Application of Branching Double Annulation Cascade (BDAC) and Ring Opening Cyclization (ROC) Strategies: Access to Diverse fused Tetrahydroisoquinoline, Quinazolinone derivatives and Rutaecarpine Alkaloid

SRILAXMI M.

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CHAPTER III: Copper-Catalyzed Intramolecular *α*-C–H Amination *via* Ring-Opening Cyclization Strategy to Quinazolin-4-ones: Development and Application in Rutaecarpine Synthesis

Declaration

I declare that this written submission represents my ideas in my own words, and where others' ideas or words have been included, I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that any violation of the above will be a cause for disciplinary action by the Institute and can also evoke penal action from the sources that have thus not been properly cited, or from whom proper permission has not been taken when needed.

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This thesis entitled "**Branching Double Annulation Cascade and Ring Opening Cyclization Strategies: An Iminium Induced Synthesis of Diverse Fused Tetrahydroisoquinoline (THIQ) and Quinazolinone Derivatives Application in Rutaecarpine**" by Srilaxmi M. is approved for the degree of Doctor of Philosophy from IIT Hyderabad.

Prof. Manas K. Ghorai (IIT-Kanpur)
Examiner

Prof. Akkattu T. Biju (IISc -Bangalore)
Examiner

Dr. D. S. Sharada
Associate Professor
Adviser

-Name and affiliation-
Co-Adviser

-Dr. Rajakumara Erappa (Assoc. Professor)
Chairman

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Srilaxmi M

Dedicated to

Grand Parents

Abstract

Application of Branching Double Annulation Cascade (BDAC) and Ring Opening Cyclization (ROC) Strategies: Access to Diverse fused Tetrahydroisoquinoline, Quinazolinone derivatives and Rutaecarpine Alkaloid

Nitrogen-containing compounds are the most common structural architectures in drug candidates, natural and biological products, and small-molecule therapeutics. *N*-heterocyclic containing natural product synthesis has been a very challenging area due to the structural complexity inherent in these molecules. The nitrogen atoms contained in these molecules are essential for their biological activity, as nitrogen can hold a positive charge as well as act as both hydrogen-bond donor and hydrogen-bond acceptor. These features are significant for the interaction between medicinal agents and their molecular targets. Although synthetic chemists have long been fascinated by natural products, for the most part they have focused on developing the chemistry in order to make precise replicates of the compounds purified from natural sources. Recently, synthetic targets concerning natural products have not been limited to precise replication of the naturally occurring compounds.

The accumulation of insights and learning in total synthesis over the last few decades should enable organic chemists to "aim higher" to integrate natural products more closely with advance in biomedical research. Today, chemists can develop synthetic strategies to make both natural products and natural product-like compounds that are comparable to true natural products in size and complexity. The ability to synthesize in vitro complex natural products, combined with strategy of diversity-oriented synthesis (DOS) of natural product-like molecules, which allows very large numbers of natural product-based compound libraries to be made quickly, has made it possible for chemists to accelerate evolution in vitro in this process. Herein, we report a novel BDAC strategy for rapid access to diverse molecular library containing unprecedented THIQ fused skeletons by using 2-(2-bromoethyl)benzaldehyde **19** as a common substrate and variety of *N,C*-, *N,O*- and *N,N*-1,5-bisnucleophiles as SBAs. Apart from that we also successfully developed a facile methodology for Copper-catalyzed intramolecular α-C–H amination *via* ring-opening cyclization strategy to quinazolin-4-one derivatives and application in Rutaecarpine synthesis.

PROPOSED CONTENTS OF THE THESIS:

Chapter I: Introduction

Chapter II: Scaffold diversity through a branching double annulation cascade strategy: An iminium induced one-pot synthesis of diverse fused tetrahydroisoquinoline (THIQ) scaffolds.

Chapter III: Copper-catalyzed intramolecular α-C–H amination *via* ring-opening cyclization strategy to quinazolin-4-ones: development and application in Rutaecarpine synthesis.

Chapter I: Introduction

Nitrogen-containing compounds are the most common structural architectures in drug candidates, natural and biological products, and small-molecule therapeutics. *N*-heterocyclic containing natural product synthesis has been a very challenging area due to the structural complexity inherent in these molecules. The nitrogen atoms contained in these molecules are essential for their biological activity, as nitrogen can hold a positive charge as well as act as both hydrogen-bond donor and hydrogen-bond acceptor. These features are significant for the interaction between medicinal agents and their molecular targets. Although synthetic chemists have long been fascinated by natural products, for the most part they have focused on developing the chemistry in order to make precise replicates of the compounds purified from natural sources. Recently, synthetic targets concerning natural products have not been limited to precise replication of the naturally occurring compounds. The accumulation of insights and learning in total synthesis over the last few decades should enable organic chemists to "aim higher" to integrate natural products more closely with advance in biomedical research. Today, chemists can develop synthetic strategies to make both natural products and natural product-like compounds that are comparable to true natural products in size and complexity. The ability to synthesize in vitro complex natural products, combined with strategy of diversity-oriented synthesis (DOS) of natural product-like molecules, which allows very large numbers of natural product-based compound libraries to be made quickly, has made it possible for chemists to accelerate evolution in vitro in this process.

Among six-membered benzoheterocycles, quinazolines and quinazolinones represent a ubiquitous class of compounds displaying a broad range of biological activities. The importance of quinazolines as medicinal agents has consequently inspired the development of various synthetic methods toward this class of compounds. Many conventional synthetic methods for the construction of quinazoline-based pre-activated substrates or multistep transformations have been reported. Transition metal-catalyzed transformations now serve as powerful tools for synthesizing these useful compounds. On the other hand, an increasing demand for clean, fast, efficient, and selective processes, has prompted utilization of readily available, less toxic, and inexpensive metal catalysts.

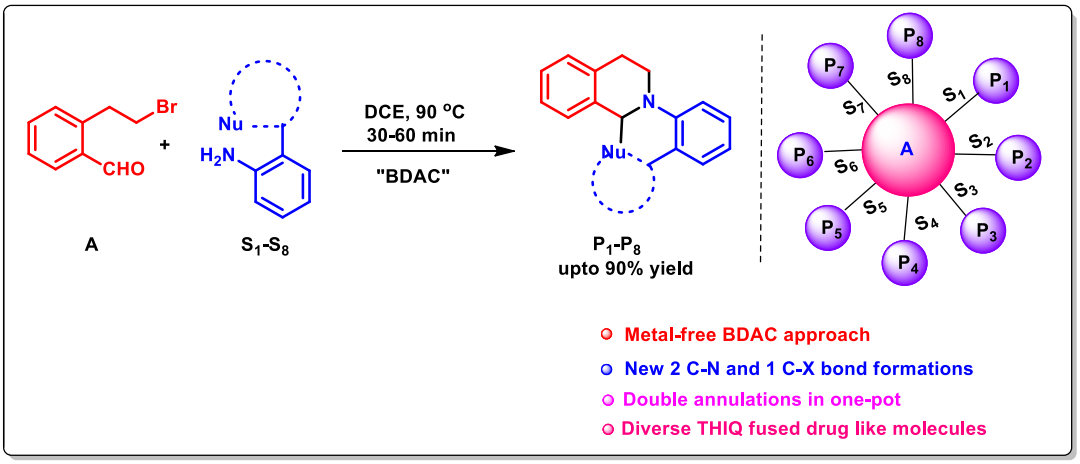
Over the past decade, substantial research interest has been focused on developing selective C-hetero bond formation reactions through Cu-catalyzed cross-dehydrogenative coupling. In most of the cases, a tertiary amine has been used as one of the partners where a C-H bond next to the heteroatom has been activated. Despite the significant advances made in this greener side of the cross coupling chemistry, application of this strategy in intramolecular C-heteroatom bond formation to synthesize pharmaceutically important and synthetically challenging heterocycles is far less studied. In this context, we planned to study cross-dehydrogenative C-N bond formation involving an amide and aniline under an O_2 atmosphere with a Cu catalyst. Formation of an iminiun ion from amide, which is essential to implement such a strategy, is challenging due to delocalization of the nitrogen lone pair to the carbonyl oxygen.

Quinazolin-4-(3*H*)-one compounds constitute the key core units of many synthetic drugs and natural products, such as luotonin A has cytotoxicity toward human cancer lines, while bouchardatine occurs in the natural product Bouchardatia neurococca. Traditionally, quinazolin-4(3*H*)-ones are prepared by the oxidative condensation of o-aminobenzamide with aldehydes or carboxylic acid derivatives under acidic or basic conditions.

Herein, we disclose a copper (I) catalyzed synthesis of quinazolin-4(3*H*)-ones from isatoicanhydride opened by benzylamine followed by C-H functionalization C-N bond forming process that uses oxygen as the oxidant and KO^{t}Bu as base and generates

CO_2 and O_2 are the direct waste products. During the course of these reactions, an iminium intermediate formed, which is subsequently trapped by an amine nucleophile.

Chapter II: Scaffold diversity through a branching double annulation cascade strategy: An iminium induced one-pot synthesis of diverse fused tetrahydroisoquinoline (THIQ) scaffolds.



In the chapter I1, we have described the synthesis of diverse fused tetrahydroisoquinoline (THIQ) scaffolds through a branching double annulation cascade strategy. A branching double annulation cascade (BDAC) strategy for diverse and complex fused THIQ scaffolds via a highly reactive iminium induced one-pot double cyclization sequence involving Pictet-Spengler type cyclization has been developed for the first time. The salient features of this protocol are direct and rapid access to unprecedented diverse fused THIQ skeletons, metal/catalyst free, cleaner reaction profile, good to excellent yields and convenient approach. This catalyst-free domino process facilitates the double annulation with variety of scaffold building agents via two C-N and one C-X (X = C, N, O) bonds formation in a single step, under uniform reaction conditions. Furthermore, we reveal an unusual dual BDAC sequence leading to N-N linked isoquinoline dimer.

The pursuit of identification of new small molecule modulators for chemical genetics and drug discovery has led to synthesis of natural product based compounds, combinatorial synthesis of libraries[1] and cascade strategies.[2] Awestruck by the nature's ability to create structurally and functionally diverse pre-validated natural product libraries from a limited pool of simple building blocks and the demand for compound libraries with structural complexity and stereo genic centers[3] has led synthetic organic chemist to explore chemical space paradigm by taking the leads from natural products, which is highly challenging.[4] To meet this challenge, diversity oriented synthesis (DOS)

has emerged as an important tool which entails efficient synthesis of skeletally, stereo chemically and functionally diverse libraries. DOS by employing folding/branching pathways, build/couple/pair (B/C/P) strategies, and structural variations in common substrates/building blocks and branching cascade approaches have successfully demonstrated in creating diverse molecular scaffolds, which serve as biological probes and potential leads for drug discovery.

In connection with our broader interests in developing synthetic strategies for diverse and complex polyheterocycles involving cascade annulations in a one-pot manner, herein, we are pleased to disclose a cascade sequence involving a highly reactive iminium intermediate and further Pictet-Spengler type cyclization for accessing three dimensional privileged THIQ compounds as branching double annulation cascade (BDAC).

Numerous strategies have been reported for the synthesis of THIQ such as Strecker lactamization/alkylations, allylation-lactamization cascade, Mukaiyama-Mannich lactamization/ alkylations, 1,3-dipolar cycloaddition reaction of azomethine imine and Grignard as well as allyltrimethoxysilane addition to imine. Latest approaches to substituted THIQ involve metal catalyzed *ortho* C-H allylation/cyclization (Scheme 1b), cross-dehydrogenative coupling (CDC) reactions and redox-neutral reactions. Recently, we have developed cascade strategies for the synthesis of THIQ in one-pot fashion. However, many of the previous reported approaches to construct complex THIQ derivatives often have limited skeletal diversity and require several steps, and hence there lies a need to develop efficient strategies for THIQ compounds. To address this challenge, we envisioned that the concept of branching cascade could be utilized, involving the reaction of a common substrate with different scaffold-building agents (SBAs). To the best of our knowledge the branching cascade pathway has not yet been reported for the synthesis of diverse and complex THIQ molecules. With this in mind, we have identified 2-(2-bromoethyl)benzaldehyde **19a** as a common substrate to generate highly reactive and versatile iminium intermediate for further diversification with wide range of SBAs **35**. THIQ with a stereo genic center at the C1 position occupy an important place among natural and unnatural compounds possessing valuable biological activities and are precursors for synthesis of complex alkaloids.

Herein, we report a novel BDAC strategy for rapid access to diverse molecular library containing unprecedented THIQ fused skeletons by using 2-(2-bromoethyl)benzaldehyde **19a** as a common substrate and variety of *N*,*C*-, *N*,*O*- and *N*,*N*-1,5-bisnucleophiles as SBAs. The synthesized molecules contain multiple privileged structures such as tetrahydroisoquinoline (coralydine **I** and (+) cripsin A **II**), benzothiadiazinedioxide (IDRA-21 **III**), imidazoquinoxaline (PPQ-102 **IV**), quinazolinone (rutaecapine **V**), pyrroloquinoxaline (**VI**) and tetrazolo[1,5-*c*]quinoxaline (**VII**), which form part of natural products and biological important molecules (Figure 1).

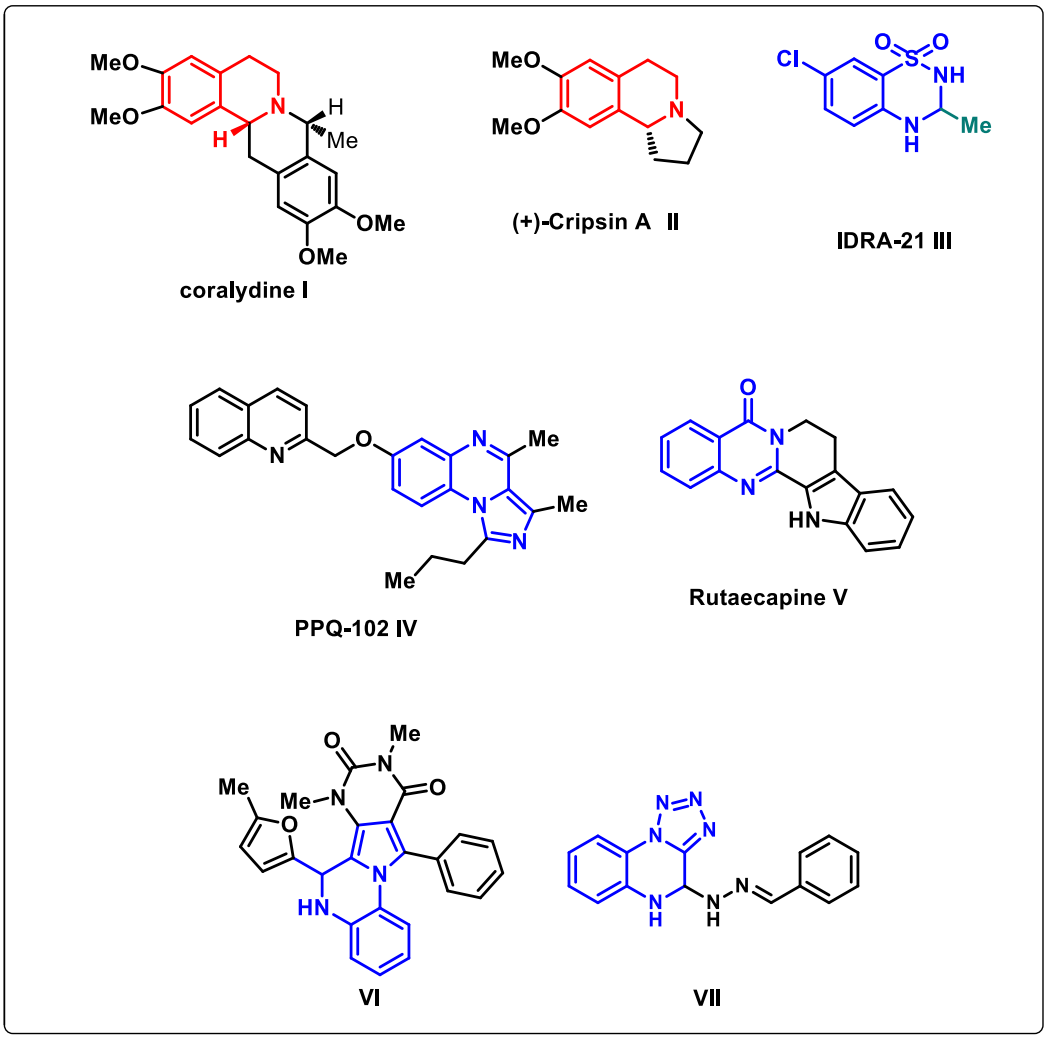
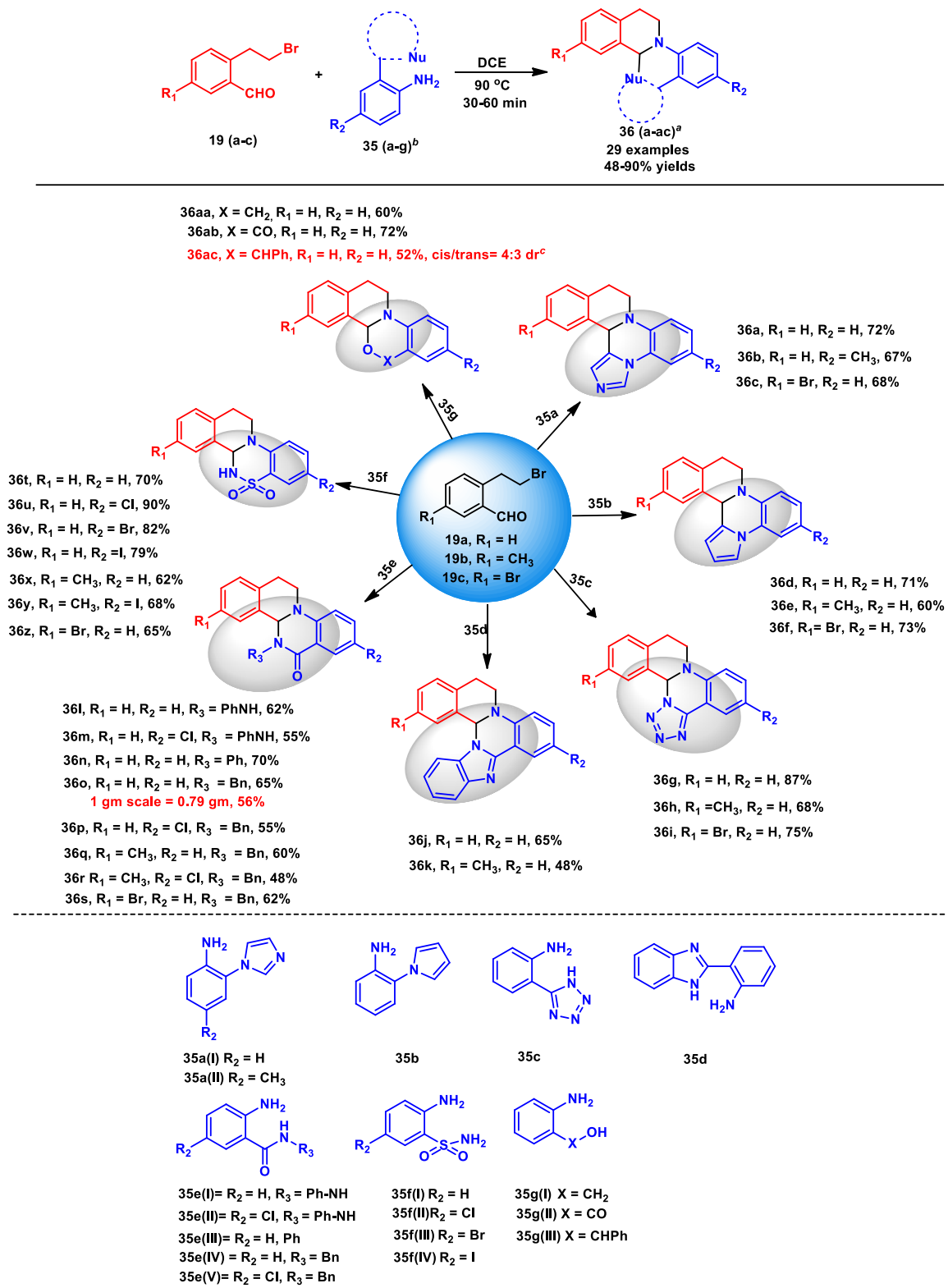


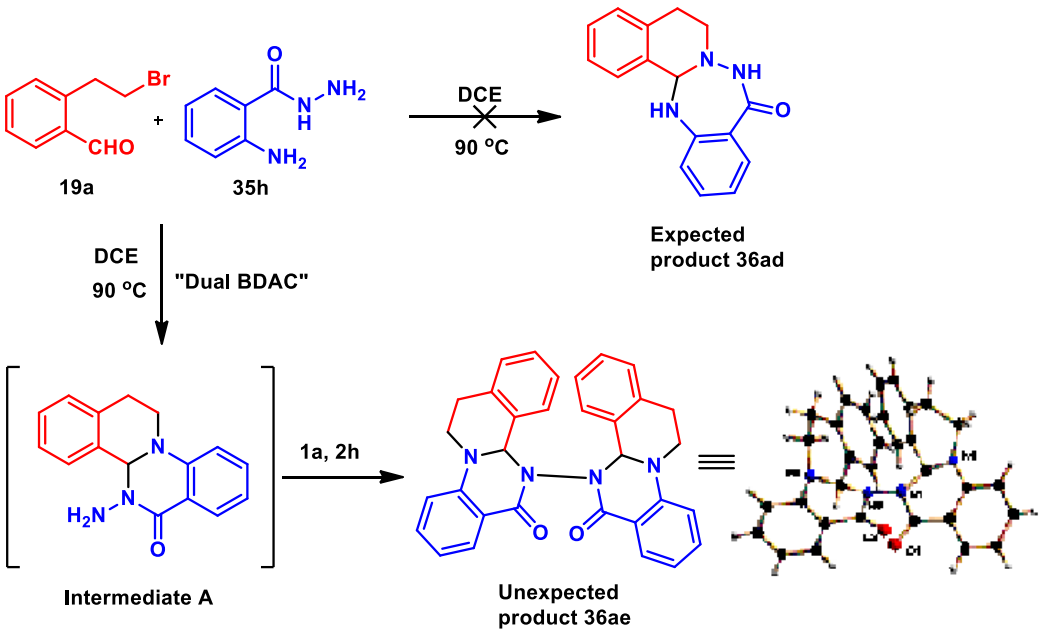
Figure 1. Naturally occurring THIQ alkaloids and representative examples of bioactive molecules containing our privileged motifs.

Figure 2. Synthesis of various diverse fused tetrahydroisoquinoline compounds 3a-3ac through branching double annulation cascade (BDAC) strategy.

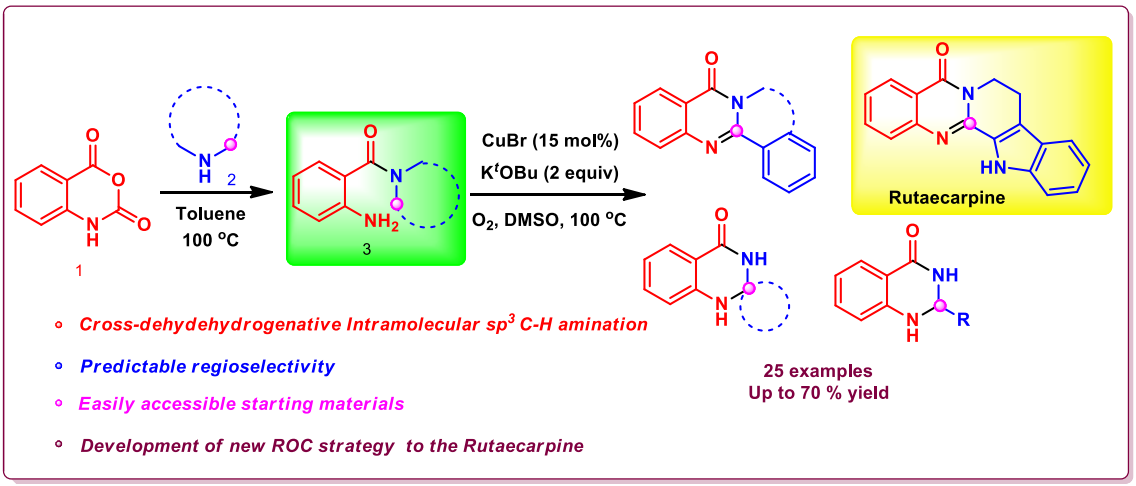


[a] Reactions were performed in DCE (1mL) with **19** (0.23 mmol), **35** (0.23 mmol) at 90 °C for 30-60 min. [b] **35a**-**35g** represent various *N,C*-, *N,O*- and *N,N*-1,5-bisnucleophiles as SBAs. [c] dr was determined by ^{1}H NMR spectroscopy.

Scheme 2. Scope of BDAC strategy with 2-aminobenzohydrazide (2h).



Chapter III : Copper-catalyzed intramolecular α-C–H amination *via* ring-opening cyclization strategy to quinazolin-4-ones: development and application in Rutaecarpine synthesis.



In this chapter III, a copper-catalysed intramolecular α-C–H amination has been developed for the synthesis of quinazolin-4(3H)-one derivatives from commercially available isatoic anhydride besides primary and secondary benzyl amines via Ring-Opening Cyclization (ROC) Strategy. This method shows good functional group tolerance and allow access to a range of 2-aryl, 2-alkyl and spiroquinazolinone

derivatives. However 2-methyl quinazolin-4(3H)-one synthesized from 2-amino-N-isopropylbenzamide by C–C bond cleavage and N-benzyl-2-(methylamino)benzamide afforded 1-methyl-2-phenylquinazolin-4(1H)-one along with 2-aryl quinazolin-4(3H)-one derivatives by N–C bond cleavage for aromatization. It is the first general method to construct the potentially useful 2-methyl quinazolin-4(3H)-one by copper-catalyzed intramolecular C–H amination. And also this ROC strategy has been successfully applied to the synthesis of quinazolinone alkaloid Rutaecarpine.

Quinazolinone is an important *N*–heterocyclic scaffold, as of their abundance in biologically active compounds and numerous natural products such as rutaecarpine, tryptanthrin, luotonin A, B, E and F and bio active compounds (Figure 1). Owing to the promising biological & medicinal activities including anticancer, anti-inflammatory, antibacterial, antihypertensive properties, synthetically quinazolinone scaffolds have been highly in demand and remains a challenge in organic synthesis. The direct functionalization of C–H bonds of organic compounds has recently emerged as a diverse atom economic carbon–heteroatom (C–X) and carbon–carbon (C–C) bond formation. Several diverse C–H functionalization methodologies without prefunctionalization of the coupling partners have been widely developed in the past decades. Previously, we have employed N-incorporation strategy for the synthesis of quinoxalines *via* dual C(sp^2)-H functionalization and also, in recent past reported on the direct cycloaminative approach to imidazole derivatives *via* dual C–H functionalization.

Over the past three decades, considerable progress has been made in the development of methods to construct sp^2 carbon–nitrogen (C–N) bonds using palladium, copper or nickel catalysis. However, formation of sp^3 C–N bonds remains one of the major challenges in the field of cross-coupling chemistry. Recently, much attention has been focused towards the development of transition-metal catalyzed intramolecular C–H amination strategies to assemble *N*–Heterocyclic compounds. In most of the cases, a tertiary amine has been used as one of the partner whereas α-C–H bond has been activated. In 2010, Maiti. D reported cross-dehydrogenative sp^3 C–O bond formation an iminium ion from amide to construct dihydro-oxazinone derivatives, and also recently he reported copper-catalysed C(sp^3-H functionalization/cyclisation of 2-amino-*N*,*N*-dialkylbezamides for the synthesis of 2,3-disubstituted-4(3*H*)-quinazolinone

derivatives.[13b] Application of this strategy in intramolecular C–heteroatom bond formation to synthesize challenging hetero cycles and pharmaceutically important compounds is less studied. Newly established methodology leading to the natural products are high demand for modern organic synthesis.

In this context, we are pleased to report intramolecular cross-dehydrogenative coupling C–N bond formation under aerobic conditions for the synthesis of quinazolin-4(3*H*)-ones from isatoic anhydride and amines (benzylic & aliphatic) with copper (I) catalyst *via* ring opening cyclisation (ROC) strategy (Scheme 1). During this process an iminium ion intermediate formation, which is subsequently trapped by an amine nucleophile.

Rutaecarpine, as a kind of natural quinazolinecarboline alkaloids isolated from fruits of evodia rutaecarpa, a plant used for treatment of headache, cholera, dysentery in Chinese medicine. Due to the medicinal importance of this alkaloid, various synthetic routes have been developed. Recently Jieping Zhu et al. synthesized rutaecarpine and (±)-evodiamine by a silver salt-catalyzed insertion of the isocyano group into the N-H bond of the tryptamine followed by in situ lactamization. Herein, we described the shorter route to rutaecarpine from isatoicanhydride and tryptoline *via* ROC strategy.

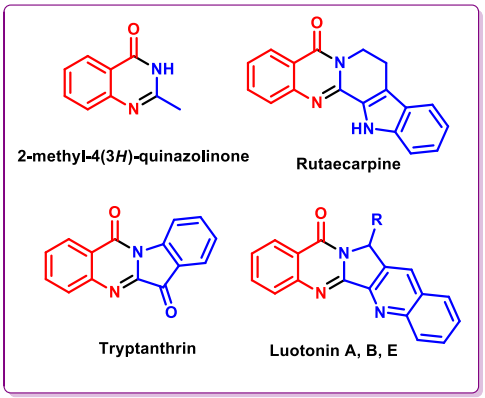
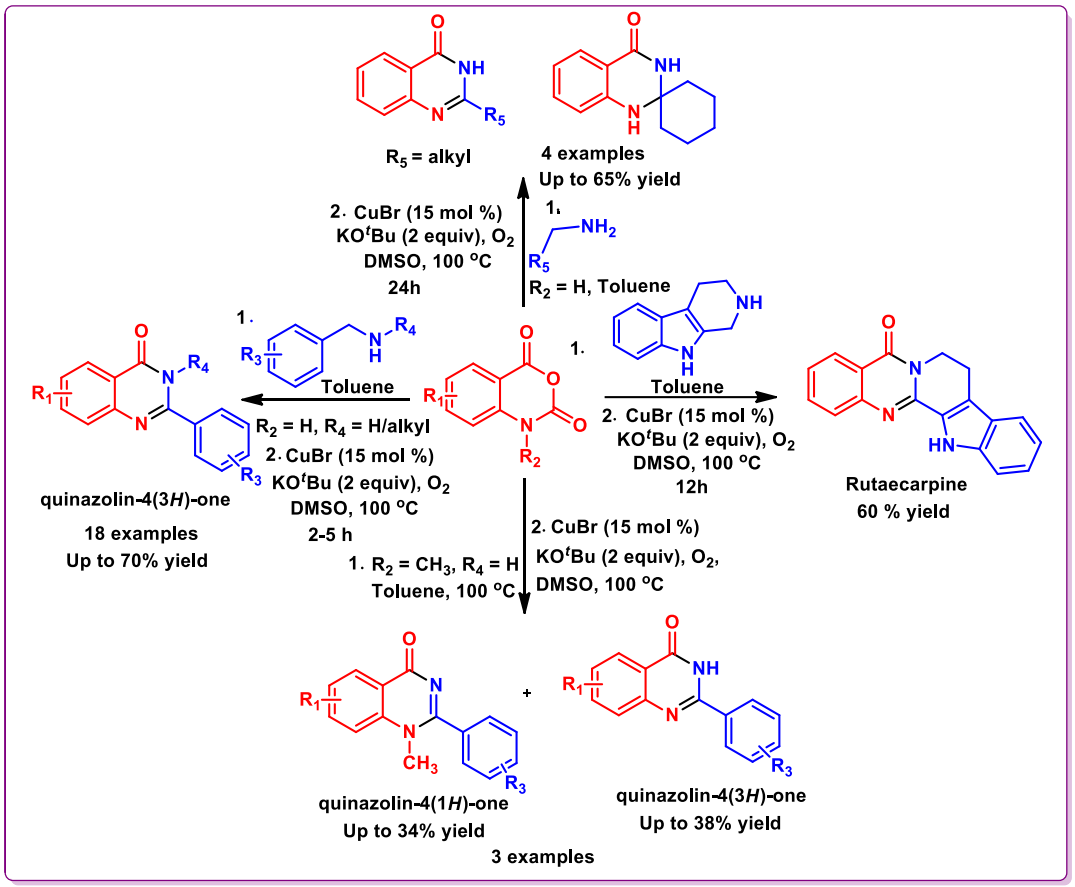
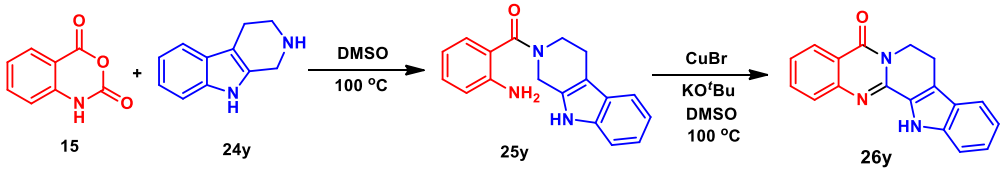


Figure 1. Quinazolinone skeleton containing natural products.

Scheme 1. Our present strategy for the synthesis of quinazolinone derivatives.



Scheme 3. Synthesis of Rutaecarpine



Nomenclature

1,10-phen	1,10-Phenanthroline
Å	Angstrom
Ac	Acetyl
AcOH	Acetic acid
Ar	Aryl
BDAC	Branching double annulation cascade
Boc	*tert*-Butyloxycarbonyl
Bpy	2,2’-Bipyridine
br	Broad (spectral)
℃	Degree Celsius
CDC	Cross-Dehydrogenative Coupling
CPD	Carbon proton decoupling
Cy	Cyclohexyl
d	Doublet (spectral)
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethene
DCM	Dichloromethane
dd	Doublet of doublet
ddd	Doublet of doublet of doublet
DMA	Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dt	Doublet of triplet
DTBP	Di-*tert*-butyl peroxide
equiv.	Equivalent(s)
Et	Ethyl
EtOH	Ethanol

EWG	Electron withdrawing group
FTIR	Fourier transform infrared spectroscopy
GC-MS	Gas chromatography–mass spectrometry
h	Hour(s)
HR-MS	High Resolution Mass Spectroscopy
Hz	Hertz
i-Pr	Isopropyl
J	Coupling Constant (in NMR Spectroscopy)
K	Kelvin (Temperature)
m	Multiplet (spectral)
*m*CPBA	*meta*-Chloroperoxybenzoic acid
MCRs	Multicomponent reactions
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mg	Milligram
MHz	Mega Hertz
min	Minute(s)
MIR-ATR	Mid infrared- Attenuated Total Reflectance
mL	milliliter(s)
mmol	Millimole(s)
Mp	Melting point
MS	Molecular sieves
NR	No reaction
n-Bu	*n*-Butyl
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
o	*Ortho*
ORTEP	Oak ridge thermal ellipsoid plot
OTf	Triflate group
P	*Para*
Ph	Phenyl
PivOH	Pivalic acid

ppm	Parts per million
psi	Pounds per square inch
q	Quartet (spectral)
R	Alkyl
Rf	Retention factor
rt	Room temperature
s	Singlet (spectral)
SF	Solvent-free
SSMR	Solid-state melt reaction
t	Triplet (spectral)
TBHP	*tert*-Butyl hydroperoxide
TBPB	*tert*-Butyl peroxybenzoate
^{t}Bu	*tert*-Butyl
Temp	Temperature
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
tert	tertiary
TFA	*Trifluoroacetic acid*
TFAA	Trifluoroacetic anhydride
THF	Tetrahyrofuran
THIQ	Tetrahydroisoquinoline
TLC	Thin layer chromatography
TMEDA	N, N, N′, N′-*Tetramethylethylenediamine*
TMS	Trimethylsilyl
XRD	X-ray *diffraction*
δ	Chemical shift in parts per million

CHAPTER I

Introduction

I. 1 Application of Heterocyclic compounds:

Heterocyclic compounds, both naturally produced and synthetically derived, often display important biological activity. In fact, more than 67% of the compounds listed in the Comprehensive Medicinal Chemistry (CMC) database contain heterocyclic rings. Synthesis of complex heterocyclic compounds is very challenging and attractive area in the field of organic chemistry.[1]

In heterocyclic derivatives Nitrogen-containing compounds are the most common structural architectures in drug candidates, natural and biological products, and small-molecule therapeutics.[2] N-heterocyclic containing natural product synthesis has been a very interesting area due to the structural complexity inherent in these molecules. The nitrogen atoms contained in these molecules are essential for their biological activity, as nitrogen can hold a positive charge as well as act as both hydrogen-bond donor and hydrogen-bond acceptor.[3] These features are significant for the interaction between medicinal agents and their molecular targets.

Natural products have proven to be cherished sources for the identification of new drug candidates, and also as tools for medicinal chemistry research and chemical biology. In fact, if we have a tendency to trace back human history, several natural product have conjointly long been wont to treat numerous human disorders and distinguished by their drug-like properties.[4] To date, thousands of bioactive compounds have been isolated from plants, microbes, marine invertebrates, and other sources. Consequently, these chemical structures are used by chemists as references to scan the range house for drug discovery efforts.[5] In the marketplace

launched drugs are either natural products themselves or natural product-derived molecules.[6]

I. 2. Diversity Oriented Synthesis:

Historically, natural product synthesis has been a very challenging area due to the structural complexity inherent in these molecules. Although synthetic chemists have long been fascinated by natural products, for the most part they have focused on developing the chemistry in order to make precise replicates of the compounds purified from natural sources. Recently, synthetic targets concerning natural products have not been limited to precise replication of the naturally occurring compounds.[7] The accumulation of insights and learning in total synthesis over the last few decades should enable organic chemists to "aim higher" to integrate natural products more closely with advance in biomedical research. Today, chemists can develop synthetic strategies to make both natural products and natural product-like compounds that are comparable to true natural products in size and complexity.[8] The ability to synthesize in vitro complex natural products, combined with strategy of diversity-oriented synthesis (DOS) of natural product-like molecules, which allows very large numbers of natural product-based compound libraries to be made quickly, has made it possible for chemists to accelerate evolution in vitro in this process.[9]

DOS is aimed at the efficient synthesis of an assembly of structurally complex and diverse molecules, which are screened for their ability to modulate a biological pathway in cells or organisms, while not relation to any specific super molecule target.[10] In other words, DOS is a means to identify simultaneously therapeutic protein targets and small molecules that can modulate the functions of these therapeutic targets.[11]

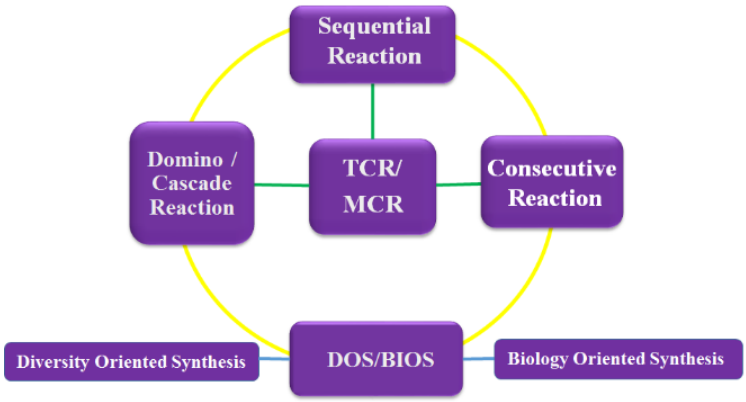


Figure 1. General reaction pathways in Organic synthesis.

As a strategy, DOS is based on forward-synthetic analysis to guide its library synthesis. DOS allows many structurally complex and diverse compounds to be prepared efficiently in a flexible and modular way for biological assays.[12] Because compounds generated from DOS by altering stereochemistry and skeletal arrays would display diverse chemical information in three-dimensional space, screening of such compounds would likely generate more hits poised for optimization. Screening of these would generate more hits. It should be noted that DOS as a synthetic strategy was not originated specifically for natural product synthesis.[13] Yet it goes without saying that the DOS approach can be used to generate analogs of natural products and thus enrich the life science discovery.[14] Therefore, DOS can obviously maximize the value of natural products in biomedical research by addressing unfavourable features of natural products.[15] For instance, natural products tend to modulate biological targets that have general functions, but do not seem to modulate more specialized targets and processes. This challenge can perhaps be tackled by means of DOS.[16]

I. 3. Importance of Tetrahydroisoquinoline:

Tetrahydroisoquinoline (THIQ) is one of the most useful starting materials for the synthesis of heterocyclic scaffolds and bioactive compounds. The literature reveals several attempts for the synthesis of THIQs *via* iminium formation and further addition of various nucleophiles. The routes include 1,3-dipolar cycloaddition of azomethine imines, Grignard as well as allyltrimethoxysilane addition to imine, asymmetric reduction of imines, Mukaiyama-Mannich lactamization/ alkylations,

allylation-lactamization cascade and various multistep processes. Therefore, the application of iminium intermediate in other new type of reactions such as cycloadditions, atom insertions will make an important approach to this research field and is highly desirable.

On the other hand, hybrid molecules embedded with different privileged scaffolds have long been attracted significantly due to their capability to enhance or modulate the biological properties of individual components.[16] Isoquinolines, especially, 1,2,3,4-tetrahydroisoquinolines [17] (THIQs I, II Figure 1).

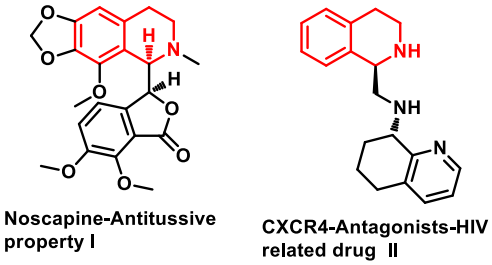


Figure 2. Drug molecules with THIQ privileged structures.

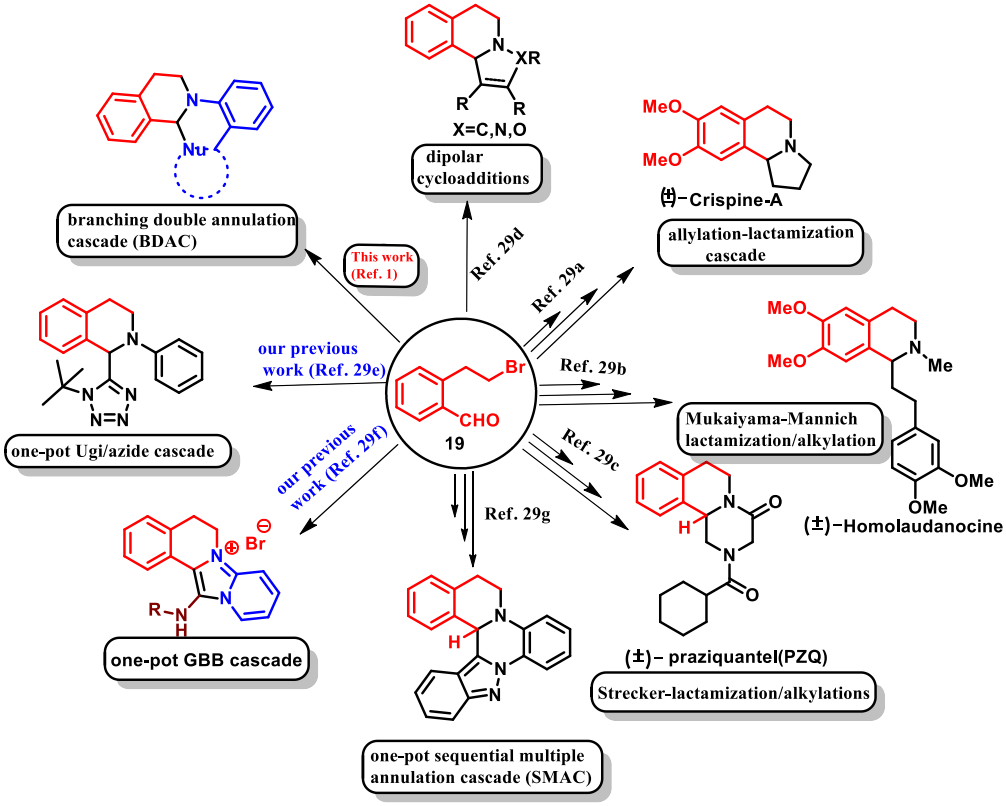
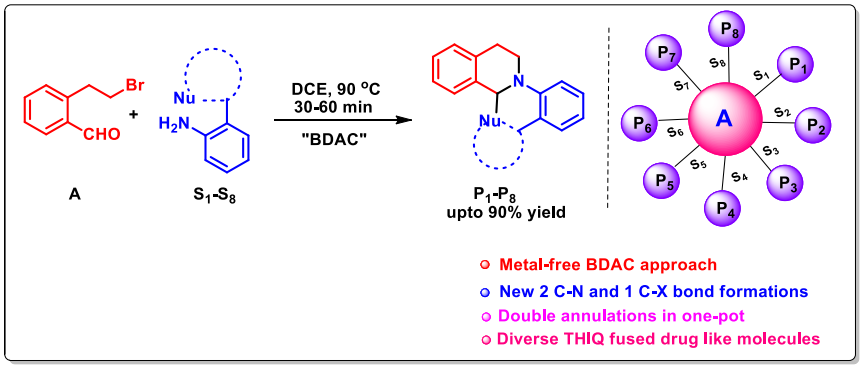


Figure 3. Various approaches to THIQ motifs starting from 2-(2-bomoethyl)benzaldehyde

In the recent times, a “branching cascade” has been proposed as a new technique of “Diversity Oriented synthesis” for the systematic exploration of chemical space.[17] Recently, we introduced the Branching Double Annulation Cascade (BDAC) as a new technique for accessing a series of multifunctional polyheterocyclic scaffolds in an efficient manner.

As part of our ongoing interest in cascade cyclization,[18] we assumed that a common type of starting material (X) would react with several bisnucleophiles (scaffold building agents, SBAs). Unlike our previous report, a major concern was that X would react with the electron rich SBAs leading to the formation of electrophile incorporated SBAs which may further react with X creating a mixture of products. The products formed have propensity to react again with electrophiles and therefore the overall process can be considered as complicated as it would be difficult to obtain any of the products in good yields. The challenge, therefore, was to search for a suitable starting material (X) and appropriate reaction conditions which should only give the desired product.



At the outset of this study, our efforts were directed towards design and synthesis of different *N*,*C*-, *N*,*O*-, and *N*,*N*-1,5-bisnucleophiles With this pool of compounds in hand, a series of annulation reactions were envisaged in order to achieve skeletal diversity. Overall, it was found that the *N*,*N*-bisnucleophiles afforded excellent yields compared to *N*,*C* and *N*,*O*-bisnucleophiles, and 2-aminobenzenesulfonamides (**2f**) though being weak nucleophile comparatively were the best among all 1,5-bisnucleophiles in terms of the reactivity and yield.

I. 4. Importance of Quinazolinones:

Among six-membered benzoheterocycles,[19] quinazolines[20] and quinazolinones[21] represent a ubiquitous class of compounds displaying a broad range of biological activities. The importance of quinazolines as medicinal agents has consequently inspired the development of various synthetic methods toward this class of compounds. Many conventional synthetic methods for the construction of quinazoline-based pre-activated substrates or multistep transformations have been reported. Transition metal-catalyzed transformations now serve as powerful tools for synthesizing these useful compounds. On the other hand, an increasing demand for clean, fast, efficient, and selective processes, has prompted utilization of readily available, less toxic, and inexpensive metal catalysts.

Over the past decade, substantial research interest has been focused on developing selective C-hetero bond formation reactions through Cu-catalyzed cross-dehydrogenative coupling.[22] In most of the cases, a tertiary amine has been used as one of the partners where a C-H bond next to the heteroatom has been activated.[23] Despite the significant advances made in this greener side of the cross coupling chemistry, application of this strategy in intramolecular C-heteroatom bond formation to synthesize pharmaceutically important and synthetically challenging heterocycles is far less studied.[24] In this context, we planned to study cross-dehydrogenative C-N bond formation under an O_2 atmosphere with a Cu catalyst. Formation of an iminiun ion from amide, which is essential to implement such a strategy, is challenging due to delocalization of the nitrogen lone pair to the carbonyl oxygen.

Quinazolin-4-(3*H*)-one compounds constitute the key core units of many synthetic drugs and natural products, represent a ubiquitous class of compounds displaying a broad range of biological activities.[25] The importance of quinazolinones as medicinal agents has consequently inspired the development of various synthetic methods toward this class of compounds. Traditionally, quinazolin-4(3*H*)-ones are prepared by the oxidative condensation of o-aminobenzamide with aldehydes or

carboxylic acid derivatives under acidic or basic conditions.[26] Many conventional synthetic methods for the construction of quinazolinone based substrates have been reported. Transition metal-catalyzed transformations now serve as powerful tools for synthesizing these useful compounds. On the other hand, an increasing demand for clean, fast, efficient, and selective processes, has prompted utilization of readily available, less toxic, and inexpensive metal catalysts.

I. 5. C-H Functionalization:

Herein, we disclose a copper (I) catalyzed synthesis of quinazolin-4(3*H*)-ones from isatoicanhydride opened by benzylamine followed by C-H functionalization C-N bond forming process that uses oxygen as the oxidant and KO^{t}Bu as base and generates CO_2 and O_2 are the direct waste products. During the course of these reactions, an iminium intermediate formed, which is subsequently trapped by an amine nucleophile. Recently, the use of Cu-catalyzed C-H functionalization reactions has gained significant traction, and a range of these methodologies relating to the construction of heterocycles have been successfully developed.[27]

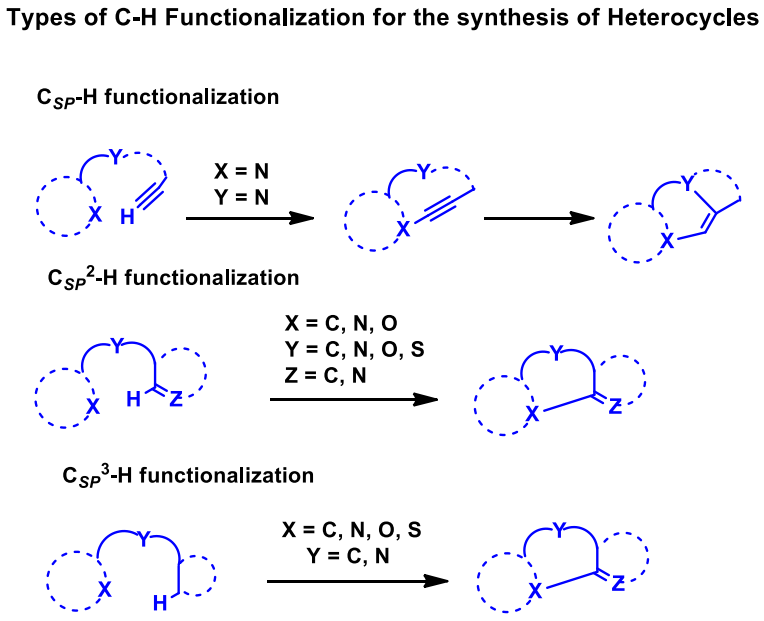


Figure 4. Intramolecular C-H functionalization.

The current work is encompassed toward organic transformations involving iminium ion intermediate by controlling the reactivity toward distal C−H functionalization. However, the prevalent intramolecular C−H amination techniques

for synthesis of quinazolinones are centered on proximal C−H bond functionalization. Intramolecular oxidative C(sp^3)−H amination is one of the most followed synthetic protocols toward *N*-heterocycle quinazolinone synthesis.[28]

It is pleasant to mention that we also successfully developed a copper catalysed intramolecular α-C–H amination for the synthesis of quinazolin-4(3H)-one derivatives from commercially available isatoic anhydride besides primary and secondary benzyl amines via Ring-Opening Cyclization (ROC) Strategy. This method, show good functional group tolerance and allow access to a range of 2-aryl, 2-alkyl and spiro quinazolinone derivatives and also 2-methyl and 2-aryl quinazolin-4(1*H*)-one derivatives by C–C and N–C bond cleavage in the progress of ROC strategy. It is the first general method to construct the potentially useful 2-methyl quinazolin-4(3H)-one by copper-catalyzed intramolecular C–H amination. And also this ROC strategy has been successfully applied to the synthesis of quinazolinone alkaloid rutaecarpine.

I. 6. REFERENCES:

1) Volla, C. M.; Atodiresei, I.; Rueping, M. *Chem. Rev.* 2013, *114*, 2390-2431.
2) Yang, Z.; Jin, X., Guaciaro, M.; Molino, B. F.; Mocek, U., Reategui, R.; Morley, T., *Org. Lett.*, 2011, *13*, 5436.
3) Lahm, G.; Deichmann, J. G.; Rauen, A. L.; Opatz, T. *J. Org. Chem.*, 2015, *80*, 2010.
4) Sawant, G.; Ghosh, S.; Banesh, S.; Bhaumik, J.; Banerjee, U. C.; *RSC Advances*, 2016, *6*, 49150.
5) Li, X., Wang, H., Lu, Z.; Zheng, X., Ni, W.; Zhu, J., Zhang, H. *J. Med. Chem.*, 2016, *59*, 8326.
6) Cahlíková, L.; Macáková, K.; Benešová, N.; Chlebek, J.; Hošťálková, A.: Opletal, L. *Elsevier*, 2014, *42*, 153.
7) Shaw, J. T.; *Nat. Prod. Rep.*, 2009, *26*, 11-26.

8) Abrams, D. J.; Provencher, P. A.; Sorensen, E. J. *Chem. Soc. Rev.* 2018, *47*, 8925-8967.

9) Yang, X. J.; Miao, F.; Yao, Y.; Cao, F. J.; Yang, R.,;Ma, Y. N.; Zhou, L. *Molecules*, 2012, *17*, 13026.

10) Kumar, A.; Srivastava, S.; Gupta, G., Chaturvedi, V.; Sinha, S.; Srivastava, R. *ACS Comb. Sci.*, 2010, *13*, 65.

11) Lenci, E.; Menchi, G.; Guarna, A.; Trabocchi, A. *J. Org. Chem.*, 2015, 80, 2182-2191.

12) Jiang, B.; Hao, W. J.; Wang, X., Shi, F.; Tu, S. J. *J. Comb. Chem*, 2009, *11*, 846-850.

13) Gigant, N.; Claveau, E.; Bouyssou, P.; Gillaizeau, I. *Org. Lett.*, 2012, *14*, 844-847.

14) Kim, J.; Kim, H.; Park, S. B. *J. Am. Chem. Soc.*, 2012, *136*, 14629-14638.

15) Devi, N.; Rawal, R. K.; Singh, V. *Tetrahedron*, 2015, *2*, 183-232.

16) Shang, S.; Tan, D. S. *Curr. Opin. Chem. Biol.*, 2005, *9*, 248-258.

17) Patil, N. T.; Shinde, V. S.; Sridhar, B. *Angew Chem. Int. Ed.*, 2013, *52*, 2251-2255.

18) (a) Shinde, A. H.; Arepally, S.; Baravkar, M. D.; Sharada, D. S. *J. Org. Chem.*, 2016, *82*, 331-342. (b) Shinde, A. H.; Vidyacharan, S.; Sharada, D. S. *Org. Biomol. Chem.*, 2016, *14*, 3207-3211.

19) Chen, L.; Li, C.; Bi, X.; Liu, H.; Qiao, R. *Adv. Synth. Catal.*, 2012, 354, 1773.

20) Zhang, J.; Yu, C.; Wang, S.; Wan, C.; Wang, Z. *Chem. Commun.* 2010, *46*, 5244.

21) Chen, D.; Chen, Q.; Liu, M.; Dai, S.; Huang, L.; Yang, J.; Bao, W. *Tetrahedron* 2013, 69, 6461.

22) (a) Li, X.; He, L.; Chen, H.; Wu, W.; Jiang, H. *J. Org. Chem.* 2013, 78, 3636. (b) Sherman, E. S.; Chemler, S. R. *Adv. Synth. Catal.*, 2009, 351, 467.

23) (a) Xu, W.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. *Org. Lett.*, 2011, 13, 1274. (b) Wang, L.-X.; Xiang, J. F.; Tang, Y.-L. *Eur. J. Org. Chem.* 2014, *2014*, 2682.

24) (a)Kloss, F.; Neuwirth, T.; Haensch, V. G.; Hertweck, C. *Angew Chem. Int. Ed.*, 2018, *57*, 14476-14481.

25) (a)Peng, L. P.; Nagarajan, S.; Rasheed, S.; Zhou, C. H. *Med. Chem. Comm*, 2015, *6*, 222-229. (b) Asif, M. *Int. J. Med. Chem.*, 2014, *2014*, 2014.

26) He, L.; Li, H.; Chen, J.; Wu, X. F. *RSC Advances*, 2014, *4*, 12065-12077.

27) Guo, X. X.; Gu, D. W.; Wu, Z.; Zhang, W. *Chem. Rev.*, 2014, *115*, 1622-1651.

28) (a) Modak, A.; Dutta, U.; Kancherla, R.; Maity, S.; Bhadra, M.; Mobin, S. M.; Maiti, D. *Org. Lett.*, 2014, *16*, 2602. (b) Gholap, A. V.; Maity, S.; Schulzke, C.; Maiti, D.; Kapdi, A. R. *Org. Biomol. Chem.*, 2017, *15*, 7140.

29) (a) Dhanasekaran, S.; Bisai, V.; Unhale, R. A.**;** Suneja, A.; Singh, V.K. Org. Lett. **2014**, *16*, 6068; (b) Dhanasekaran, S.**;** Kayet, A.*;* Suneja, A.; Bisai, V.; Singh, V. K. Org. Lett. **2015**, *17*, 2780; (c) Dhanasekaran , S.; Suneja, A.; Bisai , V.; and Singh, V. K. *Org. Lett.* **2016**, *18* , 634; (d) Milosevic, S.; Togni, A. *J. Org. Chem.* **2013**, *78* , 9638; (e) Shinde, A. H.; Archith, N.; Malipatel, S.; Sharada, D. S. *Tetrahedron Lett.* **2014**, *55*, 6821; (f) Sagar, A.; Babu, V. N.; Shinde, A. H.; Sharada, D. S. *Org. Biomol. Chem*. **2016**, *14*, 10366. (g) Sagar, A.; Babu, V. N.; Shinde, A. H.; Sharada, D. S. *Org. Biomol. Chem*. **2016**, *14*, 10366. (h) Shinde, A. H.; Vidyacharan, S.; Sharada, D. S. *Org. Biomol. Chem.* **2016**, *14*, 3207.

CHAPTER II

Scaffold Diversity through a Branching Double Annulation Cascade Strategy: An Iminium Induced One-pot Synthesis of Diverse Fused Tetrahydroisoquinoline (THIQ) Scaffolds

II.1. INTRODUCTION:

The pursuit of identification of new small molecule modulators for chemical genetics and drug discovery has led to synthesis of natural product based compounds, combinatorial synthesis of libraries[1] and cascade strategies.[2] Awestruck by the nature's ability to create structurally and functionally diverse pre-validated natural product libraries from a limited pool of simple building blocks and the demand for compound libraries with structural complexity and stereo genic centers[3] has led synthetic organic chemist to explore chemical space paradigm by taking the leads from natural products, which is highly challenging.[4] To meet this challenge, diversity oriented synthesis (DOS)[5] has emerged as an important tool which entails efficient synthesis of skeletally, stereo chemically and functionally diverse libraries.[6] DOS by employing folding[7]/branching pathways,[8] build/couple/pair (B/C/P) strategies,[9] structural variations in common substrates/building blocks[10] and branching cascade approaches[11] have successfully demonstrated in creating diverse molecular scaffolds, which serve as biological probes and potential leads for drug discovery.

In connection with our broader interests in developing synthetic strategies for diverse and complex polyheterocycles involving cascade annulations[12] in a one-pot manner, herein, we are pleased to disclose a cascade sequence involving a highly reactive iminium intermediate and further Pictet-Spengler[13] type cyclization for accessing three dimensional privileged THIQ compounds as branching double annulation cascade (BDAC).

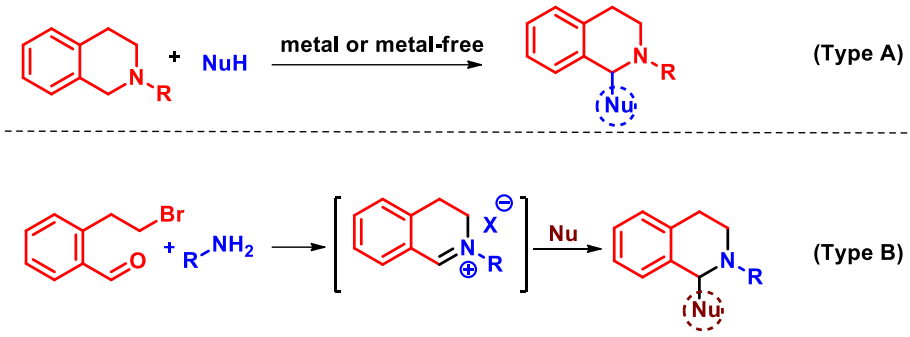
Numerous strategies have been reported for the synthesis of THIQ such as Strecker lactamization/alkylations,[14] allylation-lactamization cascade, Mukaiyama-Mannich lactamization/ alkylations, 1,3-dipolar cycloaddition reaction of azomethine imine[15] and Grignard[16] as well as allyltrimethoxysilane[17] addition to imine as shown in Scheme 1a. Latest approaches to substituted THIQ involve metal catalyzed ortho C-H allylation/cyclization (Scheme 1b),[18] cross-dehydrogenative coupling(CDC) reactions (Scheme 1c),[19] and redox-neutral reactions.[20] Recently, we have developed cascade strategies for the synthesis of THIQ in one-pot fashion.[12c,d] However, many of the previous reported approaches to construct complex THIQ derivatives often have limited skeletal diversity and require several steps, and hence there lies a need to develop efficient strategies for THIQ compounds. To address this challenge, we envisioned that the concept of branching cascade could be utilized, involving the reaction of a common substrate with different scaffold-building agents (SBAs) and Scheme 1d illustrates the general concept of substrate-based approach to scaffold diversity, which we have utilized in the present strategy. To the best of our knowledge the branching cascade pathway has not yet been reported for the synthesis of diverse and complex THIQ molecules. With this in mind, we have identified 2-(2-bromoethyl)benzaldehyde **19a** as a common substrate to generate highly reactive and versatile iminium intermediate for further diversification with wide range of SBAs **35** (Scheme 1e). THIQ with a stereo genic center at the C1 position occupy an important place among natural and unnatural compounds possessing valuable biological activities[21] and are precursors for synthesis of complex alkaloids.

II. 2. BACKGROUND:

Owing to the importance of the tetrahydroisoquinolines (THIQs) and functionalized 2*H*-indazole skeletons several reactions have been reported for the synthesis of functionalized THIQ and indazoles.

Various approaches for the synthesis of functionalized THIQs mainly fall into two general strategies *via* inter- or intramolecular nucleophilic addition to either

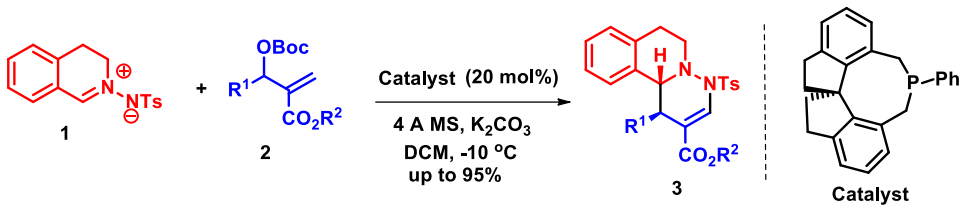
preformed precursor containing THIQ (Type A, Scheme 1)[22] or addition to *insitu* generated of isoquinolinium salts (Type B, **Scheme 1**).[23]



Scheme 1

II. 2. 1. Selective Methods for functionalized THIQ (Type A):

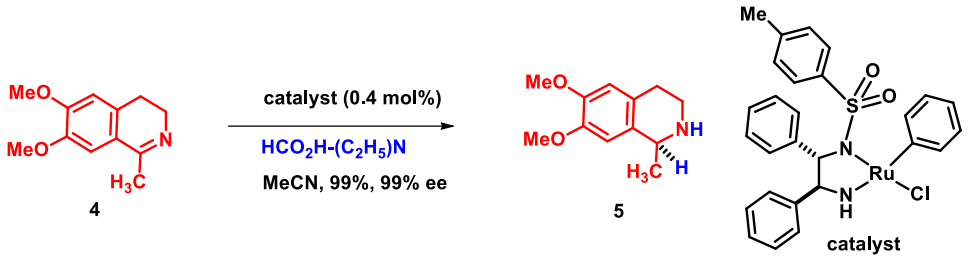
Among azomethine imine cycloaddition reaction several approaches have been developed which uses isoquinolium salts as 1,3-dipole for the cycloaddition with alkene giving rise to functionalized fused THIQs. For example, Guo and co-workers[24] have developed a [3+3] cycloaddition of Morita-Baylis- Hillman carbonates **2** with *C,N*-cyclic azomethine imines **1** for the synthesis of tetrahydropyridazinoisoquinoline derivatives **3** in good yields as shown in **Scheme 2.**



Scheme 2

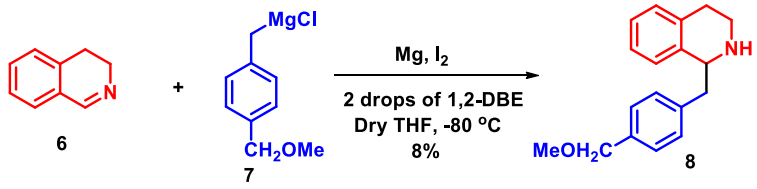
Similarly, several transformations involving reduction of isoquinolium imine, Grignard as well as trimethoxysilane addition to isoquinolium imine for the synthesis of functionalized THIQ have been reported. In 1996, Nayori *et al.*[25] have reported the asymmetric reduction of isoquinolium imine 4 using ruthenium catalyst

for the synthesis of aliphatic/aromatic substituted THIQs 5 in excellent yields and high enantioselectivities (**Scheme 3**).



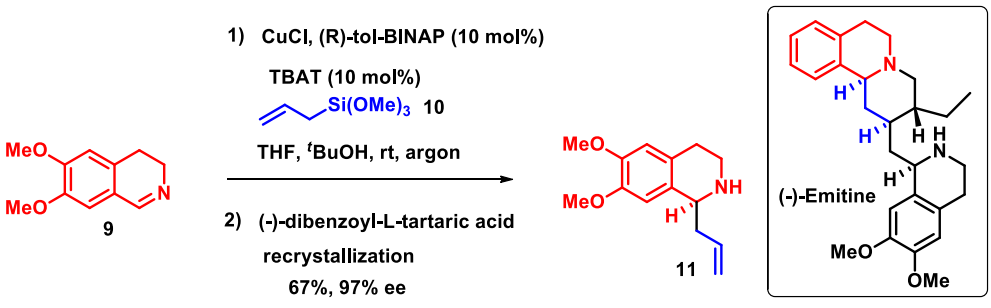
Scheme 3

In 2009, Al-Hiari *et al.*[26] have disclosed the Grignard addition to isoquinolium imine **6** using aryl magnesium halide **7** with the help of 1,2-dibromoethane for the synthesis of benzyl substituted THIQs **8** (**Scheme 4**).



Scheme 4

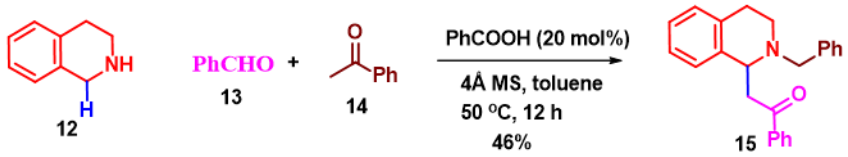
Further, Itoh e*t al.*[27] have introduced the allyltrimethoxysilane 10 addition to isoquinolium imine 9 under chiral copper catalysis for the synthesis of allyl substituted THIQs 11 and the allyl adduct thus formed was transformed to (-)-emetine in good yields (**Scheme 5**).



Scheme 5

In recent years, several approaches involving redox-neutral annulation reactions as well as cross-dehydrogenative coupling (CDC) have been developed for the

synthesis of functionalized THIQs. In 2014, Seidel *et al.*[28] have developed a complementary redox-Mannich reaction to the classic three component Mannich reaction which utilizes the same starting materials (THIQ **12**, aldehyde **13** and ketone **14**) but incorporates an isomerization step that enables the facile preparation of ring-substituted β-amino ketones **15** and occur under relatively mild conditions with the benzoic acid assistance (**Scheme 6**).



Scheme 6

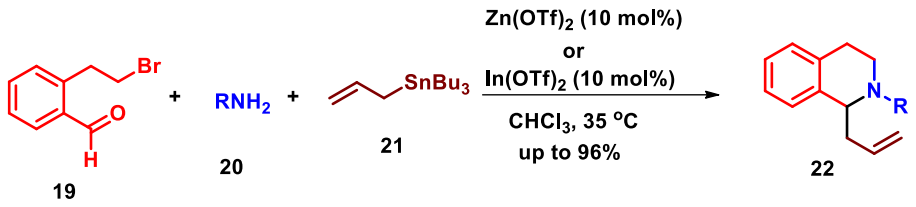
In 2014, Kobayashi *et al.*[29] have reported a copper/metal-free cross-dehydrogenative (CDC) reaction of tertiary amines **16** with nitrostyrene **17** for the synthesis of functionalized THIQ **18** using a catalytic amount of sulfuryl chloride (SO_2Cl_2) under mild aerobic conditions. On the basis of the nature of SO_2Cl_2, it was assumed that the reagent acts as a radical initiator to induce the metal-free CDC reaction *via* a radical-initiated autoxidation mechanism. (**Scheme 7**).

Scheme 7

II. 2. 2. Selective Methods for functionalized THIQ (Type B):

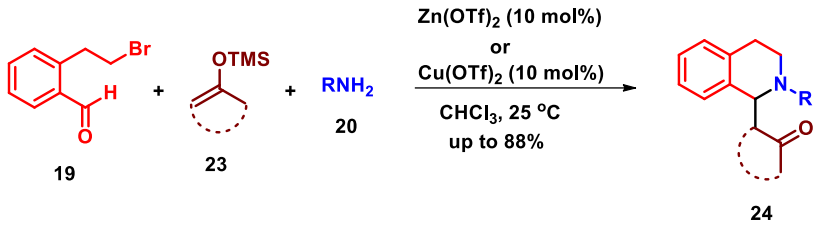
In 2014, Singh *et al.*[30a] have reported a general and highly efficient Lewis acid catalyzed one-pot allyation/ lactamization cascade for the synthesis of diversely substituted tetrahydroisoquinolines 22. The cascade effects one C-C and two C-N

bond-forming events in one-pot and the product thus obtained was successfully used for the total synthesis of (±)-crispine A (Scheme 8).



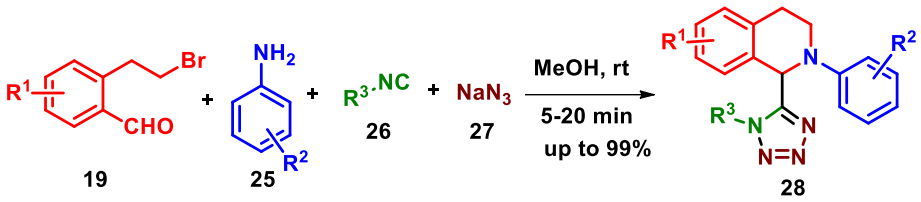
Scheme 8

Further the same group[30b] simultaneously reported the novel and efficient synthesis of a variety of tetrahydroisoquinolines *via* a Lewis acid catalyzed domino Mukaiyama-Mannich lactamization/alkylation strategy. The compounds aldehyde **19**, enolate **23** and amine **20** react in a cascade one-pot fashion under zinc or copper triflate catalyst to afford substituted THIQ framework **24**. This transformation comprises a sequential formation of three new bonds through a one-pot, three-component procedure to afford product in moderate to high yields. The product thus generated was successfully used for a concise synthesis of (±)-homolaudanosine. (Scheme 9).



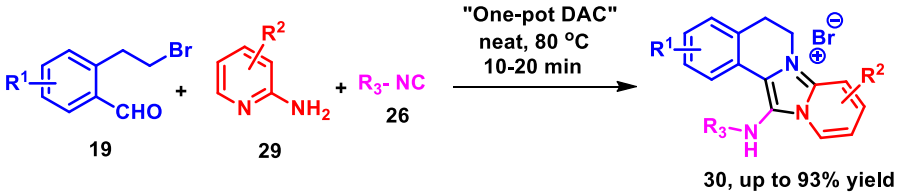
Scheme 9

In 2014 our group has[31] developed a one-pot cascade reaction of aldehyde **19**, aniline **25**, isocyanide **26** and sodium azide **27** for the synthesis of triazole substituted THIQ **28** skeleton using Ugi-azide four-component reaction (Scheme 10).

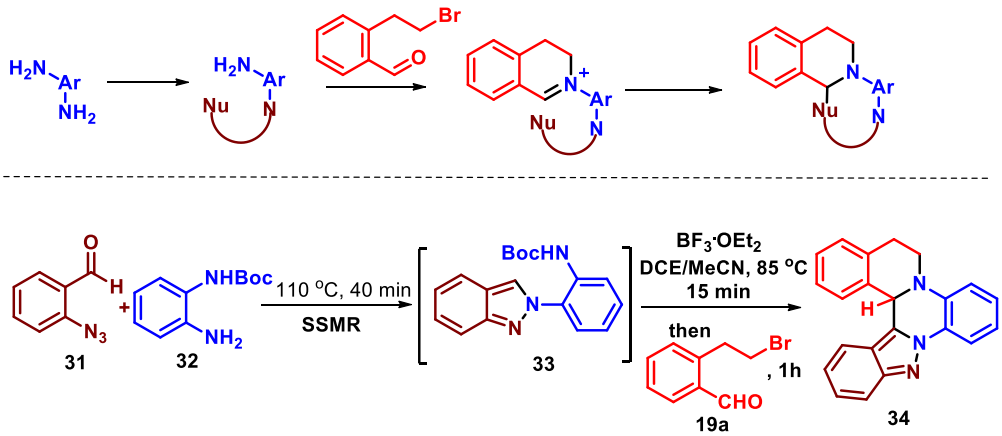


Scheme 10

Recently, we have developed a three-component cyclic iminium induced one-pot Groebke-Blackburn-Bienayme (GBB) double annulation cascade (DAC) for the synthesis of skeletally diverse DHIQ skeletons 30[32] (Scheme 11).



Scheme 11

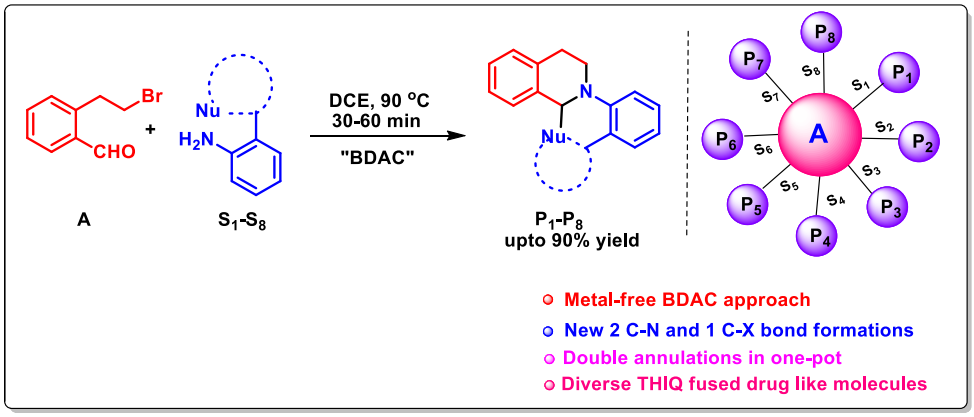


Scheme 12

Recently, we have also developed a one-pot sequential multiple annulation cascade (SMAC) strategy for the synthesis of 2*H*-indazole fused tetrahydroisoquinolinoquinoxalines and tetrahydroisoquinolinodiazepines *via* 2*H*-indazole formation and subsequent intramolecular cyclic iminium formation, and C3-functionalization of intermediate 2*H*-indazole (Scheme 13)[33].

The versatility of 2-(2-bromoethyl)benzaldehyde (**19a**) as a promising bifunctional reactant in various organic transformations has been well documented

by our group[31-33] and others,[30] especially leading to tetrahydroisoquinoline (THIQ) motifs based natural products and their analogues (Scheme 14).



Herein, we report a novel BDAC strategy for rapid access to diverse molecular library containing unprecedented THIQ fused skeletons by using 2-(2-bromoethyl)benzaldehyde 1a as a common substrate and variety of *N*,*C*-, *N*,*O*- and *N*,*N*-1,5-bisnucleophiles as SBAs. The synthesized molecules contain multiple privileged structures such as tetrahydroisoquinoline (coralydine I and (+) cripsin A II), imidazoquinoxaline (PPQ-102 III),[34] pyrroloquinoxaline (IV),[35] tetrazolo[1,5-c]quinoxaline (V),[36] quinazolinone (rutaecapine **VI**),[37] and benzothiadiazinedioxide (IDRA-21 **VII**),[38] which form part of natural products and biological important molecules (Figure 1).

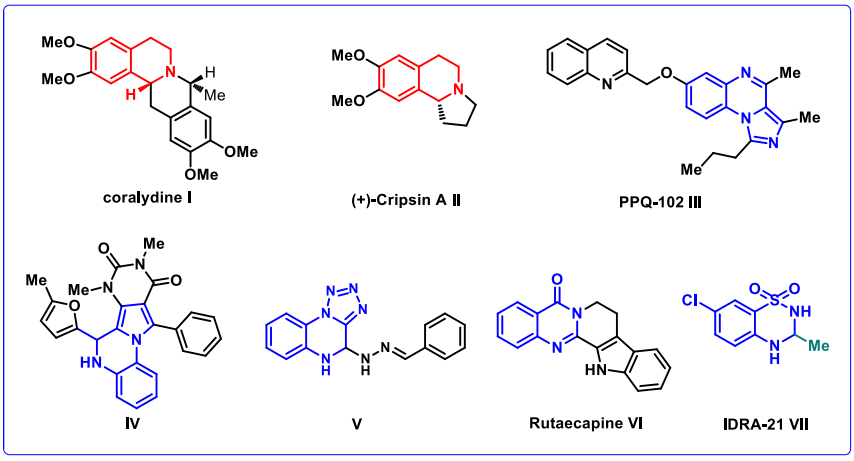


Figure 1. Naturally occurring THIQ alkaloids and representative examples of bioactive molecules containing our privileged motifs.

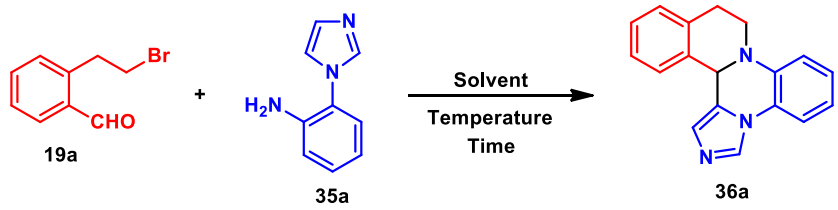
II. 3. Results and Discussion:

To this end, initially to check the feasibility of our branching cascade strategy we performed a model reaction of 2-(2-bromoethyl)benzaldehyde (**19a**) with 2-(2-aminophenyl)imidazole (**35a**) under polar protic solvents such as MeOH and EtOH at various temperatures (Table 1, entries 1-4), of which under reflux temperature in MeOH gave the desired product **36a** albeit in 47% yield (Table 1, entry 2). Inspired by this result, in order to increase the yield further, we screened the reaction under polar aprotic solvents such as acetonitrile and 1,4 dioxane, which afforded the moderate yields of the products (20-53%, Table 1, entries 5-7). We continued our attempts to optimize the yield by performing the reaction in chlorinated solvents (Table 1, entries 8-10) and to our delight, DCE at reflux temperature provided the desired product in good yield (Table 1, entry10). After having screened various solvents, we have chosen DCE as a solvent for further optimization studies. The increase in reaction temperature to 90 ^{o}C resulted in better yield of the product **36a** (75%) (Table 1, entry 11), however, further increase in temperature to 100 ^{o}C as well as the unconventional microwave heating could not improve the yield of the product further (Table 1, entries 12 and 13). Our attempts to use additives like DBU, PTSA and Et_3N have failed to improve the yield of the product (Table 1, entries 14-16). Similarly, employing dehydrating agents like 4Å molecular sieves and Na_2SO_4 did not aid in enhancing the yields (Table 1, entries 17 and 18).

At the outset of this study, our efforts were directed towards design and synthesis of different *N*,*C*-, *N*,*O*-, and *N*,*N*-1,5-bisnucleophiles (Figure 2). With this pool of compounds (**35a**-**35h**) in hand, a series of annulation reactions were envisaged in order to achieve skeletal diversity. With the standard reaction conditions in hand, we first subjected substituted imidazole based *N*,*C*-bisnucleophiles **35a**(I) and **35a**(II) leading to corresponding products **36b** and **36c** in 67% and 68% yields. In addition, we have also employed 2-(1*H*-pyrrol-1-yl)aniline (**35b**) in our cascade annulation resulting in pyrroloquinoxaline-THIQs (**36d**-**36f**) in good yields (71-73%). The fact that the more nucleophilic pyrrole substituted SBA

35b gave better yield than imidazole substituted SBA **35a** is in agreement with our proposed concept.

Table 1. Optimization conditions for the synthesis of fused Tetrahydroisoquinoline compound 3a through BDAC [a]



Entry	Solvent	Additive	Tempt °C	Time (min)	Yield (%)[b]
1	MeOH	-	rt	120	45
2	MeOH	-	reflux	60	47
3	EtOH	-	rt	120	40
4	EtOH	-	reflux	60	42
5	CH_3CN	-	rt	90	20
6	CH_3CN	-	reflux	60	53
7	1,4-Dioxane	-	reflux	60	45
8	DCM	-	rt	90	42
9	DCE	-	rt	90	56
10	DCE	-	reflux	60	66
11	**DCE**	-	**90**	**30**	**75**[c]
12	DCE	-	100	30	65
13	DCE	-	90	30	66[d]
14	DCE	DBU	90	60	0
15	DCE	PTSA	90	60	70
16	DCE	Et_3N	90	60	68
17	DCE	M.S.	90	60	70[e]
18	DCE	Na_2SO_4	90	60	69

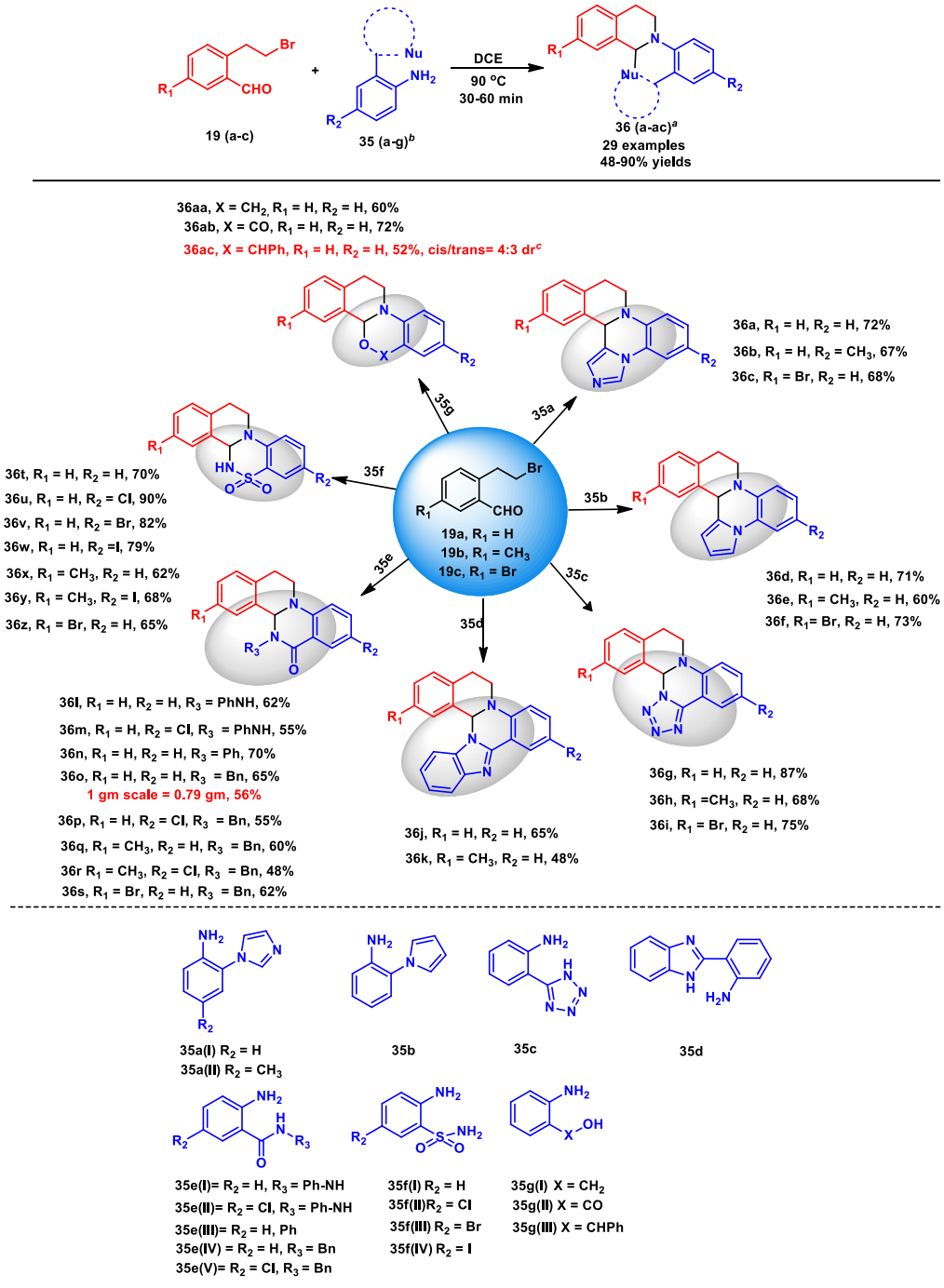
[a] Reaction conditions: **19a** (0.23 mmol), **35a** (0.23 mmol) and 1 mL of solvent; [b] Isolated yields after column chromatography; [c] No detrimental effect observed on reaction outcome by varying the concentration of reaction. [d] Unconventional microwave heating was used; [e] 4Å molecular sieves was used.

In our efforts to diversify the skeleton, we investigated azole based *N*,*N*-bisnucleophiles such as **35c** and **35d**, which resulted in the corresponding products tetrazoloquinozalino-THIQs (**36g-36i,** 75-87%) and benzimidazoquinazolino-THIQs (**36j** and **36k,** 48% and 65%). Tetrazole based SBA **35c** was the best nucleophile, which afforded the excellent yields of the corresponding products among all heterocyclic SBAs. With an aim to functionally diversify the skeleton and for comparative study, we evaluated the reactivity of the amide as *N*,*N*-bisnucleophile,

in our present strategy. To our surprise the reaction of variety of 2-aminobenzamides **35e** with **19a-19c** under standard conditions, afforded the corresponding products (**36l-36s**) in good to high yields (48-70%). It is to be noted that these products could be diversified further for various applications. The successful employment of 2-aminobenzamides **35e (I-V)**, prompted us to examine the 2-aminobenzenesulfonamides (**35f**) as a scaffold building agent for the synthesis of tetrahydrobenzothiadiazinoisoquinolino-6,6-dioxide which is a privileged scaffold present in several natural products of biological interest.[39] Accordingly, when we have reacted variety of 2-aminosulphonamides (**35f**) with **19a-19c**, afforded the products **36t-36z** in good to excellent yields (62-90%).

Encouraged by the results, we envisioned to explore the nucleophilicity of oxygen in our present strategy, by treatment of 2-aminobenzyl alcohol **35g(I)** and 2-aminobenzoic acid **35g(II)** with **19a**, which afforded **36aa** and **36ab** in 60 and 72% yields, respectively. Due to the ubiquity of THIQ based natural products containing C1 stereocenter, many research groups have focused on the introduction of a substituent at C1 position in a stereogenic fashion and also on natural products containing two contiguous and 1,3 stereocenters. Our aim to introduce stereochemical diversity in our present strategy, prompted us to examine the possibility of diastereoselectivity by employing the 1,3 stereocenter inducing SBAs. With this idea in mind, we selected the phenyl substituted secondary alcohol **35g(III)** as *N*,*O*-1,5 bisnucleophile, which afforded the expected product **36ac** although in low stereoselectivity (*cis/trans* = 4:3) as a mixture of inseparable diastereomers in 52% yield. The relative configuration of the major diastereomers was assigned to be cis based on NOE experiment. Our attempts to improve the diastereoselectivity by varying temperature, solvent system and concentration went in vein. All the compounds were confirmed by ^{1}H and ^{13}C spectroscopy and high resolution mass spectrometry. Although, the NMR spectroscopic data support the formation of fused privileged tetrahydroisoquinoline scaffolds **36**, the structures of **36p** and **36t** were unambiguously secured by X-ray crystal analyses.

Figure 2. Synthesis of various diverse fused tetrahydroisoquinoline compounds 36a-36ac through branching double annulation cascade (BDAC) strategy.

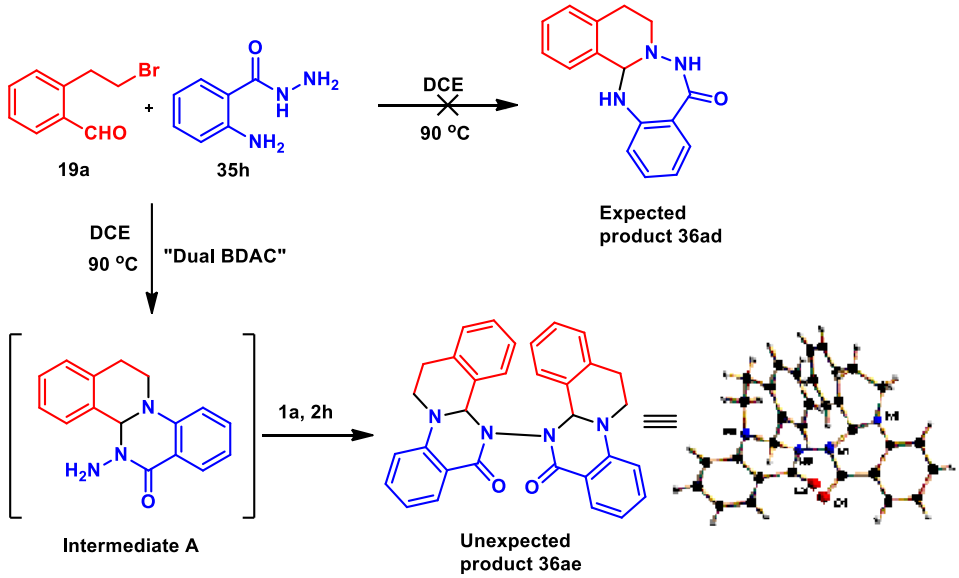


[a] Reactions were performed in DCE (1mL) with **19** (0.23 mmol), **35** (0.23 mmol) at 90 °C for 30-60 min. [b] **35a-35g** represent various *N,C*-, *N,O*- and *N,N*-1,5-bisnucleophiles as SBAs. [c]dr was determined by ^{1}H NMR spectroscopy.

In our present BDAC strategy, several diverse halo-substituted compounds have been synthesized, which could be utilized as versatile synthons for further

diversification. The present BDAC strategy was proved to be very general and versatile by enabling variety of SBAs with distinct nucleophilic centers to react with common precursor under unified reaction conditions. Overall, it was found that the *N,N*-bisnucleophiles afforded excellent yields compared to *N,C* and *N,O*-bisnucleophiles, and 2-aminobenzenesulfonamides (**35f**) though being weak nucleophile comparatively were the best among all 1,5-bisnucleophiles in terms of the reactivity and yield. The substituents such as Me and Br on common substrate **1** was non detrimental on reaction outcome and yield of the products (**36a**-**36ac**).

Scheme 13. Scope of BDAC strategy with 2-aminobenzohydrazide (35h).



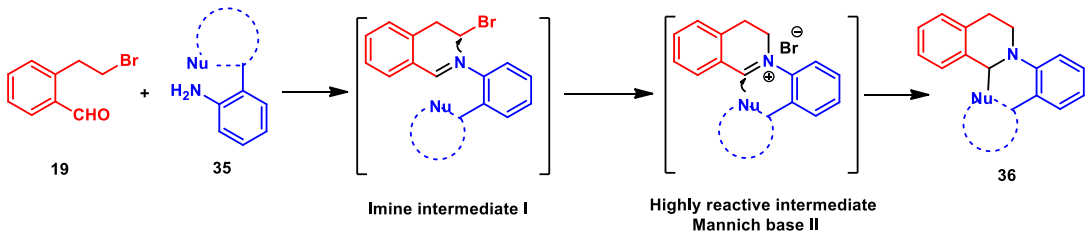
Further aiming to expand the diversity in the BDAC strategy, we envisioned that by using 2-aminobenzohydrazide (**35h**) as 1,6-bisnucleophile can result in 7-membered fused tetrahydrobenzotriazepino isoquinolinone skeleton. To our surprise, when we used 2- aminobenzohydrazide (**35h**) as *N,N*-bisnucleophile, resulted in the dimer product **3ae** instead of expected compound **36ad** (Scheme 13), which was confirmed by spectral and X-ray crystal structure analyses. The formation of **36ae** can be explained by dual BDAC reactions involving transamination of **35h** with intermediate **A** with the elimination of hydrazine hydrobromide.

After having developed the BDAC strategy for the synthesis of diverse heterocyclic scaffolds, we envisaged that it would be appropriate to check the

scalability of our BDAC strategy for the synthesis of fused tetrahydroisoquinoline compounds **36**. Accordingly, we performed the scale-up (1g scale) reaction for the synthesis of the product **36o,** resulting in 0.79 gm, 56% yield (Figure 2).

Based on the literature reports[12c,d] and experimental studies we have formulated a plausible reaction mechanism for the synthesis of diverse fused tetrahydroisoquinoline derivatives as shown in scheme 3. Initially, 2-(2-bromoethyl)benzaldehydes (**19a**) and scaffold-building agents (SBAs) **35** react to give an imine intermediate **I**, followed by an intramolecular alkylative cyclization leading to reactive Mannich base **II** which on further Pictet-Spengler[13] type annulation affords the desired product **36** (Scheme 14).

Scheme 14. Plausible reaction mechanism for the synthesis of THIQ fused compound 3.



II. 4. Conclusion:

In summary, we have successfully developed an advanced metal-free double annulation branching cascade (BDAC) strategy for the synthesis of library of 29 new, complex and diverse tetrahydroisoquinoline fused derivatives by using a variety of *N,C*-, *N,O*- and *N,N*-1,5-bisnucleophiles as a SBAs and 2-(2-bromoethyl)benzaldehydes as a common precursor under uniform reaction conditions. The important features of the present protocol are metal and catalyst-free, operational simplicity, use of simple starting materials and moderate to excellent yields. Moreover, the success of gram-scale synthesis of fused THIQ make this process useful for industrial applications. Undoubtedly, this protocol which affords three dimensional THIQ derivatives which are diverse in its coverage of chemical space, should prove useful for further scaffold innovation in drug

discovery program. Further, studies on enantioselective synthesis of these scaffolds are currently under way.

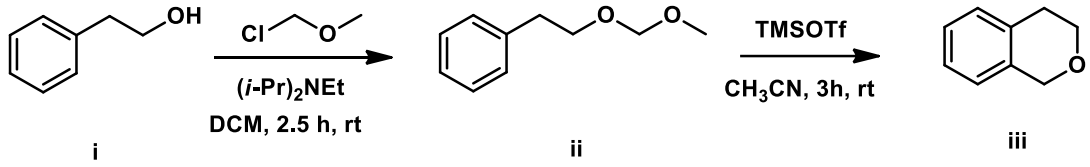
II. 5. Experimental Section

General Considerations

IR spectra were recorded on a FTIR spectrophotometer. ^{1}H NMR spectra were recorded on 400 MHz spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C NMR spectra were recorded on 100 MHz spectrometer at RT in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of triplet)]. In the 1HNMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br s. = broad singlet. The assignments of signals were confirmed by ^{1}H, ^{13}C, and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded using Q-TOF multimode source. Melting points were determined on an electro thermal melting point apparatus and are uncorrected. 2-(2-bromoethyl)benzaldehyde (**19a-19c**) were prepared by using known procedures. All the bisnucleophiles such as *N,C*-, *N,O*- and *N,N*-1,5-bisnucleophiles as a SBAs (**35a-35h)** which were either prepared in the laboratory or purchased from commercial sources. All the dry solvents such as, MeOH, EtOH and 1,4-Dioxane were dried over sodium metal and CH_3CN, DCM and DCE were dried over calcium hydride.

All small scale dry reactions were carried out using standard syringe-septum technique. Reactions were monitored by TLC on silica gel using a combination of petroleum ether and ethyl acetate as eluents. Reactions were generally run under argon atmosphere. Solvents were distilled prior to use; petroleum ether with a boiling range of 40 to 60 ˚C was used.

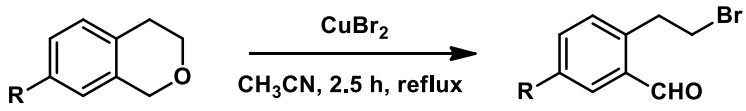
(I) General Procedure 1: Preparation of isochromans[40]



i ii iii

A mixture of the substituted phenylethyl alcohol (**i**) (4.97 mmol), chloromethylmethyl ether (7.046 mmol) and *N*,*N*-diisopropylethylamine (9.95 mmol) in dry dichloromethane (15 mL) was stirred under nitrogen atmosphere for 2.5 h at rt. The reaction mixture was then washed with water, dried (Na_2SO_4) and the solvent was removed in vaccuo. The crude MOM acetal (**ii**) was dissolved in dried acetonitrile and added to cooled (0 ^oC) solution of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (4.97 mmol). The reaction was carried out under nitrogen atmosphere for 3h. Then the mixture was quenched by the addition of l M $NaHCO_3$. The organic phase was washed with brine, dried with anhydrous sodium sulphate and evaporated under reduced pressure. Purification by column chromatography afforded corresponding substituted isochromans.

(II) General procedure 2: Preparation of 2-(2-bromoethyl)benzaldehydes (19a-19c)[40]



iii

R= H, 1a, 68%
R= Me, 1b, 74%
R= Br, 1c, 60%

To a solution of the substituted isochroman **iii** (7.46 mmol) derivatives in acetonitrile (15 mL), $CuBr_2$ (8.95 mmol) was added under nitrogen atmosphere. The solution was refluxed for about 2h and then cooled to room temperature. The reaction mixture was added water, extracted with ethyl acetate. The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4, filtered and concentrated and then purified by silica gel column chromatography to afford the products (**19a-19c)** in 68-74% yield.

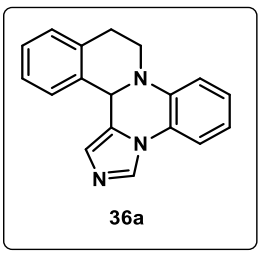
(III) General procedure 3: Synthesis of diverse scaffold containing fused tetrahydroisoquinolines (36a-36ae) through BDAC strategy: 2-(2-Bromoethyl)benzaldehydes (**19a-c**) (50 mg, 0.23 mmol) and variety of bisnucleophiles **35** (0.23 mmol) were taken in a 5 mL round bottom flask and added 1 mL of DCE heated at 90 ^{o}C. After completion of the reaction (monitored by TLC), the DCE solvent was completely evaporated under reduced pressure. The reaction mixture was quenched by aq. $NaHCO_3$ and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with brine solution and allowed to dry over anhydrous Na_2SO_4. The crude extract was purified by filtration through a silica gel (100-200 mesh) column using hexane and ethyl acetate as eluents to yield the desired product **36a-36ae**.

(IV) General procedure 4: Large scale synthesis of isoquinolinoquinazolinone 36o through BDAC strategy.

2-(2-Bromoethyl)benzaldehyde (**1a**) (1000 mg, 4.69 mmol) and *N*,*N*-bisnucleophile **35e(IV)** (790 mg, 4.69 mmol) were taken in a 25 mL round bottom flask and added 10 mL of DCE heated at 90 ^{o}C. After completion of the reaction (monitored by TLC), the DCE solvent was completely evaporated under reduced pressure. The reaction mixture was quenched by aq. $NaHCO_3$ and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with brine solution and allowed to dry over anhydrous Na_2SO_4. The crude extract was purified by filtration through a silica gel (100-200 mesh) column using hexane and ethyl acetate as eluents to yield the desired product **36o** in 56%, 790 mg.

Spectroscopic data of all unknown compounds:

***7,11b-Dihydro-6H-imidazo-6H-imidazo[1,5-a]isoquinolino[1,2-c]quinoxaline* (36a):**



36a

Physical State :Brown solid

Yield :46 mg, 72%

Mp :198−200 ^{o}C;

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3112, 2923, 2854, 1710, 1600, 1507, 1462, 1351, 1109, 746, 653;

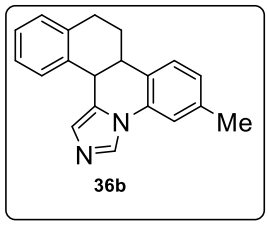
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.86 (d, J = 16.1 Hz, 1H), 3.21−3.28 (m, 1H), 3.36−3.40 (m, 1H), 3.97 (ddd, J_a = 12.5, J_b = 5.4 and J_c = 2.2 Hz, 1H), 5.53 (s, 1H),

6.92−6.97 (m, 2H), 7.05 (d, J = 7.8 Hz, 1H), 7.17−7.23 (m, 4H), 7.26−7.32 (m, 1H), 7.43 (dd, J_a = 7.8 and J_b = 1 Hz, 1H), 8.0 (s, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 27.1, 43.7, 54.7, 114.7, 115.7, 119.7, 124.6, 124.7, 126.3, 126.9, 127.4, 127.52, 129.3, 131.5, 133.1, 133.9, 137.6;

HR-MS (ESI$^+$) *m/z* calculated for $C_{18}H_{16}N_3^+$ = [M+H$^+$]: 274.1339; found: 274.1326.

***2-Methyl-7,11b-dihydro-6H-imidazo[1,5-a]isoquinolino[1,2-c]quinoxaline* (36b):**



36b

Physical State :Brown solid

Yield :45 mg, 67%

Mp :177−180 ^{o}C

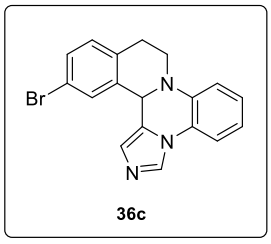
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3055, 2924, 2858, 1705, 1513, 1360, 816, 736, 651;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.32 (s, 3H), 2.82−2.87 (m, 1H), 3.19−3.24 (m, 1H), 3.28− 3.35 (m, 1H), 3.87−3.92 (m, 1H), 5.45 (s, 1H), 6.94−6.96 (m, 2H), 7.01 (d, J = 1.5 Hz, 1H), 7.13−7.16 (m, 1H), 7.19−7.22 (m, 2H), 7.24−7.25 (m, 1H), 7.30−7.33 (m, 1H), 7.97 (d, J = 1 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 20.7, 27.1, 43.9, 54.9, 115.2, 116.3, 124.7, 124.8, 126.2, 126.9, 127.3, 127.4, 127.7, 129.3, 129.8, 131.5, 133.1, 134.0, 135.4;

HR-MS (ESI$^+$) *m/z* calculated for $C_{19}H_{18}N_3^+$ = [M+H$^+$]: 288.1495; found: 288.1482.

***10-Bromo-7,11b-dihydro-6H-imidazo[1,5-a]isoquinolino[1,2-c]quinoxaline* (36c):**



36c

Physical State :Brown solid

Yield :56 mg, 68%

Mp :168−170 ^{o}C;

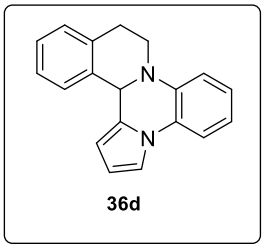
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3049, 2922, 1718, 1604, 1509, 1475, 1347, 1273, 813, 739, 651;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.78−2.82 (m, 1H), 3.2 (ddd, J_a = 16.9, J_b = 11.5 and J_c = 5.9 Hz, 1H), 3.42 (ddd, J_a = 13.2, J_b = 11.7 and J_c = 4.4 Hz, 1H), 4.02−4.07 (m, 1H), 5.56 (s, 1H), 6.92 (td, J_a = 7.7 and J_b = 1.2 Hz, 1H), 7.00−7.05 (m, 3H), 7.17−7.20 (m, 1H), 7.32 (dd, J_a = 8.3 and J_b = 1.5 Hz, 1H), 7.41−7.45 (m, 2H), 8.03 (d, J = 1 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 25.8, 43.9, 54.6, 114.8, 115.8, 119.8, 119.9, 124.4, 125.2, 126.1, 127.0, 129.7, 130.6, 131.0, 131.7, 132.9, 135.8, 136.7;

HR-MS (ESI$^+$) *m/z* calculated for $C_{18}H_{15}BrN_3^+$ = [M+H$^+$]: 352.0444; found: 352.0430.

***7,11b-Dihydro-6H-isoquinolino[2,1-a]pyrrolo[2,1-c]quinoxaline* (36d):**



36d

Physical State :Brown solid

Yield :45 mg, 71%

Mp :120−122 °C

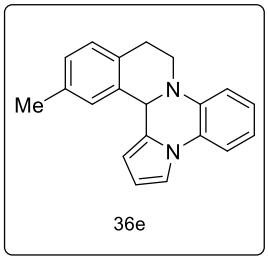
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3052, 2902, 2829, 1506, 1337, 1288, 1221, 738, 701, 643;

^1H NMR (400 MHz, $CDCl_3$) δ ppm = 2.8 (d, J = 16.1 Hz, 1H), 3.19−3.27 (m, 1H), 3.31−3.38 (m, 1H), 3.90−3.95 (m, 1H), 5.46 (s, 1H), 6.07−6.08 (m, 1H), 6.32−6.34 (m, 1H), 6.84−6.88 (m, 1H), 6.97−6.99 (m, 1H), 7.05−7.20 (m, 5H), 7.31−7.34 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 27.1, 44.0, 56.2, 105.7, 110.0, 114.5, 115.1, 115.1, 119.7, 125.0, 126.0, 127.0, 127.5, 127.7, 128.5, 129.2, 134.2, 134.4, 137.6;

HR-MS (ESI^+) *m/z* calculated for $C_{19}H_{17}N_2^+$ = [M+H^+]: 273.1386; found: 273.1382.

***10-Methyl-7,11b-dihydro-6H-isoquinolino[2,1-a]pyrrolo[2,1-c]quinoxaline* (36e):**



36e

Physical State :Brown solid

Yield: 38 mg, 60%

Mp 130−132 °C;

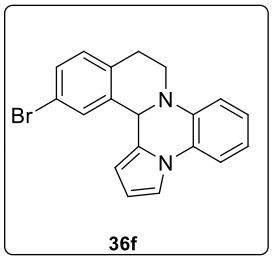
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3044, 2918, 2847, 1505, 1337, 1289, 1164, 741, 701, 610, 549;

^1H NMR (400 MHz, $CDCl_3$) δ ppm = 2.29 (s, 3H), 2.78 (d, J = 15.7 Hz, 1H), 3.17−3.25 (m, 1H), 3.34 (td, J_a = 12 and J_b = 3.9 Hz, 1H), 3.9−3.96 (m, 1H), 5.44 (s, 1H), 6.09 (d, J = 2.9 Hz, 1H), 6.34 (t, J = 3.2 Hz, 1H), 6.85−6.89 (m, 1H), 6.98−7.03 (m, 2H), 7.05−7.09 (m, 1H), 7.14 (s, 1H), 7.17 (dd, J_a = 2.7 and J_b = 1.7 Hz, 1H), 7.23 (s, 1H), 7.33 (dd, J = 7.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 21.3, 26.6, 44.1, 56.14, 105.7, 110.0, 114.4, 115.0, 115.1, 119.6, 124.9, 127.6, 127.8, 128.5, 129.0, 131.0, 134.1, 135.5, 137.6;

HR-MS (ESI^+) *m/z* calculated for $C_{20}H_{19}N_2^+$ = [M+H^+]: 287.1543; found: 287.1539.

***10-Bromo-7,11b-dihydro-6H-isoquinolino[2,1-a]pyrrolo[2,1-c]quinoxaline (36f)*:**



36f

Physical State :Brown solid

Yield :44 mg, 73%

Mp. :148−150 °C

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3048, 2919, 2833, 1508, 1340, 1165, 741, 703, 657, 538;

^1H NMR (400 MHz, $CDCl_3$) δ ppm = 2.75 (d, J = 17.6, 1H), 3.16−3.24 (m, 1H), 3.38 (ddd, J_a = 13.1, J_b = 11.6 and J_c = 4.2 Hz, 1H), 3.99 (ddd, J_a= 13.2, J_b = 5.6 and J_c = 2.2 Hz, 1H), 5.47 (s, 1H), 6.13 (dd, J_a = 3.2 and J_b = 1.2 Hz, 1H), 6.36 (t, J = 3.2 Hz, 1H), 6.87 (td, J_a = 7.6 and J_b = 1.5 Hz, 1H), 6.96−6.99 (m, 2H), 7.05−7.09 (m, 1H), 7.18 (dd, J_a = 2.9 and J_b = 1.5 Hz, 1H), 7.26−7.29 (m, 1H), 7.32 (dd, J_a = 7.8 and J_b = 1.5 Hz, 1H), 7.42 (d, J = 1 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 25.9, 44.1, 56.0, 106.2, 110.2, 114.5, 115.1, 115.2, 119.5, 119.8, 125.0, 127.0, 127.5, 130.1, 130.2, 130.8, 133.0, 136.7, 137.1;

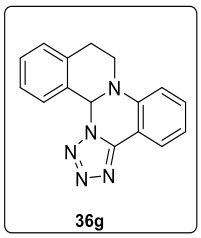
HR-MS (ESI^+) *m/z* calculated for $C_{19}H_{16}BrN_2^+$ = [M+H^+]: 351.0491; found: 351.0477.

***7, 11b-Dihydro-6H-isoquinolino[2,1-a]tetrazolo[1,5-c]quinazoline* (36g):**

Physical State :White solid

Yield :56 mg, 87%

Mp :88−90 °C;



36g

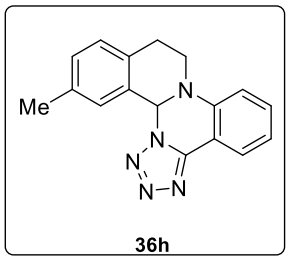
IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3067, 2922, 2854, 1720, 1655, 1614, 1489, 1387, 1295, 1238, 1119, 1031, 749, 697, 649;

^1H NMR (400 MHz, $CDCl_3$) δ ppm = 2.94 (dt, J_a = 16.6 and J_b = 4.4 Hz, 1H), 3.19−3.27 (m, 1H), 3.53−3.61 (m, 1H), 3.92−3.98 (m, 1H), 6.88 (s, 1H), 7.08 (td, J = 7.6 Hz, 1H), 7.14−7.17 (t, J = 7.6 Hz, 2H), 7.20−7.22 (m, 1H), 7.28−7.35 (m, 2H), 7.47 (ddd, J_a = 8.4, J_b = 7.2 and J_c = 1.5 Hz, 1H), 8.03 (dd, J_a = 7.6 and J_b = 1.7 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 25.8, 44.8, 72.0, 111.5, 116.2, 121.9, 126.3, 126.8, 127.7, 129.3, 129.4, 129.8, 133.4, 134.5, 143.7, 148.8;

HR-MS (ESI^+) *m/z* calculated for $C_{16}H_{14}N_5^+$ = [M+H^+]: 276.1244; found: 276.1239.

***10-Methyl-7,11b-dihydro-6H-isoquinolino[2,1-a]tetrazolo[1,5-c]quinazoline* (36h):**



36h

Physical State :White solid

Yield :43 mg 68%

Mp :170-172 °C;

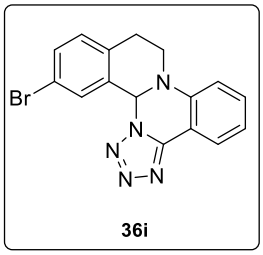
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2920, 1618, 1494, 1303, 1214, 1144, 1064, 747, 612;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.28 (s, 3H), 2.89 (dt, J_a = 16.9 and J_b = 4 Hz, 1H), 3.22(ddd, J_a = 16.5, J_b = 10.6 and J_c = 5.6 Hz, 1H), 3.54−3.61 (m, 1H), 3.95−4.01 (m, 1H), 6.89 (s, 1H), 7.04−7.15 (m, 5H), 7.45−7.49 (m, 1H), 8.04 (dd, J_a = 7.8 and J_b = 1.5 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 21.1, 25.3, 44.9, 72.1, 111.4, 115.9, 121.7, 126.4, 127.9, 129.2, 129.8, 130.3, 131.2, 133.4, 136.6, 143.6, 148.8;

HR-MS (ESI$^+$) *m/z* calculated for $C_{17}H_{16}N_5^+$ = [M+H$^+$]: 290.1400; found: 290.1395.

***10-Bromo-7,11b-dihydro-6H-isoquinolino[2,1-a]tetrazolo[1,5-c]quinazoline* (36i):**



36i

Physical State :white solid

Yield :46 mg, 75%

Mp :192−195 °C;

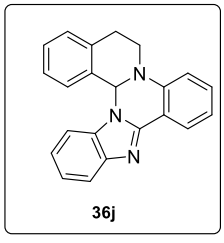
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 1618, 1580, 1488, 1304, 1220, 1139, 816, 739;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.91 (dt, J_a = 17.1 and J_b = 3.9 Hz, 1H), 3.21 (ddd, J_a = 16.6, J_b = 10.5 and J_c = 5.6 Hz, 1H), 3.59 (ddd, J_a = 14.4, J_b = 10 and J_c = 4.9 Hz, 1H), 3.99−4.05 (m, 1H), 6.91 (s, 1H), 7.05 (d, J = 8.3, 1H), 7.09−7.16 (m, 2H), 7.41−7.52 (m, 3H), 8.06 (dd, J_a = 7.6 and J_b = 1.2 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 25.1, 44.6, 71.4, 111.3, 116.0, 120.3, 122.1, 126.5, 130.4, 131.0, 132.1, 132.6, 133.3, 133.6, 143.1, 148.7;

HR-MS (ESI$^+$) *m/z* calculated for $C_{16}H_{13}BrN_5^+$ = [M+H$^+$]: 354.0349; found: 354.0343.

***6,17a-Dihydro-5H-benzo[4,5]imidazo[1,2-c]isoquinolino[2,1-a]quinazoline* (36j):**



36j

Physical State :White solid

Yield :49 mg, 65%);

Mp. :188−190 °C;

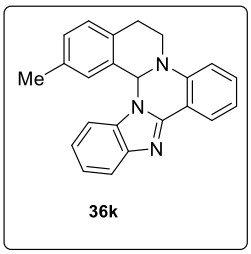
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3054, 2921, 2851, 1613, 1479, 1449, 1226, 736, 642, 546;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.86 (d, J = 17.1 Hz, 1H), 3.45−3.62 (m, 1H), 3.76−3.81 (m, 1H), 4.32−4.45 (m, 1H), 7.16−6.74 (m, 7H), 7.47−7.25 (m, 4H), 7.88−7.86 (m, 1H), 8.14 (d, J = 7.3 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 23.8, 44.9, 69.5, 109.3, 119.7, 123.0, 123.2, 125.6, 126.2, 126.6, 128.7, 129.5, 131.9, 134.3, 134.2, 134.5, 135.45, 143.8;

HR-MS (ESI^+) *m/z* calculated for $C_{22}H_{18}N_3^+$ = [M+H^+]: 324.1495; found: 324.1494.

***2-Methyl-6,17a-dihydro-5H-benzo[4,5]imidazo[1,2-c]isoquinolino[2,1-a]quinazoline* (36k):**



Physical State :White solid

Yield :36 mg, 48%

Mp. :178−180 °C;

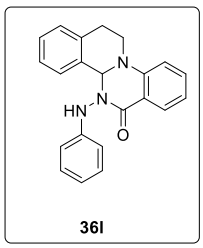
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3049, 2920, 2851, 1613, 1479, 1267, 1218, 736, 699, 641, 543;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.04 (s, 3H), 2.83 (d, J = 14.7 Hz, 1H), 3.44−3.46 (m, 1H), 3.78−3.82 (m, 1H), 4.27−4.31 (m, 1H), 6.51−6.54 (m, 1H), 6.84−7.05 (m, 5H), 7.32−7.42 (m, 4H), 7.88 (d, J = 7.3 Hz, 1H), 8.14 (d, J = 7.3 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 21.1, 23.5, 44.8, 69.3, 108.0, 109.1, 113.1, 119.5, 122.8, 123.0, 126.1, 129.3, 129.4, 131.8, 134.5, 136.3, 143.7;

HR-MS (ESI^+) *m/z* calculated for $C_{23}H_{20}N_3^+$ = [M+H^+]: 338.1652; found: 338.1650.

***5-(Phenylamino)-12,13-dihydro-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one* (36l):**



Physical State :White solid

Yield :50 mg, 62%

Mp :196−198 °C;

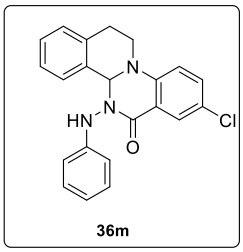
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3260, 3032, 2922, 2853, 1655, 1599, 1472, 1267, 741, 697;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.75 (dd, J_a = 16.9 and J_b = 4.6, 1H), 3.26−3.35 (m, 1H), 3.65 (ddd, J_a = 14.4, J_b = 12 and J_c = 5.4 Hz, 1H), 4.25 (dd, J_a = 14.4 and J_b = 5.1 Hz, 1H), 5.98 (s, 1H), 6.84−6.87 (m, 1H), 6.92 (t, J = 7.3 Hz, 1H), 7.01−7.04 (m, 4H), 7.09−7.15 (m, 2H), 7.22−7.26 (m, 2H), 7.31 (s, 1H), 7.38−7.42 (m, 1H), 7.53 (d, J = 7.3 Hz, 1H), 7.9 (dd, J_a = 7.8 and J_b = 1.5 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 24.4, 44.8, 75.1, 113.6, 114.2, 117.2, 119.5, 121.8, 126.2, 126.4, 128.2, 129.0, 129.3, 129.4, 134.0, 134.2, 135.3, 146.7, 147.5, 163.1;

HR-MS (ESI$^+$) *m/z* calculated for $C_{22}H_{20}N_3O^+$ = [M+H$^+$]: 342.1601; found: 342.1595.

***8-Chloro-5-(phenylamino)-12, 13-dihydro-4bH-isoquinolino[2, 1-a]quinazolin-6(5H)-one* (36m):**



36m

Physical State :White solid

Yield :48 mg, 55%

Mp :125−127 ^{o}C;

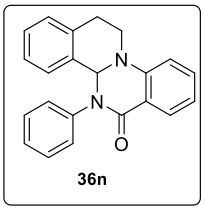
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3263, 2916, 2754, 1657, 1488, 1248, 1099, 900, 739, 691, 643, 591;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.74 (dd, J_a = 16.9 and J_b = 4.6 Hz, 1H), 2.72−2.77 (m, 1H), 3.22−3.31 (m, 1H), 3.61−3.68 (m, 1H), 4.17−4.22 (m, 1H), 5.96 (s, 1H), 6.92−6.93 (m, 2H), 6.99−7.02 (m, 2H), 7.11−7.22 (m, 2H), 7.23−7.25 (m, 2H), 7.31−7.34 (m, 1H), 7.44 (br. s, 1H), 7.53 (d, J = 7.3 Hz, 1H), 7.86−7.87 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 24.3, 45.0, 75.2, 114.1, 115.1, 118.4, 121.8, 124.8, 126.3, 126.4, 128.4, 128.9, 129.0, 129.4, 133.8, 133.9, 135.0, 146.1, 146.5, 162.1;

HR-MS (ESI$^+$) *m/z* calculated for $C_{22}H_{19}ClN_3O^+$ = [M+H$^+$]: 376.1211; found: 376.1204.

***5-Phenyl-12,13-dihydro-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one* (36n):**



36n

Physical State :White solid

Yield :54 mg, 70%

Mp :92−94 ^{o}C;

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3065, 1667, 1598, 1462, 1378, 1326, 1275, 755, 695, 662;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.83 (dd, J_a = 17.1 and J_b = 4.4, 1H), 3.26−3.29 (m, 1H), 3.72 (ddd, J_a = 14.7, J_b = 11.2 and J_c = 5.9 Hz, 1H), 4.20−4.26 (m, 1H), 6.16 (s, 1H),

6.85−6.89 (m, 1H), 6.98 (d, J = 8.3 Hz, 1H), 7.03−7.08 (m, 2H), 7.13−7.16 (m, 1H), 7.19−7.23 (m, 1H), 7.32−7.40 (m, 4H), 7.48−7.50 (m, 2H), 7.99 (dd, J_a = 7.8 and J_b = 2 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 24.6, 45.1, 75.3, 114.1, 119.2, 119.7, 125.1, 125.9, 126.2, 127.2, 128.2, 128.9, 129.1, 129.9, 133.8, 134.4, 135.6, 141.7, 147.4, 162.8;

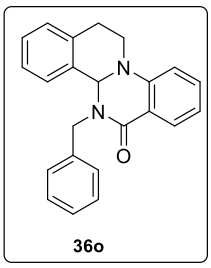
HR-MS (ESI$^+$) *m/z* calculated for $C_{22}H_{19}N_2O^+$ = [M+H$^+$]: 327.1492; found: 327.1486.

***5-Benzyl-12, 13-dihydro-4bH-isoquinolino[2,1-a]quinazolin-6(5H)- one* (36o):**

Physical State :White solid

Yield :52 mg, 65%

Mp :158−160 ^{o}C;



36o

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3030, 2917, 1648, 1601, 1475, 1261, 744, 697;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.29 (dd, J_a = 16.9 and J_b = 3.7 Hz, 1H), 3.13−3.04 (m, 1H), 3.48 (ddd, J_a = 14.1, J_b = 11.1 and J_c = 5.6 Hz, 1H), 3.98 (dd, J_a = 13.7 and J_b = 5.4 Hz, 1H), 4.36 (d, J = 15.2 Hz, 1H), 5.72−5.85 (m, 2H), 6.82−6.88 (m, 2H), 6.99−7.01 (m, 1H), 7.13−7.19 (m, 2H), 7.22−7.35 (m, 7H), 7.95 (dd, J_a = 7.8 and J_b = 1.5 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 24.5, 44.6, 49.7, 71.7, 113.7, 118.5, 119.4, 119.8, 125.9, 126.2, 127.5, 127.7, 128.3, 128.7, 129.3, 129.5, 133.4, 134.8, 137.3, 147.5, 163.5;

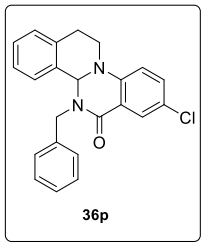
HR-MS (ESI$^+$) *m/z* calculated for $C_{23}H_{21}N_2O^+$ = [M+H$^+$]: 341.1648; found: 341.1644.

***5-Benzyl-8-chloro-12,13-dihydro-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one* (36p):**

Physical State :White solid

Yield :48 mg, 55%

Mp :210−212 ^{o}C;



36p

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3062, 2920, 1652, 1476, 1259, 737, 699, 639;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.71 (dd, J_a = 17.1 and J_b = 3.9 Hz, 1H), 3.03−3.11 (m, 1H), 3.5 (ddd, J_a = 14.2, J_b = 11 and J_c = 5.6 Hz, 1H), 3.95 (dd, J_a = 13.7 and J_b = 5.4 Hz, 1H), 4.35 (d, J = 15.2 Hz, 1H), 5.64−5.68 (m, 2H), 6.82 (d, J = 8.8

Hz, 1H), 7.02 (d, J = 6.8 Hz, 1H), 7.15−7.21 (m, 2H), 7.23−7.32 (m, 7H), 7.91 (d, J = 2.4 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 24.4, 44.7, 49.8, 71.7, 104.9, 109.8, 115.2, 124.7, 125.8, 126.4, 127.6, 127.7, 128.5, 128.7, 129.1, 129.3, 133.3, 134.5, 136.9, 146.0, 162.4;

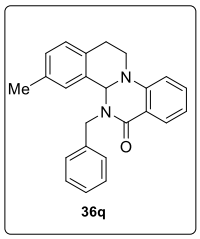
HR-MS (ESI$^+$) m/z calculated for $C_{23}H_{20}ClN_2O^+$ = [M+H$^+$]: 375.1259; found: 375.1250.

***5-Benzyl-3-methyl-12,13-dihydro-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one* (36q):**

Physical State :White solid

Yield :47 mg, 60%

Mp :158−160 ^{o}C;



36q

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3032, 2917, 1647, 1603, 1476, 1384, 1264, 1169, 818, 738, 698;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.27 (s, 3H), 2.66 (dd, J_a = 16.6 and J_b = 4.4 Hz, 1H), 3.08 (d, J = 6.4 Hz, 1H), 3.49 (ddd, J_a = 14.2, J_b = 11.2 and J_c = 5.9 Hz, 1H), 4.01 (dd, J_a = 13.9 and J_b = 5.6 Hz, 1H), 4.34 (d, J = 15.7 Hz, 1H), 5.64 (s, 1H), 5.74 (s, 1H), 6.83−6.92 (m, 3H), 6.99− 7.02 (m, 2H), 7.27−7.34 (m, 6H), 7.97 (dd, J_a = 7.8 and J_b = 1.5 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 21.2, 24.1, 44.7, 49.9, 71.8, 113.6, 118.4, 119.3, 126.4, 127.5, 127.7, 128.7, 129.0, 129.1, 129.5, 131.6, 133.4, 135.8, 137.3, 147.5, 163.5;

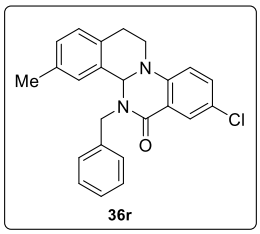
HR-MS (ESI$^+$) m/z calculated for $C_{24}H_{23}N_2O^+$ = [M+H$^+$]: 355.1805; found: 355.1799.

***5-Benzyl-8-chloro-3-methyl-12,13-dihydro-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one* (36r):**

Physical State :White solid

Yield :41 mg, 48%.

Mp :152−155 ^{o}C; 48% yield;



36r

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2912, 2753, 1649, 1454, 1255, 1103, 889, 809, 732, 698, 640, 589, 539;

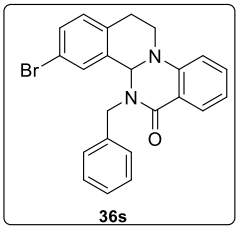
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.27 (s, 3H), 2.66 (dd, J = 16.9 and 4.6, 1H), 3.01−3.09 (m, 1H), 3.48 (ddd, J_a = 14.2, J_b = 11.2 and J_c = 5.9 Hz, 1H), 3.94 (dd, J_a = 13.7 and J_b = 5.9 Hz, 1H), 4.32 (d, J = 15.2 Hz, 1H), 5.61 (s, 1H), 5.72 (d, J = 12.2 Hz, 1H), 6.8

(d, J = 8.8 Hz, 1H), 6.9−6.92 (m, 1H), 6.99−7.01 (m, 2H), 7.24−7.33 (m, 6H), 7.91 (d, J = 2.4 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 21.2, 24.0, 44.8, 50.0, 71.8, 115.1, 119.6, 124.6, 126.3, 127.6, 127.7, 128.7, 129.1, 129.2, 129.3, 131.3, 133.2, 136.0, 137.0, 146.0, 162.4;

HR-MS (ESI$^+$) *m/z* calculated for $C_{24}H_{22}ClN_2O^+$ = [M+H$^+$]: 389.1415; found: 389.1408.

***5-Benzyl-3-bromo-12,13-dihydro-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one* (36s):**



36s

Physical State :White solid

Yield :43 mg, 62%

Mp :128−130 ^{o}C

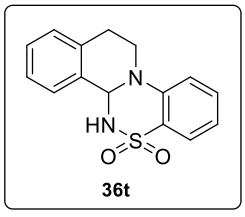
IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3340, 3057, 2919, 1647, 1603, 1477, 1260, 1167, 816, 734, 697, 629, 546;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.64 (dd, J_a = 17.1 and J_b = 4.9 Hz, 1H), 3.07−3.11 (m, 1H), 3.5 (ddd, J_a = 14.4, J_b = 11.5 and J_c = 5.9 Hz, 1H), 4.07 (dd, J_a = 14.2 and J_b = 5.9 Hz, 1H), 4.3 (d, J = 15.7 Hz, 1H), 5.6 (s, 1H), 5.81 (d, J = 15.2 Hz, 1H), 6.86−6.89 (m, 3H), 7.26−7.36 (m, 8H), 7.96 (dd, J_a = 7.8 and J_b = 1.5 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 23.6, 44.3, 50.1, 71.4, 113.4, 118.2, 119.6, 119.9, 127.6, 127.7, 128.6, 128.8, 129.62, 130.9, 131.4, 133.5, 133.6, 136.9, 146.9, 163.1;

HR-MS (ESI$^+$) *m/z* calculated for $C_{23}H_{20}BrN_2O^+$ = [M+H$^+$]: 419.0754; found: 419.0746.

***4b,5,12,13-Tetrahydrobenzo[5,6]thiadiazino[3,4-a]isoquinoline 6,6-dioxide* (36t):**



36t

Physical State :White solid

Yield :47 mg, 70%

Mp :218−220 ^{o}C;

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3231, 2922, 2853, 1597, 1481, 1449, 1318, 1274, 1158, 748, 662, 610, 556;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.98−3.14 (m, 2H), 3.46 (ddd, J_a = 12.3, J_b = 8.2 and J_c = 4.4 Hz, 1H), 3.86 (dt, J_a = 12.5 and J_b = 5.3 Hz, 1H), 4.77 (d, J = 12.7 Hz, 1H), 5.98 (d, J = 13.2 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 7.20−7.23 (m, 1H),

7.30−7.33 (m, 2H), 7.45 (ddd, J_a = 8.6, J_b = 7.1 and J_c = 1.5 Hz, 1H), 7.6 (dd, *J*a = 5.4 and J_b = 3.9 Hz, 1H), 7.78 (dd, *J*a = 7.8 and J_b = 1.5 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 29.0, 43.8, 68.5, 116.1, 119.4, 125.3, 125.4, 127.1, 127.7, 128.3, 128.7, 131.7, 133.5, 135.0, 144.5;

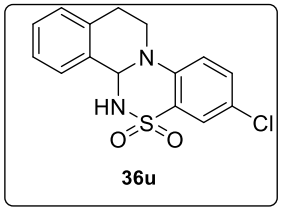
HR-MS (ESI$^+$) *m/z* calculated for $C_{15}H_{15}N_2O_2S^+$ = [M+H$^+$]: 287.0849; found: 287.0845.

***8-Chloro-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4-a]isoquinoline 6,6-dioxide* (36u):**

Physical State :White solid

Yield :69 mg, 90%

Mp :198−200 °C;



36u

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3222, 3065, 2925, 2849, 1597, 1478, 1322, 1160, 734, 666, 621, 554;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 3.0−3.1 (m, 2H), 3.46 (ddd, J_a = 12.2, J_b = 8.1 and J_c = 4.6 Hz, 1H), 3.78−3.84 (m, 1H), 4.93 (d, *J* = 12.7 Hz, 1H), 5.95 (d, *J* = 12.7 Hz, 1H), 7.0 (d, *J* = 8.8 Hz, 1H), 7.21−7.23 (m, 1H), 7.31−7.38 (m, 3H), 7.57 (dd, J_a = 5.1 and J_b = 3.7 Hz, 1H), 7.7 (d, *J* = 2.4 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 28.9, 44.0, 68.3, 117.8, 124.3, 124.7, 125.9 , 127.2, 127.7, 128.3, 128.8, 131.2, 133.6, 134.8, 143.1;

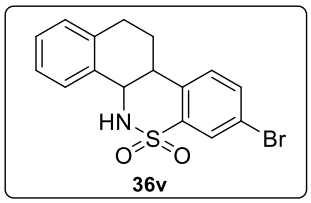
HR-MS (ESI$^+$) *m/z* calculated for $C_{15}H_{14}ClN_2O_2S^+$ = [M+H$^+$]: 321.0459; found: 321.0454.

***8-Bromo-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4-a]isoquinoline 6,6-dioxide* (36v):**

Physical State : White solid

Yield : 70 mg, 82%)

Mp : 200−202 °C;



36v

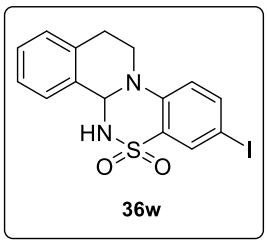
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3411, 3027, 2837, 2720, 2253, 2128, 1644, 1593, 1476, 1322, 1164, 1005, 820, 758, 617, 561;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.98−3.10 (m, 2H), 3.43−3.47 (td, J_a = 8.2 and J_b = 4.2 Hz, 1H), 3.78−3.83 (m, 1H), 4.95 (d, J = 12.7 Hz, 1H), 5.93 (d, J = 12.7 Hz, 1H), 6.93 (d, J = 9.3 Hz, 1H), 7.21−7.24 (m, 1H), 7.30−7.35 (m, 2H), 7.47−7.5 (m, 1H), 7.54−7.57 (m, 1H), 7.82 (d, J = 2.4 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 28.9, 43.9, 68.4, 111.2, 117.8, 126.3, 127.3, 127.6, 127.8, 128.3, 128.9, 131.2, 134.8, 136.4, 143.4;

HR-MS (ESI^+) *m/z* calculated for $C_{15}H_{14}BrN_2O_2S^+$ = $[M+H^+]$: 364.9954; found: 364.9948.

***8-Iodo-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4-a]isoquinoline 6,6-dioxide* (36w):**



36w

Physical State : White solid

Yield : 76 mg, 79%b

Mp : 210−212 °C;

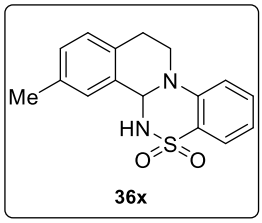
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3419, 1649, 1402, 1175, 1006, 821, 759, 618, 568;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.55−2.61 (m, 1H), 2.96−3.13 (m, 1H), 3.47 (ddd, J_a = 12.1, J_b = 7.5 and J_c = 4.4 Hz, 1H), 3.77−3.83 (m, 1H), 5.9 (d, J = 12.2 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 7.20−2.22 (m, 1H), 7.29−7.38 (m, 2H), 7.55−7.57 (m, 1H), 7.64 (dd, J_a = 8.8 and J_b = 2 Hz, 1H), 7.98 (d, J = 2 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 28.9, 43.8, 68.3, 79.9, 117.9, 126.7, 127.3, 127.6, 128.3, 128.9, 131.3, 133.4, 134.8, 142.0, 143.9;

HR-MS (ESI^+) *m/z* calculated for $C_{15}H_{14}IN_2O_2S^+$ = $[M+H^+]$: 412.9815; found: 412.9809.

***3-Methyl-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4-a]isoquinoline 6,6-dioxide* (36x):**



36x

Physical State :White solid

Yield :41 mg, 62%

Mp :228−230 °C;

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3205, 2918, 2851, 1715, 1594, 1450, 1319, 1156, 741, 664, 559;

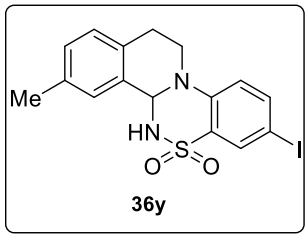
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.36 (s, 3H), 2.96−3.04 (m, 2H), 3.42 (ddd, J_a = 12.3, J_b = 8.2 and J_c = 4.2 Hz, 1H), 3.83 (dt, J_a = 12.1 and J_b = 5.2 Hz, 1H), 4.78 (d, J = 12.7 Hz,

1H), 5.92 (d, J = 13.2 Hz, 1H), 6.94−6.96 (m, 1H), 7.05−7.14 (m, 3H), 7.40−7.46 (m, 2H), 7.76 (dd, J_a = 7.8 and J_b = 1.5 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 21.1, 28.6, 43.9, 68.6, 116.1, 119.4, 125.3, 125.4, 128.2, 129.6, 131.4, 131.8, 133.5, 136.9, 144.6;

HR-MS (ESI$^+$) *m/z* calculated for $C_{16}H_{17}N_2O_2S^+$ = [M+H$^+$]: 301.1005; found: 301.1001.

***8-Iodo-3-methyl-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4 a]isoquinoline 6,6-dioxide* (36y):**



36y

Physical State :White solid

Yield :64 mg, 68%

Mp :218−220 ºC;

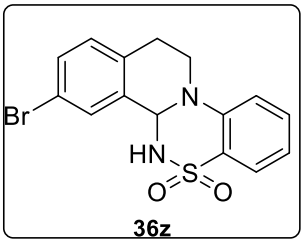
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3217, 2921, 2854, 1469, 1322, 1273, 1160, 929, 798, 730, 665;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.36 (s, 3H), 2.92− 3.05 (m, 2H), 3.41 (ddd, J_a = 12.3, J_b = 8.4 and J_c = 4.2 Hz, 1H), 3.78−3.83 (m, 1H), 4.88 (d, J = 12.7 Hz, 1H), 5.9 (d, J = 12.7 Hz, 1H), 6.81 (d, J = 9.3 Hz, 1H), 7.09−7.14 (m, 2H), 7.38 (s, 1H), 7.66 (dd, J_a = 8.8 and J_b = 2 Hz, 1H), 7.99 (d, J = 2 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 21.1, 28.5, 43.9, 68.4, 79.9, 117.9, 126.7, 128.0, 128.2, 129.7, 131.0, 131.7, 133.5, 137.1, 142.0, 143.9;

HR-MS (ESI$^+$) *m/z* calculated for $C_{16}H_{16}IN_2O_2S^+$ = [M+H$^+$]: 426.9972; found: 426.9962.

***3-Bromo-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4-a]isoquinoline 6,6-dioxide* (36z):**



36z

Physical State :White solid

Yield :54 mg, 65%

Mp :228−230 ºC;

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3213, 2924, 2852, 1706, 1598, 1478, 1319, 1161, 738, 548;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.90−2.96 (m, 2H), 3.36 (ddd, J_a = 12.5, J_b = 7.8 and J_c = 4.6 Hz, 1H), 3.74−3.79 (m, 1H), 4.83 (d, J = 12.7 Hz, 1H), 5.81 (d, J = 13.2 Hz, 1H),

6.87−6.92 (m, 1H), 7.01 (dd, J_a = 10.3 and J_b = 8.8 Hz, 2H), 7.34−7.40 (m, 2H), 7.64−7.67 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 28.6, 43.7, 67.9, 116.4, 119.8, 120.7, 125.4, 125.5, 130.0, 130.7, 131.9, 133.6, 133.9, 144.2;

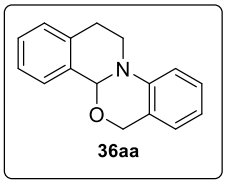
HR-MS (ESI^+) *m/z* calculated for $C_{15}H_{14}BrN_2O_2S^+$ = [M+H$^+$]: 364.9954; found: 364.9951.

***4b,6,12,13-Tetrahydrobenzo[4,5][1,3]oxazino[2,3-a]isoquinoline* (36aa):**

Physical State :White solid

Yield :33 mg, 60%

Mp :115−117 ºC;



36aa

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3035, 2933, 2897, 2838, 1602, 1491, 1455, 1389, 1287, 1228, 1193, 1154, 1056, 1029, 946, 749, 664;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.91 (dt, J_a = 15.9 and J_b = 3.5 Hz, 1H), 3.14 (ddd, J_a = 16, J_b = 10.6 and J_c = 5.1 Hz, 1H), 3.44−3.58 (m, 2H), 4.96 (d, J = 15.2 Hz, 1H), 5.22 (d, J = 14.7 Hz, 1H), 5.41 (s, 1H), 6.95−7.02 (m, 2H), 7.11 (d, J = 7.8 Hz, 1H), 7.17−7.28 (m, 4H), 7.45 (dd, J_a= 5.4 and J_b = 3.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 29.8, 46.2, 68.3, 84.4, 121.2, 121.7, 1245.0, 126.3, 126.4, 127.3, 128.3, 128.7, 133.4, 135.3, 146.0;

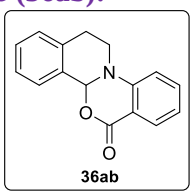
HR-MS (ESI^+) *m/z* calculated for $C_{16}H_{14}N^+$ = [[M+H$^+$]-H_2O]: 220.1120; found: 220.1113.

***12,13-Dihydrobenzo[4,5][1,3]oxazino[2,3-a]isoquinolin-6(4bH)-one* (36ab):**

Physical State :White solid

Yield :43 mg, 72%

Mp :115−117 ºC;



36ab

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 1720, 1607, 1484, 1467, 1399, 1331, 1292, 1229, 752;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 3.1 (t, J_a = 5.9, J_b = 5.9 Hz, 2H), 3.46−3.52 (m, 1H), 3.71− 3.76 (m, 1H), 6.14 (s, 1H), 7.11−7.13 (m, 2H), 7.26−7.24 (m, 1H), 7.33−7.36 (m, 2H), 7.55−7.59 (m, 2H), 8.11 (dd, J = 7.8 Hz, 1.5, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 29.0, 43.6, 85.7, 117.0, 117.2, 122.0, 127.0, 128.4, 128.6, 129.3, 130.0, 131.0, 134.7, 135.1, 150.0, 165.1;

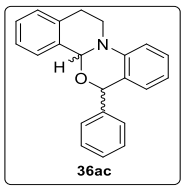
HR-MS (ESI$^+$) *m/z* calculated for $C_{16}H_{14}NO_2^+$ = [M+H$^+$]: 252.1019; found: 252.1008.

***6-Phenyl-4b,6,12,13-tetrahydrobenzo[4,5][1,3]oxazino[2,3-a]isoquinoline* (36ac):**

Physical State :Brown solid

Yield :35 mg, 52%

Mp :60−62 ^{o}C ;



36ac

IR (MIR-ATR, 4000-600 cm^{-1}): ν_{max} = 3029, 2925, 2834, 1659, 1601, 1487.44, 1455, 1391, 1221, 1146, 939, 747, 699, 644;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.85−2.99 (m, 2H), 3.18−3.23 (m, 2H), 3.55−3.60 (m, 2H), 3.71−3.72 (m, 1H), 3.98 (t, *J* = 5.9 Hz, 1H), 5.36 (s, 1H), 5.68 (s, 1H), 6.04 (s, 1H), 6.21 (s, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.85−6.88 (m, 1H), 6.97−7.05 (m, 3H), 7.15−7.16 (m, 4H), 7.21−7.25 (m, 4H), 7.29−7.32 (m, 2H), 7.33−7.43 (m, 4H), 7.43−7.51 (m, 7H);

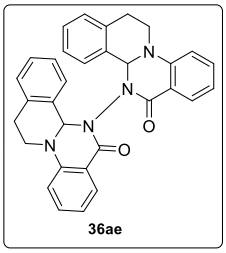
^{13}C, HMBC, HSQC NMR (100 MHz, $CDCl_3$) δ ppm = 29.7 (t, -CH_2-), 29.9 (t, -CH_2-), 46.1 (t, -CH_2-), 47.0 (t, -CH_2-), 77.07 (d, -CH-), 78.2 (d, -CH-), 81.5 (d, -CH-), 84.4 (d, -CH-), 120.9 (d, Ar-CH), 121.0 (d, Ar-CH), 121.7 (s, Ar-C), 121.8 (d, Ar-CH), 122.0 (d, Ar-CH), 125.8 (s, Ar-C), 126.3 (d, Ar-CH), 126.4 (d, Ar-CH), 127.3 (d, Ar-CH), 127.6 (d, Ar-CH), 127.9 (d, Ar-CH), 128.0 (d, 2C, Ar-CH), 128.0 (d, 2C, Ar-CH), 128.1 (d, Ar-CH), 128.2 (d, 2C, Ar-CH), 128.3 (s, Ar-C), 128.4 (d, 2C, Ar-CH), 128.5 (d, Ar-CH), 128.5 (d, 2C, Ar-CH), 128.8 (d, 2C, Ar-CH), 129.1 (d, Ar-CH), 129.4 (d, 2C, Ar-CH), 130.3 (s, Ar-C), 133.4 (s, Ar-C), 135.1 (s, Ar-C), 135.4 (s, Ar-C), 141.8 (s, Ar-C), 142.4 (s, Ar-C), 146.4 (s, Ar-C).

***12,12',13,13'-Tetrahydro-[5,5'-biisoquinolino[2,1-a]quinazoline]-6,6'(4bH,4'bH)-dione* (36ae):**

Physical State :White solid

Yield :45 mg, 38%

Mp :230−232 ^{o}C;



36ae

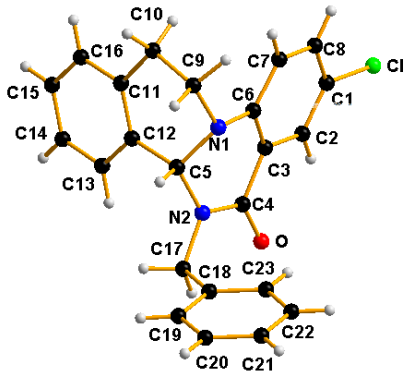
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2903, 1722, 1606, 1466, 1398, 1294, 1241, 1160, 1119, 1032, 951, 750, 697, 639;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 2.90−2.93 (m, 2H), 3.45−3.62 (m, 2H), 6.48 (s, 1H), 7.32−7.49 (m, 1H), 7.50−7.53 (m, 3H), 7.81−7.91 (m, 3H), 8.33−8.35 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 29.0, 45.0, 72.7, 118.7, 120.3, 121.7, 125.9, 127.7, 128.1, 128.9, 129.6, 130.6, 133.9, 136.4, 150.0, 166.6;

HR-MS (ESI$^+$) *m/z* calculated for $C_{32}H_{27}N_4O_2^+$ = [M+H$^+$]: 499.2129; found: 499.2127.

X-ray crystal structure data for 5-Benzyl-8-chloro-12,13-dihydro-4*bH*-isoquinolino[2,1-*a*]quinazolin-6(5*H*)-one (3p) CCDC 1478499

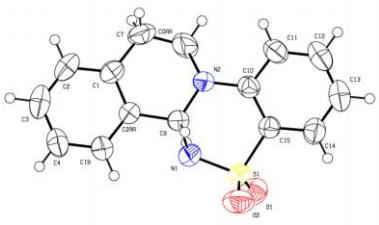


X-ray crystal structure of product **3p**. Thermal ellipsoids are drawn at 50% probability level.

Operator	K. Ravikumar
Difractometer	Oxford Super Nova
Empirical formula	$C_{23}H_{20}N_2OCl$
Formula weight	374.87
Temperature/K	300
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	13.3763(7)
b/Å	9.9725(5)
c/Å	14.0504(7)
α/°	90
β/°	96.255(4)
γ/°	90
Volume/Å^3	1863.10(16)
Z	4
ρ_{calc}g/cm^3	1.3364
μ/mm^{-1}	1.926
F(000)	787.6
Crystal size/mm^3	0.08 × 0.07 × 0.04
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.66 to 141.54
Index ranges	$-16 \leq h \leq 16$, $-12 \leq k \leq 12$, $-9 \leq l \leq 16$

Reflections collected	7614
Independent reflections	3510 [R_{int} = 0.0287, R_{sigma} = 0.0343]
Data/restraints/parameters	3510/0/250
Goodness-of-fit on F^2	1.082
Final R indexes [I>=2σ (I)]	R_1 = 0.0457, wR_2 = 0.1189
Final R indexes [all data]	R_1 = 0.0636, wR_2 = 0.1395
Largest diff. peak/hole / e $Å^{-3}$	0.20/-0.22

X-ray crystal structure data for 4b,5,12,13 Tetrahydrobenzo[5,6]thiadiazino[3,4-*a*]isoquinoline 6,6-dioxide (3t) CCDC 1478644

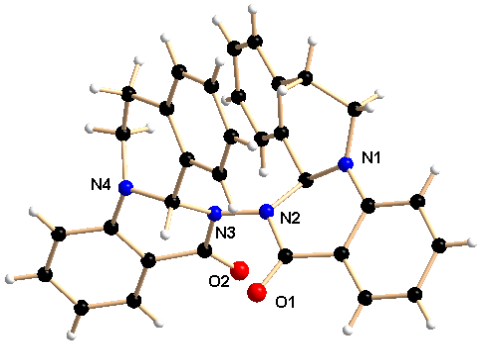


X-ray crystal structure of product **3t**. Thermal ellipsoids are drawn at 50% probability level.

Operator	Jayeeta Battacharyagee
Difractometer	Oxford Super Nova
Empirical formula	$C_{15}H_{14}NO_2S$
Formula weight	286.36
Temperature/K	293
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.9410(4)
b/Å	11.9290(5)
c/Å	13.9233(7)
α/°	90
β/°	90
γ/°	90
Volume/$Å^3$	1318.94(11)
Z	4
$\rho_{calc}g/cm^3$	1.4420
μ/mm^{-1}	2.209

F(000)	603.1
Crystal size/mm^3	0.06 × 0.05 × 0.04
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	9.76 to 141.58
Index ranges	-8 ≤ h ≤ 9, -10 ≤ k ≤ 14, -12 ≤ l ≤ 16
Reflections collected	3421
Independent reflections	2073 [R_{int} = 0.0204, R_{sigma} = 0.0317]
Data/restraints/parameters	2073/0/183
Goodness-of-fit on F^2	1.061
Final R indexes [I>=2σ (I)]	R_1 = 0.0609, wR_2 = 0.1603
Final R indexes [all data]	R_1 = 0.0627, wR_2 = 0.1628
Largest diff. peak/hole / e Å^{-3}	0.56/-0.40
Flack parameter	0.47(9)

X-ray crystal structure data for 12,12',13,13'-Tetrahydro-[5,5'-biisoquinolino[2,1-*a*]quinazoline]-6,6'(4*bH*,4'*bH*)-dione (3ae) CCDC 1478494



X-ray crystal structure of product **3ae**. Thermal ellipsoids are drawn at 50% probability level.

Operator	Jayeeta Battacharyagee
Difractometer	Oxford Super Nova
Empirical formula	$C_{4.57}H_{3.71}N_{0.57}O_{0.29}$
Formula weight	284.91
Temperature/K	293
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	10.3261(8)
b/Å	15.0211(8)
c/Å	16.2026(9)
α/°	90

β/°	90
γ/°	90
Volume/Å^3	2513.2(3)
Z	7
ρ_{calc}g/cm^3	1.3176
μ/mm^{-1}	0.668
F(000)	1051.2
Crystal size/mm^3	0.4 × 0.2 × 0.2
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.02 to 142.46
Index ranges	$-12 \leq h \leq 6$, $-18 \leq k \leq 16$, $-19 \leq l \leq 15$
Reflections collected	6242
Independent reflections	4258 [R_{int} = 0.0319, R_{sigma} = 0.0831]
Data/restraints/parameters	4258/0/342
Goodness-of-fit on F^2	1.026
Final R indexes [I>=2σ (I)]	R_1 = 0.0668, wR_2 = 0.1464
Final R indexes [all data]	R_1 = 0.1106, wR_2 = 0.1876
Largest diff. peak/hole / e Å^{-3}	0.25/-0.32
Flack parameter	0.2(8)

Mechanistic experimental study

To probe the

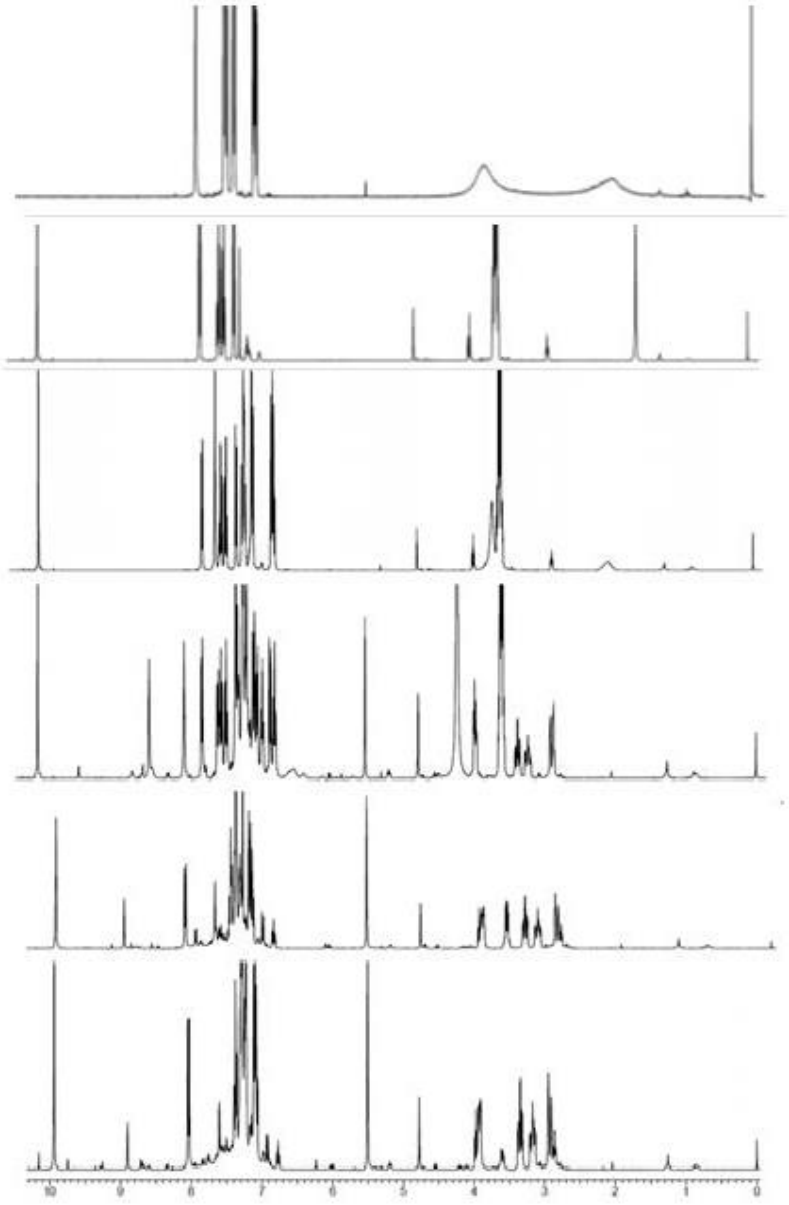


Table 2. Optimization for increasing the diastereoselectivity[a]

Entry	Solvent	Tempt (°C)	Time (min)	dr[c] (cis:trans)[d]
1	DCE	rt	90	4:3

2	DCE	reflux	30	4:3
2	MeOH	rt	90	4:3
3	MeOH	reflux	30	4:3
4	1,4-dioxane	rt	90	4:3
5	1,4-dioxane	reflux	30	4:3
6	CH_3CN	rt	90	4:3
7	CH_3CN	reflux	30	4:3

[a]Reaction conditions: **1a** (0.23 mmol), **2S**$_7$ (0.23 mmol) and 1 mL of solvent; [b] Isolated yields after column chromatography; [c]The dr value was determined by NMR spectroscopy of the crude reaction mixture; [d] Mixture of cis:trans diastereoisomers in 4:3 ratio confirmed by NOESY spectroscopy.

Copies of ^{1}H and ^{13}C NMR spectra of compounds 36a-36ac

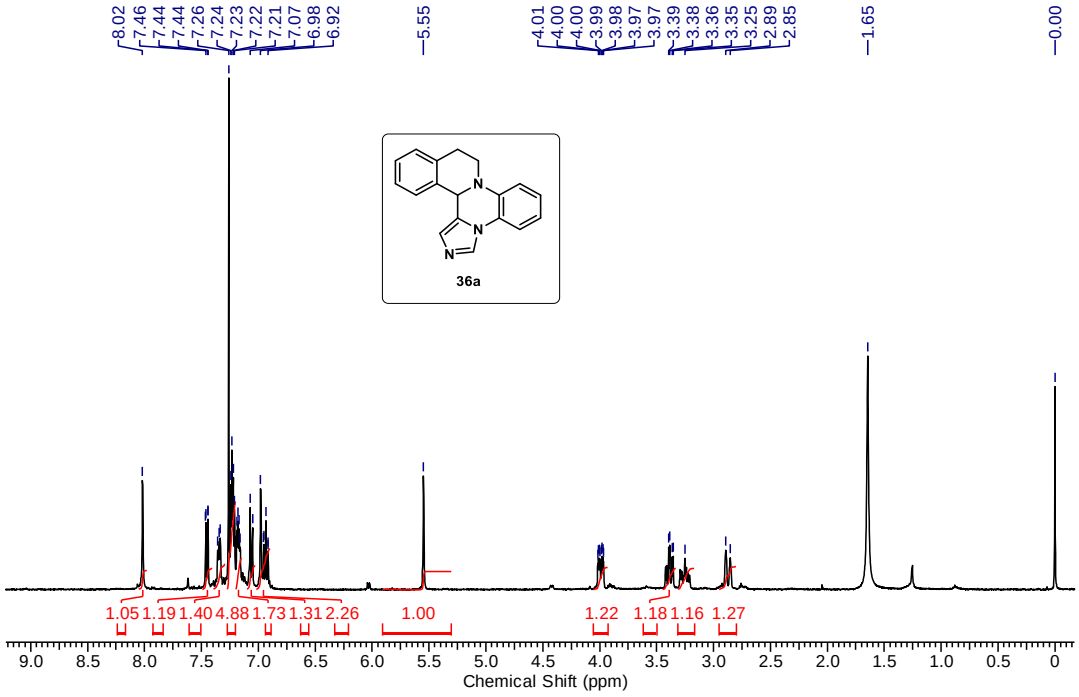


Figure 6. ^{1}H NMR (400 MHz) spectrum of compound **36a** in $CDCl_3$.

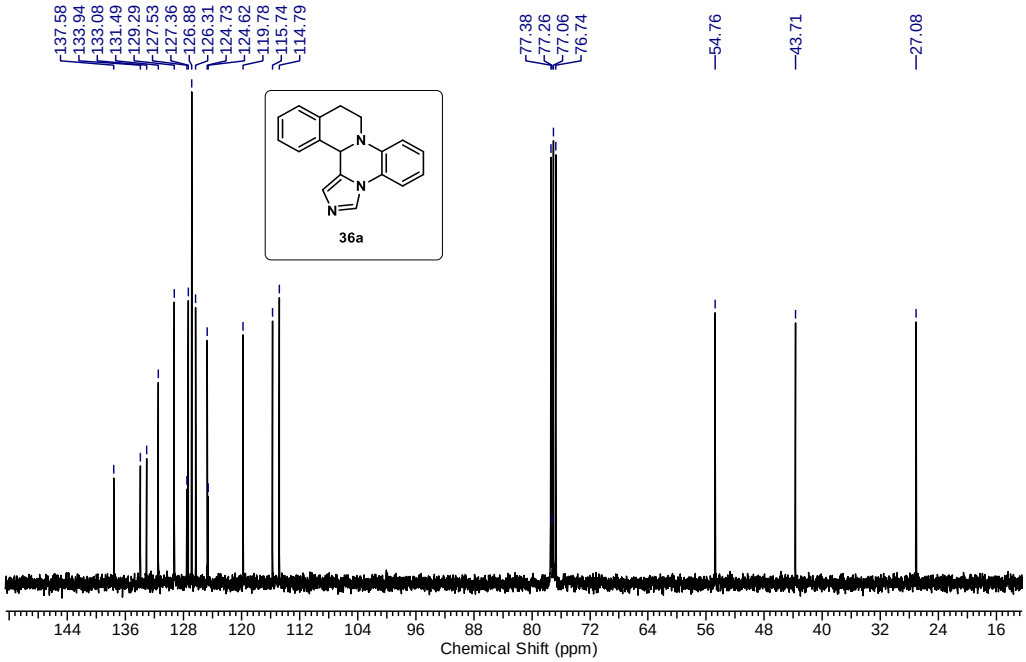


Figure 7. ^{13}C NMR (100 MHz) spectrum of compound **36a** in $CDCl_3$.

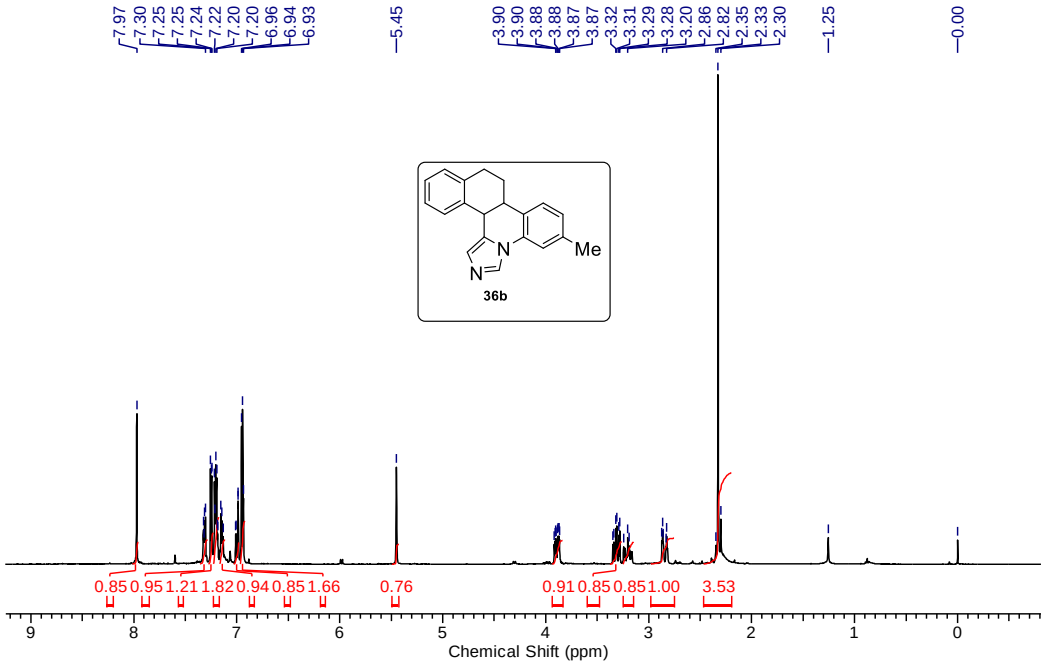


Figure 8. ^{1}H NMR (400 MHz) spectrum of compound **36b** in $CDCl_3$.

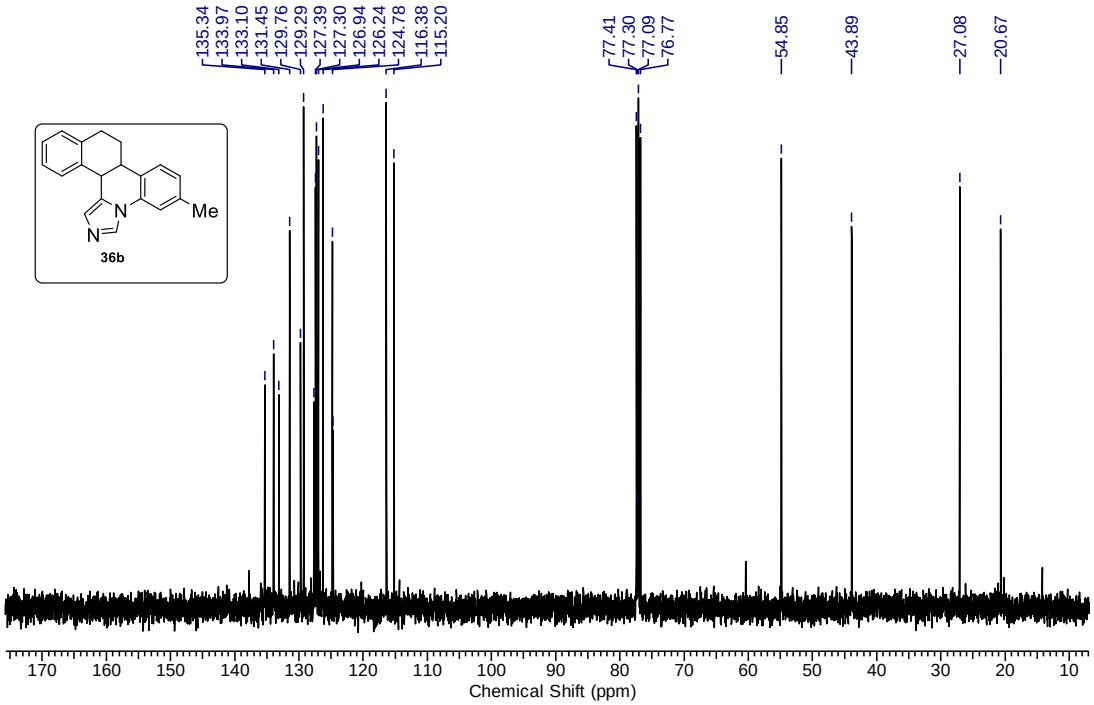


Figure 9. ^{13}C NMR (100 MHz) spectrum of compound **36b** in $CDCl_3$.

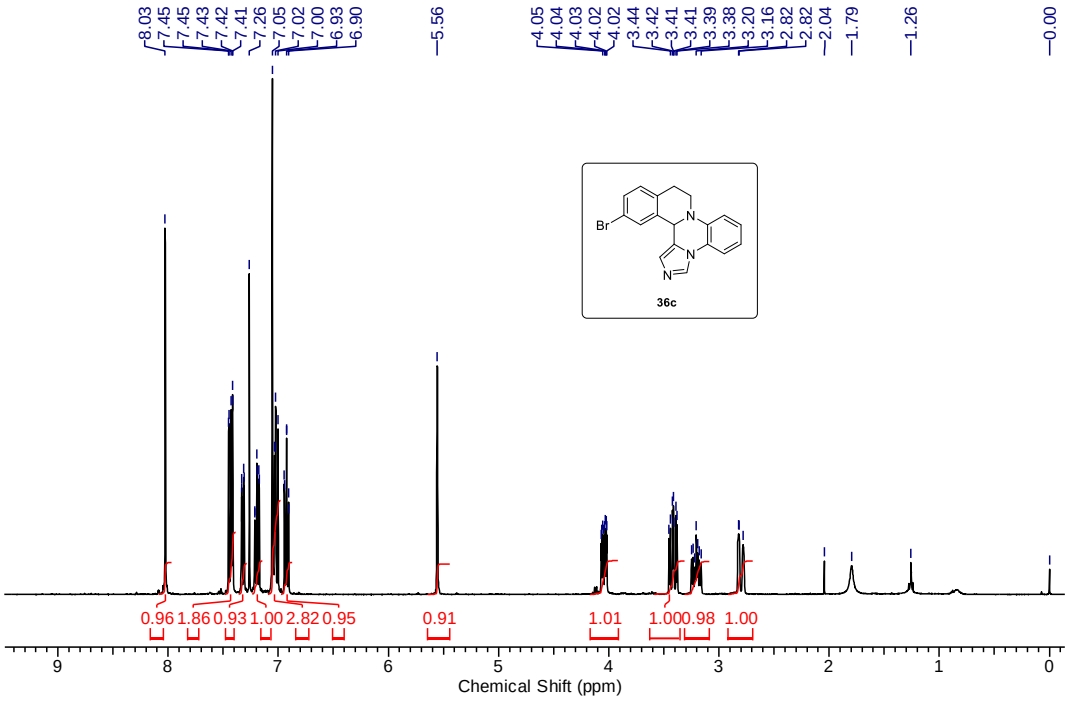


Figure 10. ^{1}H NMR (400 MHz) spectrum of compound **36c** in $CDCl_3$.

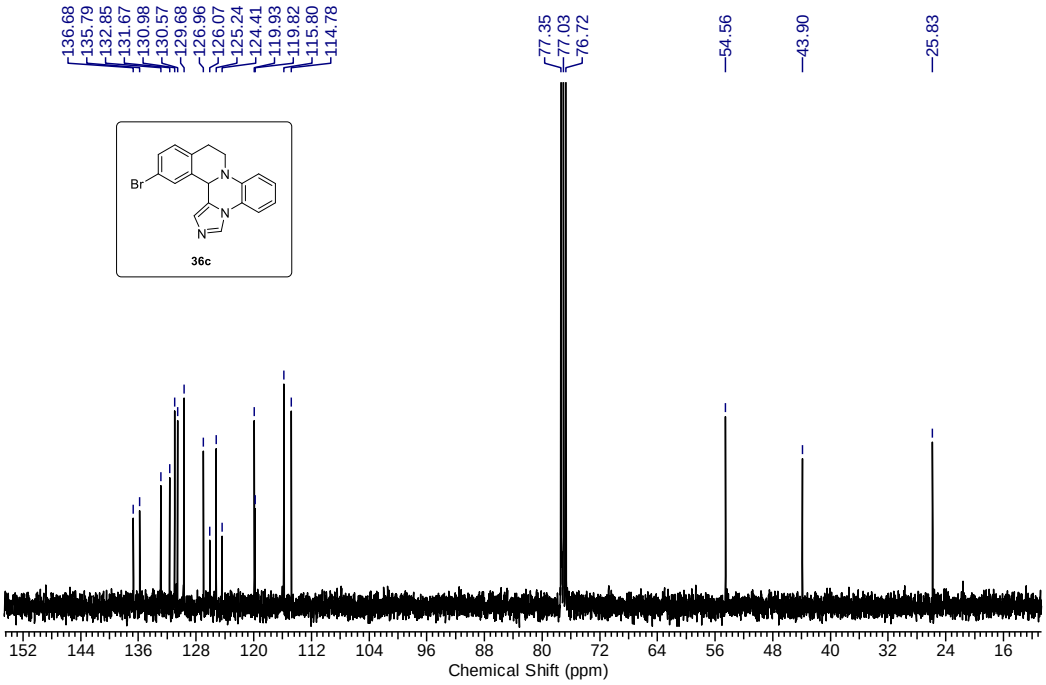


Figure 11. ^{13}C NMR (100 MHz) spectrum of compound **36c** in $CDCl_3$.

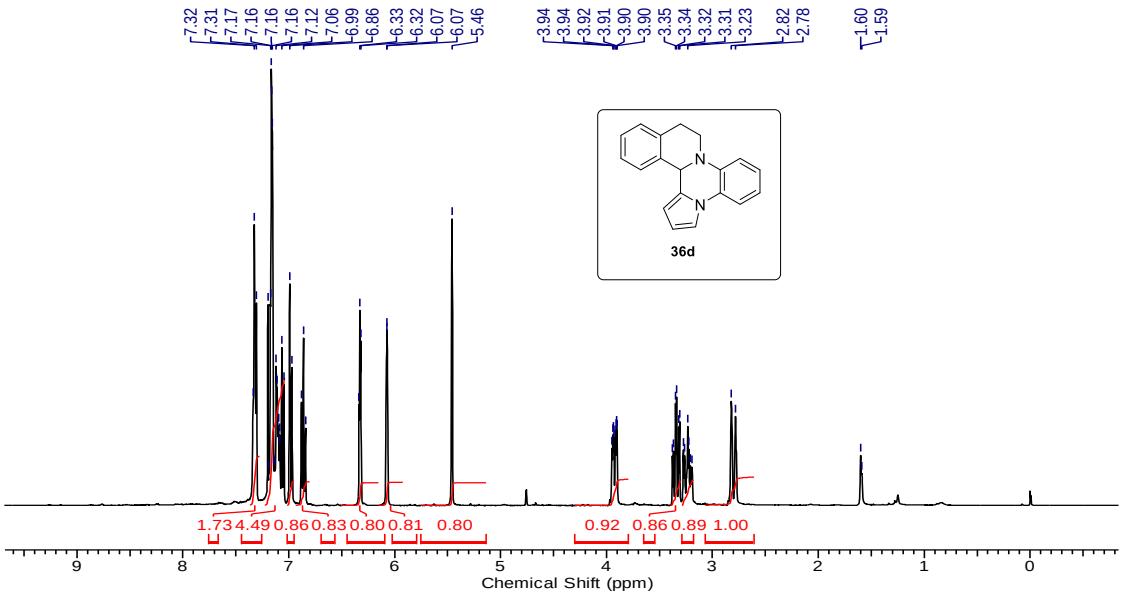


Figure 12. ^{1}H NMR (400 MHz) spectrum of compound **36d** in $CDCl_3$.

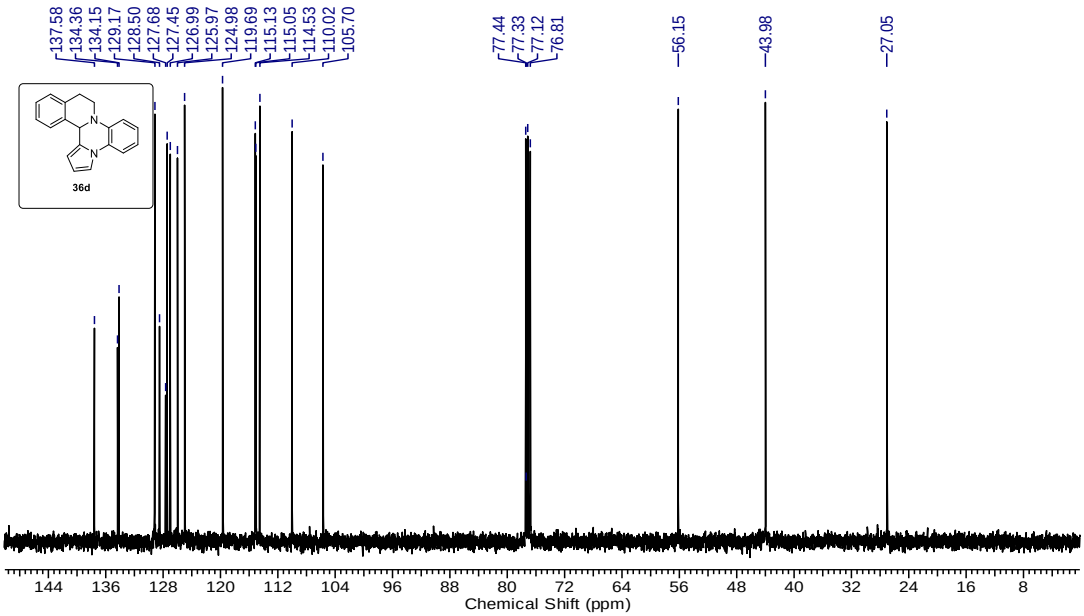


Figure 13. ^{13}C NMR (100 MHz) spectrum of compound **36d** in $CDCl_3$.

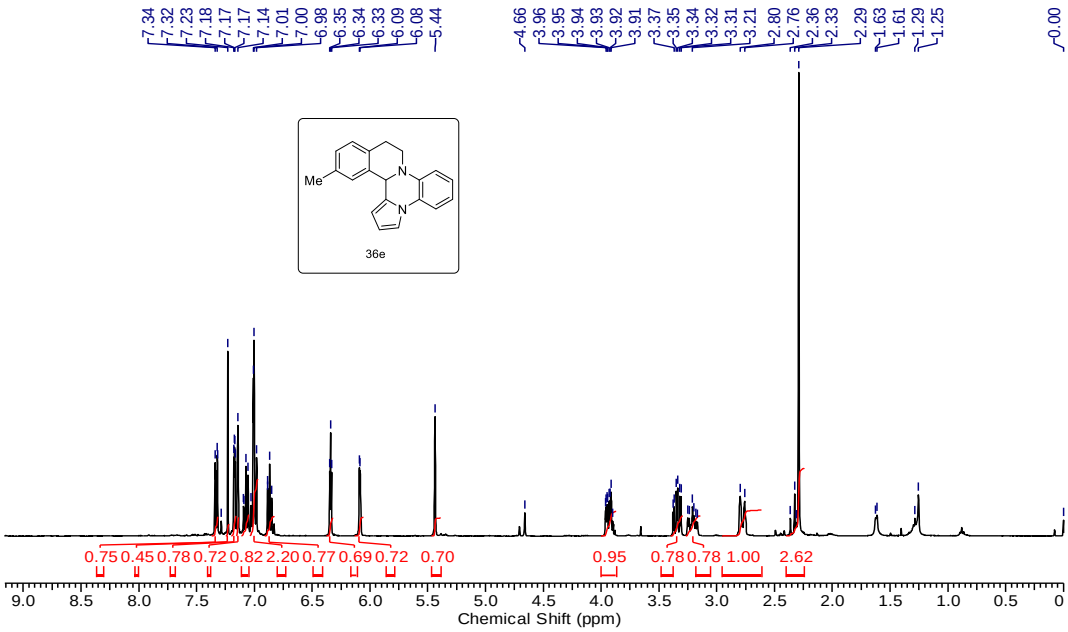


Figure 14. ^{1}H NMR (400 MHz) spectrum of compound **36e** in $CDCl_3$.

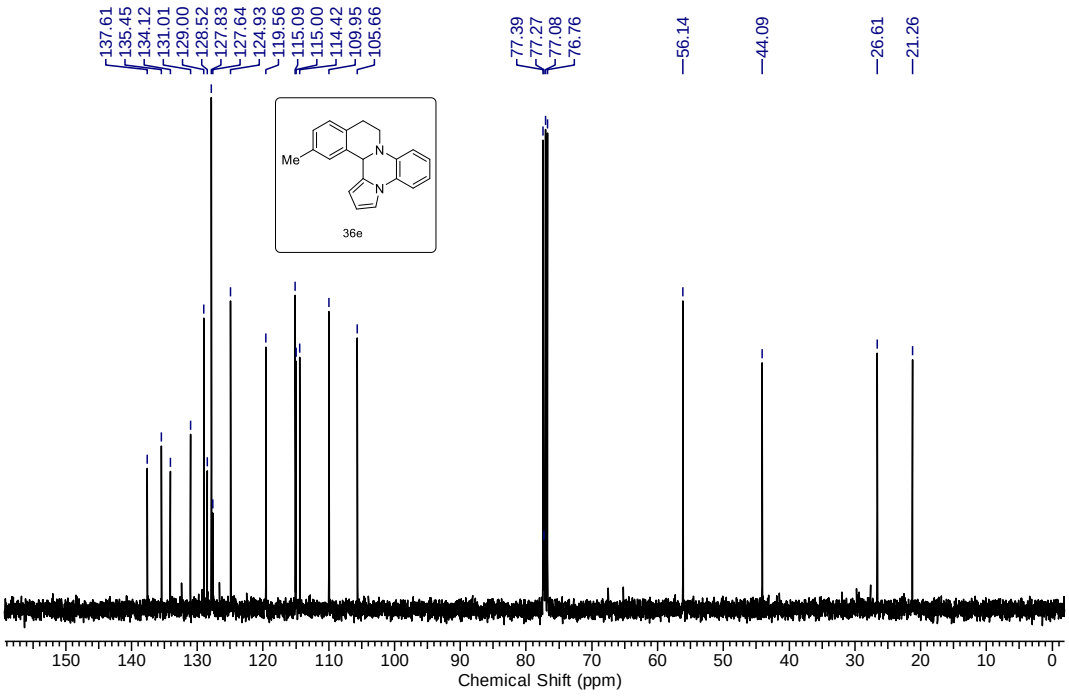


Figure 15. ^{13}C NMR (100 MHz) spectrum of compound **36e** in $CDCl_3$.

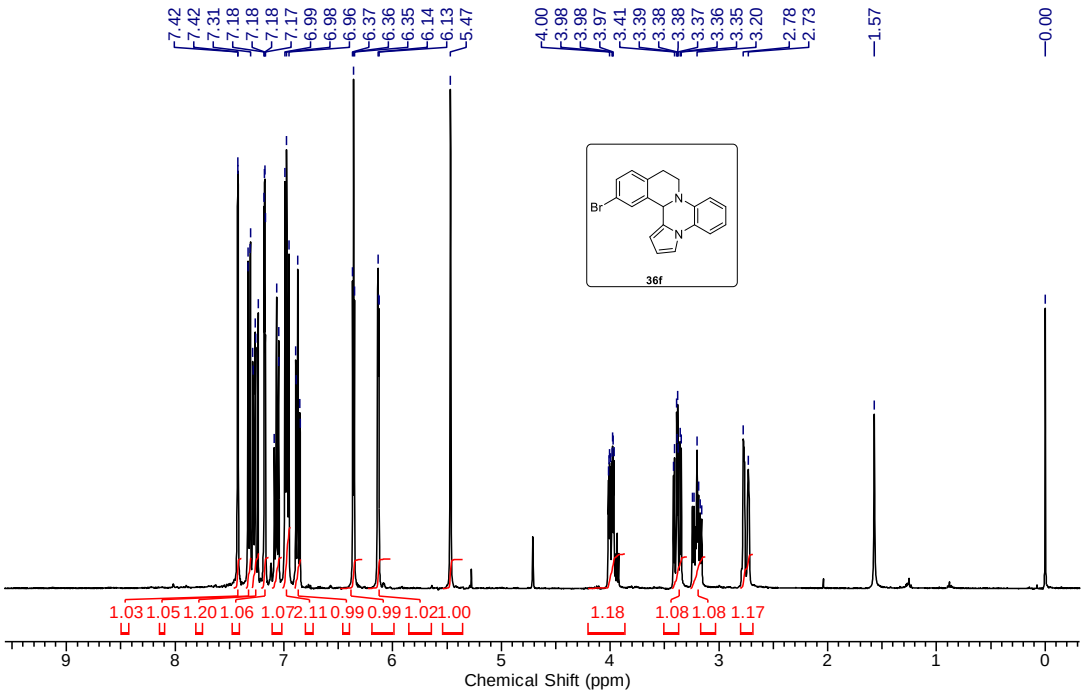


Figure 16. ^{1}H NMR (400 MHz) spectrum of compound **36f** in $CDCl_3$.

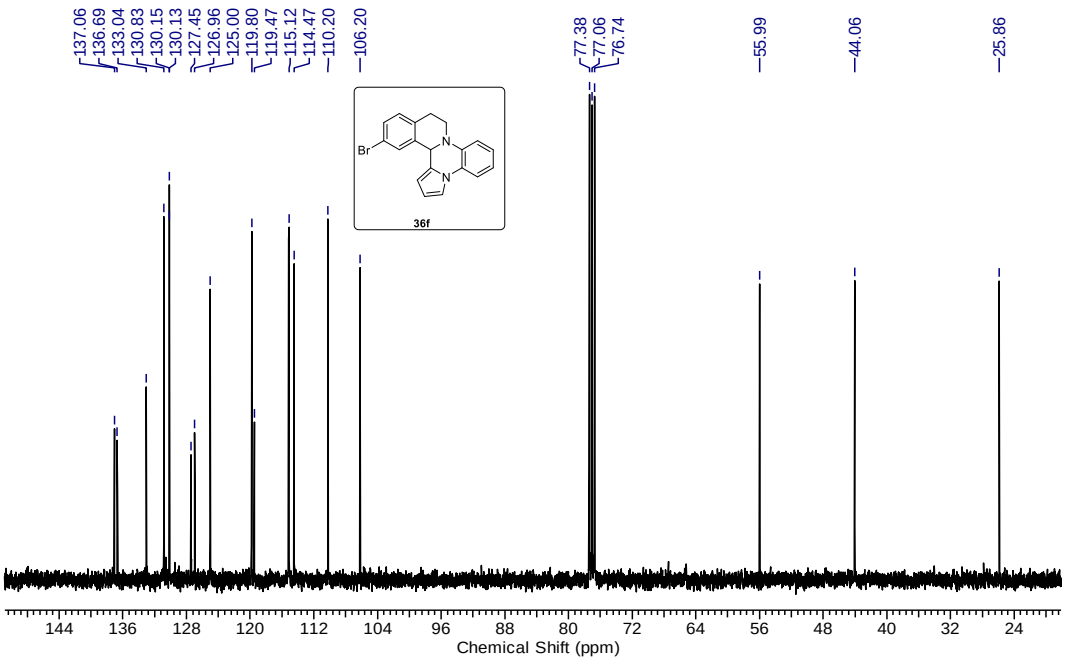


Figure 17. ^{13}C NMR (100 MHz) spectrum of compound **36f** in $CDCl_3$.

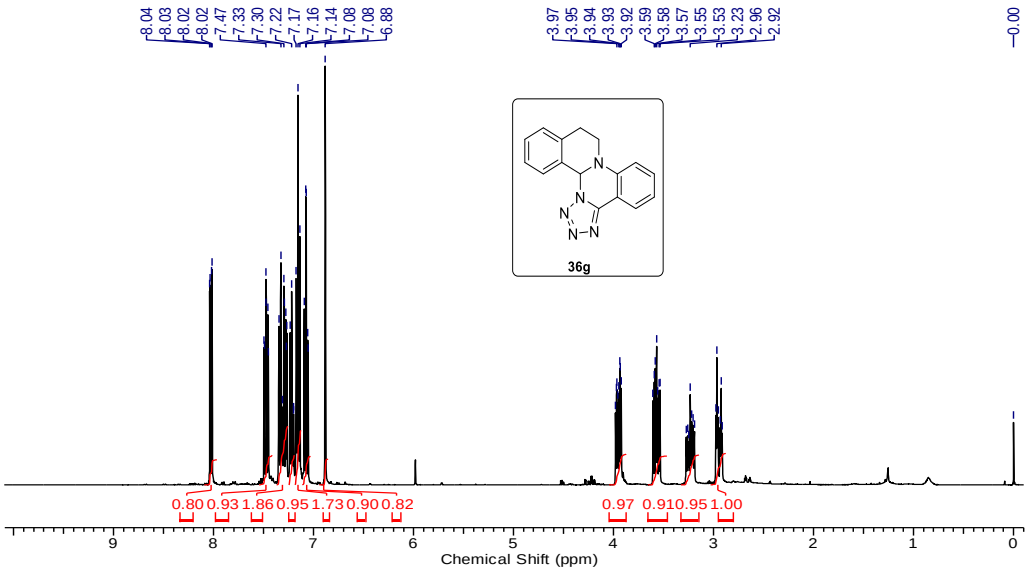


Figure 18. ^{1}H NMR (400 MHz) spectrum of compound **36g** in $CDCl_3$.

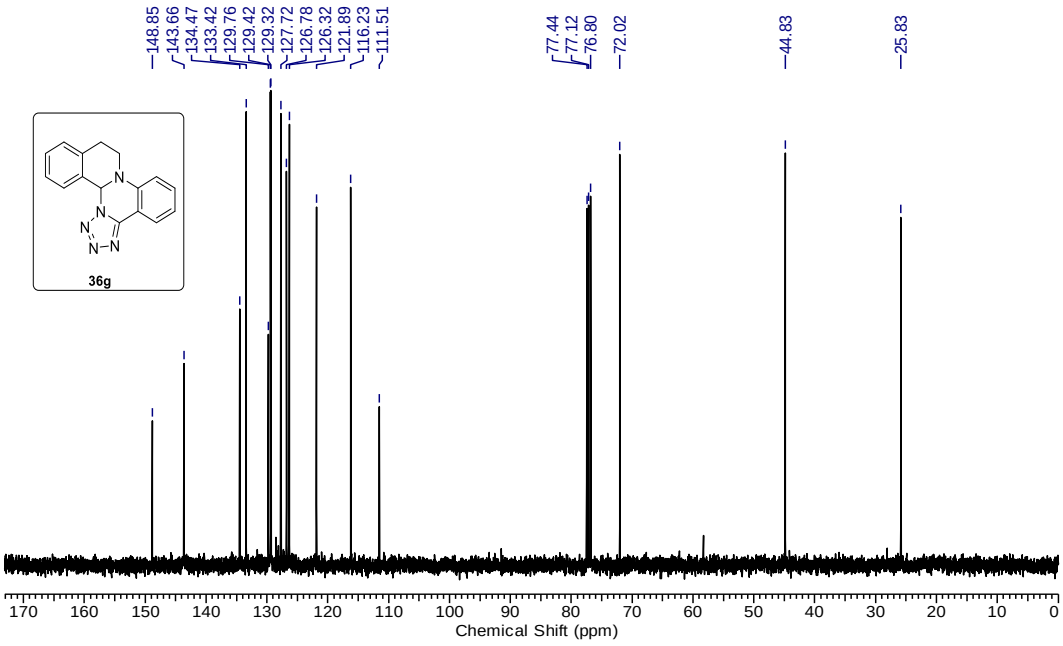


Figure 19. ^{13}C NMR (100 MHz) spectrum of compound **36g** in $CDCl_3$

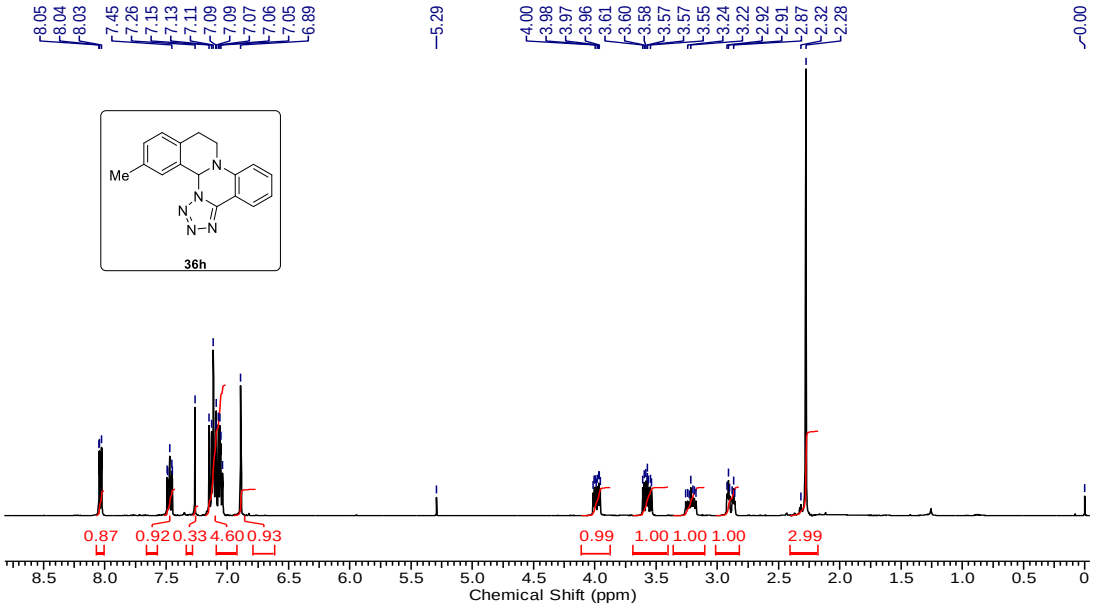


Figure 20. ^{1}H NMR (400 MHz) spectrum of compound **36h** in $CDCl_3$.

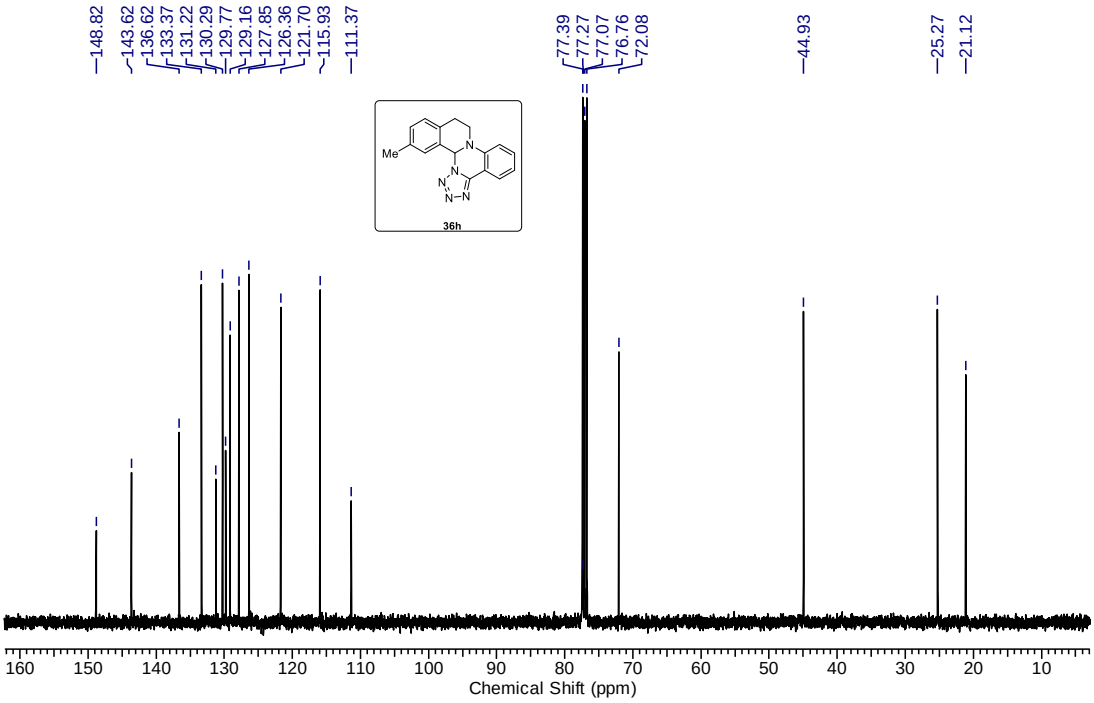


Figure 21. ^{13}C NMR (100 MHz) spectrum of compound **36h** in $CDCl_3$

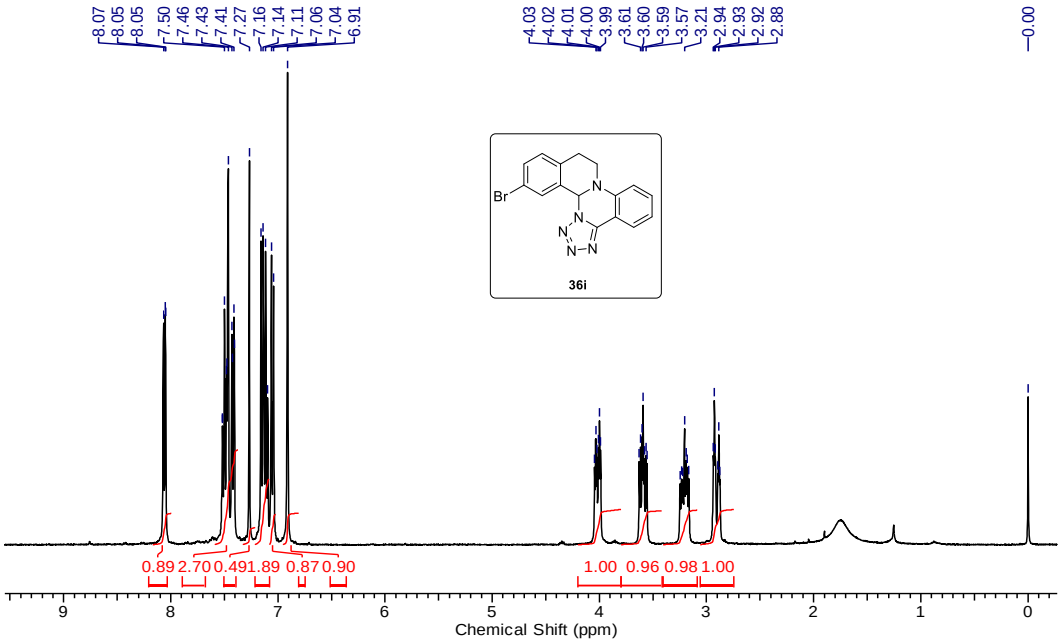


Figure 22. ^{1}H NMR (400 MHz) spectrum of compound **36i** in $CDCl_3$.

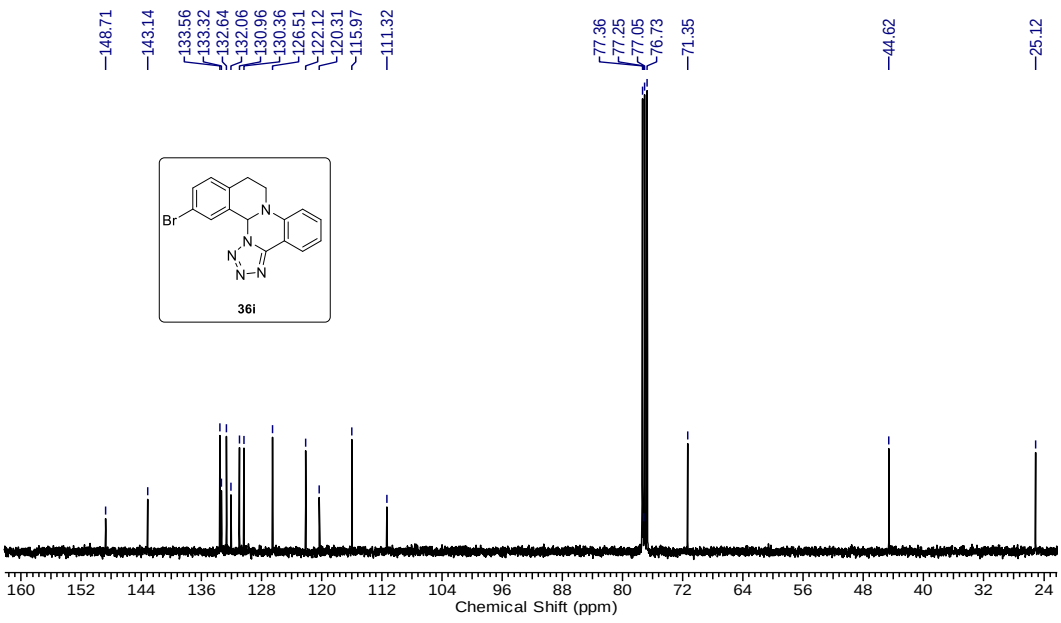


Figure 23. ^{13}C NMR (100 MHz) spectrum of compound **36i** in $CDCl_3$

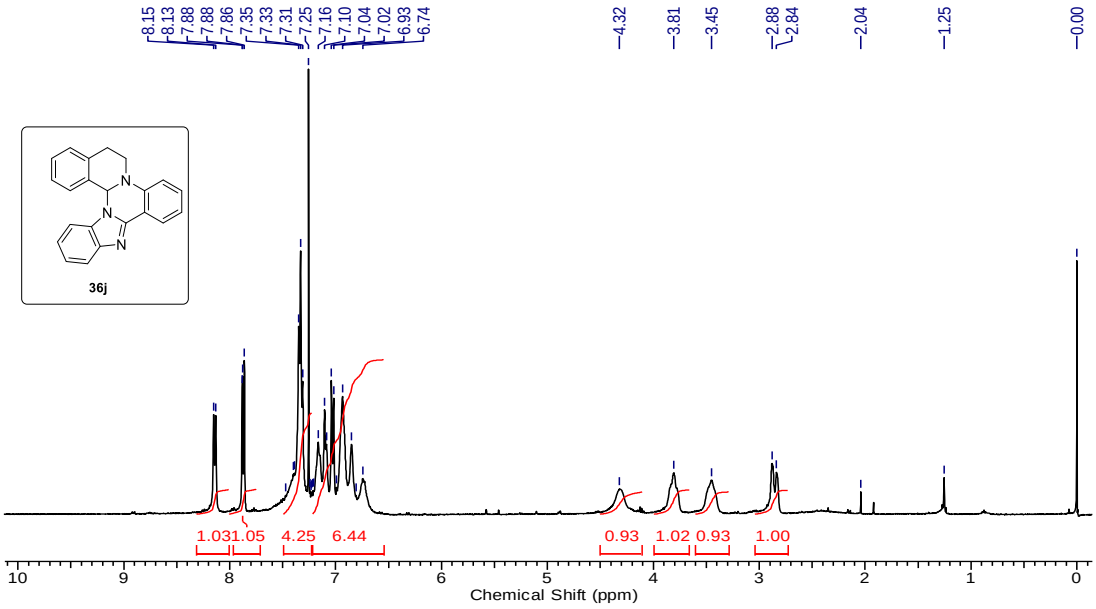


Figure 24. ^{1}H NMR (400 MHz) spectrum of compound **36j** in $CDCl_3$.

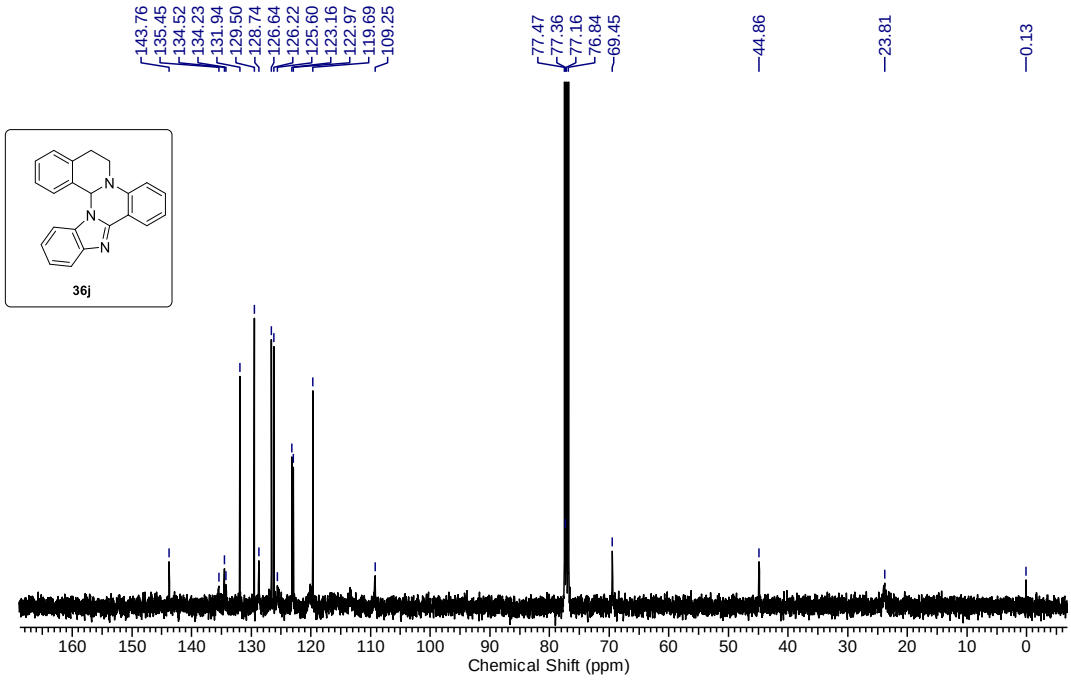


Figure 25. ^{13}C NMR (100 MHz) spectrum of compound **36j** in $CDCl_3$

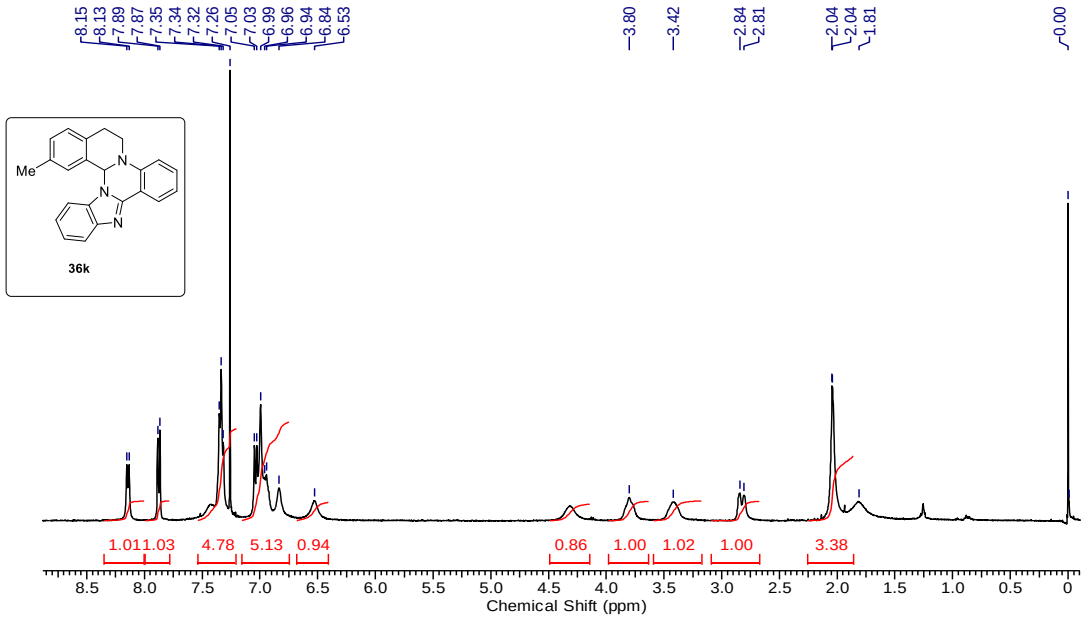


Figure 26. ^{1}H NMR (400 MHz) spectrum of compound **36k** in $CDCl_3$.

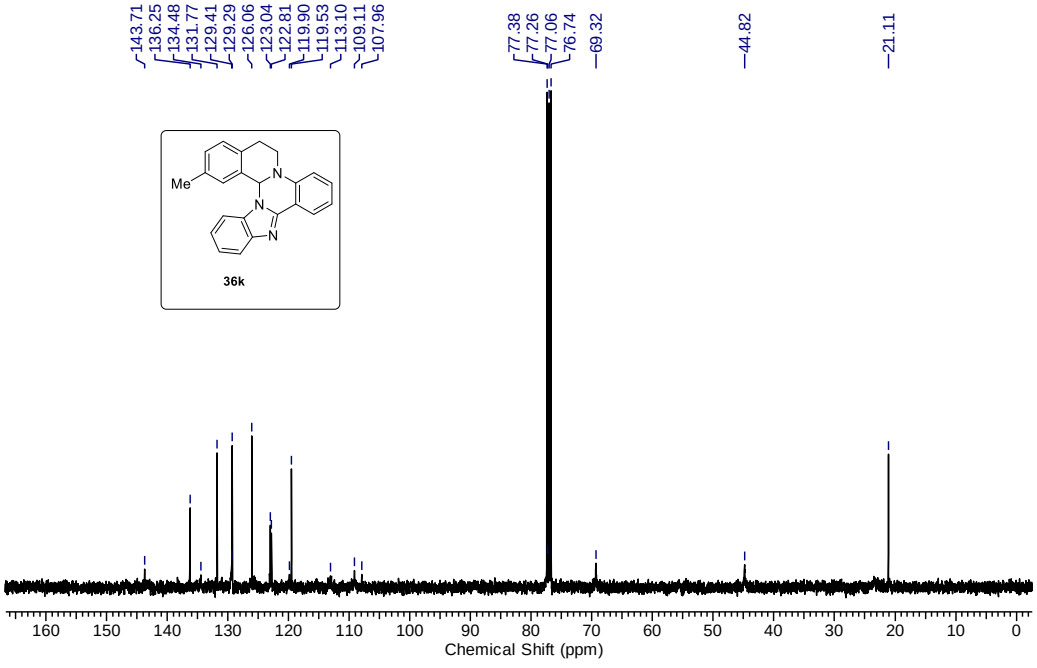


Figure 27. ^{13}C NMR (100 MHz) spectrum of compound **36k** in $CDCl_3$

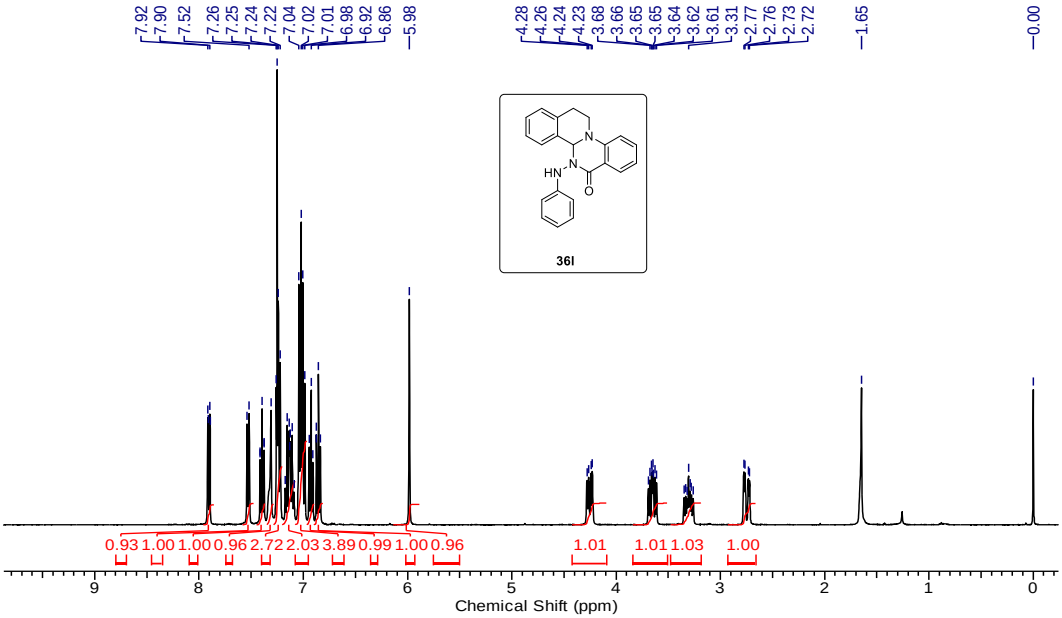


Figure 28. ^{1}H NMR (400 MHz) spectrum of compound **36l** in $CDCl_3$.

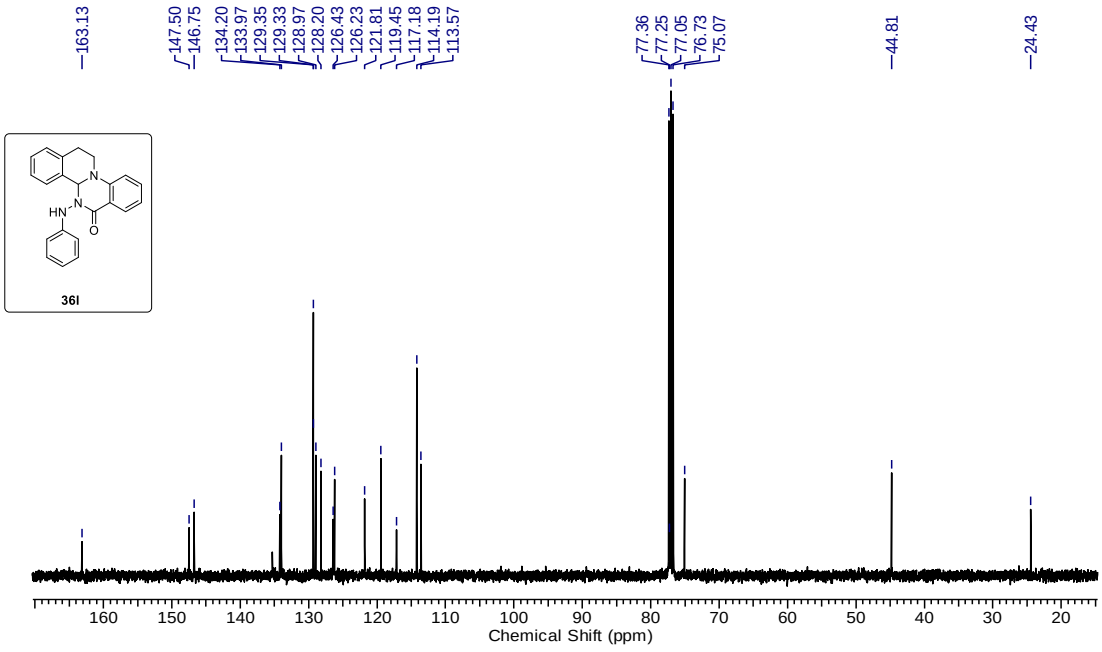


Figure 29. ^{13}C NMR (100 MHz) spectrum of compound **36l** in $CDCl_3$

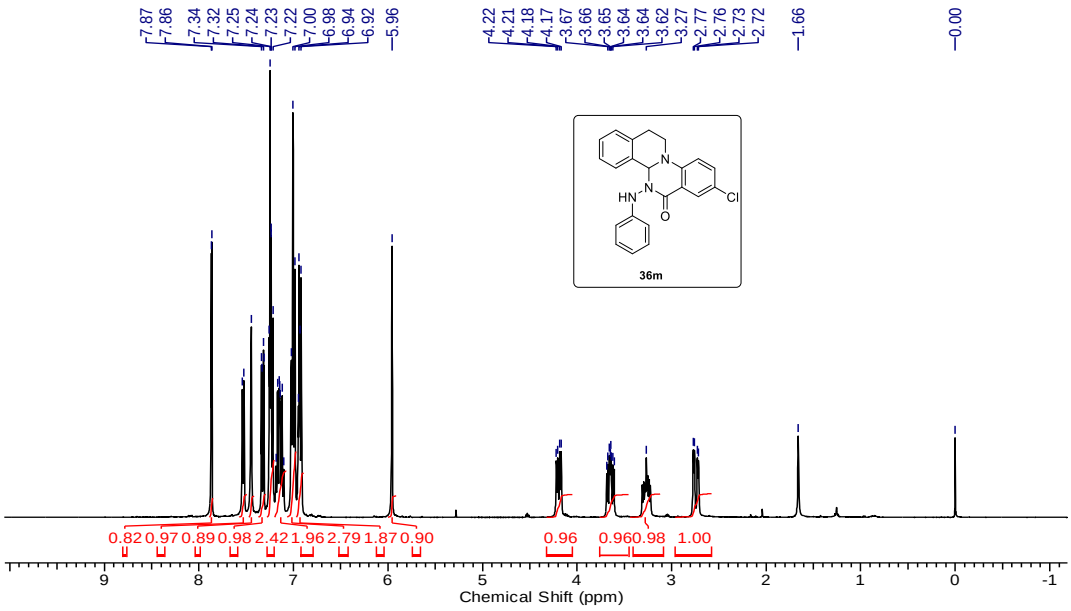


Figure 30. ^{1}H NMR (400 MHz) spectrum of compound **36m** in $CDCl_3$.

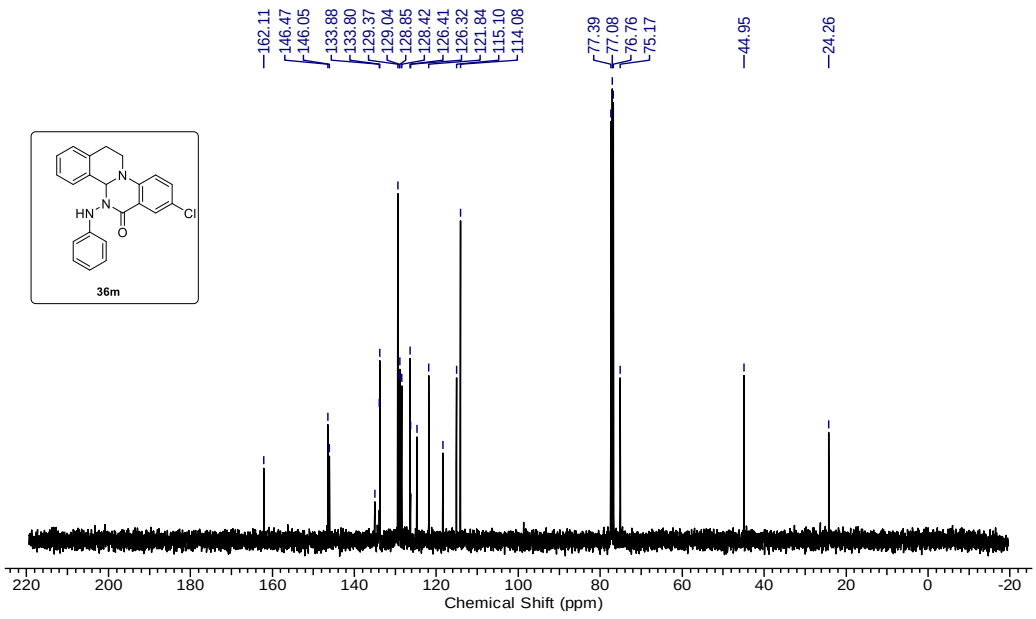


Figure 31. ^{13}C NMR (100 MHz) spectrum of compound **36m** in $CDCl_3$

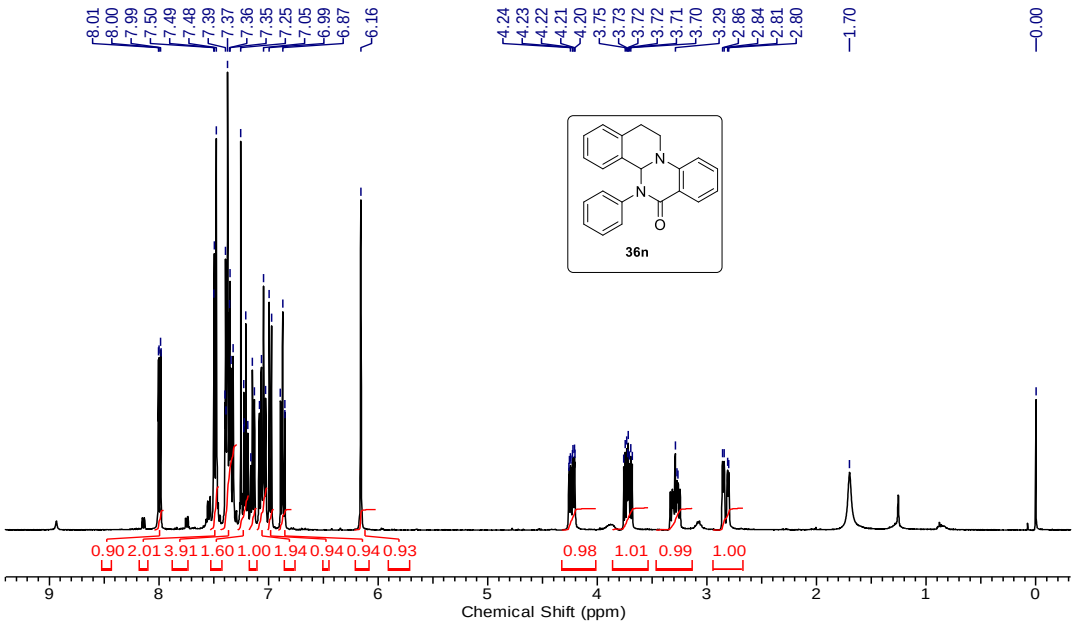


Figure 32. ^{1}H NMR (400 MHz) spectrum of compound **36n** in $CDCl_3$.

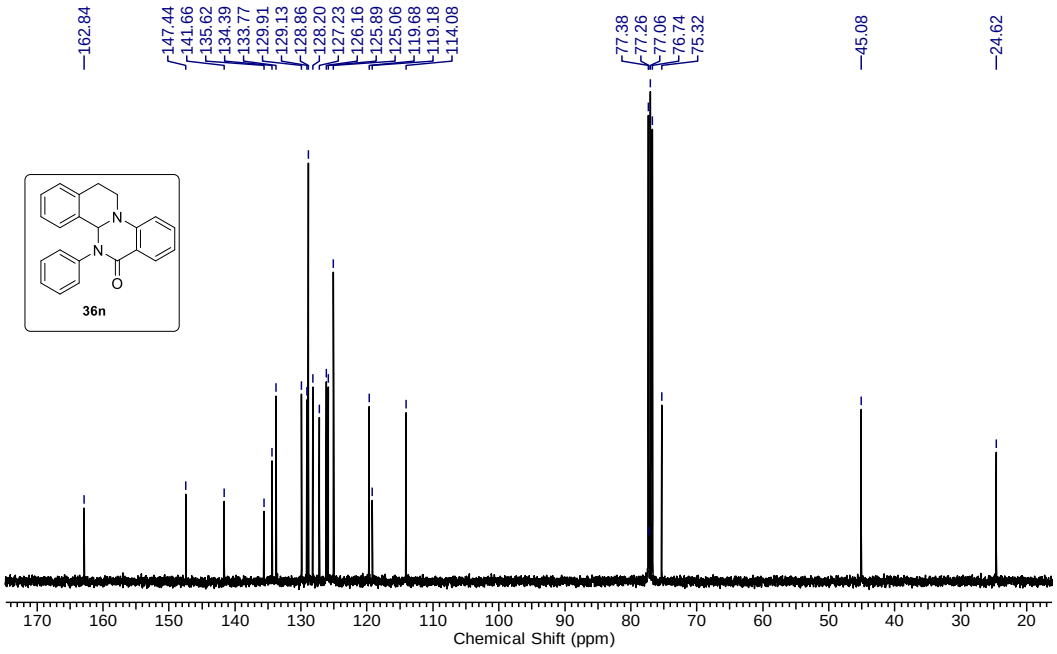


Figure 33. ^{13}C NMR (100 MHz) spectrum of compound **36n** in $CDCl_3$

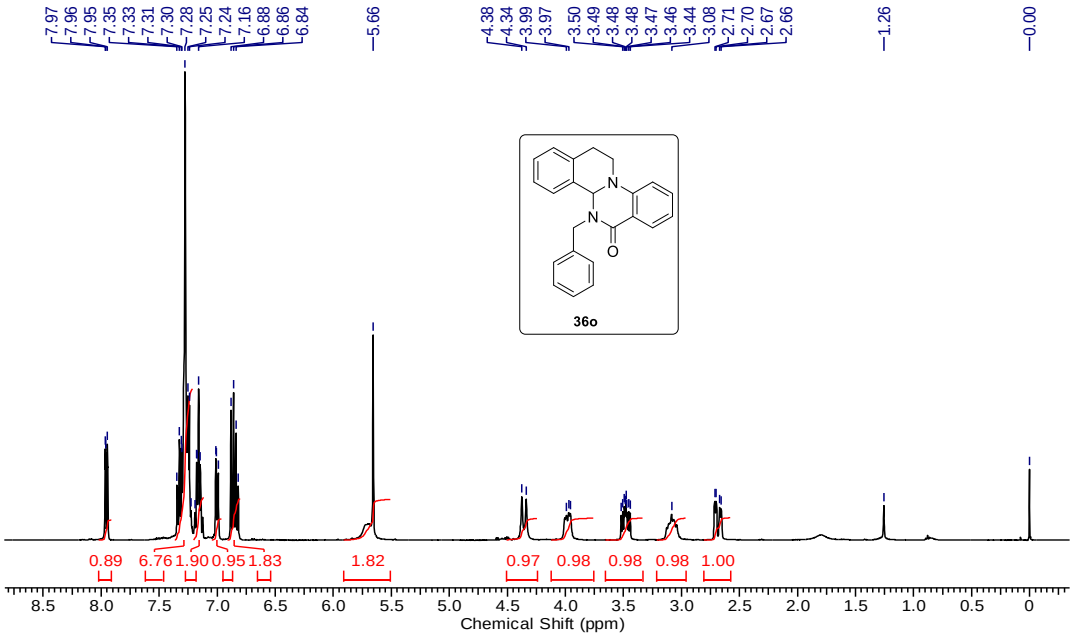


Figure 34. ^{1}H NMR (400 MHz) spectrum of compound **36o** in $CDCl_3$.

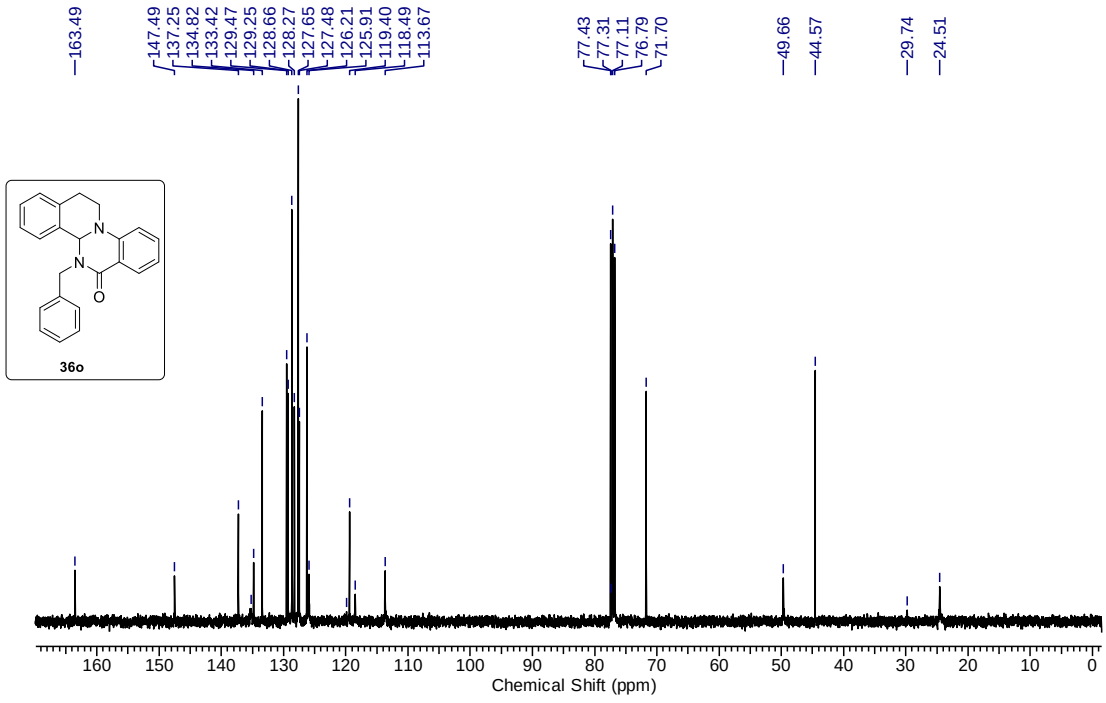


Figure 35. ^{13}C NMR (100 MHz) spectrum of compound **36o** in $CDCl_3$

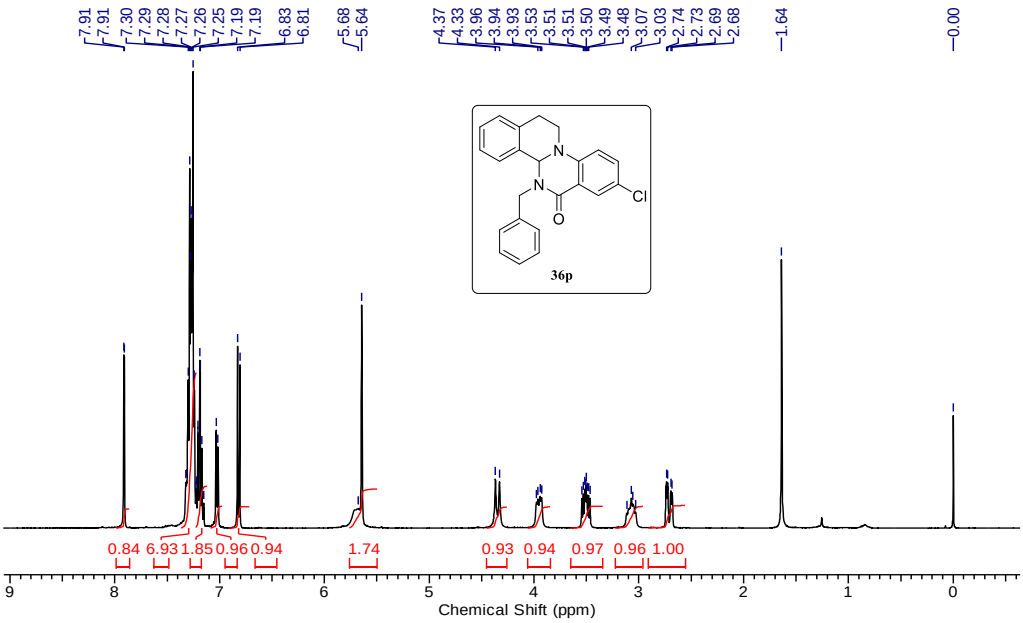


Figure 36. ^{1}H NMR (400 MHz) spectrum of compound **3p** in $CDCl_3$.

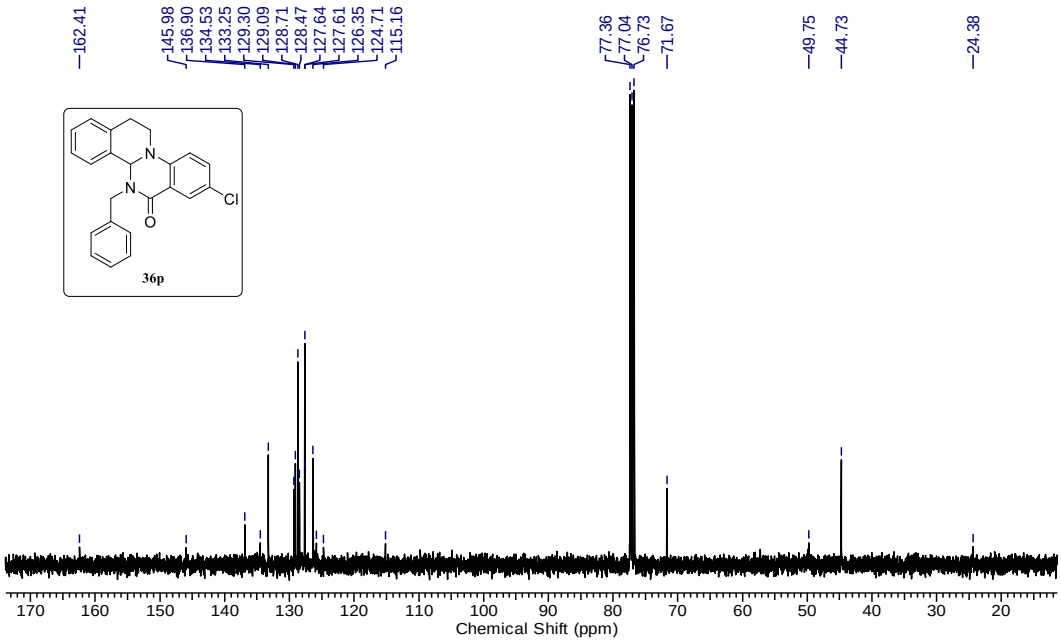


Figure 37. ^{13}C NMR (100 MHz) spectrum of compound **36p** in $CDCl_3$

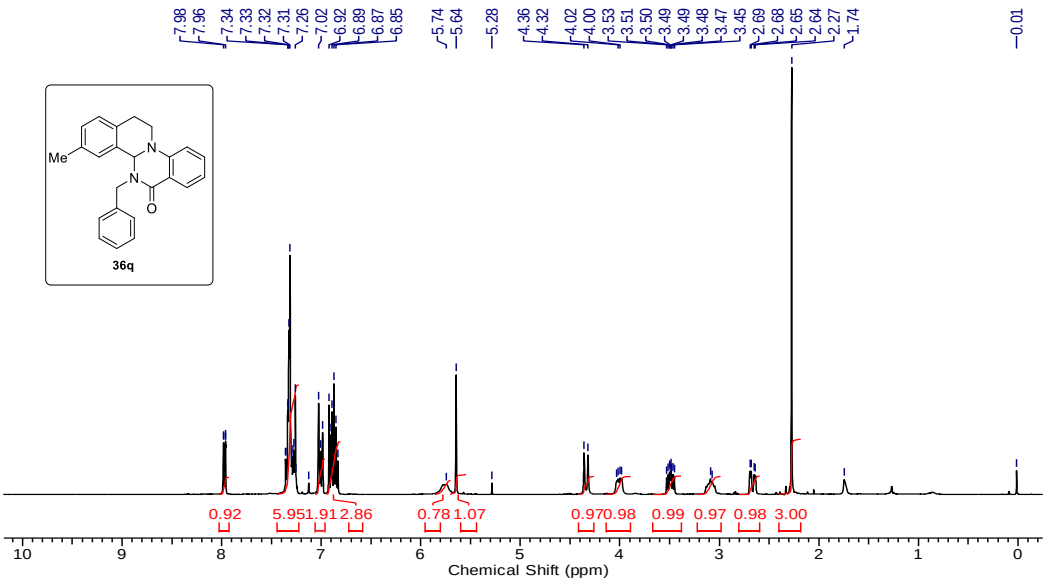


Figure 38. ^{1}H NMR (400 MHz) spectrum of compound **3q** in $CDCl_3$.

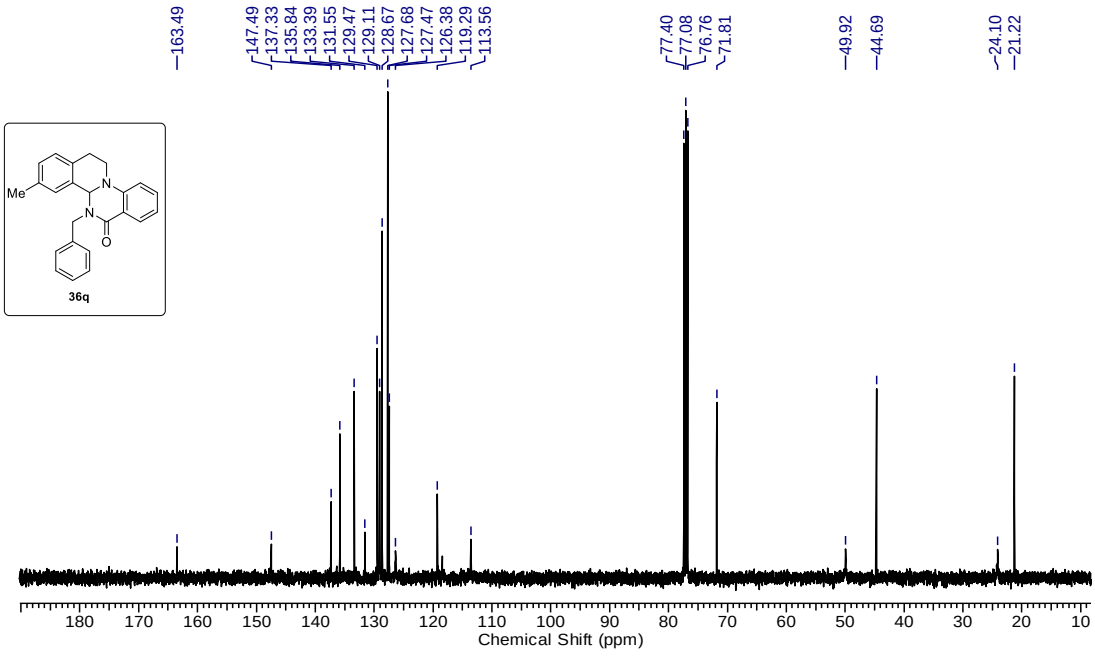


Figure 39. ^{13}C NMR (100 MHz) spectrum of compound **36q** in $CDCl_3$

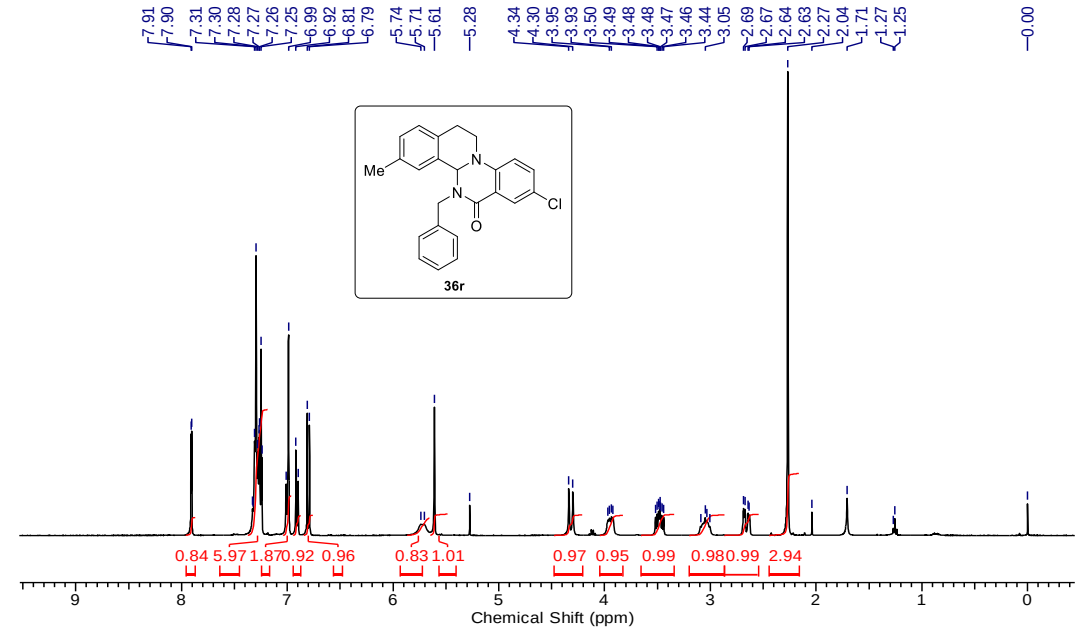


Figure 40. ^{1}H NMR (400 MHz) spectrum of compound **36r** in $CDCl_3$.

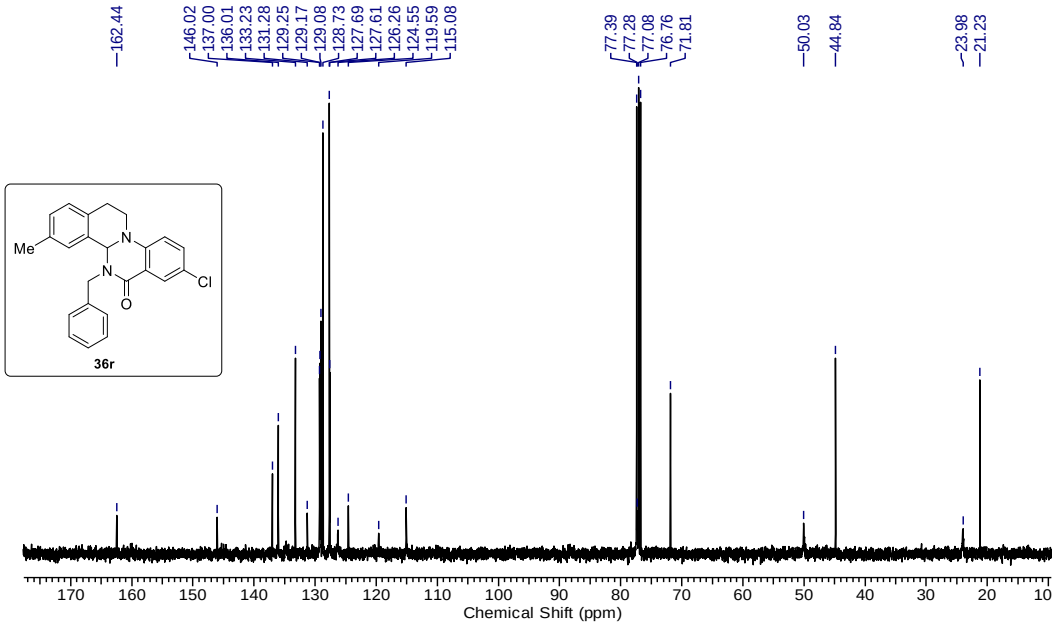


Figure 41. ^{13}C NMR (100 MHz) spectrum of compound **36r** in $CDCl_3$

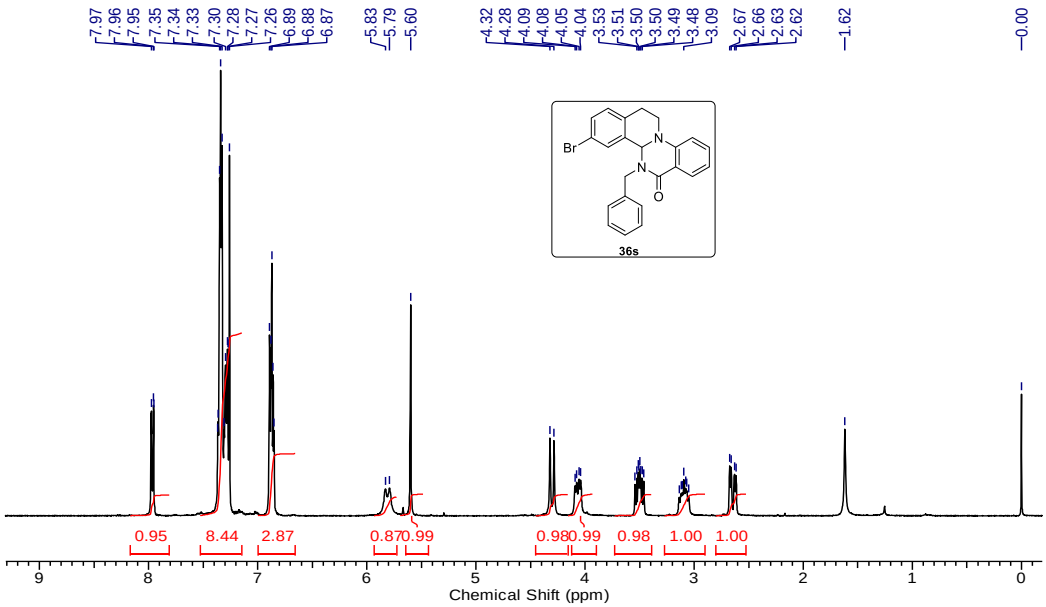


Figure 42. ^{1}H NMR (400 MHz) spectrum of compound **36s** in $CDCl_3$.

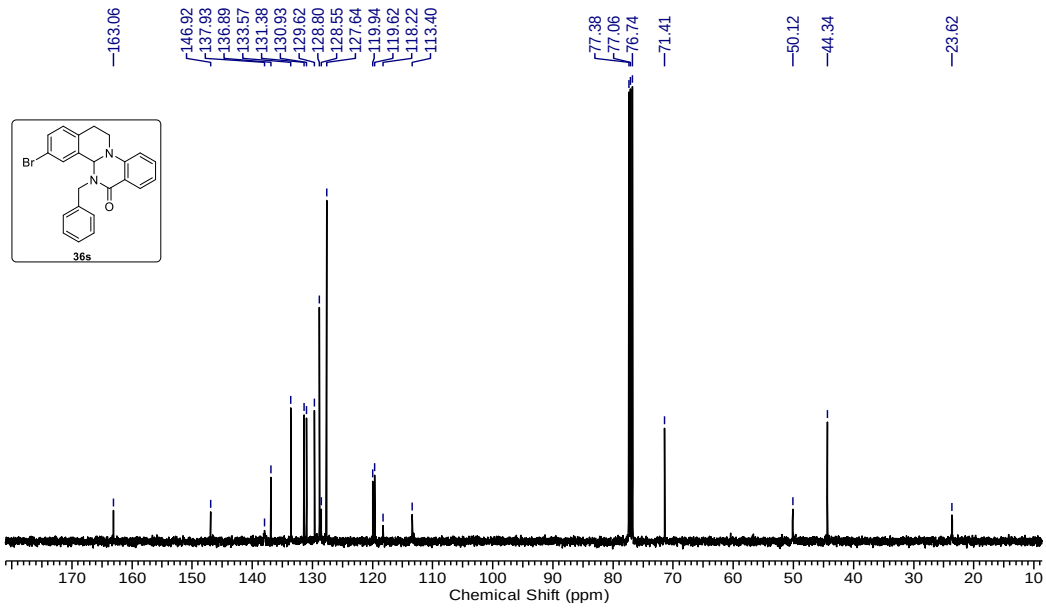


Figure 43. ^{13}C NMR (100 MHz) spectrum of compound **36s** in $CDCl_3$

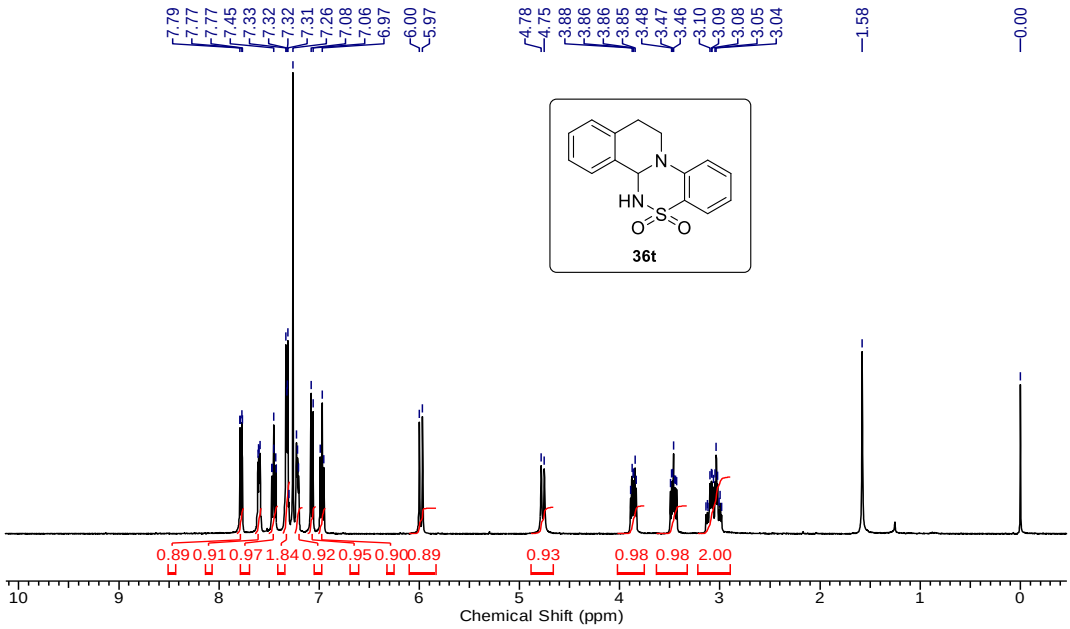


Figure 44. ^{1}H NMR (400 MHz) spectrum of compound **36t** in $CDCl_3$.

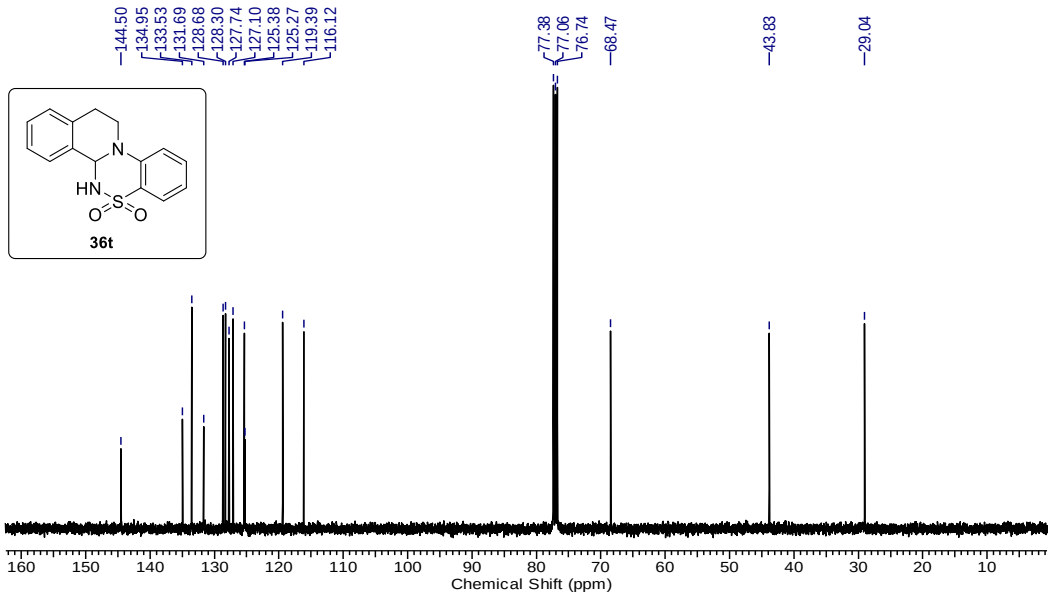


Figure 45. ^{13}C NMR (100 MHz) spectrum of compound **3t** in $CDCl_3$

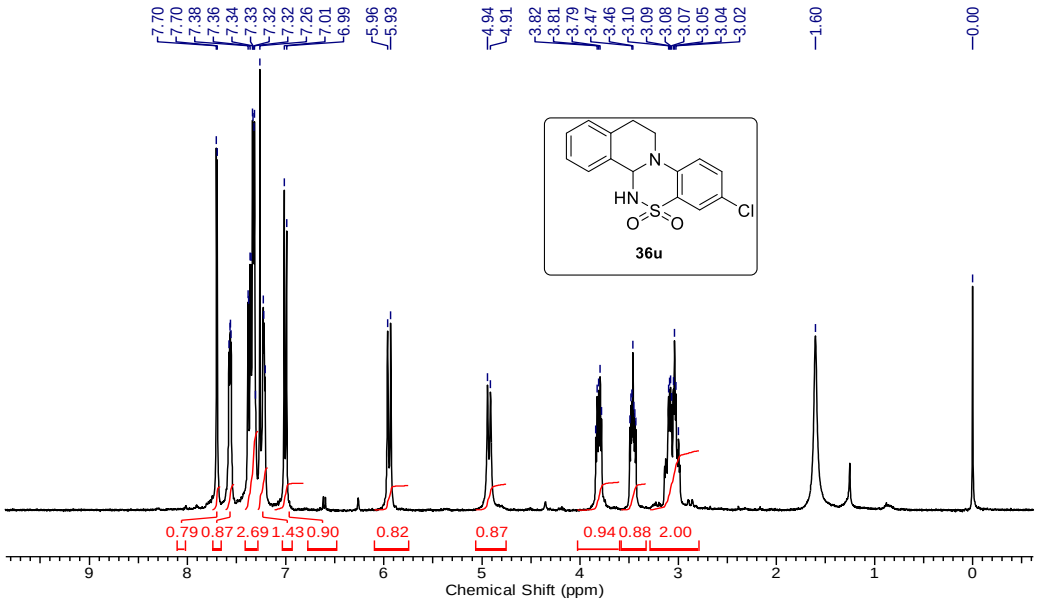


Figure 46. ^{1}H NMR (400 MHz) spectrum of compound **36u** in $CDCl_3$.

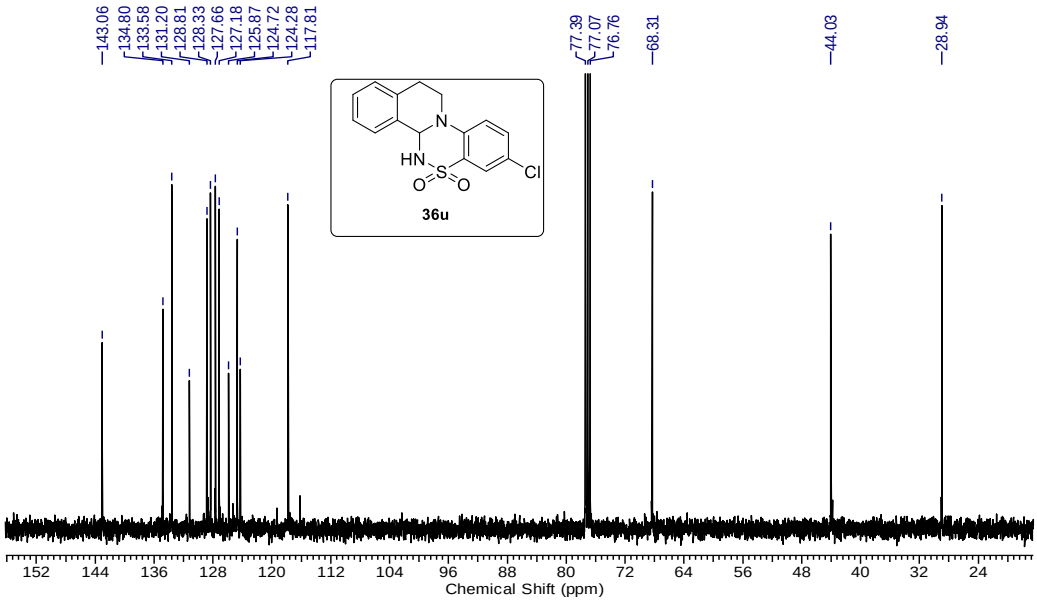


Figure 47. ^{13}C NMR (100 MHz) spectrum of compound **36u** in $CDCl_3$

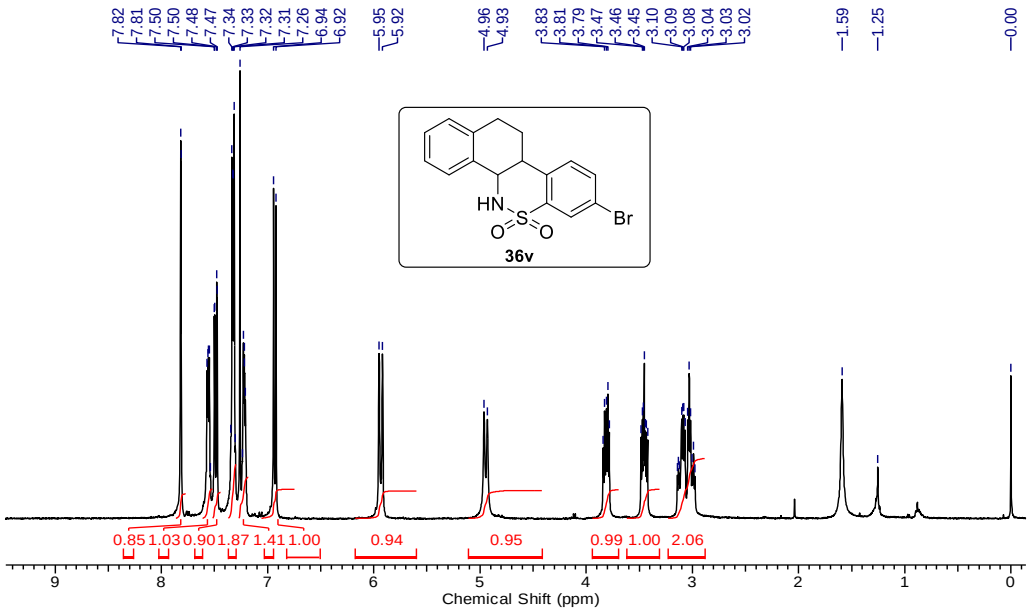


Figure 48. ^{1}H NMR (400 MHz) spectrum of compound **36v** in $CDCl_3$.

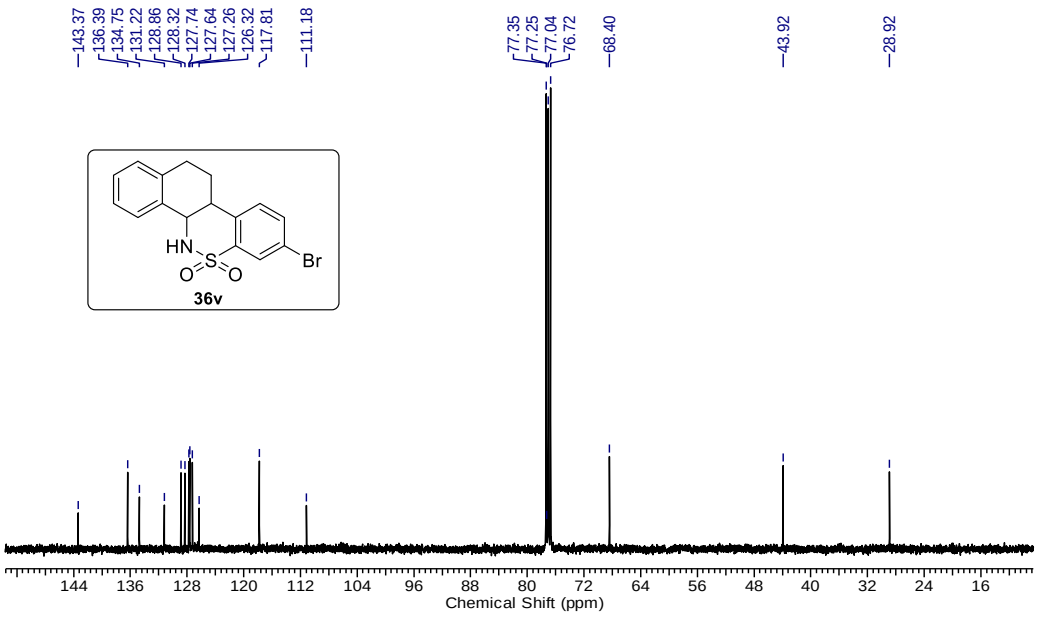


Figure 49. ^{13}C NMR (100 MHz) spectrum of compound **36v** in $CDCl_3$

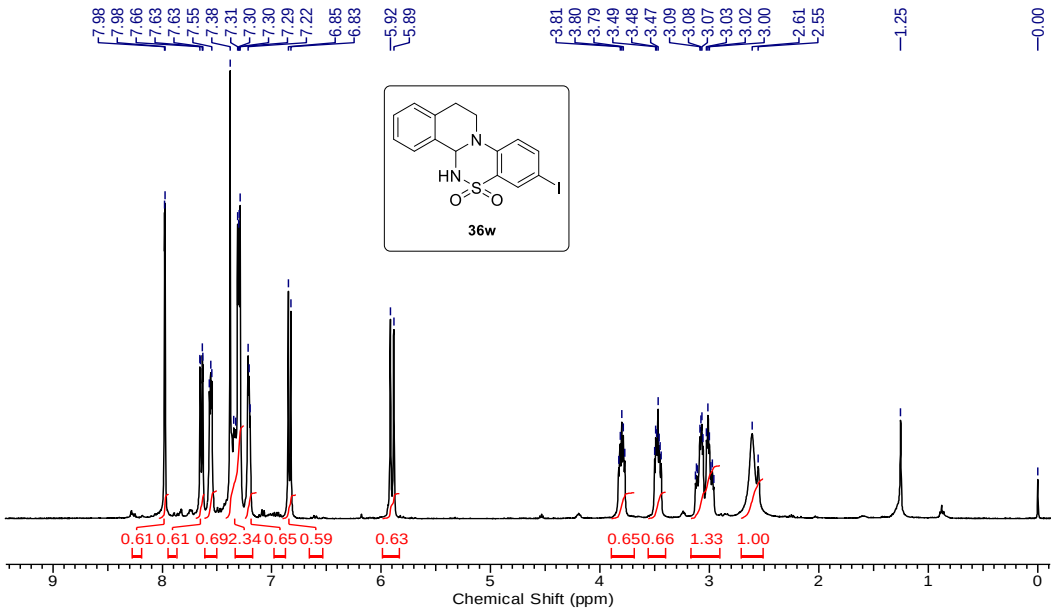


Figure 50. ^{1}H NMR (400 MHz) spectrum of compound **36w** in $CDCl_3$.

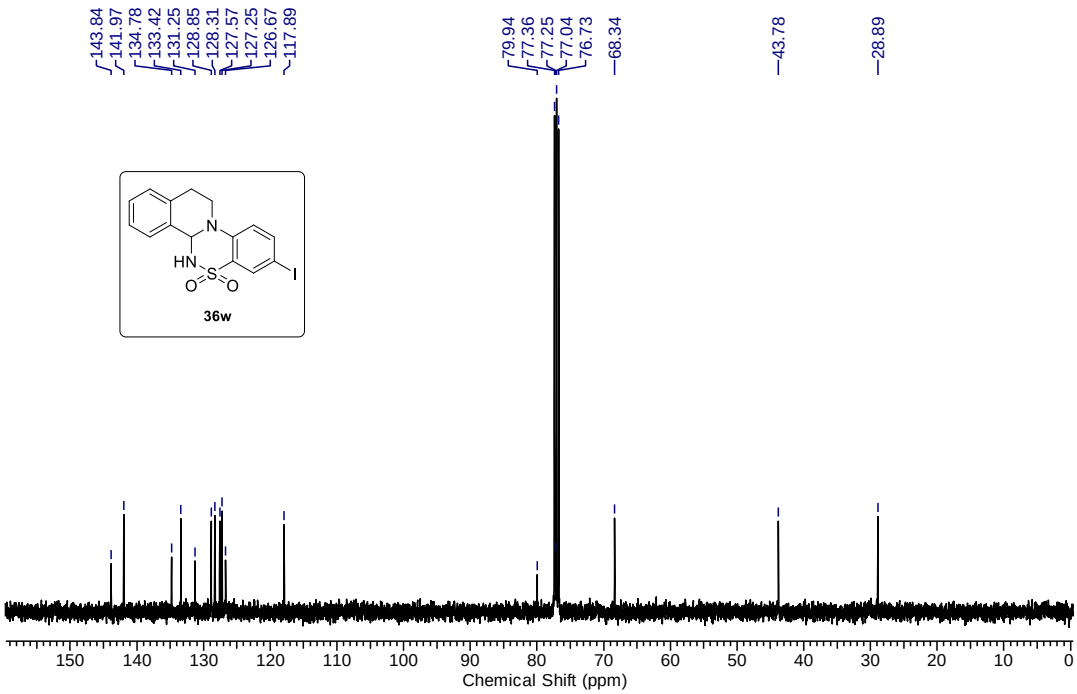


Figure 51. ^{13}C NMR (100 MHz) spectrum of compound **36w** in $CDCl_3$

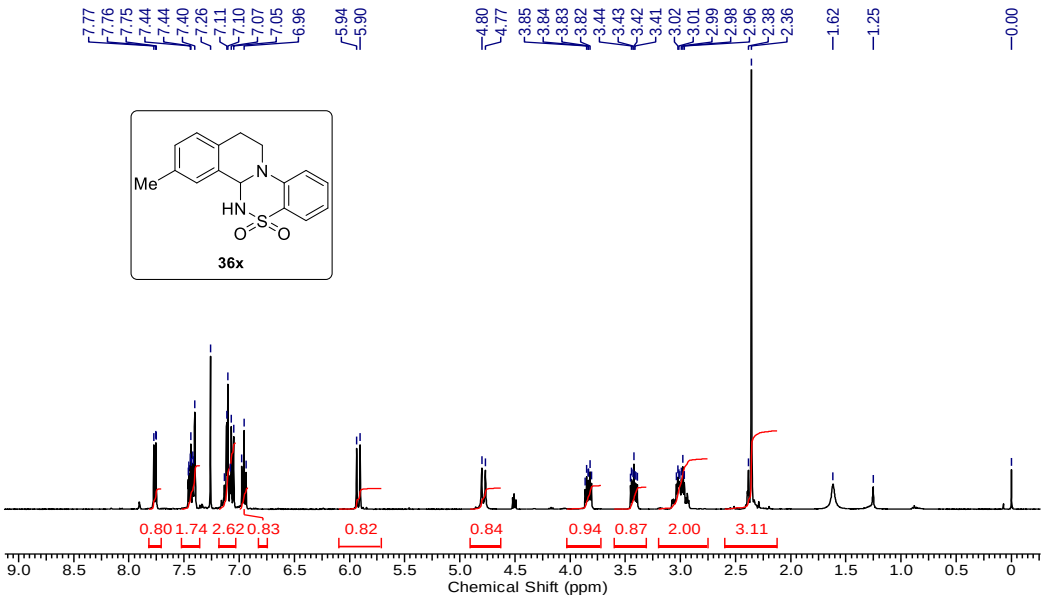


Figure 52. ^{1}H NMR (400 MHz) spectrum of compound **36x** in $CDCl_3$.

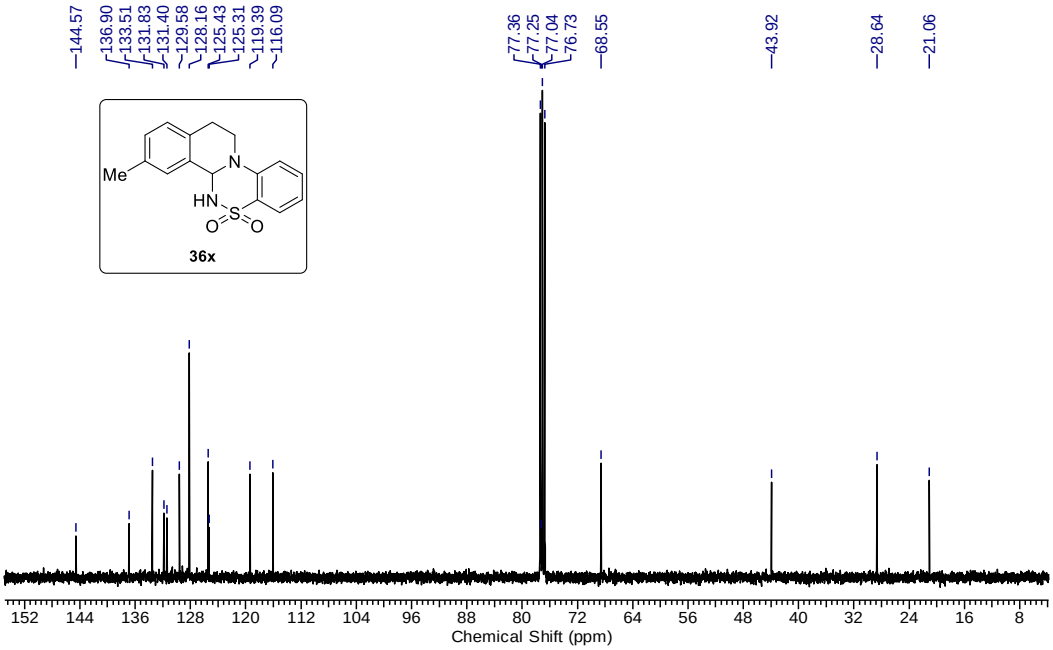


Figure 53. ^{13}C NMR (100 MHz) spectrum of compound **36x** in $CDCl_3$

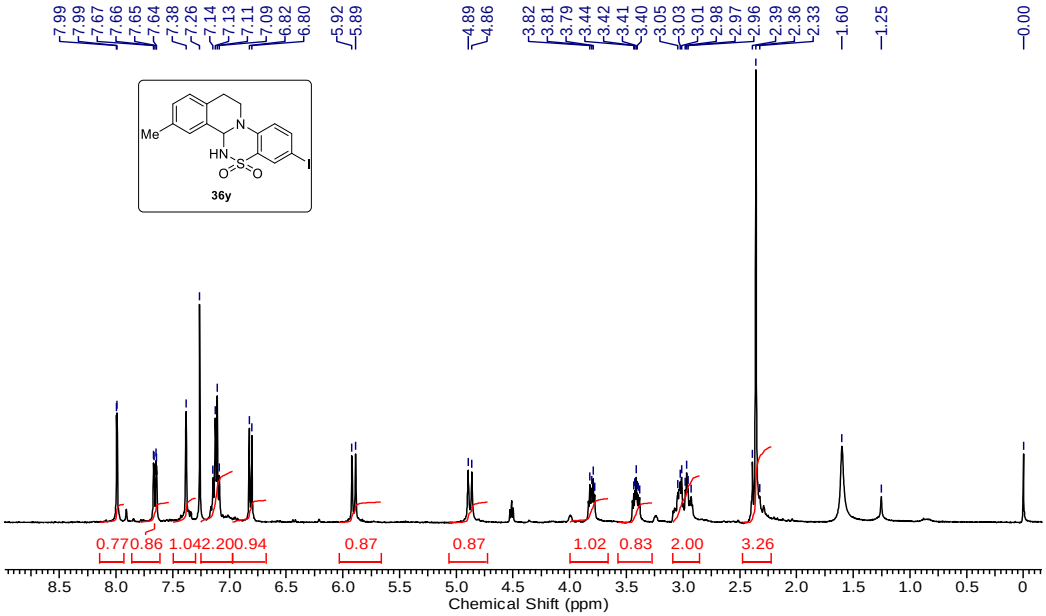


Figure 54. ^{1}H NMR (400 MHz) spectrum of compound **36y** in $CDCl_3$.

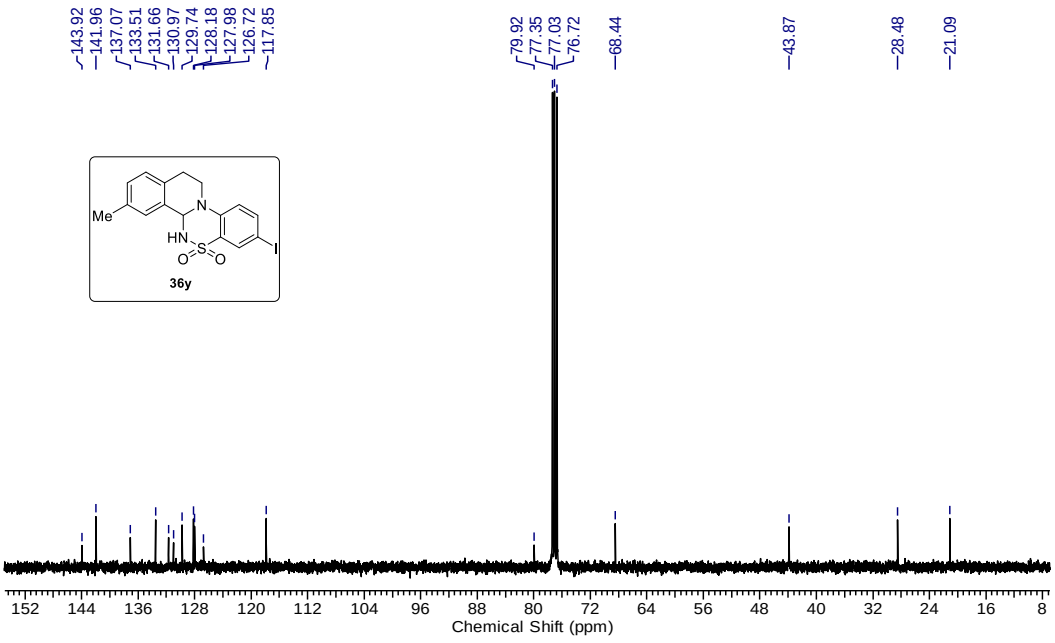


Figure 55. ^{13}C NMR (100 MHz) spectrum of compound **36y** in $CDCl_3$

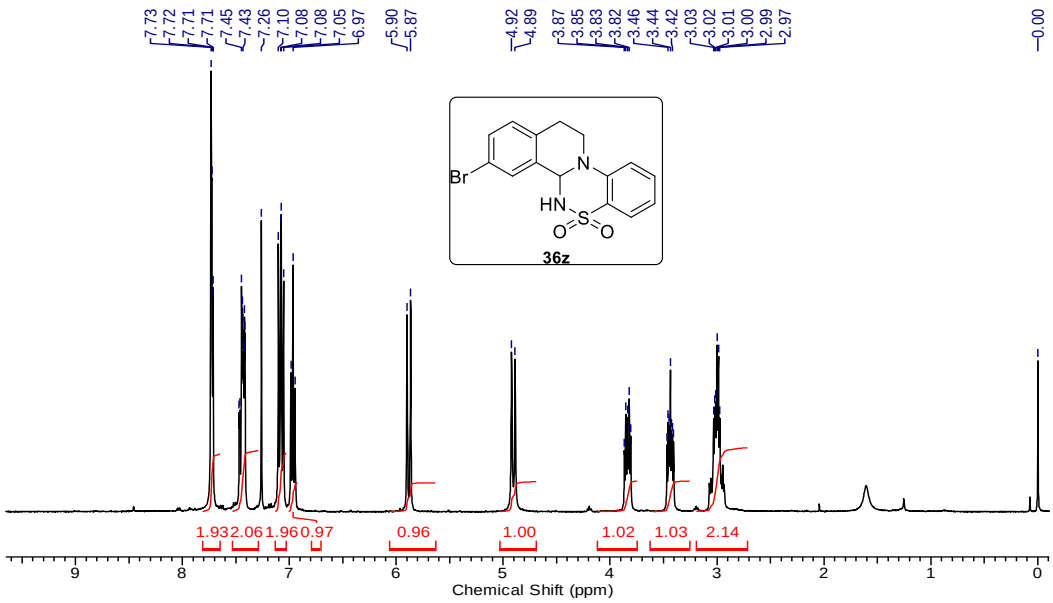


Figure 56. ^{1}H NMR (400 MHz) spectrum of compound **36z** in $CDCl_3$.

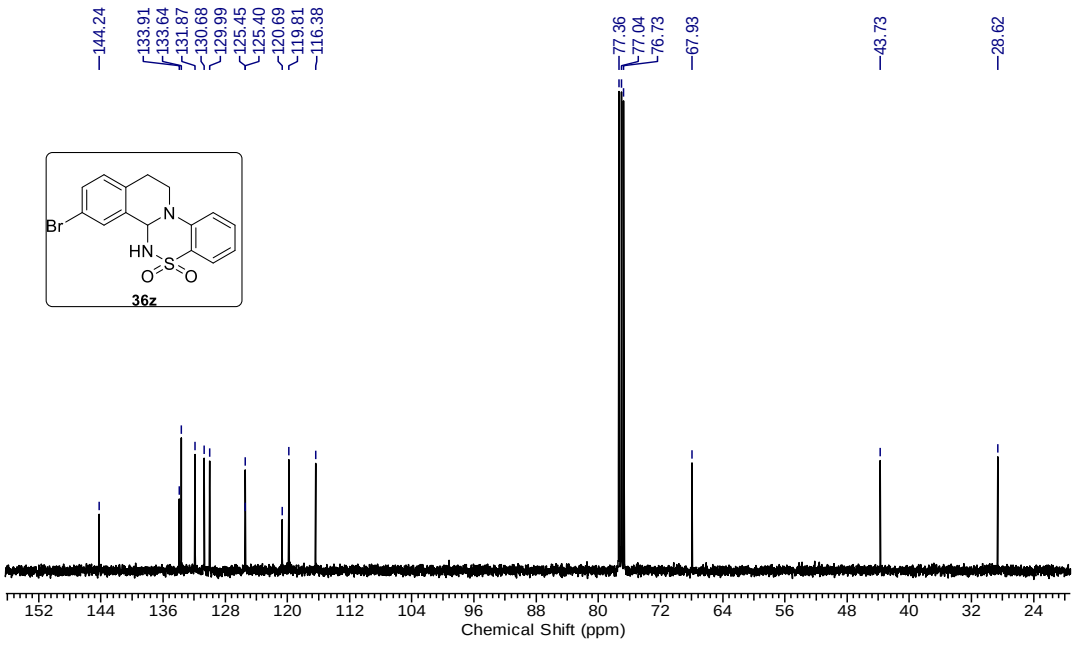


Figure 57. ^{13}C NMR (100 MHz) spectrum of compound **36z** in $CDCl_3$.

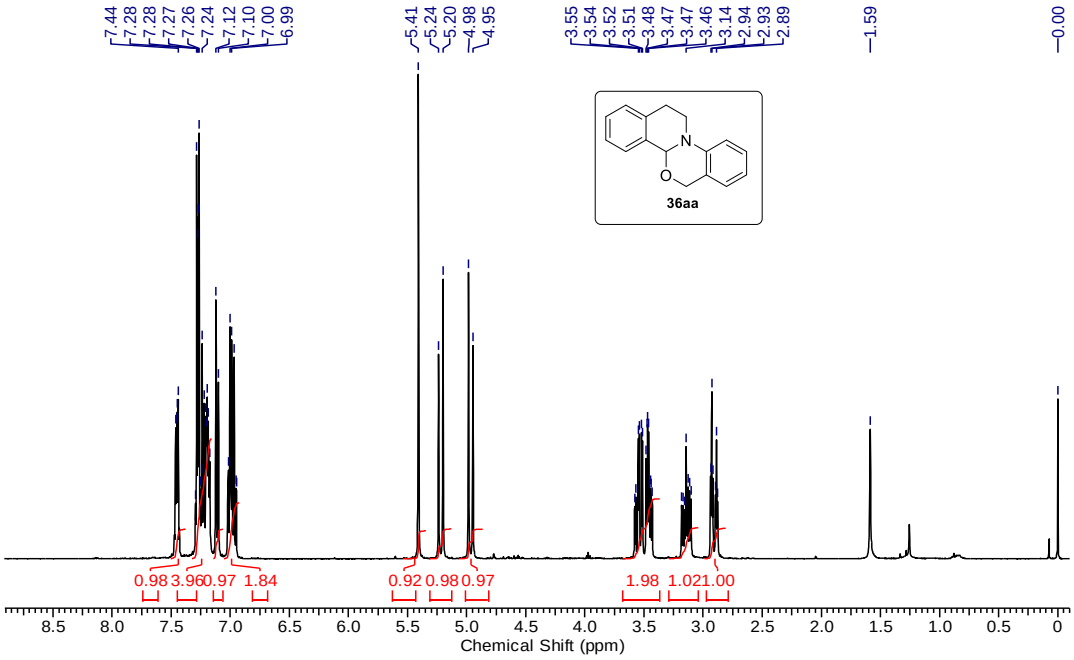


Figure 58. ^{1}H NMR (400 MHz) spectrum of compound **36aa** in $CDCl_3$.

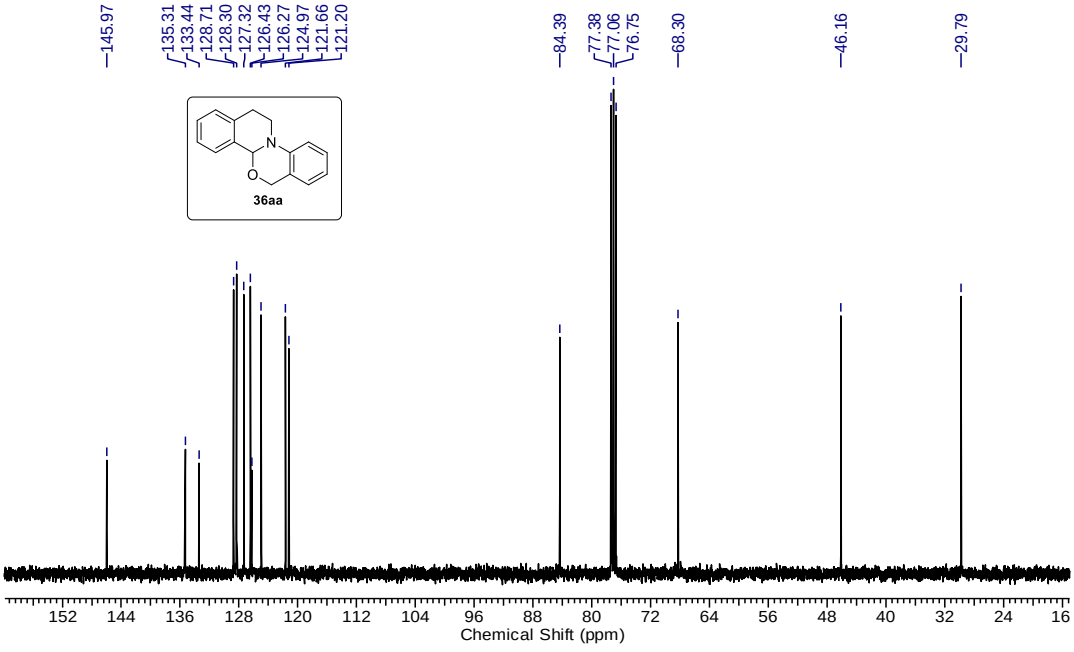


Figure 59. ^{13}C NMR (100 MHz) spectrum of compound **36aa** in $CDCl_3$.

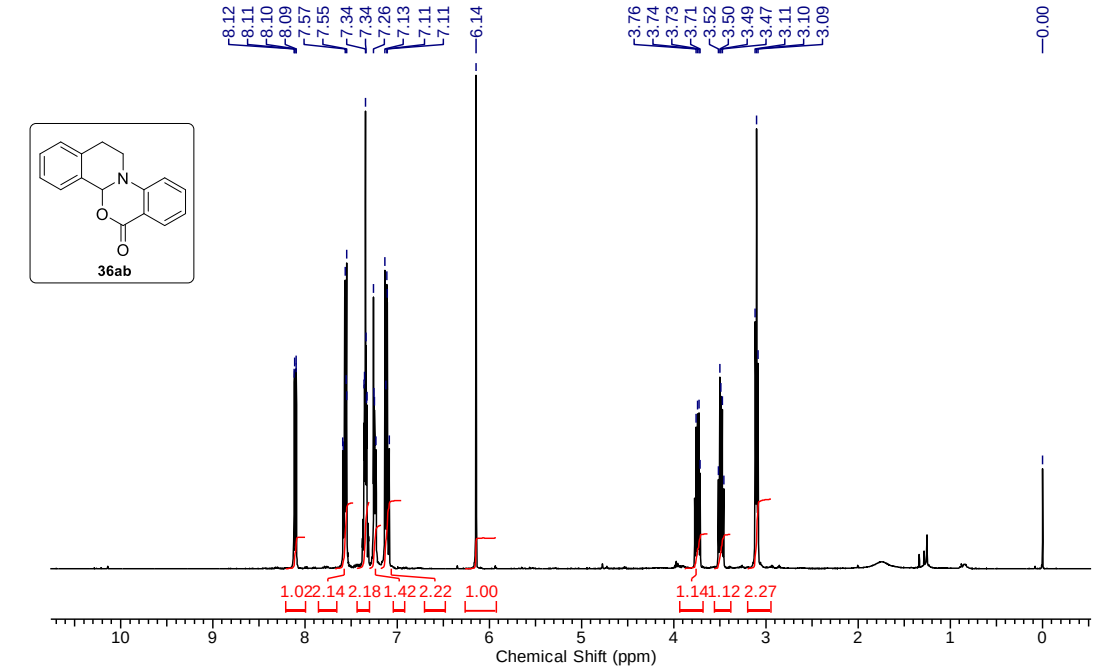


Figure 60. ^{1}H NMR (400 MHz) spectrum of compound **36ab** in $CDCl_3$.

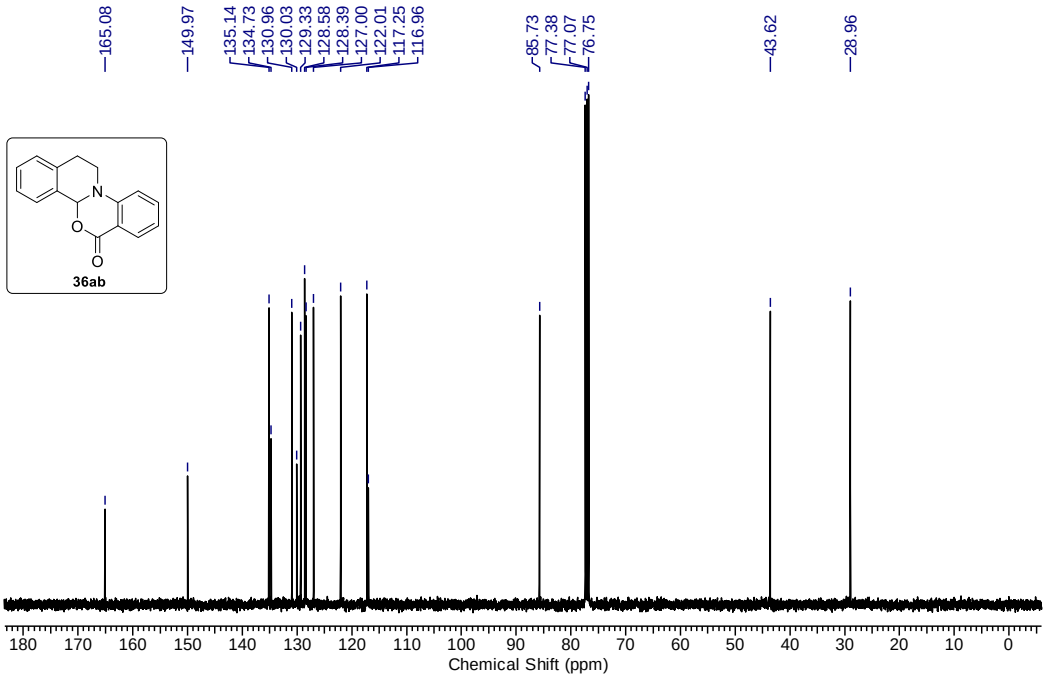


Figure 61. ^{13}C NMR (100 MHz) spectrum of compound **36ab** in $CDCl_3$

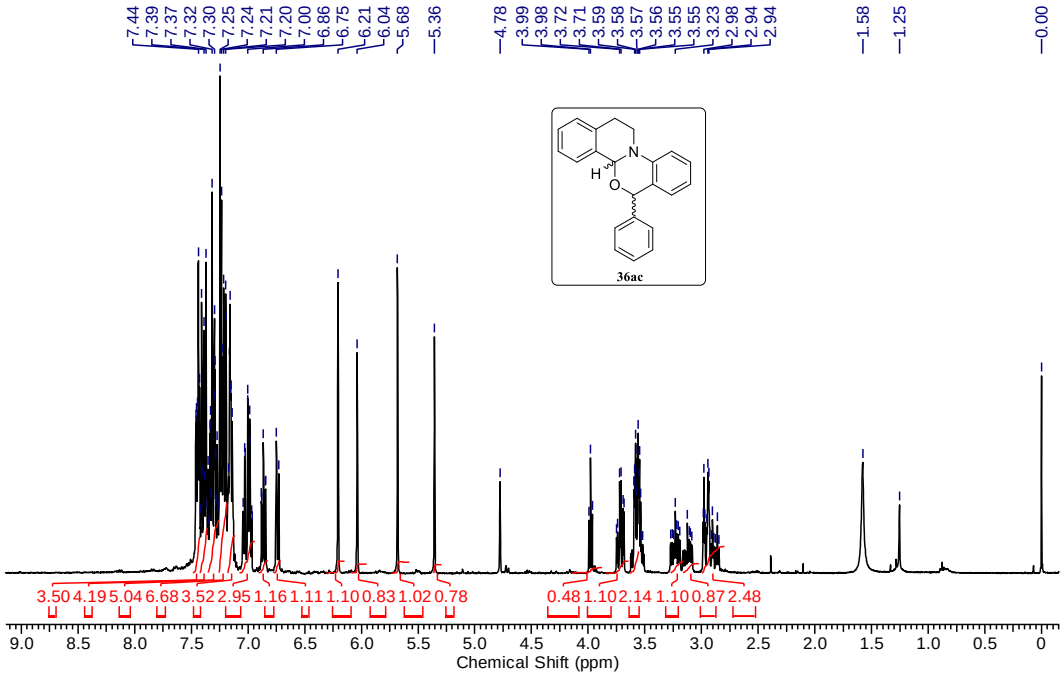


Figure 62. ^{1}H NMR (400 MHz) spectrum of compound **36ac** in $CDCl_3$.

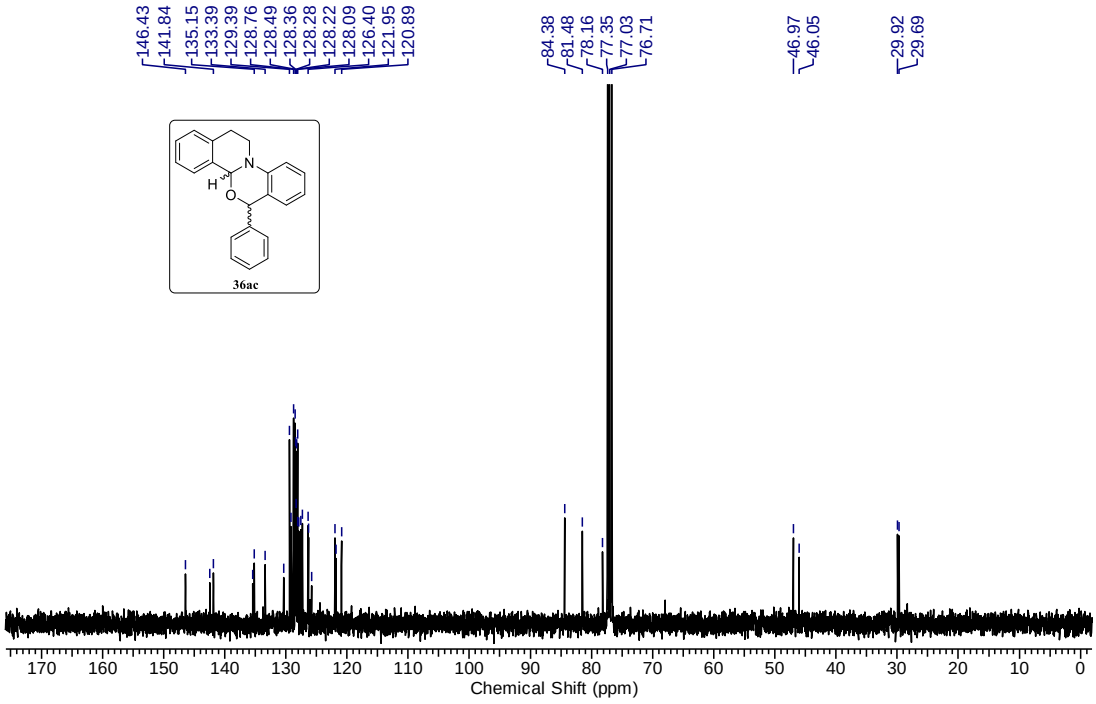


Figure 63. ^{13}C NMR (100 MHz) spectrum of compound **36ac** in $CDCl_3$

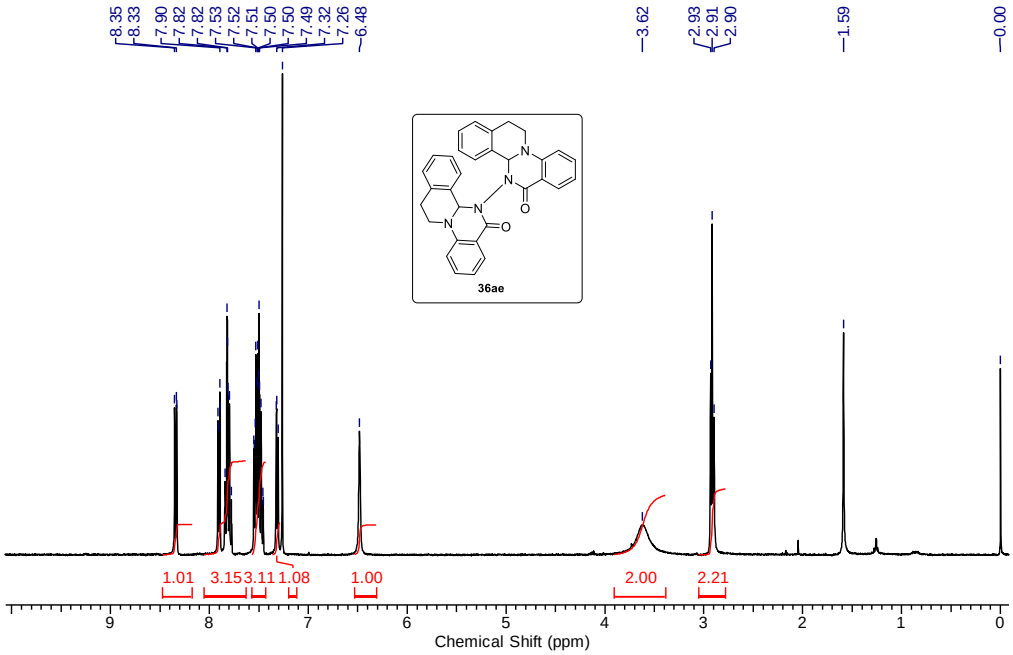


Figure 68. 1H NMR (400 MHz) spectrum of compound **36ae** in $CDCl_3$.

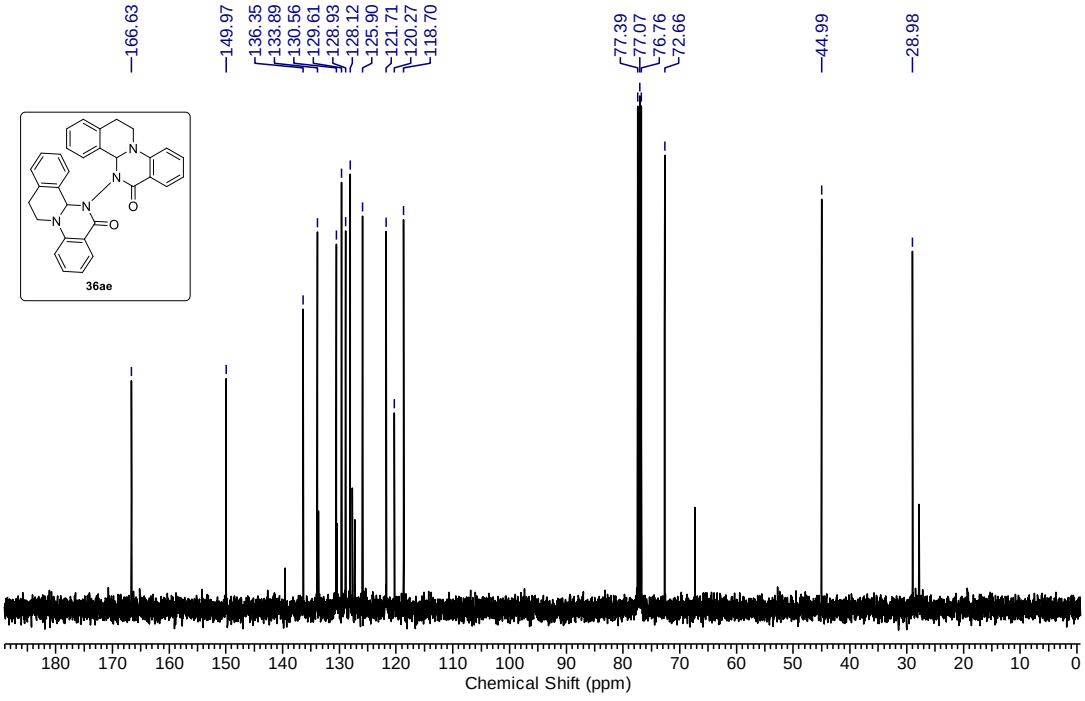


Figure 69. ^{13}C NMR (100 MHz) spectrum of compound **36ae** in $CDCl_3$

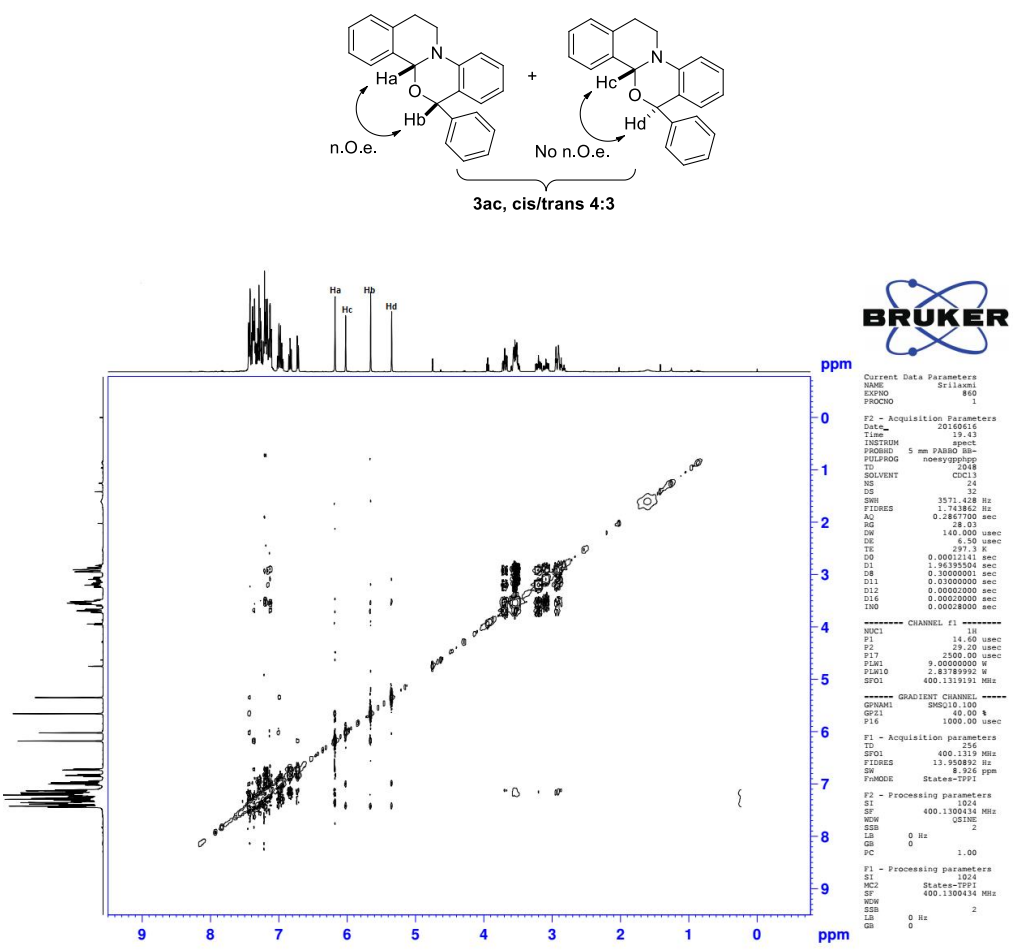


Figure 64. NOESY spectrum of compound **36ac** in $CDCl_3$

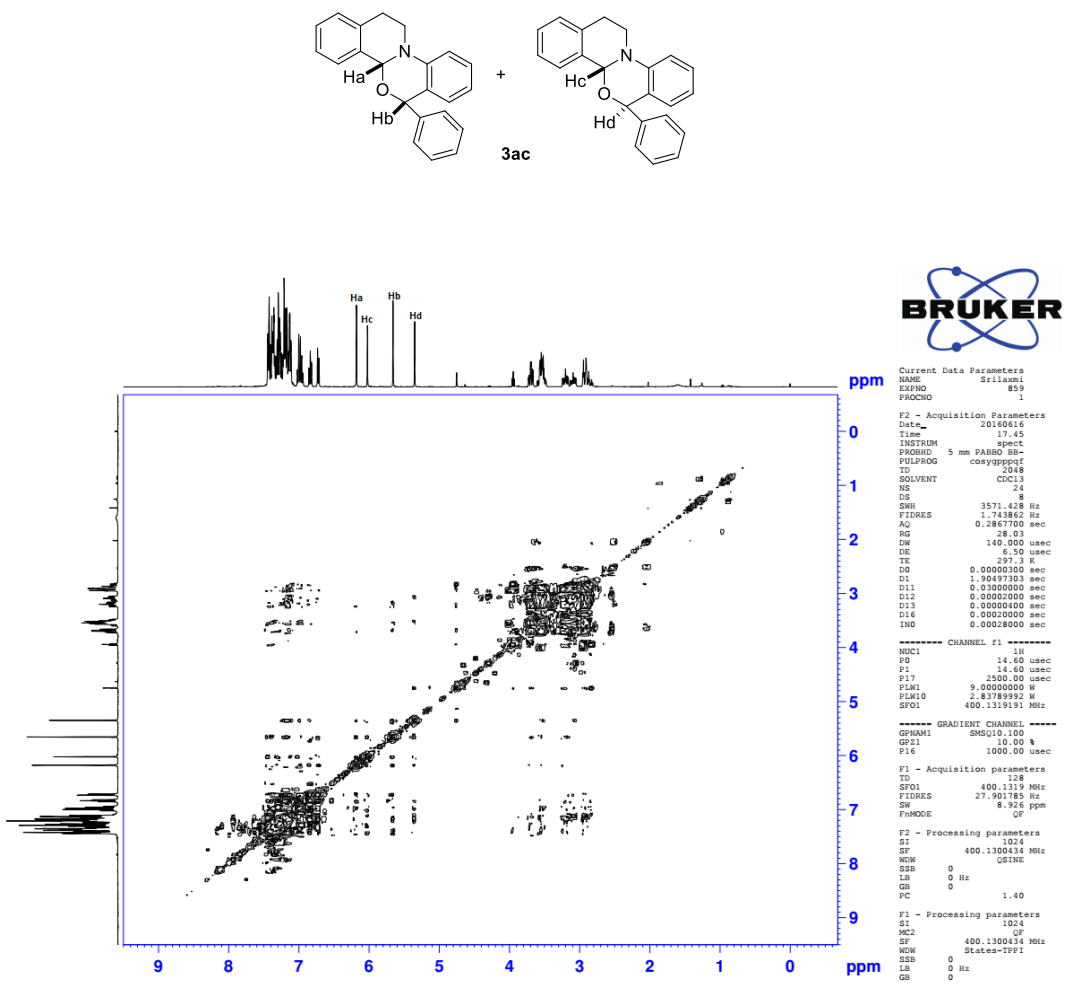


Figure 65. COSY spectrum of compound **36ac** in $CDCl_3$

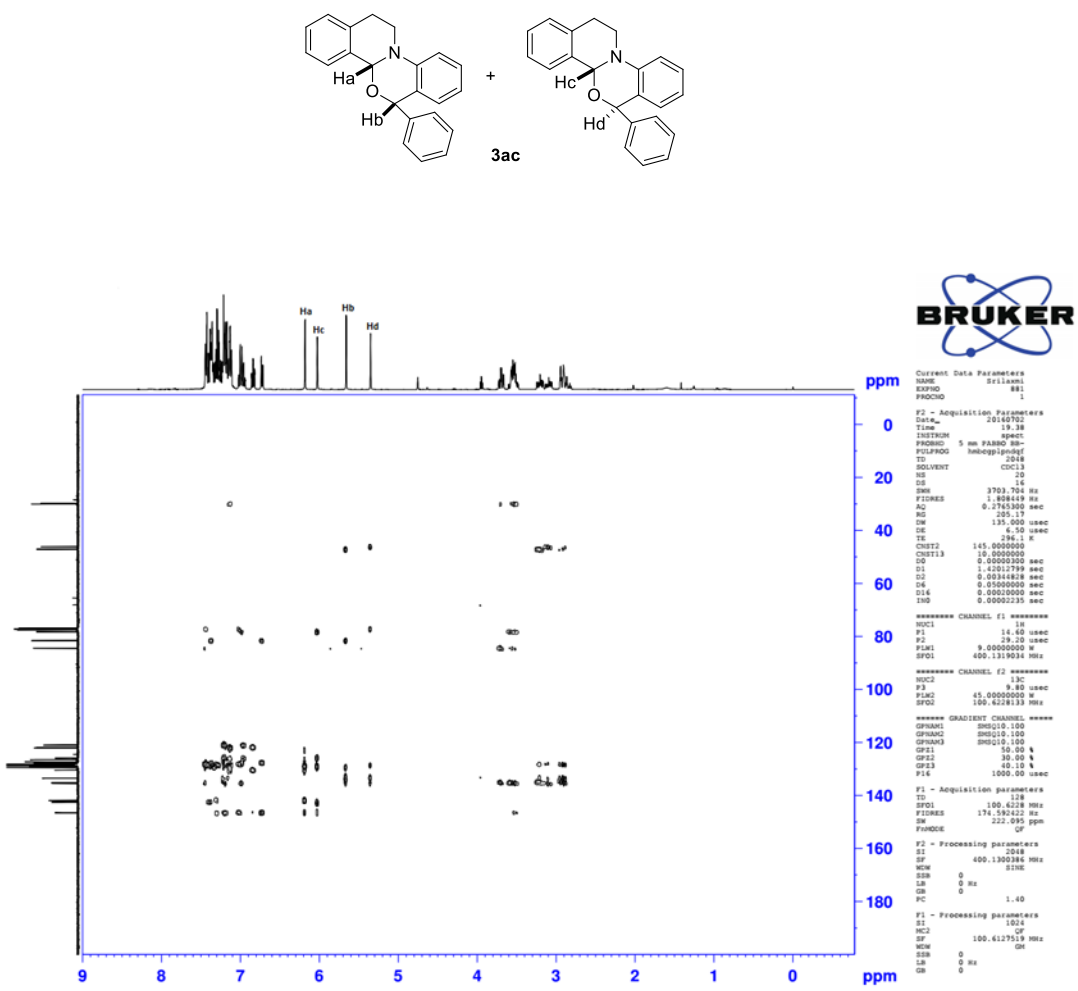


Figure 66. HMBC spectrum of compound **36ac** in $CDCl_3$

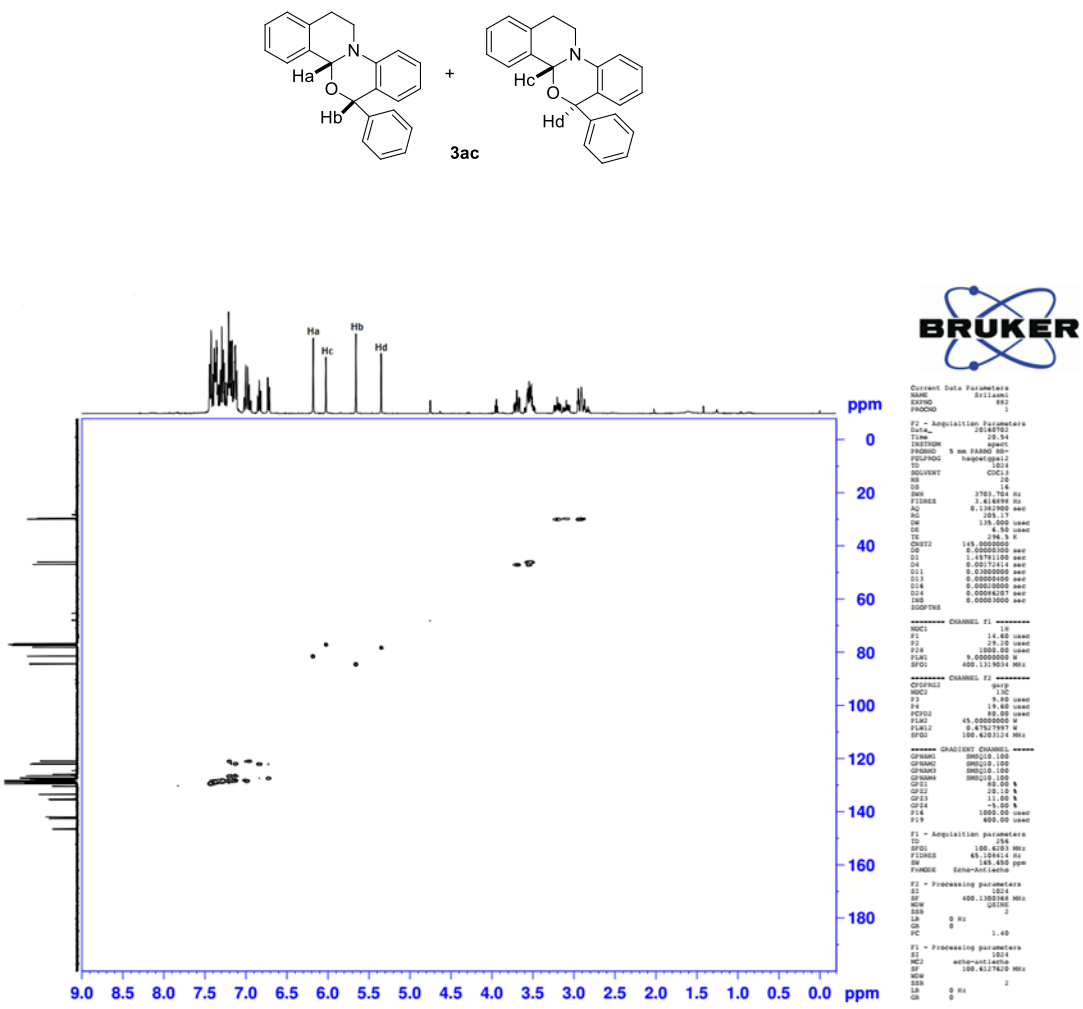


Figure 67. HSQC spectrum of compound **36ac** in $CDCl_3$

II. 6. REFERENCES:

1) (a) Walsh, D. P.; Chang, Y. T. *Chem. Rev.* 2006, *106*, 2476-2530. (b) Ahn, Y. H.; Chang, Y. T. *Acc. Chem. Res.* **2007**, *40*, 1025–1033. (c) Cragg G. M.; Grothaus P. G.; Newman, D. L. *Chem. Rev.* **2009**, *109*, 3012–3043. (d) Newman D. J.; Cragg, G. M. *J. Nat. Prod*. **2007**, *70*, 461–477.
2) (a) Zhou, L.; Li, Z.; Zou, Y.; Wang, Q.; Sanhueza, I. A.; Schoenebeck, F.; Goeke, A. *J. Am. Chem. Soc.* **2012**, *134*, 20009-20012. (b) Cruz, F. A.; Chen, Z.; Kurtoic, S. I.; Dong, V. M. *Chem. Commun.* **2016**, *52*, 5836-5839. (c) Jiao, Z. W.; Tu, Y. Q.; Zhang Q.; Liu, W.X.; Zhang, S. Y.; Wang, S. H.; Zhang, F. M.; Jiang, S. *Nat. Commun.* **2015**, doi: 10.1038/ncomms8332. (d) Bakthadoss, M.; Kannan, D.; Srinivasan, J.; Vinayagam, V. *Org. Biomol. Chem.* **2015**, *13*, 2870-2874. (e) Bakthadoss, M.; Kannan, D. *RSC Adv.* **2014**, *4*, 11723-11731. (f) Bakthadoss, M.; Devaraj, A.; Kannan, D. *Eur. J. Org. Chem.* **2014**, 1505-1513.
3) Teague, S. J.; Davis, A. M.; Leeson, P. D.; Oprea, T. *Angew. Chem., Int. Ed*. **1999**, *38*, 3743–3748.
4) (a) Renner, S.; Otterlo, W. V.; Seoane, M. D.; Möcklinghoff, S.; Hofmann, B.; Wetzel, S.; Schuffenhauer, A.; Ertl, P.; Oprea, T. A.; Steinhilber, D.; Brunsveld, L.; Rauh, D.; Waldmann, H. *Nat. Chem. Biol.* **2009**, *5*, 585-592. (b) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613–618. (c) Galloway W. R. J. D.; Spring, D. R. *Expert Opin Drug Discov.* **2009**, *4*, 467–472.
5) Schreiber, S. L.; *Science* **2000**, *287*, 1964–1969.
6) (a) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 104–109. (b) Kumagai, N.; Muncipinto, G.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 3635–3638. (c) Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46–58. (d) O'Connor, C. J.; Beckmann, H. S.; Spring, D. R. *Chem. Soc. Rev.* **2012**, *41*, 4444–4456.
7) (a) Oguri H.; Schreiber, S.L. *Org. Lett.* 2005, ***7***, 47–50. (b) Wang, Z.; Castellano, S.; Kinderman, S. S.; Argueta, C. E.; Beshir, A. B.; Fenteany, G.; Kwon, O. *Chem. Eur. J.* **2011**, *17*, 649–654.
8) (a) Robbins, D.; Newton, A. F.; Gignoux, C.; Legeay, J. C.; Sinclair, A.; Rejzek, M.; Stockman, R. A. *Chem. Sci.* **2011**, *2*, 2232–2235. (b) Schreiber, S. L. *Nature* **2009**, *457*, 153 –154

9) (a) Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Mulrooney, C. A. *J. Am. Chem. Soc.* **2010**, *132*, 16962–16976. (b) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 104–109. (c) Kwon, O.; Park, S. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 13402–13404.

10) (a) Patil, N. T.; Mutyala, A. K.; Lakshmi, P. G.; Raju, P. V.; Sridhar, B. *Eur. J. Org. Chem.* **2010**, 1999–2007. (b) Kumar K.; Waldmann, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 1740–1752.

11) (a) Patil, N. T.; Shinde, V. S.; Sridhar, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 2251–2255. (b) Liu, W.; Khedkar, V.; Baskar, B.; Schürmann, M.; Kumar, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 6900–6905. (c) Garcia-Castro, M.; Kremer, L.; Reinkemeier, C. D.; Unkelbach, C.; Strohmann, C.; Ziegler, S.; Kumar, K. *Nat. Commun.* **2015**, doi: 10.1038/ncomms7516.

12) (a) Vidyacharan, S.; Murugan, A.; Sharada, D. S. *J. Org. Chem.*, **2016**, *81*, 2837–2848. (b) Vidyacharan, S.; Shinde, A. H.; Satpathi, B.; Sharada, D. S. *Green Chem.* **2014**, *16*, 1168–1175. (c) Vidyacharan, S.; Sagar, A.; Sharada, D. S. *Org. Biomol. Chem.* **2015**, *13*, 7614–7618. (d) Shinde, A. H.; Vidyacharan, S.; Sharada, D. S. *Org. Biomol. Chem.* **2016**, *14*, 3207–3211. (e) Sagar, A.; Babu, V. N.; Sharada, D. S. *RSC Adv.* **2015**, *5*, 29066–29071. (f) Shinde, A. H.; Vidyacharan, S.; Sharada, D. S. *Tetrahedron Lett.* **2014**, *55*, 3064–3069.

13) Pictet, A.; Spengler, T. *Chem. Ber.* **1911**, *44*, 2030-2036.

14) Dhanasekaran, S.; Suneja, A.; Bisai, V.; Singh, V. K. *Org. Lett.* **2016**, *18*, 634–637.

15) (a) Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Nat. Chem.* **2011**, *3*, 642–646. (b) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 4076–4077. (c) Hashimoto, T.; Omote, M.; Maruoka, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 3489–3492.

16) (a) Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. *Org. Lett.* **2000**, *2*, 3901–3903. (b) Amat, M.; Elias, V.; Llor, N.; Subrizi, F.; Molins, E.; Bosch, J. *Eur. J. Org. Chem.* **2010**, 4017–4026.

17) Itoh, T.; Miyazaki, M.; Fukuoka, H.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2006**, *8*, 1295–1297.

18) Li, J. J.; Mei, T. S.; Yu, J. Q. *Angew. Chem.* **2008**, *120*, 6552–6555.

19) For selected CDC methods see: (a) Schweitzer-Chaput, B.; Klussmann, M. *Eur. J. Org. Chem.* **2013**, *2013*, 666-671. (b) Ueda, H.; Yoshida, K.; Tokuyama, H. *Org. Lett.* **2014**, *16*, 4194–4197. (c) Baslé, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661–3663. (d) Dhineshkumar, J.; Lamani, M.; Alagiri, K.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 1092–1095. (e) Alagiri, K.; Devadig, P.; Prabhu, K. R. *Chem. Eur. J.* **2012**, *18*, 5160–5164. (f) Chen, Q.; Zhou, J.; Wang, Y.; Wang, C.; Liu, X.; Xu, Z.; Lin, L.; Wang, R. *Org. Lett.* **2015**, *17*, 4212–4215. (g)

Huo, C.; Xie, H.; Wu, M.; Jia, X.; Wang, X.; Chen, F.; Tang, J. *Chem. Eur. J.* **2015**, *21*, 5723–5726.

20) (a) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416–417. (b) Murarka, S.; Zhang, C.; Konieczynska, M. D.; Seidel, D. *Org. Lett.* **2009**, *11*, 129–132. (c) Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226–13227.

21) (a) Aalla, S.; Gilla, G.; Bojja, Y.; Anumula, R. R.; Vummenthala, P. R.; Padi, P. R. *Org. Process Res. Dev.* **2012**, *16*, 682–686. (b) Breschi, M. C.; Calderone, V.; Digiacomo, M.; Martelli, A.; Martinotti, E.; Minutolo, S. F.; Rapposelli, S.; Balsamo, A. *J. Med. Chem.* **2004**, *47*, 5597–5600. (c) Jin, Y. C., Lee, Y. S., Kim, Y. M., Seo, H. G., Lee, J. H., Kim, H. J.; Chang, K. C. *J. Pharmacol. Exp. Ther*. **2009**, *330*, 440–448. (d) Liu, W.; Liu, S.; Jin, R.; Guo, H.; Zhao, J. *Org. Chem. Front*. **2015**, *2*, 288–299. (e) Wright, A. E.; Forleo, D. A.; Gunawardana, G. P.; Gunasekera, S. P.; Koehn F. E.; McConnell, O. J. *J. Org. Chem.* **1990**, *55*, 4508–4512. (f) Möcklinghoff, S.; Otterlo, W. V.; Rose, R.; Fuchs, S.; Zimmermann, T. J.; Seoane, M. D.; Waldmann, H.; Ottmann, C.; Brunsveld, L. *J. Med. Chem.* **2011**, *54*, 2005-2011.

22) (a) Schweitzer-Chaput, B.; Klussmann, M. *Eur. J. Org. Chem.* **2013**, 666; (b) Baslé, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661; (c) Ueda, H.; Yoshida, K.; Tokuyama, H. *Org. Lett.* **2014**, *16*, 4194; (d) Dhineshkumar, J.; Lamani, M.; Alagiri, K.; Prabhu, K. R. *Org. Lett.*, **2013**, *15*, 1092; (e) Huo, C.; Xie, H.; Wu, M.; Jia, X.; Wang, X.; Chen, F.; Tang, J. *Chem. Eur. J.* **2015**, *21*, 5723; (f) Alagiri, K.; Devadig, P.; Prabhu, K. R. *Chem. Eur. J.* **2012**, *18*, 5160; (g) Chen, Q.; Zhou, J.; Wang, Y.; Wang, C.; Liu, X.; Xu, Z.; Lin, L.; Wang, R. *Org. Lett.* **2015**, *17*, 4212.

23) (a) Shinde, A. H.; Archith, N.; Malipatel, S.; Sharada, D. S. Tetrahedron Lett. 2014, 55, 6821; (b) Sharada, D. S.; Shinde, A. H.; Patel, S. M.; Vidyacharan, S. J. Org. Chem. 2016, 81, 6463; (c) Sagar, A.; Babu, V. N.; Shinde, A. H.; Sharada, D. S. Org. Biomol. Chem. 2016, 14, 10366.

24) Zhang, L.; Liu, H.; Qiao, G.; Hou, Z.; Liu,Y.; Xiao, Y.; Guo, H.; *J. Am. Chem. Soc.*, **2015**, *137*, 4316.

25) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya,T.; Noyori, R, *J. Am. Chem. Soc.* **1996**, *118*, 4916.

26) Al-Hiari, Y. M.; Sweileh, B. A.; Shakya, A. K.; Sheikha, G. A.; Jordan, S. I. A. *J. Pharm. Sci.* **2009**, *2*, 1.

27) Itoh, T.; Miyazaki, M.; Fukuoka, H.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2006**, *8*, 7.

28) Chen, W.; Seidel, D. *Org. Lett.* **2014**, *16*, 3158.

29) Tanoue, A.; Yoo, W.-J.; Kobayashi, S. *Org. Lett.* **2014**, *16*, 2346.

30) (a) Dhanasekaran, S.; Bisai, V.; Unhale, R. A.; Suneja, A.; Singh, V.K. *Org. Lett.* **2014**, *16*, 6068; (b) Dhanasekaran, S.; Kayet, A.; Suneja, A.; Bisai, V.; Singh, V. K. *Org. Lett.* **2015**, *17*, 2780;

31) Shinde, A. H.; Archith, N.; Malipatel, S.; Sharada, D. S. *Tetrahedron Lett.* **2014**, *55*, 6821;

32) Sagar, A.; Babu, V. N.; Shinde, A. H.; Sharada, D. S. *Org. Biomol. Chem*. **2016**, *14*, 10366.

33) Sharada, D. S.; Shinde, A. H.; Patel, S. M.; Vidyacharan, S. *J. Org. Chem.* **2016**, *81*, 6463;

34) Malamas, M. S.; Stange, H.; Schindler, R.; Lankau, H. J.; Grunwald, C.; Langen, B.; Fan, K. Y. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5876–5884.

35) Sharma, M.; Pandey Snyder, D. S.; Tradtrantip, L.; Yao, C.; Kurth, M. J.; Verkman, A. S. *J. Med. Chem.* **2011**, *54*, 5468–5477.

36) Yanagihara, Y.; Kasai, H.; Kawashima, T.; Shida, T. *Jpn. J. Pharmacol.* **1988**, *48*, 91–101.

37) (a) Sharma, M.; Pandey, S.; Chauhan, K.; Sharma, D.; Kumar, B.; Chauhan, P. M. *J. Org. Chem.* 2012, *77*, 929–937. (b) Ghosh, S. K.; Nagarajan, R. *RSC Adv.* **2016**, *6*, 27378-27387.

38) Phillips, D.; Sonnenberg, J.; Arai, A. C.; Vaswani, R.; Krutzik, P. O.; Kleisli, T.; Chamberlin, A. R. *Bioorg. Med. Chem.* 2002, *10*, 1229–1248.

39) (a) For iminium ion formation see: Yang, R.; Gao, Z.-F.; Zhao, J. Y.; Li, W.-B.; Zhou, L.; Miao, F. *J. Agric. Food Chem.* **2015**, *63*, 1906-1914.

40) Zhou, M. Y.; Kong, S. S.; Zhang, L. Q.; Zhao, M.; Duan, J. A.; Ou-yang, Z.; Wang, M. *Tetrahedron Lett.*, **2013**, *54*, 3962–3964.

CHAPTER III

Copper-Catalyzed Intramolecular α-C–H Amination *via* Ring-Opening Cyclization Strategy to Quinazolin-4-ones: Development and Application in Rutaecarpine Synthesis

III. 1. INTRODUCTION:

Quinazolinone is an important *N*–heterocyclic scaffold, as of their abundance in biologically active compounds and numerous natural products such as rutaecarpine,[1] tryptanthrin,[2] luotonin A, B, E and F[3] and bio active compounds (Figure 1). Owing to the promising biological & medicinal activities including anticancer,[4] anti-inflammatory,[5] antibacterial,[6] antihypertensive[7] properties, synthetically quinazolinone scaffolds have been highly in demand and remains a challenge in organic synthesis. The direct functionalization of C–H bonds of organic compounds has recently emerged as a diverse atom economic carbon–heteroatom (C–X)[8] and carbon–carbon (C–C) bond formation.[9] Several diverse C–H functionalization methodologies without prefunctionalization of the coupling partners have been widely developed in the past decades.[10] Previously, we have employed N-incorporation strategy for the synthesis of quinoxalines *via* dual C(sp^2)-H functionalization[11a] and also, in recent past reported on the direct cycloaminative approach to imidazole derivatives *via* dual C-H functionalization.[11b]

Over the past three decades, considerable progress has been made in the development of methods to construct sp^2 carbon–nitrogen (C–N) bonds using palladium, copper or nickel catalysis. However, formation of sp^3 C–N bonds remains one of the major challenges in the field of cross-coupling chemistry. Recently, much attention has been focused towards the development of transition-metal catalyzed intramolecular C–H amination strategies to assemble *N*–Heterocyclic compounds.[12] In most of the cases, a tertiary amine has been used as one of the partner whereas α-C–H bond has been activated. Application of this

strategy in intramolecular C–heteroatom bond formation to synthesize challenging hetero cycles and pharmaceutically important compounds is less studied. Newly established methodology leading to the natural products are high demand for modern organic synthesis.[14]

In this context, we are pleased to report intramolecular cross-dehydrogenative coupling C–N bond formation under aerobic conditions for the synthesis of quinazolin-4(3*H*)-ones from isatoic anhydride and amines (benzylic & aliphatic) with copper (I) catalyst *via* ring opening cyclisation (ROC) strategy (Scheme 1). During this process an iminium ion intermediate formation, which is subsequently trapped by an amine nucleophile.

Rutaecarpine, belongs quinazolinecarboline alkaloids isolated from fruits of Evodia rutaecarpa, a plant used for treatment of headache, cholera,

and dysentery in Chinese medicine. Due to the medicinal importance of this alkaloid, various synthetic routes have been developed.[15] Recently Jieping Zhu et al. synthesized rutaecarpine and (±)-evodiamine by a silver salt-catalyzed insertion of the isocyano group into the N-H bond of the tryptamine followed by in situ lactamization.[16] Herein, we described the shorter route to rutaecarpine from isatoicanhydride and tryptoline *via* ROC strategy.

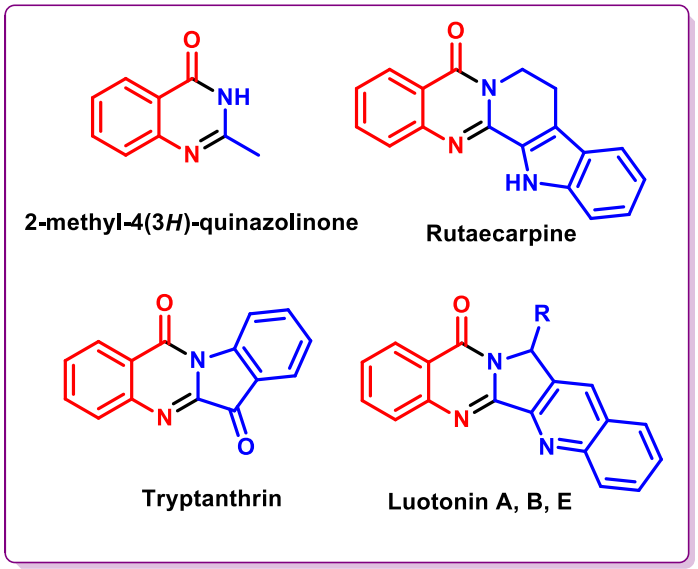
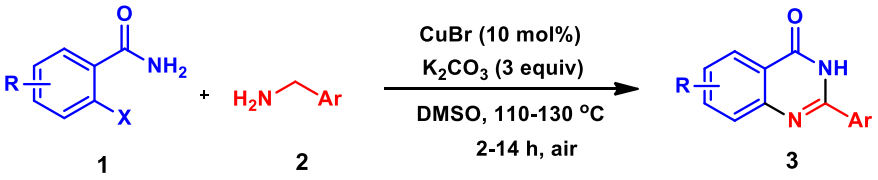


Figure 1. Quinazolinone skeleton containing natural products.

III. 2. BACKGROUND:

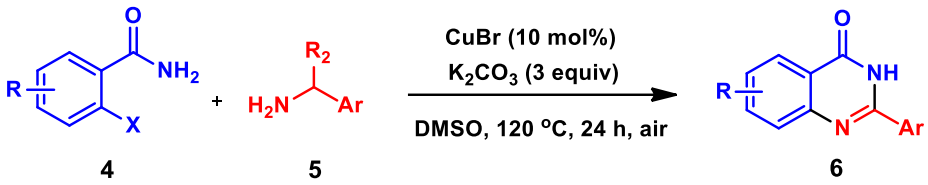
III. 2.1. Intramolecular C-H amination:

Fu and co-workers developed a simple method for the synthesis of quinazolinones via Cu-catalyzed oxidative dehydrogenation (Scheme 1).[17] The reaction of substituted 2-halobenzamides and benzylamines using CuBr as the catalyst and air as an oxidant provided quinazolinones in moderate to good yields.



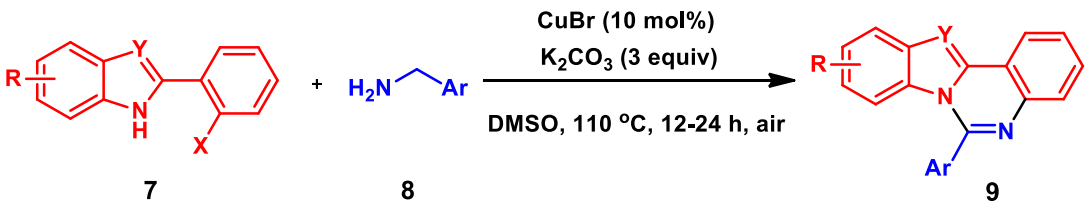
Scheme 1

Tang, Y.-L. et all, The quinazolinones were prepared by using α-substituted arylmethanamines as starting materials instead of benzylamines. This reaction proceeds through a Cu-catalyzed domino reaction involving C-C bond cleavage (Scheme 2)[18].



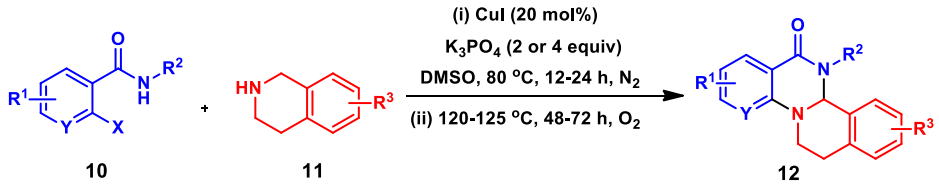
Scheme 2

Cu-catalyzed oxidative dehydrogenation was described by Zou, Zhang, and co-workers. The Cu-catalyzed reaction of 2-(2-halophenyl)-1*H*-indoles and benzylamines using air as an oxidant provided indolo[1,2-c]quinazolines (**Scheme 3**)[19].



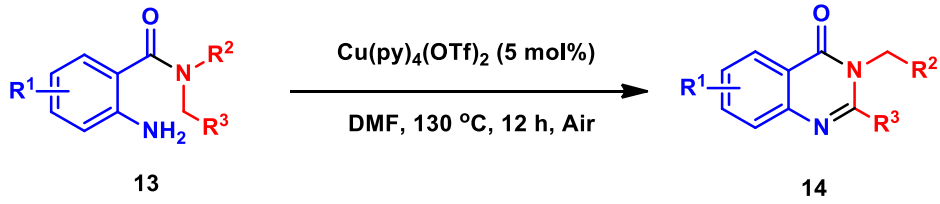
Scheme 3

Hua Fu and co-workers developed the synthesis of tetrahydroisoquinolino-[2,1-a]quinazolinones from the reaction of N-substituted benzamides and 1,2,3,4-tetrahydroisoquinolines (**Scheme 4**)[20].



Scheme 4

In 2010, Maiti. D reported recently copper-catalysed C(sp^3-H functionalization/cyclisation of 2-amino-*N*,*N*-dialkylbezamides for the synthesis of 2,3-disubstituted-4(3*H*)-quinazolinone derivatives (**Scheme 5)** [13].

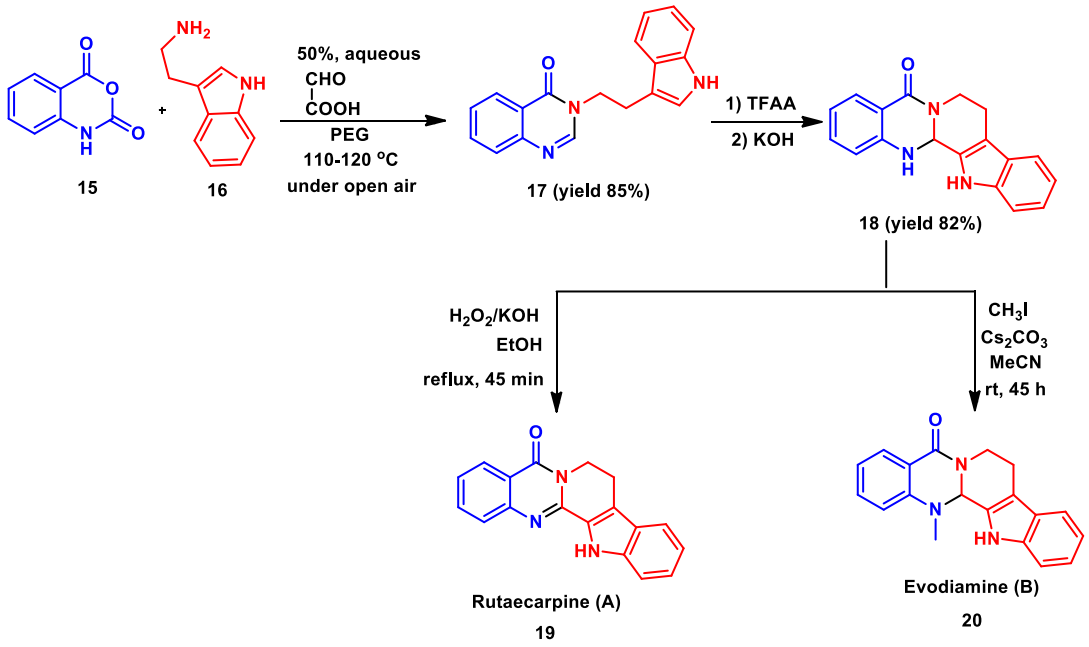


Scheme 5

III. 2.2. Rutaecarpine Synthesis:

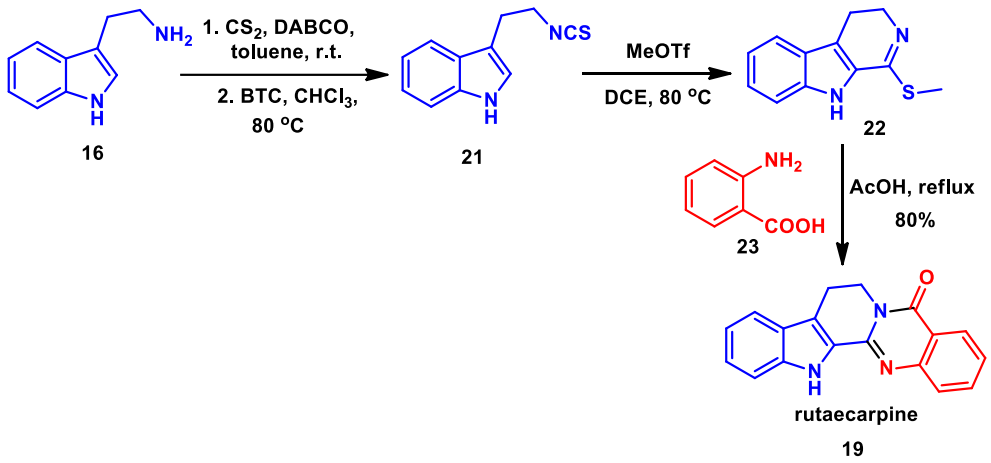
Manojit Pal and co-workers reported A dual reactant/catalyst role of glyoxylic acid in the reaction of isatoic anhydride with various amines afforded a novel, robust and rapid synthesis of 3-(un)substituted quinazolin-4(3*H*)-ones. This method

has been successfully applied to the synthesis of quinazolinone alkaloid rutaecarpine (A) and evodiamine (B) (**Scheme 6**)[1a].



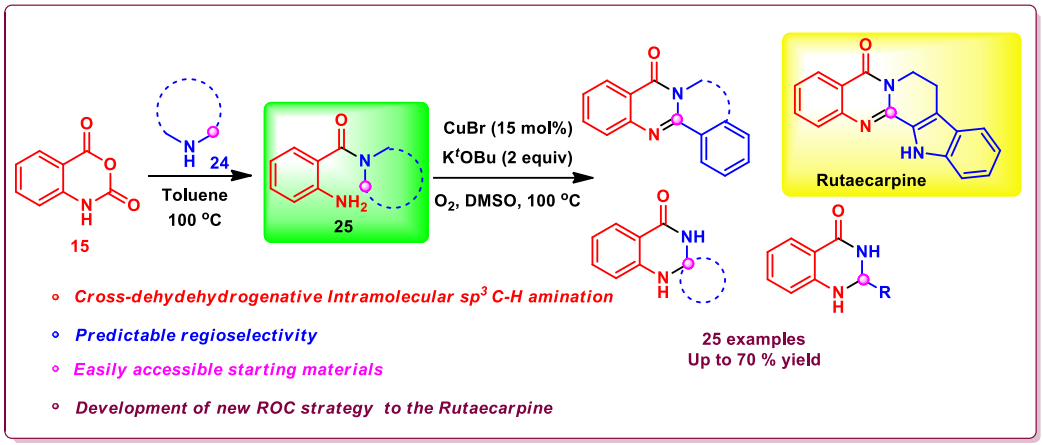
Scheme 6

Ming Li and co-workers reported A copper-catalyzed tandem arylation-cyclization process to access 1-(arylthio)isoquinolines from isothiocyanates and diaryliodonium salts is described. This method has been successfully applied to the synthesis of quinazolinone alkaloid rutaecarpine (**Scheme 7**)[21].



Scheme 7

Copper-Catalyzed Intramolecular α-C–H Amination *via* Ring-Opening Cyclization Strategy to Quinazolin-4-ones. And also this ROC strategy has been successfully applied to the synthesis of quinazolinone alkaloid rutaecarpine.



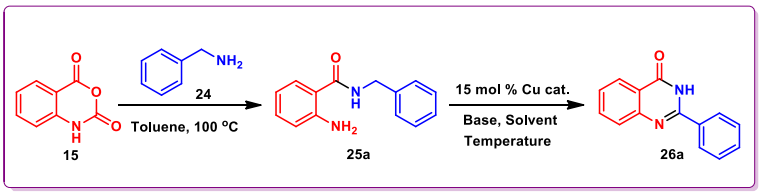
Scheme 1. Our present strategy for the synthesis of quinazolinone derivatives.

III. 3. Results and Discussion:

Initially, we embarked on our study by examining the reaction of **25a** in the presence of K_2CO_3 base and $Cu(OAc)_2$ as the catalyst at 90 °C in DMSO, 2-phenylquinazolin-4(3*H*)-one (**26a**) was afforded 45% yield (Table 1, entry 1). Further screening of various copper (II) and copper (I) catalyst could promote the reaction and CuBr was the optimal choice (Table 1, entries 1–6).

To improve the yield of the product different bases were screened with CuBr, DMSO solvent obtained the product 25–68% yield at 90 ^oC (entries 7–10). Then we investigated the different solvents such as DMF, CH_3CN, Toluene, DCE, and MeOH afforded **26a** in lower yields (entries 11–15). Among the solvents examined, DMSO exhibited the best transformation on giving the product **26a** in 68% yield (entry 9). Upon conducting the reaction under argon instead of oxygen, the reaction yield decreased to 62% (entry 16). Next, we screened the reaction by varying the temperatures at 80 ^oC, 100 ^oC and 120 ^oC, we could obtain the product **26a** in 70 % yield at 100 ^oC (entries 17–19). When reaction run in the absence of CuBr afforded **26a** in diminish yield, while absence of KO^{t}Bu reaction product did not firmed, so that this experiments indicates that copper and base were pivotal for the reaction (entries 20, 21).

Table 1. Optimization of Reaction Conditions[a]

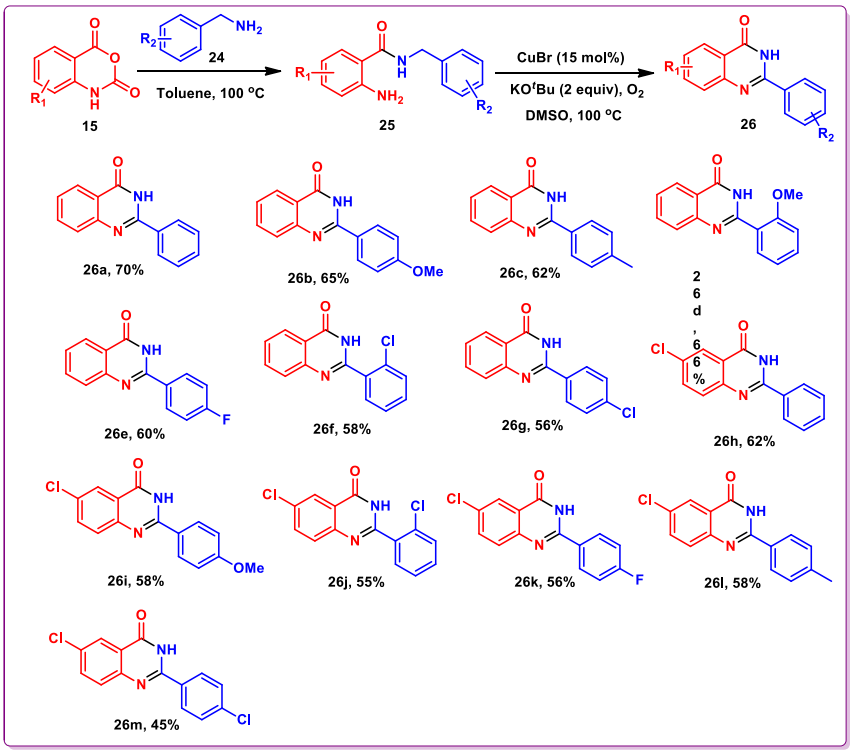


S.No.	Catalyst	Base	Solvent	Tempt (°C)	Yield (%)[b]
1	$Cu(OAc)_2$	K_2CO_3	DMSO	90	45
2	$CuBr_2$	K_2CO_3	DMSO	90	49
3	CuI	K_2CO_3	DMSO	90	52
4	CuBr	K_2CO_3	DMSO	90	55
5	Cu_2O	K_2CO_3	DMSO	90	50
6	CuBr	K_2CO_3	DMSO	90	58
7	CuBr	NaO^{t}Bu	DMSO	90	62
8	CuBr	KO^{t}Bu	DMSO	90	68
9	CuBr	NEt_3	DMSO	90	25
10	CuBr	KO^{t}Bu	DMF	90	62
11	CuBr	KO^{t}Bu	CH_3CN	90	60
12	CuBr	KO^{t}Bu	Toluene	90	n.d
13	CuBr	KO^{t}Bu	DCE	90	n.d
14	CuBr	KO^{t}Bu	MeOH	90	n.d
15	CuBr	KO^{t}Bu	DMSO	90	62[c]
16	CuBr	KO^{t}Bu	DMSO	90	64[d]
17	CuBr	KO^{t}Bu	DMSO	80	61
18	**CuBr**	**KO^{t}Bu**	**DMSO**	**100**	**70**
19	CuBr	KO^{t}Bu	DMSO	120	60
20	-	KO^{t}Bu	DMSO	100	10
21	CuBr	-	DMSO	100	0

[a]Reaction conditions: **25a** (0.22 mmol), base (0.44 mmol) and 1 mL of solvent under O_2 for 2 h; [b] Isolated yields after column chromatography; [c]Reaction was performed under argon; n.d = not detected.

With the optimized reaction conditions in hand, the scope of the reaction was investigated by varying both the benzyl amines and the isatoic anhydrides as shown in Table 2. The electronic effect on 2-amino-*N*-benzylbenzamides exerted no obvious influence upon the reaction. For example, the electron rich 2-amino-*N*-benzylbenzamides showed good reactivity to afford the corresponding quinazolin-4(3*H*)-ones (**26a**–**26d**) in 62–66% yields. At the same time, the 2-amino-*N*-benzylbenzamides with electron-withdrawing substituents, including –F, –Cl participated in the reaction smoothly afforded the products **26e**–**26g** in 56–60% yield. The relative sinking product formation observed upon varying substituents at the 5-position of 2-amino-*N*-benzylbenzamide deactivate the amine nucleophilicity, thereby decreasing the efficiency of the cyclization reaction considerably (**26h**–**26m** 45-62%).

Table 2. Scope of Isatoic anhydrides and aromaticamines.



[a]Reaction conditions: **25a** (0.22 mmol), CuBr (15 mol %), KO^{t}Bu (2 equiv), DMSO (1 mL), O$_2$, 100 °C.

The structure of the **4b** was confirmed by X-ray crystal structure analysis (Fig. 2) (CCDC 1574127).

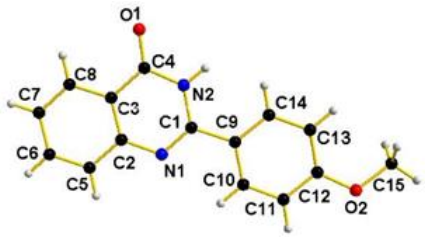
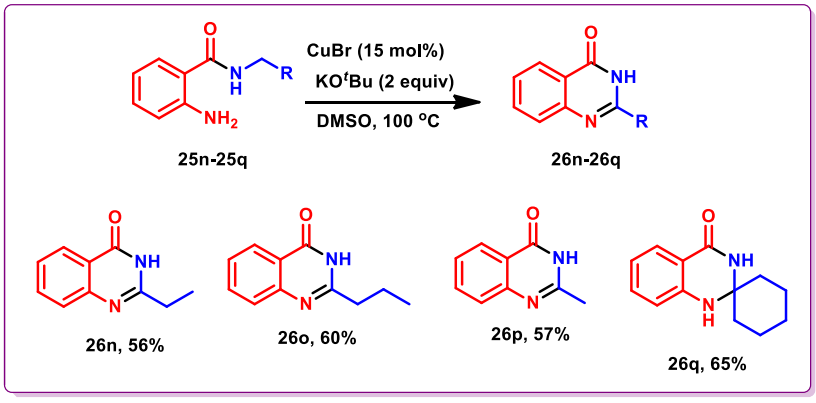


Figure 2. X-ray crystal structure of product 4b. Thermal ellipsoids are drawn at 30% probability level.

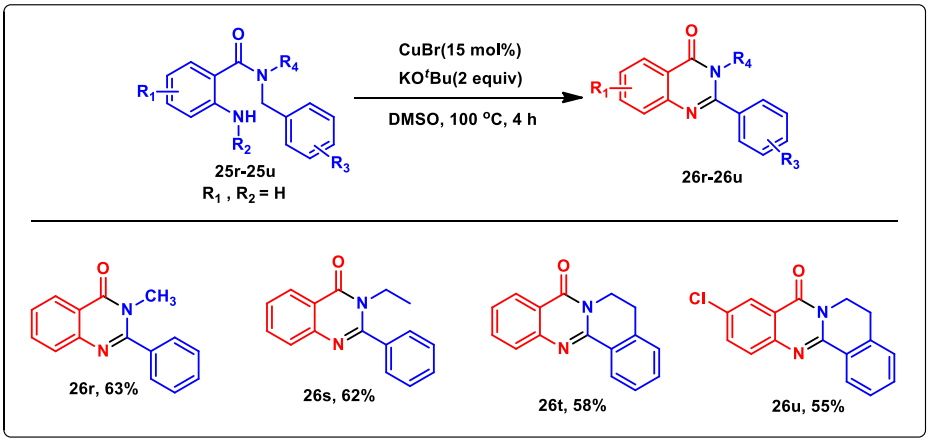
To our delight, 2-amino-*N*-alkylbenzamide derivatives synthesized from aliphatic primary amines such as n-propyl and n-butyl also underwent intramolecular α-C–H amination giving the products **26n** and **26o** in good yields. Contrarily, isopropyl amine provided unexpected product 2-methylquinazolin-4(3*H*)-one **26p** by C–C bond cleavage.[22] Differently, cyclohexyl amine afforded the 1'*H*-spiro[cyclohexane-1,2'-quinazolin]-4'(3'*H*)-one **26q** in good yield under the standard reaction condition (Table 3, entries **26n**–**26q** 56-65%**)**.

Table 3. Scope of Isatoic anhydrides and aliphatic amines



After the successful synthesis of quinazolin-4(3*H*)-ones from isatoic anhydride and primary amines (benzyl and aliphatic), attempts to examine the site selectivity aspect of the ROC strategy, a number of unsymmetrical amides, which were synthesized by isatoic anhydride and unsymmetrical secondary amines (Table 4). In spite of having two possible N-methylene sites for cross dehydrogenative coupling C–N bond formation in **26r** and **26s** selectively undergoes cyclization only at the benzylic position in the presence of an N-methyl and N-ethyl moieties. And also, complete selectivity for C–N bond formation was observed at the benzylic side of tetrahydroisoquinoline while incorporated the 2-aminobenzamide (**26t**) and 2-amino-5-chlorobenzamide (**26u**) (Table 4).

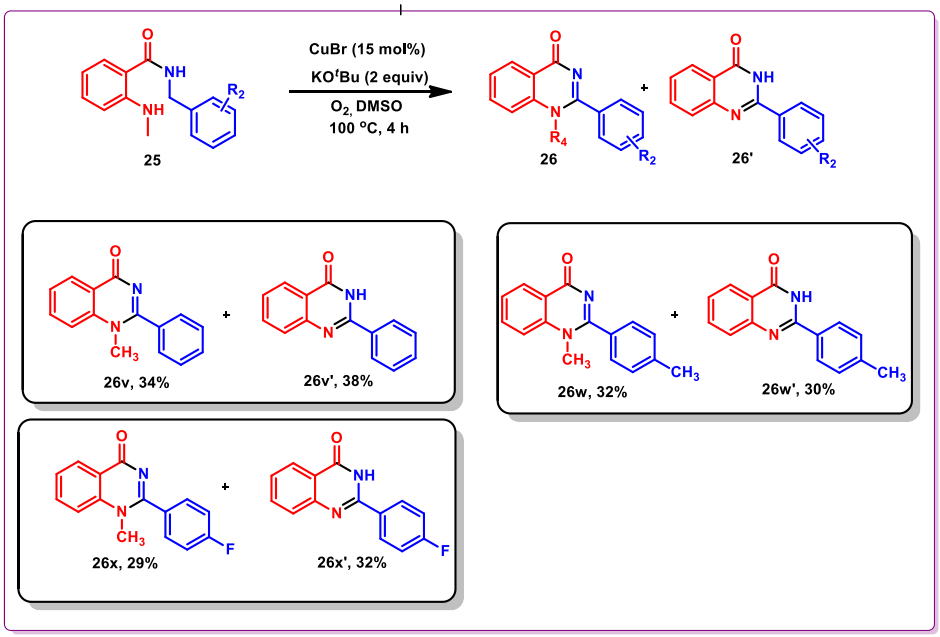
Table 4. Cyclization with Unsymmetric Amines



After having successful development of copper catalyzed intramolecular cyclization for the synthesis of quinazolin-4(3*H*)-ones **26** from 2-amino-*N*-alkylbenzamide derivatives **25**, subsequently we tested the N-methyl isatoicanhydride ring opening by benzylamine product **3** provide the 2-aryl-quinazolinones by N–C bond cleavage along with the 1-methyl-2-phenylquinazolin-4(1*H*)-one derivatives (Table 5, entries **26v**–**26x**). Compare to C–H bond cleavage, N–C bond cleavage has been receiving much attention in organic chemistry, due to the inertness of this bond.[23] To further rule out the demethylation, we performed a reaction in different solvents DMF and CH_3CN, and also at low temperature 80 °C

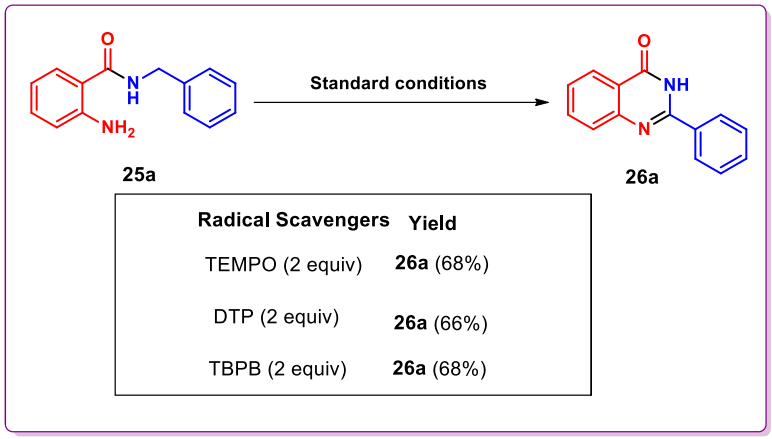
and 60 °C, which provided demethylation product along with expected product. On the basis of these experimental results, we proposed a reasonable mechanistic pathway. We have demonstrated a copper-catalyzed approach for the synthesis of 2-substituted quinazolinones through an intramolecular N–C bond cleavage with air as the oxidant under basic conditions.

Table 5. Substrate scope for the CuBr catalyzed synthesis of quinazolin-4(1*H*)-one and quinazolin-4(3*H*)-one.[a]

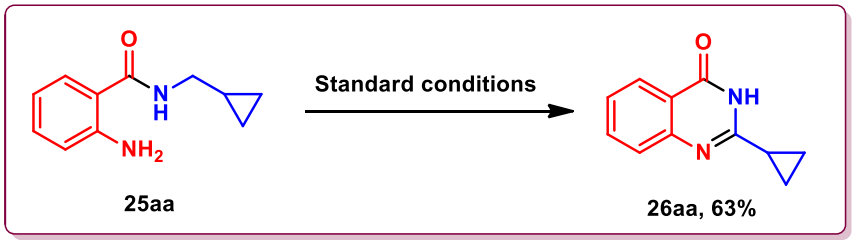


To probe the mechanism of intramolecular α-C–H amination, preliminary control experiments were conducted whether the reaction proceeds through a radical pathway, we performed the standard reaction in the presence of radical scavengers like 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), ditert-butyl peroxide (DTP) and tert-butyl peroxybenzoate (TBPB) (Scheme 8). Which showed no significant decrease in the yield of the product **26a**, and also did not observe any radical trapped intermediates. To further rule out the radical pathway, we performed a radical clock experiment under standard conditions, which provided 2-cyclopropylquinazolin-4(3*H*)-one **26aa** and no other ring-opened coupling products were observed (**Scheme 9**).

Scheme 8. Control Experiments



Scheme 9: Radical Clock Exeperiment



On the basis of the literature reports, and TEMPO/DTP/TBPB trapping experiments, a tentative ionic reaction mechanism was proposed. During the course of these reactions, an iminium ion as the key intermediate **I** in this transformation, subsequently the iminium ion underwent intramolecular cyclization followed by oxidation, to furnish the desired product **26a** (Figure 2).

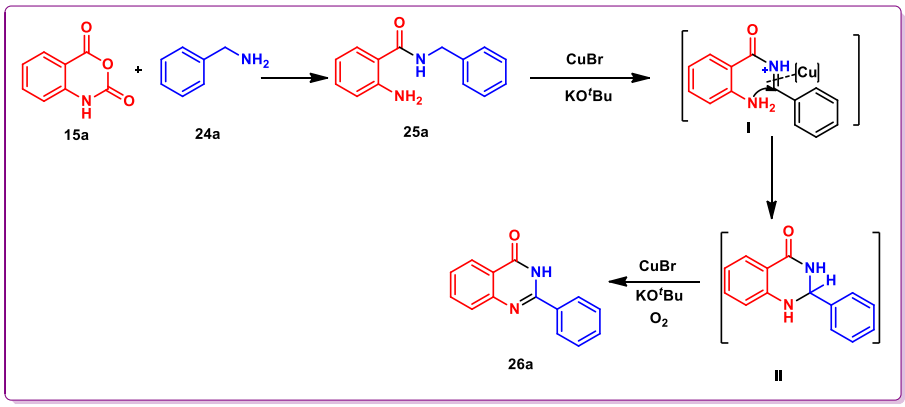
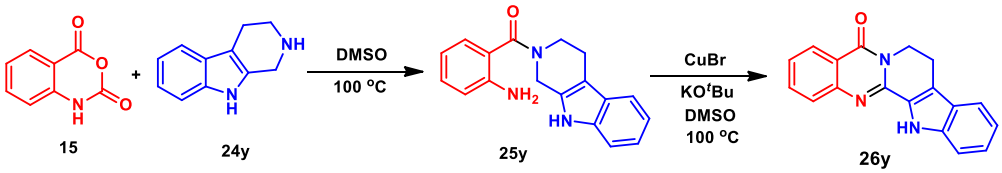
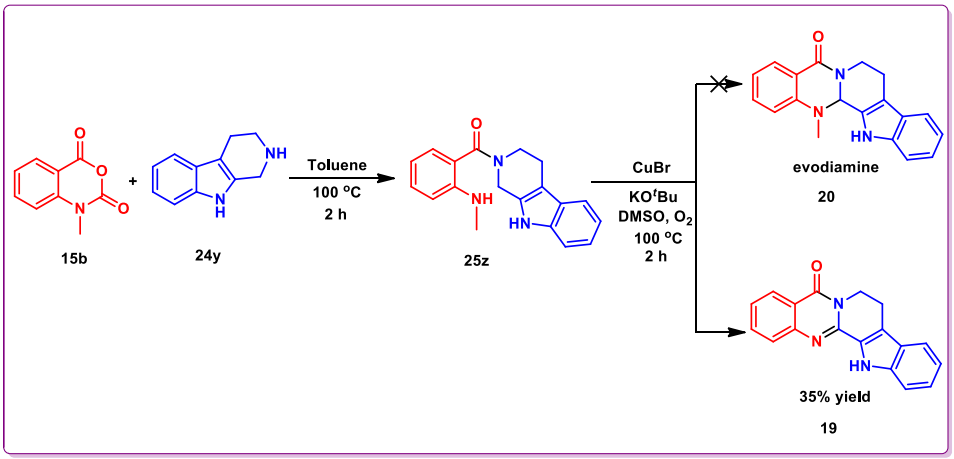


Figure 2. Plausible reaction mechanism for the synthesis of quinazolin-4(3*H*)-one **26**.

Having a developed copper-catalyzed rapid synthesis of 2-substituted quinazolin-4(3*H*)-ones, we were applied this ROC strategy for the synthesis of our target natural product rutaecarpine. Thus isatoic anhydride (**1**) was treated with tryptoline (**2y**) in DMSO solvent for 2 h give the desired product **3y.** The compound **3y** on treatment with CuBr and KO^{t}Bu under oxygen at 100 ^{o}C afforded rutaecarpine (**4y**) in 60% yield. And also we tried to apply this strategy for the synthesis of evodiamine but we failed to get expected product **4z**. When we have treated **3z** with CuBr and KO^{t}Bu under oxygen afforded rutaecarpine (**4y**) in 35% yield (Scheme 10).

Scheme 10. Synthesis of Rutaecarpine





III. 4. Conclusion:

In summary, we have developed a copper catalysed intramolecular α-C–H amination of C(sp^3)-H bond for the synthesis of quinazolin-4(3*H*)-one derivatives from commercially available isatoic anhydride and primary and secondary amines. This protocol, show good functional group tolerance and allow access to a range of 2-alkyl, spiro and quinazolin-4(1*H*)-one derivatives by C–C and N–C bond cleavage in the progress of ROC strategy. It is the first general method to construct the potentially useful 2-methyl quinazolin-4(3*H*)-one by copper-catalyzed intramolecular C–H amination. The synthetic utility of this strategy was illustrated by the convenient synthesis of rutaecarpine *via* ROC strategy.

III. 5. Experimental Section

General Considerations

IR spectra were recorded on a FTIR spectrophotometer. ^{1}H NMR spectra were recorded on 400 MHz spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C NMR spectra were recorded on 100 MHz spectrometer at RT in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of triplet)]. In the ^{1}HNMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br s. = broad singlet. The assignments of signals were confirmed by ^{1}H, ^{13}C spectra. High-resolution mass spectra (HR-MS) were recorded using Q-TOF multimode source. Melting points were determined on an electro thermal melting point apparatus and are uncorrected. 2-amino-N-benzylbenzamides (**3**) were prepared by using known procedures. All the dry solvents such as, MeOH, Toluene were dried over sodium metal and DMSO, CH_3CN and DCE were dried over calcium hydride.

All small scale dry reactions were carried out using standard syringe-septum technique. Reactions were monitored by TLC on silica gel using a combination of petroleum ether and ethyl acetate as eluents. Reactions were generally run under an oxygen atmosphere. Solvents were distilled prior to use; petroleum ether with a boiling range of 40 to 60 ˚C was used.

General Procedure 1: Preparation of 2-amino-*N*-benzylbenzamides:

Isatoic anhydride (815 mg, 5 mmol) in Toluene was treated with benzylamine (547, 5 mmol) at 100 °C for 1-2 h and monitored by TLC. After completion of the reaction, the mixture was washed with H_2O and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuum under reduced pressure and then purified by silica gel column chromatography using ethyl acetate and hexane (15/85) as eluents to afford the corresponding product **25** as a white solid (1.1 g, 98 % yield)[24].

General procedure 2: Preparation of 2-phenylquinazolin-4(3*H*)-ones through ROC Strategy: To a mixture of 2-amino-N-benzylbenzamides **25** (0.22 mmol), CuBr (15 mol %), and KO^{t}Bu (0.44 mmol) in a 10 mL Schlenk tube was added 2 mL of DMSO, and the mixture was stirred at 100 °C for 2-4 h (monitored by TLC) under an oxygen balloon. After the completion of the reaction, the reaction mixture was cooled and was quenched with ice-cold water. Then the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4. The crude extract was purified by filtration through a silica gel (100-200 mesh) column using hexane and ethyl acetate (8/2) as eluents to yield the desired quinazolinone products **26**.

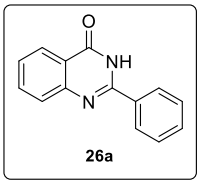
Spectroscopic data of all unknown compounds:

2-phenylquinazolin-4(3H)-one (**26a**):

Physical State:White solid

Yield:(70 %

Mp 140 ^{o}C;



26a

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3396, 1655, 1554, 1469, 995, 823, 762, 682, 616;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 7.59−7.51 (m, 4H), 7.84−7.81 (m, 2H), 8.35−8.27 (m, 3H), 11.81 (br. s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 163.98, 151.81, 149.54, 134.93, 132.83, 131.67, 129.05, 128.02, 127.46, 126.81, 126.38, 120.84.

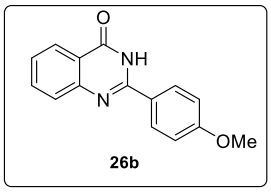
HR-MS (ESI^+) *m/z* calculated for $C_{14}H_{10}N_2O$ [M + H^+] = 223.0866, found: 223.0862.

***2-(4-methoxyphenyl) quinazolin-4(3H)-one (26b)*:**

Physical State : White solid

Yield:65 %

Mp 232 ºC;



26b

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 1679, 1600, 1523, 1479, 1247, 1177, 1030, 834, 764;

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 3.8 (s, 3H), 6.93 (d, J = 8.8, 2H), 7.35 (td, J = 7.3, 7.3, 1H), 7.69-7.63 (m, 2H), 8.14-8.10 (m, 3H);

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 162.16, 161.02, 151.08, 148.35, 133.25, 128.41, 126.39, 124.19, 119.90, 112.92, 54.36.

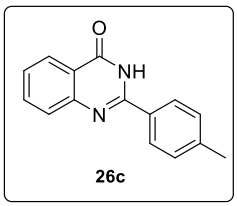
HR-MS (ESI^+) *m/z* calculated for $C_{15}H_{12}N_2O_2$ [M + H^+] = 253.0972, found: 253.0972.

***2-(p-tolyl) quinazolin-4(3H)-one (26c)*:**

Physical State :White solid

Yield:62 %

Mp. :262 ºC



26c

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3741, 1669, 1608, 1550, 1299, 941, 832, 767, 730;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 11.75 (br. s, 1H), 8.33 (d, *J* = 7.8, 1H), 8.16 (d, *J* = 7.3, 2H), 7.81-7.79 (m, 2H), 7.49 (t, *J* = 7.1, 7.1, 1H), 7.37 (d, *J* = 7.8, 2H), 2.46 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 164.00, 151.86, 149.64, 142.18, 134.84, 129.98, 129.75, 127.9, 127.38, 126.56, 126.36, 120.78, 21.56.

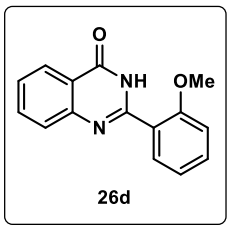
HR-MS (ESI^+) *m/z* calculated for $C_{15}H_{12}N_2O$ [M + H^+] = 237.1022, found: 237.1024.

***2-(2-methoxyphenyl) quinazolin-4(3H)-one (26d)*:**

Physical State :White solid

Yield:58%

Mp :170 ^oC;



26d

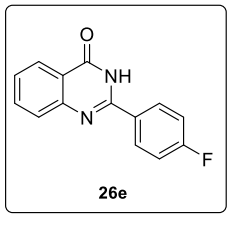
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} =3743, 1676, 1593, 1557, 1474, 1233, 1013, 745.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 10.95 (br. s., 1H), 8.51 (dd, *J* = 7.83, 1.96 Hz, 1H), 8.19 - 8.36 (m, 1H), 7.63 - 7.83 (m, 2H), 7.38 - 7.53 (m, 2H), 7.11 - 7.18 (m, 1H), 7.04 (d, *J* = 8.31 Hz, 1H), 4.03 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 161.89, 157.76, 150.77, 149.39, 134.45, 133.17, 131.51, 127.85, 126.45, 126.39, 121.83, 121.18, 119.91, 111.81, 56.14.

HR-MS (ESI^+) *m/z* calculated for $C_{15}H_{12}N_2O_2$ [M + H^+] = 253.0972, found: 253.0971.

***2-(4-fluorophenyl) quinazolin-4(3H)-one (26e)*:**



26e

Physical State : White solid

Yield : 60%

Mp : 260 ^{o}C;

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3742, 1659, 1620, 1215, 755;

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 12.09(br. s. 1H), 8.17 (dd, J = 8.1 and 6.1, 2H), 7.69-7.67 (m, 2H), 7.39-7.34 (m, 2H), 7.14-7.10 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 163.31, 151.39 (d, J_{C-F} = 227.0 Hz), 149.13, 134.39, 130.03 (d, J_{C-F} = 9.0 Hz), 129.94, 127.60, 126.06, 121.02, 115.78 (d, J_{C-F} = 22.0 Hz), 115.56.

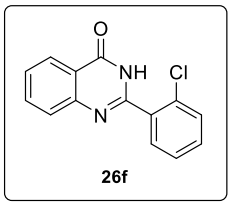
HR-MS (ESI^{+}) *m/z* calculated for $C_{14}H_9FN_2O$ [M + H^{+}] = 241.0772, found: 241.0777.

***2-(2-chlorophenyl) quinazolin-4(3H)-one (26f)*:**

Physical State : White solid

Yield : 66%

Mp : 55 ^{o}C.



26f

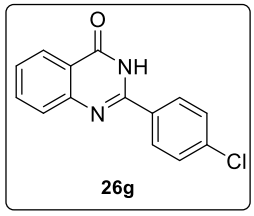
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3743, 1666, 1605, 1559, 1512, 1474, 1334, 1292, 768, 690.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 11.87 (br. s. 1H), 8.35-8.29 (m, 1H), 8.28-8.27 (m, 2H), 7.85-7.81 (m, 2H), 7.61-7.59 (m, 2H), 7.53-7.49 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 163.99, 151.79, 149.55, 134.92, 132.83, 131.66, 129.05, 128.02, 127.46, 126.80, 126.37, 120.85.

HR-MS (ESI^{+}) *m/z* calculated for $C_{14}H_9ClN_2O$ [M + H^{+}] = 257.0476, found: 257.0480.

***2-(4-chlorophenyl) quinazolin-4(3H)-one (26g)*:**



26g

Physical State :White solid

Yield:56%

Mp :200 ^{o}C;

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3742, 1740, 1703, 1641, 1516, 1462, 1515, 1240, 720;

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 12.49 (br. s. 1H), 8.25-8.18 (m, 3H), 7.77-7.73 (m, 2H), 7.53-7.48 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 167.6, 156.3, 153.8, 141.8, 139.3, 136.6, 134.5, 133.6, 133.5, 132.6, 131.5, 130.9, 126.2.

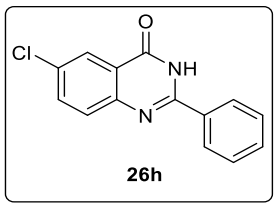
HR-MS (ESI^+) *m/z* calculated for $C_{14}H_9ClN_2O$ [M + H^+] = 257.0476, found: 257.0476.

***6-chloro-2-phenylquinazolin-4(3H)-one (26h)*:**

Physical State :White solid

Yield:62%

Mp :230 ^{o}C;



26h

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3742, 2923, 1680, 1646, 1509, 1467, 1250, 690.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 8.21-8.18 (m, 2H), 7.74-7.68 (m, 2H), 7.55 (br. s. 1H), 7.36 (d, J = 5.9, 1H).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 152.44, 147.35, 134.13, 132.33, 131.17, 131.03, 129.06, 128.44, 128.21, 127.41, 124.91, 121.93.

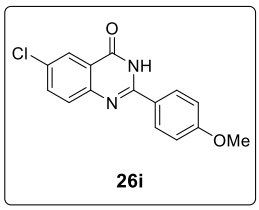
HR-MS (ESI^+) *m/z* calculated for $C_{14}H_9ClN_2O$ [M+H^+] = 257.0476, found: 257.0476.

***6-chloro-2-(4-methoxyphenyl) quinazolin-4(3H)-one (26i)*:**

Physical State :White solid

Yield:58 %

Mp :145 ºC;



26i

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3723, 1666, 1603, 1508, 1253, 1177, 1031, 832.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 11.72 (br. s. 1H), 8.28-8.17 (m, 2H), 7.76-7.68 (m, 2H), 7.39 (s, 1H), 7.03 (dd, *J* = 8.8 and 2.4, 2H), 3.89 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 163.36, 149.49, 134.66, 134.37, 129.32, 129.20, 127.51, 126.11, 126.01, 125.47, 120.86, 114.10, 55.39.

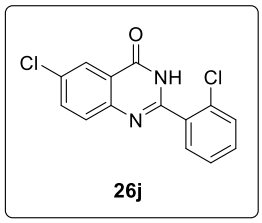
HR-MS (ESI^+) *m/z* calculated for $C_{15}H_{11}ClN_2O_2$ $[M+H^+]$ = 287.0582, found: 257.0585.

***6-chloro-2-(2-chlorophenyl) quinazolin-4(3H)-one (26j)*:**

Physical State : White solid

Yield: 55 %

Mp : 270 ºC;



26j

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3394, 1678, 995, 824, 763.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 8.14-8.12 (m, 2H), 7.81 (s, 1H), 7.65-7.7.48 (m, 2H), 7.45-7.7.43 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 160.57, 151.46, 146.38, 133.15, 131.37, 130.07, 128.17, 127.23, 126.52, 123.9, 121.

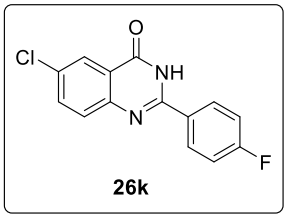
HR-MS (ESI^+) *m/z* calculated for $C_{16}H_8Cl_2N_2O$ $[M+H^+]$ = 291.0086, found: 291.0076.

***6-chloro-2-(4-fluorophenyl) quinazolin-4(3H)-one (26k)*:**

Physical State :White solid

Yield:56%

Mp :260 ^{o}C;



26k

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3419, 1655, 1506, 1420, 1288, 1182, 1023, 994, 825, 730.

H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 12.64 (br. s. 1H), 8.23 (dd, J = 8.6 and 5.1, 2H), 8.08-8.05 (m, 1H), 7.74-7.67 (m, 2H), 7.24 (t, J = 8.3, 8.3 and 8.3, 2H).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 161.41, 151.55 (d, J_{C-H} = 422.0 Hz), 147.32, 135.81, 134.34, 130.94, 130.1 (d, J_{C-H} = 9.0 Hz), 129.31, 128.72, 124.83, 115.45 (d, J_{C-H} = 21.0 Hz), 115.24.

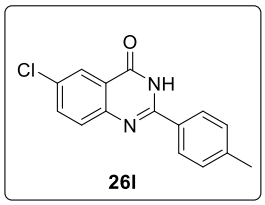
HR-MS (ESI^{+}) *m/z* calculated for $C_{14}H_8ClFN_2O$ [M+H^{+}] = 275.0382, found: 275.0382.

***6-chloro-2-(p-tolyl) quinazolin-4(3H)-one (26l)*:**

Physical State :White solid

Yield:58 %

Mp 230 ^{o}C;



26l

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2920, 1667, 1600, 1466, 1286, 762.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 12.46 (br. s. 1H), 8.20-8.09 (m, 2H), 7.9 (d, J = 3.4, 1H), 7.76-7.73 (m, 2H), 731 (d, J = 6.8, 2H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 160.39, 140.22, 132.97, 129.62, 128.38, 127.76, 126.31, 123.68, 120.75, 19.85

.

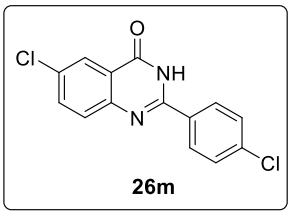
HR-MS (ESI^{+}) *m/z* calculated for $C_{15}H_{11}ClN_2O$ [M+H^{+}] = 271.0633, found: 271.0636.

***6-chloro-2-(4-chlorophenyl) quinazolin-4(3H)-one (26m)*:**

Physical State :White solid;

Yield:45 %

Mp :320 ºC.



26m

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3391, 1659, 1021, 997, 825, 763, 624.

^{1}H NMR (400MHz, DMSO-d_6) = 12.77 (br.s. 1H), 8.31 - 8.13 (m, 2H), 8.09 (s, 1H), 7.95 - 7.82 (m, 1H), 7.77 (d, *J* = 8.8 Hz, 1 H), 7.68 - 7.54 (m, 2H).

^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 176.20, 142.93, 136.49, 134.75, 131.26, 130.95, 129.67, 128.70, 128.62, 128.27, 127.81, 124.86.

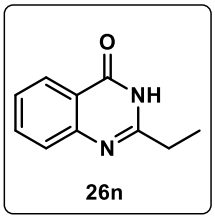
HR-MS (ESI$^+$) *m/z* calculated for $C_{14}H_8Cl_2N_2O$ [M+H$^+$] = 291.0086, found: 271.0089.

***2-ethylquinazolin-4(3H)-one* (*26n*)**:

Physical State :White solid

Yield:56 %

Mp :210 ºC;



26n

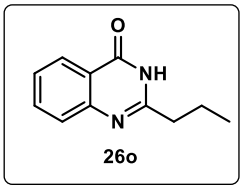
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3841, 1682, 1586, 1420, 1234, 1181, 774, 756, 692.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 12.23 (br. s., 1H), 8.30 (dd, *J* = 8.07, 1.22 Hz, 1H), 7.60 - 7.86 (m, 2H), 7.33 - 7.60 (m, 1H), 2.86 (q, *J* = 7.34 Hz, 2H), 1.47 (t, *J* = 7.58 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 164.57, 157.79, 149.53, 134.81, 127.22, 126.36, 126.24, 120.50, 29.17, 11.60.

HR-MS (ESI$^+$) *m/z* calculated for $C_{10}H_{10}N_2O$ [M+H$^+$] = 175.0866, found: 175.0865.

2-propylquinazolin-4(3H)-one (26o):



26o

Physical State :White solid

Yield:60%

Mp 180 ^{o}C;

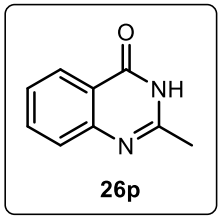
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3641, 1686, 1556, 1410, 1209, 1191, 776, 766, 698.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 12.24 (br. s., 1H), 8.30 (dd, *J* = 8.07, 1.22 Hz, 1H), 7.59 - 7.87 (m, 2H), 7.39 - 7.56 (m, 1H), 2.66 - 2.88 (m, 2H), 1.94 (dq, *J* = 15.10, 7.52 Hz, 2H), 1.09 (t, *J* = 7.34 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 164.53, 156.89, 149.53, 134.79, 127.22, 126.21, 120.48, 37.74, 21.05, 13.77.

HR-MS (ESI^+) *m/z* calculated for $C_{11}H_{12}N_2O$ $[M+H^+]$ = 189.1022, found: 189.1022.

2-methylquinazolin-4(3H)-one (26p):



26p

Physical State : White solid

Yield: 57%

Mp : 280 ^{o}C;

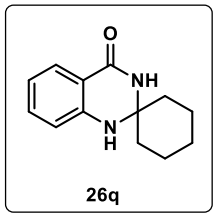
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3346, 1586, 1456, 1310, 1109, 991, 778, 798, 688.

^{1}H NMR (400MHz, DMSO-d_6) δ ppm = 12.21 (br. s., 1H), 7.99 - 8.16 (m, 1H), 7.72 - 7.85 (m, 1H), 7.48 - 7.60 (m, 1H), 7.44 (t, *J* = 7.58 Hz, 1H), 3.42 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 161.71, 154.24, 145.36, 134.27, 126.7, 125.8, 125.63, 120.56, 21.39.

HR-MS (ESI^+) *m/z* calculated for $C_9H_8N_2O$ $[M+H^+]$ = 161.0709, found: 161.0709.

1'H-spiro[cyclohexane-1,2'-quinazolin]-4'(3'H)-one (26q):



26q

Physical State :White solid

Yield: 65%

Mp :140 ^{o}C;

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3324, 3040, 1679, 1580, 1486, 1392, 1182, 1120, 982, 776, 723, 685.

^{1}H NMR (400MHz , $CDCl_3$) δ ppm = 11.29 (br. s., 1H), 8.28 (dd, *J* = 1.2, 8.1 Hz, 1H), 7.86 - 7.60 (m, 2H), 7.58 - 7.36 (m, 1H), 2.83 - 2.71 (m, 2H), 2.28 - 2.10 (m, 1H), 2.10 - 1.93 (m, 1H), 1.91 - 1.78 (m, 3H), 1.01 - 0.84 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 163.86, 156.74, 134.81, 127.22, 126.40, 126.26, 36.01, 31.38, 27.22, 22.35, 13.94

.

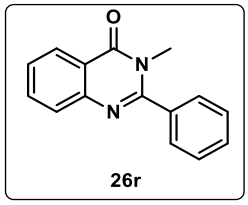
HR-MS (ESI^{+}) *m/z* calculated for $C_{13}H_{16}N_2O$ [M+H^{+}] = 217.1335, found: 217.1328.

***3-methyl-2-phenylquinazolin-4(3H)-one* (*26r*):**

Physical State :White Solid

Yield:63%

Mp :132 ^{o}C;



26r

IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 1673, 1562, 1472, 1352, 1023, 773, 641;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 8.33 (d, *J* = 8.31 Hz, 1H), 7.71 - 7.81 (m, 2H), 7.45 - 7.61 (m, 6H), 3.50 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 162.73, 156.14, 147.33, 135.42, 134.32, 130.08, 128.90, 127.51, 127.01, 126.69, 120.54, 34.28.

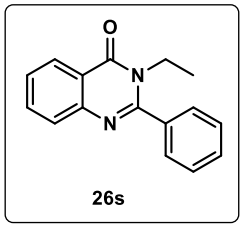
HR-MS (ESI^{+}) *m/z* calculated for $C_{15}H_{12}N_2O$ [M+H^{+}] = 237.1022, found: 237.1030.

3-ethyl-2-phenylquinazolin-4(3H)-one (26s):

Physical State :White Solid

Yield:62%

Mp 125 ^{o}C;



26s

IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 1673, 1564, 1468, 1378, 1254, 1066, 772, 701;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 8.34 (d, *J* = 7.34 Hz, 1H), 7.64 - 7.94 (m, 2H), 7.37 - 7.63 (m, 6H), 4.04 (d, *J* = 6.85 Hz, 2H), 1.22 (t, *J* = 7.09 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 162.01, 156.20, 147.21, 135.62, 134.29, 129.79, 128.82, 127.67, 127.46, 126.95, 126.71, 121.00, 41.19, 14.12.

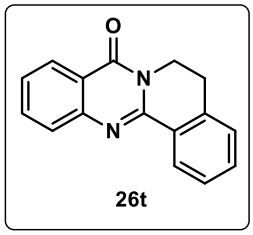
HR-MS (ESI^{+}) *m/z* calculated for $C_{16}H_{14}N_2O$ $[M+H^{+}]$ = 251.1179, found: 251.1185.

5H-isoquinolino[1,2-b] quinazolin-8(6H)-one (26t):

Physical State :White Solid;

Yield:58%;

Mp :140 ^{o}C;



26t

IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 1670, 1558, 1475, 1394, 1335, 1150, 768, 707.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 8.49 (dd, *J* = 7.82, 1.47 Hz, 1H), 8.27 - 8.39 (m, 1H), 7.70 - 7.84 (m, 2H), 7.38 - 7.57 (m, 3H), 7.22 - 7.34 (m, 1H), 4.33 - 4.48 (m, 2H), 3.11 (t, *J* = 6.60 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 161.74, 149.40, 147.84, 137.07, 134.23, 131.73, 129.6, 128.05, 127.65, 127.63, 127.51, 126.88, 126.54, 120.78, 39.63, 27.49.

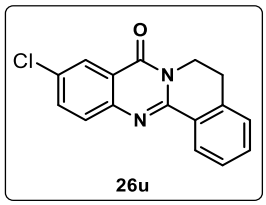
HR-MS (ESI$^+$) *m/z* calculated for $C_{16}H_{12}N_2O$ [M+H$^+$] = 249.1022, found: 249.1028.

10-chloro-5H-isoquinolino[1,2-b] quinazolin-8(6H)-one (26u):

Physical State :White Solid;

Yield: 55%

Mp 172 ^oC;



26u

IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 1672, 1555, 1466, 1394, 1335, 1240, 1153, 1067, 895, 833, 772.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 8.46 (d, *J* = 7.34 Hz, 1H), 8.27 (d, *J* = 1.96 Hz, 1H), 7.61 - 7.81 (m, 2H), 7.39 - 7.56 (m, 2H), 7.19 - 7.35 (m, 1H), 4.32 - 4.52 (m, 2H), 3.11 (t, *J* = 6.60 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 160.75, 149.63, 146.33, 137.03, 134.70, 132.21, 131.98, 129.27, 128.05, 127.72, 127.59, 126.22, 121.70, 39.77, 27.36.

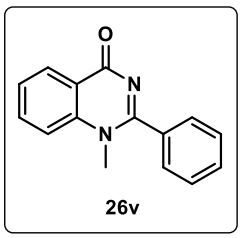
HR-MS (ESI$^+$) *m/z* calculated for $C_{16}H_{11}ClN_2O$ [M+H$^+$] = 283.0633, found: 283.0633.

1-methyl-2-phenylquinazolin-4(1H)-one (26v):

Physical State :Brown solid;

Yield: 34%

Mp :210 ^oC;



26v

IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 1640, 1602, 1519, 1458, 1393, 1257, 1144, 1071, 1036, 765, 699.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 8.42 (dd, *J* = 7.82, 1.47 Hz, 1H), 7.73 - 7.88 (m, 1H), 7.59 - 7.69 (m, 2H), 7.44 - 7.59 (m, 5H), 3.73 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 168.79, 162.49, 141.82, 134.76, 133.94, 130.73, 128.88, 128.74, 128.65, 126.27, 120.41, 115.20, 37.98.

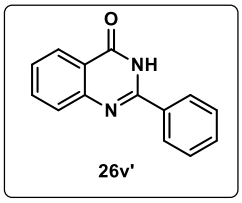
HR-MS (ESI$^+$) *m/z* calculated for $C_{15}H_{12}N_2O$ [M+H$^+$] = 237.1022, found: 237.1027.

2-phenylquinazolin-4(3H)-one (26v'):

Physical State :White Solid

Yield: 38%

Mp 142 ^oC;



26v'

IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3396, 1655, 1554, 1469, 995, 823, 762, 682, 616;

^{1}H NMR (400MHz, DMSO-d_6) = 12.56 (br. s., 1H), 8.10 - 8.25 (m, 3H), 7.80 - 7.89 (m, 1H), 7.70 - 7.80 (m, 1H), 7.37 - 7.62 (m, 4H).

^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 162.21, 152.26, 148.70, 134.57, 132.67, 131.36, 128.57, 127.73, 127.47, 126.55, 125.82, 120.94.

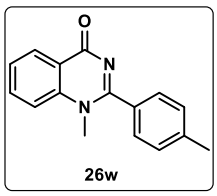
HR-MS (ESI$^+$) *m/z* calculated for $C_{14}H_{10}N_2O$ [M + H$^+$] = 223.0866, found: 223.0862.

1-methyl-2-(p-tolyl) quinazolin-4(1H)-one (26w):

Physical State :Yellow solid;

Yield: 32%

Mp :165 ^oC;



26w

IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 1688, 1619, 1514, 1464, 1418, 1286, 1041, 967, 785, 674;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 8.38 (d, *J* = 7.82 Hz, 1H), 7.66 - 7.85 (m, 1H), 7.43 - 7.60 (m, 5H), 7.21 - 7.36 (m, 2H), 3.73 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 168.87, 162.60, 141.93, 141.15, 133.81, 131.85, 129.22, 129.03, 128.59, 126.08, 120.36, 115.24, 38.12, 21.50.

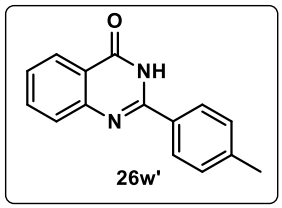
HR-MS (ESI$^+$) *m/z* calculated for $C_{16}H_{14}N_2O$ [M + H$^+$] = 251.1179, found: 251.1178.

2-(p-tolyl) quinazolin-4(3H)-one (26w'):

Physical State :White Solid;

Yield: 30%

Mp 150 ^oC;



26w'

IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3742, 1672, 1605, 1556, 1473, 1294, 767, 686.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 11.68 (br. s., 1H), 8.22 - 8.43 (m, 1H), 8.16 (m, *J* = 8.31 Hz, 2H), 7.76 - 7.85 (m, 2H), 7.49 (ddd, *J* = 7.95, 6.24, 1.96 Hz, 1H), 7.37 (m, *J* = 7.83 Hz, 2H), 2.46 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 163.96, 151.83, 149.66, 142.18, 134.83, 130.00, 129.75, 128.07, 127.91, 127.36, 126.55, 126.37, 120.79, 21.55.

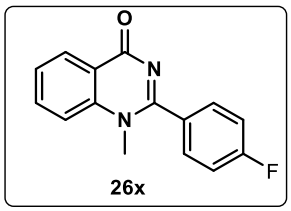
HR-MS (ESI$^+$) *m/z* calculated for $C_{15}H_{12}N_2O$ [M + H$^+$] = 237.1022, found: 237.1026.

***2-(4-fluorophenyl)-1-methylquinazolin-4(1H)-one* (*26x*):**

Physical State :White Solid;

Yield: 29%

Mp :210 ^oC;



26x

IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 1640, 1493, 1455, 1394, 1225, 1147, 856, 766, 695;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 8.33 (dd, *J* = 7.82, 1.47 Hz, 1H), 7.76 (ddd, *J* = 8.44, 7.21, 1.47 Hz, 1H), 7.61 - 7.69 (m, 2H), 7.42 - 7.53 (m, 2H), 7.12 - 7.21 (m, 2H), 3.72 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 168.65, 161.47 (d, J_{C-H} = 381.0 Hz), 141.79, 133.97, 131.35 (d, J_{C-H} = 8.0 Hz), 130.85, 128.59, 126.32, 120.33, 115.95 (d, J_{C-H} = 22.0 Hz), 115.29, 38.08.

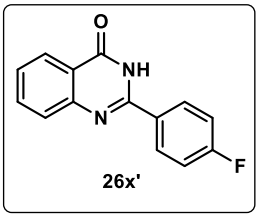
HR-MS (ESI^+) *m/z* calculated for $C_{15}H_{11}FN_2O$ [M + H^+] = 255.0928, found: 255.0921.

***2-(4-fluorophenyl) quinazolin-4(3H)-one (26x')*:**

Physical State: White solid

Yield:32%

Mp :260 ^oC;



26x'

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3742, 1659, 1620, 1215, 755;

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 12.09 (br. s. 1H), 8.17 (dd, *J* = 8.1 and 6.1, 2H), 7.69-7.67 (m, 2H), 7.39-7.34 (m, 2H), 7.14-7.10 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 163.31, 151.39 (d, J_{C-F} = 227.0 Hz), 149.13, 134.39, 130.03 (d, J_{C-F} = 9.0 Hz), 129.94, 127.60, 126.06, 121.02, 115.78 (d, J_{C-F} = 22.0 Hz), 115.56.

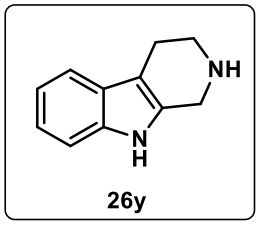
HR-MS (ESI^+) *m/z* calculated for $C_{14}H_9FN_2O$ [M + H^+] = 241.0772, found: 241.0777.

***2,3,4,9-tetrahydro-1H-pyrido[3,4-b] indole (26y)*:**

Physical State :Brown solid;

Yield:72%

Mp :152 ^oC;



26y

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3743, 3648, 1731, 1642, 1515, 1462, 1287, 801, 668;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 7.91 (br. s., 1H), 7.48 (d, *J* = 7.34 Hz, 1H), 7.20 - 7.38 (m, 1H), 7.04 - 7.18 (m, 2H), 4.00 (s, 2H), 3.17 (t, *J* = 5.62 Hz, 2H), 2.75 (t, *J* = 5.38 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 135.66, 132.74, 127.57, 121.47, 119.37, 117.86, 110.70, 108.66, 43.86, 43.16, 22.45.

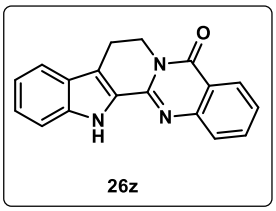
HR-MS (ESI^+) *m/z* calculated for $C_{11}H_{12}N_2$ [M + H^+] = 173.1073, found: 173.1073.

7,8-dihydroindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5(13H)-one (26z) :

Physical State : White solid

Yield: 60%

Mp : 136 ºC.



26z

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 1613, 1590, 1469, 1435, 1307, 1234, 1159, 736, 698.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 9.95 (br. s., 1H), 8.33 (dd, *J* = 8.07, 1.22 Hz, 1H), 7.54 - 7.83 (m, 3H), 7.41 (ddd, *J* = 8.19, 6.72, 1.71 Hz, 1H), 7.26 (dd, *J* = 5.14, 1.71 Hz, 2H), 7.15 (ddd, *J* = 8.07, 4.65, 3.42 Hz, 1H), 4.51 - 4.68 (m, 2H), 3.22 (t, *J* = 6.85 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 161.63, 147.41, 145.20, 138.38, 134.42, 127.29, 127.12, 126.49, 126.26, 125.57, 121.15, 120.59, 120.08, 118.49, 112.16, 41.18, 19.68.

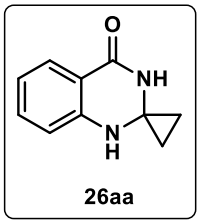
HR-MS (ESI^+) *m/z* calculated for $C_{18}H_{13}N_3O$ [M + H^+] = 288.1131, found: 288.1136.

2-cyclopropylquinazolin-4(3*H*)-one (26aa):

Physical State : White solid

Yield : 63

Mp : 230 ºC;



26aa

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2922, 2057, 1669, 1604, 1459, 1395, 981, 893, 763, 606.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 11.66 (br. s, 1H), 8.26 (d, *J* = 7.8, 1H), 7.72 (t, *J* = 7.3, 7.3, 1H), 7.6 (d, *J* = 8.3, 1H), 2.03-1.92 (m, 1H), 1.36-1.28 (m, 2H), 1.16-1.1 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 163.97, 157.96, 149.82, 134.65, 127.01, 126.28, 125.66, 120.5, 34.01, 14.72, 9.62

Elem. Anal. Calc. for $C_{11}H_{10}N_2O$ (186.0793): C, 70.95; H, 5.41; N, 15.04; found C, 70.45; H, 5.62; N, 15.48.

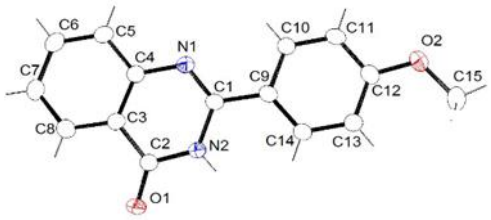


Figure 1. X-ray crystal structure of product **26b (**CCDC 1574127). Thermal ellipsoids are drawn at 30% probability level.

Operator	Jayeetha Bhattacharjee
Difractometer	Oxford Super Nova
Empirical formula	$C_{15}H_{12}N_2O_2$
Formula weight	252.27
Temperature/K	150(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	10.4890(11)
b/Å	5.0325(4)
c/Å	22.9271(16)
α/°	90.00
β/°	97.654(7)
γ/°	90.00
Volume/$Å^3$	1199.46(18)

Z	4
ρ_{calc}g/cm^3	1.397
μ/mm^{-1}	0.095
F(000)	528.0
Crystal size/mm^3	0.2 × 0.1 × 0.1
Radiation	Mo Kα (λ = 0.7107)
2Θ range for data collection/°	6.22 to 58.22
Index ranges	$-12 \leq h \leq 13$, $-6 \leq k \leq 5$, $-31 \leq l \leq 27$
Reflections collected	5189
Independent reflections	2761 [R_{int} = 0.0308, R_{sigma} = 0.0626]
Data/restraints/parameters	2761/0/173
Goodness-of-fit on F^2	0.988
Final R indexes [I>=2σ (I)]	R_1 = 0.0611, wR_2 = 0.1570
Final R indexes [all data]	R_1 = 0.1061, wR_2 = 0.2049
Largest diff. peak/hole / e Å^{-3}	0.19/-0.27

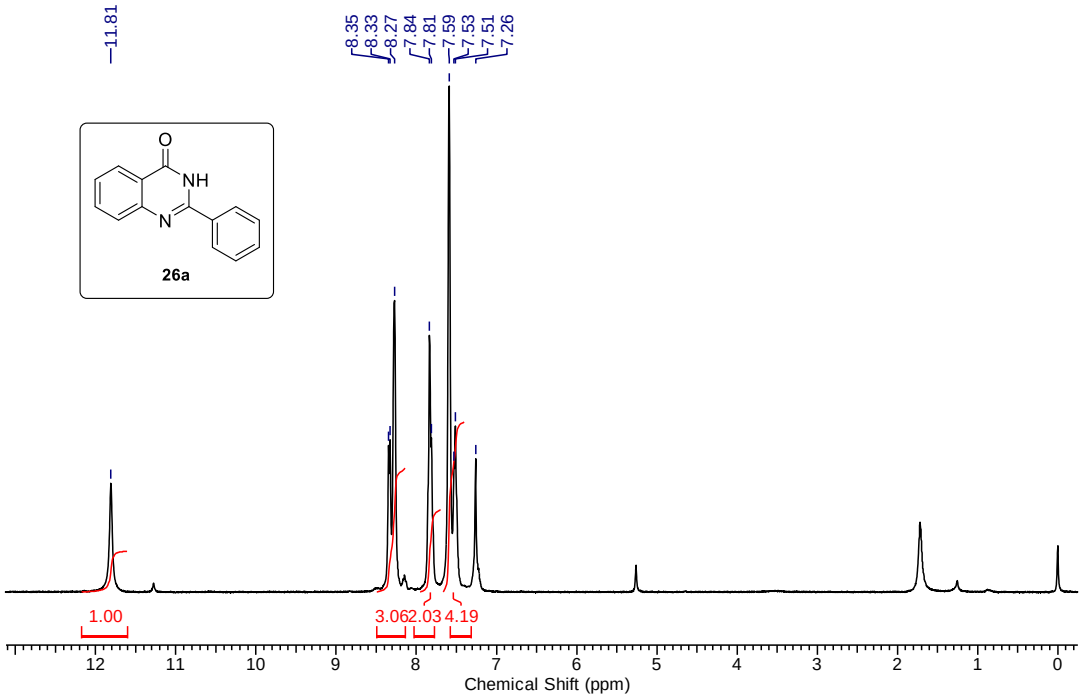


Figure 1. ^{1}H NMR (400 MHz) spectrum of compound **26a** in $CDCl_3$.

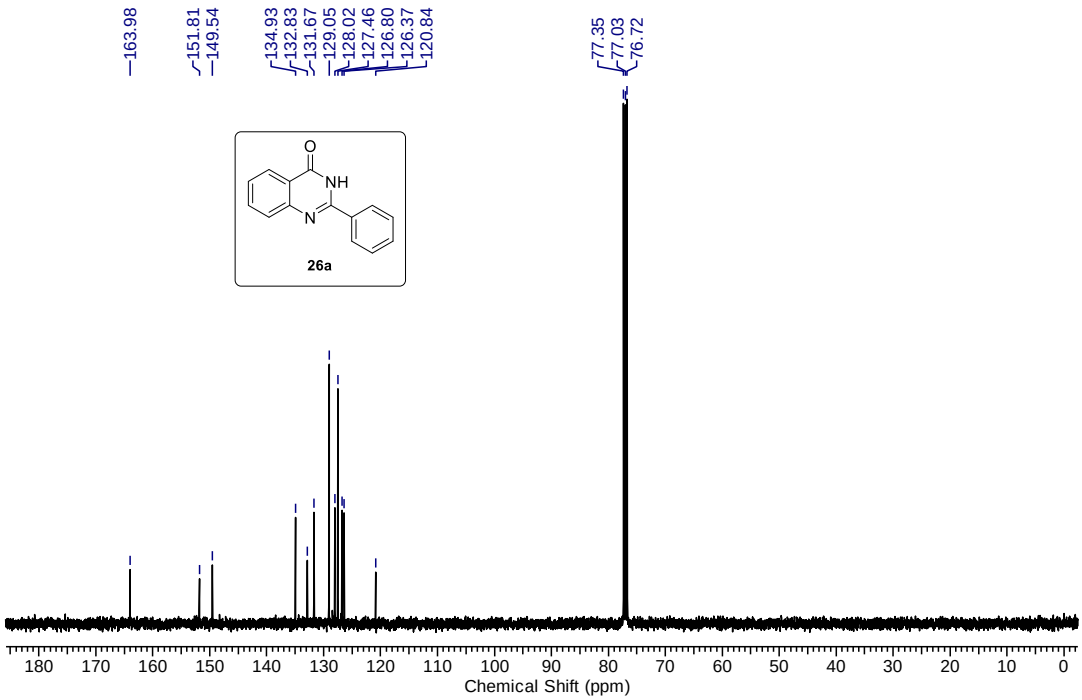


Figure 2. ^{13}C NMR (100 MHz) spectrum of compound **26a** in $CDCl_3$.

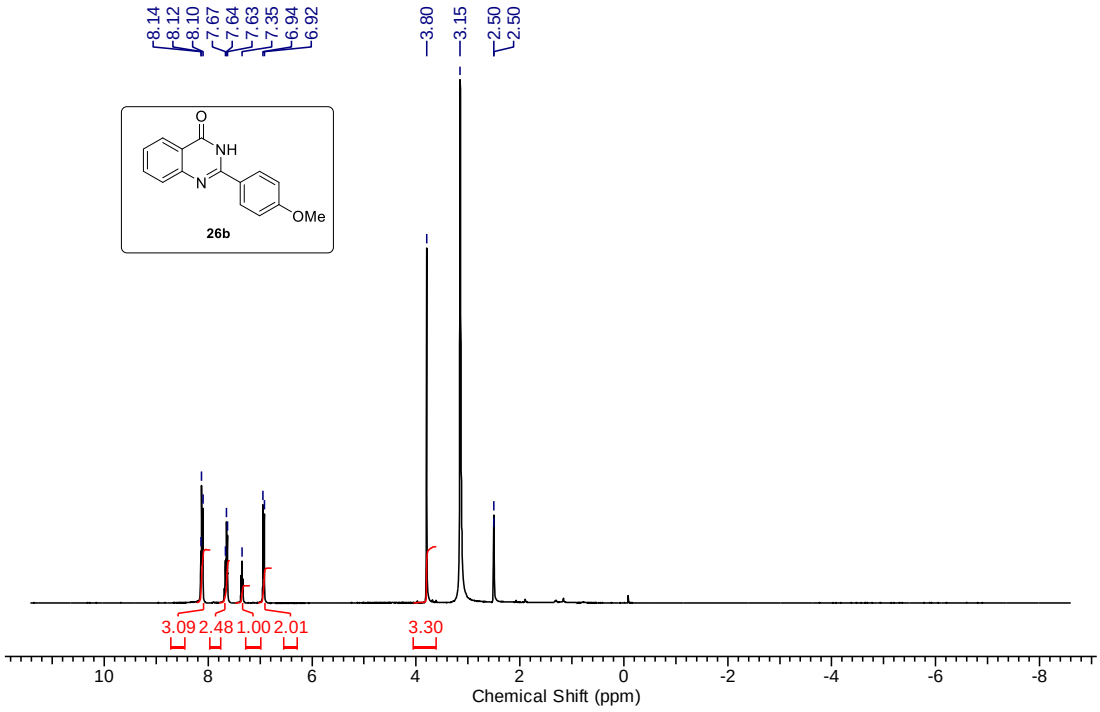


Figure 3. ^{1}H NMR (400 MHz) spectrum of compound **26b** in $CDCl_3$ + DMSO-d_6.

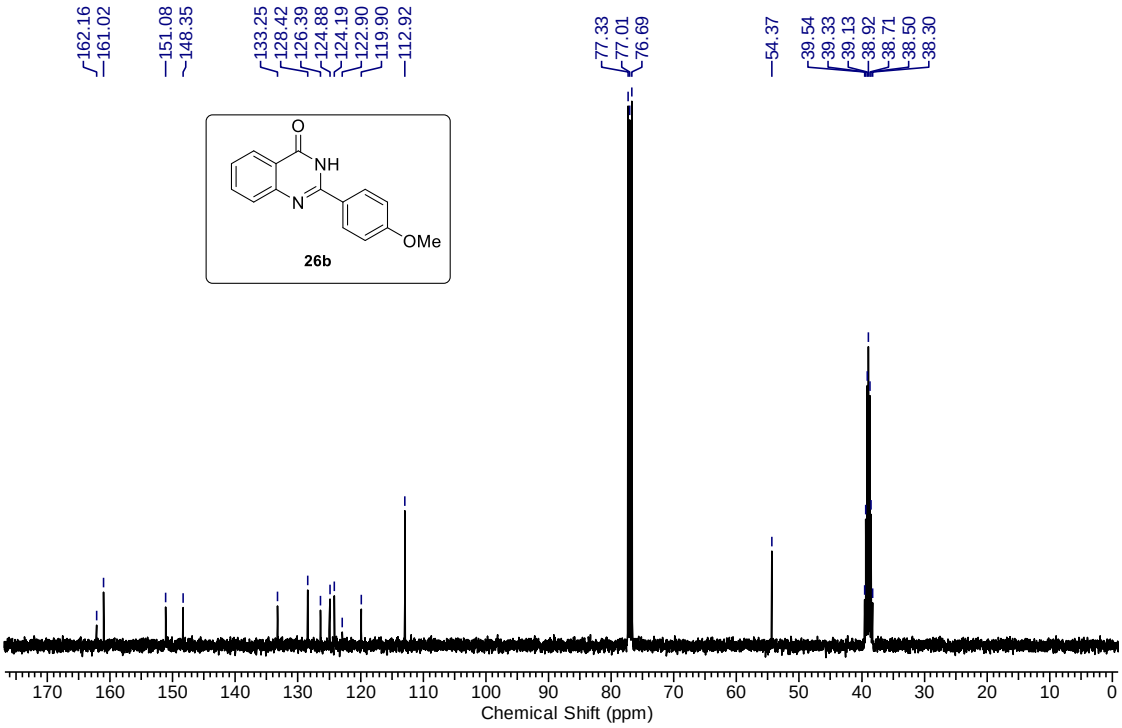


Figure 4. ^{13}C NMR (100 MHz) spectrum of compound **26b** in $CDCl_3$ + DMSO-d_6.

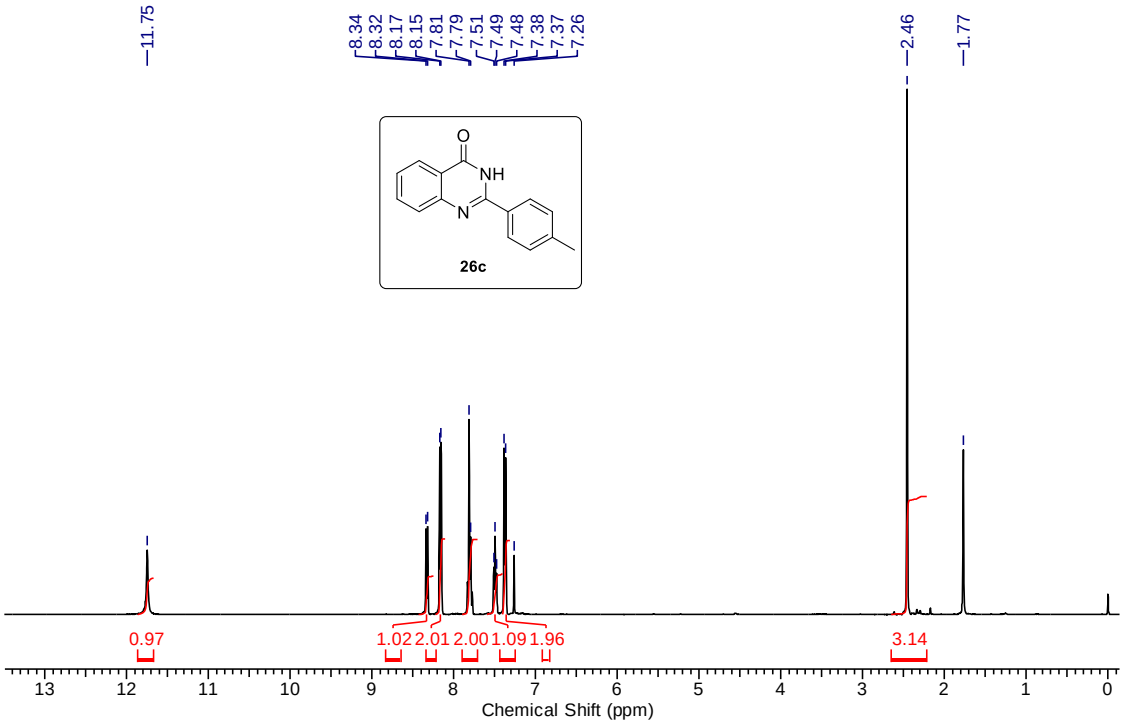


Figure 5. ^{1}H NMR (400 MHz) spectrum of compound **26c** in $CDCl_3$

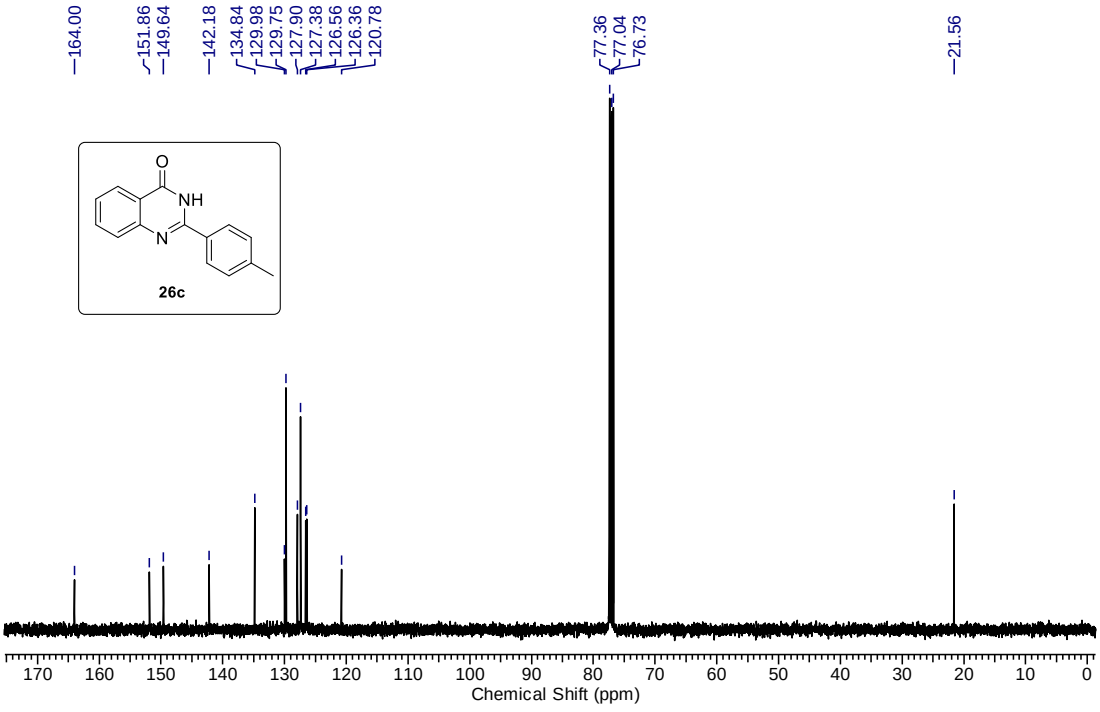


Figure 6. ^{13}C NMR (100 MHz) spectrum of compound **26c** in $CDCl_3$.

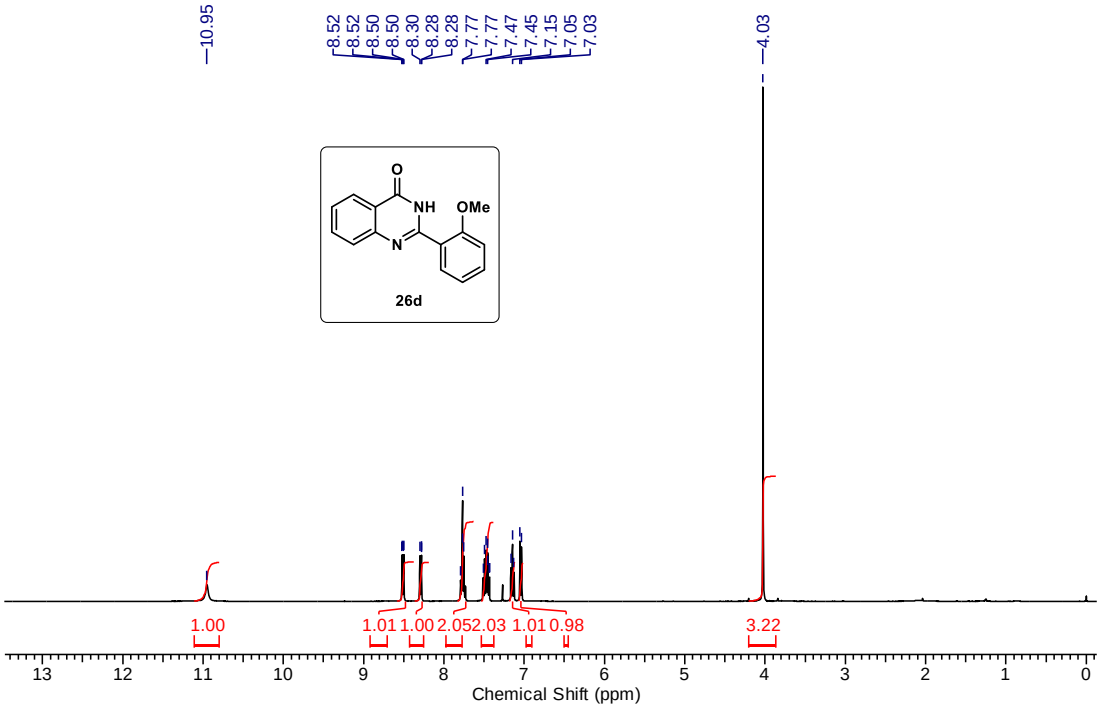


Figure 7. ^{1}H NMR (400 MHz) spectrum of compound **26d** in $CDCl_3$

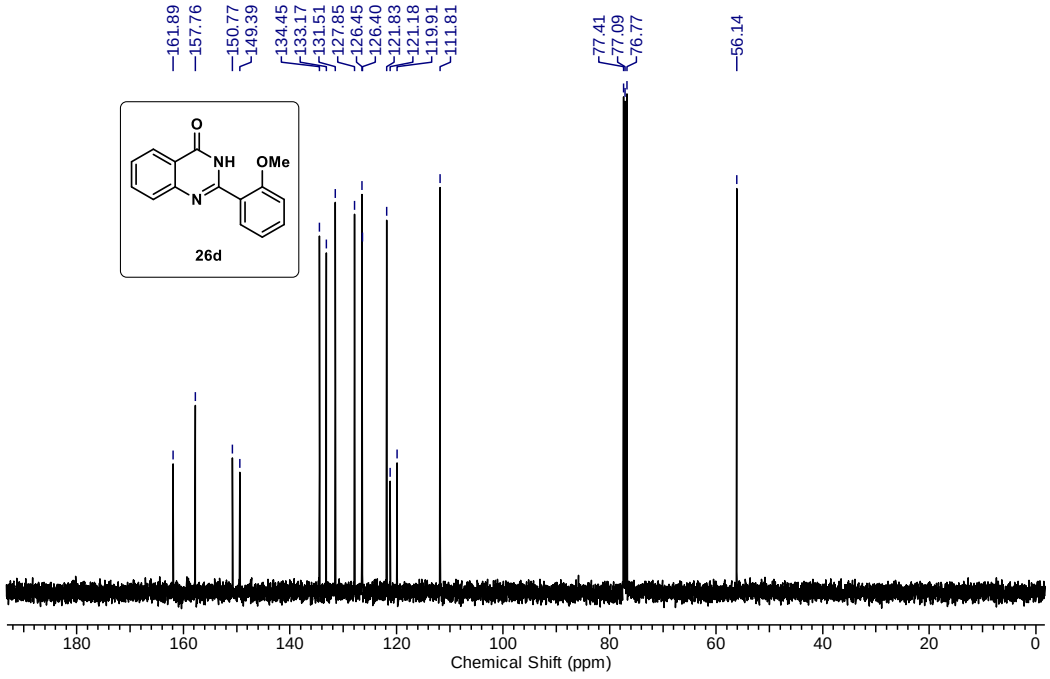


Figure 8. ^{13}C NMR (100 MHz) spectrum of compound **26d** in $CDCl_3$.

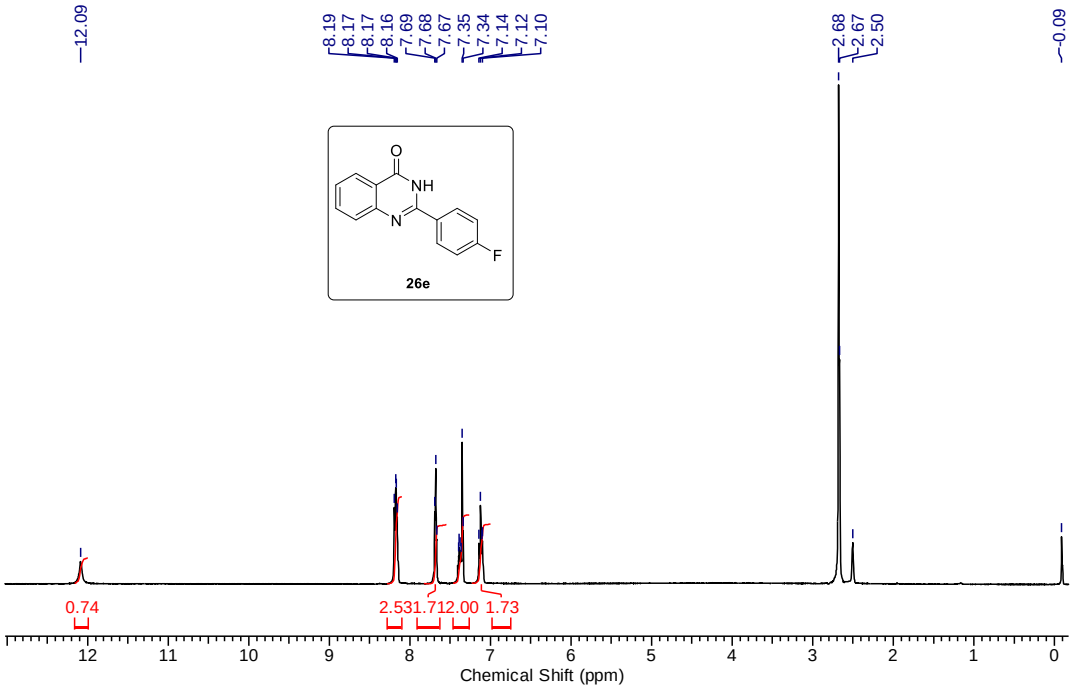


Figure 9. ^{1}H NMR (400 MHz) spectrum of compound **26e** in $CDCl_3$ + DMSO-d_6

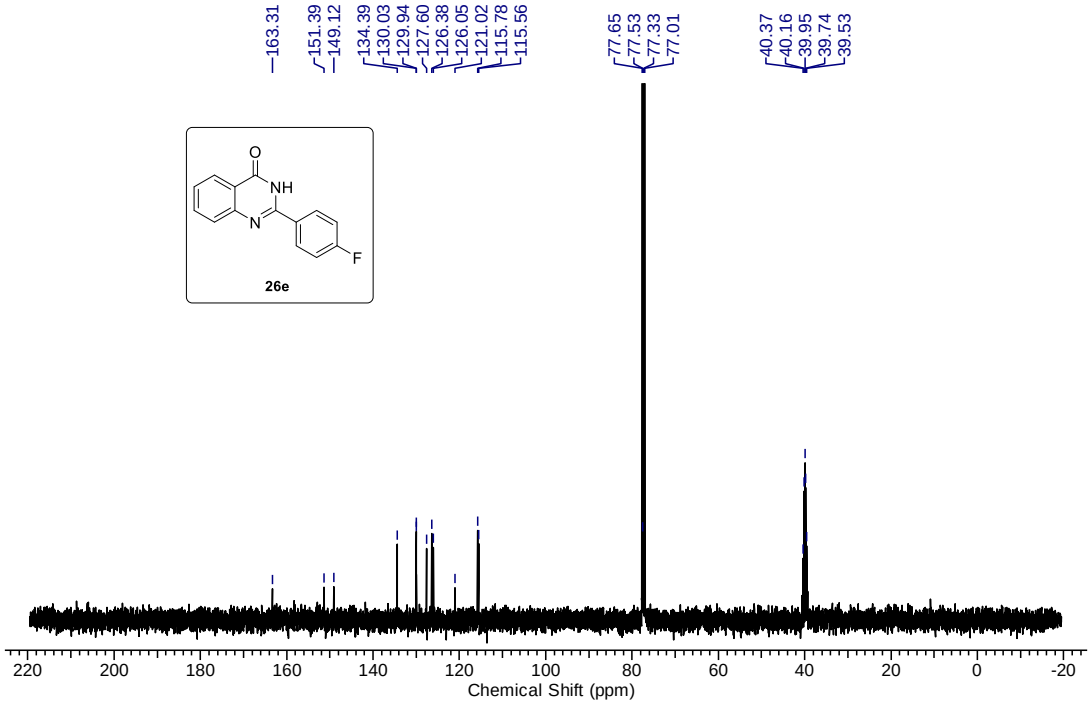


Figure 10. ^{13}C NMR (100 MHz) spectrum of compound **4e** in $CDCl_3$ + DMSO-d_6.

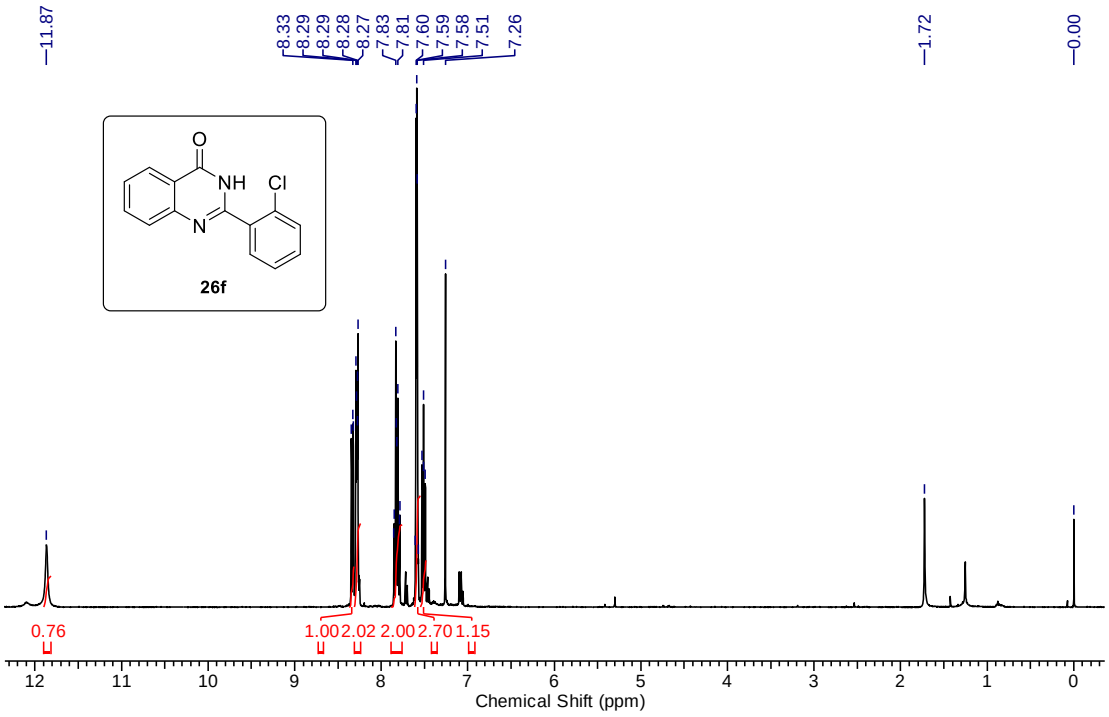


Figure 11. ^{1}H NMR (400 MHz) spectrum of compound **26f** in $CDCl_3$

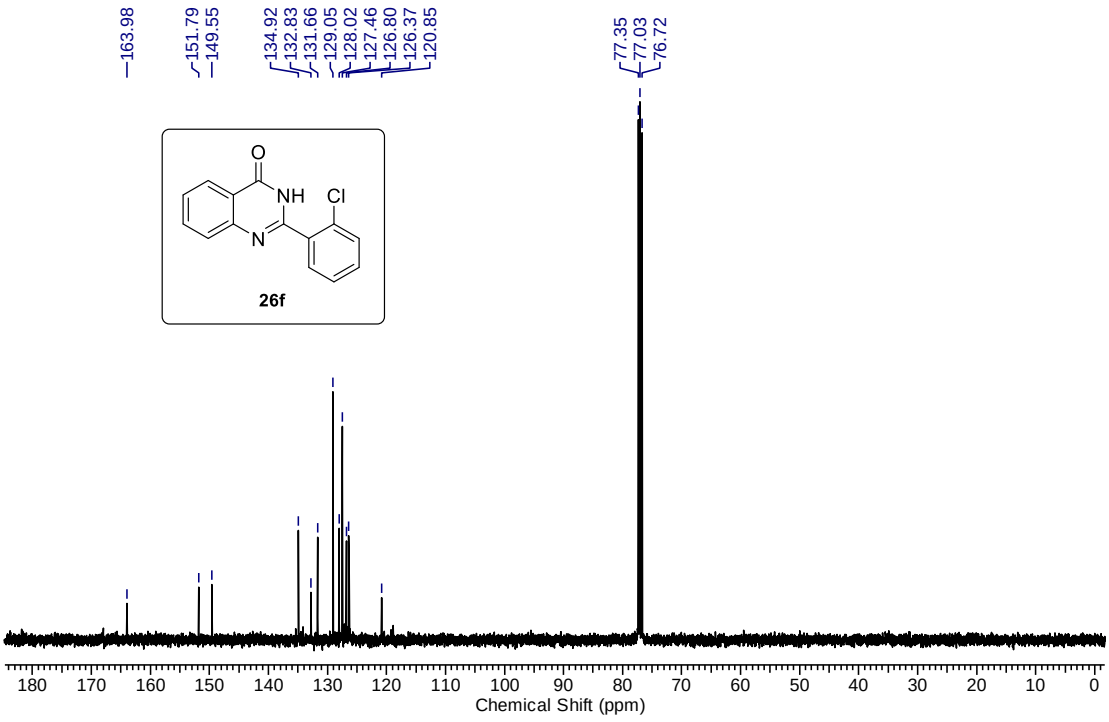


Figure 12. ^{13}C NMR (100 MHz) spectrum of compound **26f** in $CDCl_3$.

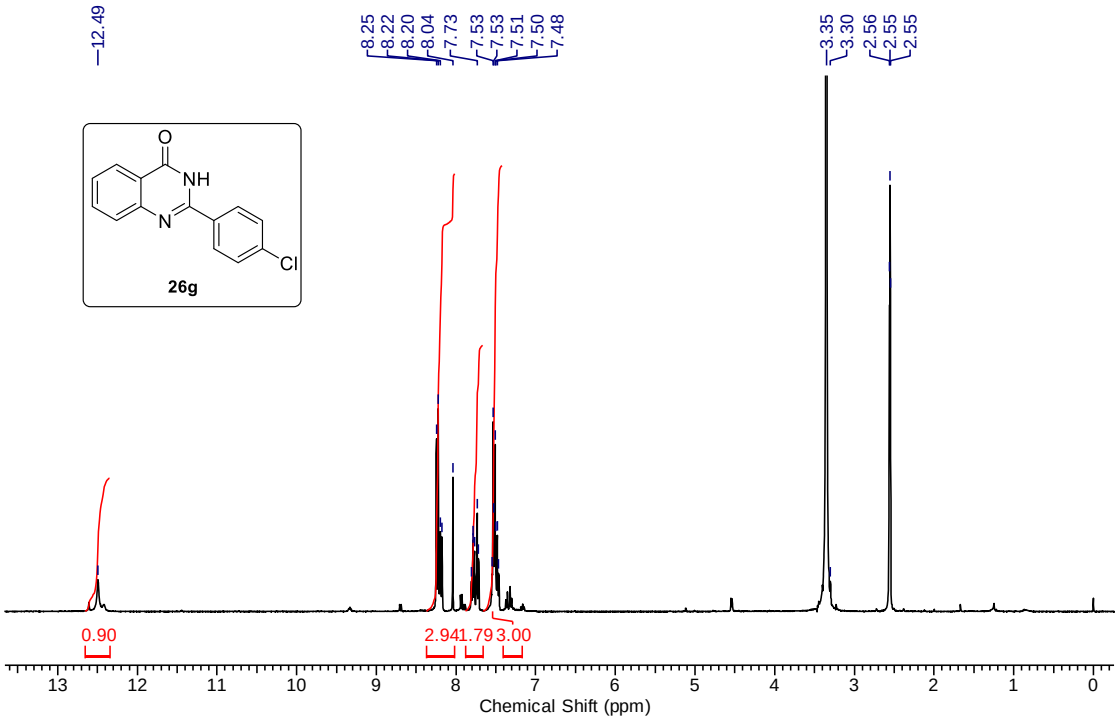


Figure 13. ^{1}H NMR (400 MHz) spectrum of compound **26g** in $CDCl_3$ + DMSO-d_6

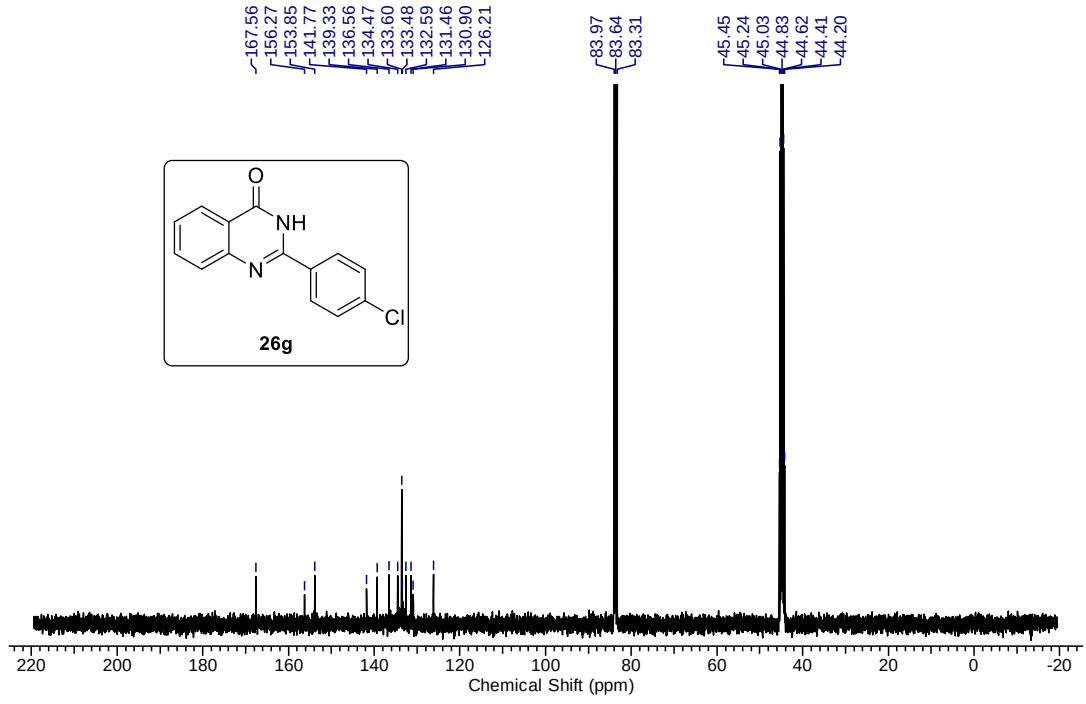


Figure 14. ^{13}C NMR (100 MHz) spectrum of compound **26g** in $CDCl_3$ + DMSO-d_6.

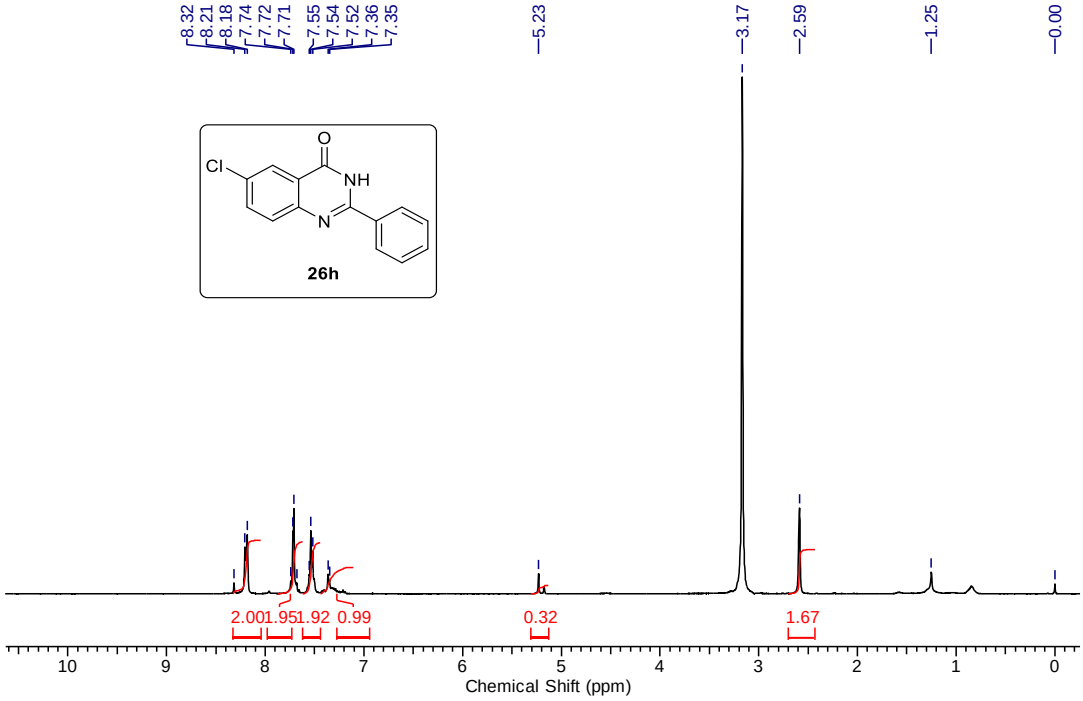


Figure 15. ^{1}H NMR (400 MHz) spectrum of compound **26h** in $CDCl_3$ + DMSO d_6.

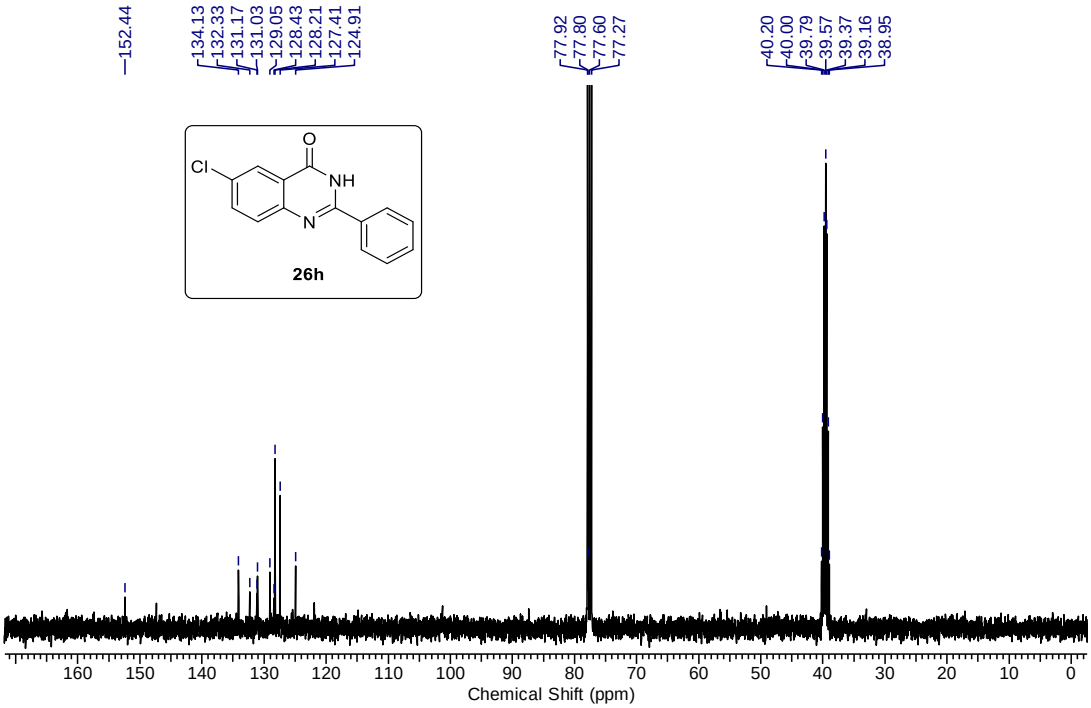


Figure 16. ^{13}C NMR (100 MHz) spectrum of compound **26h** in $CDCl_3$ + DMSO-d_6.

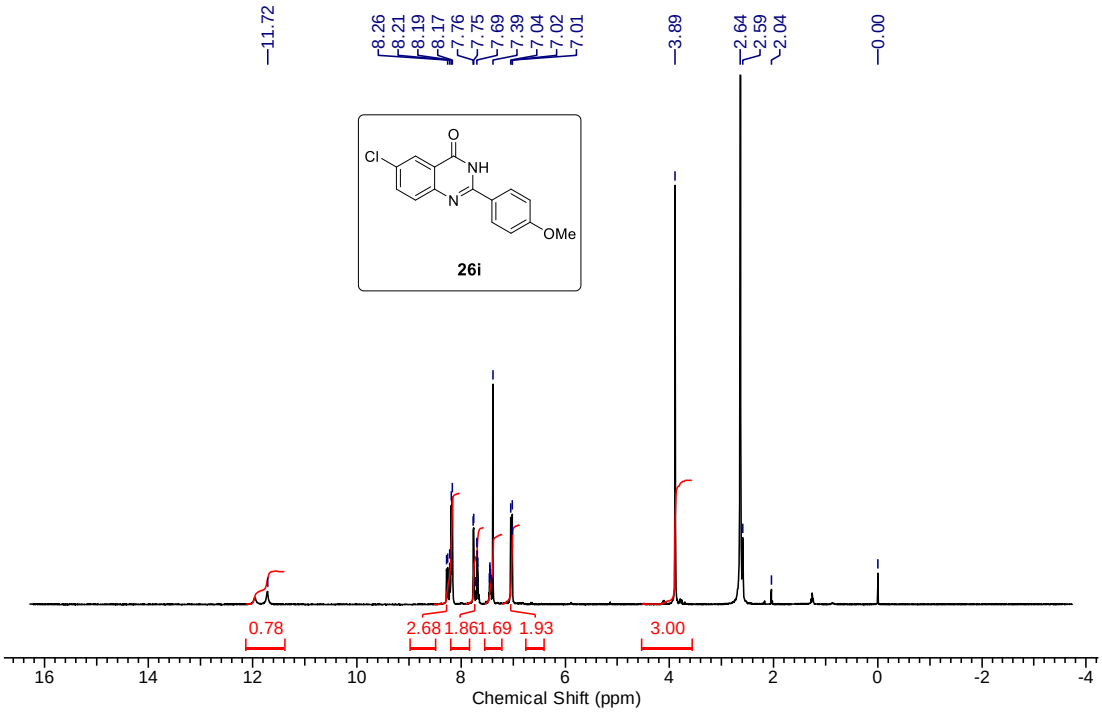


Figure 17. ^{1}H NMR (400 MHz) spectrum of compound **26i** in $CDCl_3$ + DMSO-d_6.

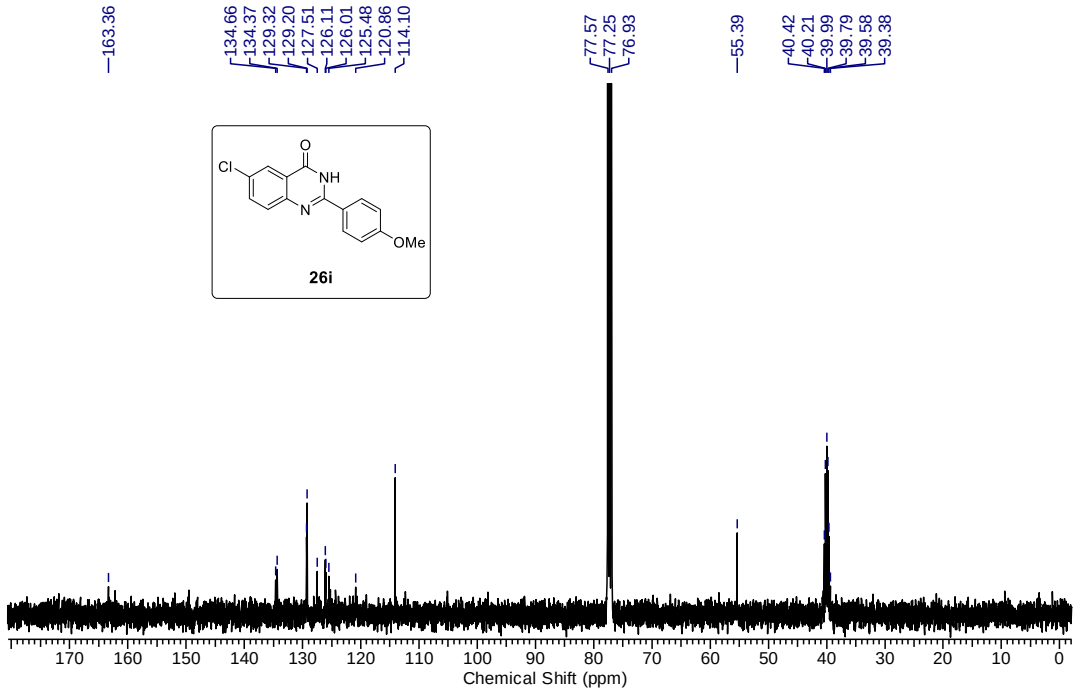


Figure 18. ^{13}C NMR (100 MHz) spectrum of compound **26i** in $CDCl_3$ + DMSO-d_6.

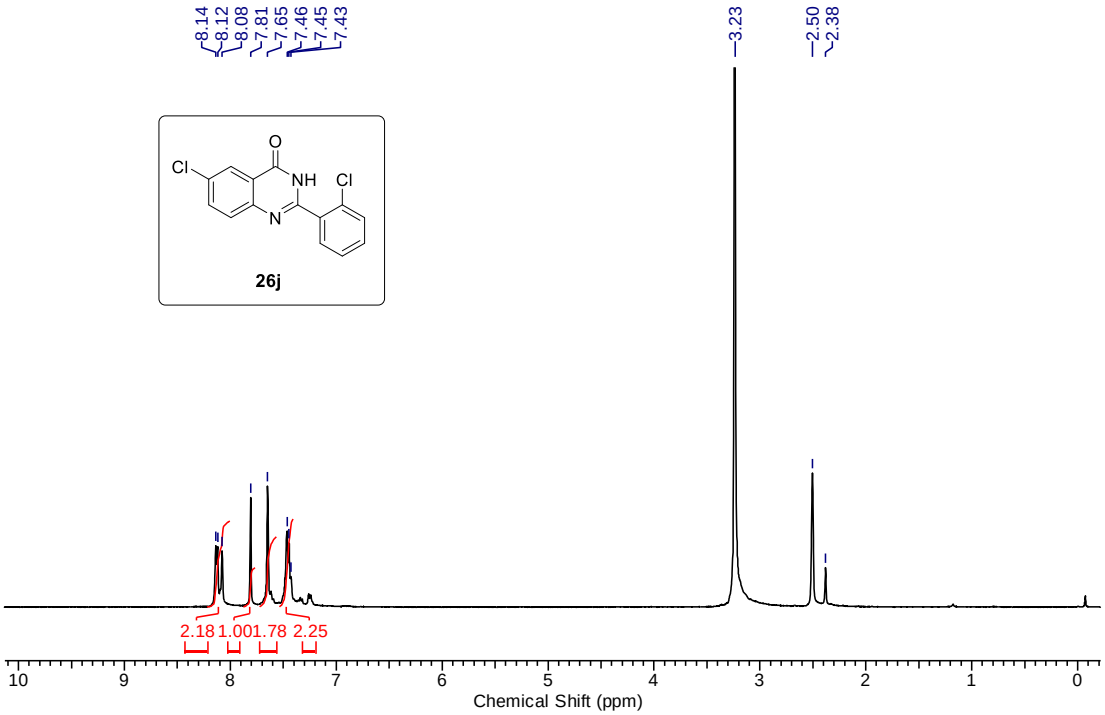


Figure 19. ^{1}H NMR (400 MHz) spectrum of compound **26j** in $CDCl_3$ + DMSO-d_6.

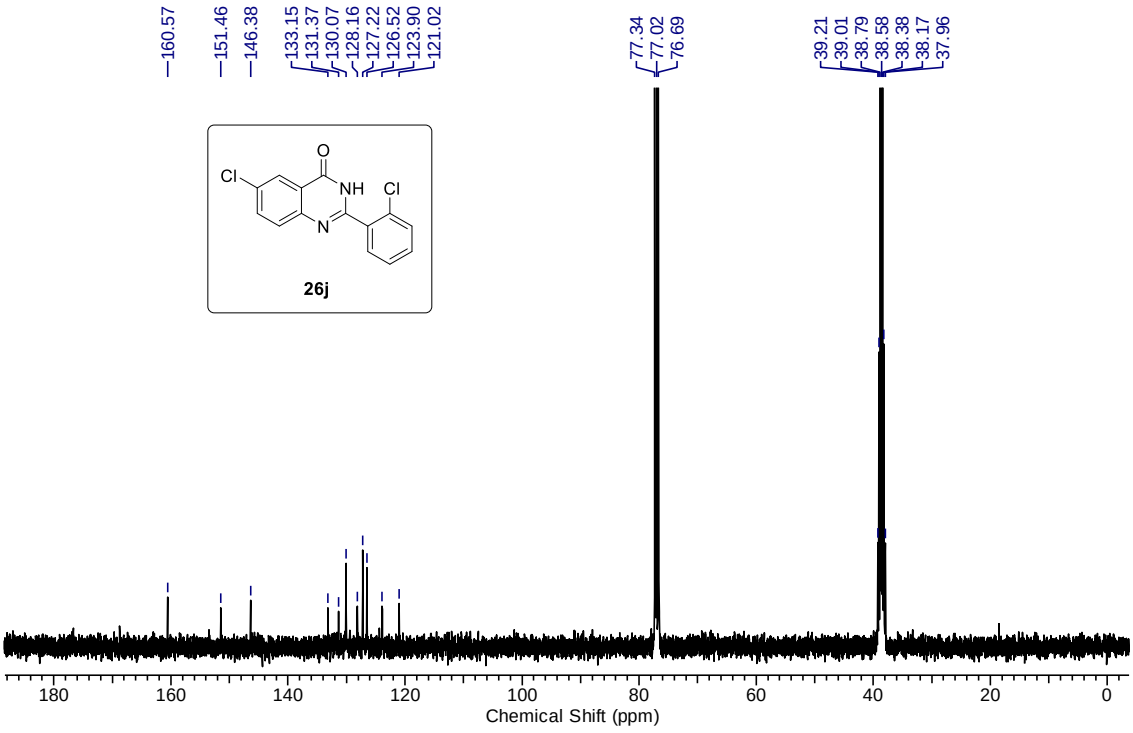


Figure 20. ^{13}C NMR (100 MHz) spectrum of compound **26j** in $CDCl_3$ + DMSO-d_6.

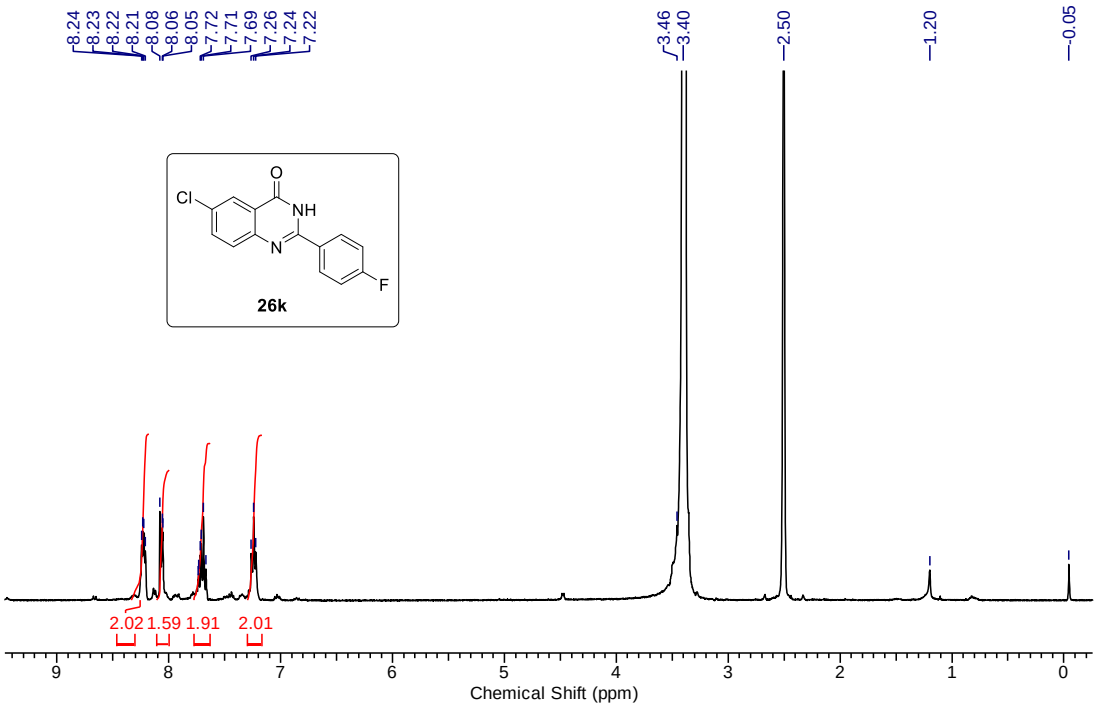


Figure 21. ^{1}H NMR (400 MHz) spectrum of compound **26k** in $CDCl_3$ + DMSO-d_6

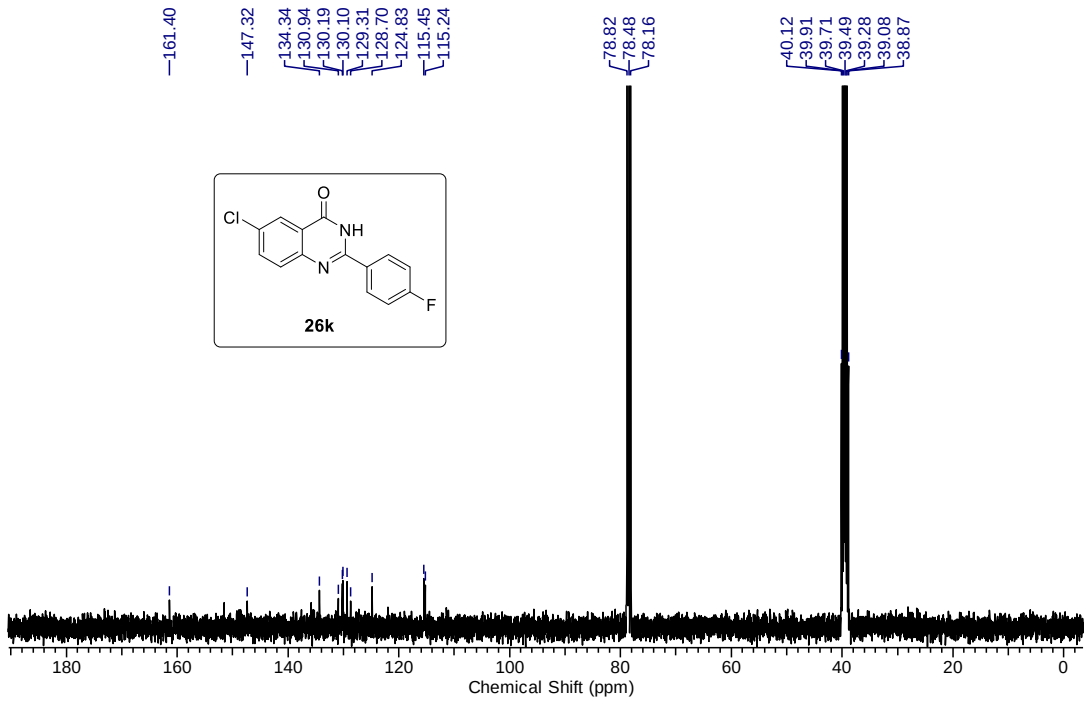


Figure 22. ^{13}C NMR (100 MHz) spectrum of compound **26k** in $CDCl_3$ + DMSO-d_6.

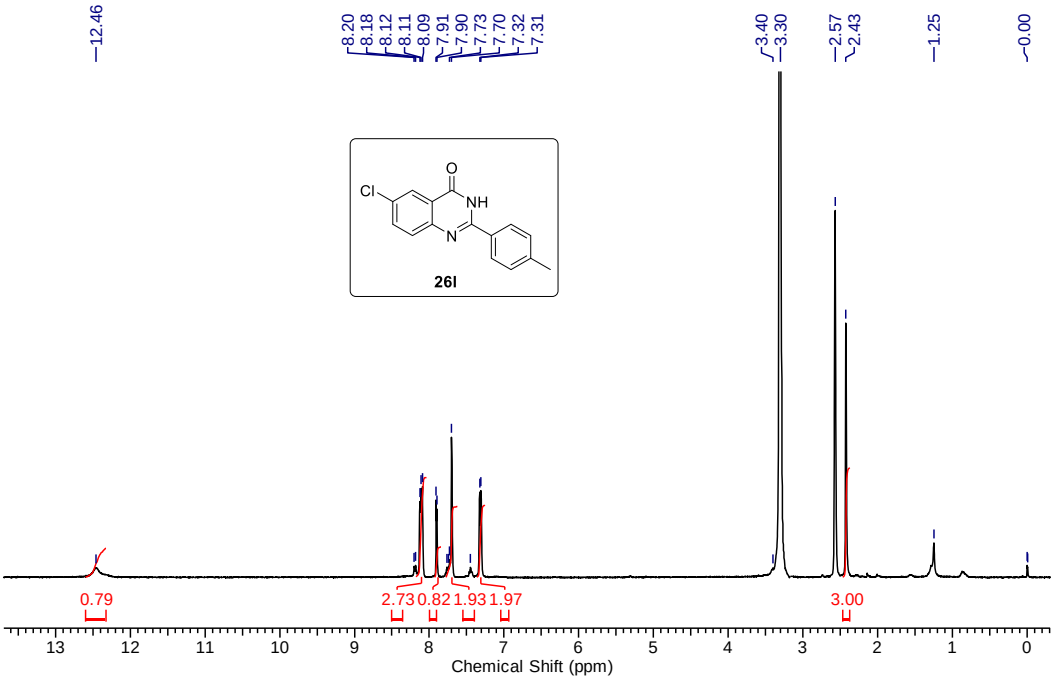


Figure 23. ^{1}H NMR (400 MHz) spectrum of compound **26l** in $CDCl_3$ + DMSO-d_6.

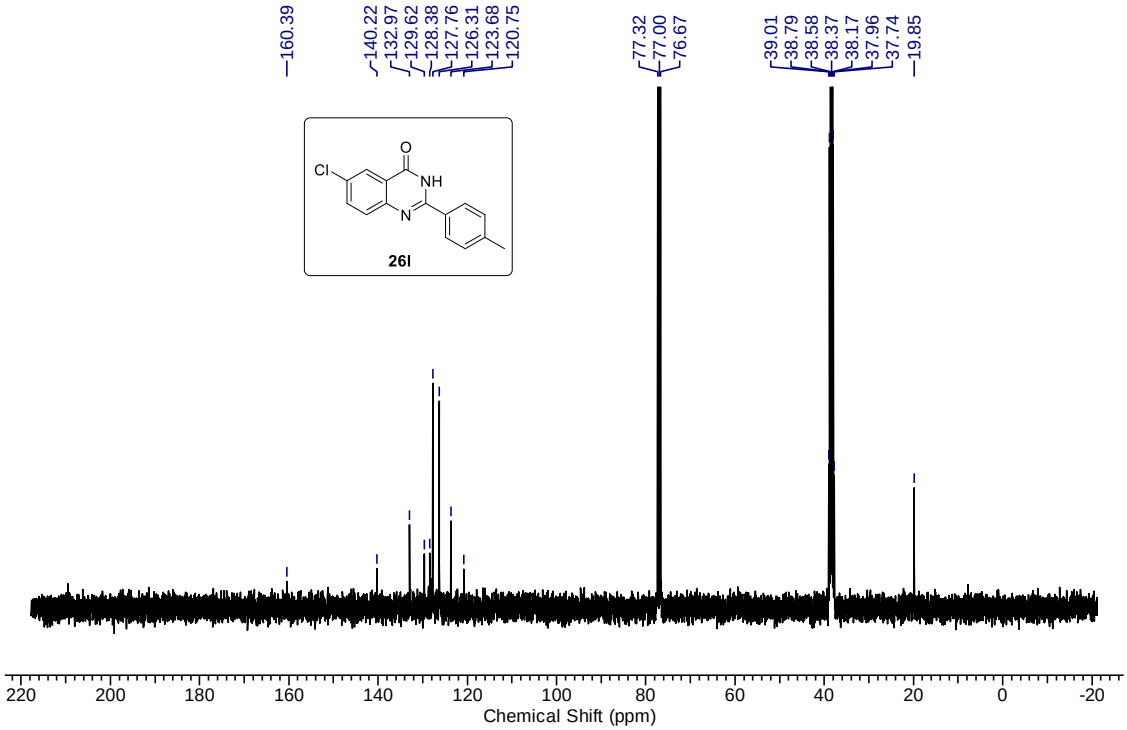


Figure 24. ^{13}C NMR (100 MHz) spectrum of compound **26l** in $CDCl_3$ + DMSO-d_6..

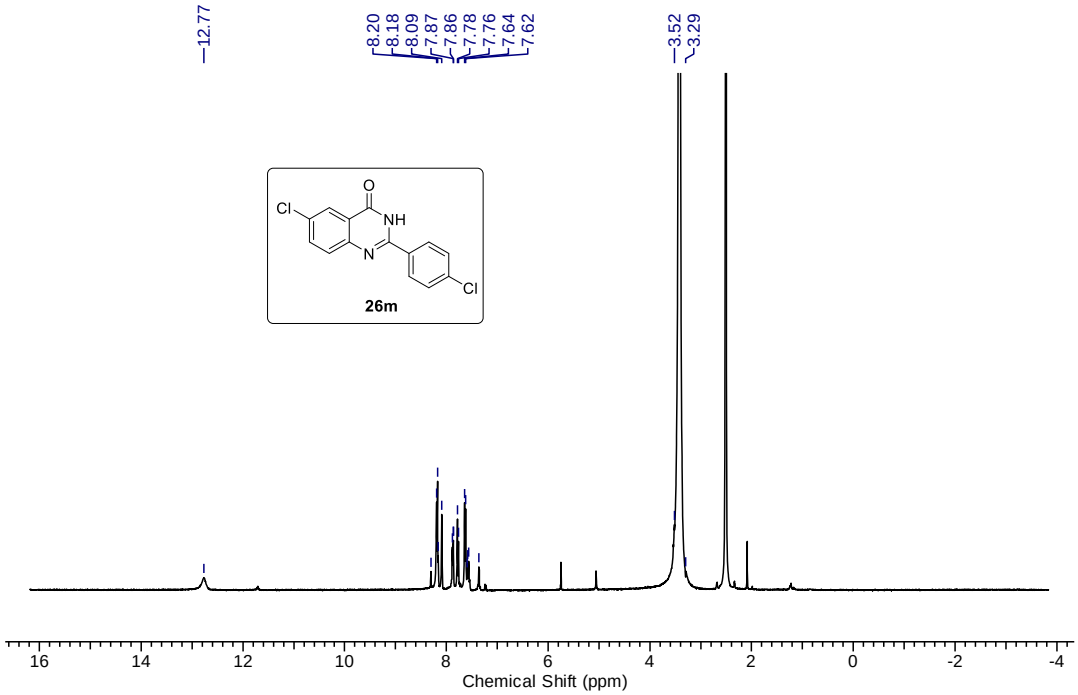


Figure 25. ^{1}H NMR (400 MHz) spectrum of compound **26m** in DMSO-d_{6}.

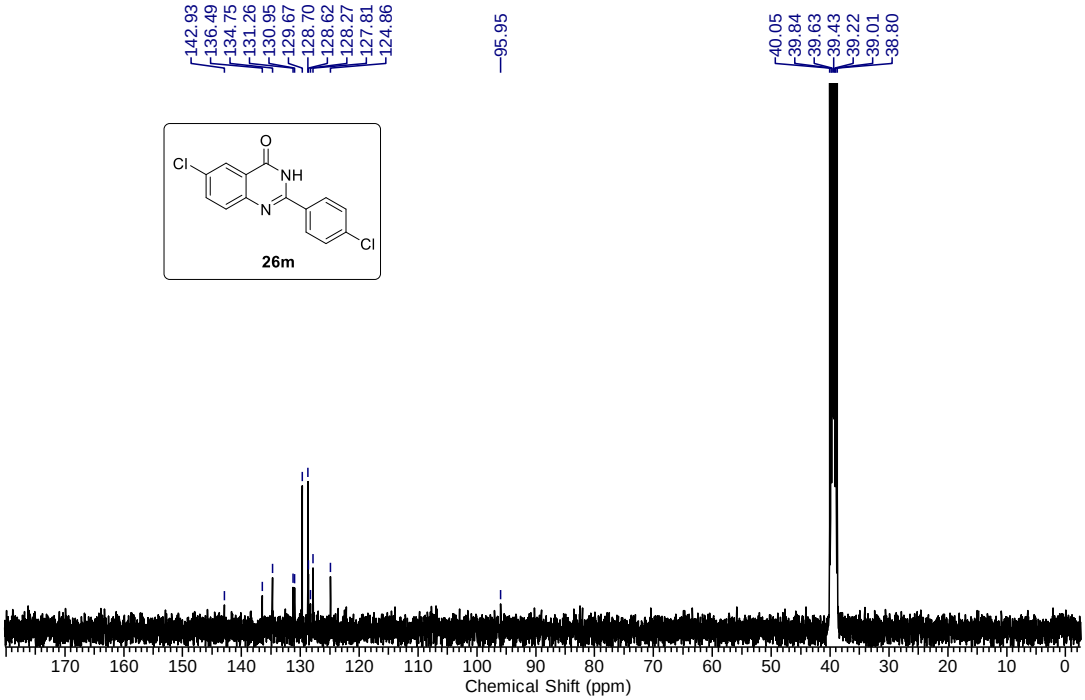


Figure 26. ^{13}C NMR (100 MHz) spectrum of compound **26m** in DMSO-d_{6}

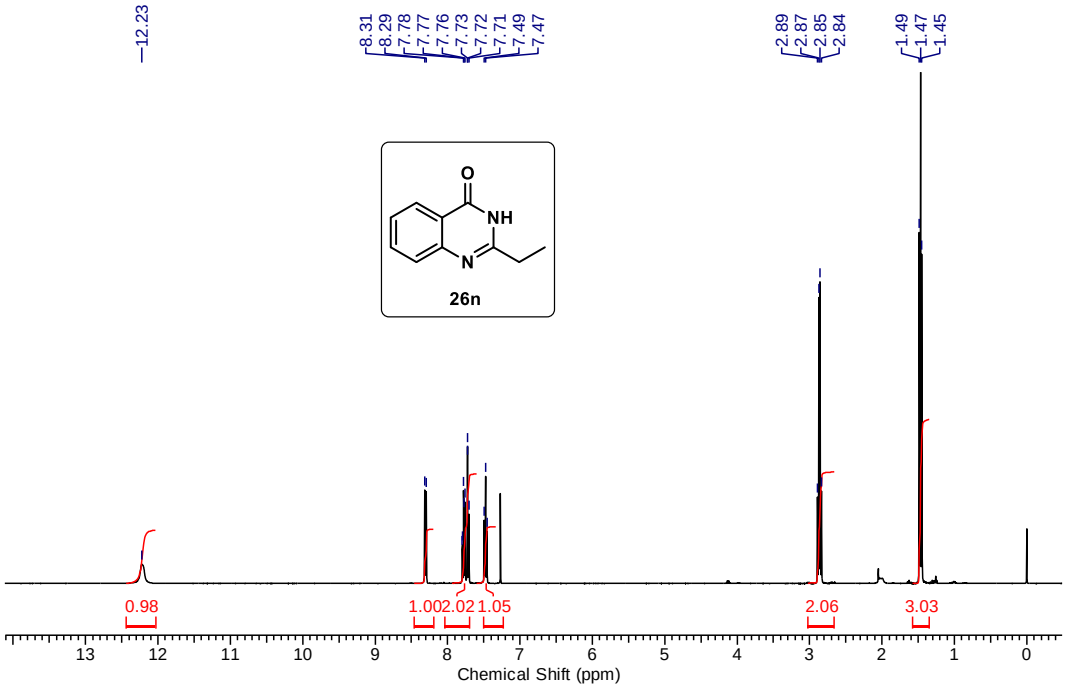


Figure 27. ^{1}H NMR (400 MHz) spectrum of compound **26n** in $CDCl_3$

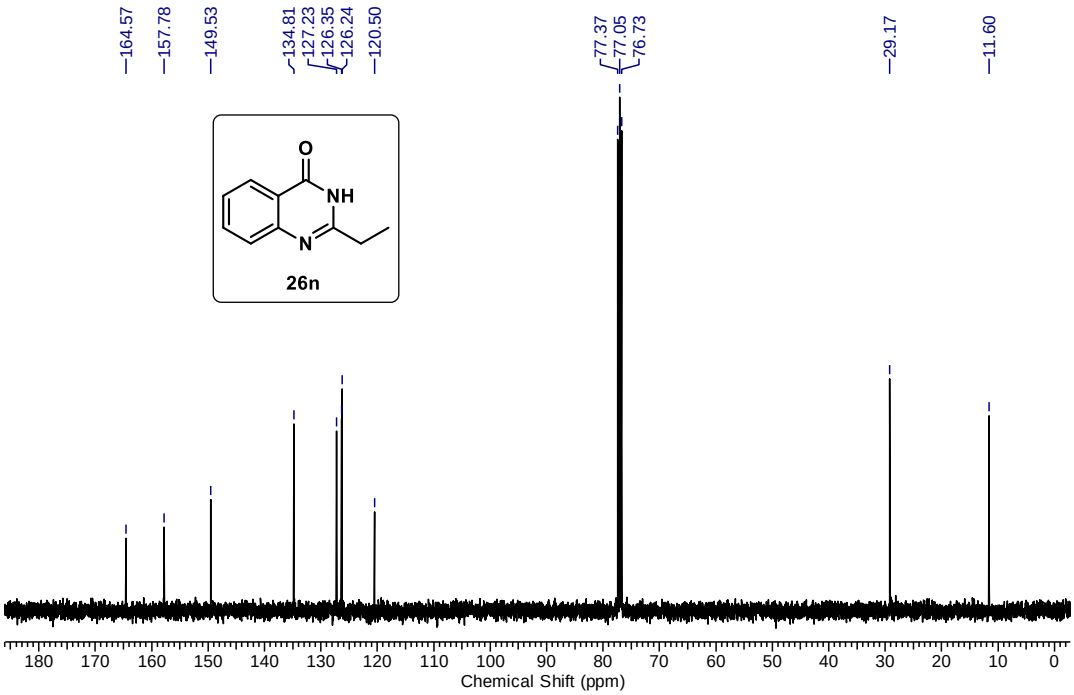


Figure 28. ^{13}C NMR (100 MHz) spectrum of compound **26n** in $CDCl_3$.

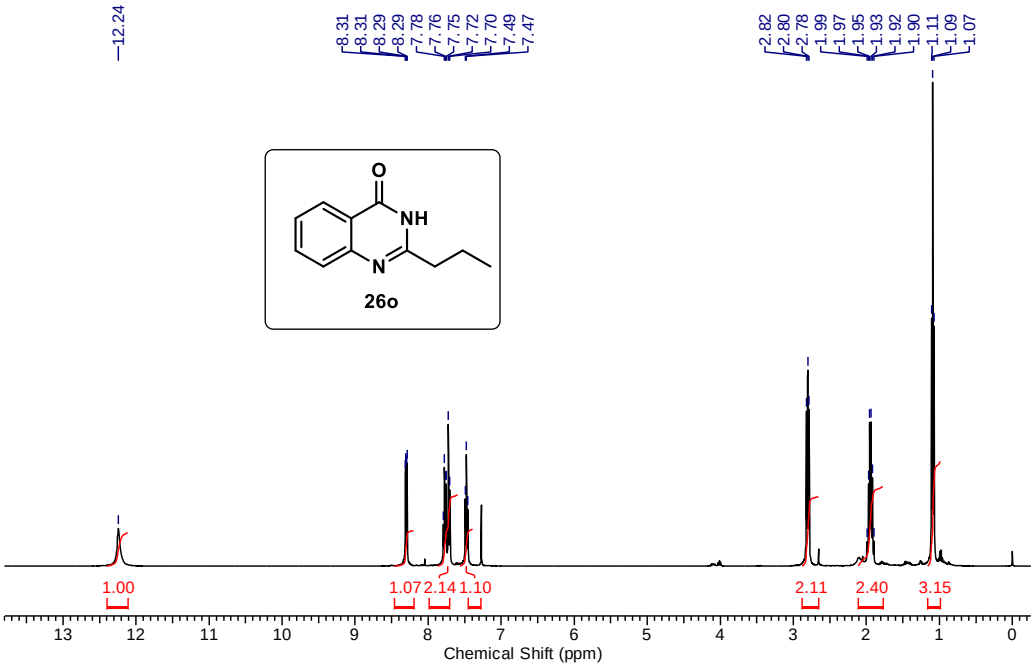


Figure 29. ^{1}H NMR (400 MHz) spectrum of compound **26o** in $CDCl_3$

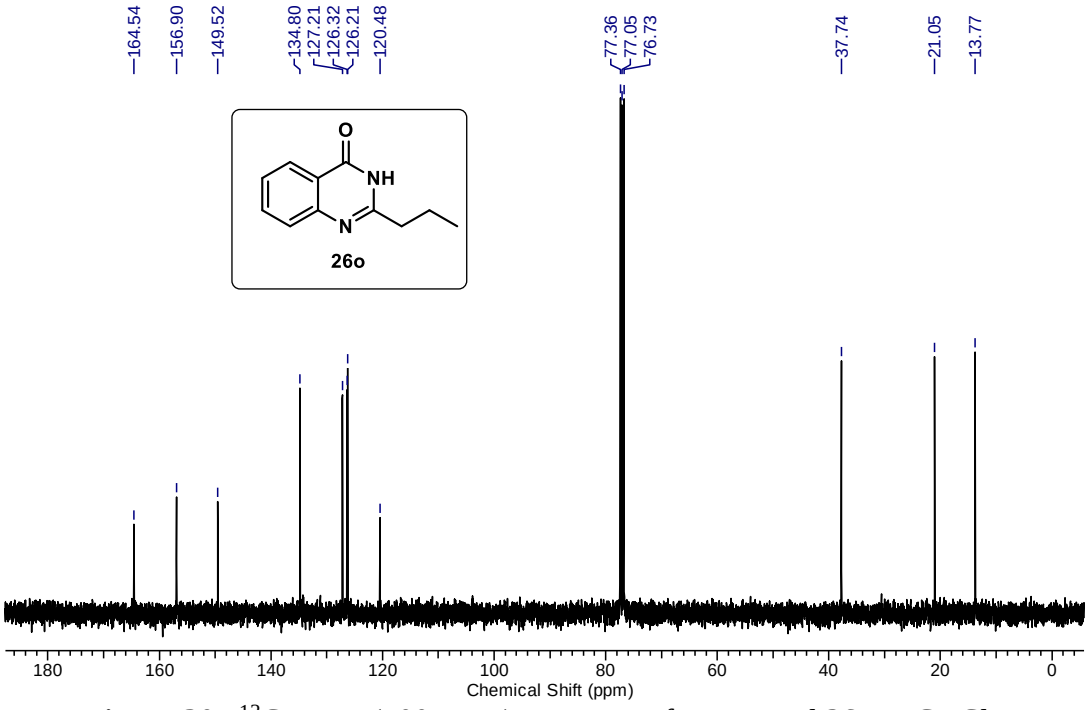


Figure 30. ^{13}C NMR (100 MHz) spectrum of compound **26o** in $CDCl_3$.

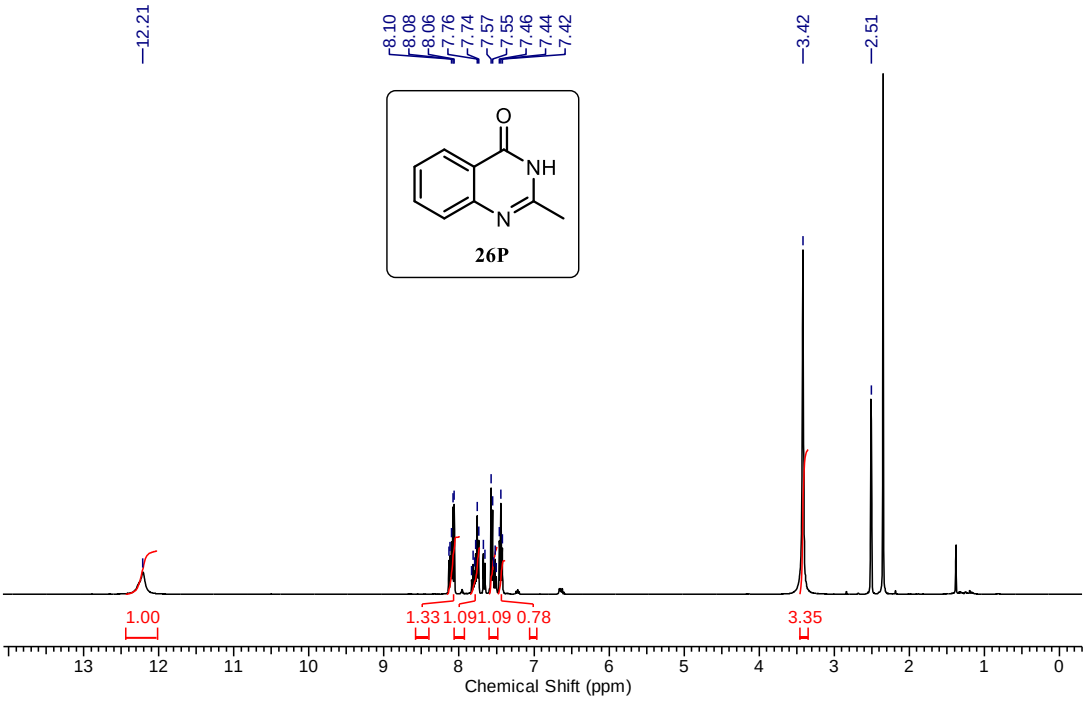


Figure 31. ^{1}H NMR (400 MHz) spectrum of compound **26p** in DMSO-d_6.

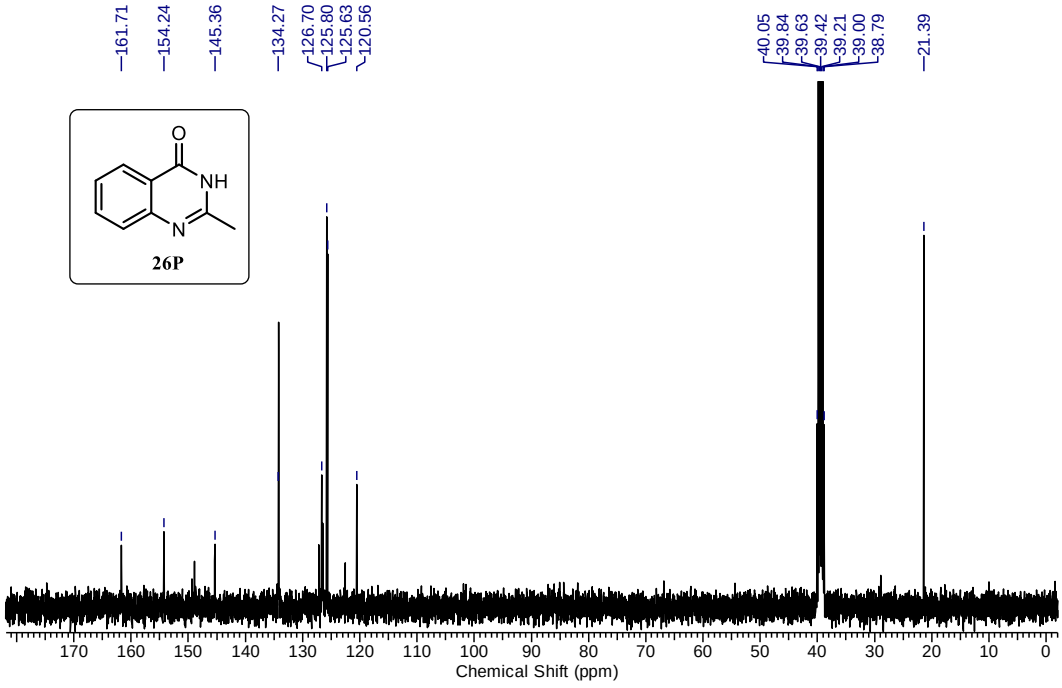
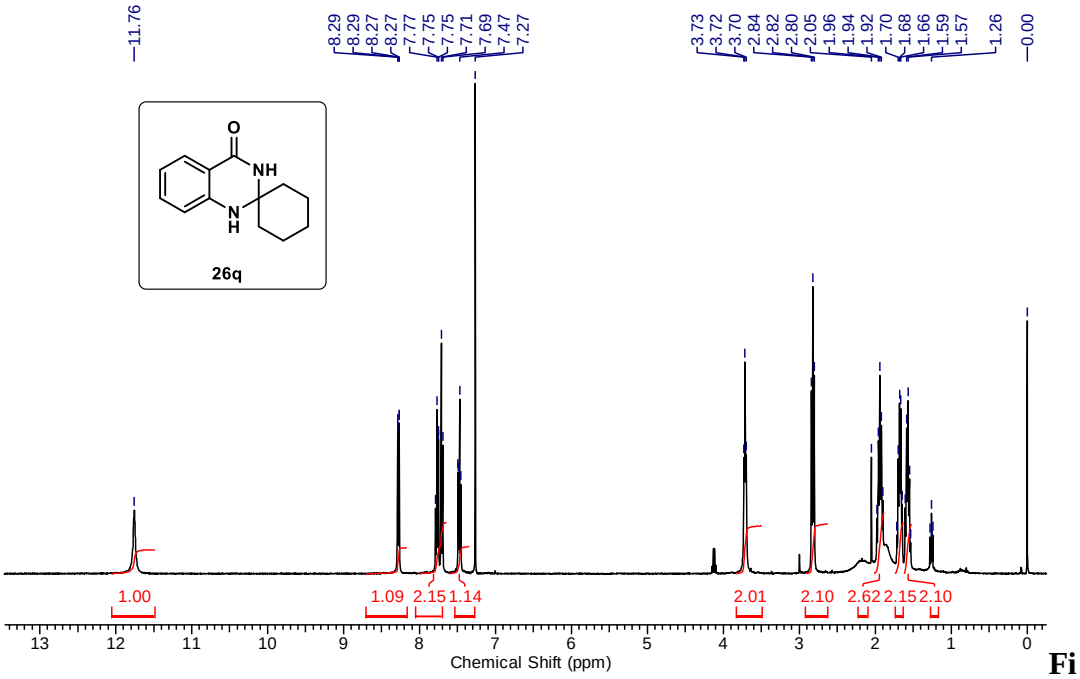


Figure 32. ^{13}C NMR (100 MHz) spectrum of compound **26p** in DMSO-d_6.



Fi

gure 33. ^{1}H NMR (400 MHz) spectrum of compound **26q** in $CDCl_3$

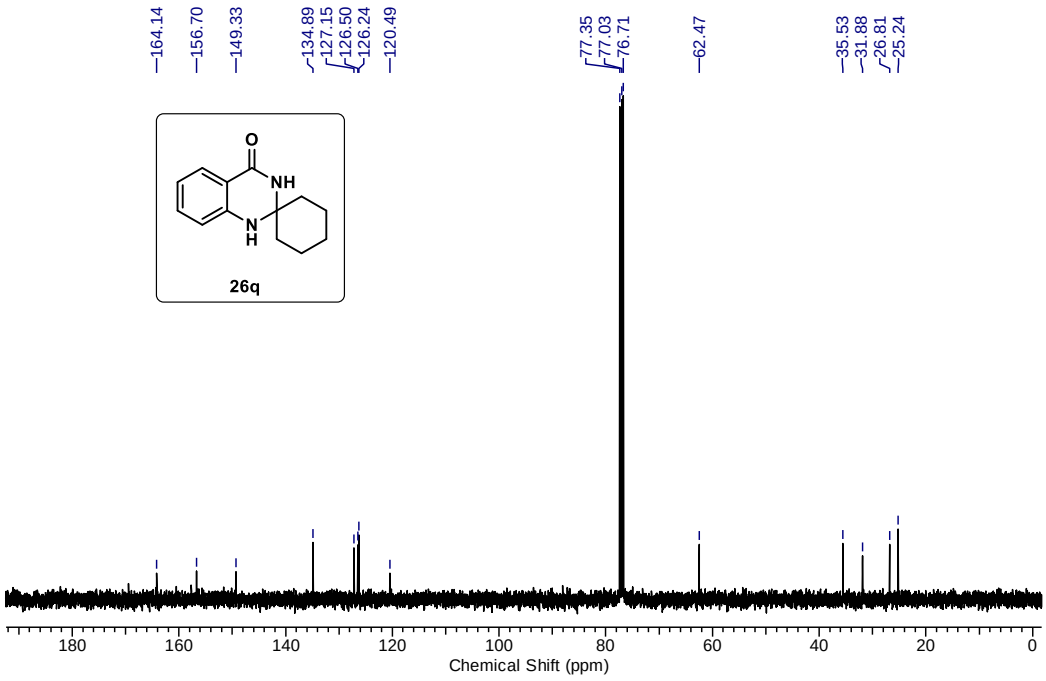


Figure 34. ^{13}C NMR (100 MHz) spectrum of compound **26q** in $CDCl_3$.

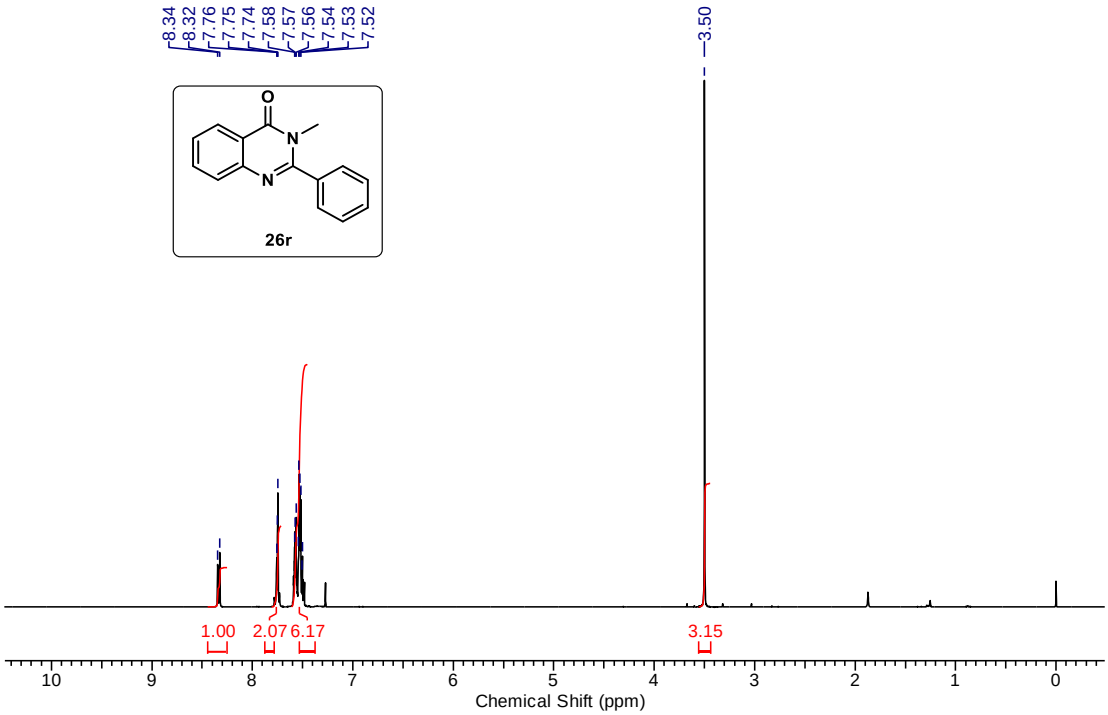


Figure 35. ^{1}H NMR (400 MHz) spectrum of compound **26r** in $CDCl_3$

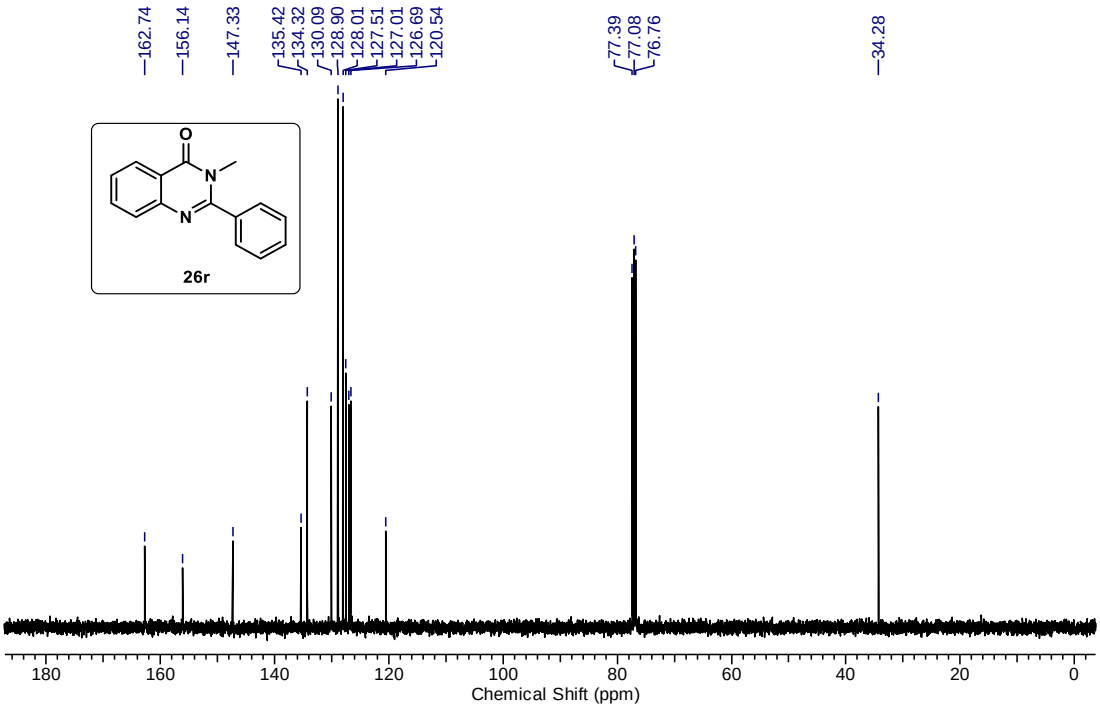


Figure 36. ^{13}C NMR (100 MHz) spectrum of compound **26r** in $CDCl_3$.

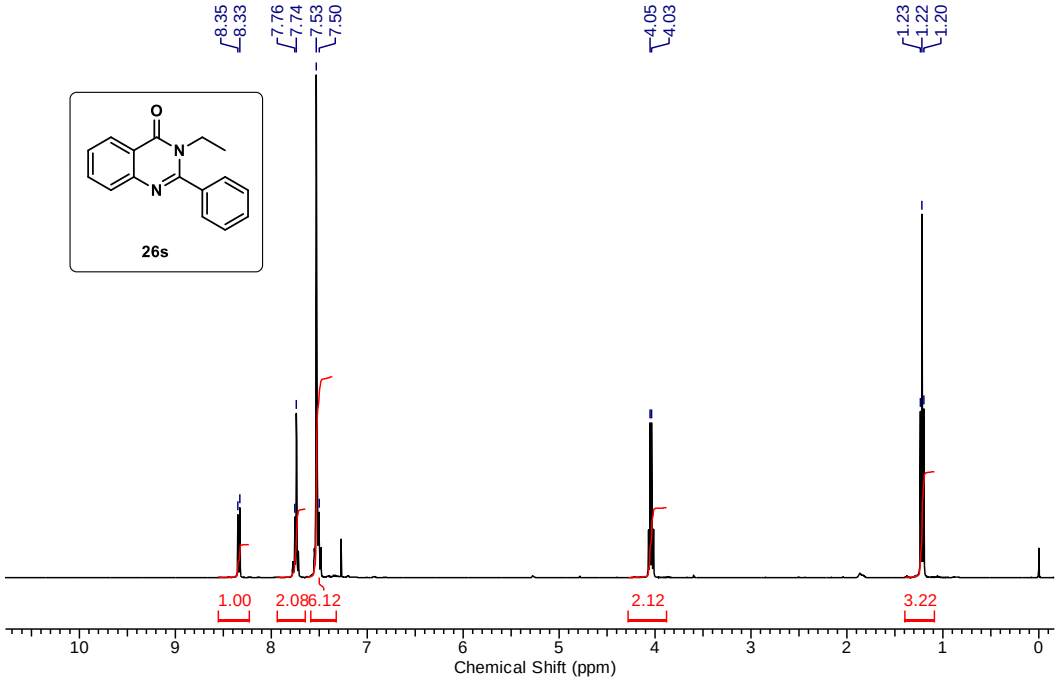


Figure 37. ^{1}H NMR (400 MHz) spectrum of compound **26s** in $CDCl_3$

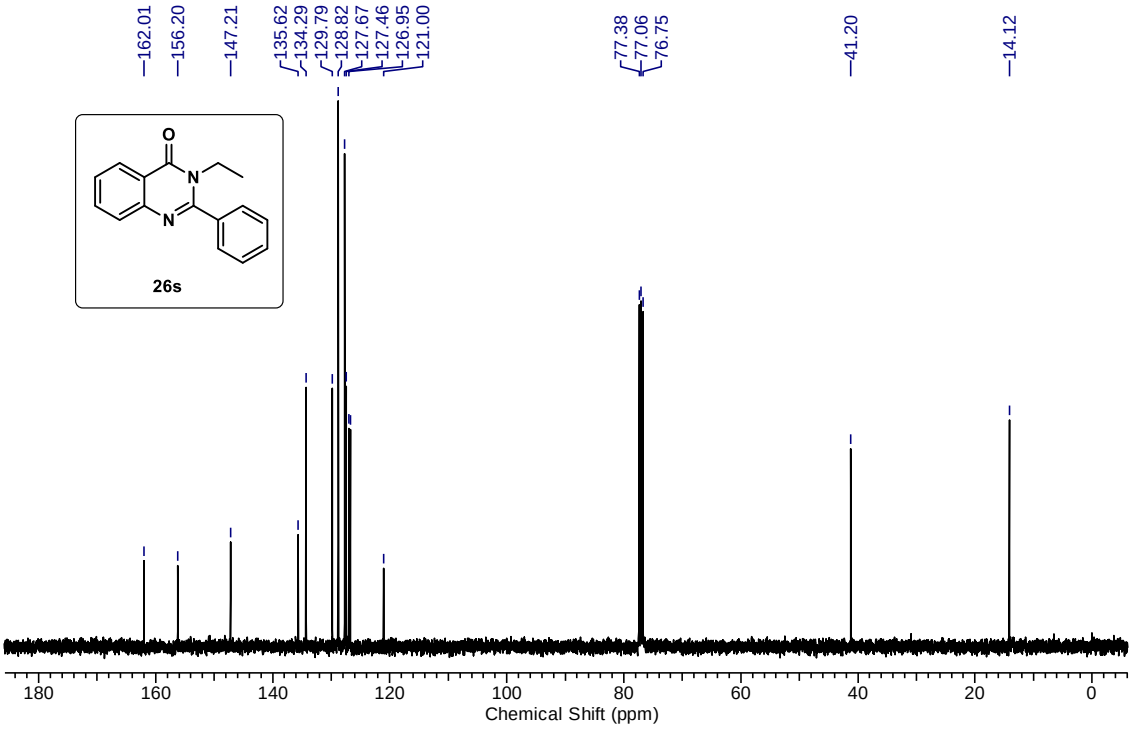


Figure 38. ^{13}C NMR (100 MHz) spectrum of compound **26s** in $CDCl_3$.

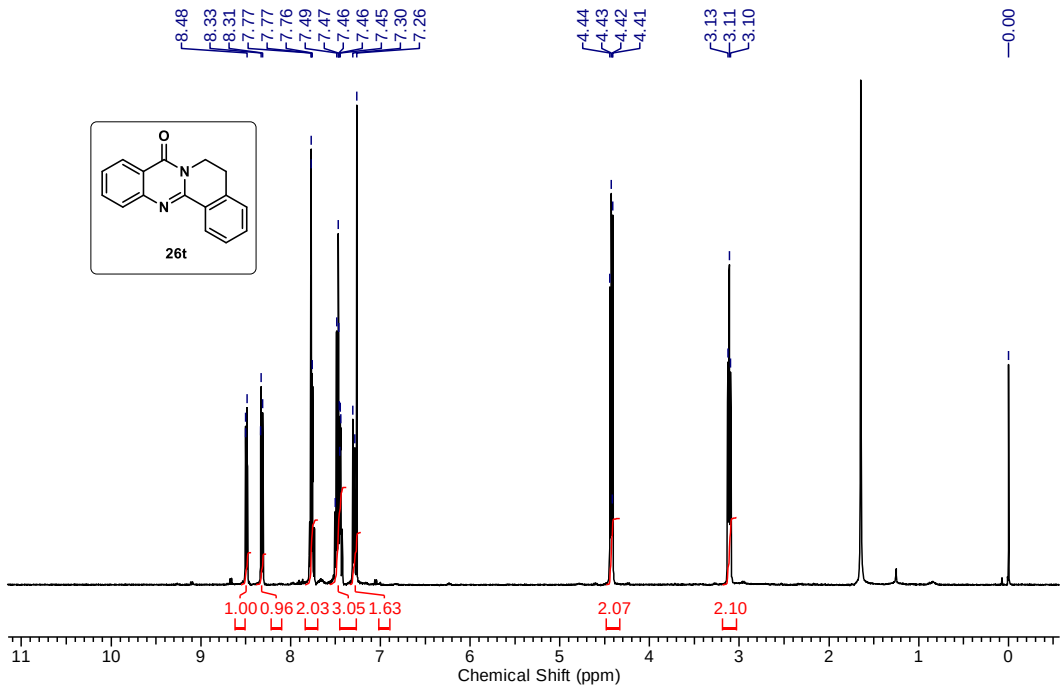


Figure 39. ^{1}H NMR (400 MHz) spectrum of compound **26t** in $CDCl_3$

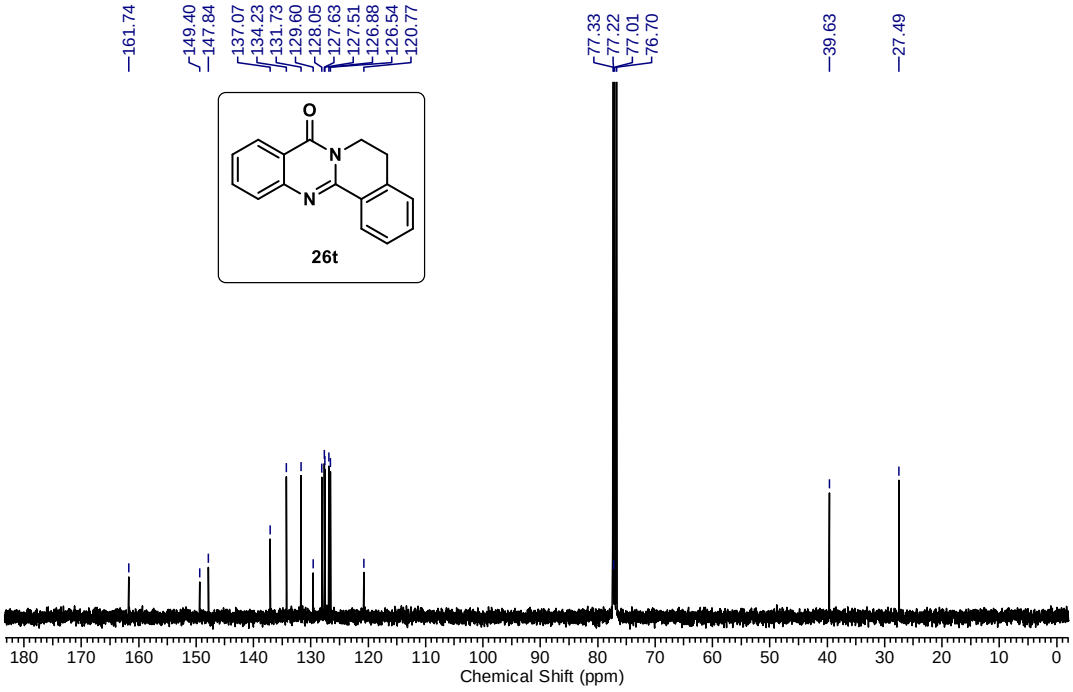


Figure 40. ^{13}C NMR (100 MHz) spectrum of compound **26t** in $CDCl_3$.

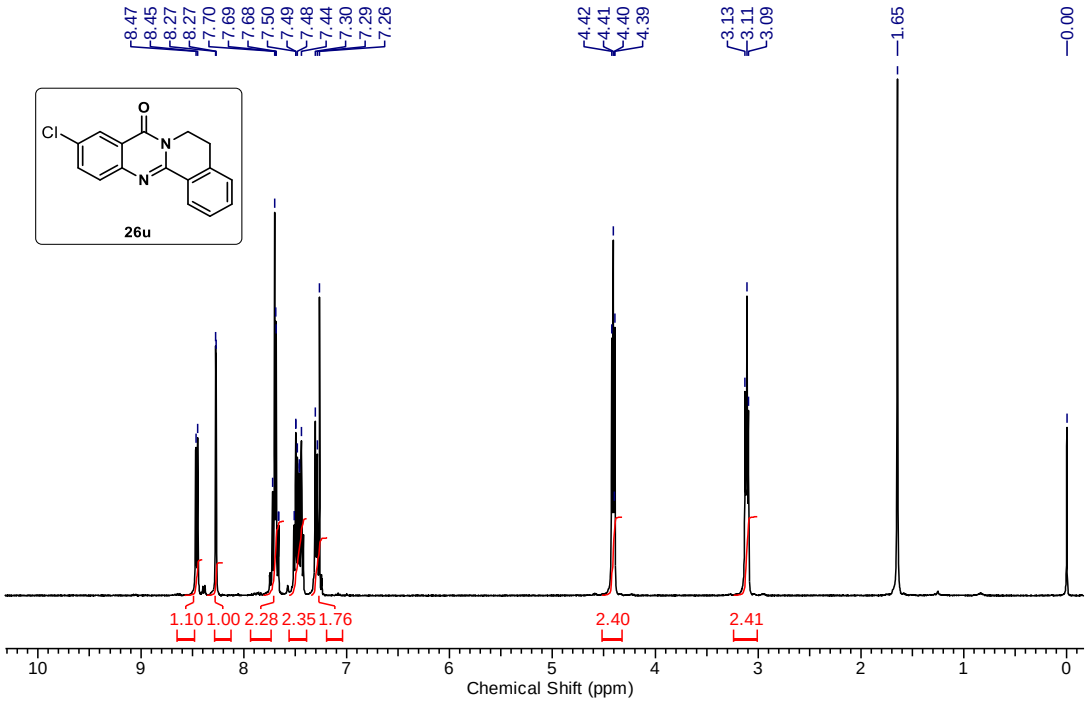


Figure 41. ^{1}H NMR (400 MHz) spectrum of compound **26u** in $CDCl_3$

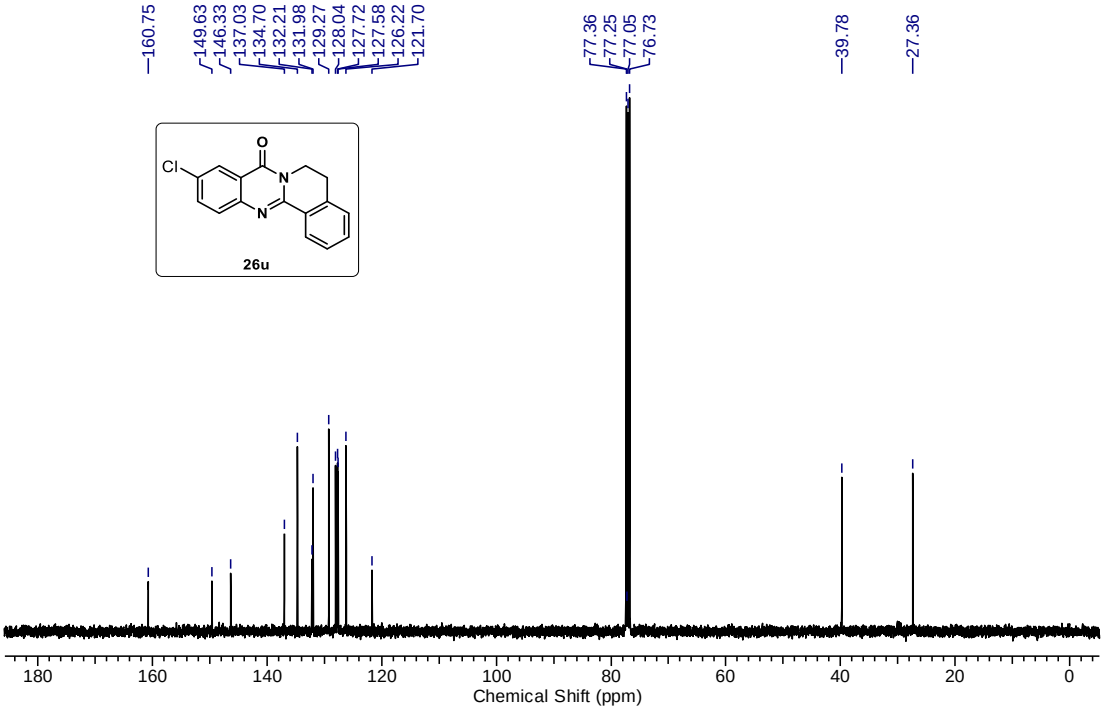


Figure 42. ^{13}C NMR (100 MHz) spectrum of compound **26u** in $CDCl_3$.

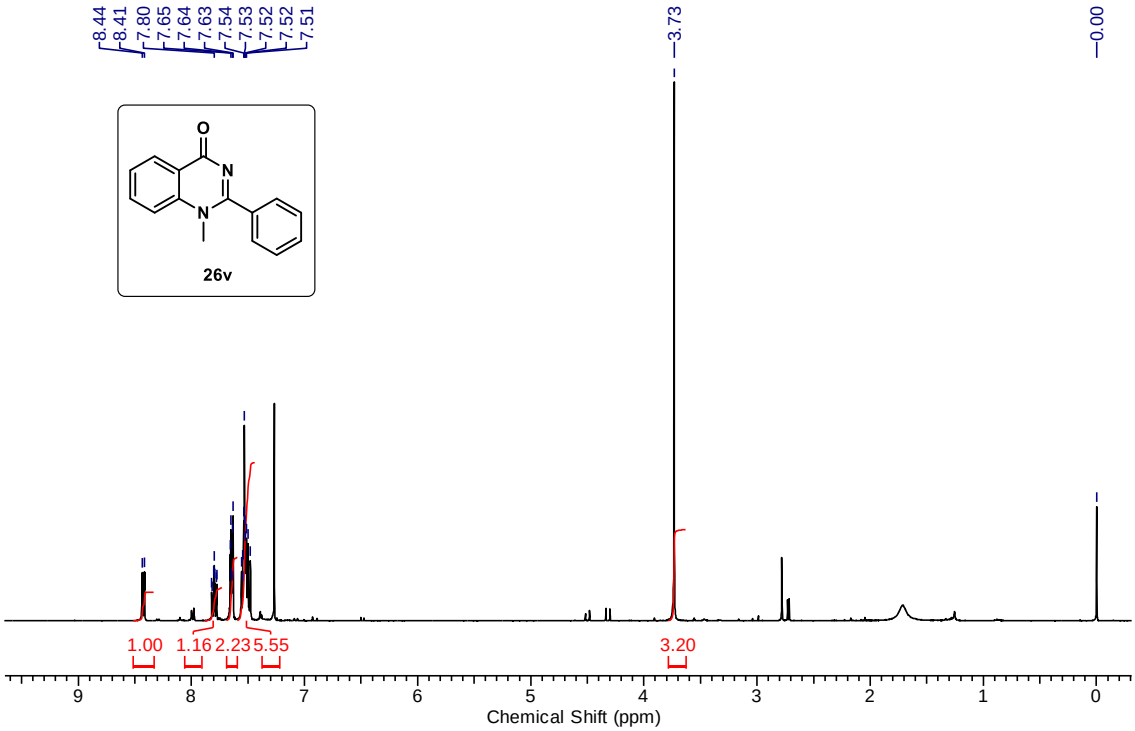


Figure 43. ^{1}H NMR (400 MHz) spectrum of compound **26v** in $CDCl_3$

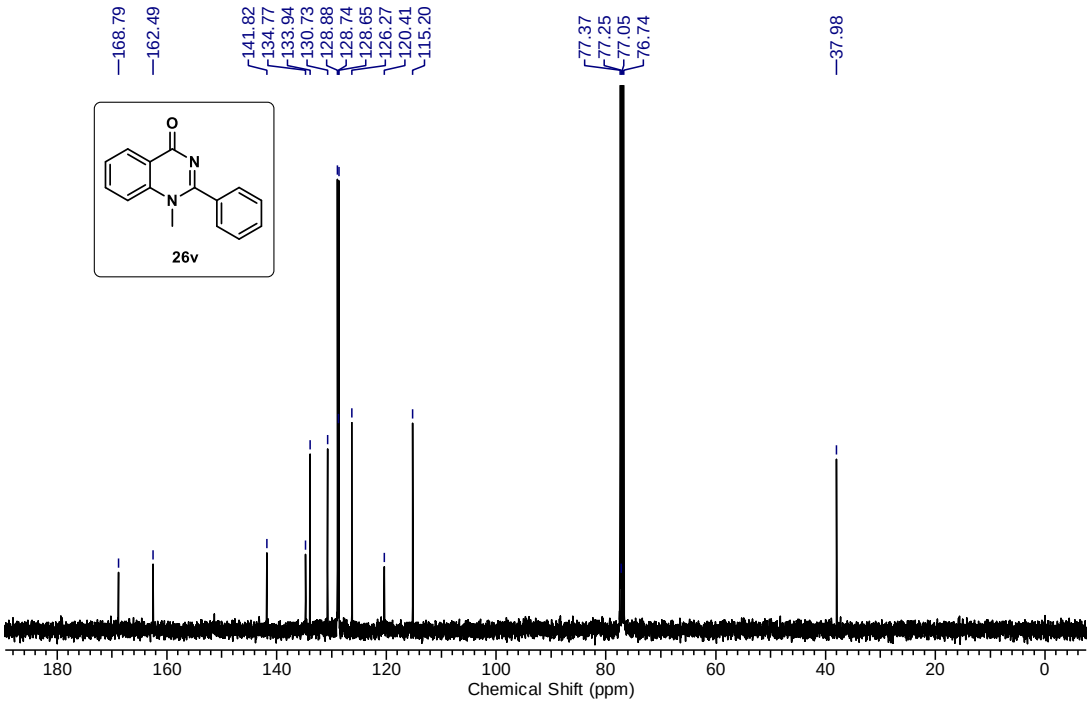


Figure 44. ^{13}C NMR (100 MHz) spectrum of compound **26v** in $CDCl_3$.

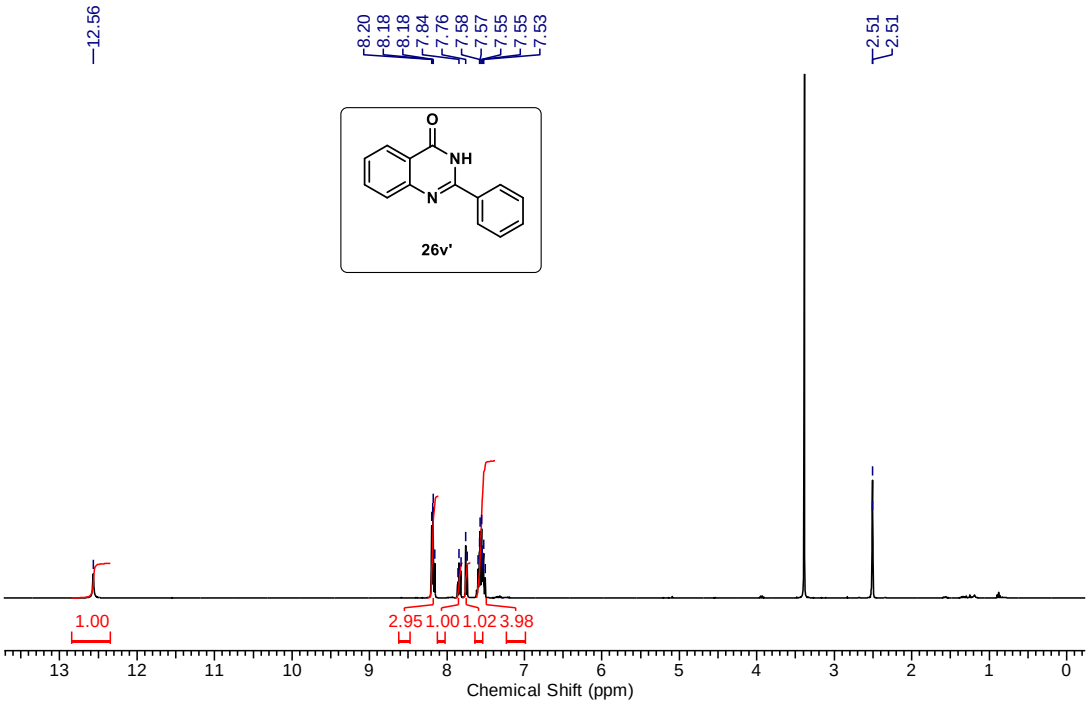


Figure 45. ^{1}H NMR (400 MHz) spectrum of compound **26v'** in $CDCl_3$ + DMSO-d_6.

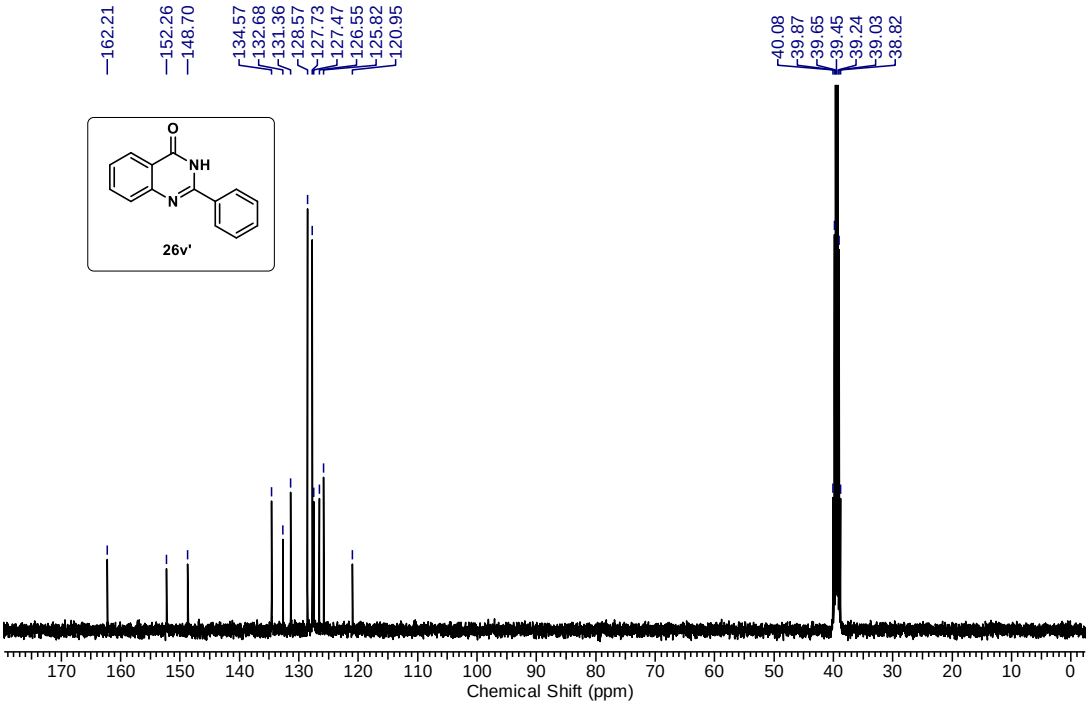


Figure 46. ^{13}C NMR (100 MHz) spectrum of compound **4v'** in. $CDCl_3$ + DMSO-d_6.

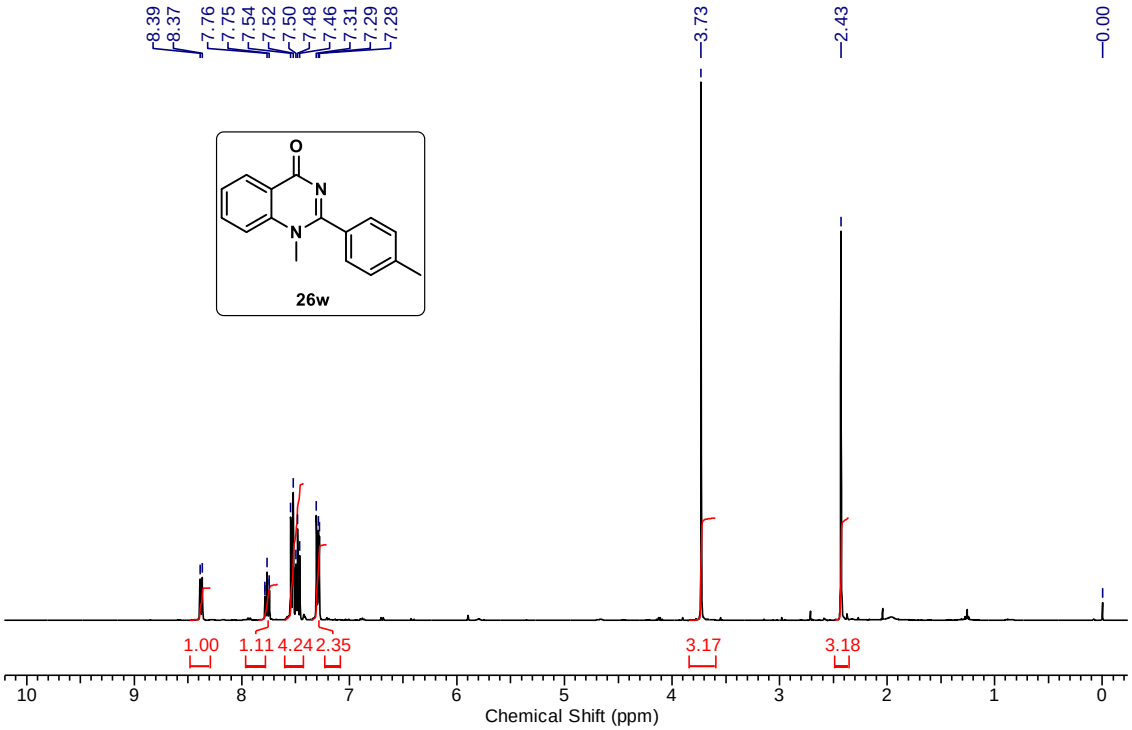


Figure 47. ^{1}H NMR (400 MHz) spectrum of compound **26w** in $CDCl_3$

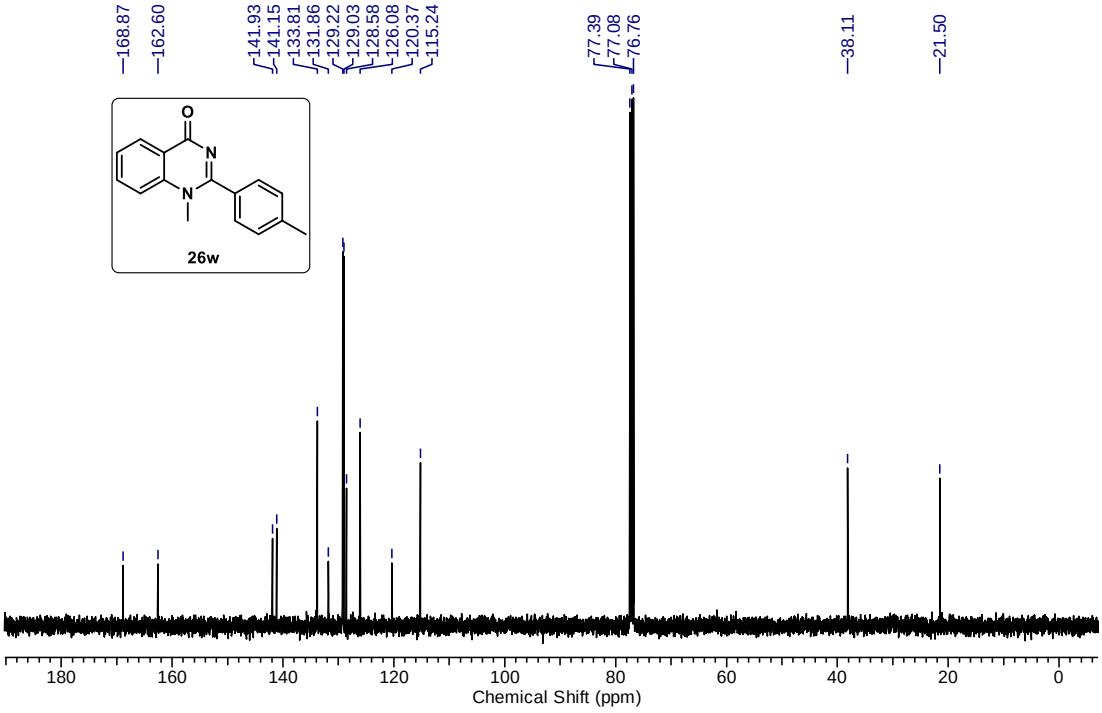


Figure 48. ^{13}C NMR (100 MHz) spectrum of compound **26w** in $CDCl_3$.

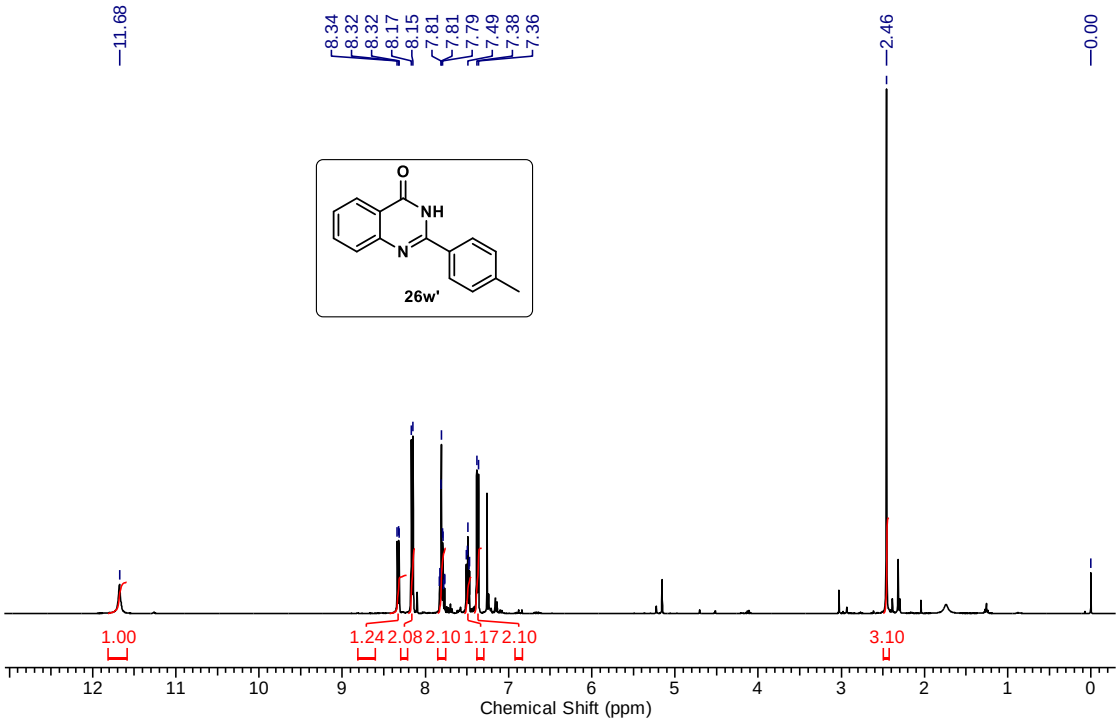


Figure 49. ^{1}H NMR (400 MHz) spectrum of compound **26w'** in $CDCl_3$

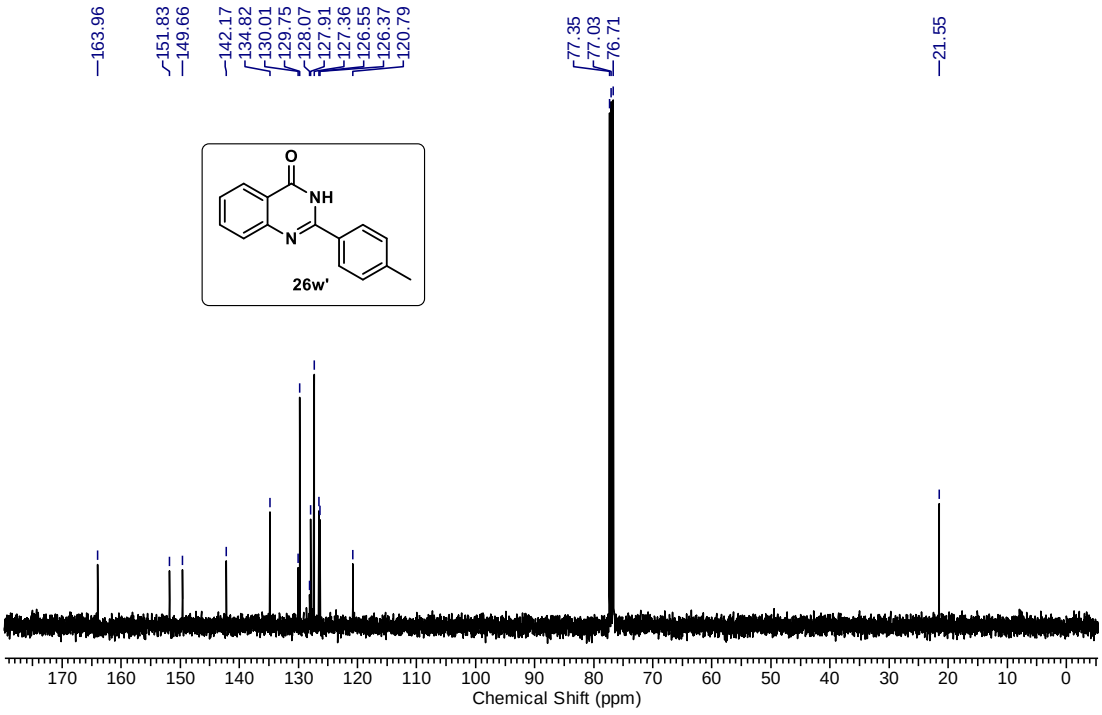


Figure 50. ^{13}C NMR (100 MHz) spectrum of compound **26w'** in $CDCl_3$.

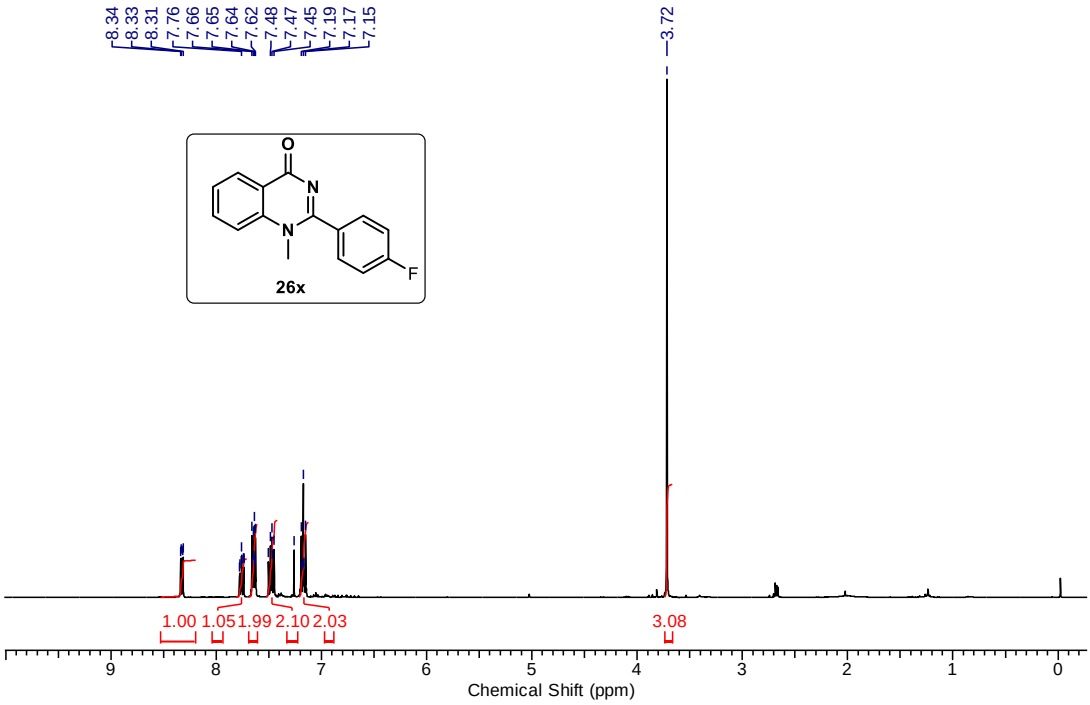


Figure 51. ^{1}H NMR (400 MHz) spectrum of compound **26x** in $CDCl_3$

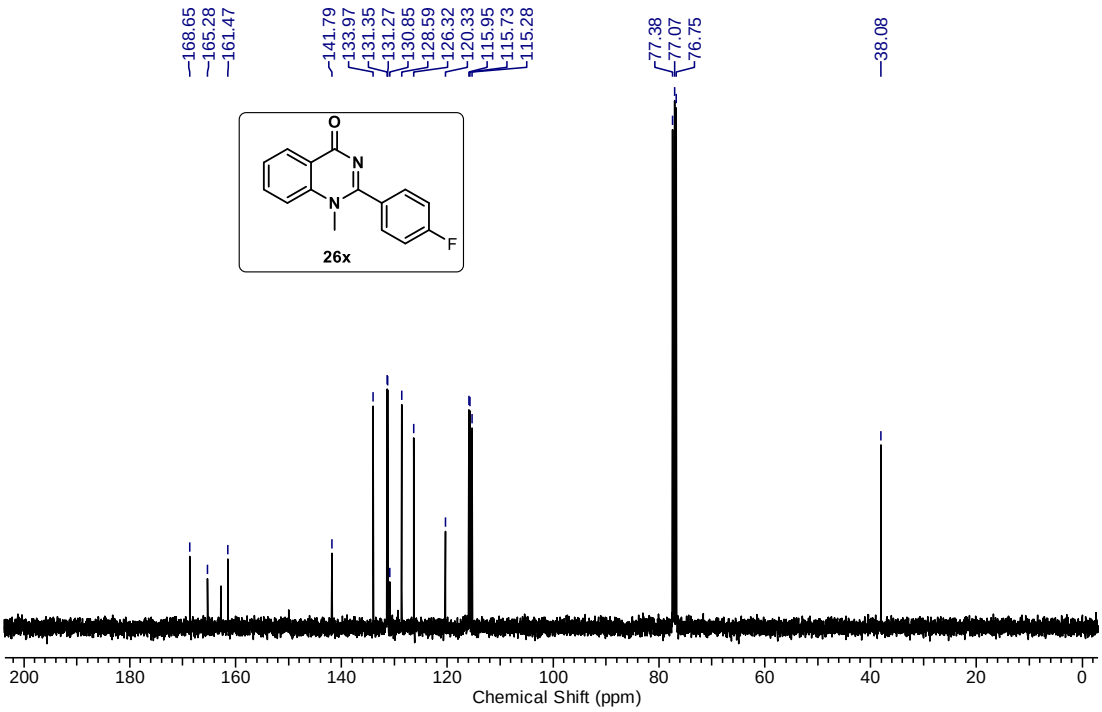


Figure 52. ^{13}C NMR (100 MHz) spectrum of compound **26x** in $CDCl_3$.

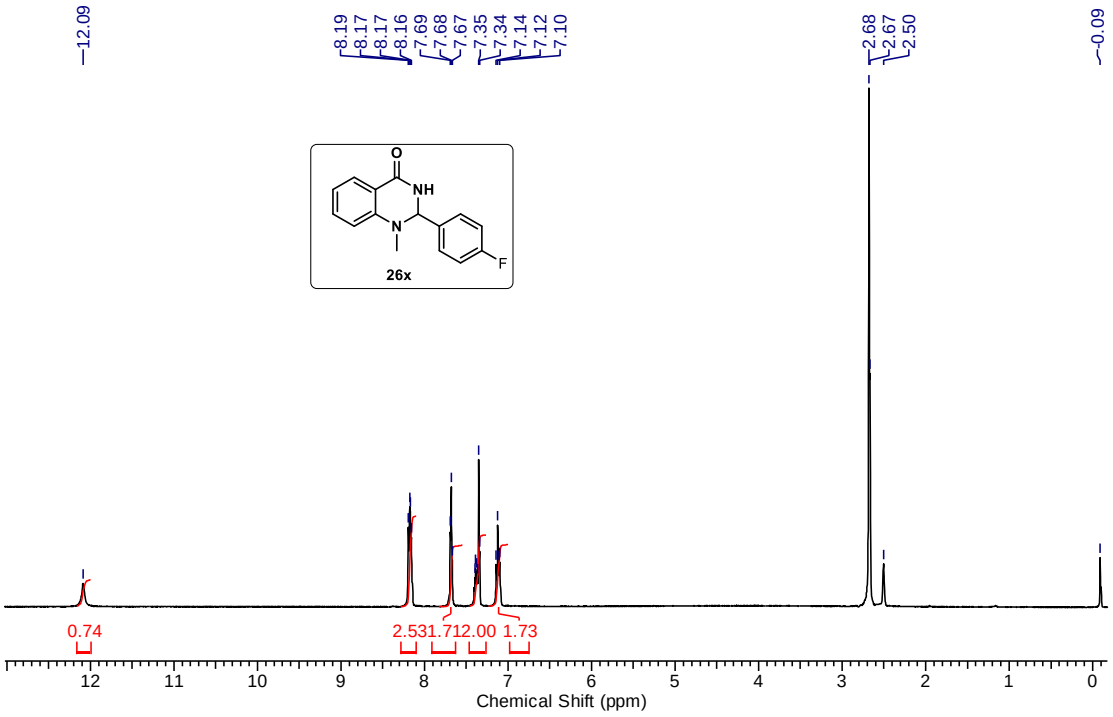


Figure 53. ^{1}H NMR (400 MHz) spectrum of compound **26x'** in $CDCl_3$ + DMSO-d_6.

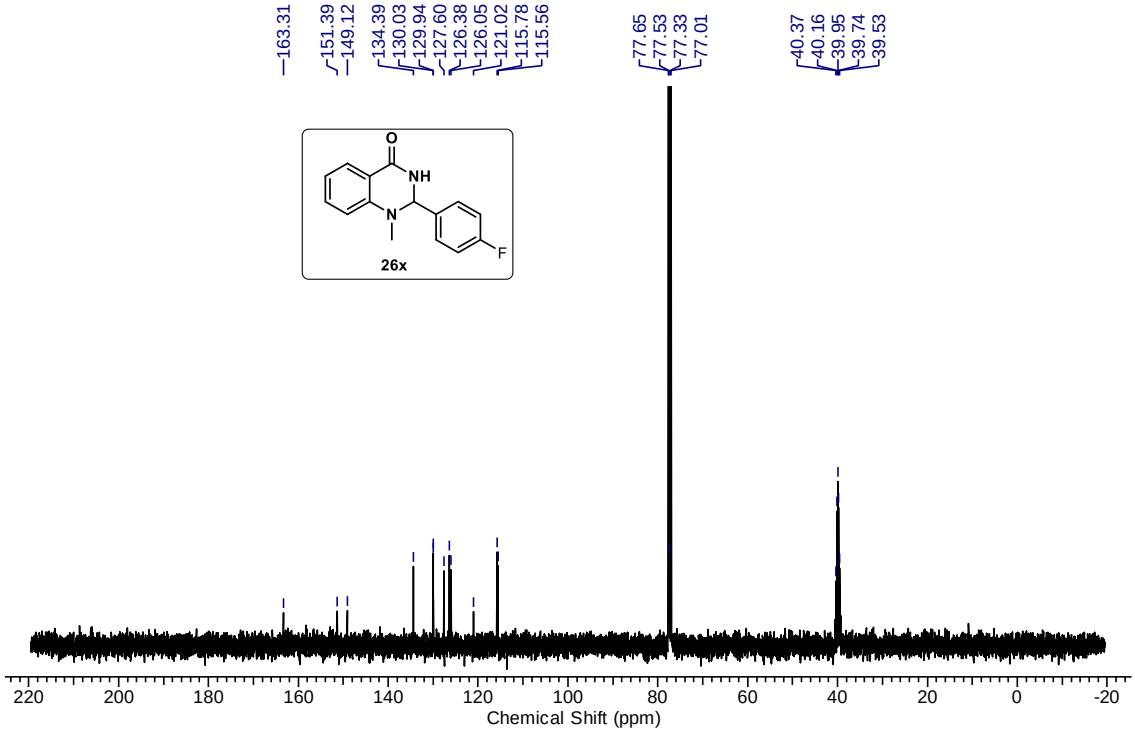


Figure 54. ^{13}C NMR (100 MHz) spectrum of compound **26x'** in $CDCl_3$ + DMSO-d_6.

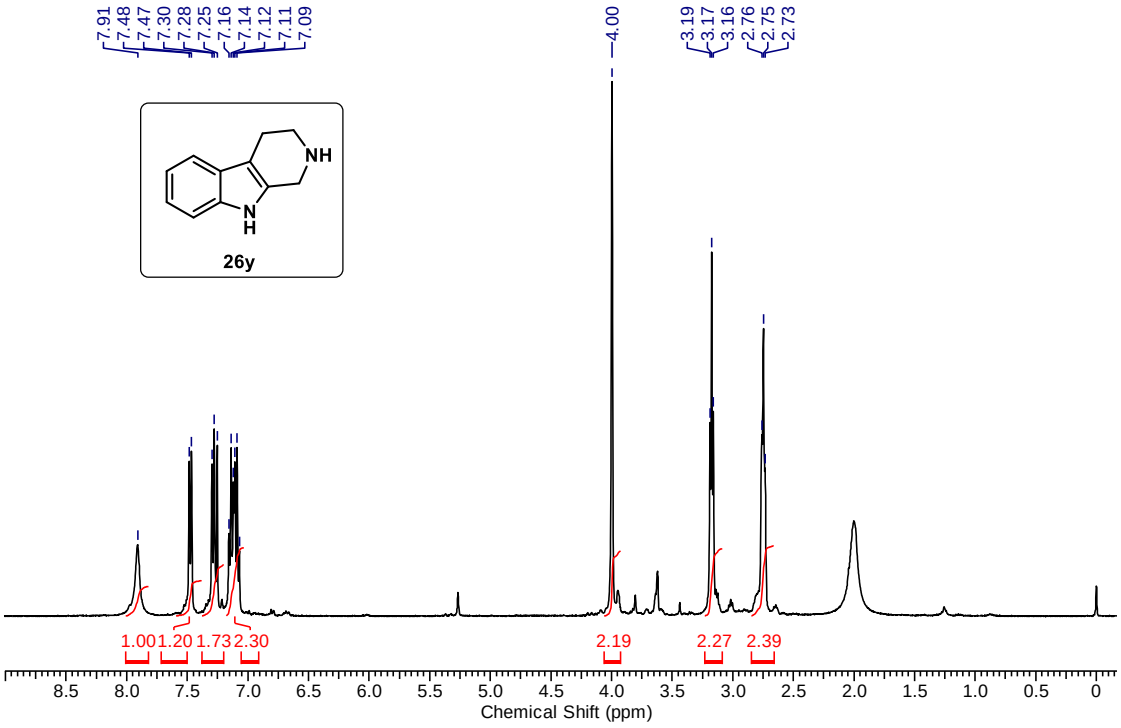


Figure 55. ^{1}H NMR (400 MHz) spectrum of compound **26y** in $CDCl_3$

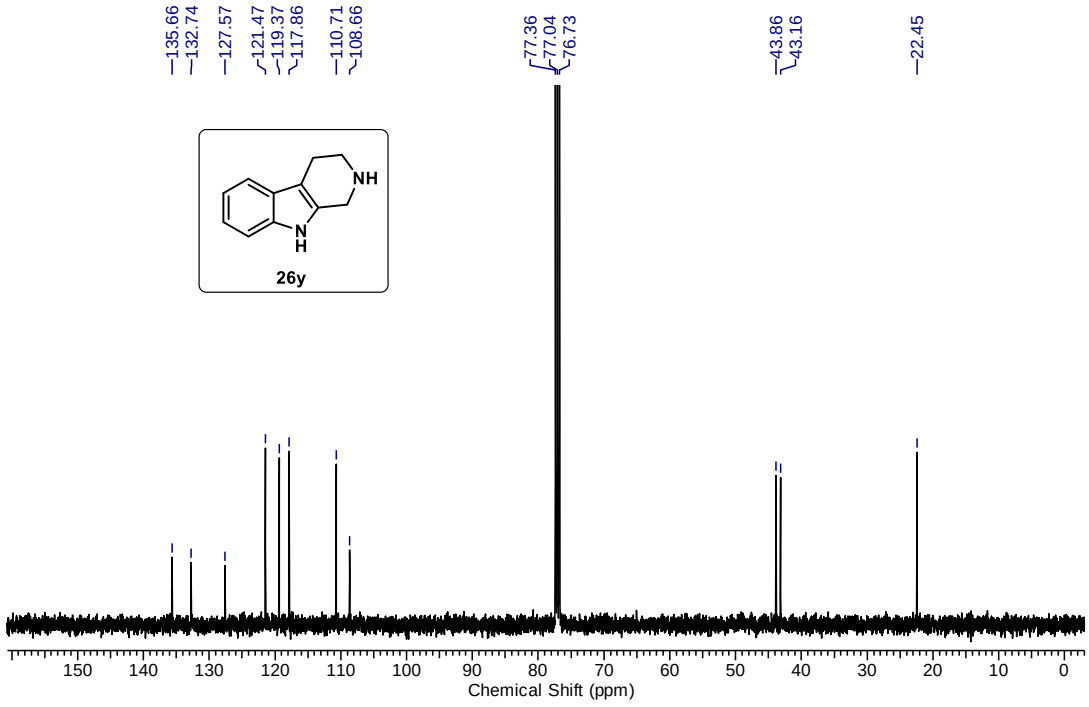


Figure 56. ^{13}C NMR (100 MHz) spectrum of compound **26y** in $CDCl_3$.

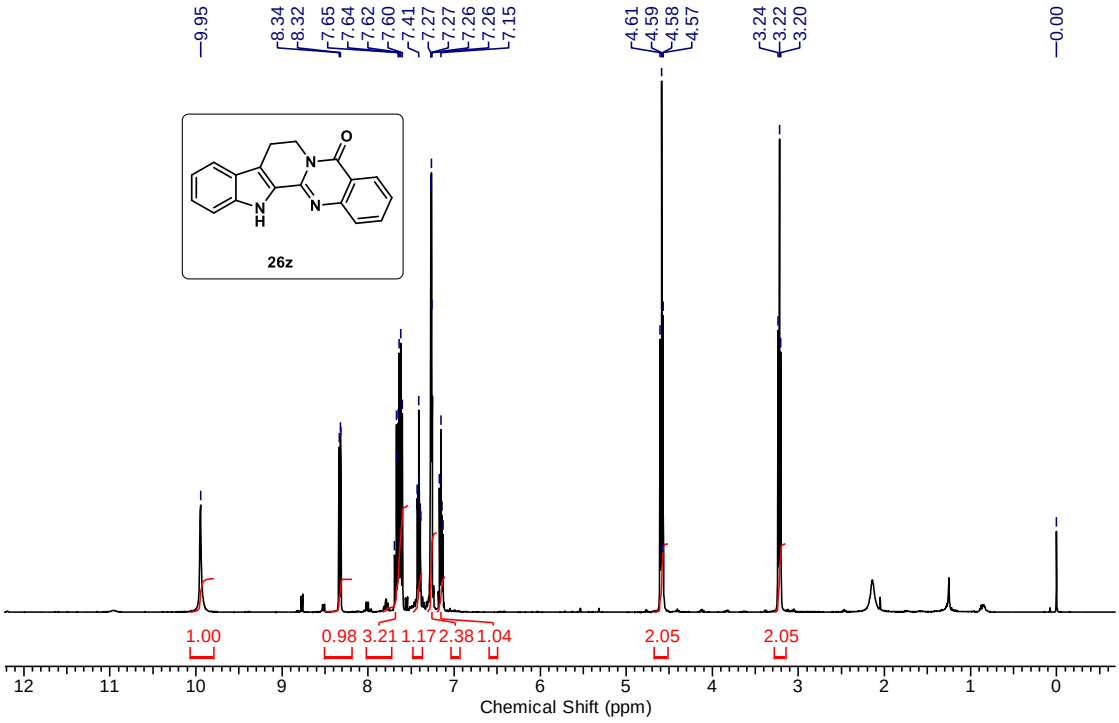


Figure 57. ^{1}H NMR (400 MHz) spectrum of compound **26Z** in $CDCl_3$

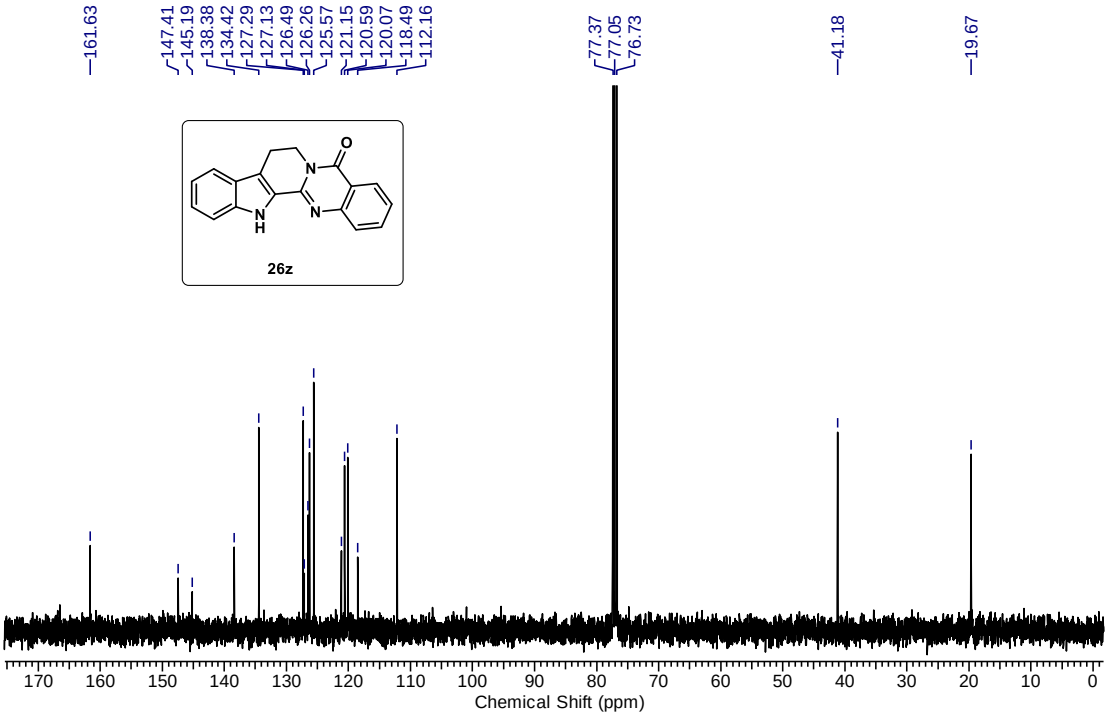


Figure 58. ^{13}C NMR (100 MHz) spectrum of compound **4y** in $CDCl_3$.

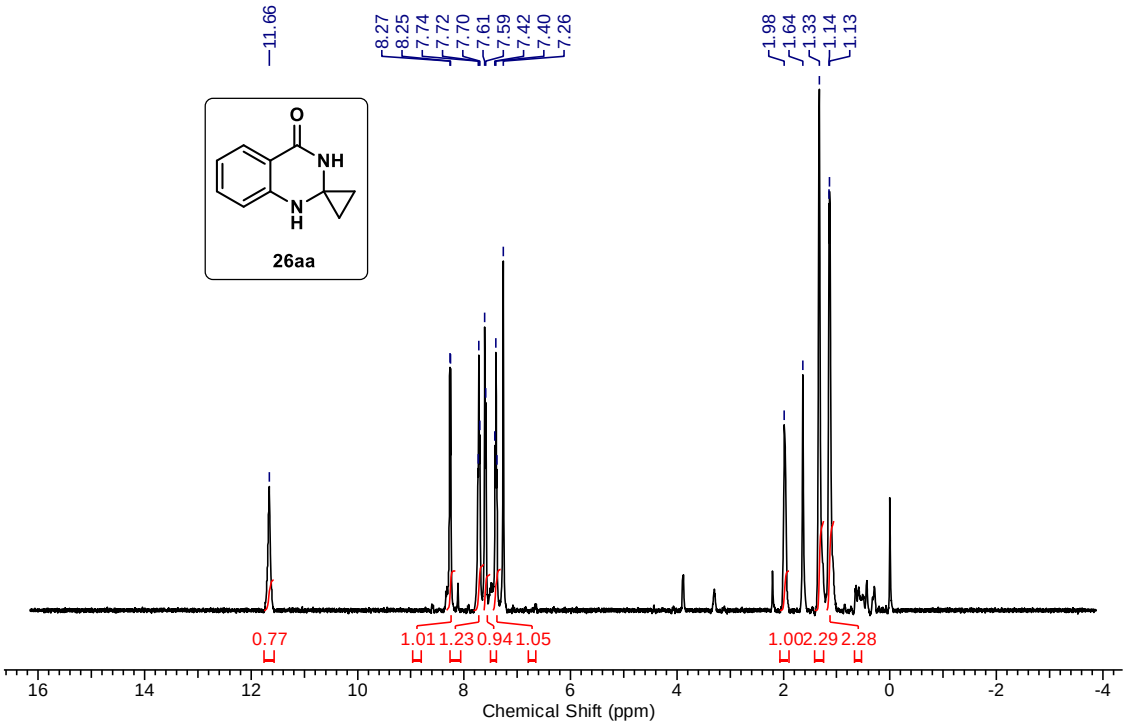


Figure 59. ^{1}H NMR (400 MHz) spectrum of compound **26aa** in $CDCl_3$

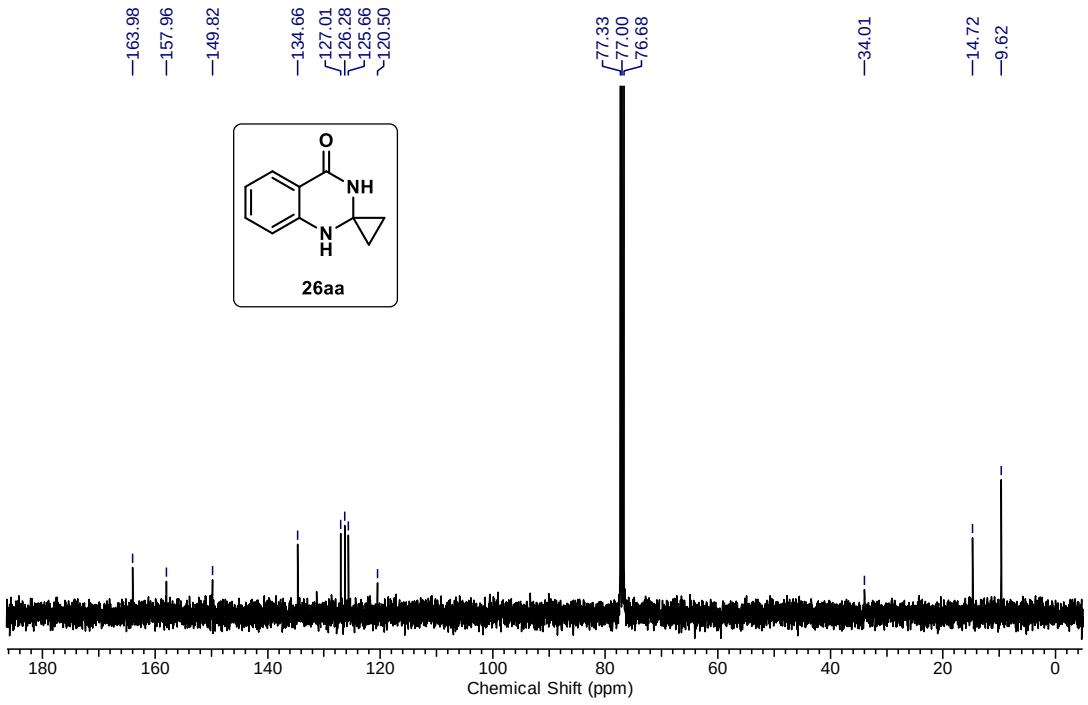


Figure 60. ^{13}C NMR (100 MHz) spectrum of compound **26aa** in $CDCl_3$.

III. 6. References:

(1) (a) Rao, K. R.; Raghunadh, A.; Mekala, R.; Meruva, S. B.; Pratap, T. V.; Krishna, T.; Pal, M. Tetrahedron Lett., 2014, 55, 6004. (b) Wen, L. R.; Dou, Q.; Wang, Y. C.; Zhang, J. W.; Guo, W. S.; Li, M. *J. Org. Chem.*, **2017**, *82*, 1428.

(2) (a) Jia, F. C.; Zhou, Z. W.; Xu, C.; Wu, Y. D.; Wu, A. X. *Org. Lett.*, **2016**, *18*, 2942-2945. (b) Zhang, S; Qi, F.; Fang, X.; Yang, D.; Hu, H.; Huang, Q.; Yang, Q. *Eur. J. Med. Chem.*, **2018,** *160*, 133.

(3) (a) Sridharan, V.; Ribelles, P.; Ramos, M. T.; Menéndez, J. C. *J. Org. Chem.*, **2009**, *74*, 5715. (b) Twin, H.; Batey, R. A. *Org. Lett.*, **2004**, 6, 4913. (c) Mhaske, S. B.; Argade, N. P. J. Org. Chem., **2004**, 69, 4563. (d) Zhu, Y. P.; Fei, Z.; Liu, M. C.; Jia, F. C.; Wu, A. X. *Org. Lett.*, **2012**, 15, 378.

(4) Chandrika, P. M.; Yakaiah, T.; Rao, A. R. R.; Narsaiah, B.; Reddy, N. C.; Sridhar, V.; Rao, J. V. *Eur. J. Med. Chem.*, **2008**, *43*, 846.

(5) (a) Alagarsamy, V.; Solomon, V. R.; Dhanabal, K. *Bioorg. Med. Chem.* **2007,** *15*, 235. (b) Baba, A.; Kawamura, N.; Makino, H.; Ohta, Y.; Taketomi, S.; Sohda, T. J. *Med. Chem.*, **1996**, *39*, 5176. (c) Rajput, C. S.; Singhal, S. *J. Pharm.*, **2013**, 2013.

(6) (a) Abd-Alla, M. A.; Ahmed, A. H. N.; El-Zohry, M. F.; Omar, F. A. Collect. Czech. *Chem. Commun.*, **1992**, *57*, 1547. (b) El-Zohry, M. F.; Ahmed, A. E. H. N.; Omar, F. A.; Abd-Alla, M. A. *J. Chem. Technol. Biotechnol.*, **1992**, *53*, 329.

(7) Yen, M.-H.; Sheu, J.-R.; Peng, I.-H.; Lee, Y.-M.; Chern, J.-W. J. *J. Pharm. Pharmacol.*, **1996**, *48*, 90.

(8) (a) Upadhyaya, K.; Thakur, R. K.; Shukla, S. K.; Tripathi, R. P. *J. Org. Chem.*, **2016**, *81*, 5046. (b) Mahesh, D.; Satheesh, V.; Kumar, S. V.; Punniyamurthy, T. *Org. Lett.*, **2017**, *19*, 6554. (c) Sau, P.; Rakshit, A.; Modi, A.; Behera, A.; Patel, B. K. *J. Org. Chem.*, **2018**, *83*, 1056. (d) Zhang, M., Ruzi, R., Li, N., Xie, J., & Zhu, C. *Org Chem Front.*, **2018**, *5*, 749. (e) Dang, P., Zheng, Z., & Liang, Y. *J. Org. Chem.*, **2017**, *82*, 2263. (f) Sangeetha, S.; Sekar, G. *Org. Lett.*, **2017**, *19*, 1670-1673. (g) Das, D.; Seidel, D. *Org. Lett.*, **2013**, *15*, 4358.

(9) (a) Gutiérrez-Bonet, A.; Juliá-Hernández, F.; de Luis, B.; Martin, R. *J. Am. Chem. Soc.*, **2016**, *138*, 6384. (b) Kumar, S.; Vasantha, V. *Org Chem Front.*, **2018**, *5*,

2630. (c) Sharma, R.; Kumar, R.; Kumar, R.; Upadhyay, P.; Sahal, D.; Sharma, U. *J. Org. Chem.*, **2018**, *83*, 12702.

(10) a) Vidyacharan, S.; Murugan, A.; Sharada, D. S. *J. Org. Chem.*, **2016**, *81*, 2837. (b) Liu, J.; Wei, W.; Zhao, T.; Liu, X.; Wu, J.; Yu, W.; Chang, J. *J. Org. Chem.*, **2016**, *81*, 9326. (c) Chen, W.; Xie, Z.; Zheng, H.; Lou, H.; Liu, L. *Org. Lett.*, **2014**, *16*, 5988. (d) Guo, A.; Han, J. B.; Tang, X. Y. *Org. Lett.*, **2018**, *20*, 2351.

(11) (a) Sagar, A.; Vidaycharan, S.; Shinde, A. H.; Sharada, D. S. *Org. Biomol. Chem.*, **2016**, *14*, 4018. (b) Arepally, S.; Babu, V. N.; Bakthadoss, M.; Sharada, D. S. *Org. Lett.*, **2017**, *19*, 5014. (b) Arepally, S.; Babu, V. N.; Bakthadoss, M.; Sharada, D. S. *Org. Lett.*, **2017**, *19*, 5014.

(12) Yang, W.; Chen, J.; Huang, X.; Ding, J.; Liu, M.; Wu, H. *Org. Lett.*, **2014,** *16*, 5418.

(13) Gholap, A. V.; Maity, S.; Schulzke, C.; Maiti, D.; Kapdi, A. R. *Org. Biomol. Chem.*, **2017,** *15*, 7140.

(14) Lahm, G.; Deichmann, J. G.; Rauen, A. L.; Opatz, T. *J. Org. Chem.*, **2015,** *80*, 2010.

(15) (a) Wen, L. R.; Dou, Q.; Wang, Y. C.; Zhang, J. W.; Guo, W. S.; Li, M. *J. Org. Chem.*, **2017,** *82*, 1428. (b) Kong, X. F.; Zhan, F.; He, G. X.; Pan, C. X.; Gu, C. X.; Lu, K.; Su, G. F. *J. Org. Chem.*, **2018,** *83*, 2006.

(16) Clemenceau, A.; Wang, Q.; Zhu, *J. Org. Lett.*, **2017**, *19*, 4872.

(17) Xu, W.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. *Org. Lett.* **2011**, *13*, 1274.

(18) Wang, L.-X.; Xiang, J.-F.; Tang, Y.-L. *Eur. J. Org. Chem. 2014*, 2682.

(19) Sang, P.; Xie, Y.; Zou, J.; Zhang, Y. *Org. Lett.* **2012**, *14*, 3894.

(20) Tian, H.; Qiao, H.; Zhu, C.; Fu, H. *RSC Adv*. **2014**, *4*, 2694.

(21) Wen, L. R.; Dou, Q.; Wang, Y. C.; Zhang, J. W.; Guo, W. S.; Li, M. *J. Org. Lett.*, **2017**, *82*(3), 1428-1436.

(22) Hu, B. Q.; Wang, L. X.; Yang, L.; Xiang, J. F.; Tang, Y. L. *Eur. J. Org. Chem.*, **2015**, *2015*, 4504.

(23) (a) Chen, X.; Chen, T.; Zhou, Y.; Han, D.; Han, L. B.; Yin, S. F. *Org. Biomol. Chem.*, **2014**, *12*, 3802. (b) Gong, J. L.; Qi, X.; Wei, D.; Feng, J. B.; Wu, X. F. *Org. Biomol. Chem.*, **2014**, *12*, 7486.

(24) Zhao, D.; Wang, T. and Li, J. X. *Chem. Comm.*, **2014**, *50*, 6471.

GRAPHICAL ABSTRACTS

Chapter I: Introduction:

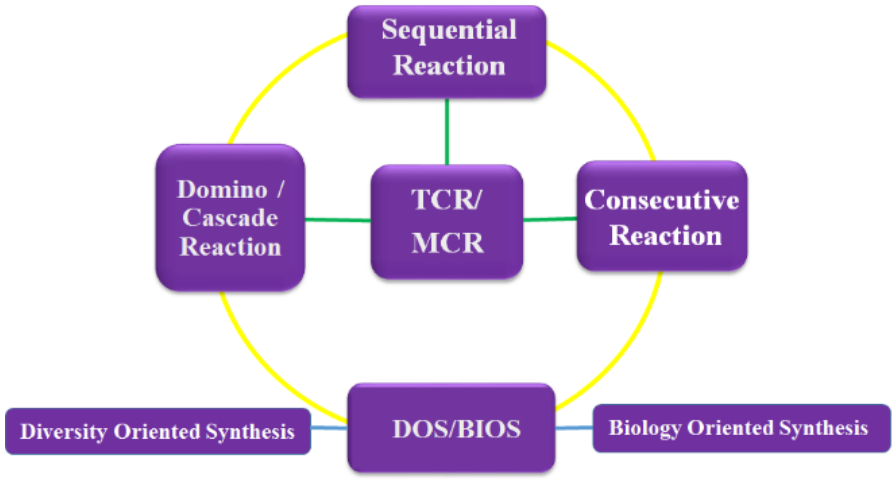
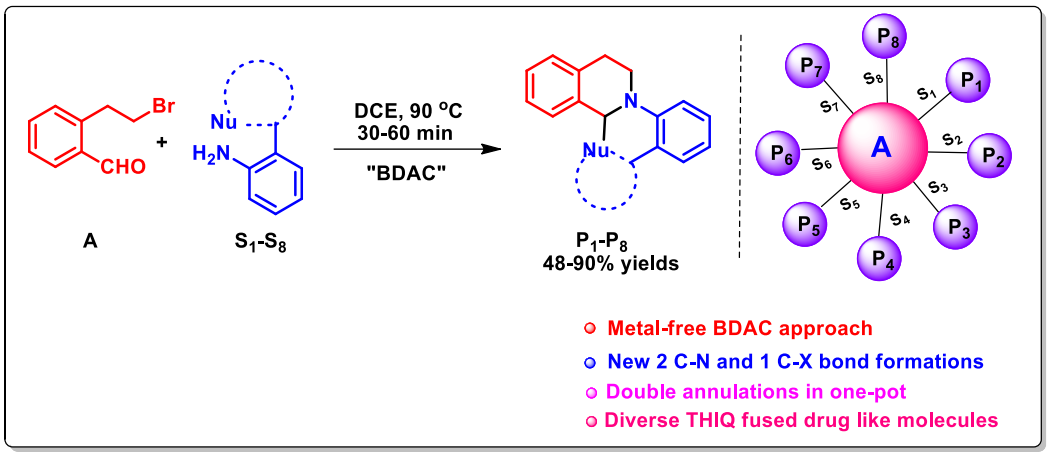
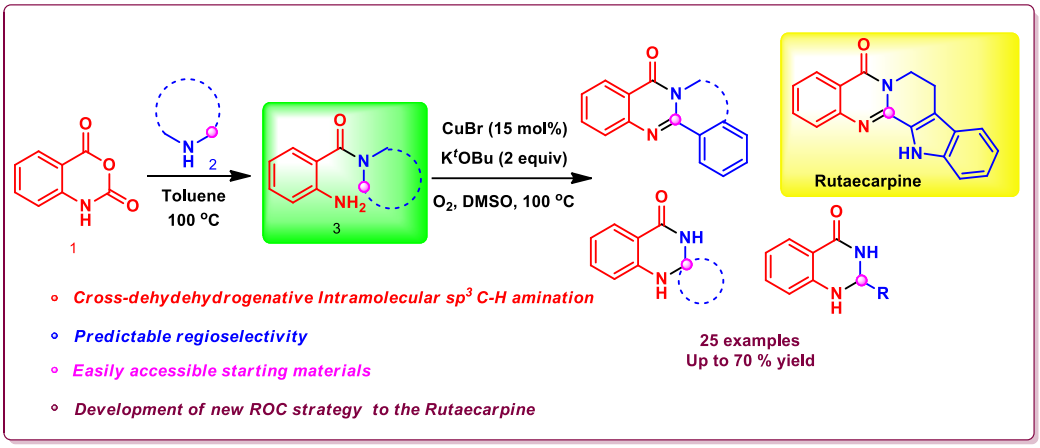


Figure 1. General reaction pathways in Organic Synthesis.

Chapter II: Scaffold diversity through a branching double annulation cascade strategy: An iminium induced one-pot synthesis of diverse fused tetrahydroisoquinoline (THIQ) scaffolds.



Chapter III : Copper-catalyzed intramolecular α-C–H amination *via* ring-opening cyclization strategy to quinazolin-4-ones: development and application in Rutaecarpine synthesis.



CURRICULUM VITAE

SRILAXMI MALIPATEL

PHONE: +91 7981365504

E-mail: srilaxmi.malipatel@gmail.com, cy13p1004@iith.ac.in

CAREER OBJECTIVE:

To pursue a scientific research career in the field of *Domino Cyclization/C-H functionalization Strategy for the Synthesis of Nitrogen Containing heterocyclic derivatives and Application in Drug Design and Discovery*, ***Organocatalysis and Photoredox catalysis in Asymmetric synthesis***.

Doctor of Philosophy: Organic Chemistry (**2013-2019**),

Indian Institute of Technology Hyderabad-502285,

Hyderabad, India.

Thesis:

Branching Double Annulation Cascade and Ring Opening Cyclization Strategies: An Iminium Induced Synthesis of Diverse Fused Tetrahydroisoquinoline (THIQ) and Quinazolinone derivatives Application in Rutaecarpine.

Advisor: Dr. D. S. Sharada

RESEARCH INTERESTS:

1) Development of novel methodologies for the synthesis of ***Nitrogen containing heterocyclic compounds*** and ***Organocatalysis in Asymmetric synthesis***.

2) Development of ***visible-light*** mediated C-H functionalization cyclization approach using metal/metal-free ***organic photoredoxcatalysis in Asymmetric synthesis***.

PERSONAL DETAILS

FULL NAME : Srilaxmi Malipatel

SEX : Female

MARITAL STATUS : Married

NATIONALITY : Indian

PRESENT MAILING ADDRESS : Srilaxmi Malipatel

Department of Chemistry

Indian Institute of Technology Hyderabad

Kandi, Sangareddy,Telangana. 502285.

India.

Email: cy13p1004@iith.ac.in

Cell #: +91 7981365504

Course	**Board/University**	**Subjects**	**Year of Passing**	**% Marks**
Ph.D.	Indian Institute of Technology Hyderabad, India	Dominocyclization/C-H functionalization	Submitted on 2nd May-2019	By research
JRF	Indian Institute of Technology Hyderabad, India	Dominocyclization	July 2013 to July 2015	By research
M. Sc.	MNR PG College, Osmania University	Organic Chemistry	2010	72.4
B.Sc.	Surya Laxmi Degree College, Osmania University	Botany, Zoology, Chemistry.	2008	82.3
Intermediate	Sri-Sai Co-operative Junior College, Board of	Botany, Zoology, Physics, Chemistry,	2005	88.3

	Intermediate Education.	English, Telugu.		
SSC (Class X)	Dayanand Vidyamandir Board of Secondary School Education.	Telugu, English, Hindi, Mathematics, General Science, Social Studies.	2003	82.7

Awards and Achievements:

- Andhra Pradesh State Eligibility Test (**APSET-2012**) for Assistant Professor/ Lecturership
- Secured **GATE 2013**.
- Junior Research Fellowship from CSIR-UGC New Delhi, India (**July 2013-2015**).
- Senior Research Fellowship from CSIR-UGC New Delhi, India (**July 2015-2019**).
- **Appreciation Award for research in chemistry** for the year **2018** given by **IITH.**

Instruments Handled:

a) IR-Spectrophotometer – Bruker, Tensor 37

Work and Research Experience

Academic experience: (Degree Lecturer)

2 years as Guest Lecturer in Chemistry (**June-2011** to **June-2013**), **NTR Govt Degree and PG College** for Womens, Mahaboob Nagar, Telangana.

Academic experience Ph.D: Indian Institute of Technology Hyderabad (**IITH**), India "**2013-2019**".

Teaching Assistant for **B.Tech Practicals-2014, IIT Hyderabad.**

Teaching Assistant for **MSc** Organic Chemistry **Practicals-2016, IIT Hyderabad.**

LIST OF PUBLICATIONS INCLUDED IN THESIS

1. Scaffold diversity through a branching double annulation cascade strategy: An iminium induced one-pot synthesis of diverse fused Tetrahydroisoquinoline (THIQ) scaffolds. Duddu S. Sharada,* Anand H. Shinde, **Srilaxmi M. Patel** and Shinde Vidyacharan. *J. Org. Chem.* **2016**, *81*, 6463-6471.
2. Copper-catalyzed intramolecular *α*-C–H amination *via* Ring-Opening Cyclization strategy to Quinazolin-4-ones: Development and application in Rutaecarpine synthesis. **Srilaxmi M. Patel**, Harika Chada, Sonika Sharma, Sonali Biswal and Duddu S. Sharada*, *Synthesis*, **2019**, DOI: 10.1055/s-0037-1611575 (*In Press*).

LIST OF PUBLICATIONS NOT INCLUDED IN THESIS:

3. A highly efficient synthesis of imidazo-fused polyheterocycles via Groebke-Blackburn-Bienayme reaction catalyzed by $LaCl_3.7H_2O$. Anand H. Shinde, **Srilaxmi Malipatel**, Bishnupada Satpathi and Duddu S. Sharada,* *Tetrahedron Lett.* **2014**, *55*, 5914-5920.
4. A facile one-pot protocol for the synthesis of tetrazolyl-tetrahydroisoquinolines *via* novel domino intramolecular cyclization/Ugi-azide sequence. Anand H. Shinde, Archith, N., **Srilaxmi Malipatel**, Duddu S. Sharada,* *Tetrahedron Lett.* **2014**, *55*, 6821-6826.
5. Design and synthesis of novel indole and carbazole based organic dyes for dye sensitized solar cells: theoretical studies by DFT/TDDFT. **Srilaxmi M. Patel**, Kuntal Pal, P. Naresh Kumar, Melepurath Deepa, and Duddu S. Sharada,* *Chemistry Select* **2018**, *3*, 1623–1628.

CONFERENCE PRESENTATIONS

1. A poster presentation titled “Scaffold Diversity through a Branching Double Annulation Cascade Strategy: An Iminium Induced One-pot Synthesis of Diverse Fused Tetrahydroisoquinoline (THIQ) Scaffolds” presented in July 14-16, 2017 “**21st CRSI national symposium in chemistry**”, organized by CSIR-**IICT Hyderabad**, India.

2. A poster presentation titled "Copper-catalyzed intramolecular α-C–H amination *via* ring-opening cyclization strategy to quinazolin-4-ones: development and application in Rutaecarpine synthesis" **National Conference on Organic Molecules As Synthons and Reagents for Innovations** (**OMSRI-2019**) held during February 8-10, 2019 organized by Department of chemistry, **IIT Roorkee**, India.

3. A poster presentation titled "Scaffold Diversity through a Branching Double Annulation Cascade Strategy: An Iminium Induced One-pot Synthesis of Diverse Fused Tetrahydroisoquinoline (THIQ) Scaffolds" **March-2017**, at **In-House Symposium**, **IIT Hyderabad**, India.

4. A poster presentation titled "Visible-Light-Mediated Nitrogen Incorporation via Dual C(sp^3)-H and C(sp^2)-H Bond Functionalization by Photo redox Catalysis" **30th March-2019 In-House Symposium**, **IIT Hyderabad**, India.