Synthesis of Nitrogenous Heterocycles *via* Multicomponent Reaction and Exploration of Naphthalen-2-ol Sulfides to Access Benzylic Ethers & Naphthofurans

A Dissertation Submitted to the
Indian Institute of Technology Guwahati
As Partial Fulfillment for the Degree of

DOCTOR OF PHILOSOPHY

By

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Oct 2016

Dedicated to

My Parents and Late Brother

INDIAN INSTITUTE OF TECHNOLOGY, GUWAHATI

Department of Chemistry

DECLARATION

I do hereby declare that the matter embodied in this thesis *entitled "Synthesis of Nitrogenous Heterocycles via Multicomponent Reaction and Exploration of Naphthalen-2-ol Sulfides to Access Benzylic Ethers & Naphthofurans"* is the result of investigation carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India, under the supervision of Prof. Abu T. Khan and co-supervision of Dr. Mohammad Qureshi. This thesis has been submitted by me to the Department of Chemistry, Indian Institute of Technology Guwahati for the award of the degree of Doctor of Philosophy.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators. I further declare that this work has not been submitted anywhere else for any degree, diploma, associateship or membership etc. of any Institute or University to the best of my knowledge.

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CERTIFICATE

This is to certify that Kobirul Islam has been working under my supervision as a registered regular Ph. D. student since July, 2011. His thesis entitled *"Synthesis of Nitrogenous Heterocycles via Multicomponent Reaction and Exploration of Naphthalen-2-ol Sulfides to Access Benzylic Ethers & Naphthofurans"* contains an authentic record of the results obtained from the research work carried out by him in the Department of Chemistry, Indian Institute of Technology Guwahati, India. I am forwarding his thesis for the Ph. D. (Science) degree from this institute. I certify that he has fulfilled all the requirements according to the rules of this institute. The investigations embodied in his thesis have not been submitted elsewhere for a degree.

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This is to certify that Kobirul Islam has completed her Ph. D. Thesis work from July, 2011 as a regular Institute Research Fellow registered for Ph. D. programme under my colleague Prof. Abu T. Khan. I have been appointed as a Co-supervisor when Prof. Khan joined as Vice-Chancellor of Aliah University in Kolkata, West Bengal on deputation from IIT Guwahati. I am forwarding his thesis as a Co-supervisor entitled *"Synthesis of Nitrogenous Heterocycles via Multicomponent Reaction and Exploration of Naphthalen-2-ol Sulfides to Access Benzylic Ethers & Naphthofurans"* for submission for the Ph. D. (Science) Degree of this Institute. I also certify that he has fulfilled all the requirements according to the rules of this Institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

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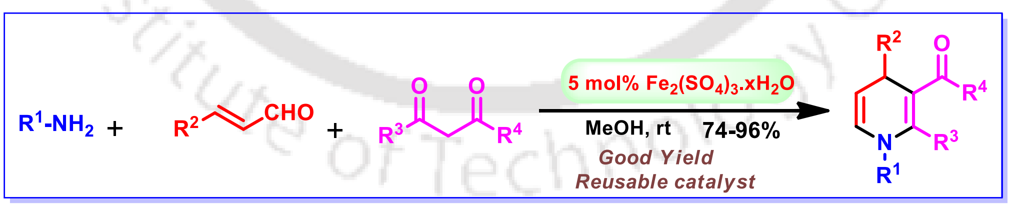
Kobirul Islam

SUMMARY OF THE THESIS

The contents of this thesis entitled *"Synthesis of Nitrogenous Heterocycles via Multicomponent Reaction and Exploration of Naphthalen-2-ol Sulfides to Access Benzylic Ethers & Naphthofurans"* have been divided into seven chapters based on the experimental results carried out by me during the period of five years.

Chapter I: The first chapter of the thesis represents a summary on different aspects of multicomponent reactions towards the synthesis of various six member nitrogen containing organic frameworks and their application in organic synthesis. This chapter mainly highlights on the synthesis of different heterocycles *via* C-C, C-N or C-O bond formations. Different approaches have been developed and applied to construct a wide collection of these heterocyclic moieties.

Chapter II: This chapter mainly focuses on the synthesis of 5,6-unsubstituted 1,4-dihydropyridine derivatives through one-pot three-component reaction from *α,β*-unsaturated aldehydes, amines and 1,3-diketones in methanol at room temperature using hydrated ferric sulfate as a catalyst. 1,4-Dihydropyridines, an important class of nitrogen heterocycles, are found in numerous synthetic pharmaceutical agents. Various 1,4-dihydropyridine-based drug molecules such as amlodipine, clevidipine, felodipine, nicardipine, etc. are already marketed to reduce systemic vascular resistance and arterial pressure. In addition, they exhibit a diverse range of biological activities.The key features of the present protocol are mild and simple reaction procedure, good to excellent yields, and use of inexpensive and recyclable catalyst.

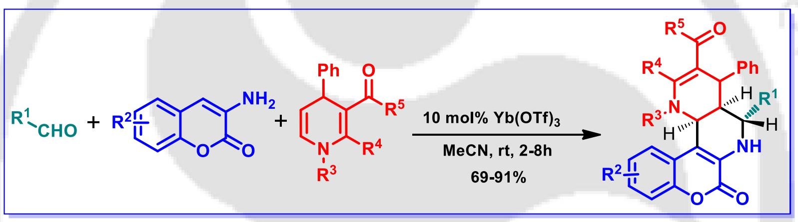


Scheme I.

Chapter III: This chapter described exploration of our synthesized C5-C6-unsubstituted 1,4-dihydropyridines for the construction of *exo*-hexahydro-1*H*-chromeno[3,4-*h*][1,6] naphthyridine-3-carboxylates *via* stereoselective Povarov reaction using 3-aminocoumarins, aldehydes and 5,6-unsubstituted 1,4-dihydropyridine derivatives employing 10 mol% of

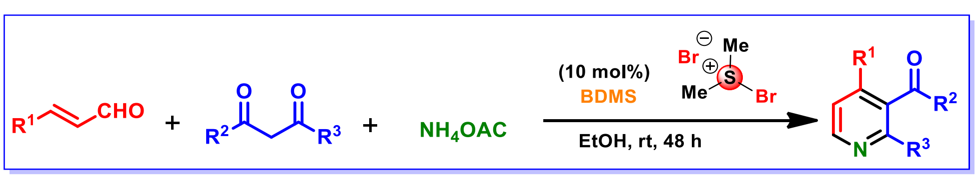
Yb(OTf)3 in acetonitrile at room temperature. One-pot Povarov reaction or the hetero Diels-Alder reaction is recognized as a potential synthetic strategy for the construction of natural and artificial polyheterocycles owing to its rich synthetic diversity. Povarov reaction generally produces both *endo*- and *exo*-isomers with poor stereoselectivity. Therefore synthesis of a single diastereomer is still a challenging task. Here in we have utilized stereoselective Povarov reaction for the synthesis of 1,6-naphthyridine derivatives. 1,6-Naphthyridines are found in many natural products and also exhibit a wide range of pharmacological activities. Due to their immense utility, researchers have been fascinated to synthesize these compounds in recent times.

The reaction condition is simple and transformation is quite effective for a wide range of substrates. The products are easily isolable in good to excellent yields without aqueous work-up and chromatographic separation.



Scheme II.

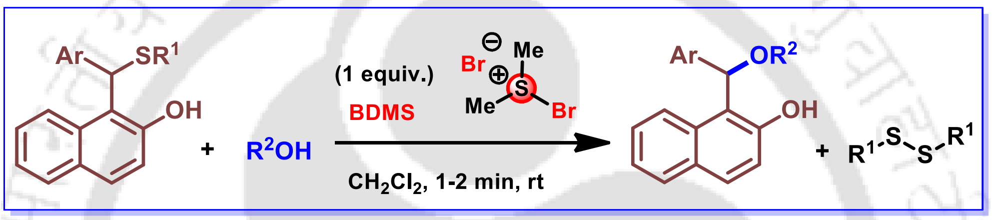
Chapter IV: In this chapter demonstrates bromodimethylsulfonium bromide (BDMS) catalyzed metal-free three components reaction for the synthesis of functionalized pyridine using *α,β*-unsaturated aldehydes, ammonium acetate and 1,3-diketones at room temperature. Our research groups have explored BDMS in various organic transformations. In this chapter we are utilizing this reagent for the construction of pyridine moiety. Pyridine is one of the significant nitrogen containing heterocycles found in many natural and synthetic pharmaceutical agents. This core unit is present in many naturally occurring compounds having biological activities. Pyridine moiety has gained a significant attention for exhibiting a broad spectrum of biological and pharmacological activities.



Scheme III.

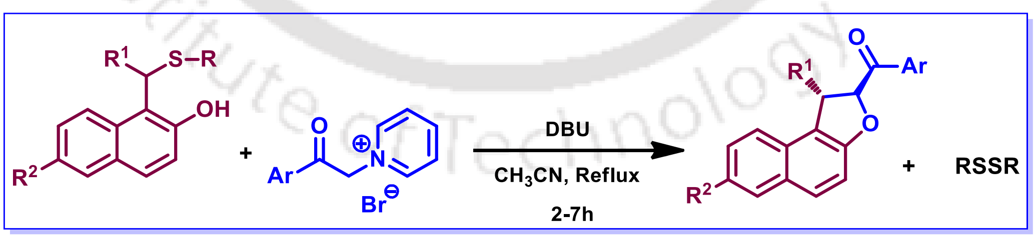
Chapter V: This chapter of the thesis represents a brief over view on *o*-(naphtho)quinone methides in the synthesis of various organic frameworks. This chapter focus on the synthesis of different ethers, naphthofurans and heterocycles by capturing *o*-(naphtho)quinone methides with different nitrogen, sulphur, oxygen and carbon nucleophiles.

Chapter VI: This chapter described direct approach for the synthesis of unsymmetrical ethers from naphthalene-2-ol sulfides in acetonitrile at room temperature by employing bromodimethylsulfonium bromide (BDMS). This protocol is useful for the preparation of highly substituted ethers and in addition, the reaction is simple, fast and effective transformation for a wide range of substrates.



Scheme IV.

Chapter VII: An efficient one-pot C-S bond cleavage and diastereoselective synthesis of 2-acyl-1,2-dihydronaphtho[2,1-*b*]furans is achieved from naphthalene-2-ol sulfides, phenacylpyridinium bromide with one equiv. of DBU in acetonitrile under reflux condition. 1,2-Dihydronaptho[2,1-*b*]furan analogues represent one of the most intense bioactive scaffolds in sheer growing pharmaceutical industries. Its basic framework is a encouraging molecule to examine the discovery of pharmacological assets.



Scheme V.

CONTENT OF THE THESIS

GENERAL REMARKS

The investigations were carried out in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781 039, Assam during the period from July, 2011 to September, 2016 as a Ph.D. student under the supervision of Prof. Abu T. Khan.

The analytical samples were routinely dried *in vacuo* at 50^{o}C for 8 hours. In TLC experiments, silica gel G (SRL) or silica gel GF 254 (SRL) were employed as adsorbent. Column chromatography was carried out with silica gel (60-120 mesh, Merck, SRL or Qualigen), for purifications of reaction mixture. After purification, the solvent was usually removed in rotavapor using Büchi R-114V instrument. Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 281 IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian 400 MHz and Bruker 600 MHz spectrometer TMS as internal reference; chemical shifts (δ scale) are reported in parts per million (ppm). ^{1}H NMR Spectra are reported in the order: multiplicity, no. of protons and coupling constant (*J* value) in hertz (Hz); signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), bs (broad singlet), dd (doublet of doublet), dq (doublet of quartet), dt (doublet of triplet) and ddt (doublet of doublet of triplet). Mass spectra were collected on Agilent Technologies 6520 Accurate-Mass Q-TOF LC/MS and WATERS MS system, Q-TOF premier and data analyzed using Mass Lynx 4.1. Elemental analyses were carried out using Perkin-Elmer 2400 Series II CHNS/O analyzer at the Department of Chemistry, Indian Institute of Technology Guwahati. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. HPLC grade DMSO and Milli-Q water was used in all the experiments.

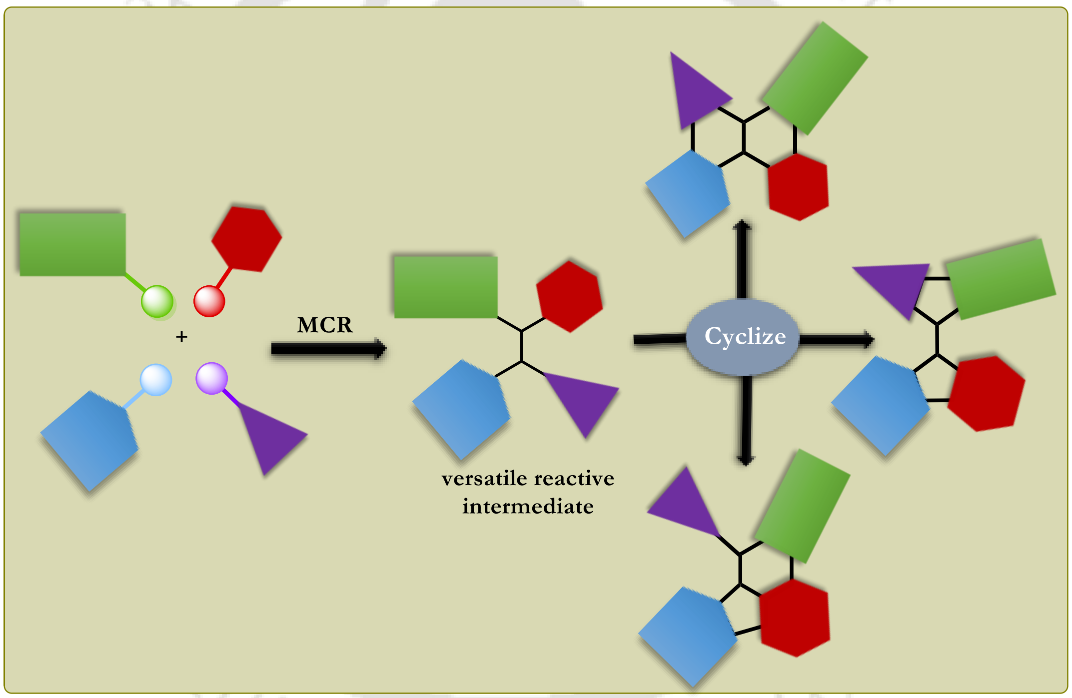
ABBREVIATIONS

Ac	acetyl
BDMS	bromodimethylsulfonium bromide
BINOL	1,1'-Bi-2-naphthol
Bn	benzyl
Bu	butyl
^{t}Bu	tert-Butyl
BuOH	butanol
Bz	benzoyl
Cbz	carboxybenzyl
CAN	cerium(IV)ammonium nitrate
CSA	camphorsulfonic acid
dA	deoxyadenosine
DBU	1,8-diazabicycloundac-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHP	dihydropyridine
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
EA	ethyl anthranilate
ee	enantiomeric excess
EVE	ethyl vinyl ether
ESI-MS	electrospray ionisation mass spectrometry
EtOH	ethanol
Et_3N	triethylamine
EWG	electron withdrawing group
HRMS	high resolution mass spectrometry
IR	infrared

MCR	multicomponent reaction
CR	component reaction
m-CPBA	*m*-chloroperoxybenzoic acid
MeOH	methanol
mp	melting point
MS	molecular sieves
MW	microwave
NAD	nicotinamide adenine dinucleotide
NMR	nuclear magnetic resonance
ORTEP	oak ridge thermal ellipsoid program
o-QM	*o*-quinone methide
o-NQM	*o*-naphthoquinone methide
Ph	phenyl
ppm	parts per million
Pr	propyl
p-TsOH	*p*-toluenesulfonic acid
PTSA	*p*-toluenesulfonic acid
Py	pyridine
rt	room temperature
SAR	Structure activity relationship
TBATB	*n*-tetrabutylammonium tribromide
TBS	*t*-butyldimethylsilyl
TBATB	tetrabutylammonium tribromide
NBS	*N*-Bromosuccinimide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
XRD	x-ray diffraction

Chapter I

An insight into the synthesis of diverse six membered nitrogen heterocycle using multicomponent reaction



CHAPTER I

An insight into the synthesis of diverse heterocyclic scaffolds through multicomponent reaction (MCR)

I.1. Introduction

Multicomponent reactions (MCRs) are effective and elegant methods for the synthesis of simple and complex heterocyclic skeletons in a modest and selective pathway. [1]MCRs generally define convergent chemical processes that involve the distinct condensation of more than two reactants to form a product that contains significant portions of all reactants, ideally all the atoms.[2] Therefore, MCRs pathway portray a sequence of more than one chemical transformations without changing the reaction condition leading to high level of molecular diversity with less time and effort. Thus simple starting materials combining through MCRs give products with diverse scaffolds as depicted in Figure 1.

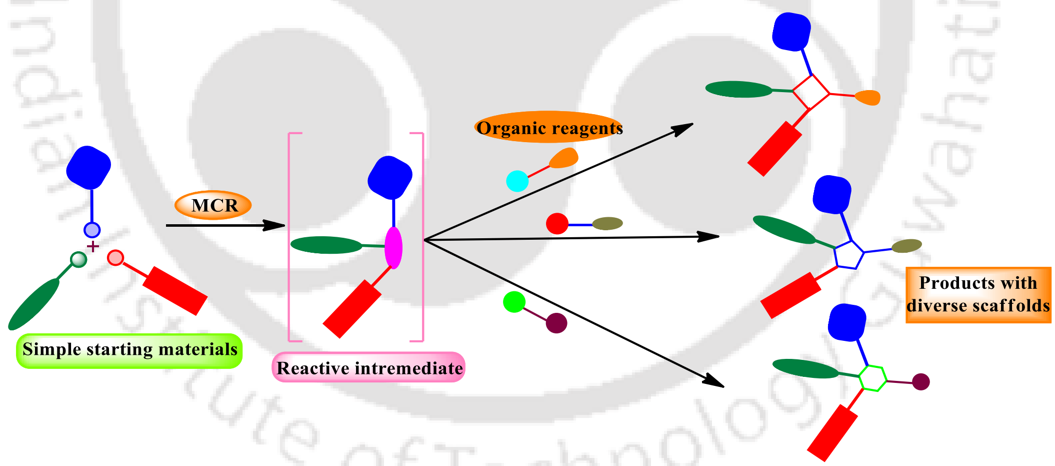


Figure 1. MCRs product with complex and diverse scaffolds.

This approach is effective for the pharmaceutical industry, for easy access of large libraries of compounds with potential biological activities.[3]

❒ I.2. Important aspects of MCRs

In recent decades, synthetic chemists have shown profound interest in multicomponent reactions. Very high levels of atom economy, the use of readily available starting materials, multiple-bond-forming efficiency and resource effectiveness which render these reactions useful for environmentally friendly alternatives are the key aspects of MCRs. [4]MCRs are one-pot methods with modest experimental conditions, avoiding time-consuming isolation and purification of synthetic intermediates, thus reduces the cost of construction highly diverse and complex molecules to a minimum. In addition, both waste production and human labor are considerably reduced. MCRs approaches are much easier to execute than a complicated multistep synthesis as depicted in Figure 2.[5]

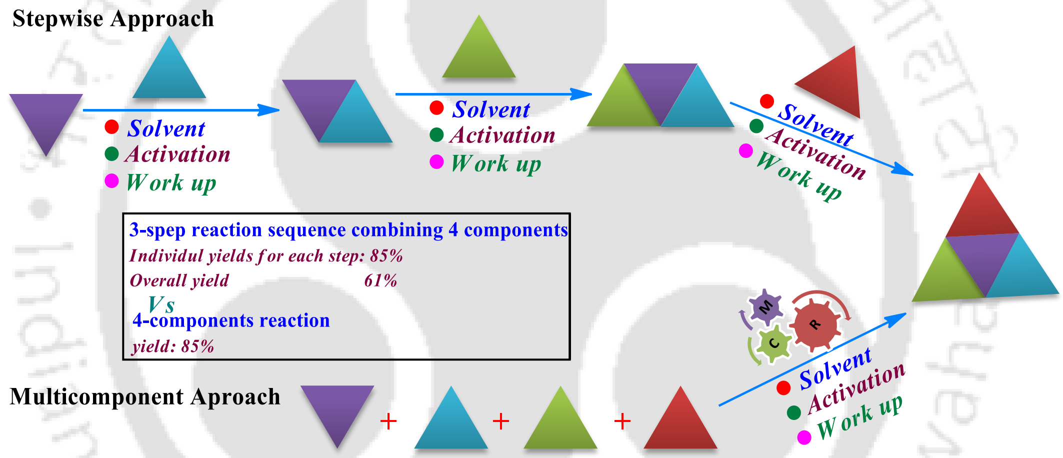


Figure 2. Step wise linear synthesis *vs* multicomponent approach.

One of the important feature of multicomponent reactions is that they are the origin of molecular diversity[6] shown in Figure 3. Therefore the scope of the substrate in the reaction protocol is always high. For instance, without any restriction, all components can be varied, the combination of each ten different starting materials in a three component reaction (3CR) would lead to the construction of up to 1000 different compounds.[7] Likewise 6CR with ten different starting compounds each would increase the amount of divergent structures dramatically to 1,000,000. Figure 3 describes various functional groups combined together to form definite intermediate which produces different products under different conditions with great molecular diversity.

For these reasons, MCRs are well adapted for combinatorial synthesis.[8] Because of this advantage, the pharmaceutical industry has fueled this resurgence for the growing demands and the needs to assemble libraries of structurally complex substances for evaluation as the lead compounds in drug discovery and development programs.[9]

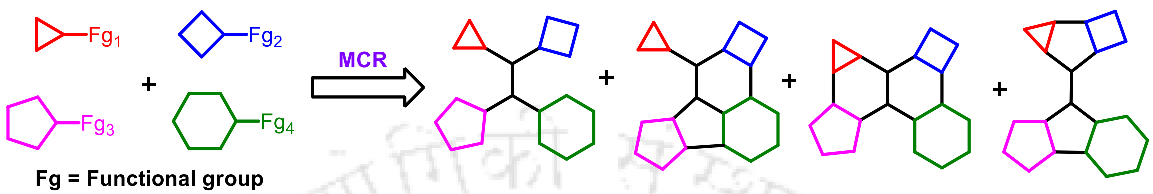


Figure 3. MCRs product with different molecular diversity.

Anastas and Warner in 1998 formulated 12 principles for green process like waste prevention, atom economy, less hazardous, safe chemical design, benign solvent, energy efficiency, renewable feedstocks, reduced use of derivatives, catalysis, design for degradation, real-time analysis and safe chemistry.[10] Multicomponent reactions achieve many of the criteria set by the green chemistry viewpoint. The evaluation of the performance of MCRs with respect to the green chemistry recommendations ascertain good compatibility of this chemistry with sustainable organic synthesis. It is noteworthy that the majority of the green criteria are inherent characteristics of MCRs. Some of these features are shown in Figure 4.[11]

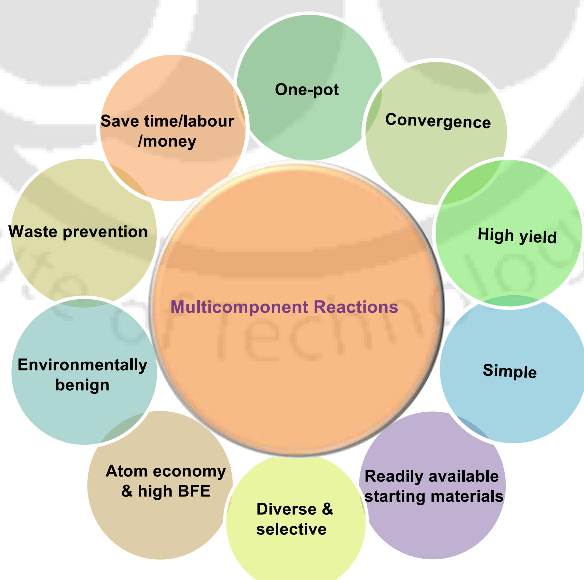


Figure 4. Characteristics feature of MCRs.

❐ I.3. Historical overview of MCRs chemistry

Multicomponent reactions have received popularity as a tool for the quick generation of small-molecular libraries. Surprisingly, MCRs approach remained unexploited for many decades. However, their attractiveness has literally blowup in the early 1990s with the beginning of combinatorial chemistry where MCRs were viewed as ideal reactions to assemble library of compounds with various molecular diversity for fulfilling the demand of pharmaceutical industries.[12] The concept of MCRs is not new in nature, adenine one of the major base constituents of DNA and RNA is formed by the condensation of five molecules of HCN.[13] The history of MCRs can be sketched in 1838 when Gerhard and Laurent described the formation of cyanohydrin imines from bitter almond oil and ammonia it is considered as the first multicomponent reaction.[14] Adolf Strecker in 1850 generalized this sequence reaction by synthesizing α-amino nitriles, an important intermediate in the synthesis of α-amino acids using amines, aldehydes, and cyanide.[15] Later on many MCRs have been developed, some of the examples are the Hantzsch dihydropyridine synthesis (1882)[16] and the Biginelli reaction (1893).[17] Isocyanide-based MCRs were introduced by Passerini[18] in 1921, whereas in 1959 Ugi[19] introduced the four component isocyanides reaction. The historical overview of MCRs is shown in Figure 5.

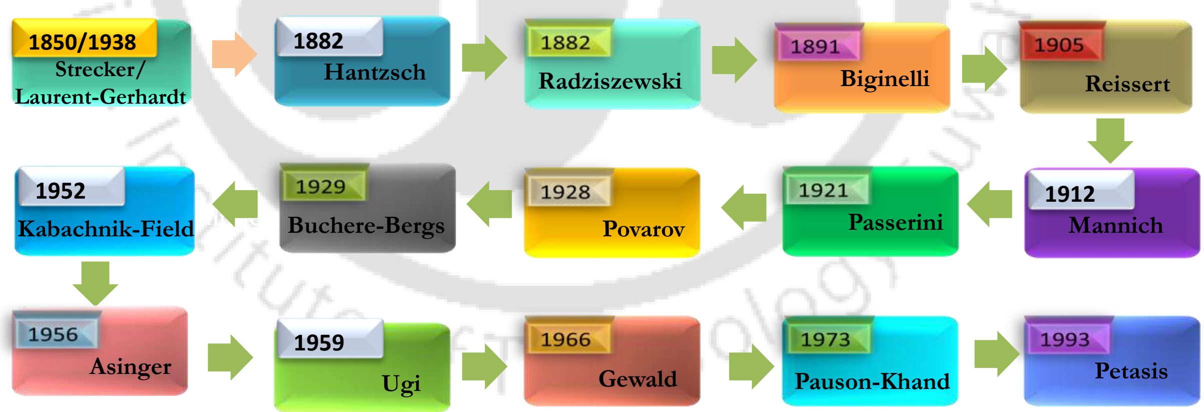


Figure 5. Historical overview of multicomponent reaction.

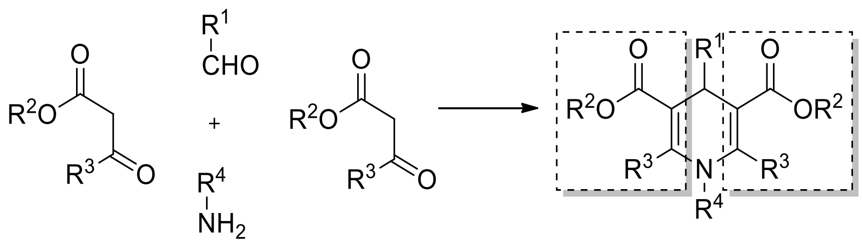
I.4. Six membered nitrogen heterocycles based on MCRs

Six-membered nitrogenous heterocyclic skeletons are prevalent in biologically active natural products. These structures have great potential in pharmaceutical and medicinal chemistry. Thus, scientists have been fascinated towards these targets with high structural diversity and stereoselectivity. The MCRs are well amenable for the construction of these heterocyclic cores and more importantly for the achievement of a high degree of both complexity and diversity for a targeted set of scaffolds by minimizing the number of synthetic operations.

I.4.1. Multicomponent cyclization reactions for the synthesis of 1,4-dihydropyridines

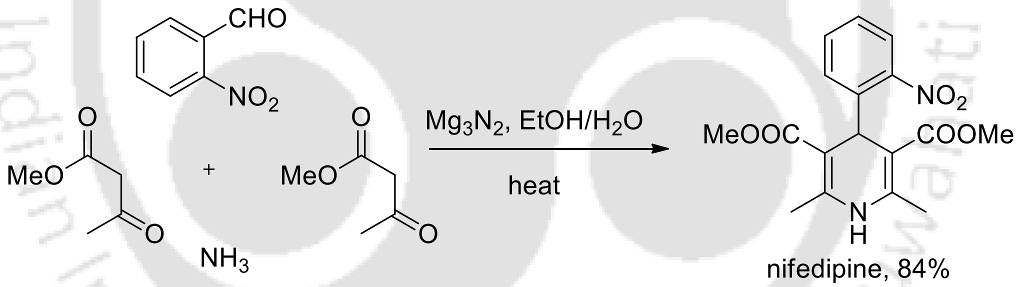
Nitrogen-containing heterocycles have drawn much attention among researchers because of the vast majority of natural products and drug like compounds are having these heterocyclic subunits.[20] These compounds show extensive biological and pharmaceutical activities are offering potential new drug candidates.[21] Therefore, synthesized of these diversely heterocyclic compounds is critical to the synthetic chemist. One of the most encouraging synthetic tactics for creating collections of small molecules by diversity-oriented synthesis (DOS) involves the sequencing of multicomponent reactions (MCRs) with subsequent alterations, including cyclizations and refunctionalizations, which form new compounds possessing increased molecular complexity and diversity.[22] The sequencing of multicomponent reactions (MCRs) and subsequent cyclization reactions are well amenable for the construction of different heterocyclic frameworks.[23]

Dihydropyridines (DHPs) show a wide range of pharmaceutical activities. In particular, 4-substituted 1,4-dihydropyridines have been recognized as an important class of heterocyclic compounds as pharmacophores.[24] Therefore they are attractive synthetic targets in organic chemistry. MCRs are the most efficient strategies to access 1,4-dihydropyridines.[25] Arthur Hantzsch in 1882 utilized one-pot, four-component MCRs reaction as an effective route for synthesizing symmetrically substituted 1,4-dihydropyridines. The classical Hantzsch reaction, which incorporates two dicarbonyl compounds, an amine and an aldehyde into a dihydropyridines (DHPs) is shown in Scheme 1.



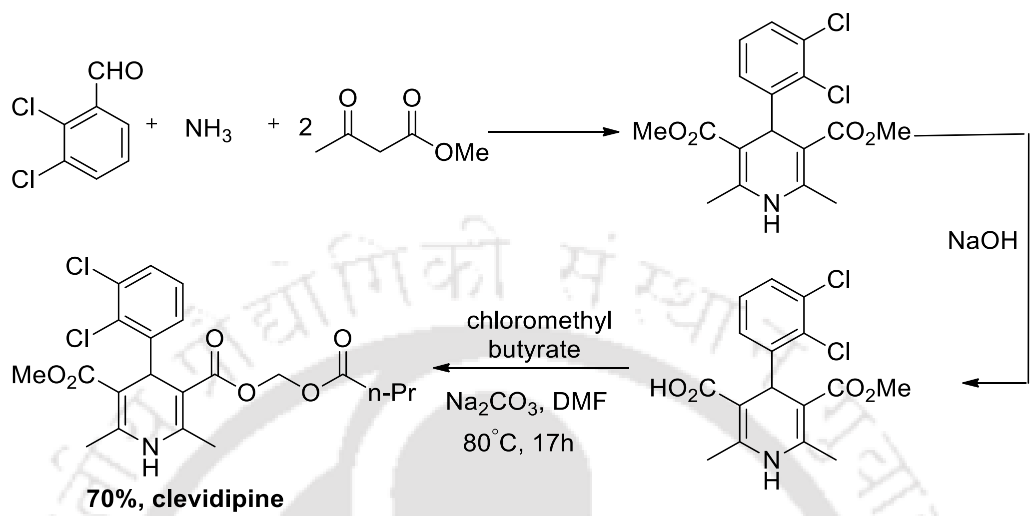
Scheme 1. Hantzsch dihydropyridine synthesis.

The outbreak interest in this class of molecules was stimulated by the isolation of NADH with its biological oxidation–reduction reactions, and the widespread attention was gathered by molecule nifedipine, an antihypertensive drug, with most of the preliminary studies based on calcium channel blocker.[26] The straightforward classical Hantzsch reaction permits the preparation of numerous 1,4-DHPs derivatives as well as several other classes of similar moieties used as potential medicines.[27] One of the earliest examples, nifedipine was introduced to the market in the 1970s as an antihypertensive and antianginal drug as shown in Scheme 2.[28]



Scheme 2. Classical Hantzsch reaction of nifedipine synthesis.

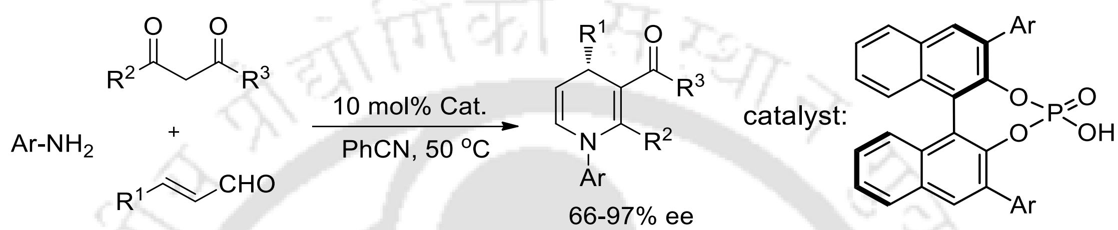
Clevidipine, a third generation calcium channel blocker was used primarily for rapid decrease and stabilization of blood pressure after cardiac surgery. It was reported that both enantiomers of clevidipine undergo esterase-mediated hydrolysis with short half-lives of around two minutes and having similar medical and physiological properties indicates it that clevidipine can be safely administered in its racemic form[29]. A standard Hantzsch synthesis among 2,3-dichlorobenzaldehyde, ammonia and methyl acetoacetate furnishes the symmetric dihydropyridine which can be a selectively mono-saponification resulting carboxylic acid group followed by alkylation with chloromethylbutyrate affords racemic clevidipine shown in Scheme 3.[30]



Scheme 3. Standard Hantzsch synthesis of clevidipine.

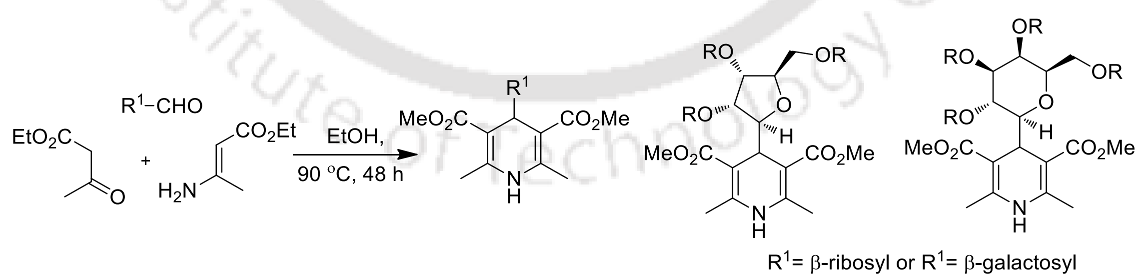
Hantzsch reaction is beneficial in DHPs synthesis but 5-unsubstituted or 5,6- unsubstituted DHPs cannot be synthesized by classical Hantzsch reaction protocol.[31] The main limitation of the Hantzsch reaction is that the 1,4-DHPs, provided by the reaction are all symmetrical in the heterocyclic moieties since this unit was constructed by employing two molecules of 1,3-dicarbonyl compounds. Although Hantzsch reactions using two different dicarbonyl compounds had been achieved later, the symmetrical 1,4-DHPs formed by the homo-condensation of same dicarbonyl compound remained more or less as side products in these reactions. In terms of biological screening, acquiring diversified derivatives of a known pharmacophore is a main and efficient approach for discovering new biologically active lead compounds. Even though many reported biologically active 1,4- DHPs are symmetrical, this was not the requirement of biological receptors but the results of employing the Hantzsch reaction for 1,4-DHPs synthesis in most cases. For the sake of finding more 1,4-DHPs possessing new and improved biological functions, the synthesis of structurally diverse 1,4-DHPs such as unsymmetrical 1,4-DHPs is pivotal work.[32] Therefore, new MCRs that are capable of generating novel unsymmetrical 1,4-DHPs have attracted significant attention in recent years. *N*-Aryl-1,4-dihydropyridines[33] and other related analogues are valuable compounds since they have applications as pharmaceuticals and agrochemicals.[34] However, it is known that the classical Hantzsch reaction is not a suitable method for the preparation of *N*-aryl-1,4-dihydropyridines. For that reason, a complementary route to the Hantzsch synthesis has been developed to obtain *N*-aryl-1,4-DHPs. This involves the coupling of aromatic amines, α,β-unsaturated aldehydes and ketoesters.

Gong *et al.*[35] reported enantioselective synthesis of 1,4-DHPs using chiral phosphoric acid as catalyst by three component Hantzsch type reaction as shown in Scheme 4.



Scheme 4. Chiral 1,4-dihydropyridines synthesis.

Artificial nucleosides, new families of nucleosides are, in fact, a current topic in medicinal chemistry owing to their well-established anticancer, antibiotic, and antiviral activities. It is well-known that the heterocyclic residue exerts a central role in biological functions of the *C*-nucleoside and therefore the synthesis and biological evaluation of these new classes of compounds with such structural diversity are of great interest. Dondoni and his groups utilized Hantzsch 3CR for the generation of *C*-nucleosides containing the DHP ring as the heterocyclic moiety bearing a sugar residue at C4 in good yields by reacting with *C*-glycosyl aldehydes, ethyl acetoacetate, and ethyl aminocrotonate in refluxing ethanol shown in Scheme 5.[36]



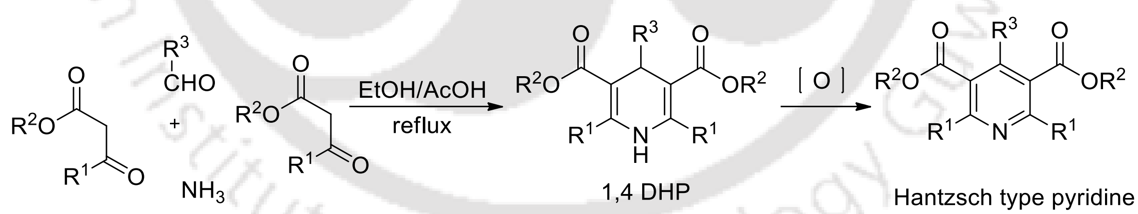
Scheme 5. Synthesis of C4-glycosylated DHPs *via* Hantzsch 3CRs.

I.4.2. Synthesis of pyridines *via* multicomponent reactions

Since the proposal of the correct structure of pyridine by Korner (1869) and Dewar (1871), pyridine ring indeed became one of the most studied nitrogen-containing heterocycles. However, this compound is fascinating to scientists mostly for its biological interests.[37] Pyridine derivatives play a crucial role in the biological activity of natural substances including vitamin B6, nicotine, or oxido-reductive NADP−NADPH coenzymes.

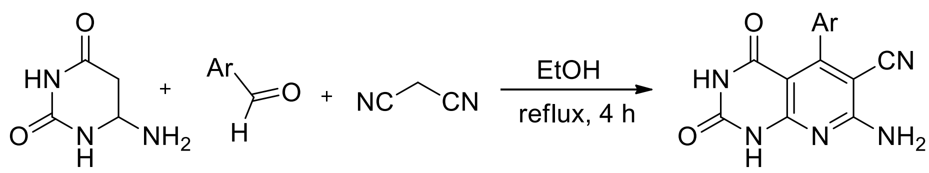
Pyridines are important fundamental heterocyclic compounds contained in many natural products and pharmaceuticals.[38] Molecules bearing this moiety exhibit a wide range of biological activities. Because of this large spectrum of applications, the selective synthesis of highly functionalized pyridine derivatives remains a preferable choice for the modern synthetic chemist. Among these methods, those involving the use of multicomponent reactions to create the pyridine ring are particularly efficient due to generation of several bonds in a single operation.[39]

One of the most popular methods for the preparation of pyridines is the Hantzsch approach, that involves one-pot pseudo-four-component reaction of 2 equivalents of a 1,3-dicarbonyl derivative, an aldehyde, and a source of ammonia to give 1,4-dihydropyridines (DHPs), followed by oxidation affords the corresponding aromatized products (Scheme 6).[40]



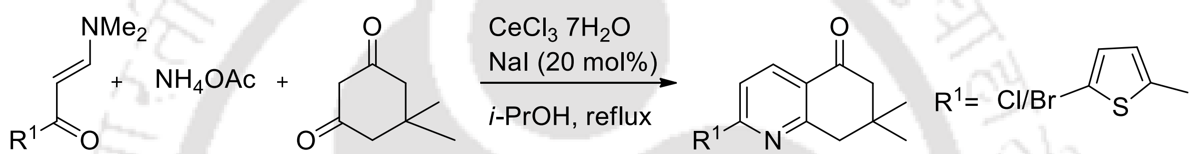
Scheme 6. General Hantzsch pyridine synthesis.

Nasr *et al.* demonstrated multicomponent synthesis of pyridopyrimidines from malononitrile, 6-aminouracil, and an aromatic aldehyde in ethanol under reflux for 4 h, affords 2-amino-3-cyanopyridines in good to excellent yields.[41] Derivative of these pyridines exhibited interesting antiviral and cytotoxic activities shown in Scheme 7.



Scheme 7. Synthesis of antiviral and cytotoxic active pyridine.

Kantevari's group reported new antitubercular pyridine derivatives synthesized through multicomponent reaction of aryl or thienyl substituted enaminoketones, cyclohexane-1,3-dione and ammonium acetate (Scheme 8). The thienyl-substituted pyridines displayed well in *vitro* antimycobacterial activity against M. *tuberculosis* $H_{37}Rv$ than ethambutol, a reference bacteriostatic drug.[42]



Scheme 8. Synthesis of antitubercular pyridines.

I.4.3. Multicomponent aza Diels-Alder reaction

The aza Diels–Alder reaction is considered as one of the most prevailing synthetic approach to access six-membered nitrogen-containing heterocycles.[43] The reaction is generally accessible with high chemo-, regio- and stereoselectivity and therefore a route to achieve biologically active molecules and natural products containing pyridine and dihydropyridine moieties.[44]

One such aza-variant is the Povarov reaction originally developed by L. S. Povarov almost 50 years ago. In this reaction *N*-arylimines (2-azadienes) react with electron-rich alkenes in a formal inverse electron demand [4+2] cycloaddition to give tetrahydroquinolines[45]. Modern variants include multicomponent reaction involving aldehyde, amine and an electron rich dienophile shown in Figure 6.[46] The nitrogen atom of these aza-heterocycles can be introduced either by the dienophile (as an imine derivative)[47] or by the diene (as a 1- or 2-azadiene)[48] which afford a wide variety of structures in an atom-economic manner. Povarov reaction cascades also convey many advantages like, high regioselectivities, convergent synthetic sequences, little waste, cheap or no catalysts required and clean reactions with few side reactions observed. Notably, these transformations often result in a significant increase in molecular complexity.

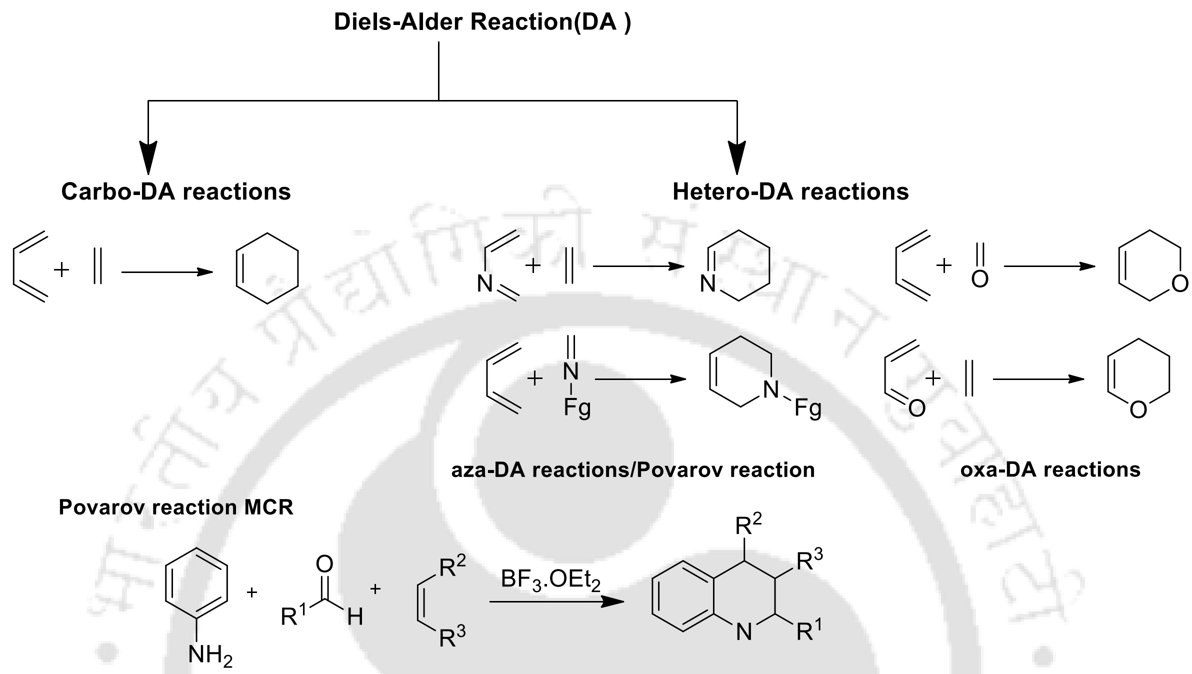
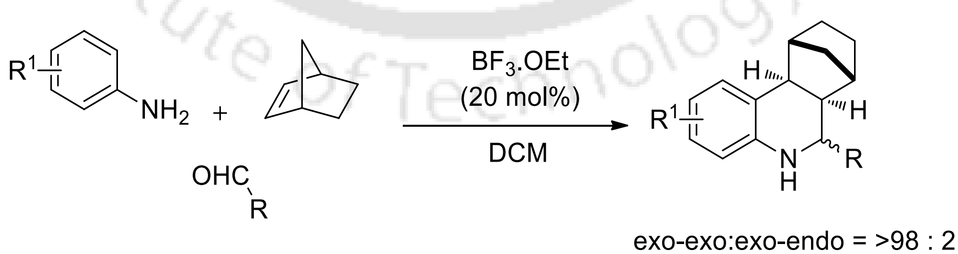


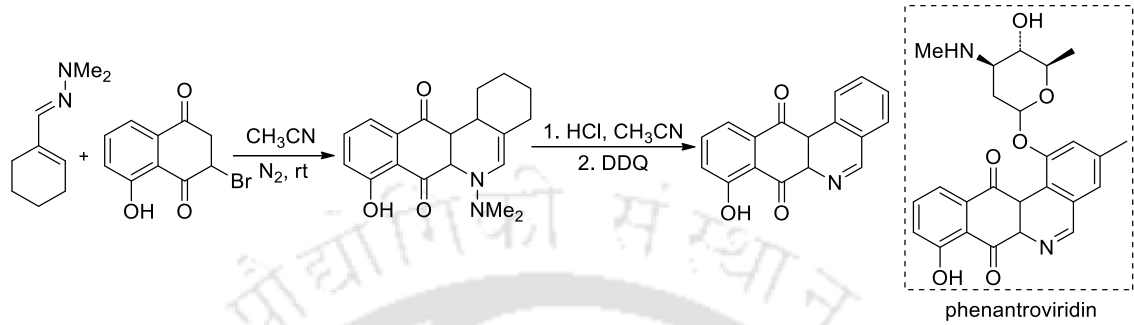
Figure 6. Diels-Alder and Povarov reaction.

Recently, Batey and his co-workers demonstrated $BF_3{\cdot}OEt_2$-catalyzed three-component reaction of aromatic aldehydes, aromatic amines and strained norbornene-derived dienophiles for diastereoselective synthesis of bridged tetrahydroquinolines in good to excellent yields (Scheme 9).[49] Other catalyst like I_2,[50] $BiCl_3$,[51] CAN[52] have been also utilised in three component Povarov reaction.



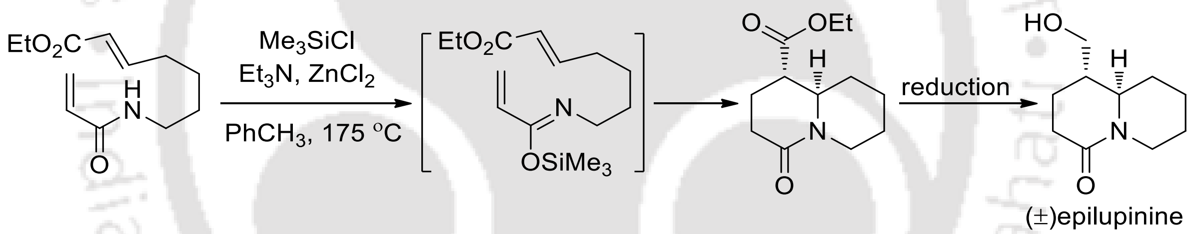
Scheme 9. Diastereoselective synthesis of bridged tetrahydroquinolines.

Valderrama *et al*. reported hetero Diels-Alder reaction of bromojuglone 1-cyclohexene carboxaldehyde dimethylhydrazone for the synthesis of cytotoxic naturally occurring phenantroviridin framework (Scheme 10).[53]



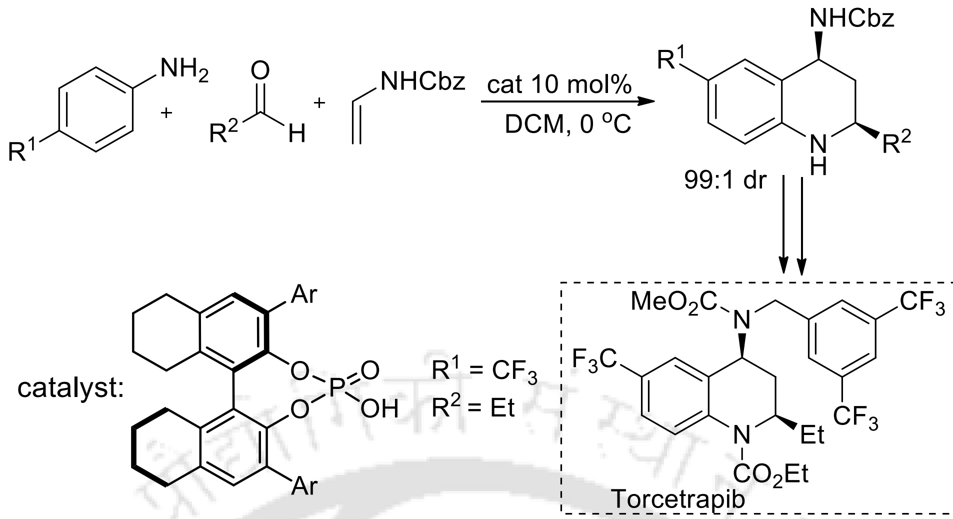
Scheme 10. Synthesis of phenantroviridin framework.

Ihara *et al*. used intramolecular imino Diels-Alder reaction to synthesize the alkaloid epi-lupinine that exhibit in *vitro* inhibitory activity against Leukaemia P-388 and lymphocytic eukaemia L1210 cells (Scheme 11).[54]



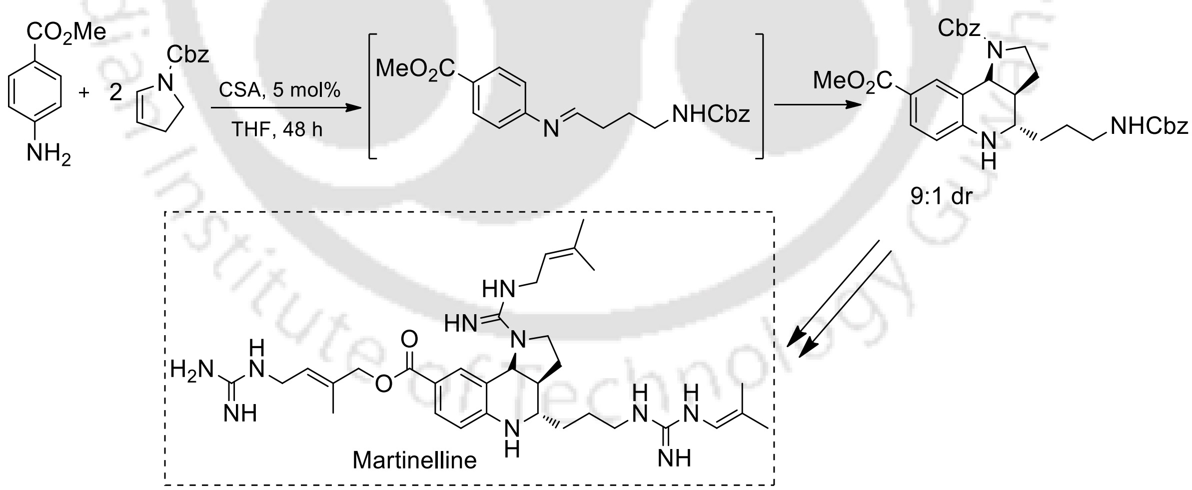
Scheme 11. Synthesis of alkaloid epi-lupinine.

Zhu and co-workers in 2009, reported the first example of three-component enantioselective Povarov reaction using enecarbamates as electron rich dienophiles leading to the rapid and efficient generation of a range of 4-amino-1,2,3,4-tetrahydroquinolines (Scheme 12). Chiral phosphoric acid was found to catalyze the three component Povarov reaction of aldehydes, anilines, and enecarbamates in high yields with excellent diastereoselectivity (>95%). It introduced for the first time, the aliphatic aldehydes in the enantioselective Povarov reaction.[55] The deprotection of *N*-Cbz of the product and *in situ* acylation of the resulting primary amine with methylchloroformate under hydrogenolysis conditions followed by benzylation of the secondary amide with 3,5-bis(trifluoromethyl)benzyl bromide afforded torcetrapibin four steps with 32% overall yield.



Scheme 12. Three-component enantioselective Povarov reaction.

The natural product martinelline is anantibiotic and G-protein coupled receptor. Batey and co-workers synthesized the tricyclic Core of this natural product by using three-component Povarov reaction using camphorsulfonic acid (CSA) as catalyst. The reaction produces *exo* cyclo-adduct as the major isomer bearing all the necessary functionalities for the successful completion of the synthesis of martinelline, which was successfully achieved in six simple additional steps (Scheme 13).[56]



Scheme 13. Synthesis of martinelline.

❒ I.5. Importance of 1,4-dihydropyridine

1,4-Dihydropyridines, an important class of nitrogen heterocycles are found in numerous pharmaceutical agents.[57] Various 1,4-dihydropyridine-based drug molecules are already marketed. The well-known examples is nifedipine (1970), an antihypertensive agent. These compounds reduce high blood pressure and severe chest pain by increasing the blood flow to the heart. Various calcium ion blocker dihydropyridines have been used, like amlodipine, by Pfizer is a superior long acting calcium channel blocker and has more desirable properties than nifedipine. Amlodipine shows less side effects and can be taken once daily

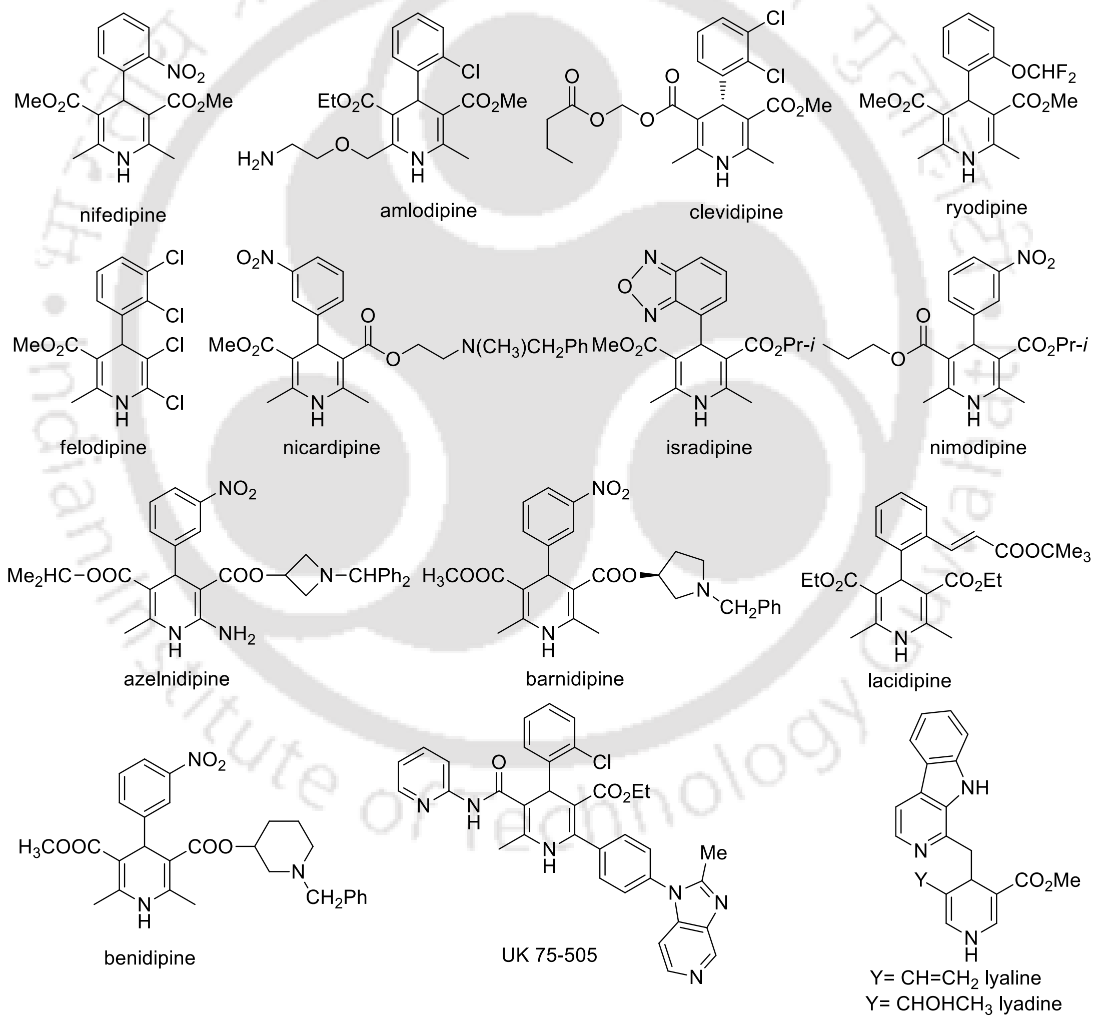
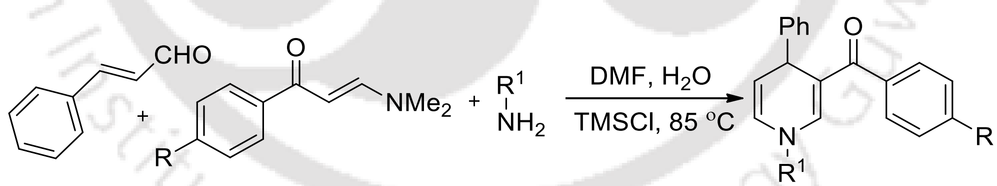


Figure 7. 1,4-Dihydropyridines in biological system and pharmaceutical.

as a tablet with no dietary restrictions. The trend to develop new ion channel blockers on the dihydropyridine scaffold continues even today with clevidipine, which obtained food and drug administration approval in 2008. In contrast, to the previous drugs clevidipine is a very short acting calcium channel blocker, which administered intravenously rather than orally. Today there are many popular drugs marketed such as felodipine, nicardipine, isradipine etc[58] where 1,4-dihydropyridine ring is present as basic scaffold shown in Figure 7. In addition, their versatile biological activities like as calcium channel blockers,[59] HIV protease inhibition,[60] inhibition of topoisomerase I,[61] MDR reversal,[62] neuroprotection,[63] radioprotection,[64] cocaine dependent regulation,[65] TGFβ signal inhibition,[66] anticonvulsant activity,[67] selective adenosine-A3 receptor antagonism,[68] etc. have also been reported. Moreover, 1,4-dihydropyridine skeleton also found in alkaloid lyaline, lyadine[69] and are also useful synthetic precursors for the preparation of piperidines and pyridines.[70,25] Therefore, it is not surprising that 1,4-dihydropyridines received daily increasing interests as synthetic targets (Figure 7).

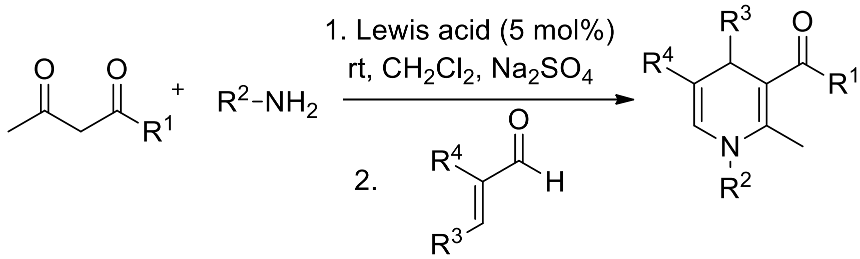
❒ I.6. Synthetic methods of 1,4 dihydropyridine using α,β-unsaturated aldehydes

Pan *et al.* utilized three-component sequential reaction of α,β-unsaturated aldehydes, amines and enaminones for the synthesis of 1,3,4-trisubstituted 1,4-dihydropyridines in aqueous DMF employing 1.0 equivalent TMSCl as the promoter. This method is also efficient for regioselective access of 1,2-dihydropyridines shown in Scheme 14.[71]



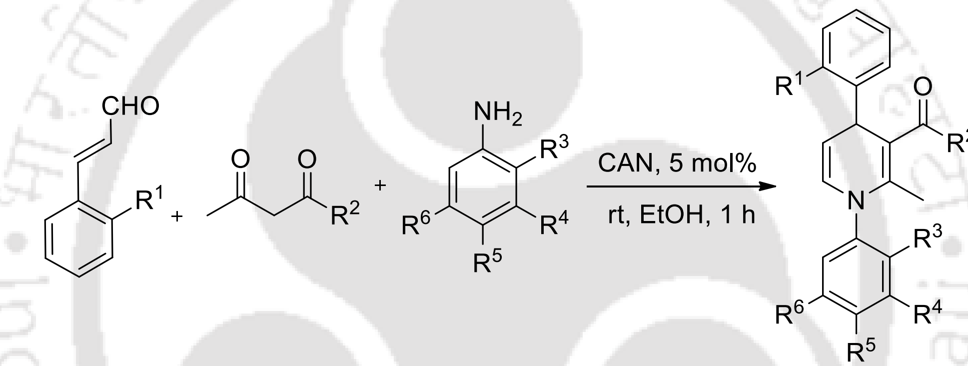
Scheme 14. Synthesis 1,4-dihydropyridines using enaminones.

Renaud *et al.* applied 5 mol% ferric chloride or scandium triflate are efficient Lewis acid catalysts for the transformation of β-enamino esters and β-enamino ketones with conjugated enals to functional 1,4-dihydropyridine derivatives. Subsequently, they also developed one-pot process of this methodology (Scheme 15).[72]



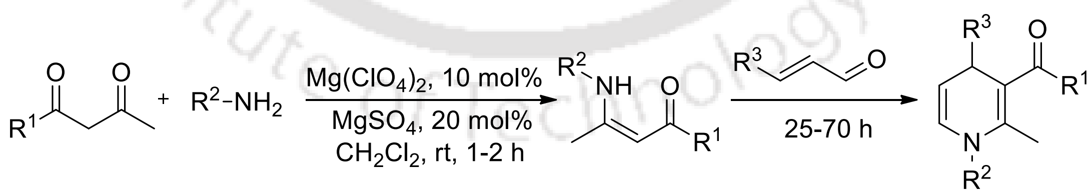
Scheme 15. Synthesis dihydropyridines by Lewis acids catalysts.

Menendez *et al.* used inexpensive cerium ammonium nitrate (CAN) as the catalyst for the three-component condensation reaction between aromatic amines, α,β-unsaturated aldehydes, and ethyl acetoacetate to produce 1,4-dihydropyridines (Scheme 16).[73]



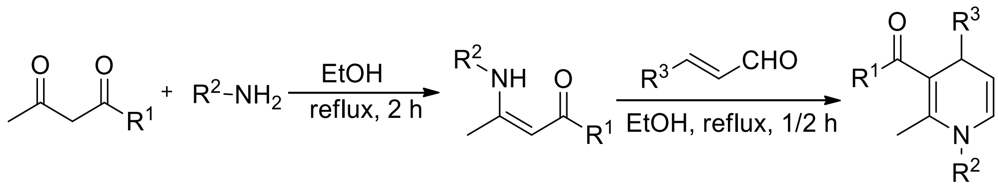
Scheme 16. Synthesis of 1,4-dihydropyridines *via* 3CR.

Sambri *et al.* have reported $MgClO_4$ as a Lewis acid catalyst to promote the synthesis of 1,2,3,4-tetrasubstituted 1,4-dihydropyridines by addition of enamino esters and ketones to enals. Sequential one-pot methodology was also accomplished (Scheme 17).[74]



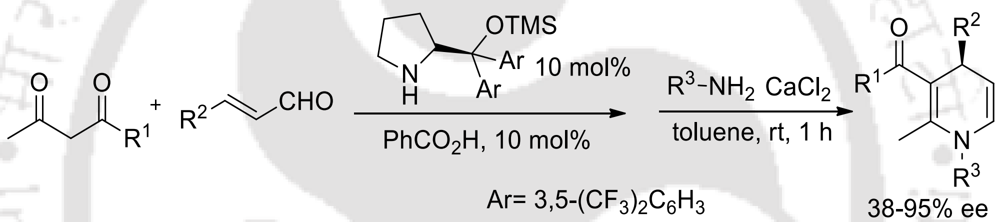
Scheme 17. Sequential one-pot synthesis of 1,4-dihydropyridines.

Catalyst free greener procedure for the synthesis of unsymmetrical 1,4 dihydropyridines was developed by Goswami, employing benzyl amines, β-keto esters to give the corresponding β-enamino esters that subsequently react with α,β-unsaturated aldehydes in ethanol under refluxing condition shown in Scheme 18.[75]



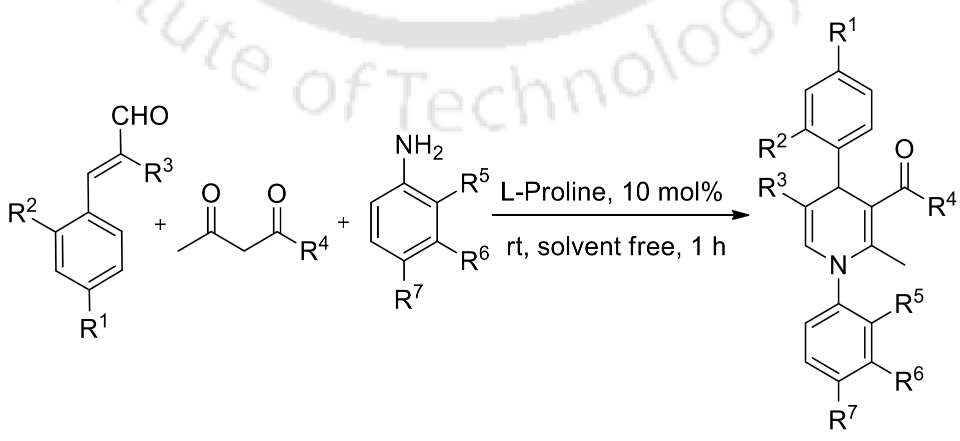
Scheme 18. Catalyst free synthesis 1,4 dihydropyridines.

Jørgensen *et al.* reported one-pot three component reaction of α,β-unsaturated aldehydes, β-diketones and primary amines for the synthesis of optically active substituted 1,4-dihydropyridinesin moderate yields with up to 95% enantioselectivity using 2-[bis(3,5-bis-trifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine as the catalyst (Scheme 19)[76]



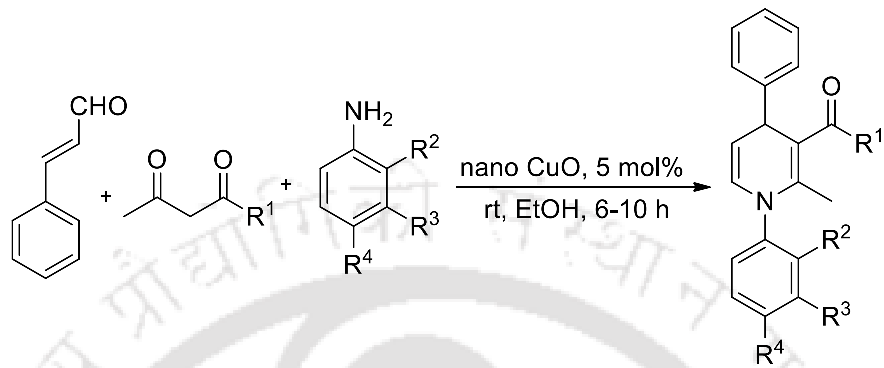
Scheme 19. Synthesis enantioselective 1,4-dihydropyridines.

Kumar *et al.* utilized organocatalyzed one-pot synthesis of 1,4-dihydropyridines using cinnamaldehyde, aniline and β-ketoesters under solvent free conditions. They studied different catalyst such as amino acids (acidic, basic and neutral), ephedrine and cinchona alkaloids, shown in Scheme 20.[77]



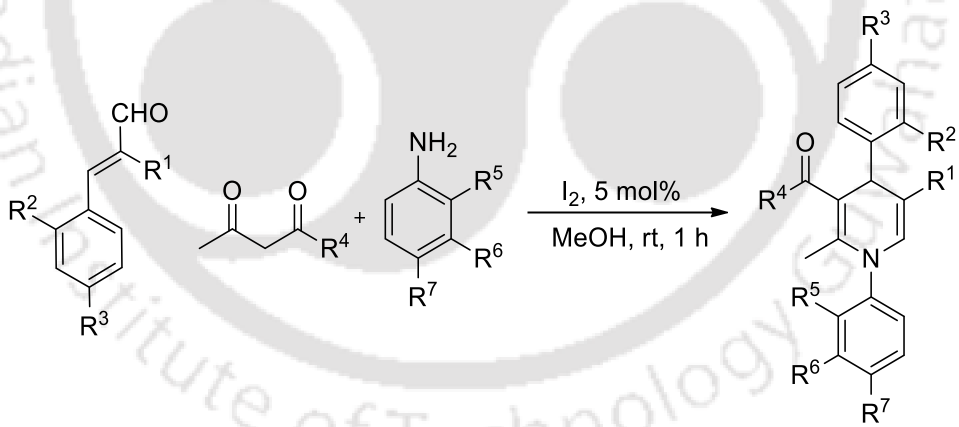
Scheme 20. Organocatalyzed one-pot synthesis of 1,4-dihydropyridines.

Kantam *et al.* reported recyclable nano-copper(II) oxide promoted the three-component coupling of cinnamaldehyde, β-ketoesters and aromatic amines to afford the 1,4-dihydropyridines in moderate to good yield (Scheme 21).[78]



Scheme 21. Synthesis 1,4-dihydropyridines *via* nano oxide catalyzed.

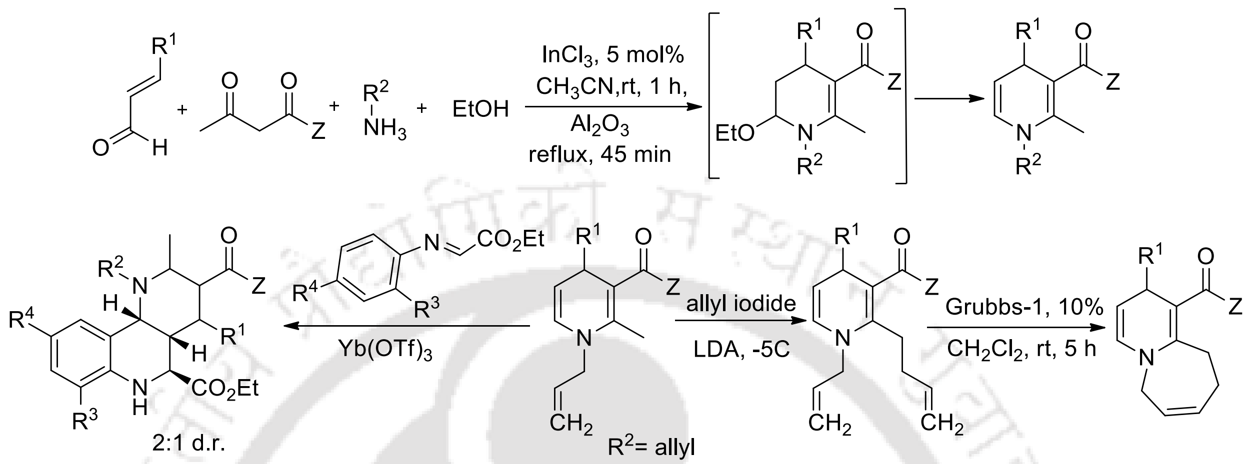
Kumar *et al.* synthesized a series of *N*-aryl-1,4-dihydropyridines using molecular iodine (5 mol%) in methanol at room temperature (Scheme 22). The synthesized compounds were screened for their antidyslipidemic and antioxidant activity. Some of these compounds exhibited potent antioxidant, promising lipid and triglyceride lowering activity.[79]



Scheme 22. Synthesis of 1,4-dihydropyridines by three-component reaction.

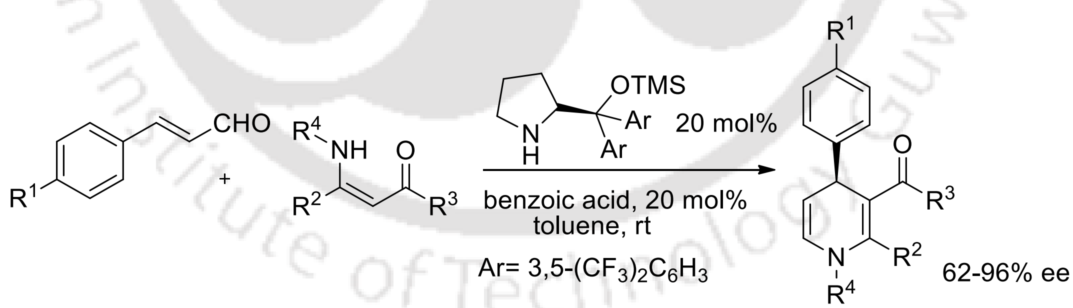
A sequential four-component reaction between α,β-unsaturated aldehydes, β-ketoesters, aliphatic amines and ethanol was demonstrated by Menendez *et al.* The reaction was catalyzed by 5 mol% indium trichloride to afford *in situ* 6-ethoxy-1,4,5,6-tetrahydropyridines, subsequently it was converted into 5,6-unsubstituted 1,4-dihydropyridines *via* ethanol elimination (Scheme 23).

The synthesized 1,4-dihydropyridines were applied as dienophiles in Povarov reactions for diastereoselective synthesis of hexahydrobenzo[*h*][1,6]-naphthyridine derivatives and homoquinolizine frameworks using ring-closing metathesis/elimination strategy.[80]



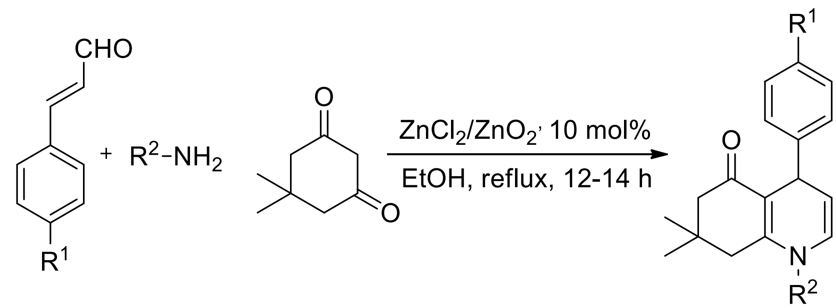
Scheme 23. Four component reaction for the synthesis of 1,4-dihydropyridines.

Kanger *et al*. developed a similar methodology as that of Jørgensen[76] for the synthesis of highly enantiomerically enriched 1,4-dihydropyridines *via* a diarylprolinol-TMS ether based catalytic aza-ene domino reaction. Both enaminones and β-enamino esters reacted with aliphatic and aromatic enals with good to excellent enantioselectivities shown in Scheme 24.[81]



Scheme 24. Enantioselective aza-ene reaction of 1,4-DHPs synthesis.

Zonouzi *et al.* reported 10 mol% $ZnCl_2$ and ZrO_2 catalyzed 1,4-dihydropyridines synthesis using cinnamaldehyde derivatives, dimedone and various amines at refluxed temperature (Scheme 25).[82]



Scheme 25. Synthesis 1,4-dihydropyridinesvia 3CR

❒ I.7. Importance of 1,6-naphthyridine

Among various *N*-heterocycles, naphthyridines occur widely among natural products and are known to exert significant biological activities such as anti-HIV-1, anticancer, antimicrobial and antifungal.[83] Marine sponges are proving to be the productive source of naphthyridine alkaloids.[84]

Nakamura *et al.* isolated alkaloid aaptamine, a marine natural product from the marine sponge *aaptos aaptos* found to possess antioxidative, antimicrobial, antifungal, antiretroviral and anticancer activities against the human germ cell, cancer cell lines NT2 and NT2-R.[85] Necatorone, a highly mutagenic pigment isolated from the fruit-bodies of the gilled toadstool Lactarius necator and its dimers, mainly responsible for the green appearance of the North American species Lactarius atroviridis. It exhibits moderate antibiotic activity against *bacillus subtilis* and *acetobactor calcoaceticus*.[86] The bronchodilator drug benafentrine, another alkaloid of this series, show an effective anti-inflammatory agent.[187] Lihouidine, a cytotoxic alkaloid pigment found in lihou reef in the coral sea[188] has naphthyridine as its core moiety. Some important naphthyridine moieties has been listed in Figure 8. Kobayashi *et al.* isolated three new heteroaromatic alkaloids, nakijinamines C-E, which are hybrid of the aaptamine and bromoindole alkaloids, possessing a taurine- or histidine-derived residue from an okinawan marine sponge suberites species. Both nakijinamines C and E showed antifungal activity against aspergillis niger.[89] Dimeric aaptamine alkaloids, suberitine A-D containing 1,6-naphthyridine rings, isolated from the marine sponge Aaptos suberitoides show potent cytotoxicity against P388 cell lines.[190]

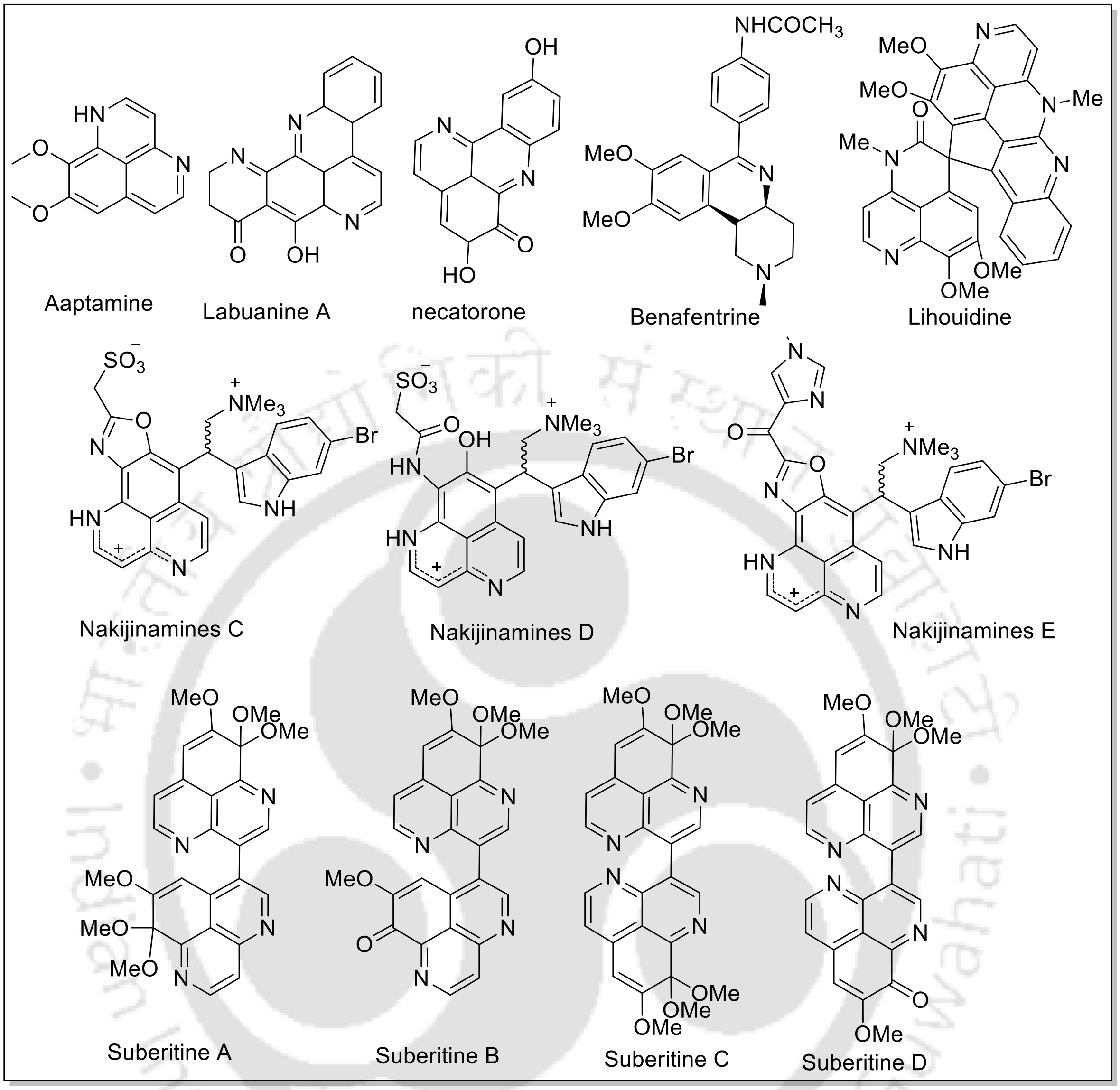


Figure 8. Naturally occurring naphthyridines.

Synthetic 1,6-naphthyridines derivatives have attractive pharmaceutical profile. L-870,810 are promising class of antiretroviral drugs developed by Merck Laboratories, with good pharmacokinetic properties, inhibitor HIV-1 integrase with potent antiviral activity in cell culture.[91] L-870,810 analog 1,6-naphthyridine-7-carboxamides with various substitutions at the 5- and 8-positions are potent HIV-1 integrase inhibitors with significantly cytotoxic activity and show effective inhibition against select oncogenic kinases (Figure 9).[92]

The new phase in the HIV-1IN inhibitors development came from the naphthyridine derivatives (L-870,812), another naphthyridine based drug that suppresses retroviral replication, *in vivo*.[93] L-900564 another series of this family has excellent cell potency and shows very good pharmacokinetic profile that inhibit HIV-1 integrase.[94] Naphthyridine moieties with side chain substitution at the three position of the central phenyl ring by

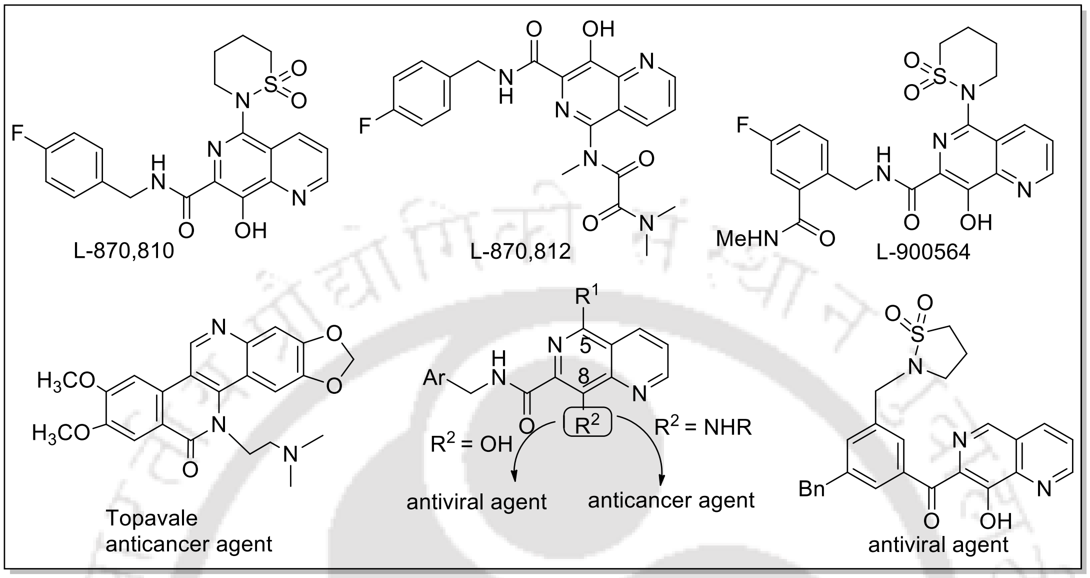
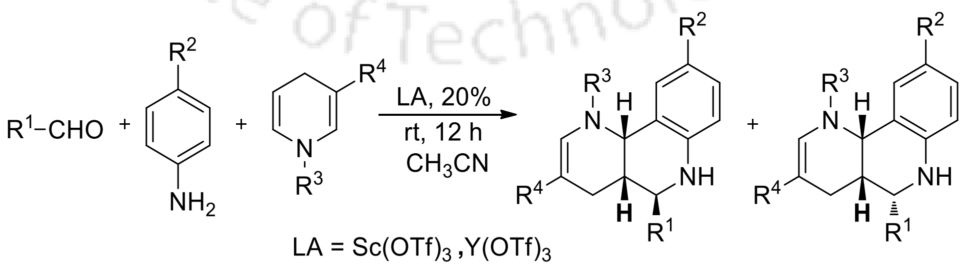


Figure 9. Important naphthyridines in pharmaceutical.

isothiazolidine 1,1-dioxide are potent pharmacokinetic.[95] Similarly 5H-8,9-dimethoxy-5-(2-*N*,*N*-dimethylaminoethyl)-2,3-methylenedioxydibenzo[*c*,*h*]1,6-naphthyridin-6-one,exhibit potent antitumor activity.[96]

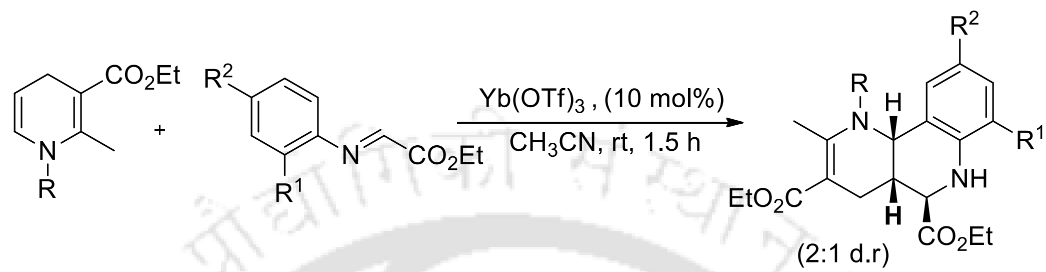
❒ I.8. Synthetic methods of 1,6-naphthyridine

Lavilla *et al.* reported Lewis acid catalyzed condensation reaction between aldehyde, aniline and *N*-alkyl-1,4 dihydropyridine as an electron rich dienophile in a formal [4+2] aza Diels-Alder reactions to afford benzonaphthyridine (Scheme 26).[97]



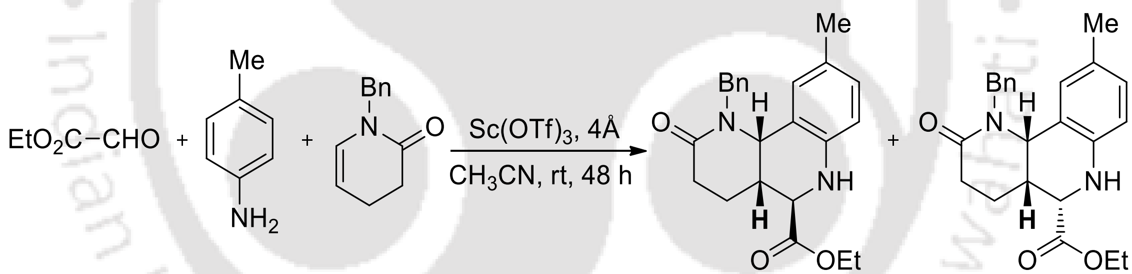
Scheme 26. Synthesis of benzonaphthyridines using aza Diels-Alder.

Menendez *et al.* developed $Yb(OTf)_3$-catalyzed Povarov reactions of 1,4-dihydropyridines as the dienophile component and imines as diene for diastereoselective synthesis of diasteroselective hexahydrobenzo[*h*][1,6]-naphthyridine derivatives containing three adjacent stereocenters as depicted in Scheme 27.[98]



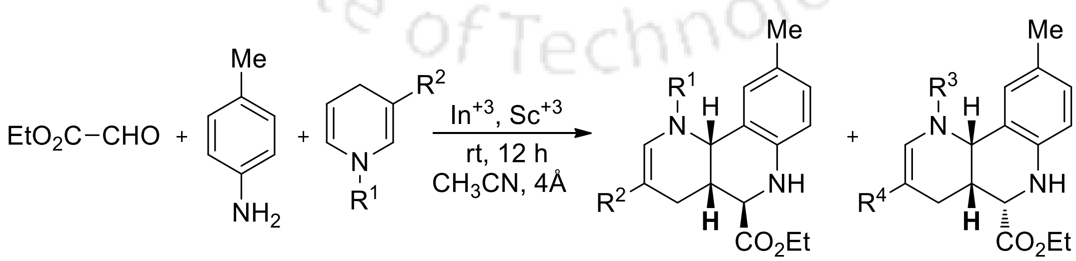
Scheme 27. Diastereoselective synthesis of hexahydrobenzo[*h*][1,6]-naphthyridines.

Lavilla's group exploited unsaturated lactam as dienophile with *p*-toluidine and ethyl glyoxalatein Povarov reaction under $Sc(OTf)_3$ catalysis in the presence of 4Å molecular sieves in acetonitrile at room temperature which afforded tetrahydroquinolines isomer in 4:3 ratio with 43% overall yield (Scheme 28).[99]



Scheme 28. Lactam as dienophile in 3CR Povarov reaction.

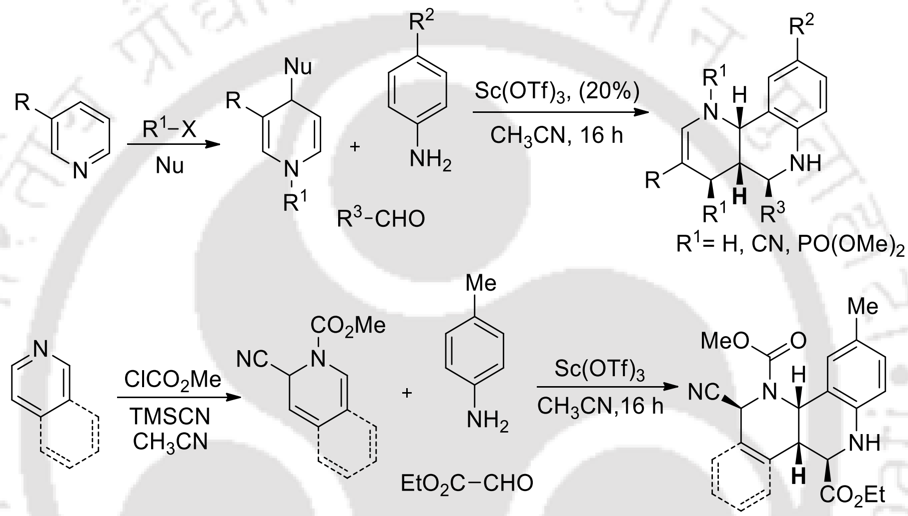
They also developed three component reaction of an *N*-alkyl-1,4-dihydropyridine with ethyl glyoxalate and aniline catalyzed by $InCl_3/Sc(OTf)_3$ in dry CH_3CN using 4Å molecular



Scheme 29. Synthesis of benzonaphthyridines catalyzed by Lewis acid.

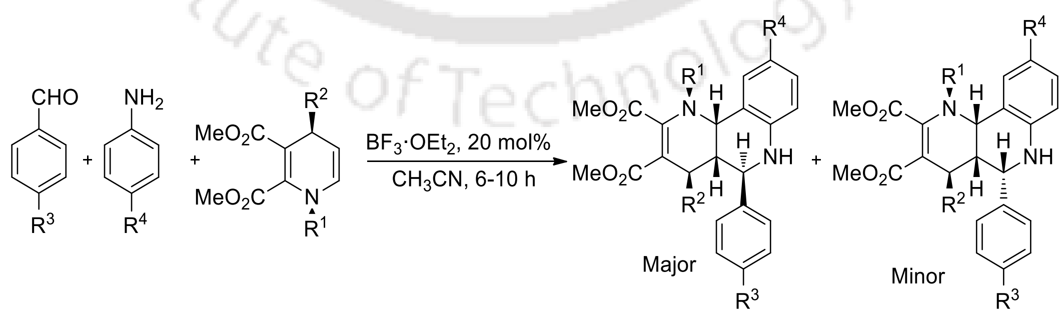
sieves which yielded 2:1 mixture of the desired benzonaphthyridinesin in 65% overall yield (Scheme 29).[100]

Further, Lavilla *et al.* extended this methodology by the use of *in situ* generated reactive 1,4-dihydropyridine *via* nucleophilic attack on pyridinium salts. The resultant intermediate undergoes Povarov reaction with aniline and aldehyde. The procedure is also an alternative way to produce substituted DHPs *via* the reaction of pyridine and isoquinoline with methyl chloroformate and TMSCN in CH_3CN. The *in situ* generated α-cyano-1,2-dihydroazines were engaged in Sc(III) catalyzed [4+2] cycloadditions with imine (Scheme 30).[101]



Scheme 30. Povarov 3CR reaction pyridinium salts as dienophile.

Khan *et al.* demonstrated $BF_3{\cdot}OEt_2$ catalyzed three component Povarov reaction of benzaldehyde, aniline and 1,4-dihydropyridine in acetonitrile for the synthesis of substituted naphthyridine derivatives (Scheme 31).[102]



Scheme 31. Synthesis of naphthyridines using $BF_3{\cdot}OEt_2$catalyst.

I.9. Importance of pyridine

Pyridines are the most prevalent heterocyclic structural units since its discovery 166 years ago. However, scientists become attracted to this moiety because of their biological properties. It plays significant role in biological activity of natural substances such as vitamin B6, nicotine, or oxido-reductive NADP–NADPH coenzymes (Figure 10). Pyridine-containing complex natural products also exist in the sesquiterpene, alkaloid, and polypeptide families.[103]

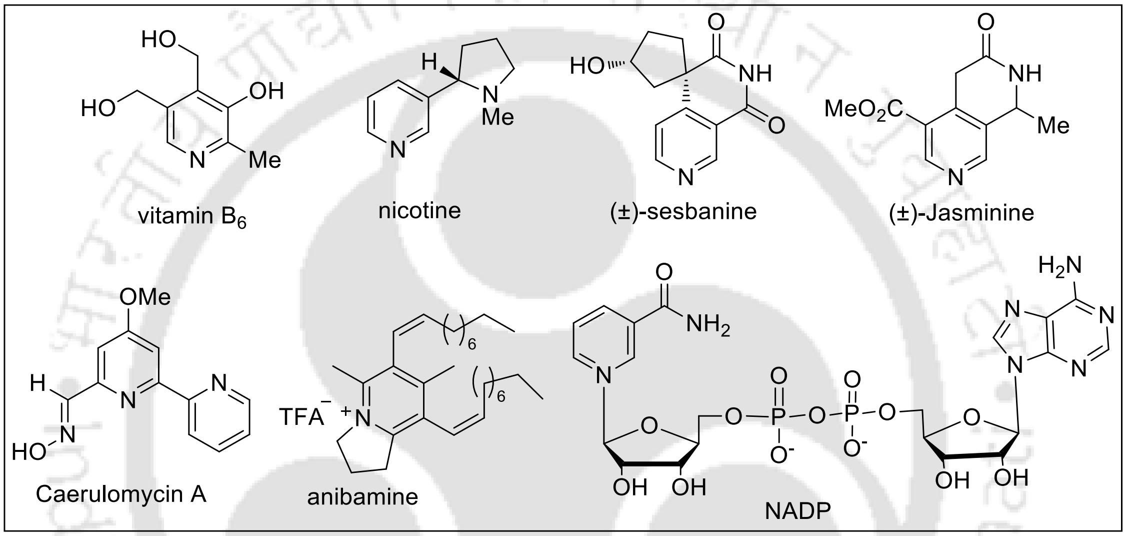


Figure 10. Natural products contains pyridine moieties.

Numerous other pyridines have been synthesized which are bioactive and shows interesting properties like antibacterial,[104] anti-inflammatory,[105] antidiabetic,[106] antiviral,[107] antiasthmatic,[108] antidepressant,[109] inhibiting acetylcholinesterase.[110] These are also used in the treatment of hypertension,[111] inhibiting HIV protease[112] and preventing apoptosis.[113] Thus, this core nucleus a major scaffold for the creation of antitumor or antiviral drugs (Figure 11). Some of these compounds are already marketed as drugs for the treatment of allergies (loratadine), ulcers (lansoprazole), depression (mirtazapine), lung cancer (crizotinib), diabetes (pigolitazone), and insomnia (eszopiclone).[114]

Pyridine-based compounds have been playing a crucial role in agrochemicals as pesticides including fungicides, insecticides and herbicides.[115] According Phillips-McDougall report,[116]

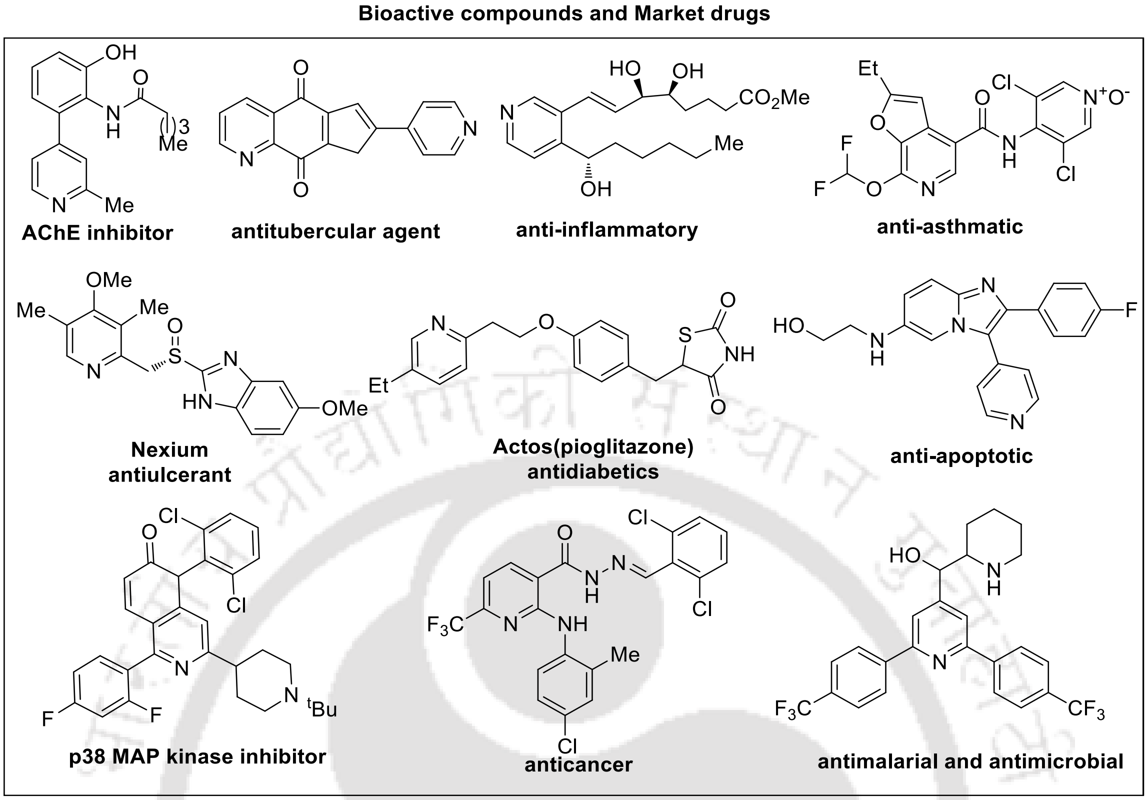


Figure 11. Pharmaceutically important pyridines.

top 45 products in 2013 with total sales of \$5 billion US accounting for nearly 10% of the world-wide agrochemical market where three pyridine-based products chlorantraniliprole, imidacloprid and paraquat with sales of \$1240, \$1070 and \$905 million respectively. The advantages of pyridine-based compounds in agrochemical, compared to their benzenoid counterparts, are higher bioactivity, lower toxicity, advanced systemic and excellent selectivity.[117] Some important pyridine derivatives those popularly used in agrochemicals are shown in Figure 12.

Pyridine based compounds popularly used in coordination chemistry as monopyridines,[118] bipyridines,[119] or terpyridines[120] for chelate metallic ions as *N*-donor ligands, affording efficient organometallic catalysts.[121] Pyridines are also encountered in materials science,[122]

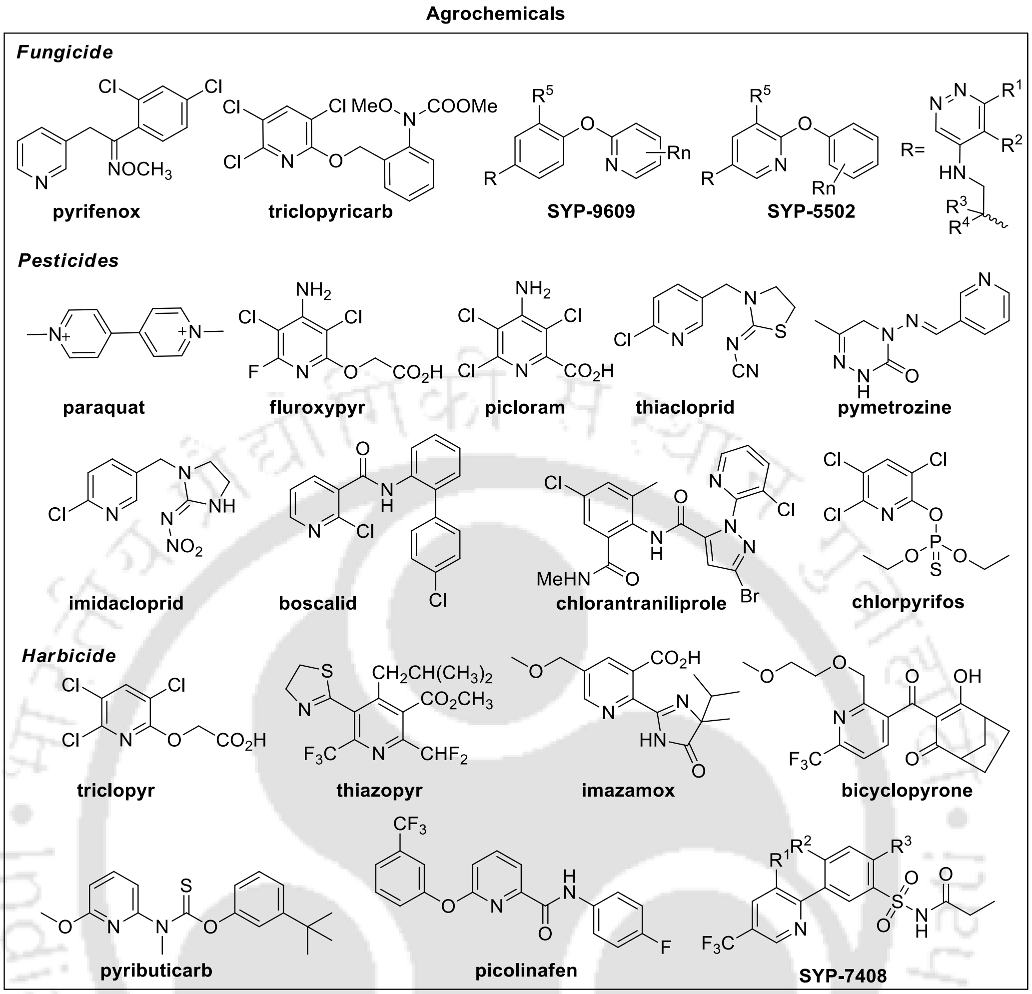


Figure 12. Pyridines used in agrochemical.

supramolecular structures,[123] polymers,[124] and in organocatalysis, as illustrated by the numerous applications of DMAP and its derivatives (Figure 13).[125]

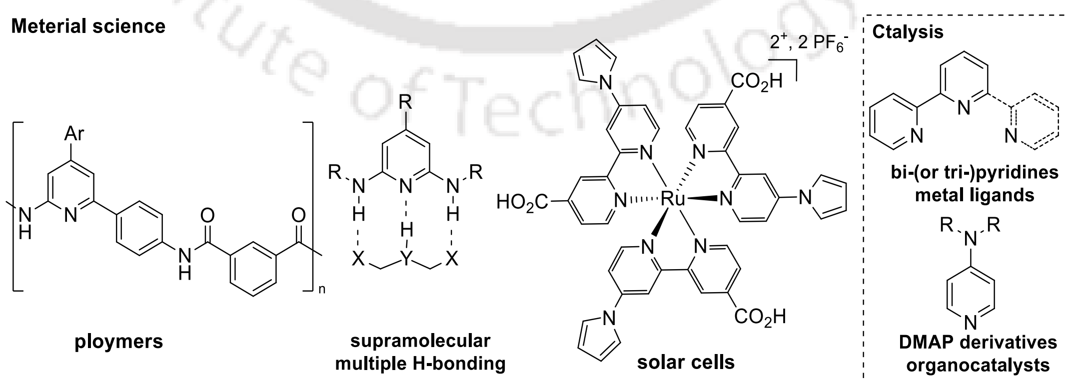
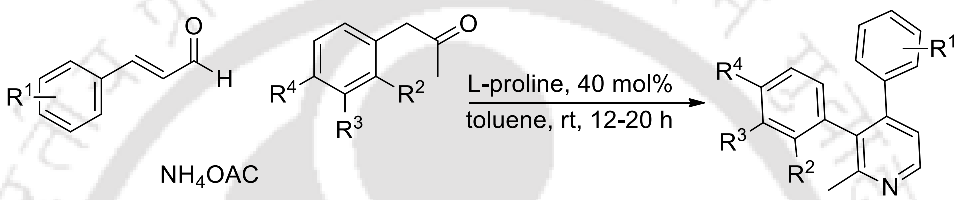


Figure 13. Pyridine in material science.

❐ I.10. Synthetic methods of pyridine using α,β-unsaturated carbonyl compounds

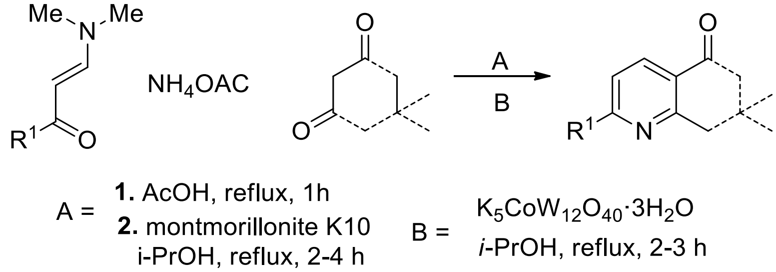
Lee *et al*. reported a novel organocatalyzed three-component reaction for the synthesis of 2,3,4-trisubstituted pyridines. Variety of pyridine derivatives have been synthesized from readily available 1,3-diphenylpropan-2-one, α,β-unsaturated aldehydes and ammonium acetate in the presence of 40 mol% L-proline in toluene at room temperature (Scheme 32). The synthesized compounds were also used for the evaluation of antibacterial activities and fluorescence sensors for Cu^{2+} ions.[126]



Scheme 32. Synthesis of pyridine derivative catalyzed by L-proline.

Numerous Michael-addition reactions have been described based on 1,3-dicarbonyl derivative, ammonia source, and Michael acceptor bearing dimethylamino substituent on position three to access pyridine derivatives. This substituent played the role of a leaving group and facilitated the final aromatization step. Pioneer works on this strategy by Al-Saleh *et al*. were reported in 2002. In this methodology acetylacetone reacts with ammonium acetate and enaminoketone in refluxing acetic acid to produce pyridine derivatives (Scheme 33, A, condition **1**).[127a] Later, they also shown that montmorillonite K10 was an efficient catalyst in 2-propanol solvent (Scheme 33, A condition **2**).[127b]

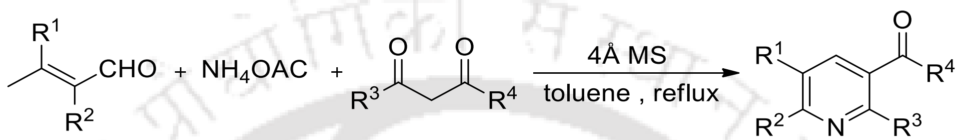
Kantevari's group has extended this methodology with cyclic or acyclic 1,3-dicarbonyl compounds (Scheme 43, B) using potassium dodecatungstocobaltatetrihydrate



Scheme 33. Initial Studies of pyridines synthesis from enaminoketones.

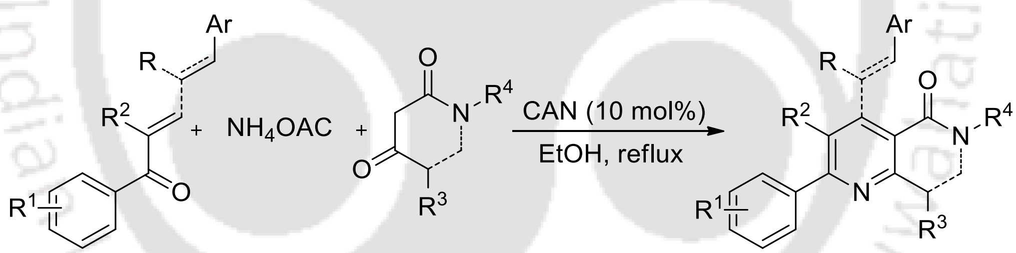
($K_5CoW_{12}O_{40}\cdot 3H_2O$)[128a,b] and heptahydrate cerium trichloride/sodium iodide system ($CeCl_3$, $7H_2O$/ NaI, 20 mol%) as the catalyst.[128c]

Rodriguez *et al*. reported metal-free, three-component reaction for the selective access to pyridines from readily available substrates. They used 4Å molecular sieves promoted Michael addition between a 1,3-dicarbonyl, α,β-unsaturated aldehydes and a synthetic equivalent of ammonia (Scheme 34).[129]



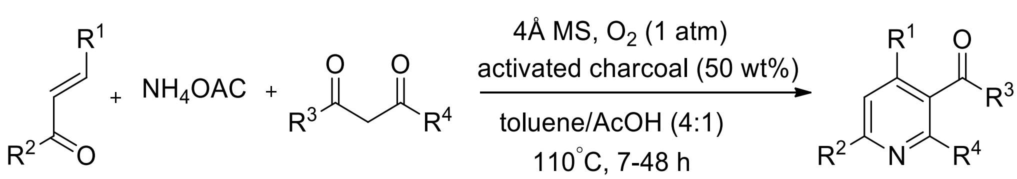
Scheme 34. Michael-initiated synthesis of polysubstituted pyridines.

Tenti *et al*. has described regioselective access to functionalized nicotinamide derivatives catalyzed by CAN. They used an ethanol solution of chalcone, β-ketoamide, and ammonium acetate with 10 mol% of the catalytic to provide nicotinamide derivatives with synthetically useful yield (Scheme 35).[130]



Scheme 35. Nicotinamide derivatives synthesis using multicomponent reaction.

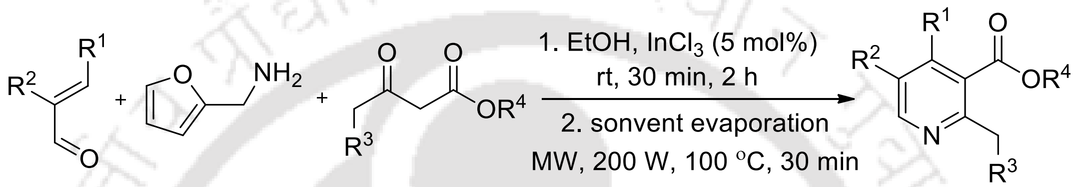
Rodriguez and his groups explored β,γ-unsaturated-α-ketocarbony under optimized dual heterogeneous oxidative process to access 4-substituted pyridines (Scheme 36)[131] with functional diversity at the 2-position in good to excellent yields. They also applied the methodology for the synthesis of 2-phosphorylated pyridines.[132]



Scheme 36. Synthesis of functionalized pyridines *via* MCR.

Menendez *et al*. adapted sequential multicomponent reaction between 2-furfurylamine, β-dicarbonyl compounds and α,β-unsaturated aldehydes in ethanol using $InCl_3$ as the catalyst. Without isolation, the product (tetrahydropyridine) was irradiated in microwave (200 W, 100 ºC) in solvent-free conditions to afford the desired highly substituted pyridine in good to excellent yields with the loss of a 2-furylmethyl side chain (Scheme 37).

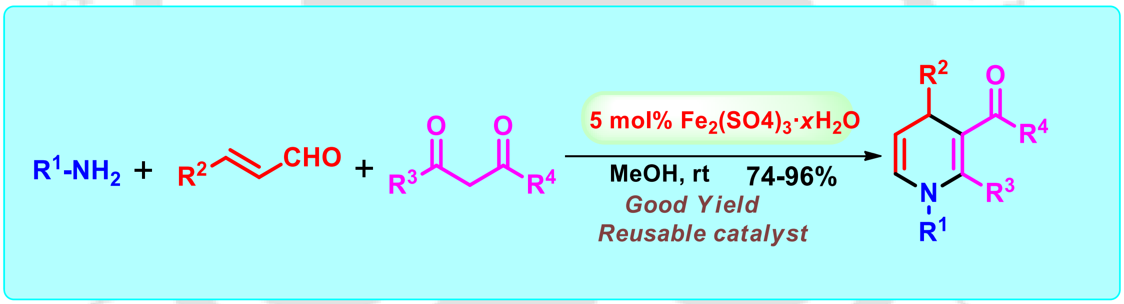
The method was also well applicable for the synthesis of quinolones, isoquinolines, phenanthridines and more complex fused pyridine systems.[133]



Scheme 37. Sequential MCR for synthesis pyridines catalyzed by $InCl_3$.

Chapter II

Hydrated ferric sulfate catalyzed synthesis of 5,6-unsubstituted 1,4-dihydropyridines using three-component reaction

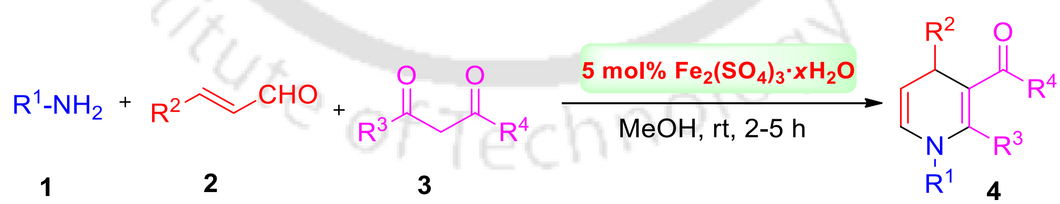


CHAPTER II

II. Hydrated ferric sulfate catalyzed synthesis of 5,6-unsubstituted 1,4-dihydropyridines using three-component reaction

Results and Discussion

Under the above mentioned section in the chapter I, we have discussed a brief literature survey of 1,4 dihydropyridine, their importance and traditional methods used for their synthesis. Some of the methods are associated with certain limitations such as use of excess[134,102] and expensive catalyst,[134] low yields,[88] requirement of multistep sequences[135] and harsh reaction conditions.[136] Consequently, there is still need to find out reusable catalyst, which provides better yields at room temperature. Recently, ferric sulfate [$Fe_2(SO_4)_3{\cdot}xH_2O$] has received considerable attention as a mild, inexpensive, and reusable catalyst for various organic transformations.[137] The unique solubility of the catalyst in acetonitrile/methanol and insolubility in DCM enables to use it as both homogenous and heterogeneous system. Moreover, it can also be easily recovered at the end of reaction by adding DCM. Due to its wide applicability as a catalyst, it was presumed that it would be an efficient catalyst for the one-pot three-component reaction for the synthesis of the 5,6-unsubstituted 1,4-dihydropyridine derivatives. In this chapter demonstration of one-pot synthesis of 5,6-unsubstituted 1,4-dihydropyridines from amines, *α,β*-unsaturated aldehydes and acyclic 1,3-carbonyl compounds has been shown (Scheme 38).

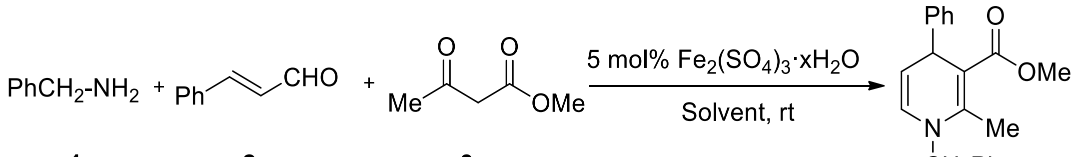


Scheme 38. One-pot synthesis of 5,6-unsubstituted 1,4-dihydropyridine derivatives.

At the beginning of our study, the mixture of benzylamine (**1a**), cinnamaldehyde (**2a**), and methyl acetoacetate (**3a**) was stirred at molar (1 equiv.) ratio in presence of 5 mol% of $Fe_2(SO_4)_3{\cdot}xH_2O$ in methanol (3 mL) for 2 h at room temperature. The product 5,6-unsubstituted 1,4-dihydropyridines (**4a**) was isolated in 92% yield after chromatographic purification (entry 1, Table 1). After spectroscopic analysis, it was found that the product was 5,6-unsubstituted 1,4-dihydropyridine derivative. The ^{1}H NMR spectrum of **4a** showed doublet at δ = 5.96 and doublet of doublet at (dd) δ = 5.0 that indicates double bond C-H proton of the unsubstituted dihydropyridine skeleton. A multiple of three protons appeared at δ = 4.68-4.55 ppm is attributed to the -CHPh and $PhCH_2$ proton of the dihydropyridine ring. The values at δ = 3.53 ppm and 2.42 ppm indicates the presence of methoxy and methyl groups in the compound **4a**. In ^{13}C NMR and IR spectra, the peaks at δ = 169.4 ppm and 1685 cm^{-1} is due to the carbonyl group. Other four peaks in ^{13}C NMR at the region from δ = 53.67, 50.64, 40.06 and 16.01 ppm is due to OMe, NCH_2Ph, CHPh and Me for the carbon atoms attached to the 5,6-unsubstituted 1,4-dihydropyridine rings. Finally peak at 320.1652 (M + H^+) in HRMS spectrum indicates that 5,6-unsubstituted 1,4-dihydropyridine skeleton was formed. Inspiried by this, same set of reactions were also carried out using 10 and 15 mol% of $Fe_2(SO_4)_3{\cdot}xH_2O$ in methanol under identical reaction condition that gives the desired product **4a** (entries 2 and 3, Table 1) in 89%, and 82% yields, respectively.

From these observations, it is clear that the yield of the product **4a** reduces slowly with increasing the amount of catalyst from 5% to 15%. To find out a suitable solvent system, similar reactions were conducted in ethanol, *i*-propanol, *n*-BuOH, DCM, acetonitrile, 1,4-dioxane, THF, DMF and DMSO under identical reaction conditions (entries 4–12, Table 1). The best yield was obtained in methanol using 5 mol% catalyst with the shortest reaction time, which are summarized in Table 1. It was also observed that no desired product was obtained in absence of catalyst even after 12 h of stirring at room temperature and only the starting substrates were recovered (entry 13, Table 1). After optimizing the reaction condition, various amines such as 4-methylbenzylamine (**1b**), methoxybenzylamine (**1c**) and *α*-methylbenzylamine (**1d**) were examined with cinnamaldehyde (**2a**) and methyl acetoacetate (**3a**) under identical reaction conditions and the desired products (**4b-d**) were isolated in good yields (entries 2-4, Table 2). Similarly, a wide variety of aliphatic amines such as *n*-butylamine (**1e**), *sec*-butylamine (**1f**), *n*-heptylamine (**1g**), 1-hexadecylamine (**1h**) and cyclohexylamine (**1i**) were also scrutinized with cinnamaldehyde (**2a**) and methyl acetoacetate (**3a**) under similar reaction conditions and the desired 5,6-unsubstituted 1,4-dihydropyridines (**4e-i**) were obtained in excellent yields (entries 5-9, Table 2).

Table 1. Effect of solvent and catalyst loading on the synthesis of 5,6-unsubstituted 1,4 dihydropyridine (**4a**)[a,b]



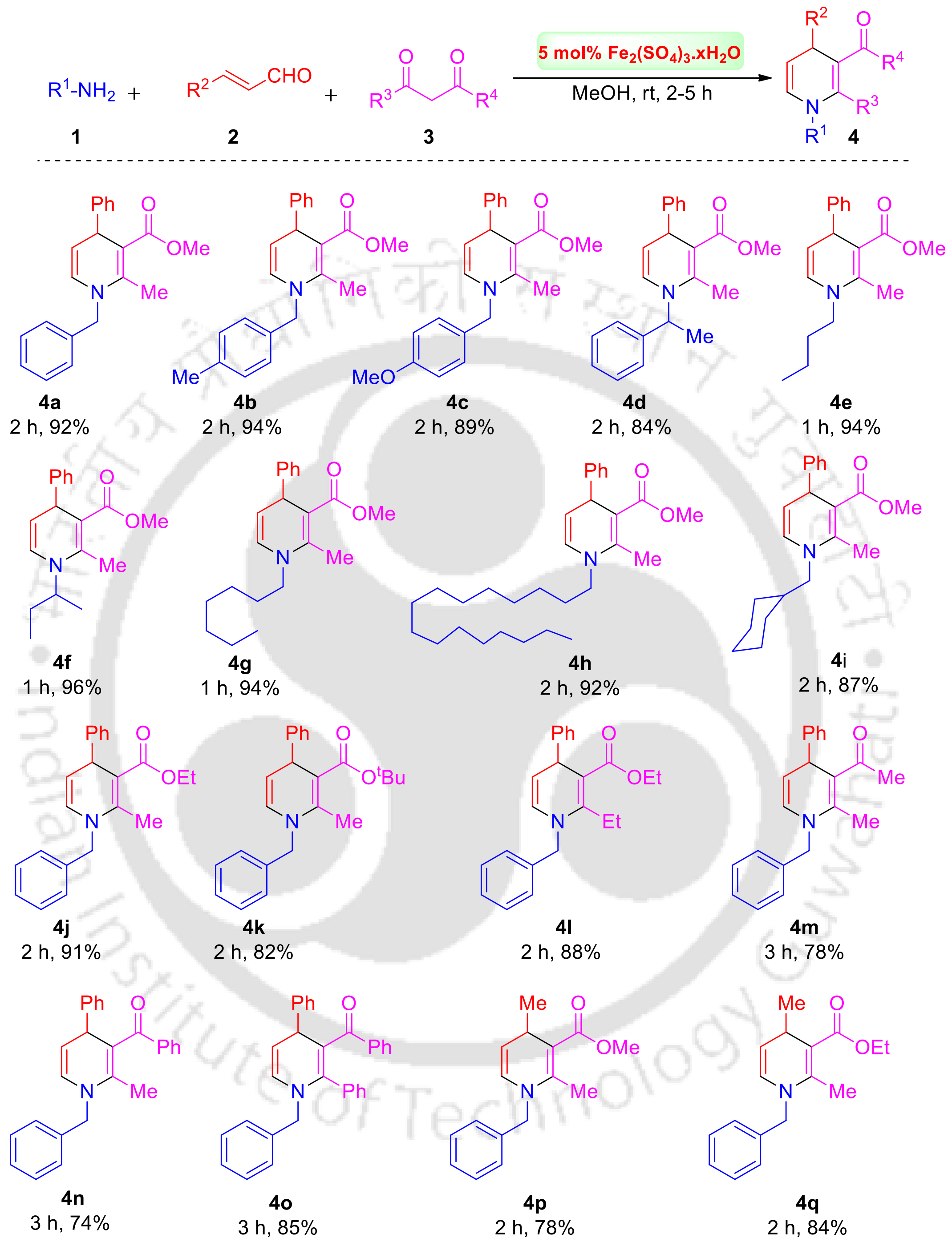
1 **2** **3** **4**

Entry	Catalyst (mol%)	Solvent	Time	Yield[b]%
1	**5**	**MeOH**	**2**	**92**
2	10	MeOH	2	89
3	15	MeOH	2	82
4	5	EtOH	2	87
5	5	Isopropanol	3	68
6	5	*n*-BuOH	3	61
7	5	DCM	6	56
8	5	CH_3CN	6	41
9	5	1,4-Dioxane	6	28
10	5	THF	6	trace
11	5	DMF	6	42
12	5	DMSO	6	45
13	None	MeOH	12	-

[a]All the reactions were performed with benzylamine (1.0 mmol), cinnamaldehyde (1.0 mmol), and methyl acetoacetate (1.0 mmol) in the presence of $Fe_2(SO_4)_3 \cdot xH_2O$ as catalyst in 3 mL of indicated solvent at room temperature. [b]Isolated yields.

Likewise, numerous *β*-keto esters such as ethyl acetoacetate (**3b**), *tert*-butyl acetoacetate

Table 2. Scope and yields of various 5,6-unsubstituted 1,4-Dihydropyridines[a,b]



[a]The reactions were carried out with amines (1.0 mmol), *α,β*-unsaturated aldehydes (1.0 mmol), and 1,3-carbonyl compound (1.0 mmol) in the presence of 5 mol% of $Fe_2(SO_4)_3 \cdot xH_2O$ in 3 mL of MeOH at room temperature. [b]Isolated yields.

(**3c**) and ethyl butyrylacetate (**3d**) on reaction with benzyl amine (**1a**) and cinnamaldehyde (**2a**) provided desired 5,6-unsubstituted 1,4-dihydropyridines (**4j-4l)** in good to excellent yields under identical reaction condition (entries 10-12, Table 2). Furthermore, various acyclic 1,3-diketones such as acetylacetone (**3e**), benzoylacetone (**3f**) and dibenzoylmethane (**3g**) on reaction with benzylamine (**1a**), cinnamaldehyde (**2a**) afforded the desired dihydropyridines (**4m-4o**) in good yields (entries 13–15, Table 2). When the similar reactions were examined with cyclic 1,3-diketone such as 1,3-cyclohexanedione and dimedone, cinnamaldehyde and benzylamine, it gave complicated reaction mixture and no desired products were isolated. It is worth while to mention that *β*-keto esters react faster as compared to acyclic 1,3-diketones in the present reaction.

To expand the scope of the present protocol, reactions were carried out with other *α,β*-unsaturated aldehyde such as crotonaldehyde (**2b**) with benzylamine (**1a**) and methyl acetoacetate/ethyl acetoacetate (**3a/b**) under similar reaction conditions and the desired dihydropyridines (**4p-4q**) were obtained in good yields (entries 16 and 17, Table 2). Unfortunately, the reaction with aromatic amine such as aniline gave non-separable complex reaction mixture under identical reaction condition.

Finally, the structure of one of the representative compounds such as **4a** was confirmed unambiguously by single crystal X-ray diffraction analysis (Figure 14).

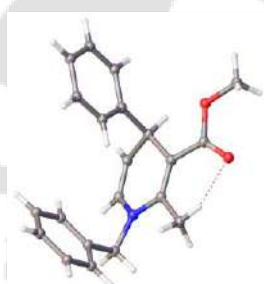
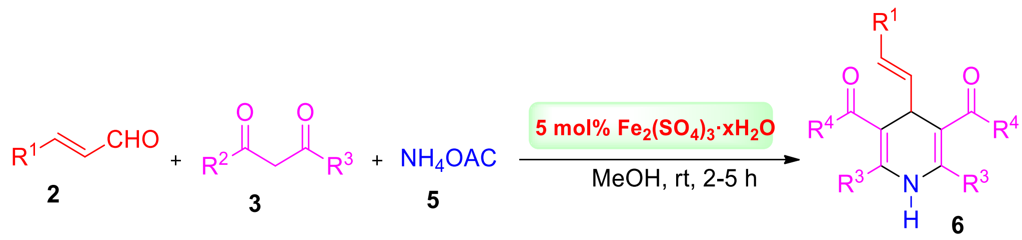


Figure 14. Single crystal X-ray structure of compound **4a**.

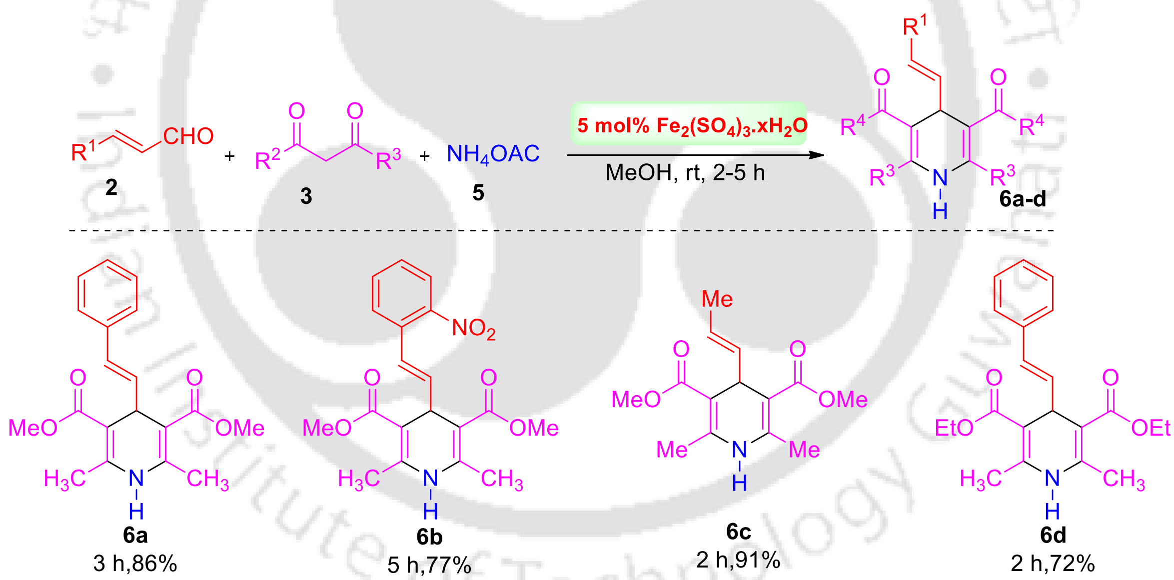
It is noteworthy to mention that when ammonium acetate (**5**) was used as an amine source instead of above mention amines, the reaction followed Hantzsch symmetric four components (4CR) dihydropyridine pathway under similar reaction condition (Scheme 39).



Scheme 39. Synthesis of Hantzsch symmetric 1,4-dihydropyridines derivatives.

To get Hantzsch symmetric highly substituted1,4-dihydropyridines **6** several reactions were performed such as cinnamaldehyde (**2a**), crotonaldehyde (**2b**), 2-nitrocinnamaldehyde (**2c**) with methyl acetoacetate/ethyl acetoacetate(**3a/b**) and ammonium acetate under indentical reaction condition and the desired dihydropyridines (**6a-d**) were obtained in good yields (entries 1-4, Table 3).

Table 3. Scope and yields of various Hantzsch symmetric 1,4-Dihydropyridines[a,b]



[a]The reactions were carried out with *α,β*-unsaturated aldehydes (1.0 mmol), ammonium acetate (1.0 mmol), and 1,3-carbonyl compound (1.0 mmol) in the presence of 5 mol% of $Fe_2(SO_4)_3\cdot xH_2O$ in 3 mL of MeOH at room temperature. [b]Isolated yields.

Finally, the structure of one of the representative compounds such as **6a** was confirmed unambiguously by single crystal X-ray diffraction analysis (Figure 15).

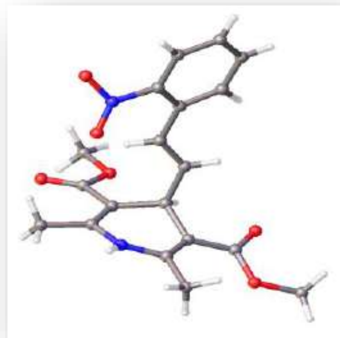
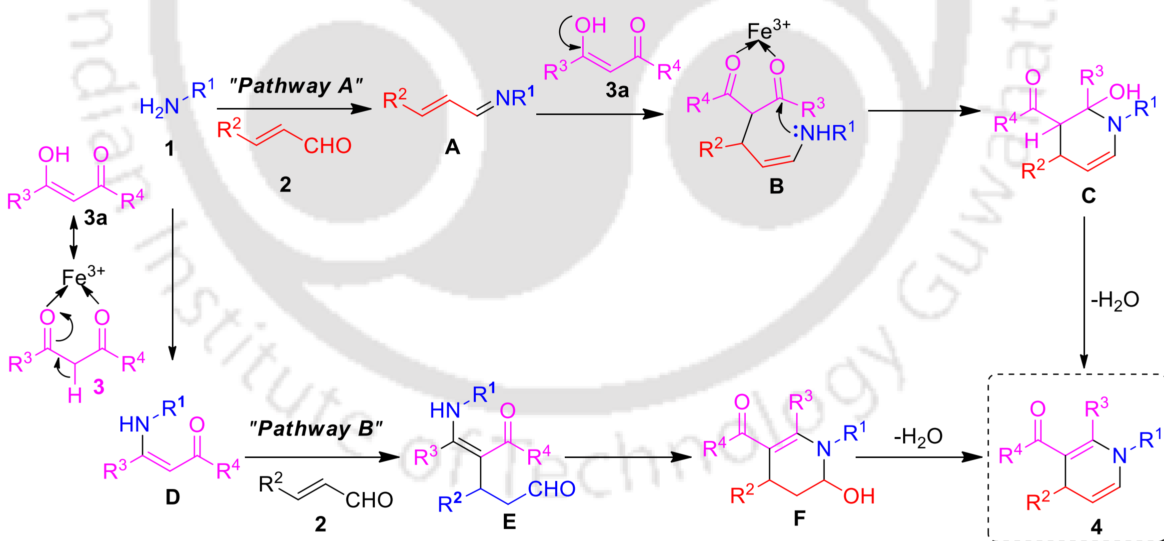


Figure 15. Single crystal X-ray structure of compound **6a**.

On the basis of the reported literature,[75,76] a plausible mechanism for the formation of substituted 5,6-unsubstituted 1,4-dihydropyridines (**4**) is depicted in Scheme 40. There are two possible mechanistic pathways. In Pathway A, a condensation reaction between amine (**1**) and *α,β*-unsaturated aldehydes (**2**) gives *α,β*-unsaturated imine intermediate **A** in the presence of catalyst $Fe_2(SO_4)_3{\cdot}xH_2O$. Then the enolized form of 1,3-diketone (**3**) reacts with *α,β*-unsaturated imine intermediate **A** to provide intermediate **B**, which undergoes



Scheme 40. Plausible mechanism for the formation of 5,6-unsubstituted 1,4-dihydropyridines (**4**)

cyclization followed by dehydration to give the desired 5,6-unsubstituted 1,4-dihydropyridine (**4**). In Pathway B, there is also another possibility. The activated 1,3-diketone (**3)** may reacts with amine **1** to form *β*-enaminones **D** as an intermediate in the initial step. The second step involves Michael addition of *α,β*-unsaturated aldehyde (**2**) to the *β*-enaminone **D** to form intermediate **E**, which undergoes intramolecular cyclisation to form hydroxyltetrahydropyridine **F**. Finally, the desired 5,6-unsubstituted 1,4-dihydropyridine (**4**) is obtained after dehydration as shown in Scheme 40.

The efficient recovery of the catalyst at the end of the reaction is highly desirable. The reusability test of the catalyst was performed. A mixture of benzylamine (**1a**, 10 mmol), cinnamaldehyde (**2a**, 10 mmol), methyl acetoacetate (**3a**, 10 mmol) and $Fe_2(SO_4)_3{\cdot}xH_2O$ (0.5 mmol, 0.205 g) was taken in 30 mL of methanol and it was stirred for 2h at room temperature. After completion of the reaction, methanol was removed in a rotatory evaporator and the crude residue was dissolved in 25 mL of dichloromethane. On adding dichloromethane, the catalyst was separated out and it was filtered off through a Büchner funnel, washed with another 5 mL of DCM and dried. The recovered catalyst was used for a similar set of reactions for three more consecutive cycles. Each reaction with recovered catalyst was carried out for 2h using the same reaction procedure. The yields and the number of experiments conducted are shown in the bar diagram in Figure 16. The required product **4a** was isolated in 86% yield after concentrating dichloromethane followed by purification through a silica gel column chromatography. The yield of the reaction decreased relatively in the fourth cycle which may be due to weight loss of the catalyst during handling in each cycle.

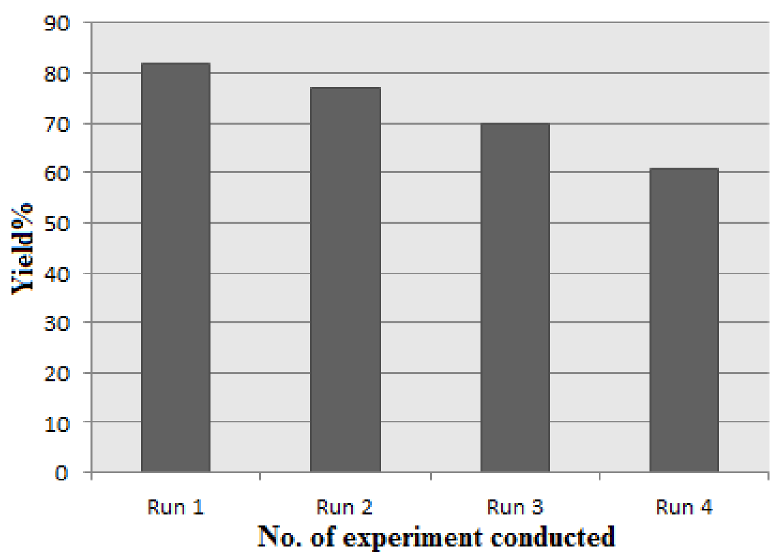


Figure 16. Reusability of the catalyst in methanol.

The efficiency and generality of the present protocol can be realized at a glance by comparing our results with those of some reported procedures as shown in Table 4. The results have been compared with respect to the mole percent of the catalyst used, reaction time and yields. It can be easily visualized that the reactions are considerably faster and give better product yields on using only 5 mol% of $Fe_2(SO_4)_3 \cdot xH_2O$ as compared to other catalyst as shown in Table 4.

Table 4. Comparison of our result with other results using different catalysts

Entry	Catalyst	Amount	Time	Yield%
1	$SO_4^{2-}/Ce_{0.07}Zr_{0.93}O_2$	20 mol%	1.5	84[134a]
2	Thiourea-Ammonium Salts	10 mol%	12	80[128]
3	Binol-derived phosphoric acid	10 mol%	--	54[134b]
4	$Sc(OTf)_3$	5 mol%	16	75[134c]
5	$Fe_2(SO_4)_3 \cdot xH_2O$	5 mol%	2	91

Conclusion

In short, the synthesis of 5,6-unsubstituted 1,4-dihydropyridines derivatives has been achieved using *α,β*-unsaturated aldehydes, amines and 1,3-diketone in the presence of catalytic amount of $Fe_2(SO_4)_3 \cdot xH_2O$ in methanol. The reaction is compatible with variety of aliphatic amine, *α,β*-unsaturated aldehydes and 1,3-diketone compounds. In comparison to other Lewis acids catalyst, $Fe_2(SO_4)_3 \cdot xH_2O$ has been found to be effective, mild, and less expensive. Moreover, due to its recyclability, the present method may open up a simple, mild and less expensive pathway for the synthesis of 5,6-unsubstituted 1,4-dihydropyridines in good yields. The application of synthesized dihydropyridines as dienophile in aza Diels-Alder reaction has discussed in Chapter III.

Chapter II

Experimental Section

- ***Hydrated ferric sulfate catalyzed synthesis of 5,6-unsubstituted 1,4-dihydropyridines using three-component reaction***

Experimental Section

General Procedure for the preparation of 5,6-unsubstituted 1,4-dihydropyridines (4): The catalyst hydrated ferric sulfate (0.021g, 0.05 mmol) was added to a stirred mixture of amine (**1**, 1 mmol) *α,β*-unsaturated aldehyde (**2**, 1 mmol) and 1,3-diketone (**3**, 1 mmol) in 3 mL of methanol and it was kept for stirring at room temperature. After completion of the reaction as monitored by TLC, methanol was removed in a rotary evaporator and the crude residue was extracted with ethyl acetate (2 x 10 mL). The organic layer was washed with water followed by brine solution and finally it was dried over anhydrous sodium sulfate. The organic extract was concentrated in a rotary evaporator and the crude residue was purified through a silica gel (60-120 mesh) column chromatography. The desired products (**4**) were eluted with a mixture of hexane/ethyl acetate (9:1).

Crystallographic Description

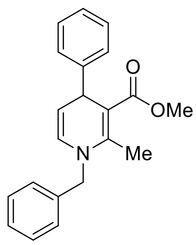
Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F^2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. Compound **4a** empirical formula $C_{21}H_{21}NO_2$, brown color crystal, formula wt 319.39, Monoclinic, '$P2_1/n$', a = 9.2797(8) Å, b = 7.6305(5) Å, c = 12.3433(9) Å, V = 868.93(11) Å^3, Z = 2, F (0 0 0) = 340.0, GOF(S) = 1.147. Final indices R_{obs} = 0.0903, wR_{obs} = 0.2634 with I> 2r (I); R_{all} = 0.1072, wR_{all} = 0.2762 for all data.

Table 5. Crystal data

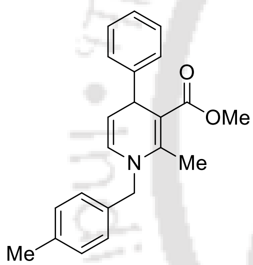
Identification code	4a	6b
Empirical formula	$C_{21}H_{21}NO_2$	$C_{19}H_{20}N_2O_6$
Formula weight	319.39	372.37
Temperature	296(2) K	296(2) K
Wavelength	0.71073Å	0.71073Å
Crystal system	'Monoclinic'	'Orthorhombic'
Space group	'P 1 21 1'	'P2(1)2(1)2(1)'
Unit cell dimensions	a = 9.2797(8)Å b = 7.6305(5)Å c = 12.3433(9)Å α = 90.00 º, β = 96.185(6)º γ = 90º	a = 7.5401(4)Å b = 8.4517(4)Å c = 29.1657(14)Å α = 90.00 º,β = 90.00º,γ =90º
Volume *Z*	868.93(11) $Å^3$ 2	1858.63(16)$Å^3$ 4
Density (calculated) Absorption coefficient *F*(000)	1.221 g/cm^3 0.078 mm^{-1} 340	1.331 g/cm^3 0.100mm^{-1} 784
Theta range for data collection	1.66º to 25.00º	1.40º to 25.00º
Index ranges Reflection collected /unique	$-11\le h\le 10$, $-9\le k\le 9$, $-13\le l\le 14$ 2865 / 2244 [R(int) =0.0447]	$-8\le h\le 8$, $-10\le k\le 10$,$-34\le l\le 34$ 3258 / 2899 [R(int) =0.0355]
Completeness to θ Refinement method	99.6% (θ = 25.00º) 'SHELXL−97 (Sheldrick, 1997)'	100% (θ = 25.00º) 'SHELXL−97 (Sheldrick, 1997)'
Goodness-of-fit on F^2 Final R indices [>2sigma(I)] R indices (all data) Largest diff. peak and hole	1.147 R_{obs} = 0.0903, wR_{obs} =0.2634 R_{all} = 0.1072, wR_{all} = 0.2762 0.504 and -0.290 e.$Å^{-3}$	1.208 R_{obs} = 0.0576, wR_{obs} = 0.1653 R_{all} = 0.0625 , wR_{all} = 0.1715 0.891 and -0.379e.$Å^{-3}$

Spectrocopic data

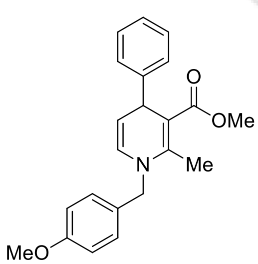
Methyl 1-benzyl-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4a): Brown Solid (0.294 g, 92%), mp 74-75 °C; R_f (10% ethyl acetate/hexane) 0.36; IR (KBr) ῡ = 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.32 (m, 2H), 7.31-7.27 (m, 5H), 7.21 (d, *J* = 7.6 Hz, 2H), 7.19-7.14 (m, 1H), 5.96 (d, *J* = 7.6 Hz, 1H), 5.0 (dd, *J* = 5.6, 7.2 Hz, 1H), 4.68-4.55 (m, 3H), 3.53 (s, 3H, OMe), 2.42 (s, 3H, Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.40, 149.13, 148.61, 131.04, 129.56, 128.86, 128.29, 127.47, 127.34, 126.19, 126.03, 108.01, 100.02, 53.67, 50.64, 40.06, 16.01 ppm; HRMS (ESI) calcd for $C_{21}H_{22}NO_2$ (M + H$^+$) 320.1651, found 320.1652.



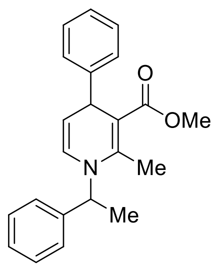
Methyl 2-methyl-1-(4-methylbenzyl)-4-phenyl-1,4-dihydropyridine-3-carboxylate (4b): Gummy liquid (0.314 g, 94%); R_f (10% ethyl acetate/hexane) 0.22; IR (KBr) ῡ = 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.23 (m, 4H), 7.18-7.14 (m, 3H) 7.10-7.08 (m, 2H), 5.95 (d, *J* = 7.2 Hz, 1H), 4.98 (dd, *J* = 5.2, 7.2 Hz, 1H), 4.63 (d, *J* = 6.0 Hz, 1H), 4.61-4.48 (m, 2H), 3.53 (s, 3H) 2.42 (s, 3H), 2.34 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.65, 149.41, 148.82, 137.35, 130.10, 129.71, 128.44, 127.50, 126.37, 126.17, 108.18, 100.11, 53.70, 50.83, 40.23, 21.24, 16.21 ppm; HRMS (ESI) calcd for $C_{22}H_{24}NO_2$ (M + H$^+$) 334.1807, found 334.1825.



Methyl 1-(4-methoxybenzyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4c): Gummy liquid (0.311 g, 89%); R_f (10% ethyl acetate/hexane) 0.21; IR (KBr) ῡ = 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21-7.12 (m, 4H), 7.10-7.03 (m, 3H), 6.80 (d, *J* = 8 Hz, 2H), 5.87 (d, *J* = 8 Hz, 1H), 4.91 (t, *J* = 6.8 Hz 1H), 4.54 (d, *J* = 6.8 Hz, 1H), 4.52-4.38 (m, 2H), 3.72 (s, 3H) 3.44 (s, 3H), 2.35 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.47, 158.98, 149.23, 148.62, 129.91, 129.47, 128.26, 127.49, 127.30, 126.01, 114.24, 108.02, 99.21, 55.33, 53.20, 50.70, 40.01, 16.04 ppm; HRMS (ESI) calcd for $C_{22}H_{24}NO_3$ (M + H$^+$) 350.1756, found 350.1764.

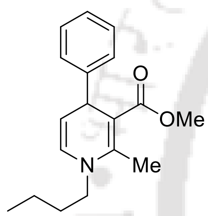


Methyl 2-methyl-4-phenyl-1-(1-phenylethyl)-1,4-dihydropyridine-3-carboxylate (4d): Gummy liquid (0.280 g, 84%); R_f (10% ethyl acetate/hexane) 0.6; IR (KBr) ῡ = 1684 cm^{-1};



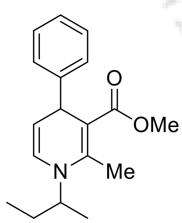
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.34 (m, 3H), 7.32-7.22 (m, 7H), 5.90 (d, *J* = 7.6 Hz, 1H), 5.28-5.18 (m, 1H), 5.02 (t, *J* = 7.2 Hz, 1H), 4.61 (d, *J* = 5.6 Hz, 1H), 3.56 (s, 3H) 2.52 (s, 3H), 1.66 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.87, 148.81, 141.83, 129.01, 128.89, 128.50, 127.56, 127.47, 126.59, 126.24, 124.93, 108.79, 100.57, 54.54, 50.93, 40.17, 20.52, 16.25 ppm; HRMS (ESI) calcd for $C_{22}H_{24}NO_2$ (M + H^+) 334.1807, found 334.1795.

Methyl 1-butyl-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4e): Gummy liquid (0.268 g, 94%); R_f (10% ethyl acetate/hexane) 0.41; IR (KBr) ῡ = 1685 cm^{-1}; ^{1}H NMR



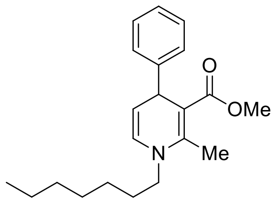
($CDCl_3$, 400 MHz) δ 7.29-7.21 (m, 3H), 7.17-7.13 (m, 2H), 5.89 (d, *J* = 7.6 Hz, 1H), 4.95 (t, *J* = 6.8, 7.2 Hz 1H), 4.55 (d, *J* = 6.0 Hz, 1H), 3.53 (s, 3H), 3.49-3.43 (m, 1H), 3.28-3.21 (m, 1H), 2.46 (s, 3H), 1.58 (quin, *J* =7.6 Hz, 2H), 1.34 (sext, *J* = 7.2 Hz, 2H), 0.95 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.72, 149.25, 149.12, 129.09, 128.41, 127.38, 126.12, 108.06, 99.35, 50.80, 50.35 40.10, 32.57, 20.07, 15.94, 14.01 ppm; HRMS (ESI) calcd for $C_{18}H_{24}NO_2$ (M + H^+) 286.1807, found 286.1791.

Methyl 1-(sec-butyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4f): Gummy liquid (0.274 g, 96%); R_f (10% ethyl acetate/hexane) 0.72; IR (KBr) ῡ = 1688 cm^{-1};



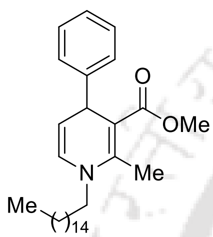
^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.29-7.16 (m, 4H), 7.15 (t, *J* = 7.2 Hz, 1H), 5.87 (d, *J* = 7.8 Hz, 1H), 4.94 (dd, *J* = 6.0, 7.2 Hz, 1H), 4.59 (d, *J* = 5.4 Hz, 1H), 3.54 (s, 3H), 3.41 (dd, *J* = 7.2, 15.0 Hz, 1H), 2.96 (dd, *J* = 7.2, 14.4 Hz, 1H), 2.46 (s, 3H), 1.91 (hept, *J* = 6.6 Hz, 1H), 0.94-0.93 (m, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 169.78, 149.44, 149.06, 129.81, 128.40, 127.36, 126.07, 107.38, 99.21, 58.0, 50.78, 40.06, 30.0, 20.22, 20.10, 16.24 ppm; HRMS (ESI) calcd for $C_{18}H_{24}NO_2$ (M + H^+) 286.1807, found 286.1809.

Methyl 1-heptyl-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4g): Gummy liquid (0.308 g, 94%); R_f (10% ethyl acetate/hexane) 0.62; IR (KBr) ῡ = 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02-6.96 (m, 4H), 6.91-6.87 (m, 1H), 5.63 (d, *J* = 8.0 Hz, 1H), 4.70 (dd, *J* = 5.6, 7.6 Hz 1H), 4.29 (d, *J* = 6.0 Hz, 1H), 3.27 (s, 3H), 3.22 (quin, *J* = 7.6 Hz, 1H), 2.96



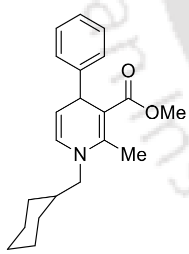
(quin, *J* = 7.2 Hz, 1H), 2.20 (s, 3H), 1.34 (t, *J* = 7.6 Hz, 2H), 1.05-1.02 (m, 8H), 0.63 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.73, 149.26, 149.14, 129.12, 128.41, 127.40, 126.13, 108.06, 99.38, 50.78, 50.63, 40.13, 31.95, 30.52, 29.24, 26.84, 22.77, 15.97, 14.26 ppm; HRMS (ESI) calcd for $C_{21}H_{30}NO_2$ (M + H$^+$) 328.2277, found 328.2276.

Methyl 1-hexadecyl-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4h): Gummy liquid (0.417 g, 92%); R_f (10% ethyl acetate/hexane) 0.49; IR (KBr) ῡ = 1690 cm^{-1};



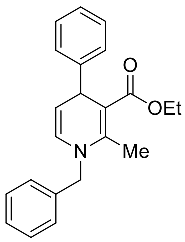
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28-7.20 (m, 4H), 7.14 (t, *J* = 6.8 Hz, 1H), 5.88 (d, *J* = 7.6 Hz, 1H), 4.95 (dd, *J* = 6.4, 7.2 Hz, 1H), 4.54 (d, *J* = 5.2 Hz, 1H), 3.52 (s, 3H), 3.51-3.42 (m, 1H), 3.26-3.18 (m, 1H), 2.45 (s, 3H), 1.39-1.22 (m, 28H), 0.87 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$**)** δ 169.71, 149.22, 149.14, 129.11, 128.40, 127.40, 126.11, 108.06, 99.42, 50.76, 50.62, 40.13, 32.13 30.52, 29.89, 28.86, 29.77 , 29.59, 29.56, 26.89, 22.89, 15.96, 14.31 ppm; HRMS (ESI) calcd for $C_{23}H_{26}NO_2$ (M + H$^+$) 454.3685, found 454.3685.

Methyl 1-(cyclohexylmethyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4i): Gummy liquid (0.283 g, 87%); R_f (10% ethyl acetate/hexane) 0.39; IR (KBr) ῡ = 1689



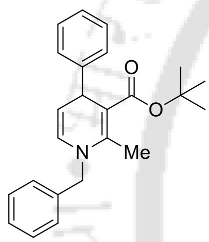
cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21-7.14 (m, 4H), 7.07 (t, *J* = 7.2Hz, 1H), 5.79 (d, *J* = 7.2 Hz, 1H), 4.85 (t, *J* = 6.8 Hz, 1H), 4.50 (d, *J* = 5.6 Hz, 1H), 3.46 (s, 3H), 3.34 (dd, *J* = 7.2, 14.4 Hz, 1H), 2.91 (dd, *J* = 7.2, 14.8 Hz, 1H), 2.37 (s, 3H), 1.68-1.51 (m, 5H), 1.50-1.47 (m, 1H), 1.20-1.05 (m, 3H), 0.86-0.78 (m, 2H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$**)** δ 169.76, 149.56, 149.02, 130.03, 128.68, 127.36, 126.07, 107.26, 99.23, 50.90, 50.78, 39.97, 39.60, 31.10 31.00, 26.52, 26.01, 16.27 ppm; HRMS (ESI) calcd for $C_{21}H_{28}NO_2$ (M + H$^+$) 326.2120, found 326.2067.

Ethyl 1-benzyl-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4j): Gummy liquid (0.304 g, 91%); R_f (10% ethyl acetate/hexane) 0.23; IR (KBr) ῡ = 1673 cm^{-1}; ^{1}H NMR



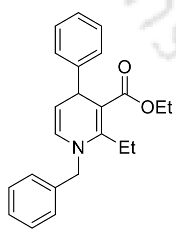
($CDCl_3$, 400 MHz) δ 7.35 (d, *J* = 7.2 Hz, 2H), 7.30-7.25 (m, 5H), 7.22 (d, *J* = 7.6 Hz, 2H), 7.18-7.14 (m, 2H), 6.95 (d, *J* = 7.6 Hz, 1H), 4.97 (dd, *J* = 5.6, 7.6 Hz, 1H), 4.67-4.54 (m, 3H), 3.97 (q, *J* = 7.2 Hz, 1H), 2.41 (s, 3H, Me), 1.08 (t, *J* = 7.2 Hz, 3H, Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.04, 148.92, 138.15, 129.50, 128.92, 128.27, 127.54, 126.25, 108.08, 100.42, 59.33, 53.72, 40.37, 16.00, 14.21 ppm; HRMS (ESI) calcd for $C_{22}H_{24}NO_2$ $(M + H^+)$ 334.1807, found 334.1702.

Tert-butyl 1-benzyl-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4k): Gummy liquid (0.297 g, 82%); R_f (10% ethyl acetate/hexane) 0.44; IR (KBr) ῡ = 1687 cm^{-1};



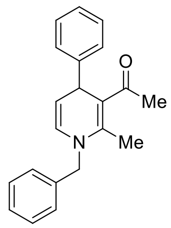
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.32 (m, 3H), 7.31-7.28 (m, 5H) 7.27-7.23 (m, 2H), 5.91 (d, *J* = 8.0 Hz, 1H), 4.92 (dd, *J* =5.2, 6.4 Hz, 1H), 4.66 (d, *J* = 5.2 Hz, 1H),), 4.65-4.53 (m, 2H) 2.41 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 168.70, 149.34, 147.82, 138.50, 129.41, 128.99, 128.34, 127.63, 127.55, 126.35, 126.01, 107.92, 102.16, 79.06, 53.78, 41.27, 28.45, 28.30, 28.25, 15.96 ppm; HRMS (ESI) calcd for $C_{24}H_{28}NO_2$ $(M + H^+)$ 362.2120, found 362.2120.

Ethyl 1-benzyl-2-ethyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4l): Gummy liquid

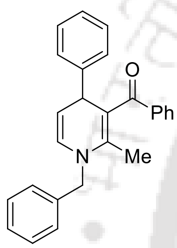


(0.306 g, 88%); R_f (10% ethyl acetate/hexane) 0.48; IR (KBr) ῡ = 1688 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.52-7.48 (m, 1H), 7.40-7.32 (m, 3H 7.30 (d, *J* = 7.2 Hz, 1H),7.28-7.24 (m, 3H), 7.23 (d, *J* = 7.6 Hz, 2H), 5.91 (d, *J* = 8.4 Hz, 1H), 4.99 (dd, *J* = 5.6, 6.8 Hz, 1H), 4.66 (d, *J* = 5.6 Hz, 1H), 4.64-4.59 (m, 2H), 3.99 (q, *J* = 7.2 Hz, 2H), 2.79-2.73 (m, 2H), 1.22 (t, *J*=7.6 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 169.50, 138.40, 129.54, 128.99, 128.96, 128.34, 127.95, 127.60, 127.55, 126.44, 126.06, 108.49, 99.41, 59.34, 53.19, 40.32, 22.18, 14.28, 13.70 ppm; HRMS (ESI) calcd for $C_{23}H_{26}NO_2$ $(M + H^+)$ 348.1964, found 348.1945.

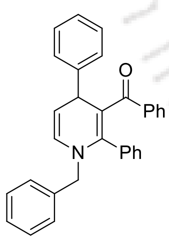
1-(1-benzyl-2-methyl-4-phenyl-1,4-dihydropyridin-3-yl)ethanone (4m): Gummy liquid (0.237 g, 78%); R_f (10% ethyl acetate/hexane) 0.13; IR (KBr) ῡ = 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.16 (m, 10H), 5.88 (d, *J* = 7.2 Hz, 1H), 5.09-5.03 (m, 3H), 4.65-4.52 (m, 2H), 4.43 (d, *J* = 5.6 Hz, 1H), 2.38 (s, 3H, Me), 2.02 (s, 3H, Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 199.37, 147.67, 137.65, 128.97, 128.66, 128.57, 127.31, 126.90, 126.50, 126.18, 125.99, 108.66, 108.49, 53.48, 40.98, 29.54, 16.38 ppm; HRMS (ESI) calcd for $C_{21}H_{22}NO$ (M + H$^+$) 304.1701, found 304.1670.



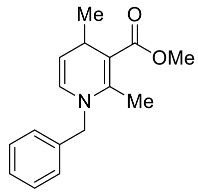
(1-benzyl-2-methyl-4-phenyl-1,4-dihydropyridin-3-yl)(phenyl)methanone (4n): Gummy Liquid (0.271 g, 74%); R_f (10% ethyl acetate/hexane) 0.24; IR (KBr) ῡ = 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.41-7.28 (m, 6H), 7.25-7.20 (m, 3H), 7.16-7.12 (m, 2H), 6.12 (d, *J* = 7.6 Hz, 1H), 5.02 (dd, *J* = 5.6, 7.6 Hz, 1H), 4.68-4.54 (m, 3H), 1.88 (s, 3H, Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 199.03, 147.38, 144.26, 141.27, 138.27, 131.28, 130.42, 128.98, 128.56, 128.44, 128.38, 127.63, 126.30, 110.78, 106.69, 53.58, 42.05, 17.64 ppm; HRMS (ESI) calcd for $C_{26}H_{24}NO$ (M + H$^+$) 366.1858, found 366.1858.



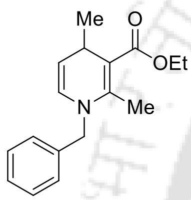
(1-benzyl-2,4-diphenyl-1,4-dihydropyridin-3-yl)(phenyl)methanone (4o): Gummy Liquid (0.364 g, 85%); R_f (10% ethyl acetate/hexane) 0.28; IR (KBr) ῡ = 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31-7.18 (m, 10H), 7.04-6.97 (m, 10H), 6.23 (d, *J* = 7.6 Hz, 1H), 5.17-5.14 (m, 1H), 4.80 (d, *J* = 5.2 Hz, 1H), 4.35 (d, *J* = 16.0 Hz, 1H), 4.22 (d, *J* = 16.0 Hz, 1H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 199.01, 147.52, 144.85, 141.63, 138.08, 131.46, 130.28, 129.92, 129.55, 129.45, 129.35, 129.13, 129.04, 128.91, 128.74, 128.51, 128.20, 128.01, 127.63, 126.40, 108.53, 53.43, 41.93, ppm; HRMS (ESI) calcd for $C_{31}H_{26}NO$ (M + H$^+$) 428.2014, found 428.1961.



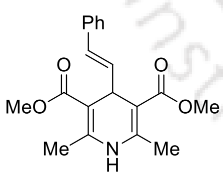
Methyl 1-benzyl-2,4-dimethyl-1,4-dihydropyridine-3-carboxylate (4p): Gummy liquid (0.201 g, 78%); R_f (10% ethyl acetate/hexane) 0.42; IR (KBr) ῡ = 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.23 (m, 3H), 7.21 (d, *J* = 6.8 Hz, 2H), 6.58 (d, *J* = 9.6 Hz, 1H), 5.05 (dd, *J* = 5.6, 9.6 Hz, 1H), 4.83 (d, *J* = 16.4 Hz, 1H), 4.37 (d, *J* = 16.8 Hz, 1H), 3.96 (t, *J* = 6.4 Hz, 1H), 3.69 (s, 3H, OMe), 2.44 (s, 3H, Me), 1.11 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 168.06, 155.38, 137.60, 128.99, 127.56, 126.26, 123.92, 112.25, 98.22, 55.62, 53.20, 50.66, 19.56, 16.66 ppm; HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ (M + H^+) 258.1494, found 258.1411.



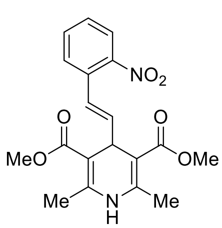
Ethyl 1-benzyl-2,4-dimethyl-1,4-dihydropyridine-3-carboxylate (4q): Gummy liquid (0.228 g, 84%); R_f (10% ethyl acetate/hexane) 46; IR (KBr) ῡ = 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.21 (m, 3H), 7.15 (d, *J* = 7.6 Hz, 2H), 6.54 (d, *J* = 9.2 Hz, 1H), 4.98 (dd, *J* = 5.2, 9.2 Hz, 1H), 4.77 (d, *J* = 16.8 Hz, 1H), 4.30 (d, *J* = 17.2 Hz, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.90 (quin, *J* = 6.4 Hz, 1H), 2.37 (s, 3H, Me), 1.22 (t, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 167.87, 155.28, 137.77, 129.09, 127.65, 126.37, 124.12, 112.24, 98.58, 59.25, 55.71, 53.25, 19.69, 16.74, 14.82, ppm; HRMS (ESI) calcd for $C_{17}H_{22}NO_2$ (M + H^+) 272.1651, found 272.1651.



(E)-dimethyl 2,6-dimethyl-4-styryl-1,4-dihydropyridine-3,5-dicarboxylate (6a): Gummy liquid (0.281 g, 86%); R_f (10% ethyl acetate/hexane) 41; IR (KBr) ῡ = 1679 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.31 (m, 2H), 7.27-7.25 (m, 2H), 7.16 (d, *J* = 7.2 Hz, 1H), 6.22-6.12 (m, 2H), 5.84 (s, 1H), 4.61 (d, *J* = 4.8 Hz, 1H), 3.72 (s, 6H), 2.33 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 168.19, 145.63, 137.84, 131.93, 128.50, 127.98, 127.04, 126.41, 101.28, 51.28, 36.28, 19.52 ppm.

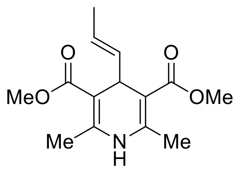


(E)-dimethyl 2,6-dimethyl-4-(2-nitrostyryl)-1,4-dihydropyridine-3,5-dicarboxylate (6b): Solid (0.286 g, 77%); R_f (10% ethyl acetate/hexane) 29; IR (KBr) ῡ = 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.87 (d, *J* = 9.0 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 9.6 Hz, 1H),6.13(dd, *J* = 15.8, 15.8 Hz, 1H), 5087 (bs, 1H), 4.64 (d, *J* = 6.0 Hz, 1H), 3.75 (s, 6H), 2.34 (s, 6H) ppm; ^{13}C NMR (150 MHz,



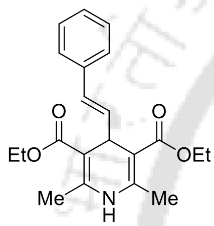
$CDCl_3$) δ 167.97, 147.92, 145.95, 137.00, 133.91, 133.04, 128.84, 127.60,124.63, 124.10, 101.93, 51.45, 36.74, 19.64 ppm.

(E)-dimethyl 2,6-dimethyl-4-(prop-1-en-1-yl)-1,4-dihydropyridine-3,5-dicarboxylate



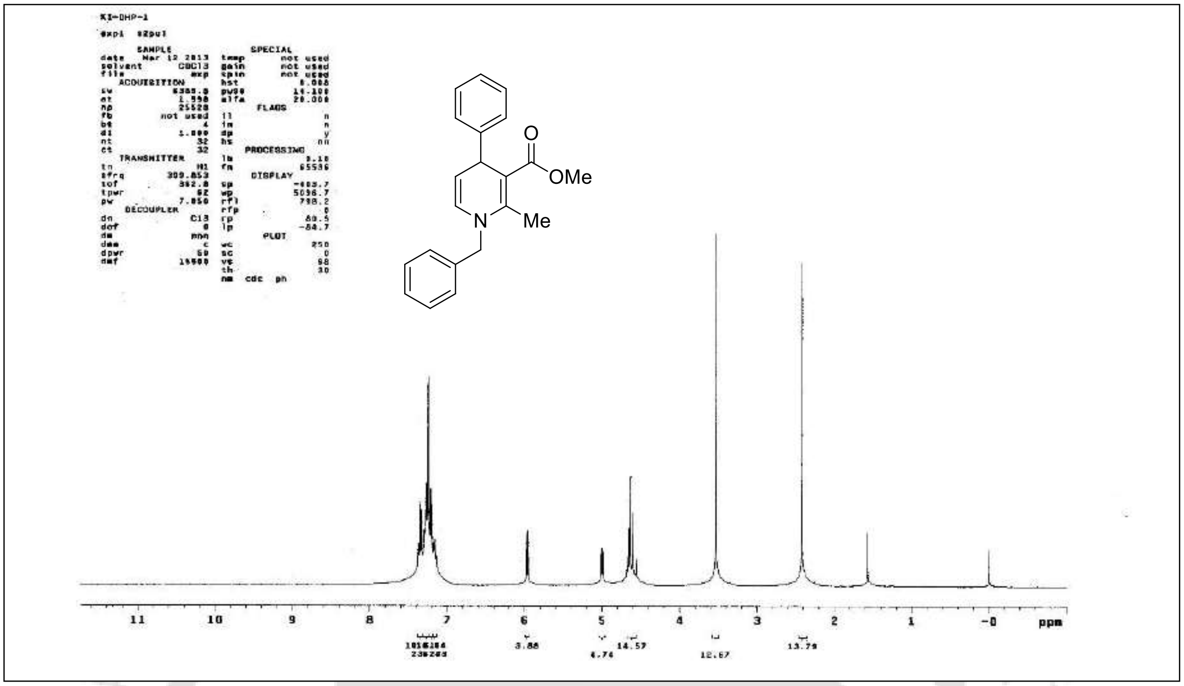
(6c): Gummy liquid (0.241 g, 91%); R_f (10% ethyl acetate/hexane) 54; IR (KBr) ῡ = 1678 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.65 (bs, 1H), 5.39-5.27 (m, 2H), 4.35 (d, J = 7.2 Hz, 1H),3.70 (s, 6H), 2.29 (s, 6H), 1.60 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.36, 144.80, 133.11, 123.63, 102.32, 51.26, 35.89, 19.66, 17.99 ppm.

(E)-diethyl 2,6-dimethyl-4-styryl-1,4-dihydropyridine-3,5-dicarboxylate (6d): Gummy

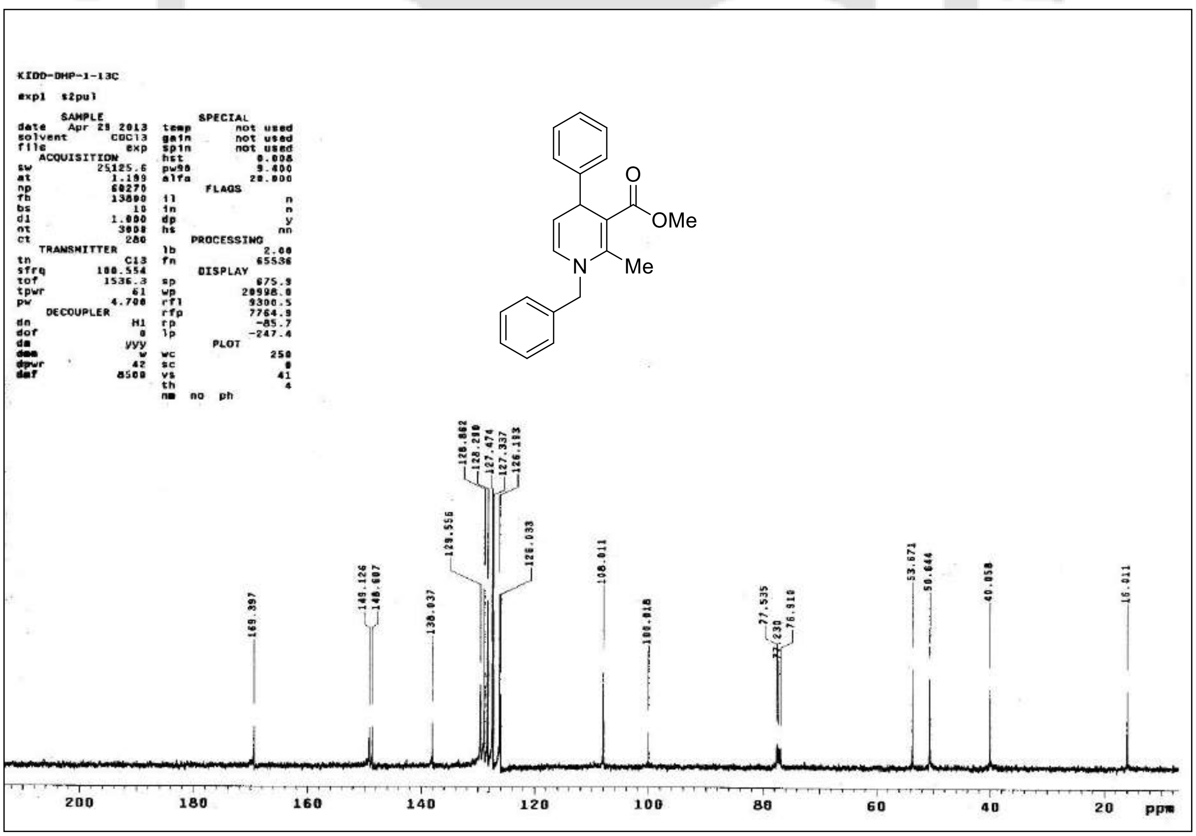


liquid (0.255 g, 72%); R_f (10% ethyl acetate/hexane) 41; IR (KBr) ῡ = 1679 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33-7.31 (m, 2H), 7.26-7.24 (m, 1H), 7.16 (t, J = 7.2 Hz, 2H), 6.25-6.14 (m, 2H), 5.67 (bs, 1H), 4.62 (d, J = 6.0 Hz, 1H), 4.21-4.16 (m, 4H),2.32 (s, 6H), 1.29 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.80, 145.18, 137.95, 131.99, 128.52, 128.18, 127.00, 126.37, 101.55, 59.93, 36.66, 19.62, 14.59 ppm.

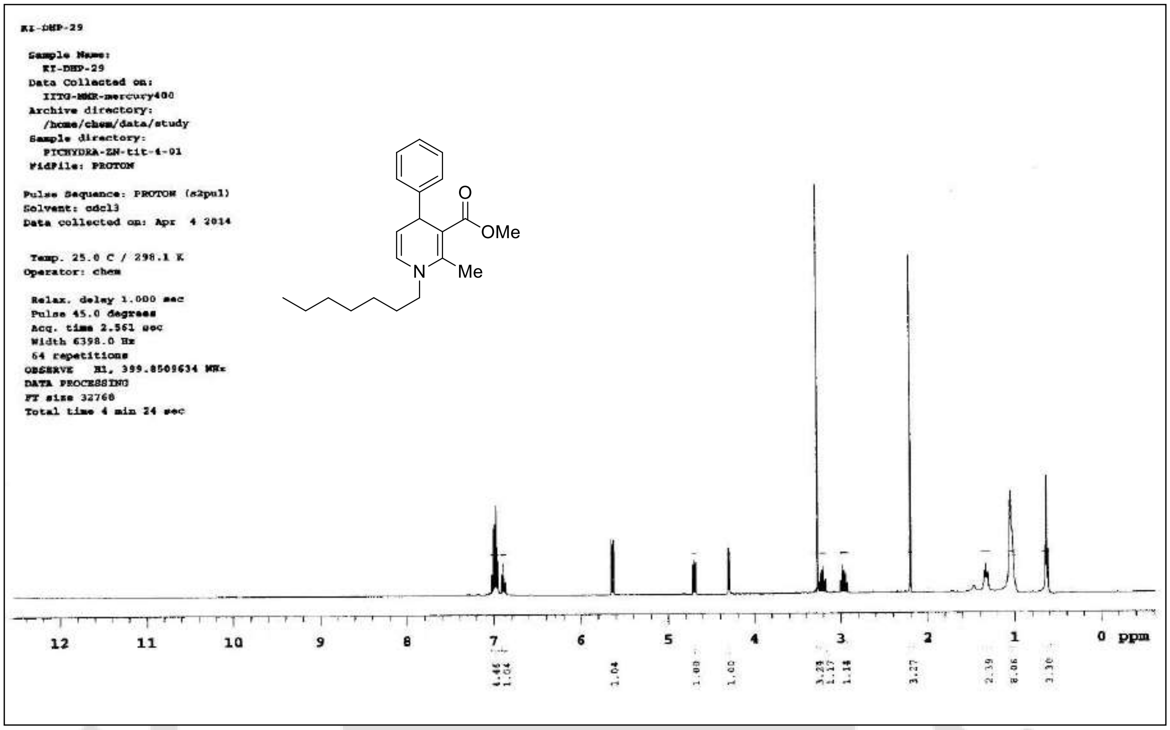
^{1}H NMR Spectra of 4a



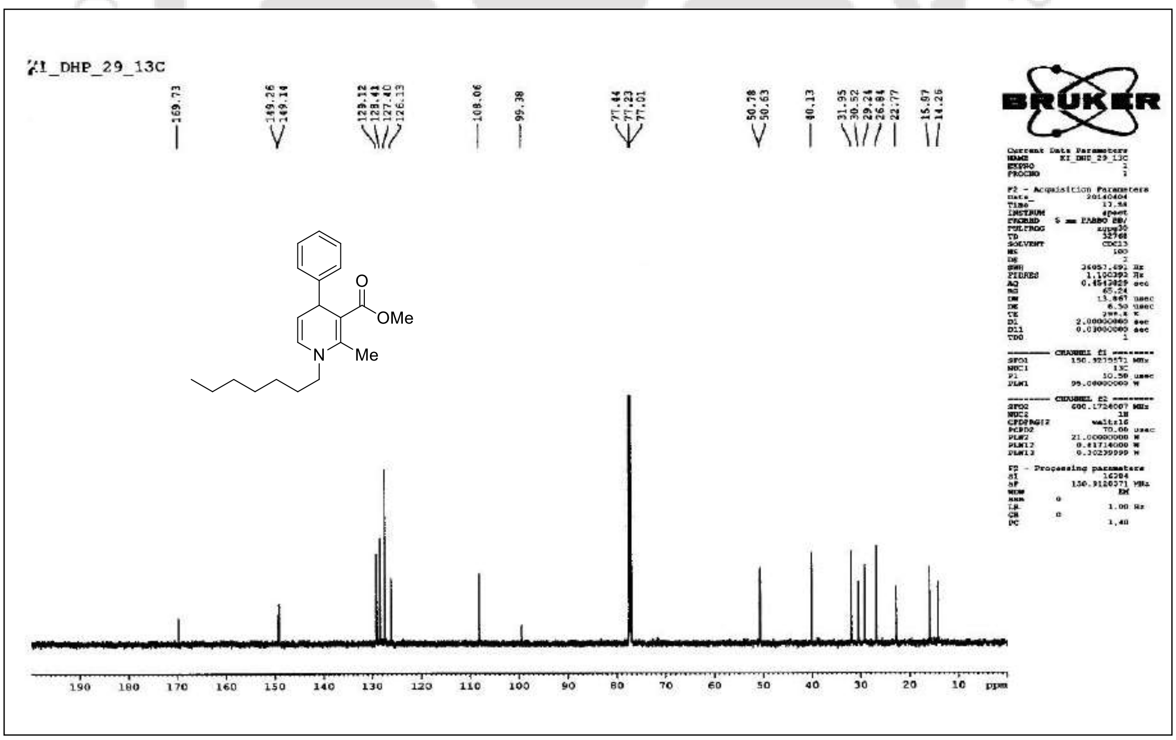
^{13}C NMR Spectra of 4a



[1]H NMR Spectra of 4g



[13]CNMR Spectra of 4g



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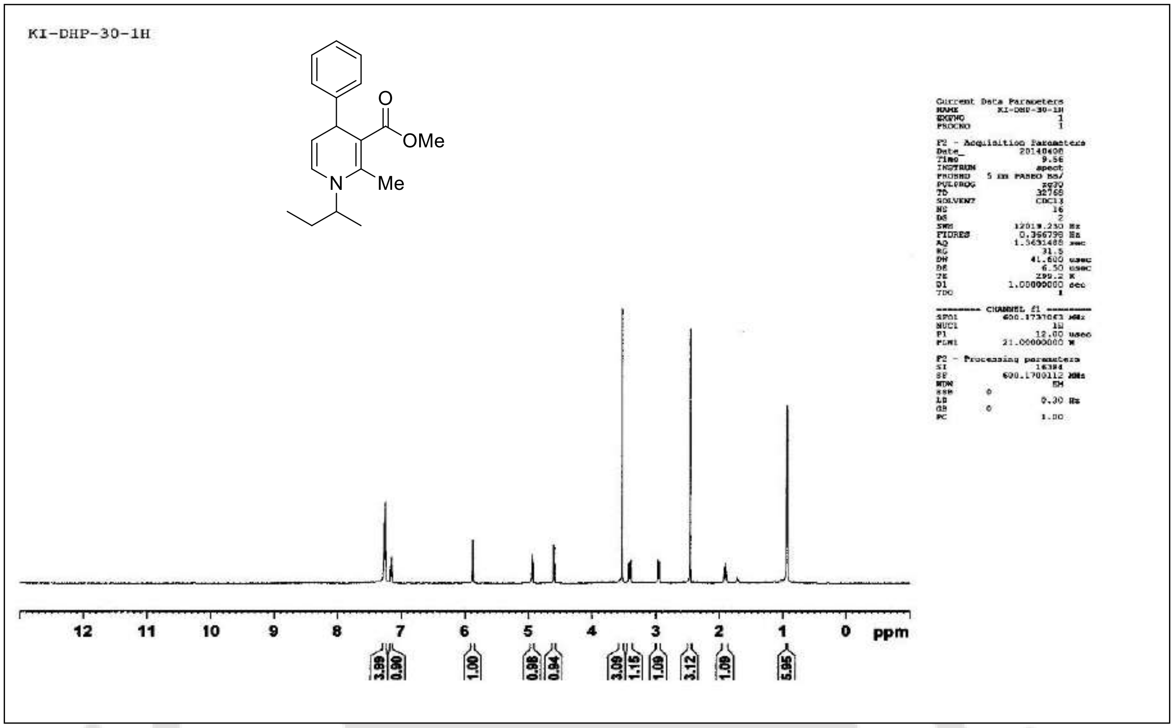
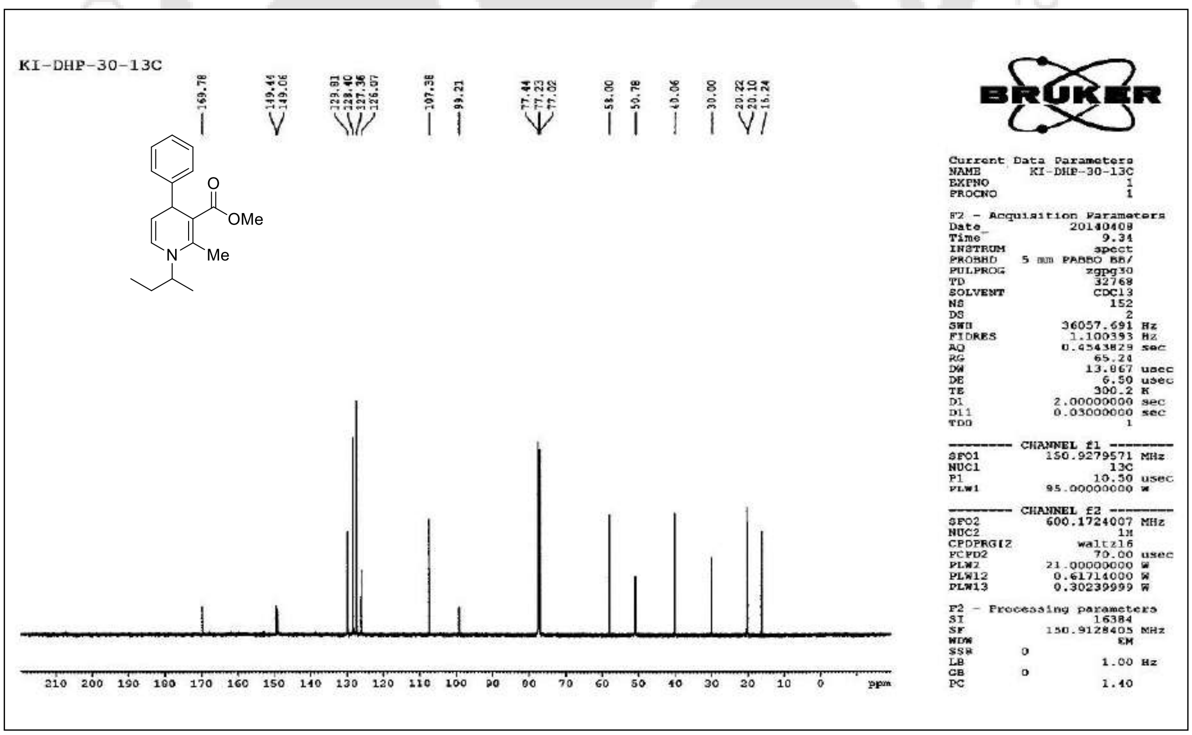
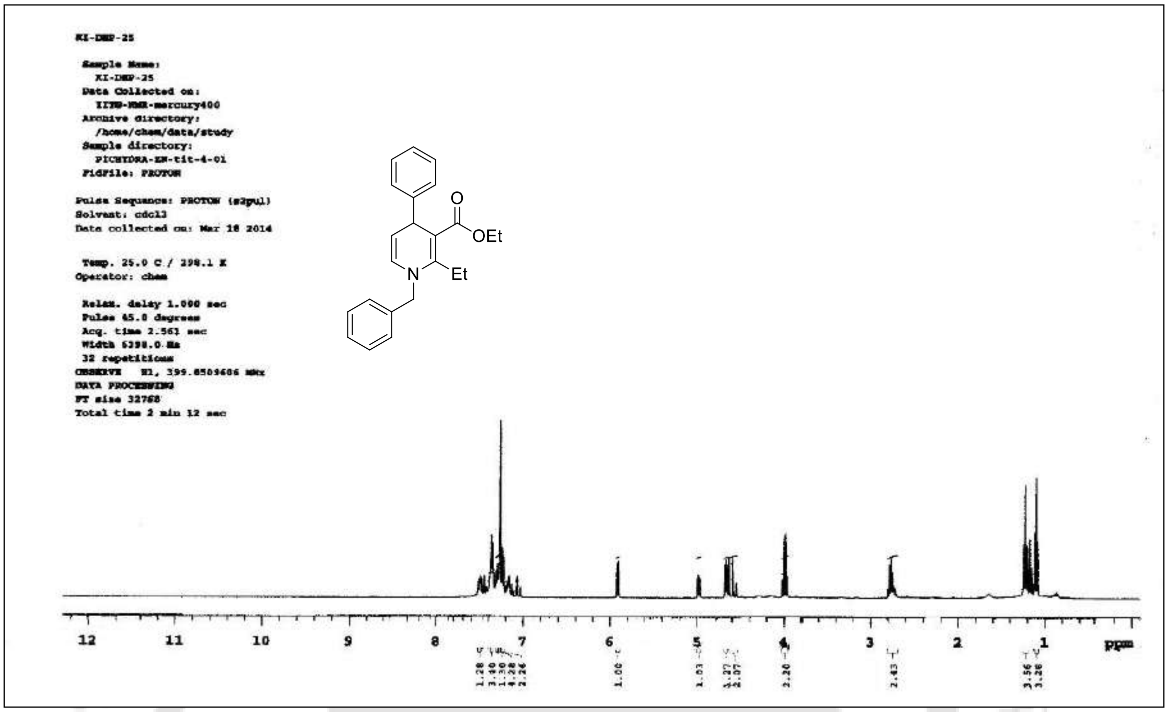


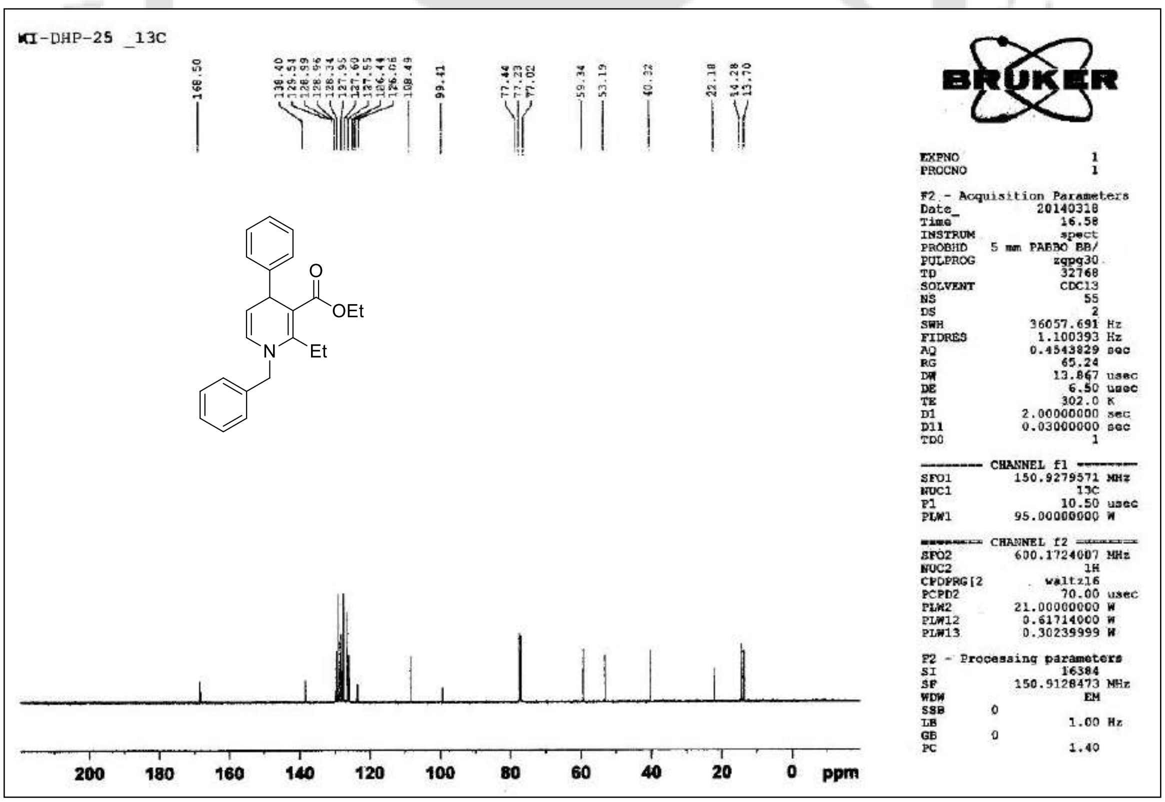
[13]C NMR Spectra of 4f



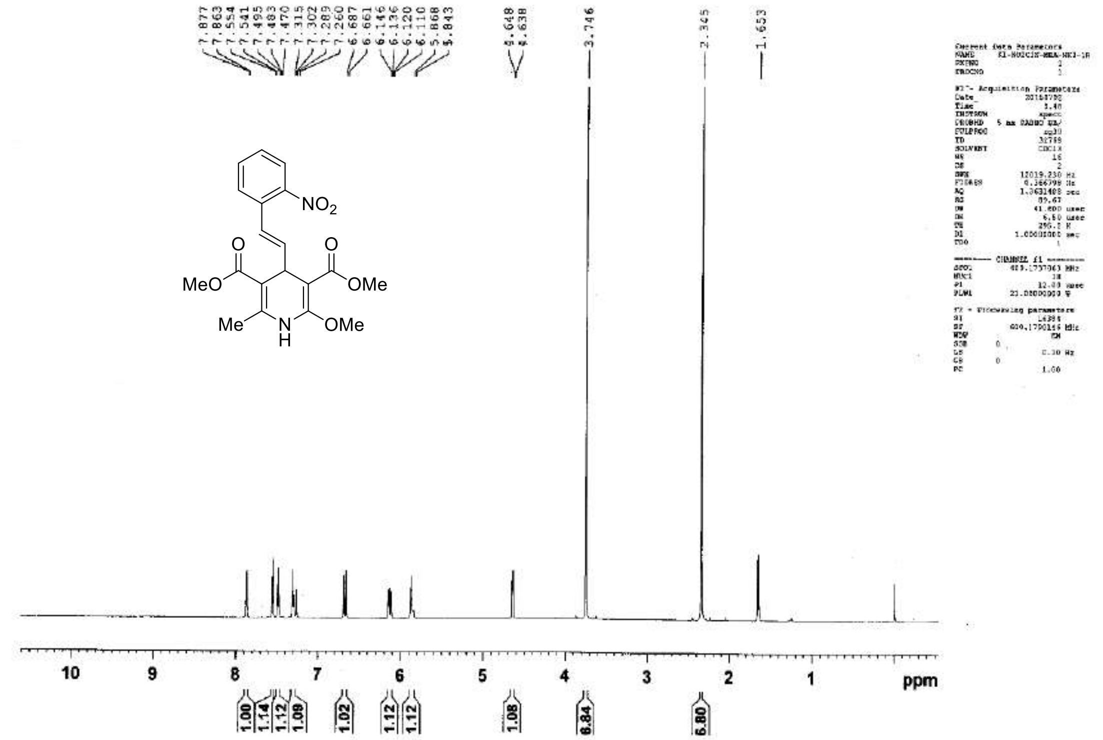
[1]H NMR Spectra of 4l



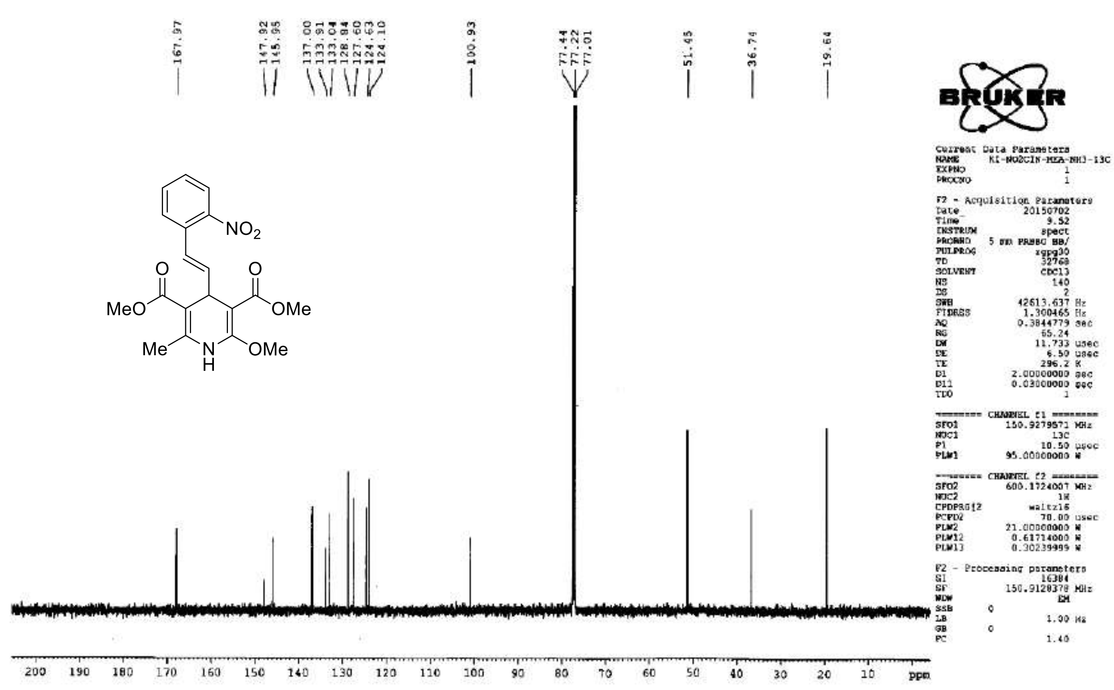
[13]C NMR Spectra of 4l



^{1}H NMR Spectra of 6b

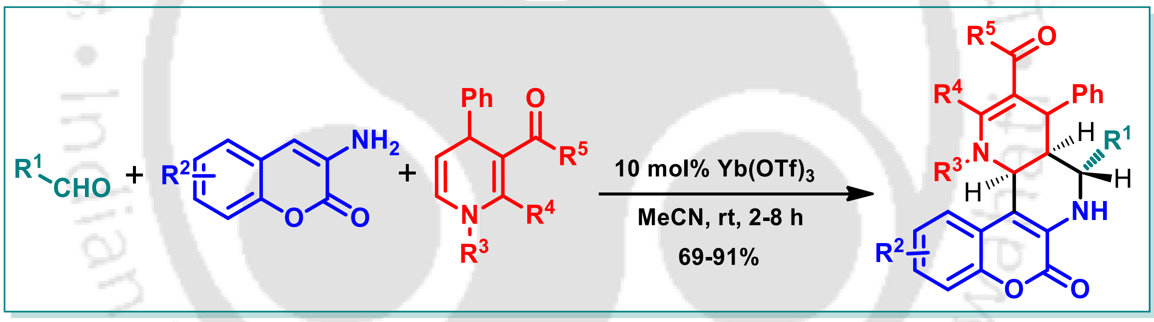


^{13}C NMR Spectra of 6b



Chapter III

Exploration of C5-C6-unsubstituted 1,4-dihydropyridines for the construction of exo-hexahydro-1H-chromeno[3,4-h][1,6]naphthy ridine-3-carboxylates using stereoselective Povarov reaction

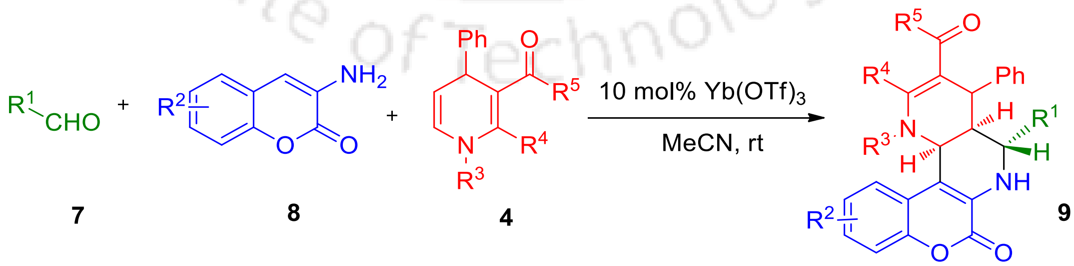


CHAPTER III

III. Exploration of C5-C6-unsubstituted 1,4-dihydropyridines for the construction of *exo*-hexahydro-1H-chromeno[3,4-*h*][1,6]naphthyridine-3-carboxylates using stereoselective Povarov reaction

Results and Discussion

The importance of Povarov reaction and their developing synthetic methods have been discussed in chapter I. In Povarov reaction generally encounters both *endo* and *exo*-isomers with poor stereoselectivity. Therefore, the major challenge is to improve its stereoselectivity. Moreover, the one-pot synthesis of a single diastereomer is still challenging.[138] In this chapter we have utilized our synthesized C5-C6-unsubstituted 1,4-dihydropyridines for the construction of a new class of heterocycles using stereoselective hetero Diels-Alder reaction. Since C5-C6-unsubstituted 1,4-dihydropyridines are particularly significant due to their substitution pattern which enables the use of dihydropyridines as the dienophile component in imino Diels-Alder reaction for the synthesis of substituted naphthyridine derivatives.[97-100] In recent years, 3-aminocoumarin has been used as a key intermediate for the construction of various heterocyclic compounds.[139] 3-aminocoumarins have also been used as the amine component in Povarov reactionby others as well as by our research group.[137,140] In this chapter demonstration of simplest, and rapid one-pot synthesis of *exo*-hexahydro-1*H*-chromeno[3,4-*h*][1,6]naphthyridine-3-carboxylate



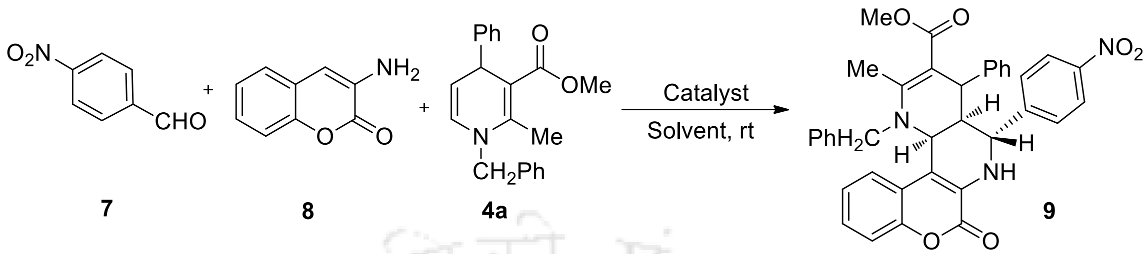
Scheme 41. Synthesis of *exo*-hexahydro-*1H*-chromeno[3,4-*h*][1,6]naphthyridine-3-carboxylate derivatives **9**.

derivatives has been executed involving $Yb(OTf)_3$ *via* imino Diels-Alder reaction using aldehydes, 3-aminocoumarins and 1,4-dihydropyridines as shown in Scheme 41.

Various 5,6-unsubstituted 1,4-dihydropyridines (**4**), were synthesized using three component cyclization of *α,β*-unsaturated aldehydes, amines and 1,3-dicarbonyl compounds with 5 mol% hydrated ferric sulfate as the catalyst in methanol at room temperature.[141] For the present study, an equimolar mixture of 4-nitrobenzaldehyde (**7**), 3-aminocoumarin (**8**) and 5,6-unsubstituted 1,4-dihydropyridines (**4**) in acetonitrile (2 mL) in the presence of 5 mol% of $Yb(OTf)_3$ was stirred at room temperature. After purification of the reaction mixture, the product *exo*-hexahydro-1*H*-chromeno[3,4-*h*][1,6]naphthyridine-3-carboxylate (**9i**) was isolated in 54% overall yield (entry 1, Table 6). The product (**9i**) was characterized by IR spectroscopy, ^{1}H NMR, ^{13}C NMR spectroscopy, and mass spectra. The ^{1}H NMR spectra of the crude reaction mixture showed the presence of only a sole diastereomeric product.

To find the optimized reaction conditions, the same set of reactions were carried out using 10 mol%, 15 mol% and 20 mol% $Yb(OTf)_3$ successively and the desired product (**9i**) was obtained in 82%, 77% and 74% yield (entries 2-4, Table 6) respectively. It was observed that the yield of the product increased significantly by increasing the amount of catalyst from 5 mol% to 10 mol%. However, no further improvement in the yield of (**9i**) was observed, even though the amount of catalyst is increased up to 20 mol% (entry 6, Table 1). For scrutinizing suitable solvent system, the similar reactions were conducted in DCM, DMF, THF, EtOH and toluene under identical reaction conditions respectively (entries 5-9, Table 6). The reaction process was restrained in terms of reaction time and yields when performed in DCM, THF, EtOH or toluene (entries 5 & 7-9, Table 6). In DMF, the reaction did not occur and most of the unreacted starting materials were recovered (entry 6, Table 6). It was noted that the shortest reaction time and the best yield were obtained in acetonitrile (entry 2, Table 6) at room temperature. To examine the efficacy of $Yb(OTf)_3$ as compared to other catalysts, several reactions were also scrutinized in the presence of catalysts such as $In(OTf)_3$, $Cu(OTf)_2$, AgOTf, I_2 and $Fe_2(SO_4)_3{\cdot}xH_2O$ under identical conditions and the results are summarized in Table 6 (entries 10-14). $In(OTf)_3$ also promoted the tandem reactions smoothly, albeit the yield of (**9i**) decreased to 72% (entry 10, Table 6).

Table 6. Optimization of reaction conditions for the synthesis of *exo*-hexahydro-1*H*-chromeno[3,4-*h*][1,6]naphthyridine-3-carboxylate **9i**[a]



Entry	Catalyst	Mol%	Solvent	Time [h]	(%)Yield[b]
1	$Yb(OTf)_3$	5	MeCN	6.0	54
2	**$Yb(OTf)_3$**	**10**	**MeCN**	**2.0**	**82**
3	$Yb(OTf)_3$	15	MeCN	2.0	77
4	$Yb(OTf)_3$	20	MeCN	2.0	74
5	$Yb(OTf)_3$	10	DCM	3.5	70
6	$Yb(OTf)_3$	10	DMF	12.0	NR
7	$Yb(OTf)_3$	10	THF	12.0	56
8	$Yb(OTf)_3$	10	EtOH	6.0	71
9	$Yb(OTf)_3$	10	Toluene	6.0	44
10	$In(OTf)_3$	10	MeCN	3.5	72
11	$Cu(OTf)_2$	10	MeCN	12.0	33
12	AgOTf	10	MeCN	12.0	NR
13	I_2	10	MeCN	12.0	32
14	$Fe_2(SO_4)_3\cdot xH_2O$	10	MeCN	12.0	NR
15	None	-	MeCN	12.0	NR

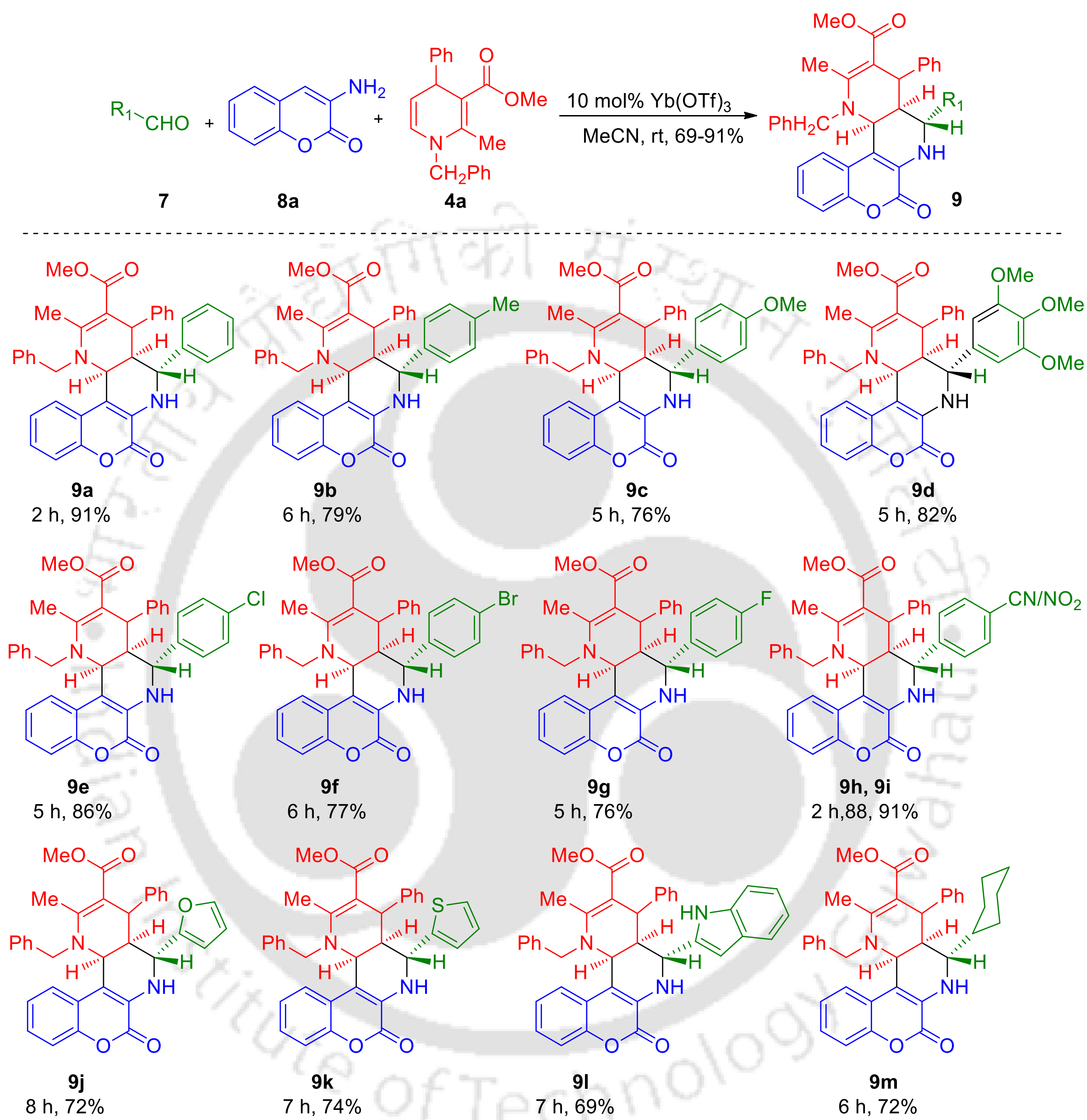
[a]Reaction conditions: 4-nitrobenzaldehyde (**7a**), 3-aminocoumarin (**8a**) and 1,4-dihydropyridines (**4a**) were taken in a 1:1:1 ratio at rt. [b]Isolated yields. NR = no reaction.

The reactions using $Cu(OTf)_2$ or I_2 as the catalyst (entries 11 & 13, Table 6) provided lower yields of (**9**). Catalysts, such as AgOTf and $Fe_2(SO_4)_3 \cdot xH_2O$ did not promote the reaction (entries 12 & 14, Table 6). The reaction did not take place in the absence of catalyst (entry 15, Table 6). Hence, the best yields were achieved by employing $Yb(OTf)_3$ as the catalyst (entry 2, Table 6) for the Povarov reactions with acetonitrile as the solvent at room temperature.

After optimization of the reaction conditions, a reaction was performed with a mixture of benzaldehyde (7**a)**, 3-aminocoumarin (**8a**) and 1,4-dihydro pyridine (**4a)** under identical conditions and the desired product (**9a**) was obtained in 91% yield (entry 1, Table 7). To explore the synthetic scope and the generality of the present protocol further, various reactions were examined with a wide variety of aromatic aldehydes containing different substituents in the aromatic ring such as OMe, Cl, Br, F and CN (**7d-h**) with 3-aminocoumarin (**8a**) and 1,4-dihydropyridine (**4a)**, respectively. The reaction time and percentage yield of the products (**9c-i**) are shown in Table 7 (entries 3-9). Among the examined aldehydes, aromatic aldehydes having strong electron-withdrawing group on the benzene ring such as 4-CN and 4-NO_2 gave the desired products in higher yields in shorter reaction time (entries 8 & 9, Table 7). For the reactions with other aldehydes, such as 4-methylbenzaldehyde (**7b)**, 4-methoxybenzaldehyde (**7c)** the corresponding product (**9b-c)** were obtained in a bit lower yields (entries 2-3, Table 7). It should be noted that functional groups such as fluoro, chloro, bromo, nitro, and methoxy, are well tolerated and preceded smoothly under the mild reaction conditions. It is worthwhile to mention that the products were isolated simply by filtration and the further purification was done by recrystallization from acetonitrile-hexane solvent system.

The same methodology was further extended with aldehydes bearing a heteroaromatic substituent such as furan-2-carbaldehyde (**7j**), 2-thiophenaldehyde (**7k**) and indole-2-carbaldehyde (**7l**) respectively and the desired products (**9j-l**) were isolated in moderate to good yields, respectively (entries 10-12, Table 7). Additionally, our protocol was further verified with aliphatic aldehyde namely cyclohexyl carboxaldehyde (**7m**) and the desired product (**9m)** was obtained in 72% yield, which is shown in Table 7 (entry 13)

Table 7. Synthesis of substituted *exo*-hexahydro-1*H*-chromeno[3,4-*h*][1,6]naphthyridine-3-carboxylate derivatives using Povarov reaction (**9**)[a,b]

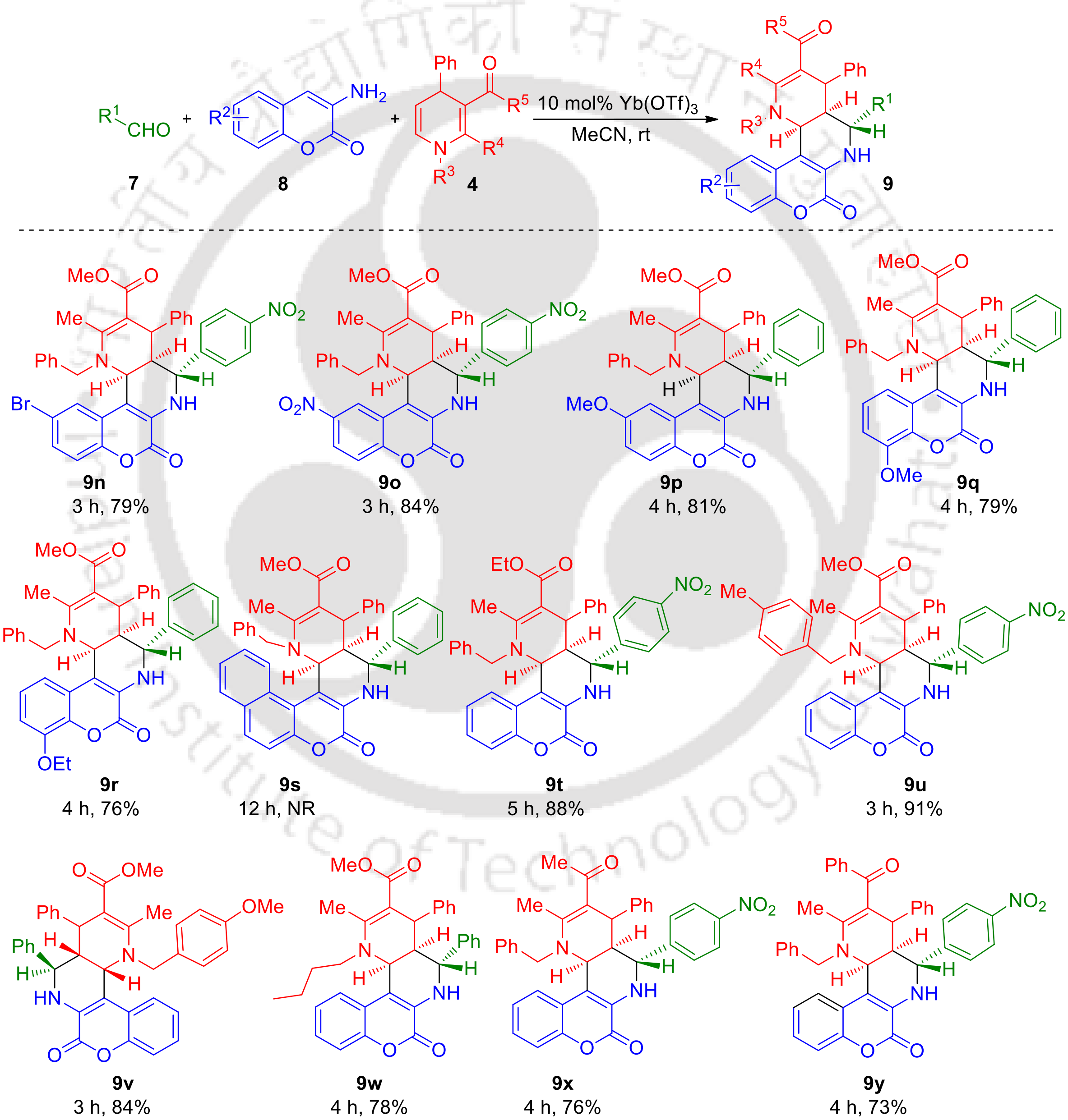


[a]Reaction conditions: Aldehyde **7** (0.5 mmol), 3-aminocoumarin **8a** (0.5 mmol), 1,4-dihydropyridine **9a**(0.5 mmol), $Yb(OTf)_3$ (10 mol%), CH_3CN (2 mL) at room temperature. [b]Isolated Yields.

For verifying the generality of the present method, other substituted 3-aminocoumarins such as 6-bromo-3-aminocoumarin (**8b**), 6-nitro-3-aminocoumarin (**8c**) and 6-methoxy-3-aminocoumarin (**8d**), 8-methoxy-3-aminocoumarin (**8e**) and 8-ethoxy-3-aminocoumarin (**8f**) were also tested with 4-nitrobenzaldehyde (**7i**) or benzaldehyde (**7a**) and 1,4-dihydropyridine (**4a**) under identical reaction conditions and the anticipated *exo*-hexahydro-1*H*-chromeno[3,4-

h][1,6]naphthyridine-3-carboxylate derivatives (**9n–r)** were obtained in good yields (entries 1-5, Table 8). However, 3-aminocoumarin derivative containing naphthyl ring (**8g**) failed to give the desired product when allowed to react with benzaldehyde (**7a**) and 1,4-dihydropyridine (**4a**) (entry 6, Table 8), which may be accounted as the inability of the

Table 8. Synthesis of substituted *exo*-hexahydro-1*H*-chromeno[3,4-*h*][1,6]naphthyridine-3-carboxylate derivatives using Povarov reaction(**9**)[a,b]



[a]Reaction conditions: Aldehyde **7** (0.5 mmol), 3-aminocoumarin **8** (0.5 mmol), 1,4-dihydropyridine **4** (0.5 mmol), $Yb(OTf)_3$ (10 mol%), CH_3CN (2 mL) at room temperature. [b] Isolated Yields.

dienophile, 1,4-substituted dihydropyridine to approach the diene in the [4+2] cycloaddition manner due to steric hindrance caused from bulkiness of the diene formed. Furthermore, the same reactions were also executed with different substituted 1,4-dihydropyridines (**4**) with aromatic aldehydes and 3-aminocoumarin to give desired products (**9t-y)** in good yields (entries 7-12, Table 8). The successful result with different aminocoumarins as amine components (**8**) and C5-C6-unsubstituted 1,4-dihydropyridines (**4**) as dienophiles shown in Table 8.

Finally, the structure of one of the descriptive compounds such as **9a** was confirmed unambiguously by single crystal X-ray diffraction analysis (Fig. 17).

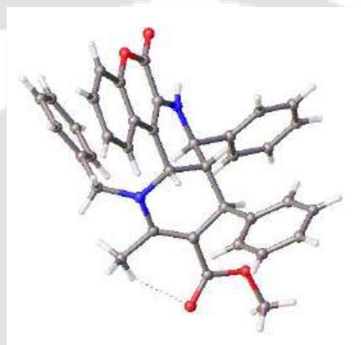


Figure 17. Single crystal X-ray structure of compound **9a**.

The product (**9a**) was characterized by IR spectroscopy, ^{1}H NMR, ^{13}C NMR spectroscopy, and mass spectra. In the IR spectrum, it showed characteristic absorptions at 3347, 1718 and

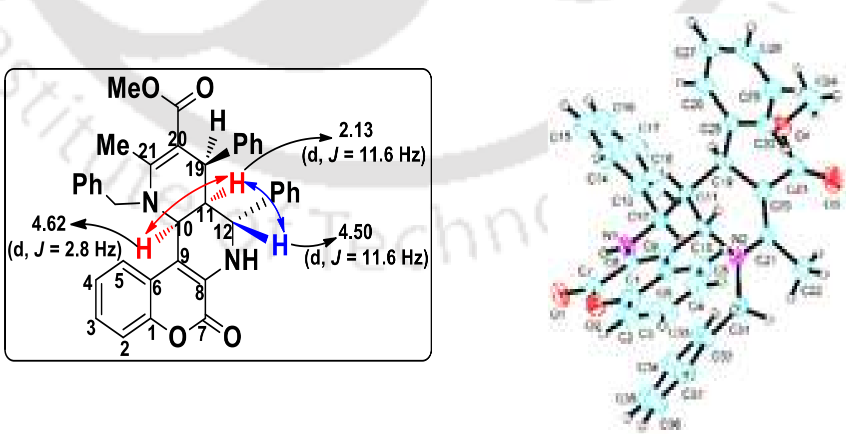
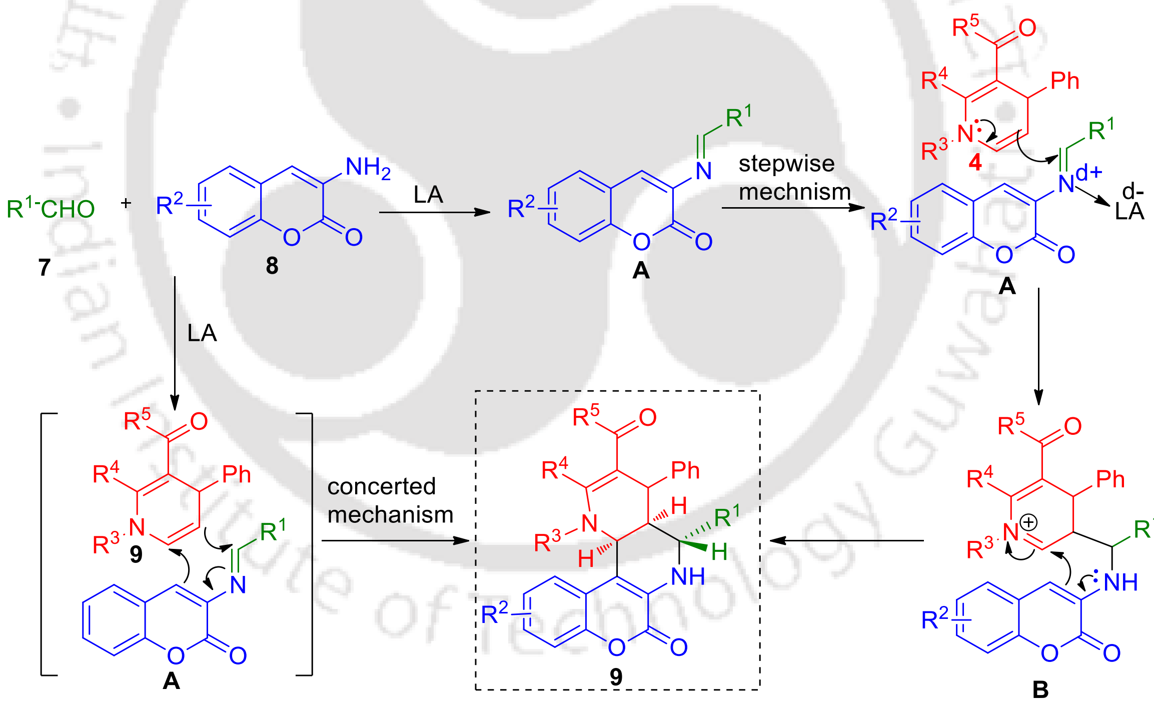


Figure 18. Stereochemistry of the fused ring junctures.

1681 cm^{-1} due to the NH and two ester carbonyl group in (**9a**). The ^{1}H NMR spectrum of (**9a**) showed a broad singlets at δ = 5.30 ppm due to the NH proton, and two singlets at δ = 2.70

and 3.46 ppm due to the Me and OMe groups in hexahydro-1*H*-chromeno[3,4-*h*][1,6]naphthyridine-3-carboxylate (**9a**). The stereochemistry of the fused ring junctures and other positions was established from their coupling constant values. The protons H_{11}, H_{12} and H_{10} appears as doublet with δ = 2.13, 4.50 and 4.62 ppm in ^{1}H NMR spectrum of (**9a**). The coupling constant between H_{11} and H_{10} ($J_{11,10}$) was found to be 2.8 Hz indicating a *cis* ring junction between the two dihydropyridine rings in (**9a**). Similarly, the coupling constant value between H_{11} and H_{12} ($J_{11,12}$) was found to be 11.6 Hz indicating the *trans* diaxial relationship between these protons as shown in Figure 18. The *exo* structure of (**9a**) is also confirmed by X-ray diffraction analysis, and its crystal structure is shown in Figure 17.

A plausible mechanism for the formation of substituted *exo*-hexahydro-1*H*-chromeno[3,4 *h*][1,6] naphthyridine-3-carboxylate derivatives (**9**) is shown in Scheme 42. It is believed that the condensation reaction between aromatic aldehydes (**7**) and 3-aminocoumarins (**8**) leads



Scheme 42. Plausible mechanism for the formation of hexahydro-1*H*-chromeno[3,4-*h*][1,6]naphthyridine-3-carboxy -late derivatives **9** using Povarov reaction.

to the formation of intermediate imines **A**, which undergoes concerted [4+2] cycloaddition reaction with dienophile C5-C6-unsubstituted 1,4-dihydropyridines (**4**) to afford the final product *exo*-hexahydro-1*H*-chromeno[3,4-*h*][1,6]naphthyridine-3-carboxylate (**9**).

Based on literature reports,[97,100] it is also possible that the reactions may proceed *via* stepwise Mannich-like process where the first step being the electrophilic interaction of the dihydropyridine with *in situ* formed imine **A** (probably activated by coordination with the Lewis acid, $Yb(OTf)_3$, to form an intermediate **B**, which would then undergo ring closure in anti-mode *via* an intramolecular attack by the position four of the coumarin ring *via* reactive intermediate **B**, to the desired product **9** as shown in Scheme 42. The stereochemical outcome can be rationalized by considering the preferential attack of the dihydropyridine from its less hindered face and the final cyclization **B** taking place in a stereo controlled manner to yield a *exo*-hexahydro-1*H*-chromeno[3,4-*h*][1,6]naphthyridine-3-carboxylate derivatives (**9**).

Conclusion

In conclusion, synthesis of *exo*-hexahydro-1*H*-chromeno[3,4-*h*][1,6]naphthyridine-3-carboxylate was developed using 5,6-unsubstituted 1,4-dihydropyridines and 3-aminocoumarins as primary building blocks. The reaction condition is simple and transformation is quite effective for a wide range of aldehydes, 3-aminocoumarins and 5,6-unsubstituted 1,4-dihydropyridines. The products are easily isolable in good to excellent yields without aqueous work-up and chromatographic separation.

Chapter III

Experimental Section

Exploration of C5-C6-unsubstituted 1,4-dihydropyridines for the construction of exo-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylates using stereo-selective Povarov reaction

Experimental Section

General procedure for the preparation of *exo*-hexahydro-1*H*-chromeno[3,4-*h*][1,6]naphthyridine-3-carboxylate derivatives (9):

Aldehyde **7** (0.5 mmol), 3-aminocoumarin (**8**) (0.5 mmol) and 10 mol% of $Yb(OTf)_3$ (10 mol%) in 2 mL of acetonitrile were taken in a 25 mL round bottomed flask and the mixture was stirred at room temperature for 10 min. Then, dihydropyridine (**4**) (0.5 mmol) was added to the mixture, and stirred at room temperature for another 2-8 h until the reaction undergoes completion. The progress of the reaction was monitored time to time by TLC. As soon as the reaction is about to reach at its end, a solid precipitate started appearing slowly after the stipulated time. The solid precipitate was filtered off through a Büchner funnel and it was washed with 10 mL of cold hexane-ethanol mixture (1:1) to remove unreacted starting materials. Finally it was dried through a vacuum pump and the pure product hexahydro-1*H*-chromeno [3,4-*h*][1,6]naphth yridine-3-carboxylate derivative (**9a-y**) was obtained in 69-91% yield after recrystallization from acetonitrile and hexane mixture.

Crystallographic Description

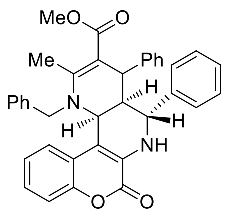
Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 296 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. Compound **9a** empirical formula '$C_{37}H_{32}N_2O_4$', colorless crystal, formula wt 568.65, monoclinic, *C* 2/*c*, a=34.741(2) Å, b = 15.2702(8) Å, c = 23.3978(12) Å, V = 12189.2(11) Å^3, Z = 16, F (0 0 0) = 4800.0, GOF(S) = 1.758. Final indices R_{obs} = 0.0861, wR_{obs} = 0.2323 with I> 2r(I); R_{all} = 0.1814, wR_{all} = 0.2479 for all data.

Table 9. Crystal data and structure refinement for **9a**.

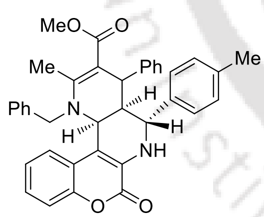
Identification code	9a
Empirical formula	$C_{37}H_{32}N_2O_4$
Formula weight	568.65
Temperature	296(2) K
Wavelength	0.71073Å
Crystal system	Monoclinic
Space group	'*C* 2/*c*'
Unit cell dimensions	a = 34.741(2)Å, b = 15.2702(8)Å c = 23.3978(12)Å α = 90º, β = 100.886(5)º,γ = 90º
Volume Z	12189.2(11)$Å^3$ 16
Density (calculated) Absorption coefficient F(000)	1.239g/cm^3 0.081mm^{-1} 4800
Theta range for data collection	1.46º to 25.50º
Index ranges Reflection collected /unique	-39≤h≤38, -9≤k≤18, -26≤l≤26 9324 / 4237 R(int) =0.0585]
Completeness to θ Refinement method	98.5% (θ = 25.50º) 'SHELXL−97(Sheldrick, 1997)'
Goodness-of-fit on F^2 Final R indices [>2sigma(I)] R indices (all data) Largest diff. peak and hole	1.758 R_{obs} = 0.0861, wR_{obs} = 0.2323 R_{all} = 0.1814, wR_{all} = 0.2479 1.373 and -0.231 e.$Å^{-3}$

Spectral data

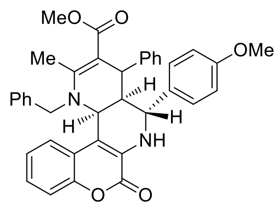
Methyl 1-benzyl-2-methyl-7-oxo-4,5-diphenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9a): White solid (0.249 g, 79%); mp 188-190 °C; R_f = 0.39 (20% ethyl acetate/hexane) ;^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50-7.40 (m, 5H), 7.29-7.24 (m, 2H), 7.22-7.09 (m, 6H), 7.02 (d, *J* = 7.2 Hz, 2H), 6.94-6.89 (m, 2H), 6.85 (d, *J* = 6.4 Hz, 2H), 5.30 (s, 1H), 4.62 (d, *J* = 2.8 Hz, 1H), 4.57 (s, 2H), 4.50 (d, *J* = 11.6 Hz, 1H), 3.83 (s, 1H), 3.46 (s, 3H), 2.70 (s, 3H), 2.13 (d, *J* = 11.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.60, 157.82, 153.86, 147.27, 146.55, 141.05, 138.90, 129.58, 129.06, 128.83, 128.49, 128.44, 127.97, 127.73, 127.00, 126.29, 125.43, 125.08, 124.28, 121.46, 120.89, 116.55, 109.99, 94.25, 55.74, 50.79, 46.72, 42.98, 39.36, 17.70 ppm; IR (KBr): ῡ = 3347 (NH), 1718 (C=O), 1681 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{37}H_{33}N_2O_4$ (M + H$^+$) 569.2440, found 569.2445.



Methyl 1-benzyl-2-methyl-7-oxo-4-phenyl-5-(p-tolyl)-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9b): White solid (0.221g, 76%); mp 154-155 °C; R_f = 0.44 (10% ethyl acetate/hexane) ;^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (d, *J* = 8.0 Hz, 2H), 7.29-7.25 (m, 4H), 7.22-7.08 (m, 6H), 7.03 (d, *J* = 7.6 Hz, 2H), 6.95-6.88 (m, 2H), 6.84 (d, *J* = 7.2 Hz, 2H), 5.27 (s, 1H), 4.61 (d, *J* = 2.8 Hz, 1H), 4.56 (s, 2H) 4.61 (d, *J* = 11.6 Hz, 1H), 3.84 (s, 1H), 3.46 (s, 3H), 2.69 (s, 3H), 2.43 (s, 3H) 2.10 (d, *J* = 16.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.56, 157.77, 153.82, 147.18, 146.62, 138.88, 138.43, 137.92, 129.68, 129.56, 128.43, 128.37, 127.80, 127.72, 126.92, 126.20, 125.28, 125.03, 124.20, 121.45, 120.81, 116.46, 109.76, 94.21, 55.39, 50.73, 46.71, 42.90, 39.34, 21.26, 17.65 ppm; IR (KBr): ῡ = 3348, 1717, 1681 cm^{-1}; HRMS (ESI) calcd for $C_{38}H_{35}N_2O_4$ (M + H$^+$) 583.2597, found 583.2598.

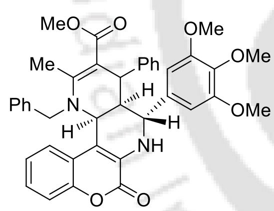


Methyl 1-benzyl-5-(4-methoxyphenyl)-2-methyl-7-oxo-4-phenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9c): White solid (0.245 g, 82%); mp 245-247 °C; R_f = 0.28 (20% ethyl acetate/hexane) ;^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 (d, *J* = 8.8 Hz, 2H), 7.29-7.25 (m, 2H), 7.24-7.14 (m, 4H), 7.12-7.08 (m, 2H),



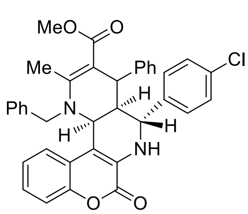
7.03 (d, *J* = 7.6 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.94-6.92 (m, 2H), 6.84 (d, *J* = 6.8 Hz, 2H), 5.26 (s, 1H), 4.61 (d, *J* = 2.4 Hz, 1H), 4.56 (s, 2H), 4.45 (d, *J* = 12.0 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 1H), 3.46 (s, 3H), 2.69 (s, 3H) 2.08 (d, *J* = 11.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.65, 159.94, 157.87, 153.85, 147.24, 146.60, 138.94, 132.85, 129.61, 129.07, 128.50, 128.44, 127.76, 126.99, 126.27, 125.36, 125.10, 124.28, 121.51, 120.89, 116.55, 114.43, 109.87, 94.26, 55.39, 55.13, 50.80, 46.79, 43.01, 39.42, 17.71 ppm; IR (KBr): ῡ = 3343, 1718, 1678 cm^{-1}; HRMS (ESI) calcd for $C_{38}H_{35}N_2O_5$ (M + H$^+$) 599.2546, found 599.2546.

Methyl 1-benzyl-2-methyl-7-oxo-4-phenyl-5-(3,4,5-trimethoxyphenyl)-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (4d): White solid (0.278 g, 86%); mp 178-180 °C; R_f = 0.15 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400



MHz) δ 7.24-7.19 (m, 2H), 7.16-7.08 (m, 4H), 7.06-7.01 (m, 2H), 6.97 (d, *J* = 7.2 Hz, 2H), 6.88-6.82 (m, 2H), 6.76 (d, *J* = 6.4 Hz, 2H), 6.58 (s, 2H), 5.24 (s, 1H), 4.53 (d, *J* = 2.8 Hz, 1H), 4.49 (d, *J* = 6.4 Hz, 2H), 4.37 (d, *J* = 11.6 Hz, 1H), 3.87-3.78 (m, 10H), 3.38 (s, 3H), 2.63 (s, 3H) 2.01 (d, *J* = 11.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.44, 157.50, 153.71, 153.52, 147.00, 146.31, 138.68, 137.94, 136.55, 129.33, 128.33, 127.66, 126.79, 126.21, 125.20, 124.85, 124.08, 121.16, 120.64, 116.20, 109.68, 104.55, 93.80, 60.80, 56.15, 55.92, 50.61, 46.47, 42.73, 39.21, 17.52 ppm; IR (KBr): ῡ = 3350, 1716, 1682 cm^{-1}; HRMS (ESI) calcd for $C_{40}H_{39}N_2O_7$ (M + H$^+$) 659.2757, found 659.2813.

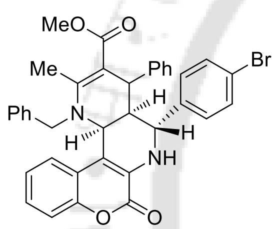
Methyl 1-benzyl-5-(4-chlorophenyl)-2-methyl-7-oxo-4-phenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (4e):



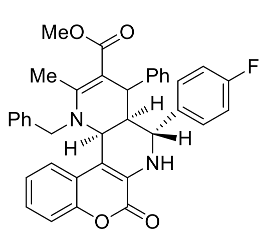
White solid (0.232 g, 77%); mp 238-239 °C; R_f = 0.39 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46-7.39 (m, 4H), 7.30-7.26 (m, 2H), 7.22-7.10 (m, 6H), 7.03 (d, *J* = 7.6

Hz, 2H), 6.94-6.88 (m, 2H), 6.83 (d, *J* = 7.2 Hz, 2H), 5.26 (s, 2H), 4.62-4.55 (m, 3H), 4.50 (d, *J* = 11.2 Hz, 1H) 3.80 (s, 1H), 3.47 (s, 3H), 2.70 (s, 3H), 2.09 (d, *J* = 11.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.39, 157.63, 153.75, 147.23, 146.23, 139.66, 138.75, 134.43, 129.35, 129.30 , 129.17, 128.45, 127.69, 126.97, 126.37, 125.52, 124.98, 124.24, 121.23, 120.86, 116.47, 110.19, 94.06, 55.09, 50.79, 50.72, 46.55, 42.92, 39.32, 17.64 ppm; IR (KBr): ῡ = 3358, 1718, 1678 cm^{-1}; HRMS (ESI) calcd for $C_{37}H_{32}ClN_2O_4$ (M + H$^+$) 603.2051, found 603.2062.

Methyl1-benzyl-5-(4-bromophenyl)-2-methyl-7-oxo-4-phenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (4f): White solid (0.262 g, 81%); mp 251-252 °C; R_f = 0.41(20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.30-7.26 (m, 2H), 7.22-7.10 (m, 6H), 7.02 (d, *J* = 7.6, 2H), 6.96-6.92 (m, 2H), 6.82 (d, *J* = 6.8 Hz, 2H), 5.24 (s, 1H), 4.61 (d, *J* = 2.4 Hz, 1H), 4.55 (d, *J* = 4.0 Hz, 2H), 4.48 (d, *J* = 11.6 Hz, 1H), 3.80 (s, 1H), 3.47 (s, 3H), 2.69 (s, 3H), 2.07 (d, *J* = 11.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.46, 157.70, 153.80, 147.30, 146.22, 140.22, 138.77, 132.19, 129.66, 129.30, 128.50, 127.72, 127.04, 126.42, 125.62, 125.03, 124.31, 122.69, 121.26, 120.91, 116.56, 110.28, 94.10, 55.21, 50.88, 50.77, 46.58, 42.93, 39.35, 17.70 ppm; IR (KBr): ῡ = 3347, 1716, 1681 cm^{-1}; HRMS (ESI) calcd for $C_{37}H_{32}BrN_2O_4$ (M + H$^+$) 647.1545, 649.1525, found 647.1558, 649.1534.

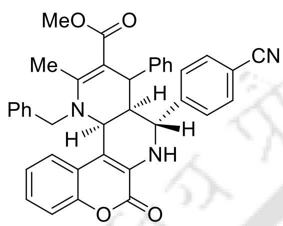


Methyl 1-benzyl-5-(4-fluorophenyl)-2-methyl-7-oxo-4-phenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (4g): White solid (0.255 g, 87%); mp 159-160 °C; R_f = 0.37 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 (dd, *J* = 5.2, 3.6 Hz, 2H), 7.24-7.18 (m, 2H), 7.16-7.05 (m, 6H), 7.05-7.02 (m, 2H), 6.94 (d, *J* = 7.6 Hz, 2H), 6.89-6.82 (m, 2H), 6.76 (d, *J* = 6.8 Hz, 2H), 5.18 (s, 1H), 4.54 (d, *J* = 2.4 Hz, 1H), 4.48 (d, *J* = 4.0 Hz, 2H), 4.42 (d, *J* = 12.0 Hz, 1H), 3.71 (s, 1H), 3.39 (s, 3H), 2.61 (s, 3H), 2.00 (d, *J* = 12 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.51, 157.77, 153.82, 147.30, 146.37, 138.84, 136.85, 129.68, 129.59, 129.47, 128.50, 127.72, 127.03, 126.39, 125.57, 125.06, 124.31, 121.35, 120.93, 116.55, 116.12, 115.90,



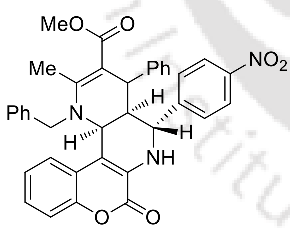
110.19, 94.13, 55.07, 50.83, 50.78, 46.66, 43.06, 39.37, 17.69 ppm; IR (KBr): ῡ = 3351, 1721, 1682 cm^{-1}; HRMS (ESI) calcd for $C_{37}H_{32}FN_2O_4$ $(M + H^+)$ 587.2346, found 587.2349.

Methyl 1-benzyl-5-(4-cyanophenyl)-2-methyl-7-oxo-4-phenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (4h): Pale-yellow solid (0.261 g, 88%); mp 245-246 °C; R_f =0.24 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.23-7.19 (m, 2H), 7.15-7.04 (m, 6H), 6.91



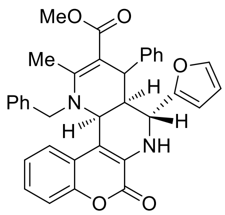
(d, *J* = 7.6 Hz, 2H), 6.9-6.82 (m, 2H), 6.73 (d, *J* = 6.4 Hz, 2H), 5.19 (s, 1H), 4.56 (d, *J* = 2.4 Hz, 1H) 4.52-4.46 (m, 3H), 3.67 (s, 1H), 3.41 (s, 3H), 2.62 (s, 3H), 2.03 (d, *J* = 11.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.42, 157.73, 153.85, 147.48, 146.78, 145.85, 138.69, 132.90, 129.26, 128.89, 128.65, 128.60, 127.70, 127.18, 126.66, 126.03, 125.05, 124.48, 121.13, 121.04, 118.56, 116.71, 112.88, 110.88, 94.10, 55.59, 51.01, 50.86, 46.53, 43.09, 39.43, 17.77 ppm; IR (KBr): ῡ = 3345, 2227, 1717, 1682 cm^{-1}; HRMS (ESI) calcd for $C_{38}H_{32}N_3O_4$ $(M + H^+)$ 594.2393, found 594.2394.

Methyl 1-benzyl-2-methyl-5-(4-nitrophenyl)-7-oxo-4-phenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9i): Yellow solid (0.279 g, 91%); mp 277-279 °C; R_f = 0.31 (20% ethyl acetate/hexane) ;^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.28-7.22 (m, 2H), 7.21-7.11 (m, 6H), 6.97-6.93



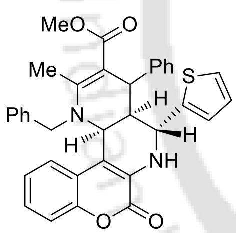
(m, 4H), 6.78 (d, *J* = 6.0 Hz, 2H), 5.26 (s, 1H), 4.63 (d, *J* = 2.8 Hz, 1H), 4.62 (s, 1H) 4.53 (d, *J* = 8.8 Hz, 2H), 3.73 (s, 1H), 3.46 (s, 3H), 2.68 (s, 3H), 2.10 (d, *J* = 11.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.31, 157.59, 153.83, 148.80, 148.23, 147.36, 145.76, 128.63, 129.13, 129.02, 128.57, 127.66, 127.09, 126.60, 125.93, 124.98, 124.40, 124.19, 120.99, 116.55, 110.85, 93.94, 55.24, 50.94, 50.78, 46.43, 43.04, 39.38, 17.71 ppm; IR (KBr): ῡ = 3336 (NH), 1716 (C=O), 1683 (C=O), 1519 (NO_2), 1345 (NO_2) cm^{-1}; HRMS (ESI) calcd for $C_{37}H_{32}N_3O_6$ $(M + H^+)$ 614.2291, found 614.2291.

Methyl 1-benzyl-5-(furan-2-yl)-2-methyl-7-oxo-4-phenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9j): Light-brown solid (0.211 g, 72%); mp 126-128 °C; R_f = 0.36 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (s, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.20-7.03 (m, 9H), 6.96-6.82 (m, 2H), 6.77 (d, *J* = 6.8 Hz, 2H),



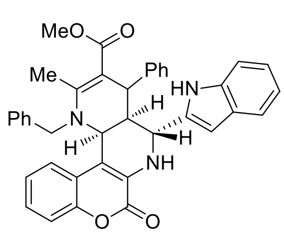
6.46 (s, 1H), 6.40 (s, 1H), 5.14 (s, 1H), 4.58-4.47 (m, 4H), 3.84 (s, 1H), 3.40 (s, 3H), 2.60 (s, 3H) 2.03 (d, *J* = 11.6 Hz, 1H) ppml; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.45, 157.56, 153.62, 152.57, 147.23, 146.44, 143.01, 138.70, 129.02, 128.41, 127.70, 126.90, 126.27, 125.46, 124.95, 124.16, 121.09, 120.77, 116.39, 110.62, 110.24, 109.76, 94.52, 50.70, 50.65, 49.31, 46.38, 39.96, 17.61 ppm; IR (KBr): ῡ = 3347, 1718, 1676 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{31}N_2O_5$ (M + H$^+$) 559.2233, found 559.2228.

Methyl 1-benzyl-2-methyl-7-oxo-4-phenyl-5-(thiophen-2-yl)-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9k): White solid (0.212 g, 74%); mp 187-188 °C; R_f = 0.22 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, *J* = 4.8 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22-7.06 (m, 10H), 6.91 (d, *J* = 7.2 Hz, 2H), 6.83



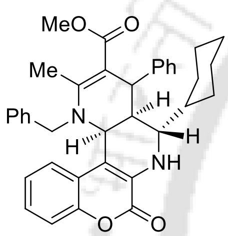
(d, *J* = 6.8 Hz, 2H), 5.37 (s, 2H), 4.83 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 2.0 Hz, 1H), 4.54 (s, 2H), 3.97 (s, 1H), 3.46 (s, 3H), 2.68 (s, 3H) 2.18 (d, *J* = 11.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.64, 157.71, 153.84, 147.43, 146.43, 144.47, 138.85, 129.00, 128.56, 127.86, 127.56, 127.10, 126.44, 126.19, 125.74, 125.11, 124.36, 121.28, 121.01, 116.62, 110.40, 94.33, 51.54, 50.90, 50.77, 46.65, 43.94, 39.71, 17.74 ppm; IR (KBr): ῡ = 3343, 1716, 1681 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{31}N_2O_4S$ (M + H$^+$) 575.2005, found 575.1998.

Methyl 1-benzyl-5-(1H-indol-3-yl)-2-methyl-7-oxo-4-phenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9l): White solid (0.209 g, 69%);



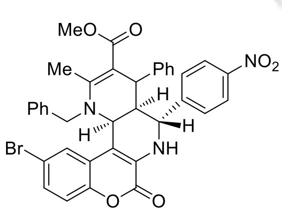
mp 244-246 °C; R_f = 0.52 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 2.0 Hz, 1H) 7.26-7.17 (m, 7H), 7.14-7.08 (m, 3H), 6.97 (d, *J* = 7.2 Hz, 3H), 6.88 (d, *J* = 6.8 Hz, 3H), 5.39 (s, 1H), 4.83 (d, *J* = 11.6 Hz, 1H), 4.67 (d, *J* = 2.0 Hz, 1H), 4.60 (s, 2H), 3.93 (s, 1H), 3.39 (s, 3H), 2.72 (s, 3H), 2.50 (d, *J* = 11.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 170.04, 158.09, 154.28, 147.39, 146.92, 139.09, 137.13, 129.86, 128.67, 128.51, 127.97, 127.14, 126.25, 125.71, 125.46, 125.26, 124.42, 124.13, 122.78, 121.78, 121.02, 120.20, 119.76, 116.74, 115.12, 111.87, 110.06, 94.45, 50.99, 50.89, 49.21, 47.16, 41.25, 40.13, 17.89 ppm; IR (KBr): ῡ = 3339, 1716, 1680 cm^{-1}; HRMS (ESI) calcd for $C_{39}H_{34}N_3O_4$ (M + H$^+$) 608.2549, found 608.2544.

Methyl 1-benzyl-5-cyclohexyl-2-methyl-7-oxo-4-phenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9m): White solid (0.206 g, 72%); mp 213-214 °C; R_f = 0.32 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41-7.22 (m, 5H), 7.21-7.08 (m, 4H), 7.10-7.02 (m, 1H), 6.92-6.73 (m, 4H), 5.29 (s, 1H), 5.04 (s, 1H),



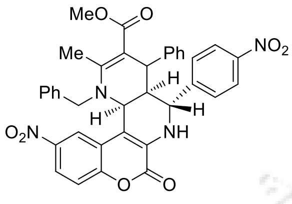
), 4.59 (s, 1H), 4.47 (s, 2H), 4.27 (s, 1H), 3.55 (s, 3H), 3.39 (d, *J* = 10.4 Hz, 1H), 2.62 (s, 3H), 2.01-1.87 (m, 4H), 1.85-1.68 (m, 3H), 1.54-1.42 (m, 3H), 1.24-1.20 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.83, 158.21, 154.57, 147.27, 146.98, 138.92, 130.20, 128.72, 128.55, 128.03, 127.10, 126.51, 125.31, 125.22, 124.38, 121.60, 120.75, 116.65, 110.02, 94.18, 54.01, 51.09, 50.85, 47.09, 39.54, 38.97, 37.32, 31.17, 29.87, 26.97, 26.54, 26.39, 25.08, 17.87 ppm; IR (KBr): ῡ =3338, 1718, 1684 cm^{-1}; HRMS (ESI) calcd for $C_{37}H_{39}N_2O_4$ (M + H$^+$) 575.2910, found 575.2912.

Methyl 1-benzyl-11-bromo-2-methyl-5-(4-nitrophenyl)-7-oxo-4-phenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9n): Yellow solid (0.273 g, 79%); mp 243-245 °C; R_f = 0.31 (20% ethyl acetate/hexane); ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.35 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.32-7.18 (m, 7H), 7.05 (d, *J* = 8.4



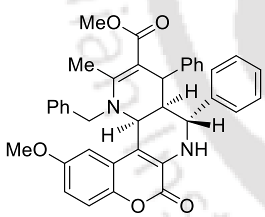
Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 3H), 6.85 (d, *J* = 6.8 Hz, 2H), 5.34 (s, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.55 (s, 2H), 4.53 (d, *J* = 2.8 Hz, 1H), 3.75 (s, 1H), 3.48 (s, 3H), 2.71 (s, 3H), 2.13 (d, *J* = 12 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): *δ* 169.56, 157.58, 154.05, 149.03, 148.92, 146.72, 146.26, 139.14, 130.45, 129.61, 129.18, 129.11, 129.02, 128.21, 127.78, 127.12, 125.41, 124.73, 124.00, 123.63, 118.64, 117.94, 110.00, 94.64, 55.80, 53.46, 51.23, 47.01, 43.59, 39.86, 17.98 ppm; IR (KBr): ῡ = 3362, 1718, 1678 cm^{-1}; HRMS (ESI) calcd for $C_{37}H_{31}BrN_3O_6$ (M + H$^+$) 694.1371, found 694.1366.

Methyl 1-benzyl-2-methyl-11-nitro-5-(4-nitrophenyl)-7-oxo-4-phenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9o): Yellow solid (0.277 g, 84%); mp 276-279 °C; R_f = 0.23(20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.35 (d, *J* = 8.8 Hz, 2H), 7.94 (dd, *J* = 8.8 Hz, 2.8 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.34-7.28 (m, 3H), 7.22-7.14 (m, 4H), 7.03 (d, *J* = 7.6 Hz, 2H), 6.83 (d, *J* = 7.2 Hz, 3H), 5.58



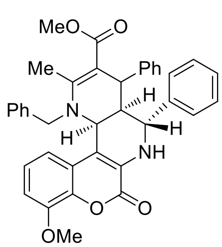
(s, 1H), 4.68 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 2.4 Hz, 1H), 4.53 (s, 2H), 3.77 (s, 1H), 3.47 (s, 3H), 2.70 (s, 3H), 2.17 (d, *J* = 11.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + CF_3COOH): *δ* 192.25, 169.41, 157.30, 150.44, 148.91, 145.46, 142.54, 137.03, 133.89, 130.77, 130.23, 130.00, 129.61, 129.27, 127.50, 127.44, 124.59, 122.73, 120.99, 118.86, 117.63, 101.71, 59.77, 57.91, 57.67, 56.44, 54.44, 44.86, 23.92 ppm; IR (KBr): ῡ = 3355, 1734, 1675, 1522, 1341 cm^{-1} HRMS (ESI) calcd for $C_{37}H_{31}N_4O_8$ (M + H$^+$) 659.2142, found 659.2158 .

Methyl 1-benzyl-11-methoxy-2-methyl-7-oxo-4,5-diphenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9p): White solid (0.242 g, 81%); mp 164-166 °C; R_f = 0.25 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54-7.42 (m, 5H), 7.28-7.18 (m, 6H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.06-7.04 (m, 2H), 7.02-6.94 (m,



2H), 6.67 (d, *J* = 7.2 Hz, 1H), 6.34 (s, 1H), 5.38 (s, 1H), 4.67-4.56 (m, 3H), 4.49 (d, *J* = 11.2 Hz, 1H), 3.84 (s, 1H), 3.46 (s, 3H), 3.31 (s, 3H), 2.68 (s, 3H), 2.16 (d, *J* = 10.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.76, 158.15, 156.22, 154.12, 146.42, 141.74, 141.02, 138.27, 129.92, 129.20, 128.99, 128.83, 128.53, 128.07, 127.85, 127.17, 126.48, 125.18, 122.37, 117.66, 112.62, 109.96, 104.44, 94.43, 55.79, 55.38, 50.96, 50.74, 47.16, 43.09, 39.36, 17.63 ppm; IR (KBr): ῡ = 3345, 1714, 1684 cm^{-1}; HRMS (ESI) calcd for $C_{38}H_{35}N_2O_5$ (M + H$^+$) 599.2546, found 599.2547.

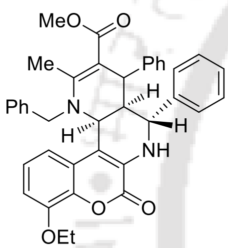
Methyl 1-benzyl-9-methoxy-2-methyl-7-oxo-4,5-diphenyl-4,4a,5,6,7,12c-hexahydro-1H-



chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9q): White solid (0.236 g, 79%); mp 215-217 °C; R_f = 0.23 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46-7.38 (m, 5H), 7.35-7.10 (m, 6H), 7.01 (d, *J* = 5.2 Hz, 2H), 6.90-6.78 (m, 3H), 6.70 (d, *J* = 7.2, 1H), 6.59-

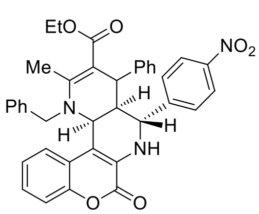
6.48 (m, 1H), 5.32 (s, 1H), 4.62-4.54 (m, 3H), 4.48 (d, *J* = 10.8, 1H), 3.88 (s, 3H), 3.82 (s, 1H), 3.44 (s, 3H), 2.68 (s, 3H), 2.12 (d, *J* = 11.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.77, 157.47, 154.09, 147.42, 146.67, 141.05, 139.09, 136.88, 129.91, 129.18, 128.95, 128.62, 128.54, 128.09, 127.85, 127.12, 126.38, 125.21, 124.18, 122.45, 113.04, 110.15, 108.27, 94.32, 56.33, 55.82, 50.93, 50.90, 47.14, 43.05, 39.44, 17.83 ppm; IR (KBr): ῡ = 3347, 1716, 1684 cm^{-1}; HRMS (ESI) calcd for $C_{38}H_{35}N_2O_5$ (M + H$^+$) 599.2546, found 599.2544.

Methyl 1-benzyl-9-ethoxy-2-methyl-7-oxo-4,5-diphenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9r): White solid (0.232 g, 76%); mp 169-170 °C; R_f = 0.22 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47-7.37 (m, 5H), 7.23 (t, *J* =7.4 Hz, 2H), 7.20-7.12 (m, 4H), 7.0 (d, *J* = 7.4 Hz, 2H), 6.85 (d, *J* = 7.5



Hz, 2H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 6.52 (d, *J* = 7.4 Hz, 1H), 5.31 (s, 1H), 4.52-4.50 (m, 3H), 4.47 (d, *J* = 11.2 Hz, 1H), 4.24-4.12 (m, 2H) 3.80 (s, 3H), 3.79 (s, 1H), 2.66 (s, 3H), 2.11 (d, *J* = 11.2 Hz, 1H), 1.43 (t, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.78, 157.67, 154.13, 146.74, 146.69, 141.11, 139.13, 137.21, 129.85, 129.18, 128.94, 128.63, 128.54, 128.10, 127.85, 127.11, 126.38, 125.23, 124.16, 122.52, 112.99, 110.27, 109.73, 94.33, 65.04, 55.82, 50.93, 50.89, 47.14, 43.09, 39.46, 17.83, 14.98 ppm; IR (KBr): ῡ = 3347, 1716, 1684 cm^{-1}; HRMS (ESI) calcd for $C_{39}H_{37}N_2O_5$ (M + H$^+$) 613.2702, found 613.2702.

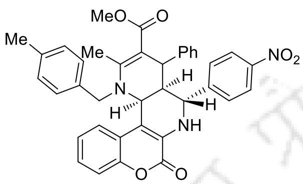
Ethyl 1-benzyl-2-methyl-5-(4-nitrophenyl)-7-oxo-4-phenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9t): Orange solid (0.276 g, 88%); mp 227-228 °C; R_f = 0.32 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (d,



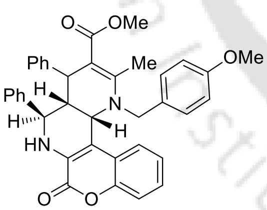
J = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.29-7.24 (m, 2H), 7.22-7.12 (m, 6H), 6.97 (d, *J* = 7.2 Hz, 4H), 6.81 (d, *J* = 6.4 Hz, 2H), 5.29 (s, 1H), 4.67-4.62 (m, 2H), 4.56 (d, *J* = 2.8 Hz, 2H), 4.02-3.90 (m, 2H), 3.78 (s, 1H), 2.70 (s, 3H), 2.12 (d, *J* = 11.2 Hz, 1H), 0.94 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.86, 157.74, 153.62, 148.96, 148.36, 147.51, 145.95, 138.78, 129.21, 129.11, 128.62, 127.74, 127.20, 126.63, 126.09, 125.08, 124.52, 124.23, 121.11, 116.72, 111.06, 94.56, 59.29, 55.37, 50.83, 46.46, 43.20, 39.54, 17.73, 14.39 ppm; IR

(KBr): ῡ = 3347, 1716, 1680, 1519, 1345 cm^{-1}; HRMS (ESI) calcd for $C_{38}H_{34}N_3O_6$ $(M + H^+)$ 628.2448, found 628.2439.

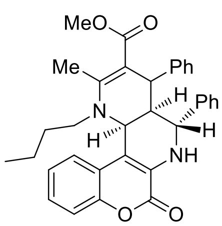
Methyl 2-methyl-1-(4-methylbenzyl)-5-(4-nitrophenyl)-7-oxo-4-phenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9u): Yellow solid (0.285 g, 91%); mp 226-228 °C; R_f = 0.29 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 7.2 Hz, 2H), 7.18 (t, *J* = 8.0 Hz, 3H), 7.12-6.84 (m, 6H), 6.71 (d, *J* = 7.2 Hz, 2H), 5.29 (s, 1H), 4.65-4.61 (s, 2H), 4.52 (s, 2H), 3.74 (s, 1H), 3.48 (s, 3H), 2.70 (s, 3H), 2.29 (s, 3H), 2.16 (d, *J* = 11.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.49, 157.85, 154.13, 148.87, 148.43, 147.56, 145.83, 136.89, 135.59, 129.35, 129.23, 129.09, 128.72, 127.75, 126.73, 126.17, 125.09, 124.59, 124.39, 121.20, 116.82, 111.18, 93.90, 55.35, 51.13, 50.68, 46.53, 43.27, 39.46, 21.15, 17.83 ppm; IR (KBr): ῡ = 3343, 1718, 1684, 1514, 1344 cm^{-1}; HRMS (ESI) calcd for $C_{38}H_{34}N_3O_6$ $(M + H^+)$ 628.2448, found 628.2446.



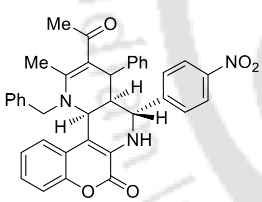
Methyl 1-(4-methoxybenzyl)-2-methyl-7-oxo-4,5-diphenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9v): White solid (0.252 g, 84%); mp 230-231 °C; R_f = 0.24 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51-7.39 (m, 5H), 7.31-7.22 (m, 2H), 7.14 (t, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.96-6.88 (m, 2H), 6.82-6.70 (m, 4H), 5.31 (s, 1H), 4.60 (s, 1H), 4.56-4.40 (m, 3H), 3.81 (s, 1H), 3.77 (s, 3H), 3.44 (s, 3H), 2.69 (s, 3H), 2.12 (d, *J* = 11.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.73, 158.64, 158.05, 154.11, 147.34, 146.62, 141.09, 130.87, 129.57, 129.15, 128.91, 128.50, 128.04, 127.79, 126.36, 125.55, 124.38, 121.54, 121.06, 116.66, 114.07, 110.24, 94.25, 55.80, 55.49, 50.88, 50.30, 46.76, 43.06, 39.39, 17.45 ppm; IR (KBr): ῡ = 3340, 1717, 1679 cm^{-1}; HRMS (ESI) calcd for $C_{38}H_{35}N_2O_5$ $(M + H^+)$ 599.2546, found 599.2517.



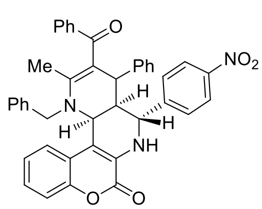
Methyl 1-butyl-2-methyl-7-oxo-4,5-diphenyl-4,4a,5,6,7,12c-hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylate (9w): White solid (0.209 g, 78%); mp 216-217 °C; R_f = 0.26 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52-7.38 (m, 5H), 7.36-7.20 (m, 6H), 7.16-7.12 (m, 1H), 6.92 (d, J = 6.8 Hz, 2H), 5.39 (s, 1H), 4.53 (s, 1H), 4.32 (d, J = 11.6 Hz, 1H), 3.69 (s, 1H), 3.40 (s, 3H), 3.28-3.12 (m, 2H), 2.68 (s, 3H), 2.02 (d, J = 12.0 Hz, 1H), 1.69-1.60 (m, 2H), 1.08-0.94 (m, 2H), 0.69-0.65 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.71, 158.42, 154.01, 147.46, 147.01, 141.01, 129.78, 129.19, 128.94, 128.48, 128.08, 127.76, 126.31, 125.86, 124.93, 122.09, 120.79, 117.08, 110.89, 94.62, 55.73, 55.79, 47.41, 46.28, 43.12, 39.39, 32.89, 19.89, 17.29, 13.54 ppm; IR (KBr): $\bar{\upsilon}$ = 3351, 1720, 1679 cm^{-1}; HRMS (ESI) calcd for $C_{34}H_{35}N_2O_4$ (M + H^+) 535.2597, found 535.2597.



3-Acetyl-1-benzyl-2-methyl-5-(4-nitrophenyl)-4-phenyl-4,4a,5,6-tetrahydro-1H-chromeno[3,4-h][1,6]naphthyridin-7(12cH)-one (9x): Brown solid (0.227 g, 76%); mp 167-170 °C; R_f = 0.12 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.8 Hz, 2H), 7.33 (t, J =7.6, 2H), 7.27-7.16 (m, 6H), 7.02-6.97 (m, 4H), 6.97 (d, J = 6.8 Hz, 2H), 5.33 (s, 1H), 4.67-4.57 (m, 4H), 3.51 (s, 1H), 2.71 (s, 3H), 2.21 (d, J = 11.2 Hz, 1H), 1.84 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.56, 157.61, 154.56, 148.64, 148.56, 147.55, 145.07, 138.30, 129.34, 129.09 (2 C), 129.02, 128.66, 128.00, 127.32, 126.24, 125.05, 124.59, 124.52, 121.06, 121.01, 116.80, 110.67, 103.53, 55.24, 50.95, 46.66, 43.43, 41.20, 29.66, 18.52 ppm; IR (KBr): $\bar{\upsilon}$ = 3345, 1718, 1624, 1520, 1344 cm^{-1}; HRMS (ESI) calcd for $C_{37}H_{32}N_3O_5$ (M + H^+) 598.2342, found 598.2374.

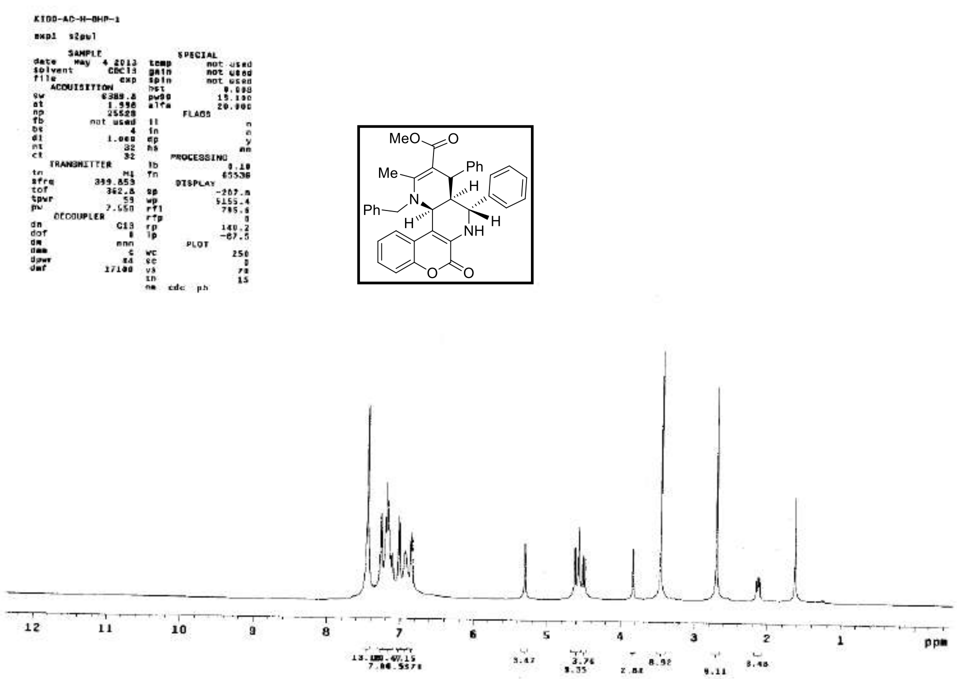


3-Benzoyl-1-benzyl-2-methyl-5-(4-nitrophenyl)-4-phenyl-4,4a,5,6-tetrahydro-1H-chromeno[3,4-h][1,6]naphthyridin-7(12cH)-one (9y): Pale-yellow solid (0.240 g, 73%); mp 295-297 °C; R_f = 0.19 (20% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 7.2 Hz, 2H), 7.28-7.32 (m, 1H), 7.28-7.09 (m, 11H), 6.99 (d, J = 7.6 Hz, 3H), 6.88 (d, J = 6.8 Hz, 2H), 5.27 (s, 1H), 4.87 (s, 1H), 4.67-4.49 (m, 3H), 3.90 (s, 1H), 2.23-2.16 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$):

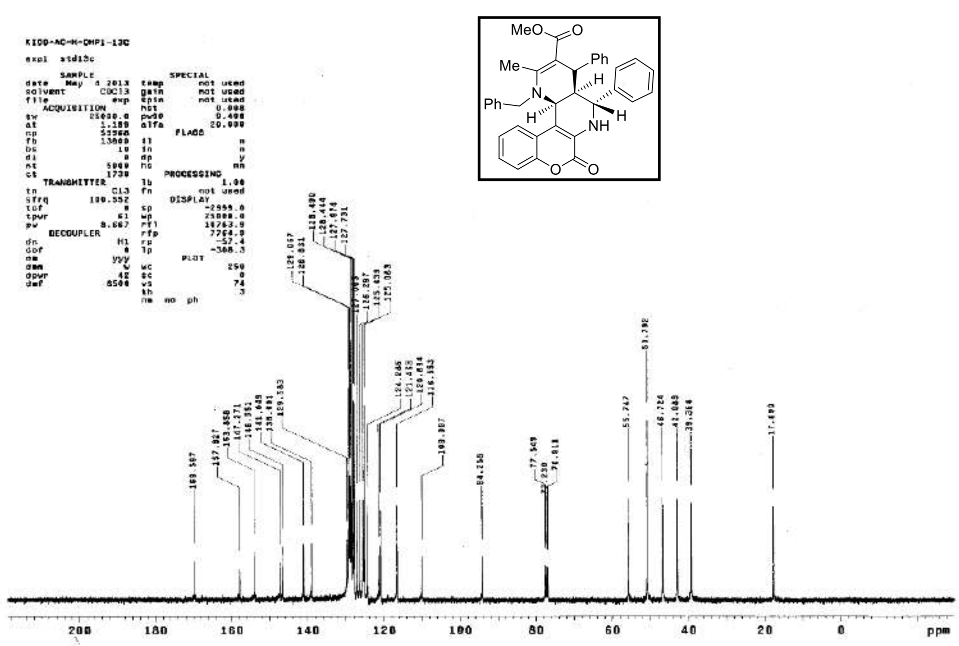


δ 197.34, 157.73, 152.34, 148.46, 147.65, 145.63, 142.77, 138.82, 130.78, 129.37, 128.84, 128.28, 128.09, 127.47, 126.94, 126.28, 125.14, 124.71, 124.51, 121.10, 116.94, 110.79, 106.94, 55.44, 50.83, 46.88, 43.60, 40.85, 20.70 ppm; IR (KBr): $\bar{\upsilon}$ = 3339, 1715, 1622, 1517, 1346 cm^{-1}; HRMS (ESI) calcd for $C_{42}H_{34}N_3O_5$ ($M + H^+$) 660.2498, found 660.2492.

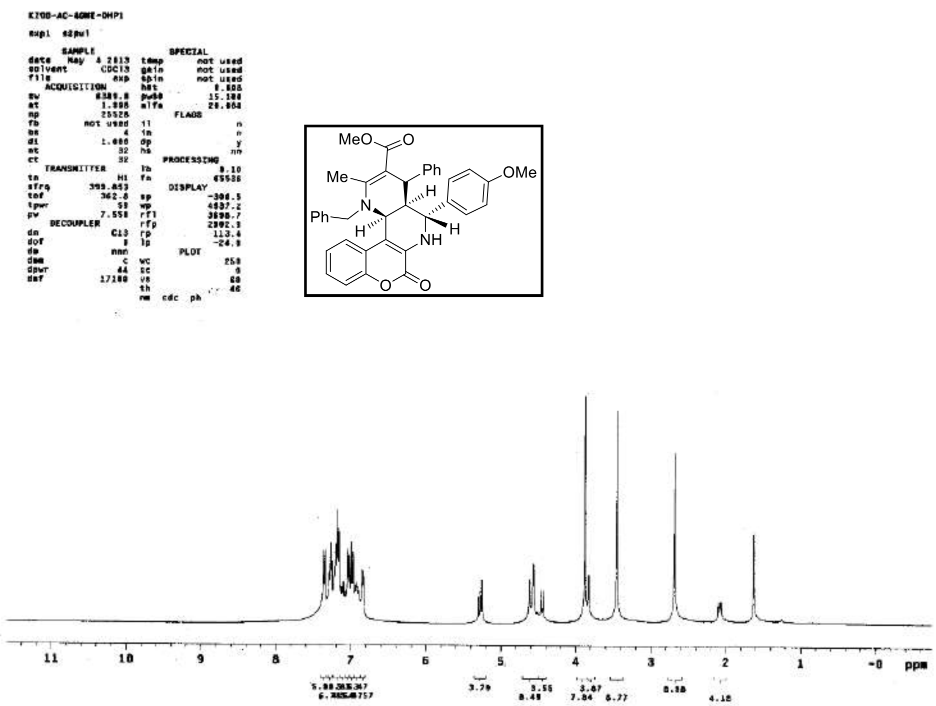
[1]H NMR spectra of 9a



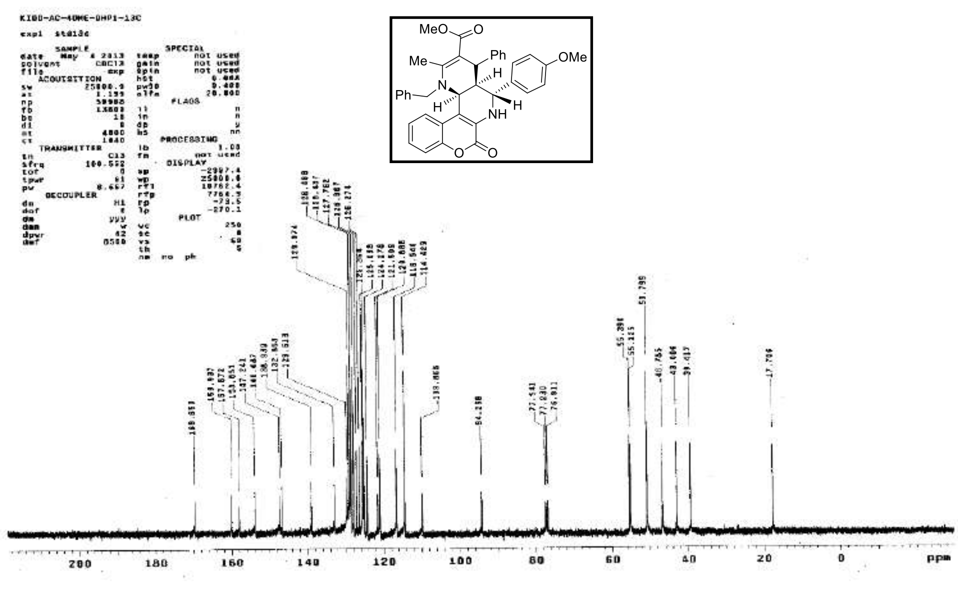
[13]C NMR spectra of 9a



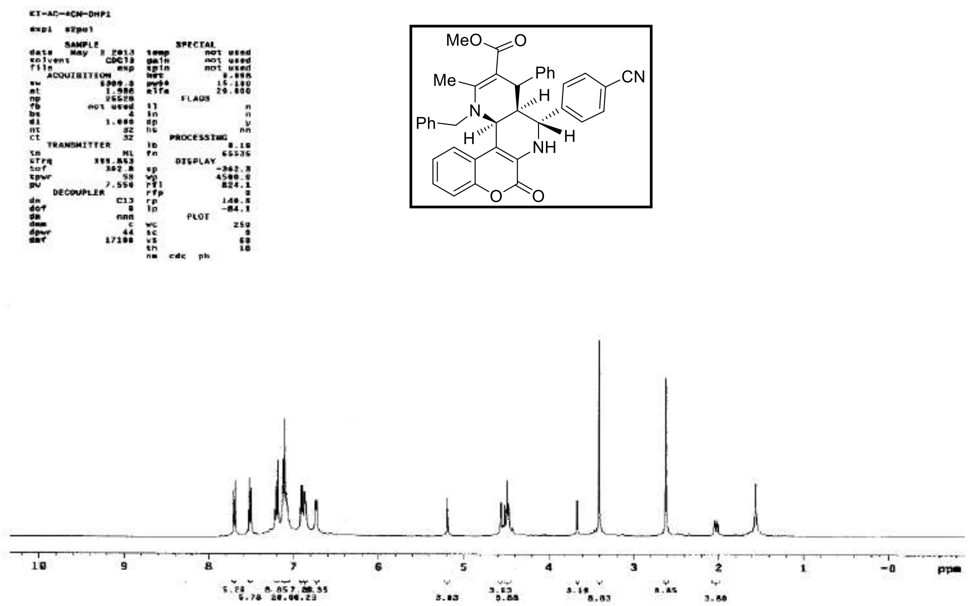
[1]H NMR spectra of 9c



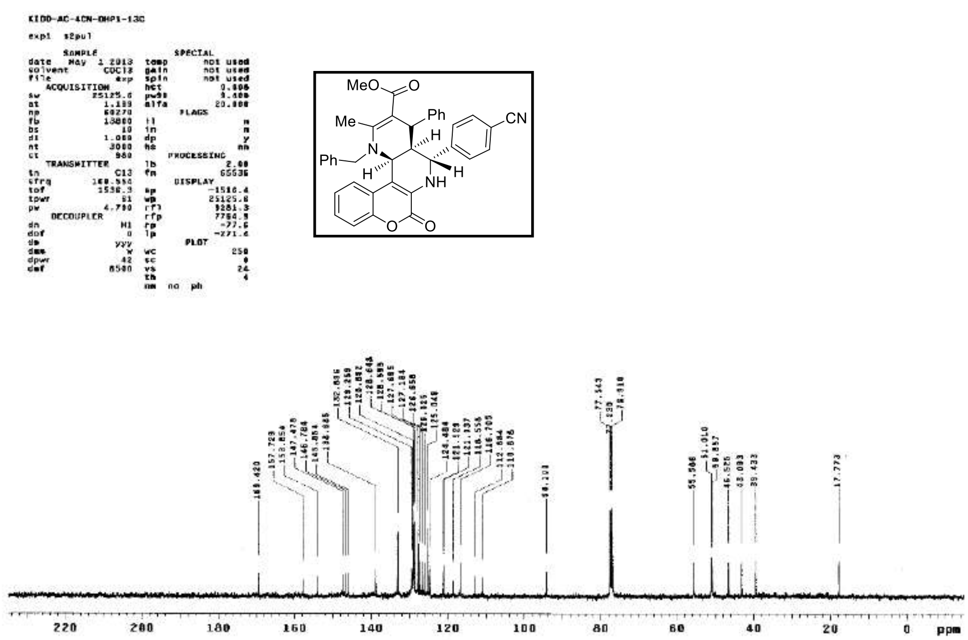
[13]C NMR spectra of 9c



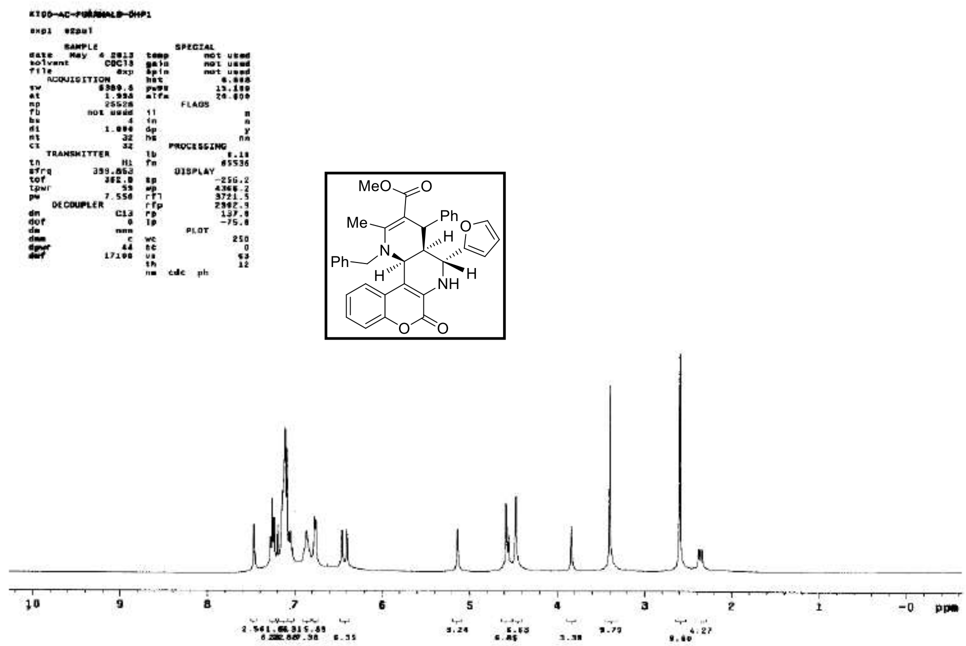
^{1}H NMR spectra of 9h



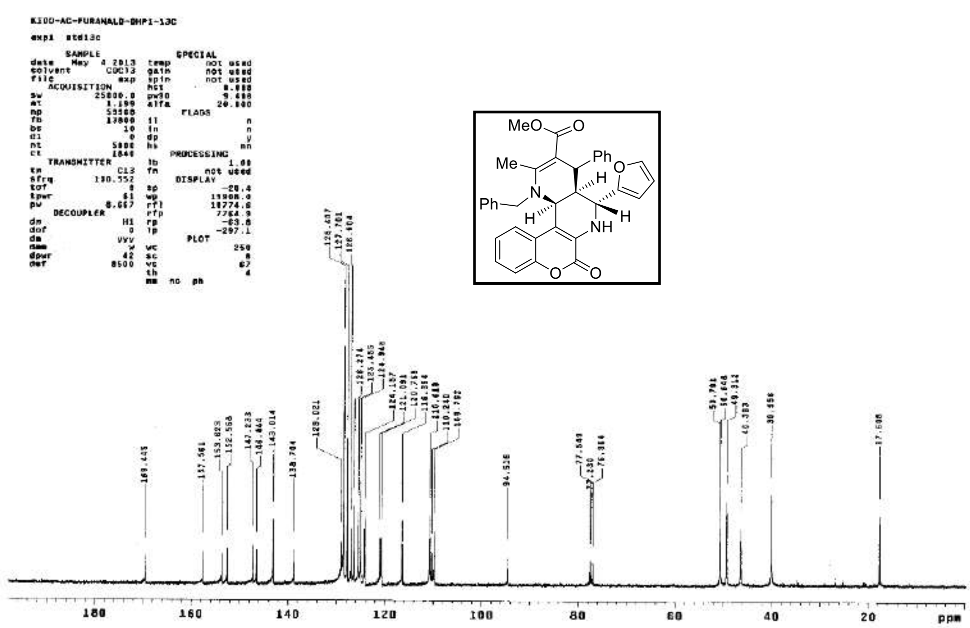
^{13}C NMR spectra of 9h



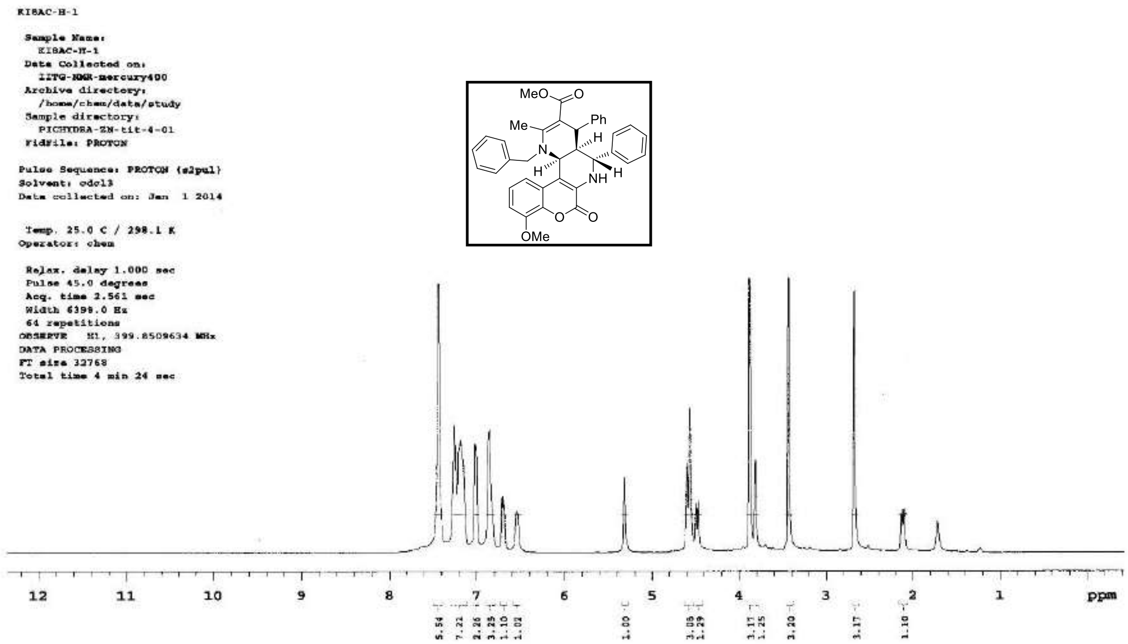
[1]H NMR spectra of 9j



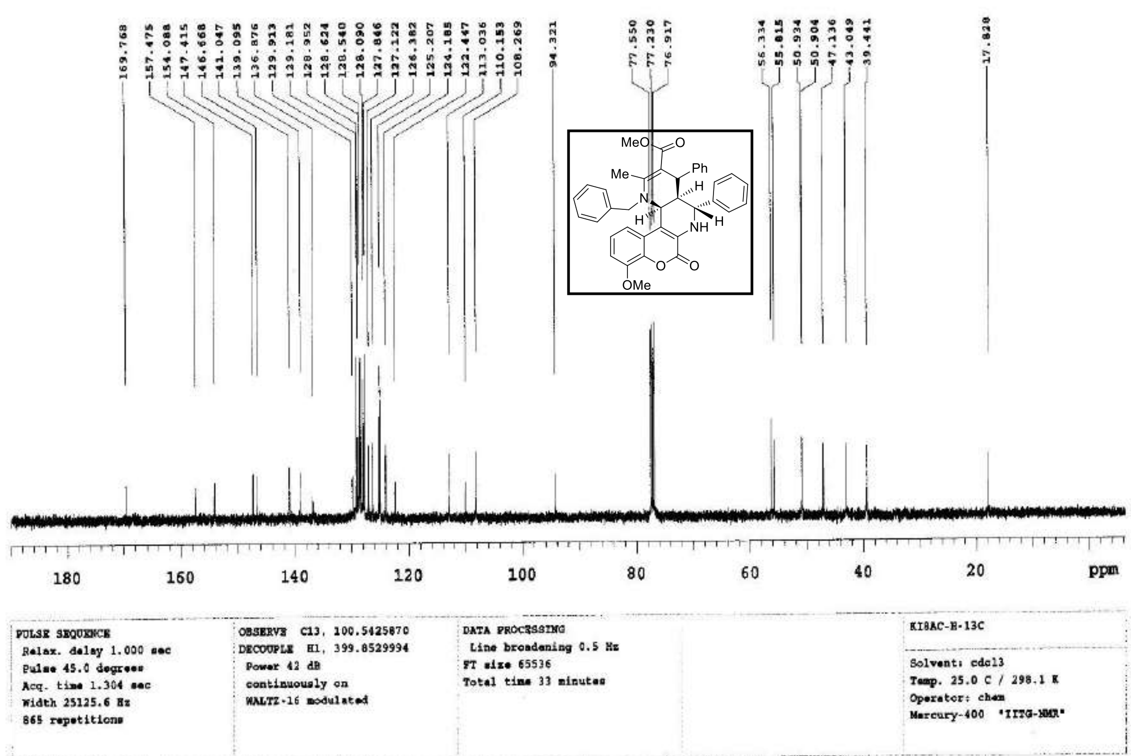
[13]C NMR spectra of 9j



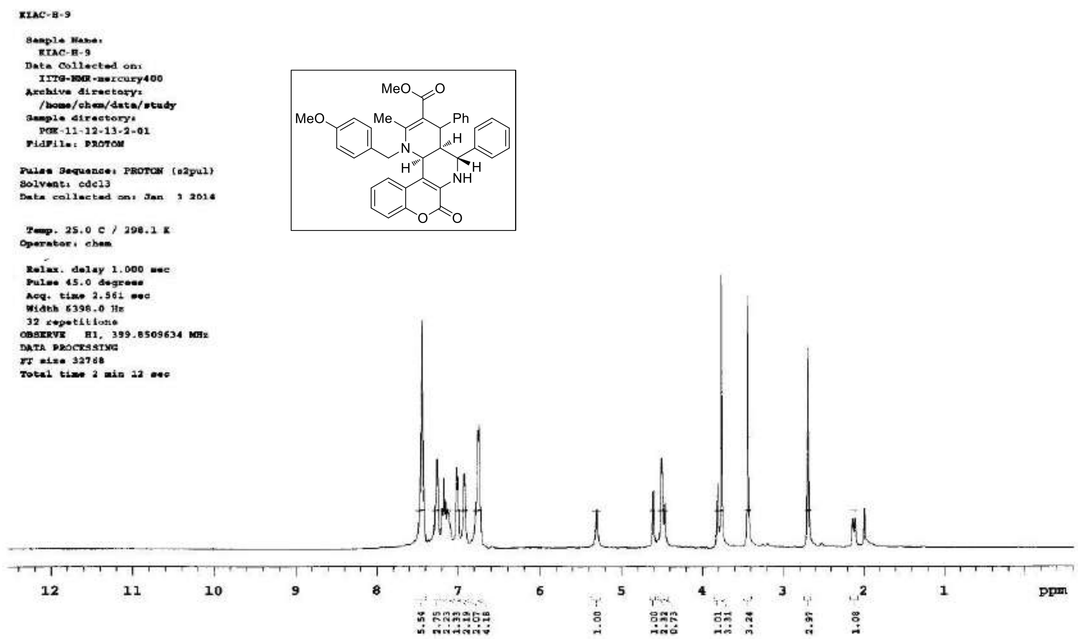
^{1}H NMR spectra of 9q



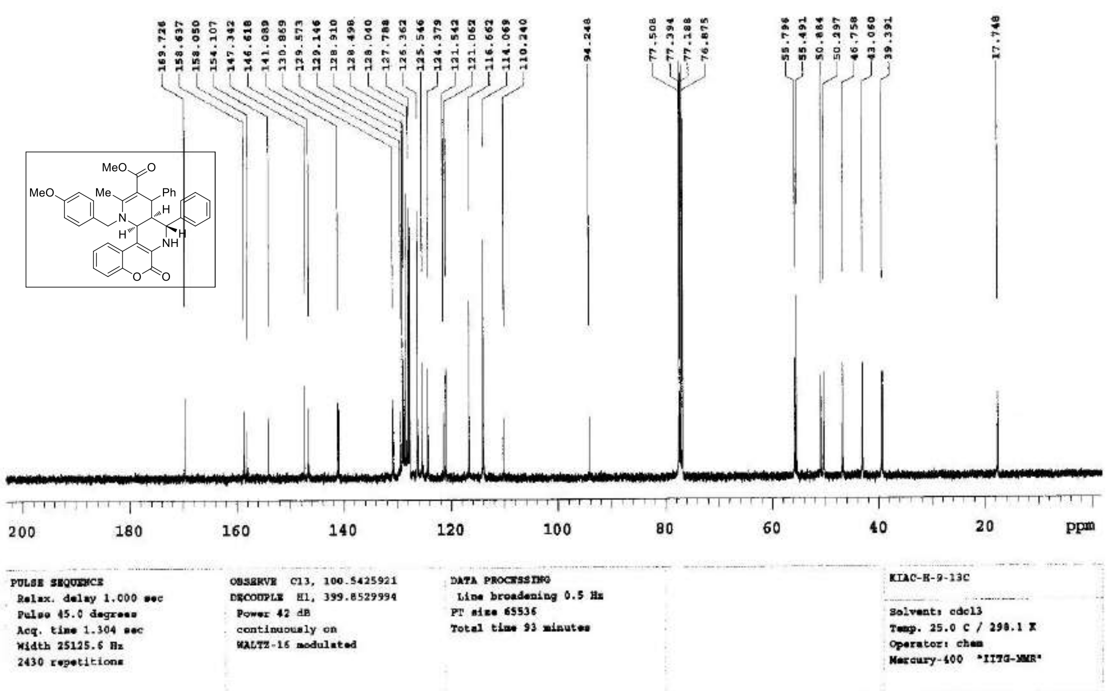
^{13}C NMR spectra of 9q



[1]H NMR spectra of 9v

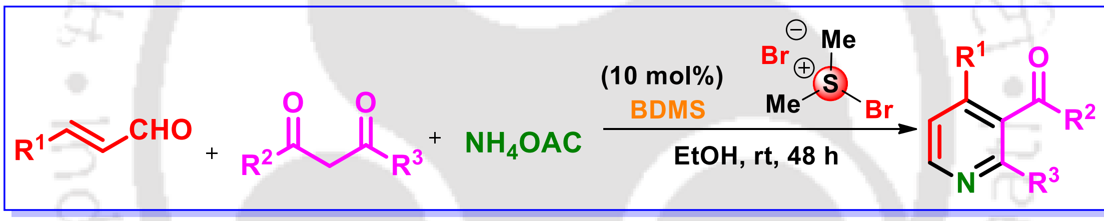


[13]C NMR spectra of 9v



Chapter IV

Bromodimethylsulfonium bromide (BDMS) catalyzed metal free three component reaction for the synthesis of functionalized pyridine

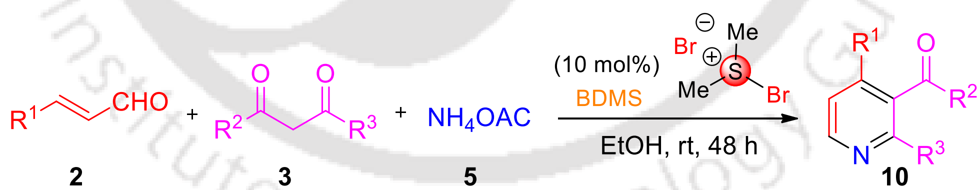


CHAPTER IV

IV. Bromodimethylsulfonium bromide (BDMS) catalyzed metal free three component reaction for the synthesis of functionalized pyridine

Results and Discussion

In chapter I, a brief literature survey of importance pyridine and its synthetic paths have been discussed. In recent time continuous efforts on exploration of Bromodimethylsulfonium Bromide (BDMS) as the catalyst in organic synthesis to access newer methodologies for the synthesis of heterocyclic scaffolds has gained significant attention. The synthesis of pyridine has long been an area of intense interest among the scientist, resulting in the development of a varied of synthetic methods. Among them the direct condensation of carbonyl compounds with a source of ammonia is well known, but the methods still suffer from lack of substrates variation. Therefore, development of new synthetic paths is still a challenge in industrial as well as an academic. In this section we have demonstrated an efficient protocol for the synthesis of substituted pyridines from *α,β*-unsaturated aldehydes, 1,3-diketones and ammonium acetate at room temperature using (BDMS) as metal-free catalyst employing multicomponent reaction strategy, is shown in Scheme 43.



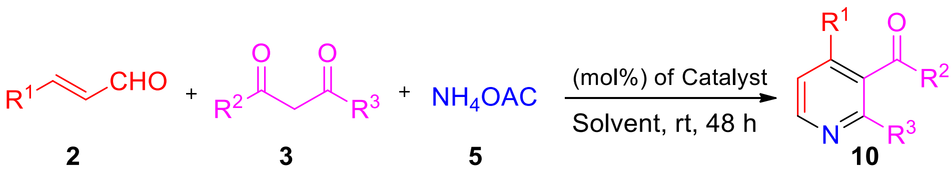
Scheme 43. Synthesis of substituted pyridine derivatives using MCR strategy.

Bromodimethylsulfonium Bromide (BDMS) is readily available and cheap catalyst used for various organic transformations. Hence, initial studies were performed using 5 mol% BDMS with cinnamaldehyde (**2a**), acetylacetone (**3a**) and ammonium acetate (**5**) at room temperature for 48 hours and gradual progress of the reaction was monitored by TLC. After usual work up followed by chromatographic purification, a gummy liquid product was isolated in 32% yield, which was characterized as 1-(2-methyl-4-phenylpyridin-3-yl)ethanone (**10a**). The product (**10a**) was characterized *via* IR, ^{1}H NMR, ^{13}C NMR and HRMS analysis. In the ^{1}H NMR spectrum of **10a,** peak at δ 8.50 ppm was found due to C-H adjacent to N of pyridine and singlet at δ 2.47 ppm, 1.47 ppm for the two Me group in the pyridine skeleton. In ^{13}C NMR and IR spectra, the peaks at δ = 205.66 ppm and 1672 cm^{-1} is attributed to the carbonyl group. In ^{13}C NMR, the peaks at δ = 32.17 and 22.53 ppm indicated that two Me groups has incorporated in the final product (**10a**). HRMS (ESI) calcd for $C_{14}H_{14}NO$ (M + H^{+}) 212.9937 confirms the presence of pyridine moiety in (**10a**).

Therefore, inspiring by these successful result various reactions were performed to investigate the optimal reaction conditions. In the presence of 10 mol% BDMS catalyst and polar EtOH solvent gave the expected pyridine derivative (**10a**) in 53% yield (entry 9, Table 10). Several reactions were performed with different mol% of catalysts and with various solvents like EtOH, BuOH, CH_3CN, DMF and DMSO. Scrutinizing catalysts like $M(OTf)_3$, triflic acid, L-proline, PTSA, and I_2 were also studied. In the initial reaction with 5 mol%, 10 mol% and 15 mol% of BDMS was used which provide 32%, 49% and 43% yield respectively (entries 2-4, Table 10) whereas without catalyst gives 12% isolated yield (Table 10, entries 1). Systematic evolution of the various solvents shows EtOH was a suitable solvent for the present method. To scrutinize the effectiveness of BDMS as compared to other catalysts, several reactions were also scrutinized such as I_2, $Sc(OTf)_3$, $Cu(OTf)_2$, $Yb(OTf)_3$, $Bi(OTf)_3$, TfOH, L-Proline and PTSA under identical conditions and the results are summarized in Table 10 (entries 11-18). After screening of solvent and catalyst it was found that the optimal conditions of this present methodology were 10 mol% BDMS in ethanol at room temperature (Table 10, entry 9).

To explore the present method, a reaction with cinnamaldehyde (**2a**), acetyl acetone (**3e**) benzoylacetone (**3f**), dibenzoylmethane (**3g**) and ammonium acetate (**5**) was done under optimized reaction conditions and the desired product (**10a-c)** was obtained in 53%, 46% and 42% yield respectively (entry 1-3, Table 11). To find the synthetic scope and the generality of the present protocol further, various reactions was examined with crotonaldehyde (**2b**), (**3e**),dibenzoylmethane (**3g**) to give the corresponding products (**10e-f)** in moderate yields (entries 5-6, Table 11), were as 4-chlorocinnamaldehyde (**2d**) reaction

Table 10. Optimization of reaction conditions for the synthesis of pyridine **10a**

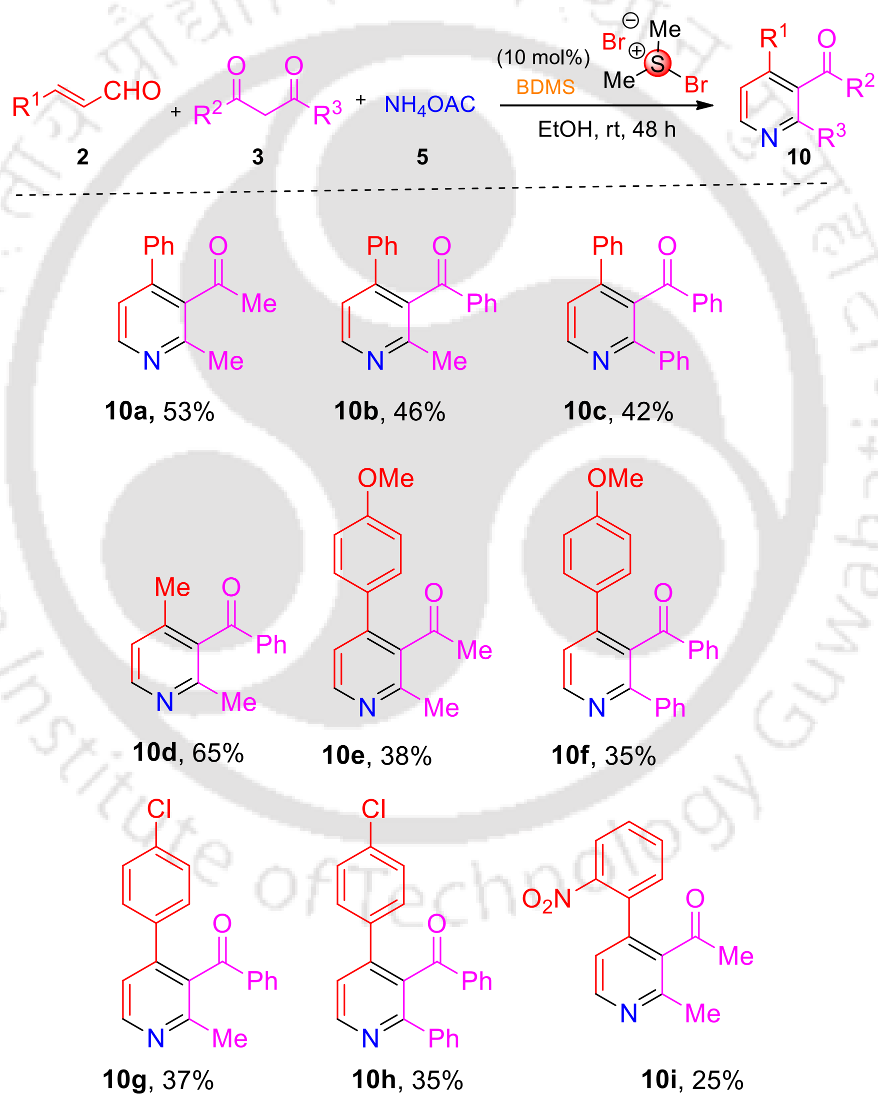


Entry	Catalyst	Solvent	(%)Yield[b,c]
1	-	CH_3OH	12
2	5 mol% BDMS	CH_3OH	32
3	10 mol% BDMS	CH_3OH	49
4	15 mol% BDMS	CH_3OH	43
5	10 mol% BDMS	CH_3CN	31
6	10 mol% BDMS	DMSO	25
7	10 mol% BDMS	DMF	11
8	10 mol% BDMS	BuOH	22
9	**10 mol% BDMS**	**EtOH**	**53**
10	10 mol% BDMS	EtOH	50[c]
11	10 mol% I_2	EtOH	40
12	10 mol% $Sc(OTf)_3$	EtOH	23
13	10 mol% $Cu(OTf)_2$	EtOH	29
14	10 mol% $Yb(OTf)_3$	EtOH	25
15	10 mol% $Bi(OTf)_3$	EtOH	18
16	Triflic Acid	EtOH	21
17	L-Proline	EtOH	15
18	PTSA	EtOH	12

[a]Reaction carried out with cinamaldehyde, **2a** (1 mmol) acetylacetone, **3a** (1 mmol) and ammonium acetate, **5** (1 mmol) at rt. [b]Isolated yields, [c]Reflux.

with benzoylacetone (**3f**), ammonium acetate (**5**) gives the corresponding products (**10d**) with good yield (entry 4, Table 11). Likewise, 4-methoxycinnamaldehyde (**2c**) react with acetylacetone benzoylacetone (**3f**) dibenzoylmethane (**3g**) and ammonium acetate (**5**) with the desired pyridines (**10g-h)** in little bit lower yields (entries 7-8, Table 11). 4-nitrocinnamaldehyde (**2e**) reaction with acetyl acetone (**3f**) and provided desired products (**10i)** low yields under same reaction conditions is shown in Table 11 (entries 10).

Table 11. Substrate scopes for substituted pyridine derivatives (**10**).[a,b]



[a]Reaction carried out with *α,β*-unsaturated aldehydes **2** (1 mmol) 1,3-diketones **3** (1 mmol) and ammonium acetate (**5**) (1 mmol) in EtOH at rt. [b]Isolated yields.

All the products were characterized by IR, NMR and HRMS analysis. Finally, the structure of one of the descriptive compounds such as (**10b**) was confirmed through single crystal X-ray diffraction analysis (Figure 19).

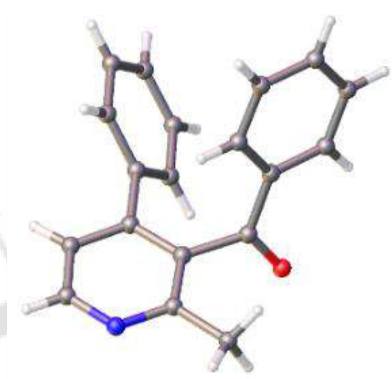
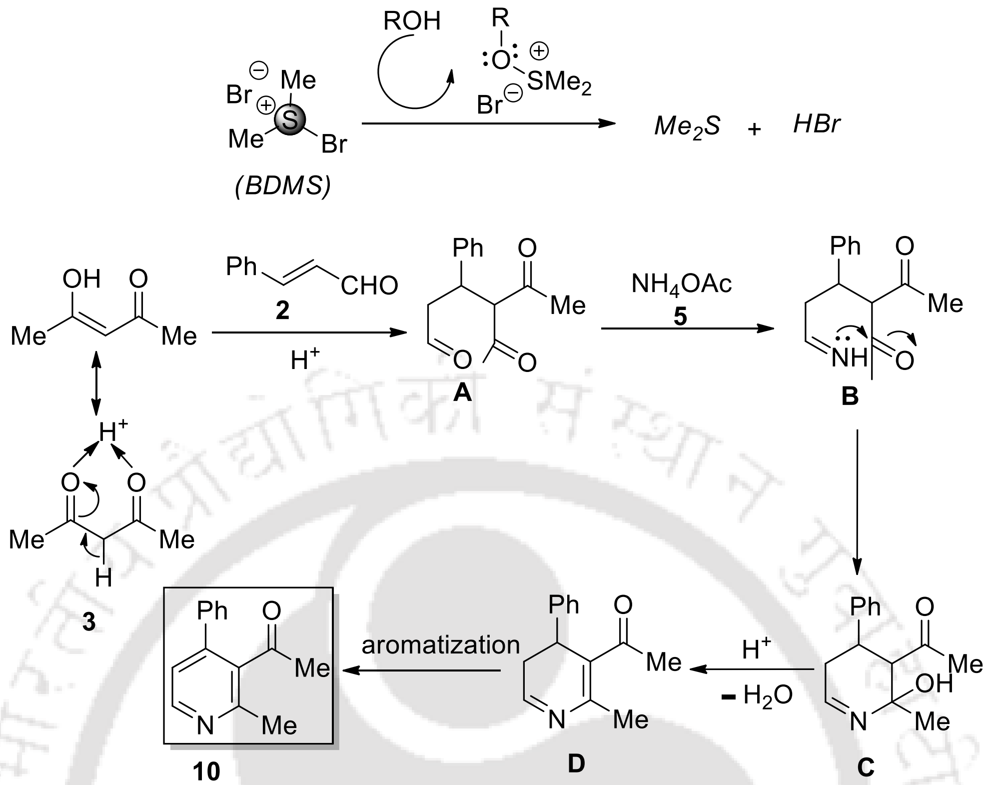


Figure 19. Single crystal X-ray structure of compound **10b**.

The formation of the product can be explained by the formation of HBr from the BDMS in ethanol, which promoted Michael addition between *α,β*-unsaturated aldehydes **2** and an enolized form of 1,3-diketones (**3**) give the intermediate **A** (Scheme 44). Alternative, which is a more conventional mechanistic pathway involved the preliminary formation of an enamino ketone intermediate was ruled out by Jean Rodriguez *et al*.[129] They isolated enamino ketone and then reaction with *α,β*-unsaturated aldehydes failed to give the desire product. So the reaction initiated by Michael addition as the first step of the sequence. The intermediate **A** then reacts with ammonium acetate to give the corresponding imine **B** which is subsequently cyclized to give **C**. After loss of water molecule leading to the dihydropyridine intermediate **D**, and aromatization gives the final product (**10**).



Scheme 44. Plausible mechanism for the formation pyridine **10**.

Conclusion

In conclusion, *α*-ketocarbonyls are useful partners in a MCR promoted by a Michael addition and it is possible to develop a synthetic method for the synthesis of substituted pyridine derivatives from readily available substrates. The procedure is simple, metal-free and one-pot. This method also gives selective access to pyridines and should be the alternative synthetic path to other well-known methods.

Chapter IV

Experimental Section

Bromodimethylsulfonium bromide (BDMS) catalyzed metal free three component reaction for the synthesis of functionalized pyridine

Experimental Section

General Procedure for the preparation of substituted pyridine derivatives (10): The catalyst bromodimethylsulfonium bromide (BDMS) 10 mol% was added to a stirred mixture *α,β*-unsaturated aldehyde (**2**, 1 mmol) 1,3-diketone (**3**, 1 mmol) and ammonium acetate (**5**, 1 mmol) in 3 mL of ethanol and it was kept for stirring at room temperature. After completion of the reaction monitored by TLC, solvent was removed in a rotary evaporator and the crude residue was extracted with ethyl acetate (2 x 10 mL). The organic layer was washed with brine solution and dried over anhydrous sodium sulfate. The organic extract was concentrated in a rotary evaporator and the crude residue was purified through a silica gel (60-120 mesh) column chromatography. The desired products (**10**) were eluted with a mixture of hexane/ethyl acetate (10:4).

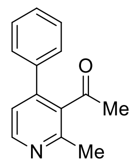
Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 296 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. Compound **10b** empirical formula '$C_{19}H_{15}NO$', colorless crystal, formula wt 273.32, 'Hexagonal', *'P6(5)'*, a= 8.7281(2) Å, b = 8.7281(2) Å, c = 34.3410(10) Å, V = 2265.60(10) Å^3, Z = 6, F (0 0 0) = 864, GOF(S) = 1.061. Final indices R_{obs} = 0.0321, wR_{obs} = 0.0636, R_{all} = *0.0471*, wR_{all} = *0.0658* for all data.

Table 12. Crystal datas and structure refinements for 10b

Identification code	10b
Empirical formula	$C_{19}H_{15}NO$
Formula weight	273.32
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	'Hexagonal'
Space group	'P6(5)'
Unit cell dimensions	*a* =8.7281(2) Å, *b* =8.7281(2) Å*c*= 4.3410(10)Å α = 90º, β = 90º, γ =120.00 º
Volume *Z*	2265.60(10) $Å^3$ 6
Density (calculated) Absorption coefficient *F*(000)	1.202 g/cm^3 0.074 mm^{-1} 864
Theta range for data collection	2.69º to 24.99º
Index ranges Reflection collected /unique	-10≤*h*≤10, -10≤*k*≤10, -40≤*l*≤40 2671 / 2032 [*R*(int) =0.0348]
Completeness to θ Refinement method	100 % (θ = 24.99º) 'SHELXL−97(Sheldrick, 1997)'
Goodness-of-fit on F^2 Final *R* indices [>2sigma(*I*)] *R* indices (all data) Largest diff. peak and hole	1.061 R_{obs} = 0.0321, wR_{obs} = 0.0636 R_{all} = 0.0471, wR_{all} = 0.0658 0.079 and --0.103 e.$Å^{-3}$

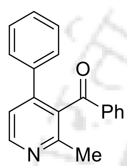
Spectral data

1-(2-methyl-4-phenylpyridin-3-yl)ethanone (10a): Gummy liquid (0.112 g, 53%); ^{1}H NMR



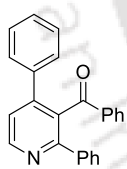
($CDCl_3$, 400 MHz) δ 8.50 (bs, 1H), 7.39 (bs, 3H), 7.29 (bs, 1H), 7.19 (bs, 1H), 7.15 (bs, 1H), 2.47 (s, 3H), 1.85 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 205.66, 153.81, 148.63, 147.37, 137.76, 136.59, 129.49, 129.29, 128.75, 122.26, 32.17, 22.53 ppm; IR (KBr): ῡ = 1672 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{14}NO$ (M + H^{+}) 212.1075, found 212.9937.

(2-methyl-4-phenylpyridin-3-yl)(phenyl)methanone (10b): Solid (0.126 g, 46%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.63(d, *J* = 5.2 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.44 (t, *J* = 7.6 Hz,



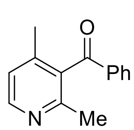
1H), 7.29 (t, *J* = 8.4 Hz, 2H), 2.25-7.19 (m, 6H), 2.47 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): *δ* 198.30, 155.41, 149.67, 148.04, 137.97, 137.13, 133.91, 133.84, 129.51, 128.84, 128.78, 128.66, 121.96, 23.23 ppm; IR (KBr): ῡ = 1682 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{16}NO$ (M + H^{+}) 274.1232, found 274.1242.

(2,4-diphenylpyridin-3-yl)(phenyl)methanone (10c): Gummy liquid (0.141 g, 42%); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.83 (d, *J* = 4.8 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.49-7.47 (m,



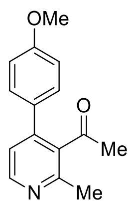
2H), 7.36 (d, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 4.8 Hz, 1H), 7.27-7.23 (m, 7H), 7.20 (t, *J* = 5.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 197.42, 157.29, 149.97, 149.42, 139.66, 138.00, 137.80, 133.76, 133.36, 129.50, 129.35, 129.23, 128.85, 128.75, 128.63, 128.61, 128.46, 128.36, 127.41, 126.55, 123.30 ppm; IR (KBr): ῡ = 1681 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{18}NO$ (M + H^{+}) 336.1388, found 336.1397.$C_{25}H_{20}NO_2$ (M + H^{+}) 366.1494, found 366.1497.

(2,4-dimethylpyridin-3-yl)(phenyl)methanone (10d): Gummy liquid (0.137 g, 65%); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.77 (d, *J* = 6.0 Hz, 2H), 7.61 (t, *J* = 6.0 Hz, 1H), 7.55 (d, *J* = 12.0

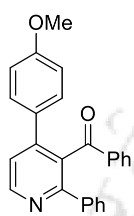


Hz, 1H), 7.48 (t, *J* = 12.0 Hz, 2H), 7.07 (d, *J* = 6.0 Hz, 1H), 2.61 (s, 3H), 2.52 (s, 3H).ppm.^{13}C NMR (150 MHz, $CDCl_3$): *δ* 197.51, 160.02, 156.57, 137.60, 137.10, 133.67, 131.17, 130.18, 128.85, 120.00, 24.84, 23.67 ppm; IR (KBr): ῡ = 1685 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{14}NO$ (M + H^{+}) 212.1075, found 212.1087.

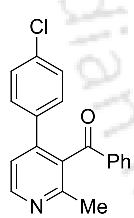
1-(4-(4-methoxyphenyl)-2-methylpyridin-3-yl)ethanone (10e): Gummy liquid (0.92 g, 38%); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.51 (d, *J* = 6.0 Hz, 1H), 7.29 (d, *J* = 12.0 Hz, 2H), 7.14 (t, *J* = 6.0 Hz, 1H), 6.97 (d, *J* = 12.0 Hz, 2H), 3.85 (s, 3H), 2.53 (s, 3H), 2.01 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): *δ* 206.64, 160.54, 153.99, 149.35, 146.18, 136.17, 130.25, 130.03, 121.83, 114.67, 55.56, 32.09, 22.89 ppm; IR (KBr): ῡ = 1679 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}NO_2$ (M + H$^+$) 242.1181, found 242.1120.



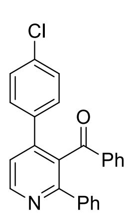
(4-(4-methoxyphenyl)-2-phenylpyridin-3-yl)(phenyl)methanone (10f): Gummy liquid (0.128 g, 35%); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.80 (d, *J* = 6.0 Hz, 1H), 7.54 (d, *J* = 12.0 Hz, 2H), 7.46 (d, *J* = 0.0 Hz, 2H), 7.35 (d, *J* = 12.0 Hz, 2H), 7.23-7.20 (m, 7H), 6.78 (d, *J* = 12.0 Hz, 2H), 3.74 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): *δ* 197.73, 159.94, 157.25, 149.88, 149.02, 139.37, 137.74, 133.63, 133.39, 130.25, 130.20, 129.48, 12931, 128.69, 128.49, 128.33, 123.29, 114.14, 55.39 ppm; IR (KBr): ῡ = 1680 cm^{-1};HRMS (ESI) calcd for$C_{25}H_{20}NO_2$ (M + H$^+$) 366.1494, found 366.1501.



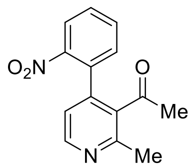
(4-(4-chlorophenyl)-2-methylpyridin-3-yl)(phenyl)methanone (10g): Gummy liquid (0.114 g, 37%); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.64 (d, *J* = 5.4 Hz, 1H), 7.87 (t, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.44-7.39 (m, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.21-7.17 (m, 3H), 2.46 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): *δ* 197.77, 155.53, 149.78, 136.95, 136.38, 134.11, 133.80, 131.00, 130.12, 129.49, 128.94, 128.39, 127.30, 121.73, 23.21 ppm; IR (KBr): ῡ =1680 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{15}ClNO$ (M + H$^+$) 308.0842, found 308.0838.



(4-(4-chlorophenyl)-2-phenylpyridin-3-yl)(phenyl)methanone (10h): Gummy liquid (0.129 g, 35%); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.84 (d, *J* = 6.0 Hz, 1H), 7.52 (d, *J* = 12.0 Hz, 2H), 7.48-7.47 (m, 1H), 7.38 (t, *J* = 12.0 Hz, 1H), 7.33 (d, *J* = 0.0 Hz, 1H), 7.20-7.24 (m, 10H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): *δ* 197.27, 157.36, 150.13, 148.20, 139.48, 137.60, 136.43, 134.98, 133.65, 130.18, 129.48, 129.34, 128.92, 128.89, 128.62, 128.42, 123.12 ppm; IR (KBr): ῡ = 1682 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{17}ClNO$ (M + H$^+$) 370.0999, found 370.1016.

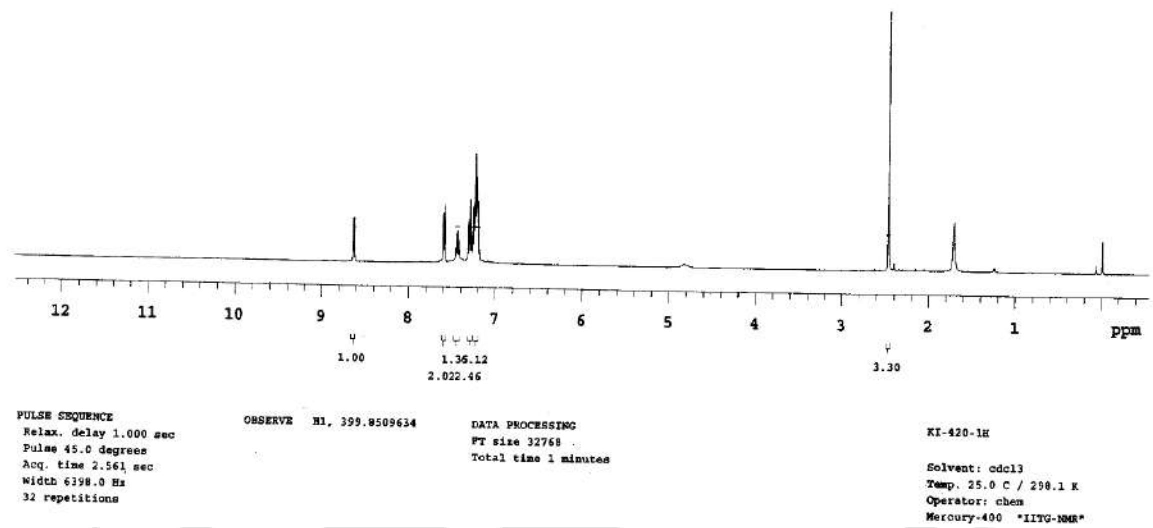


1-(2-methyl-4-(2-nitrophenyl)pyridin-3-yl)ethanone (10i): Gummy liquid (0.64 g, 25%);

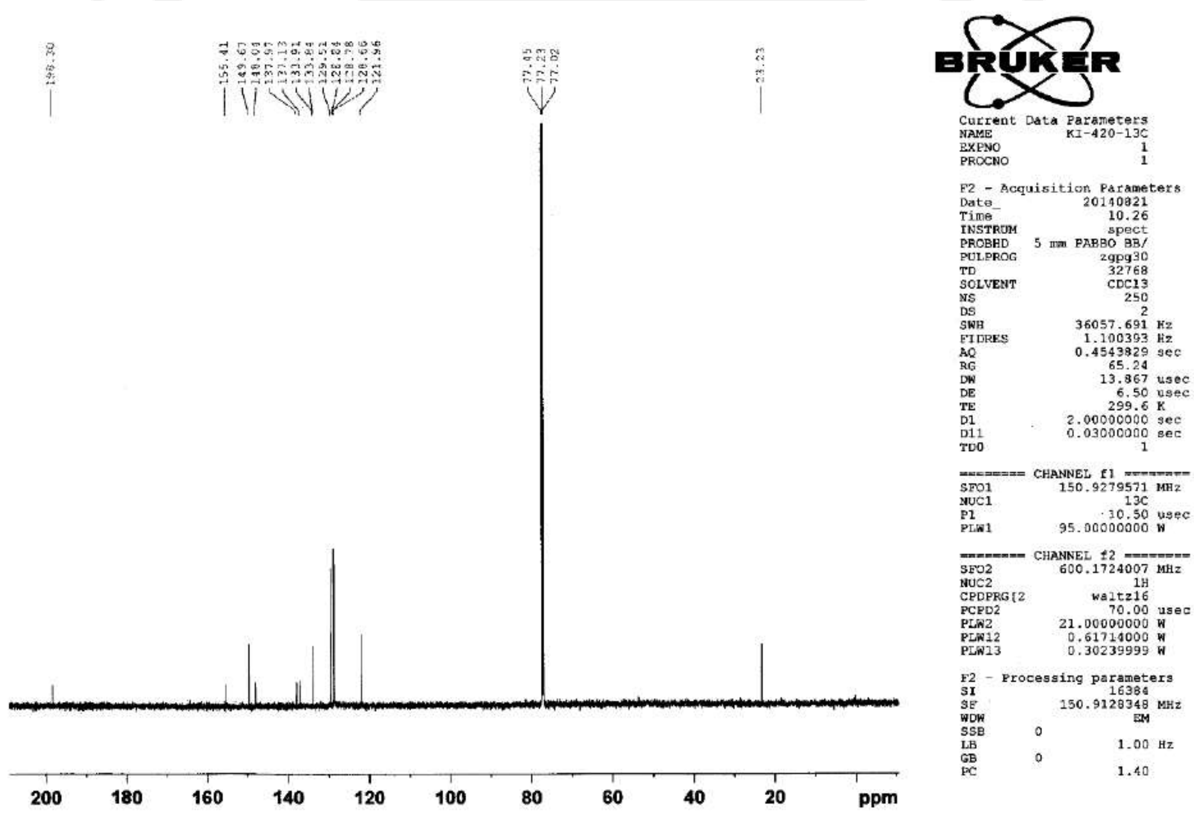


^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.62 (d, *J* = 6.0 Hz, 1H), 8.32 (d, *J* = 6.0 Hz, 2H), 7.54 (d, *J* = 6.0 Hz, 2H), 7.16 (d, *J* = 6.0 Hz, 1H), 2.58 (s, 3H), 2.07 (s, 3H). Ppm; ^{13}C NMR (150 MHz, $CDCl_3$): *δ* 205.25, 154.43, 149.82, 148.37, 144.39, 143.88, 136.12, 129.81, 128.22, 124.35, 124.28, 121.43, 32.51, 22.97 ppm; IR (KBr): ῡ = 1672 cm^{-1}; HRMS (ESI) calcd for $C_{14}H1_3N_2O_3$ (M + H^+) 257.0926, found 257.0942.

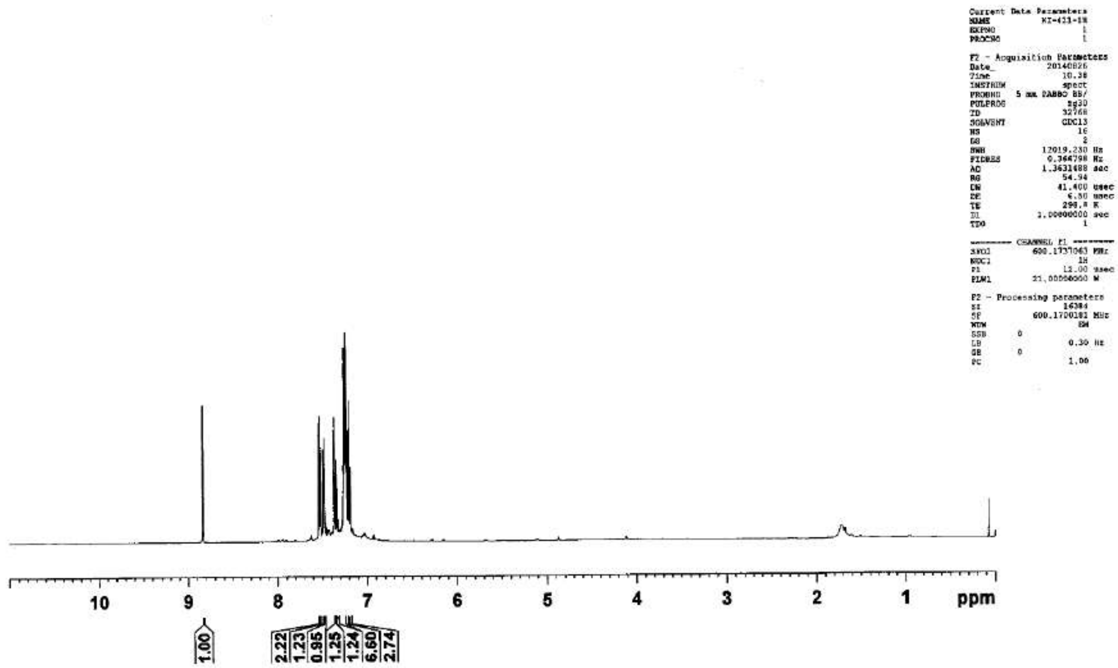
[1]H NMR spectra of 10b



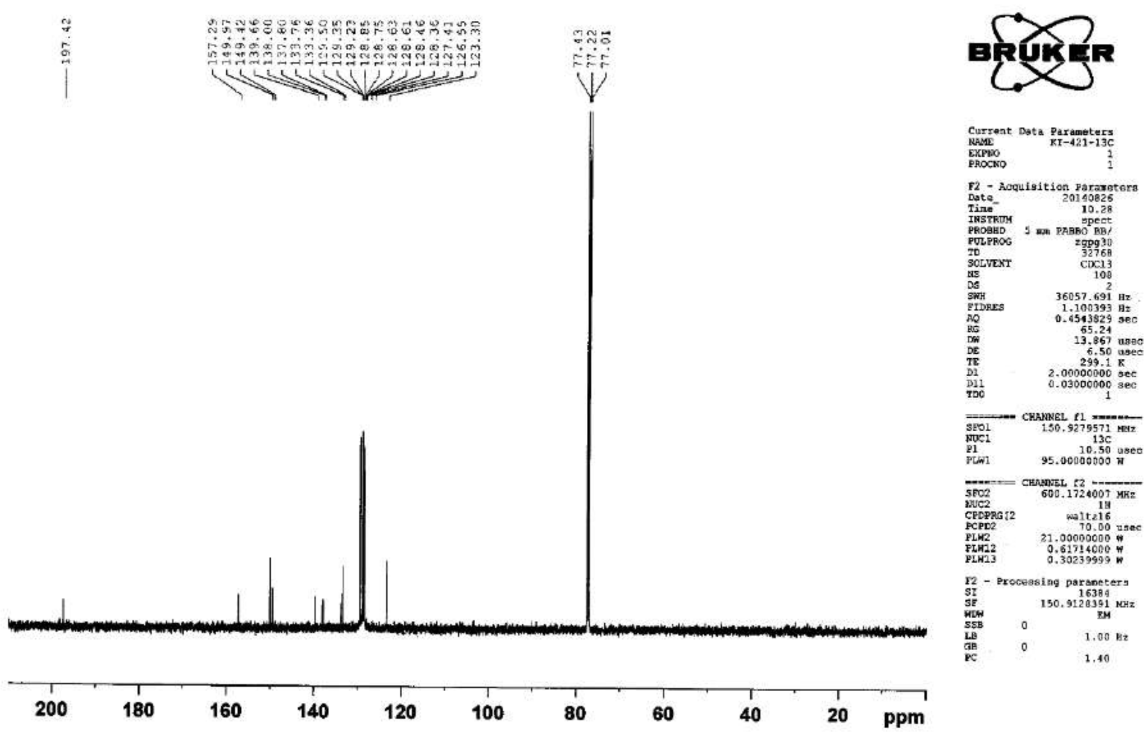
[13]C NMR spectra of 10b



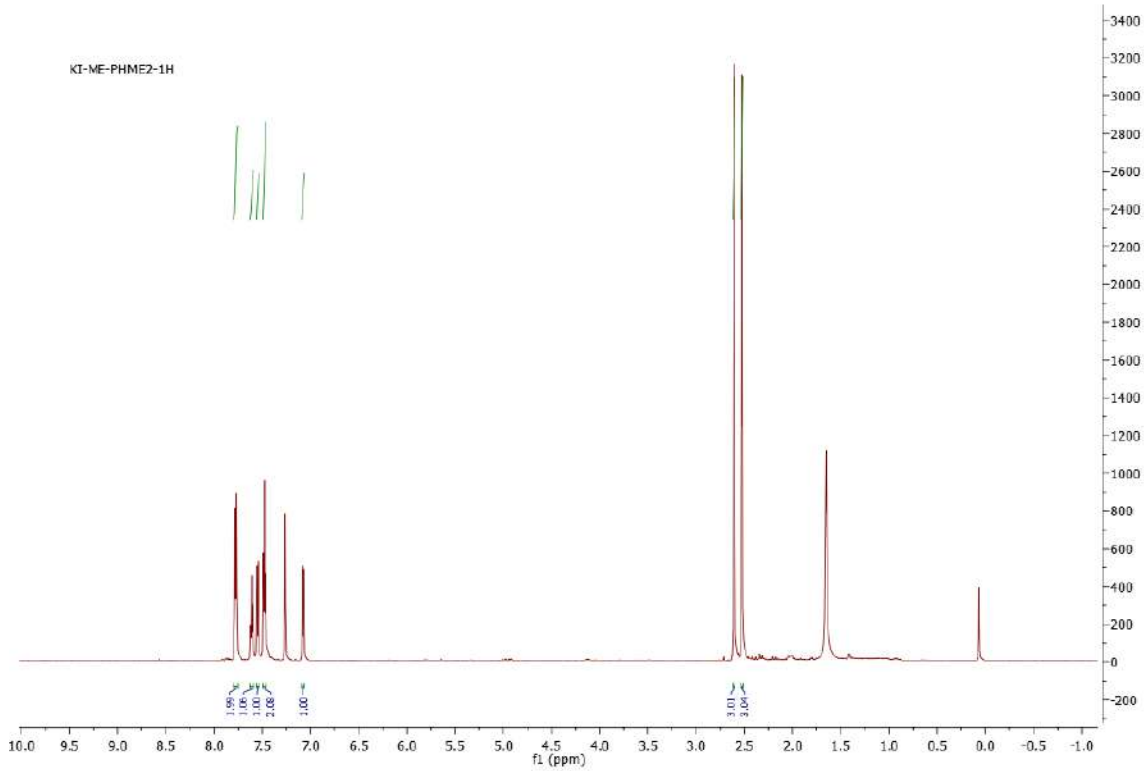
^{1}H NMR spectra of 10c



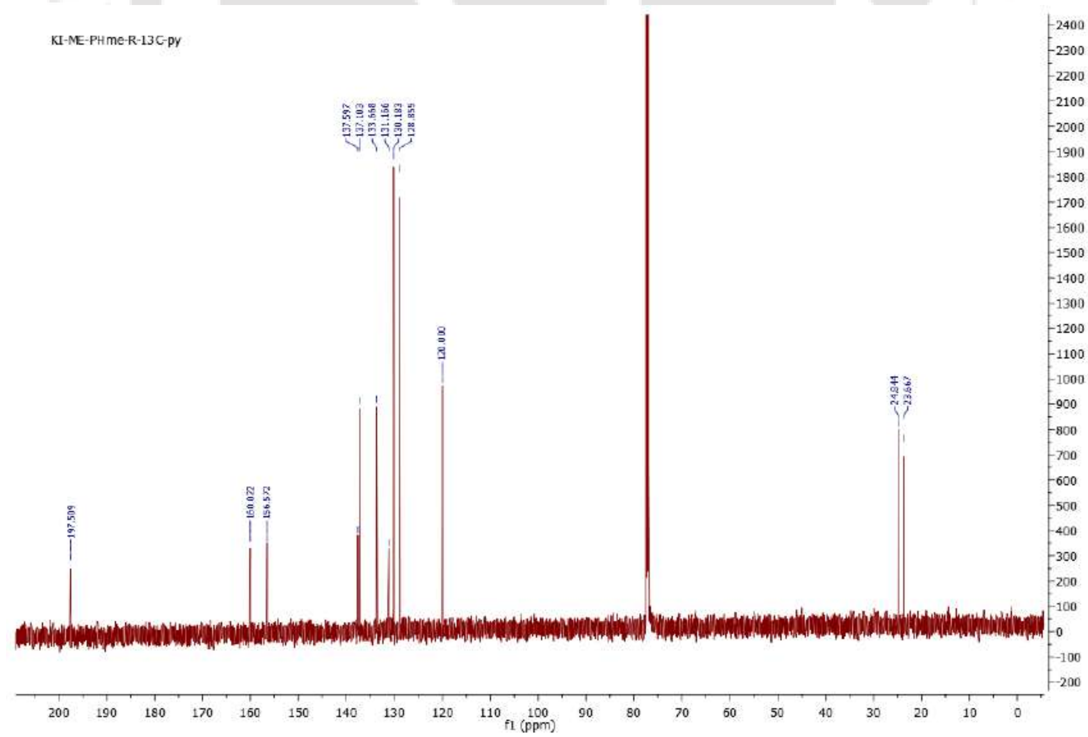
^{13}C NMR spectra of 10c



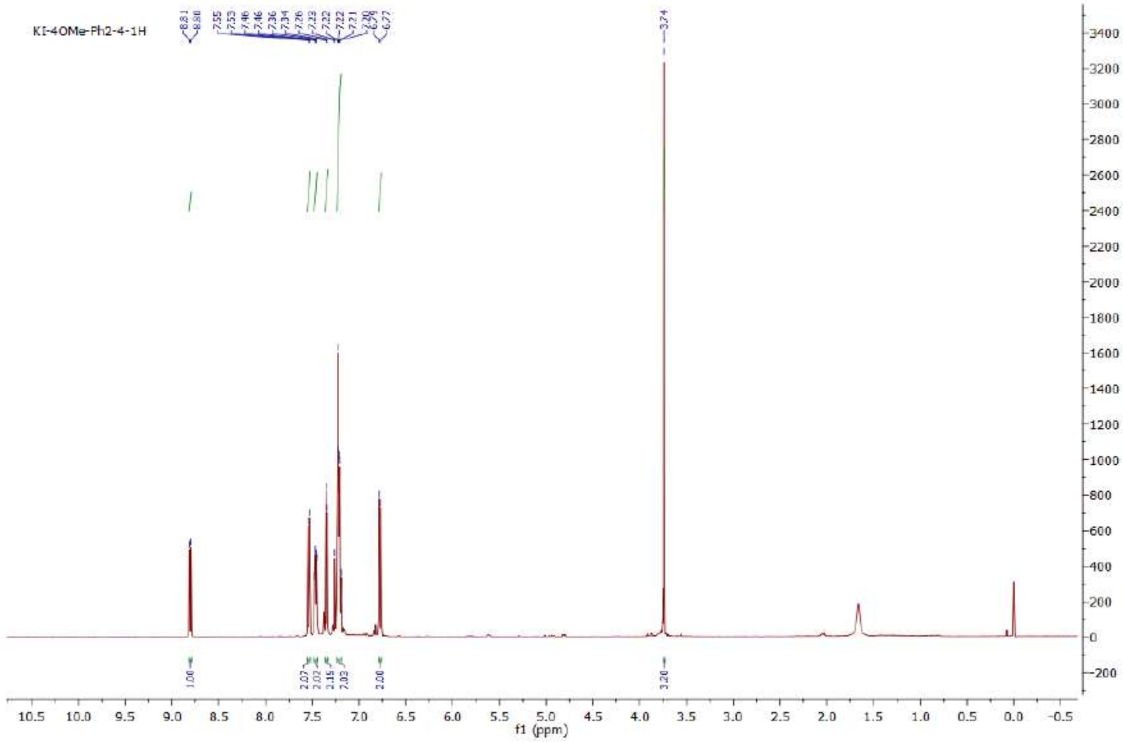
^{1}H NMR spectra of 10d



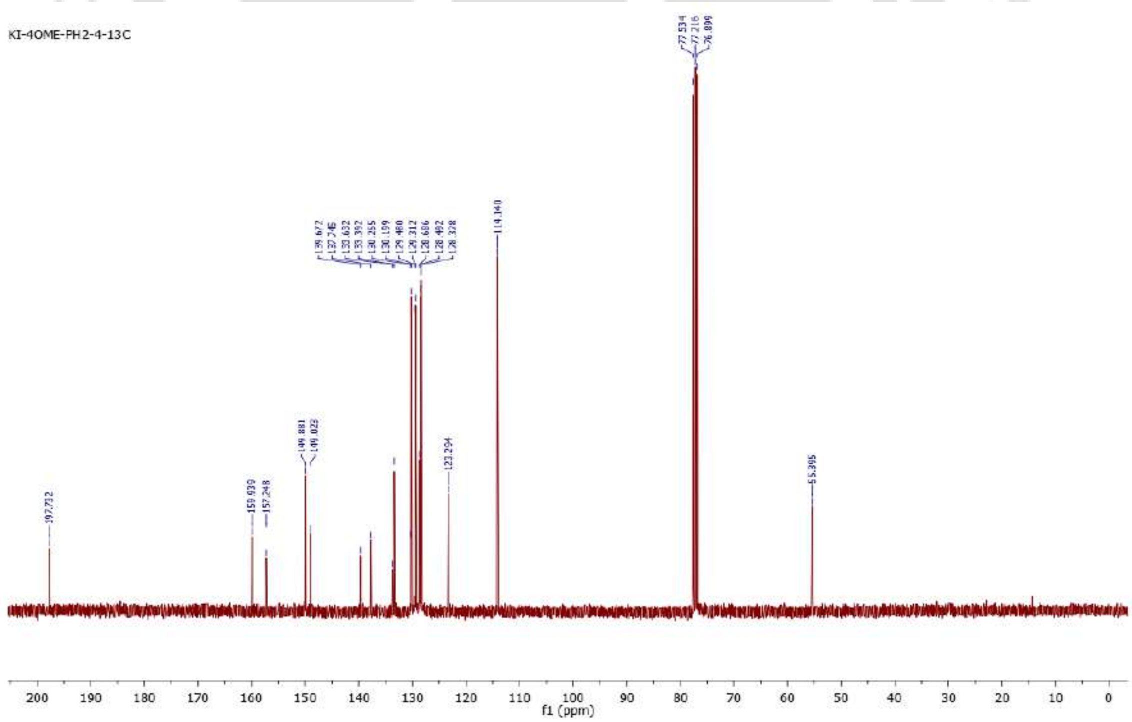
^{13}C NMR spectra of 10d



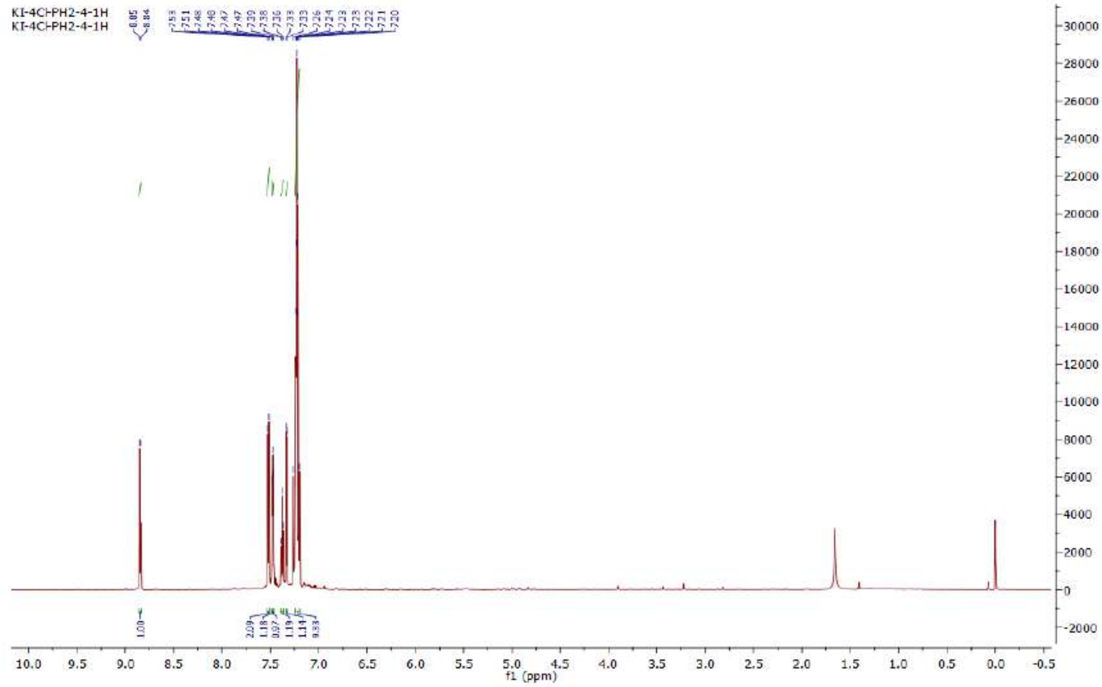
^{1}H NMR spectra of 10f



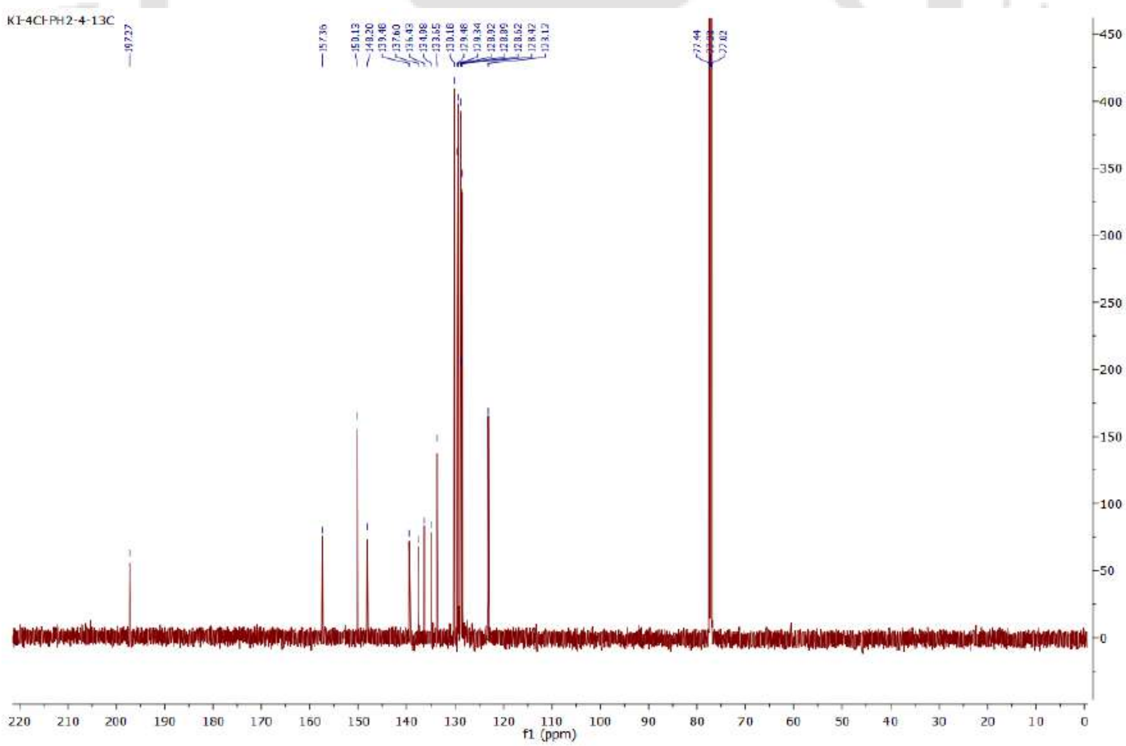
^{13}C NMR spectra of 10f



[1]H NMR spectra of 10h



[13]C NMR spectra of 10h



References

1. Orru, R. V. A.; Ruijter, E. In *Synthesis of Heterocycles via Multicomponent Reactions I & II*, ed. Maes, B. U. W.; springer: Heidelberg, Germany, **2010**.
2. Dömling. A. Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.
3. (a) Dömling, A. *Chem. Rev*. **2006**, *106*, 17. (b) Bannwarth, W.; Felder, E. *Combinatorial Chemistry*, Wiley-VCH, Weinheim, **2000**.
4. Fayol, A.; Zhu, J. *Org. Lett*. **2005**, *7*, 239.
5. Cioc, R. C.; Ruijter, E.; Orru, R. V. A. *Green Chem*. **2014**, *16*, 2958.
6. (a) Zhu, J. *Eur. J. Org. Chem*. **2003**, *7*, 1133. (b) Ganem, B. *Acc. Chem. Res*. **2009**, *42*, 463.
7. (a) Mironov, M. A. *QSAR* Comb. Sci. **2006**, *25*, 423. (b) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem. Int. Ed*. **2011**, *50*, 6234.
8. (a) Nicolaou, K. C.; Hanko, R.; Hartwig,W. *Handbook of Combinatorial Chemistry*, Wiley-VCH, Weinheim, **1912**, vol. *1–2*; (b) Czarnik, A. W.; *Org. Chem*. **1995**, *8*, 13. (c) Dolle, R. E. *J. Comb. Chem*. **2003**, *5*, 693.
9. (a) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (b) Domling, A.; Wang, W.; Wang, K. *Chem. Rev*. **2012**, *112*, 3083. (c) Brauch, S.; Berkel, S. S.; van Westermann, B. *Chem. Soc. Rev*. **2013**, *42*, 4948. (d) Bugaut, X.; Bonne, D.; Coquerel, Y.; Rodriguez, J.; Constantieux, T. *Curr. Org. Chem*. **2013**, *17*, 1920.
10. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*, Oxford University Press, New York, **1998**.
11. Cioc, R. C.; Ruijter, E.; Orru, R. V. A. *Green Chem*. **2014**, *16*, 2958.
12. Biggs-Houck, J. E.; Younai, A.; Shaw, J. T. *Curr. Opin. Chem. Biol*. **2010**, *14*, 371.
13. Glaser, R.; Hodgen, B.; Farrelly, D.; McKee, E. *Astrobiology* **2007**, *7*, 455.
14. Laurent, A.; Gerhardt, C. F. *Ann. Chem. Phys*., **1838**, *66*, 281. *Ann. Chem.* **1838**, *28*, 265.
15. Strecker, A. *Ann. Chem*. **1850**, *75*, 27.
16. Hantzsch, A. *Ann. Chem*. **1882**, *215*, 1.
17. Biginelli, P. *Ber.Dtsch. Chern. Ges*. **1891**, *24*, 1317.
18. (a) Passerini, M.; Simone, L. *Gazz. Chim. Ital*. **1921**, *51*, 126. (b) Passerini, M.; Simone, L. *Gazz. Chim. Ital*. **1931**, *61*, 964.
19. (a) Ugi, I.; Meyr, R.; Fitzer, U.; Steinbrücker, C. *Angew. Chem.* **1959**, *71*, 386. (b) Ugi, I.; Steinbrücker, C. *Angew. Chem.*, **1960**, ***72***, 267. (c) Ugi, I. *Angew. Chem.* **1962**, *74*, 9.

20. Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, **1967**; Vol. 1, p.11.
21. Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2013,** *9,* 2265.
22. Zhu, J.; Bienaymé, H. *Multicomponent Reactions*, Wiley-VCH, Weinheim, 2005.
23. Sunderhaus, J. D.; Martin, S. F. *Chem. Eur. J.* **2009**, *15,* 1300.
24. Kappe, C. O. *Eur. J. Med. Chem*. **2000**, *35*, 1043.
25. Wan, J-P.; Liu, Y. *RSC Advances*. **2012**, *2*, 9763.
26. (a) Janis, R. A.; Silver, P. J.; Triggle, D. J. *Adv. Drug Res*. **1987**, *16*, 309. (b) Bossert, F.; Vater, W. *Med. Res. Rev*. **1989**, *9*, 291.
27. Velena, A.; Zarkovic, N.; Troselj,K. G.; Bisenieks, E.; Krauze, A.; Poikans, J.; Duburs, G. *Oxid Med and Cell Longev*. **2016**, *2016*, 35.
28. Bridgwood, K. L.; Veitch, G. E.; Ley, S. V. *Org. Lett.* **2008,** *16*, 3627.
29. Rodriguez, G.; Varon, J. *Crit. Care Shock.* **2006,** *9,* 37.
30. (a) Andersen, K. H.; Nordlander, M.; Westerlund, R. C. Patent 5,856,346, 1999. (b) Vishnu, N. R.; Puruschottam, J. A.; Kumar, S. S. Patent EP 2 386 544, 2011.
31. Sammour, A.; Selim, M. I. B.; Elseen, M. M. N. *J. Prakt. Chem*. **1972**, *314*, 139.
32. Ishar, M. P. S.; Kumar, K.; Kaur, S. Kumar, S.; Girdhar, N. K.; Sachar, S.; Markawa, A.; Kapoor, A. *Org. Lett*. **2001**, *3*, 2133.
33. Geirsson, J. K. F.; Johannesdotir, J. F. *J. Org. Chem*. **1996**, *61*, 7320.
34. (a) Mauzeral, D.; Westheimer, F. H. *J. Am. Chem. Soc*. **1955**, *77*, 2261. (b) Kawase, M.; Shah, A.; Gaveriya, H.; Motohashi, N.; Sakagami, H.; Varga, A.; Molnar, J. *Bioorg. Med. Chem.* **2002**, *10*, 1051.
35. Jiang, J.; Yu, J.; Sun, X.-X.; Rao, Q.-Q.; Gong, L.-Z. *Angew. Chem., Int. Ed*. **2008**, *47*, 2458.
36. Dondoni, A.; Massi, A. *Acc. Chem. Res*. **2006**, *39*, 451.
37. Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, **1996**, *5*, 167.
38. Majumdar, K. C., Chattopadhyay, S. K., Eds. *Heterocycles in Natural Product Synthesis*; Wiley-VCH: Weinheim, 2011.
39. Diaconescu, P. L. *Acc. Chem. Res*. **2010**, *43*, 1352.
40. Stout, D. M.; Meyers, A. I. *Chem. Rev*. **1982**, *82*, 223.

41. Nasr, M. A.; Gineinah, M. M. *Arch. Pharm*. **2002**, *335*, 289.
42. Kantevari, S.; Patpi, S. R.; Sridhar, B.; Yogeeswari, P.; Sriram, D. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 1214.
43. Kobayashi, S., Jørgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Eds.; Wiley-VCH: Weinheim, 2002.
44. Masson, G.; Lalli, C.; Benohoud, M.; Dagousset, G. *Chem. Soc. Rev*. **2013**, *42*, 902.
45. Povarov, L. S. *Russ. Chem. Rev*. **1967**, *36*, 656.
46. Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721.
47. (a) Glushkov, V. A.; Tolstikov, A. G. *Russ. Chem. Rev*. **2008**, 77, 137. (b) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev*. **2011**, *111*, 2626.
48. Jiang, X.; Wang, R. *Chem. Rev*. **2013**, *113*, 5515.
49. Smith, C. D.; Gavrilyuk, J. I.; Lough, A. J.; Batey, R. A. *J. Org. Chem*. **2010**, *75*, 702.
50. Wang, X-S.; Yin, M-Y.; Wang, W.; Tu, S.-J. *Eur. J. Org. Chem*. **2012**, 4811.
51. Kouznetsov, V. V.; Gómez, C. M. M.; Ruíz, F. A. R.; del Olmo, E. *Tetrahedron Lett*. **2012**, *53*, 3115.
52. Ribelles, P.; Sridharan, V.; Villacampa, M.; Ramos. M. T.; Menéndez, J. C. *Org. Biomol. Chem*. **2013**, *11*, 569.
53. Valderrama, J. A.; Gonzalez, M. F.; Valderrama, C. *Tetrahedron* **1999**, *55*, 6039.
54. Ihara, M.; Kirihara, T.; Kawaguchi, A.; Fukumoto, K.; Kamtani, T. *Tetrahedron Lett*. **1984**, *25*, 4541.
55. Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc*. **2009**, *131*, 4598.
56. Sridharan, V.; Suryavanshi, P. A.; Menendez, J. C *Chem. Rev*. **2011**, *111*, 7157 (a) Campbell, S.; Cross, J.; Stubbs, K. EP0089167, 1983. (b) Buckley, N.; Dawson, A.; Whyte, I. *Medicine* **2007**, *35*, 599.
57. a) Resnekov, L. *Chest* **1980**, *78*, 121. (b) Gaudio, A. C.; Korolkovas, A.; Takahata, Y. *J. Pharm. Sci*. **1994**, *83*, 1110. (c) Gordeev, M. F.; Patel, D. V.; Gordon, E. M. *J. Org. Chem*. **1996**, *61*, 924. (d) Iwanami, M.; Shibanuma, T.; Fujimoto, M.; Kawai, P.; Tamazawa, K.; Takenaka, T.; Takahashi, K.; Murakami, M. *Chem. Pharm. Bull*. **1979**, *27*, 1426.

58. Bretzel, R. G.; Bollen, C. C.; Maeser, E.; Federlin, K. F. *Drugs Future* **1992**, *17*, 465.

59. Hilgeroth, A.; Lilie, H. *Eur. J. Med. Chem.* **2003**, *38*, 495.

60. Straub, T.; Boesenberg, C.; Gekeler, V.; Boege, F. *Biochemistry* **1997**, *36*, 10777.

61. Avendaño, C.; Menéndez, J. C. *Med. Chem. Rev. Online* **2004**, *1*, 419.

62. Klusa, V. *Drugs Future* **1995**, *20*, 135.

63. Donkor, I. O.; Zhou, X.; Schmidt, J.; Agrawal, K. C.; Kishore, V. *Bioorg. Med. Chem.* **1998**, *6*, 563.

64. Kuzmin, A.; Semenova, S.; Ramsey, N. F.; Zvartau, E. E.; Vanree, J. M. *Eur. J. Pharmacol*. **1996**, *295*, 19.

65. Schade, D.; Lanier, M.; Willems, E.; Okolotowicz, K.; Bushway, P.; Wahlquist, C.; Gilley, C.; Mercola, M.; Cashman, J. R. *J. Med. Chem*. **2012**, *55*, 9946.

66. Borowicz, K. K.; Gasior, M.; Kleinrok, Z.; Czuczwar, S. J. *Eur. J. Pharmacol*. **1997**, *323*, 45.

67. Li, A. H.; Moro, S.; Forsyth, N.; Melman, N.; Ji, X.-D.; Jacobson, K. A. *J. Med. Chem.* **1999**, *42*, 706.

68. Bennasar, M.-L.; Roca, T.; Monerris, M. *J. Org. Chem.* **2004**, *69*, 752.

69. Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev*. **2012**, *112*, 2642.

70. Wan, J-P.; Gan, S-F.; Sun, G-L.; Pan, Y-J. *J. Org. Chem.* **2009**, *74*, 2862.

71. Vohra, R. K.; Bruneau, C.; Renaud, J-L. *Adv. Synth. Catal*. **2006**, *348*, 2571.

72. Sridharan, V.; Perumal, P. T.; Avendano, C.; Menendez, J. C. *Tetrahedron* **2007**, *63*, 4407.

73. Bartoli, G.; Babiuch, K.; Bosco, M.; Carlone, A.; Galzerano, P.; Melchiorre, P.; Sambri, L. *Synlett.* **2007**, 2897.

74. Goswami, P. *Green Chem. Lett. Rev*. **2008**, *1*, 173.

75. Franke, P. T.; Johansen, R. L.; Bertelsen, S.; Jørgensen, A. *Chem. Asian. J*. **2008**, *3*, 216.

76. Kumar, A.; Maurya, R. A. *Tetrahedron* **2008**, *64* 3477.

77. Kantam, M. L.; Ramani, T.; Chakrapani, L.; Choudary, B. M. *Catal. Commun*. **2009**, *10*, 370.

78. Kumar, A.; Maurya, R. A.; Sharma, S.; Kumar, M.; Bhatia, G. *Eur. J. Med. Chem*. **2010**, *45*, 501.

79. Maiti, S.; Sridharan, V.; Menendez, J. C. *J. Comb. Chem.* **2010**, *12*, 713.

80. Noole, A.; Borissova, M.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2011**, *76*, 1538.

81. Zonouzi, A.; Mirzazadeh, R.; Peivandi, A.; Dehdari. S. *Heterocycles* **2012,** *85*, 2012.

82. Rudys, S.; Carla, R. L.; Eduardo, P. R.; Cikotiene, I.; Pardon, J. M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1504.

83. Larghi, E. L.; Bohn, M. L.; Kaufman, T. S. *Tetrahedron* **2009**, *65* 4257.

84. Nakamura, H.; Kobayashi, J.; Ohizumi, Y.; Hirata, Y. *Tetrahedron Lett*. **1982**, *23*, 5555.

85. Carstens, J.; Heinrich, M. R.; Steglich, W. *Tetrahedron Lett.* **2013**, *54*, 5445.

86. Freitag, A.; Wessler, I.; Racke, K. *Eur. J. Pharmacol.* **1998**, *354*, 67.

87. Bowden, B. F.; McCool, B. J.; Willis, R. H. *J. Org. Chem.* **2004**, *69*, 7791.

88. Takahashi, Y.; Kubota, T.; Shibazaki, A.; Gonoi, T.; Fromont, J.; Kobayashi, J. *Org. Lett*. **2011**, *13*, 3016.

89. Liu, C.; Tang, X.; Li, P.; Li, G. *Org. Lett*. **2012**, *14* 1994.

90. Zartman, C. B.; Bell, I. M.; Gallicchio, S. N.; Graham, S. L.; Kane, S. A.; Mallee, J. J.; Rutledge, R. Z.; Salvatore, C. A.; Vacca, J. P.; Williams, T. M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6705.

91. Zeng, L-F.; Wang, Y.; Kazemi, R.; Xu, S.; Xu, Z-L.; Sanchez, T.W.; Yang, L-M.; Debnath, B.; Odde, S .; Xie, H.; Zheng, Y-T.; Ding, J.; Neamati, N .; Long, Y-Q. *J. Med. Chem.* **2012**, *55*, 9492.

92. Esposito, F.; Tramontano, E. *Antiviral. Chem. Chemother.* **2014**; *23*:129.

93. PCT Int. Appl. (2007), WO 2007089030 A1 20070809.

94. Zhuang, L.; Wai, J.S.; Embrey, M. W.; Fisher, T. E.; Egbertson, M. S.; Payne, L. S.; Guare, J. P.; Vacca, J. P.; Hazuda, D. J.; Felock, P. J.; Wolfe, A. L.; Stillmock, K. A.; Witmer, M. V.; Moyer, G.; Schleif, W. A.; Gabryelski, L. J.; Leonard, Y. M.; Lynch, J. J.; Michelson, S. R.; Young, S. D. *J. Med. Chem.* **2003**, *46*, 453.

95. Ruchelman, A. L.; Singh, S. K.; Ray, A.; Wu, H. X.; Yang, J-M.; Li, T-K.; Liu, A.; Liub, L. F.; LaVoie, E. J. *Bioorg. Med. Chem.* **2003**, *11*, 2061.

96. Carranco, I.; Diaz, J. L.; Jimenez, O.; Vendrell, M.; Albericio, F.; Royo, M.; Lavilla, R. *J. Comb. Chem.* **2005**, *7*, 33.

97. Maiti, S.; Sridharan, V.; Menéndez, J. C. *J. Comb. Chem*. **2010**, *12*, 713.

98. Vicente-Garcia, E.; Catti, F.; Ramon, R.; Lavilla, R. *Org. Lett*. **2010**, *12*, 860.

99. Lavilla, R.; Bernabeu, M. C.; Carranco, I.; Diaz, J. L. *Org. Lett*. **2003**, *5*, 717.

100. Lavilla, R.; Carranco, I.; Dı´az, J. L.; Bernabeu, M. C.; de la Rosa, G. *Mol. Diversity* **2003**, *6*, 171

101. Khan, A. T.; Khan, M. M. *Tetrahedron Lett.* **2011**, *52*. 3455.

102. Allais, C.; Grassot, J-M.; Rodriguez, J.; Constantieux, T. *Chem. Rev*. **2014**, *114*, 10829.

103. Zhuravel, I. O.; Kovalenko, S. M.; Ivachtchenko, A. V.; Balakin, K. V.;Kazmirchuk, V. V. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5483.

104. (a) Lacerda, R. B.; de Lima, C. K. F.; da Silva, L. L.; Romeiro, N. C.; Miranda, A. L. P.; Barreiro, E. J.; Fraga, C. A. M. *Bioorg. Med. Chem.* **2009**, *17*, 74. (b) Duffy, C. D.; Maderna, P.; McCarthy, C.; Loscher, C.E.; Godson, C.; Guiry, P. *J. Chem. Med. Chem.* **2010**, *5*, 517.

105. Bahekar, R. H.; Jain, M. R.; Jadav, P. A.; Prajapati, V. M.; Patel, D. N.; Gupta, A. A.; Sharma, A.; Tom, R.; Bandyopadhya, D.; Modi, H.; Patel, P. R. *Bioorg. Med. Chem.* **2007**, *15*, 6782.

106. Rival, Y.; Grassy, G.; Taudou, A.; Ecalle, R. *Eur. J. Med. Chem*. **1991**, *26*, 13.

107. Buckley, G. M.; Cooper, N.; Davenport, R. J.; Dyke, H. J.; Galleway, F. P.; Gowers, L.; Haughan, A. F.; Kendall, H. J.; Lowe, C.; Montana, J. G.; Oxford, J.; Peake, J. C.; Picken, C. L.; Richard, M. D.; Sabin, V.; Sharpe, A.; Warneck, J. B. H. *Bioorg. Med. Chem. Lett*. **2002**, *12*,509.

108. Vacher, B.; Bonnaud, B.; Funes, P.; Jubault, N.; Koek, W.; Assié, M.-B.; Cosi, C.; Kleven, M. *J. Med. Chem*. **1999**, *42*, 1648.

109. O'Hagan, D. *Nat. Prod. Rep*. **2000**, 17, 435.

110. Abe, Y.; Kayakiri, H.; Satoh, S.; Inoue, T.; Sawada, Y.; Inamura, N.; Asano, M.; Aramori, I.; Hatori, C.; Sawai, H.; Oku, T.; Tanaka, H. *J. Med. Chem*. **1998**, *41*, 4062.

111. Horiuch, M.; Murakami, C.; Fukamiya, N.; Yu, D.; Chen, T.-H.; Bastow, K. F.; Zhang, D.-C.; Takaishi, Y.; Imakura, Y.; Lee, K.-H. *J. Nat. Prod.* **2006**, *69*, 1271.

112. Follot, S.; Debouzy, J.-C.; Crouzier, D.; Enguehard-Gueiffier, C.; Gueiffier, A.; Nachon, F.; Lefebvre, B.; Fauvelle, F. *Eur. J. Med. Chem*. **2009**, *44*, 3509.

113. (a) Almirante, L.; Polo, L.; Mugnaini, A.; Provinciali, E.; Rugarli, P.; Biancotti, A.; Gamba, A.; Murmann, W. *J. Med. Chem*. **1965**, *8*, 305. (b) Langer, S. Z.; Arbilla, S.; Benavides, J.; Scatton, B. *Adv. Biochem. Psychopharmacol*. **1990**, *46*, 61. (c) Mizushige, K.; Ueda, T.; Yukiiri, K.; Suzuki, H.; *Cardiovasc. Drug Rev*. **2002**, *20*, 163. (d) Forde, P. M.; Rudin, C. M. *Expert Opin. Pharmacother*. **2012**, *13*, 1195.

114. Guan, A-Y.; Liu, C-L.; Sun, X-F.; Xie, Y.; Wang, M-A. *Bioorg. Med. Chem.* **2016**, *24*, 342.

115. McDougall, P. *Agri. Service*: **2014**; 12, 216.

116. Liu, C. L. *Proceedings of Research and Development of New Agrochemicals*, Beijing, **2002**, 93.

117. Bora, D.; Deb, B.; Fuller, A. L.; Slawin, A. M. Z.; Derek Woollins, J.; Dutta, D. K. *Inorg. Chim. Acta.* **2010**, *363*, 1539.

118. Zhou, M-D.; Jain, K. R.; Gunyar, A.; Baxter, P. N. W.; Herdtweck, E.; Kuhn, F. E. *Eur. J. Inorg. Chem*. **2009**, 2907.

119. Husson, J.; Knorr, M. *J. Heterocycl. Chem*. **2012**, *49*, 453.

120. (a) Jarusiewicz, J.; Yoo, K.; Jung, K. *Synlett* **2009**, 482. (b) Lin, S.; Lu, X. *Org. Lett*. **2010**, *12*, 2536.

121. Müller, T. J. J., Bunz, U. H. F.*Functional Organic Materials*. Wiley-VCH: Weinheim, 2007.

122. Lehn, J.-M. *Supramolecular Chemistry Concepts and Perspectives*, VCH: Weinheim, 1995.

123. Kang, N.-G.; Changez, M.; Lee, J.-S. *Macromolecules* **2007**, *40*,8553.

124. Fu, G. C. *Acc. Chem. Res*. **2004**, *37*, 542.

125. Khanal, H. D.; Lee, Y. R. *Chem. Commun.* **2015**, *51*, 9467.

126. (a) Al-Saleh, B.; Abdelkhalik, M. M.; Eltoukhy, A. M.; Elnagdi, M. H. *J. Heterocycl. Chem*. **2002**, *39*, 1035. (b) Jagath Reddy, G.; Latha, D.; Thirupathaiah, C.; Srinivasa Rao, K. *Tetrahedron Lett*. **2005**, *46*, 301.

127. (a) Kantevari, S.; Chary, M. V.; Vuppalapati, S. V. N. *Tetrahedron* **2007**, *63*, 13024. (b) Kantevari, S.; Chary, M. V.; Vuppalapati, S. V. N.; Lingaiah, N. *J. Heterocycl. Chem*. **2008**, *45*, 1099. (c) Kantevari, S.; Putapatri, S. *Synlett* **2010**, 2251.

128. Lieby-Muller, F.; Allais, C.; Constantieux, T.; Rodriguez, J. *Chem. Commun*. **2008**, 4207.

129. Tenti, G.; Ramos, M. T.; Menendez, J. C. *ACS Comb. Sci*. **2012**, *14*, 551.

130. Allais, C.; Constantieux, T.; Rodriguez, J. *Chem. Eur. J*. **2009**, *15*, 12945.

131. Allais, C.; Lieby-Muller, F.; Constantieux, T.; Rodriguez, J. *Adv. Synth. Catal*. **2012**, *354*, 2537.

132. Raja, V. P. A.; Tenti, G.; Perumal, S.; Menendez, J. C. *Chem. Commun*. **2014**, *50*, 12270.

133. (a) Kahandal, S. S.; Kale, S. R.; Gawande, M. B.; Jayaram, R. V. *Catal. Sci. Technol*. **2014,** *4*, 672.(b) Iwanami, M.; Shibanuma, T.; Fujimoto, M.; Kawai, P.; Tamazawa, K.;

Takenaka, T.; Takahashi, K.; Murakami, M. *Chem. Pharm. Bull*. **1979**, *27*, 1426. (c) Buhler, F. R.; Kiowski, W. *J. of Hyperten*. **1987**, *S3*: 3.

134. Baumert, C.; Gunthel, M.; Krawczyk, S.; Hemmer, M.; Wersig, T.; Langner, A.; Molnar, J.; Lage, H.; Hilgeroth, A. *Bioorg. Med. Chem.* **2013**, *21*, 166.

135. Singh, L.; Ishar, M. P. S.; Elango, M.; Subramanian, V.; Gupta, V.; Kanwal, P. *J. Org. Chem*. **2008**, *73*, 2224.

136. (a) Das, D. K.; Sarkar, S.; Khan, A. T.; Saravanan, P.; Patra, S. *RSC Adv*. **2014**, *4*, 3581. (b) Khan, A. T.; Gosh, A.; Basha, R. S.; Mir, M. H. *Asian J. Org. Chem*. **2013**, *2*, 126. (c) Dar, A. A.; Ali, S.; Khan, A. T. *Tetrahedron Lett.* **2014**, *55*, 486.

137. Bhuyan, D.; Sarma, R.; Prajapati, D. *Tetrahedron Lett*. **2012**, *53*, 6460.

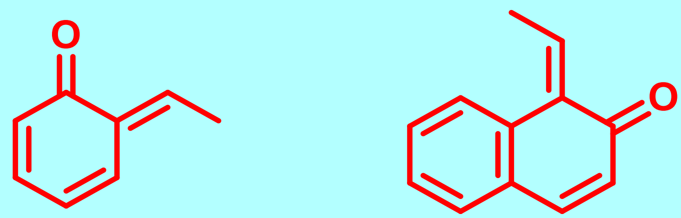
138. Khan, A. T.; Das, D. K. *Tetrahedron Lett*. **2012**, *53*, 2345.

139. (a) Kudale, A. A.; Kendall, J.; Miller, D. O.; Collins, J. L.; Bodwell, G. J. *J. Org. Chem*. **2008**, *73*, 8437. (b) Khan, A. T.; Das, D. K.; Islam, K.; Das, P. *Tetrahedron Lett*. **2012**, *53*, 6418. (c) Kudale, A. A.; Miller, D. O.; Dawe, L. N.; Bodwell, G. J. *Org. Biomol. Chem.* **2011**, *9*, 7196. (d) Zhang, L-J.; Lu, H-L.; Wu, Z-W.; Huang, Y-S. *Curr. Org. Chem*. **2013**, *17*, 2906.

140. Islam, K.; Das, D. K.; Khan, A. T. *Tetrahedron Lett*. **2014**, *55*, 5613.

Chapter V

ortho-(Naphtho)quinone methides in organic synthesis



ortho-(Naphtho)quinone methides

CHAPTER V

ortho-(Naphtho)quinone methides in organic synthesis

V.1. Introduction

The term ''quinone methide'' first appeared in 1942 to describe quinone equivalent in which one of the carbonyl oxygens is replaced by a methylene group (Figure 20).

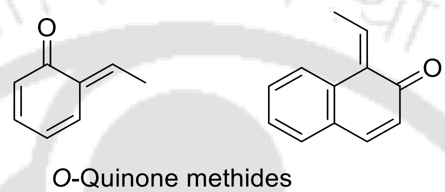


Figure 20. *ortho*-Quinone methides.

The first report on *ortho*-quinone methide (*o*-QMs) intermediate has been suggested by Fries *via* the formation of dimers and trimers for a particular reaction.[1] Gardner gave the first direct evidence of its structure by trapping the intermediate at -100 ºC in 1963.[2] The single methylene substitution is rather enough to create a highly transient intermediate which is more reactive than the parent quinone but less reactive than that of the corresponding quinodimethane in which both carbonyl oxygens are replaced by methylene groups. Quinone methides are highly polar. Although *ortho* and *para* quinone methides are the most commonly encountered isomers, *meta*-quinone methides are also known in literature. They behave as a combination of charged zwitterion and biradical (Figure 21).

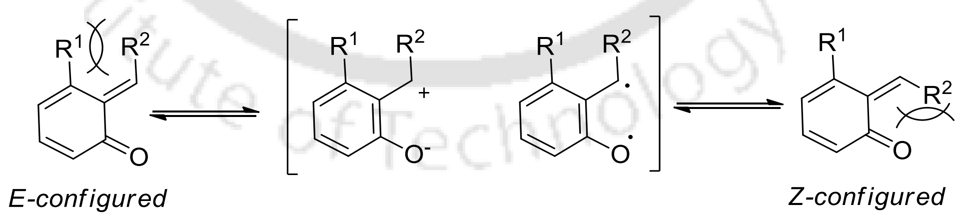
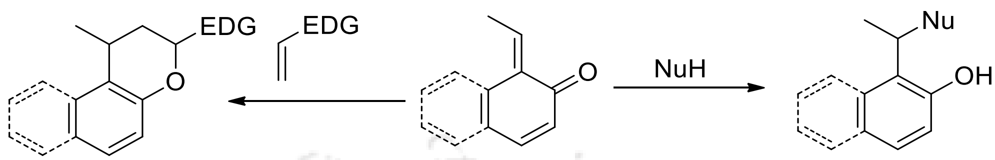


Figure 21. *o*-QMs canonical form and E/Z isomer.

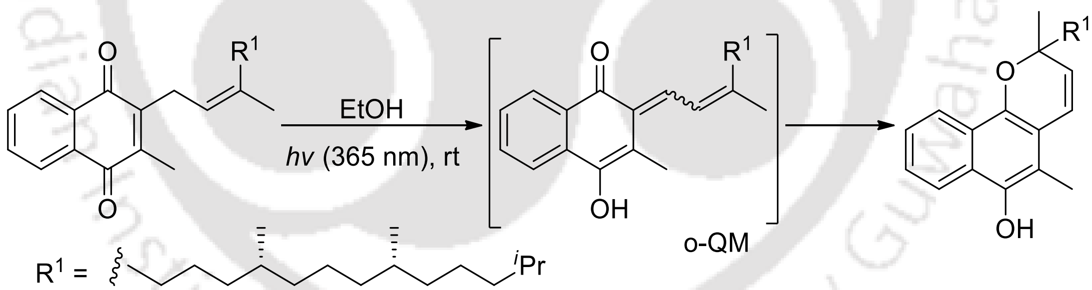
Because of their polarized nature they may react with both nucleophiles (similar to carbocations) and electrophiles (similar to phenolates). Quinone methides are much more reactive than simple enones (such as α, β-unsaturated ketones). Nucleophilic attack on a quinone methide produces an aromatic alcohol along with aromatization of the ring as the significant driving force. *o*-

(Naphtho)quinone methides can also readily engage in [4+2] cycloadditions with electron-rich dieneophiles to give chroman derivatives (Scheme 45). Due to the canonical structure they exhibit *E*/*Z* isomerism. Depending upon the steric factor, the *E* or the *Z* configuration predominates and gives diastereoselective product like in Diels-Alder reaction.



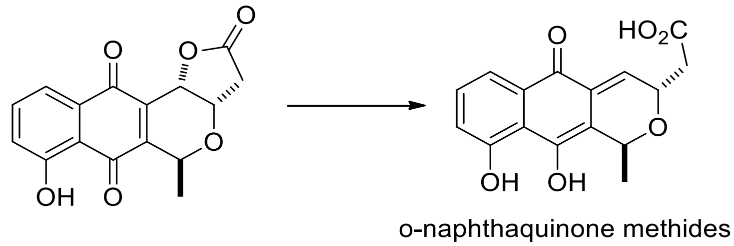
Scheme 45. Capturing of *o*-(naphtho)quinone methides by nucleophile.

o-(Naphtho)quinone methides exist widely as versatile reactive intermediates in organic synthesis, biochemistry,[3] material chemistry and pharmaceuticals.[4] The therapeutic benefits of antitumor and antibiotic drugs such as mitomycin C, vitamins E and K_1 depend on transient electrophilic nature of *o*-(naphtho)quinone methide intermediates.[5] For example, irradiation (365nm) of vitamin K_1 under nitrogen atmosphere at ambient temperature in 95% ethanol results in color change in the medium from yellow to orange (Scheme 46) due to the formation of *o*-naphthaquinone methides (o-NQMs) which after evaporation at 40 °C afforded naphthol[1,2-b]pyran in good yield.[6]



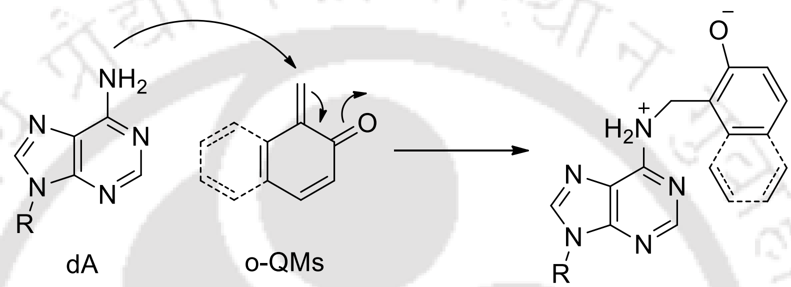
Scheme 46. *o*-(Naphtho)quinone methides intermediates from vitamin K_1.

o-(Naphtho)quinone methides have been found as bioactive species in many natural products. Some plants and insects used *o*-quinonemethides for their defense and regulation. The biological activity of kalafungin is due to the formation of reactive *o*-naphthaquinone methides (o-NQMs) upon bioreductive activation (Scheme 47).[7]



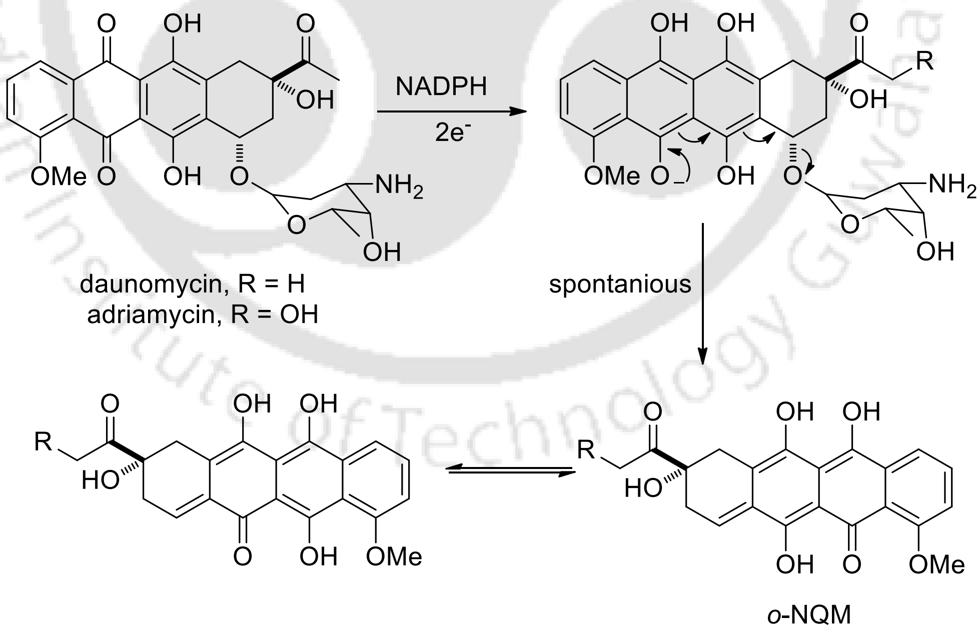
Scheme 47. Reactive *o*-naphthaquinone methides of kalafungin.

The *o*-(naphtho)quinone methides show important biological activities due to their high electrophile selectivity towards DNA and proteins (scheme 48).[8]



Scheme 48. Possible reactive locations between an *o*-QMs and dA.

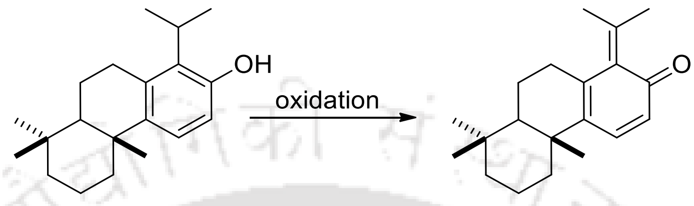
The *o*-(naphtho)quinone methides are also accountable for the bioactivity of several anti-tumor agents such as daunomycin and Adriamycin. Activity of these compounds come from the



Scheme 49. Reactive intermediates of daunomycin and adriamycin.

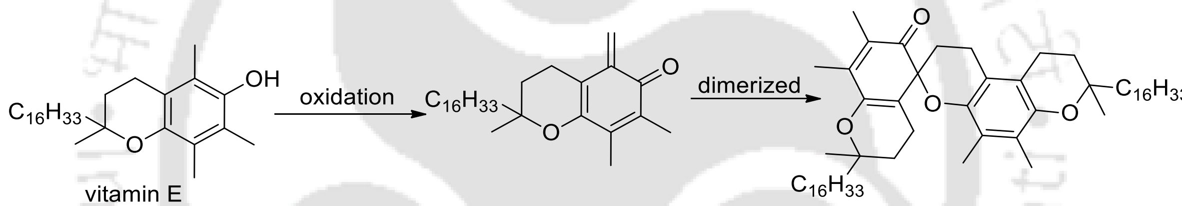
reduction of a tumor cell to phenoxide under oxygen deficient atmosphere which undergoes subsequent elimination to form *o*-NQMs and its tautomer. These reactive species further alkylate the DNA of the tumor cell (Scheme 49).[9]

Similarly the efficiency of totarol, an anti-bacterial agent is due to its ability to form *o*-QMs *via* oxidation as shown in Scheme 50.[10]



Scheme 50. Totarol oxidation to *o*-QMs.

Likewise antioxidant properties of vitamin E is because of the selective oxidation of methyl group to form *o*-QM which dimerizes further to provide its stable form (Scheme 51).[11]



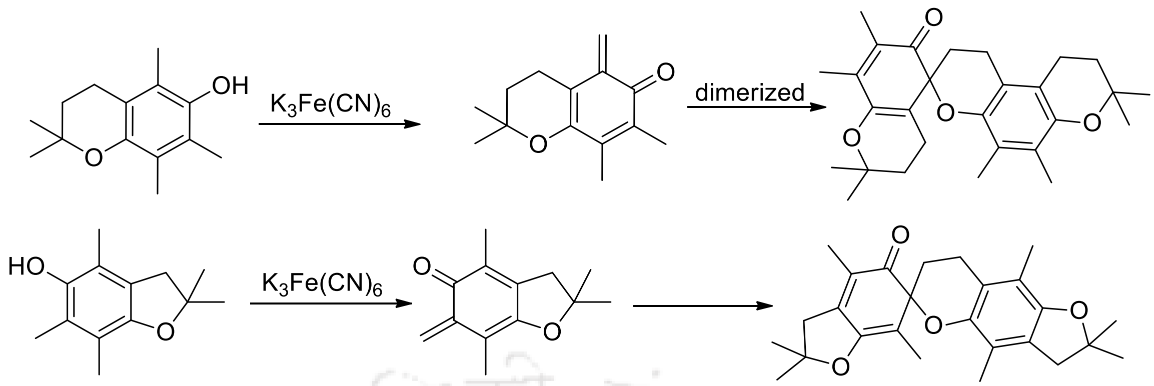
Scheme 51. *o*-QM from vitamin E.

❒ V.2. Synthetic method for the generation of *o*-(naphtho)quinone methides

Quinone methide (o-QM) intermediate are generated *via* a variety of synthetic methods, such as tautomerization, oxidation, photolysis, thermolysis, acid/base promoted reactions and olefination processes.

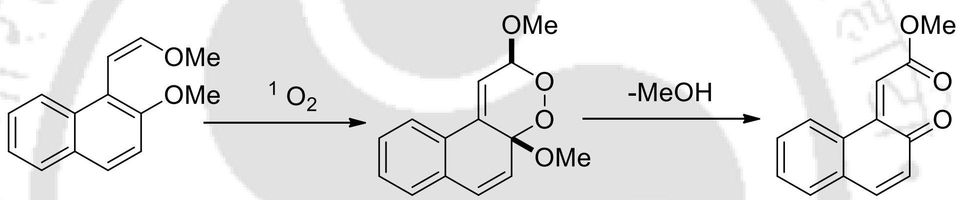
V.2.1. Oxidative methods

In biological system it has been observed that the activity of vitamin E is due to the formation of *in situ* generated *o*-QM *via* oxidation process. Dean and his group have shown the synthesis of chrome analogue of vitamin E which went through a $K_3Fe(CN)_6$ mediated oxidation to produce *o*-QM that further dimerizes in the reaction medium (Scheme 52).[12]



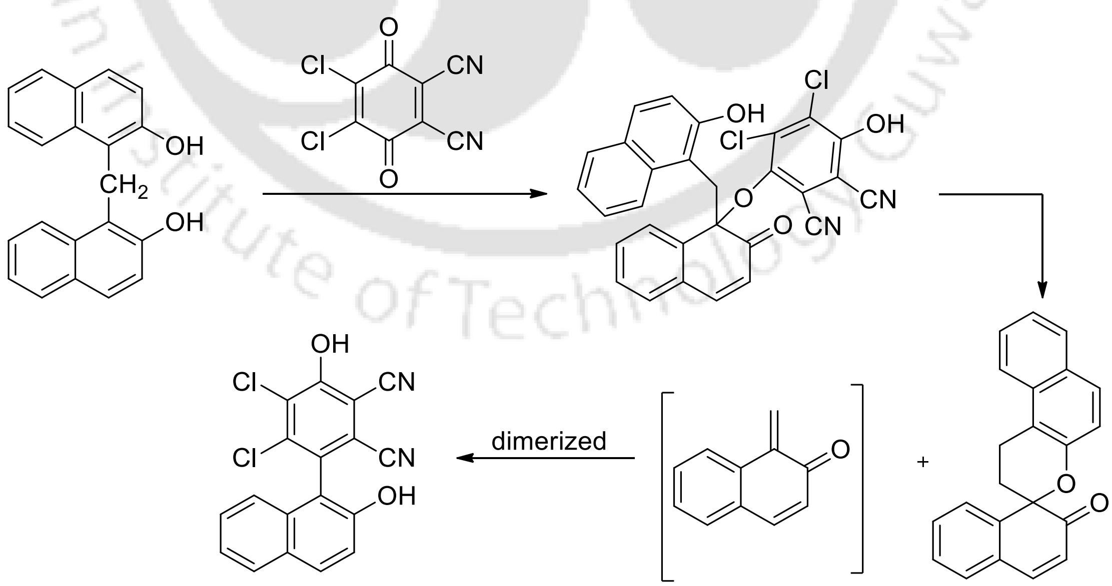
Scheme 52. Dimerization of *o*-QM.

Suzaki *et al.* discovered that the exposure of 2-methoxy-1-(2-methoxyvinyl)naphthalene in benzene in the presence of singlet oxygen [$^1O_2$] leads to *o*-naphthoquinone methides *via* peroxy intermediate (Scheme 53).[13]



Scheme 53. *o*-Naphthoquinone methides from peroxy compounds.

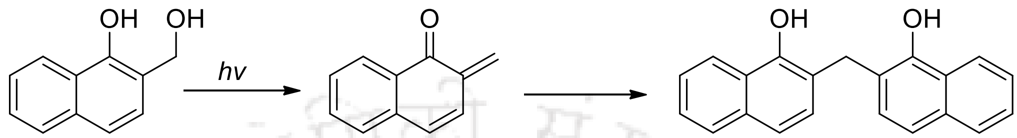
Kasturi and co-workers demonstrated the reaction of *bis*-naphthol with DDQ (1:1 molar ratio) in dry benzene to produce naphthoquinone methide dimer (Scheme 54).[14]



Scheme 54. Naphthoquinone methide dimer *via* DDQ oxidation.

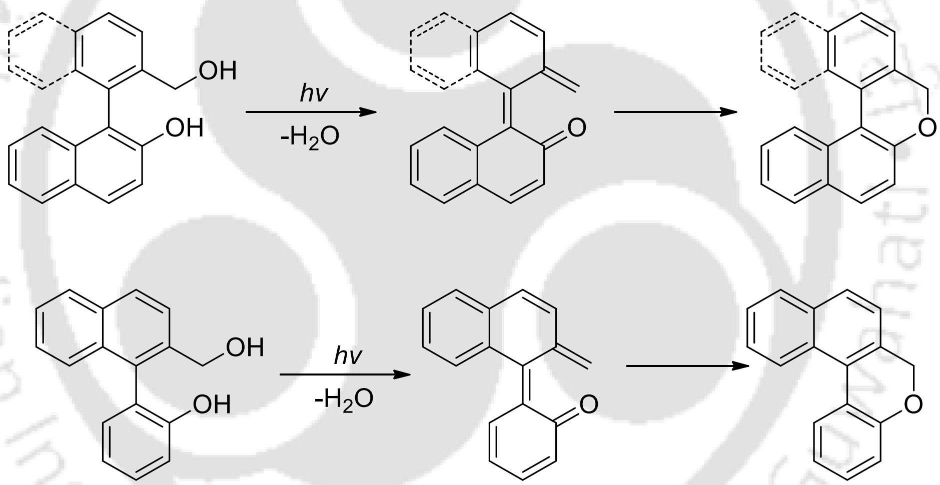
V.2.2. Photochemical generation

Recently, the Popik group has explored 2-(hydroxymethyl)-1-naphthol as a possible precursor for the photo generation of *o*-naphthaquinone methide. Further, this *o*-naphthaquinone methide intermediate undergoes self coupling to give *bis*-naphthol or [4+2] cycloaddition with vinylethers (Scheme 55).



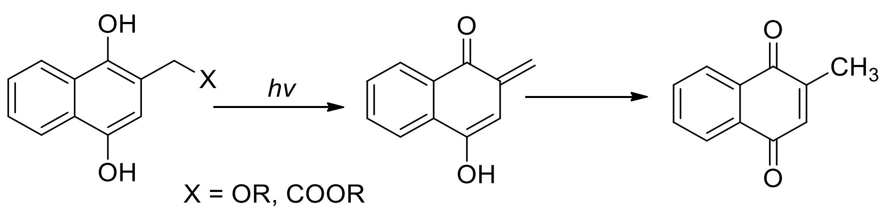
Scheme 55. Photogeneration of the *o*-naphthaquinone methide.

Biaryl systems containing naphthalene rings undergo photochemically induced dehydration. Finally, the *in situ* generated dihydrated product undergoes electrocyclic ring closing reaction to form planar diarylpyrans *via* biaryl *o*-naphthoquinone methides (Scheme 56).[15]



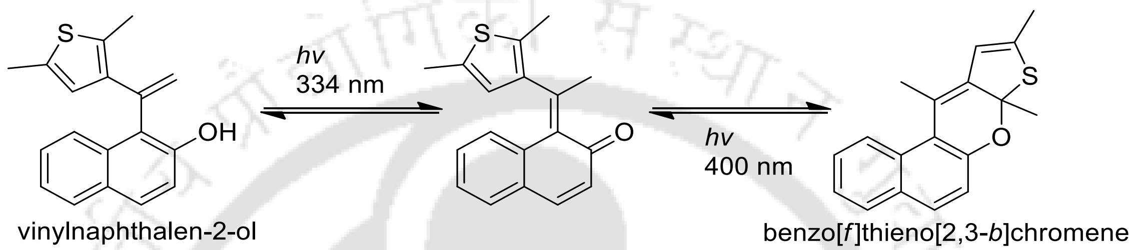
Scheme 56. Diarylpyrans from *o*-naphthoquinone methides.

1,4-Dihydroxybenzyl derivatives also follow the similar type of reaction to give *o*-naphthoquinone methides. These quinone methides rapidly tautomerized to benzoquinone in the reaction condition (Scheme 57).[16]



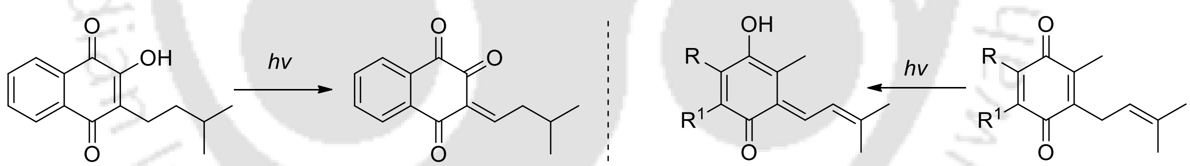
Scheme 57. Benzoquinones formation *via* 1,4-dihydroxybenzyl derivatives.

Uchida and Irie have observed the isomerization of vinyl naphthalen-2-ol on irradiation with light (334 nm) (Scheme 58). This reaction is photo reversible where an intramolecular proton transfer from the naphthol OH to the β-alkenyl carbon occurs to give intermediate *o*-naphthoquinone methides. This *o*-NQM subsequently undergoes electrocyclic ring closing to generate benzo[*f*]thieno[2,3-*b*]chromene. The reverse reaction is also presumed to go *via* the same intermediate, i.e. quinone methides can be formed *via* electrocyclic ring opening reactions.[17]



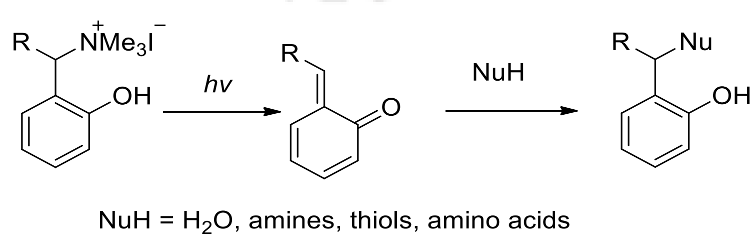
Scheme 58. Quinone methides *via* electrocyclic reaction.

It has been already discussed that vitamin K_1 and its analog co-enzyme play an essential role in biological system due to their formation of *o*-QMs upon irradiation. Ettlinger, Creed and Leary independently demonstrated that tocoquinone when irradiate with UV light produced *o*-QMs (Scheme 59).[6,18]



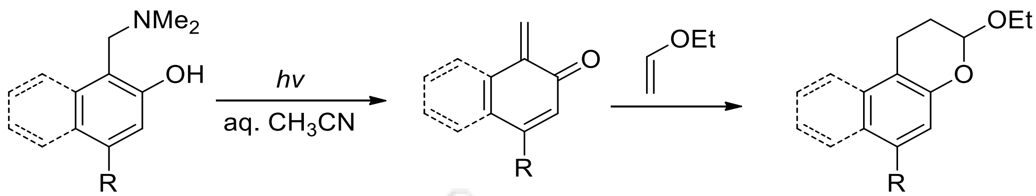
Scheme 59. *o*-Quinone methides from tocoquinone.

Freccero and his group have reported the flash photolysis of benzyl ammonium salt in water for the synthesis of *o*-QMs which undergo Michael reactions with various amines, thiols, including amino acids and glutathione (Scheme 60).[19]



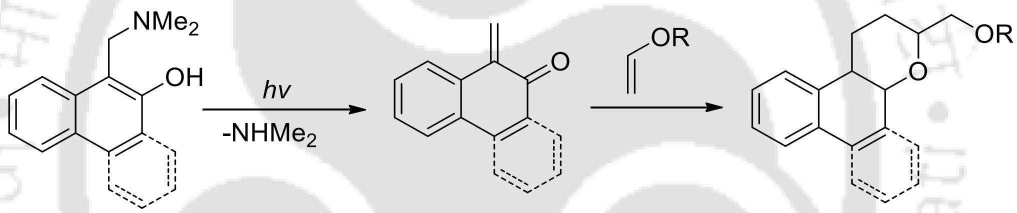
Scheme 60. Michael addition reactions of *o*-QMs.

Saito *et al.* utilized photochemical method for the generation of *o*-(naphtho)quinone methides from readily available Mannich bases (Scheme 61). This *o*-NQM was further trapped with excess of ethyl vinyl ether (EVE).[20]



Scheme 61. *o*-(Naphtho)quinone methides generation fromMannich bases.

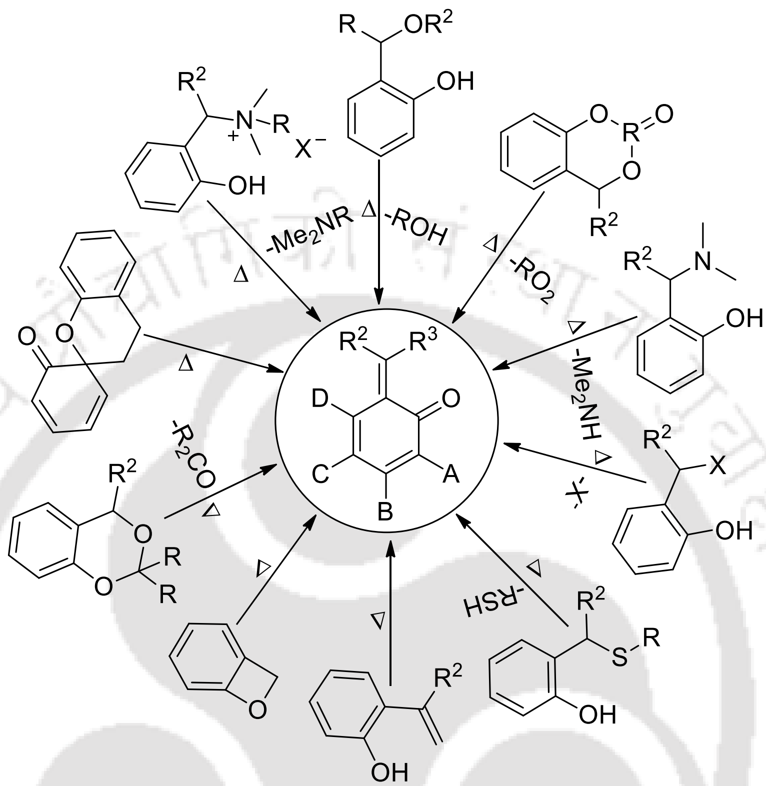
Photochemical and thermal transformation of *N*,*N*-dialkyl-9-aminomethyl-10-phenanthrols and their naphthalene analogs generates *o*-QMs precursors which readily react with alkyl vinyl ethers to give 2-alkoxydibenzo[*f*,*h*]chroman and 2-alkoxybenzo[*f*]chroman respectively (Scheme 62). These thermal and photochemical generations of QMs were accelerated by the water present in the reaction medium which helps to form an anionic micelle and vesicle.[21]



Scheme 62. Reaction *o*-QMs with alkyl vinyl ethers.

V.2.3.Thermal initiation

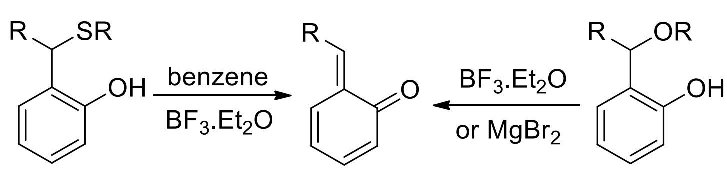
Thermolysis method is the most common method of choice among the synthetic chemists to generate *o*-QMs. Various precursors for their generation are shown in Scheme 63.[22]



Scheme 63. Thermal generation of *o*-quinone methides.

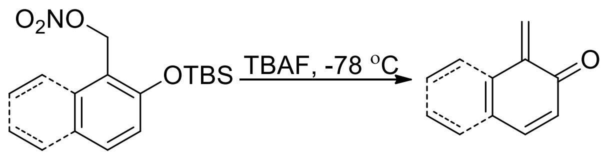
V.2.4. Acid-Base and metal triggered *o*-quinone methides formation

The tautomerization reactions are also induced by acid, base and metal salt. Lewis acid catalyzed dehydration of *o*-hydroxyl benzyl alcohols,[23] or cleavage of the methoxymethyl group of 2-(methoxymethoxy)benzyl acetates are well known.[24] Sato and his group demonstrated the assistance of $BF_3 \cdot Et_2O$ for the formation *o*-QM from *o*-(1-(alkylthio)alkyl)phenols (Scheme 64).[25]



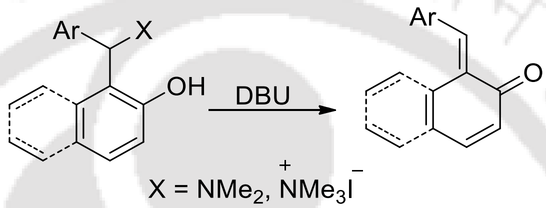
Scheme 64. *o*-QM from *o*-(1-(alkylthio)alkyl)phenols.

Varvounis *et al*. shown the generation of *o*-(naphtho)quinone methides *via* fluoride-induced desilylation of silyl derivatives of *o*-hydroxybenzyl(1-naphthylmethyl) nitrate (Scheme 65).[26]



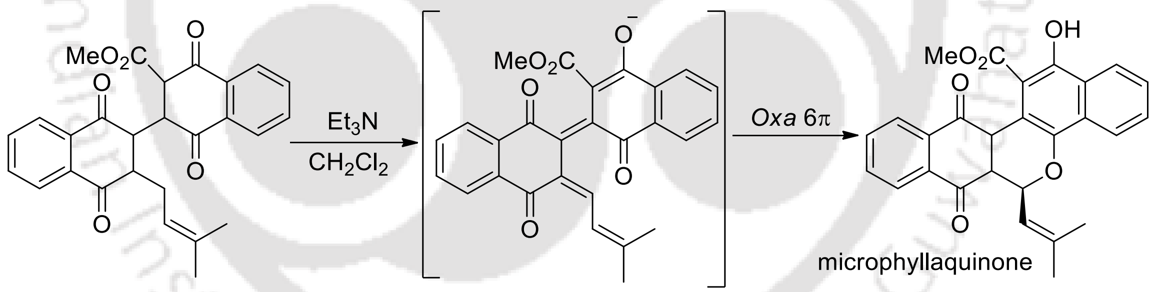
Scheme 65. *o*-(Naphtho)quinone methides *via* fluoride-induced desilylation.

Osyanin *et al.* used phenolic Mannich bases for the synthesis of *ortho*-(naphtho)quinone methide precursor. In the presence of DBU at refluxing temperature phenolic Mannich bases easily converted to *ortho*-(naphtho)quinone methide which was captured by various ylides (Scheme 66).[27]



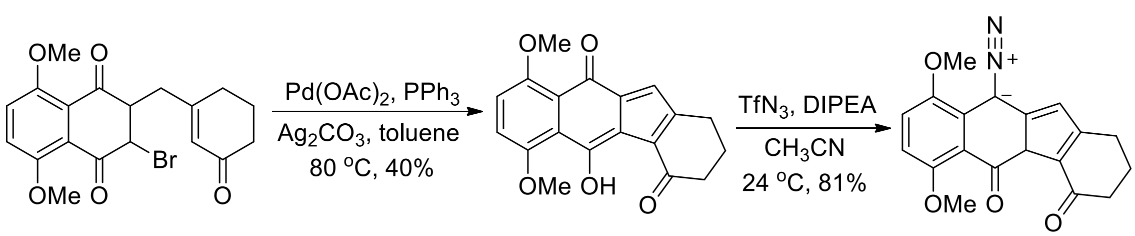
Scheme 66. BDU assisted *o*-(naphtho)quinone methide generation.

Trauner *et al.* reported biomimetic synthesis of microphyllaquinone *via* the *oxa* 6π-electrocyclization reaction of the in situ generated *ortho*-quinone methide (Scheme 67).[28]



Scheme 67. Electrocyclization of *o*-quinone methide.

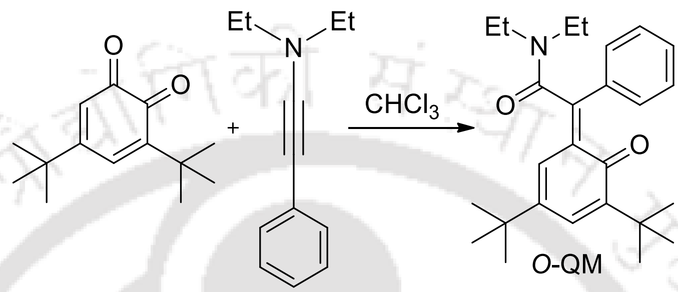
Herzon and his group used palladium catalyst for the generation *o*-naphthoquinone methides intermediate from 2,3-dihydronaphthalene-1,4-dione. The resultant intermediate was captured by trifluoromethanesulfonyl azide (Scheme 68).[29]



Scheme 68. Palladium acetate catalyzed generation of *o*-NQMs.

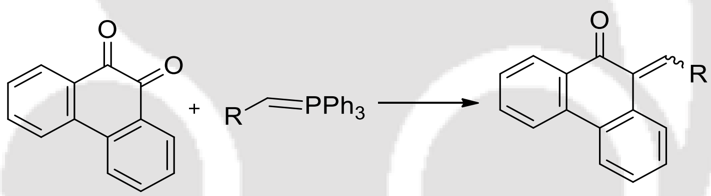
V.2.5.Olefination of quinones for generation *o*-Quinone methides

Bos *et al*. demonstrated that tertiary alkyl group substituents *o*-quinone condensed with ynamine at room temperature to generate stable isolated *o*-quinonemethide. The reaction proceeds through [2+2] cycloaddition followed by electrocyclic reaction to give *o*-QM. These *o*-QM intermediates are conjugatively stable and sterically hindered which preventing dimerization and allow to isolate (Scheme 69).[30]



Scheme 69. Isolated *o*-quinonemethide intermediate.

Shechter *et al.* demonstrated that phosphorous ylides reaction with phenanthraquinone affords *o*-QMs which was captured in the reaction medium by another ylide (Scheme 70).[31]



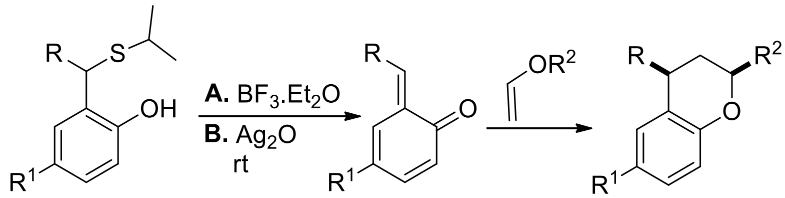
Scheme 70. Phosphorous ylides triggered generation o-QMs.

V.3. Reactions of *ortho*-(naphtho)quinone methide

The short-lived of *ortho*-(naphtho)quinone methide is because of its rapid rearomatization either by Michael reaction or [4+2] cycloaddition reaction. Sometime in high concentration of the intermediates gives dimerization and trimerization reaction.

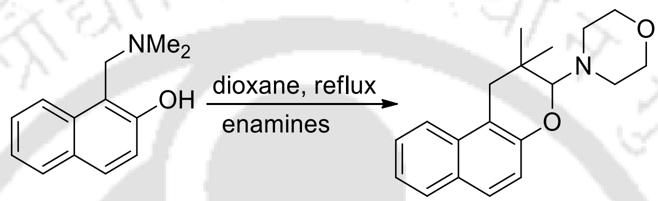
V.3.1. [4+2] Cycloaddition reaction

The most prevalent reaction of *ortho*-(naphtho)quinone methide is [4+2] Diels-Alder reaction. Sato *et al.* reported that the treatment of *o*-(1-(alkylthio)alkyl)phenols with Lewis acid produce *o*-quinone methides which participate in Diels–Alder reaction with various dienophiles (Scheme 71).[25]



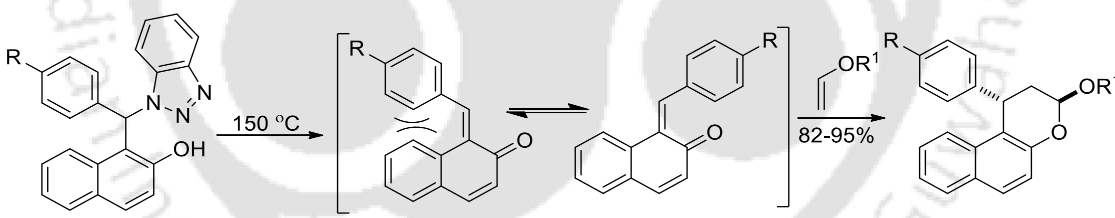
Scheme 71. Reaction of *o*-(1-(alkylthio)alkyl)phenols with dienophiles.

Strandtmann *et al*. used Mannich base to synthesized *N,O*-acetals *via* cycloaddition reaction of *in situ* generated *o*-NQM with enamines (Scheme 72).[32]



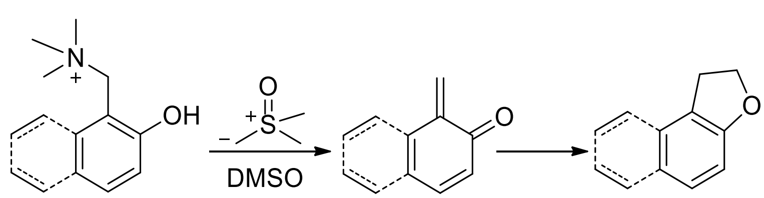
Scheme 72. Reaction *o*-NQM with enamines for the synthesis *N,O*-acetals.

Katritzky *et al*. demonstrated a thermal decomposition of 1-(triazol-1-yl)(phenyl)methyl)naphthalen-2-ol to *o*-NQM which takes part [4+2] cycloaddition reaction with olefins to chromans derivatives (Scheme 73).[33]



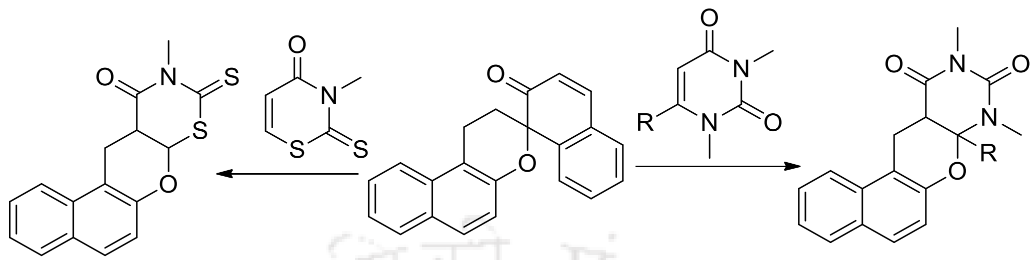
Scheme 73. 1-(triazol-1-yl)(phenyl)methyl)naphthalen-2-ol in DA reaction.

Quaternary amine salt was an alternative precursor used for the generation of *o*-NQM. Breuer *et al*. shown that quaternary amine salt reacts with dimethylsulfonium methyl ylide in DMSO to form benzo(naptha)furans (Scheme 74).[34]



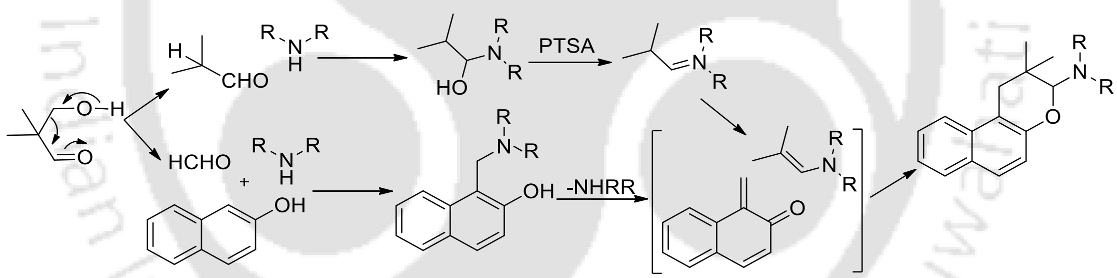
Scheme 74. Reaction of Mannich base with dimethylsulfonium methylide.

Chauhan *et al* introduced spiro dimer of napthol to generate *o*-NQM which undergoes cycloaddition reaction with various uracils to get tetracyclic products (Scheme 75).[35]



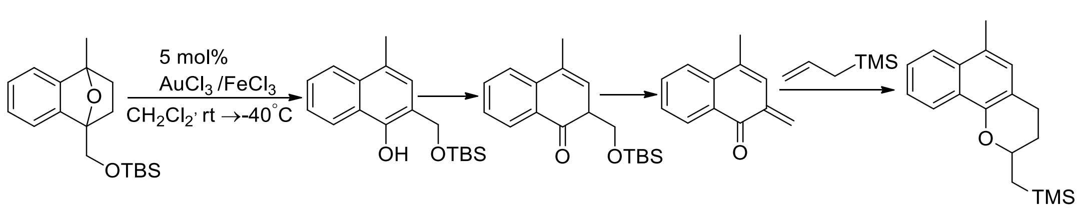
Scheme 75. Reaction of *o*-NQMwith various uracil.

Jha *et al.* shown that retro-aldol adducts of 3-hydroxy-2,2-dialkylpropanal can form both Mannich base and enamine. The Mannich base then disproportionates into *o*-NQM and regenerating the secondary amine which involved in enamine formation with 2,2-dialkylacetaldehyde. Finally, the quinone methide intermediate undergoes electrocyclic ring closure with the enamines to produce 2,2-Dialkyl-3-dialkylamino-2,3-dihydro-1H-naphtho[2,1-*b*]pyrans (Scheme 76).[36]



Scheme 76. Reaction of *o*-naphthoquinone with enamine.

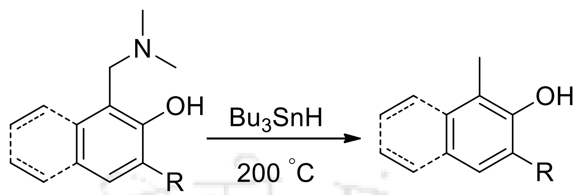
Sajiki *et al.* revealed $FeCl_3$ or $AuCl_3$ catalyzed synthesis of 1-naphthoquinone-2-methides from 1-siloxymethyl-1,4-epoxy-1,4-dihydronaphthalenes and transformation of the intermediate in an annulation reaction with various allyl silanes to afford biologically useful dihydronaphthopyran derivatives (Scheme 77).[37]



Scheme 77. Reaction of *o*-NQMswith allyl silanes to dihydronaphthopyran.

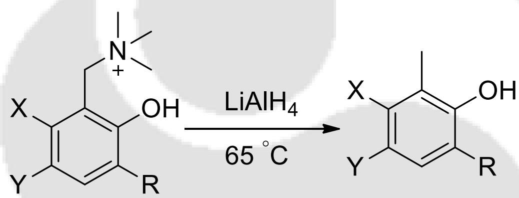
V.3.2. Addition of various nucleophiles

Chao *et al.* reported reduction of Mannich base of napthol and phenol using Bu_3SnH at 200 ºC with very high yield (Scheme 87).[38]



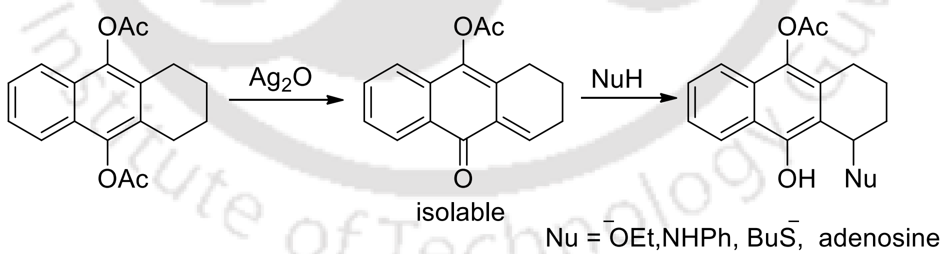
Scheme 78. Reduction of Mannich base with Bu_3SnH.

Gardner *et al*. reported reduction of quaternary amine with LAH at 65 ºC to the corresponding *o*-methyl phenols (Scheme 79).[2]



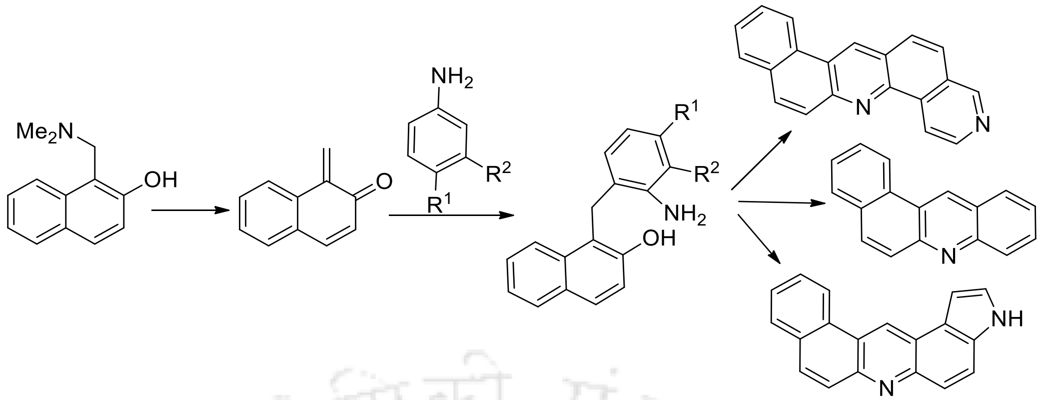
Scheme 79. Reduction of Mannich base with LAH.

Yang *et al.* developed the oxidation of anthracyclne with Ag_2O to the corresponding *o*-NQM. The isolated intermediate undergoes conjugate additions with amines, thiols, alcohols, and DNA bases (Scheme 80).[39]



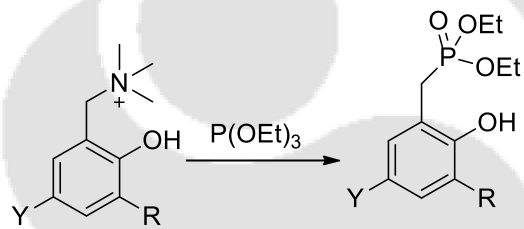
Scheme 80. Reaction of isolated *o*-NQMs intermediate with O,N,S nucleophile.

Young *et al*. utilized Mannich base of β-naphthol for the generation of *o*-NQM which reacts with aniline derivatives to give the 1,4 addition product. Subsequently, heating the 1,4 addition product gives the polycyclic heteroatomic compounds through intramolecular cyclization (Scheme 81).[40]



Scheme 81. Reaction of *o*-NQM to polycyclic heteroatomic compounds.

Pernak *et al.* demonstrated Arbusov reaction for the generating of *o*-QM from quternay amine with triethyl phosphite to the corresponding phosphate ester. (Scheme 82).[41]



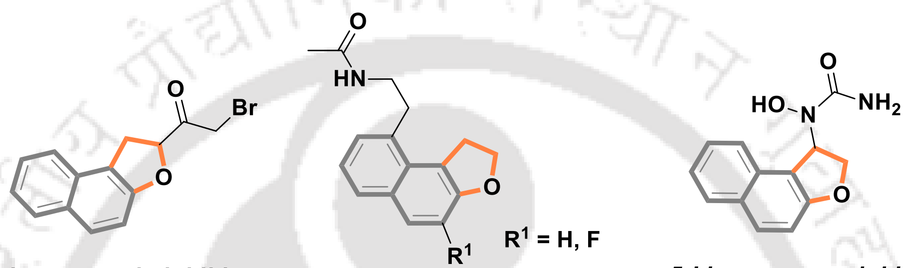
Scheme 82. Arbusov reaction of o-QM for the synthesis phosphate ester.

❒ V.4.Importance of ethers

Alkyl aryl ethers are the valuable solvents and have been extensively used for the production of fragrances, cosmetics, pharmaceutical, and dye stuffs. Nabumetone and Naproxen are used as anti-inflammatory and *trans*-3-isocamphyl-cyclohexanol as a perfume.[42] The anisole derivatives are extensively used as UV absorbers in skin protection products.[43] Moreover due to depletion of the ozone layer caused by the sun's rays, the importance of these products as UV absorbers in market is expected to grow more in future. The ether linkage adjacent to a sterically hindered carbon center is an important synthetic step for the synthesis of many biologically active compounds[44] and also used in life sciences as well as polymer industries.[45]

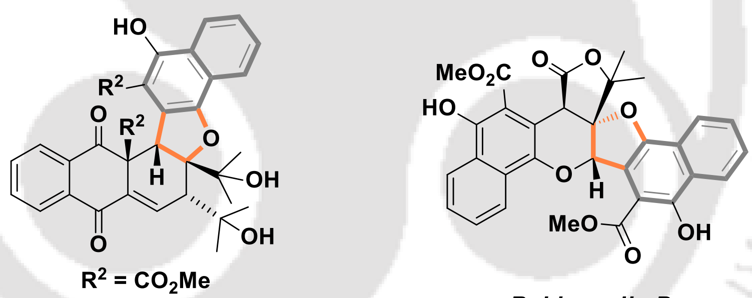
❐ V.5. Importance of 1,2-dihydronaptho[2,1-*b*]furan

1,2-dihydronaptho[2,1-*b*]furan analogues represent as one of the most intense bioactive scaffolds in sheer growing pharmaceutical industries. Its core framework is a promising molecule to investigate with the discovery of pharmacological resources such as chymotrypsin inhibitor,[46] melatonin receptor[47] and 5-lipoxygenase inhibitor[48] (Figure 22a). Its integral parts are also found in bio-significant natural products of Rubioncolin A and B[49] (Figure 22b).



α-chymotrypsin inhibitor *Melatonin receptor ligands* *5-Lipoxygenase inhibitor*

Figure 22a. Bioactive 1,2-dihydronaphtho[2,1-*b*]furans core unit

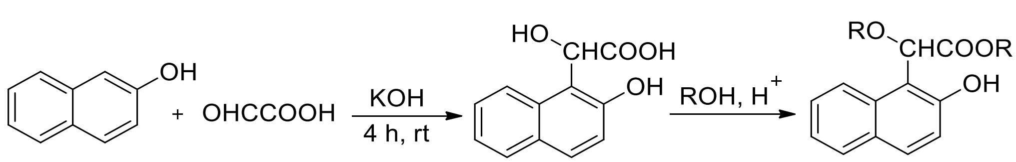


Rubioncolin A *Rubioncolin B*

Figure 22b. Natural products containing napthofuran framework

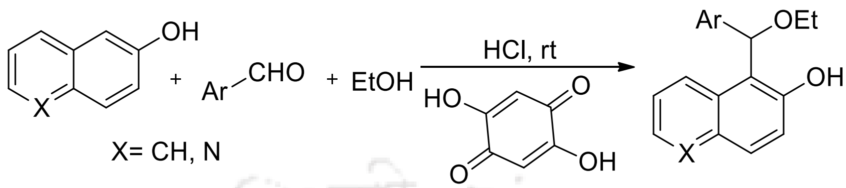
❐ V.6. Synthetic methods of unsymmetrical ethers

Yamaye *et al.* described base-catalyzed condensation of 2-naphtholwith glyoxylic acid for the preparation of α-methoxy-α-(2-methoxy-1-naphthyl)acetic acid and one of its derivatives has been resolved *via* diastereomeric salt formation (Scheme 83).[50]



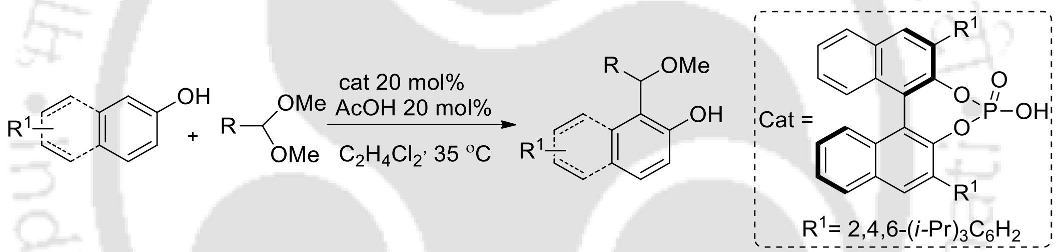
Scheme 83. Base-catalyzed condensation of 2-naphthol with glyoxylic acid.

Shaabani *et al.* demonestrated an oxy-Michael reaction between an aromatic aldehyde, EtOH and 2-naphthol or 6-hydroxyquinoline using 2,5-dihydroxy-1,4-benzoquinone as a promoter in the presence of HCl (Scheme 84).[51]



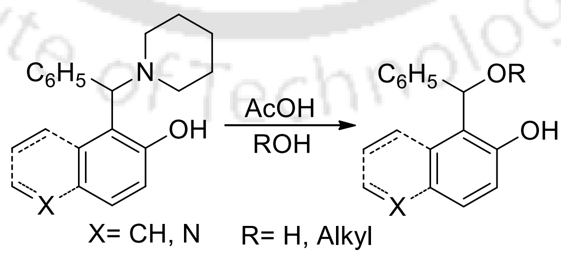
Scheme 84. Synthesis of1-[ethoxy(phenyl)methyl]-2-naphthol.

Chao-Shan Da and his group reported chiral BINOL-based phosphoric acid catalyzed asymmetric Friedel–Crafts reaction of naphthols and acetals under mild reaction conditions for the synthesis of optically active ethers. The reaction produced good yields and enantioselectivity upto 71% (Scheme 85).[52]



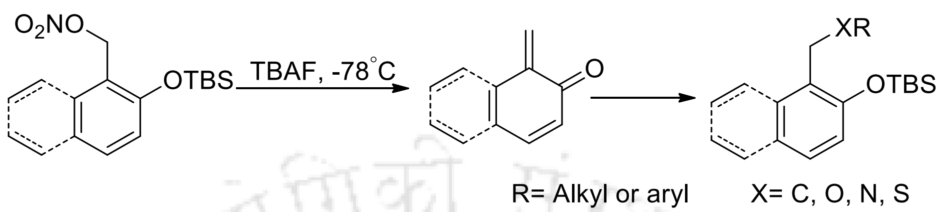
Scheme 85. Synthesis of optically active ethers using BINOL-phosphoric acid.

Miller *et al*. found that various *o/p*-substituted phenolic Mannich bases under heating condition underwent an amine elimination and subsequent addition of the solvent to the results quinone methide in the presence of Na_2EDTA or acetic acid (Scheme 86).[53]



Scheme 86. Synthesis ethers using phenolic Mannich base.

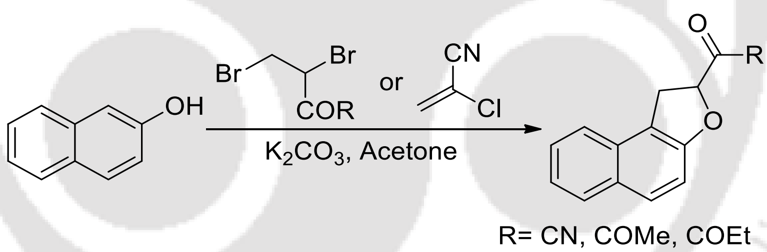
Varvounis *et al.* reported the generation of *o*-NQM from benzo and naphtho precursors bearing methylnitrate and tertbutyldimethylsilyloxy substituents at adjacent positions of the aromatic ring. The reaction involves fluoride anion nucleophilic cleavage of the silyloxy σ-bond by *n*-tetrabutylammoniumfluoride followed by concomitant elimination of a nitrate anion. The intermediate *o*-NQM was trapped by various nucleophiles such as C, O, N and S as well as dienophiles (Scheme 87).[26]



Scheme 87. Synthesis of ethers *via* fluoride anion nucleophilic cleavage of silyloxy σ-bond.

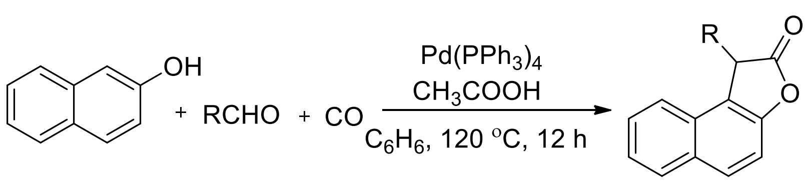
❒ V.7.Synthetic methods of 1,2-dihydronaphtho[2,1-*b*]furans

Mérour *et al* described one-pot synthesis of several functionalized 1,2-dihydronaphtho[2,1-*b*]furan derivatives from substituted 2-naphthols and ethyl 2,3-dibromopropanoates or 2-chloroacrylonitriles in the presence of K_2CO_3 in acetone (Scheme 88).[54]



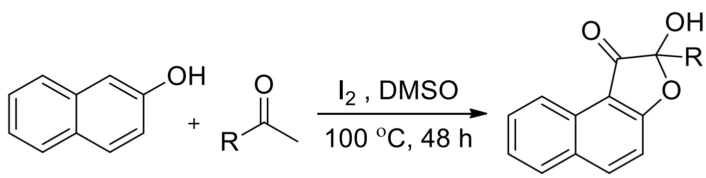
Scheme 88. Synthesis 1,2-dihydronaphtho[2,1-*b*] from ethyl 2,3-dibromopropanoates.

Miura and his group demonstrated three-component tandem reaction of 1- or 2-naphthols, aldehydes, and carbon monoxide in the presence of $Pd(PPh_3)_4/CF_3COOH$ catalytic combination under CO atmosphere in benzene at 120 ºC for the synthesis of naphthofuran-2(3*H*)-one derivatives (Scheme 89).[55]



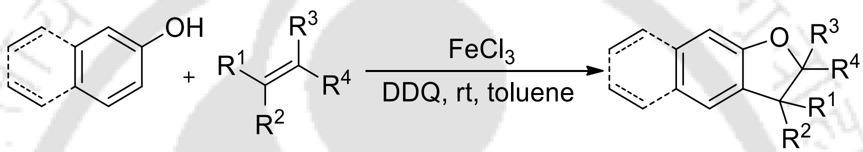
Scheme 89. Palladium catalyzedsynthesis of naphthofuran-2(3*H*)-one derivatives.

Wu *et al* developed I_2-promoted oxidative cross-coupling/annulation reaction of 2-naphthols and methyl ketones at 100 °C for the construction of naphtho[2,1-b]furan-1(2*H*)-one (Scheme 90).[56]



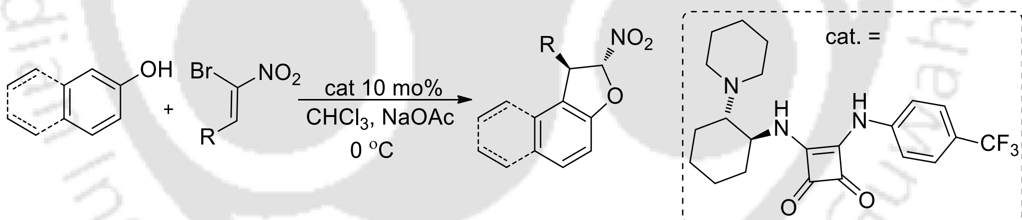
Scheme 90. I_2-promotedsynthesis of naphtho[2,1-*b*]furan-1(2*H*)-one.

Lei *et al*. demonstrared Fe-catalyzed oxidative radical cross-coupling cyclization of phenols and olefins for the synthesis of dihydrobenzofurans under mild conditions (Scheme 91).[57]



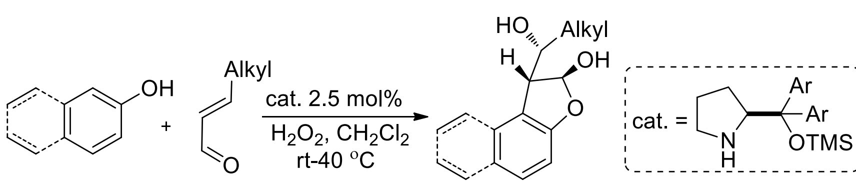
Scheme 91. Fe-catalyzed synthesis of dihydrobenzofurans.

Aleman *et al*. reported squaramide catalyzed enantioselective synthesis of trans-dihydroarylfuranderivatives using (*Z*)-bromonitroalkenes and naphthol or phenol (Scheme 92).[58]



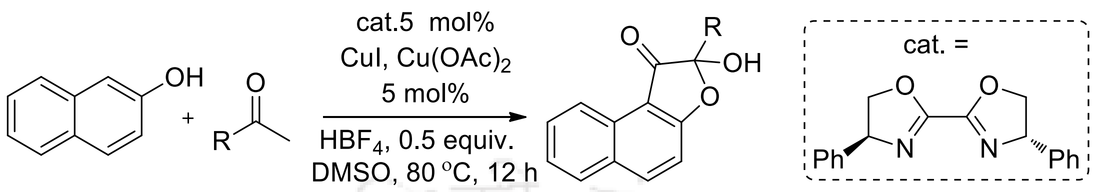
Scheme 92. Enantioselective synthesis of trans-dihydroarylfuran.

Jorgensen *et al*. utilized organo catalytic approach one-pot cascades reaction for the synthesis of optically active trans-2,3-disubstituted-2,3-dihydrobenzofurans. The reaction provided up to 97% enantiomeric excess having three contiguous stereogenic centers (Scheme 93).[59]



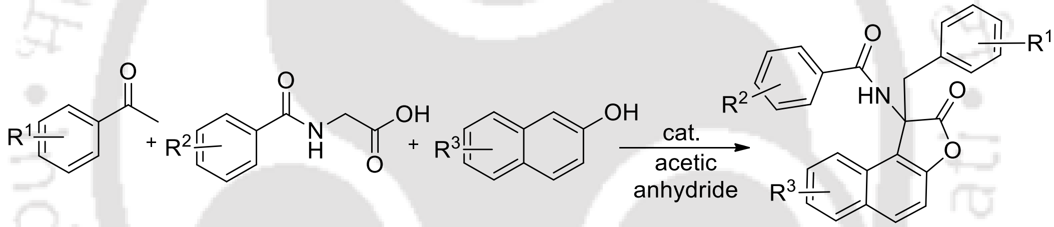
Scheme 93. Enantioselective synthesis of trans-2,3-disubstituted-2,3-dihydrobenzofurans.

Cai *et al.* developed copper-catalyzed asymmetric oxidative cross-coupling reaction of 2-naphthols with aryl methyl ketones to access enantiomerically enriched naphtho[2,1-*b*]furan-1(2*H*)-ones using molecular oxygen as an oxidant (Scheme 94).[60]



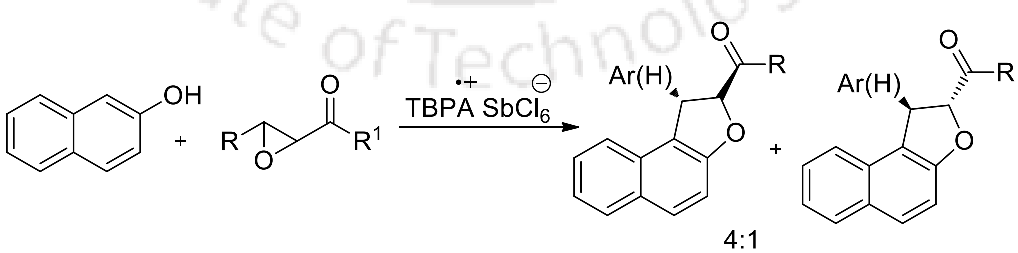
Scheme 94. Copper-catalyzed asymmetric synthesis of naphtho[2,1-*b*]furan.

Khosropour *et al.* demonstrated one-pot pseudo-four-component domino reaction of aryl aldehydes, acetic anhydride, hippuric acids, and 2-naphthols catalyzed by $H_4[Si-(W_3O_{10})_4]\cdot xH_2O$ (HSW) immobilized on silica-coated magnetitenanoparticles (SPIONs) for the synthesis of naphtho[2,1-b]furan-2(1*H*)-one derivatives (Scheme 95).[61]



Scheme 95. Synthesis of naphtho[2,1-b]furan-2(1H)-one *via* 4CR.

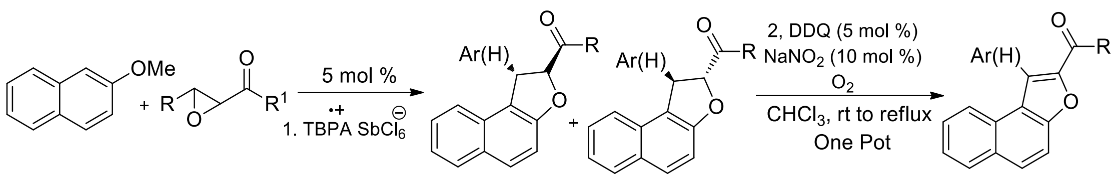
Huo *et al.* utilized Friedel-Crafts alkylation/annulation cascade reaction between chalcone epoxides and 2-naphthols for the synthesis of polysubstituted 1,2-dihydronaphtho[2,1-*b*]furans. In this reaction triarylaminium salt was used as an initiator and chalcone epoxides as a pre-electrophiles (Scheme 96).[62a,b]



Scheme 96. Synthesis 1,2-dihydronaphtho[2,1-b]furans *via* Friedel-Crafts reaction.

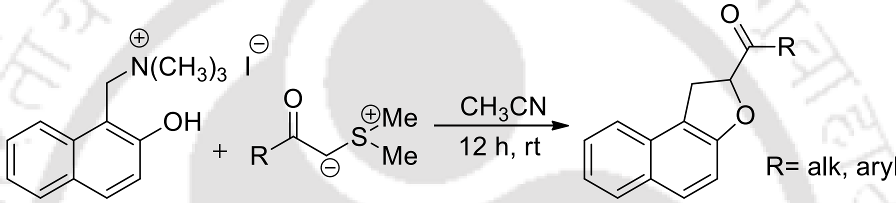
Huo *et al.* has also extended this methodology using 2-naphthyl ethers instead of 2-naphthol to access diastereomeric 1,2-dihydronaphtho[2,1-*b*]furans. Subsequent aerobic oxidation of

1,2-dihydronaphtho[2,1-*b*]furans gives aromatized naphtho[2,1-*b*]furans in one pot process (Scheme 97).[63]



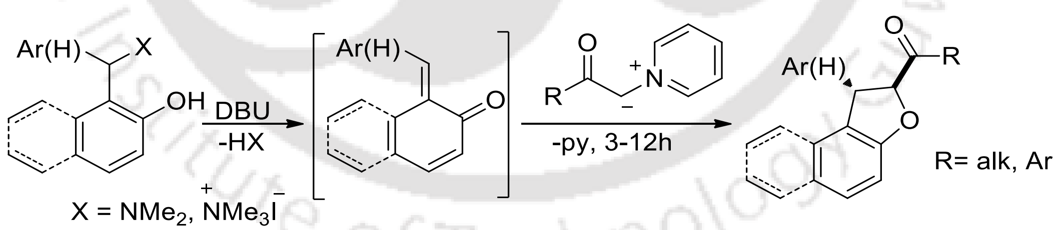
Scheme 97. Synthesis 1,2-dihydronaphtho[2,1-b]furans using 2-naphthyl ethers.

Cadona *et al.* used Mannich base and sulphonium ylides for the synthesis of 2,3 dihydrobenzofurans or 1,2-dihydronaphtho[2,1-*b*]furan derivatives (Scheme 108).[64]



Scheme 98. Synthesis 1,2-dihydronaphtho[2,1-*b*]furans using Mannich base.

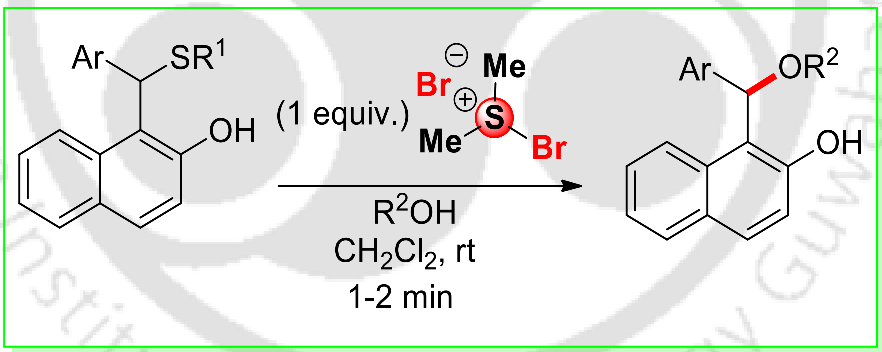
Osyanin *et al.* reported a diastereoselective synthesis of 2-acyl-1,2-dihydronaphtho(benzo)furans using (dimethylamino)methyl)-naphthalen-2-ol (phenolic Mannich bases) and pyridinium ylides under argon atmosphere. They utilized this methodology for the total synthesis of methyl (±)-7-Methoxyanodendroate (Scheme 99).[27]



Scheme 99. Synthesis of 2-acyl-1,2-dihydronaphtho(benzo)furans using pyridinium ylides.

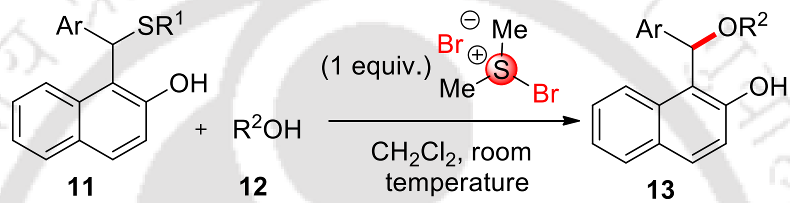
Chapter VI

A direct approach for the expedient synthesis of unsymmetrical ethers by employing bromodimethylsulfonium bromide (BDMS) mediated C-S bond cleavage of naphthalene-2-ol sulfides



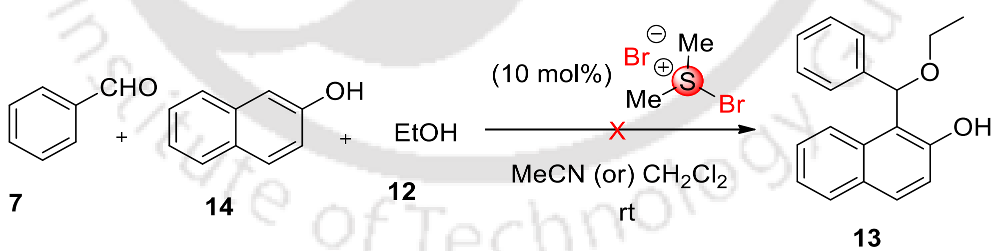
Results and Discussion

In chapter V a brief introduction on *o*-quinone methides and their synthetic utility in organic synthesis have discussed. This intermediate by capturing O and S nucleophile form various ethers. The synthetic method for the synthesis of ethers and their importance are disclosed. In this chapter a new reaction has shown for the synthesis of ether from 1-[aryl(alkyl/arylthio)methyl)-naphthalene-2-ol derivatives *via* the cleavage of C-S bond using one equivalent bromodimethylsulfonium bromide (BDMS) followed by oxa-Michael reaction with alcohols (Scheme 110).



Scheme 110. Synthesis of 1-(alkoxy(aryl)methyl)naphthalen-2-ol derivatives (**13**).

Initial attempts with a mixture of benzaldehyde (**7a**, 1 mmol), 2-naphthol (**14**, 1 mmol) and ethyl alcohol (**12a**, 2 mmol) was examined in the presence of 10 mol% of BDMS in 2 mL of CH_3CN or DCM at room temperature. Unfortunately, the attempt was unsuccessful (Scheme 111) and the expected unsymmetrical ether (**13**) is not formed instead of that we have isolated 1-bromo-2-naphthol was isolated in trace amount.



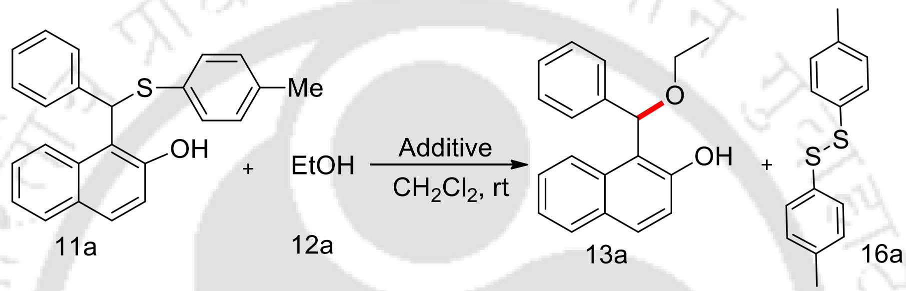
Scheme 111. Unsuccessful attempt for the synthesis of ether (**13**).

Herein an alternate strategy has been reported for the synthesis of unsymmetrical ether (**13**). Recently organic ammonium tribromides (OATB) and *in situ* generated bromonium ion utilized for C-S bond cleavage in deprotection of dithioacetals[65] and in hydrolysis of 1-thioglycosides.[66] Therefore, it might be possible to synthesize 1-(alkoxy(aryl)methyl)naphthalen-2-ol derivatives (**13**) from 1-[aryl(alkyl/arylthio)methyl)-

naphthalene-2-olderivatives (**11**) by cleavage of C-S bond through the activation with bromonium ion generated from BDMS followed by nucleophilic attack with alcohols (**12**).

Bromodimethylsulfonium bromide (BDMS) is a useful brominating agent as well as highly efficient pre-catalyst, which has been used extensively in our laboratory[67] and others[68] for numerous organic transformations. We have prepared the unsymmetrical sulfide (**11a**) from.

Table 13. Optimization of reaction conditions for the synthesis of 1-(ethoxy(phenyl)methyl)-naphthalen-2-ol (1**3a**)[a,b]



Entry	Additive	Amount (equiv.)	Reaction time	**13a** Yield[b] (%)
1	BDMS	0.10	2 h	trace
2	BDMS	0.50	2 h	44
3	BDMS	0.75	2 h	61
4	**BDMS**	**1.00**	**2 min**	**94**
5	Br_2	1.00	2 min	80
6	NBS	1.00	1 h	86
7	TBATB	1.00	1 h	72

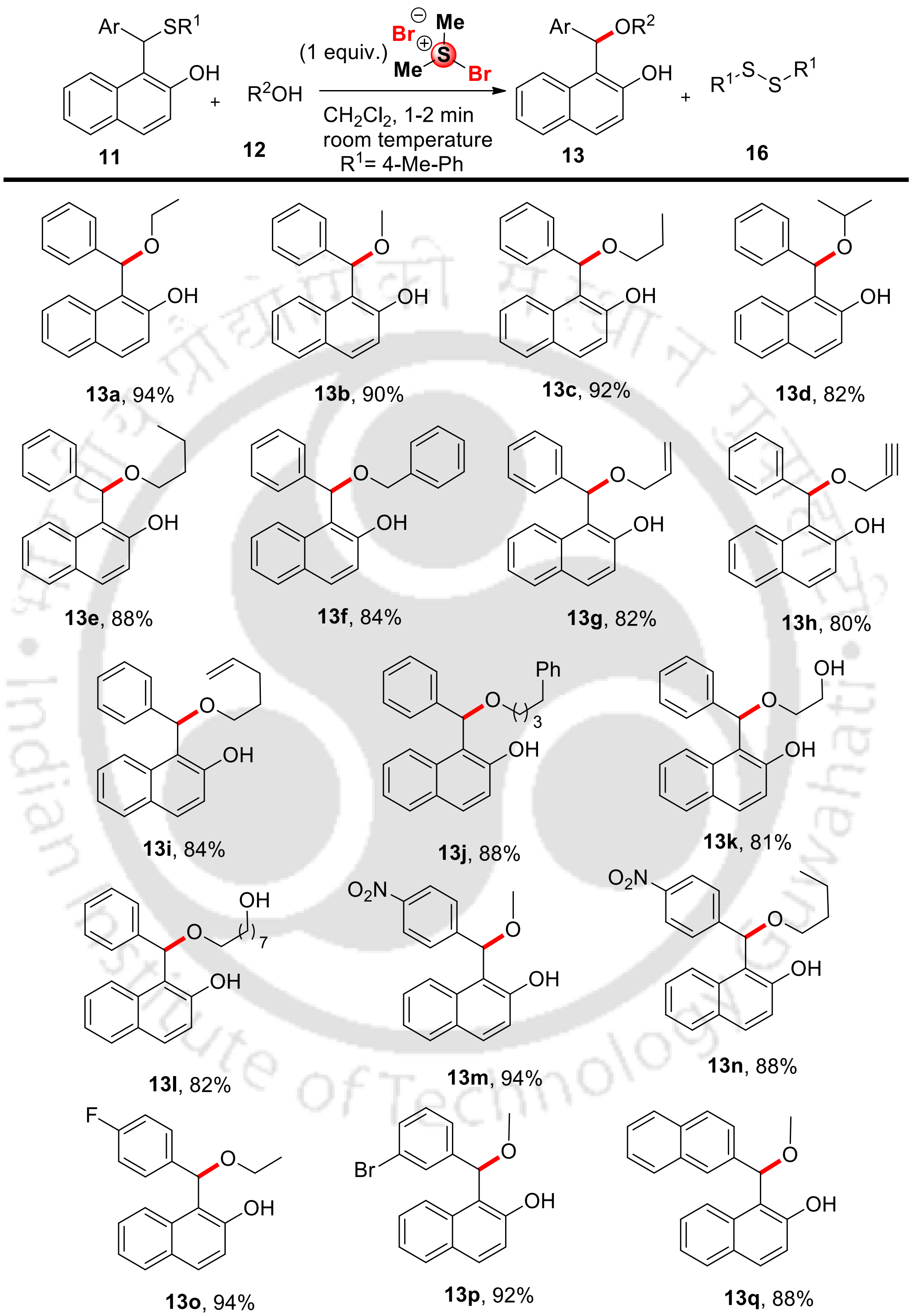
[a]All the reactions were performed with **11a** (1.0 mmol), **12a** (2.0 mmol), [b]Isolated yield.

benzaldehyde (**7a**), 2-naphthol (**14**) and 4-methylthiophenol (**15**) by following our earlier reported procedure.[69]As an initial endeavor, a trial reaction was performed with 1 mmol of sulfide (**11a**), alcohol **12** (2.0 mmol) in 2 mL of DCM. With the addition of 1 equivalent of BDMS to the reaction mixture, the reaction was completed instantaneously. After usual work up, followed by chromatographic purification, a gummy liquid product was isolated in 94% yield, which was characterized by spectroscopic techniques and found to be as 1-(Ethoxy (phenyl) methyl) naphthalen-2-ol (**13a**). IR spectrum showed characteristic strong absorptions at 3302 cm^{-1} due to the hydroxyl group of 2-naphthol. Similarly, ^{1}H NMR spectrum **13a** exhibited singlet at δ 9.38 ppm due to –OH group while ^{13}C spectrum showed peaks at δ 154.6 ppm due to the presence of the C-O carbon. Moroever, in the ^{1}H NMR spectrum of **13a,** the peak at δ 6.34 (singlet) is due to benzylic proton and at δ 3.80-3.73 ppm (multiplet), δ = 1.36 ppm (triplet) indicates the ethanol moiety present in the compound **13a.**

To ascertain the optimized conditions various trial reactions were studied in identical reaction condition with unsymmetrical sulfide **11a** using different amount of BDMS as shown in Table 13. In the presence of 0.10, 0.50 and 0.75 equivalent of BDMS the desired product **13a** was obtained along with unreacted starting material **11a** (entries 1-3, Table 13). The complete conversion was only achieved with 1.0 equivalent of BDMS using 2 mmol of EtOH in DCM (2 mL) at room temperature and the desired product **13a** was isolated in 94% (entry 4, Table 13). The required product **13a** and the by-product **16a** were characterized from ^{1}H NMR and ^{13}C NMR analysis, which encouraged to further investigate the reaction. It was observed that similar transformation is also possible using molecular bromine, NBS and TBATB however, they provide the desired product in lower yield as compared to BDMS(entries 5-7, Table 13).

After optimizing the reaction conditions, various sulfide derivatives were prepared (**11**) from aromatic aldehydes (**7**), 2-naphthol (**14**) and 4-methylthiophenol (**15**) using 10 mol% BDMS as catalyst in acetonitrile at room temperature. Next, several reactions were performed with compound **11a** and various alcohols like methanol (**12b**), *n*-propanol (**12c**), *iso*-propanol (**12d**), *n*-butanol (**12e**), benzyl alcohol (**12f**). The desired products (**13b-f)** were obtained in good yields on treatment with one equivalent of BDMS at room temperature. The reactions were completed instantaneously and the percentage yields of the products are shown in Table 14, entries 2-6.Subsequently, the reactions were carried out with different alcohols such as allyl alcohol (**12g**), propargyl alcohol (**12h**), 4-pentene-1-ol (**12i**), 4-phenylbutan-1-ol (**12j**),

Table 14. Substrate scope of various1-(alkoxy(aryl)methyl)naphthalen-2-ol derivatives **13**[a,b]



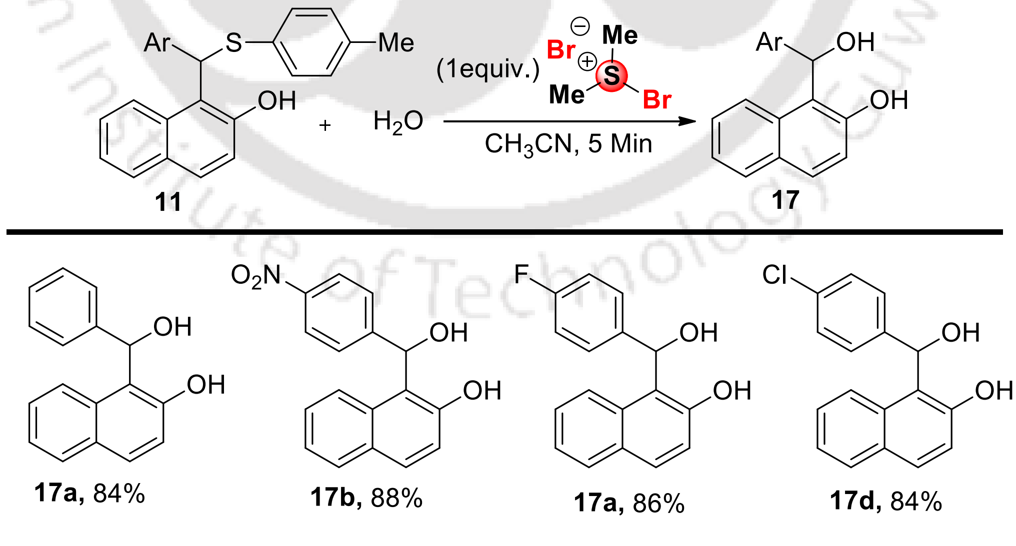
[a]The reactions were carried out with **1** (1.0 mmol) and different aliphatic alcohols **2** (2.0mmol) in the presence of one equiv. of BDMS in 2 mL of DCM at room temperature.Isolated. [a]Yield

1,2-ethanediol (**12k**) and 1,8-octanediol (**12l**) with **11a** under the identical reaction conditions and the desired products **13g-l** were isolated in good yields (Table 14, entries 7-12). The product **13k** was further confirmed by acetylation, which was characterized from ^{1}H NMR and ^{13}C NMR spectra.

To explore the synthetic scope and generality of the present protocol, other derivative of **11** containing different substituents in the aromatic ring such as NO_2, F, and Br were treated with methanol (**12b**), ethanol (**12a**) and butanol (**12b**), in the presence of one equivalent BDMS. The desired products **13m-p** were isolated in good yields. (Table 14 entries 13-16). Similarly, 1-(naphthalen-2-yl(*p*-tolylthio)methyl)naphthalen-2-ol react with methanol under similar reaction condition and the expected products **13q** obtained in 88 % yield. It is worthwhile to mention that sulphides **11** synthesized from aliphatic thiols can be transformed into the product **13** under identical reaction condition. However, the expected product does not formed in case of phenol under similar reaction condition.

Encouraged by these successful results, the synthesis of 1-(hydroxy(aryl)methyl)naphthalen-2-ol (**17**) derivatives was explored using different sulfides **11.**

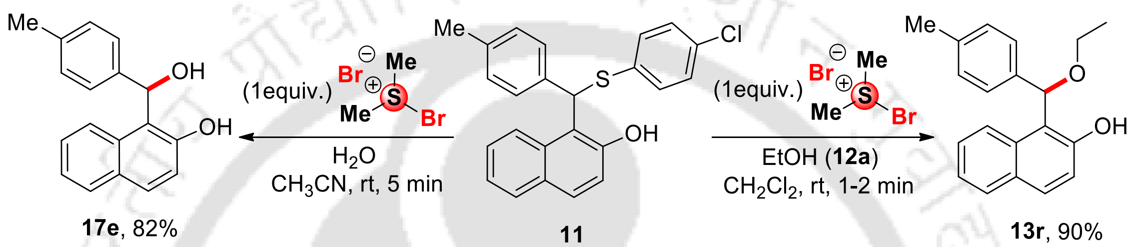
Table 15. Synthesis of substituted 1-(hydroxy(aryl)methyl) naphthalen-2-ol derivatives (**17**) using H_2O as nucleophile[a]water as a nucleophile.[a,b]



[a]The reactions were carried out with **11** (1.0 mmol) and water (40 µL) in the presence of one equiv. of BDMS in 2 mL of CH_3CN at room temperature. [b]Isolated Yield.

Various other aromatic sulfide derivatives of **11** also on treatment with one equivalent of BDMS in acetonitrile solvent at room temperature provided the expected products **17a-d** in good to excellent yield (Table 15).

The reaction was also carried out with different substituted sulphur moiety such as 1-(((4-chlorophenyl)thio)(*p*-tolyl)methyl)naphthalen-2-ol with ethanol or water under identical reaction conditions which afford the required product **13r** and **17e** with 90% and 82% yield (Scheme 112).

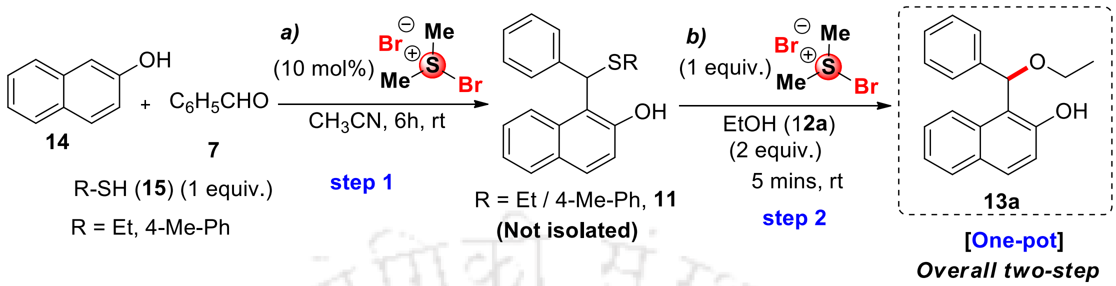


Scheme 112. Synthesis of ether **13r** and hydrins**17e** from 4-chlorophenylthio derivative.

Finally, the structures of the representative compounds 1-(alkoxy(aryl)methyl) naphthalen-2-ol such as (**13p**) and 1-(hydroxy(aryl)methyl)naphthalen-2-ol (**17a**) were also ascertained by single crystal X-ray diffraction data as shown in Figure 23.

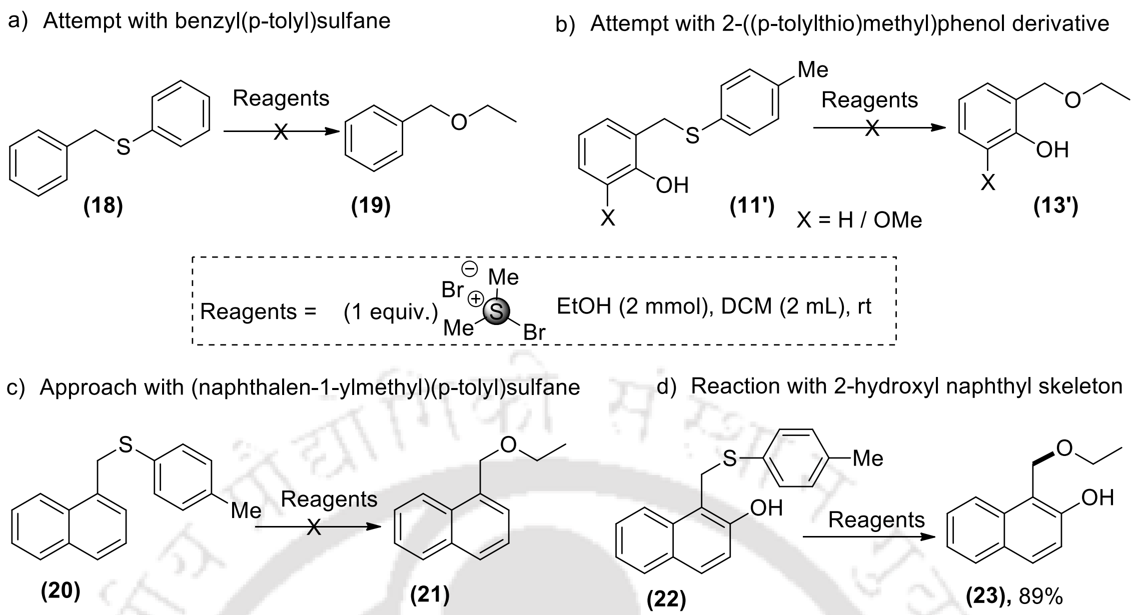
Fig. 23. Crystal structures of **13p** and **17a.**

Next, it is possible to achieve the transformation in a one-pot manner, by trapping 2-naphthoquinone-1-methide intermediate with thiol using 10 mol% BDMS followed by cleavage of it with another equivalent of BDMS. For this purpose, two set of reactions were conducted using benzaldehyde, 2-naphthol and ethane thiol or 4-methylthiophenol followed by addition of 2 equiv. of ethanol (Scheme 113) and the desired product **13a** was isolated in 64% and 70% yield, respectively. It is noteworthy to mention here that when similar reaction was carried out without consequent addition of BDMS (1.1 equivalent of BDMS at once) it gave exclusively 1-bromo-2-naphthol instead of the expected product **13a**.



Scheme 113. One-pot synthesis of 1-(alkoxy(aryl)methyl) naphthalen-2-ol (**13a**).

To understand the mechanism of the reaction, four different reactions as shown in Scheme 114. At first, the substrate benzyl(*p*-tolyl)sulfane **18** was treated with treatment of 1 equiv. BDMS in the presence of 2 mmol of ethanol in 2 mL of DCM to obtain desired product **19.** Unfortunately, the expected benzyl ethyl ether didn't formed. Next by putting a hydroxyl group at the *ortho* position of the phenyl ring, may get the expected ether **13a'** from cleavage of thioether **11a'**. In this case, the reaction failed. The failure of the reaction may be due to *ortho*-quinone-1-methide intermediate is very much less stable as compared to 2-naphthoquinone-1-methide intermediate. Subsequently, another reaction was carried out with fused aromatic ring of (naphthalen-1-ylmethyl)(*p*-tolyl)sulfane **20** under similar reaction condition and the product **21**was not formed as shown in Scheme 114. Interestingly, the installation of hydroxyl group in 2-position of (naphthalen-1-ylmethyl)(*p*-tolyl)sulfane **20** on treatment with 1 equivalent of BDMS in the presence of 2 mmol of ethanol in 2 mL of DCM which afford successfully 1-(ethoxymethyl)naphthalen-2-ol **23** in 89% yield as shown in Scheme 114. The obtained results indicated that presence of hydroxyl group in *ortho*-position of naphthalene ring in sulphide plays a crucial role for carrying out the transformations for the synthesis of unsymmetrical ether using alcohols.



Scheme 114. Investigation on reactant profiles.

Further investigation of compounds **11a** and **22** in HRMS shows (M+H) 233.0986 and 157.0662 which due to the presence of *o*-(naphtho)quinone methides (M+H) (Figure 24).

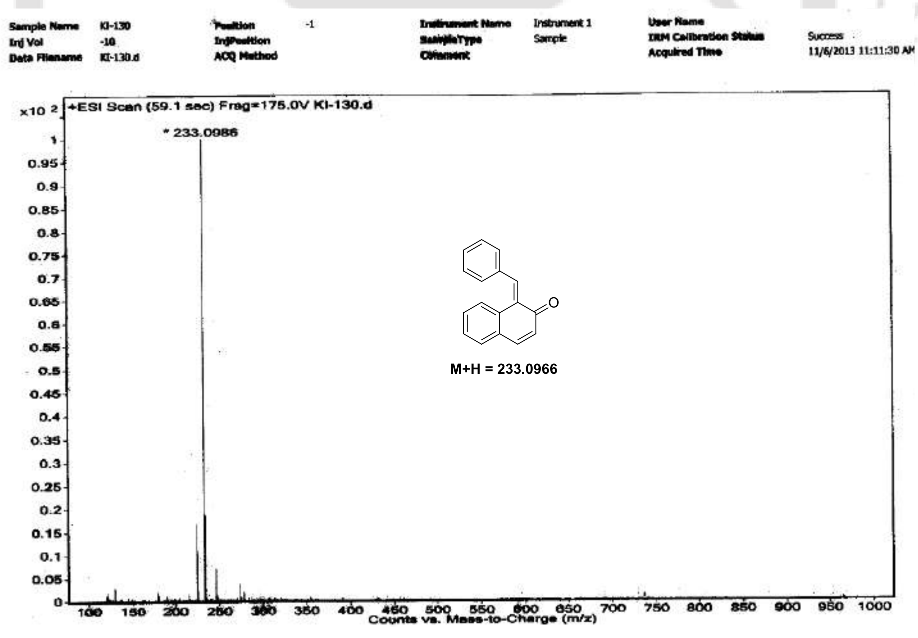
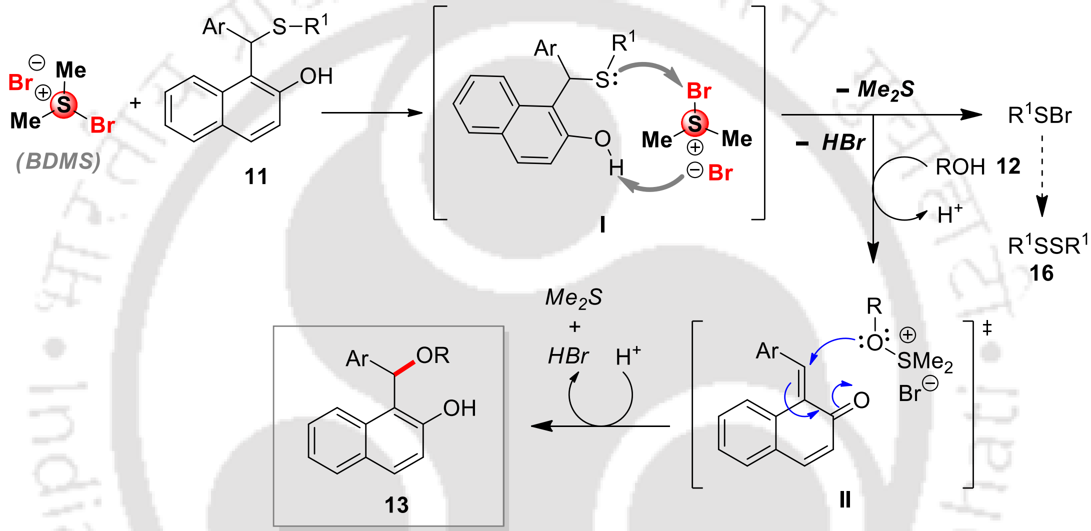


Figure 24.*o*-(Naphtho)quinone methides (M+H) from compounds **11a**.

The plausible mechanism for the formation of the product may be explained as follows: Initially, BDMS can activate the sulphur atom on **11** for cleaving C-S bond and it tend to form an intermediate **I**, then it prefer to release dimethylsulfide, HBr and R^1SBr. The incoming alcohol **12** may react with dimethyl sulphide and HBr to undergo oxa-Michael reaction which proceed through the intermediate **II**. Subsequently, the incoming H^+ ion intend to release dimethylsulfide and HBr which lead to the product **13** as shown in Scheme 115. The failure of the two reactions in Scheme 114 (**a** & **c**) and HRMS in Figure 24 evidently discard the possibility of the reaction going through direct nucleophilic substitution. The presence of -OH group at the *ortho*-position of naphthalene ring in intermediate **I** plays a prime role to facilitate the cleavage of C-S bond.



Scheme 115. Mechanism for the formation of 1-(alkoxy(aryl) methyl)naphthalen-2-ol **13**.

Conclusions

A new methodology for the synthesis of unreported unsymmetrical ether derivatives 1-(alkoxy(aryl)methyl)naphthalen-2-ols has been achieved using 1-[aryl(alkyl/aryl thio)methyl)-naphthalene-2-ol and alcohols in the presence of BDMS. This protocol might be useful for the preparation of highly substituted ethers and in addition, the reaction is simple, fast and transformation is quite effective for a wide range of substrates. Moreover, the synthesis also demonstrated that direct transformation of **13a** can be achieved in a one-pot two-step manner through consequent addition of 1.1 equiv. amount of BDMS.

Chapter VI

Experimental Section

A direct approach for the expedient synthesis of unsymmetrical ethers by employing bromodimethyl sulfonium bromide (BDMS) mediated C-S bond cleavage of naphthalene-2-ol sulfides

Experimental section

General Procedure

Synthesis of 1-(alkoxy(aryl)methyl)naphthalen-2-ol (13): In a 25 mL round bottom flask a mixture of compound **11** (1.0 mmol) and alcohol **12** (2.0 mmol) was taken in 2 mL of DCM. Then, 1 equivalent of BDMS was added to the reaction mixture and the reaction was completed instantaneously. After completion of reaction, the reaction mixture was extracted with DCM (1 x 25 mL) and washed with aqueous sodium bicarbonate. The organic layer was dried over Na_2SO_4 and it was concentrated in a rotatory evaporator. After purification through a silica gel (60-120 mesh) column chromatography, the pure product **13** was obtained in good yield.

One-pot synthesis of 1-(ethoxy(phenyl)methyl)naphthalen-2-ol derivatives (13a): Bromodimethylsulfonium bromide BDMS (0.1 mmol) was added to a mixture of benzaldehyde (1.0 mmol) and 2-naphthol (1.0 mmol) in 5 mL of acetonitrile and the reaction mixture was kept for stirring at room temperature. Then, 4-methylthiophenol (1.0 mmol) was added to it and the progress of the reaction was monitored by TLC. After 6 h of stirring, 2.0 mmol of ethanol (120 µL) and 1 equivalent BDMS were added into it and the reaction completed instantly. Then, acetonitrile was removed in a rotatory evaporator and the residue was extracted with dichloromethane (1 x 25 mL) and washed with aqueous sodium bicarbonate. The organic layer was washed with water and dried over anhydrous sodium sulfate. On concentration followed by purification through a silica gel column, the desired product **13a** was obtained.

Synthesis of 1-(hydroxy(aryl)methyl)naphthalen-2-ol (17): Into a 25 mL round bottom flask was taken 1 mmol of **11** in 2 mL of CH_3CN. To this reaction mixture, 40 µL of water and 1 equivalent of BDMS were added successively and the reaction mixture was stirred at room temperature for 5 minutes and the progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was concentrated in a rotatory evaporator and the crude residue was extracted with DCM (1 x 25 mL) and washed with water. The organic layer was dried over Na_2SO_4 and it was concentrated *in vacuo*. The pure product **17** was obtained after purification through a silica gel (60-120 mesh) column chromatography.

Crystallographic Description:

Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 296 K. Cell parameters were retrieved

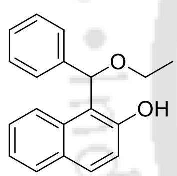
Table 16. Crystal datas and structure refinements for 13p and 17a

Identification code	13p	17a
Empirical formula	$C_{18} H_{14} Br O_2$	$C_{17} H_{14} O_2$
Formula weight	342.20	250.28
Wavelength Å	0.71073	0.71073
Temperature	296(2) K	296(2) K
Crystal system	Monoclinic	Monoclinic
Space group	*P2(1)/n*	*P2(1)/c*
Unit cell dimensions	a=13.1085(6)Å,b=7.3865(4) Å c= 16.4008(7) Å α = γ = 90.00°, β=107.548(3)°	a =4.7273(6) Å, b= 13.5885(16) Å c= 20.003(3) Å α = γ =90.00°,β=96.613(7)°
Volume Z	1514.12(13) $Å^3$ 4	1276.4(3) $Å^3$ 4
Density (calculated) Absorption coefficient	1.501 g cm^{-3} 2.716 mm^{-1}	1.302 g cm^{-3} 0.084 mm^{-1}
Reflns collected	16477	14730
Indep reflns	2659	2208
GOF	0.949	0.969
Final R indices [I>2σ(I)]	R1=0.0447 wR2 = 0.0864	R1 = 0.0434 wR2 =0.1036
R indices (all data)	R1=0.1202, wR2=0.1092	R1 = 0.0779, wR2=0.1216

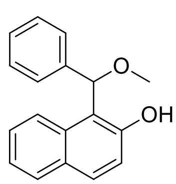
using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically.The crystal structures of**13p** and**17a** were obtained by single crystal X-ray diffraction technique. The Single crystals of **13p** was obtained by slow evaporation of dichloromethane and chloroform (1:3) solution of compound. Single crystals of **17a** was obtained by slow evaporation of dichloromethane and hexane (1:3) solution of compound. The selected crystallographic data of **13p** and**17a** are given in Table 16**.**

Spectral data

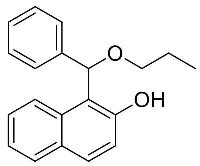
1-(Ethoxy (phenyl) methyl) naphthalen-2-ol (13a): Gummy liquid (0.261 g, 94%); R_f (2% ethyl acetate/hexane) 0.50;^{1}H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1H), 7.80-7.75 (m, 2H), 7.73 (d, J = 8.8 Hz, 1H), 7.42-7.39 (m, 3H), 7.33-7.25 (m, 4H), 7.20 (d, J = 8.8 Hz, 1H), 6.34 (s, 1H), 3.80-3.73 (m, 2H), 1.36 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6, 139.9, 132.4, 130.3, 129.0, 128.8, 128.5, 127.8, 127.0, 123.2, 121.5, 119.9, 114.9, 81.7, 66.3, 15.4 ppm; IR (KBr) ν_{max} 3302 (-OH), 1622, 1467, 1226 (C-O) cm^{-1}; Anal. Calcd for $C_{19}H_{18}O_2$ (278.35): C, 81.99; H, 6.52. Found: C, 82.14; H, 6.60.



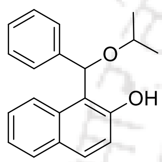
1-(Methoxy (phenyl) methyl) naphthalen-2-ol (13b): White solid (0.237 g, 90%); R_f (2% ethyl acetate/hexane) 0.65; mp 74-75°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12 (s, 1 H), 7.78-7.73 (m, 2H), 7.71 (d, J = 8.4 Hz, 1H), 7.40-7.36 (m, 3H), 7.31-7.23 (m, 4H), 7.18 (d, J = 8.4 Hz, 1H), 6.20 (s, 1H), 3.55 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 139.5, 132.4, 130.4, 129.0, 128.8, 128.5, 127.8, 127.0, 123.2, 121.4, 119.8, 114.4, 83.7, 57.9 ppm; IR (KBr) ν_{max} 3302(-OH), 1621, 1467, 1226 (C-O) cm^{-1}; Anal. Calcd for $C_{18}H_{16}O_2$ (264.32): C, 81.79; H, 6.10. Found: C, 81.94; H, 6.01; MS (ESI) calcd for $C_{18}H_{15}O_2$ (M - H^+) 263.1150, found 263.0648.



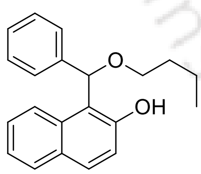
1-(Phenyl (propoxy) methyl) naphthalen-2-ol (13c): White solid (0.268 g, 92%); mp 72-73 °C; R_f (2% ethyl acetate/hexane) 0.54; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 7.78-7.70 (m, 3H), 7.41-7.36 (m, 3H), 7.30-7.22 (m, 4H), 7.18 (d, J = 8.8 Hz, 1 H), 6.31 (s, 1H), 3.70-3.57 (m, 2H), 1.78-1.68 (m, 2H), 0.97 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 139.9, 132.4, 130.2, 129.0, 128.9, 128.7, 128.4, 127.7, 126.9, 123.1, 121.5, 119.9, 115.0, 81.8, 72.4, 23.0, 10.8 ppm; IR (KBr) ν_{max} 3302 (-OH), 1601, 1467, 1226 (C-O) cm^{-1}; Anal. Calcd for $C_{20}H_{20}O_2$ (292.368): C, 82.16; H, 6.89. Found: C, 82.02; H, 6.96; MS (ESI) calcd for $C_{20}H_{19}O_2$ (M - H$^+$) 291.1385, found 291.1381.



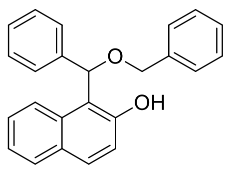
1-(Isopropoxy(phenyl)methyl)naphthalen-2-ol (13d): Light yellow solid (0.239 g, 82%); mp 43-45°C; R_f (2% ethyl acetate/hexane) 0.55; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.52 (s, 1H), 7.86-7.81 (m, 3H), 7.51-7.45 (m, 3H), 7.40-7.31 (m, 4H), 7.28 (d, J = 8.8 Hz, 1H), 6.55 (s, 1H), 4.04-3.98 (m, 1H), 1.42 (d, J = 6.0 Hz, 3H), 1.36 (d, J = 6.4 Hz, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.9, 140.3, 132.4, 130.2, 129.0, 128.8, 128.7, 128.2, 127.7, 127.0, 123.1, 121.3, 120.0, 115.5, 78.2, 71.7, 22.6, 22.0 ppm; IR (KBr) ν_{max} 3267, 1622, 1467, 1227 cm^{-1}; Anal. Calcd for $C_{20}H_{20}O_2$ (292.37): C, 82.16; H, 6.89. Found: C, 81.94; H, 6.98.



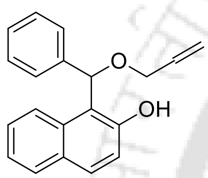
1-(Butoxy(phenyl)methyl)naphthalen-2-ol (13e): Gummy liquid (0.269 g, 88%); R_f (2% ethyl acetate/hexane) 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.8 Hz, 1H), 7.41-7.37 (m, 3H), 7.31-7.25 (m, 4H), 7.17 (d, J = 8.8 Hz, 1H), 6.31 (s, 1H), 3.74-3.62 (m, 2H), 1.70 (q, J = 6.8 Hz, 2H), 1.43 (sex, J = 7.2 Hz, 2H), 0.93 (t, J = 8.0 Hz, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ 154.5, 139.9, 132.5, 130.3, 129.0, 128.8, 128.4, 127.8, 127.0, 123.2, 121.5, 120.0, 115.0, 81.9, 70.6, 31.9, 19.6, 14.0 ppm; IR (KBr) ν_{max} 3302, 1622, 1463, 1226 (C-O) cm^{-1}; Anal. Calcd for $C_{21}H_{22}O_2$ (306.40): C, 82.32; H, 7.24. Found: C, 82.48; H, 7.34.



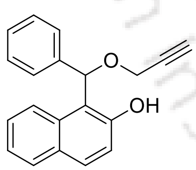
1-((Benzyloxy)(phenyl)methyl)naphthalen-2-ol (13f): Grey solid (0.285 g, 84%); mp 104-106 °C; R_f (2% ethyl acetate/hexane) 0.44; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.02 (s, 1H), 7.72-7.69 (m, 2H), 7.57 (d, J = 8.8 Hz, 1H), 7.30-7.12 (m, 13H), 6.35 (s, 1H), 4.69 (d, J = 11.6 Hz, 1H), 4.55 (d, J = 11.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.6, 139.5, 136.7, 132.6, 130.5, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 127.8, 127.1, 123.3, 121.4, 119.9, 114.5, 80.0, 71.9 ppm; IR (KBr) ν_{max} 3320, 1618, 1466, 1226 cm^{-1}; Anal. Calcd for $C_{24}H_{20}O_2$ (340.41): C, 84.68; H, 5.92 Found: C, 84.80; H, 6.01.



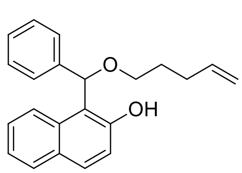
1-((Allyloxy)(phenyl)methyl)naphthalen-2-ol (13g): White solid (0.238 g, 82%); mp 60-62 °C; R_f (2% ethyl acetate/hexane) 0.44; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.14 (s, 1H), 7.77-7.30 (m, 2H), 7.70 (d, J = 8.4 Hz, 1H), 7.40-7.36 (m, 3H), 7.30-7.23 (m, 4H), 7.18 (d, J = 8.8 Hz, 1H), 6.40 (s, 1H), 6.05-5.94 (m, 1H), 5.34-5.24 (m, 2H), 4.26-4.20 (m, 1H), 4.16-4.10 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.5, 139.6, 133.4, 132.4, 130.4, 129.0, 128.9, 128.7, 128.4, 127.8, 127.0, 123.1, 121.4, 119.9, 118.9, 114.6, 80.3, 70.8 ppm; IR (KBr) ν_{max} 3312, 1621, 1600, 1467, 1225 cm^{-1}; Anal. Calcd for $C_{20}H_{18}O_2$ (290.36): C, 82.73; H, 6.25. Found: C, 82.88; H, 6.34; MS (ESI) calcd for $C_{20}H_{17}O_2$ (M - H^+) 289.1229, found 289.0776.



1-(Phenyl(prop-2-yn-1-yloxy)methyl)naphthalen-2-ol (13h): Reddish liquid (0.230 g, 80%); R_f (2% ethyl acetate/hexane) 0.35; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.59 (s, 1H), 7.80-7.74 (m, 3H), 7.44-7.39 (m, 3H), 7.34-7.27 (m, 4H), 7.19 (d, J = 8.8 Hz, 1H), 6.70 (s, 1H), 4.39 (dd, J = 2.4, 15.6 Hz, 1H), 4.29 (dd, J = 2.4, 18.0 Hz, 1H), 2.57 (t, J = 2.4 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.5, 138.8, 132.6, 130.7, 129.0, 128.8, 128.7, 128.1, 127.1, 123.3, 121.5, 119.8, 113.7, 79.4, 78.6, 76.3, 56.8 ppm; IR (KBr) ν_{max} 3350, 3290, 2118, 1622, 1468, 1224 cm^{-1}; Anal. Calcd for $C_{20}H_{16}O_2$ (288.34): C, 83.31; H, 5.59. Found: C, 83.46; H, 5.68.

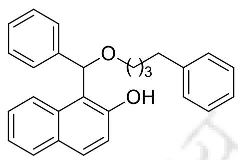


1-((Pent-4-en-1-yloxy)(phenyl)methyl)naphthalen-2-ol (13i): White(0.267 g, 84%) 58-60°C; R_f (2% ethyl acetate/hexane) 0.48; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.24 (s, 1H), 7.74-7.68 (m, 3H), 7.38-7.33 (m, 3H), 7.27-7.16 (m, 5H), 6.28 (s, 1H), 5.81-5.70 (m, 1H), 5.03-5.01 (m, 1H), 4.98-4.93 (m, 1H), 3.70-3.58 (m, 2H), 2.16-2.11 (m, 2H), 1.82-1.72 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz)

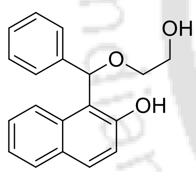


δ 154.4, 139.8, 137.8, 132.4, 130.3, 129.0, 128.9, 128.7, 128.4, 127.7, 127.0, 123.1, 121.4, 119.9, 115.5, 114.9, 81.8, 70.0, 30.4, 28.9 ppm; IR (KBr) ν_{max} 3299, 1622, 1600, 1467, 1226 cm^{-1}; Anal. Calcd for $C_{22}H_{22}O_2$ (318.41): C, 82.99; H, 6.96. Found: C, 83.16; H, 7.04; MS (ESI) calcd for $C_{22}H_{21}O_2$ (M - H^+) 317.1542, found 317.1018.

1-(Phenyl(4-phenylbutoxy)methyl)naphthalen-2-ol (13j): Yellowish liquid (0.336 g, 88 %); R_f (2% ethyl acetate/hexane) 0.43; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.24 (s, 1H), 7.74 (t, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.40-7.34 (m, 3H), 7.30-7.23 (m, 5H), 7.21-7.12 (m, 5H), 6.28 (s, 1H), 3.72-3.61 (m, 2H), 2.60 (t, *J* = 7.2 Hz, 2H), 1.74-1.69 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.4, 142.2, 139.8, 132.4, 130.3, 129.0, 128.9, 128.8, 128.6, 128.5, 128.4, 127.8, 127.0, 126.0, 123.2, 121.4, 119.9, 114.9, 81.8, 70.5, 35.7, 29.3, 28.0 ppm; IR (KBr) ν_{max} 3285, 1621, 1600, 1467, 1226 cm^{-1}; Anal. Calcd for $C_{27}H_{26}O_2$ (382.49): C, 84.78; H, 6.85. Found: C, 84.90; H, 6.93; MS (ESI) calcd for $C_{27}H_{25}O_2$ (M - H^+) 381.1855, found 381.1700.

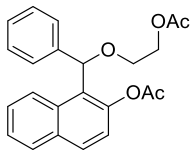


1-((2-Hydroxyethoxy)(phenyl)methyl)naphthalen-2-ol (13k): Gummy liquid (0.238 g, 81%); R_f (10% ethyl acetate/hexane) 0.13; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.97 (s, 1H), 7.78-7.73 (m, 2H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.41-7.36 (m, 3H), 7.31-7.25 (m, 4H), 7. 17 (d, *J* = 8.8 Hz, 1H), 6.38 (s, 1H), 3.83-3.74 (m, 4H), 2.16 (bs, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.3, 139.5, 132.4, 130.6, 129.1, 129.0, 128.7, 127.9, 127.1, 123.4, 121.5, 119.9, 114.5, 82.3, 71.9, 62.0 ppm; IR (KBr) ν_{max} 3317, 1621, 1600, 1467, 1224 cm^{-1}; Anal. Calcd for $C_{19}H_{18}O_3$ (294.34): C, 77.53; H, 6.16. Found: C, 77.71; H, 6.22.



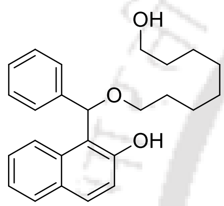
1-((2-Acetoxyethoxy)(phenyl)methyl)naphthalen-2-yl acetate (13k′): The compound **3k** (0.5 mmol) was added to a mixture of 1 mL of acetic anhydride and 1 mL of pyridine and kept for stirring overnight at room temperature. After completion of reaction, pyridine and unreacted acetic anhydride were removed by co-evaporation using toluene (1 x 2 mL) in a rotary evaporator. The resulting crude residue was purified through silica gel column to obtain pure product **3k′** in 94% yield as a gummy liquid. The product was obtained 0.138 g after purification and it was eluted with ethyl acetate and hexane (1:3).

R_f : 0.5 (2% ethyl acetate/hexane);[1]H NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 9.2 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.34-7.23 (m, 4H), 7.20-7.09 (m, 4H), 6.16



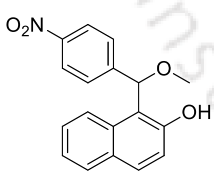
(s, 1H), 4.20-4.10 (m, 2H), 3.62-3.57 (m, 1H), 3.50-3.44 (m, 1H), 2.25 (s, 3H), 1.88 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 170.0, 148.1, 141.7, 132.8, 132.1, 130.5, 128.7, 128.3, 127.1, 126.5, 126.4, 126.0, 125.7, 121.6, 76.3, 67.2, 63.6, 21.1, 21.0 ppm; IR (KBr) ν_{max} 3058, 3022, 2928, 1766, 1730 cm^{-1}; Anal. Calcd for $C_{23}H_{22}O_5$ (378.42): C, 73.01; H, 5.86. Found: C, 73.17; H, 5.94.

1-(((8-Hydroxyoctyl)oxy)(phenyl)methyl)naphthalen-2-ol (13l): Gummy liquid (0.309 g, 82%); R_f (10% ethyl acetate/hexane) 0.26;[1]H NMR ($CDCl_3$, 400 MHz) δ 9.24 (s, 1H), 7.67



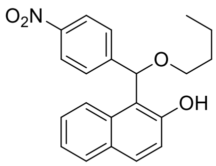
(d, J = 8.4 Hz, 2H), 7.63 (d, J = 7.6 Hz, 1H), 7.31-7.28 (m, 3H), 7.22-7.13 (m, 4H), 7.09 (d, J = 8.8 Hz, 1H), 6.21 (s, 1H), 3.59-3.49 (m, 5H), 1.63-1.57 (m, 2H), 1.46-1.42 (m, 2H), 1.35-1.21 (m, 8H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.3, 139.9, 132.3, 130.2, 128.9, 128.9, 128.7, 128.3, 127.7, 126.9, 123.1, 121.5, 119.8, 115.0, 81.7, 70.7, 62.9, 32.8, 29.7, 29.3, 26.1, 25.7 ppm; IR (KBr) ν_{max} 3303, 1622, 1601, 1463, 1226 cm^{-1}; Anal. Calcd for $C_{25}H_{30}O_3$ (378.50): C, 79.33; H, 7.99. Found: C, 79.48; H, 8.06.

1-(Methoxy(4-nitrophenyl)methyl)naphthalen-2-ol (13m): Yellow solid (0.290 g, 94%); mp 101-103°C; R_f (2% ethyl acetate/hexane) 0.24;[1]H NMR ($CDCl_3$, 400 MHz) δ 8.62 (s, 1H),

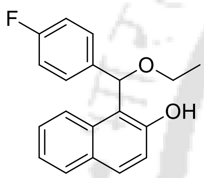


8.11 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 7.2 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 9.2 Hz, 2H), 7.46 (td, J = 8.4, 1.2 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.32 (s, 1H), 3.60 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.4, 147.8, 147.0, 132.5, 131.1, 129.3, 129.1, 128.2 127.5, 123.9, 123.58, 121.1, 119.8, 113.6, 81.4, 58.2 ppm; IR (KBr) ν_{max} 3327, 1599, 1520, 1467, 1320, 1224 cm^{-1}; Anal. Calcd for $C_{18}H_{15}NO_4$ (309.32): C, 69.89; H, 4.89; N, 4.53. Found: C, 70.07; H, 4.96; N, 4.64.

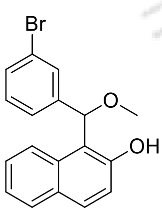
1-(Butoxy(4-nitrophenyl)methyl)naphthalen-2-ol (13n): Gummy liquid (0.308 g, 88%); R_f (2% ethyl acetate/hexane) 0.26; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.82 (s, 1H), 8.11 (d, *J* = 9.2 Hz, 2H), 7.81-7.76 (m, 2H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.45 (td, *J* = 7.2, 1.2 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 6.40 (s, 1H), 3.78-3.66 (m, 2H), 1.75-1.65 (m, 2H), 1.47-1.39 (m,2H), 0.93 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.6, 147.8, 147.3, 132.4, 131.0, 129.3, 129.1, 128.2, 127.5, 123.9, 123.5, 121.3, 119.9, 114.2, 79.8, 70.9, 31.8, 19.5, 14.0 ppm; IR (KBr) ν_{max} 3313, 1623, 1520, 1467, 1347, 1225 cm^{-1}; Anal. Calcd for $C_{21}H_{21}NO_4$ (351.40): C, 71.78; H, 6.02; N, 3.99. Found: C, 71.92; H, 5.92, N, 4.07.



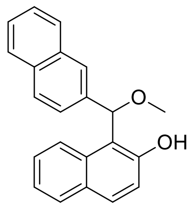
1-(Ethoxy(4-fluorophenyl)methyl)naphthalen-2-ol (13o): Gummy liquid (0.278 g, 94%); R_f (2% ethyl acetate/hexane) 0.53; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.26 (s, 1H), 7.74-7.70 (m, 2H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.38-7.24 (m, 4H), 7.18 (d, *J* = 8.8 Hz, 1H), 6.92 (t, *J* = 8.8 Hz, 2H), 6.26 (s, 1H), 3.71-3.65 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.5, 135.7, 132.3, 130.4, 129.6, 129.0, 128.9, 127.0, 123.2, 121.3, 119.8, 115.6, 115.4, 114.6, 80.8, 66.2, 15.3 ppm; IR (KBr) ν_{max} 3297, 1622, 1601, 1508, 1463, 1226 cm^{-1}; Anal. Calcd for $C_{19}H_{17}FO_2$ (296.34): C, 77.01; H, 5.78. Found: C, 77.12; H, 5.84.



1-((3-Bromophenyl)(methoxy)methyl)naphthalen-2-ol (13p): White solid (0.223 g, 92%); mp 90-92°C; R_f (2% ethyl acetate/hexane) 0.45; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.89 (s, 1H), 7.76-7.71 (m, 2H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.60-7.50 (m, 1H), 7.41-7.33 (m, 2H), 7.30-7.26 (m, 1H), 7.21-7.14 (m, 2H), 7.08-7.03 (m, 1H), 6.14 (s, 1H), 3.49 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.4, 141.9, 132.4, 131.6, 130.7, 130.4, 129.1, 129.0, 127.2, 126.3, 123.4, 122.9, 121.2, 119.9, 113.7, 82.6, 58.1 ppm; IR (KBr) ν_{max} 3318, 1622, 1599, 1468, 1224 cm^{-1}; Anal. Calcd for $C_{18}H_{15}BrO_2$ (343.21): C, 62.99; H, 4.41. Found: C, 63.14; H, 4.34; MS (ESI) calcd for $C_{18}H_{14}BrO_2$ (M - H^+) 341.0177, found 341.0165.

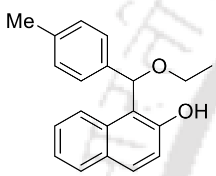


1-(Methoxy(naphthalen-2-yl)methyl)naphthalen-2-ol (13q): White solid (0.276 g, 88%); mp 98-100°C; R_f (2% ethyl acetate/hexane) 0.40; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.20 (s, 1H),



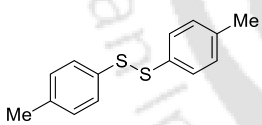
7.79-7.73 (m, 8H), 7.56 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.44-7.36 (m, 2H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 9.2 Hz, 1H), 6.36 (s, 1H), 3.60 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.5, 136.8, 133.3, 130.5, 129.0, 128.8, 128.5, 127.8, 127.0, 126.9, 126.5, 126.4, 125.7, 123.2, 121.5, 120.0, 114.3, 102.0, 84.0, 58.1 ppm; IR (KBr) ν_{max} 3300, 1622, 1599, 1466, 1225 cm^{-1}; Anal. Calcd for $C_{22}H_{18}O_2$ (314.38): C, 84.05; H, 5.77. Found: C, 84.22; H, 5.90.

1-(Ethoxy(p-tolyl)methyl)naphthalen-2-ol (13r): Yellow liquid (0.262 g, 90%); R_f (2% ethyl acetate/hexane) 0.50; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.41 (s, 1 H), 7.76-7.71 (m, 2H),



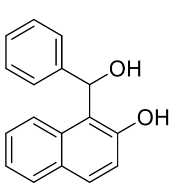
7.69 (d, *J* = 8.4 Hz, 1H), 7.36 (td, *J* = 6.8, 1.6 Hz, 1H), 7.28-7.25 (m, 3H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 8.0 Hz , 2H), 6.27 (s, 1H), 3.73-3.71 (m, 2H), 2.27 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.4, 138.1, 136.9, 132.3, 130.1, 129.4, 128.9, 127.7, 126.8, 123.0, 121.4, 119.8, 115.0, 81.6, 65.9, 21.1, 15.2 ppm; IR (KBr) ν_{max} 3287, 1622, 1600, 1467, 1226 cm^{-1}; Anal. Calcd for $C_{20}H_{20}O_2$ (292.37): C, 82.16; H, 6.89. Found: C, 82.34; H, 6.80.

Bis(4-methylphenyl)disulfide (16): Solid; mp 44-45 °C (lit. m.p 43-46°C); R_f (2% ethyl



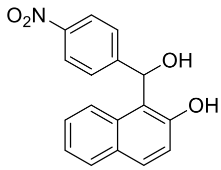
acetate/hexane) 0.80; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.0 Hz, 4H), 7.11 (d, *J* = 8 Hz, 4H), 2.32 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 134.1, 130.0, 128.7, 21.3 ppm.

1-(Hydroxy(phenyl)methyl)naphthalen-2-ol (17a): White solid (0.210 g, 84%); mp 99-



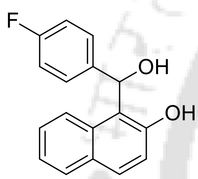
101°C; R_f (10% ethyl acetate/hexane) 0.36; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.37 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.34-7.18 (m, 7H), 7.71 (d, *J* = 8.4 Hz, 1H), 6.62 (s, 1H), 3.56 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.7, 141.5, 131.7, 130.4, 129.1, 129.0, 128.9, 128.7, 127.4, 127.0, 123.2, 121.6, 120.2, 115.9, 74.9 ppm; IR (KBr) ν_{max} 3373, 1623, 1600, 1467, 1226 cm^{-1}; Anal. Calcd for $C_{17}H_{14}O_2$ (250.29): C, 81.58; H, 5.64. Found: C, 81.35; H, 5.70; MS (ESI) calcd for $C_{17}H_{13}O_2$ (M - H^+) 249.0916, found 249.0799.

1-(Hydroxy(4-nitrophenyl)methyl)naphthalen-2-ol (17b): Reddish solid (0.260 g, 88%);



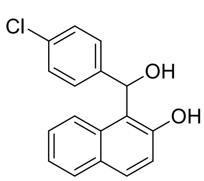
mp 130-132°C; R_f (10% ethyl acetate/hexane) 0.15; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.54 (s, 1H), 8.10 (d, J = 8.8 Hz, 2H), 7.79 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.45-7.41 (m, 1H), 7.36-7.31 (m, 1H), 7.13 (d, J = 8.8 Hz, 1H), 6.83 (s, 1H), 3.81 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 153.2, 152.1, 146.2, 131.6, 129.4, 128.5, 128.2, 126.8, 126.0, 123.2, 122.8, 122.4, 118.6, 68.4 ppm; IR (KBr) ν_{max} 3424, 1625, 1514, 1345 cm^{-1}; Anal. Calcd for $C_{17}H_{13}NO_4$ (295.29): C, 69.15; H, 4.44; N, 4.74. Found: C, 69.37; H, 4.52; N, 4.86.

1-((4-Fluorophenyl)(hydroxy)methyl)naphthalen-2-ol (17c): White solid (0.230 g, 86%); mp 101-102 °C; R_f (10% ethyl acetate/hexane) 0.31; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.19 (s,

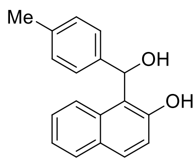


1H), 7.77-7.72 (m, 2H), 7.58 (d, J = 8.8 Hz, 1H), 7.39-7.34 (m, 3H), 7.31-7.25 (m, 1H), 7.15 (d, J = 8.8 Hz , 1H), 6.98 (t, J = 8.4 Hz, 2H), 6.72 (s, 1H), 3.27 (s, 1H) ppm; ^{1}H NMR (D_2O, 400 MHz) δ 7.76 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.39-7.25 (m, 4H), 7.15 (d, J = 8.8 Hz, 1H), 6.97 (t, J = 8.4 Hz, 2H), 6.71 (s, 1 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.5, 137.3, 131.6, 131.5, 129.2, 129.2, 129.0, 129.0, 127.1, 123.4, 121.5, 120.0, 116.2, 116.0, 115.8, 73.8 ppm; IR (KBr) ν_{max} 3372, 1622, 1467, 1226 cm^{-1}; Anal. Calcd for $C_{17}H_{13}FO_2$ (268.28): C, 76.11; H, 4.88. Found: C, 75.92; H, 4.96; MS (ESI) calcd for $C_{17}H_{12}FO_2$ (M - H^+) 267.0821, found 267.0577.

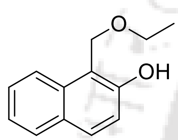
1-((4-Chlorophenyl)(hydroxy)methyl)naphthalen-2-ol (17d): White solid (0.238 g, 84%); mp 111-113 °C; R_f (10% ethyl acetate/hexane) 0.34; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, J



= 8.0 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.41-7.25 (m, 6H), 7.17 (d, J = 8.8 Hz , 1H), 6.77 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.6, 140.0, 134.4, 131.6, 130.6, 129.2, 129.1, 128.8, 127.2, 123.4, 121.5, 120.1, 116.0, 73.6 ppm; IR (KBr) ν_{max} 3378, 1622, 1467, 1226 cm^{-1}; Anal. Calcd for $C_{17}H_{13}ClO_2$ (284.74): C, 71.71; H, 4.60. Found: C, 71.48; H, 4.70.

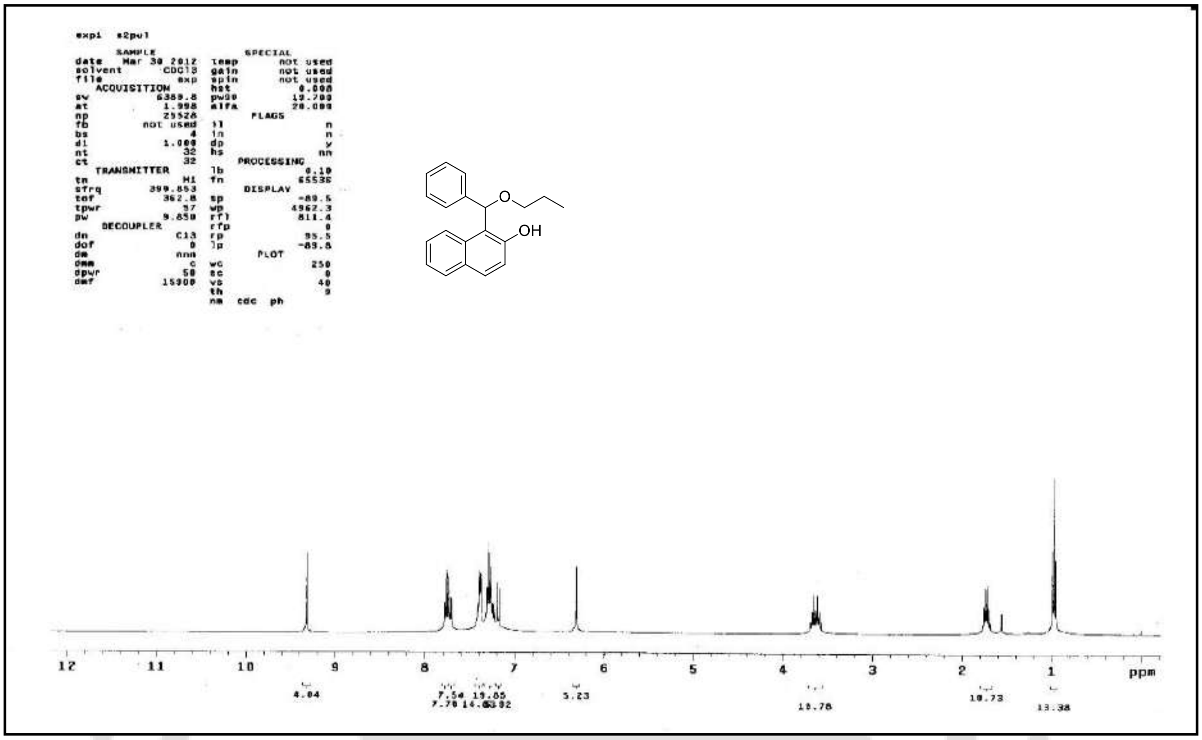


1-(Hydroxy(p-tolyl)methyl)naphthalen-2-ol (17e): White solid (0.216 g, 82%); mp 120-121°C; R_f (10% ethyl acetate/hexane) 0.35;^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.40 (s, 1H), 7.74 (t, *J* = 9.2 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.34-7.24 (m, 4H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.12 (d, *J* = 7.6 Hz , 2H), 6.73 (s, 1H), 3.14 (s, 1H), 2.30 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.8, 138.7, 138.6, 131.7, 130.3, 129.8, 128.9, 127.4, 126.9, 123.2, 121.7, 120.2, 115.9, 75.0, 21.3 ppm; IR (KBr) ν_{max} 3413, 1624, 1467, 1225 cm^{-1}; Anal. Calcd for $C_{18}H_{16}O_2$ (264.32): C, 81.79; H, 6.10. Found: C, 82.02; H, 6.16; MS (ESI) calcd for $C_{18}H_{15}O_2$ (M - H^+) 263.1072, found 263.1006.

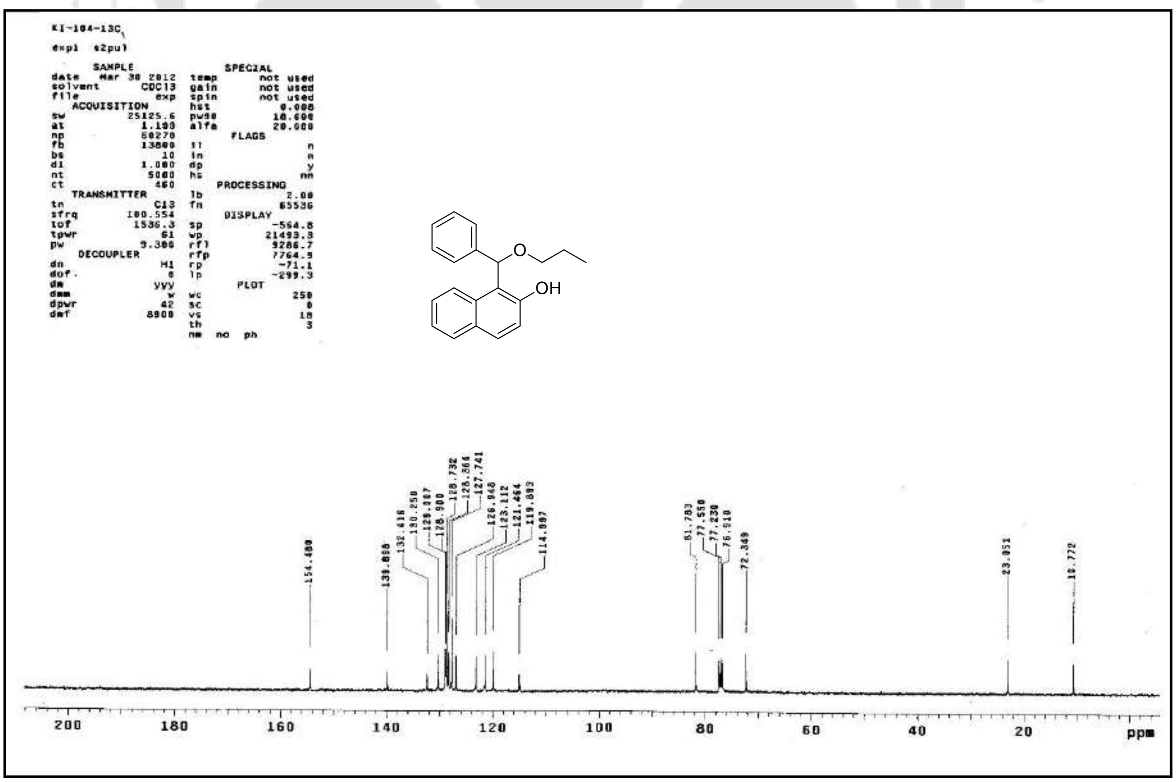


1-(ethoxymethyl)naphthalen-2-ol (23): Gummy liquid (0.170 g, 89%); R_f (10% ethyl acetate/hexane) 0.30; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.75 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.58 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.34 (td, *J* = 7.2, 1.2 Hz, 1H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 1H), 5.12 (s, 2H), 3.62 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.7, 131.8, 129.7, 128.9, 128.8, 126.7, 123.1, 121.1, 119.4, 112.1, 69.1, 67.1, 15.1 ppm; IR (KBr) ν_{max} 3311, 1624, 1468, 1227 cm^{-1}; Anal. Calcd for $C_{13}H_{14}O_2$ (202.25): C, 77.20; H, 6.98; Found: C, 77.34; H, 7.06.

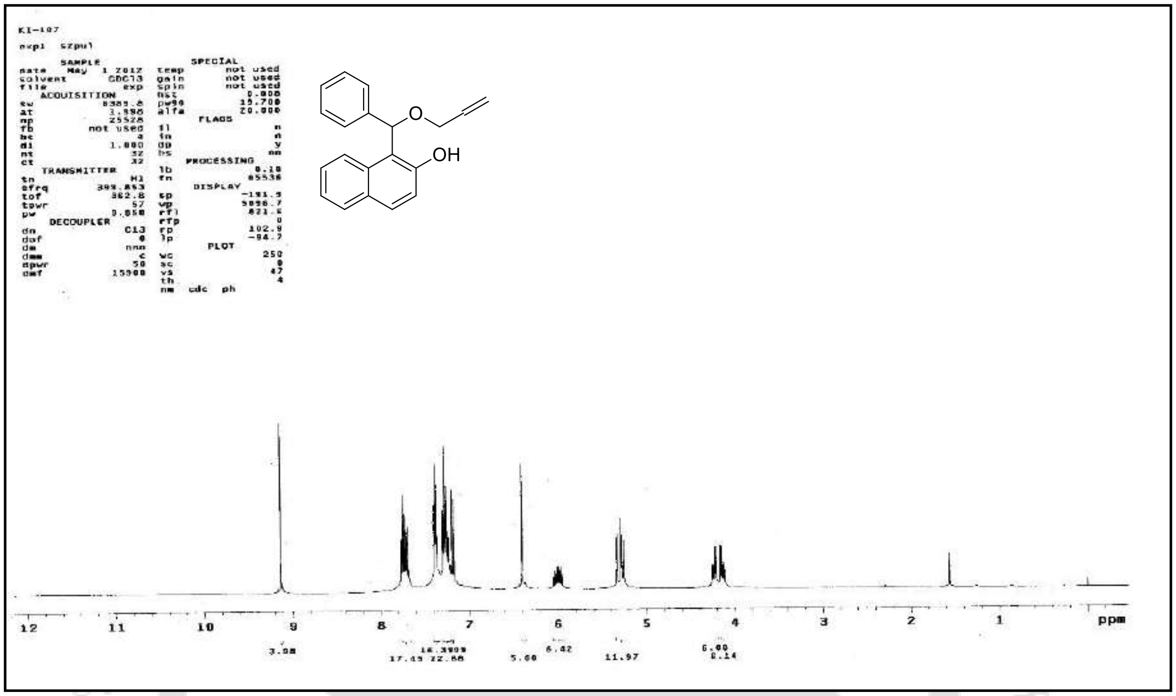
[1] H NMR spectra of 13c



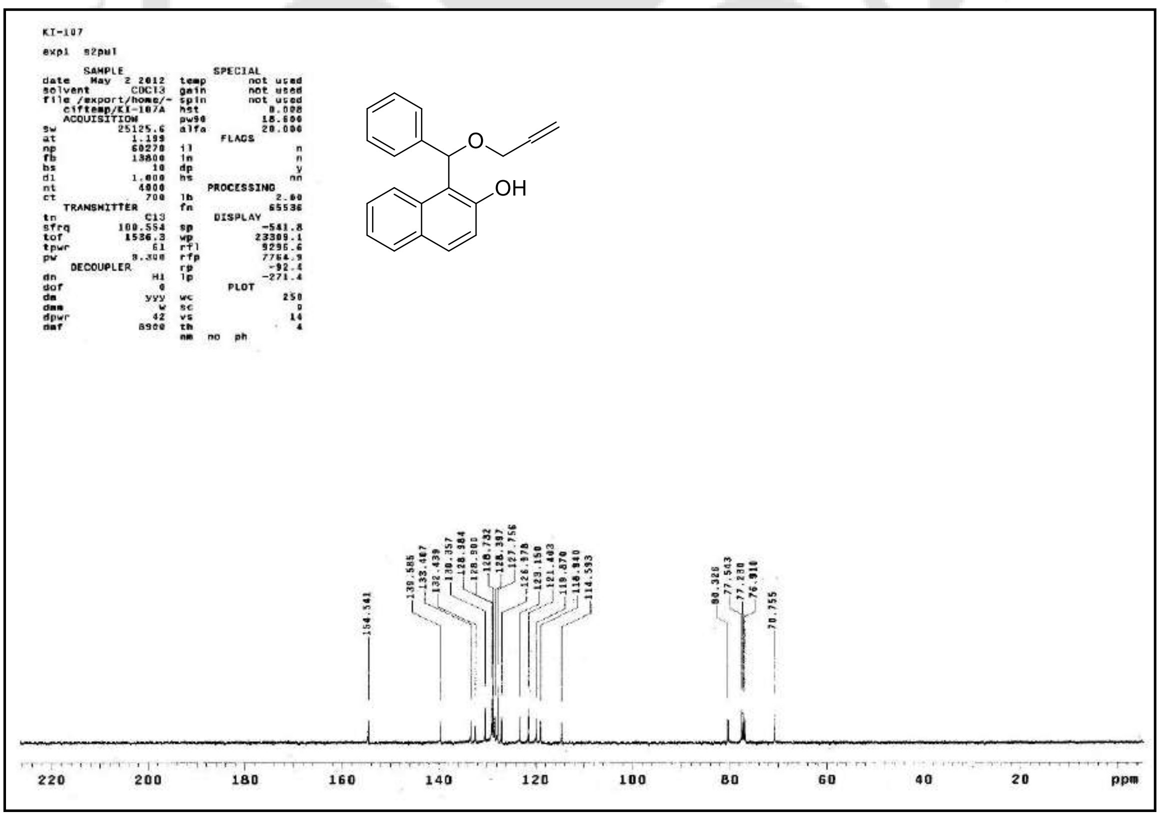
^{13}C NMR Spectra of 13c



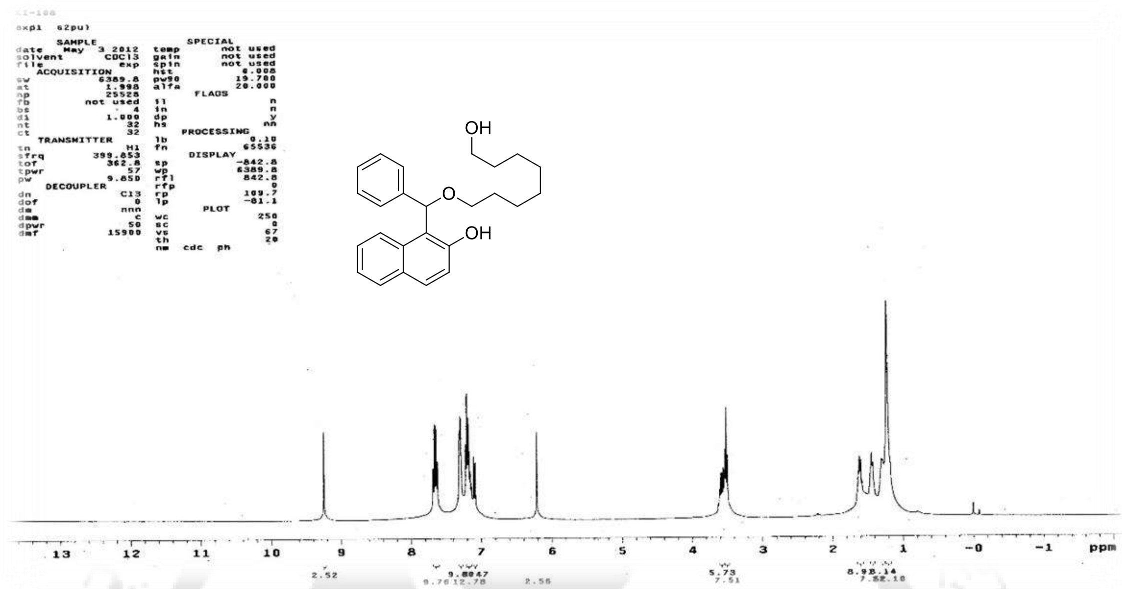
[1]H NMR spectra of 13g



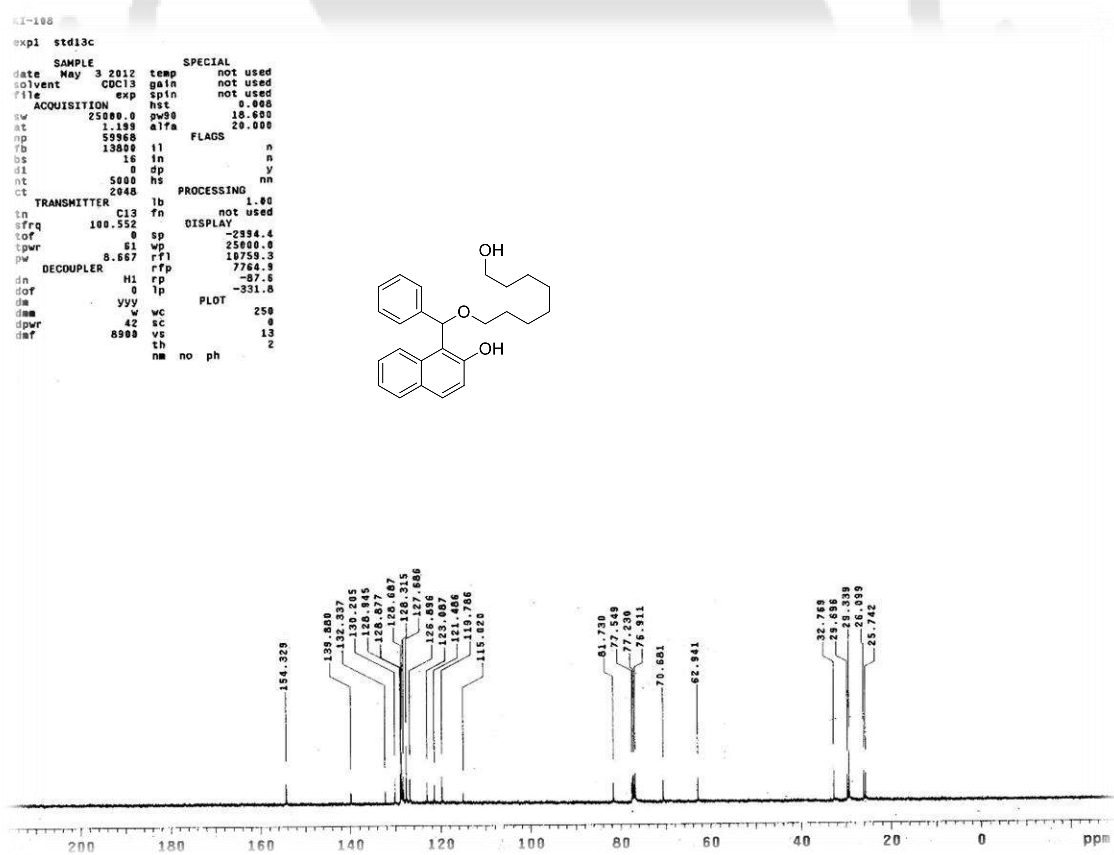
[13]C NMR Spectra of 13g



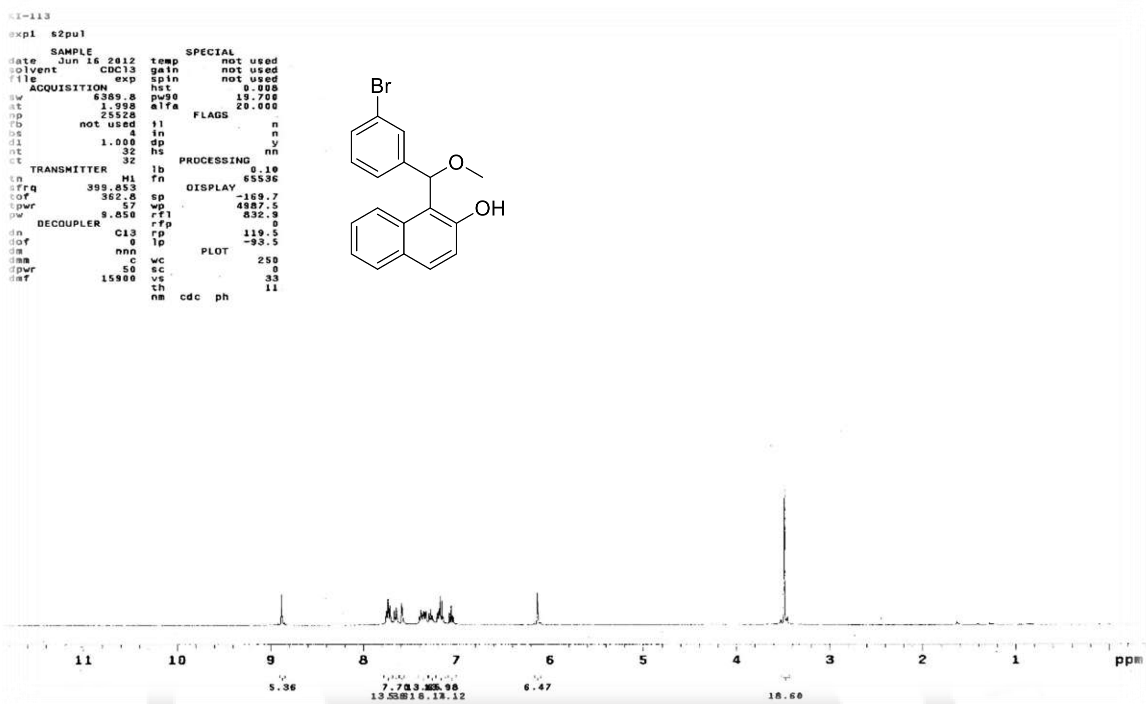
[1]H NMR spectra of 13l



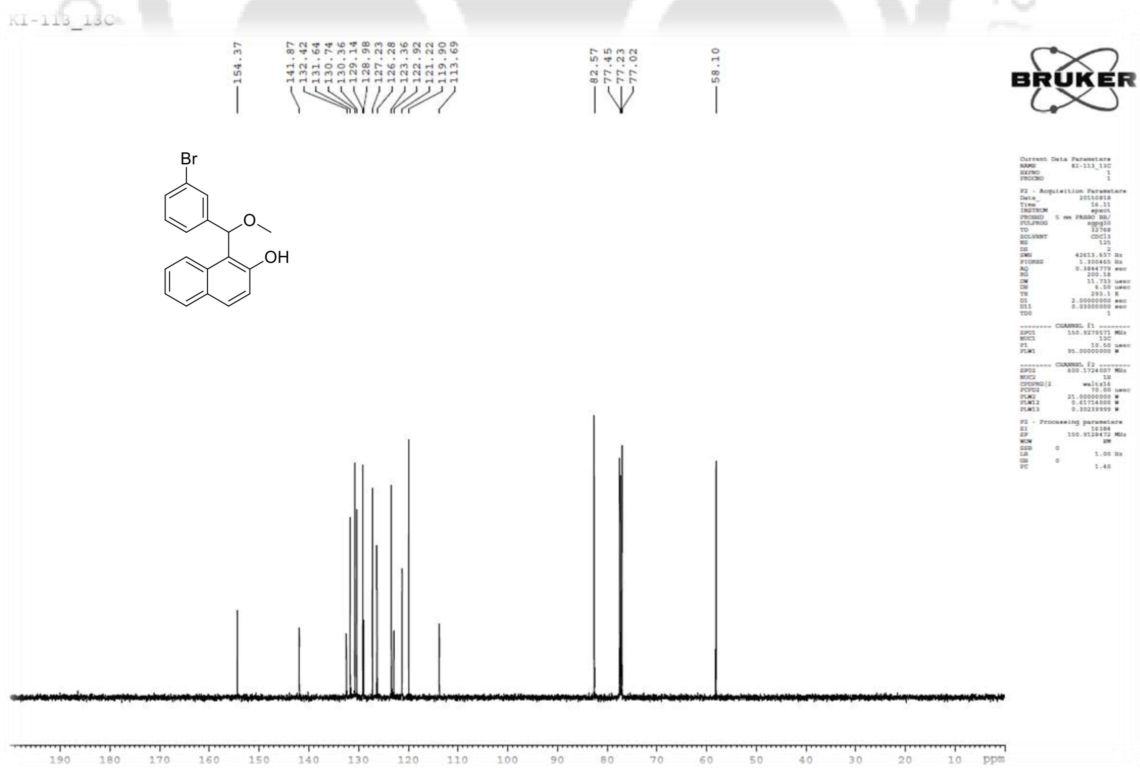
[13]C NMR Spectra of 13l



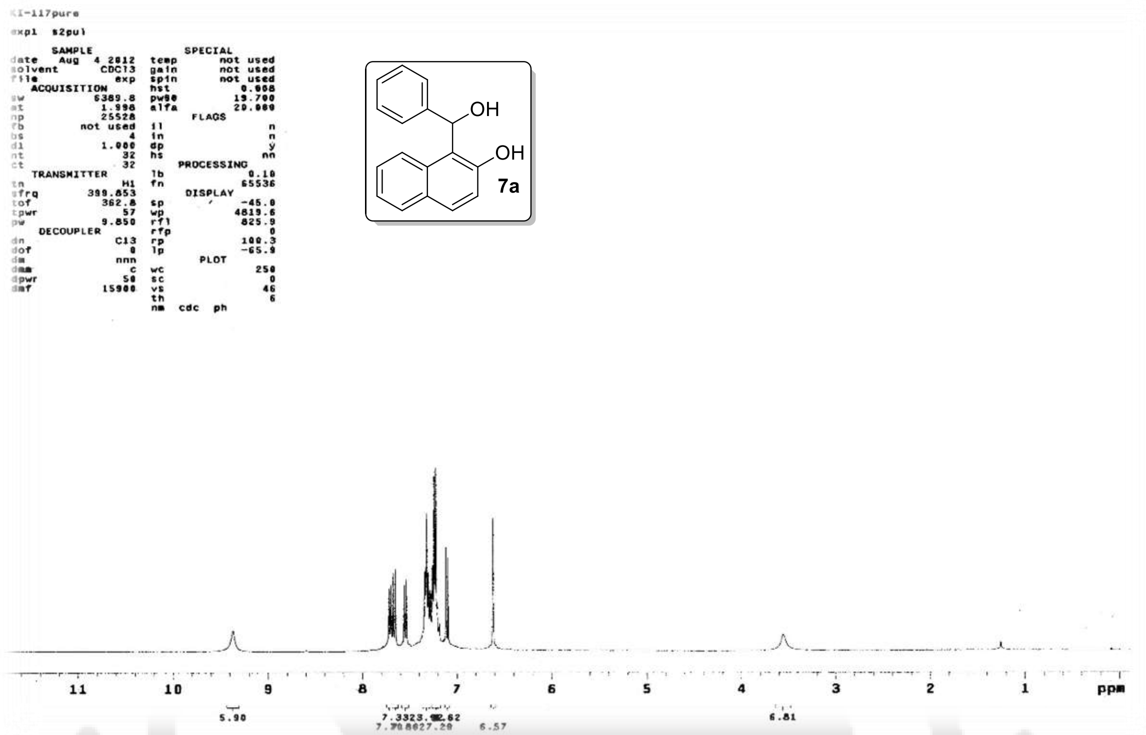
[1]H NMR spectra of 13p



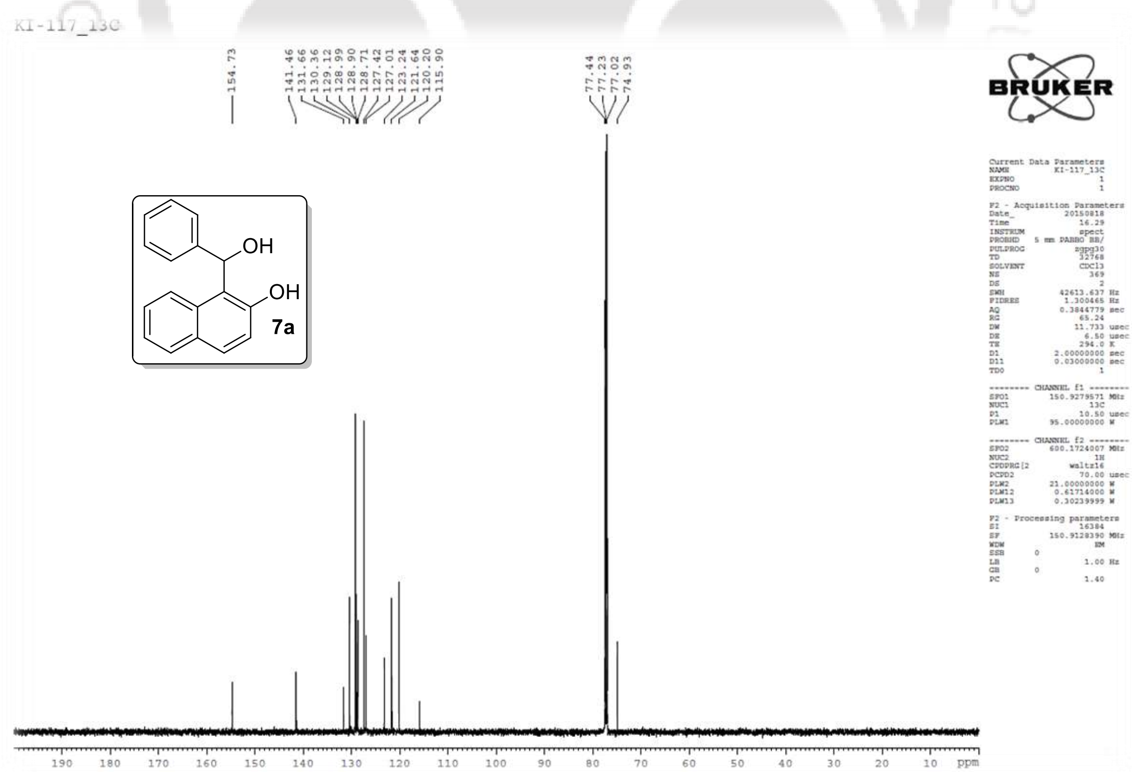
[13]C NMR Spectra of 13p



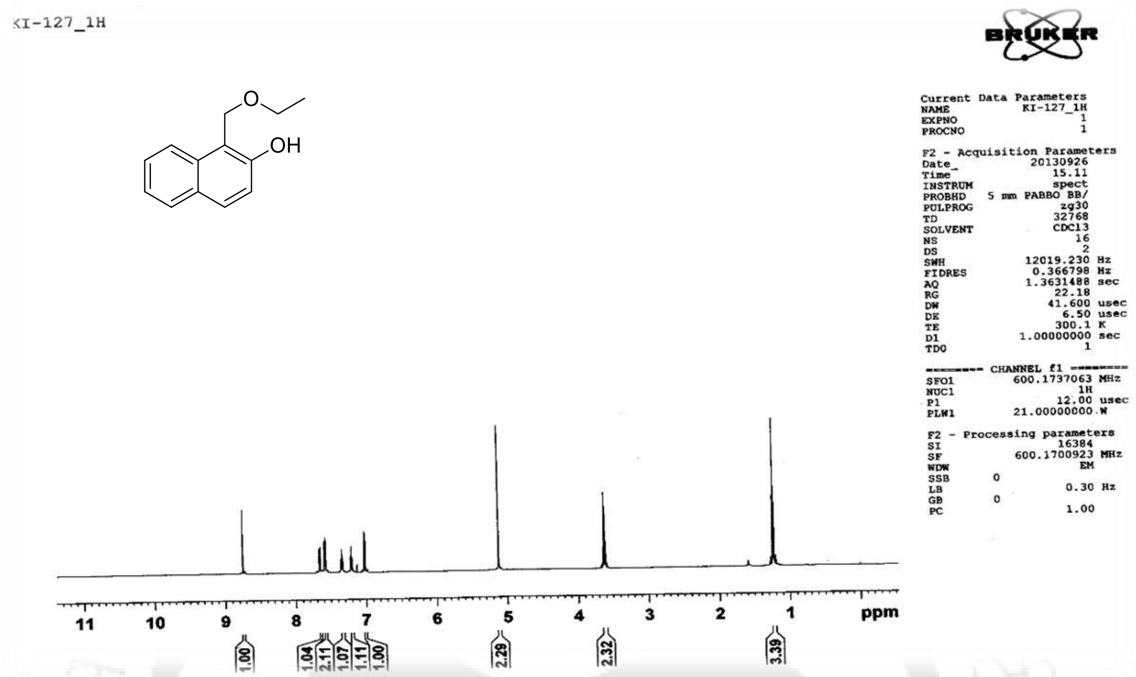
^{1}H NMR spectra of 17a



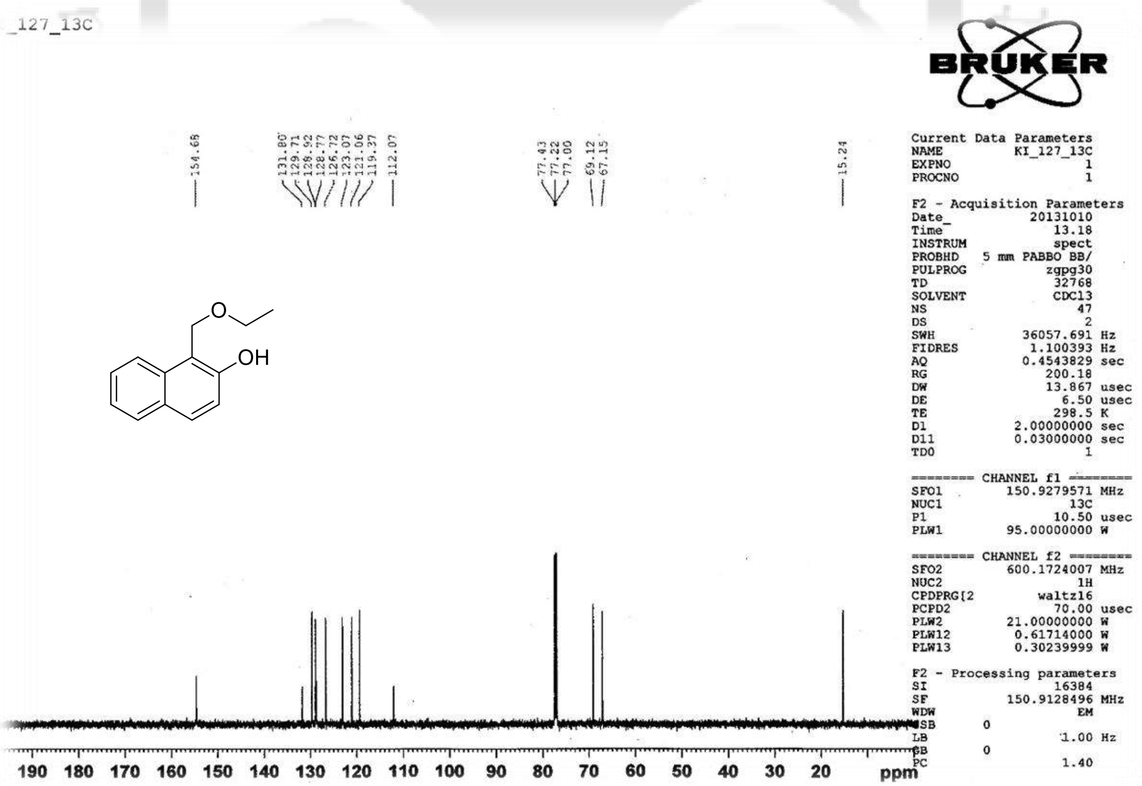
^{13}C NMR spectra of 17a



[1]H NMR spectra of 23

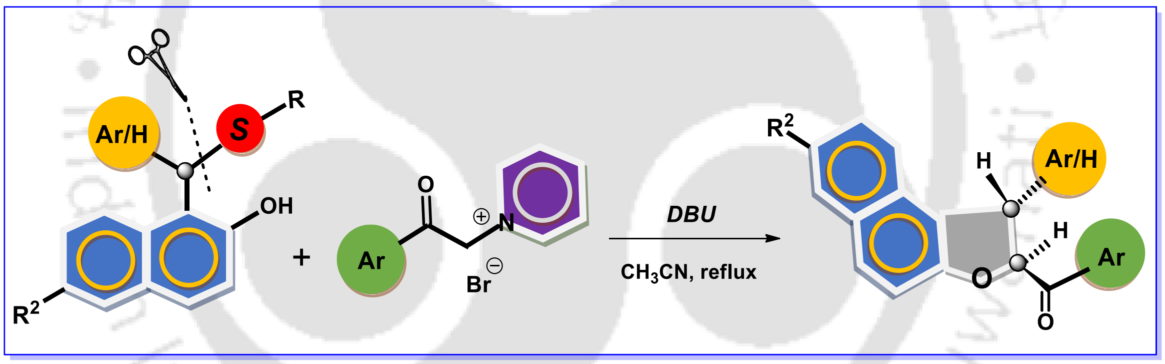


[13]C NMR spectra of 23



Chapter VII

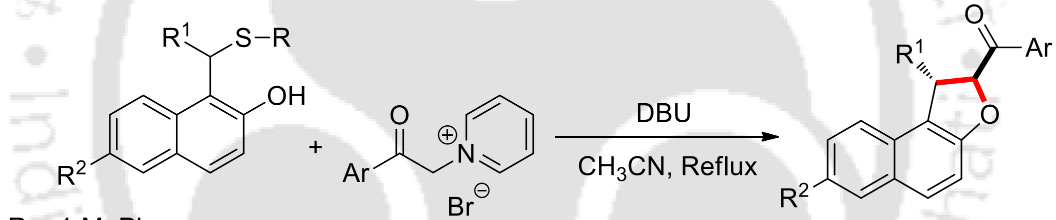
An efficient one-pot C-S bond Cleavage induced modular diastereo selective synthesis of 2-acyl-1,2-dihydronaphtho[2,1-b]furans



Results and Discussion

The importance of 1,2-dihydronaptho[2,1-*b*]furan and their synthesis have been discussed in chapter V. The literally reported methods are limited to appropriate conventional synthetic path. Therefore, the growing demand inspired us to find a new synthetic method for synthesis of 2-acyl-1,2-dihydronaphtho[2,1-*b*]furans. Chapter (VI) demonstrated the cleavage of C–S bond in napthalen-2-ol sulfide moiety for the construction of unsymmetrical ethers. From these perspective, the cleavage of C–S bond in 1-(aryl/alkyl(arylthio)methyl)-naphthalen-2-ol along with the generation of tandem C-C and C-O bond might be suitable for diastereoselective synthesis of 2-acyl-1,2-dihydronaphtho [2,1-*b*]furans.

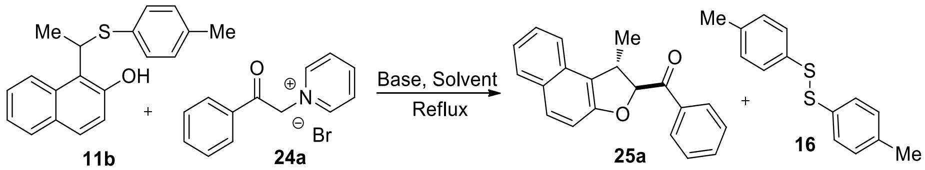
In this chapter a new diastereoselective synthesis of (1,2-dihydronaphtho[2,1-*b*]furan-2-yl)methanone has been discussed using 1-(aryl/alky l(arylthio)methyl)-naphthalen-2-ol, and pyridinium bromide in the presence of base DBU. (Scheme 116).



Scheme 116. Synthesis of (aryl)(1-aryl/alkyl-1,2-dihydronaphtho-[2,1-*b*]furan-2-yl)methanone.

Initially, a mixture of 1-(aryl/alkyl(arylthio)methyl)naphthalen-2-ol (**11**, 0.5 mmol) and pyridinium bromide (**24**, 0.5 mmol), DBU (0.1 mmol) and 2.5 mL of acetonitrile were added and allow it to reflux for 5 h. After usual work up followed by chromatographic purification a solid product was isolated in 46% yield, which was characterized by spectroscopic techniques and was found to be product ((1S,2S)-1-methyl-1,2-dihydronaphtho[2,1-b]furan-2-yl)(pheyl)methanone (**25a**). IR spectrum of (**25a**) showed characteristic strong absorption at 1692 cm^{-1} due to the presence of unsaturated carbonyl group. Likewise peak at δ 195.8 ppm in ^{13}C spectrum indicates the carbonyl carbon which also supported by ^{13}C DEPT ^{135}NMR spectra. In ^{1}H NMR, the peaks at δ 5.69 ppm (doublet), δ 4.25-4.20 ppm and 1.70

Table 17. Optimization of the reaction conditions[a]



S.No	Base (equiv)	Solvent	Time/h	**25a** Yield (%)[b]
01	-	CH_3CN[c]	5	NR
02	-	CH_3CN	4	NR
03	DBU (0.1)	CH_3CN	5	46
04	DBU (0.5)	CH_3CN	5	61
05	**DBU (1)**	**CH_3CN**	**5**	**85**
06	NaOH (1)	CH_3CN	7	48
07	TEA (1)	CH_3CN	7	55
08	DBU (1)	DMF[d]	5	76
09	DBU (1)	THF[e]	6	51
10	DBU (1)	DMSO[d]	7	69
11	DBU (1)	EtOH[f]	6	40
12	DBU (1)	Xylene[d]	7	48

[a]All the reaction were carried out in 0.5 mmol scale. [b]Isolated yield. Reaction conducted at room temperature,[c]at 80 °C, [d]65 °C,[e]and 77 °C. [f]NR = no reaction.

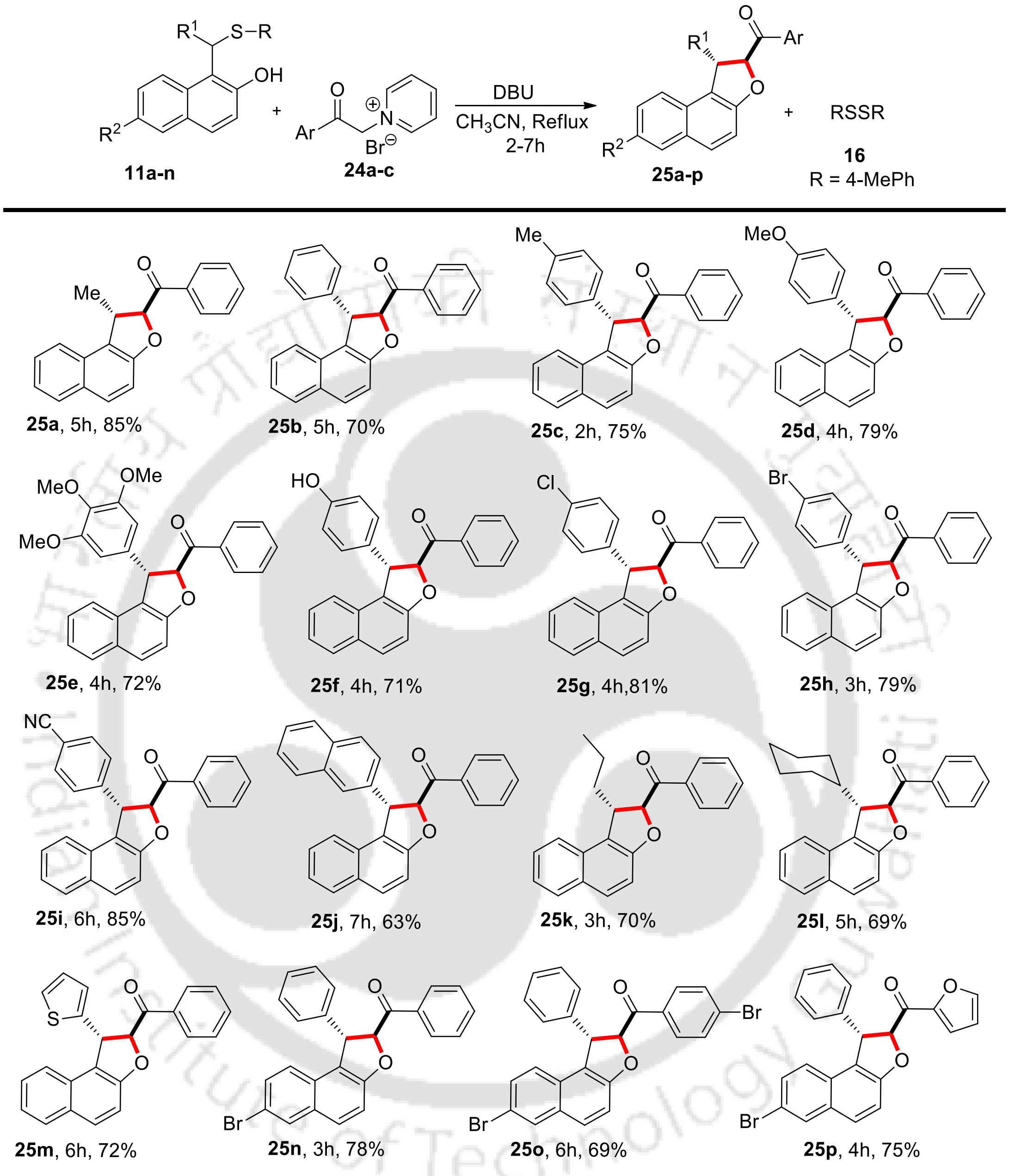
ppm (doublet) indicates the presence of two hydrogens and methyl of the furan ring. Similarly in ^{13}C NMR, the peaks at 90.9, 40.0, 20.9 ppm indicate the carbon adjacent to corbnyl, benzylic and methyl carbon of the product (**25a**).

To find out the optimized reaction condition various reactions were performed with 1-(1-(*p*-tolylthio)ethyl)-naphthalen-2-ol (**11b**) and phenacylpyridinium bromide (**24a**) as shown in Table 17. The observed results revealed that one equivalent of DBU in acetonitrile provides good yield (entry 5, Table 17). The reaction conducted in the presence of other bases such as sodium hydroxide and trimethylamine which reduced the yield significantly to 48% and 55%. (entries 6 & 7, Table 17). However, on scrutinizing with various other solvents (DMF, THF, DMSO, EtOH and Xylene) afford lower yield of the product (**25a**) (entries 8-12, Table 17).

After optimization, a series of reactions were performed with phenacylpyridinium bromide (**24a**) with different 1-((*p*-tolylthio)methyl)-naphthalen-2-ol aryl moiety such as phenyl (**11a**), 4-methylphenyl (**11c**), 4-methoxyphenyl (**11d**) in the presence of base DBU under identical reaction condition which afforded the corresponding product (**25b-d**) with 70-79% yield (Table 18). Then the reaction with different 1-((*p*-tolylthio)methyl)-naphthalen-2-ol 4-substituted aryl moiety such as 4-hydroxyphenyl (**11f)**, 4-chlorophenyl (**11g**), 4-bromophenyl (**11h**) and 4-cyanophenyl (**11i**) afforded the required product (**25f-i**) with 71-85% yield. Further, the reaction was examined using 1-((*p*-tolylthio)(3,4,5-trimethoxyphenyl)methyl)-naphthalen-2-ol (**11e**) with phenacylpyridinium bromide (**24a**) and the resultant product (**25e**) were obtained in 72% yield. Next, on reaction with 1-(naphthalen-2-yl(*p*-tolylthio)methyl)-naphthalen-2-ol (**11j**) led to the desired product (**25j**) with 63% yield. The aliphatic naphthalen-2-ol reactant (**11k-l**) on reaction with phenacylpyridinium bromide furnish to (**25k**) and (**25l)** with 70% and 69% yield. In addition, the heteroaromatic naphthalen-2-ol (**11m**) underwent reaction with phenacylpyridinium bromide which obtains (**25m**) with 72% yield.

Inspired by these successful results, we have examined the reaction with 6-bromo-1-(phenyl(*p*-tolylthio)methyl)naphthal-ene-2-ol (**11n**)with differentpyridinium bromide (**24a-c**) in acetonitrile under identical reaction condition and the desired product (**25n-p)** were obtained with 69-78% yields (Table 18).

Table 18. Synthesis of (aryl)(1-aryl/alkyl-1,2-dihydronaphtho-[2,1-*b*]furan-2-yl)methanone.



[a]All the reaction were performed using 1-(aryl/alkyl(arylthio)methyl)naphthalen-2-ol (**11**), 1-(2-oxo-2-arylethyl)pyridinium bromide (**24**) and base DBU in acetonitrile. [b]Isolated yield.

Furthermore, the structure of the product **(3a)** was confirmed through single x-ray analysis as shown in Figure 25.

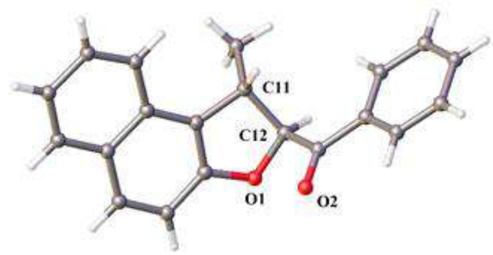
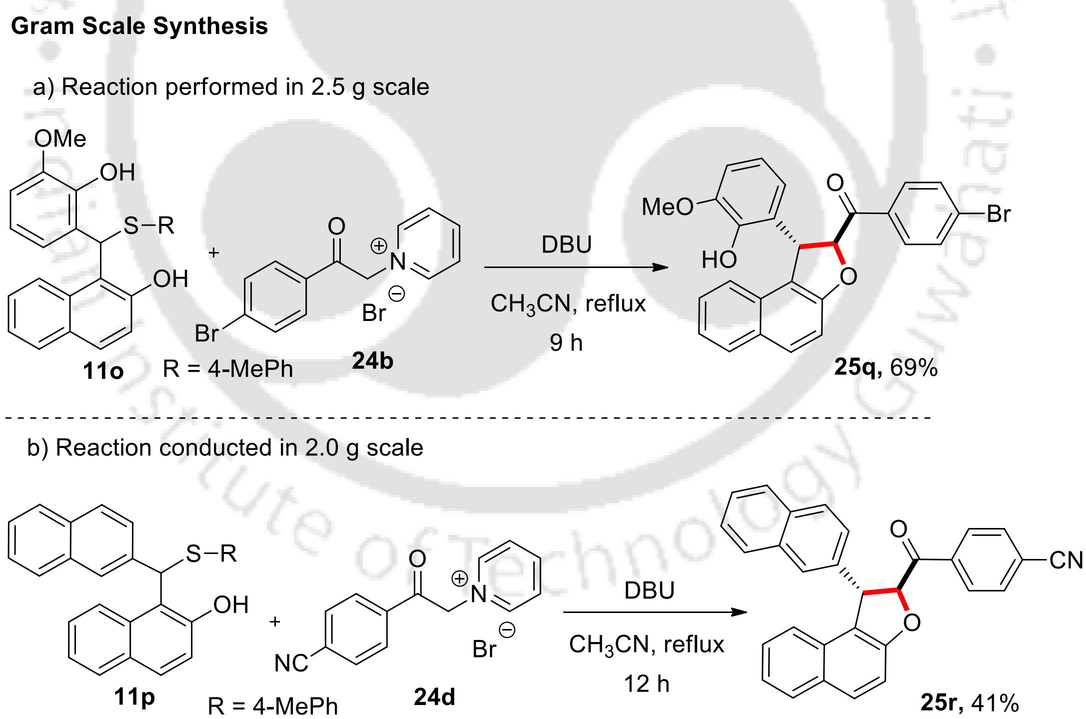


Figure 25. X-ray crystal structure of **25a**

The scalability of the reaction was tested on 2.5g scale with 1-((2-hydroxy-3-methoxyphenyl)(*p*-tolylthio)methyl)-naphthalen-2-ol (**11o**), 4-bromophenacylpyridinium bromide (**24b**) in the presence of base DBU under reflux condition and the desired product **(25q)** was obtained in 69% yield. Similarly, the reaction was conducted in 2.0 g scale with 1-(naphthalen-2-yl(*p*-tolylthio)methyl)-naphthalen-2-ol (**11p**) with 4-cyanophenacyl pyridinium bromide (**24d**) in acetonitrile under identical reaction condition which gave the required product **(25r)** in 41% yield as shown in Scheme 117.



Scheme 117. Scalable Synthesis of compounds **25q** and **25r**.

Single x-ray analysis one of the grame scale compound **(25q)** is shown in Figure 26.

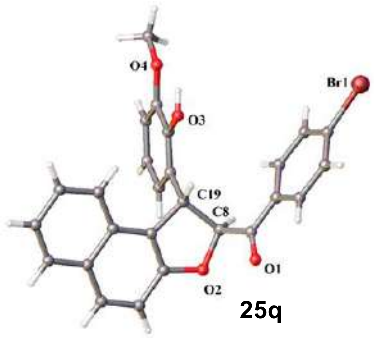
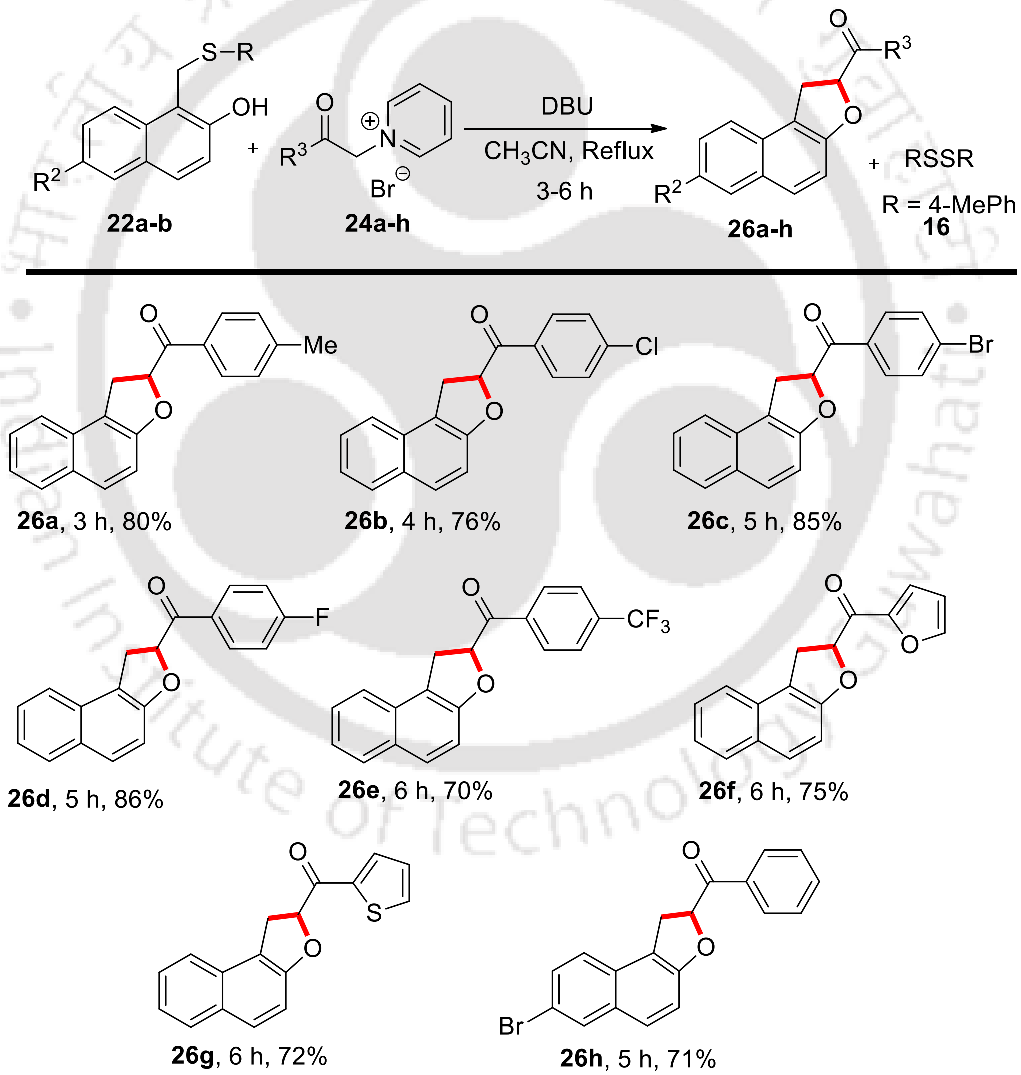


Figure 26. X-ray crystal structure of **25q**

Table 19. Synthesis of (aryl)(1,2-dihydronaphtho[2,1-*b*]furan-2-yl)methanone (**26**).[a,b]



[a]All the reaction were conducted using **22**, **24** and base DBU in 1:1 ratio in acetonitrile.
[b]Isolated yield.

Next the protocol was investigated on 1-((*p*-tolylthio)-methyl)-naphthalen-2-ol (**22a**) with different phenacylpyridiniumbromide 4-substituted moiety such as Me, Cl, Br, F and CF_3 which afforded the resultant products (**26a-e**) with 70-86% yield. Subsequent reaction with hetero aromatic pyridinium bromide resulted to **26f** and **26g** with 75% and 72% yield. Furthermore, 6-bromo-1-((*p*-tolylthio)methyl)naphtha-len-2-ol (**22b**) react with phenacylpyridinium bromide which gave the product 6h in 71% yield (Table 19). X-ray crystal structure of one of the represented compound (**26h**) are depicted in Figure 27.

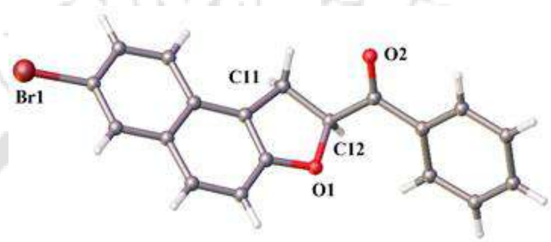
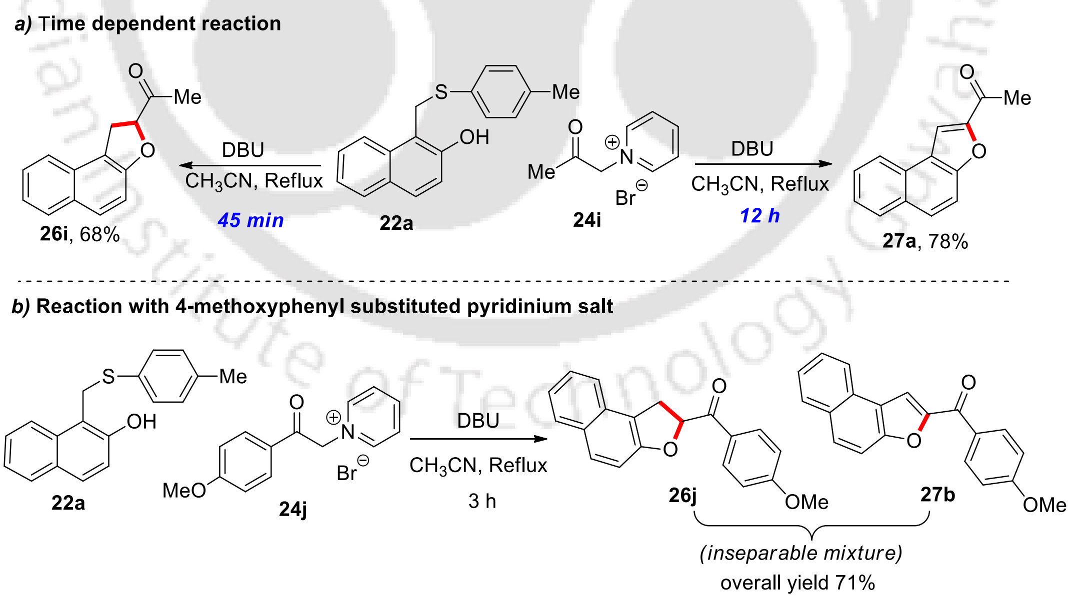


Figure 27. X-ray crystal of **26h**.

It was noteworthy that time-dependent reaction on (2-oxopropyl)pyridinium bromide (**24i**) with 1-((*p*-tolylthio)methyl)naphthalen-2-ol (**22a**) in the presence of DBU under reflux condition afforded exclusively the product **26i** with 68% yield after 45 min. On the other

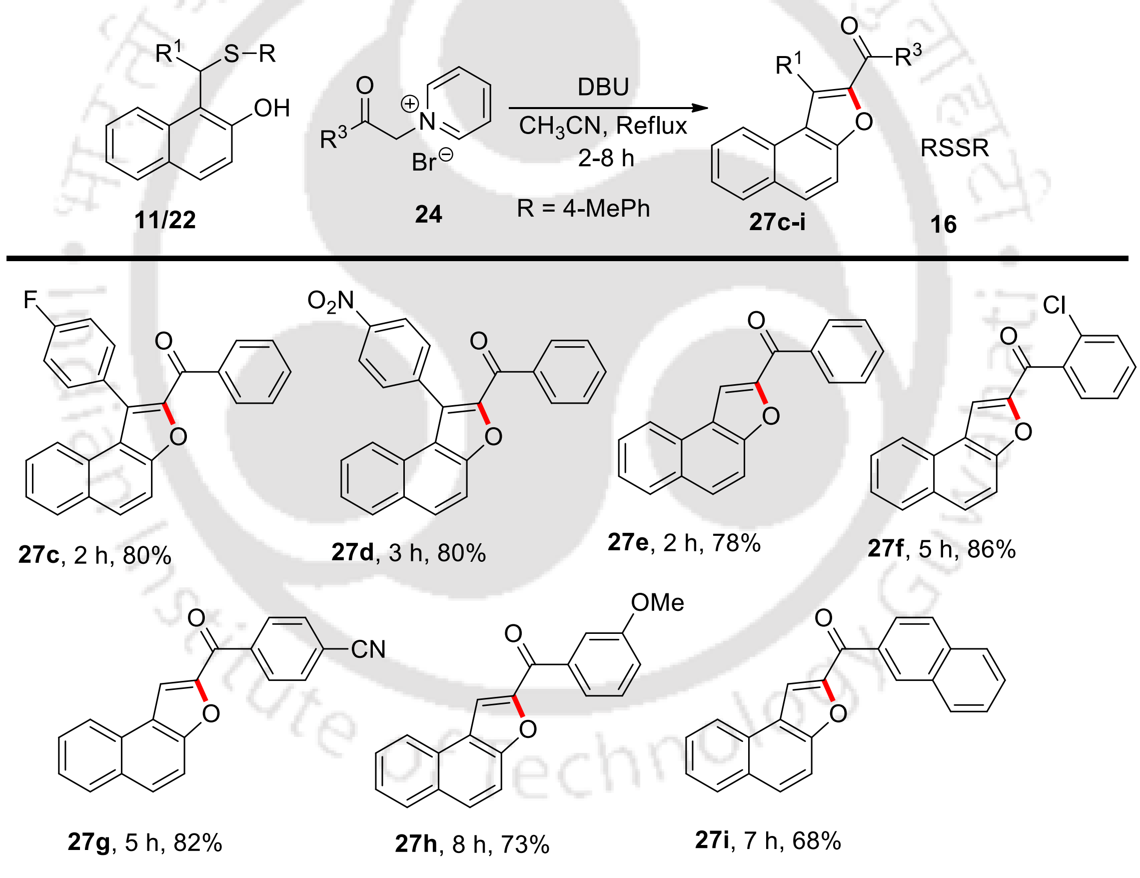


Scheme 117. Relative investigation on reaction time and products.

hand, if the reaction proceeds up to 12 h under identical reaction condition, it to aromatize 1-(naphtho[2,1-*b*]furan-2-yl)ethanone (**27a**) with 78% yield.[16,4] In addition, (2-(4-methoxyphenyl)-2-oxoethyl)pyridinium bromide (**24j**) underwent reaction with **22a** in acetonitrile which led to inseparable mixture of products **26j** and **27b** with overall 71% yield (Scheme 118).

In some cases, the selected substrates had a tendency to aromatize directly to naptho[2,1-*b*]furanproduct (**27**). It may be due to their nature to attain the thermodynamically stable product (**27)** as shown in Table 20.

Table 20. Selected substrates direct aromatization[a,b]



[a]The reaction were conducted using**11/22, 24** and base DBU in 1:1 ratio. [b]Isolated yield.

One of the single x-ray crystal structure of the aromatozed product **27a** is shown in Figure 28.

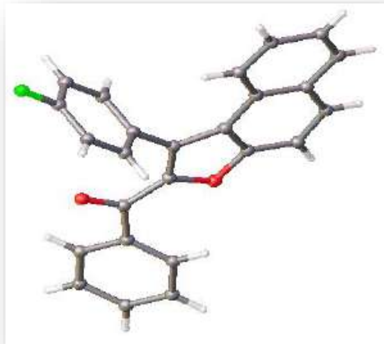
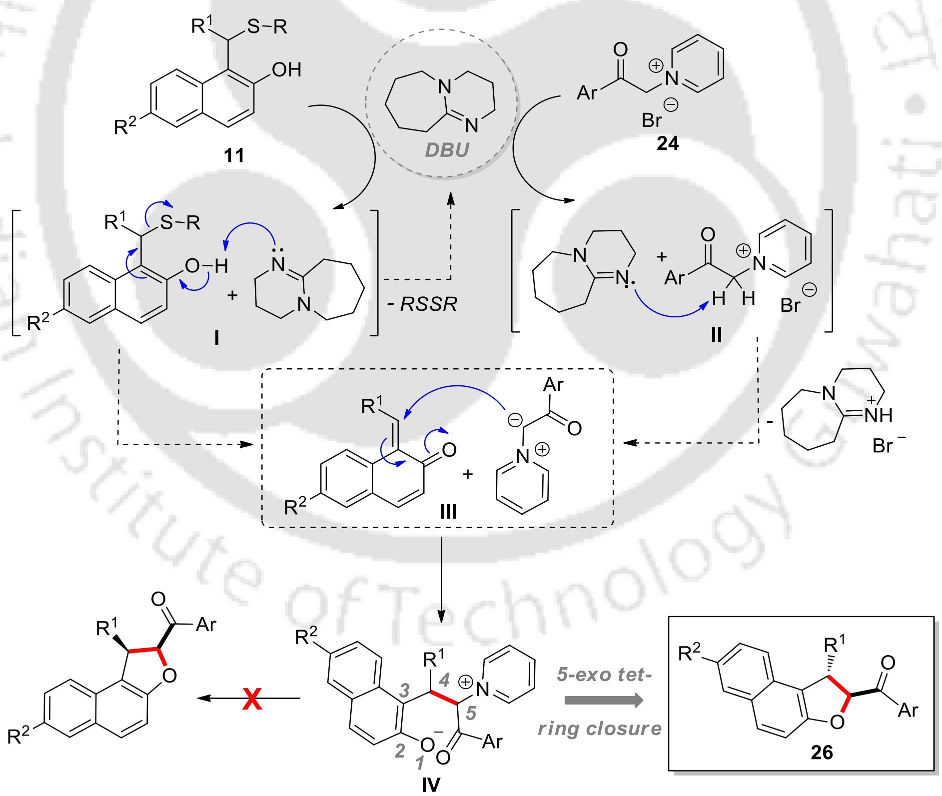


Figure 28. X-ray crystal structure of **27a.**

A plausible mechanism for this transformation is explicated as follows: At first DBU reacts with **11** to gives *o*-Quinone methide and RSSR. On the other hand, DBU reacts with pyridinium bromide



Scheme 118. Plausible mechanism for the formation of (aryl)(1-aryl/alkyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)methanone.

(**24**) *via* **II** to attain pyridinium ylide, which subsequently reacts with *o*-quinone methide to furnish **IV**. Then **IV** undergoes intramolecular oxygen cyclization through 5-*exotet*-ring closing reaction to obtain the desired diastereoselective product (**26**) as shown in Scheme 118.

Conclusions

In summary, an one-pot diastereoselective synthesis of (aryl)(1-aryl/alkyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)methanone has been developed using napthalen-2-ol sulfide through 5-*exotet*-ring closing reaction reaction *via* the formation of one C-C and C-O bond fashion. The protocol is selective, operationally simple, mild reaction condition, good yields and wide access to broad array of substrates. It also favoured to facilitate the direct gram scale diastereoselective synthesis in one-pot manner. Furthermore, the protocol was enabled to access (aryl)(1,2-dihydronaphtho[2,1-*b*]furan-2-yl)methanone in good yields.

Chapter VII

Experimental Section

An efficient one-pot C-S bond cleavage induced modular diastereo selective synthesis of 2-acyl-1,2-dihydro-naphtho[2,1-b]furans

Experimental Section

General Procedure

Synthesis of (aryl)(1-aryl/alkyl-1,2-dihydronaphtho[2,1-b]fur-an-2-yl)methanone (25): To the mixture of 1-(aryl/alkyl(arylthio)methyl)naphthalen-2-ol (**11**,0.5 mmol) and pyridinium bromide (**24**, 0.5 mmol), the base DBU (0.5 mmol) and 2.5 mL of acetonitrile was added in to it and allow it to reflux for 2-7 h. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated and the residue was extracted in ethyl acetate, washed twice with brine water. It was then concentrate under reduced pressure. The obtained residue was purified through column chromatography to afford the pure product **25**. Likewise the similar procedure was followed for the synthesis of compounds **26** and **27**.

Crystallographic Description:

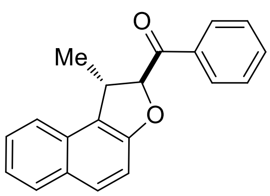
Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation ($\lambda = 0.71073$ Å) at 296 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The crystal structures of **25a, 25q** and **26h** were obtained by single crystal X-ray diffraction technique. Single crystals of **25a, 25q** and **26h** were obtained by slow evaporation of ethyl acetate and hexane (3:1) solution of the corresponding compound. The selected crystallographic data of **25a, 25q** and **26h** are given below**.** The crystals of all compounds were mounted on glass fiber.

Table 21.Crystal datas and structure refinements for 25a, 25q and 26h.

Compounds	25a	25q	26h
Empirical formula	$C_{20}H_{16}O_2$	$C_{26}H_{19}BrO_4$,$C_4H_8O_2$	$C_{19}H_{13}BrO_2$
Formula weight	288.33	563.42	365.19
Wavelength Å	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Triclinic	Triclinic
Space group	*P 21/c*	*P -1*	*P -1*
Unit cell dimensions	a =9.8859(11) Å *b*=13.6228(15) Å *c* =11.4124(12) Å α = 90.00° β=102.318(7)°γ= 90.00°	a = 9.7100(5) Å *b*=11.2600(6) Å *c* =13.5954(8) Å α =76.479(3)°β=75.547(3)°γ=84.675(3)°	a =7.7692(10) Å *b*=9.4272(14) Å *c*=10.6661(16)Å α=72.132(14)°β =83.570(12)°γ= 80.951(12)°
Volume	1501.6(3) $Å^3$	1398.57(13) $Å^3$	732.58(19) $Å^3$
Z	4	2	2
Density (calculated) Absorption coefficient	1.280 g cm^{-3} 0.082 mm^{-1}	1.338 g cm^{-3} 1.510 mm^{-1}	1.601 g cm^{-3} 2.810 mm^{-1}
Reflns collected	2172	4785	2577
Indep reflns	1765	2675	1990
GOF	1.053	1.112	0.859
Final R indices [I>2σ(I)]	*R*1=0.0442 *wR*2 = 0.1352	*R*1 = 0.0798 *wR*2 =0.2536	*R*1 = 0.0424 *wR*2 =0.1361
R indices (all data)	*R*1=0.0540	*R*1 = 0.1347	*R*1 = 0.0603

Spectral Data

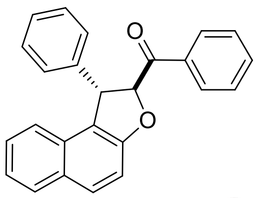
((1S,2S)-1-methyl-1,2-dihydronaphtho[2,1-b]furan-2-yl)(pheyl)methanone (25a): Solid (0.122 g, 85%); mp 130-132 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (d, J = 7.8 Hz,



2H), 7.83 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.63 (t, J = 7.8 Hz 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.45 (t, J = 7.8 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.24 (d, J = 9.0 Hz, 1H), 5.69 (d, J = 4.2 Hz, 1H), 4.25-4.20 (m, 1H), 1.70 (d, J = 6.6 Hz, 3H), ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 195.8, 156.5, 134.7, 133.8, 130.4, 130.1, 130.0, 129.2, 129.1, 129.0, 126.9, 123.3, 122.4, 121.8, 112.4, 90.9, 40.0, 20.9 ppm; ^{13}C

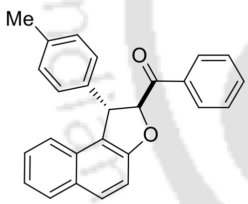
DEPT 135 NMR ($CDCl_3$) δ = 133.7, 129.9, 129.1, 129.0, 128.8, 126.8, 123.1, 122.3, 112.2, 90.7, 39.8 (CH), 20.7 (CH_3); IR (KBr) ν_{max} 1692 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{17}O_2$ (M + H^+) 289.1223, found 289.1238.

Phenyl((1S,2S)-1-phenyl-1,2-dihydronaphtho[2,1-b]furan-2-yl-)methanone (25b): Solid (0.122 g, 70%); mp 120-122 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (d, J = 7.8 Hz,



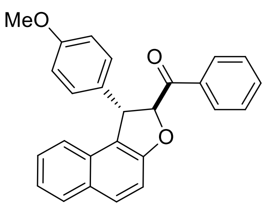
2H), 7.80-7.78 (m, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.34-7.24 (m, 9H), 5.94 (d, J = 4.8 Hz, 1H), 5.32 (d, J = 5.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.5, 157.0, 142.2, 134.2, 133.7, 130.4, 130.2, 130.0, 129.3, 129.0, 128.7, 128.6, 127.9, 127.3, 126.7, 123.1, 122.7, 119.8, 112.0, 91.5, 50.6 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 133.8, 130.5, 129.4, 129.1, 128.8, 128.7, 128.0, 127.4, 126.8, 123.2, 122.8, 112.1, 91.6, 50.7 (CH); IR (KBr) ν_{max} 1678 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{19}O_2$ (M + H^+) 351.1380, found 351.1402.

Phenyl((1S,2S)-1-(p-tolyl)-1,2-dihydronaphtho[2,1-b]furan-2-yl)methanone (25c): Solid (0.136 g, 75%); mp 91-94 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 (d, J = 7.8 Hz, 2H), 7.72-7.00 (m, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.41 (d, J = 7.8 Hz, 2H), 7.23 (d, J =



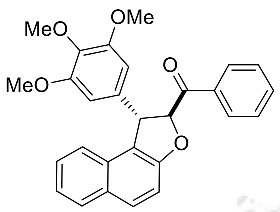
9.0 Hz, 1H), 7.19-7.16 (m, 3H), 7.08-7.04 (m, 4H), 5.84 (d, J = 5.4 Hz, 1H), 5.18 (d, J = 5.4 Hz, 1H), 2.25 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.9, 157.3, 139.6, 137.3, 134.5, 134.0, 130.6, 130.5, 130.3, 130.0, 129.6, 129.0, 128.9, 128.1, 127.0, 123.4, 123.0, 120.2, 112.3, 91.9, 50.7, 21.3 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 133.8, 130.4, 129.8, 129.3, 128.8, 128.7, 127.9, 126.8, 123.2, 122.8, 112.1, 91.6, 50.5 (CH); 21.1 (CH_3); IR (KBr) ν_{max} 1693 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{21}O_2$ (M + H^+) 365.1542, found 365.1543.

((1S,2S)-1-(4-methoxyphenyl)-1,2-dihydronaphtho[2,1-b]fura-n-2-yl)(phenyl)methanone (25d): Solid (0.150 g, 79%); mp 107-109 °C, ^{1}H NMR (600 MHz,



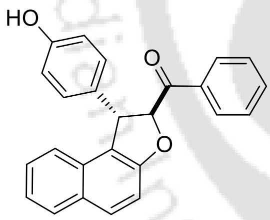
$CDCl_3$): δ 8.0 (d, J = 8.4 Hz, 2H), 7.79 (t, J = 8.4 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.49 (t, J= 7.8 Hz, 2H), 7.31 (d, J = 9.0 Hz, 2H), 7.28-7.24 (m, 2H), 7.19 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 5.92 (d, J = 5.4 Hz, 1H), 5.26 (d, J = 5.4 Hz, 1H), 3.79 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 195.0, 159.1, 157.2, 134.6, 134.5, 134.0, 130.6, 130.5, 130.3, 129.5, 129.2, 129.0, 128.9, 127.0, 123.4, 123.0, 120.2, 114.6, 112.3, 91.3, 55.4, 50.3 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 133.8, 130.5, 129.4, 129.1, 128.8, 128.7, 126.8, 123.2, 122.8, 114.5, 112.1, 91.8, 50.2 (CH); 55.3 (CH_3); IR (KBr) ν_{max} 1702(C=O) cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{21}O_3$ (M + H$^+$) 381.1491, found 381.1487.

Phenyl((1S,2S)-1-(3,4,5-trimethoxyphenyl)-1,2-dihydronapht-ho[2,1-b]furan-2-yl)methanone (25e): Solid (0.158 g, 72%); mp 174-176 °C, ^{1}H NMR (600 MHz, $CDCl_3$):



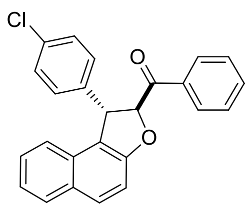
δ 8.0 (d, J = 7.8 Hz, 2H), 7.79 (t, J = 7.8 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.34 (d, J = 8.4 Hz, 1H), 7.30-7.25 (m, 3H), 6.45 (s, 2H), 5.93 (d, J = 6.0 Hz, 1H), 5.23 (d, J = 5.4 Hz, 1H), 3.83 (s, 3H), 3.72 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.9, 157.3, 153.8 138.1, 137.4, 134.5, 134.0, 130.8, 130.6, 130.2, 129.6, 128.9, 128.8, 127.0, 123.5, 123.1, 119.6, 112.3, 105.0, 91.6, 61.0, 56.3, 51.2 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 133.9, 130.7, 129.5, 128.8, 128.7, 126.9, 123.3, 122.9, 112.1, 104.9, 91.5, 51.1, (CH), 60.9, 56.1, (CH_3); IR (KBr) ν_{max} 1698(C=O) cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{25}O_5$ (M + H$^+$) 441.1702, found 441.1699.

((1S,2S)-1-(4-hydroxyphenyl)-1,2-dihydronaphtho[2,1-b]furan-2-yl)(phenyl)methanone (25f): Solid (0.129 g, 71%); mp 227-229 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (d, J = 7.2 Hz, 2H), 7.83 (t, J = 7.8 Hz, 2H), 7.62 (t, J = 7.8 Hz, 1H), 7.49



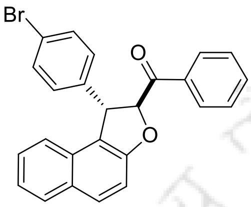
(t, J = 7.8 Hz, 2H), 7.30-7.24 (m, 5H), 7.12 (d, J = 8.4 Hz, 2H), 6.79-6.76 (m, 2H), 5.89 (d, J = 5.4 Hz, 1H), 5.22 (d, J = 5.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 195.1, 157.2, 155.1, 134.8, 134.5, 134.0, 130.7, 130.5, 130.3, 129.6, 129.5, 129.0, 128.9, 127.0, 123.4, 123.0, 120.2, 116.1, 112.3, 91.9, 50.4 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 134.0, 130.7, 129.6, 129.5, 129.0, 128.9, 127.0, 123.4, 123.0, 116.1, 112.3, 91.9, 50.4 (CH); IR (KBr) ν_{max} 1681(C=O), 3444 (OH) cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{19}O_3$ (M + H$^+$) 367.1334, found 367.1384.

((1S,2S)-1-(4-chlorophenyl)-1,2-dihydronaphtho[2,1-b]furan-2-yl)(phenyl)methanone (25g): Solid (0.155 g, 81%); mp 106-109 °C, ^{1}H NMR (600 MHz,



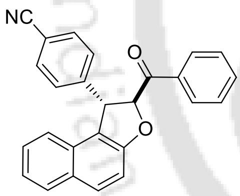
$CDCl_3$): δ 7.92 (d, J = 7.8 Hz, 2H), 7.24 (t, J = 7.2 Hz, 2H), 7.56 (t, J = 7.8 Hz, 1H), 7.42 (t, J = 7.8 Hz, 2H), 7.23-7.16 (m, 6H), 7.14 (d, J = 8.4 Hz, 2H), 5.79 (d, J = 5.4 Hz, 1H), 5.25 (d, J = 5.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.7, 157.3, 141.0, 134.5, 134.1, 133.5, 131.0, 130.4, 130.3, 129.6, 129.5, 129.1, 129.0, 127.2, 123.6, 123.0, 119.5, 112.3, 91.7, 50.1 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 133.9, 130.8, 129.4, 129.3, 128.9, 128.8, 128.7, 127.0, 123.4, 122.7, 112.1, 91.5, 49.9 (CH); IR (KBr) ν_{max} 1689 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{18}ClO_2$ (M + H$^+$) 385.0995, found 385.0907.

((1S,2S)-1-(4-bromophenyl)-1,2-dihydronaphtho[2,1-b]furan-2-yl)(phenyl)methanone (25h): Solid (0.169 g, 79%); mp 142-143 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (d, J = 7.2 Hz, 2H), 7.79 (t, J = 7.8 Hz, 2H), 7.63 (t, J = 7.8 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.44 (d, J = 7.8 Hz, 2H), 7.29-7.23 (m, 4H), 7.14 (d, J = 8.4 Hz, 2H)



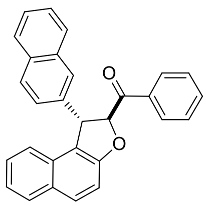
5.85 (d, J = 5.4 Hz, 1H), 5.31 (d, J = 5.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.6, 157.3, 141.6, 134.5, 134.1, 132.4, 131.0, 130.4, 130.3, 129.9, 129.6, 129.1, 129.0, 127.2, 123.6, 122.9, 121.6, 119.5 112.3, 91.6, 50.2 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 134.1, 132.4, 131.0 129.9, 129.6, 129.1, 129.0, 127.2, 123.6, 122.9, 112.3, 91.6, 50.2 (CH); IR (KBr) ν_{max} 1688(C=O) cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{18}BrO_2$ (M + H$^+$) 429.0490, found 429.0409.

4-((1S,2S)-2-benzoyl-1,2-dihydronaphtho[2,1-b]furan-1-yl)be-nzonitrile (25i): Solid (0.159 g, 85%); mp 155-157 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (d, J = 7.8 Hz, 2H),



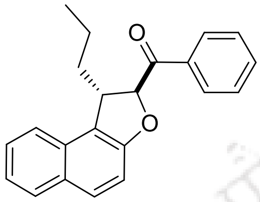
7.82 (d, J = 9.0 Hz, 2H), 7.66 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.52 (t, J = 7.8 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.30-7.28 (m, 3H), 7.19 (d, J = 6.6 Hz, 1H), 5.85 (d, J = 5.4 Hz, 1H), 5.51 (d, J = 5.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.3, 157.3, 147.8, 134.4, 134.2, 133.1, 131.3, 130.3, 130.2, 129.6, 129.2, 129.1, 129.0, 127.4, 123.6, 122.6, 118.8, 118.7, 112.3, 111.6, 91.3, 50.2 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 134.1, 133.0, 131.1 129.5, 129.0, 128.9, 128.8, 127.3, 123.6, 122.5, 112.1, 91.2, 50.0 (CH); IR (KBr) ν_{max} 1633(C=O), 2228 (CN) cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{18}NO_2$ (M + H$^+$) 376.1338, found 376.1260.

((1S,2S)-1-(naphthalen-2-yl)-1,2-dihydronaphtho[2,1-b]furan-2-



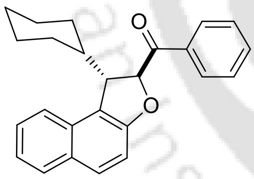
yl)(phenyl)methanone (25j): Solid (0.126 g, 63%); mp 150-151 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, J = 7.8 Hz, 2H), 7.84-7.78 (m, 6H), 7.63 (t, J = 7.2 Hz, 1H), 7.51-7.47 (m, 4H), 7.38-7.36 (m, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.25-7.12 (m, 2H), 6.03 (d, J = 5.4 Hz, 1H), 5.50 (d, J = 4.8 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.8, 157.4, 139.8, 134.4, 134.0, 133.7, 132.9, 130.8, 130.6, 130.3, 129.6, 129.4, 129.0, 128.9, 128.1, 127.9, 127.1, 126.6, 126.2, 125.9, 123.4, 123.0, 119.9, 112.3, 91.6, 51.2 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 133.9, 130.7, 129.4, 129.3, 128.8, 128.7, 127.9, 127.8, 126.9, 126.4, 126.1, 125.7, 123.3, 122.8, 112.2, 91.5, 51.0 (CH); IR (KBr) ν_{max} 1695(C=O) cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{21}O_2$(M + H$^+$) 401.1542, found 401.1506.

Phenyl((1S,2S)-1-propyl-1,2-dihydronaphtho[2,1-b]furan-2-yl-)methanone (25k): Gummy solid (0.110 g, 70%); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (d, J = 7.2 Hz, 2H),



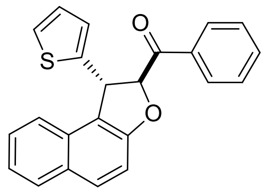
7.80 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.61 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.44 (t, J = 7.8 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 5.77 (d, J = 3.0 Hz, 1H), 4.26 (d, J = 3.6 Hz, 1H), 2.06-2.01 (m, 1H), 1.97-1.91 (m, 1H), 1.53-1.48 (m, 1H), 1.38-1.32 (m, 1H), 0.97 (t, J = 7.2 Hz, 3H), ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.4, 156.7, 134.8, 133.7, 130.6, 130.1, 129.9, 129.3, 129.2, 128.9, 126.9, 123.2, 122.6, 120.7, 112.2, 88.8, 44.4, 36.6, 19.7, 14.3 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 133.5, 129.8, 129.1, 129.0, 128.7, 126.7, 123.1, 122.5, 112.1, 88.6, 44.2 (CH), 36.4, 19.6 (CH_2), 14.1 (CH_3); IR (KBr) ν_{max} 1693 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{21}O_2$ (M + H$^+$) 317.1542, found 317.1541.

((1S,2S)-1-cyclohexyl-1,2-dihydronaphtho[2,1-b]furan-2-yl)(p-henyl)methanone (25l): Solid (0.123 g, 69%); mp 129-130 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (d, J =

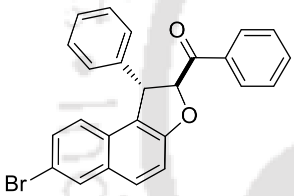


7.2 Hz, 2H), 7.80 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.45 (t, J = 7.8 Hz, 1H), 7.30 (t, J = 7.2 Hz, 1H), 7.14 (d, J = 9.0 Hz, 1H), 5.84 (d, J = 3.0 Hz, 1H), 4.24 (t, J = 3.6 Hz, 1H), 2.20-2.15 (m, 1H), 1.82 (t, J = 10.0 Hz, 2H), 1.66 (d, J = 9.6 Hz, 2H), 1.35-1.28 (m, 2H), 1.25-1.21 (m, 1H), 1.20-1.06 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 197.0, 156.8, 135.1, 133.6, 130.9, 130.2, 129.9, 129.5, 129.2, 128.8, 126.8, 123.2, 119.6, 112.1, 85.7, 49.8, 41.4, 31.9, 28.1, 26.9, 26.6, 26.5 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 133.4, 129.7, 129.3, 129.0, 128.6, 126.5, 123.0, 111.8, 85.5, 49.6, 41.2, (CH) 31.7, 27.9, 26.6, 26.4, 26.3 (CH_2); IR (KBr) ν_{max} 1681 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{25}O_2$ (M + H$^+$) 357.1855, found 357.1859.

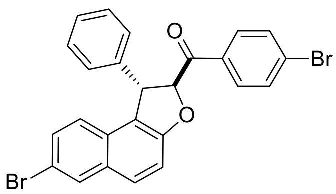
Phenyl((1S,2S)-1-(thiophen-2-yl)-1,2-dihydronaphtho[2,1-b]f-uran-2-yl)methanone (3m): Solid (0.128 g, 72%); mp 121-122 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.07 (d, J = 7.8 Hz, 2H), 7.81 (t, J = 7.8 Hz, 2H), 7.65 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.46 (d, J = 8.4 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.30-7.28 (m, 2H), 7.23 (d, J = 4.8 Hz, 1H), 6.97-6.95 (m, 2H), 6.01 (d, J = 4.8 Hz, 1H), 5.69 (d, J = 4.8 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.4, 156.9, 145.9, 134.4, 134.1, 131.1, 130.5, 130.3, 129.6, 129.0, 128.9, 127.3, 127.2, 125.7, 125.4, 123.5, 122.8, 119.4, 112.3, 91.4, 45.5 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 134.1, 131.0, 129.6, 129.0, 128.9, 127.2, 127.1, 125.7, 125.3, 123.5, 122.8, 112.3, 91.4, 45.5 (CH); IR (KBr) ν_{max} 1694 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{17}O_2S$(M + H$^+$) 357.0949, found 357.0930.



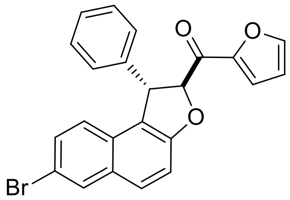
((1S,2S)-7-bromo-1-phenyl-1,2-dihydronaphtho[2,1-b]furan-2-yl)(phenyl)methanone (25n): Solid (0.167 g, 78%); mp 222-223 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (d, J = 7.8 Hz, 2H), 7.94 (s, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.63 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.34-7.24 (m, 7H), 7.15 (d, J = 7.2 Hz, 1H), 5.94 (d, J = 5.4 Hz, 1H), 5.30 (d, J = 5.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.5, 157.6, 142.2, 134.4, 134.1, 131.4, 130.9, 130.3, 129.8, 129.6, 129.4, 129.0, 128.1, 127.8, 124.7, 120.5, 117.0, 113.4, 91.8, 50.6 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 133.9, 130.8, 130.1, 129.7, 129.4 129.2, 128.8, 128.0, 127.6, 124.5, 113.2, 91.6, 50.5 (CH);IR (KBr) ν_{max} 1687 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{18}BrO_2$ (M + H$^+$) 429.0490, found 429.0375.



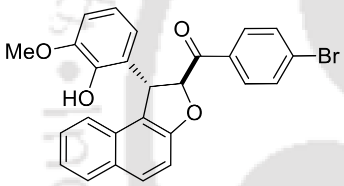
((1S,2S)-7-bromo-1-phenyl-1,2-dihydronaphtho[2,1-b]furan-2-yl)(4-bromophenyl)methanone (25o): Solid (0.174 g, 69%); mp 139-141 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.86 (d, J = 7.8 Hz, 2H), 7.69 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.35-7.23 (m, 7H), 7.15 (d, J = 9.0 Hz, 1H), 5.85 (d, J = 5.4 Hz, 1H), 5.33 (d, J = 5.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.7, 157.4, 142.0, 132.3, 131.5, 131.4, 131.1, 131.0, 130.5, 130.4, 129.9, 129.5, 129.0, 128.1, 127.9, 125.1, 124.7, 114.0, 113.3, 91.8, 50.4 ppm; IR (KBr) ν_{max} 1693 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{17}Br_2O_2$ (M + H$^+$) 506.9595, found 506.9465.



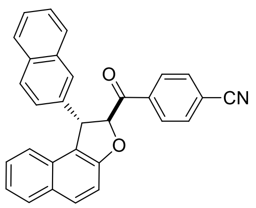
((1S,2S)-7-bromo-1-phenyl-1,2-dihydronaphtho[2,1-b]furan-2-yl)(furan-2-yl)methanone (25p): Solid (0.157 g, 75%); mp 185-187 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.66 (bs, 1H), 7.37-7.30 (m, 5H), 7.27 (d, J = 7.2 Hz, 1H), 7.22 (d, J = 7.2 Hz, 2H), 7.15 (d, J = 9.0 Hz, 1H), 6.57 (bs, 1H), 5.66 (d, J = 4.8 Hz, 1H), 5.29 (d, J = 5.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 184.1, 157.7, 150.5, 147.9, 142.1, 131.4, 130.9, 130.4, 129.9, 129.4, 129.0, 128.0, 127.8, 124.8, 120.7, 120.3, 117.1, 113.3, 112.8, 91.9, 51.2 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 147.7, 130.8, 130.2, 129.7, 129.2, 128.0, 127.6, 124.6, 120.6, 113.1, 112.6, 91.7, 51.0 (CH);IR (KBr) ν_{max} 1685 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{16}BrO_3$ (M + H$^+$) 419.0283, 421.0262 found 419.0134, 421.0263.



(4-bromophenyl)((1S,2S)-1-(2-hydroxy-3-methoxyphenyl)-1,2-dihydronaphtho[2,1-b]furan-2-yl)methanone (25q): Solid (2.055 g, 69%); mp 197-199 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 (d, J = 8.5 Hz, 2H), 7.76 (dd, J = 13.5, 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.2 Hz, 1H), 7.29-7.23 (m, 3H), 6.77-6.71 (m, 2H), 6.63 (d, J = 7.6 Hz, 1H), 5.97 (s, 1H), 5.93 (d, J = 4.8 Hz, 1H), 5.73 (d, J = 4.8 Hz, 1H) 3.89 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.1, 157.2, 146.7, 143.0, 133.3, 132.1, 131.0, 130.6, 130.4, 130.2, 129.1, 128.9, 127.7, 127.1, 123.4, 123.2, 121.2, 120.5, 120.2, 112.2, 109.7, 90.7, 56.2, 43.7 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 131.9, 130.9, 130.2, 128.7, 126.9, 123.2, 123.0, 121.0, 120.3, 112.0, 109.5, 90.5, 43.5 (CH); 56.0 (CH_3); IR (KBr) ν_{max} 1732 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{20}BrO_4$ (M + H$^+$) 475.0545, 477.0525 found 475.0540, 477.0524.

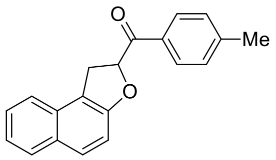


4-((1S,2S)-1-(naphthalen-2-yl)-1,2-dihydronaphtho[2,1-b]fura-n-2-carbonyl)benzonitrile (25r): Solid (0.872 g, 41%); mp 228-230 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, J = 8.4 Hz, 2H), 7.82-7.79 (m, 4H), 7.78-7.73 (m, 4H), 7.50-7.45 (m, 2H), 7.33 (d, J = 7.2 Hz, 2H), 7.29 (d, J = 8.9 Hz, 1H), 7.25-7.19 (m, 2H), 5.91 (d, J = 5.6 Hz, 1H), 5.56 (d, J = 5.6 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.1, 156.9, 139.4, 137.8, 133.7, 133.0, 132.7, 131.0, 130.5, 130.4, 130.1, 129.6, 129.1, 128.1, 128.0, 127.3, 127.1, 126.8, 126.4, 125.7, 123.8, 123.1, 119.7, 118.0, 117.2, 112.2, 91.9, 50.6 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 132.5, 130.9, 129.9, 129.4, 128.9, 127.9, 127.8, 127.1,

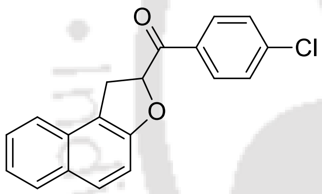


126.9, 126.6, 126.2, 125.6, 123.6, 112.9, 112.0, 91.7, 50.5 (CH); IR (KBr) ν_{max} 2229, 1695 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{20}NO_2$(M + H^+) 426.1494, found 426.1495.

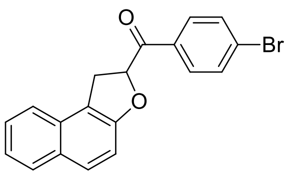
(1,2-dihydronaphtho[2,1-b]furan-2-yl)(p-tolyl)methanone (26a): Solid (0.115 g, 80%); mp 150-153 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (d, J = 7.8 Hz, 2H), 7.81 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.33-7.32 (m, 3H), 7.21 (d, J = 9.0 Hz, 1H), 6.12 (t, J = 9.6 Hz, 1H), 3.84 (d, J = 8.4 Hz, 2H), 2.45 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 195.2, 156.9, 144.9, 132.1, 130.8, 129.7, 129.7, 129.6, 129.5, 128.9, 127.0, 123.4, 122.9, 117.3, 112.3, 83.6, 32.1, 22.0 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 129.5, 129.4, 129.3, 128.7, 126.9, 123.2, 122.7, 112.1, 83.4 (CH), 31.9 (CH_2), 21.8 (CH_3); IR (KBr) ν_{max} 1699 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{17}O_2$ (M + H^+) 289.1229, found 289.1224.



(4-chlorophenyl)(1,2-dihydronaphtho[2,1-b]furan-2-yl)metha-none (26b): Solid (0.117 g, 76%); mp 163-165 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.50-7.48 (m, 3H), 7.34 (t, J = 7.8 Hz, 1H), 7.18 (t, J = 9.0 Hz, 1H), 6.04 (dd, J = 10.2, 7.2 Hz, 1H), 3.90 (dd, J = 15.6, 7.8 Hz, 1H), 3.80 (dd, J = 15.6, 10.8 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.6, 156.6, 140.4, 133.1, 130.9, 130.7, 129.8, 129.7, 129.3, 128.9, 127.2, 123.6, 122.9, 117.3, 112.2, 83.7, 31.5 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 130.7, 129.5, 129.1, 128.8, 127.0, 123.4, 122.7, 112.0, 83.5 (CH), 31.4 (CH_2); IR (KBr) ν_{max} 1686 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{14}ClO_2$ (M + H^+) 309.0682, found 309.0681.

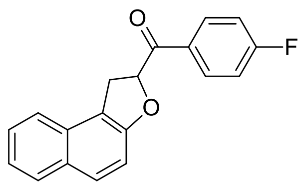


(4-bromophenyl)(1,2-dihydronaphtho[2,1-b]furan-2-yl)meth-aone (26c): Solid (0.150 g, 85%); mp 172-174 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.95 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.03 (dd, J = 10.8, 7.8 Hz, 1H), 3.89 (dd, J = 15.6, 7.8 Hz, 1H), 3.79 (dd, J = 15.6, 10.8 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.8, 156.5, 133.4, 132.3, 130.9, 130.7, 129.8, 129.7, 129.2, 128.9, 127.1, 123.5, 122.9, 117.2, 112.1, 83.7, 31.5 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 132.1, 130.8, 129.5, 128.8, 127.0, 123.4, 122.7, 112.0, 83.5

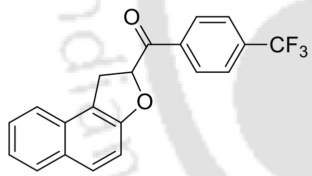


(CH), 31.4 (CH_2); IR (KBr) ν_{max} 1690 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{14}BrO_2$ (M + H^+) 353.0177, found 352.9976.

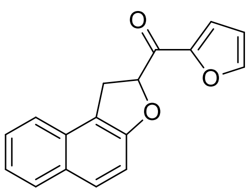
(1,2-dihydronaphtho[2,1-b]furan-2-yl)(4-fluorophenyl)metha-none (26d): Solid (0.125 g, 86%); mp 150-153 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.15-8.13 (m, 2H), 7.82 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.21-7.18 (m, 3H), 6.07 (dd, J = 10.8, 7.2 Hz, 1H), 3.91 (dd, J = 15.6, 7.2 Hz, 1H), 3.82 (dd, J = 15.6, 10.8 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.2, 167.1, 156.6, 132.3, 132.2, 130.7, 129.7, 129.0, 127.2, 123.6, 122.9, 117.3, 116.3, 116.1, 112.2, 83.8, 31.6 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 132.1, 132.0, 129.5, 128.8, 126.9, 123.4, 122.7, 116.1, 115.9, 112.0, 83.6 (CH), 31.4 (CH_2); IR (KBr) ν_{max} 1694 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{14}FO_2$ (M + H^+) 293.0978, found 293.0955.



(1,2-dihydronaphtho[2,1-b]furan-2-yl)(4-(trifluoromethyl)phe-nyl)methanone (26e): Solid (0.120 g, 70%); mp 143-145 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.20 (d, J = 7.8 Hz, 2H), 7.84 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 9 Hz, 1H), 7.60 (d, J = 6.6 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.09 (dd, J = 10.8, 6.6 Hz, 1H), 3.94 (dd, J = 15.6, 7.1 Hz, 1H), 3.84 (dd, J = 15.6, 10.8 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 195.2, 156.5, 155.1, 151.8, 137.6, 130.9, 130.8, 130.7, 130.0, 129.9, 129.8, 129.4, 129.0, 127.9, 127.2, 126.0, 125.8, 123.7, 123.6, 122.9, 117.2, 116.2, 113.0, 112.1, 83.9, 31.4 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 130.7, 129.8, 129.7, 129.6, 129.2, 128.8, 127.7, 127.0, 125.8, 125.6, 123.5, 123.4, 122.7, 116.1, 112.8, 111.9, 83.7(CH), 31.2 (CH_2); IR (KBr) ν_{max} 1698 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{14}F_3O_2$ (M + H^+) 343.0946, found 343.0951.

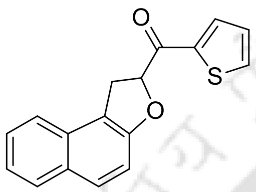


(1,2-dihydronaphtho[2,1-b]furan-2-yl)(furan-2-yl)methanone (26f): Solid (0.99 g, 75%); mp 102-106 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.82 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.68 (bs, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.49-7.47 (m, 2H), 7.34 (t, J = 7.8 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.59 (dd, J = 3.6, 1.2 Hz, 1H), 5.87 (dd, J = 11.4, 7.8 Hz, 1H), 3.88 (dd, J = 15.6, 10.8 Hz, 1H), 3.80 (dd, J = 15.6, 7.8 Hz, 1H) ppm; ^{13}C NMR (150

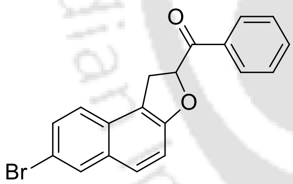


MHz, $CDCl_3$): δ 185.5, 156.8, 150.6, 147.6, 130.7, 129.8, 129.7, 128.9, 127.1, 123.5, 122.9, 120.5, 117.3, 112.7, 112.1, 84.0, 32.4 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 147.6, 129.7, 128.9, 127.1, 123.5, 122.9, 120.5, 112.7, 112.1, 83.9 (CH), 32.4 (CH_2); IR (KBr) ν_{max} 1682 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{13}O_3$ (M + H^+) 265.0865, found 265.0854.

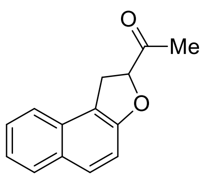
(1,2-dihydronaphtho[2,1-b]furan-2-yl)(thiophen-2-yl)methan-one (26g): Solid (0.101 g, 72%); mp 105-108 °C, ^1H NMR (600 MHz, $CDCl_3$): δ 8.03 (d, J = 3.6 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.72 (d, J = 4.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.18 (t, J = 4.8 Hz, 1H), 5.86 (t, J = 9.6 Hz, 1H), 3.88 (d, J = 9.0 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.3, 156.7, 140.6, 135.2, 134.4, 130.7, 129.8, 129.7, 128.9, 128.5, 127.2, 123.6, 123.0, 117.4, 112.1, 85.0, 32.8 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 135.1, 134.2, 129.5, 128.7, 128.3, 127.0, 123.4, 122.8, 112.0, 83.8 (CH), 32.6 (CH_2); IR (KBr) ν_{max} 1669 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{13}O_2S$ (M + H^+) 281.0636, found 281.0632.



(7-bromo-1,2-dihydronaphtho[2,1-b]furan-2-yl)(phenyl)meth-anone (26h): Solid (0.125 g, 71%); mp 172-174 °C, ^1H NMR (600 MHz, $CDCl_3$): δ 8.07 (d, J = 7.2 Hz, 2H), 7.95 (s, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.60 (d, J = 9.0 Hz, 1H), 7.54-751 (m, 3H), 7.44 (d, J = 9.0 Hz, 1H), 7.20 (d, J = 9.0 Hz, 1H), 6.14 (t, J = 9.0 Hz, 1H), 3.86-3.77 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 195.2, 157.2, 134.5, 134.0, 130.9, 130.8, 130.3, 129.3, 129.2, 129.0, 128.8, 124.6, 117.6, 117.0, 113.3, 83.5, 31.7 ppm; IR (KBr) ν_{max} 1697 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{14}BrO_2$ (M + H^+) 353.0177, found 353.0098.

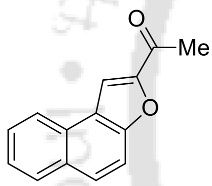


1-(1,2-dihydronaphtho[2,1-b]furan-2-yl)ethanone **(26i):** Solid (0.72 g, 68%); mp 46-48 °C, ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 9.2 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.20 (d, J = 9.2 Hz, 1H), 5.24 (dd, J = 11.2, 6.8 Hz, 1H), 3.74 (dd, J = 16.0, 11.2 Hz, 1H), 3.58 (dd, J = 15.6, 6.4 Hz, 1H), 2.34 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 209.1, 156.6, 130.6, 130.1, 129.7, 128.9, 127.2, 123.6, 122.9, 117.2, 112.0, 86.5, 32.1, 26.4 ppm; IR (KBr) ν_{max} 1721 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{13}O_2$ (M + H^+) 213.0916, found 213.0910.

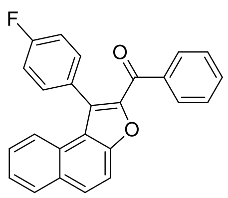


Mixture of 26j and 27b: Solid (0.116 g, 77%); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.20 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 9.0 Hz, 1H), 8.09 (d, J = 11.4 Hz, 2H), 8.03 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 9.0 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.2 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.19 (d, J = 9.0 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 9.0 Hz, 2H), 6.93 (dd, J = 10.8, 7.8 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.88-3.79 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.1, 182.5, 164.2, 163.8, 156.9, 154.5, 152.7, 132.2, 131.8, 130.8, 129.9, 129.8, 129.6, 129.3, 128.9, 128.4, 127.7, 127.6, 127.0, 125.7, 123.6, 123.4, 123.1, 122.9, 117.4, 114.8, 144.2, 114.1, 113.1, 112.3, 83.7, 55.8, 32.0 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 132.0, 131.5, 129.7, 129.4, 129.1, 128.7, 127.4, 126.8, 125.5, 123.4, 123.2, 122.7, 114.6, 114.0, 113.9, 112.9, 112.1, 83.5 (CH), 55.6 (CH_3), 31.8 (CH_2). ; IR (KBr) ν_{max} 1671 (C=O) cm^{-1}.

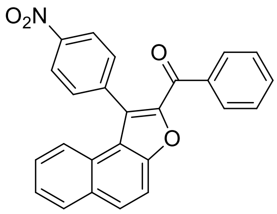
1-(naphtho[2,1-b]furan-2-yl)ethanone (27a): Solid (0.82 g, 78%); mp 110-112 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 7.8 Hz, 1H), 7.96 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 9 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 2.65 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 188.2, 154.2, 152.5, 130.7, 130.1, 129.3, 128.4, 127.6, 125.7, 123.5, 123.1, 112.9, 112.2, 26.5 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 129.9, 129.1, 127.4, 125.6, 123.3, 112.8, 112.0 (CH) 26.4 (CH_3); IR (KBr) ν_{max} 1674 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{11}O_2$ (M + H$^+$) 211.0759, found 211.0754.



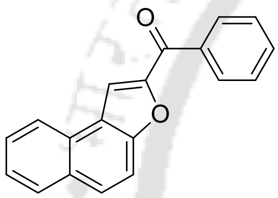
***(1-(4-fluorophenyl)naphtho[2,1-b]furan-2-yl)(phenyl)methanone* (27c):** Solid (0.150 g, 82%); mp 170-171 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.86 (m, 4H), 7.66 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.47-7.34 (m, 4H), 7.35-7.28 (m, 3H), 7.09 (t, J = 8.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.8, 164.2, 161.8, 153.1, 148.1, 137.6, 132.7, 131.9, 131.8, 131.3, 130.7, 130.6, 129.9, 129.5, 128.9, 128.8, 128.8, 128.3, 127.3 125.5, 123.3, 122.1, 116.0, 115.8, 112.9 ppm; IR (KBr) ν_{max} 1636 (C-O) cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{16}FO_2$ (M + H$^+$) 367.1134, found 367.1137.



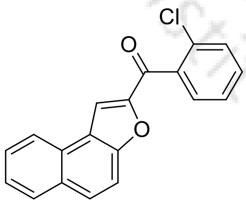
(1-(4-nitrophenyl)naphtho[2,1-b]furan-2-yl)(phenyl)methanone (27d): Solid (0.157 g, 80%); mp 182-185 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.39 (d, J = 7.2 Hz, 2H), 8.05 (d, J = 7.8 Hz, 2H), 7.99 (d, J = 9.6 Hz, 2H), 7.78-7.74 (m, 3H), 7.59 (t, J = 7.8 Hz, 1H), 7.53-7.47 (m, 4H), 7.39 (t, J = 7.8 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 184.2, 153.3, 148.1, 148.0 140.7, 137.2, 133.2, 131.4, 131.2, 131.1, 130.1, 129.8, 129.4, 128.6, 128.4, 127.7, 125.9, 124.1, 123.1, 121.7, 112.9 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 133.0, 131.0 130.9, 129.9, 129.6, 128.4, 127.5, 125.7, 123.9, 122.9, 112.7 (CH); IR (KBr) ν_{max} 1644 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{16}NO_4$ (M + H$^+$) 394.1079, found 394.1077.



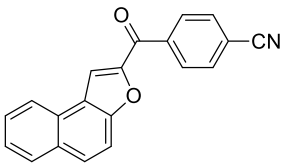
Naphtho[2,1-b]furan-2-yl(phenyl)methanone (27e): Solid (0.106 g, 78%); mp 103-104 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 7.2 Hz, 2H), 8.02 (s, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 9.0 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.67-7.64 (m, 2H), 7.59-7.55 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 184.0, 154.8, 152.2, 137.6, 133.0, 130.8, 130.3, 129.7, 129.3, 128.8, 128.4, 127.7, 125.8, 123.6, 123.1, 115.7, 113.1 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 132.8, 130.1, 129.5, 129.1, 128.6, 127.5, 125.6, 123.4, 115.5, 112.9 (CH); IR (KBr) ν_{max} 1638(C=O) cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{13}O_2$ (M + H$^+$) 273.0916, found 273.0900.



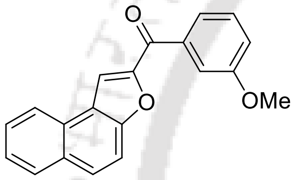
***(2-chlorophenyl)(naphtho[2,1-b]furan-2-yl)methanone* (27f):** Solid (0.122 g, 80%); mp 122-123 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.11 (d, J = 7.8 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.80 (s, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.63 (t, J = 7.2 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.57-7.50 (m, 3H), 7.44 (t, J = 7.2 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 183.4, 155.3, 151.8, 137.7, 132.1, 131.9, 131.0, 130.8, 130.6, 129.6, 129.4, 128.4, 127.8, 126.9, 125.9, 123.5, 123.2, 116.7, 113.1 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 131.7, 130.8, 130.4, 129.4, 129.2, 127.6, 126.7, 125.7, 123.4, 116.6, 112.9 (CH); IR (KBr) ν_{max} 1654 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{12}ClO_2$ (M + H$^+$) 307.0526, found 307.0526.



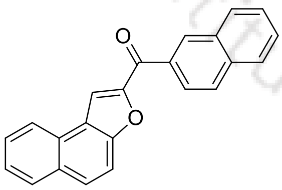
4-(naphtho[2,1-b]furan-2-carbonyl)benzonitrile (27g): Solid (0.122 g, 82%); mp 211-213 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ8.20 (t, J = 8.4 Hz, 3H), 8.09 (s, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.4 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.59 (t, J = 7.8 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 182.1, 155.2, 151.7, 140.9, 132.6, 131.2, 130.9, 130.1, 129.4, 128.3, 128.0, 126.1, 123.6, 123.1, 118.2, 116.4, 116.3, 112.9 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 132.6, 131.2, 130.1, 129.4, 128.0, 126.1, 123.6, 116.4, 112.9 (CH); IR (KBr) ν_{max} 2228 (CN), 1648 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{12}NO_2$ (M + H^{+}) 298.0868, found 298.0871.



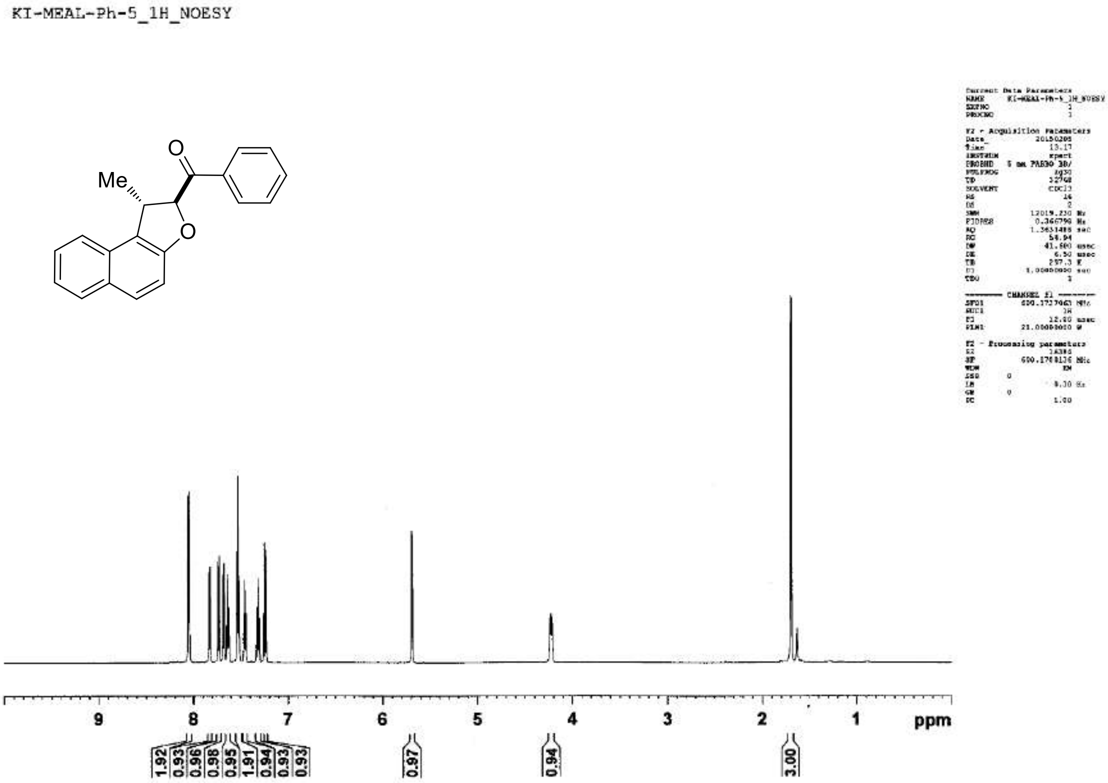
(3-methoxyphenyl)(naphtho[2,1-b]furan-2-yl)methanone (7h): Solid (0.110 g, 73%); mp 174-176 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.19 (d, J = 8.4 Hz, 1H), 8.03 (s, 1H), 7.99 (d, J = 7.2 Hz, 1H), 7.94 (d, J = 9.0 Hz, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.70 (d, J = 7.2 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.59-7.56 (m, 2H), 7.48 (t, J = 7.8 Hz, 1H), 7.20 (d, J = 7.8 Hz, 1H), 3.92 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 184.1, 160.0, 154.9, 152.1, 138.9, 130.8, 130.4, 129.8, 129.4, 128.4, 127.7, 125.8, 123.6, 123.1, 122.3, 119.4, 115.9, 114.2, 113.1, 55.8 ppm; IR (KBr) ν_{max} 1740 (C-O) cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{15}O_3$ (M + H^{+}) 303.1021, found 303.1025.



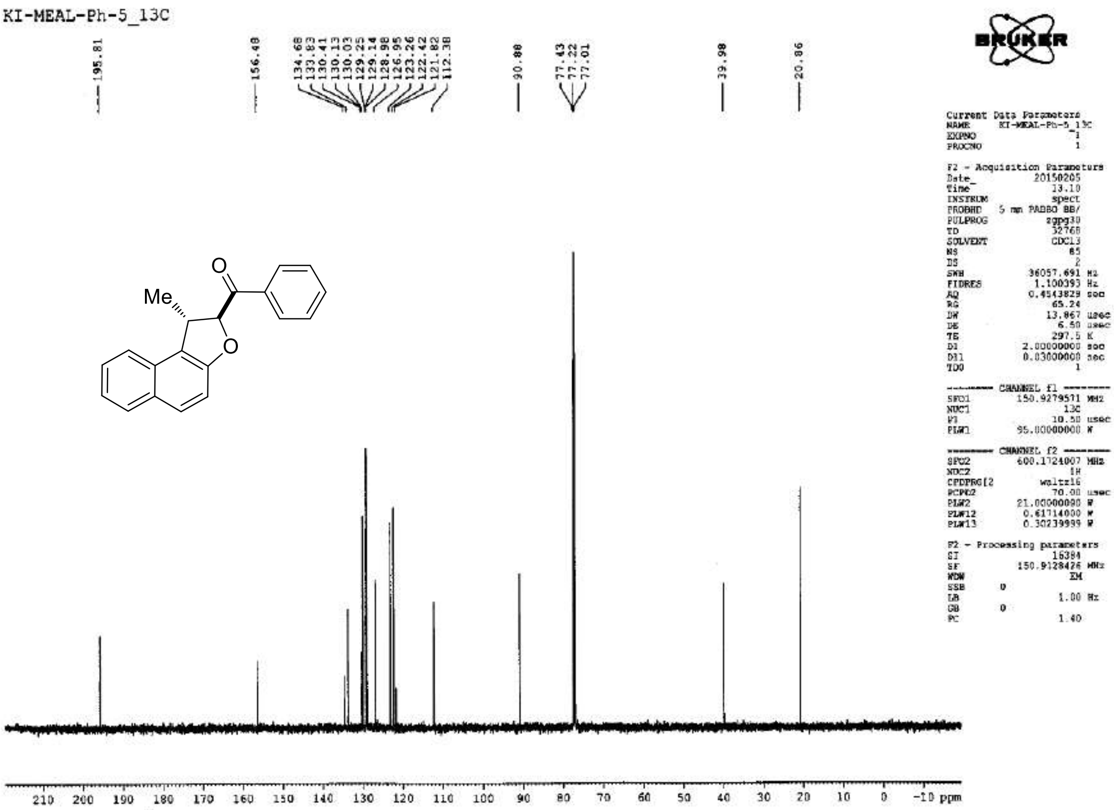
naphthalen-2-yl(naphtho[2,1-b]furan-2-yl)methanone (27i): Solid (0.109 g, 68%); mp 174-176 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.67 (bs, 1H), 8.20 (d, J = 7.8 Hz, 1H), 8.14 (dd, J = 8.4, 1.2 Hz, 1H), 8.09 (s, 1H), 8.05 (d, J = 9.0 Hz, 1H), 8.02 (d, J = 9 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.96-7.94 (m, 2H), 7.79 (d, J = 9.0 Hz, 1H), 7.68-7.60 (m, 3H), 7.57 (t, J = 7.2 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 184.0, 154.8, 152.4, 135.7, 134.9, 132.6, 131.1, 130.8, 130.4, 129.8, 129.4, 128.8, 128.7, 128.4, 128.1, 127.7, 127.2, 125.8, 125.5, 123.6, 123.2, 115.8, 113.1 ppm; ^{13}C DEPT 135 NMR ($CDCl_3$) δ = 131.0, 130.1, 129.6, 129.2, 128.6, 128.5, 127.9, 127.5, 127.0, 125.6, 125.3, 123.4, 115.6, 112.9 (CH); IR (KBr) ν_{max} 1642 (C=O) cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{15}O_2$(M + H^{+}) 323.1072, found 323.1033.



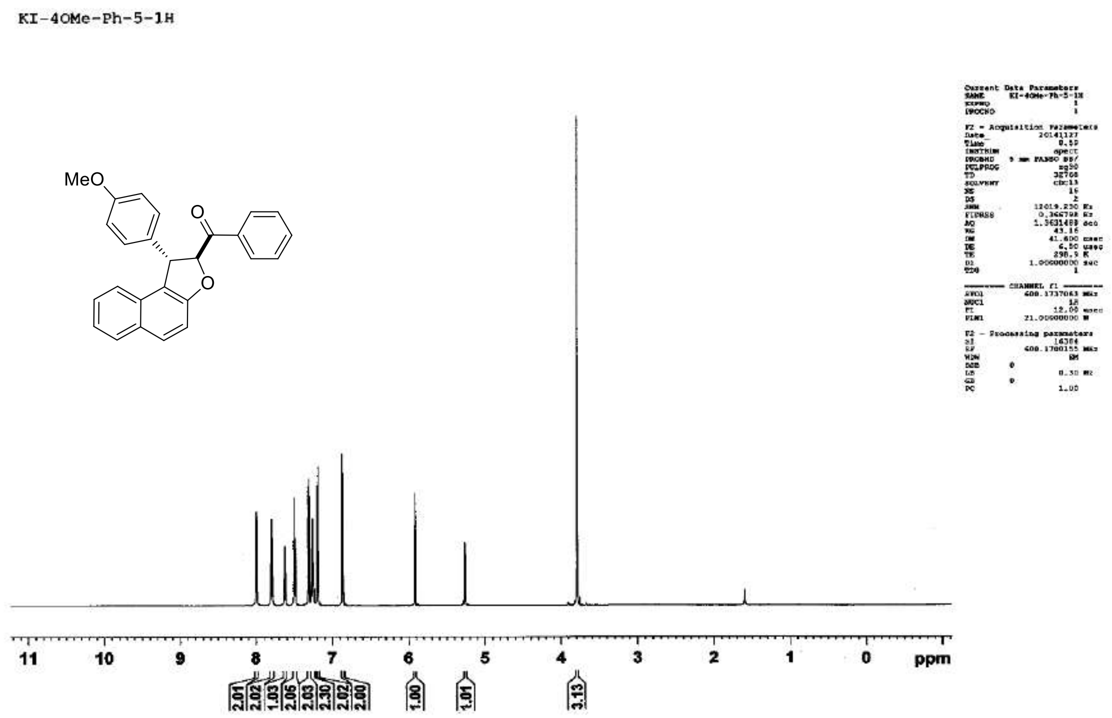
^{1}H NMR spectra of 25a



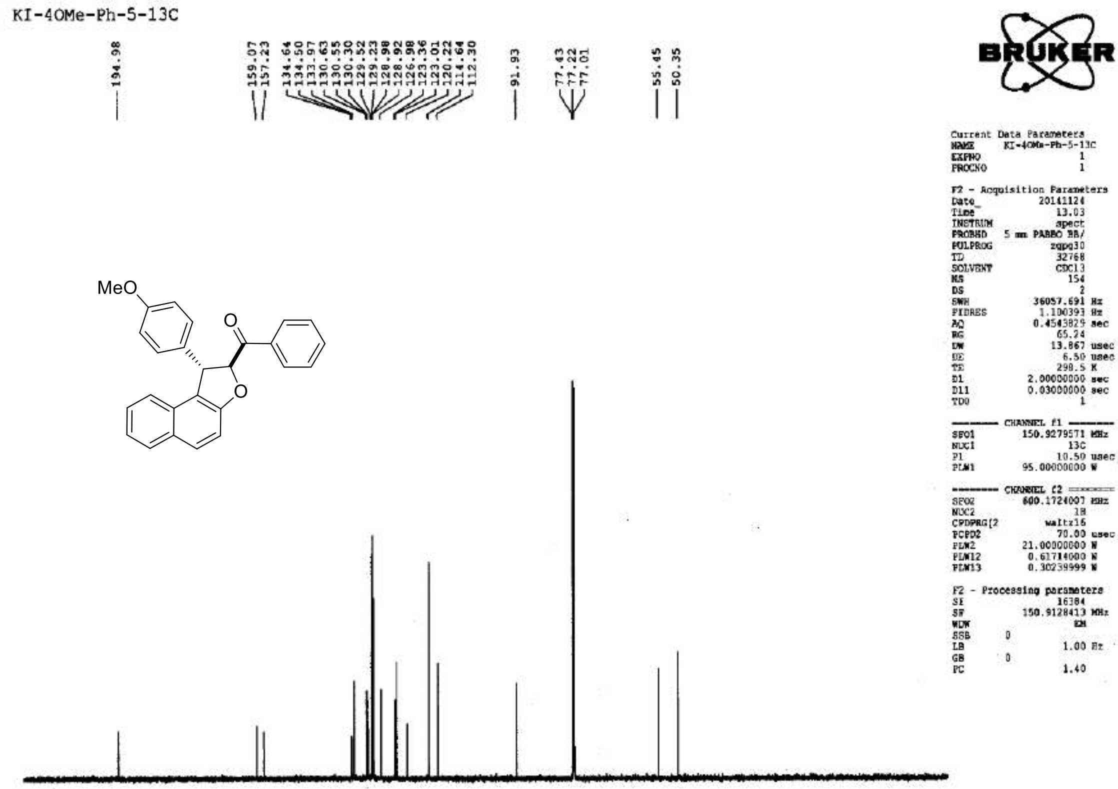
^{13}C NMR spectra of 25a



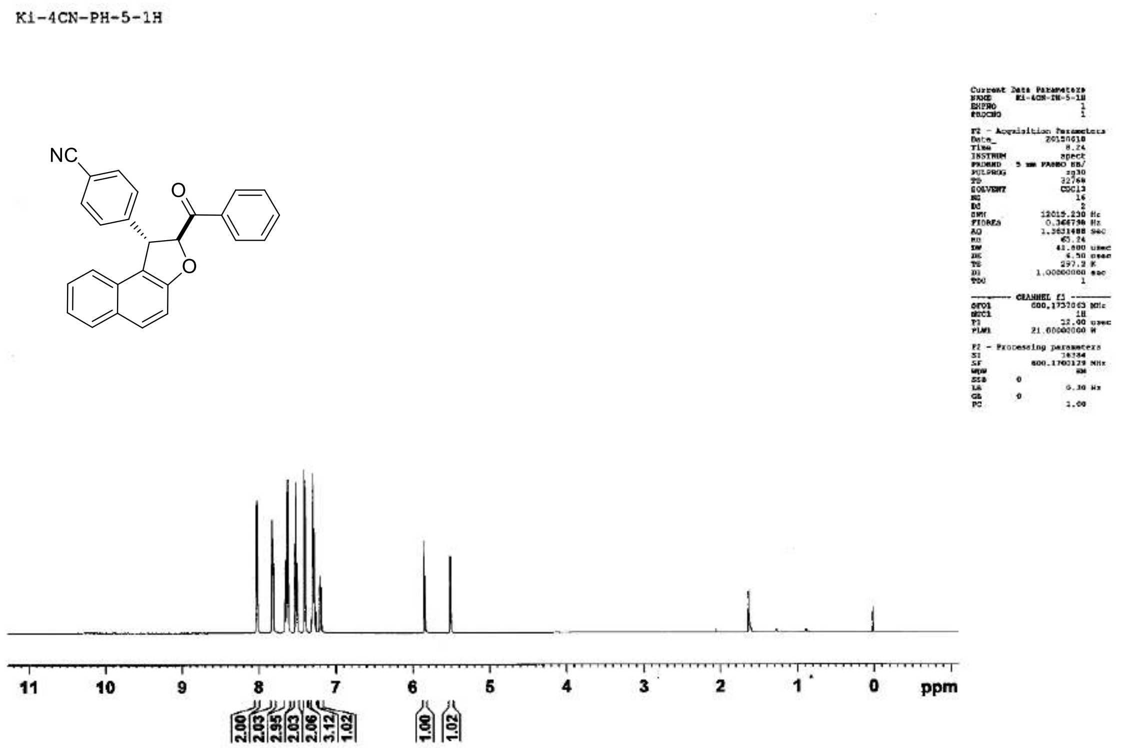
^{1}H NMR spectra of 25d



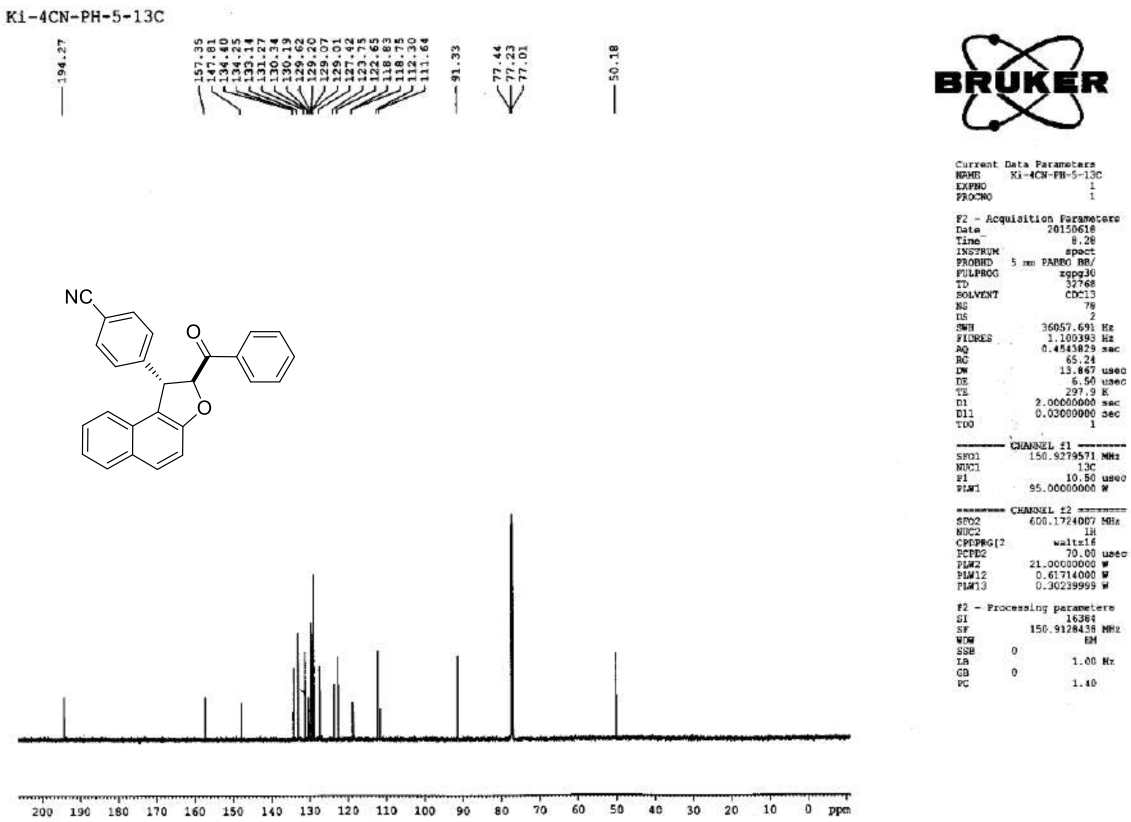
^{13}C NMR spectra of 25d



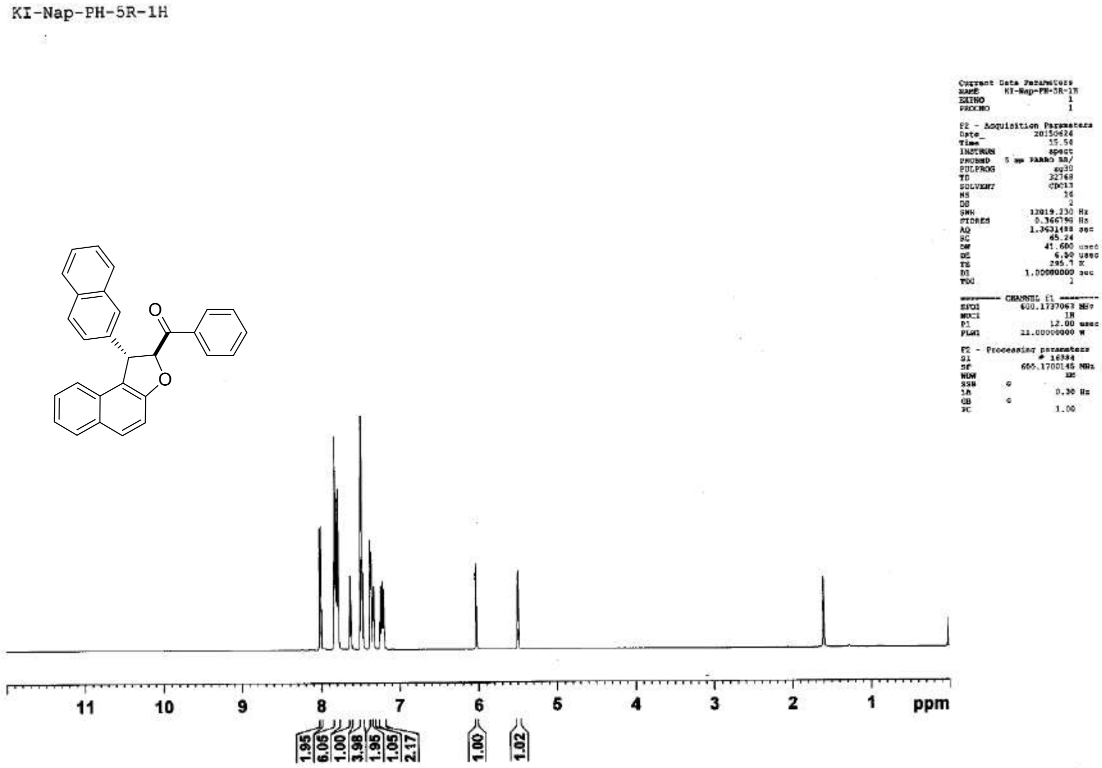
^{1}H NMR spectra of 25i



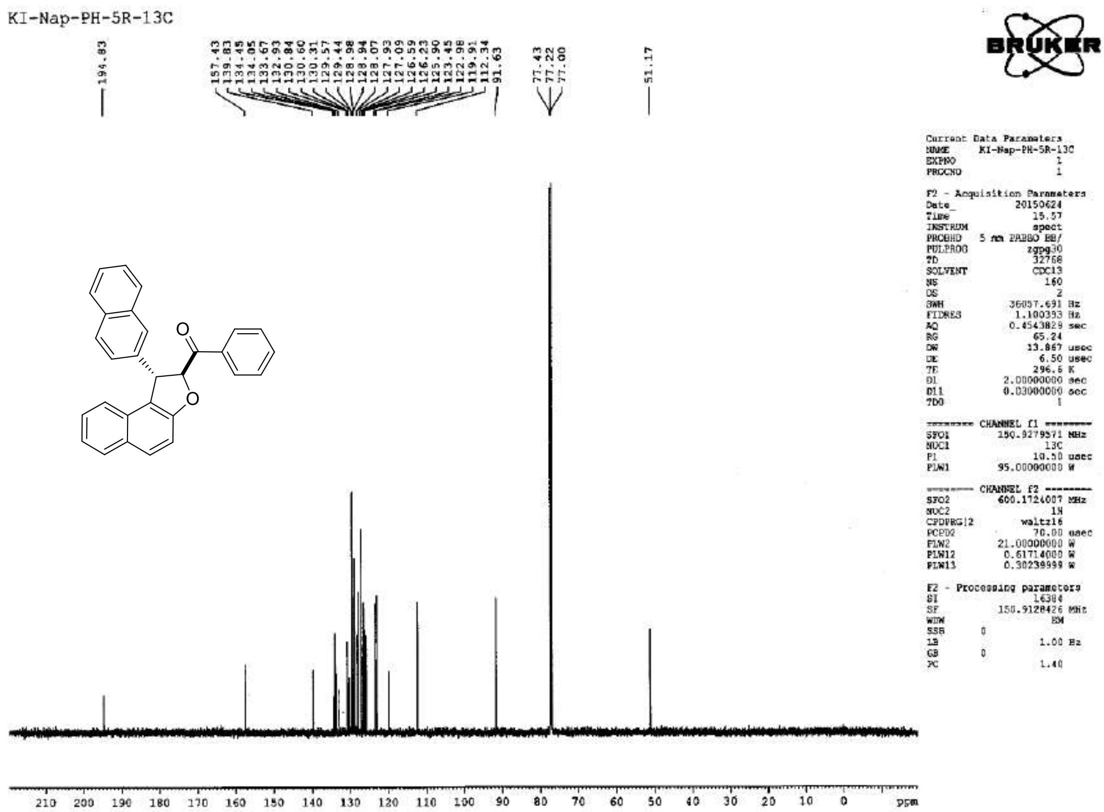
^{13}C NMR spectra of 25i



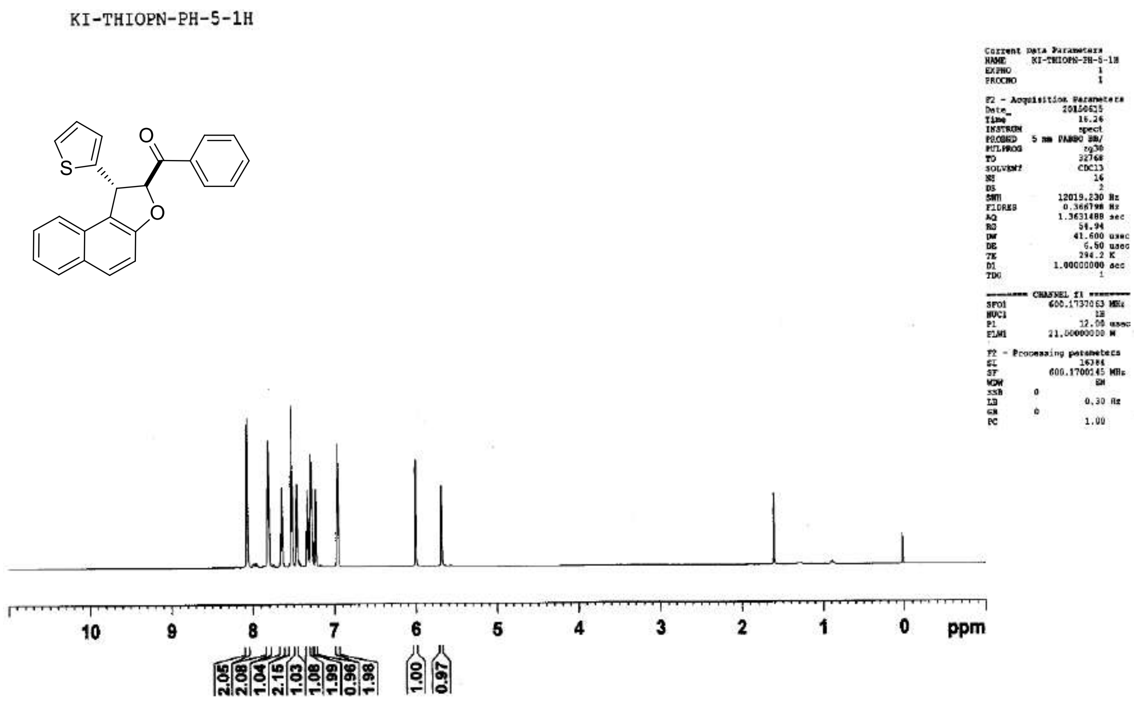
^{1}H NMR spectra of 25j



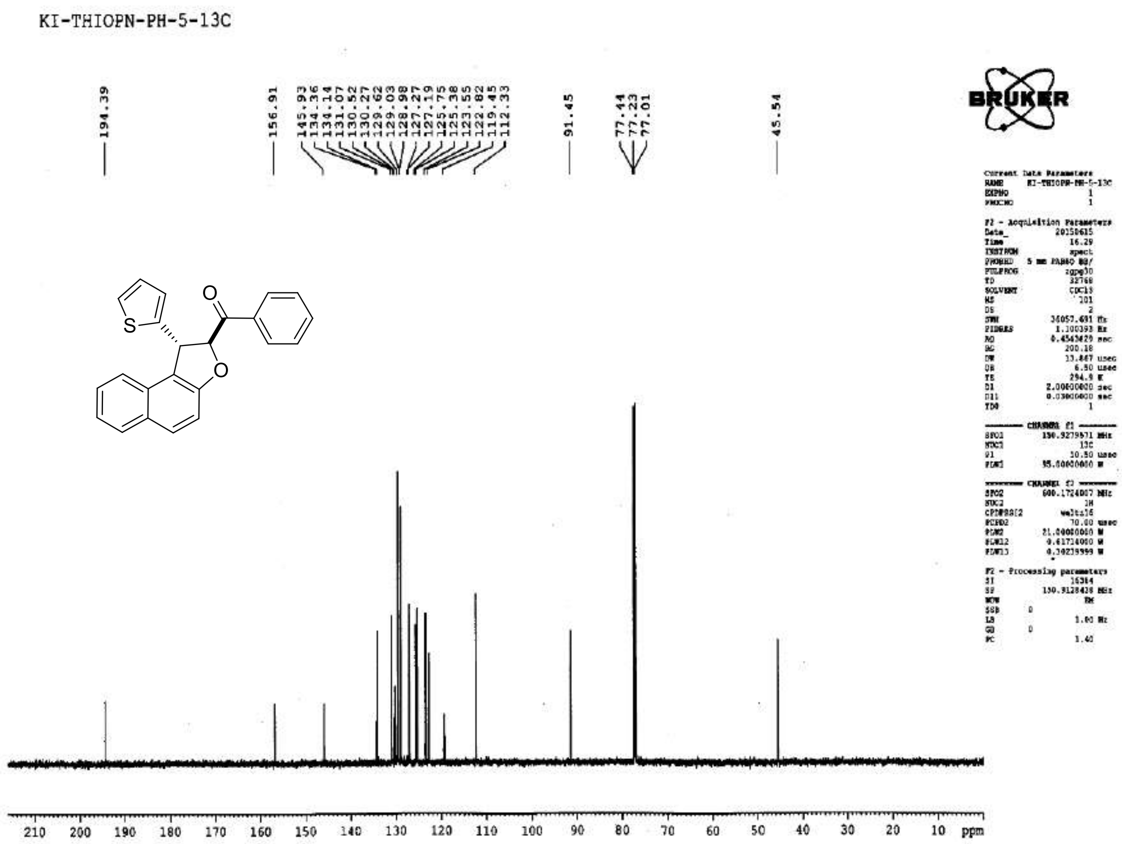
^{13}C NMR spectra of 25j



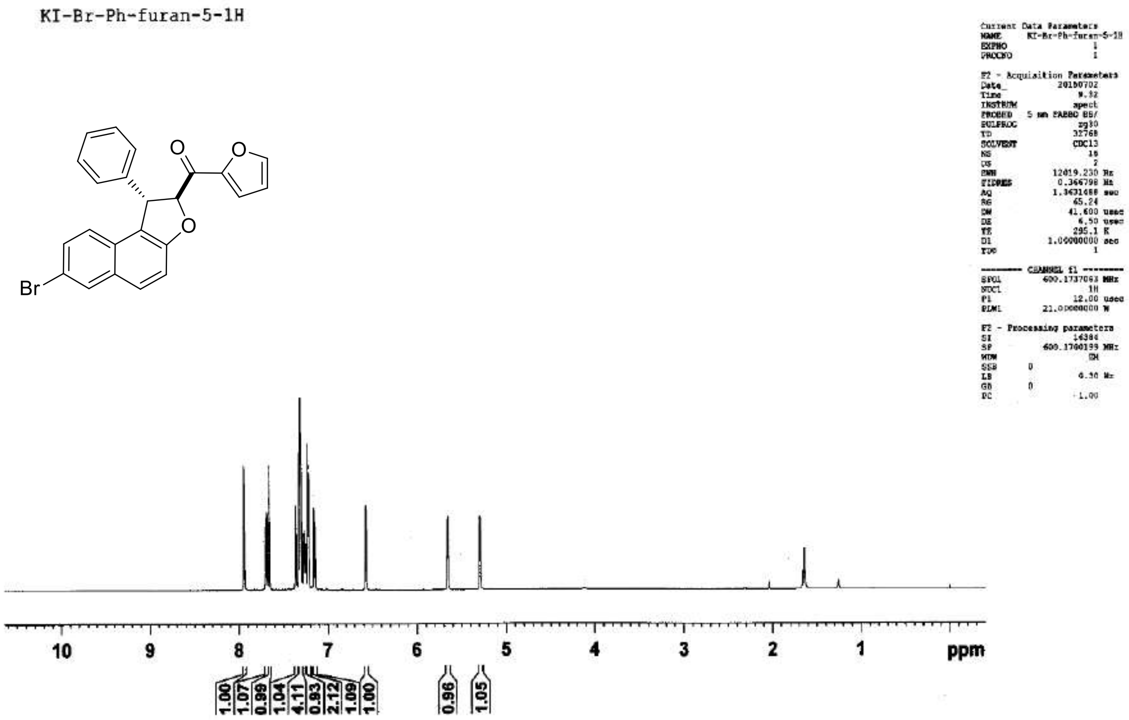
[1]H NMR spectra of 25m



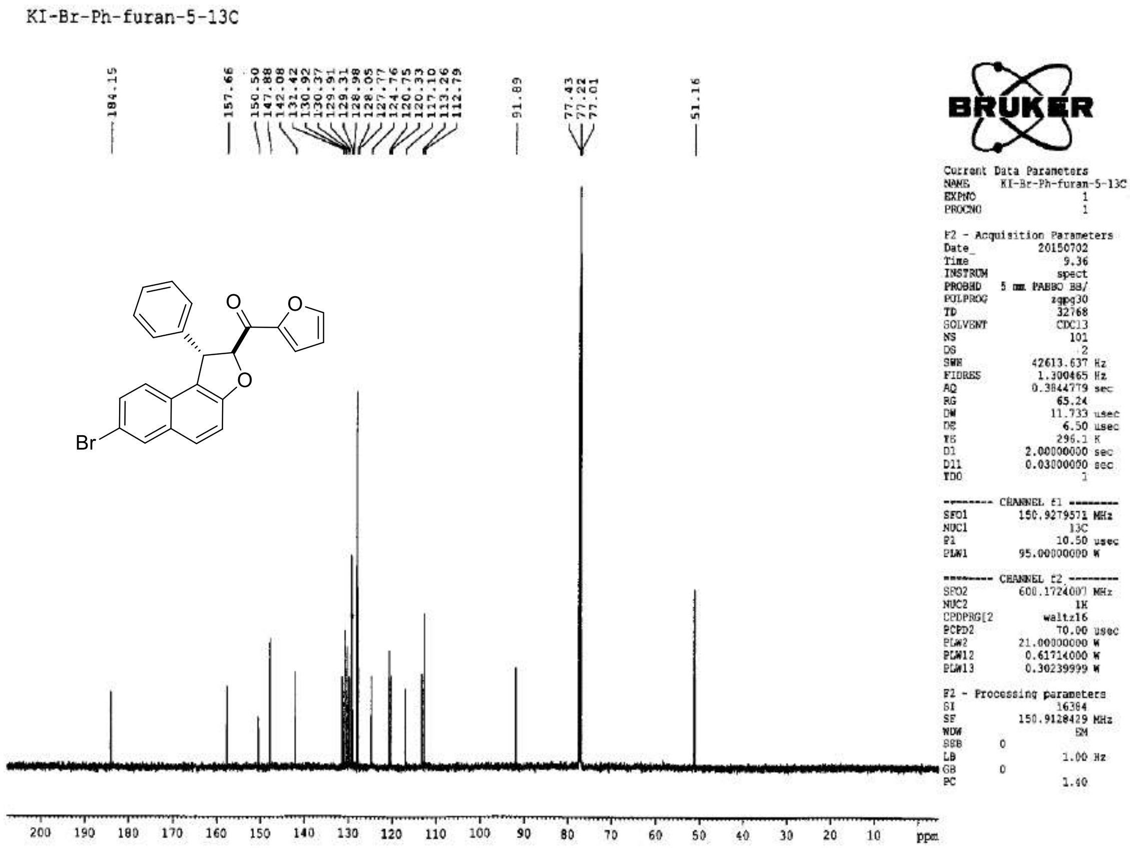
[13]C NMR spectra of 25m



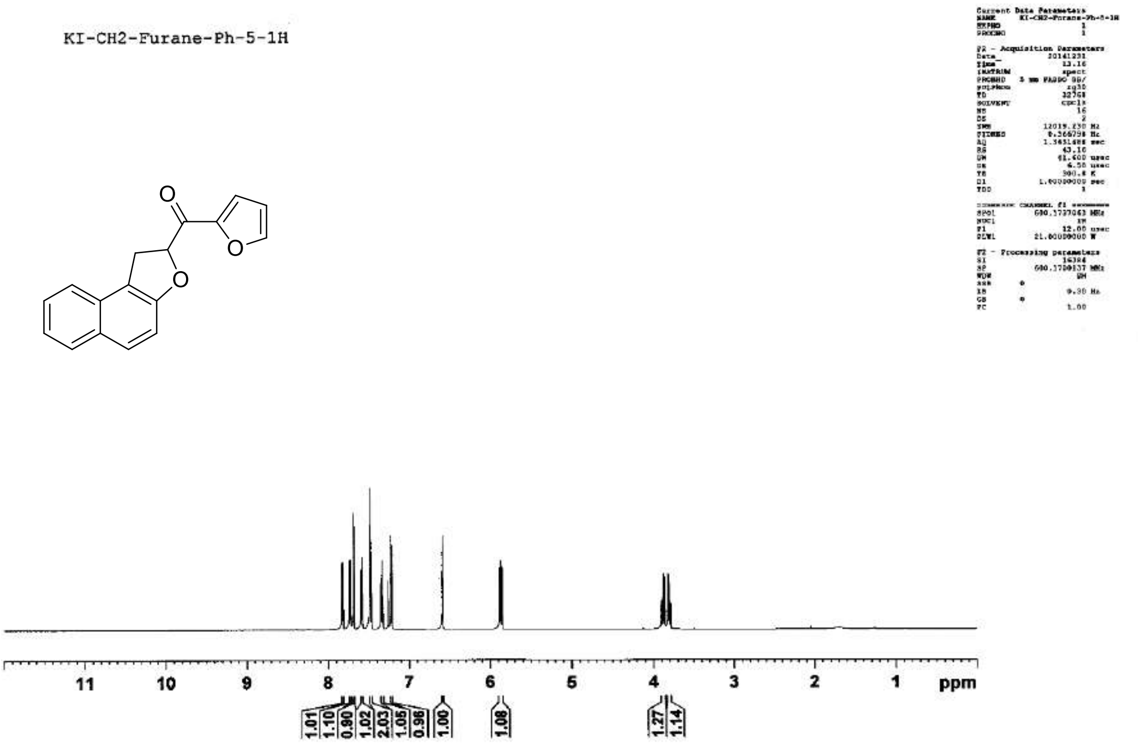
[1]H NMR spectra of 25p



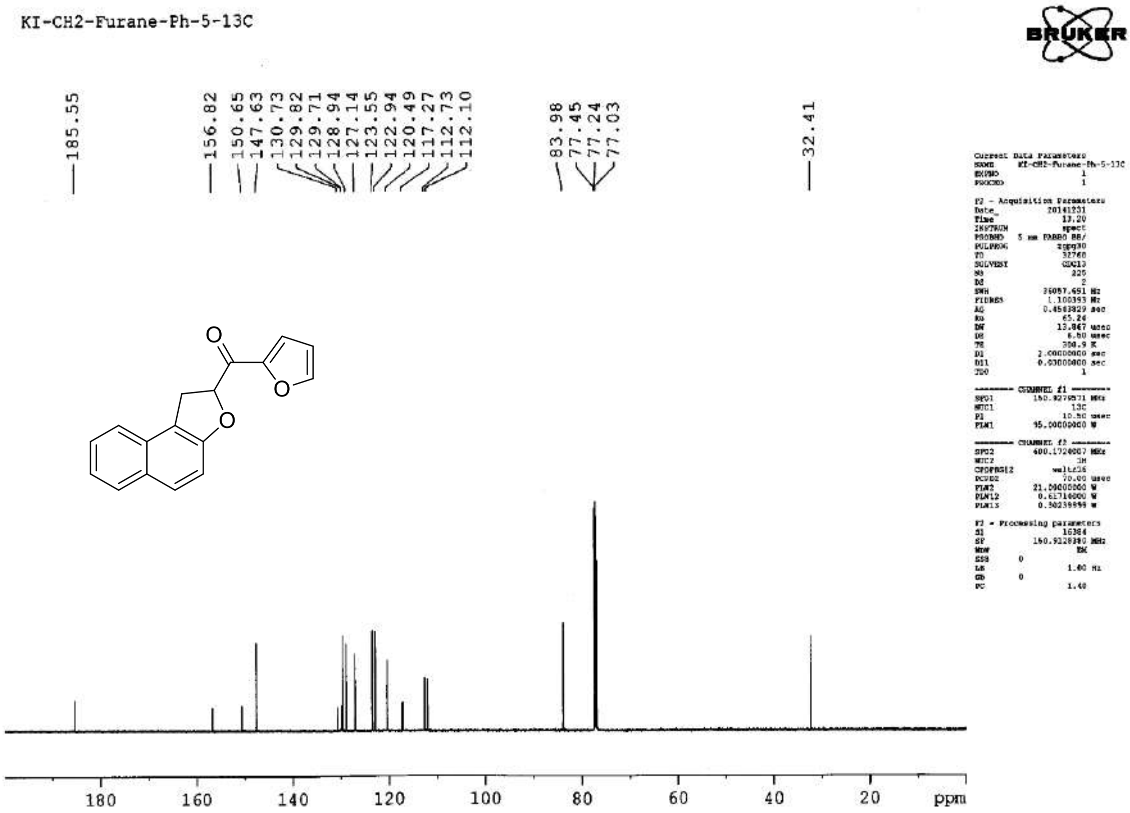
[13]C NMR spectra of 25p



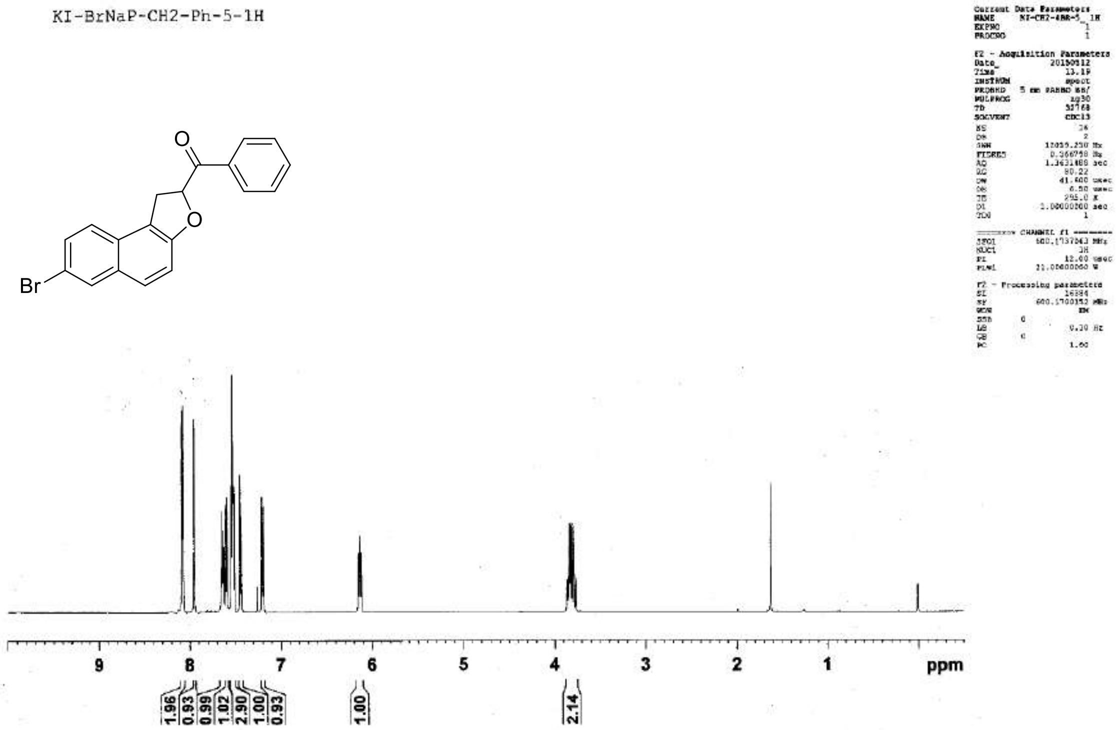
[1]H NMR spectra of 26f



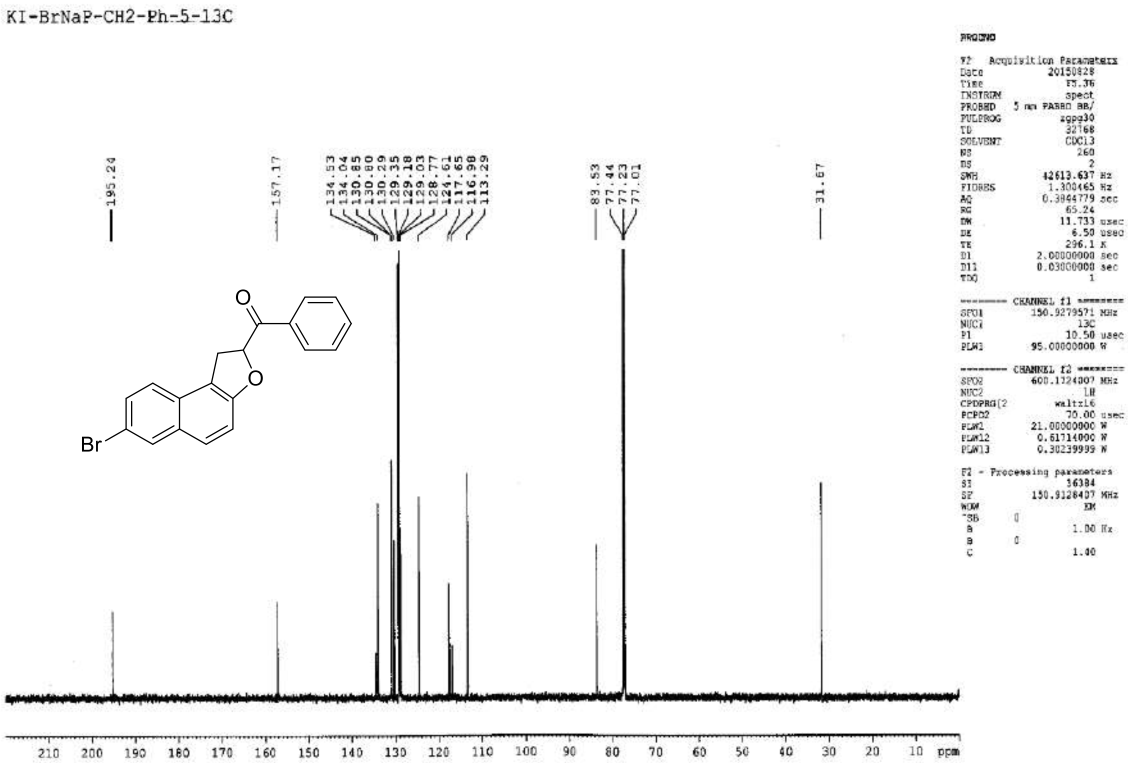
[13]C NMR spectra of 26f



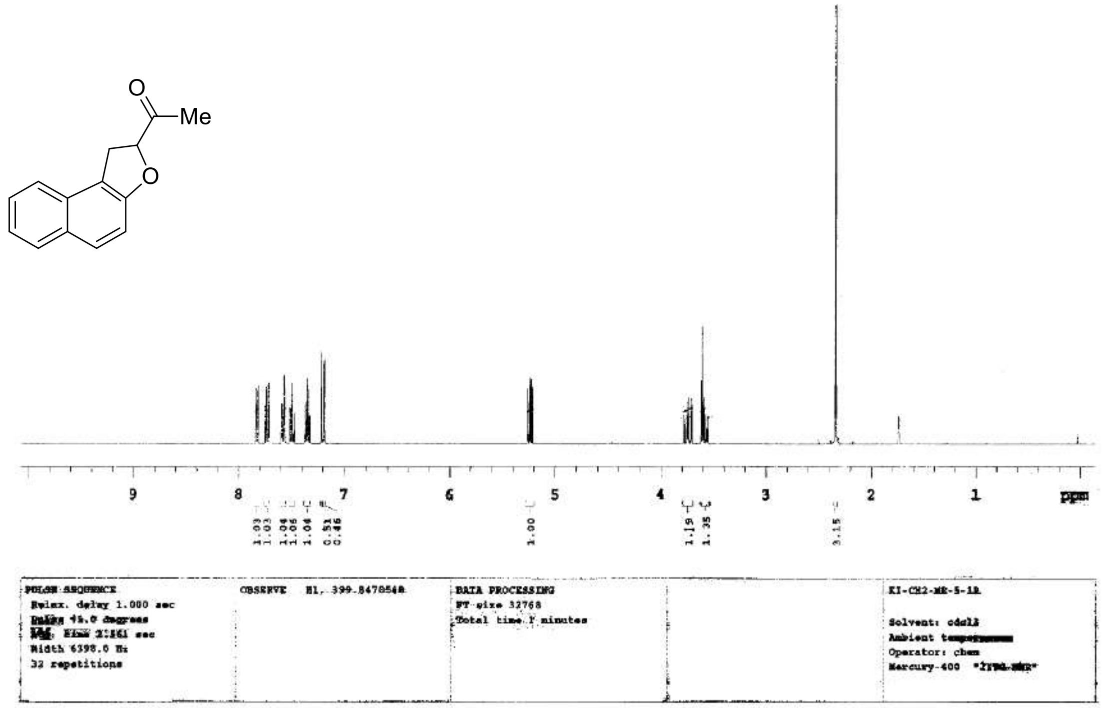
[1]H NMR spectra of 26h



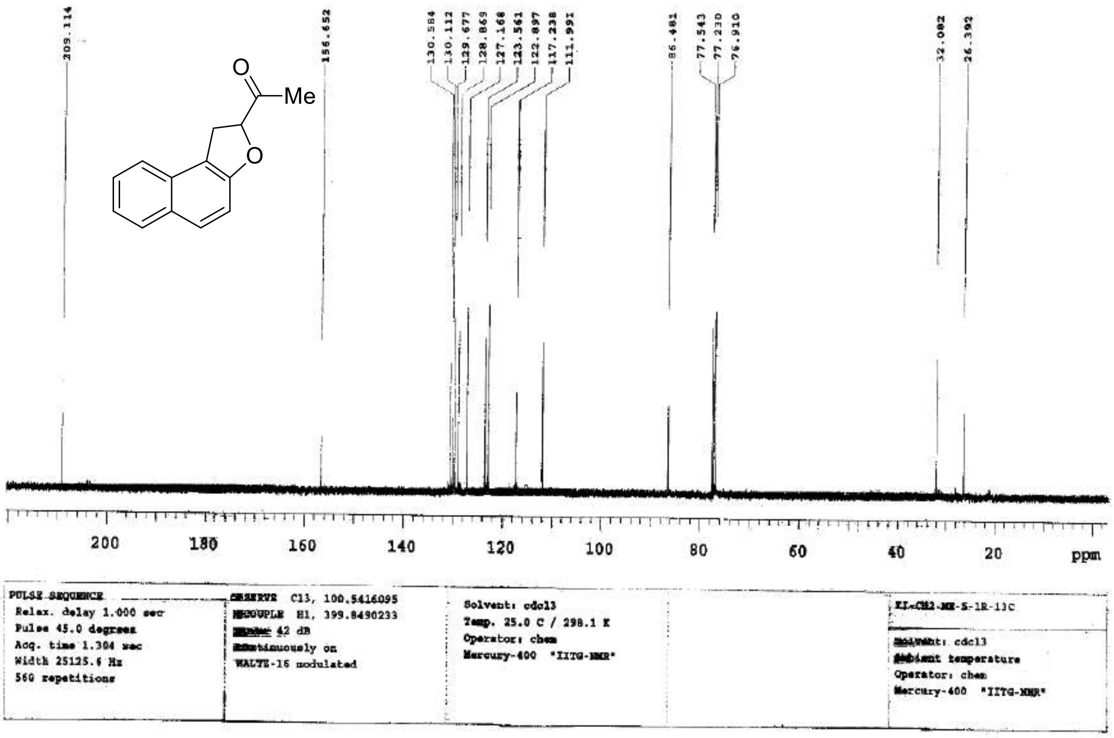
[13]C NMR spectra of 26h



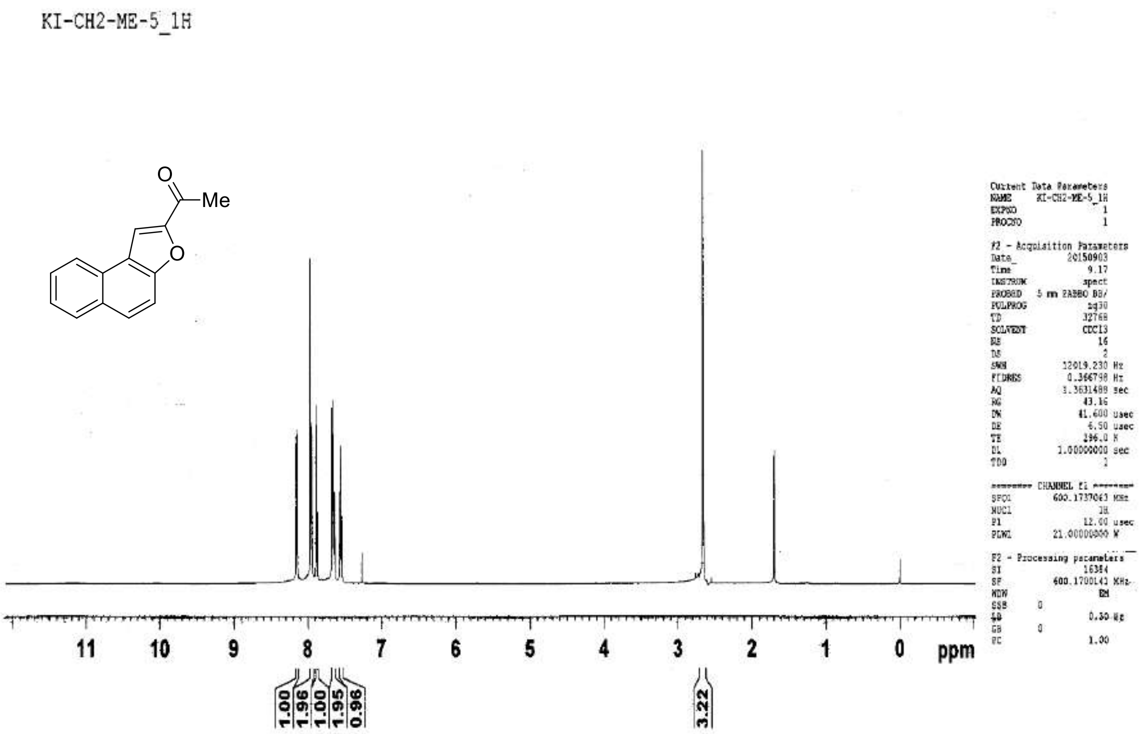
[1]H NMR spectra of 26i



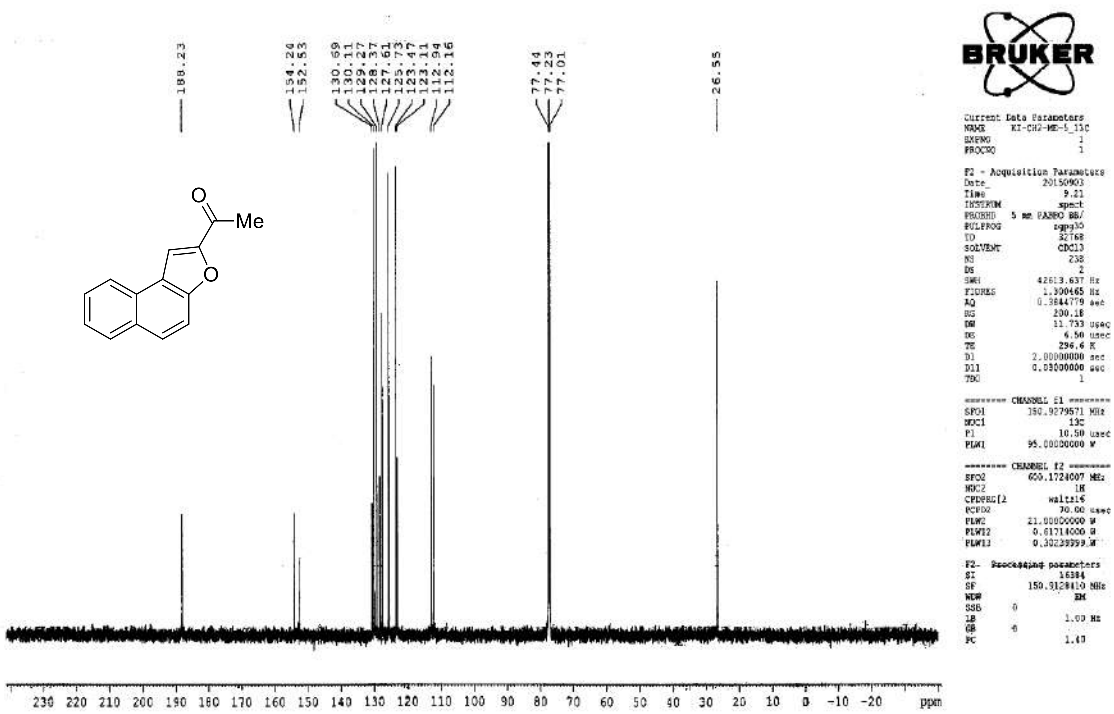
[13]C NMR spectra of 6i



^{1}H NMR spectra of 27a



^{13}C NMR spectra of 27a



References

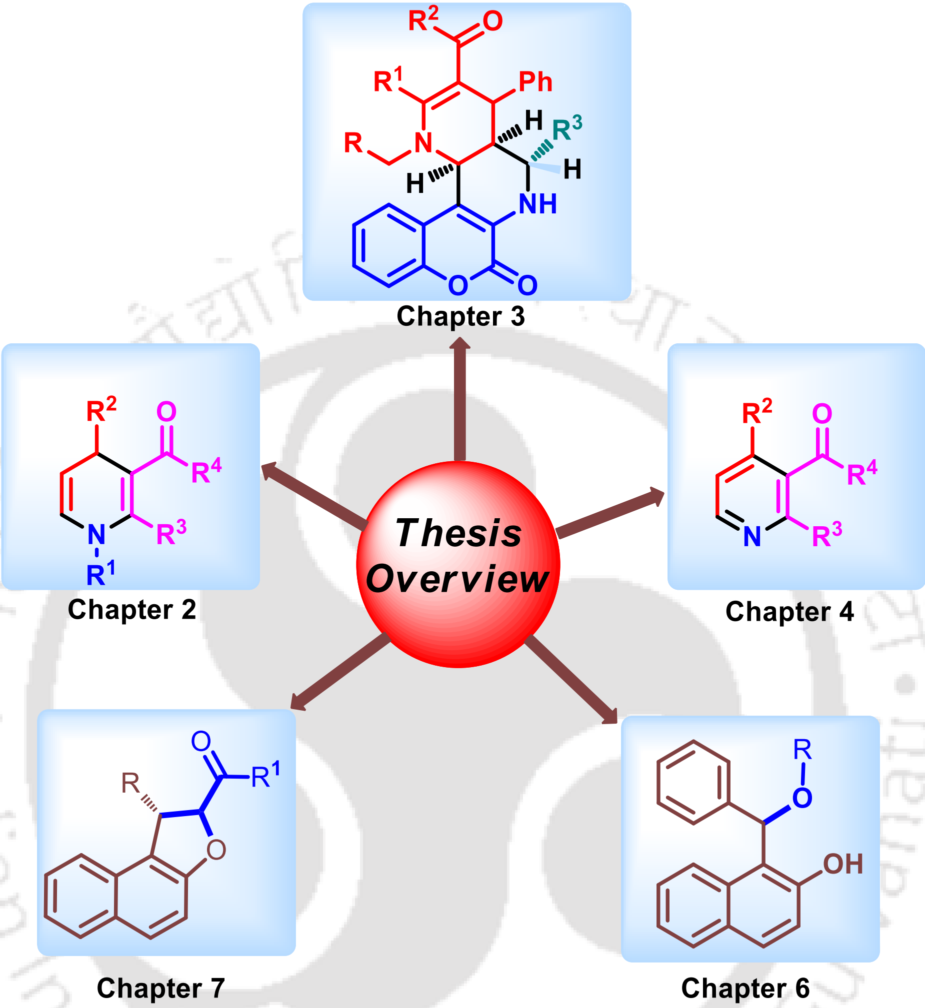
1. Fries, K. *Liebigs Ann. Chem*. **1907**, 353.
2. Gardner, P. D.; Rafsanjani, H. S.; Rand, L. *J. Am. Chem. Soc*. **1959**, *81*, 3364.
3. (a) Groszek, G.; Błazej, S.; Brud, A.; skib, D. S.; and Lemek, T. *Tetrahedron* **2006**, *62*, 2622. (b) Lukeman, M. ; Veale, D. ; Wan, P. ; Ranjit V. N. M.; Corrie, J. E. T. *Can. J. Chem*. **2004**, *82*, 240. (c) Wan, P.; Brousmiche, D.W.; Chen, C.Z.; Cole, J.; Lukeman, M.; Xu, M. *Pure Appl. Chem*. **2001**, *73*, 529.
4. Amouri, H.; Bras, J. L. *Acc. Chem. Res*. **2002**, *35*, 501.
5. Schenck, L. W.; Kuna, K.; Frank, W.; Albert, A.; Asche, C.; Kucklaender, U. *Bioorg. Med. Chem. Lett*. **2006**, *14*, 3599.
6. Creed, D.; Werbin, H.; *Tetrahedron. Lett*. **1981**, *22*, 2039.
7. Brimble, M. A.; Nairn, M. R. *Tetrahedron. Lett*. **1998**, *39*, 4879.
8. Richard, J. S.; Neal T. D., Michael, R. K.; Karl J. K. Insect *Biochem. Mol. Biol*. **2006**, *36*, 353.
9. (a) Kleyer, D. L.; Koch, T. H. *J. Am. Chem. Soc*. **1983**, *105*, 5154. (b) Gaudiano, G.; Resing, K.; Koch, T. H, *J. Am. Chem. Soc*. **1994**, *116*, 6537.
10. Evans, G. B.; Furneaux, R. H.; Gravestock, M. B.; Lynch, G. P.; Scott, G. K. *Bioorg. Med. Chem*. **1999**, *7*, 1953.
11. Chauhan, M.; Dean, F. M.; McDonal, S.; Robinson, M. S. *J. Chem. Soc. Chem. Comm*. **1971**, 1141. (b) Bowry, V. W.; Ingold, K. U. *J. Org. Chem*. **1995**, *60*, 5456.
12. Dean, F. M.; Orabi, M. O. A. *J. Chem. Soc., Perkin Trans. 1*, **1982**, 2617.
13. Matsumoto, M.; Kuroda, K.; Suzuki, Y. *Tetrahedron. Lett*. **1982**, *22*, 3253.
14. Kasturi, T. R.; Rajasekhar, B.; Raju, G. J.; Reddy, G. M.; Sivaramakrishnan, R.; Ramasubbu,Venkatesan, K. *J. Chem. Soc. Perkin Trans. I***1984**, 2375.
15. (a) Arumugam, S.; Popik, V. V. *J. Am. Chem. Soc*. **2011**, *133*, 15730. (b) Arumugam, S.; Popik, V. V. *J. Am. Chem. Soc*. **2011**, *133*, 5573.
16. Kostikov, A. P. Popik, V. V. *J. Org. Chem*. **2007**, *72*, 9190.
17. Uchida, M.; Irie, M. *Chem. Lett.* **1992**, *21*, 2257.
18. (a) Ettlinger, M. G. *J. Am. Chem. Soc*. **1950**, *72*, 3666. (b) Leary, G. *J. Chem. Soc*. **1971**, 2248.
19. Modica, E.; Zanaletti, R.; Freccero, M.; Mella, M. *J. Org. Chem*. **2001**, *66*, 41.
20. Nakatani, K.; Higashida, N.; Saito, I. *Tetrahedron Lett*. **1997**, *38*, 5005.

21. Matsumoto, J.; Ishizu, M.; Kawano, R-I.; Hesaka, D.; Shiragami, T.; Hayashi, Y.; Yamashita, T.; Yasuda, M. *Tetrahedron* **2005**, *61*, 5735.
22. De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367 and references therein.
23. Gharpure, S. J.; Sathiyanarayanan, A. M.; Jonnalagadda, P. *Tetrahedron Lett*. **2008**, *49*, 2974.
24. Radomkit, S.; Sarnpitak, P.; Tummatorn, J.; Batsomboon, P.; Ruchirawat, S.; Ploypradith, P. *Tetrahedron* **2011**, *67*, 3904.
25. (a) Inoue, T.; Inoue. S.; Sato, T. *Chem. Lett*. **1990**, 55. (b) Inoue, T.; Inoue. S.; Sato, T. *Bull. Chem. Soc. Jpn*. **1990**, *63*, 1647.
26. Shaikh, A.; Cobb, A. J. A.; Varvounis, G. *Org. Lett*. **2012**, *14*, 584.
27. Osyanin, V. A.; Osipov, D. V.; Klimochkin, Y. N. J. *Org. Chem*. **2013**, *78*, 5505.
28. Lumb, J-P.; Trauner, *Org. Lett*. **2005***7*, 5865.
29. Woo, C. M.; Lu, L.; Gholap, S. L.; Smith, D. R.; Herzon, S. B. *J. Am. Chem. Soc*. **2010**, *132*, 2540.
30. Verboom, W.; Bos, H. J. T. *Tetrahedron Lett*. **1978**, *19*, 1229.
31. Sullivan, W. W.; Ullman, D.; Shechter, H. *Tetrahedron Lett*. **1969**, *10*, 457.
32. Strandtmann, von M.; Cohen, M.P.; Shavel Jr. J. *Tetrahedron Lett*. **1965**, *6*, 3103.
33. Katritzky, A. R.; Lan, X.; Lam, J. N. *Chem. Ber*. **1991**, *124*, 1809.
34. Breuer, E.; Melumad, D. *Tetrahedron Lett*. **1968**, *10*, 1875.
35. Chauhan, M. S.; Mckinnon, D. M. *Can. J. Chem*. **1981**, *59*, 2223.
36. Huang, P-J. J.; Cameron, T. S.; Jha, A. *Tetrahedron Lett*. **2009**, *50*, 51.
37. Sawama, Y.; Shishido, Y.; Yanase, T.; Kawamoto, K.; Goto, R.; Monguchi, Y.; Kita, Y.; Sajiki, H. *Angew. Chem. Int. Ed*. **2013**, *52*, 1515.
38. Chao, H. S. I. *Synth. Commun*. **1988**, *18*, 1207.
39. Angle, S. R.; Yang, W. *J. Am. Chem. Soc*. **1990**, *112*, 4524. Angle, S. R.; Yang, W. *Tetrahedron Lett*. **1992**, *33*, 6089.
40. (a) Bilgic, O.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1*, **1980**, 1233. (b) Asherson, J. L.; Bilgic, O.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 3041.
41. Pernak, J.; Kmiecik, R.; Weglewski, *J. Synth. Commun*. **2000**, *30*, 1535.
42. Bauer, K.; Garbe, D.; Surburg, H. Common Fragrance and Flavor Materials, 3rd ed.; WILEY-VCH: 1997; 76.
43. Fuhrmann, F.; Talbiersky, *J. Org. Process Res. Dev*. **2005**, *9*, 206.
44. (a) Buckingham, J. Dictionary of Natural Products, University: Cambridge, MA, 1994; (b) T. F. Woiwode, C. Rose and T. J. Wandless, *J. Org. Chem*.**1998**, *63*, 9594.

45. (a) Ambade, A. V.; Kumar, A. *Prog. Polym. Sci*. **2000**, *25*, 1141. (b) Beldi, M.; Medimagh, R.; Chatti, S.; Marque, S.; Prim, D.; Loupy, A.; Delolme, F. *Eur. Polym. J.* **2007**, *43*, 3415.
46. Pattabiraman, T. N.; Lawson, W. B. *Biochem. Biophys. Acta* **1972**, *258*, 548.
47. North, P. C.; Ladlow, M. WO 95/29173, 1995.
48. Adams, J. L.; Garigipati, R. S.; Sorenson, M.; Schmidt, S. J.; Brian, W. R.; Newton, J. F.; Tyrrell, K. A.; Garver, E.; Yodis, L. A.; Chabot-Fletcher, M.; Tzimas, M.; Webb, E. F.; Breton, J. J.; Griswold, D. E. *J. Med. Chem*. **1996**, *39*, 5035.
49. (a) Qiao, Y. F.; Takeya, K.; Itokawa, H.; Iitaka, Y. *Chem. Pharm. Bull*. **1990**, *38*, 2896. (b) Lumb, J.-P.; Choong, K. C.; Trauner, D. *J. Am. Chem. Soc*. **2008**, *130*, 9230. (c) Elsohly, M. A.; Slatkin, D. J.; Knapp, J. E.; Doorenbos, N. J.; Quimby, M. W.; Schiff, P. L.; Gopalakrishna, E. M.; Watson, W. H. *Tetrahedron* **1977**, *33*, 1711.
50. Yamaye, M.; Okano, H.; Motoyanagi, Y.; Cho, N.; Yoshinaga, N.; Tsuru, T.; Mukae, K. *Synthesis* **2004**, 0341.
51. Keshipour, S.; Shaabani. A.; Pedarpour, M.; Sarvary, A. *Res Chem Intermed*. **2014**, *40*. 149.
52. Qina, L.; Wang, p.; Zhang, Y.; Ren, Z.; Zhang, X.; Da, C-S. *Synlett* **2016**, *27*, 571.
53. Mohrle, H.; Miller, C. *Arch. Pharm*. **1983**, *316*, 229.
54. Arrault, A.; Touzeau, F.; Guillaumet, G.; Merour, J.-Y. *Synthesis* **1999**, 1241.
55. Satoh, T.; Tsuda, T.; Kushino, Y.; Miura, M.; Nomura, M. *J. Org. Chem*. **1996**, *61*, 6476.
56. Gao, Q.; Wu, x.; Liu, S.; Wu, A. *Org. Lett*. **2014**, *16*, 1732.
57. Huang, Z.; Jin, L.; Feng, y.; Peng, P.; Yi, H.; Lei, A. *Angew. Chem. Int. Ed*. **2013**, *52*, 7151.
58. Jarava-Barrera, C.; Esteban, A.; Navarro-Ranninger,C.; Parra, A.; Aleman, J. *Chem. Commun*. **2013**, *49*, 2001.
59. Albrecht, L.; Ransborg, L. K.; Lauridsen, V.; Overgaard, M.; Jorgensen, K. A. *Angew. Chem., Int. Ed*. **2011**, *50*, 12496.
60. Deng, T.; Wang, H.; Cai, C. *Eur. J. Org. Chem*. **2015**, 1569.
61. Salami-Ranjbaran, E.; Khosropour, A. R.; Mohammadpoor-Baltork, I.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V. *ACS Comb. Sci*. **2015**, *17*, 452.
62. (a) Huo, C.; Xu, X.; An, J.; Jia, X.; Wang, X.; Wang, C. *J. Org. Chem*. **2012**, *77*, 8310. (b)Huo, C.; An, J.; Chang, W.; Jia, X.; Kang, L.; Wu, M. *Tetrahedron* **2013**, *69*, 6375.
63. Huo, C.; An, J.; Xu, X.; Jia, X.; Wang, X.; Wang, C. *Tetrahedron Lett*. **2013**, *54*, 1145.

64. Cadona, L.; Croce, P. D. *Synthesis* **1976**, 800.
65. (a) Mondal, E.; Bose, G.; Khan, A. T.*Synlett.* **2001**, 785. (b) Mondal, E.; Bose, G.; Sahu, P. R.; Khan, A. T. *Chem. Lett*. **2001**, 1158.
66. (a) Barua, P. M. B.; Sahu, P. R.; Mondal, E.; Bose, G.; Khan, A. T. *Synlett.* 2002, 81. (b) Mondal, E.; Barua, P. M. B.; Bose, G.; Khan, A. T. *Chem. Lett*. **2002**, 210.
67. Choudhury, L. H.; Parvin, T.; Khan, A. T. *Tetrahedron* **2009**, *65*, 9513.
68. (a) Gazi, S.; Ananthakrishnan, R. *RSC Adv*. **2012**, *2*, 7781. (b) Yadav, D. K.; Patel, R.; Srivastava, V. P.; Watal, G.; Yadav, L. D. S. *Tetrahedron Lett*. **2010**, *51*, 5701. (c) Jiang, B.; Dou, Y.; Xu, X.; Xu, M. *Org. Lett*. **2008**, *10*, 593.
69. Khan, A. T.; Ali, S.; Dar, A. A.; Lal, M. *Tetrahedron Lett*. **2011**, *52*, 5157.

Schematic Overview of the Thesis



List of Publications:

1. Hydrated Ferric Sulfate Catalyzed Synthesis of 5,6-Unsubstituted 1,4-Dihydropyridines
   Using Three-Component Reaction
   Islam, K.; Das, D. K. Khan, A. T.*Tetrahedron Lett*. **2014**, *55*, 5613.

2. Exploration of C5-C6-Unsubstituted 1,4-Dihydropyridines for the construction of exo-Hexahydro-1H-chromeno[3,4-h][1,6]naphthyridine-3-carboxylates using Stereoselective Povarov Reaction
   Islam, K.; Das, D. K.; Akram, E.; Khan, A.T. *Synthesis*, **2015**, *47*, 2745.

3. Metal free synthesis of substituted pyridine *via* Bromodimethylsulfonium Bromide (BDMS) catalyzed multicomponent reaction
   Islam, K.; Basha, R. S.; Khan, A.T (*Under communication*).

4. A direct approach for the expedient synthesis of unsymmetrical ethers by employing bromodimethylsulfonium bromide (BDMS) mediated C-S bond cleavage of naphthalene-2-ol sulfides
   Islam, K.; Basha, R. S.; Dar, A. A. Das, D. K.; Khan, A.T. *RSC Adv*. **2015**, *5*, 79759.

5. An efficient one-pot C-S bond cleavage induced modular diastereo selective synthesis of 2-acyl-1,2-dihydronaphtho[2,1-b]furans
   Islam, K.; Basha, R. S.; Khan, A.T. (*Under communication*).

6. A simple and expedient synthesis of functionalized pyrido[2,3-c] coumarin derivatives using molecular iodine catalyzed three-component reaction
   Khan, A. T.; Das, D. K.; Islam, K.; Das, P. *Tetrahedron Lett*. **2012**, *53*, 6418.