N-Propargylamines: A Key Precursor for the Construction of Functionalized Nitrogen and Sulfur Heterocycles

A Dissertation Submitted in Partial Fulfilment for the

Degree of

Doctor of Philosophy

Submitted by

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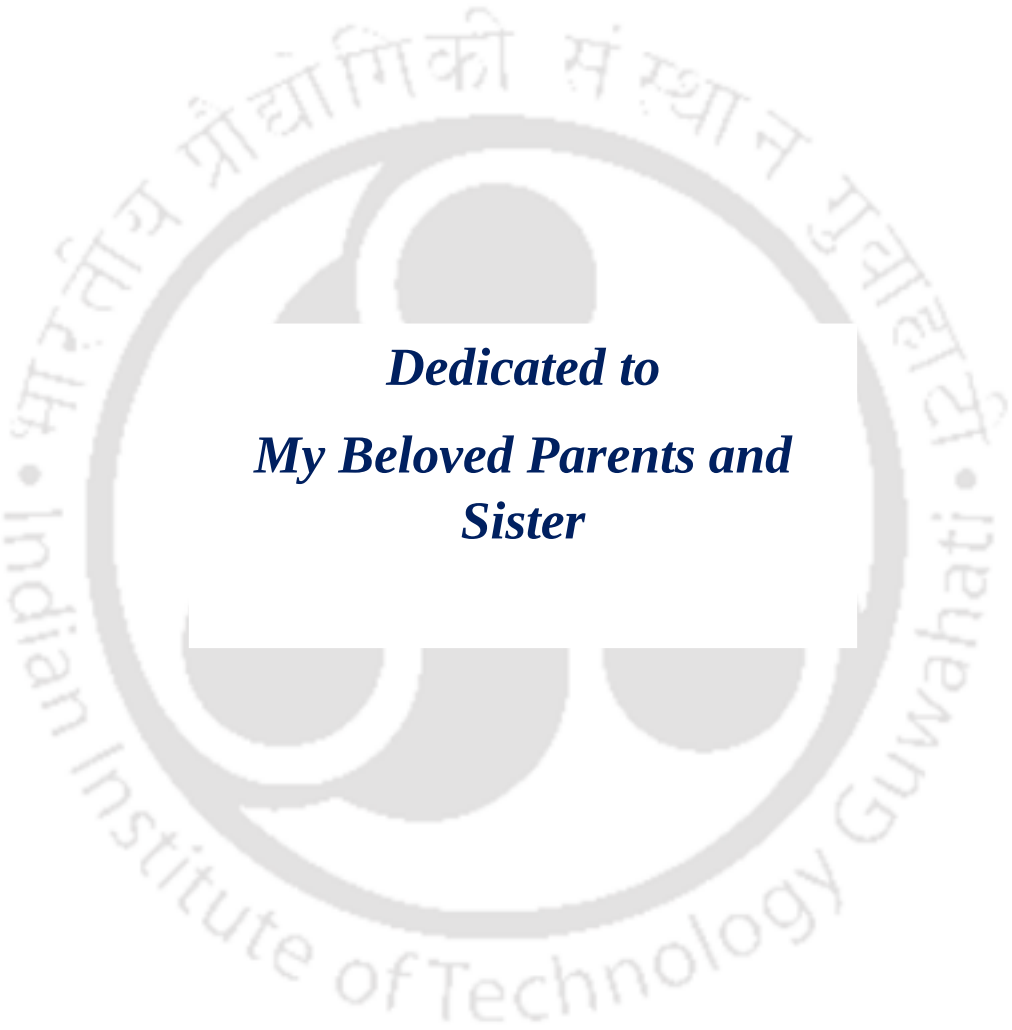

Dedicated to

My Beloved Parents and Sister

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled "***N-Propargylamines: A Key Precursor for the Construction of Functionalized Nitrogen and Sulfur Heterocycles"*** is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the guidance of Prof. Anil K. Saikia.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

August, 2023 (Bipin Kumar Behera)

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CERTIFICATE

This is to certify that **Bipin Kumar Behera** has been working under my supervision since July 2017 as a regular registered Ph. D. student. I am forwarding his thesis entitled "***N-Propargylamines: A Key Precursor for the Construction of Functionalized Nitrogen and Sulfur Heterocycles***" being submitted to the Indian Institute of Technology, Guwahati for the award of Doctor of Philosophy in Chemistry. I certify that he has fulfilled all the requirement according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

August, 2023
IIT Guwahati

Prof. Anil K. Saikia
Supervisor

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Above all, I owe it all to Almighty Lord (Shree Jagannath) for granting me the wisdom, health, and strength to undertake this research life and completion of this difficult yet fulfilling journey.

Sincerely,

Bipin

LIST OF ABBREVIATIONS

Ac	Acetyl	LED	Light Emitting Diode
$AgSCF_3$	Silver(I)trifluoromethanethiolate		
Bn	benzyl	LDA	lithiumdiisopropyl amine
Boc	*tert*-Butyloxycarbonyl	*m*-CPBA	*meta*-chloroperbenzoic acid
BBr_3	Boron tribromide		
Bu	Butyl	mp	melting point
BHT	Butylated Hydroxyl Toluene		
CAN	ceric ammonium nitrate	MS	molecular sieves
CCDC	cambridge crystallographic data centre	m/z	mass to charge ratio
Cbz	carboxybenzyl	NCS	*N*-chlorosuccinimide
CSA	camphorsulfonic acid	NIS	*N*-iodosuccinimide
Cy	cyclohexyl	NMR	nuclear magnetic resonance
DCE	1,2-dichloroethane	ORTEP	oak ridge thermal ellipsoid plot
DCM	Dichloromethane	Ph	phenyl
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone	PCl_3	phosphorus trichloride
DABSO	(1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide	PMB	*p*-methoxy benzyl
		PIDA	Phenyliodine(III) diacetate
DIPEA	*N*,*N*-diisopropylethylamine	TBP	*tri n*-butylphosphine
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene	$POCl_3$	phosphoryl chloride
DMF	*N*, *N*-dimethylformamide	$P(OEt)_3$	triethylphosphite
DMSO	dimethylsulfoxide	PPh_3	triphenyphosphine
de	diastereomeric excess	ppm	parts per million
Eosin Y	Eosin Yellowish	Pr	propyl
ee	enantiomeric excess	*p*-TSA	*p*-toluenesulfonic acid
HRMS	high resolution mass spectrometry	rt	room temperature
HFIP	Hexafluoroisopropanol	TBAF	tetrabutylammonium fluoride

ICl	iodine monochloride	$TMSCF_3$	Trifluoromethyltrimethyl Silane
IR	infrared	^{t}Bu	*tert*- Butyl
LA	Lewis acid	THF	tetrahydrofuran
Tf	trifluoromethanesulfonyl	TMS	trimethylsilyl
TFA	trifluoroacetic acid	TMEDA	*N*,*N*,*N*′,*N*′-tetramethylenediamine
TIPS	triisopropylsilyl	Ts	*p*-toluenesulfonyl
TLC	thin layer chromatography	TBHP	tert-Butyl hydroperoxide
		TEMPO	(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl

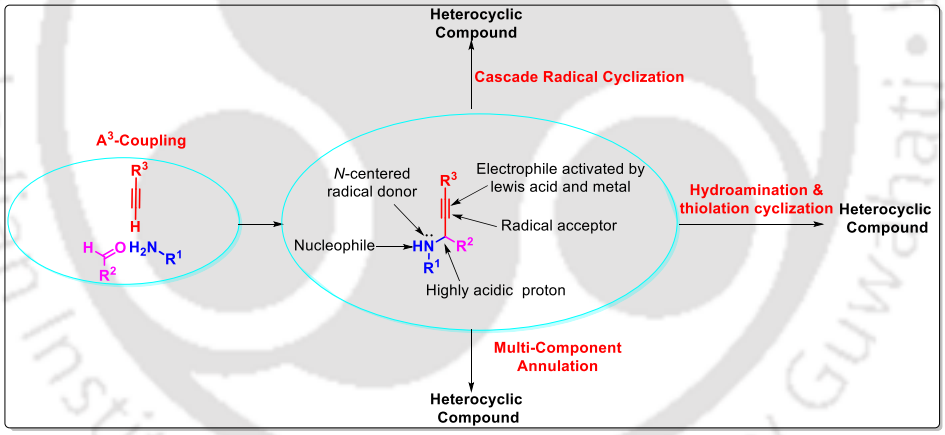
Abbreviations for intensities of ^{1}H-NMR signals

s	singlet	t	triplet
d	doublet	q	quartet
dd	doublet of doublet	m	multiplet
ddd	doublet of doublet of doublet	brs	broad signal
dddd	doublet of doublet of doublet of doublet	Hz	Hertz
dt	doublet of triplet	MHz	Mega-Hertz

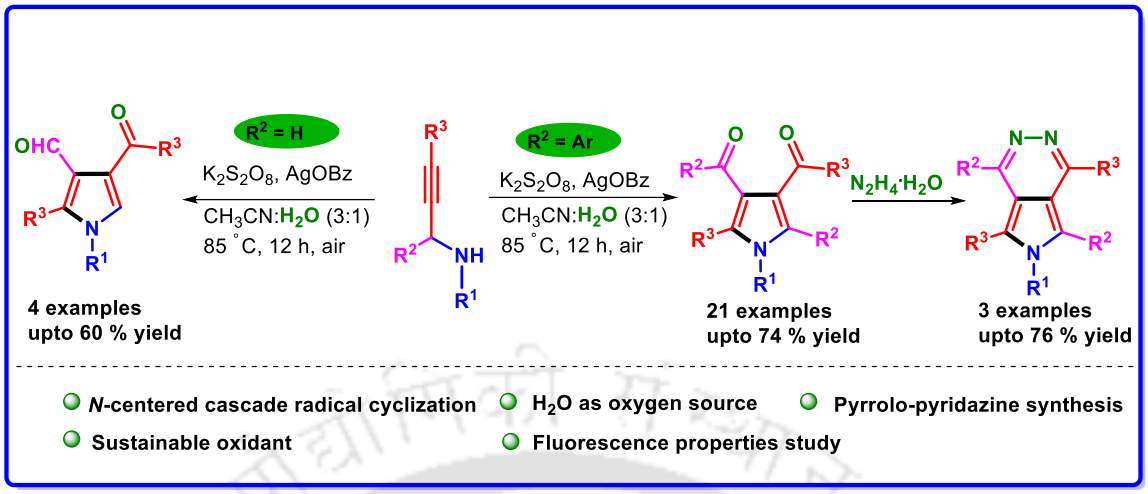
Abstract

The contents of the present thesis entitled as "***N-Propargylamines: A Key Precursor for the Construction of Functionalized Nitrogen and Sulfur Heterocycles"*** have been divided into five chapters based on the results achieved from the experimental works performed during the entire course of the PhD research programme.

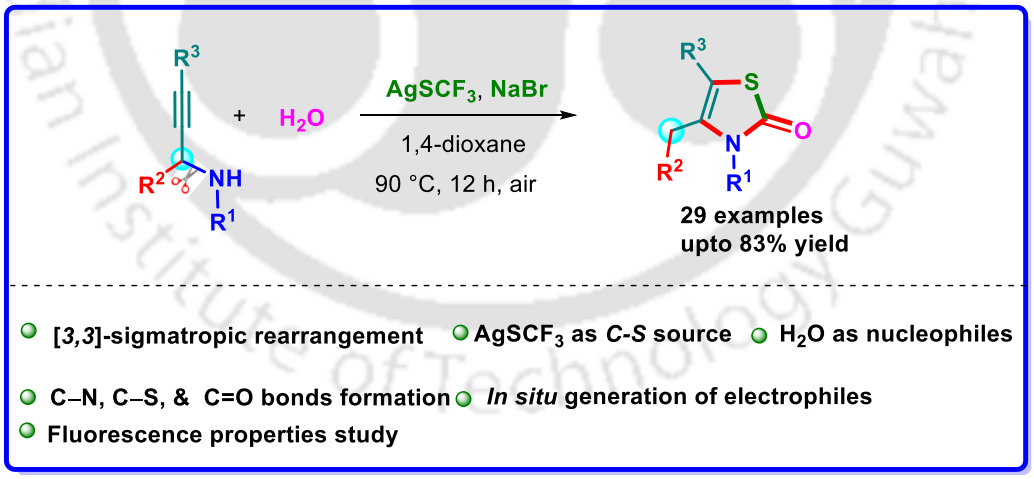
Chapter 1 highlights an overview of *N*-propargylamines. This includes a brief discussion about synthetic reactivity and utility of *N*-propargylamines. It emphasizes on its unique structure bearing both free amine and an alkyne group, thus focusing on its dual role either as nucleophile and electrophile or as *N*-centered radical donor and radical acceptor. Several efficient methodologies with *N*-propargylamines as starting precursors are described, which utilizes thermal/photo induced cascade radical cyclization, tandem multi-component annulation and hydroamination/ hydrothiolation cyclization.



Chapter 2 highlights an efficient methodology developed for the synthesis of tetra- and penta-substituted pyrroles *via* *N*-centered radical initiated oxidative self-dimerization of *N*-propargylamines catalyzed by silver benzoate in the presence of $K_2S_2O_8$. The protocol provides a simple route for the synthesis of highly functionalized pyrroles with two carbonyl groups in the side chain. The methodology can be extended towards the synthesis of fluorescent pyrrolo[3,4-d]pyridazine derivatives.

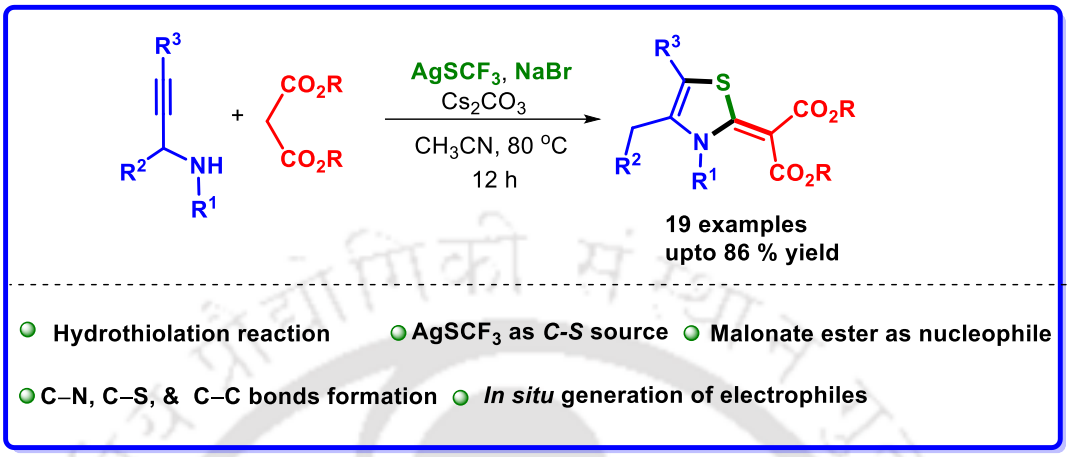


Chapter 3 represents an efficient methodology for the synthesis of both di- and trisubstituted thiazol-2-ones from *N*-propargylamines *via* [3,3]-sigmatropic rearrangement/5-*exo*-dig cyclization. The protocol utilizes silver(I) trifluoromethanethiolate ($AgSCF_3$) as a *C*–*S* source and eco-friendly H_2O as nucleophile under open air condition. The methodology can be extended for the synthesis of bioactive analog of thiozole-2-thione derivatives and photophysical properties have been studied for some synthesized compounds.

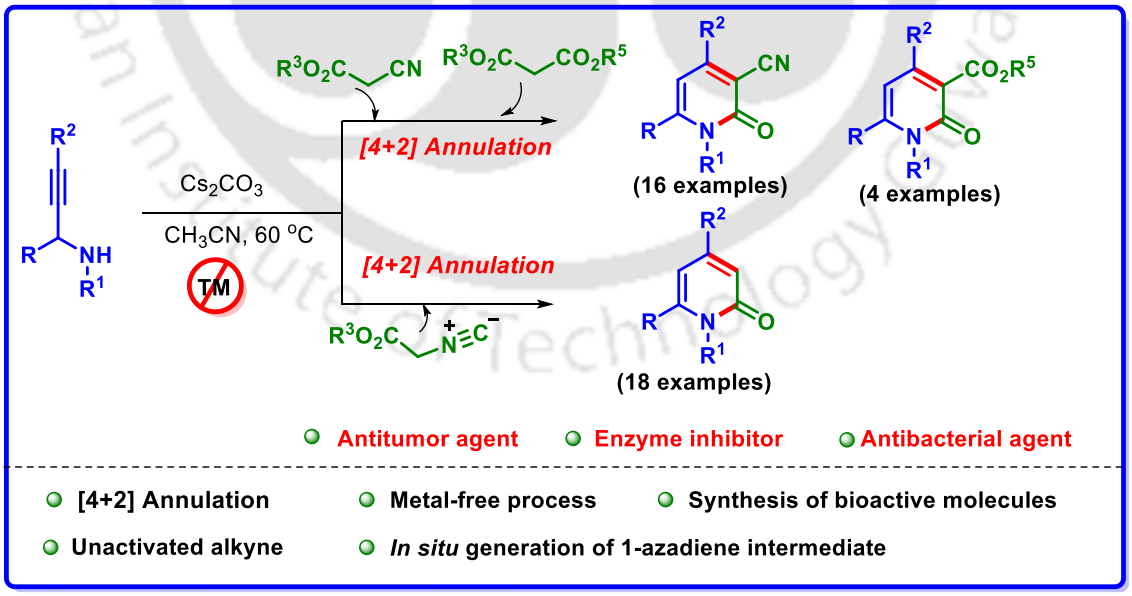


Chapter 4 describes an efficient methodology developed for the synthesis of methylene-dihydrothiazole derivatives *via* Michael-addition followed by hydrothiolation of *N*-propargylamines. The protocol utilizes silver(I)trifluoromethanethiolate ($AgSCF_3$) as a *C*–

S source and malonate ester derivatives as nucleophiles. The reaction is compatible with many functional groups with moderated to good yield.



Chapter 5 highlights a facile and efficient synthesis of structurally diversified 2-pyridones is demonstrated using the [4+2] annulation of *in situ* generated azadienes from *N*-propargylamines and active-methylene compounds. The reaction is promoted by an inorganic base giving moderate to good yields. The developed methodology is applicable for direct and formal synthesis of various bioactive molecules. The synthetic utility of the protocol was also illustrated by late stage functionalization of the products.



CONTENTS

Chapter 5. Base Promoted [4+2] Annulation Reaction of *In Situ* Generated Azadienes with Active-methylene Compounds: Access to Highly Functionalized 2-Pyridones

CHAPTER 1

Synthetic Reactivity and Utility of *N*-propargylamines

1.1. Heterocyclic Compounds

Organic molecules can be broadly classified into acyclic and cyclic compounds. The cyclic compound containing only carbon skeleton is called carbocyclic molecule and the cyclic system containing carbon along with one heteroatom are called heterocyclic compounds. Though many heteroatoms are known to be part of the heterocyclic systems, nitrogen, oxygen and sulfur are the most prevalent. Heterocyclic compounds can be further classified as aliphatic and aromatic heterocycles. The aliphatic heterocycles are the cyclic molecules that do not contain any double bond such as aziridine **1**, oxirane **2**, thiirane **3**, azetidine **4**, oxetane **5**, thietene **6**, pyrrolidine **7**, tetrahydrofuran **8**, tetrahydrothiophene **9**, piperidine **10**, tetrahydropyran **11**, tetrahydrothiopyran **12** (*figure 1.1.1*).

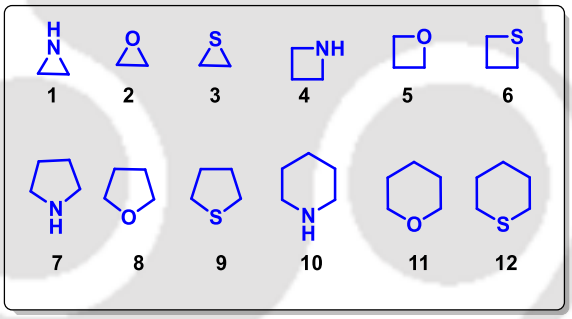


Figure 1.1.1. *Some Examples of Aliphatic Heterocyclic Compounds.*

On the other hand, aromatic heterocycles are those which contain a heteroatom in the ring and follow Huckel's rule i.e. being conjugated, planar and have (4n+2) π electron system such as pyrrole **13**, furan **14**, thiophene **15**, thiazole **16**, imidazole **17**, pyridine **18**, pyridone **19,** pyridazine **20**, pyrimidine **21**, pyrazine **22** (*figure 1.1.2*). Heterocycles are the most important and relevant traditional division of organic chemistry, and research attentive on heterocycles are increasing because of their anti-microbial, medicinal, and industrial applications. For instance, heterocyclic

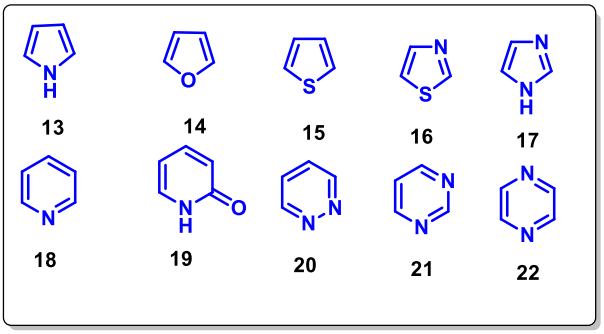


Figure 1.1.2. *Some Example of Aromatic Heterocyclic Compound.*

molecules play a vital role in the formation of many naturally occurring molecules including nucleic acids like DNA and RNA, photosynthesizing pigment chlorophyll and the oxygen transporting agent hemoglobin vitamins and others.[1] Due to their ubiquitous presence, heterocyclic chemistry has fascinated many scientists and has become a vast, expanding research area of chemistry.

1.1.1. Importance of Pyrroles, Thiazoles and Pyridones

Out of different heterocyclic motifs, five and six-membered nitrogen and sulfur-containing heterocycles like pyrrole, thiazole and pyridone are the key structural fragments, ubiquitous in many natural products and bioactive molecules. Among them, pyrrole is one of the most important five-membered nitrogenous heterocycles, which is found in a broad range of natural products, bioactive molecules and also found to have vast application in materials science. Pyrrole was first isolated in 1857 from the products of bone pyrolysis, and identified as biologically relevant when it was recognized as a structural framework of photosynthesizing pigment chlorophyll and oxygen transporting agent heme. For instance, storniamide A,[2a] is a selective inhibitor disclosed reverse the multidrug-resistant (MDR) phenotype, atorvastatin,[2b,c] is one of the top-selling worldwide cholesterol-lowering drug, pyrrole containing alkaloid neolamellarin A,[2d] which is derived from sponges are widely used as Hypoxia-inducible factor-1inhibitor (*figure 1.1.1.1*).

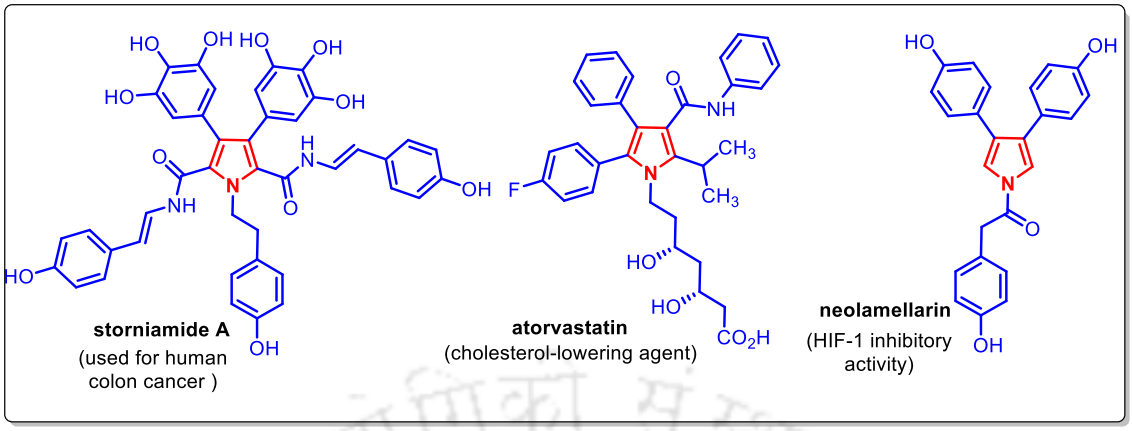


Figure 1.1.1.1. *Examples of Bioactive Pyrrole Derivatives.*

Similarly, thiazole is a five membered aromatic heterocyclic molecule having both nitrogen and sulfur and belongs to the azole family of heterocycles and occupies an important place in chemistry. In 1887, it was first discovered by J. H. Weber and Hantzsch,[3a] and later in 1889, the sturucture was confirmed.[3b] Thiazole based Cobicistat is a potent cytochrome P450 inhibitor booster for HIV protease inhibitors,[3c] thiazole containing antibiotic Cefotaxime is used to treat urinary tract infections and joint infections,[3d] Ixabepilone is a thiazole based pharmaceutical drug potent for breast cancer[3e] (*figure 1.1.1.2*).

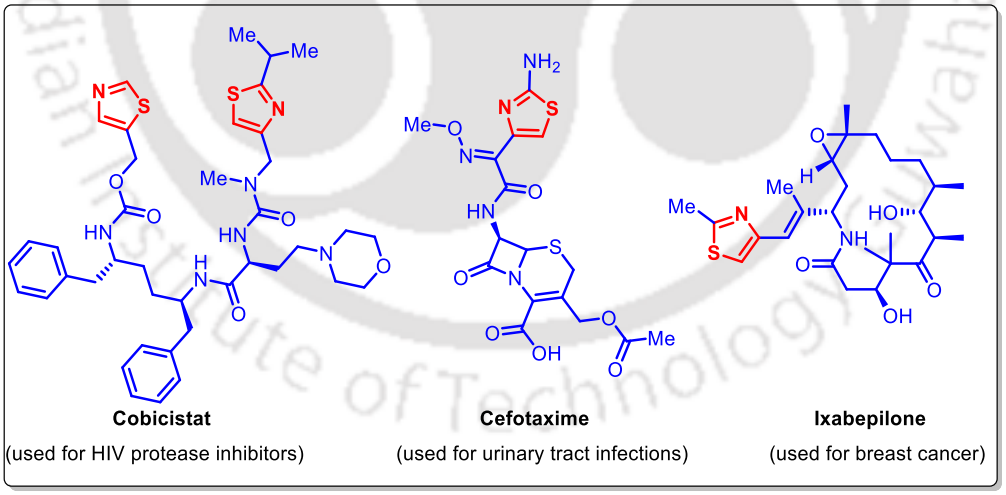


Figure 1.1.1.2. *Examples of Bioactive Thiazole Derivatives.*

Among all the synthetic and naturally occurring six-membered nitrogenous heterocycles, 2-pyridones heterocycles having an amide linkage have been widely employed as versatile scaffolds in medicinal chemistry, and natural product due to their unique structural characteristic along with broad range of biological applications. Pyridone based scaffold, tazemetostat is a selective cancer

drug that can be used as a potent inhibitor of EZH2, which helps to keep the cancer cells from growing,[4a] Doravirine is a non-nucleoside reverse transcriptase inhibitor to treat HIV infection,[4b] and Duvelisib is a 2-pyridone containing an anti-cancer drug used to treat blood cells cancer, e.g. chronic lymphocytic leukemia,[4c] (*figure 1.1.1.3*).

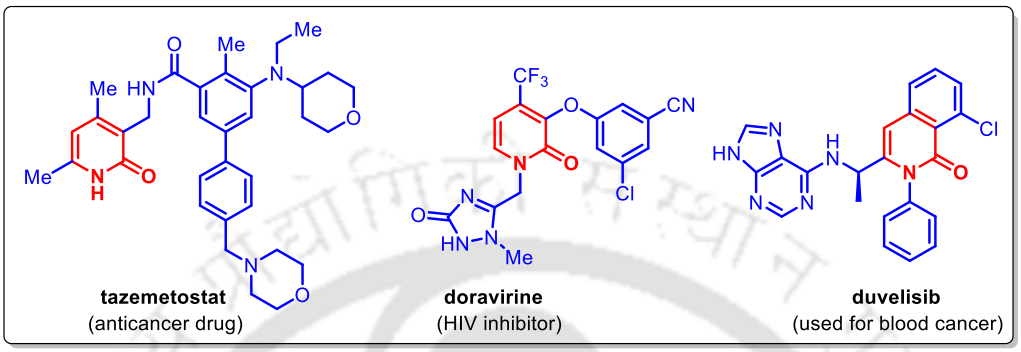


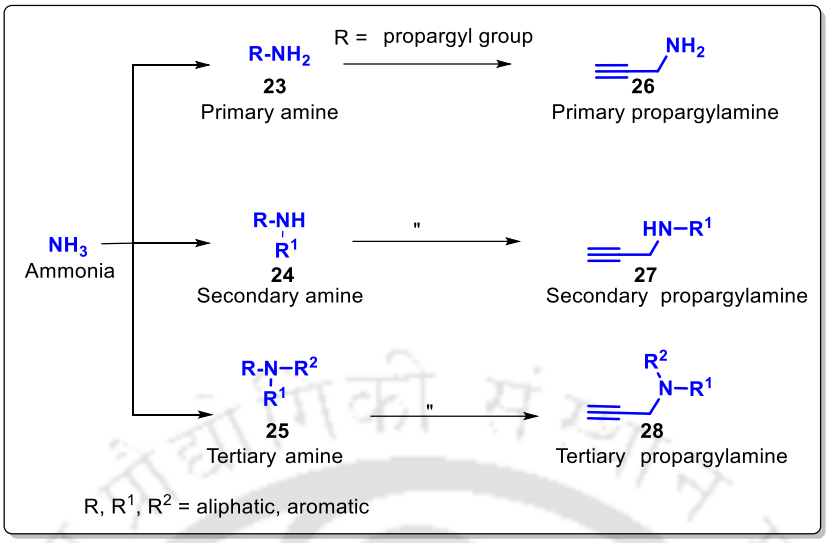
Figure 1.1.1.3. *Examples of Bioactive 2-Pyridone Derivatives.*

We have shown above, the various application of nitrogen and sulphur heterocycles with regards to natural products, and drug discovery. Because of this, new emerging strategies for the synthesis of nitrogen and sulfur heterocycles using readily available starting precursor with less number of steps, environment-friendly, and with a wide range of substrate scope are still of great interest. To accomplish such goals, recently, the versatile and powerful starting material *N*-propargylamines which is derived from multi-component A^3-coupling reaction is gaining significant interest towards the construction of various bioactive and natural product containing nitrogen and sulfur heterocycles.

1.2. An Overview of *N*-propargylamines

1.2.1. Classification of *N*-propargylamines

Amines are aliphatic and aromatic derivatives of ammonia. Depending on the number of alkyl groups substituting the amines, it can be classified as primary amines **23**, secondary amines **24** and tertiary amines **25**. But, when an alkyl group of primary amine is replaced by propargyl group, it is termed as primary propargylamine **26**. Similarly, when alkyl group of secondary amine and tertiary amines is replaced by a propargyl group, it is called secondary **27** and tertiary-propargylamines **28** receptively (*Scheme 1.2.1.1*).



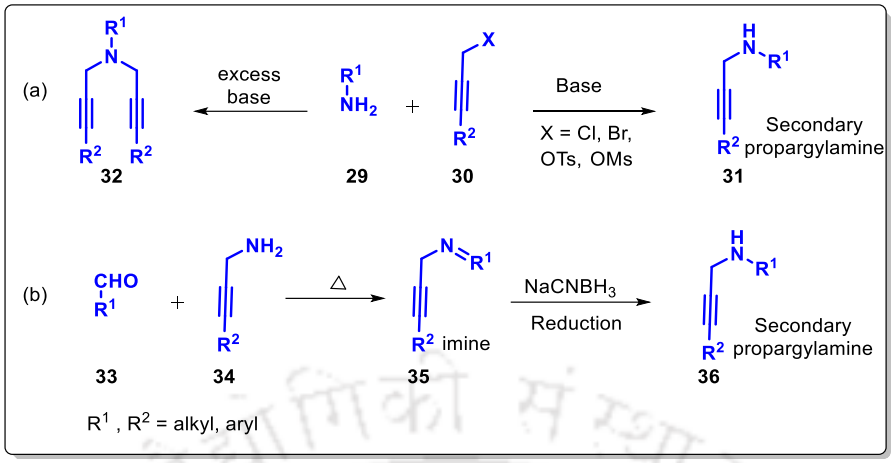
Scheme 1.2.1.1. *Classification of N-propargylamine.*

1.2.2. Synthetic Strategies for *N*-propargylamine

In the past decades, several group developed many strategies to synthesize structurally simple propargylamines by applying nucleophilic addition reaction, reductive amination and transition-metal catalyzed coupling reaction of aldehyde, amine and alkyne.

1.2.2.1. Synthesis of *N*-propargylamine using Alkylation and Reductive Amination Approach

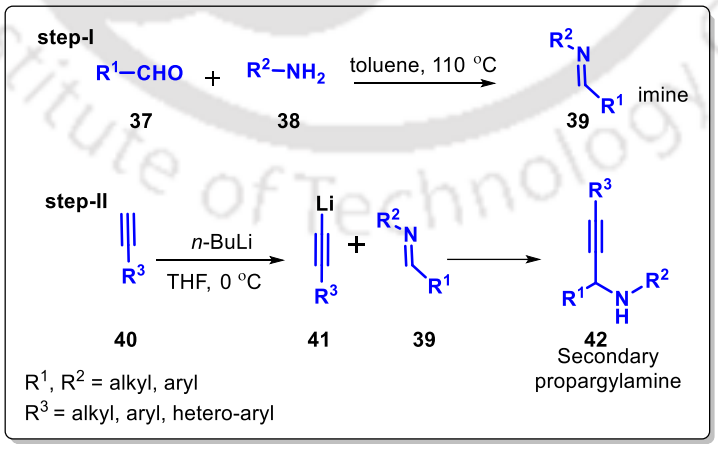
In general, structurally simple *N*-propargylamines **31** can be prepared by alkylation of amines **30** with propargylic halides, sulfonates derivatives **30** in presence of base (*Scheme 1.2.2.1a*).[5a-5g] However, this strategy has limitation such as, in presence of excess base di-propargyl substituted product **32** is formed. Apart from this, another method also has been used for the synthesis of secondary *N*-propargylamines **36** by using reductive amination reactions of primary *N*-propargylamines **34** and aldehydes **33** in the presence of mild reducing agents like sodiumcyanoborohydride ($NaCNBH_3$), sodium triacetoxyborohydride (*Scheme 1.2.2.1b*).[5h]



Scheme 1.2.2.1. *Synthesis of N-propargylamine using Alkylation and Reductive Amination Approach.*

1.2.2.2. Synthesis of *N*-propargylamine using Nucleophilic Addition of Lithium Acetylide to Imines

N-propargylamines are also synthesised by strong base promoted nucleophilic addition of alkali metal coordinated alkynylides **41** to imine **39** electrophiles under anhydrous conditions at low temperatures. The reaction takes place in two step process. Initially, imines **39** are formed by the condensation of aldehydes **37** and amines **38**. Further, the imines **39** will react with *in situ* generated metal alkynylides **41** from the reaction of alkynes **40** with metals to give propargylamines **42** (*Scheme 1.2.2.2*).[6]



Scheme 1.2.2.2. *Synthesis of N-propargylamine using Nucleophilic Addition of Lithium Acetylide to Imines Approach.*

But this method has some drawbacks such as, it requires stoichiometric amount of explosive and moisture sensitive reagents like *n*-butyllithium, low functional groups tolerance, and lower yield of the product. Owing to these limitations, nucleophilic addition of lithium acetylide to imines approach is limited towards the synthesis of *N*-propargylamine derivatives.

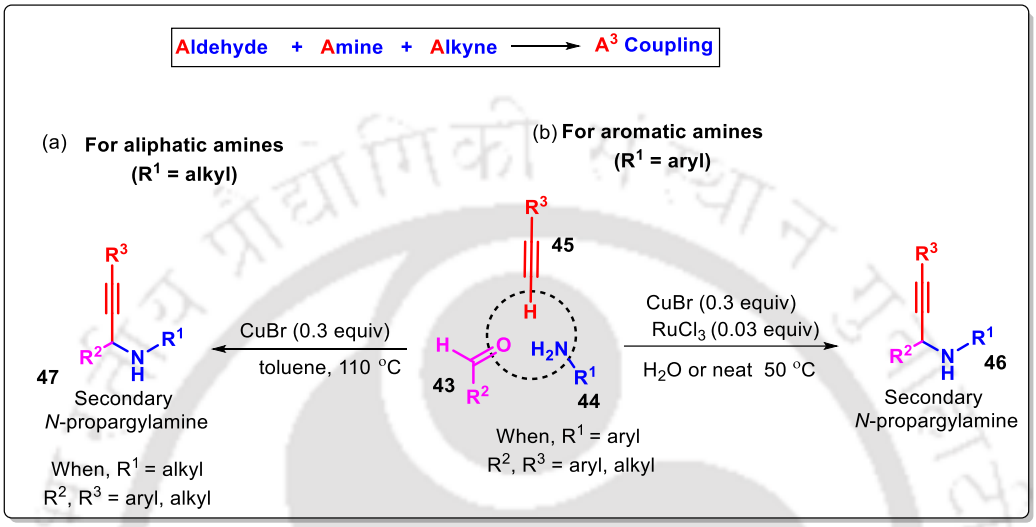
To overcome all these limitations, in the last decade an efficient and highly atom economic strategy has been developed towards the synthesis of *N*-propargylamines using one-pot, transition-metal catalysed and multi-component reaction of amines, aldehydes and alkynes. This approach is commonly called as A^3-coupling reaction and it has become a straight forward strategy towards the synthesis of *N*-propargylamines.

1.2.2.3. Synthesis of *N*-propargylamine using Traditional Approach A^3-Coupling

The A^3 coupling reaction is a transition-metal catalyzed, one pot and highly atom economic three-component coupling of commercially available reagents aldehydes, amines and alkynes to afford *N*-propargylamines. It is characterized by an eco-friendly strategy with H_2O as the only byproduct, chemoselectivity, applicability to a broad range of substrates and high product yields.

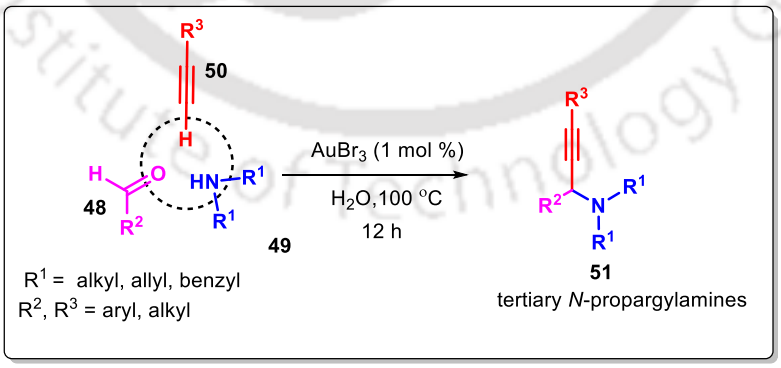
In 2002, the term 'A^3-coupling' was first introduced by the Chinese scientist Li based on the three characteristic reactants involved in the reaction.[7a] But in fact, in 1953 Guermont and co-workers first reported A^3-coupling reaction towards the synthesis of propargylic amino ethers *via* Mannich reaction of secondary amines, trioxane and alkynes in presents of copper catalyst.[7b] However, the extensive development of this protocol started at the end of the 1990s for the synthesis of propargylamines *via* three component coupling reaction of secondary amines, aldehydes, terminal alkynes. In 1998, Dax and co-workers established resin attached three component coupling of secondary amines, aldehyde and alkyne, promoted by CuCl (2.0 equiv) to afford *N*-propargylamines.[7c] In the same year, Dyatkin and Rivero independently described a polymer-supported synthesis of *N*-propargylamines by using aryl alkynes with different aldehydes and secondary amines in presence of catalytic amount of CuCl (10 mol%).[7d] However, these above described procedures are not convenient towards the synthesis of *N*-propargylamine derivatives. But in the beginning of 2000s, Li and co-workers first time developed an efficient A^3-coupling reaction of both aromatic and aliphatic aldehydes **43**, aryl amines **44** and terminal alkynes **45** by using bi-metallic Cu-Ru catalyst in water as a solvent or in neat conditions with excellent yields

without using any polymer support (*Scheme 1.2.2.3a*).[7a] Moreover, this method is not suitable for the synthesis of *N*-propargylamine **47** derived from aliphatic amines due to less yield of product, therefore higher temperature conditions are required for A^3-coupling reaction of aldehyde, aliphatic amine and terminal alkyne (*Scheme 1.2.2.3b*).[7e]



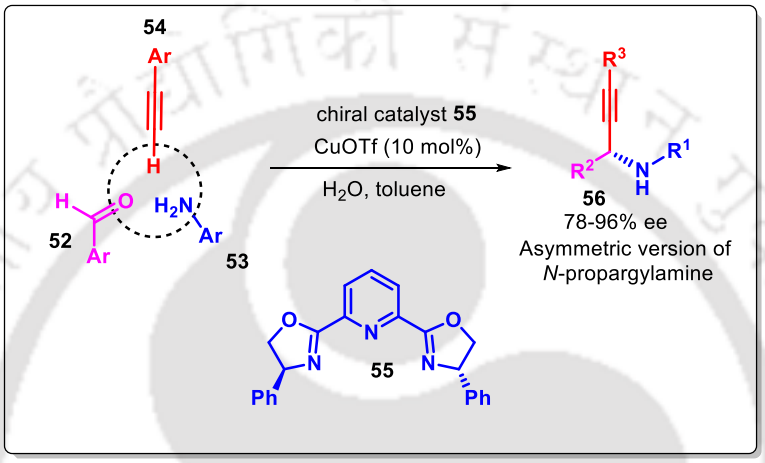
Scheme 1.2.2.3. *Synthesis of N-propargylamine using Traditional A^3-Coupling Approach.*

Similarly, in 2003, again Li and co-workers also extended A^3-coupling reaction of aldehydes **48**, secondary amines **49** and alkynes **50** towards the synthesis of tertiary *N*-propargylamines **51** by using mild and efficient Au(III) catalyst in water as a solvent system in good to excellent yields (*Scheme 1.2.2.3c*).[7f]



Scheme 1.2.2.3c. *Synthesis of Tertiary N-propargylamine using Traditional A^3-Coupling Approach.*

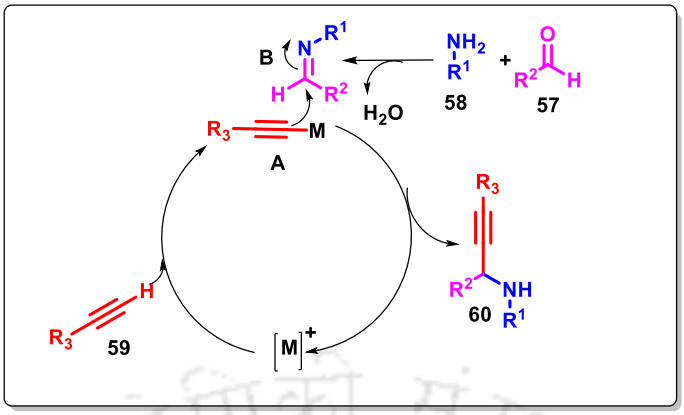
The asymmetric version of this coupling reaction is defined as AA^3-coupling. Interestingly, in 2002, Li group again, described the asymmetric version of A^3-coupling reaction of aryl aldehydes **52**, aryl amines **53** and phenylacetylene **54** derivatives by adding chiral ligand tridentate bis(oxazolinyl) pyridine(pybox) **55** in combination with Cu salt in presence of water or toluene as solvent with excellent enantiomeric excess of product chiral *N*-propargylamines **56** (*Scheme 1.2.2.3d*).[7g]



Scheme 1.2.2.3d. *Synthesis of Asymmetric N-propargylamine using Traditional AA^3-Coupling Approach.*

A^3-coupling reaction has been explored with different metal catalysts such as Cu,[8] Fe,[9] Zn,[10] Ag,[11] Ir,[12] In,[13]and Au[14]. Out of these metal catalysts, Cu catalysts are more efficiencies for the synthesis of *N*-propargylamines.[8]

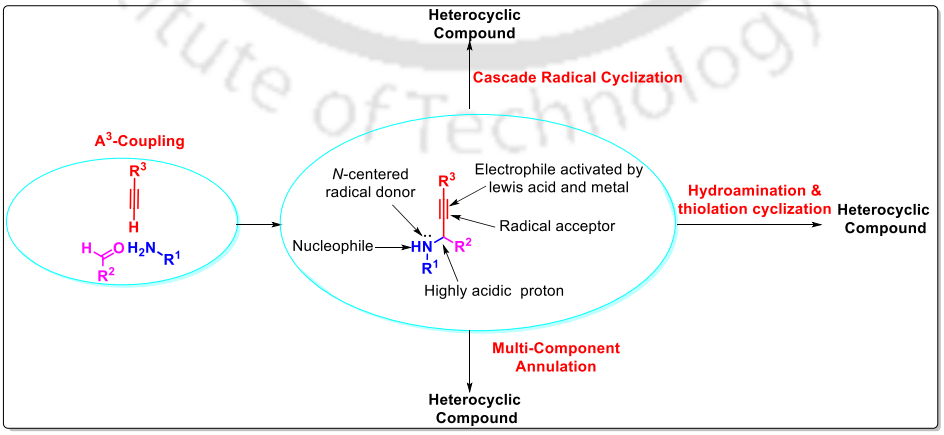
The plausible mechanism of formation of *N*-propargylamines **60** from A^3-coupling shows that, initially the more acidic hydrogen of acetylene **59** is activated by metal catalyst to afford metal acetylide **A**. Subsequently, the adduct acetylide **A** react with *in situ* generated imine intermediate **B** under nucleophilic addition to give *N*-propargylamine **60** (*Scheme 1.2.2.3e*).



Scheme 1.2.2.3e. *Plausible Mechanism of A^3-Coupling Reaction.*

1.2.3. Utility of *N*-propargylamine in Organic Transformation

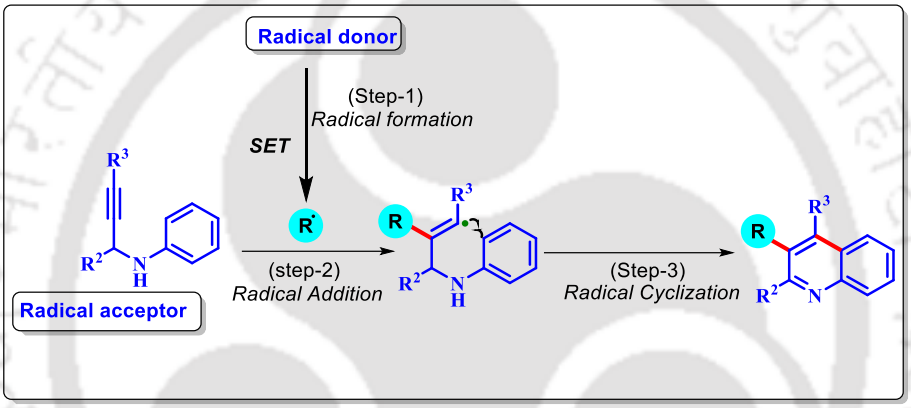
In recent years, the use of *N*-propargylamines have been widely employed as a versatile building block for the construction of a variety of nitrogenous heterocycles and it is gaining importance in modern organic synthesis. Owing to its unique structure bearing both free amine and an alkyne group, it plays the dual role of either nucleophile and electrophile, or as *N*-centered radical donor and radical acceptor. On the other hand, the conjugated phenyl-group and highly acidic tertiary proton alpha to nitrogen atom also plays a vital role for the designing of diverse molecules. In this regard, several efficient methodologies have been developed by using both thermal/photo induced cascade radical cyclization, tandem multi-component annulation and hydroamination/ hydrothiolation cyclization to obtain different heterocycles showing pharmaceutical activities (*Scheme 1.2.3*).[15]



Scheme 1.2.3. *General Reactivity of N-propargylamines.*

1.2.3.1. Outlines of the Cascade Radical Cyclization Involving *N*-propargylamine

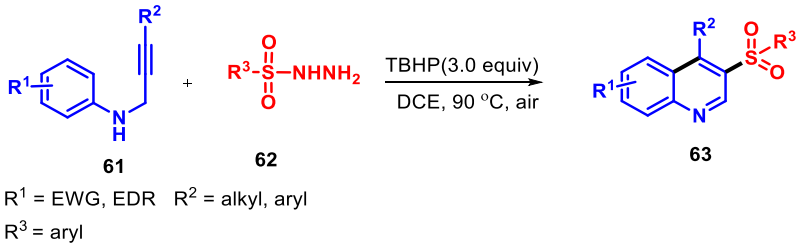
Cascade radical annulation is an attractive synthetic strategy due to its high atom- and step-economy to construct carbo- and heterocycles, which have many uses in natural product and pharmaceutical industry.[16] Radical acceptors containing unsaturated bonds play a crucial role in highly rapid and efficient cascade radical annulation. In this context, the major highlights of the latest cascade radical cyclization methodologies that have been developed by using *N*-propargylamines as a radical acceptor towards the synthesis of different bioactive heterocycles are discussed below.



Scheme 1.2.3.1. *General Cascade Radical Cyclization of N-propargylamine.*

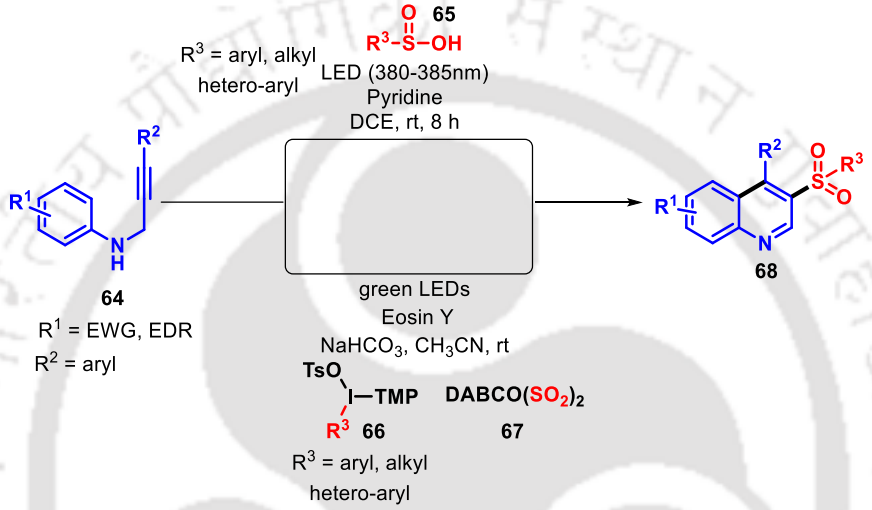
1.2.3.1.1. Addition of *S*-centered Radical to Alkynes of *N*- Propargylamine

In 2016, Zhao group reported a thermally cascade radical reaction for the synthesis of 3-arylsulfonylquinoline derivatives **63** *via* the treatment of sulfone radical source sulfonylhydrazine **62** with *N*-propargylaniline **61** in the presence of TBHP as oxidant in DCE at 90 °C with good yield (*Scheme 1.2.3.1.1a*).[17a]



Scheme 1.2.3.1.1a. *Cascade Radical Cyclization of N-propargylamine with Tosyl-hydrazine.*

Similarly, in 2018, Li group reported visible light mediated metal-free cascade radical strategy to synthesize 3-sulfonated quinoline derivatives **68** from *N*-propargylaniline **64** and sulfinic acids **65** as a source of sulfonyl radical precursor. The methodology utilizes molecular oxygen in air as oxidant and pyridine as an additive (*Scheme 1.2.3.1.1b*).[17b] In the same year, Zhang group developed a visible light induced radical addition strategy to synthesize the same 3-sulfonated quinoline derivatives **68** by using iodonium salt derivatives **66** with DABSO **67** as source of sulfonyl radical precursor (*Scheme 1.2.3.1.1b*).[17c]

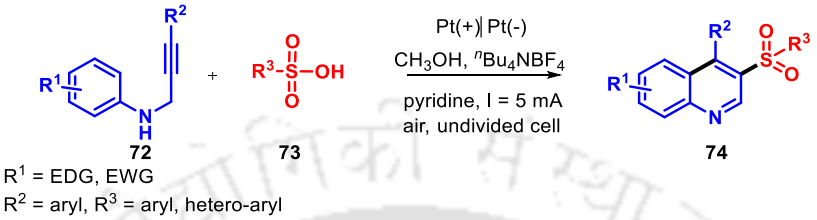


***Scheme 1.2.3.1.1b**. Radical Cyclization of N-propargylamine with DABSO and Sulfonic acid.*

In 2020, Huang group reported an efficient visible-light mediated radical cascade protocol of *N*-propargylanilines **69** with cheap and green sodium alkyl sulfonates **70** as sulfonyl radical precursors and *tert*-butylperoxybenzoate (TBPB) as oxidant at room temperature for the synthesis of 3-sulfonyl quinolone **71** derivatives (*Scheme 1.2.3.1.1c*).[17d]

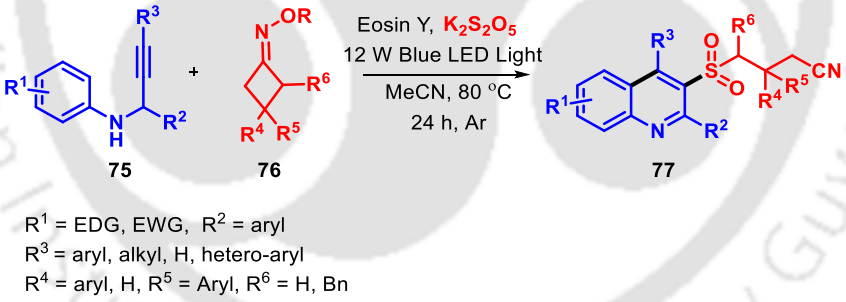
***Scheme 1.2.3.1.1c**. Cascade Radical Cyclization of N-propargylamine with Sodium Sulfonates.*

Interestingly, in the next year, Wang group has established an eco-friendly electrochemical oxidative tandem radical cyclization protocol for the construction of 3-sulfonyl quinolones **74** from *N*-propargylamines **72** and sulfinic acid derivatives **73** under oxidant free and undivided electrolysis condition with good yields (*Scheme 1.2.3.1.1d*).[17e]



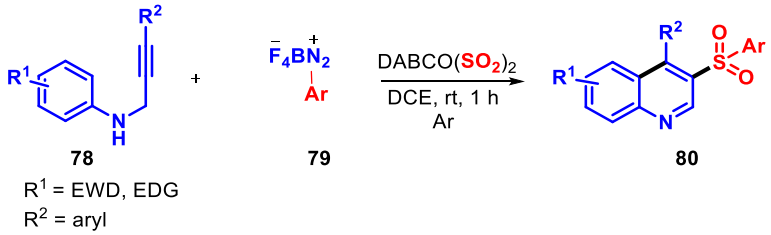
***Scheme 1.2.3.1.1d**. Electrochemical Cascade Radical Cyclization of N-propargylamine.*

Similarly, Zhang group in 2021, reported a visible-light induced tandem radical annulation of *N*-propargylanilines **75** with cyclobutanone oxime ester as radical precursor **76**. The reaction utilizes potassium disulfite as oxidant and Eosin Y as the photosensitizer for the construction of cyano-alkylsulfonylated quinolin derivatives **77** under thermal condition with wide range of substrate scope (*Scheme 1.2.3.1.1e*).[17f]



***Scheme 1.2.3.1.1e.** Radical Cyclization of N-propargylamine with Cyclobutanone Oxime-ester.*

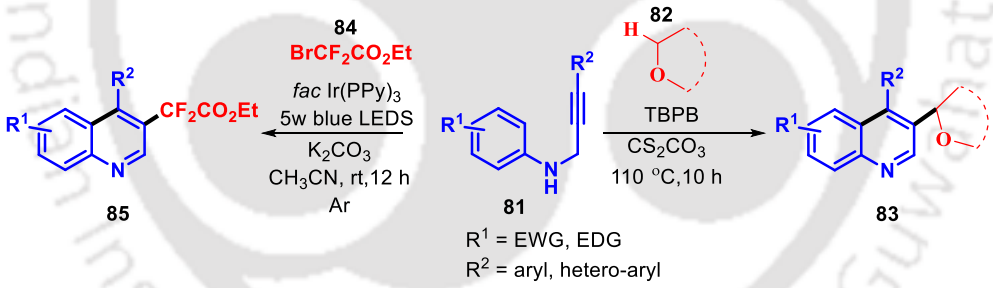
Recently, in 2022, Mal group has developed a one-pot and sustainable strategy of cascade radical cyclization protocol without using any external additive for the synthesis of 3-sulfonyl quinolones **80**. The protocol instead uses diazonium tetrafluoroborate **79**, *N*-propargylamines **78** and DABSO as sulfone source under argon atmosphere at room temperature (*Scheme 1.2.3.1.1f*).[17g]



Scheme 1.2.3.1.1f. *Radical Cyclization of N-propargylamine with Diazonium Tetrafluoroborates.*

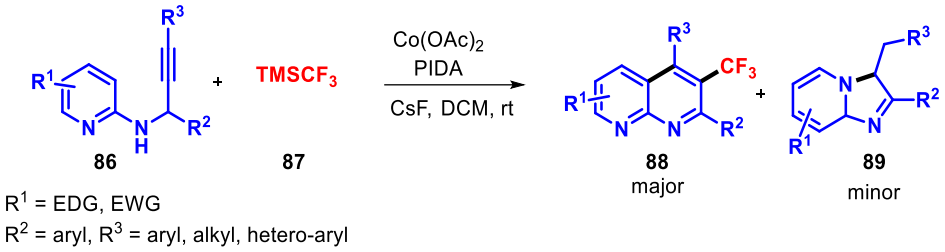
1.2.3.1.2. Addition of *C*-centered Radical to Alkynes of *N*-propargylamine

In 2018, Wang group demonstrated a *tert*-butylperoxybenzoate (TBPB) induced and Cs_2CO_3 mediated cascade radical cyclisation of *N*-propargylaniline **81** with C(SP^3)-H bond activation of ether derivative **82**, to build a variety of 3-alkylated quinolines **83** under metal free condition at 110 ^oC temperature (*Scheme 1.2.3.1.2a*).[17h] In the same year, Sun group established free radical mediated visible light induced, fac-Ir(ppy)$_3$ catalysed cascade annulation reaction of *N*-propargylaniline **81** to difluoroacetylated quinolines **85** by using bromodifluoroacetate derivative **84** as fluorine resource at room temperature (*Scheme 1.2.3.1.2b*).[17i]



Scheme 1.2.3.1.2b*. Radical Reaction of N-propargylamines with Ethers, Bromodifluoroacetates.*

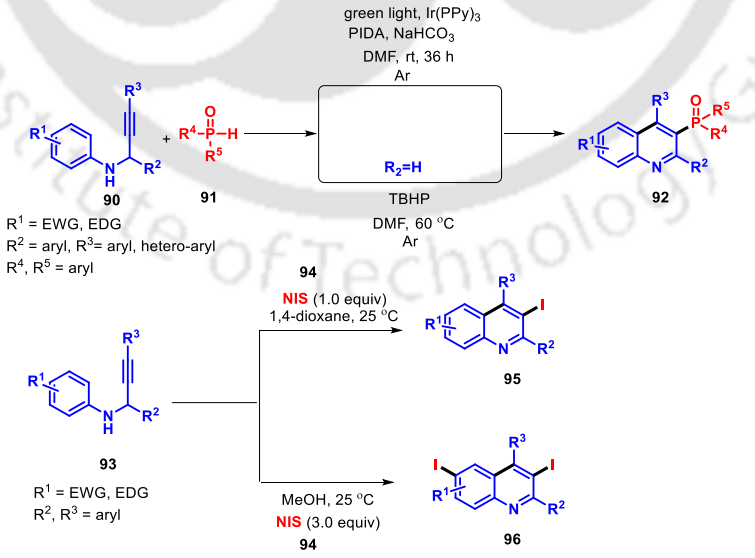
Similarly, Wang group has developed an unprecedent installation of a trifluoromethyl group *via* radical pathway towards the synthesis of trifluoromethylated 1,8-naphthyridine derivatives **88** from *N*-propargyralpyridine **86**. The combination of $Co(OAc)_2$ as catalyst and PIDA as oxidant, $TMSCF_3$ **87** as trifluoromethyl radical source and CsF changes the reaction direction which avoids the formation of commonly observed 5-*exo*-dig cyclisation involving *N*-atom of pyridine ring **89** instead to form unusual 6-*endo*-dig cyclisation involving *C*-atom of pyridine ring (*Scheme 1.2.3.1.2c*).[17j]



Scheme 1.2.3.1.2c. *Cascade Radical Cyclization of N-propargylamine with $TMSCF_3$.*

1.2.3.1.3. Addition of Phosphorus and Halogen Centered Radical to Alkynes of *N*-propargylamine

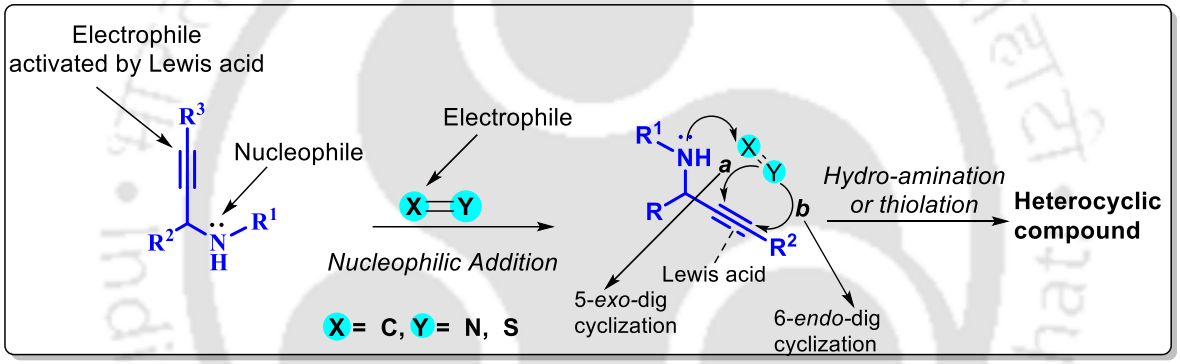
Pan group, in 2017, reported a photocatalyzed, radical mediated synthesis of 3-phosphorylate quinolines **92** by using *N*-propargylaniline **90** as radical acceptor species with phosphorus radical source diphenylphosphineoxide **91** in the presence of photocatalyst $Ir(PPy)_3$, oxidant PIDA and $NaHCO_3$ as additive in DMF at room temperature (*Scheme 1.2.3.1.3a*).[17k] However, in the previous year, Zhao group already reported the thermally mediated version of this synthesis from *N*-propargylaniline **90** by using TBHP as oxidant and (*Scheme 1.2.3.1.3a*).[17l] In the same year, Pan group established a solvent-controlled metal-free radical pathway for the synthesis both mono-iodoquinolines **95** and di-iodoquinolines **96** by using 1,4-dioxane and methanol as the solvent respectively by the combination of *N*-propargylanilines **93** and *N*-iodosuccinimide (NIS) **94** as a source of iodine radical (*Scheme 1.2.3.1.3a*).[17m]



Scheme 1.2.3.1.3a. *Radical Reaction of N-propargylamine with Diphenylphosphineoxide and NIS.*

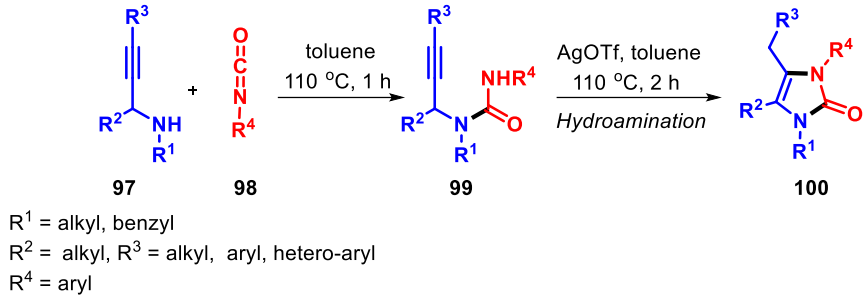
1.2.3.2. Outlines of the Cascade Hydroamination and Hydrothiolation Cyclization Involving *N*- propargylamine

The direct addition of nitrogen and hydrogen on carbon-carbon multiple bonds results in the hydroamination reaction. Hydroamination possess a significant challenge due to repulsion between a lone pair of "*N* " and the olefin/alkyne π-system, and it is also challenging to regulate the regioselectivity of hydroamination.[18a] Sulfur version of this reaction is called as hydrothiolation reaction. As a crucial step in the complete synthesis of natural and bio-active compounds, hydroamination/hydrothiolation has been employed by numerous research groups.[18b] In this context, synthesis of different heterocyclic compounds from *N*-propargylamines by utilizing hydroamination/hydrothiolation as the key step by different groups are discussed below.



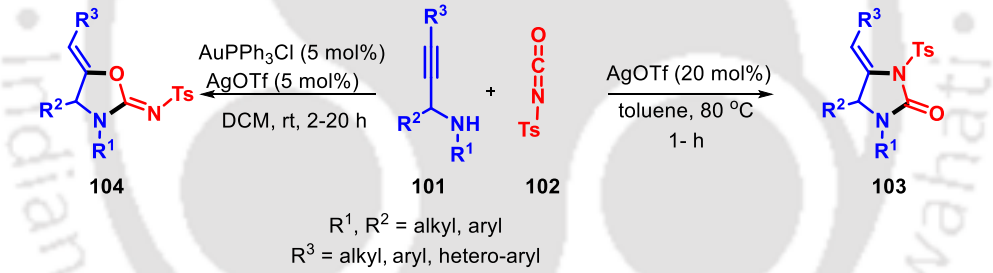
Scheme 1.2.3.2. *Hydroamination and Thiolation Cyclization of N-Propargylamine.*

In 2011, Vander der Eycken group synthesised highly substituted 2-imidazolone derivatives **100** by Ag(I) catalyzed hydroamination of *N*-propargylic urea **99** in good yields. The corresponding *N*-propargylic urea derivative was synthesized from secondary *N*-propargylamines **97**, on treatment with electron deficient isocyanate **98** molecules in toluene at 110 ^{o}C without using any base (*Scheme 1.2.3.2a*).[18c]



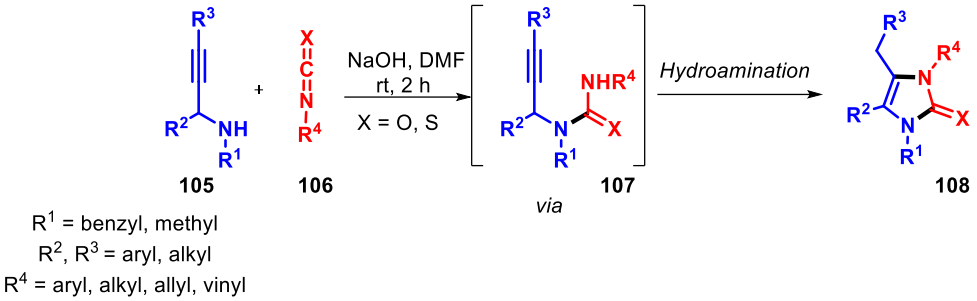
***Scheme 1.2.3.2a**. Cascade Hydroamination Reaction of N-propargylamines with Isocyanates.*

Further, the same group in 2013, developed a protocol towards the synthesis of both *O*- and *N*-selective cycloisomerization product oxazolidin-2-imine **104** and imidazolidin-2-one **103** receptively from *N*-propargylic urea, in good yields. The variation in the product formed was based on the selection of the metal catalyst. The reaction with AgOTf as the solo catalyst gave selectively imidazolidin-2-one **103** as the major product, whereas in presence of dual catalyst Au(I)/AgOTf in DCM produced oxazolidin-2-imine **104** in 90% yield (*Scheme 1.2.3.2b*).[18d]



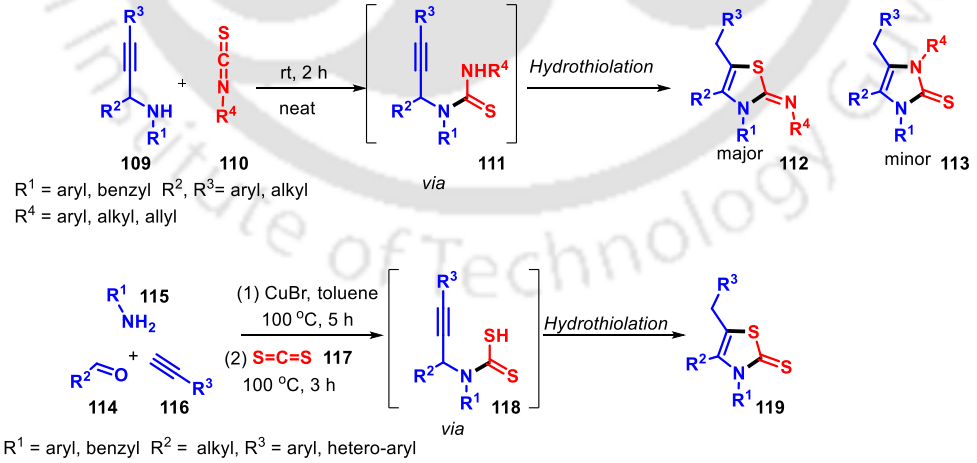
***Scheme 1.2.3.2b**. Cascade Cyclization of N-propargylamines with Isocyanates.*

Interestingly, in 2014, Dethe and co-workers reported an efficient, transition metal-free base promoted highly regioselective synthesis of imidazole-2-one/imidazole-2-thione derivatives **108** *via* hydroamination of secondary *N*-propargylamine **105** and alkylisothiocyanates **106** at room temperature with good yields (*Scheme 1.2.3.2c*).[18e]



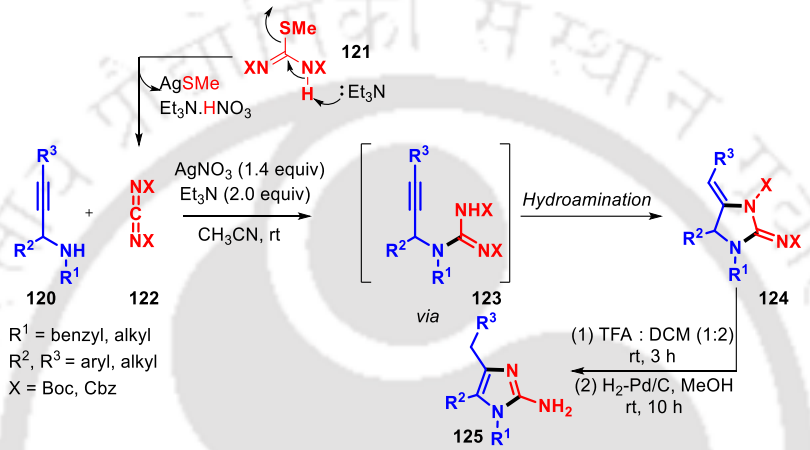
Scheme 1.2.3.2c*. Cascade Hydroamination Reaction of N-propargylamines with Isothiocyanates.*

Further, Dethe and co-workers in 2017, developed a strategy for thiol-yne coupling reaction of *N*-propargylamines **109** with alkylisothiocyanates **110** under metal- and solvent-free conditions towards the synthesis of thiazolidin-2-ylideneanamines **112** with good yield. The reaction proceeds *via in situ* generation of intermediate *N*-propargylthiourea **111**, which undergoes intramolecular hydrothiolation cyclisation under bond anion relay chemistry by the attack of the sulfur not the nitrogen to the alkyne (*Scheme 1.2.3.2d*).[18f] Similarly, in the same year, Vander Eycken group developed one-pot two-step approach for the synthesis of hydrothiolation product thiazolidin-2-thiones **119** by using carbon disulfide **117** as sulfur source and CuBr as catalyst. Initially the *N*-propargylamine is formed by the coupling of aldehyde **114**, amine **115** and alkyne **116** *via* A^3-coupling followed by reaction with carbon disulfide **117** electrophile to afford thiazolidin-2-thione **119** derivatives (*Scheme 1.2.3.2d*).[18g]



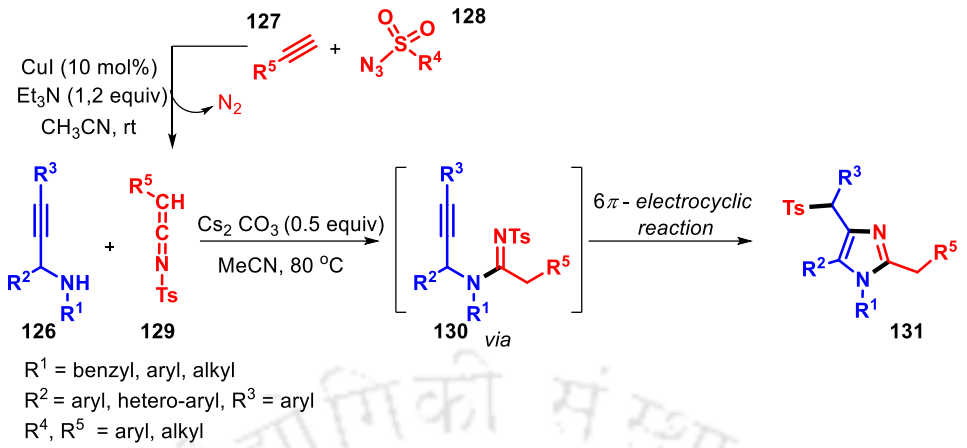
Scheme 1.2.3.2d*. Cascade Hydrothiolation Reaction of N-propargylamines with Isothiocyanates and Carbondisulfides.*

Van der Eycken and co-workers for the first time used a very reactive heteroallene carbodiimides **122** as an electrophile for the hydroamination reaction of *N*-propargylamine **120**. Initially, in presence of $AgNO_3$/ Et_3N, the protected form of carbodiimides **122** electrophile is formed *in situ* form *S*-methylisothioureas **121** which undergoes tandem guanylation followed by hydroamination reaction with secondary *N*-propargylamines **120** to afford 2-iminoimidazolines **124**. Further, Boc deprotection of compound **124** followed by isomerisation produced the alkaloid *2*-aminoimidazoles **125** (*Scheme 1.2.3.2e*).[18h]



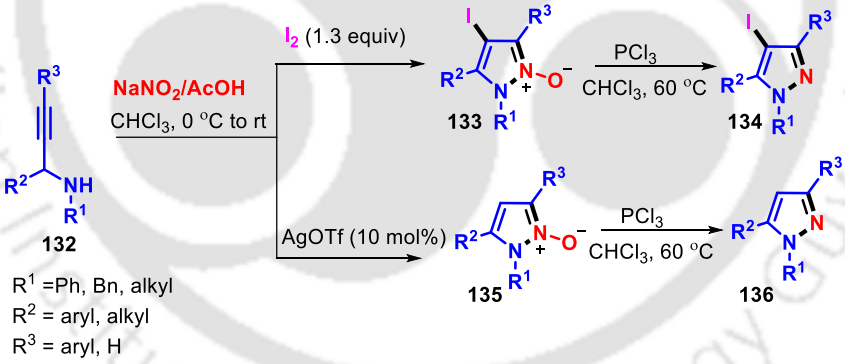
Scheme 1.2.3.2e. *Cascade Hydroamination Reaction of N-propargylamines with Carbodiimides.*

Apart from other heteroallene molecules, ketenimines is a type of heteroallene electrophile species which contain only one heteroatom in their cumulene skeleton. In this regard, Wang group for the first time introduced *N*-Sulfonyl ketenimine **129** as electrophile to react with secondary *N*-propargylamine **126** for the synthesis of highly functionalized imidazole derivatives **131** *via* hydroamination type reaction followed by tosyl group migration. Initially, this reaction takes place by *in situ* generation of *N*-sulfonyl ketenimine precursor **129** from terminal alkyne **127** and sulfonyl azides **128** in presence of catalytic amount of CuI and Et_3N. Further reaction with *N*-propargylamine **126** generates stable intermediate *N*-propargylimidamide **130** which undergoes 6π-electrocyclic reaction to afford the product tetra-substituted imidazole derivatives **131** (*Scheme 1.2.3.2f*).[18i]



Scheme 1.2.3.2f. *Cascade Hydroamination Reaction of N-propargylamines with Ketenimines.*

Saikia and group has developed an efficient Lewis acid promoted synthesis of 4-iodopyrazole-*N*-oxide **133** and pyrazole-*N*-oxide **135** derivatives from *N*-propargylamines **132** in presence of $NaNO_2$/AcOH as "*NO*" source with excellent yield *via* hydroamination type of reaction. The *N*-oxide derivetives can be transformed to pyrazoles **136** by treatment with phosphorous trichloride (PCl_3) (*Scheme 1.2.3.2g*).[18j, k]

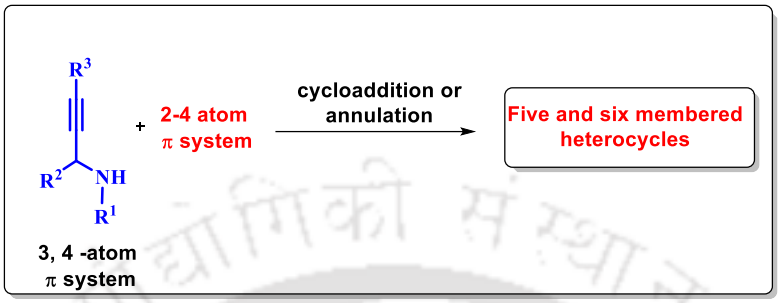


Scheme 1.2.3.2g. *Hydroamination type Reaction of N-propargylamine with $NaNO_2$/AcOH.*

1.2.3.3. Outlines of the Cycloaddition/Annulation Reaction Involving *N*-propargylamine

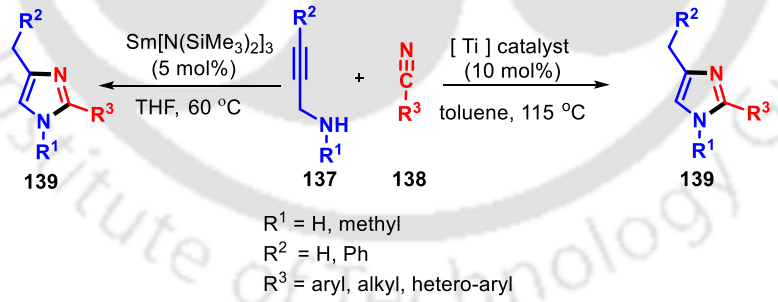
The cycloaddition annulation reaction is one of the most powerful tool for generating highly congested and strained different membered heterocycles, that are often difficult to form or possess incompatible substituents arrays.[19] In this context, intrinsically very reactive *N*-propargylamine

have proven to be immensely useful as a three and four component synthon in different annulation strategies, affording rapid access to a range of highly substituted heterocycles in a regio and stereospecific manner (*Scheme 1.2.3.3*).



Scheme 1.2.3.3*. Cycloaddition /Annulation Reaction of N-propargylamine.*

In 2010, Xie and co-workers has developed an efficient atom-economical strategy for the synthesis of substituted imidazoles derivatives **139** from *N*-propargylamines **137** and alkyl nitrile derivatives **138** with excellent regioselectvity. The reaction proceeds *via* cascade [3+2] annulation of *N*-propargylamines and electron deficient species catalyzed by titanium amide complex.[20a] But, Zhou group modified this methodology for the synthesis of same substituted imidazoles **139** from readily available *N*-propargylamines **137** by screening with samarium based catalyst instead of titanium-catalyst under ambient reaction conditions (*Scheme 1.2.3.3a*).[20b]



Scheme 1.2.3.3a*. [3+2] Annulation Reaction of N-propargylamine with Nitriles.*

In 2011, again Xie group has established an efficient titanacarborane monoamide complex catalyzed synthesis of 2-aminoimidazole derivatives **142** *via* [3+2] annulation of both primary and secondary *N*-propargylamines **140** and carbodiimides **141** electrophile in excellent yields (*Scheme 1.2.3.3b*).[20c]

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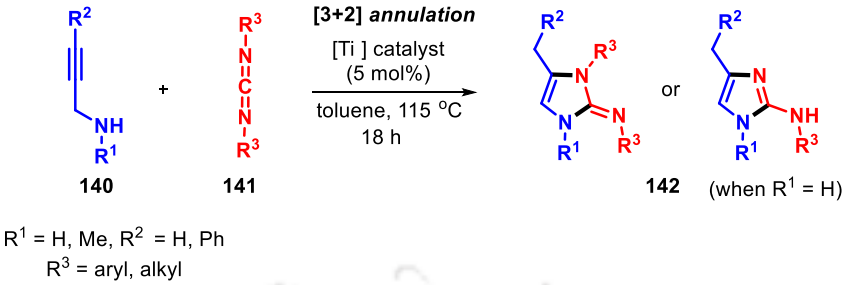
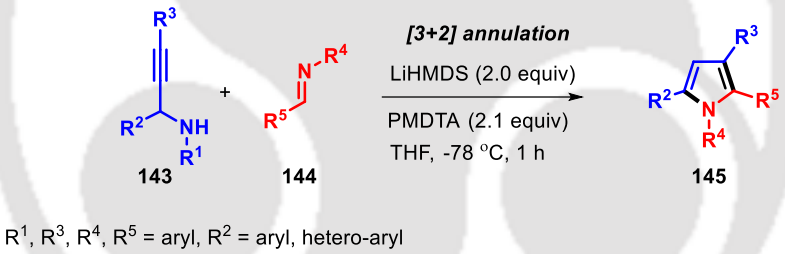


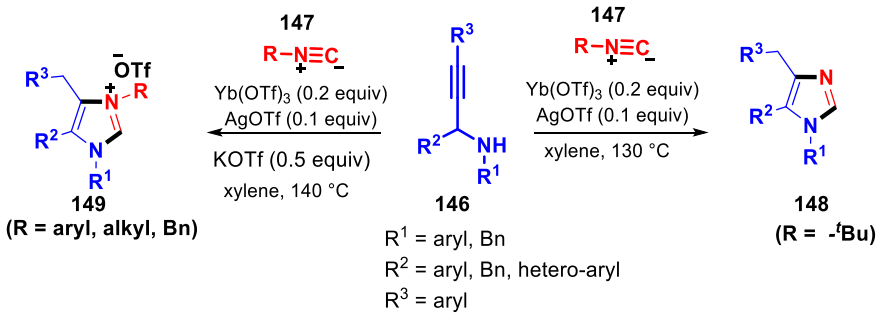
Scheme 1.2.3.3b*. [3+2] Annulation Reaction of N- propargylamines with Carbodiimides.*

In 2013, Hu *et al.* developed a robust one-pot synthesis of tetra-substituted pyrrole **145** scaffold by [3+2] annulation cyclization of secondary *N*-propargylamines **143** with imines **144** in presence of pentamethyldiethylenetriamine (PMDTA) as the additive and bis(trimethylsilyl)amide (LiHMDS) as base at -78 °C. The reaction proceeds in an ionic pathway and has a broad range of substrate scope (*Scheme 1.2.3.3c*).[20d]



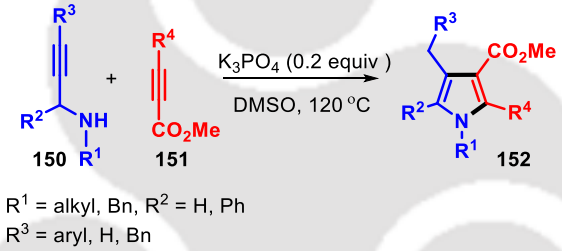
Scheme 1.2.3.3c*. [3+2] Annulation Reaction of N- Propargylamines with Imines.*

Interestingly, in 2015, Zhu group has reported a Lewis acid promoted, [3+2] annulation of *N*-propargylamines **146** and two-atom component isonitriles **147** towards the synthesis of both imidazoles **148** and imidazoliums **149** at high temperature. The variable product of this annulation depends upon the substituents of isonitriles i.e. the reaction of *N*-propargylamines **146** with *tert*-butylisonitrile afforded imidazoles **148** whereas the same reaction with aryl, primary and secondary isonitriles, resulted in the imidazoliums **149** in excellent yields (*Scheme 1.2.3.3d*).[20e]



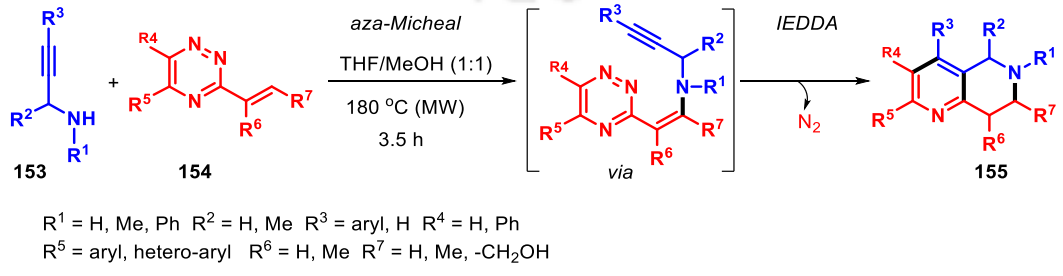
***Scheme 1.2.3.3d**. [3+2] Annulation Reaction of N-propargylamines with* Isonitriles.

In 2015, Jin and his group has developed a base-catalyzed synthesis of polysubstituted pyrroles **152** *via* [3+2] annulation of activated alkynes **151** and *N*-propargylamines **150** with moderate to good yield. The reaction was performed at high temperature in dimethylsulfoxide (DMSO) solvent (*Scheme 1.2.3.3e*).[20f]



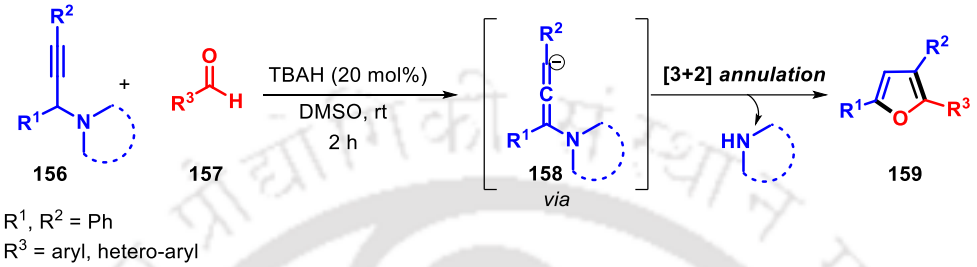
***Scheme 1.2.3.3e**. [3+2] Annulation Reaction of N-propargylamines with Activated-alkynes.*

In 2017, an unprecedented domino aza-Micheal-inverse electron demand Diels-Alder reaction between *N*-propargylamines **153** and 3-vinyl-1,2,4-triazine **154** derivatives to access highly substituted tetrahydro-1,6-naphthyridines **155** has been established by Suzenet and co-workers. The reaction takes place *via* aza-Micheal addition followed by inverse electron demand Diels-Alder reaction (*IEEDA*) under microwave irradiation at 180 °C in THF/MeOH (1:1) mixture of solvents (*Scheme 1.2.3.3f*).[20g]



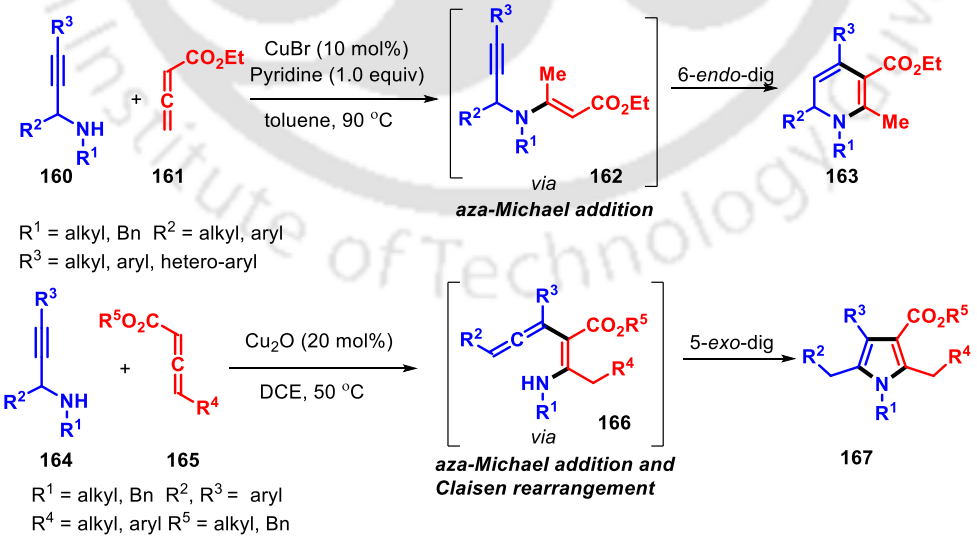
***Scheme 1.2.3.3f**. [4+2] Cycloaddition Reaction of* Triazines *with N-propargylamines.*

In 2018, similarly, Shen group reported a metal-free [3+2] annulation protocol towards the synthesis of tri-substituted furans **159** from tertiary *N*-propargylamines **156** and aldehydes **157** *via* allenyl anion intermidate **158**. The reaction is initiated by a catalytic amount of an inorganic base tetrabutylammonium hydroxide (TBAH) in room temperature under open air atmosphere (*Scheme 1.2.3.3g*).[20h]



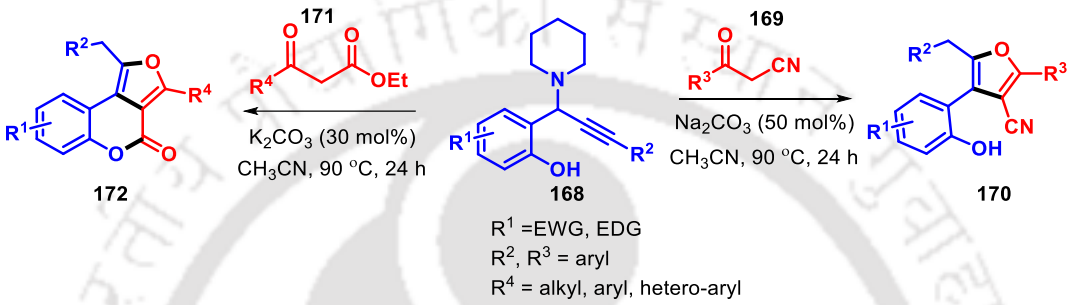
Scheme 1.2.3.3g. *[3+2] Annulation of N-*propargylamines *with Aldehydes.*

In 2019, Peshkov and group has developed a Cu-catalyzed strategy for the synthesis of dihydropyridines **163** from secondary *N*-propargylamines **160** and ethyl buta-2,3-dienoate **161** *via* 6-*endo*-dig cyclization of *in situ* generated *N*-propargylic enaminoesters **162** intermediate (*Scheme 1.2.3.3h*).[20i] In 2020, interestingly Tan *et al.* reported a methodology to develop an efficient condition for constructing highly functionalized pyrrole derivatives through 5-*exo*-dig cyclization of intermediate **166** which is generated *via* aza-Michael addition followed by Claisen rearrangement of *N*-propargylamines **164** and allenoate derivatives **165** (*Scheme 1.2.3.3h*).[20j]



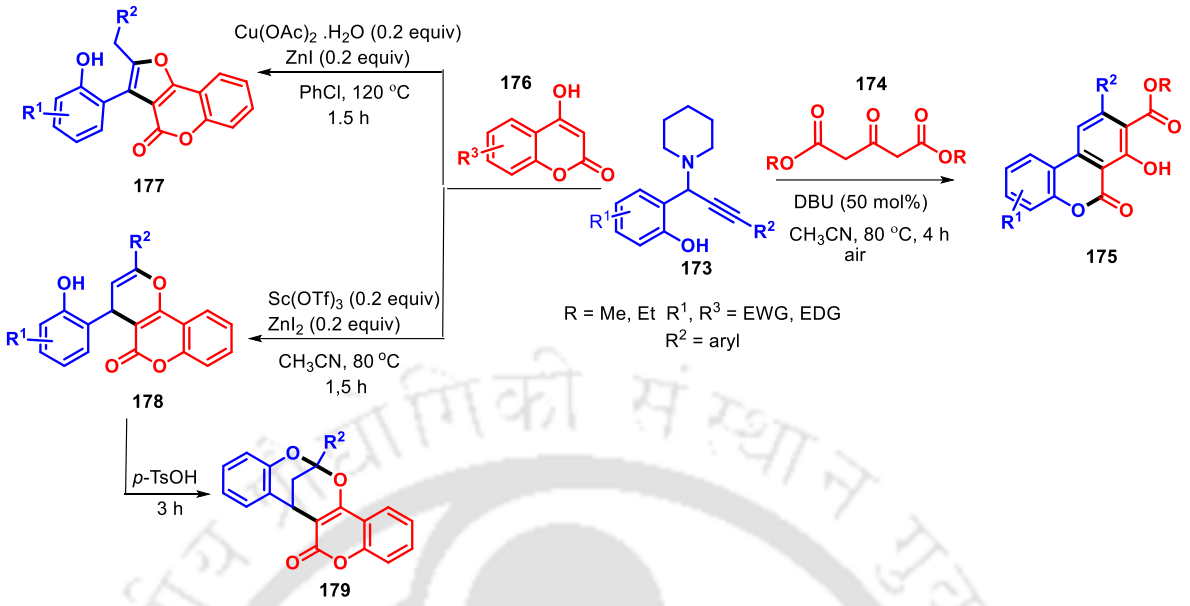
Scheme 1.2.3.3h. *Annulation Reaction of N-*propargylamines *with Allenoates.*

Sang and co-workers have reported a cascade one pot [3+2] annulation reaction of *o*-hydroxyphenyl propargylamines **168** with *β*-ketonitriles **169** and *β*-ketoesters **171** towards regiospecific synthesis of tetra-substituted furans **170** and furo[3,4-*c*]coumarins **172** receptively. The reaction takes place by using catalytic amount of inexpensive environmentally friendly carbonate as the base and proceeds through Michael addition followed by 5-*exo*-dig annulation (*Scheme 1.2.3.3i*).[20k]



Scheme 1.2.3.3i*. [3+2] annulation of N-*propargylamines *with β-keto Nitriles and Esters.*

Recently, Kwong and group extended this base promoted one pot annulation strategy for the synthesis of substituted benzo[*c*]chromen-6-one **175** scaffolds from *o*-hydroxy phenyl propargylamines **173** and dimethyl 3-oxoglutarates **174** *via* Micheal-addition followed by lactonization, 6*π*-electrocyclization and aromatization under open air atmosphere (*Scheme 1.2.3.3j*).[20l] Similarly, Yang and co-workers have also reported a Lewis acid catalyzed regioselective cascade annulation reaction of *o*-hydroxyphenyl propargylamines **173** and 4-hydroxycoumarin **176** derivatives to furnished pyrano[3,2-*c*]coumarin **177** and furano[3,2-*c*]coumarin **178** derivatives with excellent yields. The *o*-hydroxyl substituted pyrano[3,2-c] coumarins **178** can also be transformed into the corresponding coumarin-derived dioxabicycles **179** by using *p*-toluenesulfonicacid (PTSA) in acetonitrile at 80 °C (*Scheme 1.2.3.3j*).[20m]



Scheme 1.2.3.3j. *Cascade Annulation Reaction of N-*propargylamines *with 3-Oxoglutarates and 4-Hydroxycoumarins.*

In summary, the above-mentioned literatures give the idea that how *N*-propargylamines can be synthesized *via* A^3-coupling reaction and can trigger the different cascade cyclizations leading to heterocycles. Taking cues from the above literatures synthesis of heterocycles from *N*-propargylamines triggered by cascade radical cyclization, hydroamination/hydrothiolation cyclization and cycloaddition annulation have been designed.

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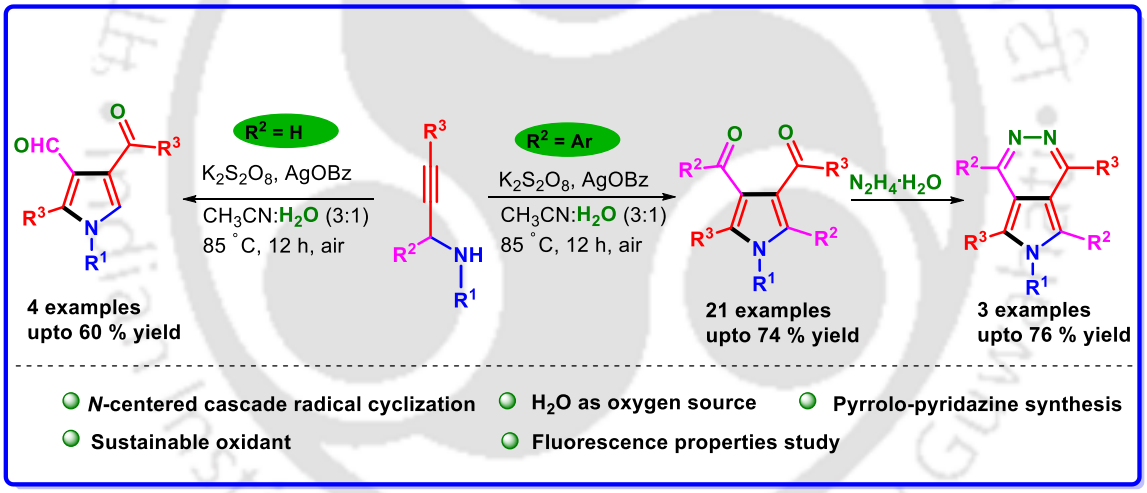
CHAPTER 2

$K_2S_2O_8$-Mediated Synthesis of Highly Functionalized Pyrroles *via* Oxidative Self-dimerization of *N*-Propargylamines

Abstract: This chapter highlights an efficient methodology developed for the synthesis of tetra- and penta-substituted pyrroles *via* *N*-centered radical initiated oxidative self-dimerization of *N*-propargylamines catalyzed by silver benzoate in the presence of $K_2S_2O_8$. The protocol provides a simple route for the synthesis of highly functionalized pyrroles with two carbonyl groups in the side chain. The methodology can be extended towards the synthesis of fluorescent pyrrolo[3,4-d]pyridazine derivatives.



2.1. Introduction

Substituted pyrroles are important unit in many biologically active molecules and natural products.[1] For example, tri-substituted pyrrole HDACs is a histidine deacetylase inhibitor,[2] tetra-substituted pyrrole SU11248 is an anti-cancer drug used primarily for the treatment of renal cell carcinoma and gastrointestinal stromal tumors,[3] and lynamicin D, a natural product isolated from marine actinomycete, found to be active against both gram-positive and gram-negative organisms, and drug resistant pathogens such as methicillin resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*.[4] On the other hand, penta-substituted pyrrole DP-TPPNa is a fluorescent probe for detection of bovine serum albumin (BSA),[5] and atorvastatin is a cholesterol-lowering agent[6] (*Figure 2.1*). They are also employed as building blocks in material chemistry.[7]

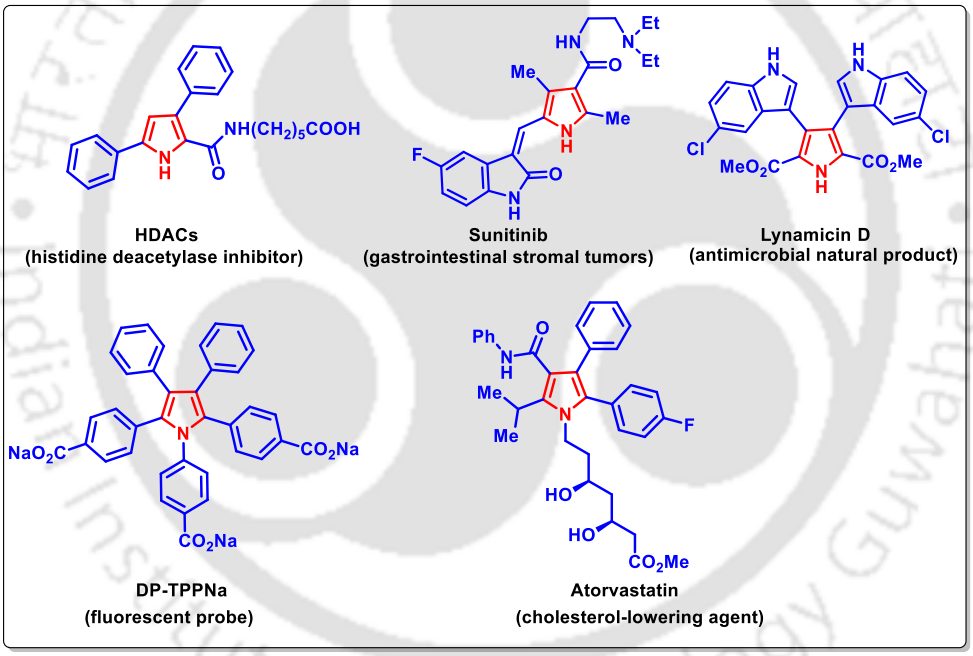
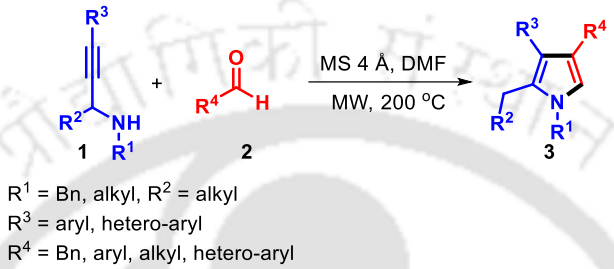


Figure 2.1. *Examples of Bioactive Pyrroles.*

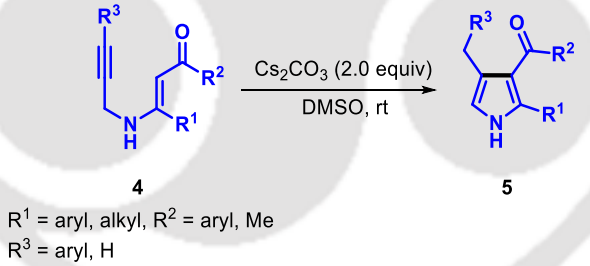
2.2. Literature Survey for the Synthesis of Substituted Pyrroles from Propargylamine Derivatives

In 2008, Organ and co-workers reported a convenient method for the synthesis of highly substituted pyrroles **3** from *N*-propargylamines **1** and aldehydes **2**. The reaction takes place by microwave irradiation in presence of 4 Å of molecular sieves at 200 °C in dimethylformamide (DMF) (*scheme 2.2.1*).[8a]



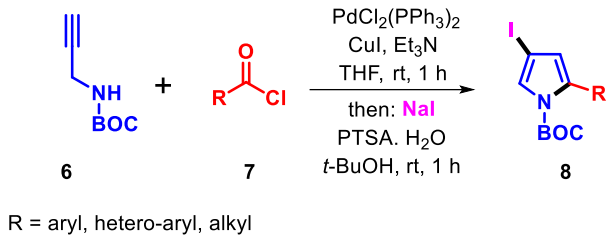
Scheme 2.2.1. *Synthesis of Substituted Pyrroles from N-propargylamines and Aldehydes.*

In the same year, Cacchi and co-workers designed a cascade intramolecular cyclization of *N*-Propargylic *β*-enaminones **4** to 2,3,4-trisubstituted pyrroles **5** in moderate to good yields, using Cs_2CO_3 as a base at room temperature in dimethylsulfoxide (DMSO) (*scheme 2.2.2*).[8b]



Scheme 2.2.2. *Base Promoted Intramolecular Cyclization of N-Propargylic-enaminones.*

Similarly, Muller's group developed an efficient, one-pot three component reaction of *N*-Boc-protected propargylamine **6**, acid chlorides **7** and NaI, catalyzed by palladium towards the synthesis of *N*-Boc-4-iodopyrroles **8**. The reaction starts with the formation of an alkynone intermediate *via* cross-coupling of alkyne derivative **6** with acid chloride **7**, and then the cyclocondensation reaction occurs in the presences of NaI furnishing the corresponding pyrroles **8** in good yields (*scheme 2.2.3*).[8c]

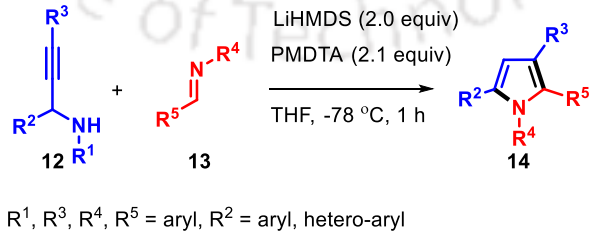


Scheme 2.2.3. *Pd/Cu-Catalyzed Synthesis of Substituted Pyrroles from Acid chlorides.*

In 2011, Trost and co-workers demonstrated an atom-economic cascade reaction of protected form of electron deficient propargylamines **9** and readily available alkynes **10** for the synthesis of 2,4-disubstituted pyrroles **11** by using Pd(II)-catalyst and tris-(2,6-dimethoxyphenyl)phosphine (TDMPP) as a ligand. The reaction was performed at ambient temperature under open air condition giving the corresponding pyrroles in good to excellent yields (*scheme 2.2.4*).[8d]

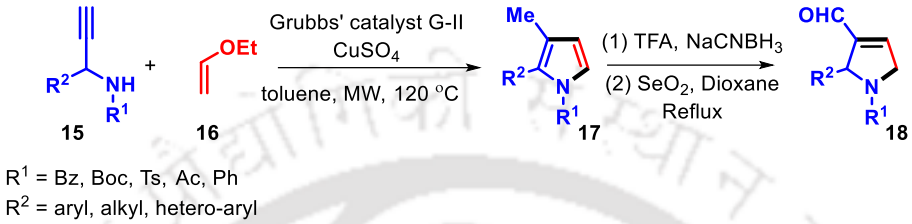
Scheme 2.2.4. *Transition-metal Catalyzed Synthesis of Substituted Pyrroles from Acetylene.*

In 2013, Hu *et al.* developed a robust one-pot synthesis of tetra-substituted pyrrole **14** scaffold by treatment of secondary *N*-propargylamines **12** with imines **13** in the presence of pentamethyldiethylenetriamine (PMDTA) as the additive and bis(trimethylsilyl)amide (LiHMDS) as base at -78 ^{o}C. The reaction proceeds in an ionic pathway and has a broad range of substrate scope (*scheme 2.2.5*).[8e]



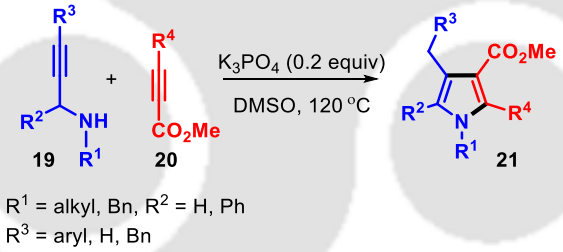
Scheme 2.2.5. *Synthesis of Tetra-substituted Pyrroles from N-propargylamine and Imines.*

Chachignon *et al.* in 2015, reported an interesting method for synthesis of 1,2,3-substituted pyrroles **17** *via* enyne cross metathesis of *N*-propargylamines **15** with ethylvinyl ether **16** in the presence of Grubbs' catalyst under microwave irradiation. Moreover, this method was further utilized for the synthesis of dihydropyrrole drivatives **18** with aldehyde group at 3-position (*scheme 2.2.6*).[8f]



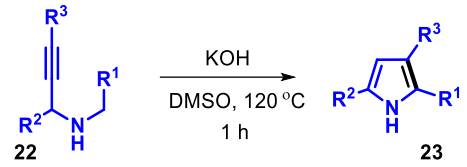
Scheme 2.2.6. *Synthesis of Functionalized Pyrroles via Cross-metathesis Cyclization.*

In the same year, Jin and his group has developed a base-catalyzed synthesis of polysubstituted pyrroles **21** *via* Michael addition of activated alkynes **20** with *N*-propargylamines **19** followed by carbocyclization. The reaction was performed at high temperature in dimethylsulfoxide (DMSO) solvent (*scheme 2.2.7*) .[8g]



Scheme 2.2.7. *Base-mediated Synthesis of Substituted Pyrroles by using Activated Alkynes.*

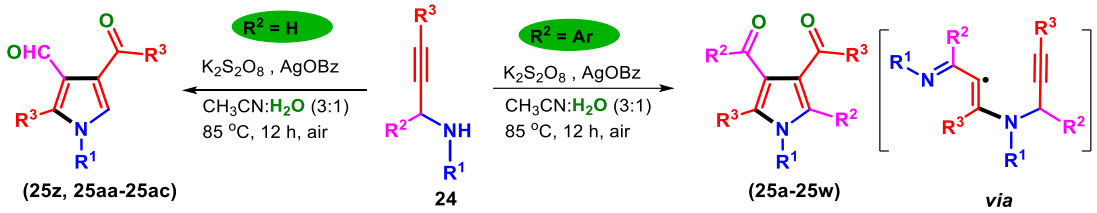
In 2018, Verma and co-workers, demonstrated an efficient KOH/DMSO mediated intramolecular cyclization of *N*-propargylamines **22** towards the synthesis of tri-substituted pyrroles **23** in good to excellent yields. Moreover, synthetic utility of this reaction can be extended further for the synthesis of key precursor in natural products (*scheme 2.2.8*).[8h]



Scheme 2.2.8. *KOH/DMSO Promoted Synthesis of Substituted Pyrroles from N-propargylamines.*

Present Work

In recent years, radical reactions have attracted broad attention in organic synthesis. Especially, $K_2S_2O_8$ was found to be a useful oxidant in oxidative reactions because of its characteristics of easy availability, good stability, and low toxicity. Thus, studies focusing on the development of $K_2S_2O_8$ mediated oxidative reactions meet the requirements of sustainable chemistry.[9] In the same time, the ease of preparation of *N*-propargylamines from aldehydes, amines and alkynes *via* A^3-coupling are gaining importance in organic synthesis as synthetic precursors due to their ability to form various nitrogen heterocyclic compounds.[10] Although a number of methods procedures have been developed for the synthesis of pyrroles from *N*-propargylamines using metal catalyzed multicomponent reactions[8] including classical Paal-Knorr,[11a] and Hantzsch synthesis.[11b] under ionic pathways, the major concern of these reported reactions are the limited substitution on the pyrrole ring, simple pyrrole products, harsh reaction conditions and low yields. Synthesis of functionalized pyrroles directly from *N*-propargylamines under radical pathway without a coupling partner have not been reported yet. Keeping these challenges in mind, this chapter describes, a radical initiated direct transformation of *N*-propargylamines into 1,2,3,4,5-pentasubstituted pyrroles having two carbonyl groups in the side chain catalyzed by AgOBz in presence of $K_2S_2O_8$ under open air condition with moderated to good yield (*scheme 2.2.9*).



Scheme 2.2.9. *Synthesis of highly Functionalized Pyrroles via Cascade Radical Cyclization of N-Propargylamines.*

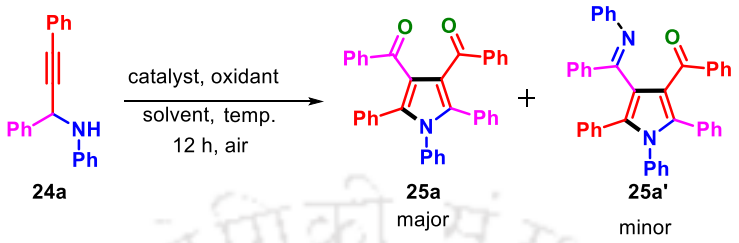
2.3. Result and Discussion

To start the reaction, **24a** was chosen as model compound. The reaction of **24a** with 2.0 equivalents of $K_2S_2O_8$ and 20 mol% of $AgNO_3$ was carried out in nitrogen atmosphere in acetonitrile at 82 ^oC, which gave compound imine **25a′** in 39% yield, (*Table 2.3.1,* entry 1). Refluxing the same reaction in open air gave penta-substituted pyrrole **25a** in 25% yield along with the imine **25a′** in 20% yield (*Table 2.3.1,* entry 2). The formation of **25a** in open air indicates that the **25a′** is an intermediate and water is required for hydrolysis of **25a′** to **25a**. With an increase in load of oxidant to 3.0 equivalents, the yields of **25a** and **25a′** were also found to increase to 33% and 25% yields, respectively (*Table 2.3.1,* entry 3). The reaction was then performed in 3:1 acetonitrile and water, assuming compound **25a′** will be converted into **25a** *via* hydrolysis, and to our delight, the desired product **25a** was obtained predominantly in 52% yield (*Table 2.3.1,* entry 4). On switching the catalyst to AgOBz, an increment in the yield of **25a** was observed to 57%, which was further improved to 71% when load of catalyst was raised to 30 mol% and temperature to 85 ^oC (*Table 2.3.1,* entries 5 and 6). There was no significant elevation in the yield with the use of increased amount of $K_2S_2O_8$ (*Table 2.3.1,* entry 7). Thus fixing the catalytic load to 30 mol%, oxidant to 3.0 equivalents and temperature at 85 ^oC, various other silver catalysts like $AgPF_6$, Ag_2O, Ag_2CO_3, AgOAc were used to screen the reaction, but they didn't show much effect on the yield (*Table 2.3.1,* entries 11-14). The desired product was not obtained when the reaction was performed with other solvents like DMF and DMSO (*Table 2.3.1,* entries 9 and 10). Other oxidizing agents such as $Na_2S_2O_8$, $(NH_4)_2S_2O_8$, oxone etc. were found to be inefficient compared to $K_2S_2O_8$ (*Table 2.3.1,* entries 16-19). Neither potassium persulfate, nor AgOBz alone was enough to give the required product (*Table 2.3.1,* entries 15 and 20). Therefore, 3.0 equivalents of $K_2S_2O_8$, and 0.3 equivalents of AgOBz in 3:1 CH_3CN/H_2O solvent at 85 ^oC is the optimized condition for the reaction. The structure of compounds was confirmed from standard spectroscopic experiments and finally by *X*-ray crystallographic analysis of compound **25a** and **25a′**.[12]

With the established optimal conditions in hand, the scope of this reaction was explored. *N*-propargylamines derived from various aldehydes, alkynes were examined, and the result was summarized in *Scheme 2.3.2*. It was observed that both electron-donating as well as electron-withdrawing groups in the aromatic ring were equally well-tolerated giving corresponding products **25a**-**25l** in good yields. Even sterically hindered *N*-propargylamine derived from bulky

2-bromobenzaldehyde gave product **25d** in acceptable yield. Substrate derived from 2-naphthaldehyde **24k** also provided **25k** in good yield.

Table 2.3.1. Optimization of the Reaction[a]



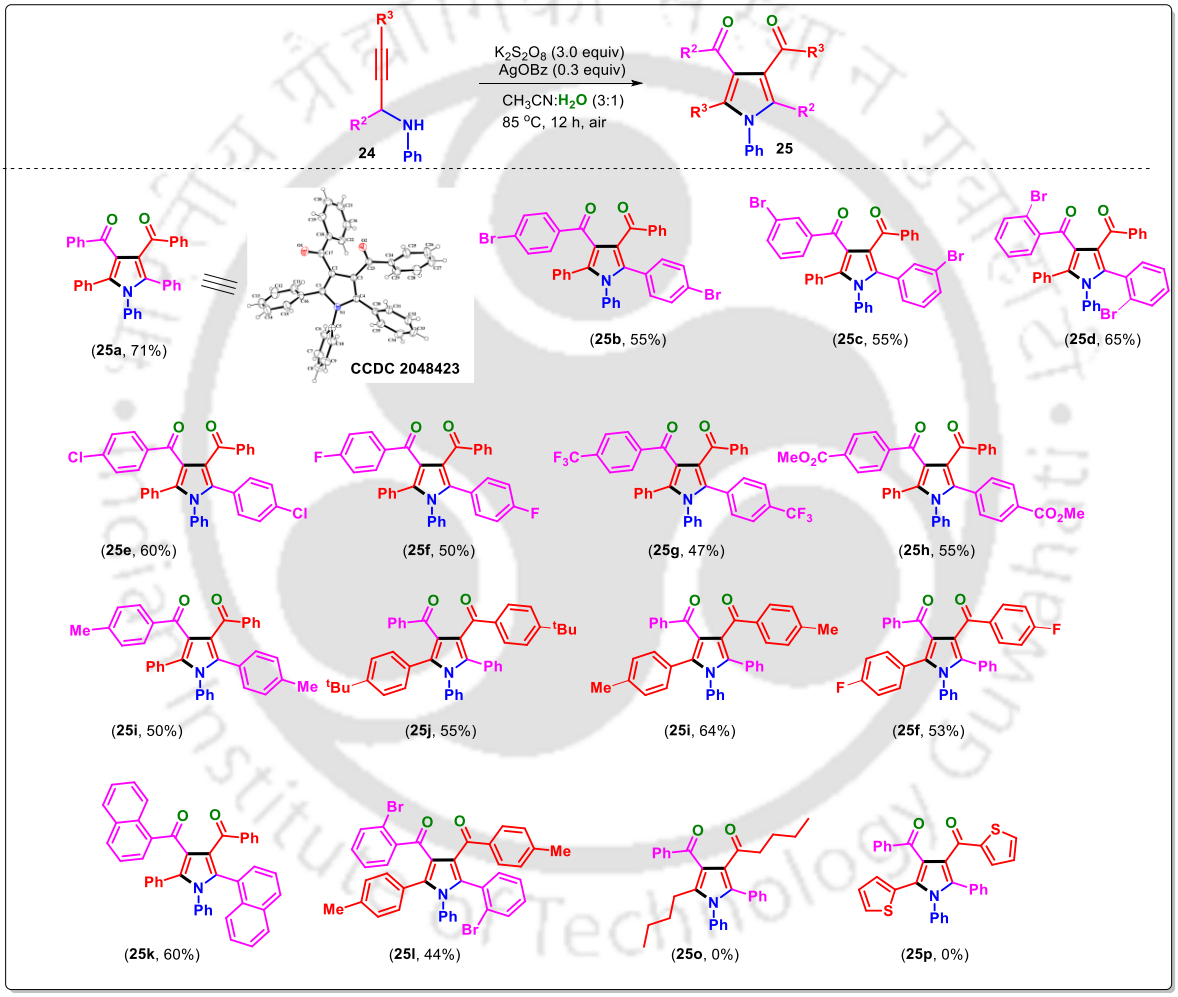
24a → **25a** major + **25a'** minor

entry	catalyst (mol %)	oxidant (equiv)	solvent	t (^oC)	yield (%)[b]	
					25a	**25a'**
1	$AgNO_3$ (20)	$K_2S_2O_8$ (2)	CH_3CN	80	_	39[c]
2	$AgNO_3$ (20)	$K_2S_2O_8$ (2)	CH_3CN	80	25	20
3	$AgNO_3$ (20)	$K_2S_2O_8$ (3)	CH_3CN	80	33	25
4	$AgNO_3$ (20)	$K_2S_2O_8$ (3)	CH_3CN/H_2O (3:1)	80	52	trace
5	AgOBz (20)	$K_2S_2O_8$ (3)	CH_3CN/H_2O (3:1)	80	57	trace
6	**AgOBz (30)**	**$K_2S_2O_8$ (3)**	**CH_3CN/H_2O** (3:1)	**85**	**71**	**0**
7	AgOBz (30)	$K_2S_2O_8$ (4)	CH_3CN/H_2O (3:1)	90	62	_
8	AgOBz (30)	$K_2S_2O_8$ (3)	CH_3CN/H_2O (3:2)	100	58	_
9	AgOBz (30)	$K_2S_2O_8$ (3)	DMF/H_2O (3:1)	90	trace	_
10	AgOBz (30)	$K_2S_2O_8$ (3)	$DMSO/H_2O$ (3:1)	90	N.R.	_
11	$AgPF_6$ (30)	$K_2S_2O_8$ (3)	CH_3CN/H_2O (3:1)	85	62	_
12	Ag_2O (30)	$K_2S_2O_8$ (3)	CH_3CN/H_2O (3:1)	85	53	_
13	Ag_2CO_3(30)	$K_2S_2O_8$ (3)	CH_3CN/H_2O (3:1)	85	47	_
14	AgOAc(30)	$K_2S_2O_8$ (3)	CH_3CN/H_2O (3:1)	85	50	_
15	_	$K_2S_2O_8$ (3)	CH_3CN/H_2O (3:1)	85	N.R.	_
16	AgOBz (30)	$(NH_4)_2S_2O_8$ (3)	CH_3CN/H_2O (3:1)	85	32	_
17	AgOBz (30)	$Na_2S_2O_8$ (3)	CH_3CN/H_2O (3:1)	85	48	_
18	AgOBz (30)	Oxone (3)	CH_3CN/H_2O (3:1)	85	N.R.	_
19	AgOBz (30)	O_2	CH_3CN/H_2O (3:1)	85	N.R.	_
20	AgOBz (30)	_	CH_3CN/H_2O (3:1)	85	N.R.	_

[a]Reaction conditions: **24a** (0.4 mmol, 1.0 equiv), solvent (4.0 mL) under air, 12 h [b]Isolated yield. [c]Under N_2 atmosphere.

Due to the instability of the vinyl carbocation **E**, (*Scheme 2.3.7*) in alkyl substituted alkyne substrate **24o**, the desired product **25o** was not formed (*Scheme 2.3.2*). The substrate with

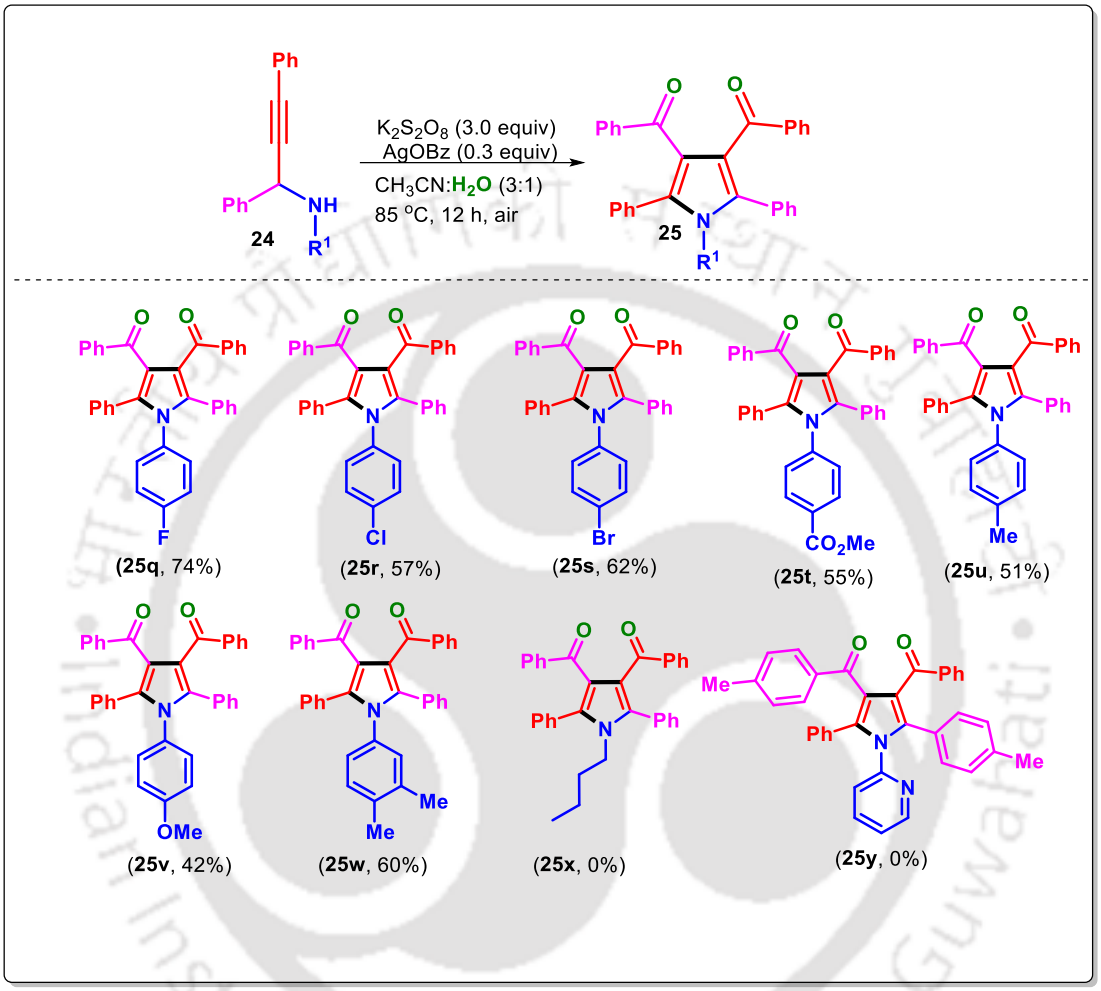
heteroaromatic ring **24p** failed to provide desired product **25p**. This might be due to the oxidation of thiophene moiety under the strong oxidizing environment. Surprisingly, *N*-propargylamines derived from alkynes having 4-fluoro and 4-methyl groups in the aromatic ring **24m** and **24n** gave the products similar to the products **25f** and **25i**, obtained from starting materials **24f** and **24i**, respectively. Next, the *N*-propargylamines derived from different amines were examined and they also showed excellent reactivity furnishing products **25q**-**25w** in high yields. However, alkyl amines **24x** failed to give the desired product **25x** (*Scheme2.3.3).*



[a] Reaction condition: **24** (0.4 mmol), $K_2S_2O_8$ (1.2 mmol), CH_3CN: H_2O (3:1) in air for 12 h at 85 °C. [b] Isolated yield.

Scheme 2.3.2. *Scope of Synthesis of Penta-substituted Pyrroles from N-Propargylamines derived from Aldehydes and Alkynes.*[a,b]

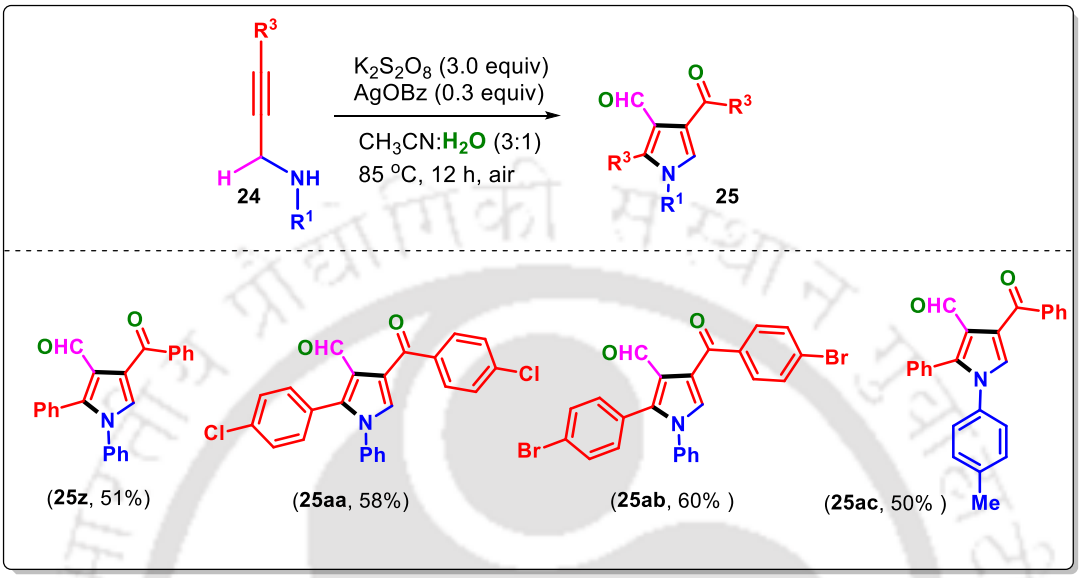
Similarly, pyridyl substituted *N*-propargylamine **24y** also could not provide any product. In a quest, to explore further scope of this reaction, substrate having 1-substituted *N*-propargylamines **24z**, **24aa**-**24ac** were subjected to standard reaction conditions, and tetra-substituted pyrroles with



[a] Reaction condition: **24** (0.4 mmol), $K_2S_2O_8$ (1.2 mmol), CH_3CN: H_2O (3:1) in air for 12 h at 85 °C. [b] isolated yield.

Scheme 2.3.3. *Scope of Synthesis of Penta-substituted Pyrroles from N-Propargylamines derived from Amines.*[a]

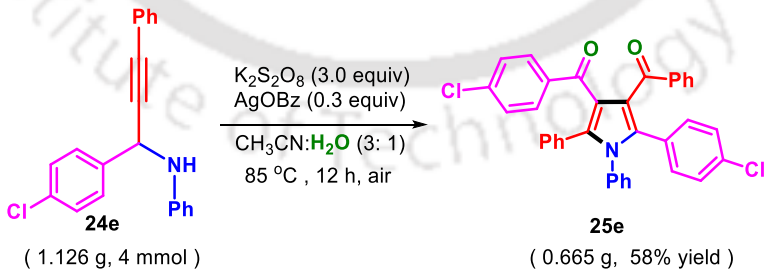
an aldehydic group at 3-position were obtained successfully in moderate to good yields (*Scheme 2.3.4*). Structure of all the compounds were confirmed by ^{1}H & $^{13}C\{^{1}H\}$ NMR spectroscopy, IR, mass spectrometry.



[a] Reaction condition: **24**(0.4 mmol), $K_2S_2O_8$ (1.2 mmol), CH_3CN: H_2O (3:1) in air for 12 h at 85 °C. [b]Isolated yield.

Scheme 2.3.4. *Scope of Synthesis of Tetra-substituted Pyrroles from N-Propargylamines derived from Amines and Alkynes.*[a,b]

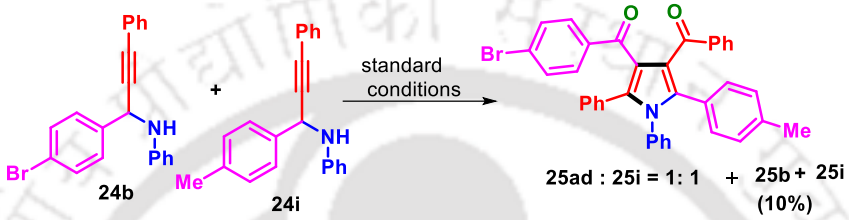
A gram scale synthesis was carried out to reveal the scalability of our methodology. Compound **24e** (1.126 g) under standard reaction conditions furnished **25e** (0.66 g) in 58% yield (*Scheme 2.3.5*).



Scheme 2.3.5. *Gram-Scale Synthesis.*

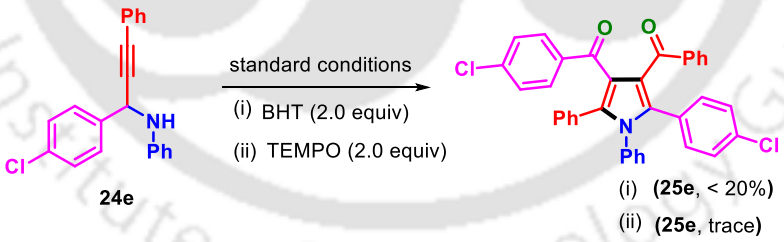
2.3.6. Control Experiments

To investigate the formation of cross-over products two electronically different *N*-propargyl amines **24b** and **24i** were subjected to standard reaction conditions (*Scheme 2.3.6a*), and it was observed that cross-over product **25ad** was obtained along with the self-dimerization product **25i**, as an inseparable mixture overall 40 mg with a ratio of 1:1, which was confirmed by ^{1}H NMR and HRMS. The self-dimerization product **25b** also obtained in 10% yield.



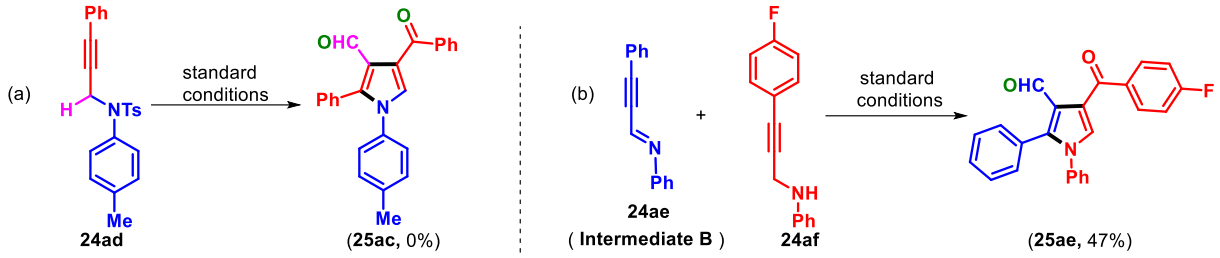
Scheme 2.3.6a. *Cross-Over Experiment.*

To investigate the reaction pathway, the reaction was, also performed separately in presence of BHT and TEMPO. The reaction of **24e** with 2.0 equivalents TEMPO gave trace amount of **25e** under the standard reaction conditions. Similarly, same reaction when performed in presence of 2.0 equivalents of BHT furnished product **25e** in less than 20% yield (*Scheme 2.3.6b*). These two reactions in presence of radical scavenging agents proved that the reaction proceeds *via* radical mechanism.



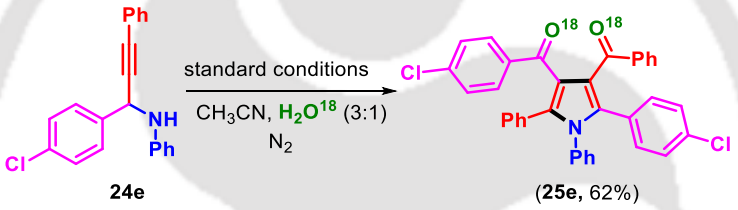
Scheme 2.3.6b. *To Confirm Reaction Pathway.*

Further, when *N*-tosylated propargylamine **24ad** was subjected to standard reaction conditions, the starting material remained unconsumed even after two days (*Scheme 2.3.6c*). This confirms the requirement of secondary amines for the formation of iminium intermediate **B** (*Scheme 2.3.7*) in the present methodology. Again, in order to ensure the formation of intermediate **B**, an intermolecular reaction was done with isolated imine **24ae** and *N*-propargylamine **24af** which gave the desired product **25ae** with 47% yield (*Scheme 2.3.6c*).



Scheme 2.3.6c. *To Confirm the Formation of Intermediate* ***B****.*

To identify the source of oxygen in product **25e**, the reaction of *N*-propargylamine **24e** was performed in presence of isotopically labelled H_2O^{18} under nitrogen atmosphere. The incorporation of an O^{18}-labeled product suggest that water is the source of oxygen in the keto group which was confirmed by $^{13}C\{^1H\}$ i.e splitting of carbonyl peak due to presence of both labelled and unlabeled '*O*' of the carbonyl groups (*Figure 2.3.6da)* and HRMS (*Figure 2.3.6db)*.



Scheme 2.3.6d. *To Confirm Source of Oxygen.*

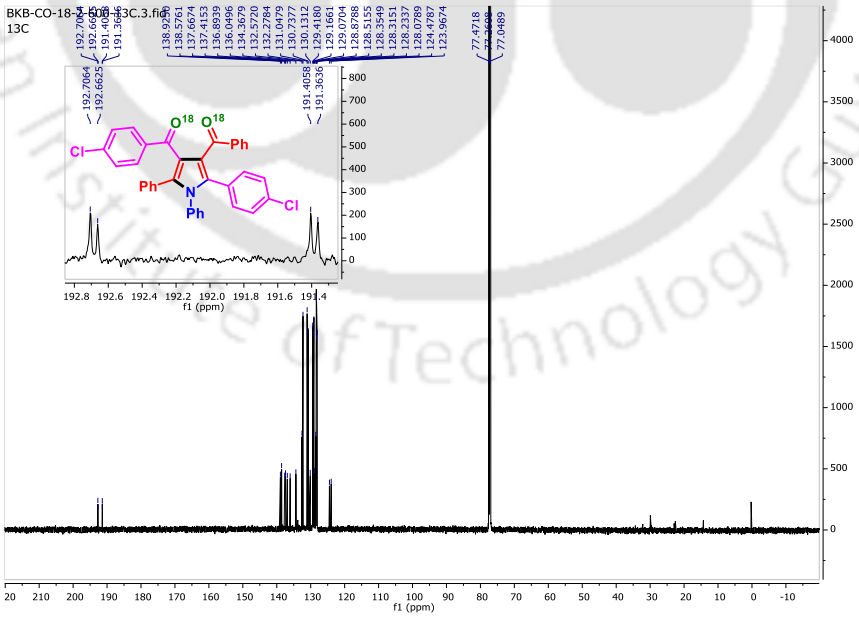


Figure 2.3.6da. *$^{13}C\{^1H\}$ NMR Study for the H_2O^{18} Labelled Experiment.*

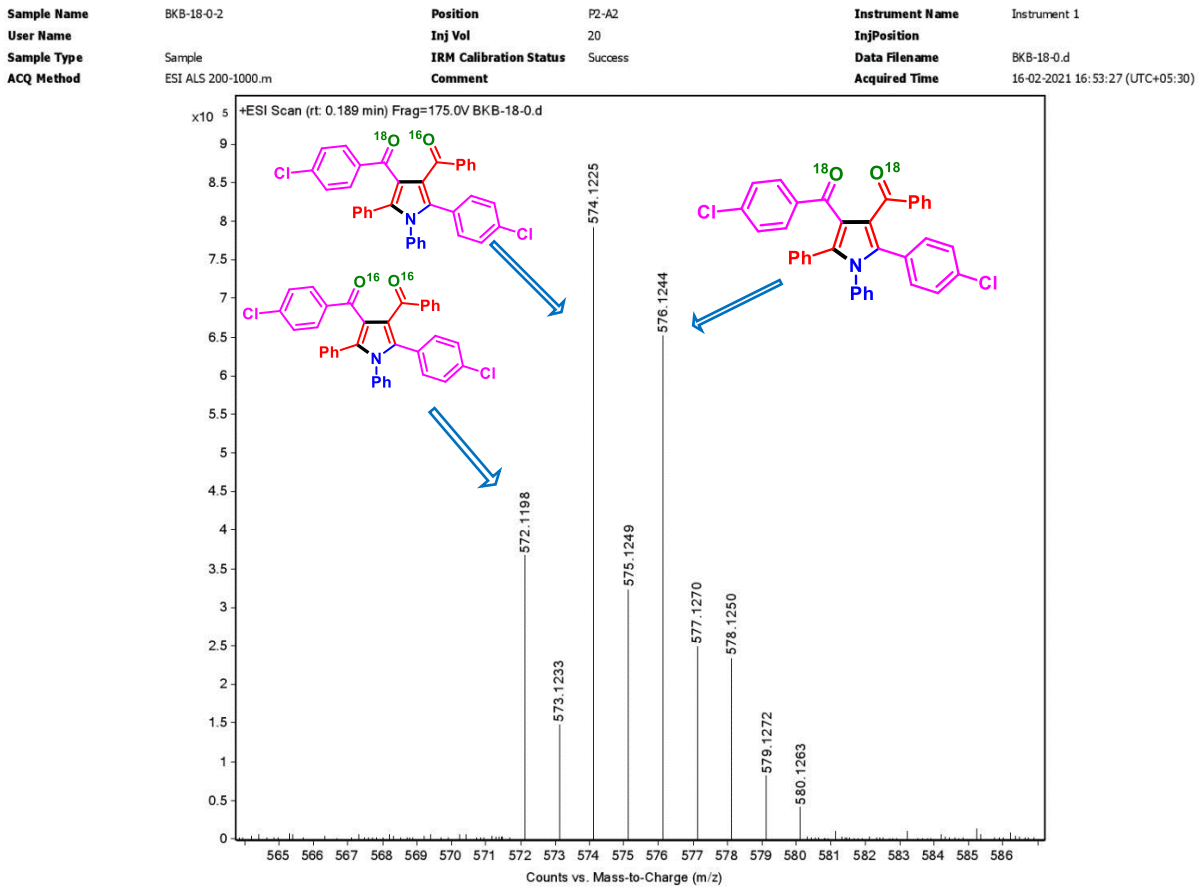
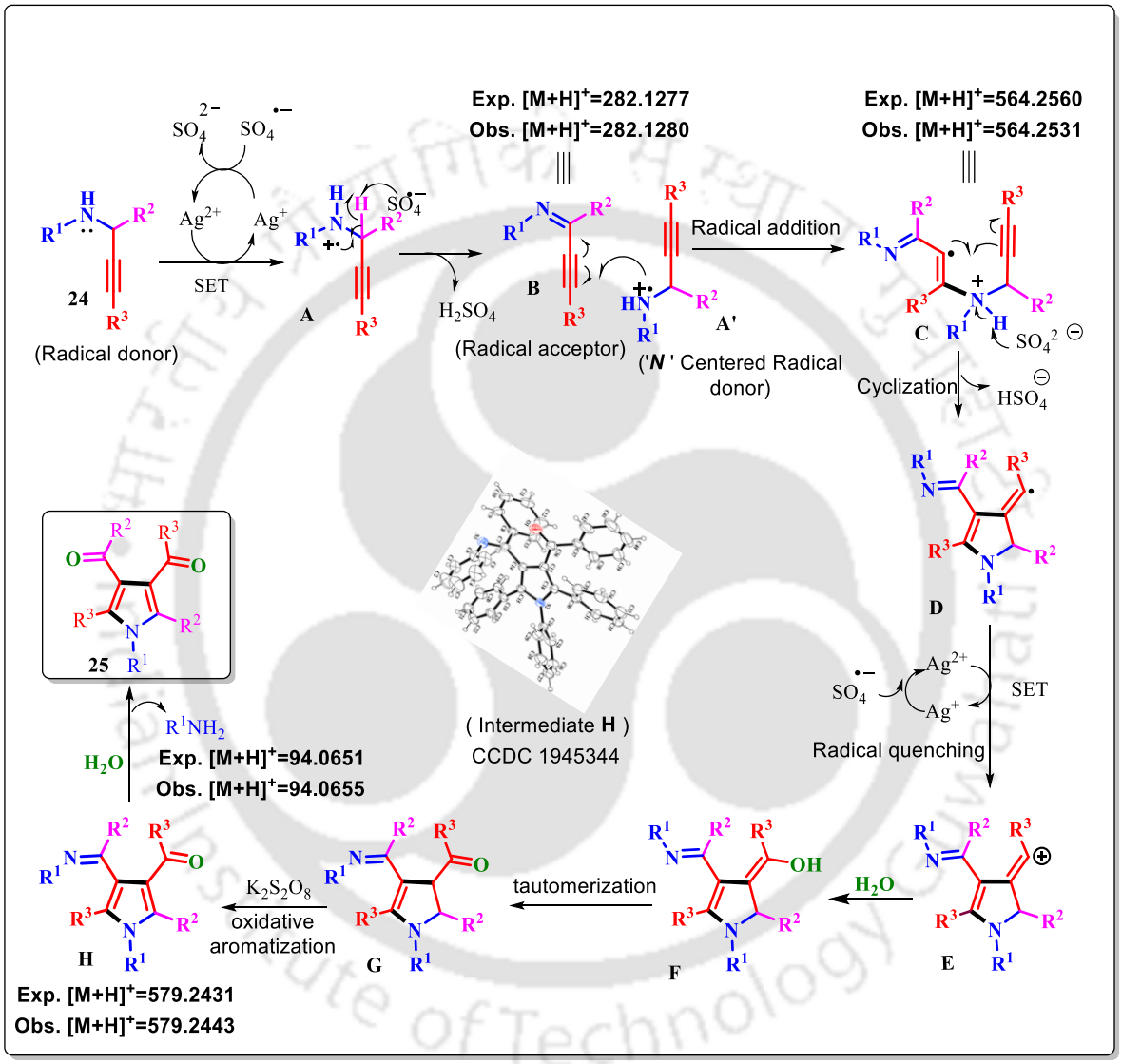


Figure 2.3.6db. *HRMS Study for the H_2O^{18} Labelled Experiment During the Synthesis of Compound* ***25e****.*

2.3.7. Plausible Mechanism

As per the experimental results obtained and previous reports,[13] a plausible mechanism is proposed (*Scheme 2.3.7*). Initially, silver(I) is oxidized to silver(II) species in the presence of $K_2S_2O_8$, which then abstracts one electron from nitrogen atom of *N*-propargylamine **24** to form radical cation intermediate **A**, which after the homolytic cleavage of nearby tertiary-proton forms imine intermediate **B**.[13b] The homolytic cleavage of the alkyne of intermediate **B** undergoes a coupling reaction with *N*-centered radical intermediate **A'** to generate radical intermediate **C**, which further undergoes subsequent cyclization to form vinyl radical intermediate **D**. The intermediate **D**, after silver catalyzed SET process generates vinyl carbocation **E**, which reacts with H_2O molecule to

give adduct **G** *via* keto-enol tautomerization of **F**.[13c] The adduct **G** undergoes oxidative aromatization by $K_2S_2O_8$ to give separable intermediate **H**, which on hydrolysis gives desired compound **25** (*Scheme 2.3.8*). Intermediates **B**, **C** and **H** were detected by taking HRMS at different time intervals (*Figure 2.3.7a).*



Scheme 2.3.7. *Plausible Mechanism of the Reaction.*

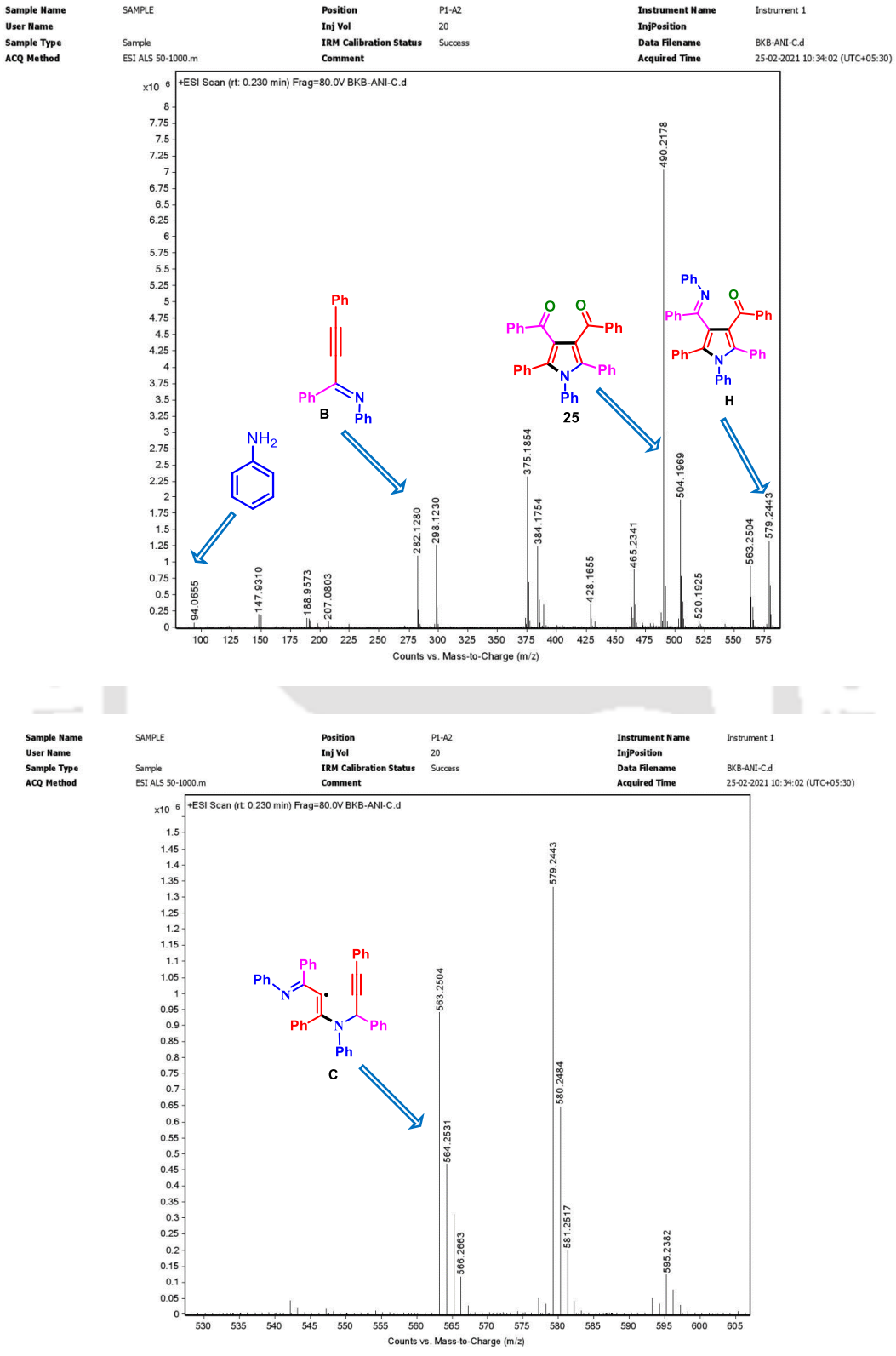
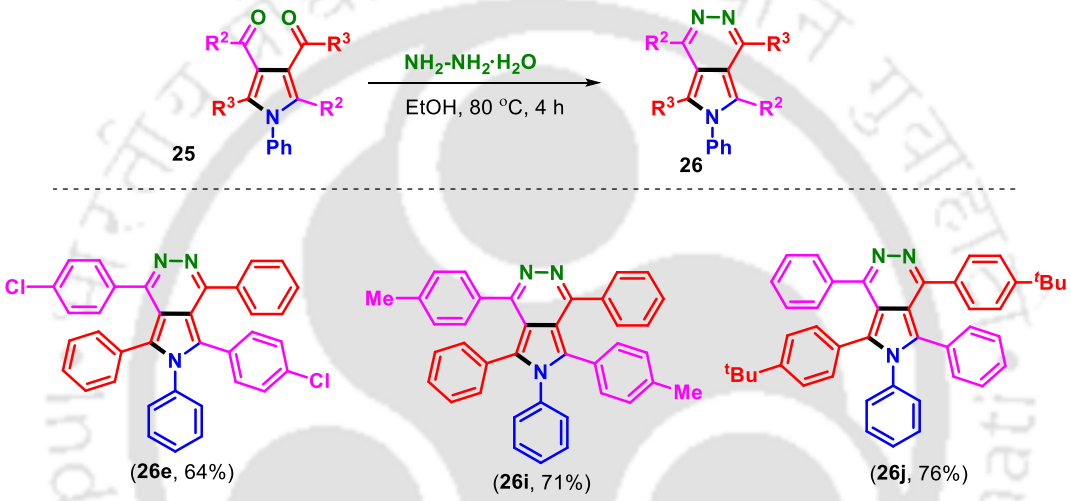


Figure 2.3.7a. *HRMS Study for the Detection of Reaction Intermediates.*

2.4. Post-synthetic Application

The utility of the methodology is extended towards the synthesis of pyrrolo[3,4-*d*]pyridazine **26e**, **26i** and **26j** (*Scheme 2.4*). It may be noted that pyrrolo[3,4-*d*]pyridazines are considered as high-affinity non-amino acid ligands for α2δ subunit of voltage gated calcium channels,[14] and aspartic protease endothiapepsin (EP) inhibition.[15] Thus the reaction penta-substituted dicarbonyl pyrrole derivatives (**25e**, **25i** and **25j**) with hydrazine hydrate in ethanol at 80 °C resulted in pyrrolepyridazine derivatives (**26e**, **26i** and **26j**) in 64, 71 and 76% yields, respectively.



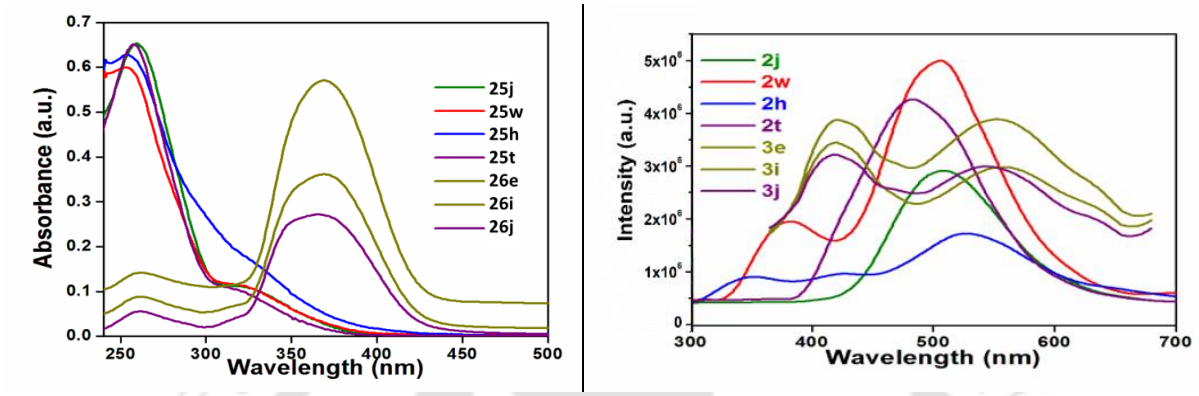
[a] Reaction condition: **25** (2.0 mmol), $NH_2NH_2 \cdot H_2O$ (10.0 mmol), EtOH (3.0 mL) in N_2 for 4 h at 80 °C. [b] Isolated yield.

Scheme 2.4. *Scope of Synthesis of Pyrrolo[3,4-d]pyridazine Derivatives.*[a,b]

2.4. 1. UV-VIS and Fluorescence study

Literature study shows that most of the pyrrole compounds are fluorescent. Therefore, the ultra-violet absorbance (λ_{abs}) and fluorescence (λ_{em}) for selected compounds **25** (**25j**, **25w**, **25h** and **25t**) and **26** (**26e**, **26i** and **26j**) were studied in chloroform. The UV-Vis and fluorescence spectra of compounds **25j**, **25w**, **25h**, **25t**, **25e**, **25i** and **25j** are shown in (*Figure 2.4.1*), respectively. It was observed that, due to the presence of two carbonyl group in the side chain of compound **25**, it might be quenching the fluorescence property. Therefore, compounds **25j**, **25w**, **25h** and **25t** shows the emission maxima (λ_{em}) at 490, 512, 533 and 491 nm, respectively, which exhibit fluorescent emissions in the range of 480-540 nm. However, there is an enhancement of fluorescence and red

shift in the compounds **26e**, **26i** and **26j** in the range of 550-570 nm, due to the extra conjugation offered by the pyridazine moiety. The absorption peak (λ_{abs}) and calculated molar extinction coefficient (ϵ) are summarized in (*Table 2.4.1*). From the above observations, it is evident that these compounds can be used in organic light-emitting diodes.[5]



(a) *UV-VIS Spectra* (b) *Fluorescence Spectra*

Figure 2.4.1. *UV-VIS and Fluorescence Spectra.*

Table 2.4.1. *Photophysical Studies data of Compounds* ***25j***, ***25w***, ***25h***, ***25t, 26e, 26i*** *and* ***26j***

entry	compound	λ_{max} (nm)[a]	absorbance at λ_{max}	ε (1 x 10^4 M^{-1} cm^{-1})	λ_{em} (nm)[b]
(1)	**25j**	259	0.653	6.53	490
(2)	**25w**	253	0.599	5.99	512
(3)	**25h**	254	0.627	6.27	533
(4)	**25t**	258	0.650	6.50	491
(5)	**26e**	374	0.563	5.63	566
(6)	**26i**	375	0.355	3.55	565
(7)	**26j**	365	0.270	2.70	560

[a]Absorption wavelengths. [b]Emission wavelengths in chloroform at a concentration of (1 x 10^{-5} M).

2.5. Crystallographic Description

The structure of all compounds was confirmed from standard spectroscopic experiments and finally by *X*-ray crystallographic analysis of compound **25a** (*figure 2.5a*) and **25a′** (*figure 2.5b*)

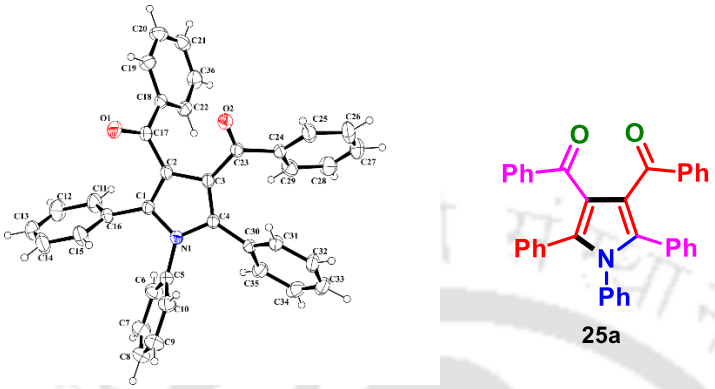
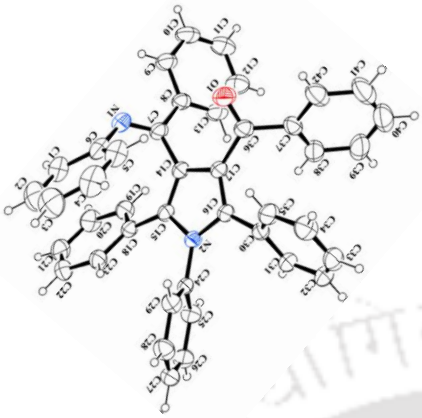
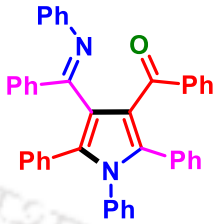


Figure 2.5a. *ORTEP diagram of compound* ***25a****, thermal ellipsoids are drawn on 30% probability level.*

Compound **25a**	**CCDC 2048423**
Formula	$C_{36}H_{25}NO_2$
Formula weight	503.57
T/K	293(2)
Crystal system	Triclinic
Space group	P-1
a/Å	11.424(9)
b/Å	11.472(7)
c/Å	11.795(11)
α/°	103.45(2)
β/°	108.00(3)
γ/°	103.86(2)
V/Å^3	1346.4(18)
Z	2
Abs. Coeff./mm^{-1}	0.076
Abs. Correction	none
GOF on F^2	1.084
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0620
	wR2 = 0.1716
R indices [all data]	*R1* = 0.1200
	wR2 = 0.2284





25a′

Figure 2.5b. *ORTEP diagram of compound* ***25a′****, thermal ellipsoids are drawn on 35% probability level.*

Compound **25a′**	**CCDC 1945344**
Formula	$C_{42}H_{30}N_2O$
Formula weight	578.68
T/K	296(2)
Crystal system	Triclinic
Space group	P-1
a/Å	10.159(7)
b/Å	12.217(8)
c/Å	14.466(9)
α/°	101.33(2)
β/°	101.07(2)
γ/°	107.50(2)
V/Å^3	1617.2(18)
Z	2
Abs. Coeff./mm^{-1}	0.071
Abs. Correction	None
GOF on F^2	0.982
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0483
R indices [all data]	*wR2* = 0.0817 *R1* = 0.0845 *wR2* = 0.0970

Conclusion

In conclusion, an efficient methodology for the synthesis of tetra- and penta-substituted pyrrole derivatives by oxidative self-dimerization of *N*-propargylamines catalyzed by silver benzoate in presence of potassium persulphate ($K_2S_2O_8$) in good yields has been reported. The reaction is compatible to many functional groups. The major advantage of the reaction is that the starting material can be synthesized from readily available aldehydes, amines and alkynes by A^3-coupling reaction. The methodology can be extended towards the synthesis of fluorescence active pyrroloepyridazine derivatives.

2.6. Experimental Section

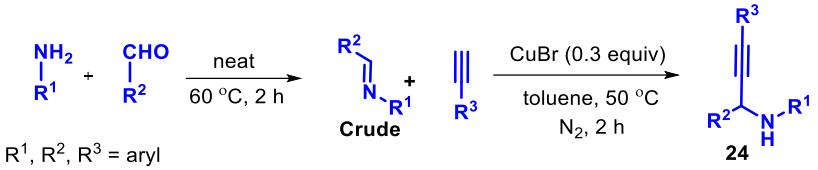
2.6.1. Instrumentation and Characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (600 MHz, 400 MHz) or $^{13}C\{H\}$ (150 MHz, 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

2.6.2. Experimental Procedure for Starting-material Synthesis

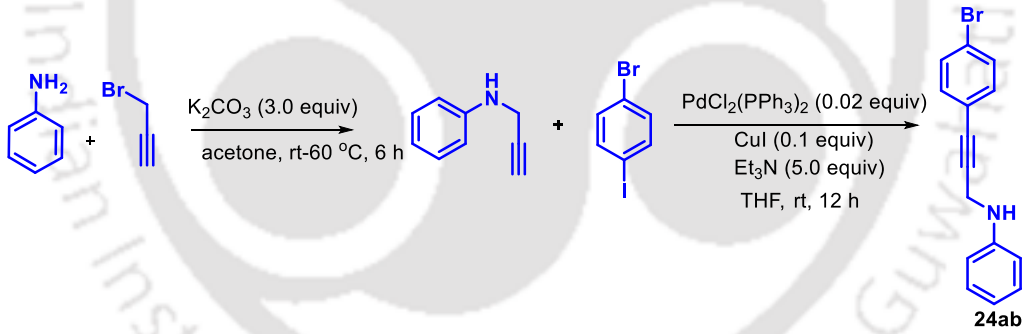
The starting material *N*-propargylamines (**24b**, **24g**, **24t**, **24q**),[16] (**24a**, **24c**, **24e**, **24n**, **24s**, **24v**),[17a] **24d**,[17b] (**24i**, **24j**, **24t**, **24o**),[17c] (**24p**),[17g] (**24f**, **24q**),[17d] **24x**,[17e] **24k**,[17f] **24y**,[17h] (**24z**, **24ac**, **24af**),[18a] (**24aa**),[19] (**24ad**),[18b] and **24ae**[18c] were prepared as per the literature procedure and the spectroscopic data are in good agreement with the literature one.

2.6.2.1. General Procedure for the Synthesis of Compounds 24h, 24l, 24m, 24w



A mixture of aldehyde (5.0 mmol, 1.0 equiv) and amine (7.5 mmol, 1.5 equiv) was heated in a round bottom flask at 60 °C in an oil bath for two hours in open air. Then, the crude was transferred to another round bottom flask and heated at 50 °C in an oil bath for 2 h with copper(I) bromide (1.5 mmol, 0.3 equiv) and acetylene (10.0 mmol, 2.0 equiv) in dry toluene (4 mL) under nitrogen. Then, the reaction mixture was poured into water, and extracted with EtOAc (3 × 20 mL). The organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude product was then purified using column chromatography over silica gel to get corresponding product.

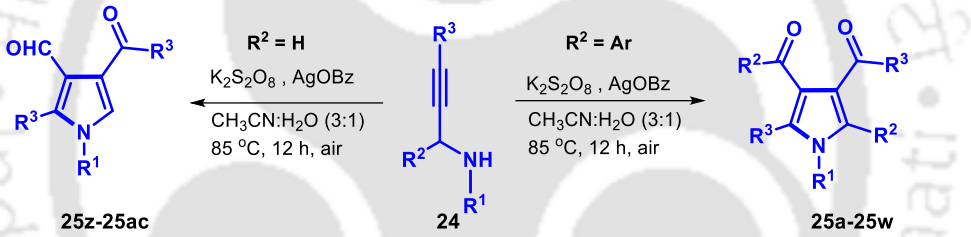
2.6.2.2. Experimental Procedure for the Synthesis of Compounds 24ab



A solution of aniline (5 mmol, 1.0 equiv) and K_2CO_3 (15 mmol, 3.0 equiv) in acetone (5 mL) was stirred under N_2 atmosphere for 15 min at room temperature and then propargyl bromide (7.5 mmol, 1.5 equiv) was added drop wise. The mixture was stirred at 60 °C for 6 h in an oil bath. After completion of the starting material, the solvent was removed under reduced pressure. The reaction mixture was diluted with ethyl acetate, washed with brine solution. The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give *N*-(2-propynyl)aniline (393 mg, 72% yield) as light yellow oil.

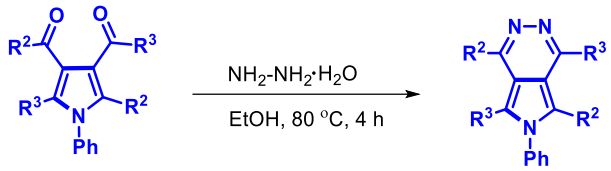
To a stirred solution of 1-bromo-4-iodobenzene (3.6 mmol, 1.2 equiv), bis(triphenylphosphine)palladiumdichloride (0.15 mmol, 0.02 equiv) and copper iodide (0.3 mmol, 0.1 equiv) in triethylamine (12 mL) was added *N*-(2-propynyl)aniline (3 mmol, 1.0 equiv) at room temperature under N_2 atmosphere. Then the mixture was stirred at room temperature for 12 h. After completion of the starting material, the solvent was removed under reduced pressure. The reaction mixture was diluted with ethyl acetate, washed with brine solution. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography using ethyl acetate and hexane as eluents over silica gel to give *N*-(3-(4-bromophenyl)prop-2-yn-1-yl)aniline **24ab**.

2.6.3. General Experimental Procedure for the Synthesis of Compounds 25a-25ae



To a stirred solution of $K_2S_2O_8$ (1.2 mmol, 3.0 equiv) and Ag(OBz) (0.12 mmol, 0.3 equiv) in CH_3CN/H_2O (3:1, 4 mL) was added *N*-propargylamines **24** (0.4 mmol, 1.0 equiv) dropwise. Then the mixture was stirred at 85 °C under an open air atmosphere in an oil bath and the reaction time was monitored by TLC. After completion of the reaction, the solvent was removed completely under reduced pressure. The residue was diluted with ethyl acetate and saturated brine solution. The mixture was shaked properly and then the organic layer was separated. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding product.

2.6.4. General Experimental Procedure for the Synthesis of Compounds 26e, 26i-26j



25 **26**

To a stirred solution of (1,2,5-triphenyl-1*H*-pyrrole-3,4-diyl)bis(phenylmethanone) **25** derivative (0.2 mmol, 1.0 equiv) in ethanol (3.0 mL) was added hydrazine hydrate ($N_2H_4 \cdot H_2O$) (1.0 mmol, 5.0 equiv) drop wise. Then the mixture was refluxed under nitrogen atmosphere in an oil bath and after completion of the starting material, the solvent was removed under reduced pressure. The crude was subjected to column chromatography over silica gel to give the corresponding product **26**.

2.7. References:

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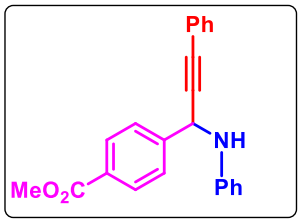
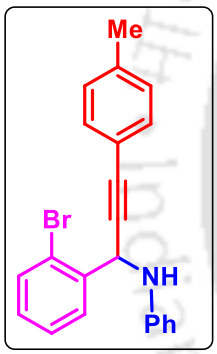
2.8. Characterization Data

Methyl 4-(3-phenyl-1-(phenylamino)prop-2-yn-1-yl)benzoate (24h):



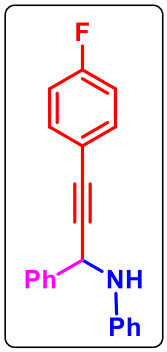
Pale yellow solid; R_f (hexane/EtOAc, 19:1) 0.55; mp 100–102 °C. Yield 790 mg, 78%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 8.4 Hz, 2 H), 7.42–7.39 (m, 2 H), 7.30–7.28 (m, 3 H), 7.21 (t, *J* = 7.2 Hz, 2 H), 6.80 (t, *J* = 7.2 Hz, 1 H), 6.74 (d, *J* = 8.0 Hz, 2 H), 5.55 (s, 1 H), 3.92 (s, 3 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 167.0, 146.5, 146.1, 132.0, 130.4, 130.1, 129.5, 128.8, 128.5, 127.5, 122.7, 119.1, 114.4, 87.9, 85.8, 52.4, 50.7; **IR** (KBr, neat) 3376, 2953, 2275, 1718, 1503, 1277, 961, 748, 692 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{20}NO_2$ $(M + H)^+$ 342.1489, found 342.1486.

***N*-(1-(2-Bromophenyl)-3-(*p*-tolyl)prop-2-yn-1-yl)aniline (24l):**



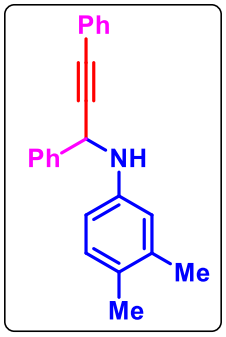
Yellow oil ; R_f (hexane/EtOAc, 19:1) 0.55; Yield 900 mg, 80%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.6 Hz, 1 H), 7.60 (d, *J* = 8.0 Hz, 1 H), 7.35–7.29 (m, 3 H), 7.18 (t, *J* = 7.6 Hz, 3 H), 7.08 (d, *J* = 8.0 Hz, 2 H), 6.77 (t, *J* = 7.2 Hz, 1 H), 6.70 (d, *J* = 8.0 Hz, 2 H), 5.77 (s, 1 H), 4.24 (bs, 1 H), 2.32 (s, 3 H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 146.5, 139.0, 138.8, 133.5, 131.1, 129.8, 129.4, 129.2, 129.1, 128.2, 123.7, 119.7, 118.9, 114.2, 87.1, 85.3, 51.1, 21.7; **IR** (KBr, neat) 3394, 2922, 1695, 1503, 1262, 815, 751 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{19}BrN$ $(M + H)^+$376.0695, found 376.0698.

***N*-(3-(4-Fluorophenyl)-1-phenylprop-2-yn-1-yl)aniline (24m):**



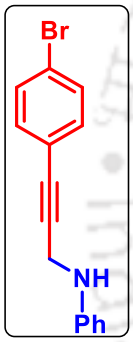
Brown gummy; R_f (hexane/EtOAc, 50:1) 0.56; Yield 540 mg, 60%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.6 Hz, 2 H), 7.42–7.31 (m, 5 H), 7.21 (t, *J* = 7.6 Hz, 2 H), 6.96 (t, *J* = 8.0 Hz, 2 H), 6.80–6.76 (m, 3 H), 5.47 (s, 1 H), 4.14 (bs, 1 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 163.9, 161.5, 139.8, 146.7, 133.9, 133.8, 129.4, 129.1, 128.4, 127.5, 118.8, 115.8, 115.6, 114.3, 88.4, 84.2, 50.8; **IR** (KBr, neat) 3058, 1600, 1498, 1228, 1092, 731, 689 cm^{-1}; **HRMS** (ESI) calcd. for $C_{21}H_{17}FN$ $(M + H)^+$ 302.1340, found 302.1336.

***N*-(1,3-Diphenylprop-2-yn-1-yl)-3,4-dimethylaniline (24w):**



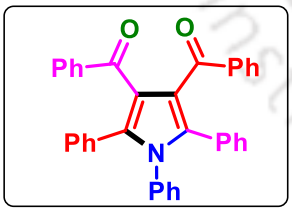
Yellow gummy; R_f (hexane/EtOAc, 50:1) 0.58; Yield 727 mg, 78%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.2 Hz, 2 H), 7.42–7.36 (m, 4 H), 7.33–7.31 (m, 1 H), 7.26 (d, *J* = 2.4 Hz, 2 H), 7.25 (d, *J* = 1.2 Hz, 1 H), 6.95 (d, *J* = 8.0 Hz, 1 H), 6.60 (d, *J* = 2.4 Hz, 1 H), 6.54 (dd, *J* = 5.6 and 8.0 Hz, 1 H), 5.45 (s, 1 H), 3.97 (bs, 1 H), 2.20 (s, 3 H), 2.16 (s, 3 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 145.0, 140.3, 137.4, 132.0, 130.4, 129.0, 128.5, 128.4, 128.2, 127.1, 126.1, 123.1, 116.2, 111.7, 89.1, 85.1, 51.1, 20.3, 19.0; **IR** (KBr, neat) 3032, 2860, 2914, 1613, 1485, 1262, 738, 695 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{22}N$ $(M + H)^+$ 312.1747, found 312.1743.

***N*-(3-(4-Bromophenyl)prop-2-yn-1-yl)aniline (24ab):**



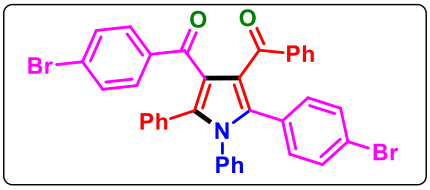
Brown gummy; R_f (hexane/EtOAc, 9:1) 0.58; Yield 530 mg, 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 5.6 Hz, 2 H), 7.25–7.21 (m, 4 H), 6.79 (t, *J* = 4.8 Hz, 1 H), 6.72 (d, *J* = 5.6 Hz, 2 H), 4.12 (s, 2 H), 3.94 (s, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 147.2, 133.3, 131.7, 129.4, 122.6, 122.0, 118.8, 113.7, 87.8, 82.4, 34.1; IR (KBr, neat) 3398, 2930, 1620, 1513, 1365, 862, 736, 625 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{13}BrN$ $(M + H)^+$ 286.0226, found 286.0227.

1,2,5-Triphenyl-1*H*-pyrrole-3,4-diyl)bis(phenylmethanone) (25a):



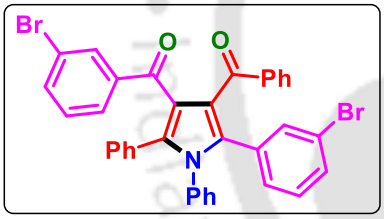
Brown solid; R_f (hexane/EtOAc, 7:3) 0.60; mp 156–158 °C. Yield 71 mg,71%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 2 H), 7.60 (dd, *J* = 8.4 and 2.2 Hz, 3 H), 7.48 (t, *J* = 7.2 Hz, 2 H), 7.27 (t, *J* = 7.2 Hz, 2 H), 7.18–7.11 (m, 6 H), 7.09–7.03 (m, 8 H), 6.95 (dd, *J* = 7.8 and 2.4 Hz, 2 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.9, 139.2, 137.3, 137.2, 133.9, 132.2, 131.1, 130.5, 130.4, 129.5, 128.9, 128.7, 128.2, 128.1, 128.1, 128.0, 127.9, 124.3; **IR** (KBr, neat) 2923, 2671, 1686, 1606, 1294, 709 cm^{-1}; **HRMS** (ESI) calcd. for $C_{36}H_{26}NO_2$ $(M + H)^+$504.1958, found 504.1959.

4-Benzoyl-5-(4-bromophenyl)-1,2-diphenyl-1*H*-pyrrol-3-yl)(4-bromophenyl)methanone (25b):



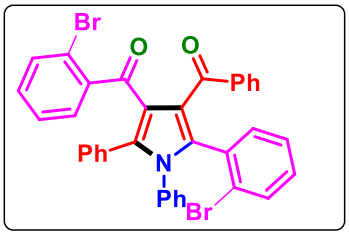
Pale yellow solid; R_f (hexane/EtOAc, 7:3) 0.60; mp 221–223 °C. Yield 71 mg, 55%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.4 Hz, 1 H), 7.46 (t, *J* = 8.4 Hz, 2 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 2 H), 6.92 (d, *J* = 8.4 and 1.8 Hz, 2 H), 7.23–7.18 (m, 7 H), 7.10–7.02 (m, 6 H), 6.96 (dd, *J* = 7.8 and 1.4 Hz, 2 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.7, 191.5, 138.9, 137.8, 137.7, 136.8, 136.0, 132.7, 132.6, 132.5, 131.8, 131.7, 131.3, 131.1, 131.0, 130.8, 130.0, 129.4, 129.2, 129.0, 128.5, 128.3, 128.2, 128.1, 127.3, 124.4, 123.9, 122.7; **IR** (KBr, neat) 2930, 1659, 1597, 1400, 1214, 1088, 696 cm^{-1}; **HRMS** (ESI) calcd. for $C_{36}H_{24}Br_2NO_2$ $(M + H)^+$ 662.0148, found 662.0148.

(4-Benzoyl-5-(3-bromophenyl)-1,2-diphenyl-1*H*-pyrrol-3-yl)(3-bromophenyl)methanone (25c):



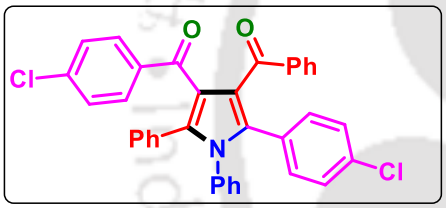
Pale yellow solid; R_f(hexane/EtOAc, 7:3) 0.64; mp 232–234 °C. Yield 72 mg, 55%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.2 Hz, 2 H), 7.59 (d, *J* = 7.0 Hz, 1 H), 7.43–7.34 (m, 2 H), 7.25–7.19 (m, 7 H), 7.14–7.03 (m, 7 H), 7.00–6.97 (m, 3 H), 6.93 (t, *J* = 8.4 Hz, 1 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.5, 191.0, 140.7, 138.9, 138.1, 136.7, 135.6, 135.0, 134.0, 132.5, 132.3, 132.2, 131.2, 130.0, 129.7, 129.6, 129.4, 129.3, 129.1, 129.0, 128.6, 128.4, 128.2, 128.1, 127.9, 124.8, 123.8, 122.3, 121.9; **IR** (KBr, neat) 2856, 1654, 1597, 1405, 1217, 735 cm^{-1}; **HRMS** (ESI) calcd. for $C_{36}H_{24}Br_2NO_2$ $(M + H)^+$ 660.0168, found 660.0168.

4-Benzoyl-5-(2-bromophenyl)-1,2-diphenyl-1*H*-pyrrol-3-yl)(2-bromophenyl)methanone (25d):



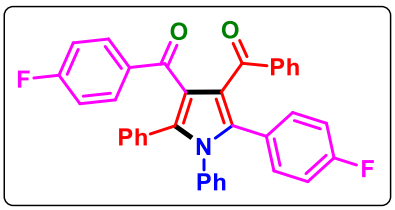
Reddish brown solid; R_f(hexane/EtOAc, 7:3) 0.64; mp 208–210 °C. Yield 85 mg, 65%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.4 Hz, 2 H), 7.39–7.36 (m, 2 H), &.33–7.27 (m, 4 H), 7.20 (dt, *J* = 7.4 and 1.2 Hz, 2 H), 7.16–7.06 (m, 6 H), 7.04–6.94 (m, 7 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.7, 190.3, 141.0, 139.5, 139.0, 136.8, 136.0, 134.4, 133.7, 133.3, 132.5, 132.4, 131.9, 131.3, 131.2, 130.9, 130.5, 130.1, 129.4, 128.9, 128.5, 128.2, 127.6, 126.9, 126.8, 125.8, 125.1, 123.4, 121.0; **IR** (KBr, neat) 2855, 1655, 1595, 1401, 1274, 698 cm^{-1}; **HRMS** (ESI) calcd. for $C_{36}H_{24}Br_2NO_2$ $(M + H)^+$ 660.0168, found 660.0169.

4-Benzoyl-5-(4-chlorophenyl)-1,2-diphenyl-1*H*-pyrrol-3-yl)(4-chlorophenyl)methanone (25e):



Creamy solid; R_f(hexane/EtOAc, 7:3) 0.60; mp 221–223 °C. Yield 69mg, 60%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.4 Hz, 2 H), 7.54 (t, *J* = 8.4 Hz, 2 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 7.25–7.18 (m, 5 H), 7.15–7.02 (m, 9 H), 7.00–6.95 (m, 4 H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 192.7, 191.4, 138.9, 138.6, 137.7, 137.4, 136.9, 136.0, 134.4, 132.6, 132.3, 131.0, 130.1, 129.4, 129.2, 129.1, 128.9, 128.5, 128.4, 128.3, 128.2, 128.1, 124.5, 123.9; **IR** (KBr, neat) 2932, 1693, 1596, 1401, 1229, 700 cm^{-1}; **HRMS** (ESI) calcd. for $C_{36}H_{24}Cl_2NO_2$ $(M + H)^+$ 572.1179, found 572.1181.

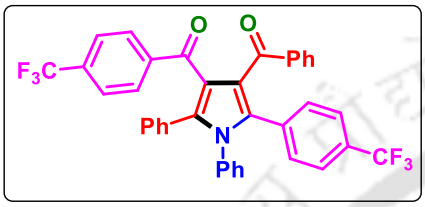
4-Benzoyl-5-(4-fluorophenyl)-1,2-diphenyl-1*H*-pyrrol-3-yl)(4-fluorophenyl)methanone (25f)



White solid; R_f (hexane/EtOAc, 7:3) 0.50; mp 166–168 °C. Yield 54mg, 50%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.4 Hz, 1 H), 7.67–7.61 (m, 3 H), 7.48 (t, *J* = 7.4 Hz, 1 H), 7.44 (t, *J* = 7.4 Hz, 1 H), 7.23–7.16 (m, 5 H), 7.12–7.03 (m, 6 H), 6.98 (d, *J* = 7.4 Hz, 2 H), 6.80 (t, *J* = 8.6 Hz, 2 H), 6.77 (t, *J* = 8.6 Hz, 2 H): **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.8, 191.2, 165.2 (d, *J* = 252.0 Hz), 162.4 (d, *J* = 247.2 Hz), 138.9, 137.3, 137.0, 136.3, 135.4 (d, *J* = 2.8 Hz), 133.8, 132.8 (d, *J* = 8.3 Hz), 132.4, 131.9 (d, *J* = 9.2 Hz), 131.0, 130.3,

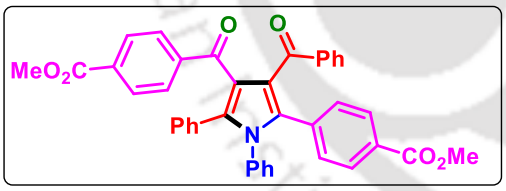
130.2, 129.7, 129.4, 129.0 (d, *J* = 3.6 Hz), 128.6, 128.3 (d, *J* = 14.0 Hz), 128.0 (d, *J* = 13.0 Hz), 126.4(d, *J* = 3.4 Hz), 115.1 (d, *J* = 21.6 Hz),**^{19}F NMR**(376 MHz, C_6F_6/$CDCl_3$) δ 48.70 (s, -F), 55.00 (s, -F); **IR** (KBr, neat) 2926, 1656, 1597, 1421, 1227, 700 cm^{-1}; **HRMS** (ESI) calcd. for $C_{36}H_{24}F_2NO_2$ $(M + H)^+$ 540.1770, found 540.1791.

4-Benzoyl-1,2-diphenyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrrol-3-yl)(4-(trifluoromethyl)-phenyl)methanone (25g):



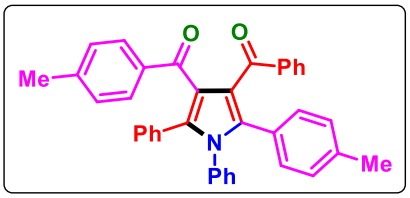
Red gummy; R_f (hexane/EtOAc, 7:3) 0.50; mp 169–171 °C. Yield 60mg, 47%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67–7.61 (m, 3 H), 7.40–7.33 (m, 5 H), 7.28–7.01 (m, 13 H), 6.98 (t, *J* = 6.8 Hz, 2 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.7, 191.3, 141.9, 138.6, 137.7 (q, *J* = 215.0 Hz), 135.7, 134.0, 133.3 (q, *J* = 32.2 Hz), 132.8, 131.3, 131.1, 129.5, 129.3, 129.2, 129.0, 128.7, 128.6, 128.4, 128.1, 125.2, 125.0 (q, *J* = 21.0 Hz), 123.8, 122.7, 122.5; **^{19}F NMR**(376 MHz, C_6F_6/$CDCl_3$) δ 98.61 (s, -CF_3), 98.89 (s, -CF_3); **IR** (KBr, neat) 2857, 1662, 1597, 1398, 1171, 717 cm^{-1}; **HRMS** (ESI) calcd. for $C_{38}H_{24}F_6NO_2$ $(M + H)^+$ 640.1706, found 640.1723.

Methyl 4-(3-benzoyl-4-(4-(methoxycarbonyl)benzoyl)-1,5-diphenyl-1*H*-pyrrol-2-yl)benzoate (25h):



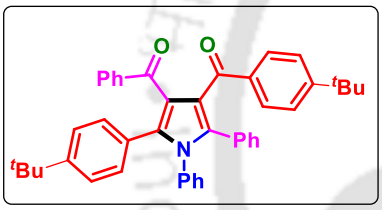
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 169–171°C. Yield 68mg, 55%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2 H), 7.74 (d, *J* = 8.2 Hz, 2 H), 7.65 (d, *J* = 8.2 Hz, 3 H), 7.31 (t, *J* = 7.4 Hz, 1 H), 7.22–7.13 (m, 6 H), 7.11–6.98 (m, 7 H), 6.94 (d, *J* = 7.0 Hz, 2 H), 3.89 (s, 3 H), 3.84 (s, 3 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.7, 191.9, 166.8, 166.6, 142.4, 138.7, 138.3, 136.8, 136.0, 135.0, 132.8, 132.7, 131.0, 130.9, 130.4, 130.0, 129.5, 129.4, 129.3, 129.2, 129.0, 128.7, 128.6, 128.4, 128.3, 128.1, 125.0, 124.1, 52.5, 52.4; **IR** (KBr, neat) 2850, 1720, 1642, 1405, 1280, 730 cm^{-1}; **HRMS** (ESI) calcd. for $C_{40}H_{30}NO_6$ $(M + H)^+$ 620.2068, found 620.2068.

4-Benzoyl-1,2-diphenyl-5-(*p*-tolyl)-1*H*-pyrrol-3-yl)(p-tolyl)methanone (25i):



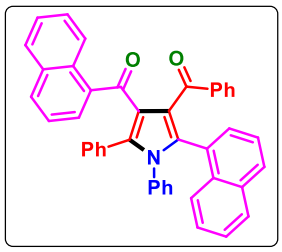
Pale yellow solid; R_f (hexane/EtOAc, 7:3) 0.50; mp 185–187 °C. Yield 53 mg, 50%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.4 Hz, 2 H), 7.50 (d, *J* = 8.0 Hz, 2 H), 7.27 (t, *J* = 7.4 Hz, 1 H), 7.17–7.03 (m, 10 H), 6.96–6.90 (m, 6 H), 6.84 (d, *J* = 8.0 Hz, 2 H), 2.25 (s, 3 H), 2.17 (s, 3 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 193.0, 192.7, 142.8, 139.3, 137.8, 137.5, 137.4, 136.8, 136.7, 133.8, 132.0, 131.1, 130.9, 130.6, 130.4, 129.6, 129.4, 129.2, 128.8, 128.7, 128.6, 128.1, 127.9, 127.8, 127.5, 124.4, 124.0, 21.7, 21.4; **IR** (KBr, neat) 2930, 1658, 1603, 1399, 1225, 706 cm^{-1}; **HRMS** (ESI) calcd. for $C_{38}H_{30}NO_2$ $(M + H)^+$ 532.2271, found 532.2279.

4-Benzoyl-5-(4-(*tert*-butyl)phenyl)-1,2-diphenyl-1*H*-pyrrol-3-yl)(4-(*tert*-butyl)phenyl)-methanone (25j):



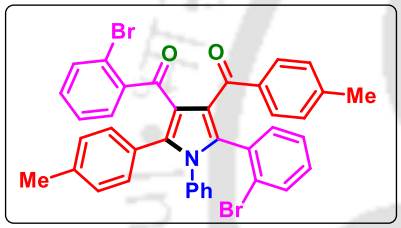
Pale yellow solid; R_f (hexane/EtOAc, 8:2) 0.50; mp 261–263 °C. Yield 68mg, 55%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52–7.48 (m, 4H), 7.28–7.23 (m, 1 H), 7.20–7.02 (m, 14 H), 6.97–6.92 (m, 4 H), 1.24 (s, 9 H), 1.17 (s, 9 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 193.1, 192.7, 155.6, 150.9, 139.5, 137.7, 137.4, 137.0, 136.8, 131.9, 131.1, 130.8, 130.7, 129.3, 129.2, 128.8, 128.7, 128.2, 128.0, 127.9, 127.8, 127.4, 125.0, 124.8, 124.5, 124.1, 35.1, 34.7, 31.3, 31.2, **IR** (KBr, neat) 2964, 1660, 1601, 1403, 1229, 698 cm^{-1}; **HRMS** (ESI) calcd. for $C_{44}H_{42}NO_2$ $(M + H)^+$ 616.3210, found 616.3210.

4-(1-Naphthoyl)-2-(naphthalen-1-yl)-1,5-diphenyl-1*H*-pyrrol-3-yl)(phenyl)methanone (25k):



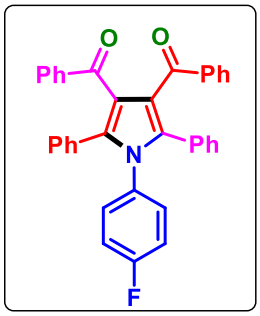
Brown solid; R_f (hexane/EtOAc, 7:3) 0.65; mp 224–226 °C. Yield 72mg, 60%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (s, 1 H), 7.78–7.67 (m, 4 H), 7.65–7.56 (m, 5 H), 7.54–7.49 (m, 2 H), 7.45–7.35 (m, 3 H), 7.21–7.10 (m, 7 H), 7.06–7.01 (m, 7 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 193.1, 192.8, 139.1, 137.5, 137.3, 137.1, 136.5, 135.3, 133.9, 132.8, 132.6, 132.4, 132.1, 131.6, 131.1, 130.6, 130.4, 129.3, 129.2, 129.0, 128.7, 128.3, 128.1, 128.0, 127.9, 126.6, 126.4, 126.3, 125.1, 124.9, 124.6; **IR** (KBr, neat) 2923, 1686, 1601, 1418, 1227, 750 cm^{-1}; **HRMS** (ESI) calcd. for $C_{44}H_{30}NO_2$ $(M + H)^+$ 604.2271, found 604.2272.

4-(2-Bromobenzoyl)-2-(2-bromophenyl)-1-phenyl-5-(*p*-tolyl)-1*H*-pyrrol-3-yl)(*p*-tolyl)-methanone (25l):



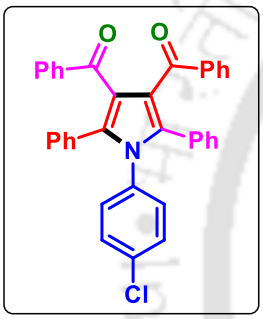
Pale yellow solid; R_f (hexane/EtOAc, 7:3) 0.50; mp 216–218 °C. Yield 60 mg, 44%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2 H), 7.38 (dd, *J* = 7.6 and 1.6 Hz, 1 H), 7.31 (dd, *J* = 8.0 and 1.0 Hz, 1 H), 7.20 (dt, *J* = 7.6 Hz, 2 H), 7.13 (dt, *J* = 7.6 and 1.0 Hz, 1 H), 7.08–6.92 (m, 12 H), 6.79 (d, *J* = 7.8 Hz, 2 H), 2.31 (s, 3 H), 2.15 (s, 3 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.5, 190.4, 143.0, , 141.1, 139.7, 138.0, 136.9, 136.5, 135.6, 134.5, 133.3, 132.4, 132.1, 131.2, 131.0, 130.9, 130.4, 129.6, 128.9, 128.8, 128.5, 128.3, 128.2, 127.1, 126.8, 126.7, 125.9, 125.3, 123.3, 121.9, 21.9, 21.4; **IR** (KBr, neat) 2788, 1651, 1596, 1399, 1248, 700 cm^{-1}; **HRMS** (ESI) calcd. for $C_{38}H_{28}Br_2NO_2$ $(M + H)^+$ 688.0481, found 688.0504.

1-(4-Fluorophenyl)-2,5-diphenyl-1*H*-pyrrole-3,4-diyl)bis(phenylmethanone) (25q):



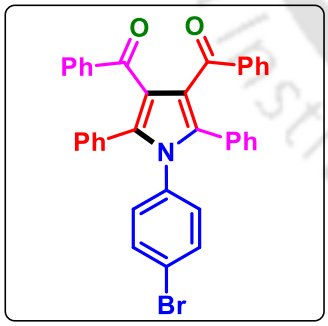
Brown solid; R_f (hexane/EtOAc, 7:3) 0.60; mp 207–209 °C. Yield 77mg, 74%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.2 Hz, 4 H), 7.29 (t, *J* = 7.4 Hz, 2 H), 7.15–7.04 (m, 14 H), 6.94–6.90 (m, 2 H), 6.86 (t, *J* = 7.8 Hz, 2 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.8, 161.9 (d, *J* = 247.5 Hz), 139.1, 137.3, 133.2 (d, *J* = 3.3 Hz), 132.3, 131.1, 129.4, 128.2, 128.1, 128.0, 124.4, 116.0 (d, *J* = 22.8 Hz); **^{19}F** (376 MHz, $CDCl_3/C_6F_6$) δ 49.2; **IR** (KBr, neat) 2985, 1734, 1369, 1237,1049, 635 cm^{-1}; **HRMS** (ESI) calcd. for $C_{36}H_{25}FNO_2$ $(M + H)^+$ 522.1864, found 522.1868.

1-(4-Chlorophenyl)-2,5-diphenyl-1*H*-pyrrole-3,4-diyl)bis(phenylmethanone) (25r):



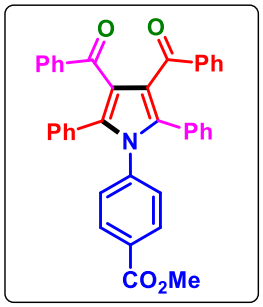
Reddish brown solid; R_f(hexane/EtOAc, 7:3) 0.50; mp 200–202 °C. Yield 61mg, 57%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.2 Hz, 3 H), 7.30 (t, *J* = 7.2 Hz, 2 H), 7.16–7.02 (m, 17 H), 6.88 (d, *J* = 8.6 Hz, 2 H), **^{13}C{^{1}H}** NMR (100 MHz, $CDCl_3$) δ 192.7, 139.0, 137.2, 135.8, 134.1, 132.3, 131.1, 130.3, 130.2, 129.4, 129.2, 128.3, 128.2, 128.1, 124.5; **IR** (KBr, neat) 2926, 1693, 1583, 1399, 1289, 710 cm^{-1}; **HRMS** (ESI) calcd. for $C_{36}H_{25}ClNO_2$ $(M + H)^+$ 538.1568, found 538.1571.

1-(4-Bromophenyl)-2,5-diphenyl-1*H*-pyrrole-3,4-diyl)bis(phenylmethanone) (25s):



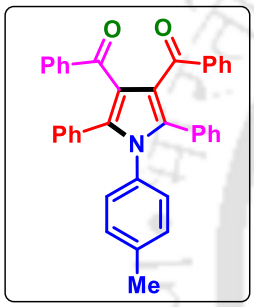
Brown solid; R_f (hexane/EtOAc, 7:3) 0.60; mp 203–205 °C. Yield 72 mg, 62%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.4 Hz, 4 H), 7.31–7.27 (m, 4 H), 7.15–7.08 (m, 10 H), 7.04–7.00 (m, 4 H), 6.81 (dd, *J* = 6.8 and 1.8 Hz, 2 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.7, 139.0, 137.1, 136.4, 132.3, 131.1, 130.6, 130.2, 129.4, 128.3, 128.2, 128.1, 124.6, 122.2; **IR** (KBr, neat) 2926, 1692, 1599, 1494, 1286, 710 cm^{-1}; **HRMS** (ESI) calcd. for $C_{36}H_{25}BrNO_2$ $(M + H)^+$ 582.1063, found 582.1064.

Methyl 4-(3,4-dibenzoyl-2,5-diphenyl-1*H*-pyrrol-1-yl)benzoate (25t):



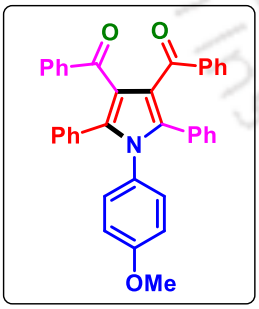
Pale yellow solid; R_f(hexane/EtOAc, 7:3) 0.50; mp 225–227 °C. Yield 62mg, 55%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ7.86 (d, *J* = 8.4 Hz, 2 H), 7.62–7.59 (m, 3 H), 7.34–7.28 (m, 2 H), 7.18–7.01 (m, 17 H), 3.89 (s, 3 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.7, 166.3, 141.3, 139.0, 137.0, 132.3, 131.1, 130.3, 130.2, 129.7, 129.4, 129.2, 128.4, 128.2, 128.1, 124.7, 52.6; **IR** (KBr, neat) 2923, 1722, 1657, 1412, 1284, 692 cm^{-1}; **HRMS** (ESI) calcd. for $C_{38}H_{28}NO_4$ $(M + H)^+$ 562.2013, found 562.2012.

2,5-Diphenyl-1-(*p*-tolyl)-1*H*-pyrrole-3,4-diyl)bis(phenylmethanone) (25u):



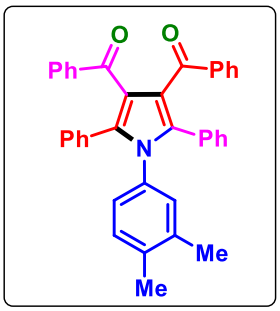
Pale yellow solid; R_f(hexane/EtOAc, 7:3) 0.50; mp 233–235 °C. Yield 53 mg, 51%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61–7.59 (m, 3 H), 7.31–7.26 (m, 2 H), 7.19–7.05 (m, 15 H), 6.95 (d, *J* = 8.2 Hz, 2 H), 6.83 (d, *J* = 8.2 Hz, 2 H), 2.26 (s, 3 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.9, 139.3, 138.1, 137.4, 134.6, 132.2, 131.1, 130.6, 129.5, 129.4, 128.8, 128.1, 128.0, 127.9, 124.2, 21.3, **IR** (KBr, neat) 2921, 1687, 1606, 1424, 1294, 710 cm^{-1}; **HRMS** (ESI) calcd. for $C_{37}H_{28}NO_2$ $(M + H)^+$ 518.2115, found 518.2117.

1-(4-Methoxyphenyl)-2,5-diphenyl-1*H*-pyrrole-3,4-diyl)bis(phenylmethanone) (25v):



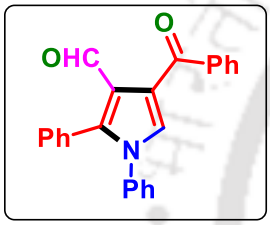
Reddish brown solid; R_f(hexane/EtOAc, 7:3) 0.50; mp 164–166 °C. Yield 44 mg, 42%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60–7.58 (m, 4 H), 7.31–7.26 (m, 2 H), 7.15–7.05 (m, 14 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 6.66 (d, *J* = 8.4 Hz, 2 H), 3.72 (s, 3 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 193.0, 159.0, 139.2, 137.5, 132.2, 131.1, 130.6, 130.1, 129.4, 128.0, 129.9, 124.1, 116.3, 114.1, 55.5; **IR** (KBr, neat) 2925, 1689, 1601, 1454, 1286, 705 cm^{-1}; **HRMS** (ESI) calcd. for $C_{37}H_{28}NO_3$ $(M + H)^+$ 534.2064, found 534.2061.

1-(3,4-Dimethylphenyl)-2,5-diphenyl-1*H*-pyrrole-3,4-diyl)bis(phenylmethanone) (25w):



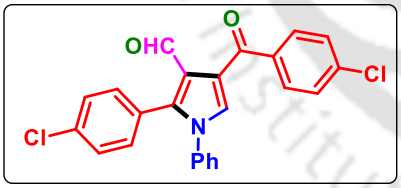
Pale yellow solid; R_f (hexane/EtOAc, 7:3) 0.50; mp 173–175 °C. Yield 64 mg, 60%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60–7.57 (m, 4 H), 7.30–7.25 (m, 3 H), 7.14–7.10 (m, 4 H), 7.09–7.04 (m, 9 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 6.69–6.65 (m, 2 H), 2.14 (s, 3 H), 2.03 (s, 3 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 193.0, 139.3, 137.4, 137.3, 136.6, 134.8, 132.1, 131.1, 130.7, 130.0, 129.9, 129.4, 128.0, 127.9, 127.8, 126.3, 124.1, 19.8, 19.6; **IR** (KBr, neat) 2920, 1737, 1649, 1406, 1242, 752 cm^{-1}; **HRMS** (ESI) calcd. for $C_{38}H_{30}NO_2$ $(M + H)^+$ 532.2271, found 532.2271.

4-Benzoyl-1,2-diphenyl-1*H*-pyrrole-3-carbaldehyde (25z):



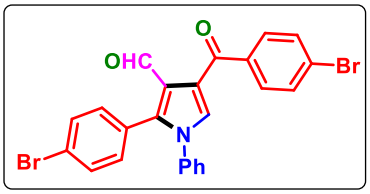
Reddish gummy; R_f (hexane/EtOAc, 8:2) 0.50; Yield 36 mg, 51%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 10.14 (s, 1 H), 7.97 (d, *J* = 7.8 Hz, 2 H), 7.58 (t, *J* = 7.2 Hz, 1 H), 7.49 (t, *J* = 7.8 Hz, 2 H), 7.35–7.28 (m, 9 H), 7.11–7.10 (m, 2 H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 191.5, 187.4, 141.4, 139.2, 138.2, 132.7, 131.3, 129.8, 129.7, 129.6, 129.3, 129.1, 128.6, 128.4, 126.2, 124.7, 123.0; **IR** (KBr, neat) 2923, 1682, 1499, 1227, 764, 699 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{18}NO_2$ $(M + H)^+$ 352.1332, found 352.1337.

4-(4-Chlorobenzoyl)-2-(4-chlorophenyl)-1-phenyl-1*H*-pyrrole-3-carbaldehyde (25aa):



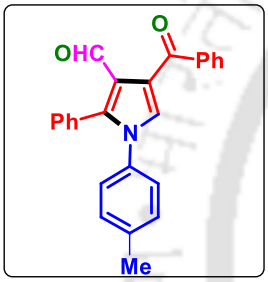
Pale yellow solid; R_f (hexane/EtOAc, 8:2) 0.50; mp 110–112 °C. Yield 49 mg, 58%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 10.14 (s, 1 H), 7.90 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.36–7.35 (m, 3 H), 7.29–7.26 (m, 3 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 7.1–7.09 (m, 2 H), **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 123.2, 124.6, 126.2, 127.5, 128.8, 128.9, 129.0, 129.8, 129.9, 131.0, 132.6, 135.6, 137.5, 137.9, 139.2, 139.7, 187.1, 190.1; **IR** (KBr, neat) 2925, 1678, 1481, 1227, 759 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{16}Cl_2NO_2$ $(M + H)^+$ 420.0553, found 420.0554.

4-(4-Bromobenzoyl)-2-(4-bromophenyl)-1-phenyl-1*H*-pyrrole-3-carbaldehyde (25ab):



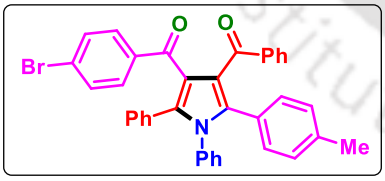
Reddish brown solid; R_f (hexane/EtOAc, 8:2) 0.50; mp 115–117 °C. Yield 61mg, 60%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 10.15 (s, 1 H), 7.82 (d, *J* = 8.4 Hz, 2 H), 7.63 (d, *J* = 8.4 Hz, 2 H), 7.44 (d, *J* = 8.4 Hz, 2 H), 7.36–7.35 (m, 3 H), 7.27 (d, *J* = 6.4 Hz, 1 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 7.10–7.08 (m, 2 H), **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ190.2, 187.1, 139.7, 137.9, 137.8, 132.8, 132.0, 131.7, 131.1, 130.0, 129.8, 128.0, 127.8, 126.6, 124.0, 123.2; **IR** (KBr, neat) 2926, 1678, 1476, 1266, 754 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{16}Br_2NO_2$ $(M + H)^+$ 507.9542, found 507.9547.

4-Benzoyl-2-phenyl-1-(*p*-tolyl)-1*H*-pyrrole-3-carbaldehyde (25ac):



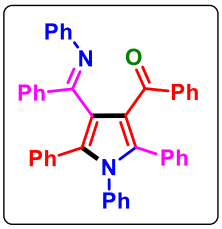
Reddish brown gummy; R_f (hexane/EtOAc, 8:2) 0.50; Yield 37 mg, 50%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ10.13 (s, 1 H), 7.96 (d, *J* = 7.2 Hz, 2 H), 7.58 (t, *J* = 7.2 Hz, 1 H), 7.48 (t, *J* = 7.8 Hz, 2 H), 7.36–7.30 (m, 3 H), 7.28–7.25 (m, 3 H), 7.10 (d, *J* = 8.2 Hz, 2 H), 6.98 (d, *J* = 8.2 Hz, 2 H), 2.33 (s, 3 H), **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 191.5, 187.4, 141.4, 139.3, 138.6, 135.7, 132.7, 131.3, 130.1, 129.9, 129.7, 129.2, 128.6, 128.3, 125.9, 124.6, 123.0, 21.3; **IR** (KBr, neat) 2923, 1674, 1479, 1224, 702 cm^{-1}; **HRMS** (ESI) calcd. for $C_{25}H_{20}NO_2$ $(M + H)^+$ 366.1489, found 366.1489.

4-Benzoyl-1,2-diphenyl-5-(*p*-tolyl)-1*H*-pyrrol-3-yl)(4-bromophenyl)methanone (25ad), and 21i (21ad:21i = 1:1)



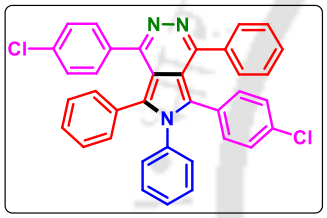
Brown gummy; R_f (hexane/EtOAc, 4:1) 0.50; Yield 40 mg; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58–7.56 (m, 3 H), 7.51–7.47 (m, 4 H), 7.31–7.25 (m, 3 H), 7.20–7.11 (m, 14 H), 7.10–7.02 (m, 8 H), 6.96–6.89 (m, 12 H), 6.84 (d, *J* = 7.8 Hz, 2 H), 2.26 (s, 3 H), 2.25 (s, 3 H), 2.17 (s, 3 H); **HRMS** (ESI) calcd. for **2ad**-$C_{37}H_{27}BrNO_2$ $(M + H)^+$ 596.1220, found 596.1244; **2i**-$C_{38}H_{30}NO_2$ $(M + H)^+$ 532.2271, found 532.2294.

(*E*)-Phenyl(1,2,5-triphenyl-4-(phenyl(phenylimino)methyl)-1*H*-pyrrol-3-yl)methanone (25a′):



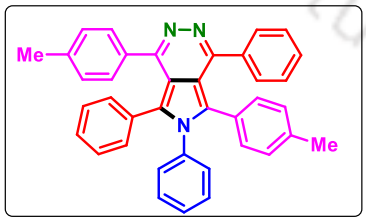
Pale yellow solid; R_f (hexane/EtOAc, 8:2) 0.50; mp 168–170 °C .Yield 45 mg, 39%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.10–7.97 (m, 2 H), 7.40 (d, *J* = 7.6 Hz, 2 H), 7.3–7.28 (m, 3 H), 7.14–7.06 (m, 6 H), 6.97–6.88 (m, 8 H), 6.80–6.78 (m, 3 H), 6.85 (t, *J* = 7.6 Hz, 2 H), 6.57 (d, *J* = 7.6 Hz, 2 H), 6.54 (d, *J* = 7.6 Hz, 2 H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 192.6, 163.8, 151.9, 140.8, 138.5, 137.9, 137.4, 134.4, 130.0, 129.6, 128.8, 128.6, 128.3, 128.0, 127.9, 127.5, 127.4, 124.3, 122.9, 121.0; **IR** (KBr, neat) 2925, 1634, 1594, 1207, 737, 695 cm^{-1}; **HRMS** (ESI) calcd. for $C_{42}H_{31}N_2O$ $(M + H)^+$ 579.2431, found 579.2422.

1,5-bis(4-Chlorophenyl)-4,6,7-triphenyl-6*H*-pyrrolo[3,4-*d*]pyridazine (26e):



Pale yellow solid; R_f (hexane/EtOAc, 4:6) 0.50; mp 203–205 °C. Yield 145 mg, 64%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.2 Hz, 2 H), 7.29–7.27 (m, 2 H), 7.26–7.23 (m, 2 H), 7.20 (t, *J* = 7.2 Hz, 2 H), 7.15–7.08 (m, 3 H), 7.01 (d, *J* = 8.4 Hz, 2 H), 6.99–6.94 (m, 4 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 6.78 (d, *J* = 7.2 Hz, 2 H), 6.69 (d, *J* = 8.4 Hz, 2 H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 137.3, 137.0, 135.6, 134.0, 132.9, 131.8, 130.8, 130.6, 129.6, 129.3, 129.0, 128.9, 128.8, 128.5, 128.0, 127.8, 127.7, 127.6, 127.5, 127.2; **IR** (KBr, neat) 2926, 1669, 1494, 1089, 697 cm^{-1}; **HRMS** (ESI) calcd. for $C_{36}H_{23}Cl_2N_3$ $(M + H)^+$ 568.1342, found 568.1342.

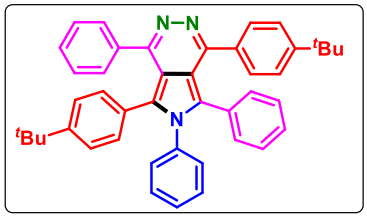
1,5,6-Triphenyl-4,7-di-*p*-tolyl-6*H*-pyrrolo[3,4-*d*]pyridazine (26i):



Pale yellow solid; R_f (hexane/EtOAc, 3:7) 0.50; mp 235–237 °C. Yield 149 mg, 71%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.2 Hz, 2 H), 7.24–7.20 (m, 3 H), 7.19–7.15 (m, 3 H), 7.06–7.01 (m, 3 H), 6.96 (d, *J* = 7.6 Hz, 2 H), 6.90 (t, *J* = 7.8 Hz, 2 H), 6.82 (d, *J* = 7.8 Hz, 2 H), 6.77 (d, *J* = 7.2 Hz, 2 H), 6.70 (d, *J* = 8.0 Hz, 2 H), 6.64 (d, *J* = 8.0 Hz, 2 H), 2.26 (s, 3H), 2.20 (s, 3 H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 155.8, 155.7, 137.9, 137.8, 137.4, 137.2, 134.3, 131.9, 131.6, 131.1, 129.6, 129.4, 129.3, 128.7, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.4, 127.3, 115.0, 114.9, 21.5, 21.4; **IR** (KBr, neat) 2960,

1667, 1409, 1266, 697 cm^{-1}; **HRMS** (ESI) calcd. for $C_{38}H_{30}N_3$ $(M + H)^+$ 528.2434, found 528.2435.

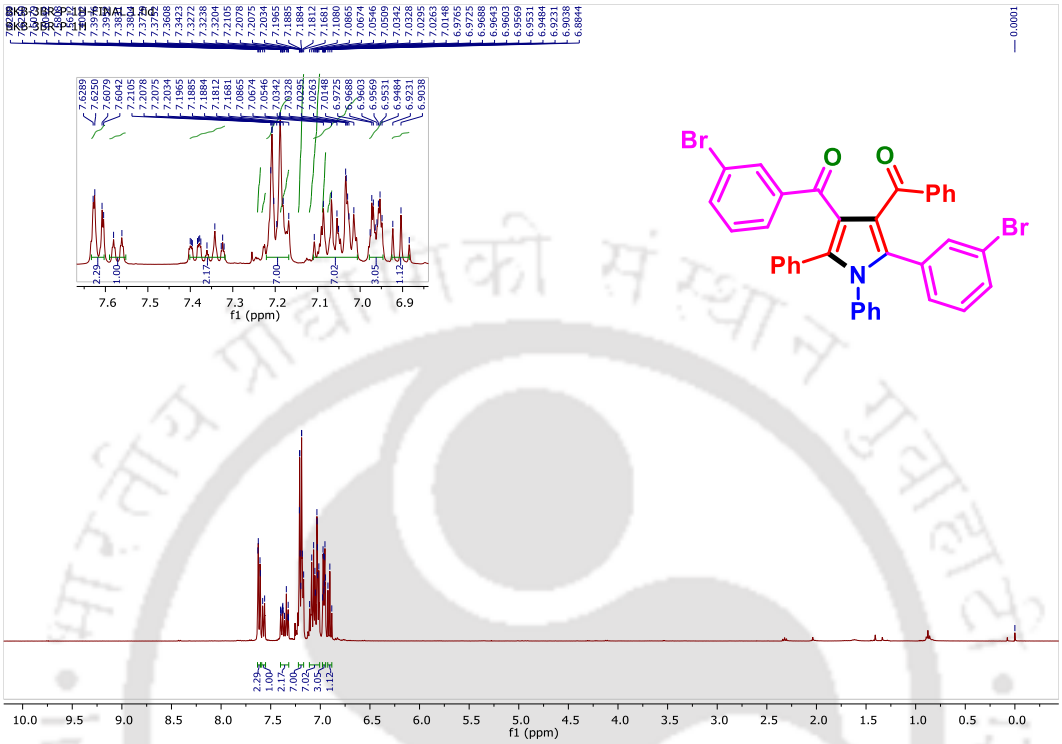
1,5-bis(4-(*tert*-Butyl)phenyl)-4,6,7-triphenyl-6*H*-pyrrolo[3,4-*d*]pyridazine (26 j):



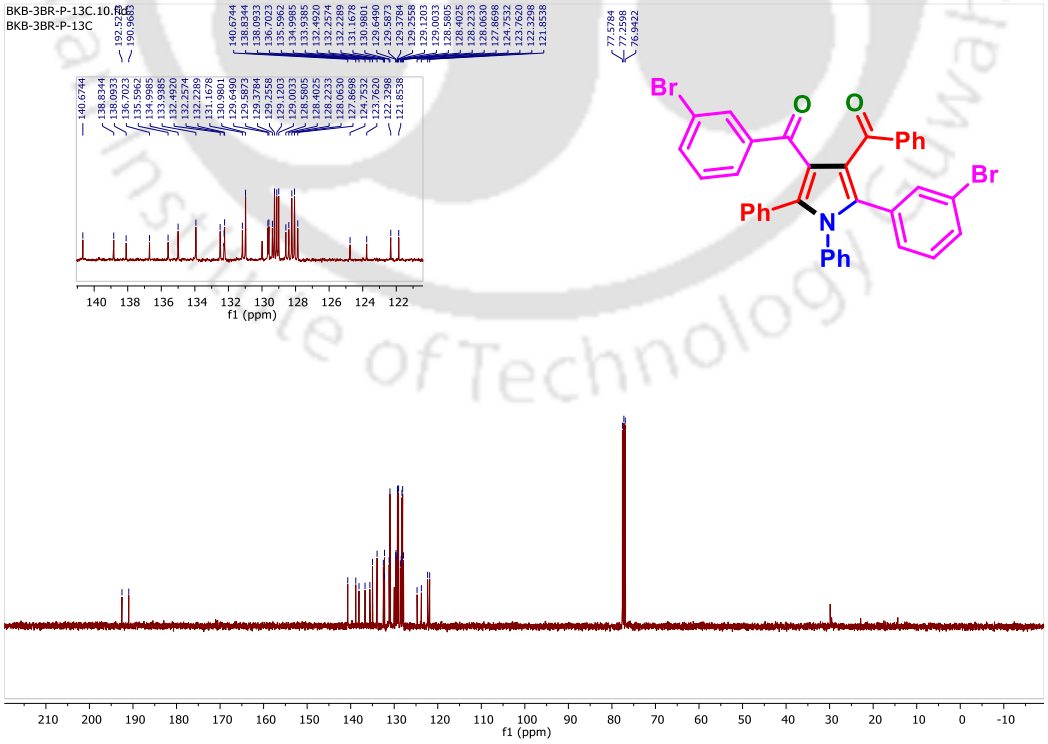
Pale yellow solid; R_f (hexane/EtOAc, 4:6) 0.50; mp 216–218 °C. Yield 185 mg, 76%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.2 Hz, 2 H), 7.25–7.21 (m, 3 H), 7.18 (t, *J* = 7.2 Hz, 2 H), 7.12 (t, *J* = 7.4 Hz, 1 H), 7.04–6.98 (m, 7 H), 6.89–6.85 (m, 4 H), 6.74 (d, *J* = 7.2 Hz, 2 H), 6.67 (d, *J* = 8.2 Hz, 2 H), 1.26 (s, 9 H), 1.22 (s, 9 H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 156.0, 155.9, 151.1, 150.6, 137.7, 137.0, 133.9, 131.8, 131.3, 131.0, 129.5, 129.3, 129.0, 128.9, 128.7, 128.6, 128.5, 128.0, 127.6, 127.4, 127.3, 124.4, 124.3, 115.2, 115.0, 34.7, 34.6, 31.5, 31.4; **IR** (KBr, neat) 2960, 1666, 1409, 1266, 697 cm^{-1}; **HRMS** (ESI) calcd. for $C_{44}H_{42}N_3$ $(M + H)^+$ 612.3373, found 612.3381.

2.9. Representative Spectra

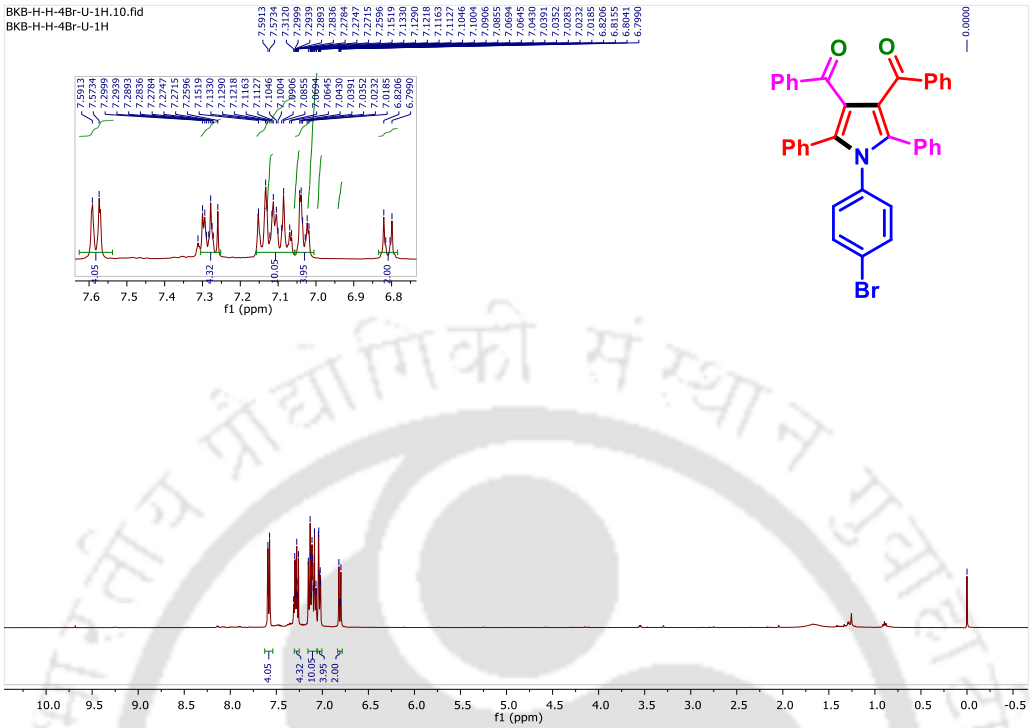
^{1}H NMR spectrum of compound **25c** (400 MHz, $CDCl_3$)



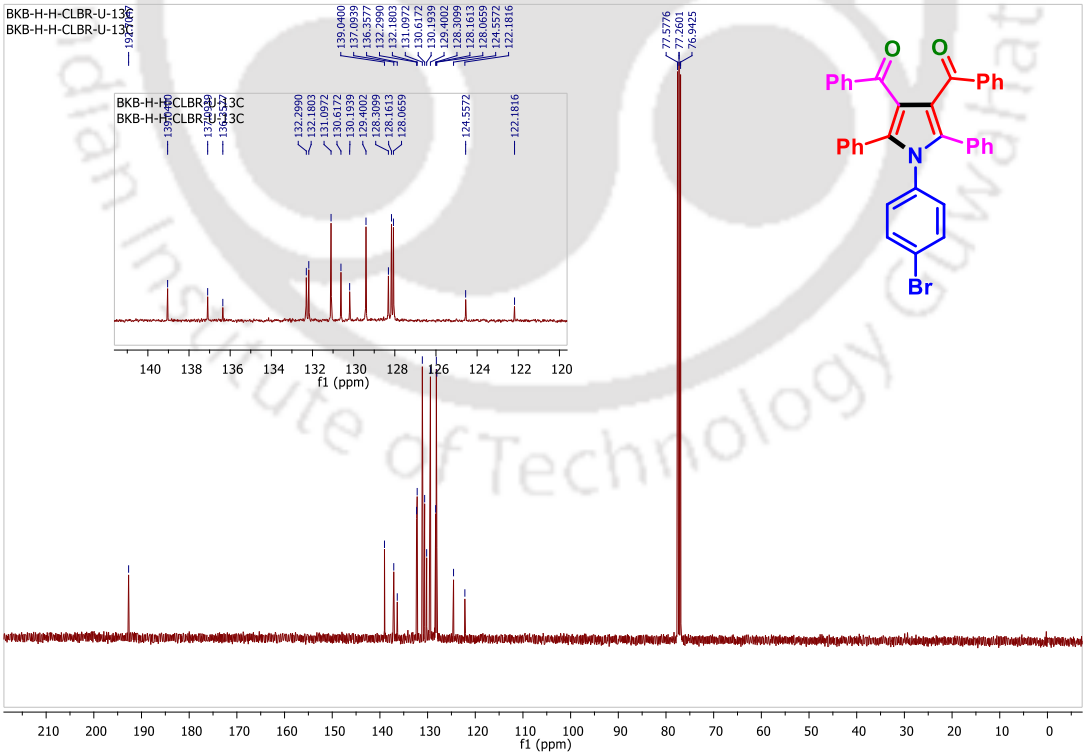
^{13}C{^{1}H} NMR spectrum of compound **25c** (100 MHz, $CDCl_3$)



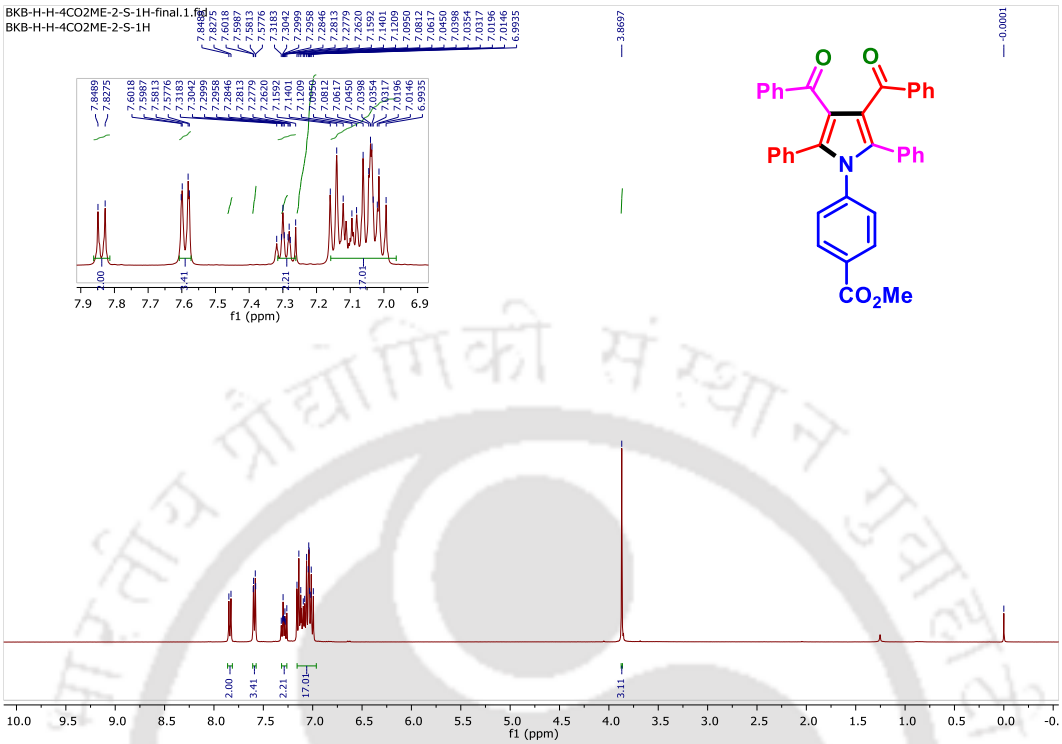
^{1}H NMR spectrum of compound **25s** (400 MHz, $CDCl_3$)



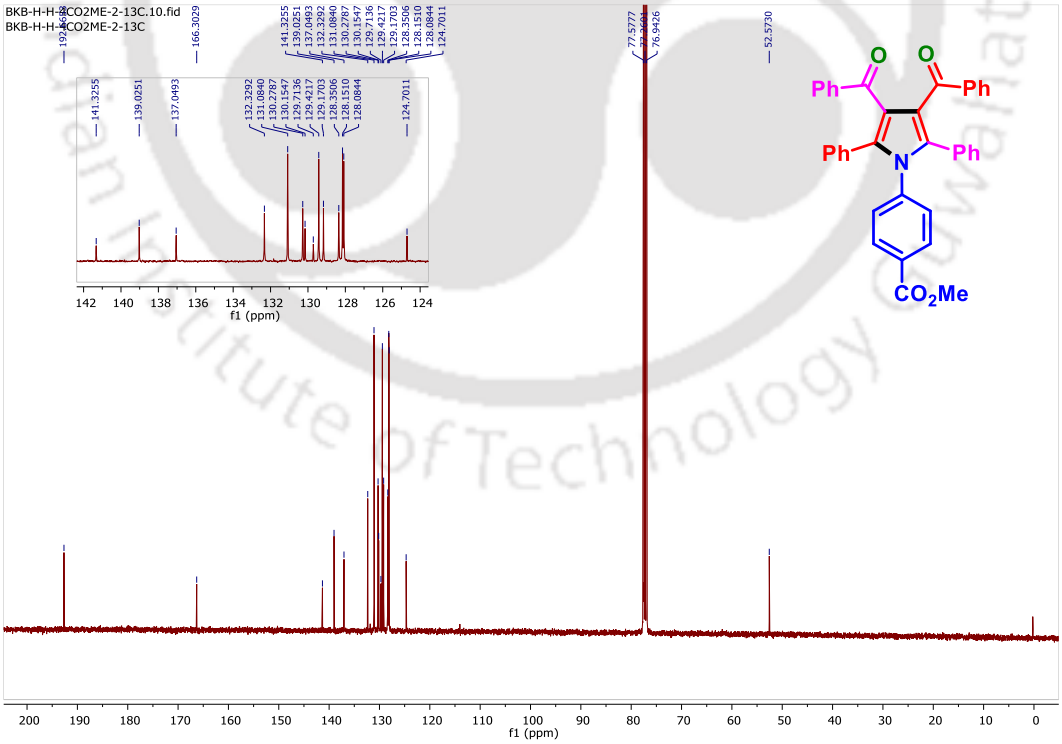
^{13}C{^{1}H} NMR spectrum of compound **25s** (100 MHz, $CDCl_3$)



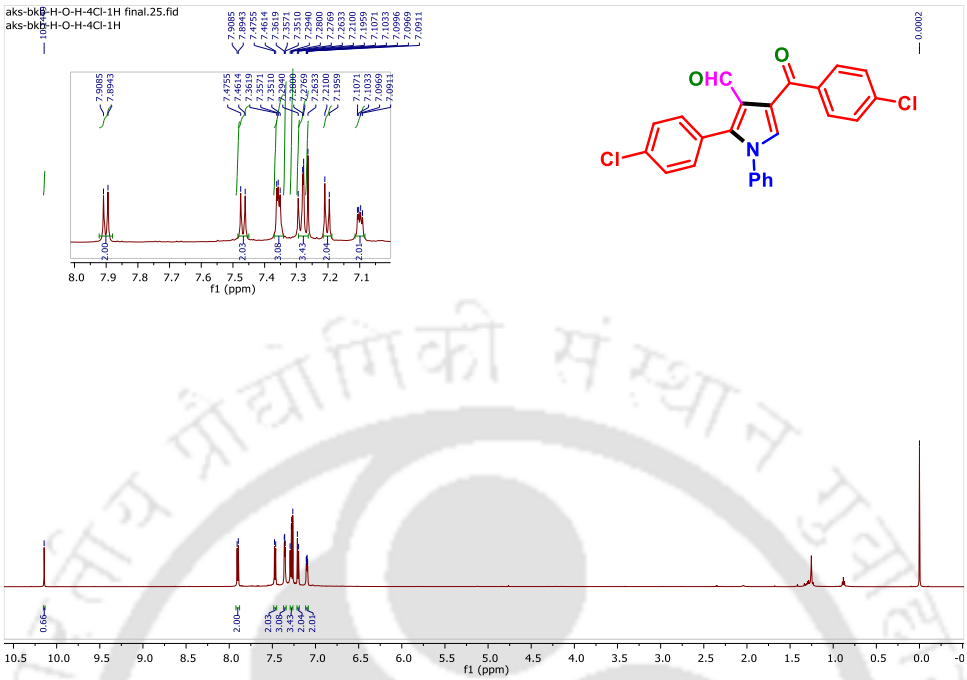
^{1}H NMR spectrum of compound **25t** (400 MHz, $CDCl_3$)



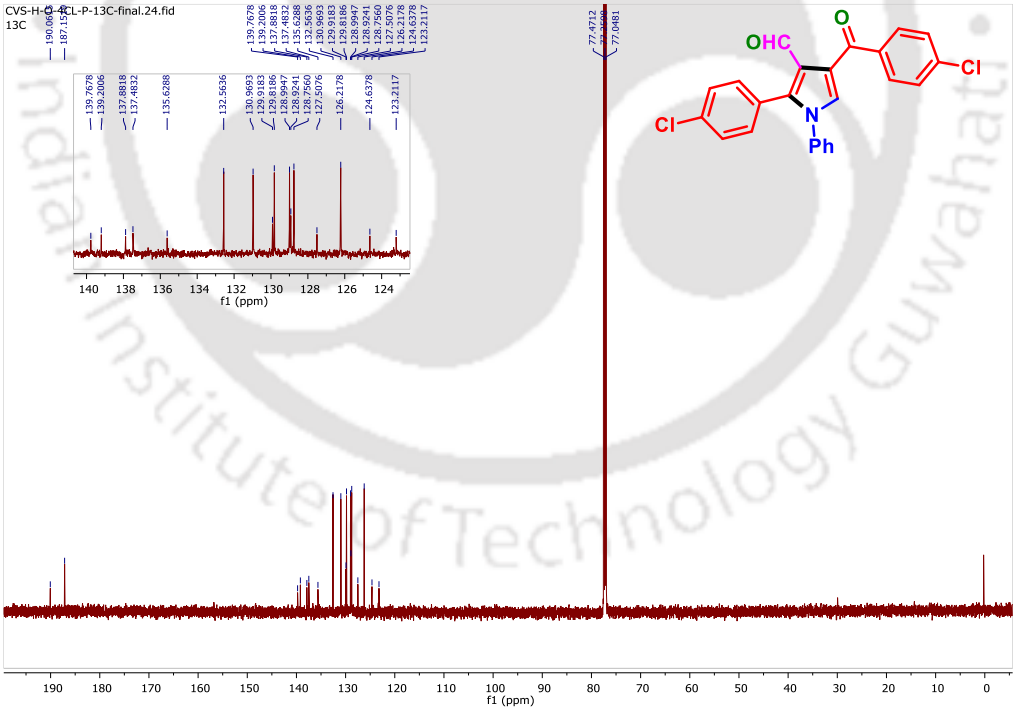
^{13}C{^{1}H} NMR spectrum of compound **25t** (100 MHz, $CDCl_3$)



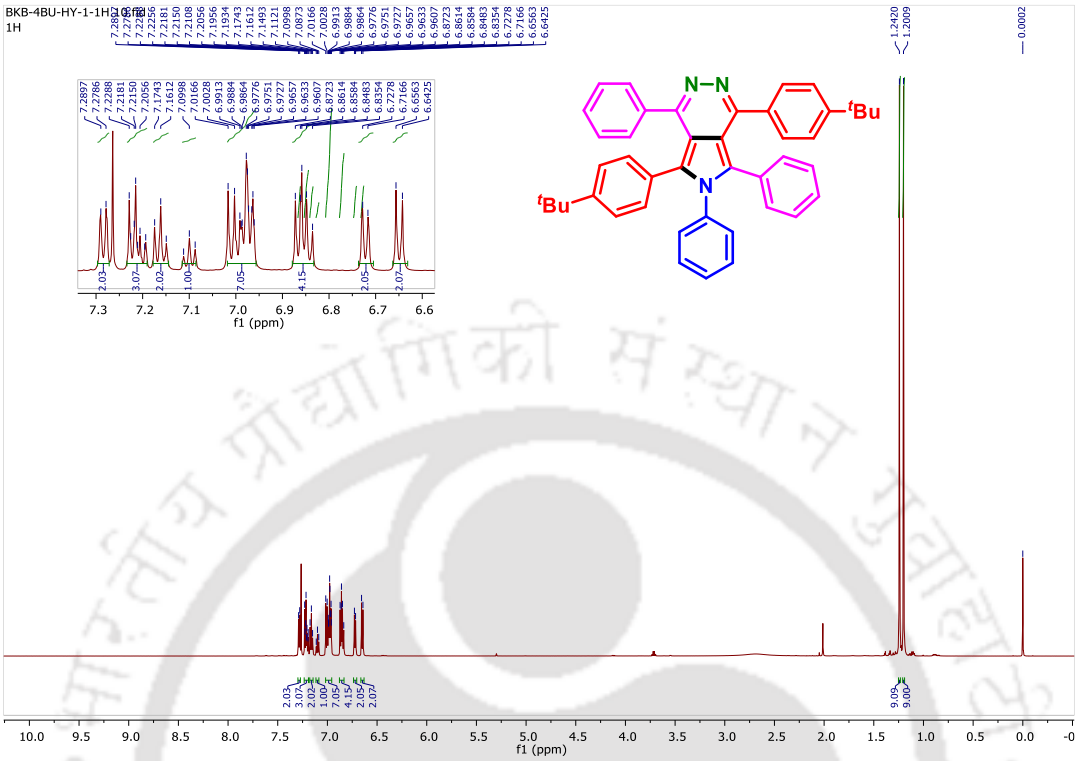
^{1}H NMR spectrum of compound **25aa** (400 MHz, $CDCl_3$)



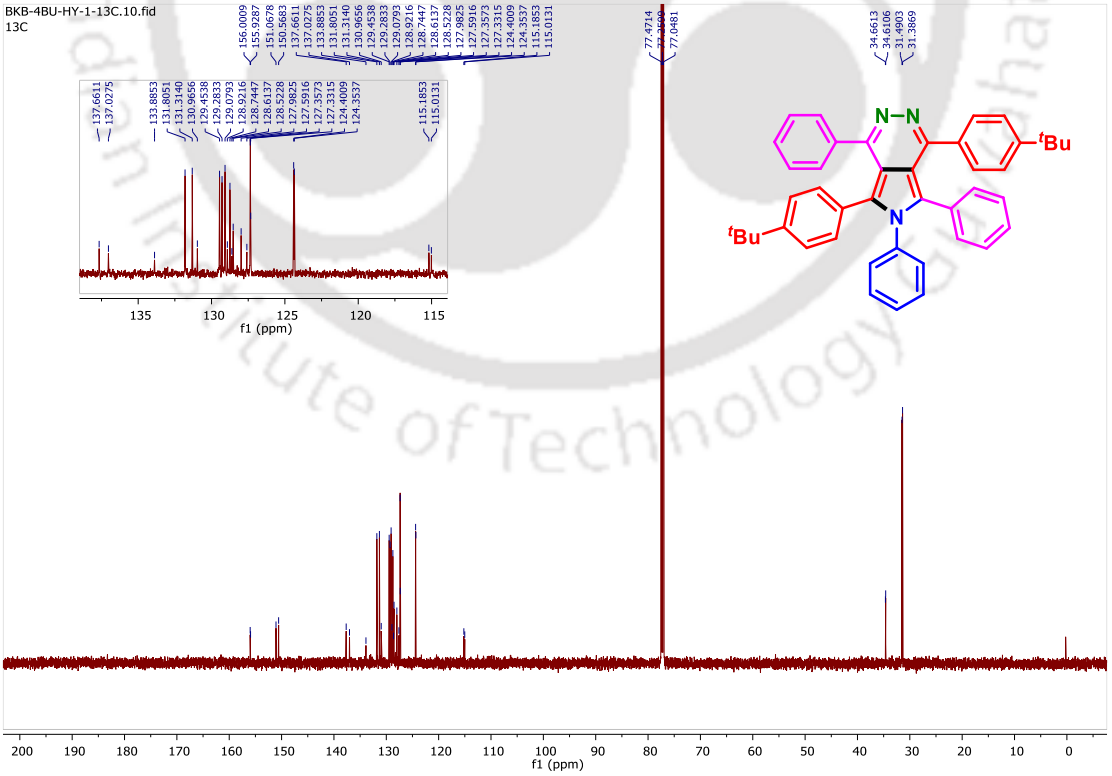
^{13}C{^{1}H} NMR spectrum of compound **25aa** (100 MHz, $CDCl_3$)



^{1}H NMR spectrum of compound **26j** (400 MHz, $CDCl_3$)



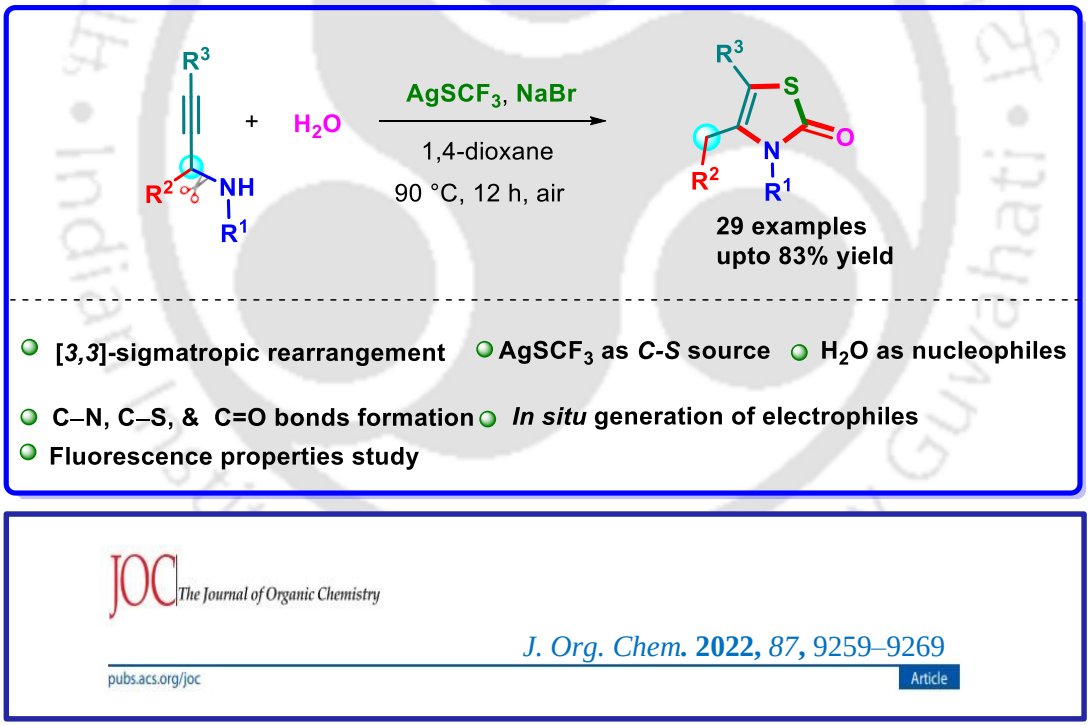
^{13}C{^{1}H} NMR spectrum of compound **26j** (100 MHz, $CDCl_3$)



CHAPTER 3

Synthesis of Thiazole-2(3*H*)-ones *via* [3,3]-Sigmatropic Rearrangement/5-*exo*-dig Cyclization of *N*-Propargylamines

Abstract: This chapter represents an efficient methodology for the synthesis of both di- and trisubstituted thiazol-2-ones from *N*-propargylamines *via* [3,3]-sigmatropic rearrangement/5-*exo*-dig cyclization. The protocol utilizes silver(I) trifluoromethanethiolate ($AgSCF_3$) as a *C*–*S* source and eco-friendly H_2O as nucleophile under open air condition. The methodology can be extended for the synthesis of bioactive analog of thiozole-2-thione derivatives and photophysical properties have been studied for some synthesized compounds.



3.1. Introduction

The thiazolone belongs to an important class of five-membered heterocyclic skeletons which ubiquitously occur in natural products and pharmacologically active molecules.[1] Among them, thiazol-2-one derivatives have widespread applications in pharmacological profiles and broad biological activities including anti-mycobacterial and antitumor activities.[2] For instance, sibenadet (**A**)[3] is a β_2-adrenoreceptor agonist for the treatment of asthma; isatoribine (**B**)[4] is a selective agonist of TLR7; tiaramide (**C**)[5a] is commonly used as nonsteroidal anti-inflammatory and analgesic drugs; chlobenthiazone (**D**)[5b] is widely used as herbicides and fungicides in agriculture; compound **E** is an inhibitor of the histone reader BRD4 bromodomain;[5c] pioglitazone (**F**)[5d] is an antidiabetic agent (*Figure 3.1*). Owing to their importance in agriculture, pharmaceutical and material chemistry, there is a need to develop a new and efficient methodology for the synthesis of highly substituted thiazol-2-one derivatives.

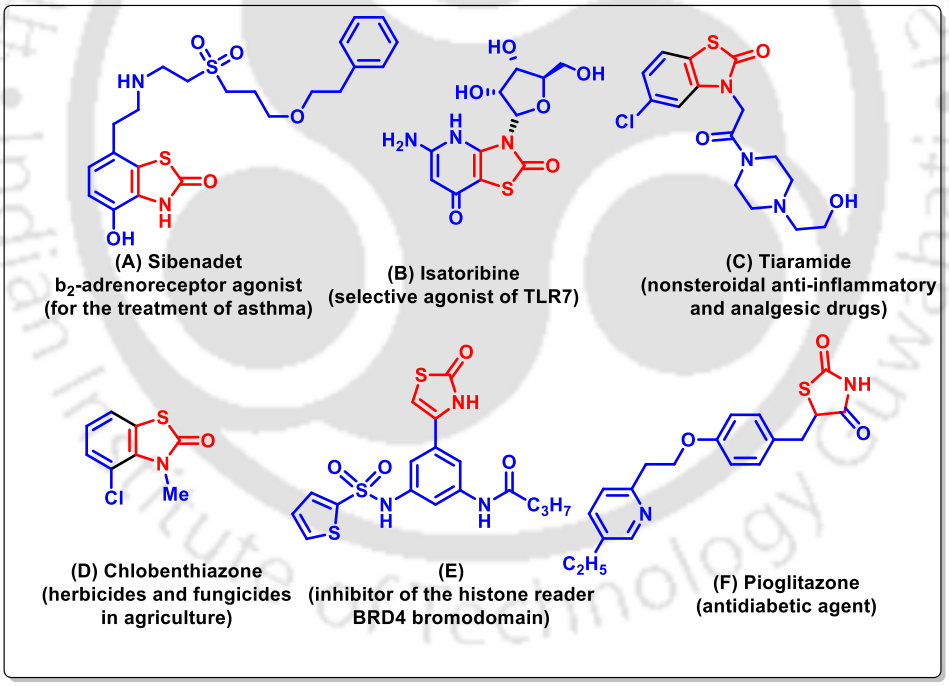
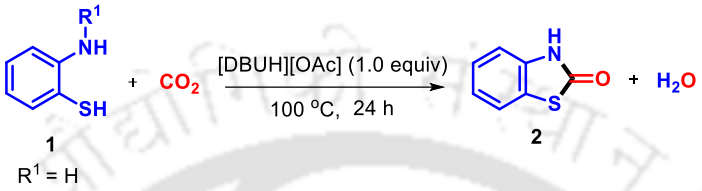


Figure 3.1. *Examples of Bioactive Thiazol-2-one.*

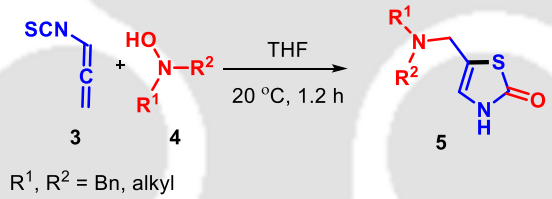
3.2. Literature Survey for the Synthesis of Substituted Thiazol-2-one Derivatives

Liu and co-workers described an efficient DBU based ionic-liquid catalyzed, one-pot two component synthesis of benzothiazol-2-one **2** derivatives in good yields. The reaction utilizes aminothiophenol **1** and CO_2 as carbonyl source under solvent free condition (*scheme 3.2.1*).[6a]



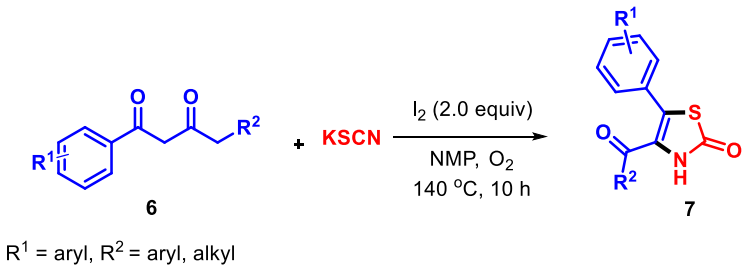
Scheme 3.2.1. *Ionic-liquid Catalyzed Synthesis of Benzothiazol-2-one from Aminothiophenol.*

In 2014, Lang and co-workers explored a useful transition metal free intramolecular cyclization between allenylisothiocyanates **3** with *N*, *N*-disubstituted hydroxylamines **4** that leads to substituted thiazol-2-one **5** in THF at room temperature (*scheme 3.2.2*).[6b]



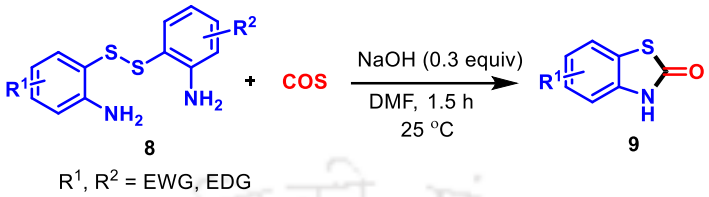
Scheme 3.2.2. *Synthesis of Thiazol-2ones by Nucleophilic Addition of Allenylisothiocyanates.*

A comprehensive iodine promoted synthesis of substituted thiazol-2(3*H*)-one **7** derivatives *via* [3+2] cyclization of active-methylene compounds containing diketone **6** with KSCN was reported by Yan and co-workers in 2021. The reaction was performed at high temperature conditions by using *N*-methyl-2-pyrrolidone (NMP) as a solvent (*scheme 3.2.3*).[6c]



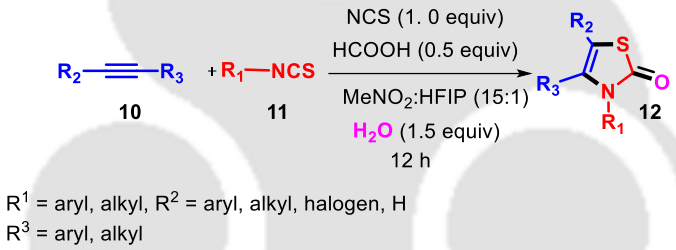
Scheme 3.2.3. *Synthesis of Thiazol-2-one via [3+2] Cyclization of Diketones and KSCN.*

Zhu and co-workers has developed an efficient and highly atom economic strategy towards the synthesis of the benzothiazol-2-one **9** scaffold by treatment of disulfide derivatives **8** with carbonyl sulfide(COS) in presence strong base NaOH in DMF at room temperature (*scheme 3.2.4*).[6d]



Scheme 3.2.4. *Synthesis of Benzothiazol-2-ones by Cascade Reaction of Disulfide and COS.*

Very recently, Jiang and co-workers reported an interesting method for synthesis of non-aromatic five membered thiazol-2(3*H*)-one derivativs **12** using alkyne **10**, isothiocyanates derivatives **11** and water as a solvent. The reaction proceeds in presence of *N*-chlorophthalimide (NCPI) as a radical initiator and is compatible with a broad range of substrates (*scheme 3.2.5*).[6e]

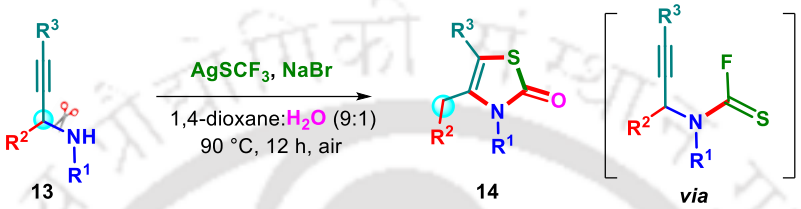


Scheme 3.2.5*. Synthesis of Non-aromatic Thiazol-2-ones from Alkynes via Domino Radical Cyclization.*

Present Work

Very recently, silver(I) trifluoromethanethiolate ($AgSCF_3$) was found to be a useful reagent in different nucleophilic addition reactions, because -SCF_3 anion easily undergoes decomposition to form carbonothioicdifluoride ($S{=}CF_2$) and fluoride anion,[7] and of its characteristics of easy availability, good stability, low toxicity. In the other hand, the ease of preparation of *N*-propargylamines from aldehydes, amines and alkynes *via* A^3 coupling and their ability to form various nitrogen and sulfur heterocyclic compounds which is the core unit of different natural products.[8] In the past decades, several synthetic procedures have been developed for the synthesis of thiazol-2-one derivatives.[6] The major concerns of these reactions are the use of strong acid like

HCl, hazardous chemicals such as thiocyanates, isothiocyanates and limited substitution on the thiazol-2-one ring. Therefore, the development of more efficient and general strategies for the synthesis of thiazol-2-ones from easily and readily available starting materials is highly desirable, which still remains challenging. Keeping all these in mind, herein, we report the synthesis of thiazole-2-one derivatives *via* [3,3]-sigmatropic rearrangement and 5-*exo*-dig cyclization of *N*-propargylamines using $AgSCF_3$ as electrophile and H_2O as "oxygen" source (*Scheme 3.2.6*).

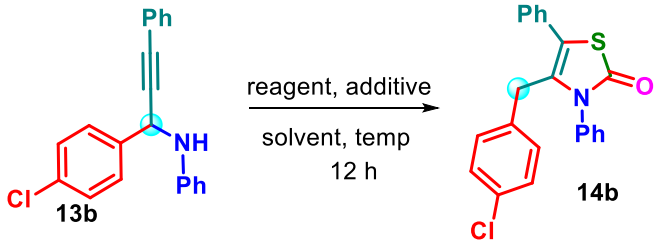


Scheme 3.2.6. *Synthesis of Highly Functionalized Thiazol-2-ones from N-propargylamines via [3,3]-Sigmatropic Rearrangement.*

3.3. Result and Discussion

Considering **13b** as model substrate, it was treated with 1.0 equiv of $AgSCF_3$ and 1.2 equiv of NaBr in acetonitrile at room temperature for 12 hours, but the starting material was recovered in 85% instead of desired product (*Table 3.3.1*, entry 1). When the reaction was performed at 80 ^oC, thiazol-2(3*H*)-one **14b** was obtained in 54% yield (*Table 3.3.1*, entry 2). In order to check the role of solvents, the reaction was conducted in different solvents like toluene, dimethylformamide (DMF) and chlorobenzene which produced 62, 30 and 60% yields (*Table 3.3.1*, entries 3-4 and 6), respectively, whereas no product was obtained in case of dimethylsulfoxide (DMSO) (*Table 3.3.1*, entry 5). On the other hand, an increased yield of 67% was observed in 1,4-dioxane (*Table 3.3.1*, entry 7). Inspired by this, the amounts of $AgSCF_3$ and NaBr were increased to 1.2 and 1.5 equiv, respectively, and to our delight the reaction gave 76% yield (*Table 3.3.1*, entry 8). When the reaction was performed in absence of water, the yield of the product was found to be 61% (*Table 3.3.1*, entry 9). Whereas, the reaction when performed in (1,4-dioxane: H_2O = 1:1), the yield diminished to 34% (*Table 3.3.1*, entry 10). It was observed that the reaction under the similar

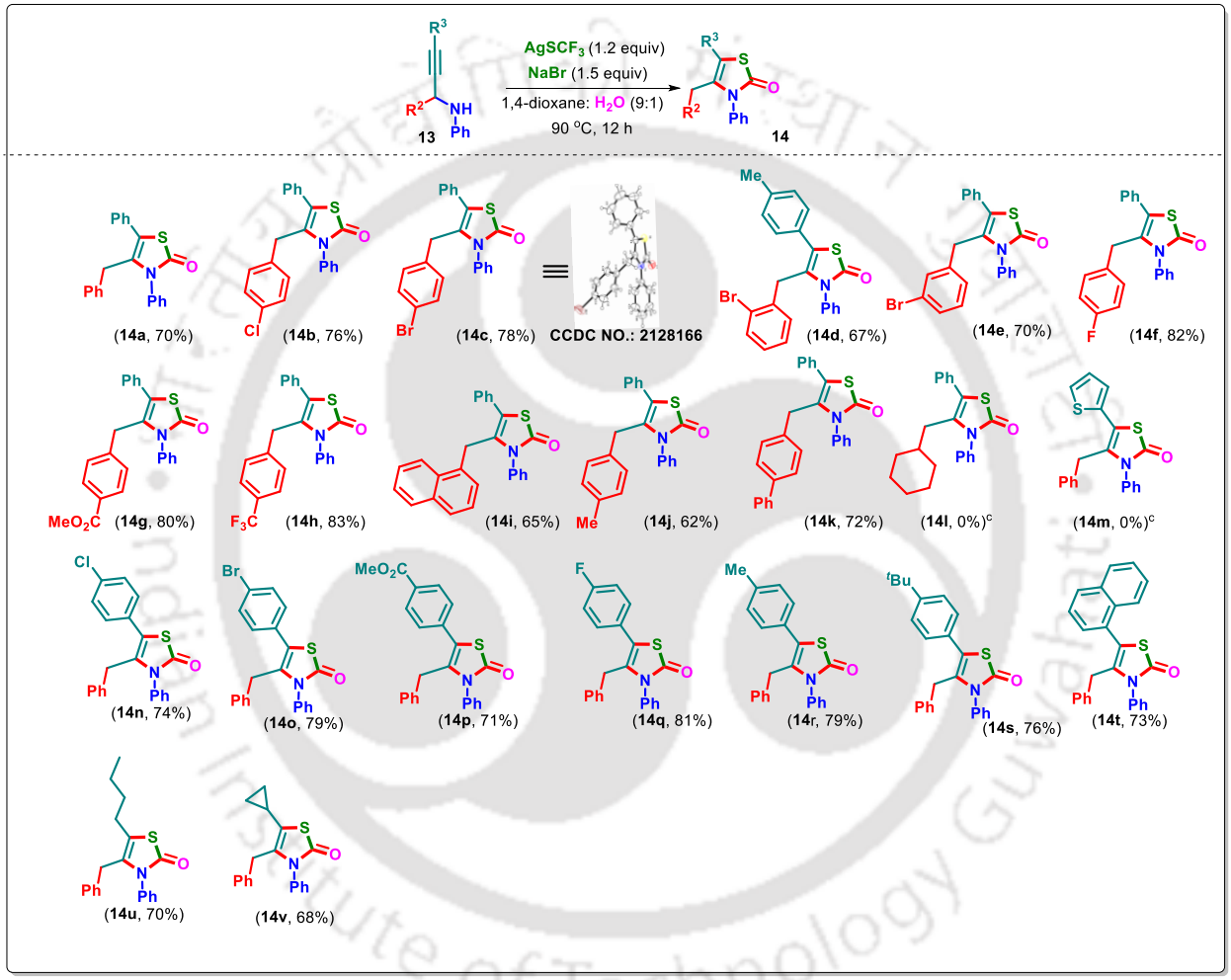
Table 3.3.1. Optimization of the Reaction [a]



Entry	Reagent (equiv)	Additive (equiv)	Solvent	T(°C)	%yield[b]
1	$AgSCF_3$ (1)	NaBr (1.2)	CH_3CN	rt	-[c]
2	$AgSCF_3$ (1)	NaBr (1.2)	CH_3CN/H_2O	80	54
3	$AgSCF_3$ (1)	NaBr (1.2)	toluene/H_2O	90	62
4	$AgSCF_3$ (1)	NaBr (1.2)	DMF/H_2O	90	30
5	$AgSCF_3$ (1)	NaBr (1.2)	DMSO/H_2O	90	-[c]
6	$AgSCF_3$ (1)	NaBr (1.2)	PhCl/H_2O	90	60
7	$AgSCF_3$ (1)	NaBr (1.2)	1,4-dioxane/H_2O	90	67
8	**$AgSCF_3$ (1.2)**	**NaBr (1.5)**	**1,4-dioxane/H_2O**	**90**	**76**
9	$AgSCF_3$ (1.2)	NaBr (1.5)	1,4-dioxane	90	61
10	$AgSCF_3$ (1.2)	NaBr (1.5)	1,4-dioxane/H_2O	90	34[d]
11	$AgSCF_3$ (1.2)	NaBr (1.5)	1,4-dioxane/H_2O	100	72
12	$AgSCF_3$ (1.5)	NaBr (2)	1,4-dioxane/H_2O	90	70
13	$AgSCF_3$ (1.2)	KBr (1.5)	1,4-dioxane/H_2O	90	74
14	$AgSCF_3$ (1.2)	LiBr (1.5)	1,4-dioxane/H_2O	90	Trace
15	$AgSCF_3$ (1.2)	Bu_4NI (1.5)	1,4-dioxane/H_2O	90	42
16	$AgSCF_3$ (1.2)	TBAB (1.5)	1,4-dioxane/H_2O	90	32
17	$AgSCF_3$ (1.2)	–	1,4-dioxane/H_2O	90	-[c]

[a]Reaction conditions: **13b** (0.4 mmol, 1.0 equiv), solvent 4.0 mL (9:1), 12 h, [b]Isolated yield, [c]No reaction,[d]solvent 4.0 mL (1:1).

With these optimal conditions in hand, the reaction was screened with substrates derived from different *N*-propargylamines. At first, substrates with different R^2 groups were investigated (*Scheme 3.3.2*). It was observed that phenyl **13a** as well as aromatic groups with electron-withdrawing substituent **13b-13c**, **13e-13h** gave good yields except for sterically hindered *o*-bromophenyl substituted substrate **13d**. Sterically hindered 1-naphthyl substituted substrate **13i** furnished a lower yield.

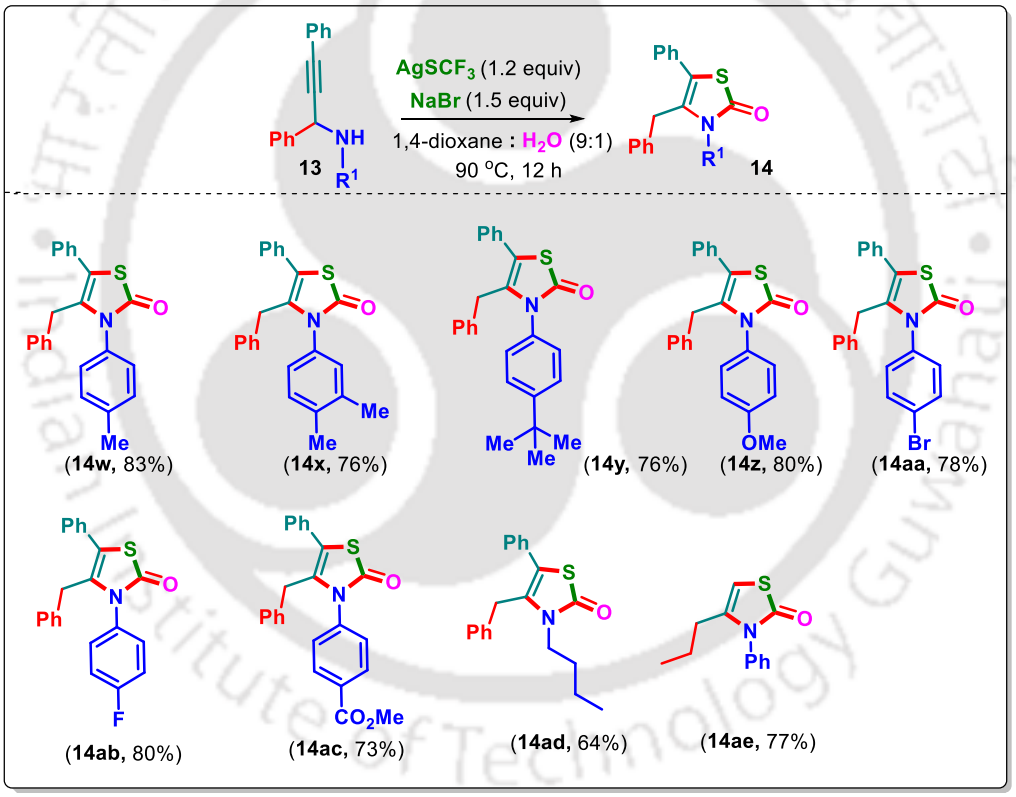


[a] Reaction condition: **13** (0.4 mmol), $AgSCF_3$ (0.48 mmol), NaBr (0.6 mmol) (1,4-dioxane: H_2O (9:1) in air for 12 h at 90 °C, [b]Isolated yield, [c]Inseperable mixture.

Scheme 3.3.2*. Scope of Substituted Thiazol-2-ones from N-propargylamines derived from different Aldehydes and Alkynes.*[a,b]

Substrate with biphenyl group **13k** also produced a good yield. On the other hand, substrates having an electron-donating methyl substituent on phenyl group compound **13j** gave lower yield whereas cyclohexyl group **13l** and alkyne substituted thiophenyl group **13m** gave an inseparable

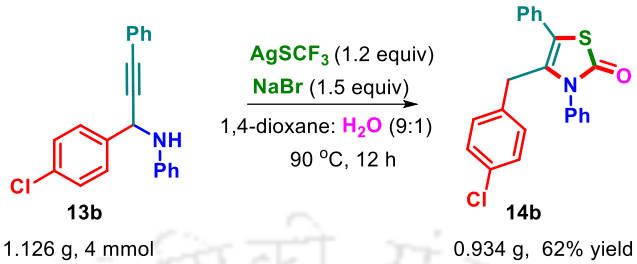
complex mixture. Also, different electron withdrawing substituents on R^3 in the alkyne side-chain **13n**-**13q** gave good yields (*Scheme 3.3.2*). Tolyl **13r**, *p-tert*-butyl phenyl substituted alkyne **13s**, butyl **13u** and cyclopropyl substituted alkyne **13v** produced moderate yields (*Scheme 3.3.2*). This is due to the reduction of electrophilicity of alkyne group by these electron-donating groups. There was no role of groups R^1 in the rate of the reaction as both electron-donating as well as electron-withdrawing groups produced similar yields except butyl substituted substrate compound **13ad** which yielded 64% of the product **14ad** and, in addition to the internal alkynes, terminal alkyne substituent **13ae** also produced a good yield (*Scheme 3.3.3*). The structure of compounds was determined by ^{1}H, ^{13}C{^{1}H} NMR spectroscopy, mass spectrometry and finally by *X*-ray crystallographic analysis.[9]



[a] Reaction condition: **13** (0.4 mmol), $AgSCF_3$ (0.48 mmol), NaBr (0.6 mmol) (1,4-dioxane: H_2O (9:1) in air for 12 h at 90 °C, [b]Isolated yield.

Scheme 3.3.3*. Scope of Substituted Thiazol-2-ones from N-propargylamines derived from different substituted Amines.*[a,b]

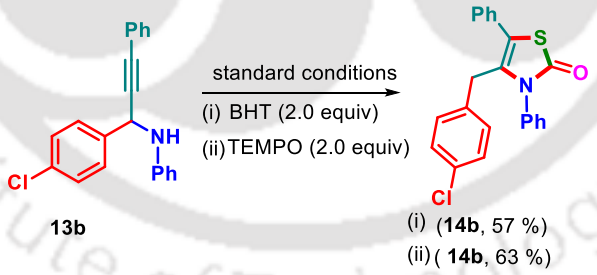
The scalability of the methodology was carried out with 4.0 mmol scale of compound **13b** and the yield of the product **14b** was found to be 62% (*Scheme 3.3.4*).



Scheme 3.3.4. *Gram-Scale Synthesis.*

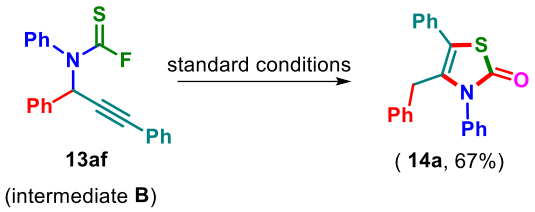
3.3.5. Control Experiments

To investigate the reaction pathway, initially, the reaction was performed separately in the presence of BHT and TEMPO. The reaction of **13b** with 2.0 equivalents of TEMPO gave the corresponding product **14b** with 63% yield under the standard reaction conditions. Similarly, same reaction when performed in presence of 2.0 equivalents of BHT furnished product **14b** with 57% yield (*Scheme 3.3.5a*) The above two radical scavenging agents did not inhibit the cyclization reactions. These results proved that the reaction might proceeds *via* an ionic pathway.



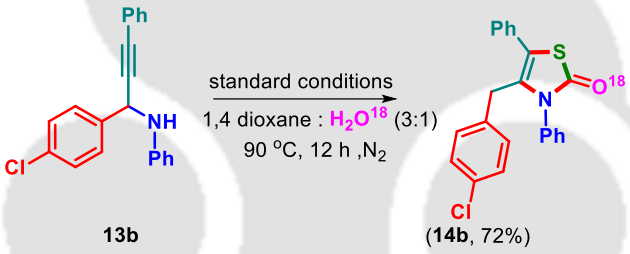
Scheme 3.3.5a. *To Confirm Reaction Pathway.*

Furthermore, intermediate[10] **13af**, was subjected to standard reaction conditions, the corresponding thiozole product **14a** was obtained in 67% yield (*Scheme 3.3.5b*). This confirms that the reaction proceeds *via* intermediate **13af**.



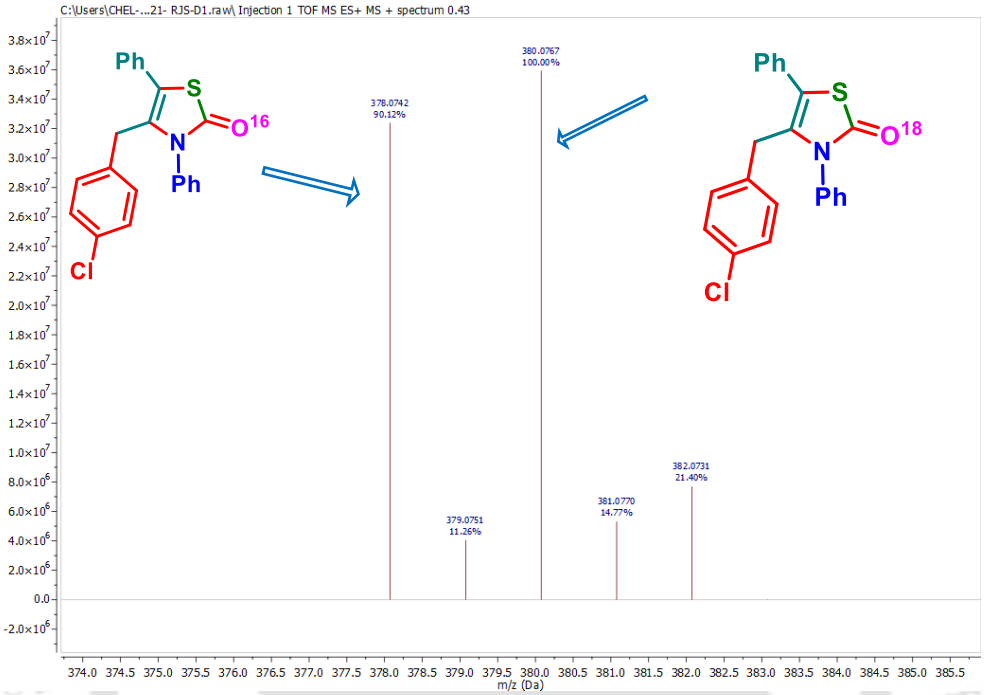
Scheme 3.3.5b. *To Confirm the Formation of Intermediate* ***B****.*

To identify the source of oxygen in product **14b**, the reaction of *N*-propargylamine **13b** was performed in presence of isotopically labelled H_2O^{18} under nitrogen atmosphere. The incorporation of an O^{18}-labeled product suggested that water was the source of oxygen in the keto group (*Scheme 3.3.5c*), which was confirmed through HRMS and NMR analysis. In the HRMS analysis, two peaks at 378.0742 (for unlabeled **14b**) and 380.0767 (for labelled **14b**) were observed indicating the involvement of O^{18} labelled water in the reaction. Again, in $^{13}C\{^1H\}$ NMR one extra peaks at 171.60 also indicates the presence of O^{18} oxygen in the molecule (*Figure 3.3.5c*).



Scheme 3.3.5c. *To Confirm Source of Oxygen.*

HRMS Spectrum of O^{18} Labelled Experiment of Compound **14b**



$^{13}C\{^{1}H\}$ NMR Spectrum of O^{18} Labelled Experiment of Compound **14b** (125 MHz, $CDCl_3$)

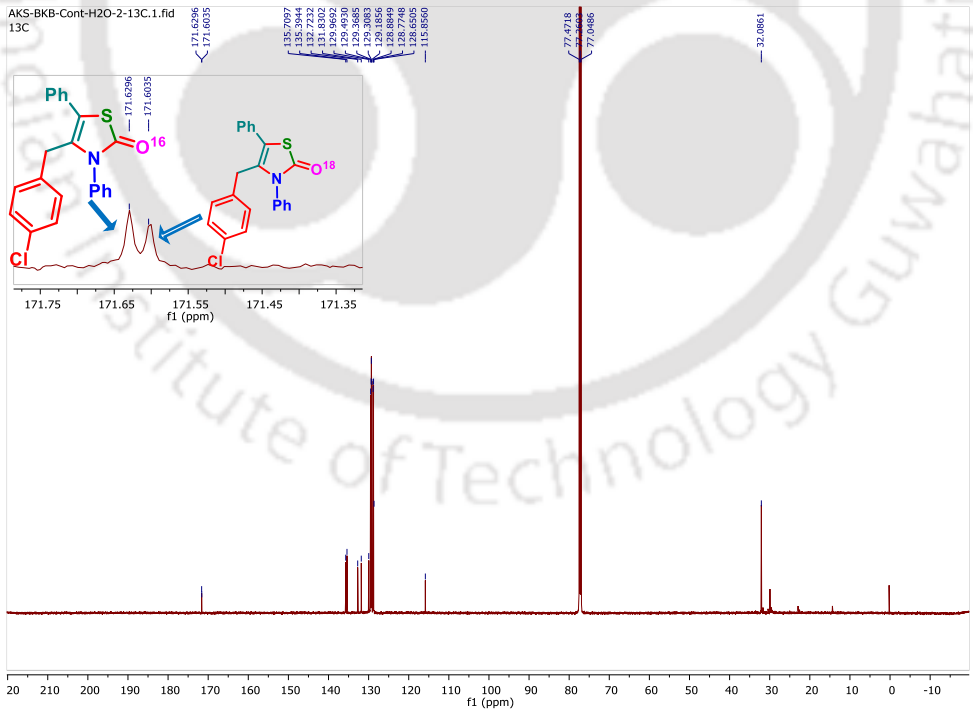
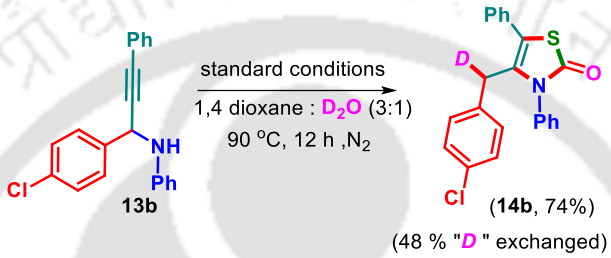


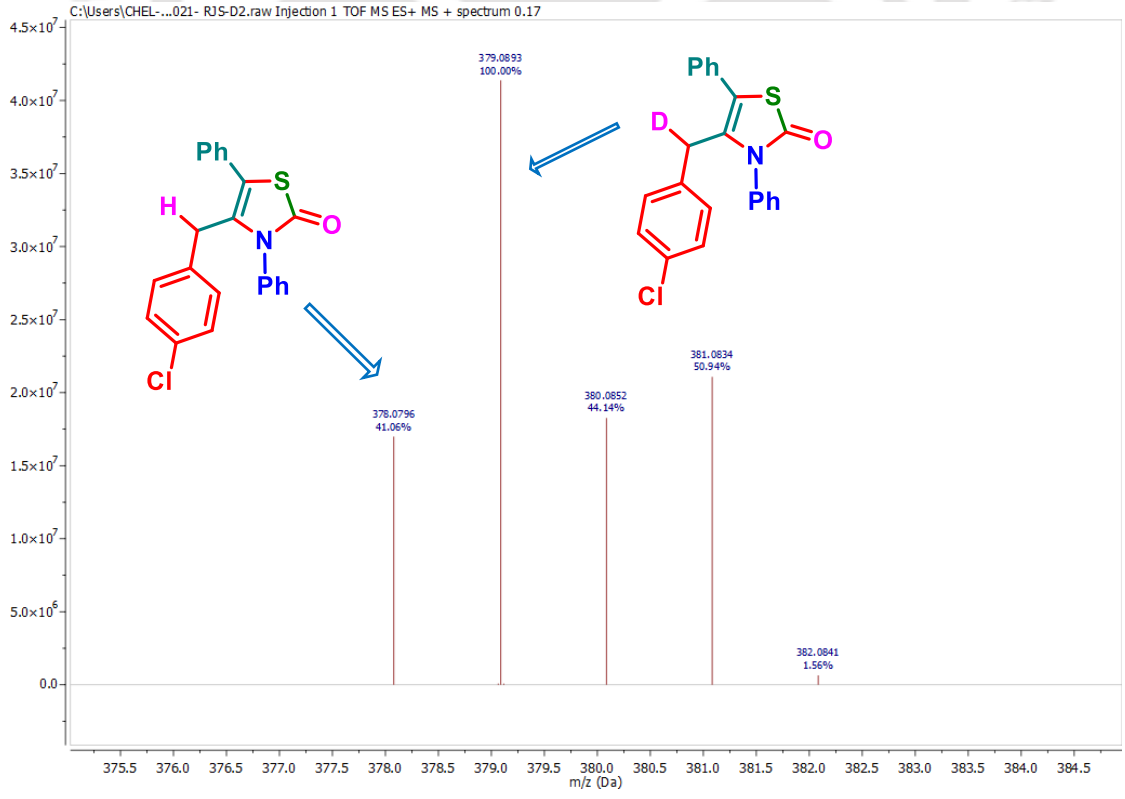
Figure 3.3.5c. *HRMS and $^{13}C\{^{1}H\}$ NMR Study for the H_2O^{18} Labelled Experiment During the Synthesis of Compound* ***14b****.*

Similarly, in order to ensure the source of benzylic protonation in product **14b**, the reaction of *N*-propargylamine 1**3b** was performed in presence of isotopically labelled D_2O under nitrogen atmosphere, 48% '*D*' exchanged product **14b** was obtained which suggested that water was the source for protonation (*Scheme 3.3.5d*). HRMS analysis showed peak at 379.0893 for '*D*' labelled **14b**; a new peak at 3.71 (with a 48% deuterium exchange) for methylene protons in ^{1}H NMR and a triplet at 31.8 (t, J = 18.8 Hz) in ^{13}C{^{1}H} NMR spectrum, also confirmed the participation of '*D*' labelled water in the reaction (*Figure 3.3.5d*).

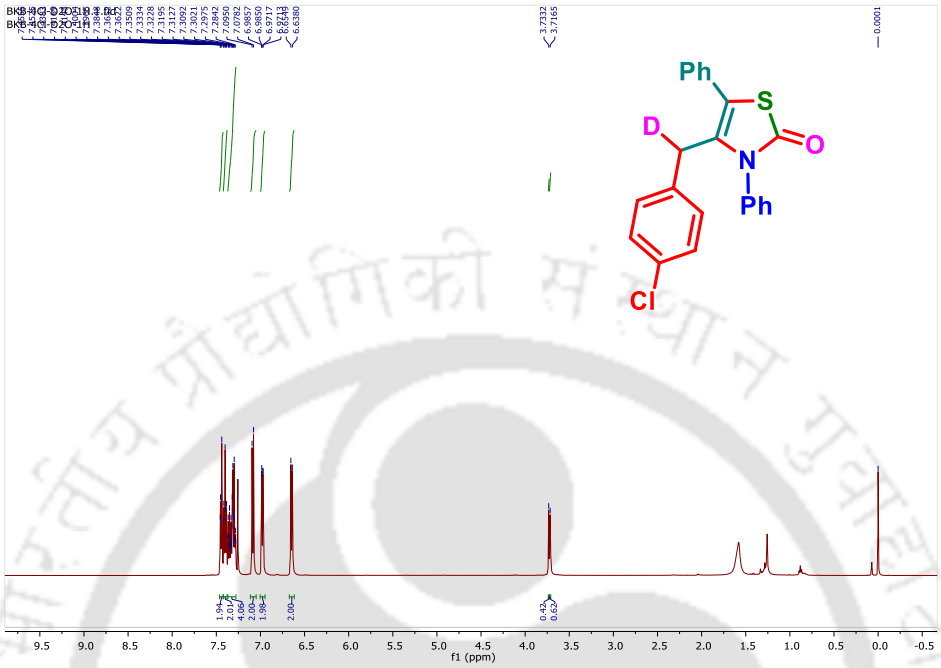


Scheme 3.3.5d. *To Confirm Source Benzylic Protonation.*

HRMS Spectrum of '*D*' Labelled Experiment of Compound **14b**



^{1}H NMR Spectrum of '*D*' Labelled Experiment of Compound **14b** (125 MHz, $CDCl_3$)



^{13}C{^{1}H} NMR Spectrum of '*D*' Labelled Experiment of Compound **14b** (125 MHz, $CDCl_3$)

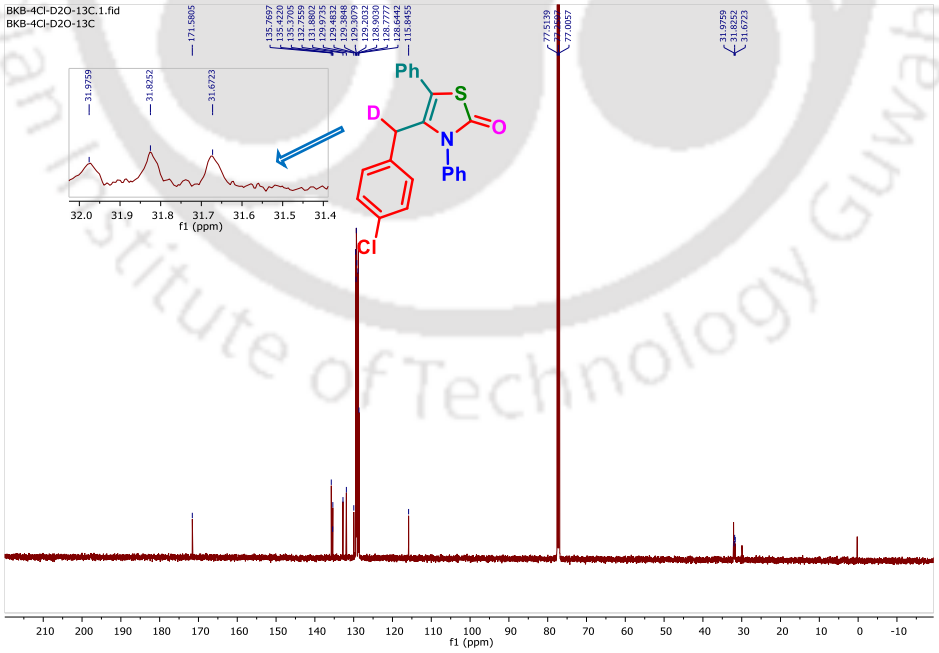
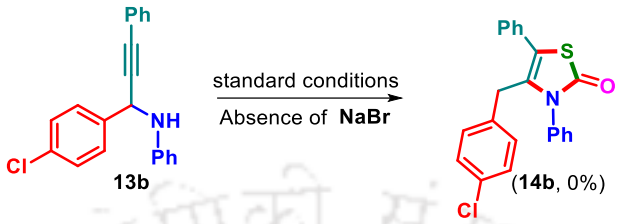


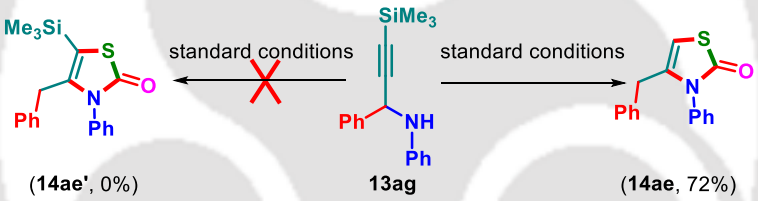
Figure 3.3.5d. *HRMS and ^{1}H, ^{13}C{^{1}H} NMR Study for the Deuterium Labelled Experiment During the Synthesis of Compound* ***14b****.*

The reaction of *N*-propargylamine **13b** was also performed in the absence of NaBr. Product **14b** was not observed, which signified the importance of NaBr in generating the electrophile CSF_2 for the nucleophilic attack to take place (*Scheme 3.3.5e*).



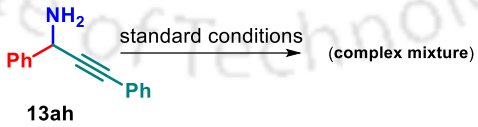
Scheme 3.3.5e. *To Confirm Role of Additive.*

Furthermore, for the detection of fluoride ions, trimethylsilyl substituted propargyl amine **13ag** was reacted under the standard reaction conditions. The formation of the product **14ae** *via* desilylation by *in situ* generated HF confirmed the presence of fluoride ions (*Scheme 3.3.5f*).



Scheme 3.3.5f. *Detection of Fluoride ions.*

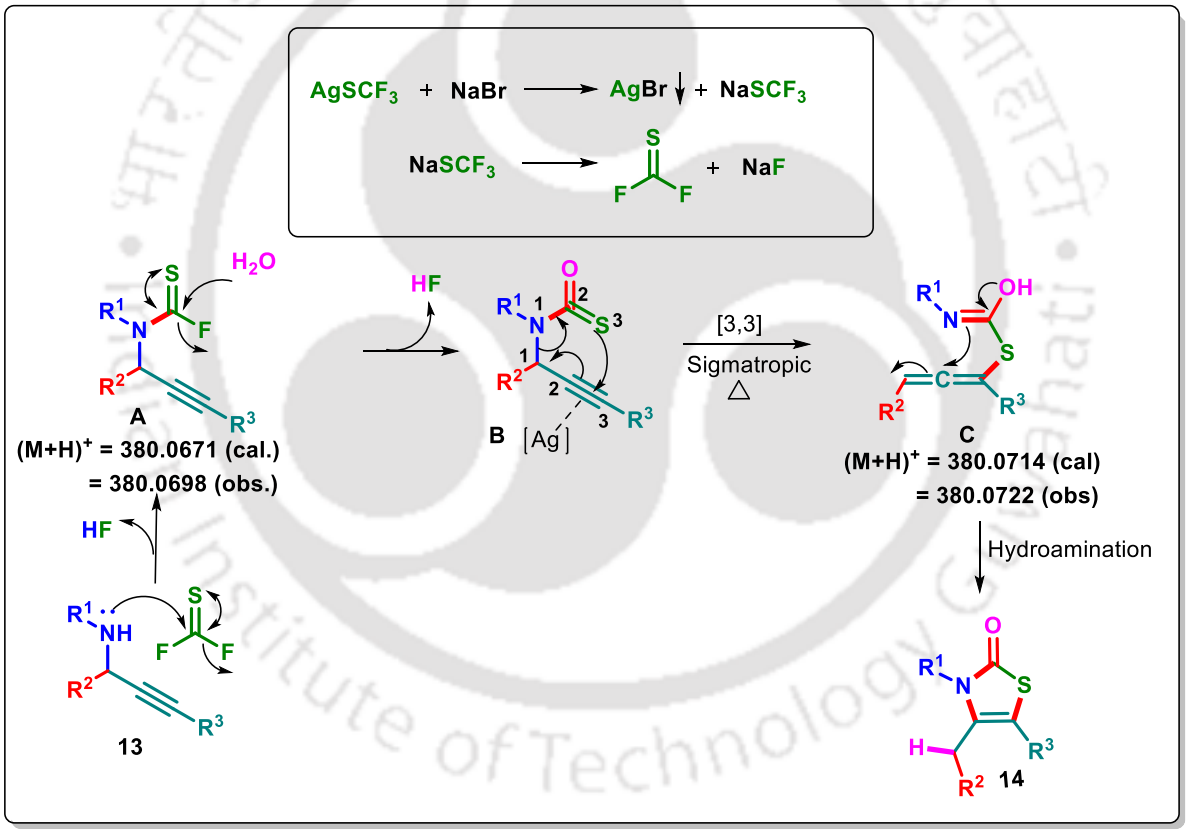
The reaction with primary amine **13ah** in the standard reaction conditions resulted in the formation of a complex mixture. This result indicated that R^1 (alkyl or aryl) group was essential in the reaction (*Scheme 3.3.5g*).



Scheme 3.3.5g. *To Confirm the Reactivity of Secondary N-propargylamine.*

3.3.6. Plausible mechanism

As per the information gathered from the above experiments and previous reports a plausible mechanism is proposed (*Scheme 3.3.6*). Initially, $AgSCF_3$, which acts as electrophilic precursor reacts with NaBr to give $NaSCF_3$ and AgBr as a precipitate. Subsequently, NaF is released from $NaSCF_3$ to form thiocarbonyldifluoride (CSF_2).[11] Then the propargylamines **13** react with *in situ* generated CSF_2 to form thiocarbamoyl fluoride adduct **A**, which further reacts with water to form the intermediate **B** with the release of HF. Finally, [3,3]-sigmatropic rearrangement, followed by 5- *exo*-dig cyclization converts the unstable intermediate **C** to the product **14**. Intermediates **A** and **C** were detected in HRMS experiments at different time intervals (*Figure 3.3.6.1)*.



Scheme 3.3.6. *Plausible Mechanism.*

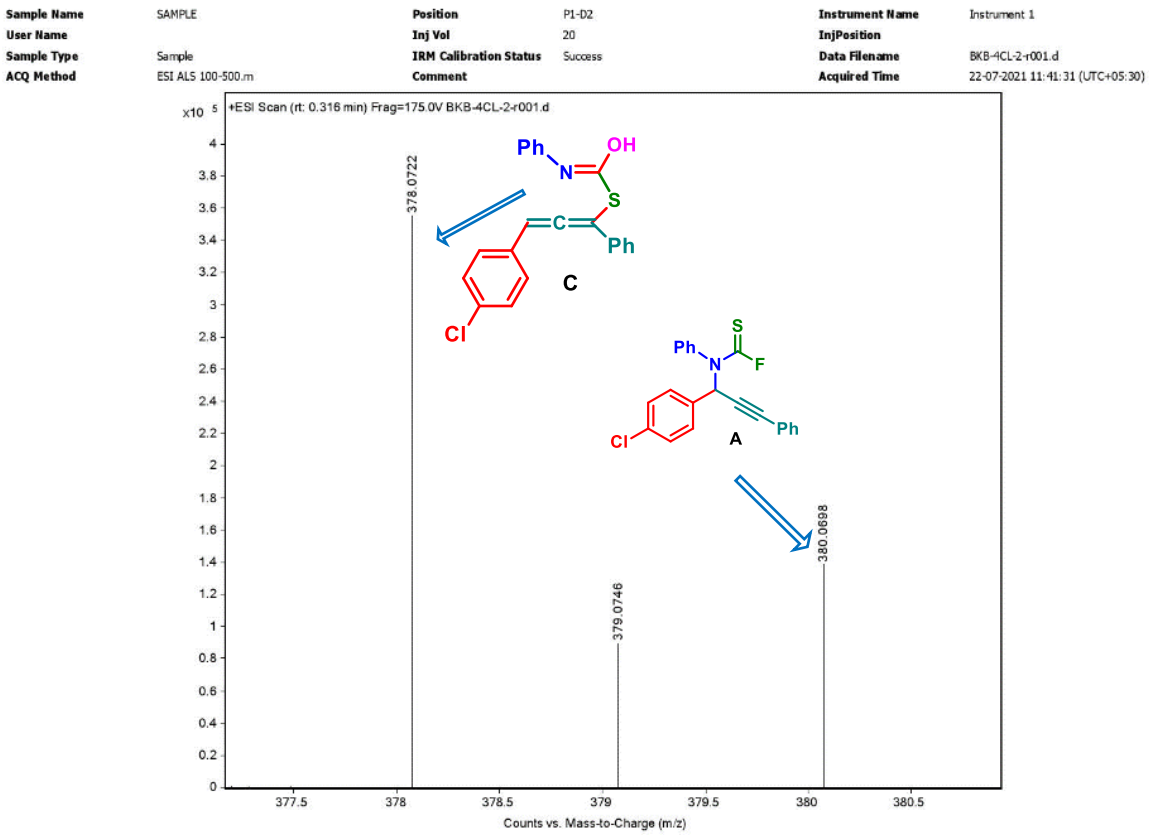
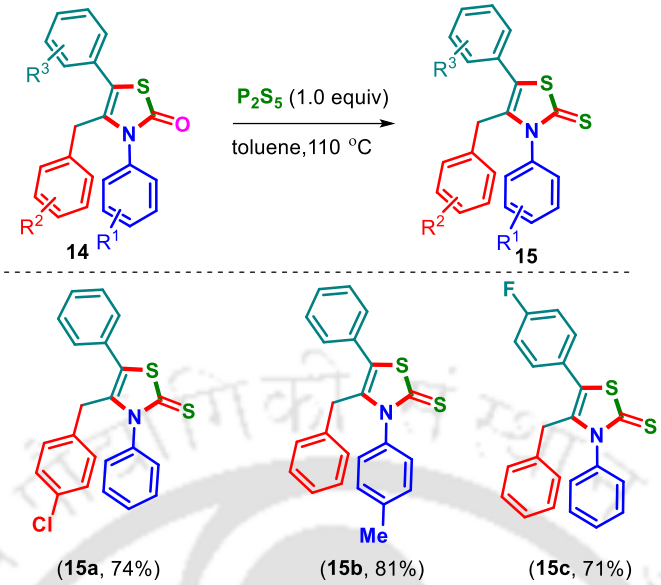


Figure 3.3.6.1. *HRMS Study for the Detection of Reaction Intermediates.*

3.4. Post-synthetic Application

The utility of the methodology is extended towards the synthesis of its thione analogue. Thus, the reaction of **14** with 1.0 equiv of phosphorous pentasulfide (P_2S_5) in refluxing toluene produced thiozole-2(3*H*)-thiones derivatives **15** with good yields (*Scheme 3.4*). It may be noted that thiazole-thiones have antitubercular,[12] and anticancer activity.[12b] They are also used as synthetic precursors in organic synthesis.[13]

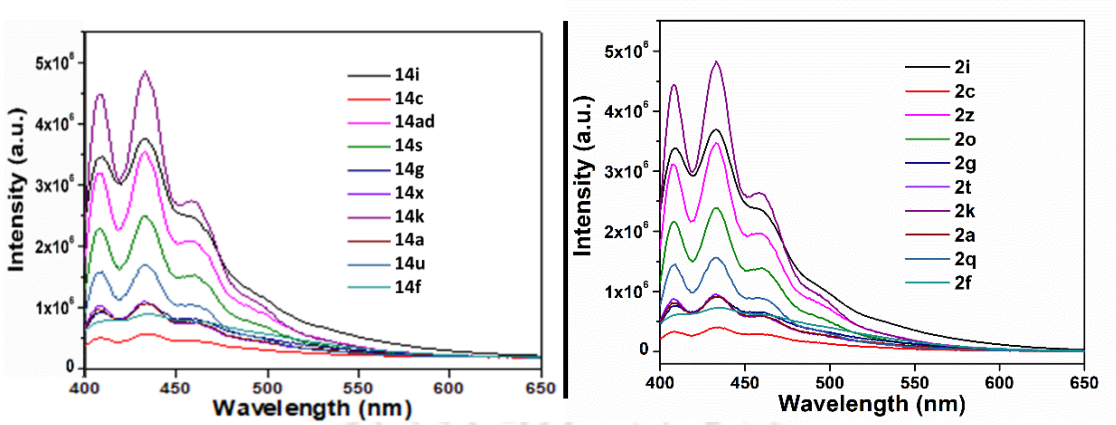


[a]Reaction condition: **14** (0.4 mmol), P_2S_5 (0.4 mmol), toluene (3.0 mL) in N_2 for 4 h at 110 °C, [b]Isolated yield.

Scheme 3.4. *Scope of Synthesis of Thiazole-2-thione Derivatives.* [a,b]

3.4.1. UV-VIS and Fluorescence study

Considering the potential of π-conjugated sulfur and nitrogen heterocycles in photoelectronic fields,[14] the ultra-violet absorbance (λ_{abs}) and fluorescence emission (λ_{em}) for some selected compounds **14a**, **14c**, **14f**, **14g**, **14i**, **14k**, **14s**, **14u**, **14x** and **14ad** were studied in chloroform, which are shown in (*Figure 3.4.1)* It was observed that all the compounds with 340-370 nm photoexcitation showed three different fluorescent emission bands in the region 400-410 nm (violet region), 430-440 (blue region) and 450-470 nm (greenish-blue region), which might be due to the formation of three excited species because of the presence of adjacent nitrogen and sulphur atoms in conjugation with the carbonyl group. The absorption peak (λ_{abs}) and calculated molar extinction coefficient (ϵ) are summarized in (*Table 3.4.1*). As these compounds have fluorescence property, they could be considered as good organic fluorophores having important applications in material sciences.



(a) *UV-VIS spectra* (b) *Fluorescence spectra*

Figure 3.4.1. *UV-VIS and Fluorescence Spectra.*

Table 3.4.1. *Photophysical Studies data of Some Selected Compounds.*

entry	compound	λ_{max} (nm)[a]	absorbance at λ_{max}	ε (1 x 10^4 M^{-1} cm^{-1})	λ_{em} (nm)[b]
(1)	**14i**	350	0.452	4.52	408, 432, 457
(2)	**14c**	347	0.071	0.71	408, 433, 403
(3)	**14ad**	348	0.161	1.61	407, 433, 458
(4)	**14s**	346	0.098	0.98	408, 433, 458
(5)	**14g**	361	0.010	0.10	407, 433, 461
(6)	**14x**	352	0.056	0.56	407, 433, 461
(7)	**14k**	344	0.106	1.06	408, 433, 458
(8)	**14a**	349	0.196	1.96	407, 433, 461
(9)	**14u**	348	0.088	0.88	408, 432, 460
(10)	**14f**	350	0.027	0.27	410, 434, 466

[a]Absorption wavelengths. [b]Emission wavelengths in chloroform at a concentration of (1 x 10^{-5} M).

3.5. Crystallographic Description

The structure of all compounds were confirmed from standard spectroscopic experiments and finally by *X*-ray crystallographic analysis of compound **14c** (*figure 3.5*)

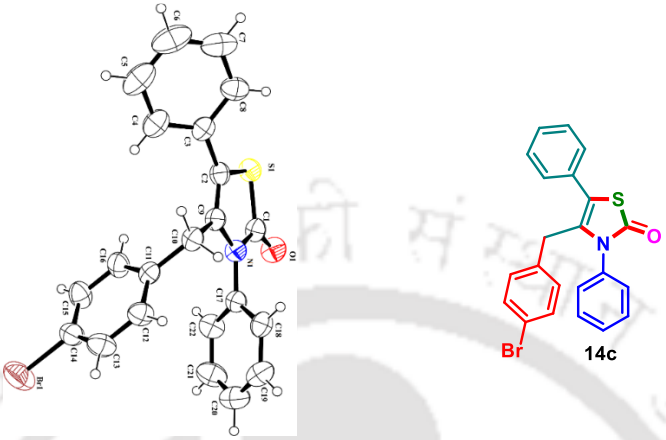


Figure 3.5. *ORTEP diagram of compound* ***14c****, thermal ellipsoids are drawn on 35% probability level.*

Compound **14c**	**CCDC 2128166**
Formula	$C_{22}H_{16}BrNOS$
Formula weight	421.0136
T/K	273(2)
Crystal system	monoclinic
Space group	P 21/c
a/Å	14.9645(6)
b/Å	16.8878(7)
c/Å	7.7990(3)
α/°	90
β/°	100.2690(10)
γ/°	90
V/Å^3	1939.37(13)
Z	4
Abs. Coeff./mm^{-1}	2.237
Abs. Correction	multi-scan
GOF on F^2	1.305
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0465 *wR2* = 0.0861
R indices [all data]	*R1* = 0.1351 *wR2* = 0.1796

Conclusion

In conclusion, an efficient methodology for the synthesis of substituted thiazolones has been developed from *N*-propargylamines in good yields by using $AgSCF_3$ as a C-S source and H_2O as Oxygen source *via* hydroamination under open air condition. The methodology can also be extended for the synthesis of bioactive analogue thiozolethione derivatives. Some of the compounds have shown photophysical properties.

3.6. Experimental Section

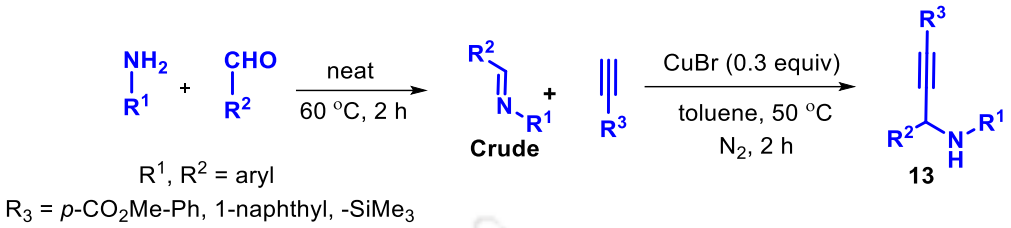
3.6.1. Instrumentation and Characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (600 MHz, 500 MHz and 400 MHz) or $^{13}C\{^1H\}$ (150 MHz, 125 MHz and 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

3.6.2. Experimental Procedure for Starting-material Synthesis

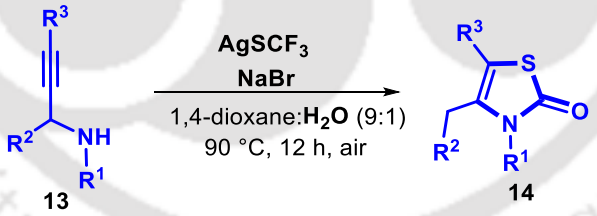
The starting material *N*-propargylamines (**13a-13j**, **13q-13s**, **13u**, **13w**, **13x**, **13z-13ad**) were prepared following our previous work,[15a] and the other starting material **13k**,[15b] **13l**,[15c] **13v** and **13m**,[15d] **13y** and **13n**,[15e] **13ae**,[15f] **13af**,[15g] **13ah**,[15h] **13o**,[15i] were synthesized according to reported literatures. The spectroscopic data of the above compounds are in good agreement with the literature one. The experimental procedure and the characterization data of the remaining starting material *N*-propargylamines (**13p**, **13t** and **13ag**) is given as follows.

3.6.2.1. General Experimental Procedure for the Synthesis of Compounds 13p, 13t and 13ag



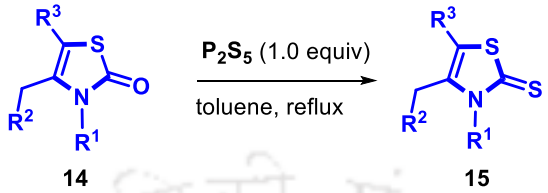
A mixture of the aldehyde (5.0 mmol, 1.0 equiv) and amine (7.5 mmol, 1.5 equiv) was heated in a round bottom flask at 60 °C in an oil bath for two hours in open air. Then, the crude was transferred to another round bottom flask and heated at 50 °C in an oil bath for 2 h with copper(I) bromide (1.5 mmol, 0.3 equiv) and acetylene (10.0 mmol, 2.0 equiv) in dry toluene (4 mL) under nitrogen. Then, the reaction mixture was poured into water, and extracted with EtOAc (3 x 20 mL). The organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude product was then purified using column chromatography over silica gel to get corresponding product.

3.6.3. General Experimental Procedure for the Synthesis of Compounds 14a-14z and 14aa-14ae



To a stirred solution of $AgSCF_3$ (0.6 mmol, 1.2 equiv)[16] and NaBr (0.48 mmol, 1.5 equiv) in 1,4 dioxane: H_2O (1.8 mL: 0.2 mL) was added *N*-propargylamines (0.4 mmol, 1.0 equiv) dropwise at room temperature. Then the mixture was stirred in an oil bath at 90 °C and the reaction time was monitored by TLC. After completion of the reaction, the solvent was removed completely under reduced pressure. The residue was diluted with ethyl acetate and saturated brine solution. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to get the corresponding product.

3.6.4. General Experimental Procedure for the Synthesis of Compounds 15a-15c



To a stirred solution of P_2S_5 (0.2 mmol, 1.0 equiv) in toluene (3.0 mL), thiazole-2-one derivatives **14** (0.2 mmol, 1.0 equiv) was added drop-wise. The mixture was then refluxed in an oil bath under nitrogen atmosphere in an oil bath and after completion of the starting material, the reaction mixture was poured into water, and extracted with EtOAc (3 × 20 mL). The organic layers were washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude was then purified using column chromatography over silica gel to get corresponding product **15**.

3.7. References:

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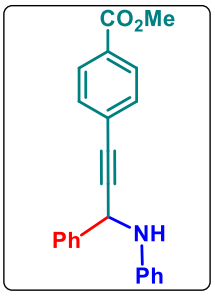
(16) Hydrofluoric acid (HF) is toxic, therefore, while performing the reaction nitrile gloves, safety glass, face shield and apron were used. The waste material after work up was stored in a plastic container.

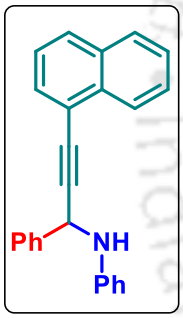
3.8. Characterization Data

Methyl 4-(3-phenyl-3-(phenylamino)prop-1-yn-1-yl)benzoate (13p):



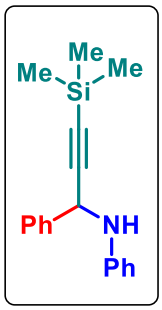
Yellow solid; R_f (hexane/EtOAc, 19:1) 0.60; mp 122–124 °C. Yield 124 mg, 73%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.0 Hz, 2 H), 7.64 (d, *J* = 7.5 Hz, 2 H), 7.46–7.39 (m, 4 H), 7.36–733 (m, 1 H), 7.24–720 (m, 2 H), 6.84–6.72 (m, 3 H), 5.51 (s, 1 H), 4.14 (bs, 1 H), 3.89 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 166.7, 146.6, 139.5, 131.9, 129.8, 129.6, 129.4, 129.1, 128.4, 127.7, 127.5, 118.9, 114.3, 91.8, 84.5, 52.4, 50.9; **IR** (KBr, neat) 3420, 2922, 1689, 1500, 1248, 870, 743 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{20}NO_2$ $(M + H)^+$ 342.1489, found 342.1485.

***N*-3-(Naphthalen-1-yl)-1-phenylprop-2-yn-1-yl)aniline (13t):**



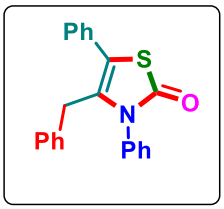
Yellow solid; R_f (hexane/EtOAc, 19:1) 0.55; mp 112–114 °C. Yield 123 mg, 74%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13–8.04 (m, 1 H), 7.79–7.71 (m, 4 H), 7.63–7.61 (m, 1 H), 7.45–7.39 (m, 4 H), 7.36–7.32 (m, 2 H), 7.25–7.21 (m, 2 H), 6.88–6.78 (m, 3 H), 5.66 (s, 1 H), 4.19 (bs, 1 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 146.8, 139.8, 133.6, 133.2, 130.7, 129.4, 129.0, 128.9, 128.4, 128.3, 127.6, 126.9, 126.5, 126.3, 125.3, 120.6, 119.0, 114.7, 93.6, 83.5, 51.2; **IR** (KBr, neat) 3396, 2912, 1691, 1500, 1265, 826, 753 cm^{-1}; **HRMS** (ESI) calcd. for $C_{25}H_{20}N$ $(M + H)^+$ 334.1590, found 334.1573.

***N*-1-Phenyl-3-(trimethylsilyl)prop-2-yn-1-yl)aniline (13ag):**



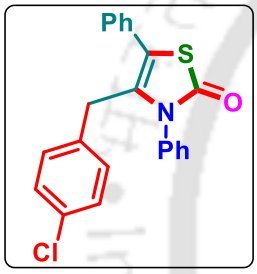
Yellow oil; R_f (hexane/EtOAc, 19:1) 0.60; Yield 108 mg, 78%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.4 Hz, 2 H), 7.23–7.20 (m, 2 H), 7.18–7.16 (m, 1 H), 7.04–7.01 (m, 2 H), 6.63–6.59 (m, 1 H), 6.57–6.54 (m, 2 H), 5.12 (s, 1 H), 3.89 (bs, 1 H), 0.00 (s, 9 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 146.8, 139.8, 129.3, 128.9, 128.2, 127.4, 118.7, 114.3, 105.0, 90.0, 51.1, 0.1.; **IR** (KBr, neat) 3445, 2956, 1682, 1504, 1273, 892, 740 cm^{-1}; **HRMS** (ESI) calcd. for $C_{18}H_{22}NSi$ $(M + H)^+$ 280.1516, found 280.1492.

4-Benzyl-3,5-diphenylthiazol-2(3*H*)-one (14a):



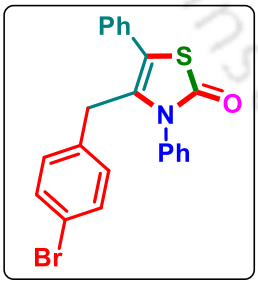
Light brown solid; R_f (hexane/EtOAc, 9:1) 0.60; mp 152–154 °C. Yield 120 mg, 70%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 8.3 and 1.4 Hz, 2 H), 7.39 (t, *J* = 7.4 Hz, 2 H), 7.34 (d, *J* = 7.4 Hz, 1 H), 7.29 (d, *J* = 7.2 Hz, 1 H), 7.26 (d, *J* = 8.2 Hz, 2 H), 7.14–7.10 (m, 3 H), 6.98–6.93 (m, 2 H), 6.76–6.70 (m, 2 H), 3.77 (s, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.7, 136.9, 135.8, 132.0, 130.5, 129.3, 129.22, 129.2, 129.1, 128.9, 128.6, 128.4, 128.0, 126.8, 115.5, 32.7; **IR** (KBr, neat) 2931, 1684, 1651, 1491, 1344, 1124, 749 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{18}NOS$ $(M + H)^+$ 344.1104, found 344.1124.

4-4-Chlorobenzyl)-3,5-diphenylthiazol-2(3*H*)-one (14b):



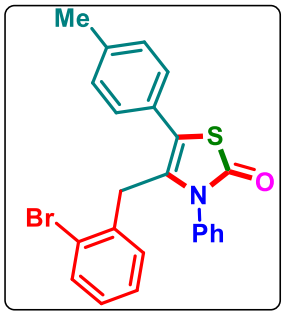
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.60; mp 186–188 °C. Yield 143 mg, 76%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47–7.27 (m, 8 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 6.98 (dd, *J* = 7.9 and 1.8 Hz, 2 H), 6.65 (d, *J* = 8.4 Hz, 2 H), 3.73 (s, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.5, 135.7, 135.4, 132.7, 131.8, 129.9, 129.4, 129.38, 129.3, 129.28, 129.2, 128.9, 128.7, 128.6, 115.8, 32.1; **IR** (KBr, neat) 2923, 1657, 1486, 1349, 1089, 752 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{17}ClNOS$ $(M + H)^+$ 378.0714, found 378.0717.

4-4-Bromobenzyl)-3,5-diphenylthiazol-2(3*H*)-one (14c):



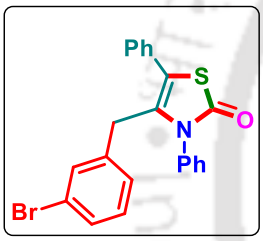
Light brown solid; R_f (hexane/EtOAc, 9:1) 0.60; mp 182–184 °C. Yield 164 mg, 78%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.3 Hz, 2 H), 7.40 (t, *J* = 7.6 Hz, 2 H), 7.37–7.34 (m, 1 H), 7.32 (dd, *J* = 10.5 and 7.4 Hz, 3 H), 7.26–7.23 (m, 2 H), 6.98 (d, *J* = 7.2 Hz, 2 H), 6.59 (d, *J*= 8.1 Hz, 2 H), 3.71 (s, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.5, 135.9, 135.7, 131.8, 131.7, 129.8, 129.7, 129.5, 129.3, 129.29, 129.2, 128.9, 128.6, 120.7, 115.9, 32.1; **IR** (KBr, neat) 2918, 1661, 1489, 1346, 11069, 755 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{17}BrNOS$ $(M + H)^+$ 422.0209, found 422.0213.

4-2-Bromobenzyl)-3-phenyl-5-(*p*-tolyl)thiazol-2(3*H*)-one (14d):



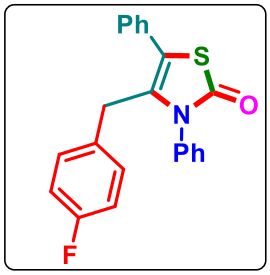
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.64; mp 181–183 °C. Yield 145 mg, 67%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.0 Hz, 1 H), 7.30–7.27 (m, 3 H), 7.26–7.21 (m, 3 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 7.12 (d, *J* = 7.6 Hz, 1 H), 7.02 (t, *J* = 7.6 Hz, 1 H), 6.98 (d, *J* = 6.9 Hz, 2 H), 3.84 (s, 2 H), 2.35 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.6, 138.5, 136.4, 135.6, 132.9, 129.9, 129.5, 129.4, 129.29, 129.2, 128.8, 128.77, 128.7, 128.5, 127.7, 124.5, 116.5, 33.0, 21.4; **IR** (KBr, neat) 2923, 1662, 1494, 1346, 1022, 752 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{19}BrNOS$ $(M + H)^+$ 436.0365, found 436.0391.

4-3-Bromobenzyl)-3,5-diphenylthiazol-2(3*H*)-one (14e):



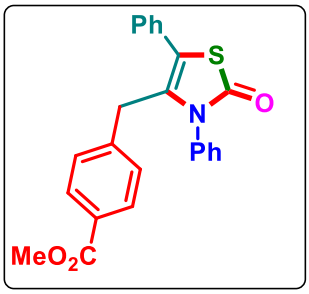
Light brown solid; R_f (hexane/EtOAc, 9:1) 0.60; mp 185–187 °C. Yield 147 mg, 70%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.6 Hz, 2 H), 7.43–7.39 (m, 2 H), 7.38–7.33 (m, 2 H), 7.31 (t, *J* = 7.6 Hz, 2 H), 7.25 (d, *J* = 7.6 Hz, 1 H), 7.01–6.95 (m, 3 H), 6.74 (s, 1 H), 6.68 (d, *J* = 7.6 Hz, 1 H), 3.74 (s, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.5, 139.1, 135.7, 131.8, 131.3, 130.1, 130.0, 129.7, 129.4, 129.36, 129.33, 129.3, 128.9, 128.7, 126.6, 122.6, 115.9, 32.3; **IR** (KBr, neat) 2926, 1664, 1489, 1349, 1069, 757 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{17}BrNOS$ $(M + H)^+$ 422.0209, found 422.0210.

4-4-Fluorobenzyl)-3,5-diphenylthiazol-2(3*H*)-one (14f):



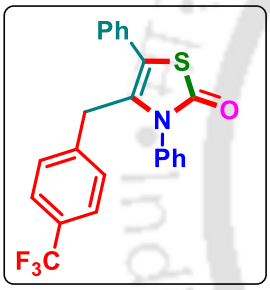
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.60; mp 157–159 °C. Yield 148 mg, 82%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.2 Hz, 2 H), 7.40 (t, *J* = 7.7 Hz, 2 H), 7.37–7.33 (m, 1 H), 7.33–7.26 (m, 3 H), 6.97 (d, *J* = 7.7 Hz, 2 H), 6.80 (t, *J* = 8.2 Hz, 2 H), 6.66 (dd, *J* = 8.3 and 5.3 Hz, 2 H), 3.74 (s, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.6, 161.8 (d, *J* = 243.8 Hz) 135.8, 132.5 (d, *J* = 2.5 Hz), 131.9, 130.3, 129.55, 129.5, 129.4, 129.3, 129.24, 129.2, 128.8, 128.6, 115.3 (d, *J* = 21.5 Hz), 31.9; **^{19}F NMR** (470 MHz, C_6F_6/$CDCl_3$) δ 45.81 (s, -F); **IR** (KBr, neat) 2921, 164, 1504, 1351, 1217, 757 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{17}FNOS$ $(M + H)^+$ 362.1009, found 362.1011.

Methyl 4-((2-oxo-3,5-diphenyl-2,3-dihydrothiazol-4-yl)methyl)benzoate (14g):



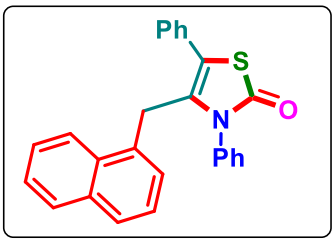
Pale yellow solid; R_f (hexane/EtOAc, 8:2) 0.50; mp 190–192 °C. Yield 160 mg, 80%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 2 H), 7.45 (d, *J* = 7.2 Hz, 2 H), 7.40 (t, *J* = 7.6 Hz, 2 H), 7.36 (d, *J* = 7.2 Hz, 1 H), 7.31 (d, *J* = 7.4 Hz, 1 H), 7.27 (d, *J* = 7.6 Hz, 2 H), 6.96 (d, *J* = 7.4 Hz, 2 H), 6.81 (d, *J* = 8.1 Hz, 2 H), 3.89 (s, 3 H), 3.82 (s, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ171.5, 167.0, 142.3, 135.7, 131.8, 129.9, 129.6, 129.5, 129.3, 129.2, 128.9, 128.7, 128.1, 116.1, 52.3, 32.8; **IR** (KBr, neat) 2920, 1719, 1661, 1491, 1274, 1102, 753 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{20}NO_3S$ $(M + H)^+$ 402.1158, found 402.1169.

3,5-Diphenyl-4-(4-(trifluoromethyl)benzyl)thiazol-2(3*H*)-one (14h):



Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.60; mp 188–190 °C. Yield 170 mg, 83%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 8.0 and 1.5 Hz, 2 H), 7.41 (t, *J* = 7.4 Hz, 2 H), 7.37 (d, *J* = 7.7 Hz, 2 H), 7.32 (d, *J* = 7.4 Hz, 1 H), 7.30–7.24 (m, 3 H), 6.98–6.94 (m, 2 H), 6.83 (d, *J* = 8.0 Hz, 2 H), 3.83 (s, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.4, 141.1, 135.7, 131.8, 129.5, 129.37, 129.34, 129.2, 128.8, 128.7, 128.4, 125.5 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 267.5 Hz), 116.2, 32.6; **^{19}F NMR** (376 MHz, C_6F_6/$CDCl_3$) δ 99.26 (s, -CF_3); **IR** (KBr, neat) 2926, 1657, 1319, 1109, 1067, 592 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{17}F_3NOS$ $(M + H)^+$ 412.0977, found 412.1004.

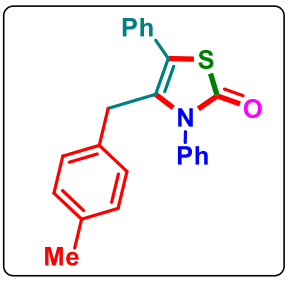
4-(Naphthalen-1-ylmethyl)-3,5-diphenylthiazol-2(3*H*)-one (14i):



Light brown gummy; R_f (hexane/EtOAc, 9:1) 0.50; Yield 127 mg, 65%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.77–7.75 (m, 1 H), 7.62 (d, *J* = 7.6 Hz, 2 H), 7.51 (d, *J* = 7.1 Hz, 2 H), 7.45–7.42 (m, 2 H), 7.39 (t, *J* = 7.4 Hz, 2 H), 7.34 (d, *J* = 7.1 Hz, 1 H), 7.27 (t, *J* = 7.4 Hz, 1 H), 7.19 (t, *J* = 7.6 Hz, 2 H), 7.14 (s, 1 H), 6.96 (d, *J* = 7.6 Hz, 2 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 3.92 (s, 2 H); **^{13}C{^{1}H} NMR** (125MHz, $CDCl_3$) δ 171.7, 135.8, 134.4, 133.5, 132.4, 132.1, 130.3, 129.3, 129.28, 129.21, 129.1, 128.9, 128.5, 128.4, 127.8, 126.7, 126.4, 126.2, 125.9,

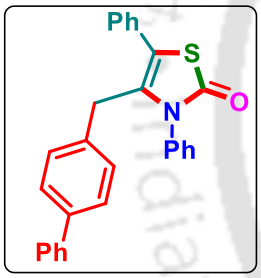
115.6, 32.8; **IR** (KBr, neat) 2925, 1659, 1486, 1346, 1122, 754 cm^{-1}; **HRMS** (ESI) calcd. for $C_{26}H_{20}NOS$ $(M + H)^+$ 394.1260, found 394.1283.

4-(4-Methylbenzyl)-3,5-diphenylthiazol-2(3*H*)-one (14j):



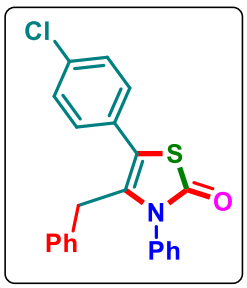
Light brown gummy; R_f (hexane/EtOAc, 9:1) 0.50; Yield 110 mg, 62%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.8 Hz, 2 H), 7.26 (dt, *J* = 15.0, 7.4 Hz, 4 H), 7.19 (d, *J* = 7.8 Hz, 2 H), 7.11–7.10 (m, 2 H), 6.94 (d, *J* = 7.4 Hz, 2 H), 6.75–6.70 (m, 2 H), 3.75 (s, 2 H), 2.35 (s, 3 H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 171.7, 138.4, 136.9, 135.8, 130.1, 129.8, 129.2, 129.05, 129.02, 129.0, 128.9, 128.5, 128.0, 126.7, 115.5, 32.6, 21.4; **IR** (KBr, neat) 2960, 1789, 1586, 1491, 1024, 752 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{20}NOS$ $(M + H)^+$ 358.1260, found 358.1264.

4-([1,1'-Biphenyl]-4-ylmethyl)-3,5-diphenylthiazol-2(3*H*)-one (14k):



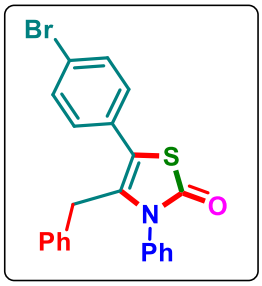
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.50; mp 197–199 °C. Yield 150 mg, 72%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53–7.49 (m, 4 H), 7.41 (q, *J* = 7.8 Hz, 4 H), 7.37–7.34 (m, 3 H), 7.29–7.24 (m, 4 H), 6.99 (d, *J* = 7.4 Hz, 2 H), 6.80 (d, *J* = 7.8 Hz, 2 H), 3.80 (s, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.7, 140.8, 139.7, 135.9, 135.8, 132.0, 130.5, 129.3, 129.25, 129.22, 129.1, 129.0, 128.9, 128.5, 127.5, 127.2, 127.1, 115.5, 32.3; **IR** (KBr, neat) 2926, 1776, 1546, 1451, 1029, 729 cm^{-1}; **HRMS** (ESI) calcd. for $C_{28}H_{22}NOS$ $(M + H)^+$ 420.1417, found 420.1419.

4-Benzyl-5-(4-chlorophenyl)-3-phenylthiazol-2(3*H*)-one (14n):



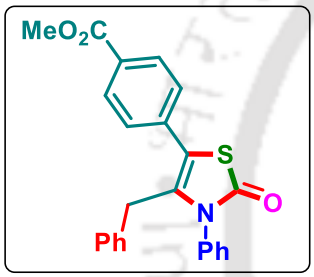
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.60; mp 188–190 °C. Yield 140 mg, 74%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40–7.38 (m, 2 H), 7.36–7.34 (m, 2 H), 7.32–7.29 (m, 1 H), 7.28–7.23 (m, 2 H), 7.13–7.12 (m, 3 H), 6.95 (d, *J* = 7.3 Hz, 2 H), 6.73–6.71 (m, 2 H), 3.74 (s, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.4, 136.5, 135.6, 134.4, 131.0, 130.5, 130.3, 129.4, 129.3, 129.2, 128.8, 128.7, 127.9, 126.9, 114.1, 32.6; **IR** (KBr, neat) 2926, 1655, 1487, 1351, 1086, 750 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{17}ClNOS$ $(M + H)^+$ 378.0714, found 378.0709.

4-Benzyl-5-(4-bromophenyl)-3-phenylthiazol-2(3*H*)-one (14o):



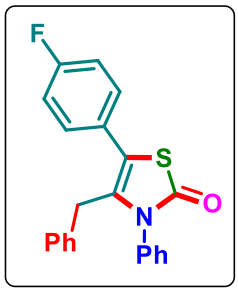
Light brown solid; R_f (hexane/EtOAc, 9:1) 0.60; mp 180–182 °C. Yield 166 mg, 79%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 2 H), 7.35–7.30 (m, 3 H), 7.28–7.24 (m, 2 H), 7.16–7.10 (m, 3 H), 6.95 (d, *J* = 7.6 Hz, 2 H), 6.73–6.71 (m, 2 H), 3.74 (s, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.4, 136.5, 135.6, 132.4, 131.0, 130.9, 130.6, 129.3, 129.2, 128.8, 128.7, 127.9, 126.9, 122.5, 114.2, 32.6; **IR** (KBr, neat) 2912, 1652, 1486, 1340, 1105, 752 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{17}BrNOS$ $(M + H)^+$ 422.0209, found 422.0206.

Methyl 4-(4-benzyl-2-oxo-3-phenyl-2,3-dihydrothiazol-5-yl)benzoate (14p):



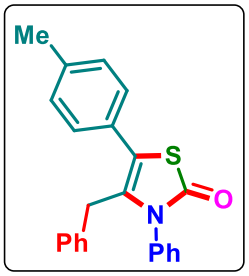
Pale yellow solid; R_f (hexane/EtOAc, 8:2) 0.50; mp 188–190 °C. Yield 142 mg, 71%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2 H), 7.53 (d, *J* = 8.4 Hz, 2 H), 7.34–7.27 (m, 3 H), 7.14–7.13 (m, 3 H), 6.96 (d, *J* = 7.5 Hz, 2 H), 6.77–6.72 (m, 2 H), 3.92 (s, 3 H), 3.80 (s, 2 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.2, 166.7, 136.7, 136.4, 135.5, 131.8, 130.4, 129.8, 129.4, 129.3, 128.9, 128.85, 128.8, 128.0, 127.0, 114.5, 52.5, 32.8; **IR** (KBr, neat) 2922, 1720, 1651, 1494, 1272, 1112, 745 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{20}NO_3S$ $(M + H)^+$ 402.1158, found 402.1156.

4-Benzyl-5-(4-fluorophenyl)-3-phenylthiazol-2(*3H*)-one (14q):



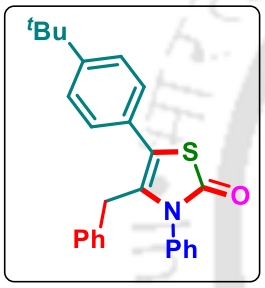
Pale yellow gummy; R_f (hexane/EtOAc, 9:1) 0.60; Yield 146 mg, 81%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 8.6 and 5.4 Hz, 2 H), 7.29 (d, *J* = 7.1 Hz, 1 H), 7.25 (t, *J* = 7.4 Hz, 2 H), 7.13–7.10 (m, 3 H), 7.08 (t, *J* = 8.6 Hz, 2 H), 6.95 (d, *J* = 7.4 Hz, 2 H), 6.74–6.69 (m, 2 H), 3.72 (s, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.5, 162.8 (d, *J* = 247.5 Hz) 136.7, 135.7, 131.0 (d, *J* = 8.7 Hz) 130.7, 129.3, 129.1, 128.8, 128.6, 127.9, 126.9, 120.4, 116.2 (d, *J* = 22.5 Hz) 114.2, 32.5; **^{19}F NMR** (376 MHz, $C_6F_6/CDCl_3$) δ 49.06 (s, -F); **IR**(KBr, neat) 2926, 1659, 1494, 1351, 1195, 1027, 694 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{17}FNOS$ $(M + H)^+$ 362.1009, found 362.1014.

4-Benzyl-3-phenyl-5-(*p*-tolyl)thiazol-2(3*H*)-one (14r):



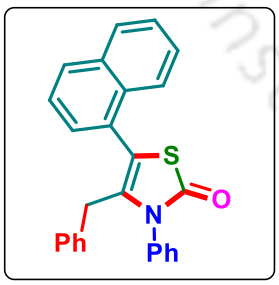
Dark yellow solid; R_f (hexane/EtOAc, 9:1) 0.60; mp 160–162 °C. Yield 141 mg, 79%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.9 Hz, 2 H), 7.30–7.23 (m, 4 H), 7.19 (d, *J* = 7.4 Hz, 2 H), 7.11–7.10 (m, 2 H), 6.94 (d, *J* = 7.4 Hz, 2 H), 6.73 (dd, *J* = 7.0 and 2.9 Hz, 2 H), 3.75 (s, 2 H), 2.35 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.7, 138.4, 136.9, 135.9, 130.2, 129.8, 129.2, 129.0, 129.0, 128.9, 128.5, 128.0, 126.7, 115.5, 32.6, 21.4; **IR** (KBr, neat) 2918, 1659, 1597, 1489, 1351, 1017, 732 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{20}NOS$ $(M + H)^+$ 358.1260, found 358.1260.

4-Benzyl-5-(4-(*tert*-butyl)phenyl)-3-phenylthiazol-2(3*H*)-one (14s):



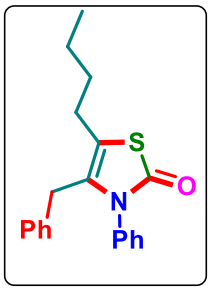
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.50; mp 151–153 °C. Yield 151 mg, 76%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40–7.30 (m, 4 H), 7.31–7.22 (m, 3 H), 7.14–7.08 (m, 3 H), 6.94 (d, *J* = 7.6 Hz, 2 H), 6.79–6.70 (m, 2 H), 3.77 (s, 2 H), 1.32 (s, 9 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.7, 151.6, 137.0, 135.9, 130.1, 129.2, 129.06, 129.05, 128.9, 128.8, 128.6, 128.1, 126.7, 126.1, 115.5, 34.9, 32.7, 31.4; **IR** (KBr, neat) 2955, 1692, 1494, 1266, 730 cm^{-1}; **HRMS** (ESI) calcd. for $C_{26}H_{26}NOS$ $(M + H)^+$ 400.1730, found 400.1742.

4-Benzyl-5-(naphthalen-1-yl)-3-phenylthiazol-2(3*H*)-one (14t):



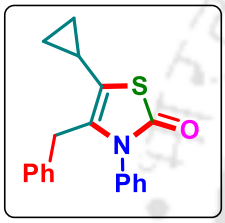
Light brown gummy; R_f (hexane/EtOAc, 9:1) 0.50; Yield 143 mg, 73%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.4 Hz, 1 H), 7.91 (d, *J* = 7.0 Hz, 2 H), 7.67–7.66 (m, 1 H), 7.63–7.60 (m, 1 H), 7.58–7.48 (m, 3 H), 7.34 –7.28 (m, 3 H), 7.06–6.96 (m, 4 H), 6.55 (d, *J* = 7.0 Hz, 2 H), 3.54 (s, 2 H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 172.3, 136.5, 136.0, 134.1, 133.1, 132.6, 129.9, 129.8, 129.4, 129.1, 129.0, 128.8, 128.3, 128.2, 127.2, 126.65, 126.63, 125.6, 125.5, 120.5, 112.5, 33.1; **IR** (KBr, neat) 2931, 1689, 1491, 1311, 1122, 774 cm^{-1}; **HRMS** (ESI) calcd. for $C_{26}H_{20}NOS$ $(M + H)^+$ 394.1260, found 394.1278.

4-Benzyl-5-butyl-3-phenylthiazol-2(3*H*)-one (14u):



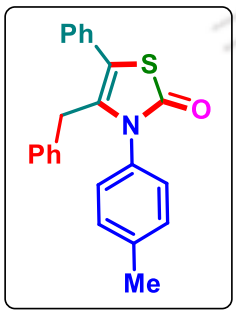
Light brown gummy; R_f (hexane/EtOAc, 9:1) 0.40; Yield 113 mg, 70%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31–7.24 (m, 3 H), 7.12 (t, *J* = 3.2 Hz, 3 H), 6.92 (d, *J* = 7.4 Hz, 2 H), 6.74–6.72 (m, 2 H), 3.60 (s, 2 H), 2.64–2.58 (m, 2 H), 1.63–1.57 (m, 2 H), 1.45–1.38 (m, 2 H), 0.94 (t, *J* = 7.6 Hz, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.8, 136.9, 136.0, 129.28, 129.2, 128.9, 128.8, 128.5, 127.9, 126.7, 115.8, 32.8, 31.9, 27.1, 22.5, 13.9; **IR** (KBr, neat) 2925, 1662, 1494, 1346, 1032, 697 cm^{-1}; **HRMS** (ESI) calcd. for $C_{20}H_{22}NOS$ $(M + H)^+$ 324.1417, found 324.1432.

4-Benzyl-5-cyclopropyl-3-phenylthiazol-2(3*H*)-one (14v):



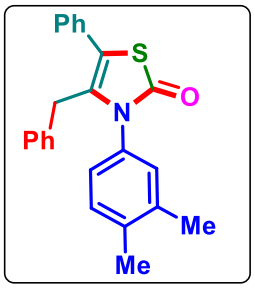
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.50; mp 151–153 °C. Yield 104 mg, 68%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31–7.25 (m, 3 H), 7.14–7.13 (m, 3 H), 6.92 (d, *J* = 7.2 Hz, 2 H), 6.78–6.76 (m, 2 H), 3.72 (s, 2 H), 1.91–1.87 (m, 1 H), 0.96 - 0.91 (m, 2 H), 0.75– 0.71 (m, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.3, 137.1, 135.9, 131.1, 129.3, 128.97, 128.95, 128.6, 128.1, 126.7, 117.4, 32.4, 8.4, 7.8; **IR** (KBr, neat) 2926, 1679, 1494, 1334, 1024, 695 cm^{-1}; **HRMS** (ESI) calcd. for $C_{19}H_{18}NOS$ $(M + H)^+$ 308.1104, found 308.1116.

4-Benzyl-5-phenyl-3-(*p*-tolyl)thiazol-2(3*H*)-one (14w):



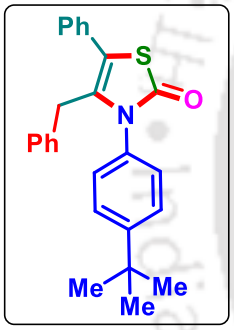
Red gummy; R_f (hexane/EtOAc, 9:1) 0.60; Yield 148 mg, 83%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46–7.44 (m, 2 H), 7.37 (t, *J* = 7.4 Hz, 2 H), 7.33 (d, *J* = 7.4 Hz, 1 H), 7.16–7.10 (m, 3 H), 7.05 (d, *J* = 8.0 Hz, 2 H), 6.83 (d, *J* = 8.0 Hz, 2 H), 6.80–6.74 (m, 2 H), 3.76 (s, 2 H), 2.31 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.8, 139.1, 137.0, 133.2, 132.1, 130.7, 129.9, 129.2, 129.1, 128.64, 128.61, 128.4, 128.1, 126.8, 115.2, 32.6, 213; **IR** (KBr, neat) 2918, 1657, 1509, 1351, 1029, 767 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{20}NOS$ $(M + H)^+$ 358.1260, found 358.1260.

4-Benzyl-3-(3,4-dimethylphenyl)-5-phenylthiazol-2(3*H*)-one (14x):



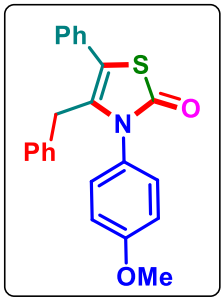
Light brown solid; R_f (hexane/EtOAc, 9:1) 0.50; mp 165–167 °C. Yield 141 mg, 76%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.4 Hz, 2 H), 7.37 (t, *J* = 7.4 Hz, 2 H), 7.32–7.29 (m, 1 H), 7.17–7.09 (m, 3 H), 7.02 (d, *J* = 7.4 Hz, 1 H), 6.80–6.74 (m, 2 H), 6.72 (d, *J* = 7.4 Hz, 1 H), 6.61 (s, 1 H), 3.74 (s, 2 H), 2.21 (s, 3 H), 2.06 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.8, 137.85, 137.81, 137.2, 133.3, 132.2, 130.9, 130.3, 130.0, 129.17, 129.11, 128.5, 128.3, 128.2, 126.7, 125.9, 115.1, 32.7, 19.7, 19.6; **IR** (KBr, neat) 2921, 1662, 1494, 1356, 1029, 735 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{22}NOS$ $(M + H)^+$ 372.1417, found 372.1420.

4-Benzyl-3-(4-(*tert*-butyl)phenyl)-5-phenylthiazol-2(3*H*)-one (14y):



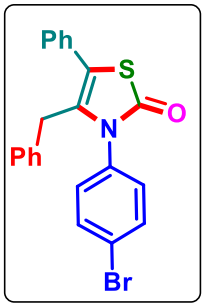
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.40; mp 191–193 °C. Yield 103 mg, 76%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.35–7.31 (m, 1 H), 7.26–7.23 (m, 2 H), 7.10–7.06 (m, 3 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 6.69 (d, *J* = 6.0 Hz, 2 H), 3.75 (s, 2 H), 1.28 (s, 9 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.8, 152.1, 137.0, 133.1, 132.1, 130.9, 129.24, 129.20, 128.5, 128.4, 128.2, 128.1, 126.7, 126.2, 115.2, 34.8, 32.7, 31.4; **IR** (KBr, neat) 2928, 1724, 1671, 1436, 1274, 1109, 697 cm^{-1}; **HRMS** (ESI) calcd. for $C_{26}H_{26}NOS$ $(M + H)^+$ 400.1730, found 400.1732.

4-Benzyl-3-(4-methoxyphenyl)-5-phenylthiazol-2(3*H*)-one (14z):



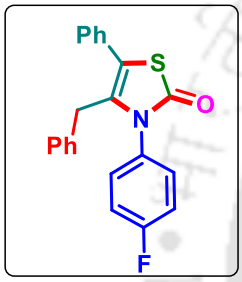
Black gummy; R_f (hexane/EtOAc, 9:1) 0.70; Yield 149 mg, 80%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47–7.43 (m, 2 H), 7.37 (t, *J* = 7.1 Hz, 2 H), 7.33 (d, *J* = 7.1 Hz, 1 H), 7.16–7.11 (m, 3 H), 6.85–6.83 (m, 2 H), 6.80–6.73 (m, 4 H), 3.76 (d, *J* = 2.0 Hz, 5 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 172.0, 159.9, 137.0, 132.1, 130.9, 130.0, 129.19, 129.10, 128.6, 128.44, 128.40, 128.0, 126.8, 115.1, 114.5, 55.7, 32.6; **IR** (KBr, neat) 2841, 1653, 1505, 1247, 1025, 700 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{20}NO_2S$ $(M + H)^+$ 374.1209, found 374.1241.

4-Benzyl-3-(4-bromophenyl)-5-phenylthiazol-2(3*H*)-one (14aa):



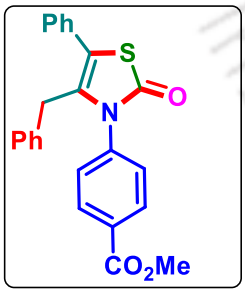
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.60; mp 180–182 °C. Yield 164 mg, 78%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.6 Hz, 2 H), 7.41–7.34 (m, 5 H), 7.17–7.13 (m, 3 H), 6.82 (d, *J* = 8.2 Hz, 2 H), 6.77–6.75 (m, 2 H), 3.76 (s, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.5, 136.6, 134.8, 132.5, 131.8, 130.5, 130.1, 129.29, 129.20, 128.8, 128.6, 128.0, 127.0, 123.3, 115.9, 32.6; **IR** (KBr, neat) 2923, 1667, 1487, 1351, 1069, 764 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{17}BrNOS$ $(M + H)^+$ 422.0209, found 422.0200.

4-Benzyl-3-(4-fluorophenyl)-5-phenylthiazol-2(3*H*)-one (14ab):



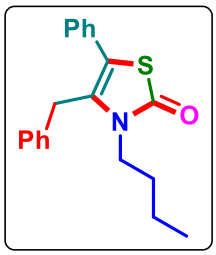
Light brown solid; R_f (hexane/EtOAc, 9:1) 0.60; mp 177–179 °C. Yield 146 mg, 81%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.2 Hz, 2 H), 7.39 (t, *J* = 7.2 Hz, 2 H), 7.35–7.32 (m, 1 H), 7.16–7.12 (m, 3 H), 6.92–6.90 (m, 4 H), 6.77– 6.75 (m, 2 H), 3.76 (s, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.7, 162.7 (d, *J* = 247.5 Hz), 136.7, 131.0 (d, *J* = 8.7 Hz), 130.8, 130.7, 130.3, 129.2, 129.1, 128.7, 128.5, 128.0, 126.9, 116.2 (d, *J* = 22.5 Hz), 115.6, 32.6; **^{19}F NMR** (470 MHz, C_6F_6/$CDCl_3$) δ 49.97 (s, -F); **IR** (KBr, neat) 2918, 1672, 1509, 1359, 1214, 1020, 695 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{17}FNOS$ $(M + H)^+$ 362.1009, found 362.1014.

Methyl 4-(4-benzyl-2-oxo-5-phenylthiazol-3(2*H*)-yl)benzoate (14ac):



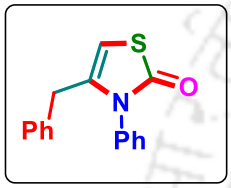
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.70; mp 156–158 °C. Yield 146 mg, 73%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.5 Hz, 2 H), 7.48–7.46 (m, 2 H), 7.42–7.38 (m, 2 H), 7.36 (d, *J* = 7.2 Hz, 1 H), 7.15–7.08 (m, 3 H), 7.05 (d, *J* = 8.5 Hz, 2 H), 6.73–6.71 (m, 2 H), 3.92 (s, 3 H), 3.78 (s, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.4, 166.3, 139.8, 136.5, 131.7, 130.69, 130.64, 130.0, 129.3, 129.2, 129.0, 128.8, 128.0, 127.0, 116.2, 52.6, 32.6; **IR** (KBr, neat) 2926, 1679, 1494, 1334, 1024, 695 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{20}NO_3S$ $(M + H)^+$ 402.1158, found 402.1194.

4-Benzyl-3-butyl-5-phenylthiazol-2(3*H*)-one (14ad):



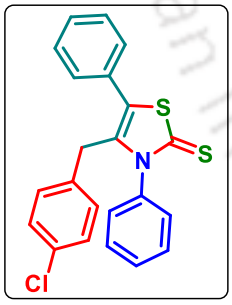
Pale yellow gummy; R_f (hexane/EtOAc, 9:1) 0.40; Yield 103 mg, 64%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37–7.25 (m, 8 H), 7.16 (d, *J* = 7.0 Hz, 2 H), 3.97 (s, 2 H), 3.51–3.46 (m, 2 H), 1.48–1.41 (m, 2 H), 1.25–1.19 (m, 2 H), 0.82 (t, *J* = 7.4 Hz, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.7, 137.1, 132.2, 129.5, 129.3, 129.1, 129.0, 128.2, 127.8, 127.3, 115.2, 44.1, 32.2, 31.2, 20.2, 13.8; **IR** (KBr, neat) 2930, 1657, 1602, 1454, 1321, 1028, 700 cm^{-1}; **HRMS** (ESI) calcd. for $C_{20}H_{22}NOS$ $(M + H)^+$ 324.1417, found 324.1421.

4-Benzyl-3-phenylthiazol-2(3*H*)-one (14ae):



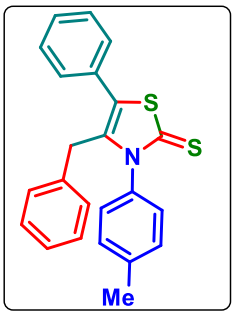
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.50; mp 157–159 °C. Yield 102 mg, 77%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42–7.38 (m, 3 H), 7.21–7.19 (m, 3 H), 7.13–7.09 (m, 2 H), 6.93–6.91 (m, 2 H), 5.74 (s, 1 H), 3.49 (s, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 172.9, 136.2, 135.7, 135.6, 129.7, 129.3, 129.0, 128.8, 128.7, 127.2, 98.2, 36.1; **IR** (KBr, neat) 2946, 1662, 1605, 1412, 1256, 1097, 695 cm^{-1}; **HRMS** (ESI) calcd. for $C_{16}H_{14}NOS$ $(M + H)^+$ 268.0791, found 268.0793.

4-(4-Chlorobenzyl)-3,5-diphenylthiazole-2(3*H*)-thione (15a):



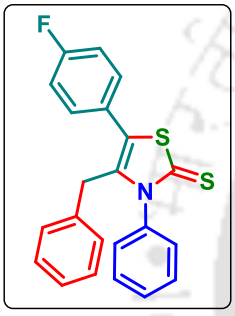
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.40; mp 179–181 °C. Yield 145 mg, 74%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45–7.36 (m, 6 H), 7.34–7.32 (m, 2 H), 7.10 (d, *J* = 8.2 Hz, 2 H), 6.96 (d, *J* = 7.7 Hz, 2 H), 6.63 (d, *J* = 8.2 Hz, 2 H), 3.76 (s, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 189.3, 137.9, 136.8, 134.8, 132.9, 130.3, 129.7, 129.6, 129.5, 129.32, 129.30, 129.1, 128.8, 128.7, 125.8, 32.9; **IR** (KBr, neat) 3051, 2923, 1656, 1342, 1072, 1089, 515 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{16}ClNNaS_2$ $(M + Na)^+$ 416.0305, found 416.0283.

4-Benzyl-5-phenyl-3-(*p*-tolyl)thiazole-2(3*H*)-thione (15b):



Light brown gummy; R_f (hexane/EtOAc, 9:1) 0.40; Yield 151 mg, 81%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48–7.38 (m, 5 H), 7.18–7.09 (m, 5 H), 6.81 (d, *J* = 8.1 Hz, 2 H), 6.76–6.69 (m, 2 H), 3.82 (s, 2 H), 2.35 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 188.0, 140.0, 138.2, 136.2, 135.1, 130.2, 129.5, 129.3, 129.1, 128.7, 128.1, 128.0, 127.1, 126.5, 33.4, 21.5; **IR** (KBr, neat) 3045, 2976, 1647, 1341, 1087, 1124, 541 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{20}NS_2$ $(M + H)^+$ 374.1032, found 374.1029.

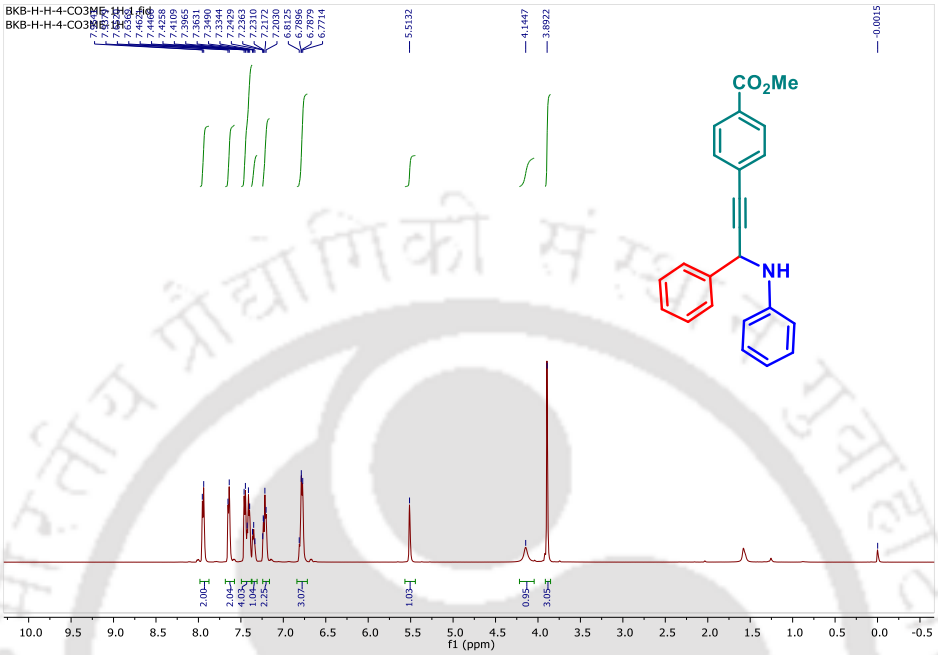
4-Benzyl-5-(4-fluorophenyl)-3-phenylthiazole-2(3*H*)-thione (15c):



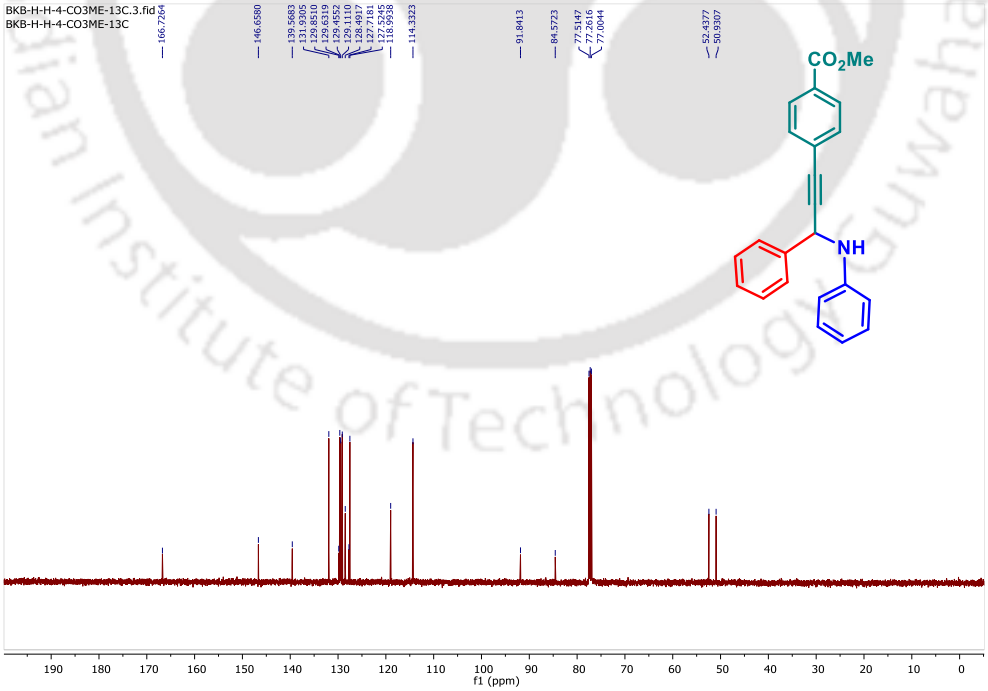
Light brown gummy; R_f (hexane/EtOAc, 9:1) 0.60; Yield 133 mg, 71%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.4–7.45 (m, 2 H), 7.41–7.38 (m, 1 H), 7.32 (t, *J* = 7.7 Hz, 2 H), 7.17–7.12 (m, 5 H), 6.93 (d, *J* = 7.7 Hz, 2 H), 6.67 (d, *J* = 6.8 Hz, 2 H), 3.79 (s, 2 H).; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 186.79, 162.0 (d, *J* = 245.0 Hz), 138.8, 137.3, 135.7, 131.2, 131.2 (d, *J* = 3.3 Hz), 129.7, 128.9, 128.2, 127.9, 127.3, 126.5, 116.0 (d, *J* = 21.5 Hz), 33.4; **^{19}F NMR** (470 MHz, C_6F_6/$CDCl_3$) δ 46.94 (s, -F); **IR** (KBr, neat) 2968, 1645, 1512, 1386, 1232, 1042, 676 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{17}FNS_2$ $(M + H)^+$ 378.0781, found 378.0777.

3.9. Representative Spectra

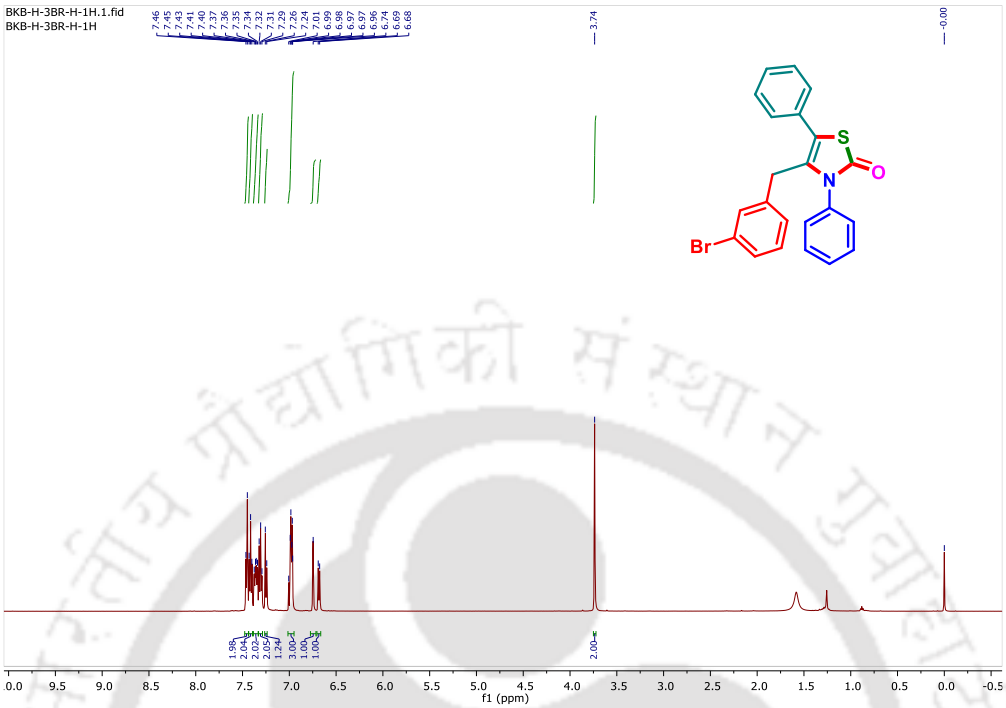
^{1}H spectrum of compound **13p** (400 MHz, $CDCl_3$)



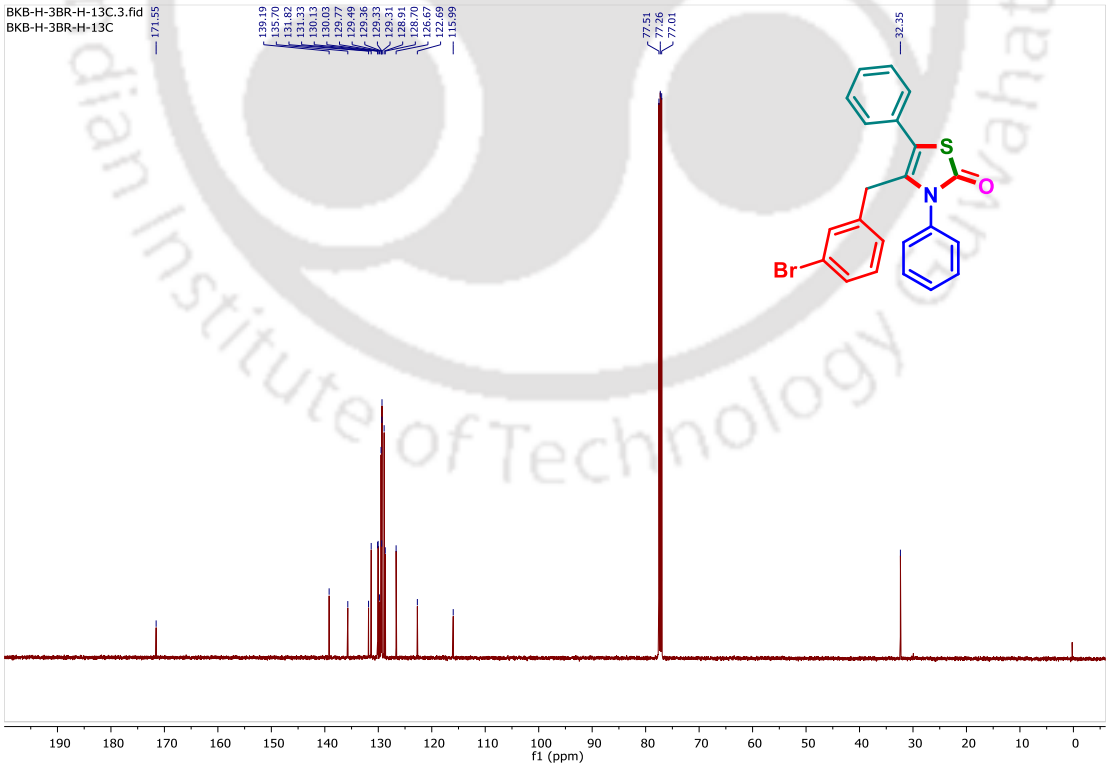
^{13}C{^{1}H} NMR spectrum of compound **13p** (100 MHz, $CDCl_3$)



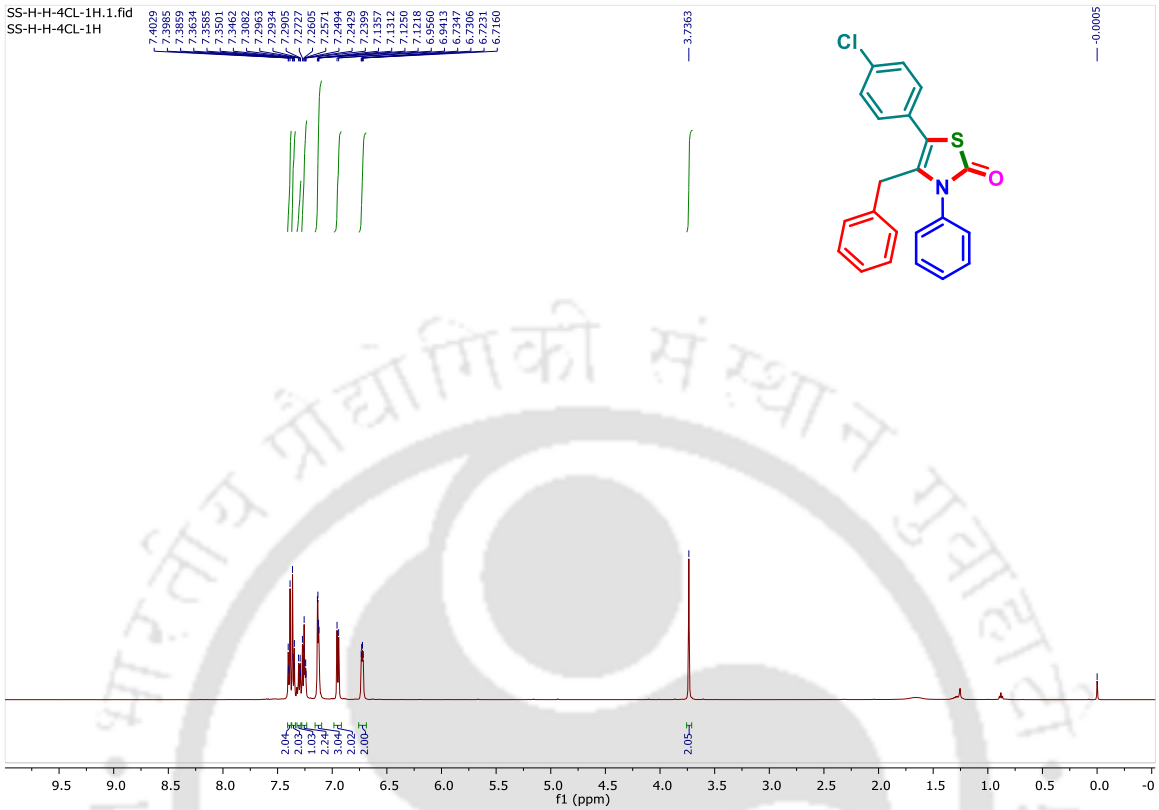
^{1}H spectrum of compound **14e** (500 MHz, $CDCl_3$)



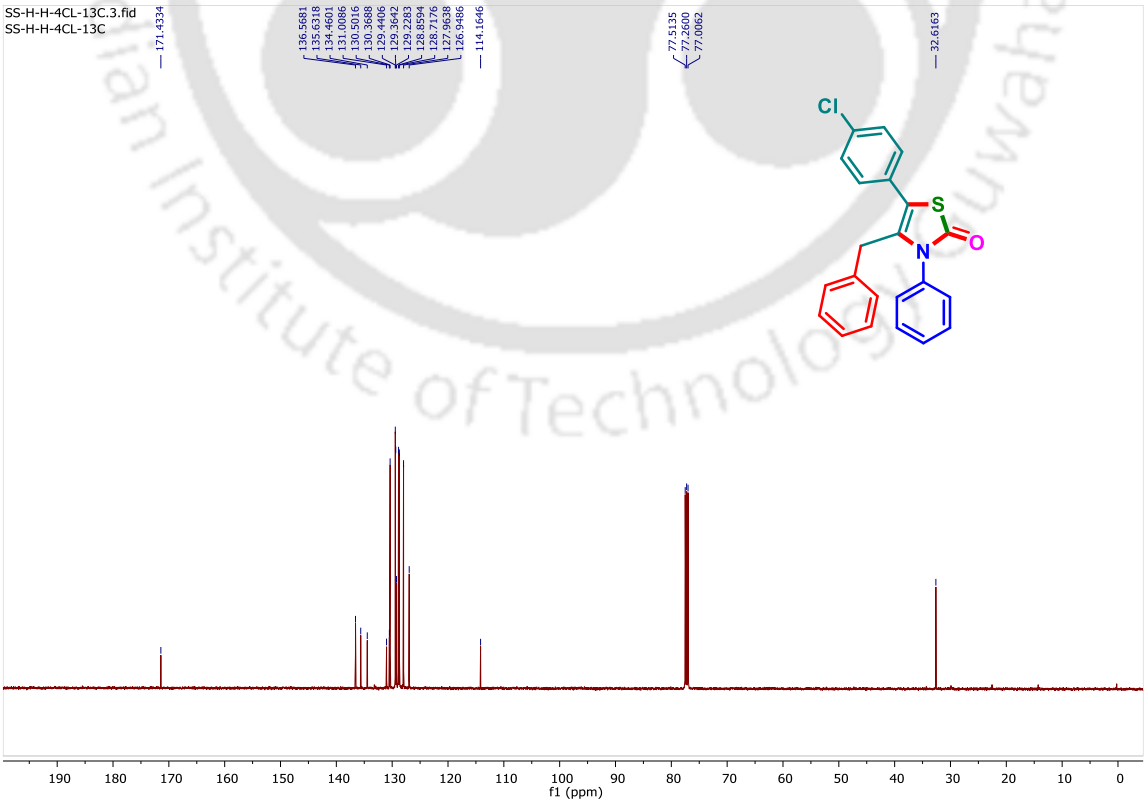
^{13}C{^{1}H} NMR spectrum of compound **14e** (125 MHz, $CDCl_3$)



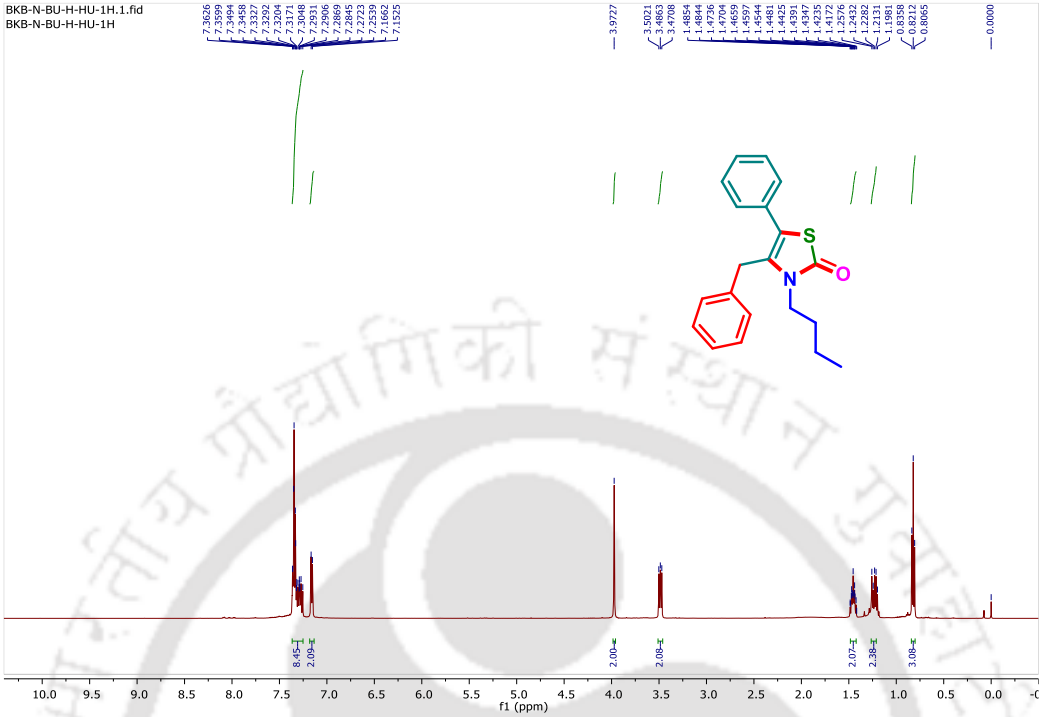
^{1}H spectrum of compound **14n** (500 MHz, $CDCl_3$)



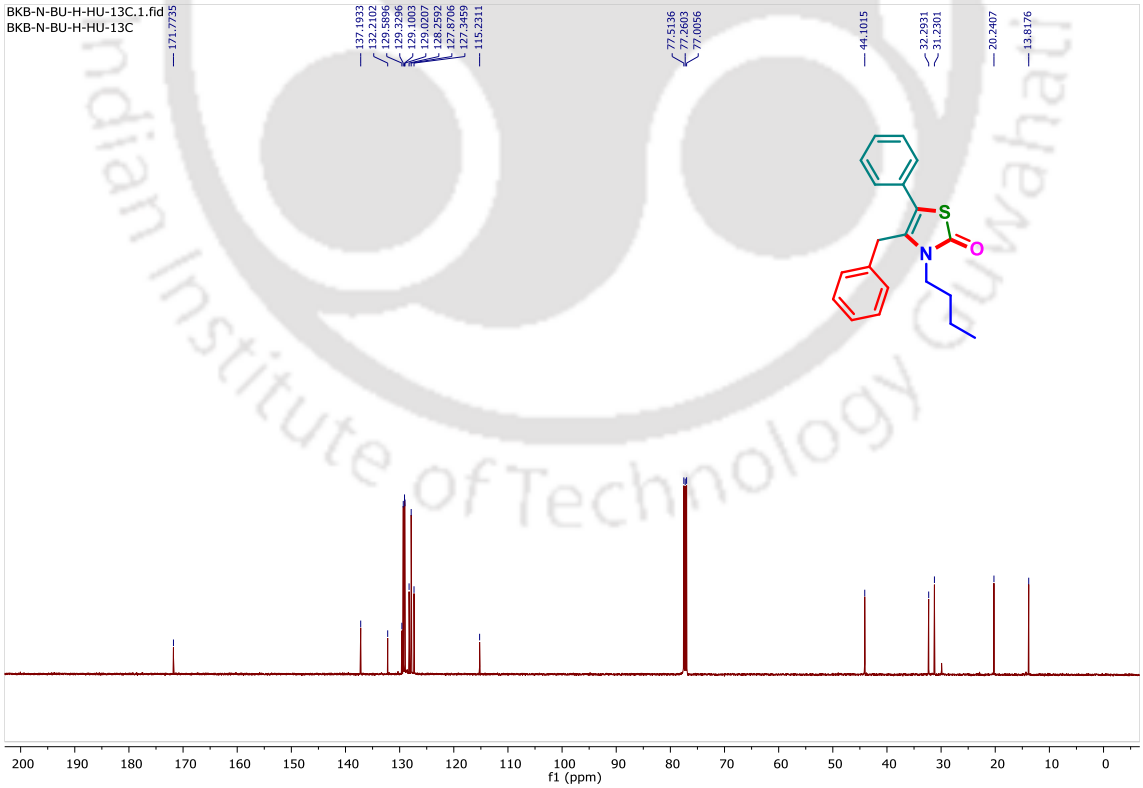
^{13}C{^{1}H} NMR spectrum of compound **14n** (125 MHz, $CDCl_3$)



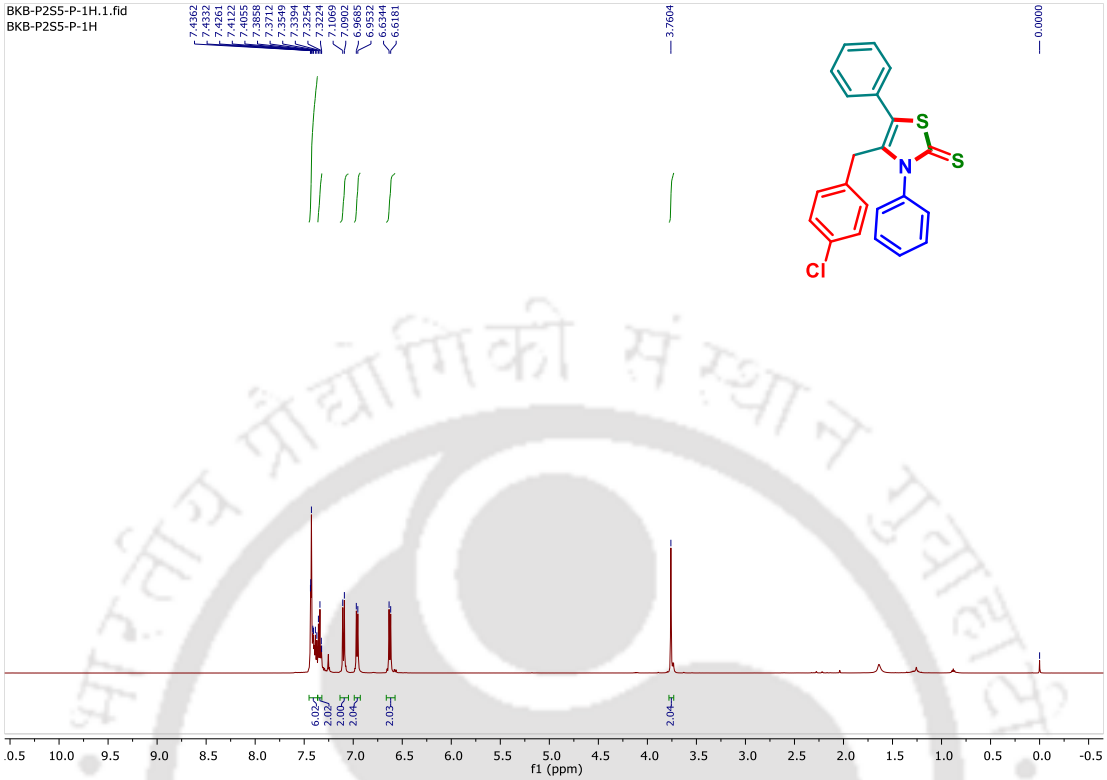
^{1}H spectrum of compound **14ad** (500 MHz, $CDCl_3$)



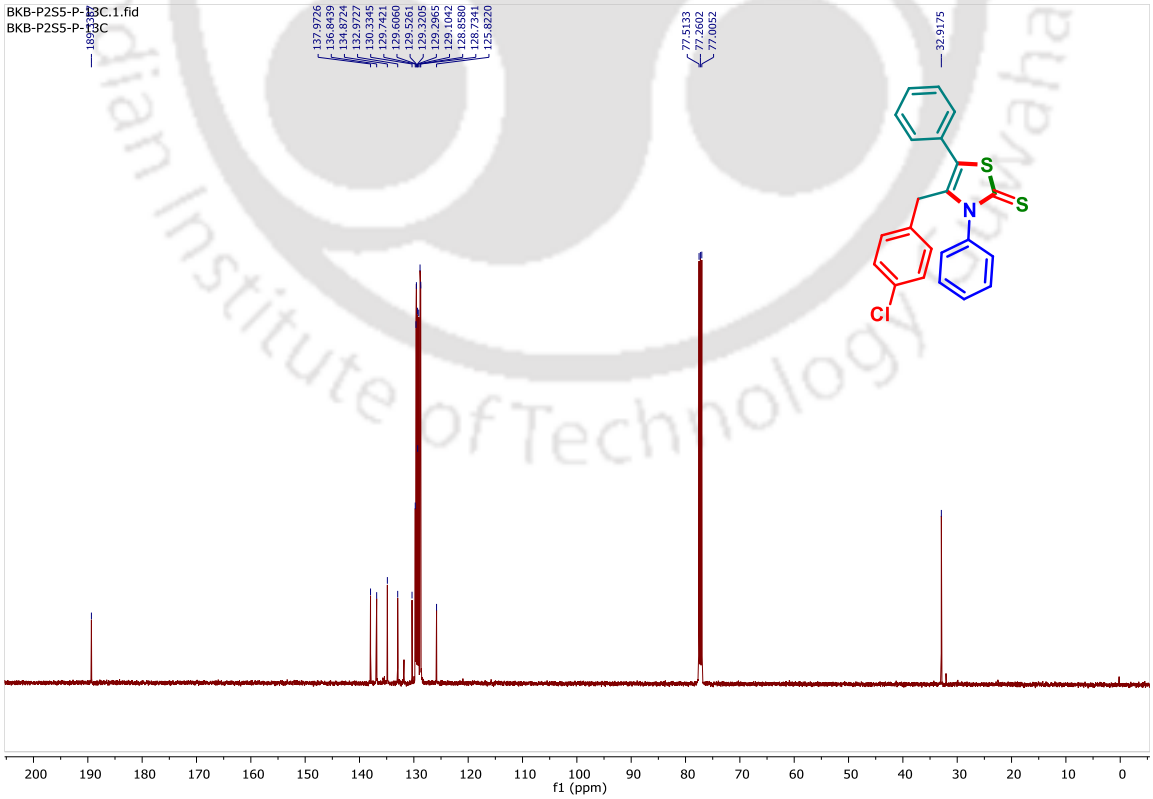
^{13}C{^{1}H} NMR spectrum of compound **14ad** (125 MHz, $CDCl_3$)



^{1}H spectrum of compound **15a** (500 MHz, $CDCl_3$)



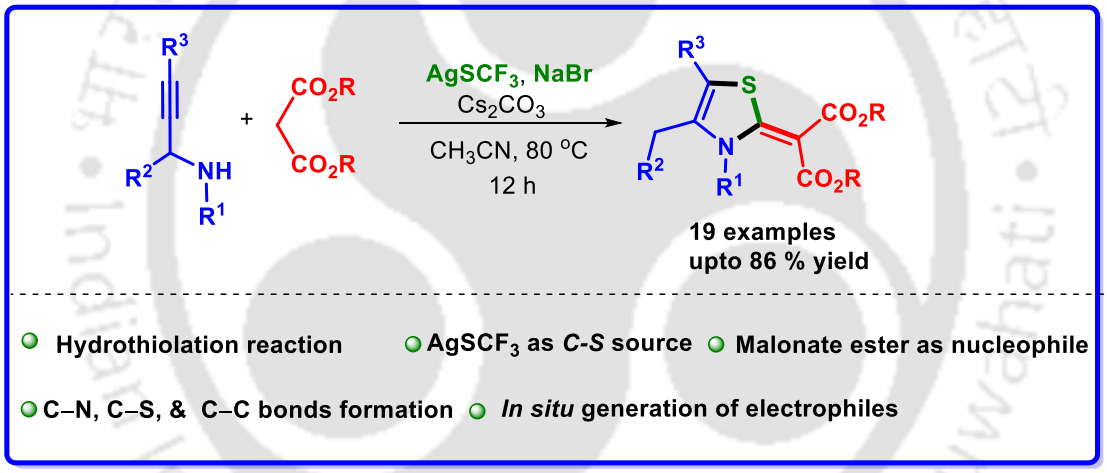
^{13}C{^{1}H} NMR spectrum of compound **15a** (125 MHz, $CDCl_3$)



CHAPTER 4

Base Promoted Synthesis of Methylene-dihydrothiazole Derivatives from *N*-propargylamines *via* Hydrothiolation Reaction

Abstract: This chapter describes an efficient methodology developed for the synthesis of methylene-dihydrothiazole derivatives *via* Michael-addition followed by hydrothiolation of *N*-propargylamines. The protocol utilizes silver(I)trifluoromethanethiolate ($AgSCF_3$) as a *C*–*S* source and malonate ester derivatives as nucleophiles. The reaction is compatible with many functional groups moderated to good yield.



Manuscript under preparation.

4.1. Introduction

Nitrogen and sulphur containing heterocycles are important class of structural scaffolds in organic chemistry. [1] Among them, methylene-dihydrothiazole heterocyclic moiety is an important class of five-membered heterocyclic skeleton, which ubiquitously occur in natural products and pharmacologically active molecules and have widespread applications in pharmacological profiles and broad biological activities (*Figure 4.1.1*).[2] Owing to their various utilities in pharmaceuticals, natural products and starting material precursors, there is a need to develop a new and potent strategy for the construction of highly substituted methylene-dihydrothiazole derivatives.

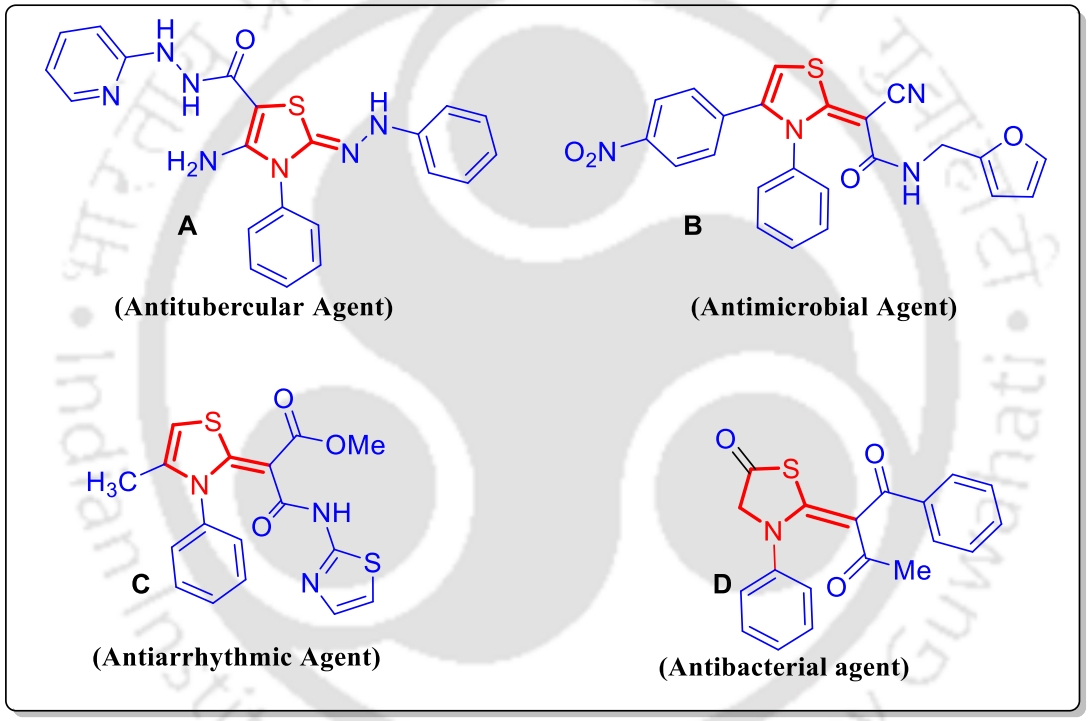
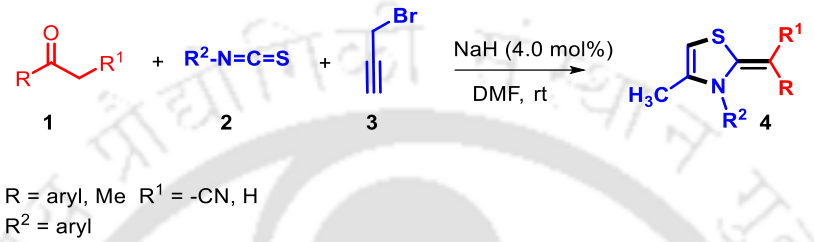


Figure 4.1.1. *Some Bioactive Methylene-dihydrothiazoles Derivatives.*

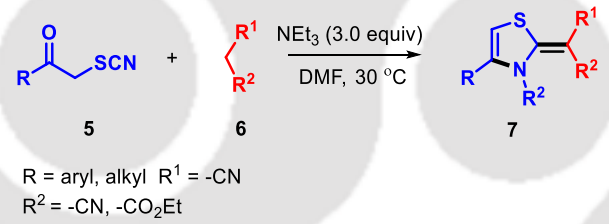
4.2. Literature Survey for the Synthesis of Substituted 2-Methylene-2,3-dihydrothiazoles

Junjappa and co-workers demonstrated, a base mediated synthesis of 2-methylene-2,3-dihydrothiazoles **4** by reacting with acetophenone derivatives **1**, propargylbromides **3** and phenyl isothiocyanate **2** *via* hydroamination pathway (*scheme 4.2.1*).[3a]



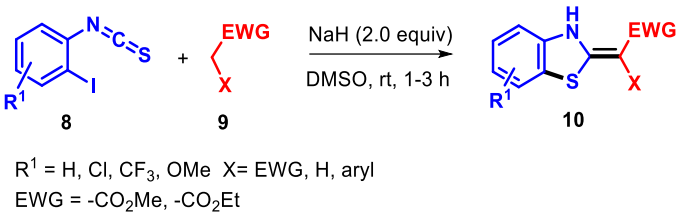
Scheme 4.2.1. *Synthesis of Dihydrothiazoles from Acetophenones and Phenyl-isothiocyanates.*

In 2011, Wurtthner and co-workers explored an efficient transition-metal free intermolecular cyclization between isothiocyanate derivatives **5** with activemethylene compounds **6** that leads to 2-methylene-2,3-dihydrothiazoles **5** in DMF at room temperature (*scheme 4.2.2*).[3b]



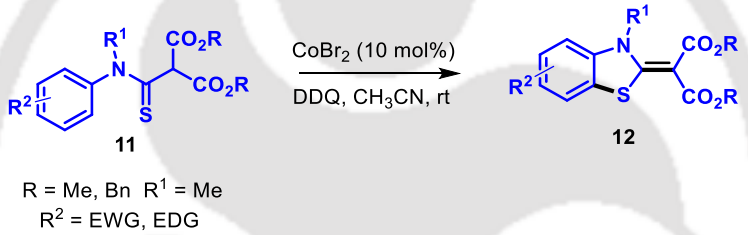
Scheme 4.2.2. *Synthesis of Dihydrothiazoles from Active-methylene compounds and Isothiocyanates.*

Base promoted a comprehensive synthesis of 2-substituted benzothiazoles **10** derivatives from the treatment of active-methylene compound **9** with 2-iodoarylisothioacyanates **8** as C-S source was reported by Ila and co-workers in 2019. The reaction was undertaken under room temperature within 1-3 h, through radical intermediate pathway (*scheme 4.2.3*).[3c]



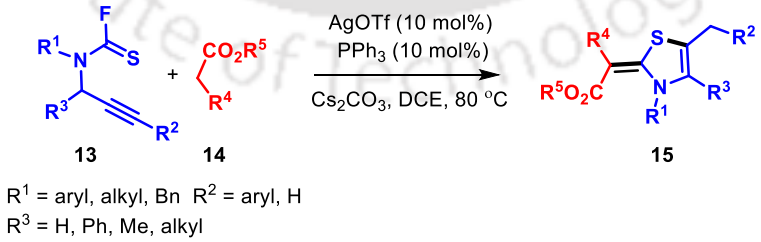
Scheme 4.2.3. *Synthesis of Benzothiazoles from Active-methylene compounds and 2-Iodoarylisothioacyanates.*

Jiang and co-workers introduced an efficient and highly atom economy intramolecular C-H thiolation strategy towards synthesis of benzothiazole derivatives **12** starting from thioamide derivatives **11** by using cheap catalyst $CoBr_2$ in CH_3CN at room temperature with good yield (*scheme 4.2.4*).[3d]



Scheme 4.2.4. *Synthesis of Benzothiazoles from Thioamide Derivatives.*

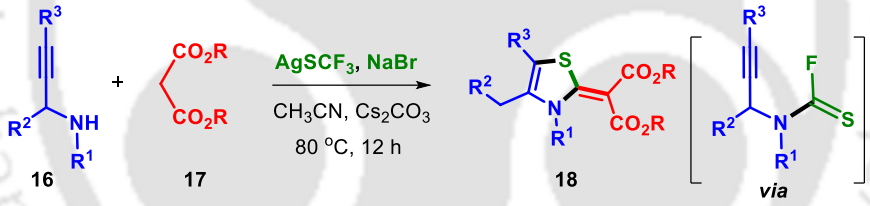
Very recently, Jiang and co-workers developed an interesting strategy for synthesis of five membered methylene-dihydrothiazoles **15**. The reaction proceeds through the addition of *N*-propargyl thiocarbamoyl fluorides **13** and malonate esters **14** in presence of Cs_2CO_3, AgOTf and PPh_3 as a ligand in CH_3CN *via* hydrothiolation (*scheme 4.2.5*).[3e]



Scheme 4.2.5. *Synthesis of Dihydrothiazoles from N-propargylthiocarbamoyl Fluorides.*

Present Work

Atom-economical hydrothiolation or thiol-yne coupling reaction plays a significant role towards the synthesis of various heterocyclic scaffold due to its ability to control the regioselectvity and nucleophilic character of sulphur.[4] On other hand, silver(I) trifluoromethanethiolate ($AgSCF_3$) was found to be a useful C-S source in different nucleophilic addition reactions, as it easily undergoes decomposition to a highly electrophilic species carbonothioicdifluoride ($S{=}CF_2$).[5] In the past decades, several synthetic procedures have been developed for the synthesis of methylene-dihydrothiazole derivatives.[3] The major concerns of these reactions are the use of hazardous chemicals such as isothiocyanates, involvement of multi-step reactions and limited substitution on the methylene-dihydrothiazoles. Therefore, the development of a more efficient and general methodology for the synthesis of methylene-dihydrothiazoles from easily and readily available starting materials is highly desirable. Therefore, herein we report the synthesis of methylene-dihydrothiazole derivatives *via* nucleophilic addition followed by hydrothiolation of *N*-propargylamines using $AgSCF_3$ as electrophile and malonate esters as nucleophiles (*Scheme 4.2.6*).



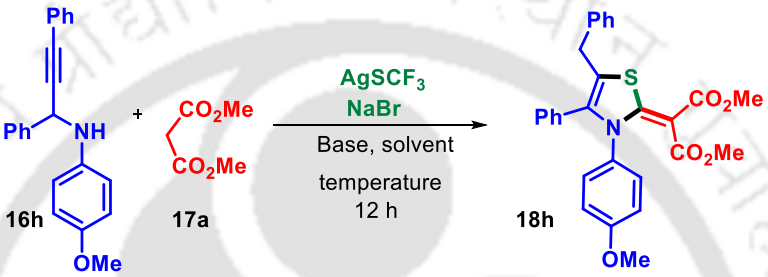
Scheme 4.2.6. *Synthesis of Dihydrothiazoles from N-propargylamines and Malonate Esters.*

4.3. Result and Discussion

To initiate the reaction, **16h** was chosen as the model substrate and treated with 1.0 equiv of Cs_2CO_3 in CH_3CN at room temperature for 12 h, but only starting material was recovered (*Table 4.3.1*, entry 1). We predicted that the increase in temperature may lead to the product formation and therefore, the reaction was carried out at 80 °C. Interestingly, the reaction gave the product **18h** with 34% yield (*Table 4.3.1*, entry 2). The result suggests that temperature had a significant role in this cyclization. While increasing the loading of base to 1.2 equiv, to our delight an increased yield 74% was observed (*Table 4.3.1*, entry 4). However, no significant change in the yield of the product **18h** was observed on increasing the reagent load as well as temperature (*Table 4.3.1*, entry

5-6). In order to check the role of solvent, the reaction was performed in dimethylsulfoxide (DMSO) but no desired product was obtained. The reaction in other solvent like toluene, THF and 1,4-dioxane produced 30%, 40% and 26% yields (*Table 4.3.1*, entries 3-6), respectively. On the other hand, the use of other inorganic bases such as K_2CO_3 and Na_2CO_3, failed to improve the yield while no desired product was obtained with the use of organic bases such as DBU and DABCO (*Table 4.3.1*, entries 15–16).

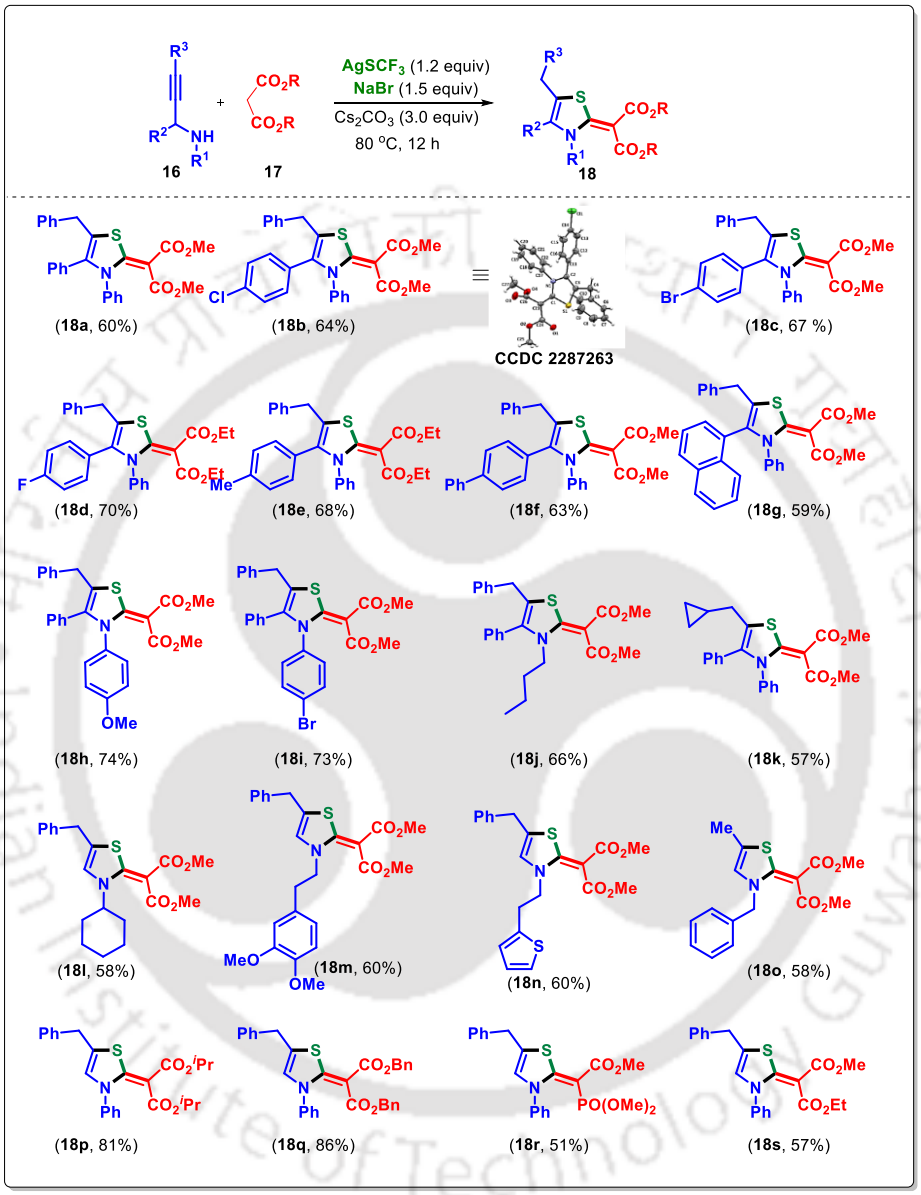
Table 4.3.1. Optimization of the Reaction[a]



Entry	Base (equiv)	Solvent	T(°C)	%yield[b]
1	Cs_2CO_3 (1.0)	CH_3CN	rt	N.R
2	Cs_2CO_3 (1.0)	CH_3CN	80	34
3	Cs_2CO_3 (2.0)	CH_3CN	80	43
4	**Cs_2CO_3 (3.0)**	**CH_3CN**	**80**	**74**
5	Cs_2CO_3 (4.0)	CH_3CN	80	58
6	Cs_2CO_3 (3.0)	CH_3CN	90	55
10	Cs_2CO_3 (3.0)	DMSO	80	N.R
11	Cs_2CO_3 (3.0)	toluene	80	30
12	Cs_2CO_3 (3.0)	THF	80	48
13	Cs_2CO_3 (3.0)	1,4-dioxane	80	26
14	K_2CO_3 (3.0)	CH_3CN	80	42
15	Na_2CO_3 (3.0)	CH_3CN	80	21
16	DBU (3.0)	CH_3CN	80	NR
17	DABCO	CH_3CN	80	NR

[a]Reaction conditions: **16h** (0.6 mmol, 1.0 equiv), **$AgSCF_3$** (0.72 mmol, 1.2 equiv), **NaBr** (0.9 mmol, 1.5 equiv), **17a** (1.2 mmol, 2.0 equiv), solvent 4.0 mL, 12 h, [b]Isolated yield, N.R =No reaction.

With these optimal conditions in hand, the scope of the reaction was explored with substrates derived from different *N*-propargylamines (*Scheme 4.3.2*). It was observed that R^2 group containing phenyl **16a** as well as aromatic groups bearing both electron-withdrawing and electron-



[a] Reaction condition: **16** (0.6 mmol, 1.0 equiv), $AgSCF_3$ (0.72 mmol, 1.2 equiv), KBr (0.9 mmol, 1.5 equiv), Cs_2CO_3 (1.8 mmol, 3.0 equiv), **17** (1.2 mmol, 2.0 equiv) in air for 12 h at 80 °C. [b]Isolated yield.

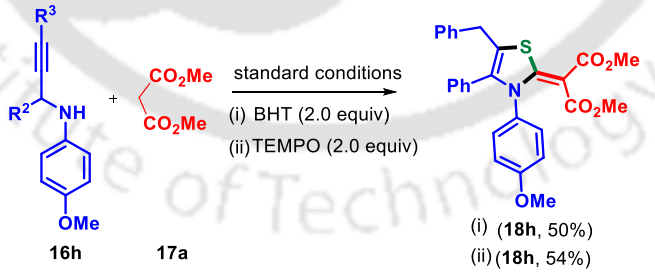
Scheme 4.3.2*. Scope of Substituted Methylene-dihydrothiazole derived from different N-propargylamines*[a,b]

donating substituents gave products **18a**, **18b-18e** in good yields. Substrate with biphenyl group **16f** also produced a good yield but sterically hindered 1-naphthyl substituted substrate **16g**

furnished a lower yield. On the other hand, different electron donating and electron withdrawing substituents in the alkyne side-chain (R^3) and amine side-chain (R^1) **16h-16j** gave **18h-18j** in good yields (*Scheme 4.3.2*). It is noteworthy that, even if strained cyclic substituents cyclopropyl alkyne substituents **16k** also provided decent yield (*Scheme 4.3.2*). In a quest, to explore further scope of this reaction, substrate having 1-substituted *N*-propargylamines **16l-16s** were subjected to standard reaction condition, and tri-substituted dihydrothiazole derivatives **18l-18s** were obtained successfully in moderate to good yields, similar to the compound reported by Jiang group[3e]. Furthermore, substrates **17** could be smoothly extended to diisopropyl and dibenzyl malonates giving products **18p-18q**. Methyl 2-(dimethoxyphosphoryl)acetate and ethyl 3-oxobutanoate as substrate **17** also gave their corresponding products **18r** and **18s** in moderate yields, respectively (*Scheme 4.3.2*). The structure of compounds was determined by ^{1}H, ^{13}C{^{1}H} NMR, mass spectrometry and finally by *X*-ray crystallographic analysis.[6]

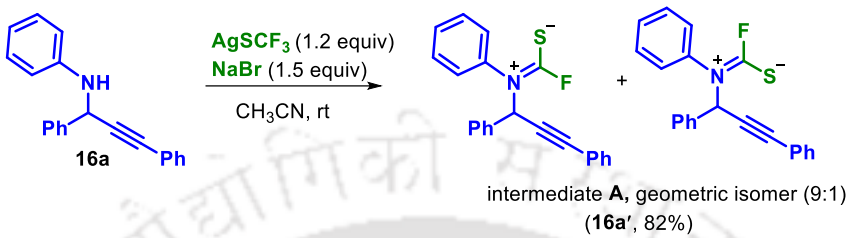
4.3.3. Control Experiments

To investigate the reaction pathway, initially, the reaction was performed separately in the presence of BHT and TEMPO. The reaction of **16h** with 2.0 equivalents of TEMPO gave the corresponding product **18h** with 54% yield under the standard reaction conditions. Similarly, same reaction when performed in presence of 2.0 equivalents of BHT furnished product **18h** with 50% yield. The above two radical scavenging agents did not inhibit the cyclization reactions. These results proved that the reaction might proceeds *via* an ionic pathway (*Scheme 4.3.3a*).



Scheme 4.3.3a. *To Confirm Reaction Pathway.*

In order to confirm the *in situ* generation of intermediate **A** (**16a'**) (*Scheme 4.3.4*), compound **16a** was treated with $AgSCF_3$ and NaBr without using malonate ester at room temperature, **16a'** was obtained with 82% yield as a mixture of geometric isomers (9:1) (*Scheme 4.3.3b*), which was detected by ^{1}H NMR (*Figure 4.3.3b*) $^{13}C\{^{1}H\}$, ^{19}F NMR (*Figure 4.3.3b'*).



Scheme 4.3.3b. *To Confirm the Formation of Intermediate* ***A***.

^{1}H Spectrum of Compound **16a'** (500 MHz, $CDCl_3$)

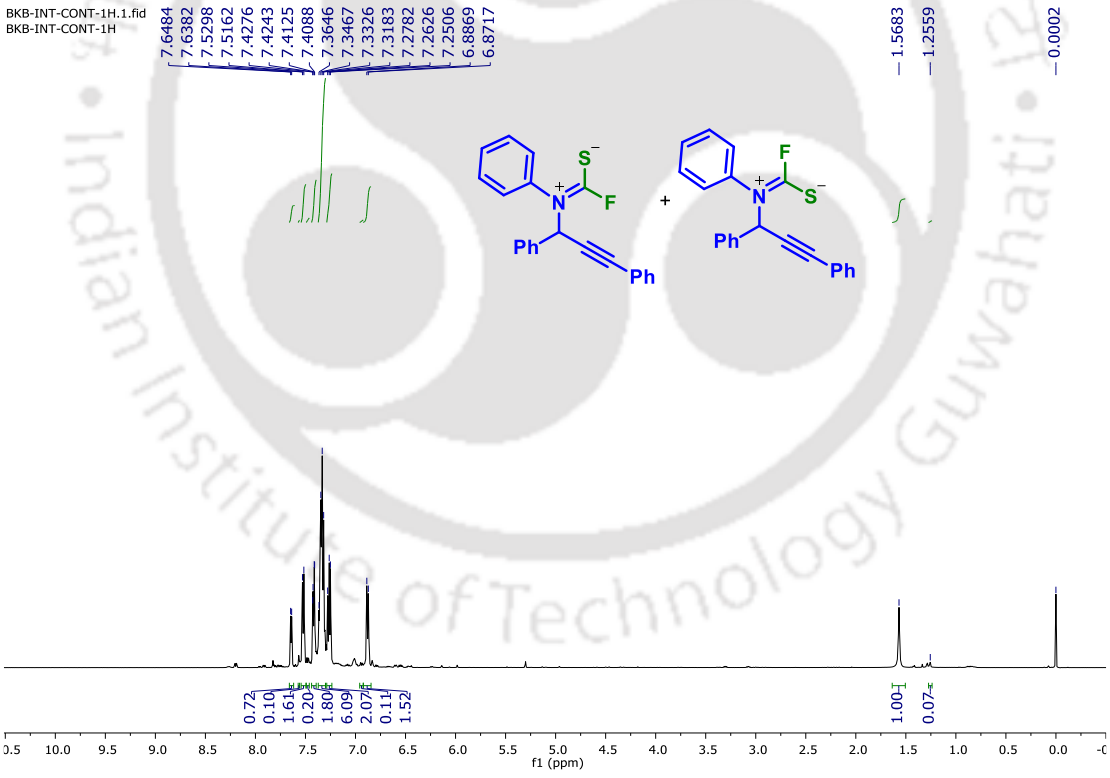
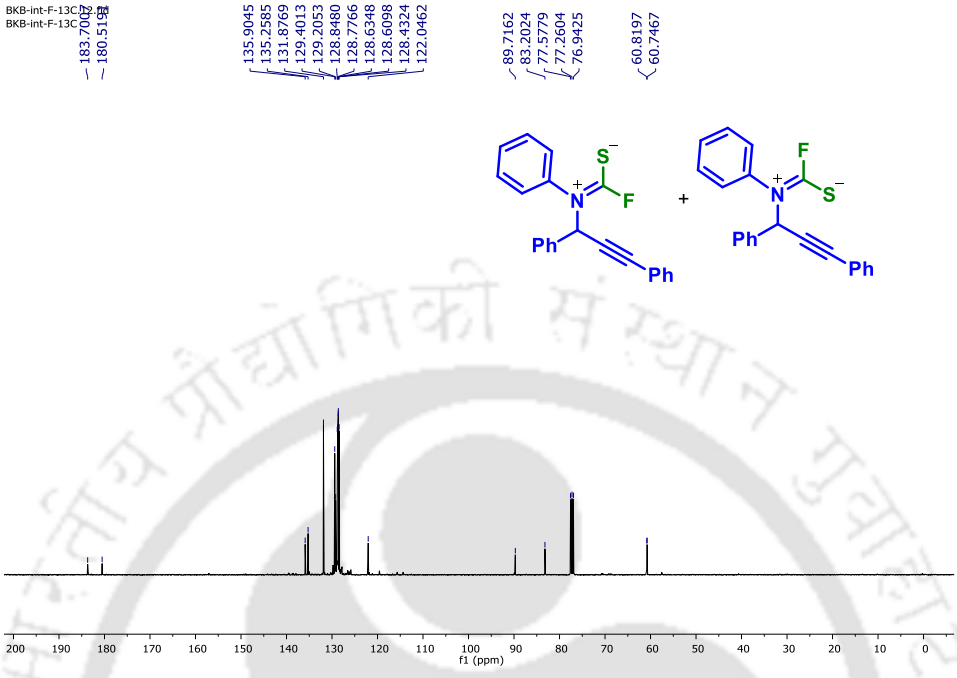


Figure 4.3.3b. *^{1}H NMR Study for in situ generation of Intermediate* ***A*** *(**16a'**).*

$^{13}C\{^{1}H\}$ NMR Spectrum of Compound **16a'** (125 MHz, $CDCl_3$)



^{19}F NMR Spectrum of Compound **16a'** (370 MHz, $C_6F_6/CDCl_3$)

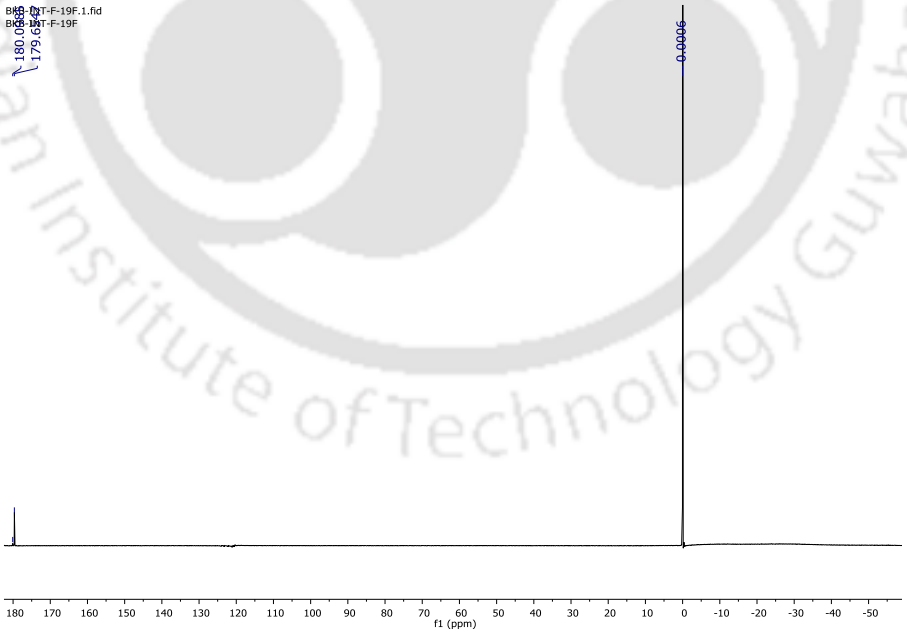
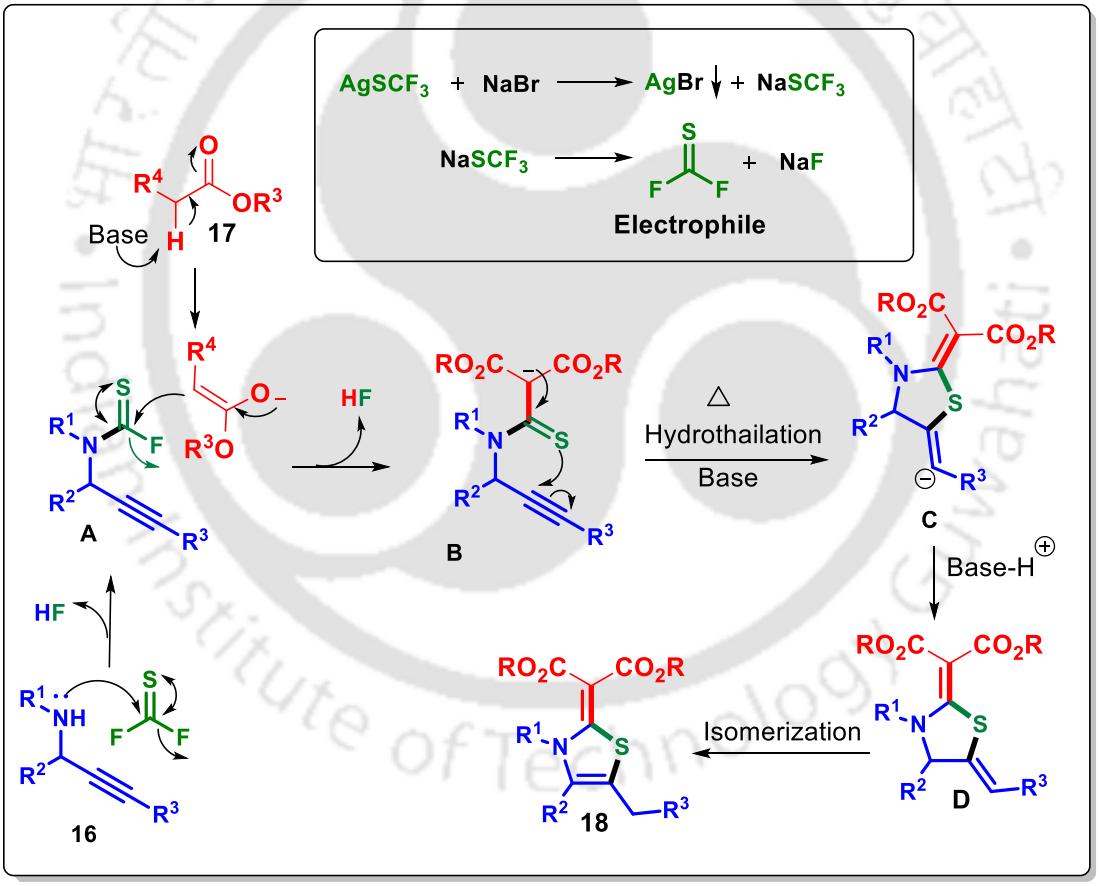


Figure 4.3.3b'. *$^{13}C\{^{1}H\}$, ^{19}F NMR Study for in situ generation of of Intermediate* ***A (16a')***.

4.3.4. Plausible Mechanism

As per the information gathered from the above experiments and previous reports a plausible mechanism is proposed (*Scheme 4.3.4*). Initially, $AgSCF_3$, which acts as electrophilic precursor reacts with NaBr to give $NaSCF_3$ and AgBr as a precipitate. Subsequently, NaF is released from $NaSCF_3$ to form thiocarbonyldifluoride (CSF_2).[7] Then the propargylamines **16** react with *in situ* generated CSF_2 to form thiocarbamoyl fluoride adduct **A**, which further reacts with malonate ester to form the intermediate **B** with the release of HF. Finally, hydrothilation reaction and proton abstraction occurs and followed by isomerization of unstable intermediate **D** to form desired product **18**.



Scheme 4.3.4. *Plausible Mechanism of the Reaction.*

4.4. Crystallographic Description

The structure of all compounds was confirmed from standard spectroscopic experiments and finally by *X*-ray crystallographic analysis of compound **18b** (*figure 4.4*)

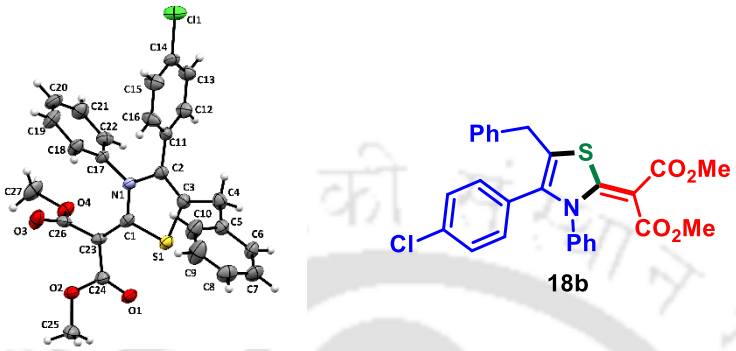


figure 4.4. *ORTEP diagram of compound* ***18b****, thermal ellipsoids are drawn on 30% probability level.*

Compound **18b**	**CCDC 2287263**
Formula	$C_{27}H_{22}ClNO_4S$
Formula weight	491.96
T/K	296(2)
Crystal system	Triclinic
Space group	P -1
a/Å	9.738(2)
b/Å	10.456(2)
c/Å	12.569(3)
α/°	97.343(6)
β/°	98.153(6)
γ/°	107.774(6)
V/Å^3	1186.4(5)
Z	2
Abs. Coeff./mm^{-1}	0.284
Abs. Correction	multi-scan
GOF on F^2	0.924
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0743 *wR2* = 0.1676
R indices [all data]	*R1* = 0.2429 *wR2* = 0.2675

Conclusion

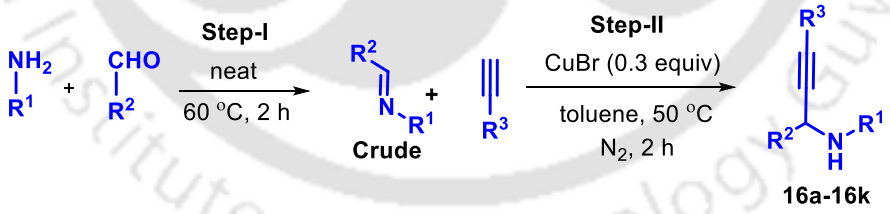
In conclusion, an efficient methodology for the synthesis of highly substituted methylene-dihydrothiazole derivatives has been developed from easily prepared starting material *N*-propargylamine in good yields by using $AgSCF_3$ as a C-S source and malonate ester as a nucleophile *via* hydrothailation under open air condition in single step.

4.5. Experimental Section

4.5.1. Instrumentation and Characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (600 MHz, 500 MHz and 400 MHz) or $^{13}C\{^1H\}$ (150 MHz, 125 MHz and 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

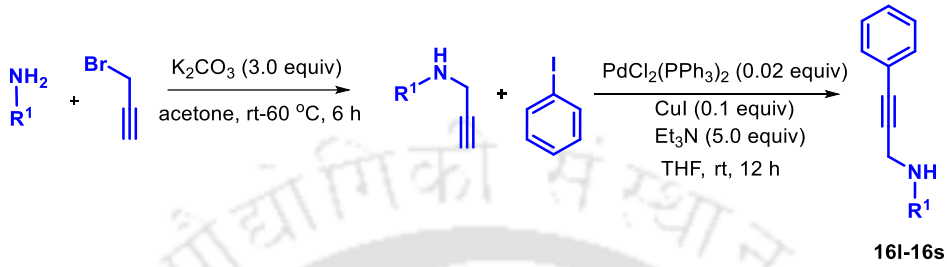
4.5.2. General Experimental Procedure for Starting-materials 16a-16k



A mixture of aldehyde (5.0 mmol, 1.0 equiv) and amine (7.5 mmol, 1.5 equiv) was heated at 60 °C for two hours. Then, crude imine transfers to another two neck round bottom flask and copper(I) bromide (1.5 mmol, 0.3 equiv) and acetylene (10.0 mmol, 2.0 equiv) and dry toluene (4.0 mL) were added into the mixture under nitrogen. And the resulting mixture was heated at 50 °C in an oil bath for 4 h. The reaction mixture was poured into water, and extracted with EtOAc (3 × 20 mL). The organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was

removed under reduced pressure. The crude product was then purified using column chromatography over silica gel to get corresponding product **16a-16k**.

4.5.3. General Experimental Procedure for Starting-materials 16l-16s

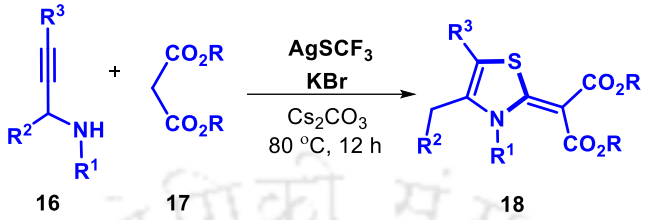


16l-16s

A solution of amines (5 mmol, 1.0 equiv) and K_2CO_3 (15 mmol, 3.0 equiv) in acetone (5 mL) was stirred under N_2 atmosphere for 15 min at room temperature and then propargyl bromide (7.5 mmol, 1.5 equiv) was added drop wise. The mixture was stirred at 60 °C for 6 h in an oil bath. After completion of the starting material, the solvent was removed under reduced pressure. The reaction mixture was diluted with ethyl acetate, washed with brine solution. The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to get corresponding product *N*-(2-propynyl)amines.

To a stirred solution of 4-iodobenzene (3.6 mmol, 1.2 equiv), bis(triphenylphosphine)palladiumdichloride (0.15 mmol, 0.02 equiv) and copper iodide (0.3 mmol, 0.1 equiv) in triethylamine (12 mL) was added *N*-(2-propynyl)amines (3 mmol, 1.0 equiv) at room temperature under N_2 atmosphere. Then the mixture was stirred at room temperature for 12 h. After completion of the starting material, the solvent was removed under reduced pressure. The reaction mixture was diluted with ethyl acetate, washed with brine solution. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography using ethyl acetate and hexane as eluents over silica gel to give **16l-16s**.

4.5.4. General Experimental Procedure for the Synthesis of Compounds 18a-18s



To a stirred solution of $AgSCF_3$ (0.72 mmol, 1.2 equiv), NaBr (0.9 mmol, 1.5 equiv), malonate ester **17** (1.2 mmol, 2.0 equiv) and Cs_2CO_3(1.8 mmol, 3.0 equiv) in CH_3CN (1.8 mL: 0.2 mL) was added *N*-propargylamines **16** (0.6 mmol, 1.0 equiv) dropwise at room temperature. Then the mixture was stirred in an oil bath at 80 °C and the reaction time was monitored by TLC. After completion of the reaction, the solvent was removed completely under reduced pressure. The residue was diluted with ethyl acetate and saturated brine solution. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to get the corresponding product **18**.

4.6. References:

(1) (a) Rouf, A.; Tanyeli, C. *Eur. J. Med. Chem.* **2015**, *97*, 911–927. (b) Fu, P.; MacMillan, J. B. *J. Nat. prod.* **2015**, *78*, 548–551.

(2) (a) Atta, A.; Fahmy, S.; Rizk, O.; Sriram, D.; Mahran, M. A.; Labouta, I. M. *Bioorg. Chem.* **2018**, *80*, 721−732 (b) Salem, M. A. *Croat. Chem. Acta*. **2017**, *90*, 6−15. (c) Amr, A. E.-G. E.; Sabrry, N. M.; Abdalla, M. M.; Abdel-Wahab, B. F. *Eur. J. Med. Chem*. **2009**, *44*, 725−735. (d) Fadda, A. A.; El-badraw, A. M.; Refat, H. M.; Abdel-Latif, E. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2016**, *191*, 778– 785.

(3) (a) Bhattacharjee, S. S.; Asokan, C.V.; Ila, H.; Junjappa, H. *Synthesis*, **1982**; *12*, 1062–1064. (b) Burckstummer, H.; Tulyakova, E.V.; Deppisch, M.; Lenze, M.R.; Kronenberg, N.M.; Gsanger, M.; Stolte, M.; Meerholz, K.; Wurthner, F. *Angew. Chem.* **2011**, *123*, 11832–11836. (c) Kumar, Y.; Ila, H. *Org. Lett.* **2019**. *21*, 7863–7867.

(d) Yao, Z.; Cai, Z.; Zhen, L.; Jiang, L. *Org. Lett.* **2020**, *22*, 4505–4510. (e) Cai, Z.; Zhou, J.; Yu, M.; Jiang, L.; *Org. Lett.* **2021**, *24*, 293–298.

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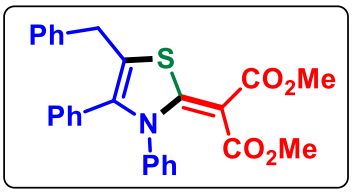
(5) Dmowski, W.; Haas, A. *J. Chem. Soc., Perkin Trans*. **1988**, *1*, 1179–1181. (b) Clark, J. H.; Tavener, S. J. *J. Fluorine Chem*. **1997**, *85*, 169–172. (c) Tavener, S. J.; Adams, D. J.; Clark, J. H. *J. Fluorine Chem*. **1999**, *95*, 171–176.

(6) The crystallographic data for the compound **18b** has been deposited with the Cambridge crystallographic data centre as supplementary publication no. CCDC 2287263.

(7) (a) Liu, J.-B.; Xu, X.-H.; Chen, Z.-H.; Qing, F.-L. *Angew. Chem. Int. Ed.* **2015**, *54*, 897–900. (b) Zhen, L.; Fan, H.; Wang, X.; Jiang, L. *Org. Lett*. **2019**, *21*, 2106–2110. (c) Zhen, L.; Yuan, K.; Li, X.-Y.; Zhang, C.; Yang, J.; Fan, H.; Jiang, L. *Org. Lett.* **2018**, *20*, 3109–3113.

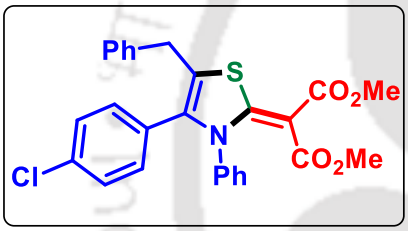
4.7. Characterization Data

Dimethyl 2-(5-benzyl-3,4-diphenylthiazol-2(3*H*)-ylidene)malonate (18a):



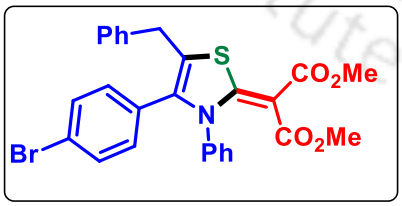
Brown solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 182–184 °C. Yield 165 mg, 60%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.02–6.01 (m, 3 H), 6.01–5.92 (m, 6 H), 5.77 (d, *J* = 7.4 Hz, 2 H), 5.73–5.70 (m, 2 H), 5.60 (d, *J* = 8.4 Hz, 2 H), 2.47 (s, 2 H), 2.10 (s, 6 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 167.3, 165.5, 138.5, 138.0, 136.4, 135.1, 132.0, 129.1, 129.0, 128.9, 128.7, 128.6, 128.5, 128.0, 125.1, 123.0, 88.8, 50.5, 33.1. **IR** (KBr, neat) 2922, 1761, 1497, 1242, 709 cm^{-1}; **HRMS** (ESI) calcd. for $C_{27}H_{24}NO_4S$ $(M + H)^+$ 458.1421, found 458.1440.

Dimethyl 2-(5-benzyl-4-(4-chlorophenyl)-3-phenylthiazol-2(3*H*)-ylidene)malonate (18b):



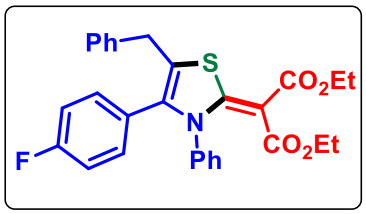
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 202–204 °C. Yield 188 mg, 64%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.05–6.01 (m, 2 H), 5.98–5.92 (m, 6 H), 5.87 (d, *J* = 7.4 Hz, 2 H), 5.76–5.71 (m, 2 H), 5.62 (d, *J* = 8.4 Hz, 2 H), 2.47 (s, 2 H), 2.10 (s, 6 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 167.1, 165.0, 138.7, 138.3, 136.6, 135.5, 132.4, 129.2, 129.0, 128.8, 128.7, 128.7, 128.6, 128.5, 127.2, 123.3, 87.8, 51.5, 33.2. **IR** (KBr, neat) 2948, 1748, 1487, 1296, 699 cm^{-1}; **HRMS** (ESI) calcd. for $C_{27}H_{23}ClNO_4S$ $(M + H)^+$ 491.0958, found 491.0973.

Dimethyl 2-(5-benzyl-4-(4-bromophenyl)-3-phenylthiazol-2(3*H*)-ylidene)malonate (18c):



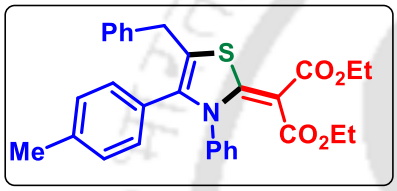
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 212–214 °C. Yield 215 mg, 67%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.02–6.01 (m, 2 H), 5.92–5.90 (m, 6 H), 5.88 (d, *J* = 7.4 Hz, 2 H), 5.73–5.70 (m, 2 H), 5.60 (d, *J* = 8.4 Hz, 2 H), 2.47 (s, 2 H), 2.10 (s, 6 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 167.1, 165.0, 138.7, 138.3, 136.6, 135.5, 132.4, 129.2, 129.0, 128.8, 128.7, 128.7, 128.6, 128.5, 127.2, 123.3, 87.8, 51.5, 33.2. **IR** (KBr, neat) 2948, 1748, 1487, 1296, 699 cm^{-1}; **HRMS** (ESI) calcd. for $C_{27}H_{23}BrNO_4S$ $(M + H)^+$ 536.0526, found 536.0539.

Diethyl 2-(5-(4-fluorobenzyl)-3,4-diphenylthiazol-2(3*H*)-ylidene) malonate (18d):



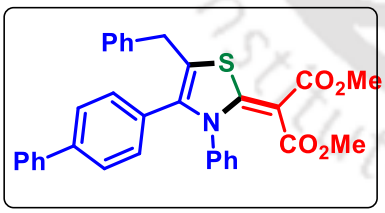
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 200–202 °C. Yield 211 mg, 70%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.22– 7.19 (m, 2 H), 7.17– 7.09 (m, 4 H), 7.08–7.03 (m, 2 H), 6.96–6.90 (m, 2 H), 6.89–6.79 (m, 4 H), 3.69 (q, *J* = 7.1 Hz, 4 H), 3.64 (s, 2 H), 1.04 (t, *J* = 7.2 Hz, 6 H). **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 166.8, 164.0,163.9, 161.9, 138.6, 138.4, 136.6, 133.0 (d, *J* = 33.5 Hz), 129.1, 129.0, 128.9, 128.7, 128.6, 127.1, 122.4, 115.7 (d, *J* = 86.7 Hz), 88.7, 60.2, 33.1, 14.3. **IR** (KBr, neat) 2947, 1747, 1485, 1076, 700 cm^{-1}; **HRMS** (ESI) calcd. for $C_{29}H_{27}FNO_4S$ $(M + H)^+$ 504.1639, found 504.1656.

Diethyl 2-(5-benzyl-3-phenyl-4-(*p*-tolyl)thiazol-2(3*H*)-ylidene)malonate (18e):



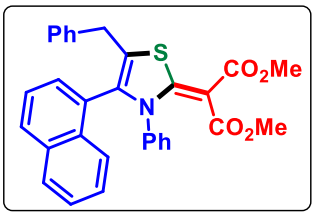
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 200–202 °C. Yield 210 mg, 70%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26–7.20 (m, 2 H), 7.19–7.10 (m, 4 H), 7.05–7.01 (m, 2 H), 6.98–6.90 (m, 2 H), 6.90–6.80 (m, 4 H), 3.68 (q, *J* = 7.1 Hz, 4 H), 3.64 (s, 2 H), 2.34 (s, 3 H), 1.04 (t, *J* = 7.2 Hz, 6 H). **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 167.4, 165.0, 138.6, 138.4, 136.4, 135.4, 132.7, 133.5, 129.3, 129.0, 128.7, 128.5, 128.4, 126.1, 121.2, 118.2, 89.1, 61.4, 34.1, 21.5, 14.1. **IR** (KBr, neat) 2967, 1748, 1430, 1014, 707 cm^{-1}; **HRMS** (ESI) calcd. for $C_{30}H_{30}NO_4S$ $(M + H)^+$ 500.1890, found 500.1896.

Dimethyl 2-(4-([1,1'-biphenyl]-4-yl)-5-benzyl-3-phenylthiazol-2(3*H*)-ylidene)malonate (18f):



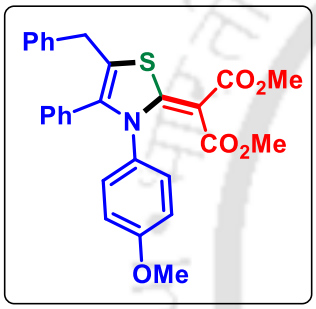
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 212–214 °C. Yield 201 mg, 63%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2 H), 7.20–7.15 (m, 4 H), 7.11–7.08 (m, 1 H), 7.05–7.02 (m, 2 H), 6.99–6.91 (m, 6 H), 6.80–6.75 (m, *J* = 14.8, 7.6 Hz, 4 H), 3.54 (s, 2 H), 3.11 (s, 6 H). **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 167.2, 165.4, 141.8, 140.1, 138.9, 138.6, 132.2, 131.5, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.1, 127.2, 127.8, 127.0, 79.3, 51.5, 33.3.**IR** (KBr, neat) 2924, 1758, 1467, 1212, 704 cm^{-1}; **HRMS** (ESI) calcd. for $C_{33}H_{28}NO_4S$ $(M + H)^+$ 534.1734, found 534.1759.

Dimethyl 2-(5-benzyl-4-(naphthalen-1-yl)-3-phenylthiazol-2(3*H*)-ylidene)malonate (18g):



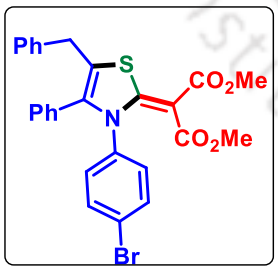
Brown gummy; R_f (hexane/EtOAc, 1:1) 0.50; Yield 179 mg, 59%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31–7.28 (m, 2 H), 7.21–7.12 (m, 2 H), 7.11–7.09 (m, 1 H), 7.05–7.01 (m, 2 H), 6.70–6.91 (m, 6 H), 6.80–6.75 (m, *J* = 14.8, 7.4 Hz, 4 H), 3.50 (s, 2 H), 3.10 (s, 6 H). **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 167.5, 165.3, 141.8, 140.0, 138.9, 138.5, 134.4, 133.5, 132.4, 132.2, 131.5, 129.3, 129.2, 129.1, 128.9, 128.8, 128.7, 128.6, 128.2, 127.3, 127.1, 127.0, 80.1, 51.4, 32.1.**IR** (KBr, neat) 2950, 1762, 1452, 1271, 756 cm^{-1}; **HRMS** (ESI) calcd. for $C_{31}H_{26}NO_4S$ $(M + H)^+$ 508.1583, found 508.1591.

Dimethyl 2-(5-benzyl-3-(4-methoxyphenyl)-4-phenylthiazol-2(3*H*)-ylidene)malonate (18h):



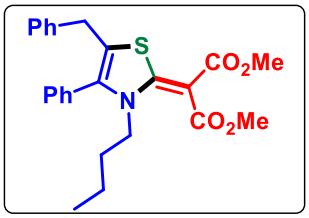
Brown Solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 182–184 °C. Yield 216 mg, 74%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.04–5.96 (m, 6 H), 5.91–5.87 (m, 2 H), 5.73–5.69 (m, 2 H), 5.66 (d, *J* = 8.9 Hz, 2 H), 5.43 (d, *J* = 9.0 Hz, 2 H), 2.47 (d, *J* = 4.0 Hz, 5 H), 2.13 (s, 6 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 167.3, 165.5, 159.2, 138.6, 138.3, 131.6, 131.1, 130.1, 129.9, 129.2, 128.9, 128.7, 128.5, 127.1, 122.6, 114.0, 87.2, 55.6, 51.5, 33.2. **IR** (KBr, neat) 2960, 1666, 1409, 1266, 697 cm^{-1}; **HRMS** (ESI) calcd. for $C_{28}H_{26}NO_5S$ $(M + H)^+$ 488.1526, found 488.1538.

Dimethyl 2-(5-benzyl-3-(4-bromophenyl)-4-phenylthiazol-2(3*H*)-ylidene)malonate (18i):



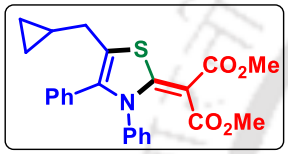
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 221–223 °C. Yield 234 mg, 73%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.10–6.08 (m, 2 H), 5.93–5.91 (m, 6 H), 5.90 (d, *J* = 7.4 Hz, 2 H), 5.76–5.74 (m, 2 H), 5.60–5.58 (m, 2 H), 2.50 (s, 2 H), 2.12 (s, 6 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 167.5, 165.1, 138.6, 138.2, 136.3, 135.7, 132.6, 129.2, 129.1, 128.8, 128.7, 128.6, 128.5, 128.4, 127.3, 123.4, 89.8, 50.1, 34.7. **IR** (KBr, neat) 2967, 1731, 1486, 1293, 679 cm^{-1}; **HRMS** (ESI) calcd. for $C_{27}H_{23}BrNO_4S$ $(M + H)^+$ 536.0526, found 536.0533.

Dimethyl 2-(5-benzyl-3-butyl-4-phenylthiazol-2(3*H*)-ylidene)malonate (18j):



Brown gummy; R_f (hexane/EtOAc, 1:1) 0.40; Yield 173 mg, 66%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.10–6.08 (m, 2 H), 5.92–5.90 (m, 6 H), 5.76–5.74 (m, 2 H), 2.48 (s, 2 H), 3.53–3.50 (m, 2 H), 2.12 (s, 6 H) 1.50–1.42 (m, 2 H), 1.20–1.19 (m, 2 H), 0.80 (t, *J* = 7.4 Hz, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 167.5, 165.1, 138.2, 137.1, 132.2, 129.5, 129.3, 129.1, 129.0, 128.2, 127.8, 127.3, 88.2, 50.9, 34.3, 32.8, 31.3, 20.0, 13.7. **IR** (KBr, neat) 2941, 1765, 1485, 1253, 675 cm^{-1}; **HRMS** (ESI) calcd. for $C_{25}H_{18}NO_4S$ $(M + H)^+$ 438.1734, found 438.1752.

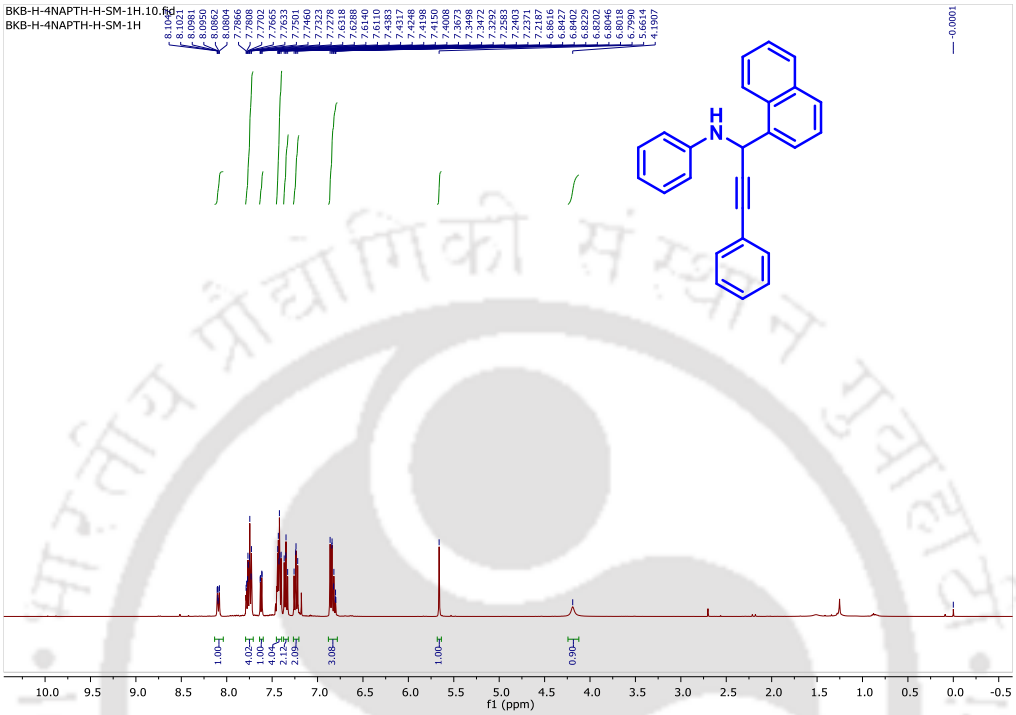
Dimethyl 2-(5-(cyclopropylmethyl)-3,4-diphenylthiazol-2(3*H*)-ylidene)malonate (18k):



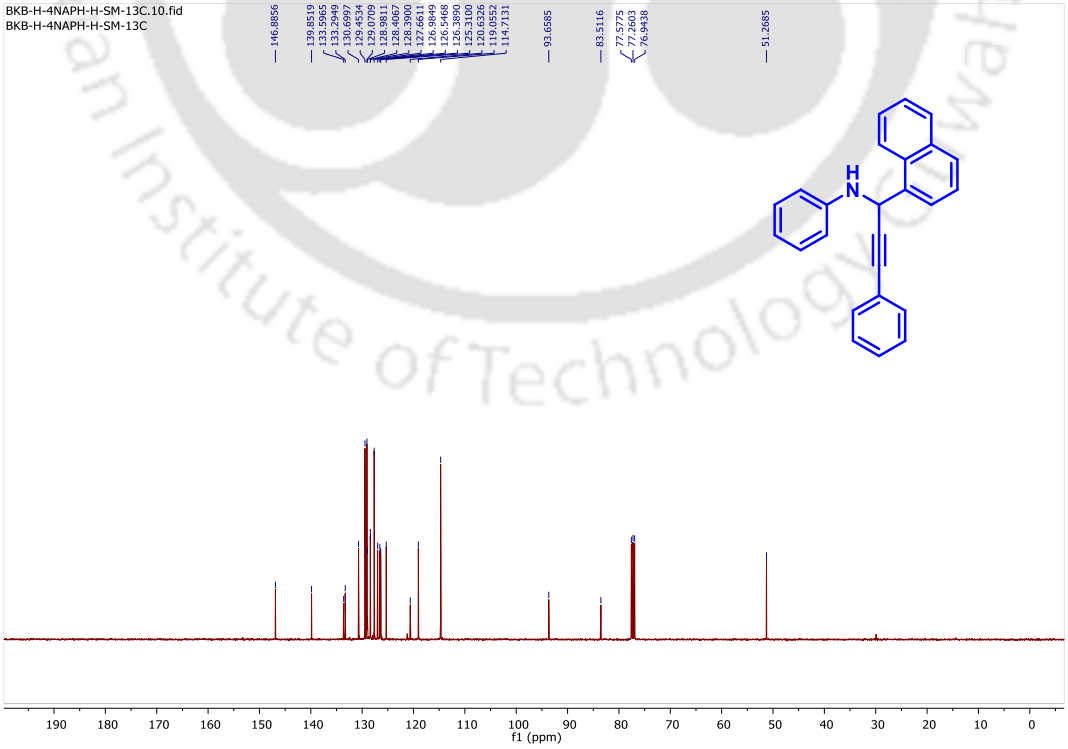
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.40; Yield 144 mg, 57%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.16–6.12 (m, 2 H), 5.91–5.90 (m, 6 H), 5.80–5.74 (m, 2 H), 2.46–2.41 (m, 2 H), 2.32 (s, 6 H) 1.90–1.87 (m, 1 H), 0.94–0.92 (m, 2 H), 0.73– 0.62 (m, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 167.2, 165.6, 138.1, 132.0, 129.6, 129.5, 129.2, 129.1, 128.2, 127.9, 127.4, 88.6, 50.3, 34.2, 32.1, 8.9, 7.4 **IR** (KBr, neat) 2935, 1773, 1441, 1283, 670 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{24}NO_4S$ $(M + H)^+$ 422.1421, found 422.1440.

4.8. Representative Spectra

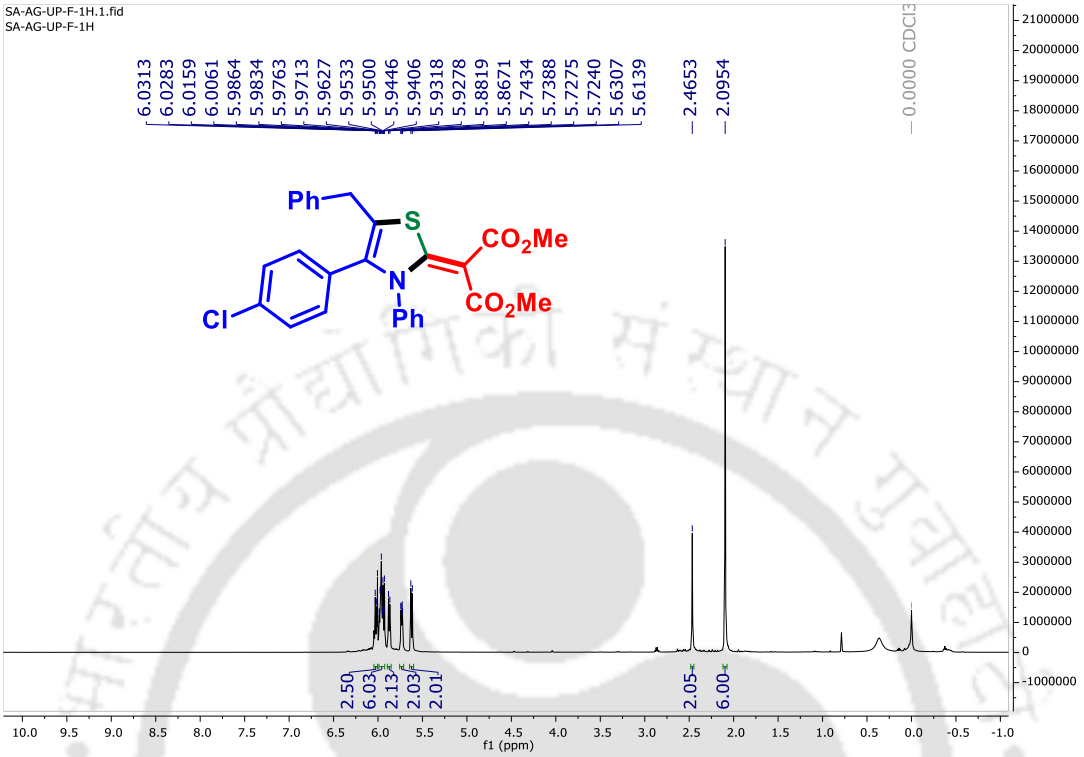
^{1}H spectrum of compound **16g** (400 MHz, $CDCl_3$)



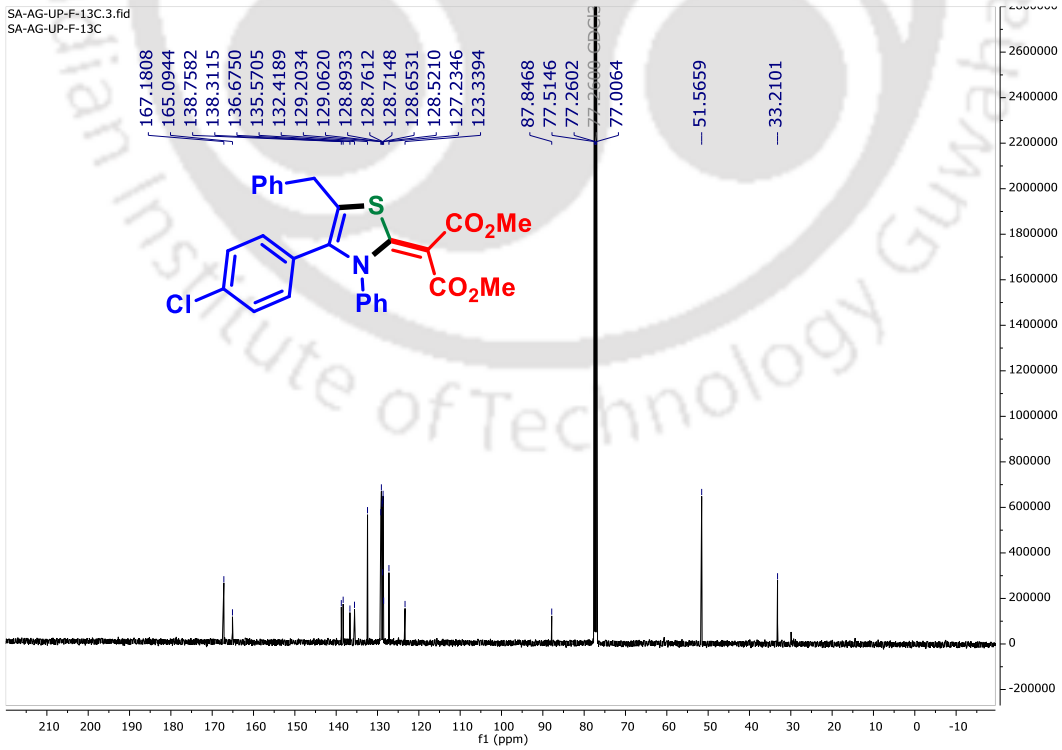
^{13}C{^{1}H} NMR spectrum of compound **16g** (100 MHz, $CDCl_3$)



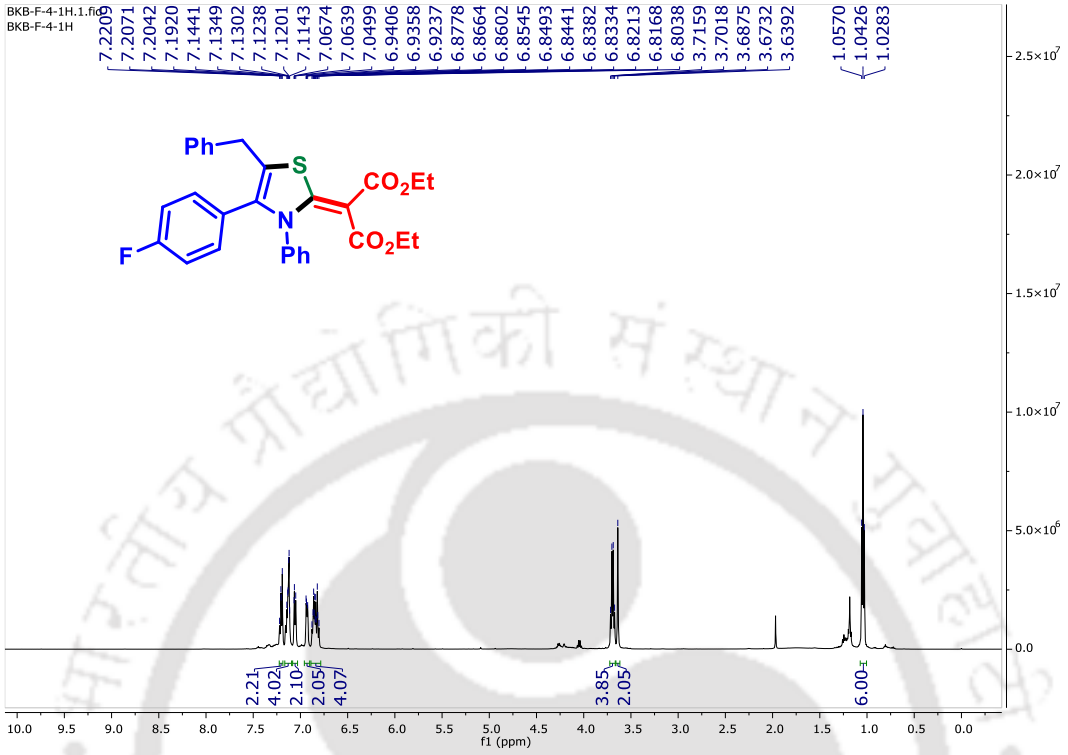
^{1}H NMR spectra of compound **18b** (500MHz, $CDCl_3$)



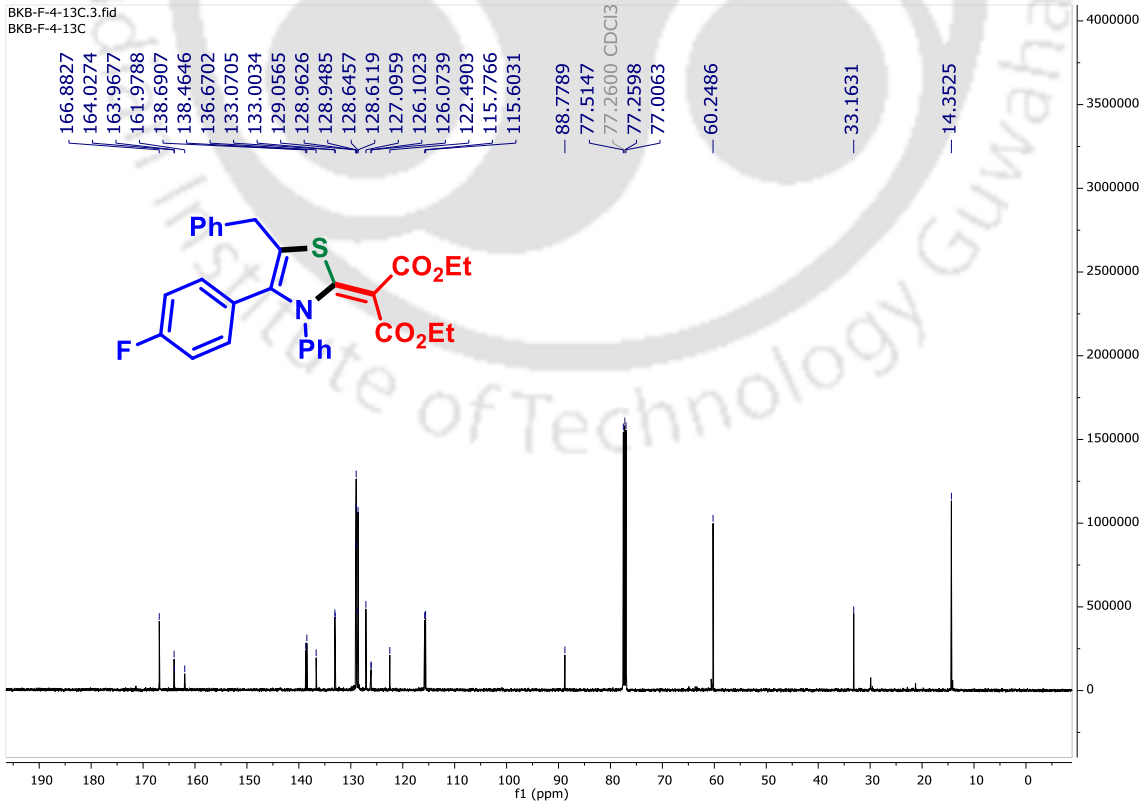
^{13}C{^{1}H} NMR spectra of compound **18b** (500 MHz, $CDCl_3$)



^{1}H NMR spectra of compound **18d** (500MHz, $CDCl_3$)



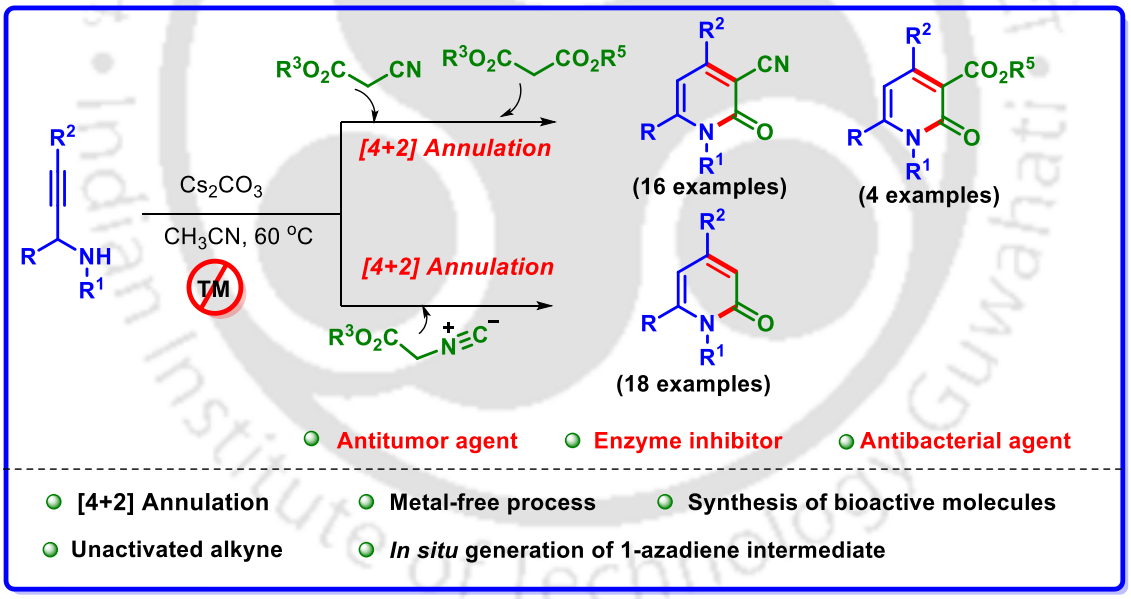
^{13}C{^{1}H} NMR spectra of compound **18d** (500 MHz, $CDCl_3$)



CHAPTER 5

Base Promoted [4+2] Annulation Reaction of *In Situ* Generated Azadienes from *N*-propargylamines with Active-methylene Compounds: Access to Highly Functionalized 2-Pyridones

Abstract: This chapter highlights a facile and efficient synthesis of structurally diversified 2-pyridones is demonstrated using the [4+2] annulation of *in situ* generated azadienes from *N*-propargylamines and active-methylene compounds. The reaction is promoted by an inorganic base giving moderate to good yields. The developed methodology is applicable for direct and formal synthesis of various bioactive molecules. The synthetic utility of the protocol was also illustrated by late stage functionalization of the products.



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J. Org. Chem. 2023, 88, 15041
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Article

5.1. Introduction

The 2-pyridone scaffold is an important and ubiquitous class of six-membered heterocyclic skeleton which is found in numerous biologically active natural products with potent pharmacological, organic-materials and agrochemical activities.[1] Among them, the 2-pyridone moiety possessing strong electron-withdrawing group like nitrile at position 3 have immense biological activities including anticancer, antiviral, anti-inflammatory, cardiotonic, and antibacterial activities (*Figure 5.1*).

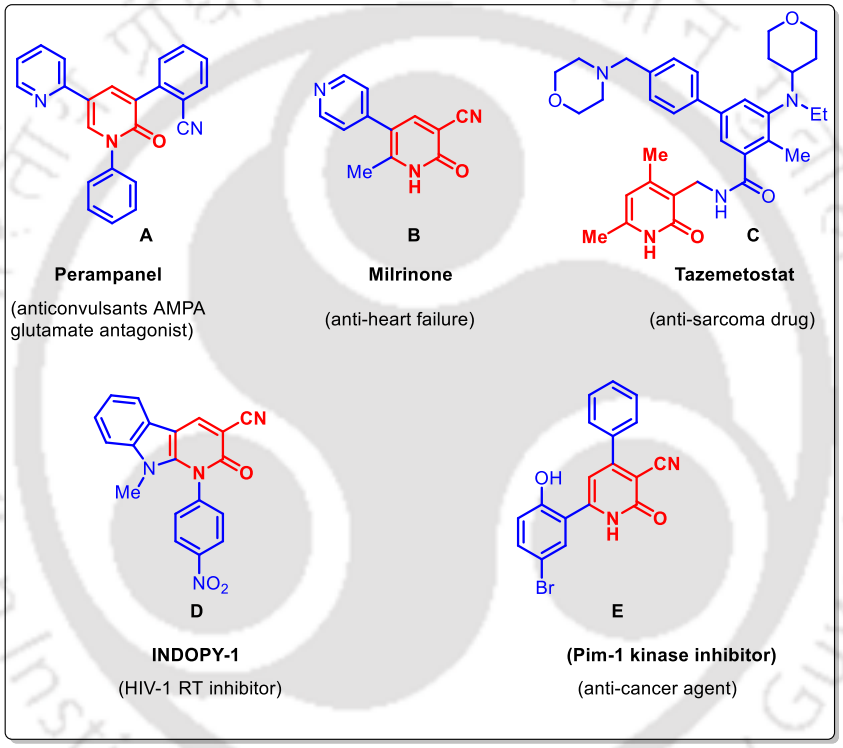


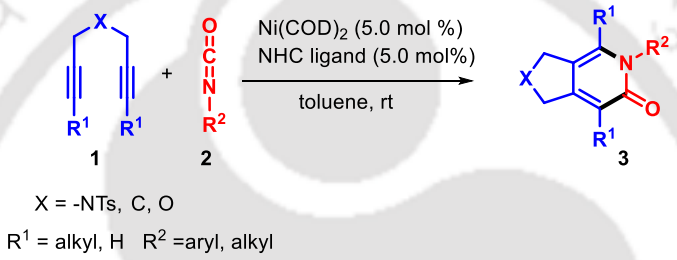
Figure 5.1. *Some Biologically Active 2-Pyridones.*

For instance, Perampanel **A**,[1a] is AMPA glutamate receptor antagonist used to treat partial-onset seizures; milrinone **B**,[1b] used as a phosphodiesterase III inhibitor for the treatment of heart failure; tazemetostat [1c] is commonly used as anti-sarcoma drug; INDOPY-1[1d] is widely used as HIV-1 RT Inhibitor and Pim-1 kinase inhibitor **E**,[1e] is an anti-cancer agent (*Figure 5.1*). Substituted 2-pyridones are also important intermediates for the synthesis of vitamins [2a] as well as in photo and dye industries. [2b] Besides, it has been widely employed as starting precursors for the synthesis of

many biological active fused heterocycles through C–H activation and C–H functionalization.[2c, d] Owing to their importance in medicinal and pharmaceutical chemistry and diverse applications, there is a need to develop a new and efficient methodology for the synthesis of highly substituted 2-pyridones.

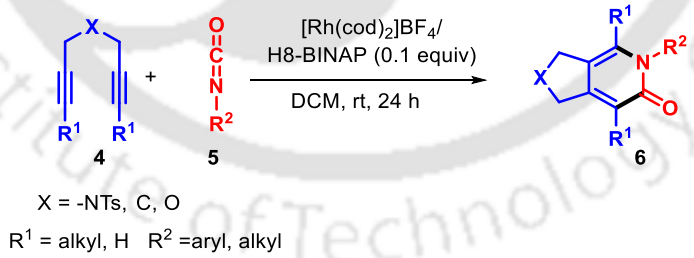
5.2. Literature Survey for the Synthesis of Substituted 2-Pyridones

In 2004, Louie and co-workers reported a useful strategy for the synthesis of fused 2-pyridones **3** from the treatment of alkynes **1** with isocyanate derivatives **2**. The reaction takes place by atom-economic cycloaddition reaction of alkynes **1** and isocyanates **2** catalyzed by Ni(0) in combination with *N*-heterocyclic carbenes (NHC) in toluene at room temperature (*scheme 5.2.1*).[3a]



Scheme 5.2.1. *Ni-Catalysed Synthesis of Fused 2-Pyridones from Alkynes and Isocyanates.*

In the next year, Tanaka and co-workers designed an intermolecular enantioselective [2+2+2] cycloaddition reaction of alkynes **4** and isocyanates **5** to afford fused 2-pyridones **6** in moderate to good yields, using Rh catalyst at room temperature in DCM (*scheme 5.2.2*).[3b]

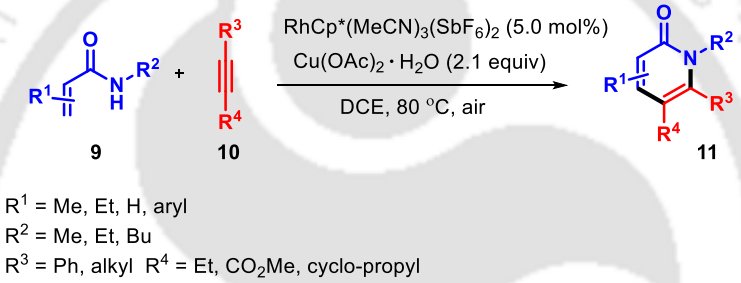


Scheme 5.2.2. *Rh-Catalysed Synthesis of Fused 2-Pyridones from Alkynes and Isocyanates.*

In 2008, same group demonstrated Au-catalyzed intramolecular cascade reaction of *N*-alkenyl alkynylamides **7** for the synthesis of fused 2-pyridones **8** *via* cyclo-isomerization. The reaction was performed at room temperature under open air conditions giving the corresponding 2-pyridones in good to excellent yields (*scheme 5.2.3*).[3c]

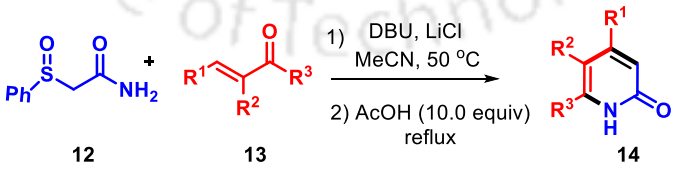
Scheme 5.2.3. *Au-Catalysed Synthesis of Fused 2-Pyridones from N-*alkenyl alkynylamides.

In 2011, Hyster *et al.* developed a Rh-catalyzed robust one-pot synthesis of highly substituted 2-pyridones **11** scaffold by coupling of acrylamides **9** with alkynes **10** in presence of stoichiometric amount of $Cu(OAc)_2$ and air as oxidant in DCE at -78 °C. The reaction proceeds *via* C-H activation pathway and has a broad range of substrate scope (*scheme 5.2.4*).[3d]



Scheme 5.2.4. *Synthesis of Substituted 2-Pyridones from Acrylamides and* Alkynes.

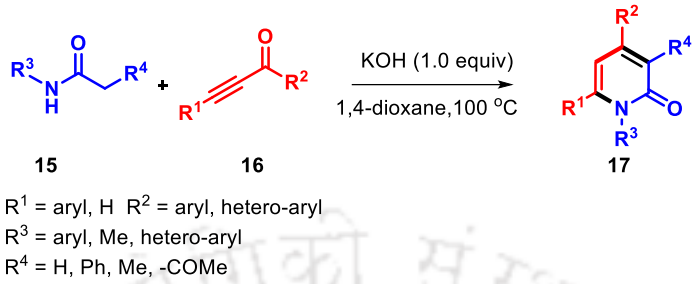
Fujii *et al.* in 2012, reported an interesting method for synthesis of 4,5,6-substituted 2-pyridones **14** *via* 1, 4-addition of 2-phenylsulfinyl-acetamide **12** and *α, β*-unsaturated ketones **13** followed by sulfoxide elimination. Initially the Michael addition reaction proceeds smoothly in the presence of DBU and lithium chloride (LiCl) in CH_3CN at 50 °C, subsequently cyclization is facilitated by the addition of acetic acid at reflux condition (*scheme 5.2.5*).[3e]



Scheme 5.2.5. *Synthesis of Substituted 2-Pyridones from Acetamides and Unsaturated Ketones.*

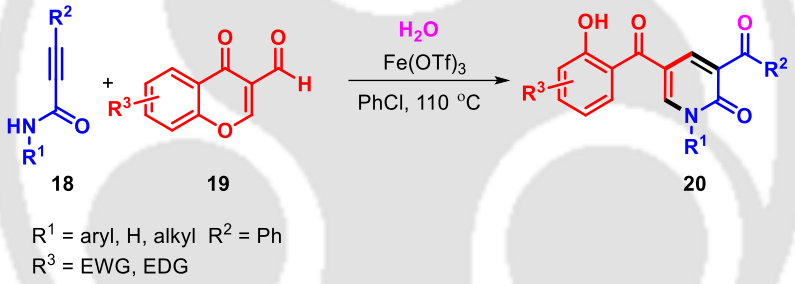
In 2018, Pan and co-workers, demonstrated an efficient transition metal-free intermolecular cyclization of amides **15** and ynones **16** towards the synthesis of tetra-substituted 2-pyridones **17** in good to excellent yields. The reaction proceeds *via* 1,4 addition of amides **15** and ynones **16**

followed by knoevenagel condensation to afford corresponding product 2-pyridones **17** (*scheme 5.2.6*).[3f]



Scheme 5.2.6. *Synthesis of Substituted 2-Pyridones from Amides and* Ynones.

Recently, Lee and co-workers, has demonstrated an efficient eco-friendly Fe(III) catalyzed cascade cyclization of readily accessible 3-formylchromone **19** derivatives and propiolamides **18** towards the construction of substituted 2-pyridone **20** with a broad range of substrates (*scheme 5.2.6*).[3g]

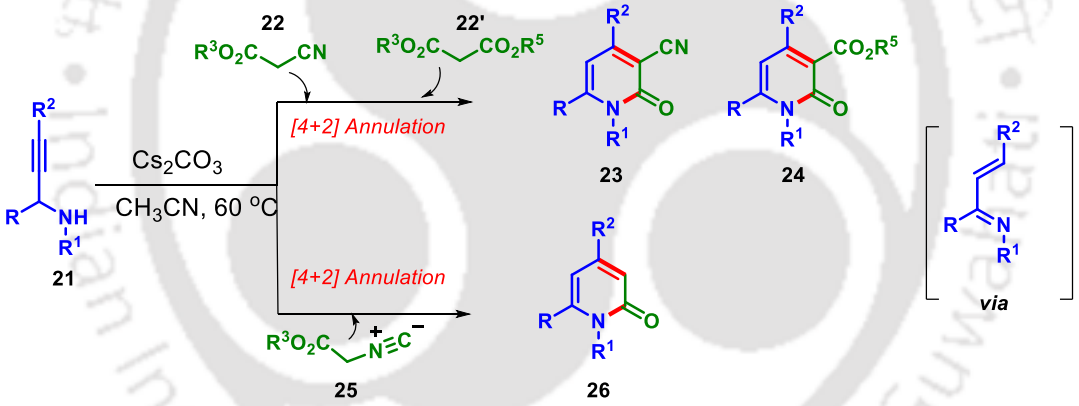


Scheme 5.2.7. *Synthesis of Substituted 2-Pyridones from 3-formylchromones and Propiolamides.*

Present Work

The [4+2] annulation reaction is one of the most powerful tool for generating highly congested and strained six membered heterocycles,[4] that are often difficult to form or possess incompatible substituents arrays. In this context, intrinsically electron deficient 1-azadienes have proven to be immensely useful as a four component synthon in [4+2] annulation strategy, affording rapid access to a range of highly substituted heterocycles in a regio and stereospecific manner by using different cycloadditions and multicomponent annulation reaction.[5] On the other hand, the unique ability of *N*-propargylamines, synthesized from aldehydes, amines and alkynes *via* A^3-coupling, to generate 1-azadiene precursor *in situ* for the participation in various annulation reactions towards the synthesis of different functionalized heterocycles has not been well explored.[6] Over the years,

several strategies were implemented like cycloaddition,[3a-b] and C-H activation[3d] using transition metal catalyst and transition metal-free multicomponent condensation reaction[3e-j] for the synthesis of 2-pyridones derivatives. Although several known metal-free methods exist for synthesis of 2-pyridones, the major concerns of these reactions are use of restricted starting materials,[3i-j] harsh reaction conditions[3j] and along with the synthesis of less substituted 2-pyridone ring.[3h] Therefore, designing of a transition metal-free route for synthesis of highly functionalised 2-pyridones in particular, 2-pyridones having cyano and carboxylic functionality at 3-position from easily and readily available starting materials is highly desirable and challenging. Keeping these challenges in mind, we have, demonstrated an unprecedented Cs_2CO_3 mediated protocol for the synthesis of highly functionalized 2-pyridones from four component synthon *N*-propargylamines as a 1-azadiene precursor and alkylcyanoacetate, alkylisocyanoacetate and malonic ester derivatives as two carbon- π component *via* [4+2] annulation reaction without using any alkyne activation metal source (*scheme 5.2.8*).

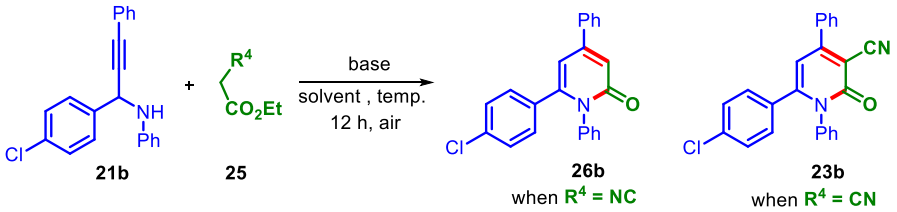


Scheme 5.2.8. *Base Promoted Synthesis of Functionalized 2-Pyridones from N-Propargylamines.*

5.3. Result and Discussion

To initiate the reaction, **21b** and ethylisocyanoacetate **25** were chosen as the model substrates and treated with 1.0 equiv of Cs_2CO_3 in toluene at 25 °C for 12 h, but only starting material was recovered (*Table 5.3.1*, entry 1). We envisioned that the increase in temperature may lead to the product formation and therefore, the reaction was carried out at 60 °C. To our delight, the reaction gave the product **26b** with 51% yield (*Table 5.3.1*, entry 2). The result suggests that temperature had a significant role in this cyclization. In order to check the role of solvent, the reaction was

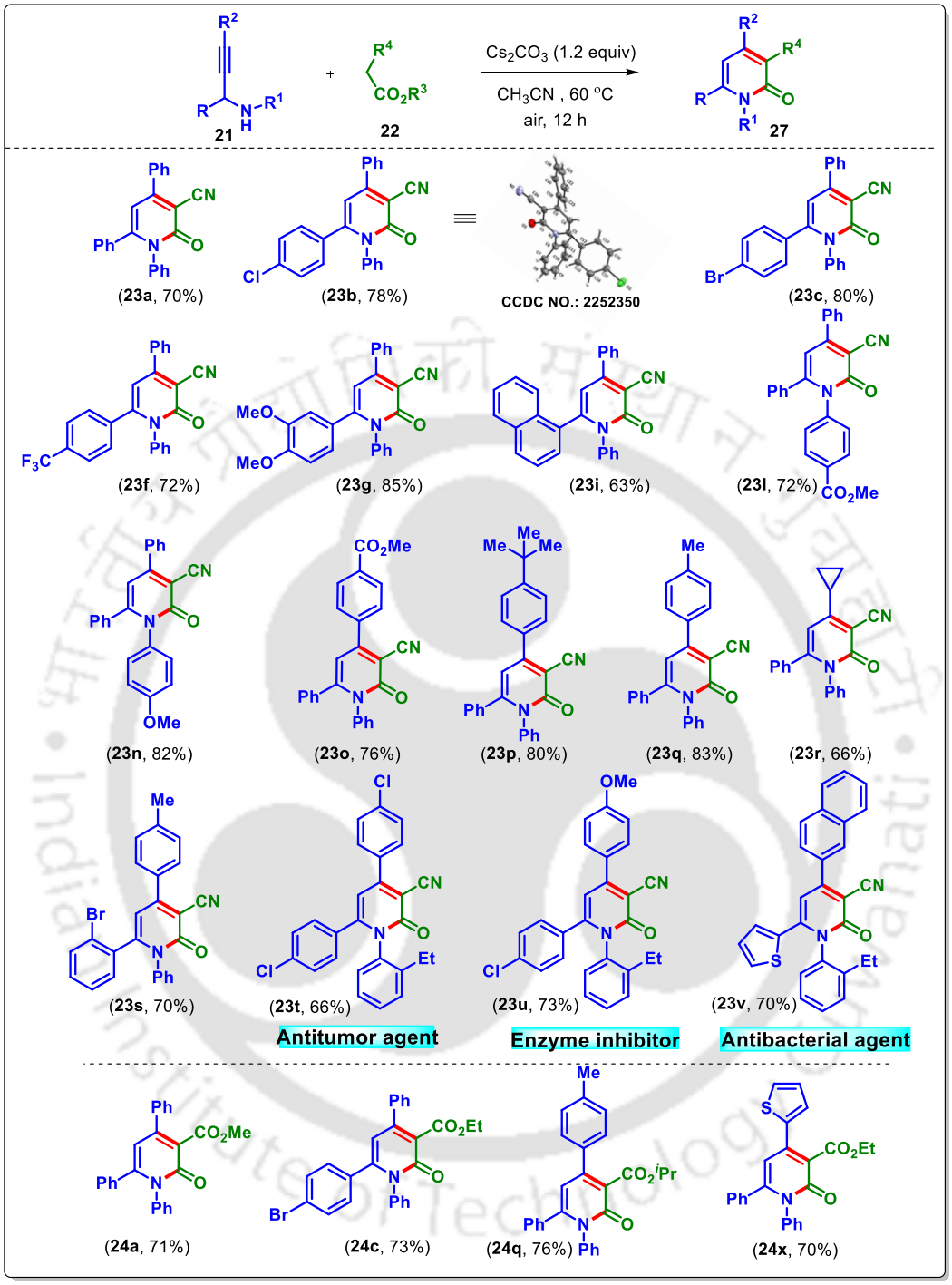
Table 5.3.1. Optimization of the Reaction[a]



entry	base (equiv)	solvent	t (°C)	%yield[b] 26b	%yield[b] 23b
1	Cs_2CO_3 (1.0)	toluene	rt	N.R[c]	-
2	Cs_2CO_3 (1.0)	toluene	60	51	-
3	Cs_2CO_3 (1.0)	1,4-dioxane	60	40	-
4	Cs_2CO_3 (1.0)	THF	60	33	-
5	Cs_2CO_3 (1.0)	DMSO	60	42	-
6	Cs_2CO_3 (1.0)	DMF	60	47	-
7	Cs_2CO_3 (1.0)	CH_3CN	60	66	-
8	**Cs_2CO_3 (1.2)**	**CH_3CN**	**60**	**75**	-
9	Cs_2CO_3 (1.5)	CH_3CN	60	70	-
10	Cs_2CO_3 (1.2)	CH_3CN	82	64	-
11	Cs_2CO_3 (3.0)	CH_3CN	60	-	63
12	K_2CO_3 (1.2)	CH_3CN	60	63	-
13	Na_2CO_3 (1.2)	CH_3CN	60	12	-
14	K^{t}OBu (1.2)	CH_3CN	60	18	-
15	Ag_2CO_3 (1.2)	CH_3CN	60	45	-
16	DBU (1.2)	CH_3CN	60	N.R[c]	-
17	KOH (1.2)	CH_3CN	60	N.R[c]	-
18	DABCO (1.2)	CH_3CN	60	N.R[c]	-

[a]Reaction conditions: **21b** (0.62 mmol, 1.0 equiv), base, reagent **25** (1.24 mmol, 2.0 equiv) solvent (4.0 ml), 12 h. [b]isolated yield. [c]N.R = No reaction.

performed with different solvents like 1,4-dioxane, THF and dimethylsulfoxide (DMSO), dimethylformamide (DMF) which produced 40%, 33%, 42% and 47% yields (*Table 5.3.1*, entries 3-6), respectively. While using CH_3CN, an increased yield of 66% was observed (*Table 5.3.1*, entry 7). To improve the reaction yield, the loading of base was increased to 1.2 equiv and surprisingly 75% yield was obtained (*Table 5.3.1*, entry 8). However, no significant change in the yield of the desired product was observed on increasing the reagent load as well as temperature



[a]Reaction conditions: **21** (0.62 mmol), **22** (1.24 mmol), Cs_2CO_3 (0.74 mmol), CH_3CN (4 mL), in air for 12 h.

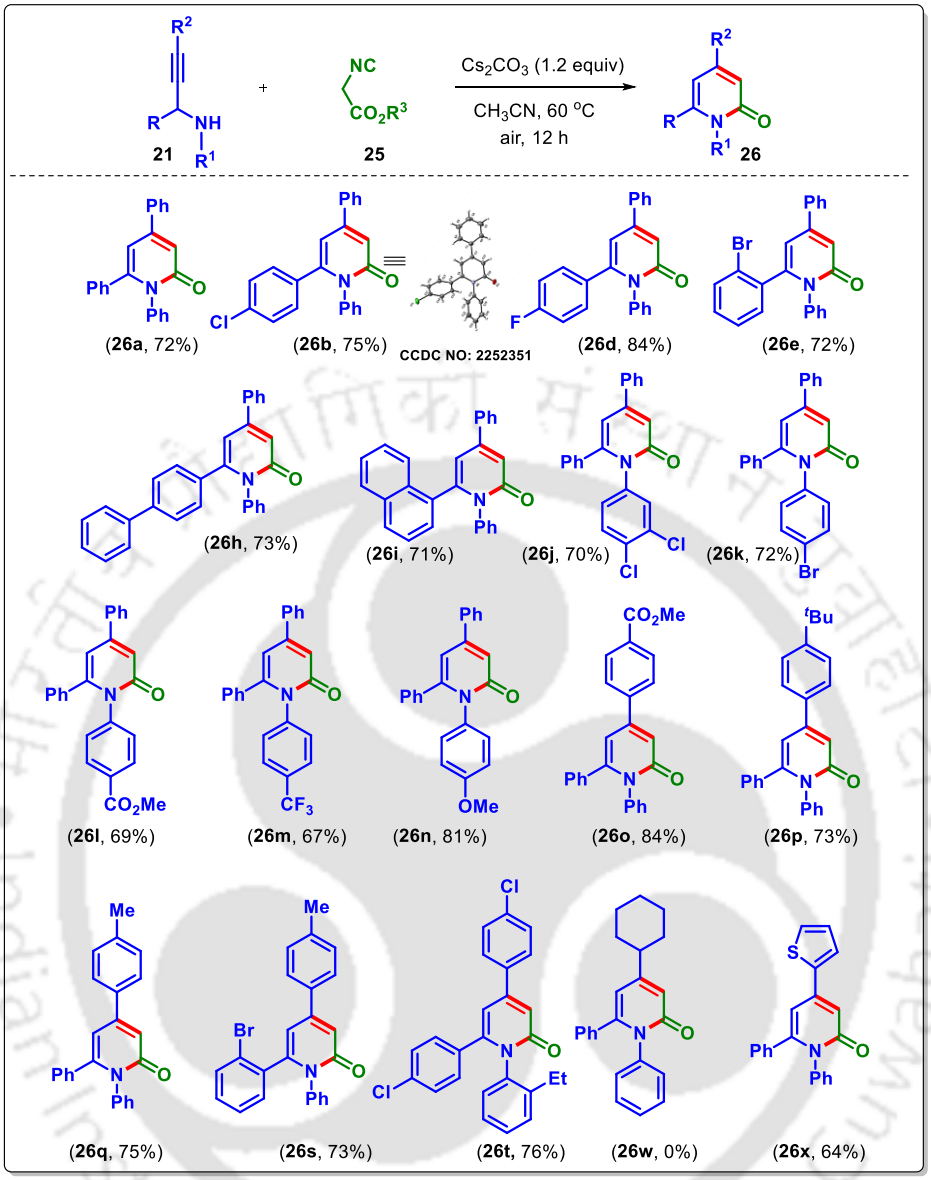
Scheme 5.3.2. *Scope of Synthesis of 3-Cyano and 3-Carboxylate 2-Pyridone Derivatives from N-propargylamines.*[a]

(*Table 5.3.1*, entry 9-10). Again, further increasing the load of base to 3.0 equiv and switching the reagent to ethyl cyanoacetate furnished the product **23b** in 63% yield (*Table 5.3.1*, entry 11). On

the other hand, the use of other bases such as K_2CO_3, Na_2CO_3, K^{t}OBu, Ag_2CO_3, failed to improve the yield (*Table 5.3.1*, entry 12-15), while no desired product was obtained with the use of bases such as DBU, KOH and DABCO (*Table 5.3.1*, entries 16–18).

With the established optimal conditions in hand, we explored the scope of various substituted *N*-propargylamines **21** with ethylcyanoacetates and malonic ester derivatives **22** for the formation of tetra-substituted 2-pyridones **27** (*Scheme 5.3.2*). It was observed that both electron–donating groups (EDG) as well as electron–withdrawing groups (EWG) in the *N*-propargylamines gave corresponding products (**23a-23r**) in good yields. It is noteworthy that even sterically hindered and strained cyclic substituents like naphthyl and cyclopropyl groups also provided **23i** and **23r** in 63% and 66% yields, respectively. Disubstituted *N*-propargylamines with both EDGs, EWGs and heteroatom containing core also reacted smoothly under the standard conditions to give product **23s** as well as biologically active compounds[7] **23t**, **23u** and **23v** in moderate to good yields. The scope of the reaction was also further investigated with various substituted *N*-propargylamines and different malonate derivatives furnishing products (**24a**, **24c**, **24q** and **24x**) in decent yields as depicted in (*Scheme 5.3.2*).

Furthermore, the protocol was also evaluated for the synthesis of tri-substituted 2-pyridones **26** by switching the 2-atom component to alkylisocyanoacetates **25** (*Scheme 5.3.3*). *N*-propargylamines possessing various EDGs and EWGs gave corresponding tri-substituted 2-pyridones in good yields. Strongly electron withdrawing substituents like $–CO_2Me$, $–CF_3$ groups and sterically hindered substituent like naphthyl systems were also well tolerated affording the products **26l**, **26m**, and **26i** in acceptable yields. Similarly, the reaction was carried out with both di and tri-substituted *N*-propargylamines along with heteroatom containing core like thiophene to give corresponding products **26s**, **26t** and **26x** with decent yields (*Scheme 5.3.3*). However, cyclohexyl substituted *N*-propargylamine failed to give the desired product **26w** due to lack of stabilization of the intermediate **A** (*Scheme 5.3.5*). The structure of all the compounds was determined by ^{1}H, ^{13}C{^{1}H} NMR, IR spectroscopy, mass spectrometry and finally by *X*-Ray crystallographic analysis of the compounds **23b** and **26b**.[8]

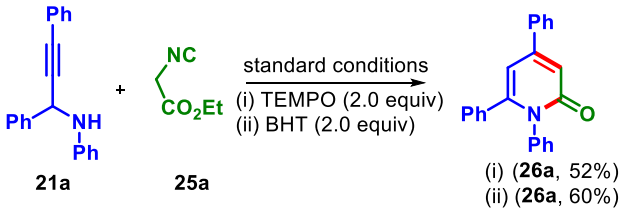


[a]Reaction conditions: **21** (0.62 mmol), **25** (1.24 mmol), Cs_2CO_3 (0.74 mmol), CH_3CN (4 mL), in air for 12 h.

Scheme 5.3.3. *Scope of Synthesis of Tri-substituted 2-Pyridone Derivatives from N-propargylamines.*[a]

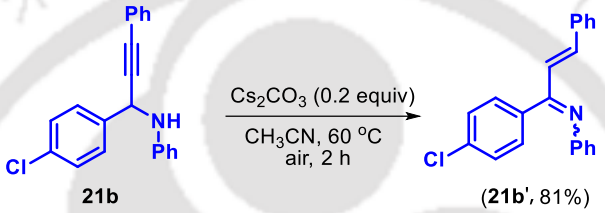
5.3.4. Control Experiments

To investigate the proposed mechanistic hypothesis, some control experiments were carried out. Initially, a reaction between **21a** and **25a** in the presence of radical scavengers viz. TEMPO and BHT, did not affect the yield of product **26a**, thereby ruling out any possibility of a radical pathway (*Scheme 5.3.4a*).



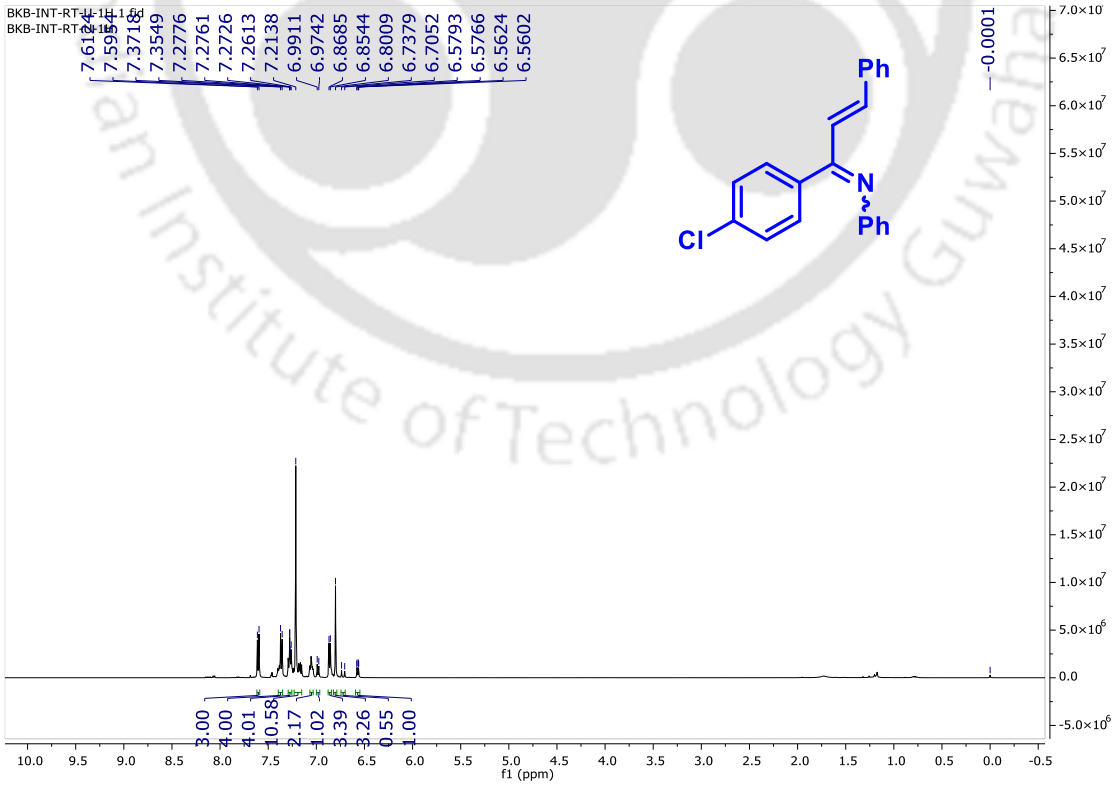
Scheme 5.3.4a. *To Confirm Reaction Pathway.*

In order to confirm the *in situ* generation of intermediate **C** (*Scheme 5.3.5*), compound **21b** was treated with Cs_2CO_3 and **21b′** was obtained with 81% yield as a mixture of geometric isomers (*Scheme 5.3.4b*), which was detected by NMR (*Figure 5.3.4b*) and HRMS (*Figure 5.3.4b'*) analysis.



Scheme 5.3.4b. *To Confirm In Situ Generation of 1-Azadiene Intermediate **21b′**.*

^{1}H Spectrum of Compound **21b'** (500 MHz, $CDCl_3$)



$^{13}C\{^{1}H\}$ NMR Spectrum of Compound **21b'** (125 MHz, $CDCl_3$)

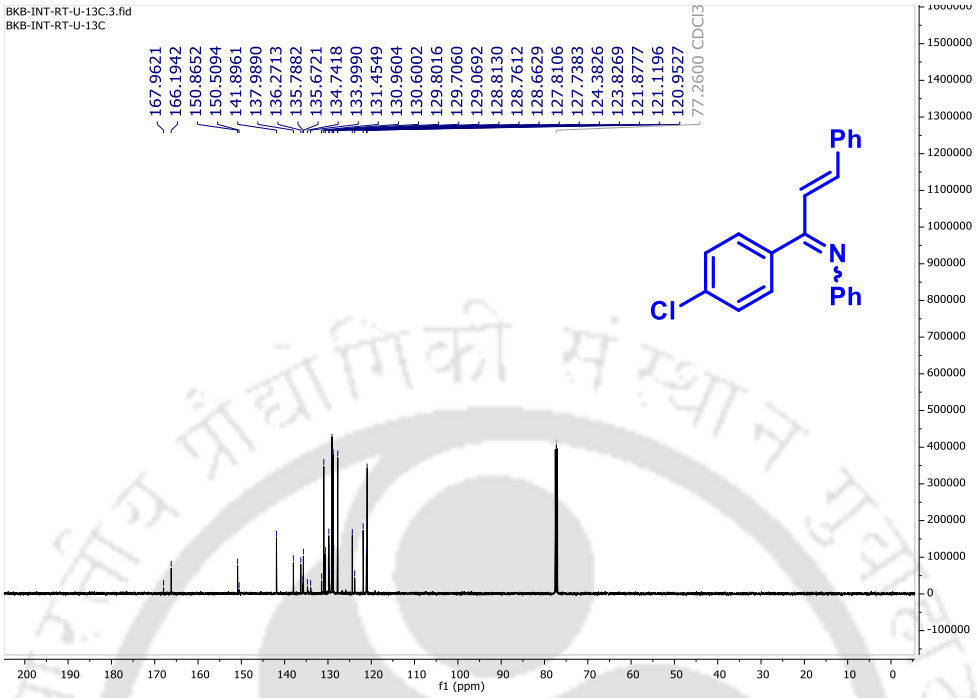


Figure 5.3.4b. *^{1}H, $^{13}C\{^{1}H\}$ NMR Study for in situ Generation of 1-Azadiene Intermediate **21b'**.*

HRMS Spectrum of Compound **21b'**

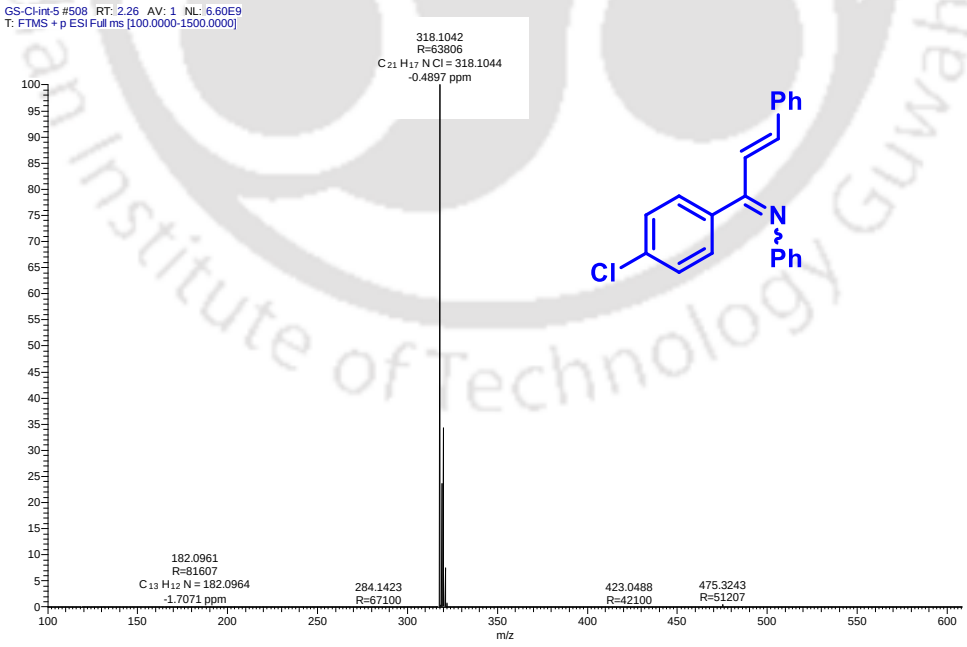
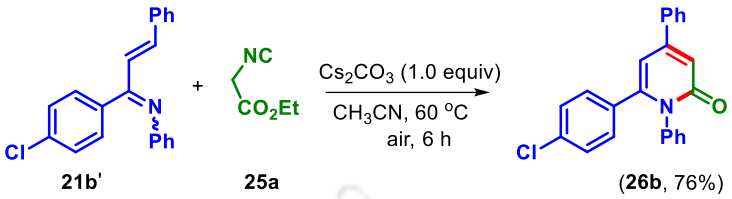


Figure 5.3.4b'. *HRMS Study for in situ Generation of 1-Azadiene Intermediate **21b'**.*

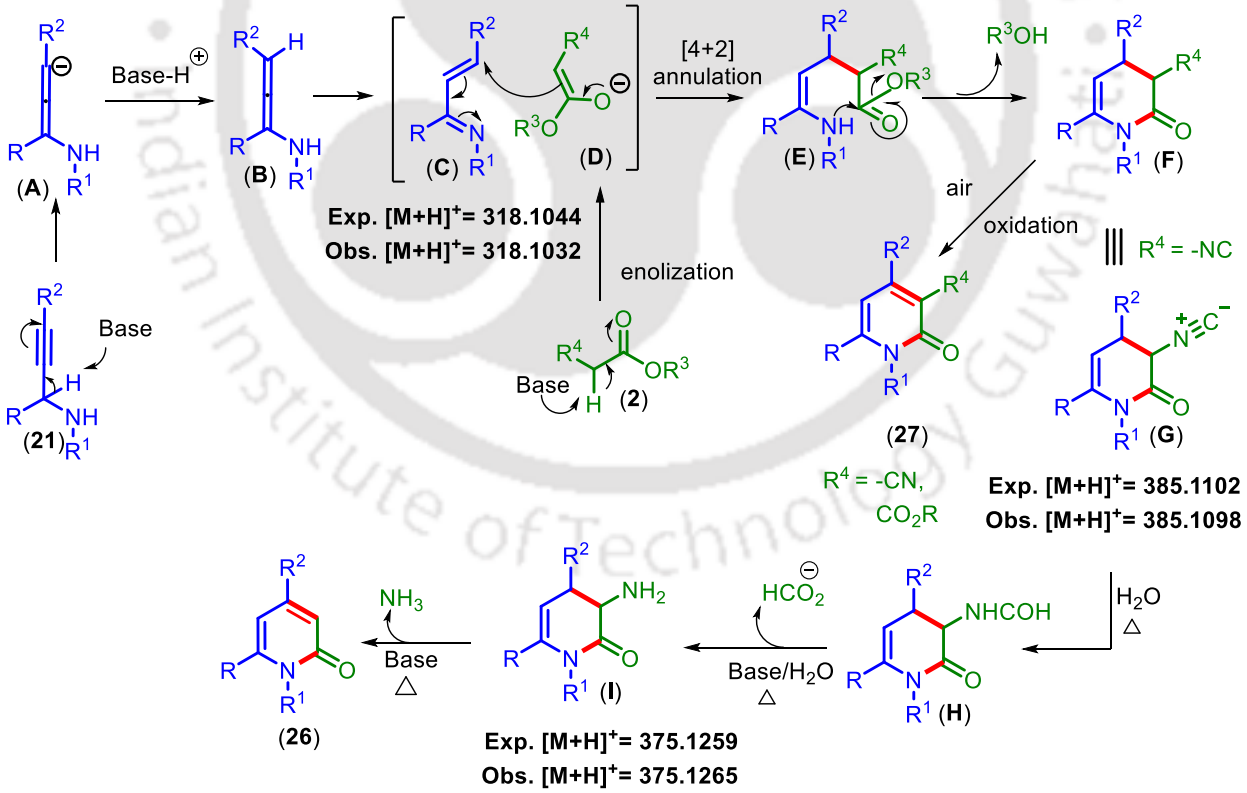
Furthermore, the role of activemethylene derivatives was ensured by reacting isolated intermediate **21b´** with **25a** to give the desired product **26b** in 76% yield (*Scheme 5.3.4c*).



Scheme 5.3.4c. *To Confirm the Role of Activemethylene Compound.*

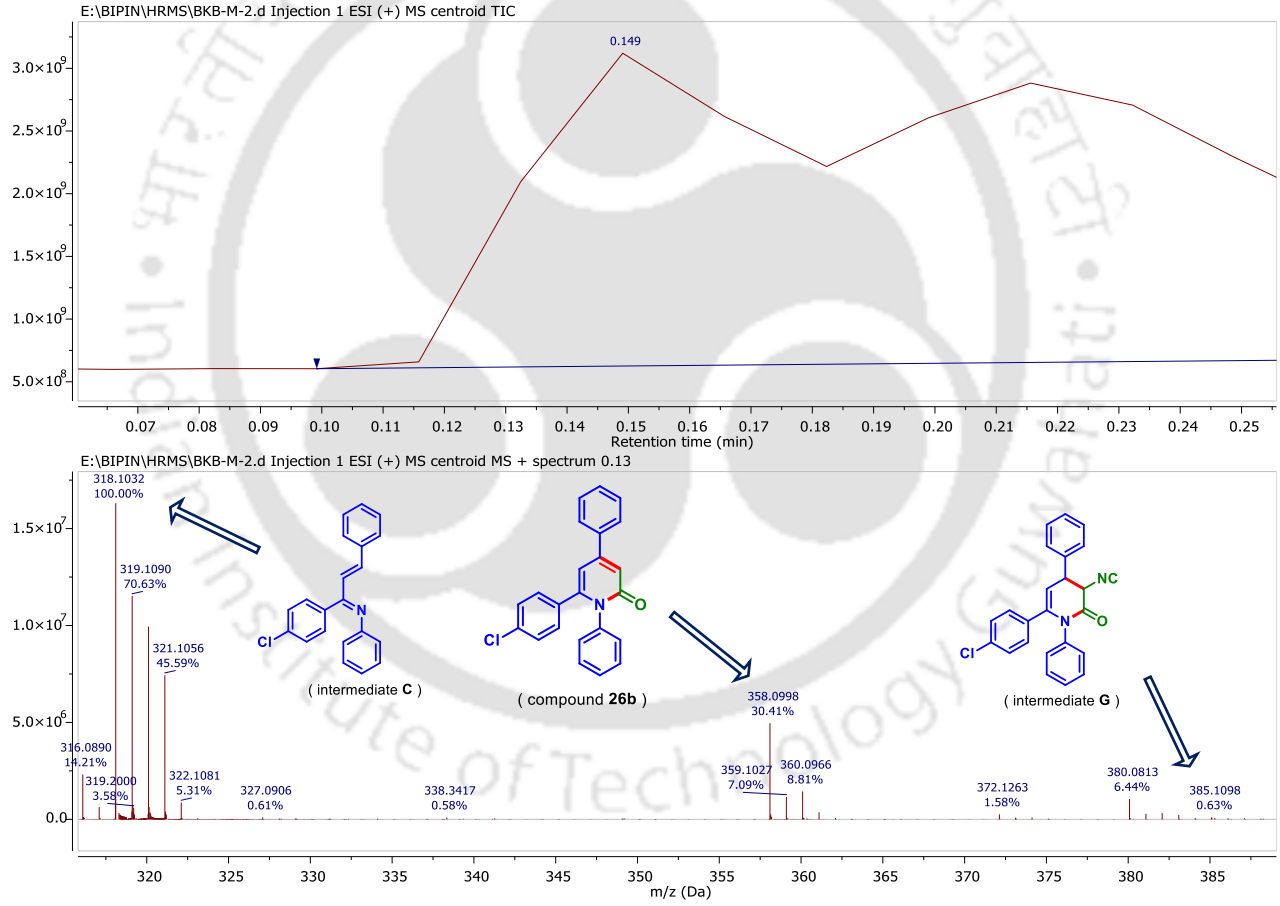
5.3.5. Plausible Mechanism

Based on the previous literature and with the support of control experiments, a plausible mechanism is proposed (*Scheme 5.3.5*). Initially, the reaction proceeds by the *in situ* formation of intermediate **C** from *N*-propargylamine **21** with proton abstraction by base followed by isomerization of intermediate **B**.[9a-b] Subsequently, [4+2] annulation reaction occurs between enol



Scheme 5.3.5. *Plausible Mechanism.*

ether **D** and 1-azadienes **C** to form the intermediate **E**. Thereafter, lactam intermediate **F** is formed *via* intramolecular cyclization with the elimination of an alcohol molecule. The unstable intermediate **F** containing nitrile and carboxylic groups undergo aerobic oxidative aromatization[9b] to give functionalized 2-pyridones **27**. However, in presence of very unstable isocyanides substituent, intermediate **G** undergoes hydrolysis to give unstable formamide intermediate **H**, which after base hydrolysis and subsequent elimination of carboxylate ion gives intermediate **I**. Finally, the intermediate **I**, after elimination of ammonia[9c] gives desired tri-substituted 2-pyridones **26**. Intermediates **C, G** and **I** were detected in HRMS experiments at different time intervals (*Figure 5.3.5)*.



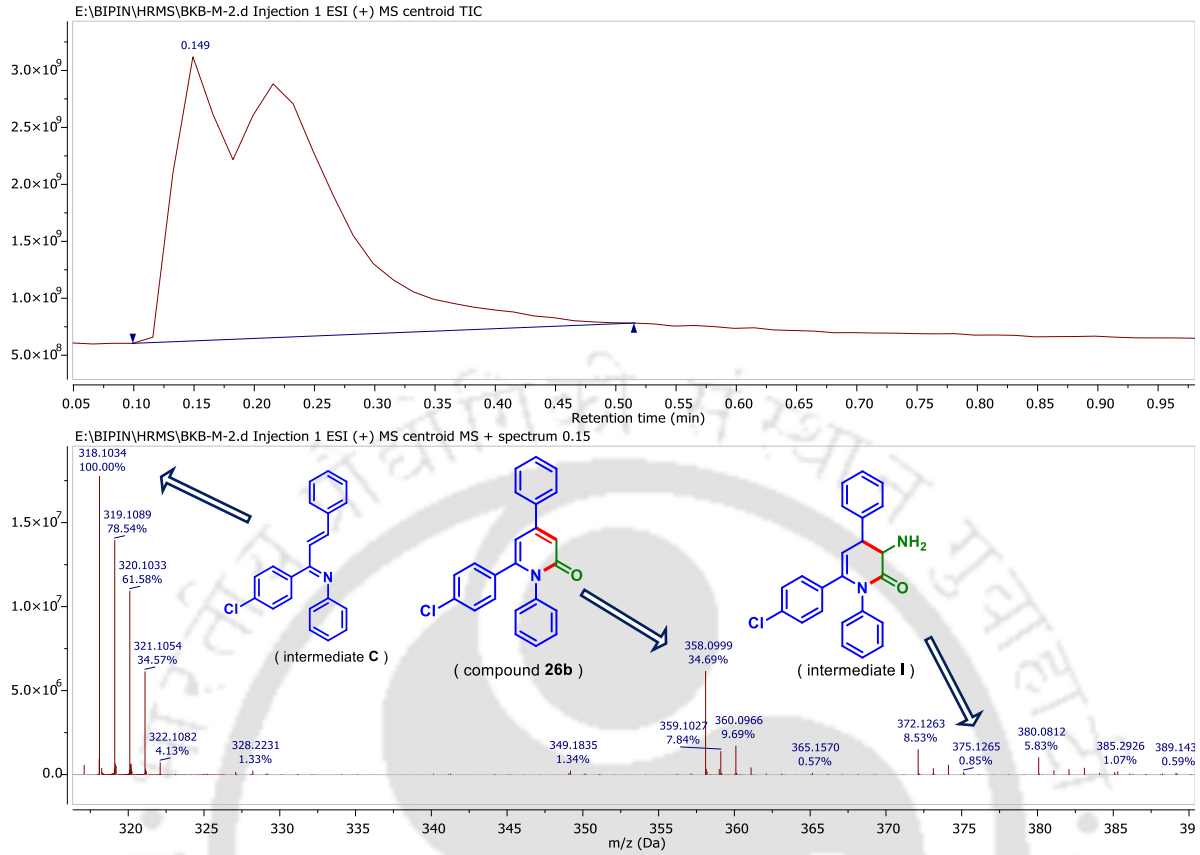
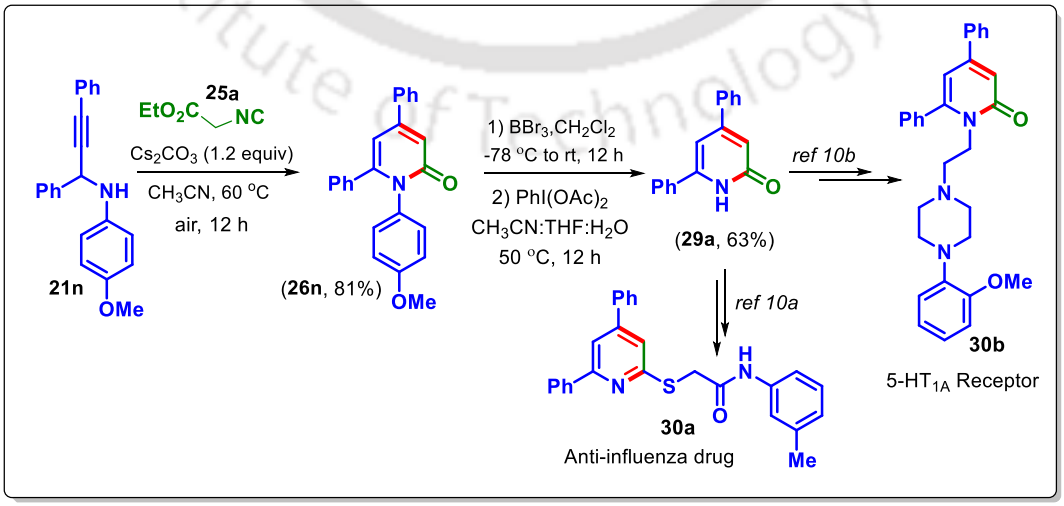


Figure 5.3.5. *HRMS Study for the Detection of Reaction Intermediates.*

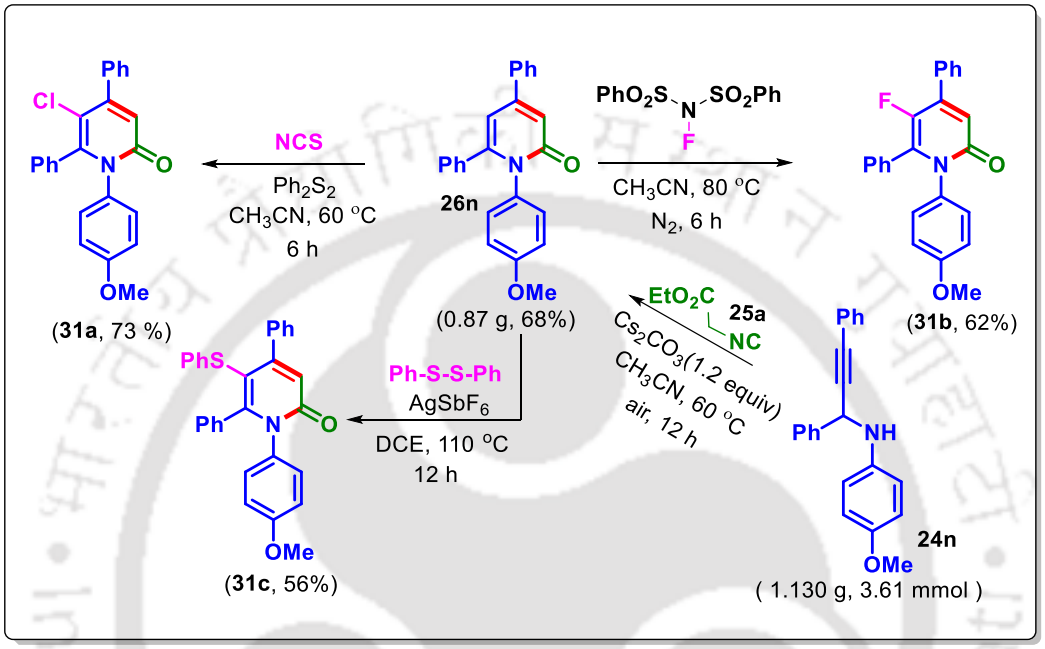
5.4. Post-synthetic Application

To illustrate the application of our methodology, the key precursor **29a** was obtained by deprotection of PMP group from **26n**, which can then be converted to bioactive compounds anti-influenza agent **30a**[10a] and 5-HT$_{1A}$ Receptor **30b**[10b] (*Scheme 5.4a*).



Scheme 5.4a. *Synthesis of the Key Precursor of Anti-Influenza Agent and 5-HT$_{1A}$ Receptor.*

The utility of the methodology is also extended towards the synthesis of 5-halo-functionalized products **31a** and **31b** with good yields from **26n** by using *N*-chlorosuccinimide (NCS) and *N*-fluorobenzenesulfonimide (NFSI) as chlorine and fluorine sources, respectively (*Scheme 5.4b*).



Scheme 5.4b. *C-H Functionalization of 2-Pyridone and Gram Scale Synthesis.*

Also, the compound **26n** was transformed to its 5-thio-functionalized product **31c,** mediated by $AgSbF_6$ with diphenyldisulfide as a thioaryl source, which was confirmed from literature reports.[11] A gram scale synthesis was carried out to reveal the scalability of our methodology (*Scheme 5.4b*).

5.5. Crystallographic Description

The structure of all compounds was confirmed from standard spectroscopic experiments and finally by *X*-ray crystallographic analysis of compound **23b** (*figure 5.5a*) and **26b** (*figure 5.5b*)

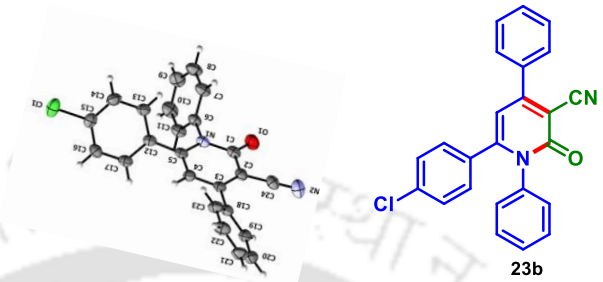


Figure 5.5a *ORTEP diagram of compound* ***23b****, thermal ellipsoids are drawn on 30% probability level.*

Compound **23b**	**CCDC 2252350**
Formula	$C_{24}H_{15}ClN_2O$
Formula weight	382.8470
T/K	298(2)
Crystal system	monoclinic
Space group	P 21/c
a/Å	19.5299(13)
b/Å	9.6555(7)
c/Å	22.4034(15)
α/°	90
β/°	113.768(2)
γ/°	90
V/Å^3	3866.3(5)
Z	8
Abs. Coeff./mm^{-1}	0.214
Abs. Correction	multi-scan
GOF on F^2	1.412
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0690
	wR2 = 0.1904
R indices [all data]	*R1* = 0.1115
	wR2 = 0.2234

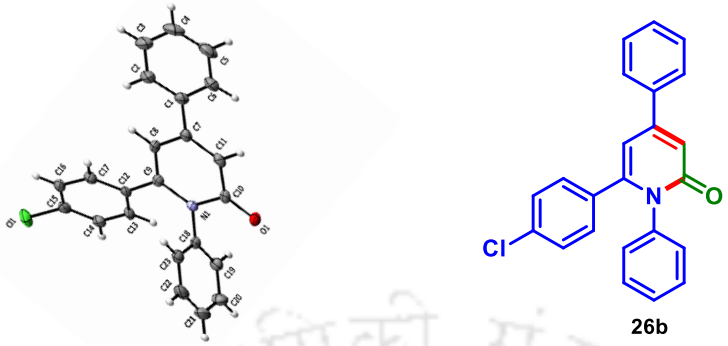


Figure 5.5b. *ORTEP diagram of compound* ***26b****, thermal ellipsoids are drawn on 30% probability level.*

Compound **26b**	**CCDC 2252351**
Formula	$C_{23}H_{16}ClNO$
Formula weight	357.8370
T/K	297(2)
Crystal system	monoclinic
Space group	P 21/n
a/Å	5.9343(5)
b/Å	24.216(2)
c/Å	12.7082(12)
α/°	90
β/°	96.801(3)
γ/°	90
V/Å^3	1813.4(3)
Z	4
Abs. Coeff./mm^{-1}	0.222
Abs. Correction	multi-scan
GOF on F^2	1.318
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.1111 *wR2* = 0.1679
R indices [all data]	*R1* = 0.1385 *wR2* = 0.1768

Conclusion

In conclusion, we have described a base-promoted synthesis of tri- and tetra-substituted 2-pyridones from *N*-propargylamines under transition-metal and additive-free conditions *via* [4+2] annulation. The methodology is compatible with a variety of functional groups giving moderate to good yields. One of the major advantage of the reaction is that the starting materials can be easily synthesized from readily available aldehydes, amines, and alkynes by A^3-coupling reaction. Further the synthetic utility of this methodology is explored for the synthesis of key intermediates of bioactive compounds and important C-H functionalized product.

5.6. Experimental Section

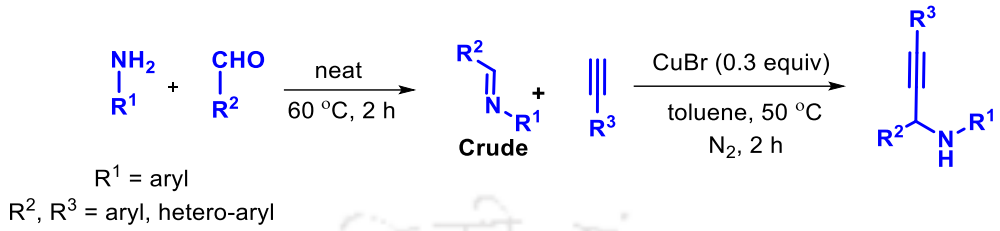
5.6.1. Instrumentation and Characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (600 MHz, 500 MHz and 400 MHz) or $^{13}C\{^1H\}$ (150 MHz, 125 MHz and 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

5.6.2. Experimental Procedure for Starting-material Synthesis

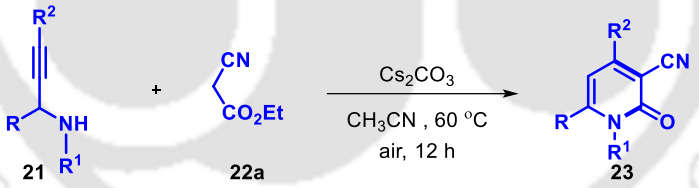
The starting material *N*-propargylamines (**21a-21k**, **21m-21s**, **21w**) were prepared following our previous reports.[12] The spectroscopic data of the above compounds were in good agreement with the literature one. The experimental procedure and the characterization data of the remaining starting material *N*-propargylamines (**21l**, **21t-21v**, **21x** and **21y**) were given as follows:

5.6.2.1. General Experimental Procedure for the Synthesis of Compounds 21l, 21t-21v, 21x and 21y



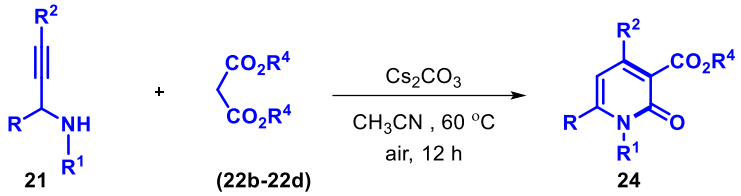
A mixture of aldehyde (5.0 mmol, 1.0 equiv) and amine (7.5 mmol, 1.5 equiv) was heated in a round bottom flask at 60 °C in an oil bath for two hours in open air. Then, the crude was transferred to another round bottom flask and heated at 50 °C in an oil bath for 2 h with copper(I) bromide (1.5 mmol, 0.3 equiv) and acetylene (10.0 mmol, 2.0 equiv) in dry toluene (4 mL) under nitrogen. Then, the reaction mixture was poured into water, and extracted with EtOAc (3 × 20 mL). The organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude product was then purified using column chromatography over silica gel to get corresponding product.

5.6.3. General Experimental Procedure for Synthesis of Compounds 23



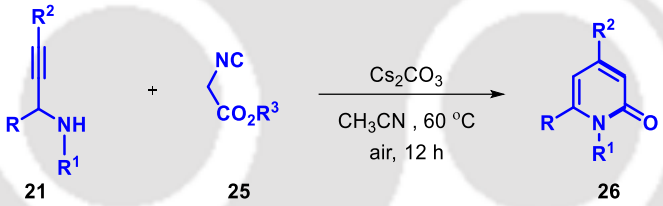
To a stirred solution of Cs_2CO_3 (0.74 mmol, 1.2 equiv), *N*-propargylamines **21** (0.62 mmol, 1.0 equiv) in CH_3CN (4.0 mL) was added ethylcyanoacetate **22a** (1.24 mmol, 2.0 equiv) dropwise. Then the mixture was stirred in an oil bath at 60 °C under open air atmosphere and the reaction time was monitored by TLC. After completion of the reaction, the solvent was removed completely under reduced pressure. The residue was diluted with ethyl acetate and saturated brine solution. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding desired product **23**.

5.6.4. General Experimental Procedure for Synthesis of Compounds 24



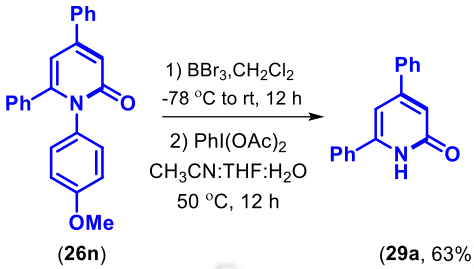
To a stirred solution of Cs_2CO_3 (0.74 mmol, 1.2 equiv), *N*-propargylamines **21** (0.62 mmol, 1.0 equiv) in CH_3CN (4.0 mL) was added malonate ester **22b-22d** (1.24 mmol, 2.0 equiv) dropwise. Then the mixture was stirred in an oil bath at 60 °C under open air atmosphere and the reaction time was monitored by TLC. After completion of the reaction, the solvent was removed completely under reduced pressure. The residue was diluted with ethyl acetate and saturated brine solution. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding desired product **24**.

5.6.5. General Experimental Procedure for Synthesis of Compounds 26



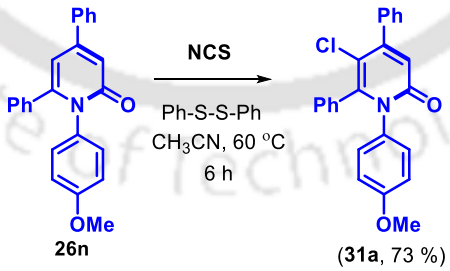
To a stirred solution of Cs_2CO_3 (0.74 mmol, 1.2 equiv), *N*-propargylamines **21** (0.62 mmol, 1.0 equiv) in CH_3CN (4.0 mL) was added alkylisocyanoacetate **25** (1.24 mmol, 2.0 equiv) dropwise. Then the mixture was stirred in an oil bath at 60 °C under open air atmosphere and the reaction time was monitored by TLC. After completion of the reaction, the solvent was removed completely under reduced pressure. The residue was diluted with ethyl acetate and saturated brine solution. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding desired product **26**.

5.6.6. Experimental Procedure for Synthesis of Compound 29a



To a stirred solution of **26n** (0.2 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at -78 °C, BBr_3 (1.0 M in CH_2Cl_2, 5.0 equiv) was added and the resulting mixture was allowed to warm to room temperature over a period of 12 h. The reaction was quenched with 1 M aq. NaOH (10 mL) at 0 °C and neutralized with 1 M aq. HCl and the resulting mixture extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude demethylated product. The obtained crude product was dissolved in a mixed solvent of $CH_3CN/THF/H_2O$ (5/1/2, 16 mL). To the stirred solution at 50 °C, $PhI(OAc)_2$ was added in five batches (0.6 mmol, 3.0 equiv) and the resulting mixture was stirred at 50 °C for 24 h. The reaction was quenched by adding saturated aq. $NaHCO_3$ (20 mL) and the resulting mixture was extracted with $CHCl_3$/MeOH (3/1, 3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel giving the compound **29a** with 63% yield.

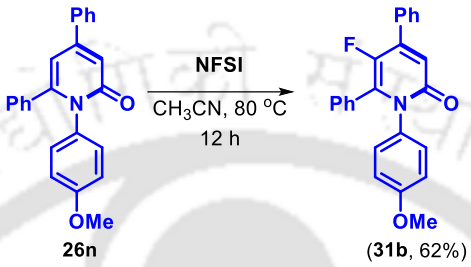
5.6.7. Experimental Procedure for Synthesis of Compound 31a



To a stirred solution of *N*-Chlorosuccinimide (0.4 mmol, 1.0 equiv), Diphenyl disulfide (0.6 mmol, 1.5 equiv) in CH_3CN (4.0 mL) was added 2-pyridone **26n** (0.4 mmol, 1.0 equiv) dropwise. Then the mixture was stirred in an oil bath at 60 °C under nitrogen atmosphere and the reaction time was monitored by TLC. After completion of the reaction, the solvent was removed completely

under reduced pressure. The residue was diluted with ethyl acetate and saturated brine solution. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding desired product **31a** with 73% yield.

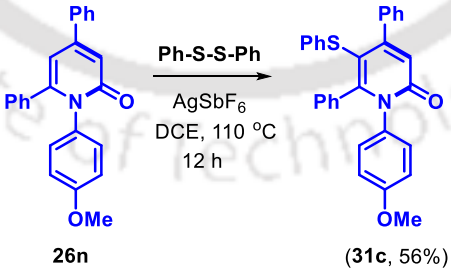
5.6.8. Experimental Procedure for Synthesis of Compound 31b



26n (**31b**, 62%)

To a stirred solution of *N*-Fluorobenzenesulfonimide (0.8 mmol, 2.0 equiv) in CH_3CN (4.0 mL) was added 2-pyridone **26n** (0.4 mmol, 1.0 equiv) dropwise. Then the mixture was stirred in an oil bath at 80 °C under nitrogen atmosphere and the reaction time was monitored by TLC. After completion of the reaction, the solvent was removed completely under reduced pressure. The residue was diluted with ethyl acetate and saturated brine solution. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding desired product **31b** with 62% yield.

5.6.9. Experimental Procedure for Synthesis of Compound 31c



26n (**31c**, 56%)

To a stirred solution of diphenyl disulfide (0.4 mmol, 1.0 equiv), silver hexafluoroantimonate (0.4 mmol, 1.0 equiv), in DCE (4.0 mL) was added 2-pyridone **26n** (0.4 mmol, 1.0 equiv) dropwise. Then the mixture was stirred in an oil bath at 110 °C under nitrogen atmosphere and the reaction time was monitored by TLC. After completion of the reaction, the solvent was removed completely

under reduced pressure. The residue was diluted with ethyl acetate and saturated brine solution. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding desired product **31c** with 56% yield.

5.7. References:

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(8) The crystallographic data for compounds **23b** and **26b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 2252350 and 2252351 respectively.

(9) (a) Xin, X.; Wang, D.; Li, X.; Wan, B. *Angew. Chem. Int. Ed*. **2012**, *51*, 1693–1697. (b) Mishra, P. K.; Verma, S.; Kumar, M.; Verma, A. K. *Org. Lett*. **2018**, *20*, 7182–7185. (c) Gao, P.; Wang, J.; Bai, Z. J.; Shen, L.; Yan, Y. Y.; Yang, D. S.; Fan, M. J.; Guan, Z. H. *Org. Lett*. **2016**, *18*, 6074–6077.

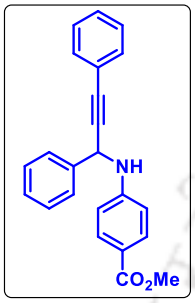
(10) (a) Trist, I. M. L.; Nannetti, G.; Tintori, C.; Fallacara, A. L.; Deodato, D.; Mercorelli, B.; Palu, G.; Wijtmans, M.; Gospodova, T.; Edink, E.; Verheij, M.; Esch, I. D.; Viteva, L.; Loregian, A.; Botta, M. *J. Med. Chem*. **2016**, *59*, 2688–2703. (b) Paluchowska, M. H.; Bugno, R.; Charakchieva-Minol, S.; Wesolowska, A.; Chojnacka-Wojcik, E. *Pol. J. Pharmacol*. **2002**, *54*, 641–646.

(11) (a) Zhu, Y. Q.; He, J. L.; Niu, Y. X.; Kang, H. Y.; Han, T. F.; Li, H. Y. *J. Org. Chem.* **2018**, *83*, 9958–9967. (b) Sakurai, F.; Yukawa, T.; Taniguchi, T. *Org. Lett.* **2019**, *21*, 7254–7257.

(12) (a) Behera, B. K.; Sahu, A. K.; Devi, N. R.; Saikia, A. K. *J. Org. Chem.* **2021**, *86*, 12481–12493. (b) Behera, B. K.; Shit, S.; Biswas, S.; Saikia, A. K. *J. Org. Chem.* **2022**, *87*, 9259–9269.

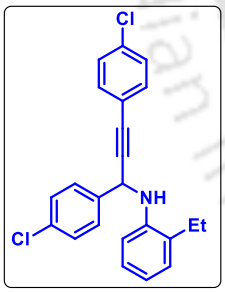
5.8. Characterization Data

Methyl 4-((1,3-diphenylprop-2-yn-1-yl)amino)benzoate (21l):



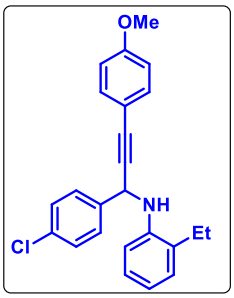
Yellow solid; R_f (hexane/EtOAc, 19:1) 0.60; mp 123–125 ºC. Yield 1210 mg, 71%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.5 Hz, 2 H), 7.64 (d, *J* = 7.5 Hz, 2 H), 7.46 (d, *J* = 7.5 Hz, 2 H), 7.42–7.39 (m, 2 H), 7.38–7.32 (m, 1 H), 7.23–7.20 (m, 2 H), 6.83–6.75 (m, 3 H), 5.51 (s, 1 H), 4.16 (s, 1 H), 3.90 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 166.7, 146.6, 139.5, 131.9, 129.8, 129.6, 129.4, 129.1, 128.5, 127.7, 127.5, 118.9, 114.3, 91.8, 84.5, 52.4, 50.8; **IR** (KBr, neat) 2928, 1734, 1640, 1463, 1362, 1220, 738 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{20}NO_2$ $(M + H)^+$ 342.1489, found 342.1488.

***N*-(1,3-Bis(4-chlorophenyl)prop-2-yn-1-yl)-2-ethylaniline (21t):**



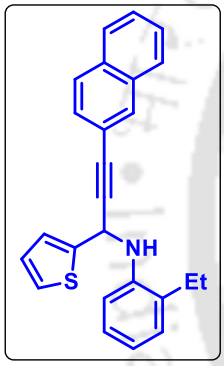
Yellow viscous liquid; R_f (hexane/EtOAc, 19:1) 0.60; Yield 1156 mg, 61%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.2 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 7.19 (d, *J* = 8.2 Hz, 2 H), 7.07–7.04 (m, 2 H), 6.74–6.71 (m, 2 H), 5.43 (s, 1 H), 3.98 (s, 1 H), 2.45 (q, *J* = 7.5 Hz, 2 H), 1.19 (t, *J* = 7.5 Hz, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 143.9, 138.5, 134.7, 134.2, 133.2, 129.2, 128.9, 128.8, 128.3, 127.1, 121.2, 119.0, 112.3, 89.4, 84.4, 50.3, 24.1, 13.2; **IR** (KBr, neat) 2931, 1625, 1525, 1480, 1234, 1023, 638 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{20}Cl_2N$ $(M + H)^+$380.0967, found 380.0962.

***N*-1-(4-Chlorophenyl)-3-(4-methoxyphenyl)prop-2-yn-1-yl)-2-ethylaniline (21u):**



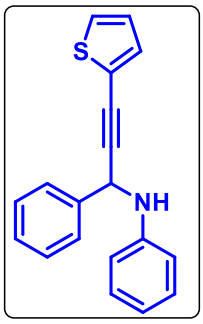
Yellow viscous liquid; R_f (hexane/EtOAc, 19:1) 0.60; Yield 1200 mg, 64%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2 H), 7.26 (t, *J* = 8.0 Hz, 4 H), 7.06–7.00 (m, 2 H), 6.75–6.68 (m, 4 H), 5.40 (s, 1 H), 3.69 (s, 3 H), 2.44 (q, *J* = 7.5 Hz, 2 H), 1.17 (t, *J* = 7.5 Hz, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 159.9, 144.0, 134.3, 139.0, 133.9, 133.4, 129.1, 128.8, 128.2, 127.1, 118.8, 114.8, 114.1, 112.2, 86.9, 85.4, 55.5, 50.3, 24.1, 13.2; **IR** (KBr, neat) 2956, 1639, 1546, 1472, 1262, 1103, 625 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{23}ClNO$ $(M + H)^+$ 376.1463, found 376.1452.

2-Ethyl-*N*-(3-(naphthalen-2-yl)-1-(thiophen-2-yl)prop-2-yn-1-yl)aniline (21v):



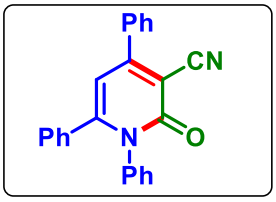
Yellow solid; R_f (hexane/EtOAc, 19:1) 0.60; mp 122–124 °C. Yield 1101 mg, 60%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.16 (s, 1 H), 7.94–7.89 (m, 3 H), 7.77–7.75 (m, 1 H), 7.55–7.53 (m, 2 H), 7.31–7.23 (m, 2 H), 7.19–7.16 (m, 2 H), 7.00–6.98 (m, 1 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 6.84 (t, *J* = 7.3 Hz, 1 H), 5.75 (s, 1 H), 4.23 (s, 1 H), 2.59 (q, *J* = 7.3 Hz, 2 H), 1.31 (t, *J* = 7.3 Hz, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 144.2, 137.2, 133.6, 133.4, 132.5, 129.0, 128.8, 128.4, 128.2, 127.9, 127.3, 127.2, 127.1, 126.6, 126.5, 126.2, 125.5, 122.9, 118.8, 112.2, 92.7, 51.3, 24.1, 13.2; **IR** (KBr, neat) 2972, 1616, 1540, 1436, 1290, 1133, 648 cm^{-1}; **HRMS** (ESI) calcd. for $C_{25}H_{22}NS$ $(M + H)^+$ 368.1467, found 368.1473.

***N*-(1-Phenyl-3-(thiophen-2-yl)prop-2-yn-1-yl)aniline (21x):**



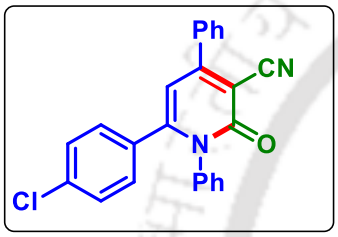
Yellow solid; R_f (hexane/EtOAc, 19:1) 0.60; mp 141–143 °C. Yield 968 mg, 67%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.5 Hz, 2 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.35–7.30 (m, 1 H), 7.21–7.18 (m, 3 H), 7.16 (d, *J* = 3.5 Hz, 1 H), 6.91 (t, *J* = 4.4 Hz, 1 H), 6.79–6.73 (m, 3 H), 5.49 (s, 1 H), 4.13 (s, 1 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 146.6, 139.6, 132.4, 129.4, 129.0, 128.3, 127.5, 127.2, 127.1, 122.9, 118.8, 114.2, 92.6, 78.5, 51.0; **IR** (KBr, neat) 2948, 1641, 1562, 1423, 1267, 1198, 642 cm^{-1}; **HRMS** (ESI) calcd. for $C_{19}H_{16}NS$ $(M + H)^+$ 290.0998, found 290.0981.

2-Oxo-1,4,6-triphenyl-1,2-dihydropyridine-3-carbonitrile (23a):



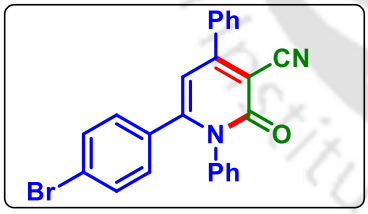
Brown solid; R_f (hexane/EtOAc, 1:1) 0.60; mp 213–215 °C. Yield 151 mg, 70%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.75–7.70 (m, 2 H), 7.55–7.51 (m, 3 H), 7.32–7.24 (m, 4 H), 7.21(t, *J* = 7.4 Hz, 2 H), 7.14–7.11(m, 4 H), 6.47 (s, 1 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$)) δ 161.5, 159.5, 153.7, 137.5, 135.9, 134.5, 131.0, 129.7, 129.3, 129.2, 128.9, 128.5, 128.3, 115.9, 109.6, 101.7; **IR** (KBr, neat) 2935, 2221, 1628, 1581, 1496, 1025, 836, 721 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{17}N_2O$ $(M + H)^+$ 349.1335, found 349.1342.

6-(4-Chlorophenyl)-2-oxo-1,4-diphenyl-1,2-dihydropyridine-3-carbonitrile (23b):



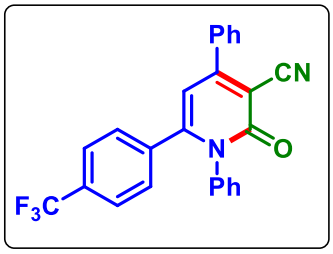
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.60; mp 234–236 °C. Yield 185 mg, 78%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.7–7.69 (m, 2 H), 7.55–7.51 (m, 3 H), 7.34–7.27 (m, 3 H), 7.19 (d, *J* = 8.2 Hz, 2 H), 7.1–7.07 (m, 4 H), 6.43 (s, 1 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 161.4, 159.5, 152.4, 137.3, 136.1, 135.7, 132.9, 131.1, 130.3, 129.4, 129.3, 129.2, 128.9, 128.8, 128.3, 115.7, 109.6, 102.1; **IR** (KBr, neat) 2935, 2221, 1628, 1581, 1496, 1025, 836, 721 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{16}ClN_2O$ $(M + H)^+$ 383.0946, found 383.0951.

6-(4-Bromophenyl)-2-oxo-1,4-diphenyl-1,2-dihydropyridine-3-carbonitrile (23c):



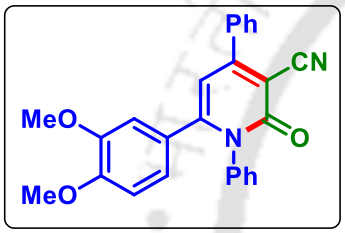
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 234–236 °C. Yield 211 mg, 80%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71–7.70 (m, 2 H), 7.55–7.51 (m, 3 H), 7.35–7.31 (m, 5 H), 7.11 (d, *J* = 7.2 Hz, 2 H), 7.02 (d, *J* = 8.2 Hz, 2 H), 6.44 (s, 1 H); **^{13}C{^{1}H} NMR** (125 MHz $CDCl_3$) δ 161.4, 159.5, 152.4, 137.3, 135.7, 133.4, 131.8, 131.2, 130.5, 129.5, 129.3, 129.2, 128.9, 128.3, 124.4, 115.7, 109.7, 102.1; **IR** (KBr, neat) 2941, 2224, 1660, 1572, 1491, 1020, 839, 722 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{16}BrN_2O$ $(M + H)^+$ 427.0441, found 427.0409.

2-Oxo-1,4-diphenyl-6-(4-(trifluoromethyl)phenyl)-1,2-dihydropyridine-3-carbonitrile (23f):



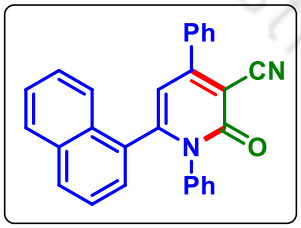
Colourless solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 214–216 °C. Yield 186 mg, 72%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73–7.70 (m, 2 H), 7.54–7.53 (m, 3 H), 7.50 (d, *J* = 8.1 Hz, 2 H), 7.34–7.28 (m, 5 H), 7.13– 7.09 (m, 2 H), 6.46 (s, 1 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 161.2, 159.5, 151.9, 137.9, 137.0, 135.6, 131.8, 131.5, 131.3, 129.6, 129.5, 129.4, 129.3, 128.9, 128.3, 125.5 (q, J = 3.8 Hz), 122.5, 115.6,109.9; **^{19}F NMR** (376 MHz, $CDCl_3$) δ 63.03 (s, -CF_3); **IR** (KBr, neat) 2960, 2218, 1608, 1542, 1482, 1029, 862, 711 cm^{-1}; **HRMS** (ESI) calcd. for $C_{25}H_{16}F_3N_2O$ $(M + H)^+$ 417.1209, found 417.1200.

6-(3,4-Dimethoxyphenyl)-2-oxo-1,4-diphenyl-1,2-dihydropyridine-3-carbonitrile (23g):



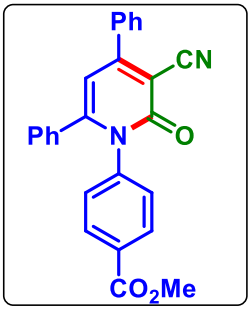
Pale yellow solid; R_f (hexane/EtOAc, 3:2) 0.40; mp 226–228 °C. Yield 215 mg, 85%; Yield **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74–7.68 (m, 2 H), 7.56–7.50 (m, 3 H), 7.35–7.29 (m, 3 H), 7.15 (d, *J* = 6.8 Hz, 2 H), 6.86–6.84 (m, 1 H), 6.73 (d, *J* = 8.4 Hz, 1 H), 6.50–6.45 (m, 2 H), 3.83 (s, 3 H), 3.60 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ161.6, 159.4, 153.5, 150.3, 148.6, 137.8, 136.0, 130.9, 129.3, 129.2, 128.9, 128.9, 128.3, 126.9, 122.3, 116.0, 112.2, 110.8, 109.5, 101.2, 56.1, 56.0; **IR** (KBr, neat) 2941, 2204, 1694, 1541, 1452, 1041, 824, 751 cm^{-1}; **HRMS** (ESI) calcd. for $C_{26}H_{21}N_2O_3$ $(M + H)^+$ 409.1547, found 409.1538.

6-(Naphthalen-1-yl)-2-oxo-1,4-diphenyl-1,2-dihydropyridine-3-carbonitrile (23i):



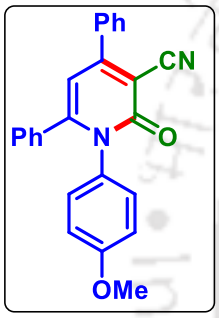
Brown gummy; R_f (hexane/EtOAc, 1:1) 0.50; Yield 155 mg, 63%; Yield **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78–7.73 (m, 5 H), 7.60 (d, *J* = 8.6 Hz, 1 H), 7.56–7.53 (m, 3 H), 7.52–7.49 (m, 2 H), 7.28–7.26 (m, 2 H), 7.22 (d, *J* = 7.2 Hz, 1 H), 7.19–7.16 (m, 2 H), 7.09 (dd, *J* = 8.6, 1.9 Hz, 1 H), 6.58 (s, 1 H); **^{13}C{^{1}H}NMR** (125 MHz, $CDCl_3$) δ 161.6, 159.5, 153.7, 137.5, 135.9, 133.2, 132.6, 132.0, 131.0, 129.3, 129.2, 128.9, 128.5, 128.3, 128.1, 127.9, 127.8, 127.2, 125.4, 115.9, 110.1, 101.7; **IR** (KBr, neat) 2945, 2210, 1671, 1551, 1411, 1125, 885, 706 cm^{-1}; **HRMS** (ESI) calcd. for $C_{28}H_{19}N_2O$ $(M + H)^+$399.1492, found 399.1494.

Methyl 4-(3-cyano-2-oxo-4,6-diphenylpyridin-1(2*H*)-yl)benzoate (23l):



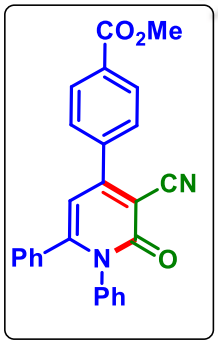
Pale yellow solid; R_f (hexane/EtOAc, 3:2) 0.40; mp 214–216 °C. Yield 181 mg, 72%; Yield **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.3 Hz, 2 H), 7.75–7.69 (m, 2 H), 7.53–7.52 (m, 3 H), 7.27–7.24 (m, 1 H), 7.22–7.19 (m, 4 H), 7.13 (d, *J* = 7.3 Hz, 2 H), 6.50 (s, 1 H), 3.89 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 166.1, 161.2, 159.7, 153.2, 141.4, 135.6, 134.0, 131.1, 130.5, 130.0, 129.2, 129.1, 128.8, 128.6, 128.3, 115.7, 109.9, 101.6, 52.5; **IR** (KBr, neat) 2940, 2206, 1701, 1546, 1421, 1021, 847, 711 cm^{-1}; **HRMS** (ESI) calcd. for $C_{26}H_{19}N_2O_3$ $(M + H)^+$ 407.1390, found 407.1393.

1-(4-Methoxyphenyl)-2-oxo-4,6-diphenyl-1,2-dihydropyridine-3-carbonitrile (23n):



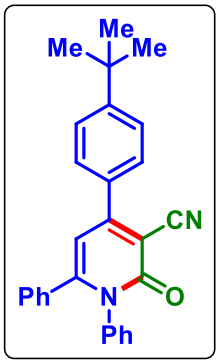
Brown solid; R_f (hexane/EtOAc, 3:2) 0.40; mp 230–232 °C. Yield 192 mg, 82%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74–7.69 (m, 2 H), 7.55–7.51 (m, 3 H), 7.27–7.21 (m, 3 H), 7.17–7.13 (m, 2 H), 7.02 (d, *J* = 8.8 Hz, 2 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 6.45 (s, 1 H), 3.75 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 161.8, 159.6, 159.3, 154.0, 135.9, 134.7, 131.0, 130.1, 129.9, 129.6, 129.2, 128.9, 128.5, 128.3, 115.9, 114.5, 109.6, 101.5, 55.6; **IR** (KBr, neat) 2950, 2213, 1664, 1578, 1423, 1056, 853, 780 cm^{-1}; **HRMS** (ESI) calcd. for $C_{25}H_{19}N_2O_2$ $(M + H)^+$ 379.1441, found 379.1460.

Methyl 4-(3-cyano-2-oxo-1,6-diphenyl-1,2-dihydropyridin-4-yl)benzoate (23o):



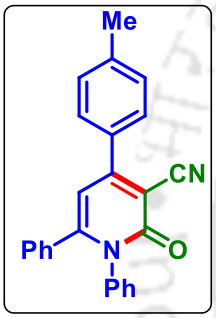
Pale yellow solid; R_f (hexane/EtOAc, 3:2) 0.40; mp 216–218 °C. Yield 191 mg, 76%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.5 Hz, 2 H), 7.79 (d, *J* = 8.5 Hz, 2 H), 7.33–7.28 (m, 3 H), 7.23–7.20 (m, 3 H), 7.15–7.11 (m, 4 H), 6.46 (s, 1 H), 3.97 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 166.4,161.2, 158.3, 154.2, 140.0, 137.3, 134.3, 132.3, 130.4, 129.9, 129.3, 129.1, 128.9, 128.8, 128.5, 128.4, 115.5, 109.2, 102.1, 52.7; **IR** (KBr, neat) 2931, 2204, 1711, 1532, 1410, 1012, 828, 720 cm^{-1}; **HRMS** (ESI) calcd. for $C_{26}H_{19}N_2O_3$ $(M + H)^+$407.1390, found 407.1390

4-(4-(*Tert*-butyl)phenyl)-2-oxo-1,6-diphenyl-1,2-dihydropyridine-3-carbonitrile (23p):



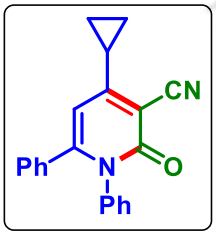
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 232–234 °C. Yield 200 mg, 80%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2 H), 7.54 (d, *J* = 8.2 Hz, 2 H), 7.31–7.23 (m, 4 H), 7.20 (t, *J* = 7.8 Hz, 2 H), 7.12 (t, *J* = 7.4 Hz, 4 H), 6.47 (s, 1 H), 1.36 (s, 9 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 161.6, 159.3, 154.6, 153.5, 137.5, 134.6, 132.9, 129.6, 129.2, 129.0, 128.9, 128.8, 128.4, 128.2, 126.2, 116.1, 109.6, 101.6 35.2, 31.4; **IR** (KBr, neat) 2905, 2221, 1611, 1590, 1406, 1081, 821, 780 cm^{-1}; **HRMS** (ESI) calcd. for $C_{28}H_{25}N_2O$ $(M + H)^+$ 405.1961, found 405.1982.

2-Oxo-1,6-diphenyl-4-(*p*-tolyl)-1,2-dihydropyridine-3-carbonitrile (23q):



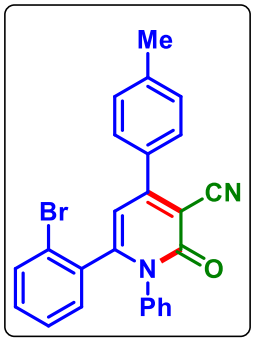
Brown solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 204–206 °C. Yield 186 mg, 83%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.29–7.23 (m, 4 H), 7.20 (t, *J* = 7.4 Hz, 2 H), 7.13–7.09 (m, 4 H), 6.46 (s, 1 H), 2.43 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 161.6, 159.4, 153.5, 141.5, 137.5, 134.6, 132.9, 130.0, 129.6, 129.2, 129.0, 128.9, 128.8, 128.4, 128.3, 116.1, 109.6, 101.2, 21.6; **IR** (KBr, neat) 2935, 2241, 1646, 1552, 1406, 1003, 862, 775 cm^{-1}; **HRMS** (ESI) calcd. for $C_{25}H_{19}N_2O$ $(M + H)^+$ 363.1492, found 363.1486.

4-Cyclopropyl-2-oxo-1,6-diphenyl-1,2-dihydropyridine-3-carbonitrile (23r):



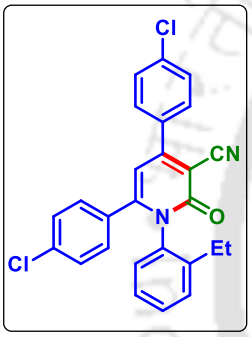
Brown solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 194–196 °C. Yield 128 mg, 66%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27–7.20 (m, 4 H), 7.19–7.16 (m, 2 H), 7.08–6.99 (m, 4 H), 5.66 (s, 1 H), 2.41–2.36 (m, 1 H), 1.35–1.31 (m, 2 H), 1.05–0.99 (m, 2 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 165.5, 160.6, 153.7, 137.5, 134.7, 129.5, 129.1, 128.9, 128.8, 128.7, 128.4, 115.7, 103.0, 102.7, 15.5, 11.5; **IR** (KBr, neat) 2920, 2211, 1631, 1567, 1449, 1036, 834, 783 cm^{-1}; **HRMS** (ESI) calcd. for $C_{21}H_{17}N_2O$ $(M + H)^+$ 313.1335, found 313.1329.

6-(2-Bromophenyl)-2-oxo-1-phenyl-4-(*p*-tolyl)-1,2-dihydropyridine-3-carbonitrile (23s):



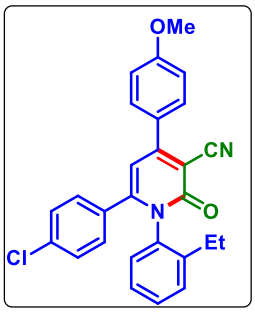
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 236–238 °C. Yield 191 mg, 70%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.1 Hz, 2 H), 7.46 (d, *J* = 7.7 Hz, 1 H), 7.33 (d, *J* = 7.7 Hz, 3 H), 7.27–7.24 (m, 3 H), 7.18–7.15 (m, 1 H), 7.14–7.09 (m, 3 H), 6.41 (s, 1 H), 2.43 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 161.5, 159.3, 151.6, 141.7, 137.0, 135.4, 133.1, 132.8, 131.2, 131.1, 129.9, 129.4, 129.3, 128.9, 128.8, 128.4, 127.7, 127.2, 122.6, 115.9, 109.9, 102.1, 21.7; **IR** (KBr, neat) 2945, 2208, 1640, 1511, 1470, 1027, 806, 745 cm^{-1}; **HRMS** (ESI) calcd. for $C_{25}H_{18}BrN_2O$ $(M + H)^+$441.0597, found 441.0603.

4,6-Bis(4-chlorophenyl)-1-(2-ethylphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (23t):



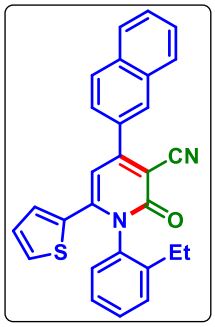
Brown gummy; R_f (hexane/EtOAc, 3:2) 0.40; Yield 182 mg, 66%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.5 Hz, 2 H), 7.52 (d, *J* = 8.5 Hz, 2 H), 7.31–7.28 (m, 1 H), 7.26–7.24 (m, 1 H), 7.20–7.15 (m, 3 H), 7.06 (d, *J* = 8.5 Hz, 2 H), 7.03 (d, *J* = 7.7 Hz, 1 H), 6.39 (s, 1 H), 2.50–2.53 (m, 1 H), 2.34–2.26 (m, 1 H), 1.18 (t, *J* = 7.5 Hz, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 160.9, 158.2, 153.1, 140.5, 137.5, 136.4, 135.7, 134.0, 132.4, 130.1, 130.0, 129.7, 129.6, 129.2, 129.1, 128.7, 126.9, 115.7, 109.1, 101.9, 23.8, 13.5; **IR** (KBr, neat) 2971, 2220, 1655, 1597, 1488, 1091, 822, 750 cm^{-1}; **HRMS** (ESI) calcd. for $C_{26}H_{19}Cl_2N_2O$ $(M + H)^+$445.0869, found 445.0874.

6-(4-Chlorophenyl)-1-(2-ethylphenyl)-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (23u):



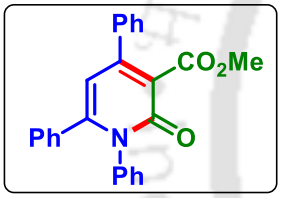
Brown gummy; R_f (hexane/EtOAc, 3:2) 0.40; Yield 199 mg, 73%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.8 Hz, 2 H), 7.31–7.24 (m, 3 H), 7.20–7.14 (m, 3 H), 7.08–7.00 (m, 4 H), 6.43 (s, 1 H), 3.89 (s, 3 H), 2.50–2.44 (m, 1 H), 2.34–2.36 (m, 1 H), 1.18 (t, *J* = 7.5 Hz, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 162.2, 161.4, 158.9, 152.4, 140.7, 136.2, 135.9, 132.7, 130.2, 130.1, 129.9, 129.3, 129.1, 128.7, 127.7, 126.9, 116.3, 114.7, 109.4, 100.8, 55.7, 23.9, 13.5; **IR** (KBr, neat) 2965, 2221, 1632, 1529, 1431, 1011, 831, 742cm^{-1}**; HRMS** (ESI) calcd. for $C_{27}H_{22}ClN_2O_2$ $(M + H)^+$441.1364, found 441.1368.

1-(2-Ethylphenyl)-4-(naphthalen-2-yl)-2-oxo-6-(thiophen-2-yl)-1,2-dihydropyridine-3-carbonitrile (23v):



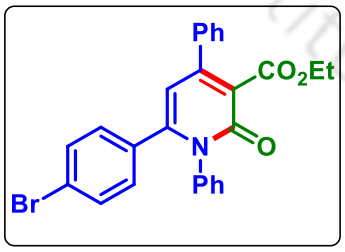
Brown gummy; R_f (hexane/EtOAc, 3:2) 0.40; Yield 187 mg, 70%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.12–8.11 (m, 1 H), 7.70–7.65 (m, 3 H), 7.58 (dd, *J* = 5.1, 1.1 Hz, 1 H), 7.53 (d, *J* = 8.6 Hz, 1 H), 7.46–7.41 (m, 2 H), 7.21–7.17 (m, 2 H), 7.12–7.11 (m, 1 H), 7.06–7.01 (m, 3 H), 6.61 (s, 1 H), 2.5–2.43 (m, 1 H), 2.33–2.26 (m, 1 H), 1.11 (t, *J* = 7.5 Hz, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 161.5, 153.8, 150.3, 140.8, 137.2, 136.0, 133.3, 132.5, 131.6, 131.5, 131.2, 129.7, 129.4, 129.3, 129.0, 128.5, 128.0, 127.9, 127.8, 127.2, 126.7, 125.3, 116.7, 108.6, 98.1, 23.9, 13.5; **IR** (KBr, neat) 2941, 2211, 1631, 1545, 1458, 1121, 804, 724cm^{-1}; **HRMS** (ESI) calcd. for $C_{28}H_{21}N_2SO$ $(M + H)^+$433.1369, found 433.1368.

Methyl 2-oxo-1,4,6-triphenyl-1,2-dihydropyridine-3-carboxylate (24a):



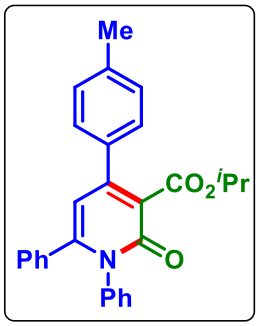
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 211–213 °C. Yield 168 mg, 71%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54–7.49 (m, 2 H), 7.44–7.43 (m, 3 H), 7.28–7.25 (m, 2 H), 7.22–7.16 (m, 4 H), 7.15–7.11 (m, 4 H), 6.37 (s, 1 H), 3.73 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 167.2, 160.7, 150.8, 150.4, 138.1, 137.6, 135.3, 129.6, 129.3, 129.2, 129.1, 129.0, 128.9, 128.4, 128.3, 127.7, 123.0, 109.6, 52.6; **IR** (KBr, neat) 2925, 1730, 1649, 1487, 1374, 1058, 696 cm^{-1}; **HRMS** (ESI) calcd. for $C_{25}H_{20}NO_3$ $(M + H)^+$ 382.1438, found 382.1444.

Ethyl 6-(4-bromophenyl)-2-oxo-1,4-diphenyl-1,2-dihydropyridine-3-carboxylate (24c):



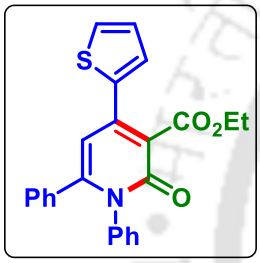
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 222–224 °C. Yield 214 mg, 73%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53–7.49 (m, 2 H), 7.45–7.41 (m, 3 H), 7.32–7.25 (m, 5 H), 7.12 (d, *J* = 7.4 Hz, 2 H), 7.00 (d, *J* = 8.0 Hz, 2 H), 6.32 (s, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 1.12 (t, *J* = 7.1 Hz, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 166.3, 160.6, 150.6, 148.9, 137.9, 137.5, 134.2, 131.6, 130.6, 129.6, 129.2, 129.2, 128.9, 128.6, 127.8, 123.7, 123.5, 109.6, 61.7, 14.1; **IR** (KBr, neat) 2941, 1735, 1629, 1462, 1360, 1021, 603 cm^{-1}; **HRMS** (ESI) calcd. for $C_{26}H_{21}BrNO_3$ $(M + H)^+$ 474.0699, found 474.0715.

Isopropyl 2-oxo-1,6-diphenyl-4-(*p*-tolyl)-1,2-dihydropyridine-3-carboxylate (24q):



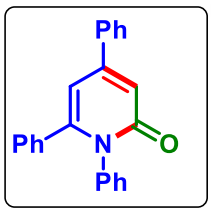
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 218–220 °C. Yield 199 mg, 76%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 2 H), 7.27–7.10 (m, 12 H), 6.34 (s, 1 H), 5.11 (hept, *J* = 6.3 Hz, 1 H), 2.39 (s, 3 H), 1.16 (d, *J* = 6.3 Hz, 6 H);**^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 166.3, 160.3, 150.3, 149.9, 139.6, 138.2, 135.4, 134.8, 129.5, 129.3, 129.1, 128.9, 128.9, 128.3, 128.2, 127.8, 123.4, 109.6, 69.4, 21.7, 21.5; **IR** (KBr, neat) 2962, 1728, 1632, 1401, 1328, 1079, 686 cm^{-1}; **HRMS** (ESI) calcd. for $C_{28}H_{26}NO_3$ $(M + H)^+$ 424.1907, found 424.1909.

Ethyl 2-oxo-1,6-diphenyl-4-(thiophen-2-yl)-1,2-dihydropyridine-3-carboxylate (24x):



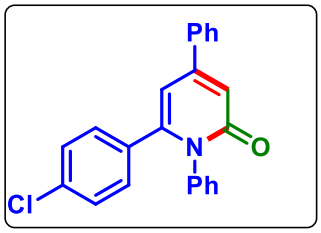
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 201–203 °C. Yield 174 mg, 70%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 4.8 Hz, 1 H), 7.45 (d, *J* = 3.5 Hz, 1 H), 7.29–7.23 (m, 3 H), 7.22–7.17 (m, 3 H), 7.13–7.08 (m, 5 H), 6.47 (s, 1 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 1.31 (t, *J* = 7.1 Hz, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 166.9, 160.8, 149.9, 141.8, 138.4, 137.9, 135.1, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 128.4, 128.3, 128.3, 121.8, 108.7, 62.1, 14.2; **IR** (KBr, neat) 2982, 1741, 1632, 1462, 1342, 1121, 652 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{20}NO_3S$ $(M + H)^+$ 402.1158, found 402.1170.

1,4,6-Triphenylpyridin-2(1*H*)-one (26a):



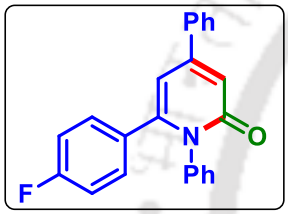
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 216–218 °C. Yield 144 mg, 72%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 6.3 Hz, 2 H), 7.48–7.43 (m, 3 H), 7.27–7.24 (m, 2 H), 7.21–7.10 (m, 8 H), 6.92 (s, 1 H), 6.54 (s, 1 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 163.8, 151.6, 149.6, 138.7, 137.7, 136.0, 129.7, 129.3, 129.2, 129.1, 129.0, 128.6, 128.2, 128.1, 127.0, 116.4, 107.8; **IR** (KBr, neat) 2939, 1656, 1521, 1370, 1154, 1082, 642 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{17}NaNO$ $(M + Na)^+$ 346.1202, found 346.1217.

6-(4-Chlorophenyl)-1,4-diphenylpyridin-2(1*H*)-one (26b):



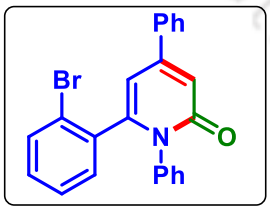
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 231–233 °C. Yield 166 mg, 75%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.0 Hz, 2 H), 7.48–7.43 (m, 3 H), 7.30–7.27 (m, 2 H), 7.25–7.22 (m, 1 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.11–7.06 (m, 4 H), 6.92 (s, 1 H), 6.51 (s, 1 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 163.7, 151.5, 148.3, 138.4, 137.5, 134.9, 134.3, 130.5, 129.9, 129.3, 129.2, 129.1, 128.5, 128.4, 128.0, 116.7, 108.0; **IR** (KBr, neat) 2934, 1675, 1511, 1342, 1162, 1071, 669 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{17}ClNO$ $(M + H)^+$358.0993, found 358.1018.

6-(4-Fluorophenyl)-1,4-diphenylpyridin-2(1*H*)-one (26d):



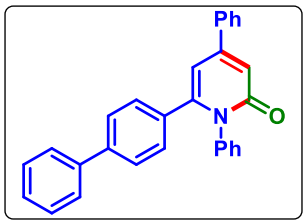
Brown solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 221–223 °C. Yield 178 mg, 84%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.6 Hz, 2 H), 7.49–7.45 (m, 3 H), 7.30–7.27 (m, 2 H), 7.26–7.22 (m, 1 H), 7.14–7.09 (m, 4 H), 6.92 (s, 1 H), 6.87 (t, *J* = 8.4 Hz, 2 H), 6.52 (s, 1 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 163.7, 162.6 (d, *J* = 248.1 Hz), 151.6, 148.6, 138.6, 137.6, 132.0 (d, *J* = 3.7 Hz), 131.2, 131.1, 129.9, 129.3, 129.2, 129.1, 128.3, 127.0, 116.6, 115.3 (d, *J* = 21.5 Hz), 108.0; **^{19}F NMR** (470 MHz, C_6F_6/$CDCl_3$) δ 49.84 (s, -F); **IR** (KBr, neat) 2946, 1681, 1580, 1381, 1136, 1071, 695 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{17}FNO$ $(M + H)^+$ 342.1289, found 342.1272.

6-(2-Bromophenyl)-1,4-diphenylpyridin-2(1*H*)-one (26e):



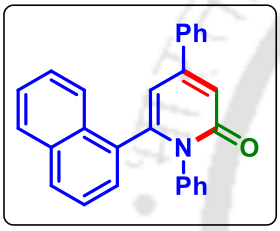
Brown solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 233–235 °C. Yield 179 mg, 72%;**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.2 Hz, 2 H), 7.50–7.34 (m, 5 H), 7.27–7.04 (m, 7 H), 6.97 (d, *J* = 6.0 Hz, 1 H), 6.49 (s, 1 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 163.6, 151.3, 147.7, 138.1, 137.4, 136.5, 132.7, 131.8, 130.4, 129.8, 129.2, 128.6, 128.5, 128.0, 127.0, 126.8, 123.4, 117.0, 108.0; **IR** (KBr, neat) 2948, 1669, 1516, 1346, 1135, 1067, 653 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{17}BrNO$ $(M + H)^+$ 402.0488, found 402.0521.

6-([1,1'-Biphenyl]-4-yl)-1,4-diphenylpyridin-2(1*H*)-one (26h):



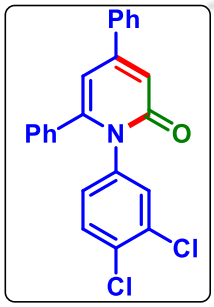
Yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 236–238 °C. Yield 181 mg, 73%;**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.0 Hz, 2 H), 7.5–7.45 (m, 5 H), 7.40 (t, *J* = 8.0 Hz, 4 H), 7.35–7.27 (m, 3 H), 7.24–7.20 (m, 3 H), 7.16 (d, *J* = 7.6 Hz, 2 H), 6.93 (s, 1 H), 6.60 (s, 1 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 163.9, 151.6, 149.4, 141.3, 140.1, 138.7, 137.7, 134.8, 129.8, 129.7, 129.3, 129.2, 129.0, 129.0, 128.3, 127.1, 127.2, 127.0, 126.7, 116.4, 107.9; **IR** (KBr, neat) 2952, 1691, 1552, 1310, 1182, 1094, 634 cm^{-1}; **HRMS** (ESI) calcd. for $C_{29}H_{21}NaNO$ $(M + Na)^+$ 422.1515, found 422.1531.

6-(Naphthalen-1-yl)-1,4-diphenylpyridin-2(1*H*)-one (26i):



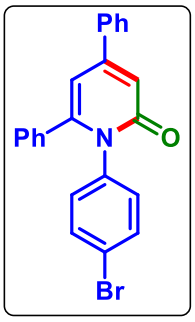
Brown solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 241–243 °C. Yield 164 mg, 71%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78 (s, 1 H), 7.77–7.72 (m, 2 H), 7.71–7.68 (m, 2 H), 7.56 (d, *J* = 8.5 Hz, 1 H), 7.49–7.45 (m, 5 H), 7.26–7.22 (m, 2 H), 7.20–7.15 (m, 3 H), 7.12–710 (m, 1 H), 6.96 (s, 1 H), 6.66 (s, 1 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 163.9, 151.7, 149.7, 138.7, 137.7, 133.5, 132.9, 132.8, 129.9, 129.4, 129.3, 129.0, 128.9, 128.4, 128.3, 127.9, 127.7, 127.2, 127.1, 126.8, 126.3, 116.5, 108.4; **IR** (KBr, neat) 2985, 1658, 1583, 1392, 1104, 1041, 647 cm^{-1}; **HRMS** (ESI) calcd. for $C_{27}H_{20}NO$ $(M + H)^+$ 374.1539, found 374.1585.

1-(3,4-Dichlorophenyl)-4,6-diphenylpyridin-2(1*H*)-one (26j):



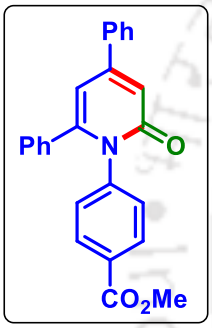
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 211–213 °C. Yield 170 mg, 70%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.1 Hz, 2 H), 7.48 (d, *J* = 6.8 Hz, 3 H), 7.40–7.38 (m, 1 H), 7.26–7.22 (m, 5 H), 7.17–7.15 (m, 1 H), 7.08 (d, *J* = 8.4 Hz, 1 H), 6.92 (s, 1 H), 6.56 (s, 1 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 162.9, 152.2, 149.3, 137.4, 135.6, 135.2, 134.9, 134.0, 131.9, 130.2, 130.0, 129.3, 129.2, 128.8, 128.3, 127.9, 127.1, 116.2, 108.0; **IR** (KBr, neat) 2962, 1649, 1523, 1331, 1145, 1040, 628 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{15}Cl_2NNaO$ $(M + Na)^+$ 414.0423, found 414.0436.

1-(4-Bromophenyl)-4,6-diphenylpyridin-2(1*H*)-one (26k):



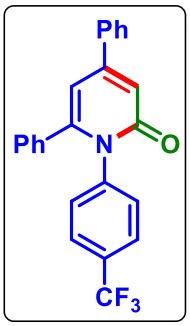
Brown solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 211–213 °C. Yield 179 mg, 72%;**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66–7.64 (m, 2 H), 7.46–7.47 (d, *J* = 7.0 Hz, 3 H), 7.40 (d, *J* = 8.4 Hz, 2 H), 7.25–7.20 (m, 3 H), 7.14 (d, *J* = 6.7 Hz, 2 H), 7.00 (d, *J* = 8.4 Hz, 2 H), 6.90 (s, 1 H), 6.55 (s, 1 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 163.6, 151.8, 149.3, 137.7, 137.5, 135.5, 132.2, 130.9, 129.9, 129.3, 129.2, 128.9, 128.4, 127.0, 122.2, 116.3, 108.1; **IR** (KBr, neat) 2962, 1678, 1535, 1341, 1124, 1071, 621 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{17}BrNO$ $(M + H)^+$ 402.0488, found 402.0486.

Methyl 4-(2-oxo-4,6-diphenylpyridin-1(2*H*)-yl)benzoate (26l):



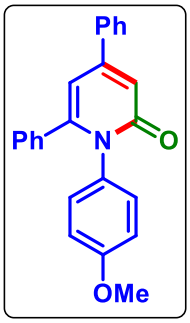
Pale yellow solid; R_f (hexane/EtOAc, 3:2) 0.50; mp 227–229 °C. Yield 163 mg, 69%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2 H), 7.68–7.64 (m, 2 H), 7.49–7.46 (m, 2 H), 7.24–7.16 (m, 6 H), 7.15–7.12 (m, 2 H), 6.92 (s, 1 H), 6.58 (s, 1 H), 3.88 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 166.4, 163.5, 151.9, 149.1, 142.8, 137.5, 135.4, 130.3, 129.9, 129.7, 129.5, 129.2, 129.1, 128.9, 128.4, 127.0, 116.3, 108.2, 52.4; **IR** (KBr, neat) 2925, 1668, 1542, 1331, 1174, 1091, 687 cm^{-1}; **HRMS** (ESI) calcd. for $C_{25}H_{19}NNaO_3$ $(M + Na)^+$ 404.1257, found 404.1272.

1,4-Diphenyl-6-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one (26m):



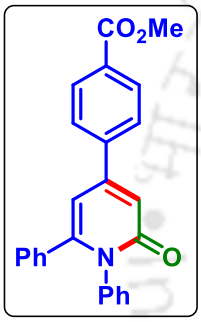
Brown solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 203–205 °C. Yield 162 mg, 67%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68–7.64 (m, 2 H), 7.50–7.43 (m, 5 H), 7.31–7.25 (m, 5 H), 7.14–7.10 (m, 2 H), 6.96 (d, *J* = 1.7 Hz, 1 H), 6.55 (d, *J* = 1.7 Hz, 1 H); **^{13}C{^{1}H}** NMR (125 MHz, $CDCl_3$) δ 163.6, 151.6, 148.0, 139.4, 138.3, 137.4, 130.0, 129.7, 129.4, 129.3, 129.2, 128.7, 127.0, 125.2 (q, *J* = 3.8 Hz), 117.2, 108.3; **^{19}F NMR** (376 MHz, $CDCl_3$) δ 62.85 (s, -CF_3); **IR** (KBr, neat) 2928, 1659, 1589, 1321, 1124, 1067, 694 cm^{-1};**HRMS** (ESI) calcd. for $C_{24}H_{17}F_3NO$ $(M + H)^+$ 392.1257, found 392.1252.

1-(4-Methoxyphenyl)-4,6-diphenylpyridin-2(1*H*)-one (26n):



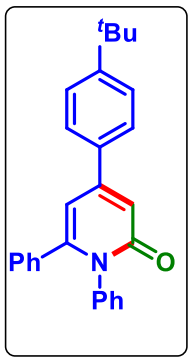
Pale yellow solid; R_f (hexane/EtOAc, 3:2) 0.50; mp 214–216 °C. Yield 177 mg, 81%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67–7.65 (m, 2 H), 7.48–7.44 (m, 3 H), 7.24–7.18 (m, 3 H), 7.17–7.13 (m, 2 H), 7.03 (d, *J* = 8.7 Hz, 2 H), 6.92 (d, *J* = 2.0 Hz, 1 H), 6.78 (d, *J* = 8.7 Hz, 2 H), 6.54 (d, *J* = 2.0 Hz, 1 H), 3.74 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 164.2, 159.1, 151.5, 150.0, 137.8, 136.1, 131.4, 130.1, 129.7, 129.3, 129.2, 128.6, 128.2, 127.0, 116.3, 114.3, 107.8, 55.5; **IR** (KBr, neat) 2973, 1652, 1339, 1114, 1049, 567 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{20}NO_2$ $(M + H)^+$ 354.1489, found 354.1498.

Methyl 4-(2-oxo-1,6-diphenyl-1,2-dihydropyridin-4-yl)benzoate (26o):



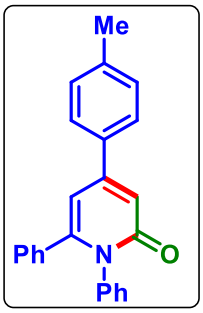
Pale yellow solid; R_f (hexane/EtOAc, 3:2) 0.50; mp 229–231 °C. Yield 198 mg, 84%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.5 Hz, 2 H), 7.73 (d, *J* = 8.5 Hz, 2 H), 7.28 (t, *J* = 7.5 Hz, 2 H), 7.24–7.11 (m, 8 H), 6.95 (d, *J* = 2.0 Hz, 1 H), 6.54 (d, *J* = 2.0 Hz, 1 H), 3.95 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 166.7, 163.6, 150.4, 150.0, 142.0, 138.5, 135.6, 131.2, 130.4, 129.2, 129.1, 129.0, 128.7, 128.3, 128.1, 127.0, 117.1, 107.4, 52.5; **IR** (KBr, neat) 2992, 1728, 1535, 1362, 1146, 1022, 651 cm^{-1}; **HRMS** (ESI) calcd. for $C_{25}H_{20}NO_3$ $(M + H)^+$ 382.1438, found 382.1448.

4-(4-(*Tert*-butyl)phenyl)-1,6-diphenylpyridin-2(1*H*)-one (26p):



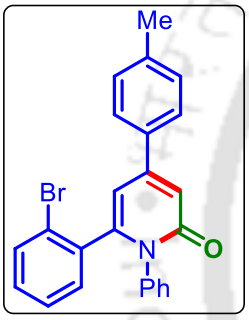
Brown solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 239–241 °C. Yield 172 mg, 73%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 2 H), 7.50 (d, *J* = 8.2 Hz, 2 H), 7.29–7.25 (m, 2 H), 7.22–7.11 (m, 8 H), 6.93 (d, *J* = 2.0 Hz, 1 H), 6.56 (d, *J* = 2.0 Hz, 1 H), 1.36 (s, 9 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 163.9, 153.2, 151.4, 149.5, 138.8, 136.0, 134.7, 129.3, 129.3, 128.9, 128.6, 128.2, 128.1, 126.7, 126.2, 115.9, 107.8, 35.0, 31.4; **IR** (KBr, neat) 2935, 1662, 1551, 1338, 1102, 1074, 678 cm^{-1}; **HRMS** (ESI) calcd. for $C_{27}H_{25}NNaO$ $(M + Na)^+$ 402.1828, found 402.1846.

1,6-Diphenyl-4-(*p*-tolyl)pyridin-2(1*H*)-one (26q):



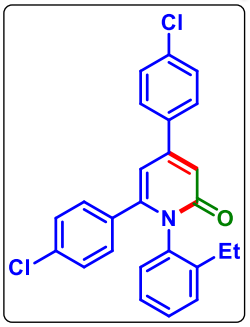
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 206–208 °C. Yield 157 mg, 75%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.9 Hz, 2 H), 7.27 (t, *J* = 8.4 Hz, 4 H), 7.22–7.10 (m, 8 H), 6.91 (d, *J* = 2.0 Hz, 1 H), 6.54 (d, *J* = 2.0 Hz, 1 H), 2.41 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 163.9, 151.4, 149.5, 140.0, 138.7, 136.0, 134.7, 129.9, 129.4, 129.3, 128.9, 128.6, 128.2, 128.1, 126.9, 115.8, 107.8, 21.5; **IR** (KBr, neat) 2941, 1698, 1548, 1350, 1100, 1052, 637 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{19}NNaO$ $(M + Na)^+$ 360.1359, found 360.1371.

6-(2-Bromophenyl)-1-phenyl-4-(*p*-tolyl)pyridin-2(1*H*)-one (26s):



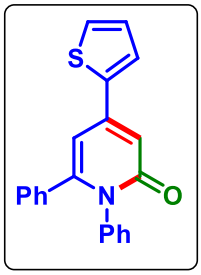
Brown solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 224–226 °C. Yield 189 mg, 73%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.40–7.34 (m, 1 H), 7.29–7.23 (m, 4 H), 7.20–7.10 (m, 4 H), 7.07–7.03 (m, 1 H), 6.95 (d, *J* = 2.0 Hz, 1 H), 6.50 (d, *J* = 2.0 Hz, 1 H), 2.41 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 163.8, 151.2, 147.6, 140.1, 138.2, 136.6, 134.5, 132.8, 131.8, 130.4, 129.9, 129.2, 128.6, 128.5, 128.1, 126.9, 123.5, 116.5, 108.0, 21.5; **IR** (KBr, neat) 2942, 1688, 1502, 1351, 1104, 1020, 612 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{18}BrNNaO$ $(M + Na)^+$ 440.0444, found 440.0459.

4,6-Bis(4-chlorophenyl)-1-(2-ethylphenyl)pyridin-2(1*H*)-one (26t):



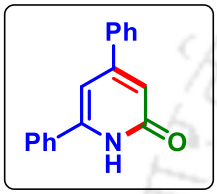
Brown solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 231–233 °C. Yield 197 mg, 76%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.6 Hz, 2 H), 7.45 (d, *J* = 8.6 Hz, 2 H), 7.27–7.21 (m, 2 H), 7.17–7.13 (m, 3 H), 7.09–7.03 (m, 3 H), 6.90 (d, *J* = 2.0 Hz, 1 H), 6.47 (d, *J* = 2.0 Hz, 1 H), 2.52–2.43 (m, 1 H), 2.36–2.26 (m, 1 H), 1.17 (t, *J* = 7.6 Hz, 3 H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 163.4, 150.4, 148.9, 140.7, 136.8, 136.1, 135.9, 135.1, 133.7, 130.3, 129.5, 129.3, 128.9, 128.4, 128.3, 126.6, 116.7, 107.4, 23.8, 13.5; **IR** (KBr, neat) 2949, 1682, 1591, 1350, 1118, 1062, 652 cm^{-1}; **HRMS** (ESI) calcd. for $C_{25}H_{20}Cl_2NO$ $(M + H)^+$ 420.0916, found 420.0912.

1,6-Diphenyl-4-(thiophen-2-yl)pyridin-2(1*H*)-one (26x):



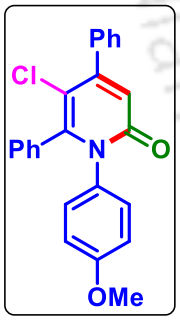
Brown solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 210–212 °C. Yield 131 mg, 64%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 3.7 Hz, 1 H), 7.43 (d, *J* = 5.0 Hz, 1 H), 7.25 (t, *J* = 7.5 Hz, 2 H), 7.21–7.15 (m, 4 H), 7.14–7.08 (m, 5 H), 6.93 (d, *J* = 2.0 Hz, 1 H), 6.53 (d, *J* = 2.0 Hz, 1 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 163.6, 149.8, 144.4, 140.6, 138.5, 135.7, 129.3, 129.2, 128.9, 128.7, 128.6, 128.3, 128.2, 128.1, 126.5, 113.9, 106.5; **IR** (KBr, neat) 2918, 1675, 1330, 1129, 1025, 571 cm^{-1}; **HRMS** (ESI) calcd. for $C_{21}H_{16}NOS$ $(M + H)^+$ 330.0947, found 330.0913.

4,6-Diphenylpyridin-2(1*H*)-one (29a):



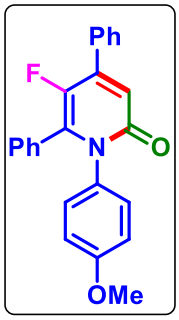
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.60; mp 209–211 °C. Yield 31 mg, 63%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.1 Hz, 2 H), 7.60–7.53 (m, 2 H), 7.49–7.35 (m, 6 H), 6.69 (d, *J* = 2.7 Hz, 2 H); **^{13}C{^{1}H} NMR** (125 MHz $CDCl_3$) δ 165.5, 154.2, 146.9, 138.3, 133.9, 130.4, 129.7, 129.5, 129.2, 127.2, 126.9, 115.4, 105.2; **IR** (KBr, neat) 2972, 1680, 1341, 1120, 1042, 559 cm^{-1}; **HRMS** (ESI) calcd. for $C_{17}H_{14}NO$ $(M + H)^+$ 248.1070, found 248.1065.

5-Chloro-1-(4-methoxyphenyl)-4,6-diphenylpyridin-2(1*H*)-one (31a):



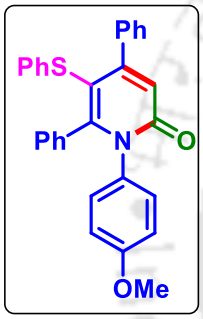
Pale yellow solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 224–226 °C. Yield 113 mg, 73%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 6.6 Hz, 2 H), 7.53–7.46 (m, 3 H), 7.24–7.19 (m, 3 H), 7.16–7.13 (m, 2 H), 7.07 (d, *J* = 9.0 Hz, 2 H), 6.81 (d, *J* = 9.0 Hz, 2 H), 6.34 (s, 1 H), 3.78 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 160.4, 159.3, 149.1, 147.3, 137.6, 135.3, 131.6, 130.0, 129.3, 129.2, 128.8, 128.7, 128.6, 128.3, 122.9, 114.3, 110.0, 55.6; **IR** (KBr, neat) 2978, 1685, 1369, 1148, 1020, 572 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{19}ClNO_2$ $(M + H)^+$ 388.1099, found 388.1095.

5-Fluoro-1-(4-methoxyphenyl)-4,6-diphenylpyridin-2(1*H*)-one (31b):



Brown gummy; R_f (hexane/EtOAc, 1:1) 0.50; Yield 92 mg, 62%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53–7.51 (m, 2 H), 7.40–7.37 (m, 2 H), 7.35–7.30 (m, 3 H), 7.28–7.26 (m, 3 H) 6.95 (d, *J* = 8.8 Hz, 2 H), 6.71 (d, *J* = 9.0 Hz, 2 H), 6.53 (d, *J* = 2.6 Hz, 1 H), 3.67 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ163.1, 158.8, 150.5, 143.9, 143.7, 134.2, 131.4, 130.2, 129.9, 129.4, 128.7, 128.6, 128.5, 128.0, 127.7, 126.7, 114.2, 55.3; **^{19}F NMR**(470 MHz, C_6F_6/$CDCl_3$) δ 24.3 (s, -F); **IR** (KBr, neat) 2979, 1695, 1378, 1172, 1041, 570 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{19}FNO_2$ $(M + H)^+$ 372.1394, found 372.1385.

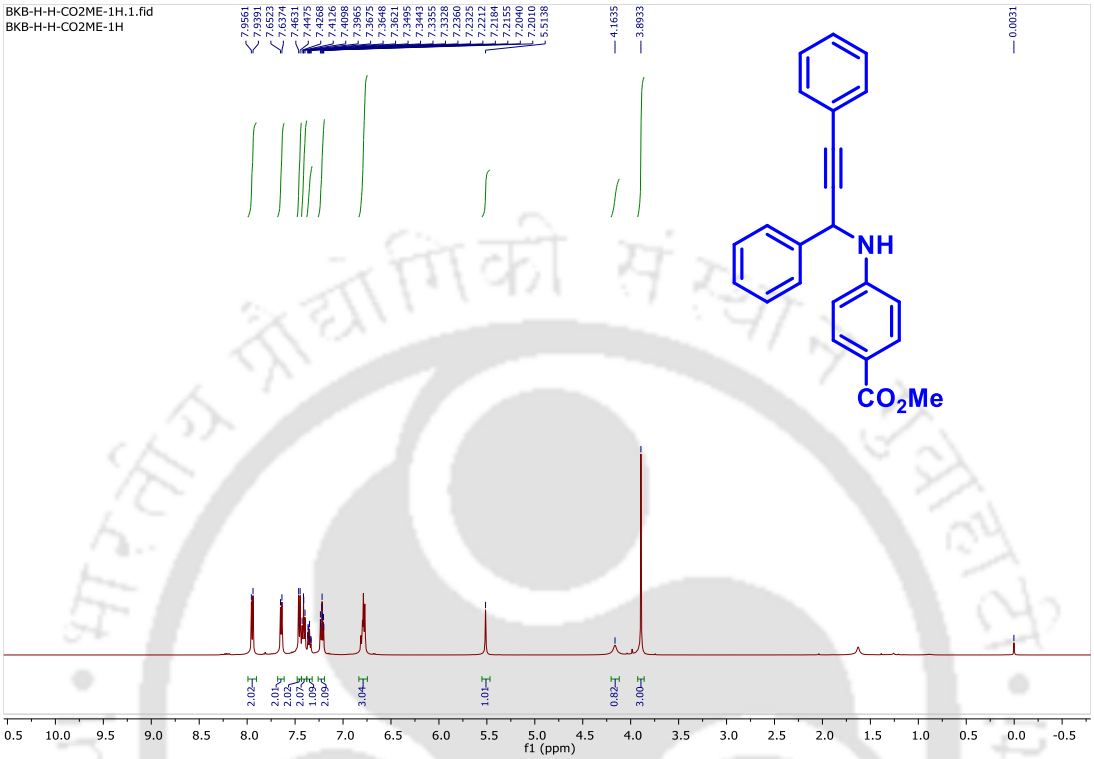
1,4,6-Triphenyl-5-(phenylthio)pyridin-2(1*H*)-one (31c):



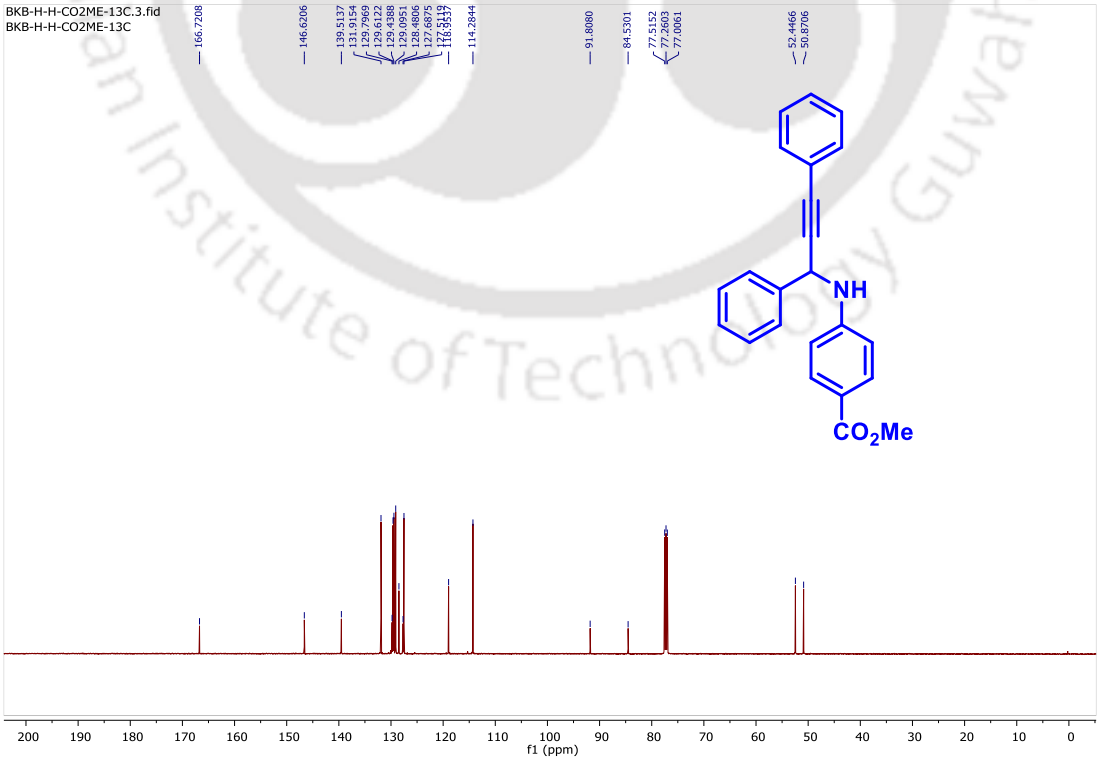
Brown solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 232–234 °C. Yield 103 mg, 56%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40–7.37 (m, 2 H), 7.32–7.31 (m, 2 H), 7.18–7.16 (m, 2 H), 7.14–7.06 (m, 8 H), 7.02–6.99 (m, 1 H), 6.94 (d, *J* = 8.4 Hz, 2 H), 6.67 (d, *J* = 8.4 Hz, 2 H), 6.31 (s, 1 H), 3.65 (s, 3 H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 162.6, 159.1, 157.4, 149.6, 139.4, 137.0, 135.5, 131.7, 130.1, 129.1, 129.0, 128.9, 128.7, 128.6, 128.5, 128.3, 128.2, 125.9, 121.5, 114.2, 110.5, 55.6; **IR** (KBr, neat) 2957, 1680, 1359, 1140, 1074, 591 cm^{-1}; **HRMS** (ESI) calcd. for $C_{30}H_{24}NO_2S$ $(M + H)^+$462.1552, found 462.1559.

5.9. Representative Spectra

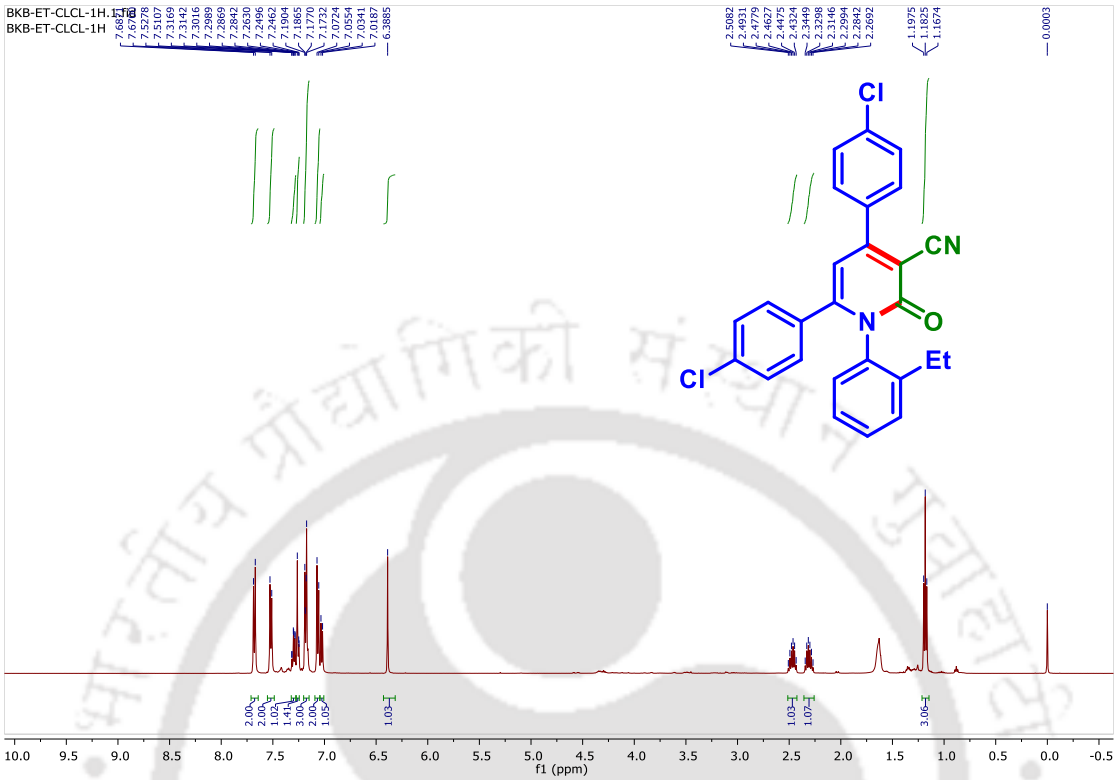
^{1}H spectrum of compound **21l** (500 MHz, $CDCl_3$)



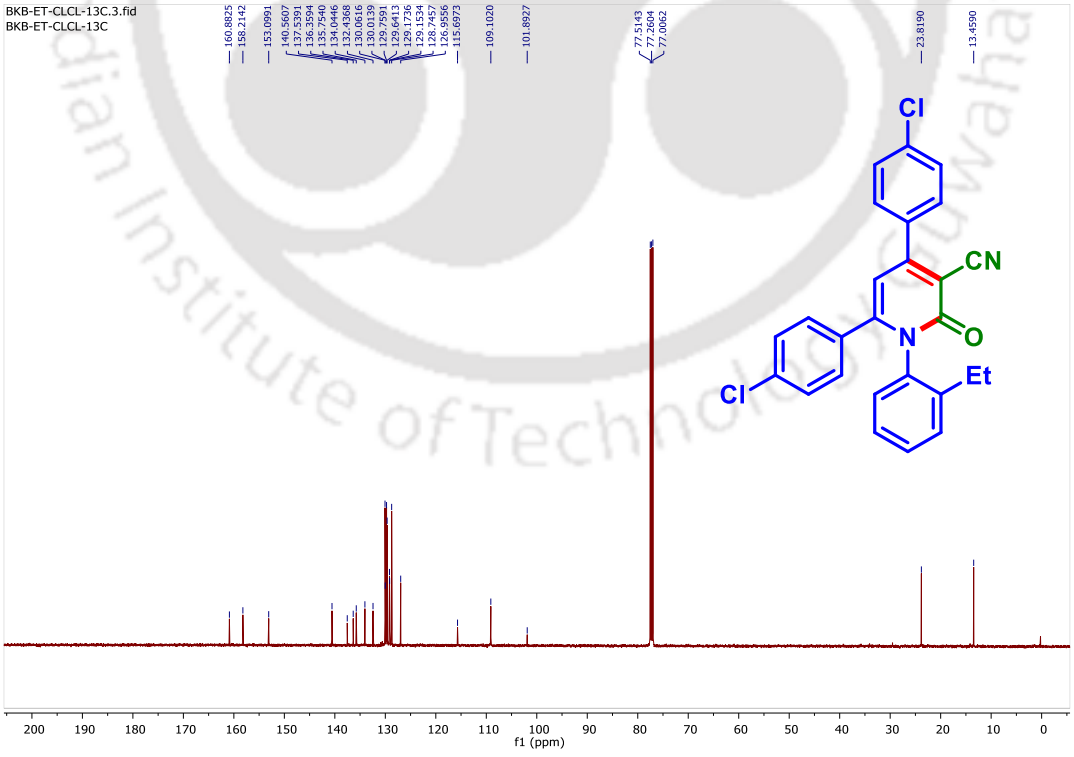
^{13}C{^{1}H} NMR spectrum of compound **21l** (125 MHz, $CDCl_3$)



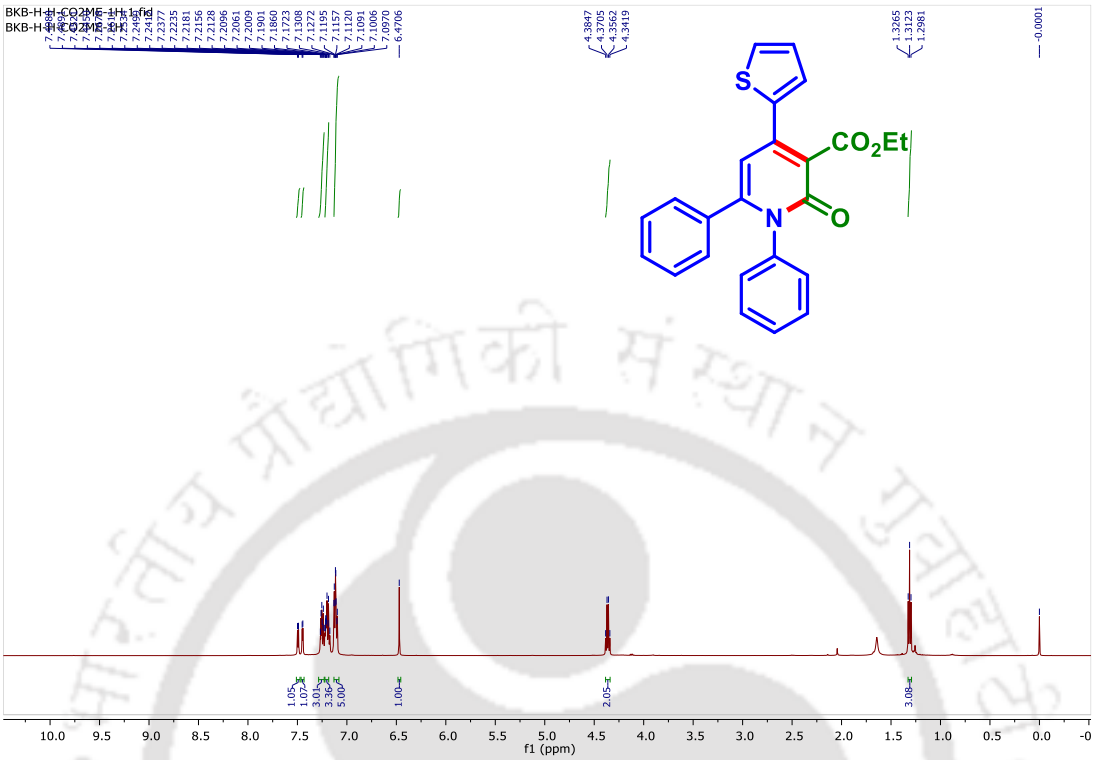
^{1}H spectrum of compound **23t** (500 MHz, $CDCl_3$)



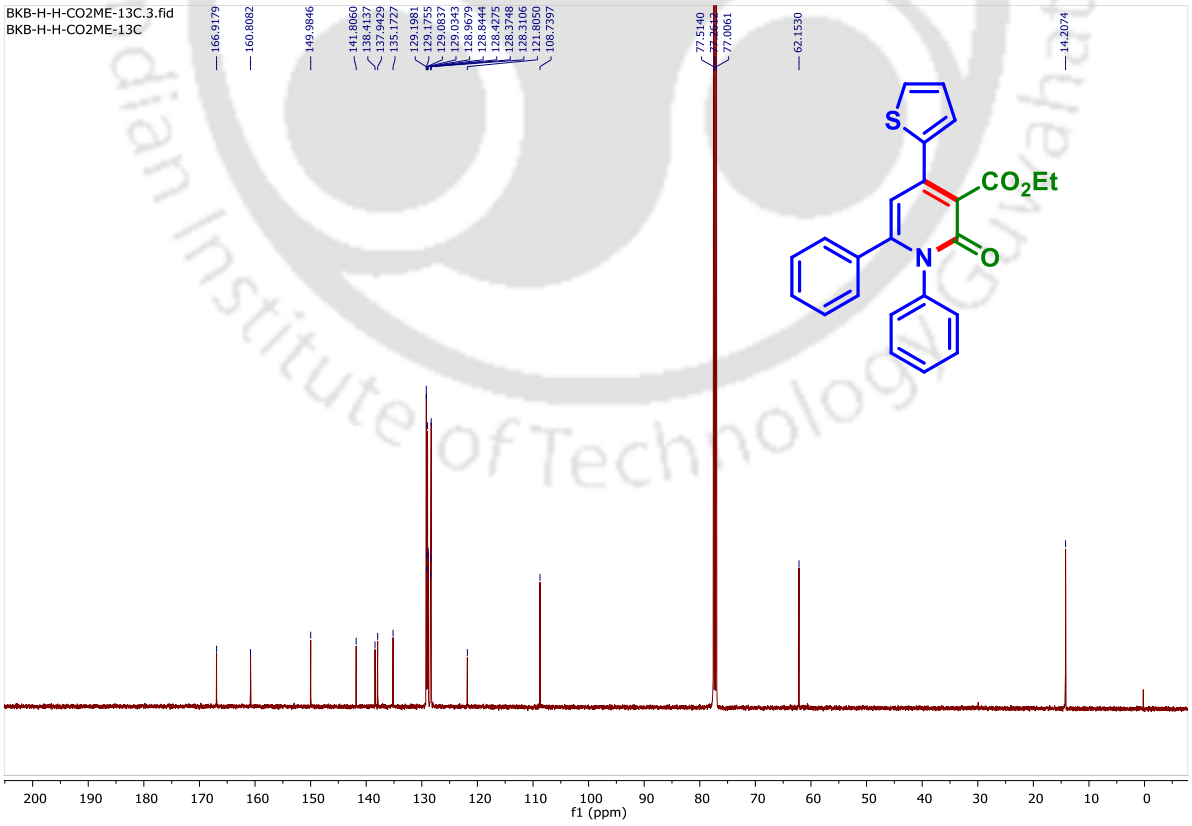
^{13}C{^{1}H} NMR spectrum of compound **23t** (125 MHz, $CDCl_3$)



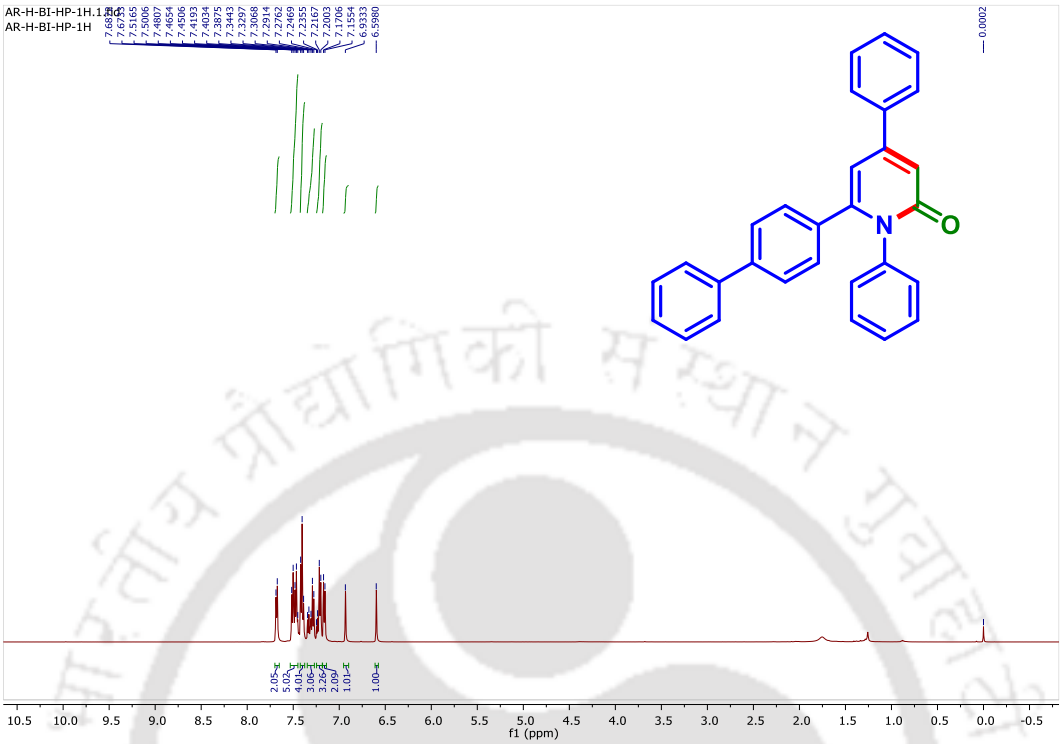
^{1}H spectrum of compound **24x** (500 MHz, $CDCl_3$)



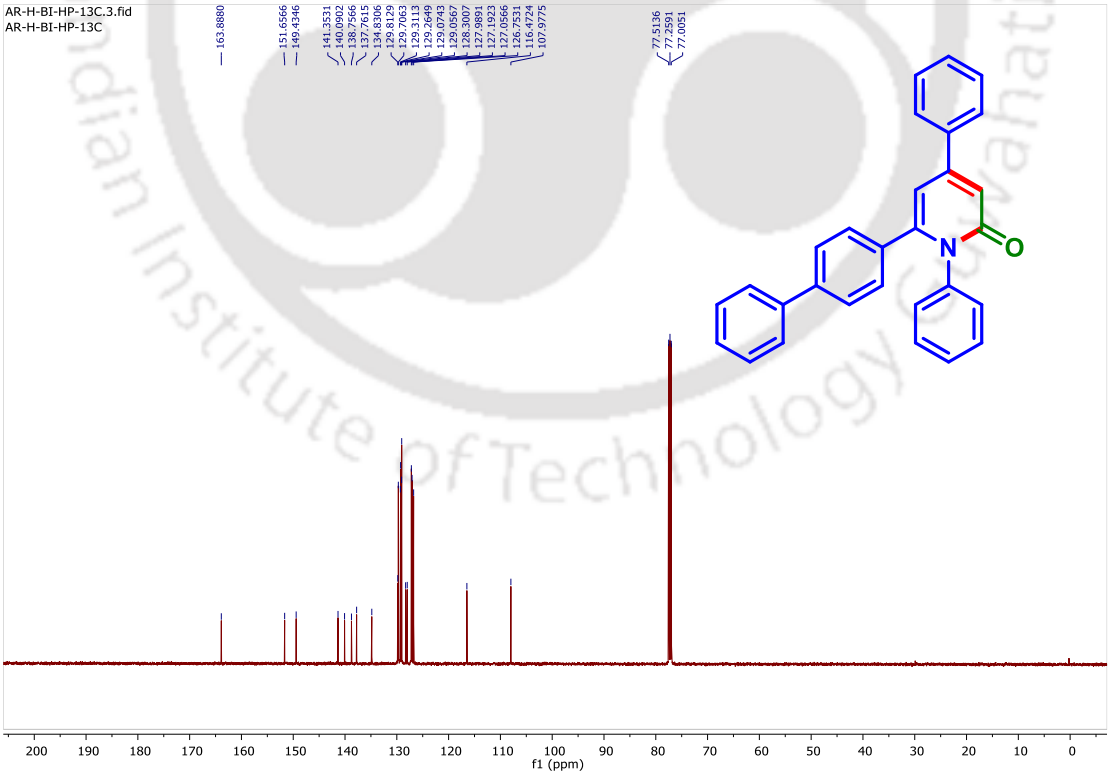
^{13}C{^{1}H} NMR spectrum of compound **24x** (125 MHz, $CDCl_3$)



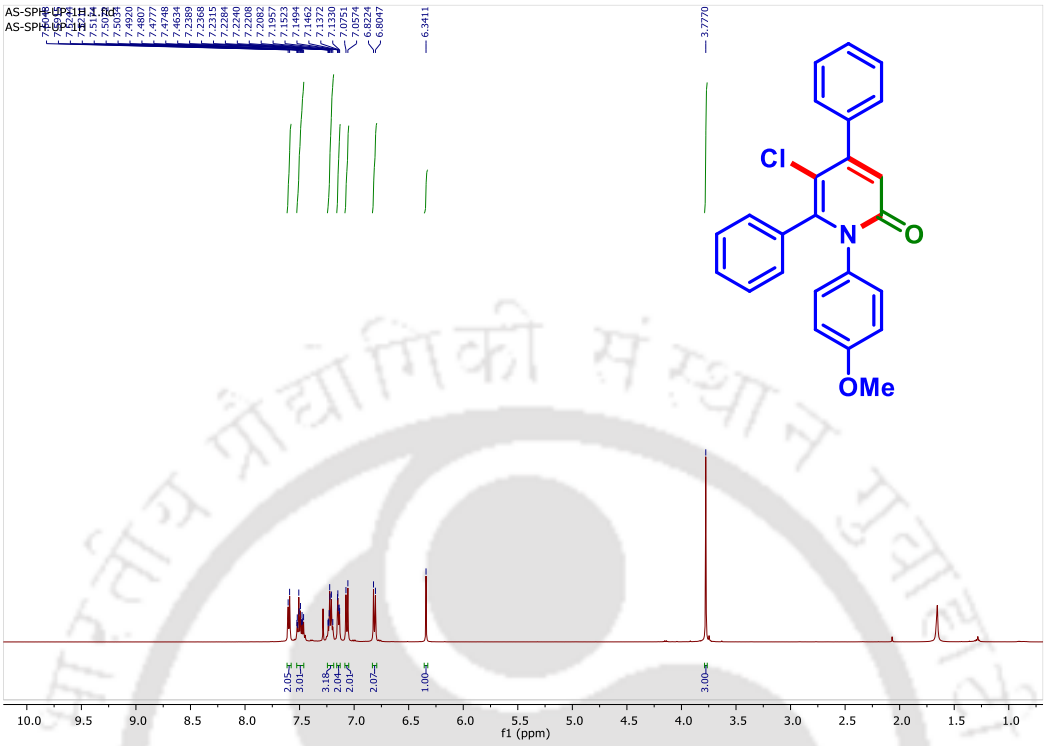
^{1}H spectrum of compound **26h** (500 MHz, $CDCl_3$)



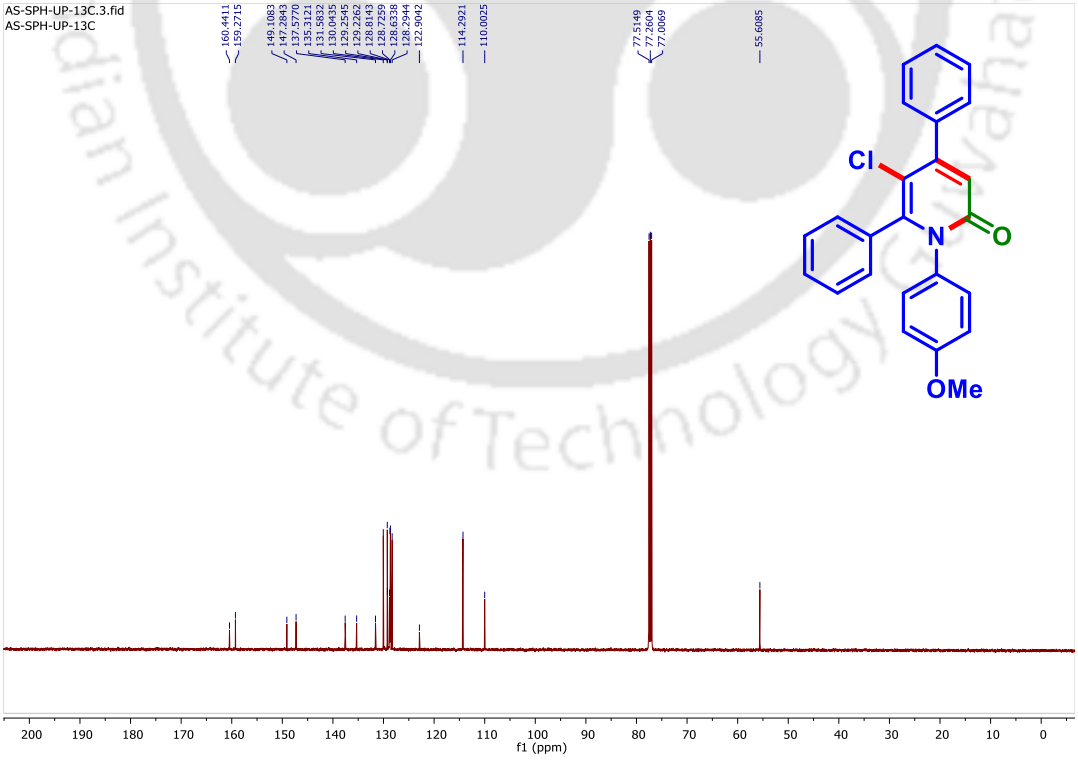
^{13}C{^{1}H} NMR spectrum of compound **26h** (125 MHz, $CDCl_3$)



^{1}H spectrum of compound **31a** (600 MHz, $CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of compound **31a** (125 MHz, $CDCl_3$)



List of Publications

1. $K_2S_2O_8$-Mediated Synthesis of Highly Functionalized Pyrroles *via* Oxidative Self-Dimerization of *N*-Propargylamines.

   Behera, B. K.; Sahu, A. K.; Devi, N. R.; Saikia, A. K. *J. Org. Chem.* **2021**, *86*, 12481.

2. Synthesis of Thiazole-2(3*H*)-ones *via* [3,3]-Sigmatropic Rearrangement/5-*exo*-dig Cyclization of *N*-Propargylamines.

   Behera, B. K.; Shit, S.; Biswas, S.; Saikia, A. K. *J. Org. Chem.* **2022**, *87*, 9259.

3. Base-Promoted [4 + 2] Annulation Reaction of In Situ-Generated Azadienes from *N*-Propargylamines with Active Methylene Compounds: Access to Highly Functionalized 2-Pyridones.

   Behera, B. K.; Arandhara, P. J.; Porashar, B.; Bora, S. K.; Saikia, A. K. *J. Org. Chem.* **2023**, *88*, 15041.

4. Synthesis of 2-Methylenedihydrothiazoles *via* Micheal addition/5-*exo*-dig Cyclization of *N*-Propargylamines.

   Behera, B. K.; Saikia, A. K. **2023** (*manuscript under preparation*).

5. Regio- and Chemoselective Synthesis of 3-(Dihydrofuran-3(2*H*)-ylidene) isobenzofuran-1(3*H*)-imines via Tandem Alkynyl Prins- and Intramolecular Oxycyclization Reactions. Shit, S.; **Behera, B. K.**; Biswas, S.; Saikia, A. K. *J. Org. Chem.* **2023**, *88*, 10884.

6. Synthesis of 1, 2, 3-triazole-fused *N*-heterocycles from *N*-alkynyl hydroxyisoindolinones and sodium azide *via* Huisgen reaction.

   Arandhara, P. J.; **Behera, B. K.**; Biswas, S.; Saikia, A. K. *Org. Biomol. Chem.* **2023**, *21*, 8772.

7. Leveraging cascade alkynyl Prins cyclization towards the stereoselective synthesis of spiro-furan quinazolinone scaffolds.

   Biswas, S.; Shit, S.; **Behera, B. K.**; Sahu, A. K.; Saikia, A. K. *Chem. Commun.*, **2023**, 59, 14301.

8. Synthesis of dibenzocyclohepta[1,2-a] naphthalene derivatives from phenylacetaldehyde and alkynyl benzyl alcohols via sequential electrophilic addition and double Friedel–Crafts reactions.

   Sahu, A. K.; Unnava, R.; **Behera, B. K.**; Saikia, A. K. *Org. Biomol. Chem.* **2021**, *19*, 2430.

9. Synthesis of 4-Vinyl-1,2,3,4-tetrahydroisoquinoline from *N*-Tethered Benzyl-Alkenol Catalyzed by Indium(III) Chloride: Formal Synthesis of (+/-)-Isocyclocelabenzine.

   Devi, N. R.; Shit, S.; **Behera, B. K.**; Saikia, A. K. *Synthesis*, **2020**, *52*, 1425.

10. Stereo- and Regioselective Synthesis of 4-Vinylpyrrolidine from *N*-Tethered Alkyne-Alkenol

    Devi, N. R.; **Behera, B. K.**; Saikia, A. K. *ACS Omega*. **2018**, *3*, 576.