


Figure 1.6. Stepwise Monitoring towards the Formation of Tetrahydro-*β*-carboline Fused Oxo and Thio Hydantoin Analogues on Ionic Liquid Support in $CDCl_3$ as solvent at 25 ^{0}C.

Moreover, all the intermediates of ionic liquid supported products could be confirmed with mass spectra (MS). A fascinating advantage of this strategy is that the cation of ionic liquid supported products could be detected easily as the most prominent peak in the MS obtained by fast atom bombardment (FAB) as shown in Table 1.1.

Table 1.1. Mass Spectral Study of Ionic-Liquid Supported Intermediates.

Entry	Products	FAB found (100%)	Yields (%)
1	**1c**	$M^+ = 127$	98
2	**3**	$M^+ = 413$	95
3	**4d**	$M^+ = 353$	91[a]

[a]yields of two steps

This fourteen member molecular library with high degree of purity has been obtained after three steps traceless synthesis on ionic liquid support under microwave irradiation. The analytical data including crude yield and purity were reported in Table 1.2.

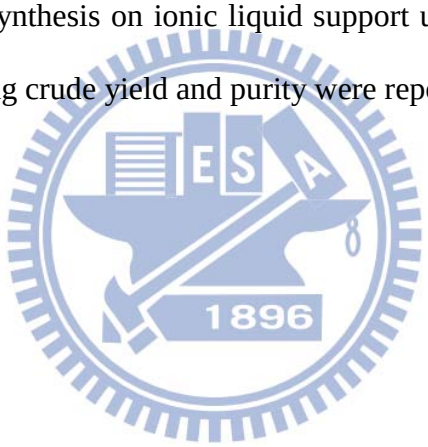
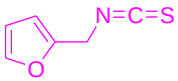
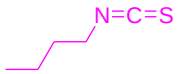
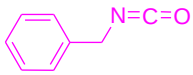
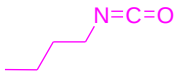
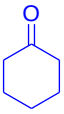
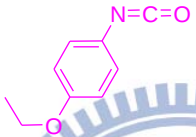
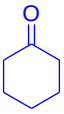
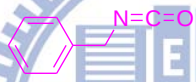
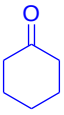
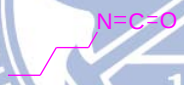
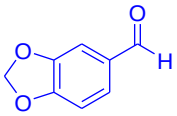
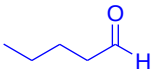
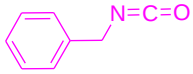
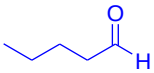
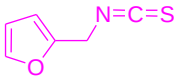
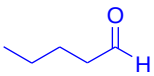
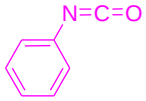
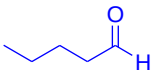
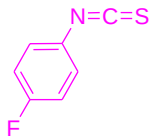
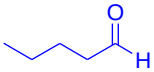
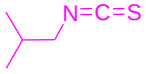
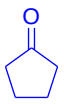
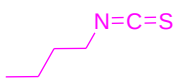


Table 1.2. Microwave Assisted, Ionic-Liquid Supported Synthesis of Tetrahydro-*β*-carboline hydantoin and thio hydantoins (6a-6n).

Entry	R_1COR_2	R_3NCX	LRMS[a]	Isolated yield[b] (%)	Crude Purity[c] (%)
6a			366	82	94
6b			342	80	76
6c			359	82	81
6d			326	85	89
6e			430	76	79
6f			400	95	98
6g			366	90	86
6h			433	77[d]	92
6i			388	75[d]	77
6j			394	82[d]	72
6k			374	80[d]	78
6l			408	83[d]	73
6m			370	83[d]	87
6n			368	75	79

[a]LRMS were detected with ESI ionization source. [b]Yields were based on loading of ionic liquid soluble support. [c]Determined by HPLC analysis (UV detection at 254 nm of the crude product. [d] Isolated as only *trans* isomer.

The predominantly *trans* stereochemistry of tetrahydro-β-carboline hydantoins **6h-6m** is based on spectral data through the comparison with earlier works by Cook's research group.[125] In order to further confirm the obtained results, we undertook the 1D NOE analysis of compound **6l** which showed that there is no correlation between C_2-Ha and C_{12}-Hb protons clearly to demonstrate the *trans* stereochemistry (Figure 1.7). Moreover, the irradiation of Hf caused the enhancement of He and Hb by 9.00 % and 2.03% respectively which further enhanced the Hd by 2.70 %. Similarly, the irradiation of Hc caused the enhancement of Ha and Hd by 4.86 % and 23.48 %. In the same way, the irradiation of He caused the enhancement of Hb and Hf signals by 1.81 and 12.4% respectively. We also obtained the signal enhancement of Hc by 3.18% followed by irradiation of Ha. The NOE spectrum has been attached in supporting information.

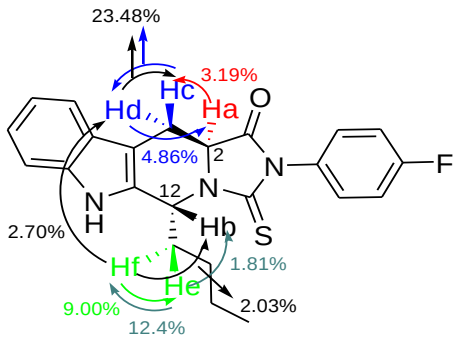


Figure 1.7. Some Important NOE Interactions in 6l trans Isomer

1.13. Dihydro and Tetrahydroquinazoline derivatives and its importance and synthesis.

In persistence of our efforts to develop novel and efficient ionic liquid-supported routes, leading to heterocyclic derivatives with potentially attractive pharmacological properties, we turned our attention to quinazolines analogues. Since quinazolines heterocycles have a great significant impact on drug discovery process for their significant role in all levels of biology including cell growth, signaling, proliferation and sensing quinazolines are extensively used in therapeutics. Likewise, dihydroquinazolines and tetrahydroquinazolins are biologically important pharmacophore and center structural skeleton in a range of natural products and synthetic drugs. They posses anti-inflammatory, antiviral, anticancer agents, anticonvulsants, antimalarial, antibacterial, and analgesic properties, and Anti Alzheimer's.[112] Additionally, they have been employed as most potent inhibitors on tyrosine kinase and cellular phosphorylation.[113] Recently it has been found that the 3,4-dihydrquinazoline derivatives such as **1C, 1D** in (Figure 1.8) has acted as potent T-type Ca^{2+} channel blockers. Their blocking effect has been evaluated against two isoforms of T type Ca^{2+} channel subfamily and N-type Ca^{2+} channel.[114] Moreover, the quinazoline skeleton found in the natural product likes vasicine and deoxypeganine **1E** showed bronchodialatory**,** thrombopoeitic and antihistamine activity.[115] Another interesting feature of basic quinazoline moiety was found in the drug molecule named as Iressa **1F,** erlotinib **1G,** an epidermal growth factor receptor for the treatment of lung cancer.[116]

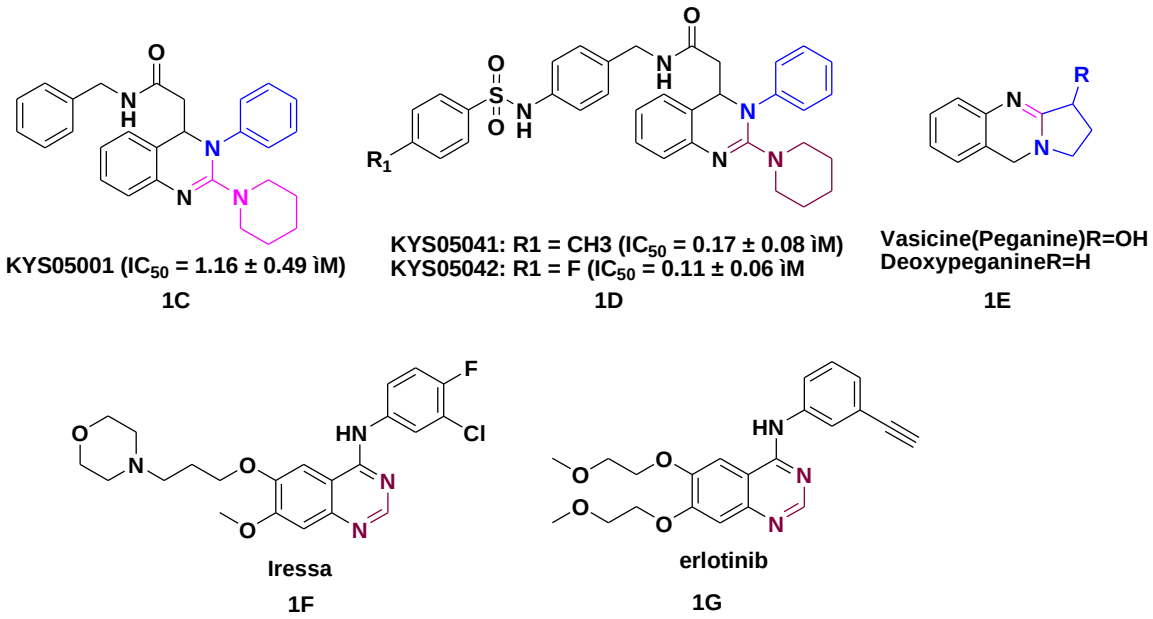
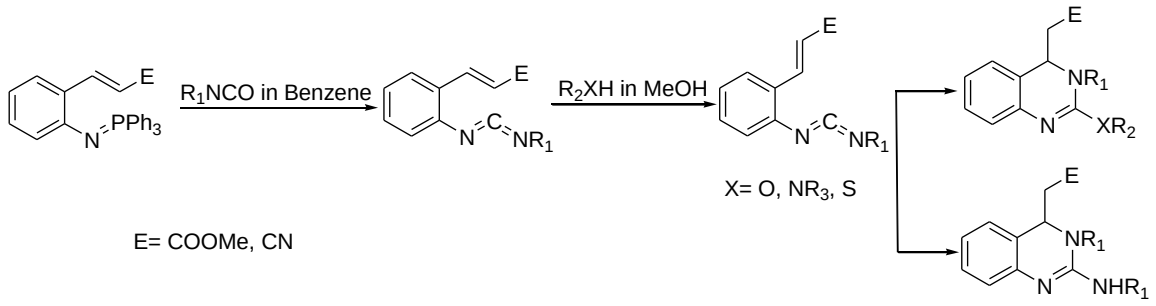


Figure 1.8. Representative examples of biologically active quinazoline derivatives.

Access to these kinds of bioactive molecules in a shorter pathway is still a big challenge to the medicinal chemists. Moreover, it is to be noted that there are numerous supported methods reported earlier to develop well-organized methodologies and processes for the high-throughput synthesis of these pharmacologically interesting libraries for drug discovery

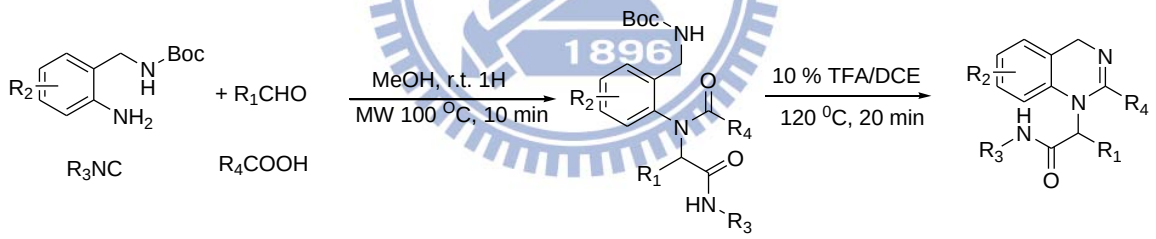
1.14. Chemical methods for synthesizing Dihydro and Tetrahydroquinazoline derivatives

In 1996, Saito *et. al.* had synthesized the dihydroquinazoline derivatives by the initial addition of nucleophiles such as alcohol, amine or thiols to the carbodiimide cumulenic system followed by intramolecular hetero conjugated addition leads to annulation as shown in Scheme 1.51.[116]



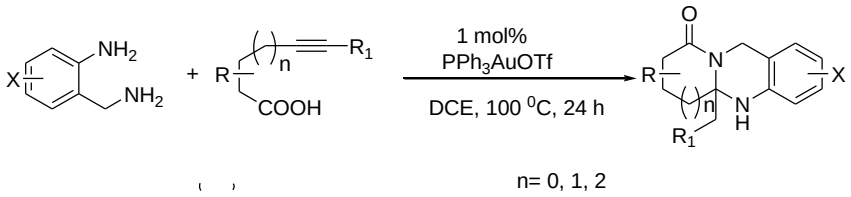
Scheme 1.51. Saito's Carbodiimide-Mediated Synthesis of Dihydroquinazolines.

In 2010, Hulme *et. al*. had developed the novel solution phase approach to the synthesis of dihydroquinazolines and fused dihydroquinazoline-benzodiazepine analogs. The synthetic strategy involves the employment of the Ugi reaction to assemble the desired diversity and further acid treatment enables ring-closing transformations under microwave irradiation as shown in Scheme 1.52.[117]



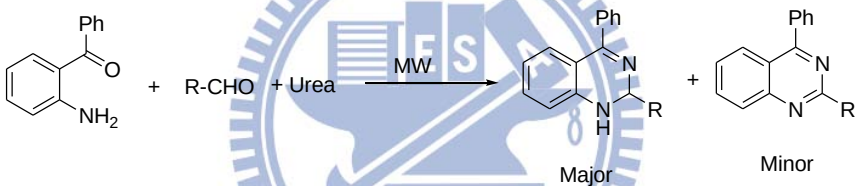
Scheme 1.52. Hulme's solution phase approach to Dihydroquinazolines.

In 2010, Patil *et. al.* has used the gold (I)-catalyzed formal double hydroamination of alkynes, bearing a tethered carboxylic group, for the synthesis of fused dihydrobenzimidazoles and tetrahydroquinazoline derivatives as shown in Scheme 1.53.[118]



Scheme 1.53. Patil's gold (I)-catalyzed synthesis of tetrahydroquinazoline derivatives.

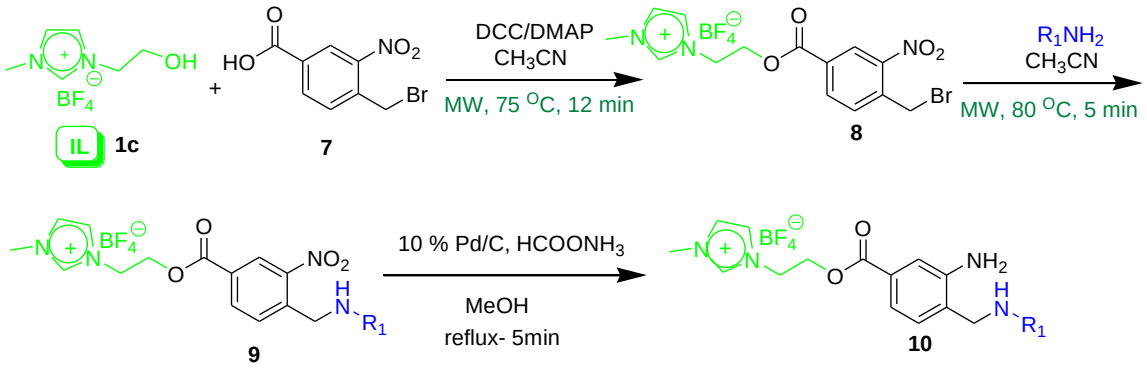
In 2011, Prajapati *et. al.* had used the solvent and catalyst-free synthesis of dihydroquinazolines using 2-aminobenzophenone and aldehydes under microwave irradiation with urea as an environmentally benign source of ammonia within minutes with small amount of quinazolines as the minor product as shown in Scheme 1.54.[119]



Scheme 1.54. Microwave assisted synthesis of dihydroquinazoline derivatives by Prajapati *et. al.*

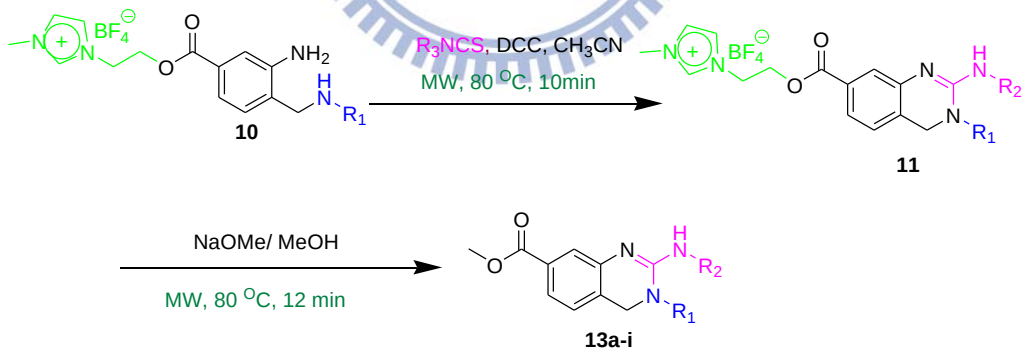
1.15. Results and Discussion

To discover the scope of the ionic liquid supported synthesis and to achieve the synthesis of dihydroquinazoline and tetrahydroquinazolin derivatives, commercially available 4-bromomethyl-3-nitro benzoic acid **7** was chosen as primary precursor. Condensation of 4-bromomethyl-3-nitro benzoic acid with ionic liquid **1c**, under DCC mediated coupling reaction generates the ionic liquid conjugates **8**. The coupling reaction was eventually carried out in ranges of condition as shown in **Table 1.3** using anhydrous acetonitrile as solvent and 4-(dimethylamino) pyridine (DMAP) as a catalyst in Scheme 1.55. After the completion of the reaction, the insoluble DCU was filtered off and ionic liquid conjugates **8** were purified by precipitating out the reaction mixtures with excess of cold ether. Initial diversification of the ionic liquid conjugates **8** were done only by reacting with various primary amines. The nucleophillic substitution reaction of ionic liquid conjugates **8** with primary amine functionality was carried in acetonitrile as a solvent in room temperature for 2 hrs. The same set of reactions when carried out under mild microwave irradiation it tooks only 5 mins for completion. Hence microwave irradiation, demonstrated numerous advantages not only drastically reducing the reaction time but also by improving the reaction yield significantly. To obtain the substituted *o*-phenylene diamine conjugates **10**, the conjugate **9** were subjected with neutral reduction utilizing a suspension of zinc dust and ammonium formate methanol as a solvent in room temperature for 3-5 mins. Completion of the reaction has been checked by changing the colour from black to bright blue on TLC plate.



Scheme 1.55. Ionic liquid supported synthesis of *o*-phenylenediamine 10.

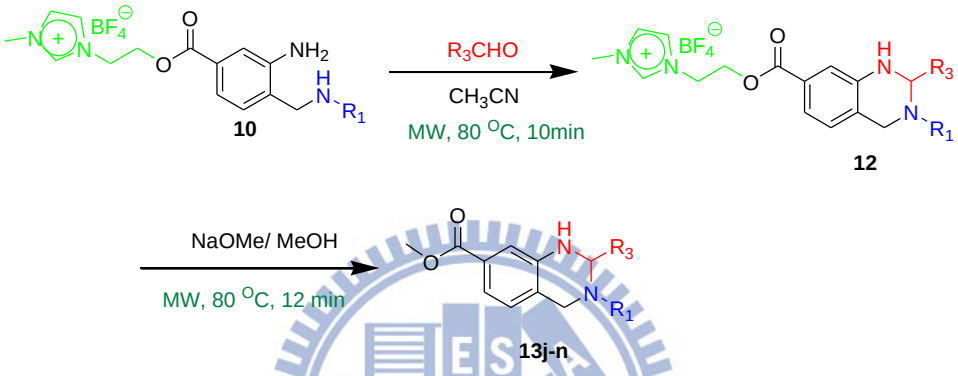
After completion of the reaction, reaction mixtures were filtered through fritted funnel to get rid of the Pd/C. The reaction mixture evaporated to obtain the compound **10**. Amine conjugates **10** were obtained in pure, form by further precipitation in cold ether. Our main objective was the construction of quinazoline ring with introduction of additional sets of diversity.



Scheme 1.56. Microwave Assisted Synthesis of Dihydroquinazoline synthesis

It has been understood that the elaboration of intermediate **10** to the desired core structure required one carbon electrophile. In an effort to build the quinazoline motif to mimic the

bioactive compound as mentioned earlier in Figure 1.7, we decided to explore cyclization using various isothiocyanates. Hence the amine conjugates **10** were condensed with selective isothiocyanates using dicyclohexyl urea (DCC) as an activating agent in anhydrous acetonitrile under microwave irradiation at 80 °C to furnish the dihydroquinazolin conjugate **11** in 12 minutes as shown in Scheme 1.56.

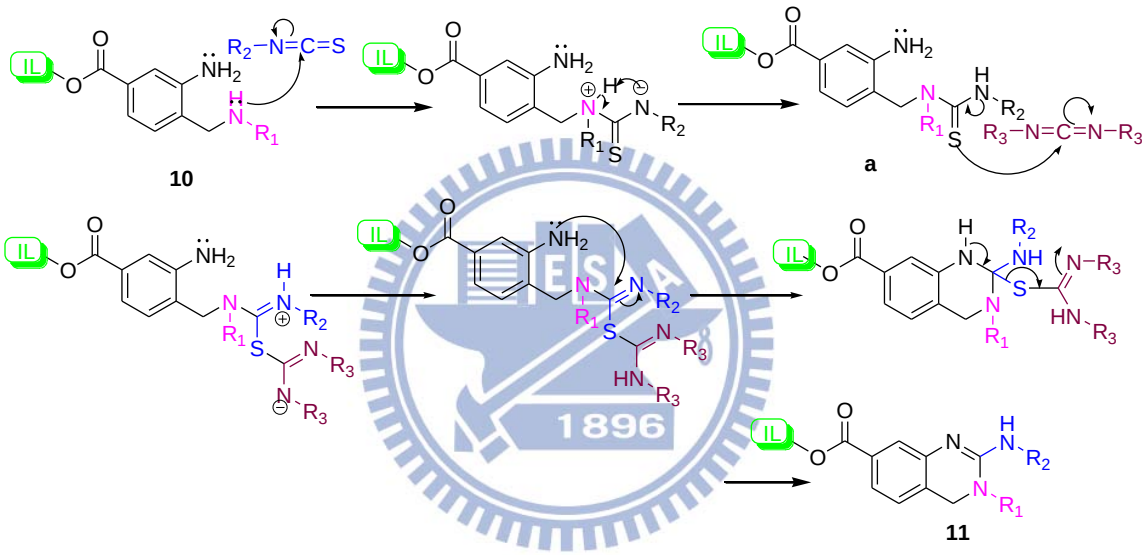


Scheme 1.57. Microwave Assisted Synthesis of Tetrahydroquinazoline synthesis

However, it has been observed that the same reaction required 10 hours under refluxing condition resulted the consumption of time, which in turn reflects the superiority of microwave irradiation. The insoluble byproduct dicyclohexyl urea (DCU) was formed during the activation, after the completion of the reaction the insoluble dicyclohexyl urea (DCU) was filtered off, the product dihydroquinazolin conjugate **11** was collected by ether solvent precipitation. The formation of the product dihydroquinazolin conjugate **11** involves the nucleophillic attack of secondary amine group on the isothiocyanates moiety to form intermediate '**a**'. For mechanistic investigation, intermediate '**a**' was isolated before addition of the coupling reagents (DCC) and characterized (see Supporting Information). The coupling agent (DCC) promotes the further activation of thiocarbonyl

(C=S) moiety of intermediate '**a**'; which after cyclization and electronic reorganization generate the target compounds **11**. Additionally, the isolated intermediate '**a**' was also reacted separately with DCC that provided the same results which supports the predicted mechanism shown in Scheme 1.58.

Scheme 1.58. General plausible mechanism towards the formation of Dihydroquinazoline Derivatives on ionic liquid support.



To synthesize the tetrahydroquinazolin library, the ionic liquid immobilized diamine **10** was subjected to various aldehyde in acetonitrile as solvent under focused microwave irradiation at the temperature 80 ^{o}C, for 12 mins (Scheme 1.57). It is interesting to notice that unlike other solid support, the main advantage of ionic liquid support was its direct reaction monitoring capacity by ^{1}H NMR spectroscopy as well as mass spectroscopy. Finally the product was cleaved from the ionic liquid tag provides highly pure analogs. To exhibit the product conversion quantitatively, we examined the proton ^{1}H NMR and MS spectroscopy in each intermediate step having IL-tag. It has been observed that

protons of -CH_2CH_2OH group of free IL was appeared in 3.94 ppm in proton NMR spectra whereas the same protons were shifted to 4.88 ppm after attachment to the 4-bromometyl 3-nitro benzoic acid **7** due to electron withdrawing nature of ester linkage to IL-tag and more significantly the CH_2 proton attached to the -Br group appeared around 5.00 ppm. The 2nd step which involves the nucleophillic substitution reaction of primary amine was evident from the shifting of signals of CH_2 protons from 5.00 ppm to 4.33 ppm because of the electron donating nature of primary amine functionality. The subsequent reduction of nitro group to amine functionality was confirmed from the shifting of CH_2 proton to further upfield *i.e.* around 3.49 ppm as shown in Figure 1.8.

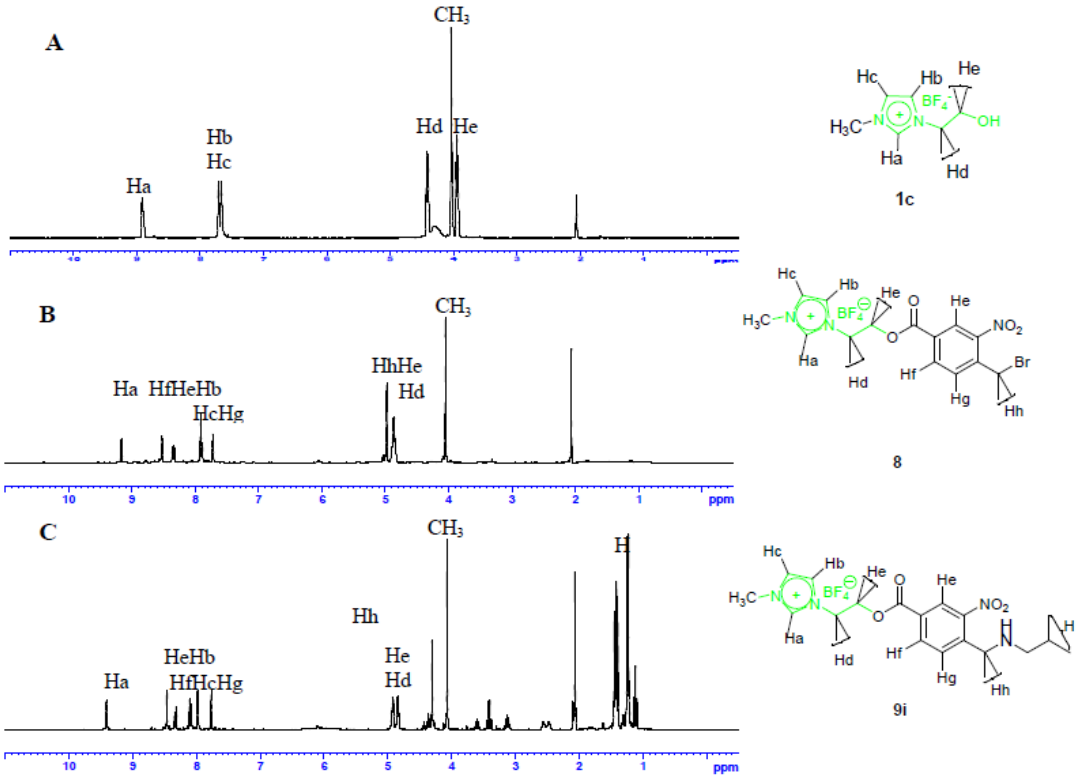


Figure 1.8. Stepwise formation of the ionic liquid bound intermediate in $CDCl_3$ at 25^0C **9i.**

Final cyclisation with differently substituted isothicyanate generated the electon withdrawing tetrahydro quinazoline derivatives was observed in proton NMR spectra. The previously appeared upfield CH_2 protons at 3.49 ppm become deshielded and moved to 3.99 ppm. Finally, the cleavage of product from ionic liquid support was observed from the absence of signals around 4.80 ppm due to the -CH_2CH_2- group of ionic liquid moiety. Observed characteristic signals of different proton are in agreement with structure **12.** Moreover, all the intermediates of IL- supported products could be confirmed with mass spectra (MS) which has been shown in Table 1.4. By employing the most wanted reaction sequence, we have introduced two diverse substitutions that have unstipulated number of building blocks readily available. The analytical data including crude yield and purity were reported in Table 1.5.

Table 1.3. Comparison of Microwave and Conventional Heating for the Coupling Step, S_NAr Reactions, Cyclisation, and Cleavage steps

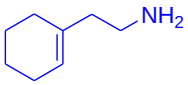
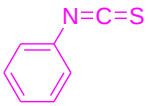
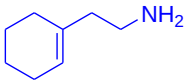
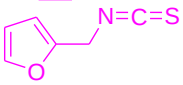
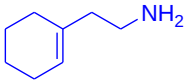
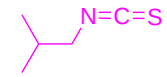
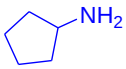
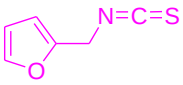
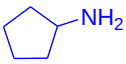
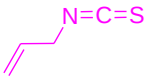
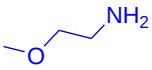
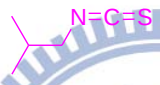
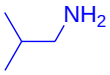
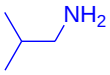
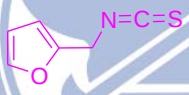
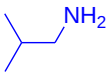
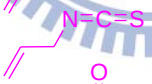
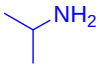
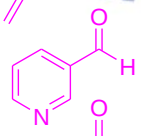
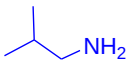
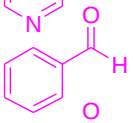
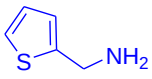
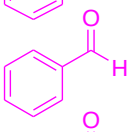
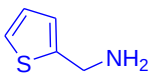
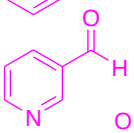
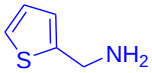
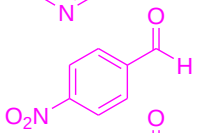
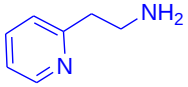
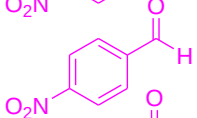
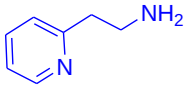
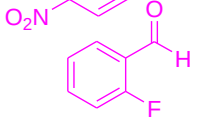
Entry	Substrates	Products	Optimized reaction condition	
			Time[a] (h)	Time[b] (h)
1	**7**	**8**	12	0.2
2	**8**	**9**	0.5	0.1
3	**10**	**11**	12	0.2
4	**10**	**12**	12	0.2
5	**11,12**	**13,14**	12	0.2

[a] Reflux conditions. [b] Biotage Initiator

Table 1.4. Mass Spectral Study of Ionic-Liquid Supported Intermediates.

Entry	Products	FAB and ESI found (100%)	Yields (%)
1	**8j**	$M^+ = 368$	95
2	**9j**	$M^+ = 347$	91
3	**10j**	$M^+ = 317$	93
4	**13j**	$M^+ = 382$	94

Table 1.5. Microwave Assisted, IL Supported Synthesis of Di-hydroquinazolines Tetrahydroquinazolines (13a-q).

Entry	R_1	R_2/R_3	LRMS[a]	Isolated yield[b] (%)	Crude Purity[c] (%)
13a			390	70	76
13b			394	71	76
13c			370	71	71
13d			354	85	88
13e			314	82	90
13f			320	70	70
13g			318	80	83
13h			342	84	95
13i			302	70	72
13j			288	85	98
13k			311	82	85
13l			324	74	76
13m			364	78	81
13n			365	78	81
13o			410	91	95
13p			419	81	82
13q			391	81	82

[a]LRMS were detected with ESI ionization source. [b]Yields were based on loading of ionic liquid soluble support. [c]Determined by HPLC analysis at UV 254 nm of the crude produc

1.16. Conclusions

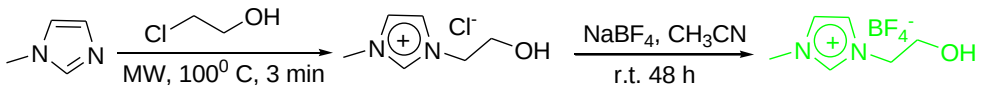
In this study, an efficient gram scale synthesis of pharmacologically interesting tri-substituted indole alkaloids and dihydro and tetrahydroquinazolines through use of commercially available building blocks have been demonstrated. Final libraries are usually obtained in high purity and yield just by simple precipitation and washings of each IL attached intermediate with minimum column purification. In contrast to the solid-phase synthesis, the reaction progress of IL bound support was successfully monitored by conventional analytical technique without the *cleave-&-analyze* method.

1.17. General Methods

Acetonitrile was distilled from calcium hydride before use. All reactions were performed under an inert atmosphere with unpurified reagents and dry solvents. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel-coated Kieselgel 60 F254 plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (Merck, 230-400 mesh). All the microwave experiments were conducted in a Biotage initiator under optimized reaction conditions of power and pressure. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker DX-300 spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale from an internal standard. High-resolution mass spectra (HRMS) were recorded on a JEOL TMS-HX 110 mass spectrometer. Optical rotations are reported as $[\alpha]^{25}_{D}$. Analytical HPLC analyses were recorded with UV detection at λ=254nm (column: Sphereclone 5μ Si (250 x 4.6 mm).

1.18. Experimental Section

General Procedure for the Synthesis of Ionic Liquid (IL) bound 1c.

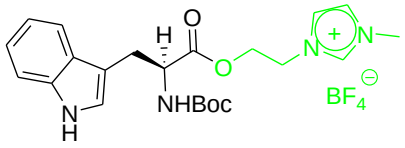


1a **1b** **1c**

A mixture of 1-Methylimidazole **1a** (1.0 g, 12.2 mmol) and 2-Chloroethanol (0.975 g, 12.2 mmol) was placed in a 10 mL microwave vial, and the vial was then irradiated for 3 min at 100^{o} C. After the reaction was cooled to ambient temperature, the formed viscous solid was successively washed with ether (20 mL×3), and then dried under vacuum for 6 h. The hydroxyl-functionalized ionic liquid **1b** was obtained as white crystals (1.85 g, 94 %). **^{1}H NMR** (300 MHz, D_2O): δ 3.79(s, 3H), 3.82 (t, J = 3.7 Hz, 2H), 4.20 (t, J = 4.0 Hz, 2H), 7.34 (s, 1H), 7.39 (s, 1H), 8.64 (s, 1H).

$NaBF_4$ (2.5 g, 22.8 mmol) and dry acetonitrile (50 mL) was stirred at room temperature for 48 h under nitrogen. The so formed white precipitate was filtered off and washed with acetonitrile (30 mL×3). Concentration of combined filtrates gave product **1c** as light yellow oil (2.39 g, 98%). **^{1}H NMR** (300 MHz, acetone-d_6): δ 3.94(t, J = 5.1 Hz, 2H), 4.04 (s, 3H), 4.42 (t, J = 5.1 Hz, 2H), 7.66 (s, 1H), 7.70 (s, 1H), 8.91 (s, 1H); MS (FAB): m/z 127 (M^+);

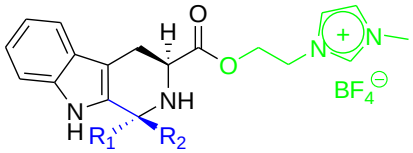
General Procedure for the Synthesis of Ionic Liquid (IL) bound Boc-*L*-tryptophan (3).



3

Boc-L-tryptophan **2** (0.76 g, 2.52 mmol), 1-Methyl-3-ethyl imidazolium tetrafluoroborate **1** (0.40 g, 1.87 mmol) and *N, N'*-dimethylamino pyridine (DMAP) (0.005 g) are placed in a dry, nitrogen-purged 100 mL round-bottom flask containing dry CH_3CN (15 mL). To the mixtures were added dropwise *N, N'*-dicyclohexylcarbodiimide (DCC) (0.54 g, 2.62 mmol) dissolved in dry CH_2Cl_2 (5 mL) for a period of 5 minutes. The reaction mixtures were stirred for another 15 minutes at room temperature. Then this O-acylation reaction was carried out in a tube using microwave radiation at 40 w (80 °C, 1 bar) for 12 minutes. After the completion of the reaction, the insoluble DCU byproduct was allowed to settle, and the reaction mixtures were filtered and washed with CH_3CN (50 mLx3). The solvent was evaporated, and the residue was again precipitated with cold ether which was filtered through fritted funnel to remove any unreacted acid and DCC, finally collected and dried under vacuum gave product **3** as pale white solid (1.18 g, 95%).

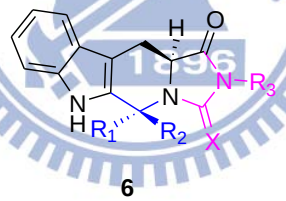
General Procedure for the Preparation Ionic Liquid (IL) bound Tetrahydro-β-carboline (4).



4

Ionic Liquid bound Boc-L-tryptophan **3** (1.30 g, 2.60 mmol) was dissolved in 20 % TFA (4 mL) in H_2O-IPA (1:1, 16 mL). The mixtures were irradiated in a pressurized microwave reactor at 40 w (80 °C, 2 bar) for 10 minutes. After Boc protective group was removed, various aldehydes or ketones (5 mmol) were added to the reaction mixtures. Then the reaction mixtures were further irradiated in a microwave oven at 40 w (80 °C, 2 bar) for 10 minutes with aldehydes and power 70 w (130 ^{o}C, 9 bar) for 20 minutes with ketones in one pot manner. After completion of the reaction time, the solvent was evaporated under reduced pressure. The residue was dissolved in acetonitrile, dried over anhydrous $MgSO_4$ and precipitated with cold ether and filtered through a fritted funnel to remove any unreacted aldehydes or ketones used in the Pictet-Spenger reaction. Finally the product obtained is the ionic liquid supported tetrahydro-β-carboline derivatives **4.**

Procedure for the Synthesis of Tetracyclic tetrahydro-β-carboline Derivatives (6).



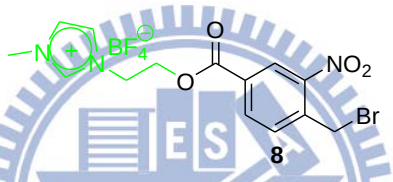
6

X = O or S

The tricyclic tetrahydro-β-carboline Derivatives **4** (1.0 mmol) was dissolved in H_2O-IPA (1:1, 10 mL) mixtures and treated with substituted isocyanates or isothiocyanates (1.8 mmol) in triethylamine (0.30g, 3.0 mmol). The reaction mixtures was kept into microwave synthesis apparatus and irradiated at 40 w (80 °C, 2 bar) for 12 minutes. After the completion of the reaction time, TLC was checked which indicates the complete release of the targeted compound from ionic liquid support. Then mix solvents were removed under reduced pressure. The residue was dissolved in acetontrile again, dried over anhydrous $MgSO_4$ and precipitated with cold ether which was then filtered through

fritted funnel and the residue was repeatedly washed with ether (50 mLx3). The combined filtrate were subjected to evaporation to obtain the crude compounds **6** and was checked by crude HPLC for crude purity with UV detection at λ=254nm (column:Sphereclone 5μ Si (250 x 4.6 mm);gradient: 35 % ethyl acetate in hexane; flow rate: 1 (mL/min). The crude mixtures were further purified by column chromatography and eluted with ethyl acetate: hexane (1:9) to afford the final compounds in 75-95 % yields and 72-94 % purities.

General procedure for the synthesis of ionic liquid (IL) bound 4-bromomethyl-3-nitrobenzene carboxylates 8.

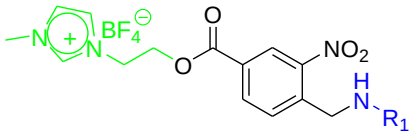


8

4-Bromometyl 3-nitro benzoic acid **7** (0.63 g, 2.43 mmol), 1-methyl-3-ethyl imidazolium tetrafluoroborate **1c** (0.40 g, 1.87 mmol) and *N, N'*-dimethylamino pyridine (DMAP) (0.005 g) are placed in a dry, nitrogen-purged 100 mL round-bottom flask containing dry CH_3CN (15 mL). *N, N'*-dicyclohexylcarbodiimide (DCC) (0.54 g, 2.62 mmol) dissolved in dry CH_2Cl_2 (5 mL) was added drop wise to the mixtures for a period of 5 minutes. The reaction mixtures were stirred for another 15 minutes at room temperature. Then this O-acylation reaction was carried out in a sealed vessel using microwave radiation at (75 °C, 1 bar) for 12 minutes. After the completion of the reaction, the reaction mixtures were allowed to settle, and the insoluble dicylohexyl urea (DCU) was filtered off and washed with CH_3CN (50 mLx3). The solvent was evaporated, and the residue so left was precipitated with cold ether, filtered through fritted funnel dried under vacuum, gave product **8** as pale white solid. **^{1}H NMR** (300 MHz, acetone-d_6) δ 9.26 (d, J = 5.1 Hz,

2H), 4.04 (s, 3H), 4.42 (t, J = 5.1 Hz, 2H), 7.66 (s, 1H), 7.70 (s, 1H), 8.91 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.8, 148.7, 137.9, 137.8, 134.7, 133.8, 131.5, 126.5, 124.5, 123.5, 64.4, 48.9, 36.2; MS (FAB): *m/z* [M^+] (100%): 368.

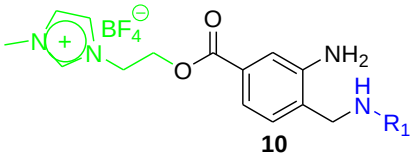
General procedure for the preparation ionic liquid (IL) bound 4-((substituted amino) methyl)-3-nitrobenzene carboxylates.



9

Ionic liquid bound 4-bromomethyl-3-nitrobenzene carboxylates **8** (1.0 g, 2.19 mmol) in acetonitrile (15 mL) as treated with various primary amines (1.5 equiv). The reaction mixtures were irradiated in a pressurized microwave reactor at 80 °C, 0 w 1 bar for 5 minutes to complete reaction and the reaction mixtures was evaporated washed with cold ether (75 mL), dried to obtain the ionic liquid (IL) bound 4-((substituted amino)methyl)-3-nitrobenzene carboxylates **9**.

General procedure for the preparation ionic liquid (IL) bound 3-amino-4-((substituted amino) methyl) benzene carboxylates 10.

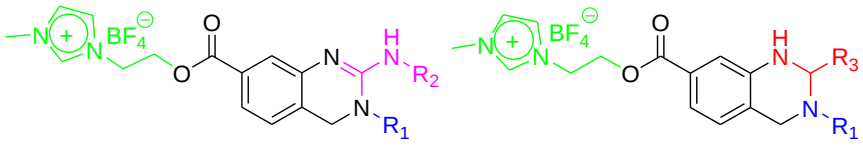


10

To a solution of **8** in methanol (15 mL), 10 % Pd/C (5 equiv) and ammonium formate (7 equiv) were added. The crude mixtures were stirred for 5 min for complete reduction of

nitro group. The reaction mixtures were filtered through filter paper to remove 10 % Pd/C. The solvent was evaporated to dryness. Acetonitrile (10 mL) was added to salt out ammonium formate to obtain the ionic liquid (IL) bound 3-Amino-4-((substituted amino) methyl) benzene carboxylates **10**.

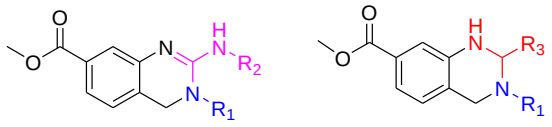
General procedure for the preparation ionic liquid (IL) bound dihydro (11) and tetrahydro quinazolin derivatives 12.



11 **12**

To a stirred solution of ionic liquid (IL) bound 3-amino-4-((substituted amino) methyl) benzene carboxylates **5** in dry CH_3CN (20 mL), *N, N'*-dicyclohexylcarbodiimide (DCC) (0.54 g, 2.62 mmol, 1 equiv) as activating agent and various isothiocyanates (1.05 mmol, 5.0 equiv) were added. The reaction mixture was sealed and exposed under pressured microwave irradiation at 80 ^{o}C for 10 minutes. Upon completion of the irradiation time, the insoluble DCU was allowed to settle, and the reaction mixtures were filtered and washed with CH_3CN (50 mLx3). The crude product mixtures were purified by precipitation with cold ether and dried to obtain the conjugate **11** in high purity. In case of tetrahydroquinazoline derivatives **12**, various aldehydes (3 equiv) were added to the stirred solution of IL-conjugates **5** in dry CH_3CN (20 mL). The reaction mixtures was sealed and irradiated under pressured microwave irradiation at 80 ^{o}C for 10 minutes. Upon completion of the irradiation time, the crude product mixtures were purified by precipitation with cold ether and dried to obtain the conjugate **12** in high purity.

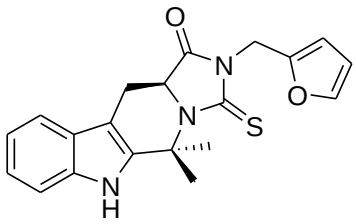
General procedure for the cleavage of ionic liquid (IL) bound substituted dihydro and tetrahydro quinazolin derivatives 13a-n.



13a-n

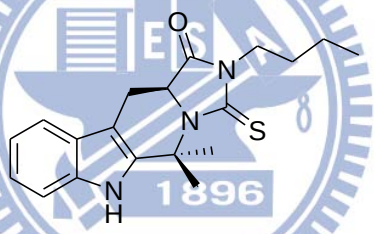
To a solution of conjugates **11** and **12** in methanol (20 mL), NaOMe (100 mg) was added and sealed. The reaction mixture was irradiated under pressured microwave irradiation at 80 ^{o}C for 12 minutes. After completion of the reaction, the crude product was precipitated with excess of cold ether (100 mL), the ionic liquid was filtered off and subjected to rota-vapor. The residue was dried under vacuum, and subjected to crude HPLC analysis with UV detection at λ=254 nm (column: Sphereclone 5μ Si (250 x 4.6 mm); gradient: 35 % ethyl acetate in hexane; flow rate: 1 mL/min.). The residue was dissolved in dichloromethane (5 mL) and again subjected to rotavapor. The slurry obtained was loaded on silica gel column and eluted with a mixture of ethyl acetate and hexane (1:4) to get the title compounds **13a-n** in good yields.

(11a*S*)-2-(Furan-2-ylmethyl)-5,5-dimethyl-3-thioxo-2,3,5,6,11,11a-hexahydro-1*H*-imidazo[1',5':1,6]pyrido[3,4-*b*]indol-1-one (6a).



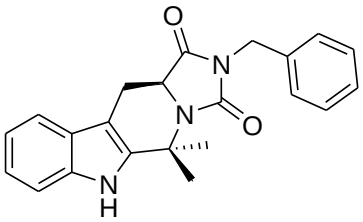
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.40-7.38 (m, 2H), 7.28-7.19 (m, 2H), 6.46 (d, *J* = 3.2 Hz, 1H), 6.35 (dd, *J* =7.3, 3.2 Hz, 1H), 5.14 (s, 2H), 4.33 (dd, *J* = 11.4, 4.4 Hz, 1H), 3.45 (dd, *J* = 15.0, 4.4 Hz, 1H), 2.87 (dd, *J* = 15.0, 11.4 Hz, 1H), 2.30 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 171.7, 149.5, 142.8, 139.4, 136.6, 126.3, 123.2, 120.7, 118.8, 111.6, 110.9, 110.0, 105.6, 60.2, 60.0, 37.7, 29.5, 24.1, 22.9 ppm; MS (ESI): *m/z* 366 (MH^+); HRMS (ESI) calcd for: $C_{20}H_{19}N_3O_2SNa$: *m/z* 388.1096; Found: 388.1098 (M+Na); $[\alpha]_D^{25}$ = -4.5 (*c* = 0.2, $CHCl_3$); IR(KBr): 3338, 3027, 2923, 1730, 1596, 1446 cm^{-1}.

(11a*S*)-2-butyl-5,5-dimethyl-3-thioxo-2,3,5,6,11,11a-hexahydro-1*H*-imidazo[1',5':1,6]pyrido[3,4-*b*]indol-1-one (6b).



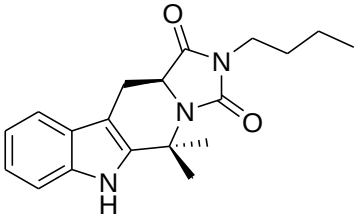
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.28-7.17 (m, 2H), 4.28 (dd, *J* = 11.4, 4.4 Hz, 1H), 3.90 (t, *J* = 7.5 Hz, 2H), 3.45 (dd, *J* = 15.0, 4.4 Hz, 1H), 2.84 (dd, *J* = 15.0, 11.4 Hz, 1H), 2.31 (s, 3H), 1.99 (s, 3H), 1.74-1.68 (m, 2H), 1.45-1.37 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.7, 172.1, 139.6, 136.5, 126.4, 123.2, 120.7, 118.8, 111.5, 105.8, 60.0, 59.8, 41.3, 30.1, 29.6, 24.1, 23.0, 20.5, 14.2 ppm; MS (ESI): *m/z* 342 (MH^+); HRMS (ESI) calcd for $C_{19}H_{23}N_3OSNa$: *m/z* 364.1459; Found: 364.1456 (M+Na); $[\alpha]_D^{25}$ = -24.6 (*c* = 0.1, $CHCl_3$); IR(KBr): 3349, 1720, 1627, 1436 cm^{-1}.

(11a*S*)-2-benzyl-5,5-dimethyl-5,6,11,11a-tetrahydro-1*H*-imidazo[1',5':1,6]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (6c).



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.53 (d, J = 7.4 Hz, 1H), 7.48-7.46 (m, 2H), 7.39-7.31 (m, 4H), 7.28-7.16 (m, 2H), 4.74 (s, 2H), 4.27 (dd, J = 11.4, 4.6 Hz, 1H), 3.90 (dd, J = 14.9, 4.6 Hz, 1H), 2.83 (dd, J = 14.9, 11.4 Hz, 1H), 2.04 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 154.7, 139.0, 136.6, 136.5, 129.7, 129.1, 129.0, 128.3, 127.8, 126.7, 122.9, 120.5, 118.8, 111.5, 105.8, 56.7, 55.9, 42.6, 28.6, 26.5, 23.3 ppm; MS (FAB): *m/z* 360 (MH+); HRMS (ESI) calcd for $C_{22}H_{21}N_3O_2Na$: *m/z* 382.1531; Found: 382.1535 (M+Na); $[\alpha]_D^{25}$ = -28.8 (*c* = 0.05, $CHCl_3$); IR(KBr): 3330, 2923, 1760, 1702, 1596, 1448 cm^{-1}.

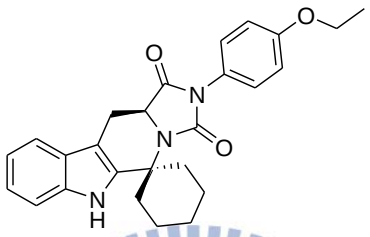
(11a*S*)-2-butyl-5,5-dimethyl-5,6,11,11a-tetrahydro-1*H*-imidazo[1',5':1,6]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (6d).



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.28-7.15 (m, 2H), 4.25 (dd, J = 11.4, 4.4 Hz, 1H), 3.58 (t, J = 7.2 Hz, 2H), 3.40 (dd, J = 14.9, 4.4 Hz, 1H), 2.83 (dd, J = 14.9, 11.4 Hz, 1H), 2.06 (s, 3H), 1.77 (s, 3H), 1.70-1.65 (m, 2H), 1.43-1.35 (m, 2H), 0.97 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz,

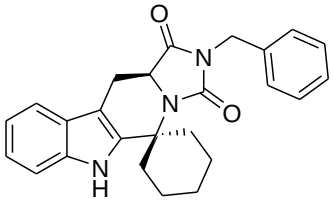
$CDCl_3$) δ 172.3, 155.1, 139.1, 136.6, 126.6, 123.0, 120.5, 118.8, 111.5, 105.9, 56.4, 55.8, 38.9, 30.7, 28.7, 26.5, 23.3, 20.5, 14.1 ppm; MS (ESI): *m/z* 326 (MH^+); HRMS (ESI) calcd for $C_{19}H_{23}N_3O_2Na$: *m/z* 348.1688; Found: 348.1685 (M+Na); $[\alpha]_D^{25}$ = -35.5 (*c* = 0.15, $CHCl_3$); IR (KBr): 3338, 2960, 1762, 1702, 1454 cm^{-1}.

(11a'*S*)-2'-(4-ethoxyphenyl)-11',11a'-dihydrospiro[cyclohexane-1,5'-imidazo[1',5':1,6]pyrido[3,4-*b*]indole]-1',3'(2'*H*,6'*H*)-dione (6e).



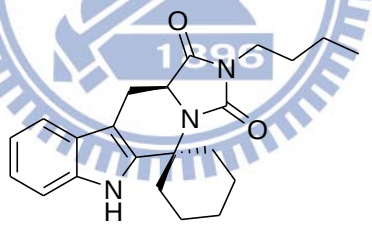
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.46-7.33 (m, 3H), 7.46-7.17 (m, 2H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 4.46 (dd, *J* = 11.2, 4.8 Hz, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.49 (dd, *J* = 15.1, 4.8 Hz, 1H), 2.98 (dd, *J* = 15.1, 11.2 Hz, 1H), 2.41 (m, 1H), 2.11-1.94 (m, 2H), 1.94-1.65 (m, 7H), 1.45 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 159.0, 154.1, 139.7, 136.1, 128.2, 126.2, 124.5, 123.0, 122.9, 120.5, 118.6, 115.3, 115.2, 111.6, 106.3, 64.1, 59.6, 55.6, 35.8, 33.8, 24.6, 24.1, 24.0, 23.9, 15.2 ppm; MS (ESI): *m/z* 430 (MH^+); HRMS (ESI): calcd for $C_{26}H_{27}N_3O_3Na$: *m/z* 452.1950; Found: 452.1947 (M+Na); $[\alpha]_D^{25}$ = -93.0 (*c* = 0.14, $CHCl_3$); IR (KBr): 3413, 2933, 1766, 1710, 1512 cm^{-1}.

(11a'*S*)-2'-benzyl-11',11a'-dihydrospiro[cyclohexane-1,5'-imidazo[1',5':1,6]pyrido[3,4-*b*]indole]-1',3'(2'*H*,6'*H*)-dione (6f).



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.55 (d, J = 7.3 Hz, 1H), 7.48 (d, J = 6.8 Hz, 2H), 7.42-7.30 (m, 4H), 7.28-7.17 (m, 2H), 4.78 (d, J = 14.6 Hz, 1H), 4.72 (d, J = 14.6 Hz, 1H), 4.34 (dd, J = 11.1, 4.7 Hz, 1H), 3.41 (dd, J = 15.0, 4.7 Hz, 1H), 2.86 (dd, J = 15.0, 11.1 Hz, 1H), 2.33 (m, 1H), 2.10-1.97 (m, 2H), 1.84-1.73 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 154.7, 139.6, 136.7, 136.0, 129.2, 129.0, 128.9, 128.3, 127.7, 126.2, 122.9, 120.6, 118.7, 111.6, 106.4, 59.4, 56.7, 45.1, 42.6, 36.0, 33.8, 32.3, 24.7, 23.9 ppm; MS (ESI): *m/z* 400 (MH^+); HRMS (ESI): calcd for $C_{25}H_{25}N_3O_2Na$: *m/z* 422.1844; Found: 422.1846 (M+Na); $[\alpha]_D^{25}$ = -113.7 (*c* = 0.13, $CHCl_3$); IR (KBr): 3417, 2925, 1762, 1704, 1600, 1492, 1452 cm^{-1}.

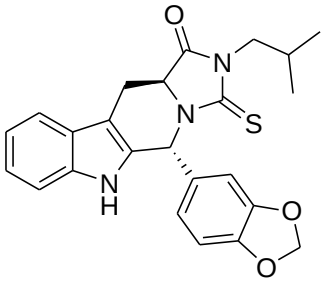
(11a'*S*)-2'-butyl-11',11a'-dihydrospiro[cyclohexane-1,5'-imidazo[1',5':1,6]pyrido[3,4-*b*]indole]-1',3'(2'*H*,6'*H*)-dione (6g).



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.28-7.15 (m, 2H), 4.30 (dd, J = 11.2, 4.9 Hz, 1H), 3.58 (t, J = 7.1 Hz, 2H), 3.40 (dd, J = 15.0, 4.9 Hz, 1H), 2.85 (dd, J = 15.0, 11.2, Hz, 1H), 2.37 (m, 1H), 2.13-1.98 (m, 2H), 1.90-1.68 (m, 7H), 1.80-1.65 (m, 2H), 1.42-1.35 (m, 2H) 0.98 (t, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 154.9, 139.7, 136.1, 126.3, 122.8, 120.5, 118.6, 111.6, 106.4, 59.2, 56.6, 56.5, 38.9, 36.1, 33.8, 30.7, 24.7, 24.0, 23.9, 20.5, 14.2 ppm; MS (ESI): *m/z* 366 (MH^+); HRMS (ESI) calcd for $C_{22}H_{27}N_3O_2Na$: *m/z* 388.2001; Found:

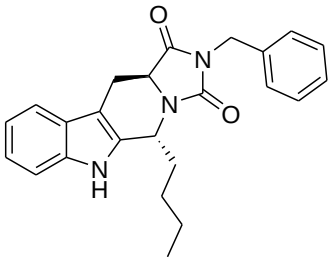
388.2003 (M+Na); $[\alpha]_D^{25}$ = -232.0 (*c* = 0.2, $CHCl_3$); IR (KBr): 3413, 2933, 1766, 1710, 1512 cm^{-1}.

(5*R*,11a*S*)-5-(1,3-benzodioxol-5-yl)-2-(2-methylpropyl)-3-thioxo-2,3,5,6,11,11a-hexahydro-1*H*-imidazo[1',5':1,6]pyrido[3,4-*b*]indol-1-one (6h).



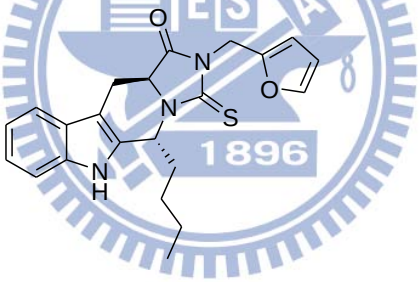
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.56 (d, *J* = 7.3 Hz, 1H), 7.33-7.17 (m, 3H), 7.01 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.96 (m, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 5.95 (dd, *J* = 5.1, 1.2 Hz, 2H), 4.42 (dd, *J* = 11.2, 5.8 Hz, 1H), 3.68 (dd, *J* = 7.3, 3.1 Hz, 2H), 3.54 (dd, *J* = 15.1, 5.8 Hz, 1H), 2.93 (dd, *J* = 15.1, 11.2 Hz, 1H), 2.30 (sept, *J* = 7.0 Hz, 1H), 0.96 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.3, 173.9, 148.5, 137.0, 132.4, 131.3, 126.3, 123.4, 123.1, 120.7, 118.9, 111.6, 110.9, 109.3, 108.9, 107.9, 101.8, 55.9, 55.4, 48.9, 27.5, 24.4, 20.5, 20.4 ppm; MS (EI): *m/z* 433 (M^+); HRMS (ESI) calcd for $C_{24}H_{23}N_3O_3SNa$: *m/z* 456.1358; Found: 456.1355 (M+Na); $[\alpha]_D^{25}$ = -75.3 (*c* = 0.2 , $CHCl_3$); IR (KBr): 3357, 2960, 1737, 1637, 1457 cm^{-1}.

(5*R*,11a*S*)-2-benzyl-5-butyl-5,6,11,11a-tetrahydro-1*H*-imidazo[1',5':1,6]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (6i)



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.50-7.44 (m, 3H), 7.38-7.30 (m, 4H), 7.24-7.13 (m, 2H), 5.27 (t, *J* = 7.2 Hz, 1H), 4.77 (d, *J* = 14.6 Hz, 1H), 4.72 (d, *J* = 14.6 Hz, 1H), 4.34 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.40 (dd, *J* = 15.3, 5.7 Hz, 1H), 2.76 (dd, *J* = 15.3, 11.0 Hz, 1H), 2.01 (m, 1H), 1.78 (m, 1H), 1.44-1.32 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 155.7, 136.7, 136.5, 133.0, 129.2, 128.9, 128.3, 126.6, 122.9, 120.5, 118.6, 111.5, 106.3, 54.3, 49.1, 42.8, 36.2, 28.2, 23.9, 23.1, 14.4 ppm; MS (ESI): *m/z* 388 (MH^+); HRMS (ESI): calcd for $C_{24}H_{25}N_3O_2Na$: *m/z* 410.1844; Found: 410.1842 (M+Na); $[\alpha]_D^{25}$ = -72.4 (*c* = 0.1, $CHCl_3$); IR (KBr): 3324, 2923, 1764, 1706, 1450 cm^{-1}.

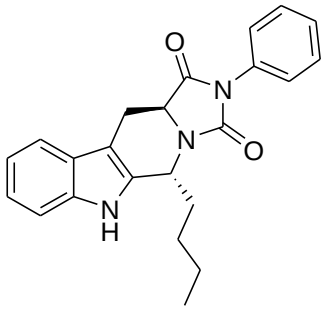
(5*R*,11a*S*)-5-butyl-2-(furan-2-ylmethyl)-3-thioxo-2,3,5,6,11,11a-hexahydro-1*H*-imidazo[1',5':1,6]pyrido[3,4-*b*]indol-1-one (6j).



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.42-7.38 (m, 2H), 7.24-7.13 (m, 3H), 6.48 (dd, *J* = 6.6, 3.2 Hz, 1H), 6.36 (dd, *J* = 6.6, 3.2 Hz, 1H), 5.88 (t, *J* = 6.0 Hz 1H), 5.17 (s, 2H), 4.40 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.29 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.46 (dd, *J* = 15.0, 12.0 Hz, 1H), 2.16 (m, 1H), 1.89 (m, 1H), 1.46-1.32 (m, 4H), 0.91 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.7, 173.4, 149.3, 142.8, 136.7, 132.4, 126.3, 123.0, 120.5, 118.6, 111.3, 110.9, 110.0, 106.1, 57.1, 53.1, 38.2, 35.0, 27.9, 23.7, 23.2, 14.3 ppm; MS (ESI): *m/z* 394 (MH^+); HRMS (ESI) calcd for $C_{22}H_{23}N_3O_2SNa$: *m/z* 416.1409;

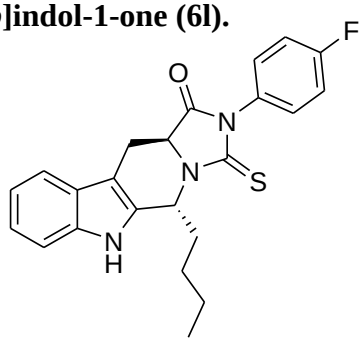
Found: 416.1405 (M+Na); $[\alpha]_D^{25}$ = -166.1 (*c* = 0.2, $CHCl_3$); IR (KBr): 3399, 2931, 1747, 1623, 1463 cm^{-1}.

(5*R*,11a*S*)-5-butyl-2-phenyl-5,6,11,11a-tetrahydro-1*H*-imidazo[1',5':1,6]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (6k).



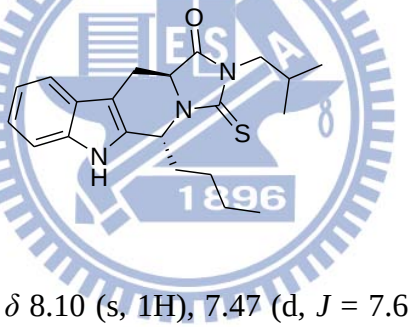
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.55-7.49 (m, 5H), 7.41-7.33 (m, 3H), 7.22 (m, 1H), 5.38 (t, *J* = 5.6 Hz, 1H), 4.50 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.51 (dd, *J* = 15.0, 5.7 Hz, 1H), 2.97 (dd, *J* = 15.0, 10.9 Hz, 1H), 2.08 (m, 1H), 1.85 (m, 1H), 1.58-1.26 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 154.8, 136.7, 132.9, 132.0, 129.6, 129.5, 128.6, 126.7, 126.5, 123.0, 120.8, 120.6, 120.5, 118.6, 111.5, 106.3 54.3, 49.3, 36.1, 28.2, 23.1, 14.4 ppm; MS (ESI): *m/z* 374 (MH^+); HRMS (ESI) calcd for $C_{23}H_{23}N_3O_2Na$: *m/z* 396.1688; Found: 396.1691 (M+Na); $[\alpha]_D^{25}$ = -72.4 (*c* = 0.05, $CHCl_3$); IR (KBr): 3318, 2923, 1714, 1596, 1492, 1444 cm^{-1}.

(5*R*,11a*S*)-5-butyl-2-(4-fluorophenyl)-3-thioxo-2,3,5,6,11,11a-hexahydro-1*H*-imidazo[1',5':1,6]pyrido[3,4-*b*]indol-1-one (6l).



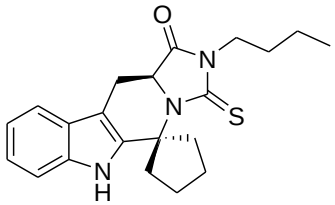
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.38-7.40 (m, 3H), 7.28-7.18 (m, 4H), 5.98 (t, J = 5.5 Hz, 1H), 4.64 (dd, J = 11.0, 5.9 Hz, 1H), 3.53 (dd, J = 15.2, 5.9 Hz, 1H), 2.98 (dd, J = 15.2, 11.0 Hz, 1H), 2.26 (m, 1H), 1.94 (m, 1H), 1.50-1.41 (m, 4H), 0.94 (t, J = 7.0 Hz, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.2, 173.3, 136.9, 132.7, 130.9, 130.7, 128.2, 128.1, 126.4, 123.1, 120.6, 118.6, 117.0, 116.8, 116.5, 111.6, 105.9 57.7, 53.5, 34.9, 28.0, 23.3, 14.4 ppm; MS (ESI): *m/z* 408 (MH^+); HRMS (ESI) calcd for $C_{23}H_{22}FN_3OSNa$: *m/z* 430.1365; Found: 430.1362 (M+Na); $[\alpha]_D^{25}$ = -108.9 (*c* = 0.2, $CHCl_3$); IR (KBr): 3357, 2923, 1743, 1598, 1454 cm^{-1}.

(5*R*,11a*S*)-5-butyl-2-(2-methylpropyl)-3-thioxo-2,3,5,6,11,11a-hexahydro-1*H*-imidazo[1',5':1,6]pyrido[3,4-*b*]indol-1-one (6m).



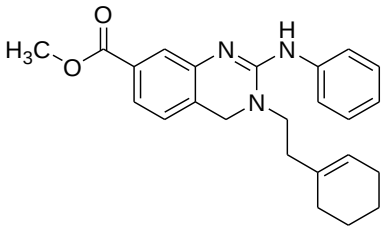
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.36 (dd, J = 7.8, 3.0 Hz, 1H), 7.28-7.14 (m, 2H), 5.90 (t, J = 5.4 Hz, 1H), 4.42 (dd, J =12.0, 5.9 Hz, 1H), 3.76 (d, J = 7.3 Hz, 2H), 3.39 (dd, J =15.0, 5.9 Hz, 1H), 2.66 (dd, J =15.0, 12.0 Hz, 1H), 2.37 (m, 1H), 2.20 (m, 1H), 1.90 (m, 1H), 1.50-1.30 (m, 4H), 0.99-0.94 (m, 6H), 0.90 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.9, 174.3, 136.8, 132.9, 126.5, 123.0, 120.6, 118.6, 111.5, 106.2, 57.1, 53.0, 48.9, 35.1, 28.0, 27.8, 24.2, 23.5, 20.5, 20.4, 14.4 ppm; MS (ESI): *m/z* 370 (MH^+); HRMS (ESI): calcd for $C_{21}H_{27}N_3OSNa$: *m/z* 392.1772; Found: 392.1771 (M+Na); $[\alpha]_D^{25}$ = -71.9 (*c* = 0.2, $CHCl_3$); IR (KBr): 3399, 2931, 1747, 1623, 1463 cm^{-1}.

(11a'*S*)-2'-butyl-3'-thioxo-2',3',11',11a'-tetrahydrospiro[cyclopentane-1,5'-imidazo[1',5':1,6]pyrido[3,4-*b*]indol]-1'(6'*H*)-one (6n).



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.39 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.25-7.16 (m, 2H), 4.29 (dd, *J* = 11.5, 4.5 Hz, 1H), 3.92 (t, *J* = 7.5 Hz, 2H), 3.44 (dd, *J* = 14.9, 4.5 Hz, 1H), 2.85 (dd, *J* = 14.9, 11.5 Hz, 1H), 2.78 (m, 1H), 2.58 (m, 1H), 2.42 (m, 1H), 2.24 (m, 1H), 2.01-1.90 (m, 4H), 1.73-1.67 (m, 2H), 1.47-1.37 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 172.2, 141.3, 136.7, 126.1, 123.0, 120.7, 118.7, 111.5, 105.3, 69.2, 61.5, 41.2, 38.8, 38.0, 30.2, 28.8, 26.8, 23.1, 20.5, 14.2 ppm; MS (ESI): *m/z* 368 (MH^+); HRMS (ESI) calcd for $C_{21}H_{25}N_3OSNa$: *m/z* 390.1616; Found: 390.1618 (M+Na); $[\alpha]_D^{25}$ = -6.5 (*c* = 0.2, $CHCl_3$); IR (KBr): 3401, 2923, 1728, 1596, 1490, 1444 cm^{-1}.

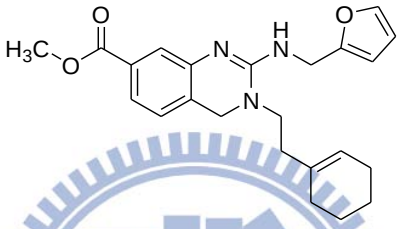
Methyl 3-[2-(cyclohex-1-en-1-yl)ethyl]-2-(phenylamino)-3,4-dihydroquinazoline-7-carboxylate (13a)



^{1}H NMR (300MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.37 (dd, *J* = 6.1, 1.7 Hz, 1H), 7.35-7.32 (m, *3*H), 7.31 (d, *J* = 1.7 Hz, 1H), 7.23 (m, 1H), 7.14 (d, *J* = 6.1 Hz, 1H), 5.48 (m, 1H), 5.20 (s, 2H), 4.62 (brs, 1H), 3.89 (s, 3H), 3.57 (t, *J* = 7.4 Hz, 1H), 2.18 (t, *J* = 7.4 Hz, 1H),

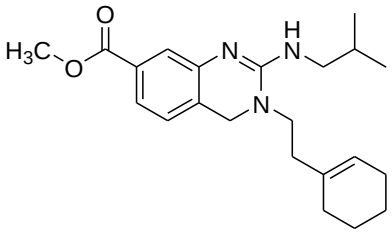
1.98-1.88 (m, 4H), 1.62-1.50 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.9, 167.6, 146.6, 140.0, 134.8, 131.5, 131.3, 129.2, 126.5, 126.4, 125.0, 124.5, 118.9, 116.8, 53.9, 52.5, 48.2, 35.5, 29.0, 25.6, 23.1, 22.5 ppm. MS (ESI): m/z 390 (MH^+); HRMS (ESI) calcd for: $C_{24}H_{28}N_3O_2$: m/z 390.2181. Found 390.2184; IR(KBr): 3322, 2925, 1707, 1600, 1533, 1448 cm^{-1}.

Methyl 3-[2-(cyclohex-1-en-1-yl)ethyl]-2-[(furan-2-ylmethyl)amino]-3,4-dihydroquinazoline-7-carboxylate (13b)



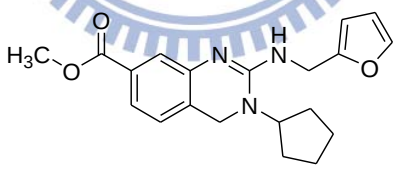
^{1}H NMR (300MHz, $CDCl_3$) δ 7.36 (dd, *J* = 6.0, 1.1 Hz, 1H), 7.32 (dd, *J* = 6.0, 1.1 Hz, 1H), 7.09 (d, *J* = 8.9 Hz, 1H), 6.33 (t, *J* = 3.0 Hz, 1H), 6.30 (d, *J* = 3.0 Hz, 1H), 5.93 (t, *J* = 3.0 Hz, 1H), 5.48 (m, 1H), 5.25 (s, 2H), 4.90 (d, *J* = 6.0 Hz, 2H), 3. 98 (s, 3H), 3.39 (t, *J* = 7.4 Hz, 2H), 2.08 (t, *J* = 7.4 Hz, 2H), 1.98-1.88 (m, 2H), 1.80-1.78 (m, 2H), 1.60-1.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.9, 151.8, 146.7, 134.9, 131.2, 131.1, 125.0, 124.9, 119.0, 116.5, 111.1, 108.9, 54.2, 52.5, 47.4, 43.8, 35.2, 28.8, 25.5, 23.0, 22.5 ppm. MS (ESI): m/z 394 (MH^+); HRMS (EI) calcd for: $C_{23}H_{27}N_3O_2$: m/z 393.2052. Found 393.2055; IR(KBr): 3337, 2927, 1704, 1633 cm^{-1}.

Methyl 3-[2-(cyclohex-1-en-1-yl)ethyl]-2-[(2-methylpropyl)amino]-3,4-dihydroquinazoline-7-carboxylate (13c)



^{1}H NMR (300MHz, $CDCl_3$) δ 7.34-7.28 (m, 2H), 7.09 (d, *J* = 7.7 Hz, 1H), 5.67 (t, *J* = 4.8 Hz, 1H), 5.41 (brs, 1H), 5.18 (s, 2H), 3.88 (s, 3H), 3.52 (t, *J* = 6.3 Hz, 2H), 3.38 (t, *J* = 7.7 Hz, 2H), 2.04 (t, *J* = 7.7 Hz, 2H), 1.97-1.88 (m, 2H), 1.89-1.83(m, 2H), 1.63-1.49 (m, 4H), 0.95 (d, *J* = 6.3 Hz, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 181.4, 167.6, 146.6, 134.7, 131.4, 131.3, 124.9, 124.6, 118.7, 116.6, 54.3, 54.0, 52.5, 47.3, 35.3, 28.9, 28.6, 25.6, 23.1, 22.4, 20.7 ppm. MS (ESI): m/z 370 (MH^+) . HRMS (ESI) calcd for: $C_{22}H_{32}N_3O_2$: m/z 370.2494. Found 370.2496. IR(KBr): 3324, 2925, 1710, 1631, 1529, 1438 cm^{-1}.

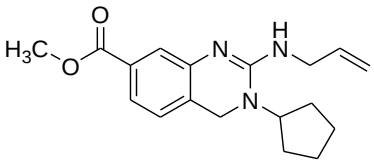
Methyl 3-cyclopentyl-2-[(furan-2-ylmethyl)amino]-3,4-dihydroquinazoline-7-carboxylate (13d)



^{1}H NMR (300MHz, $CDCl_3$) δ 7.39 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.35 (d, *J* = 1.4 Hz, 1H), 7.27 (m, 1H), 7.04 (d, *J* = 7.9 Hz, 1H), 6.27 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.17 (d, *J* = 3.1 Hz 1H), 5.74 (t, *J* = 4.4 Hz, 1H), 5.29 (t, *J* = 8.5 Hz, 1H), 4.83 (d, *J* = 4.8 Hz 1H), 4.62 (s, 2H), 3.95(m, 1H), 3.88 (s, 2H), 1.99-1.93 (m, 2H), 1.69-1.55 (m, 4H), 1.48-1.41 (m, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 182.7, 167.4, 151.3, 144.1, 142.5, 130.7, 127.7, 125.8, 120.4, 117.5, 110.8, 108.0, 61.7, 52.5, 47.2, 43.6, 29.3, 24.2 ppm. MS (ESI) m/z 354

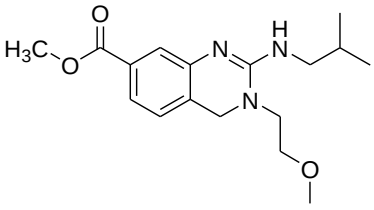
(MH^+). HRMS (ESI) calcd for: $C_{20}H_{24}N_3O_3$: m/z 354.1818 . Found 354.1815. IR(KBr): 3365, 2952, 1708, 1631, 1529, 1436 cm^{-1}.

Methyl 3-cyclopentyl-2-(prop-2-en-1-ylamino)-3,4-dihydroquinazoline-7-carboxylate (13e)



^{1}H NMR (300MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.9, 1.4 Hz 1H), 7.41 (d, *J* = 1.4 Hz 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 5.84 (m, 1H), 5.44 (t, *J* = 5.3 Hz, 2H), 5.38 (m, 1H), 5.10-5.02 (m, 2H), 4.61 (s, 2H), 4.30 (t, *J* = 5.3 Hz, 2H), 3.89 (s, 3H), 2.03-1.95 (m, 2H), 1.69-1.55 (m, 4H), 1.48-1.41 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 182.9, 167.4, 144.0, 134.2, 130.8, 127.6, 125.7, 120.4, 117.5, 117.0, 61.8, 52.6, 49.0, 47.0, 29.3, 24.2 ppm. MS (ESI) m/z 314 (MH^+). HRMS (ESI) calcd for: $C_{18}H_{24}N_3O_2$: m/z 314.1868 . Found 314.1866. IR(KBr): 3370, 2954, 1710, 1631, 1577, 1444 cm^{-1}.

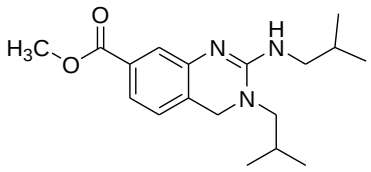
Methyl3-(2-methoxyethyl)-2-[(2-methylpropyl)amino]-3,4-dihydroquinazoline-7-carboxylate (13f)



^{1}H NMR (300MHz, $CDCl_3$) δ 7.50 (t, *J* = 8.1, Hz 1H), 7.32-7.28 (m, *2*H), 7.05 (d, *J* = 8.1 Hz 1H), 5.26 (s, 2H), 3.89 (s, 3H), 3.52 (t, *J* = 8.4 Hz, 2H), 3.45 (t, *J* = 5.7 Hz, 2H), 3.30 (s, 3H), 1.97-1.88 (m, *2*H), 0.87 (d, *J* = 8.4 Hz, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 184.2, 167.6, 146.8, 131.6, 131.4, 125.1, 118.6, 116.5, 72.1, 59.6, 54.9, 54.5, 52.5, 49.7, 28.4,

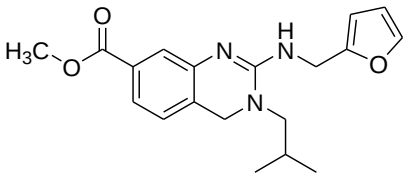
20.7 ppm; MS (ESI) m/z 320 (MH^+). HRMS (ESI) calcd for: $C_{17}H_{26}N_3O_3$: m/z 320.1974 . Found 320.1977. IR(KBr): 3338, 2952, 1728, 1629, 1579, 1240 cm^{-1}.

Methyl 3-(2-methylpropyl)-2-[(2-methylpropyl)amino]-3,4-dihydroquinazoline-7-carboxylate (13g)



^{1}H NMR (300MHz, $CDCl_3$) δ 7.32 (dd, *J* = 7.8, 1.5 Hz 1H), 7.29 (d, *J* = 1.5 Hz 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 5.84 (m, 1H), 5.62 (t, *J* = 5.2 Hz, 2H), 5.22 (s, 2H), 3.87 (s, 3H), 3.51 (dd, *J* = 6.8, 5.2, Hz 1H 2H), 3.16(d, *J* = 7.6 Hz 1H), 2.06 (m, 1H), 1.93 (m, 1H), 0.91 (t, 6.8 Hz, 12H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 182.1, 167.5, 146.5, 131.3, 131.2, 124.9, 118.9, 116.8, 55.1, 54.4, 54.3, 52.5, 28.5, 27.6, 20.9, 20.7 ppm. MS (ESI) m/z 318 (MH^+). HRMS (ESI) calcd for: $C_{18}H_{28}N_3O_2$ m/z 318.2181. Found 318.2179. IR(KBr): 3370, 2954, 1710, 1631, 1577, 1444 cm^{-1}.

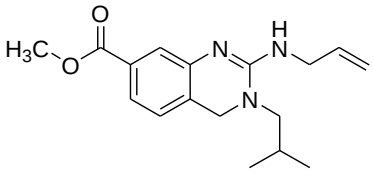
Methyl 2-[(furan-2-ylmethyl)amino]-3-(2-methylpropyl)-3,4-dihydroquinazoline-7-carboxylate (13h).



^{1}H NMR (300MHz, $CDCl_3$) δ 7.35-7.28 (m, 3H), 7.04 (d, *J* = 7.8 Hz 1H), 6.32 (dd, , *J* =3.2, 2.0 Hz, 1H), 6.27 (d, *J* =3.2 Hz, 1H), 5.94 (t, *J* = 4.6 Hz, 1H), 5.22 (s, 1H), 4.88 (d, *J* = 4.6 Hz, 1H), 3.90 (s, 3H), 3.15 (d, *J* = 7.6 Hz, 2H), 2.05-1.99 (m, 1H) 0.86 (d, *J* = 6.7 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 181.9, 167.6, 151.2, 146.4, 142.6, 131.3, 131.2,

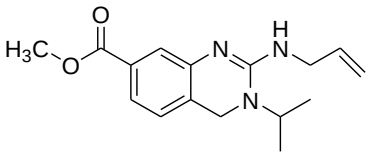
124.8, 118.9, 116.8, 110.9, 108.3, 55.0, 54.5, 52.5, 43.8, 27.5, 20.8 ppm; MS (ESI) m/z 342 (M^+). HRMS (ESI) calcd for: $C_{19}H_{24}N_3O_3$ m/z 342.1818. Found 342.1817. IR(KBr): 3446, 2927, 1704, 1531, 1438 cm^{-1}.

Methyl 3-(2-methylpropyl)-2-(prop-2-en-1-ylamino)-3,4-dihydroquinazoline-7-carboxylate (13i)



^{1}H NMR (300MHz, $CDCl_3$) δ 7.31 (dd, *J* = 7.7, 1.6 Hz 1H), 7.28 (d, *J* = 1.6 Hz 1H), 7.03 (d, *J* = 7.7 Hz 1H), 5.90 (m, 1H), 5.73 (t, *J* = 5.1 Hz, 1H), 5.19 (s, 2H), 5.15-5.11 (m, 1H), 4.34-4.30 (m, *2*H), 3.85 (s, 3H), 3.16 (d, *J* = 7.7 Hz, 2H), 2.06 (m, 1H), 0.83 (d, *J* = 7.7 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 182.1, 167.6, 146.4, 134.3, 131.2, 130.8, 124.9, 118.9, 117.3, 116.8, 55.0, 54.4, 52.5, 49.2, 27.5, 20.8 ppm; MS (ESI) m/z 302 (MH^+). HRMS (ESI) calcd for: $C_{17}H_{24}N_3O_2$: m/z 302.1868. Found 302.1867. IR(KBr): 3370, 2954, 1710, 1631, 1577, 1444 cm^{-1}.

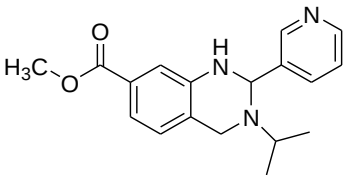
Methyl 3-(propan-2-yl)-2-(prop-2-en-1-ylamino)-3,4-dihydroquinazoline-7-carboxylate (13j)



^{1}H NMR (300MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.3, 1.4 Hz, 1H), 7.42 (d, *J* = 3.3 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 5.80 (m, 1H), 5.46-5.37 (m, 2H), 5.07-4.99 (m, 2H), 4.60 (s, 2H), 4.31-4.26 (m, 2H), 3.89 (s, 3H), 1.21 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 182.1,166.9,

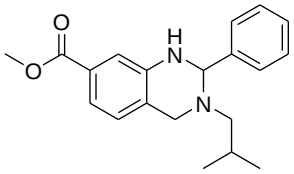
143.7, 133.8, 130.5, 127.5, 125.1, 119.9, 117.1, 116.5, 52.1, 51.5, 48.5, 45.3, 19.9 ppm; MS (ESI) m/z 288 (MH^+). HRMS (ESI) calcd for: $C_{16}H_{22}N_3O_2$: m/z 288.1712. Found 288.1710. IR(KBr): 3376, 2954, 1712, 1629, 1577, 1444 cm^{-1}.

Methyl 3-(propan-2-yl)-2-(pyridin-3-yl)-1,2,3,4-tetrahydroquinazoline-7-carboxylate (13k)



^{1}H NMR (300MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.51 (dd, *J* = 4.8 Hz, 1H), 7.76 (dt, *J* = 6.8, 1.5 Hz, 1H), 7.34~7.22 (m, 3H), 6.93 (d, *J* = 7.6 Hz, 1H), 5.39 (s, 1H), 4.64 (brs, NH), 3.88 (s, 3H), 3.72 (dd, *J* = 36.9, 16.8 Hz, 2H), 2.97~2.87 (m, 1H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.08 (d, *J* = 6.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.3, 149.2, 149.0, 142.2, 138.3, 135.0, 129.2, 127.0, 125.3, 123.7, 119.0, 114.9, 68.6, 52.4, 49.9, 44.3, 22.2, 20.4 ppm. MS (ESI) m/z 311 (M^+) HRMS (EI) calcd for: $C_{18}H_{21}N_3O_2$: m/z 311.1634. Found 311.1639. IR(KBr): 3394, 1706, 1297 cm^{-1}.

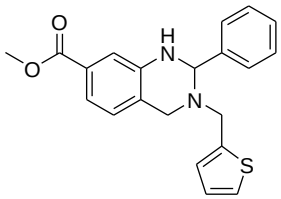
Methyl 3-isobutyl-2-phenyl-1,2,3,4-tetrahydro-7-quinazolinecarboxylate (13l)



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65-7.43 (m, 2H), 7.38-7.28 (m, 5H), 6.94 (d, *J* =7.8 Hz, 1H), 5.10 (s, 1H), 4.52 (s, 1H), 3.91 (s, 3H), 3.76 (d, *J* = 16.7 Hz, 2H), 3.56 (d, *J* = 16.7 Hz, 2H), 2.41 (dd, *J* = 7.8, 13.8 Hz, 1H), 2.24 (dd, *J* = 7.0, 12.6 Hz, 1H), 1.84 (m, 1H),

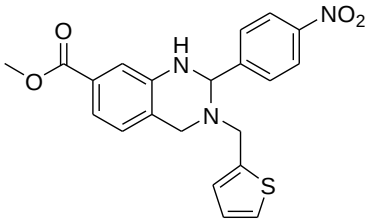
0.93 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.4, 142.7, 129.1, 128.9, 128.5, 127.8, 127.7, 127.2, 126.9, 125.2, 118.3, 114.2, 72.5, 60.0, 52.0, 49.9, 26.0, 19.0 ppm; MS (EI): *m/z* 324 (M^+); HRMS (ESI) calcd for: $C_{19}H_{22}N_2O_2$: *m/z* 324.1838; Found: 324.1833 (M+H); IR(KBr): 3386, 1706, 1502, 1295 cm^{-1}.

Methyl 2-phenyl-3-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-7-carboxylate (13m)



^{1}H NMR (300MHz, $CDCl_3$): δ 7.53-7.50 (m, 2H), 7.38-7.26 (m, 6H), 6.98-6.92 (m, 3H), 5.21 (s, 2H), 4.55 (s, 2H), 3.89 (s, 3H), 3.87-3.82(m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.8, 143.3, 142.4, 142.3, 129.8, 128.9, 128.3, 128.1, 127.4, 126.9, 126.2, 125.7, 124.0, 119.0, 115.0, 71.2, 52.4, 51.7, 48.8 ppm; MS (EI) m/z 364 (M+1). HRMS (ESI) calcd for: $C_{21}H_{20}N_2O_2S$: m/z 364.1245. Found 364.1243. IR(KBr): 3380, 1705, 1616, 1505 cm^{-1}.

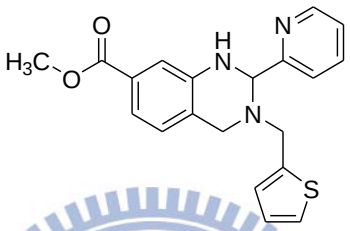
Methyl 2-(4-nitrophenyl)-3-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-7-carboxylate(13n)



^{1}H NMR (300MHz, $CDCl_3$): δ 8.17 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.69(d, *J* = 8.7 Hz, 2H), 7.43 (d, *J* = 1.5 Hz, 1H), 7.39 (d, *J* = 1.5 Hz, 1H), 7.30 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.98-6.91 (m, 3H), 5.23 (d, *J* = 2.7 Hz, 1H) 4.63 (d, *J* = 3.6 Hz, 1H), 4.08-3.68 (m, 5H); ^{13}C-

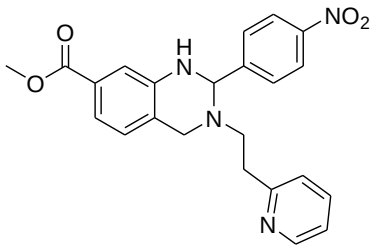
NMR (75 MHz, $CDCl_3$) δ 167.2, 147.6, 140.8, 130.5, 129.8, 128.1, 127.8, 126.7, 126.4, 125.7, 124.3, 124.1, 123.7, 119.3, 115.0, 70.5, 69.3, 52.1, 51.7 ppm. MS(ESI) m/z 410 (M+1). HRMS (ESI) calcd for: $C_{21}H_{20}N_3O_4S$: m/z 410.1174. Found 410.1176. IR(KBr): 2931, 1708, 1600, 1505 cm^{-1}.

Methyl 2-(pyridin-3-yl)-3-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-7-carboxylate(13o)



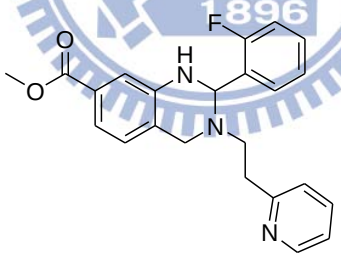
^1H NMR (300MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.8 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.78 (td, *J* = 7.8, 1.5 Hz, 1H), 7.45 (d, *J* = 1.2 Hz, 1H), 7.38 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.29-7.23 (m, 2H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.91 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.82 (d, *J* = 3.3 Hz, 1H), 5.52 (s, 1H), 4.25 (d, *J* = 17.1 Hz, 1H), 3.95 (d, *J* = 3.9 Hz, 1H), 3.90 (s, 3H), 3.70 (dd, *J* = 38.1, 13.5 Hz, 2H) ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.3, 159.9, 148.4, 142.4, 137.3, 129.6, 127.9, 126.7, 125.9, 125.2, 123.2, 122.4, 119.1, 115.7, 114.6, 72.1, 69.3, 52.0, 50.7, 47.1 ; MS (EI) m/z 365 (M^+) . HRMS (ESI) calcd for: $C_{20}H_{19}NO_2S$ ： m/z 365.1198.Found 365.1201

Methyl 2-(phenyl)-3-[2-(pyridin-2-yl)ethyl]-1,2,3,4-tetrahydroquinazoline-7-carboxylate(13p)



^{1}H NMR (300MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.8 Hz, 1H), 8.09 (dd, *J* = 9.3, 1.8 Hz, 1H), 7.60 (td, *J* = 7.5, 1.8 Hz, 1H), 7.35-7.31(m, 3H), 7.18-7.11(m, 2H), 6.91 (d, *J* = 7.5 Hz, 1H), 5.27 (d, *J* = 2.4 Hz, 2H), 4.78 (d, *J* = 8.7 Hz, 1H), 4.73 (d, *J* = 3.9 Hz, 1H), 3.87 (s, 3H), 3.15-2.89 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.2, 159.6, 149.6, 148.5, 147.4, 141.2, 137.0, 129.6, 128.1, 127.7, 123.7, 123.6, 121.6, 119.1, 115.2, 71.3, 52.3, 52.0, 48.1, 36.7 ppm; MS(ESI) m/z 419 (M+1) . HRMS (ESI) calcd for: $C_{23}H_{23}N_4O_2$: m/z 419.1719.Found 419.1717. IR(KBr): 2925, 1712, 1294 cm^{-1}.

Methyl 2-(2-fluorophenyl)-3-[2-(pyridin-2-yl)ethyl]-1,2,3,4-tetrahydroquinazoline-7-carboxylate(13q)



^{1}H NMR (300MHz, $CDCl_3$) δ 8.45 (dd, *J* = 4.2, 0.9 Hz, 1H), 7.56 (td, *J* = 4.2, 1.8 Hz, 1H), 7.35-7.17 (m, 4H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.06-6.95 (m, 4H), 5.58 (d, *J* = 2.4 Hz, 1H), 4.54 (s, 1H), 3.96 (d, *J* = 4.2 Hz, 1H); 3.90-3.47(m, 6H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 167.3, 159.9, 149.0, 142.3, 136.4, 129.7, 129.1, 128.4, 128.3, 127.4, 123.7, 123.4, 121.2, 118.6, 115.8, 115.5, 114.4, 66.7, 53.4, 52.0, 49.0, 36.9. MS (ESI) m/z 392 (MH^+) HRMS (ESI) calcd for: $C_{23}H_{23}FN_3O_2$：m/z 392.1774. Found 392.1775

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Chapter Two

Novel Approach Toward Synthesis of Skeletally Diverse Benzimidazole-pyrrolo[1,2-a]quinoxaline by S_NAr/Pictet-Spengler Reaction and Benzimidazole-(alkyloxy)-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxalin by S_NAr/Partial Nitro Group Reduction Reaction

2.0 Introduction

As it has been perceived that cells are the fundamental building blocks human body and of all living organism. In our living body cancer develops out of normal cells. As the requirement of the body, normal cells reproduce and die when the body doesn't need them. It has been observed that cancer happens to occur when the growth of cells in the body is out of control and cells separate very rapidly as shown in Figure 2.0. In normal tissues, the rates of growth of new cell and death of old cells are always reserved in balance. In cancer cell, this balance is disorder.[1]

Figure 2.0. Defination of Cancers. Courtesy

"http://www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer"

2.1. Different Causes Cancer?[2-3]

2.1.1 There are numerous causes of cancers, including:

- Drinking excess alcohol
- Carcinogenic chemicals
- Environmental toxins, such as certain toxic mushrooms and a kind of poison that can grow on peanut plants (aflatoxins)
- Genetic problems
- Extreme sunlight exposure
- Obesity
- Viruses
- Radiation

2.1.2. Genetic Factor Leads to Cancer

- Anti-oncogenes
- Activation Of Proto-oncogenes
- Insensitivity to growth-inhibitory
- Irregular signaling pathway
- Apoptosis
- Abnormal cell cycle regulation
- Metastasis
- Angiogenesis

2.2. Metastatic Cancer

It has been perceived that most of the cancer mortality arises form the effect of Metastasis. Metastasis, normally occurs when the cancer cell penetrate into lymphatic and blood vessels, distributed through the bloodflow, which then occupy and promote in normal tissues. In broader concept, Metastasis has the ability to permeate to other tissues and organs that makes cancer a potentially life-threatening disease. Metastasis concept has been shown in Figure 2.1.[4]

Figure 2.1. Malignant Vs Benign tumors, courtesy from 'http://www.cancer.gov/cancertopics/understandingcancer/angiogenesis/page1'

2.3. What is tumor angiogenesis?

Normally the emergence of new capillaries from pre-existing blood vessels is called angiogenesis. To grow beyod normal limit the tumor cells need independent blood supply, neutients and oxygen. The propagation of blood vessels which can penetrates into

cancerous growths, supplying nutrients and oxygen and removing waste products is called the tumor angiogenesis as shown in Figure 2.2. [5-8]

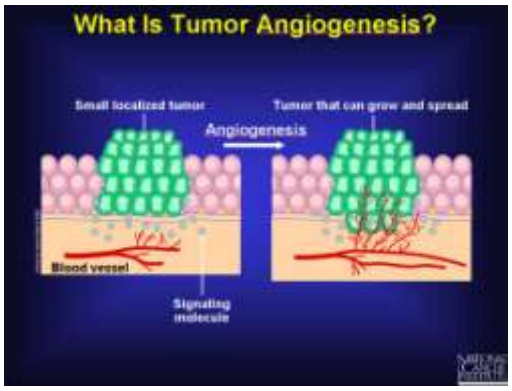


Figure 2.2. Tumor Angiogenesis, courtesy from 'http://www.cancer.gov/cancertopics/understandingcancer/angiogenesis/page1'

2.4. The angiogenesis signaling cascade

The gowth factor VEGF and bFGF has been produced by the tumor cells. As soon as they meet endothelial cells surface, they bind to sequence specific proteins, called receptors, which is located on the outer surface of the cells. When VEGF or bFGF binds to its appropriate receptor it activates a relay proteins that further transmits a signal into the nucleus of the endothelial cells. The nuclear signal directs a group of genes to further generate products which could be needed for new endothelial cell growth as shown in Figure 2.3.[9-1]

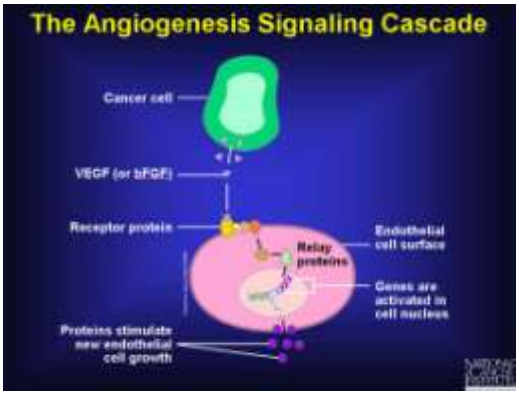


Figure 2.3. The angiogenesis signaling cascade, courtesy from 'http://www.cancer.gov/cancertopics/understandingcancer/angiogenesis/page13'

2.5. The VEGF ligand is the predominant regulator of tumor angiogenesis

For the tumor angiogenesis, VEGF ligand has been identified as the most prominent regulator. VEGF help to creat new vasculature establish for very beginning stage of tumor development. It has well established fact that, VEGF may stimulate tumor growth at both primary and metastatic sites that form the building blocks of a new vascular network. VEGF help to creat existing vasculature survive, allowing tumors to sustain their metabolic requirements over their entire life cycle, throughout tumor development, as shown in Figure 2.4.[12-16]

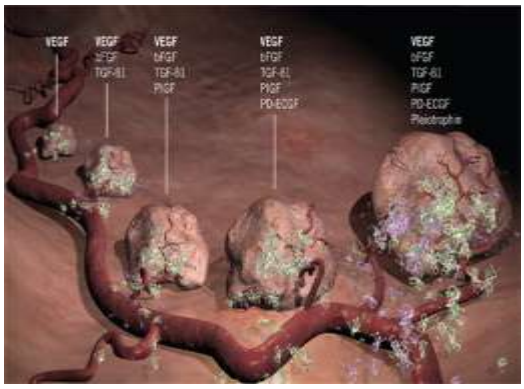


Figure 2.4. VEGF ligand for tumor angiogesis, courtesy from 'http://www.biooncology.com/research-education/vegf/ligand/index.html'

2.6. VEGF

The VEGF which stands for "vascular endothelial growth factor" is a chemical signal produced by cells that stimulates the growth of new blood vessels. When blood circulation is inadequate in our body tt is part of the system that restores the oxygen supply to tissues When VEGF overexpress, this plays an important role in angiogenesis. VEGF stimulates vascular endothelial cell growth, survival, and proliferation. The VEGF is a family of 6 structurally related proteins that promote the growth and differentiation of the vascular system, especially blood and lymph vessels. The six members are VEGF-A, placenta growth factor, VEGF-B, VEGF-C, VEGF-D and VEGF-E as shown in Table 2.0.[17-18]

Table 2. 0. VEGF family and its receptors along with functions

VEGF Family Members	Receptors	Functions
VEGFA	VEGFR-1, VEGFR-2,	Angiogenesis, vascular
VEGF-B	VEGFR-1	Not established
VEGF-C	VEGFR-2, VEGFR-3	Lymphagiogenesis
VEGF-D	VEGFR-2, VEGFR-3	Lymphagiogenesis
VEGF-E (viral factor)	VEGFR-2	Angiogenesis
Placental growth factor (PIGF)	VEGFR-1, neuropilin-1	Angiogenesis Inflammation

2.7. VEGF receptors

Vascular endothelial growth factor (VEGF) ligands mediate their angiogenic effects by binding to specific VEGF receptors. Receptor dimerization and subsequent signal transduction occurs next. VEGF ligands bind to 3 primary receptors and 2-co-receptors. As results these six members can bind and activate the tyrosine kinase receptors, VEGF receptors 1, 2, and 3, which promote the propagation, endurance, and migration of endothelial cells. VEGFR-1 is able to bind VEGF-A, VEGF-B, and PlGF. VEGFR-2 is activated basically by VEGF-A, but of VEGF-C, VEGF-D, and VEGF-E may also activate this receptor. So, basically the angiogenesis is regulated by VEGFR-1 and VEGFR-2 as mentioned in Figure 2.5. Endothelial expression of VEGF receptors varies

among the 3 primary recetors; VEGFR-2 is expressed on almost all endothelial cells, where as VEGFR-1 and -3 are selectively expressed in distinct vascular beds.[19-21]

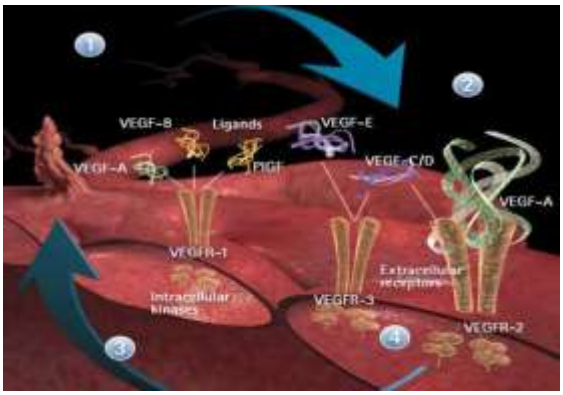


Figure 2.5. VEGF ligand and receptors, courtesy from 'http://www.biooncology.com/research-education/vegf/vegf/vegf-pathway/index.html'

2.8. The strategies for inhibiting the VEGF pathway

There are two primary pathways for inhibiting the VEGF signaling pathway which includes inhibiting either the VEGF ligand or the VEGF receptor. These are explained as below.[22-24]

2.8.1. Extra cellular targeting of the VEGF ligand

It has been known that VEGF ligand could be targeted by ligand-binding antibodies and soluble receptors. These agents work extracellularly to provide particular inhibition of the VEGF pathway without creating problems to other non-VEGF related targets.[25-27]

2.8.2. Intra cellular targeting of the VEGF receptor

This starategy involves the targeting of VEGF receptor which include tyrosine kinase inhibitors (TKIs) and receptor antibodies. There are some agents which could target the VEGF receptor intracellularly, some are mentioned as TKIs, which have a wider range of inhibitory effects but they could disrupt other secondary pathways that are also mediated through receptor kinases.[28-29]

2.9. Lymphangiogenesis

It is well known fact that for tumor growth, invasion, and metastasis, lymphangiogenesis (lymph vessel growth) and angiogenesis (blood vessel growth) are the main factors. The formation of lymphatic vessels from pre-existing lymphatic vessels is called lymphangiogenesis. It plays an important role in promoting metastasis. It has been found that vascular endothelial growth factor receptor-3 (VEGFR-3) mediates lymphangiogenesis by binding to its two ligands, VEGF-C and VEGF-D. They belong to the larger family which also includes VEGF, placenta growth factor (PlGF) and VEGF-B, VEGF-C and VEGF-D are ligands for the endothelial cell specific tyrosine kinase receptors VEGFR-2 and VEGFR-3. VEGF-C induces lymphatic vessel growth, but high levels of VEGF-C also resulted in blood vessel growth. Normally it has been found that the lymphatic vessels are also involved in lymph node and systemic metastasis of cancer cells. Thus, it is desirable to develop novel drugs that inhibit the VEGFR-3/ligand signaling pathway for cancer treatment as shown in Figure 2.6.[30-32]

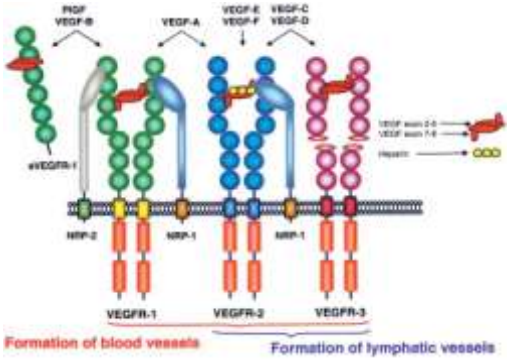


Figure 2.6. Angiogenesis and lymphogenesis, courtsey from

'http://www.rosenthallab.com/gallery/detail.php?fileName=VEGF_VEGFR.jpeg'

2.10. How cancer can be treated?

- Surgery - the cancerous tissue may be cut out by a surgeon. It is a difficult process to destroy the cancerous cell.

- Radiotherapy - a beam of high-energy radiation destroys the cancer cells and can affect some normal cells as well, producing some side effects.

- Chemotherapy - chemicals which has been used for to destroy cancer cells. This treatment may also have many other side effects and may affect other parts of the body.

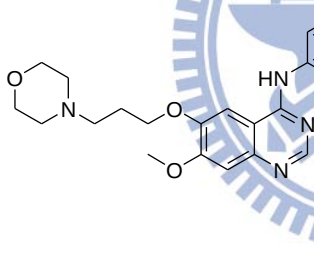
- Combination therapy - this may involve all, some or a combination of some of the above processes.

- If cancer is detected and treated at an early stage there is a greater chance of a cure and possibly less extensive treatment.

To slow down or prevent the growth and spread of cancer cells in humans, researchers are now thinking for angiogenesis inhibitors. Two dozen angiogenesis inhibitors are currently being tested in cancer patients to answer this question. Depending on their mechanism of action the inhibitors being tested fall into several different categories. Some inhibit endothelial cells directly, while others inhibit the angiogenesis signaling cascade or block the ability of endothelial cells to break down the extracellular matrix as shown in Figure 1.18. [33-36]

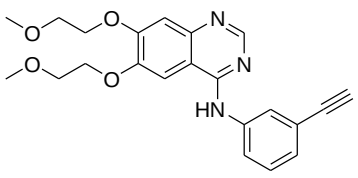
2.11. Small molecules for Inhibtion of Angiogenesis process.

2.11.1 Gefitinib



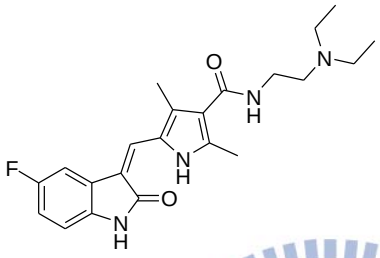
Gefitinib, the trade name Iressa is a drug used in the treatment of cancer like non-small cell lung and breast cancer. Gefitinib is the first selective inhibitor of epidermal growth factor receptor's. Gefitinib inhibits EGFR tyrosine kinase by attaching to the adenosine triphosphate (ATP)-binding site of the enzyme.[37-38]

2.11.2. Erlotinib hydrochloride



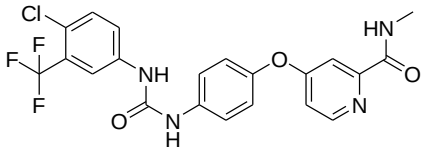
Erlotinib hydrochloride is a drug used for treatment of non-small cell lung cancer, pancreatic cancer and several other types of cancer. It is a tyrosine kinase inhibitor, which acts on the epidermal growth factor receptor.[39-40]

2.11.3. Sunitinib



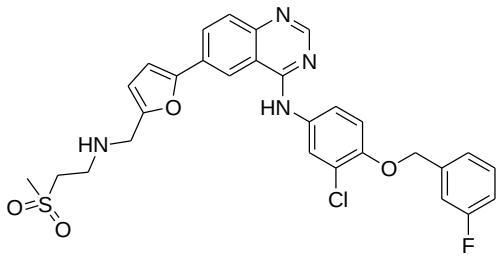
Sunitinib malate is a multitarget oral tyrosine kinase receptor inhibitor which was approved by FDA in for the treatment of renal cells carcinoma. Sunitinib inhibits cellular signaling by targeting multiple receptor tyrosine kinases (RTKs).[41]

2.11.4. Sorafenib



Sorafenib is a small molecule drug approved for the treatment of primary kidney cancer and advanced primary liver cancer. [42]

2.11.5. Lapatinib



Lapatinib used in the form of lapatinib ditosylate, is an orally active drug for breast cancer and different solid tumours. Lapatinib, the first of its type of dual inhibitor of epidermal growth factor receptorand human epidermal growth factor receptor 2 tyrosine kinases, was approved by the US Food and Drug Administration in 2007.[43-44]

2.12 .Protein Lysine Methyltransferase G9a Inhibitors

Methylation of Lysine 9 of histone H3 (H3K9) and lysine 373 (K373) of p53 has been catalyzed by protein lysine methyltransferase G9a, which is often overexpressed in human cancers. Dimethylation of p53 K373 results in the inactivation of p53 gene and also genetic reduced of G9a, inhibits cancer cell growth by the dimethylation mechanism. Protein lysine methyltransferases (PKMTs) that catalyze mono, di, or trimethylation of lysine residues of various proteins including histones have received great attention because of the essential function of histone lysine methylation in many biological processes such as gene expression and transcriptional regulation, heterochromatin formation, and X chromosome inactivation as shown in Figure 2.7. The dimethylation of p53 K373 results in the inactivation of p53, which is concerned in over 50% of cancers. These interpretation suggest that inhibition of G9a is a potential approach for cancer

treatment. Till date the researcher has found a only one small molecule BIX01294, which is G9a inhibitor. Thus, small molecule PKMT inhibitors could play an important role in stem cell biology and regenerative medicine.

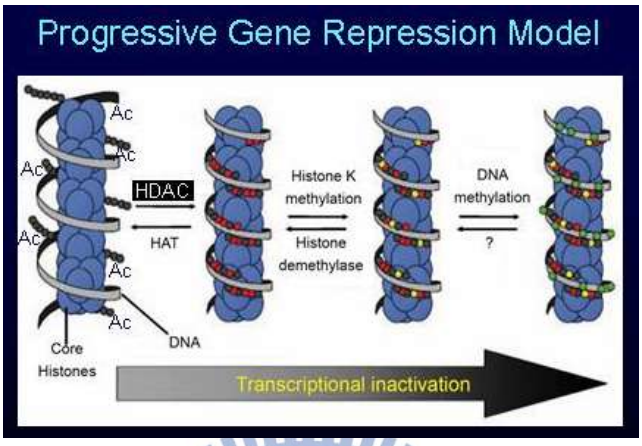


Figure 2.7. Histone K methylation, *courtsey.* Galinari *et al, cell res,* **2007**, 17, 195.

In Figure 2.8 has shown a small molecule BIX 01294, which can inhibit G9a.[45-47]

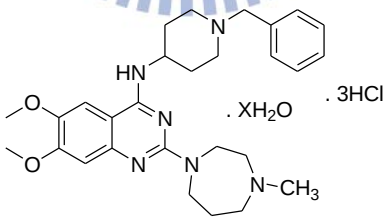


Figure 2.8. BIX 01294 is a selective histone methyl transferase inhibitor

2.13. Soluble Polymer Supported Organic Synthesis

Generally classical reaction has been carried out in solution phase involving the separation of the desired product from reagents and by-products after the reaction. This purification step can however turn out to be extremely time consuming and often meticulous. In 1963 Merrifield first introduced the solid-phase synthesis of peptide and oligosaccharide. This methodology, which was limited to the synthesis of peptides and oligosaccharides[48] however remained predominantly limited to this field until the introduction of liquid phase techniques. To evade the drawbacks innate to solid-supported technologies such as, nonlinear kinetics, unequal distribution to the chemical reaction, solvation problems, alternative approaches using homogeneous ′beadless′ phase-tagged chemistry have been introduced to facilitate separation whilst retaining solution phase kinetics. Amongst all of these beadless approaches, soluble polymer phase attaching of substrates enable easy separation, monitoring, analysis and characterisation has become the method of choice.[49] The polymers employed as soluble supports in liquid phase organic synthesis possess some qualities such as a) easy availability, b) good mechanical and chemical stabilities, c) homogeneous reaction condition, d) having appropriate functional groups for easy anchoring to organic moiety and more importantly showing high solubility to dissolve molecular entities etc.[50] Moreover, it has been observed that polymer supports normally used in organic synthesis are macromolecules varying different sizes. These supports should with stand the reaction condition used in solution phase chemistry and consequently most polymer supports used in liquid phase synthesis possess alkyl ether backbone structures. By variation of functional groups of backbone structures, polymer properties are determined and may provide sites for attachment of

organic moieties. There are number of polymers which are normally used for small molecule organic synthesis. These includes polyethylene glycol (PEG), polystyrene, poly (propylene oxide), poly(vinyl alcohol), polyethylene imine, polyacrylic acid, polyacryl amide, PEG with 3,5-diisocyanatobenzyl chloride, and cellulose (Figure 1.21).[51]

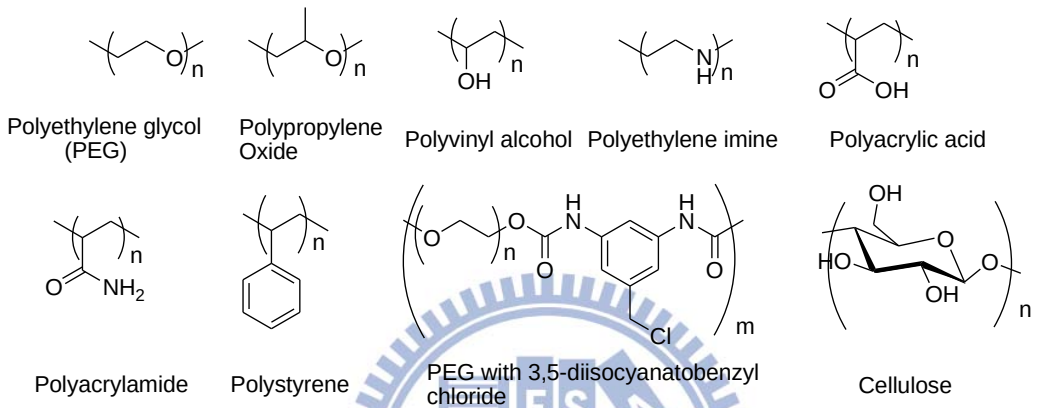


Figure 2.9. Different Soluble Supports used in Small Molecule Organic Synthesis

2.13.1. Application and recent development of polyethylene glycol as soluble support in organic synthesis

Among all polymer support, polyethylene glycol has been frequently used in small molecule organic synthesis. Polyethylene glycol (PEG) (Figure 2.10) is a polyether compound which has many applications from industrial manufacturing to medicine.

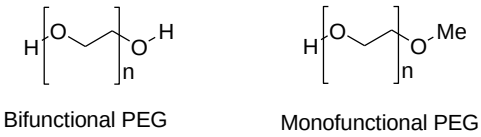


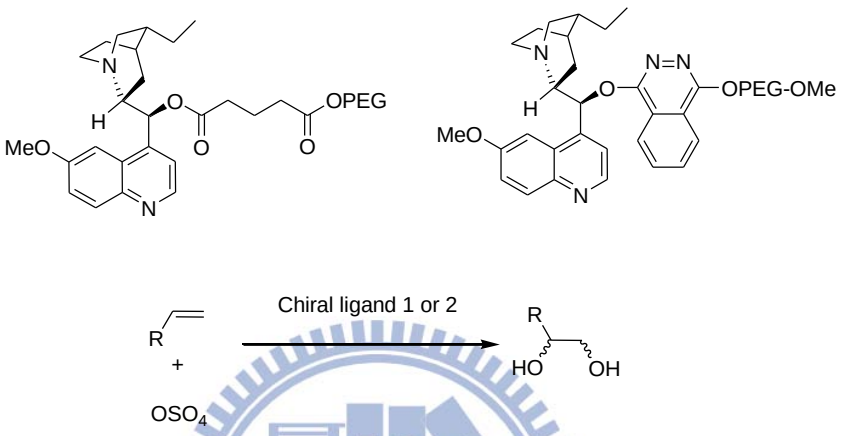
Figure 2.10. Different PEG Soluble Supports.

PEGs are commercially available over a wide range of molecular weights from 200 g/mol to 10,000,000 g/mol and are prepared by polymerization of ethylene oxide. PEG has different physical properties (e.g., viscosity) due to chain length effects and their chemical properties are nearly identical and PEO with different molecular weights find use in different applications.[52-54]

2.13.2. PEG for Small molecule Synthesis

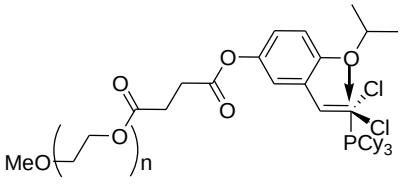
Polyethylene glycol has long been applied as soluble polymer supports for the synthesis of oligopeptide, oligosaccharide as well as small molecules. Normally for the supported synthesis PEG_{5000} and PEG_{4000}, PEG_{6000} are used as soluble supports based on the loading capacity and hydroxyl functionalities contained. PEG_{5000} contains one hydroxyl group and its loading capacity is 0.2 mmol/g, whereas PEG_{4000} and PEG_{6000} consist of two hydroxyl groups and their loading capacities are 0.5 mmol/g and 0.33 mmol/g, respectively. Employed as a protecting group, this linear homopolymer exhibits solubility in a wide range of organic solvents and water. PEG_{5000} and PEG_{4000}, PEG_{6000} in can be use as a support but some cases low moleucular weight PEG can be use a solvent. High molecular weight PEG is insoluble in hexane, diethyl ether and *tert*-butyl methyl ether, and these solvents have been used to induce PEG precipitation.[55-56] Primarily, the uses of these polymers in synthesis have fallen into one of two areas: (A) the use of the polymer as a support for reactants or (B) the use of the polymer as a support for reagents and catalysts during a reaction. Both of these methods allow rapid product purification and the ability to drive a given reaction to completion through the use of an excess of reagents.

In 1996 Janda *e.t al.* has developed first soluble polymeric attached chiral chincona ligand to carry out the asymmetric hydroxylation. They believe that MeO-PEG polymer will useful effecting the separation of catalyst from product in homogeneous industrial applications as shown in scheme 1.[57]



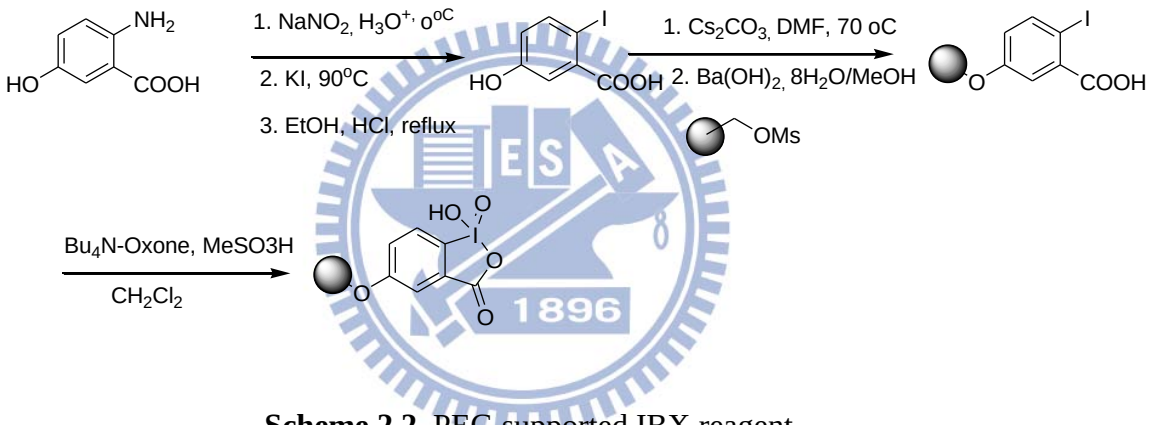
Scheme 2.0 Asymmetric hydroxylation using PEG supported catalyst

MeOPEG-5000 was coupled to a substituted styrene using a succinate linker to provide, MeO-PEG-supported Grubbs type catalyst, after treatment with a ruthenium alkylidene in figure 1.23. This catalyst was used for the ring-closing metathesis reaction of a number of dienes and demonstrated excellent conversions (>92%) for all studied examples and only a slight decrease in catalytic activity after repeated use.[58]



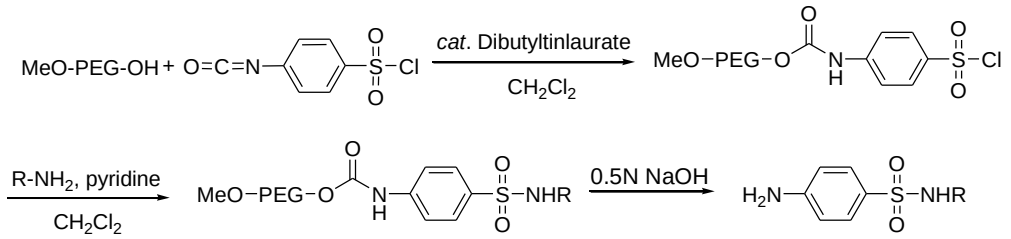
Scheme 2.1. Grubbs catalyst in PEG support

Recently, Janda and co-workers have reported a soluble polymer-supported version of IBX that has the advantage of being soluble in a greater range of solvents. This reagent was prepared by first synthesizing the appropriate m-hydroxyiodobenzoic acid in scheme 2. Loading of this compound onto NCPS, followed by ester hydrolysis and oxidation of the iodine from I(III) to I(V), led to NCPS-supported reagent. Using 2 equiv of NCPS supported IBX, it was demonstrated that the conversion of benzyl alcohol to benzaldehyde proceeded in quantitative yield after only 1 h in methylene chloride as in scheme 2.[59]



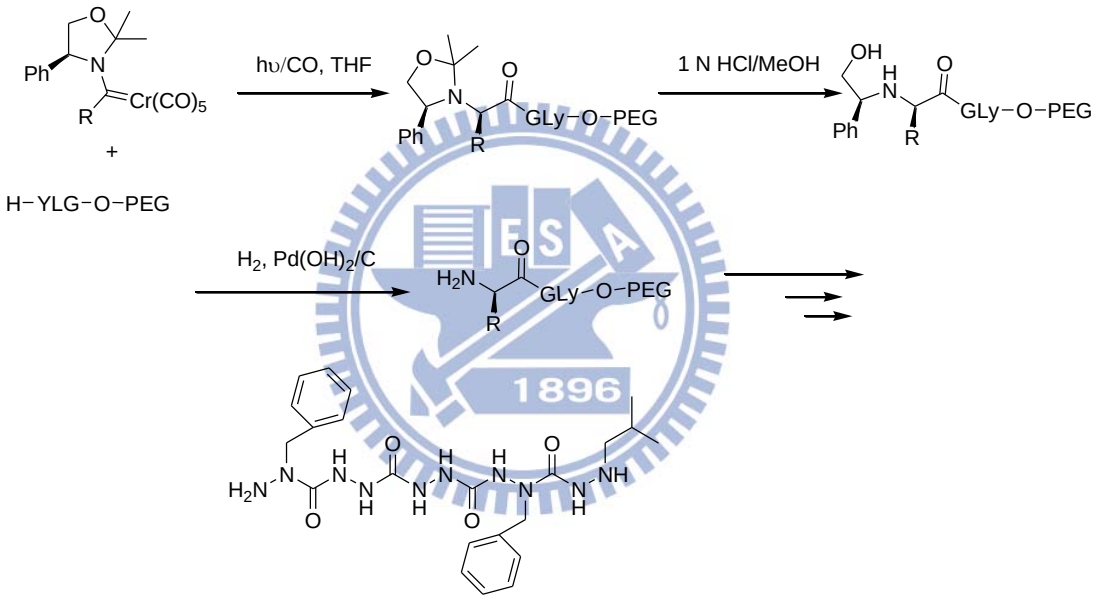
Scheme 2.2. PEG supported IBX reagent

Till date several research efforts has been published using PEG as soluble supports. Janda *et* al. first reported the synthesis of sulfonamide libraries using the PEG as a support. This was the first report of the use of PEG in small organic molecule synthesis shown in Scheme 2.3.[60]



Scheme 2.3. Synthesis of sulfonamide in PEG support.

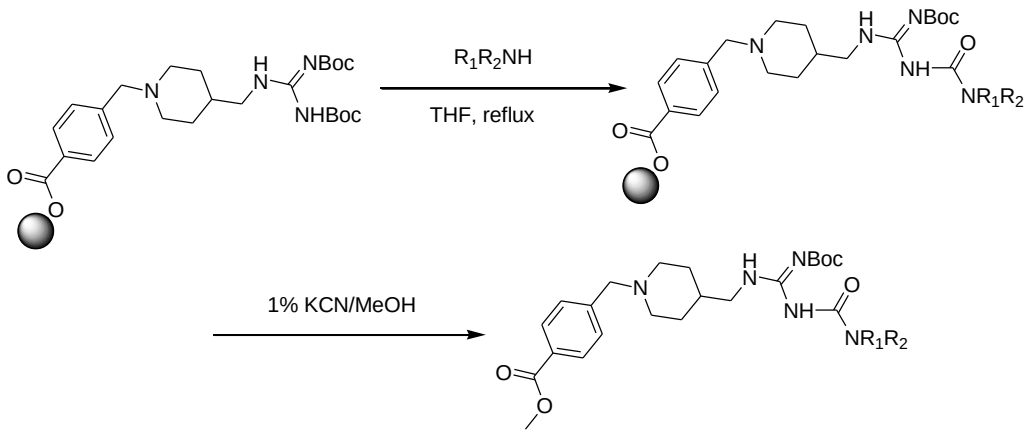
Similar methodology was applied for the synthesis of a new class of peptidomimetics called azetides as shown in Scheme 2.4.[61]



Peptidomimetric azatide Tyr-Gly-Gly-Ph-Leu prepared by PEG support

Scheme 2.4. Synthesis of peptide by PEG support.

Subsequently, in the year 1999, first our lab has developed pharmacologically interesting guanidine and urea functional groups by combinatorial approach using soluble PEG support in Scheme 2.5.[62]



Scheme 2.5. Synthesis of guanidine and urea functional group

2.14. Pyrrolo[1,2-*a*]quinoxalines its importance and synthesis

The heterocyclic compounds with azole-fused quinoxaline rings such as imidazo[1,2-*a*]quinoxalines, imidazo[1,5-*a*]quinoxalines, [1,2,4]triazolo[4,3-*a*]quinoxalines, 1*H*-imidazo[4,5-*b*]quinoxalines, and pyrrolo[1,2-*a*]quinoxalines are known to demonstrate a ample range of pharmacological activities.[63-67,] It has been observed that many best selling drugs contain structurally complex biheterocyclic moiety as a key component.[68] Our research group has been long involved in developing the novel therapeutics in quinoxaline analogues as quinoxaline skeleton fused with pyrrole is most representative structure with extensive chemical and biological profiles (Figure. 2.11 A).[69] Recently, it was identified that the pyrrolo[1,2-*a*]quinoxaline derivatives are In binding studies shows several pyrroloquinoxaline compounds proved to be potent and selective 5-HT3 receptor ligands as well as potent antileshmanial agents (Figure. 2.11 B, C).[70] Furthermore, the pyrrolo[1,2-*a*]quinoxaline derivatives anchored benzimidazole moiety are shown to

exhibit as an antiulcer agent (Figure. 2.11 D).[71] **It** is noticed that the several bis pyrrolo[1,2-*a*]quinoxalines possesses *in vitro* anti-malerial activity.[72]

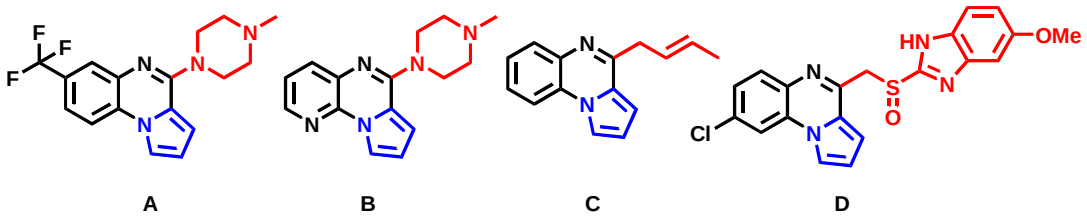
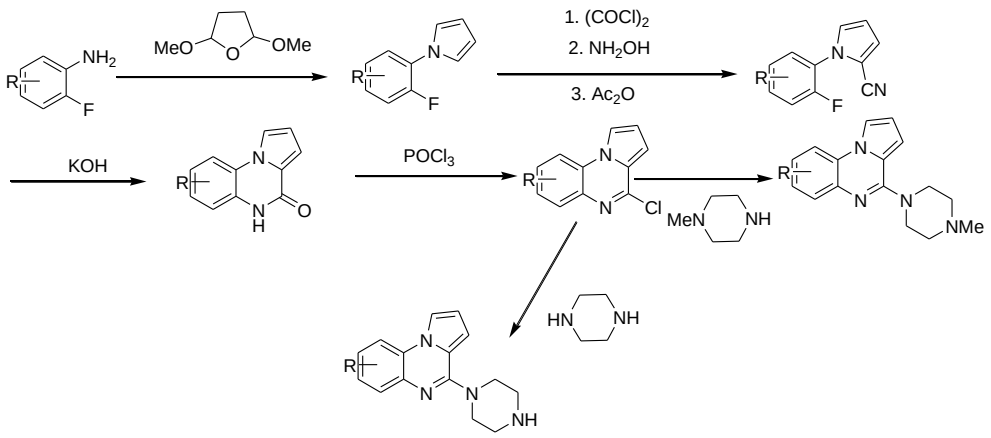


Figure 2.11. Representative examples of biologically active pyrrolo[1,2-*a*]quinoxalines.

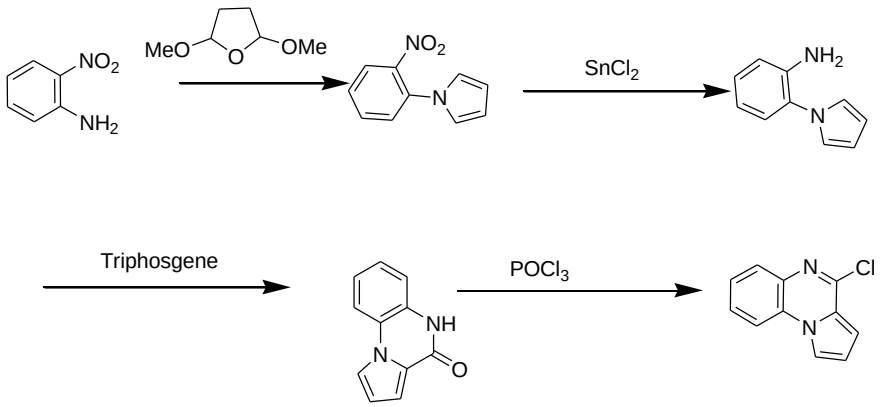
2.15. Various method of preparation of Pyrrolo[1,2-*a*]quinoxalines derivatives

In 1997, for the first time Campiani *et. al.* had described the synthesis and the biological evaluation of a series of novel pyrroloquinoxaline derivatives. They used the o-fluoroaniline which underwent Clauson-Kaas reaction to give the corresponding arylpyrroles and subsequently transformed into 1-aryl-2-cyanopyrroles through a one-pot sequence involving formylation, oximation,and dehydration. The intermediates were progressively cyclized to the desired pyrrolo[1,2-*a*]quinoxalinones by basification in ethylene glycol at high temperature. Upon treatment of pyrrolo[1,2-*a*]quinoxalinones with $POCl_3$ and Nucleophillic aromatic substitution to generate the target pyrrolo[1,2-*a*]quinoxalines as shown in Scheme 2.6.[73]



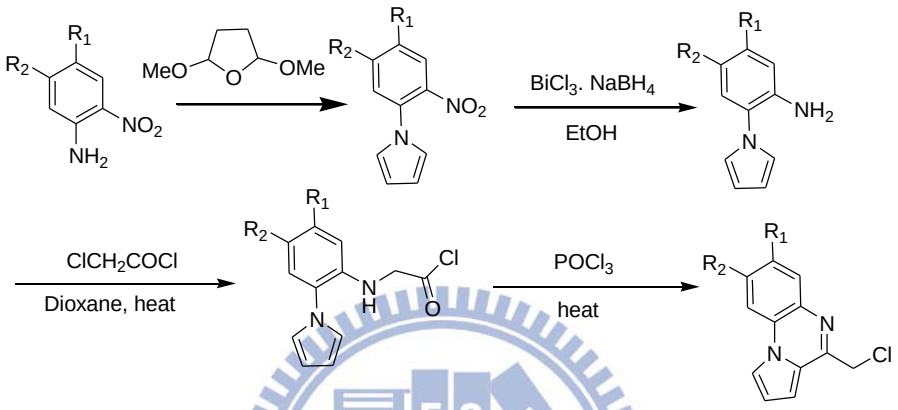
Scheme 2.6. Synthesis of pyrrolo[1,2-*a*]quinoxalines.

Simailarly, In 1999 the Campiani *et. al.* has modified the procedure for the synthesis of pyrroloquinoxaline moiety. Instead of o-fluoroaniline they took o-onitroaniline which underwent the same set of Clauson-Kaas reaction to give the corresponding arylpyrroles. Subsequently reduction of nitro group ortho to the pyrrole moiety with $SnCl_2$ and cyclisation with triphosgene generated the pyrrolo[1,2-*a*]quinoxalinones. The desired compounds were achived by the Reaction of $POCl_3$ with pyrrolo [1,2-*a*]quinoxalinones as shown in the Scheme 2.7.[74]



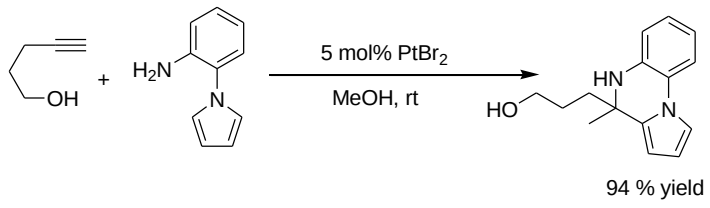
Scheme 2.7. Synthesis of pyrrolo[1,2-*a*]quinoxalines by Campiani *et. al.*

In 2007, Vidaillac *et. al.* has synthesized a series of pyrrolo[1,2-*a*]quinoxaline derivatives, sharing structural analogies with omeprazole, a eukaryotic efflux pump inhibitor (EPI) used as an antiulcer agent. But instead of cyclisating with triphosgene they used chloroacetyl chloride and $POCl_3$ to obtain the target structures as drawn in Scheme 2.8.[75]



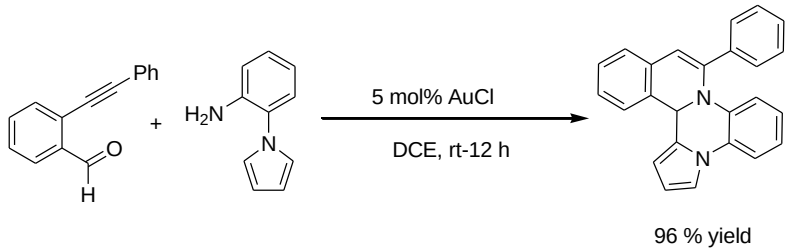
Scheme 2.8. Synthesis of pyrrolo[1,2-*a*]quinoxalines by Vidaillac *et. al.*.

In 2009, For the first time, Patil *et. al.* has developed an efficient method for Markownikoff's hydroamination-hydroarylation of alkynols using $PtBr_2$ as catalyst. The platinum-catalyzed reactions of alkynols with amino group containing aromatics were achieved in methanol over a reaction time of 6-24 h and temperature ranging from r.t to 80 ^oC in Scheme 2.9.[76]



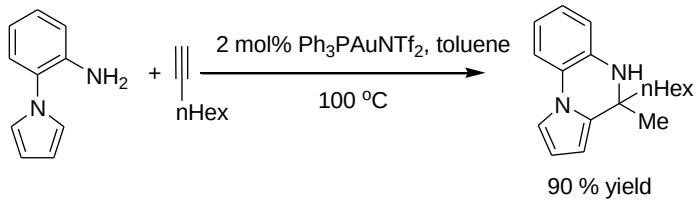
Scheme 2.9. Synthesis of pyrrolo[1,2-*a*]quinoxalines by $PtBr_2$ catalysed reaction by Patil *et. al.*

Subsequently in 2010, Patil *et. al.* has developed a gold(I)-catalyzed, coupling–cyclization technique for the synthesis of isoquinoline- fused polycyclic compounds. The reaction composed of *o*-alkynylbenzaldehydes and aromatic amines having tethered nucleophiles in Scheme 2.10.[77]



Scheme 2.10. AuCl catalysed synthesis of pyrrolo[1,2-*a*]quinoxalines

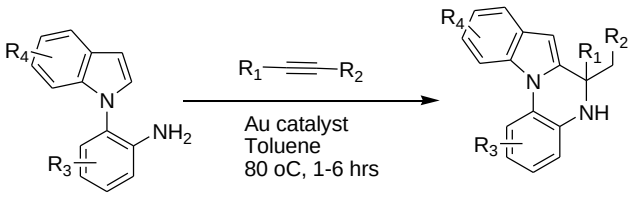
In the same year, Patil *et. al.* has developed an efficient method for formal Markownikoff hydroamination/ hydroarylation and double hydroamination of terminal alkynes using 2–5 mol-% of $Ph_3PAuNTf_2$ in toluene at 100 °C has been developed scheme 2.11. [78]



Scheme 2.11. Synthesis of pyrrolo[1,2-*a*]quinoxalines by Au catalysed reaction

In 2011, Liu *et. al.* has developed an efficient tandem process of hydroamination and hydroarylation using a gold catalyst to enable and study the reactions between pyrrole-

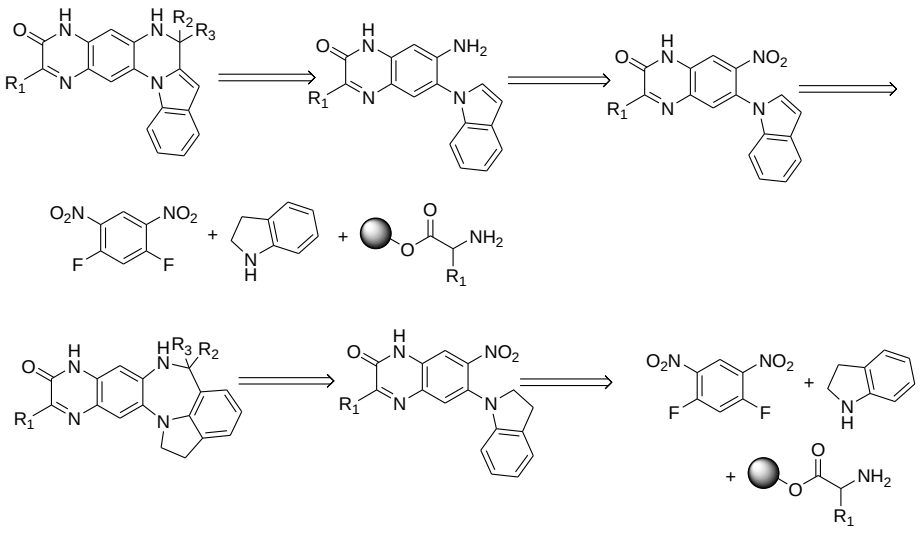
substituted anilines and alkynes. The gold (I)-catalyzed reactions were accomplished in toluene at 80 ^{o}C over a reaction time of 1-6 h in scheme 2.12. [79]



R^1= aryl, alkyl
R^2=H, aryl, alkyl
R^3=H, Me, OMe, CN
R^4=H, Me, Et, OMe, CN, F

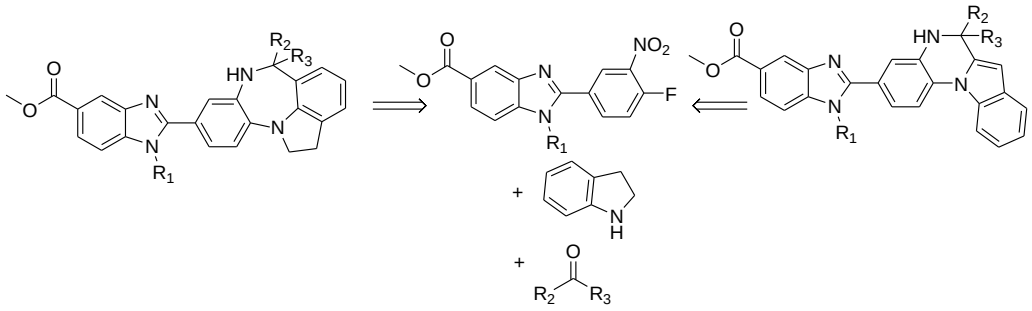
Scheme 2.12. Synthesis of pyrrolo[1,2-*a*]quinoxalines by Au catalysed reaction

In 2010, Our lab has described the synthesis diverse indolo-fused pyrazino-/diazepinoquinoxalinones using amino acid and indoline-substituted dinitrobenzene on a soluble polymer support (PEG) and its further reductive double-ring closure to afford structurally diverse final compounds. To furnish these novel scaffolds traceless synthesis of quinoxalinones coupled with application of the Pictet-Spengler-type condensation reaction uder microwave irradiation has been developed in Scheme 2.13. [80]



Scheme 2.13. Synthesis of indolo-fused pyrazino-/diazepinoquinoxalinones on PEG support

In 2011, Our lab has developed the diversity-oriented synthesis of novel benzimidazole linked indolo-benzodiazepine/quinoxaline ring systems using poly-(ethylene glycol) as soluble polymer support. To construct these types of privileged heterocyles commercially available 4-fluoro-3-nitrobenzoic acid and indoline were along with focused microwave irradiation in Scheme 2.14.[81]

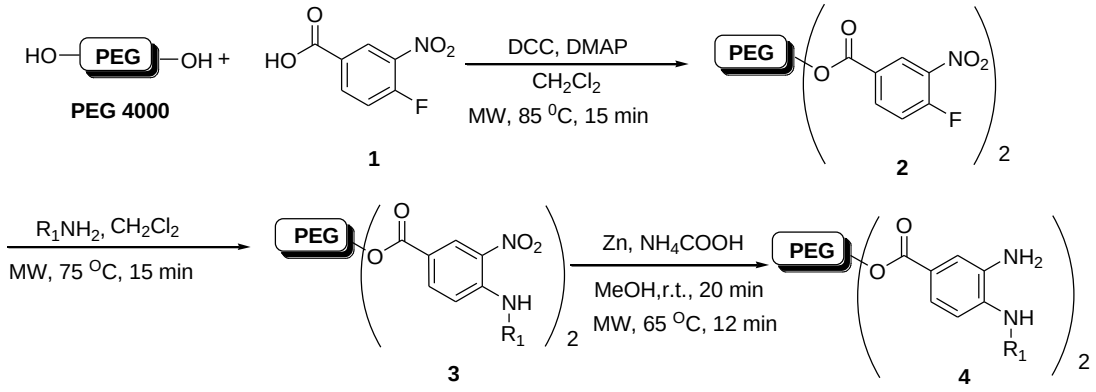


Scheme 2.14. Synthesis of benzimidazole linked indolo-benzodiazepine/quinoxaline on PEG support.

However, it has observed that for the construction of both tetrahydro-β-carbolines and tetrahydroisoquinolines the Pictet-Spengler reaction,[82a] which entails the cyclization of electron-rich aryl or heteroaryl groups onto imine or iminium ion electrophiles, has long been a standard method.[82b] For assemble diverse benzimidazole-pyrrolo[1,2-a]quinoxaline core small molecules, here for the first time we have described an application of S_NAr reaction and subsequent Pictet-Spengler cyclization involving electron-rich heteroaryl pyrrole groups onto iminium ion electrophiles. To the best of our knowledge, no research group ever reported the nucleophilic aromatic substitution reaction of pyrrole ring to the aromatic substrate directly and subsequent Pictet-spengler reaction. Prompted by this observation, we undertook the present investigation and the results of our studies are reported herein.

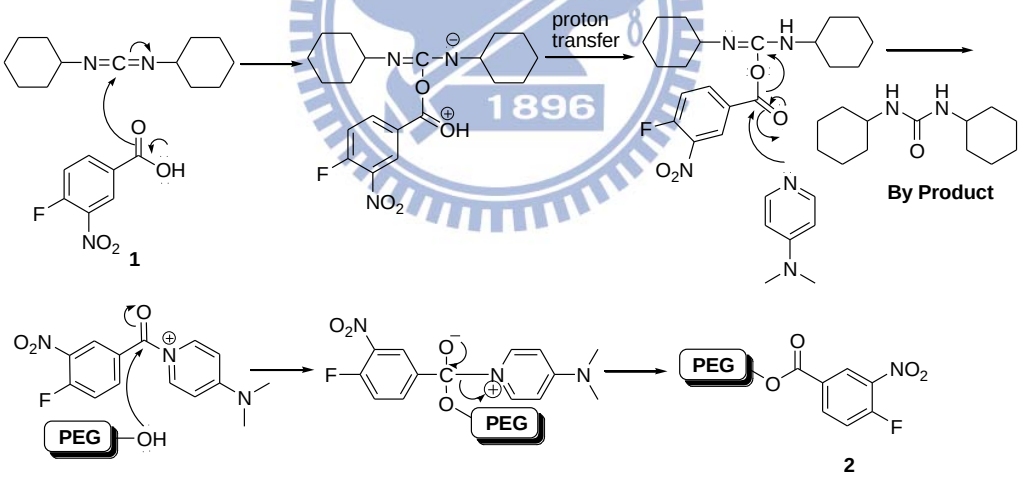
2.16. Results and Discussions

The present approach initiated with the synthesis of polymer immobilized *o*-phenylene diamine **3** from 4-fluoro-3-nitrobenzoic acid **1** with built-in structural diversity (R_1) through three step protocol as developed by our group previously.[83]



Scheme 2.15. PEG supported synthesis of *o*-phenylenediamine 4.

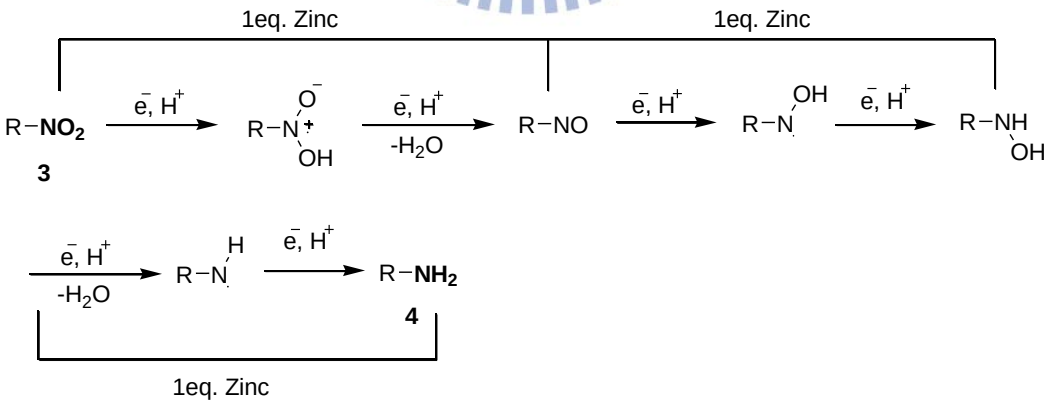
The synthetic method depicted in Scheme 2.15 was utilized HO-PEG-OH (MW: 4000) as a soluble support was reacted with the commercially available 4-fluoro-3-nitrobenzoic acid **1** through the *N,N'*-dicyclohexylcarbodiimide (DCC) and catalytic amount of 4-dimethylaminopyridine (DMAP) activation to afford the polymer immobilized *o*-fluoronitrobenzene **2** as pale yellow compounds in quantitative yields. However, we have observed that completion of the reaction was achieved in 1 day at room temperature condition. But with the application of sealed vessel microwave irradiation (80 °C, 2 bar), the same reaction completed in 20 minutes. After completion of the reaction time, the insoluble DCU was filtered off and purified by precipitating out the reaction mixtures with cold ether. The mechanism of the formation of compound **2** was explained in Scheme 2.16.



Scheme 2.16. **Mechanism of formation of compound 2 on soluble support**

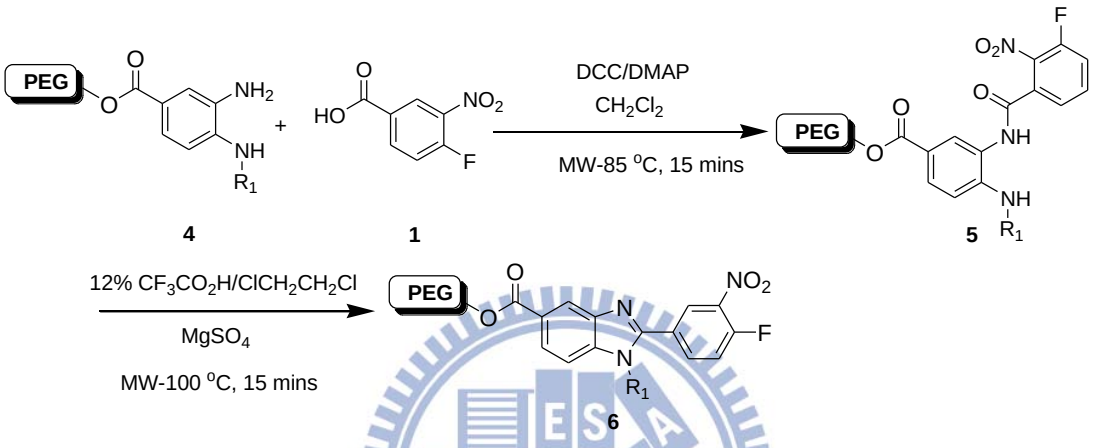
The first point of structural diversity was introduced by nucleophilic aromatic substitution (SnAr) of readily available primary amines with **1** via an *ipso*-fluoro

displacement to give polymer bound yellow nitroaniline compound **2**. NMR analysis of **2** showed complete conversion to **3** after a reaction time of 12 h at room temperature. The reaction proceeded efficiently with various amines without cleavage of the ester bond at the polymer attached site. With the application of microwave irradiation (100 °C, 2 bar) reduced the reaction time to 10 minutes. Purification was achieved by the precipitation with cold ether. Reduction of the aryl nitro group in the resulting polymer immobilized nitro derivative **3** was successfully accomplished with a suspension of $Zn/HCOONH_4$ in methanol to afford immobilized diamine **4** at room temperature for 20 minutes. Formation of the amine conjugates **4** was confirmed from change of yellow to blue color upon spotting on the TLC plate. Upon completion of the reaction, reaction mixtures were filtered through fritted funnel to get rid of the Zn. The reaction mixtures were evaporated and dichloromethane was added to salt out the ammonium formate to obtain the colourless compound **4.** The exact mechanism reharding the formation of compound **4** was observed in Scheme 2.17.



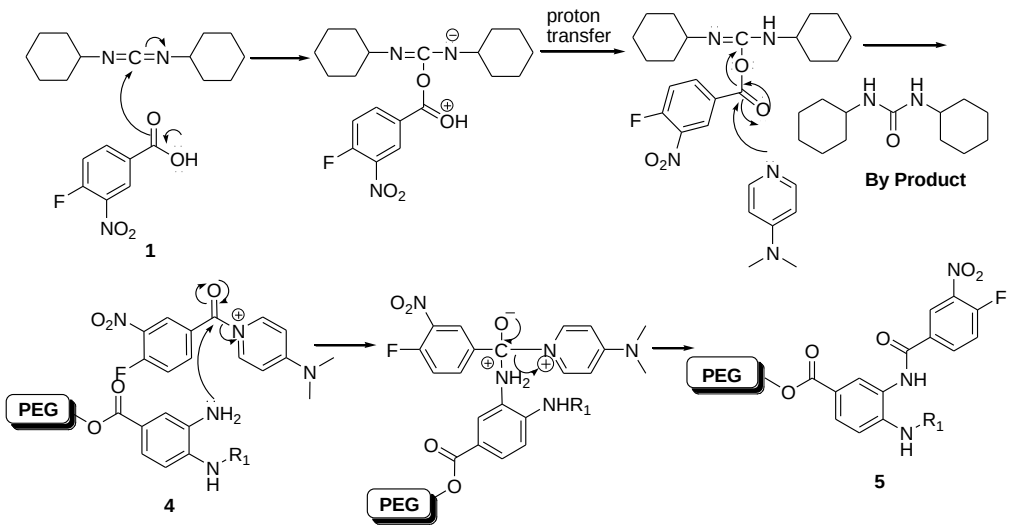
Scheme 2.17. Mechanism of formation of compound 4 on soluble support.

To construct the benzimidazole ring in the present synthesis another molecule of 4-fluoro-3-nitrobenzoic acid **1** has been used in presence of DCC/DMAP coupling reagent to afford the polymer immobilized **5** as pale brownish compounds in quantitative yields in Scheme 2.18.



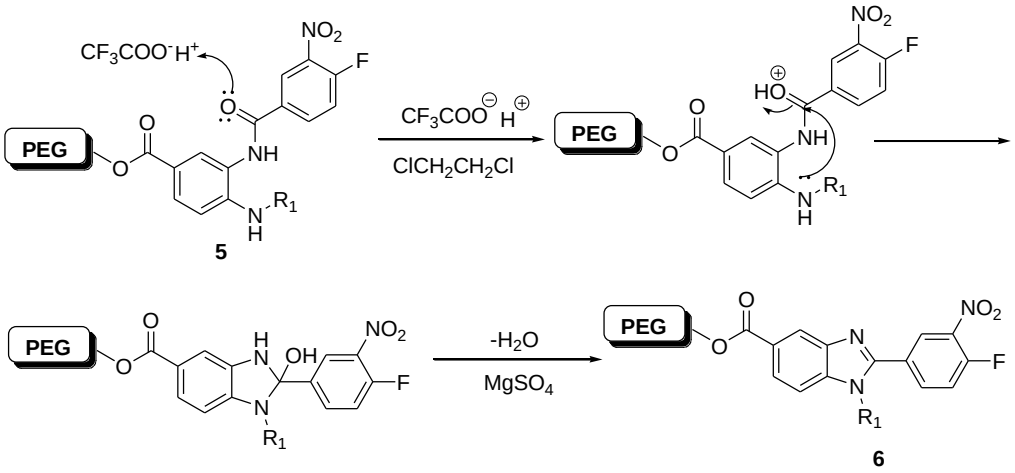
Scheme 2.18. PEG supported synthesis of o-nitrofluoro benzimidazol derivatives 6.

However, we have observed that completion of the reaction was achieved in 2 day at room temperature condition. But with the application of sealed vessel microwave irradiation (85 °C, 2 bar), the same reaction completed in 15 minutes. After completion of the reaction time, the insoluble DCU was filtered off and purified by precipitating out the reaction mixtures with cold ether. The mechanism of the formation of compound **5** was explained in Scheme 2.19.



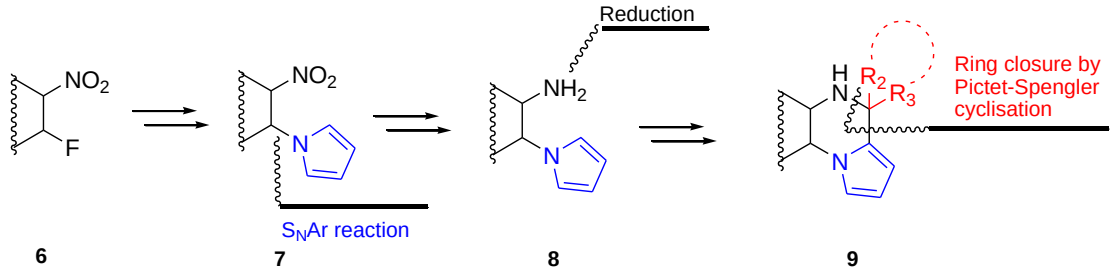
Scheme 2.19. **Mechanism of formation of compound 5 on soluble support**

The obtained anilide conjugates **5** were converted into benzimidazoles **6** by an intramolecular ring closure through the nucleophilic attack of the secondary amine on to the amide carbonyl which was induced by a mild acid (12 % TFA). Addition of anhydrous magnesium sulphate in this transformation reduced the reaction time, by facilitating the removal of water during this step, which needed 15 h under refluxing conditions in dichloroethane. The time for the formation of benzimidazole was reduced to 15 minutes by domestic MW reactor. However, the reaction time was reduced to 5 minutes in sealed vessel MW conditions (5 bar, 100 ^{0}C). Magnesium sulphate was filtered off and the polymer conjugate **6** was purified by precipitating out the reaction mixtures with excess of cold ether. The mechanism of the formation of the compound was described in Scheme 2.20.



Scheme 2.20. **Mechanism of formation of compound 6 on soluble support**

We envisioned applying the aromatic nucleophilic substitution (S_NAr) reaction by pyrrole moiety at the aromatic fluoride position of polymer immobilized substrate **6**. Our synthetic strategy is depicted in Scheme 17. The nitro group in the polymer conjugates 7 could be reduced to deliver **8**. Pictet-Spengler reaction is planned to use for ring closure to generate pyrrole fused quinoxaline skeleton **9** in Scheme 2.21.

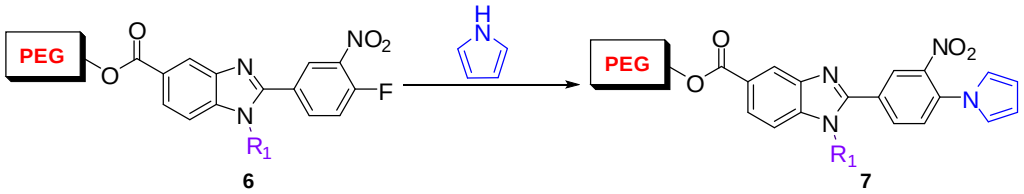


Scheme 2.21. Retrosynthetic pathway for the synthesis of pyrrolo[1,2-*a*]quinoxalines

In an effort to attain the target molecule as per our synthetic plan, compound **6** was subjected to S_NAr reaction with pyrrole Table 2.1. For preliminary optimization of the

S_NAr reaction conditions, the present coupling reactions were conducting by conventional thermal heating for 24 h, as well as microwave irradiation at 135 °C for 10 min in dichloromethane resulting into no desired product (entry 1). The main purpose to implement microwave irradiation was investigated with the aim to reduce reaction time and to increase reaction efficiency. Subsequently, addition of triethyl amine as a base also failed to generate the polymer immobilized compound **7** (entry 2). We further observed that the use of polar aprotic solvent acetonitrile (entry 3) or non-polar solvent toluene with triethyl amine (entry 4) under refluxing conditions for 24 h or microwave irradiation at 135 °C for 10 min did not generate any coupling product. We then focused our investigation on the scope of inorganic base catalyzed S_NAr reaction of polymer immobilized substrate **6** with pyrrole. The addition of inorganic base such as Cs_2CO_3 in dichloromethane (entry 5) solution under the same reaction conditions also failed to produce the desired results. This could be attributed to the insolubility of inorganic base into dichloromethane solvent. Surprisingly, the desired product **7** was finally obtained in 80 % yield in refluxing conditions of DMF with K_2CO_3 after 18 h and microwave irradiation at 135 °C in 10 min (entry 6). Furthermore, the use of Cs_2CO_3 in DMF solvent produces the polymer immobilized compound **7** with significantly improved yield up to 95 % in 16 h under refluxing conditions and 10 min under microwave irradiation at 135 °C (entry 7).

Table 2.1. Reaction optimization for the S_NAr reaction of pyrrole on compound 6



6 7

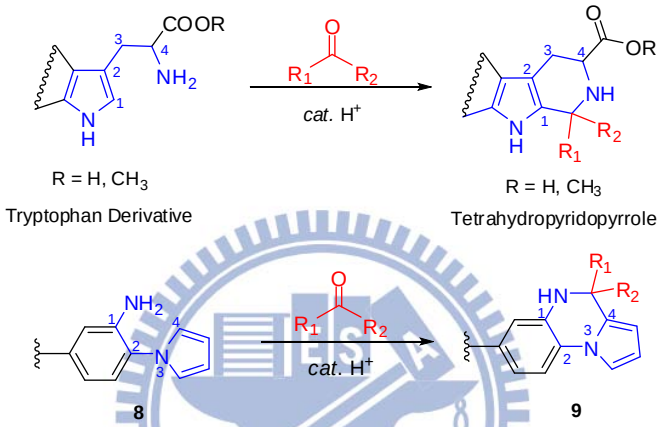
Entry	Bases	Solvents	Optimized reaction condition			Isolated yield[d]
			Time[a] (h)	Time[b] (h)	Temp[c] (^oC)	
1	- - -	DCM	24	0.16	135	No reaction
2	Et_3N	EDC	24	0.16	135	No reaction
3	Et_3N	ACN	24	0.16	135	No reaction
4	Et_3N	Toluene	24	0.16	135	No reaction
5	Cs_2CO_3	DCM	24	0.16	135	No reaction
6	K_2CO_3	DMF	18	0.16	135	80 %
7	Cs_2CO_3	DMF	16	0.16	135	95 %

[a] Reflux conditions [b] Biotage Initiator [c] Microwave Temperature

[d] Isolated yield is based on purified compound after cleavage

For the synthesis of pyrrole attached polymer immobilized compound **7**, we found that cesium carbonate was effective base in S_NAr reaction with DMF solvent. Polar, aprotic, high boiling DMF absorbs microwave energy efficiently, under microwave irradiation conditions, and allows the facile product formation. After completion of the reaction, the polymer conjugates were purified by precipitation of the reaction mixture with cold ether to remove the excess pyrrole and side products without the need of regular column purification. However, in an attempt to increase the structural diversity for the target library, the nitro group ortho to the pyrrole moiety of polymer ester conjugates **7** was

reduced with zinc dust in methanol buffered with ammonium formate. Formation of the amine conjugates **8** was achieved at room temperature for 30 minutes however, microwave irradiation condition reduced the reaction time to 10 min. After completion of the reaction, excess zinc dust and ammonium formate was removed by successive filtration to obtain the compound **8**. The structrure of compound **8** was confirmed by proton NMR spectroscopy of PEG supported compound **8**.

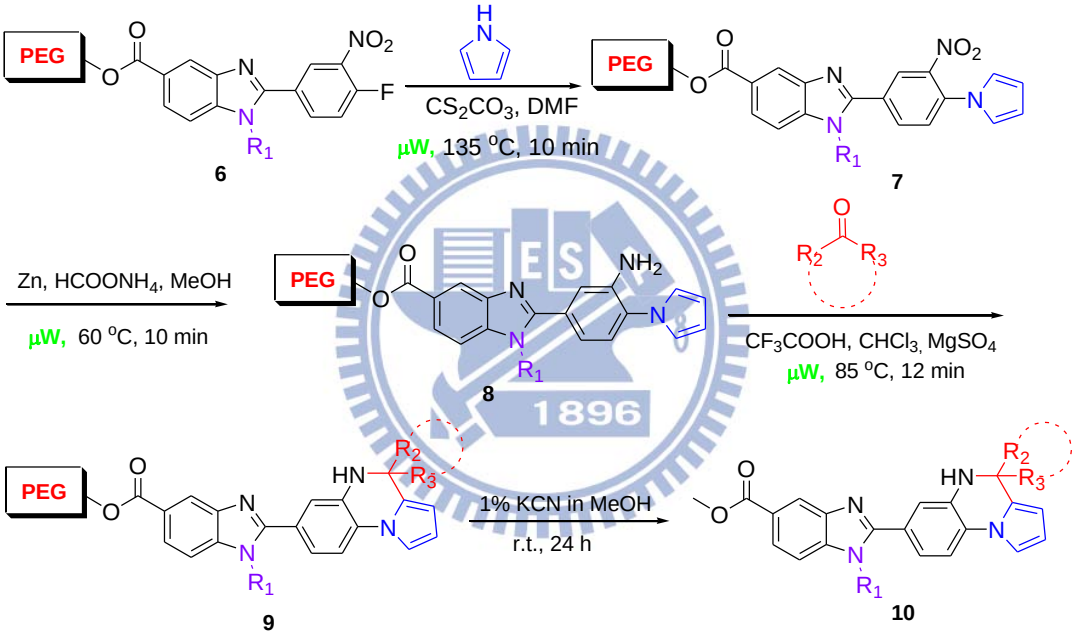


Scheme 2.22 Acid catalyzed Pictet-Spengler cyclization.

The relative structural study revealed the resemblance between the polymer conjugates **8** and tryptophan derivatives for Pictet-Spengler reaction in Scheme 2.22. In the polymer conjugates **8**, the aromatic amine functionality originated from C-1 of the aromatic ring as an analogy of tryptophan derivatives where aliphatic amine originates from C-4 of the heteroaromatic ring. In addition to these similarities, we assume that the C-4 required for the desired C-C bond formation is contiguous to the nitrogen atom of the aromatic moiety in the polymer conjugates **8** which is similar to the C-1 of the tryptophan derivative. All there analogy gratifies the elementary precondition for the Pictet-Spengler cyclization. Based on these correlation, we envisaged to utilize the amine functionality of polymer

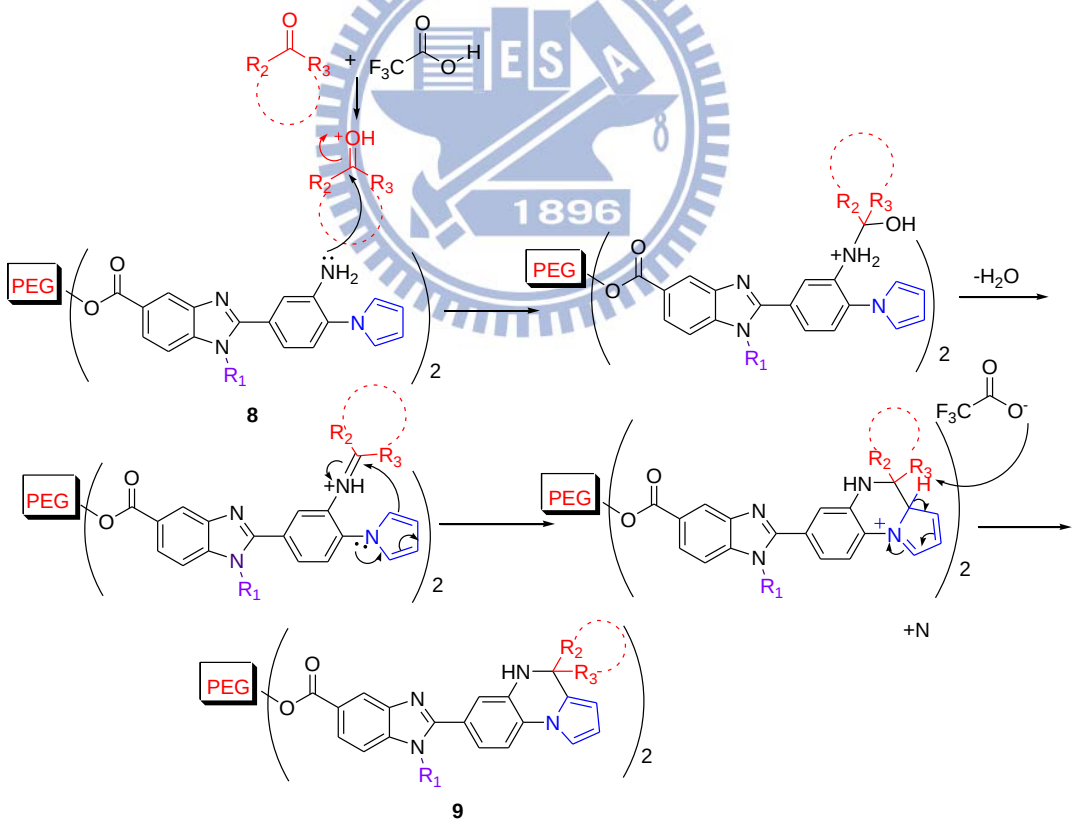
conjugates **8** for the ring closure using Pictet-Spengler reaction with various ketones. The use of ketones in Pictet-Spengler reaction of aromatic amines with pyrrole moiety is unlikeness to a traditional Pictet-Spengler reaction which involve a reactive aldehydes with the aliphatic amine connected to the carbon of an activated aromatic moiety.

Scheme 2.23. Novel microwave assisted polymer supported approach for the synthesis of benzimidazole-pyrrolo [1,2-*a*] quinoxalines.



Accordingly, the polymer conjugates **8** were treated with various ketones using 1 % TFA as an acid catalyst in chloroform under refluxing condition in Scheme 2.23. The desired polymer conjugates **9** were furnished after 12 h. However, the same Pictet-Spengler reaction was achieved under pressured microwave irradiation at 85 °C within 12 min. The polymer conjugates **9** were separated by precipitation and purified by washing with cold ether to remove excess reagents. The Pictet-Spengler reaction was confirmed by

proton NMR spectrums of compound **9**. The peak corresponds to the proton at 2-possition on pyrrol ring was absent along with one of the amine proton peak. Also the introduction of peaks corresponds to keto-alkyl chain were clearly indicates the Pictet-Spengler cyclization. Here we developed the new application of the Pictet-Spengler cyclization at pyrrole moiety of the conjugates **8** to provide a hitherto unknown bi-heterosystem of pyrroloquinoxalines **9**. The generalization of this methodology and the expansion of the skeletal diversity was achieved using various symmetrical and unsymmetrical ketones in Pictet-Spengler cyclization. Moreover, the spiro element has been successfully introduced as an additional feature of the structural diversity on the pyrrolo[1,2-*a*]quinoxaline skeleton by using the cyclic ketones.



Scheme 2.24. Plausible Pictet-Spengler like cyclization mechanism towards the formation of pyrrolo[1,2-*a*]quinoxalines 9 on polymer support.

The cyclization products **9** were obtained through an iminium intermediate and then preceded non-traditional Pictet-Spengler reactions, as shown in Scheme 2.24.[84] Polymer conjugates **8** reacts with ketones in the presence of TFA as an acid catalyst to give an iminium ion with the liberation of water. The iminium ion derived from aniline moiety is going to be more electrophilic than that of aliphatic amines. This enhances carbon-carbon bond formation with the C-4 of the pyrrole ring because the nature of electron-deficient imines provides a driving force for cyclization. The endo cyclization to create a new carbon-carbon bond between a carbon nucleophile of unreactive aromatic pyrrole and the electrophilic Schiff's base is successful to deliver an N-heterocyclic ring of polymer bound benzimidazole-pyrrolo quinoxalines **9**.

Highly substituted pyrrolo[1,2-*a*]quinoxalines were finally cleaved from polymer support using 1 % KCN solution in MeOH at room temperature for 24 hours. The PEG was precipitated out from reaction mixtures by addition of cold ether and removed by filtration. The filtrates were evaporated to provide polymer free benzimidazole-pyrrolo[1,2-*a*]quinoxaline derivatives **10** of 75-99 % purity as assessed by HPLC analysis in Table 2.2. The removal of polymer support was confirmed by the proton NMR spectrum where the characteristic peaks of polyethylene glycol at 3.5 ppm were absent in figure 2.12. Additionally, mass spectroscopy also confimers the structures of final products. It is worth to note that, diverse benzimidazole-pyrroloquinoxaline small molecule analogues have been synthesized via a novel S_NAr/Pictet-Spengler cyclization under focused microwave irradiation.

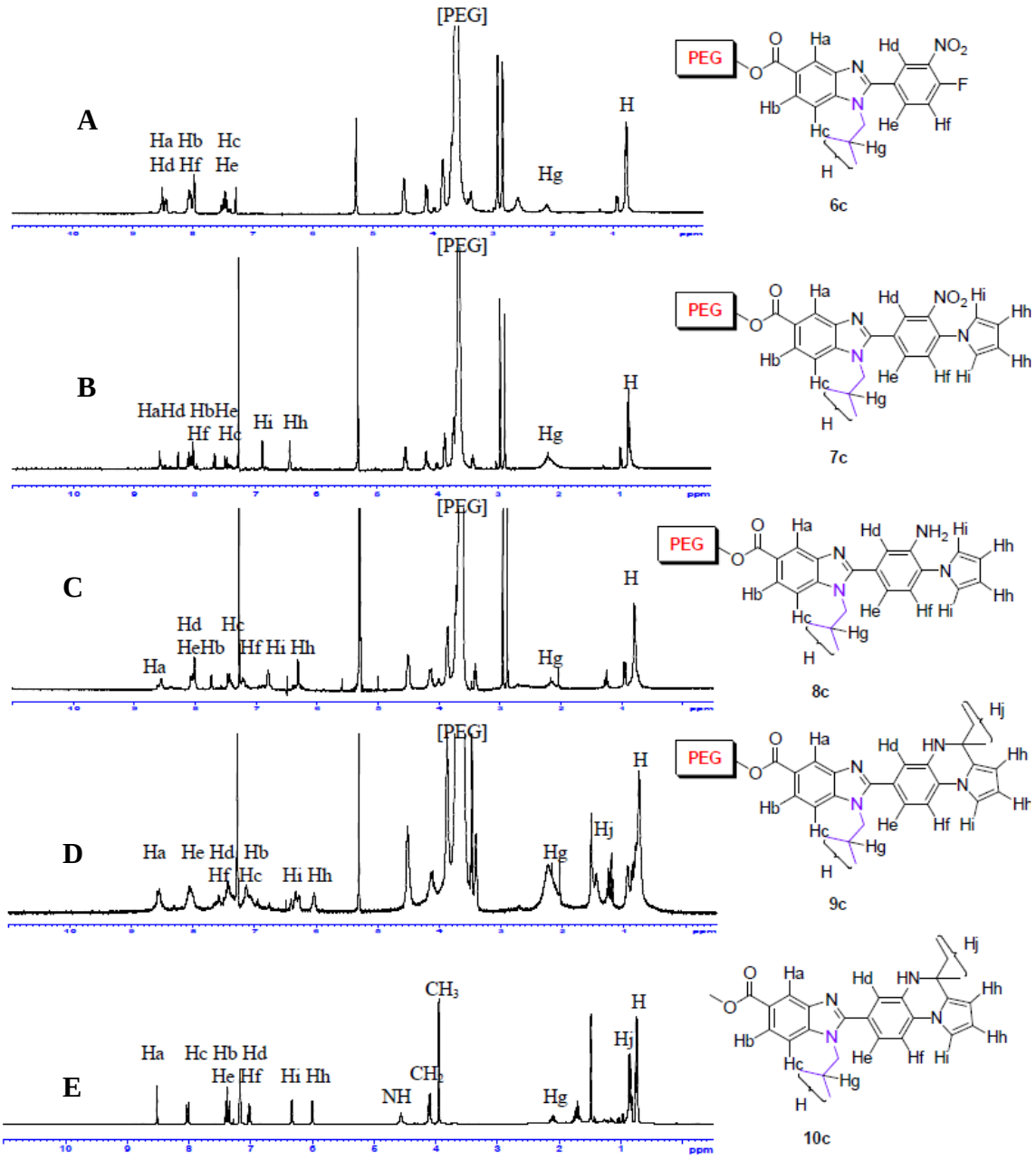
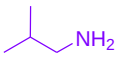
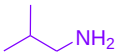
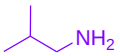
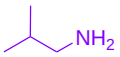
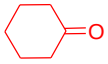
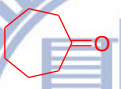
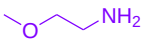
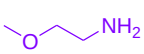
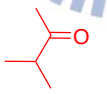
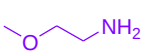
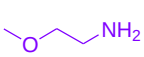
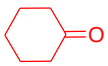
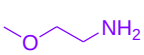
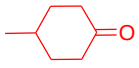
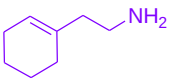
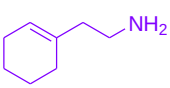
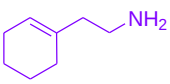
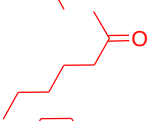
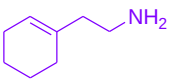
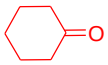


Figure 2.12. Stepwise Monitoring towards the Formation of Benzimidazole-pyrrolo[1,2-*a*]quinoxaline on PEG Support in $CDCl_3$ as solvent at 25 ^{0}C.

Table 2.2. Synthesis of benzimidazole-pyrrolo[1,2-*a*]quinoxaline derivatives (10a-10r).

Entry	R_1NH_2	R_2COR_3	LRMS[a]	Isolated yield[b]	Purity[c]
10a			429	82%	91%
10b			455	90%	98%
10c			443	87%	88%
10d			469	85%	92%
10e			429	84%	93 %
10f			483	72%	75%
10g			485	83%	92%
10h			499	86%	76%
10i			431	89%	99%
10j			445	81%	98%
10k			459	83%	93%
10l			457	83%	88%
10m			471	80%	87%
10n			485	77%	83%
10o			481	82%	92%
10p			495	90%	94%
10q			537	84%	88%
10r			521	75%	80%

[a]LRMS were detected with ESI ionization source. [b]Determined based on the weight of crude samples (%). [c]Determined by HPLC analysis (UV detection at 254 nm of the crude product (%).

Furthermore, the structure of the present skeleton is confirmed by single crystal X-ray analysis. The ORTEP diagram for compound **10h** is depicted in figure. 2.13. In present biheterocyclic configuration, the pyrrolo-quinoxaline moiety and benzimidazole moiety remain perpendicular to each other whereas spiro ethyl cyclohexane ring acquires chair conformation.

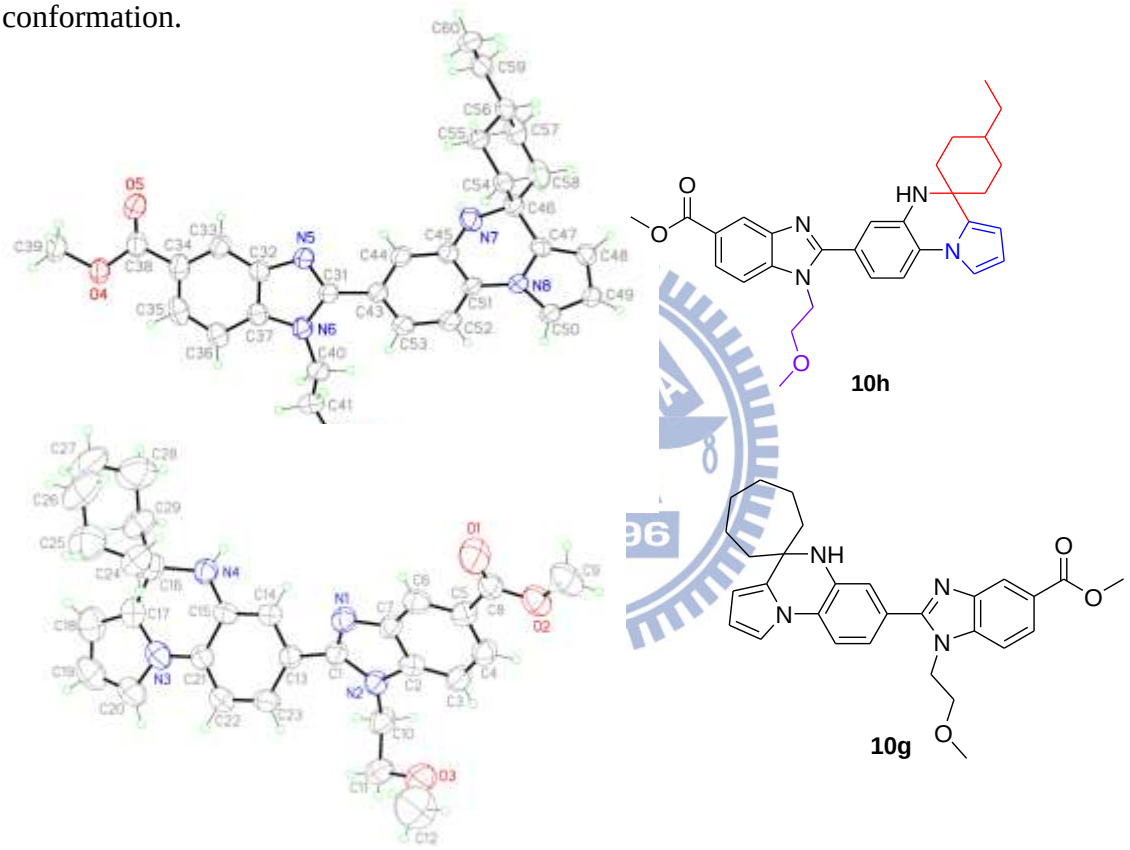
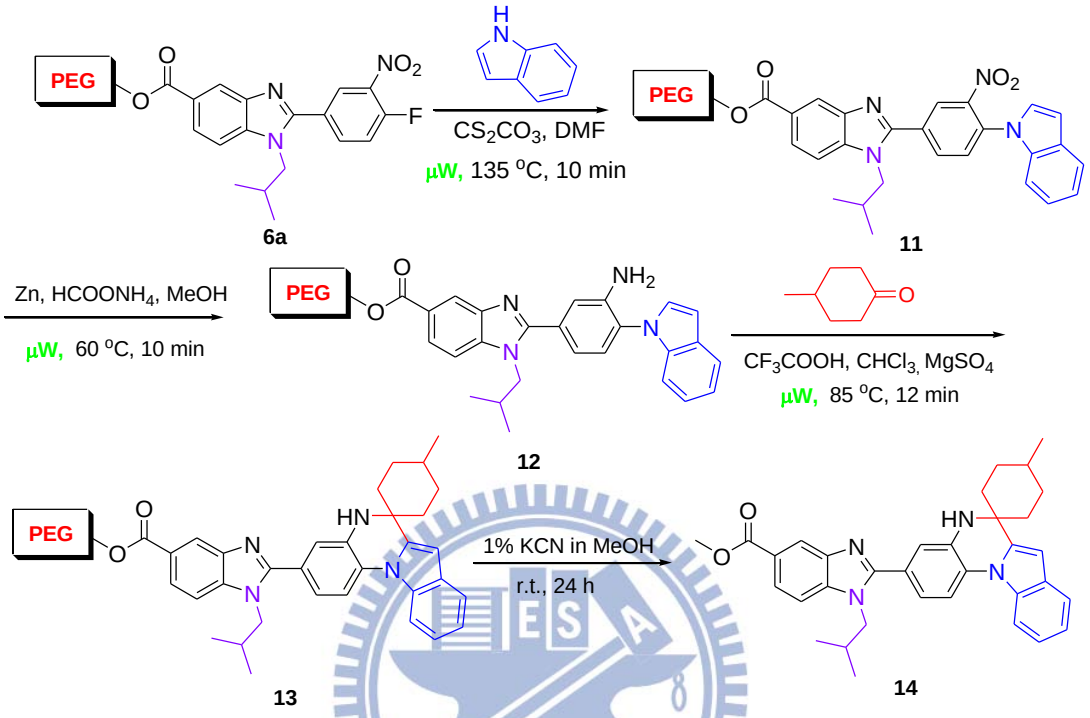


Figure 2.13. ORTEP diagram of compound 10h and 10g.

After the successful synthesis of benzimidazole-pyrrolo[1,2-*a*]quinoxaline derivatives **10a-r**, we then turned our attention to use the indole instead of pyrrole as a nucleophile for the aromatic nucleophilic substitution reaction on polymer immobilzed

substrate **6a** as shown in Scheme 2.25. However quick search revealed that to construct benzimidazole-indolo [1,2-*a*]quinoxaline moiety few lituratures is there where indoline has been used as a nucleophile and further oxidation of indoline to indole moiety and subsequent pictet-spengler reaction has been described. In our case to deversify the methodology we have incorporated the indole moiety instead of pyrrole moity by SnAr reaction in to the aromatic ring system. However, the desired reaction proceeded smoothly to generate the polymer immobilzed substrate **11**, which further underwent the reduction of nitro group ortho to the indole N1 of the aromatic substrate **11** to obtained the PEG supported compound **12**. With the PEG supported compound **12**, we then carried out the Pictet-Spengler reactions with 4-methylcyclohexanone under microwave irradiations at 85 °C within 12 min using 1 % TFA as an acid catalyst in chloroform solution. After completion of the reaction, the polymer conjugates **13** were separated by precipitation and purified by washing with cold ether to remove excess reagents. The desired indolo [1,2-*a*] quinoxalines were finally cleaved from polymer support using 1 % KCN solution in MeOH at room temperature for 24 hours. The polymeric support was precipitated out from reaction mixtures by addition of cold ether and removed by filtration. The filtrates were evaporated and subsequently purified by column chromatography to provide polymer free benzimidazole-indolo [1,2-*a*]quinoxaline derivative **14** in good yields.

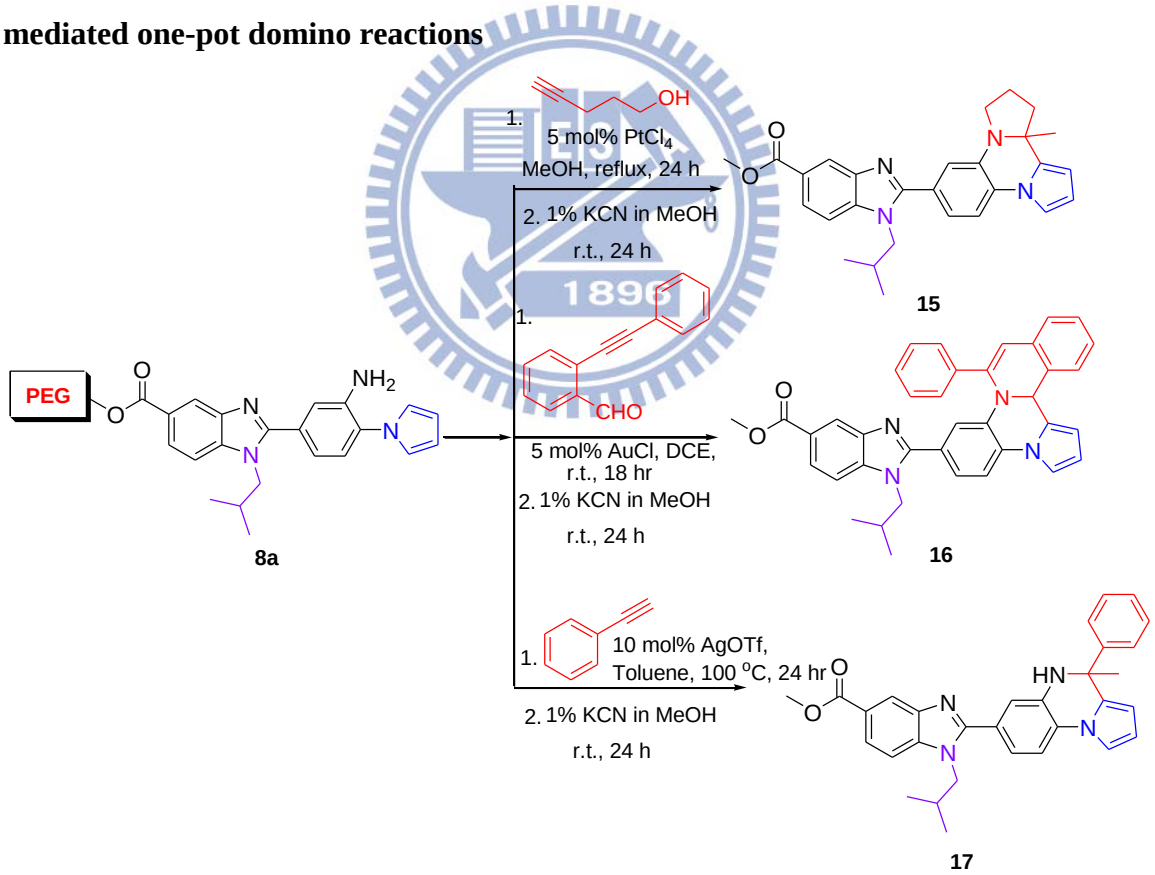
Scheme 2.25. Novel microwave assisted polymer supported approach for the synthesis of benzimidazole-indolo [1,2-*a*] quinoxalines.



To explore further application scopes of the polymer immobilized substrate **8a**, we carried out the transition metal catalysed organic transformations using various alkyne as shown in the Scheme 2.26. Treatment of the polymer immobilized substrates **8a** with pent-4-yne-1-ol in the presence of 5 mol % of $PtCl_4$ at reflux temperature for 24 hrs using dry MeOH as solvent generated the substituted pyrrolo[1,2-a]quinoxalines derivatives.[85a] Subsequent cleavage of polymer support from the substrates using 1 % KCN in methanol at room temperature for 24 hours to obtain the benzimidazole-pyrrolo[1,2-*a*]quinoxaline derivatives **15** in good yields. Subsequently, we have investigated that Au and Ag metal catalysed transformation can be used to prepare benzimidazole-pyrrolo[1,2-*a*]quinoxaline derivatives by the treatment of polymer

immobilized substrate **8a** and 1-alkynylbenzaldehyde and phenyl acetylene respectively under the optimized reaction conditions.[85b,c] We have observed good yields under the optimal conditions, a relatively longer time (18 h) was needed to complete the starting material. After cessation of the reaction, the desired pyrrolo[1,2-*a*] quinoxalines were finally cleaved from polymer support using 1 % KCN solution in MeOH at room temperature for 24 hours to obtain the different derivatives of benzimidazole-pyrrolo[1,2-*a*]quinoxalines **16** and **17** in good yields.

Scheme 2.26. Synthesis of benzimidazole-pyrrolo[1,2-*a*]quinoxalines via metal-mediated one-pot domino reactions



2.17. Pyrrolo[1,2-*a*]quinoxalinones its importance and synthesis:

Numerous pharmaceutically important molecules, including antipsychotic agent **A**,[86] anti-HIV agent **B**,[87] adenosine A3 receptor modulator **C**,[88] and antitumor agent **D** in Figure 2.14[89] contains pyrrolo[1,2-*a*]quinoxalineone moiety as key constituents. In addition, pyrrolo[1,2-*a*]quinoxalineone compounds have afford as key intermediates for the congregation of numerous heterocycles that exhibited a wide range of biological activities. Beside this Pyrrolo[1,2-a]quinoxalines moiety are best known for antiviral and antiallergic activity. [90-91]

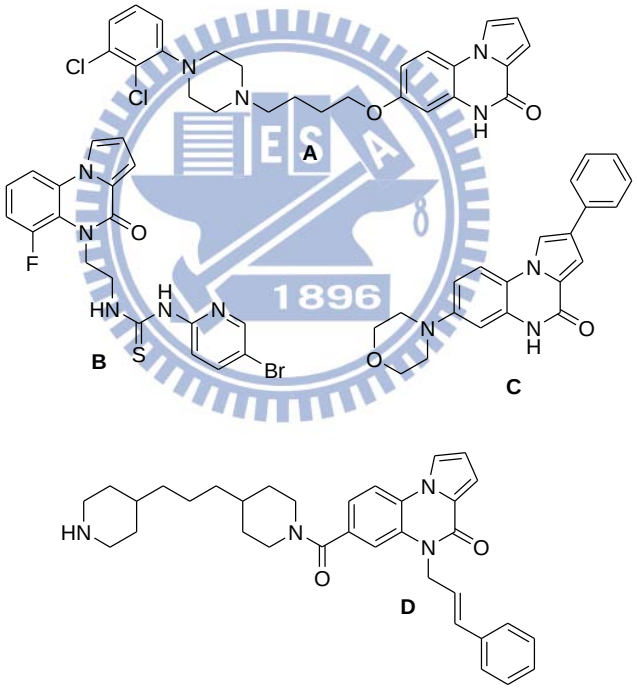
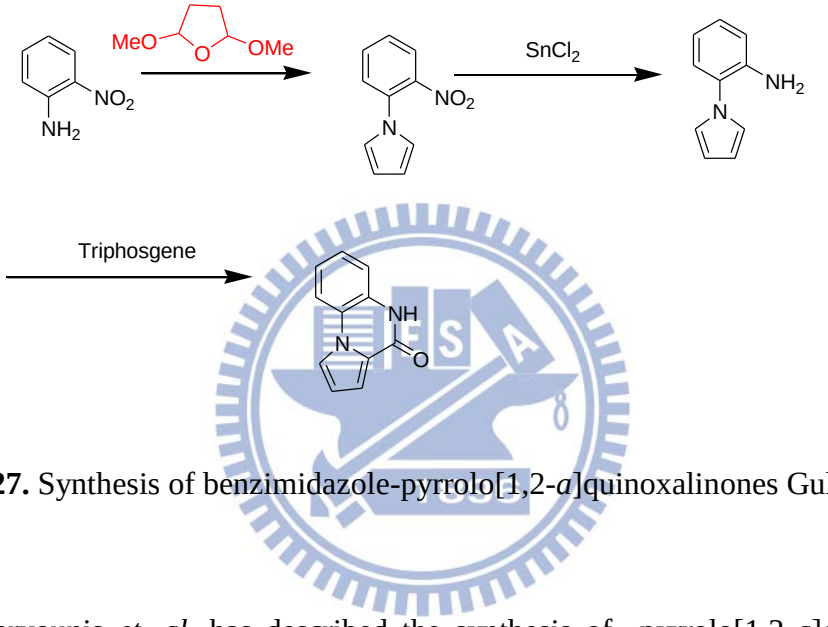


Figure 2.14. Representative examples of biologically active pyrrolo[1,2-*a*]quinoxalineone.

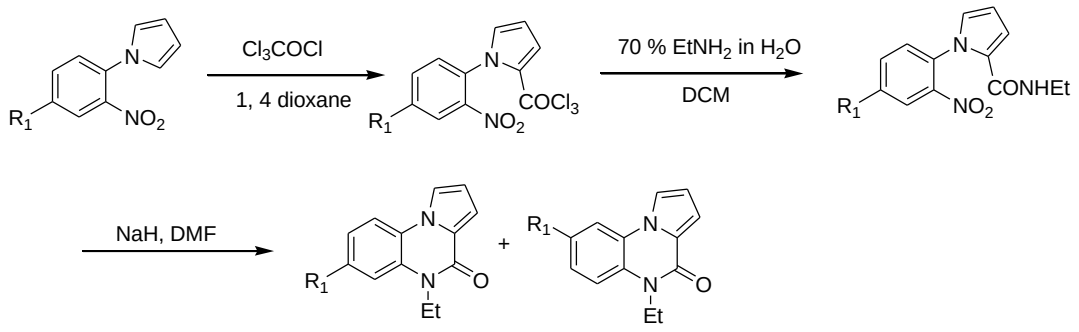
To construct the pyrrolo[1,2-*a*]quinoxalinone moiety very few literature methods are there. The general method for the building of pyrrolo[1,2-*a*]quinoxalineones initiates

from 2-nitroanilines and proceeds in three steps pyrrole ring construction, nitro group reduction, and cyclization with triphosgene. In 2004 Guillon *et. al.* has constructed pyrrole moiety by reaction with o-nitro aniline with DMT group. To construct the privileged heterocyles pyrrolo[1,2-*a*]quinoxalinone they reduced nitro group by $SnCl_2$ cyclised by triphosgene to provides the desired building block pyrrolo[1,2-*a*]quinoxalinone in Scheme 2.27.[92]



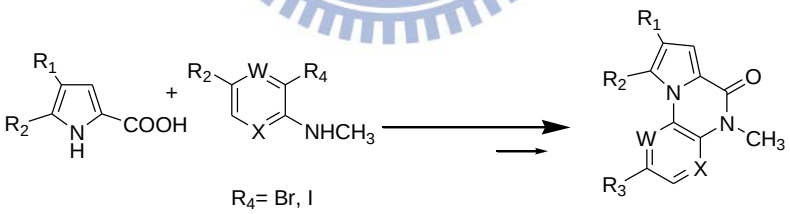
Scheme 2.27. Synthesis of benzimidazole-pyrrolo[1,2-*a*]quinoxalinones Gullion *et. al.*

In 2004 Varvounis *et. al.* has described the synthesis of pyrrolo[1,2-*a*]quinoxalinone moiety starting from they reduced nitro group by $SnCl_2$ cyclised by triphosgene to provides the desired building block pyrrolo[1,2-*a*]quinoxalinone in Scheme 2.28.[93]



Scheme 2.28. Synthesis of benzimidazole-pyrrolo[1,2-*a*]quinoxalinones by Varvounis *et. al.*

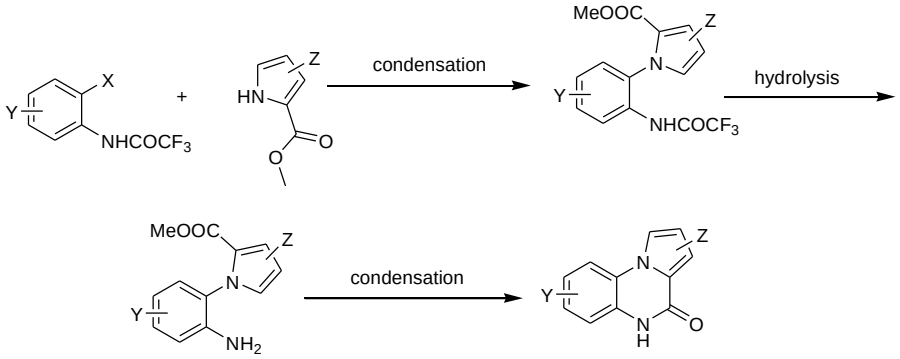
In 2005, Beccalli *et. al.* have developed the Pd catalysed synthetic route to arrive at the pyrrolo[1,2-*a*]quinoxalinones. They have used Pd-catalyzed Buchwald-Hartwig coupling followed by intramolecular C-N bond formation strategy to assemble the tricyclic compounds from 2-haloanilines and pyrrole-2-carboxylic acids as shown in the Scheme 2.29. [94]



Scheme 2.29. Synthesis of pyrrolo[1,2-*a*]quinoxalinones by Beccalli *et. al.*

In 2008, Ma *et. al.* had used the Ullmann coupling of 2-iodotrifluoroacetanilide with pyrrole-2-carboxylate methyl ester using CuI/L-proline as catalyst The reaction between 2-iodotrifluoroacetanilide with pyrrole-2-carboxylate methyl ester proceeded well in DMSO at optimum temperature to afford coupling product in good yield which

underwent an efficient hydrolysis and intramolecular cyclisation to afford the pyrrolo[1,2-*a*]quinoxalinone moiety in good yield as shown in Scheme 2.30. [95]



Scheme 2.30. Synthesis of pyrrolo[1,2-*a*]quinoxalinones via Ullmann coupling methods by Ma *et. al.*

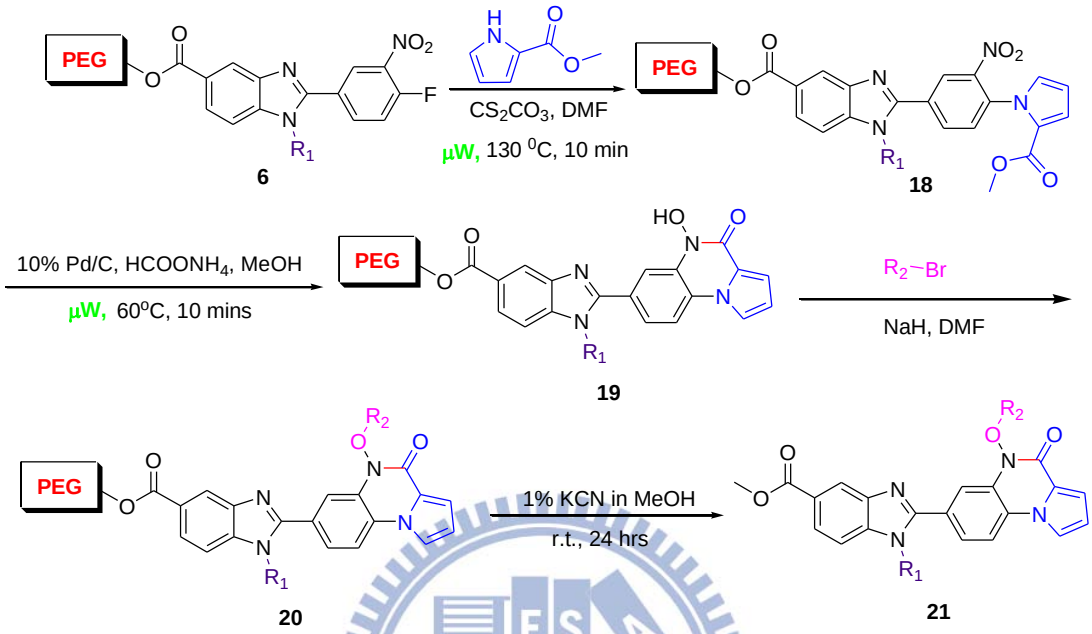
There are very few literature where preparation of previleged heterocyles pyrrolo[1,2-*a*]quinoxalineone has been described there is no such literature to construct the important biheterocyles benzimidazole moiety linked pyrrolo[1,2-*a*]quinoxalineone moiety. Since we know benzimidazole moiety exhibit antiarrhythmic, antihistamine, antiulcer, anticancer, inotropic, fungicidal, anthelmintical, and antiviral activities.[96] So construction of hitertho biherocyles benzimidazole moiety linked pyrrolo[1,2-*a*]quinoxalineone is an important challenge to us. Prompted by this observation, we undertook the present investigation and the results of our studies are reported herein.

2.18. Result and Discussion:

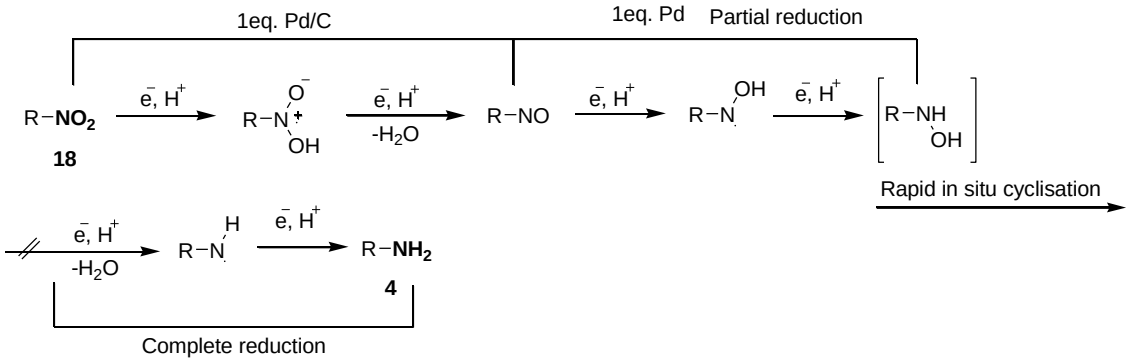
The present strategy commenced with the aromatic nucleophilic substitution of pyrrole 2 carboxylate onto PEG immobilized benzimidazole linked o-fluoro nitrobenzene.

For incorporation the pyrrole 2-carboxylate moiety into the aromatic ring we have screend several reaction conditions. But we have observed the desired product **18** was finally obtained in 80 % yield in refluxing conditions of DMF with K_2CO_3 after 18 h and microwave irradiation at 135 °C in 10 min as shown in scheme 26. Furthermore, the use of Cs_2CO_3 in DMF solvent produces the polymer immobilized compound **18** with significantly improved yield up to 95 % in 16 h under refluxing conditions and 10 min under microwave irradiation at 135 °C. To confirm the product formation by proton NMR spectroscopy a small portion of the reaction mixture was pulled out, the compound was precipitated and washed with cold ether and dried to record the proton NMR spectrum to monitor the progression of reaction. Upon completion of the reaction, the polymer bound compound mixtures were purified by the same precipitation and washing protocol. The ^{1}H NMR confirmed that the pyrrole-2-carboxylate moiety has been introduced into the aromatic system. The signal at 6.5 ppm, 6.9 ppm, 7.2 ppm corresponds to the three aromatic proton of pyrrole moiety attachéd to the polymer conjugates **18**. After incorporation of pyrrole 2 carboxylate moiety into the aromatic system **18** we plannd to cyclise this product in Scheme 2.31. In the next step, the nitro functionality in polymer pyrrole carboxylate conjugate was partial reduced to N-hydroxy compound and which subsequently reduced to in situ cyclic amide **19** using 10 % Pd/C and ammonium formate in methanol under microwave irradiation at 60 ^{o}C.

Scheme 2.31. Novel Microwave-Assisted Polymeric Approach to Benzimidazole-Pyrrolo [1,2-*a*] quinoxalines.



Formation of the conjugates N-hydroxy cyclic amide **19** was confirmed from change of yellow to blue color upon spotting on the TLC plate and also confirmed by the proton NMR analysis. Upon completion of the reaction, reaction mixtures were filtered through celite bed fritted funnel to get rid of the Pd/C. The reaction mixtures were evaporated and dichloromethane was added to salt out the ammonium formate finally filtered through celite bed fritted funnel to get rid of ammonium formate to obtain the compound **19.**



Scheme 2.32. **Partial Nitro reduction to Benzimidazole-N-hydroxypyrrolo[1,2-*a*]quinoxalineone 19**

The exact mechanism regarding the formation of compound **19** was observed in Scheme 2.32. Here we have observed that the aromatic protons of the pyrrole moiety has been shifted to the downfield. No loss of yield was observed during this reductive transformation, suggesting that the polymer support remained intact throughout the reaction. In order to introduce the second point of structural diversity into the N-hydroxy cyclic amide polymer conjugates, we further reacted different alkyl bromides with N-hydroxy cyclic amide polymer conjugates. For this reaction we have tried different reaction conditions a) sodium hydride and dichloromethane solvent, b) sodium hydride in THF solvent, the reaction does not proceed at al . We have observed the SN_2 reaction of N-hydroxy cyclic amide polymer conjugates with different alkyl bromide in presence of sodim hydride as base in polar DMF solvent proceded smoothly under the room-temperature conditions for 24 hrs. The formation of the target polymer conjugates were confirmed from the appearance of corresponding alkyl proton in the aliphatic region of the NMR spectrum as in Figure 2.15. After completion of the reaction, the DMF solvent was reduced inder reduce pressure and the reaction mixture was taken in DCM solvent.

The cold ether was added to the reaction mixture and stirrd for some times to undergo complete precipitation, filtered through the fritted funnel and dried to obtain the O-alkylated polymer conjugates. Finally, polymer support was cleaved in a potassium cyanide solution in methanol to provides benzoimidazole-alkoxy-pyrrolo [1,2-*a*]quinoxalineone in good yields (Table 2.3).

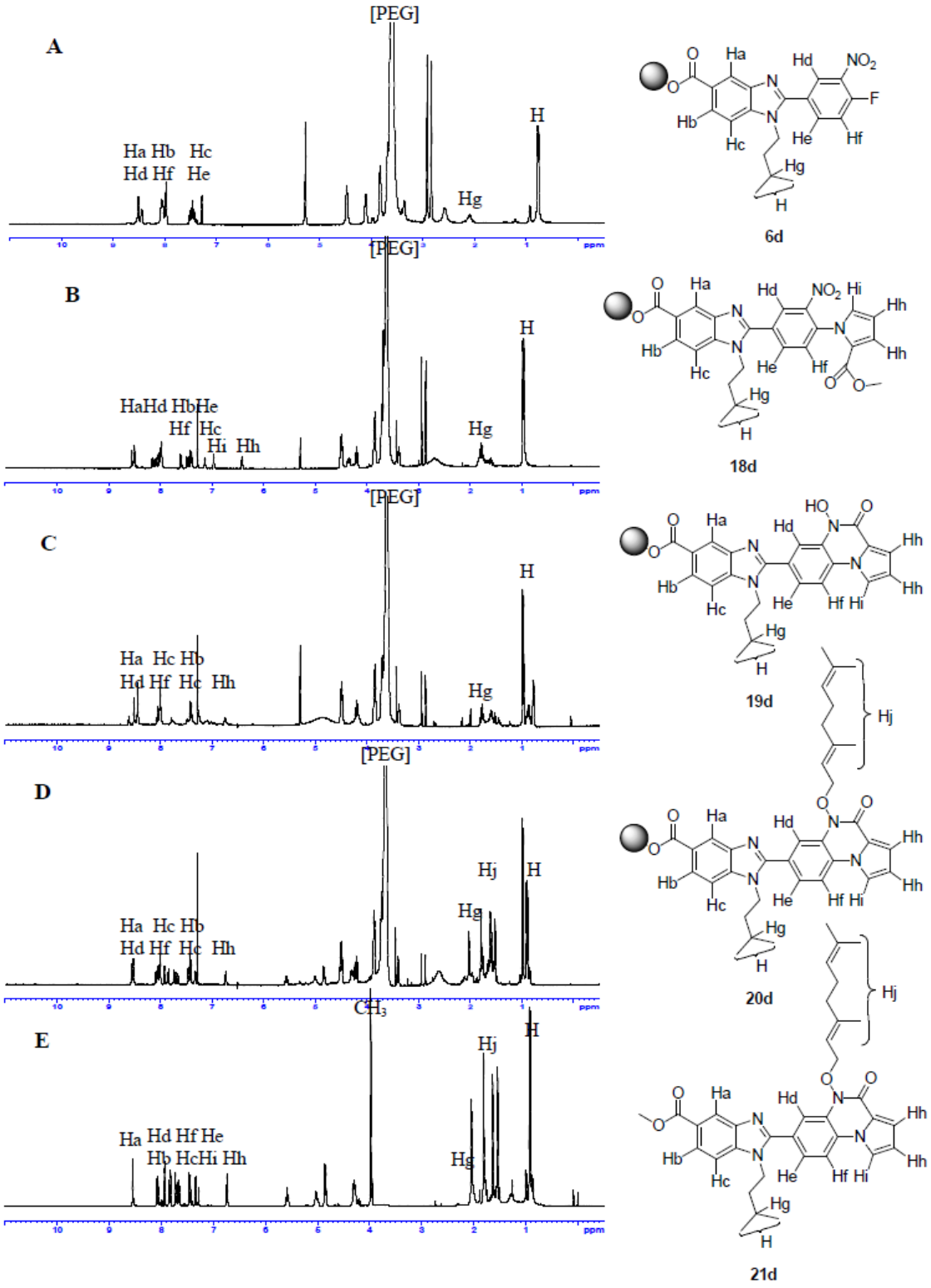
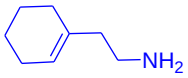
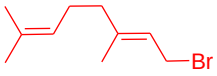
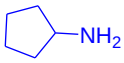
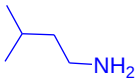
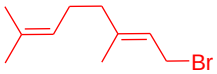
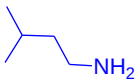
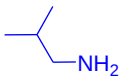
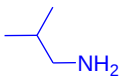
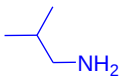
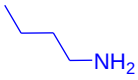
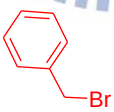
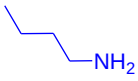
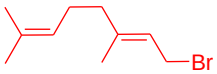
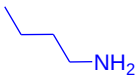
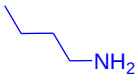
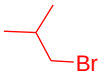
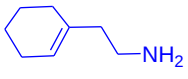
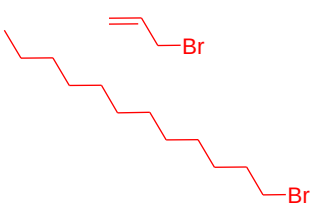
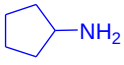


Figure 2.15. Stepwise Monitoring towards the Formation of Benzimidazole-alkoxy-pyrrolo[1,2-*a*]quinoxalineone on PEG Support in $CDCl_3$ at 25^{o}C

In most of the cases, a cleavage reaction was completed at room temperature within 24 h. The crude mixture was concentrated; the polymer was precipitated out with excess of cold ether and removed by filtration. The filtrate was dried and subjected to HPLC analysis, which depicted high purity and excellent yield of all the compounds without further purification. The completion of cleavage from the polymer support was verified by observing the disappearance of characteristic set of peaks corresponding to polymer protons.

Table 2.3. Synthesis of benzimidazole-pyrrolo[1,2-*a*]quinoxalinone derivatives (21a-21o).

Entry	R_1NH_2	R_2—Br	LRMS[a]	Isolated yield[b]	Purity[c]
21a			619	82%	88%
21b			457	88%	92%
21c			485	76%	77%
21d			581	85%	94%
21e			561	80%	82%
21f			547	75%	79 %
21g			501	78%	83 %
21h			487	84%	80 %
21i			521	81%	83 %
21j			567	77%	81 %
21k			501	60%	63 %
21l			487	78%	94 %
21m			507	60%	64%
21n			569	70%	76%
21o			467	83%	83%

[a]LRMS were detected with ESI ionization source. [b]Determined based on the weight of crude samples (%). [c]Determined by HPLC analysis (UV detection at 254 nm of the crude product (%).

The structure of the final compounds was also unequivocally confirmed by the X-ray crystallographic study. The X-ray crystallographic data of **21K** are in full agreement with its structure. The benzimidazole ring was situated in the perpendicular plan where as alkoxy-pyrrolo[1,2-*a*]quinoxalineone remains to the plane in Figure 2.16.

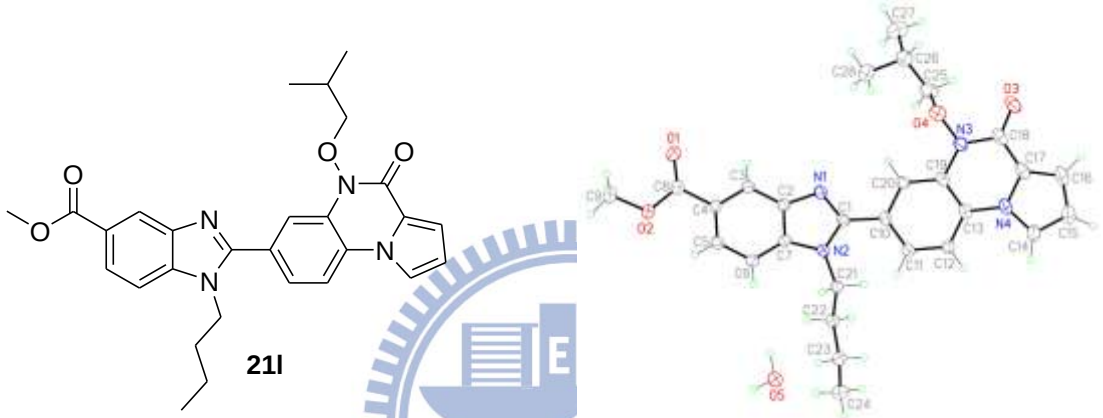


Figure 2.16. X-ray crystallographic structure of of the Benzimidazole-Pyrrolo[1,2-*a*]quinoxalineone **21l**

2.19. Conclusion

We have successfully developed novel synthesis of biologically promising novel derivatives of benzimidazole-pyrrolo[1,2-*a*]quinoxaline and benzimidazole-Pyrrolo[1,2-*a*]quinoxalineone on soluble polymer support under microwave condition. Linear sequence of nucleophilic aromatic substitution, nitro reduction and Pictet-Spengler cyclization and partial nitro reduction on polymer support in conjugation with microwave

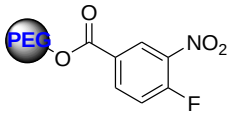
irradiation were effectively used to develop short synthesis of benzimidazole linked bi-heterocyclics

2.20. General remarks

Dichloromethane and chloroform was distilled from calcium hydride before use. All reactions were performed under an inert atmosphere with unpurified reagents and dry solvents. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel-coated Kieselgel 60 F254 plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (Merck, 230-400 mesh). All the microwave heating experiments were conducted under optimized reaction conditions of power and temperature in a closed vessel in a Biotage initiator model no: Initiator US, 355286, 10429-22T, using IR sensor as internal probe for the control of temperature and compressed air system for cooling. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker DX-300 spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale from an internal standard. High-resolution mass spectra (HRMS) were recorded on a JEOL TMS-HX 110 mass spectrometer. Analytical HPLC analyses were recorded with UV detection at λ=254nm (column: Sphereclone 5μ Si (250 x 4.6 mm).

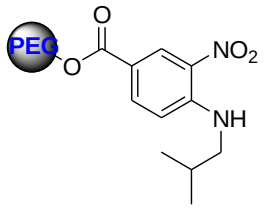
2.21. Experimental Section

General Procedure for the Synthesis of PEG bound 4-Fluoro-3-nitro benzoic acid 2.



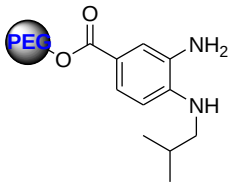
4-Fluoro-3-nitro benzoic acid **1** (0.690 g, 3.73 mmol, 2.80 Equiv), PEG-4000 (5.30 g, 1.33 mmol, 1.0 Equiv) and *N, N'*-dimethylamino pyridine (DMAP) (0.005 g) are placed in a dry, nitrogen-purged 100 mL round-bottom flask containing dry CH_2Cl_2 (15 mL). To the mixtures were added dropwise *N, N'*-dicyclohexylcarbodiimide (DCC) (0.890 g, 4.32 mmol, 3.2 Equiv) dissolved in dry CH_2Cl_2 (5 mL) for a period of 5 minutes. The reaction mixtures were stirred for another 15 minutes at room temperature. Then this O-acylation reaction was carried out in a 80 ml sealed CEM microwave vessel using microwave irradiation at (85 °C) for 15 minutes. After the completion of the reaction, the insoluble DCU byproduct was allowed to settle, and the reaction mixtures were filtered and washed with CH_2Cl_2 (50 mLx3). The solvent was evaporated, and the residue was again precipitated with cold ether which was filtered through fritted funnel to remove any unreacted acid and DCC, finally collected and dried under vacuum. The crude product PEG bound 4-Fluoro-3-nitro benzoic acid **2** obtaind 5.4 gm as light yellow solid in high purity.

General Procedure for the Substitution isobutyl amine on PEG bound 4-Fluoro-3-nitro benzoic acid 2.



Isobutyl amine (0.454 gm, 6.23 mmol, 5.0 Equiv) was added to the PEG bound 4-Fluoro-3-nitro benzoic acid 2 (5.40 gm, 1.25 mmol, 1.0 Equiv) solution in dry CH_2Cl_2 (10 mL) at room temperature for 5 minutes. The reaction mixtures were sealed and irradiated at 75 ^oC for 15 mins of on 80 ml CEM microwave vessel. After completion of the reaction time, the reaction mixtures were cool and precipitated with slow addition of cold ether (100 mL) which was filtered through a fritted funnel to obtain the PEG bound 4-alkyl amino-3-nitro benzoic acid **3,** 5.5 gm as yellow solid in high purity.

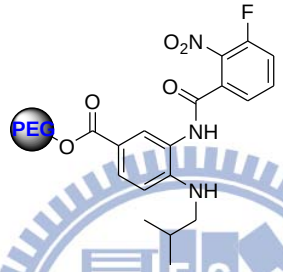
General Procedure for the Reduction of the Aryl nitro group in PEG bound 4-isobutyl amino-3-nitro benzoic acid 3.



To a solution of **5** (5.50 gm, 1.24 mmol, 1.0 equiv) in dry methanol (10 mL), Zn (1.61 gm, 24.8 mmol, 20.0 equiv) and ammonium formate (1.21 gm, 18.6 mmol, and 15.0 equiv) were added. The reaction mixture was stirred at room temperature and subsequently irradiated in sealed microwave vial (80 ml) at 65 ^oC for 12 mins to obtain

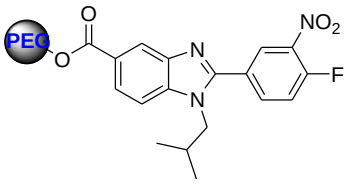
the polymer bound conjugates. After completion, the mixtures were filtered with Celite to remove zinc and the filtrate was collected and concentrated under reduced pressure. Then dichloromethane (25 mL) was added to precipitate ammonium formate, and the mixture was again passed through a thin layer of Celite to remove ammonium formate and dried to yield the compound 4 in 5.2 gm colourless solid in high yield.

General Procedure for the Preparation of Polymer Bound 3-(4-Fluoro-3-nitrobenzamido)-4-(substituted amino) carboxylates 5.



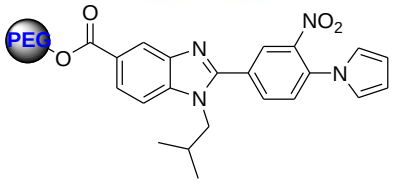
Polymer bound *o*-phenylene diamine **4** (1.0 g, 0.23 mmol, 1.0 equiv) dissolved in (5 mL) of dichloromethane was added to a solution of 4-fluoro-3-nitrobenzoic acid (0.11 g, 0.60 mmol, 2.6 equiv) in dichloromethane (5 mL) in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) (0.12 g, 0.60 mmol, 2.6 equiv) and *N*,*N*′-dimethylamino pyridine (DMAP) (2 mg). The reaction mixture was stirred at room temperature and subsequently irradiated in sealed microwave vial (10 ml) for 85 ^{o}C 15 mins to obtain the polymer bound amide conjugates **5**. After completion of the reaction, the suspensible dicyclohexyl urea (DCU) was filtered through filter paper. The reaction mixtures were precipitated by slow addition of cold ether and precipitated amide conjugate was filtered through fritted funnel. The crude product was washed successively with ether (50 mL × 3) to remove the undesired impurity and dried for further steps to obtain **5** as light brown solid.

General Procedure for the Preparation of Polymer Bound 2-(4-fluoro-3-nitrophenyl)-1-alkyl-1*H*-benzo[*d*]imidazole carboxylates 6.



To a solution of **5** in 1, 2-dichloroethane, trifluoroacetic acid (0.5 mL) and $MgSO_4$ (0.5 g) were added and irradiated under sealed microwave vial (10 ml) 100 ^oC for 15 mins. After completion of the reaction, $MgSO_4$ was removed through celite. The reaction mixtures were cooled and precipitated by slow addition of excess of cold ether (100 mL) and filtered through a fritted funnel to obtain the compound **6** in high purity in quantitative yields as light green solid 5.3 gm.

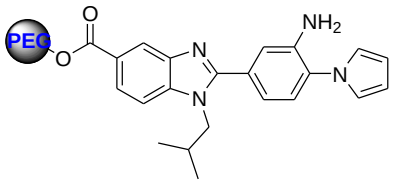
General Procedure for the Preparation of Polymer Bound 1-alkyl-2-(3-nitro-4-(1H-pyrrol-1-yl)phenyl)-1H-benzo[d]imidazole-5-carboxylate 7.



Pyrrole (0.14 g, 2.14 mmol, 5 equiv) and Cs_2CO_3 (0.69 g, 2.14 mmol, 5 equiv) was added to the solution of **6** (2.0 g, 0.43 mmol, 1 equiv) in dimethyl formamide (10 mL) in a 20 mL microwave vial. The vial was sealed and the reaction mixtures were irradiated in a microwave reactor at 135 °C for 10 minutes to obtain the polymer conjugate **7.** After being cooled to room temperature, the reaction mixtures were precipitated by slow

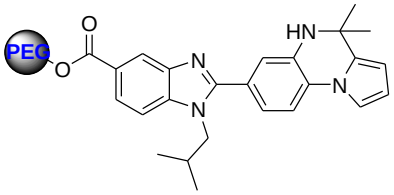
addition of cold ether and precipitated pyrrole bound polymer conjugates **7** were filtered through fritted funnel. The crude product was washed in succession with ether (100 mL×3) to remove the undesired impurity and dried for next steps.

General Procedure for the Preparation of Polymer Bound 2-(3-amino-4-(1H-pyrrol-1-yl)phenyl)-1-alkyl-1H-benzo[d]imidazole-5-carboxylate 8.



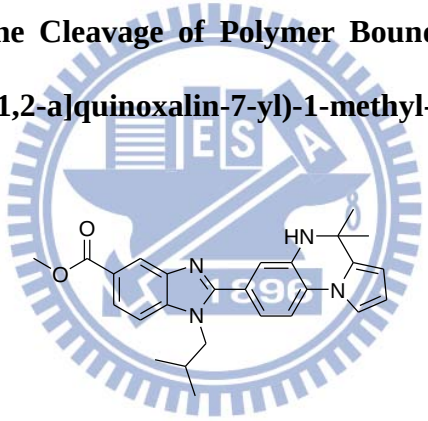
To a solution of **7** (2.14 g, 0.45 mmol) in methanol (10 ml), zinc dust (0.58 g, 9.0 mmol, 20.0 equiv) and ammonium formate (0.29 g, 4.50 mmol, and 10.0 equiv) were added in a 20 mL microwave vial. The vial was sealed and the reaction mixtures were irradiated in a microwave reactor at 60 °C for 10 minutes. After being cooled to ambient temperature, the reaction mixtures were then subjected to centrifugation for removal of Zn and filtered through fritted funnel and the supernatant liquid was concentrated by rotary evaporation. Dichloromethane (10 mL) was then added to salt out ammonium formate. The reaction mixtures were filtered through fritted funnel again to remove ammonium formate to obtain the polymer bound 2-(3-amino-4-(1H-pyrrol-1-yl)phenyl)-1-alkyl-1H-benzo[d]imidazole-5-carboxylate **8.**

General Procedure for the Preparation of Polymer Bound 2-(4,4-dialkyl-4,5-dihydropyrrolo[1,2-a]quinoxalin-7-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxylate 9.



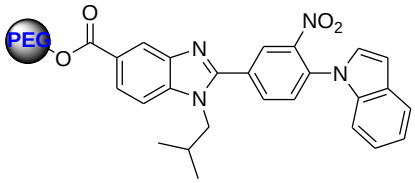
To a stirred solution of polymer bound 2-(3-amino-4-(1H-pyrrol-1-yl)phenyl)-1-alkyl-1H-benzo[d]imidazole-5-carboxylate conjugates **8** in $CHCl_3$ (10 mL), ketones (1.05 mmol, 5.0 equiv), trifluoro acetic acid (TFA) 0.05 ml and $MgSO_4$ (20 mg) were added in 20 mL microwave vial. The vial was sealed and the reaction mixtures were irradiated in a microwave reactor at 85 °C for 12 minutes. After cooling to room tempaeratue, the crude product mixtures were purified by precipitation with cold ether (100 mL×3) and dried to obtain the conjugate **9** in high purity.

General Procedure for the Cleavage of Polymer Bound Substituted alkyl 2-(4,4-alkyl-4,5-dihydropyrrolo[1,2-a]quinoxalin-7-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxylate10.



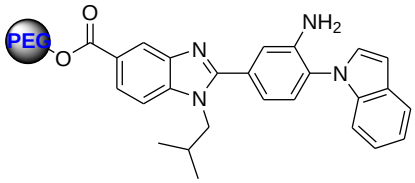
To a solution of conjugates **10** in methanol (20 mL), KCN (100 mg) was added and stirred for 24 hours at room temperature. After completion of the reaction, excess of cold ether (100 mL) was added, the polymer was filtered off and filtrate was subjected to evaporation. The residue was dried under vacuum, and submitted to crude HPLC analysis with UV detection at λ = 254 nm (column: Sphereclone 5μ Si (250 x 4.6 mm); gradient: 35 % ethyl acetate in hexane; flow rate: 1 mL/min.). The slurry obtained was loaded on silica gel column and eluted with a mixture of ethyl acetate and hexane (1:4) to get the title compounds **10** as a solid in 75-99 % overall yields.

General Procedure for the Preparation of Polymer Bound 1-isobutyl-2-(3-nitro-4-(1H-indole-1-yl)phenyl)-1H-benzo[d]imidazole-5-carboxylate 11.



Indole (0.24 g, 2.14 mmol, 5 equiv) and Cs_2CO_3 (0.69 g, 2.14 mmol, 5 equiv) was added to the solution of **6a** (2.0 g, 0.43 mmol, 1 equiv) in dimethyl formamide (10 mL) in a 20 mL microwave vial. The vial was sealed and the reaction mixtures were irradiated in a microwave reactor at 135 °C for 10 minutes to obtain the polymer conjugate **11.** After being cooled to room temperature, the reaction mixtures were precipitated by slow addition of cold ether and precipitated pyrrole bound polymer conjugates **11** were filtered through fritted funnel. The crude product was washed in succession with ether (100 mL×3) to remove the undesired impurity and dried for next steps.

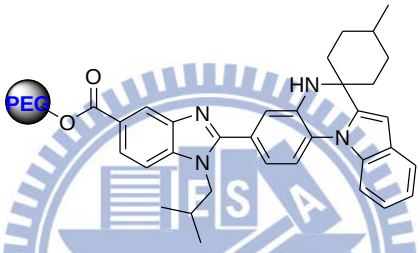
General Procedure for the Preparation of Polymer Bound 2-(3-amino-4-(1H-indole-1-yl)phenyl)-1-isobutyl -1H-benzo[d]imidazole-5-carboxylate 12.



To a solution of **11** (2.00 g, 0.41 mmol) in methanol (10 ml), zinc dust (0.53 g, 8.20 mmol, 20.0 equiv) and ammonium formate (0.27 g, 4.10 mmol, and 10.0 equiv) were added in a 20 mL microwave vial. The vial was sealed and the reaction mixtures were irradiated in a microwave reactor at 60 °C for 10 minutes. After being cooled to ambient temperature, the reaction mixtures were then subjected to centrifugation for removal of

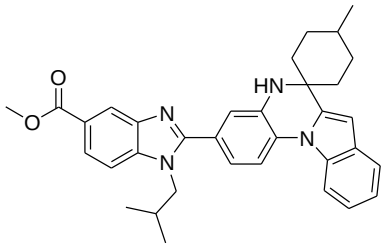
Zn and filtered through fritted funnel and the supernatant liquid was concentrated by rotary evaporation. Dichloromethane (10 mL) was then added to salt out ammonium formate. The reaction mixtures were filtered through fritted funnel again to remove ammonium formate to obtain the polymer bound 2-(3-amino-4-(1H-indole-1-yl)phenyl)-1-isobutyl-1H-benzo[d]imidazole-5-carboxylate **12.**

General Procedure for the Preparation of Polymer Bound 2-(4,4-dialkyl-4,5-dihydropyrrolo[1,2-a]quinoxalin-7-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxylate 13.



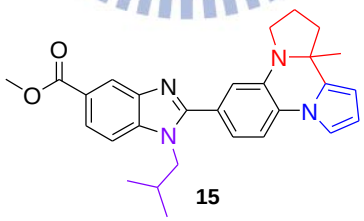
To a stirred solution of polymer bound 2-(3-amino-4-(1H-indole-1-yl)phenyl)-1-isobutyl-1H-benzo[d]imidazole-5-carboxylate conjugates **12** in $CHCl_3$ (10 mL), 4-methylcyclohexanone (1.05 mmol, 5.0 equiv), trifluoro acetic acid (TFA) 0.05 ml and $MgSO_4$ (20 mg) were added in 20 mL microwave vial. The vial was sealed and the reaction mixtures were irradiated in a microwave reactor at 85 °C for 12 minutes. After cooling to room tempaeratue, the crude product mixtures were purified by precipitation with cold ether (100 mL×3) and dried to obtain the conjugate **13** in high purity.

General Procedure for the Cleavage of Polymer Bound Substituted alkyl 2-(4,4-alkyl-4,5-dihydropyrrolo[1,2-a]quinoxalin-7-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxylate 14.



To a solution of conjugates **13** in methanol (20 mL), KCN (100 mg) was added and stirred for 24 hours at room temperature. After completion of the reaction, excess of cold ether (100 mL) was added, the polymer was filtered off and filtrate was subjected to evaporation. The residue was dried under vacuum, and and was purified by silica gel column and eluted with a mixture of ethyl acetate and hexane (1:4) to get the title compounds **14** as a pale yellow solid in 94 % yield.

General Procedure for the synthesis of methyl 2-(12b-methyl-1,2,3,12b-tetrahydrodipyrrolo[1,2-*a*:2,1-*c*]quinoxalin-6-yl)-1-isobutyl-1*H*-benzo[*d*]imidazole-5-carboxylate 15.

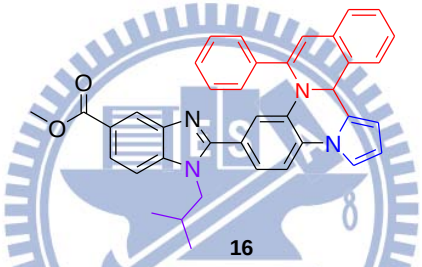


15

To a stirred solution of polymer bound 2-(3-amino-4-(1H-pyrrol-1-yl)phenyl)-1-isobutyl-1H-benzo[d]imidazole-5-carboxylate conjugates 8a (1.5 gm, 0.32 mm, 1.0 equiv) in MeOH (10 mL), pent-4-yn-1-ol (0.08 gm, 0.95 mmol, 3.0 equiv), $PtCl_4$ (5.3 mg, 5 mol-%) were added in 50 mL flask under argon atmosphere. The mixture was stirred at at 100 ^oC for 24 h. After completion of the reaction time, reaction mixture was filtered through

celite pad. The crude product mixtures were purified by precipitation with cold ether (100 mL×3) and dried to obtain the polymer bound conjugate **15** in high purity. To a solution of conjugates **15** in methanol (20 mL), KCN (100 mg) was added and stirred for 24 hours at room temperature. After completion of the reaction, excess of cold ether (100 mL) was added, the polymer was filtered off and filtrate was subjected to evaporation. The residue was dried under vacuum. The residue was purified by flash silica gel column chromatography as a white solid in 81 % yield.

General Procedure for the synthesis of methyl 1-isobutyl-2-(10-phenyl-15b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*c*]quinoxalin-7-yl)-1*H*-benzimidazole-5-carboxylate 16.

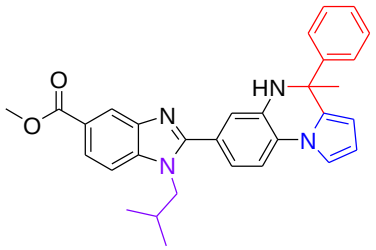


16

To a stirred solution of polymer bound 2-(3-amino-4-(1H-pyrrol-1-yl)phenyl)-1-isobutyl-1H-benzo[d]imidazole-5-carboxylate conjugates 8a (1.5 gm, 0.32 mm, 1.0 equiv) in DCE (10 mL), 2-(phenylethynyl)benzaldehyde (0.19 gm, 0.95 mmol, 3.0 equiv), AuCl (3.6 mg, 5 mol-%) were added in 50 mL flask under nitrogen atmosphere. The mixture was stirred at room temperaturefor 12 h. After completion of the reaction time, reaction mixture was filtered through celite pad. The crude product mixtures were purified by precipitation with cold ether (100 mL×3) and dried to obtain the polymer bound conjugate **16** in high purity. To a solution of conjugates **15** in methanol (20 mL), KCN (100 mg) was added and stirred for 24 hours at room temperature. After completion of the reaction, excess of cold ether (100 mL) was added, the polymer was filtered off and filtrate was subjected to evaporation. The residue was dried under vacuum. The residue

was purified by flash silica gel column chromatography as a pale yellow solid in 79 % yield.

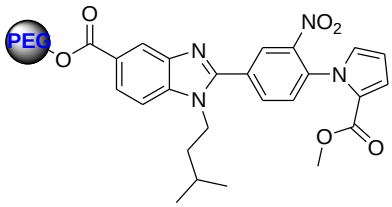
General Procedure for the synthesis of methyl 1-isobutyl-2-(4-methyl-4-phenyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1*H*-benzimidazole-5-carboxylate 17.



17

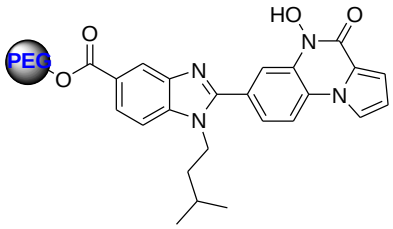
To a stirred solution of polymer bound 2-(3-amino-4-(1H-pyrrol-1-yl)phenyl)-1-isobutyl-1H-benzo[d]imidazole-5-carboxylate conjugates 8a (1.5 gm, 0.32 mm, 1.0 equiv) in toluene (10 mL), phenyl acetylene (0.10 gm, 0.95 mmol, 3.0 equiv), AgOTf (8.1 mg, 10 mol-%) were added in 50 mL flask under nitrogen atmosphere. The mixture was heated with stirring for 24 h. After completion of the reaction time, reaction mixture was filtered through celite pad. The crude product mixtures were purified by precipitation with cold ether (100 mL×3) and dried to obtain the polymer bound conjugate **17** in high purity. To a solution of conjugates **15** in methanol (20 mL), KCN (100 mg) was added and stirred for 24 hours at room temperature. After completion of the reaction, excess of cold ether (100 mL) was added, the polymer was filtered off and filtrate was subjected to evaporation. The residue was dried under vacuum. The residue was purified by flash silica gel column chromatography as a white solid in 65 % yield.

General Procedure for the Preparation of Polymer Bound methyl 1-isopentyl-2-4-[2-(methoxycarbonyl)-1*H*-1-pyrrolyl]-3-nitrophenyl-1*H*-benzo[*d*]imidazole-5-carboxylate (18d)



To a solution of **6** (5.3 g, 1.13 mmol, 1 equiv) in dimethyl formamide (10 mL) was added pyrrole 2-carboxylate (0.706 g, 5.65 mmol, 5 equiv) and Cs_2CO_3 (1.84 g, 5.65 mmol, 5 equiv) in a sequential order. Then the reaction mixtures were irradiated with stirring in a 20 mL microwave process vial for 10 minutes at 130°C (2 bar) to obtain the polymer conjugate **18.** After completion of the reaction, the reaction mixtures were precipitated by slow addition of cold ether and precipitated pyrrole carboxylate bound polymer conjugates **18** were filtered through fritted funnel. The crude product was washed in succession with ether (100 mL×3) to remove the undesired impurity and dried for next steps.

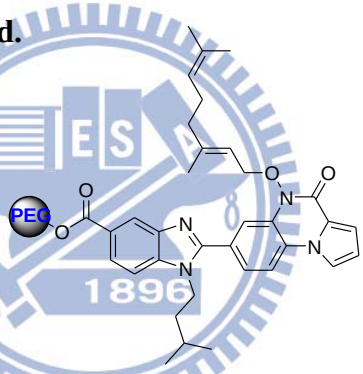
General Procedure for the Preparation of Polymer Bound methyl 2-(5-hydroxy-4-oxo-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1-isopentyl-1*H*-benzo[*d*]imidazole-5-carboxylate 19d.



To a solution of **18** (5.40 g, 1.10 mmol) in methanol, 10 % Pd/C (1.20 g, 11.00 mmol, 10.0 equiv) and ammonium formate (0.720 g, 11.00 mmol, and 10.0 equiv) were added.

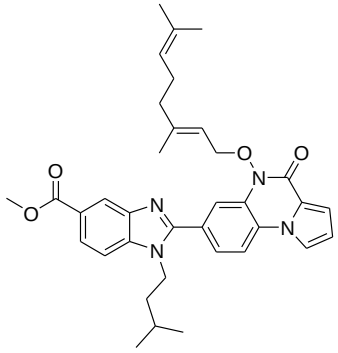
The reaction mixtures were exposed under pressured microwave irradiation for 10 minutes at 60 ^{o}C in 1 bar pressure. After completion, the reaction mixtures were filtered through Celite bed for removal of Pd/C and the supernatant liquid was concentrated by rotary evaporation. Dichloromethane (10 mL) was then added to salt out ammonium formate. The reaction mixtures were filtered through fritted funnel again to remove ammonium formate to obtain the polymer bound 2-(3-amino-4-(1H-pyrrol-1-yl)phenyl)-1-alkyl-1H-benzo[d]imidazole-5-carboxylate **19d.**

General Procedure for the Preparation of Polymer Bound 2-(5-[(2*E*)-3,7-dimethyl-2,6-octadienyl]oxy-4-oxo-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1-isopentyl-1*H*-benzo[*d*]imidazole-5-carboxylat 20d.



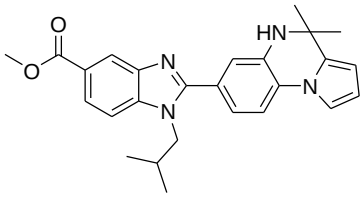
To a stirred solution of polymer bound **19d** (5.40 g, 1.10 mmol) in DMF, NaH (1.20 g, 11.00 mmol, 5.0 equiv) was added. The reaction mixtures were cooled in ice bath. Alkyl bromide was added to the reaction mixture dropwise manner. The reaction mixture was stirred for 36 hrs. After completion of the reaction, the reaction mixtures were precipitated by slow addition of cold ether the precipitated compound were filtered throgh fritted funnel to obtain the polymer bound 2-(3-amino-4-(1H-pyrrol-1-yl)phenyl)-1-alkyl-1H-benzo[d]imidazole-5-carboxylate **20d.**

General Procedure for the Cleavage of Polymer Bound Substituted alkyl 2-(4,4-alkyl-4,5-dihydropyrrolo[1,2-a]quinoxalin-7-yl)-1-methyl-1H-benzo[d]imidazole-5-carboxylate 21d.



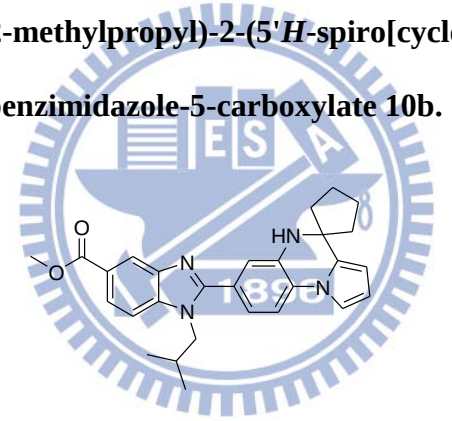
To a solution of conjugates **20d** in methanol (20 mL), KCN (100 mg) was added and stirred for 24 hours at room temperature. After completion of the reaction, excess of cold ether (100 mL) was added, the polymer was filtered off and filtrate was subjected to evaporation. The residue was dried under vacuum, and submitted to crude HPLC analysis with UV detection at λ = 254 nm (column: Sphereclone 5μ Si (250 x 4.6 mm); gradient: 35 % ethyl acetate in hexane; flow rate: 1 mL/min.). The slurry obtained was loaded on silica gel column and eluted with a mixture of ethyl acetate and hexane (1:4) to get the title compounds **21d** in 75-98 % overall yields.

Methyl 2-(4,4-dimethyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1-(2-methylpropyl)-1*H*-benzimidazole-5-carboxylate 10a.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, *J* = 1.1 Hz, 1H), 8.03 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 1.7 Hz, 1H), 7.16 (dd, *J* = 2.8, 1.4 Hz, 1H), 7.06 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.33 (t, *J* = 3.3 Hz, 1H), 6.02 (dd, *J* = 3.3, 1.4 Hz 1H), 4.53 (brs, NH), 4.12 (d, *J* = 7.6 Hz, 2H), 3.95 (s, 3H), 2.10 (m, 1H), 1.49 (s, 6H), 0.75 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.2, 142.8, 139.5, 136.5, 135.3, 126.8, 126.7, 124.8, 124.5, 122.4, 119.7, 117.3, 114.9, 114.5, 111.1, 110.6, 102.9, 52.5, 52.4, 51.9, 29.8, 29.7, 29.3, 20.4; MS (ESI) *m/z*: 429 (MH^+); HRMS (ESI, m/z) calcd for $C_{26}H_{29}N_4O_2$: *m/z* 429.2290; Found 429.2288 (M+H); IR (cm^{-1}, KBr): 3236, 2958, 1710, 1610, 1494, 1326.

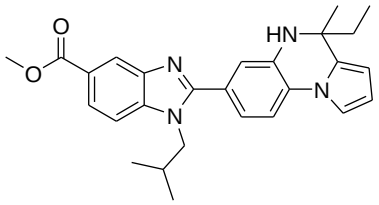
Methyl 1-(2-methylpropyl)-2-(5'*H*-spiro[cyclopentane-1,4'-pyrrolo[1,2-*a*]quinoxalin]-7'-yl)-1*H*-benzimidazole-5-carboxylate 10b.



^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.51 (d, *J* = 1.2 Hz, 1H), 8.02 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.20 (d, *J* = 1.6 Hz, 1H), 7.18 (dd, *J* =2.7, 1.2 Hz, 1H), 7.05 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.33 (t, *J* = 3.2 Hz, 1H), 6.02 (dd, *J* = 3.2, 1.2 Hz, 1H), 4.65 (brs, NH), 4.10 (d, *J* = 7.6 Hz, 2H), 3.95 (s, 3H), 2.11-2.00 (m, 3H), 1.89 -1.85 (m, 2H), 1.82-1.76 (m, 4H), 0.73 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.2, 142.9, 139.5, 136.8, 134.9, 127.3, 126.7, 124.8, 124.5, 122.4, 119.8, 117.3, 114.9, 114.7, 111.0, 110.6, 103.1, 62.7, 52.5, 40.1, 29.3, 23.9, 20.4; MS

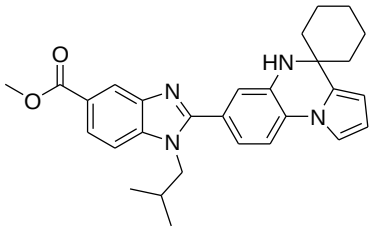
(ESI) *m/z*: 455 (MH^+); HRMS (ESI, m/z) calcd for $C_{28}H_{31}N_4O_2$: *m/z* 455.2447; Found 455.2446 (M+H); IR (cm^{-1}, KBr): 3319, 2956, 1714, 1608, 1494.

Methyl 2-(4-ethyl-4-methyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1-(2-methylpropyl)-1*H*-benzimidazole-5-carboxylate 10c.



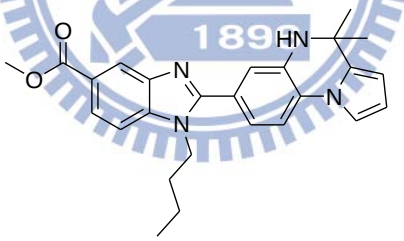
^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.37 (t, *J* = 8.6 Hz, 2H), 7.17 (s, 2H), 7.02(d, *J* = 8.2 Hz, 1H), 6.33 (t, *J* = 2.7 Hz, 1H), 5.99 (t, *J* =1.7 Hz, 1H), 4.56 (brs, NH), 4.09 (d, *J* = 7.5 Hz, 2H), 3.95 (s, 3H), 2.10 (m, 1H), 1.75-1.66 (q, *J* = 6.8 Hz, 2H), 1.48 (s, 3H) 0.84 (t, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.3, 142.8, 139.5, 136.6, 133.8, 126.8, 126.5, 124.8, 124.5, 122.4, 119.3, 116.8, 114.8, 114.4, 111.0, 110.6, 104.1, 55.0, 52.5, 35.3, 30.1, 29.3, 27.2, 20.4, 9.2; MS (ESI) *m/z*: 443 (MH^+); HRMS (ESI, m/z) calcd for $C_{27}H_{31}N_4O_2$: *m/z* 443.2447; Found 443.2444 (M+H); IR (cm^{-1}, KBr): 3236, 2960, 1710, 1610, 1496, 1295.

Methyl 1-(2-methylpropyl)-2-(5'*H*-spiro[cyclohexane-1,4'-pyrrolo[1,2-*a*]quinoxalin]-7'-yl)-1*H*-benzimidazole-5-carboxylate 10d.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 1.0 Hz, 1H), 8.02 (dd, J = 8.6, 1.0 Hz, 1H), 7.39 (d, J = 8.1, 1H), 7.38 (d, J = 8.6, 1H), 7.27 (d, J = 1.7 Hz, 1H), 7.17 (dd, J = 2.8, 1.5 Hz, 1H), 7.07 (dd, J = 8.1, 1.7 Hz, 1H), 6.34 (t, J = 3.3 Hz, 1H), 6.07 (dd, J = 3.3, 1.5 Hz, 1H), 4.85 (brs, NH), 4.09 (d, J = 7.6 Hz, 2H), 3.95 (s, 3H), 2.09 (m, 1H), 1.93-1.89 (m, 2H), 1.79-1.63 (m, 5H), 1.56-1.43 (m, 2H), 1.33 (m, 1H), 0.73 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.2, 142.9, 139.5, 135.9, 127.1, 126.9, 124.8, 124.5, 122.4, 122.3, 119.9, 114.9, 114.6, 111.1, 110.6, 110.5, 103.3, 53.1, 52.5, 52.4, 36.6, 29.2, 25.5, 21.9, 20.4; MS (ESI) *m/z*: 469 (MH^+); HRMS (ESI, m/z) calcd for $C_{29}H_{33}N_4O_2$: *m/z* 469.2603 Found 469.2605 (M+H); IR (cm^{-1}, KBr): 3319, 2929, 1712, 1608, 1494.

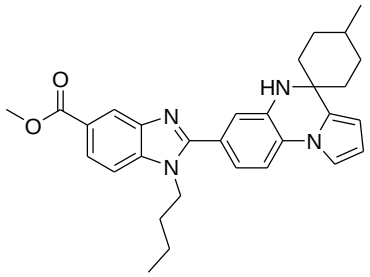
Methyl 1-butyl-2-(4,4-dimethyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1*H*-benzimidazole-5-carboxylate 10e.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 1.3 Hz, 1H), 8.05 (dd, J = 8.5, 1.3 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.20 (d, J = 1.8 Hz, 1H), 7.18 (dd, J = 3.2, 1.5 Hz, 1H), 7.18 (dd, J = 8.2, 1.8 Hz, 1H), 6.35 (t, J = 3.2 Hz, 1H), 6.05 (dd, J =3.2, 1.5 Hz, 1H), 4.29 (t, J = 7.6 Hz, 2H), 4.17 (brs, NH), 3.97 (s, 3H), 1.89-1.75 (quint, J = 7.5 Hz, 2H), 1.54 (s, 6H) 1.33-1.26 (sext, J = 7.5 Hz, 2H), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 155.8, 143.0, 139.3, 136.4, 135.2, 126.9, 126.6, 124.9, 124.6, 122.4, 119.7, 117.2, 114.9, 114.5, 111.1, 110.1, 103.0, 52.5, 52.0, 45.1, 32.2, 30.0,

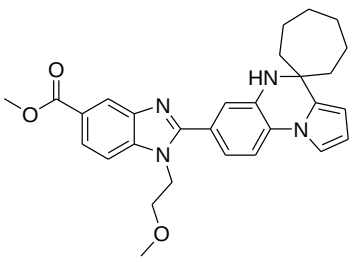
20.3, 14.0; MS (ESI) *m/z*: 429 (MH^+); HRMS (ESI, m/z) calcd for $C_{26}H_{29}N_4O_2$: *m/z* 429.2290; Found 429.2292 (M+H); IR (cm^{-1}, KBr): 3342, 2954, 1710, 1610, 1494, 1296.

Methyl 1-butyl-2-(4-methyl-5'*H*-spiro[cyclohexane-1,4'-pyrrolo[1,2-*a*]quinoxalin]-7'-yl)-1*H*-benzimidazole-5-carboxylate 10f.



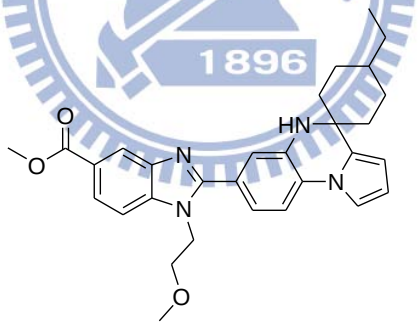
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, *J* = 1.1 Hz, 1H), 8.05 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.28 (s, 1H), 7.19 (dd, *J* = 2.8, 1.4 Hz, 1H), 7.10 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.36 (t, *J* = 3.4 Hz, 1H), 6.05 (dd, *J* = 3.4, 1.4 Hz, 1H), 4.68 (brs, NH), 4.30 (t, *J* = 7.6 Hz, 2H), 3.98 (s, 3H), 2.06 -2.02 (m, 2H), 1.89-1.78 (quint, *J* = 7.3 Hz, 2H), 1.77 -1.68 (m, 6H), 1.34 -1.25 (sext, *J* = 7.3 Hz, 2H), 1.21 (m, 1H), 0.99 (d, *J* = 6.4 Hz, 3H) 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 155.7, 142.9, 139.3, 136.0, 135.7, 127.3, 126.5, 124.9, 124.6, 122.4, 119.8, 117.4, 114.9, 114.6, 111.2, 110.1, 102.8, 52.6, 52.5, 45.2, 36.2, 32.2, 32.1, 30.4, 22.8, 20.3, 14.0; MS (ESI) *m/z*: 483 (MH^+); HRMS (ESI, m/z) calcd for $C_{30}H_{35}N_4O_2$: *m/z* 483.2760; Found 483.2757 (M+H); IR (cm^{-1}, KBr): 3236, 2925, 1712, 1608, 1494.

Methyl 1-(2-methoxyethyl)-2-(5'*H*-spiro[cycloheptane-1,4'-pyrrolo[1,2-*a*]quinoxalin]-7'-yl)-1*H*-benzimidazole-5-carboxylate 10g.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 1.1 Hz, 1H), 8.03 (dd, J = 8.5, 1.1 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.35 (d, J = 1.6 Hz, 2H), 7.17 (dd, J = 8.2, 1.6 Hz, 1H), 7.14 (dd, J = 2.8, 1.4 Hz, 1H), 6.33 (t, J = 3.2 Hz, 1H), 6.08 (dd, J = 3.2, 1.4 Hz, 1H), 4.78 (brs, NH), 4.43 (t, J = 5.2 Hz, 2H), 3.95 (s, 3H), 3.74 (t, J = 5.2 Hz, 2H), 3.25 (s, 3H), 2.12-2.04 (m, 2H), 1.92-1.87 (m, 2H), 1.58-1.53 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.3, 142.9, 139.6, 136.6, 136.2, 126.2, 125.1, 122.4, 122.0, 120.0, 117.7, 114.7, 114.4, 110.9, 110.6, 103.4, 71.2, 59.5, 57.2, 52.5, 45.3, 40.8, 30.7, 23.0; MS (ESI) *m/z*: 485 (MH^+); HRMS (ESI, m/z) calcd for $C_{29}H_{33}N_4O_3$: *m/z* 485.2553; Found 485.2550 (M+H); IR (cm^{-1}, KBr): 3236, 2919, 1708, 1610, 1500.

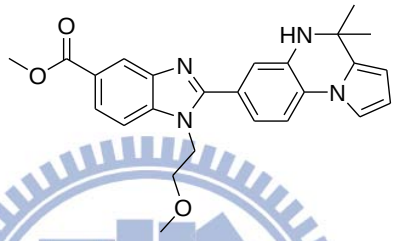
Methyl 2-(4-ethyl-5'*H*-spiro[cyclohexane-1,4'-pyrrolo[1,2-*a*]quinoxalin]-7'-yl)-1-(2-methoxyethyl)-1*H*-benzimidazole-5-carboxylate 10h.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 1.2 Hz, 1H), 8.03 (dd, J = 8.5, 1.2 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.39 (d, J = 1.7 Hz, 1H), 7.20 (dd, J = 8.2, 1.7 Hz, 1H), 7.16 (dd, J = 2.8, 1.4 Hz, 1H), 6.34 (t, J = 3.4 Hz, 1H), 6.03 (dd, J = 3.4, 1.4 Hz 1H), 4.85 (brs, NH), 4.44 (t, J = 5.5 Hz, 2H), 3.95 (s, 3H), 3.75 (t, J = 5.5 Hz, 2H), 3.26 (s, 3H), 2.06-2.02 (m, 2H), 1.78-1.69 (m, 4H), 1.33-1.24 (quint, J = 7.3 Hz, 2H), 1.21-1.10 (m, 3H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1,

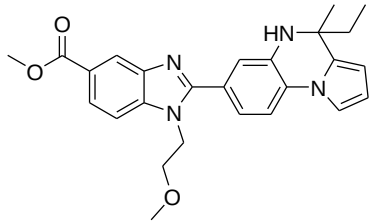
156.2, 143.0, 139.6, 136.2, 135.8, 127.3, 126.3, 125.0, 124.6, 122.3, 120.2, 117.8, 114.8, 114.5, 111.1, 110.5, 102.8, 71.2, 59.5, 53.0, 52.5, 45.4, 38.7, 36.2, 30.1, 28.0, 11.9; MS (ESI) *m/z*: 499 (MH^+); HRMS (ESI, m/z) calcd for $C_{30}H_{35}N_4O_3$: *m/z* 499.2709; Found 499.2708 (M+H); IR (cm^{-1}, KBr): 3278, 2925, 1710, 1610, 1494.

Methyl 2-(4,4-dimethyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1-(2-methoxyethyl)-1*H*-benzimidazole-5-carboxylate 10i.



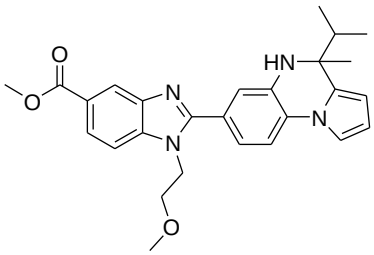
^{1}H NMR (300MHz, $CDCl_3$) δ 8.50 (d, *J* = 1.0 Hz, 1H), 8.03 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.48 (d, *J* = 8.5, Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.27 (d, *J* = 1.4 Hz, 1H), 7.19 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.16 (dd, *J* = 2.8, 1.4 Hz, 1H), 6.33 (t, *J* = 3.1 Hz, 1H), 6.03 (dd, *J* = 3.1, 1.4 Hz, 1H), 4.44 (t, *J* = 5.5 Hz, 2H), 3.97 (brs, NH), 3.95 (s, 3H), 3.75 (t, *J* = 5.5 Hz, 2H), 3.26 (s, 3H), 1.50 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ168.1, 156.2, 142.9, 139.6, 136.4, 135.3, 126.8, 126.2, 125.0, 124.6, 122.3, 120.1, 117.6, 114.8, 114.5, 111.1, 110.6, 102.9, 71.2, 59.5, 52.5, 51.9, 45.3, 29.9; MS (ESI): m/z 431 (MH^+); HRMS (ESI) calcd for $C_{25}H_{27}N_4O_3$: m/z 431.2083. Found 431.2082; IR (cm^{-1}, KBr): 3234, 2948, 1710, 1610, 1494.

Methyl 2-(4-ethyl-4-methyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1-(2-methoxyethyl)-1*H*-benzimidazole-5-carboxylate 10j.



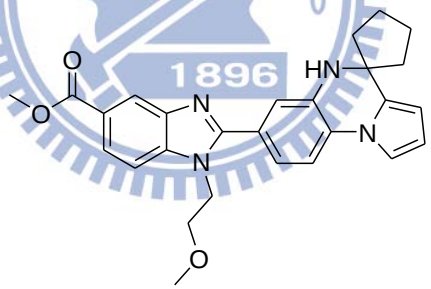
^{1}H NMR (300MHz, $CDCl_3$) δ 8.50 (d, *J* = 1.3 Hz, 1H), 8.02 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.27 (d, *J* = 1.7 Hz, 1H), 7.15 (dd, *J* = 2.8, 1.5 Hz, 1H), 7.14 (d, *J* = 8.2, 1.7 Hz, 1H), 6.33 (t, *J* = 3.2 Hz, 1H), 5.99 (dd, *J* = 3.2, 1.5 Hz, 1H), 4.55 (brs, NH), 4.42 (t, *J* = 5.5 Hz, 2H), 3.94 (s, 3H), 3.73 (t, *J* = 5.5 Hz, 2H), 3.25 (s, 3H), 1.76-1.66 (q, *J* = 6.4 Hz, 2H), 1.48 (s, 3H), 0.86 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 168.1, 156.3, 142.9, 139.6, 136.6, 133.8, 126.6, 126.2, 124.9, 124.6, 122.3, 119.7, 117.1, 114.7, 114.3, 111.0, 110.6, 104.1, 71.2, 59.5, 55.0, 52.5, 45.3, 35.3, 27.3, 9.2; MS (ESI): m/z 445 (MH^+); HRMS (ESI) calcd for $C_{26}H_{29}N_4O_3$: m/z 445.2240. Found 445.2242; IR (cm^{-1}, KBr): 3245, 2962, 1712, 1610, 1496.

Methyl 1-(2-methoxyethyl)-2-[4-methyl-4-(propan-2-yl)-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl]-1*H*-benzimidazole-5-carboxylate 10k.



^{1}H NMR (300MHz, $CDCl_3$) δ 8.51 (d, *J* = 1.1 Hz, 1H), 8.04 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 1.6 Hz, 1H), 7.18 (dd, *J* = 3.0, 1.5 Hz, 1H), 7.15 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.35 (t, *J* = 3.4 Hz, 1H), 6.03 (dd, *J* = 3.4, 1.5 Hz, 1H), 4.45 (t, *J* = 5.5 Hz, 2H), 4.31(brs, NH), 3.97 (s, 3H), 3.77 (t, *J* = 5.5 Hz, 2H), 3.28 (s, 3H), 1.98 (sept, *J* = 6.4 Hz, 1H), 1.52 (s, 3H), 0.91-0.85 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.2, 142.9, 139.6, 136.3, 133.3, 126.8, 126.3, 125.0, 124.6, 122.3, 119.6, 116.4, 114.6, 114.2, 110.9, 110.5, 105.3, 71.2, 59.5, 54.9, 52.5, 45.4, 35.3, 27.3, 9.2; MS (ESI): m/z 459 (MH^+); HRMS (ESI) calcd for $C_{27}H_{31}N_4O_3$: m/z 459.2396. Found 459.2394; IR (cm^{-1}, KBr): 3266, 2958, 1712, 1610, 1498.

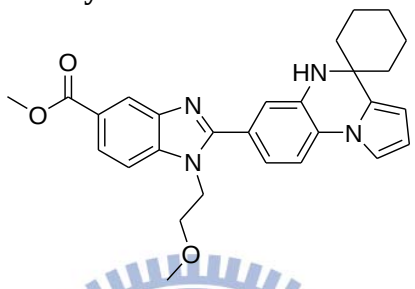
Methyl 1-(2-methoxyethyl)-2-(5'*H*-spiro[cyclopentane-1,4'-pyrrolo[1,2-*a*]quinoxalin]-7'-yl)-1*H*-benzimidazole-5-carboxylate 10l.



^{1}H NMR (300MHz, $CDCl_3$) δ 8.51 (d, *J* = 1.1 Hz, 1H), 8.03 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.27 (d, *J* = 1.7 Hz, 1H), 7.21(dd, *J* = 8.2, 1.7 Hz, 1H), 7.18 (dd, *J* = 2.9, 1.4 Hz, 1H), 6.34 (t, *J* = 3.4 Hz 1H), 6.03 (dd, *J* = 3.4, 1.4 Hz, 1H), 4.45 (t, *J* = 5.5 Hz, 2H), 4.41(brs, NH), 3.96 (s, 3H), 3.76 (t, *J* = 5.5 Hz, 2H), 3.27 (s, 3H), 2.12-2.01 (m, 2H), 1.93-.81 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.2, 142.9, 139.6, 136.6, 134.9, 127.4, 126.2, 125.0, 122.3, 120.3, 117.6, 114.9, 114.7, 114.2, 111.0, 110.5, 103.1, 71.2, 62.7, 59.5, 52.5, 45.4, 40.2, 23.9; MS (ESI): m/z

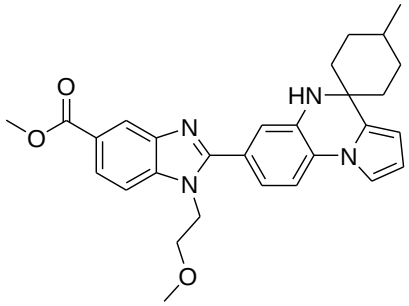
457 (MH^+); HRMS (ESI) calcd for $C_{27}H_{29}N_4O_3$: m/z 457.2240. Found 457.2237; IR (cm^{-1}, KBr): 3322, 2944, 1710, 1608, 1494 cm^{-1}.

Methyl 1-(2-methoxyethyl)-2-(5'*H*-spiro[cyclohexane-1,4'-pyrrolo[1,2-*a*]quinoxalin]-7'-yl)-1*H*-benzimidazole-5-carboxylate 10m.



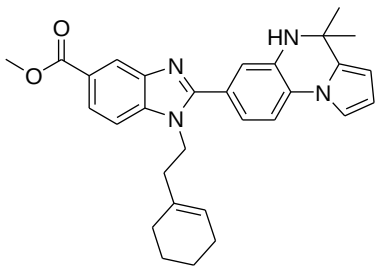
^{1}H NMR (300MHz, $CDCl_3$) δ 8.50 (d, *J* = 1.1 Hz, 1H), 8.03 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.40 (d, *J* = 1.7 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.21 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.15 (dd, *J* = 2.6, 1.4 Hz, 1H), 6.34 (t, *J* = 3.4 Hz, 1H), 6.08 (dd, *J* = 3.4, 1.4 Hz, 1H), 4.80 (brs, NH), 4.48 (t, *J* = 5.4 Hz, 2H), 3.98 (s, 3H), 3.77 (t, *J* = 5.4 Hz, 2H), 3.28 (s, 3H), 1.96 -1.92 (m, 3H), 1.82-1.70 (m, 5H), 1.60-1.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 156.0, 142.9, 139.4, 135.9, 127.3, 125.2, 124.8, 122.1, 120.3, 120.3, 117.7, 114.8, 114.5, 114.2, 111.1, 110.6, 103.4, 71.2, 59.5, 53.1, 52.5, 45.5, 36.7, 32.0, 22.0; MS (ESI): m/z 471 (MH^+); HRMS (ESI) calcd for $C_{28}H_{31}N_4O_3$: m/z 471.2396. Found 471.2394; IR (cm^{-1}, KBr): 3322, 2929, 1710, 1610, 1495.

Methyl 1-(2-methoxyethyl)-2-(4-methyl-5'*H*-spiro[cyclohexane-1,4'-pyrrolo[1,2-*a*]quinoxalin]-7'-yl)-1*H*-benzimidazole-5-carboxylate 10n.



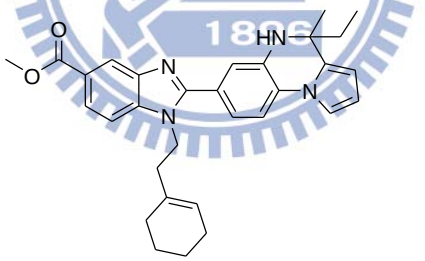
^{1}H NMR (300MHz, $CDCl_3$) δ 8.51 (d, *J* = 1.0 Hz, 1H), 8.03 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 1.6 Hz, 1H), 7.39 (dd, *J* = 8.2 Hz, 1H), 7.22 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.15 (dd, *J* = 2.8, 1.2 Hz, 1H), 6.35 (t, *J* = 3.3 Hz, 1H), 6.04 (dd, *J* = 3.3, 1.2 Hz, 1H), 4.76 (brs, NH), 4.50 (t, *J* = 5.3 Hz, 2H), 3.98 (s, 3H), 3.77 (t, *J* = 5.3 Hz, 2H), 3.28 (s, 3H), 2.06-2.01 (m, 2H), 1.80-1.67 (m, 4H), 1.27-1.14 (m, 3H), 0.99 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 156.0, 142.2, 142.0, 139.4, 136.0, 135.7, 127.4, 124.9, 124.8, 121.0, 120.3, 117.7, 114.8, 114.6, 111.1, 110.6, 102.8, 71.1, 59.5, 52.5, 45.5, 36.2, 32.0, 30.4, 23.1, 14.5; MS (ESI): m/z 485 (MH^+); HRMS (ESI) calcd for: $C_{29}H_{33}N_4O_3$: m/z 485.2553. Found 485.2552; IR (cm^{-1}, KBr): 3322, 2929, 1710, 1610, 1492 .

Methyl 1-[2-(cyclohex-1-en-1-yl)ethyl]-2-(4,4-dimethyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1*H*-benzimidazole-5-carboxylate 10o.



^{1}H NMR (300MHz, $CDCl_3$) δ 8.50 (d, *J* = 1.1 Hz, 1H), 8.03 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 1.5 Hz, 1H), 7.16 (d, *J* = 3.2, 1.4 Hz, 1H), 7.09 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.33 (t, *J* = 3.2 Hz, 1H), 6.03 (dd, *J* = 3.2, 1.4 Hz, 1H), 5.18 (m, 1H), 4.67 (brs, NH), 4.36 (t, *J* = 7.0 Hz, 2H), 3.96 (s, 3H), 2.36 (t, *J* = 7.0 Hz, 2H), 1.93-1.78 (m, 4H), 1.50 (s, 6H), 1.46-1.45 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 155.8, 142.2, 139.0, 136.6, 135.3, 133.4, 126.8, 126.0, 125.1, 125.0, 124.6, 122.1, 119.4, 117.2, 114.8, 114.5, 111.1, 110.4, 102.9, 52.5, 51.9, 44.3, 38.2, 29.8, 28.6, 25.5, 22.9, 22.3; MS (ESI): m/z 481 (MH^+); HRMS (ESI) calcd for $C_{30}H_{33}N_4O_2$: m/z 481.2603. Found 481.2606; IR (cm^{-1}, KBr): 3340, 2929, 1700, 1606, 1498.

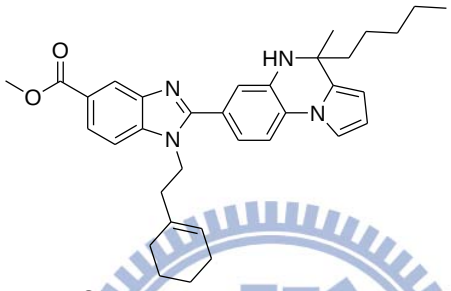
Methyl 1-[2-(cyclohex-1-en-1-yl)ethyl]-2-(4-ethyl-4-methyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1*H*-benzimidazole-5-carboxylate 10p.



^{1}H NMR (300MHz, $CDCl_3$) δ 8.51 (d, *J* = 1.0 Hz, 1H), 8.03 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 1.5 Hz, 1H), 7.14 (dd, *J* = 2.8, 1.3 Hz, 1H), 7.09 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.35 (t, *J* = 3.2 Hz, 1H), 6.02 (dd, *J* = 3.2, 1.3 Hz, 1H), 5.18 (m, 1H), 4.42 (t, *J* = 7.2 Hz, 2H), 4.28 (brs, NH), 3.98 (s, *3*H), 2.38 (t, *J* = 7.2 Hz, 2H), 1.84-1.66 (m, 6H), 1.54 (s, 3H), 1.46-1.44 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 155.9, 139.2, 136.6, 135.3, 133.8, 133.5, 126.5,

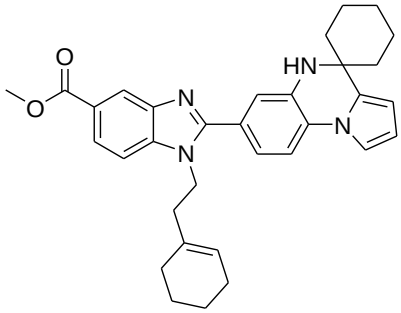
126.4, 125.1, 124.9, 124.5, 122.3, 119.1, 116.7, 114.7, 114.3, 111.0, 110.3, 104.1, 55.0, 52.5, 44.3, 38.2, 35.4, 28.6, 27.3, 25.5, 23.0, 22.3, 9.8; MS (ESI): m/z 495 (MH^+); HRMS (ESI) calcd for: $C_{31}H_{35}N_4O_2$: m/z 495.2760. Found 495.2763; IR (cm^{-1}, KBr): 3340, 2925, 1700, 1605, 1496.

Methyl 1-[2-(cyclohex-1-en-1-yl)ethyl]-2-(4-methyl-4-pentyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1*H*-benzimidazole-5-carboxylate 10q.



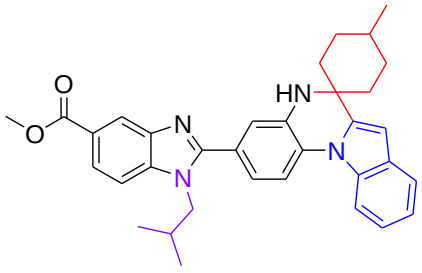
^{1}H NMR (300MHz, $CDCl_3$) δ 8.50 (d, *J* = 1.1 Hz, 1H), 8.04 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 1.2 Hz, 1H), 7.17 (d, *J* = 2.8, 1.1 Hz, 1H), 7.05 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.34 (t, *J* = 3.2 Hz, 1H), 6.00 (dd, *J* = 3.2, 1.1 Hz, 1H), 5.19 (m, 1H), 4.39 (brs, NH), 4.42 (t, *J* = 7.5 Hz, 2H), 3.96 (s, *3*H), 2.37 (t, *J* = 7.5 Hz, 2H), 1.84-1.78 (m, 4H), 1.72-1.65 (m, 3H), 1.50 (s, 3H), 1.48-1.43 (m, 4H), 1.32-1.13 (m, 6H), 0.83 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 168.1, 155.9, 139.2, 136.6, 134.0, 133.4, 133.5, 126.5, 126.3, 125.1, 124.9, 124.6, 122.3, 119.1, 116.7, 114.7, 114.7, 114.3, 111.0, 110.3, 104.1, 54.8, 52.3, 44.3, 42.8, 38.2, 32.4, 28.6, 28.0, 25.5, 24.5, 23.0, 22.3, 14.4; MS (ESI): m/z 537 (MH^+); HRMS (ESI) calcd for: $C_{34}H_{41}N_4O_2$: m/z 537.3229. Found 537.3232; IR (cm^{-1}, KBr): 3234, 2929, 1712, 1610, 1496.

Methyl-1-[2-(cyclohex-1-en-1-yl)ethyl]-2-(5'*H*-spiro[cyclohexane-1,4'-pyrrolo[1,2-*a*]quinoxalin]-7'-yl)-1*H*-benzimidazole-5-carboxylate 10r.



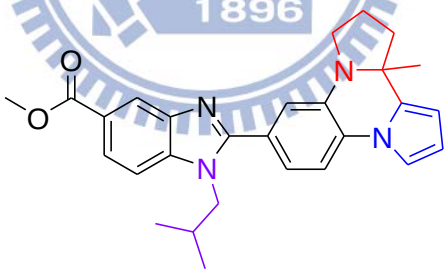
^{1}H NMR (300MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.39 (m, 3H), 7.17 (s, 1H), 7.09 (dd, J = 8.2, 1.5 Hz, 1H), 6.34 (t, J = 3.4 Hz, 1H), 6.07 (dd, J = 3.4, 1.3 Hz, 1H), 5.16 (m, 1H), 4.93 (brs, NH), 4.35 (t, J = 7.0 Hz, 2H), 3.96 (s, 3H), 2.35 (t, J = 7.0 Hz, 2H), 1.94-1.89 (m, 2H), 1.81-1.75 (m, 6H), 1.69-1.62 (m, 4H), 1.50-1.434 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 155.9, 142.9, 139.2, 135.9, 135.8, 133.5, 127.2, 126.5, 125.5, 125.1, 124.8, 124.5, 122.3, 119.7, 117.3, 114.8, 114.5, 111.0, 110.3, 103.2, 53.1, 52.5, 44.3, 38.2, 36.6, 28.6, 25.6, 25.5, 22.9, 22.3, 21.9; MS (ESI): m/z 521 (MH^+); HRMS (ESI) calcd for: $C_{33}H_{37}N_4O_2$: m/z 521.2916. Found 521.2915; IR (cm^{-1}, KBr): 3322, 2927, 1710, 1612, 1492.

Methyl 1--(2-methylpropyl)-2-(4-methyl-5'*H*-spiro[cyclohexane-1,4'-indolo[1,2-*a*]quinoxalin]-7'-yl)-1*H*-benzimidazole-5-carboxylate 14.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, J = 1.3 Hz, 1H), 8.05 (dd, J = 8.3, 1.3 Hz, 1H), 8.01 (s, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 1.2 Hz, 1H), 7.31-7.20 (m, 3H), 6.44 (s, 1H), 4.69 (brs, NH), 4.18 (t, J = 7.5 Hz, 2H), 3.98 (s, 3H), 2.21 (sept, J = 6.7 Hz, 1H), 2.17-2.07 (m, 2H), 1.90-1.80 (sext, J = 7.1 Hz, 2H), 1.75 - 1.70 (m, 2H), 1.27-1.09 (m, 3H), 0.97 (d, J = 8.6 Hz, 3H), 0.78 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.1, 144.2, 142.9, 139.6, 136.3, 134.5, 130.5, 128.9, 126.2, 126.0, 124.6, 122.9, 122.5, 121.6, 121.5, 120.9, 117.8, 116.9, 112.1, 110.6, 97.1, 53.0, 52.6, 52.5, 35.1, 32.2, 30.3, 29.3, 22.8, 20.4; MS (ESI) *m/z*: 533 (MH^+); HRMS (EI) calcd for: $C_{34}H36N_4O_2$: m/z 532.2838. Found 532.2842; IR (cm^{-1}, KBr): 3278, 2905, 1712, 1610, 1448.

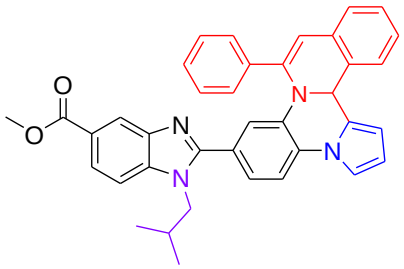
Methyl 2-(12b-methyl-1,2,3,12b-tetrahydrodipyrrolo[1,2-*a*:2,1-*c*]quinoxalin-6-yl)-1-isobutyl-1*H*-benzo[*d*]imidazole-5-carboxylate 15.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 1.0 Hz, 1H), 8.03 (dd, J = 8.6, 1.0 Hz, 1H), 7.38 (dd, J = 8.6, 3.7 Hz, 2H), 7.17- 7.13 (m, 2H), 7.05 (d, J = 8.1 Hz, 1H), 6.34 (t, J = 3.1 Hz, 1H), 6.01 (dd, J = 3.1, 1.4 Hz 1H), 4.11 (d, J = 7.5 Hz, 2H), 3.97 (s, 3H), 3.54 (t, J = 6.0 Hz, 2H), 2.12 (sext, J = 6.8 Hz, 1H), 1.88-1.77 (m, 2H), 1.60 (t, J = 6.5 Hz, 2H), 1.27 (s, 3H), 0.76 (d, J = 6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.2, 142.8, 139.5, 136.4, 133.6, 126.9, 126.4, 124.9, 124.5, 122.4, 119.5, 116.9, 114.8, 114.4, 111.1,

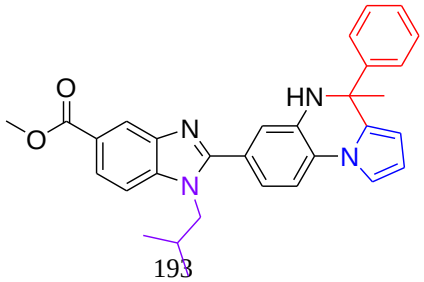
110.6, 104.2, 63.1, 54.6, 52.5, 39.4, 30.129.3, 28.2, 28.1, 20.4; MS (EI) *m/z*: 454 (M^+); HRMS (EI) calcd for: $C_{28}H_{30}N_4O_2$: m/z 454.2369. Found 454.2366; IR (cm^{-1}, KBr): 2925, 1712, 1612, 1500, 1294.

Methyl 1-isobutyl-2-(10-phenyl-15b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*c*]quinoxalin-7-yl)-1*H*-benzimidazole-5-carboxylate 16.



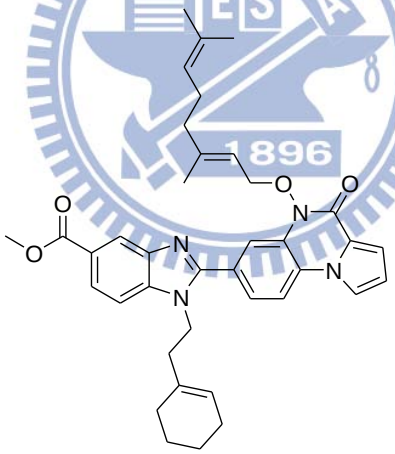
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, *J* = 1.3 Hz, 1H), 7.95 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.87 (d, *J* = 1.1 Hz, 1H), 7.85 (s, 1H), 7.48-7.39 (m, 6H), 7.29-7.24 (m, 4H), 7.17-7.15 (m, 2H), 6.95 (t, *J* = 7.1 Hz, 2H), 6.59 (t, *J* = 3.2 Hz, 1H), 6.53 (d, *J* = 1.4 Hz, 1H), 6.42 (d, *J* = 3.2 Hz, 1H), 5.71 (s, 1H), 3.93 (s, 3H), 3.46 (dd, *J* = 14.3, 6.4 Hz, 1H), 3.20 (dd, *J* = 14.3, 8.5 Hz, 1H), 1.74 (m, 1H), 0.52 (d, *J* = 6.7 Hz, 3H), 0.39 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 155.9, 143.0, 142.8, 130.2, 135.9, 133.6, 132.8, 132.7, 129.7, 129.5, 128.6, 128.2, 127.9, 126.5, 125.5, 124.8, 124.7, 124.3, 124.0, 122.5, 122.3, 119.9, 118.0, 115.7, 115.3, 111.6, 110.4, 109.0, 57.3, 52.5, 51.5, 30.1, 28.9, 20.6, 19.9; MS (ESI) *m/z*: 577(MH^+); HRMS (EI) calcd for: $C_{38}H_{32}N_4O_2$: m/z 576.2525. Found 576.2529; IR (cm^{-1}, KBr): 2954, 1712, 1610, 1486, 1292.

Methyl 1-isobutyl-2-(4-methyl-4-phenyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1*H*-benzimidazole-5-carboxylate 17.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.33-7.27 (m, 3H), 7.24 (t, *J* = 2.9 Hz, 1H), 7.20-7.12 (m, 3H), 7.07 (d, *J* = 8.6 Hz, 1H), 6.42 (t, *J* = 2.9 Hz, 1H), 6.15 (t, *J* = 1.4 Hz, 1H), 4.14 (d, *J* = 7.2 Hz, 2H), 3.97 (s, 3H), 2.14 (sext, *J* = 6.6 Hz, 1H), 1.94 (s, 3H), 0.74 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.0, 146.3, 142.8, 139.5, 136.3, 133.6, 128.9, 128.7, 127.4, 127.2, 126.9, 125.9, 124.8, 124.6, 122.5, 120.3, 117.3, 115.1, 115.0, 111.2, 110.5, 105.6, 57.5, 52.6, 34.3, 25.9, 25.3, 20.5; MS (ESI) *m/z*: 491(MH^+); HRMS (EI) calcd for: $C_{31}H_{30}N_4O_2$: m/z 490.2369. Found 490.2375; IR (cm^{-1}, KBr): 3322, 2956, 1712, 1616, 1496, 1295.

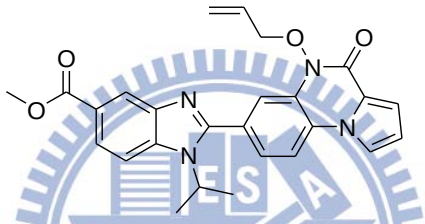
Methyl 1-[2-(1-cyclohexenyl)ethyl]-2-(5-[(2*Z*)-3,7-dimethyl-2,6-octadienyl]oxy-4-oxo-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1*H*-benzo[*d*]imidazole-5-carboxylate (21a)



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, *J* = 1.3 Hz, 1H), 8.07 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.95 (d, *J* = 1.5 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.73 (dd, *J* = 2.7, 1.4 Hz, 1H), 7.67 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.34 (dd, *J* = 3.9, 1.3 Hz, 1H), 6.73 (dd, *J* = 2.8, 1.4 Hz, 1H), 5.58 (t, *J* =7.5 Hz, 1H), 5.27 (m, 1H), 5.03 (m, 1H), 4.86 (d, *J* = 7.5 Hz, 2H), 4.38 (t, *J* = 6.9 Hz, 2H), 3.97 (s, 3H), 2.43 (t, *J* = 7.3 Hz, 2H), 2.04-2.03 (m,

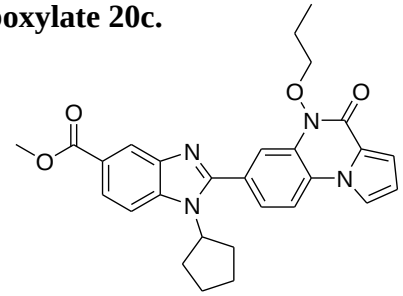
3H), 1.80-1.77 (m, 7H), 1.63 (m, 3H), 1.54 (m, 2H), 1.51-1.45 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ168.0, 154.5, 152.5, 147.7, 143.0, 139.4, 133.2, 132.3, 129.6, 128.0, 125.3, 125.2, 125.0, 124.9, 124.1, 124.0, 123.9, 122.7, 117.4, 116.4, 115.4, 115.0, 114.4, 114.3, 110.4, 72.6, 52.5, 44.5, 39.6, 37.6, 28.7, 26.7, 26.0, 25.5, 23.0, 22.3, 18.0, 17.2; MS (ESI) *m/z*: 619 (MH^+); HRMS (ESI, m/z) calcd for $C_{38}H_{43}N_4O_4$: *m/z* 619.3284; Found 619.3280 (M+H); IR(cm^{-1}, KBr): 2925, 1712, 1673, 1295.

Methyl 2-[5-(allyloxy)-4-oxo-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl]-1-isopropyl-1*H*-benzo[*d*]imidazole-5-carboxylate 21b.



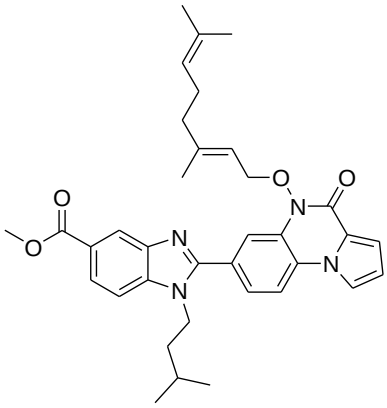
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, *J* = 1.3 Hz, 1H), 8.02 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.85 (d, *J* =8.3, 1H), 7.82 (d, *J* = 1.5 Hz 1H), 7.72 (dd, *J* = 2.6, 1.2 Hz 1H), 7.67 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.59 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.31 (dd, *J* = 3.9, 1.3 Hz, 1H), 6.71 (dd, *J* = 3.8, 2.9 Hz, 1H), 6.15 (m, 1H), 5.34 (d, *J* = 12.5 Hz, 2H), 5.20 (m, 1H), 5.01 (m, 1H), 4.41 (t, *J* = 7.2 Hz, 2H), 3.99 (s, 3H), 2.37 (t, *J* = 7.2 Hz, 2H), 1.84-1.77 (m, 9H), 1.45 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 155.5, 154.5, 139.2, 133.2, 132.1, 130.2, 125.6, 125.3, 125.1, 125.0, 124.2, 123.5, 122.6, 117.9, 117.7, 117.0, 115.4, 114.5, 114.2, 110.5, 52.6, 44.3, 44.0, 38.1, 28.7, 25.5, 22.9, 22.3; MS (ESI) *m/z*: 457 (MH^+); HRMS (ESI, m/z) calcd for $C_{26}H_{29}N_4O_4$: *m/z* 457.1876; Found 457.1874 (M+H); IR(cm^{-1}, KBr): 2933, 1718, 1608, 1297.

Methyl 1-cyclopentyl-2-(4-oxo-5-propoxy-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1*H*-benzo[*d*]imidazole-5-carboxylate 20c.



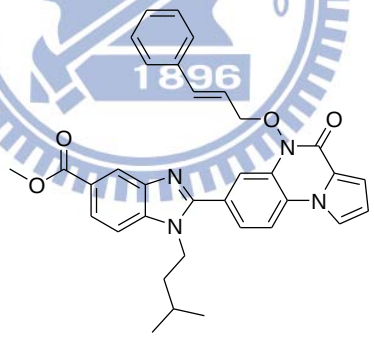
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 1.3 Hz, 1H), 8.03 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.88-7.84 (m, 2H), 7.73 (m, 1H), 7.62 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.34 (dd, *J* = 3.9, 1.1 Hz, 1H), 6.73 (dd, *J* = 6.4, 2.8 Hz, 1H), 4.99 (m, 1H), 4.29 (t, *J* = 7.0 Hz, 1H), 3.98 (s, 3H), 2.38-2.33 (m, 2H), 2.17-2.10 (m, 4H), 1.96-1.85 (m, 3H),1.82-1.77 (m, 3H), 1.12-1.04 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 155.1, 152.3, 143.8, 136.9, 131.8, 130.2, 129.3, 128.4, 128.0, 125.2, 125.0, 124.4, 124.2, 123.7, 123.2, 117.3, 116.7, ; MS (ESI) *m/z*: 485 (MH^+); HRMS (ESI, m/z) calcd for $C_{28}H_{29}N_4O_4$: *m/z* 485.2189; Found 485.2187 (M+H); IR(cm^{-1}, KBr): 2956, 1716, 1670, 1218.

Methyl 2-(5-[(2*Z*)-3,7-dimethyl-2,6-octadienyl]oxy-4-oxo-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1-isopentyl-1*H*-benzo[*d*]imidazole-5-carboxylate 21d.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 1.4 Hz, 1H), 8.08 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.94 (d, *J* = 1.4 Hz, 1H), 7.84 (d, *J* = 8.6 Hz, 1H), 7.73(m,1H), 7.67 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.35 (dd, *J* = 3.8, 1.1 Hz, 1H), 6.74 (dd, *J* = 3.8 Hz, 1H), 5.58(t, *J* = 7.6 Hz,1H) 5.03 (m, 1H), 4.85 (d, *J* = 7.6 Hz, 1H), 4.27 (t, *J* = 8.1 Hz, 2H), 3.95(s, 3H), 2.05-2.00 (m, 5H), 1.81 (m, 4H), 1.77 (m, 2H),1.63 (m, 3H), 1.60 (m, 1H), 1.50 (s, 3H), 0.92(d *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 154.4, 152.5, 147.7, 143.1, 139.3, 132.3, 129.6, 127.9, 125.2, 125.0, 124.9, 124.0, 123.9, 122.8, 117.4, 115.4, 115.0, 114.5, 114.3, 113.8, 113.6, 110.2, 72.6, 82.6, 44.0, 39.1, 26.7, 26.0, 22.7, 18.0, 17.2 ; MS (ESI) *m/z*: 581 (MH^+); HRMS (ESI, m/z) calcd for $C_{35}H_{41}N_4O_4$: *m/z* 581.3128; Found 581.3126 (M+H); IR(cm^{-1}, KBr): 2925, 1714, 1668, 1299.

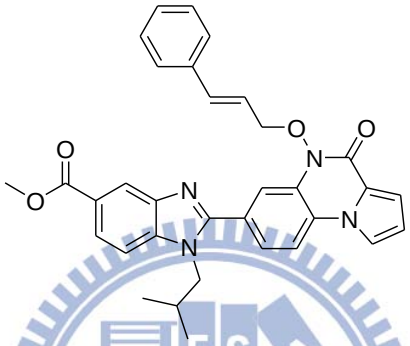
Methyl 1-isopentyl-2-(4-oxo-5-[(*Z*)-3-phenyl-2-propenyl]oxy-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1*H*-benzo[*d*]imidazole-5-carboxylate 21e.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, *J* = 1.1 Hz, 1H), 8.04 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.97 (dd, *J* = 1.7 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.70 (dd, *J* = 2.7, 1.4 Hz, 1H), 7.63 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 7.37-7.32 (m, 3H), 7.26-7.24 (m, 3H), 6.80 (dd, *J* =15.8 Hz, 1H), 6.71 (dd, *J* = 3.9, 2.9 Hz,1H) 6.52 (m, 1H), 4.98 (d, *J* = 6.9 Hz, 2H), 4.25 (t, *J* = 7.8 Hz, 2H), 3.93(s, 3H), 1.75-1.68 (m, 2H), 1.63-1.52 (m, 1H), 0.86 (d, *J* = 6.5 Hz, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 154.3, 152.5, 143.0, 139.3,

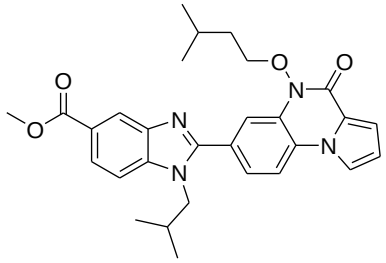
138.2, 136.1, 129.5, 129.0, 125.0, 128.9, 127.9, 127.8, 125.2, 125.0, 124.1, 123.8, 122.7, 121.5, 117.6, 115.5, 115.0, 114.5, 110.3, 52.6, 44.1, 39.0, 26.4, 22.7; MS (ESI) *m/z*: 561 (MH^+); HRMS (ESI, m/z) calcd for $C_{34}H_{33}N_4O_4$: *m/z* 561.2502; Found 561.2499 (M+H); IR(cm^{-1}, KBr): 2958, 1712, 1662, 1367.

Methyl 1-isobutyl-2-(4-oxo-5-[(*Z*)-3-phenyl-2-propenyl]oxy-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1*H*-benzo[*d*]imidazole-5-carboxylate 21f.



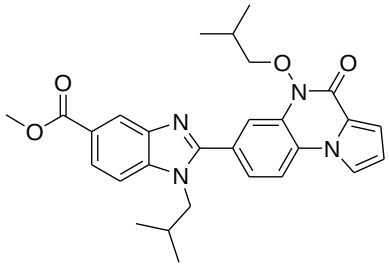
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.07 (d, *J* = 9.0 Hz, 1H), 7.90 (s, 1H), 7.84 (m, 1H), 7.74 (dd, *J* = 2.8, 1.4 Hz, 1H), 7.67 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 1H), 7.41-7.37 (m, 3H), 7.33-7.28 (m, 2H), 6.82 (d, *J* =15.6 Hz, 1H), 6.76 (dd, *J* = 3.8, 2.8 Hz, 2H) 6.54 (m, 1H), 5.01 (d, *J* = 6.9 Hz, 2H), 4.14 (t, *J* = 7.5 Hz, 2H), 3.99 (s, 3H), 2.48 (m, 2H), 0.78 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 154.8, 152.5, 142.9, 139.6, 138.1, 136.2, 129.6, 129.1, 128.9, 128.5, 127.3, 126.8, 125.3, 125.2, 124.9, 124.1, 123.9, 123.6, 122.8, 121.5, 117.4, 115.4, 115.1, 114.6, 114.5, 110.8, 52.7, 52.5,29.5, 20.5; MS (ESI) *m/z*: 547 (MH^+); HRMS (ESI, m/z) calcd for $C_{33}H_{31}N_4O_4$: *m/z* 547.2345; Found 547.2342 (M+H); IR(cm^{-1}, KBr): 2927, 1714, 1668, 1297.

Methyl 1-isobutyl-2-[5-(isopentyloxy)-4-oxo-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl]-1*H*-benzo[*d*]imidazole-5-carboxylate 21g.



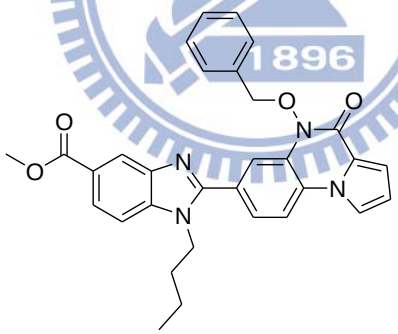
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.09 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.88-7.84 (m, 2H), 7.73 (dd, *J* = 2.7, 1.3 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.35 (d, *J* = 2.6 Hz, 1H), 6.76 (t, *J* =3.8 Hz, 1H), 4.35 (t, *J* = 7.0 Hz, 2H), 4.17 (dd, *J* = 7.6, 2.5 Hz, 2H), 3.99 (s, 3H), 2.17 (m, 2H), 1.80 (m, 1H), 1.03-0.98(m, 6H), 0.82-0.78 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 155.6, 155.1, 154.8, 152.3, 142.9, 139.5, 139.4,130.1, 129.3, 128.4, 128.1, 125.2, 124.9, 124.7, 124.0, 123.9, 123.8, 122.5, 122.7, 117.4, 116.7, 115.6, 115.5, 114.8, 114.4, 114.3, 110.7, 110.5, 52.6, 52.5, 40.3, 26.7, 25.5, 23.1, 23.0, 29.9, 20.4, 20.3 ; MS (ESI) *m/z*: 501 (MH^+); HRMS (ESI, m/z) calcd for $C_{29}H_{33}N_4O_4$: *m/z* 501.2502; Found 501.2506 (M+H); IR(cm^{-1}, KBr): 2958, 1712, 1658, 1295.

Methyl 2-(5-isobutoxy-4-oxo-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1-isobutyl-1*H*-benzo[*d*]imidazole-5-carboxylate 21h.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, *J* = 1.2 Hz, 1H), 8.08 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.89 (d, *J* = 1.2 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.74 (t, *J* = 1.3 Hz, 1H), 7.65 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.47 (6, *J* = 8.6 Hz, 1H), 7.34 (dd, *J* = 3.9, 1.2 Hz, 1H), 6.75(t, *J* = 2.7 Hz, 1H), 4.17 (d, *J* = 7.6 Hz, 2H), 4.09 (d, *J* = 6.7 Hz, 2H), 3.96 (s, 3H), 2.29 (m, 1H), 2.15 (m, 1H), 1.12 (d, *J* = 6.7 Hz, 6H), 0.79 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 154.8, 152.2, 145.4, 143.0, 139.5, 129.3, 128.5, 125.2, 125.1, 124.9, 124.8, 124.2, 123.2, 122.9, 117.3, 115.5, 114.7, 114.4, 114.3, 110.7, 109.9, 53.2, 52.7, 52.6, 52.5, 29.6, 29.4, 28.1, 20.5, 20.4, 19.7; MS (ESI) *m/z*: 487 (MH^+); HRMS (ESI, m/z) calcd for $C_{28}H_{31}N_4O_4$: *m/z* 487.2345; Found 487.2342 (M+H); IR(cm^{-1}, KBr): 2954, 1718, 1668, 1297.

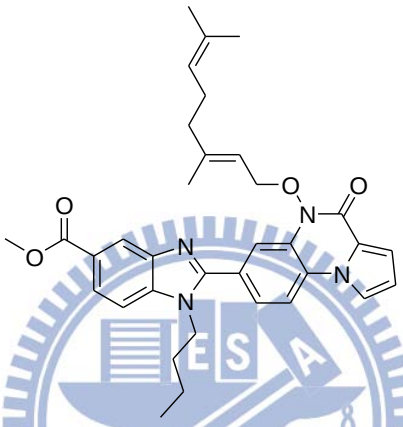
Methyl 2-[5-(benzyloxy)-4-oxo-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl]-1-butyl-1*H*-benzo[*d*]imidazole-5-carboxylate 21i.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, *J* = 1.2 Hz, 1H), 8.09 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.90 (d, *J* = 1.5 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.75 (t, *J* = 1.4 Hz, 1H), 7.69 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.62 (d, *J* = 3.3 Hz, 1H), 7.61 (d, *J* = 1.7 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.40-7.38 (m, 4H), 6.77 (t, *J* = 7.6 Hz, 1H), 4.22 (t, *J* = 7.8 Hz, 2H), 3.97 (s, 3H), 1.83-1.73 (m, 2H), 1.30-1.21 (m, 2H), 0.79 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 154.4, 152.4, 143.1, 139.4, 133.9, 130.4, 129.5, 129.2, 128.1, 125.2,

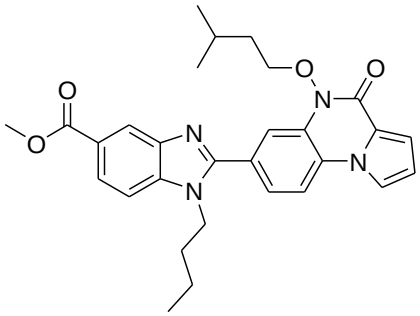
124.9, 124.1, 124.0, 122.8, 117.4, 115.5, 114.8, 11454, 110.3, 52.6, 45.3, 32.3, 20.3, 13.8; MS (ESI) *m/z*: 521 (MH^+); HRMS (ESI, m/z) calcd for $C_{31}H_{29}N_4O_4$: *m/z* 521.2189; Found 521.2187 (M+H); IR(cm^{-1}, KBr): 2954, 1716, 1671, 1299.

Methyl 1-butyl-2-(5-[(2*Z*)-3,7-dimethyl-2,6-octadienyl]oxy-4-oxo-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1*H*-benzo[*d*]imidazole-5-carboxylate 21j



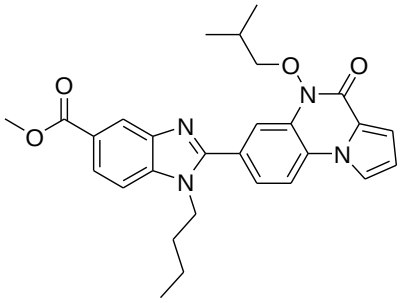
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 1.0 Hz, 1H), 8.07 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.93 (d, *J* = 1.7 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.68 (m, 1H), 7.56 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.33 (d, *J* = 3.9, 1.3 Hz, 1H), 6.73 (t, *J* = 2.9 Hz, 1H), 5.56 (m, 1H), 5.03 (m, 1H), 4.85 (d, *J* = 7.6 Hz, 2H), 4.29 (t, *J* = 7.6 Hz, 2H), 3.97 (s, 3H), 2.03 (d, *J* = 2.8 Hz, 4H), 1.81 (s, 3H), 1.63 (s, 3H), 1.53 (s, 3H), 1.39-1.26 (m, 2H), 0.90 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 154.3, 152.5, 147.7, 143.1, 139.4, 129.6, 127.9, 125.2, 125.0, 124.9, 124.1, 124.0, 123.9, 122.8, 117.4, 116.4, 115.4, 114.9, 114.4, 114.3, 110.3, 72.6, 52.6, 45.4, 40.1, 32.4, 26.7, 26.0, 20.4, 18.0, 17.2, 13.9; MS (ESI) *m/z*: 567 (MH^+); HRMS (ESI, m/z) calcd for $C_{34}H_{39}N_4O_4$: *m/z* 567.2971; Found 567.2973 (M+H); IR(cm^{-1}, KBr): 2925, 1718, 1664, 1297.

Methyl 1-butyl-2-[5-(isopentyloxy)-4-oxo-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl]-1*H*-benzo[*d*]imidazole-5-carboxylate 21k.



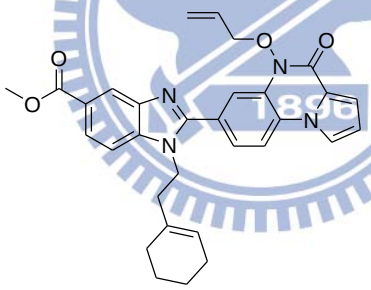
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 1.2 Hz, 1H), 8.09 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.89-7.84 (m, 2H), 7.73 (m, 1H), 7.68 (d, *J* = 8.5, 1.7 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.34 (dd, *J* = 3.8, 2.7 Hz, 1H), 6.75 (q, *J* = 3.1 Hz, 1H), 4.37-4.28 (m, 4H), 3.98 (s, 3H), 1.91-1.78 (m, 6H), 1.35-1.30 (m, 2H), 1.03-1.00 (m, 6H), 0.94-0.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 154.5, 152.3, 143.1, 139.3, 129.6, 127.9, 125.2, 125.0, 124.9, 124.1, 124.0, 123.9, 122.8, 117.4, 116.4, 115.4, 114.9, 114.4, 114.3, 110.3, 72.6, 52.6, 45.4, 40.1, 32.4, 26.7, 26.0, 20.4, 18.0, 17.2, 13.9; MS (ESI) *m/z*: 501 (MH^+); HRMS (ESI, m/z) calcd for $C_{29}H_{33}N_4O_4$: *m/z* 501.2502; Found 501.2500 (M+H); IR(cm^{-1}, KBr): 2954, 1714, 1670, 1295.

Methyl 1-butyl-2-(5-isobutoxy-4-oxo-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl)-1*H*-benzo[*d*]imidazole-5-carboxylate 21l.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.07 (d, *J* = 9.0 Hz, 1H), 7.90 (s, 1H), 7.84 (m, 1H), 7.72 (s, 1H), 7.60 (m, 1H), 7.43 (d, *J* = 12 Hz, 1H), 7.32 (s, 1H), 7.28 (s, 1H), 6.73 (s, 1H), 4.30 (t, *J* = 6.0 Hz, 2H) 4.12 (d, *J* = 9 Hz, 1H), 3.97 (s, 3H), 2.06 (m, 1H), 1.84 (t, *J* = 6.0 Hz, 2H), 1.35-1.26 (m, 2H), 1.12(d, *J* = 6.0 Hz, 2H), 1.02 (d, *J* = 6.0 Hz, 2H), 0.78 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 154.5, 152.2, 143.0, 139.3, 125.2, 125.0, 124.9, 124.2, 124.0, 123.2, 117.7, 117.4, 116.7, 115.5, 114.6, 114.4, 114.3, 113.9, 52.5, 45.5, 32.4, 28.2, 20.5, 19.6, 13.9, MS (ESI) *m/z*: 487 (MH^+); HRMS (ESI, m/z) calcd for $C_{28}H_{31}N_4O_4$: *m/z* 487.2345; Found 487.2342 (M+H); IR(cm^{-1}, KBr): 2929, 1718, 1660, 1297.

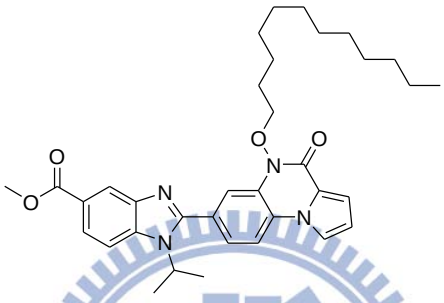
Methyl 2-[5-(allyloxy)-4-oxo-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl]-1-[2-(1-cyclohexenyl)ethyl]-1*H*-benzo[*d*]imidazole-5-carboxylate 21m.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 1.4 Hz, 1H), 8.09 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.76 (dd, *J* = 2.8, 1.4 Hz, 1H), 7.68 (d, *J* = 1.4 Hz, 1H), 7.64 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 1H), 7.33 (dd, *J* = 3.9, 1.3 Hz, 1H), 6.77 (dd, *J* = 3.9, 2.8 Hz, 1H), 6.00 (m, 1H), 5.34 (d, *J* = 12.5 Hz, 2H), 5.20 (d, *J* = 4.2 Hz 1H), 5.01 (m, 1H), 4.41 (t, *J* = 7.2 Hz, 2H), 3.99 (s, 3H), 2.37 (t, *J* = 7.2 Hz, 2H), 1.84-1.77 (m, 6H), 1.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 155.5, 154.5, 139.2, 133.2, 132.1, 130.2, 125.6, 125.3, 125.1, 125.0, 124.2, 123.5, 122.6, 117.9, 117.7, 117.0,

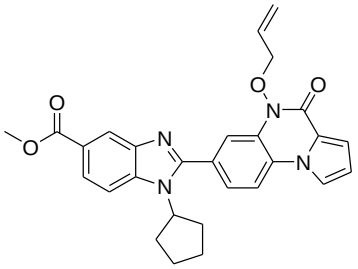
115.4, 114.5, 114.2, 110.5, 52.6, 44.3, 44.0, 38.1, 28.7, 25.5, 22.9, 22.3; MS (ESI) *m/z*: 507 (MH^+); HRMS (ESI, m/z) calcd for $C_{31}H_{31}N_4O_4$: *m/z* 507.2396; Found 507.2394 (M+H); IR(cm^{-1}, KBr): 2923, 1714, 1643, 1378.

Methyl 2-[5-(dodecyloxy)-4-oxo-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl]-1-(propan-2-yl)-1*H*-benzimidazole-5-carboxylate



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, *J* = 1.0 Hz, 1H), 8.06 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.86 (d, *J* =8.4 Hz, 1H), 7.72 (t, *J* = 1.3 Hz 1H), 7.68 (s, 1H), 7.64 (s, 1H), 7.53 (d, *J* = 8.4, 1.8 Hz, 1H), 7.28 (dd, *J* = 2.5, 1.5 Hz, 1H), 6.73 (t, *J* = 2.9 Hz, 1H), 4.93 (m, 1H), 4.31 (t, *J* = 7.2 Hz, 2H), 3.98 (s, 3H), 1.73 (d, *J* =6.9 Hz, 9H), 1.46-1.41 (m, 2H), 1.26-1.22 (m, 20H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 155.6, 154.3, 137.0, 130.3, 127.3, 125.8, 125.2, 124.7, 124.1, 123.7, 122.7, 117.4, 116.7, 115.6, 114,4, 113.8, 112.5, 49.9, 42.0, 32.3, 30.0, 29.9, 29.8, 29.7, 23.1, 21.9; MS (ESI) *m/z*: 569 (MH^+); HRMS (ESI, m/z) calcd for $C_{35}H_{45}N_4O_4$: *m/z* 569.3491; Found 569.3488 (M+H); IR(cm^{-1}, KBr): 2925, 1714, 1656, 1295.

Methyl 1-cyclopentyl-2-[4-oxo-5-(prop-2-en-1-yloxy)-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-7-yl]-1*H*-benzimidazole-5-carboxylate



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, *J* = 1.3 Hz, 1H), 7.99 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.84 (d, *J* =8.6 Hz, 1H), 7.72 (dd, *J* = 2.5, 1.3 Hz 1H), 7.55 (s, 1H), 7.52 (d, *J* = 3.5 Hz, 1H), 7.27 (dd, *J* = 2.8, 1.3 Hz, 1H), 6.70 (t, *J* = 3.7 Hz, 1H), 5.99 (m, 1H), 5.19 (dd, *J* = 15.3, 10.6 Hz, 2H), 4.95 (t, *J* = 2.1 Hz, 3H), 4.90 (m,1H), 3.95 (s, 1H), 2.33-2.27 (m, 2H), 2.12-2.06 (m, 3H), 1.77-1.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 155.5, 155.1, 143.5, 136.8, 132.0, 130.0, 127.7, 125.0, 124.8, 124.4, 123.4, 122.9, 118.0, 117.3, 117.1, 115.5, 114.4, 114.1, 112.0, 58.3, 52.5, 43.9, 30.9, 25.5; MS (ESI) *m/z*: 467 (MH^+); HRMS (ESI, m/z) calcd for $C_{28}H_{27}N_4O_4$: *m/z* 467.2083; Found 467.2082 (M+H); IR(cm^{-1}, KBr): 2954, 1720, 1656, 1299.

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Chapter Three

Synthesis of Skeletally Diverse benzimidazole-imidazo[1,2-*a*]-pyridine via Ugi-Multicomponent Reaction in Neat Condition

3.0 Multicomponent Reactions

It has been perceived that a reaction which can easy to perform, give maximum yields, utilize readily available starting materials, be a one-pot reaction and be environmentally friendly is called the best chemical reaction. Very few reactions come close to attaining this ideality; however, multicomponent reactions are most excellent positioned to accomplish these criteria.[1] When more than two reactants combine in a sequential manner to give highly selective products that preserve majority of the atoms of the starting material by definition, these are called multicomponent reactions. Usually multicomponent reactions (MCRs) are highly convergent reactions as in Figure 3.0. They have very good bond forming capabilities, with high atom efficiency, and higher yields in comparison to a parallel multistep reaction.[2] Thus, there is a network of reaction equilibria, which all finally flow into an irreversible step yielding the product. The nature of multicomponent reaction conditions depends upon solvent, temperature, catalyst, concentration, the kind of starting materials and functional groups varies. Such considerations are of particular importance in connection with the design and discovery of novel MCRs. [3-4]

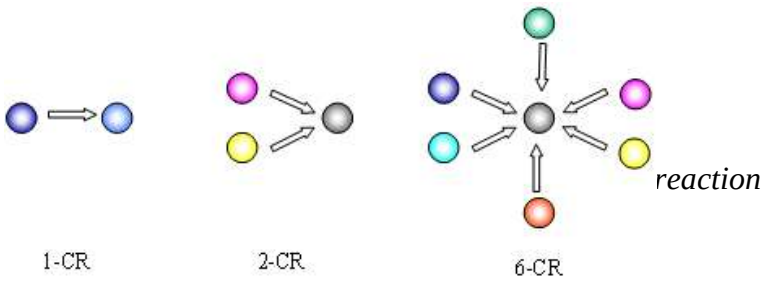


Figure 3.0 Courtesy from A. Dömling, *Org. Chem. Highlights* 2004, April 5.

3.1. History and Types Multicomponent Reactions

More than 150 years, the multicomponent reactions have been known to all. The Strecker amino acid synthesis in 1850 where α-amino acids could be derived from α-amino cyanides is the first multicomponent reaction. Isocyanide based MCRs are the most familiar among all other MCR. Since it is well known that the isocyanide is an extraordinary functional group which can take part reaction very easily so now a day's isocyanide based MCRs are most frequently used reaction. [5-6]

Examples of three component reactions:

- Strecker amino acid synthesis
- Biginelli reaction
- Mannich reaction
- Hantzsch pyridine synthesis
- Passerini reaction

Examples of four component reactions

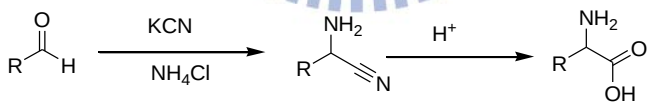
- Ugi reaction

3.2. Nature of multicomponent reaction

It has been observed that the exact nature of the multicomponent reaction is often difficult to assess, for more than three component multicomponent reactions, these reactions are more likely to involve a series of bimolecular reactions and finally provides the targeted molecules. Now a days MCR's are an important tool in new drug discovery.[7]

3.3. Strecker amino acid synthesis

Adolph Strecker derived the Strecker amino acid synthesis was first multicomponent reaction where amino acid was synthesized from an aldehyde (or ketone). In the presence of potassium cyanide the aldehyde is condensed with ammonium chloride to form an α-aminonitrile, which is subsequently hydrolyzed to give the desired amino-acid as shown in Scheme 3.0.



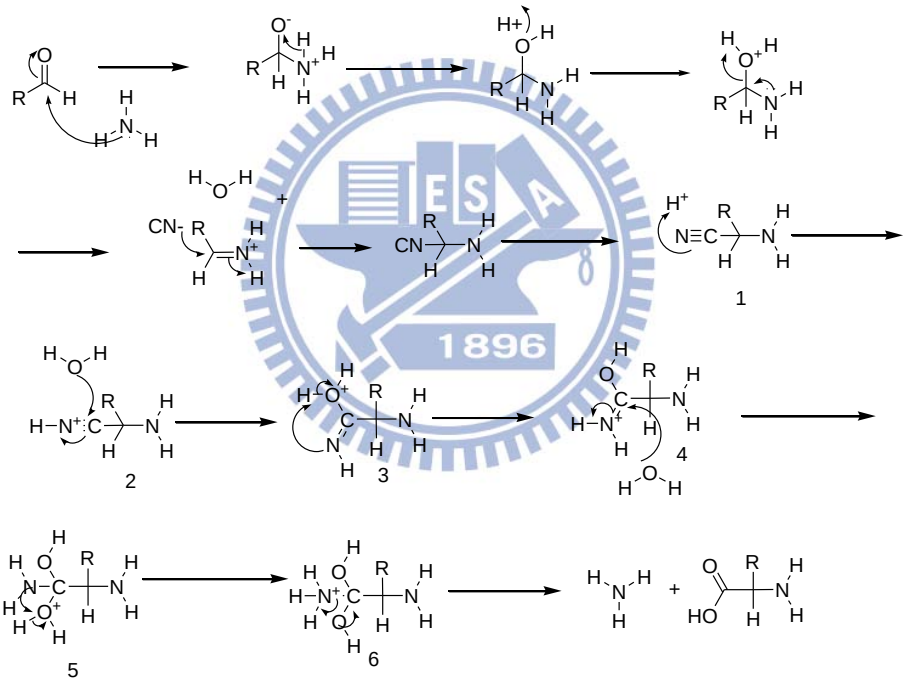
Scheme 3.0 Strecker amino acid synthesis.

Primary and secondary amines provides substituted amino acids where usage of ammonium salts gives unsubstituted amino acids. Likewise, α, α-disubstituted amino acids could be synthesized the usage of ketones, instead of aldehydes. The Adolph Strecker synthesized compound was the racemic α-amino nitriles but recently several

procedures has been developed to synthesized asymmetric α-amino nitriles using chiral auxiliarie or asymmetric catalysts.[8-11]

3.3.1. Reaction Mechanism

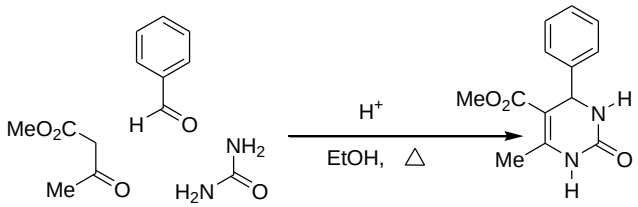
The reaction mechanism for this reaction is sketched below in scheme 3.1. The reaction mechanism involves the nucleophilic addition of ammonia to aldehyde to form iminium ion by elimination of water. Subsequently second nucleophilic addition of the cyanide ion forms the aminonitrile.



Scheme 3.1. Mechanism of strecker amino acid synthesis

3.4. Biginelli Reaction

The Biginelli reaction is a multiple-component chemical reaction where 3 starting material such as an active methylene compound, an aryl aldehyde, and urea in presence polar solvent provides 3,4-dihydropyrimidin-2(1*H*)-ones as provided in Scheme 3.2.

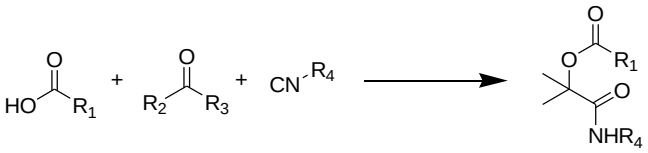


Scheme 3.2. Biginelli multicomponent reaction

Usually this reaction is catalyzed by differnet Brønsted acids and or by any type of Lewis acids such as boron trifluoride. The products of the Biginelli reaction, are the heterocyclic main scaffold Dihydropyrimidinones, are widely used in the pharmaceutical industry as calcium channel blockers, antihypertensive agents, and alpha-1-a-antagonists.[13-20]

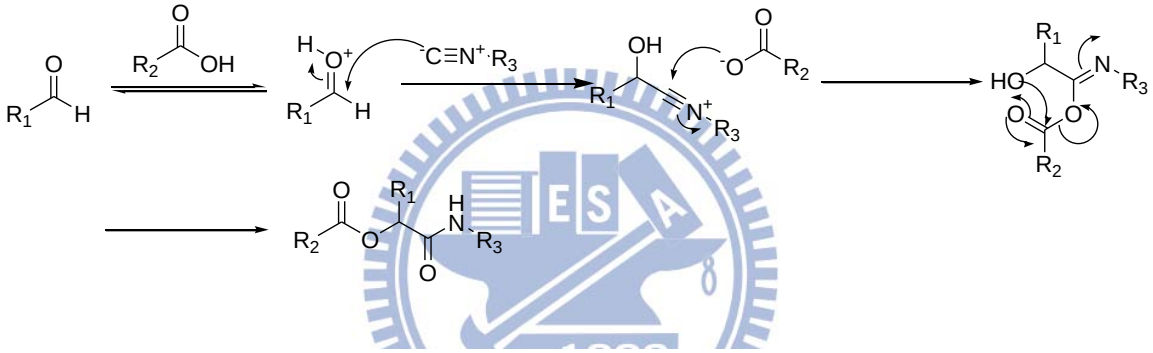
3.5. Passerini reation

Isocyanides has umpolung effect for which it can play a dual role as both nucleophile and electrophile. It can allow help to carry out the interesting multicomponent reactions to. Passerini Reaction is one of the first multicomponent reactions using isocyanides as the main starting material. To construct the α-acyloxy amide moiety the Passerini reaction is the main chemical reaction where an isocyanide, an aldehyde (or ketone), and a carboxylic acid react together in one pot manner as in Scheme 3.3.



Scheme 3.3. Passerini multicomponent reaction

The passerini multicomponent organic reaction was first discovered Mario Passerini 1921. Now a days this isocyanide based multi-component reactions are playing a central role in combinatorial chemistry.[21-23] The mchenism has been depicted as below in Scheme 3.4.

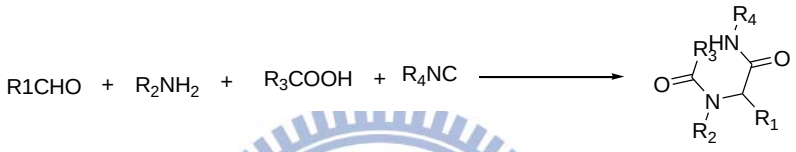


Scheme 3.4. Mechanism of passerini multicomponent reaction

In polar solvents such as methanol or water, the usually the reaction proceeds by the protonation of the carbonyl followed by nucleophilic addition of the isocyanide to give the nitrilium ion, addition of a carboxylate provide the intermediate then acyl group transfer and amide tautomerization provides the final product.[24-25]

3.6. Ugi Reaction

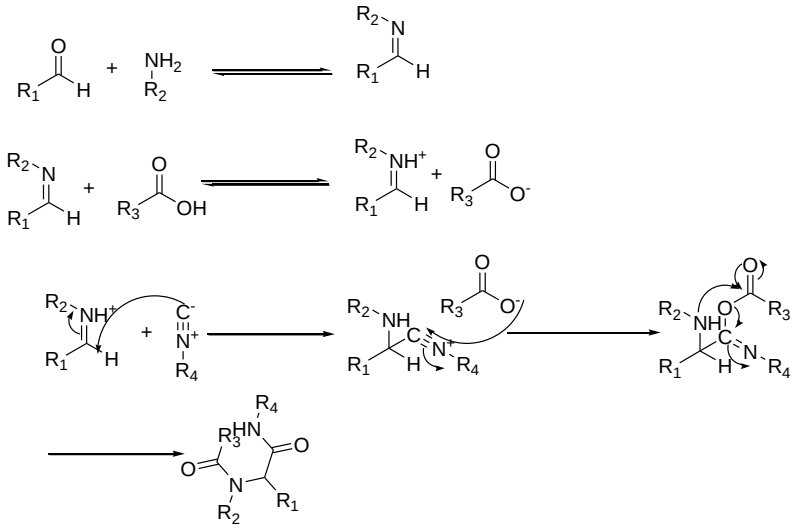
The Ugi four-component condensation (U-4CC) between an aldehyde, an amine, a carboxylic acid and an isocyanide allows the rapid preparation of α-aminoacyl amide derivatives as shown in Scheme 3.5. The Ugi Reaction products can exemplify a wide variety of substitution patterns, and constitute peptidomimetics that have potential pharmaceutical applications. This reaction is thus very important tool for generating heterocyclic compound libraries for screening purposes.



Scheme 3.5. Ugi multicomponent reaction.

3.6.1. Mechanism of the Ugi Reaction

The mechanism is believed to involve a prior formation of an imine by condensation of the amine with the aldehyde, followed by addition of the carboxylic acid oxygen and the imino carbon across the isocyanide carbon; the resulting acylated isoamide rearranges by acyl transfer to generate the final product in Scheme 3.6.[26-30]

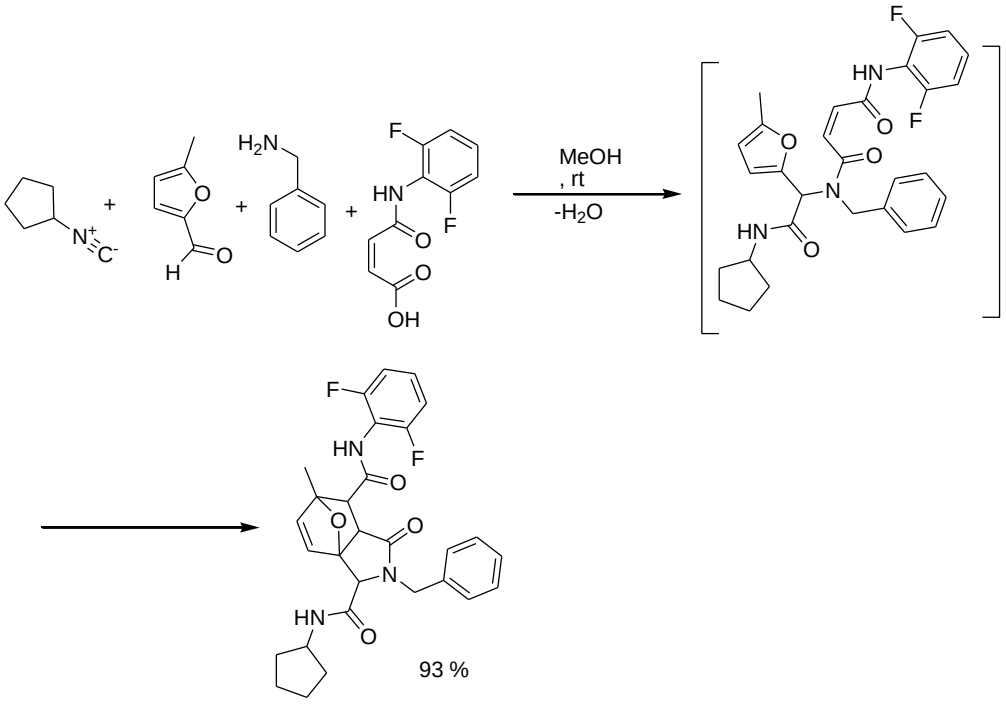


Scheme 3.6. Mechanism of Ugi multicomponent reaction.

The usage of bifunctional reaction components greatly increases the diversity of possible reaction products. Likewise, several combinations lead to structurally interesting products. The Ugi reaction has been applied in combination with an intramolecular Diels-Alder reaction in an extended multistep reaction.[31-35]

3.6.1. Ugi-Diels-Alder reaction

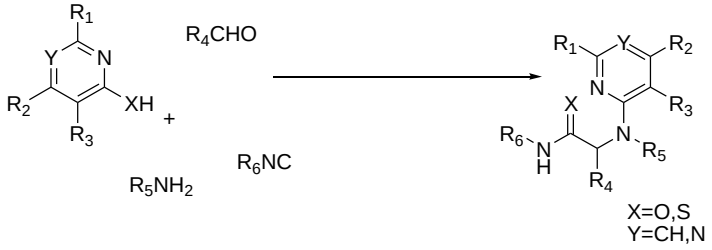
In the year 2006, Ivachtchenko *et. al.* has described the unexpected rearrangement of 2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1-one products of the tandem Ugi 4CC/ intramolecular Diels-Alder reaction in 85 % H_3PO_4 as in scheme 3.7.[36]



Scheme 3.7. Example of Ugi Diels-Alder reaction.

3.6.2. Ugi-Smiles reaction

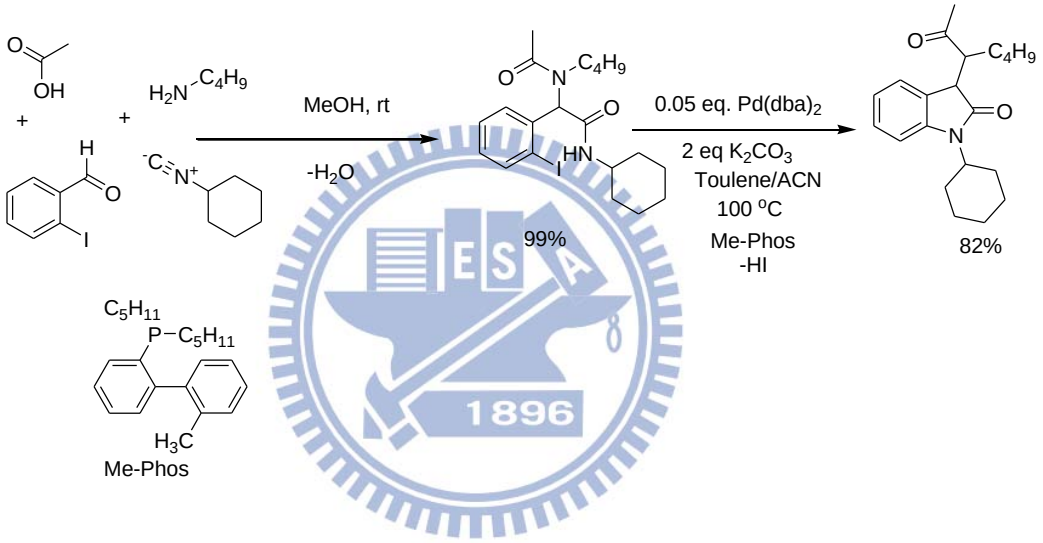
In the same year 2006, Oble *et. al*. has described new heterocyclic scaffolds synthesis prepared by the coupling of heteroaromatic phenols (pyridines, pyrimidines) with carbonyl compounds, amines, and isocyanides in Scheme 3.8. This transformation related to the Ugi reaction involves a Smiles rearrangement. [37]



Scheme 3.8. Example of Ugi-Smiles reaction.

3.6.3. Ugi-Buchwald-Hartwig reaction

A two-step sequence involving an Ugi four-component reaction (Ugi-4CR) and a palladium-catalyzed intramolecular amidation of aryl iodide has been developed for rapid access to functionalized oxindole in Scheme 3.9. Microwave heating was used to accelerate and to improve the efficiency of the intramolecular Buchwald Hartwig reaction.[38]

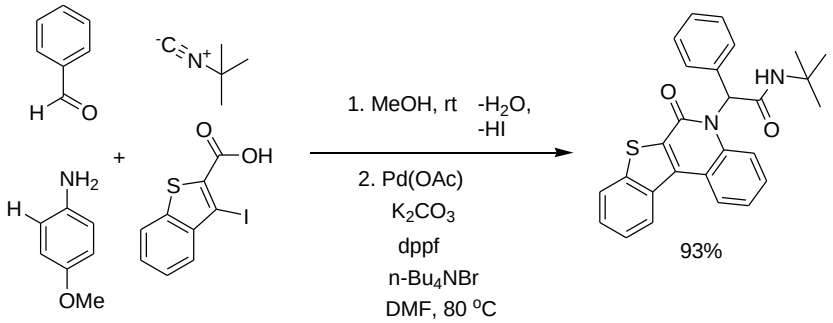


Scheme 3.9. Example of Ugi-Buchwald-Hartwig reaction.

3.6.4. Ugi-Heck reaction

In the same year 2006, Yang *et. a.l* has described two types of quinoline scaffolds which can be constructed in a combinatorial format via the Ugi four-component reaction (U-4CR) and Pd-catalyzed intramolecular arylation reaction. For this reaction they have taken commercially available starting material substituted benzaldehyde, different amine

and various isocyanide and ortho iodo substituted acid. In presence of polar solvent underwent ugi multicomponent reaction which after further heck coupling reaction provides quinoline scaffolds in Scheme 3.10.[39]



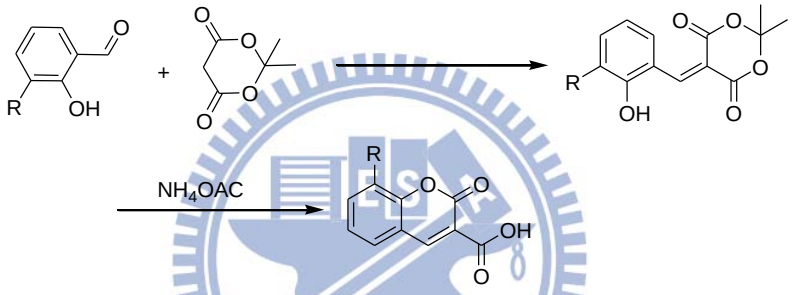
Scheme 3.10. Example of Ugi-Heck reaction.

3.7. Solvent-free synthesis

It is well known that evading the use of solvents in synthesis can reduce environmental contamination and even be more convenient than using solvent-based synthesis. As a society we are progressively more aware of the environmental impact of human activity, and accordingly of the need to develop cleaner and extra energy-efficient technologies. It has lengthy been recognised that the large-scale use of volatile organic solvents has significant inference for environmental pollution. Approaches to the problems accessible by organic solvents comprise the use of more benign solvents (especially water and supercritical CO_2), or solvents with negligible vapour pressures (ionic liquids). It has also been thought that 'the best solvent is no solvent'. In spite of the power of this announcement, our use and understanding of solvent-free synthesis, especially where

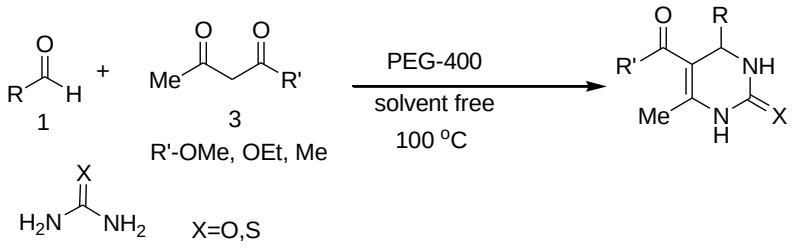
solid starting materials are concerned, has stay behind undeveloped in contrast to solvent based methods. The question normally asked when planning synthesis is still 'which solvent we could use?', and not 'do I require using a solvent?' As solvent-free synthesis turn into morewidely examined many people are likely to be impressed at the series of reactions, even among solid starting materials.[40-41]

In 2000, Scott *et. al.* has described the efficient synthesis of 3-Carboxycoumarins, an important class of biologically active compounds, without use volatile organic solvents as shown in Scheme 3. 11.



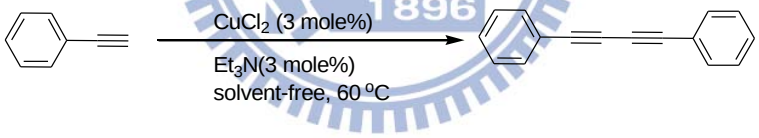
Scheme 3.11. Solvent-free synthesis of coumarin.

In the year 2007, Sain *et. al.* has described PEG-assisted solvent and catalyst free synthesis of 3,4-dihydropyrimidinones under mild and neutral reaction conditions . They use of PEG-400 as a promoter for the synthesis of 3,4-dihydropyrimidinones under mild and neutral solvent-free conditions in Scheme 3.12.[43]



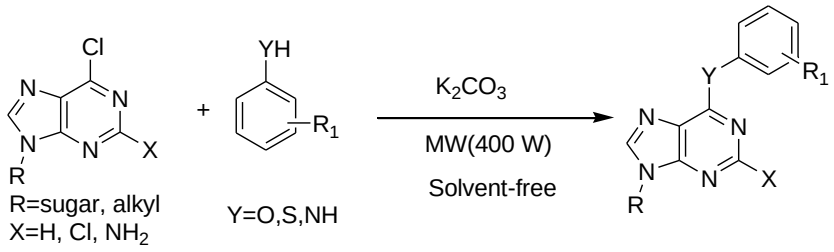
Scheme 3.12. Solvent free synthesis of 3,4-dihydropyrimidinones.

In the year 2010, Chen *et. al.* has developed an environmentally friendly and highly efficient method for copper-catalyzed cycloaddition of organic azides and terminal alkynes under solvent-free conditions. The protocol uses the inexpensive and easy-to-prepare $Cu(PPh_3)_2NO_3$ complex as the catalyst for terminal alkyne azide reaction.[44] In the same year 2010, Chen *et. al.* had developed an environmentally friendly, efficient method for transforming terminal acetylenes into 1,3-diynes based on catalytic amounts of a Cu(II) salt and base under solvent free conditions. The developed process match to the principles of 'green' chemistry and attend to the shortage of such methods for the synthesis of 1,3-diynes. The reaction is quite broad and results in good yields. Interestingly, the system also permit the synthesis of unsymmetric 1,3-diynes by cross-coupling of two different terminal alkynes as shown in Scheme 3.13.[45]



Scheme 3.13. Solvent free synthesis of glassier reaction.

In the same year, Guo *et. al.* has developed an efficient method for the synthesis of C_6-functionalized purine nucleosides *via* the direct nucleophilic substitution reaction of 6-chloropurine derivatives with various mild nucleophiles. The eco-friendly solvent-free process provides good to high isolated yields within a short reaction time (5 min) under microwave irradiated conditions in scheme 3.14.[46]



Scheme 3.14 Solvent free synthesis of SnAr reaction.

3.8. Benzimidazole-Imidazo[1,2-*a*]pyridine, its importance and synthesis

In the annals heterocyclic chemistry, discovering a novel methodology for the synthesis of novel biherocyclic compounds is a great deal of research. Due to enrichment in screening methods in the pharmaceutical industry, there is a constant requirement for novel methods that can be conceded out under simpler, milder, or more effective conditions. Since modern drug discovery depends heavily on the use of the rapid assembly of complex, drug like molecular frameworks, the multi component condensation (MCC) reactions are now a days a useful reaction to prepare such kind of molecular framework.[47-50]

To construct large number of nitrogen substituted libraries of highly substituted diversity point, now a days Ugi multicomponent reactions (MCRs) have become a powerful tools. Ugi MCR in which three or more substrates react in a one-pot procedure to assemble the complex molecules in one pot manner has become popular choice in academia and industry. In modern organic and combinatorial chemistry the multi-component Ugi reaction belongs to the most interesting diversity-generating reactions. One of the most

important applications of the Ugi reaction is the synthesis of the different type of heterocycles.[51-53] In this respect, methodologies leading to the synthesis of nitrogen-bridgehead heterocycles containing an imidazole ring are particularly appealing because this moiety is a common structural motif in biologically active compounds produced by nature. Imidazo[1,2-*a*]pyridine derivatives are probably the most widely used heterocyclic system from the bridged-imidazole group and form the framework of marketed drugs like Zolpidem, Olprinone, and Divalpon, as well as other pharmacologically important molecules.[54-57]

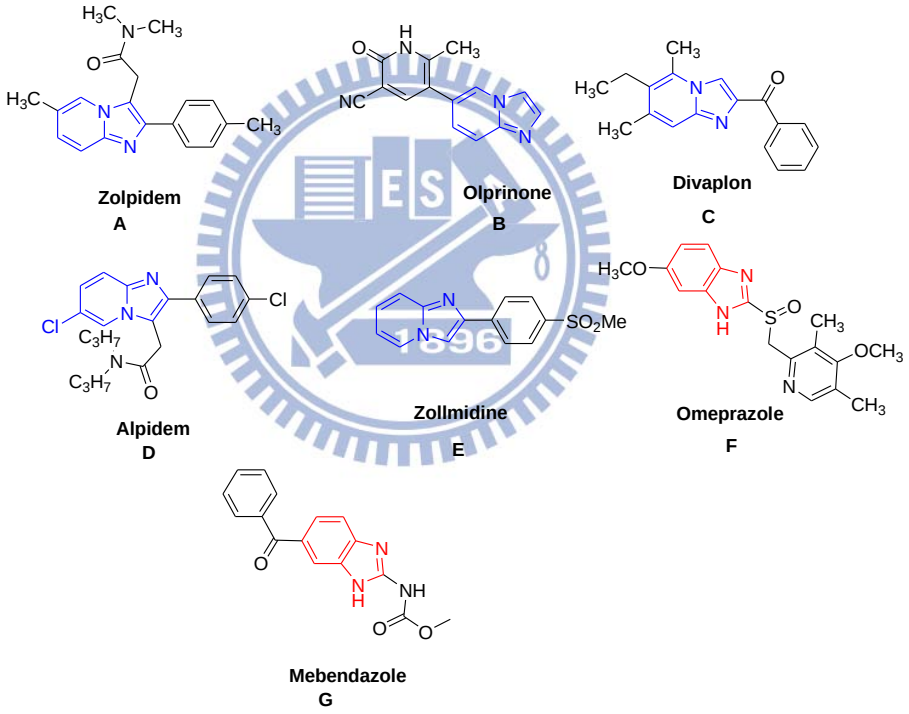
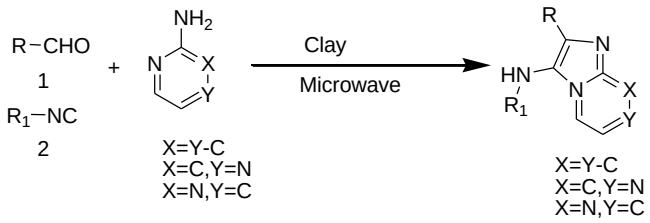


Figure 3.1. Representative examples of biologically active Imidazo[1,2-*a*]pyridine and benzimidazole compound.

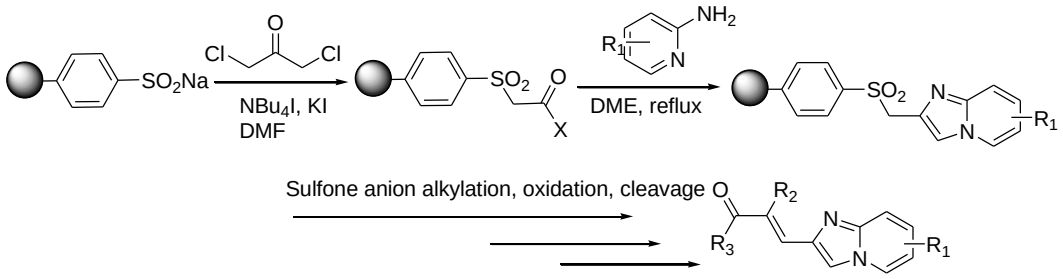
3.9. Chemical methods for synthesizing imidazo[1,2-a]pyridines

For the first time in the 1999, Verma *et. al.* has described the efficient synthesis imidazo[1,2-a] annulated pyridines, pyrazines and pyrimidines derivaties. A rapid one-pot solvent-free synthesis of imidazo[1,2-a] annulated pyridines, pyrazines and pyrimidines has been described in the presence of recyclable montmorillonite K-10 clay under microwave irradiation in Scheme 3.15.[58]



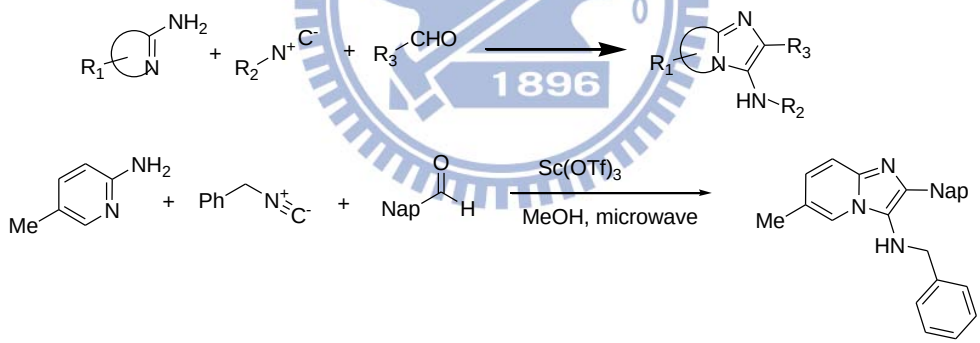
Scheme 3.15. Solvent free synthesis of imidazo[1,2-a] annulated pyridines, pyrazines and pyrimidines derivaties by Verma *et al.*

In the year 2002, Lam *et. al.* has described the preparation imidazo[1,2-a]pyridine library on a solid support. A sulfone linker has been used as support to carry out all the reactions. The Key steps in the solid-phase synthetic procedure involves (i) alpha-haloketone resin development by sulfinate-sulfone alkylation by 1,3 dichloropropane 2 one, (ii) imidazo[1,2-a]pyridine ring construction by treatment with 2-aminopyridine, (iii) sulfone anion alkylation, and (iv) traceless product release by oxidation-elimination in Scheme 3.16.[59]



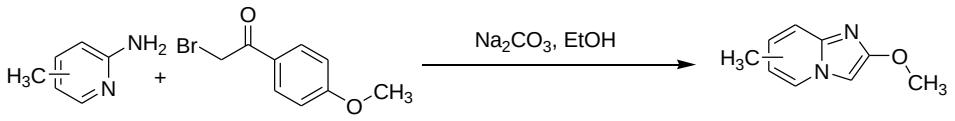
Scheme 3.16. Preparation imidazo[1,2-a]pyridine library on a solid support

In the year 2003, Ireland *et. al.* has described the Ugi multicomponent reaction substituted amino pyridine moiety various isocynide and different aldehyde. A variety of fused 3-aminoimidazoles has been synthesised by a microwave assisted Ugi three-component coupling (3CC) reaction catalysed by scandium triflate in methanol as solvent in Scheme 3.17.[60]



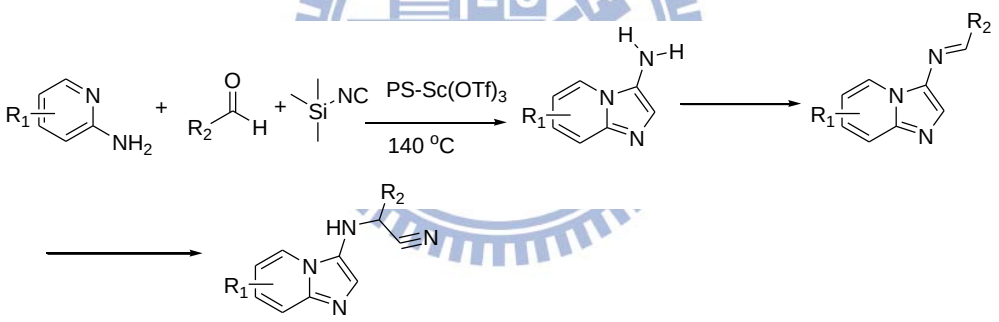
Scheme 3.17. Preparation imidazo[1,2-a]pyridine library by Ireland *et. al.* .

In the same year 2003, Zhuang *et. al.* has described the efficient synthesis of imidazo[1,2-*a*]pyridine derivatives using 2 amino pyridine and substituted 2-bromo pyridine. The reaction has been carried out in presence of sodium carbonate as a base in ethanol solvent under refluxing condition as shown in Scheme 3.18.[61]



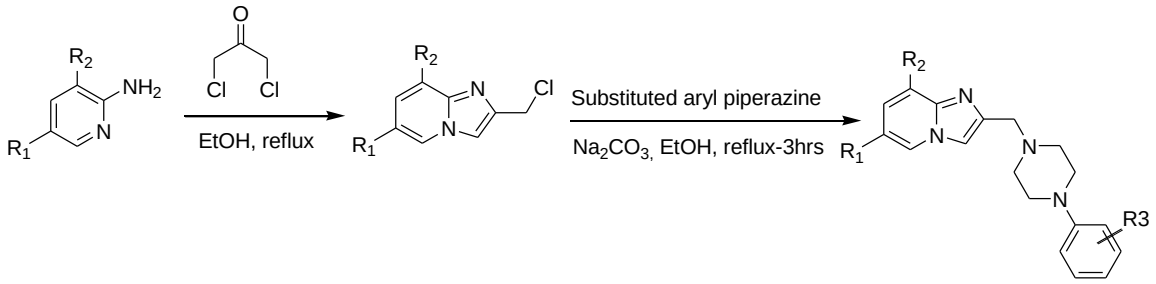
Scheme 3.18. Zhuang *et. al*. methods for the synthesis of imidazo[1,2-a]pyridine library

In the year 2006, Schwerkoske *et.al.* has described a novel one step solution phase synthesis of an array of 3-aminoimidazo[1,2-a]pyridines. In this work they have modified the reaction scheme. Instead of taking different isocyanide they used trimethylsilylcyanide (TMSCN) as starting material. The desired product were obtaind by reactions with mixing alpha-amino-pyridine, aldehyde and trimethylsilylcyanide (TMSCN) in methanol catalyzed by scandium triflate as shown in Scheme 3.19.[62]



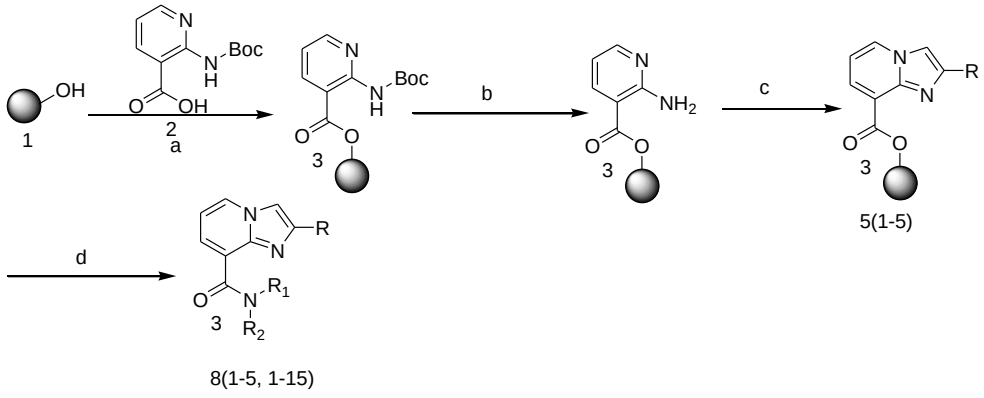
Scheme 3.19. Preparation imidazo[1,2-a]pyridine library by Masquelin *et. al.*

In the year 2006, Gueiffier *et. a.l* has described the synthesis of novel 2-[(4-phenylpiperazin-1-yl)methyl]imidazoazines in scheme 3.20. For this reaction, they have taken substituted 2-amino pyridine and 1,3 dichloropropane 2 one in ethanol solvent under refluxing condition. Further they have modified their compound by different secondary amine.[63]



Scheme 3.20. Preparation of imidazo[1,2-a]pyridine library by Guwiffier *et. al.*

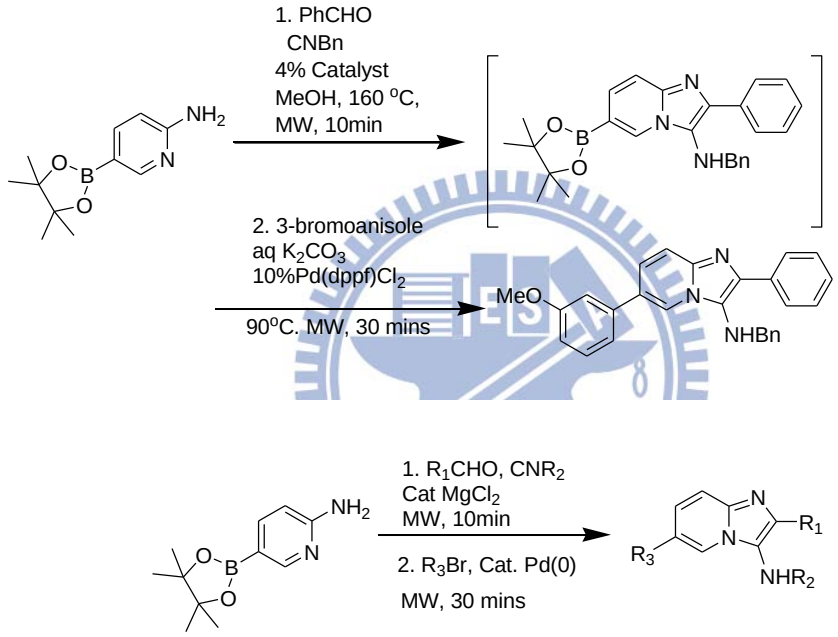
In the year 2007, Kamal *et. al.* has described the efficient solid phase synthesis of a library of Imidazo[1,2a] pyridine-8-carboxamides. For this NHBoc protected 2 amino nicotinic acid has been taken and esterified by polymer support. After polymer attached with 2 NHBoc protected 2 amino noctinic acid Boc group has been removed by acidic medium.The reaction of different alpha-haloketones, with polymer-bound 2-aminonicote yield polymer-bound imidazo[1,2-*a*]pyridine moiety. The resulting polymer-bound imidazo[1,2-*a*]pyridines were finally cleaved from the solid-support with an excess of primary or secondary amines in Scheme 3.21.[64]



Reagent and conditions: (a) EDC, DMAP, CH_2Cl_2, DMF(1:1), 48 h; (b) 4 N HCl in 1,4 dioxane;
(c) $_XCH_2COR$ 4(1, 5), EtOH, reflux for 5 h; (d()i)R_1R_2NH8(1-15), py, 18-24 h;
(ii) amine extraction(SLE method)

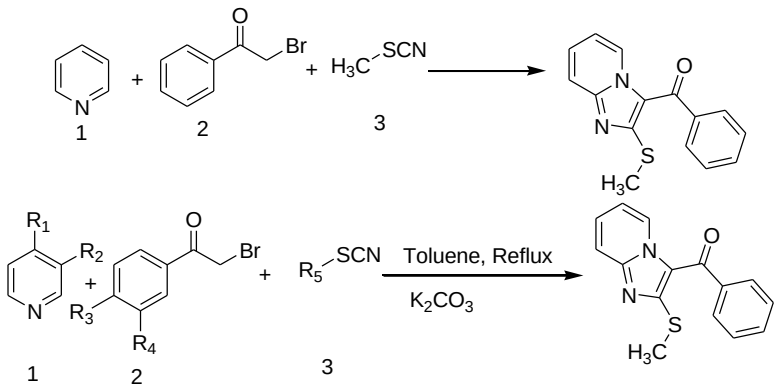
Scheme 3.21. Preparation imidazo[1,2-a]pyridine library by Kamal *et. al.*

In the same year 2007, DiMauro *et. al.* has described the rapid and efficient synthesis of various 2,6-disubstituted- 3-amino-imidazopyridines using a microwave-assisted onepot cyclization/Suzuki coupling. For this reaction they use the 2-aminopyridine-5-boronic acid pinacol ester and various aldehyde and different isonitrile . The boronate functional group is remarkably tolerant to the Lewis acid catalyzed cyclizations, and the subsequent Pd(0)-catalyzed Suzuki coupling reactions proceed cleanly in the presence of magnesium salts in Scheme 3.22. [65]



Scheme 3.22. Preparation imidazo[1,2-a]pyridine library by DiMauro *et. al.*

In the year 2010, Kianmehr *et. al.* has modified the procedure for the synthesis of imidazo[1,2-*a*]pyridine moiety. They described one-pot, three-component reaction between pyridine, phenacyl bromide, and thiocyanate in refluxing condition in ethanol solvent. The reaction provides the resultant fully substituted imidazo[1,2-*a*]pyridine derivatives in good yields without using any catalyst or activation in scheme 3.23.[66]

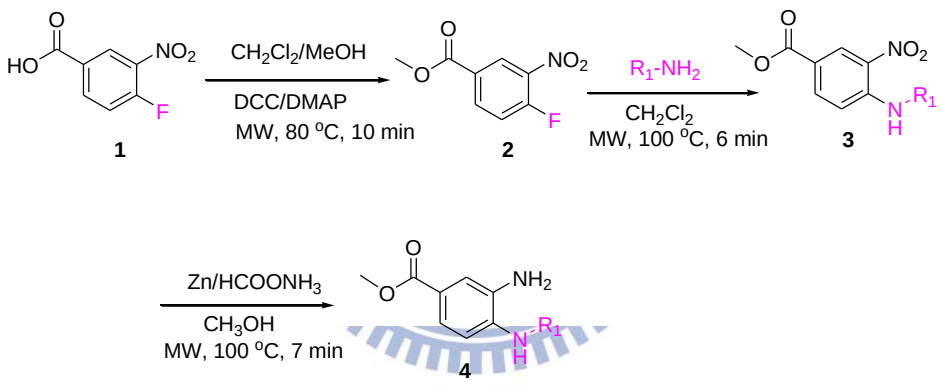


Scheme 3.23. Preparation imidazo[1,2-a]pyridine library by Kianmehr *et. al.*

3.10. Result and Discussion

To construct the benzimidazole-imidazo[1,2-*a*]-pyridine moiety our target compound, we took the two common building block 4-fluro-3 nitro benzoic acid **1** and 2-amino nicotinic acid 5 in Scheme 3.24. Our presence strategy commenced with esterfication of 4-fluro-3-nitro benzoic acid by DCC/DMAP coupling reagent. Fot esterification reaction we dissolve our compound 4-fluro-3 nitro benzoic acid in 8:2 DCM/MeOH. Cat DMAP has been added to the reaction mixture. The ester coupling reagent DCC in DCM solvent was added drop wise. In the room temperature condition where the reaction took 24 hrs for completion of starting material and it took only 10 mins at 80 ^{o}C under microwave condition. The reaction has been monitor by TLC and proton NMR spectroscopy. After completion of the reaction time, the insoluble DCU was filtered off and the reaction mixture was purified by sodium bi carbonate washing to remove excess acid starting material. In the proton NMR spectra the methyl signal appears at 3.95 ppm. To bring the second element of diversity in the 4-fluoro 3-nitro benzoic ester various primary amine

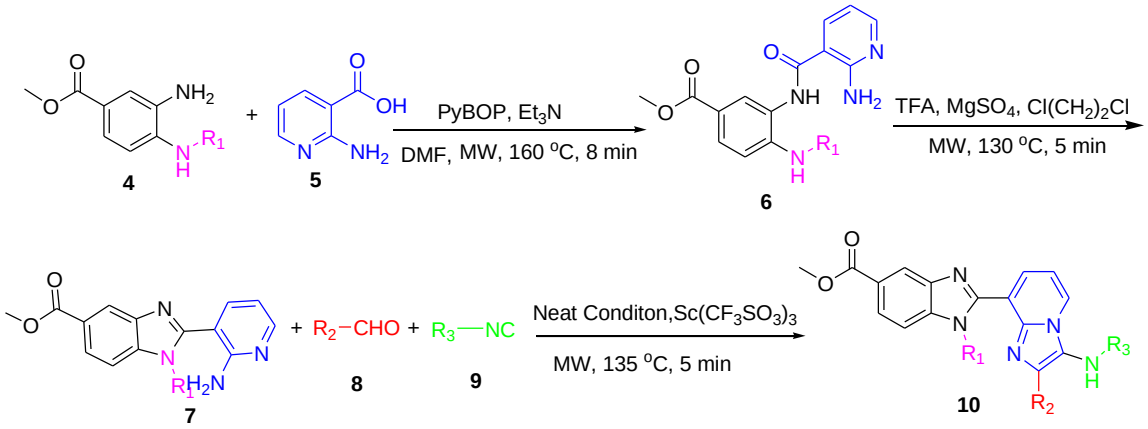
has been introduced by SnAr reaction in DCM solvent. This SnAr reaction under room temperature condition took 18 hrs to complete the starting material. The same set of reaction under microwave irradiation took only 6 mins at 100 ^{o}C to provide o-nitro phenylene amine **3**. The reaction has been monitor by TLC and proton NMR spectroscopy. After completion of the reaction the reaction mixture was washed with water to remove the little excess primary amine. The proton nmr spectra corresponding primary amine peaks appears which confirms the complete formation of o-nitro phenyl amine ester. For the next step we planned to do nitro reduction to couple with another building block 2-amino nicotinic acid.



Scheme 3.24. General strategy of microwave assisted synthesis of substituted o-phenylene diamine 4.

For this we have done neutral reduction of o-nitro phenyl amine ester by Zn/HCOONH$_3$ and MeOH as a solvent. In the room temperature condition we observed the yellow reaction mixture was converted to colorless after1-2 hrs. TLC has been checked TLC indicates complete formation o-phenylene diamine ester **4**. Under microwave irradiation it tooks 7 min at 100 ^{o}C temperature. After completion of the reaction, reaction mixtures

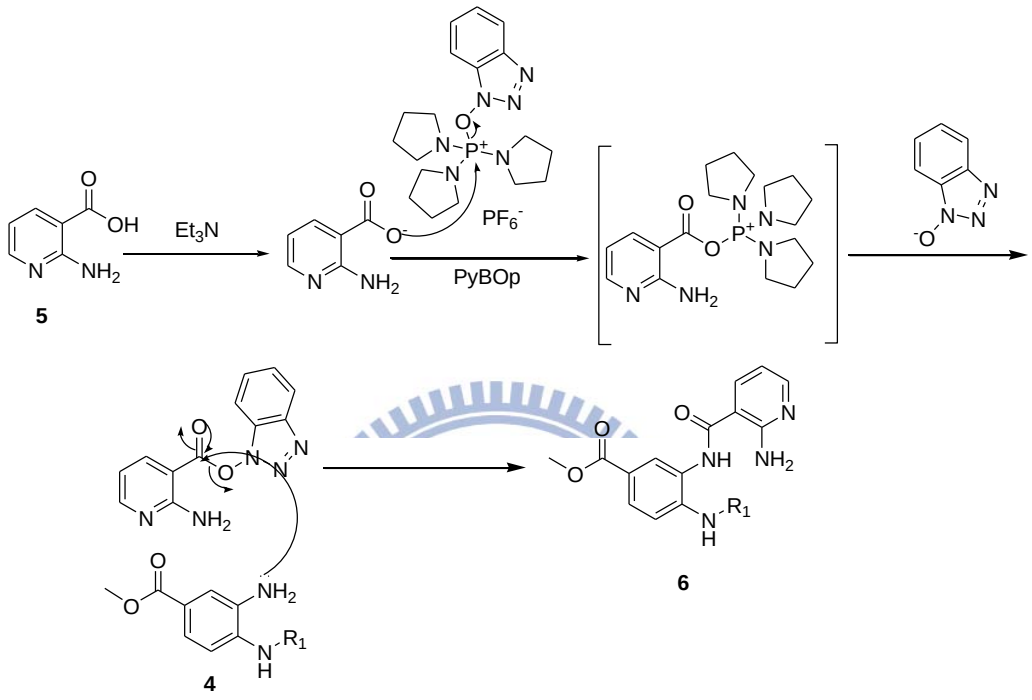
were filtered through fritted funnel to get rid of the Zn. The reaction mixtures were evaporated and dichloromethane was added to salt out the ammonium formate to obtain the compound **4.**[67-69] To construct the the biheterocycles we did the most essential reaction ie coupling between 2-amino nicotinic acid **5** with o-phenylene diamine **4** by coupling reagent in Scheme 3.25.



Scheme 3.25. General strategy of microwave assisted synthesis of substituted benzimidazole-imidazo[1,2-*a*]-pyridine 10.

For this amide coupling reaction we screened several coupling reagent. First we tried DCC/DMAP coupling in DCM solvent for 24 hrs. But surprisingly DCC activation of amine functionality leads to complex reaction mixtures. After 24 hrs reaction TLC has been checked we have observed there is no amide bond formation. In the next we have tried EDC/HOBt, diisopropyl amine. In the next we have tried DCC/HOBt, diisopropyl amine; however this reaction condition fails to obtain the target molecule. In an effort to attain the desired target molecule **6**, the amide most essential coupling reaction has been carried out by via PyBop activation as in Scheme 3.26. However the anilide conjugates **6**

has been obtained by the condensation of acid **5** with o-phenylene diamine **4** through *in-situ* generated PyBop/Et_3N activated ester in *N*,*N*'-dimethylformamide in 24 hours in room temperature. The mechanism of the reaction has been depicted in Scheme 3.26.



Scheme 3.26. Plausible mechanism towards the formation of amide bonds

After completion of the reaction time, the reaction mixture was filtered through fritted funnel to separate the insoluble starting material and the solvent was removed under reduced pressure. The reaction mixture was diluted with DCM further washed by sodium bicarbonate solution to remove any unreacted acid. The proton NMR confirms the corresponding peak of 2-amino nicotinic acidamide in the target anilide conjugate in Figure 3.2. For the construction of benzimidazole ring, anilide conjugates **6** were

subjected to acid catalyzed cyclisation in presence of 10 % trifluoroacetic acid in 1,2-dichloroethane under refluxing condition for 18 hours

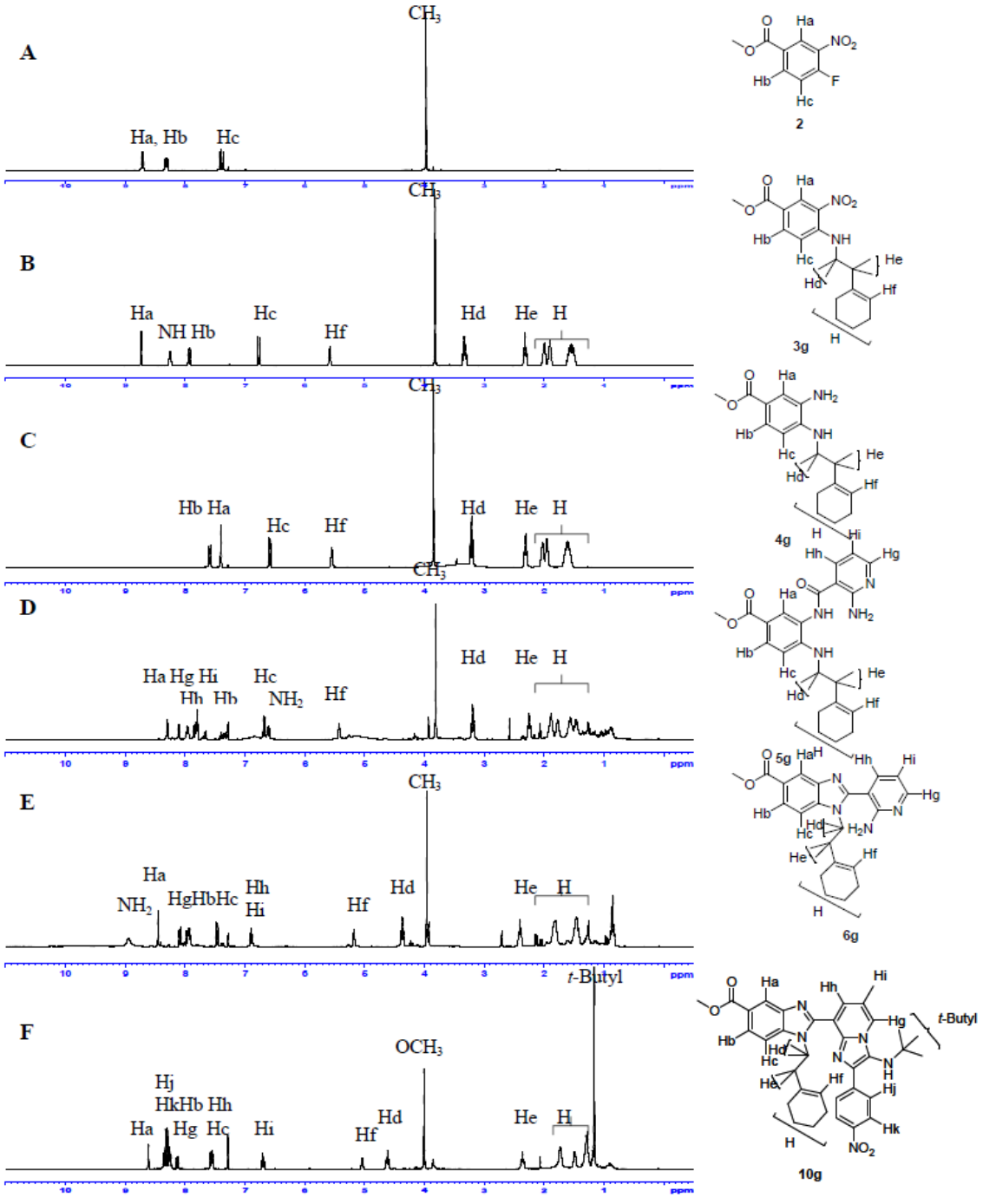
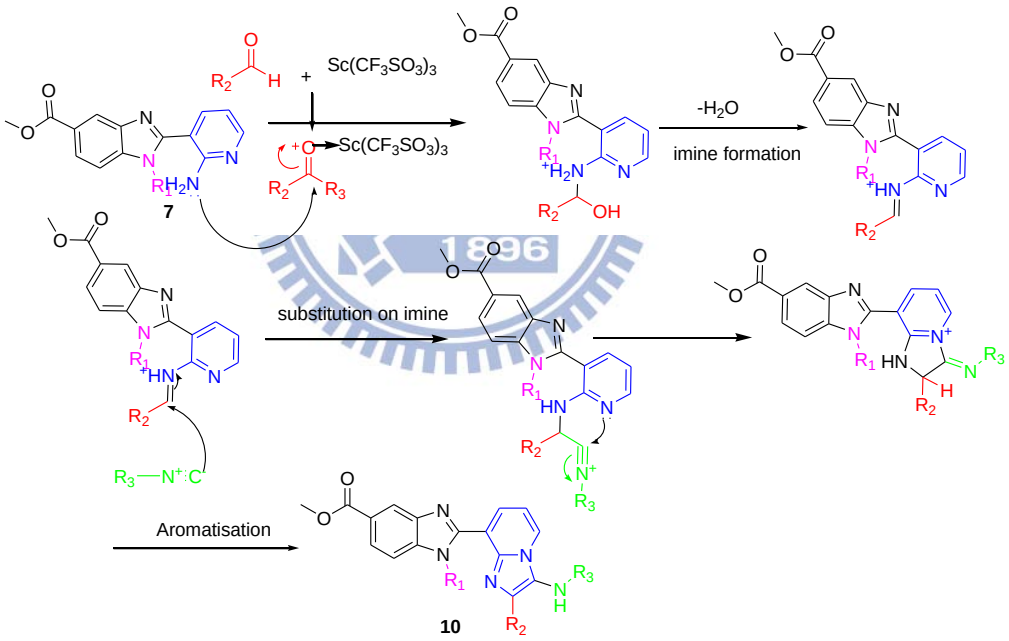


Figure 3.2 Stepwise formation of compound **2** to **10g** in $CDCl_3$ as solvent at 25 ^{0}C

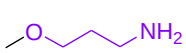
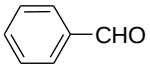
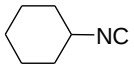
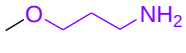
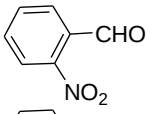
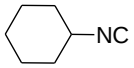
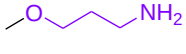
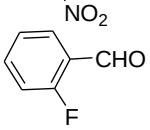
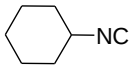
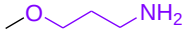
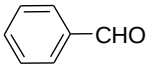
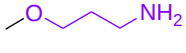
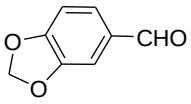
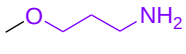
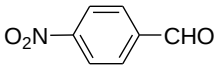
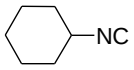
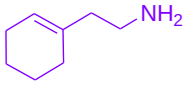
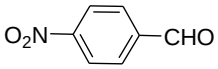
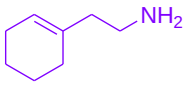
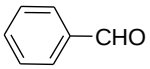
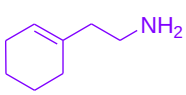
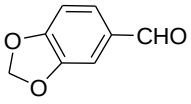
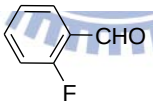
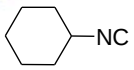
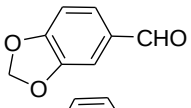
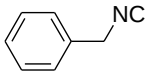
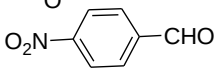
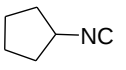
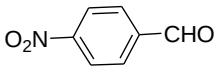
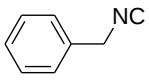
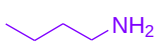
The formation of the benzimidazole linked amino pyridine **7** was achieved by the intramolecular cyclization facilitated by the protonation of amide carbonyl by trifluoroacetic acid. However, it has been observed that addition of $MgSO_4$ facilitates cyclization by accelerating the removal of water and shortens the reaction time to 10 hours. In order to achieve the target compound quickly, we applied the microwave irradiation under sealed vessel condition (130 ^{o}C) at this stage, which further reduced the reaction time to 5 minutes. After completion of the reaction, $MgSO_4$ was filtered off, the solvent was removed under reduce pressure and the reaction mixture was washed with water to remove any extra TFA. Our main goal was the construction of imidazo[1,2-*a*]-pyridine ring in conjunction with introduction of additional sets of diversity. In an effort to mimic the bioactive compound as mentioned earlier in Figure 3.0, we decided to explore the building of imidazo[1,2-*a*]-pyridine ring with various aldehyde **8** isocyanide **9**. Hence the amine pyridine conjugates **7** were subjected to undergo ugi multicomponent reaction in methanol solvent scandium triflet as catalyst under refluxing condition. We observed to complete the starting material to the targeted product it took 36 hrs in refluxing condition. In case of some electron withdrawing aldehyde time is about 18-24 hrs. The same set of reaction under sealed microwave irradiation took 160 $^{\circ}$C for 20 minutes to furnish the benzimidazole-imidazo[1,2-*a*]-pyridine as shown in figure. In order to shorten the reaction time and to carry out the reaction in milder condition the different substituted benzimidazole linked amino pyridine, different isocyanide **9** and various aldehyde **8** catalytic scandium triflate has been subjected under solvent free condition. The reaction mixture has been heated at 100-120 ^{o}C for 8 mins. The same set of reaction when carried out under microwave irradiation it took only 5 mins at 135 ^{o}C.

After completion of the reaction the reaction mixture was diluted with dicholomethane solvent and TLC has been checked which indicates the complete formation of product as in Table 3.0. To purify the compound the reaction mixture was washed with 1 (N) HCl/water to remove the excess undesired isocyanide and excess benzimidazole linked amino pyridine starting material. The mechanism for this Ugi type reaction has been depicted here. The mechanism involves the in imine formation of benzimidazole linked amino pyridine with different aldehyde in presence of scandium triflet catalyst, 2) subsequent isocyanide attak on iminium ion 3) intramolecular ring closure reaction by nitrogen lone pair of pyridine moiety 4) aromatization in Scheme 3.27.



Scheme 3.27. Plausible Ugi like reaction mechanism towards the formation of benzimidazole-imidazo[1,2-a]-pyridine.

Table 3.0 Synthesise of Benzimidazole- Imidazo[1,2-*a*]pyridine in neat condition under microwave irradiation

Entry	R_1NH_2	R_2CHO	R_3NC	LRMS[a]	Isolated yield[b]
10a				538	72%
10b				583	83%
10c				556	89%
10d				512	80%
10e				556	84%
10f				583	86%
10g				593	82%
10h				548	90%
10i				592	87%
10j				540	81%
10k				574	83%
10l				553	83%
10m				575	80%
10n				548	77%
10o				481	82%
10p				537	86%

However the final product was purified by column chromatography 50 % EA/Hex as an eluent. However the final product formation was confirmed by the appearance of peak for corresponding aldehyde and isocyanide group and little downfield shift of aromatic proton as shown in Figure 3.2.

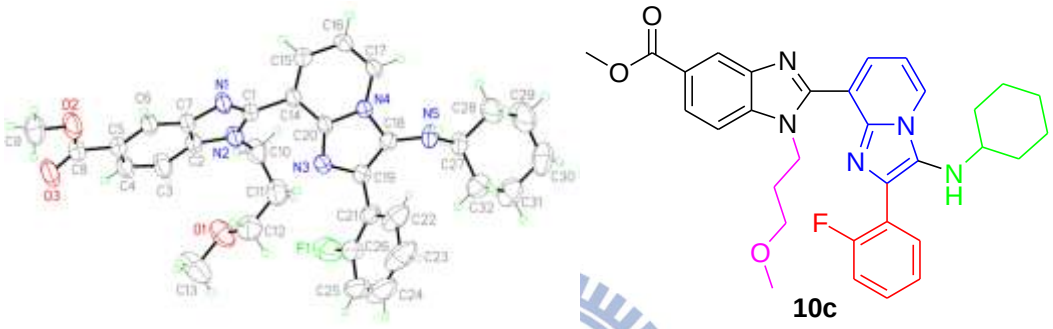


Figure 3.4. ORTEP diagram of compound **10c**.

The X-ray crystal structure of compound **10c** indicates that the formation of biheterocyclic novel compounds benzimidazole-imidazo[1,2-*a*]-pyridine where benzimidazole ring and imidazo[1,2-*a*]-pyridine ring are perpendicular to each other which unequivocally confirms its structure in Figure 3.4.

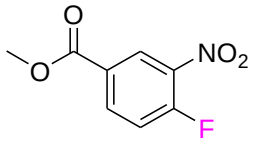
3.11. Conclusions

In conclusion, we have successfully developed novel application of Ugi reaction for the efficient synthesis of biologically promising novel derivatives of benzimidazole-imidazo[1,2-*a*]-pyridine in neat condition under microwave irradiation. Linear sequence of amino acid coupling reaction, cyclisation and Ugi multicomponent reaction neat

condition in conjugation with microwave irradiation are the key step to develop short synthesis of benzimidazole linked imidazo[1,2-*a*]- pyridine. The variety of primary amines, aldehydes and isocyanaide are used to bring into the additional diversity in the targeted skeleton. The use of microwave promoted Ugi reaction in neat condition with shorter time and high yields in table 1 opens new pathway for the efficient synthesis of related novel diversified biheterocyclic molecules benzimidazole-imidazo[1,2-*a*]-pyridine of medicinal interest.

3.12. Experimenatal Scetion

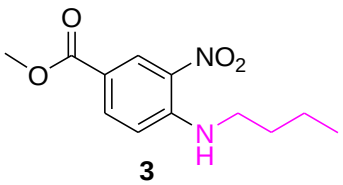
General Procedure for the Preparation of compound methyl 4-fluoro-3-nitrobenzoate 2.



2

To a solution 4-Fluoro-3-nitrobenzoic acid **1** (600 mg, 3.24 mmol, 1.0 equiv) in Dichloromethane/MeOH (DCM/MeOH) (8:2 ml) was added of *N, N'*-dicyclohexylcarbodiimide (DCC) (935 mg, 4.54 mmol, 1.4 equiv) in Dichloromethane (DMAP) was added (0.05 mg) in a sequential order. The resulting slurry was stirred for 5 minutes at room temperature. The reaction mixtures were subsequently irradiated with stirring in a 10 mL microwave process vial at (70 °C) for 12 minutes to obtain methyl 4-fluoro-3-nitrobenzoate **2**. After completion of the reaction, the suspensible byproducts were filtered through filter paper. The filtrate was evaporated to dryness.White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71(dd, *J* = 7.2, 2.2 Hz, 1H), 8.31 (m, 1H), 7.39 (t, *J* = 8.7 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 160.2, 156.6, 137.0, 136.9, 128.2, 128.1, 127.6, 127.5, 119.4, 119.1, 53.3.

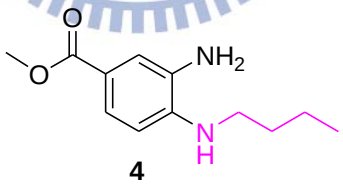
General Procedure for the Preparation of methyl 4-(butylamino)-3-nitrobenzoate 3.



3

To a solution of methyl 4-fluoro-3-nitrobenzoate **2** (630 mg, 3.15 mmol, 1.0 equiv) in dichloromethane, 1-butylamine (344 mg, 4.72 mmol, 1.5 equiv) was added and the mixture was subsequently irradiated with stirring in a 10 mL microwave process vial (80 ^{o}C) for 5 minutes. After completion of the reaction, the reaction mixtures were extracted by water and evaporated to dryness gave the methyl 4-(butylamino)-3-nitrobenzoate **3**. Yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, *J* = 2.0 Hz, 1H), 8.27 (s, 1H), 7.94 (dd, *J* = 9.04, 1.7 Hz, 1H), 6.78 (d, *J* = 9.04 Hz, 1H), 3.82 (s, 3H), 3.28 (q, *J* = 7.06 Hz, 2H) 1.68 (pent, *J* = 7.30 Hz, 2H), 1.44 (sext, *J* = 7.30 Hz, 2H), 0.94 (t, *J* = 7.30 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 148.1, 136.5, 131.3, 129.8, 117.2, 113.9, 52.4, 43.3, 31.12, 20.6, 14.1.

General Procedure for the Preparation of methyl 3-amino-4-(butylamino)benzoate 4.

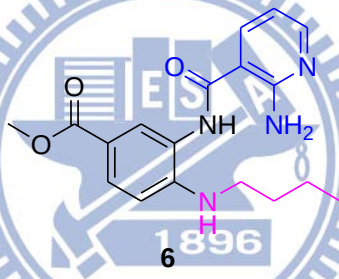


4

To a solution of methyl 4-(butylamino)-3-nitrobenzoate 3 (816 mg, 3.23 mmol, 1.0 equiv) in methanol, Zn (1.05 g, 16.20 mmol, 5.0 equiv.) and ammonium formate (1.50 g, 22.66 mmol, and 7.0 equiv) were added. The reaction mixtures was subsequently irradiated with stirring in a 10 mL microwave process vial for 5 minutes in the appropriate mode of pressure and temperature to complete reduction of nitro group. After completion, the reaction mixtures were then subjected to centrifugation for removal of Zn

on was concentrated by rotary evaporation. Dicholoromethane (10 mL) was then added to salt out ammonium formate. The reaction mixtures were filtered through fritted funnel to remove ammonium formate to obtain the methyl 3-amino-4-(butylamino)benzoate **4.** Brownish solid**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.41 (d, *J* = 1.9 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 3.85 (s, 3H), 3.30 (brs, 2H) 3.17 (t, *J* = 6.3 Hz, 3H), 1.64 (pent, *J* = 7.30 Hz, 2H), 1.45 (sext, *J* = 7.30 Hz, 2H), 0.97 (t, *J* = 7.30 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 143.6, 132.4, 124.7, 118.7, 118.4, 109.5, 52.0, 43.7, 31.9, 20.7, 14.3.

General Procedure for the Preparation of methyl 3-(2-aminonicotinamido)-4-(butylamino)benzoate 6.

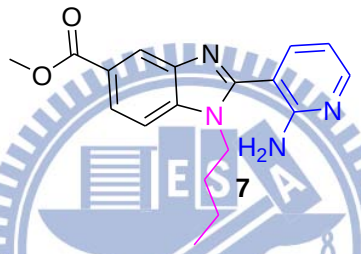


6

To a solution of 2-aminonicotinic acid **5** (139 mg, 0.67 mmol, 3.0 equiv) in *N, N'*-dimethylformamide (DMF/Et3N) (3:7) was added PyBOP (91 mg, 0.67 mmol, 3.0 equiv) in a sequential order. The resulting slurry was stirred for 5 minutes at room temperature and then added 3-amino-4-(butylamino)benzoate **4** (1.0 g, 0.22 mmol, 1.0 equiv) in *N, N'*-dimethylformamide (5 mL) (DMF). The reaction mixtures were subsequently heated with stirring in a 10 mL microwave process vial for 10 minutes at 160 oC of temperature to obtain **6**. After completion of the reaction, the suspensible byproducts were filtered through filter paper. The reaction mixtures were partitioned by sodium bicarbonate solution and ethyl acetate to remove the undesired impurity and dried for further steps.

Pale white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.64 (dd, *J* = 7.2, 2.1 Hz, 1H), 8.49-8.44 (m, 1H), 7.92 (d, *J* = 1.7 Hz, 1H), 7.74 (d, *J* = 1.7 Hz, 1H), 7.65 (dd, *J* = 7.2, 2.1 Hz, 1H), 4.90 (t, *J* = 5.8 Hz, 2H), 4.84 (t, *J* = 5.8 Hz, 2H) 4.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 160.1, 156.5, 137.7, 137.5, 127.9, 124.5, 123.5, 119.8, 119.5, 64.5, 48.4, 36.2; MS (ESI) *m/z*: 343 (MH^+);

General Procedure for the Preparation of methyl 2-(2-aminopyridin-3-yl)-1-butyl-1H-benzo[d]imidazole-5-carboxylate 7.

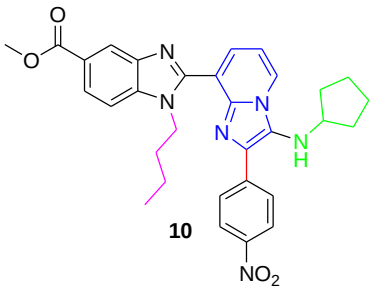


7

To a solution of methyl 3-(2-aminonicotinamido)-4-(butylamino)benzoate **6** in 1,2-dichloroethane, trifluoroacetic acid (0.5 mL) and MgSO4 (500 mg) was added and the mixture was subsequently heated with stirring in a 10 mL microwave process vial for 8 minutes in the appropriate mode of pressure and temperature. After completion of the reaction, MgSO4 was removed through celite. The reaction mixtures were partitioned by water and ethyl acetate (100 mL) to obtain the methyl 2-(2-aminopyridin-3-yl)-1-butyl-1H-benzo[d]imidazole-5-carboxylate **7** in high purity. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55(brs, NH), 8.45 (s, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 7.99 (dd, *J* =7.5, 1.4 Hz, 1H), 7.88 (t, *J* = 6.1 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 6.92 (d, *J* = 6.4, 1.0 Hz, 1H), 4.28 (t, *J* = 7.7 Hz, 2H), 3.94 (s, 3H), 3.19-3.09 (m, 2H), 1.91-1.77 (m, 6H), 1.41-1.22 (m, 4H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 155.1, 148.2, 142.3, 141.9, 138.8,

138.2, 126.4, 123.0, 113.4, 111.6, 110.9, 52.9, 46.9, 32.2, 26.9, 20.5, 14.1, MS (ESI) *m/z*: 325 (MH^+);

General Procedure for the Preparation of methyl 1-butyl-2-(3-(cyclopentylamino)-2-(4-nitrophenyl)imidazo[1,2-a]pyridin-8-yl)-1H-benzo[d]imidazole-5-carboxylate 10l.

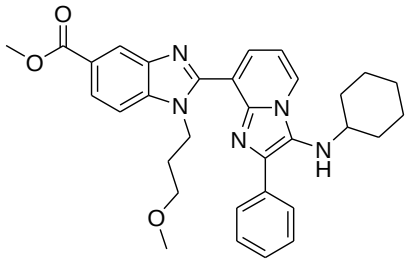


10

To a 10 mL microwave process vial methyl 2-(2-aminopyridin-3-yl)-1-butyl-1H-benzo[d]imidazole-5-carboxylate (100 mg,), 4-nitro benzaldehyde (80 mg,) Cyclopetyl isocyanide and scandium triflet (10 mg) was added. The microwave vial was sealed and irradiated at 140 oC for 3 mins. After completion the reaction mixture was diluted with dichloromethane. The slurry was loaded on silica gel column and eluted with a mixture of ethyl acetate and hexane (1:3) to get the title compounds **10l** in good yields. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.36 (d, J = 8.7 Hz, 1H), 8.27 (d, J = 8.7 Hz, 2H), 8.20 (dd, J = 7.3, 1.2 Hz, 2H), 8.12 (dd, J = 7.3, 1.2 Hz, 1H), 7.58 (s, 1H), 7.55 (d, J = 1.5 Hz, 1H), 6.80 (t, J = 6.9 Hz, 1H), 4.48 (t, J = 7.4 Hz, 2H), 4.00 (s, 3H), 3.77 (m, 2H), 1.83-1.76 (m, 6H), 1.73-1.62 (m, 4H), 1.13 (sext, J = 7.2 Hz, 2H), 0.69 (t, J = 7.2 Hz 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 152.0, 147.1, 143.5, 141.2, 139.6, 135.5, 128.7, 128.5, 127.9, 127.0, 124.9, 124.8, 124.7, 127.2, 122.8, 120.8, 112.1, 110.6, 59.8, 52.6, 45.7, 34.1, 32.0, 24.1, 20.3, 13.8; MS (ESI) *m/z*: 553 (MH^+); HRMS (ESI, m/z) calcd for

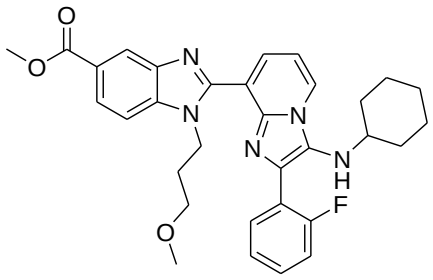
$C_{31}H_{33}N_6O_4$: *m/z* 553.2563; Found 553.2566 (M+H); IR (cm^{-1}, KBr): 3421, 3245, 2967, 1712, 1440, 1214.

Methyl 2-[3-(cyclohexylamino)-2-phenylimidazo[1,2-*a*]pyridin-8-yl]-1-(3-methoxypropyl)-1*H*-benzo[*d*]imidazole-5-carboxylate 10a.



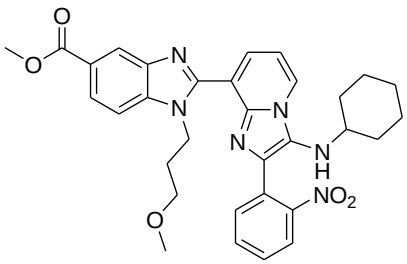
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.28 (d, *J* = 6.7 Hz, 1H), 8.09 (d, *J* = 8.1 Hz, 1H), 8.04 (d, *J* = 7.3 Hz, 2H), 7.59 (t, *J* = 7.7 Hz, 2H), 7.44 (t, *J* =7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 6.89 (t, *J* = 6.97 Hz, 1H), 4.71 (t, *J* = 6.8 Hz, 2H), 3.98 (s, 3H), 3.14-3.08 (m, 2H), 3.06 (s, 3H), 2.03 -1.95 (m, 2H), 1.89-1.85 (m, 3H), 1.77-1.73 (m, 4H), 1.37-1.18 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 152.6, 143.4,139.9, 139.1, 137.7, 134.7, 129.9, 127.9, 127.7, 127.6, 126.1, 125.0, 124.9, 124.7, 122.7, 120.3, 111.6, 110.5, 69.2, 58.9, 57.4, 52.5, 42.7, 34.6, 30.2, 26.1, 25.2, MS (ESI) *m/z*: 538 (MH^+); HRMS (ESI, m/z) calcd for $C_{32}H_{36}N_5O_3$: *m/z* 538.2818; Found 538.2815 (M+H); IR (cm^{-1}, KBr): 3417, 3216, 2929, 1714, 1617, 1295.

Methyl 2-[3-(cyclohexylamino)-2-(2-nitrophenyl)imidazo[1,2-*a*]pyridin-8-yl]-1-(3-methoxypropyl)-1*H*-benzo[*d*]imidazole-5-carboxylate 10b.



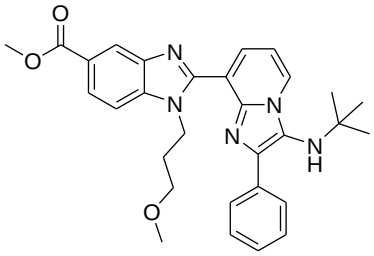
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.21 (d, *J* = 6.8 Hz, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.65-7.59 (m, 2H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 6.84 (t, *J* = 6.9 Hz, 1H), 4.63 (t, *J* = 6.8 Hz, 2H), 3.96 (s, 3H), 3.53 (d, *J* = 4.2 Hz 1H), 3.14-3.12 (m, 2H), 3.11 (s, 3H), 2.89 (s, 1H), 1.94-1.86 (m, 2H), 1.82 (m, 2H), 1.66 (m, 2H), 0.89-0.86 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 152.5, 143.3,139.9, 139.1, 137.7, 134.7, 129.9, 127.9, 127.7, 127.6, 126.1, 125.0, 124.9, 124.7, 122.7, 120.3, 111.6, 110.5, 69.2, 58.9, 57.4, 52.5, 42.7, 34.6, 30.2, 26.1, 25.2, MS (ESI) *m/z*: 583 (MH^+); HRMS (ESI, m/z) calcd for $C_{32}H_{35}N_6O_5$: *m/z* 583.2669; Found 583.2672 (M+H); IR (cm^{-1}, KBr): 3412, 3226, 2931, 1712, 1619, 1529, 1297.

Methyl 2-[3-(cyclohexylamino)-2-(2-fluorophenyl)imidazo[1,2-*a*]pyridin-8-yl]-1-(3-methoxypropyl)-1*H*-benzo[*d*]imidazole-5-carboxylate 10c.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.33 (d, *J* = 6.8 Hz, 1H), 8.07 (td, *J* = 8.5, 1.5 Hz, 1H), 7.62 (d, *J* = 6.8 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.36-7.32 (m, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.20-7.12 (m, 1H), 6.96 (d, *J* = 6.8 Hz, 1H), 4.66 (t, *J* = 6.8 Hz, 2H), 3.96 (s, 3H), 3.57 (t, *J* = 7.8 Hz 1H), 3.11 (t, *J* = 5.6 Hz 1H), 3.05 (s, 3H), 2.75 (brs, NH), 2.02-1.94 (m, 2H), 1.76-1.74 (m, 2H), 1.63 (m, 2H), 1.53 (s, 1H), 1.13-1.11 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 161.6, 158.3, 152.4, 143.4,139.8, 139.6, 133.0, 132.3, 132.2, 129.9, 129.7, 128.0, 127.6, 125.2, 125.1, 124.7, 122.8, 120.4, 116.2, 115.8, 111.7, 110.5, 69.2, 58.7, 57.1, 52.5, 42.6, 34.4, 30.2, 25.2, 24.8, MS (ESI) *m/z*: 556 (MH^+); HRMS (ESI, m/z) calcd for $C_{32}H_{34}FN_5O_3$: *m/z* 556.2724; Found 556.2726 (M+H); IR (cm^{-1}, KBr): 3413, 3234, 2929, 1710, 1619, 1214.

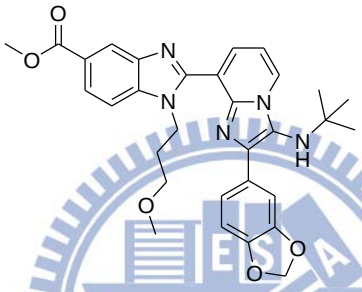
Methyl 2-[3-(*tert*-butylamino)-2-phenylimidazo[1,2-*a*]pyridin-8-yl]-1-(3-methoxypropyl)-1*H*-benzo[*d*]imidazole-5-carboxylate 10d.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.38 (d, *J* = 6.6 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 8.4 Hz, 2H), 7.42 (t, *J* =7.2 Hz, 2H), 7.33 (d, *J* = 7.2 Hz, 1H), 6.84 (t, *J* = 6.9 Hz, 1H), 4.69 (t, *J* = 6.7 Hz, 2H), 3.98 (s, 3H), 3.47 (brs, NH), 3.10 (t, *J* = 5.6 Hz, 2H), 3.05 (s, 3H), 2.00 -1.97 (m, 2H), 1.09 (s, 9H); ^{13}C NMR

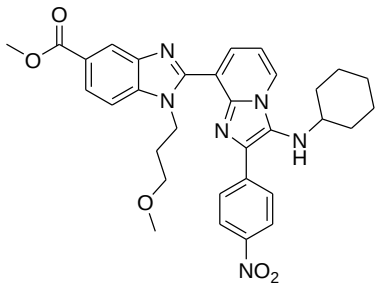
(75 MHz, $CDCl_3$) δ 168.2, 152.5, 143.3, 140.6, 139.8, 139.5, 135.3, 132.9, 130.2, 128.7, 128.4, 128.0, 127.9, 125.8, 124.8, 122.6, 119.9, 111.3, 110.5, 69.2, 58.7, 57.0, 52.5, 42.7, 30.8, 30.2, MS (ESI) *m/z*: 512 (MH^+); HRMS (ESI, m/z) calcd for $C_{30}H_{34}N_5O_3$: *m/z* 512.2662; Found 512.2660 (M+H); IR (cm^{-1}, KBr): 3421, 3245, 2967, 1712, 1440, 1214.

Methyl 2-[2-(1,3-benzodioxol-5-yl)-3-(*tert*-butylamino)imidazo[1,2-*a*]pyridin-8-yl]-1-[2-(3-methoxypropyl]-1*H*-benzo[*d*]imidazole-5-carboxylate 10e



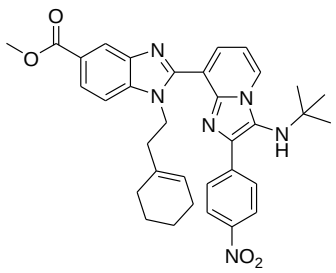
^1H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.35 (d, J = 6.9 Hz, 1H), 8.09 (dd, J = 1.4, 8.6 Hz, 1H), 7.57 (t, J = 6.9 Hz, 2H), 7.46 (d, J =1.3 Hz, 1H), 7.42 (dd, J = 8.0, 1.4 Hz, 1H), 6.88-6.82 (m, 2H), 6.00 (s, 2H), 4.67 (t, J = 6.7 Hz, 2H), 3.98 (s, 3H), 3.10 (t, J = 5.7 Hz, 2H), 3.05 (s, 3H), 2.01 -1.93 (m, 2H), 1.76 (brs, NH), 1.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 152.5, 148.0, 147.5, 143.4, 140.1, 139.8, 139.3, 129.4, 127.8, 125.7, 124.8, 124.1, 122.4, 119.8, 111.3, 110.5, 109.2, 108.6, 101.4, 69.2, 58.8, 57.0, 52.5, 42.7, 30.8, 30.6, 30.2; MS (ESI) *m/z*: 556 (MH^+); HRMS (ESI, m/z) calcd for $C_{31}H_{34}N_5O_5$: *m/z* 556.2560; Found 556.2561 (M+H); IR (cm^{-1}, KBr): 3417, 3255, 2931, 1712, 1617.

Methyl 2-[3-(cyclohexylamino)-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-8-yl]-1-(3-methoxypropyl)-1*H*-benzo[*d*]imidazole-5-carboxylate 10f.



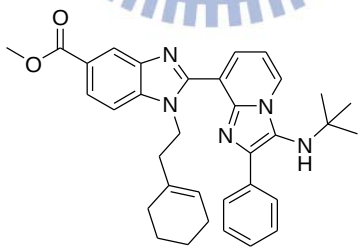
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.31-8.24 (m, 5H), 8.10 (dd, *J* = 5.4, 0.9 Hz, 1H), 7.64 (d, *J* = 3.9 Hz, 1H), 7.58 (d, *J* =5.4 Hz, 1H), 6.95 (t, *J* = 4.2 Hz, 1H), 4.61 (t, *J* = 4.2 Hz, 2H), 3.98 (s, 3H), 3.29 (brs, NH), 3.10 (t, *J* = 1.5 Hz, 2H), 3.04 (s, 3H), 2.00 (t, *J* = 3.6 Hz, 2H), 1.88-1.86 (m, 2H), 1.75-1.74 (m, 2H), 1.64 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 151.6, 146.7,143.1, 140.8, 139.4, 135.1, 128.2, 127.4, 127.1, 124.6, 124.5, 124.4, 123.8, 122.5, 120.6, 111.9, 110.1, 68.9, 58.4, 57.2, 52.1, 42.3, 34.4, 29.8, 25.6, 24.8; MS (ESI) *m/z*: 583 (MH^+); HRMS (ESI, m/z) calcd for $C_{32}H_{35}N_6O_5$: *m/z* 583.2669; Found 583.2667 (M+H); IR (cm^{-1}, KBr): 3410, 3245, 2933, 1714, 1602, 1513, 1338.

Methyl 2-[3-(*tert*-butylamino)-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-8-yl]-1-[2-(1-cyclohexenyl)ethyl]-1*H*-benzo[*d*]imidazole-5-carboxylate 10g.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.37 (d, *J* = 8.8 Hz, 2H), 8.30 (d, *J* = 8.8 Hz, 2H), 8.21 (s, 1H), 8.12 (dd, *J* = 8.6 Hz, 1H), 7.55 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.32 (dd, *J* =7.8, 1.5 Hz, 1H), 7.28 (s, 1H), 7.21 (s, 5H), 7.14 (dd, *J* =9.7, 1.5 Hz, 1H), 6.70 (t, *J* = 6.9 Hz, 1H), 5.04 (m, 2H), 4.61 (t, *J* = 6.2 Hz, 2H), 4.00 (s, 3H), 3.85 (brs, NH), 2.35 (t, *J* = 7.1 Hz, 2H), 1.73-1.70 (m, 3H), 1.39-1.36 (m, 2H), 1.29-1.25 (m, 3H), 1.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ168.1, 152.2, 147.2, 143.4, 141.9, 139.8, 139.6, 137.9, 133.7, 128.9. 128.8, 126.4, 125.6, 124.9, 124.0, 122.7, 120.5, 111.7, 110.6, 57.3, 52.6, 44.8, 38.3, 30.1, 28.3, 25.4, 22.8, 22.2; MS (ESI) *m/z*: 593 (MH^+); HRMS (ESI, m/z) calcd for $C_{34}H_{36}N_6O_4$: *m/z* 593.2876; Found 593.2872 (M+H); IR (cm^{-1}, KBr): 3423, 3241, 2933, 1714, 1604, 1336.

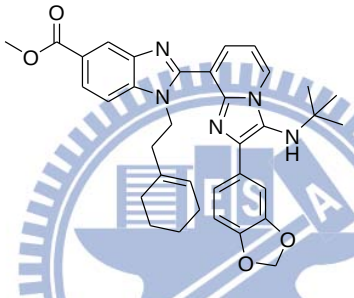
Methyl 2-[3-(*tert*-butylamino)-2-phenylimidazo[1,2-*a*]pyridin-8-yl]-1-[2-(1-cyclohexenyl)ethyl]-1*H*-benzo[*d*]imidazole-5-carboxylate 10h.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.31 (d, *J* = 7.0 Hz, 2H), 8.09 (dd, *J* = 8.6, 1.5 Hz, 2H), 7.97 (d, *J* = 7.7 Hz, 2H), 7.57 (d, *J* = 7.0 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.45-7.40 (m, 2H), 7.34-7.30 (m, 2H), 6.73 (t, *J* = 7.0 Hz, 1H), 5.02 (m, 1H), 4.70 (t, *J* = 7.0 Hz, 2H), 3.99 (s, 3H), 3.67 (brs, NH), 2.32 (t, *J* = 7.0 Hz, 2H), 1.70-1.62 (m, 3H),

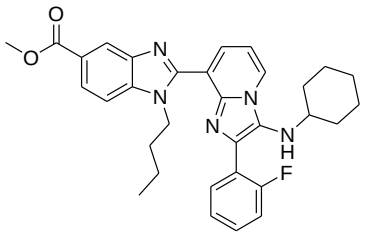
1.47-1.45 (m, 2H), 1.35-1.25 (m, 3H), 1.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ168.2, 152.7, 143.3, 140.4, 139.8, 135.4, 133.9, 128.7, 128.6, 128.2, 128.0, 125.7, 124.8, 124.7, 124.6, 122.7, 120.1, 111.3, 110.4, 56.9, 52.5, 44.7, 38.4, 30.8, 28.2, 25.4, 22.8, 22.3; MS (ESI) *m/z*: 548 (MH^+); HRMS (ESI, m/z) calcd for $C_{34}H_{37}N_5O_2$: *m/z* 548.3025; Found 548.3023 (M+H); IR (cm^{-1}, KBr): 3424, 3241, 2931, 1712, 1440, 1617, 1216.

Methyl 2-[2-(1,3-benzodioxol-5-yl)-3-(*tert*-butylamino)imidazo[1,2-*a*]pyridin-8-yl]-1-[2-(1-cyclohexenyl)ethyl]-1*H*-benzo[*d*]imidazole-5-carboxylate 10i



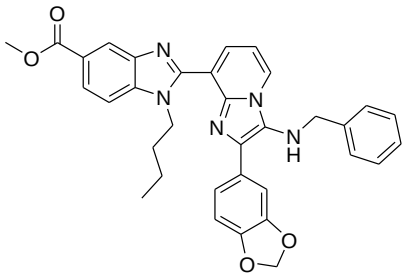
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.34 (d, J = 6.8 Hz, 1H), 8.01 (dd, J = 1.2, 8.6 Hz, 1H), 7.61 (d, J = 7.0 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.48 (d, J =1.3 Hz, 1H), 7.43 (dd, J = 8.1, 1.3 Hz, 1H), 6.89 (s, 1H), 6.86 (m, 1H), 6.00 (s, 2H), 5.03 (brs, NH), 4.67 (t, J = 7.1 Hz, 2H), 3.97 (s, 3H), 2.28 (t, J = 7.1 Hz, 2H), 1.75-1.73 (m, 5H), 1.49 - 1.43 (m, 3H), 1.31-1.27 (m, 2H), 1.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 152.7, 148.0, 147.5, 143.4, 140.2, 139.7, 139.0, 133.8, 129.4, 128.1, 125.6, 124.8, 124.7, 124.3, 122.6, 122.4, 119.8, 111.2, 110.4, 109.2, 108.6, 56.9, 52.5, 44.7, 38.4, 30.9, 30.8, 28.2, 25.4, 22.8, 22.2; MS (ESI) *m/z*: 592 (MH^+); HRMS (ESI, m/z) calcd for $C_{35}H_{38}N_5O_4$: *m/z* 592.2923; Found 592.2920 (M+H); IR (cm^{-1}, KBr): 3424, 3241, 2931, 1712, 1438, 1216.

Methyl 1-butyl-2-[3-(cyclohexylamino)-2-(2-fluorophenyl)imidazo[1,2-*a*]pyridin-8-yl]-1*H*-benzo[*d*]imidazole-5-carboxylate 10j.



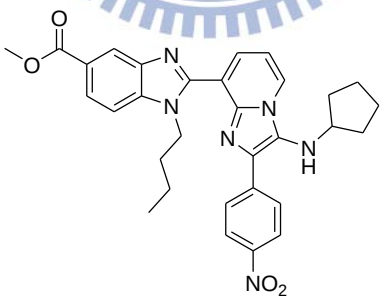
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.33 (d, J = 6.9 Hz, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 7.5 Hz, 2H), 7.61 (d, J = 6.9 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.36-7.31 (m, 1H), 7.23 (d, J = 7.5 Hz, 1H), 6.96 (dd, J = 6.9, 1.0 Hz, 1H), 4.50 (t, J = 7.2 Hz, 2H), 3.96 (s, 3H), 3.58 (d, J = 7.7 Hz 1H), 2.76(brs, NH), 1.76-1.73 (m, 4H), 1.71-1.63 (m, 2H), 1.53 (m, 1H), 1.15-1.08 (m, 7H), 0.68 (t, J = 7.7 Hz 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 161.6, 158.4, 152.4, 143.6,139.7, 139.6, 133.0, 132.2, 132.1, 129.9, 129.7, 125.2, 125.1, 125.0, 124.6, 122.8, 122.7, 122.5, 120.5, 116.2, 115.9, 111.7, 110.4, 57.1, 52.5, 45.7, 34.4, 32.1, 26.0, 25.2, 20.3, 13.7, MS (ESI) *m/z*: 540 (MH^+); HRMS (ESI, m/z) calcd for $C_{32}H_{35}FN_5O_2$: *m/z* 540.2775; Found 540.2777 (M+H); IR (cm^{-1}, KBr): 3413, 3234, 2929, 1712, 1664, 1214.

Methyl 2-[2-(1,3-benzodioxol-5-yl)-3-(benzylamino)imidazo[1,2-*a*]pyridin-8-yl]-1-butyl-1*H*-benzo[*d*]imidazole-5-carboxylate 10k.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 6.5 Hz, 2H), 7.67 (d, *J* = 1.4 Hz, 1H), 7.64 (d, *J* = 1.4 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.33-7.32 (m, 3H), 7.29-7.25 (m, 3H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.31 (t, *J* = 6.9 Hz, 1H), 5.98 (s, 2H), 4.98 (brs, NH), 4.51 (t, *J* = 7.1 Hz, 2H), 4.25 (d, *J* = 4.8 Hz, 2H), 3.99 (s, 3H), 1.70 (quin, *J* = 7.1 Hz, 2H), 1.06 (sext, *J* = 7.1 Hz, 2H), 0.68 (t, *J* = 7.1 Hz 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 148.3, 147.4, 143.4, 139.8, 139.6, 138.4, 136.7, 129.0, 128.9, 128.7, 127.4, 127.5, 126.6, 124.8, 124.7, 122.6, 121.4, 119.2, 110.8, 110.5, 108.9, 108.2, 101.4, 52.6, 52.5, 45.6, 31.9, 20.2, 13.8; MS (ESI) *m/z*: 574 (MH^+); HRMS (ESI, m/z) calcd for $C_{34}H_{32}N_5O_4$: *m/z* 574.2454; Found 574.2456 (M+H); IR (cm^{-1}, KBr): 3421, 3245, 2967, 1710, 1440, 1214.

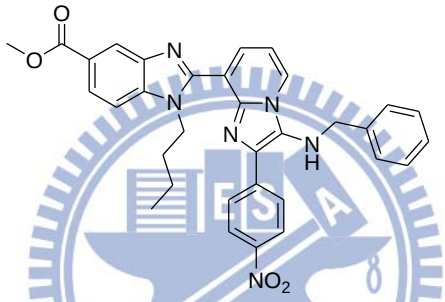
Methyl 1-butyl -2-[3-(cyclopentylamino)-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-8-yl-1*H*-benzo[*d*]imidazole-5-carboxylate 10l.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.36 (d, *J* = 8.7 Hz, 1H), 8.27 (d, *J* = 8.7 Hz, 2H), 8.20 (dd, *J* = 7.3, 1.2 Hz, 2H), 8.12 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.58 (s, 1H), 7.55 (d, *J* = 1.5 Hz, 1H), 6.80 (t, *J* = 6.9 Hz, 1H), 4.48 (t, *J* = 7.4 Hz, 2H), 4.00 (s, 3H), 3.77 (m, 2H), 1.83-1.76 (m, 6H), 1.73-1.62 (m, 4H), 1.13(sext, *J* = 7.2 Hz, 2H), 0.69 (t, *J* = 7.2

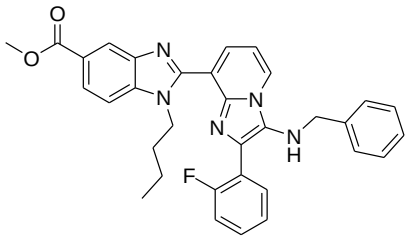
Hz 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 152.0, 147.1, 143.5, 141.2, 139.6, 135.5, 128.7, 128.5, 127.9, 127.0, 124.9, 124.8, 124.7, 127.2, 122.8, 120.8, 112.1, 110.6, 59.8, 52.6, 45.7, 34.1, 32.0, 24.1, 20.3, 13.8; MS (ESI) *m/z*: 553 (MH^+); HRMS (ESI, m/z) calcd for $C_{31}H_{33}N_6O_4$: *m/z* 553.2563; Found 553.2566 (M+H); IR (cm^{-1}, KBr): 3421, 3245, 2967, 1712, 1440, 1214.

Methyl 1-butyl-2-(4-nitrophenyl)-3-(benzylamino)imidazo[1,2-*a*]pyridin-8-yl]-1*H*-benzo[*d*]imidazole-5-carboxylate 10m.



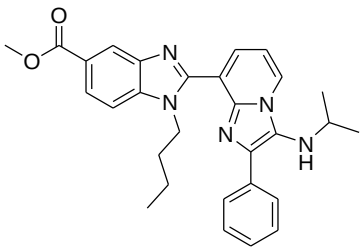
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.30 (d, J = 8.6 Hz, 1H), 8.25 (d, J = 8.6 Hz, 2H), 8.12 (d, J = 8.6, 1.2 Hz, 2H), 7.90 (d, J = 6.7 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.45 (d, J = 6.7 Hz, 1H), 7.30-7.29 (m, 5H), 6.51 (t, J = 6.7 Hz, 1H), 4.73 (brs, NH), 4.46 (t, J = 6.8 Hz, 2H), 4.29 (s, 2H), 4.01 (s, 3H),1.75 (q, J = 6.7 Hz, 2H), 1.11 (sext, J = 7.2 Hz, 2H), 0.70 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 152.0, 147.0, 143.3, 140.9, 139.5, 139.3, 139.1, 134.7, 129.2, 128.8, 128.6, 128.3, 128.0, 127.7, 124.9, 124.7, 124.3, 122.7, 120.3, 111.8, 110.6, 52.9, 52.6, 45.7, 31.9, 20.3, 13.9; MS (ESI) *m/z*: 575 (MH^+); HRMS (ESI, m/z) calcd for $C_{33}H_{31}N_6O_4$: *m/z* 575.2407; Found 575.2411 (M+H); IR (cm^{-1}, KBr): 2950, 1712, 1513, 1340.

Methyl 2-[3-(benzylamino)-2-(2-fluorophenyl)imidazo[1,2-*a*]pyridin-8-yl]-1-butyl-1*H*-benzo[*d*]imidazole-5-carboxylate 10n.



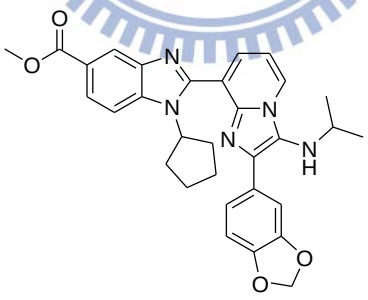
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 8.07 (dd, *J* = 8.6, 1.5 Hz, 2H), 7.74 (t, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 7.0 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.32 (dd, *J* =7.8, 1.5 Hz, 1H), 7.28 (s, 1H), 7.21 (s, 5H), 7.14 (dd, *J* =9.7, 1.5 Hz, 1H), 6.95 (t, *J* = 6.7, 1.4 Hz, 1H), 4.50 (t, *J* = 7.1 Hz, 2H), 4.11 (t, *J* = 6.2 Hz, 2H), 3.97 (s, 3H),1.73 (q, *J* = 7.3 Hz, 2H), 1.11 (sext, *J* = 7.3 Hz, 2H), 0.72 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 161.6, 158.4, 152.2, 143.4, 139.6, 139.5, 139.2, 132.2, 132.1, 130.0. 129.9. 128.8, 128.5, 128.0, 127.9, 127.8, 124.9, 124.8, 124.7, 122.8, 122.2, 120.5, 116.1, 115.8, 111.9, 110.4, 52.8, 52.5, 45.7, 32.1, 20.3, 13.8; MS (ESI) *m/z*: 548 (MH^+); HRMS (ESI, m/z) calcd for $C_{33}H_{31}FN_5O_2$: *m/z* 548.2462; Found 548.2459 (M+H); IR (cm^{-1}, KBr): 3421, 3245, 2967, 1708, 1446, 1299.

Methyl 1-butyl-2-[2-phenyl-3-(propan-2-ylamino)imidazo[1,2-*a*]pyridin-8-yl]-1*H*-benzimidazole-5-carboxylate 10º.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 1.0 Hz, 1H), 8.32 (dd, *J* = 6.7, 1.0 Hz, 1H), 8.08 (dd, *J* = 1.4, 8.5 Hz, 1H), 8.02 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.63 (d, *J* =7.0 Hz, 1H), 7.56 (dd, *J* = 8.6 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.31 (d, *J* = 7.3 Hz, 2H), 6.96 (t, *J* = 6.7 Hz, 1H), 4.55(t, *J=7.2 Hz*, 2H), 3.98 (s, 3H), 3.48 (m, 1Hz), 3.25 (brs, NH), 1.74 (q, *J* = 7.2 Hz, 2H), 1.15 (d, J= 6.3 Hz, 6H), 1.12-1.08 (m, 2H), 0.68(t, *J=7.3 Hz*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 152.6, 143.6, 139.8, 139.2, 138.0, 134.6, 128.9, 127.9, 127.6, 126.1, 124.9, 124.7, 122.8, 120.5, 111.7, 110.4, 52.5, 49.7, 45.7, 32.0, 23.6, 20.3; MS (ESI) *m/z*: 481 (MH^+); HRMS (ESI, m/z) calcd for $C_{29}H_{31}N_5O_2$: *m/z* 481.2478; Found (M+H); IR (cm^{-1}, KBr): 3212, 2958, 1716, 1442.

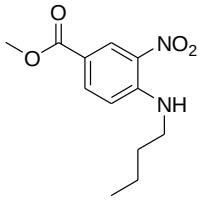
Methyl 2-[2-(1,3-benzodioxol-5-yl)-3-(propan-2-ylamino)-2,3-dihydroimidazo[1,2-*a*]pyridin-8-yl]-1-cyclopentyl-1*H*-benzimidazole-5-carboxylate 10p.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 1.5 Hz, 1H), 8.25 (dd, *J* = 6.5, 1.0 Hz, 1H), 8.02 (dd, *J* = 1.5, 8.5 Hz, 1H), 7.60-7.57 (m, 2H), 7.55 (dd, *J* = 6.5, 1.5 Hz, 2H), 6.90 (t, *J* = 6.5 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 5.98 (s, 2H), 4.89 (q, *J=8.5 Hz*, 1H), 3.96 (s, 3H), 3.45 (quart, *J* = 6.2 Hz, 1Hz), 3.21 (brs, NH), 2.35-2.48 (m, 4H), 2.01-1.95(m, 2H), 1.67-1.60 (m, 2H), 1.15 (d, *J=6.2 Hz*, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 152.3,

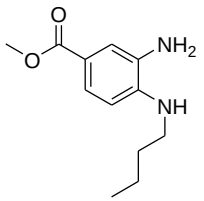
147.8, 146.9, 139.0, 137.4, 136.6, 128.4, 127.4, 127.3, 124.9, 124.4, 124.2, 122.6, 120.8, 111.7, 111.2, 108.4, 107.7, 101.0, 58.7, 52.1, 49.1, 30.4, 25.3, 23.5; MS (ESI) *m/z*: 537 (MH^+); HRMS (ESI, m/z) calcd for $C_{31}H_{31}N_5O_4$: *m/z* 537.2376; Found (M+H); IR (cm^{-1}, KBr): 3222, 2960, 1716, 1442

Methyl 4-(butylamino)-3-nitrobenzoate(3j)



Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.0 Hz, 1H), 8.28 (t, *J* = 5.6 Hz, 1H), 7.95 (dd, *J* = 9.0, 1.7 Hz, 1H), 6.80 (d, *J* = 9.0 Hz, 1H), 3.83 (s, 3H), 3.31-3.27 (q, *J* = 5.6 Hz, 2H), 1.75-1.65 (pent, *J* = 7.4 Hz, 2H), 1.51-1.39 (sext, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 2H), ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 148.1, 136.5, 131.3, 129.8, 117.2, 113.9, 52.4, 43.3, 31.2, 20.5, 14.1;

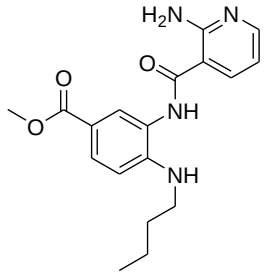
Methyl 3-amino-4-(butylamino)benzoate(4j)



Brown solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.39 (dd, *J* = 12.2, 1.9 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 3.81 (s, 3H), 3.31 (brs, 2H), 3.17 (t, *J* = 6.3 Hz, 1H), 1.69-1.59 (pent, *J* = 7.4 Hz, 2H), 1.51-1.39 (sext, *J* = 7.4 Hz, 2H), 0.96 (t, *J* =

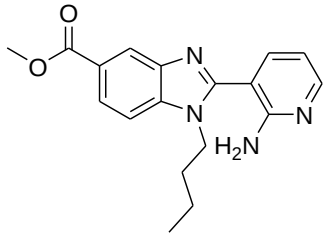
7.4 Hz, 2H), ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 143.6, 132.4, 124.7, 118.7, 118.4, 109.5, 52.0, 43.8, 31.9, 20.7, 14.3;

Methyl 3-[(2-amino-3-pyridyl)carbonyl]amino-4-(butylamino)benzoate(6j)



^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58(brs, NH), 8.27 (d, *J* = 7.6 Hz, 1H), 8.16 (d, *J* = 4.7, 1.5 Hz, 1H), 7.85 (t, *J* =5.5, 1.5 Hz, 1H), 6.66 (d, *J* = 9.2 Hz, 1H), 6.60 (d, *J* = 3.4, 4.8 Hz, 1H), 6.49 (brs, 2H), 3.81 (s, 3H), 1.80-1.77 (m, 2H), 1.65-1.52 (m, 2H), 1.46-1.34 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 167.4, 159.6, 152.3, 148.4, 137.8, 130.5, 129.5, 122.5, 117.9, 112.6, 110.7, 110.3, 51.9, 43.6, 31.7, 20.7, 14.3; MS (ESI) *m/z*: 343 (MH^+);

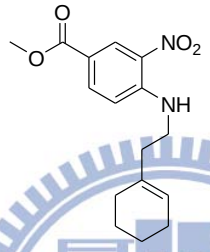
Methyl 2-(2-amino-3-pyridyl)-1-butyl-1*H*-benzo[*d*]imidazole-5-carboxylate 7j.



^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55(brs, NH), 8.45 (s, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 7.99 (dd, *J* =7.5, 1.4 Hz, 1H), 7.88 (t, *J* = 6.1 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 6.92 (d, *J* =

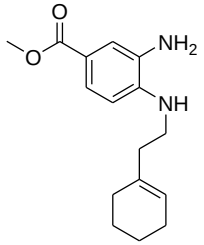
6.4, 1.0 Hz, 1H), 4.28 (t, *J* = 7.7 Hz, 2H), 3.94 (s, 3H), 3.19-3.09 (m, 2H), 1.91-1.77 (m, 6H), 1.41-1.22 (m, 4H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 155.1, 148.2, 142.3, 141.9, 138.8, 138.2, 126.4, 123.0, 113.4, 111.6, 110.9, 52.9, 46.9, 32.2, 26.9, 20.5, 14.1; MS (ESI) *m/z*: 325 (MH^+);

Methyl 4-[2-(1-cyclohexenyl)ethyl]amino-3-nitrobenzoate(3g)



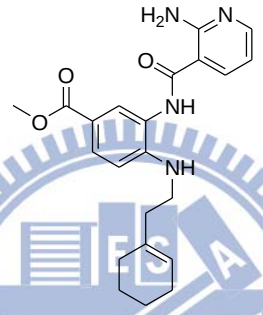
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.75 (d, *J* = 1.9 Hz, 1H), 8.28 (t, *J* = 5.6 Hz, 1H), 7.95 (dd, *J* = 9.0, 1.9 Hz, 1H), 6.79 (d, *J* = 9.0 Hz, 1H), 5.60 (m, 1H), 3.83 (s, 3H), 3.36-3.30 (q, *J* = 6.6 Hz, 2H), 2.31 (t, *J* = 6.6 Hz, 2H), 1.97-1.99 (m, 2H), 1.88-1.91 (m 2H), 1.62-1.47 (m, 4H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 147.9, 136.5, 133.9, 131.4, 129.7, 125.9, 117.1, 114.1, 52.4, 41.2, 37.2, 27.9, 25.6, 23.1, 22.6;

Methyl 3-amino-4-[2-(1-cyclohexenyl)ethyl]aminobenzoate 4g.



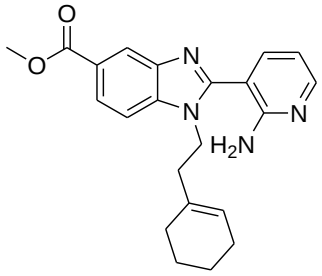
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, J = 8.3, 1.8 Hz, 1H), 7.40 (t, J = 1.8 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H), 5.55 (m, 1H), 3.85 (s, 3H), 3.38 (brs, 2H), 3.21 (t, J = 6.8 Hz, 2H), 2.31 (t, J = 6.8 Hz, 2H), 1.98-2.01 (m, 2H), 1.94 -1.93 (m 2H), 1.68-1.55 (m, 4H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 143.4, 135.1, 132.7, 124.6, 124.2, 118.8, 118.2, 109.6, 52.0, 41.6, 37.9, 28.3, 25.7, 23.3, 22.8; ;

Methyl 3-[(2-amino-3-pyridyl)carbonyl]amino-4-[2-(1-cyclohexenyl)ethyl]aminobenzoate 6g.



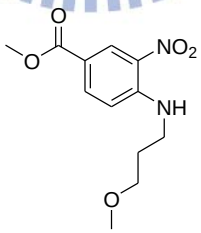
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.11 (d, J = 3.0 Hz, 1H), 7.97(d, J = 6.0 Hz, 1H), 7.84 (d, J = 6.0 Hz, 1H), 7.35 (m, 1H), 6.68 (d, J = 9.0 Hz, 2H), 6.60 (d J = 9.0 Hz, 2H), 5.42 (s, 1H), 3.81 (s, 3H), 3.19 (t, J = 6.0 Hz, 2H), 2.25 (t, J = 6.0 Hz, 2H), 1.88-1.90 (m, 3H), 1.77-1.75 (m, 3H), 1.60-1.53 (m, 3H), 1.48-1.43 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 158.8, 151.0, 148.2, 137.7, 134.9, 131.0, 129.4, 124.8, 121.6, 118.1, 112.5, 110.0, 110.5, 52.1, 40.8, 37.7, 27.9, 25.5, 23.1, 22.6; MS (ESI) *m/z*: 395 (MH^+);

Methyl 2-(2-amino-3-pyridyl)-1-[2-(1-cyclohexenyl)ethyl]-1*H*-benzo[*d*]imidazole-5-carboxylate 7g.



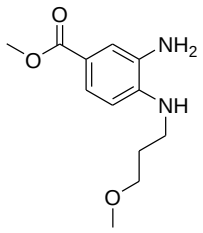
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (brs, NH), 8.45 (s, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 7.99 (dd, *J* =7.5, 1.4 Hz, 1H), 7.88 (t, *J* = 6.1 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 6.92 (d, *J* = 6.4, 1.0 Hz, 1H), 4.28 (t, *J* = 7.7 Hz, 2H), 3.94 (s, 3H), 3.19-3.09 (m, 2H), 1.91-1.77 (m, 6H), 1.41-1.22 (m, 4H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 155.1, 148.2, 142.3, 141.9, 138.8, 138.2, 126.4, 123.0, 113.4, 111.6, 110.9, 52.9, 46.9, 32.2, 26.9, 20.5, 14.1; MS (ESI) *m/z*: 377 (MH^+);

Methyl 4-[(3-methoxypropyl)amino]-3-nitrobenzoate 3a



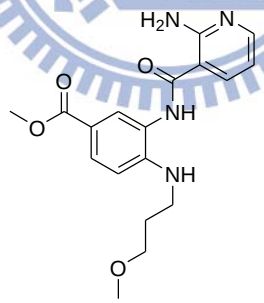
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.77 (d, *J* = 1.9 Hz, 1H), 8.63 (t, *J* = 5.4 Hz, 1H), 7.96 (dd, *J* = 9.0, 1.9 Hz, 1H), 6.83 (d, *J* = 9.0, 3.5 Hz, 1H), 3.84 (s, 3H), 3.53-3.50(m, 2H), 3.47-3.40 (m, 2H), 3.35 (s, 3H), 2.00-1.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 148.1, 136.5, 131.5, 129.8, 117.1, 113.8, 70.9, 59.2, 51.4, 41.7, 29.0;

Methyl 3-amino-4-[(3-methoxypropyl)amino]benzoate 4a.



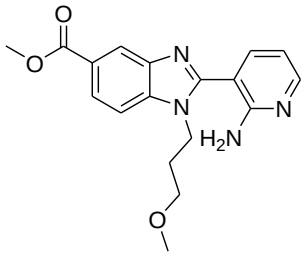
Brown solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.3, 1.9 Hz, 1H), 7.40 (d, J = 1.9 Hz, 1H), 6.59 (d, J = 8.3 Hz, 1H), 3.85 (s, 3H), 3.54 (t, J = 5.7 Hz, 2H), 3.36 (s, 3H), 3.29 (t, J = 6.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 143.4, 132.6, 124.5, 118.9, 118.1, 109.4, 71.8, 59.2, 51.9, 42.3, 31.3, 29.5;

Methyl 3-[(2-amino-3-pyridyl)carbonyl]amino-4-[(3-methoxypropyl)amino]benzoate 6a.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 3.0 Hz, 1H), 8.10 (s, brsNH), 8.03-8.01 (m, 2H), 7.89-7.86 (m, *2*H), 7.33 (m, 1H), 6.71-6.66 (m, 2H), 3.84 (s, 3H), 3.51 (t, J = 6.0 Hz, 2H), 3.31 (t, J = 6.0 Hz, 2H), 3.20 (s, 3H), 2.00-1.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 158.9, 151.4, 148.3, 137.4, 131.0, 129.3, 126.7, 125.0, 121.5, 119.2, 118.2, 112.8, 110.6, 59.1, 52.1, 46.7, 42.6, 29.1; MS (ESI) *m/z*: 359 (MH^+);

Methyl 2-(2-amino-3-pyridyl)-1-(3-methoxypropyl)-1*H*-benzo[*d*]imidazole-5-carboxylate 7a.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, *J* = 0.9 Hz NH), 8.12 (dd, *J* = 5.0, 1.7 Hz, 1H), 7.98 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.61 (dd, *J* =7.6, 1.7 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 6.72 (dd, *J* = 5.1, 7.6 Hz, 1H), 6.16 (brs, 2H), 4.32(t, *J=6.8 Hz*, 2H), 3.89 (s, 3H), 3.18 (t, *J*=5.4 Hz, 2H), 3.16 (s, 3H), 2.00-1.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 158.1, 152.5, 149.6, 142.5, 138.8, 138.3, 125.1, 124.9, 122.2, 113.2, 110.3, 108.7, 68.8, 58.9, 52.5, 42.4, 30.2; MS (ESI) *m/z*: 341 (MH^+);

3.18. References

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Chapter Four

4.0. Andrographolide and Andrographolide analogues its importance and synthesis

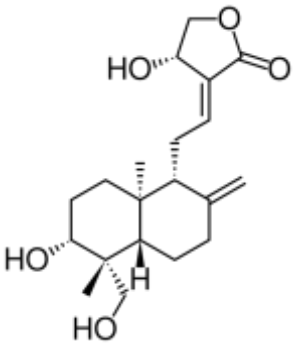


Figure 4.0. Andrographolide plant, courtesey.

http://www.hccbif.info/Antidiabetic/andrographolide_1.html

Andrographolide 3-[2-[decahydro-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2 ethylene-1- napthalenyl]ethylidene]dihydro- 4-hydroxy-2(3*H*)-furanone) is a labdane diterpenoid that is the major bioactive component of the medicinal plant *Andrographis paniculata* as in figure 10. Andrographolide is an extremely bitter substance extracted from the stem and leaves of the andrographis paniculata, which is grown for medicinal purposes in China and India.[1-2]

4.1. Medicinal use

Andrographolide exhibits anti-inflammatory, anti-infective, anti-hepatotoxic, antiviral, and anticancer activities. The anticancer activity of andrographolide includes growth

suppression, apoptosis promotion, antiangiogenesis, and antitransformation. Andrographis and its various components have demonstrated a variety of effects in the body. Aspects stimulate the general immune activities, others inhibit the body's inflammatory mechanism and still others demonstrate not only anti-microbial abilities, but also are instrumental in killing certain tumor cells. Studies have also indicated that the active chemical, Andrographolide, helps to stop the clumping of blood platelets which is the clotting process that can lead to heart attacks.[3-6]

4.2. Anti-inflammatory

There appears to be a significant presence of flavanoids in the Andrographis Paniculata herb, which always have an anti-inflammatory affect. In vitro studies have shown that the flavinoid activities supressed the genetic expression of neutrofils, an inflammatory agent. Similarly, studies have indicated that a variety of inflammatory proteins, including COX-2, are reduced by the presence of Andrographolide.[7-8]

4.3. Anti-cancer

Andrographis paniculata plant extract is known to possess a variety of pharmacological activities. Andrographolide, the major constituent of the extract is implicated towards its pharmacological activity. Andrographolide treatment inhibited the in vitro proliferation of different tumor cell lines, representing various types of cancers. The compound exerts direct anticancer activity on cancer cells by cell-cycle arrest at G0/G1 phase through induction of cell-cycle inhibitory protein p27 and decreased expression of cyclin-dependent kinase 4 (CDK4). Immunostimulatory activity of andrographolide is evidenced

by increased proliferation of lymphocytes and production of interleukin-2. Andrographolide also enhanced the tumor necrosis factor-alpha production and CD marker expression, resulting in increased cytotoxic activity of lymphocytes against cancer cells, which may contribute for its indirect anticancer activity and hence has the potential for being developed as a cancer therapeutic agent. [9-10]

4.4. Anti-diabetic agents

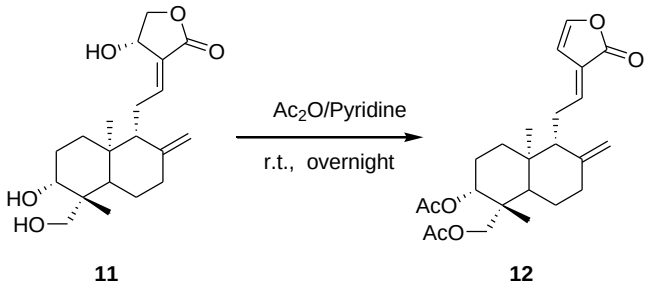
While all anti-diabetic agents can decrease blood glucose level directly or indirectly, few are able to protect and preserve both pancreatic beta cell mass and their insulin-secreting functions. Thus, there is an urgent need to find an agent or combination of agents that can lower blood glucose and preserve pancreatic beta cells at the same time. Here, they report a dualfunctional andrographolide-lipoic acid conjugate. The anti-diabetic and beta cell protective activities of the novel andrographolide-lipoic acid conjugate (AL-1) were investigated. It lowers plasma glucose in STZ-diabetic rats by increasing glucose utilization.[11]

4.5. Antiviral

Andrographis paniculata has been reported to have antiviral, antipyretic and anticancer activities.[12]

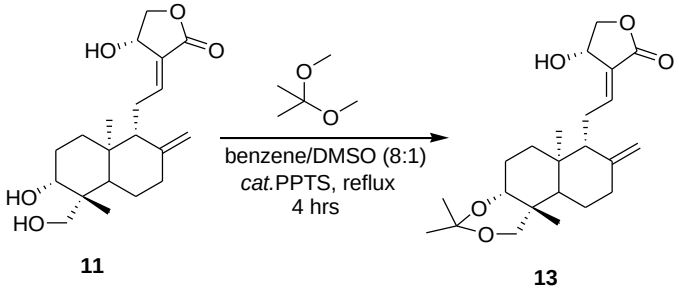
4.6. Result and discussion

Src oncogenes are deservingly associated with cancer initiation and progression because of their elevated expression and aberrant activation. Due to this property, Src is becoming a promising molecular target for anti-cancer therapy. Interestingly, it has never been reported that andrographolide or its analogues inhibits the activity of the *v-Src* oncoprotein. This is our effort to establish that parent compound **11** and some of its analogues, we synthesized in our lab blocks *v-Src*-induced morphological transformation and anchorage-independent cell growth leads to the degradation of *v-Src*- protein via ubiquitination, the attenuation of the phospho-Erk1/2 level and the delay of E-cadherin down regulation. The synthetic pathways used in the present work are outlined in this dissertation and all employed andrographolide **11** as one of the starting materials. Reaction of andrographolide **11** with excess of acetic anhydride in presence of pyridine as solvent resulted the acetylation of C-9 and C-19 OH groups into OAc groups, where as the C-14 OH group underwent dehydration to form the diacetylated andrographolide analogs **12**. The reaction was stirred under room temperature for 24 hours. Snce the reaction was carried out under basic solvents so the primary hydroxy group adjacent to lactone moiety has been eliminated as shown in Scheme 4.0.



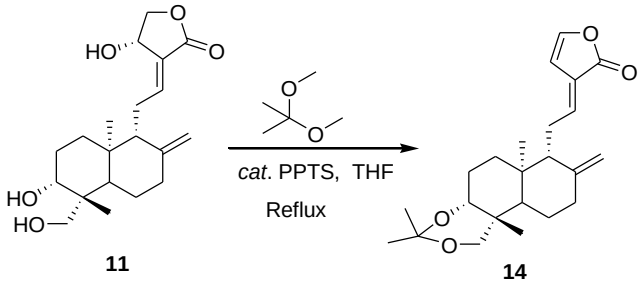
Scheme 4.0. Synthesis of diacetylated andrographolide analog 12

Sunsequently, our next target was the protection of C-9 and C-19 OH of andrographolide **11** with 2,2 dimethoxy propane in presence of benzene/DMSO sovent to provide the double OH protected analogs **13**. The reaction has been carried out for 4 hrs under reflux temperature to yield the 3,19-Isopropylideneandrographolide analogs **13** as shown in Scheme 4.1.



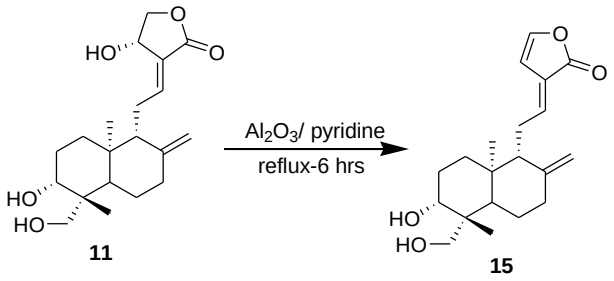
Scheme 4.1. Synthesis of 3,19-Isopropylideneandrographolide analog 13.

But it has been observed that when andrographolide **11** was treated with 2,2-dimethoxy propane and pyridinium-*p*-toluene sulfonate reagent, we found that the primary hydroxyl group elimination adjacent to lactone ring and dimethyl protection of two germinal hydroxyl group to obtain the compound **14** as shown in Scheme 4.2. Since the primary hydroxyl group near lactone ring is very labile it is easily removed in little base medium. Here pyridinim paratoluene sulphonate act as base.



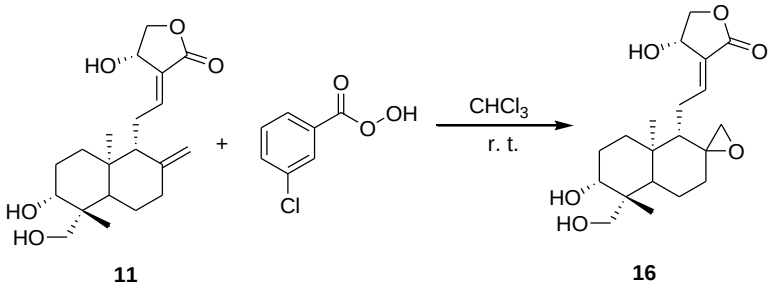
Scheme 4.2. Synthesis of andrographolide analog 14.

Similarly to obtain the C-14 dehydrated andrographolide analogs 5, we treated the Here andrographolide **11** with alumina using pyridine as a solvent. The reaction has been performed under refluxing conditions for 6 hrs to obtain the compound **15** as shown in the Scheme 4.3.



Scheme 4.3. Synthesis of dehydrated andrographolide analog 15.

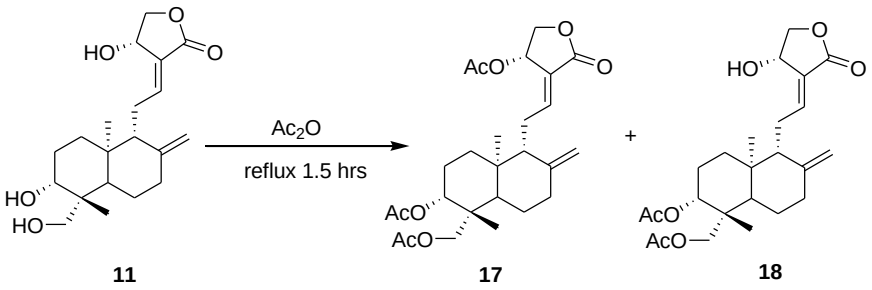
In the following scheme the andrographolide **11** has been treated with *m*-Choloro peroxy benzoic acid in choloroform solution under room temperature for 12 hrs. The epoxydation of exocyclic double bond provided the analogs **16** as shown in Scheme 4.4.



Scheme 4.4. Synthesis of epoxy substituted andrographolide analog 16.

In the following scheme we planned to treat the andrographolide **11** by acetic anhydride. For this reaction we took andrographolide **11** and acetic anhydride as solvent. The

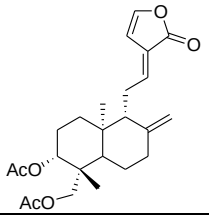
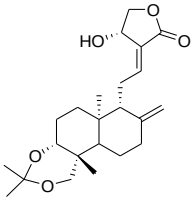
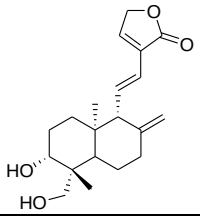
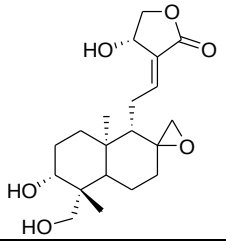
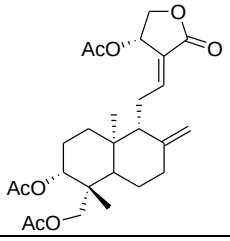
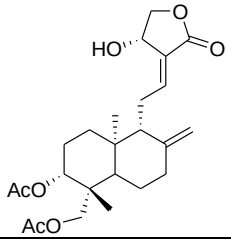
reaction has been carried out in refluxing conditions for 2 hrs. After completion of the reaction, as checked by TLC indicated the formation of two products. After purification of reaction mixture we obtained the triacetylated product and diacetylated andrographolide analogs **17** and **18** respectively as shown in Scheme 4.5.



11 **17** **18**

Scheme 4.5. Synthesis of tri and diacetyled andrographolide analogs 17 and 18.

Table 4.0 Tabular form of Andrographolide analogs

Compound Code	Compound No	Structure
NCTU-SUN-50	12	
NCTU-SUN-30	13	
NCTU-SUN-48	15	
NCTU-SUN-381	16	
NCTU-SUN-322	17	
NCTU-SUN-323	18	

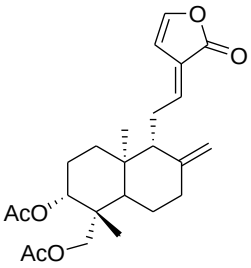
4.7. Application of andrographolide and its analogs for potential targets

It is important to know that the nuclear factor kappaB (NF-κB), a transcription factor, plays an important part in carcinogenesis as well as in the regulation of immune and inflammatory responses. NF-kappaB induces the expression of diverse target genes that endorse cell proliferation, control apoptosis, facilitate angiogenesis and further stimulate invasion and metastasis. Furthermore, many cancer cells show aberrant or constitutive NF-kappaB activation which mediates resistance to chemo- and radio-therapy. Therefore, it is important to inhibit the NF-κB activation and its signaling pathways which offer a potential cancer therapy. In addition, recent studies have shown that NF-ΚB can also play a tumor suppressor role in certain settings. Herein, we demonstrated that the andrographolide and its analogs able to target NF-κB in cancer therapy. The bioassay data has been incorporated in Appendix. Tumor necrosis factor (TNF) promotes the inflammatory response, which in turn causes many of the clinical problems associated with autoimmune disorders such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, psoriasis, hidradenitis suppurativa and refractory asthma. These disorders are sometimes treated by using a **TNF inhibitor**. The important side effects that have been most extensively related to TNF-alpha blockers include: lymphoma, infections, congestive heart failure, demyelinating disease, a lupus-like syndrome, induction of auto-antibodies, injection site reactions, and systemic side effects

4.8. Conclusion: Hence Andrographolide analogs has been synthesized and tested for bioassy

4.9 Experimental Section

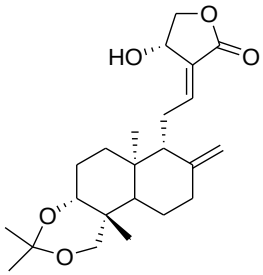
(1*R*,2*S*,4a*R*,5*S*,8a*S*)-2-(acetyloxy)-1,4a-dimethyl-6-methylene-5-[2-(2-oxo-2,3-dihydro-3-furanyliden)ethyl]perhydro-1-naphthalenylmethyl acetate (12)



NCTU-SUN-050

^{1}H NMR (300MHz, $CDCl_3$) δ 7.02 (dd, *J* = 3.3, 1.6 Hz, 1H), 6.71 (t, *J* = 7.2 Hz,1H), 6.18 (dd, *J* = 3.5, 0.8 Hz, 1H), 4.89 (s, 1H), 4.62 (dd, *J* = 11.3, 4.6 Hz, 1H), 4.46 (s, 1H), 4.40 (d, *J* = 11.7 Hz, 1H), 4.13 (d, *J* = 11.7 Hz, 1H), 2.52-2.41 (m, 3H), 2.06 (s, 6H), 2.05-1.71 (m, 6H), 1.56- 1.35 (m, 3H), 1.05 (s, 3H), 0.80 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.3, 170.9, 168.3, 146.9, 145.9, 144.4, 126.3, 109.2, 105.4, 80.1, 65.1, 56.4, 55.6, 41.7, 39.5, 38.3, 37.4, 26.3, 24.6, 23.1, 21.6, 21.5, 15.0.

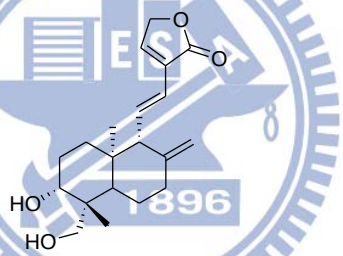
(4*R*)-3-(*E*)-2-[(1*S*,4a*S*,5*R*,6*S*,8a*R*)-6-methoxy-5-(methoxymethyl)-5,8a-dimethyl-2-methyleneperhydro-1-naphthalenyl]ethylidene-4-hydroxytetrahydro-2-furanone (13)



NCTU-SUN-030

^{1}H NMR (300MHz, $CDCl_3$) δ 6.93 (t, *J* = 6.7 Hz, 1H), 5.01 (d, *J* =5.1 Hz, 1H), 4.90 (s, 1H), 4.63 (s, 1H), 4.45(dd, *J* = 10.4, 6.2 Hz, 1H), 4.26 (d, *J* = 10.4 Hz, 1H), 3.97 (d, *J* = 11.6 Hz, 1H), 3.49 (dd, *J* = 8.4, 3.2Hz, 1H), 3.38 (brs, OH), 3.18 (d, *J* =11.6 Hz, 1H), 2.57 (t, *J* = 6.8 Hz, 2H), 2.42(m, 1H), 1.04- 1.93 (m, 2H), 1.86-1.71 (m, 4H),1.41 (s, 3H), 1.36 (s, 3H), 1.33-1.32 (m, 3H), 1.92(s, 3H), 0.95(s, 3H), ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ170.9, 149.6, 147.3, 128.3, 109.4, 99.6, 76.7, 66.4, 64.2, 56.4, 52.6, 38.8, 38.3, 38.1, 27.6, 26.5, 25.7, 25.4, 16.6.

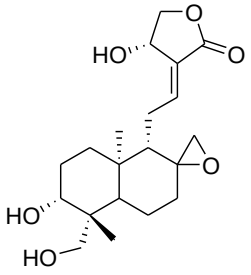
3-(*E*)-2-[(1*S*,4a*S*,5*R*,6*S*,8a*R*)-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methyleneperhydro-1-naphthalenyl]-1-ethenyl-2,5-dihydro-2-furanone(15)



NCTU-SUN-48

^{1}H NMR (300MHz, $CDCl_3$) δ 7.18 (s, 1Ha), 6.89 (dd, *J* = 15.8, 10.0 Hz,1Hb), 6.13 (d, *J* = 15.8 Hz, 1Hc), 4.83 (s, 2Hd.e), 4.80 (d, *J* = 11.3 Hz, 1Hf), 4.54 (s, 1H), 4.23 (d, *J* = 11.3 Hz, 1Hj), 3.50 (dd, *J* = 5.1, 11.1 Hz, 1Hm), 3.35 (d, *J* = 11.1 Hz, 1Hn), 2.97-2.82 (brs, 2-OH), 2.46 (d, *J* = 11.1 Hz,1Hl), 2.33 (d, *J* = 10.0 Hz, 1Hk), 2.10-1.84 (m, 1H), 1.84-1.73(m, 3H).), 1.57-1.50 (m, 2H), 1.28 (s, 3H), 1.36-1.14 (m, 3H), 0.83 (s, 3H).

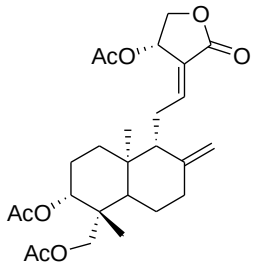
(3*E*,4*S*)-4-hydroxy-3-{2-[(1*S*,5*R*,6*R*,8a*R*)-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyloctahydro-1*H*-spiro[naphthalene-2,2'-oxiran]-1-yl]ethylidene}dihydrofuran-2(3*H*)-one



NCTU-SUN-381

^{1}H NMR (300MHz, $CDCl_3$) δ 6.81 (dd, *J* = 10.3, 5.7 Hz, 1H), 4.98(d, *J* =4.8 Hz, 1H), 4.39 (dd, *J* = 10.3, 6.0 Hz, 1H), 4.31 (s, 1H), 4.26 (d, *J* = 10.3 Hz, 1H), 4.21-4.08 (m, 2H), 3.49 (t, *J* =6.4 Hz, 1H), 3.35 (s, 3H), 2.87(d, *J* = 1.6 Hz, 1H), 2.66 (d, *J* = 3.5 Hz, 1H), 2.08 (s, 3H), 2.04-1.73 (m, 6H), 1.47- 1.43(m, 2H), 1.26 (t, *J* = 7.2 Hz 7H), 0.83 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ171.7, 170.9, 146.7, 129.4, 80.4, 74.2, 65.6, 64.3, 60.9, 60.6, 54.9, 53.8, 51.3, 43.0, 40.1, 37.2, 36.3, 27.7, 23.2, 21.7, 21.5, 15.6, 14.6.

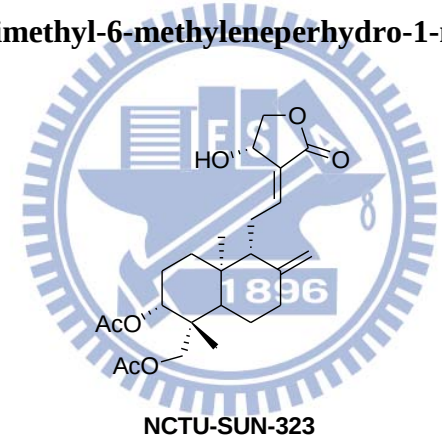
(3*R*)-4-((*E*)-2-(1*S*,4a*S*,5*R*,6*S*,8a*R*)-6-(acetyloxy)-5-[(acetyloxy)methyl]-5,8a-dimethyl-2-methyleneperhydro-1-naphthalenylethylidene)-5-oxotetrahydro-3-furanyl acetate(17)



NCTU-SUN-322

^{1}H NMR (300MHz, $CDCl_3$) δ 6.87 (dd, *J* = 6.7, 1.4Hz, 1H), 5.89 (d, *J* =5.9 Hz, 1H), 4.86 (S, 1H), 4.57 (d, *J* =11.2, 4.0 Hz, 1H), 4.51(d, *J* = 5.2 Hz, 1H), 4.48 (d, *J* = 1.7 Hz, 1H), 4.32 (d, *J* = 11.7 Hz, 1H), 4.21 (dd, *J* = 11.2, 1.7Hz, 1H), 4.08(d, *J* = 11.7 Hz, 1H), 2.41~2.36 (m, 3H), 2.09 (s, 3H), 2.01 (s, 3H) 2.00 (s, 3H), 1.97-1.65 (m, 6H), 1.45 (m, 1H),1.34~1.24 (m, 2H), 0.99 (s, 3H), 0.72 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ171.3, 170.9, 170.8, 169.4, 150.5, 72.0, 68.1, 65.0, 56.1, 55.5, 41.6, 39.3, 38.2, 37.3, 25.5, 24.9, 24.6, 23.0, 21.6, 21.5, 21.1, 14.9.

((1*R*,2*S*,4a*R*,5*S*,8a*S*)-2-(acetyloxy)-5-2-[(4*R*)-4-hydroxy-2-oxotetrahydro-3-furanyliden]ethyl-1,4a-dimethyl-6-methyleneperhydro-1-naphthalenyl)methyl acetate(18)



NCTU-SUN-323

^{1}H NMR (300MHz, $CDCl_3$) δ 6.87 (dd, *J* = 6.7, 1.4Hz, 1H), 5.89 (d, *J* =5.9 Hz, 1H), 4.86 (S, 1H), 4.57 (d, *J* =11.2, 4.0 Hz, 1H), 4.51(d, *J* = 5.2 Hz, 1H), 4.48 (d, *J* = 1.7 Hz, 1H), 4.32 (d, *J* = 11.7 Hz, 1H), 4.21 (dd, *J* = 11.2, 1.7Hz, 1H), 4.08(d, *J* = 11.7 Hz, 1H), 2.41~2.36 (m, 3H), 2.09 (s, 3H), 2.01 (s, 3H) 2.00 (s, 3H), 1.97-1.65 (m, 6H), 1.45 (m, 1H),1.34~1.24 (m, 2H), 0.99 (s, 3H), 0.72 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ171.3, 170.9, 170.8, 169.4, 150.5, 72.0, 68.1, 65.0, 56.1, 55.5, 41.6, 39.3, 38.2, 37.3, 25.5, 24.9, 24.6, 23.0, 21.6, 21.5, 21.1, 14.9.

4.10.References

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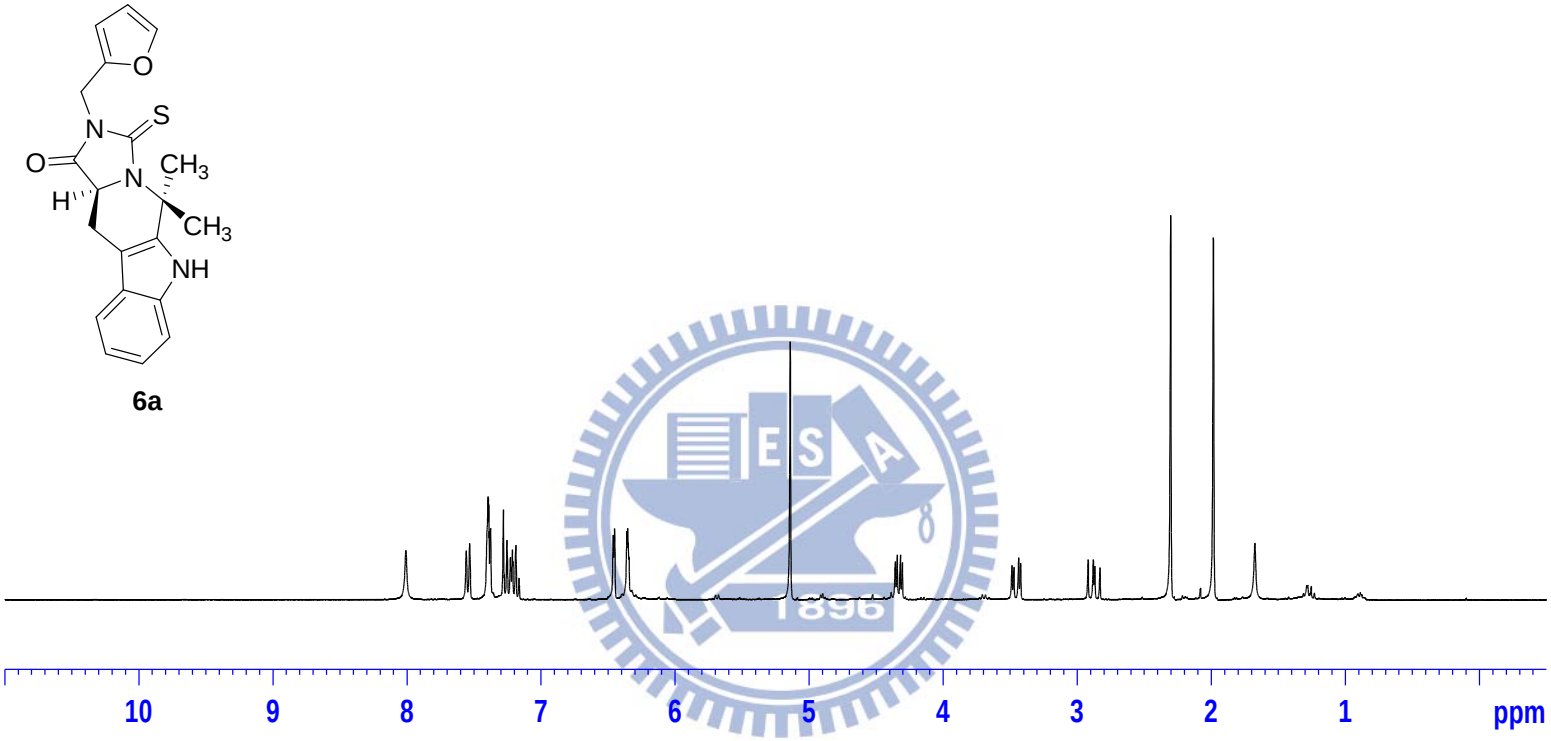
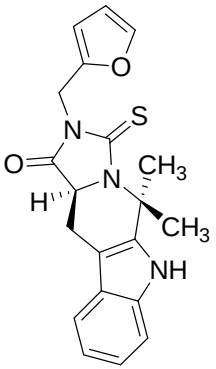
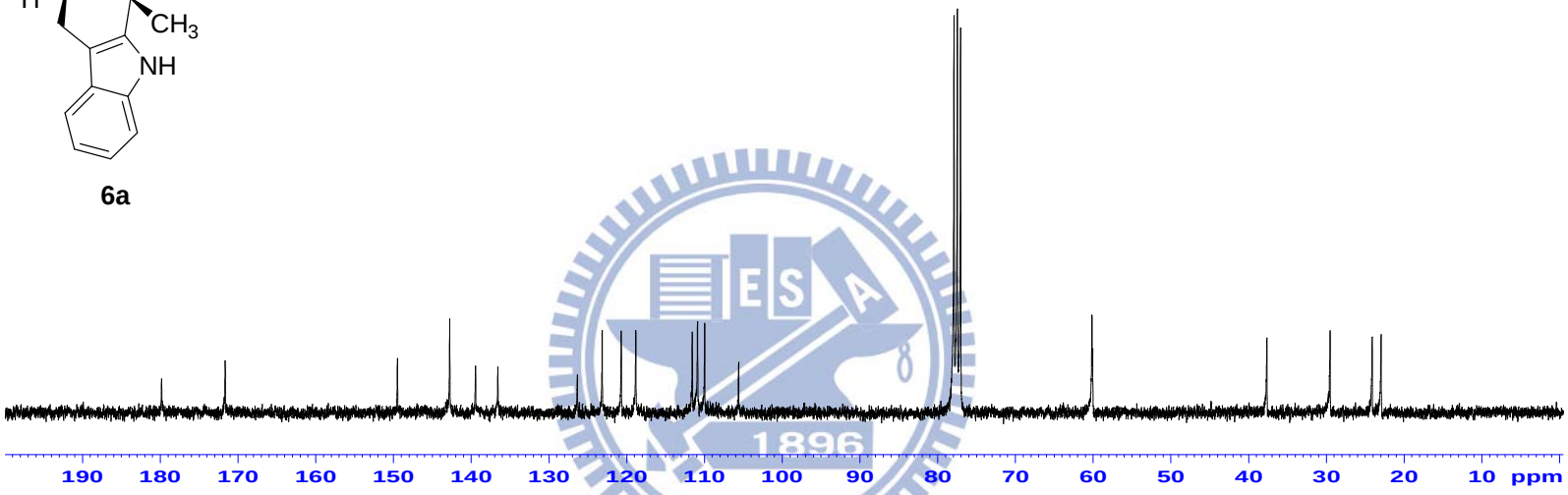


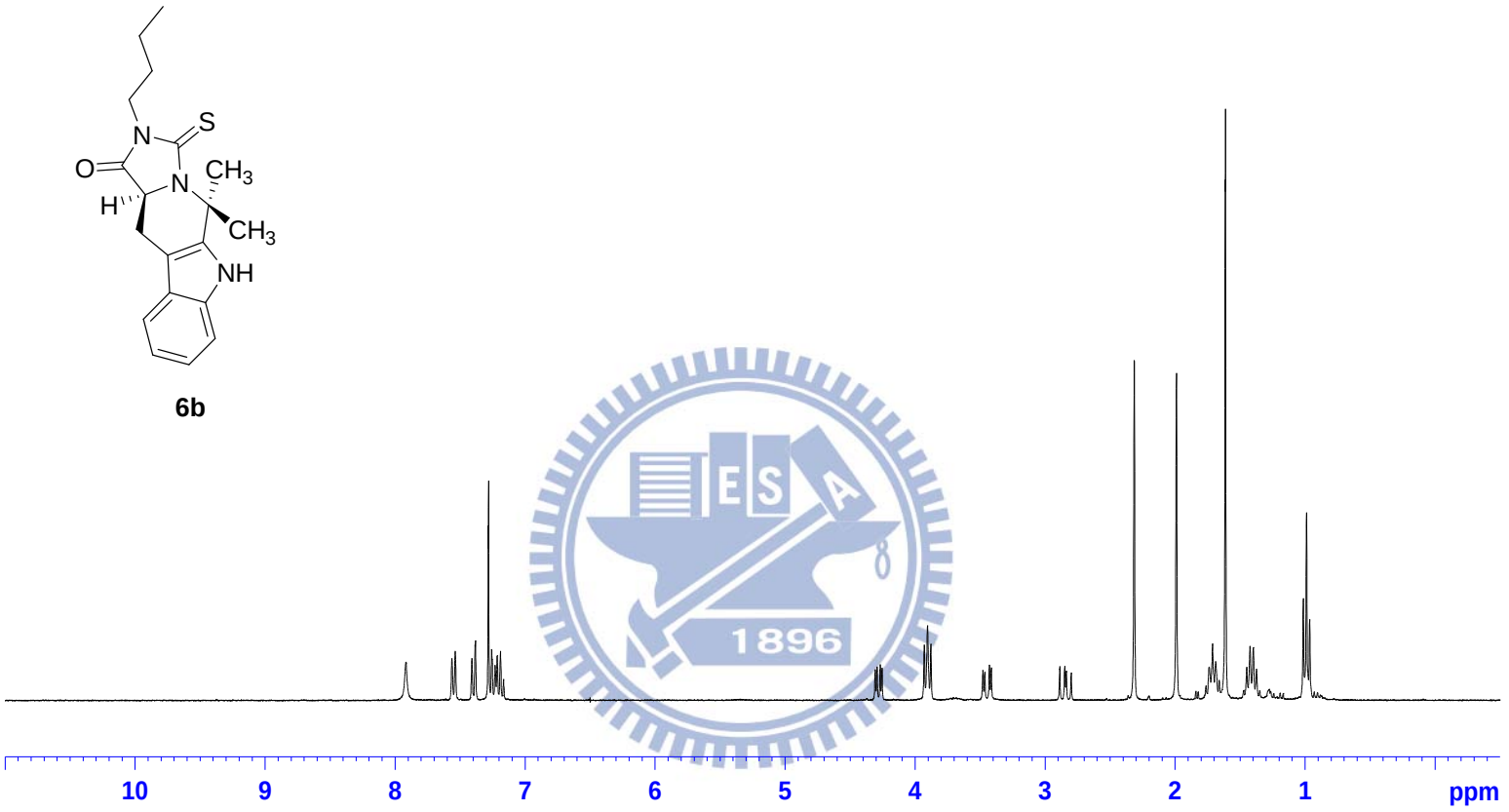
^{1}HNMR spectrum (300 MHz) of compound 6a in $CDCl_3$



6a

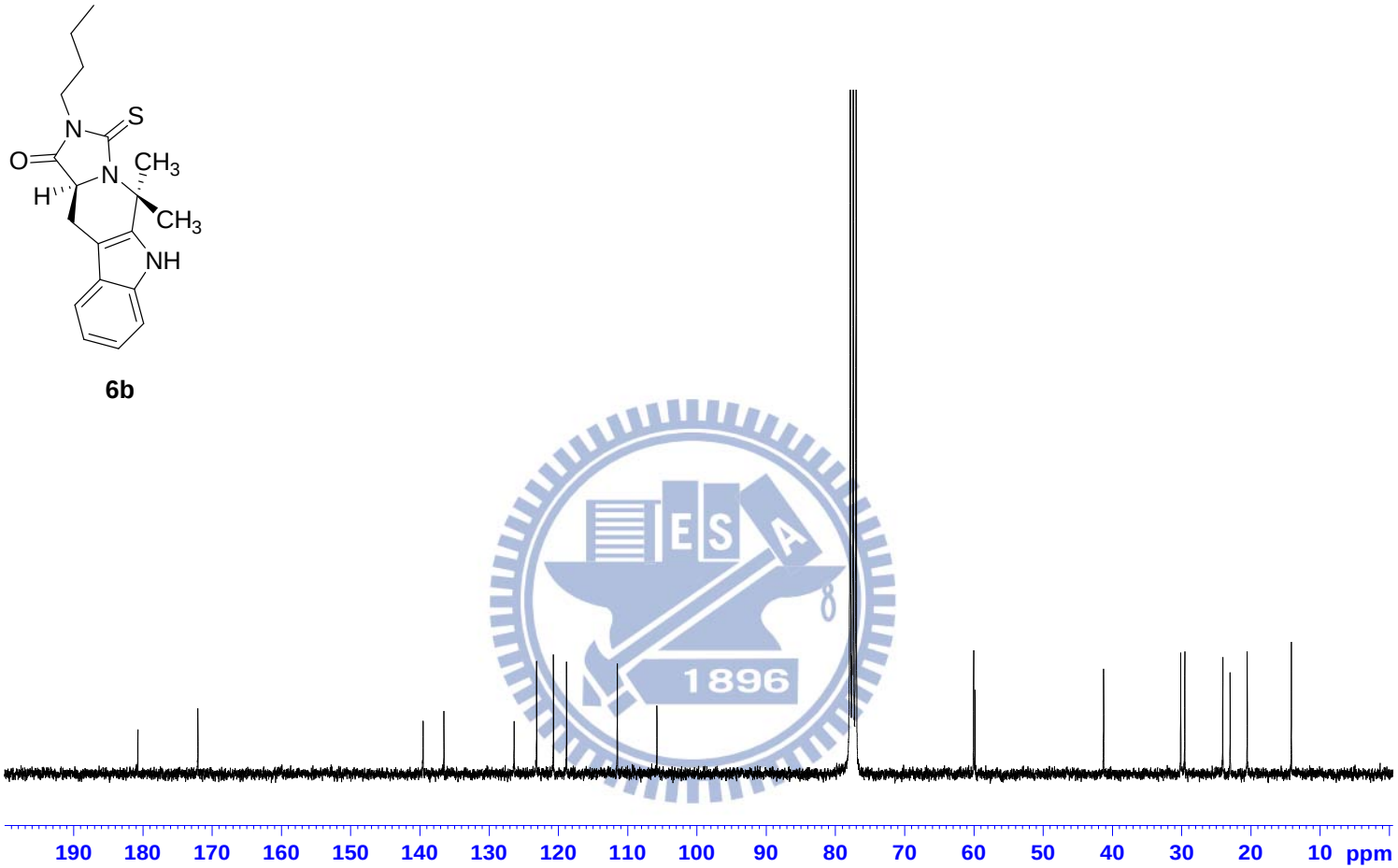


^{13}C NMR spectrum (75 MHz) of compound 6a in $CDCl_3$



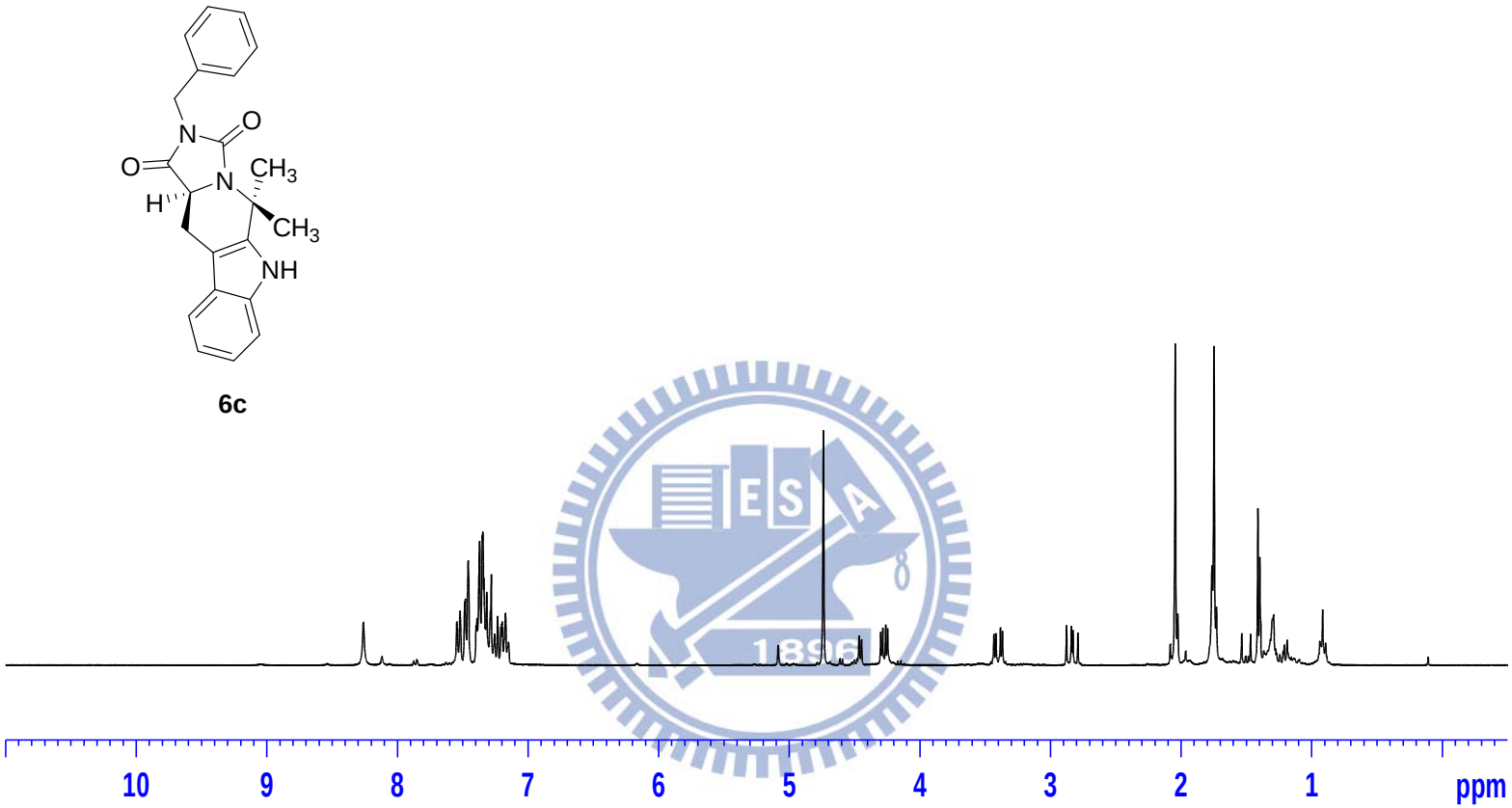
6b

^{1}HNMR spectrum (300 MHz) of compound 6b in $CDCl_3$



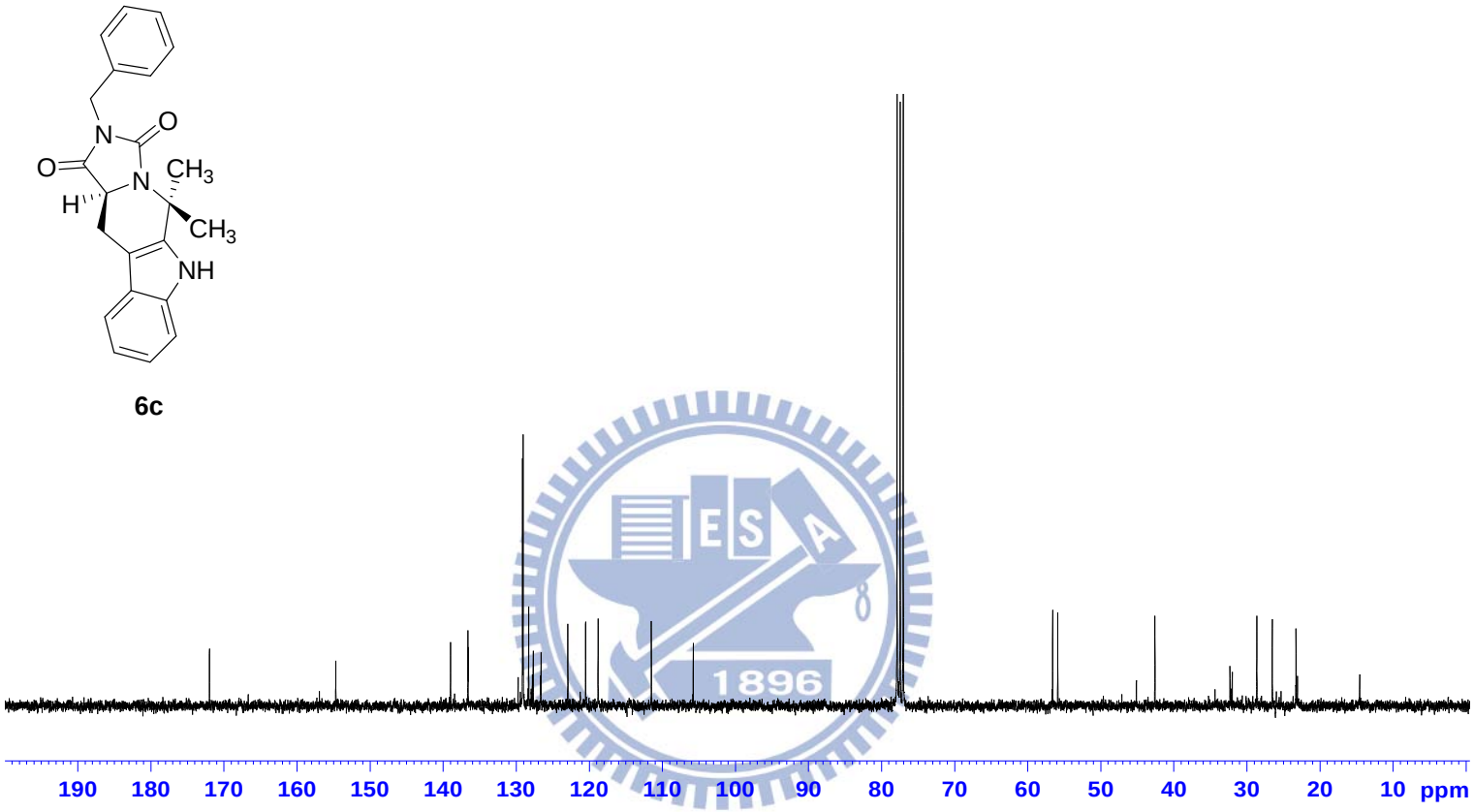
6b

^{13}C NMR spectrum (75 MHz) of compound 6b in $CDCl_3$



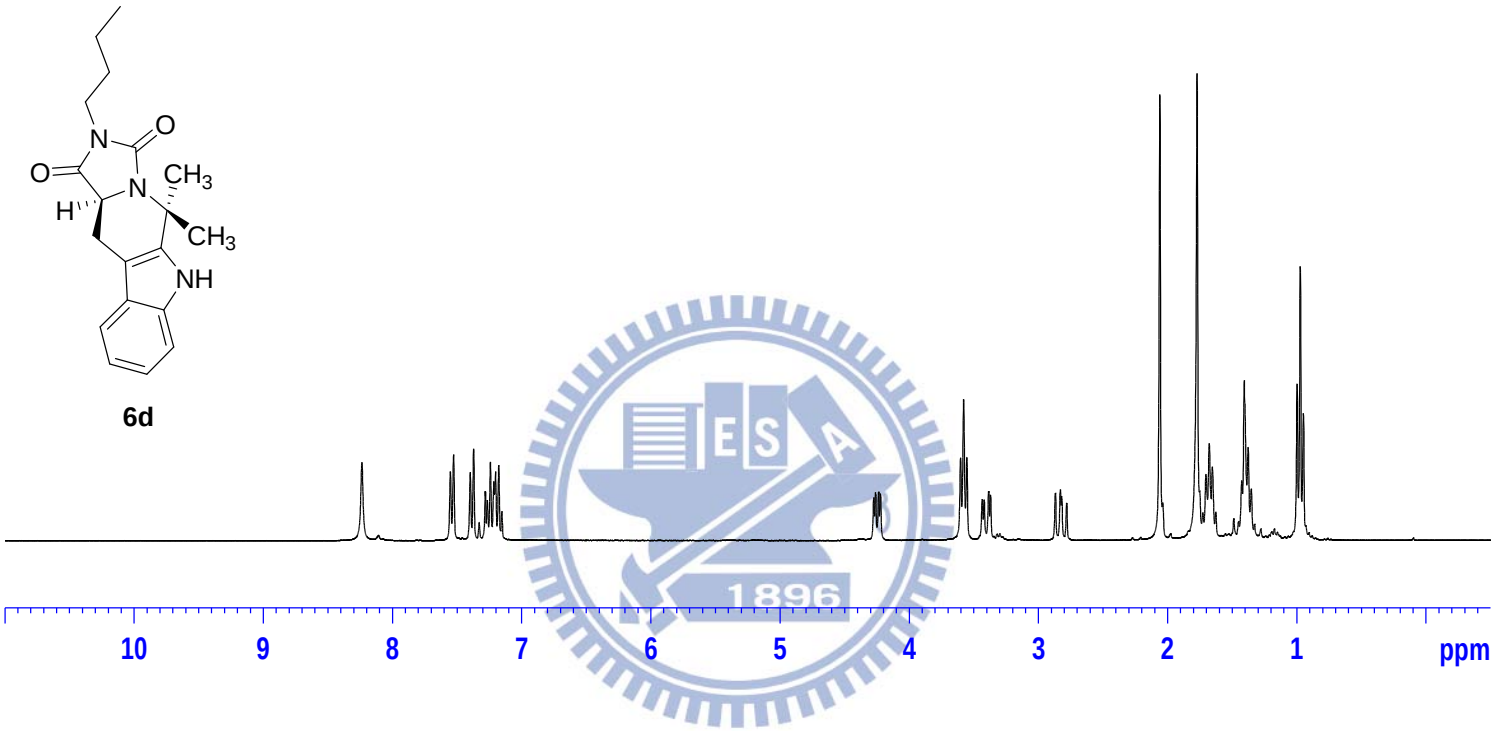
6c

^{1}HNMR spectrum (300 MHz) of compound 6c in $CDCl_3$



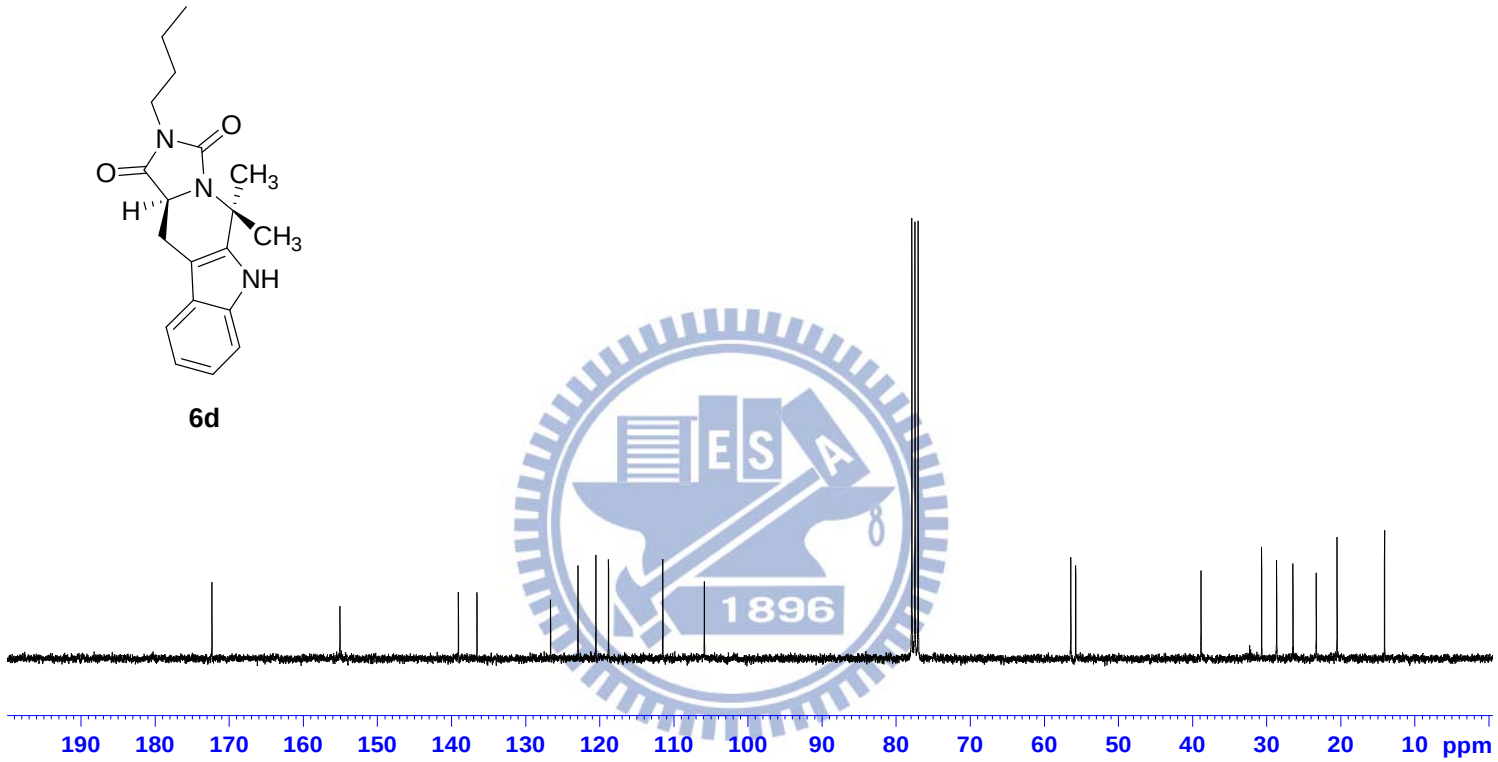
6c

^{13}C NMR spectrum (75 MHz) of compound 6c in $CDCl_3$

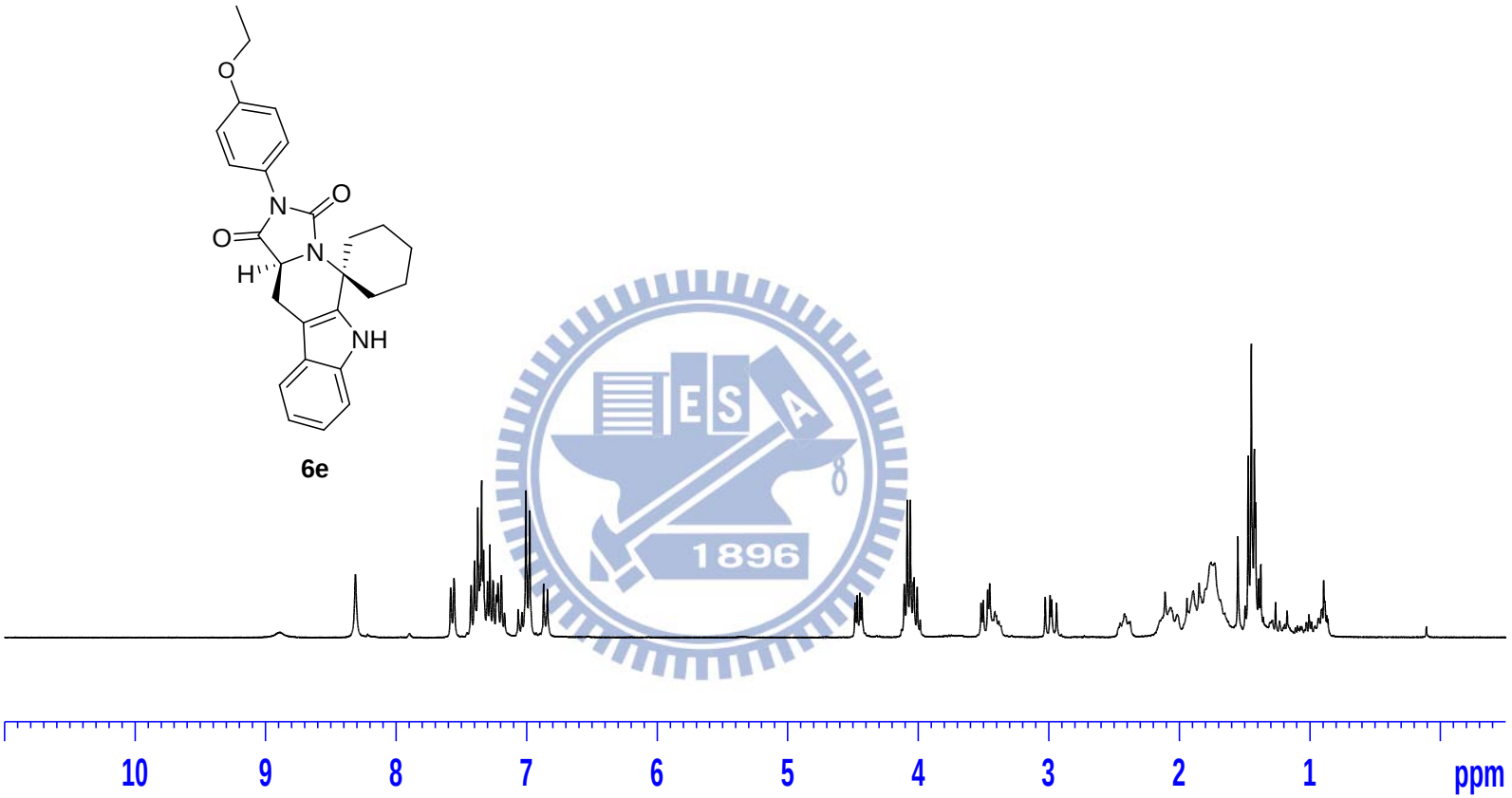


6d

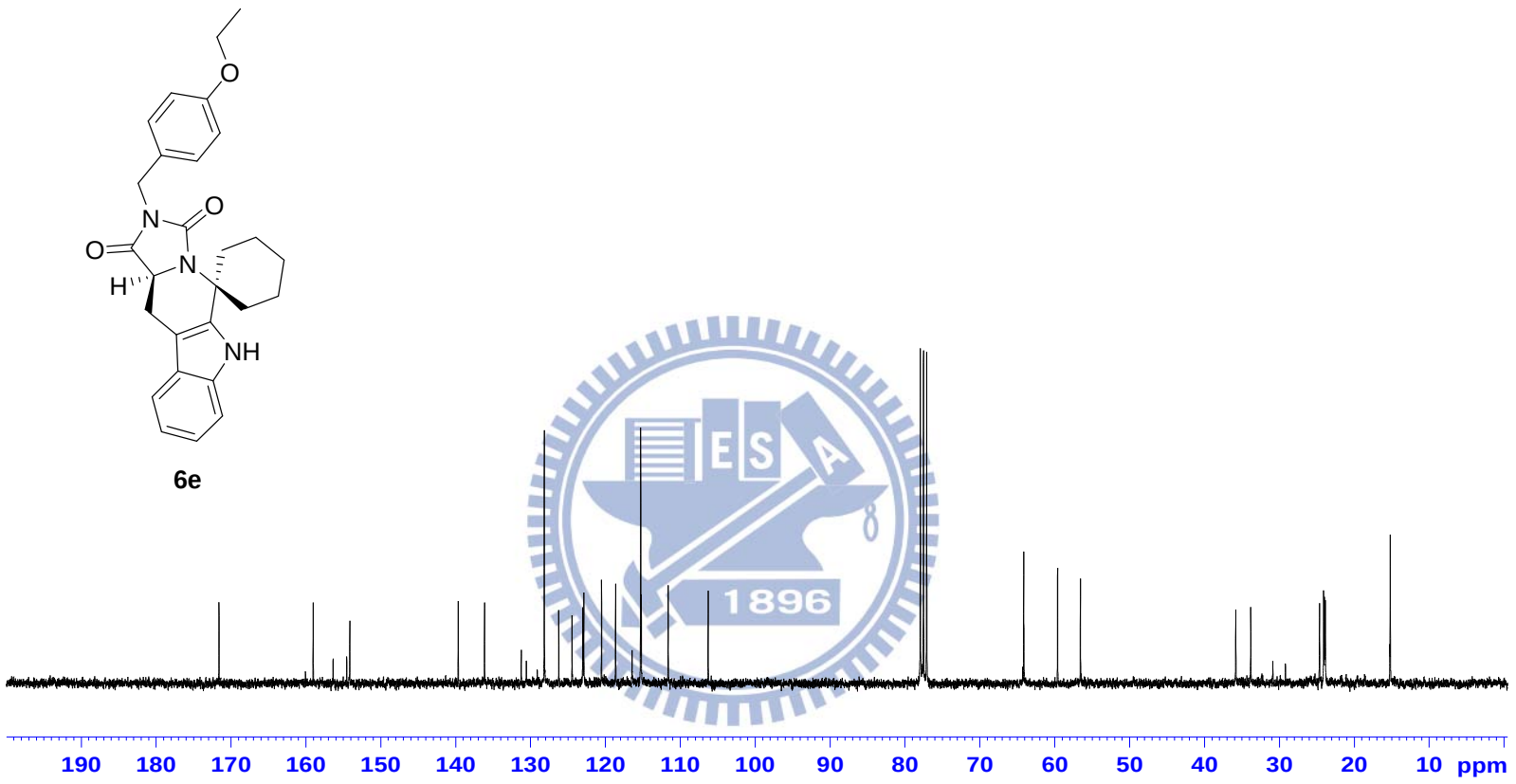
^{1}HNMR spectrum (300 MHz) of compound 6d in $CDCl_3$



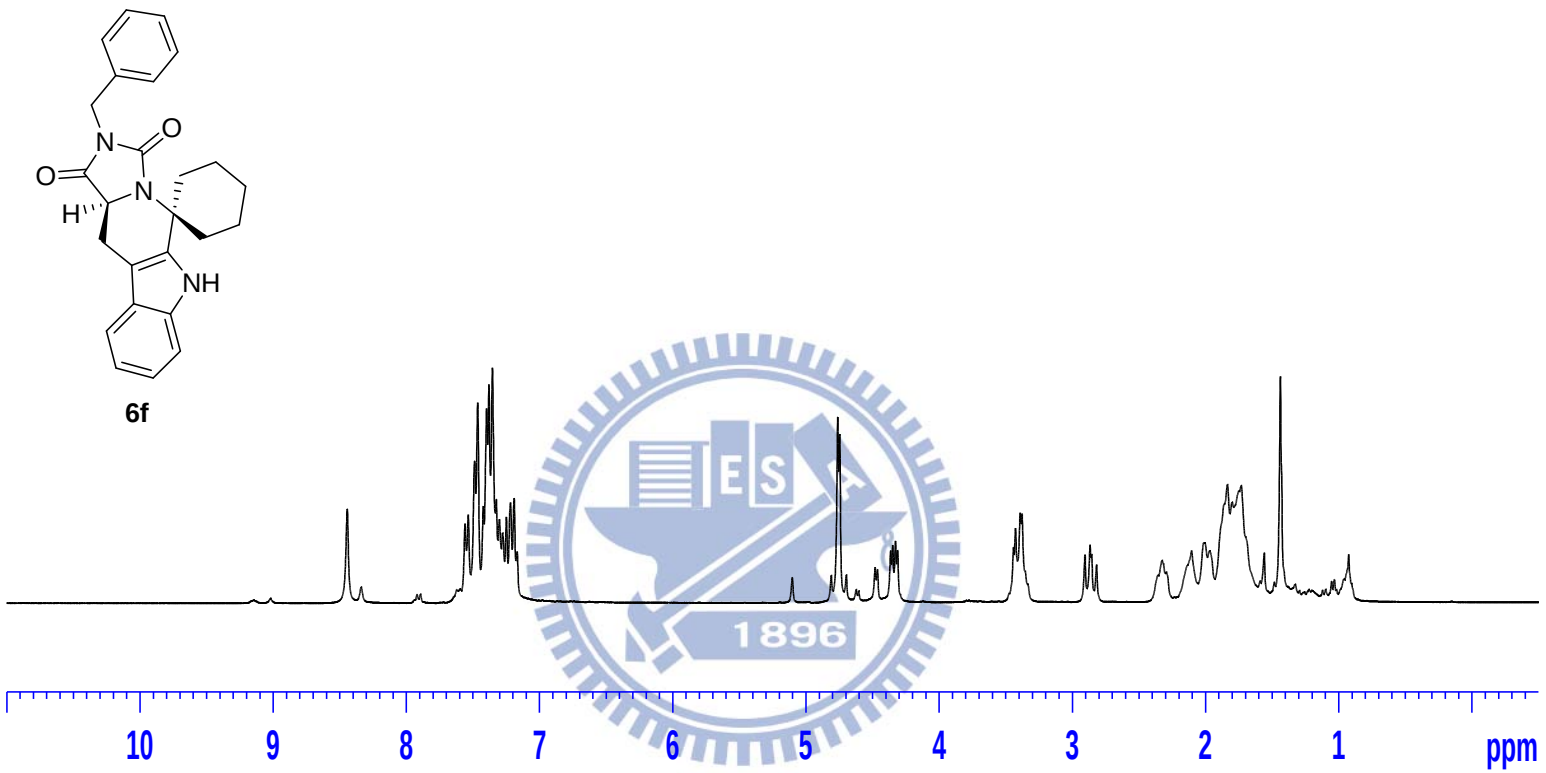
^{13}C NMR spectrum (75 MHz) of compound 6d in $CDCl_3$



^{1}HNMR spectrum (300 MHz) of compound 6e in $CDCl_3$

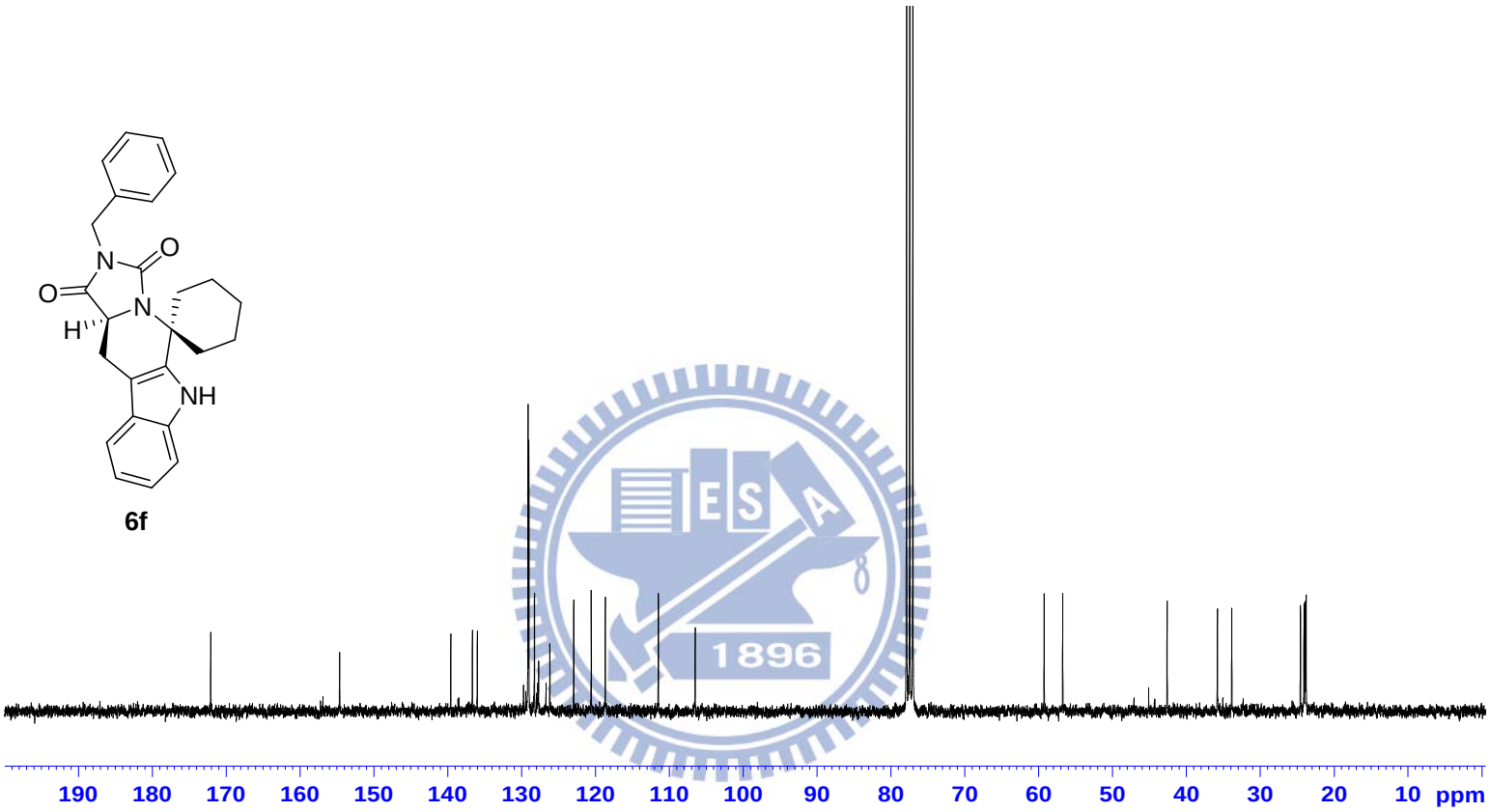


^{13}C NMR spectrum (75 MHz) of compound 6e in $CDCl_3$

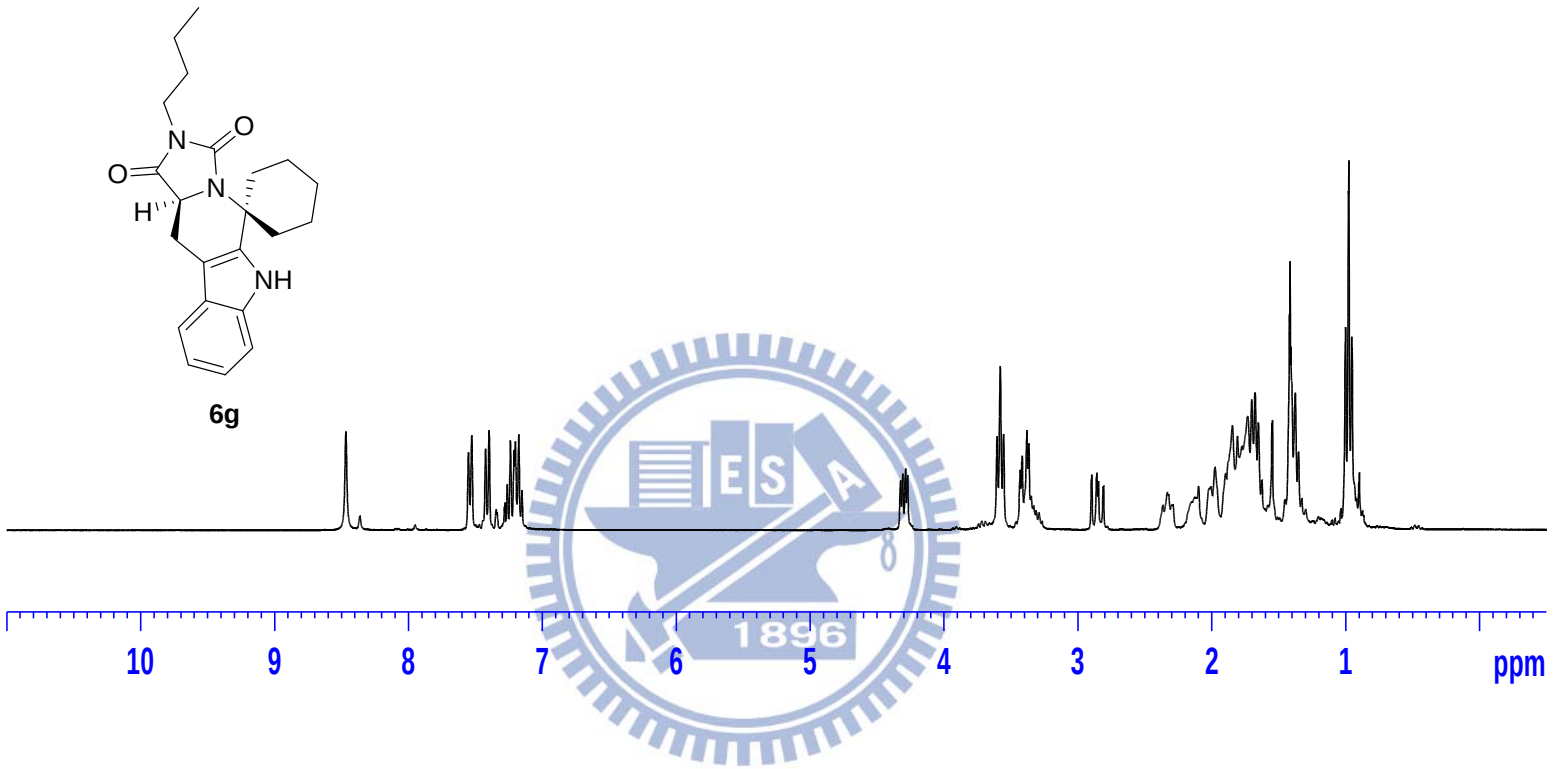


6f

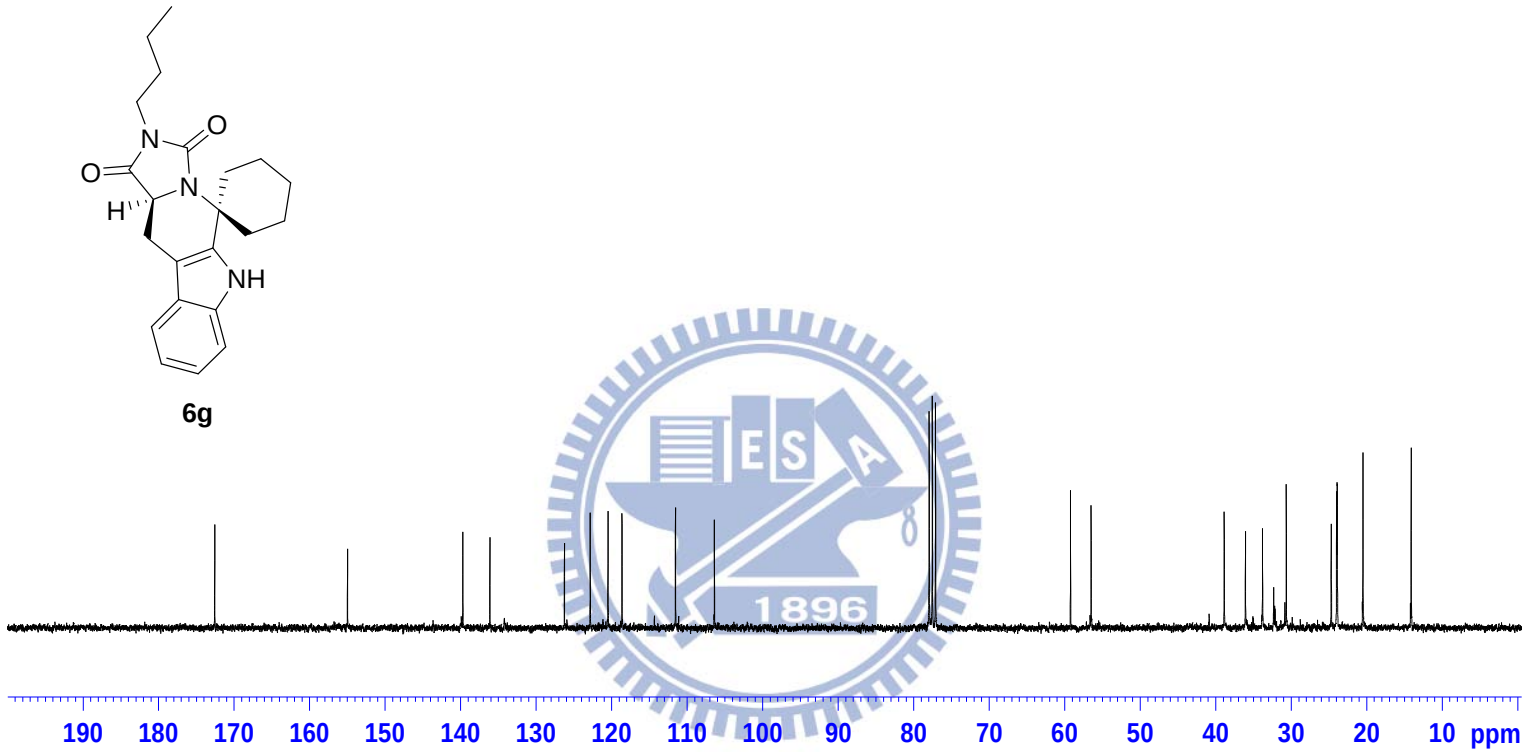
^{1}HNMR spectrum (300 MHz) of compound 6f in $CDCl_3$



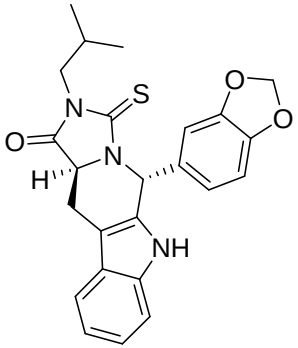
^{13}C NMR spectrum (75 MHz) of compound 6f in $CDCl_3$



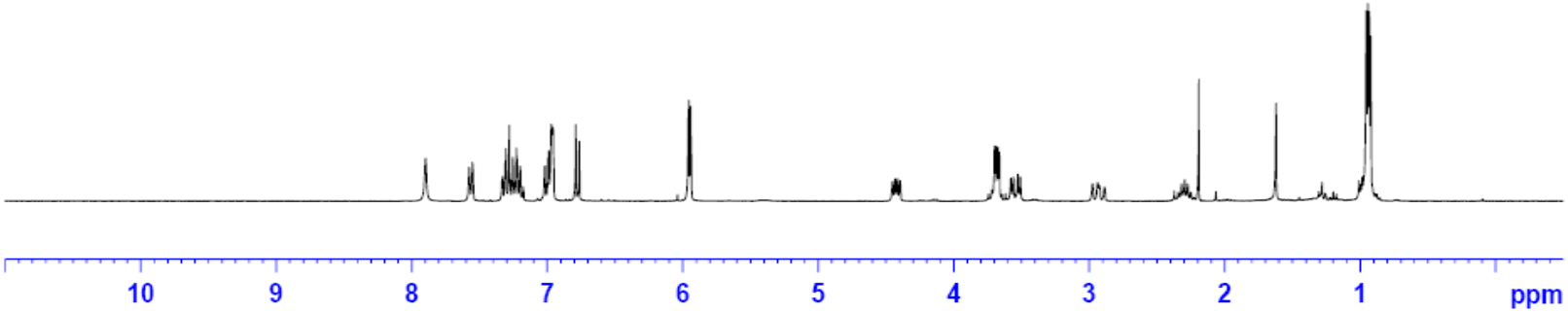
^{1}HNMR spectrum (300 MHz) of compound 6g in $CDCl_3$



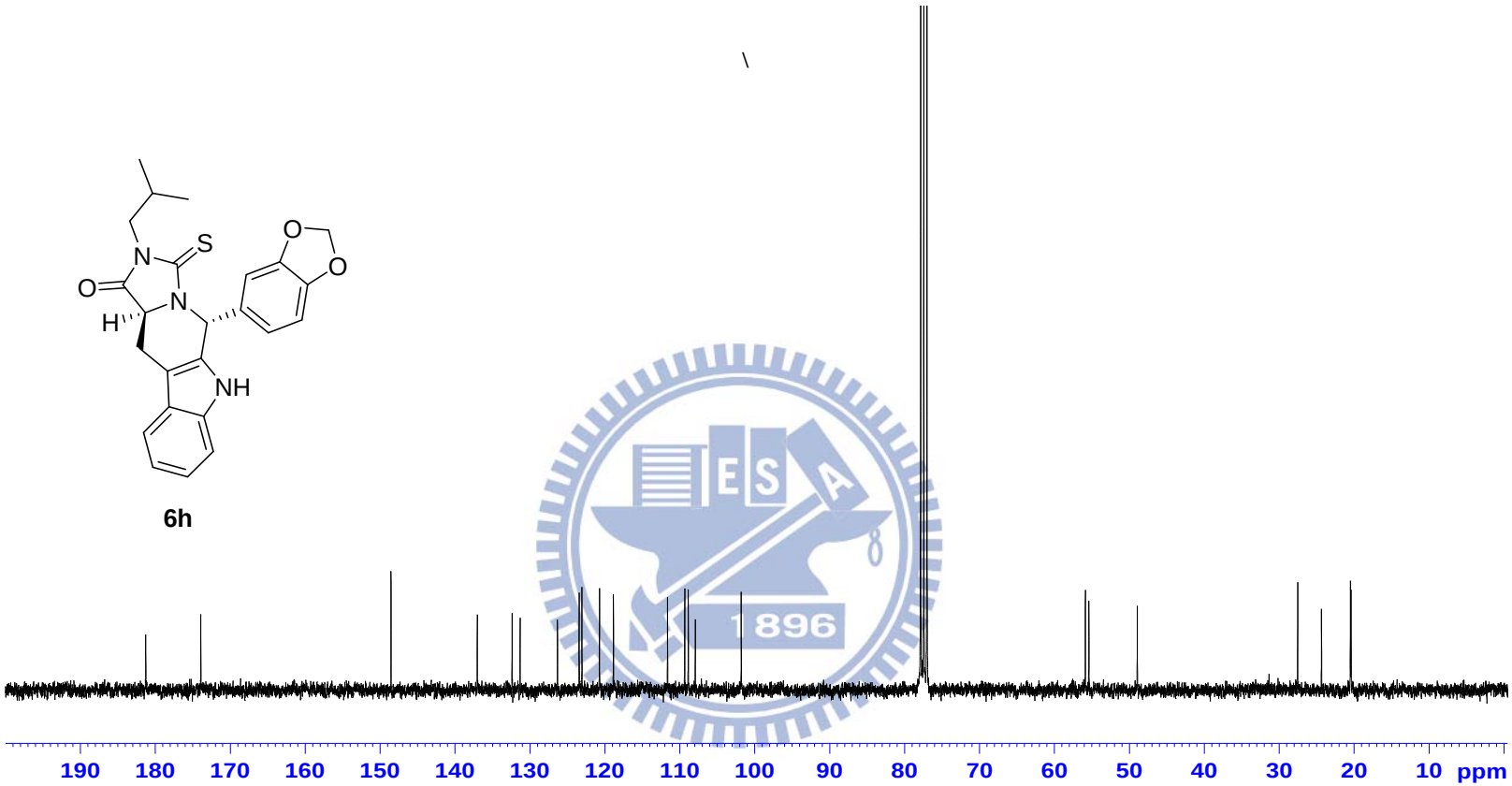
^{13}C NMR spectrum (75 MHz) of compound 6g in $CDCl_3$



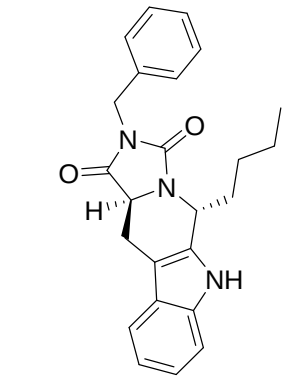
6h



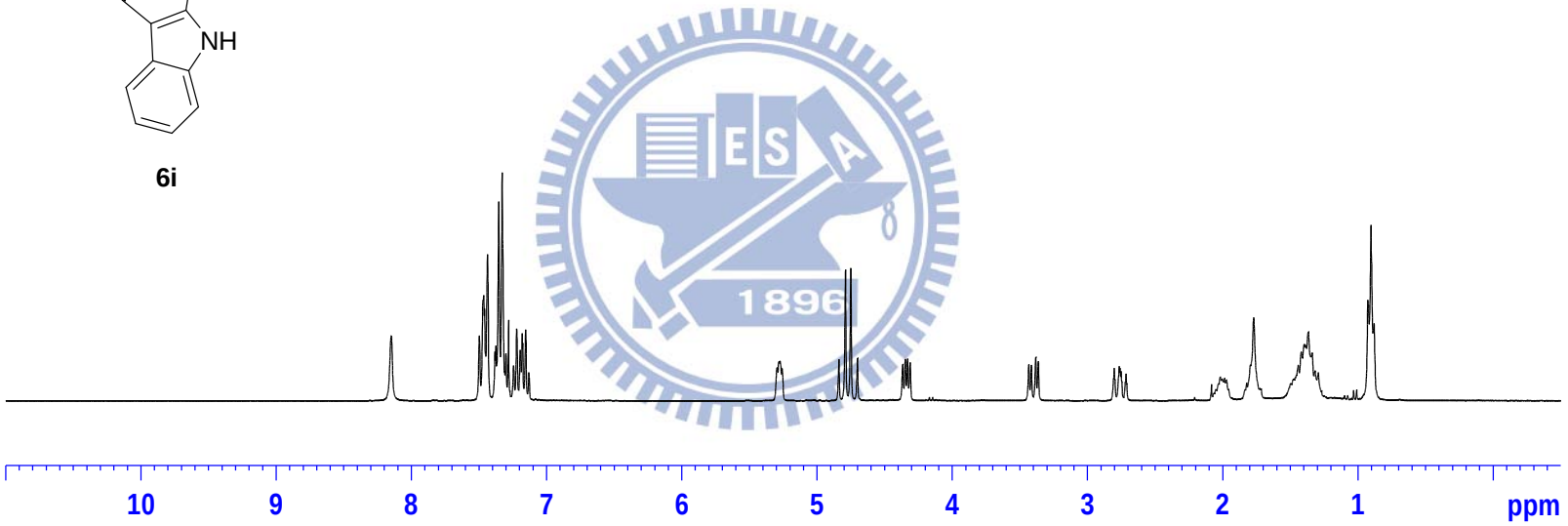
^{1}HNMR spectrum (300 MHz) of compound 6h in $CDCl_3$



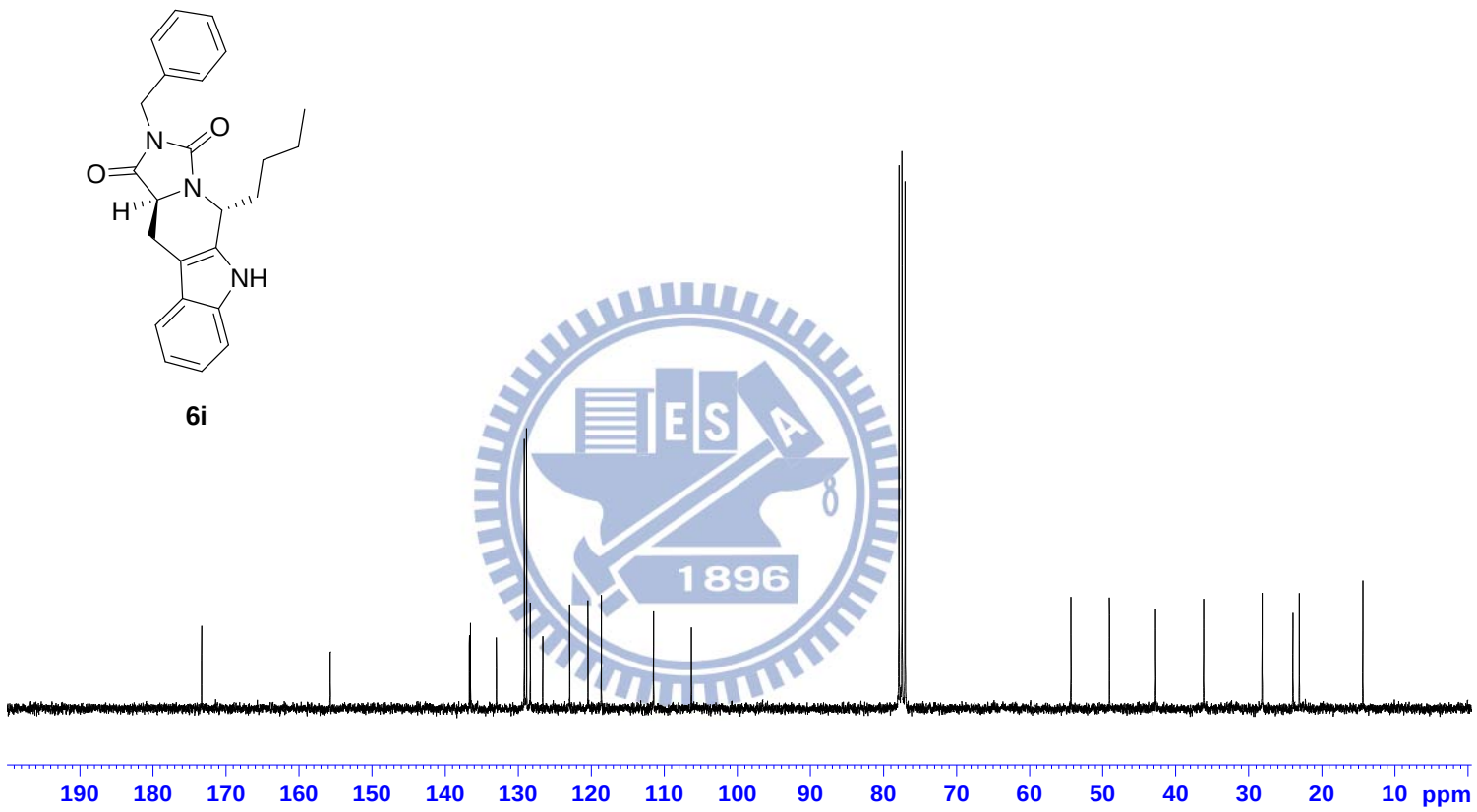
^{13}C NMR spectrum (75 MHz) of compound 6h in $CDCl_3$



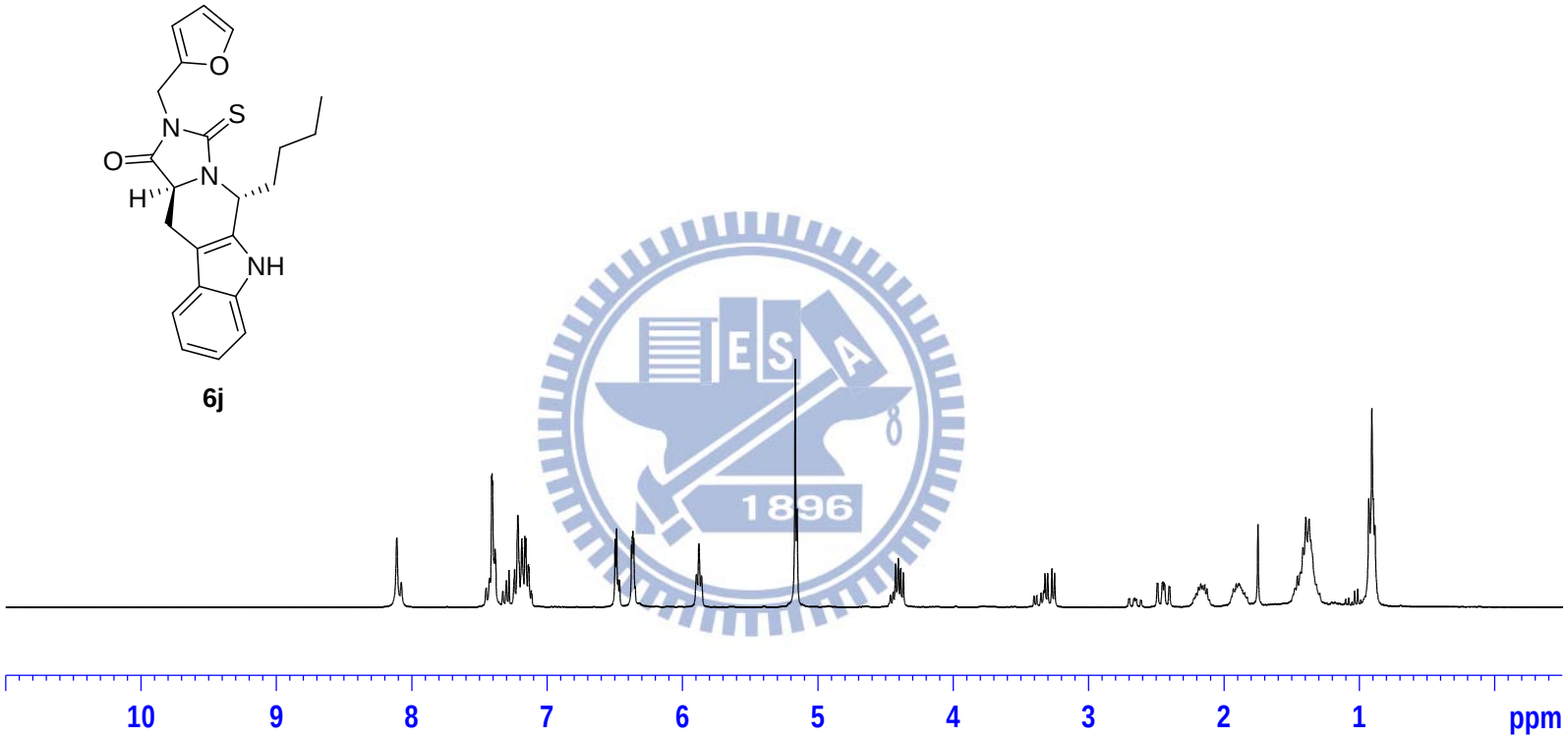
6i



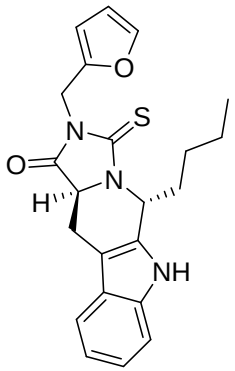
^{1}HNMR spectrum (300 MHz) of compound 6i in $CDCl_3$



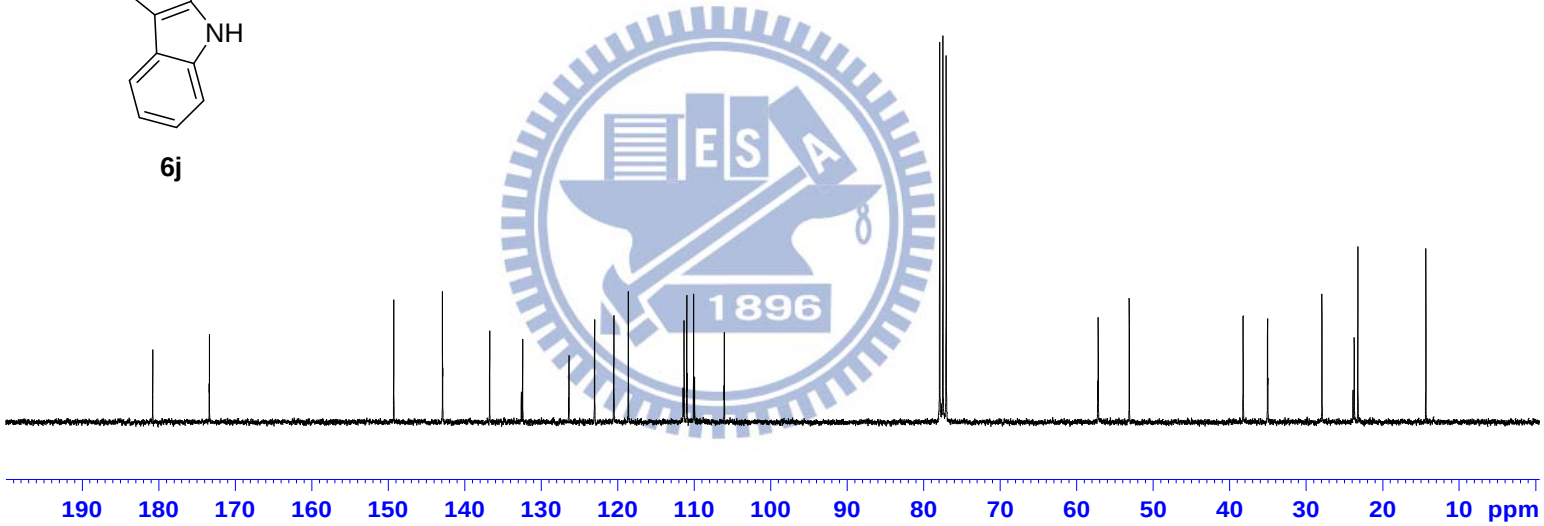
^{13}C NMR spectrum (75 MHz) of compound 6i in $CDCl_3$



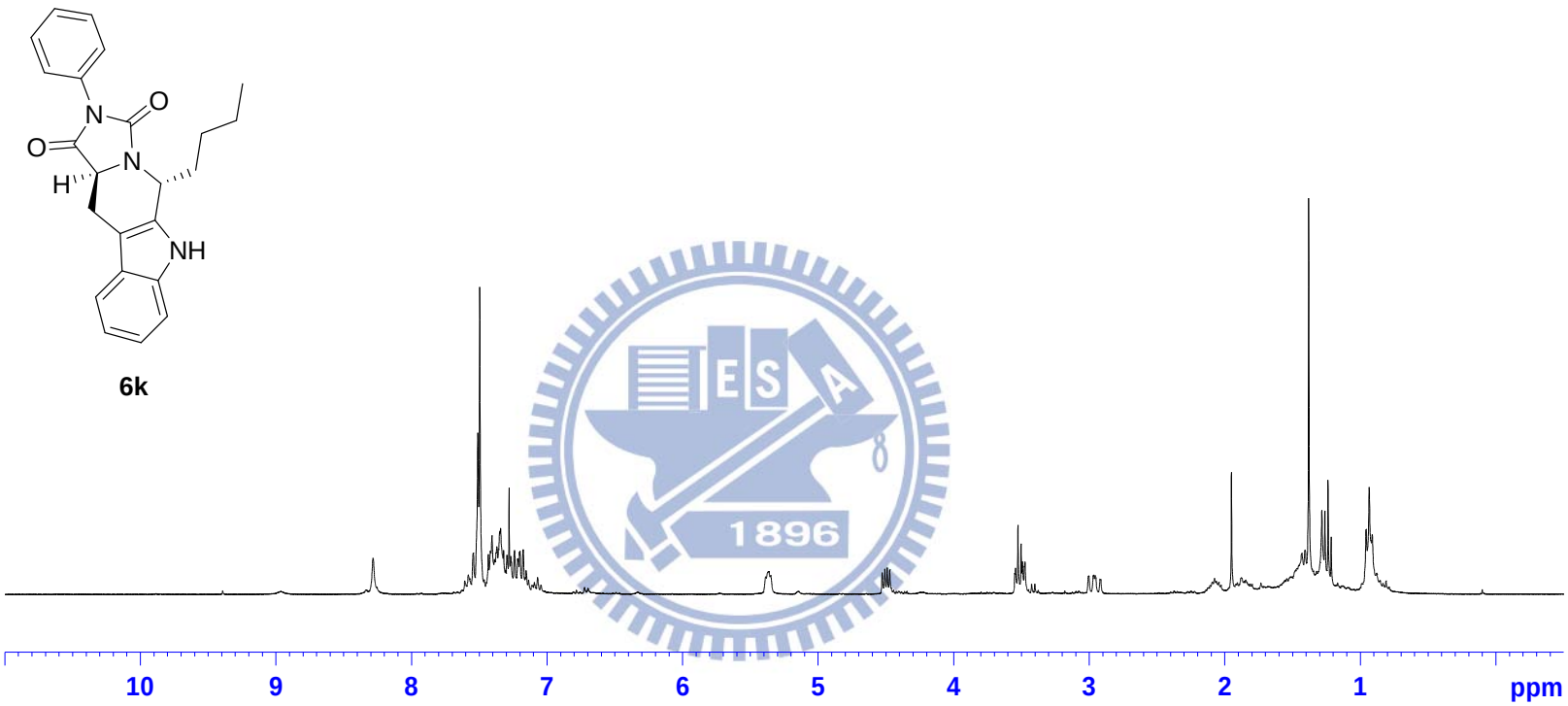
^{1}HNMR spectrum (300 MHz) of compound 6j in $CDCl_3$



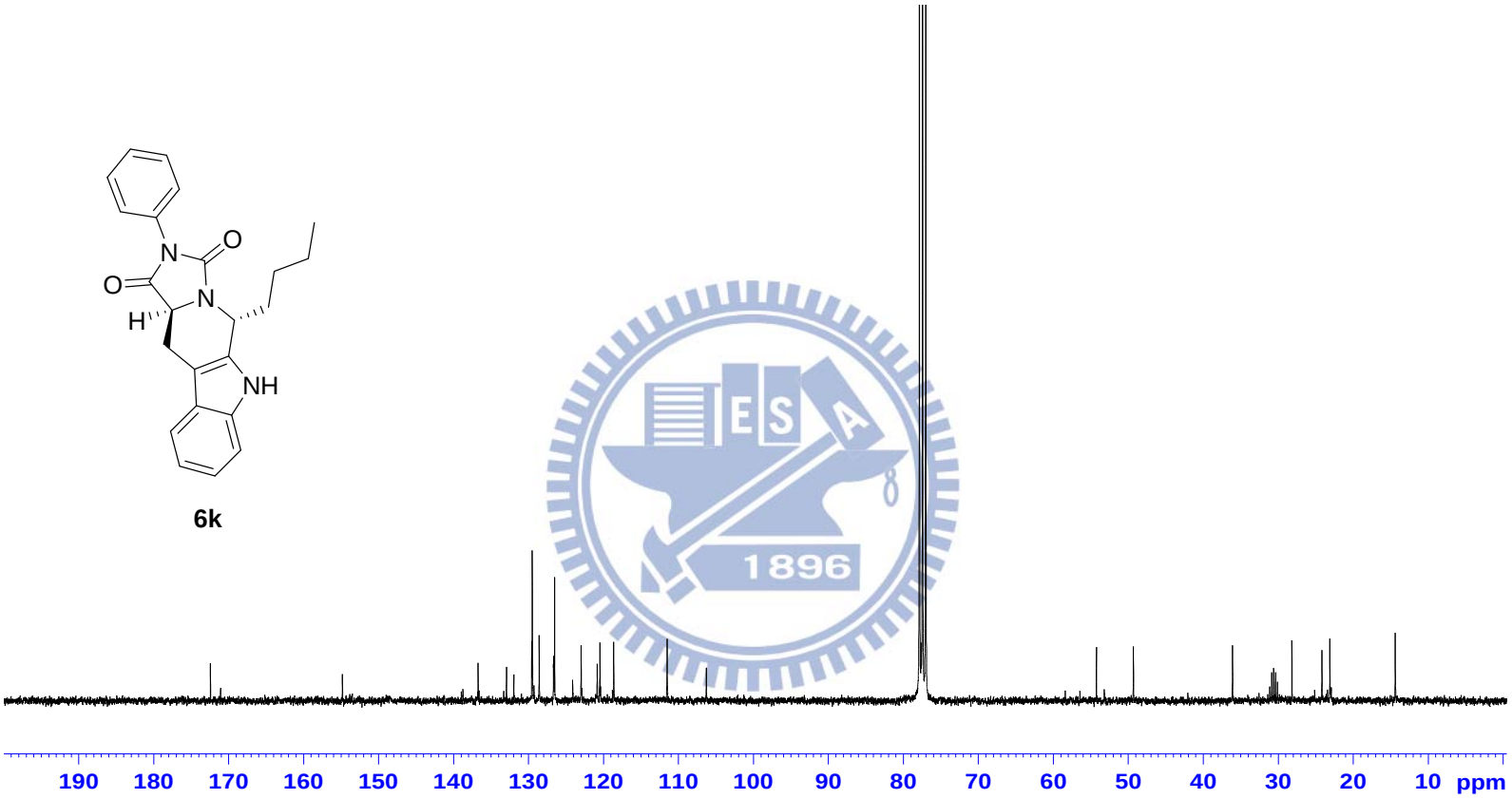
6j



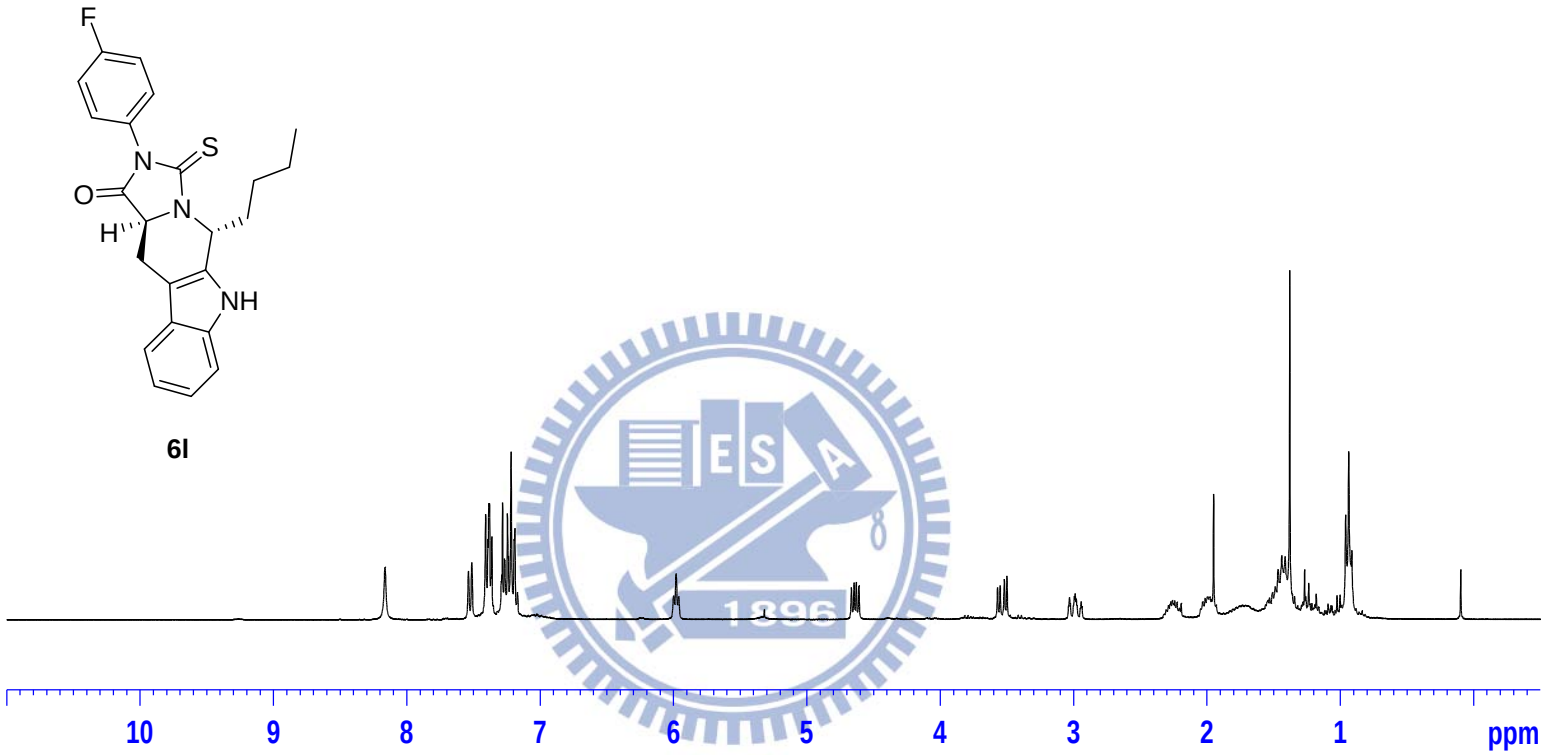
^{13}C NMR spectrum (75 MHz) of compound 6j in $CDCl_3$



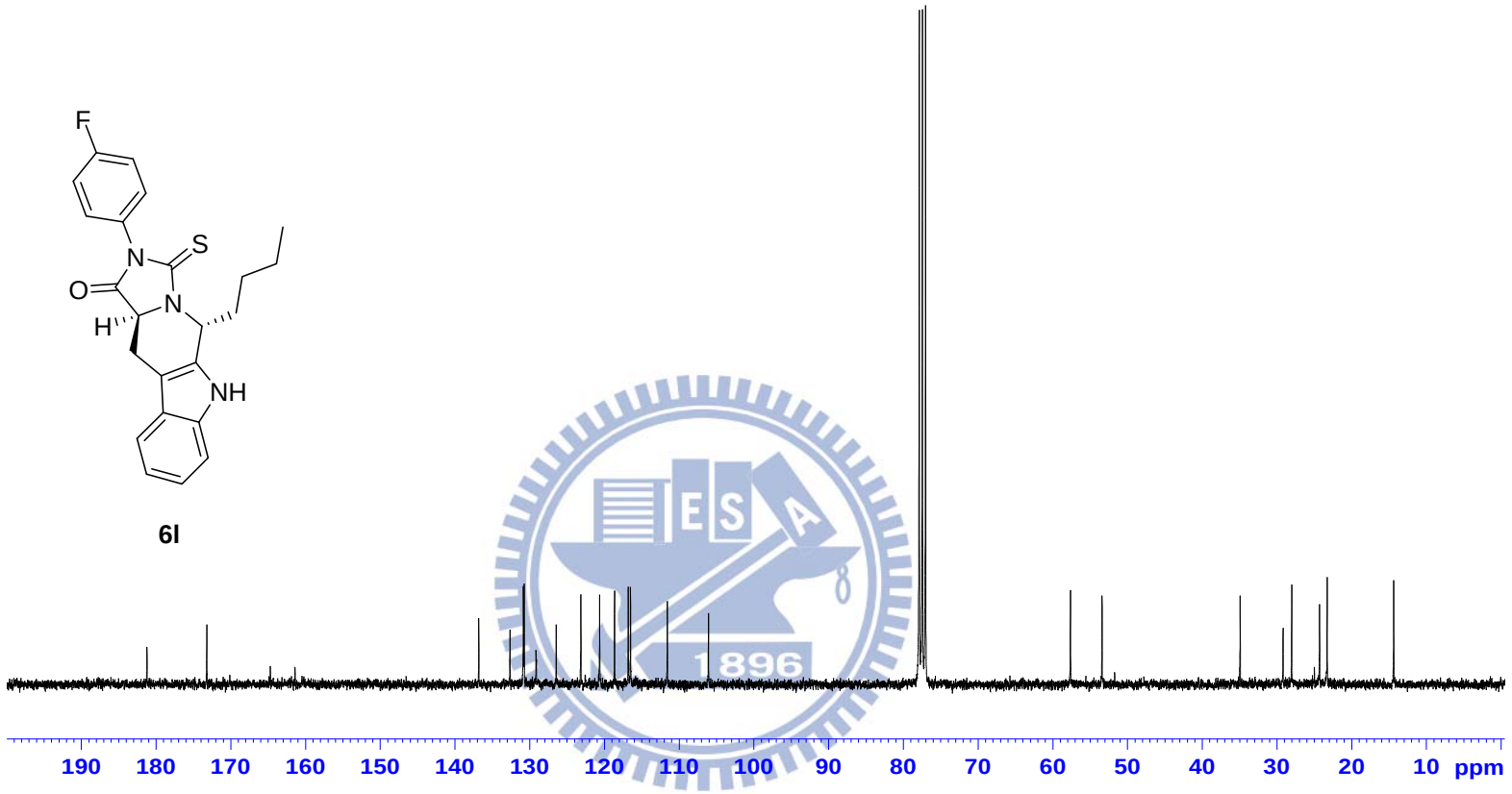
^{1}HNMR spectrum (300 MHz) of compound 6k in $CDCl_3$



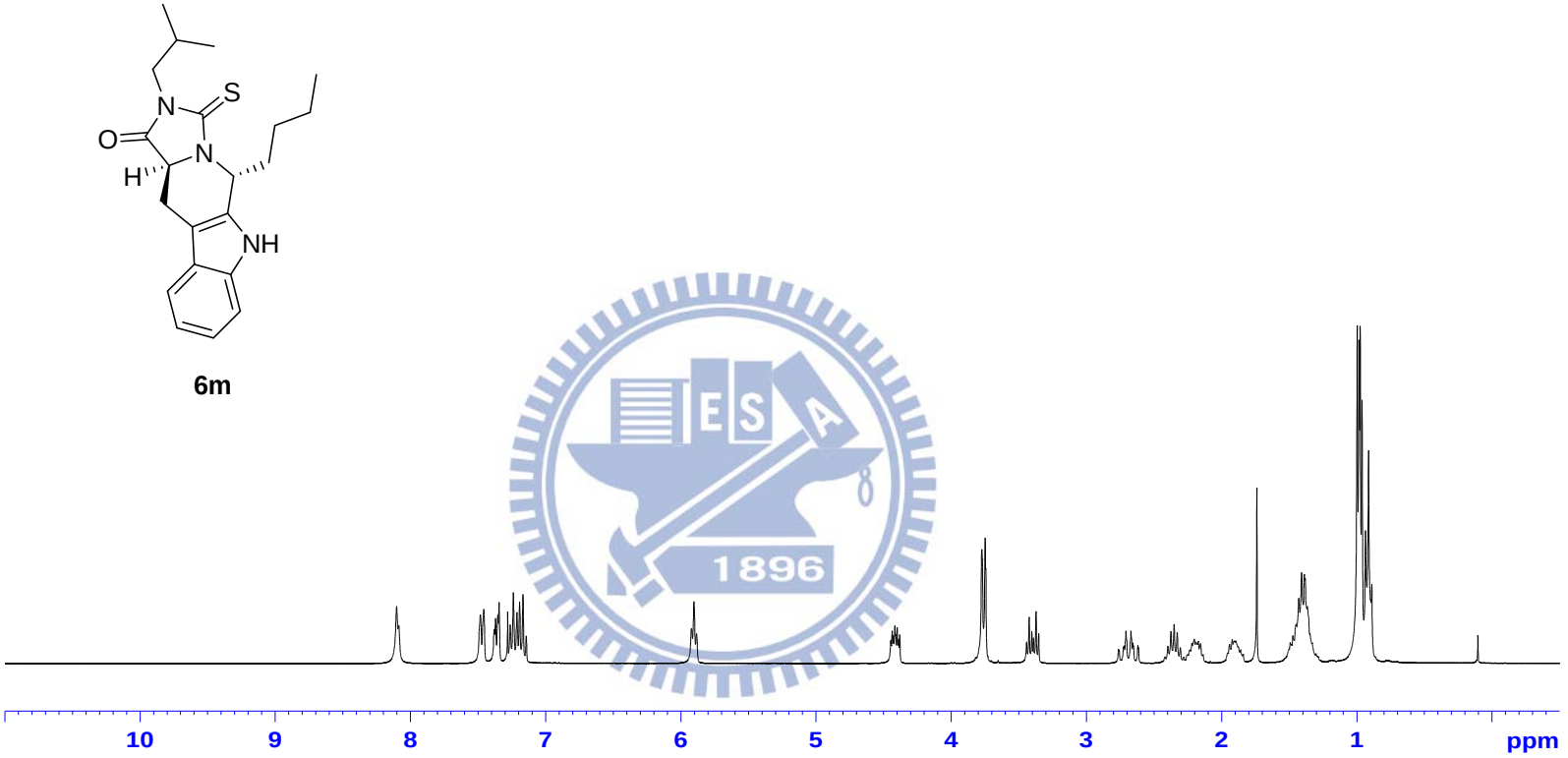
^{13}C NMR spectrum (75 MHz) of compound 6k in $CDCl_3$



^{1}HNMR spectrum (300 MHz) of compound 6l in $CDCl_3$

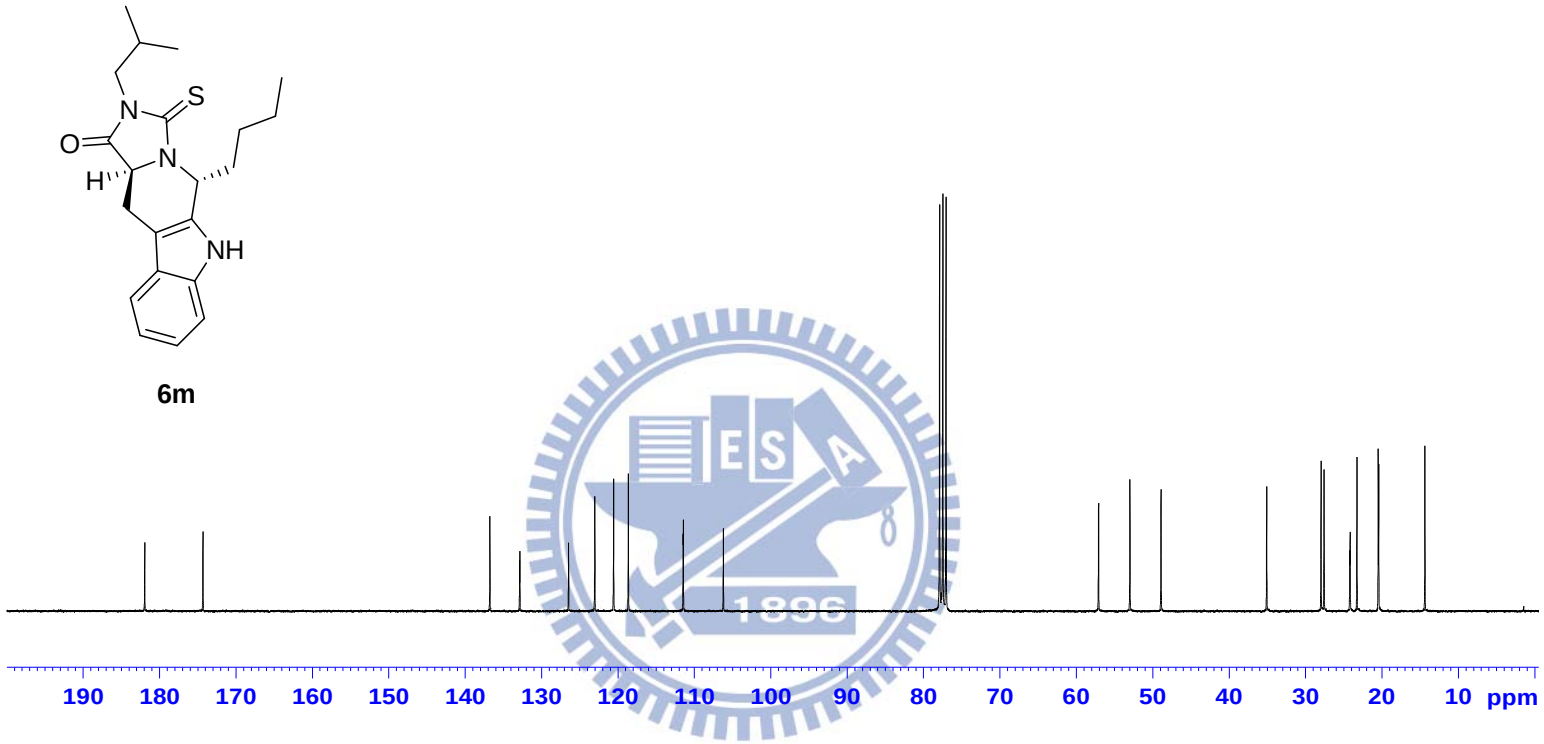


^{13}C NMR spectrum (75 MHz) of compound 6l in $CDCl_3$

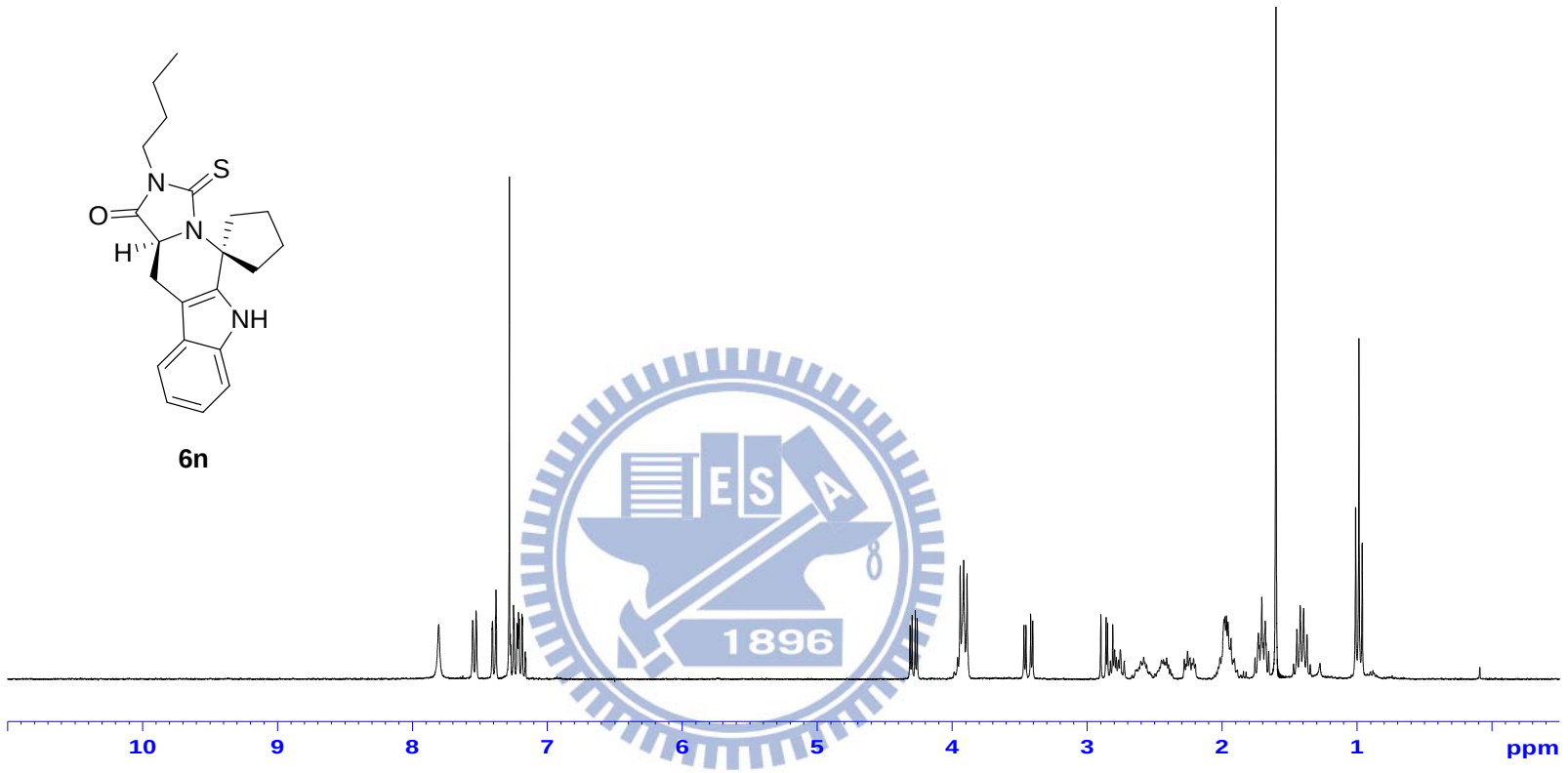


6m

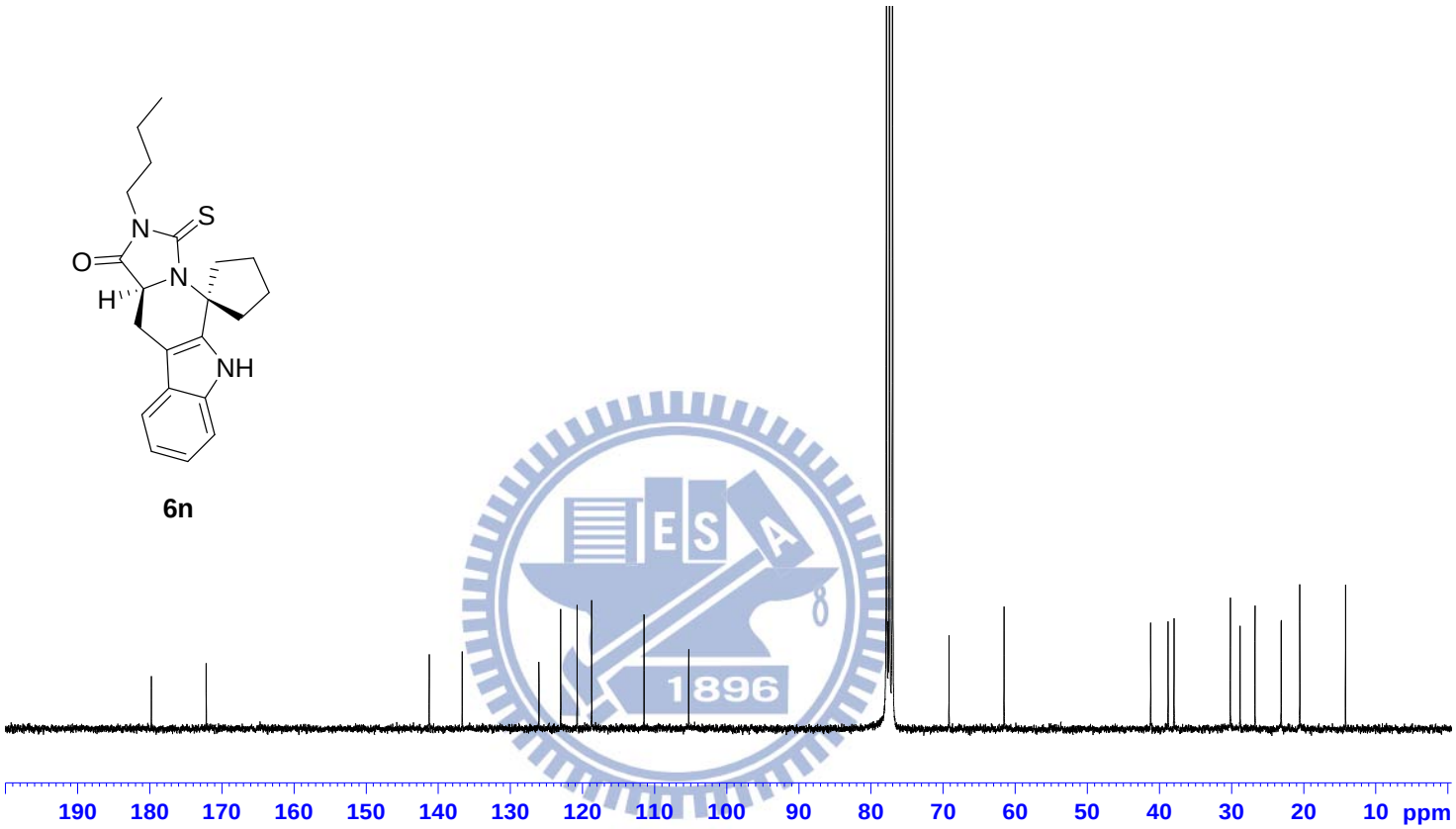
^{1}HNMR spectrum (300 MHz) of compound 6m in $CDCl_3$



^{13}C NMR spectrum (75 MHz) of compound 7a in $CDCl_3$



^{1}HNMR spectrum (300 MHz) of compound 6n in $CDCl_3$



^{13}C NMR spectrum (75 MHz) of compound 6n in $CDCl_3$

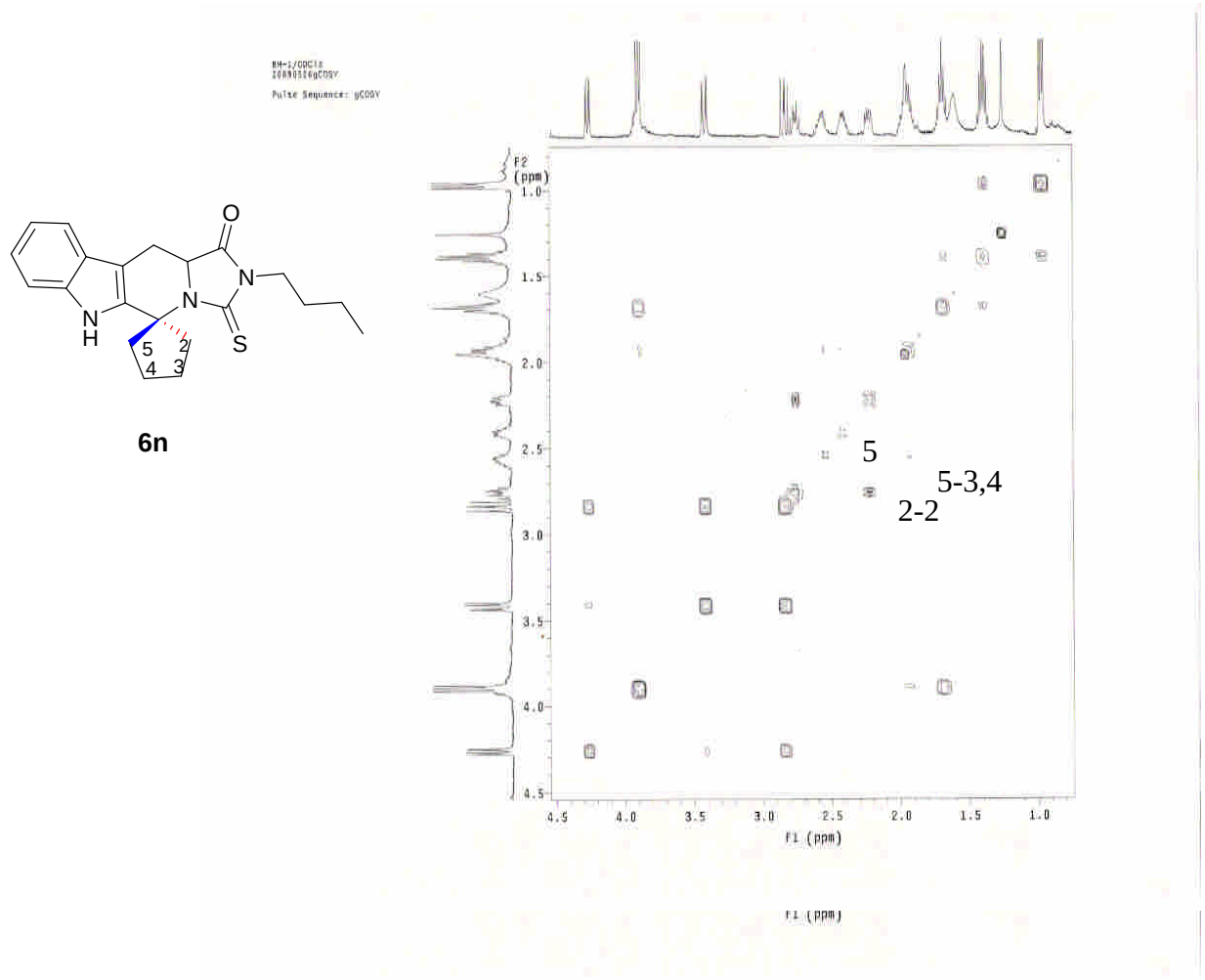


Figure 1. ^{1}H-^{1}H COSY Spectra of Compound **6n**

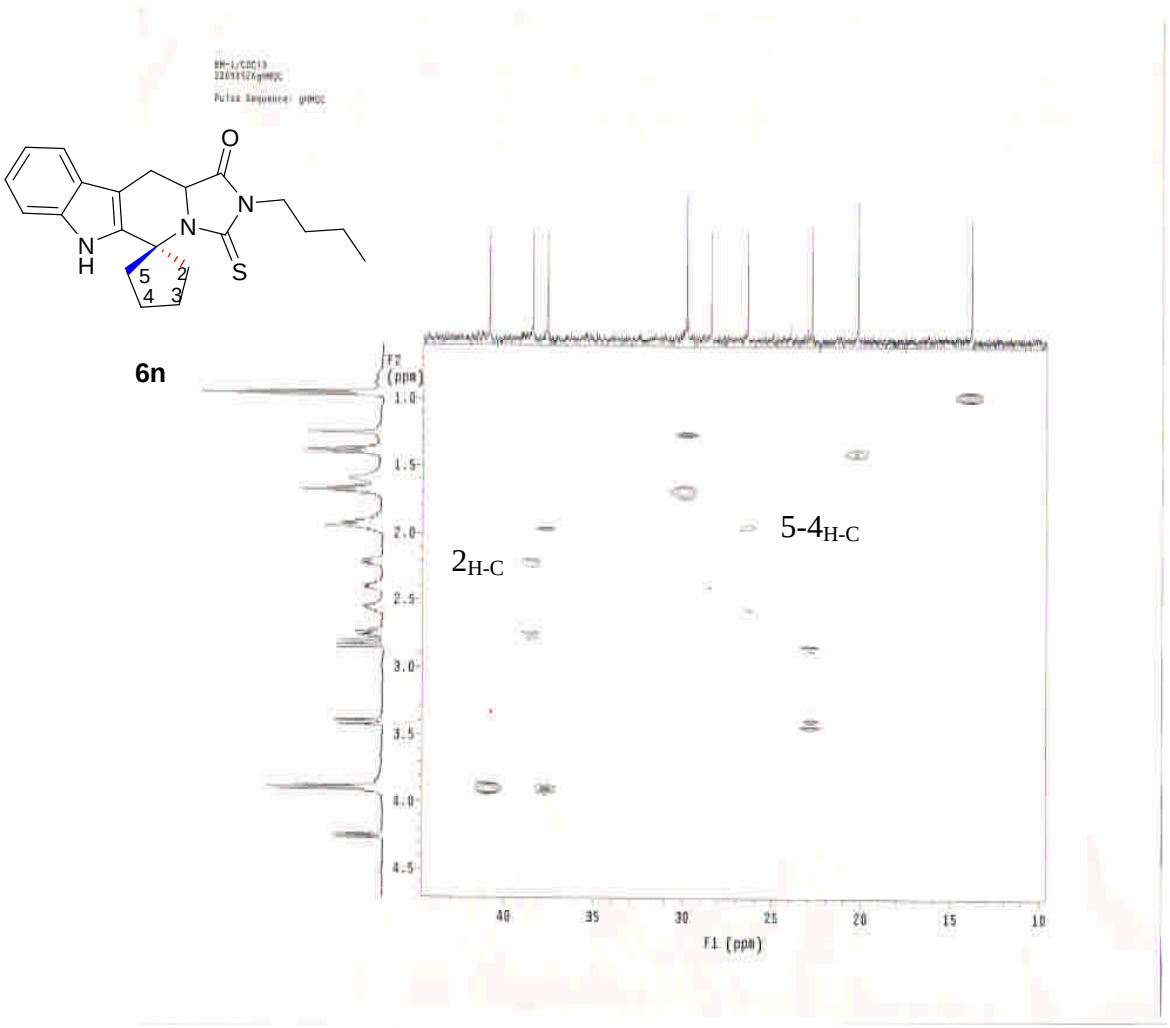
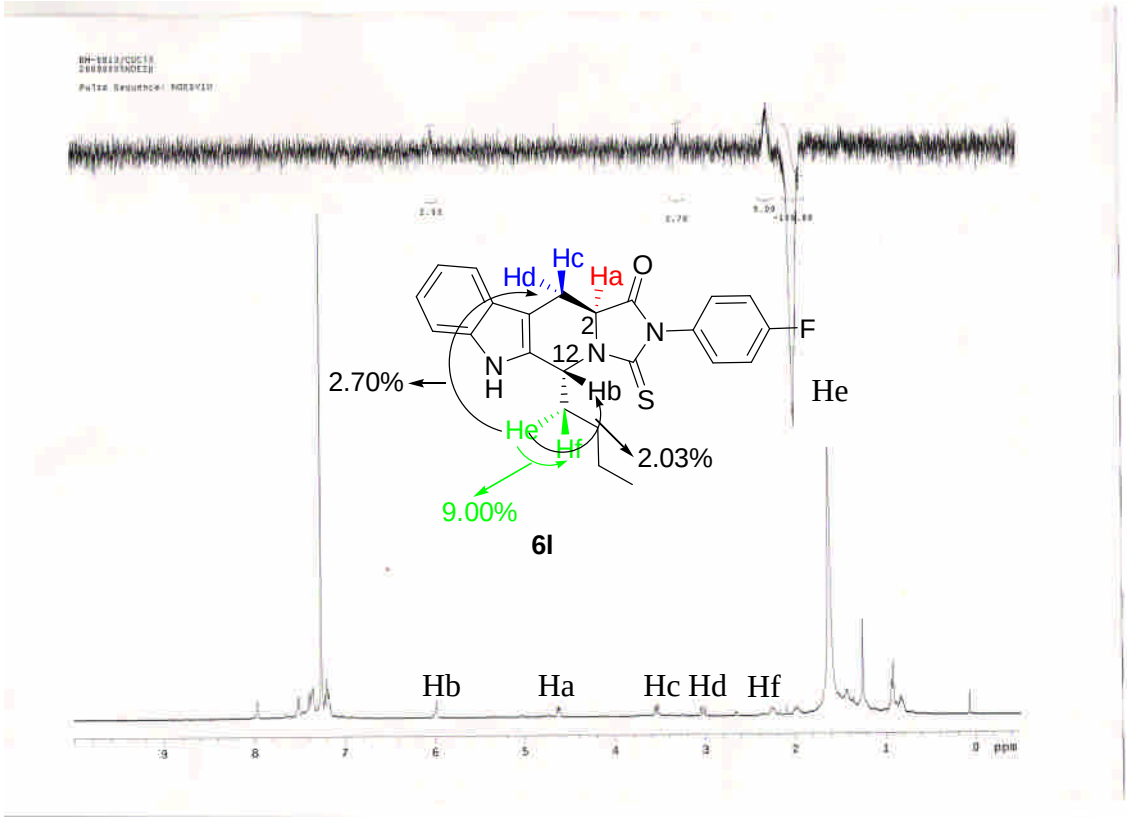
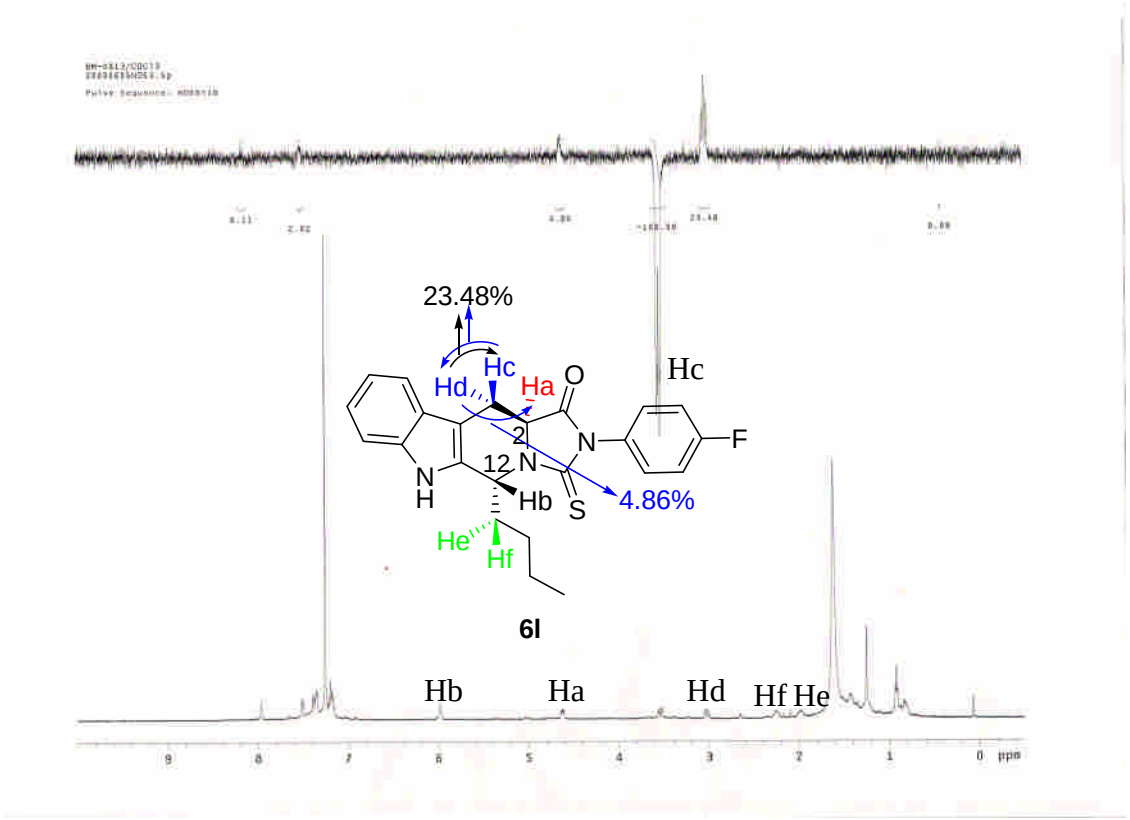


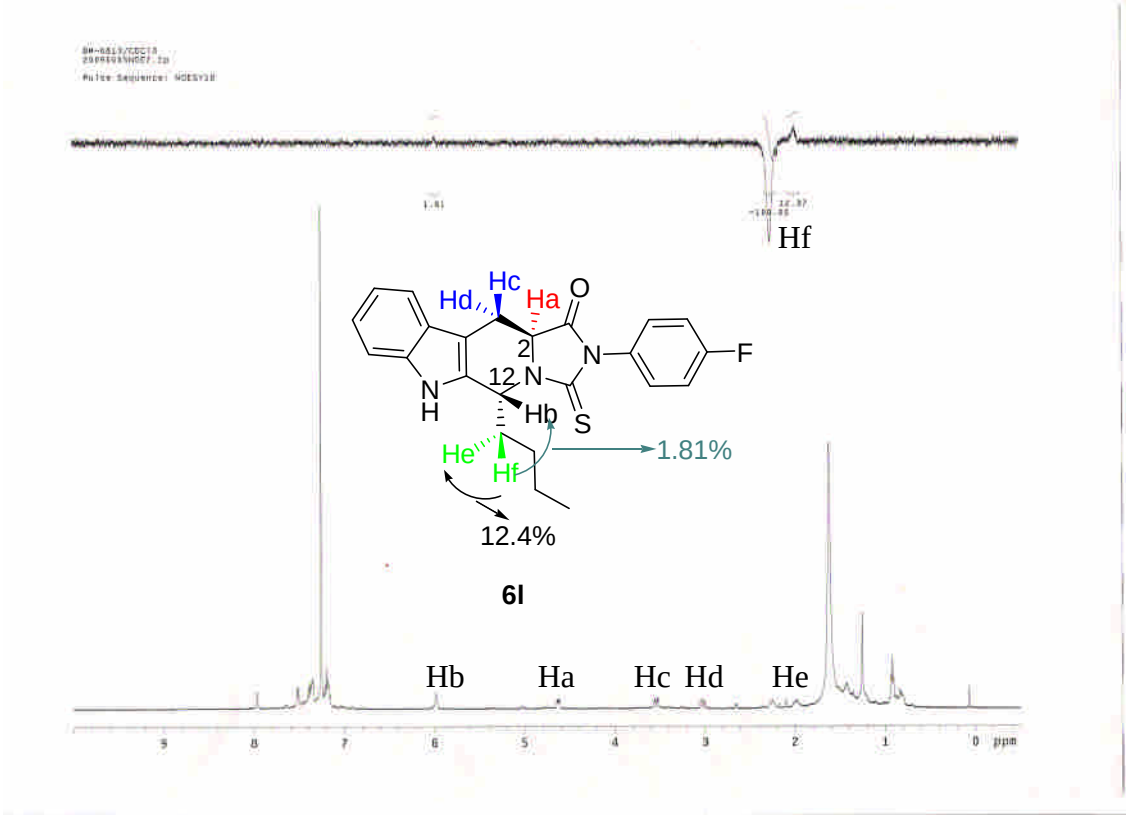
Figure 1. ^{1}H-^{13}C COSY Spectra of Compound **6n**



Some Parts of NOE interaction of compound 6l



Some Parts of NOE interaction of compound 6l



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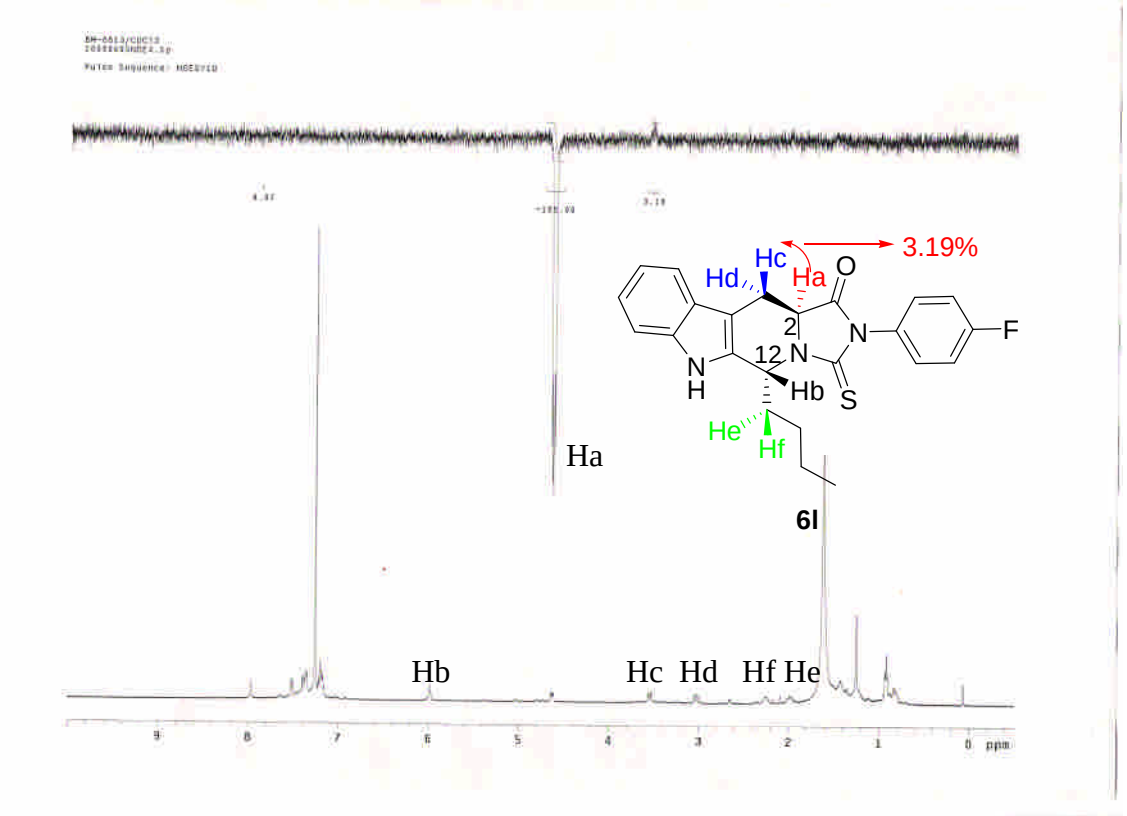
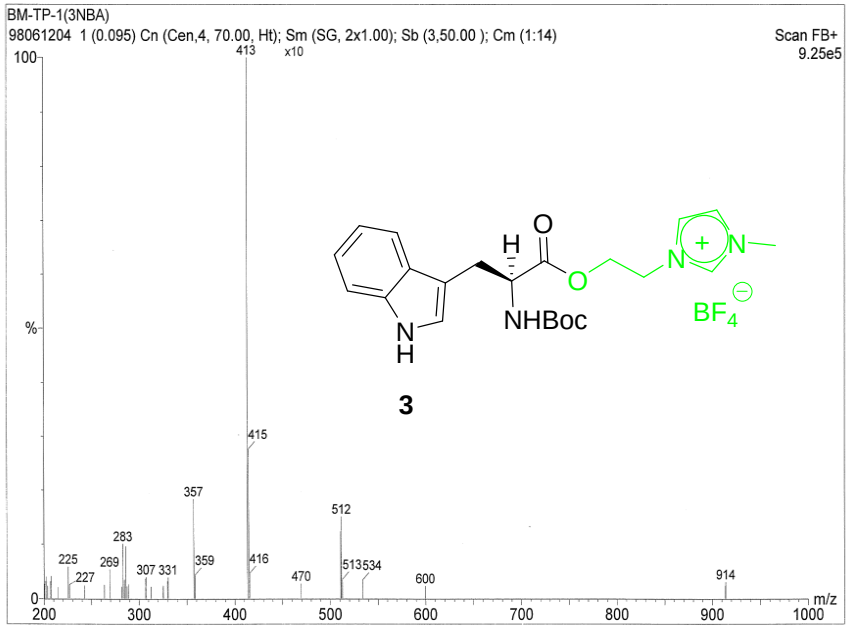
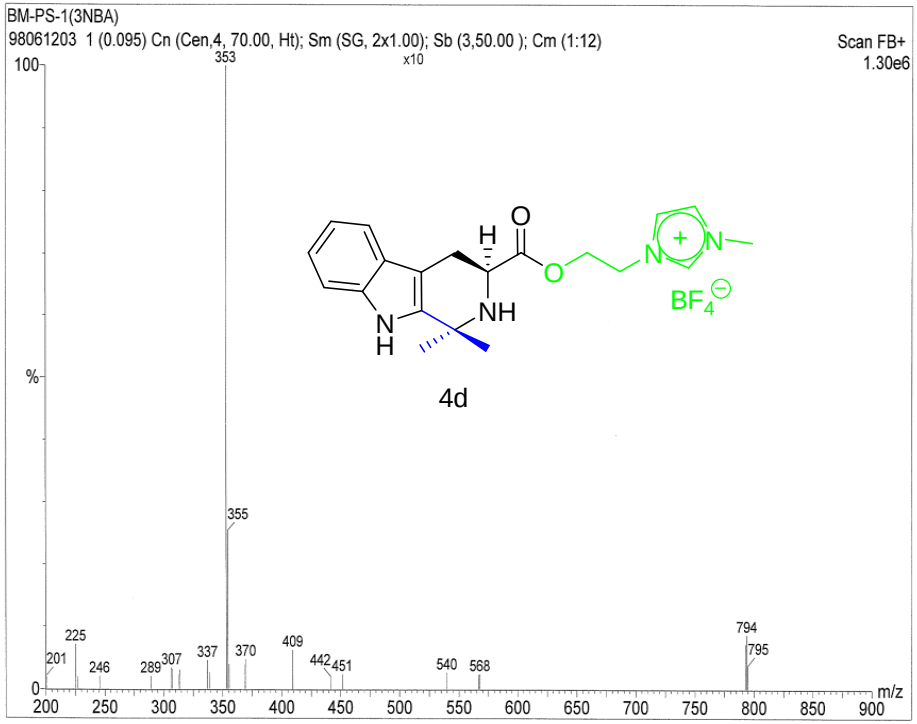


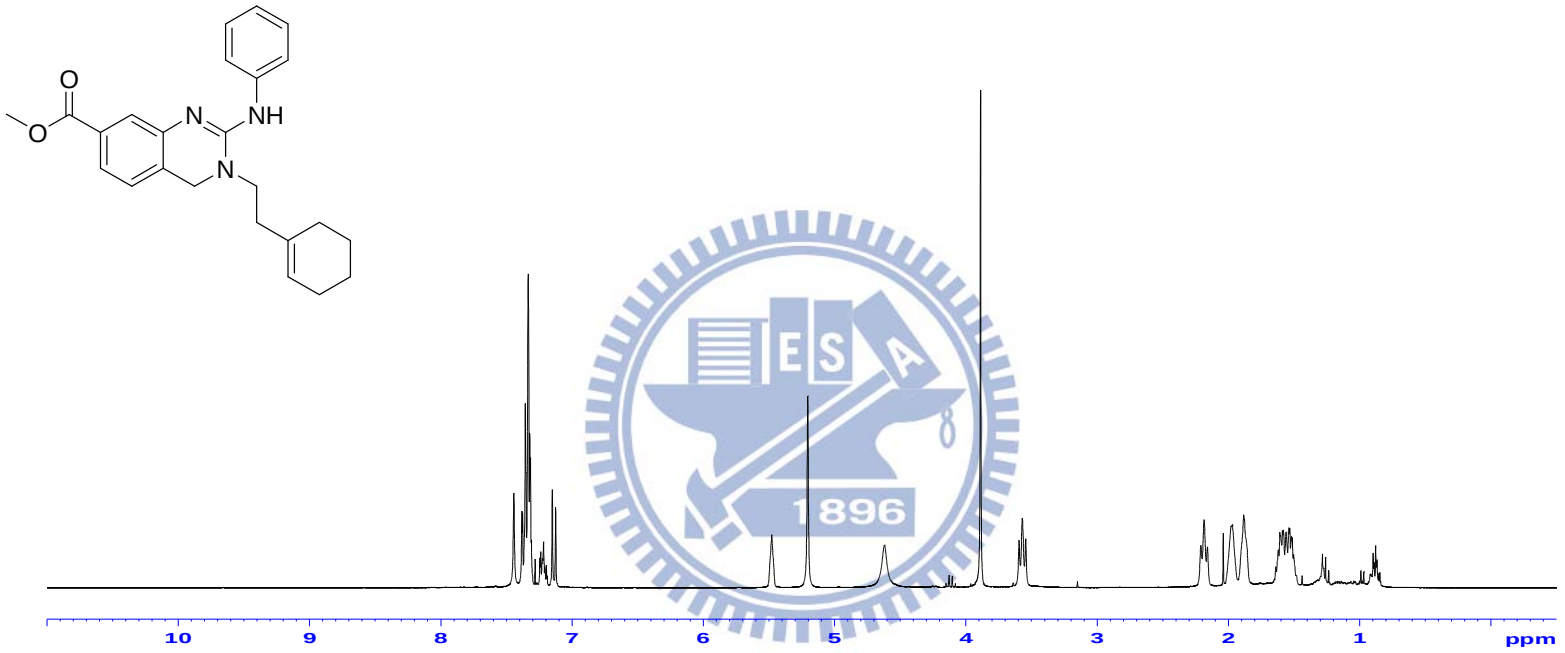
Some Parts of NOE interaction of compound 6l



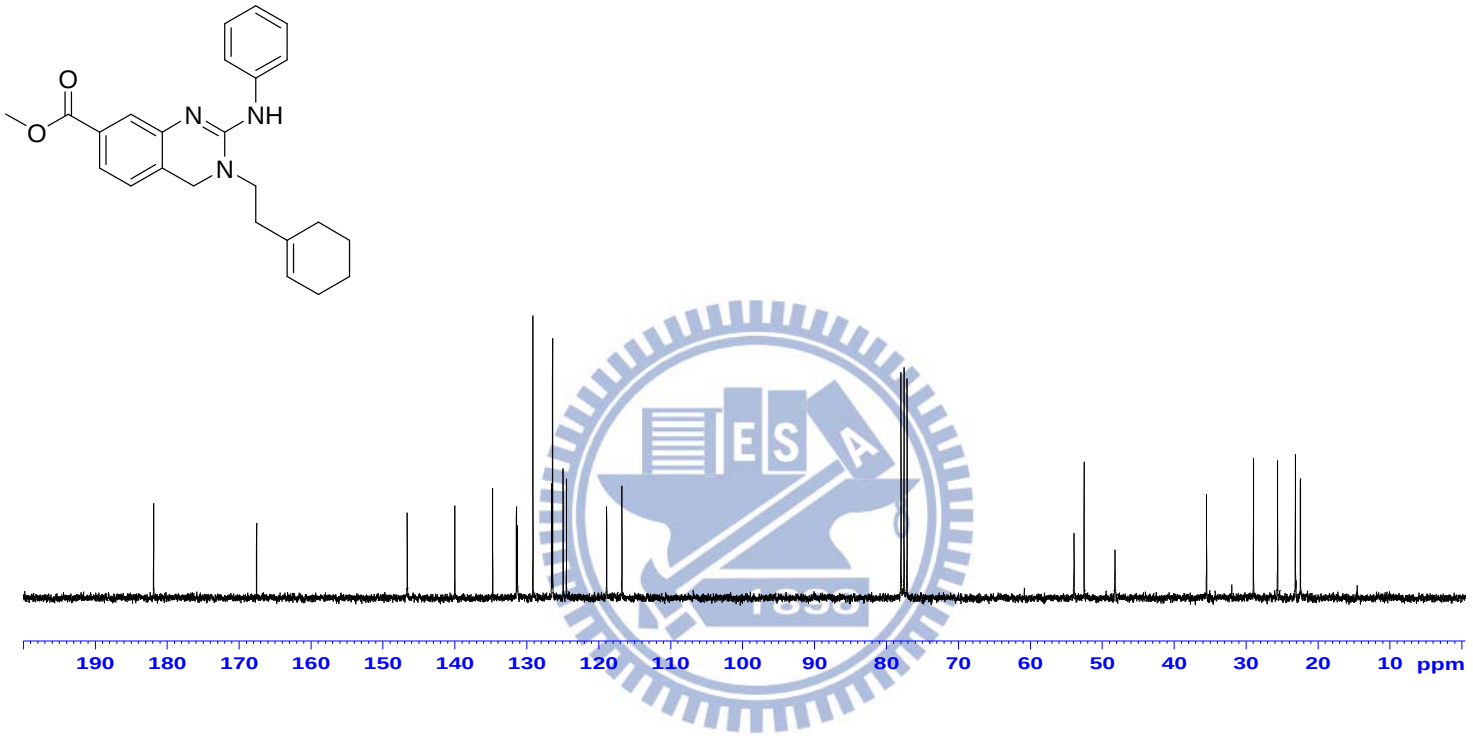
IL-supported Intermediate mass spectra for compound 3



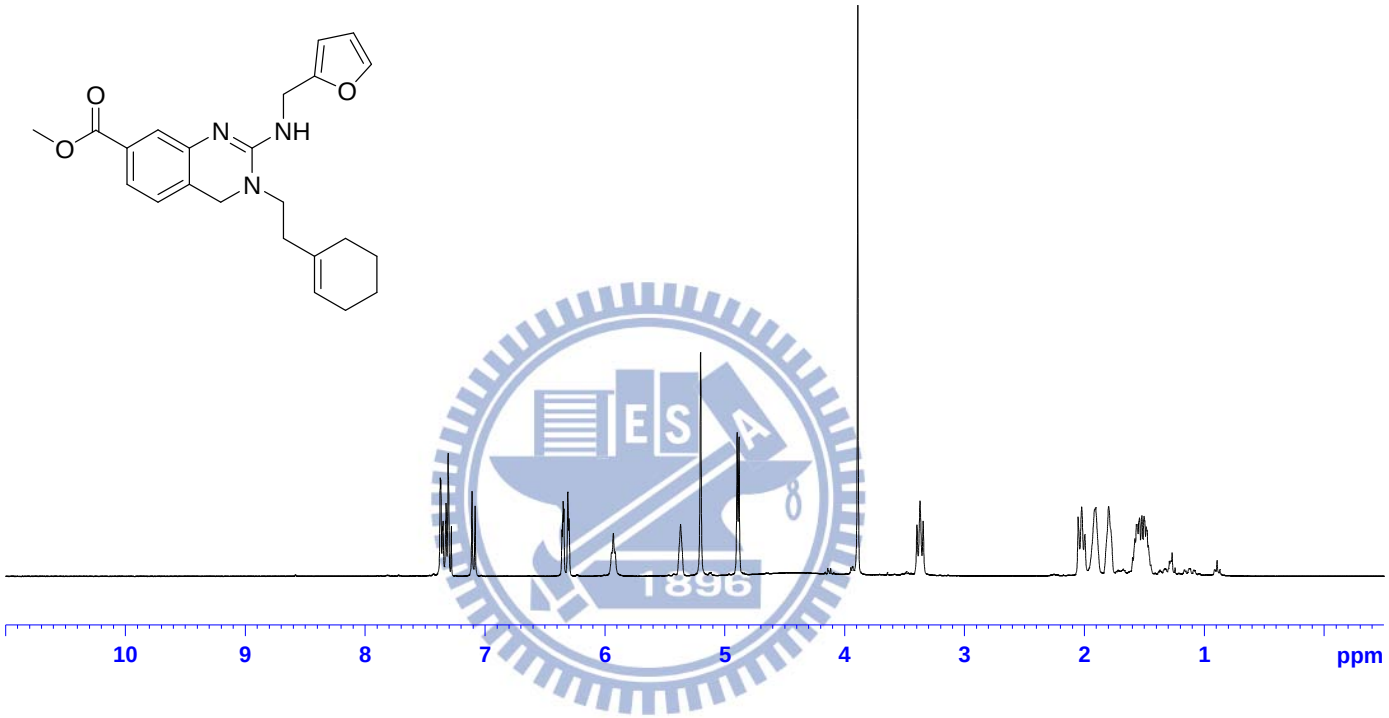
IL-supported Intermediate mass spectra for compound 4d



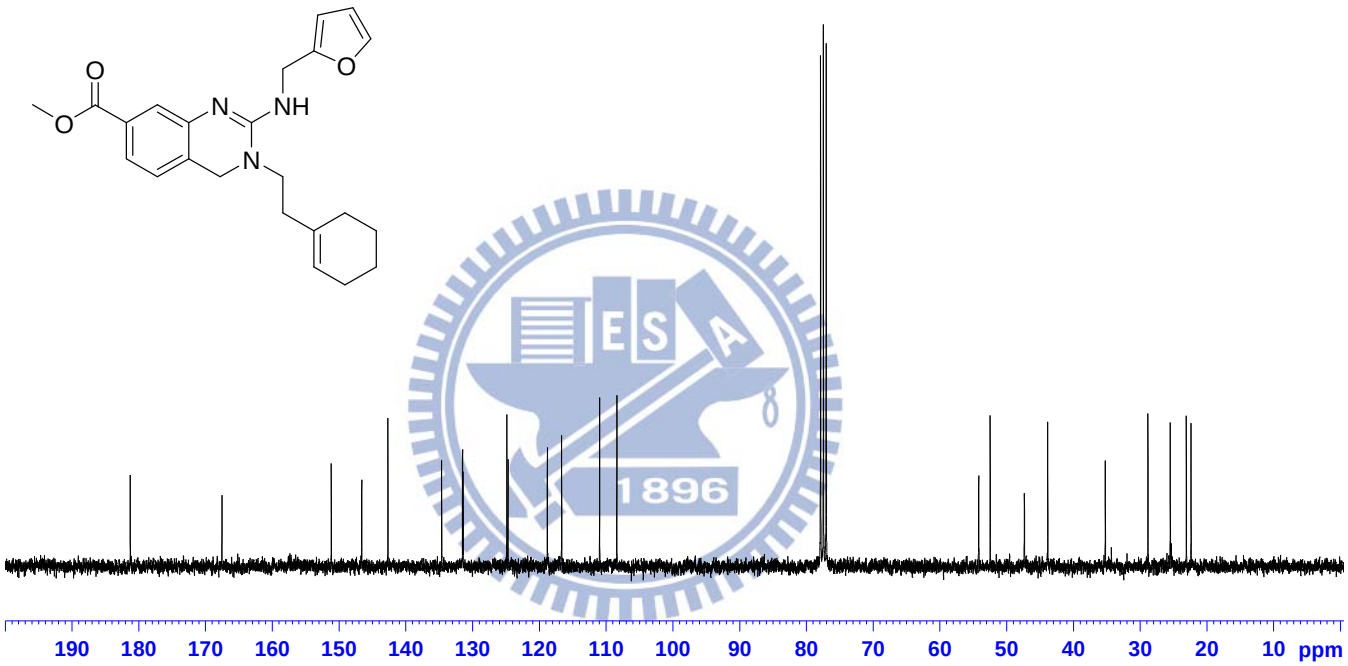
^{1}HNMR spectrum (300 MHz) of compound 13a in $CDCl_3$



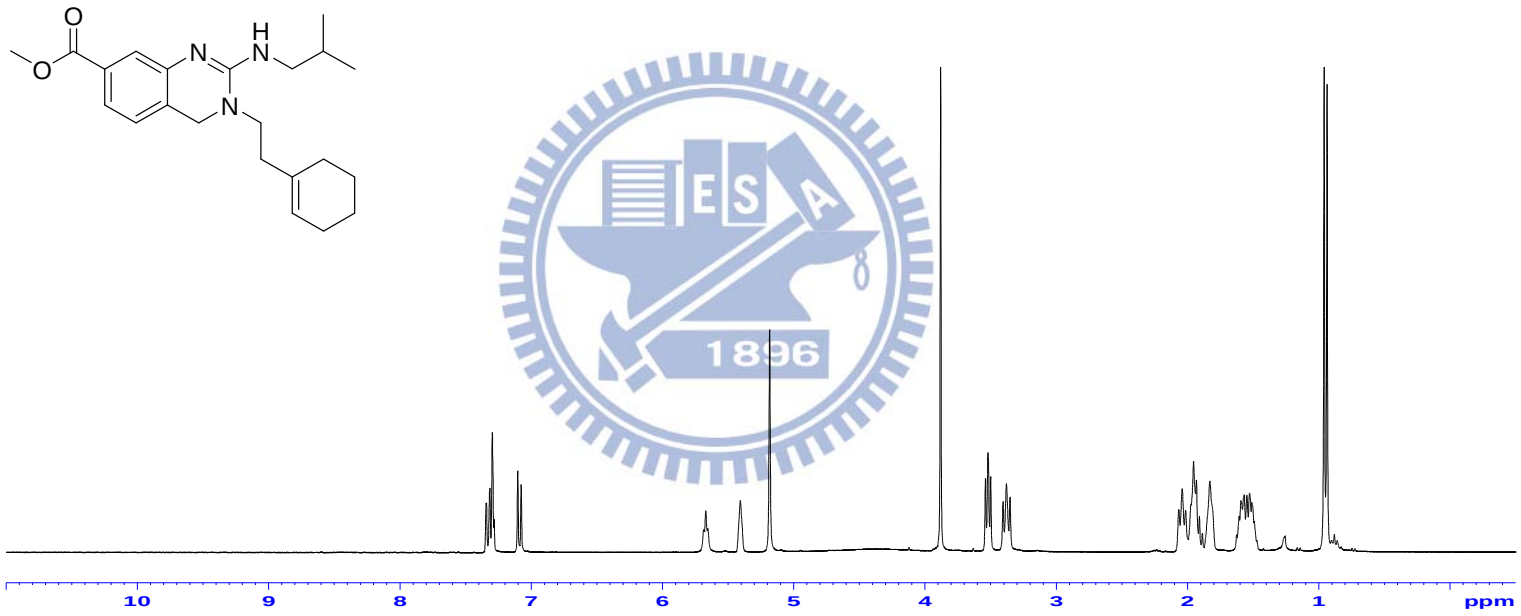
^{13}C NMR spectrum (75 MHz) of compound 13a in $CDCl_3$



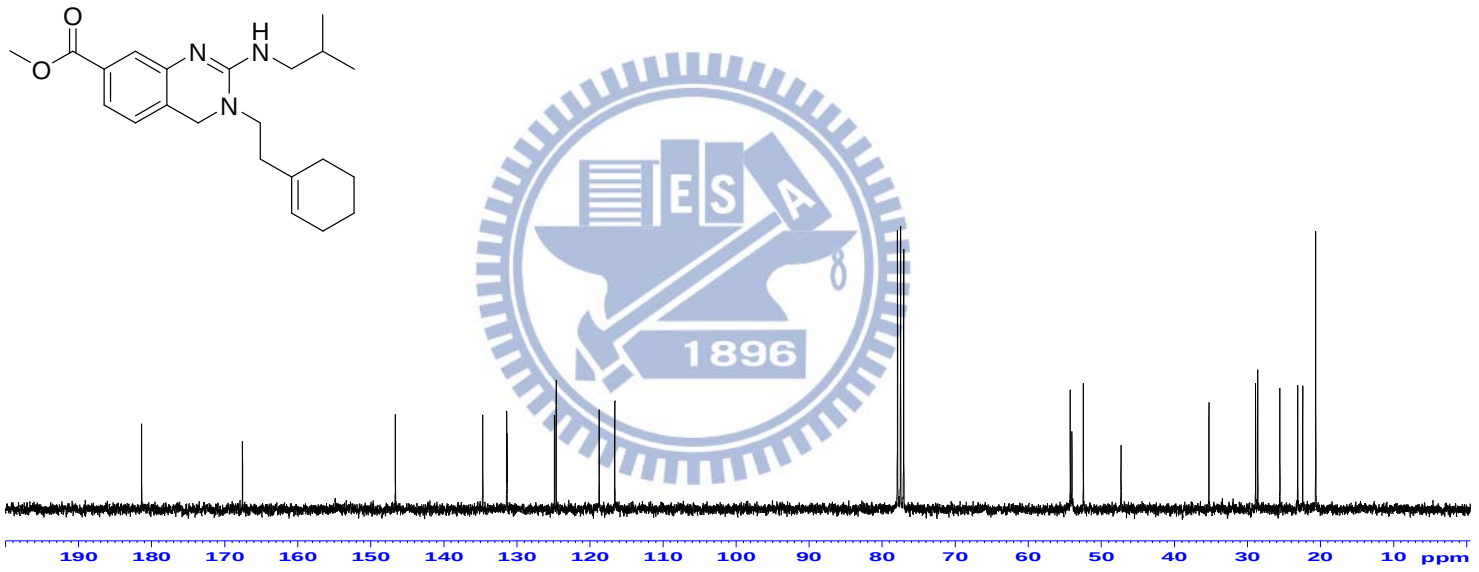
^{1}HNMR spectrum (300 MHz) of compound 13b in $CDCl_3$



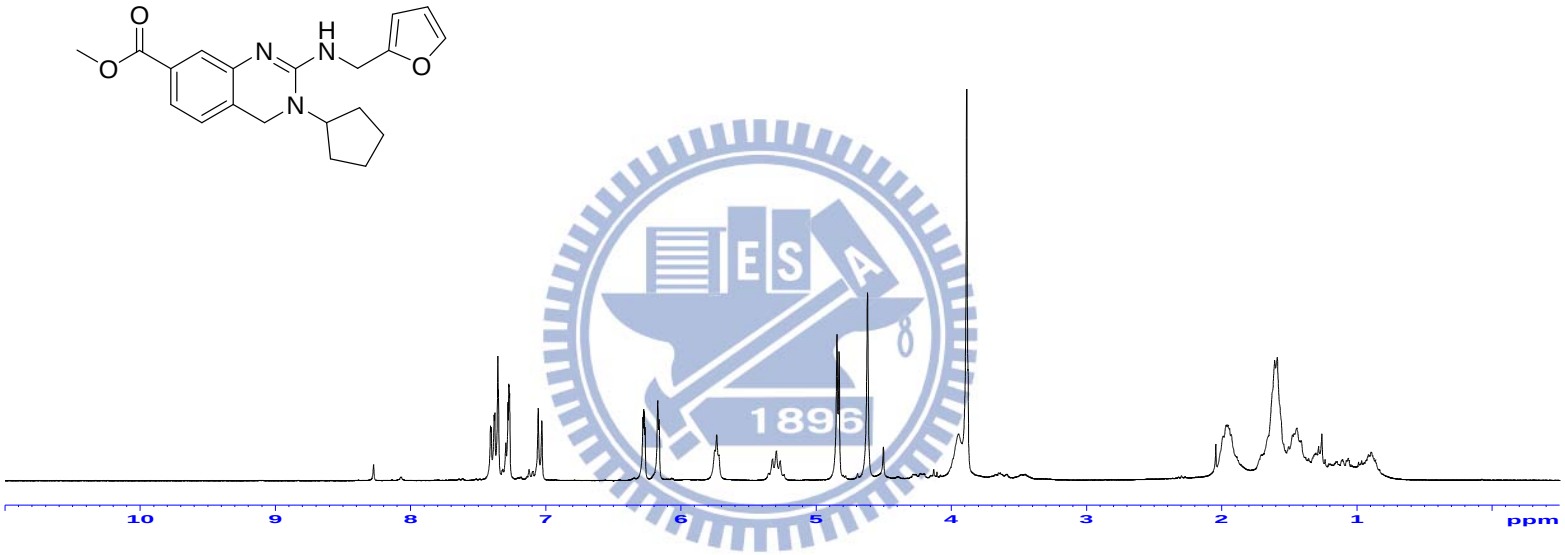
^{13}C NMR spectrum (75 MHz) of compound 13b in $CDCl_3$



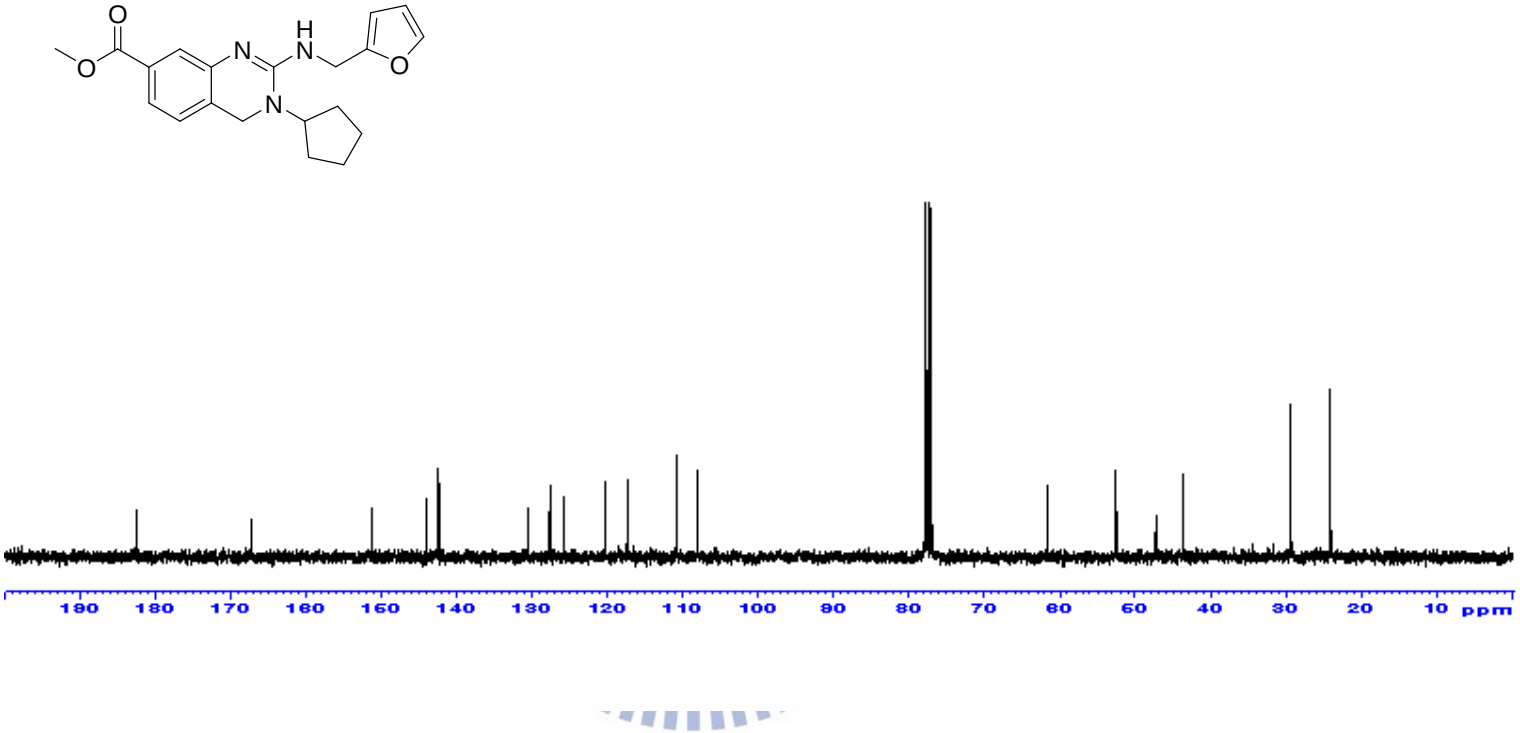
^{1}HNMR spectrum (300 MHz) of compound 13b in $CDCl_3$



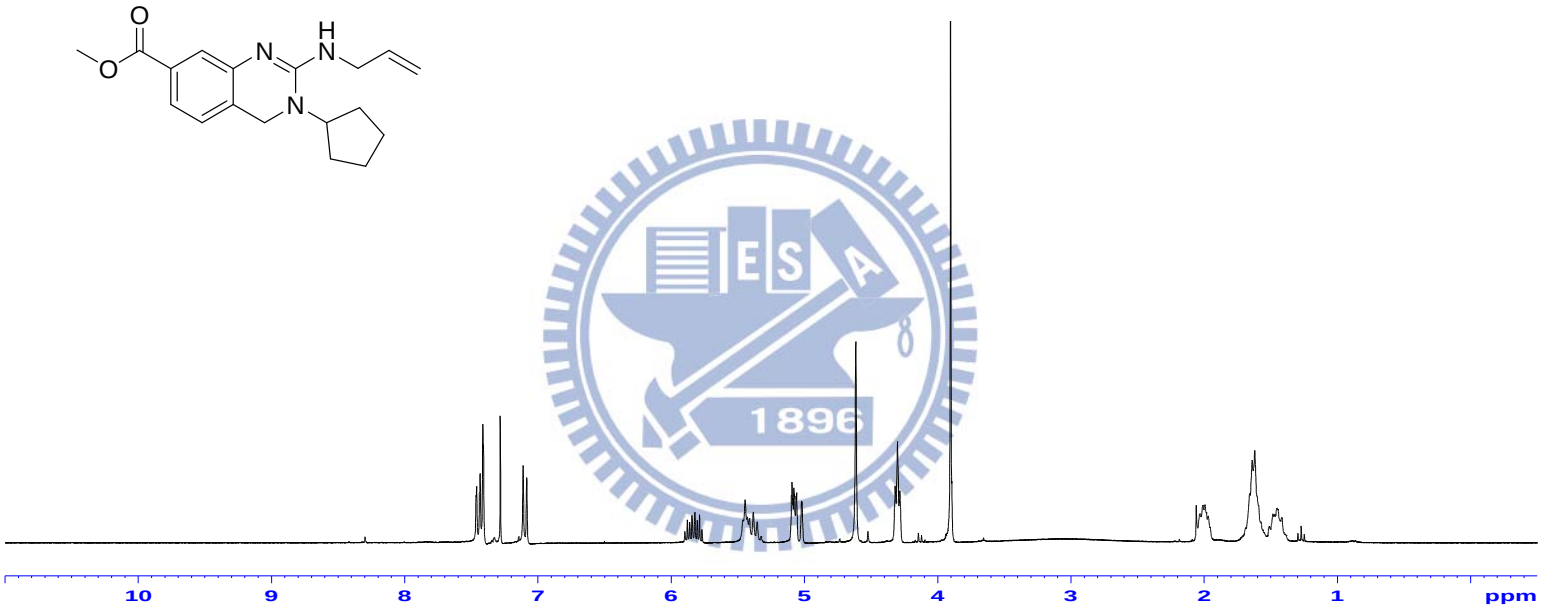
^{13}C NMR spectrum (75 MHz) of compound 13c in $CDCl_3$



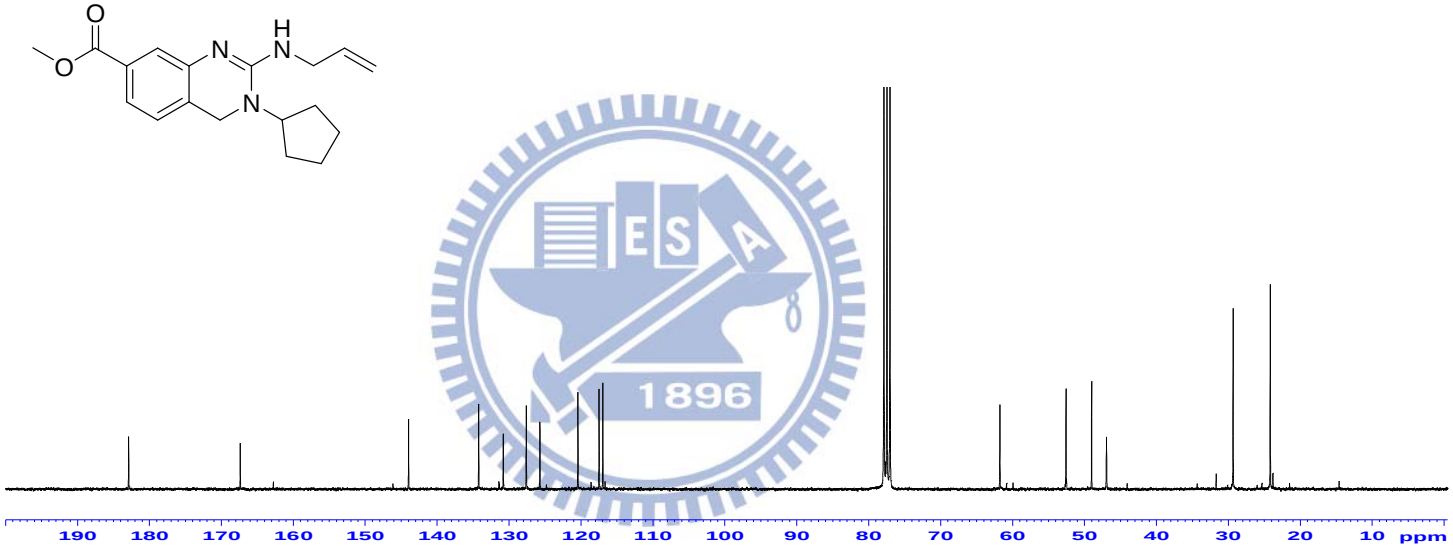
^{1}HNMR spectrum (300 MHz) of compound 13d in $CDCl_3$



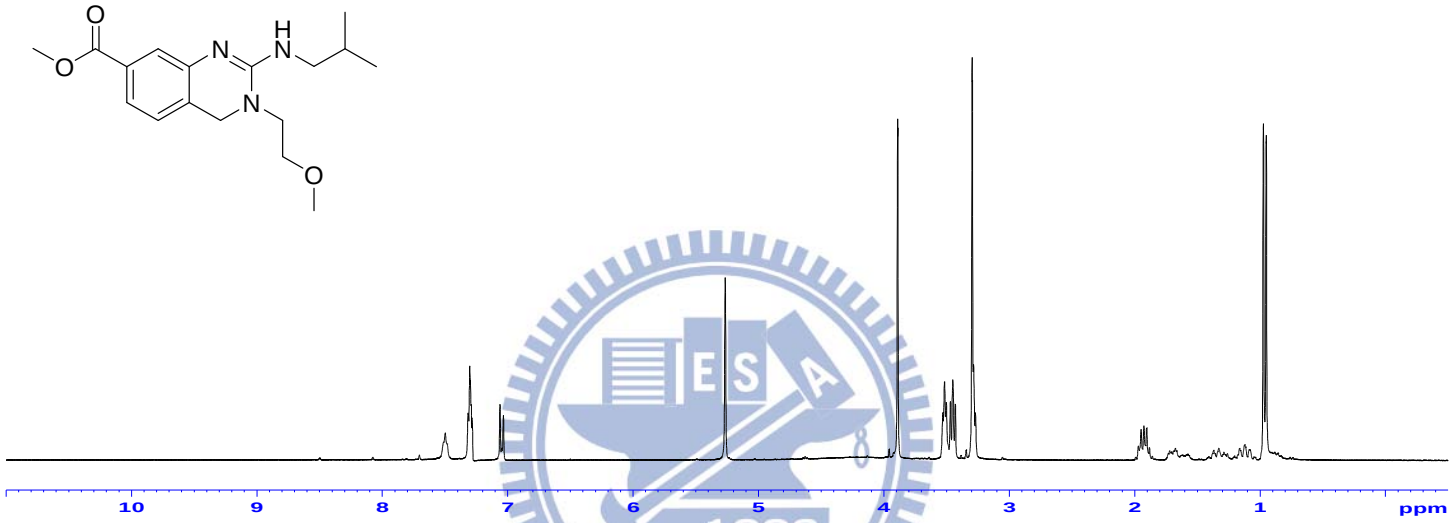
^{13}C NMR spectrum (75 MHz) of compound 13d in $CDCl_3$



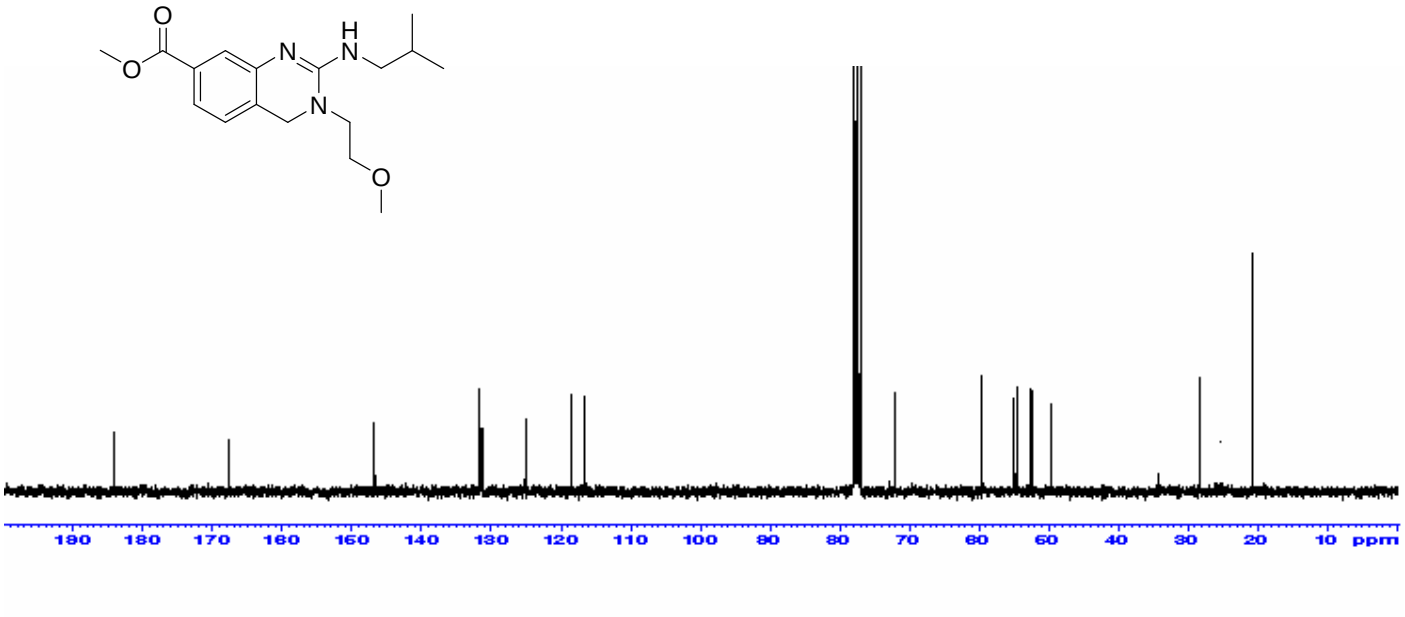
^{1}HNMR spectrum (300 MHz) of compound 13e in $CDCl_3$



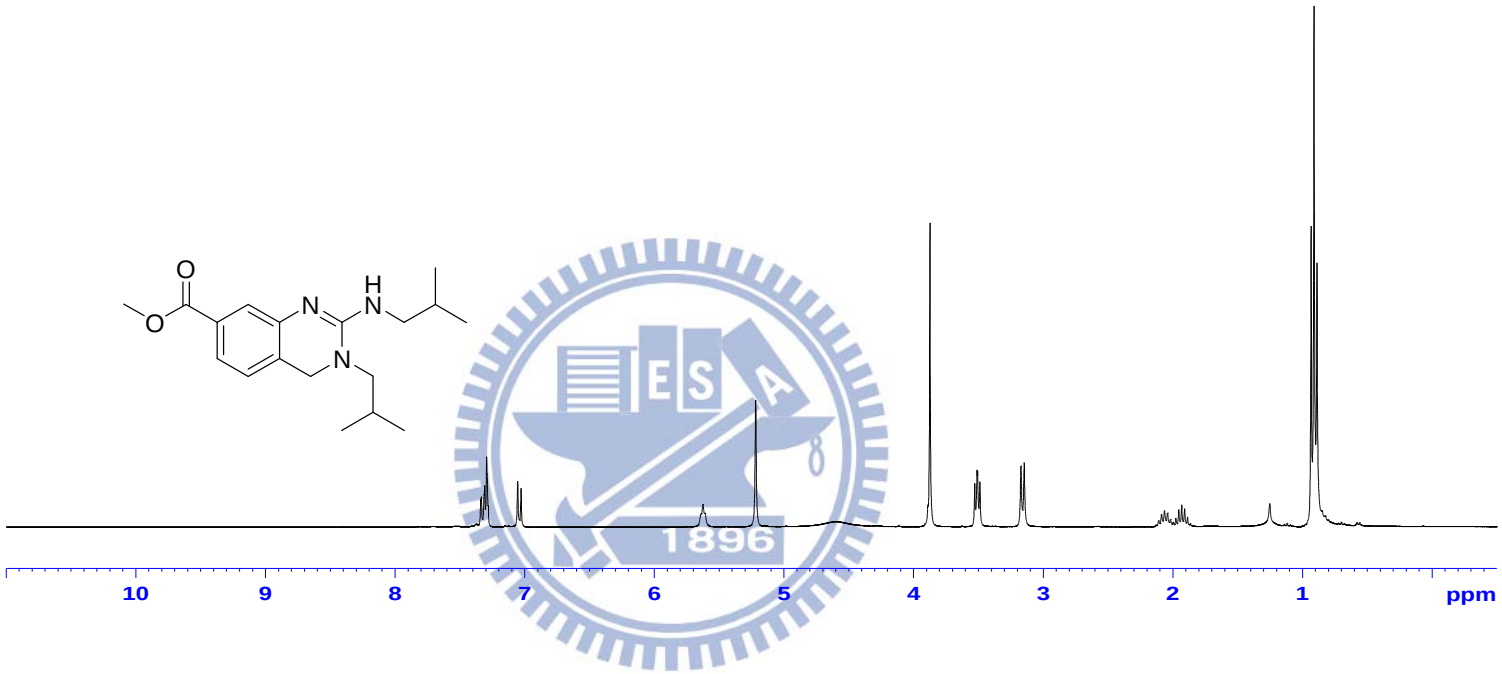
^{13}C NMR spectrum (75 MHz) of compound 13e in $CDCl_3$



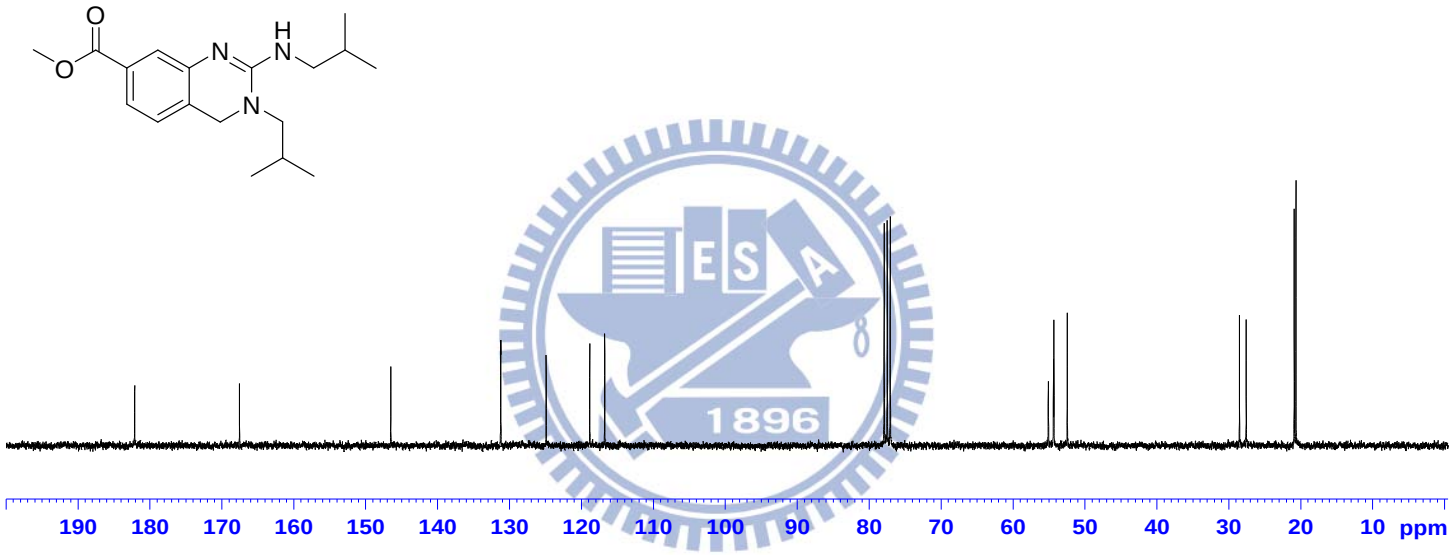
^{1}HNMR spectrum (300 MHz) of compound 13f in $CDCl_3$



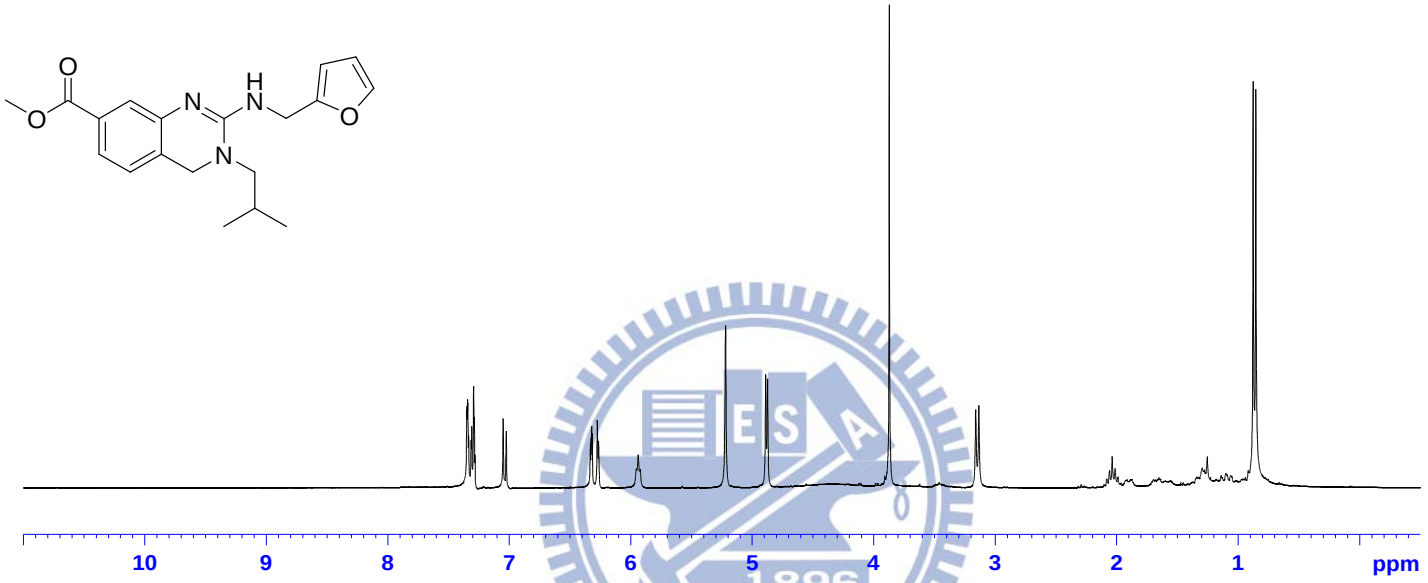
^{13}C NMR spectrum (75 MHz) of compound 13f in $CDCl_3$



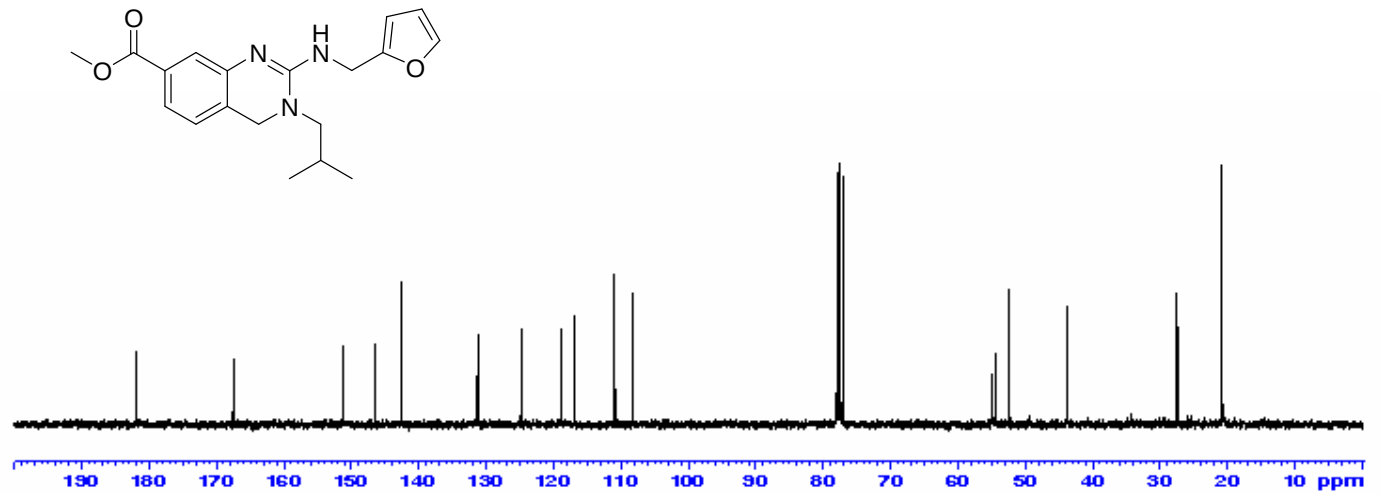
^{1}HNMR spectrum (300 MHz) of compound 13g in $CDCl_3$



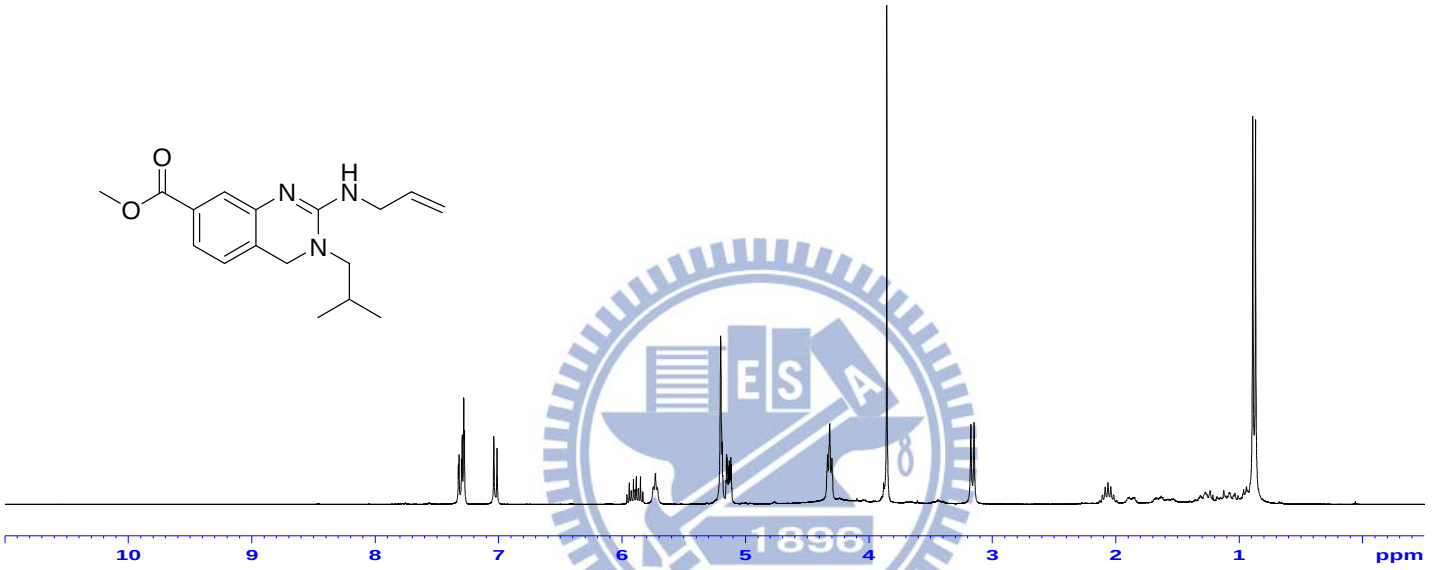
^{13}C NMR spectrum (75 MHz) of compound 13g in $CDCl_3$



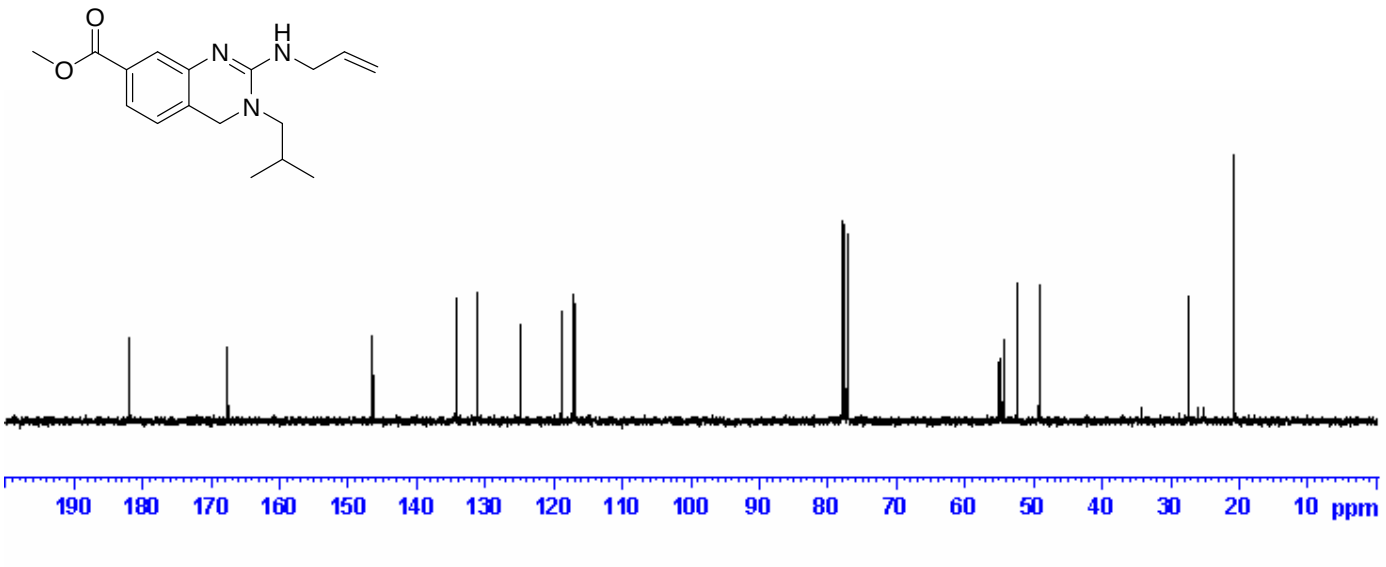
^{1}HNMR spectrum (300 MHz) of compound 13h in $CDCl_3$



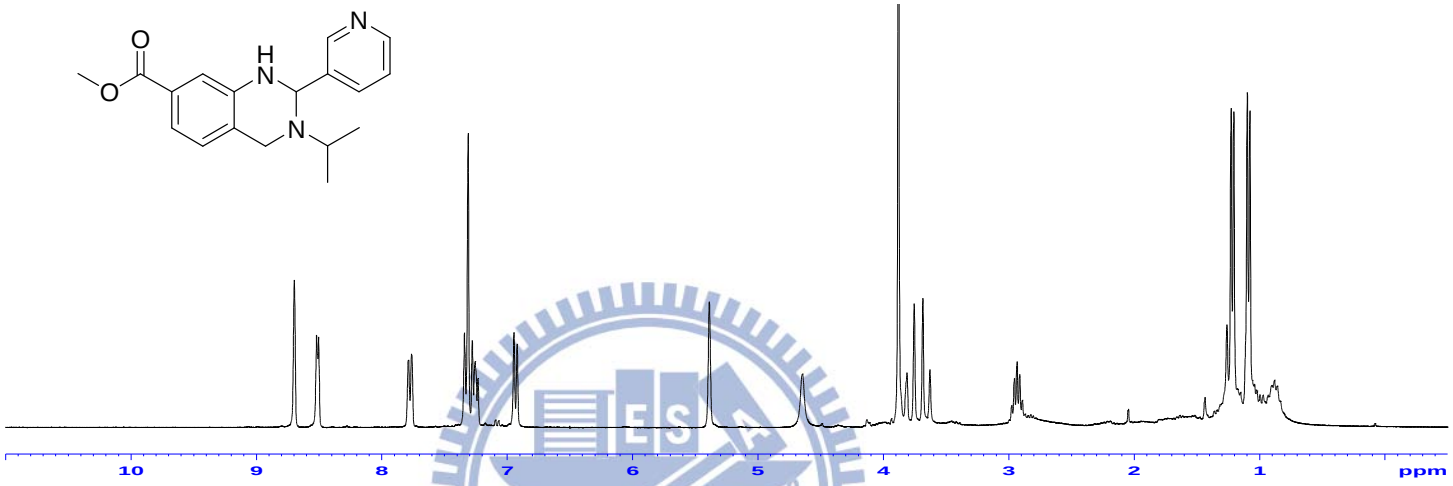
^{13}C NMR spectrum (75 MHz) of compound 13h in $CDCl_3$



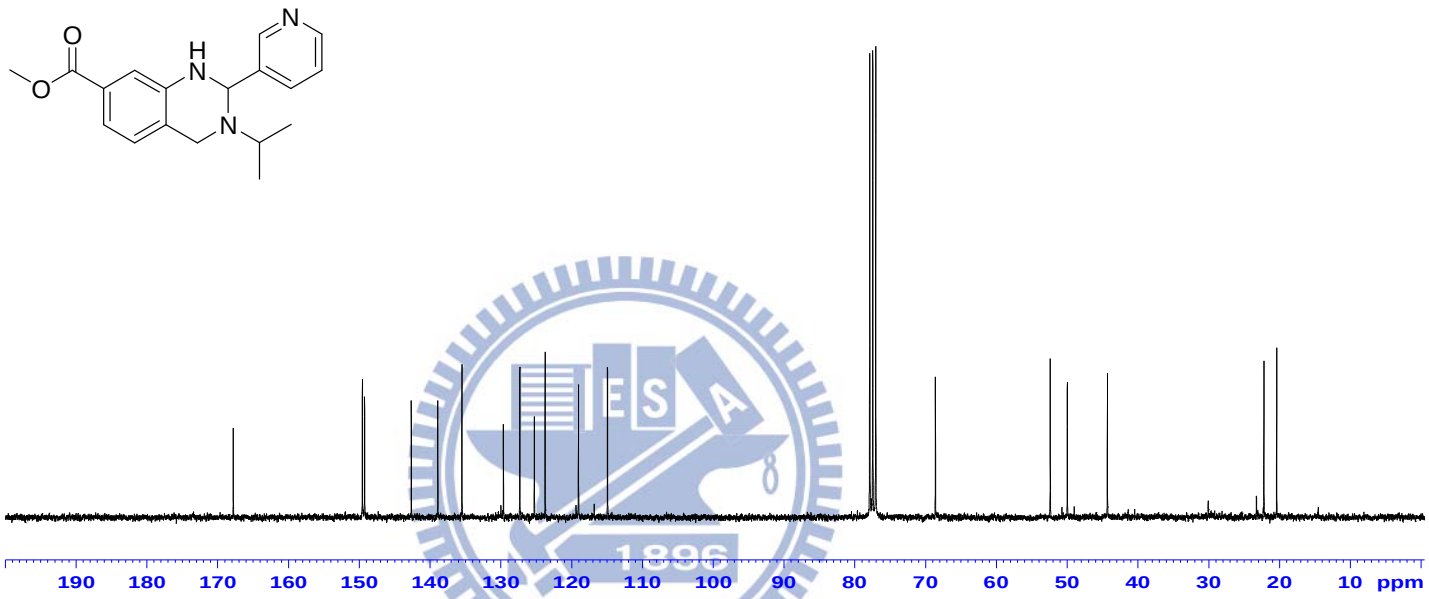
^{1}HNMR spectrum (300 MHz) of compound 13i in $CDCl_3$



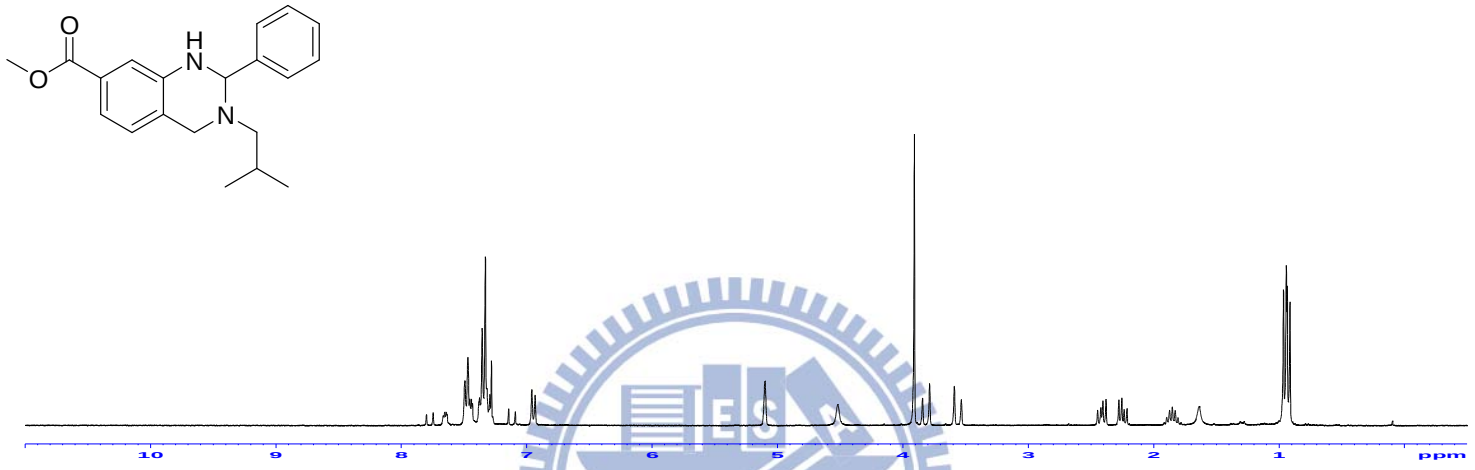
^{13}C NMR spectrum (75 MHz) of compound 13i in $CDCl_3$



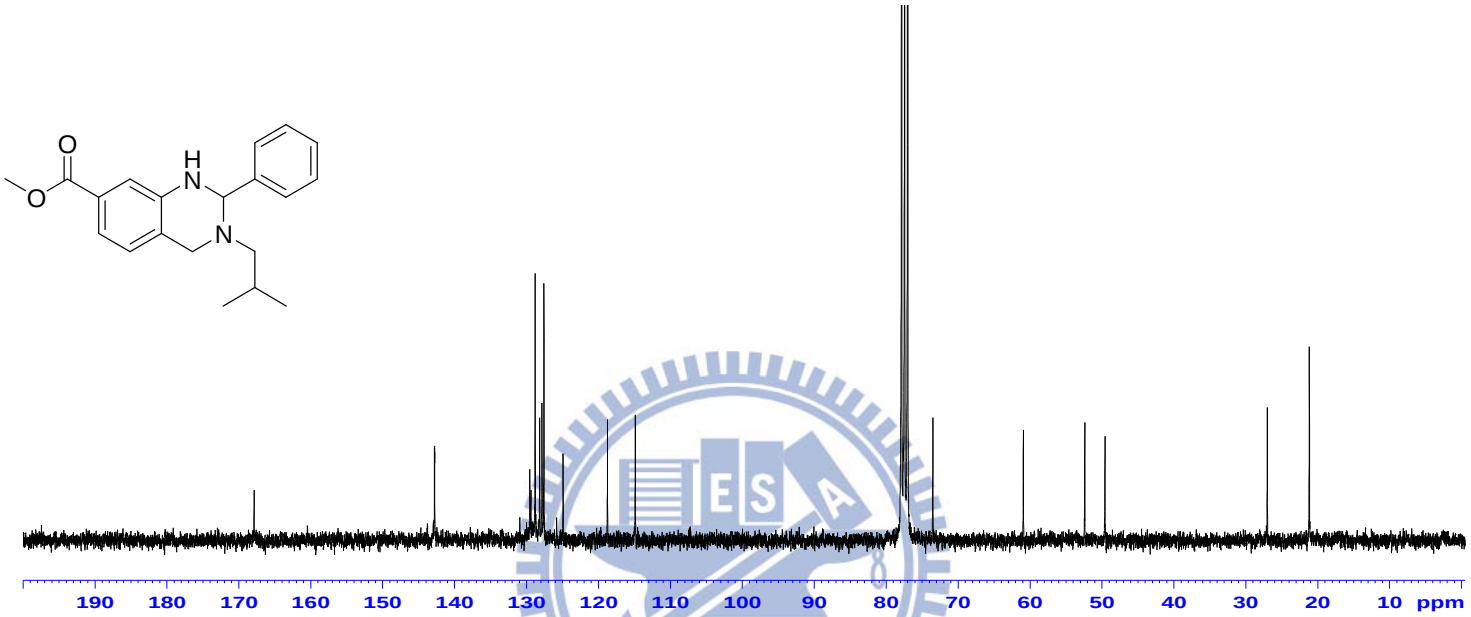
^{1}HNMR spectrum (300 MHz) of compound 13k in $CDCl_3$



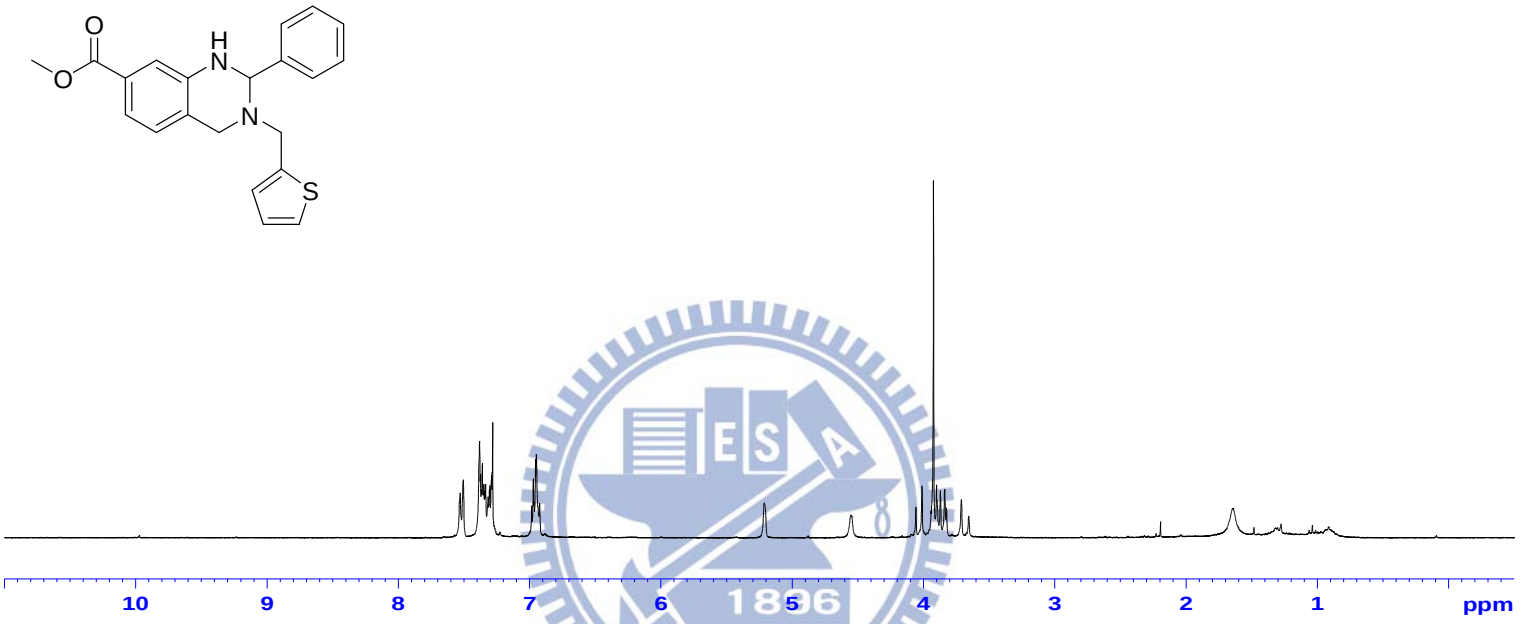
^{13}C NMR spectrum (75 MHz) of compound 13k in $CDCl_3$



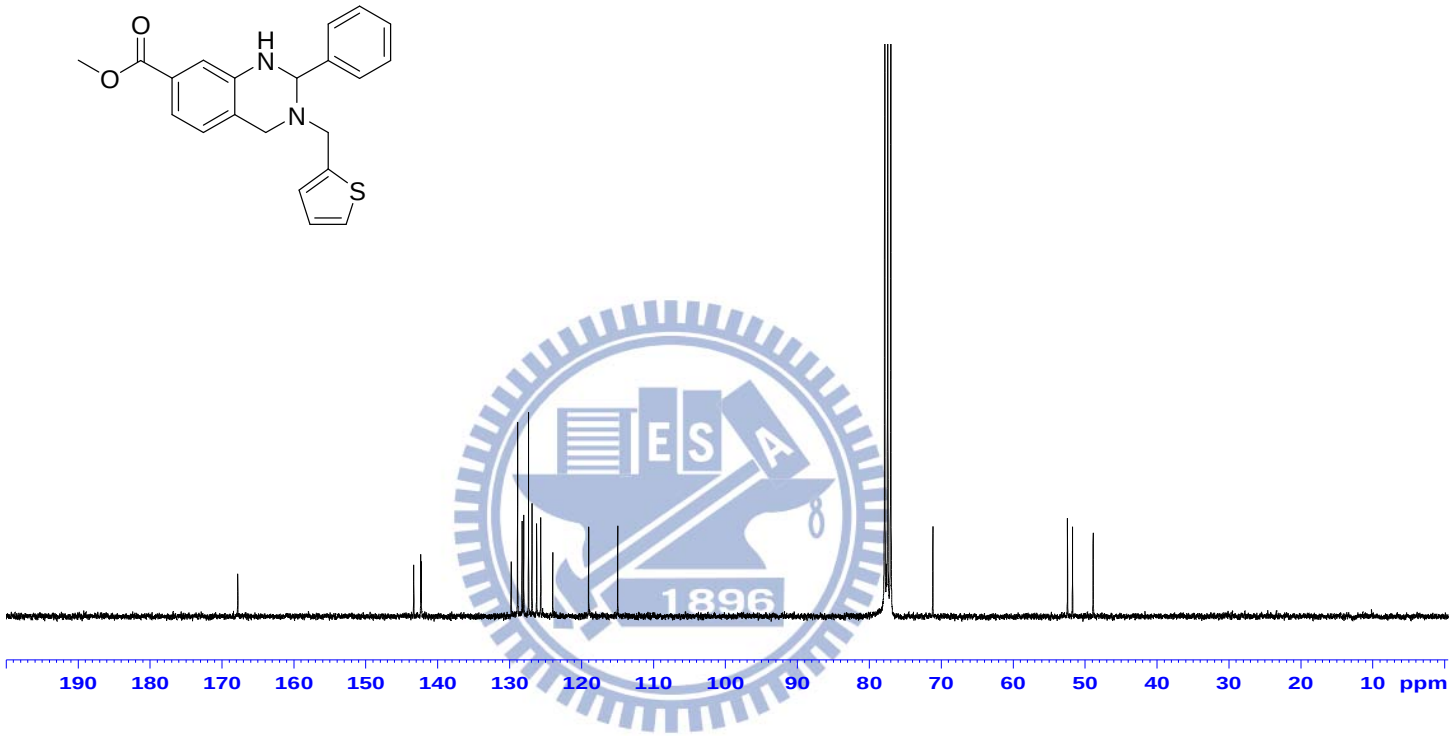
^{1}HNMR spectrum (300 MHz) of compound 13l in $CDCl_3$



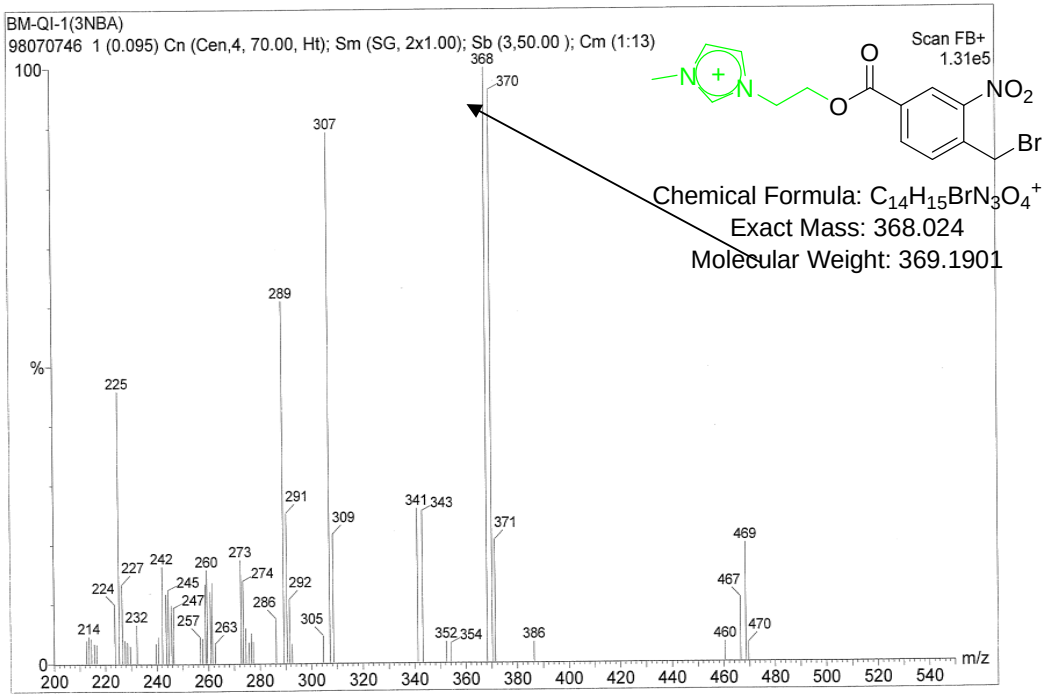
^{13}C NMR spectrum (75 MHz) of compound 13l in $CDCl_3$



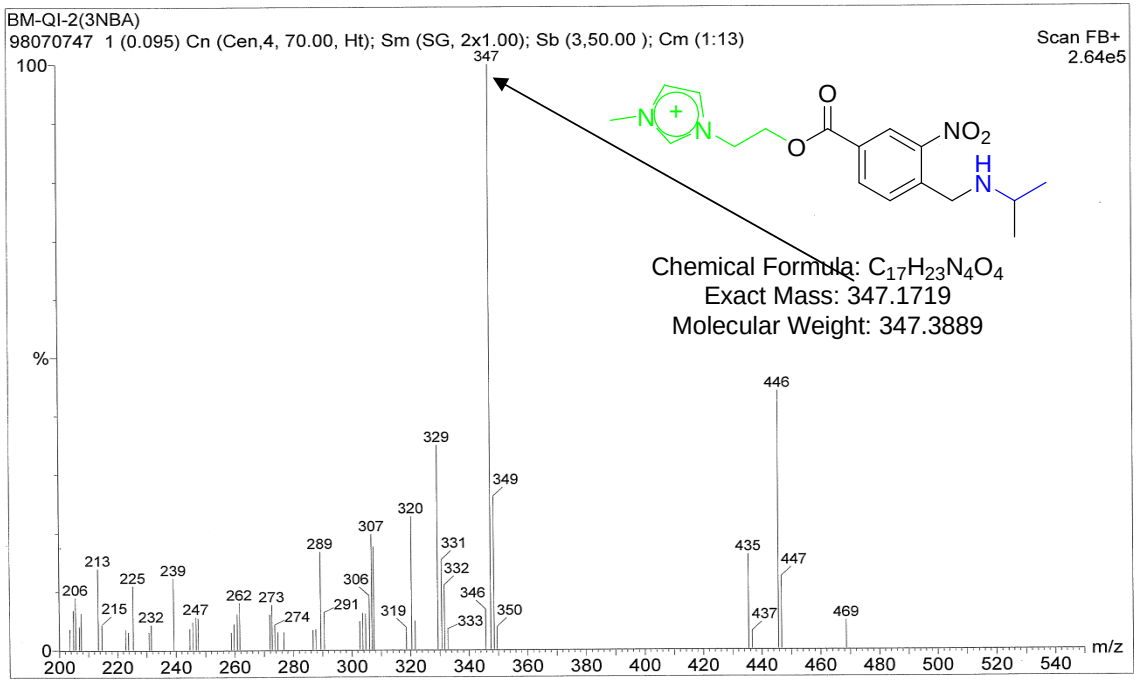
^{1}HNMR spectrum (300 MHz) of compound 13m in $CDCl_3$



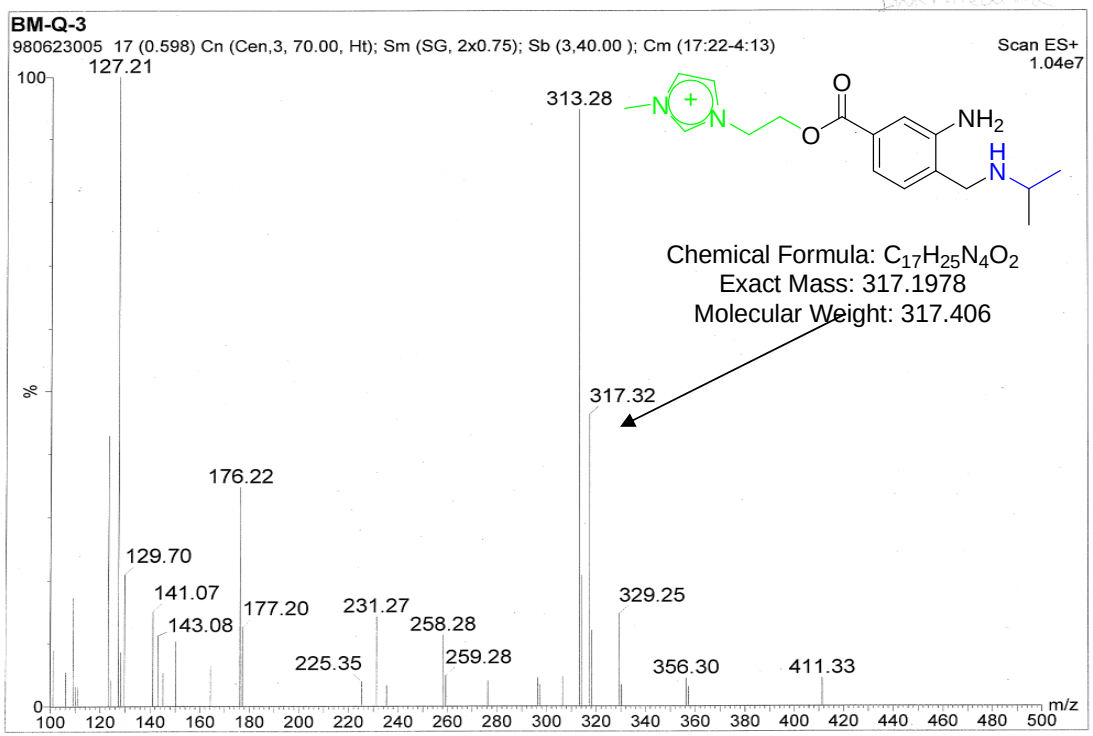
^{13}C NMR spectrum (75 MHz) of compound 13m in $CDCl_3$



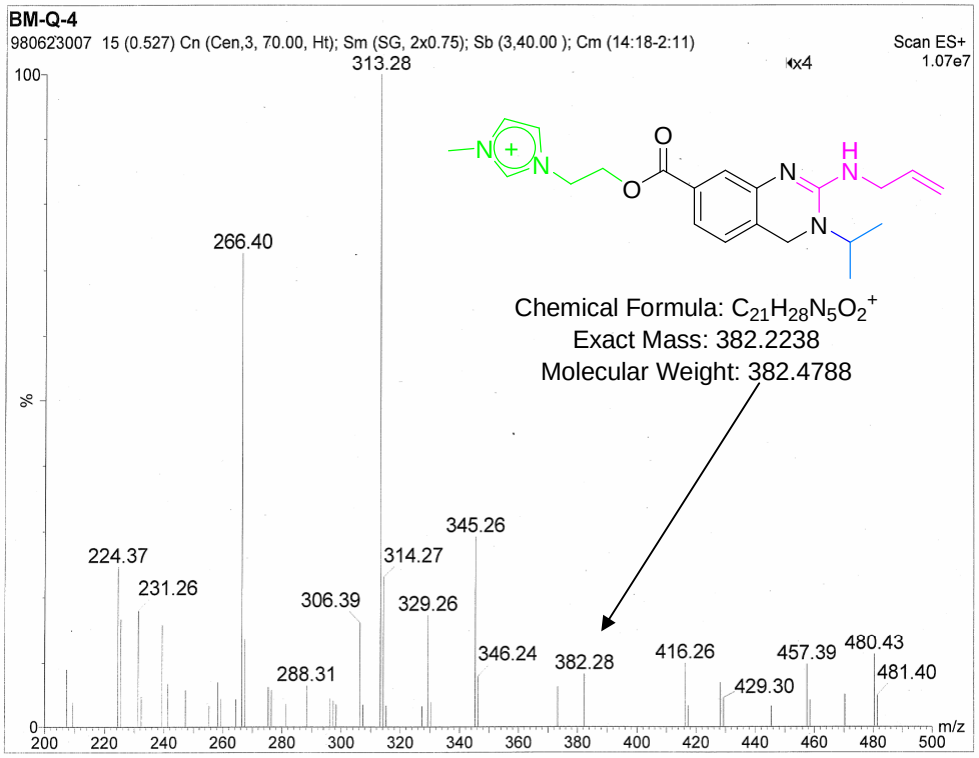
LR Mass Spectrum of Compound 13n



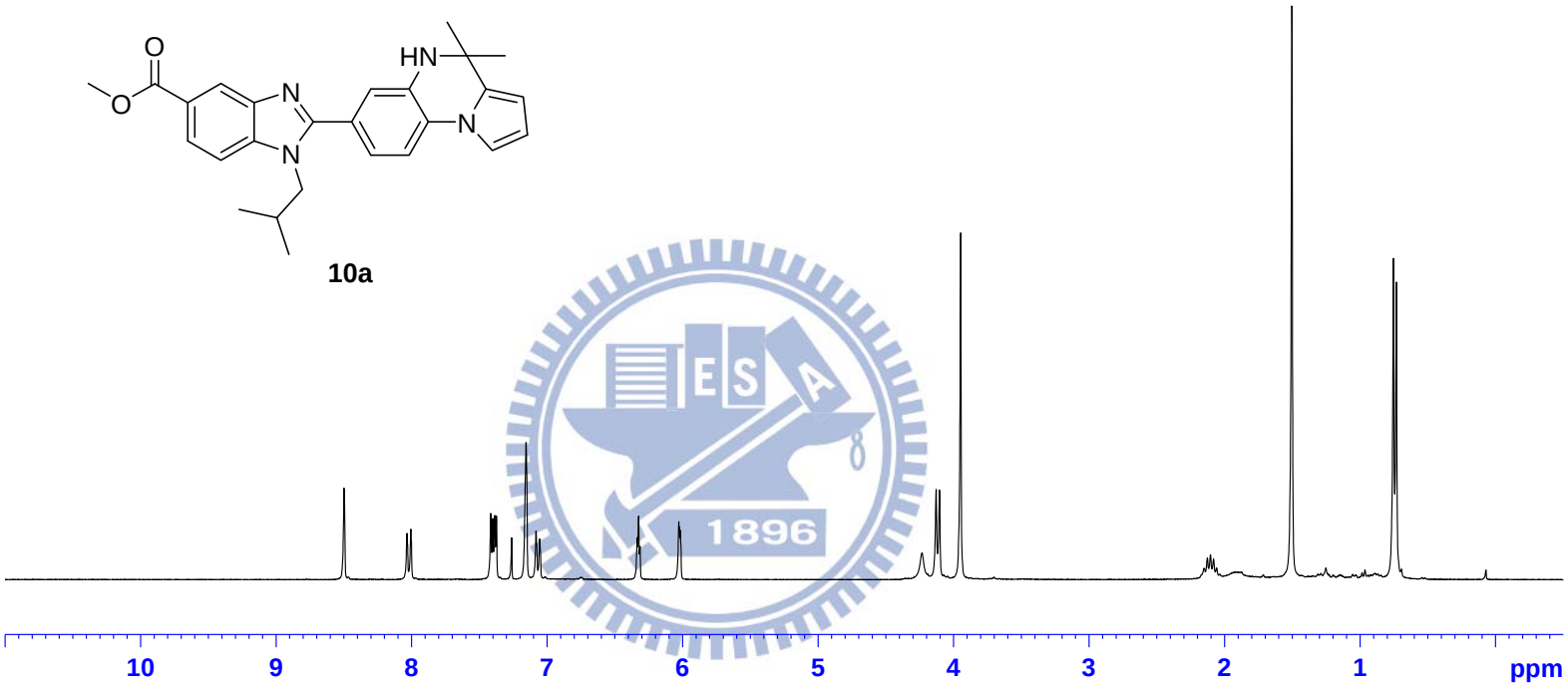
LR Mass Spectrum of Compound 13n



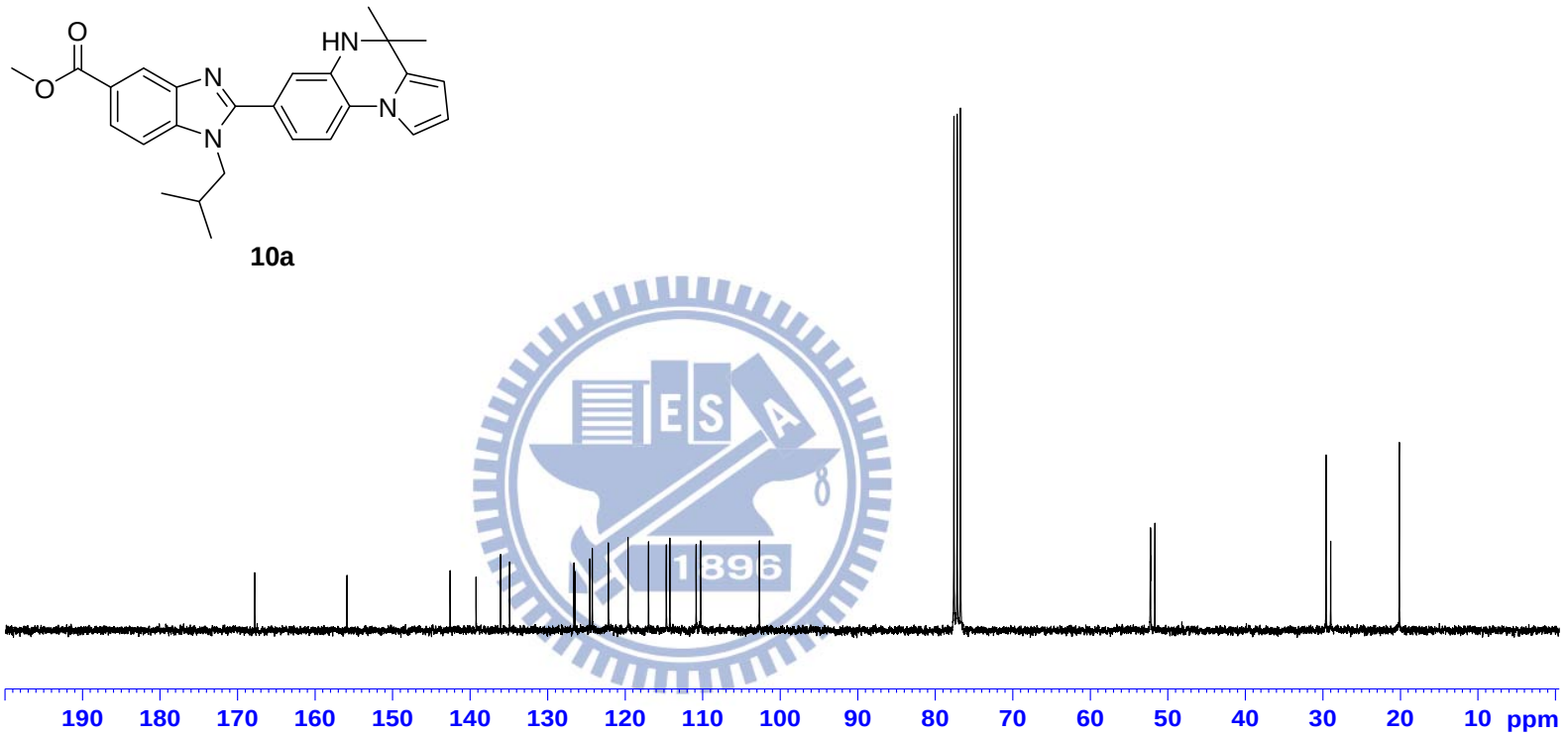
LR Mass Spectrum of Compound 13n



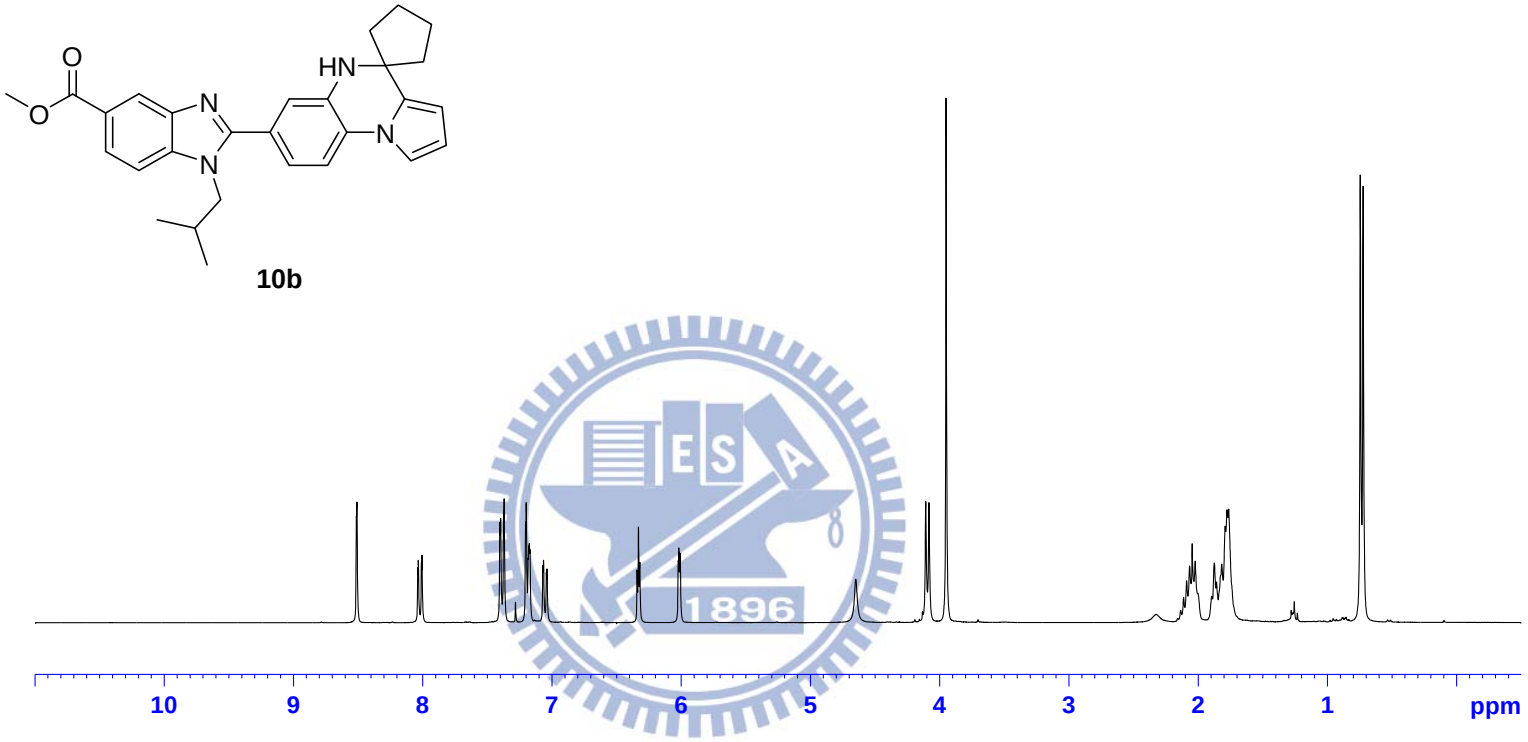
LR Mass Spectrum of Compound 13n



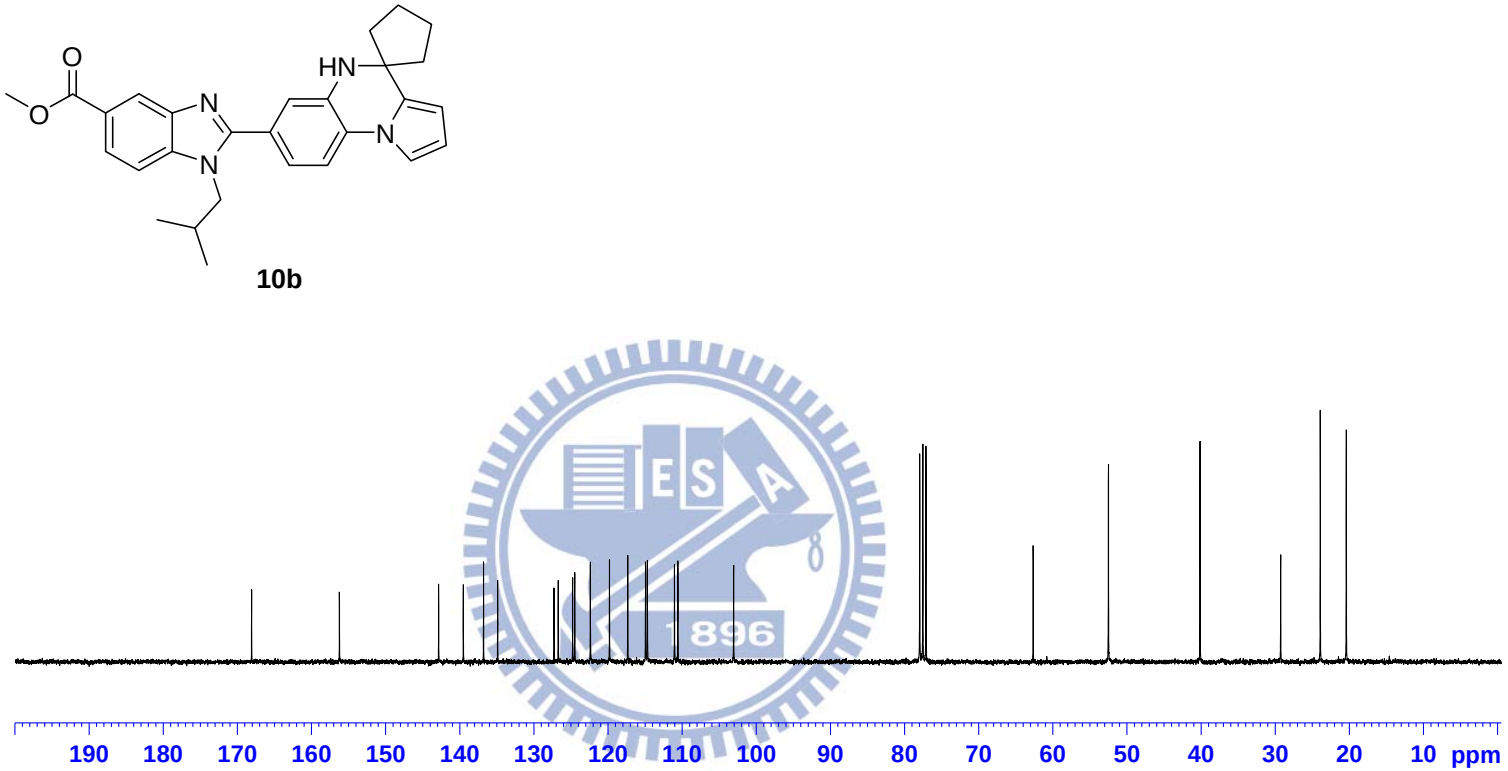
^{1}HNMR spectrum (300 MHz) of compound 10a in $CDCl_3$



^{13}C NMR spectrum (75 MHz) of compound 10a in $CDCl_3$

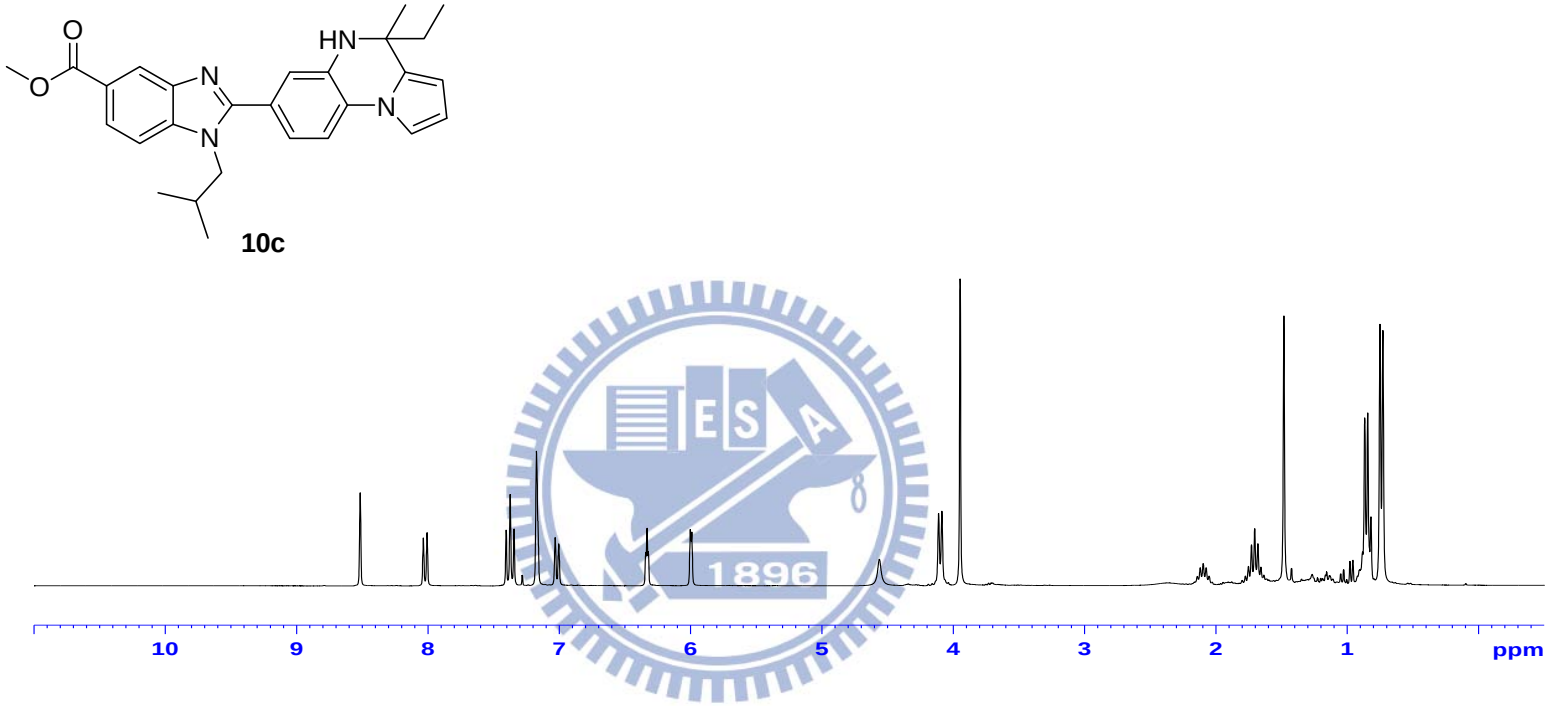


^{1}HNMR spectrum (300 MHz) of compound 10b in $CDCl_3$

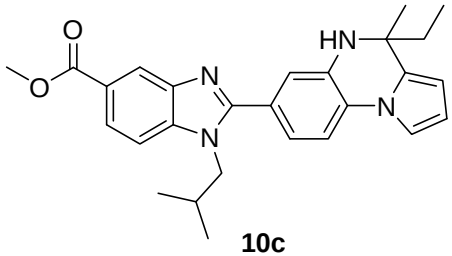


10b

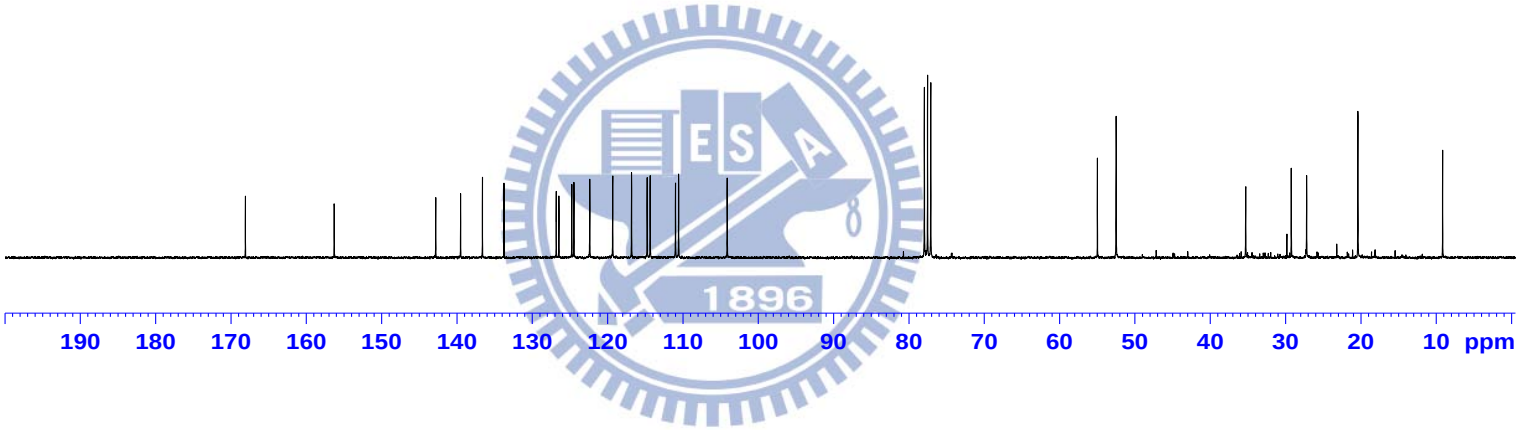
^{13}C NMR spectrum (75 MHz) of compound 10b in $CDCl_3$



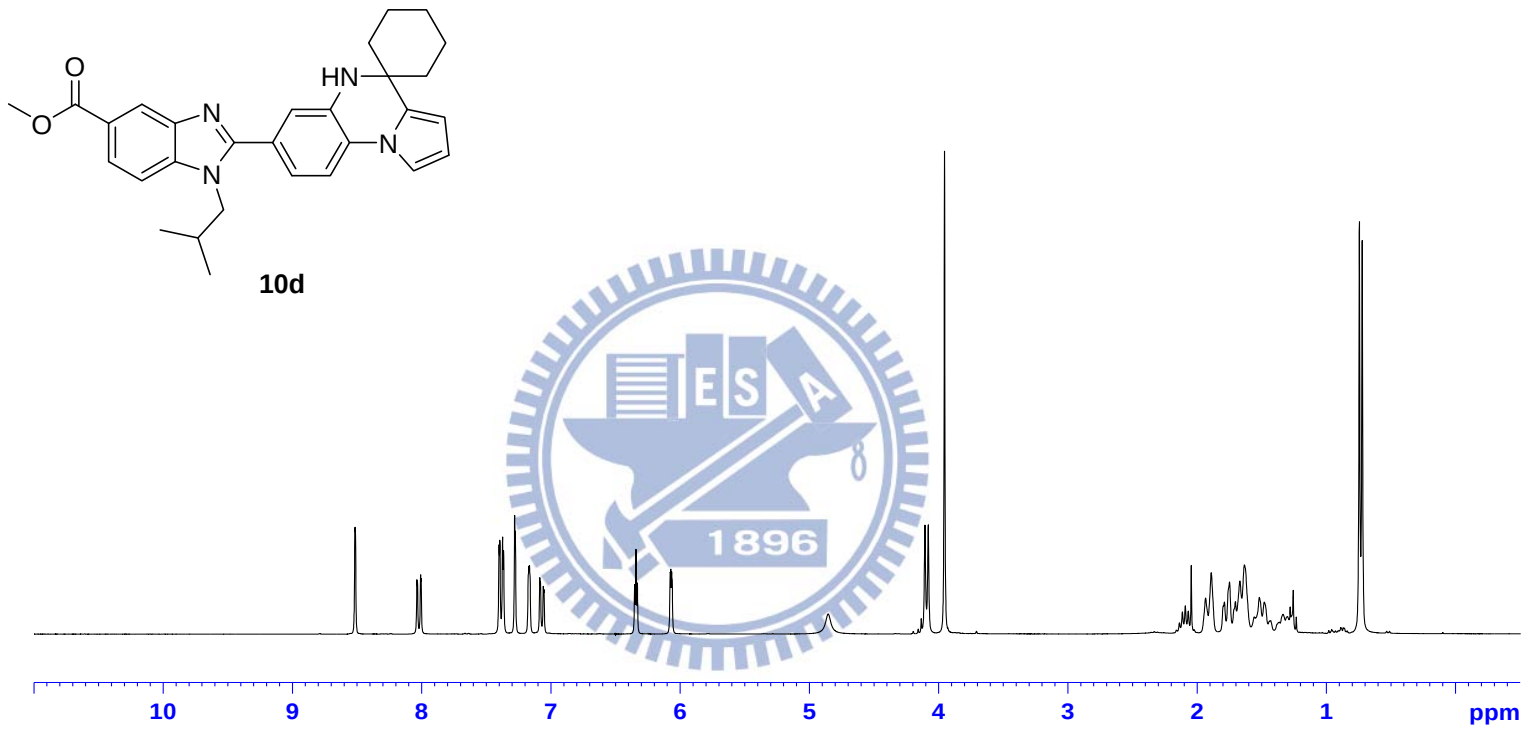
^{1}HNMR spectrum (300 MHz) of compound 10c in $CDCl_3$



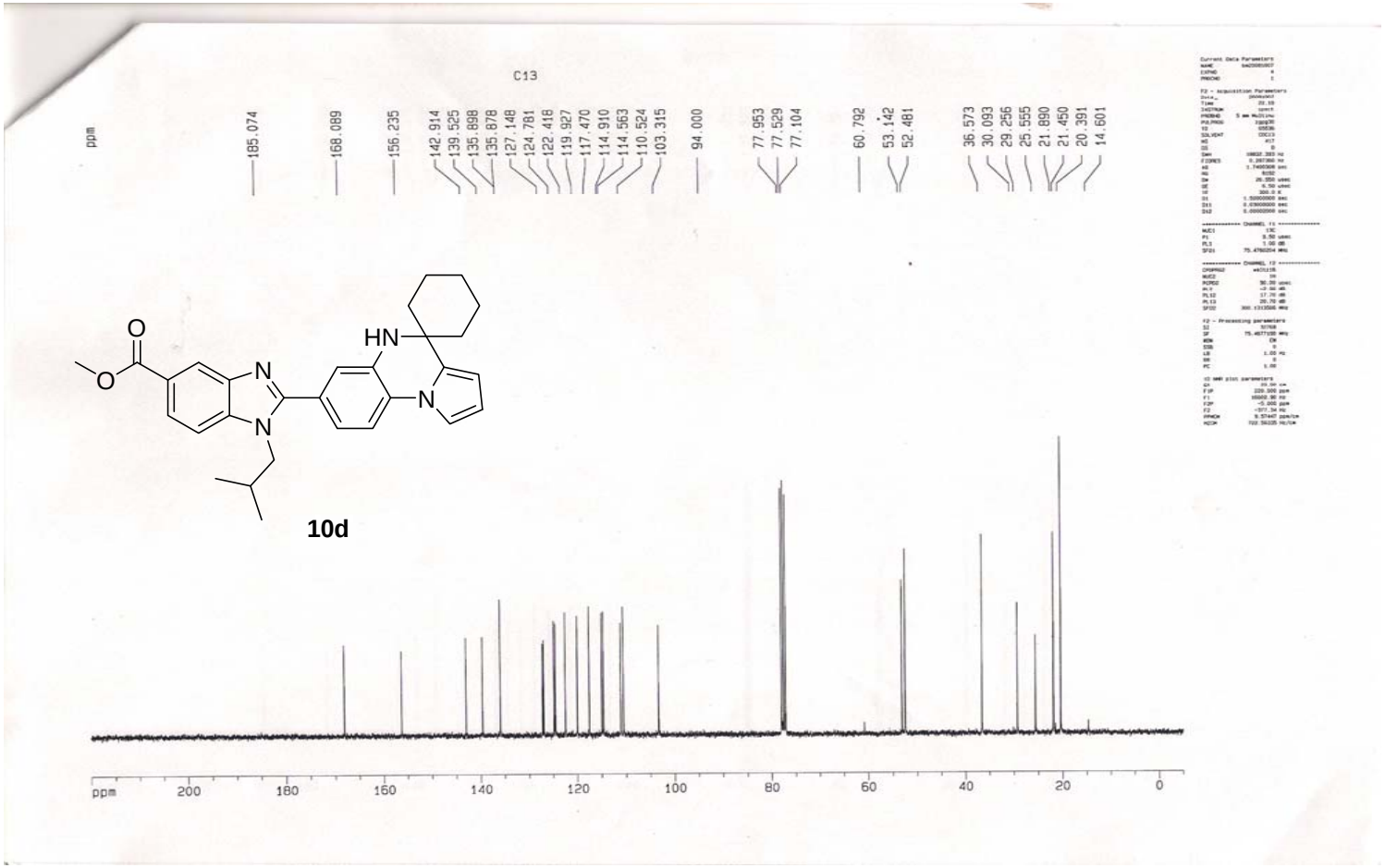
10c



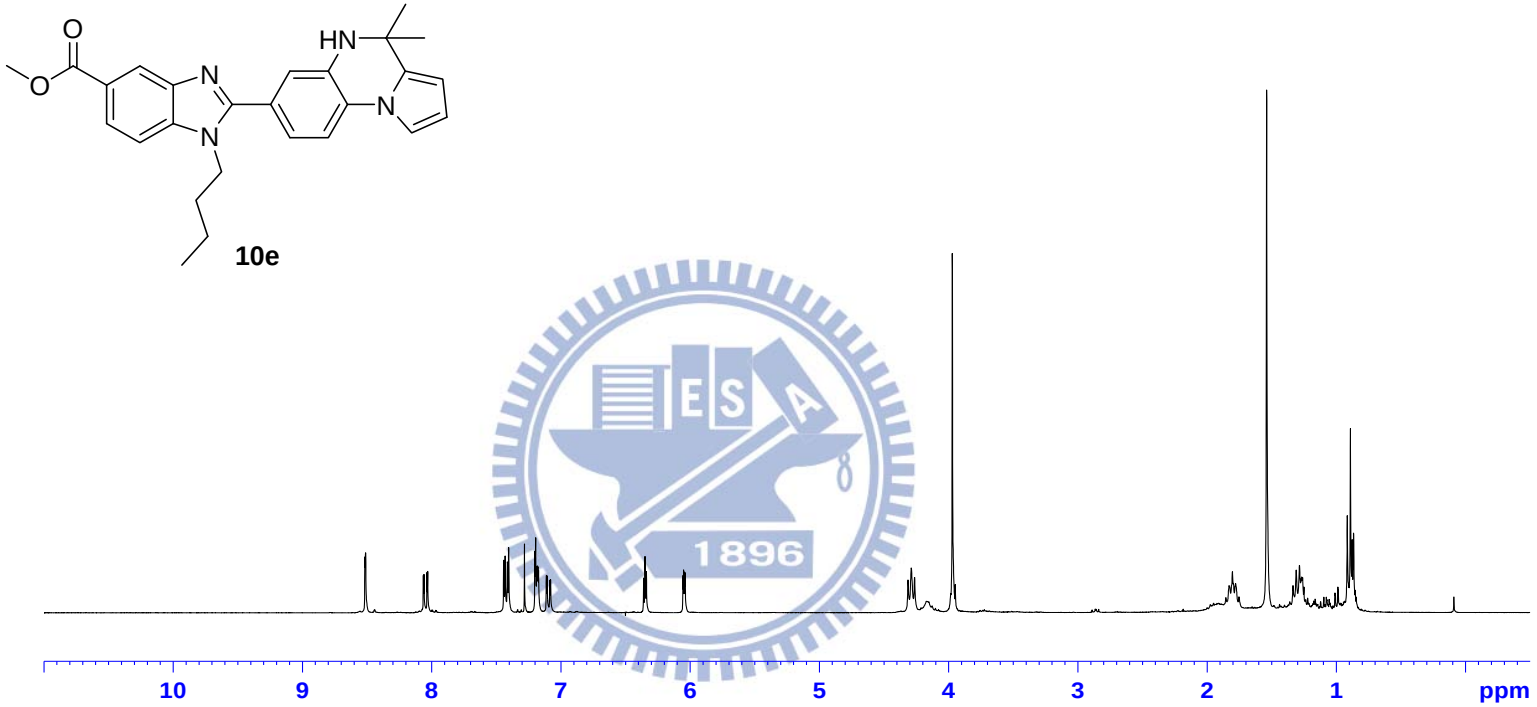
^{13}C NMR spectrum (75 MHz) of compound 10c in $CDCl_3$



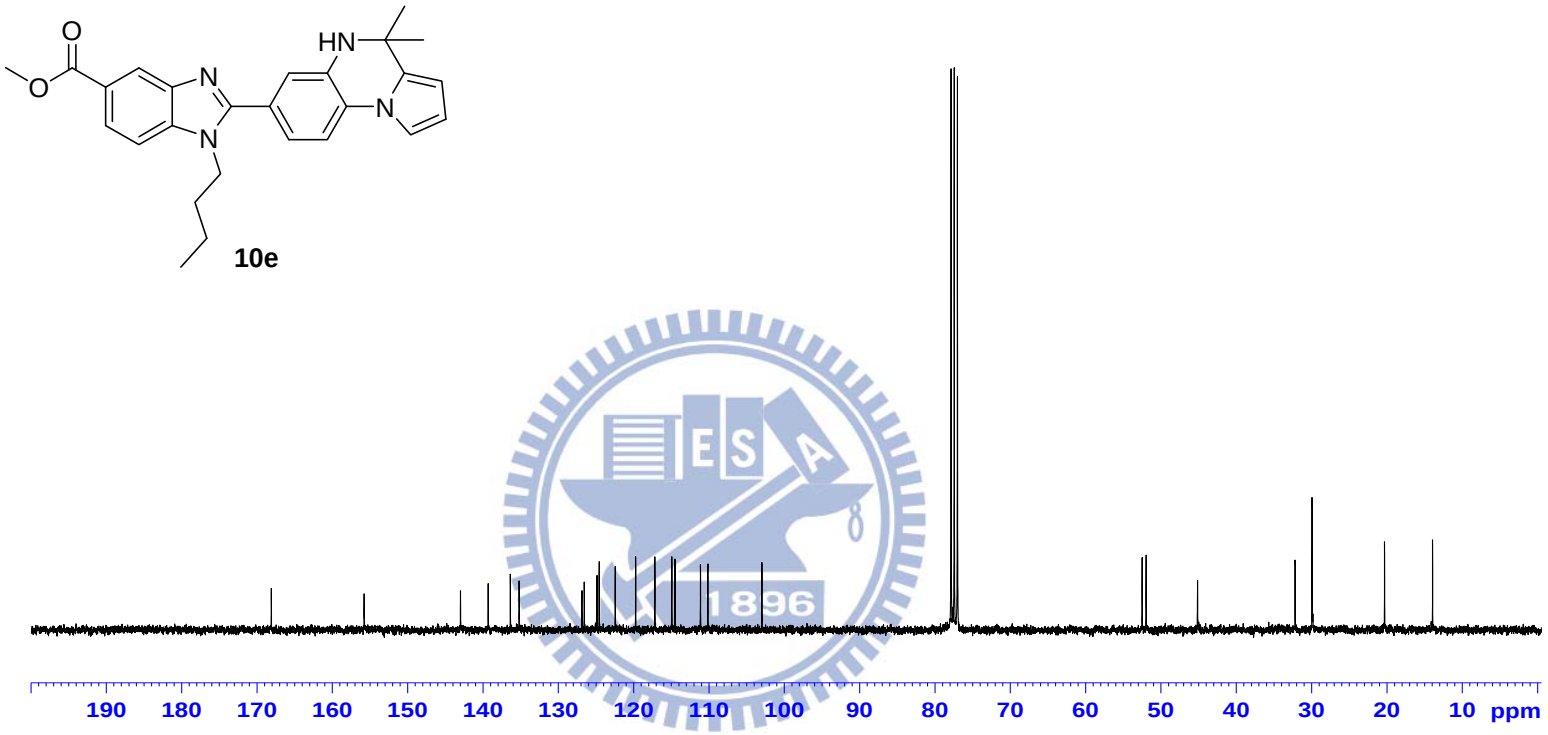
^{1}HNMR spectrum (300 MHz) of compound 10d in $CDCl_3$



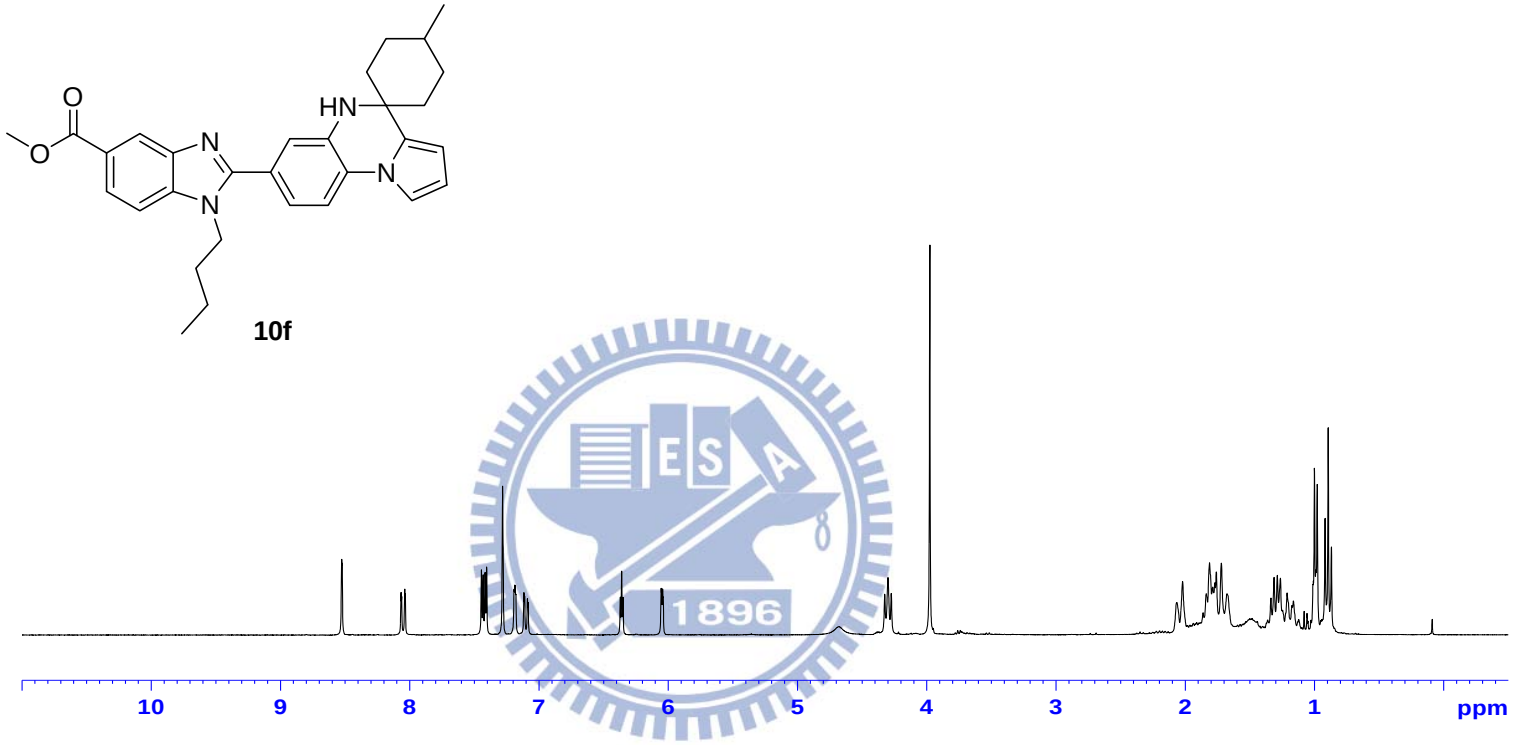
^{13}C NMR spectrum (75 MHz) of compound 10d in $CDCl_3$



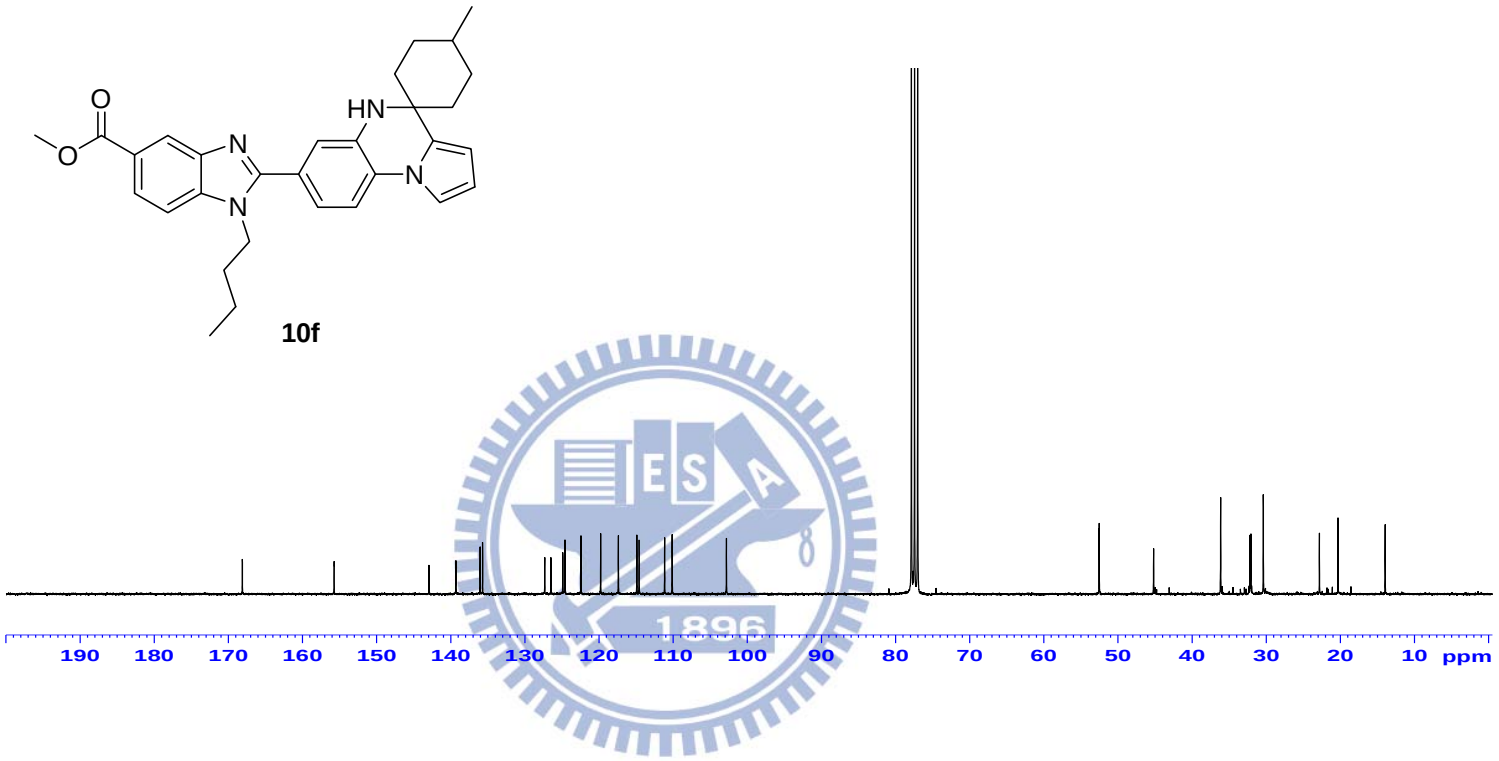
^{1}HNMR spectrum (300 MHz) of compound 10e in $CDCl_3$



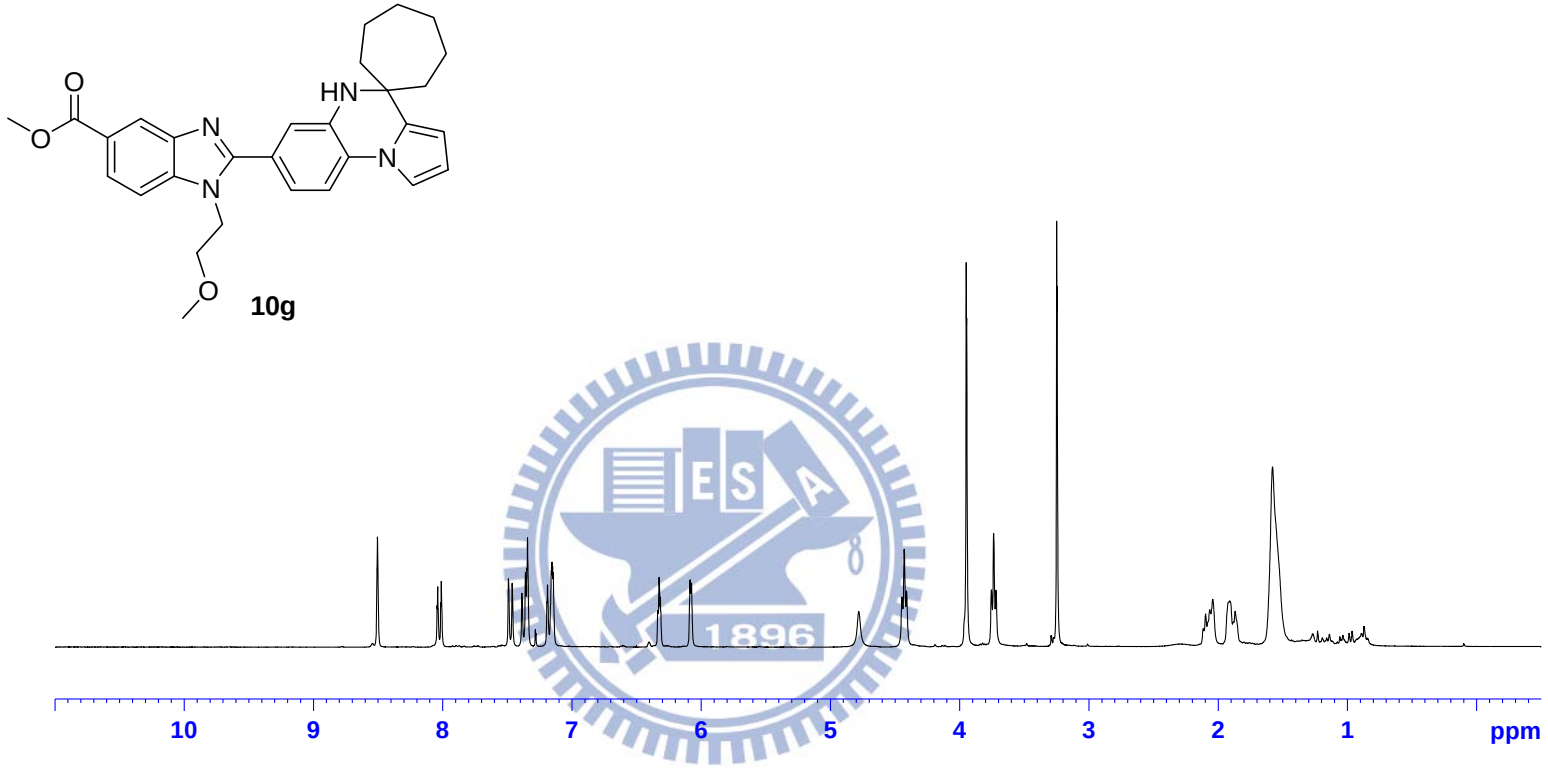
^{13}C NMR spectrum (75 MHz) of compound 10e in $CDCl_3$



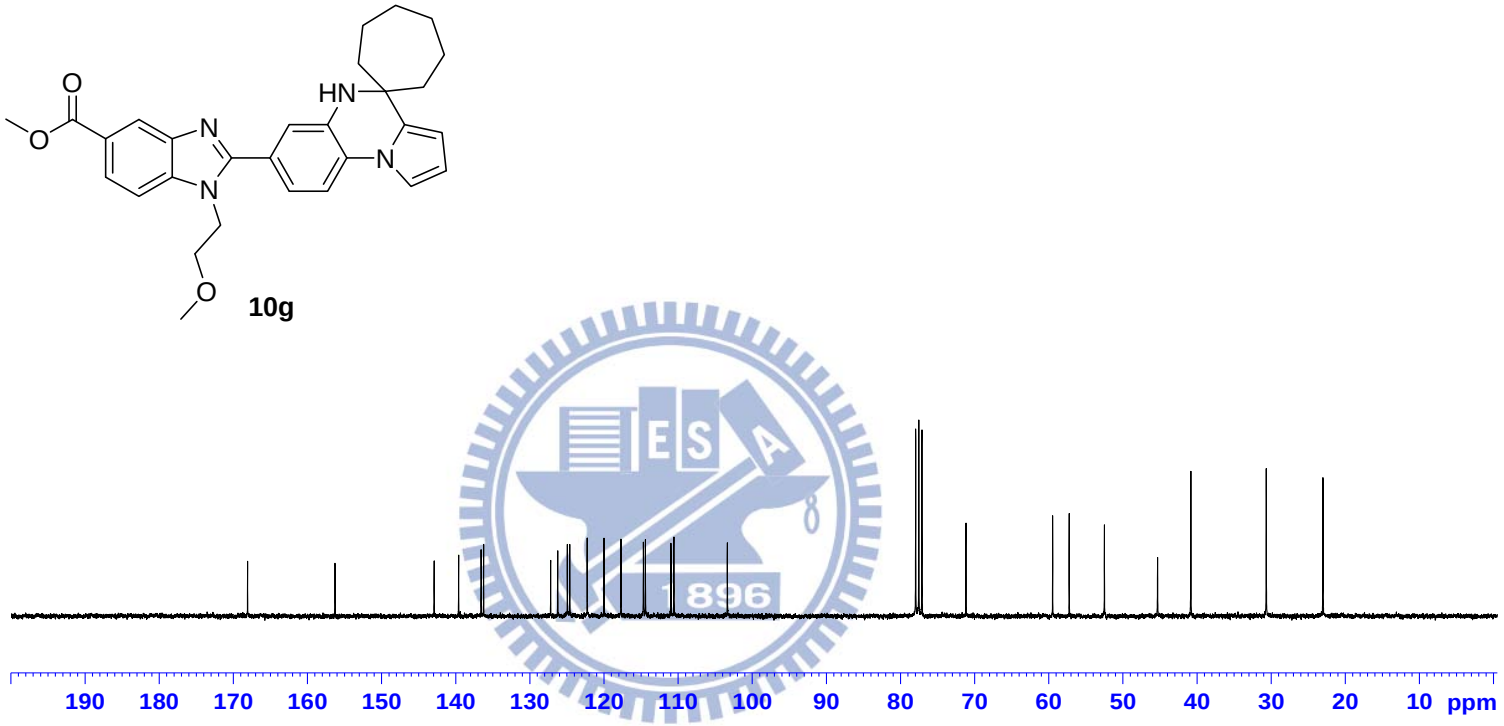
^{1}HNMR spectrum (300 MHz) of compound 10f in $CDCl_3$



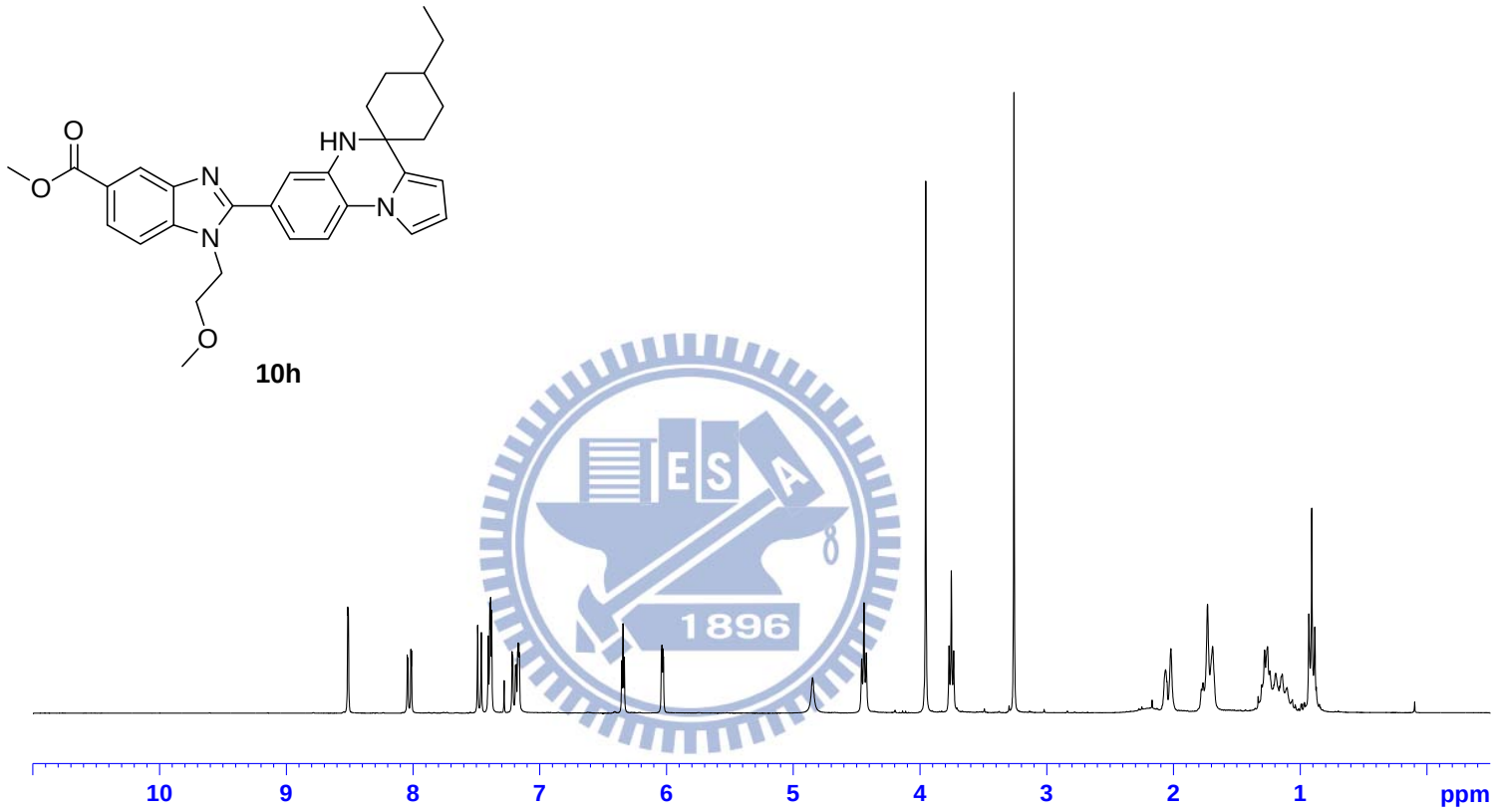
^{13}C NMR spectrum (75 MHz) of compound 10f in $CDCl_3$



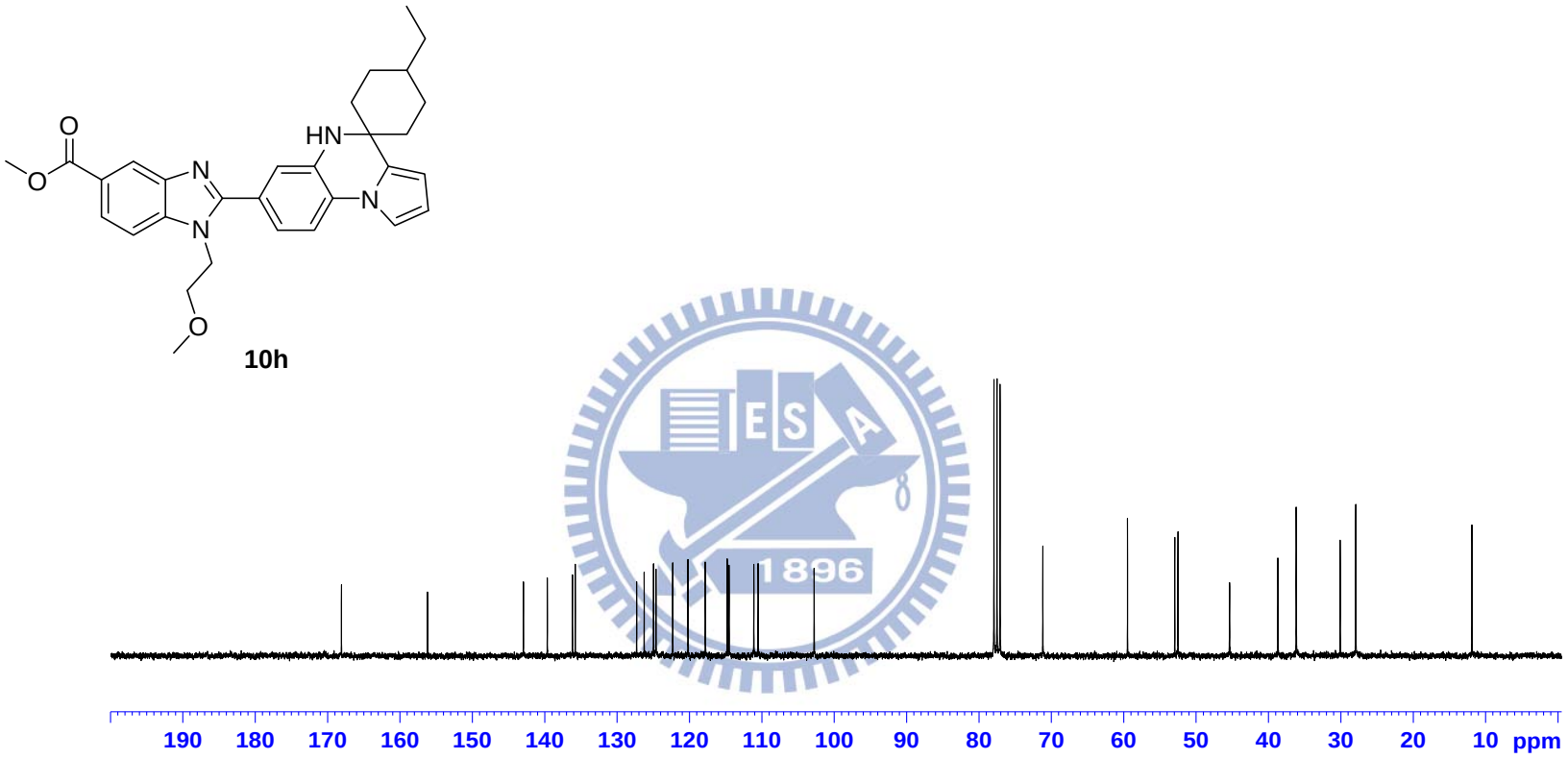
^{1}HNMR spectrum (300 MHz) of compound 10g in $CDCl_3$



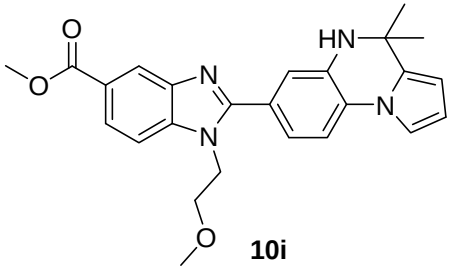
^{13}C NMR spectrum (75 MHz) of compound 10g in $CDCl_3$



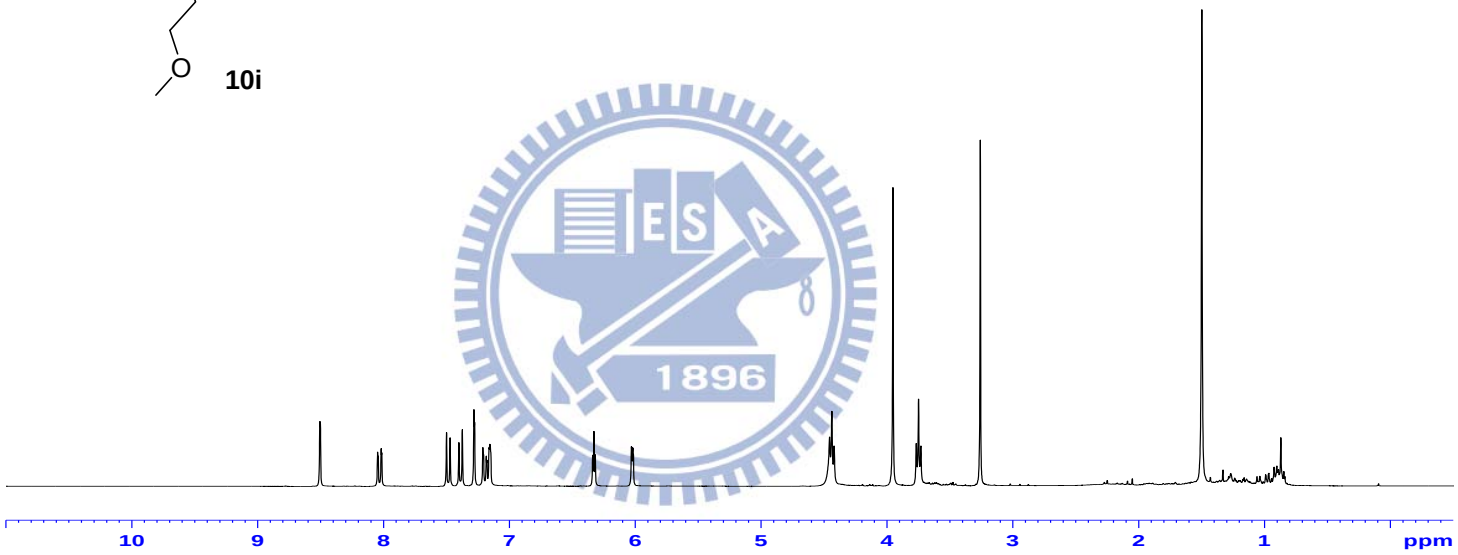
^{1}HNMR spectrum (300 MHz) of compound 10h in $CDCl_3$



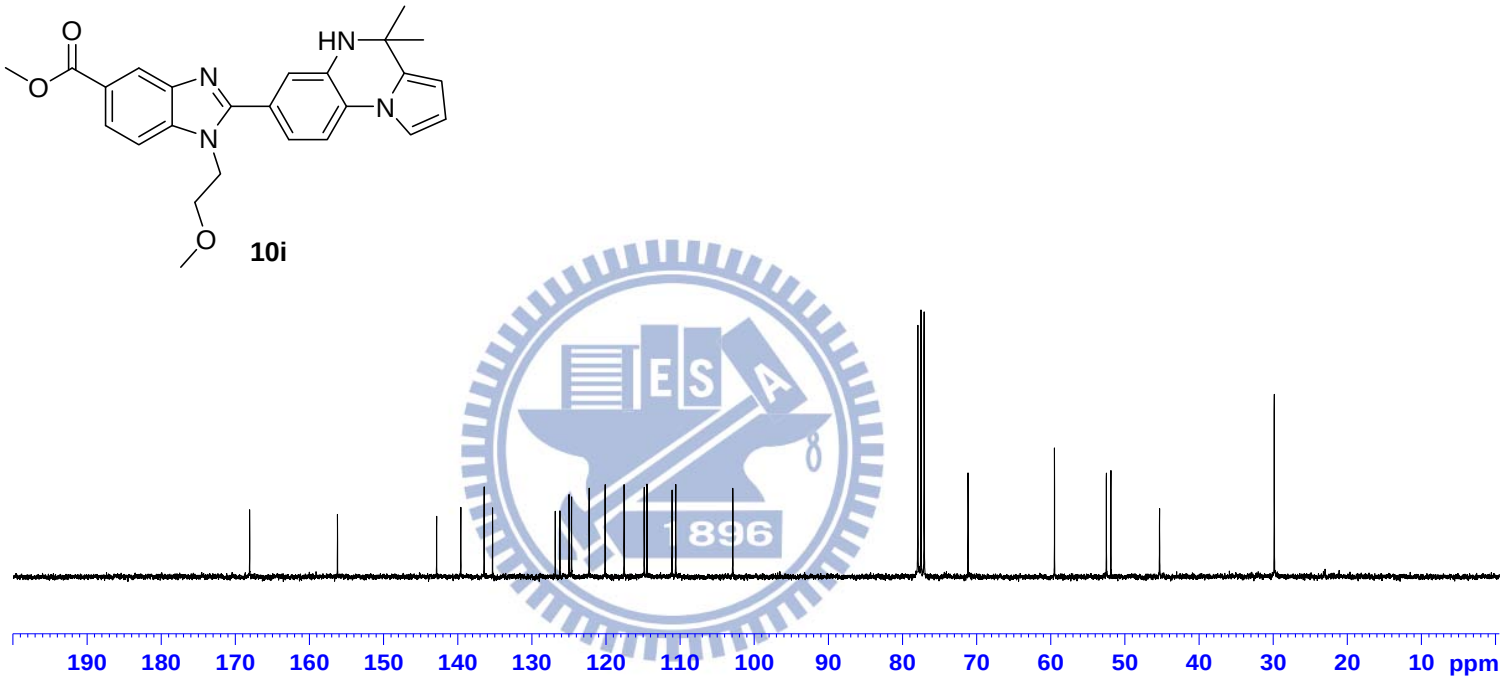
^{13}C NMR spectrum (75 MHz) of compound 10h in $CDCl_3$



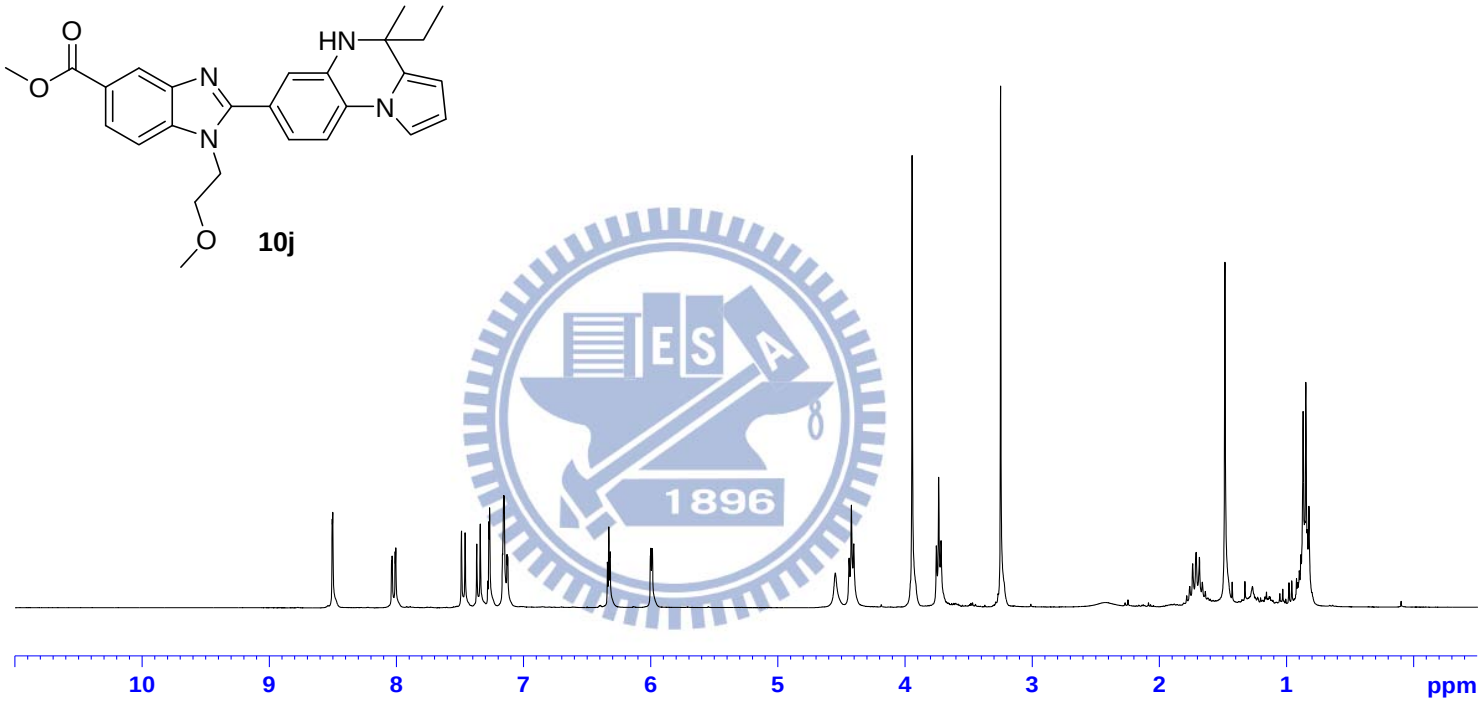
10i



^{1}HNMR spectrum (300 MHz) of compound 10i in $CDCl_3$



^{13}C NMR spectrum (75 MHz) of compound 10i in $CDCl_3$



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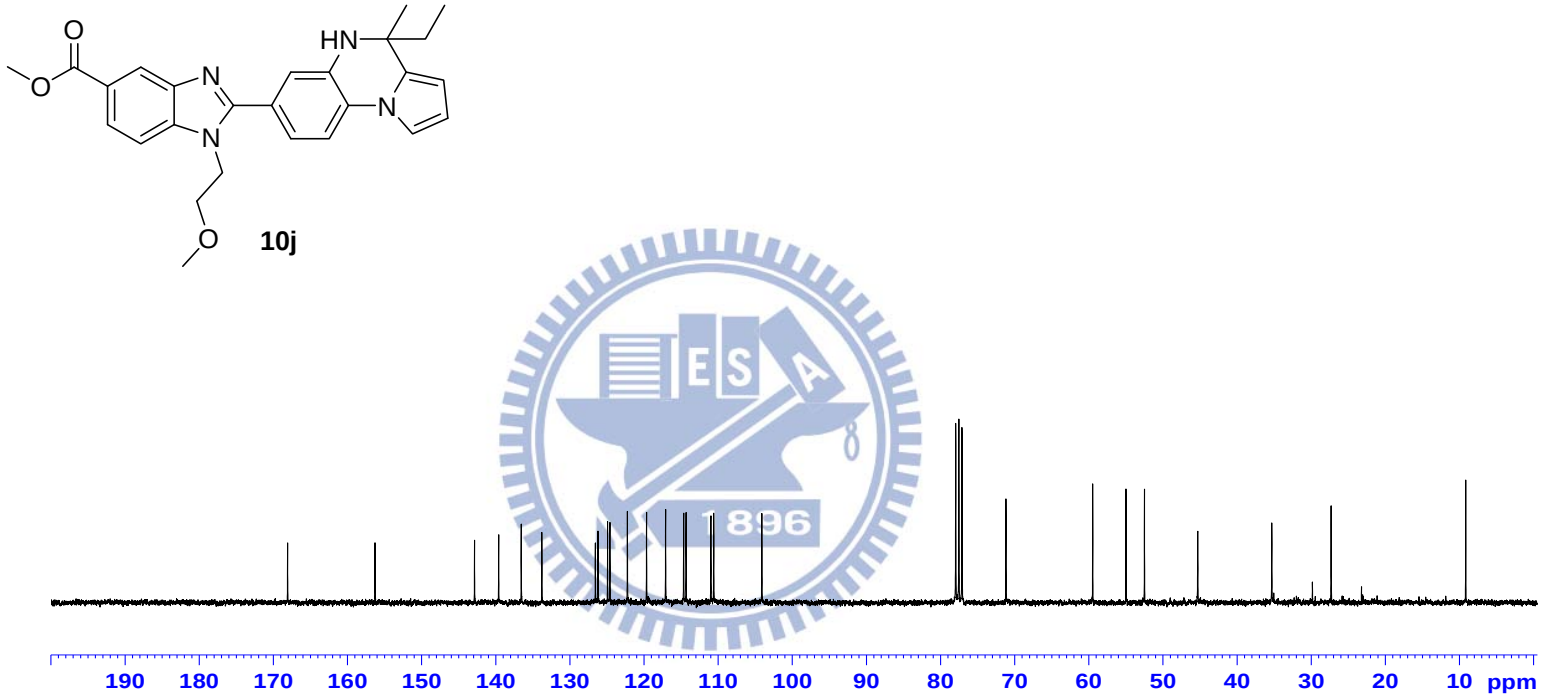

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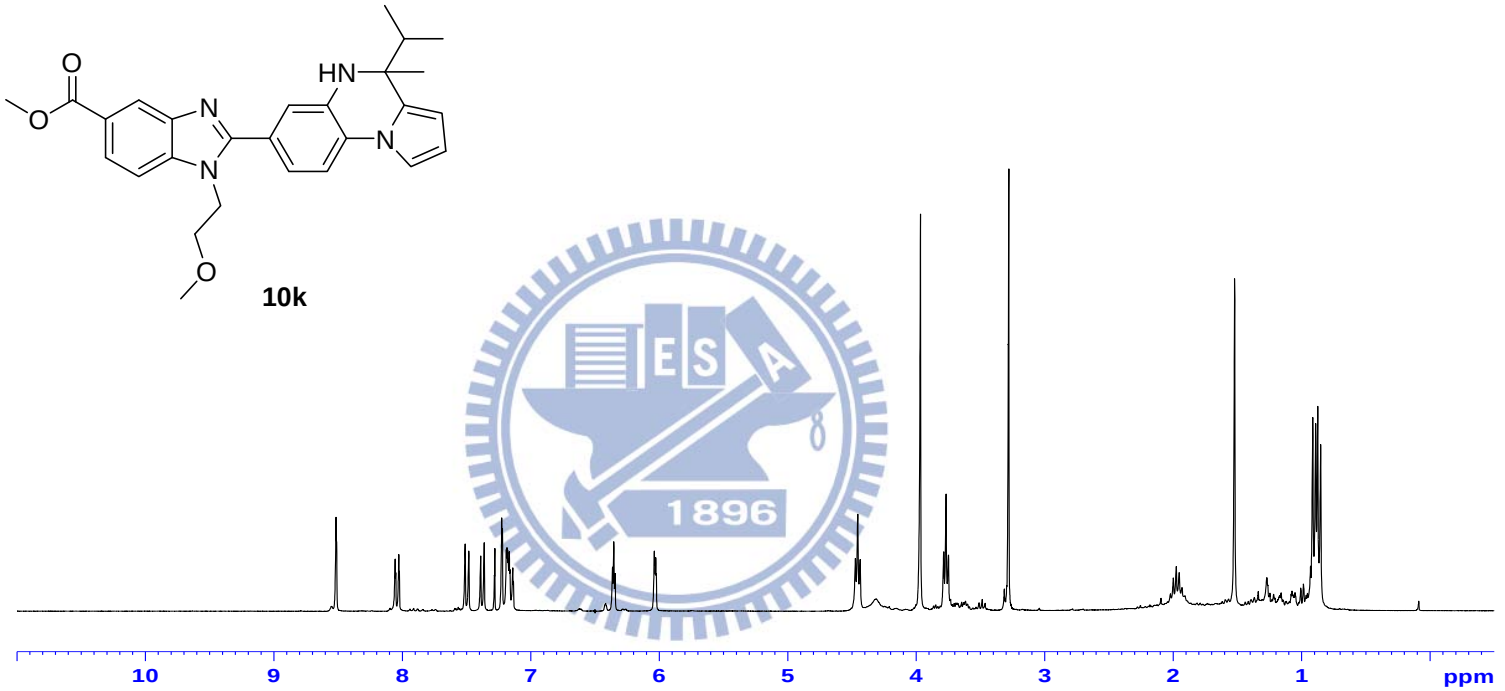
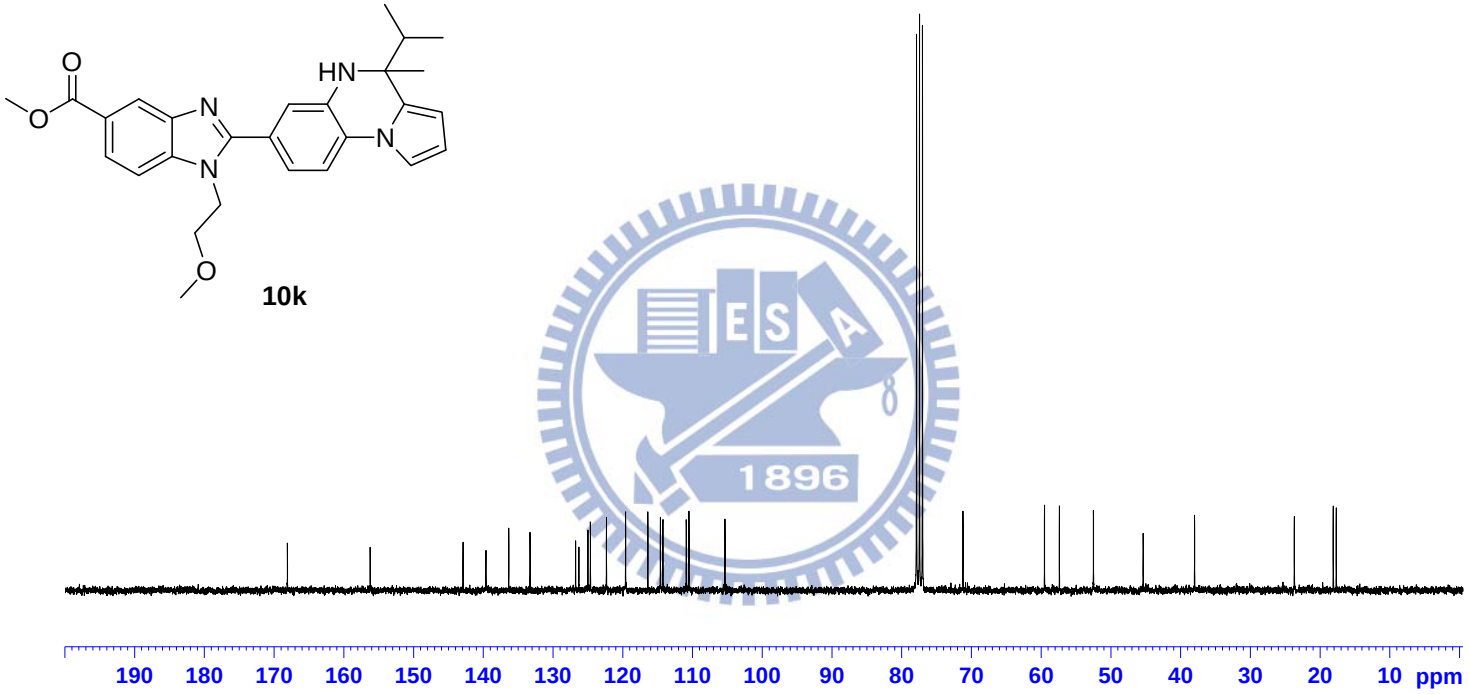
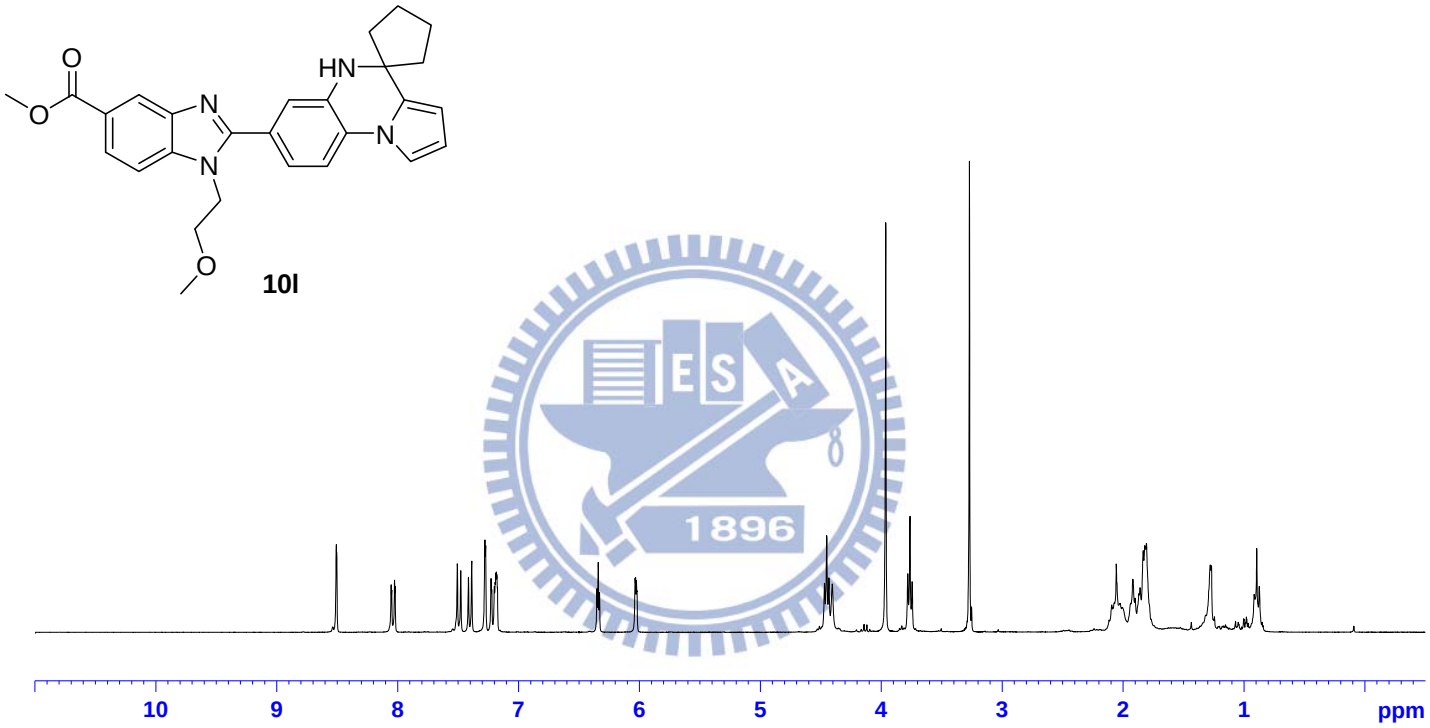


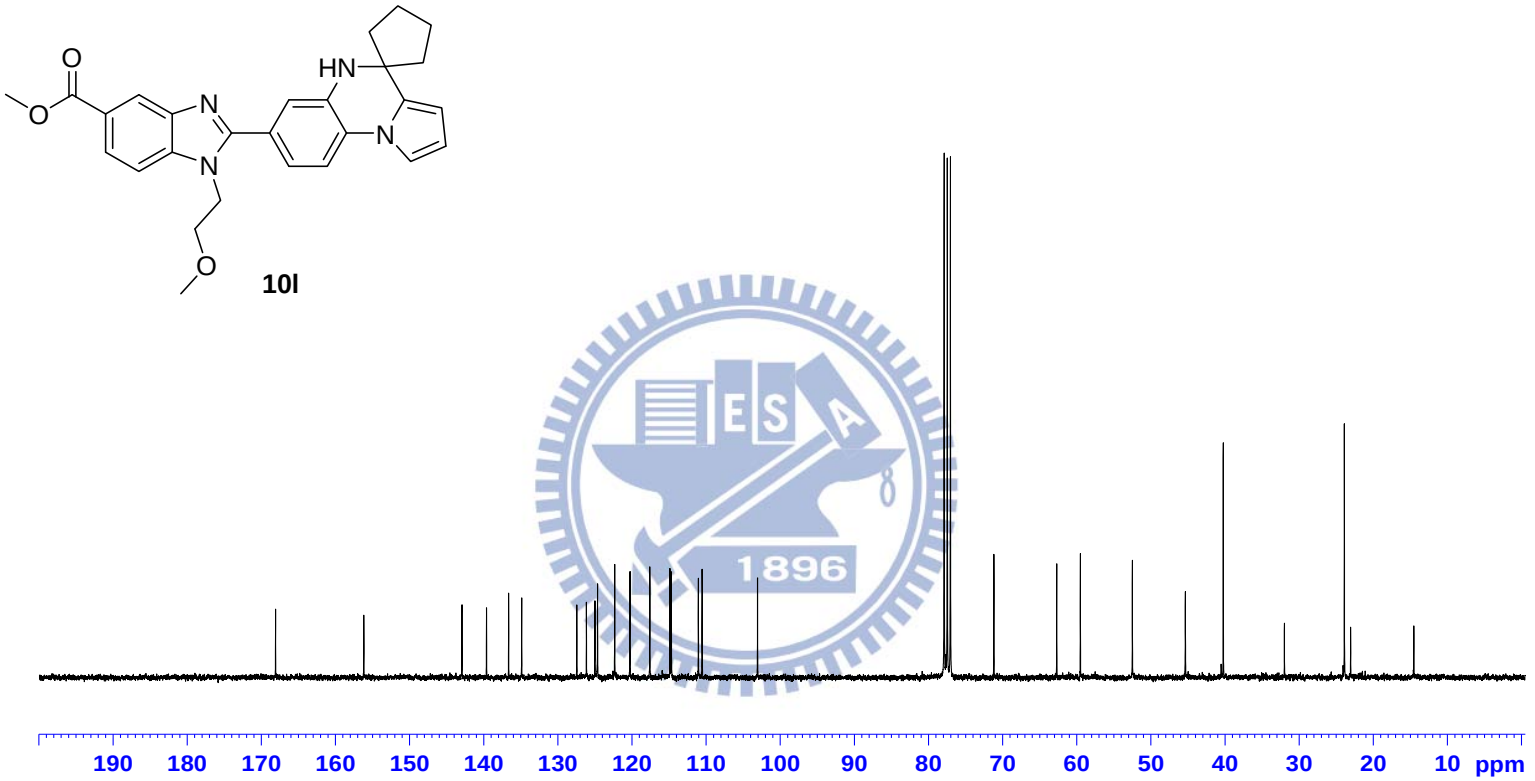
^{1}HNMR spectrum (300 MHz) of compound 10k in $CDCl_3$



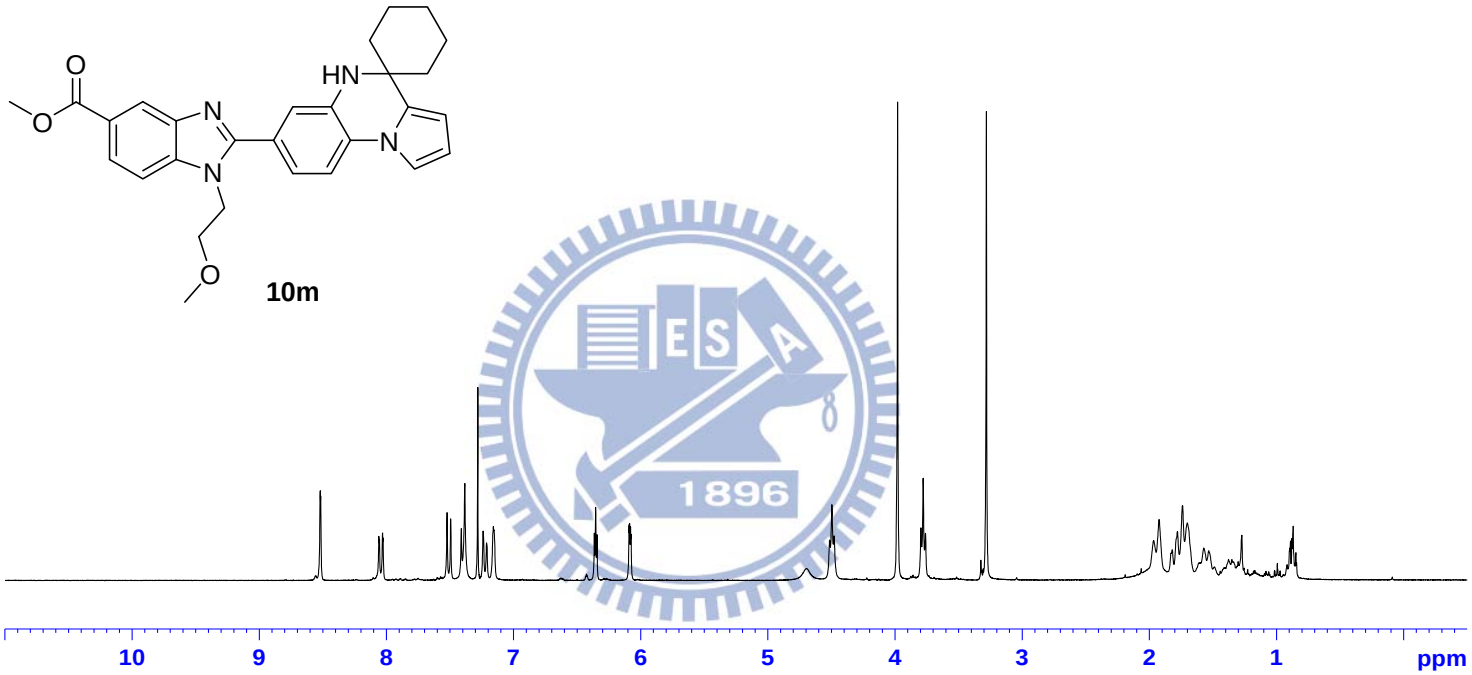
^{13}C NMR spectrum (75 MHz) of compound 10k in $CDCl_3$



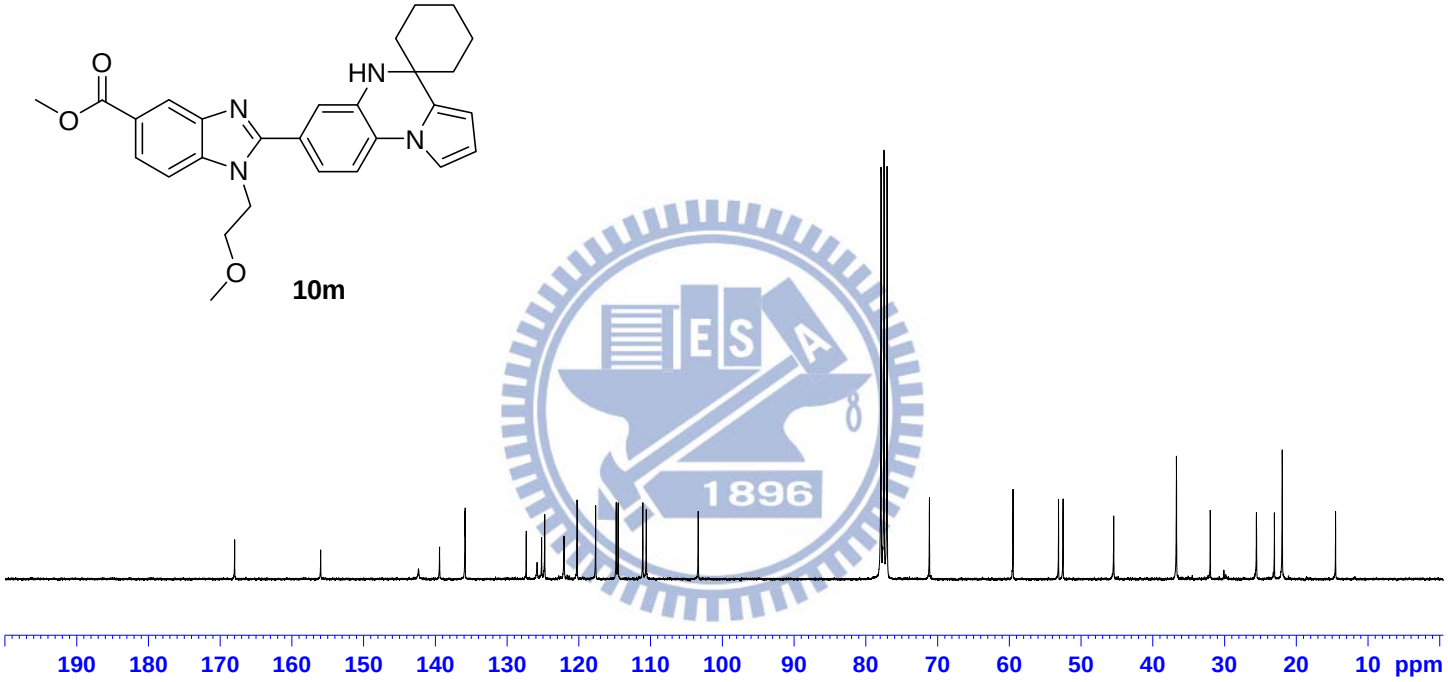
^{1}HNMR spectrum (300 MHz) of compound 10l in $CDCl_3$



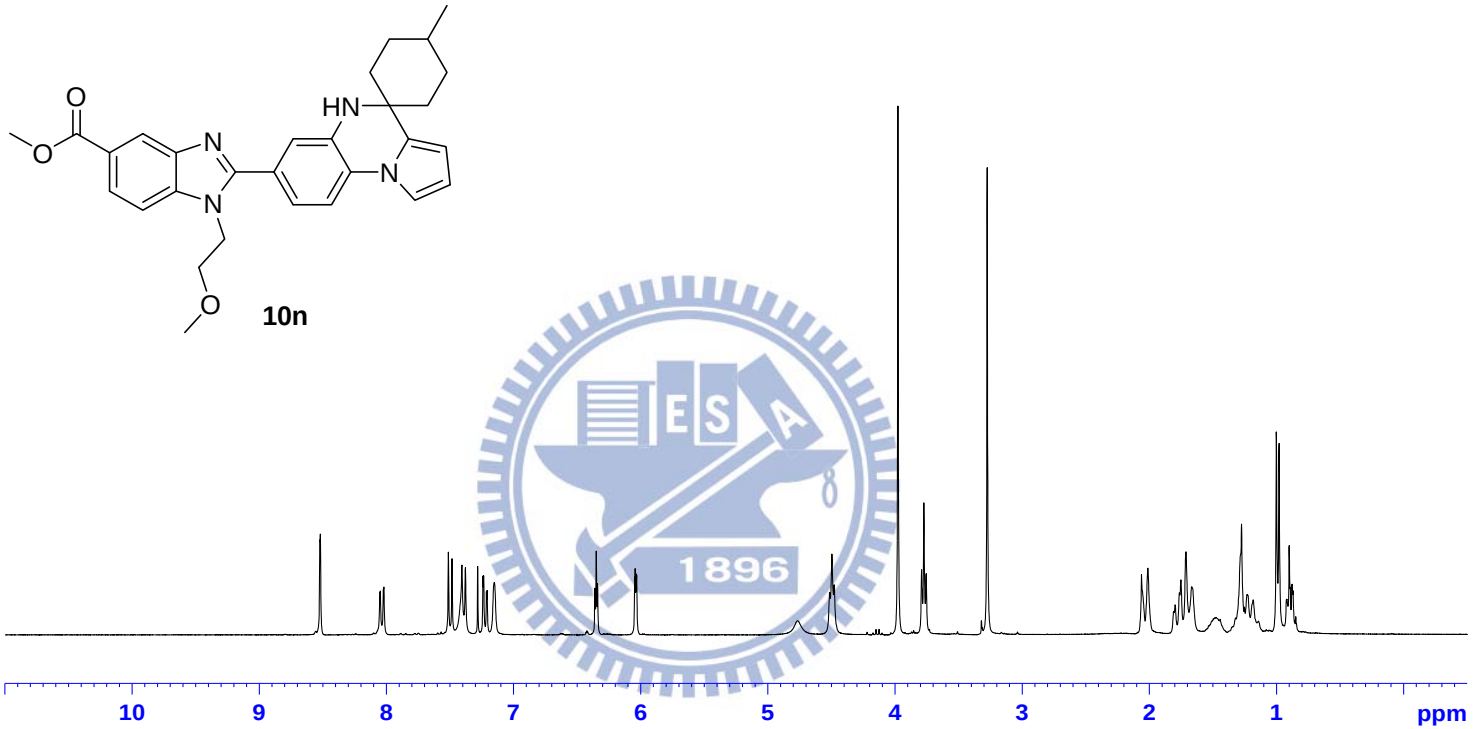
^{13}C NMR spectrum (75 MHz) of compound 10l in $CDCl_3$



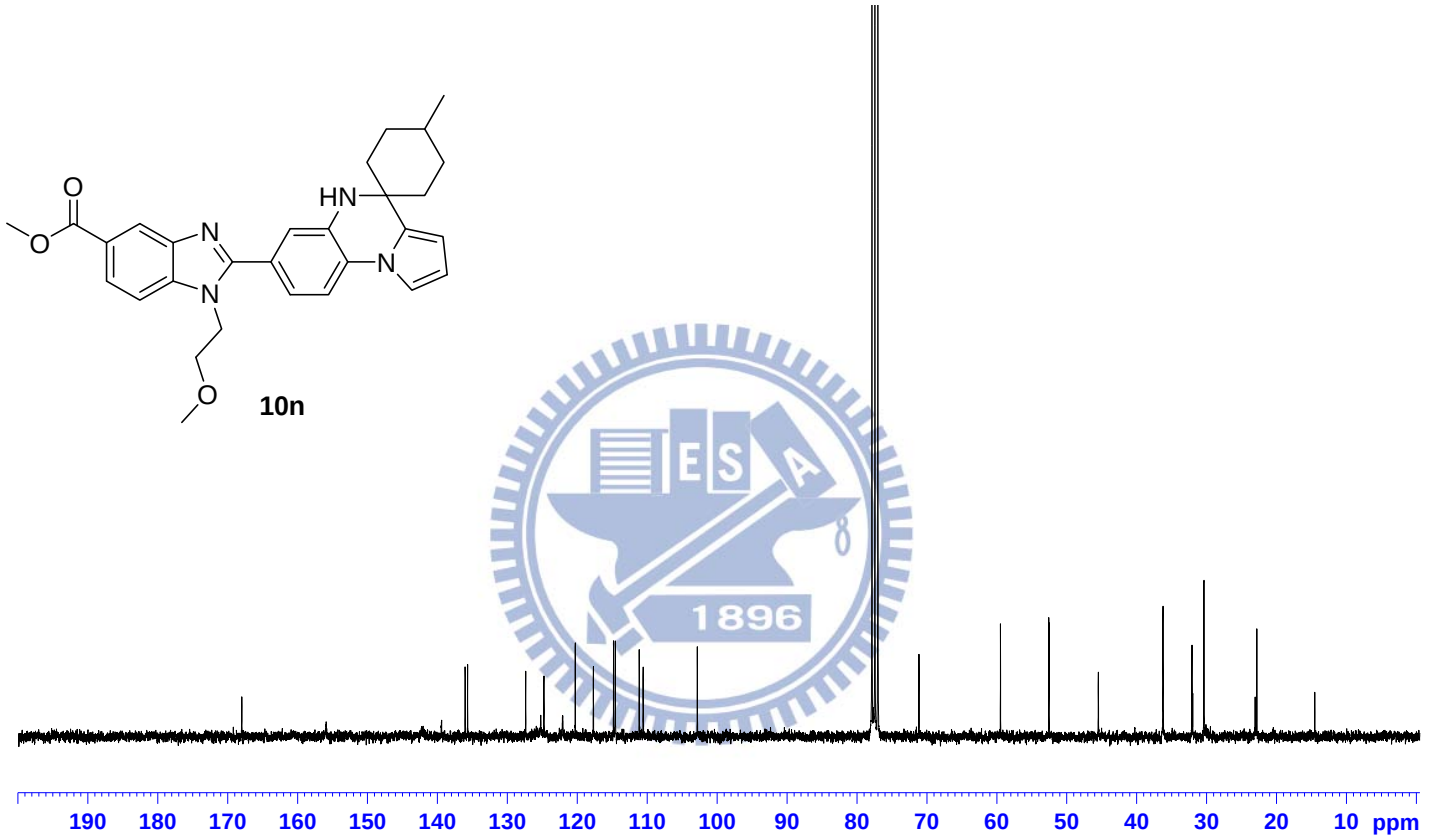
^{1}HNMR spectrum (300 MHz) of compound 10m in $CDCl_3$



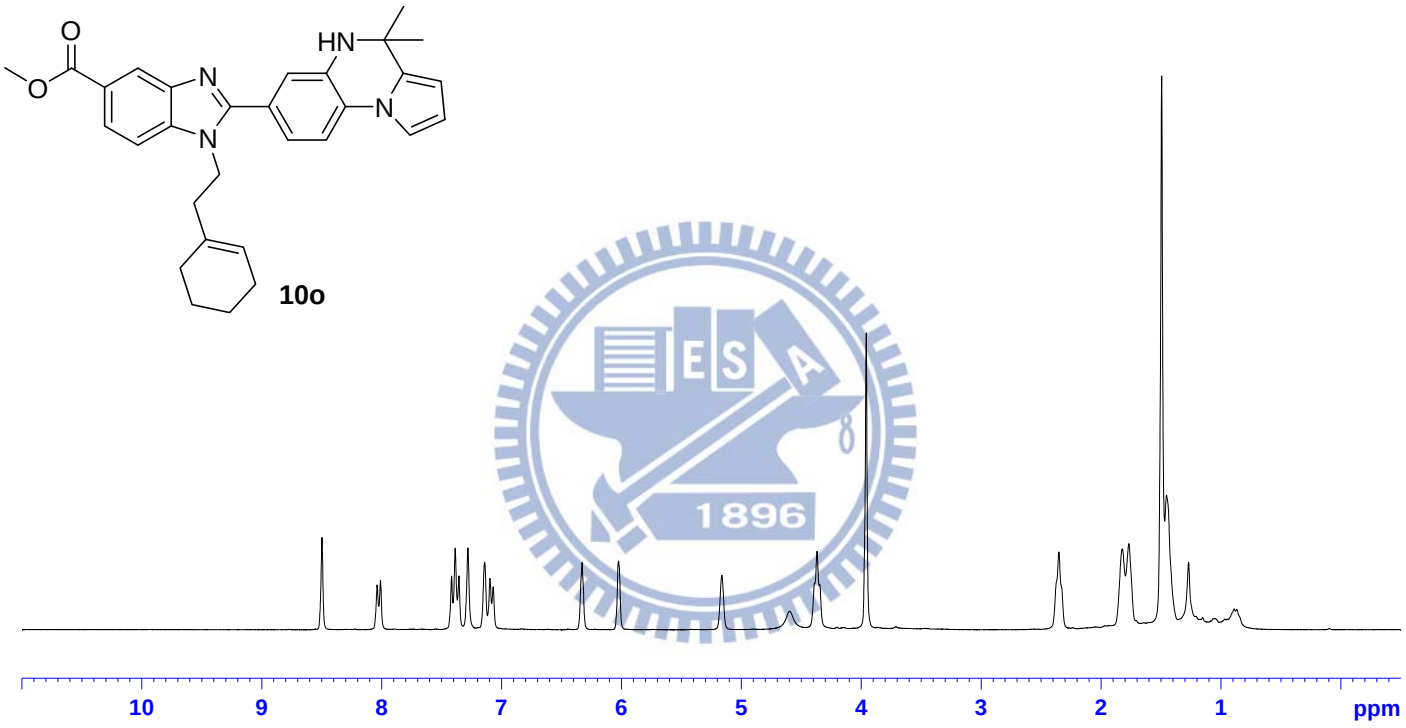
^{13}C NMR spectrum (75 MHz) of compound 10m in $CDCl_3$



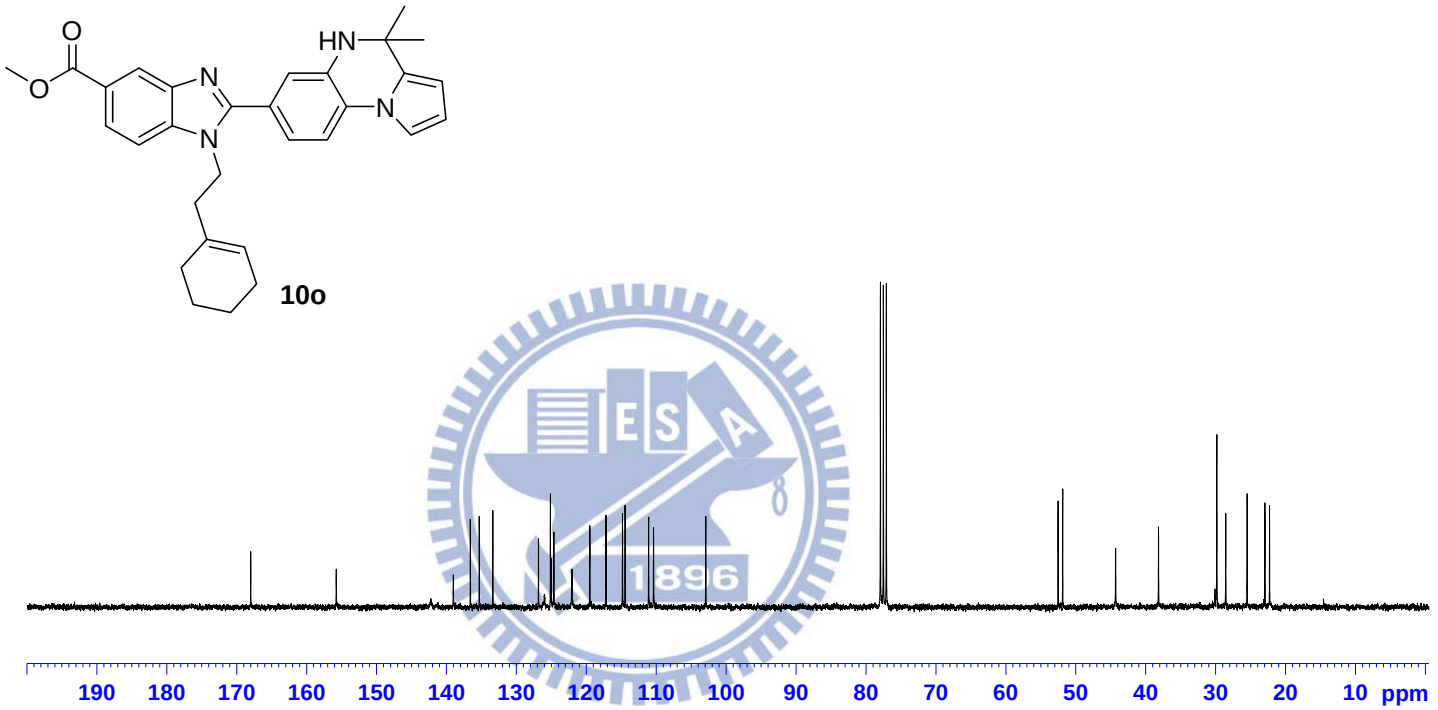
^{1}HNMR spectrum (300 MHz) of compound 10n in $CDCl_3$



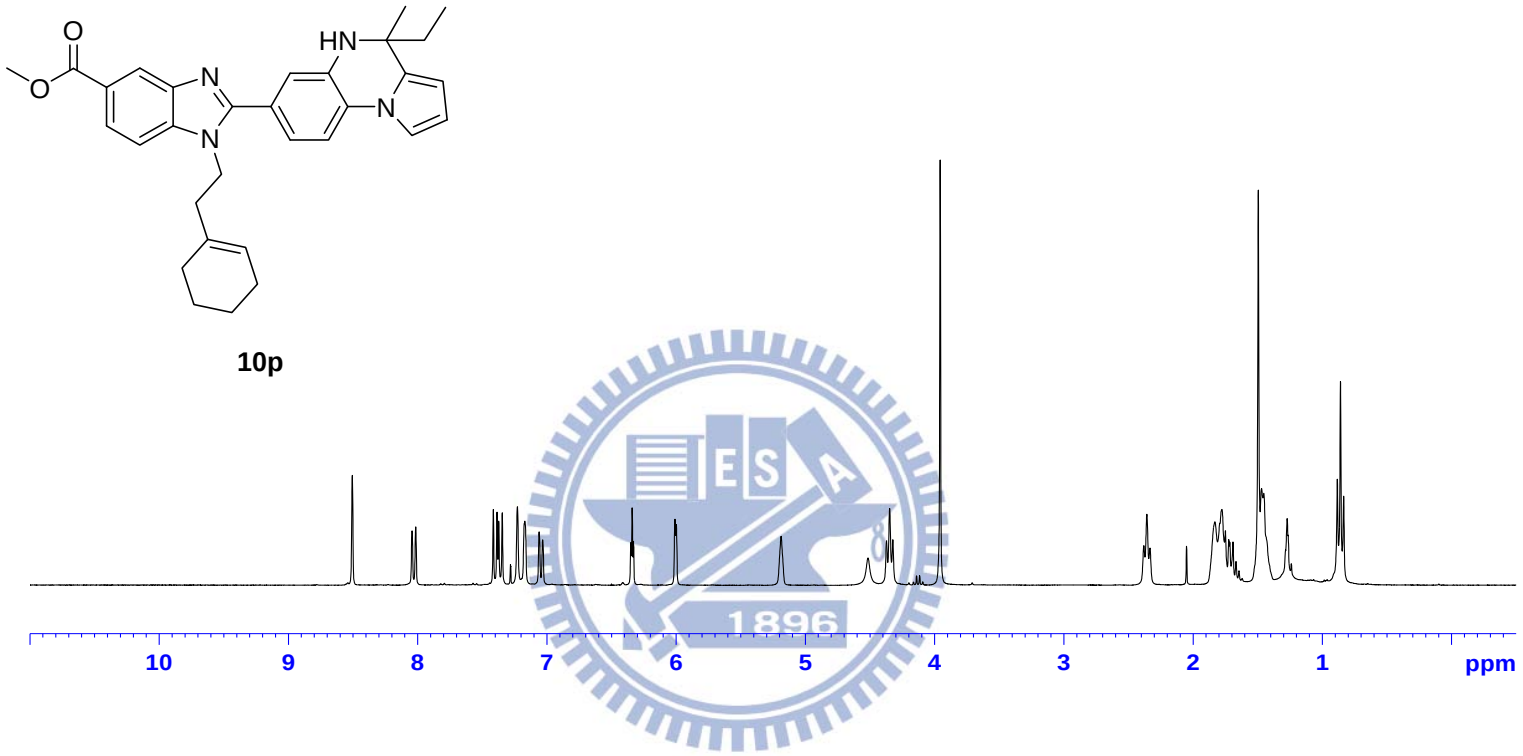
^{13}C NMR spectrum (75 MHz) of compound 10n in $CDCl_3$



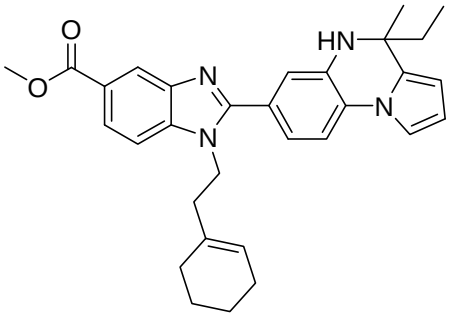
^{1}HNMR spectrum (300 MHz) of compound 10o in $CDCl_3$



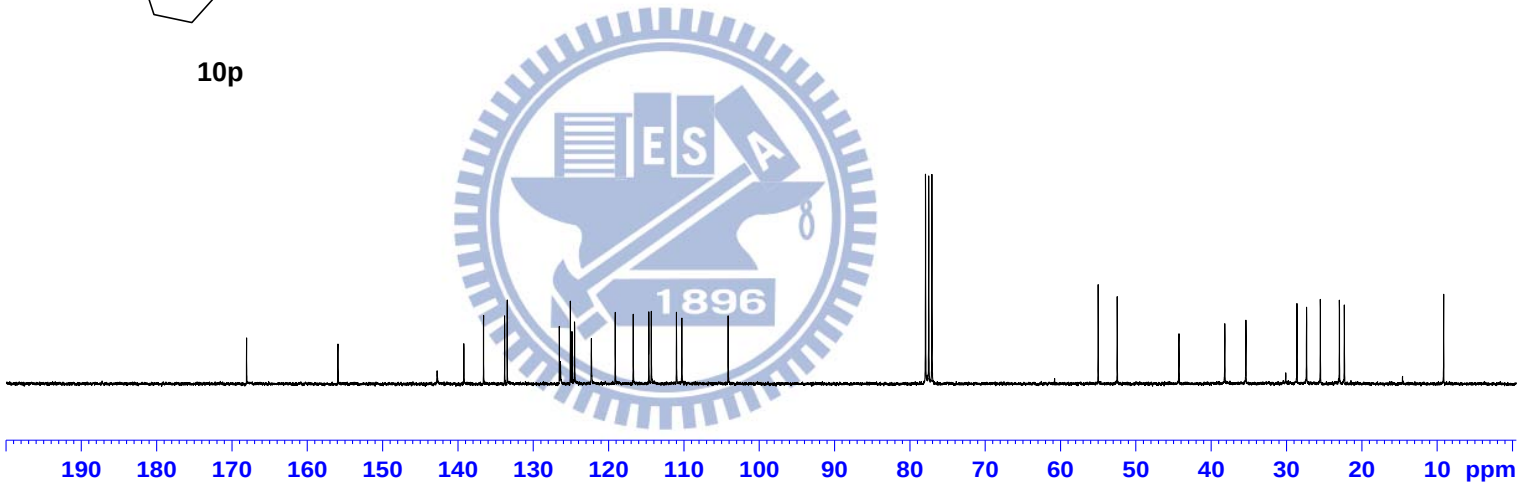
^{13}C NMR spectrum (75 MHz) of compound 10o in $CDCl_3$



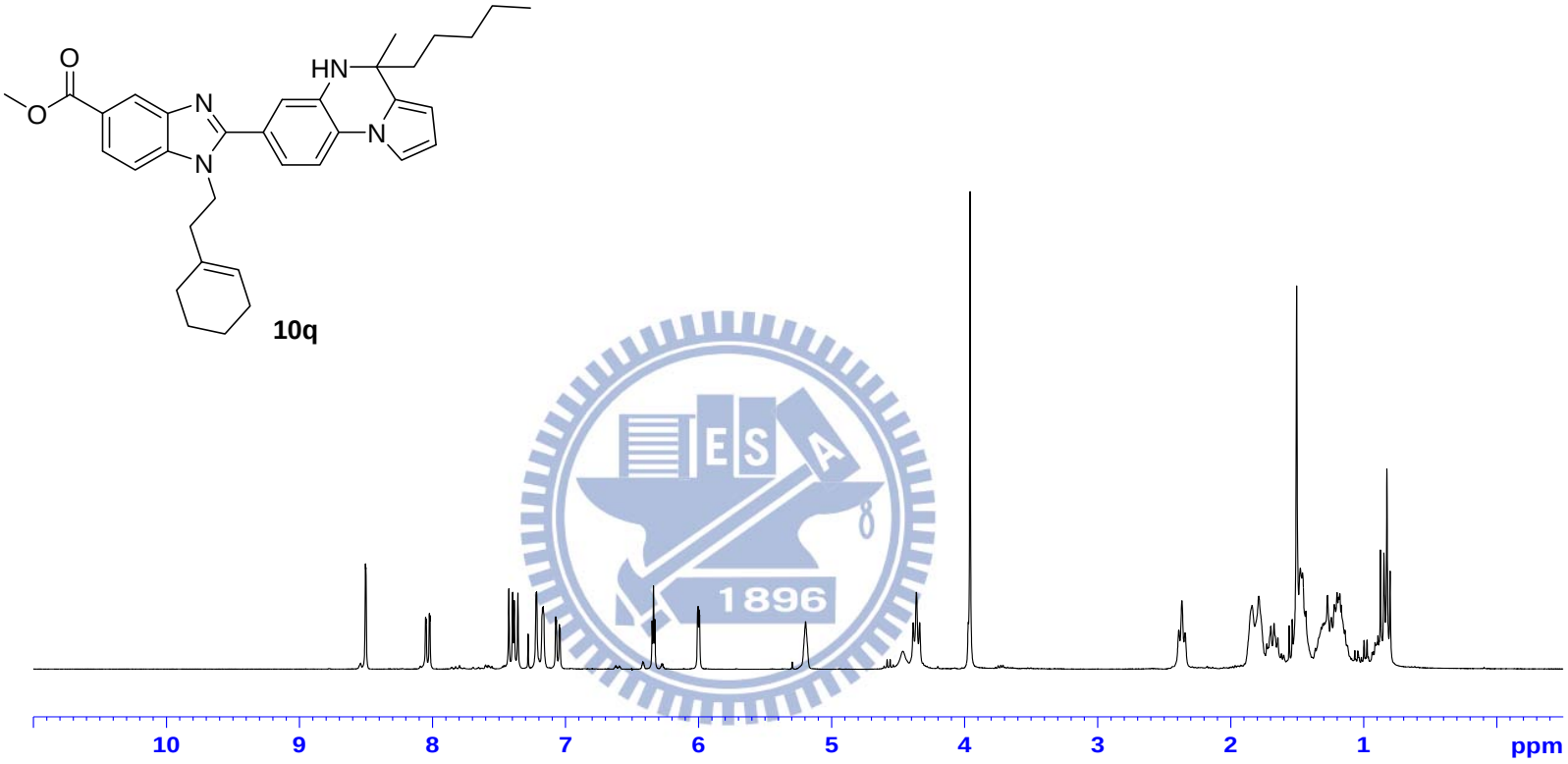
^{1}HNMR spectrum (300 MHz) of compound 10p in $CDCl_3$



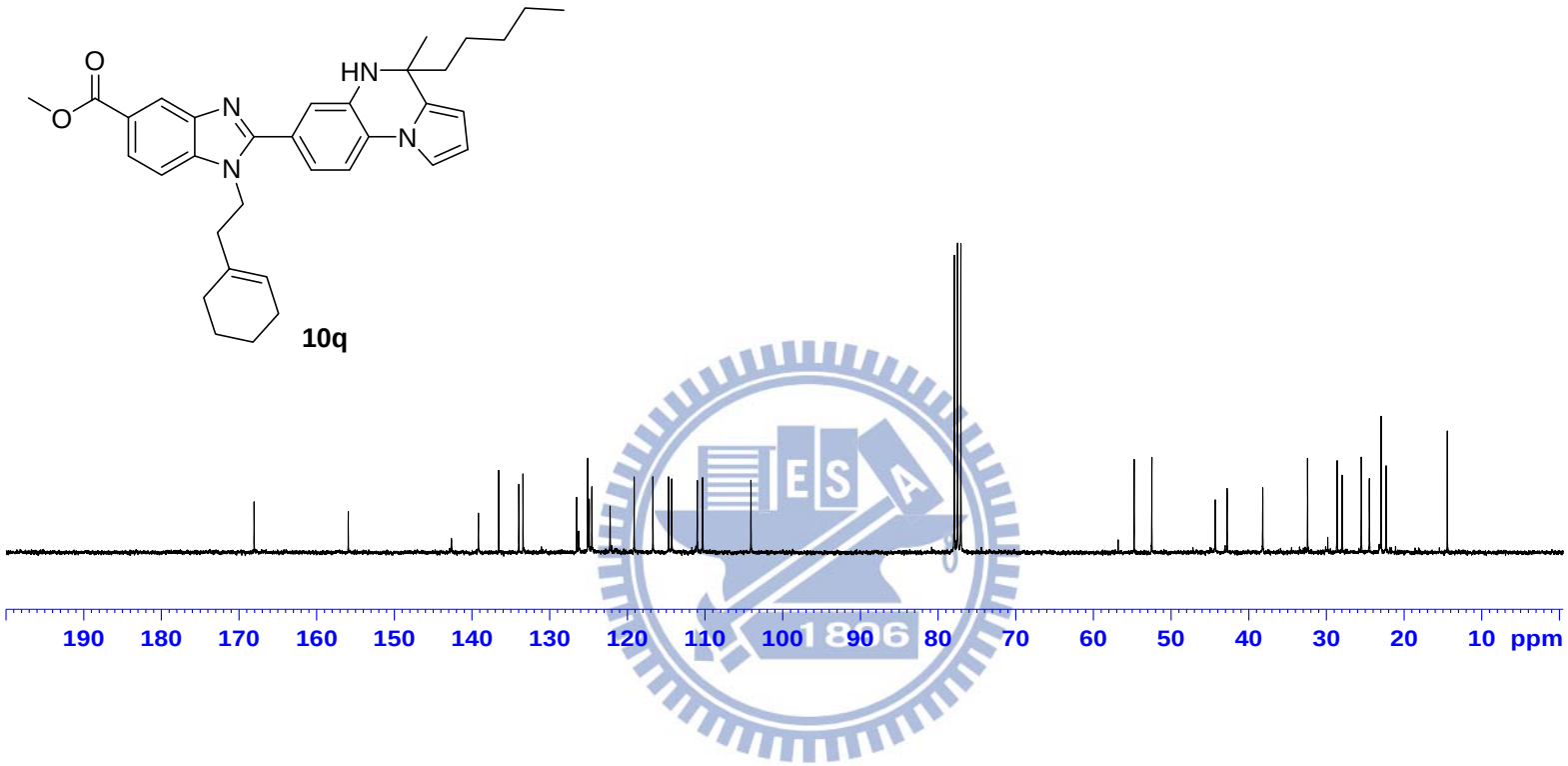
10p



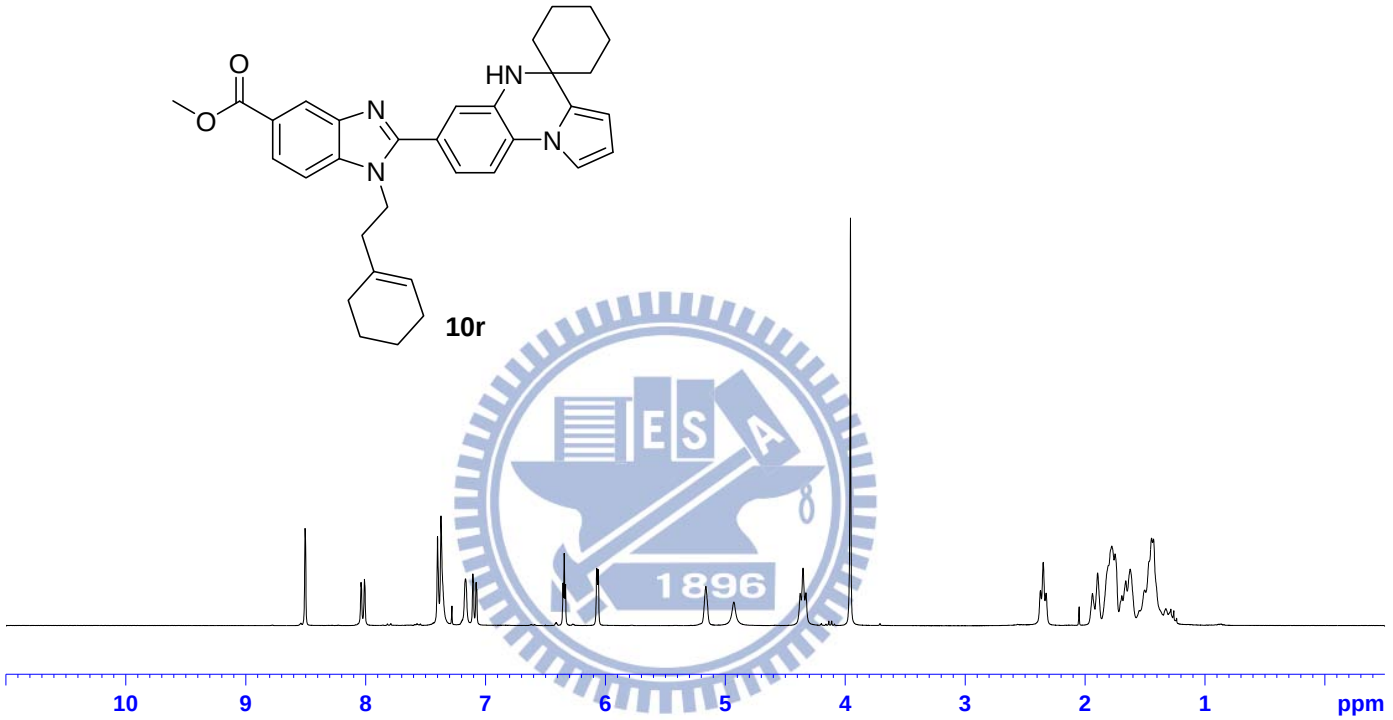
^{13}C NMR spectrum (75 MHz) of compound 10p in $CDCl_3$



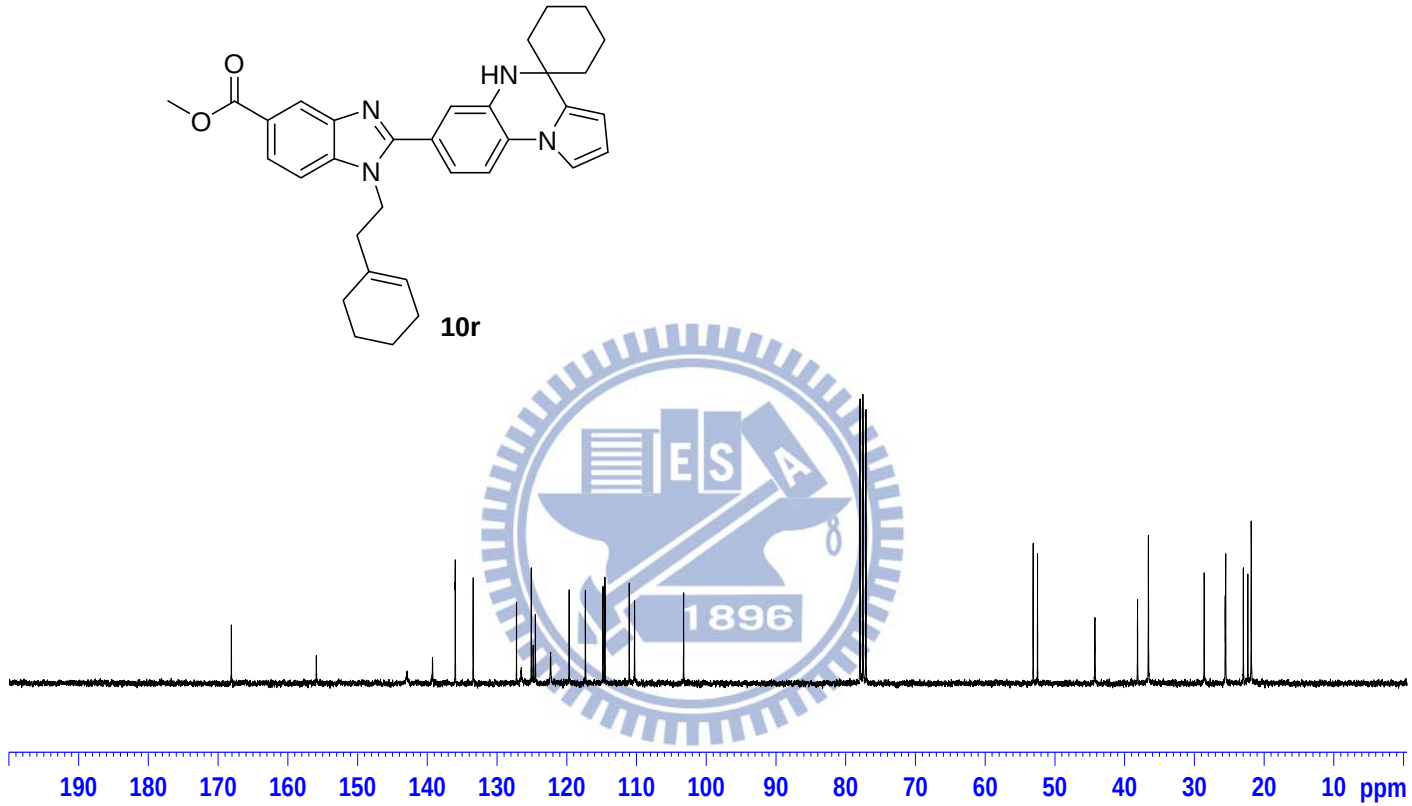
^{1}HNMR spectrum (300 MHz) of compound 10q in $CDCl_3$



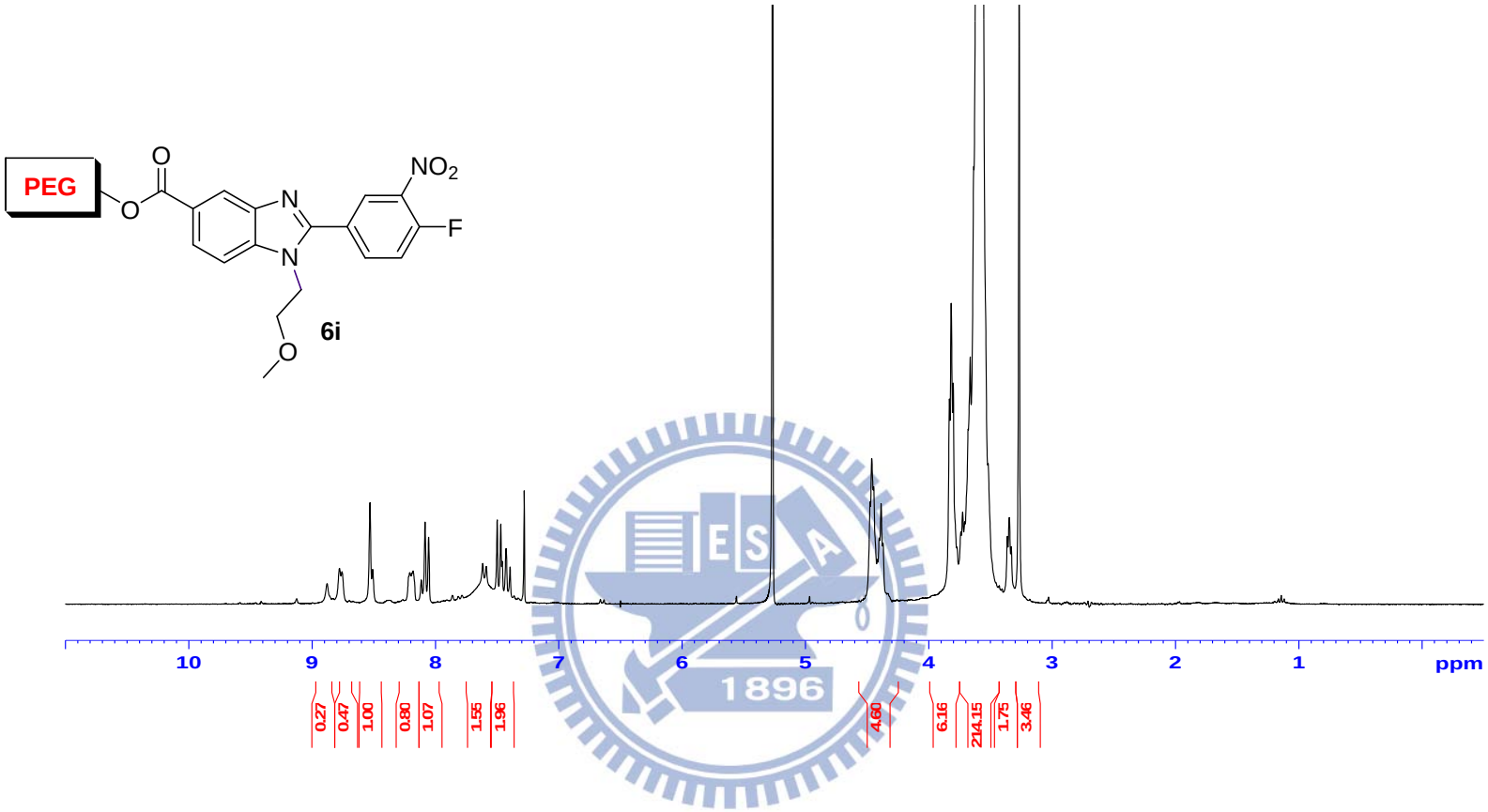
^{13}C NMR spectrum (75 MHz) of compound 10q in $CDCl_3$



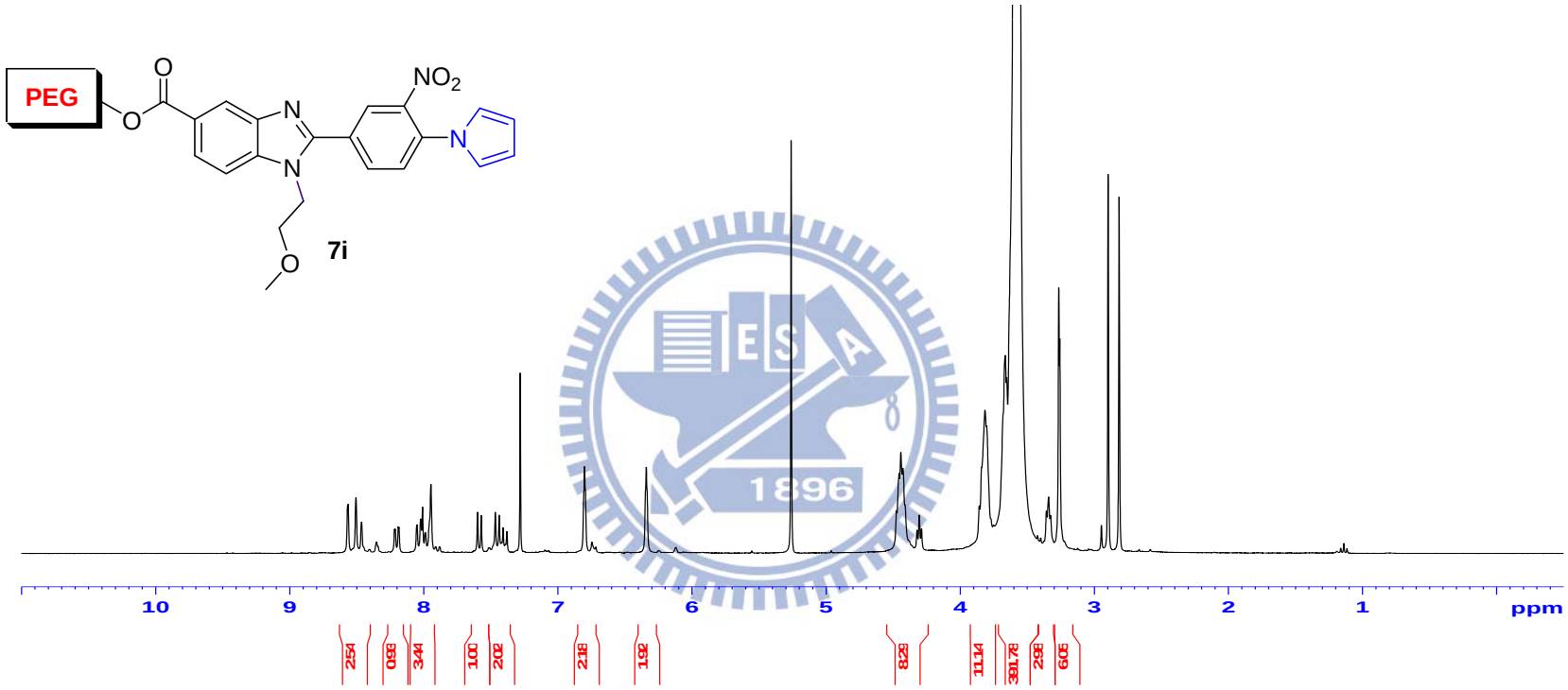
^{1}HNMR spectrum (300 MHz) of compound 10r in $CDCl_3$



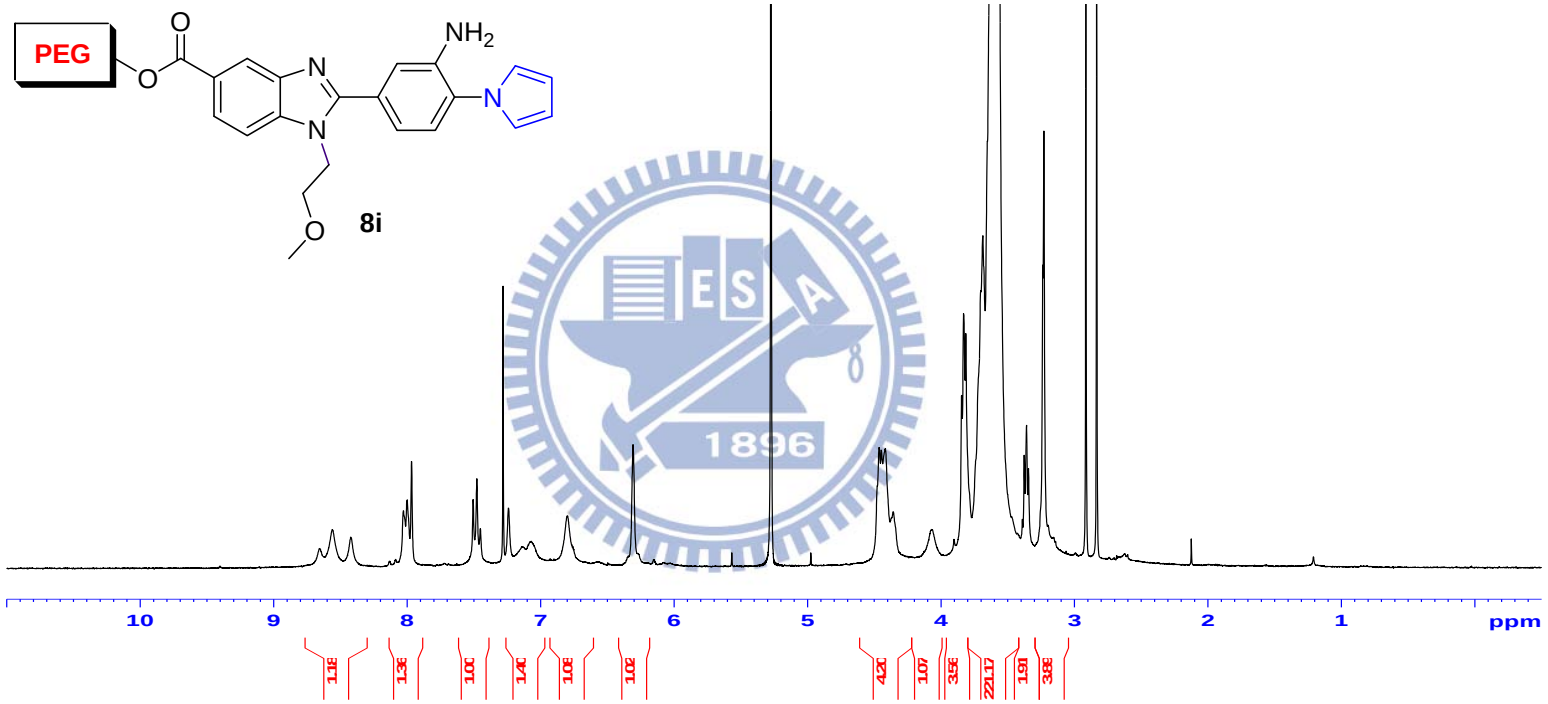
^{13}C NMR spectrum (75 MHz) of compound 10r in $CDCl_3$



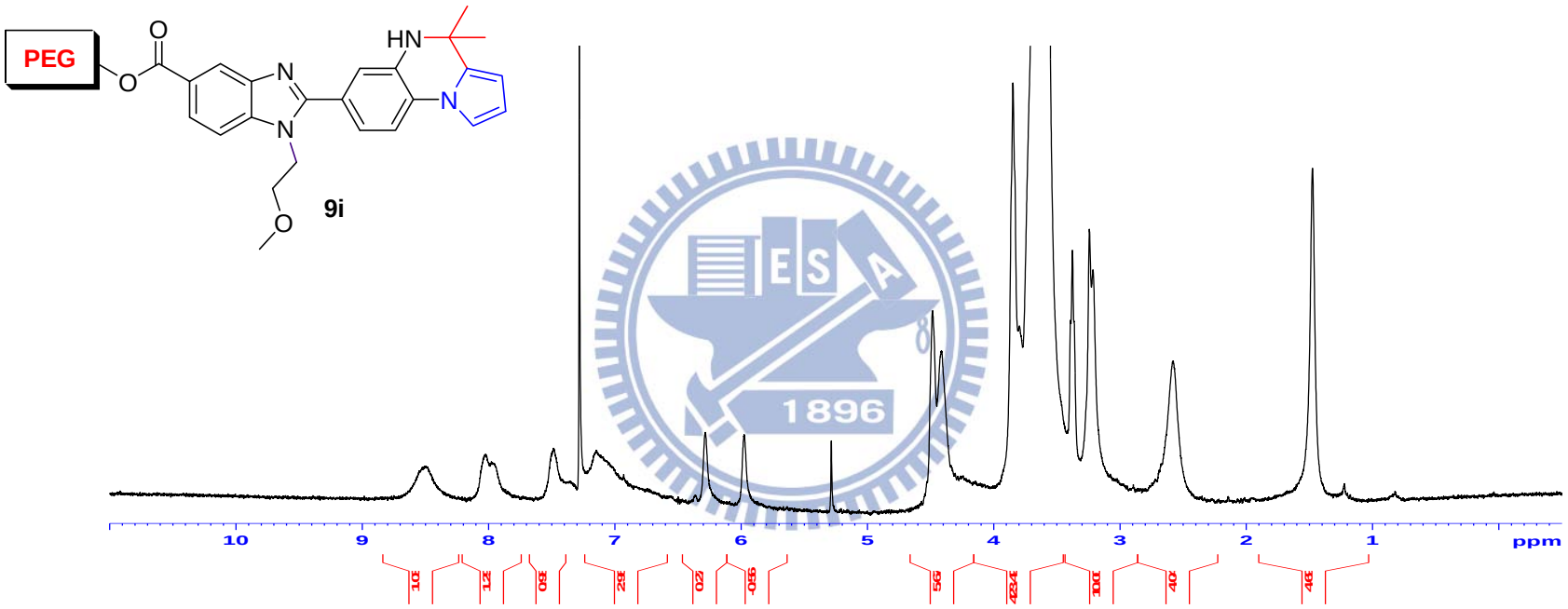
[1]HNMR spectrum (300 MHz) of intermediate compound 6i in $CDCl_3$



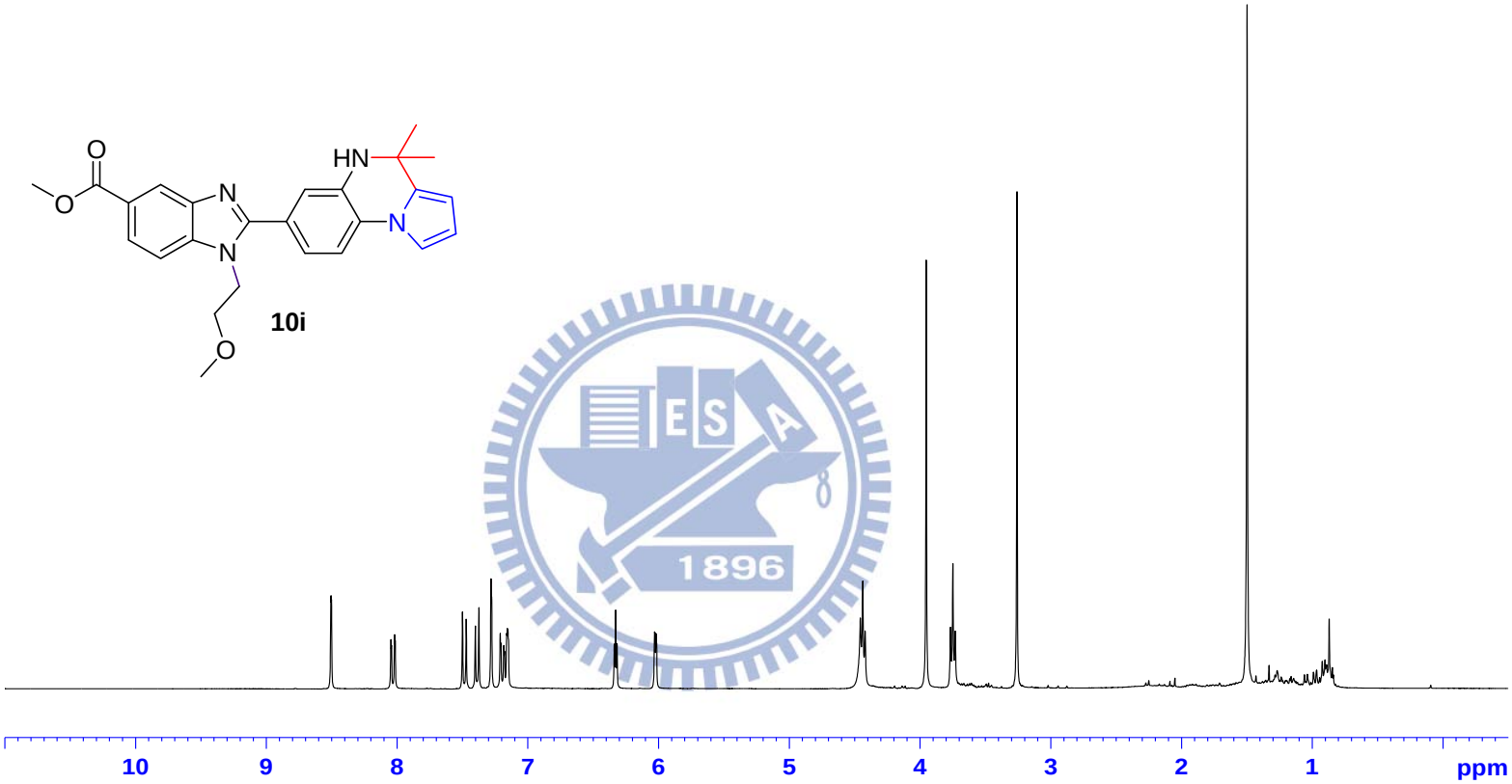
[1]HNMR spectrum (300 MHz) of intermediate compound 7i in $CDCl_3$



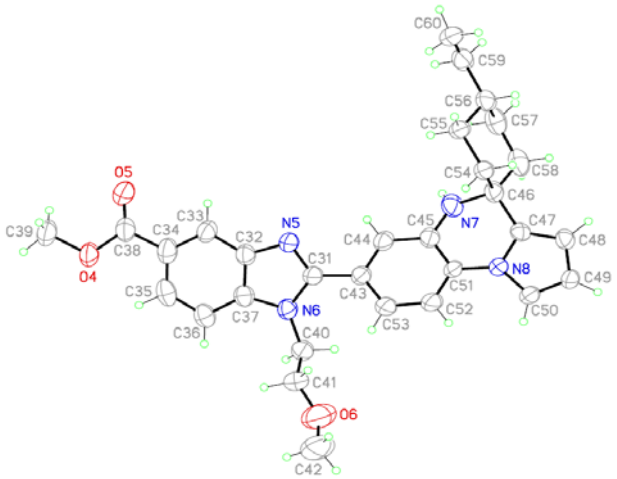
^{1}HNMR spectrum (300 MHz) of intermediate compound 8i in $CDCl_3$

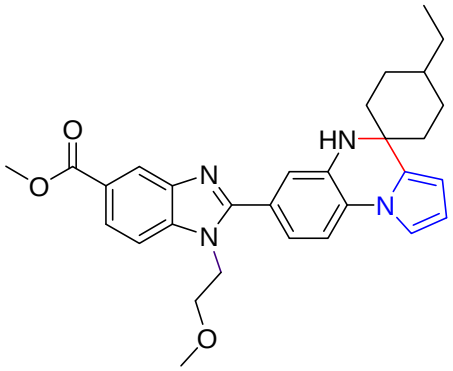


^{1}HNMR spectrum (300 MHz) of intermediate compound 9i in $CDCl_3$



^{1}HNMR spectrum (300 MHz) of final compound 10i in $CDCl_3$





10h

ORTEP diagram of Methyl

2-(4-ethyl-5'*H*-spiro[cyclohexane-1,4'-pyrrolo[1,2-*a*]quinoxalin]-7'-yl)

-1-(2-methoxyethyl)-1*H*-benzimidazole-5-carboxylate (10h)

Table 1. Crystal data and structure refinement for **10h**

Identification code	101119lts	
Empirical formula	C30 H34 N4 O3	
Formula weight	498.61	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 12.3481(6) Å	α= 105.903(2)°.
	b = 15.7551(8) Å	β= 108.938(2)°.
	c = 16.7496(9) Å	γ = 93.046(2)°.
Volume	2927.8(3) $Å^3$	
Z	4	
Density (calculated)	1.131 Mg/m^3	
Absorption coefficient	0.074 mm^{-1}	
F(000)	1064	
Crystal size	0.15 x 0.15 x 0.05 mm^3	
Theta range for data collection	1.77 to 26.42°.	
Index ranges	-15<=h<=15, -19<=k<=17, -20<=l<=18	
Reflections collected	43472	
Independent reflections	11900 [R(int) = 0.0937]	
Completeness to theta = 26.42°	98.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9486 and 0.6811	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11900 / 20 / 717	
Goodness-of-fit on F^2	0.956	
Final R indices [I>2sigma(I)]	R1 = 0.0861, wR2 = 0.2406	
R indices (all data)	R1 = 0.1378, wR2 = 0.2707	
Largest diff. peak and hole	0.823 and -0.380 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 101119LTs. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	806(3)	3630(2)	1630(2)	54(1)
C(2)	1736(3)	4440(2)	1144(2)	57(1)
C(3)	2503(4)	4795(2)	825(2)	73(1)
C(4)	2306(5)	5590(3)	638(3)	79(1)
C(5)	1365(5)	6018(3)	752(3)	96(2)
C(6)	602(4)	5658(3)	1063(3)	87(2)
C(7)	791(4)	4862(2)	1244(2)	68(1)
C(10)	-701(3)	4603(3)	1901(3)	79(1)
C(11)	-202(4)	5285(3)	2818(3)	87(2)
C(12)	52(4)	4418(3)	3800(3)	92(2)
C(13)	492(3)	2923(2)	1979(2)	53(1)
C(14)	-623(3)	2436(3)	1642(2)	59(1)
C(15)	-851(3)	1775(2)	1990(2)	57(1)
C(16)	5(3)	1598(2)	2665(2)	53(1)
C(17)	-1241(3)	532(3)	3010(3)	70(1)
C(18)	-1020(3)	-12(3)	3519(3)	75(1)
C(19)	211(3)	80(3)	3930(3)	67(1)
C(20)	692(3)	687(2)	3639(2)	54(1)
C(21)	1925(3)	1011(2)	3781(2)	48(1)
C(22)	1137(3)	2085(2)	3006(2)	49(1)
C(23)	1361(3)	2736(2)	2646(2)	47(1)
C(24)	2719(3)	1033(2)	4704(2)	52(1)
C(25)	3997(3)	1273(2)	4848(2)	48(1)
C(26)	4364(3)	665(2)	4135(2)	46(1)
C(27)	3573(3)	639(2)	3215(2)	47(1)
C(28)	2299(3)	382(2)	3069(2)	49(1)
C(29)	5639(3)	953(2)	4314(2)	52(1)
C(30)	6133(3)	358(3)	3692(3)	66(1)
C(31)	4777(3)	6894(2)	6276(2)	42(1)
C(32)	5351(3)	6314(2)	5201(2)	44(1)
C(33)	6002(3)	6022(2)	4663(2)	51(1)
C(34)	5418(3)	5473(2)	3807(2)	57(1)

C(35)	4213(3)	5209(2)	3486(2)	58(1)
C(36)	3563(3)	5488(2)	4012(2)	53(1)
C(37)	4157(3)	6046(2)	4872(2)	44(1)
C(40)	2598(3)	6279(2)	5548(2)	55(1)
C(41)	1829(3)	6853(3)	5106(3)	68(1)
C(42)	4(4)	7333(4)	4919(4)	127(2)
C(43)	4796(2)	7357(2)	7166(2)	44(1)
C(44)	5732(3)	7292(2)	7891(2)	45(1)
C(45)	5833(3)	7734(2)	8757(2)	51(1)
C(46)	7149(3)	8379(2)	10305(2)	51(1)
C(51)	5005(3)	8266(3)	8898(2)	72(1)
C(52)	4106(3)	8345(3)	8201(3)	81(1)
C(53)	3977(3)	7894(2)	7332(2)	60(1)
C(54)	7877(2)	9123(2)	10192(2)	45(1)
C(55)	8994(2)	8855(2)	10071(2)	46(1)
C(56)	9736(3)	8583(2)	10852(2)	50(1)
C(57)	9047(3)	7829(2)	10973(2)	63(1)
C(58)	7896(3)	8062(2)	11057(2)	63(1)
C(59)	10875(3)	8315(3)	10761(2)	66(1)
C(60)	11644(3)	9011(3)	10644(3)	80(1)
N(1)	1722(3)	3661(2)	1377(2)	56(1)
N(2)	207(3)	4332(2)	1557(2)	64(1)
N(3)	1975(2)	1927(2)	3713(2)	49(1)
N(4)	-197(2)	960(2)	3068(2)	54(1)
N(5)	5720(2)	6842(2)	6074(2)	43(1)
N(6)	3791(2)	6428(2)	5568(2)	45(1)
N(7)	6702(2)	7613(2)	9478(2)	54(1)
O(3)	593(2)	4954(2)	3438(2)	76(1)
O(6)	810(3)	6777(2)	5280(3)	106(1)
C(8)	2901(15)	5999(11)	334(12)	64(3)
C(9)	3645(8)	7225(6)	24(6)	74(2)
O(1)	2800(5)	6803(3)	317(4)	58(1)
O(2)	3529(6)	5546(5)	-34(5)	83(1)
C(8')	3339(12)	6008(11)	293(11)	64(3)
C(9')	5257(7)	6218(6)	307(6)	74(2)
O(1')	4347(5)	5783(3)	509(3)	58(1)
O(2')	3102(6)	6593(5)	-103(5)	83(1)

C(38)	6004(9)	5085(7)	3212(7)	50(2)
C(39)	5891(8)	4333(7)	1735(5)	72(2)
O(4)	5289(6)	4698(5)	2348(4)	59(2)
O(5)	7037(6)	5167(5)	3450(5)	63(2)
C(38')	6321(12)	5318(12)	3307(11)	50(2)
C(39')	6525(11)	4285(10)	2043(8)	72(2)
O(4')	5793(8)	4622(8)	2556(7)	59(2)
O(5')	7346(9)	5554(6)	3561(8)	63(2)
N(8)	5105(5)	8873(4)	9724(4)	36(1)
C(47)	6060(8)	8858(5)	10435(6)	36(2)
C(48)	5883(7)	9297(5)	11198(6)	44(2)
C(49)	4791(5)	9622(5)	10936(4)	44(1)
C(50)	4338(5)	9349(4)	10046(4)	44(1)
N(8')	5161(5)	8500(4)	9863(4)	36(1)
C(47')	6186(9)	8570(6)	10548(6)	36(2)
C(48')	6017(8)	8958(5)	11329(6)	44(2)
C(49')	4842(5)	9124(5)	11100(4)	44(1)
C(50')	4337(5)	8826(5)	10216(4)	44(1)

Table 3. Bond lengths [Å] and angles [°] for 101119LTs.

C(1)-N(1)	1.333(5)
C(1)-N(2)	1.375(4)
C(1)-C(13)	1.480(5)
C(2)-N(1)	1.388(5)
C(2)-C(3)	1.389(6)
C(2)-C(7)	1.407(5)
C(3)-C(4)	1.387(5)
C(3)-H(3)	0.9500
C(4)-C(8)	1.259(14)
C(4)-C(5)	1.414(7)
C(4)-C(8')	1.730(12)
C(5)-C(6)	1.380(7)
C(5)-H(5)	0.9500
C(6)-C(7)	1.383(6)
C(6)-H(6)	0.9500
C(7)-N(2)	1.383(6)
C(10)-N(2)	1.452(5)
C(10)-C(11)	1.518(5)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-O(3)	1.416(5)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-O(3)	1.418(5)
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-C(23)	1.387(4)
C(13)-C(14)	1.395(5)
C(14)-C(15)	1.382(5)
C(14)-H(14)	0.9500
C(15)-C(16)	1.379(5)
C(15)-H(15)	0.9500
C(16)-N(4)	1.408(5)
C(16)-C(22)	1.413(4)

C(17)-C(18)	1.346(6)
C(17)-N(4)	1.384(4)
C(17)-H(17)	0.9500
C(18)-C(19)	1.431(5)
C(18)-H(18)	0.9500
C(19)-C(20)	1.374(5)
C(19)-H(19)	0.9500
C(20)-N(4)	1.377(4)
C(20)-C(21)	1.501(4)
C(21)-N(3)	1.478(4)
C(21)-C(24)	1.529(4)
C(21)-C(28)	1.541(4)
C(22)-C(23)	1.382(5)
C(22)-N(3)	1.389(4)
C(23)-H(23)	0.9500
C(24)-C(25)	1.526(4)
C(24)-H(24A)	0.9900
C(24)-H(24B)	0.9900
C(25)-C(26)	1.524(4)
C(25)-H(25A)	0.9900
C(25)-H(25B)	0.9900
C(26)-C(27)	1.521(4)
C(26)-C(29)	1.523(4)
C(26)-H(26)	1.0000
C(27)-C(28)	1.525(4)
C(27)-H(27A)	0.9900
C(27)-H(27B)	0.9900
C(28)-H(28A)	0.9900
C(28)-H(28B)	0.9900
C(29)-C(30)	1.508(5)
C(29)-H(29A)	0.9900
C(29)-H(29B)	0.9900
C(30)-H(30A)	0.9800
C(30)-H(30B)	0.9800
C(30)-H(30C)	0.9800
C(31)-N(5)	1.313(4)
C(31)-N(6)	1.385(4)

C(31)-C(43)	1.461(4)
C(32)-N(5)	1.377(4)
C(32)-C(37)	1.391(4)
C(32)-C(33)	1.397(4)
C(33)-C(34)	1.382(5)
C(33)-H(33)	0.9500
C(34)-C(35)	1.403(5)
C(34)-C(38)	1.439(11)
C(34)-C(38')	1.589(16)
C(35)-C(36)	1.377(5)
C(35)-H(35)	0.9500
C(36)-C(37)	1.391(4)
C(36)-H(36)	0.9500
C(37)-N(6)	1.383(4)
C(40)-N(6)	1.467(4)
C(40)-C(41)	1.506(5)
C(40)-H(40A)	0.9900
C(40)-H(40B)	0.9900
C(41)-O(6)	1.387(4)
C(41)-H(41A)	0.9900
C(41)-H(41B)	0.9900
C(42)-O(6)	1.454(6)
C(42)-H(42A)	0.9800
C(42)-H(42B)	0.9800
C(42)-H(42C)	0.9800
C(43)-C(53)	1.400(4)
C(43)-C(44)	1.411(4)
C(44)-C(45)	1.387(4)
C(44)-H(44)	0.9500
C(45)-C(51)	1.395(5)
C(45)-N(7)	1.397(4)
C(46)-C(47')	1.398(11)
C(46)-N(7)	1.482(4)
C(46)-C(58)	1.526(5)
C(46)-C(54)	1.530(5)
C(46)-C(47)	1.622(9)
C(51)-C(52)	1.366(6)

C(51)-N(8)	1.413(7)
C(51)-N(8')	1.499(7)
C(52)-C(53)	1.386(5)
C(52)-H(52)	0.9500
C(53)-H(53)	0.9500
C(54)-C(55)	1.522(4)
C(54)-H(54A)	0.9900
C(54)-H(54B)	0.9900
C(55)-C(56)	1.517(4)
C(55)-H(55A)	0.9900
C(55)-H(55B)	0.9900
C(56)-C(57)	1.522(5)
C(56)-C(59)	1.531(5)
C(56)-H(56)	1.0000
C(57)-C(58)	1.527(5)
C(57)-H(57A)	0.9900
C(57)-H(57B)	0.9900
C(58)-H(58A)	0.9900
C(58)-H(58B)	0.9900
C(59)-C(60)	1.506(6)
C(59)-H(59A)	0.9900
C(59)-H(59B)	0.9900
C(60)-H(60A)	0.9800
C(60)-H(60B)	0.9800
C(60)-H(60C)	0.9800
N(3)-H(3A)	0.8800
N(7)-H(7)	0.8800
C(8)-O(2)	1.272(12)
C(8)-O(1)	1.287(16)
C(9)-O(1)	1.487(9)
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(8')-O(2')	1.271(17)
C(8')-O(1')	1.276(15)
C(9')-O(1')	1.462(8)
C(9')-H(9'1)	0.9800

C(9')-H(9'2)	0.9800
C(9')-H(9'3)	0.9800
C(38)-O(5)	1.194(10)
C(38)-O(4)	1.370(10)
C(39)-O(4)	1.468(8)
C(39)-H(39A)	0.9800
C(39)-H(39B)	0.9800
C(39)-H(39C)	0.9800
C(38')-O(5')	1.198(12)
C(38')-O(4')	1.358(12)
C(39')-O(4')	1.464(11)
C(39')-H(39D)	0.9800
C(39')-H(39E)	0.9800
C(39')-H(39F)	0.9800
N(8)-C(47)	1.385(9)
N(8)-C(50)	1.392(8)
C(47)-C(48)	1.369(10)
C(48)-C(49)	1.444(9)
C(48)-H(48)	0.9500
C(49)-C(50)	1.342(8)
C(49)-H(49)	0.9500
C(50)-H(50)	0.9500
N(8')-C(47')	1.381(10)
N(8')-C(50')	1.389(8)
C(47')-C(48')	1.371(10)
C(48')-C(49')	1.434(10)
C(48')-H(48')	0.9500
C(49')-C(50')	1.338(8)
C(49')-H(49')	0.9500
C(50')-H(50')	0.9500
N(1)-C(1)-N(2)	113.2(4)
N(1)-C(1)-C(13)	123.1(3)
N(2)-C(1)-C(13)	123.7(3)
N(1)-C(2)-C(3)	128.9(3)
N(1)-C(2)-C(7)	110.1(4)
C(3)-C(2)-C(7)	120.9(4)
C(4)-C(3)-C(2)	116.7(4)

C(4)-C(3)-H(3)	121.6
C(2)-C(3)-H(3)	121.6
C(8)-C(4)-C(3)	125.4(8)
C(8)-C(4)-C(5)	112.5(8)
C(3)-C(4)-C(5)	122.1(5)
C(8)-C(4)-C(8')	12.3(12)
C(3)-C(4)-C(8')	113.5(7)
C(5)-C(4)-C(8')	124.3(6)
C(6)-C(5)-C(4)	120.8(4)
C(6)-C(5)-H(5)	119.6
C(4)-C(5)-H(5)	119.6
C(5)-C(6)-C(7)	117.2(5)
C(5)-C(6)-H(6)	121.4
C(7)-C(6)-H(6)	121.4
C(6)-C(7)-N(2)	132.0(4)
C(6)-C(7)-C(2)	122.2(5)
N(2)-C(7)-C(2)	105.8(3)
N(2)-C(10)-C(11)	111.2(3)
N(2)-C(10)-H(10A)	109.4
C(11)-C(10)-H(10A)	109.4
N(2)-C(10)-H(10B)	109.4
C(11)-C(10)-H(10B)	109.4
H(10A)-C(10)-H(10B)	108.0
O(3)-C(11)-C(10)	112.4(3)
O(3)-C(11)-H(11A)	109.1
C(10)-C(11)-H(11A)	109.1
O(3)-C(11)-H(11B)	109.1
C(10)-C(11)-H(11B)	109.1
H(11A)-C(11)-H(11B)	107.9
O(3)-C(12)-H(12A)	109.5
O(3)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
O(3)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(23)-C(13)-C(14)	120.2(4)
C(23)-C(13)-C(1)	117.5(3)

C(14)-C(13)-C(1)	122.2(3)
C(15)-C(14)-C(13)	119.2(3)
C(15)-C(14)-H(14)	120.4
C(13)-C(14)-H(14)	120.4
C(16)-C(15)-C(14)	120.9(3)
C(16)-C(15)-H(15)	119.6
C(14)-C(15)-H(15)	119.6
C(15)-C(16)-N(4)	123.0(3)
C(15)-C(16)-C(22)	120.3(4)
N(4)-C(16)-C(22)	116.7(3)
C(18)-C(17)-N(4)	108.6(3)
C(18)-C(17)-H(17)	125.7
N(4)-C(17)-H(17)	125.7
C(17)-C(18)-C(19)	107.9(4)
C(17)-C(18)-H(18)	126.1
C(19)-C(18)-H(18)	126.1
C(20)-C(19)-C(18)	106.9(4)
C(20)-C(19)-H(19)	126.6
C(18)-C(19)-H(19)	126.6
C(19)-C(20)-N(4)	108.1(3)
C(19)-C(20)-C(21)	132.2(3)
N(4)-C(20)-C(21)	119.6(3)
N(3)-C(21)-C(20)	107.3(3)
N(3)-C(21)-C(24)	109.3(3)
C(20)-C(21)-C(24)	110.2(3)
N(3)-C(21)-C(28)	111.0(3)
C(20)-C(21)-C(28)	109.4(3)
C(24)-C(21)-C(28)	109.7(3)
C(23)-C(22)-N(3)	121.8(3)
C(23)-C(22)-C(16)	118.5(3)
N(3)-C(22)-C(16)	119.6(3)
C(22)-C(23)-C(13)	120.9(3)
C(22)-C(23)-H(23)	119.5
C(13)-C(23)-H(23)	119.5
C(25)-C(24)-C(21)	112.2(3)
C(25)-C(24)-H(24A)	109.2
C(21)-C(24)-H(24A)	109.2

C(25)-C(24)-H(24B)	109.2
C(21)-C(24)-H(24B)	109.2
H(24A)-C(24)-H(24B)	107.9
C(26)-C(25)-C(24)	112.8(3)
C(26)-C(25)-H(25A)	109.0
C(24)-C(25)-H(25A)	109.0
C(26)-C(25)-H(25B)	109.0
C(24)-C(25)-H(25B)	109.0
H(25A)-C(25)-H(25B)	107.8
C(27)-C(26)-C(29)	113.2(3)
C(27)-C(26)-C(25)	110.7(3)
C(29)-C(26)-C(25)	109.8(3)
C(27)-C(26)-H(26)	107.7
C(29)-C(26)-H(26)	107.7
C(25)-C(26)-H(26)	107.7
C(26)-C(27)-C(28)	112.0(3)
C(26)-C(27)-H(27A)	109.2
C(28)-C(27)-H(27A)	109.2
C(26)-C(27)-H(27B)	109.2
C(28)-C(27)-H(27B)	109.2
H(27A)-C(27)-H(27B)	107.9
C(27)-C(28)-C(21)	112.0(2)
C(27)-C(28)-H(28A)	109.2
C(21)-C(28)-H(28A)	109.2
C(27)-C(28)-H(28B)	109.2
C(21)-C(28)-H(28B)	109.2
H(28A)-C(28)-H(28B)	107.9
C(30)-C(29)-C(26)	114.8(3)
C(30)-C(29)-H(29A)	108.6
C(26)-C(29)-H(29A)	108.6
C(30)-C(29)-H(29B)	108.6
C(26)-C(29)-H(29B)	108.6
H(29A)-C(29)-H(29B)	107.5
C(29)-C(30)-H(30A)	109.5
C(29)-C(30)-H(30B)	109.5
H(30A)-C(30)-H(30B)	109.5
C(29)-C(30)-H(30C)	109.5

H(30A)-C(30)-H(30C)	109.5
H(30B)-C(30)-H(30C)	109.5
N(5)-C(31)-N(6)	112.5(3)
N(5)-C(31)-C(43)	122.9(3)
N(6)-C(31)-C(43)	124.6(3)
N(5)-C(32)-C(37)	110.7(3)
N(5)-C(32)-C(33)	129.2(3)
C(37)-C(32)-C(33)	120.0(3)
C(34)-C(33)-C(32)	117.8(3)
C(34)-C(33)-H(33)	121.1
C(32)-C(33)-H(33)	121.1
C(33)-C(34)-C(35)	121.4(3)
C(33)-C(34)-C(38)	122.7(5)
C(35)-C(34)-C(38)	115.8(4)
C(33)-C(34)-C(38')	108.0(5)
C(35)-C(34)-C(38')	130.4(6)
C(38)-C(34)-C(38')	17.1(6)
C(36)-C(35)-C(34)	121.4(3)
C(36)-C(35)-H(35)	119.3
C(34)-C(35)-H(35)	119.3
C(35)-C(36)-C(37)	116.9(3)
C(35)-C(36)-H(36)	121.6
C(37)-C(36)-H(36)	121.6
N(6)-C(37)-C(32)	105.3(3)
N(6)-C(37)-C(36)	132.1(3)
C(32)-C(37)-C(36)	122.6(3)
N(6)-C(40)-C(41)	113.0(3)
N(6)-C(40)-H(40A)	109.0
C(41)-C(40)-H(40A)	109.0
N(6)-C(40)-H(40B)	109.0
C(41)-C(40)-H(40B)	109.0
H(40A)-C(40)-H(40B)	107.8
O(6)-C(41)-C(40)	107.2(3)
O(6)-C(41)-H(41A)	110.3
C(40)-C(41)-H(41A)	110.3
O(6)-C(41)-H(41B)	110.3
C(40)-C(41)-H(41B)	110.3

H(41A)-C(41)-H(41B)	108.5
O(6)-C(42)-H(42A)	109.5
O(6)-C(42)-H(42B)	109.5
H(42A)-C(42)-H(42B)	109.5
O(6)-C(42)-H(42C)	109.5
H(42A)-C(42)-H(42C)	109.5
H(42B)-C(42)-H(42C)	109.5
C(53)-C(43)-C(44)	118.9(3)
C(53)-C(43)-C(31)	123.6(3)
C(44)-C(43)-C(31)	117.4(3)
C(45)-C(44)-C(43)	121.0(3)
C(45)-C(44)-H(44)	119.5
C(43)-C(44)-H(44)	119.5
C(44)-C(45)-C(51)	118.6(3)
C(44)-C(45)-N(7)	121.3(3)
C(51)-C(45)-N(7)	120.0(3)
C(47')-C(46)-N(7)	105.5(4)
C(47')-C(46)-C(58)	102.5(4)
N(7)-C(46)-C(58)	109.1(3)
C(47')-C(46)-C(54)	119.1(4)
N(7)-C(46)-C(54)	110.8(3)
C(58)-C(46)-C(54)	109.3(3)
C(47')-C(46)-C(47)	19.2(5)
N(7)-C(46)-C(47)	108.0(4)
C(58)-C(46)-C(47)	118.0(4)
C(54)-C(46)-C(47)	101.5(4)
C(52)-C(51)-C(45)	120.9(3)
C(52)-C(51)-N(8)	113.7(4)
C(45)-C(51)-N(8)	124.6(4)
C(52)-C(51)-N(8')	130.0(4)
C(45)-C(51)-N(8')	107.6(4)
N(8)-C(51)-N(8')	27.1(2)
C(51)-C(52)-C(53)	121.4(3)
C(51)-C(52)-H(52)	119.3
C(53)-C(52)-H(52)	119.3
C(52)-C(53)-C(43)	119.2(3)
C(52)-C(53)-H(53)	120.4

C(43)-C(53)-H(53)	120.4
C(55)-C(54)-C(46)	112.8(3)
C(55)-C(54)-H(54A)	109.0
C(46)-C(54)-H(54A)	109.0
C(55)-C(54)-H(54B)	109.0
C(46)-C(54)-H(54B)	109.0
H(54A)-C(54)-H(54B)	107.8
C(56)-C(55)-C(54)	111.2(3)
C(56)-C(55)-H(55A)	109.4
C(54)-C(55)-H(55A)	109.4
C(56)-C(55)-H(55B)	109.4
C(54)-C(55)-H(55B)	109.4
H(55A)-C(55)-H(55B)	108.0
C(55)-C(56)-C(57)	109.8(3)
C(55)-C(56)-C(59)	112.9(3)
C(57)-C(56)-C(59)	110.5(3)
C(55)-C(56)-H(56)	107.8
C(57)-C(56)-H(56)	107.8
C(59)-C(56)-H(56)	107.8
C(56)-C(57)-C(58)	112.5(3)
C(56)-C(57)-H(57A)	109.1
C(58)-C(57)-H(57A)	109.1
C(56)-C(57)-H(57B)	109.1
C(58)-C(57)-H(57B)	109.1
H(57A)-C(57)-H(57B)	107.8
C(46)-C(58)-C(57)	113.8(3)
C(46)-C(58)-H(58A)	108.8
C(57)-C(58)-H(58A)	108.8
C(46)-C(58)-H(58B)	108.8
C(57)-C(58)-H(58B)	108.8
H(58A)-C(58)-H(58B)	107.7
C(60)-C(59)-C(56)	115.7(3)
C(60)-C(59)-H(59A)	108.3
C(56)-C(59)-H(59A)	108.3
C(60)-C(59)-H(59B)	108.3
C(56)-C(59)-H(59B)	108.3
H(59A)-C(59)-H(59B)	107.4

C(59)-C(60)-H(60A)	109.5
C(59)-C(60)-H(60B)	109.5
H(60A)-C(60)-H(60B)	109.5
C(59)-C(60)-H(60C)	109.5
H(60A)-C(60)-H(60C)	109.5
H(60B)-C(60)-H(60C)	109.5
C(1)-N(1)-C(2)	104.6(3)
C(1)-N(2)-C(7)	106.3(3)
C(1)-N(2)-C(10)	128.6(4)
C(7)-N(2)-C(10)	123.9(3)
C(22)-N(3)-C(21)	118.2(2)
C(22)-N(3)-H(3A)	120.9
C(21)-N(3)-H(3A)	120.9
C(20)-N(4)-C(17)	108.6(3)
C(20)-N(4)-C(16)	122.3(3)
C(17)-N(4)-C(16)	129.0(3)
C(31)-N(5)-C(32)	105.2(2)
C(37)-N(6)-C(31)	106.3(2)
C(37)-N(6)-C(40)	124.9(2)
C(31)-N(6)-C(40)	128.6(3)
C(45)-N(7)-C(46)	117.2(3)
C(45)-N(7)-H(7)	121.4
C(46)-N(7)-H(7)	121.4
C(11)-O(3)-C(12)	113.4(3)
C(41)-O(6)-C(42)	112.8(4)
C(4)-C(8)-O(2)	116.3(13)
C(4)-C(8)-O(1)	122.1(9)
O(2)-C(8)-O(1)	121.2(11)
C(8)-O(1)-C(9)	115.6(7)
O(2')-C(8')-O(1')	121.7(10)
O(2')-C(8')-C(4)	118.5(9)
O(1')-C(8')-C(4)	119.5(12)
O(1')-C(9')-H(9'1)	109.5
O(1')-C(9')-H(9'2)	109.5
H(9'1)-C(9')-H(9'2)	109.5
O(1')-C(9')-H(9'3)	109.5
H(9'1)-C(9')-H(9'3)	109.5

H(9'2)-C(9')-H(9'3)	109.5
C(8')-O(1')-C(9')	119.2(9)
O(5)-C(38)-O(4)	123.5(9)
O(5)-C(38)-C(34)	121.7(8)
O(4)-C(38)-C(34)	114.5(8)
C(38)-O(4)-C(39)	114.5(6)
O(5')-C(38')-O(4')	120.2(13)
O(5')-C(38')-C(34)	131.6(12)
O(4')-C(38')-C(34)	105.9(8)
O(4')-C(39')-H(39D)	109.5
O(4')-C(39')-H(39E)	109.5
H(39D)-C(39')-H(39E)	109.5
O(4')-C(39')-H(39F)	109.5
H(39D)-C(39')-H(39F)	109.5
H(39E)-C(39')-H(39F)	109.5
C(38')-O(4')-C(39')	115.5(10)
C(47)-N(8)-C(50)	108.9(6)
C(47)-N(8)-C(51)	115.1(5)
C(50)-N(8)-C(51)	134.1(5)
C(48)-C(47)-N(8)	107.9(7)
C(48)-C(47)-C(46)	129.8(7)
N(8)-C(47)-C(46)	122.3(7)
C(47)-C(48)-C(49)	106.9(7)
C(47)-C(48)-H(48)	126.6
C(49)-C(48)-H(48)	126.6
C(50)-C(49)-C(48)	108.1(6)
C(50)-C(49)-H(49)	126.0
C(48)-C(49)-H(49)	126.0
C(49)-C(50)-N(8)	108.2(6)
C(49)-C(50)-H(50)	125.9
N(8)-C(50)-H(50)	125.9
C(47')-N(8')-C(50')	109.0(6)
C(47')-N(8')-C(51)	125.9(6)
C(50')-N(8')-C(51)	124.3(5)
C(48')-C(47')-N(8')	107.6(8)
C(48')-C(47')-C(46)	135.4(8)
N(8')-C(47')-C(46)	116.1(7)

C(47')-C(48')-C(49')	107.0(7)
C(47')-C(48')-H(48')	126.5
C(49')-C(48')-H(48')	126.5
C(50')-C(49')-C(48')	108.3(6)
C(50')-C(49')-H(49')	125.8
C(48')-C(49')-H(49')	125.8
C(49')-C(50')-N(8')	108.1(6)
C(49')-C(50')-H(50')	126.0
N(8')-C(50')-H(50')	126.0

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 101119LTs. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	51(2)	53(2)	38(2)	-3(2)	0(2)	20(2)
C(2)	77(2)	44(2)	34(2)	0(1)	6(2)	20(2)
C(3)	122(4)	50(2)	43(2)	10(2)	24(2)	30(2)
C(4)	117(4)	45(2)	46(2)	8(2)	-2(2)	7(2)
C(5)	124(4)	38(2)	72(3)	6(2)	-26(3)	13(3)
C(6)	91(3)	42(2)	76(3)	-6(2)	-20(3)	18(2)
C(7)	76(3)	44(2)	45(2)	-9(2)	-12(2)	21(2)
C(10)	49(2)	60(2)	90(3)	-13(2)	2(2)	23(2)
C(11)	55(2)	71(3)	101(3)	-25(2)	28(2)	6(2)
C(12)	73(3)	96(3)	88(3)	-23(3)	50(3)	-14(2)
C(13)	48(2)	52(2)	42(2)	-6(2)	10(2)	14(2)
C(14)	45(2)	69(2)	42(2)	-5(2)	4(2)	22(2)
C(15)	40(2)	64(2)	50(2)	0(2)	8(2)	8(2)
C(16)	35(2)	65(2)	46(2)	-1(2)	12(2)	8(2)
C(17)	39(2)	87(3)	66(3)	3(2)	17(2)	1(2)
C(18)	53(2)	91(3)	83(3)	23(3)	33(2)	0(2)
C(19)	53(2)	83(3)	64(2)	16(2)	25(2)	2(2)
C(20)	38(2)	69(2)	49(2)	6(2)	18(2)	4(2)
C(21)	42(2)	55(2)	41(2)	6(1)	15(1)	3(1)
C(22)	39(2)	56(2)	39(2)	-5(2)	14(1)	7(1)
C(23)	39(2)	52(2)	37(2)	-4(1)	11(1)	9(1)
C(24)	46(2)	64(2)	41(2)	8(2)	16(2)	6(2)
C(25)	41(2)	56(2)	38(2)	6(1)	10(1)	4(1)
C(26)	44(2)	45(2)	45(2)	9(1)	16(1)	6(1)
C(27)	44(2)	47(2)	47(2)	7(1)	19(2)	8(1)
C(28)	43(2)	58(2)	39(2)	8(1)	14(1)	5(2)
C(29)	43(2)	55(2)	57(2)	17(2)	14(2)	9(2)
C(30)	52(2)	77(3)	81(3)	27(2)	33(2)	22(2)
C(31)	39(2)	42(2)	42(2)	6(1)	15(1)	7(1)
C(32)	52(2)	43(2)	38(2)	11(1)	18(1)	15(1)
C(33)	56(2)	58(2)	44(2)	15(2)	24(2)	23(2)
C(34)	78(3)	51(2)	47(2)	12(2)	28(2)	25(2)

C(35)	84(3)	42(2)	38(2)	2(1)	18(2)	6(2)
C(36)	60(2)	44(2)	45(2)	4(1)	13(2)	4(2)
C(37)	50(2)	37(2)	42(2)	9(1)	15(1)	4(1)
C(40)	43(2)	57(2)	51(2)	-1(2)	16(2)	-6(2)
C(41)	38(2)	94(3)	63(2)	11(2)	19(2)	8(2)
C(42)	80(3)	144(5)	123(5)	-9(4)	29(3)	54(3)
C(43)	36(2)	45(2)	44(2)	-1(1)	16(1)	-2(1)
C(44)	41(2)	41(2)	49(2)	-1(1)	23(2)	-3(1)
C(45)	40(2)	56(2)	44(2)	-4(2)	18(2)	-15(2)
C(46)	48(2)	56(2)	37(2)	-4(1)	16(2)	-8(2)
C(51)	29(2)	110(3)	48(2)	-24(2)	17(2)	-6(2)
C(52)	34(2)	107(3)	59(2)	-32(2)	11(2)	7(2)
C(53)	36(2)	71(2)	50(2)	-10(2)	12(2)	4(2)
C(54)	37(2)	45(2)	44(2)	0(1)	13(1)	3(1)
C(55)	36(2)	46(2)	50(2)	4(1)	16(1)	4(1)
C(56)	48(2)	47(2)	41(2)	0(1)	10(2)	11(1)
C(57)	86(3)	46(2)	43(2)	3(2)	15(2)	5(2)
C(58)	78(3)	57(2)	42(2)	2(2)	20(2)	-12(2)
C(59)	66(2)	76(2)	43(2)	2(2)	10(2)	40(2)
C(60)	40(2)	110(3)	65(3)	-13(2)	19(2)	10(2)
N(1)	75(2)	47(2)	39(2)	6(1)	16(1)	22(1)
N(2)	66(2)	44(2)	50(2)	-10(1)	0(2)	19(1)
N(3)	35(1)	59(2)	35(1)	-2(1)	4(1)	6(1)
N(4)	36(2)	68(2)	49(2)	3(1)	17(1)	0(1)
N(5)	41(1)	45(1)	40(1)	5(1)	15(1)	9(1)
N(6)	45(2)	41(1)	42(1)	-1(1)	17(1)	0(1)
N(7)	55(2)	49(2)	44(2)	0(1)	17(1)	-12(1)
O(3)	52(2)	85(2)	64(2)	-21(1)	23(1)	-8(1)
O(6)	70(2)	101(2)	134(3)	7(2)	44(2)	5(2)
C(8)	106(11)	55(3)	51(3)	10(2)	52(6)	43(6)
C(9)	78(4)	70(4)	82(4)	27(3)	37(3)	-2(3)
O(1)	68(2)	50(2)	59(2)	13(2)	30(2)	-2(2)
O(2)	89(3)	81(3)	88(4)	33(3)	39(3)	6(3)
C(8')	106(11)	55(3)	51(3)	10(2)	52(6)	43(6)
C(9')	78(4)	70(4)	82(4)	27(3)	37(3)	-2(3)
O(1')	68(2)	50(2)	59(2)	13(2)	30(2)	-2(2)
O(2')	89(3)	81(3)	88(4)	33(3)	39(3)	6(3)

C(38)	62(6)	40(6)	47(3)	5(4)	29(4)	-2(4)
C(39)	82(6)	81(4)	53(5)	1(4)	41(5)	8(6)
O(4)	63(5)	64(2)	44(3)	-3(2)	26(3)	2(4)
O(5)	65(4)	69(5)	55(3)	4(4)	33(3)	13(3)
C(38')	62(6)	40(6)	47(3)	5(4)	29(4)	-2(4)
C(39')	82(6)	81(4)	53(5)	1(4)	41(5)	8(6)
O(4')	63(5)	64(2)	44(3)	-3(2)	26(3)	2(4)
O(5')	65(4)	69(5)	55(3)	4(4)	33(3)	13(3)
N(8)	34(2)	39(3)	35(2)	10(2)	14(2)	9(2)
C(47)	37(3)	30(5)	38(3)	5(3)	13(2)	-4(3)
C(48)	41(3)	46(5)	38(3)	5(3)	13(2)	-1(3)
C(49)	41(2)	48(3)	39(3)	2(2)	20(2)	3(3)
C(50)	35(2)	48(3)	43(3)	3(2)	16(2)	5(3)
N(8')	34(2)	39(3)	35(2)	10(2)	14(2)	9(2)
C(47')	37(3)	30(5)	38(3)	5(3)	13(2)	-4(3)
C(48')	41(3)	46(5)	38(3)	5(3)	13(2)	-1(3)
C(49')	41(2)	48(3)	39(3)	2(2)	20(2)	3(3)
C(50')	35(2)	48(3)	43(3)	3(2)	16(2)	5(3)

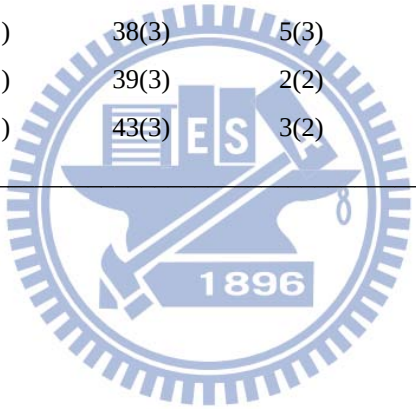
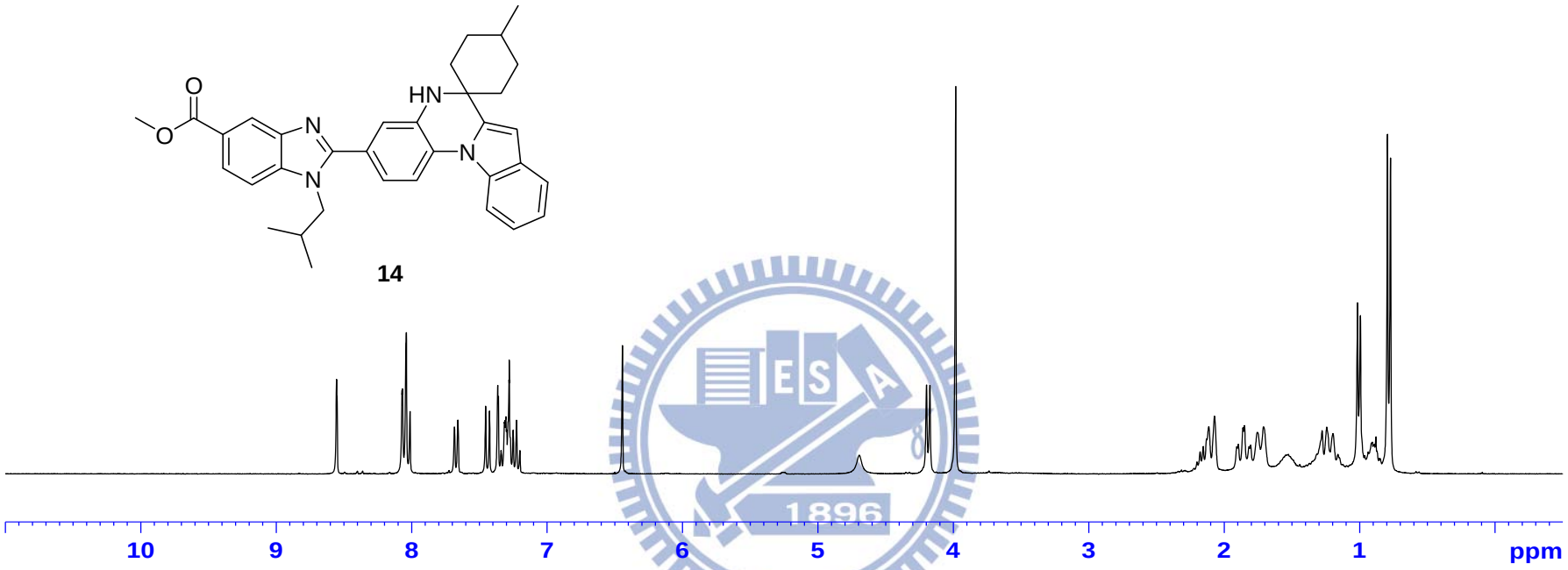


Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 101119LTs.

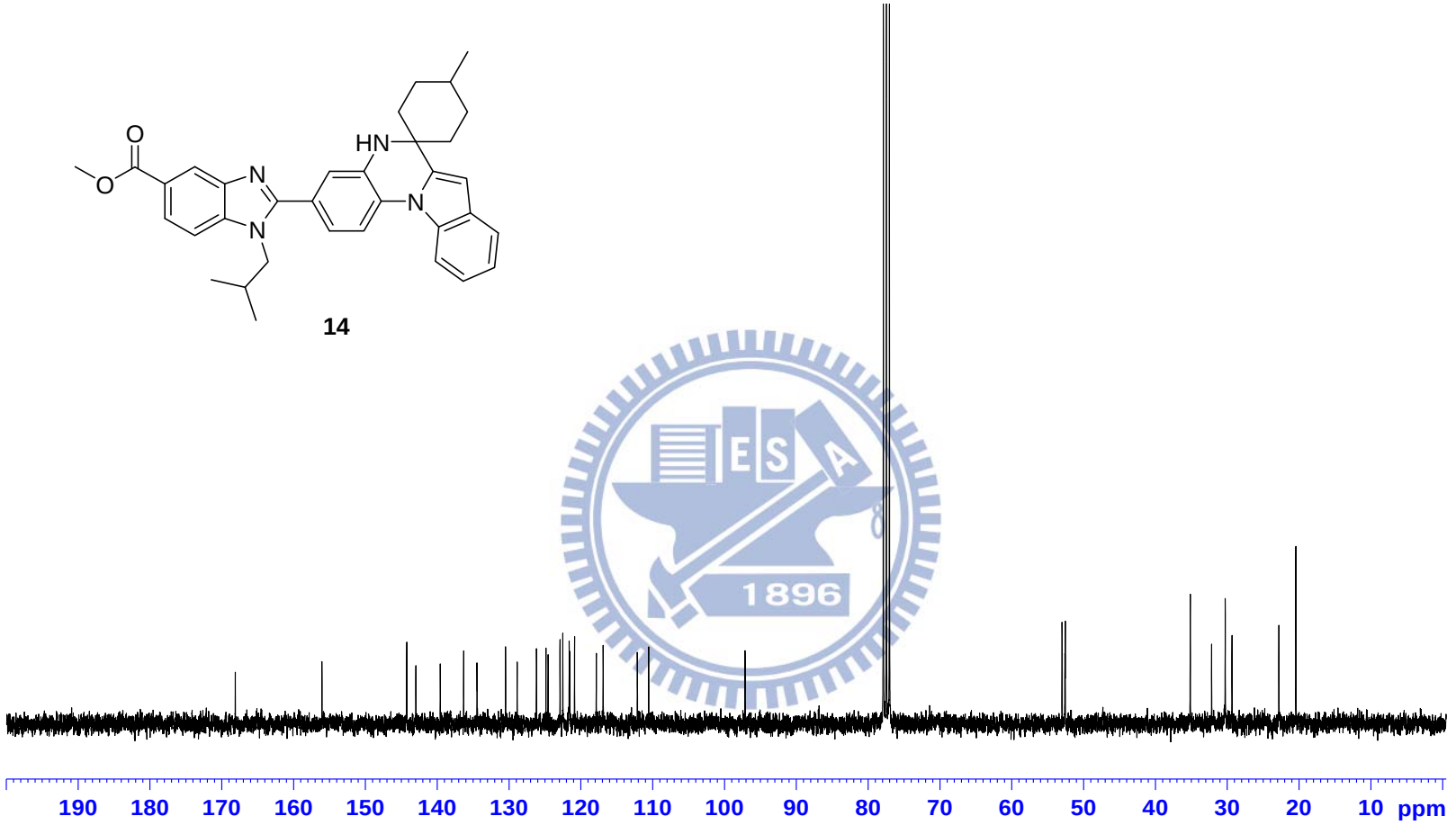
	x	y	z	U(eq)
H(3)	3131	4507	739	88
H(5)	1257	6560	614	115
H(6)	-27	5945	1150	105
H(10A)	-1132	4072	1932	95
H(10B)	-1253	4863	1493	95
H(11A)	196	5827	2779	104
H(11B)	-842	5459	3031	104
H(12A)	-465	4753	4057	139
H(12B)	645	4258	4264	139
H(12C)	-399	3874	3331	139
H(14)	-1218	2558	1180	71
H(15)	-1607	1439	1761	69
H(17)	-1989	610	2669	84
H(18)	-1581	-390	3593	90
H(19)	618	-221	4327	81
H(23)	2122	3061	2859	57
H(24A)	2516	1477	5157	62
H(24B)	2591	440	4783	62
H(25A)	4146	1899	4854	58
H(25B)	4475	1233	5435	58
H(26)	4278	46	4179	55
H(27A)	3785	201	2763	56
H(27B)	3689	1233	3137	56
H(28A)	2167	-238	3082	58
H(28B)	1815	403	2476	58
H(29A)	5739	1566	4274	63
H(29B)	6094	976	4928	63
H(30A)	6008	-258	3704	100
H(30B)	6966	564	3881	100
H(30C)	5745	379	3088	100
H(33)	6818	6196	4879	61

H(35)	3837	4831	2894	69
H(36)	2748	5308	3798	64
H(40A)	2612	6406	6164	66
H(40B)	2265	5643	5229	66
H(41A)	2214	7483	5345	81
H(41B)	1664	6646	4458	81
H(42A)	364	7962	5185	190
H(42B)	-702	7249	5054	190
H(42C)	-193	7162	4274	190
H(44)	6302	6941	7784	54
H(52)	3557	8717	8314	97
H(53)	3341	7949	6854	72
H(54A)	7411	9289	9669	54
H(54B)	8071	9656	10720	54
H(55A)	8804	8349	9519	56
H(55B)	9435	9363	10012	56
H(56)	9933	9109	11397	60
H(57A)	9516	7692	11513	75
H(57B)	8894	7287	10460	75
H(58A)	7453	7528	11073	76
H(58B)	8055	8536	11627	76
H(59A)	11317	8160	11297	80
H(59B)	10689	7770	10246	80
H(60A)	11257	9117	10077	120
H(60B)	12378	8799	10649	120
H(60C)	11798	9568	11130	120
H(3A)	2520	2361	4110	58
H(7)	6973	7104	9442	64
H(9A)	4420	7097	308	111
H(9B)	3653	7872	192	111
H(9C)	3419	6983	-622	111
H(9'1)	5215	5899	-296	111
H(9'2)	6016	6208	732	111
H(9'3)	5147	6838	349	111
H(39A)	6247	4821	1600	108
H(39B)	5334	3918	1185	108
H(39C)	6494	4015	2010	108

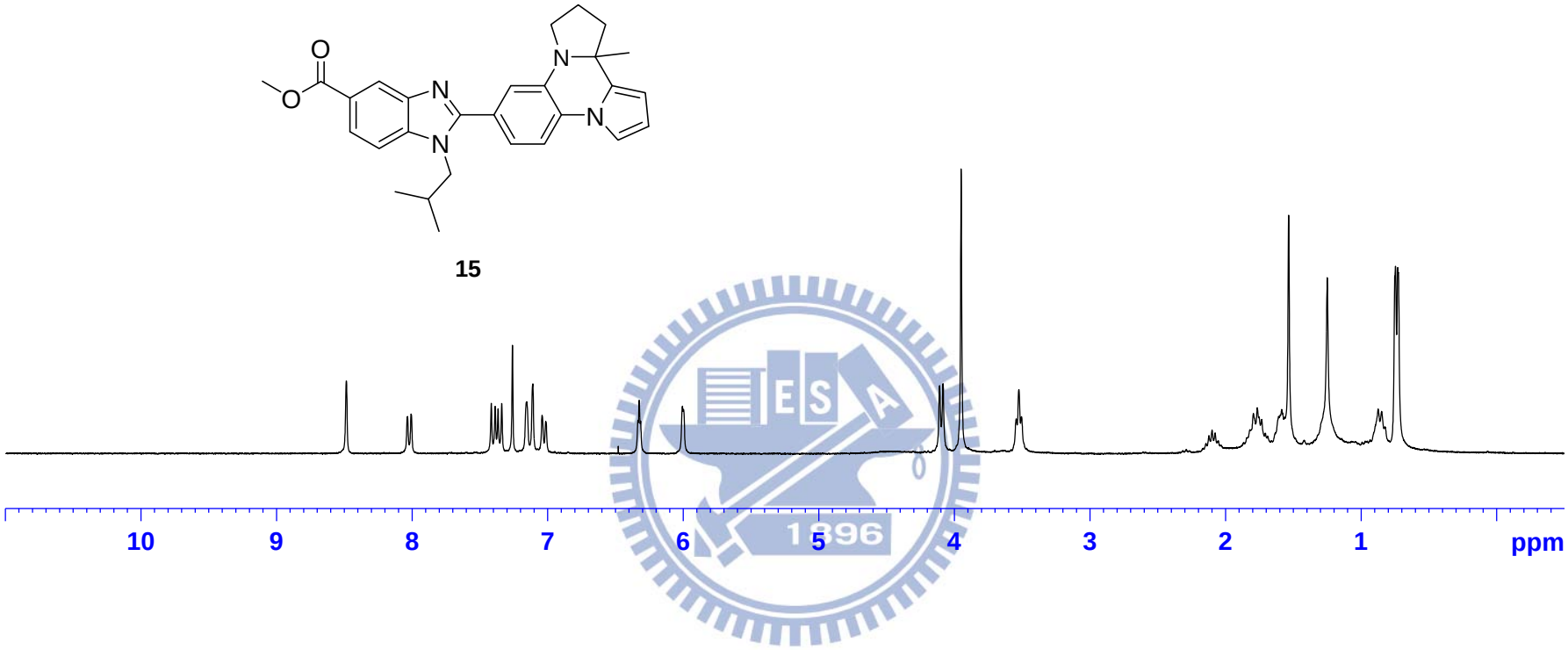
H(39D)	6711	4733	1781	108
H(39E)	6110	3732	1569	108
H(39F)	7243	4165	2434	108
H(48)	6383	9374	11788	53
H(49)	4453	9968	11325	53
H(50)	3617	9463	9696	53
H(48')	6572	9091	11910	53
H(49')	4483	9399	11507	53
H(50')	3552	8835	9888	53



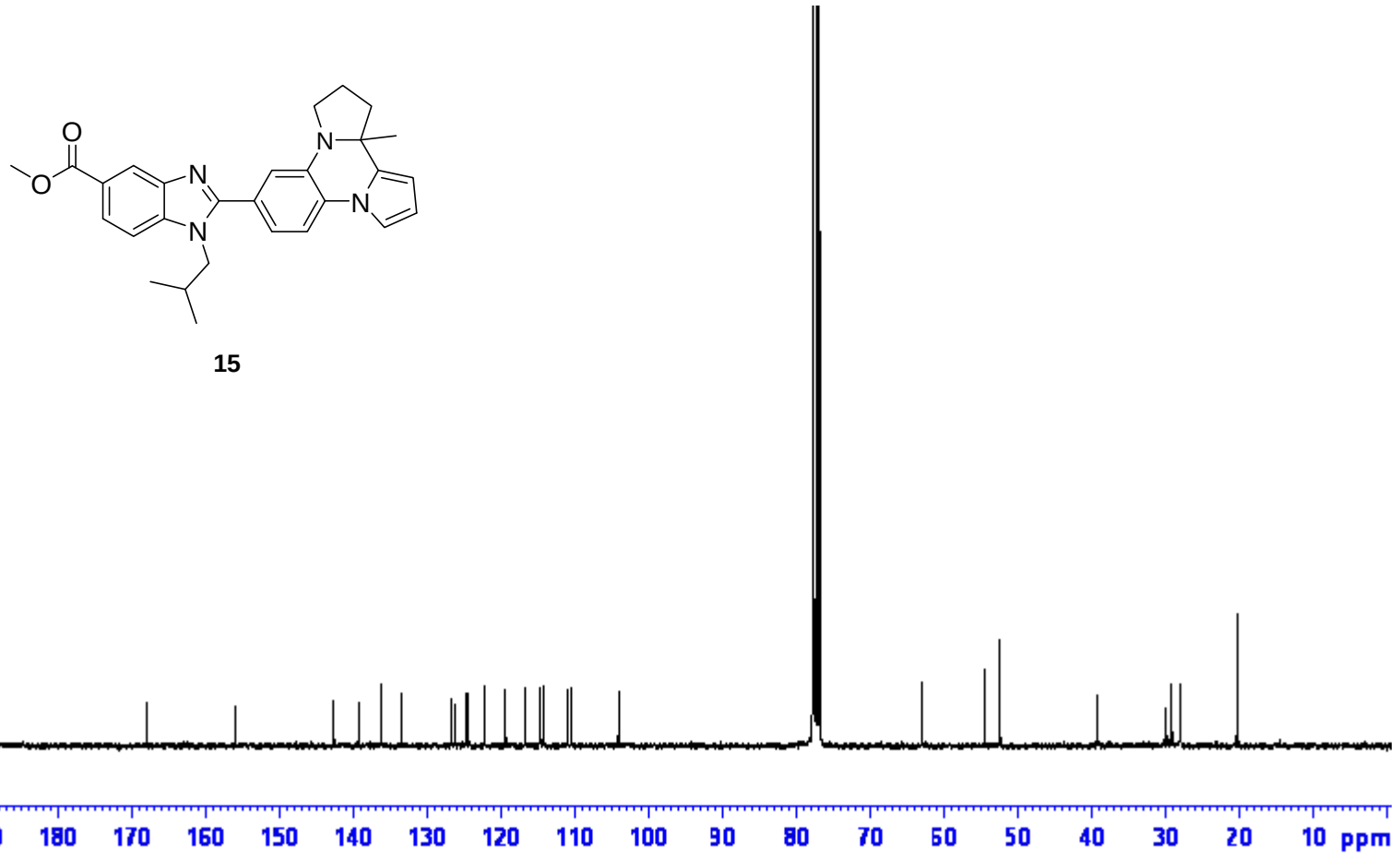
^{1}H NMR Spectrum of Compound 14 in $CDCl_3$



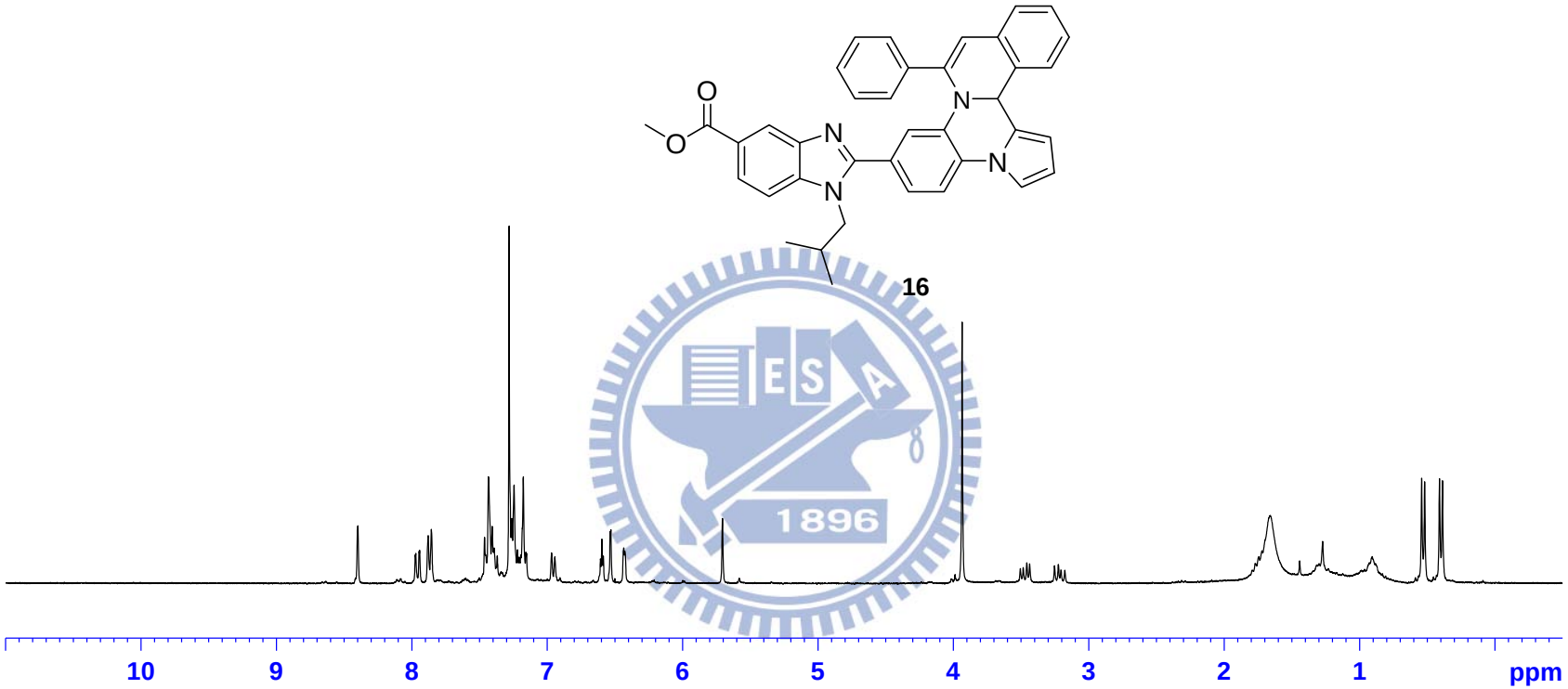
^{13}C NMR Spectrum of Compound 14 in $CDCl_3$



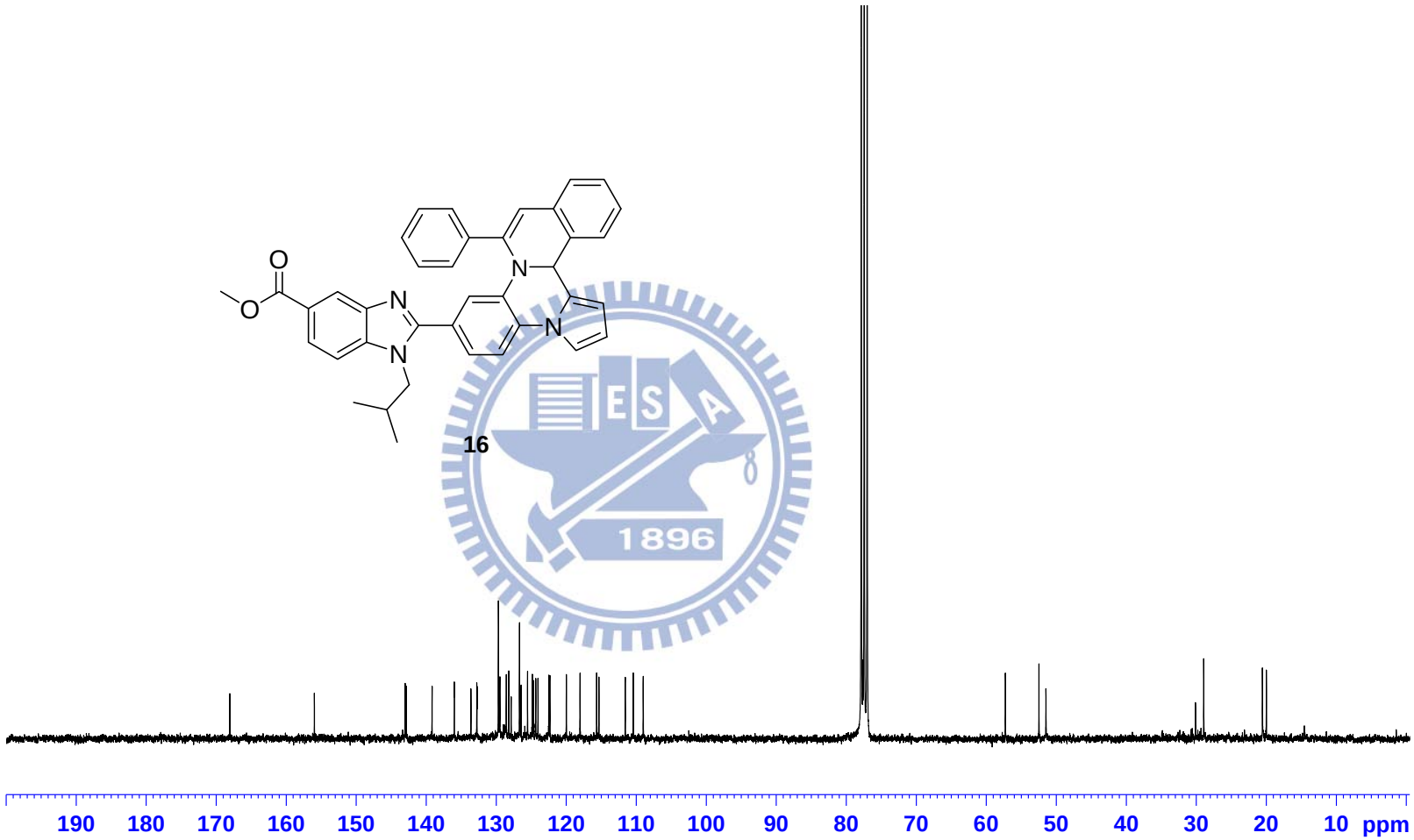
^{1}H NMR Spectrum of Compound 15 in $CDCl_3$



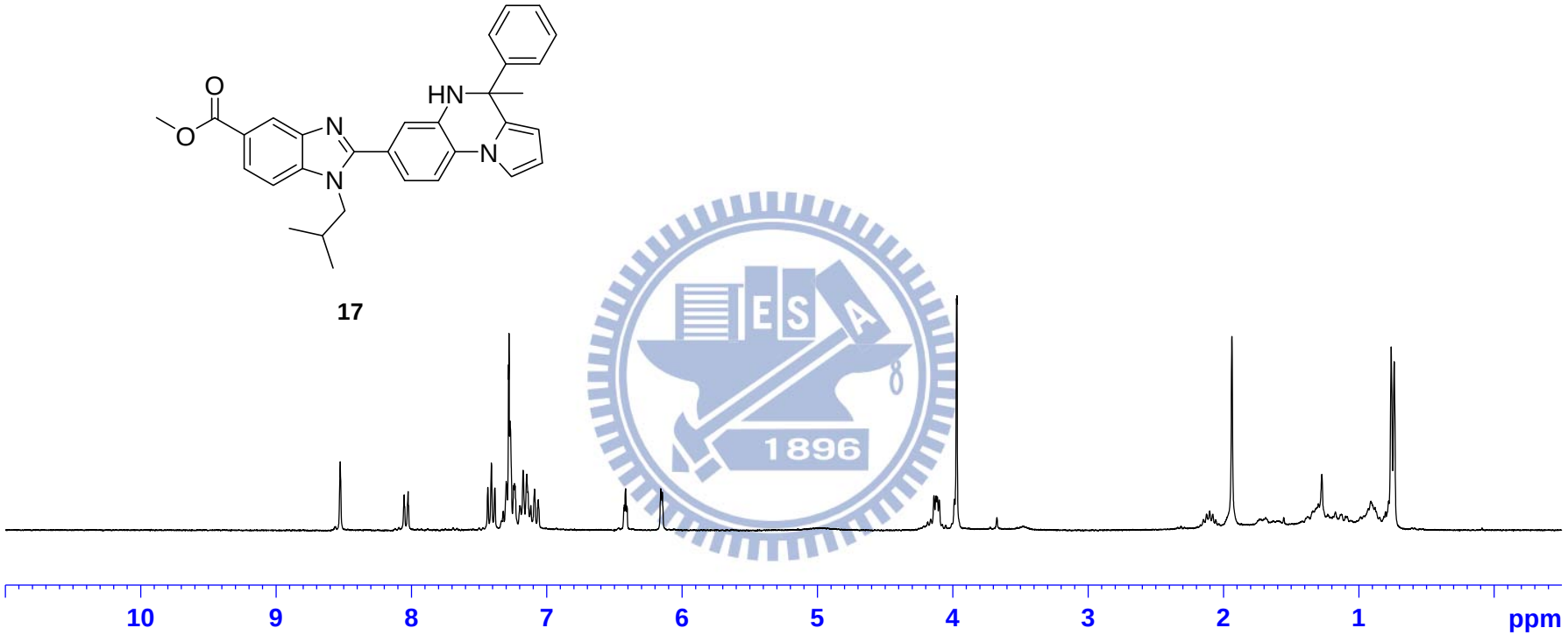
^{13}C NMR Spectrum of Compound 14 in $CDCl_3$



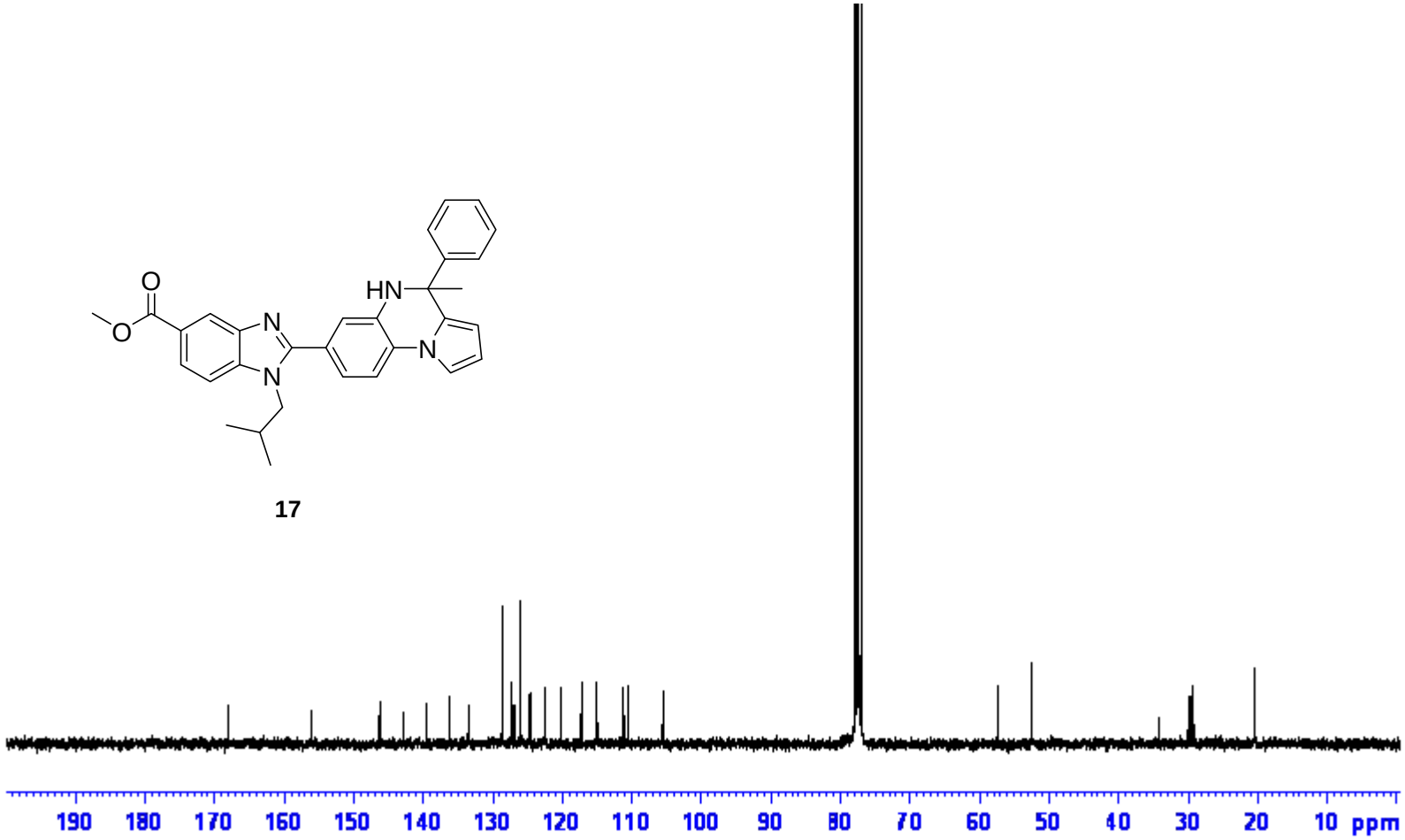
^{1}H NMR Spectrum of Compound 16 in $CDCl_3$



^{13}C NMR Spectrum of Compound 16 in $CDCl_3$

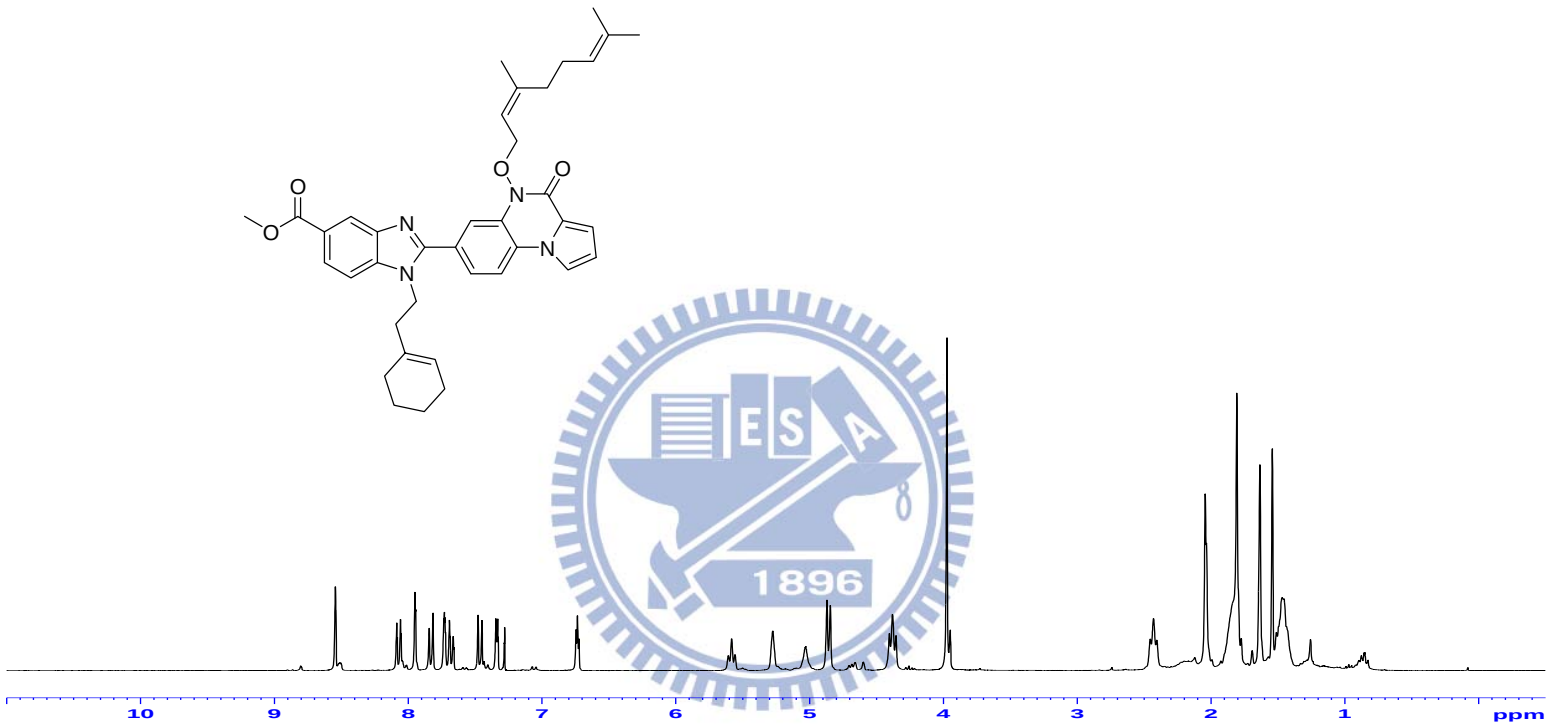


^{1}H NMR Spectrum of Compound 17 in $CDCl_3$

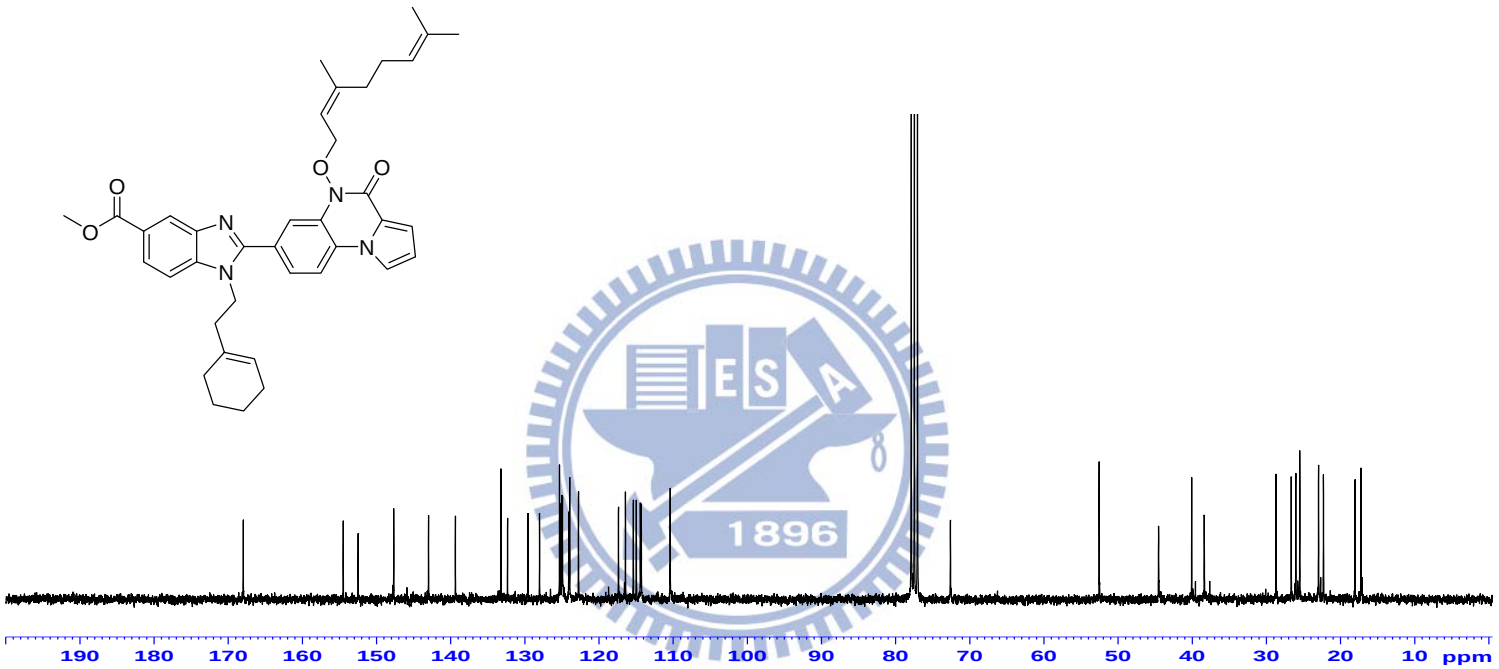


17

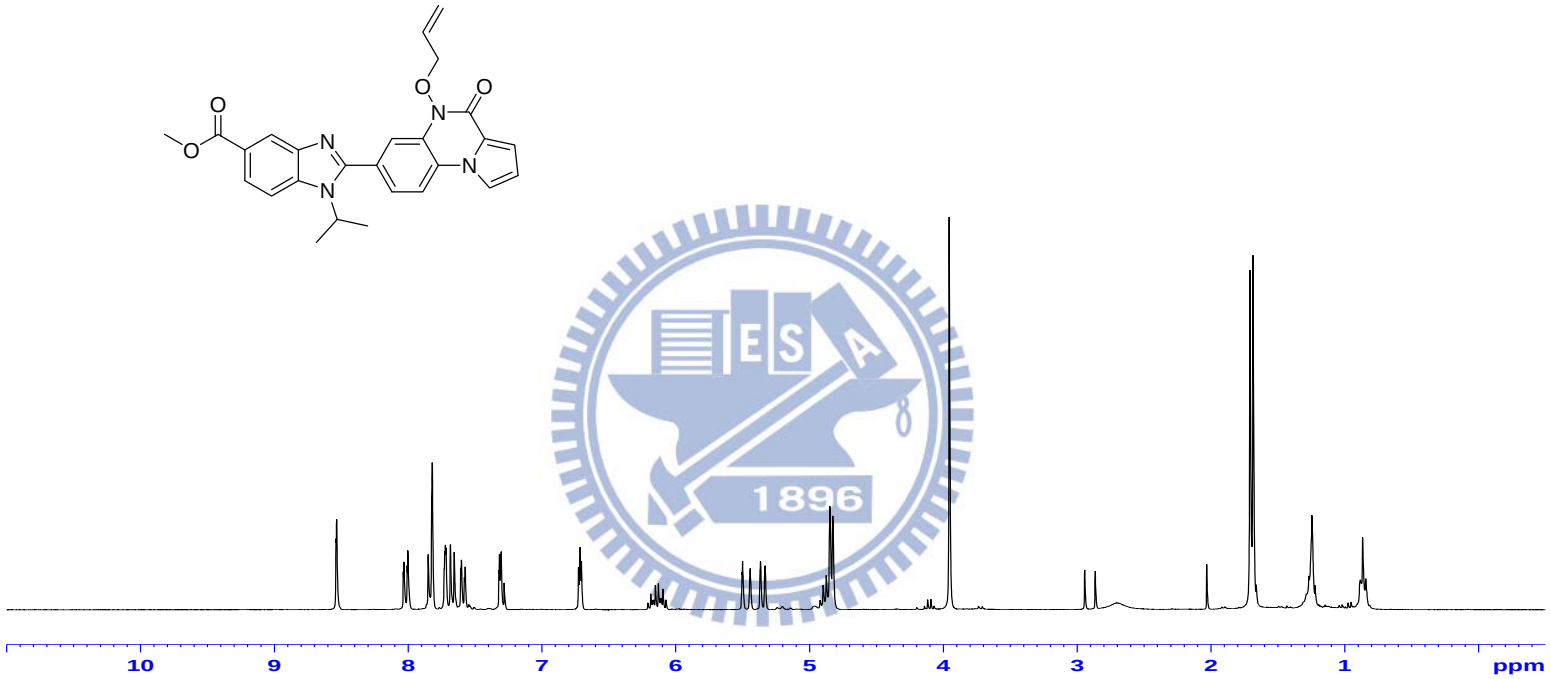
^{13}C NMR Spectrum of Compound 17 in $CDCl_3$



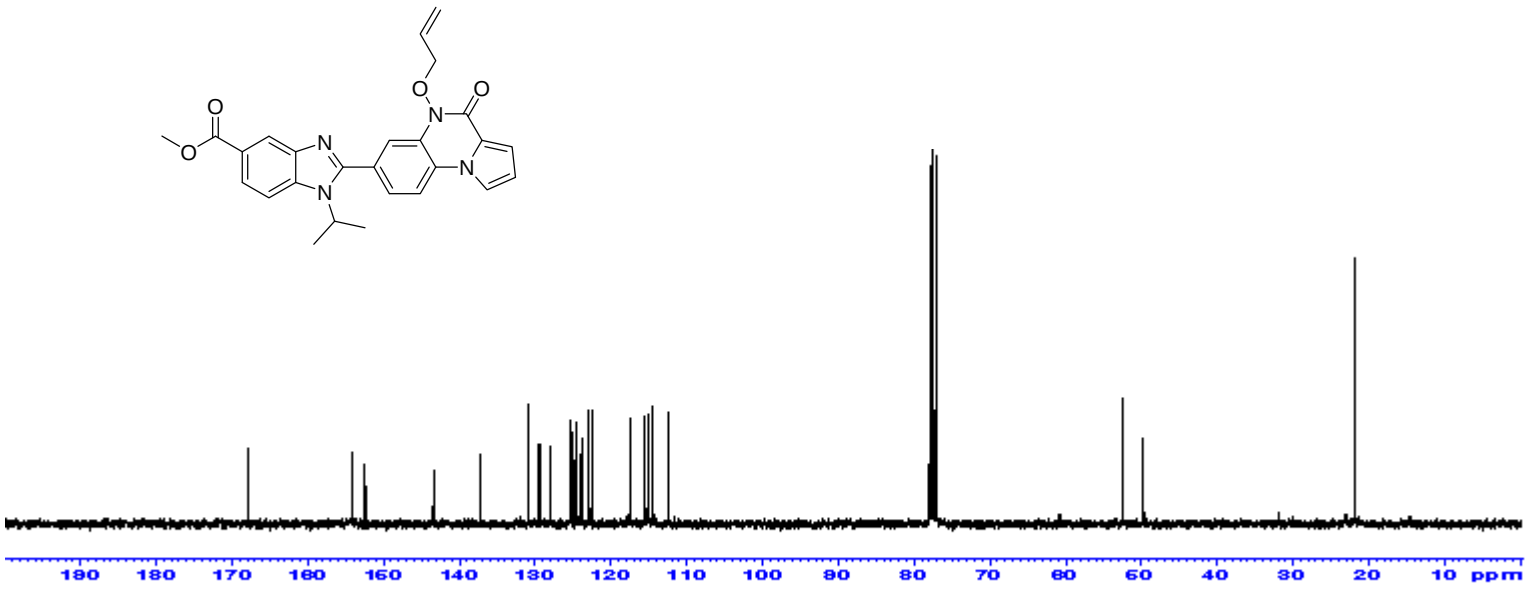
^{1}HNMR spectrum (300 MHz) of compound 21a in $CDCl_3$



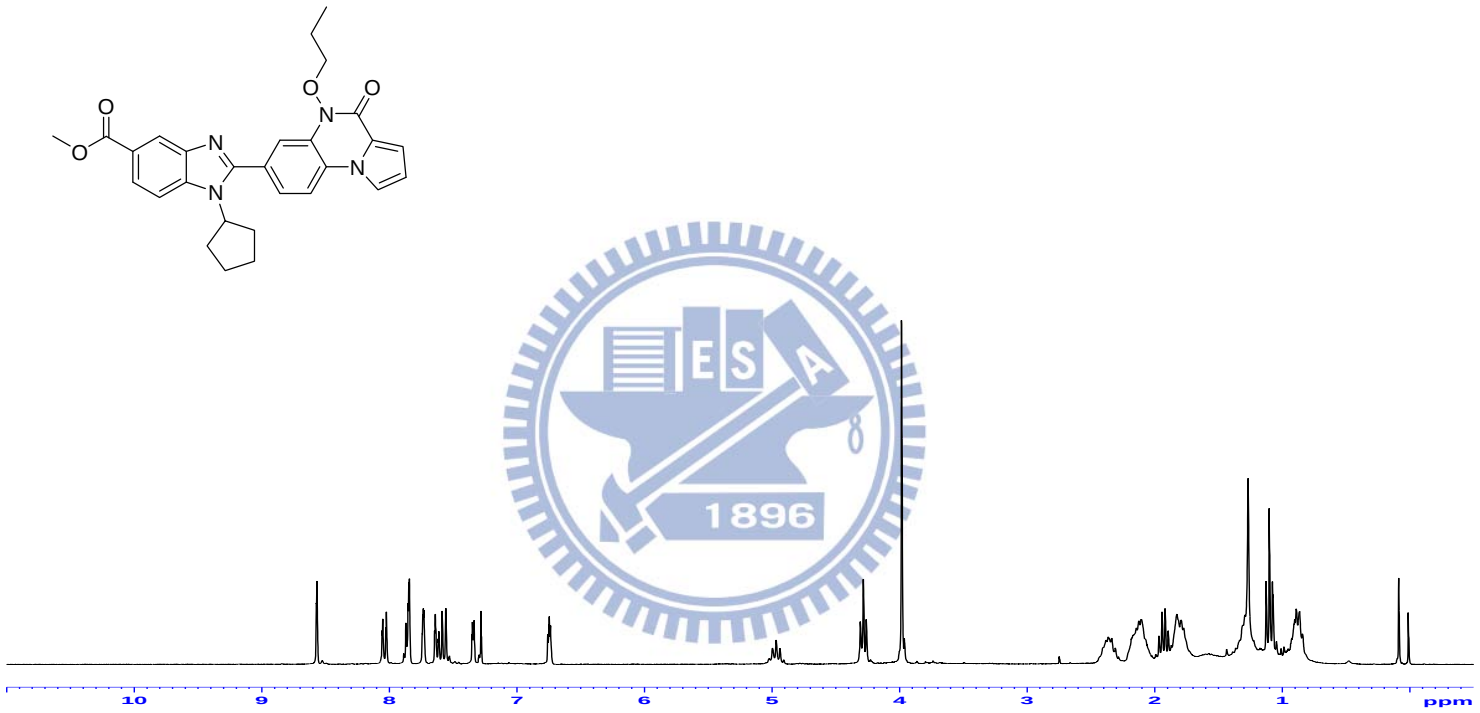
^{13}C NMR spectrum (75 MHz) of compound 21a in $CDCl_3$



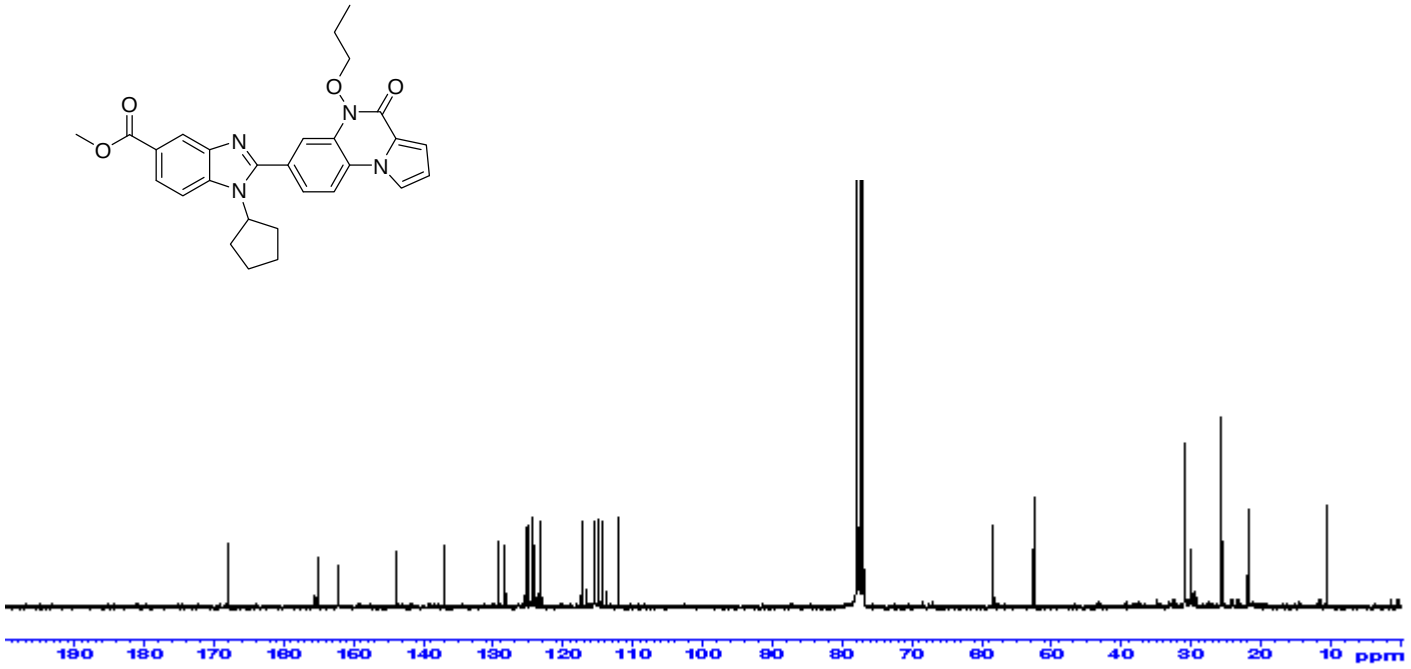
^{1}HNMR spectrum (300 MHz) of compound 21b in $CDCl_3$



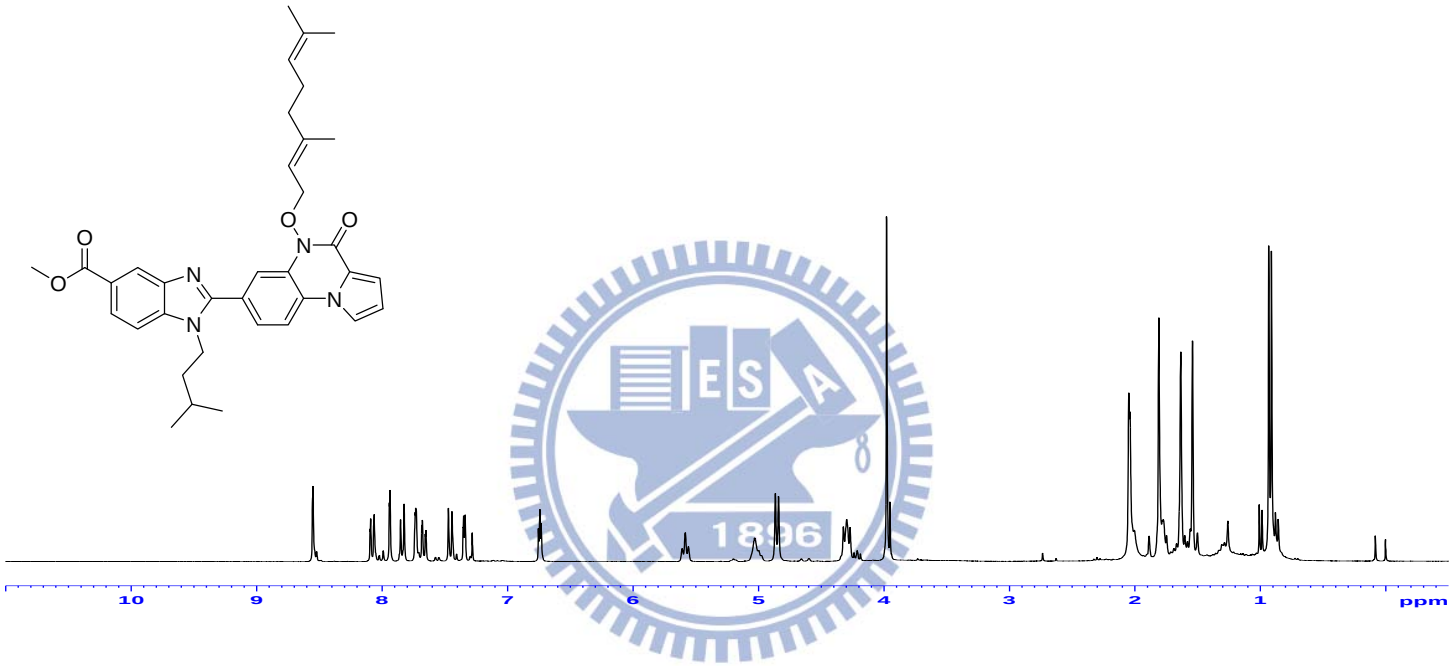
^{13}C NMR spectrum (75 MHz) of compound 21b in $CDCl_3$



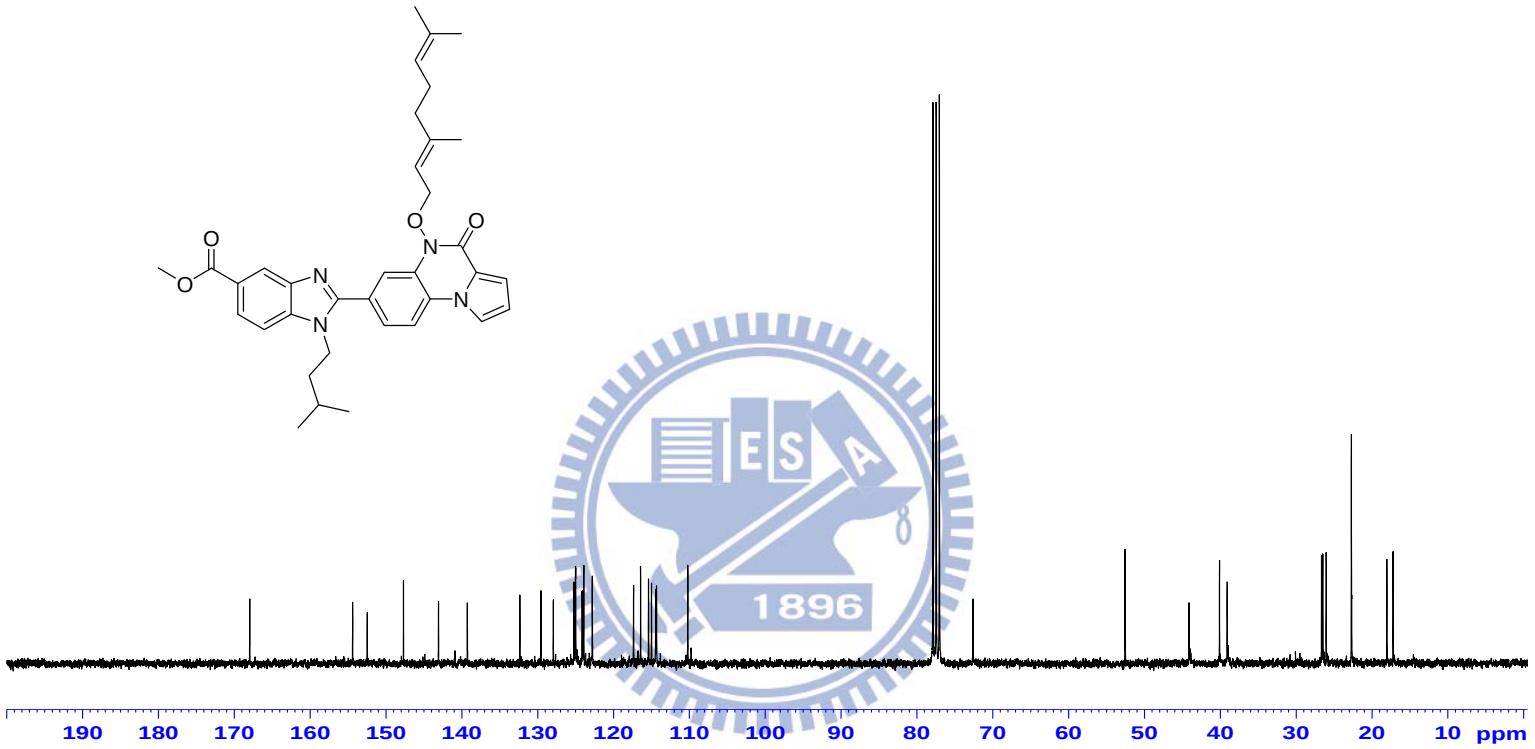
^{1}HNMR spectrum (300 MHz) of compound 21c in $CDCl_3$



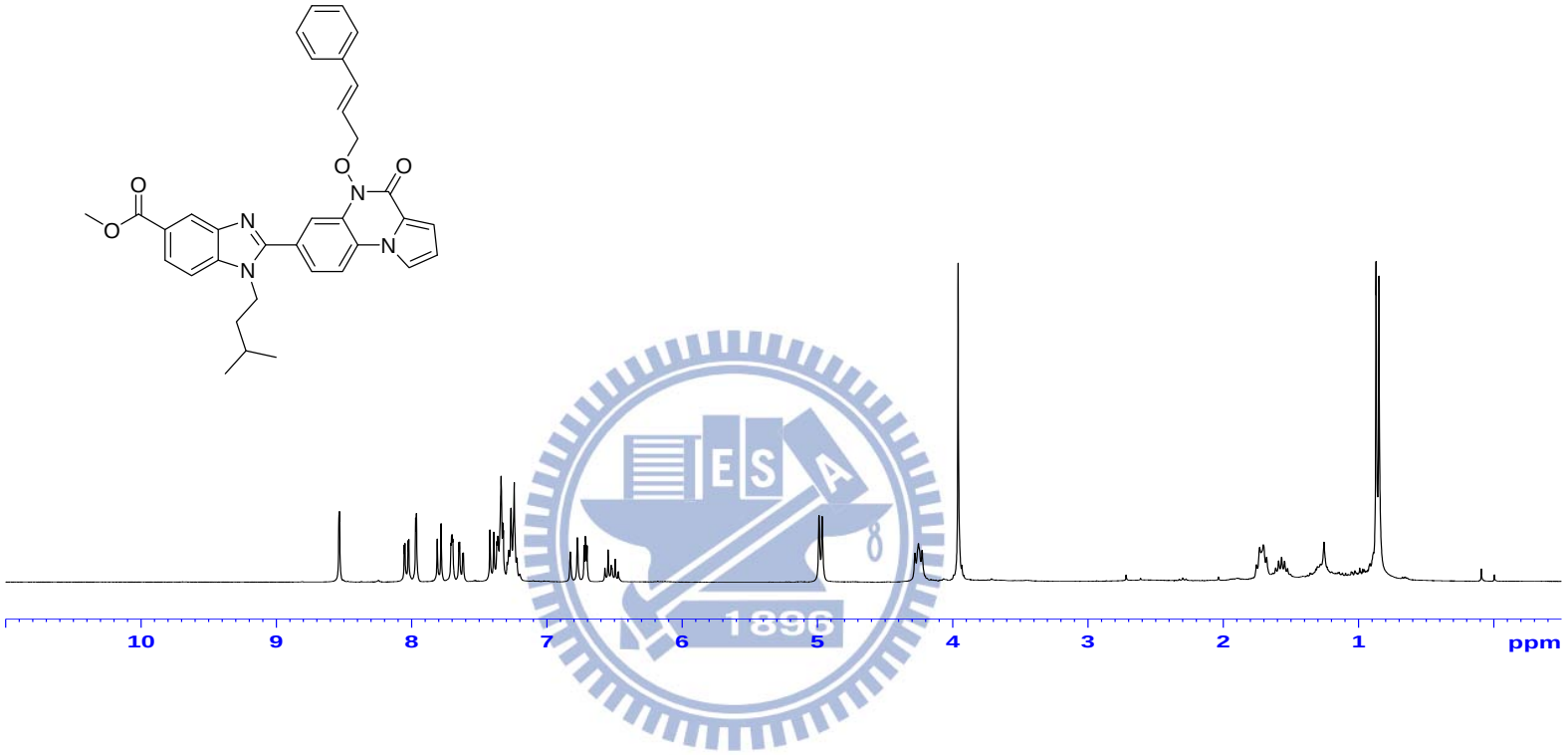
^{13}C NMR spectrum (75 MHz) of compound 21c in $CDCl_3$



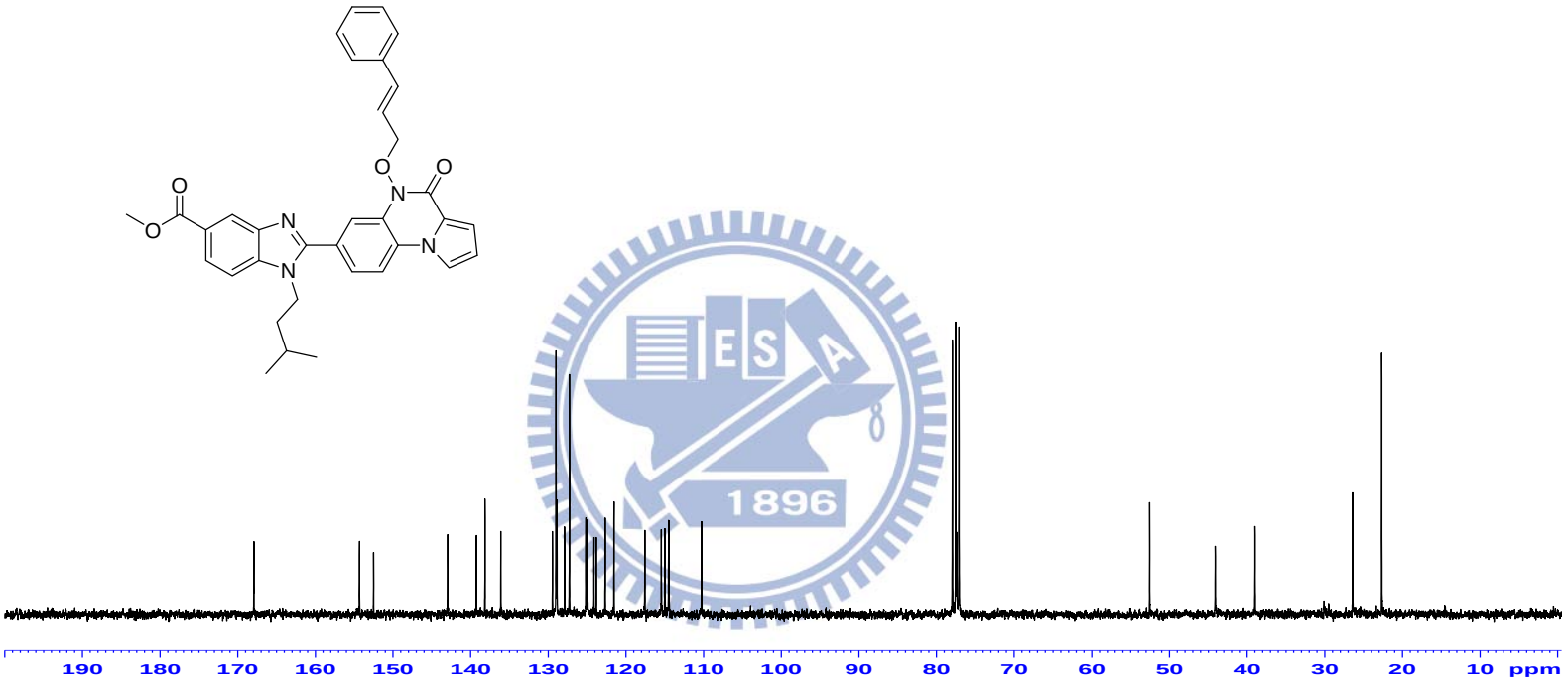
^{1}HNMR spectrum (300 MHz) of compound 21d in $CDCl_3$



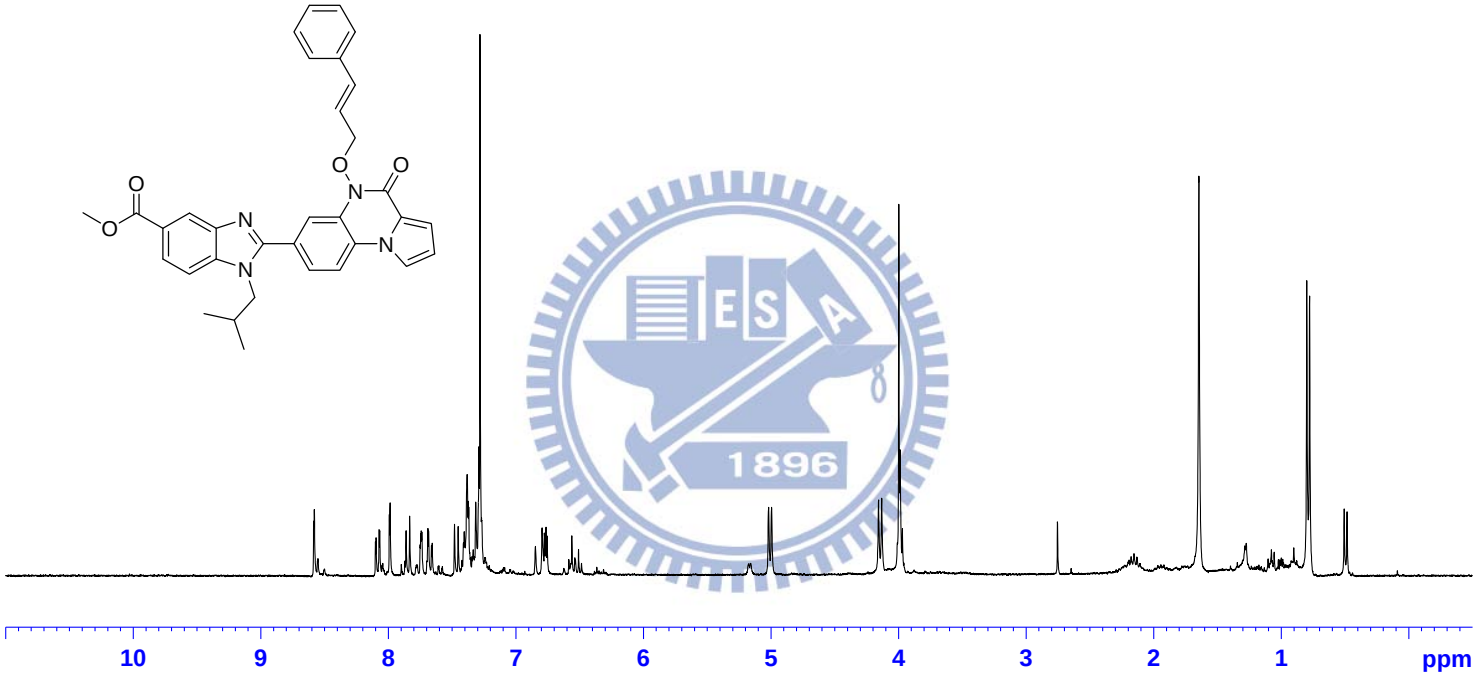
^{13}C NMR spectrum (75 MHz) of compound 21d in $CDCl_3$



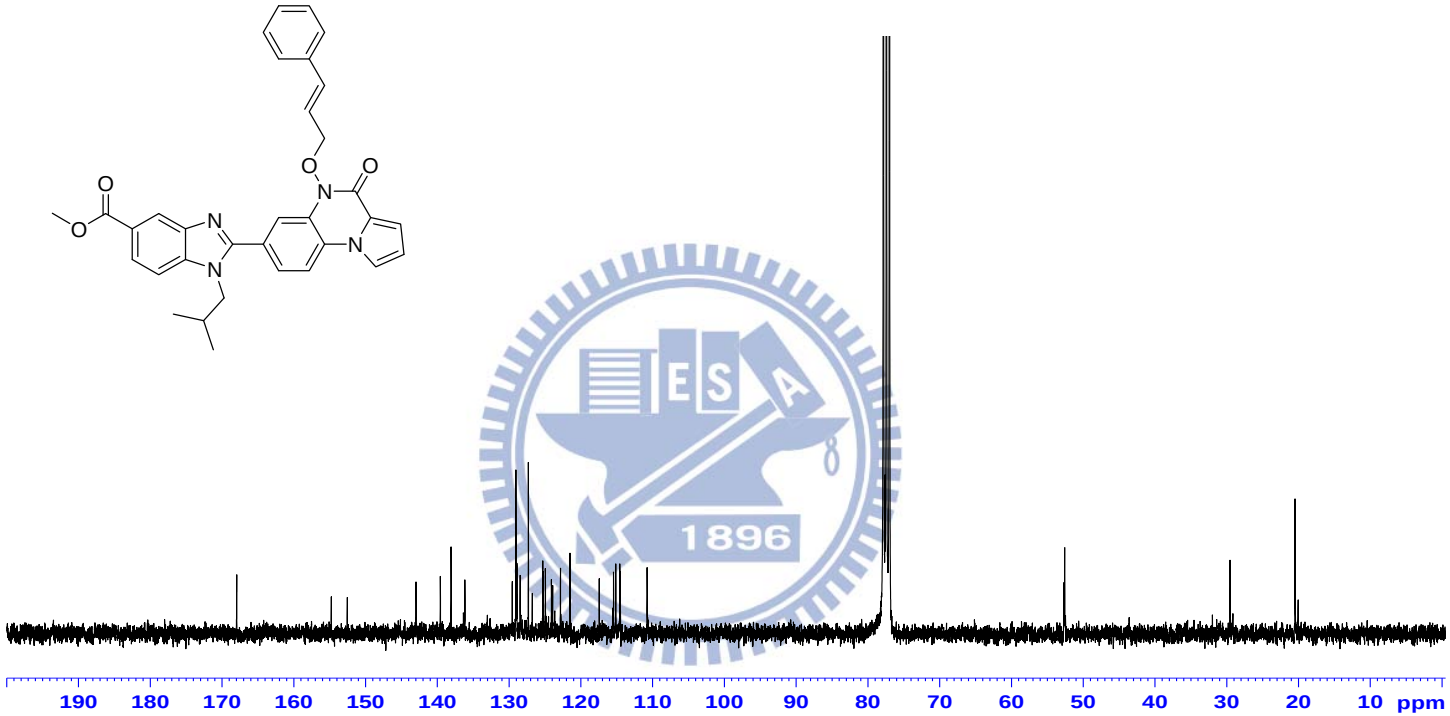
^{1}HNMR spectrum (300 MHz) of compound 21e in $CDCl_3$



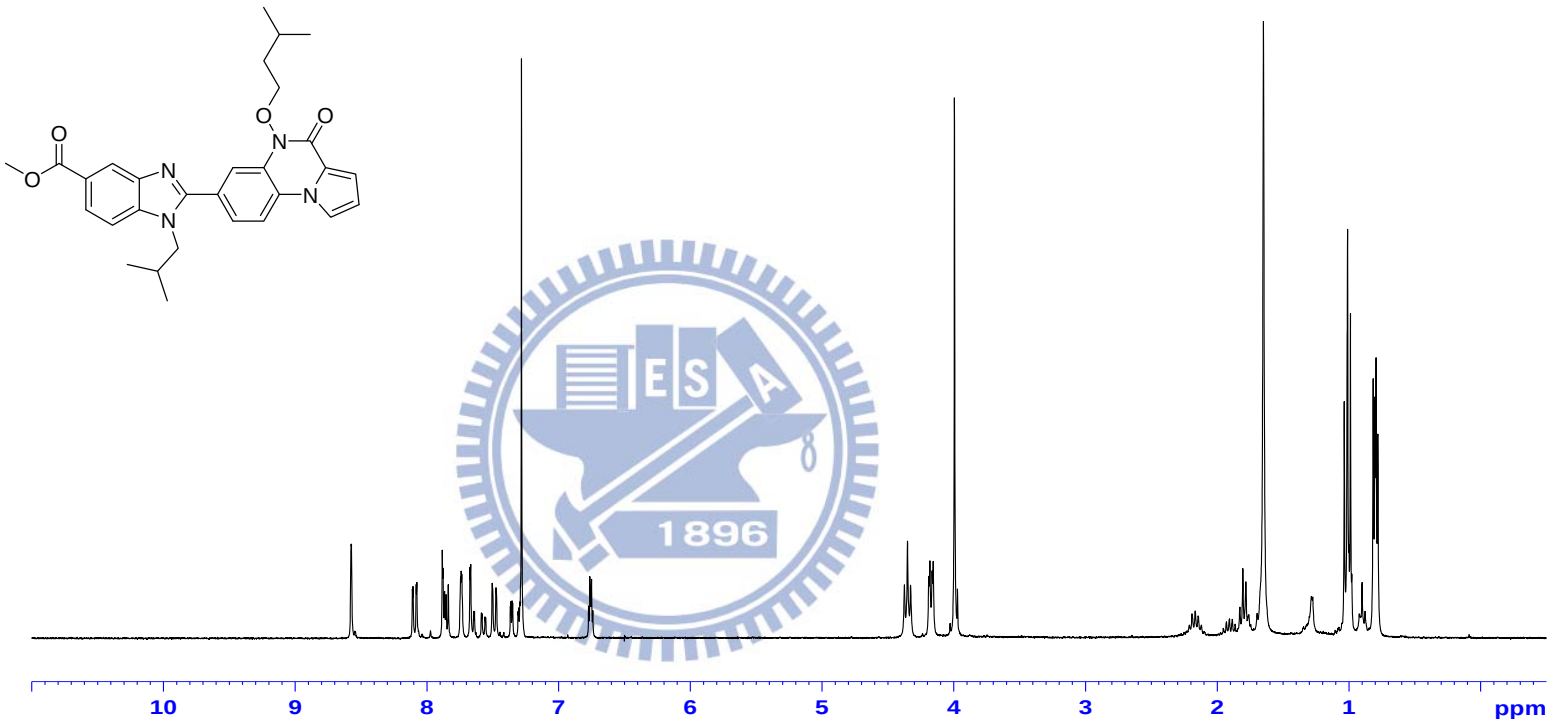
^{13}C NMR spectrum (75 MHz) of compound 21e in $CDCl_3$



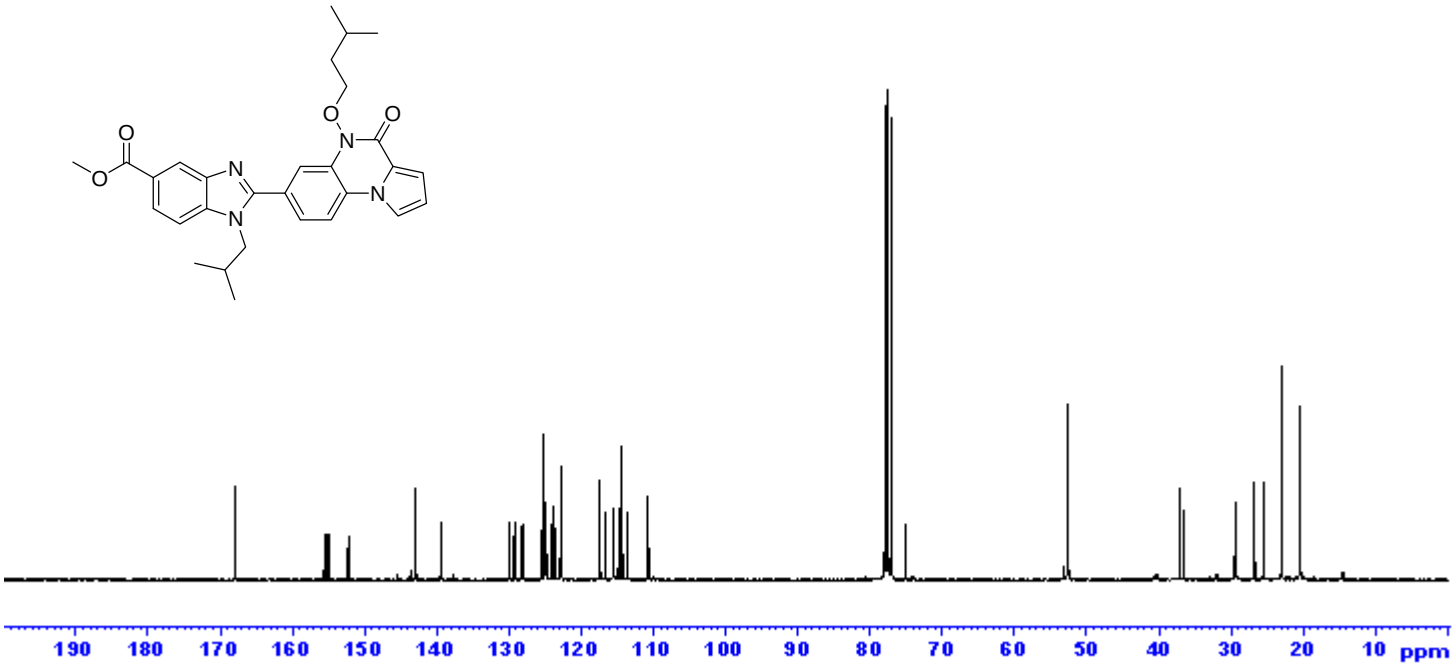
^{1}HNMR spectrum (300 MHz) of compound 21f in $CDCl_3$



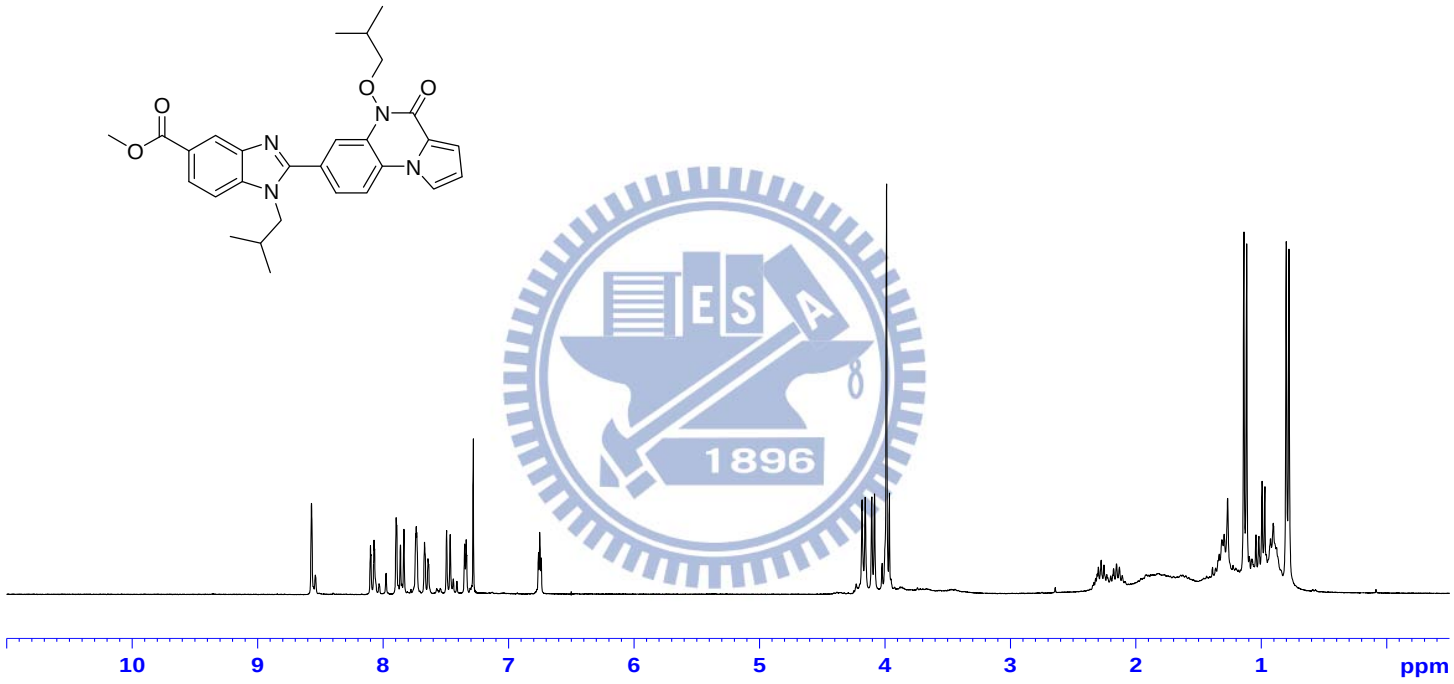
^{13}C NMR spectrum (75 MHz) of compound 21f in $CDCl_3$



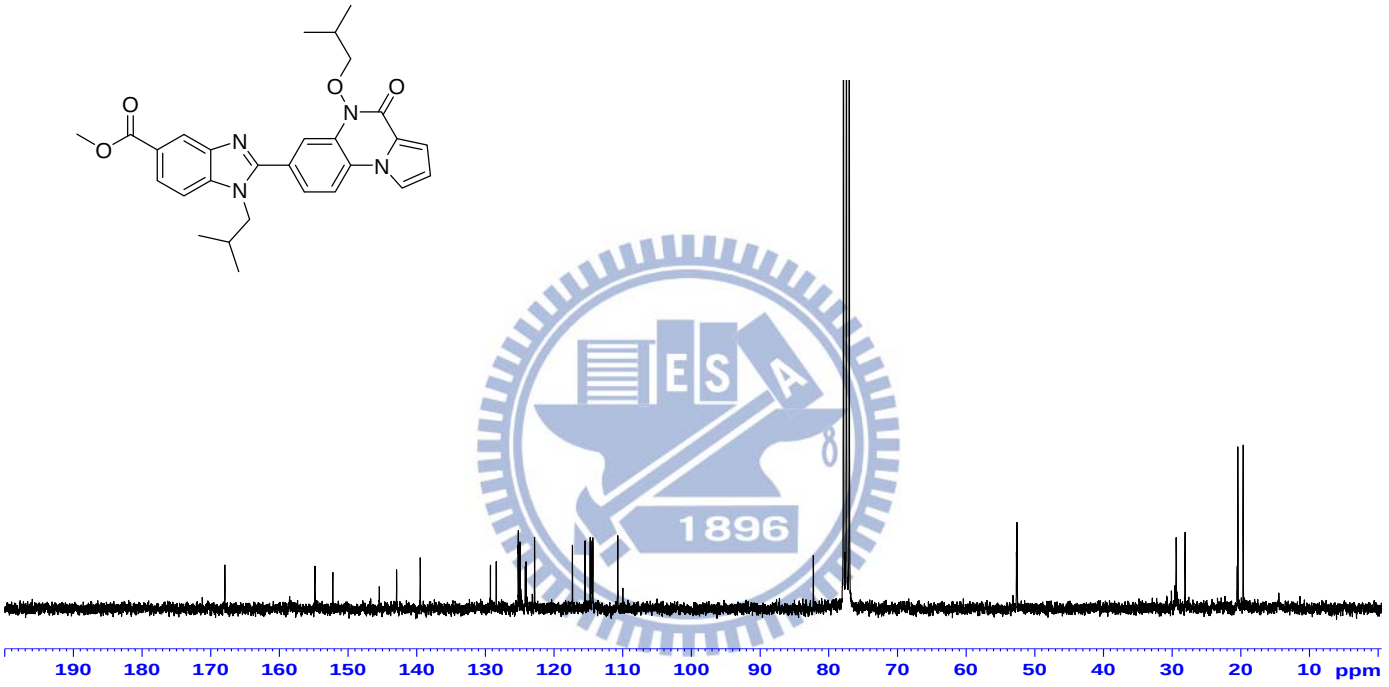
^{1}HNMR spectrum (300 MHz) of compound 21g in $CDCl_3$



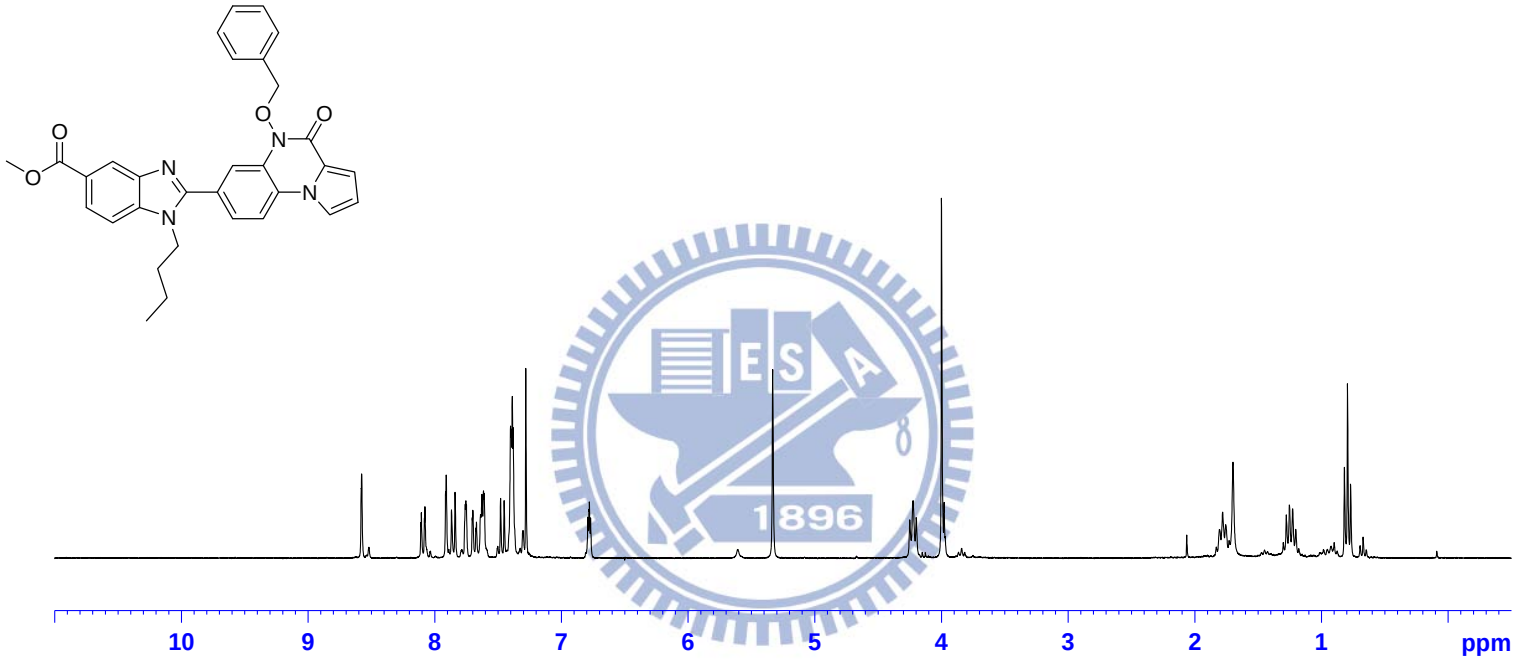
^{13}C NMR spectrum (75 MHz) of compound 21g in $CDCl_3$



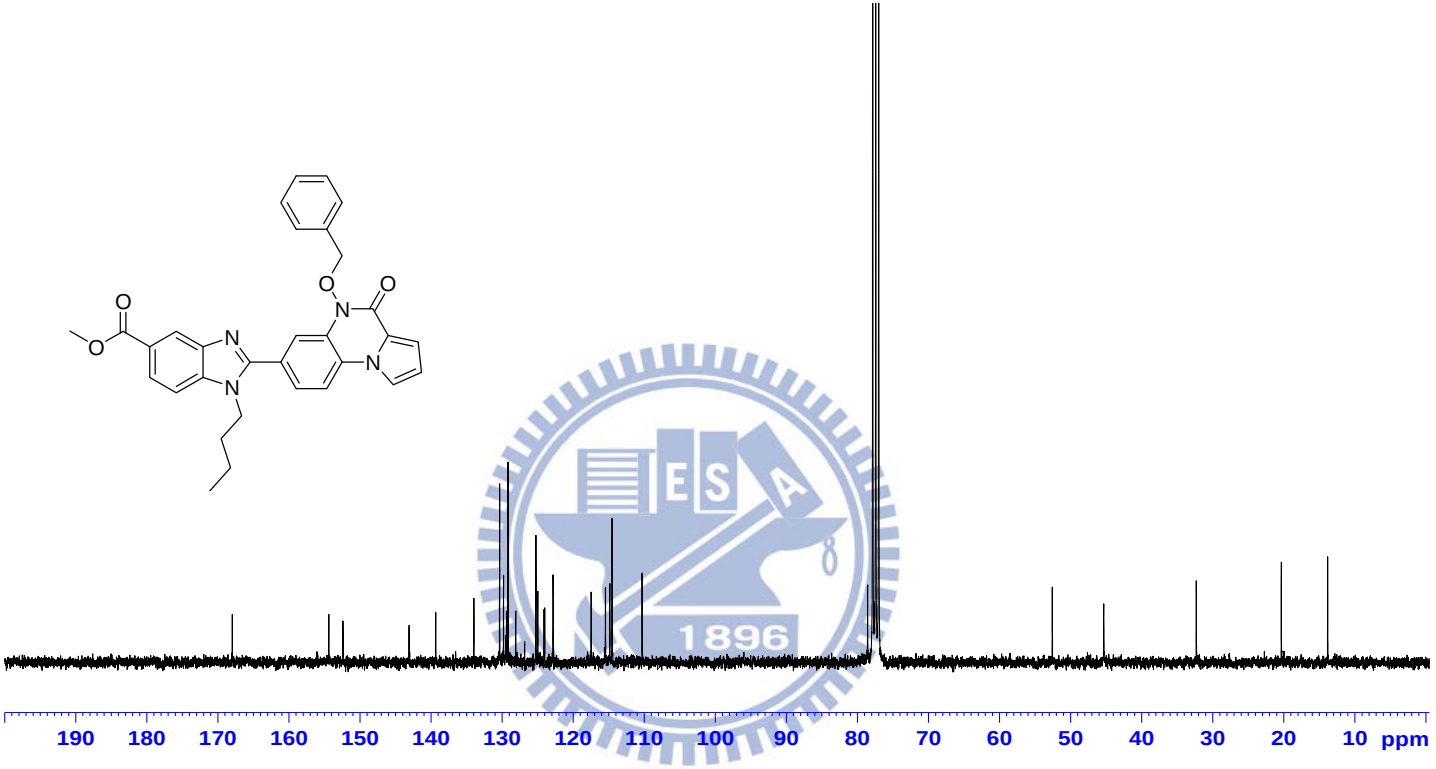
^{1}HNMR spectrum (300 MHz) of compound 21h in $CDCl_3$



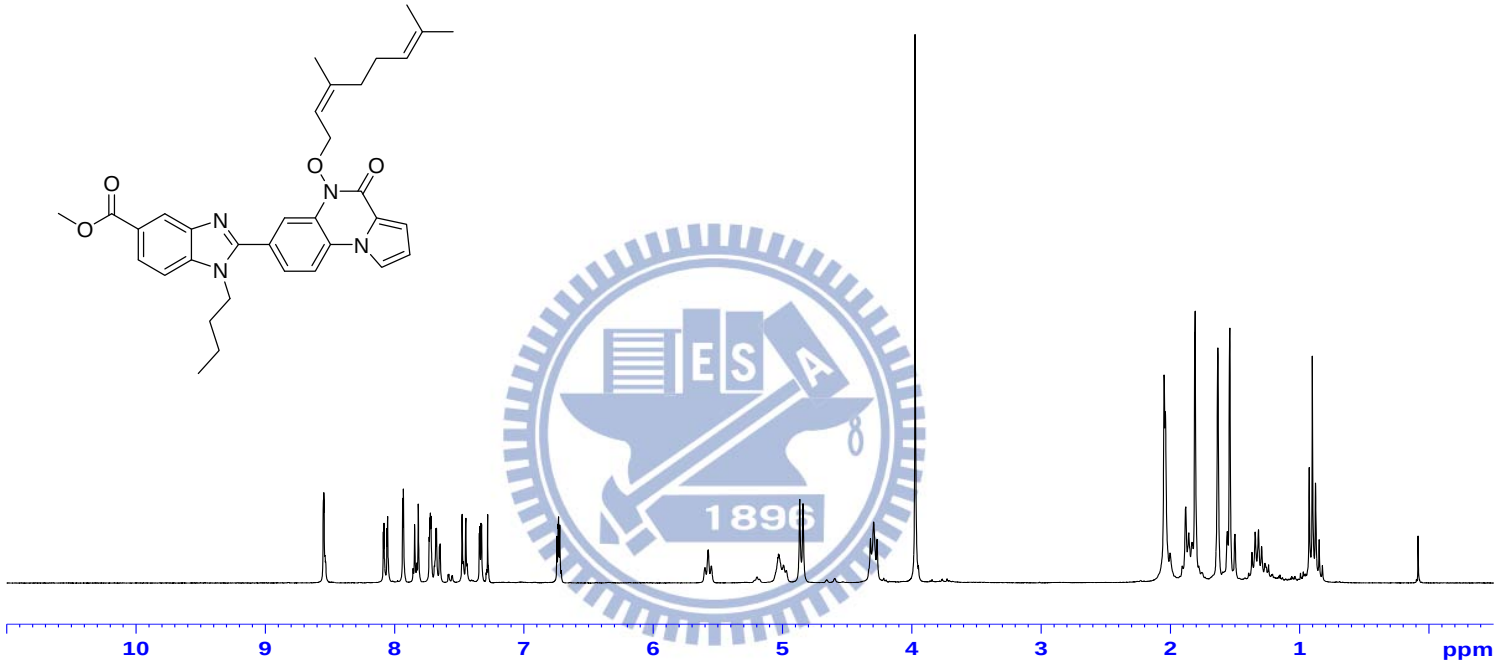
^{13}C NMR spectrum (75 MHz) of compound 21h in $CDCl_3$



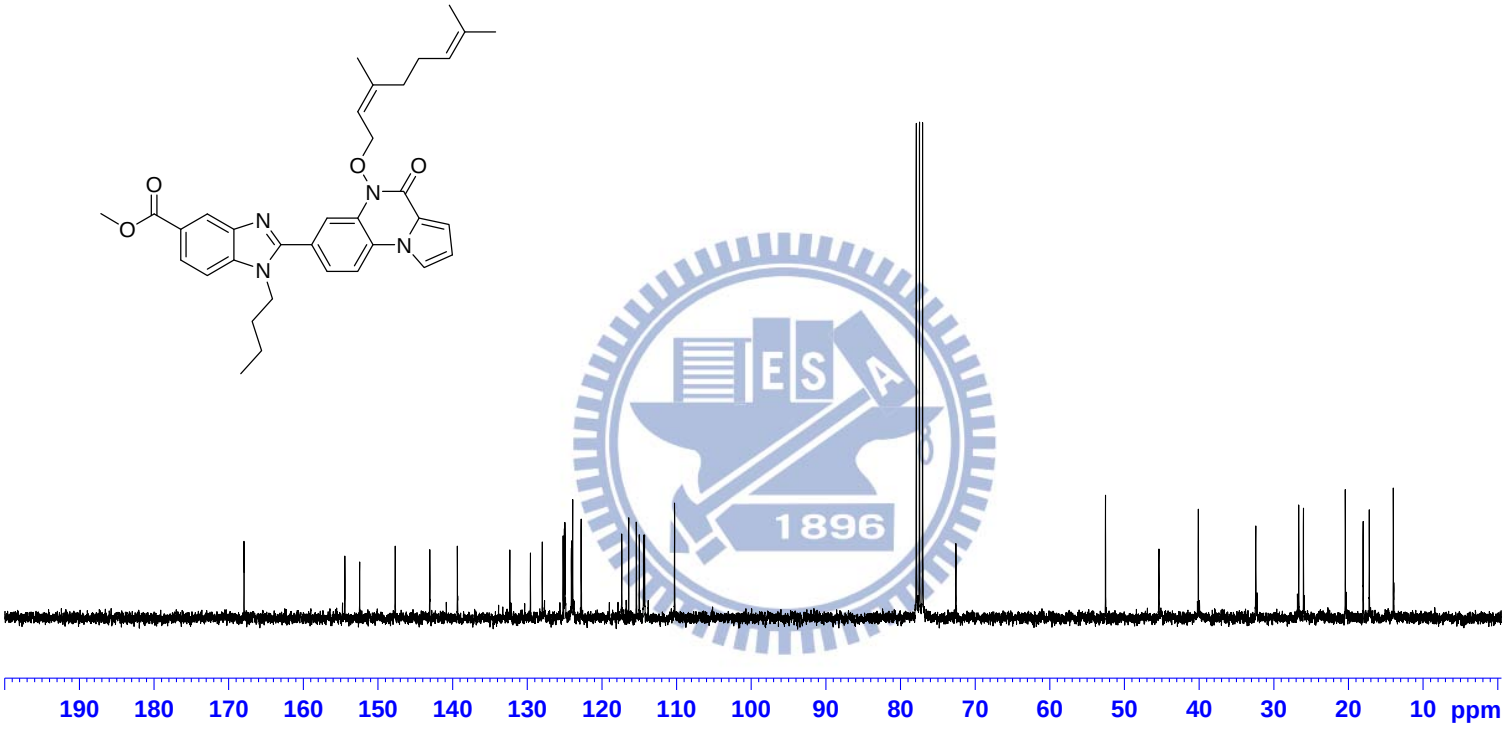
^{1}HNMR spectrum (300 MHz) of compound 21i in $CDCl_3$



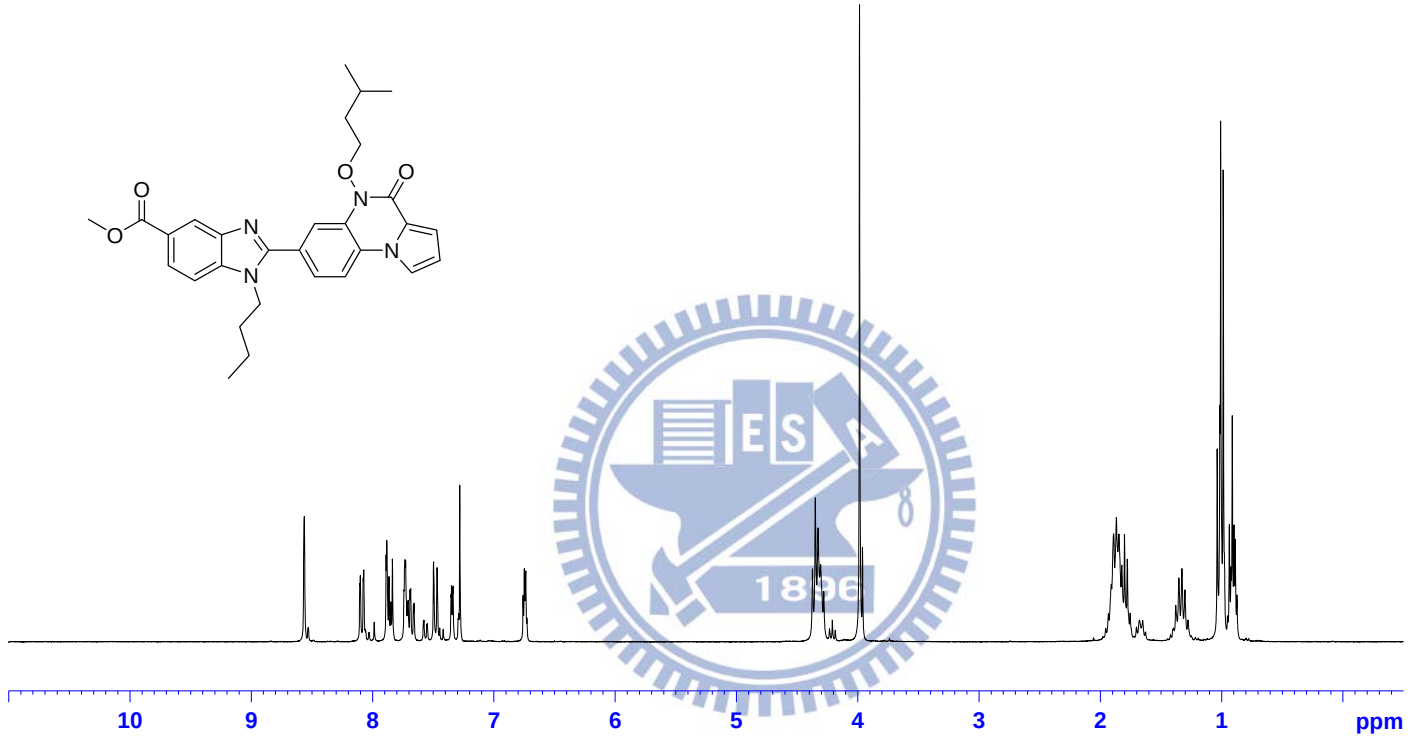
^{13}C NMR spectrum (75 MHz) of compound 21i in $CDCl_3$



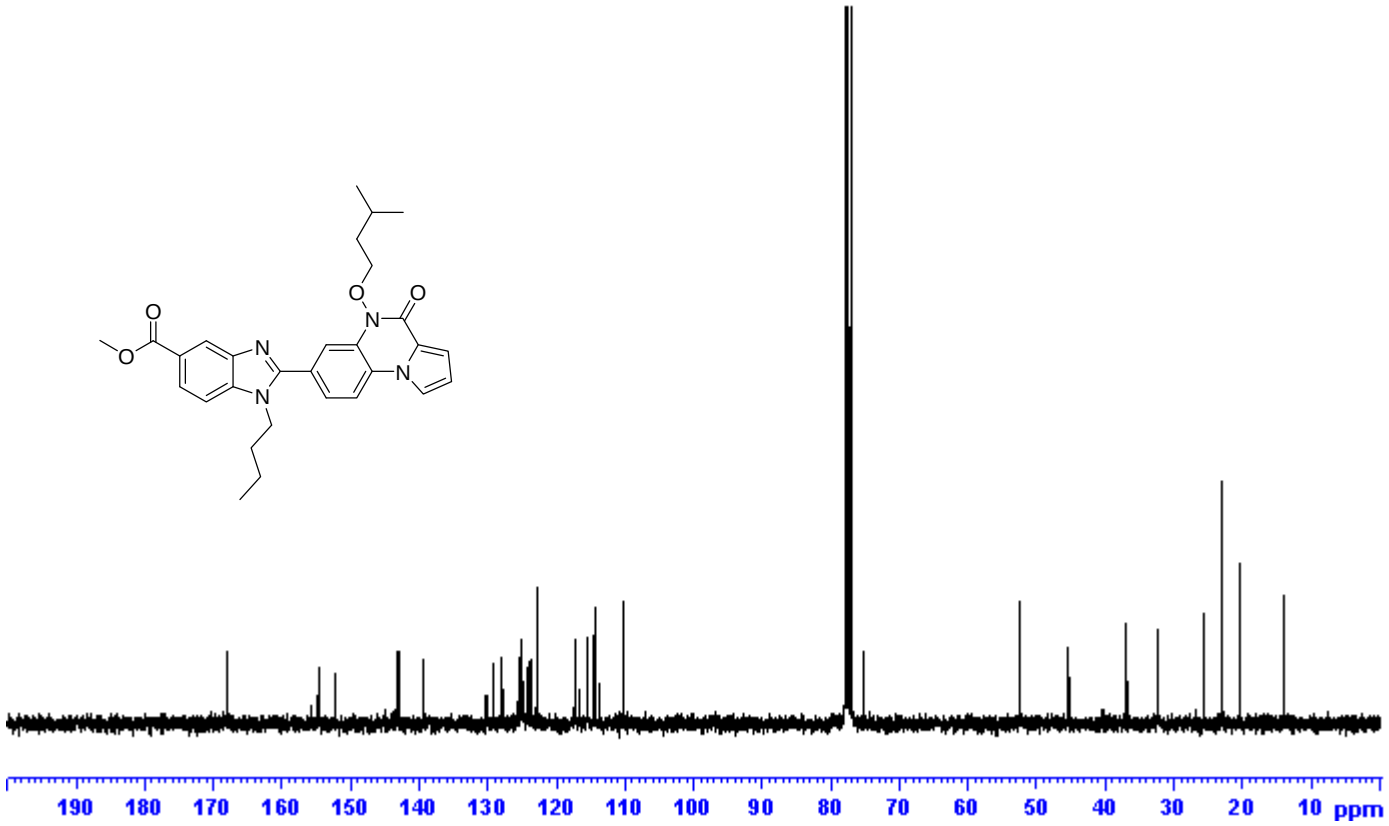
^{1}HNMR spectrum (300 MHz) of compound 21j in $CDCl_3$



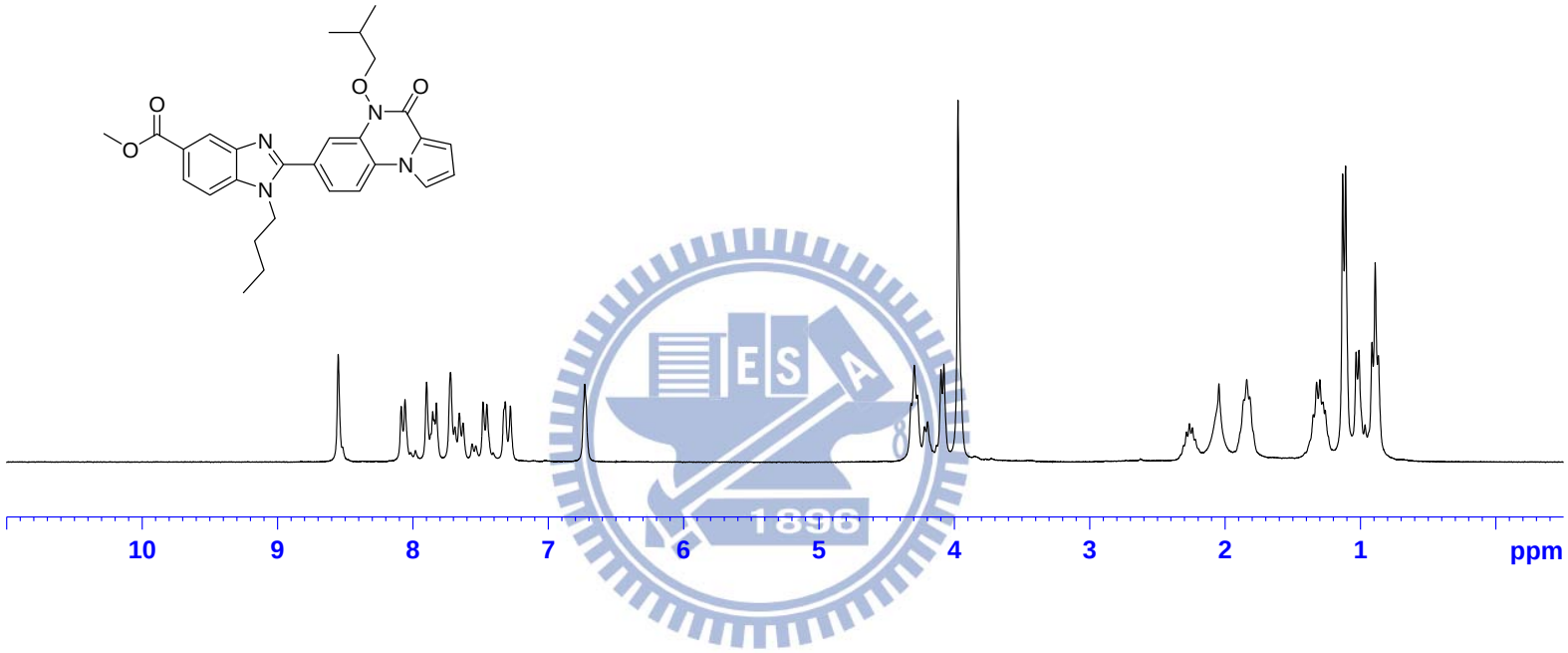
^{13}C NMR spectrum (75 MHz) of compound 21j in $CDCl_3$



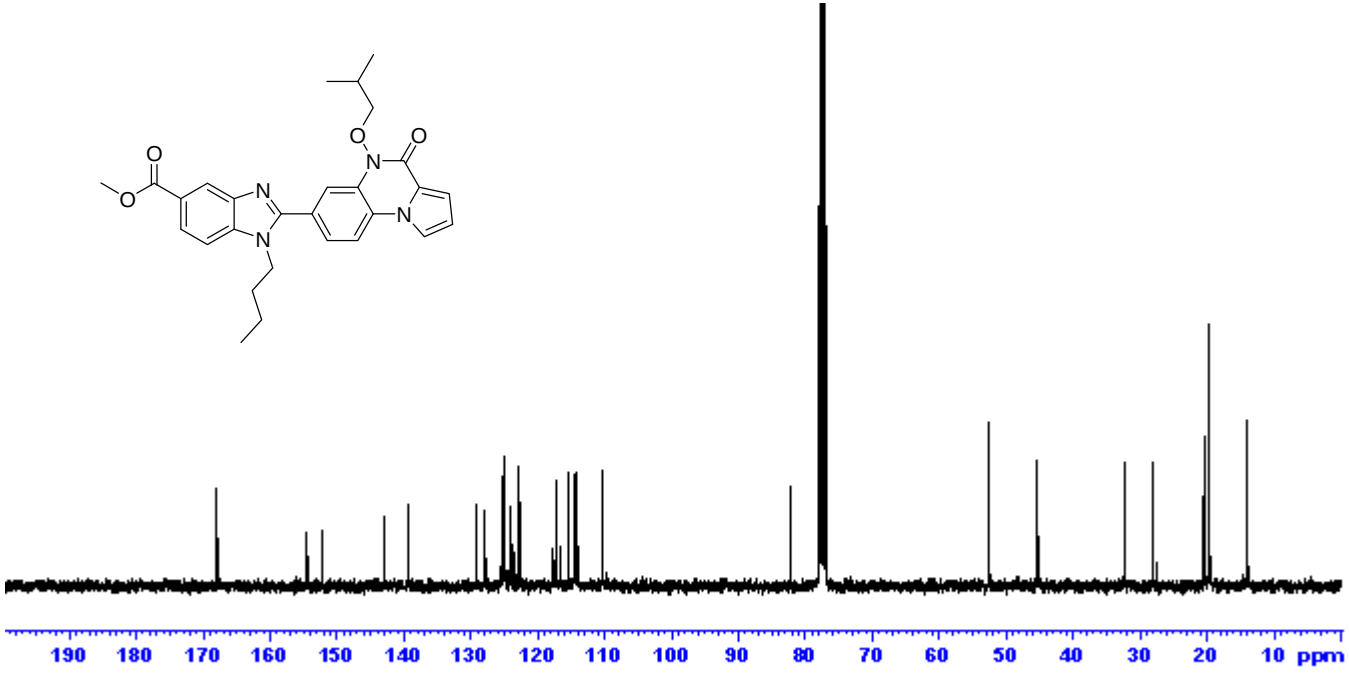
^{1}HNMR spectrum (300 MHz) of compound 21k in $CDCl_3$



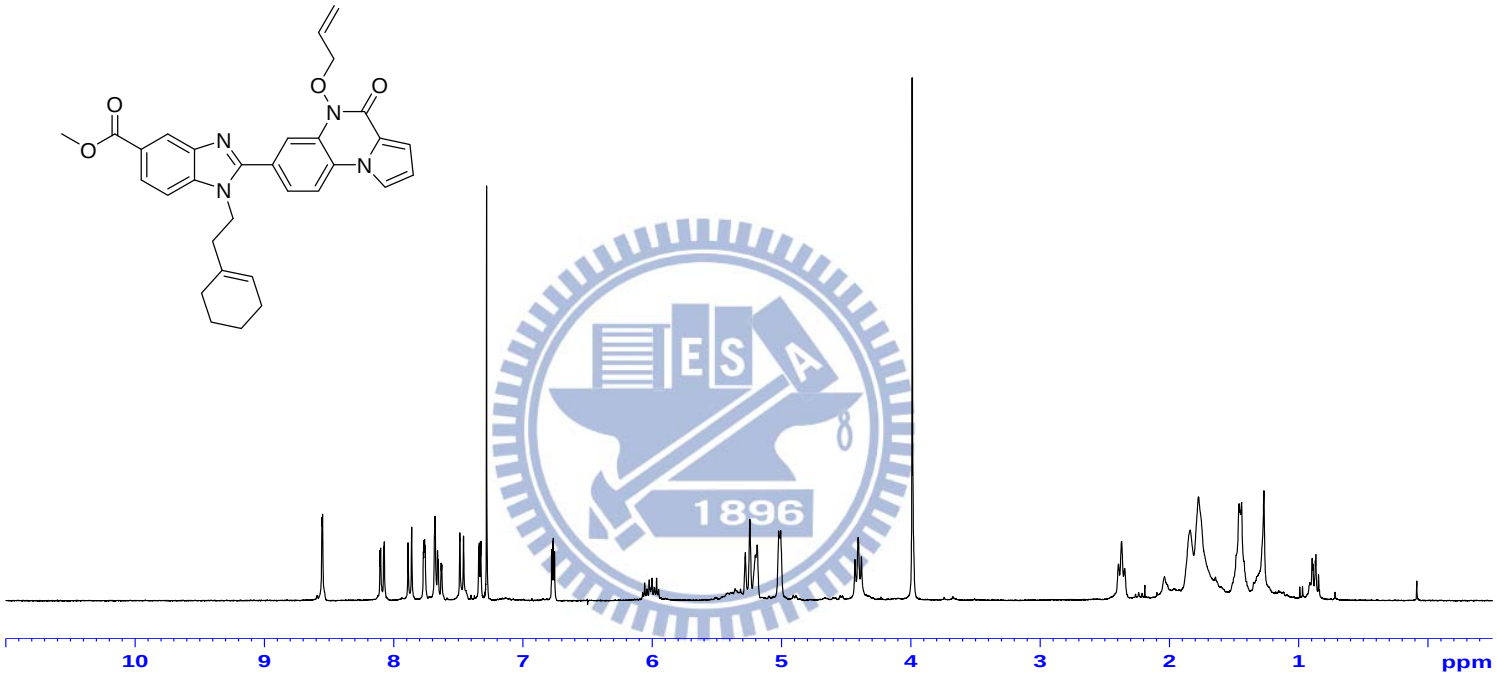
^{13}C NMR spectrum (75 MHz) of compound 21k in $CDCl_3$



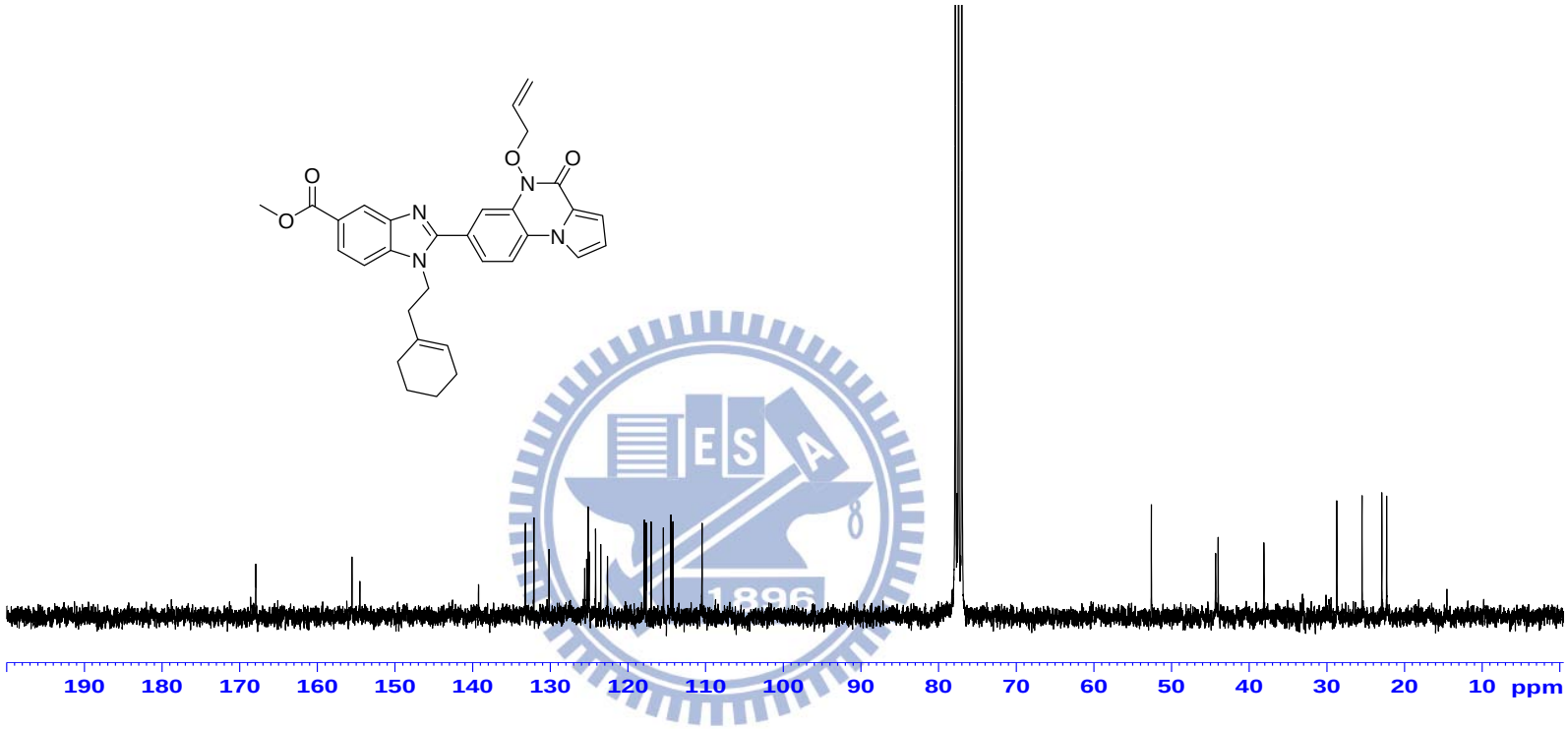
^{1}HNMR spectrum (300 MHz) of compound 21l in $CDCl_3$



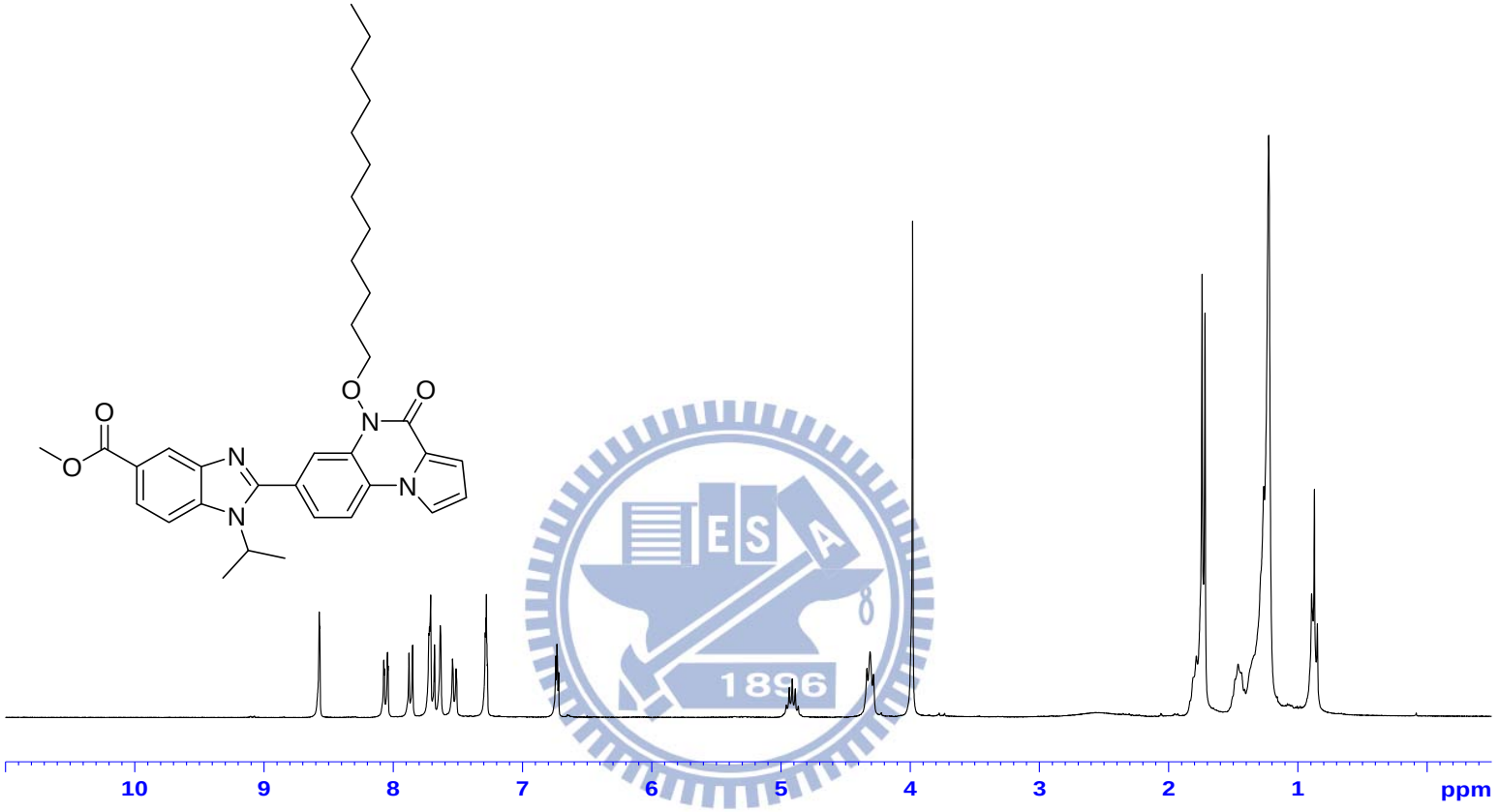
^{13}C NMR spectrum (75 MHz) of compound 21l in $CDCl_3$



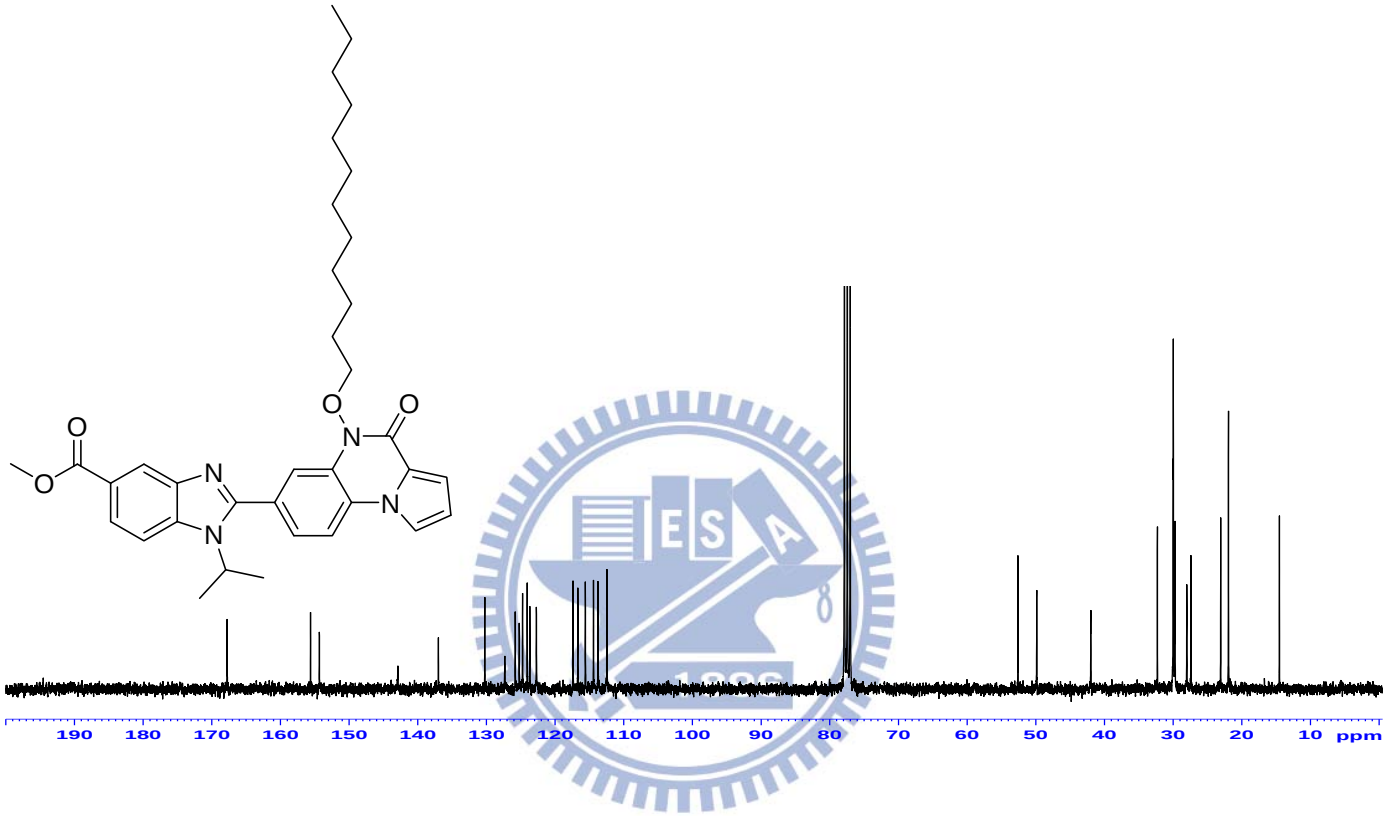
^{1}HNMR spectrum (300 MHz) of compound 21m in $CDCl_3$



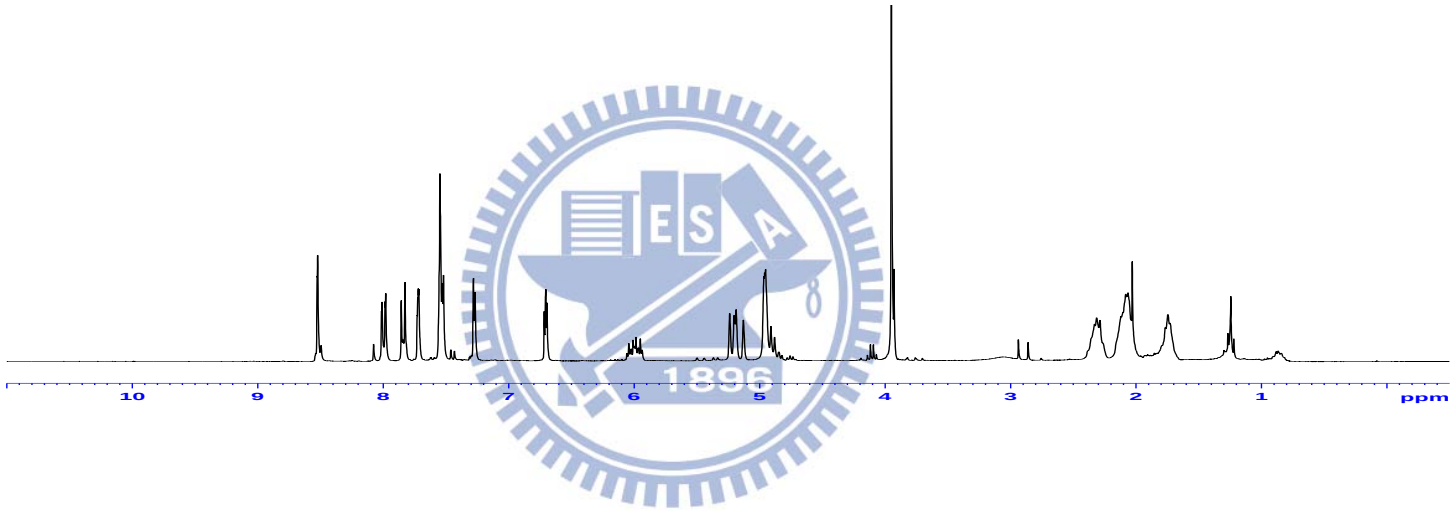
^{13}C NMR spectrum (75 MHz) of compound 21m in $CDCl_3$



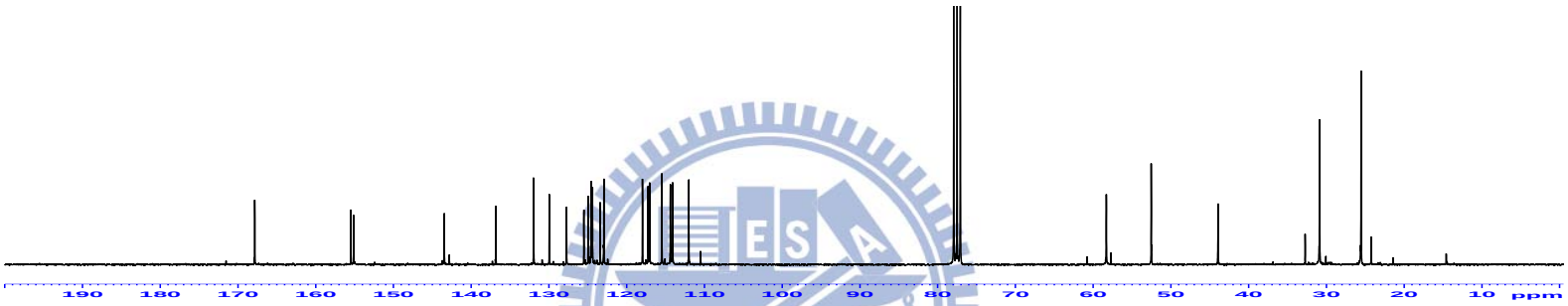
^{1}HNMR spectrum (300 MHz) of compound 21m in $CDCl_3$



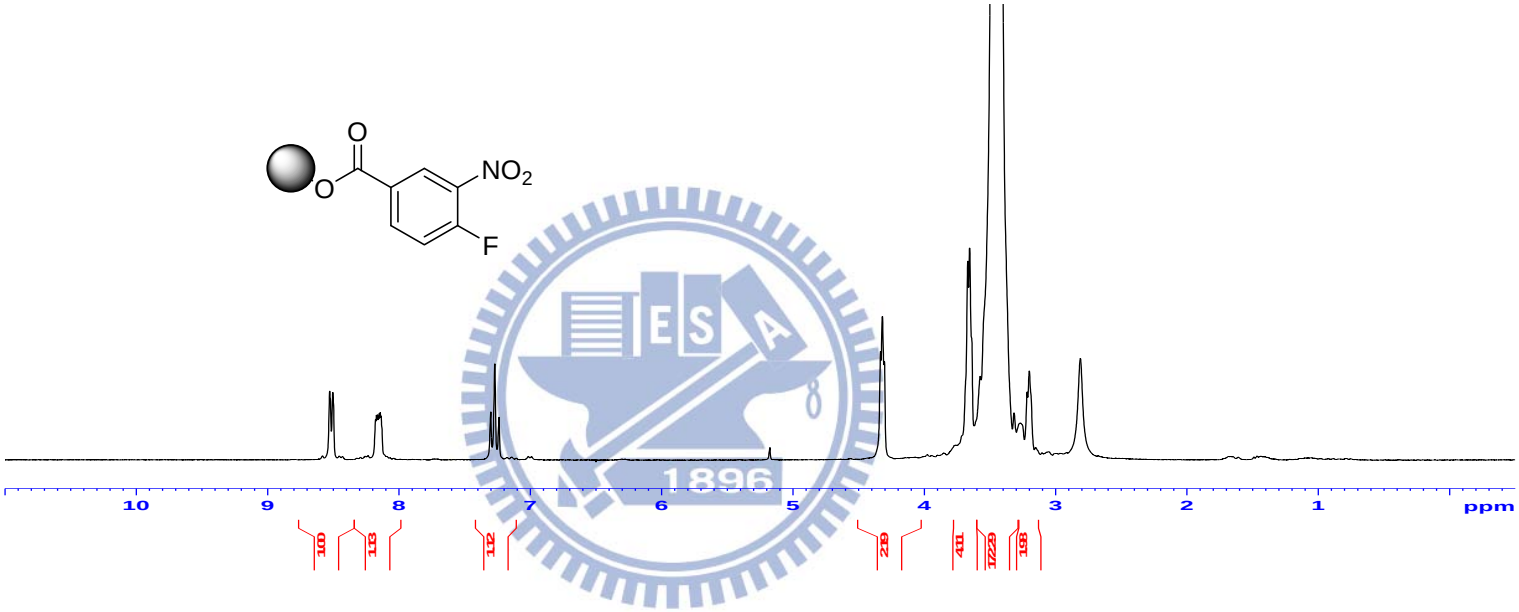
^{13}C NMR spectrum (75 MHz) of compound 21m in $CDCl_3$



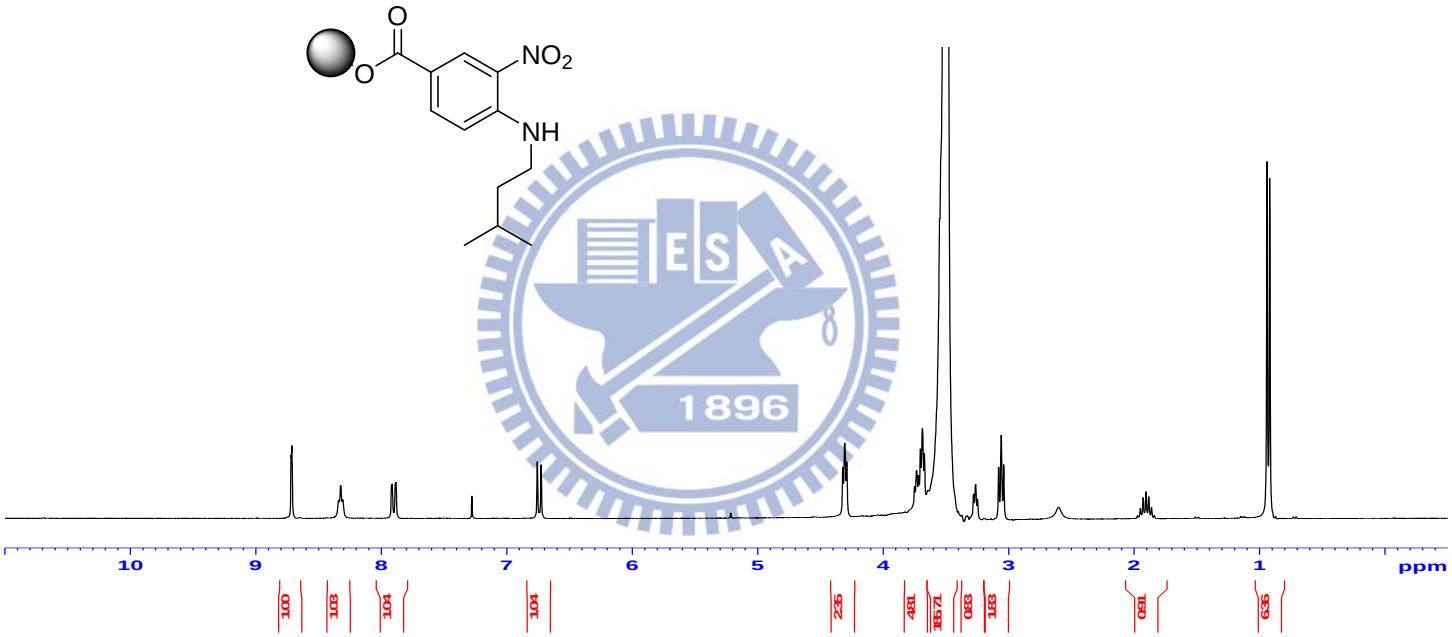
^{1}HNMR spectrum (300 MHz) of compound 21m in $CDCl_3$



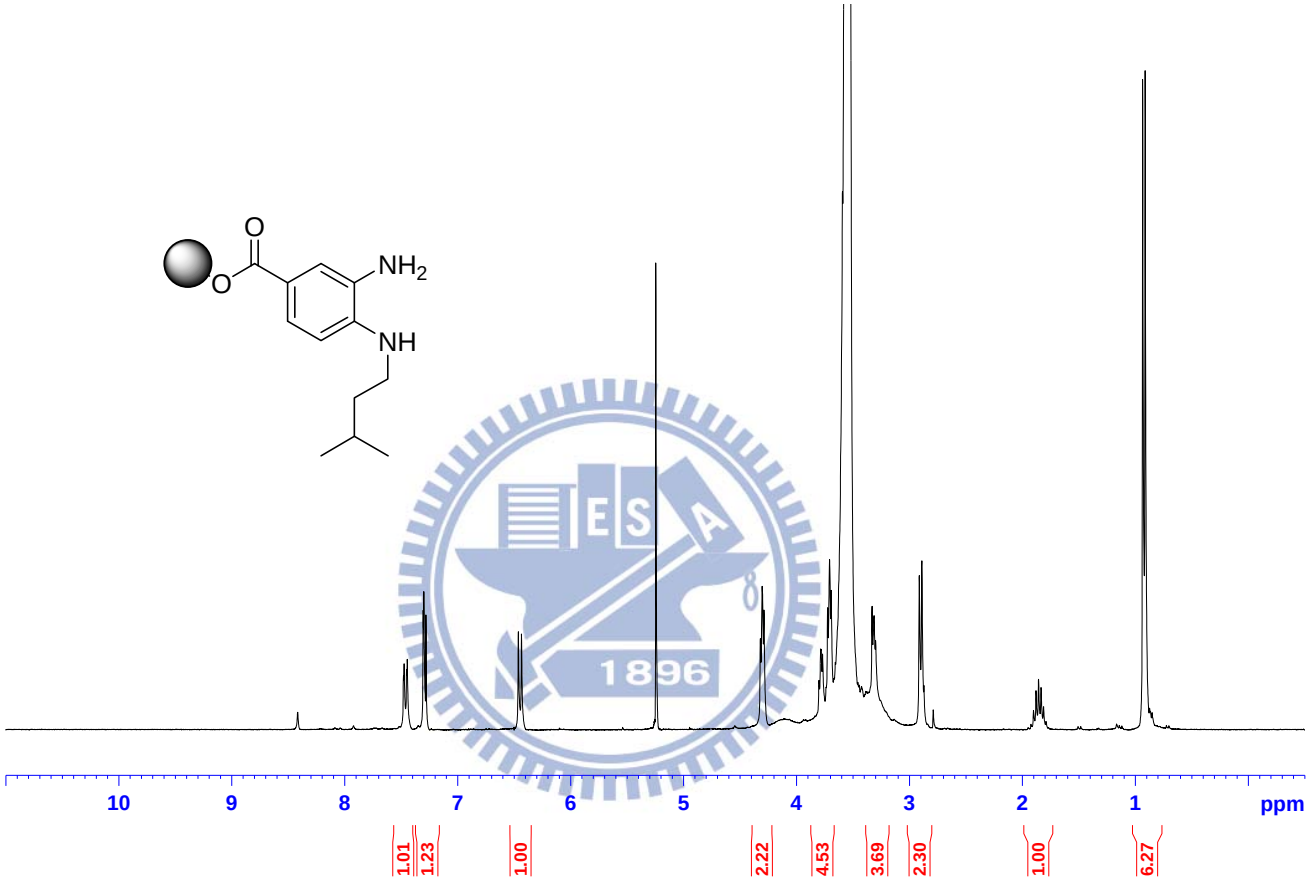
^{13}C NMR spectrum (75 MHz) of compound 21m in $CDCl_3$



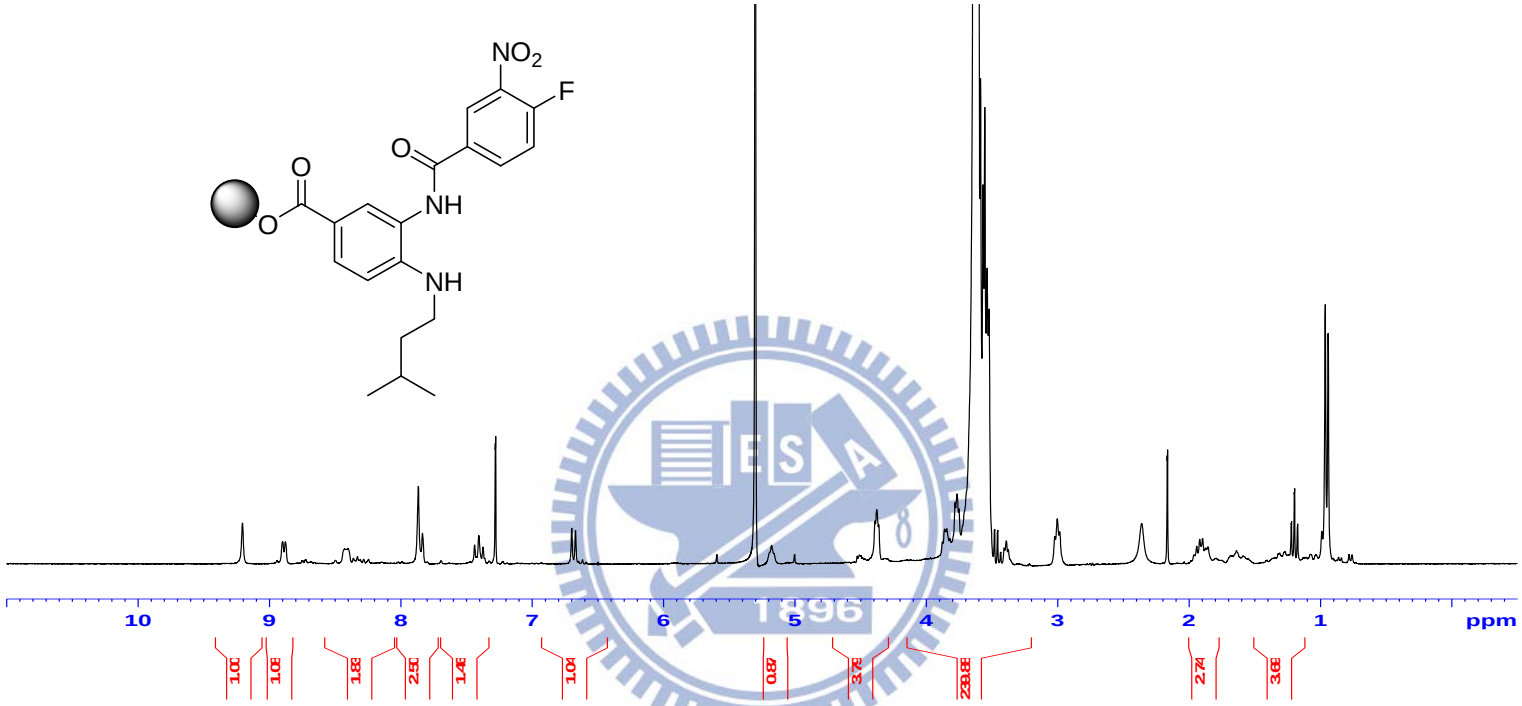
Stepwise ^{1}HNMR spectrum (300 MHz) of compound 4a in $CDCl_3$



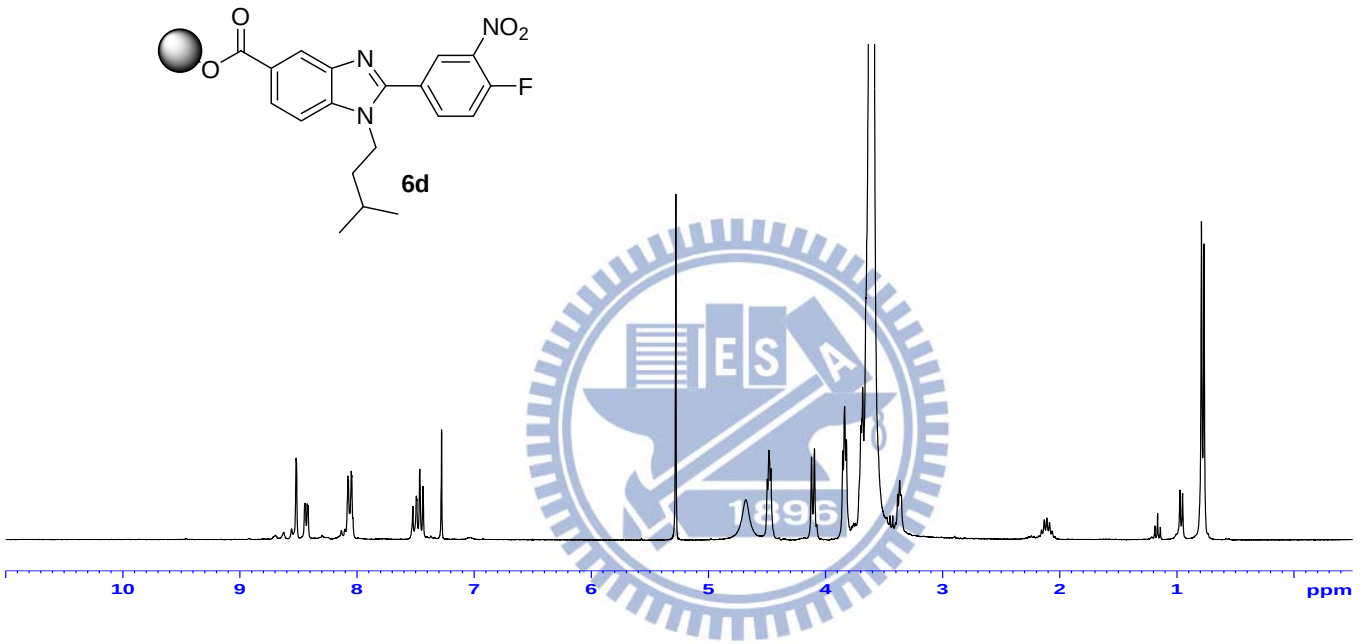
^{1}HNMR spectrum (300 MHz) of compound 4b in $CDCl_3$



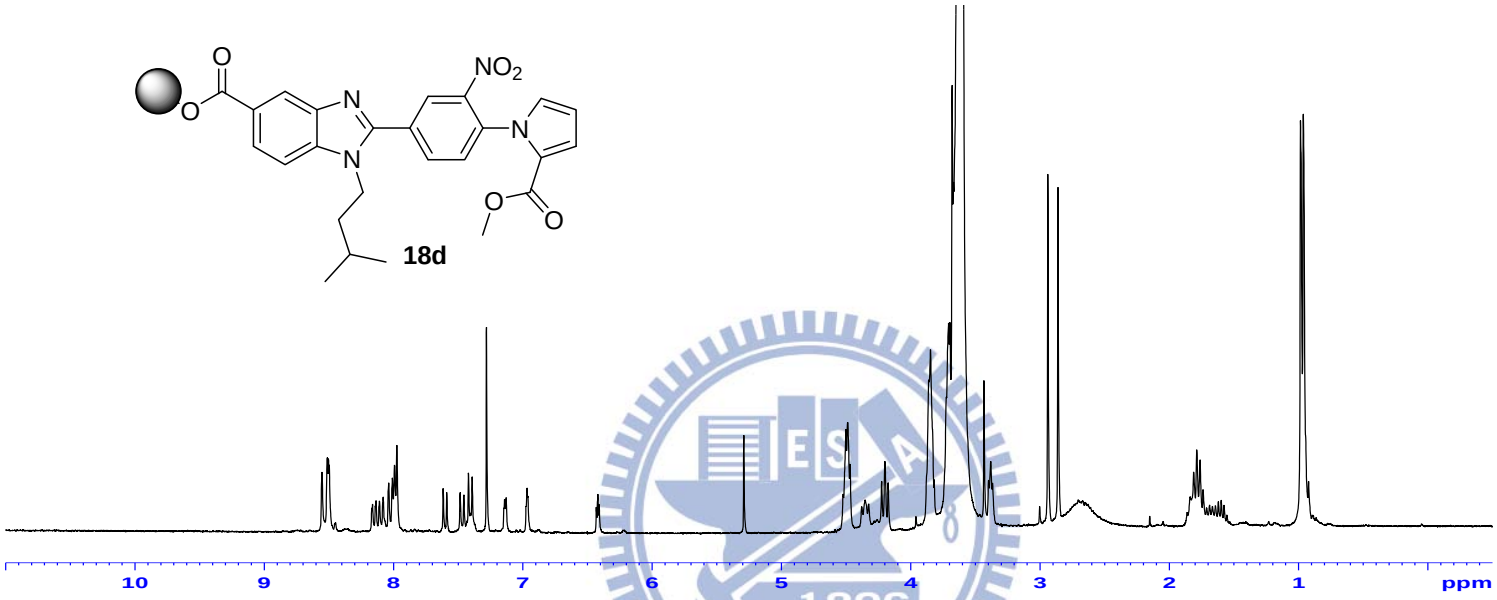
^{1}HNMR spectrum (300 MHz) of compound 4d in $CDCl_3$



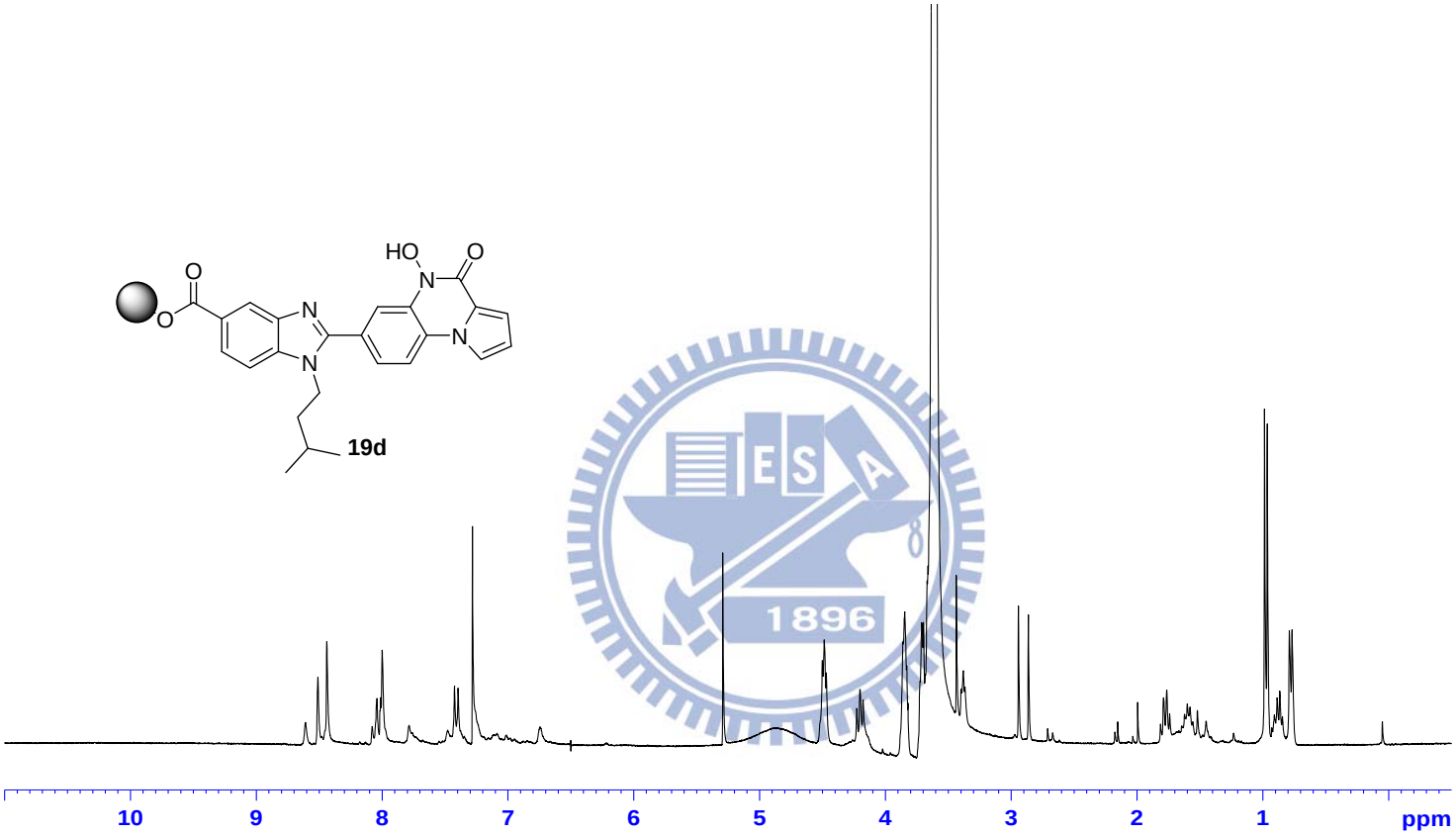
^{1}HNMR spectrum (300 MHz) of compound 5d in $CDCl_3$



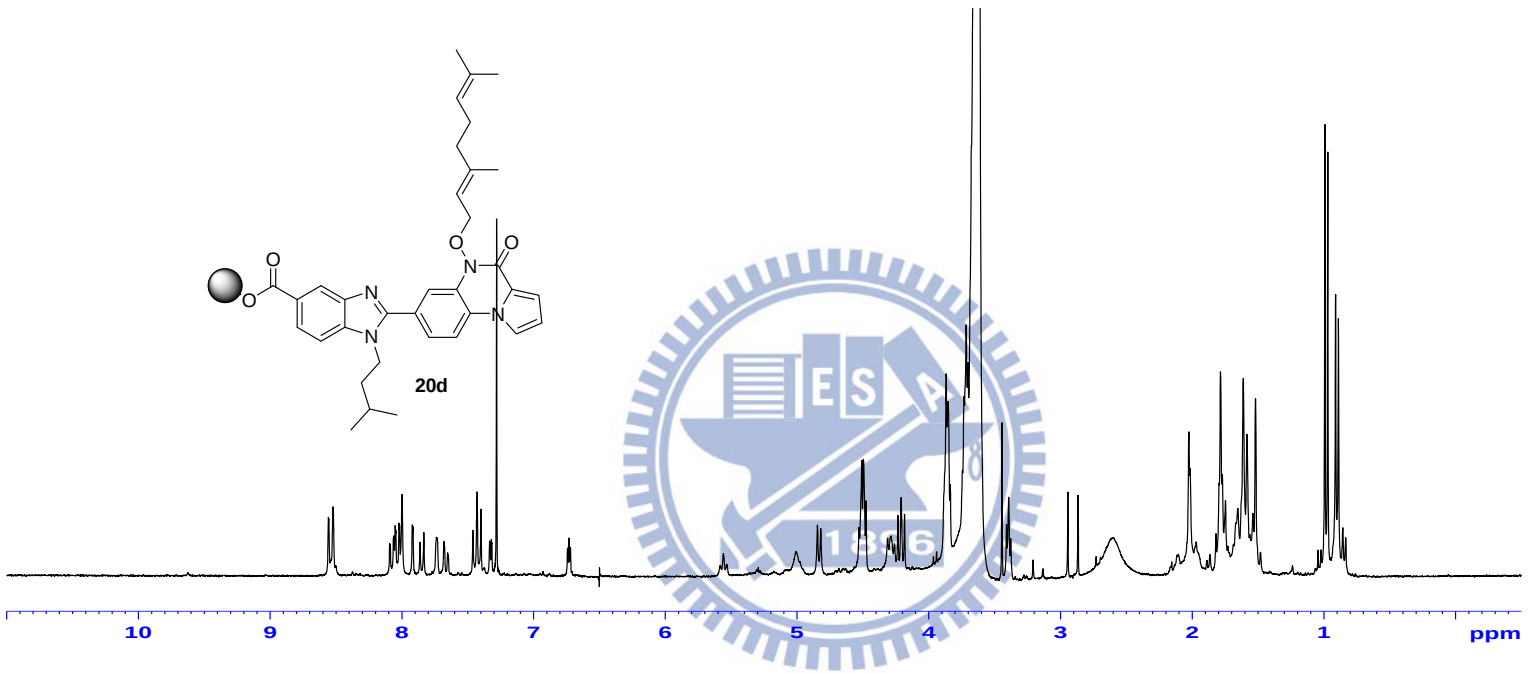
^{1}HNMR spectrum (300 MHz) of compound 10a in $CDCl_3$



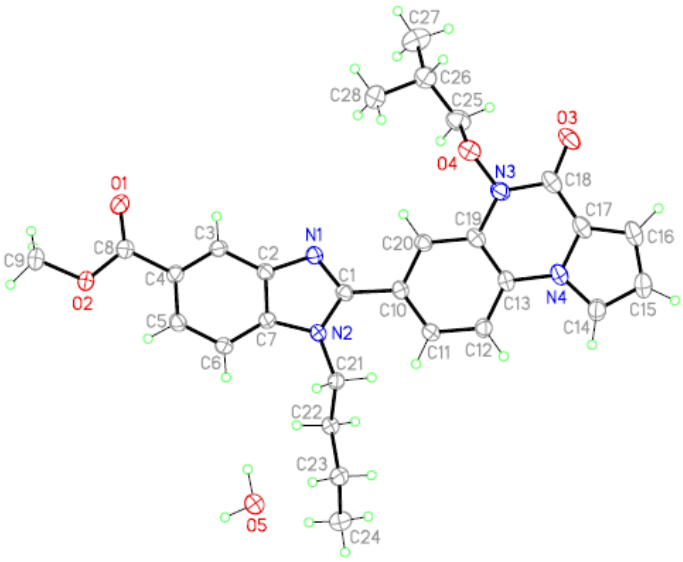
^{1}HNMR spectrum (300 MHz) of compound 18d in $CDCl_3$

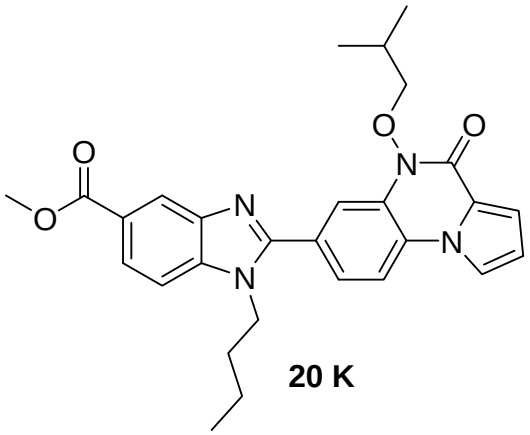


^{1}HNMR spectrum (300 MHz) of compound 19d in $CDCl_3$



^{1}HNMR spectrum (300 MHz) of compound 20d in $CDCl_3$





X-ray crystallographic structure of of the Benzimidazole-Pyrrolo[1,2-*a*]quinoxalineone **21l**

Table 1. Crystal data and structure refinement for mo_100342lt_0m.

Identification code	mo_100342lt_0m	
Empirical formula	C28 H32 N4 O5	
Formula weight	504.58	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 13.6708(4) Å	α= 90°.
	b = 7.8280(2) Å	β= 97.7770(10)°.
	c = 24.0197(7) Å	γ = 90°.
Volume	2546.83(12) $Å^3$	
Z	4	
Density (calculated)	1.316 Mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	1072	
Crystal size	0.20 x 0.20 x 0.12 mm^3	
Theta range for data collection	1.63 to 26.38°.	
Index ranges	-17<=h<=17, -9<=k<=9, -30<=l<=13	
Reflections collected	20132	
Independent reflections	5202 [R(int) = 0.0255]	
Completeness to theta = 26.38°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7454 and 0.6410	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5202 / 0 / 338	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0527, wR2 = 0.1370	
R indices (all data)	R1 = 0.0663, wR2 = 0.1459	
Largest diff. peak and hole	0.783 and -0.394 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for mo_100342lt_0m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	1490(1)	8368(2)	2139(1)	21(1)
C(2)	2544(1)	8262(2)	2888(1)	20(1)
C(3)	3038(1)	8148(3)	3434(1)	22(1)
C(4)	4059(1)	8259(3)	3508(1)	22(1)
C(5)	4591(1)	8503(3)	3050(1)	24(1)
C(6)	4114(1)	8635(3)	2508(1)	23(1)
C(7)	3091(1)	8483(2)	2437(1)	20(1)
C(8)	4586(2)	8151(3)	4091(1)	26(1)
C(9)	6119(2)	7792(3)	4661(1)	36(1)
C(10)	547(1)	8428(2)	1761(1)	21(1)
C(11)	416(1)	7705(3)	1225(1)	23(1)
C(12)	-484(1)	7829(3)	883(1)	24(1)
C(13)	-1266(1)	8674(2)	1072(1)	22(1)
C(14)	-2486(2)	8303(3)	203(1)	30(1)
C(15)	-3466(2)	8719(3)	62(1)	34(1)
C(16)	-3775(2)	9563(3)	521(1)	33(1)
C(17)	-2983(2)	9639(3)	939(1)	28(1)
C(18)	-2891(2)	10333(3)	1500(1)	29(1)
C(19)	-1151(1)	9377(3)	1613(1)	23(1)
C(20)	-247(1)	9251(2)	1954(1)	22(1)
C(21)	2679(1)	8763(3)	1396(1)	21(1)
C(22)	3034(1)	7094(3)	1162(1)	23(1)
C(23)	3503(2)	7398(3)	633(1)	29(1)
C(24)	3751(2)	5752(4)	351(1)	43(1)
C(25)	-2114(2)	9843(3)	2737(1)	35(1)
C(26)	-1918(2)	10794(3)	3280(1)	36(1)
C(27)	-2329(2)	9815(4)	3742(1)	50(1)
C(28)	-827(2)	11099(4)	3443(1)	48(1)
N(1)	1545(1)	8207(2)	2691(1)	22(1)
N(2)	2401(1)	8539(2)	1961(1)	20(1)
N(3)	-1957(1)	10205(2)	1796(1)	26(1)
N(4)	-2186(1)	8859(2)	740(1)	25(1)

O(1)	4191(1)	8283(2)	4509(1)	38(1)
O(2)	5556(1)	7904(2)	4107(1)	29(1)
O(3)	-3573(1)	10987(2)	1709(1)	35(1)
O(4)	-1799(1)	10977(2)	2314(1)	32(1)
O(5)	4430(1)	1878(2)	1381(1)	34(1)

Table 3. Bond lengths [Å] and angles [°] for mo_100342lt_0m.

C(1)-N(1)	1.324(2)
C(1)-N(2)	1.377(2)
C(1)-C(10)	1.473(3)
C(2)-N(1)	1.385(2)
C(2)-C(3)	1.395(3)
C(2)-C(7)	1.407(3)
C(3)-C(4)	1.386(3)
C(4)-C(5)	1.413(3)
C(4)-C(8)	1.487(3)
C(5)-C(6)	1.378(3)
C(6)-C(7)	1.391(3)
C(7)-N(2)	1.381(2)
C(8)-O(1)	1.209(2)
C(8)-O(2)	1.336(2)
C(9)-O(2)	1.446(2)
C(10)-C(20)	1.394(3)
C(10)-C(11)	1.397(3)
C(11)-C(12)	1.387(3)
C(12)-C(13)	1.386(3)
C(13)-C(19)	1.400(3)
C(13)-N(4)	1.404(3)
C(14)-N(4)	1.369(3)
C(14)-C(15)	1.375(3)
C(15)-C(16)	1.398(3)
C(16)-C(17)	1.376(3)
C(17)-N(4)	1.389(3)
C(17)-C(18)	1.443(3)
C(18)-O(3)	1.230(3)
C(18)-N(3)	1.377(3)
C(19)-C(20)	1.391(3)
C(19)-N(3)	1.398(2)
C(21)-N(2)	1.468(2)
C(21)-C(22)	1.527(3)
C(22)-C(23)	1.518(3)
C(23)-C(24)	1.515(3)
C(25)-O(4)	1.458(3)

C(25)-C(26)	1.494(3)
C(26)-C(28)	1.509(3)
C(26)-C(27)	1.518(4)
N(3)-O(4)	1.375(2)

N(1)-C(1)-N(2)	112.87(17)
N(1)-C(1)-C(10)	123.15(17)
N(2)-C(1)-C(10)	123.94(17)
N(1)-C(2)-C(3)	130.46(17)
N(1)-C(2)-C(7)	110.03(16)
C(3)-C(2)-C(7)	119.51(17)
C(4)-C(3)-C(2)	117.84(17)
C(3)-C(4)-C(5)	121.66(18)
C(3)-C(4)-C(8)	117.94(17)
C(5)-C(4)-C(8)	120.38(18)
C(6)-C(5)-C(4)	121.18(18)
C(5)-C(6)-C(7)	116.73(18)
N(2)-C(7)-C(6)	131.45(17)
N(2)-C(7)-C(2)	105.49(16)
C(6)-C(7)-C(2)	123.05(17)
O(1)-C(8)-O(2)	122.80(18)
O(1)-C(8)-C(4)	124.31(19)
O(2)-C(8)-C(4)	112.89(16)
C(20)-C(10)-C(11)	118.99(18)
C(20)-C(10)-C(1)	117.77(17)
C(11)-C(10)-C(1)	123.24(17)
C(12)-C(11)-C(10)	120.77(18)
C(13)-C(12)-C(11)	120.00(18)
C(12)-C(13)-C(19)	119.89(18)
C(12)-C(13)-N(4)	122.25(18)
C(19)-C(13)-N(4)	117.86(18)
N(4)-C(14)-C(15)	108.3(2)
C(14)-C(15)-C(16)	107.8(2)
C(17)-C(16)-C(15)	107.7(2)
C(16)-C(17)-N(4)	107.8(2)
C(16)-C(17)-C(18)	131.2(2)
N(4)-C(17)-C(18)	120.97(18)
O(3)-C(18)-N(3)	121.4(2)

O(3)-C(18)-C(17)	124.3(2)
N(3)-C(18)-C(17)	114.31(18)
C(20)-C(19)-N(3)	121.59(18)
C(20)-C(19)-C(13)	119.81(18)
N(3)-C(19)-C(13)	118.60(17)
C(19)-C(20)-C(10)	120.51(18)
N(2)-C(21)-C(22)	111.90(15)
C(23)-C(22)-C(21)	111.45(17)
C(24)-C(23)-C(22)	112.8(2)
O(4)-C(25)-C(26)	105.66(19)
C(25)-C(26)-C(28)	111.1(2)
C(25)-C(26)-C(27)	110.2(2)
C(28)-C(26)-C(27)	109.9(2)
C(1)-N(1)-C(2)	105.03(15)
C(1)-N(2)-C(7)	106.58(15)
C(1)-N(2)-C(21)	131.03(16)
C(7)-N(2)-C(21)	122.39(15)
O(4)-N(3)-C(18)	117.10(16)
O(4)-N(3)-C(19)	116.99(16)
C(18)-N(3)-C(19)	125.90(18)
C(14)-N(4)-C(17)	108.41(17)
C(14)-N(4)-C(13)	129.36(18)
C(17)-N(4)-C(13)	122.18(18)
C(8)-O(2)-C(9)	115.98(16)
N(3)-O(4)-C(25)	109.82(16)

Symmetry transformations used to generate equivalent atoms:

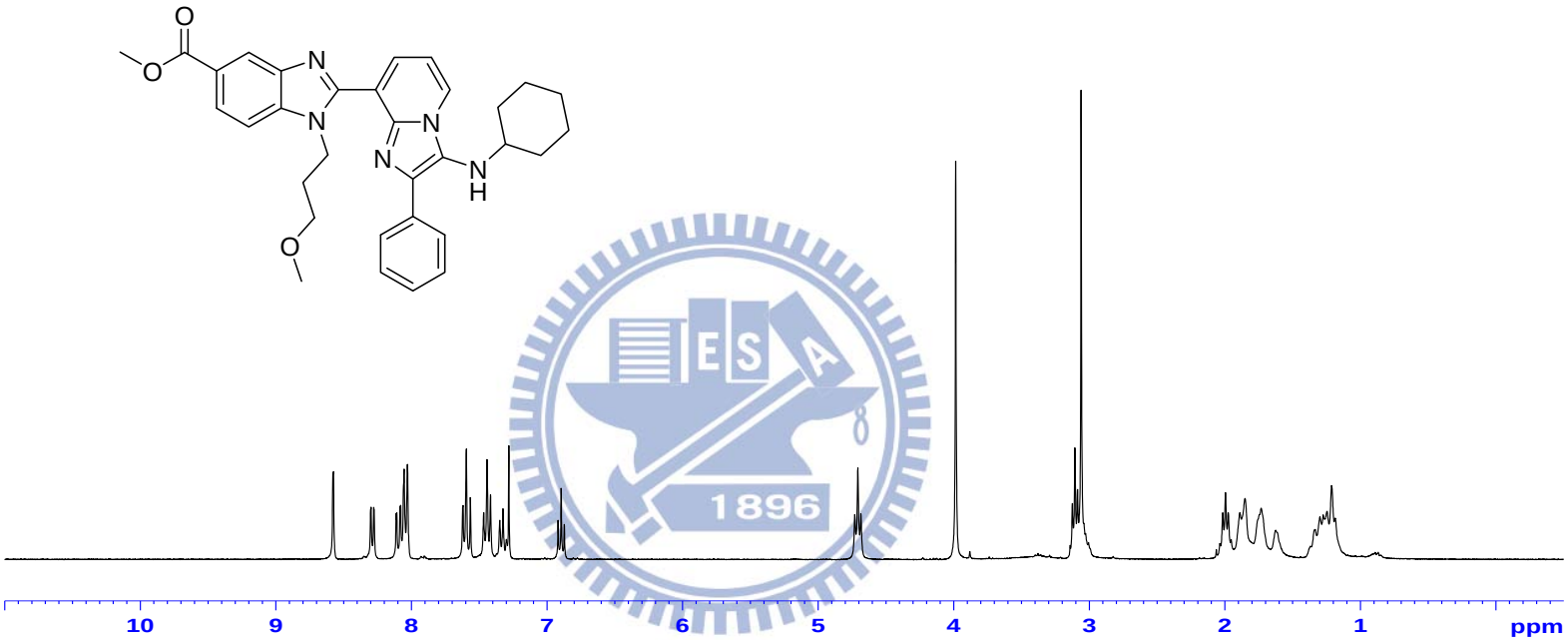
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for mo_100342lt_0m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	19(1)	19(1)	24(1)	-2(1)	4(1)	0(1)
C(2)	19(1)	20(1)	23(1)	-3(1)	4(1)	-1(1)
C(3)	22(1)	24(1)	20(1)	-2(1)	4(1)	0(1)
C(4)	22(1)	22(1)	20(1)	-2(1)	1(1)	0(1)
C(5)	18(1)	27(1)	26(1)	-4(1)	3(1)	-1(1)
C(6)	20(1)	28(1)	22(1)	-1(1)	5(1)	-1(1)
C(7)	21(1)	21(1)	20(1)	-2(1)	2(1)	0(1)
C(8)	22(1)	30(1)	24(1)	-3(1)	1(1)	-1(1)
C(9)	26(1)	52(2)	26(1)	-1(1)	-4(1)	4(1)
C(10)	18(1)	21(1)	24(1)	1(1)	2(1)	-1(1)
C(11)	20(1)	25(1)	24(1)	-1(1)	4(1)	2(1)
C(12)	21(1)	27(1)	23(1)	0(1)	1(1)	-2(1)
C(13)	19(1)	20(1)	27(1)	4(1)	0(1)	-1(1)
C(14)	26(1)	35(1)	27(1)	2(1)	-2(1)	0(1)
C(15)	27(1)	38(1)	35(1)	7(1)	-5(1)	0(1)
C(16)	21(1)	34(1)	42(1)	10(1)	-1(1)	3(1)
C(17)	21(1)	25(1)	37(1)	7(1)	4(1)	3(1)
C(18)	21(1)	24(1)	41(1)	6(1)	5(1)	3(1)
C(19)	18(1)	20(1)	31(1)	1(1)	4(1)	0(1)
C(20)	20(1)	22(1)	24(1)	-2(1)	4(1)	-1(1)
C(21)	19(1)	25(1)	19(1)	2(1)	2(1)	-2(1)
C(22)	20(1)	26(1)	23(1)	-1(1)	2(1)	1(1)
C(23)	24(1)	40(1)	23(1)	-2(1)	3(1)	-1(1)
C(24)	39(1)	59(2)	30(1)	-11(1)	4(1)	11(1)
C(25)	35(1)	35(1)	38(1)	4(1)	13(1)	1(1)
C(26)	35(1)	37(1)	36(1)	-2(1)	4(1)	6(1)
C(27)	61(2)	55(2)	36(1)	-5(1)	12(1)	0(1)
C(28)	38(1)	69(2)	35(1)	-14(1)	-4(1)	8(1)
N(1)	18(1)	25(1)	23(1)	-3(1)	2(1)	-1(1)
N(2)	16(1)	24(1)	21(1)	0(1)	2(1)	1(1)
N(3)	23(1)	27(1)	30(1)	-3(1)	5(1)	3(1)
N(4)	18(1)	26(1)	31(1)	5(1)	1(1)	2(1)
O(1)	27(1)	66(1)	20(1)	-2(1)	2(1)	1(1)

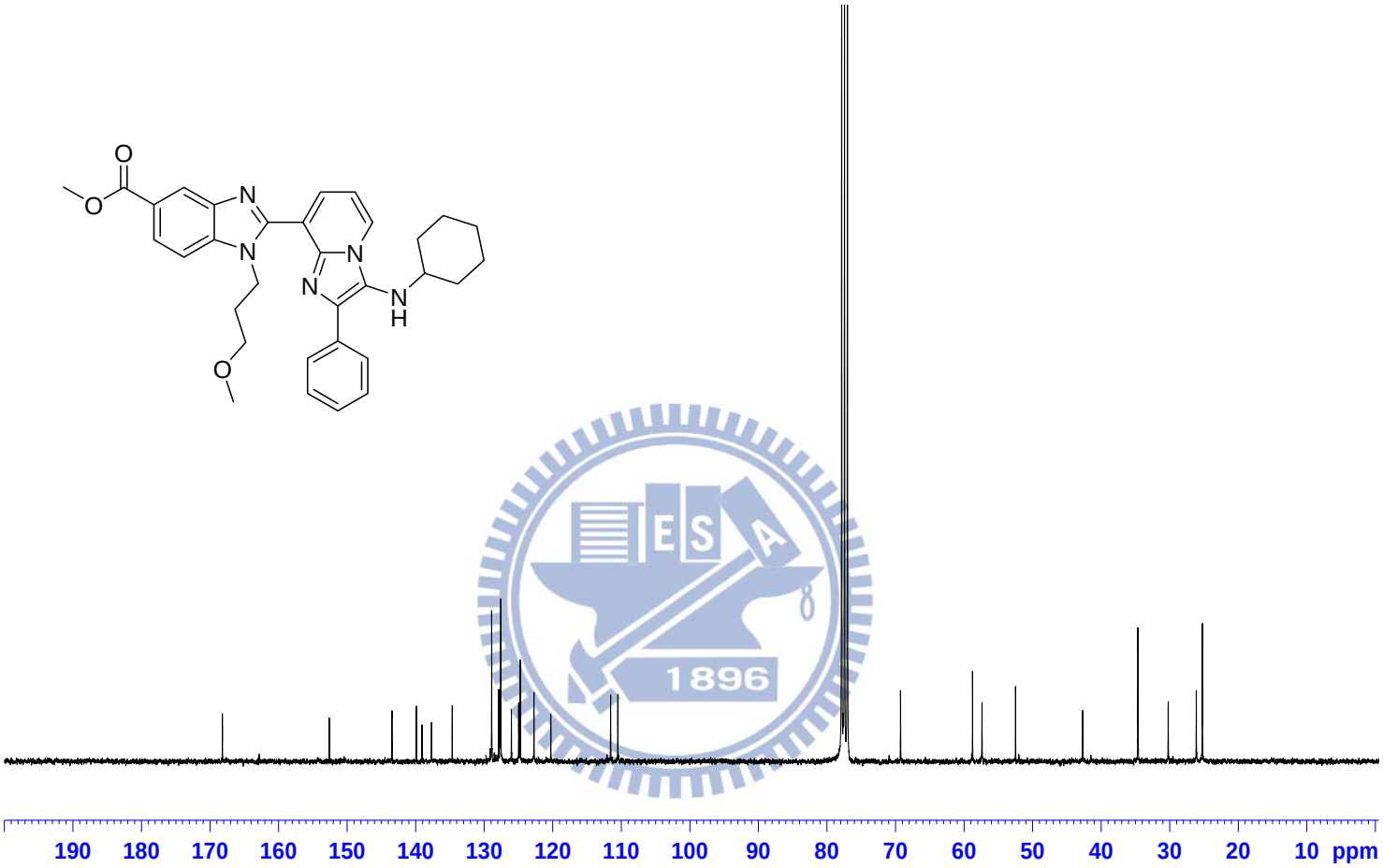
O(2)	22(1)	43(1)	21(1)	-2(1)	-2(1)	3(1)
O(3)	23(1)	36(1)	46(1)	-2(1)	7(1)	8(1)
O(4)	29(1)	31(1)	35(1)	0(1)	8(1)	2(1)
O(5)	24(1)	46(1)	31(1)	-3(1)	3(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for mo_100342lt_0m.

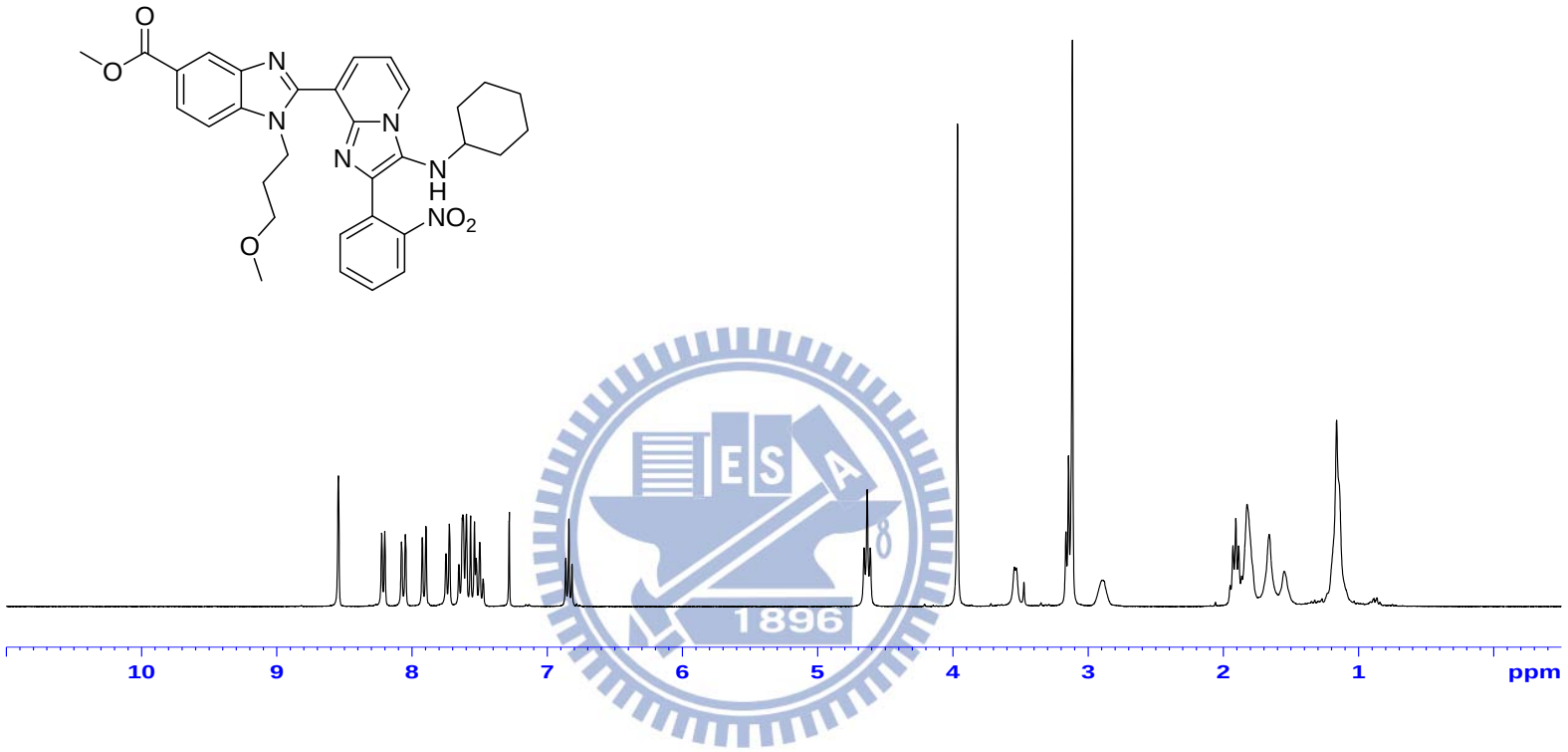
	x	y	z	U(eq)
H(3)	2693	8002	3739	26
H(5)	5276	8577	3115	28
H(6)	4458	8816	2205	27
H(9A)	6028	8817	4867	53
H(9B)	6806	7656	4627	53
H(9C)	5896	6828	4856	53
H(11)	937	7134	1096	28
H(12)	-562	7345	526	28
H(14)	-2094	7742	-26	36
H(15)	-3853	8480	-278	41
H(16)	-4403	9996	539	39
H(20)	-171	9719	2313	26
H(21A)	3200	9610	1411	25
H(21B)	2114	9186	1146	25
H(22A)	3511	6557	1444	28
H(22B)	2478	6322	1078	28
H(23A)	3054	8063	371	35
H(23B)	4102	8059	728	35
H(24A)	4191	5082	609	64
H(24B)	4063	6013	26	64
H(24C)	3156	5118	238	64
H(25A)	-1741	8785	2757	42
H(25B)	-2810	9577	2649	42
H(26)	-2251	11903	3234	43
H(27A)	-3017	9583	3629	75
H(27B)	-2253	10485	4080	75
H(27C)	-1978	8757	3810	75
H(28A)	-489	10022	3484	72
H(28B)	-720	11710	3793	72
H(28C)	-577	11758	3156	72
H(1)	5025	1605	1492	80
H(2)	4224	2379	1699	



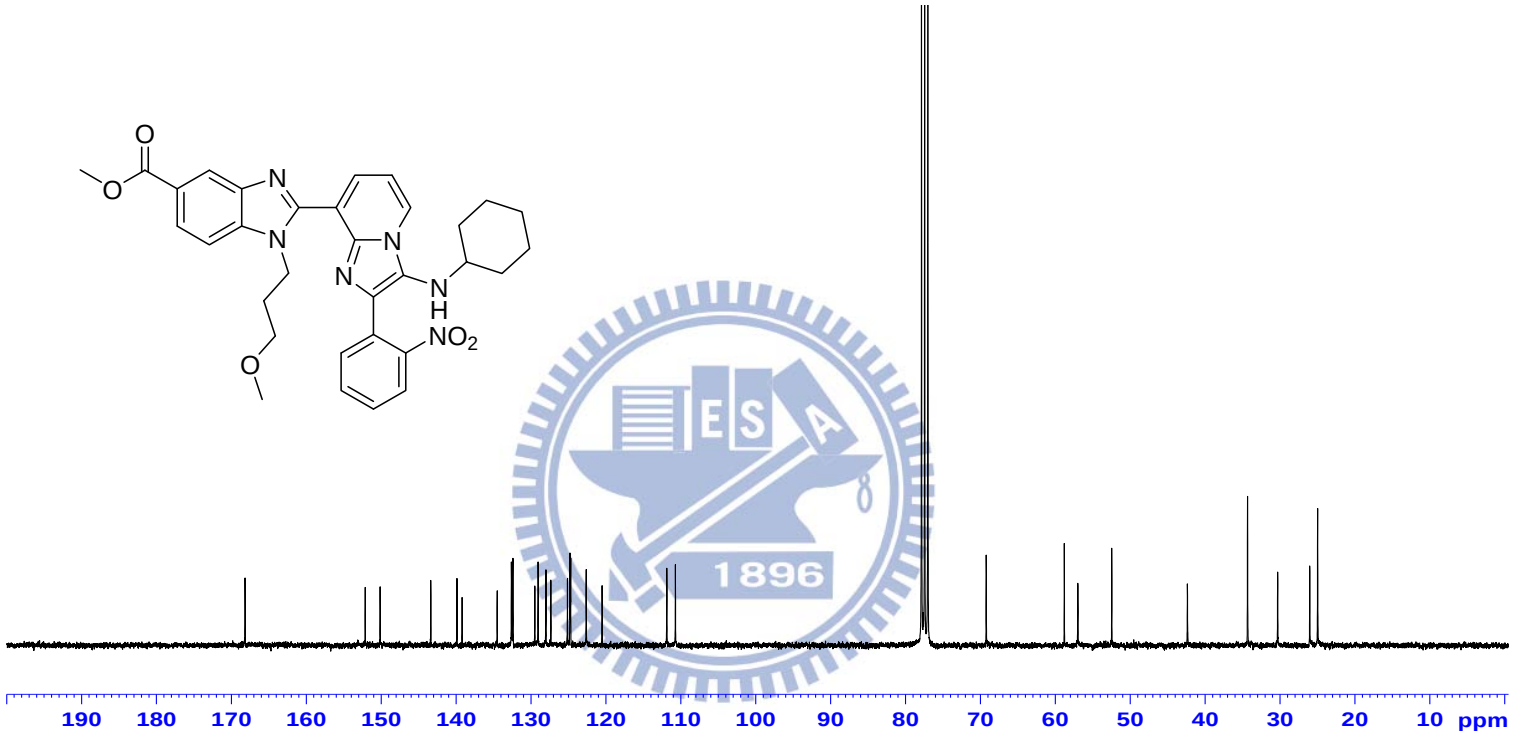
^{1}HNMR spectrum (300 MHz) of compound 10a in $CDCl_3$



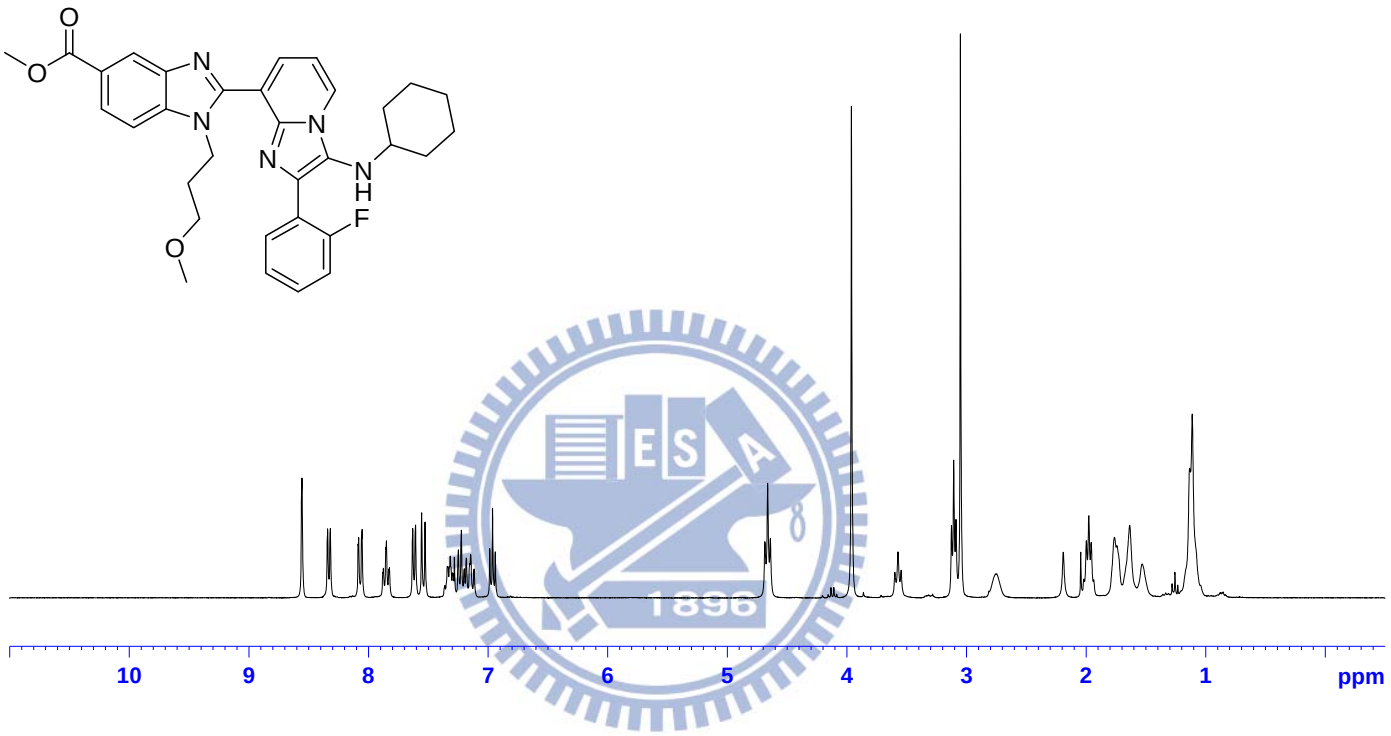
^{13}C NMR spectrum (75 MHz) of compound 10a in $CDCl_3$



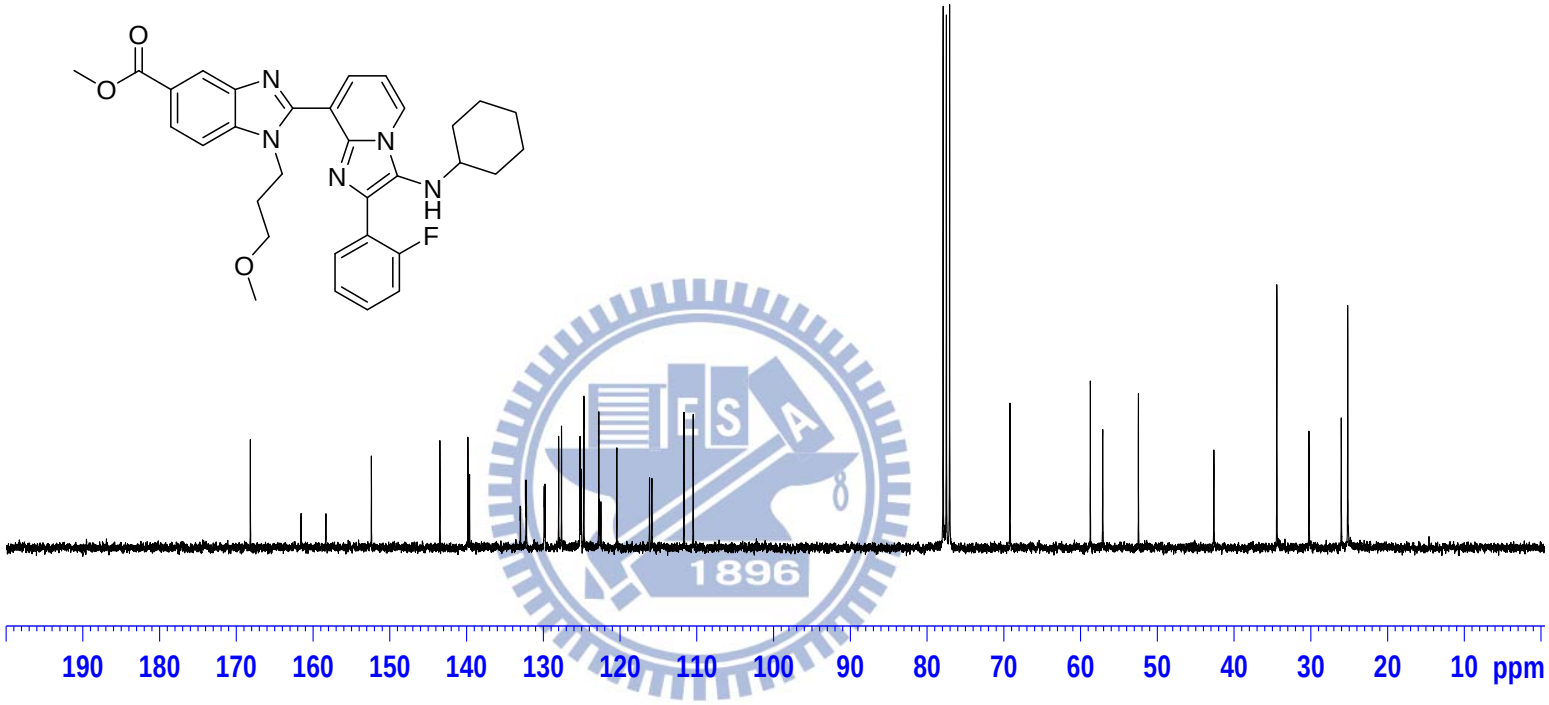
^{1}HNMR spectrum (300 MHz) of compound 10b in $CDCl_3$



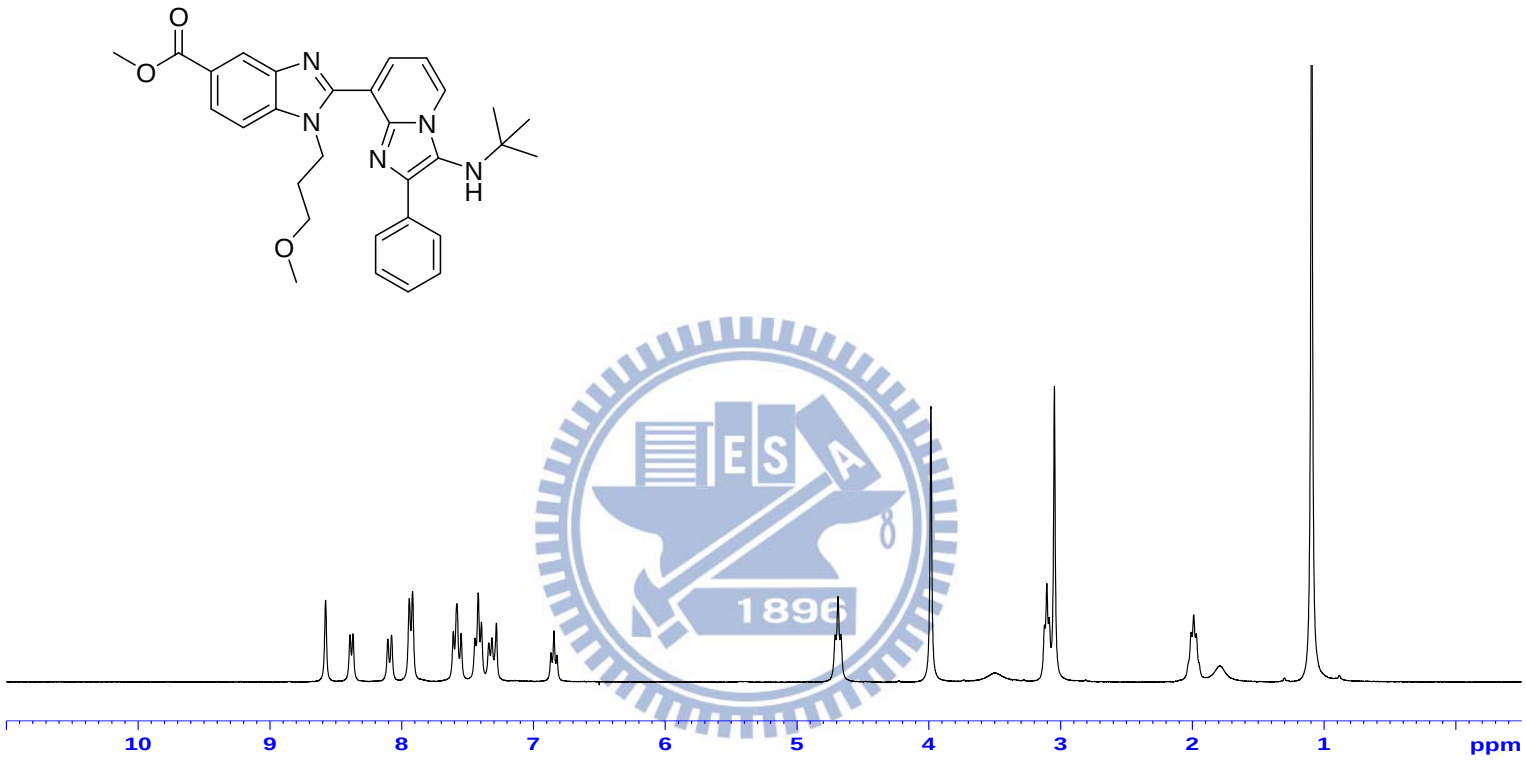
^{13}C NMR spectrum (75 MHz) of compound 10b in $CDCl_3$



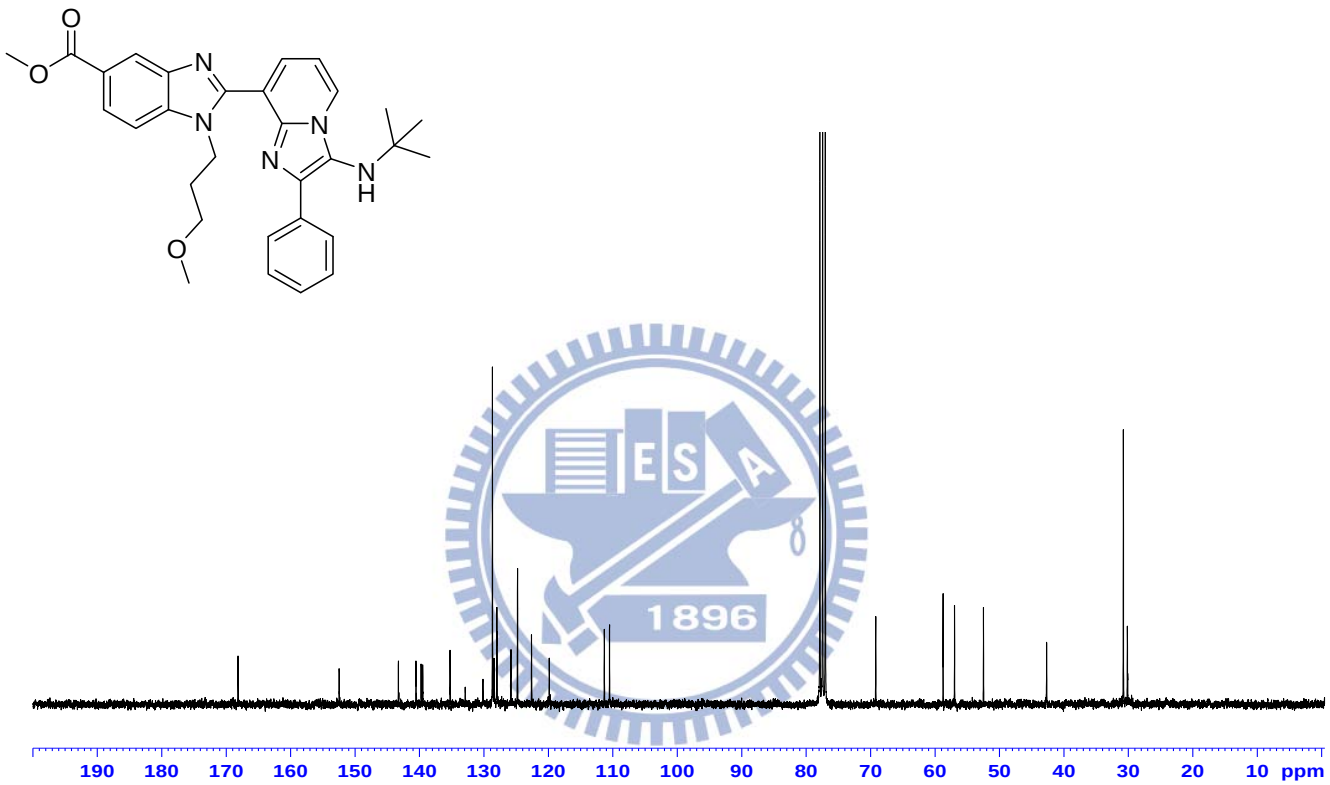
^{1}HNMR spectrum (300 MHz) of compound 10c in $CDCl_3$



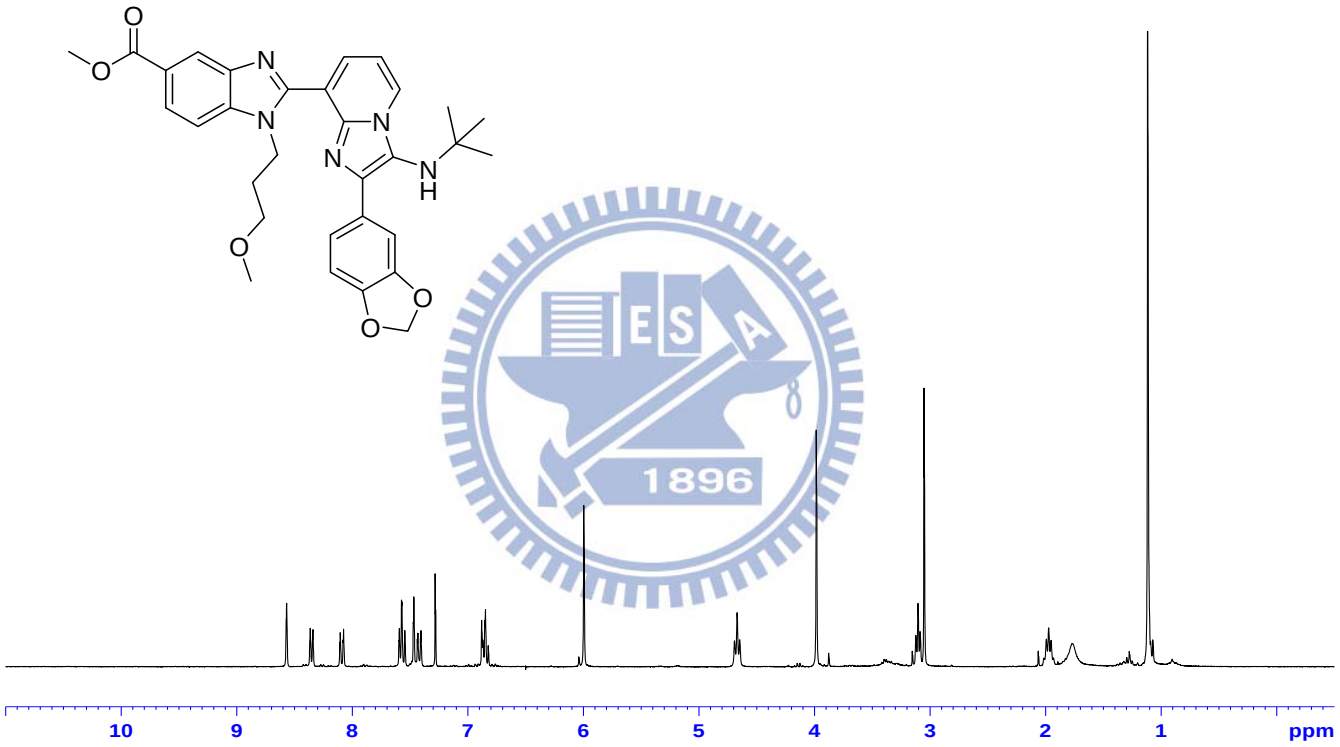
^{13}C NMR spectrum (75 MHz) of compound 10c in $CDCl_3$



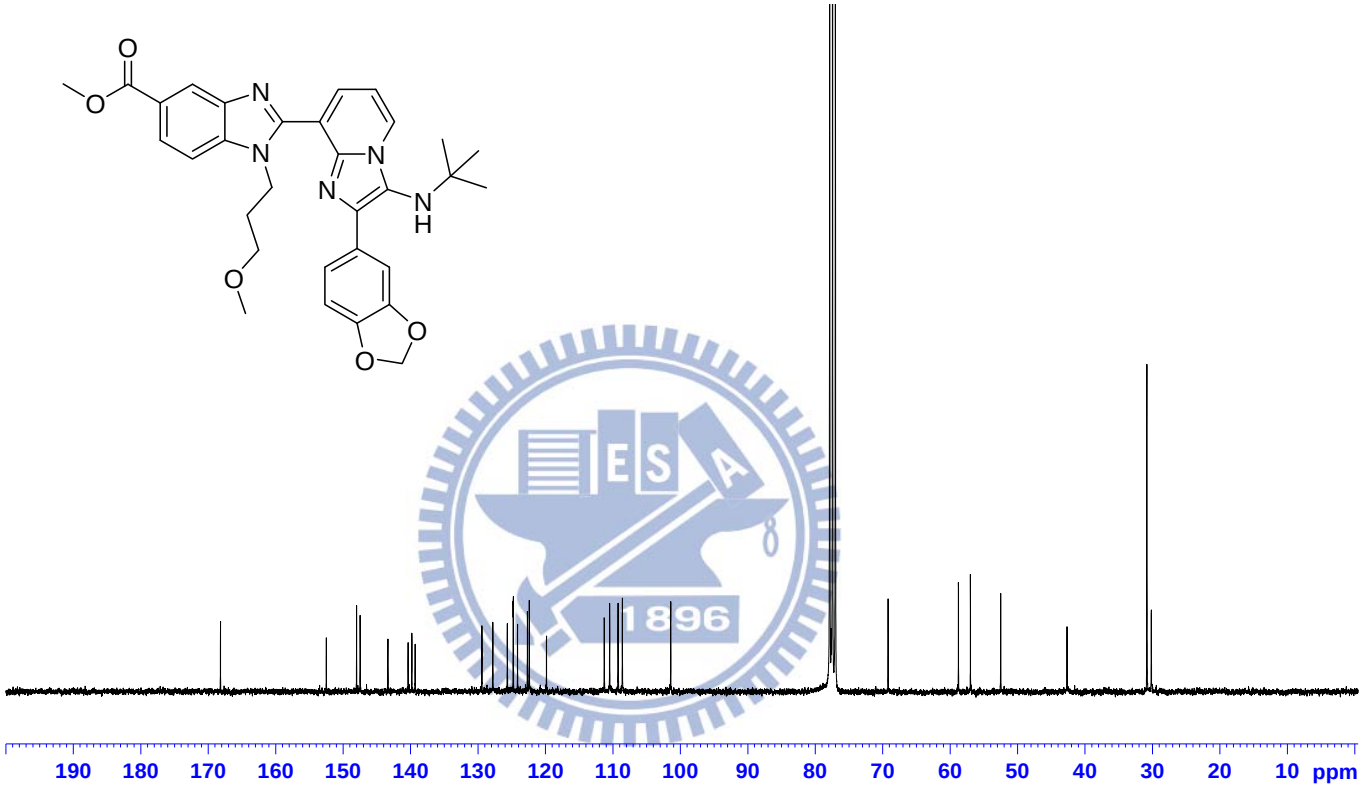
^{1}HNMR spectrum (300 MHz) of compound 10d in $CDCl_3$



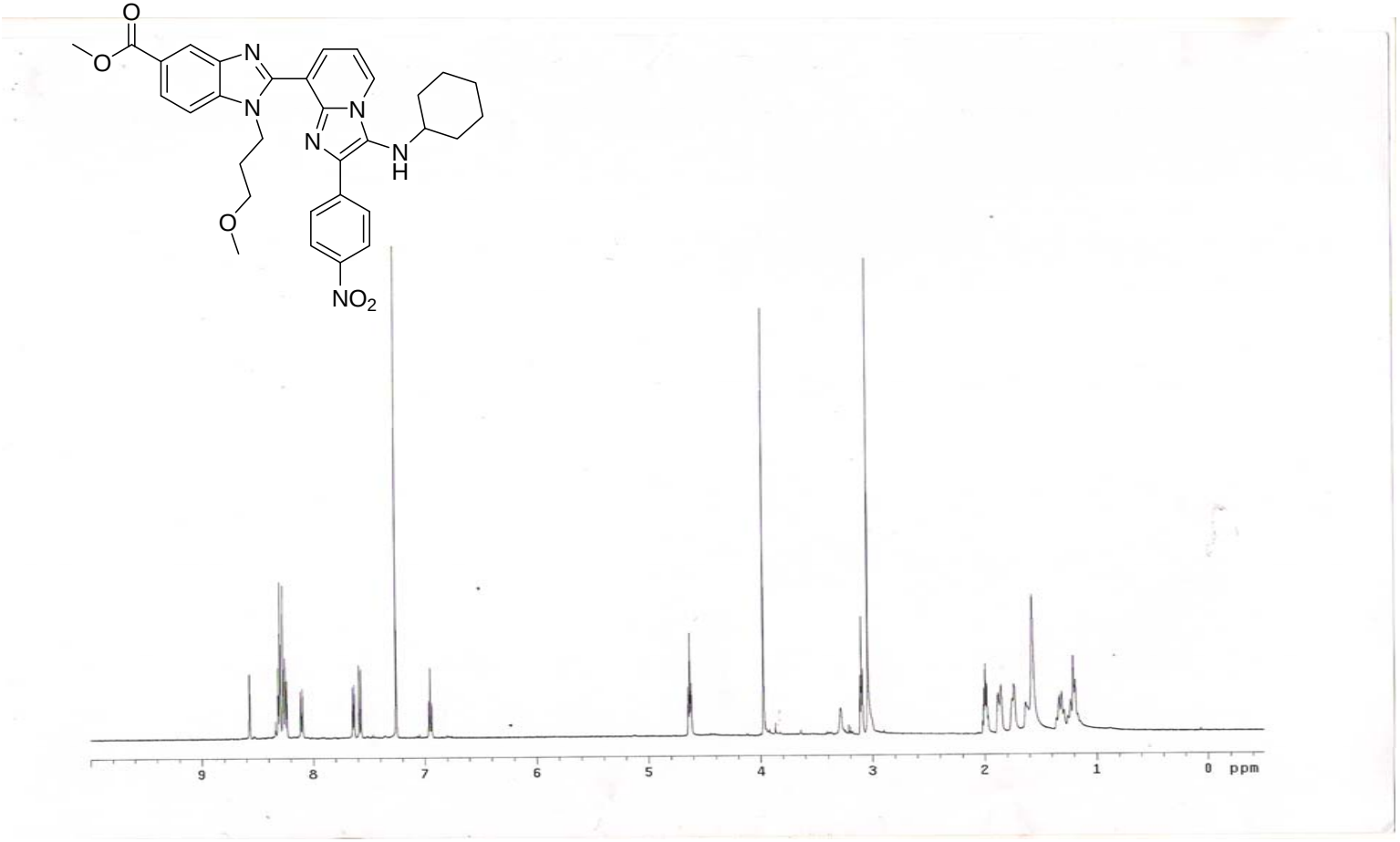
^{13}C NMR spectrum (75 MHz) of compound 10d in $CDCl_3$



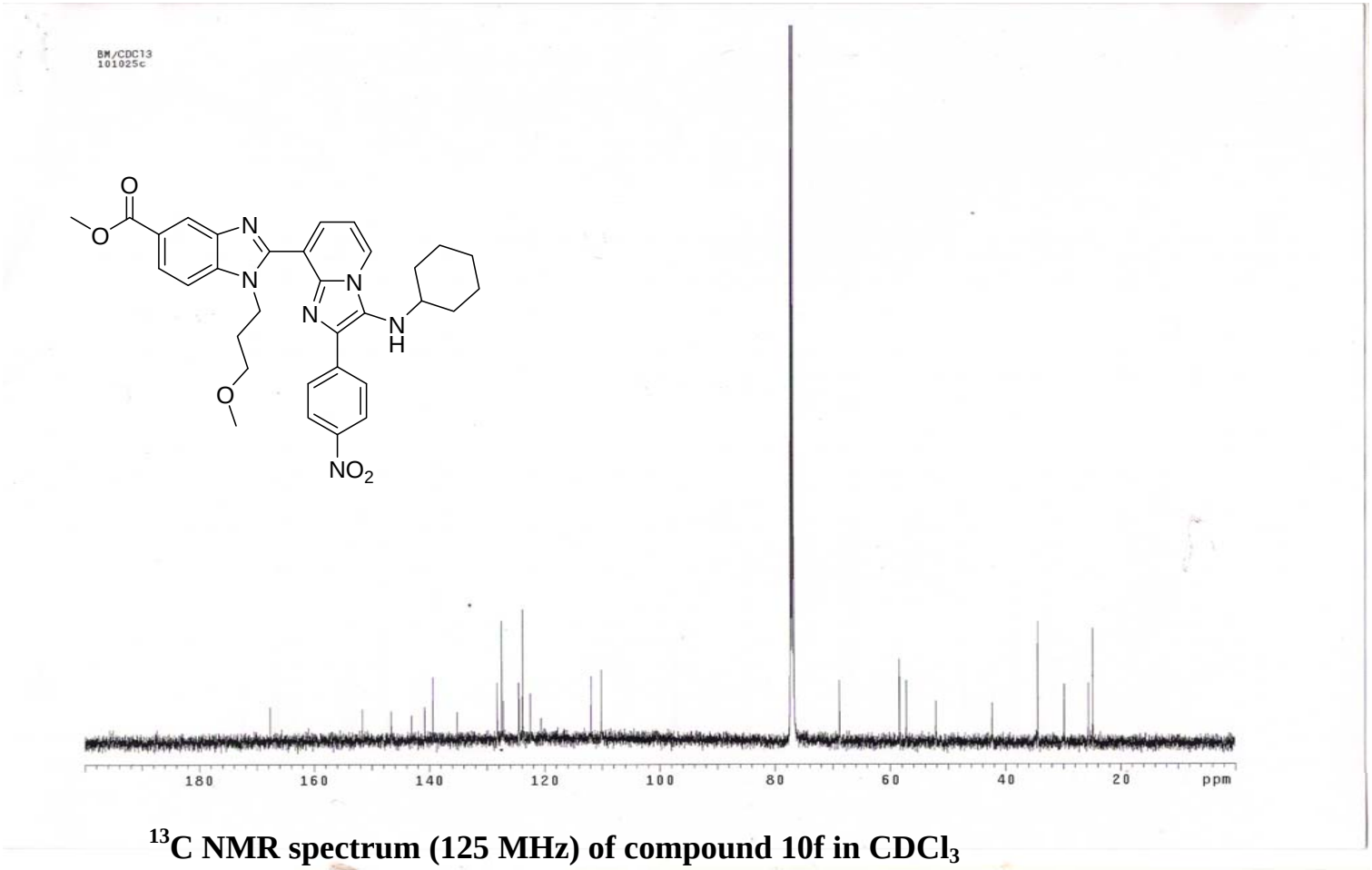
^{1}HNMR spectrum (300 MHz) of compound 10e in $CDCl_3$



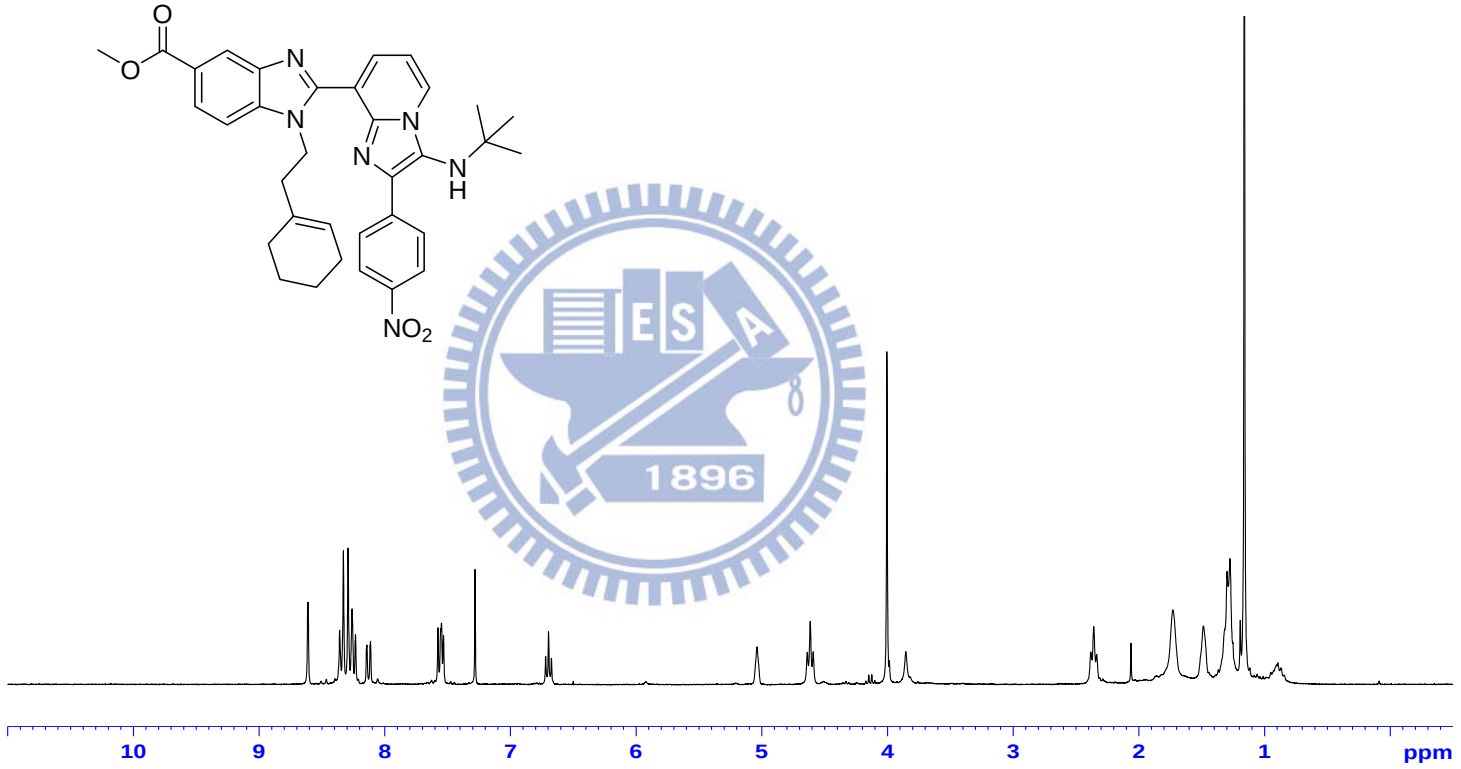
^{13}C NMR spectrum (75 MHz) of compound 10e in $CDCl_3$



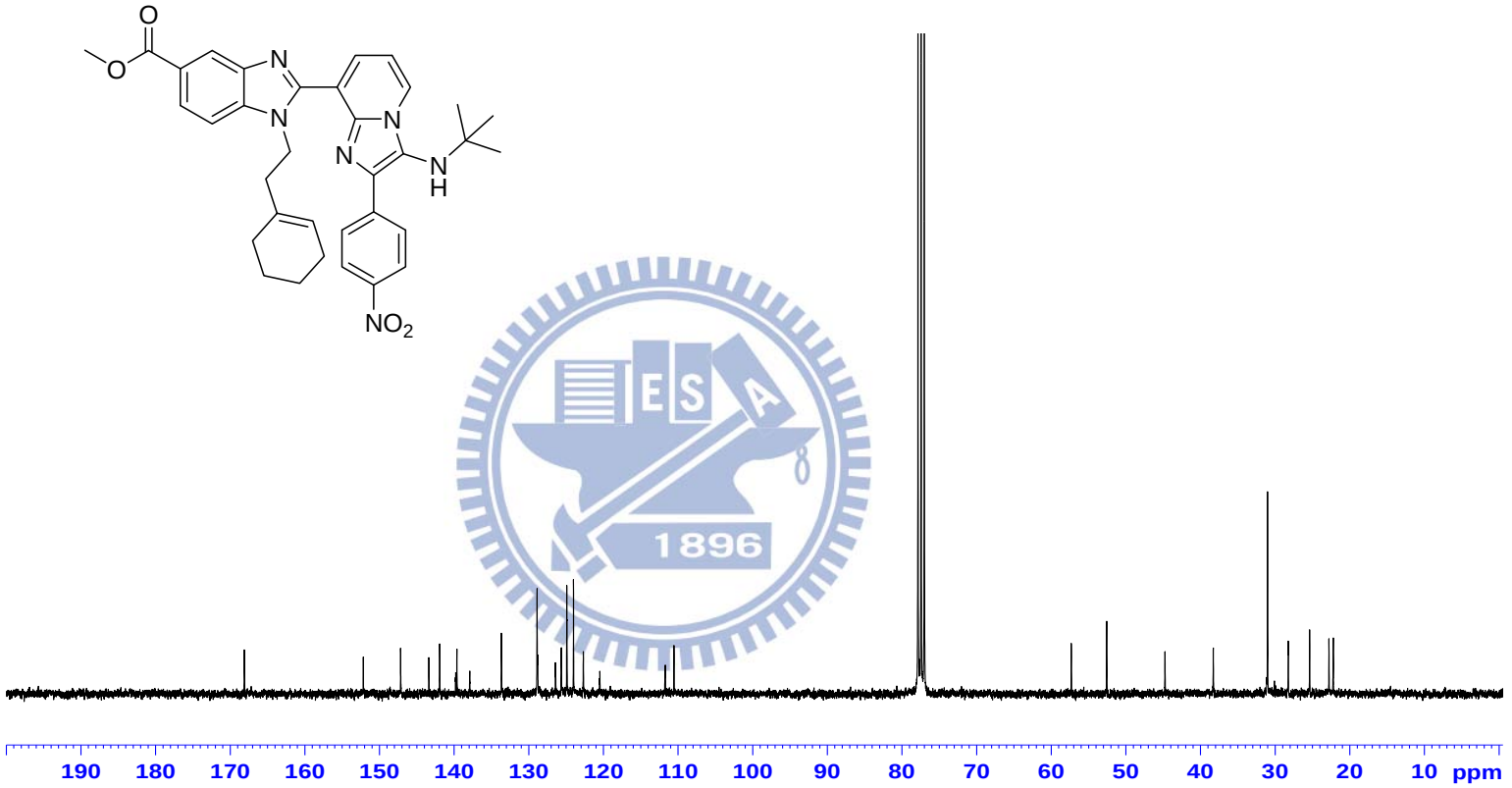
^{1}HNMR spectrum (500 MHz) of compound 10f in $CDCl_3$



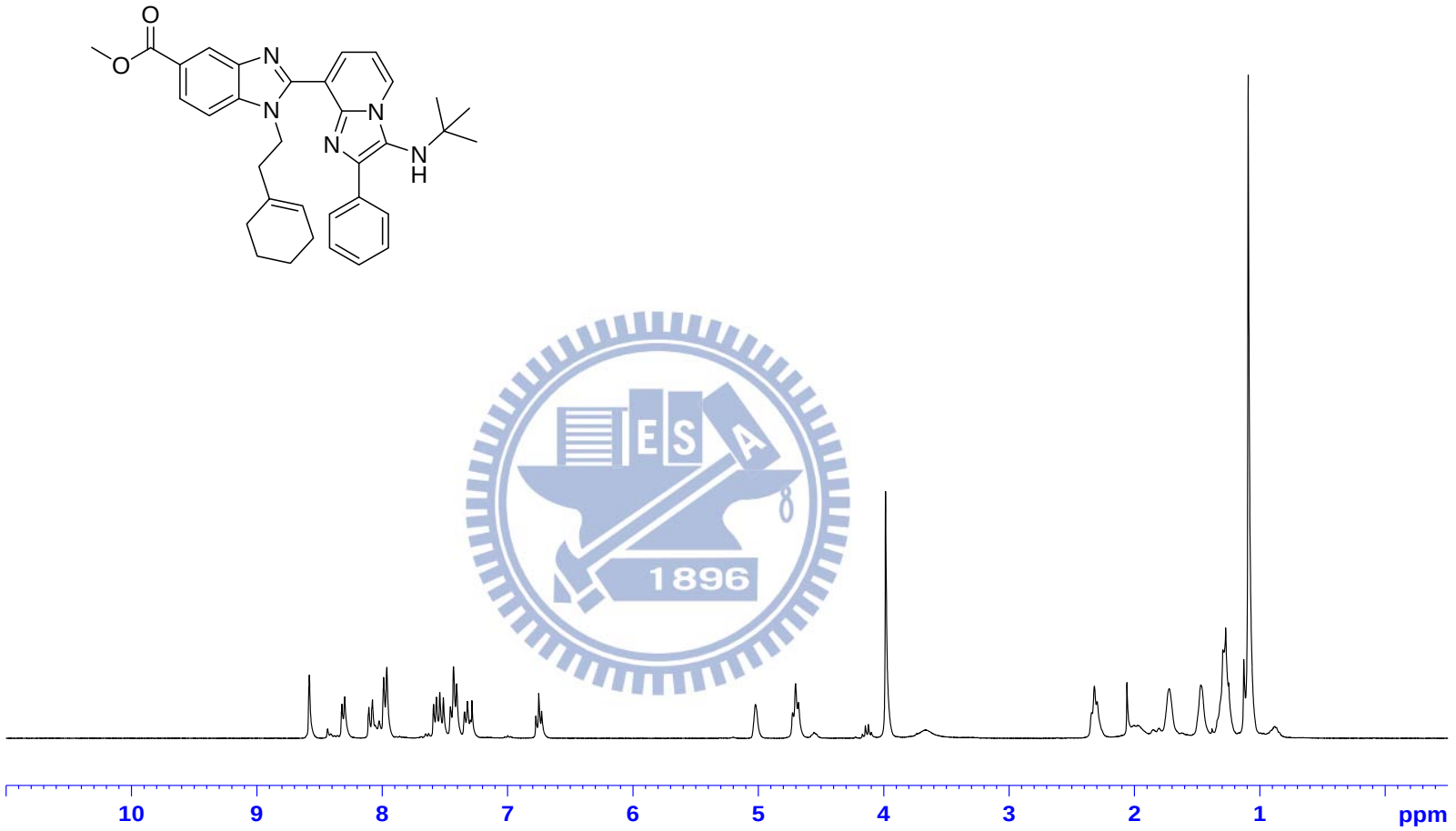
^{13}C NMR spectrum (125 MHz) of compound 10f in $CDCl_3$



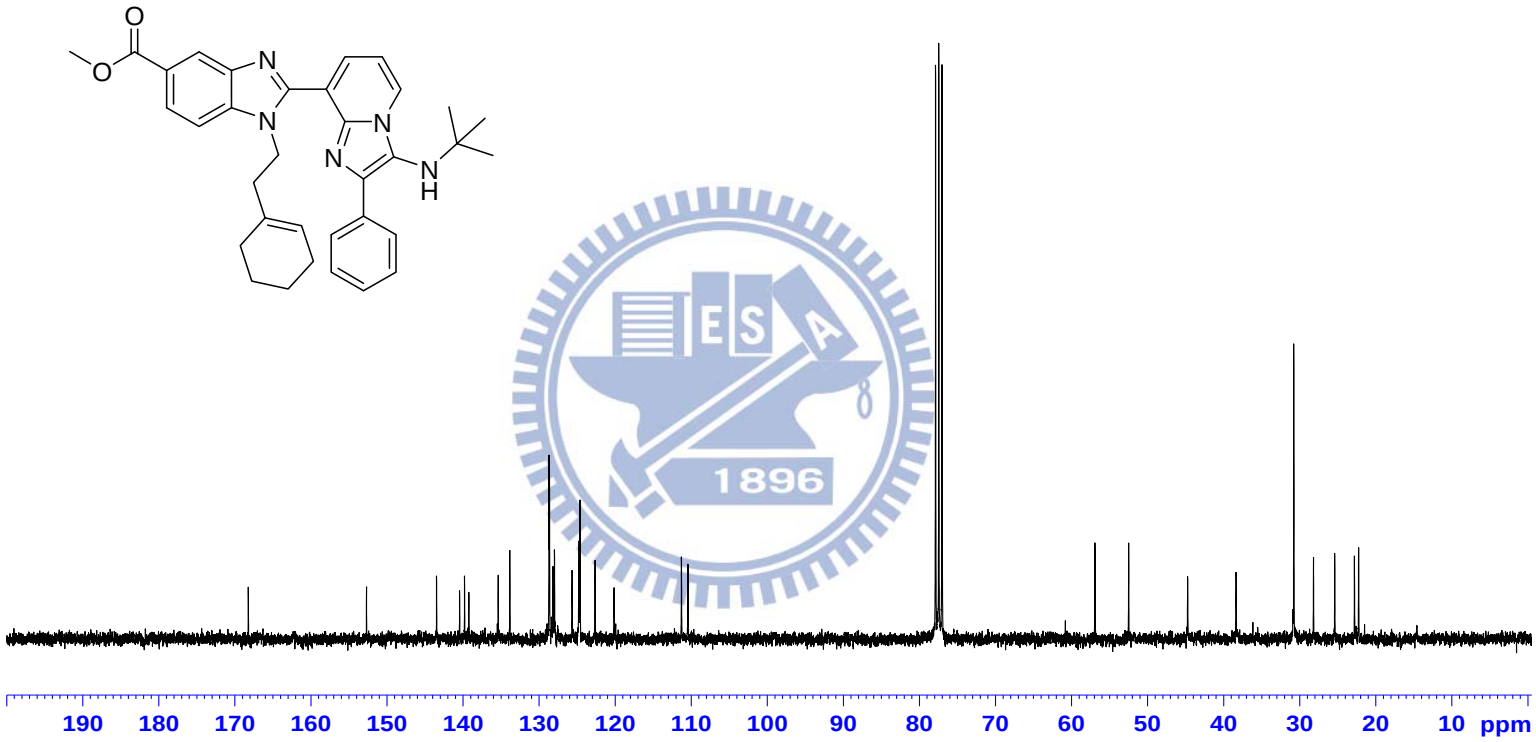
^{1}HNMR spectrum (300 MHz) of compound 10g in $CDCl_3$



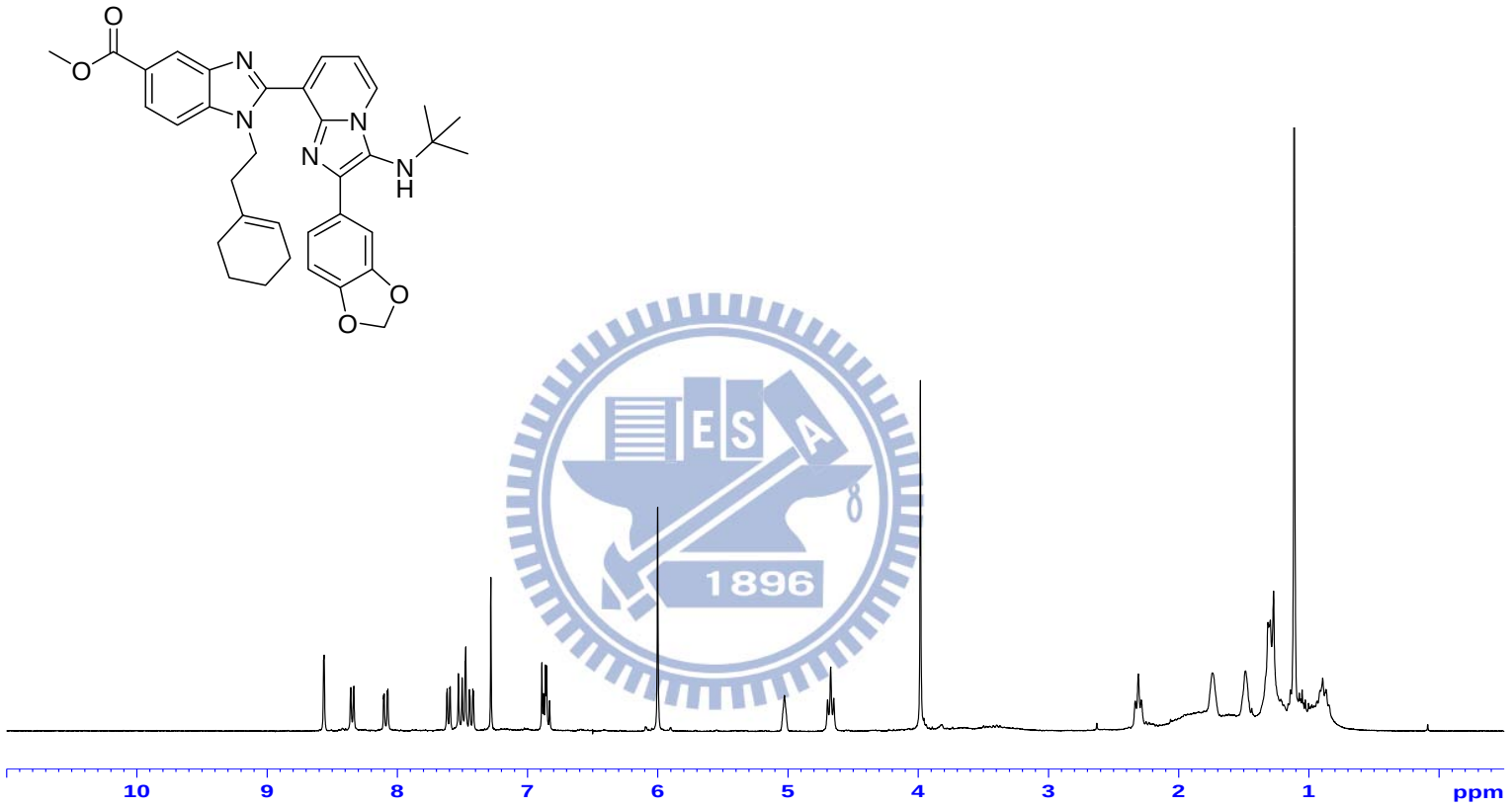
^{13}C NMR spectrum (75 MHz) of compound 10g in $CDCl_3$



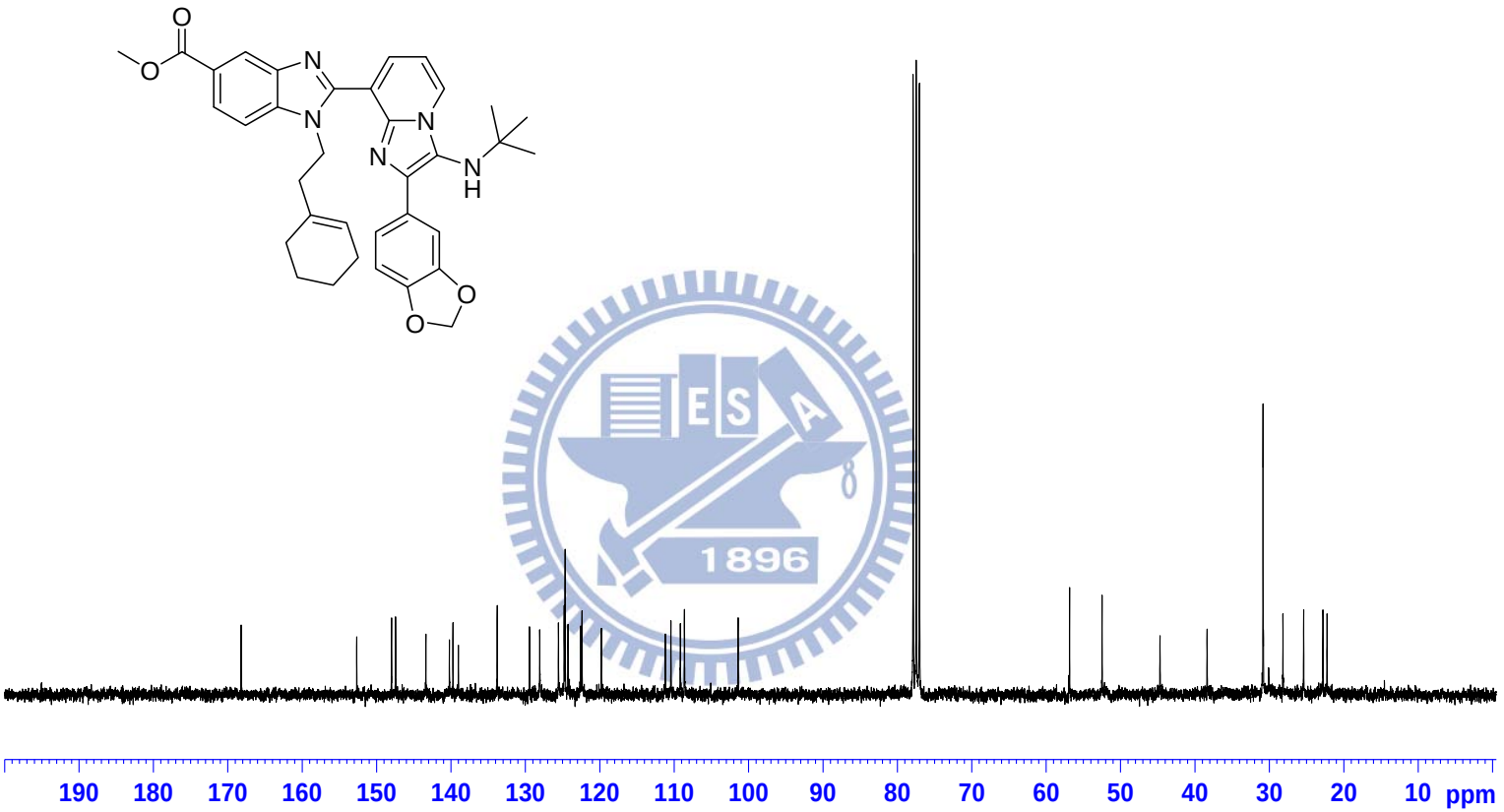
^{1}HNMR spectrum (300 MHz) of compound 10h in $CDCl_3$



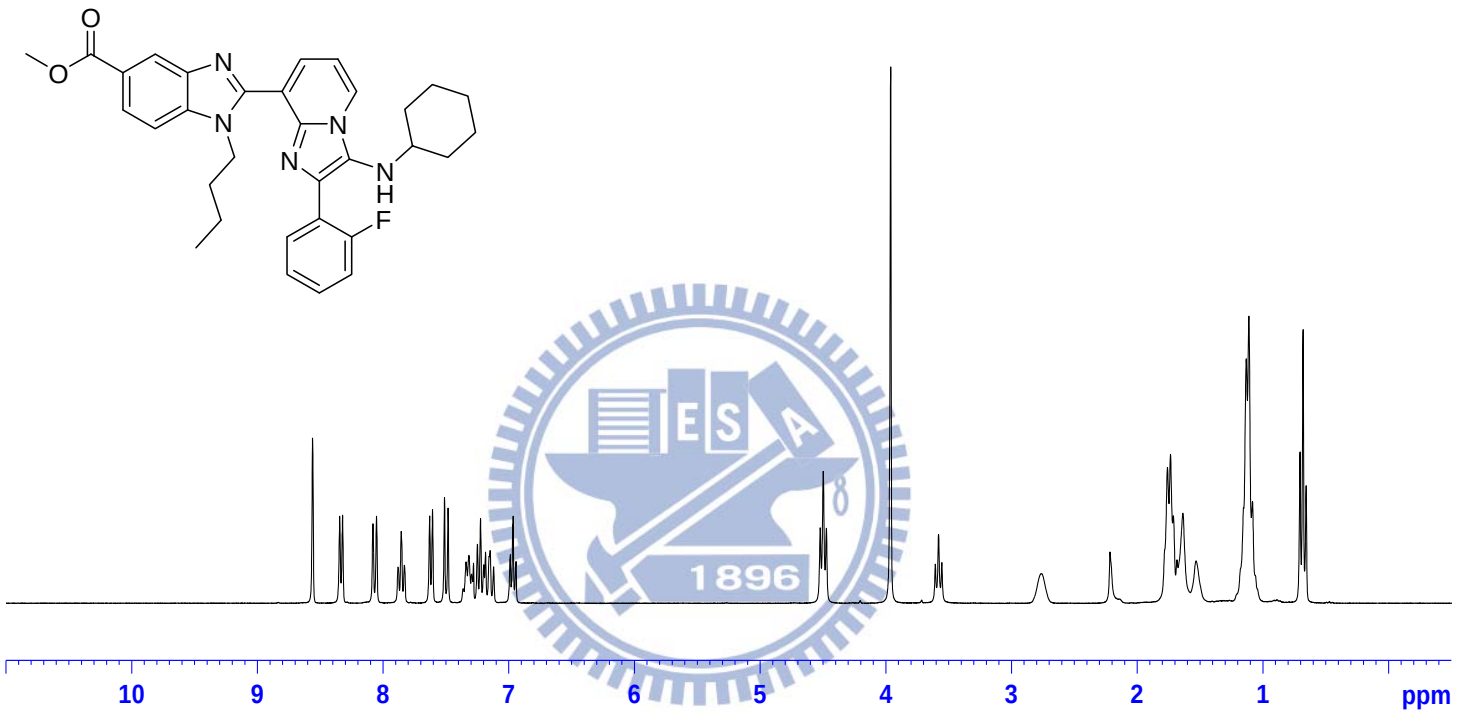
^{13}C NMR spectrum (75 MHz) of compound 10h in $CDCl_3$



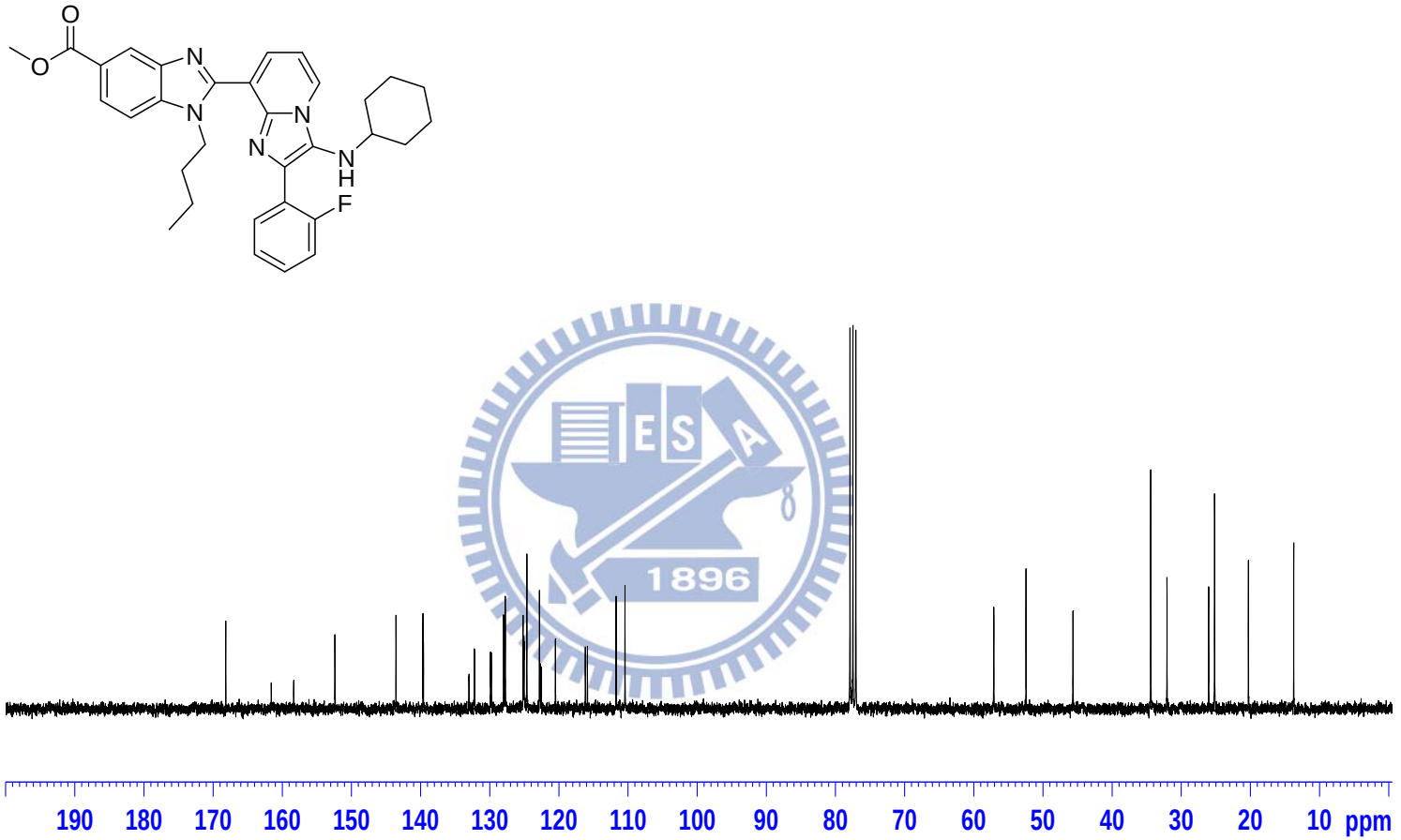
^{1}HNMR spectrum (300 MHz) of compound 10i in $CDCl_3$



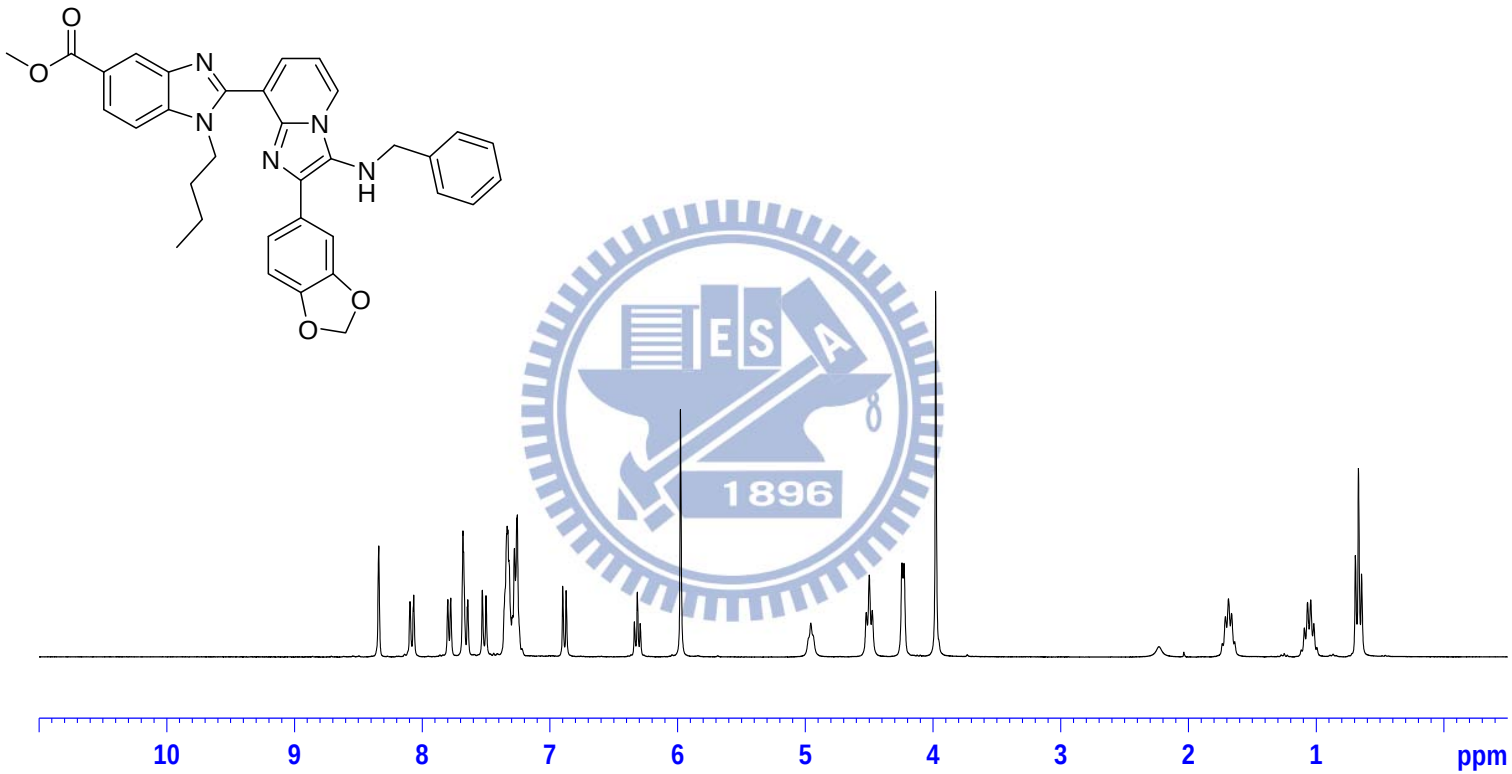
^{13}C NMR spectrum (75 MHz) of compound 10i in $CDCl_3$



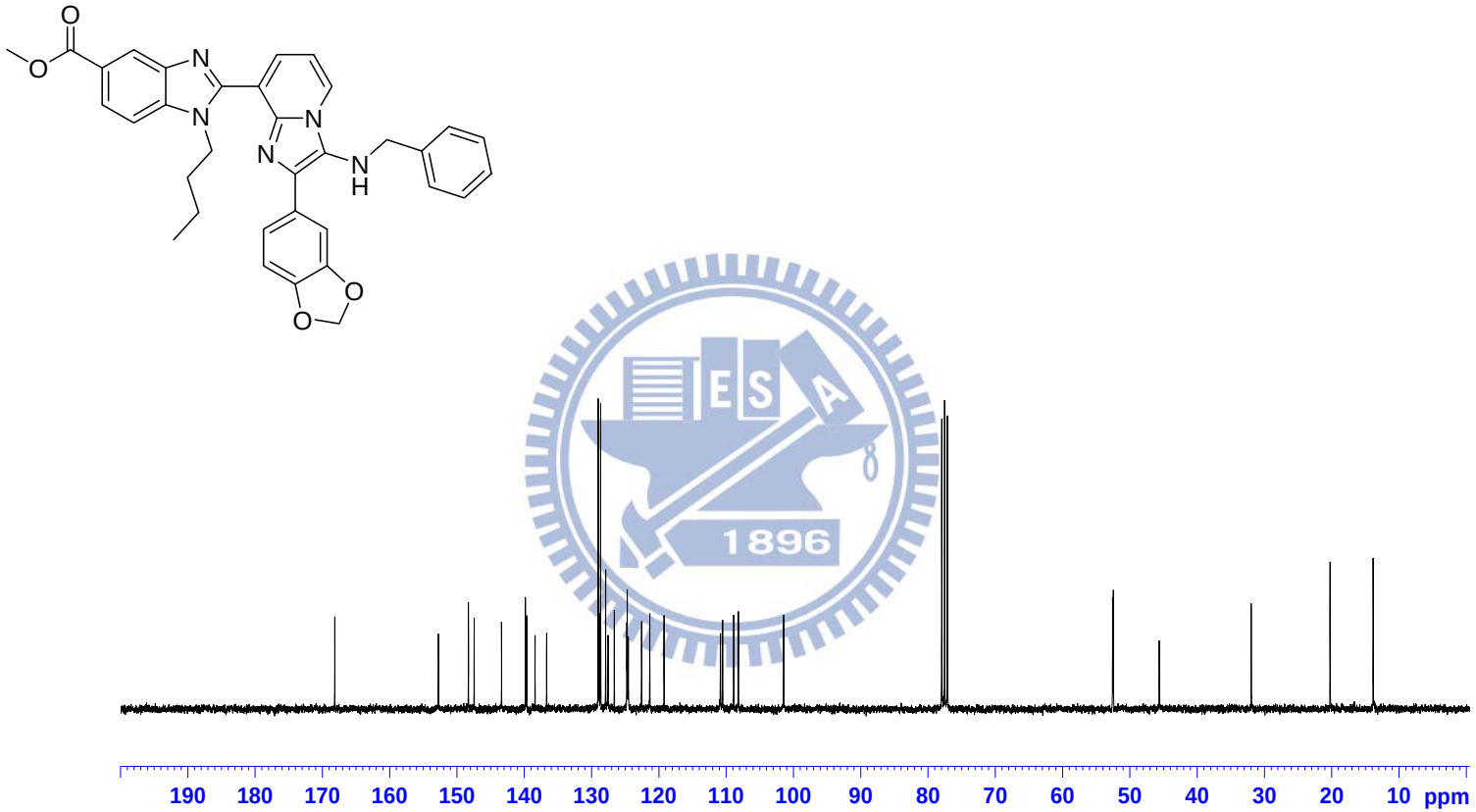
^{1}HNMR spectrum (300 MHz) of compound 10j in $CDCl_3$



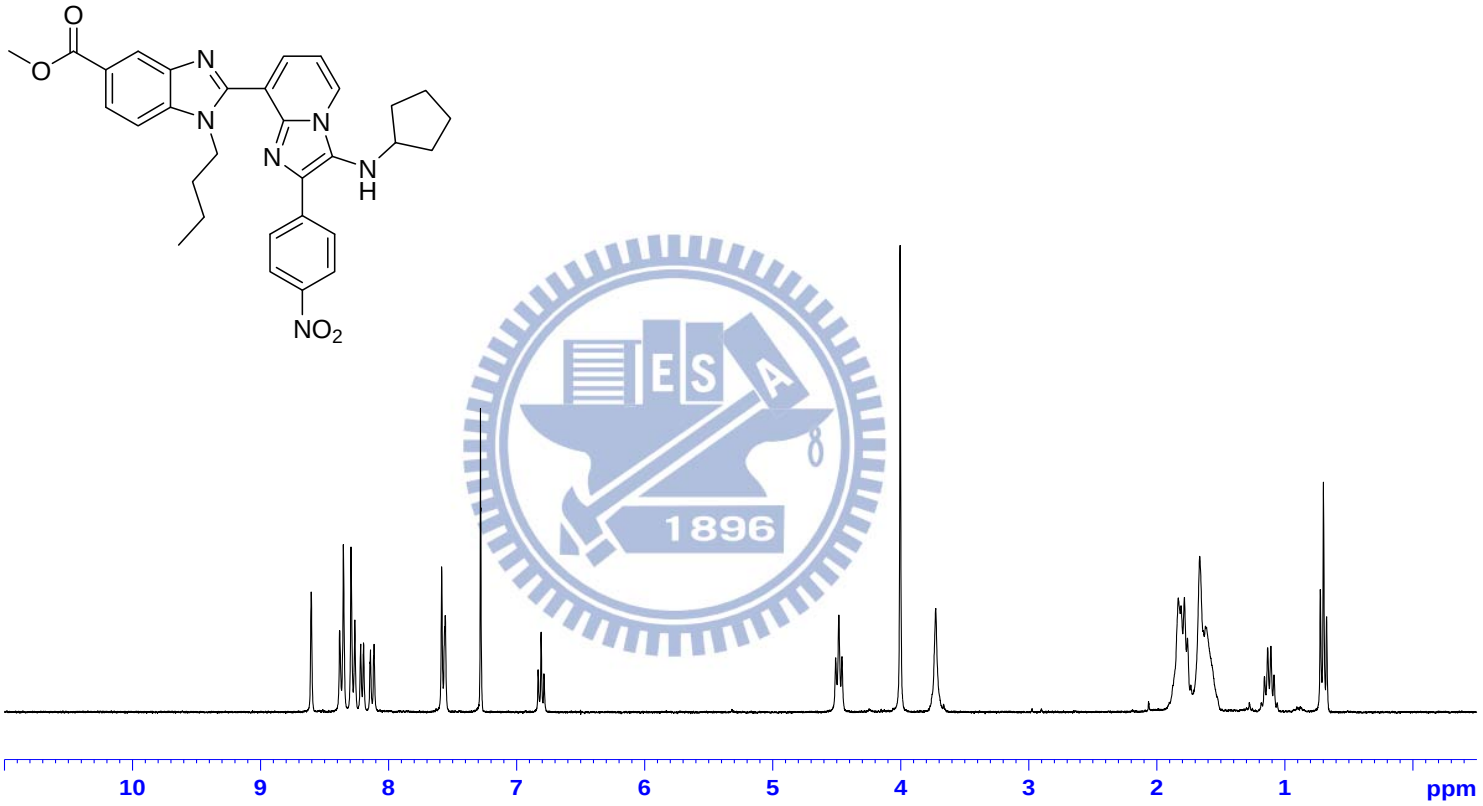
^{13}C NMR spectrum (75 MHz) of compound 10j in $CDCl_3$



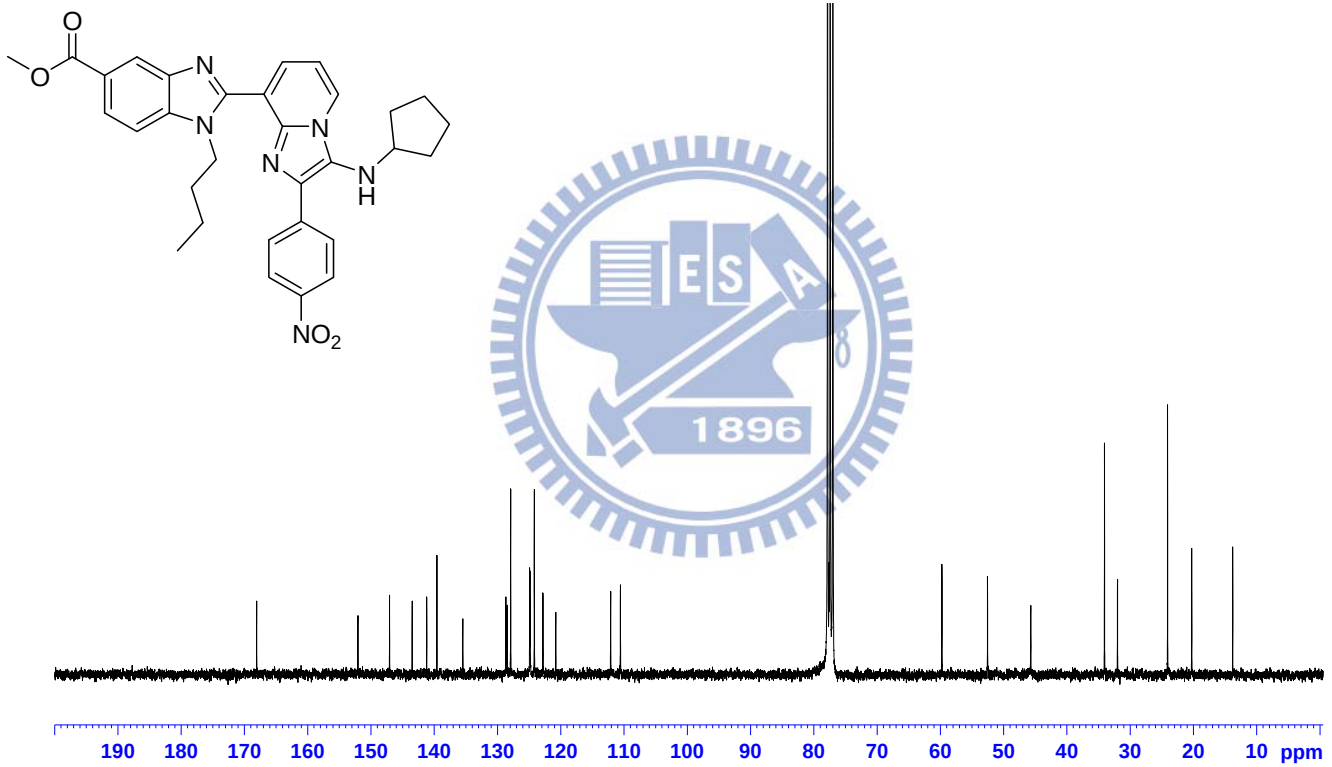
^{1}HNMR spectrum (300 MHz) of compound 10k in $CDCl_3$



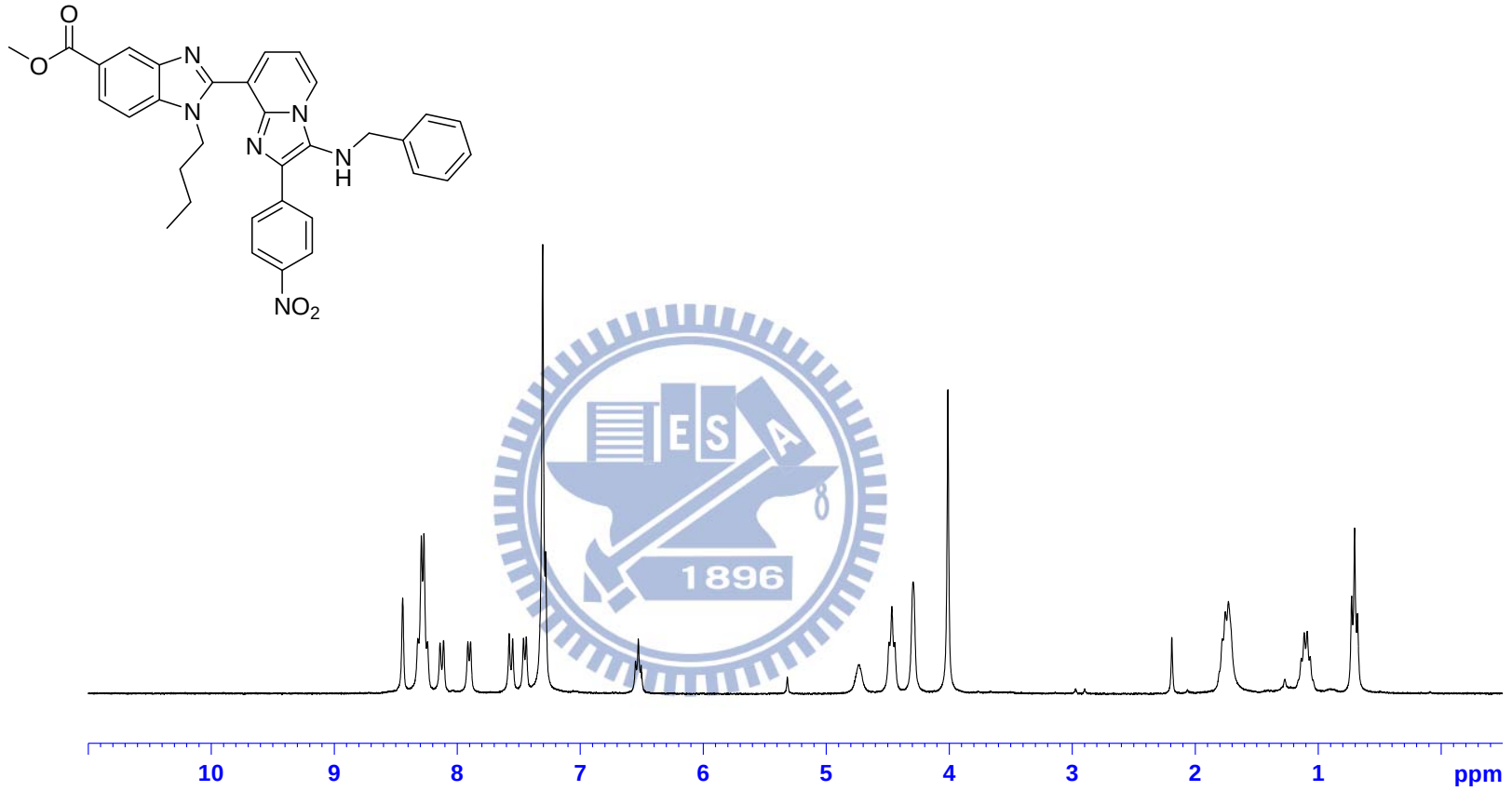
^{13}C NMR spectrum (75 MHz) of compound 10k in $CDCl_3$



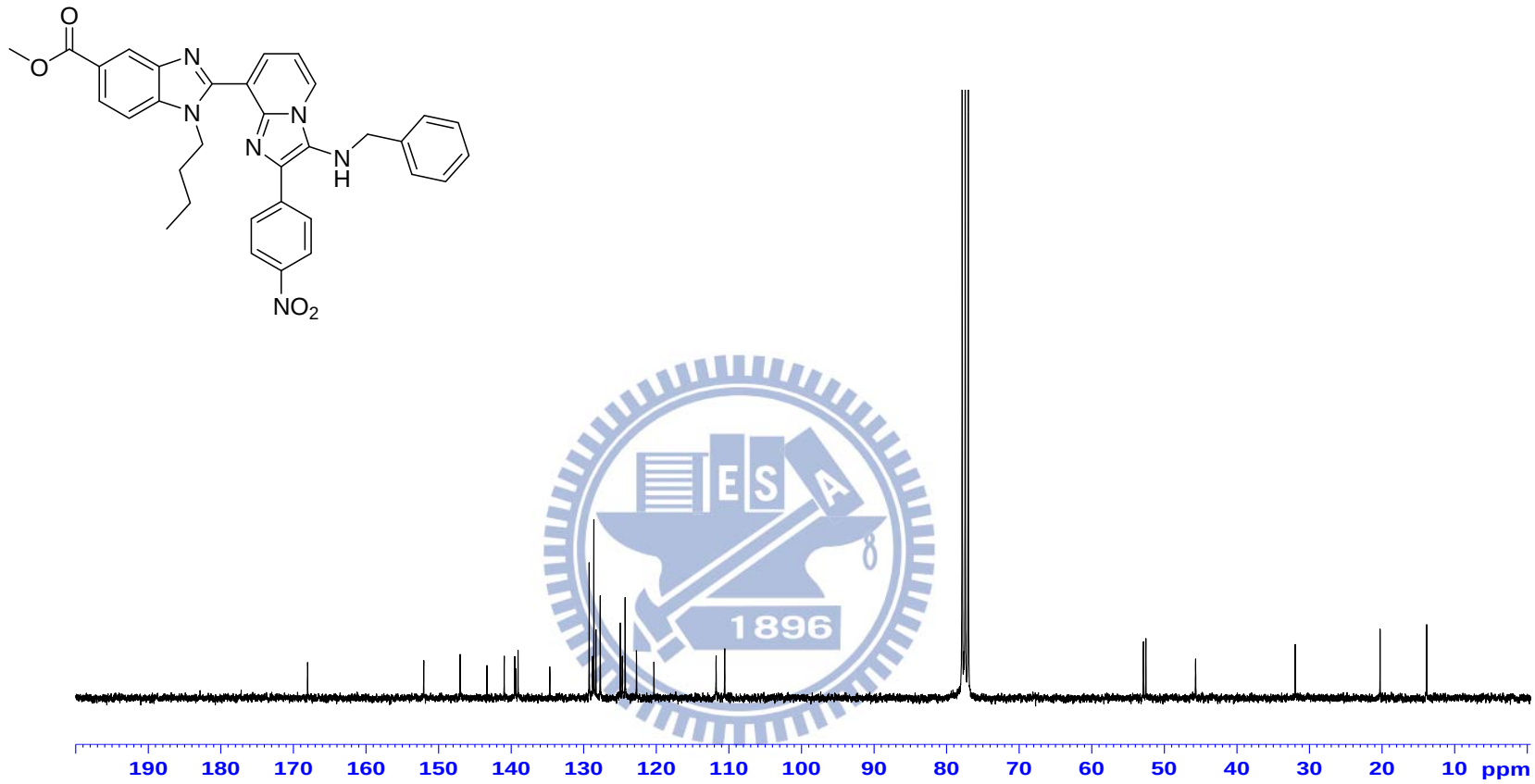
^{1}HNMR spectrum (300 MHz) of compound 10l in $CDCl_3$



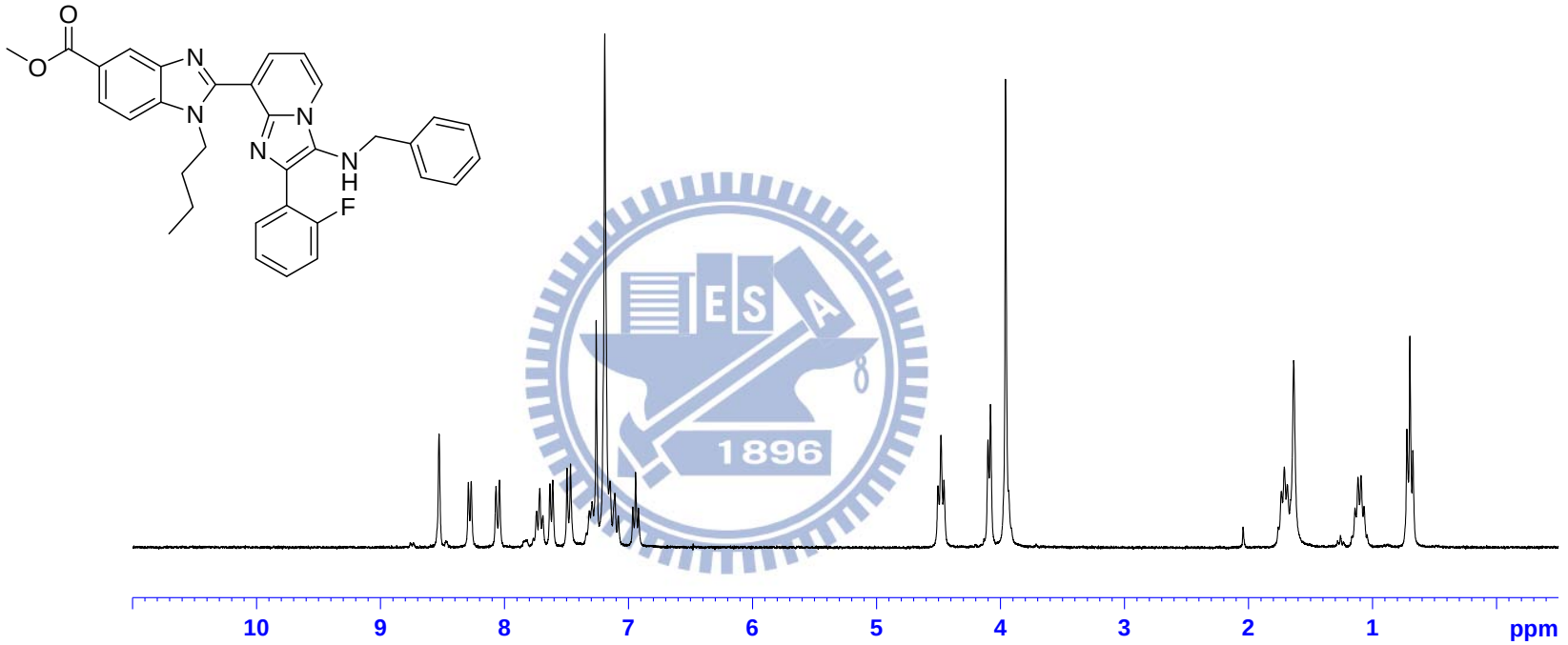
^{13}C NMR spectrum (75 MHz) of compound 10l in $CDCl_3$



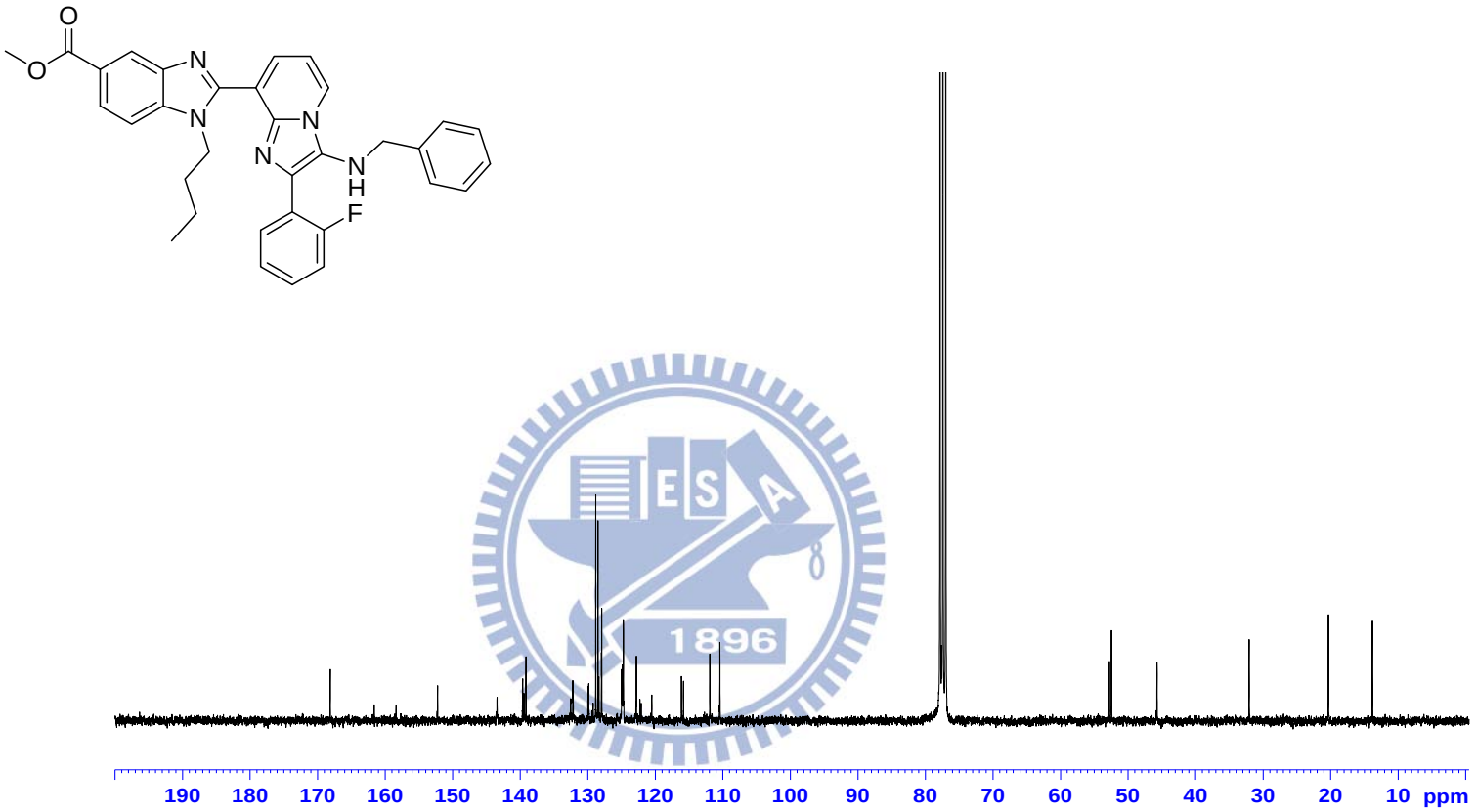
^{1}H NMR spectrum (75 MHz) of compound 10m in $CDCl_3$



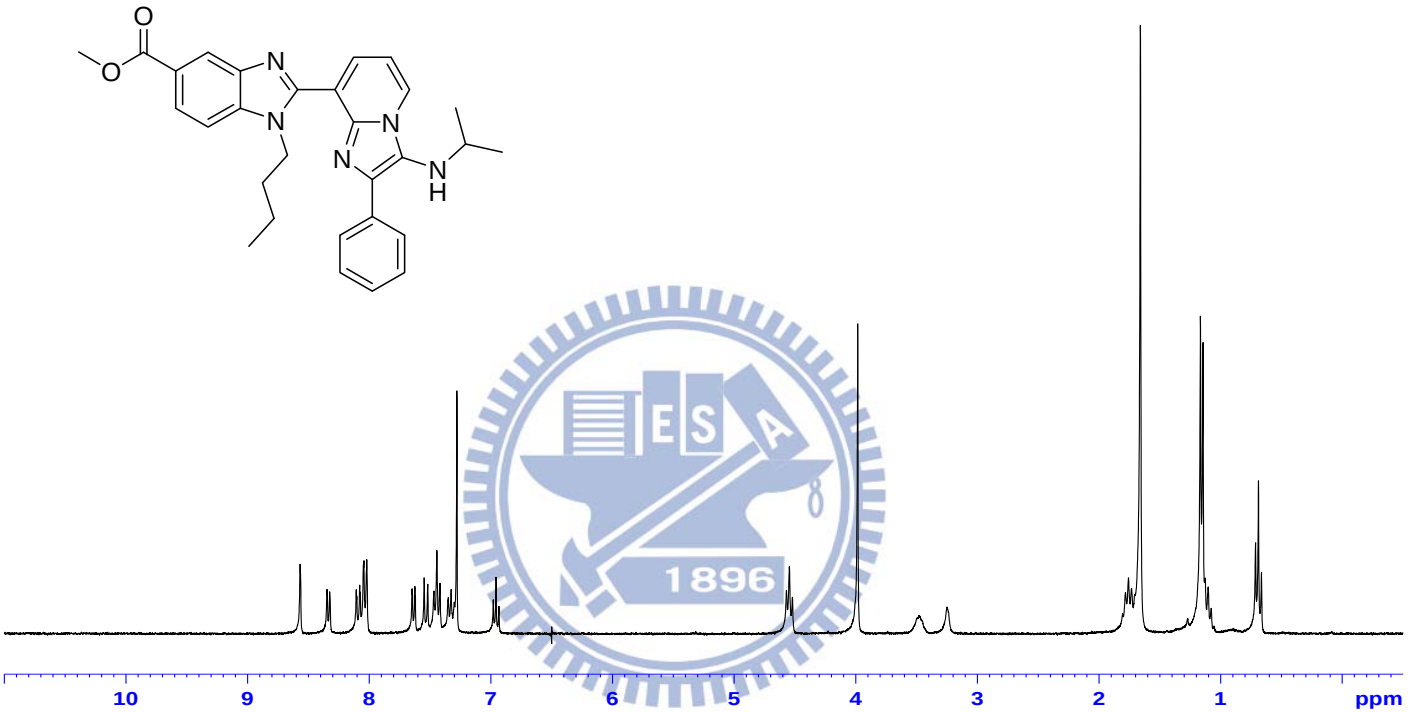
^{13}C NMR spectrum (75 MHz) of compound 10m in $CDCl_3$



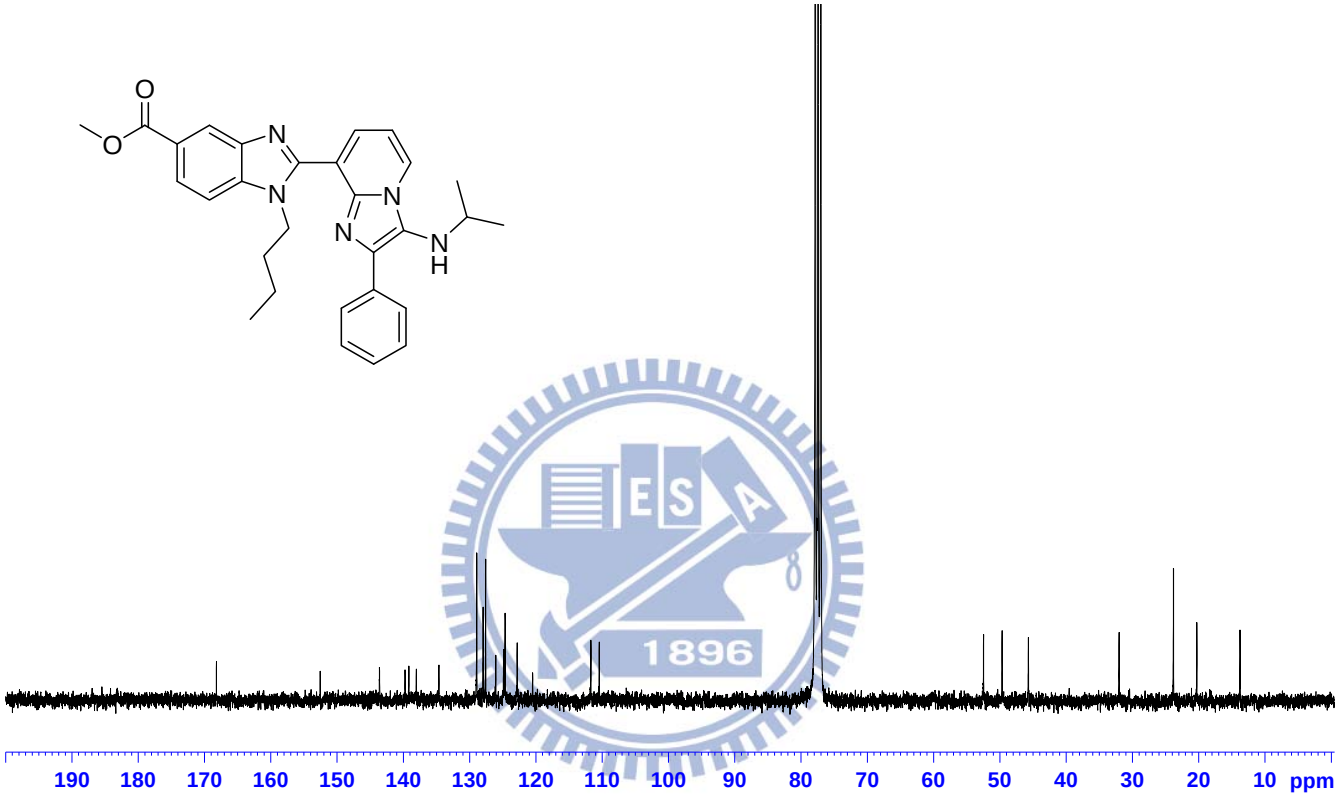
^{1}HNMR spectrum (300 MHz) of compound 10n in $CDCl_3$



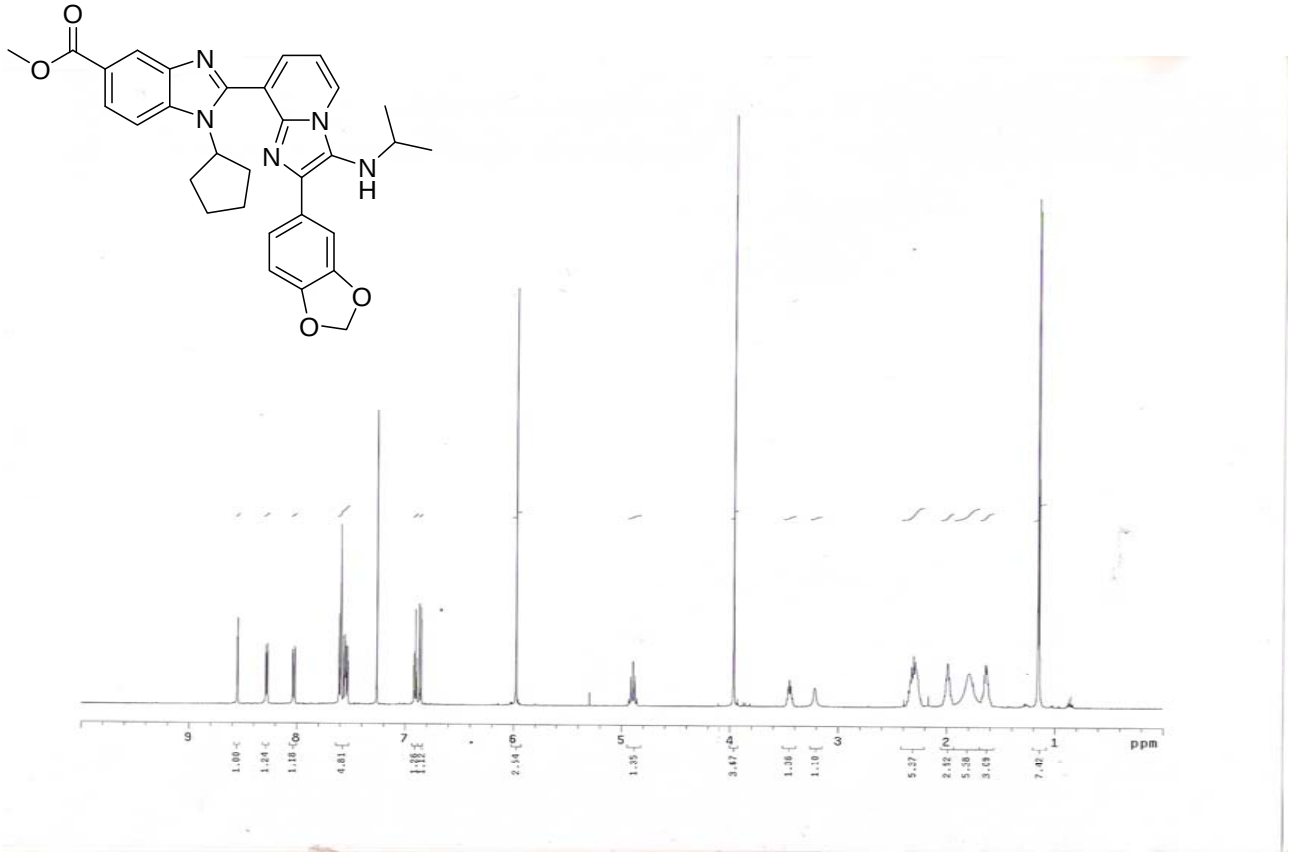
^{13}C NMR spectrum (75 MHz) of compound 10n in $CDCl_3$



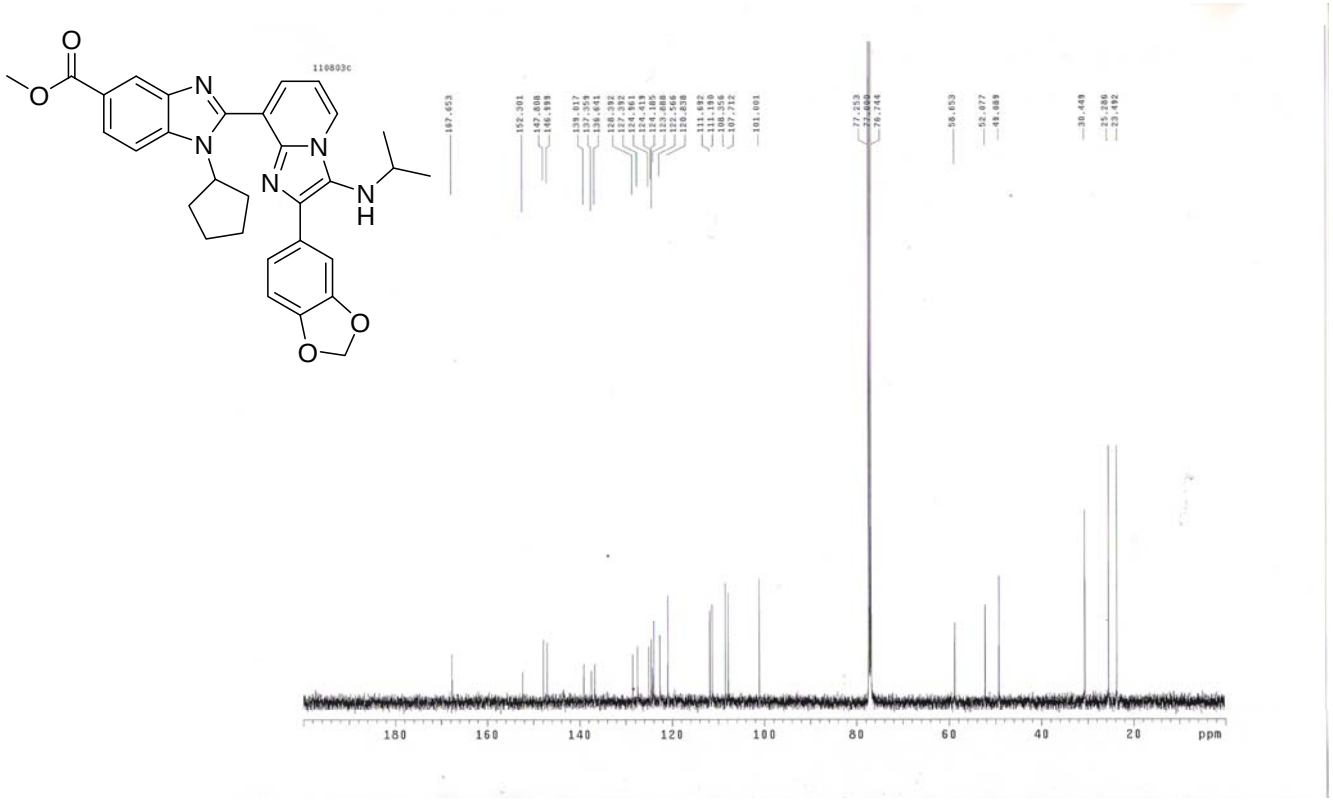
^{1}HNMR spectrum (300 MHz) of compound 10o in $CDCl_3$



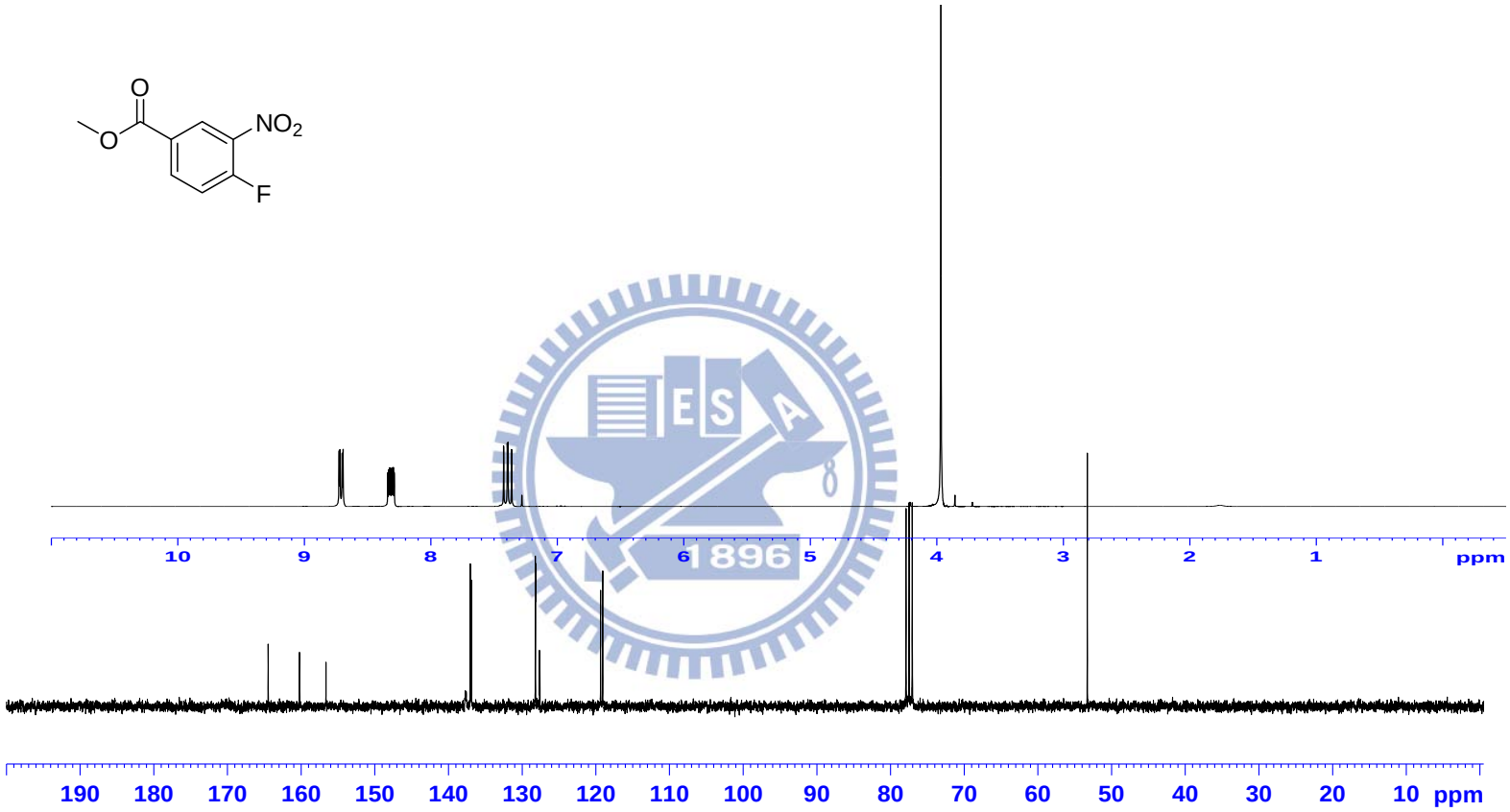
^{13}C NMR spectrum (125 MHz) of compound 10o in $CDCl_3$



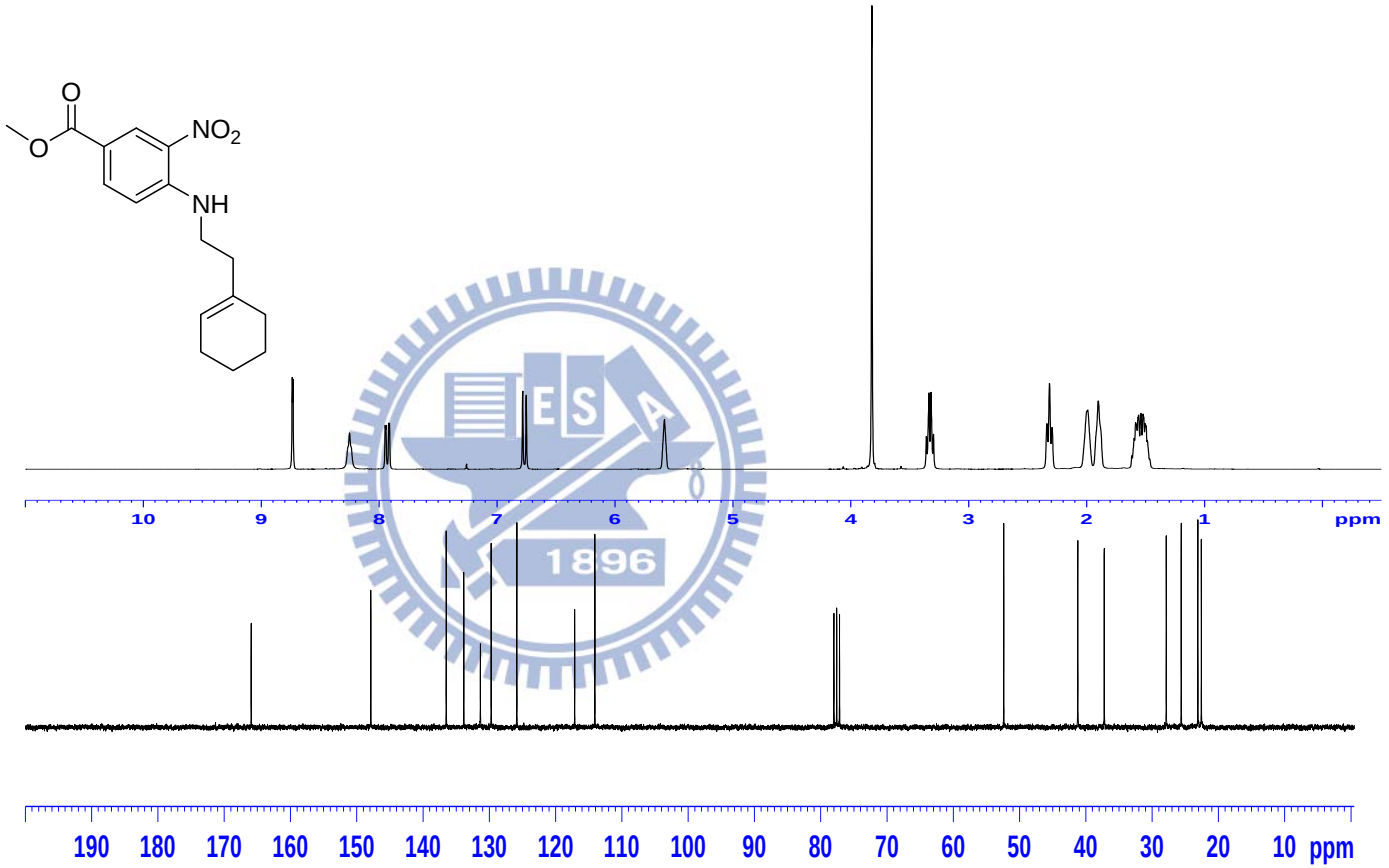
^{1}HNMR spectrum (500 MHz) of compound 10p in $CDCl_3$



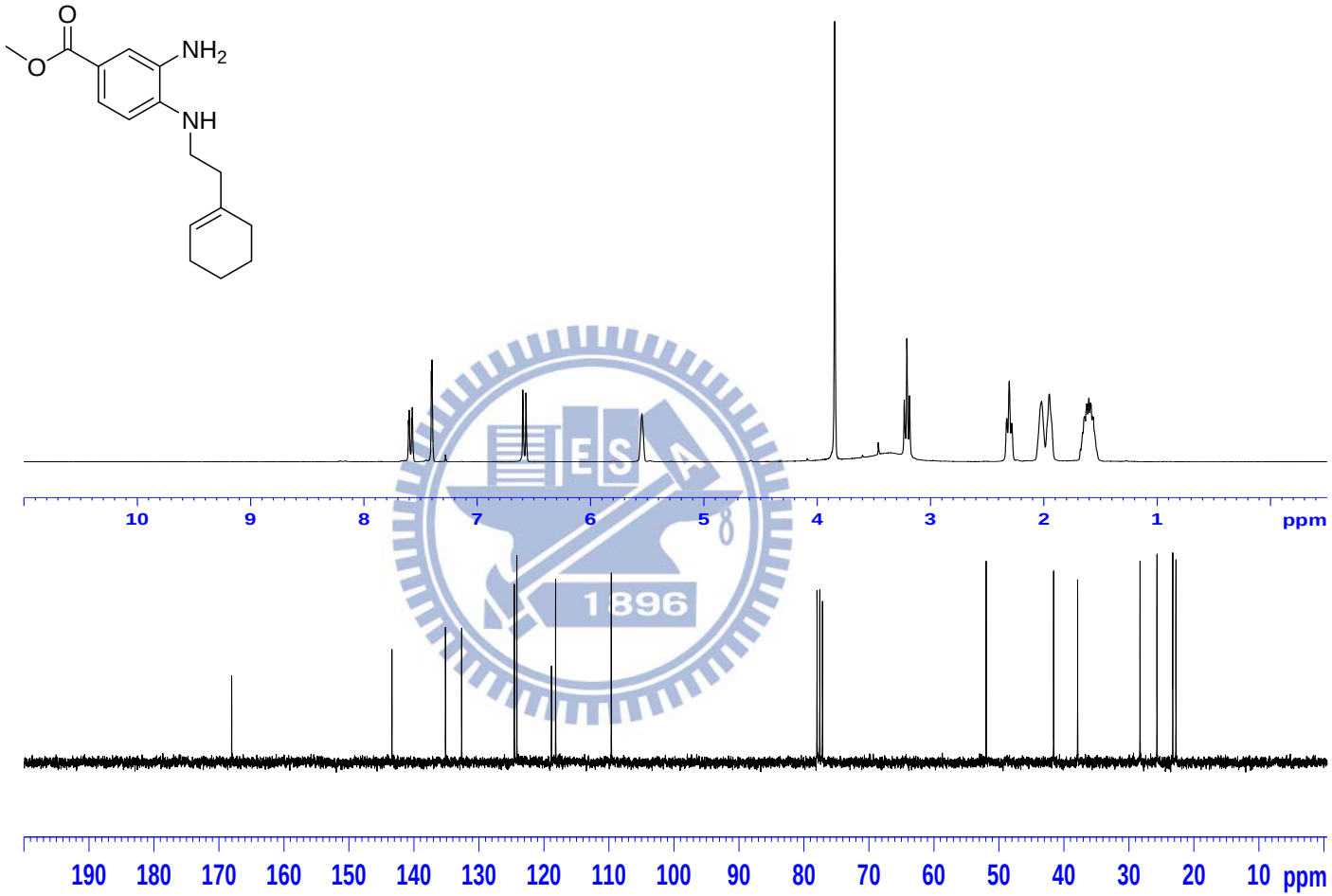
^{13}C NMR spectrum (125 MHz) of compound 10p in $CDCl_3$



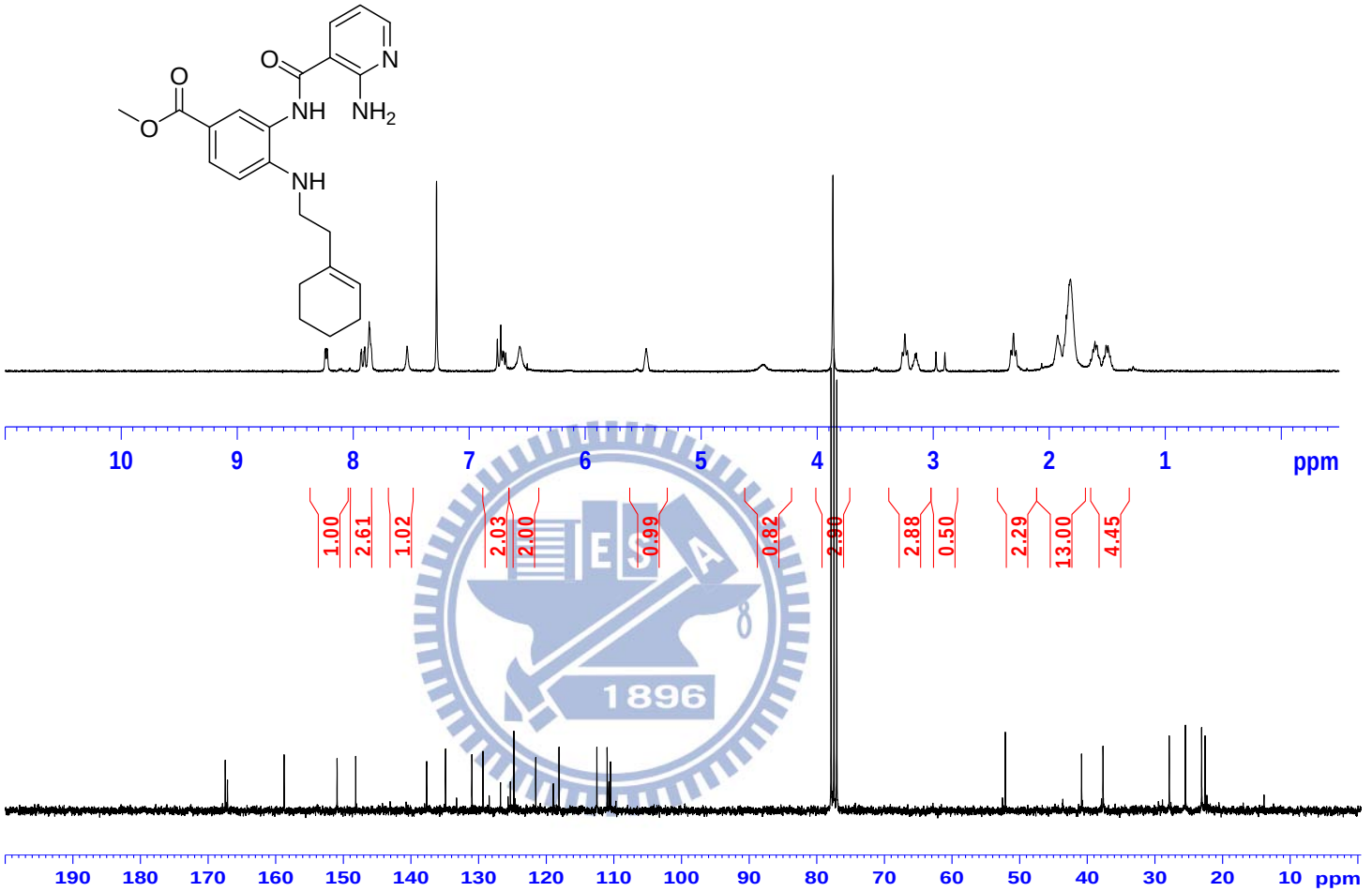
^{1}HNMR spectrum (300 MHz) and ^{13}C NMR spectrum (75 MHz) of intermediate compound 1 in $CDCl_3$



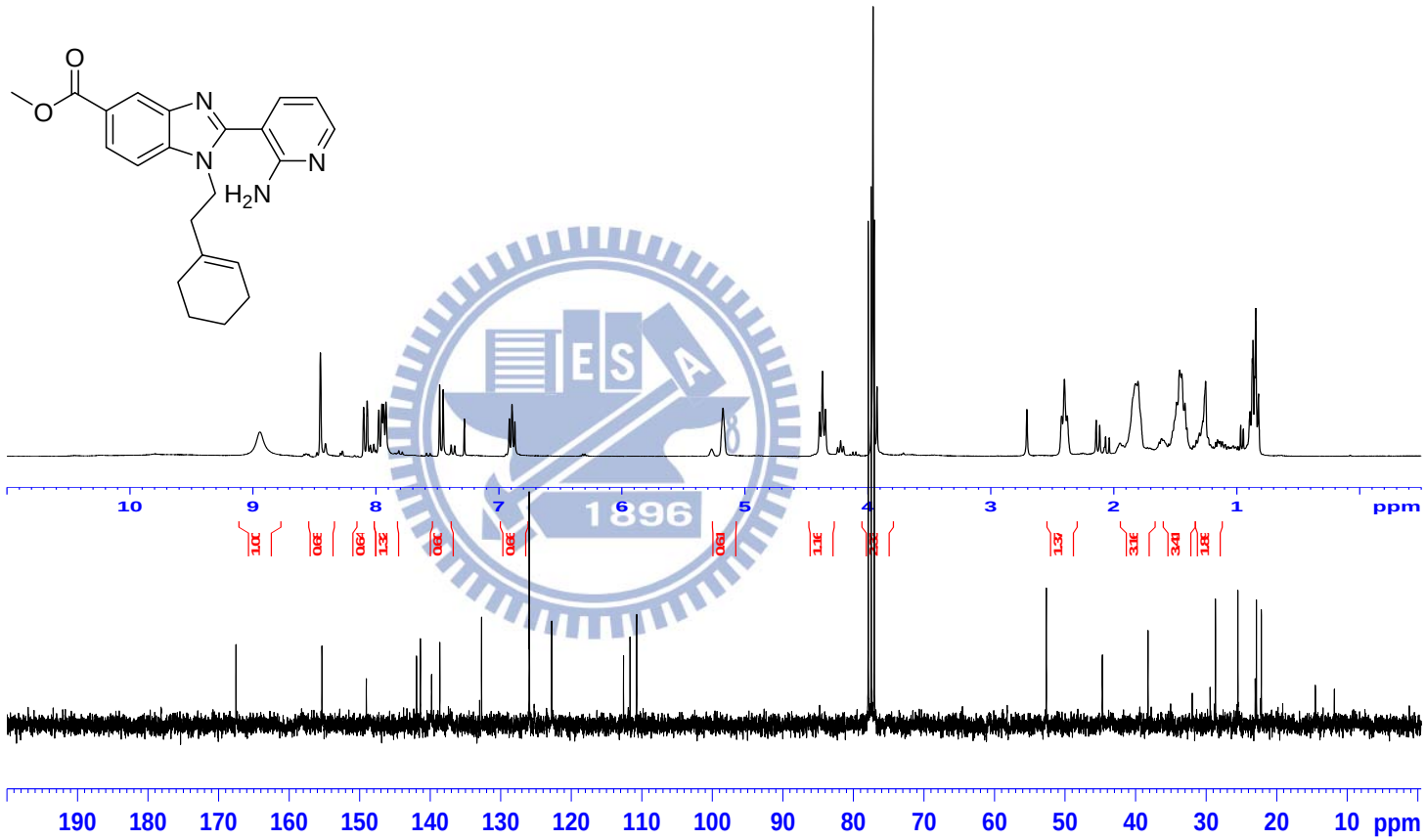
^{1}HNMR spectrum (300 MHz) and ^{13}C NMR spectrum (75 MHz) of intermediate compound 2g in $CDCl_3$



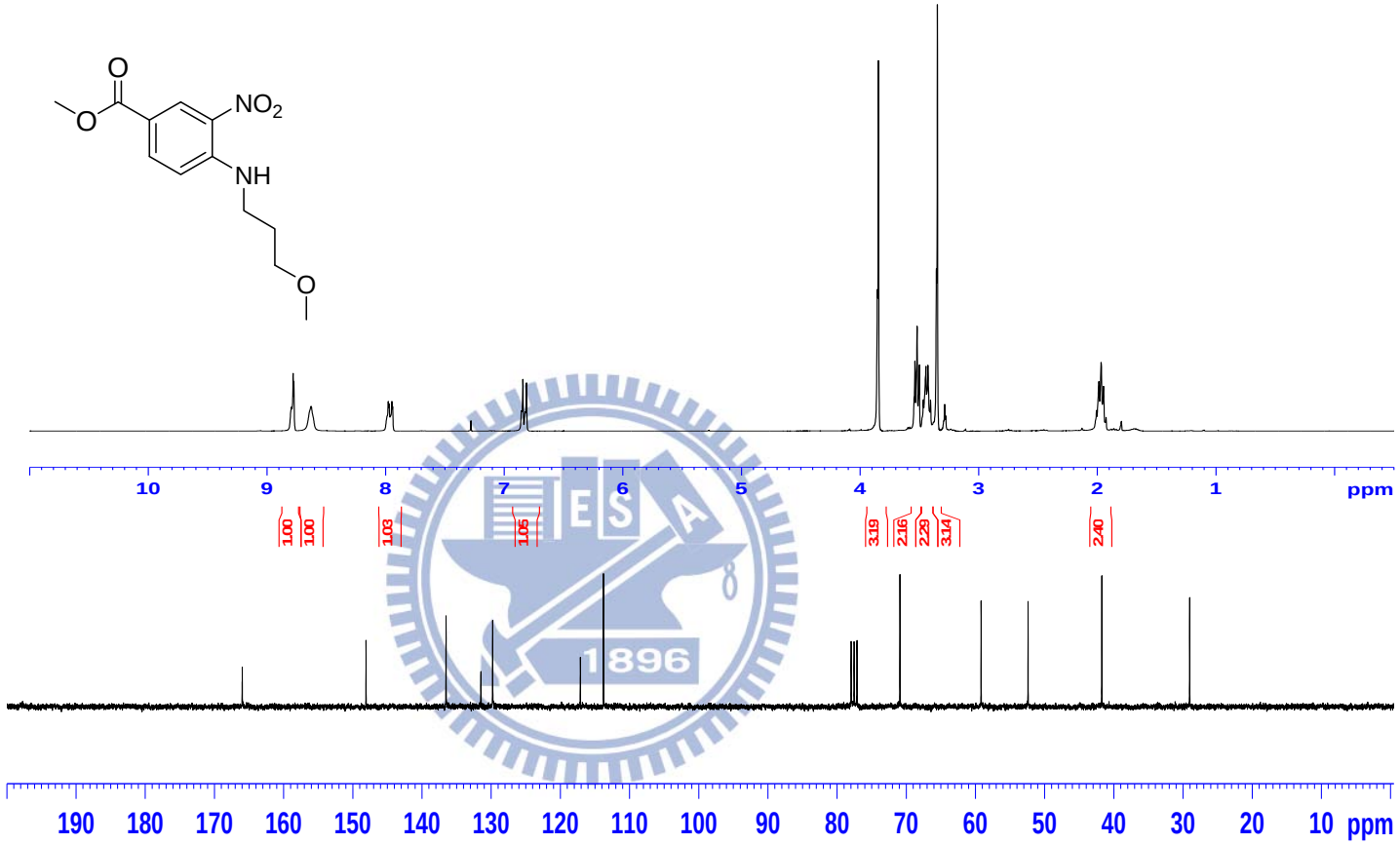
^{1}HNMR spectrum (300 MHz) and ^{13}C NMR spectrum (75 MHz) of intermediate compound 3g in $CDCl_3$



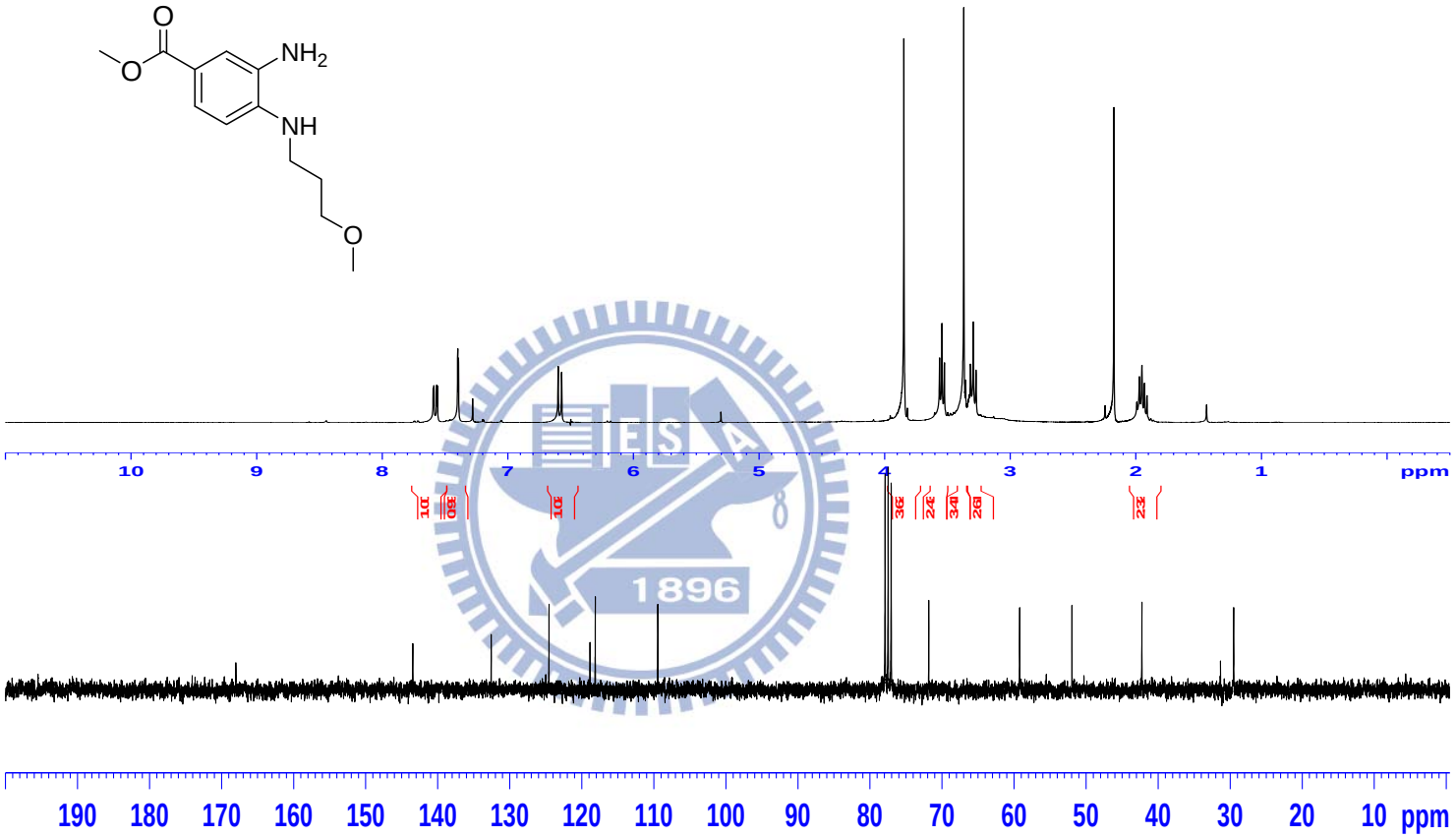
^{1}HNMR spectrum (300 MHz) and ^{13}C NMR spectrum (75 MHz) of intermediate compound 4g in $CDCl_3$



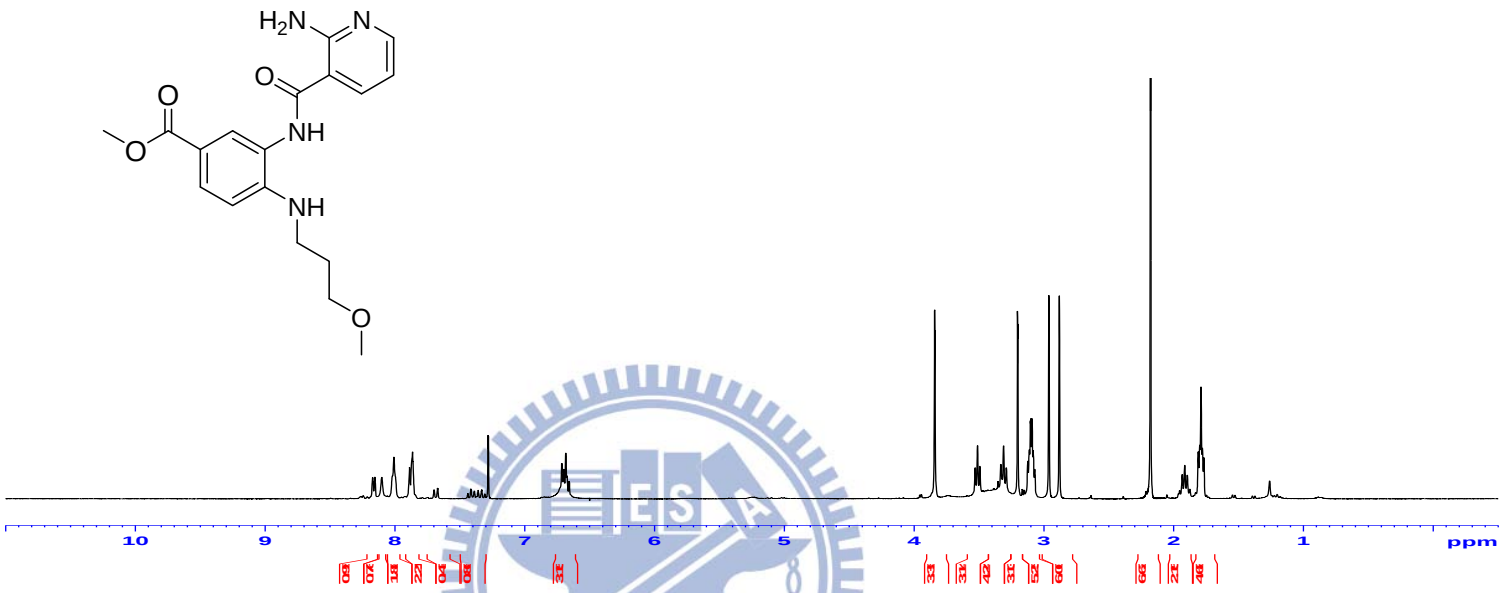
^{1}HNMR spectrum (300 MHz) and ^{13}C NMR spectrum (75 MHz) of intermediate compound 5g in $CDCl_3$



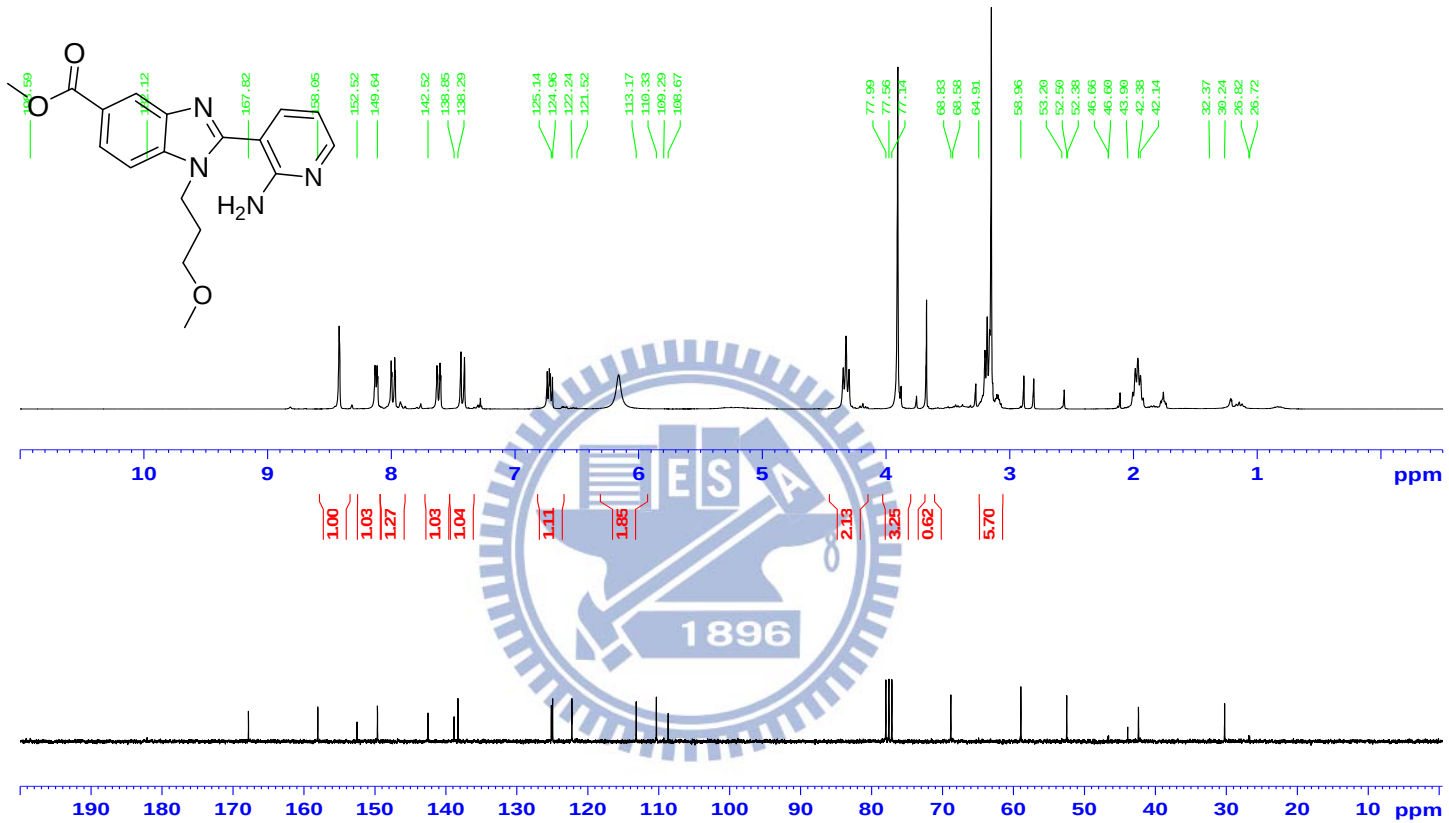
^{1}HNMR spectrum (300 MHz) and ^{13}C NMR spectrum (75 MHz) of intermediate compound 2a in $CDCl_3$



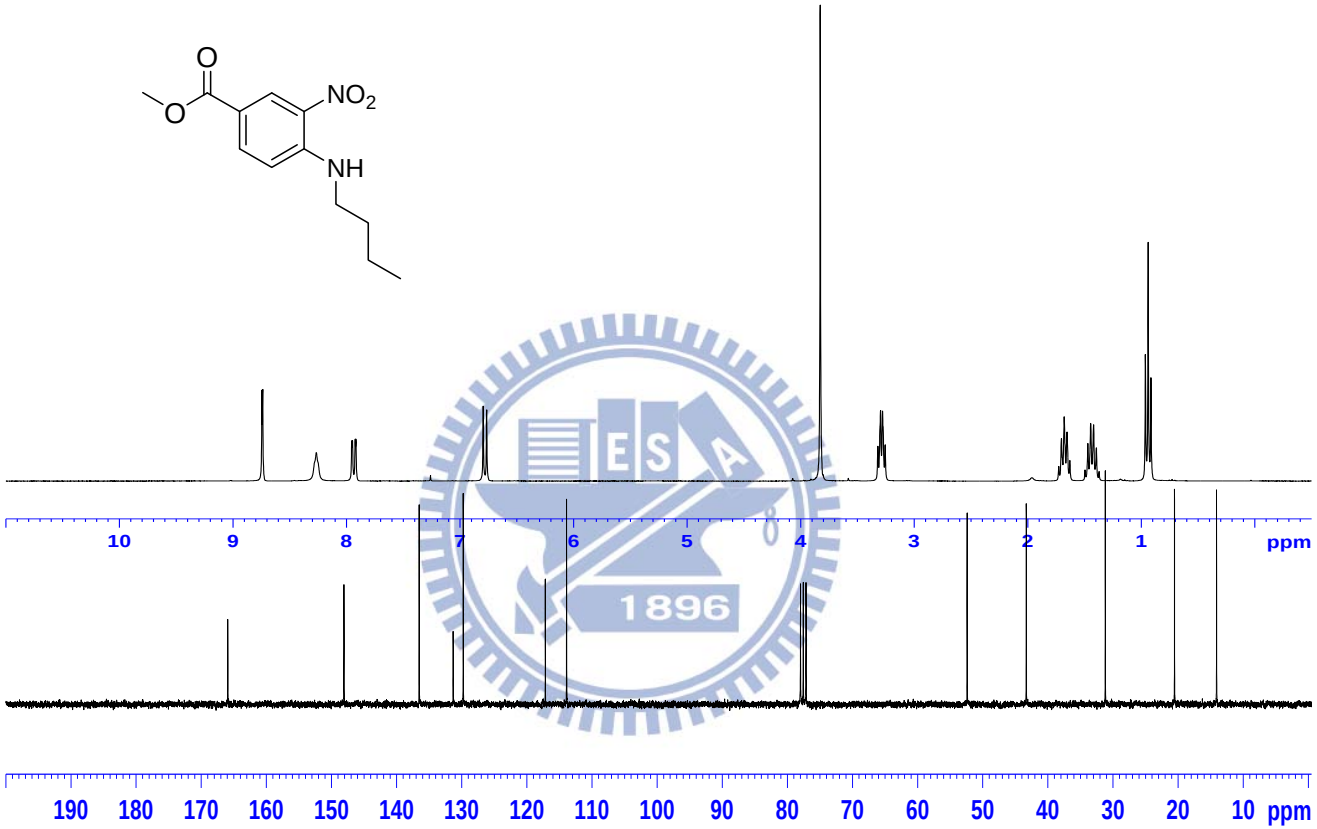
^{1}HNMR spectrum (300 MHz) and ^{13}C NMR spectrum (75 MHz) of intermediate compound 3a in $CDCl_3$



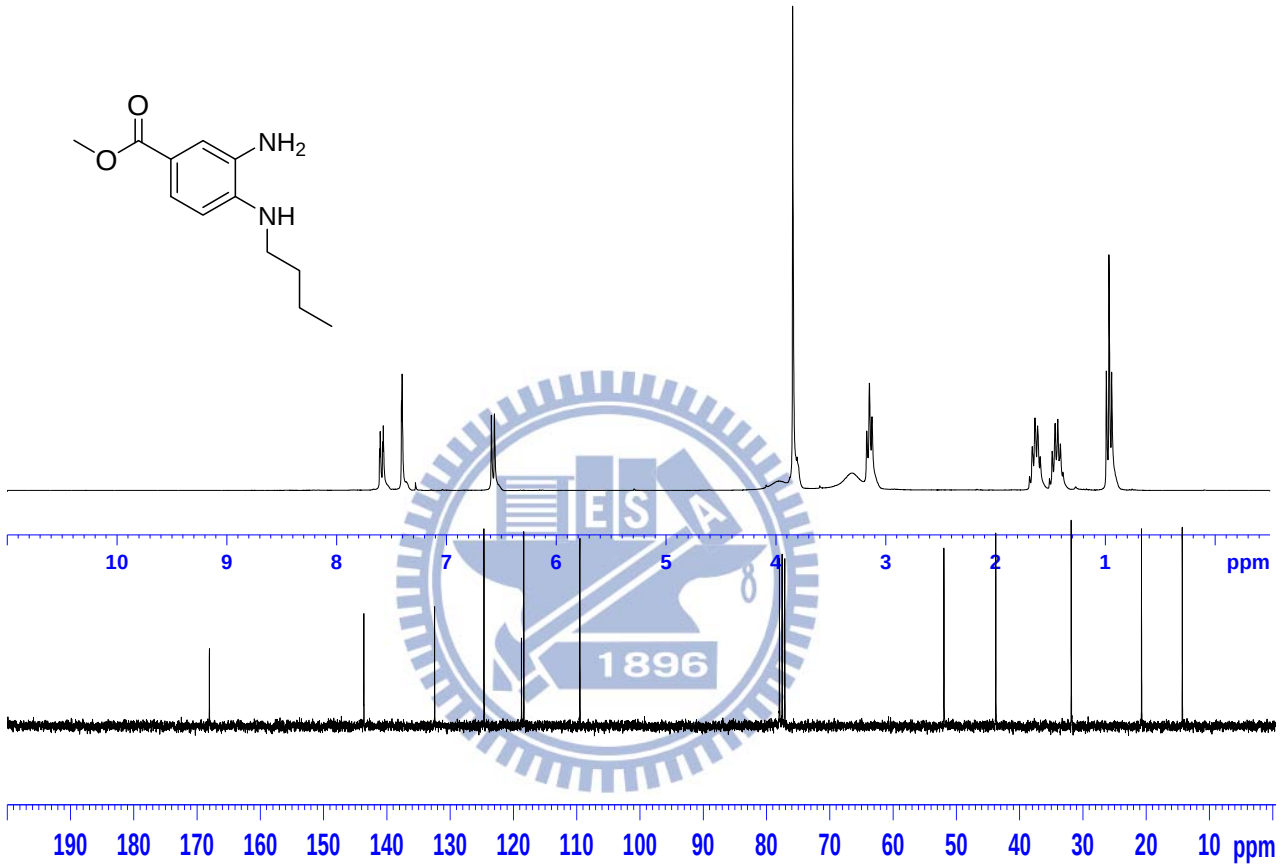
^{1}HNMR spectrum (300 MHz) and ^{13}C NMR spectrum (75 MHz) of intermediate compound 4a in $CDCl_3$



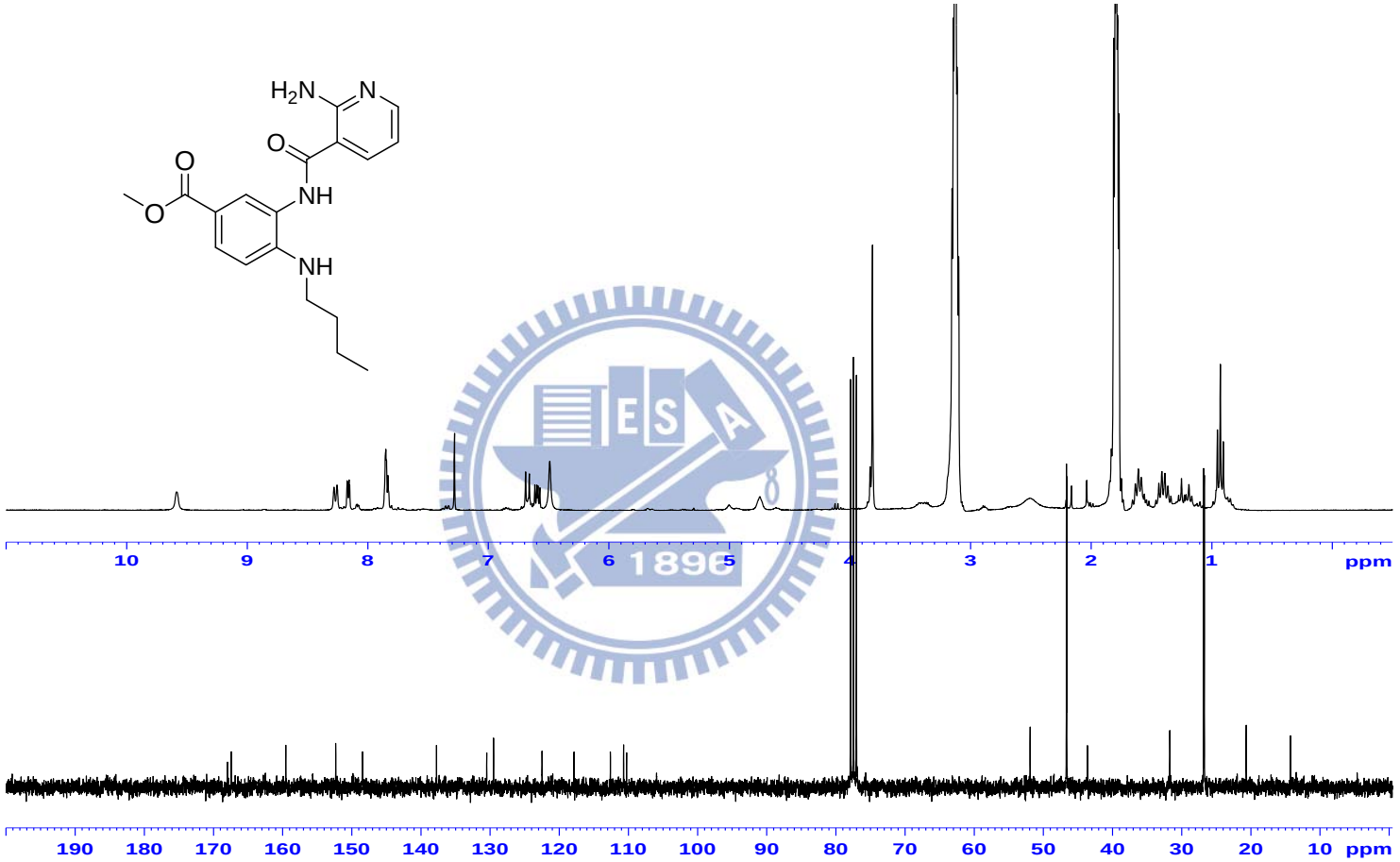
^{1}HNMR spectrum (300 MHz) and ^{13}C NMR spectrum (75 MHz) of intermediate compound 5a in $CDCl_3$



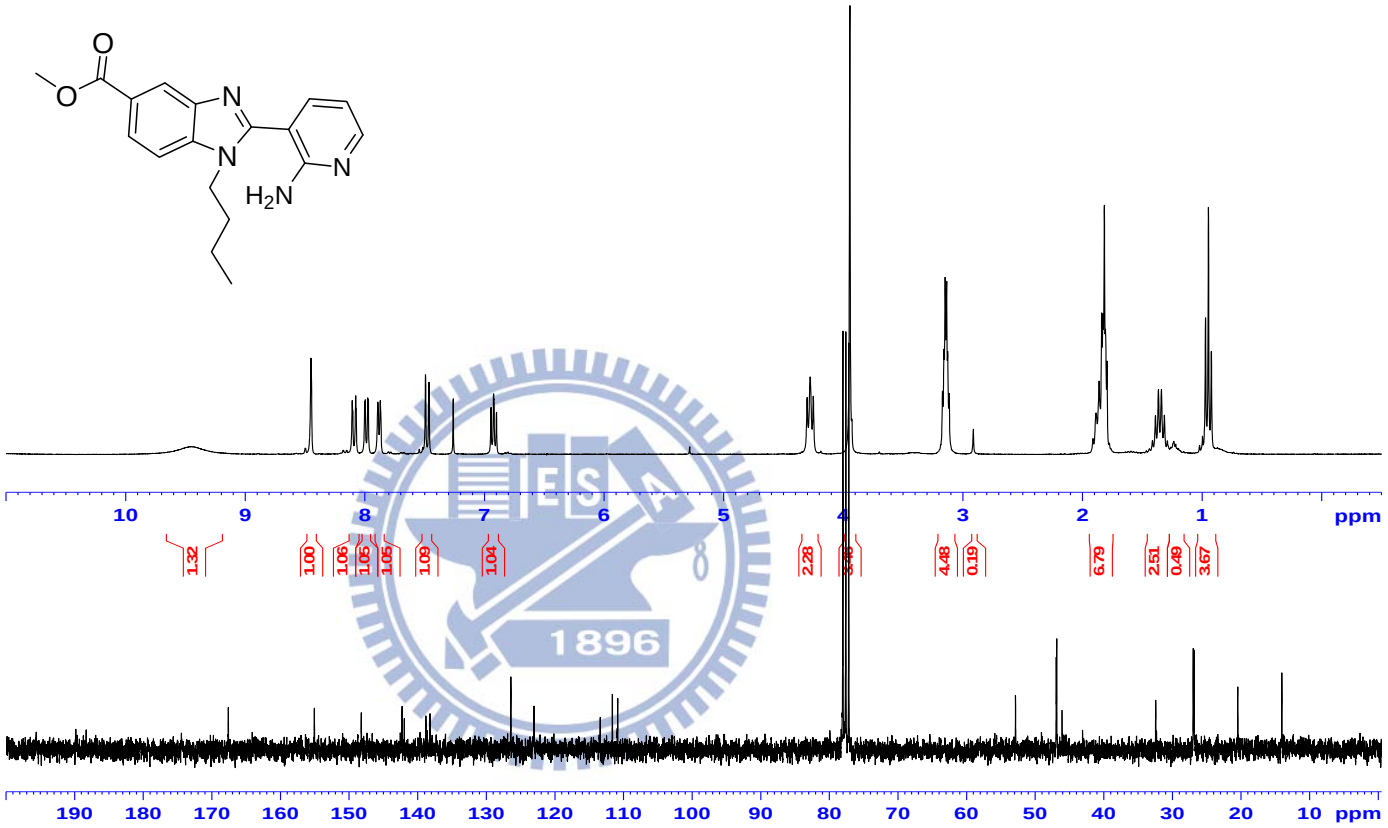
^{1}HNMR spectrum (300 MHz) and ^{13}C NMR spectrum (75 MHz) of intermediate compound 2j in $CDCl_3$



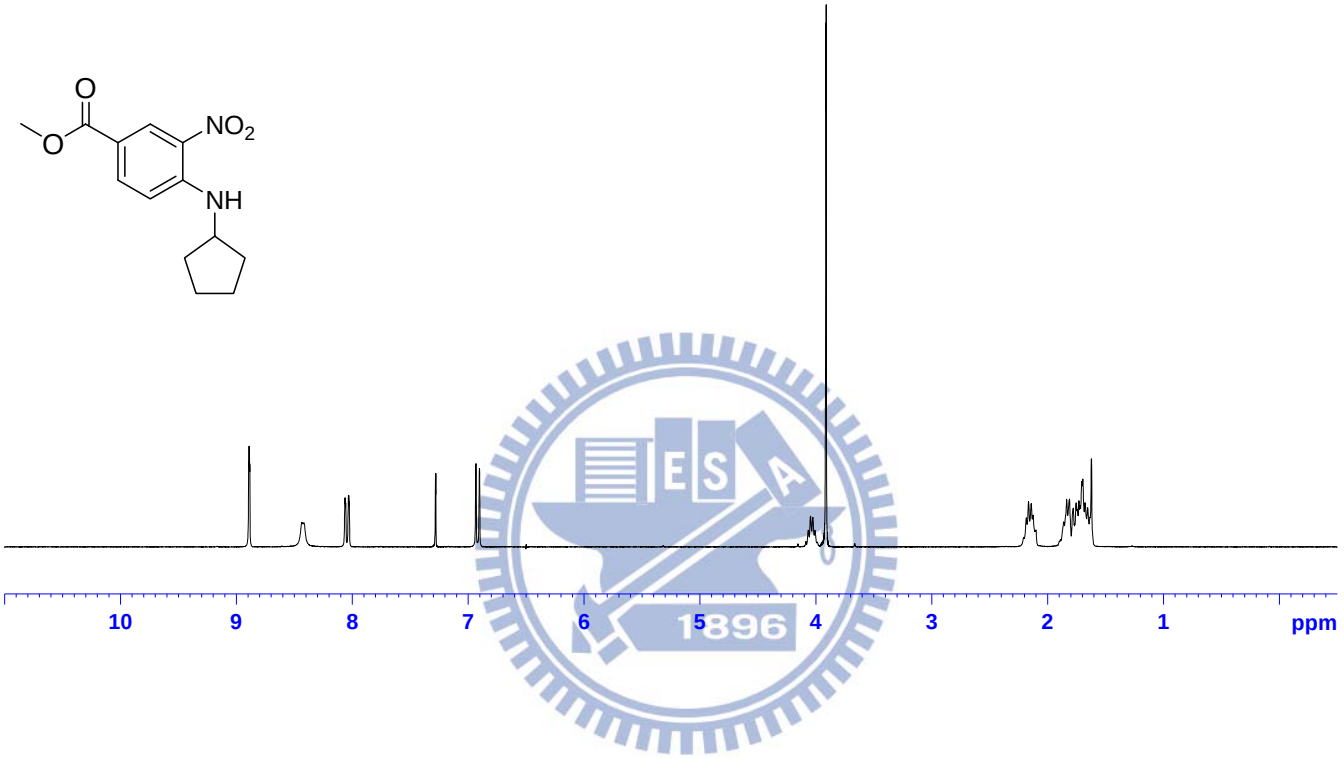
^{1}HNMR spectrum (300 MHz) and ^{13}C NMR spectrum (75 MHz) of intermediate compound 3j in $CDCl_3$



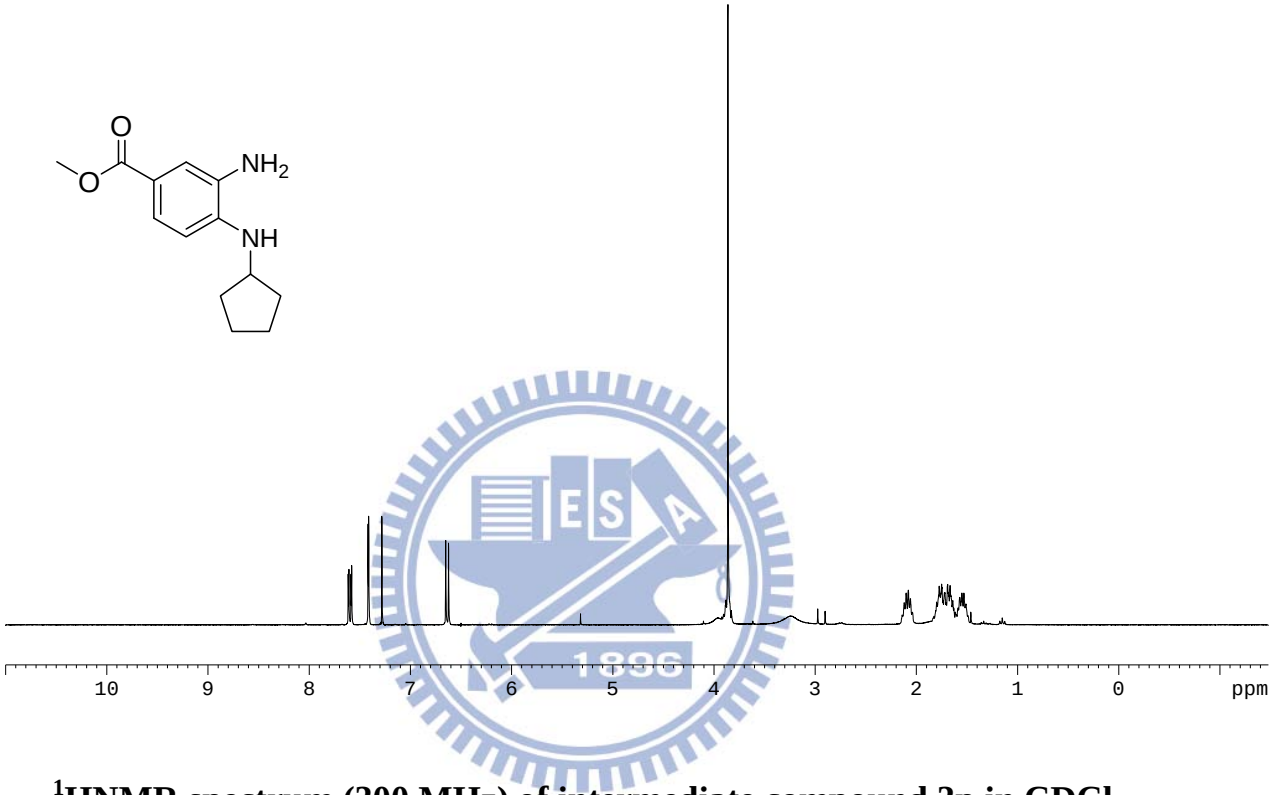
^{1}HNMR spectrum (300 MHz) and ^{13}C NMR spectrum (75 MHz) of intermediate compound 4j in $CDCl_3$



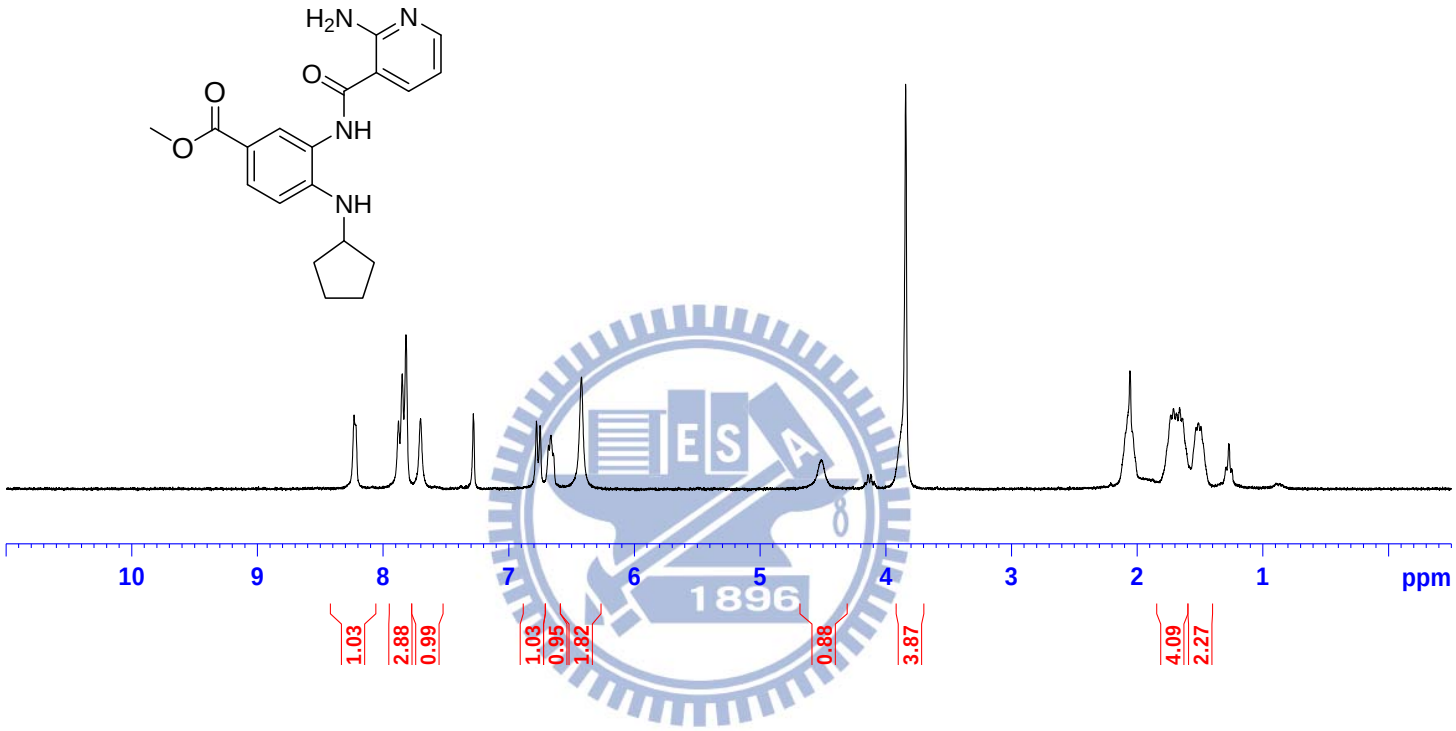
^{1}HNMR spectrum (300 MHz) and ^{13}C NMR spectrum (75 MHz) of intermediate compound 5j in $CDCl_3$



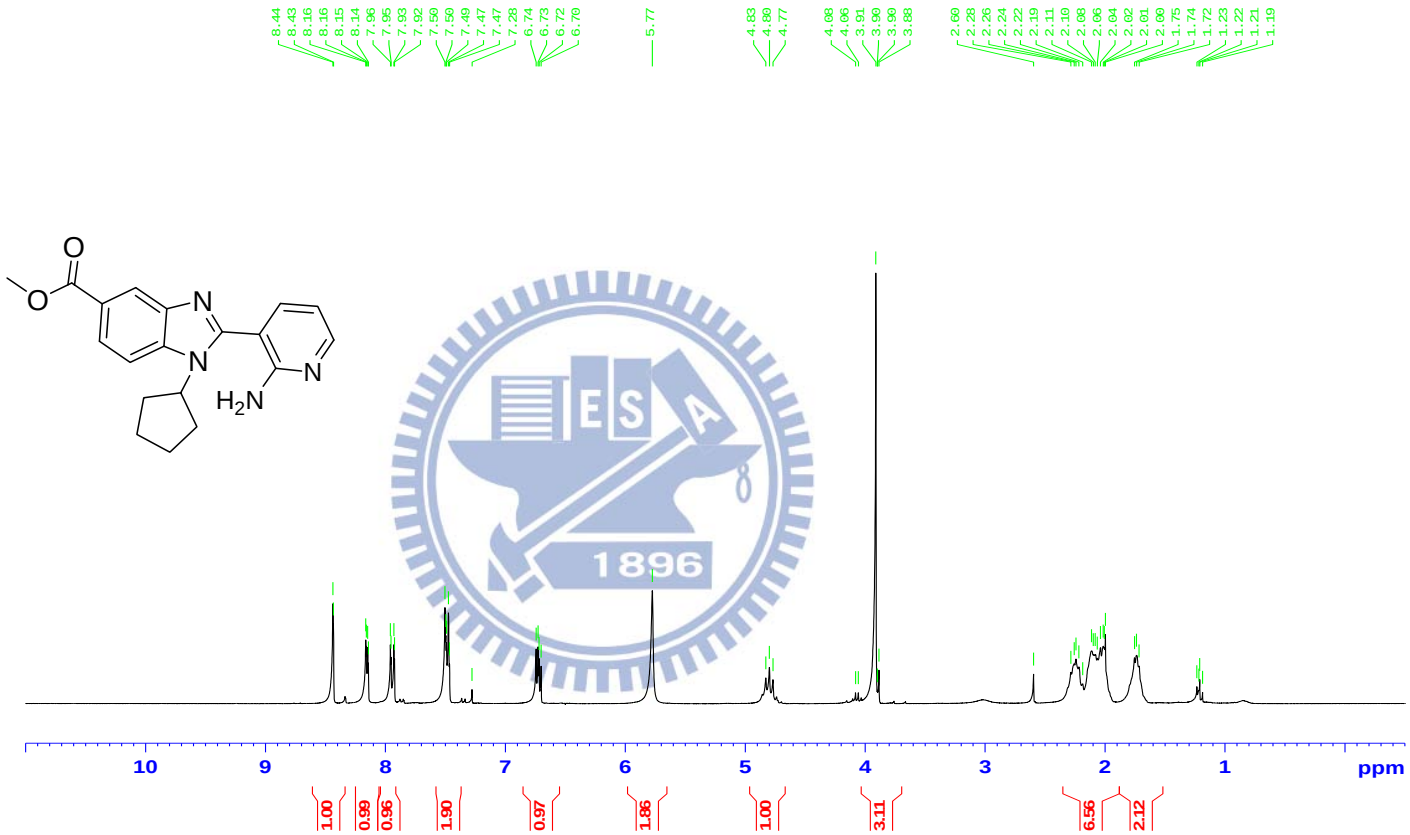
^{1}HNMR spectrum (300 MHz) of intermediate compound 2p in $CDCl_3$



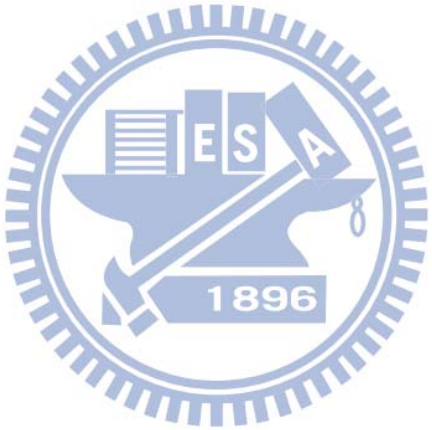
^{1}HNMR spectrum (300 MHz) of intermediate compound 3p in $CDCl_3$

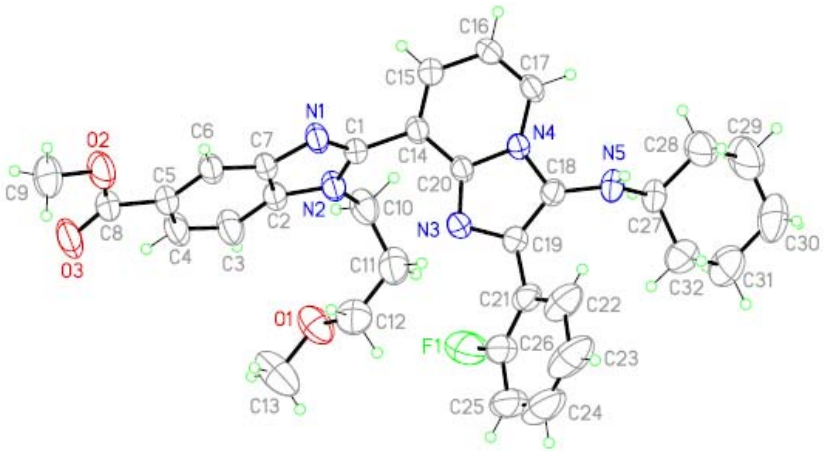


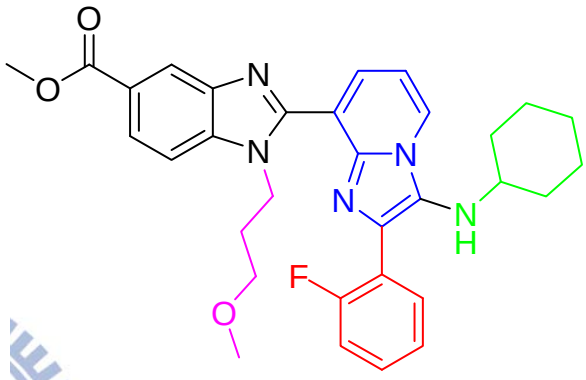
^{1}HNMR spectrum (300 MHz) of intermediate compound 4p in $CDCl_3$



^{1}HNMR spectrum (300 MHz) of intermediate compound 5p in $CDCl_3$


E S A
1896





10C

ORTEP diagram of compound 10c.

Table 1. Crystal data and structure refinement for 10c.

Identification code	101141_0m	
Empirical formula	C32 H34 F N5 O3	
Formula weight	555.64	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 1 2/c 1	
Unit cell dimensions	a = 26.3870(9) Å	α= 90°.
	b = 8.2165(3) Å	β= 113.9640(10)°.
	c = 29.0458(9) Å	γ = 90°.
Volume	5754.6(3) $Å^3$	
Z	8	
Density (calculated)	1.283 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	2352	
Crystal size	0.20 x 0.18 x 0.18 mm^3	
Theta range for data collection	1.69 to 26.40°.	
Index ranges	-32<=h<=32, -9<=k<=10, -29<=l<=36	
Reflections collected	22660	
Independent reflections	5865 [R(int) = 0.0247]	
Completeness to theta = 26.40°	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9486 and 0.9200	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5865 / 0 / 372	
Goodness-of-fit on F^2	1.029	
Final R indices [I>2sigma(I)]	R1 = 0.0504, wR2 = 0.1514	
R indices (all data)	R1 = 0.0730, wR2 = 0.1752	
Largest diff. peak and hole	0.414 and -0.429 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 101141_0m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	9004(1)	3716(2)	470(1)	36(1)
C(2)	8322(1)	3728(2)	723(1)	41(1)
C(3)	7963(1)	3588(3)	965(1)	55(1)
C(4)	7435(1)	4147(3)	710(1)	55(1)
C(5)	7258(1)	4842(3)	229(1)	45(1)
C(6)	7614(1)	4954(3)	-12(1)	46(1)
C(7)	8152(1)	4379(2)	241(1)	40(1)
C(8)	6685(1)	5466(3)	-12(1)	51(1)
C(9)	6015(1)	6660(4)	-746(1)	79(1)
C(10)	9234(1)	2539(3)	1341(1)	54(1)
C(11)	9552(1)	3714(4)	1756(1)	65(1)
C(12)	9210(1)	4786(3)	1933(1)	64(1)
C(13)	8586(1)	4771(5)	2323(1)	102(1)
C(14)	9557(1)	3468(2)	464(1)	36(1)
C(15)	9646(1)	2300(2)	173(1)	41(1)
C(16)	10165(1)	2192(2)	136(1)	42(1)
C(17)	10576(1)	3250(2)	383(1)	40(1)
C(18)	10822(1)	5729(2)	938(1)	37(1)
N(3)	9992(1)	5860(2)	1005(1)	39(1)
C(20)	9987(1)	4588(2)	725(1)	35(1)
C(21)	10635(1)	8132(3)	1401(1)	49(1)
C(22)	10926(1)	9338(3)	1264(1)	73(1)
C(23)	11013(1)	10856(4)	1498(1)	98(1)
C(24)	10822(1)	11197(4)	1858(2)	107(1)
C(25)	10546(1)	10037(5)	2004(1)	96(1)
C(26)	10458(1)	8543(3)	1773(1)	65(1)
C(27)	11810(1)	5087(3)	1387(1)	45(1)
C(28)	12209(1)	4327(4)	1194(1)	75(1)
C(29)	12686(1)	3468(4)	1607(1)	95(1)
C(30)	12985(1)	4566(4)	2042(1)	89(1)
C(31)	12595(1)	5331(4)	2240(1)	86(1)

C(32)	12114(1)	6201(3)	1823(1)	67(1)
F(1)	10187(1)	7450(2)	1923(1)	98(1)
N(1)	8588(1)	4348(2)	88(1)	42(1)
N(2)	8872(1)	3318(2)	866(1)	42(1)
C(19)	10504(1)	6571(2)	1132(1)	39(1)
N(4)	10487(1)	4437(2)	674(1)	34(1)
N(5)	11359(1)	5937(2)	975(1)	43(1)
O(1)	8914(1)	3825(2)	2140(1)	68(1)
O(2)	6544(1)	5879(2)	-493(1)	68(1)
O(3)	6373(1)	5603(2)	194(1)	71(1)

Table 3. Bond lengths [Å] and angles [°] for 101141_0m.

C(1)-N(1)	1.310(2)
C(1)-N(2)	1.369(2)
C(1)-C(14)	1.479(2)
C(2)-N(2)	1.379(2)
C(2)-C(7)	1.393(3)
C(2)-C(3)	1.395(3)
C(3)-C(4)	1.365(3)
C(3)-H(3)	0.9300
C(4)-C(5)	1.404(3)
C(4)-H(4)	0.9300
C(5)-C(6)	1.384(3)
C(5)-C(8)	1.477(3)
C(6)-C(7)	1.390(3)
C(6)-H(6)	0.9300
C(7)-N(1)	1.390(2)
C(8)-O(3)	1.204(2)
C(8)-O(2)	1.334(3)
C(9)-O(2)	1.438(3)
C(9)-H(9A)	0.9600
C(9)-H(9B)	0.9600
C(9)-H(9C)	0.9600
C(10)-N(2)	1.467(2)
C(10)-C(11)	1.506(3)
C(10)-H(10A)	0.9700
C(10)-H(10B)	0.9700
C(11)-C(12)	1.494(3)
C(11)-H(11A)	0.9700
C(11)-H(11B)	0.9700
C(12)-O(1)	1.406(3)
C(12)-H(12A)	0.9700
C(12)-H(12B)	0.9700
C(13)-O(1)	1.416(3)
C(13)-H(13A)	0.9600
C(13)-H(13B)	0.9600

C(13)-H(13C)	0.9600
C(14)-C(15)	1.361(3)
C(14)-C(20)	1.418(3)
C(15)-C(16)	1.420(2)
C(15)-H(15)	0.9300
C(16)-C(17)	1.347(3)
C(16)-H(16)	0.9300
C(17)-N(4)	1.373(2)
C(17)-H(17)	0.9300
C(18)-C(19)	1.373(3)
C(18)-N(5)	1.388(2)
C(18)-N(4)	1.393(2)
N(3)-C(20)	1.321(2)
N(3)-C(19)	1.379(2)
C(20)-N(4)	1.392(2)
C(21)-C(26)	1.381(3)
C(21)-C(22)	1.406(3)
C(21)-C(19)	1.468(3)
C(22)-C(23)	1.393(4)
C(22)-H(22)	0.9300
C(23)-C(24)	1.362(5)
C(23)-H(23)	0.9300
C(24)-C(25)	1.367(5)
C(24)-H(24)	0.9300
C(25)-C(26)	1.372(4)
C(25)-H(25)	0.9300
C(26)-F(1)	1.327(3)
C(27)-N(5)	1.475(2)
C(27)-C(32)	1.504(3)
C(27)-C(28)	1.513(3)
C(27)-H(27)	0.9800
C(28)-C(29)	1.515(3)
C(28)-H(28A)	0.9700
C(28)-H(28B)	0.9700
C(29)-C(30)	1.492(4)
C(29)-H(29A)	0.9700

C(29)-H(29B)	0.9700
C(30)-C(31)	1.507(4)
C(30)-H(30A)	0.9700
C(30)-H(30B)	0.9700
C(31)-C(32)	1.530(3)
C(31)-H(31A)	0.9700
C(31)-H(31B)	0.9700
C(32)-H(32A)	0.9700
C(32)-H(32B)	0.9700
N(5)-H(5)	0.8600

N(1)-C(1)-N(2)	113.21(15)
N(1)-C(1)-C(14)	122.41(15)
N(2)-C(1)-C(14)	124.38(15)
N(2)-C(2)-C(7)	105.38(15)
N(2)-C(2)-C(3)	132.56(18)
C(7)-C(2)-C(3)	122.06(17)
C(4)-C(3)-C(2)	116.91(19)
C(4)-C(3)-H(3)	121.5
C(2)-C(3)-H(3)	121.5
C(3)-C(4)-C(5)	122.02(18)
C(3)-C(4)-H(4)	119.0
C(5)-C(4)-H(4)	119.0
C(6)-C(5)-C(4)	120.75(18)
C(6)-C(5)-C(8)	120.85(19)
C(4)-C(5)-C(8)	118.40(18)
C(5)-C(6)-C(7)	117.92(18)
C(5)-C(6)-H(6)	121.0
C(7)-C(6)-H(6)	121.0
N(1)-C(7)-C(6)	129.58(17)
N(1)-C(7)-C(2)	110.11(15)
C(6)-C(7)-C(2)	120.31(16)
O(3)-C(8)-O(2)	122.77(19)
O(3)-C(8)-C(5)	124.9(2)
O(2)-C(8)-C(5)	112.36(17)
O(2)-C(9)-H(9A)	109.5

O(2)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
O(2)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
N(2)-C(10)-C(11)	114.32(19)
N(2)-C(10)-H(10A)	108.7
C(11)-C(10)-H(10A)	108.7
N(2)-C(10)-H(10B)	108.7
C(11)-C(10)-H(10B)	108.7
H(10A)-C(10)-H(10B)	107.6
C(12)-C(11)-C(10)	115.81(19)
C(12)-C(11)-H(11A)	108.3
C(10)-C(11)-H(11A)	108.3
C(12)-C(11)-H(11B)	108.3
C(10)-C(11)-H(11B)	108.3
H(11A)-C(11)-H(11B)	107.4
O(1)-C(12)-C(11)	109.5(2)
O(1)-C(12)-H(12A)	109.8
C(11)-C(12)-H(12A)	109.8
O(1)-C(12)-H(12B)	109.8
C(11)-C(12)-H(12B)	109.8
H(12A)-C(12)-H(12B)	108.2
O(1)-C(13)-H(13A)	109.5
O(1)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
O(1)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(15)-C(14)-C(20)	119.03(16)
C(15)-C(14)-C(1)	121.62(16)
C(20)-C(14)-C(1)	118.98(15)
C(14)-C(15)-C(16)	120.46(17)
C(14)-C(15)-H(15)	119.8
C(16)-C(15)-H(15)	119.8
C(17)-C(16)-C(15)	120.88(17)

C(17)-C(16)-H(16)	119.6
C(15)-C(16)-H(16)	119.6
C(16)-C(17)-N(4)	118.93(15)
C(16)-C(17)-H(17)	120.5
N(4)-C(17)-H(17)	120.5
C(19)-C(18)-N(5)	132.88(17)
C(19)-C(18)-N(4)	104.73(15)
N(5)-C(18)-N(4)	122.36(16)
C(20)-N(3)-C(19)	105.32(14)
N(3)-C(20)-N(4)	111.27(15)
N(3)-C(20)-C(14)	130.31(15)
N(4)-C(20)-C(14)	118.34(15)
C(26)-C(21)-C(22)	116.4(2)
C(26)-C(21)-C(19)	123.3(2)
C(22)-C(21)-C(19)	120.2(2)
C(23)-C(22)-C(21)	119.6(3)
C(23)-C(22)-H(22)	120.2
C(21)-C(22)-H(22)	120.2
C(24)-C(23)-C(22)	121.3(3)
C(24)-C(23)-H(23)	119.4
C(22)-C(23)-H(23)	119.4
C(23)-C(24)-C(25)	120.2(3)
C(23)-C(24)-H(24)	119.9
C(25)-C(24)-H(24)	119.9
C(24)-C(25)-C(26)	118.6(3)
C(24)-C(25)-H(25)	120.7
C(26)-C(25)-H(25)	120.7
F(1)-C(26)-C(25)	116.8(3)
F(1)-C(26)-C(21)	119.3(2)
C(25)-C(26)-C(21)	123.8(3)
N(5)-C(27)-C(32)	111.97(18)
N(5)-C(27)-C(28)	110.41(16)
C(32)-C(27)-C(28)	110.40(19)
N(5)-C(27)-H(27)	108.0
C(32)-C(27)-H(27)	108.0
C(28)-C(27)-H(27)	108.0

C(27)-C(28)-C(29)	112.3(2)
C(27)-C(28)-H(28A)	109.1
C(29)-C(28)-H(28A)	109.1
C(27)-C(28)-H(28B)	109.1
C(29)-C(28)-H(28B)	109.1
H(28A)-C(28)-H(28B)	107.9
C(30)-C(29)-C(28)	111.9(3)
C(30)-C(29)-H(29A)	109.2
C(28)-C(29)-H(29A)	109.2
C(30)-C(29)-H(29B)	109.2
C(28)-C(29)-H(29B)	109.2
H(29A)-C(29)-H(29B)	107.9
C(29)-C(30)-C(31)	111.6(2)
C(29)-C(30)-H(30A)	109.3
C(31)-C(30)-H(30A)	109.3
C(29)-C(30)-H(30B)	109.3
C(31)-C(30)-H(30B)	109.3
H(30A)-C(30)-H(30B)	108.0
C(30)-C(31)-C(32)	111.5(2)
C(30)-C(31)-H(31A)	109.3
C(32)-C(31)-H(31A)	109.3
C(30)-C(31)-H(31B)	109.3
C(32)-C(31)-H(31B)	109.3
H(31A)-C(31)-H(31B)	108.0
C(27)-C(32)-C(31)	111.8(2)
C(27)-C(32)-H(32A)	109.3
C(31)-C(32)-H(32A)	109.3
C(27)-C(32)-H(32B)	109.3
C(31)-C(32)-H(32B)	109.3
H(32A)-C(32)-H(32B)	107.9
C(1)-N(1)-C(7)	104.73(14)
C(1)-N(2)-C(2)	106.57(14)
C(1)-N(2)-C(10)	127.12(15)
C(2)-N(2)-C(10)	126.25(15)
C(18)-C(19)-N(3)	111.78(16)
C(18)-C(19)-C(21)	127.48(17)

N(3)-C(19)-C(21)	120.46(16)
C(17)-N(4)-C(20)	122.35(14)
C(17)-N(4)-C(18)	130.64(15)
C(20)-N(4)-C(18)	106.88(14)
C(18)-N(5)-C(27)	117.83(15)
C(18)-N(5)-H(5)	121.1
C(27)-N(5)-H(5)	121.1
C(12)-O(1)-C(13)	112.5(2)
C(8)-O(2)-C(9)	116.59(19)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 101141_0m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

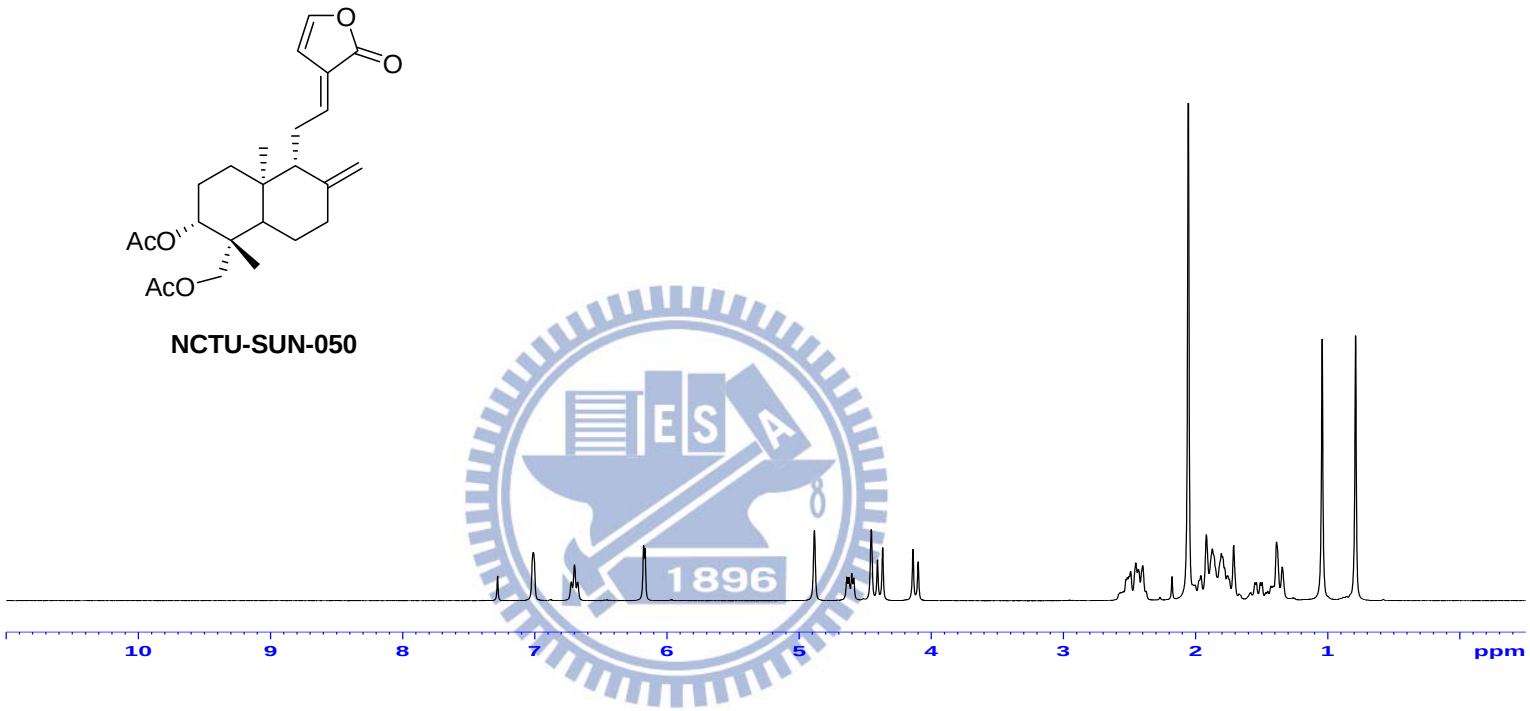
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	29(1)	42(1)	37(1)	-5(1)	13(1)	-1(1)
C(2)	31(1)	52(1)	43(1)	-2(1)	17(1)	1(1)
C(3)	42(1)	80(2)	51(1)	10(1)	26(1)	6(1)
C(4)	40(1)	79(2)	58(1)	2(1)	31(1)	2(1)
C(5)	31(1)	53(1)	53(1)	-7(1)	18(1)	2(1)
C(6)	33(1)	60(1)	44(1)	0(1)	16(1)	5(1)
C(7)	28(1)	52(1)	41(1)	-4(1)	16(1)	1(1)
C(8)	33(1)	58(1)	61(1)	-10(1)	19(1)	2(1)
C(9)	41(1)	93(2)	88(2)	4(2)	11(1)	22(1)
C(10)	45(1)	73(2)	46(1)	18(1)	20(1)	18(1)
C(11)	47(1)	105(2)	40(1)	11(1)	15(1)	3(1)
C(12)	68(2)	74(2)	47(1)	8(1)	22(1)	1(1)
C(13)	109(3)	116(3)	108(2)	23(2)	72(2)	48(2)
C(14)	29(1)	43(1)	36(1)	2(1)	14(1)	4(1)
C(15)	35(1)	43(1)	45(1)	-6(1)	16(1)	-1(1)
C(16)	40(1)	41(1)	50(1)	-7(1)	22(1)	4(1)
C(17)	32(1)	46(1)	46(1)	-1(1)	21(1)	7(1)
C(18)	32(1)	44(1)	34(1)	0(1)	11(1)	-1(1)
N(3)	32(1)	46(1)	39(1)	-4(1)	15(1)	5(1)
C(20)	28(1)	42(1)	35(1)	1(1)	13(1)	6(1)
C(21)	40(1)	48(1)	44(1)	-8(1)	3(1)	6(1)
C(22)	72(2)	52(1)	71(2)	-4(1)	3(1)	-12(1)
C(23)	101(2)	50(2)	99(2)	-8(2)	-7(2)	-15(2)
C(24)	86(2)	68(2)	114(3)	-46(2)	-14(2)	13(2)
C(25)	70(2)	100(2)	94(2)	-56(2)	8(2)	17(2)
C(26)	52(1)	73(2)	60(1)	-22(1)	13(1)	9(1)
C(27)	31(1)	56(1)	46(1)	7(1)	13(1)	-2(1)
C(28)	56(1)	97(2)	63(1)	-6(1)	15(1)	23(1)
C(29)	66(2)	115(3)	94(2)	7(2)	22(2)	40(2)
C(30)	44(1)	121(3)	83(2)	21(2)	4(1)	9(2)
C(31)	62(2)	120(3)	56(1)	1(2)	0(1)	5(2)

C(32)	58(1)	80(2)	52(1)	-7(1)	10(1)	2(1)
F(1)	109(1)	120(1)	88(1)	-36(1)	62(1)	-17(1)
N(1)	29(1)	59(1)	40(1)	3(1)	16(1)	5(1)
N(2)	32(1)	56(1)	39(1)	4(1)	16(1)	6(1)
C(19)	34(1)	43(1)	36(1)	-3(1)	11(1)	2(1)
N(4)	27(1)	40(1)	35(1)	-1(1)	13(1)	3(1)
N(5)	29(1)	54(1)	44(1)	7(1)	13(1)	-4(1)
O(1)	72(1)	79(1)	64(1)	19(1)	41(1)	22(1)
O(2)	39(1)	95(1)	66(1)	4(1)	17(1)	24(1)
O(3)	42(1)	92(1)	91(1)	0(1)	38(1)	11(1)

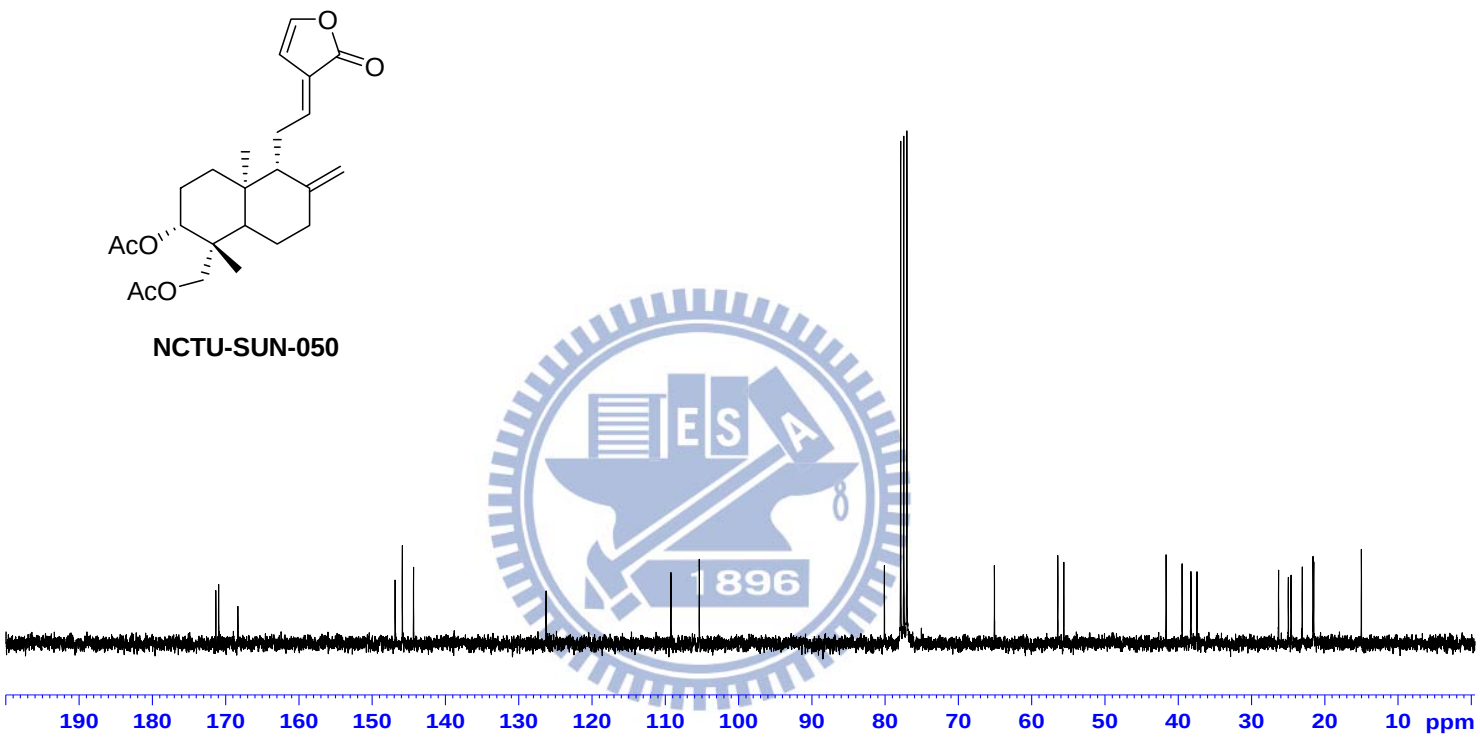
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 101141_0m.

	x	y	z	U(eq)
H(3)	8078	3135	1285	66
H(4)	7185	4065	861	66
H(6)	7497	5400	-333	55
H(9A)	5728	5971	-731	118
H(9B)	5949	6854	-1091	118
H(9C)	6014	7678	-583	118
H(10A)	9496	1844	1278	65
H(10B)	9009	1850	1454	65
H(11A)	9803	3094	2042	78
H(11B)	9776	4399	1641	78
H(12A)	9449	5539	2185	76
H(12B)	8953	5415	1652	76
H(13A)	8822	5471	2588	153
H(13B)	8384	4064	2451	153
H(13C)	8330	5418	2053	153
H(15)	9365	1568	-3	49
H(16)	10222	1380	-61	51
H(17)	10915	3177	356	48
H(22)	11059	9125	1019	88
H(23)	11205	11651	1406	118
H(24)	10881	12222	2006	128
H(25)	10420	10256	2253	115
H(27)	11644	4210	1508	54
H(28A)	12355	5169	1048	90
H(28B)	12010	3552	931	90
H(29A)	12545	2535	1722	114
H(29B)	12944	3074	1471	114
H(30A)	13171	5416	1938	107
H(30B)	13266	3948	2309	107
H(31A)	12797	6106	2503	104

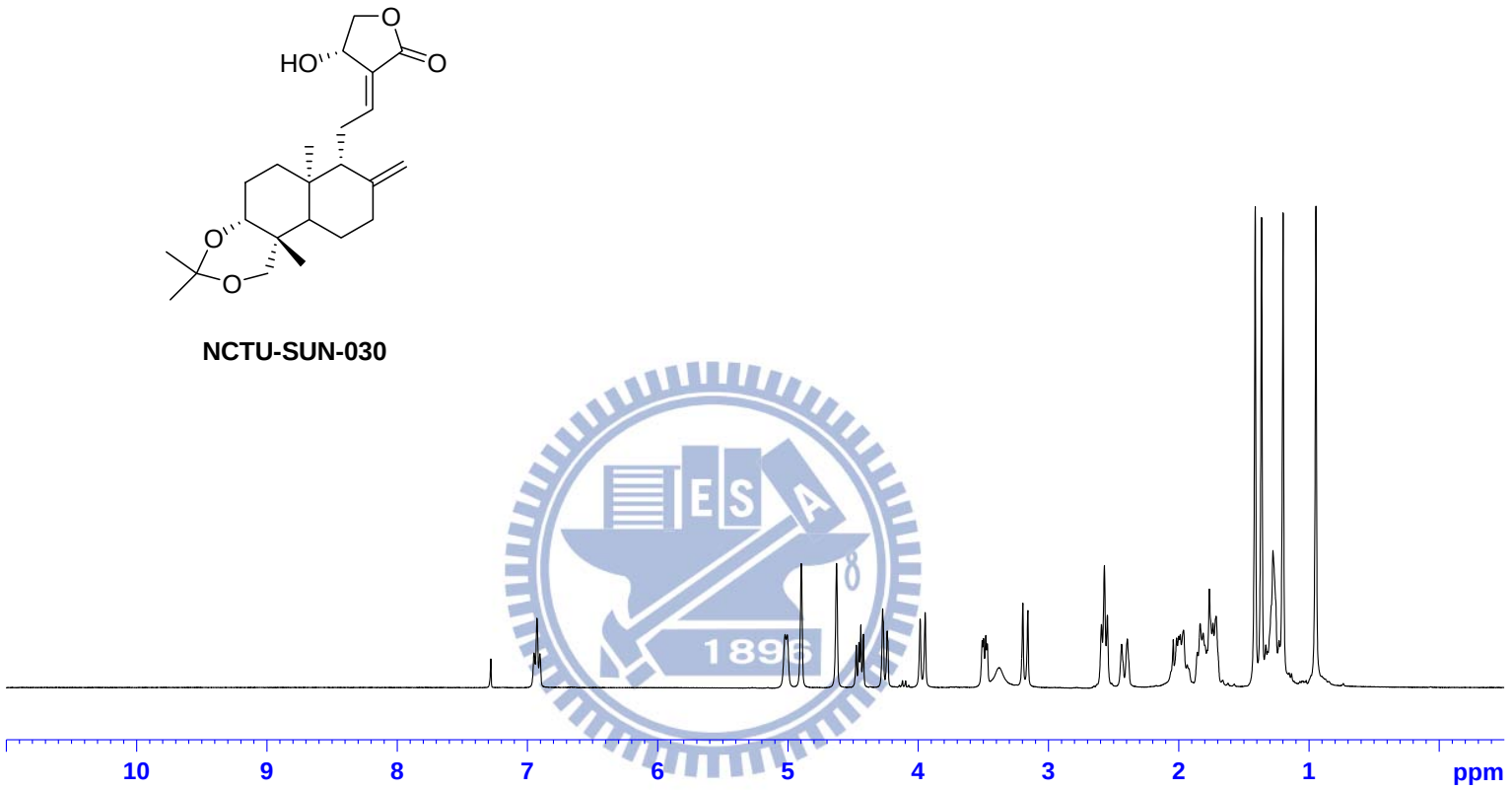
H(31B)	12448	4495	2388	104
H(32A)	11858	6610	1958	81
H(32B)	12258	7125	1705	81
H(5)	11427	6541	765	52



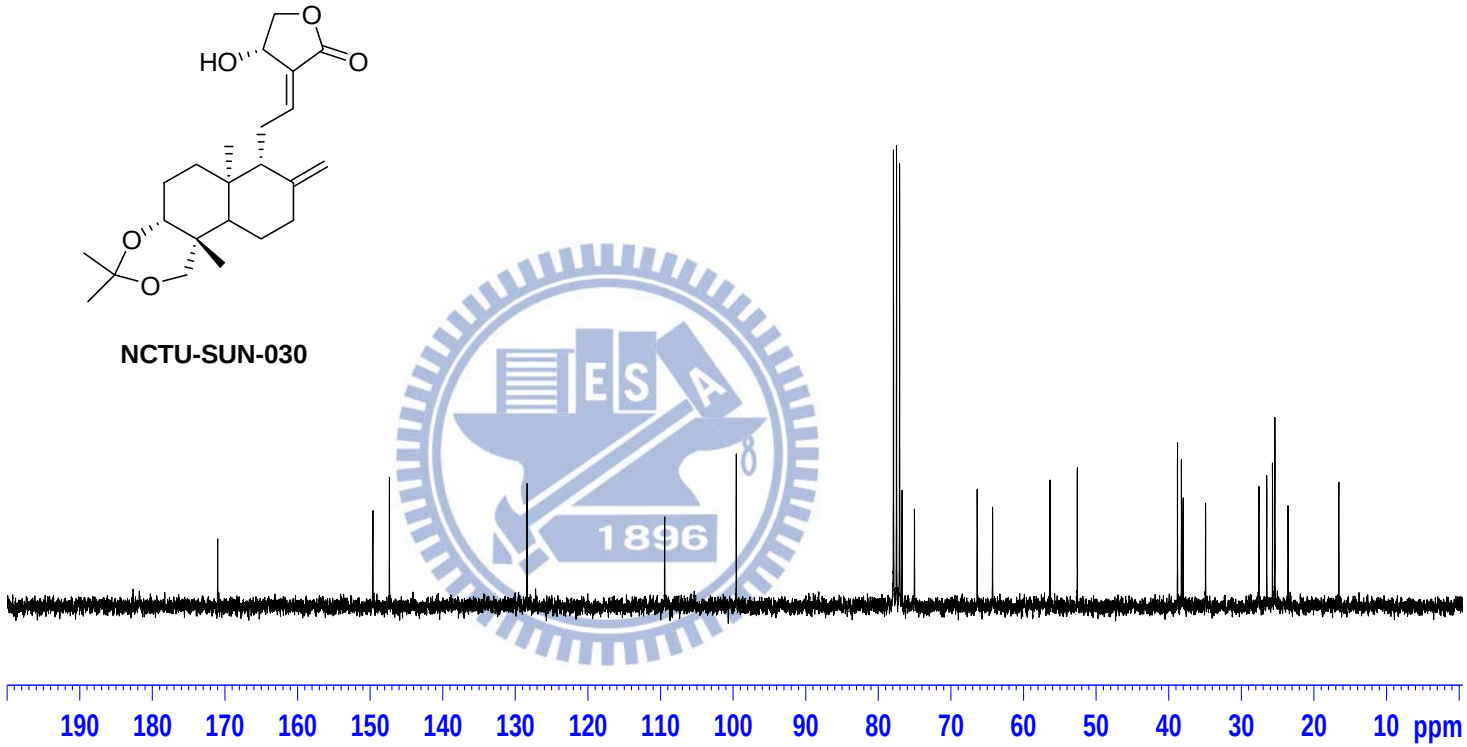
^{1}HNMR spectrum (300 MHz) of compound NCTU-SUN-050(12) in $CDCl_3$



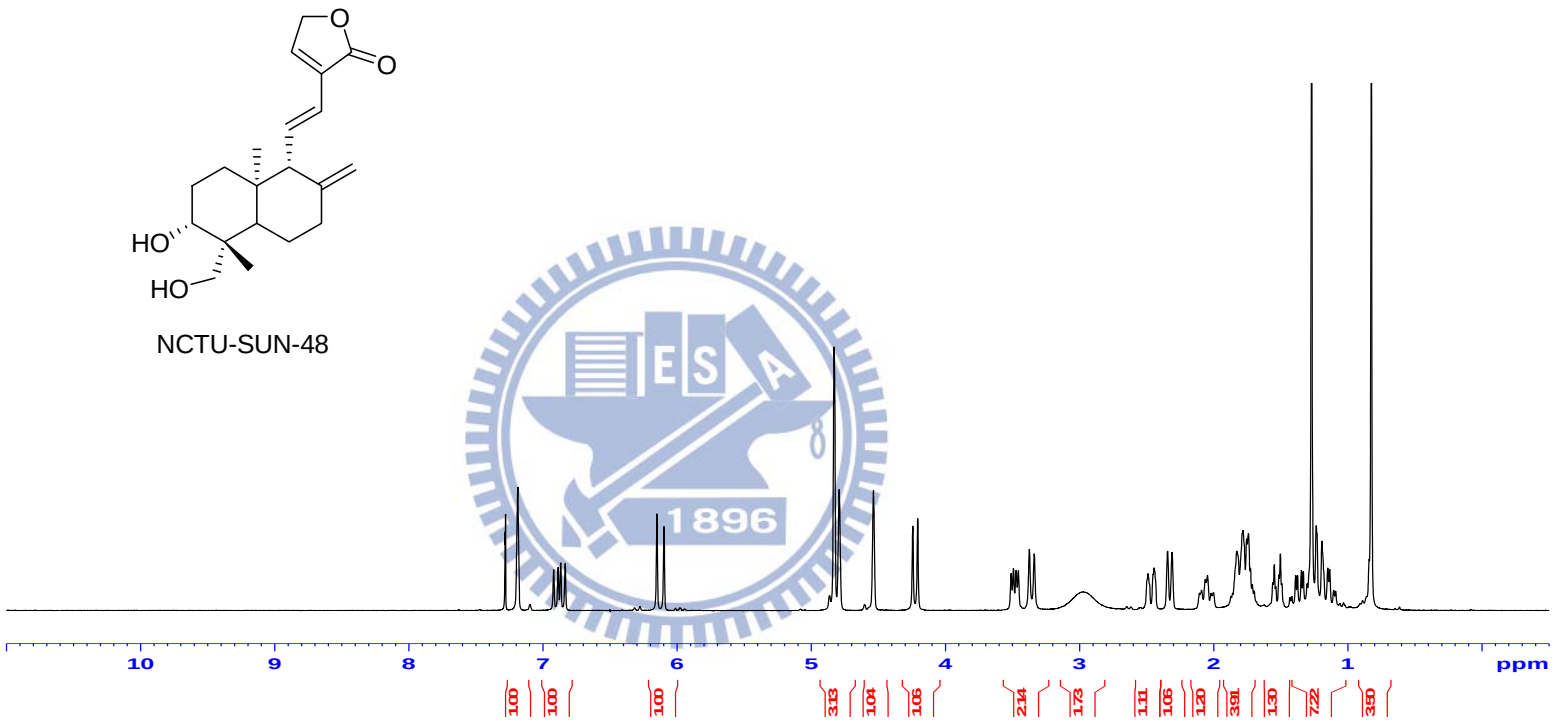
^{13}C NMR spectrum (75 MHz) of compound NCTU-SUN-050(12) in $CDCl_3$



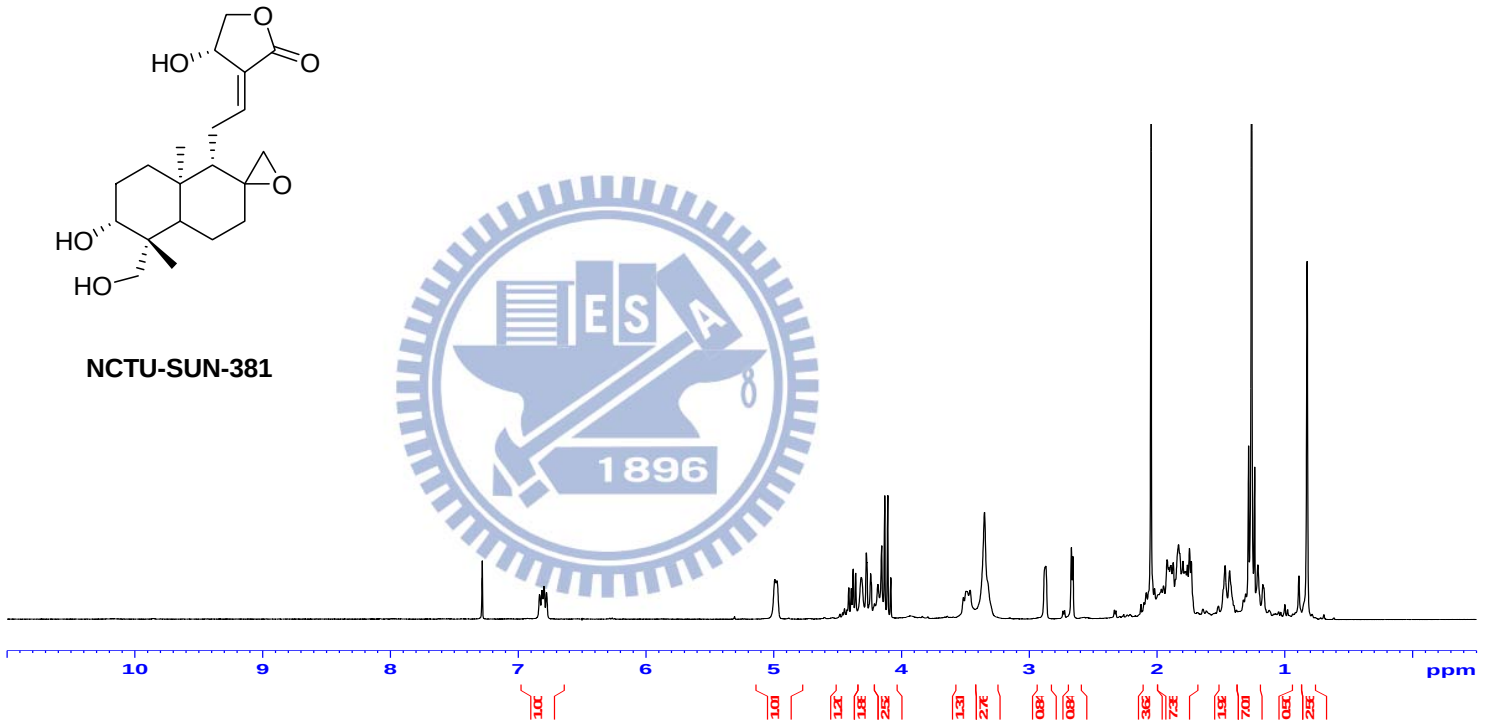
^{1}HNMR spectrum (300 MHz) of compound NCTU-SUN-030(13) in $CDCl_3$



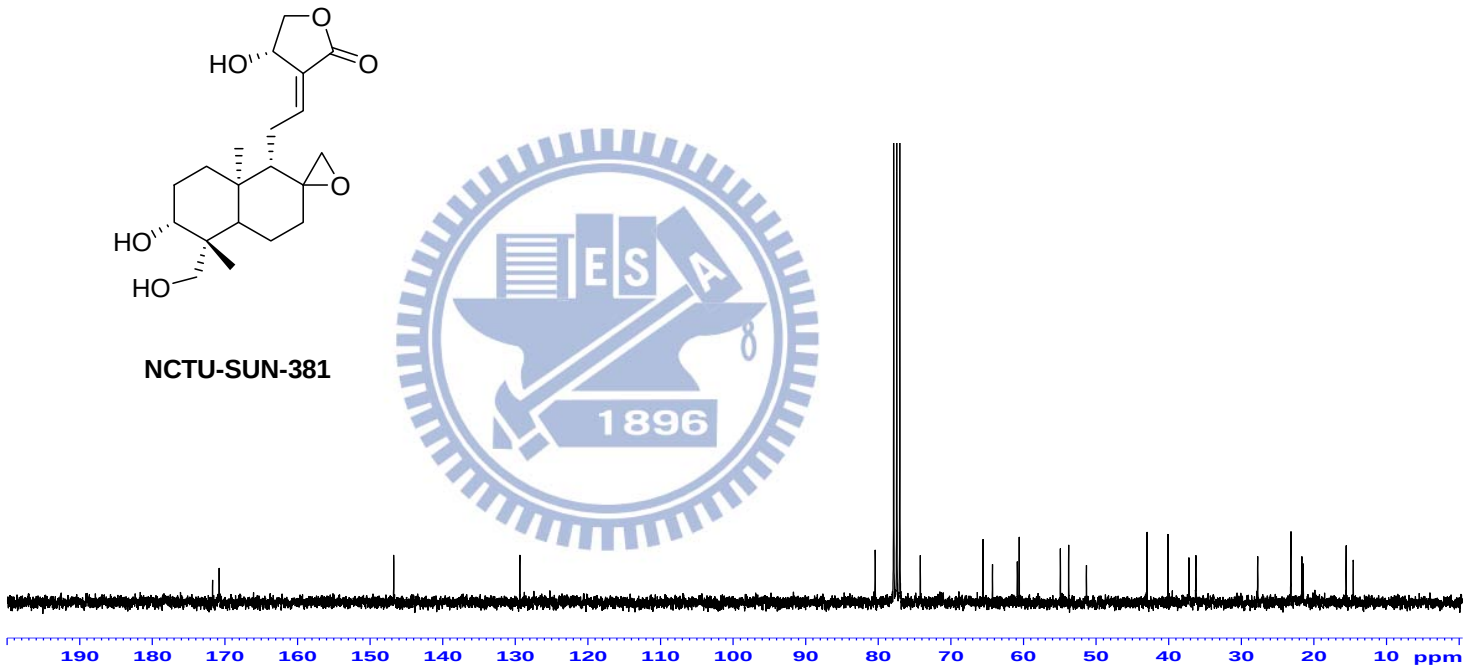
^{13}C NMR spectrum (75 MHz) of compound NCTU-SUN-030(13) in $CDCl_3$



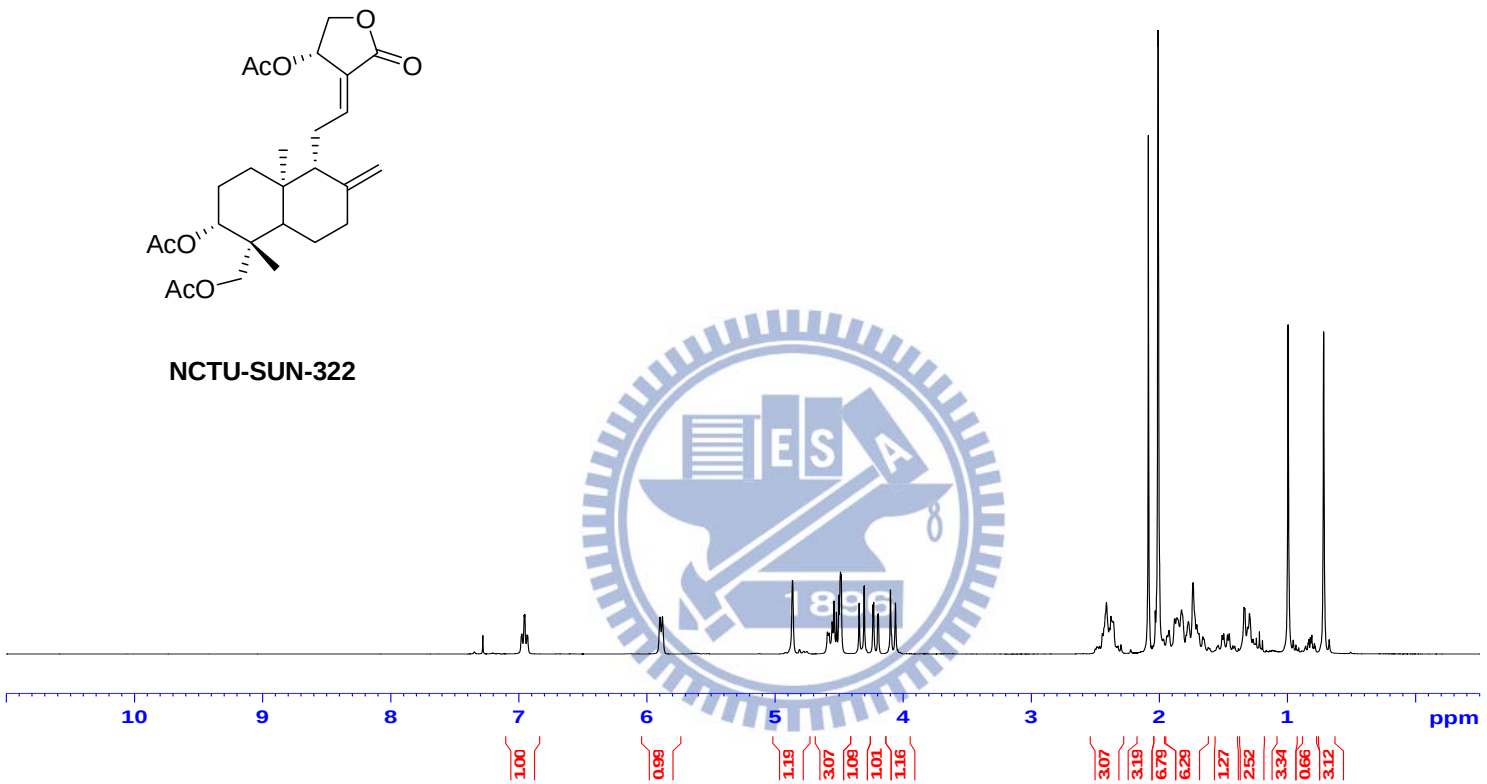
^{13}C NMR spectrum (75 MHz) of compound NCTU-SUN-048(15) in $CDCl_3$



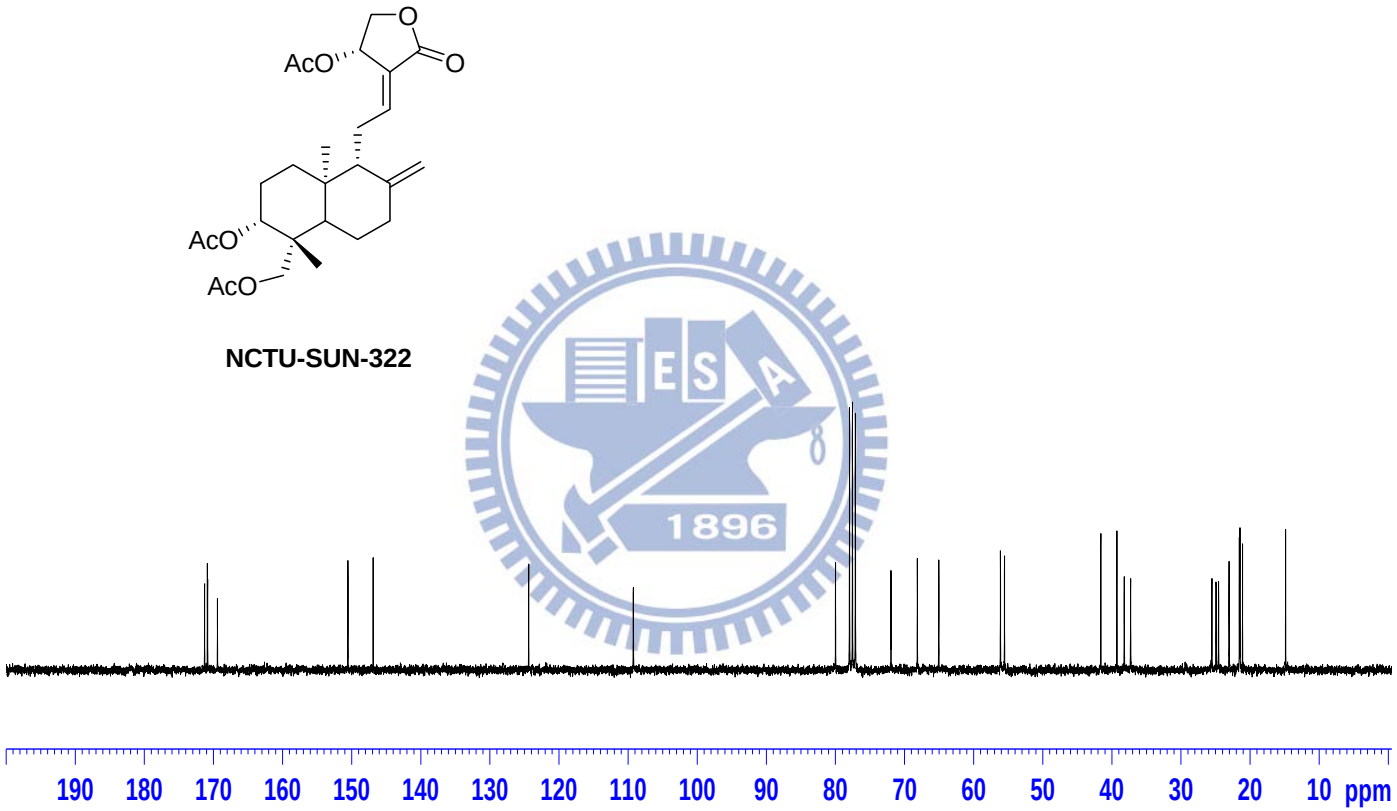
^{1}HNMR spectrum (300 MHz) of compound NCTU-SUN-381(16) in $CDCl_3$



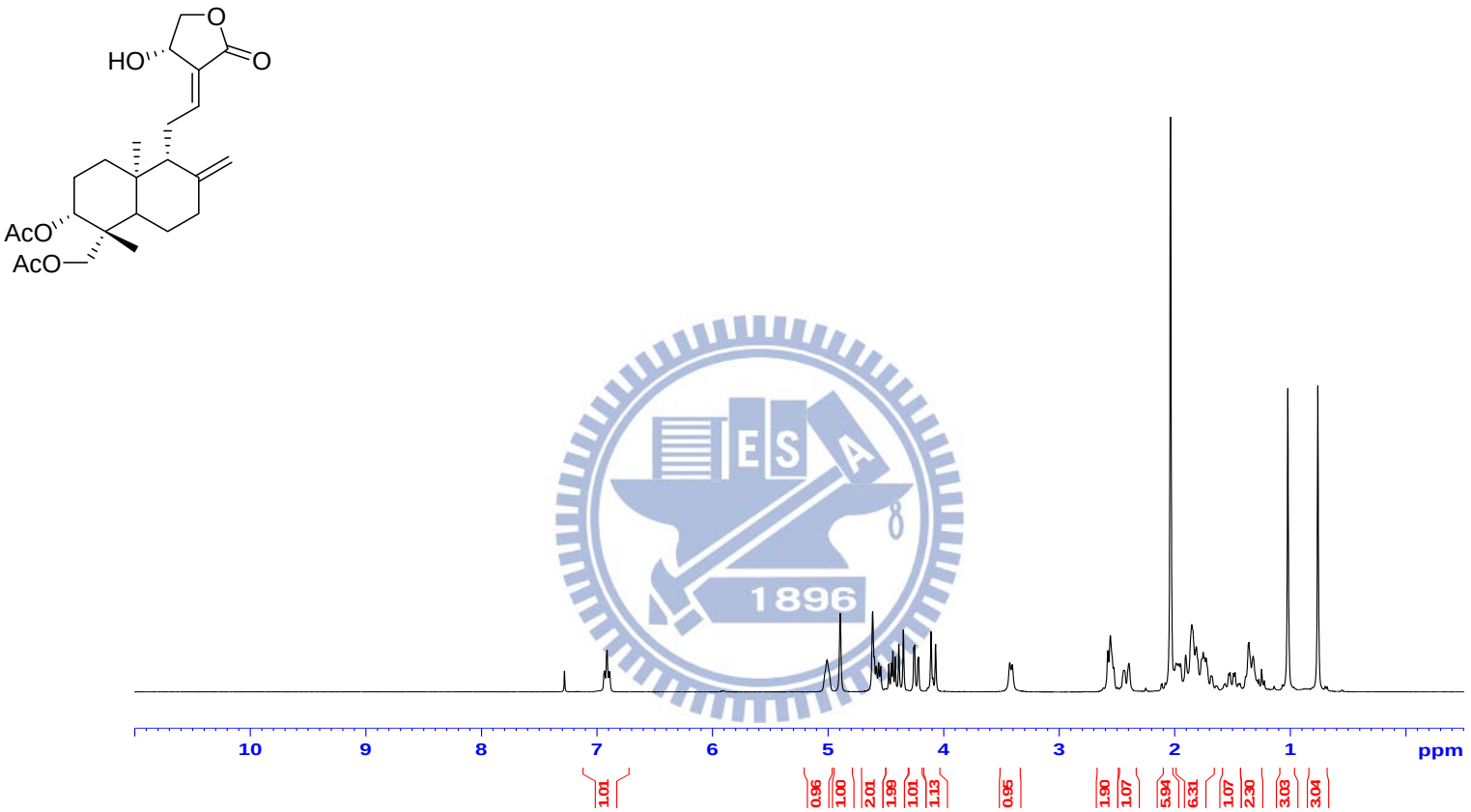
^{13}C NMR spectrum (75 MHz) of compound NCTU-SUN-381(16) in $CDCl_3$



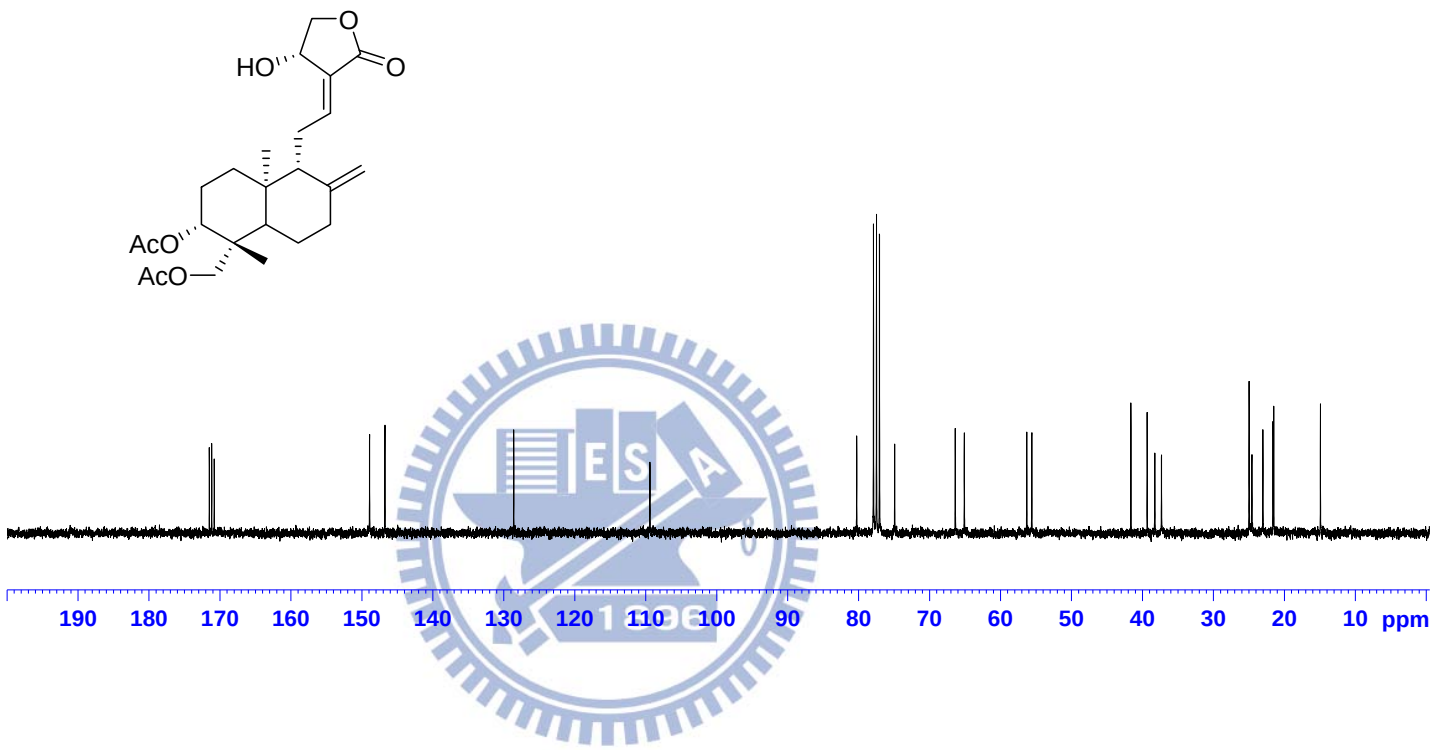
^{1}HNMR spectrum (300 MHz) of compound NCTU-SUN-322(17) in $CDCl_3$



^{13}C NMR spectrum (75 MHz) of compound NCTU-SUN-322(17) in $CDCl_3$



^{1}H NMR spectrum (75 MHz) of compound NCTU-SUN-323(18) in $CDCl_3$



^{13}C NMR spectrum (75 MHz) of compound NCTU-SUN-323(18) in $CDCl_3$

APPENDIX

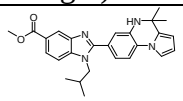
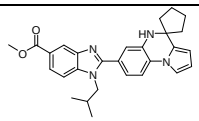
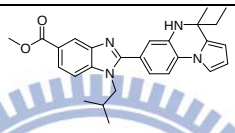
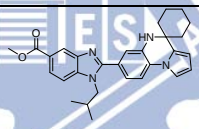
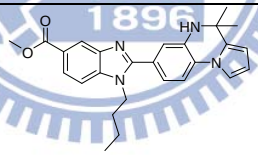
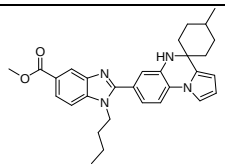
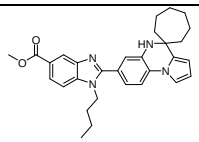
KIRA ELISA assay (*in vitro* method for detecting VEGFR-3 activity).

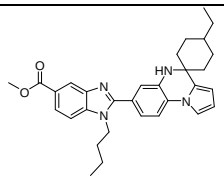
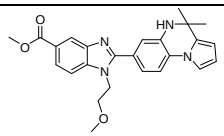
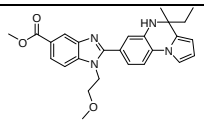
H928 cells (2 ¥ 105) in 100 ml medium were added to each well in a flat bottom 24-well culture plate and cultured overnight at 37 ˚C in 5% CO_2 . After the supernatants were removed, the cells were serum-starved for 24 h. A medium containing a test compound was added into each well and the cell culture was incubated for 30 min before it was stimulated by recombinant VEGF-C for 15 min. After the supernatants were removed, 100 ml of a lysis buffer were added into each well to lyse the cells and solubilize the VEGFR-3. The lysis buffer included 150mM NaCl containing 50mMHepes (Genentech media prep), 0.5% Triton-X100 (Genentech media prep), 0.01% thimerosol, 30 kIU/ml aprotinin (ICN Biochemicals, Aurora, Ohio), 1mM4-(2-aminoethyl)benzenesulfonyl fluoride hydrochloride (AEBSF;ICN Biochemicals), and 2 mM sodium orthovanadate. The plate was then put on a plate shaker (Bellco Instruments Vineland, N.J.) and the substance in each well of the plate underwent mixing for 60 minutes at room temperature. While the cells get soluble, an ELISA microtiter plate (Nunc Maxisorp, Inter Med, Denmark) coated overnight at 4 ◦C with the affinity-purified polyclonal anti- VEGFR-3 (2.5 mg/well block buffer (PBS containing 0.5% BSA and 0.01% thimerosol)) for 60min at room temperature with gentle agitation. The anti-VEGFR-3 coated plate was subsequently washed twice with a wash buffer (PBS containing 0.05% Tween 20 and 0.01% thimerosol). The lysate containing solubilizedVEGFR- 3 from the cell culture microtiter well was transferred (85 ml/well) to the anti-VEGFR-3 coated ELISA plate and incubated for 2 h at room temperature with gentle agitation.

The unbound receptors were removed by washing with a wash buffer. 100 ml of biotinylated 4G10 (antiphosphotyrosine) diluted to 0.2 mg ml-1 in dilution buffer (PBS containing 0.5% BSA, 0.05% Tween 20, 5mM EDTA, and 0.01% thimerosol) were added into each well. After incubation for 2 h at room temperature, the plates were washed and 100 ml HRP-conjugated streptavidin (Zymed Laboratories, San Francisco,Calif.) diluted 1 : 2000 in dilution bufferwas further added. After the free avidin conjugate was washed away, 100 ml freshly prepared substrate solution (tetramethyl benzidine, TMB) was added to each well. The reaction was allowed to proceed for 10 min and the color development was stopped by the addition of 100 ml/well 1.0 M H3PO4. The absorbance at 450 nm and the absorbance at a reference wavelength of 650 nm (*A*450/650) were measured using an ELISA reader and the data were repeated 3 times. The inhibition efficacy of each test compound is expressed as an inhibition percentage calculated according to following formula: 1 - [(*C* - *A*)/(*B* - *A*)] ¥ 100. In this formula, *A* is the basal amount of phosphotyrosine detected in a blank control, *B* is the amount of phosphotyrosine detected with VEGFR-C only, and *C* is the amount of phosphotyrosine detected with a test compound andVEGF-C.

CHAPTER TWO

Percentage of VEGFR-3 Inhibition data

Compound Code	Structure *Incl* (Molecular Weight)	VEGFR-3 inhibtion Data
10a	 Chemical Formula: $C_{26}H_{28}N_4O_2$ Exact Mass: 428.2212 Molecular Weight: 428.5261	8.2%
10b	 Chemical Formula: $C_{28}H_{30}N_4O_2$ Exact Mass: 454.2369 Molecular Weight: 454.5634	54.2%
10c	 Chemical Formula: $C_{27}H_{30}N_4O_2$ Exact Mass: 442.2369 Molecular Weight: 442.5527	20.6%
10d	 Chemical Formula: $C_{29}H_{32}N_4O_2$ Exact Mass: 468.2525 Molecular Weight: 468.59	54.2%
10e	 Chemical Formula: $C_{26}H_{28}N_4O_2$ Exact Mass: 428.2212 Molecular Weight: 428.5261	72.7%
10f	 Chemical Formula: $C_{30}H_{34}N_4O_2$ Exact Mass: 482.2682 Molecular Weight: 482.6166	90%
10g	 Chemical Formula: $C_{30}H_{34}N_4O_2$ Exact Mass: 482.2682 Molecular Weight: 482.6166	72.7%

10h	 Chemical Formula: $C_{31}H_{36}N_4O_2$ Exact Mass: 496.2838 Molecular Weight: 496.6431	64.8%
10i	 Chemical Formula: $C_{25}H_{26}N_4O_3$ Exact Mass: 430.2005 Molecular Weight: 430.4989	56.88%
10j	 Chemical Formula: $C_{26}H_{28}N_4O_3$ Exact Mass: 444.2161 Molecular Weight: 444.5255	61.08%

AlphaLISA G9a Histone H3-Lysine N-methyltransferase inhibitors Assay

The AlphaLISA technology allows performing no-wash homogeneous proximity immunoassays using Alpha Donor and AlphaLISA Acceptor beads. In this technical note, we present the optimization of an epigenetic enzymatic assay using a biotinylated histone H3-derived peptide as substrate. Detection of the modified substrate was performed by the addition of Streptavidin (SA) Alpha Donor beads and AlphaLISA Acceptor beads conjugated to an antibody (Ab) directed against the epigenetic mark of interest. Upon laser irradiation of the beads-target complexes at 680 nm, short-lived singlet oxygen molecules produced by the Donor beads can reach the Acceptor beads in proximity to generate an amplified chemiluminescent signal at 615 nm.

The intensity of light emission is proportional to the level of biotinylated substrate modification.

Reagents needed for the assay:

Anti-methyl-Histone H3 Lysine 9 (H3K9me2) AlphaLISA Acceptor Beads

Alpha Streptavidin Donor beads

Histone H3 (1-21) peptide, biotinylated

AlphaLISA 5X Epigenetics Buffer

G9a (human), recombinant

White opaque OptiPlate™-384 microplates

S-(5'-Adenosyl)-L-methionine chloride (SAM)

Standard Protocol

• Dilute G9a enzyme, inhibitors, SAM and biotinylated peptide substrate in Assay Buffer just before use.

• Add to the wells of a white OptiPlate-384 microplate:

– 5 µL inhibitor (2X) or Assay Buffer

– 2.5 µL of enzyme (4X)

–pretreated for 30 min

– 2.5 µL of biotinylated Histone H3 (1-21) peptide/SAM mix (4X). For SAM titration, add SAM dilutions independently of substrate.

• Cover the plate with TopSeal-A film and incubate at room temperature (RT).

• Prepare 1X Epigenetics Buffer 1 as recommended in the buffer technical data sheet.

• Prepare Acceptor beads at 100 µg/mL in 1X Epigenetics Buffer 1 (final concentration of 20 µg/mL in 25 µL total assay volume).

• Add 5 µL Acceptor beads. Addition of Acceptor beads prepared in Epigenetics Buffer 1 stops the enzymatic reaction.

• Cover with TopSeal-A film and incubate for 60 min at RT.

• Prepare Streptavidin Donor beads at 50 µg/mL in 1X Epigenetics Buffer 1 (final concentration of 20 µg/mL in 25 µL total assay volume in subdued light).

• Add 10 µL Donor beads in subdued light.

• Cover with a TopSeal-A film and incubate in the dark for 30 min at RT.

• Read signal in Alpha mode with EnVision® or EnSpire® readers as represented in figure 1.36.

Biotinylated Histone H3 (1-21) peptide Substrate Sequence:

ARTKQTARKSTGGKAPRKQLA-GG-K(BIOTIN)-NH2

SAM is prepared at 30 mM in 5 mM H_2SO_4/10% ethanol (v/v) in H_2O, aliquoted and stored at -80 °C.

Assay Buffer: 50 mM Tris-HCl, pH 9.0, 50 mM NaCl, 1 mM DTT, 0.01% Tween-20,

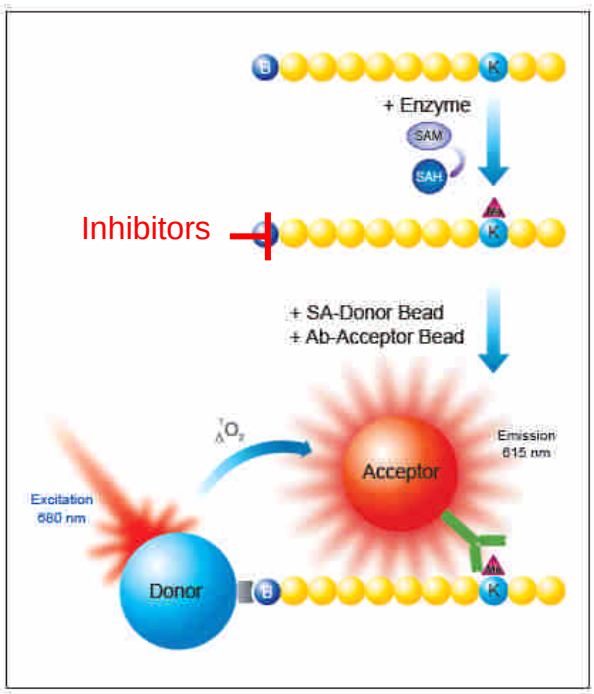
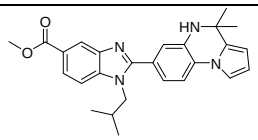
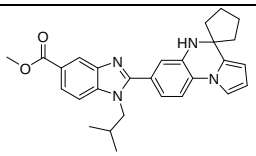
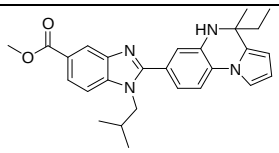
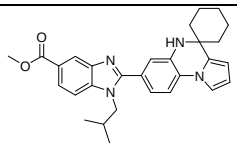
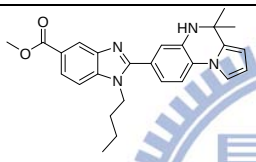
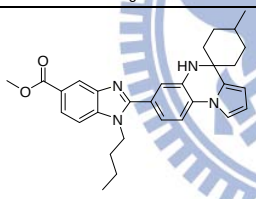
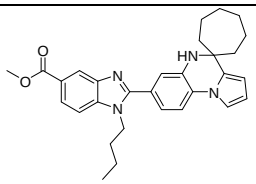
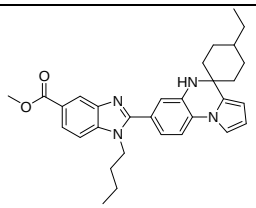


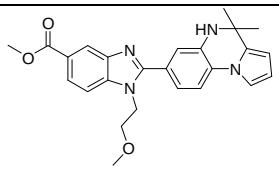
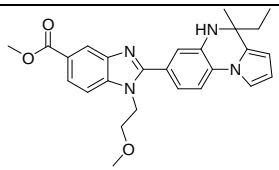
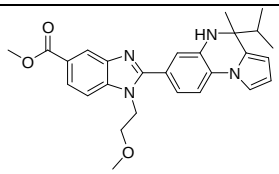
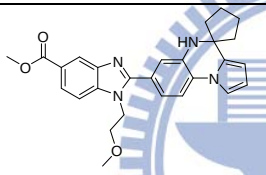
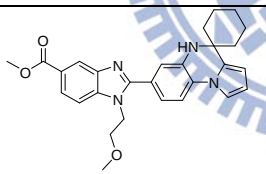
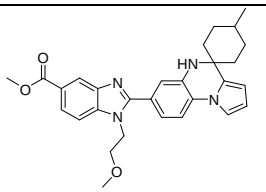
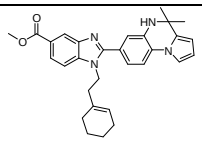
Figure 1.36. Schematic representation of the AlphaLISA detection of a modified histone peptide.

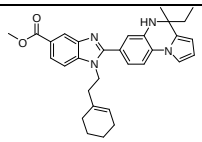
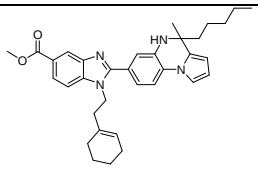
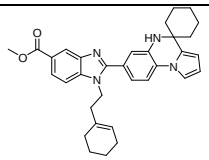
CHAPTER TWO

G9a Histone H3-Lysine N-methyltransferase Inhibitors Activity

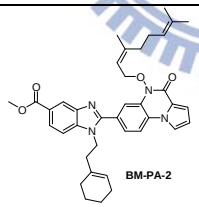
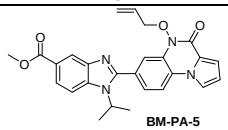
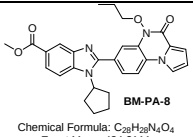
Compound Code	Structure *Incl* (Molecular Weight)	Concentration in μM	G9a Inhibition Data as compared to BIX01294
10a	 Chemical Formula: $C_{26}H_{28}N_4O_2$ Exact Mass: 428.2212 Molecular Weight: 428.5261	**0.5385**	**22%**

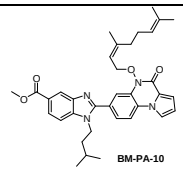
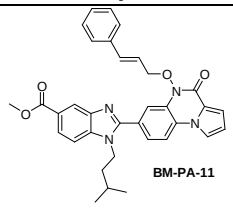
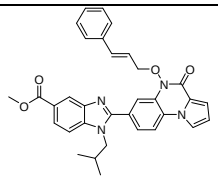
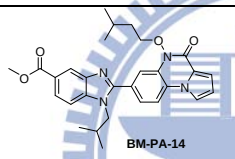
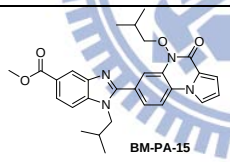
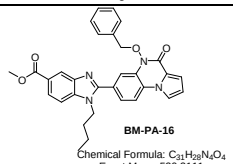
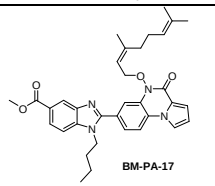
10b	 Chemical Formula: $C_{28}H_{30}N_4O_2$ Exact Mass: 454.2369 Molecular Weight: 454.5634	**0.432**	**48%**
10c	 Chemical Formula: $C_{27}H_{30}N_4O_2$ Exact Mass: 442.2369 Molecular Weight: 442.5527	**0.4969**	**32%**
10d	 Chemical Formula: $C_{29}H_{32}N_4O_2$ Exact Mass: 468.2525 Molecular Weight: 468.59	**0.5401**	**21%**
10e	 Chemical Formula: $C_{26}H_{28}N_4O_2$ Exact Mass: 428.2212 Molecular Weight: 428.5261	**0.4318**	**48%**
10f	 Chemical Formula: $C_{30}H_{34}N_4O_2$ Exact Mass: 482.2682 Molecular Weight: 482.6166	**0.5473**	**20%**
10g	 Chemical Formula: $C_{30}H_{34}N_4O_2$ Exact Mass: 482.2682 Molecular Weight: 482.6166	**0.5089**	**29%**
10h	 Chemical Formula: $C_{31}H_{36}N_4O_2$ Exact Mass: 496.2838 Molecular Weight: 496.6431	**0.4646**	**40%**

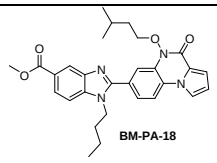
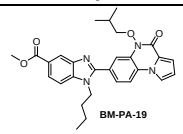
10i	 Chemical Formula: $C_{25}H_{26}N_4O_3$ Exact Mass: 430.2005 Molecular Weight: 430.4989	**0.4394**	**46%**
10j	 Chemical Formula: $C_{26}H_{28}N_4O_3$ Exact Mass: 444.2161 Molecular Weight: 444.5255	**0.4893**	**34%**
10k	 Chemical Formula: $C_{27}H_{30}N_4O_3$ Exact Mass: 458.2318 Molecular Weight: 458.5521	**0.495**	**41%**
10l	 Chemical Formula: $C_{27}H_{28}N_4O_3$ Exact Mass: 456.2161 Molecular Weight: 456.5362	**0.5451**	**20%**
10m	 Chemical Formula: $C_{28}H_{30}N_4O_3$ Exact Mass: 470.2318 Molecular Weight: 470.5628	**0.412**	**53%**
10n	 Chemical Formula: $C_{29}H_{32}N_4O_3$ Exact Mass: 484.2474 Molecular Weight: 484.5894	**0.4165**	**52%**
10o	 Chemical Formula: $C_{30}H_{32}N_4O_2$ Exact Mass: 480.2525 Molecular Weight: 480.6007	**0.4876**	**34%**

10p	 Chemical Formula: $C_{31}H_{34}N_4O_2$ Exact Mass: 494.2682 Molecular Weight: 494.6273	**0.5271**	**24%**
10q	 Chemical Formula: $C_{34}H_{40}N_4O_2$ Exact Mass: 536.3151 Molecular Weight: 536.707	**0.5887**	**9%**
10r	 Chemical Formula: $C_{33}H_{36}N_4O_2$ Exact Mass: 520.2838 Molecular Weight: 520.6645	**0.4842**	**35%**

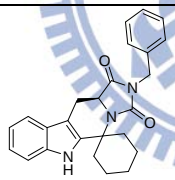
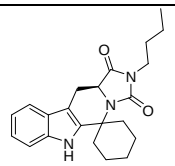
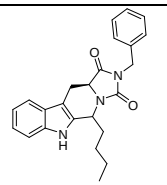
G9a Histone H3-Lysine N-methyltransferase Inhibitors Activity

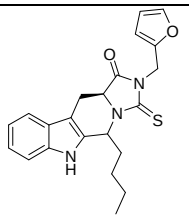
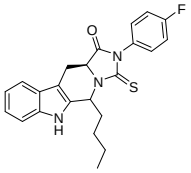
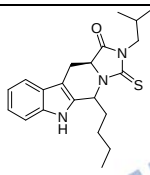
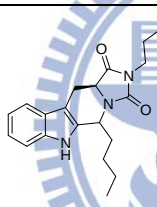
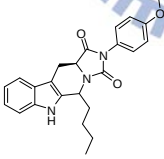
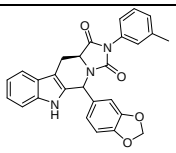
NO.	Structure *Incl* (Molecular Weight)	G9a Inhibition data
21a	 **BM-PA-2** Chemical Formula: $C_{38}H_{42}N_4O_4$ Exact Mass: 618.3206 Molecular Weight: 618.7645	-9.26%
21b	 **BM-PA-5** Chemical Formula: $C_{26}H_{24}N_4O_4$ Exact Mass: 456.1798 Molecular Weight: 456.4932	-0.7419%
21c	 **BM-PA-8** Chemical Formula: $C_{28}H_{28}N_4O_4$ Exact Mass: 484.2111 Molecular Weight: 484.5463	-5.46%

21d	 **BM-PA-10** Chemical Formula: $C_{35}H_{40}N_4O_4$ Exact Mass: 580.305 Molecular Weight: 580.7165	1.15%
21e	 **BM-PA-11** Chemical Formula: $C_{34}H_{32}N_4O_4$ Exact Mass: 560.2424 Molecular Weight: 560.6423	6.03%
21f	 Chemical Formula: $C_{33}H_{30}N_4O_4$ Exact Mass: 546.2267 Molecular Weight: 546.6157 **BM-PA-12**	2.41%
21g	 **BM-PA-14** Chemical Formula: $C_{29}H_{32}N_4O_4$ Exact Mass: 500.2424 Molecular Weight: 500.5888	-13.06%
21h	 **BM-PA-15** Chemical Formula: $C_{28}H_{30}N_4O_4$ Exact Mass: 486.2267 Molecular Weight: 486.5622	-1.41%
21i	 **BM-PA-16** Chemical Formula: $C_{31}H_{28}N_4O_4$ Exact Mass: 520.2111 Molecular Weight: 520.5784	-7.96%
21j	 **BM-PA-17** Chemical Formula: $C_{34}H_{38}N_4O_4$ Exact Mass: 566.2893 Molecular Weight: 566.6899	-36.26%

21k	 BM-PA-18 Chemical Formula: $C_{29}H_{32}N_4O_4$ Exact Mass: 500.2424 Molecular Weight: 500.5888	-6.26%
21l	 BM-PA-19 Chemical Formula: $C_{28}H_{30}N_4O_4$ Exact Mass: 486.2267 Molecular Weight: 486.5622	-4.94%

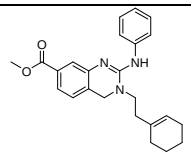
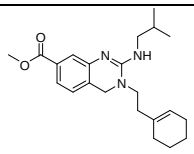
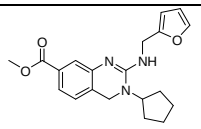
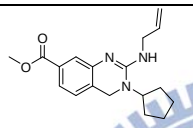
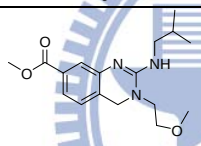
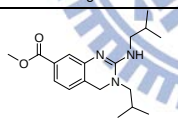
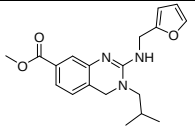
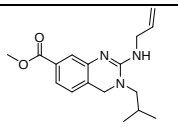
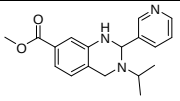
CHAPTER ONE

No	Structure *Incl* (Molecular Weight)	G9-Inhibition Assay as compared to BIX
6f	 Chemical Formula: $C_{25}H_{25}N_3O_2$ Exact Mass: 399.1947 Molecular Weight: 399.4849	4.88%
6g	 Chemical Formula: $C_{22}H_{27}N_3O_2$ Exact Mass: 365.2103 Molecular Weight: 365.4687	3.28%
6i	 Chemical Formula: $C_{24}H_{25}N_3O_2$ Exact Mass: 387.1947 Molecular Weight: 387.4742	4.38%

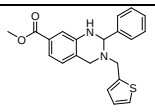
6j	 Chemical Formula: $C_{22}H_{23}N_3O_2S$ Exact Mass: 393.1511 Molecular Weight: 393.5019	1.8%
6l	 Chemical Formula: $C_{23}H_{22}FN_3OS$ Exact Mass: 407.1468 Molecular Weight: 407.5037	3.36%
6m	 Chemical Formula: $C_{21}H_{27}N_3OS$ Exact Mass: 369.1875 Molecular Weight: 369.5236	3.2%
6o	 Chemical Formula: $C_{21}H_{27}N_3O_2$ Exact Mass: 353.2103 Molecular Weight: 353.458	-0.7853%
6p	 Chemical Formula: $C_{25}H_{27}N_3O_3$ Exact Mass: 417.2052 Molecular Weight: 417.5002	10.33%
6q	 Chemical Formula: $C_{27}H_{21}N_3O_4$ Exact Mass: 451.1532 Molecular Weight: 451.4733	7.31%

No	Compound Structure	G9-Inhibition Assay as compared to BIX

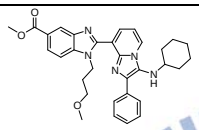
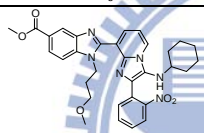
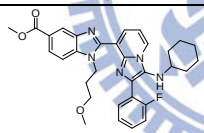
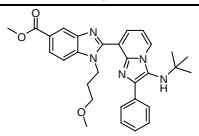
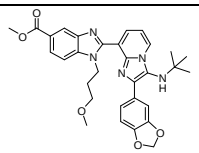
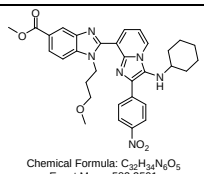
M

13a	 Chemical Formula: $C_{24}H_{27}N_3O_2$ Exact Mass: 389.2103 Molecular Weight: 389.4901	-2.06%
13b	 Chemical Formula: $C_{22}H_{31}N_3O_2$ Exact Mass: 369.2416 Molecular Weight: 369.5004	7.51%
13c	 Chemical Formula: $C_{20}H_{23}N_3O_3$ Exact Mass: 353.1739 Molecular Weight: 353.4149	13.19%
13d	 Chemical Formula: $C_{18}H_{23}N_3O_2$ Exact Mass: 313.179 Molecular Weight: 313.3941	0.314%
13e	 Chemical Formula: $C_{17}H_{25}N_3O_3$ Exact Mass: 319.1896 Molecular Weight: 319.3987	11.14%
13f	 Chemical Formula: $C_{18}H_{27}N_3O_2$ Exact Mass: 317.2103 Molecular Weight: 317.4259	11.5%
13g	 Chemical Formula: $C_{19}H_{23}N_3O_3$ Exact Mass: 341.1739 Molecular Weight: 341.4042	4.15%
13h	 Chemical Formula: $C_{17}H_{23}N_3O_2$ Exact Mass: 301.179 Molecular Weight: 301.3834	5.53%
13j	 Chemical Formula: $C_{18}H_{21}N_3O_2$ Exact Mass: 311.1634 Molecular Weight: 311.3782	4.11%

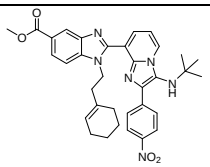
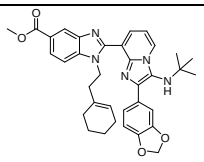
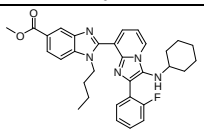
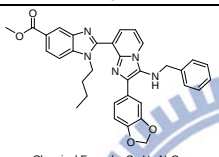
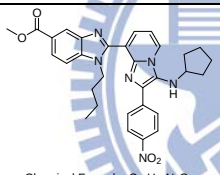
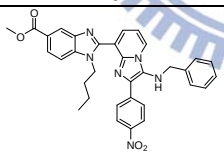
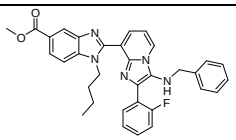
N

13l	 Chemical Formula: $C_{21}H_{20}N_2O_2S$ Exact Mass: 364.1245 Molecular Weight: 364.4607	4.9%

Chapter Three

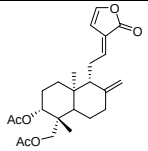
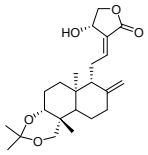
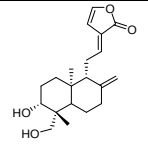
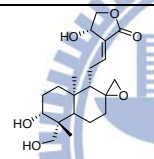
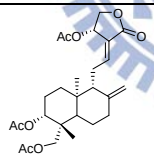
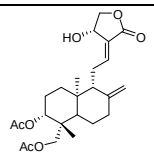
No	Compound Str	G9-Inhibition Assay as compared to BIX
10a	 Chemical Formula: $C_{32}H_{36}N_6O_3$ Exact Mass: 537.274 Molecular Weight: 537.652	8.3%
10b	 Chemical Formula: $C_{32}H_{34}N_6O_5$ Exact Mass: 582.2591 Molecular Weight: 582.6496	-6.25%
10c	 Chemical Formula: $C_{32}H_{34}FN_6O_3$ Exact Mass: 555.2646 Molecular Weight: 555.6425	1.51%
10d	 Chemical Formula: $C_{30}H_{33}N_5O_3$ Exact Mass: 511.2583 Molecular Weight: 511.6147	3.56%
10e	 Chemical Formula: $C_{31}H_{33}N_5O_5$ Exact Mass: 555.2482 Molecular Weight: 555.6242	5.67%
10f	 Chemical Formula: $C_{32}H_{34}N_6O_5$ Exact Mass: 582.2591 Molecular Weight: 582.6496	-3.85%

O

10g	 Chemical Formula: $C_{34}H_{36}N_6O_4$ Exact Mass: 592.2798 Molecular Weight: 592.6874	2.61%
10i	 Chemical Formula: $C_{35}H_{37}N_5O_4$ Exact Mass: 591.2846 Molecular Weight: 591.6994	12.09%
10j	 Chemical Formula: $C_{32}H_{34}FN_5O_2$ Exact Mass: 539.2697 Molecular Weight: 539.6431	17.47%
10k	 Chemical Formula: $C_{34}H_{31}N_5O_4$ Exact Mass: 573.2376 Molecular Weight: 573.641	-2.53%
10l	 Chemical Formula: $C_{31}H_{33}N_6O_4$ Exact Mass: 552.2485 Molecular Weight: 552.6236	-1.05%
10m	 Chemical Formula: $C_{32}H_{30}N_6O_4$ Exact Mass: 574.2329 Molecular Weight: 574.6291	-2.08%
10n	 Chemical Formula: $C_{33}H_{29}FN_5O_2$ Exact Mass: 547.2384 Molecular Weight: 547.622	-6.5%

CHAPTER FOUR

G9-Inhibition Assay as compared to BIX

12	 Chemical Formula: $C_{24}H_{32}O_6$ Exact Mass: 416.2199 Molecular Weight: 416.5073 **NCTU-SUN-050**	10.27%
13	 Chemical Formula: $C_{23}H_{34}O_5$ Exact Mass: 390.2406 Molecular Weight: 390.5131 **NCTU-SUN-030**	8%
14	 Chemical Formula: $C_{20}H_{28}O_4$ Exact Mass: 332.1988 Molecular Weight: 332.4339 **NCTU-SUN-48**	-2.29%
16	 Chemical Formula: $C_{20}H_{30}O_6$ Exact Mass: 366.2042 Molecular Weight: 366.4486 **NCTU-SUN-381**	8.16%
17	 Chemical Formula: $C_{28}H_{36}O_8$ Exact Mass: 476.241 Molecular Weight: 476.5592 **NCTU-SUN-322**	10.17%
18	 Chemical Formula: $C_{24}H_{34}O_7$ Exact Mass: 434.2305 Molecular Weight: 434.5226 **NCTU-SUN-323**	16.48%

Q

CHAPTER FOUR

Suppression Assay of NF-κB activation (Luciferase assay)

RAW 264.7/Luc-P1 cells, an LPS responsive cell line with an integrated reporter gene (pELAM1-Luc), were generated from the RAW 264.7 cell line. Seed cells (RAW264.7/Luc-P1 cells, and RAW 264.7 were cultured on $4x10^5$ cells/ well, in MP-24 plates), and incubate these cells overnight at 37^oC, 5 % CO_2 incubator.

Preparation of luciferin assay buffer: Add 300 µl of ATP (100 mM) with 5 µl DTT (1 M) + 4.65 ml assay buffer + 50 µl luciferin buffer (100x)

Luciferase Reporter Assays: The RAW 264.7/Luc-P1 cells ($4x10^5$ cells in 24-well plates) were treated with andrographolide and its analogs or vehicle (0.1% DMSO) for 1 h and incubate for 5 hrs. After 5 hrs briefly wash cells with 1X PBS. Then add 100 µl 1X passive lysis buffer (PLB) into each well, and incubate the sample for 15 min at RT with gentle shaking. Add 20 µl cell extract into a 96-well-optiplate (white). Then add 100 µl luciferin assay buffer and immediately measure luminescence by VICTOR2 Multi-label Readers as shown in Figure 4.1.

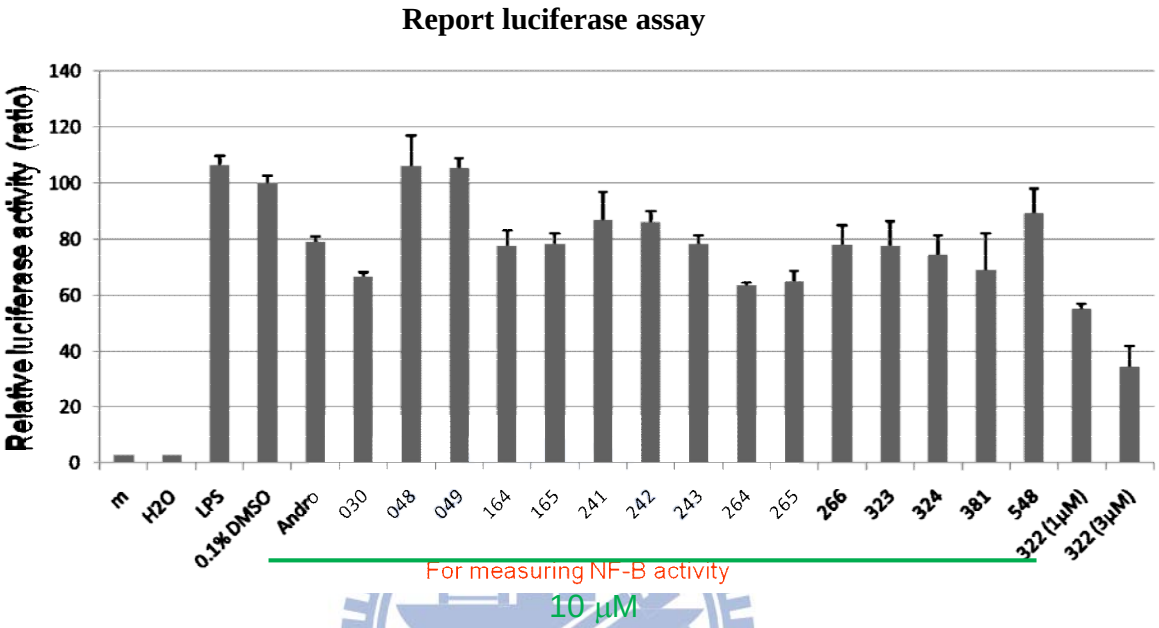


Figure 4.1. Assay of NF-κB activation

Suppress the production of NO in RAW 264.7 macrophages

Seed cells RAW 264.7 were cultured on $4x10^5$ cells/ well, in MP-24 plates with 200 µl of culture medium and incubated overnight. The cells were treated with different concentrations of andrographolide and its analogs or vehicle (0.1% DMSO) for 1 hour, followed by LPS treatment (1 µg/ml) for 24 hours. NO production was detected using 100 µl of Griess reagent (1% sulphanilamide and 0.1% naphthylenediamine in 5 % phosphoric acid) to 100 µl samples of medium. Data are presented as mean ± SEM from three independent experiments as shown in figure. The

data indicate that androgarpholide or its analogs can inhibit LPS-induced NO production in a concentration-dependent manner in figure 12.

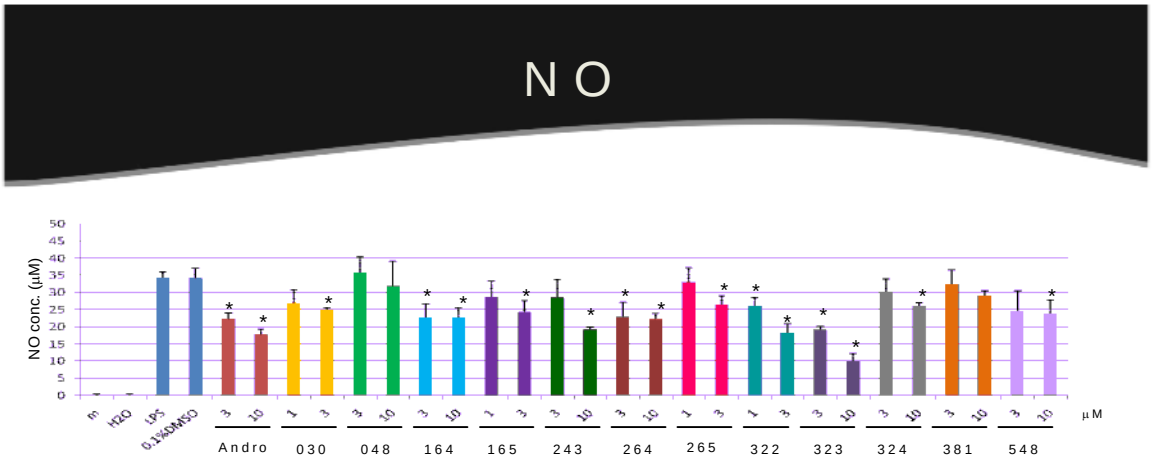


Figure 4.2. Suppress the production of NO in RAW 264.7 macrophages

Enzyme-Linked Immunosorbent Assay (ELISA)

It was used to quantitatively determine cytokine concentration in cell culture medium.

Materials and Reagents：Mouse TNF-a ELISA kit (R&D):

Capture Antibody – 160 mg/ml (dilute to a working concentration of 0.8 mg/ml in PBS)

Detection Antibody - 30 mg/ml (dilute to a working concentration of 150 ng/ml in Reagent Diluent)

Standard - 270 ng/ml [a seven point standard curve using 2-fold serial dilutions in Reagent Diluent, and a standard with highest concentration (2000 pg/ml) is recommended]

Streptavidin-HRP - 1.0 ml

- 1X PBS

- Wash buffer

- Reagent diluent

- Substrate solution (3,3',5, 5'-tetramethylbenzidine, TMB)

- 1N HCl

Sample preparation involves the follwing procedures

1. Seed cells (RAW 264.7 cell $2x10^5$ cells/ well, in MP-24 plates) and incubate overnight

2. Add compounds in cell culture and incubate for 24 hrs

3. Collect supernatant

ELISA - Plate pretreatment

Procedures: 1. To coat plates, add 100 µl capture Ab. (200X dil. in PBS) into 96-well microplates and leave plates at RT overnight

2. Wash plates 3 times with wash buffer

3. Add 300 µl of reagent diluent to each well, leave plates at RT for 1 hr (or store the plates at 4 ^oC)

4. Wash plates 3 times with wash buffer

Assay procedure

Add 100 µl samples or STDs (diluted in reagent diluent) into pre-treated plates and incubate the sample plates for 2 hr at room temperature thenWash plates 3 times with

wash buffer. Add 100 µl detection Ab. (200 x dilution in reagent diluent), and incubate the sample plates for 2 hr at room temperature. Further wash plates 3 times with wash buffer. Add 100 µl Streptavidin-HRP. (200x dilution in reagent diluent), incubate the sample plates for 20 min at room temperature and again wash plates 3 times with wash buffer. Add 100 µl substrate solution (TMB) and incubate the sample plates for 20 min at room temperature. Add 50 µl stop solution (1N HCl or 2N H_2SO_4). Then determine the optical density of each well immediately, using ELISA reader set to 450 nm as shown in figure 13.

ELISA TNF-α

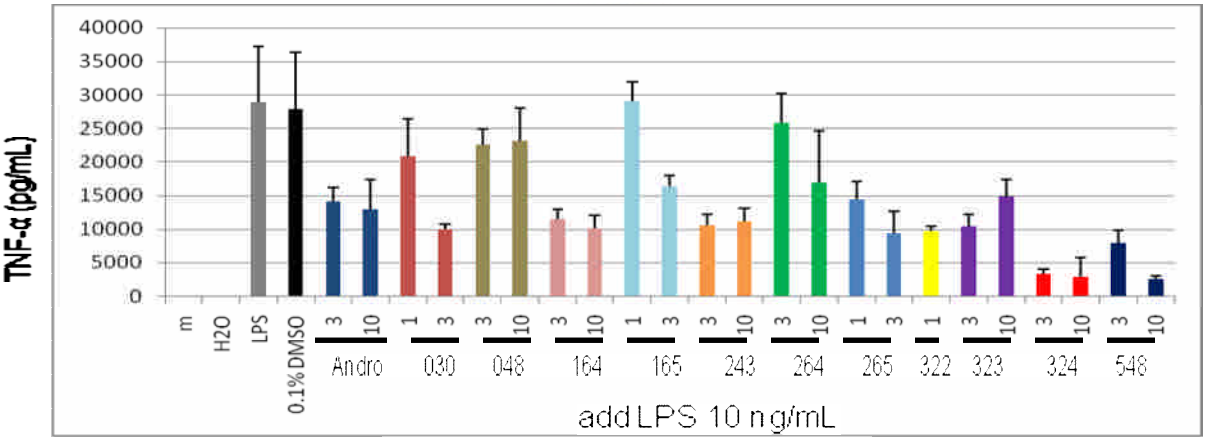


Figure 4.3 Enzyme-Linked Immunosorbent Assay (ELISA) of andrographolide analogs