

Synthesis of Complex Nitrogen Heterocyclic Compounds

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

Doctor of Philosophy in Chemistry



Submitted by

Ramanjaneyulu Unnava

**Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati-781039, Assam, India
August 2017**



**Dedicated
To
My Parents**



INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled “**Synthesis of Complex Nitrogen Heterocyclic Compounds**” is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the guidance of Professor 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.

7th September, 2017
IIT Guwahati

(Ramanjaneyulu Unnava)



Indian Institute of Technology Guwahati

Department of Chemistry

North Guwahati, Guwahati-781039, India

Phone: +91 (361) 2582316; Fax: +91 (361) 2690762

e-mail: asaikia@iitg.ernet.in

Dr. Anil K. Saikia
Professor

CERTIFICATE

This is to certify that Mr. **Ramanjaneyulu Unnava** has been working under my supervision since July 2012 as a regular registered Ph. D. student. I am forwarding his thesis entitled “**Synthesis of Complex Nitrogen Heterocyclic Compounds**” being submitted for the Ph. D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

7th September, 2017
IIT Guwahati

Prof. Anil K. Saikia
Supervisor

ACKNOWLEDGEMENTS

The journey of PhD without company is as difficult as finding colours in the darkness. I will be failing in my duty if I don't acknowledge all those beautiful minds that have directly or indirectly helped me in the time of need. I thank all of you for your praiseworthy cooperation, motivation and support that made me to groom.

At first I extend my heartfelt thanks to my thesis advisor Prof. Anil K. Saikia for accepting me into his group and his invaluable guidance, unlisted encouragement, inspiration and scientific advices throughout my Ph. D. program, which helped me to enhance my knowledge and inspired me to take right decisions at crucial moments. I am thankful to him for giving me the freedom to carry out my own ideas and I find myself privileged to have worked under his spiritual guidance. Without his inspiration, it would have not been possible to complete this study.

I would like to express my sincere gratitude to all my doctoral committee members, Prof. V. Manivannan, Prof. Aditya Narayan Panda and Prof. Vikas Kumar Dubey for their insightful advices and valuable suggestions during my doctoral studies. My honest regards to all the faculty of the Department of Chemistry for their motivation and encouragement.

I am very grateful to acknowledge the Council of Scientific and Industrial Research (CSIR), New Delhi, India for financial support and IIT Guwahati for all the facilities that were made available to me. I also thank Central Instrument Facility (CIF), IIT Guwahati for providing the instrument facility and DST for providing the X-ray facility.

I am also indebted to all the members of the IITG staff for the valuable services they have provided. In particular, I would like to thank Mr. Chandan Borgohain, Mr. Kh. Kesho Singh, Imdadul Islam and all other NMR and HRMS operators for their efforts in measuring my samples. I acknowledge the help rendered by Dr. Babulal Das, Technical Officer, for collecting the X-ray crystal data. I would like to thank my department colleagues, Miss. Nibedita Behera, Dr. Vikas and Dr. Bigyan for solving X-ray crystal structures.

Further, I would like to thank all my past and present group members for their friendship and assistance. I especially thank Dr. Kiran Indukuri for his assistance in familiarizing me with laboratory techniques and valuable discussions in this journey. I am thankful to Archana K. Sahu for her helping hand at the end of my Ph.D. program. I thank the other members, Dr. Somesekhar, Dr. Pipas Saha, Dr. Paramartha Gogoi, Manash, Sujit, Madhurjya, Renubala, Upasana, Malay and Riya for their help.

I extend my sincere thanks to other friends in IITG, especially Ramesh, Vishnu, Pradeep, Radhakrishna, Abishek Ajmani, Srinu, Sateesh, Ganesh, Bali Reddy, Dr. Suchandra, Dr. Mohan, Karuna, Wajid, Rajendra, Jagath, Krishna Pavan, Yaswanth, Sunku, Narendra Naik, Nagireddy, Satti, Vinod, Sunil, Bargav, Vijay, Gopi kiran and Bharathiraja for their support during this Ph.D. program.

I also take this opportunity to thank all of my Ph.D. batchmates (July, 12), the other research scholars in the chemistry department and all my IITG friends, who have shared their thoughts and views with me.

I owe my heartfelt thanks to my dearest friends from outside IITG, Rajesh, Rajendra, Venkateswarlu, Siva koti, Rajesh, Mahesh, Brahma Reddy, Hamenth, Pitchiah, Kasi, Naresh, Ravi and Sravani for their constant support and encouragement.

Finally, I feel a deep sense of gratitude to my parents (Unnava Sambaiah & Anjamma) and my loving cousins Narasimha, Srinu, Dileep and Kishore. Without their love, care, support and encouragement, it would have not been possible.

Ramanjaneyulu Unnava

LIST OF ABBREVIATIONS

Ac	acetyl	LAH	lithiumaluminium hydride
Bn	benzyl	LDA	lithiumdiisopropyl amine
Boc	<i>tert</i> -Butyloxycarbonyl	<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
Bu	butyl	mp	melting point
CAN	ceric ammonium nitrate	MS	molecular sieves
CCDC	cambridge crystallographic data centre	m/z	mass to charge ratio
Cbz	carboxybenzyl	NBS	<i>N</i> -bromosuccinimide
CSA	camphorsulfonic acid	NIS	<i>N</i> -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
DMAP	4-Dimethylaminopyridine	PMB	<i>p</i> -methoxy benzyl
DIPEA	<i>N,N</i> -diisopropylethylamine	TBP	<i>tri n</i> -butylphosphine
DMEDA	<i>N,N'</i> -dimethylethylenediamine	POCl ₃	phosphoryl chloride
DMF	<i>N, N</i> -dimethylformamide	P(OEt) ₃	triethylphosphite
DMSO	dimethylsulfoxide	PPh ₃	triphenylphosphine
de	diastereomeric excess	ppm	parts per million
dr	diastereomeric ratio	Pr	propyl
ee	enantiomeric excess	<i>p</i> -TSA	<i>p</i> -toluenesulfonic acid
HRMS	high resolution mass spectrometry	rt	room temperature
IBD	Iodobenzene diacetate	TBAF	tetrabutylammonium fluoride
ICl	iodine monochloride	TBD	triazabicyclodecene
IR	infrared	<i>t</i> Bu	<i>tert</i> - Butyl
LA	Lewis acid	THF	tetrahydrofuran

Tf	trifluoromethanesulfonyl	TMS	trimethylsilyl
TFA	trifluoroacetic acid	TMEDA	<i>N,N,N',N'</i> -tetramethylenediamine
TIPS	triisopropylsilyl	Ts	<i>p</i> -toluenesulfonyl
TLC	thin layer chromatography		

Abbreviations for intensities of ^1H -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 this thesis have been divided into five chapters based on the results of experimental work performed during the complete course of the research period. The chapter 1 mainly discusses about synthetic strategy and utility of propargylamines. Chapter 2 describes regioselective one-pot, three-component synthesis of substituted 2*H*-indazoles from 2-nitroarylaldehyde, alkyne and amine catalyzed by CuBr/Zn(OTf)₂ system. Chapter 3 illustrates Ag(OTf) catalyzed synthesis of substituted pyrazole *N*-oxides and pyrazoles from propargylamines. Chapter 4 demonstrates synthesis of highly substituted 4-iodopyrazole *N*-oxides and pyrazoles from propargylamines. Chapter 5 explains that, a facile synthesis of benzo[1,4]oxazepine fused tetrahydroisoquinoline and tetrahydro- β -carboline analogues *via* Pictet-Spengler reaction of intramolecular cyclic iminium ion intermediates. Each chapter constitute four sections, describing introduction, present work, experimental work and spectral data, respectively.

Chapter 1: Introduction on Synthetic Utility of A³-Coupling

Amines are aliphatic and aromatic derivatives of ammonia. Depending on the number of hydrocarbon groups replacing the hydrogen atoms in ammonia, amines can be categorized as primary, secondary and tertiary. One organic group attached to the nitrogen atom in ammonia is termed as primary, whereas those with two or three organic groups attached are secondary and tertiary amines, respectively. For example, one propargyl group attached to the nitrogen atom in ammonia is termed as propargylamine. Similarly, propargyl group with either one or two of organic groups like aliphatic/aromatic attached are named as secondary and tertiary propargylamines. Due to all-encompassing features of propargylamines, till date, numerous building blocks of nitrogen heterocycles as well as bioactive molecules have been developed in synthetic organic chemistry. In this thesis, our research interest mainly emphasizes on synthesis of complex nitrogen heterocycles using propargylamine intermediates.

Classically, propargylamines are prepared by the nucleophilic addition of metal alkynylides to imine electrophiles. This reaction sequence involves condensation of primary or secondary amines with aldehydes to form an imine or iminium ions followed by subsequent nucleophilic addition of *in situ* generated metal alkynylides. The existing method suffers from certain

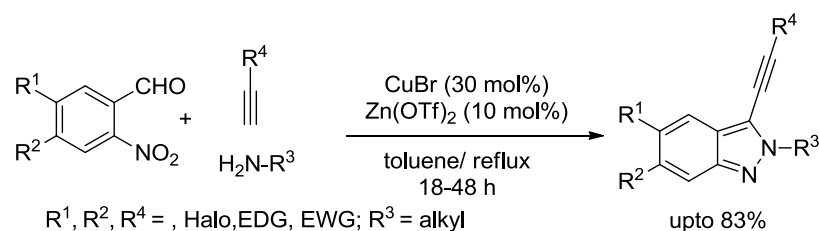
drawbacks like, it requires stoichiometric amount of strong bases like butyllithium, harsh reaction conditions and low functional groups tolerance.

To overcome these complications, in last few years an efficient transition-metal catalyzed one-pot, three-component reaction has been developed from commercially available aldehyde, alkyne and amines. This method commonly named as A^3 -coupling. The term A^3 was introduced by Li group and it has established a straightforward approach towards propargylamines. Interestingly, A^3 -coupling reaction has been studied with different metal catalysts, especially coinage metals such as Cu, Ag and Au as well as Zn, Fe, In, and Ir. Out of these copper catalysts are highly effective for the synthesis of propargylamines.

Recently, A^3 -coupling reactions play a key role for the construction of various building blocks of nitrogen-containing heterocycles as well as biologically active compounds, pharmaceuticals and natural products. Due to the flexibility of propargylamines, it can involve in different tandem cyclisation reactions and has become a powerful tool to build structurally diverse *N*-heterocyclic compound libraries. Moreover, complexity of propargylamine bearing additional functional groups could also be achieved easily.

Chapter 2: Regioselective One-Pot, Three-Component Synthesis of Substituted 2*H*-Indazoles from 2-Nitroarylaldehyde, Alkyne and Amine Catalyzed by CuBr/Zn(OTf)₂ System

Indazoles are important class of nitrogen heterocycles, found rarely in nature and show significant biological importance in the medicinal chemistry. Recently, several methods have been employed for the synthesis of 2*H*-indazole. However, methods for synthesis of 2*N*,3*C*-substituted 2*H*-indazole are limited. Even though there are few strategies have developed for the synthesis of highly substituted 2*H*-indazole, these methods suffer from drawbacks such as multistep, low selectivity, and low yields. Multicomponent reactions are gaining importance in heterocyclic chemistry due to their ability to form a series of bonds in a single step. Here in we describe a regioselective synthesis of 3-(arylethynyl)-2*H*-indazoles derivatives *via* copper(I) bromide/zinc(II) triflate catalyzed one-pot, three component reaction using 2-nitroarylaldehydes, alkynes and amines as starting materials. (**Scheme 1**).



Scheme 1: Synthesis of 3-alkynyl-2H-indazole and the scope of the reaction

The reaction is highly regioselective and only 2*N*-substituted product could be obtained in high purity without any regioisomeric product. The compound 2-(3,4-dimethoxyphenethyl)-3-(phenylethynyl)-2*H*-indazole was determined from ^1H and ^{13}C NMR and mass spectrometry experiments. Further, the structure of the compounds was confirmed by X-ray analysis (**Figure 1**).

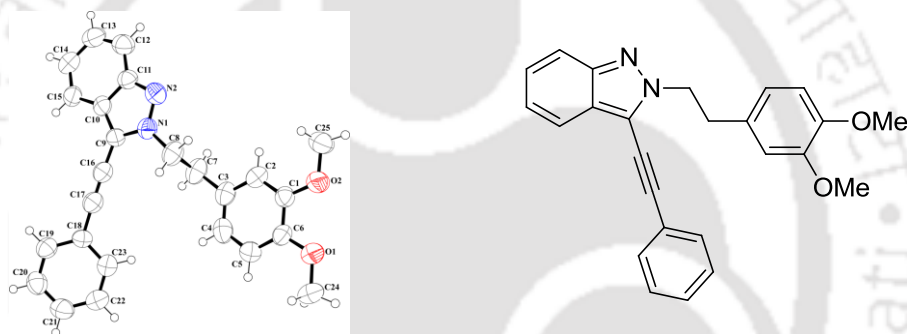


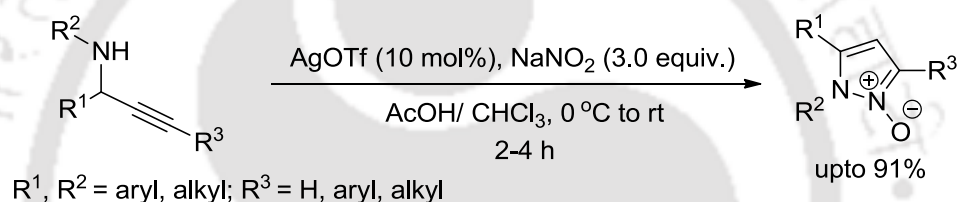
Figure 1: ORTEP diagram of compound 2-(3,4-dimethoxyphenethyl)-3-(phenylethynyl)-2*H*-indazole

In conclusion, we have developed a practical and general one-pot procedure for the synthesis of 2*H*-indazoles from *ortho*-nitroarylaldehydes, primary amines and alkynes catalyzed by CuBr and Zn(OTf)₂. This versatile one-pot, three-component procedure is a novel approach for the synthesis of highly substituted 2*H*-indazoles.

Chapter 3: Synthesis of Substituted Pyrazole *N*-Oxides and Pyrazoles from Propargylamines

Pyrazoles are important class of nitrogen heterocyclic compounds due to their broad range of biological activities and also they are found in many pharmaceutical and agrochemical substances. Pyrazoles are generally synthesized by classical cyclocondensation of hydrazine derivatives with 1,3-diketones and α,β -unsaturated aldehydes and ketones. In addition, they also synthesized by 1,3-dipolar cycloaddition of diazoalkanes or nitrilimines with alkenes or

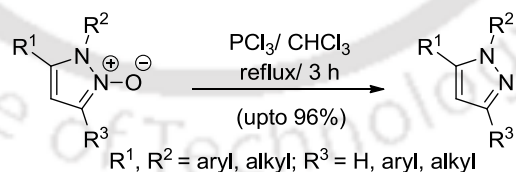
alkynes. Recently, halo cyclisation reactions also established for the synthesis of pyrazole. Similarly, Pyrazole *N*-oxides are gaining considerable interest as synthetic intermediates for the synthesis of highly substituted pyrazoles due to their regioselectivity and monoselectivity. Pyrazole *N*-oxides are susceptible to regioselective metalation and subsequent functionalization reactions. The functionalized pyrazole *N*-oxides could be easily reduced to pyrazole. Pyrazole *N*-oxides are prepared by the direct oxidation of pyrazoles with peracids, nitrosation of α -bromo- α,β -unsaturated ketoximes, and cyclisation of alkynyl nitrosoamine. The major drawback of existing methods is low yields, multistep synthesis, and lack of regioselectivity. In continuation of previous chapter, we present in this chapter, a silver(I) catalyzed mild and efficient synthesis of substituted pyrazole *N*-oxides from propargylamines using $\text{NaNO}_2/\text{AcOH}$ in one step process is described. (**Scheme 2**).



Scheme 2: Synthesis of substituted pyrazole *N*-oxides and the scope of the reaction

Cleavage of *N*-oxide bond:

Deoxygenation of *N*-oxide was achieved by using PCl_3 in chloroform under reflux for 3 h gave corresponding pyrazoles (**Scheme 5**).

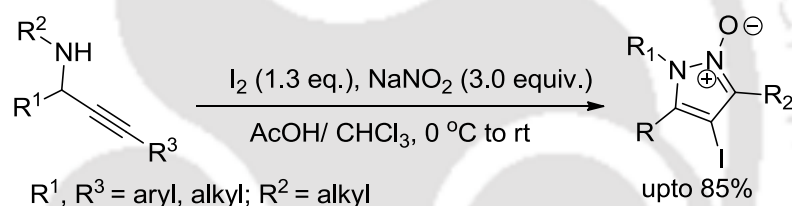


Scheme 3: Synthesis of pyrazoles from pyrazole *N*-oxides

In conclusion, a mild and efficient method has developed for the synthesis of substituted pyrazole *N*-oxide from propargylamine in excellent yields. The reaction is compatible with a wide range of functional groups such as ester, ether, nitrile, $-\text{NO}_2$, and halides. The pyrazole *N*-oxide can be converted to pyrazole and chlorinated pyrazole under different reaction conditions. Nitroaryl substituted pyrazole can be converted to pyrazolo-*N*-oxide-cinnoline, pyrazolo-quinoline and pyrazolo-cinnoline.

Chapter 4: Synthesis of Highly Substituted 4-Iodopyrazoles *N*-Oxides and Pyrazoles from Propargylamines

In previous chapter we described a methodology for the synthesis of 1,5 and 1,3,5-substituted pyrazole *N*-oxides and pyrazoles from propargylamines using AgOTf and NaNO₂/AcOH. Simultaneously, we also synthesised a few derivatives of highly substituted 4-chloropyrazole from 1,3,5-trisubstituted pyrazole *N*-oxides. These results encouraged us for further synthesis of highly substituted pyrazole *N*-oxides and pyrazoles *via* iodine mediated electrophilic cyclization reactions. This chapter demonstrates one-pot synthesis of highly substituted 4-iodopyrazole *N*-oxide and pyrazoles from propargylamines using NaNO₂ and iodine *via* 5-*endo-dig*-cyclisation process. To demonstrate further applicability of the iodopyrazole *N*-oxides, the iodo functionality was used for the Suzuki, Heck and Sonogashira cross-coupling reactions (**Scheme 4**).



Scheme 4: Synthesis of 4-iodopyrazole *N*-oxides and scope of the reaction

The structure of the compounds is determined by NMR and mass spectrometry. It was further confirmed by X-ray crystallographic analysis of compound 5-(2-chlorophenyl)-4-iodo-1-phenethyl-3-phenyl-1*H*-pyrazole 2-oxide (**Figure 2**).

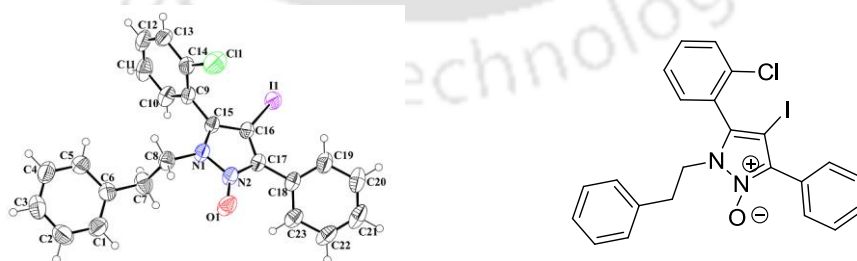
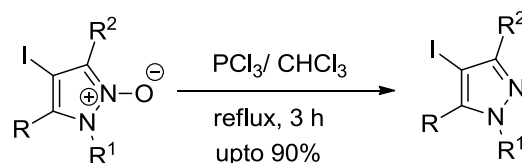


Figure 2: ORTEP diagram of compound 5-(2-chlorophenyl)-4-iodo-1-phenethyl-3-phenyl-1*H*-pyrazole 2-oxide

The reduction of pyrazole *N*-oxide to pyrazole can be achieved by treatment of phosphorous trichloride in refluxing chloroform for 3 h (**Scheme 5**).

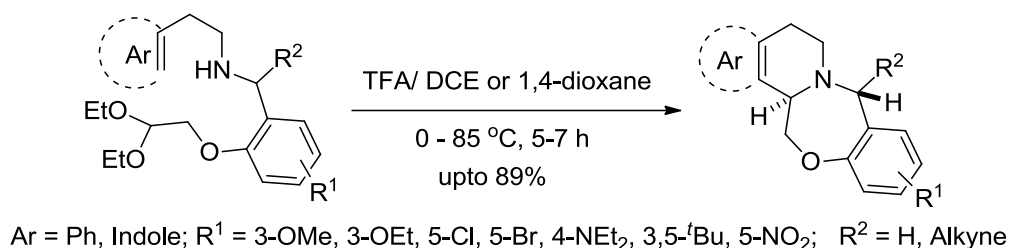


Scheme 5: 4-Iodopyrazole *N*-oxides to 4-iodopyrazoles

In conclusion, a mild and efficient method has been developed for the synthesis of iodo substituted pyrazole *N*-oxide from propargyl amine in good yields. The reaction is compatible with a wide range of functional groups such as ester, ether, -NO₂, nitrile and halides. The iodo functionality was also successfully applied for Suzuki, Heck and Sonogashira cross-coupling reactions. Some of the pyrazole *N*-oxides were converted to pyrazoles by the treatment with phosphorous trichloride in refluxing chloroform.

Chapter 5: Intramolecular Pictet-Spengler Reaction of Cyclic Iminium Ions: A Novel Access to Benzo[1,4]oxazepine Fused Tetrahydroisoquinoline and Tetrahydro- β -carboline Analogous

Synthesis of new class of heterocycles with diverse functionalities is always on forefront of attention in synthetic organic chemistry because of their high use in introducing new bioactive agents in medicinal chemistry. Particularly, synthesis of fused tetrahydroisoquinoline and tetrahydro- β -carboline scaffolds has a special interest to synthetic community. The Pictet-Spengler reaction is one of the leading techniques for construction of such valuable nitrogen heterocyclic compounds with wide range of biological activity and a diverse pharmacological profile. Recently, Ugi multicomponent reaction and subsequent acid promoted intramolecular Pictet-Spengler reaction is used for the synthesis of such privileged architectures. The reaction mechanism suggests that *in situ* generated *N*-acyliminium ion intermediates plays a key step for the development of novel library of heterocyclic compounds. Similarly, a few reports also describe the formation of such compounds *via* intramolecular Pictet-Spengler of cyclic iminium ion intermediates. This is due to less electrophilic character of cyclic iminium ions compared to cyclic *N*-acyliminium ions. In this chapter, describes a methodology for the facile synthesis of a new class of polyheterocyclic skeletons such as benzo[1,4]oxazepino-fused tetrahydroisoquinoline and tetrahydro- β -carboline scaffolds by reaction of 2-(2,2-diethoxyethoxy)benzaldehyde with 2-phenylethylamine and tryptamine, respectively *via* an *in situ* generated iminium ion and subsequent Pictet-Spengler reaction (**Scheme 6**).



Scheme 6: Synthesis of benzo[1,4]oxazepino-fused tetrahydroisoquinoline and tetrahydro- β -carboline analogues

The structure of the compounds was determined by NMR and mass spectrometry. The *trans* stereochemistry of the compound (8*R**,14*aR**)-2,3-dimethoxy-8-(phenylethynyl)-6,8,14,14a-tetrahydro-5*H*-benzo[6,7][1,4]oxazepino[3,4-*a*]isoquinoline was confirmed by X-ray crystallographic analysis (**Figure 3**).

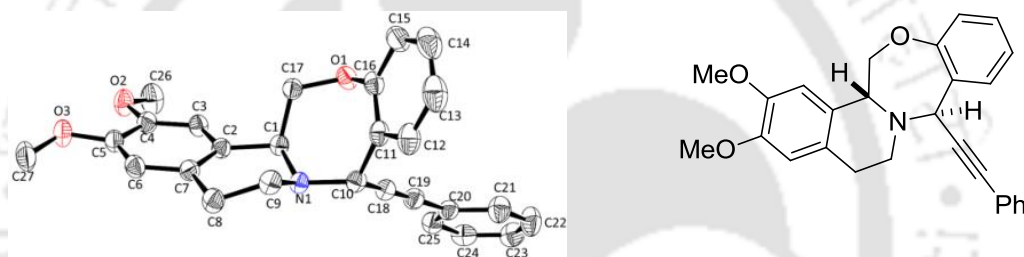


Figure 3: Crystal structure of (8*R**,14*aR**)-2,3-dimethoxy-8-(phenylethynyl)-6,8,14,14a-tetrahydro-5*H*-benzo[6,7][1,4]oxazepino[3,4-*a*]isoquinoline

In conclusion, a straight forward synthesis of a new class of benzo[1,4]oxazepino fused tetrahydroisoquinoline and tetrahydro- β -carboline frameworks has been achieved in good yields. The synthetic strategy features an efficient generation of cyclic iminium ion to construct the benzo[1,4]oxazepino unit, and an intramolecular Pictet-Spengler reaction to install the tetrahydroisoquinoline or tetrahydro- β -carboline rings as the key steps.

Index

Statement	i
Certificate	ii
Acknowledgements	iii
List of Abbreviations	v
Abstract	vii
Index	xiv

Chapter 1: Synthetic Strategy and Utility of A³-Coupling Reactions 01

1.1. Classification of amines	01
1.2. Synthetic strategies for propargylamine	01
1.2.1. General approach towards propargylamine synthesis	01
1.2.2 Classical approach towards propargylamine synthesis	02
1.2.3 Traditional approach towards propargylamine synthesis	03
1.2.3.1. A ³ -Coupling	03
1.3. A ³ -Coupling in organic synthesis	04
1.3.1. Secondary propargylamines <i>via</i> A ³ -coupling in organic transformation	05
1.3.2. Tertiary propargylamines <i>via</i> A ³ -coupling in organic transformation	09
1.4. Synthesis of heterocycles <i>via</i> tandem A ³ -coupling reaction	13
1.4.1. Role of functional amines in tandem A ³ -coupling reaction	13
1.4.1.1. Tandem A ³ -coupling with aromatic amines	14
1.4.1.2. Tandem A ³ -coupling with heterocyclic amines	15
1.4.1.3. Tandem A ³ -coupling with <i>ortho</i> -heteroaryl amines	16
1.4.2. Role of functional aldehydes in tandem A ³ -coupling reaction	19
1.4.2.1. Tandem A ³ -coupling with heteroaryl aldehydes	19
1.4.2.2. Tandem A ³ -coupling with <i>ortho</i> -functional arylaldehydes	21
1.4.3. Role of functional alkynes in tandem A ³ -coupling reaction	24
1.5. More than three components in A ³ -coupling reaction	26
1.6. Intramolecular A ³ -coupling reaction	28
1.7. References	29

Chapter 2: Regioselective One-Pot, Three-Component Synthesis of Substituted 2H-Indazoles from 2-Nitroarylaldehyde, Alkyne and Amine Catalyzed by CuBr/Zn(OTf)₂ System	35
2.1. Introduction	35
2.2. Biological importance of 2H-indazoles	35
2.3. Literature methods for the synthesis of 2H-indazoles	36
2.3.1. Synthesis of 2H-indazoles from 2-nitroarylaldehydes	37
2.3.2. Synthesis of 2H-indazoles from 2-azidoarylaldehydes	40
2.3.3. Other approaches for the synthesis of 2 <i>N</i> ,3 <i>C</i> -substituted 2H-indazoles	41
2.4. Results and discussions	43
2.5. Experimental section	49
2.5.1 Instrumentation and characterization	49
2.5.2. General procedure for the synthesis of 3-(arylethynyl)-2H-indazoles (75)	50
2.6. References	51
2.7. Characterization data	54
2.8. Selected spectra	60
2.9. Crystal parameters	62
Chapter 3: Synthesis of Substituted Pyrazole <i>N</i>-Oxides and Pyrazoles from Propargylamines	65
3.1. Introduction	65
3.2. Literature methods for the synthesis of pyrazole and pyrazole <i>N</i> -oxides	66
3.3. Results and discussions	70
3.4. Applications of pyrazole <i>N</i> -oxides	75
3.5. Experimental section	80
3.5.1. Instrumentation and characterization	80
3.5.2. General procedures for the synthesis of propargylamine (38)	80
3.5.2.1. Synthesis of propargylamines (38a-38n)	80
3.5.2.2. Synthesis of propargylamines (38o-38w)	80
3.5.3. General procedure for the synthesis of pyrazole <i>N</i> -oxides (39)	81
3.5.4. Typical procedure for the reduction of pyrazole <i>N</i> -oxide with PCl ₃ (42)	81

3.5.5. Typical procedure for the synthesis of 4-chloropyrazoles (43)	81
3.5.6. Experimental procedure for the reduction of nitro group (44)	82
3.5.7. Experimental procedure for the synthesis of pyrazolo- <i>N</i> -oxide-cinnoline (45)	82
3.5.8. Typical procedure for the formylation of pyrazole (46)	82
3.5.9. Experimental procedure for the synthesis of pyrazolo-quinoline (47)	82
3.5.10. Experimental procedure for the reduction of nitro group (48)	83
3.5.11. Experimental procedure for the synthesis of pyrazolo-cinnoline (49)	83
3.6. References	84
3.7. Characterization data	88
3.8. Selected spectra	112
Chapter 4: Synthesis of Highly Substituted 4-Iodopyrazole <i>N</i>-Oxides and Pyrazoles from Propargylamines	117
4.1. Importance of molecular iodine in organic transformations	117
4.2. Literature methods for the synthesis of iodopyrazoles	117
4.2.1. Direct iodination of pyrazoles	117
4.2.2. Synthesis of iodopyrazoles using Sandmeyer reaction conditions	119
4.2.3. Electrophilic cyclisation towards 4-iodopyrazoles synthesis	120
4.3. Results and discussion	122
4.4. Experimental section	129
4.4.1. Instrumentation and characterization	129
4.4.2. General procedure for the synthesis of propargylamines (34)	129
4.4.3. General procedure for the synthesis of 4-iodopyrazole <i>N</i> -oxides (35)	130
4.4.4. Experimental procedure for the synthesis of compound 37 (Suzuki coupling)	130
4.4.5. Experimental procedure for the synthesis of compound 39 (Heck coupling)	130
4.4.6. Experimental procedure for the synthesis of compound 40 (Sonogashira coupling)	130
4.4.7. Typical procedure for the synthesis of 4-iodopyrazoles (41)	131
4.5. References	132
4.6. Characterization data	134
4.7. Selected spectra	145
4.8. Crystal parameters	148

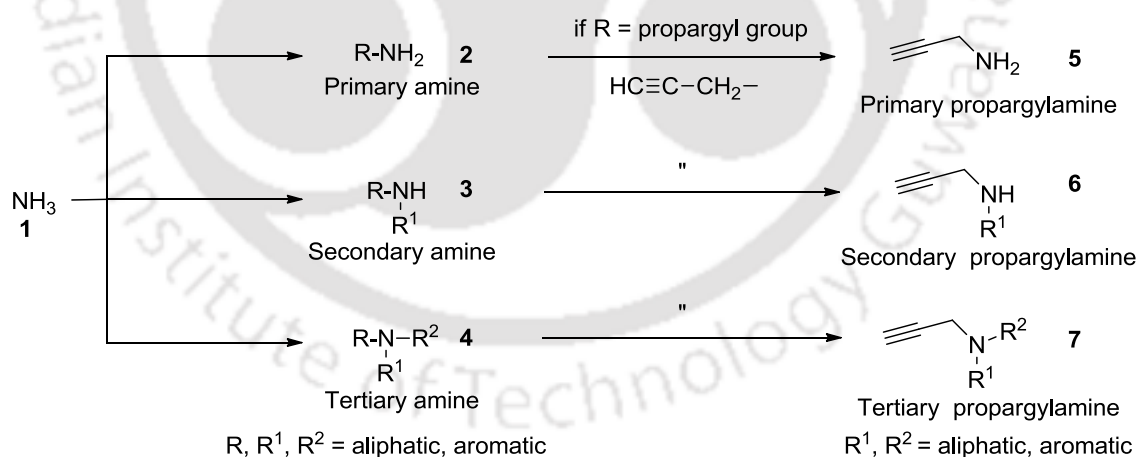
Chapter 5: Intramolecular Pictet-Spengler Reaction of Cyclic Iminium ions: A Novel Access to Benzo[1,4]oxazepine Fused Tetrahydroisoquinoline and Tetrahydro-β-carboline Analogous	151
5.1. Importance of seven membered fused tetrahydroisoquinoline and tetrahydro- β -carboline analogous	151
5.2. Literature methods of Pictet-Spengler reaction	152
5.2.1. Pictet-Spengler reaction via intramolecular <i>N</i> -acyliminium ion intermediates	152
5.2.2. Intramolecular Pictet-Spengler reaction of cyclic iminium ion intermediates	156
5.3. Present work	158
5.4. Experimental section	168
5.4.1. Instrumentation and Characterisation	168
5.4.2. General procedure for the synthesis of propargylamines (74)	168
5.4.3. General procedure for the synthesis of substituted benzo[1,4]oxazepine fused tetrahydroisoquinoline derivatives (75)	169
5.4.4. General procedure for the synthesis of secondary amines (76)	169
5.4.5. General procedure for the synthesis of benzo[1,4]oxazepine fused tetrahydroisoquinoline derivatives (77)	169
5.4.6. General procedure for the synthesis of secondary amines (79)	170
5.4.7. Typical procedure for the synthesis of benzo[1,4]oxazepine fused tetrahydro- β -carboline derivatives (80)	170
5.5. References	171
5.6. Characterization data	173
5.7. Selected spectra	196
5.8. Crystal parameters	199
List of Publications	201

Chapter 1

Synthetic Strategy and Utility of A³-Coupling Reactions

1.1. Classification of amines

Amines are aliphatic and aromatic derivatives of ammonia. Depending on the number of hydrocarbon groups replacing the hydrogen atoms in ammonia, amines can be categorised as primary, secondary and tertiary. One organic group attached to the nitrogen atom in ammonia is termed as primary **2**, whereas, those with two or three organic groups attached are secondary **3** and tertiary amines **4**, respectively. For example, one propargyl group attached to the nitrogen atom in ammonia is termed as propargylamine **5**. Similarly, propargyl group with either one or two of organic groups like aliphatic/aromatic attached are named as secondary **6** and tertiary propargylamines **7** (*Scheme 1.1*). Due to all-encompassing features of propargylamines, till date, numerous building blocks of nitrogen heterocycles as well as bioactive molecules have been developed in synthetic organic chemistry.¹ In this thesis, our research interest mainly emphasizes on synthesis of complex nitrogen heterocycles using propargylamine intermediates.

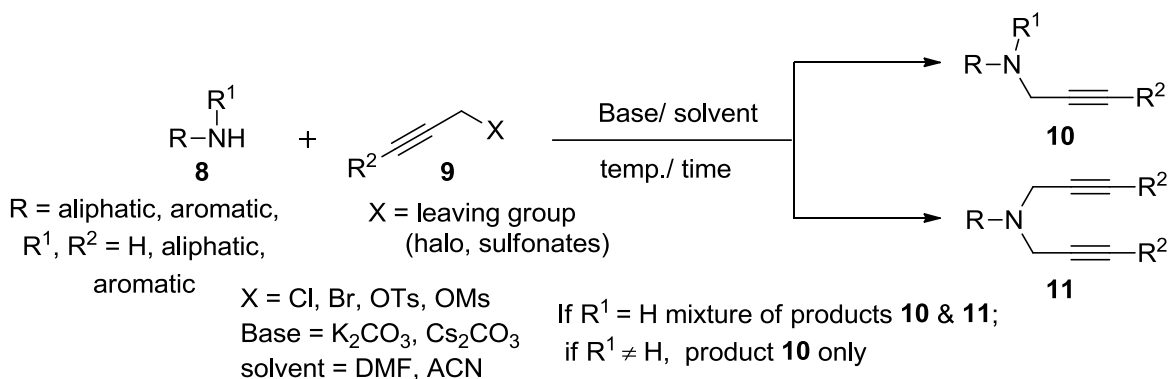


Scheme 1.1. Classification of amines

1.2. Synthetic strategies for propargylamine

1.2.1. General approach towards propargylamine synthesis

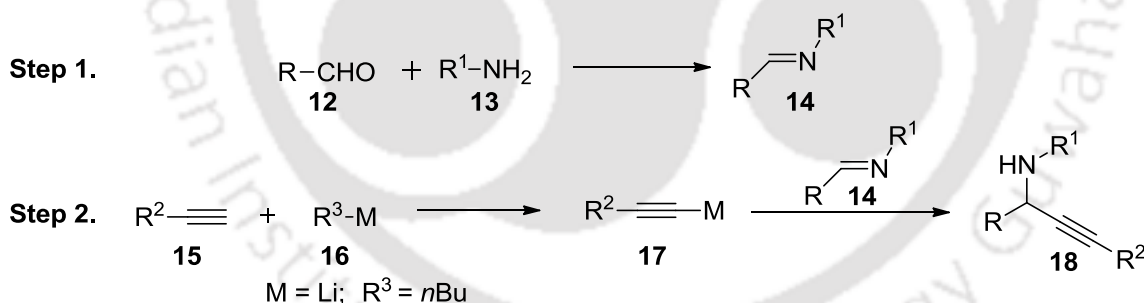
Generally, propargylamines are prepared by simple alkylation of amines **8** with propargyl halide/sulfonates **9** in presence of base (*Scheme 1.2.1.1*).² However, this method has some disadvantages such as, it requires excess amount of amine and formation di alkylated products.



Scheme 1.2.1.1. General approach towards propargylamine synthesis

1.2.2. Classical approach towards propargylamine synthesis

Propargylamines are classically synthesised by the nucleophilic addition of metal alkynylides to imine electrophiles in presence of strong base at low temperatures. The reaction proceeds in two step protocol. Initially, imines **14** are prepared from aldehydes **12** and amines **13**. Further, the imines are involved in nucleophilic addition reaction with the metal alkynylides **17**, which are in situ generated from the deprotonation of acetylenes **15** with strong base, butyllithium **16** to give propargylamines **18** (Scheme 1.2.2.1).³



Scheme 1.2.2.1. Classical approach towards propargylamine synthesis

The classical approach suffers from certain drawbacks such as, it requires stoichiometric amount of highly reactive and moisture sensitive organometallic reagents like butyllithium, harsh reaction conditions and low functional groups tolerance. Due to these limitations, classical method is fairly unattractive for the synthesis of propargylamine derivatives.

To overcome all these complications, in last few years an efficient and atom economic approach has been developed for the synthesis of propargylamines using transition-metal catalysed, one-pot and three-component reaction from commercially available starting materials such as aldehydes, amines and alkynes. This method is commonly named as

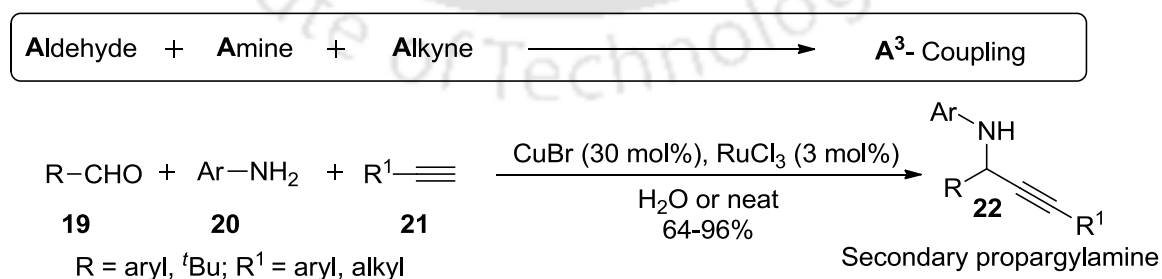
A^3 -coupling and it has become a straight forward approach for the synthesis of propargylamines.

1.2.3. Traditional approach towards propargylamine synthesis

1.2.3.1. A^3 -Coupling

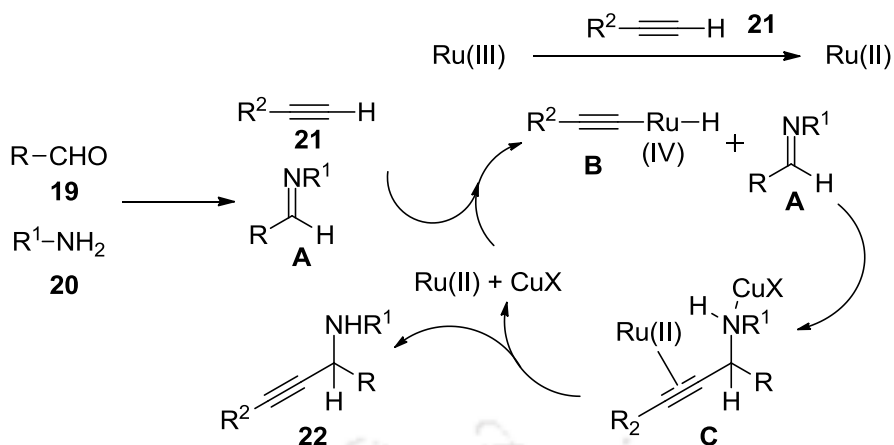
The first example of A^3 -coupling reaction reported by Guermont for the synthesis of propargylic amino ethers *via* copper catalysed Mannich reaction of terminal alkynes, secondary amines and trioxane.⁴ Similarly, a few researchers also followed this method for the synthesis of propargylamines *via* three component coupling reaction of aldehydes, alkynes, and secondary amines. For example, Dax and coworkers established a solid-phase, resin attached three component coupling of aldehyde, alkyne, and secondary amines with 2.0 equivalents of CuCl to afford propargylamines.⁵ In the same way, Dyatkin and Rivero reported a polymer-supported aryl alkynes with various aldehydes and secondary amines in presence of catalytic amount of CuCl.⁶ However, these procedures are not convenient for the synthesis of propargylamine derivatives.

After a number of contributions, in 2002, Li and Wei first time developed an efficient protocol for the synthesis of secondary propargylamines **22**. They used bi-metallic Cu-Ru catalyst and one-pot, three-component reaction from commercially available starting materials such as aldehydes **19**, arylamines **20** and alkynes **21** in water as a solvent or in neat conditions with 64-96% yields (*Scheme 1.2.3.1*).⁷ The term A^3 was introduced by the same (Li) group based on the three characteristic reactants involved in the reaction. Moreover, this method was failed to give desired product, when aliphatic aldehyde having α -hydrogen involved in this reaction.



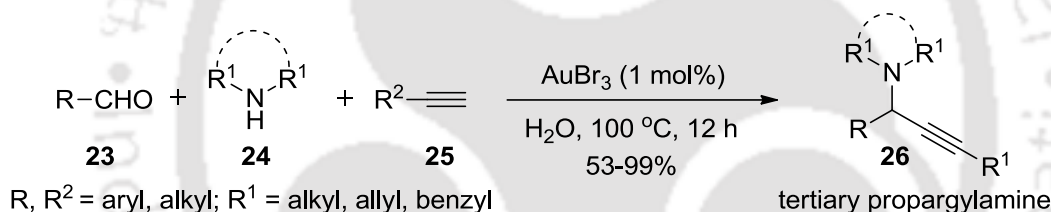
Scheme 1.2.3.1. A^3 -Coupling

The tentative mechanism of the reaction shows that $C-H$ activation of terminal alkyne **21** by the metal catalyst afforded metal acetylide **B**. The in situ generated metal acetylide **B**, further involves in nucleophilic addition to imine **A**, which was also in situ generated from aldehyde **19** and amine **20** to give propargylamine **22** (*Scheme 1.2.3.2*).



Scheme 1.2.3.2. Proposed mechanism of A³-coupling reaction

In a similar way, they extended this methodology for the synthesis of tertiary propargylamines **26**. A mild and efficient gold catalyzed A³-coupling reaction of secondary amines **24**, aldehydes **23** and terminal alkynes **25** gave tertiary propargylamines **26** in good to excellent yields (Scheme 1.2.3.3).⁸



Scheme 1.2.3.3. A³-Coupling towards tertiary propargylamine

Interestingly A³-coupling reaction has been explored with variety of metal catalysts, especially coinage metals such as Cu,⁹ Ag¹⁰ and Au¹¹ as well as Zn,¹² Ni,¹³ Fe,¹⁴ In,¹⁵ Ir,¹⁶ Co,¹⁷ Hg¹⁸ and Cd¹⁹. Out of these, copper catalysts are highly effective for the synthesis of propargylamines.⁹ Similarly, asymmetric version of this reaction is referred as AA³-coupling.²⁰ If, one of the A³-coupling partners *i.e.* aldehyde is replaced by ketone, named as KA²-coupling reaction.²¹

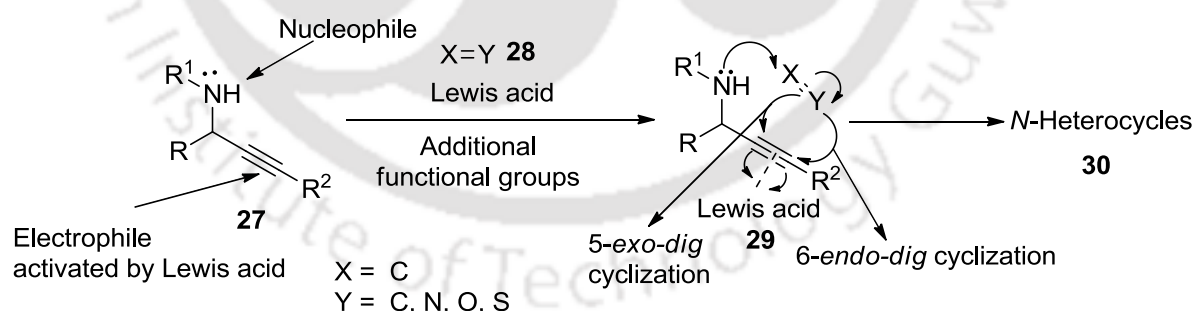
1.3. A³-Coupling in organic synthesis

Nitrogen heterocycles are important class of structural scaffolds in organic chemistry. There are many well-known nitrogen heterocyclic compounds and this number is still growing rapidly due to their invaluable utilities. Nitrogen heterocycles are abundant in natural products, such as alkaloids as well as in synthetic products, and find wide applications in drug discovery.²² Because of this, the emerging new methods for the synthesis of nitrogen heterocyclic compounds using readily accessible starting materials with less number of steps,

broad range of substrate scope, high selectivity, eco-friendly and easy purification procedures are still in great demand. To achieve such goals, recently, A^3 -coupling reaction is gaining considerable interest for the construction of various building blocks of nitrogen heterocycles^{9b} as well as biologically active compounds, pharmaceuticals and natural products.²³ Moreover, due to the flexibility of propargylamines, and its involvement in different tandem cyclization reactions A^3 -coupling has become a powerful tool to build structurally diverse range of *N*-heterocyclic compound libraries.²⁴ Similarly, they also act as a key intermediates for the construction of other heterocycles²⁵ as well as carbocyclic compounds.²⁶ Furthermore, complexity of propargylamine bearing additional functional groups could also be achieved.²⁷

1.3.1. Secondary propargylamines via A^3 -coupling in organic transformation

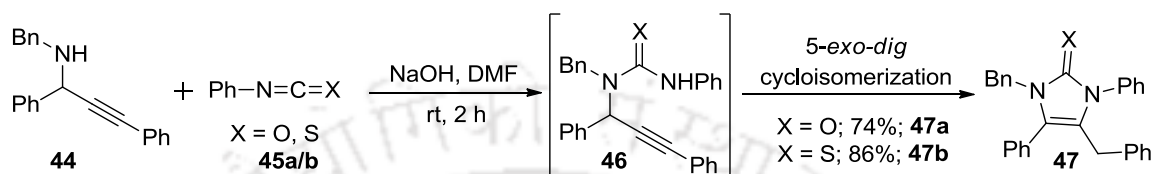
Transition metal catalyzed A^3 -coupling reaction of aldehyde alkyne and primary amine gives secondary propargylamine. Due to the free “NH” functionality, the secondary propargylamine **27** can participate in Lewis acid promoted nucleophilic addition reaction with additional functionalities to form a new C-N bond as shown in *Scheme 1.3.3.1*. Simultaneously, other end of the propargylamine i.e. alkyne also get activated by the Lewis acid followed by intramolecular electrophilic (5-*exo-dig*/6-*endo-dig*) cyclization to produce a variety of *N*-heterocycles (*Scheme 1.3.1.1*).



Scheme 1.3.1.1.

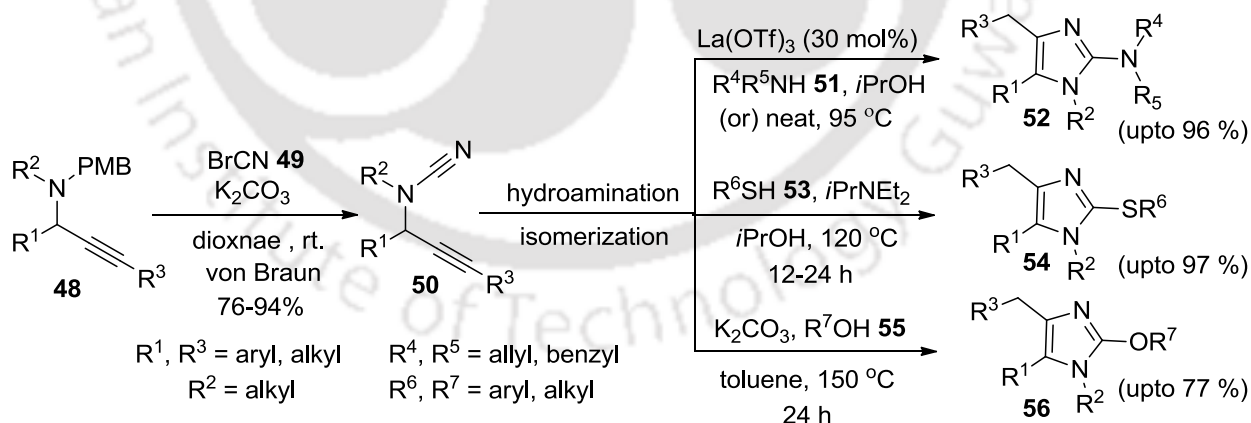
Secondary propargylamines are key intermediates for the synthesis of 2-aminoimidazoles and its alkaloids. Van der Eycken and coworkers reported a novel and efficient synthesis of 2-aminoimidazoles **35** in good yields. The synthesis started from $\text{AgNO}_3/\text{Et}_3\text{N}$ promoted intramolecular electrophilic cyclization of in situ generated propargyl guanidine intermediates **33** to give *N*-protected 2-iminoimidazolines **34**. The propargyl guanidine intermediates **33** were obtained from secondary propargylamines **31** and thiourea **32**. Further, Boc deprotection of compound **34** followed by isomerisation resulted in the 2-aminoimidazole derivatives **35**.

Dethe and coworkers reported a novel, one-pot and highly regioselective synthesis of imidazole-2-one/imidazole-2-thiones (**47a/b**) in good yields starting from secondary propargylamine **44** and phenyl (thio)isocyanate (**45a/b**). The reaction mechanism shows that, strong base promoted 5-*exo-dig* cycloisomerization of in situ generated propargylic (thio)urea **46**, which was obtained from propargylamine **44** and phenyl (thio)isocyanate (**45a/b**) (Scheme 1.3.1.5).³⁰



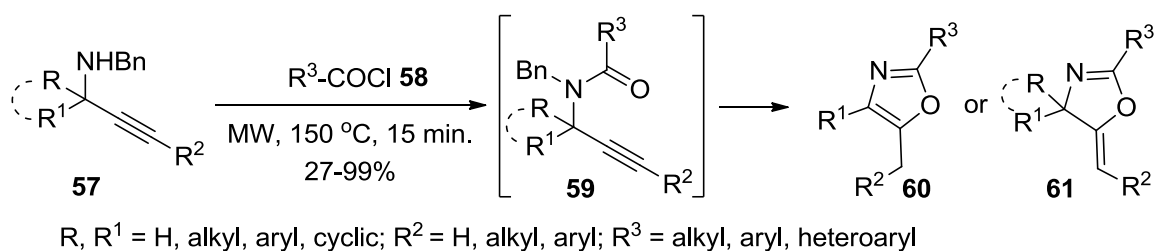
Scheme 1.3.1.5.

Looper and coworkers described a facile synthesis of 2-amino-imidazole derivatives **52** in three step process. Initially, propargyl cyanamides **50** were synthesized via von Braun cyanation of tertiary propargylamines **48** with cyanogen bromide **49** in the presence of K₂CO₃. The Lanthanum(III)-promoted intramolecular hydroamination-isomerization of propargyl cyanamides **50** with secondary amines **51** resulted in 2-aminoimidazoles **52** in good yields.^{23f} Similarly, 2-thio- **54** and 2-oxoimidazoles **56** were also obtained, when thiols **53** and alcohols **55** were used as nucleophiles under basic conditions (Scheme 1.3.1.6).³¹



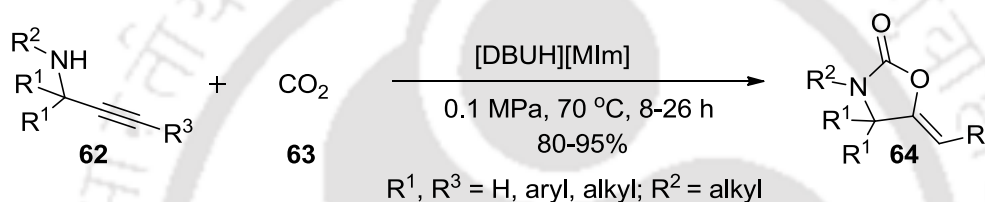
Scheme 1.3.1.6.

Strand and coworkers reported a short route for synthesis of di- and tri-substituted oxazoles **60** and dihydrooxazole **61** derived from *N*-benzyl propargylamine and acid chlorides under microwave assisted solvent free reaction conditions. Initially, propargylamines **57** reacted with acid chlorides **58** to furnish *N*-propargyl amide intermediates **59**, which further underwent 5-*exo-dig* cyclization followed by cleavage of benzyl group to produce the target products **60/61** (Scheme 1.3.1.7).³²



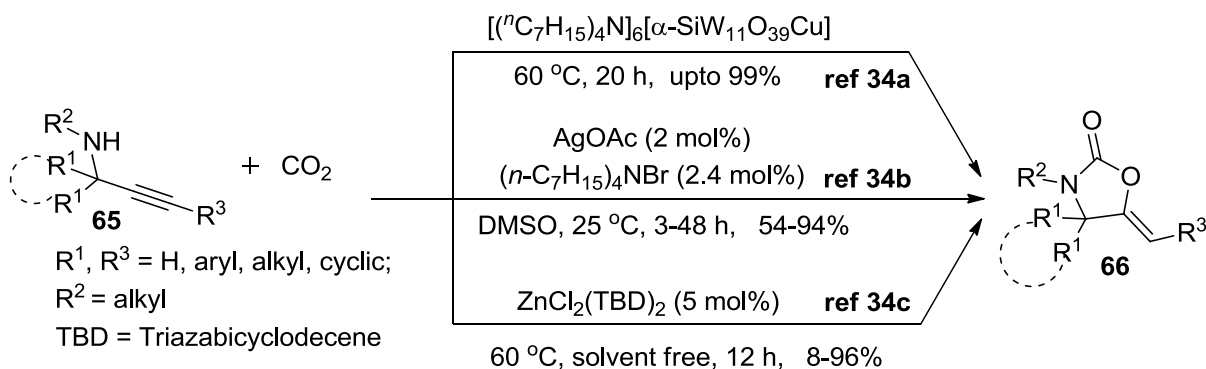
Scheme 1.3.1.7.

Recently, Han and coworkers employed a green protocol for the synthesis of oxazolidinones **64** from propargylamines **62** and atmospheric CO_2 **63** using recyclable protic ionic liquids such as 1,8-diazabicyclo-[5.4.0]-7-undecenium 2-methylimidazolid [DBUH][MIm] (Scheme 1.3.1.8).³³



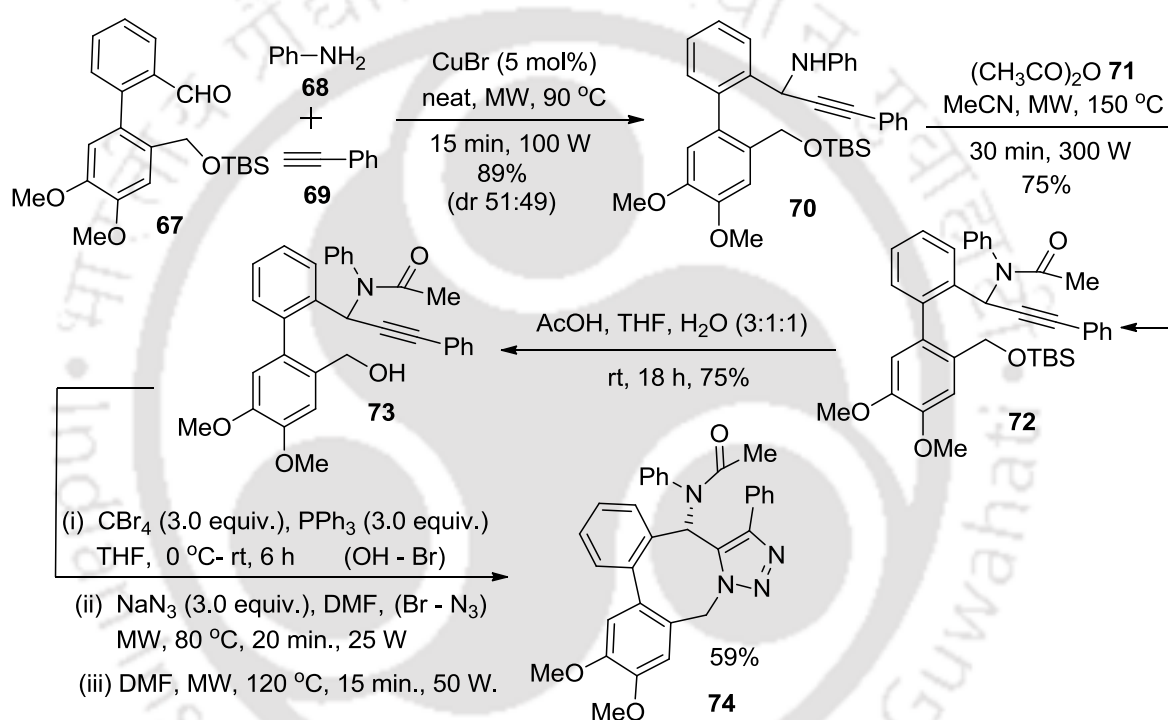
Scheme 1.3.1.8.

Following the same approach, in 2016, He and coworkers^{34a} reported an efficient and cost-effective synthesis of oxazolidinones **66** derived by the chemical fixation of CO_2 with propargylic amines **65** under halogen-free and bifunctional copper(II) substituted polyoxometalate-based ionic liquid $[(n\text{-C}_7\text{H}_{15})_4\text{N}][\alpha\text{-SiW}_{11}\text{O}_{39}\text{Cu}]$ medium. Later on, the similar results have been attained by the same group using catalytic amount of AgOAc and $(n\text{-C}_7\text{H}_{15})_4\text{NBr}$ at ambient temperature.^{34b} In addition, they also demonstrated an elegant protocol for the synthesis of oxazolidinones **66** using the similar process with $\text{ZnCl}_2(\text{TBD})_2$ under solvent free reaction conditions (Scheme 1.3.1.9).^{34c}



Scheme 1.3.1.9.

Another interesting application of A^3 -coupling reaction has been reported by Van der Eycken and coworkers utilized a microwave assisted diastereoselective synthesis of aza-analogues of (-)-Steganacins in a sequence of reactions. The diastereoselective A^3 -coupling reaction of aldehyde **67**, aniline **68** and phenylacetylene **69** in the presence of copper(I) bromide gave propargylamine **70** in 89% yield (dr = 51:49). The compound **70** was *N*-acylated with acetic anhydride **71** followed by desilylation in acetic acid to afford the compound **73** via **72**. This on subsequent involvement in Appel reaction, azidation and intramolecular click reaction accomplished the (-)-Steganacin derivative **74** (Scheme 1.3.1.10).³⁵

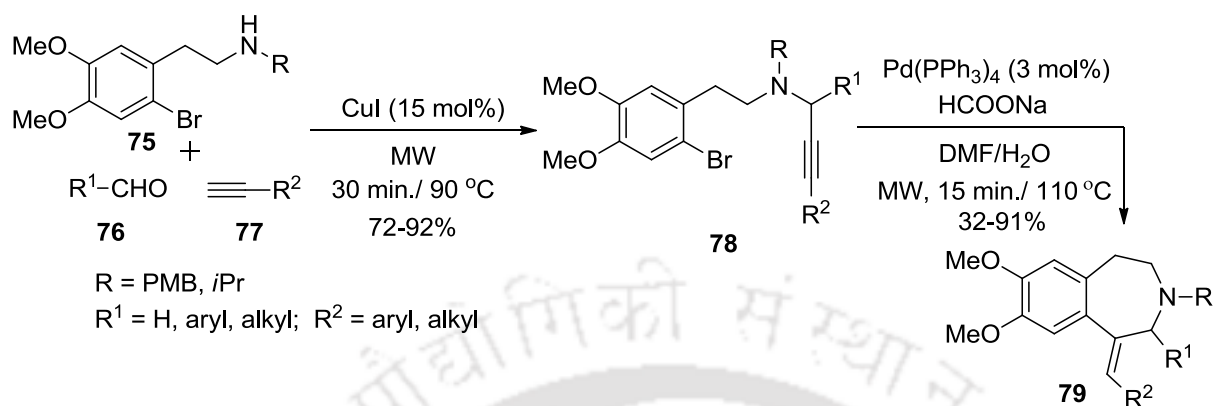


Scheme 1.3.1.10.

1.3.2. Tertiary propargylamines via A^3 -coupling in organic transformation

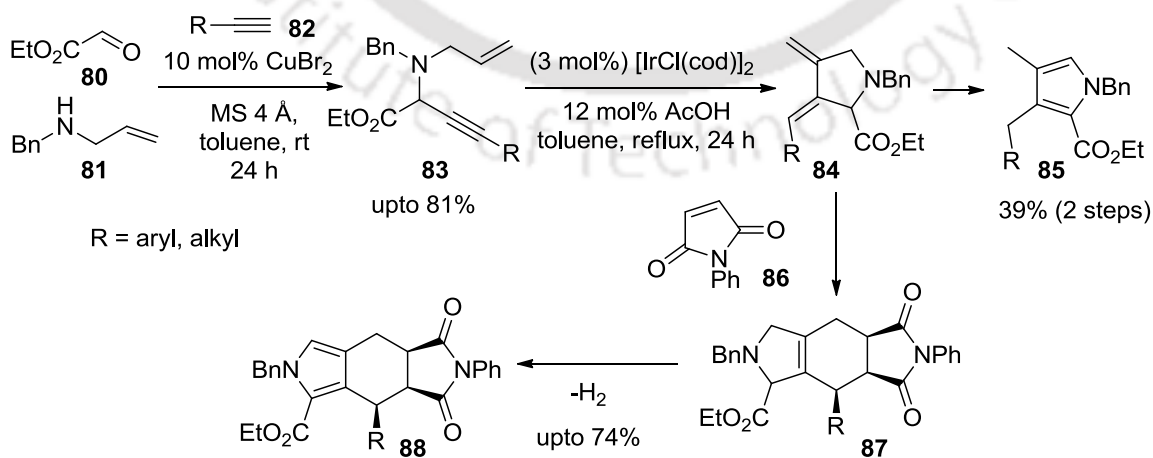
Secondary amines are involved in A^3 -coupling to give tertiary propargylamines. Moreover, complex propargylamines, bearing additional functional groups are highly useful to achieve new class of complex nitrogen heterocycles. Van der Eycken and coworkers described an efficient microwave assisted two-step protocol for the synthesis of 3-benzazepine frame-works **79** in good yields. The reaction sequence initiated with Cu(I)-catalyzed A^3 -coupling reaction of amines **75**, aldehydes **76** and alkynes **77** to give tertiary propargylamines **78** in 72-92% yields. The corresponding propargylamines **78** are involved in palladium-catalyzed

intramolecular hydroarylation reaction with acetylene moiety to give 3-benzazepine derivatives **79** (Scheme 1.3.2.1).³⁶



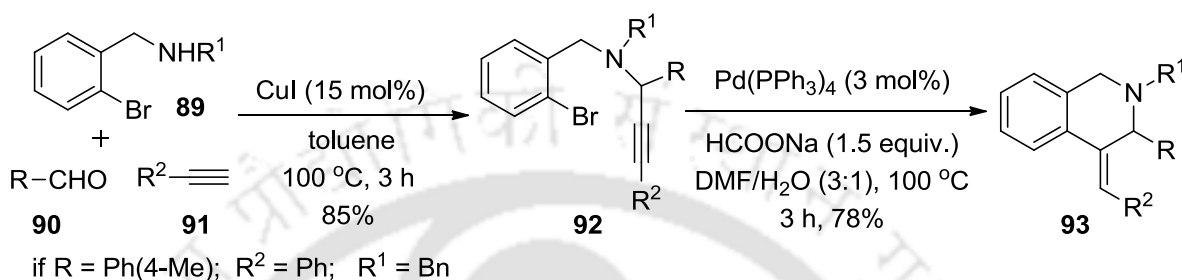
Scheme 1.3.2.1.

Yamamoto and coworkers demonstrated a facile synthesis of polycyclic pyrrole-2-carboxylates via A^3 -coupling intermediates. The synthesis started with copper catalyzed A^3 -coupling of glyoxlate **80**, benzylallylamine **81** and alkynes **82** to produce substituted propargylamines with 1,6-enyne skeleton **83**. This is further underwent cycloisomerization/dehydrogenative reaction with iridium catalyst to furnish polysubstituted pyrrole-2-carboxylate **85** via exocyclic 1,3-dienes **84**. In a similar way, the exocyclic 1,3-dienes system **84** was reacted with *N*-phenyl maleimide **86** in Diels-Alder reaction/dehydrogenative aromatization sequence to afford a polycyclic pyrroles **88** via **87** in good yields (Scheme 1.3.2.2).^{27a}



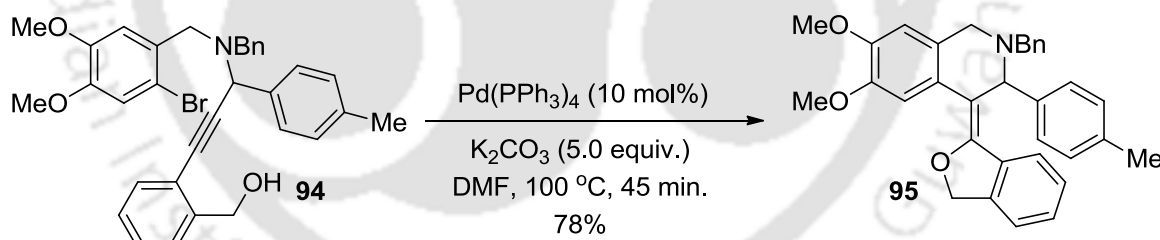
Scheme 1.3.2.2.

Perumal and coworkers described a concise protocol for the synthesis of functionalised tetrahydroisoquinolines **93** from regio- and stereoselective palladium-catalyzed 6-*exo-dig* carbocyclization of 2-bromo-*N*-propargylbenzylamine **92** in 78% yield. 2-Bromo-*N*-propargylbenzylamine was synthesized *via* one-pot, three component reaction of 2-bromobenzylamine **89**, aldehyde **90** and alkyne **91** in presence of copper(I) catalyst (Scheme 1.3.2.3).³⁷



Scheme 1.3.2.3.

The same group was effectively transformed functionalized propargylamine **94** into (*E*)-4-(isobenzofuran-1(3*H*)-ylidene)-1,2,3,4-tetrahydroisoquinoline **95** in 78% yield using palladium catalysed reaction of highly regio- and stereoselective 6-*exo-dig* cyclization and 5-*exo-dig* cyclization process (Scheme 1.3.2.4).^{27b}

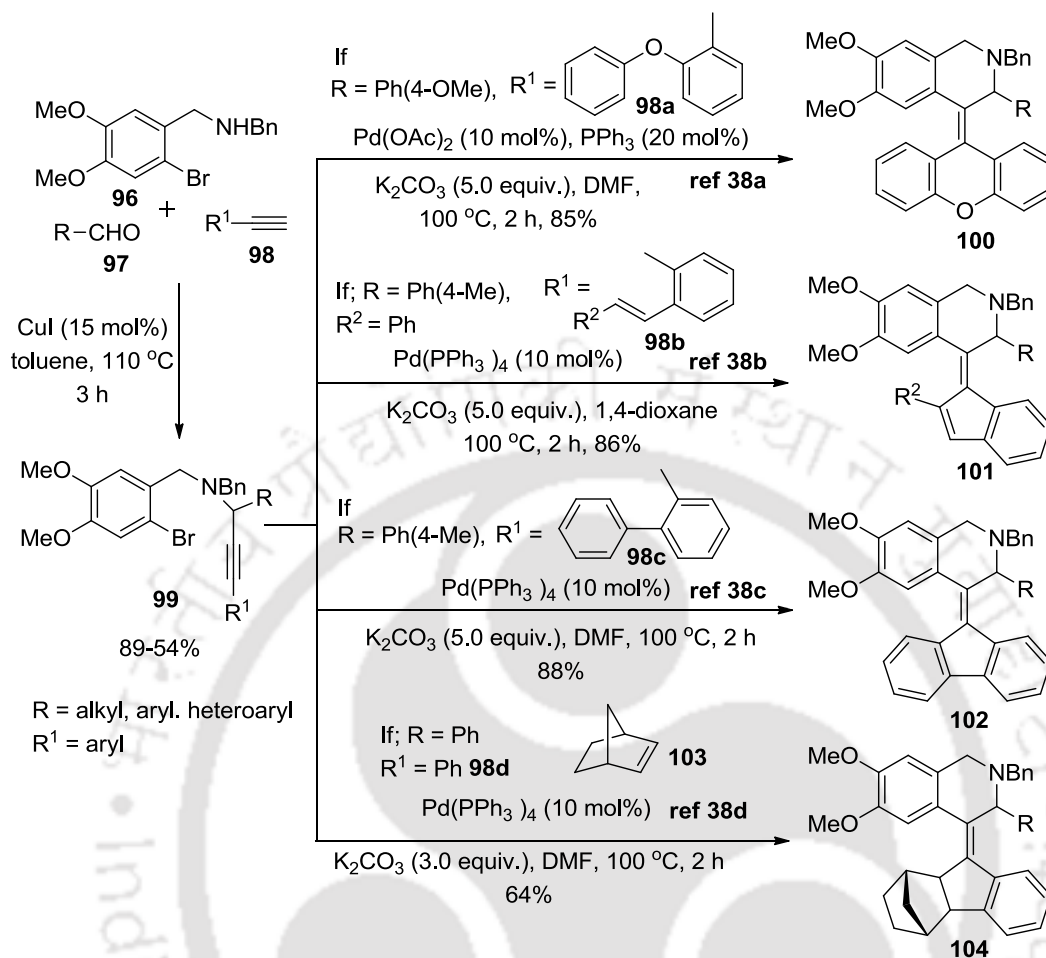


Scheme 1.3.2.4.

In 2013, they synthesized tetrasubstituted olefin based xanthene derivative **100** in 85% yield *via* intramolecular carbopalladation followed by *C-H* activation of 2-bromobenzyl-*N*-propargylamine **99a** using palladium(II) catalyst in presence of K₂CO₃ at 100 °C (Scheme 1.3.2.5).^{38a} Similarly, by changing the alkyne in A³-coupling such as (*E*)-1-ethynyl-2-styrylbenzene **98b**, tertasubstituted olefinic compound **101** was obtained in 86% yield.^{38b} In the same way biphenyl acetylene **98c** gave compound **102** in 88% yield.^{38c} Furthermore, they also demonstrated the synthesis of helical olefin fused 1,2,3,4-tetrahydroisoquinoline **104** derived from 2-bromobenzyl-*N*-propargylamine **99d** and norbornene **103** *via* double carbopalladation followed by *C-H* activation process.^{38d} For all these cases, propargylamines

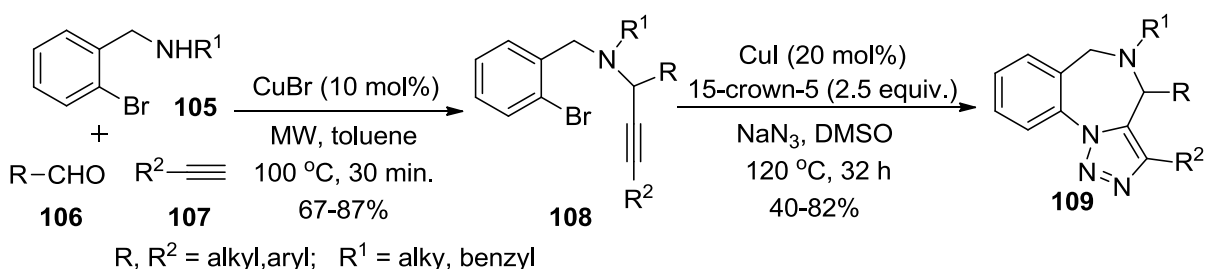
99 were synthesised by known A³-coupling reaction of secondary amines, aldehydes and

alkynes using catalytic amount of copper(I) iodide in toluene at 110 °C (Scheme 1.3.2.5).³⁸



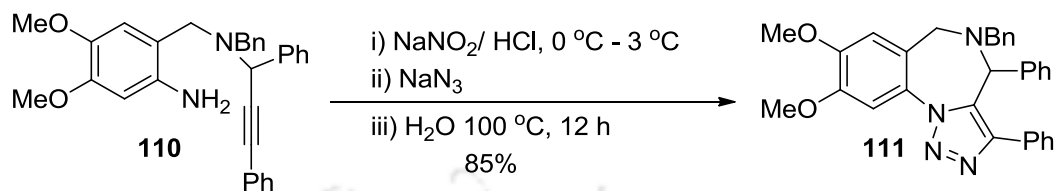
Scheme 1.3.2.5.

Van der Eycken and coworkers described an exceptional one-pot copper(I)-catalyzed azidation-cyclization of *ortho*-bromobenzylpropargylamine **108** to accomplish the synthesis of [1,2,3]triazolo[1,5-*a*][1,4]benzodiazepines **109** in good yields (Scheme 1.3.2.6).³⁹ The propargylamines **108** were prepared by using A³-coupling reaction of secondary amines **105**, aldehydes **106** and alkynes **107** with catalytic amount of copper(I) bromide under microwave conditions.



Scheme 1.3.2.6.

Perumal and coworkers developed a general and convenient highly diversified one-pot procedure for the synthesis of [1,2,3]triazolo[1,5-*a*][1,4]benzodiazepine derivative **111** in 85% yields. The sequence started from diazotization of primary amine **110**, azidation followed by intramolecular click reaction to afford the fused triazoles **111** (Scheme 1.3.2.7).⁴⁰



Scheme 1.3.2.7.

1.4. Synthesis of heterocycles via tandem A³-coupling reaction

A³-coupling reaction has gained the prominence due to the excellent functional group tolerance and has become a versatile tool for the synthesis of structurally diverse heterocyclic compounds *via* tandem cyclization. In this tandem process, in situ generated propargylamines having secondary functional groups, which involve in tandem cyclization provide substituted heterocycles with the formation of at least three new chemical bonds. Moreover, differently modified *ortho*-functionality located in any one of the precursors of A³-coupling reaction is gaining attention to produce differently substituted heterocyclic core skeletons in organic synthesis as outlined below.

1.4.1. Functional amines play a crucial role in tandem A³-coupling reaction

1.4.2. Functional aldehydes play a crucial role in tandem A³-coupling reaction

1.4.3. Functional alkynes play a crucial role in tandem A³-coupling reaction

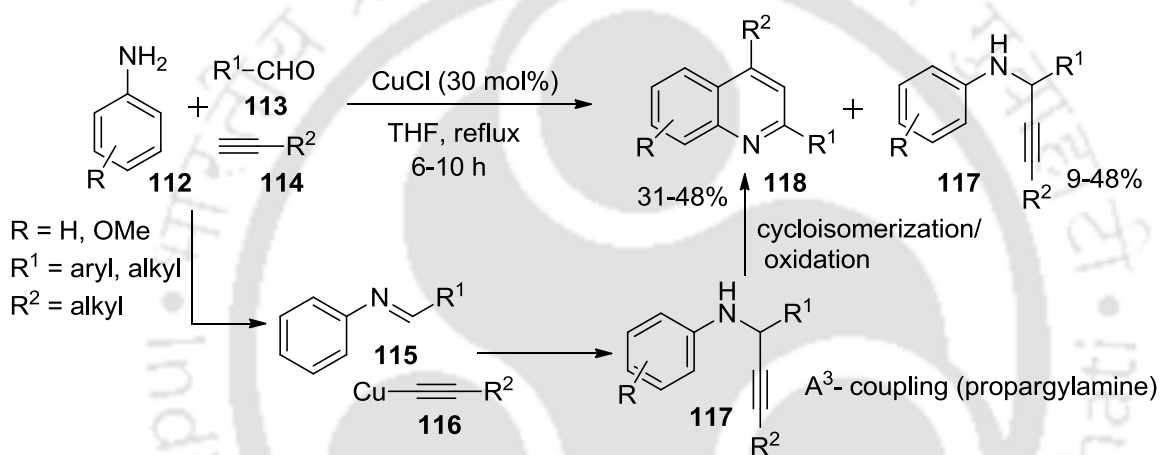
1.4.4. More than three components in tandem A³-coupling reaction

1.4.1. Role of functional amines in tandem A³-coupling reaction

Amines are one of the starting precursors in A³-coupling reaction. Due to the most versatile structural variability and flexibility of amines, it can easily participate in A³-coupling to produce a variety of propargylamines. Moreover, different functional groups having amines are involved in tandem A³-coupling reaction to produce different kind of heterocyclic compounds.

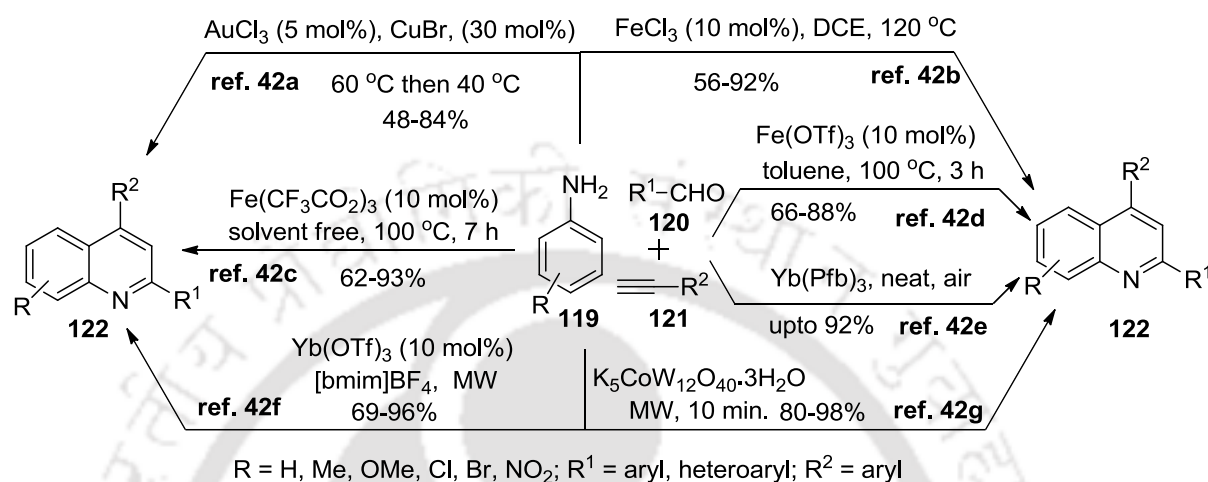
1.4.1.1. Tandem A³-coupling with aromatic amines

Iqbal and coworkers⁴¹ reported a general and straight forward approach for the synthesis of functionalised quinolines **118** from arylamines **112**, aldehydes **113** and alkynes **114** in presence of copper (I) chloride catalyst with satisfactory yields. However, some substrates yielded only *N*-arylpropargylamines **117** as side products (Scheme 1.4.1.1.1). The reaction mechanism exhibit, nucleophilic addition of in situ generated copper-acetylide **116** to imine **115**, which was also obtained in situ from arylamine **112** and aldehyde **113** giving *N*-aryl propargylamine **117**. Finally, propargylamine **117** underwent intramolecular cycloisomerization/oxidation to give the desired products **118** (Scheme 1.4.1.1.1).



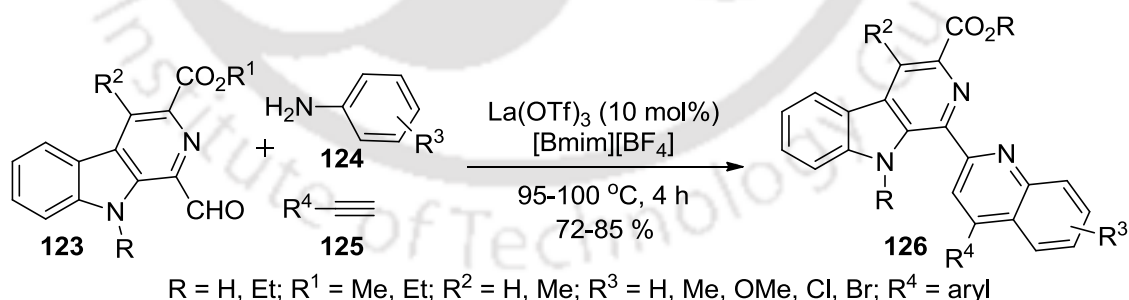
Several researchers have also been reported for the synthesis of functionalized quinolones **122** using tandem A³-coupling reaction with variety of aromatic amines **119** as well as aldehydes **120** and alkynes **121** in presence of different catalysts. Wang and group reported 2,4-disubstituted quinoline derivatives **122** via an effective one-pot AuCl₃ and CuBr bis-catalyzed multicomponent reaction (A³-coupling) in good yields.^{42a} Similarly, Wang and coworkers developed an economical approach for the synthesis of functionalised quinolines **122** using catalytic amount of FeCl₃ in 1,2-dichloroethane as solvent at 120 °C with good to excellent yields.^{42b} In the same way, other iron catalysts such as Fe(CF₃CO₂)₃^{42c} and Fe(OTf)₃^{42d} have also been employed for the synthesis of quinoline derivatives **122**. Further, Wang and group^{42e} reported the same protocol switching to a recoverable catalyst, Yb(Pfb)₃ under neat conditions. On the other hand, microwave assisted A³-coupling reactions is also established for the synthesis of substituted quinolines with wide range of applications in shorter reaction time and high yields. For example, Kumar^{42f} *et al.* described microwave assisted Yb(OTf)₃ catalyzed ionic liquids mediated multicomponent reaction of anilines **119**, aldehydes **120** and alkynes

121 to form substituted quinolines in good yields with broad scope of applications. Mohammadpoor-Baltork and coworkers^{42g} also employed the same multicomponent reaction for the synthesis of quinolines **122** in presence of recyclable potassium dodecatungstocobaltate trihydrate ($K_5CoW_{12}O_{40} \cdot 3H_2O$) under solvent free microwave conditions (*Scheme 1.4.1.1.2*).



Scheme 1.4.1.1.2.

Nagarajan and coworkers reported a simple and efficient synthesis of lavendamycin analogues **126** in good yields via $La(OTf)_3$ catalyzed A^3 -coupling reaction of carboline aldehydes **123**, anilines **124**, and phenylacetylenes **125** in presence of environmentally friendly ionic liquids $[Bmim][BF_4]$ at 100 °C (*Scheme 1.4.1.1.3*).⁴³



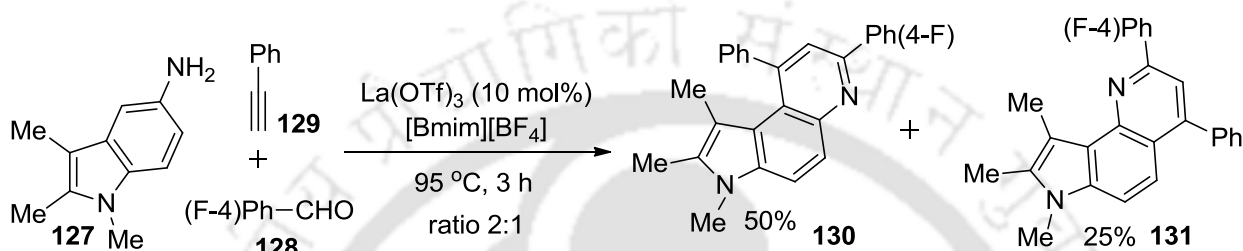
Scheme 1.4.1.1.3.

1.4.1.2. Tandem A^3 -coupling with heterocyclic amines

Synthesis of new class of heterocycles and their derivatives is always on forefront of attention in synthetic organic chemistry because of their immense use in introducing new bioactive agents in medicinal chemistry. Recently, A^3 -coupling reaction with different heterocyclic amines has been employed to synthesize such privileged architectures. Particularly,

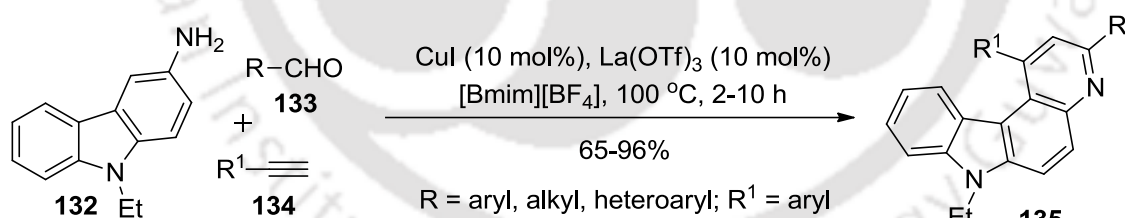
heteroarylamines, having *ortho*-heteroatom play a crucial role to construct building blocks of fused nitrogen heterocycles.

Nagarajan and coworkers reported the simple modification of amine in A^3 -coupling reaction that led to formation of a mixture of compounds such as pyrrolo[3,2-*f*]- and pyrrolo[2,3-*h*]quinolone (**130** & **131**) in 50% and 25% yield, respectively. The tandem A^3 -coupling reaction of 5-aminoindole **127**, benzaldehyde **128** and phenylacetylene **129** was carried out in ionic liquid catalysed by $\text{La}(\text{OTf})_3$ (Scheme 1.4.1.2.1).⁴⁴



Scheme 1.4.1.2.1.

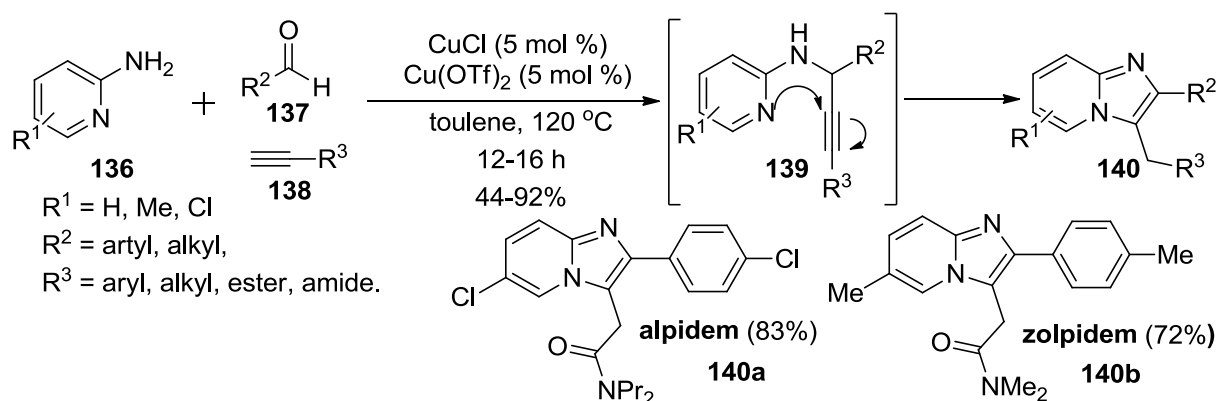
In continuation, Nagarajan and group reported an efficient synthesis of isoellipticine derivatives **135** by $\text{CuI}/\text{La}(\text{OTf})_3$ promoted multicomponent reaction of aminocarbazole **132**, aldehydes **133**, and alkynes **134** in ionic liquid $[\text{Bmim}][\text{BF}_4]$ at 100 °C (Scheme 1.4.1.2.2).⁴⁵



Scheme 1.4.1.2.2.

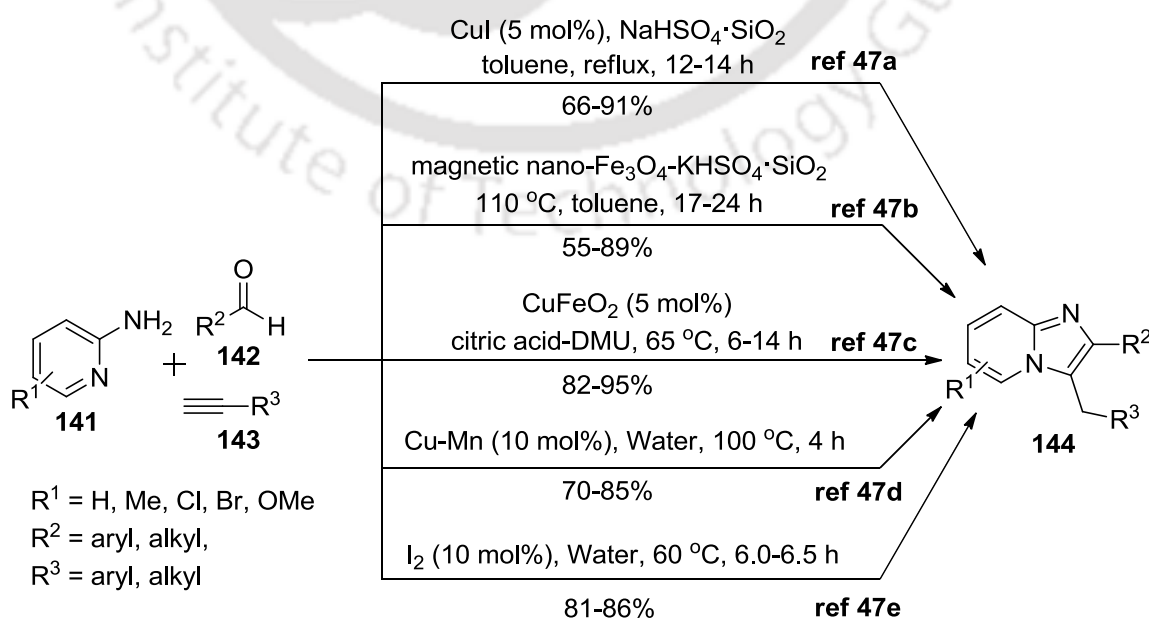
1.4.1.3. Tandem A^3 -coupling with *ortho*-heteroaryl amines

Gevorgyan and coworkers employed a versatile bis-copper-catalysed one-pot three-component reaction of 2-aminopyridines **136**, aldehydes **137** and alkynes **138**, which resulted in imidazopyridine in good yields. The reaction proceeds *via* 5-*exo-dig*-cycloisomerization of in-situ generated *N*-heteroaryl propargylamine to give imidazopyridine derivatives in moderate to good yields (Scheme 1.4.1.3.1).⁴⁶ In addition, using this protocol they successfully achieved pharmacologically important molecules such as alpidem **140a** and zolpidem **140b** in 83% and 72% yield, respectively.



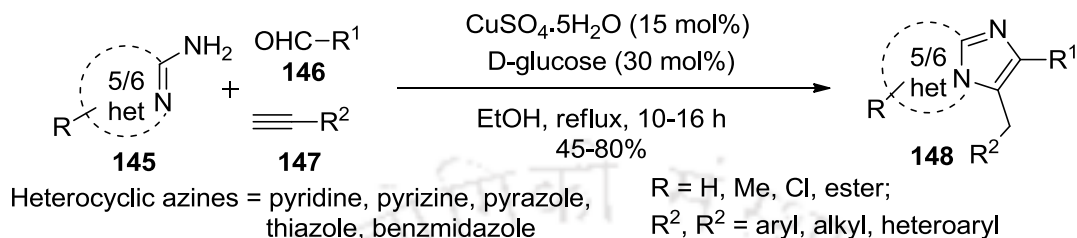
Scheme 1.4.1.3.1.

Ghosh and group^{47a} described a direct approach towards the synthesis of imidazo[1,2-*a*]pyridines **144** using 2-aminopyridines **141**, aldehydes **142** and alkynes **143** with CuI-NaHSO₄·SiO₂ in toluene at refluxed temperature. Later on, Singh and coworkers^{47b} repeated the same approach in presence of catalytic amount of recyclable magnetic Fe₃O₄-KHSO₄·SiO₂ nanoparticles. Similar results have also been achieved by Zhang *et al.* using recyclable CuFeO nanoparticles with citric acid-dimethylurea melt as a green solvent.^{47c} Furthermore, Cu-Mn spinel oxide catalyzed one-pot three component synthesis of imidazo[1,2-*a*]pyridines **144** in aqueous medium was demonstrated by Vishwakarma *et al.* in 2013.^{47d} Finally, Siddiqui and coworkers reported an economical approach for the synthesis of imidazo[1,2-*a*]pyridines **144** from a three component reaction of amines **141**, aldehydes **142** and alkynes **143** with catalytic system of iodine in water with good yields (Scheme 1.4.1.3.2).^{47e}



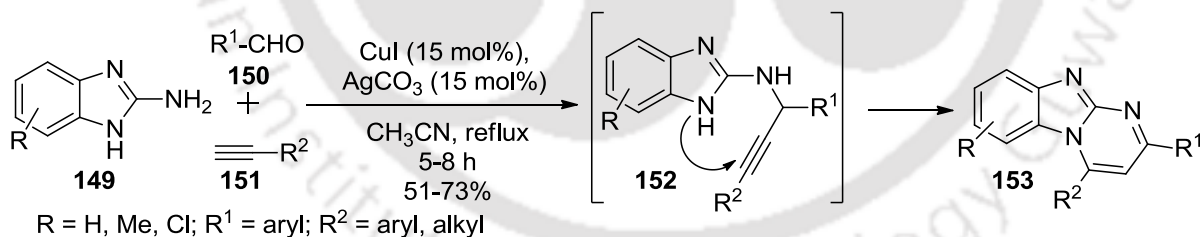
Scheme 1.4.1.3.2.

Guchhait and coworkers described a simple and environmentally benign cascade approach for the synthesis of *N*-fused imidazoles **148** in good yields. The cascade reaction was derived from various heterocyclic azines **145**, aldehydes **146** and alkynes **147** with $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and glucose, in ethanol at reflux conditions (Scheme 1.4.1.3.3).⁴⁸

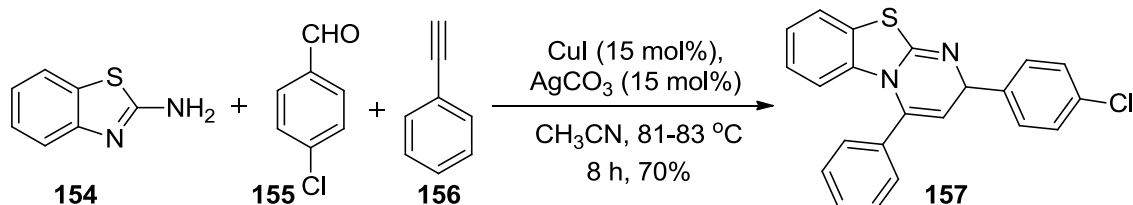


Scheme 1.4.1.3.3.

Kumar and coworkers reported an efficient and one-pot, three component reaction for the synthesis of functionalised imidazo[1,2-*a*]pyrimidine scaffolds **153** in good yields. The cascade reaction participated *via* transition metal (Cu/Ag) catalyzed regioselective 6-*endo-dig* cyclization of propargylamine intermediate **152**, which was in situ generated from 2-aminobenzimidazole **149**, aldehyde **150** and alkyne **151** under tandem A^3 -coupling process (Scheme 1.4.1.3.4).⁴⁹ Additionally, this strategy was applied to synthesis of thiazolopyrimidine **157** in 70% yield using benzo[*d*]thiazol-2-amine **154** (Scheme 1.4.1.3.5).⁴⁹



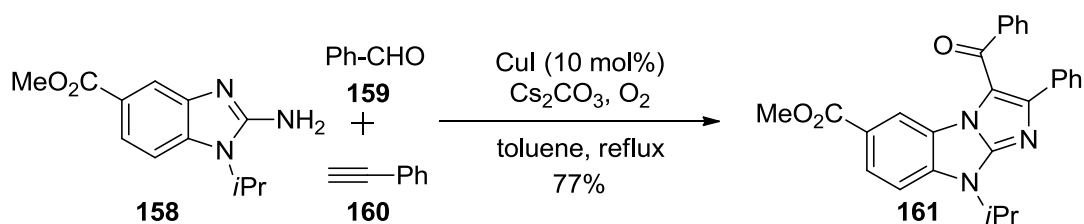
Scheme 1.4.2.3.4.



Scheme 1.4.2.3.5.

Sun and group described a novel aerobic oxidative 5-*exo-dig* cyclization-ketonization of cascade approach for the synthesis benzoimidazo[1,2-*a*]imidazolone **161** *via* copper(I) iodide

with base mediated three component reaction of *N*-alkyl-2-aminobenzimidazole **158**, benzaldehyde **159** and phenylacetylene **160** (Scheme 1.4.1.3.6).⁵⁰



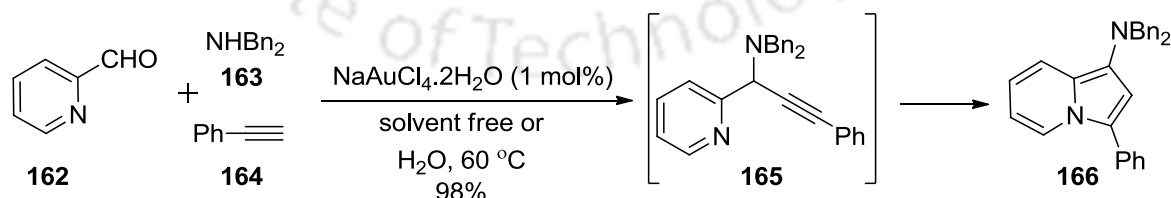
Scheme 1.4.2.3.6.

1.4.2. Role of functional aldehydes in tandem A³-coupling reaction

The second partner of the A³-coupling reaction *i.e.* high electrophilic nature of aldehydes plays a predominant role in A³-coupling reaction. In addition, tandem A³-coupling reaction with functional aldehydes is often employed to design various substituted heterocycles as well carbocyclic compounds.

1.4.2.1. Tandem A³-coupling with heteroaryl aldehydes

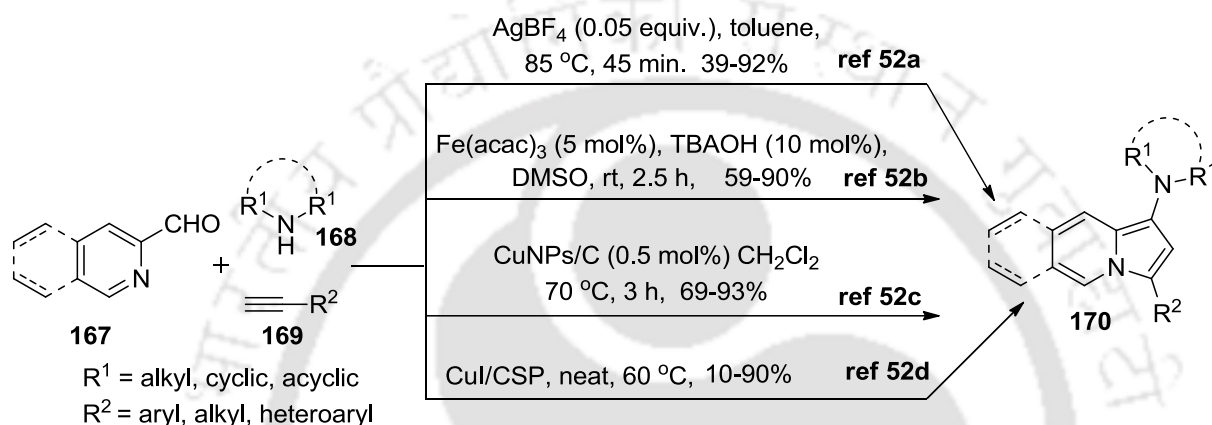
Liu and coworkers developed an atom economic approach for the synthesis of substituted amino indazoline **166** from the three component reaction of pyridin-2-aldehyde **162**, secondary amine **163** and terminal alkyne **164** in presence of 1 mol% of gold(III) catalyst. The reaction mechanism shows that, in situ generated propargylamine, from three components (A³-coupling), followed 5-*endo-dig*-cycloisomerization, to produce the final product **166** (Scheme 1.4.2.1.1).⁵¹



Scheme 1.4.2.1.1.

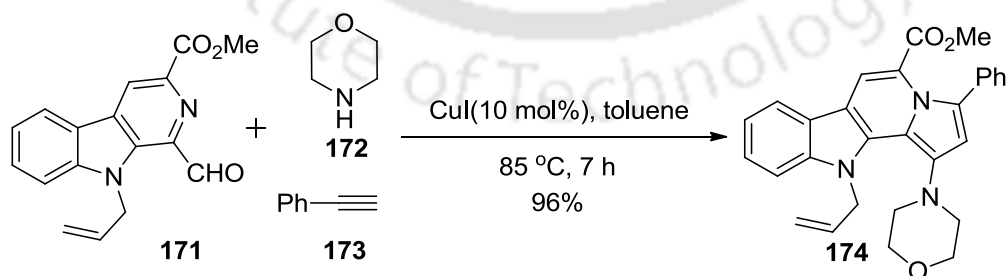
Similarly, some other research groups also utilized this method for the synthesis of aminoindazoline derivatives using different catalysts (Scheme 1.4.2.1.2.) Liu and coworkers^{52a} reported an efficient, one-pot synthesis of aminoindazolines **170** from heteroaryl aldehydes **167**, secondary amines **168**, and terminal alkynes **169** catalyzed by AgBF₄ in moderate to good

yields. Further, the same approach was employed by Bobade *et al.* using catalytic amount of $\text{Fe}(\text{acac})_3/\text{TBAOH}$ with diverse range of heteroarylaldehydes **167** and secondary amines **168** with alkynes **169**.^{52b} In a similar way, copper nanoparticles supported three component synthesis of indolizines **170** was achieved by Alonso group in dichloromethane as solvent at 70 °C.^{52c} Following this method, Rawat and coworkers employed a green A^3 -coupling reaction of heteroaryl aldehydes **167**, secondary amines **168**, and alkynes **169** by switching over to recyclable catalyst system of CuI/CSP under neat conditions to afford indolizines **170** (Scheme 1.4.2.1.2).^{52d}

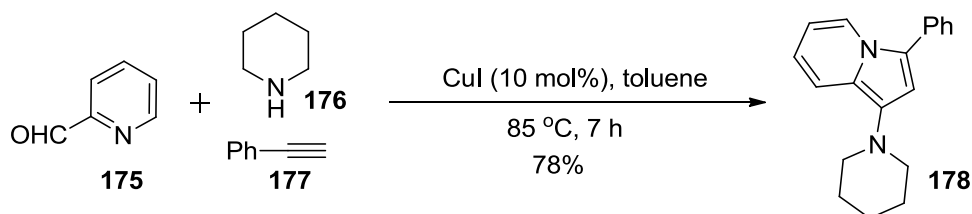


Scheme 1.4.2.1.2.

Batra and coworkers reported a tandem A^3 -coupling/cycloisomerization reaction between substituted 1-formyl-9H- β -carboline **171**, with morpholine **172** and phenylacetylene **173** in presence of copper(I) catalyst to afford polycyclic 3-aminoindolizino-[8,7-*b*]indole **174** in 96% yield (Scheme 1.4.2.1.3).⁵³ Under the similar reaction conditions picolinaldehyde **175** gave aminoindolizine **178** in 78% yield (Scheme 1.4.2.1.4).⁵³

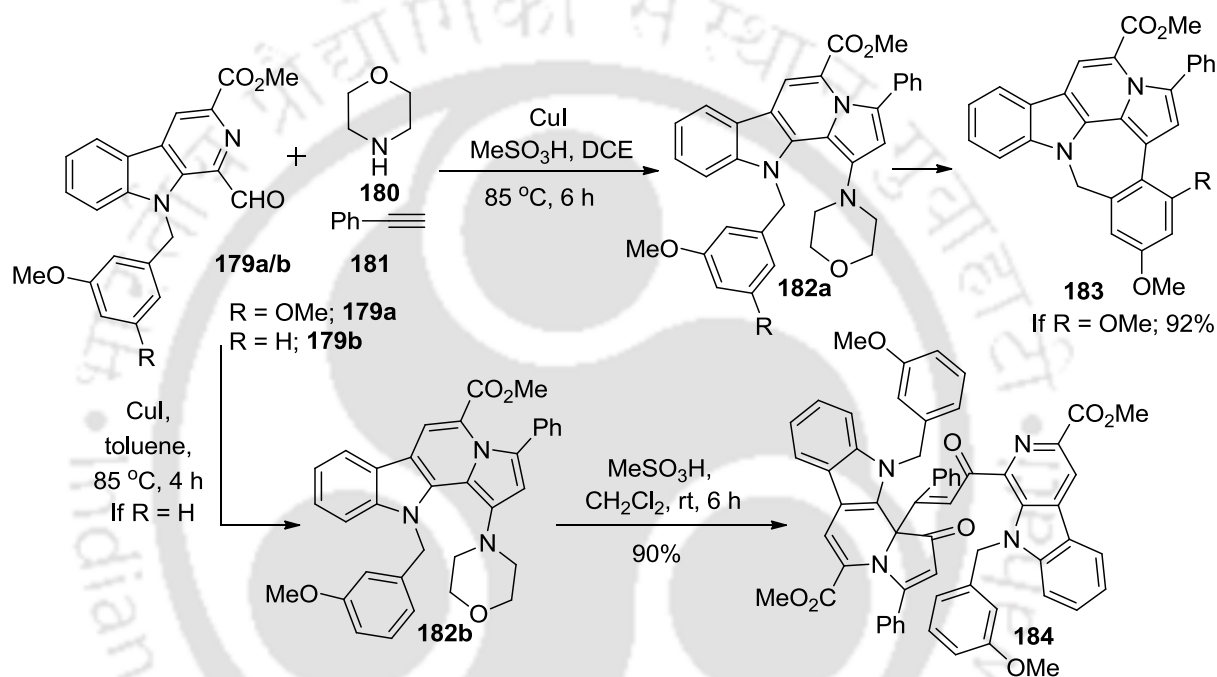


Scheme 1.4.2.1.3.



Scheme 1.4.2.1.4.

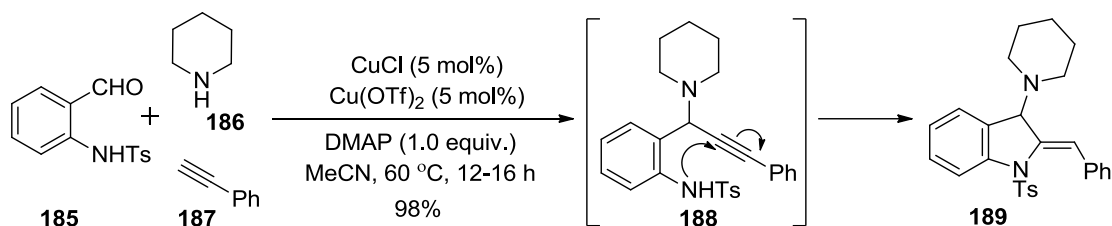
Recently, the same group described a divergent synthesis of fused- β -carboline analogous in one-pot fashion. A triple cooperative catalyst-mediated A^3 -coupling reaction of 1-formyl- N -substituted- β -carboline **179a**, morpholine **180** and phenylacetylene **181** gave an intermediate 3-aminoindolizino-[8,7-*b*]indole **182a**, which simultaneously participated in intramolecular Csp^2 - Csp^2 Friedel-Crafts arylation to produce polycyclic- β -carboline **183** in 92% yield. In addition, two- step process of the same tandem A^3 -coupling reaction with **179b** in toluene accomplished **182b**. The compound **182b** was further treated with methanesulfonic acid to result an unprecedented product **184** in 90% yield (Scheme 1.4.2.1.5).⁵⁴



Scheme 1.4.2.1.5.

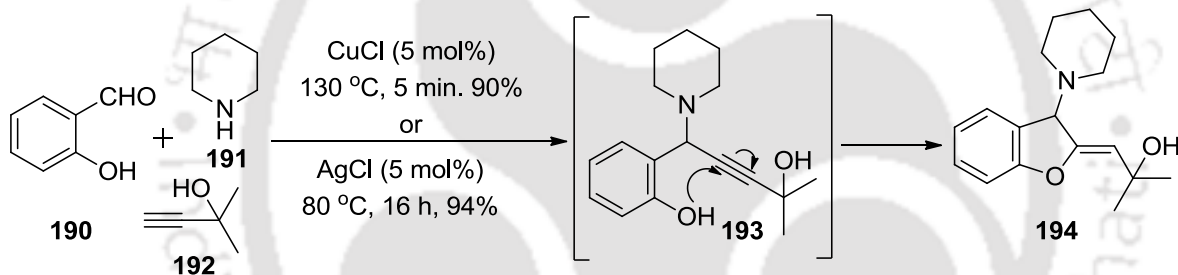
1.4.2.2. Tandem A^3 -coupling with *ortho*-functional arylaldehydes

Different *ortho*-functionalised aldehydes are the key substrates in A^3 -coupling reactions for the construction of variety of heterocyclic core units. Initially, the aldehyde function was involved in A^3 -coupling to produce propargylamine. Simultaneously, *ortho*-function of the aldehyde effectively incorporates in cyclization to give the corresponding heterocyclic products. Gevorgyan and coworkers reported a novel one-pot three component synthesis of 3-aminoindoline **189** in 98% yield from 2-aminobenzaldehyde **185**, piperidine **186** and phenylacetylene **187** using $\text{CuCl}/\text{Cu}(\text{OTf})_2$ co-catalyst (Scheme 1.4.2.2.1).⁵⁵ The mechanism of the reaction exhibit, A^3 -coupling and then subsequent intramolecular hydroamination of in situ formed propargylamine, gives the final product **189**.



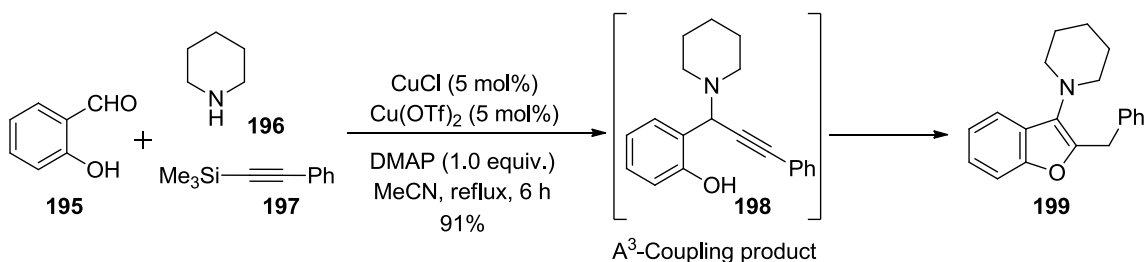
Scheme 1.4.2.2.1.

Salicylaldehyde is a versatile and commercially available starting material for the synthesis of diverse range of heterocycles in organic synthesis. Li and coworkers described the synthesis of dihydrobenzofuran **194** via transition metal catalyzed A³-coupling reaction of salicylaldehyde **190**, secondary amine **191** and alkynes **192** followed by intramolecular 5-*exo-dig*-cyclization of **193**. A³-coupling reaction product **193** is the key intermediate (**193**) for the formation of the desired product **194** (Scheme 1.4.2.2.2).⁵⁶



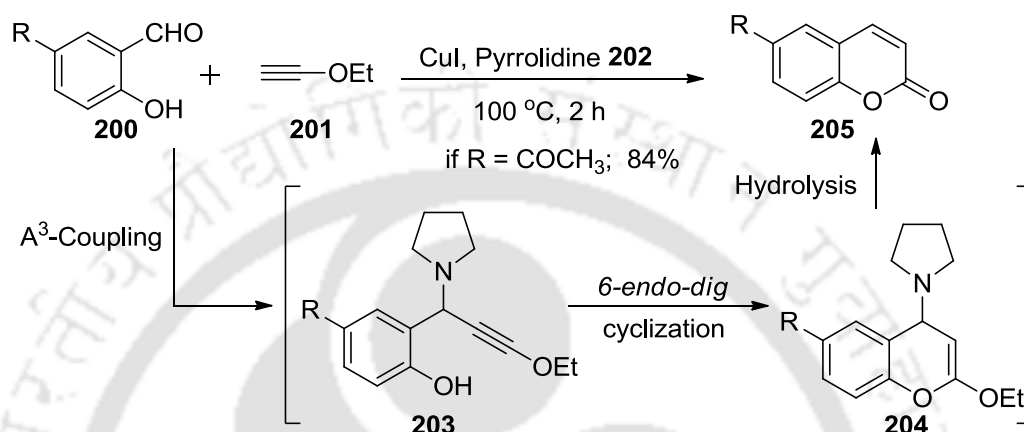
Scheme 1.4.2.2.2.

Sakai and coworkers employed a tandem A³-coupling/cycloisomerization reaction of salicylaldehyde **195**, secondary amine **196** and trimethylsilyl alkyne **197** using catalytic amount of CuCl/Cu(OTf)₂ in presence of DMAP to afford 3-aminobenzofuran **199** in 91% yield (Scheme 1.4.2.2.3).⁵⁷ The reaction proceeds with in situ deprotection of silyl group to give terminal acetylide that serve as nucleophile and add to imine resulting propargylamine intermediate **198**. This is further involved in 5-*exo-dig*-cycloisomerization to afford the desired product **199**.



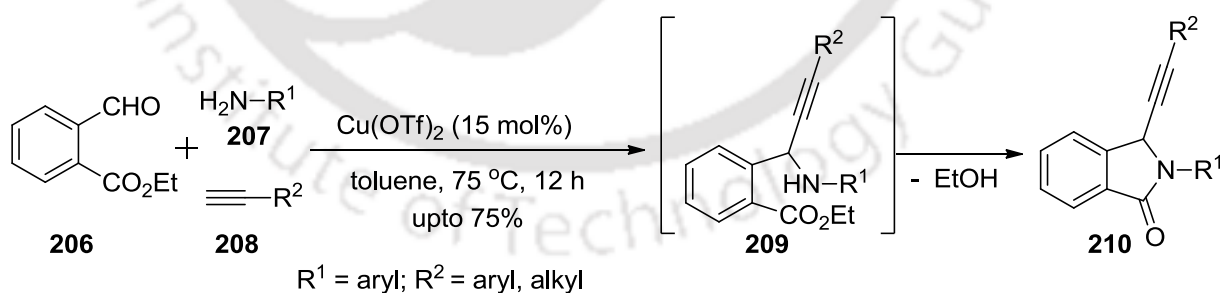
Scheme 1.4.2.2.3.

Reddy and coworkers reported a straight forward approach for the construction of coumarin derivative **205** via tandem A³-coupling/cycloisomerization in presence of copper(I) catalyst. The tandem cyclization proceeds via in situ generated propargylamine **203** from salicylaldehyde **200**, pyrrolidine **202** and ethoxyacetylene **201** followed by 6-*endo-dig* cyclization to give the resultant vinyl ether intermediate **204**. The intermediate **204** finally underwent hydrolysis to give coumarin **205** (Scheme 1.4.2.2.4).⁵⁸



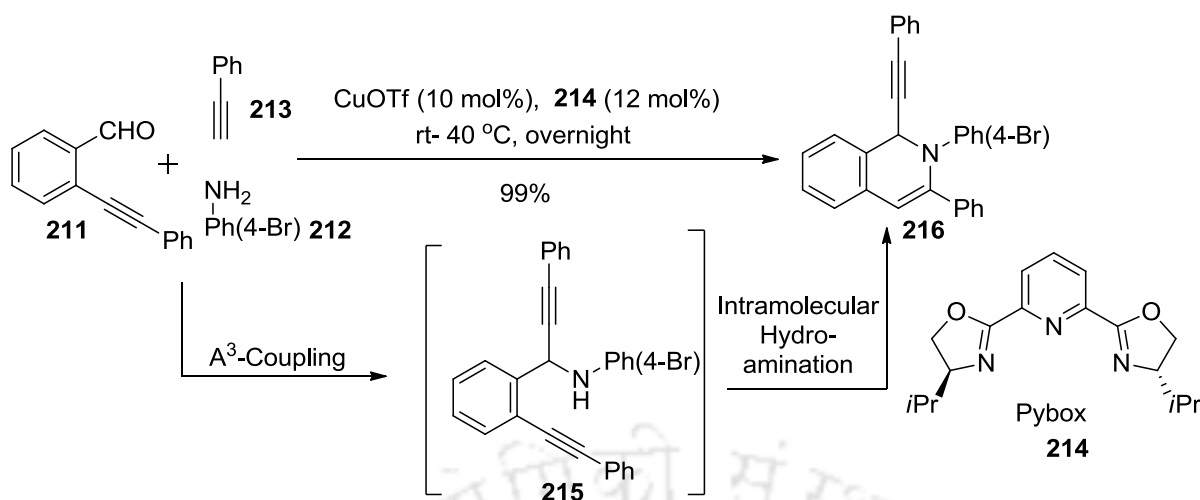
Scheme 1.4.2.2.4.

Propargyl-isoindolinones **210** were effectively synthesised by Li and group in 2012 using copper(II) catalysed tandem A³-coupling reaction of 2-formylbenzoate **206**, aniline **207**, and phenylacetylene **208** followed by intramolecular amidation of in situ formed propargylamine **209** in 75% yield (Scheme 1.4.2.2.5).⁵⁹



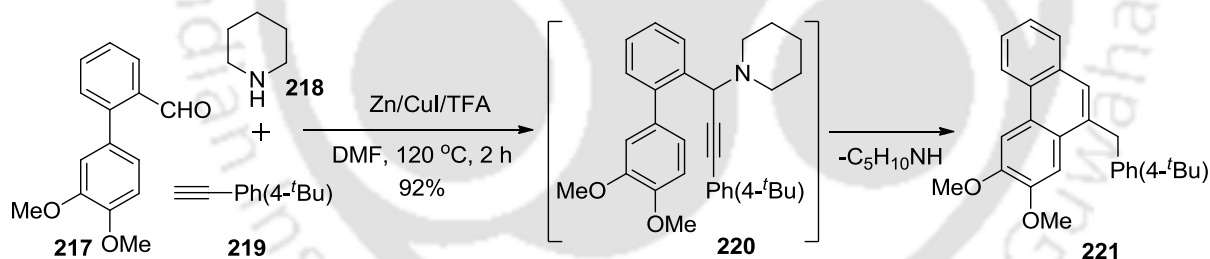
Scheme 1.4.2.2.5.

Yao and group described a CuOTf/Pybox **214** catalysed one-pot, three component tandem A³-coupling reaction of 2-(phenylethynyl)benzaldehyde **211**, arylamine **212** and alkyne **213** followed by hydro amination **215** to give 1,2-dihydroisoquinoline **216** in 99% yield (Scheme 1.4.2.2.6).⁶⁰



Scheme 1.4.2.2.6.

Recently, A³-coupling reaction is also useful for the construction of carbocyclic ring systems. Kundu and coworkers demonstrated one-pot, Zn/CuI/TFA-mediated domino three component reaction of biphenyl aldehyde **217**, piperidine **218**, and arylethyne **219** to give phenanthrene derivative **221** in 92% yield. The synthesis started from three component reaction of in situ generated propargylamine **220** followed by intramolecular carbon-carbon cycloisomerization with the elimination of piperidine **218** to give the final product (Scheme 1.4.2.2.7).²⁶

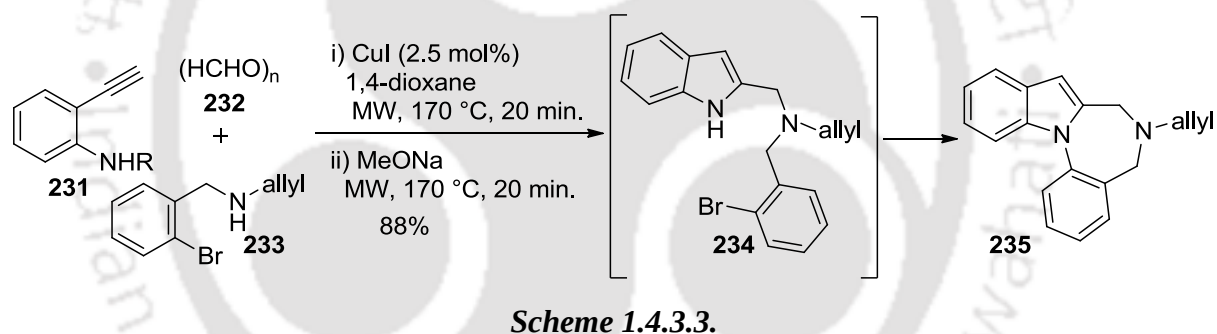
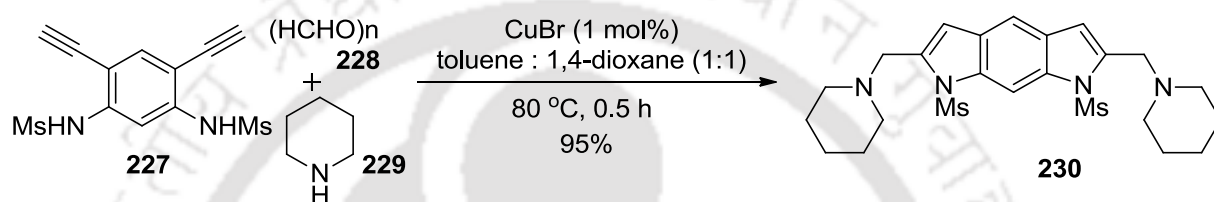
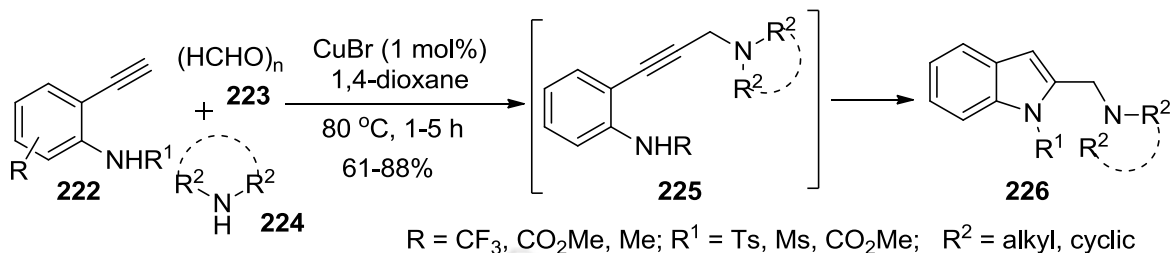


Scheme 1.4.2.2.7.

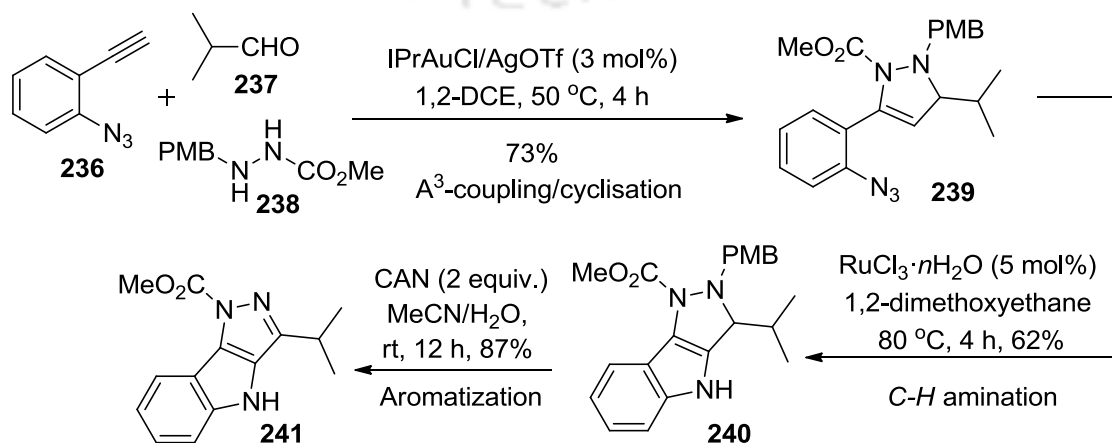
1.4.3. Role of functional alkynes in tandem A³-coupling reactions

Functional alkynes are also gaining attention in tandem A³-coupling for the development of substituted heterocyclic ring systems in organic synthesis. Fujii and coworkers reported a novel domino reaction of copper(I) bromide catalysed A³-coupling of bifunctional alkyne **222**, formaldehyde **223** and secondary amines **224** followed by 5-*endo-dig* cyclization of in situ formed propargylamine **225** to furnish 2-(aminomethyl)indoles **226** in good yields (Scheme 1.4.3.1).^{61a} The same group in 2009, achieved a bis-cyclized pyrroloindole **230** in 95% yields via copper bromide catalysed tandem double A³-coupling reaction between compound **227**, *para*-formaldehyde **228** and piperidine **229** (Scheme 1.4.3.2).^{61b} Further, inspiring applicability of this method was demonstrated by the same group through a concise route for the synthesis

of indole-fused-1,4-diazepine **235**, using copper(I) catalysed same A^3 -coupling with *N*-(2-bromobenzyl)prop-2-en-1-amine **233** and subsequent intramolecular cyclization/*N*-arylation **234** sequence under microwave irradiation (Scheme 1.4.3.3).^{61c}



Fujii and coworkers described an efficient route for the synthesis of pyrazolo-[4,3-*b*]indoles **241** in three step process. The sequence initiated from, $\text{IPrAuCl}/\text{AgOTf}$ promoted tandem A^3 -coupling of 1-azido-2-ethynylbenzene **236**, isobutyraldehyde **237** and hydrazine derivative



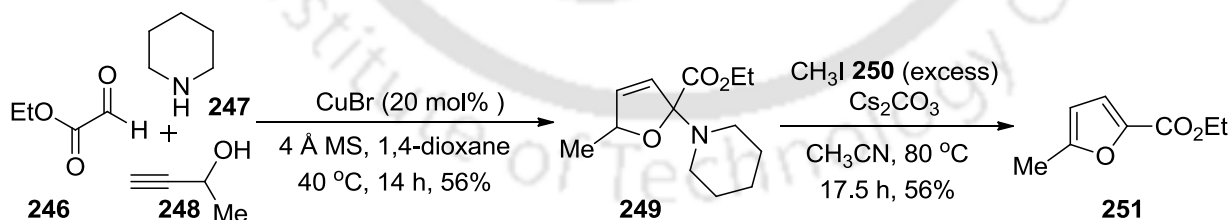
238 to afford dihydropyrazole **239** in 73% yield. Further, successive involvement in Ru(III)-catalysed intramolecular *C-H* amination of the compound **240** gave dihydropyrazolo[4,3-*b*]indole **240** with 62% yield. Finally, deprotection of *para*-methoxy benzyl group followed by dehydrogenative oxidation of compound **240** in presence of ceric ammonium nitrate accomplished the aromatized pyrazolo-[4,3-*b*]indole **241** in 87% yield (Scheme 1.4.3.4).⁶²

Kabalka and coworkers reported a novel, cuprous iodide and alumina mediated, multicomponent synthesis of 2-(dialkylaminomethyl)benzo[*b*]furans **245** derived from *ortho*-ethynylphenol **242**, *para*-formaldehyde **243** and secondary amines **244** under solvent free microwave conditions (Scheme 1.4.3.5).⁶³



Scheme 1.4.3.5.

An effective approach towards 2,5-polysubstituted dihydrofuran **249** was developed by Ma and coworkers from easily available starting materials, ethyl glyoxalate **246**, piperidine **247**, and propargylic alcohol **248** using copper(I) bromide as a catalyst. The resulting product **249** was treated with excess of methyl iodide **250** in presence of base to furnish 2,5-di-substituted furan **251** in 56% yield (Scheme 1.4.3.6).^{25a}

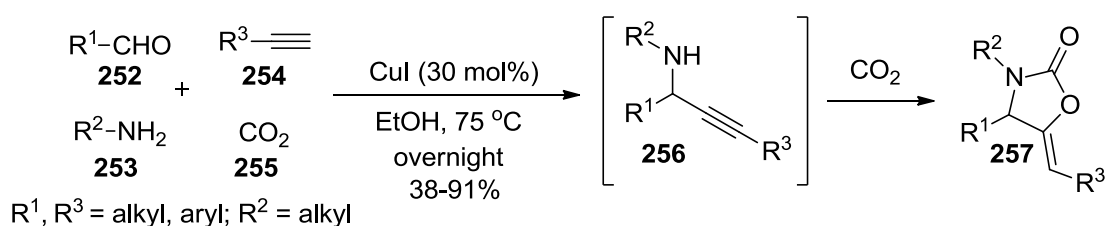


Scheme 1.4.3.6.

1.5. More than three components in A³-coupling reaction

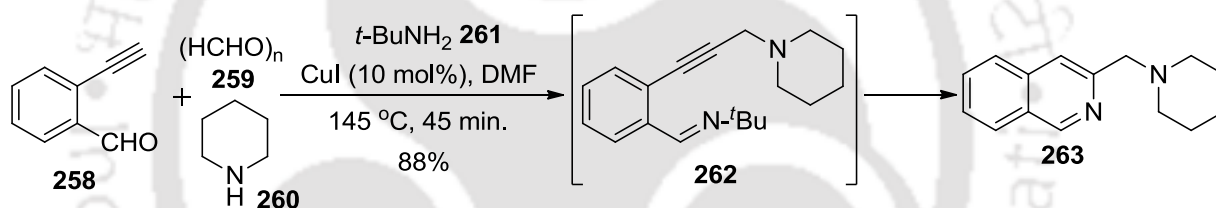
Li and coworkers interestingly reported a novel one-pot copper-catalyzed four component tandem cyclization of aldehydes **252**, amines **253**, alkynes **254** and CO₂ **255** to give oxazolidinones **257** in good yields. The mechanistic insight of the reaction reveals that

carboxylative cyclization of in situ generated propargylamines **256** lead to formation of oxazolidinones **257** (Scheme 1.5.1).⁶⁴



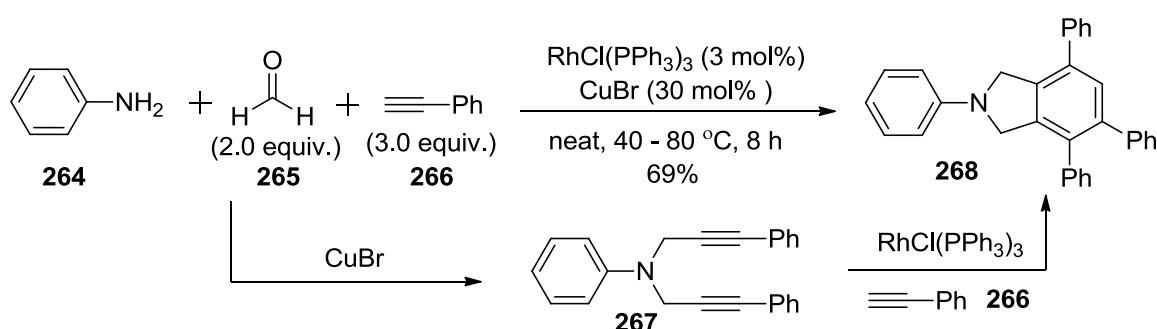
Scheme 1.5.1.

Fujii and coworkers demonstrated an efficient domino four component reaction for the synthesis of 3-(aminomethyl)isoquinolines **263** from 2-ethynylbenzaldehyde **258**, *para*-formaldehyde **259**, piperidine **260** and *tert*-butylamine **261** using catalytic amount of copper(I) system in 88% yield. This reaction proceeds via copper(I) mediated 6-*endo-dig*-cyclization of in situ formed propargylamine **262**, followed by removal of *t*-Bu group (Scheme 1.5.2).⁶⁵



Scheme 1.5.2.

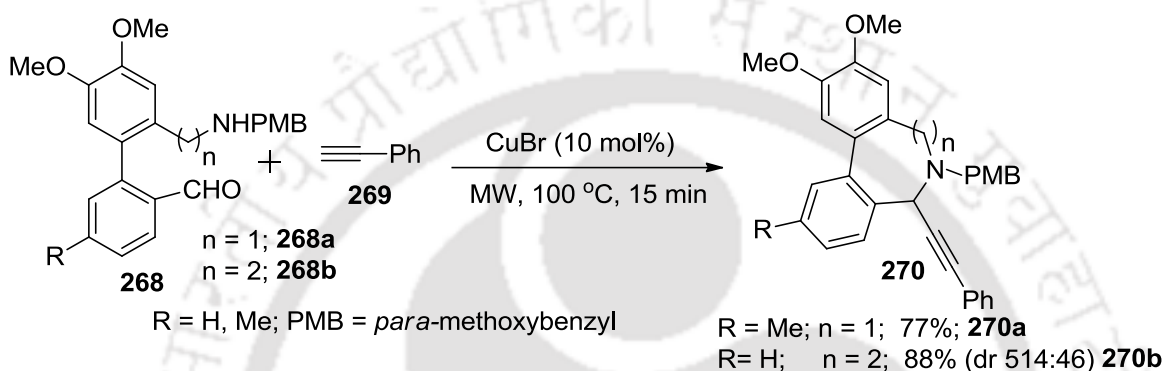
A tandem cyclization to tetra substituted isoindoline **268** was reported by Li and coworkers via double A^3 -coupling reaction of aniline **264** with two equivalents of formaldehyde **265** and three equivalents of phenylacetylene **266** in presence of copper/rhodium co-catalysts. The reaction mechanism shows that, copper(I) bromide promoted double A^3 -coupling reaction followed by [2+2+2] cycloaddition reaction of in situ generated propargylamine **267** with alkyne **266** in presence of Wilkinson's catalyst gives isoindoline **268** (Scheme 1.5.3).⁶⁶



Scheme 1.5.3.

1.6. Intramolecular A³-coupling

Van der Eycken and coworkers reported a microwave assisted copper(I) promoted intramolecular A³-coupling reaction with compound **268a** and phenylacetylene **269** to give 5-alkynyl-6,7-dihydro-5*H*-dibenzo[*c,e*]azepine derivative **270a** in 77% yield. Simultaneously, this strategy was also applied for the construction of 5,6,7,8-tetrahydridibenzo[*c,e*]azocine **270b** using compound **268b** under similar reaction conditions. The corresponding derivative **270b** was obtained in 88% yield as diastereomeric mixture (dr = 54:46) (Scheme 1.6.1).⁶⁷



Scheme 1.6.1.

Conclusion

From the overview of the literature, A³-coupling reaction is a straight forward route for the synthesis of a versatile synthetic intermediate propargylamine. Due to the versatility and flexibility of the propargylamine, it acts as a key intermediate for the construction of various heterocyclic building blocks such as imidazoles, imidazolines, oxazoles, oxazolidines, pyrroles, pyrrolidines, quinoline, indoles, imidazopyridine, indazolines, benzo furans, furans and some other complex and fused heterocycles as well as bioactive natural products that have been developed in modern synthetic organic chemistry. Moreover, A³-coupling partners having additional functional groups most often involves in tandem cyclization reaction, is a powerful tool for the synthesis of diverse oriented substituted heterocycles. Complex propargylamines bearing additional groups also attract attention for synthesis of a new class of heterocycles in synthetic organic community.

1.7. References

1. (a) Ryu, I.; Miyazato, H.; Kuriyama, H.; Matsu, K.; Tojino, M.; Fukuyama, T.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2003**, *125*, 5632-5633. (b) Shi, M.; Shen, Y.-M. *J. Org. Chem.* **2002**, *67*, 16-21. (c) Brunel, P.; Monot, J.; Kefalidis, C. E.; Maron, L.; Martin-Vaca, B.; Bourissou, D. *ACS Catal.* **2017**, *7*, 2652-2660. (d) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391-4394. (e) Fujiwara, S.-i.; Shikano, Y.; Shin-ike, T.; Kambe, N.; Sonoda, N. *J. Org. Chem.* **2002**, *67*, 6275-6278. (f) Vessally, E.; Soleimani-Amiri, S.; Hosseini, A.; Edjlalid, L.; Bekhradnia, A. *RSC Adv.* **2017**, *7*, 7079-7091. (g) Shen, H.; Xie, Z. *J. Am. Chem. Soc.* **2010**, *132*, 11473-11480. (h) Jayaprakash, K.; Venkataharam, C. S.; Balasubramanian, K. K. *Tetrahedron Lett.* **1999**, *40*, 6493-6496. (i) Chachignon, H.; Scalacci, N.; Petricci, E.; Castagnolo, D.; *J. Org. Chem.* **2015**, *80*, 5287-5295. (j) Chen, J. S.; Properzi, R.; Uccello, D. P.; Young, J. A.; Dushin, R. G.; Starr, J. T. *Org. Lett.* **2014**, *16*, 4146-4149. (k) Xia, Y. Y.; Chen, L. Y.; Lv, S.; Sun, Z. H.; Wang, B. *J. Org. Chem.* **2014**, *79*, 9818-9825. (l) Ohta, Y.; Kubota, Y.; Watabe, T.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 6299-6302. (m) Donald, J. R.; Wood, R. R.; Martin, S. F. *ACS Comb. Sci.* **2012**, *14*, 135-143. (n) Nguyen, H. H.; Palazzo, T. A.; Kurth, M. J. *Org. Lett.* **2013**, *15*, 4492-4495. (o) Bhonde, V. R.; Looper, R. E. *J. Am. Chem. Soc.* **2011**, *133*, 20172-20174. (p) Mao, F.; Li, J.; Wei, H.; Huang, L.; Li, X. *J. Enzyme Inhib Med Chem*, **2015**, *30*, 995-1001.
2. (a) Marshall, J. A.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 3238-3239. (b) Yoshida, Y.; Tanabe, Y. *Synthesis*. **1997**, *5*, 533-535. (c) Holman, M. A.; Williamson, N. M.; Ward A. D.; *Aust. J. Chem.* **2005**, *58*, 368-374 (d) Basu, B.; Paul, S.; Nanda, A. K. *Green Chem.* **2009**, *11*, 1115-1120. (e) Zhang, X.; Yao, T.; Campo, M. A.; Larock, R. C. *Tetrahedron*. **2010**, *66*, 1177-1187. (f) Médoc, M.; Sobrio, F. *J. Org. Chem.* **2015**, *80*, 10086-10097. (g) Castillo, J.-C.; Orrego-Hernández, J.; Portilla, J. *Eur. J. Org. Chem.* **2016**, 3824-3835.
3. (a) Wada, M.; Sakurai, Y.; Akiba K.-y. *Tetrahedron Lett.* **1984**, *25*, 1083-1084. (b) Magueur, G.; Crousse, B.; Bonnet-Delpon, D.; *Tetrahedron Lett.* **2005**, *46*, 2219-2221. (c) Ma, Y.; Lobkovsky, E.; Collum, D. B.; *J. Org. Chem.* **2005**, *70*, 2335-2337. (d) Aubrecht, K. B.; Winemiller, M. D.; Callum, D. B.; *J. Am. Chem. Soc.* **2000**, *122*, 11084-11089.
4. Guermont, J. P. *Bull. Soc. Chim. Fr.* **1953**, 386-390.
5. McNally, J. J.; Youngman, M. A.; Dax, S. L. *Tetrahedron Lett.* **1998**, *39*, 967-970.
6. Dyatkin, A. B.; Rivero, R. A.; *Tetrahedron Lett.* **1998**, *39*, 3647-3650.

7. Li, C.-J.; Wei, C. *Chem. Commun.* **2002**, 268-269.
8. We, C.; Li, C.-J.; *J. Am. Chem. Soc.* **2003**, 125, 9584-9585.
9. (a) Meyet, C. E.; Pierce, C. J.; Larsen, C. H. *Org. Lett.* **2012**, 14, 964-967. (b) Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2012**, 41, 3790-3807. (c) Sharma, N.; Sharma, U. K.; Mishra, N. M.; Van der Eycken, E. V. *Adv. Synth. Catal.* **2014**, 356, 1029-1037.
10. (a) Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.* **2003**, 5, 4473-4475. (b) Li, Z.; Wei, C.; Chen, L.; Varmab, R. S.; Lia, C.-J. *Tetrahedron Lett.* **2004**, 45, 2443-2446. (c) Yao, X.; Li, C.-J. *Org. Lett.* **2005**, 7, 4395-4398.
11. (a) Huang, J.-L.; Gray, D. G.; Li, C.-J. *Beilstein J. Org. Chem.* **2013**, 9, 1388-1396. (b) Price, G. A.; Brisdon, A. K.; Flower, K. R.; Pritchard, R. G.; Quayle, P. *Tetrahedron Lett.* **2014**, 55, 151-154.
12. (a) Ramu, E.; Varala, R.; Sreelatha, N.; Adapa, S. R.; *Tetrahedron Lett.* **2007**, 48, 7184-7190. (b) Zani, L.; Alesi, S.; Cozzi, P. G.; Bolm, C. *J. Org. Chem.* **2006**, 71, 1558-1562.
13. Samai, S.; Nandi, G. C.; Singh, M. S.; *Tetrahedron Lett.* **2010**, 51, 5555-5558.
14. (a) Li, P.; Zhang, Y.; Wang, L. *Chem. Eur. J.* **2009**, 15, 2045-2049. (b) Chen, W.-W.; Nguyen, R. V.; Li, C.-J. *Tetrahedron Lett.* **2009**, 50, 2895-2898.
15. Zhang, Y.; Li, P.; Wang, M.; Wang, L. *J. Org. Chem.* **2009**, 74, 4364-4367.
16. (a) Sakaguchi, S.; Kubo, T.; Ishii, Y. *Angew. Chem. Int. Ed.* **2001**, 40, 2534-2536. (b) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, 3, 4319-4321.
17. Chen, W. W.; Bi, H. P.; Li, C. J. *Synlett.* **2010**, 475-479.
18. Li, P.; Wang, L.; *Chin. J. Chem.* **2005**, 23, 1076-1080.
19. Raghuvanshi, D. S.; Singh, K. N. *Synlett.* **2011**, 373-377.
20. Wei, C.; Li, Z.; Li, C.-J. *Synlett.* **2004**, 1472-1483.
21. (a) Pereshivko, O. P.; Peshkov, V. A.; Van der Eycken, E. V. *Org. Lett.* **2010**, 12, 2638-2641. (b) Palchak, Z. L.; Nguyen, P. T.; Larsen, C. H. *Beilstein J. Org. Chem.* **2015**, 11, 1425-1433.
22. (a) Cabrele, C.; Reiser, O. *J. Org. Chem.* **2016**, 81, 10109-10125. (b) Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2013**, 9, 2265-2319. (c) Hügel, H. M. *Molecules.* **2009**, 14, 4936-4972. (d) Chemler, S. R. *Org. Biomol. Chem.* **2009**, 7, 3009-3019. (e) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem. Rev.* **2015**, 115, 2596-2697. (f) Nakamura, I.; Yamamoto, Y.; *Chem. Rev.* **2004**, 104, 2127-2198. (g) Eguchi, S.; *ARKIVOC.* **2005**, 98-119. (h) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, 57, 10257-10274. (i) Asif, M. *IJBC.* **2017**, 2, 146-152. (h) Ziegler, J.; Facchini, P. J. *Annu. Rev. Plant Biol.* **2008**, 59, 735-769. (j) Newman, D. J.; Cragg,

- G. M. *J. Nat. Prod.* **2012**, 75, 311-335. (k) Gomtsyan, A. *Chem Heterocycl Comp.* **2012**, 48, 7-10. (l) Arora, P.; Arora, V.; Lamba, H. S.; Wadhwa, D. *IJPSR*, **2012**, 3, 2947-2954. (m) Taylor, A. P.; Robinson, R. P.; Fobian, Y. M.; Blakemore, D.C.; Jonesb, L. H.; Fadeyi, O. *Org. Biomol. Chem.* **2016**, 14, 6611-6637.
23. (a) Gibbons, J. B.; Gligorich, K. M.; Welm, B. E.; Looper, R. E. *Org. Lett.* **2003**, 14, 4734-4737. (b) Gommermann, N.; Knochel, P. *Chem. Commun.* **2004**, 2324-2325. (c) Xu, Q.; Rozners, E. *Org. Lett.* **2005**, 7, 2821-2824. (d) Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2006**, 8, 1529-1532. (e) Roy, B.; Raj, R.; Mukhopadhyay, B. *Tetrahedron Lett.* **2009**, 50, 5838-5841. (f) Giles, R. L.; Sullivan, J. D.; Steiner, A. M.; Looper, R. E. *Angew. Chem. Int. Ed.* **2009**, 48, 3116-3120. (g) Ermolat'ev, D. S.; Bariwal, J. B.; Steenackers, H. P. L.; De Keersmaecker, S. C. J.; Van der Eycken, E. V. *Angew. Chem. Int. Ed.* **2010**, 49, 9465-9468. (h) Singh, R. P.; Das, J.; Yousufuddin, M.; Gout, D.; Lovely, C. J. *Org. Lett.* **2017**, 19, 4110-4113.
24. Liu, Y. *ARKIVOC*, **2014**, 1-20.
25. (a) Fan, W.; Ma, S. *Eur. J. Org. Chem.* **2015**, 3531-3539. (b) Li, J.; Rudolph, M.; Rominger, F.; Xie, J.; Hashmi A. S. K. *Adv. Synth. Catal.* **2016**, 358, 207-211.
26. Saifuddin, M.; Agarwal, P. K.; Kundu, B. *J. Org. Chem.* **2011**, 76, 10122-10128.
27. Yamamoto, Y.; Hayashi, H.; Saigoku, T.; Nishiyama, H. *J. Am. Chem. Soc.* **2005**, 127, 10804-10805. (b) Nandakumar, A.; Kiruthika, S. E.; Naveen K.; Perumal, P. T.; *Org. Biomol. Chem.* **2014**, 12, 876-880.
28. Peshkov, V. A.; Pereshivko, O. P.; Sharma, S.; Meganathan, T.; Parmar, V.S.; Ermolat'ev, D. S.; Van der Eycken, E.V. *J. Org. Chem.* **2011**, 76, 5867-5872.
29. Pereshivko, O. P.; Peshkov, V. A.; Jacobs, J.; Meervelt, L. V.; Van der Eycken, E. V. *Adv. Synth. Catal.* **2013**, 355, 781-789.
30. Ranjan, A.; Yerande, R.; Wakchaure, P. B.; Yerande, S. G.; Dethe, D. H. *Org. Lett.* **2014**, 16, 5788-5791.
31. Giles, R. L.; Nkansah, R. A.; Looper, R. E. *J. Org. Chem.* **2010**, 75, 261-264.
32. Wachenfeldt, H. v.; Paulsen, F.; Sundin, A.; Strand, D. *Eur. J. Org. Chem.* **2013**, 4578-4585.
33. Hu, J.; Ma, J.; Zhu, Q.; Zhang, Z.; Wu, C.; Han, B. *Angew. Chem. Int. Ed.* **2015**, 54, 5399-5403.
34. (a) Wang, M.-Y.; Song, Q.-W.; Ma, R.; Xie, J.-N.; He L.-N. *Green Chem.* **2016**, 18, 287. (b) Song, Q.-W.; He L.-N. *Adv. Synth. Catal.* **2016**, 358, 1251-1258. (c) Liu, X.; Wang, M.-Y.; Wang, S.-Y.; Wang, Q.; He, L.-N. *ChemSusChem.* **2017**, 10, 1210-1216.

35. Mont, N.; Mehta, V. P.; Appukkuttan, P.; Beryozkina, T.; Toppet, S.; Van Hecke, K.; Van Meervelt, L.; Voet, A.; DeMaeyer, M.; Van der Eycken, E. *J. Org. Chem.* **2008**, *73*, 7509-7516.
36. Peshkov, V. A.; Pereshivko, O. P.; Donets, P. A.; Mehta V. P.; Van der Eycken, E. V. *Eur. J. Org. Chem.* **2010**, 4861-4867.
37. Nandakumar, A.; Muralidharan, D.; Perumal, P. T. *Tetrahedron Lett.* **2011**, *52*, 1644-1648.
38. (a) Nandakumar A.; Perumal, P. T. *Org. Lett.* **2013**, *15*, 382-385. (b) Naveen, K.; Muralidharan, D.; Perumal, P. T. *Eur. J. Org. Chem.* **2014**, 1172-1176. (c) Naveen, K.; Nandakumar A.; Perumal, P. T. *Synthesis.* **2015**, *47*, 1633-1642. (d) Naveen, K.; Nandakumar A.; Perumal, P. T. *RSC Adv.* **2015**, *5*, 74438-74446.
39. Hooyberghs, G.; De Coster, H.; Vachhani, D. D.; Ermolat'ev, D. S.; Van der Eycken, E. V. *Tetrahedron.* **2013**, *69*, 4331-4337.
40. Sudhapriya, N.; Nandakumar, A.; Arun, Y.; Perumal, P. T.; Balachandran, C.; Emi, N. *RSC Adv.* **2015**, *5*, 66260-66270.
41. Huma, H. Z. S.; Halder, R.; Kalra, S. S.; Das, J.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6485-6488.
42. (a) Xiao, F.; Chen, Y.; Liu, Y.; Wang, J. *Tetrahedron.* **2008**, *64*, 2755-2761. (b) Zhang, Y.; Li, P.; Wang, L. J. *Heterocycl. Chem.* **2011**, *48*, 153-157. (c) Zhang, M.; Wang, T.; Xiong, B.; Yan, F.; Wang, X.; Ding, Y.; Song, Q. *Heterocycles.* **2012**, *85*, 639-649. (d) Yao, C.; Qin, B.; Zhang, H.; Lu, J.; Wang, D.; Tu, S. *RSC Adv.* **2012**, *2*, 3759-3764. (e) Tang, J.; Wang, L.; Mao, D.; Wang, W.; Zhang, L.; Wu, S.; Xie, Y. *Tetrahedron.* **2011**, *67*, 8465-8469. (f) Kumar, A.; Rao, V. K. *Synlett.* **2011**, 2157-2162. (g) Anvar, S.; Mohammadpoor-Baltork, I.; Tangestaninejad, S.; Moghadam, M.; Mirkhani, V.; Khosropour, A. R.; Kia, R. *RSC Adv.* **2012**, *2*, 8713-8720.
43. Ramesh, S.; Nagarajan, R. *Tetrahedron.* **2013**, *69*, 4890-4898.
44. Ramesh, S.; Nagarajan, R. *Synlett.* **2012**, *23*, 717-722.
45. Gaddam, V.; Ramesh, S.; Nagarajan, R. *Tetrahedron.* **2010**, *66*, 4218-4222.
46. Chernyak, N.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2010**, *49*, 2743-2746.
47. (a) Mishra, S.; Ghosh, R. *Synthesis.* **2011**, *21*, 3463-3470. (b) Guntreddi, T.; Allam, B. K.; Singh, K. N. *Synlett.* **2012**, *23*, 2635-2638. (c) Lu, J.; Li, Ma, X.-T.; E.-Q.; Mo, L.-P.; Zhang, Z.-H. *ChemCatChem.* **2014**, *6*, 2854-2859. (d) Bharate, J. B.; Guru, S. K.; Jain, S. K.; Meena, S.; Singh, P. P.; Bhushan, S.; Singh, B.; Bharate, S. B. Vishwakarma, R. A. *RSC Adv.* **2013**, *3*, 20869-20876. (e) Siddiqui, I. R.; Rai, P.; Rahila, Srivastava, A.; Shamim, S. *Tetrahedron Lett.* **2014**, *55*, 1159-1163.

48. Guchhait, S. K.; Chandgude, A. L.; Priyadarshani, G. *J. Org. Chem.* **2012**, 77, 4438-4444.
49. Kumar, A.; Kumar, M.; Maurya, S.; Khanna, R. S. *J. Org. Chem.* **2014**, 79, 6905-6912.
50. Selvaraju, M.; Ye, T.-Y.; Li, C.-H.; Ho, P.-H.; Sun, C.-M. *Chem. Commun.* **2016**, 52, 6621-6624.
51. Yan, B.; Liu, Y. *Org. Lett.* **2007**, 9, 4323-4326.
52. (a) Bai, Y.; Zeng, J.; Ma, J.; Gorityala, B. K.; Liu, X.-W. *J. Comb. Chem.* **2010**, 12, 696-699. (b) Patil, S. S.; Patil, S. V.; Bobade, V. D. *Synlett.* **2011**, 16, 2379-2383. (c) Albaladejo, M. J.; Alonso, F.; Yus, M. *Chem. Eur. J.* **2013**, 19, 5242-5245. (d) Rajesh, U. C.; Purohit, G.; Rawat, D. S. *ACS Sustainable Chem. Eng.* **2015**, 3, 2397-2404.
53. Dighe, S. U.; Hutait, S.; Batra, S. *ACS Comb. Sci.* **2012**, 14, 665-672.
54. Dighe, S. U.; Yadav, V. D.; Mahar, R.; Shukla, S. K.; Batra, S. *Org. Lett.* **2016**, 18, 6010-6013.
55. Chernyak, D.; Chernyak N.; Gevorgyan, V. *Adv. Synth. Catal.* **2010**, 352, 961-966.
56. Nguyen, R.-V.; Li, C.-J. *Synlett.* **2008**, 12, 1897-1901.
57. Sakai, N.; Uchida, N.; Konakahara, T.; *Tetrahedron Lett.* **2008**, 49, 3437-3440.
58. Reddy, M. S.; Thirupathi, N.; Haribabu, M. *Beilstein J. Org. Chem.* **2013**, 9, 180-184.
59. Sun, L. X.; Zeng, T.; Jiang, D.; Dai, L.-Y.; Li, C.-J. *Can. J. Chem.* **2012**, 90, 92-99.
60. Yu, M.; Wang, Y.; Li, C.-J. Yao, X. *Tetrahedron Lett.* **2009**, 50, 6791-6794.
61. (a) Ohno, H.; Ohta, Y.; Oishi, S.; Fujii, N. *Angew. Chem. Int. Ed.* **2007**, 46, 2295-2298. (b) Suzuki, Y.; Ohta, Y.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, 74, 4246-4251. (c) Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, 10, 3535-3538.
62. Hou, Z.; Oishi, S.; Suzuki, Y.; Kure, T.; Nakanishi, I.; Hirasawa, A.; Tsujimoto, G.; Ohno, H.; Fujii, N. *Org. Biomol. Chem.* **2013**, 11, 3288-3296.
63. Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron Lett.* **2001**, 42, 6049-6051.
64. Yoo, W.-J.; Li, C.-J. *Adv. Synth. Catal.* **2008**, 350, 1503-1506.
65. Ohta, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2008**, 835-837.
66. Bonfielda, E. R.; Li, C.-J. *Adv. Synth. Catal.* **2008**, 350, 370-374.
67. Bariwal, J. B.; Ermolat'ev, D. S.; Glasnov, T. N.; Hecke, K. V.; Mehta, V. P.; Meervelt, L. V.; Kappe, C. O.; Van der Eycken, E. V. *Org. Lett.* **2010**, 12, 2774-2777.

CHAPTER 2

Regioselective One-Pot, Three-Component Synthesis of Substituted 2*H*-Indazoles from 2-Nitroarylaldehyde, Alkyne and Amine Catalyzed by CuBr/Zn(OTf)₂ System

2.1. Introduction

Indazoles are one of the important classes of nitrogen heterocycles found rarely in nature and have a significant biological importance in the medicinal chemistry.¹ Indazoles are bioisosteres of indoles and benzimidazoles in pharmaceutical chemistry.² Prof. Emil Fischer³ stated that the molecular structure of indazole resembles “pyrazole ring condensed with benzene ring.” This 10 π -electron containing heteroaromatic molecule, indazole exist in three tautomeric forms. They are 1*H*-indazole **1a**, 2*H*-indazole **1b** and 3*H*-indazole **1c** as shown in Figure 2.1.1. In majority of cases, 1*H*-indazoles **1a** are more stable compared to 2*H*-indazole **1b** by approximately 2-4 kcal/mol, and only a handful of examples of 3*H*-indazoles **1c** have been reported in the literature so far.^{1b,2}

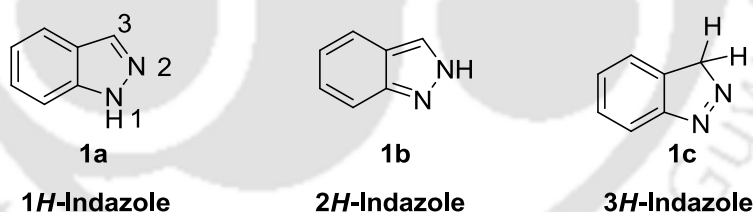


Figure 2.1.1. The tautomers of indazole

Out of these three isomers the chemistry of 1*H*-indazole is well explored than others.^{1b} Besides that, the chemistry of 2*H*-indazoles is also has been gradually established due to their high importance in biological as well as medicinal chemistry. Recently, a few of the 2*H*-indazole derivatives are clinically approved for the treatment various deceases.

2.2. Biological importance of 2*H*-indazoles

Over the years, 2*H*-indazoles are gaining considerable interest due to their presence in imidazole I₂ receptors,⁴ 5-HT_{1A} receptors⁵ and antiangiogenic active compounds.⁶ Moreover,

recent studies illustrate that few of the 2*H*-indazole core skeleton based scaffolds have been used for the development of new chemotherapeutic agents. For example, pazopanib (**2**) is a commercial drug and marketed under the brand name “Votrient,” contains a 2*H*-indazole nucleus (shown in *Figure 2.2.1*). Pazopanib (**2**) is a potent vascular endothelial growth factor (VEGF) receptor inhibitor under clinical development for renal-cell cancer and other solid tumors.⁷ Similarly, a poly (ADP-ribose) polymerase inhibitor “Niraparib” (**3**) originally named as MK-4827 displays antiproliferation activity against BRCA-deficient cancer cells.⁸ Compound **4** i.e. 3-chloro-2-(4-hydroxyphenyl)-2*H*-indazol-5-ol act as the selective ligand for Estrogen receptor β .⁹ 2*H*-Indazole core skeleton having compound **5** act as glucokinase activators for the treatment of type 2 diabetes mellitus.¹⁰ Compound **6** displays neuroprotective voltage-dependent sodium channel modulator, oxadiazolylindazole.¹¹

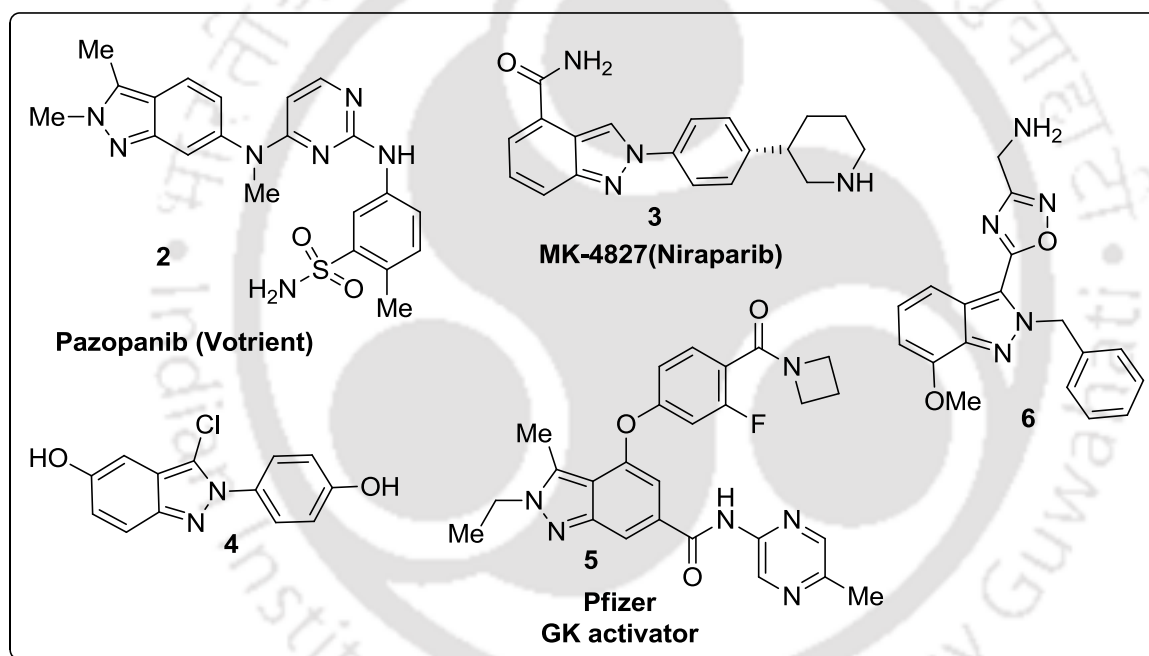


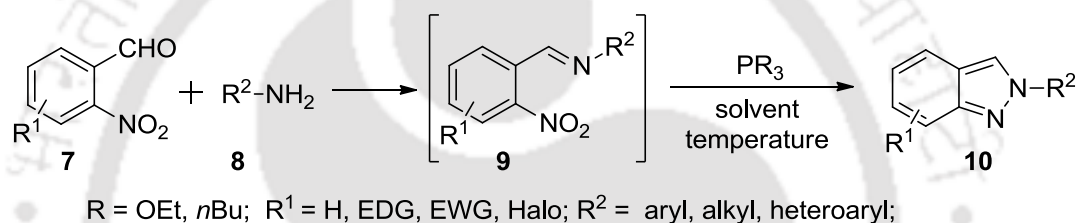
Figure 2.2.1. Some biologically active 2*H*-indazole derivatives

2.3. Literature methods for synthesis of 2*H*-indazoles

Several methods have been employed for the synthesis of indazoles for last two decades using various retro-synthetic routes. However, most of them are restricted to the thermodynamically favoured either 1*H*-indazole exclusively or mixtures of 1*H*- and 2*H*-indazoles.¹² Even though, a few reports are available in literature for the regioselective synthesis of 2*H*-indazole derivatives and some of them are discussed below.

2.3.1. Synthesis of 2H-indazoles from 2-nitroarylaldehydes

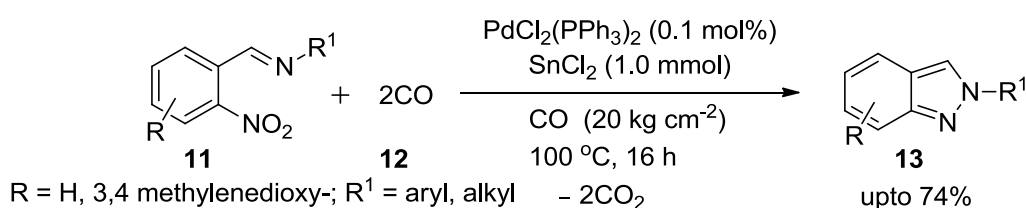
Cadogan and Mackie^{13a} in 1968 reported a direct approach for the synthesis of 2-aryl-2H-indazoles **10** via reductive cyclization of 2-nitrobenzaldimines **9** in the presence of triethyl phosphite at high temperatures in good yields. 2-Nitrobenzaldimines **9** are obtained from the condensation of 2-nitrobenzaldehydes **7** and primary amines **8**. After several years, the same reaction was reinvestigated by Bose and coworkers^{13b} using microwave-assisted conditions. The major advantages of this method were to avoid conventional heating process and reduce the prolonged time of reaction. Similarly, Aspnes and coworkers^{13c} reported a tri-*n*-butylphosphine mediated condensation-Cadogan reductive cyclization of 2-nitrobenzaldehydes **7** and amines **8** under mild reaction conditions to afford 2H-indazoles **10** in 25-87% yields (Scheme 2.3.1.1).



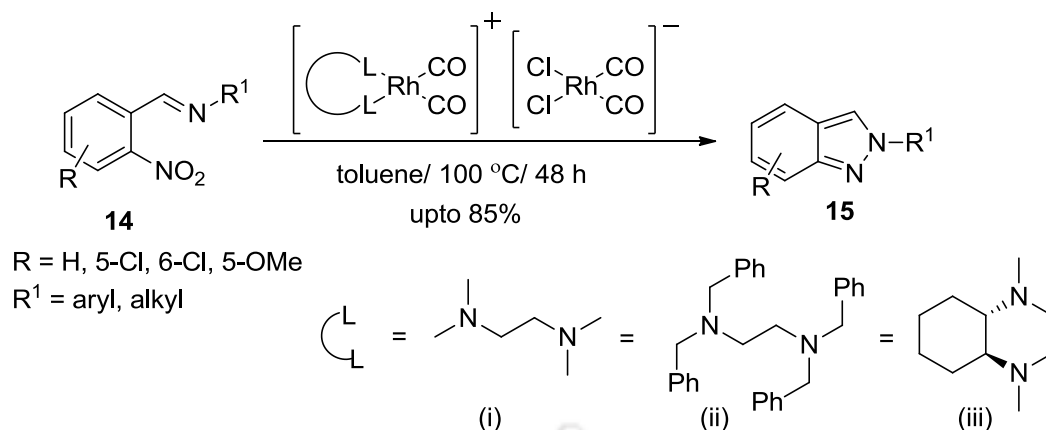
Ref No.	Reaction conditions	Yield (%)
13a	P(OEt) ₃ , 150 °C, 8 h	67-78%
13b	P(OEt) ₃ , MW, 10 min.	60-65%
13c	P(<i>n</i> -Bu) ₃ , <i>i</i> PrOH, 80 °C, 16 h	25-87%

Scheme 2.3.1.1.

Watanabe and coworkers described a novel synthesis of 2H-indazoles **13** starting from 2-nitrobenzylidenes **11** via a palladium catalyzed followed by tin(II) chloride promoted reductive *N*-heterocyclization under 20 kg cm⁻² of initial CO pressure at 100 °C (Scheme 2.3.1.2).^{14a} In continuation, Alper and coworkers established a similar approach for the synthesis of 2H-indazoles **15** with the catalytic amount of ionic diamine rhodium complexes at 100 °C in toluene as solvent (Scheme 2.3.1.3).^{14b}

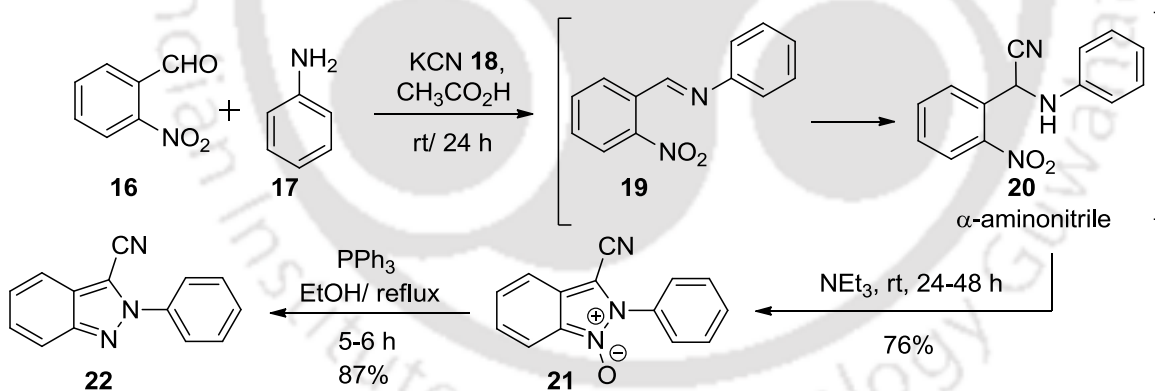


Scheme 2.3.1.2.



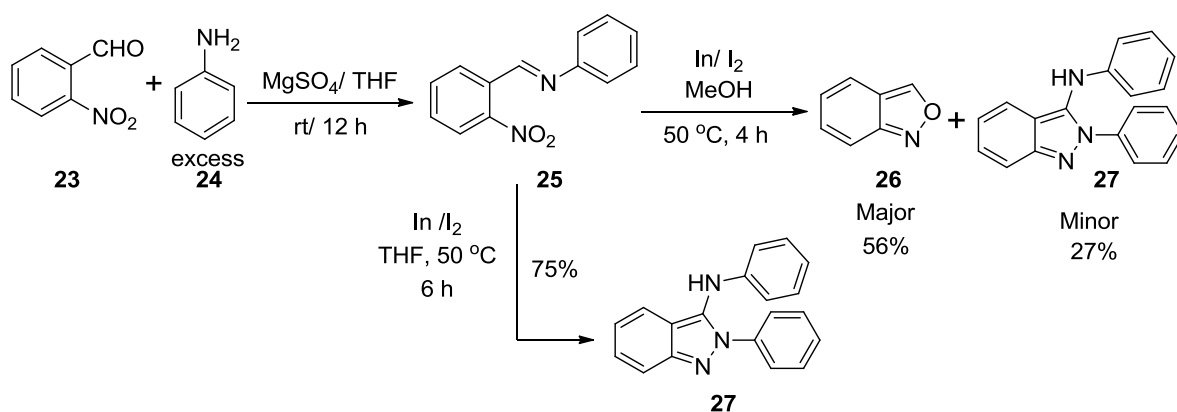
Scheme 2.3.1.3.

Gerpe and coworkers developed a multistep reaction for the synthesis of 3-Cyano-2*H*-indazole in good yields. The reaction sequence started with an acid mediated nucleophilic attack of cyanide **18** on imine **19** to give α -aminonitrile intermediate **20**. This was further treated with NEt_3 to give 3-cyano-2*H*-indazole *N*¹-oxide **21** in 76% yield. The resulting compound **21** was reduced to 2*H*-indazole **22** by using triphenylphosphine in ethanol under refluxing conditions (Scheme 2.3.1.4).¹⁵



Scheme 2.3.1.4.

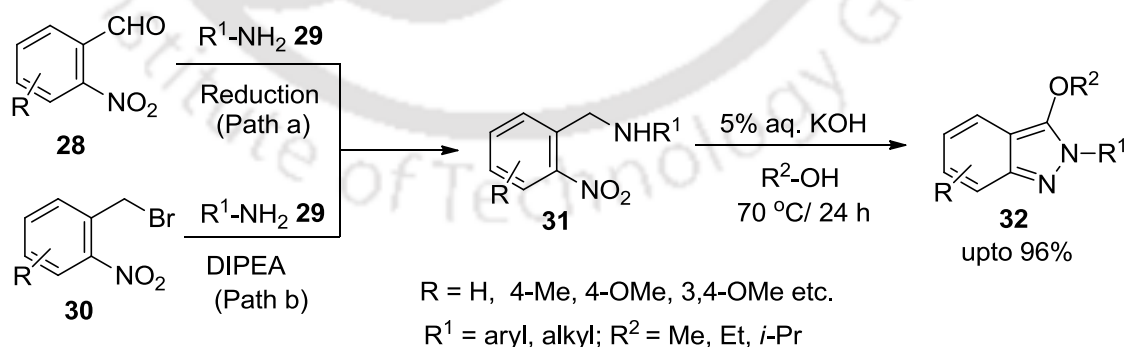
Kim and coworkers reported a facile the synthesis of 3-anilino-2-aryl-2*H*-indazole (**27**) via indium-iodine promoted reductive *N*-heterocyclization of aldimine **25** derived from 2-nitroarylaldehyde **23** with excess aniline **24** at 50 °C. Solvent plays a key role in this reaction for the formation of final products. When the reaction was performed in protic solvent like MeOH, a mixture of products **26** and **27** were obtained in 56% and 27% yield. Whereas, the use of aprotic solvent furnished 3-anilino-2-aryl-2*H*-indazole **27**, exclusively in 75% yield (Scheme 2.3.1.5).¹⁶



Scheme 2.3.1.5.

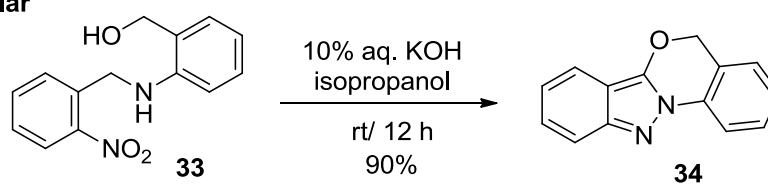
Kurth and coworkers demonstrated a mild efficient approach for the synthesis of 3-alkoxy-2H-indazoles **32** (Scheme 2.3.1.6).^{17a} 2-Nitrobenzylamines **31** were subjected to treatment with aqueous KOH in alcoholic solvents (like methanol, ethanol and isopropanol) at 70°C to afford 3-alkoxy-2H-indazoles **32** in excellent yields. The mechanism of the reaction shows that alcoholic solvents itself act as nucleophiles in this reaction. Later on, the same strategy was applied to an intramolecular version of the reaction using 10% of aqueous KOH/isopropanol at room temperature to form 5H-benzo[4,5][1,3]oxazino[3,2-b]indazole **34** in 90% yield (Scheme 2.3.1.7).^{17b} The corresponding 2-nitrobenzylamines derivatives **31/33** were prepared by using known procedures of aldimines reduction (path a) and/or *N*-benzylation of primary amines **29** with 2-nitrobenzyl bromides **30** (path b).

Intermolecular



Scheme 2.3.1.6.

Intramolecular

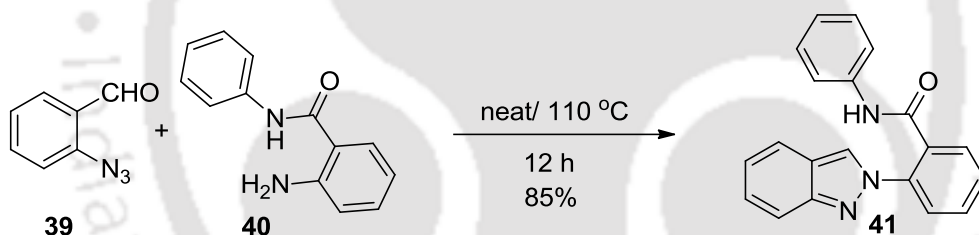
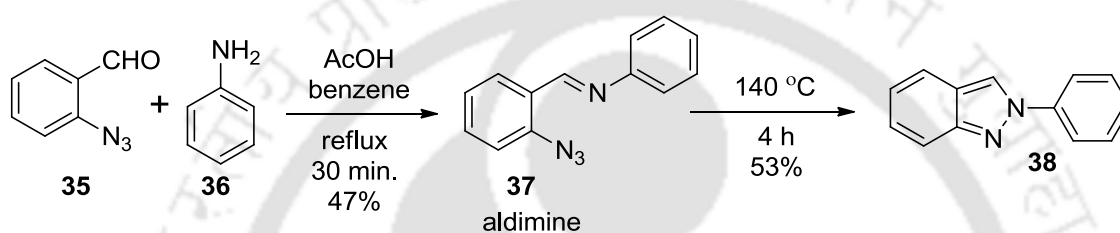


Scheme 2.3.1.7.

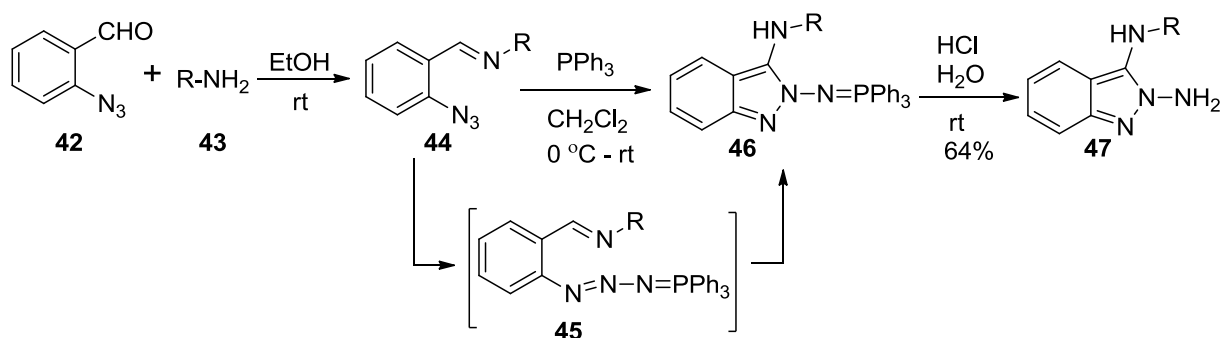
2.3.2. Synthesis of 2H-indazoles from 2-azidoarylaldehydes

In a similar way a few reports are showing the efficient synthesis of 3-substituted-2H-indazoles derived from 2-azidoarylaldehyde and primary amines using with different catalysts.

Dyall and coworkers described a straight forward approach for the synthesis of 2H-indazole **38** from pyrolysis of 2-azidoarylaldimine **37** in good yields. The aldimine **37** was obtained from condensation of 2-azidoarylaldehyde **35** and aniline **36** (Scheme 2.3.2.1).^{18a} Recently, Sharada and group modified the same approach with anthranilamide **40** for the synthesis of functionalized 2H-indazole **41** in 85% yield via solid state melt reaction at 110 °C (Scheme 2.3.2.2).^{18b}

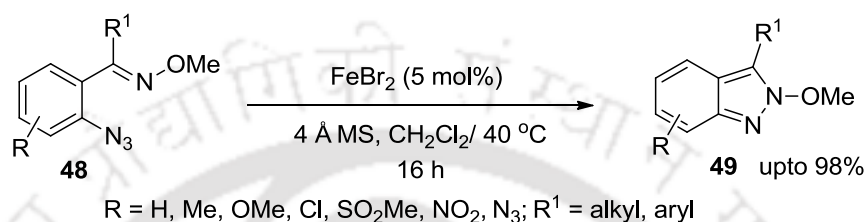


Molina and coworkers established a procedure for the synthesis of 2,3-diamino-2H-indazoles. Initially, 2-azidobenzaldimine **44** undergoes aza-wittig with triphenylphosphine and then subsequent cyclization of intermediate **45** in dichloromethane at 0 °C leads to a cyclic



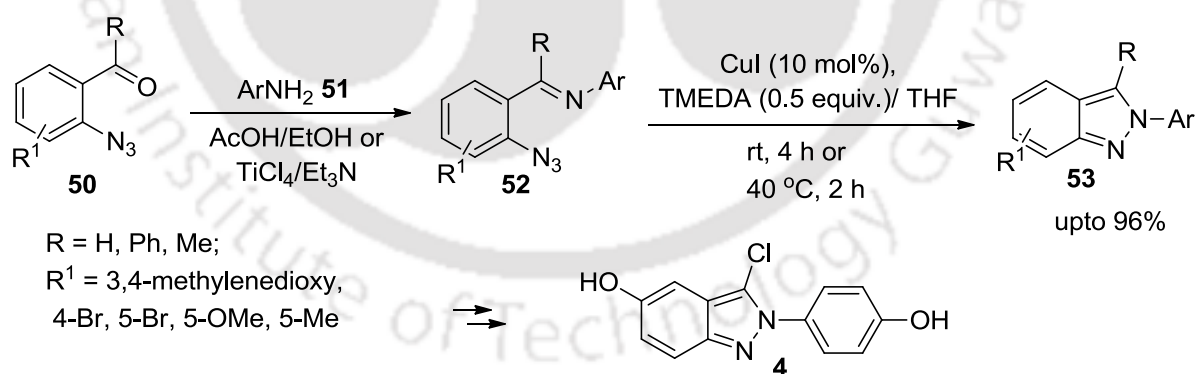
intermediate phosphazide **46**. The hydrolysis of phosphazide **46** forms the diamino substituted 2*H*-indazole **47** (Scheme 2.3.2.3).¹⁹

Driver and coworkers designed a mild and efficient reaction using 2-azidoketoximes **48** in presence of catalytic amount of iron(II) bromide for the synthesis of 3-substituted 2*H*-indazoles **49** in good yields via *N-N* bond formation. (Scheme 2.3.2.4).²⁰



Scheme 2.3.2.4.

A facile synthesis of substituted 2*H*-indazoles **53** has been employed by Rao and coworkers using copper-catalysed intramolecular amination of compound **52**, which was obtained from readily available starting materials such as 2-azidocarbonyl compounds **50** and arylamines **51** under mild reaction conditions (Scheme 2.3.2.5).²¹ This method was eventually utilized for the synthesis of a highly selective oestrogen receptor ligand **4** in three steps.

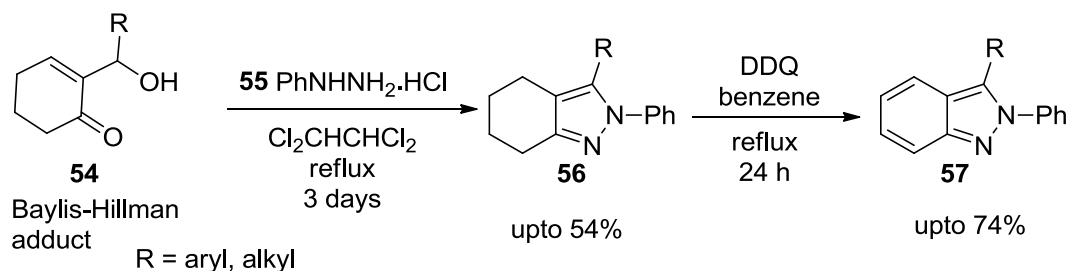


Scheme 2.3.2.5.

2.3.3. Other approaches for the synthesis of 2*N*,3*C*-substituted 2*H*-indazoles

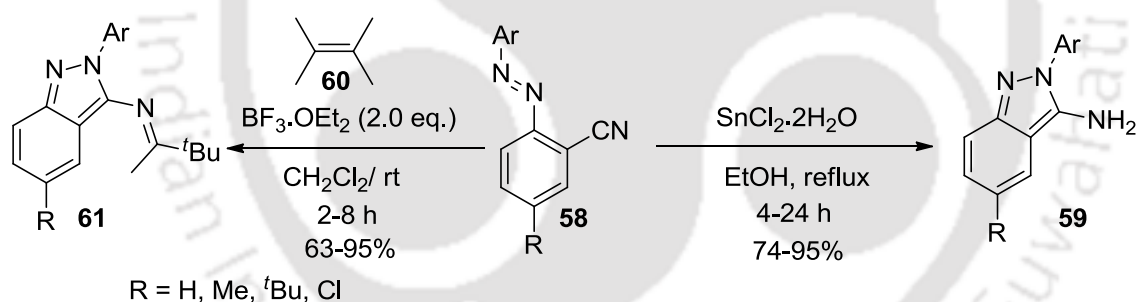
Kim and his group reported a two-step procedure for the synthesis of 3-substituted 2*H*-indazoles **57** from Baylis-Hillman adducts **54**. Condensation between 2-(hydroxymethyl)cyclohex-2-enone derivatives **54** and phenylhydrazene hydrochloride **55**

leads to form an intermediate **56**, which upon oxidation with DDQ afforded the desired products **57** in good yields (*Scheme 2.3.3.1*).²²



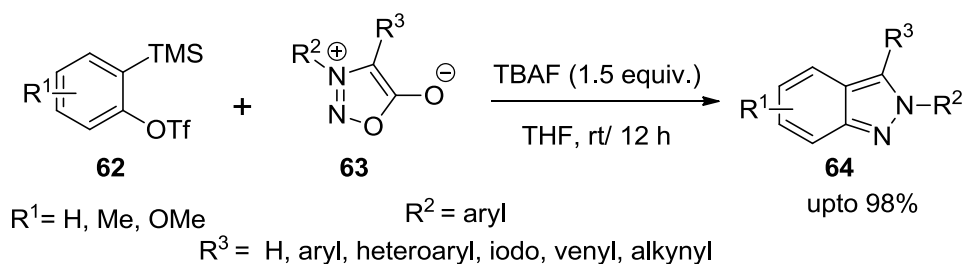
Scheme 2.3.3.1.

Haley and coworkers²³ have described a novel approach for the synthesis of 2-aryl-3-amino-2H-indazoles **59** in good to excellent yields via SnCl₂·2H₂O promoted intramolecular cyclization reaction of 2-(argiodiazenyl)benzonitrile **58**. In addition the cyclization 2-(argiodiazenyl) benzonitriles **58** were trapped with 2,3-dimethyl-2-butene **60** to form 2-aryl-3-imino-2H-indazoles **61** in presence of strong Lewis acid like BF₃·Et₂O (*Scheme 2.3.3.2*).



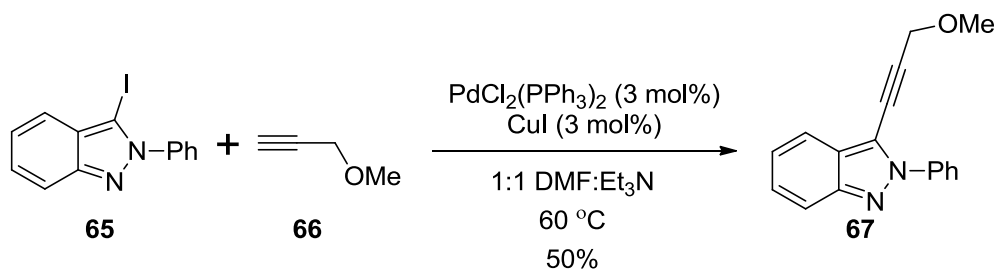
Scheme 2.3.3.2.

Shi group demonstrated the regioselective synthesis of 2H-indazoles **64** via [3+2] dipolar cycloaddition of various substituted sydnones **63** with silylaryl triflates **62** under metal free reaction conditions in moderate to excellent yields (*Scheme 2.3.3.3*).^{24a}



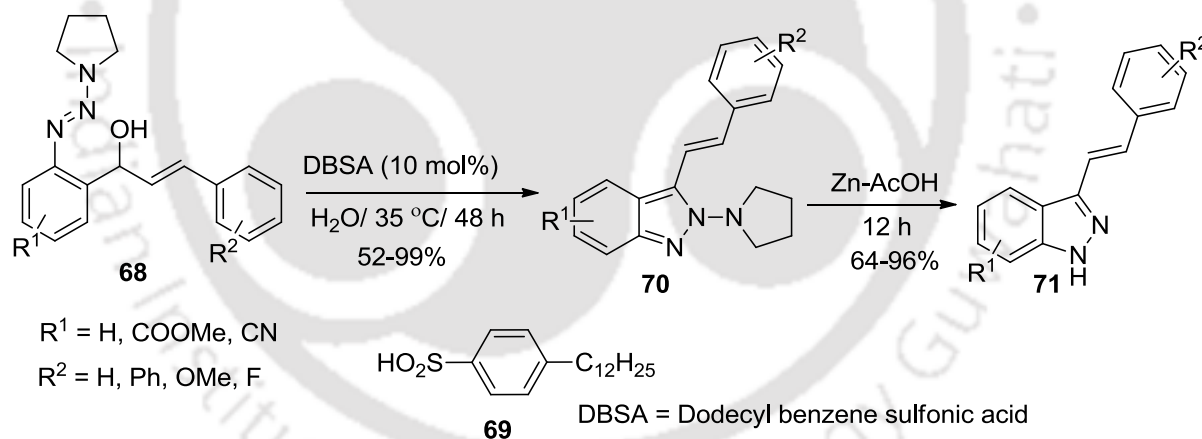
Scheme 2.3.3.3.

Further, by the same group 3-iodo-2*H*-indazole **65** was converted to 3-alkynyl-2*H*-indazole **67** in 50% yields using Sonogashira reaction conditions (Scheme 2.3.3.4).^{24b}



Scheme 2.3.3.4.

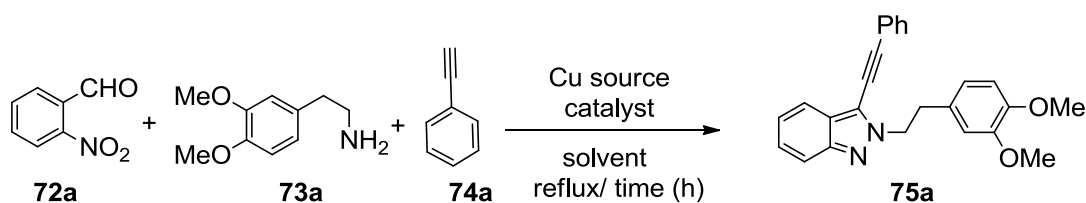
Brønsted acid catalyzed stereoselective synthesis of *trans*-3-alkenyl-2*H*-indazoles **70** has been reported by Ren and coworkers. Triazenylaryl allylic alcohols **68** were treated with 10 mol% DBSA **69** in water to afford *trans*-3-alkenyl-2*H*-indazoles **70**. Additionally, the compound **70** was converted to 1*H*-Indazoles **71** by the cleavage of *N-N* bond when treated with Zn-AcOH at ambient temperature (Scheme 2.3.3.5).²⁵



Scheme 2.3.3.5.

2.4. Results and discussions

Despite the existence of several synthetic routes to 2*H*-indazoles in the literature,^{1b,26} the direct methods for the synthesis of 2*N*,3*C*-substituted 2*H*-indazoles are rare and challenging to organic chemists. These reported methods mainly suffer with drawbacks, such as, multistep synthesis,²⁷ and low selectivity.²⁸ This chapter describes, the regioselective synthesis of 3-alkynyl-2*H*-indazole derivatives *via* copper(I) bromide/zinc(II) triflate catalyzed one-pot, three component reaction using 2-nitroarylaldehydes, alkynes and amines as starting materials.

Table 2.4.1. Optimization of the reaction^a

Entry	Cu source (mol%)	Catalyst (mol%)	Solvent	Time (h)	Yield (%) ^b
1	CuBr (30)	In(OTf) ₃ (10)	toluene	21	40
2	CuBr (30)	Sn(OTf) ₂ (10)	toluene	24	50
3	CuBr (30)	Zn(OTf)₂ (10)	toluene	18	83
4	CuBr (100)	Zn(OTf) ₂ (10)	toluene	18	80
5	CuBr (30)	Bi(OTf) ₂ (10)	toluene	24	35
6	CuBr (30)	Ag(OTf) (10)	toluene	24	37
7	CuBr (30)	Sc(OTf) ₂ (10)	toluene	24	32
8	CuBr (30)	FeCl ₃ (100)	toluene	24	33
9	CuBr (30)	ZnCl ₂ (100)	toluene	24	32
10	CuBr (30)	SnCl ₂ ·2H ₂ O (100)	toluene	24	36
11	CuBr (30)	InCl ₃ (10)	1,4-dioxane	24	12
12	CuBr (30)	P(Ph) ₃ (100)	toluene	24	-- ^c
13	CuBr (30)	P(OEt) ₃ (100)	toluene	24	17
14	CuBr (30)	Zn(OTf) ₂ (10)	1,4-dioxane	24	-- ^c
15	--	Zn(OTf) ₂ (10)	toluene	24	-- ^c
16	CuBr (30)	--	toluene	36	28
17	CuI (30)	Zn(OTf) ₂ (10)	toluene	24	28
18	CuCl (30)	Zn(OTf) ₂ (10)	toluene	24	63

^aReaction conditions: Aldehyde **72a** (0.5 mmol), Amine **73a** (0.5 mmol), Alkyne **74a** (1.0 mmol), Solvent (8 mL). ^bRefers to isolated yield. ^cCorresponding imine was isolated.

Initially 2-nitrobenzaldehyde **72a**, 2-(3,4-dimethoxyphenyl) ethanamine **73a** and ethynylbenzene **74a** were treated with CuBr (30 mol%) and In(OTf)₃ (10 mol%) in dry toluene at reflux conditions and it led to the formation of 2-(3,4-dimethoxyphenethyl)-3-(phenylethynyl)-2H-indazole **75a** in 40% yield (Table 2.4.1; entry 1). Similarly, under the same reaction conditions Sn(OTf)₂ gave 50% yield (entry 2). Zn(OTf)₂ was found to be more

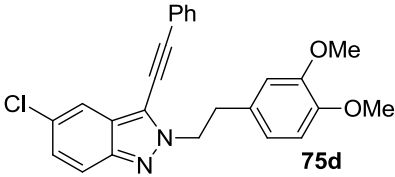
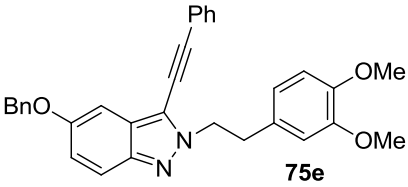
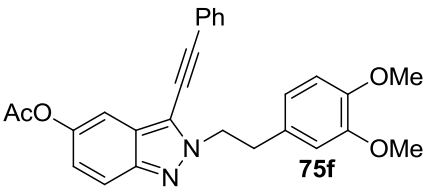
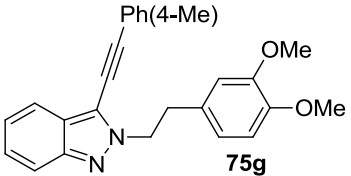
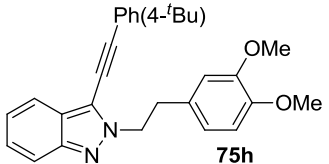
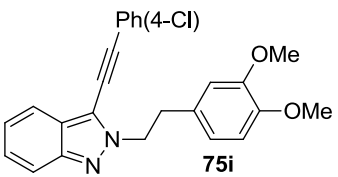
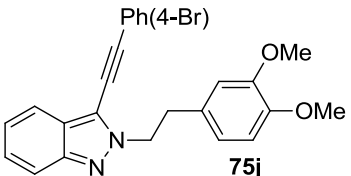
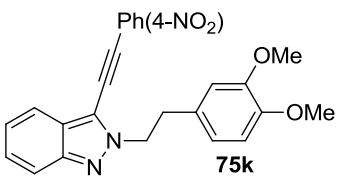
reactive and yielded 83% (entry 3). When the amount of CuBr was increased to 1.0 equivalent 80% of the product was formed (entry 4). Other Lewis acids and copper salts were also screened and the results were shown in *Table 2.4.1*. It was observed that bismuth, scandium and silver triflates gave lower yields (entries 5-7). Other metal salts such as FeCl₃, ZnCl₂, SnCl₂·2H₂O and InCl₃ were also found to be less effective in this reaction (entries 8-11). In the case of phosphorous reagents, PPh₃ produced only imine (entry 12), whereas P(OEt)₃ gave 17% of the desired product (entry 13). Reaction with CuBr/Zn(OTf)₂ in 1,4-dioxane (entry 14) and Zn(OTf)₂ (entry 15) alone in toluene gave the corresponding imines. Whereas, CuBr alone gave trace amount of the desired product (entry 16). Other copper salts such as CuI and CuCl gave the resultant product in 28% and 63% yields, respectively (entries 17-18).

With the established optimal conditions in hand, the scope of this reaction was investigated, and the results are summarised in *Table 2.4.2*.

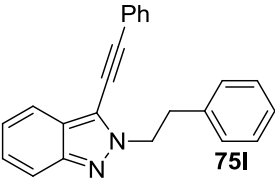
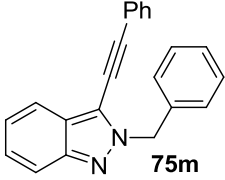
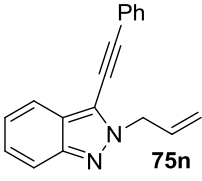
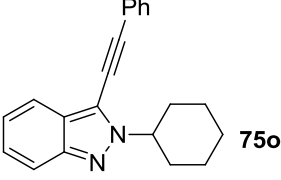
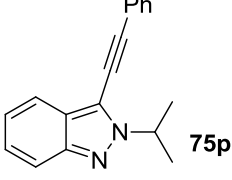
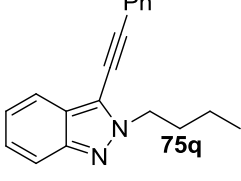
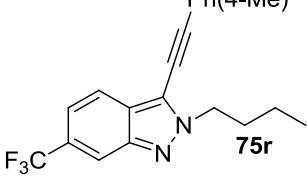
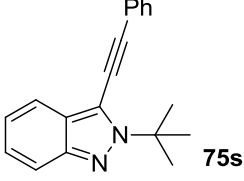
Table 2.4.2. Substrates scope of the reaction

Entry	Product (75)	Time (h)	Yield (%) ^a
1	 75a	18	83
2	 75b	24	57
3	 75c	36	79

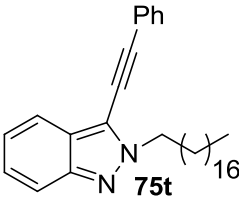
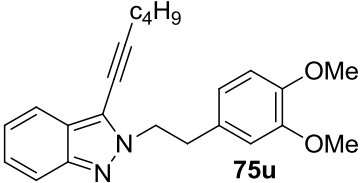
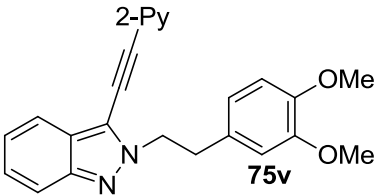
Continuation....

Entry	Product (75)	Time (h)	Yield (%) ^a
4	 75d	48	71
5	 75e	48	30
6	 75f	48	35
7	 75g	36	60
8	 75h	48	57
9	 75i	36	62
10	 75j	36	65
11	 75k	24	81

Continuation....

Entry	Product (75)	Time (h)	Yield (%) ^a
12	 75l	48	78
13	 75m	36	48
14	 75n	24	59
15	 75o	24	66
16	 75p	24	66
17	 75q	24	70
18	 75r	30	60
19	 75s	24	51

Continuation....

Entry	Product (75)	Time (h)	Yield (%) ^a
20		24	56
21		72	0 ^b
22		72	0 ^c

^aIsolated yield. ^bImine was isolated in 90% yield. ^cImine was isolated in 85% yield.

2-Nitroarylaldehydes having electron-withdrawing groups were transformed into 2*H*-indazoles in 60-79% yields (Table 2.4.2; **75b-d**, **75r**). Similarly, acetylenes containing electron-withdrawing or electron-donating groups on the aromatic ring were produced the desired products in 57-81% yields (**75g-k**, **75r**). On the other hand, acetylene with alkyl side chain **75u** was failed to give the desired product, rather the corresponding imine was recovered in 90% yield. Similarly, heterocyclic alkyne **75v** also gave imine in 85% yield. The scope of the reaction was also extended to various substituted primary amines and obtained the products in moderate to good yields as depicted in Table 2.4.2. The reaction with aromatic amines under the same reaction conditions gave quinolines.²⁹

The reaction is highly regioselective and only 2*N*-substituted product could be obtained in high purity without any regioisomeric products as determined from ¹H and ¹³C NMR analysis of crude product. The structure of the compounds was further confirmed by X-ray analysis³⁰ of compound **75a** (Figure 2.4.1).

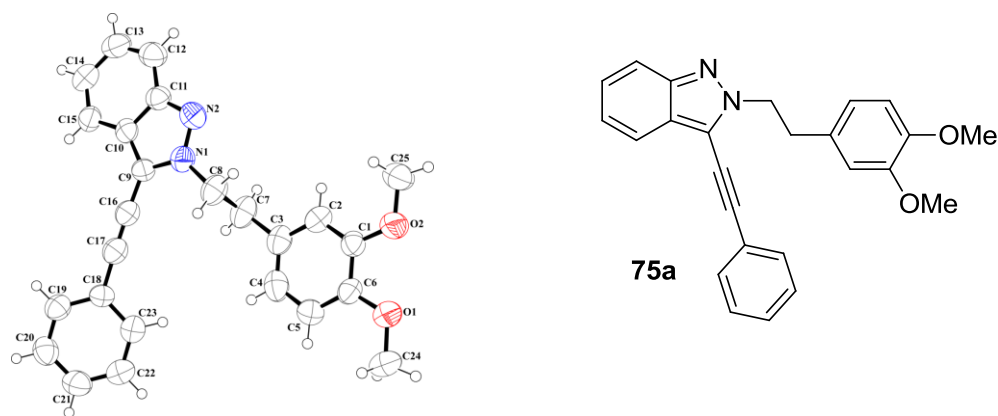


Figure 2.4.1. ORTEP diagram of compound 2-(3,4-dimethoxyphenethyl)-3-(phenylethynyl)-2H-indazole **75a**

Conclusions

In conclusion, we have developed a practical and general one-pot procedure for the synthesis of 2H-indazoles from *ortho*-nitroarylaldehydes, primary amines and alkynes catalyzed by CuBr and Zn(OTf)₂. This versatile one-pot, three-component procedure is a novel approach for the synthesis of highly substituted 2H-indazoles.

2.5. Experimental section

2.5.1. Instrumentation and characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. The solvents were of commercial grade and purified according to established procedures. Organic extracts were dried with anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. 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 open capillary tubes using a Büchi B-540 melting point apparatus and are uncorrected. Elemental analysis was performed with a Perkin-Elmer 2400 elemental analyzer. Fourier transform-infra red (FT-IR) spectra were recorded on Nicolet Impact-410 instrument either as neat liquid or KBr pellets. NMR spectra were recorded in CDCl₃ with tetramethylsilane as the internal standard for ¹H (400, 600 MHz) or ¹³C (75, 100, 150 MHz). HRMS spectra were recorded in ESI mode using Agilent Q-TOF mass spectrometer. Crystal Data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromatic MoK α radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections.

Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F^2 . All non-hydrogen atomic positions were located in different Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

2.5.2. General procedure for the synthesis of 3-(arylethynyl)-2*H*-indazoles (75):

To a mixture of CuBr (30 mol%), 2-nitrobenzaldehydes **72** (0.5 mmol), and Zn(OTf)₂ (10 mol%) in 3 mL of dry toluene, amines **73** (0.55 mmol) and alkynes **74** (1.0 mmol) were added by dissolving in 5 mL of toluene and the reaction mixture was refluxed for specified time. After completion of the reaction, the reaction was cooled; the solvent was removed under rotary evaporator, diluted with water and then extracted with ethyl acetate. The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over Na₂SO₄ and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding products **75**.

2.6. References:

1. (a) Schmidt, A. *Adv. Heterocycl. Chem.* **2003**, 85, 67-171. (b) Gaikwad, D. D.; Chapolikar, A. D.; Devkate, C. G.; Warad, K. D.; Tayade, A. P.; Pawar, R. P.; Dom A. *J. Eur. J. Med. Chem.* **2015**, 90, 707-731. (c) Shrivastava, A.; Chakraborty, A. K.; Upmanyu, N.; Singh, A. *Austin J Anal Pharm Chem.* **2016**, 4, 1076-1098. (d) Rosati, O.; Curini, M.; Marcotullio, M. C.; Macchiarulo, A.; Perfumi, M.; Mattioli, L.; Rismondob, F.; Cravotto, G. *Bioorg. Med. Chem.* **2007**, 15, 3463-3473. (e) Thangadurai, A.; Minu, M.; Wakode, S.; Agrawal, S.; Narasimhan, B. *Med Chem Res.* **2012**, 21, 1509-1523. (f) Uchiyama, N.; Shimokawa, Y.; Kikura-Hanajiri, R.; Demizu, Y.; Goda, Y.; Hakamatsuka, T. *Forensic Toxicol.* **2015**, 33, 244-259.
2. (a) Schmidt, A.; Beutler A.; Snovydyovych, B. *Eur. J. Org. Chem.* **2008**, 4073-4095. (b) Fludzinski, P.; Evrard, D. A.; Bloomquist, W. E.; Lacefield, W. B.; Pfeifer, W.; Jones, N. D.; Deeter, J. B.; Cohen, M. L. *J. Med. Chem.* **1987**, 30, 1535-1537.
3. Fischer, E. *Ber.* **1880**, 13, 679-682. (b) Fischer, E.; Kuzel. *Ann.* **1883**, 221, 261.
4. Saczewski, F.; Saczewski, J.; Hudson, A. L.; Tyacke, R. J.; Nutt, D. J.; Man, J.; Tabin, P. *Eur. J. Pharm. Sci.* **2003**, 52, 209-216.
5. (a) Andreonati, S.; Sava, V.; Makan, S.; Kolodeev, G. *Pharmazie.* **1999**, 54, 99-101. (b) Paluchowska, M. H.; Duszynska, B.; Klodzinska, A. Tatarzynska, E. *Pol. J. Pharmacol.* **2000**, 52, 209-216.
6. Huang, L.-J.; Shih, M.-L.; Chen, H.-S.; Pan, S.-L.; Teng, C.-M.; Lee F.-Y.; Kuo, S.-C. *Bioorg. Med. Chem.* **2006**, 14, 528-536.
7. Harris, P. A.; Boloor, A.; Cheung, M.; Kumar, R.; Crosby, R. M.; Davis-Ward, R. G.; Epperly, A. H.; Hinkle, K. W.; Hunter, R. N.; Johnson, J. H.; Knick, V. B.; Laudeman, C. P.; Luttrell, D. K.; Mook, R. A.; Nolte, R. T.; Rudolph, S. K.; Szewczyk, J. R.; Truesdale, A. T.; Veal, J. M.; Wang, L.; Stafford, J. A. *J. Med. Chem.* **2008**, 51, 4632-4640.
8. Jones, P.; Altamura, S; Boueres, J.; Ferrigno, F.; Fonsi, M.; Giomini, C.; Lamartina, S.; Monteagudo, E.; Ontoria, J. M.; Orsale, V. M.; Palumbi, M. C.; Pesci, S.; Roscilli, G.; Scarpelli, R.; Schultz-Fademrecht, C.; Toniatti C.; Rowley, M. *J. Med. Chem.* **2009**, 52, 170-7185.
9. Angelis, M. D.; Stossi, F.; Carlson, K. A.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2005**, 48, 1132-1144.
10. Pfeifferkorn, J. A.; Tu, M.; Filipski, K. J.; Guzman-Perez, A.; Bian, J.; Aspnes, G. E.; Sammons, M. F.; Song, W.; Li, J.-C.; Jones, C. S.; Patel, L.; Rasmusson, T.; Zeng, D;

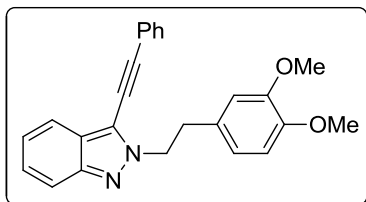
- Karki, K.; Hamilton, M.; Hank, R.; Atkinson, K.; Litchfield, J.; Aiello, R.; Baker, L.; Barucci, N.; Bourassa, P.; Bourbonnais, F.; D'Aquila, T.; Derksen, D. R.; MacDougall, M.; Robertson, A. *Bioorg. Med. Chem. Lett.* **2012**, 22, 7100-7105.
11. Clutterbuck, L. A.; Posada, C. G.; Visintin, C.; Riddal, D. R.; Lancaster, B.; Gane, P. J.; Garthwaite J.; Selwood, D. L. *J. Med. Chem.* **2009**, 52, 2694-2707.
12. (a) López-Alvarado, P.; Avendaño C.; Menendez, J. C. *J. Org. Chem.* **1995**, 60, 5678-5682. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, 39, 2941-2944. (c) Fedorov A. Y.; Finet, J.-P. *Tetrahedron Lett.* **1999**, 40, 2747-2748. (d) Slade, D. J.; Pelz, N. F.; Bodnar, W.; Lampe, J. W.; Watson, P. S. *J. Org. Chem.* **2009**, 74, 6331-6334.
13. (a) Cadogan, J. I. G.; Mackie, R. K. *Org. synth.* **1968**, 48, 113. (b) Varughese, D. J.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **2006**, 47, 6795-6797. (c) Gunung, N. E.; Wei, L.; Aspnes, G. E. *Org. Lett.* **2014**, 16, 3114-3117.
14. (a) Akazome, M., Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, 59, 3375-3380. (b) Okuro, K.; Gurnham, J.; Alper, H. *Tetrahedron Lett.* **2012**, 53, 620-622.
15. Gerpe, A.; Aguirre, G.; Boiani, L.; Cerecetto, H.; González, M.; Olea-Azar, C.; Rigol, C.; Maya, J. D.; Morello, A.; Piro, O. E.; Arán, V. J.; Azqueta, A.; de Ceráin, A. L.; Monge, A.; Rojas, M. A.; Yaluff, G. *Bioorg. Med. Chem.* **2006**, 14, 3467-3480.
16. Ahn, G. H.; Lee, J. J.; Jun, Y. M.; Lee, B. M.; Kim, B. H. *Org. Biomol. Chem.* **2007**, 5, 2472-2485.
17. (a) Mills, A. D.; Nazer, M. Z.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2006**, 71, 2687-2689. (b) Butler, J. D.; Solano, D. M.; Robins, L. I.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2008**, 73, 234-240. (c) Solano, D. M.; Butier, J. D.; Haddadin, M. J.; Kurth, M. J. *Org. Synth.* **2010**, 87, 339-349.
18. (a) Dyal L. K.; Holmes A.-L. *Aust. J. Chem.* **1988**, 41, 1677-1686. (b) Vidyacharan, S.; Adhikari, C.; Krishna, V. S.; Reshma, R. S.; Sriram, D.; Sharada D. S. *Bioorg. Med. Chem. Lett.* **2017**, 27, 1593-1597.
19. Molina, P.; Arques, A.; Vinader, M. V. *J. Org. Chem.* **1990**, 55, 4724-4731.
20. Stockes, B. J.; Vogel, C. V.; Urnezis, L. k.; Pan, M.; Driver, T. G. *Org. Lett.* **2010**, 12, 2884-2887.
21. Hu, J.; Cheng, Y.; Yang Y.; Rao, Y. *Chem. Commun.* **2011**, 47, 10133-10135.
22. Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2005**, 46, 5387-5391.
23. Shirtcliff, L. D.; Rivers, J.; Haley, M. M. *J. Org. Chem.* **2006**, 71, 6619-6622.

24. (a) Wu, C.; Fang, Y.; Larock, R. C.; Shi, F. *Org. Lett.* **2010**, *12*, 2234-2237. (b) Fang, Y.; Wu, C.; Larock, R. C.; Shi, F. *J. Org. Chem.* **2011**, *76*, 8840-8851.
25. Yang, W.; Yang, Z.; Xu, L.; Zhang, L.; Xu, X.; Miao, M.; Ren, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 14135-14139.
26. (a) Taher, A.; Ladwa, S.; Rajan, S. T.; Weaver, G. W. *Tetrahedron Lett.* **2000**, *41*, 9893-9897. (b) Song, J. J.; Yee, N. K. *Org. Lett.* **2000**, *2*, 519-521. (c) Kumar, M. R.; Park, A.; Park, N.; Lee, S. *Org. Lett.* **2011**, *13*, 3542-3545. (d) Haag, B.; Peng Z.; Knochel, P. *Org. Lett.* **2009**, *11*, 4270-4273.
27. (a) Halland, N.; Nazaré, M.; R'kyek, O.; Alonso, J.; Urmann, M.; Lindenschmidt, A. *Angew. Chem. Int. Ed.* **2005**, *48*, 6879-6882. (b) Mills, A. D.; Maloney, P.; Hassanein, E.; Haddadin, M. J.; Kurth, M. J. *J. Comb. Chem.* **2007**, *9*, 171-177. (c) Avila, B.; Solano, D. M.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2011**, *13*, 1060-1063. (d) Li, H.; Li, P.; Wang, L. *Org. Lett.* **2013**, *15*, 620-623. (e) Sudhapriya, N.; Nandakumara A.; Perumal P. T. *RSC Adv.* **2014**, *4*, 58476-58480.
28. (a) Lian, Y.; Bergman, R. G.; Lavis, L. D.; Ellman, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 7122-7125. (b) Hattori, H.; Yamaguchi, K.; Yamaguchi, J.; Itami, K. *Tetrahedron.* **2012**, *68*, 7605-7612.
29. Cao, K.; Zhang, F.-M.; Tu, Y.-Q.; Zhuo, X.-T. Fan, C.-A. *Chem. Eur. J.* **2009**, *15*, 6332-6334.
30. The crystallographic data for the compounds **75a** has been deposited with the Cambridge crystallographic data centre as supplementary publication nos. CCDC1008821.

2.7. Characterization data

2-(3,4-Dimethoxyphenethyl)-3-(phenylethynyl)-2H-indazole (75a):

Red solid; mp 118-120 °C; R_f (hexane/EtOAc 4:1) 0.52; yield 159 mg, 83%; $^1\text{H NMR}$ (400

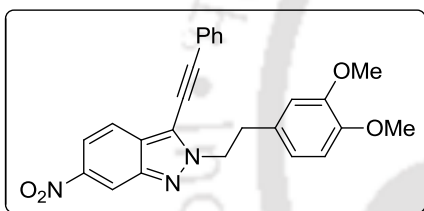


MHz, CDCl_3): δ 7.74 (t, $J = 9.2$ Hz, 2 H), 7.53 (s, 2 H), 7.40 (s, 3 H), 7.73 (t, $J = 7.6$ Hz, 1 H), 7.17 (t, $J = 7.2$ Hz, 1 H), 6.74 (s, 2 H), 6.43 (s, 1 H), 4.77 (t, $J = 6.8$ Hz, 2 H), 3.79 (s, 3 H), 3.56 (s, 3 H), 3.27 (t, $J = 6.8$ Hz, 2 H); $^{13}\text{C NMR}$ (100 MHz,

CDCl_3): δ 149.0, 148.2, 148.0, 131.6, 130.4, 129.2, 128.6, 126.7, 124.2, 122.8, 122.3, 120.9, 120.1, 119.1, 117.9, 112.0, 111.5, 100.3, 77.0, 55.9, 55.6, 53.6, 36.7; **IR** (KBr, neat) 2925, 2853, 1592, 1516, 1464, 1263, 1238, 1156, 1139, 1028, 751, 690 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{23}\text{N}_2\text{O}_2$ ($M + \text{H}$) $^+$ 383.1754, found 383.1761.

2-(3,4-Dimethoxyphenethyl)-6-nitro-3-(phenylethynyl)-2H-indazole (75b):

Yellow solid; mp 160-162 °C; R_f (hexane/EtOAc 7:3) 0.50; yield 160 mg, 75%; $^1\text{H NMR}$ (400

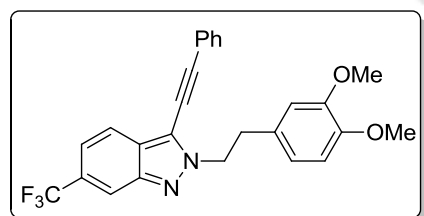


MHz, CDCl_3): δ 8.75 (s, 1 H), 7.98 (d, $J = 9.2$ Hz, 1 H), 7.84 (d, $J = 9.2$ Hz, 1 H), 7.55 (d, $J = 7.6$ Hz, 2 H), 7.43 (d, $J = 5.6$ Hz, 3 H), 6.75-6.69 (m, 2 H), 6.48 (s, 1 H), 4.84 (t, $J = 6.8$ Hz, 2 H), 3.80 (s, 3 H), 3.60 (s, 3 H), 3.31 (t, $J =$

7.2 Hz, 2 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 149.2, 148.3, 147.3, 146.3, 131.8, 129.9, 129.8, 128.9, 126.4, 121.7, 121.6, 121.0, 120.7, 116.7, 116.0, 112.0, 111.7, 101.5, 75.7, 56.1, 55.8, 54.4, 36.6; **IR** (KBr, neat) 2923, 1561, 1529, 1519, 1503, 1346, 1267, 1235, 1159, 1029, 837, 754 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{22}\text{N}_3\text{O}_4$ ($M + \text{H}$) $^+$ 428.1605, found 428.1613.

2-(3,4-Dimethoxyphenethyl)-3-(phenylethynyl)-6-(trifluoromethyl)-2H-indazole (75c):

Pale yellow solid; mp 94-96 °C; R_f (hexane/EtOAc 7:3) 0.55; yield 178 mg, 79%; $^1\text{H NMR}$

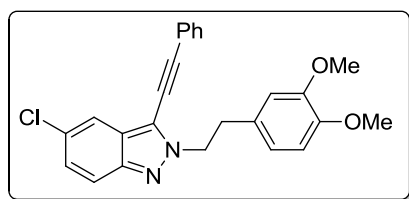


(400 MHz, CDCl_3): δ 8.08 (s, 1 H), 7.83 (d, $J = 8.4$ Hz, 1 H), 7.57-7.53 (m, 2 H), 7.42 (s, 3 H), 7.33 (d, $J = 8.4$ Hz, 1 H), 6.75-6.70 (m, 2 H), 6.45 (s, 1 H), 4.81 (t, $J = 6.8$ Hz, 2 H), 3.80 (s, 3 H), 3.58 (s, 3 H), 3.29 (t, $J = 6.8$ Hz, 2 H);

$^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 149.2, 148.2, 146.7, 131.7, 130.1, 129.6, 129.1 (q, $J = 33.0$ Hz), 128.8, 125.2, 124.6 (q, $J = 271.5$ Hz), 122.0, 121.5, 121.0, 120.0, 118.6, 116.5 (q, $J = 4.5$ Hz), 112.0, 111.6, 101.0, 76.2, 56.0, 55.7, 54.0, 36.7; $^{19}\text{F NMR}$ (376 MHz, $\text{C}_6\text{F}_6/\text{CDCl}_3$): δ 99.44; **IR** (KBr, neat) 2934, 2202, 1516, 1463, 1337, 1253, 1160, 1121, 1045, 808, 755, 688 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_2$ ($M + \text{H}$) $^+$ 451.1628, found 451.1628.

5-Chloro-2-(3,4-dimethoxyphenethyl)-3-(phenylethynyl)-2H-indazole (75d):

Pale yellow solid; mp 83-85 °C; R_f (hexane/EtOAc 4:1) 0.51; yield 148 mg, 71%; $^1\text{H NMR}$

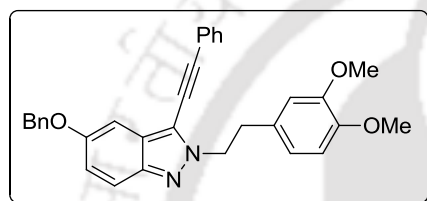


(400 MHz, CDCl_3): δ 7.71 (s, 1 H), 7.68 (d, $J = 9.2$ Hz, 1 H), 7.54-7.51 (m, 2 H), 7.43-7.39 (m, 3 H), 7.28-7.24 (m, 1 H), 6.75-6.69 (m, 2 H), 6.46 (s, 1 H), 4.75 (t, $J = 7.2$ Hz, 2 H), 3.80 (s, 3 H), 3.59 (s, 3 H), 3.27 (t, $J = 7.2$ Hz, 2 H); ^{13}C

NMR (100 MHz, CDCl_3): δ 149.5, 148.5, 146.9, 132.0, 130.5, 130.0, 129.8, 129.1, 128.4, 124.9, 122.4, 121.3, 119.8, 119.4, 119.3, 112.3, 112.0, 101.1, 76.7, 56.3, 56.0, 54.1, 37.0; **IR** (KBr, neat) 2932, 2834, 1515, 1463, 1327, 1263, 1237, 1157, 1028, 804, 756, 690 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{22}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 417.1364, found 417.1366.

5-(Benzyloxy)-2-(3,4-dimethoxyphenethyl)-3-(phenylethynyl)-2H-indazole (75e):

Pale yellow semisolid; R_f (hexane/EtOAc 4:1) 0.51; yield 73 mg, 30%; $^1\text{H NMR}$ (400 MHz,

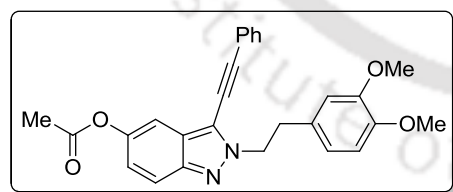


CDCl_3): δ 7.66 (d, $J = 9.2$ Hz, 1 H), 7.56-7.53 (m, 2 H), 7.49 (d, $J = 7.2$ Hz, 2 H), 7.43-7.34 (m, 6 H), 7.11 (d, $J = 8.8$ Hz, 1 H), 7.04 (s, 1 H), 6.75 (s, 2 H), 6.45 (s, 1 H), 5.11 (s, 2 H), 4.73 (t, $J = 7.6$ Hz, 2 H), 3.81 (s, 3 H), 3.58

(s, 3 H), 3.26 (t, $J = 7.2$ Hz, 2 H); $^{13}\text{C NMR}$ (150 MHz, DCI_3): δ 155.5, 149.2, 148.1, 145.0, 137.1, 131.7, 130.6, 129.2, 128.8, 128.7, 128.2, 127.9, 124.5, 122.6, 121.7, 121.0, 119.5, 118.4, 112.2, 111.6, 100.3, 98.3, 77.4, 70.6, 56.1, 55.7, 53.6, 36.8; **IR** (KBr, neat) 2925, 2850, 1633, 1516, 1464, 1262, 1236, 1189, 1027, 807, 756 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{32}\text{H}_{29}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 489.2173, found 489.2171.

2-(3,4-Dimethoxyphenethyl)-3-(phenylethynyl)-2H-indazol-5-yl acetate (75f):

Pale yellow semisolid; R_f (hexane/EtOAc 7:3) 0.54; yield 77 mg, 35%; $^1\text{H NMR}$ (400 MHz,

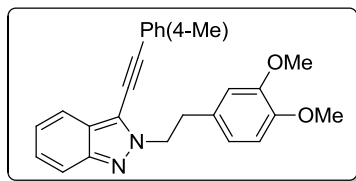


CDCl_3): δ 7.75 (d, $J = 9.2$ Hz, 1 H), 7.54-7.51 (m, 2 H), 7.45-7.38 (m, 4 H), 7.06 (d, $J = 8.8$ Hz, 1 H), 6.76-6.72 (m, 2 H), 6.48 (s, 1 H), 4.77 (t, $J = 7.2$ Hz, 2 H), 3.80 (s, 3 H), 3.61 (s, 3 H), 3.27 (t, $J = 7.6$ Hz, 2 H), 2.34 (s, 3

H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 170.1, 149.2, 148.2, 146.5, 146.4, 131.7, 130.3, 129.4, 128.8, 123.9, 122.8, 122.3, 121.0, 119.8, 119.3, 112.1, 111.6, 111.2, 100.8, 76.7, 56.1, 55.8, 53.9, 36.8, 21.3; **IR** (KBr, neat) 2921, 2851, 1757, 1655, 1516, 465, 1261, 1208, 1158, 1028, 806, 757, 668 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{27}\text{H}_{25}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 441.1809, found 441.1811.

2-(3,4-Dimethoxyphenethyl)-3-(p-tolylethynyl)-2H-indazole (75g):

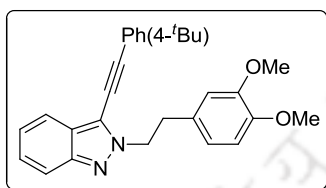
Red solid; mp 74-76 °C; R_f (hexane/EtOAc 4:1) 0.55; yield 119 mg, 60%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.72 (t, $J = 7.6$ Hz, 2 H), 7.41 (d, $J = 7.6$ Hz, 2 H), 7.31 (t, $J = 8.0$ Hz, 1 H), 7.19 (d, $J = 8.0$ Hz, 2 H), 7.14 (t, $J = 7.2$ Hz, 1 H), 6.73 (s, 2 H), 6.43 (s, 1 H), 4.75 (t, $J = 7.2$



Hz, 2 H), 3.79 (s, 3 H), 3.55 (s, 3 H), 3.25 (t, $J = 7.2$ Hz, 2 H), 2.39 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 149.1, 148.2, 148.0, 139.6, 131.6, 130.5, 129.5, 126.7, 124.1, 122.7, 121.0, 120.2, 119.4, 119.3, 117.9, 112.0, 111.5, 100.6, 76.4, 56.0, 55.7, 53.6, 36.7, 21.8; **IR** (KBr, neat) 2925, 2853, 1625, 1515, 1464, 1263, 1238, 1139, 1028, 815, 748 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 397.1911, found 397.1915.

3-((4-(*tert*-Butyl)phenyl)ethynyl)-2-(3,4-dimethoxyphenethyl)-2H-indazole (75h):

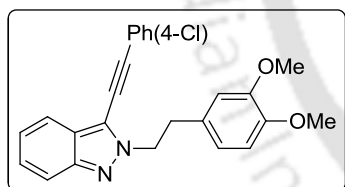
Pale yellow semisolid; R_f (hexane/EtOAc 4:1) 0.56; yield 125 mg, 57%; ^1H NMR (600 MHz,



CDCl_3): δ 7.76-7.71 (m, 2 H), 7.48 (d, $J = 7.8$ Hz, 2 H), 7.42 (d, $J = 7.8$ Hz, 2 H), 7.33 (t, $J = 7.8$ Hz, 1 H), 7.16 (t, $J = 7.2$ Hz, 1 H), 6.75 (s, 2 H), 6.48 (s, 1 H), 4.77 (t, $J = 7.8$ Hz, 2 H), 3.81 (s, 3 H), 3.58 (s, 3 H), 3.28 (t, $J = 7.2$ Hz, 2 H), 1.35 (s, 9 H); ^{13}C NMR (150 MHz, CDCl_3): δ 152.9, 149.2, 148.3, 148.1, 131.5, 130.5, 126.8, 125.8, 124.2, 122.8, 121.0, 120.2, 119.5, 119.5, 118.0, 112.1, 111.6, 100.7, 76.5, 56.1, 55.7, 53.7, 36.8, 35.2, 31.4 (3C); **IR** (KBr, neat) 2920, 1630, 1516, 1464, 1263, 1028, 747, 600 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{29}\text{H}_{31}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 439.2380, found 439.2385.

3-((4-Chlorophenyl)ethynyl)-2-(3,4-dimethoxyphenethyl)-2H-indazole (75i):

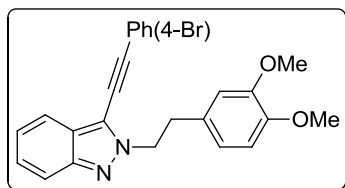
Colourless solid; mp 112-114 $^\circ\text{C}$; R_f (hexane/EtOAc 4:1) 0.52; yield 129 mg, 62%; ^1H NMR



(400 MHz, CDCl_3): δ 7.76 (d, $J = 9.2$ Hz, 1 H), 7.70 (d, $J = 8.4$ Hz, 1 H), 7.44 (d, $J = 8.8$ Hz, 2 H), 7.39-7.32 (m, 3 H), 7.17 (t, $J = 6.8$ Hz, 1 H), 6.75-6.70 (m, 2 H), 6.38 (s, 1 H), 4.76 (t, $J = 7.6$ Hz, 2 H), 3.80 (s, 3 H), 3.55 (s, 3 H), 3.27 (t, $J = 7.6$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 149.1, 148.4, 148.1, 135.4, 132.8, 130.5, 129.1 (2C), 126.9, 124.4, 123.1, 121.0, 120.9, 120.1, 118.1, 112.1, 111.6, 99.2, 78.1, 56.1, 55.7, 53.8, 36.8; **IR** (KBr, neat) 2916, 2844, 1633, 1516, 1468, 1263, 1027, 789, 748 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{22}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 417.1364, found 417.1364.

3-((4-Bromophenyl)ethynyl)-2-(3,4-dimethoxyphenethyl)-2H-indazole (75j):

Pale yellow semisolid; mp 104-106 $^\circ\text{C}$; R_f (hexane/EtOAc 4:1) 0.53; yield 150 mg, 65%; ^1H NMR

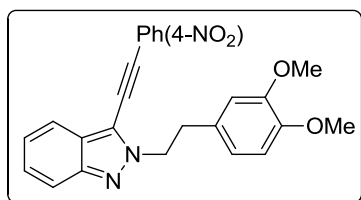


(400 MHz, CDCl_3): δ 7.76 (d, $J = 8.8$ Hz, 1 H), 7.70 (d, $J = 8.0$ Hz, 1 H), 7.53 (d, $J = 8.4$ Hz, 2 H), 7.38-7.31 (m, 3 H), 7.17 (t, $J = 7.2$ Hz, 1 H), 6.75-6.69 (m, 2 H), 6.38 (s, 1 H), 4.76 (t, $J = 7.2$ Hz, 2 H), 3.79 (s, 3 H), 3.55 (s, 3 H), 3.27 (t, $J = 7.6$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 149.1, 148.3, 148.1, 132.9, 132.0, 130.4, 126.8, 124.3, 123.6, 123.0, 121.3, 120.9, 120.0, 118.9, 118.1, 112.1, 111.6, 99.2, 78.2, 56.0, 55.7,

53.7, 36.7; **IR** (KBr, neat) 2932, 1624, 1515, 1463, 1263, 1139, 1010, 821, 747 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{22}\text{BrN}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 461.0859, found 461.0856.

2-(3,4-Dimethoxyphenethyl)-3-((4-nitrophenyl)ethynyl)-2H-indazole (75k):

Yellow solid; mp 154-156 °C; R_f (hexane/EtOAc 7:3) 0.55; yield 173 mg, 81%; **¹H NMR** (400

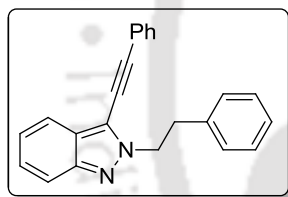


MHz, CDCl_3): δ 8.25 (d, J = 8.4 Hz, 2 H), 7.79 (d, J = 8.4 Hz, 1 H), 7.71 (d, J = 8.0 Hz, 1 H), 7.63 (d, J = 8.8 Hz, 2 H), 7.37 (t, J = 8.0 Hz, 1 H), 7.22 (t, J = 7.2 Hz, 1 H), 6.72 (s, 2 H), 6.33 (s, 1 H), 4.79 (t, J = 6.8 Hz, 2 H), 3.77 (s, 3 H), 3.53 (s, 3 H),

3.29 (t, J = 6.8 Hz, 2 H); **¹³C NMR** (100 MHz, CDCl_3): δ 149.1, 148.3, 148.2, 147.5, 133.6, 132.1, 130.3, 129.2, 127.0, 124.7, 123.9, 123.6, 120.9, 119.8, 118.3, 112.1, 111.5, 98.4, 82.2, 56.0, 55.7, 53.9, 36.7; **IR** (KBr, neat) 2927, 2851, 2202, 1592, 1516, 1463, 1342, 1262, 1238, 1140, 1107, 1028, 855, 748, cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{22}\text{N}_3\text{O}_4$ ($\text{M} + \text{H}$)⁺ 428.1605, found 428.1600.

2-Phenethyl-3-(phenylethynyl)-2H-indazole (75l):

Red solid; mp 70-72 °C; R_f (hexane/EtOAc 4:1) 0.60; yield 126 mg, 78%; **¹H NMR** (400



MHz, CDCl_3): δ 7.77-7.73 (m, 2 H), 7.58-7.54 (m, 2 H), 7.43-7.40 (m, 3 H), 7.36-7.16 (m, 7 H), 4.80 (t, J = 8.0 Hz, 2 H), 3.35 (t, J = 8.0 Hz, 2 H); **¹³C NMR** (100 MHz, CDCl_3): δ 148.3, 137.9, 131.7, 129.2, 129.0, 128.9, 128.8, 127.0, 126.7, 124.3, 122.9, 122.4, 120.1, 118.9,

118.1, 100.6, 77.1, 53.5, 37.2; **IR** (KBr, neat) 2926, 1518, 1493, 1464, 1364, 1283, 1076, 747, 689 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{23}\text{H}_{19}\text{N}_2$ ($\text{M} + \text{H}$)⁺ 323.1543, found 323.1550.

2-Benzyl-3-(phenylethynyl)-2H-indazole (75m):

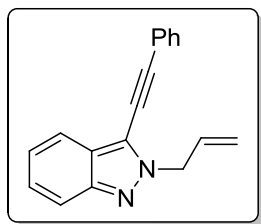
Colourless solid; mp 78-80 °C; R_f (hexane/EtOAc 9:1) 0.62; yield 74 mg,

48%; **¹H NMR** (400 MHz, CDCl_3): δ 7.76 (t, J = 7.6 Hz, 2 H), 7.58-7.54 (m, 2 H), 7.40-7.27 (m, 9 H), 7.19 (t, J = 7.6 Hz, 1 H), 5.76 (s, 2 H); **¹³C NMR** (100 MHz, CDCl_3): δ 148.4, 136.2, 131.7, 129.3, 129.0, 128.8,

128.7, 128.3, 128.2, 126.8, 124.7, 123.0, 122.4, 120.2, 118.3, 101.0, 77.5, 55.9; **IR** (KBr, neat) 2952, 2852, 1494, 1455, 1443, 1283, 1172, 1097, 748, 706, 689 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{22}\text{H}_{17}\text{N}_2$ ($\text{M} + \text{H}$)⁺ 309.1386, found 309.1396.

2-Allyl-3-(phenylethynyl)-2H-indazole (75n):

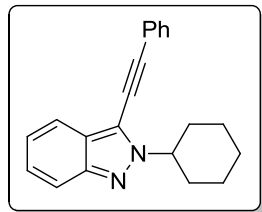
Pale yellow semi solid; R_f (hexane/EtOAc 9:1) 0.59; yield 76 mg, 59%; **¹H NMR** (400 MHz, CDCl_3): δ 7.77 (t, J = 8.4 Hz, 2 H), 7.61-7.58 (m, 2 H), 7.43-7.40 (m, 3 H), 7.35-7.31 (m, 1 H), 7.20-7.16 (m, 1 H), 6.19-6.09 (m, 1 H), 5.34-5.28 (m, 2 H), 5.21 (d, J = 6.0 Hz, 2 H); **¹³C**



NMR (150 MHz, CDCl_3): δ 148.4, 132.3, 131.7, 129.3, 128.8, 126.8, 124.7, 123.0, 122.5, 120.1, 119.2, 118.9, 118.3, 100.9, 77.2, 54.6; **IR** (KBr, neat) 2924, 2853, 1529, 1465, 1364, 1218, 1091, 927, 748, 689 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{18}\text{H}_{15}\text{N}_2$ ($\text{M} + \text{H}$)⁺ 259.1230, found 259.1236.

2-Cyclohexyl-3-(phenylethynyl)-2H-indazole (75o):

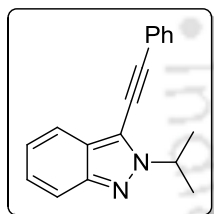
Pale yellow semi solid; R_f (hexane/EtOAc 9:1) 0.61; yield 99 mg, 66%; **¹H NMR** (400 MHz,



CDCl_3): δ 7.77 (d, $J = 8.8$ Hz, 2 H), 7.62-7.58 (m, 2 H), 7.45-7.39 (m, 3 H), 7.31 (t, $J = 8.0$ Hz, 1 H), 7.16 (t, $J = 8.0$ Hz, 1 H), 4.82-4.74 (m, 1 H), 2.22-2.12 (m, 4 H), 2.32-1.95 (m, 2 H), 1.82-1.76 (m, 1 H), 1.57-1.34 (m, 3 H); **¹³C NMR** (100 MHz, CDCl_3): δ 147.9, 131.6, 129.2,

129.0, 128.8, 126.4, 124.4, 122.7, 120.0, 118.2, 117.7, 100.8, 77.5, 61.4, 33.2, 25.9, 25.5; **IR** (KBr, neat) 2931, 2854, 1452, 1352, 1280, 1211, 1010, 746, 868 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{21}\text{H}_{21}\text{N}_2$ ($\text{M} + \text{H}$)⁺ 301.1699, found 301.1696.

2-Isopropyl-3-(phenylethynyl)-2H-indazole (75p):

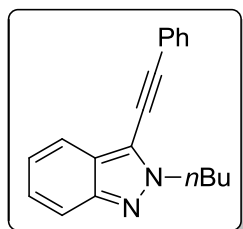


Pale yellow semi solid; R_f (hexane/ EtOAc 9:1) 0.62; yield 83 mg, 64%;

¹H NMR (600 MHz, CDCl_3): δ 7.80-7.77 (m, 2 H), 7.62 (t, $J = 4.2$ Hz, 2 H), 7.44-7.39 (m, 3 H), 7.33 (t, $J = 7.8$ Hz, 1 H), 7.18 (t, $J = 7.8$ Hz, 1 H), 5.26-5.20 (m, 1 H), 1.71 (d, $J = 7.2$ Hz, 6 H); **¹³C NMR** (150 MHz, CDCl_3): δ 147.9, 131.6, 129.2, 128.8, 126.4, 124.5, 122.7, 122.6, 120.0,

118.2, 117.6, 100.8, 77.3, 53.8, 22.9; **IR** (KBr, neat) 2923, 1641, 1459, 1347, 1276, 1235, 1082, 746, 689 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{18}\text{H}_{17}\text{N}_2$ ($\text{M} + \text{H}$)⁺ 261.1386, found 261.1389.

2-Butyl-3-(phenylethynyl)-2H-indazole (75q):



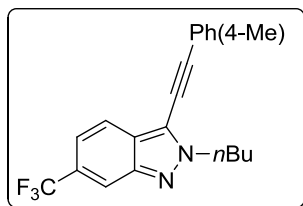
Pale yellow semi solid; R_f (hexane/EtOAc 9:1) 0.64; yield 96 mg, 70%;

¹H NMR (400 MHz, CDCl_3): δ 7.76 (t, $J = 9.6$ Hz, 2 H), 7.62-7.59 (m, 2 H), 7.43-7.40 (m, 3 H), 7.33 (t, $J = 7.2$ Hz, 1 H), 7.17 (t, $J = 7.2$ Hz, 1 H), 4.60 (t, $J = 7.6$ Hz, 2 H), 2.05 (t, $J = 7.2$ Hz, 2 H), 1.44-1.36 (m, 2 H), 0.98 (t, $J = 7.2$ Hz, 3 H); **¹³C NMR** (100 MHz, CDCl_3): δ 148.1,

131.6, 129.2, 128.8, 126.5, 124.4, 122.8, 122.5, 120.0, 118.8, 118.1, 100.6, 77.4, 51.8, 32.7, 20.1, 13.8; **IR** (KBr, neat) 2958, 2929, 2871, 2659, 2206, 2107, 1625, 1597, 1492, 1464, 1364, 1284, 1084, 746, 689 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{19}\text{H}_{19}\text{N}_2$ ($\text{M} + \text{H}$)⁺ 275.1543, found 275.1552.

2-Butyl-3-(p-tolyethynyl)-6-(trifluoromethyl)-2H-indazole (75r):

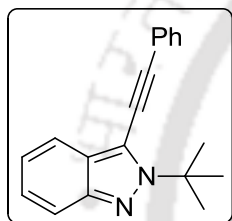
Pale yellow solid; mp 84-86 °C; R_f (hexane/EtOAc 9:1) 0.58; yield 107 mg, 60%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 8.06 (s, 1 H), 7.86 (d, $J = 8.4$ Hz, 1 H), 7.50 (d, $J = 7.8$ Hz, 2 H), 7.32



(d, $J = 9.0$ Hz, 1 H), 7.23 (d, $J = 7.8$ Hz, 2 H), 4.62 (t, $J = 7.2$ Hz, 2 H), 2.41 (s, 3 H), 2.05 (t, $J = 7.2$ Hz, 2 H), 1.43-1.38 (m, 2 H), 0.98 (t, $J = 7.2$ Hz, 3 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 146.6, 140.0, 131.7, 129.6, 128.7 (q, $J = 33.0$ Hz), 125.3, 124.7 (q, $J = 270.0$ Hz), 121.5, 119.8, 119.0, 118.4, 116.5 (q, $J = 4.5$ Hz), 101.5, 75.9, 52.2, 32.6, 21.8, 20.0, 13.8; $^{19}\text{F NMR}$ (376 MHz, $\text{C}_6\text{F}_6/\text{CDCl}_3$): δ 99.43; **IR** (KBr, neat) 2926, 1653, 1455, 1337, 1252, 1164, 1123, 1084, 1045, 809 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{21}\text{H}_{20}\text{F}_3\text{N}_2$ ($\text{M} + \text{H}$) $^+$ 357.1573, found 357.1572.

2-(*tert*-Butyl)-3-(phenylethynyl)-2H-indazole (75s):

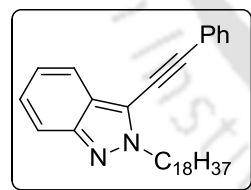
Pale yellow solid; mp 92-94 °C; R_f (hexane/EtOAc 9:1) 0.70; yield 70 mg, 51%; $^1\text{H NMR}$



(400 MHz, CDCl_3): δ 7.77 (d, $J = 8.4$ Hz, 2 H), 7.62-7.58 (m, 2 H), 7.44-7.39 (m, 3 H), 7.33-7.28 (m, 1 H), 7.17 (t, $J = 7.2$ Hz, 1 H), 1.97 (s, 9 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 146.3, 131.3, 129.1, 128.8, 128.7, 126.8, 126.3, 123.0, 122.8, 119.8, 118.4, 101.3, 79.5, 63.1, 30.1; **IR** (KBr, neat) 2925, 1653, 1456, 1369, 1343, 1261, 1205, 1028, 746, 688, 668 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{19}\text{H}_{19}\text{N}_2$ ($\text{M} + \text{H}$) $^+$ 275.1543, found 275.1544.

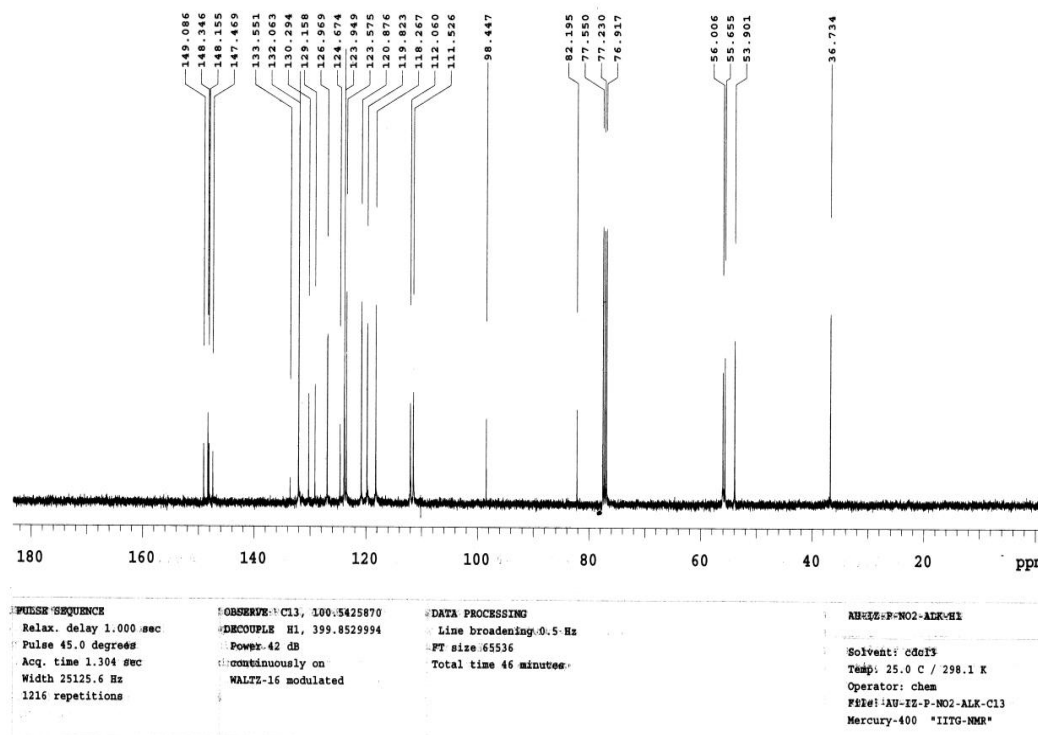
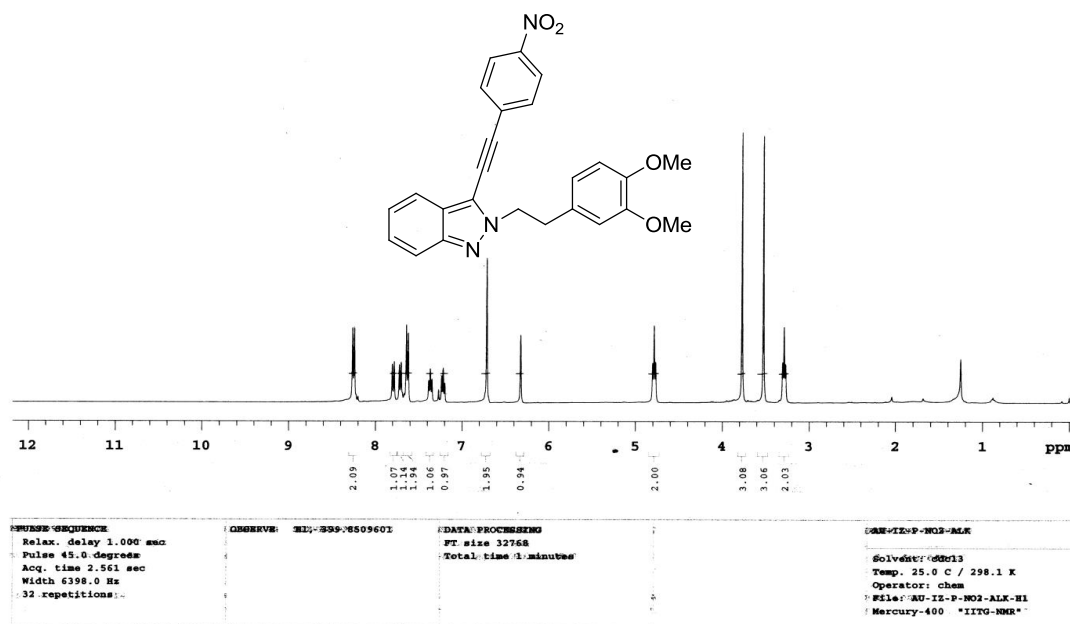
2-Octadecyl-3-(phenylethynyl)-2H-indazole (75t):

Pale yellow solid; mp 81-83 °C; R_f (hexane/EtOAc 9:1) 0.78; yield 132 mg, 56%; $^1\text{H NMR}$



(400 MHz, CDCl_3): δ 7.75 (t, $J = 9.2$ Hz, 2 H), 7.63-7.58 (m, 2 H), 7.43-7.39 (m, 3 H), 7.32 (t, $J = 8.0$ Hz, 1 H), 7.17 (t, $J = 7.6$ Hz, 1 H), 4.59 (t, $J = 6.8$ Hz, 2 H), 2.09-2.03 (m, 2 H), 1.37-1.21 (m, 30 H), 0.88 (t, $J = 7.2$ Hz, 3 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 148.1, 131.6, 129.2, 128.8, 126.5, 124.4, 122.8, 122.6, 120.1, 118.7, 118.1, 100.6, 77.4, 52.1, 32.1, 30.7, 29.9 (4C), 29.8 (3C), 29.8, 29.8, 29.7, 29.6, 29.3, 26.8, 22.9, 14.3; **IR** (KBr, neat) 2920, 2852, 2213, 1641, 1465, 1368, 1279, 1025, 745, 688 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{33}\text{H}_{47}\text{N}_2$ ($\text{M} + \text{H}$) $^+$ 471.3734, found 471.3721.

^1H and ^{13}C spectra of compound 2-(3,4-dimethoxyphenethyl)-3-((4-nitrophenyl)ethynyl)-
2H-indazole (75k)



2.9. Crystal parameters

The crystal parameters of compound **75a**

	CCDC1008821
Formula	C ₂₅ H ₂₂ N ₂ O ₂
Formula weight	382.45
<i>T</i> /K	296(2)
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
<i>a</i> /Å	5.1346(2)
<i>b</i> /Å	15.0120(4)
<i>c</i> /Å	26.4598(7)
<i>α</i> /°	90.00
<i>β</i> /°	90.00
<i>γ</i> /°	90.00
<i>V</i> /Å ³	2039.54(11)
<i>Z</i>	4
Abs. Coeff./mm ⁻¹	0.080
Abs. Correction	Multi-scan
GOF on <i>F</i> ²	1.299
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> 1 = 0.0335 <i>wR</i> 2 = 0.0707
<i>R</i> indices [all data]	<i>R</i> 1 = 0.0371 <i>wR</i> 2 = 0.0719

CHAPTER 3

Synthesis of Substituted Pyrazole *N*-Oxides and Pyrazoles from Propargylamines

3.1 Introduction

Synthesis of small molecules is often preferable to introduce new drug candidates with high biological evolution in medicinal chemistry.¹ Among all the small molecules, pyrazoles occupy prime position due their existence in many pharmaceutical and agrochemical substances.² Apart from these, pyrazoles are considered as an important class of nitrogen heterocyclic compounds due to their immense range of biological activities such as analgesic,³ antibacterial,⁴ antimicrobial,⁵ antiviral,⁶ antidepressant,⁷ antihypertensive⁸ and anticancer properties.⁹ The structure of the pyrazole is characterised with two nitrogen atoms placed at adjacent positions along with three carbon atoms in an aromatic five membered aza-heterocyclic ring system. They are the class of compounds with $C_3H_4N_2$ formula. The first natural pyrazole derivative 3-*n*-nonylpyrazole (**1**) was isolated in 1954 by Japanese researchers from *Houttuynia Cordata*, a plant of the “*piperaceae*” family from tropical Asia.¹⁰ They further observed its antimicrobial activity. Similarly another derivative 3-(1-pyrazolyl)-alanine (**2**) has been isolated from watermelon seeds (*Citrullus Vulgaris*).¹⁰

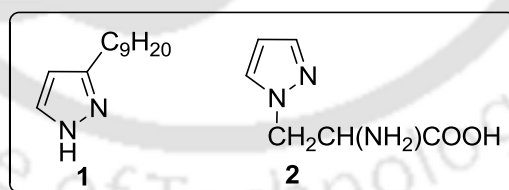


Figure 3.1.1. Natural pyrazole derivatives

In past decades, the basic skeleton having pyrazole ring engaged with significant number of blockbuster drug molecules as shown in Figure 3.1.2. For example, a well-known commercialized drug celecoxib (**3**) having pyrazole key unit was marketed with a brand name Celebrex. Celebrex act as selective inhibitors of cyclo-oxygenase-2 (COX-2) as well as shows anti-inflammatory, analgesic and antipyretic activities.¹¹ Similarly, Deracoxib (**4**) a well-known drug in veterinary medicine shows a non-steroidal anti-inflammatory properties of the coxib class.¹² Another pyrazole based drug Rimonabant (**5**) (marketed as Acomplia and

Zimulti), act as CB1 receptor and also used for the treatment of anorectic antiobesity until 2009.¹³ Likewise *N*-methyl-5-aryl substituted pyrazole derivative such as Tamangrel (**6**) recognized as APD791, is a novel high-affinity 5-HT_{2A} receptor antagonist.¹⁴ MK-0893 (**7**) having a pyrazole basic skeleton is a potent glucagon receptor inhibitor for treatment type II diabetes.¹⁵ Similarly, 1,3,5-trisubstituted pyrazole G4-1 (**8**) exhibits proteasome inhibitor properties.¹⁶ 3-Bromo substituted pyrazole frame-work nelotanserine (ADP-125) (**9**) displays a potent and highly selective inverse agonist of the 5HT_{2A} receptor.¹⁷ Some of the poly substituted pyrazole derivatives have been used as ligands in cross-coupling reactions.¹⁸

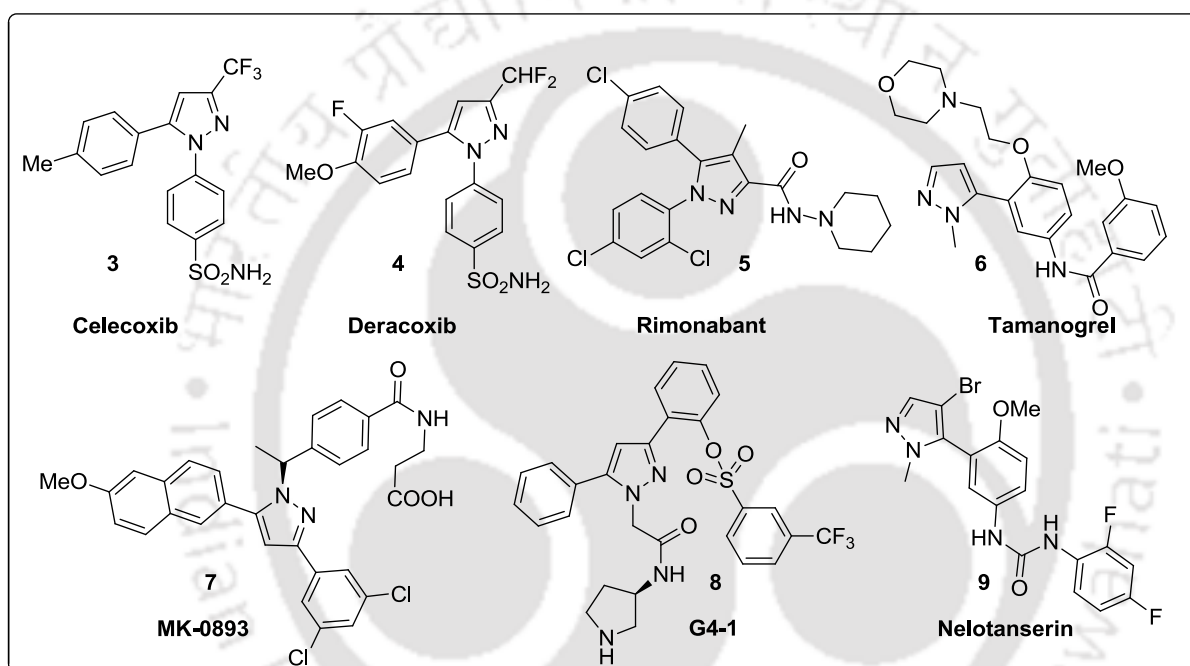


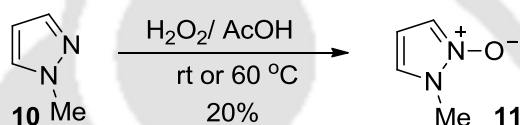
Figure 3.1.2. Some pyrazole based biologically active scaffolds

3.2. Literature methods for the synthesis of pyrazole and pyrazole *N*-oxides

The first pyrazole derivative, 1-phenyl-3-methyl-5-pyrazolone was reported by a German chemist “Ludwig Knorr” in 1883.¹⁹ Since then various synthetic routes have been developed for the construction of pyrazole building blocks in aza-heterocyclic chemistry.²⁰ Generally, the majority of the pyrazoles are prepared by classical cyclocondensation of hydrazine derivatives with 1,3-diketones and α,β -unsaturated carbonyl compounds.²¹ Moreover, they are also synthesized by 1,3-dipolar cycloaddition of diazoalkanes or nitrilimines with alkenes or alkynes.²² Furthermore, *N*-bromosuccinimide (NBS)-mediated cyclization of vinylhydrazones to give pyrazoles have been reported.²³ Recently, Rao and coworkers synthesized pyrazoles from 3-ethoxycyclobutanones with monosubstituted hydrazines catalyzed by Lewis acid

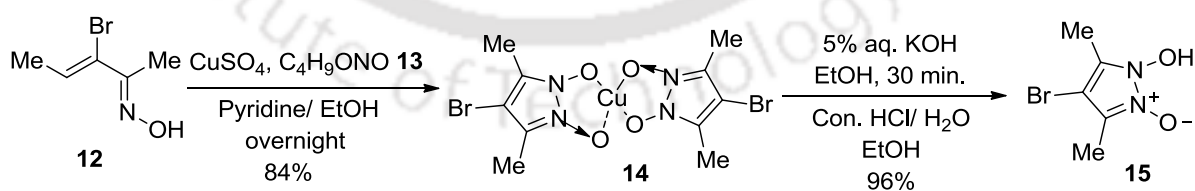
(SnCl_4 or $\text{BF}_3 \cdot \text{Et}_2\text{O}$).²⁴ Taran *et al.* developed a one-pot synthesis of 1,4-disubstituted pyrazoles using copper-catalyzed sydnone-alkyne cycloaddition reactions.²⁵ Pt-catalyzed [3,3]-sigmatropic rearrangement/cyclization cascade reaction of *N*-propargylhydrazones demonstrated by Zhan and group.²⁶ Wu and coworkers depicted radical addition of hydrazones by α -bromo ketones in presence of visible light catalysts²⁷ are some of the methods have been studied for the synthesis of pyrazole derivatives. Similarly, a few of pyrazole *N*-oxide and pyrazoles literature methods are discussed below.

Pyrazole *N*-oxides were prepared by the direct oxidation of pyrazoles with per acids. 1-Methyl pyrazole **10** was treated with H_2O_2 in AcOH at room temperature or 60 °C to obtain 1-methylpyrazole-2-oxide **11** (Scheme 3.2.1).²⁸



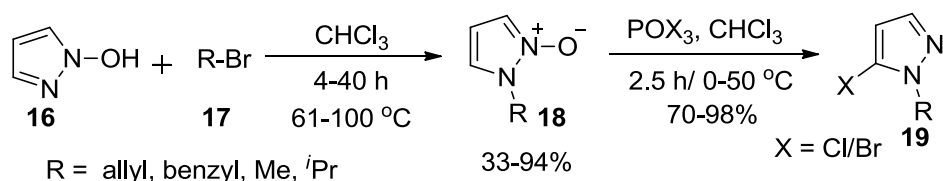
Scheme 3.2.1.

Hansen and coworkers have demonstrated a two-step procedure for the synthesis of substituted-1-hydroxypyrazole-2-oxides. Initially, oxime of 3-bromo-3-penten-2-one **12** was involved in nitrosation reaction with butyl nitrite **13** in the presence of copper(II) sulphate and pyridine in aqueous ethanol to produce an insoluble copper complex **14** in 84% yield. Which upon treatment with aqueous potassium hydroxide and then subsequent acidification affords the 3,5-dimethyl-4-bromo-1-hydroxypyrazole-2-oxide **15** in 96% yield (Scheme 3.2.2).²⁹



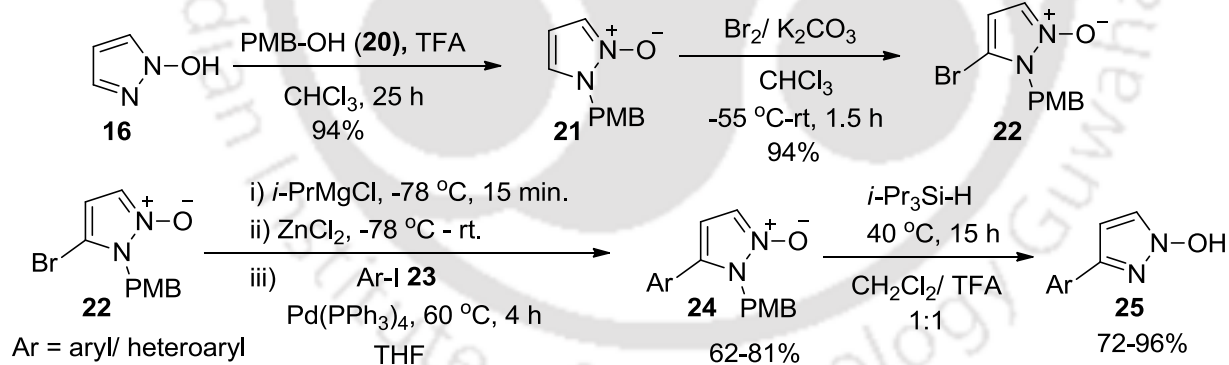
Scheme 3.2.2.

Vedsø and coworkers³⁰ described a facile synthesis of 2-alkylpyrazole-1-oxides **18** in good yields by the simple and selective *N*-alkylation of 1-hydroxypyrazole **16** with excess alkyl bromides **17** at 61-100 °C (Scheme 3.2.3). The corresponding *N*-oxides **18** were treated with phosphorous oxyhalides in order to get 1-alkyl-5-halopyrazoles **19** in good to excellent yields.



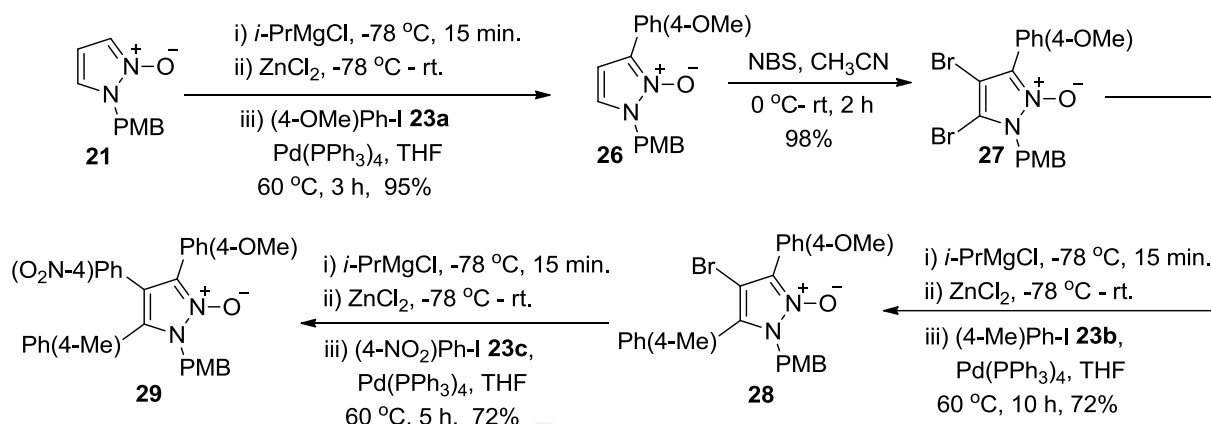
Scheme 3.2.3.

The regio- and monoselective reactions of pyrazole *N*-oxides make them attractive for the synthesis of substituted pyrazole derivatives. Vedsø and coworkers³¹ reported a selective C-5 aryl/heteroarylation on pyrazole-*N*-oxide in multi-step process. The reaction sequence initiated from TFA mediated selective benzylation of 1-hydroxypyrazole **16** with 4-methoxybenzyl alcohol **20** to form 1-(4-methoxybenzyl)-1*H*-pyrazole 2-oxide **21** in 94% yield, which after selective monobromination in presence of Br₂ afforded the 5-bromo-1-(4-methoxybenzyl)-1*H*-pyrazole-2-oxide **22** in 94% yield. Upon subsequent treatment with Grignard reagent, transmetallation with ZnCl₂ and palladium catalysed cross-coupling of aryl/heteroaryl iodo compounds **23** gave C-5 aryl/heteroaryl-pyrazole *N*-oxide **24** in good yields. The respective pyrazole-*N*-oxide **24** was exclusively transformed into C-3 aryl/heteroarylated *N*-hydroxypyrazole **25** by TFA mediated debenylation using *i*-Pr₃Si-H (Scheme 3.2.4).



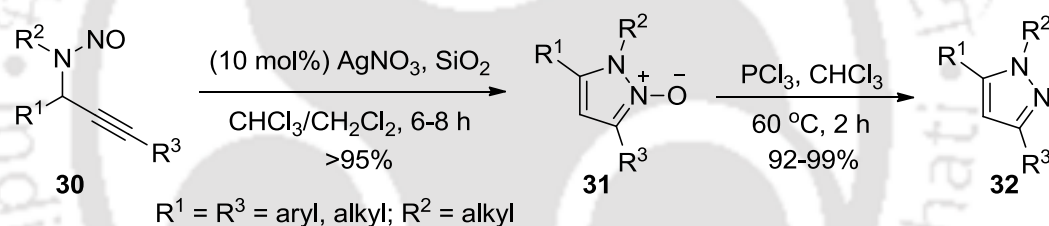
Scheme 3.2.4.

Similarly, in 2002 the same group achieved highly substituted C-arylpyrazole *N*-oxide **29** from the sequential arylation of 1-(4-methoxybenzyl)-1*H*-pyrazole 2-oxide **21** in multi-step process. The sequence initiated from deprotonation of compound **21** with isopropyl magnesium chloride and then transmetallation followed by cross-coupling reaction to obtain C-3 arylated pyrazole *N*-oxide **26** exclusively in 95% yield. This was further treated with excess NBS giving a double brominated compound **30** in 98% yield. Finally compound **27** undergoes in regioselective sequential arylation (Scheme 3.2.5.) to give a highly substituted C-arylpyrazole *N*-oxide **29** via **28**.³²



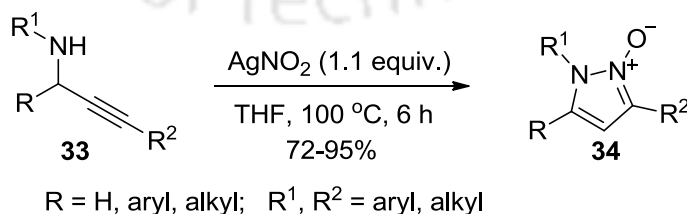
Scheme 3.2.5.

Knight and his group developed an efficient method for highly regiospecific synthesis of *N*-alkylpyrazole *N*-oxides **31** using catalytic amount of silica supported silver nitrate via 5-*endo-dig* cyclization of homoalkynyl nitrosamines **30** in excellent yields. The pyrazole-*N*-oxides were further treated with PCl₃ to furnish the resultant pyrazole derivatives **32** (Scheme 3.2.6).³³



Scheme 3.2.6.

Recently, Yuan and coworkers described a direct approach for the synthesis of pyrazole *N*-oxides **34** in good to excellent yields from propargylamines **33** and stoichiometric amount of AgNO₂ via tandem oxidation/cyclization reaction at 100 °C (Scheme 3.2.7).³⁴

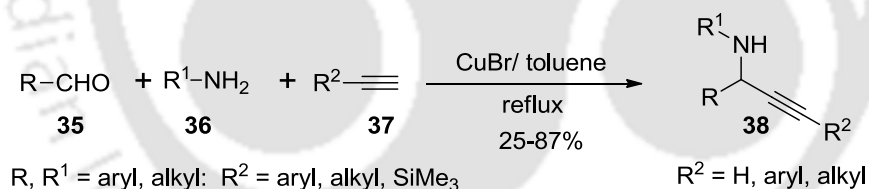


Scheme 3.2.7.

3.3. Results and discussions

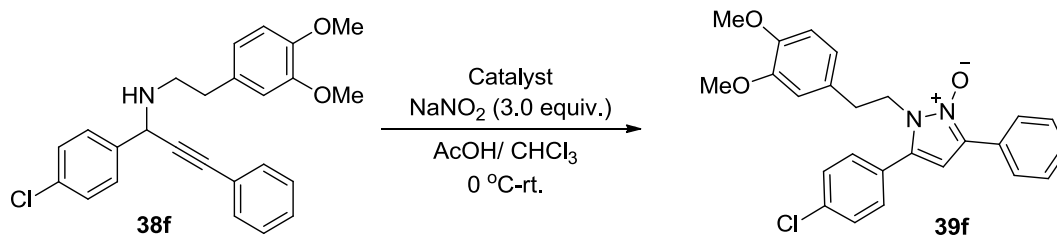
From the overview of literature, it is observed that most of the classical methods suffer from lack of regioselectivity. Although 1,3-dipolar cycloaddition reactions are highly regioselective, the synthesis of 1,3-dipolar species is difficult. Apart from this, pyrazole *N*-oxides are considered as synthetic intermediates for the synthesis of substituted pyrazole derivatives via regio- and monoselective reactions of pyrazole *N*-oxides. The major drawback of existing methods is low yields and multistep process. Therefore, there is an increasing interest in developing new methods for synthesis of substituted pyrazole *N*-oxides and pyrazoles. Hence, in this chapter we describes a direct, mild and efficient synthesis of substituted pyrazole *N*-oxides from secondary propargylamines using catalytic amount of silver(I) triflate with $\text{NaNO}_2/\text{AcOH}$ in excellent yields. The resulting pyrazole *N*-oxides were treated with PCl_3 in chloroform at reflux conditions in order to get the corresponding pyrazoles.

Initially, propargylic amines **38** were easily synthesized in one step process via A^3 -coupling reaction of aldehydes **35**, amines **36** and alkynes **37** catalyzed by copper(I) bromide (*Scheme 3.3.1*). The reaction is compatible with all functional groups present in aldehydes, alkynes and amines gave good yields.³⁵



Scheme 3.3.1.

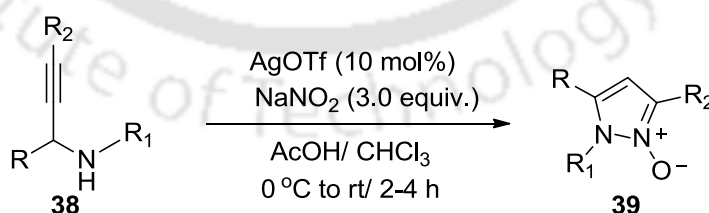
In an initial investigation of this reaction 1.0 equivalent of propargylamine **38f** was treated with 10 mol% of AgOTf , 3.0 equivalents of sodium nitrite and acetic acid in CH_3CN , CHCl_3 and CH_2Cl_2 at 0°C to room temperature for 3.0 h and 5-(4-chlorophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-1*H*-pyrazole 2-oxide **39f** was obtained in 83%, 86% and 85% yields, respectively (*Table 3.3.1*; entries 1-3). The reaction was also performed with FeCl_3 in acetonitrile under catalytic and stoichiometric amounts. With 10 mol% of FeCl_3 in 48 h (entry 4) it produced only trace amount of the product; however with 1.0 equivalent (entry 5) it gave 35% of the desired product in 15 h. From these observations, it was concluded that 10 mol% of AgOTf in chloroform at 0°C to room temperature is the optimum condition for the respective transformation (entry 2).

Table 3.3.1. Optimization of the reaction conditions

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%) ^a
1	Ag(OTf) (10)	CH ₃ CN	3	83
2	Ag(OTf) (10)	CHCl ₃	3	86
3	Ag(OTf) (10)	CH ₂ Cl ₂	3	85
4	FeCl ₃ (10)	CH ₃ CN	48	Trace
5	FeCl ₃ (100)	CH ₃ CN	15	35

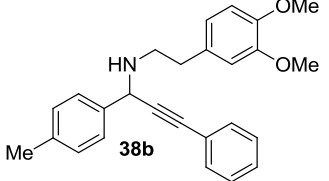
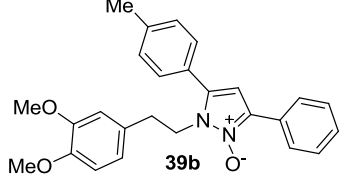
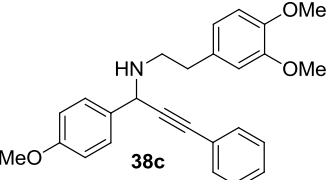
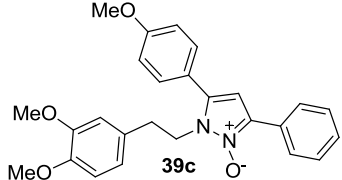
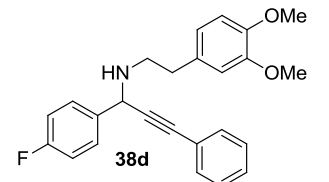
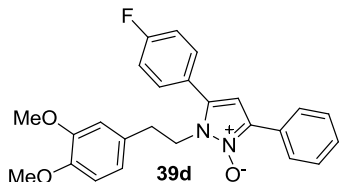
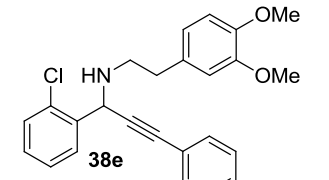
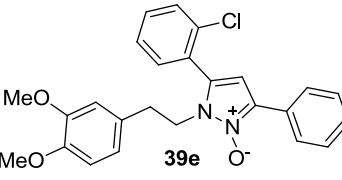
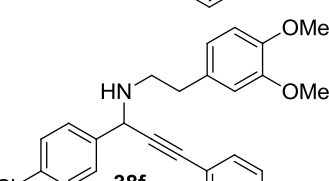
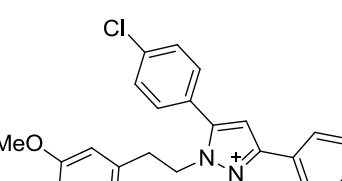
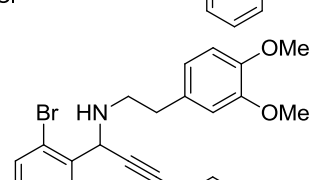
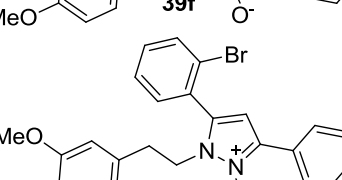
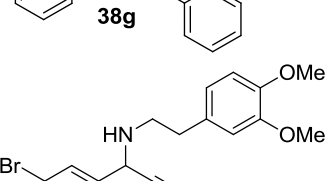
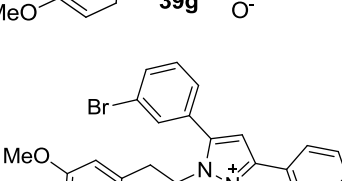
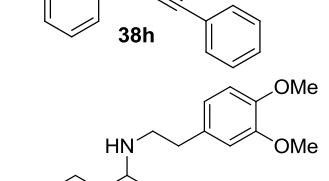
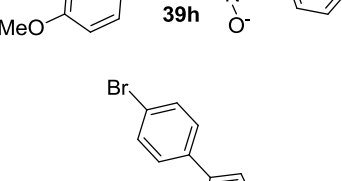
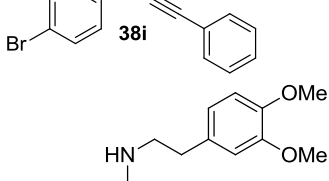
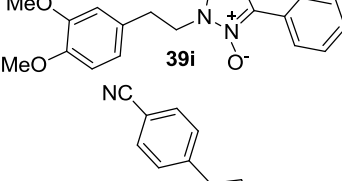
^aYield refers to isolated yield.

With the optimized conditions in hand, the scope of the reaction was examined with a variety of substrates and the results are represented in *Table 3.3.2*. It was observed that both alkyl and aryl substituents in alkyl side chain gave the desired pyrazole *N*-oxides in excellent yields (*Table 3.3.2*; **39a-39w**).

Table 3.3.2. Substrates scope of the reaction^a

Entry	Substrate (38)	Product (39)	Time (h)	Yield (%) ^b
1			2.5	91

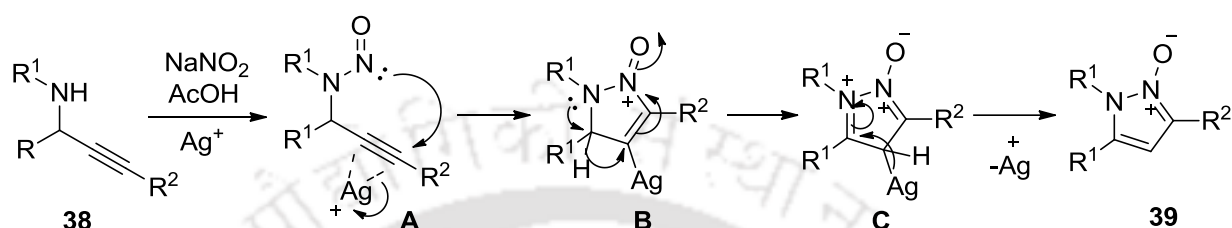
Continuation...

Entry	Substrate (38)	Product (39)	Time (h)	Yield (%) ^b
2	 38b	 39b	2.5	84
3	 38c	 39c	2.5	85
4	 38d	 39d	2.5	89
5	 38e	 39e	3.0	87
6	 38f	 39f	3.0	86
7	 38g	 39g	3.0	87
8	 38h	 39h	2.5	88
9	 38i	 39i	2.5	88
10	 38j	 39j	3.0	87

Entry	Substrate (38)	Product (39)	Time (h)	Yield (%) ^b
11			3.5	82
12			4.0	83
13			2.5	88
14			4.0	84
15			2.5	86
16			2.5	78
17			3.0	89
18			2.5	90
19			2.5	88

Continuation....

The mechanism of the reaction can be explained as follows. The reaction of amine **38** with sodium nitrite in acetic acid generates homopropargyl-*N*-nitrosamine **A**. The alkyne group of **A** was activated by Ag^+ to form silver complex, which undergoes 5-*endo-dig* cyclization to give an intermediate **B**. The hydride shift from **B** and finally removal of Ag^+ from **C** gives final product **39** (Scheme 3.3.3).

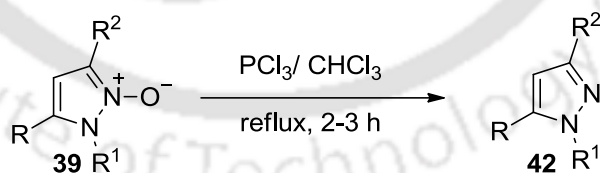


Scheme 3.3.3. Plausible mechanism of the reaction

3.4. Applications of pyrazole *N*-oxides

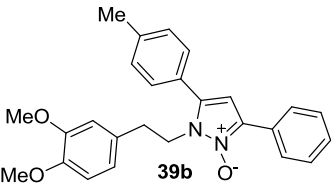
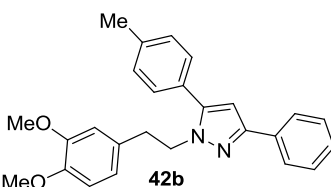
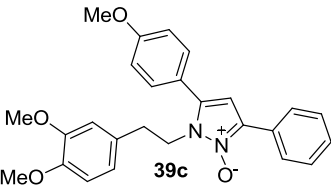
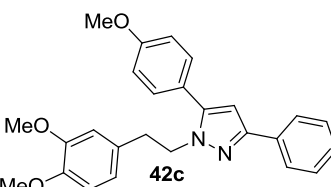
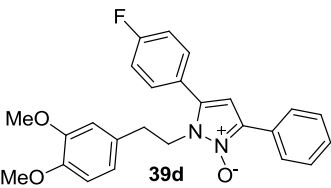
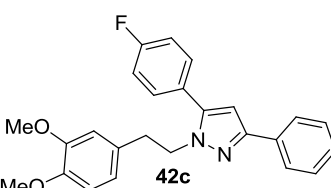
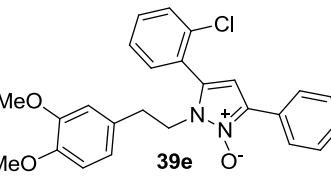
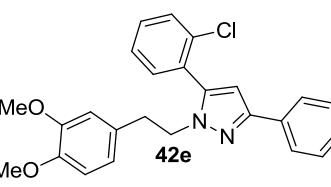
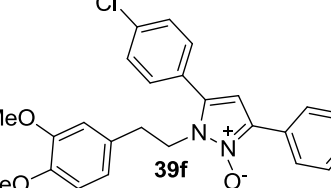
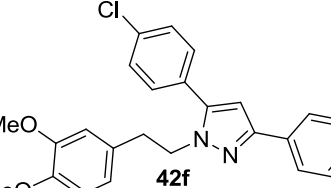
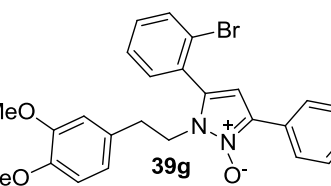
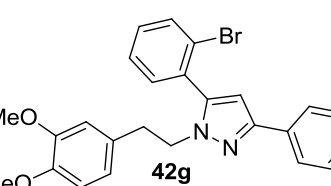
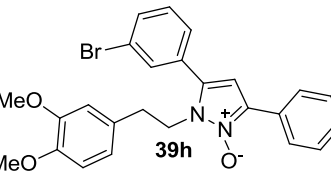
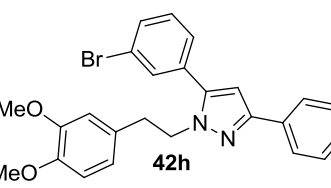
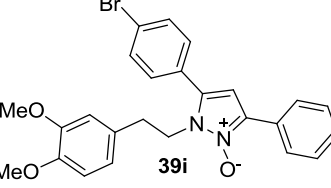
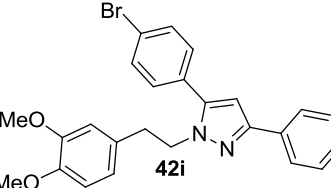
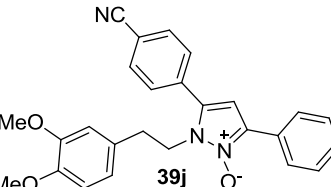
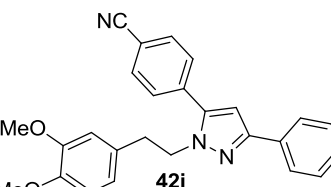
The pyrazole *N*-oxides **39** can be reduced to pyrazoles **42** by treatment with phosphorous trichloride in chloroform at refluxing conditions. As shown in Table 3.4.1, various pyrazole *N*-oxides having aryl and alkyl side chains (**39a-39v**) were effectively transformed to pyrazoles **42** in excellent yields.

Table 3.4.1. Cleavage of *N*-oxide bond^a



Entry	Substrate (39)	Product (42)	Time (h)	Yield (%) ^b
1	 39a	 42a	2.5	96

Continuation....

Entry	Substrate (39)	Product (42)	Time (h)	Yield (%) ^b
2	 39b	 42b	2.5	94
3	 39c	 42c	2.5	94
4	 39d	 42c	3.0	95
5	 39e	 42e	3.0	92
6	 39f	 42f	3.0	91
7	 39g	 42g	3.0	91
8	 39h	 42h	2.5	93
9	 39i	 42i	2.5	94
10	 39j	 42j	3.0	92

Continuation....

Entry	Substrate (39)	Product (42)	Time (h)	Yield (%) ^b
11			3.0	90
12			3.0	91
13			2.5	93
14			3.0	91
15			2.5	91
16			2.5	93
17			2.5	88
18			2.5	92
19			3.0	90

Continuation....

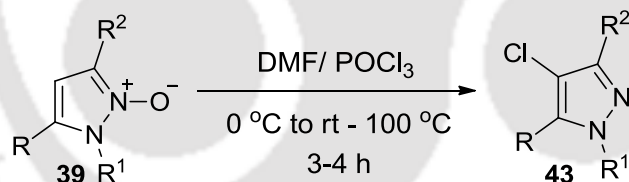
Entry	Substrate (39)	Product (42)	Time (h)	Yield (%) ^b
20			2.5	94

Reaction conditions^a: Pyrazole *N*-oxide **39** (0.15 mmol), PCl₃ (0.9 mmol), and CHCl₃ (1.0 mL); Yield refers to isolated yield.^b Compounds are characterised by ¹H, ¹³C NMR, IR and mass spectrometry.

Similarly, 1,5-disubstituted pyrazole-*N*-oxide **39v** and *N*-arylpyrazole-*N*-oxide **39w** were also reduced to the corresponding pyrazoles **42v** and **42w** gave in 90% and 94% yields, respectively.

To investigate the applicability of the pyrazole-*N*-oxides, pyrazole-*N*-oxides were subjected to reacts with phosphorous oxychloride in DMF at 100 °C surprisingly we found a highly substituted 4-chloropyrazoles in 67-73% yields (Table 3.4.2).²⁹

Table 3.4.2. Synthesis of 4-chloropyrazoles^a



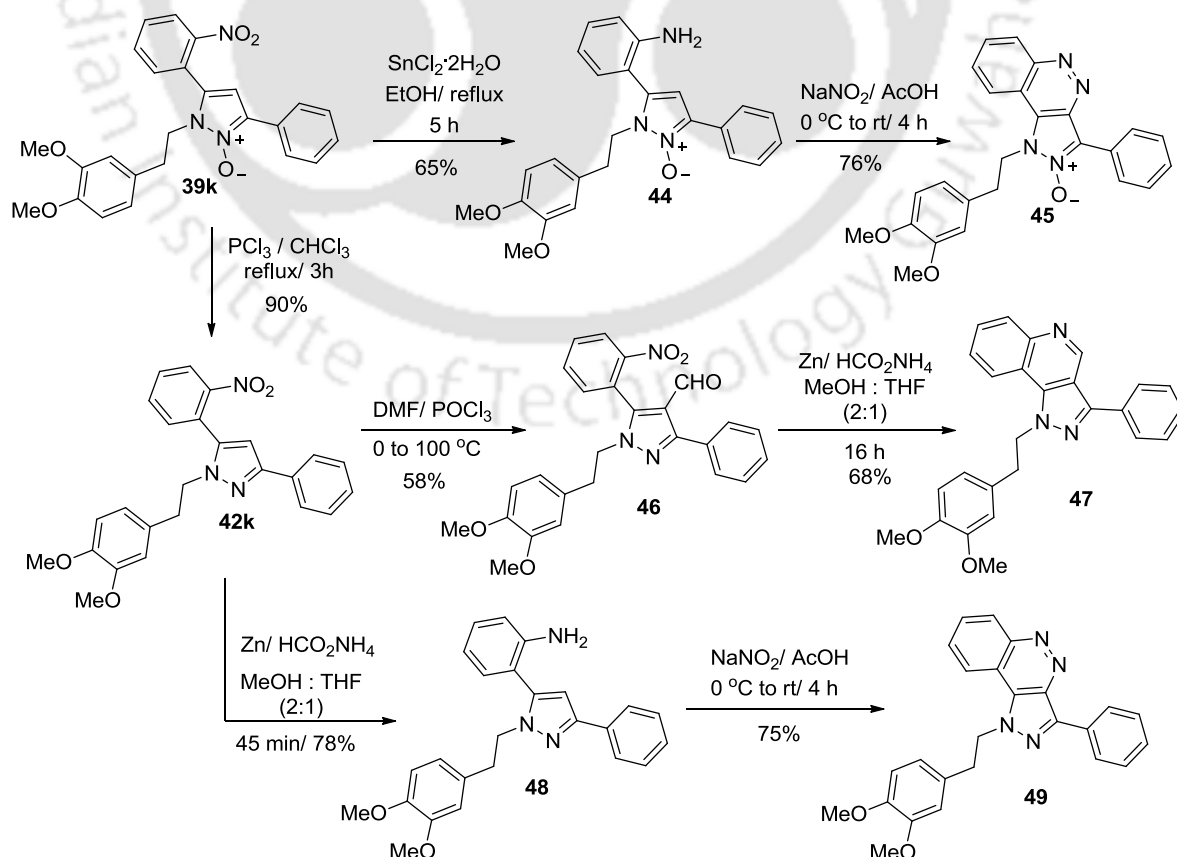
Entry	Substrate (39)	Product (43)	Time (h)	Yield (%) ^b
1			3.5	73
2			3.5	66

Continuation....

Entry	Substrate (39)	Product (43)	Time (h)	Yield (%) ^b
3			3.5	67
4			3.5	69

Reaction conditions^a: Pyrazole *N*-oxide **39** (0.3 mmol), POCl₃ (2.4 mmol), and DMF (1.0 mL); Yield refers to isolated yield.^b Compounds are characterised by ¹H, ¹³C NMR, IR and mass spectrometry.

In order to further investigate the scope of pyrazole *N*-oxide, 2-nitroaryl substituted pyrazole *N*-oxide **39k** was reduced to amine **44** followed by diazotization and cyclization to give pyrazolo-*N*-oxide-cinnoline **45** in 76% yield (Scheme 3.4.1).³⁶ Sequentially the same substrate **39k** was treated with PCl₃ in refluxing chloroform to obtain the resultant pyrazole **42k** in 90% yield, which was subjected to react with POCl₃ in DMF (Vilsmeier-Haak reaction conditions) to produce 4-formylated pyrazole **46** in 58% yield.^{37a}



Scheme 3.4.1. Synthesis of various complex *N*-heterocycles from pyrazole-*N*-oxides

The compound **46** was reacted with excess of zinc and ammonium formate to form a tricyclic compound pyrazoloquinoline **47** in 68% yield *via* a reductive coupling procedure.³⁸ Similarly, reduction of **42k** with zinc and ammonium formate furnished an amino compound **48**, which after diazotization followed by cyclization gave pyrazolo-cinnoline **49** in 75% yield. (*Scheme 3.4.1*).³⁶

Conclusions

In conclusion, we have developed a mild and efficient method for the synthesis of substituted pyrazole *N*-oxides from propargylamines in excellent yields. The reaction is compatible with a wide range of functional groups such as ester, ether, nitrile, -NO₂, and halides. The pyrazole *N*-oxide can be converted to pyrazole and chlorinated pyrazole under different reaction conditions. Nitroaryl substituted pyrazole can be converted to pyrazolo-*N*-oxide-cinnoline **45**, pyrazolo-quinoline **47** and pyrazolo-cinnoline **49**.

3.5. Experimental section

3.5.1. Instrumentation and characterisation

As described in chapter 2 section 2.5.1.

3.5.2. General procedures for the synthesis of propargylamines (38)

3.5.2.1. Synthesis of propargylamines (38a-38n):

To a mixture of CuBr (30 mol%), aldehyde **35** (2.0 mmol), 3,4-dimethoxy phenyl ethyl amine **36a** (2.1 mmol) and acetylenes **37** (4 mmol) were added by dissolving in 3 mL of dry toluene and the reaction mixture was stirred at 100 °C for 4-6 h. After completion of the reaction, the reaction was cooled; the solvent was removed under rotary evaporator, diluted with saturated ammonium chloride and then extracted with ethyl acetate. The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over Na₂SO₄ and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to obtain the corresponding product.

3.5.2.2. Synthesis of propargylamines (38o-38w):

To a mixture of CuBr (30 mol%), aldehyde **35** (2.0 mmol), benzyl amine **36b** (2.5 mmol) and

acetylenes **37** (4 mmol) were added by dissolving in 3 mL of dry toluene and the reaction mixture was stirred at 110 °C for 2-4 h time. After completion of the reaction, the reaction was cooled; the solvent was removed under rotary evaporator, diluted with saturated ammonium chloride and then extracted with ethyl acetate. The organic layer was further washed with water for 3 times. The combined organic layers were dried over Na₂SO₄ and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the desired product.

3.5.3. General procedure for the synthesis of pyrazole *N*-oxides (**39**):

Propargylamine **38** (0.3 mmol), NaNO₂ (0.9 mmol) and Ag(OTf) (0.03 mmol) in anhydrous CHCl₃ (1 mL) was stirred at 0 °C followed by slow addition of Acetic acid (0.6 mL). Then reaction mixture stirred at room temperature for 2-4 h. After completion of the reaction the mixture was poured into water (10 ml) and diluted with saturated NaHCO₃ solution and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding product **39**.

3.5.4. Typical procedure for the reduction of pyrazole *N*-oxide with PCl₃ (**42**):

To a stirred solution of pyrazole *N*-oxide **39** (0.15 mmol) in CHCl₃ (1.5 mL) was added phosphorus trichloride (0.9 mmol) and the reaction mixture was heated to 60 °C. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into ice-cold water. The aqueous layer basified with NaOH and the product was extracted with DCM. The organic layer was dried over Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography by elution with hexane/ EtOAc to give the desired product **42**.

3.5.5. Typical procedure for the synthesis of 4-chloropyrazoles (**43**):

To a mixture of compound **39** (0.3 mmol), in anhydrous DMF (1.0 mL), added phosphoryl chloride (2.4 mmol) drop by drop at 0 °C under N₂ atmospheric condition, then the reaction mixture was stirred at room temperature for 1 h. Further, the reaction mixture was heated to 100 °C for 3.5 h, the reaction mixture was poured into ice cold water and treated with saturated bicarbonate solution, and extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to achieve the resultant product **43**.

3.5.6. Experimental procedure for the reduction of nitro group:

Under N₂ atmosphere compound **39k** (0.3 mmol) in anhydrous ethanol (4 mL) was added to SnCl₂·2H₂O (1.5 mmol) and the reaction mixture was stirred at 80 °C for 5 h. After completion of the reaction (monitored by TLC), the mixture was filtered through celite, and washed with saturated NaHCO₃ solution. The layers were separated and the aqueous layer was further extracted with ethyl acetate. The combined organic layers was dried over Na₂SO₄ and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding product **44**.

3.5.7. Experimental procedure for the synthesis of pyrazolo-*N*-oxide-cinnoline 45:

To a mixture of compound **44** (0.15 mmol) and NaNO₂ (0.45 mmol) in DCM (1.0 mL) was slowly added AcOH (0.5 mL) at 0 °C. Then the reaction mixture was stirred at room temperature. Upon completion of the reaction (monitored by TLC), the reaction mixture was poured into ice cold water, diluted with saturated NaHCO₃ and the organic layer was extracted with DCM (3x5 mL) washed with brine solution for 2-3 times. The combined organic layers were dried over Na₂SO₄ and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to accomplish the resultant product **45**.

3.5.8. Typical procedure for the formylation of pyrazole:

To a mixture of compound **42k** (0.3 mmol), in anhydrous DMF (1.0 mL), added phosphoryl chloride (3.0 mmol) drop by drop at 0 °C under N₂ atmospheric condition, then the reaction mixture was stirred at room temperature for 1 h. Further, the reaction mixture was heated to 100 °C for 6 h, the reaction mixture was poured into ice cold water and treated with saturated bicarbonate solution, and extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to form the desired product **46**.

3.5.9. Experimental procedure for the synthesis of pyrazolo-quinoline 47:

To a stirred mixture of ammonium formate (1.5 mmol) in anhydrous MeOH and THF (2:1) were added nitro compound **46** (0.15 mmol) and Zn dust (1.5 mmol) and the reaction mixture stirred for 15 h, at room temperature and the mixture was filtered off. The organic layer was evaporated and the residue dissolved in DCM, washed with brine solution for 2-3 times. The combined organic layers were dried over Na₂SO₄ and concentrated in rotary evaporator. The

crude was subjected to column chromatography over silica gel to give the consequent product **47**.

3.5.10. Experimental procedure for the reduction of nitro group:

To a stirred mixture of ammonium formate (3.0 mmol) in anhydrous MeOH:THF (2:1) were added nitro compound **42k** (0.30 mmol) and Zn dust (3.0 mmol) and the reaction mixture stirred for 45 minutes at room temperature, the mixture was filtered off. The organic layer was evaporated and the residue dissolved in DCM, and washed with brine solution for 2-3 times. The combined organic layers were dried over Na₂SO₄ and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the subsequent product **48**.

3.5.11. Experimental procedure for the synthesis of pyrazolo-cinnoline (49):

To a mixture of compound **48** (0.15 mmol) and NaNO₂ (0.45 mmol) in DCM (1.0 mL), AcOH (0.5 ml) was slowly added at 0 °C. Then the reaction mixture was stirred at room temperature. Upon completion of the reaction (monitored by TLC), the reaction mixture was poured into ice cold water, diluted with saturated NaHCO₃ and the organic layer was extracted with DCM (3x5 mL) and washed with brine solution for 2-3 times. The combined organic layers were dried over Na₂SO₄ and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to afford the resultant product **49**.

3.6. References

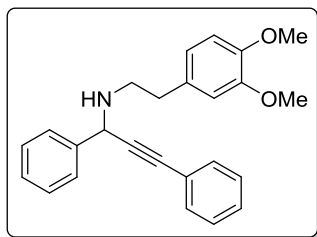
1. (a) Hoelder, S.; Clarke, P. A.; Workman, P. *Mol Oncol.* **2012**, 6, 155-176. (b) Fischer, P. *M. Med. Res. Rev.* **2017**, 37, 314-367. (c) Ursu, A.; Schöler, H. R.; Waldmann, H. *Nat Chem Biol.* **2017**, 13, 560-563.
2. (a) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. *Targets Heterocycl. Syst.* **2002**, 6, 52-98. (b) Lamberth, C. *Heterocycles.* **2007**, 71, 1467-1502. (b) Seltzman, H. H. *Drug Dev. Res.* **2009**, 70, 601-615. (c) Kumar, K. A.; Jayaroopa, P. *Int. J. PharmTech Res.* **2013**, 5, 1473-1486.
3. (a) Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S. R.; McCallion, D.; Pertwee, R.; Makriyannis, A. *J. Med. Chem.* **1999**, 42, 769-776. (b) Ochi, T.; Jobo-Magari, K.; Yonezawa, A.; Matsumori, K.; Fujii, T. *Euro. J. Pharmacol.* **1999**, 365, 259-566.
4. (a) Abdel-Hafez, E. S. M. N.; Abuo-Rahma, G. E. D. A. A.; Abdel-Aziz, M.; Radwan, M. F.; Farag, H. H. *Bioorg. Med. Chem.* **2009**, 17, 3829-3837. (b) Castagnolo, D.; Manetti, F.; Radi, M.; Bechi, B.; Pagano, M.; De Logu, A.; Meleddu, R.; Saddi, M.; Botta, M. *Bioorg. Med. Chem.* **2009**, 17, 5716-5721. (c) Gomha, S. M.; Hassaneen, H. M. E. *Molecules.* **2011**, 16, 6549-6560.
5. (a) Bekhit, A. A.; Ashour, H. M. A.; Guemei, A. A. *Arch. Pharm. Chem. Life Sci.* **2005**, 338, 167-174. (b) Sharshira, E. M.; Hamada, N. M. M. *Molecules.* **2012**, 17, 4962-4971.
6. (a) Millis, D. L.; Weigel, J. P.; Moyers, T.; Buonomo, F. C. *Vet. Ther.* **2002**, 3, 453-464. (b) Ouyang, G.; Cai, X. J.; Chen, Z.; Song, B. A.; Bhadury, P. S.; Yang, S.; Jin, L. H.; Xue, W.; Hu, D. Y.; Zeng, S. *J. Agril. Food Chem.* **2008**, 56, 10160-10167.
7. Moore, K. W.; Bonner, K.; Jones, E. A.; Emms, F.; Leeson, P. D.; Marwood, R.; Patel, S.; Rowley, M.; Thomas, S.; Carling, R. W. *Bioorg. Med. Chem. Lett.* **2009**, 9, 1285-1290.
8. (a) Arya, V. P.; Grewal, R. S.; Kaul, C. L.; Ghate, S. P.; Mehta, D. V.; George, T. *J. Pharm. Sci.* **1969**, 58, 432-440. (b) Almansa, C.; Gomez, L. A.; Cavalcanti, F. L.; de Arriba, A. F.; Garcia-Rafanell, J.; Form, J. *J. Med. Chem.* **1997**, 40, 547-558.
9. (a) Stauffer, S. R.; Coletta, C. J.; Tedesco, R.; Nishiguchi, G.; Carlson, K.; Sun, J.; Katzenellenbogen, J. A. *Bioorg. Med. Chem.* **2001**, 9, 141-150. (b) Wasyluk, C.; Zeng, H.; Castell, C.; Debussche, L.; Multon, M.-C.; Wasyluk, B. *Cancer Res.* **2008**, 68, 1275-1283.
10. Behr, L. C.; Fusco, R.; Jarboe, C. H., *The Chemistry of Heterocyclic Chemistry: Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings*; Wiley & Sons: London, 1967.

11. (a) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Doctor, S.; Grevato, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Gregory, S. A.; Icoboldt, C. M.; Perkus, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347-1365. (b) Amgad, G.; Habeeb, P. N.; Rao, P.; Knaus, E. E. *J. Med. Chem.* **2001**, *44*, 3039-3042. (c) Ahlström, M. M.; Ridderström, M.; Zamora, I.; Luthman, K. *J. Med. Chem.* **2007**, *50*, 4444-4452.
12. (a) Millis, D. L.; Weigel, J. P.; Moyers, T.; Buonomo, F. C.; *Compend. Contin. Educ. Pract. Vet.* **2002**, *3*, 7. (b) Mills, D. L.; Weigel, J. P.; Moyers, T.; Buonomo, F. C. *Vet. Ther.* **2002**, *3*, 453-464.
13. (a) Lan, Ruoxi.; Liu, Qian.; Fan, Pusheng.; Lin, Sonyuan.; Fernando, S. R.; McCallion, D.; Pertwee, R.; Makriyannis A. *J. Med. Chem.* **1999**, *42*, 769-776. (b) Kotagiri, V. K.; Suthrapu, S.; Reddy, J. M.; Rao, C. P.; Bollugoddu, V.; Bhattacharya, A.; Bandichhor, R. *Org. Process Res. Dev.* **2007**, *11*, 910-912.
14. Adams, J. W.; Ramirez, J.; Shi, Y.; Thomsen, W.; Frazer, J.; Morgan, M.; Edwards, J. E.; Chen, W.; Teegarden, B. R.; Xiong, Y.; Al-Shamma, H.; Behan, D. P.; Connolly, D. T. *J. Pharmacol. Exp. Ther.* **2009**, *331*, 96-103.
15. (a) Guzman-Perez, A.; Pfefferkorn, J. A.; Lee, E. C.Y.; Stevens, B. D.; Aspnes, G. E.; Bian, J.; Didiuk, M. T.; Filipski, K. J.; Moore, D.; Perreault, C.; Sammons, M. F.; Tu, M.; Brown, J.; Atkinson, K.; Litchfield, J.; Tan, B.; Samas, B.; Zavadoski, W. J.; Salatto, C. T.; Treadway, J. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3051-3058. (b) Xiong, Y.; Guo, J.; Candelore, M. R.; Liang, R.; Miller, C.; Dallas-Yang, Q.; Jiang, G.; McCann, P. E.; Qureshi, S. A.; Tong, X.; Xu, S. S.; Shang, J.; Vincent, S. H.; Tota, L. M.; Wright, M. J.; Yang, X.; Zhang, B. B.; Tata, J. R.; Parmee, E. R. *J. Med. Chem.* **2012**, *55*, 6137-6148.
16. Miller, Z.; Kim, K.-S.; Lee, D.-M.; Kasam, V.; Baek, S. E.; Lee, K. H.; Zhang, Y.-Y.; Ao, L.; Carmony, K.; Lee, N.-R.; Zhou, S.; Zhao, Q.; Jang, Y.; Jeong, H.-Y.; Zhan, C.-G.; Lee, W.; Kim, D.-E.; Kim K. B. *J. Med. Chem.* **2015**, *58*, 2036-2041.
17. (a) Dosa, P. I.; Strah-Pleyne, S.; Jayakumar, H.; Casper, M.; Decaire, M.; Xiong, Y.; Lehmann, J.; Choi, K.; Elwell, K.; Wong, A.; Webb, R. R.; Adams, J. W.; Ramirez, J.; Richman, J. G.; Thomsen, W.; Semple, G.; Teegarden, B. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5486-5489. (b) Xiong, Y.; Teegarden, B. R.; Choi, J.-S. K.; Strah-Pleyne, S.; Decaire, M.; Jayakumar, H.; Dosa, P. I.; Casper, M. D.; Pham, L.; Feichtinger, K.; Ullman, B.; Adams, J.; Yuskina, D.; Frazer, J.; Morgan, M.; Sadeque, A.; Chen, W.;

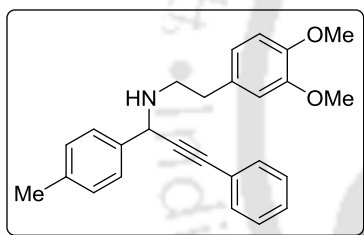
- Webb, R. R.; Connolly, D. T.; Semple, G.; Al-Shamma, H. *J. Med. Chem.* **2010**, *53*, 4412-4421.
18. (a) Singer, R. A.; Caron, S.; McDermott, R. E.; Arpin, P.; Do, N. M. *Synthesis*. **2003**, *11*, 1727-1731. (b) Singer, R. A.; Dore, M.; Sieser, J. E.; Berliner, M. A. *Tetrahedron Lett.* **2006**, *47*, 3727-3731.
19. Knorr, L. *Berichte der deutschen chemischen Gesellschaft*. **1883**, *16*, 2597-2599.
20. (a) Cacchi, S.; Fabrizi, G.; Carangio, A. *Synlett*. **1997**, 959-961. (b) Almirante, N.; Cerri, A.; Fedrizzi, G.; Marazzi, G.; Santagostino, M. *Tetrahedron Lett.* **1998**, *39*, 3287-3290. (c) Fustero, S.; Saánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984-7034. (d) Nair, A.; Biju, A. T.; Mohanan, K.; Suresh, E. *Org. Lett.* **2006**, *8*, 2213-2216. (e) Martin, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 7079-7082. (f) Neumann, J. J.; Suri, M.; Glorius, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 7790-7794. (g) Sha, Q.; Wei, Y.; *Synthesis*. **2013**, *45*, 413-420.
21. (a) Katritzky, A. R.; Wang, M.; Zhang, S.; Voronkov, M. V.; Steel, P. J. *J. Org. Chem.* **2001**, *66*, 6787-6791. (b) Fustero, S.; Román, R.; Sanz-Cervera, J. F.; Simón-Fuentes, A.; Cuñat, A. C.; Villanova, S.; Murguía, M. *J. Org. Chem.* **2008**, *73*, 3523-3529. (c) Garcia, H.; Iborra, S.; Miranda, M. A. *Heterocycles*. **1991**, *32*, 1745-1755. (c) Baldwin, J. E.; Pritchard, G. J.; Rathmell, R. E. *J. Chem. Soc. Parkin Trans. 1* **2001**, 2906-2908.
22. (a) Padwa, A.; Pearson, W. H.; Eds. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products*; Wiley: New York, **2002**. (b) Kobayashi, S.; Hirabayashi, R.; Shimizu, H.; Ishitani, H.; Yamashita, Y. *Tetrahedron Lett.* **2003**, *44*, 3351-3354. (c) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381-5383.
23. Sar, D.; Paul, R.; Sengoden, M.; Punniyamurthy, T. *Asian J. Org. Chem.* **2014**, *3*, 638-643.
24. Shan, G.; Liu, P.; Rao, Y. *Org. Lett.* **2011**, *13*, 1146-1149.
25. Specklin, S.; Decuypere, E.; Plougastel, L.; Aliani, S.; Taran, F. *J. Org. Chem.* **2014**, *79*, 7772-7777.
26. Wen, J.-J.; Tang, H.-T.; Xiong, K.; Ding, Z.-C.; Zhan, Z.-P. *Org. Lett.* **2014**, *16*, 5940-5943.
27. Fan, X.-W.; Lei, T.; Zhou, C.; Meng, Q.-Y.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *J. Org. Chem.* **2016**, *81*, 7127-7133.
28. Panlell, E. W. *Tetrahedron Lett.* **1970**, *11*, 3941-3942.
29. Hansen, J. F.; Easter, J.A.; Eckert, D.A.; Hunt, K.J.; Little, D. A. *J. Heterocycl. Chem.* **1994**, *31*, 281-286.

30. Eskildsen, J.; Vedsø, P.; Begtrup, M. *Synthesis*. **2001**, 1053-1056.
31. Eskildsen, J.; Kristensen, J.; Vedsø, P.; Begtrup, M. *J. Org. Chem.* **2001**, 66, 8654-8656.
32. Paulson, A.; Eskildsen, J.; Vedsø, P.; Begtrup, M. *J. Org. Chem.* **2002**, 67, 3904-3907.
33. Hayes, S. J.; Knight, D. W.; O'Halloran M.; Pickering, S. R. *Synlett*. **2008**, 2188-2190.
34. Yuan, B.; Zhang, F.; Li, Z.; Yang, S.; Yan, R. *Org. Lett.* **2016**, 18, 5928-5931.
35. (a) Peshkov, V. A.; Pereshivko, O. P.; Sharma, S.; Meganathan, T.; Parmar, V. S.; Ermolat'ev, D. S.; Van der Eycken, E. V. *J. Org. Chem.* **2011**, 76, 5867-5872. (b) Ranjan, A.; Yerande, R.; Wakchaure, P. B.; Yerande, S. G. Dethe, D. H. *Org. Lett.* **2014**, 16, 5788-5791.
36. Shen, Y.; Shang, Z.; Yang, Y.; Zhu, S.; Qian, X.; Shi, P.; Zheng, J.; Yang, Y.; *J. Org. Chem.* **2015**, 80, 5906-5909. (b) Tonk, R. K.; Bawa, S.; Chawla, G.; Deora, G. S.; Kumar, S.; Rathore, V.; Mulakayala, N.; Rajaram, A.; Kalla, A. M.; Afzal, O. *Euro. J. Med. Chem.* **2012**, 57, 176-184.
37. (a) Yamamoto, S.; Tomita, N.; Suzuki, Y.; Suzuki, T.; Kaku, T.; Hara, T.; Yamaoka, M.; Kanzaki, N.; Hasuoka, A.; Baba, A.; Ito, M. *Bioorg. Med. Chem.* **2012**, 20, 2338-2352.
38. (a) Li, D.; Zhao, B.; LaVoie, E. J. *J. Org. Chem.* **2000**, 65, 2802-2805. (b) J. Eskildsen, N. Ostergard, P. Vedsø, M. Begtrup, *Tetrahedron*. **2002**, 58, 7635-7644 and references cited therein.

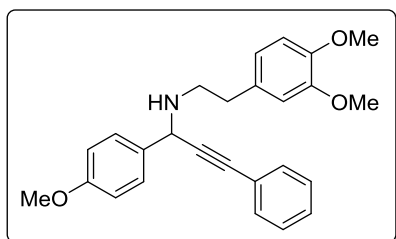
3.7. Characterization data

***N*-(3,4-Dimethoxyphenethyl)-1,3-diphenylprop-2-yn-1-amine (38a):**

Orange gum; R_f (hexane/EtOAc 5:1) 0.50; yield 631 mg, 85 %; ^1H NMR (600 MHz, CDCl_3): δ 7.55 (d, $J = 7.2$ Hz, 2 H), 7.46-7.44 (m, 2 H), 7.37 (t, $J = 7.8$ Hz, 2 H), 7.31-7.28 (m, 4 H), 6.80-6.77 (m, 2 H), 6.75 (s, 1 H), 4.84 (s, 1 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 3.12 (ddd, $J = 11.4, 7.2$ and 3.0 Hz, 1 H), 3.01 (ddd, $J = 11.4, 6.6$ and 4.8 Hz, 1 H), 2.87-2.78 (m, 2 H), 1.81 (brs, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 149.1, 147.6, 140.5, 132.6, 131.9, 128.7, 128.4, 128.3, 127.9, 127.8, 123.3, 120.8, 112.1, 111.5, 89.4, 85.6, 56.1, 56.0, 54.8, 48.5, 35.9; IR (KBr, neat) 3293, 3025, 2986, 1629, 1596, 1498, 1450, 1265, 1232, 1192, 1057, 869, 716 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{26}\text{NO}_2$ ($\text{M} + \text{H}$) $^+$ 372.1958, found 372.1956.

***N*-(3,4-Dimethoxyphenethyl)-3-phenyl-1-(*p*-tolyl)prop-2-yn-1-amine (38b):**

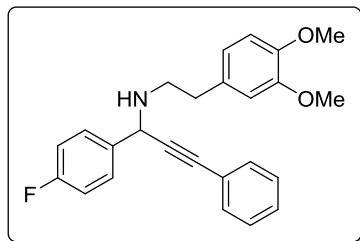
Orange gum; R_f (hexane/EtOAc 5:1) 0.50; yield 562 mg, 73 %; ^1H NMR (600 MHz, CDCl_3): δ 7.44-7.41 (m, 4 H), 7.30-7.27 (m, 3 H), 7.16 (d, $J = 7.8$ Hz, 2 H), 6.79-6.75 (m, 2 H), 6.74 (s, 1 H), 4.79 (s, 1 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.09 (ddd, $J = 11.4, 7.2$ and 4.2 Hz, 1 H), 2.99 (ddd, $J = 11.4, 7.2$ and 4.8 Hz, 1 H), 2.84-2.77 (m, 2 H), 2.34 (s, 3 H), 1.81 (brs, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 149.1, 147.6, 137.6, 137.5, 132.6, 131.8, 129.3, 129.2, 128.9, 128.4, 128.3, 127.6, 123.3, 120.8, 112.1, 111.4, 89.6, 85.4, 56.1, 55.9, 54.5, 48.5, 35.8, 21.3; IR (KBr, neat) 3315, 3024, 2820, 1627, 1530, 1454, 1303, 1233, 1191, 1053, 848, 753, 716 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{28}\text{NO}_2$ ($\text{M} + \text{H}$) $^+$ 386.2115, found 386.2115.

***N*-(3,4-Dimethoxyphenethyl)-1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-amine (38c):**

Orange gum; R_f (hexane/EtOAc 4:1) 0.50; yield 577 mg, 72 %; ^1H NMR (600 MHz, CDCl_3): δ 7.46 (d, $J = 8.4$ Hz, 2 H), 7.45-7.43 (m, 2 H), 7.30-7.27 (m, 3 H), 6.88 (d, $J = 8.4$ Hz, 2 H), 6.79-6.75 (m, 2 H), 6.74 (s, 1 H), 4.80 (s, 1 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.10 (ddd, $J = 11.4, 7.2$ and 4.2 Hz, 1 H), 2.99 (ddd, $J = 11.4, 7.2$ and 4.2 Hz, 1 H), 2.87-2.76 (m, 2 H), 2.15 (brs, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 159.3, 149.0, 147.6, 132.5, 131.8, 128.9, 128.4, 128.3, 123.2, 120.8, 114.0, 112.0, 111.4, 89.6, 85.5, 56.0, 55.9, 55.4, 54.1, 48.4, 35.8; IR (KBr, neat) 3351, 3004, 2834, 1602, 1504, 1459, 1140, 1030, 817, 529 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{28}\text{NO}_3$ ($\text{M} + \text{H}$) $^+$ 402.2064, found 402.2065.

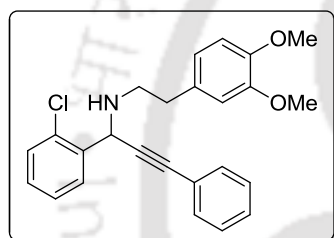
***N*-(3,4-Dimethoxyphenethyl)-1-(4-fluorophenyl)-3-phenylprop-2-yn-1-amine (38d):**

Yellow gum; R_f (hexane/EtOAc 5:1) 0.50; yield 536 mg, 69 %; $^1\text{H NMR}$ (400 MHz, CDCl_3):



δ 7.53-7.50 (m, 2 H), 7.46-7.44 (m, 2 H), 7.33-7.31 (m, 3 H), 7.04 (t, $J = 8.8$ Hz, 2 H), 6.81-6.78 (m, 2 H), 6.75 (s, 1 H), 4.81 (s, 1 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 3.09 (ddd, $J = 14.4$, 7.2 and 4.4 Hz, 1 H), 2.99 (ddd, $J = 11.2$, 6.8 and 4.4 Hz, 1 H), 2.88-2.75 (m, 2 H), 1.69 (brs, 1 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ

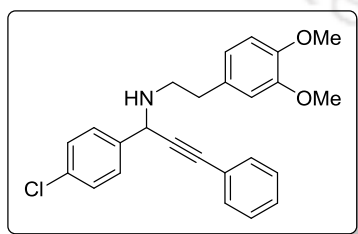
162.5 (d, $J = 244.8$ Hz), 149.1, 147.6, 136.3, 132.5, 131.9, 129.4 (d, $J = 8.4$ Hz), 128.5, 123.1, 120.8, 115.4 (d, $J = 21.3$ Hz), 112.0, 111.4, 89.2, 85.8, 56.1, 55.9, 54.1, 48.4, 35.9; $^{19}\text{F NMR}$ (376 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$): 46.91; IR (KBr, neat) 3024, 2881, 1629, 1597, 1500, 1402, 1223, 1161, 1054, 933, 851, 717, 575 cm^{-1} ; HRMS (ESI) calcd. For $\text{C}_{25}\text{H}_{25}\text{FNO}_2$ ($\text{M} + \text{H}$) $^+$ 390.1864, found 390.1865.

***N*-(3,4-dimethoxyphenethyl)-1-(2-chlorophenyl)-3-phenylprop-2-yn-1-amine (38e):**

Orange gum; R_f (hexane/EtOAc 5:1) 0.50; yield 599 mg, 74 %;

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.72 (d, $J = 7.6$ Hz, 1 H), 7.46-7.43 (m, 2 H), 7.36 (d, $J = 7.6$ Hz, 1 H), 7.31-7.28 (m, 4 H), 7.26-7.21 (m, 1 H), 6.80-6.73 (m, 2 H), 6.74 (s, 1 H), 5.23 (s, 1 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.11 (ddd, $J = 11.2$, 7.2 and 2.4

Hz, 1 H), 3.01 (ddd, $J = 13.6$, 6.8 and 4.4 Hz, 1 H), 2.89-2.76 (m, 2 H), 1.78 (brs, 1 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 148.5, 147.0, 137.3, 132.8, 131.8, 131.3, 129.3, 128.9, 128.7, 127.9, 126.7, 122.5, 120.3, 111.4, 110.9, 88.2, 84.8, 55.4, 55.3, 51.3, 48.2, 35.2; IR (KBr, neat) 3061, 2935, 2833, 1597, 1513, 1415, 1265, 1235, 1153, 1029, 840, 758, 693 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{25}\text{ClNO}_2$ ($\text{M} + \text{H}$) $^+$ 406.1568, found 406.1578.

***N*-(3,4-dimethoxyphenethyl)-1-(4-chlorophenyl)-3-phenylprop-2-yn-1-amine (38f):**

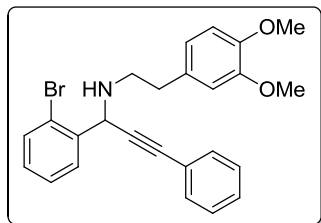
Orange gum; R_f (hexane/EtOAc 5:1) 0.50; yield 639 mg, 79 %;

$^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.50 (d, $J = 7.8$ Hz, 2 H), 7.46-7.45 (m, 2 H), 7.35-7.32 (m, 5 H), 6.80 (d, $J = 7.8$ Hz, 1 H), 6.77 (d, $J = 8.4$ Hz, 1 H), 6.75 (s, 1 H), 4.81 (s, 1 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 3.11-3.06 (m, 1 H), 3.01-2.97 (m, 1 H), 2.86-

2.77 (m, 2 H), 1.63 (brs, 1 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 148.5, 147.1, 138.5, 132.9, 131.9, 131.2, 128.6, 128.1, 127.9, 127.7, 127.1, 122.4, 120.2, 111.5, 111.0, 88.6, 85.4, 55.3, 55.2, 53.3, 47.8, 35.3; IR (KBr, neat) 3355, 3061, 3003, 2834, 1663, 1600, 1531, 1452, 1367, 1274, 1145, 1085, 1022, 832, 761, 694 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{25}\text{ClNO}_2$ ($\text{M} + \text{H}$) $^+$ 406.1568, found 406.1564.

1-(2-Bromophenyl)-N-(3,4-dimethoxyphenethyl)-3-phenylprop-2-yn-1-amine (38g):

Orange gum; R_f (hexane/EtOAc 5:1) 0.50; yield 646 mg, 72 %; $^1\text{H NMR}$ (400 MHz, CDCl_3):

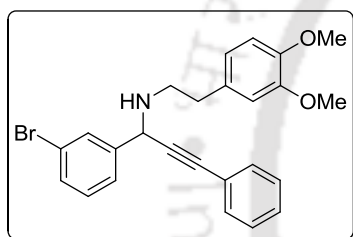


δ 7.74 (d, $J = 7.6$ Hz, 1 H), 7.55 (d, $J = 8.0$ Hz, 1 H), 7.44-7.47 (m, 2 H), 7.29-7.35 (m, 4 H), 7.15 (t, $J = 7.6$ Hz, 1 H), 6.75-6.81 (m, 3 H), 5.20 (s, 1 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 3.12 (ddd, $J = 14.0, 11.2$ and 6.8 Hz, 1 H), 3.03 (ddd, $J = 14.4, 12.0$ and 7.2 Hz, 1 H), 2.90-2.77 (m, 2 H), 1.79 (brs, 1 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3):

δ 149.0, 147.5, 139.4, 133.2, 132.4, 131.9, 129.6, 129.5, 128.4, 128.3, 127.9, 123.7, 123.0, 120.8, 111.9, 111.3, 88.5, 85.5, 56.02, 55.9, 54.3, 48.7, 35.7; **IR** (KBr, neat) 3319, 2933, 2834, 1592, 1514, 1463, 1263, 1152, 1027, 806, 757, 693 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{25}\text{BrNO}_2$ ($M + \text{H}$) $^+$ 450.1063, found 450.1069.

1-(3-Bromophenyl)-N-(3,4-dimethoxyphenethyl)-3-phenylprop-2-yn-1-amine (38h) :

Orange gum; R_f (hexane/EtOAc 5:1) 0.50; yield 628 mg, 70 %; $^1\text{H NMR}$ (400 MHz, CDCl_3):

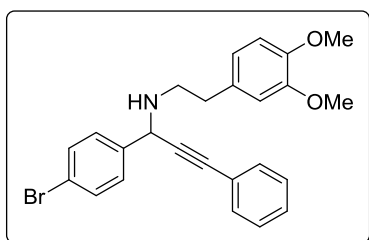


δ 7.71 (s, 1 H), 7.49-7.41 (m, 4 H), 7.33-7.30 (m, 3 H), 7.25 (t, $J = 8.0$ Hz, 1 H), 6.81-6.77 (m, 2 H), 6.75 (s, 1 H), 4.79 (s, 1 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 3.08 (ddd, $J = 10.8, 7.6$ and 3.6 Hz, 1 H), 2.98 (ddd, $J = 10.8, 7.2$ and 4.4 Hz, 1 H), 2.87-2.75 (m, 2H), 1.62 (brs, 1 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 148.5,

147.0, 142.3, 131.9, 131.3, 130.4, 130.2, 129.6, 127.9, 125.9, 122.4, 122.1, 120.2, 111.4, 110.9, 88.3, 85.5, 55.4, 55.3, 53.5, 47.9, 35.3; **IR** (KBr, neat) 3316, 2988, 2825, 1630, 1596, 1510, 1480, 1265, 1164, 1069, 855, 817, 755, 718, 579 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{25}\text{BrNO}_2$ ($M + \text{H}$) $^+$ 450.1063, found 450.1063.

1-(4-Bromophenyl)-N-(3,4-dimethoxyphenethyl)-3-phenylprop-2-yn-1-amine (38i):

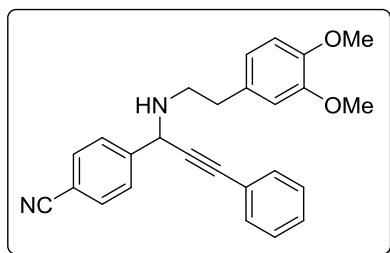
Orange gum; R_f (hexane/EtOAc 5:1) 0.50; yield 655 mg, 73 %; $^1\text{H NMR}$ (600 MHz, CDCl_3):



δ 7.47-7.43 (m, 6 H), 7.31-7.25 (m, 3 H), 6.76-6.74 (m, 3 H), 4.78 (s, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 3.08 (ddd, $J = 11.2, 7.2$ and 4.4 Hz, 1 H), 2.98 (ddd, $J = 11.2, 6.8$ and 4.4 Hz, 1 H), 2.84-2.75 (m, 2 H), 1.61 (brs, 1 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 148.7, 147.3, 139.2, 132.1, 131.5, 131.3, 129.2,

128.2, 122.7, 121.4, 120.5, 111.7, 111.1, 88.6, 85.6, 55.7, 55.6, 53.7, 48.0, 35.6; **IR** (KBr, neat) 3310, 3057, 2996, 2828, 1591, 1529, 1501, 1402, 1321, 1278, 1225, 1164, 1069, 1010, 853, 817, 549 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{25}\text{BrNO}_2$ ($M + \text{H}$) $^+$ 450.1063, found 450.1065.

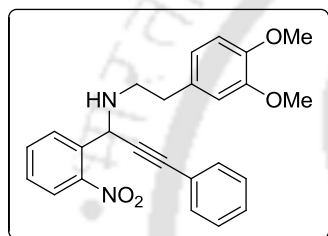
4-((3,4-Dimethoxyphenethyl)amino)-3-phenylprop-2-yn-1-yl)benzonitrile (38j):



Yellow gum; R_f (hexane/EtOAc 4:1) 0.51; yield 594 mg, 75 %; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.69-7.65 (m, 2 H), 7.64-7.58 (m, 2 H), 7.45-7.42 (m, 2 H), 7.32-7.28 (m, 3 H), 6.80-6.74 (m, 2 H), 6.74 (s, 1 H), 4.86 (s, 1 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.06 (ddd, $J = 10.8, 7.2$ and 2.4 Hz, 1 H), 2.98 (ddd, $J = 10.2, 7.2$ and 3.0 Hz, 1 H), 2.85-2.76 (m, 2 H), 1.63 (brs, 1 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 148.9, 147.5, 145.6, 132.3, 132.1, 131.7, 128.5, 128.4, 122.5, 120.6, 118.8, 111.9, 111.5, 111.3, 87.9, 86.4, 55.9, 55.8, 54.1, 48.2, 35.7; **IR** (KBr, neat) 3310, 2944, 2826, 2228, 1600, 1504, 1459, 1325, 1264, 1191, 1064, 852, 757, 688, 569 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 397.1911, found 397.1917.

***N*-(3,4-Dimethoxyphenethyl)-1-(2-nitrophenyl)-3-phenylprop-2-yn-1-amine (38k):**

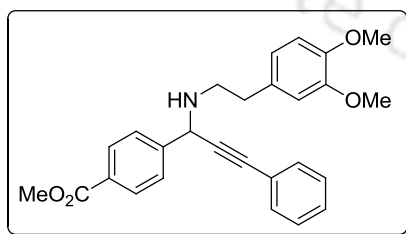
Brown gum; R_f (hexane/EtOAc 4:1) 0.51; yield 723 mg, 87 %; $^1\text{H NMR}$ (400 MHz, CDCl_3):



δ 7.94 (d, $J = 8.0$ Hz, 1 H), 7.80 (d, $J = 8.4$ Hz, 1 H), 7.57 (t, $J = 7.6$ Hz, 1 H), 7.45-7.42 (m, 3 H), 7.32-7.31 (m, 3 H), 6.79-6.76 (m, 2 H), 6.73 (s, 1 H), 5.50 (s, 1 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.10 (ddd, $J = 11.2, 7.6$ and 3.2 Hz, 1 H), 3.00 (ddd, $J = 11.6, 7.2$ and 4.8 Hz, 1 H), 2.85-2.70 (m, 2 H), 1.75 (brs, 1 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 149.2, 148.9, 147.4, 134.5, 132.6, 132.2, 131.7, 129.8, 128.6, 128.5, 128.3, 124.5, 122.5, 120.6, 111.9, 111.3, 87.3, 86.4, 55.8, 55.7, 50.7, 48.9, 35.6; **IR** (KBr, neat) 3347, 3003, 2954, 2833, 2199, 1598, 1498, 1414, 1275, 1142, 1054, 842, 691 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{25}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 417.1809, found 417.1807.

***N*-(3,4-Dimethoxyphenethyl)-1-(4-(methoxycarbonyl)phenyl)-3-phenylprop-2-yn-1-amine (38l):**

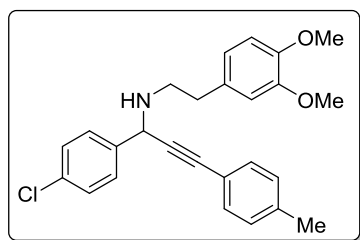
Orange gum; R_f (hexane/EtOAc 5:1) 0.45; yield 729 mg, 85 %; $^1\text{H NMR}$ (400 MHz, CDCl_3):



δ 8.03 (d, $J = 8.0$ Hz, 2 H), 7.63 (d, $J = 8.0$ Hz, 2 H), 7.45-7.43 (m, 2 H), 7.30-7.28 (m, 3 H), 6.79-6.76 (m, 2 H), 6.74 (s, 1 H), 4.87 (s, 1 H), 3.90 (s, 3 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.08 (ddd, $J = 12.0, 7.6$ and 6.0 Hz, 1 H), 2.98 (ddd, $J = 12.8, 6.8$ and 4.8 Hz, 1 H), 2.85-2.76 (m, 2 H), 1.69 (brs, 1 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 166.9, 149.0, 147.5, 145.4, 132.3, 131.7, 129.9, 129.6, 128.4, 128.4, 127.7, 120.7, 112.0, 111.4, 88.6, 86.0, 55.9, 55.8, 54.3, 52.2, 48.4, 35.8; **IR** (KBr, neat) 3411, 2948, 2851, 2203, 1729, 1628, 1500, 1451, 1279, 1114, 1016, 854, 818, 572 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{27}\text{H}_{28}\text{NO}_4$ ($\text{M} + \text{H}$) $^+$ 430.2013, found 430.2013.

1-(4-Chlorophenyl)-*N*-(3,4-dimethoxyphenethyl)-3-(*p*-tolyl)prop-2-yn-1-amine (38m):

Orange red gum; R_f (hexane/EtOAc 4:1) 0.51; yield 578 mg, 69 %; $^1\text{H NMR}$ (600 MHz,

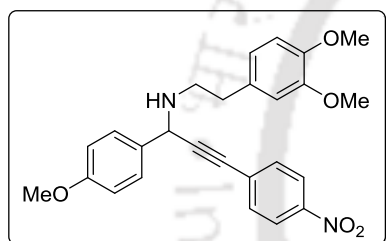


CDCl_3): δ 7.47 (d, J = 8.4 Hz, 2 H), 7.32 (d, J = 7.8 Hz, 2 H), 7.29 (d, J = 8.4 Hz, 2 H), 7.08 (d, J = 7.8 Hz, 2 H), 6.77-6.72 (m, 2 H), 6.72 (s, 1 H), 4.77 (s, 1 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 3.05 (ddd, J = 11.4, 7.2 and 2.4 Hz, 1 H), 2.96 (ddd, J = 11.4, 7.2 and 4.2 Hz, 1 H), 2.82-2.73 (m, 2 H), 2.31 (s, 3 H), 1.63

(brs, 1 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 149.0, 147.5, 139.0, 138.4, 133.4, 132.4, 131.6, 129.1, 129.0, 128.6, 120.7, 119.8, 111.9, 111.3, 88.1, 85.9, 55.9, 55.8, 53.9, 48.2, 35.8, 21.5; **IR** (KBr, neat) 3310, 3026, 2833, 2201, 1590, 1506, 1408, 1227, 1138, 1093, 1016, 818, 721 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{27}\text{ClINO}_2$ ($M + \text{H}$) $^+$ 420.1725, found 420.1725.

N-(3,4-Dimethoxyphenethyl)-1-(4-methoxyphenyl)-3-(4-nitrophenyl)prop-2-yn-1-amine (38n):

Orange red gum; R_f (hexane/EtOAc 4:1) 0.51; yield 640 mg, 72 %; $^1\text{H NMR}$ (600 MHz,

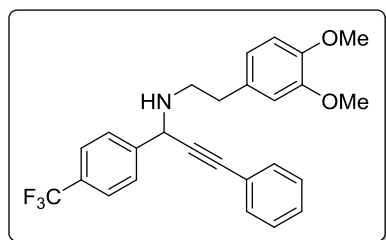


CDCl_3): δ 8.14 (d, J = 9.0 Hz, 2 H), 7.54 (d, J = 8.4 Hz, 2 H), 7.42 (d, J = 8.4 Hz, 2 H), 6.89 (d, J = 8.4 Hz, 2 H), 6.79-6.74 (m, 2 H), 6.73 (s, 1 H), 4.79 (s, 1 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 3.06 (ddd, J = 11.4, 7.2 and 4.8 Hz, 1 H), 2.95 (ddd, J = 11.4, 6.6 and 4.8 Hz, 1 H), 2.84-2.76 (m, 2 H),

1.69 (brs, 1 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 159.4, 148.9, 147.5, 147.0, 132.5, 132.3, 131.8, 130.1, 128.7, 123.8, 123.6, 120.7, 114.1, 112.0, 111.3, 95.5, 83.5, 56.0, 55.9, 55.4, 54.2, 48.5, 35.8; **IR** (KBr, neat) 3310, 2984, 2888, 1629, 1592, 1561, 1500, 1456, 1343, 1167, 1110, 1048, 995, 854, 750, 714 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_5$ ($M + \text{H}$) $^+$ 447.1914, found 447.1922.

N-(3,4-Dimethoxyphenethyl)-3-phenyl-1-(4-(trifluoromethyl)phenyl)prop-2-yn-1-amine (38o):

Pale yellow gum; R_f (hexane/EtOAc 4:1) 0.51; yield 632 mg, 72%; $^1\text{H NMR}$ (600 MHz,



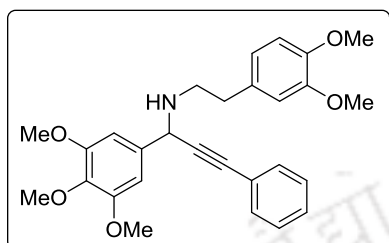
CDCl_3): δ 7.67 (d, J = 7.8 Hz, 2 H), 7.60 (d, J = 7.8 Hz, 2 H), 7.44 (d, J = 3.0 Hz, 2 H), 7.29 (d, J = 1.8 Hz, 3 H), 6.78 (d, J = 7.8 Hz, 1 H), 6.76 (d, J = 7.2 Hz, 1 H), 6.74 (s, 1 H), 4.87 (s, 1 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.10-3.05 (m, 1 H), 3.01-2.97 (m, 1 H), 2.85-2.76 (m, 2 H), 1.71 (brs, 1 H); $^{13}\text{C NMR}$

(100 MHz, CDCl_3): δ 149.1, 147.7, 144.4, 132.3, 131.8, 130.0, 129.9 (q, J = 31.5 Hz), 128.6, 128.5, 128.1, 125.6, 125.5, 125.3 (q, J = 271.5 Hz), 122.8, 120.8, 112.0, 111.5, 88.5, 86.2, 56.0, 55.9, 54.3, 48.3, 35.8; $^{19}\text{F NMR}$ (376 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$): 99.29; **IR** (KBr, neat) 2936,

2835, 1618, 1591, 1517, 1416, 1236, 1161, 1066, 1029, 759, 691 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{25}\text{F}_3\text{NO}_2$ ($\text{M} + \text{H}$)⁺ 440.1832, found 440.1835.

***N*-(3,4-dimethoxyphenethyl)-3-phenyl-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-amine (38p):**

Pale brown gum; R_f (hexane/EtOAc 3:1) 0.51; yield 626 mg, 68%; **^1H NMR** (600 MHz, CDCl_3): δ 7.43 (s, 2 H), 7.30 (s, 3 H), 6.78-6.75 (m, 5 H),

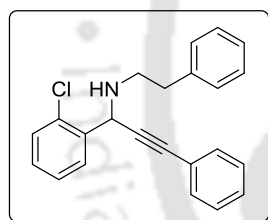


4.76 (s, 1 H), 3.85 (s, 6 H), 3.83 (s, 6 H), 3.81 (s, 3 H), 3.14-3.07 (m, 1 H), 3.03-2.96 (m, 1 H), 2.85-2.79 (m, 2 H), 1.96 (brs, 1 H); **^{13}C NMR** (150 MHz, CDCl_3): δ 153.3, 149.0, 147.5, 137.5, 136.0, 132.4, 131.7, 128.4, 128.3, 123.0, 120.7,

112.0, 111.4, 104.6, 89.2, 85.6, 60.9, 56.3, 56.2, 56.0, 55.9, 54.8, 48.4, 35.7; **IR** (KBr, neat) 3450, 3001, 2936, 2835, 1649, 1590, 1513, 1461, 1415, 1333, 1262, 1236, 1127, 1027, 1008, 762 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{28}\text{H}_{32}\text{NO}_5$ ($\text{M} + \text{H}$)⁺ 462.2275, found 462.2268.

1-(2-Chlorophenyl)-*N*-phenethyl-3-phenylprop-2-yn-1-amine (38q):

Orange gum; R_f (hexane/EtOAc 9:1) 0.51; yield 477 mg, 69 %; **^1H NMR** (600 MHz, CDCl_3):

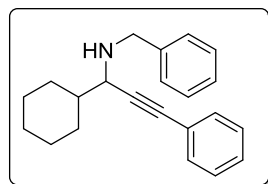


δ 7.72 (d, $J = 7.2$ Hz, 1 H), 7.45-7.41 (m, 3 H), 7.33 (d, $J = 8.4$ Hz, 1 H), 7.27-7.23 (m, 3 H), 7.22-7.15 (m, 6 H), 5.23 (s, 1 H), 3.12 (ddd, $J = 10.2$, 7.2 and 4.2 Hz, 1 H), 3.02 (ddd, $J = 10.8$, 7.8 and 4.2 Hz, 1 H), 2.90-2.81 (m, 2 H), 1.75 (brs, 1 H); **^{13}C NMR** (100 MHz, CDCl_3): δ 139.8, 137.8, 133.4, 132.2, 131.9, 129.9, 129.4, 129.2, 129.1, 128.8,

128.6, 128.5, 128.4, 127.2, 126.3, 123.0, 88.5, 85.3, 51.8, 48.7, 36.2; **IR** (KBr, neat) 3354, 3065, 2954, 2837, 1640, 1526, 1450, 1274, 1157, 1085, 1027, 963, 827, 793, 691 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{23}\text{H}_{21}\text{ClN}$ ($\text{M} + \text{H}$)⁺ 346.1357, found 346.1357.

***N*-Benzyl-1-cyclohexyl-3-phenylprop-2-yn-1-amine (38s):**

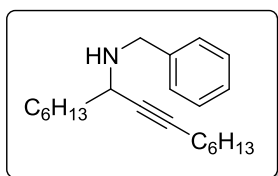
Pale yellow oil; R_f (hexane/EtOAc 9:1) 0.51; yield 375 mg, 62%; **^1H NMR** (400 MHz, CDCl_3): δ 7.47-7.43 (m, 2 H), 7.40 (d, $J = 7.2$ Hz, 2 H), 7.35-7.29 (m,



5 H), 7.23 (d, $J = 7.6$ Hz, 1 H), 4.10 (d, $J = 13.2$ Hz, 1 H), 3.88 (d, $J = 13.2$ Hz, 1 H), 3.39 (d, $J = 5.6$ Hz, 1 H), 1.90-1.76 (m, 3 H), 1.69-1.55 (m, 4 H), 1.27-1.15 (m, 5 H); **^{13}C NMR** (100 MHz, CDCl_3): δ 140.4,

131.9, 128.6, 128.6, 128.4, 128.0, 127.1, 123.7, 90.4, 84.9, 55.6, 51.9, 42.9, 30.4, 28.9, 26.7, 26.4, 26.3; **IR** (KBr, neat) 3026, 2851, 1620, 1529, 1499, 1450, 1219, 1166, 1050, 849, 753, 580 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{22}\text{H}_{26}\text{N}$ ($\text{M} + \text{H}$)⁺ 304.2060, found 304.2060.

***N*-Benzylpentadec-8-yn-7-amine (38u):**



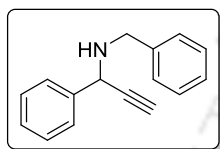
Light yellow oil; R_f (hexane/EtOAc 19:1) 0.51; yield 313 mg, 50 %;

$^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.35 (d, $J = 7.2$ Hz, 2 H), 7.30 (t, $J = 7.8$ Hz, 2 H), 7.23 (t, $J = 7.2$ Hz, 1 H), 4.00 (d, $J = 13.2$ Hz, 1 H), 3.79 (d, $J = 13.2$ Hz, 1 H), 3.33 (dd, $J = 7.2$ and 1.8 Hz, 1 H), 2.22 (t, $J =$

7.2 Hz, 2 H), 1.62-1.58 (m, 1 H), 1.57-1.49 (m, 3 H), 1.47-1.40 (m, 4 H), 1.34-1.26 (m, 11 H), 0.91-0.86 (m, 6 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 140.5, 128.5, 128.4, 127.0, 84.1, 81.7, 51.6, 49.8, 36.6, 32.0, 31.5, 29.3, 29.2, 28.7, 26.2, 22.8, 18.9, 14.2; **IR** (KBr, neat) 3327, 2959, 2854, 1627, 1531, 1500, 1460, 1221, 1105, 789 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{22}\text{H}_{36}\text{N}$ ($\text{M} + \text{H}$) $^+$ 314.2842, found 314.2840.

N-Benzyl-1-phenylprop-2-yn-1-amine (38v):

Pale yellow oil; R_f (hexane/EtOAc 19:1) 0.51; yield 110 mg, 25%; $^1\text{H NMR}$ (600 MHz,

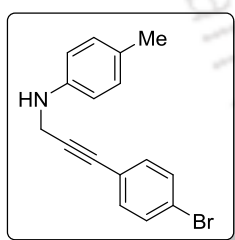


CDCl_3): δ 7.54 (d, $J = 6.0$ Hz, 2 H), 7.37-7.18 (m, 8 H), 4.57 (s, 1 H), 3.93 (d, $J = 13.2$ Hz, 1 H), 3.89 (d, $J = 14.4$ Hz, 1 H), 2.52 (s, 1 H), 1.71 (brs, 1 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 139.9, 139.8, 128.7, 128.6, 128.0,

127.7, 127.3, 83.9, 73.7, 53.0, 51.1; **IR** (KBr, neat) 3295, 3062, 3030, 2841, 1601, 1530, 1498, 1453, 1103, 1026, 794, 699 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{16}\text{H}_{16}\text{N}$ ($\text{M} + \text{H}$) $^+$ 222.1277, found 222.1252.

N-(3-(4-bromophenyl)prop-2-yn-1-yl)-4-methylaniline (38x):

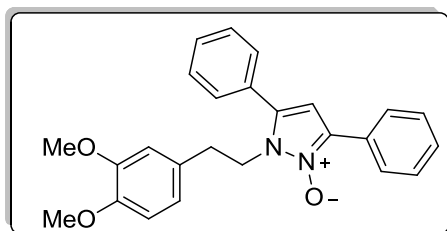
Pale yellow solid; mp 85-87 $^{\circ}\text{C}$; R_f (hexane/EtOAc 19:1) 0.5; yield 448 mg, 75%; $^1\text{H NMR}$



(400 MHz, CDCl_3): δ 7.41 (d, $J = 8.8$ Hz, 2 H), 7.25 (d, $J = 8.8$ Hz, 2 H), 7.04 (d, $J = 8.0$ Hz, 2 H), 6.66 (d, $J = 8.8$ Hz, 2 H), 4.11 (s, 2 H), 3.83 (brs, 1 H), 2.26 (s, 3 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 144.8, 133.3, 131.6, 129.9, 128.0, 122.5, 122.0, 113.9, 88.1, 82.3, 34.9, 20.6; **IR** (KBr, neat) 3395, 3286, 2921, 2867, 1620, 1523, 1480, 1404, 1315, 1251,

1127, 1083, 908, 811 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{16}\text{H}_{15}\text{BrN}$ ($\text{M} + \text{H}$) $^+$ 300.0382, found 300.0382.

1-(3,4-Dimethoxyphenethyl)-3,5-diphenyl-1H-pyrazole 2-oxide (39a):



Orange red gummy oil; R_f (hexane/EtOAc 3:2) 0.51;

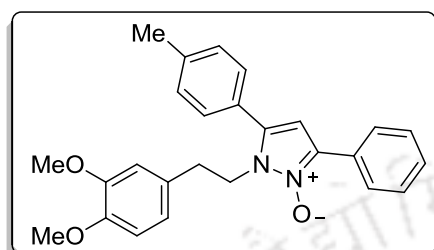
yield 109 mg, 91%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 8.22 (d, $J = 8.4$ Hz, 2 H), 7.45 (t, $J = 7.2$ Hz, 2 H), 7.35-7.34 (m, 4 H), 7.11-7.08 (m, 2 H), 6.61 (d, $J = 8.4$ Hz, 1 H), 6.46 (d, $J = 7.8$ Hz, 1 H), 6.40 (s, 1 H), 6.36 (s, 1 H), 4.46 (t, $J = 6.6$ Hz, 2 H), 3.79 (s, 3 H), 3.63 (s, 3 H), 3.04 (t, $J = 6.6$ Hz, 2 H); $^{13}\text{C NMR}$

(150 MHz, CDCl_3): δ 148.9, 147.9, 133.8, 130.1, 129.8, 129.2, 128.9, 128.8, 128.7, 128.4,

128.3, 126.4, 121.0, 111.9, 111.3, 99.1, 56.0, 55.6, 46.0, 33.9; **IR** (KBr, neat) 2999, 2834, 1515, 1478, 1332, 1262, 1143, 1027, 854, 757 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{25}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 401.1860, found 401.1860.

1-(3,4-Dimethoxyphenethyl)-3-phenyl-5-(*p*-tolyl)-1*H*-pyrazole 2-oxide (39b):

Orange red gummy oil; R_f (hexane/EtOAc 3:2) 0.51; yield 110 mg, 89%; **¹H NMR** (400 MHz,

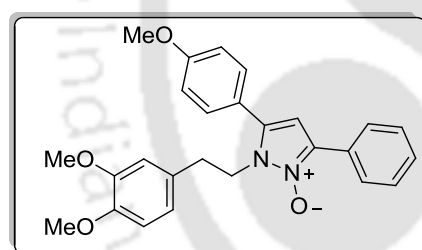


CDCl_3): δ 8.13 (d, $J = 7.2$ Hz, 2 H), 7.34 (t, $J = 7.6$ Hz, 2 H), 7.24 (t, $J = 6.4$ Hz, 1 H), 7.06 (d, $J = 7.2$ Hz, 2 H), 6.89 (d, $J = 6.8$ Hz, 2 H), 6.54 (d, $J = 6.0$ Hz, 1 H), 6.38 (d, $J = 7.6$ Hz, 1 H), 6.31 (s, 1 H), 6.23 (s, 1 H), 4.34 (t, $J = 6.8$ Hz, 2 H), 3.69 (s, 3 H), 3.54 (s, 3 H), 2.94 (t, $J =$

6.4 Hz, 2 H), 2.26 (s, 3 H); **¹³C NMR** (100 MHz, CDCl_3): δ 148.8, 147.7, 138.9, 133.7, 129.8, 129.8, 129.3, 128.5, 128.4, 128.3, 128.2, 126.2, 126.1, 120.9, 111.8, 111.1, 98.7, 55.8, 55.4, 45.7, 33.8, 21.2; **IR** (KBr, neat) 3001, 2835, 1610, 1512, 1469, 1345, 1256, 1083, 983, 848, 820, 728 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{27}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 415.2016, found 415.2017.

1-(3,4-Dimethoxyphenethyl)-5-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazole 2-oxide (39c):

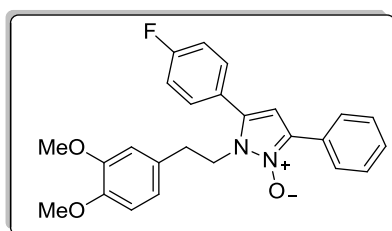
Orange red gummy oil; R_f (hexane/EtOAc 3:2) 0.51; yield 116 mg, 90%; **¹H NMR** (400 MHz,



CDCl_3): δ 8.24 (d, $J = 8.0$ Hz, 2 H), 7.47 (t, $J = 7.6$ Hz, 2 H), 7.38 (t, $J = 6.8$ Hz, 1 H), 7.04 (d, $J = 6.8$ Hz, 2 H), 6.90 (d, $J = 7.6$ Hz, 2 H), 6.67 (d, $J = 7.2$ Hz, 1 H), 6.51 (d, $J = 8.0$ Hz, 1 H), 6.44 (s, 1 H), 6.32 (s, 1 H), 4.44 (t, $J = 6.4$ Hz, 2 H), 3.83 (s, 6 H), 3.68 (s, 3 H), 3.06 (t, $J = 6.4$

Hz, 2 H); **¹³C NMR** (100 MHz, CDCl_3): δ 160.1, 148.9, 147.8, 133.6, 130.0, 129.9, 129.8, 128.7, 128.6, 128.4, 126.4, 121.6, 121.0, 114.2, 111.9, 111.2, 98.6, 56.0, 55.6, 55.4, 45.8, 33.9; **IR** (KBr, neat) 3000, 2935, 2833, 1585, 1515, 1472, 1342, 1264, 1235, 1140, 1029, 852, 820, 756, 707, 666 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$)⁺ 431.1965, found 431.1965.

1-(3,4-Dimethoxyphenethyl)-5-(4-fluorophenyl)-3-phenyl-1*H*-pyrazole 2-oxide (39d):

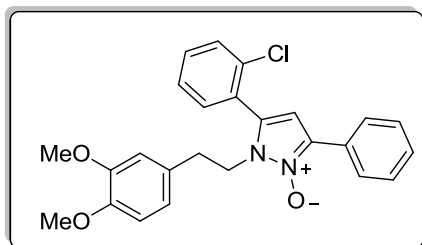


Light yellow gummy oil; R_f (hexane/EtOAc 4:1) 0.51; yield 111 mg, 89%; **¹H NMR** (400 MHz, CDCl_3): δ 8.24 (d, $J = 7.6$ Hz, 2 H), 7.48 (t, $J = 7.2$ Hz, 2 H), 7.38 (t, $J = 7.6$ Hz, 1 H), 7.08-7.01 (m, 4 H), 6.66 (d, $J = 8.4$ Hz, 1 H), 6.45 (d, $J = 8.0$ Hz, 1 H), 6.40 (s, 1 H), 6.35 (s, 1 H), 4.45 (t, $J = 6.4$ Hz,

2 H), 3.83 (s, 3 H), 3.67 (s, 3 H), 3.07 (t, $J = 6.8$ Hz, 2 H); **¹³C NMR** (100 MHz, CDCl_3): δ 164.3 (d, $J = 248.6$ Hz), 149.0, 147.9, 132.7, 130.5, 130.4, 130.0, 129.9, 128.8, 128.3, 126.4, 125.5, 121.1, 116.0 (d, $J = 21.3$ Hz), 112.0, 111.3, 99.2, 56.0, 55.7, 46.0, 33.8; **¹⁹F NMR** (376

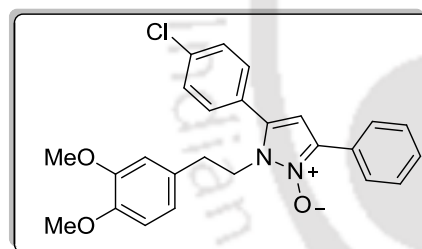
MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ 51.53 (s, C-F); IR (KBr, neat) 3059, 2935, 2835, 1610, 1503, 1488, 1276, 1252, 1135, 1035, 849, 734, 693, 583 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{24}\text{FN}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 419.1765, found 419.1770.

5-(2-Chlorophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-1H-pyrazole 2-oxide (39e):



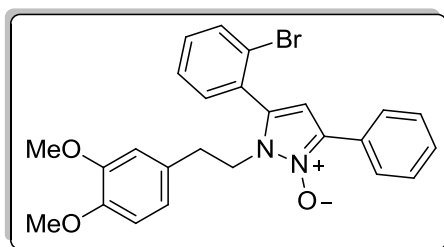
Orange red gummy oil; R_f (hexane/EtOAc 3:2) 0.51; yield 113 mg, 87%; ¹H NMR (400 MHz, CDCl_3): δ 8.25 (d, J = 8.0 Hz, 2 H), 7.49-7.43 (m, 3 H), 7.39-7.32 (m, 2 H), 7.19 (t, J = 7.2 Hz, 1 H), 6.73 (d, J = 7.6 Hz, 1 H), 6.65 (d, J = 8.4 Hz, 1 H), 6.41 (d, J = 8.0 Hz, 1 H), 6.37 (s, 1 H), 6.35 (s, 1 H), 4.31 (t, J = 6.4 Hz, 2 H), 3.83 (s, 3 H), 3.63 (s, 3 H), 3.04 (t, J = 6.4 Hz, 2 H); ¹³C NMR (100 MHz, CDCl_3): δ 148.9, 147.8, 133.9, 132.3, 130.8, 130.0, 129.8, 129.7, 128.6 (2C), 128.3, 128.1, 126.8, 126.3, 121.0, 111.8, 111.2, 100.1, 56.0, 55.6, 46.3, 33.4; IR (KBr, neat) 2934, 2834, 1513, 1481, 1345, 1263, 1142, 1030, 851, 754, 631 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{24}\text{ClN}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 435.1470, found 435.1470.

5-(4-Chlorophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-1H-pyrazole 2-oxide (39f):



Orange red gummy oil; R_f (hexane/EtOAc 3:2) 0.51; yield 118 mg, 91%; ¹H NMR (400 MHz, CDCl_3): δ 8.24 (d, J = 8.8 Hz, 2 H), 7.48 (t, J = 7.2 Hz, 2 H), 7.38 (t, J = 6.0 Hz, 1 H), 7.34 (d, J = 6.8 Hz, 2 H), 6.99 (d, J = 6.4 Hz, 2 H), 6.65 (d, J = 8.0 Hz, 1 H), 6.46 (d, J = 8.4 Hz, 1 H), 6.38 (s, 1 H), 6.36 (s, 1 H), 4.46 (t, J = 6.8 Hz, 2 H), 3.84 (s, 3 H), 3.67 (s, 3 H), 3.06 (t, J = 6.4 Hz, 2 H); ¹³C NMR (100 MHz, CDCl_3): δ 148.6, 147.6, 134.5, 132.1, 129.5, 129.4, 129.3, 128.6, 128.4, 128.3, 127.9, 127.4, 126.0, 120.8, 111.7, 111.1, 98.8, 55.6, 55.2, 45.6, 33.3; IR (KBr, neat) 2935, 2835, 1513, 1487, 1356, 1267, 1142, 1029, 757 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{24}\text{ClN}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 435.1470, found 435.1470.

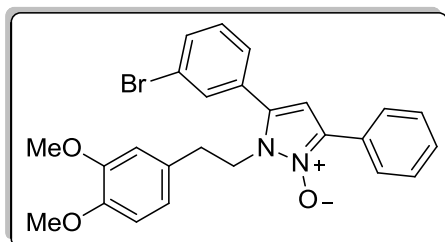
5-(2-Bromophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-1H-pyrazole 2-oxide (39g):



Plae orange red solid ; mp 122-124 °C; R_f (hexane/EtOAc 3:2) 0.51; yield 124 mg, 87%; ¹H NMR (400 MHz, CDCl_3): δ 8.21 (d, J = 8.8 Hz, 2 H), 7.57 (d, J = 7.6 Hz, 1 H), 7.42 (t, J = 7.6 Hz, 2 H), 7.32 (t, J = 7.2 Hz, 1 H), 7.24-7.15 (m, 2 H), 6.61 (t, J = 7.6 Hz, 2 H), 6.37 (d, J = 8.4 Hz, 1 H), 6.30 (s, 2 H), 4.24 (t, J = 6.8 Hz, 2 H), 3.78 (s, 3 H), 3.58 (s, 3 H), 3.00 (t, J = 6.8 Hz, 2 H); ¹³C NMR (100 MHz, CDCl_3): δ 148.8, 147.7, 132.8, 132.5, 131.1, 130.9, 130.1, 130.0, 129.5, 128.6, 128.5, 128.2, 127.2, 126.2, 124.1, 121.0, 111.7, 111.2, 99.8, 55.9, 55.5, 46.3, 33.5; IR (KBr, neat) 3060, 3000, 2929, 2834, 1594, 1515, 1479, 1271, 1261, 1203, 1029, 757, 700, 631 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{24}\text{BrN}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 451.1365, found 451.1365.

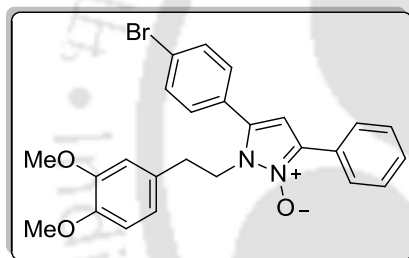
1423, 1335, 1265, 1143, 1029, 920, 807, 760, 694, 632 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{24}\text{BrN}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 479.0965, found 479.0962.

5-(3-Bromophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-1H-pyrazole 2-oxide (39h):



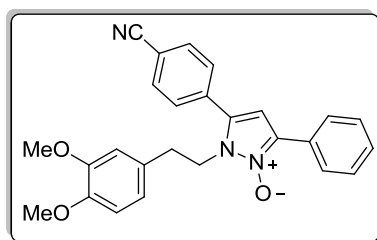
Orange red semisolid; R_f (hexane/EtOAc 3:2) 0.51; yield 126 mg, 88%; **^1H NMR** (400 MHz, CDCl_3): δ 8.22 (d, J = 8.8 Hz, 2 H), 7.48 (t, J = 8.0 Hz, 3 H), 7.38 (t, J = 7.6 Hz, 1 H), 7.23 (d, J = 7.6 Hz, 1 H), 7.13 (s, 1 H), 7.04 (d, J = 8.8 Hz, 1 H), 6.67 (d, J = 8.0 Hz, 1 H), 6.47 (d, J = 8.4 Hz, 1 H), 6.40 (s, 1 H), 6.37 (s, 1 H), 4.46 (t, J = 6.8 Hz, 2 H), 3.84 (s, 3 H), 3.66 (s, 3 H), 3.09 (t, J = 6.8 Hz, 2 H); **^{13}C NMR** (100 MHz, CDCl_3): δ 148.9, 147.9, 132.1, 131.8, 131.1, 130.2, 130.1, 129.5, 128.8, 128.7, 128.1, 126.9, 126.3, 122.7, 121.0, 111.9, 111.1, 99.5, 55.9, 55.6, 46.2, 33.6; **IR** (KBr, neat) 2934, 2834, 1511, 1489, 1335, 1139, 1075, 978, 813, 632 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{24}\text{BrN}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 479.0965, found 479.0967.

5-(4-Bromophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-1H-pyrazole 2-oxide (39i):

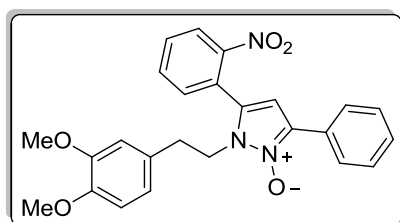


Brown red semisolid; R_f (hexane/EtOAc 3:2) 0.51; yield 126 mg, 88%; **^1H NMR** (600 MHz, CDCl_3): δ 8.21 (d, J = 7.8 Hz, 2 H), 7.46 (t, J = 7.8 Hz, 4 H), 7.37 (t, J = 7.2 Hz, 1 H), 6.91 (d, J = 7.8 Hz, 2 H), 6.63 (d, J = 7.8 Hz, 1 H), 6.44 (d, J = 7.8 Hz, 1 H), 6.35 (s, 1 H), 6.34 (s, 1 H), 4.45 (t, J = 6.6 Hz, 2 H), 3.82 (s, 3 H), 3.65 (s, 3 H), 3.04 (t, J = 6.6 Hz, 2 H); **^{13}C NMR** (150 MHz, CDCl_3): δ 149.0, 148.0, 132.6, 132.0, 131.8, 130.2, 130.0, 129.8, 128.8, 128.3, 126.4, 123.3, 121.2, 112.0, 111.3, 99.3, 56.1, 55.7, 46.1, 33.8; **IR** (KBr, neat) 3000, 2833, 1515, 1482, 1342, 1263, 1071, 850, 788, 735 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{24}\text{BrN}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 479.0965, found 479.0968.

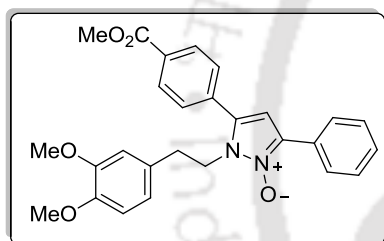
5-(4-Cyanophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-1H-pyrazole 2-oxide (39j):



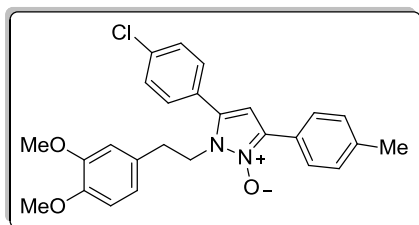
Yellow semisolid; R_f (hexane/EtOAc 3:2) 0.51; yield 110 mg, 87%; **^1H NMR** (600 MHz, CDCl_3): δ 8.20 (d, J = 7.8 Hz, 2 H), 7.62 (d, J = 7.8 Hz, 2 H), 7.48 (t, J = 7.2 Hz, 2 H), 7.39 (t, J = 7.2 Hz, 1 H), 7.13 (d, J = 7.8 Hz, 2 H), 6.59 (d, J = 7.8 Hz, 1 H), 6.43 (s, 1 H), 6.40 (d, J = 7.8 Hz, 1 H), 6.32 (s, 1 H), 4.50 (t, J = 6.6 Hz, 2 H), 3.82 (s, 3 H), 3.63 (s, 3 H), 3.06 (t, J = 6.6 Hz, 2 H); **^{13}C NMR** (150 MHz, CDCl_3): δ 148.8, 147.9, 133.4, 132.3, 131.6, 130.3, 129.3, 128.9, 128.7, 128.5, 127.8, 126.2, 121.0, 118.2, 112.1, 111.9, 111.2, 100.1, 55.9, 55.6, 46.2, 33.5; **IR** (KBr, neat) 3087, 2937, 2835, 2228, 1609, 1508, 1470, 1347, 1112, 979, 848, 778, cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{24}\text{N}_3\text{O}_3$ ($\text{M} + \text{H}$)⁺ 426.1812, found 426.1815.

1-(3,4-Dimethoxyphenethyl)-5-(2-nitrophenyl)-3-phenyl-1H-pyrazole 2-oxide (39k):

Orange red solid; mp 108-110 °C; R_f (hexane/EtOAc 1:1) 0.51; yield 109 mg, 82%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.23 (d, $J = 8.8$ Hz, 2 H), 8.06 (d, $J = 8.4$ Hz, 1 H), 7.59 (t, $J = 9.2$ Hz, 1 H), 7.53-7.46 (m, 3 H), 7.39 (t, $J = 7.6$ Hz, 1 H), 6.71 (d, $J = 7.2$ Hz, 1 H), 6.68 (d, $J = 8.4$ Hz, 1 H), 6.45 (d, $J = 8.0$ Hz, 1 H), 6.40 (s, 1 H), 6.36 (s, 1 H), 4.21 (t, $J = 6.8$ Hz, 2 H), 3.86 (s, 3 H), 3.66 (s, 3 H), 3.09 (t, $J = 6.8$ Hz, 2 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 148.9, 148.6, 147.9, 133.4, 133.0, 130.6, 130.1, 129.5, 128.6, 128.0, 127.7, 126.2, 124.6, 123.5, 121.1, 111.8, 111.2, 99.6, 56.0, 55.6, 46.6, 33.3; **IR** (KBr, neat) 3003, 2834, 1612, 1521, 1487, 1346, 1141, 1028, 983, 853, 783, 752 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{24}\text{N}_3\text{O}_5$ ($\text{M} + \text{H}$) $^+$ 446.1710, found 446.1709.

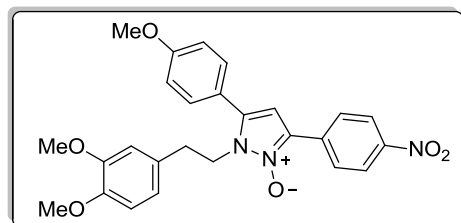
1-(3,4-Dimethoxyphenethyl)-5-(4-(methoxycarbonyl)phenyl)-3-phenyl-1H-pyrazole 2-oxide (39l):

Orange red semisolid; R_f (hexane/EtOAc 1:1) 0.51; yield 116 mg, 85%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.24 (d, $J = 7.6$ Hz, 2 H), 8.04 (d, $J = 8.0$ Hz, 2 H), 7.49 (t, $J = 7.2$ Hz, 2 H), 7.41 (t, $J = 7.6$ Hz, 1 H), 7.19 (d, $J = 8.8$ Hz, 2 H), 6.62 (d, $J = 8.0$ Hz, 1 H), 6.45-6.43 (m, 2 H), 6.39 (s, 1 H), 4.52 (t, $J = 6.4$ Hz, 2 H), 3.96 (s, 3 H), 3.83 (s, 3 H), 3.65 (s, 3 H), 3.07 (t, $J = 6.8$ Hz, 2 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 166.5, 149.0, 148.0, 133.6, 132.7, 130.4, 130.3, 130.1, 129.9, 129.6, 128.9, 128.8, 128.5, 128.1, 126.4, 121.1, 112.1, 111.4, 99.9, 56.0, 55.7, 52.5, 46.3, 33.8; **IR** (KBr, neat) 2954, 2836, 1720, 1611, 1515, 1437, 1279, 1102, 379, 850, 730 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{27}\text{H}_{27}\text{N}_2\text{O}_5$ ($\text{M} + \text{H}$) $^+$ 459.1914, found 459.1914.

5-(4-Chlorophenyl)-1-(3,4-dimethoxyphenethyl)-3-(p-tolyl)-1H-pyrazole 2-oxide (39m):

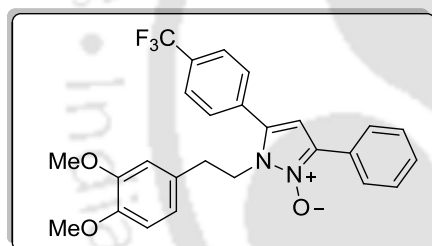
Light yellow semisolid; R_f (hexane/EtOAc 3:2) 0.51; yield 118 mg, 88%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 8.13 (d, $J = 8.4$ Hz, 2 H), 7.33 (d, $J = 7.8$ Hz, 2 H), 7.29 (d, $J = 7.8$ Hz, 2 H), 6.98 (d, $J = 8.4$ Hz, 2 H), 6.64 (d, $J = 8.4$ Hz, 1 H), 6.46 (d, $J = 7.8$ Hz, 1 H), 6.37 (s, 1 H), 6.33 (s, 1 H), 4.45 (t, $J = 6.6$ Hz, 2 H), 3.83 (s, 3 H), 3.66 (s, 3 H), 3.05 (t, $J = 6.6$ Hz, 2 H), 2.40 (s, 3 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 149.0, 148.0, 138.8, 135.0, 132.5, 130.2, 129.8, 129.7, 129.5, 129.0, 127.9, 126.3, 125.5, 121.1, 112.0, 111.3, 99.1, 56.0, 55.7, 46.0, 33.8, 21.5; **IR** (KBr, neat) 3004, 2832, 1608, 1508, 1447, 1346, 1087, 978, 844, 778, 686 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{26}\text{ClN}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 449.1626, found 449.1627.

1-(3,4-Dimethoxyphenethyl)-5-(4-methoxyphenyl)-3-(4-nitrophenyl)-1H-pyrazole 2-oxide (39n):



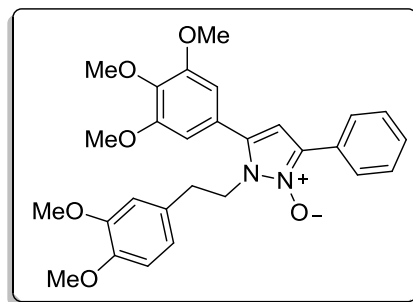
Light yellow semisolid; R_f (hexane/EtOAc 1:1) 0.51; yield 119 mg, 84%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 8.43 (d, $J = 8.4$ Hz, 2 H), 8.29 (d, $J = 9.0$ Hz, 2 H), 7.04 (d, $J = 8.4$ Hz, 2 H), 6.91 (d, $J = 8.4$ Hz, 2 H), 6.67 (d, $J = 8.4$ Hz, 1 H), 6.49 (d, $J = 7.8$ Hz, 1 H), 6.42 (s, 1 H), 6.39 (s, 1 H), 4.45 (t, $J = 6.6$ Hz, 2 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.67 (s, 3 H), 3.04 (t, $J = 6.6$ Hz, 2 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 160.5, 149.1, 148.0, 147.0, 134.7, 134.0, 130.0, 129.7, 127.9, 126.6, 124.1, 121.1, 121.0, 114.4, 111.9, 111.3, 98.8, 56.1, 55.7, 55.6, 46.0, 33.8; **IR** (KBr, neat) 2936, 2836, 1615, 1520, 1495, 1343, 1254, 1108, 1032, 979, 855, 740 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}_6$ ($\text{M} + \text{H}$) $^+$ 476.1816, found 476.1818.

1-(3,4-Dimethoxyphenethyl)-3-phenyl-5-(4-(trifluoromethyl)phenyl)-1H-pyrazole 2-oxide (39o):



Light yellow semisolid; R_f (hexane/EtOAc 3:2) 0.51; yield 120 mg, 86%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 8.21 (d, $J = 7.8$ Hz, 2 H), 7.58 (d, $J = 7.8$ Hz, 2 H), 7.46 (t, $J = 7.8$ Hz, 2 H), 7.37 (t, $J = 7.8$ Hz, 1 H), 7.13 (d, $J = 7.8$ Hz, 2 H), 6.57 (d, $J = 7.8$ Hz, 1 H), 6.39 (s, 2 H), 6.31 (s, 1 H), 4.49 (t, $J = 6.6$ Hz, 2 H), 3.80 (s, 3 H), 3.59 (s, 3 H), 3.04 (t, $J = 6.6$ Hz, 2 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 148.9, 148.0, 132.8, 132.2, 131.0, 130.7 (q, $J = 31.5$ Hz), 130.2, 129.5, 128.9, 128.8, 128.6, 128.1, 126.4, 125.7, 125.8, 123.9 (q, $J = 271.5$ Hz), 121.1, 111.9, 111.2, 99.8, 55.9, 55.6, 46.2, 33.7; $^{19}\text{F NMR}$ (376 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ 99.05 (s, C-F); **IR** (KBr, neat) 3064, 3001, 2932, 2835, 1647, 1609, 1517, 1493, 1429, 1264, 1233, 1157, 1029, 845, 763, 695 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 469.1734, found 469.1738.

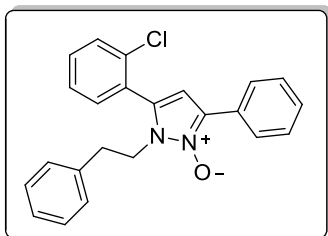
1-(3,4-Dimethoxyphenethyl)-3-phenyl-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole 2-oxide (39p):



Light yellow semisolid; R_f (hexane/EtOAc 1:1) 0.40; yield 117 mg, 80%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.21 (d, $J = 7.2$ Hz, 2 H), 7.45 (t, $J = 7.2$ Hz, 2 H), 7.35 (t, $J = 6.4$ Hz, 1 H), 6.60 (d, $J = 8.4$ Hz, 1 H), 6.44 (d, $J = 8.0$ Hz, 1 H), 6.39 (s, 1 H), 6.33 (s, 1 H), 6.28 (s, 2 H), 4.49 (t, $J = 6.8$ Hz, 2 H), 3.86 (s, 3 H), 3.82 (s, 6 H), 3.78 (s, 3 H), 3.65 (s, 3 H), 3.06 (t, $J = 6.0$ Hz, 2 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 153.5, 153.2, 148.9, 147.7, 138.8, 133.9, 130.0, 129.9, 128.7, 128.3, 126.4, 124.8, 121.0, 112.1, 111.2, 105.7, 99.0, 61.1, 61.0,

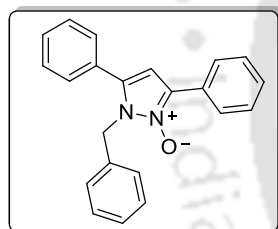
56.3, 56.3, 55.9, 55.8, 55.7, 46.1, 33.8; **IR** (KBr, neat) 3061, 2999, 2934, 2835, 1650, 1586, 1516, 1463, 1329, 1263, 1127, 1027, 1004, 844, 763, 697, cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{28}\text{H}_{31}\text{N}_2\text{O}_5$ ($\text{M} + \text{H}$)⁺ 491.2177, found 491.2171.

5-(2-Chlorophenyl)-1-phenethyl-3-phenyl-1H-pyrazole 2-oxide (39q):



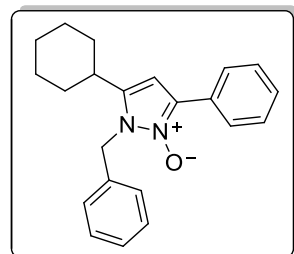
Orange red gummy oil; R_f (hexane/EtOAc 7:3) 0.49; yield 100 mg, 89%; **¹H NMR** (400 MHz, CDCl_3): δ 8.26 (d, $J = 7.6$ Hz, 2 H), 7.51-7.47 (m, 3 H), 7.40-7.35 (m, 2 H), 7.22-7.15 (m, 4 H), 6.93-6.91 (m, 2 H), 6.77 (d, $J = 7.2$ Hz, 1 H), 6.40 (s, 1 H), 4.30 (t, $J = 6.8$ Hz, 2 H), 3.08 (t, $J = 6.8$ Hz, 2 H); **¹³C NMR** (100 MHz, CDCl_3): δ 137.8, 134.3, 132.4, 131.0, 129.9, 129.8, 129.7, 129.2, 128.8, 128.7, 128.7, 128.5, 128.3, 127.1, 126.8, 126.5, 100.4, 46.1, 34.2; **IR** (KBr, neat) 3062, 3028, 2926, 2854, 1601, 1515, 1478, 1400, 1362, 1234, 1134, 1073, 955, 798, 756, 699 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{23}\text{H}_{20}\text{ClN}_2\text{O}$ ($\text{M} + \text{H}$)⁺ 375.1259, found 375.1260.

1-Benzyl-3,5-diphenyl-1H-pyrazole 2-oxide (39r):



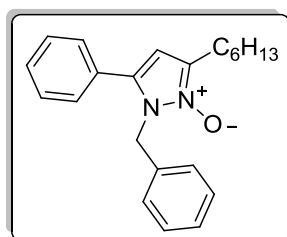
Pale yellow solid: mp 115-117 °C; R_f (hexane/EtOAc 7:3) 0.51; yield 88 mg, 90%; **¹H NMR** (400 MHz, CDCl_3): δ 8.26 (d, $J = 7.6$ Hz, 2 H), 7.41 (t, $J = 7.2$ Hz, 2 H), 7.34-7.29 (m, 6 H), 7.25-7.19 (m, 3 H), 7.13 (d, $J = 6.4$ Hz, 2 H), 6.52 (s, 1 H), 5.44 (s, 2 H); **¹³C NMR** (100 MHz, CDCl_3): δ 135.9, 133.4, 129.5, 129.0, 128.9, 128.7, 128.5, 128.4, 128.2, 128.1, 127.6, 126.9, 126.2, 99.3, 47.0; **IR** (KBr, neat) 3061, 2925, 2853, 1602, 1517, 1432, 1312, 1227, 1181, 1076, 1028, 935, 757, 730, 696 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}$ ($\text{M} + \text{H}$)⁺ 327.1492, found 327.1489.

1-Benzyl-5-cyclohexyl-3-phenyl-1H-pyrazole 2-oxide (39s):



Orange red gummy oil; R_f (hexane/EtOAc 7:3) 0.51; yield 87 mg, 88%; **¹H NMR** (400 MHz, CDCl_3): δ 8.22 (d, $J = 7.2$ Hz, 2 H), 7.43 (t, $J = 7.6$ Hz, 2 H), 7.35-7.30 (m, 3 H), 7.28 (d, $J = 7.6$ Hz, 1 H), 7.22 (d, $J = 7.6$ Hz, 2 H), 6.21 (s, 1 H), 5.47 (s, 2 H), 2.45 (t, $J = 7.2$ Hz, 1 H), 1.79 (d, $J = 10.0$ Hz, 4 H), 1.72 (d, $J = 8.4$ Hz, 1 H), 1.34 (t, $J = 11.2$ Hz, 3 H), 1.26 (t, $J = 10.4$ Hz, 2 H); **¹³C NMR** (100 MHz, CDCl_3): δ 138.6, 136.1, 129.2, 129.0, 128.8, 128.6, 128.4, 127.9, 127.0, 126.4, 95.7, 45.6, 35.7, 32.8, 26.3, 25.8; **IR** (KBr, neat) 3063, 2929, 2853, 1555, 1513, 1489, 1418, 1224, 1190, 1104, 993, 758, 704 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}$ ($\text{M} + \text{H}$)⁺ 333.1961, found 333.1968.

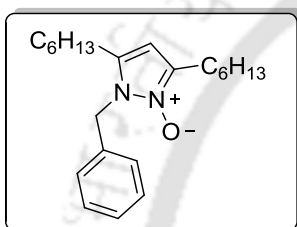
1-Benzyl-3-hexyl-5-phenyl-1H-pyrazole 2-oxide (39t):



Pale yellow gummy oil; R_f (hexane/EtOAc 7:3) 0.51; yield 86 mg, 86%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.35 (m, 3 H), 7.29-7.19 (m, 5 H), 7.09 (d, $J = 7.2$ Hz, 2 H), 6.11 (s, 1 H), 5.42 (s, 2 H), 2.75 (t, $J = 8.0$ Hz, 2 H), 1.75-1.68 (m, 2 H), 1.42-1.26 (m, 6 H), 0.89 (t, $J = 6.8$ Hz, 3 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 136.1, 133.0, 132.5, 129.3, 128.9, 128.8, 128.7, 128.1, 127.6, 127.0, 100.7, 47.1, 31.5, 28.9, 26.8, 24.8, 22.5, 14.1; **IR** (KBr, neat) 3064, 2955, 2927, 2856, 1604, 1558, 1501, 1474, 1362, 1269, 1186, 1076, 1031, 960, 792, 730, 699, 660 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 335.2118, found 335.2114.

1-Benzyl-3,5-dihexyl-1H-pyrazole 2-oxide (39u):

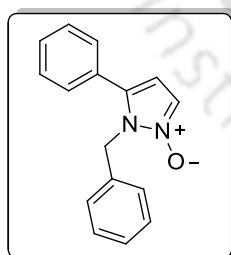
Orange red gummy oil; R_f (hexane/EtOAc 7:3) 0.51; yield 87 mg, 85%; $^1\text{H NMR}$ (600 MHz,



CDCl_3): δ 7.30 (t, $J = 7.2$ Hz, 2 H), 7.25 (t, $J = 7.2$ Hz, 1 H), 7.18 (d, $J = 7.8$ Hz, 2 H), 5.76 (s, 1 H), 5.37 (s, 2 H), 2.69 (t, $J = 7.2$ Hz, 2 H), 2.42 (d, $J = 7.8$ Hz, 2 H), 1.69-1.63 (m, 2 H), 1.55-1.45 (m, 2 H), 1.04-1.38 (m, 2 H), 1.32-1.30 (m, 4 H), 1.29-1.25 (m, 4 H), 1.24-1.20 (m, 2 H), 0.90-0.85 (m, 6 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 136.0, 132.8, 131.9, 128.8, 127.9, 127.1, 98.6, 45.7, 31.7, 31.5, 29.1, 28.8, 27.6, 27.1, 26.1, 25.0, 22.7, 22.6, 14.2, 14.1; **IR** (KBr, neat) 2854, 1531, 1504, 1296, 1212, 970, 728 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{22}\text{H}_{35}\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 343.1744, found 343.2749.

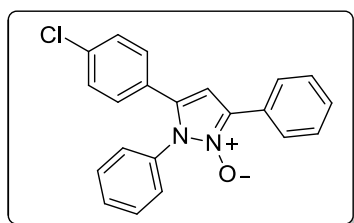
1-Benzyl-5-phenyl-1H-pyrazole 2-oxide (39v):

Colorless gummy oil: R_f (hexane/EtOAc 7:3) 0.56; yield 51 mg, 68%; $^1\text{H NMR}$ (600 MHz,



CDCl_3): δ 7.39 (s, 3 H), 7.34 (s, 1 H), 7.28-7.24 (m, 5 H), 7.11 (d, $J = 7.2$ Hz, 2 H), 6.23 (d, $J = 3.0$ Hz, 1 H), 5.44 (s, 2 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 135.9, 134.2, 129.3, 129.2, 129.1, 128.9, 128.4, 127.9, 127.0, 119.7, 101.1, 47.1; **IR** (KBr, neat) 3146, 3032, 2925, 1642, 1569, 1494, 1375, 1248, 1184, 1031, 978, 848, 782, 658 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 251.1179, found 251.1189.

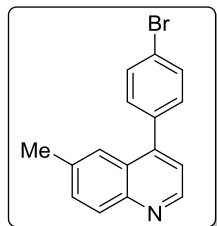
5-(4-Chlorophenyl)-1,3-diphenyl-1H-pyrazole 2-oxide (39w):



Pale yellow solid: mp 211-213 $^{\circ}\text{C}$; R_f (hexane/EtOAc 3:2) 0.50.; yield 94 mg, 91%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.26 (d, $J = 8.0$ Hz, 2 H), 7.50-7.47 (m, 5 H), 7.40 (s, 3 H), 7.25 (d, $J = 7.6$ Hz, 2 H), 7.16 (d, $J = 8.4$ Hz, 2 H), 6.74 (s, 1 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 134.7, 133.3, 131.7, 130.3, 129.8, 129.6, 129.5, 129.2, 129.0, 128.9, 128.8, 128.0, 127.5, 126.7, 100.0; **IR** (KBr, neat) 2985, 2900, 1487, 1411, 1234, 1124, 1013, 786, 707, 690 cm^{-1} ; **HRMS** (ESI) calcd. for

$C_{21}H_{16}ClN_2O$ ($M + H$)⁺ 347.0946, found 347.0946.

4-(4-Bromophenyl)-6-methylquinoline (40):

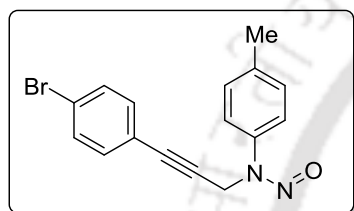


Pale yellow semisolid; R_f (hexane/EtOAc 5:1) 0.61; yield 16 mg, 19 %; ¹H NMR (600 MHz, CDCl₃): δ 8.88 (s, 1 H), 8.11 (d, J = 8.4 Hz, 1 H), 7.69 (d, J = 8.4 Hz, 2 H), 7.60 (d, J = 9.0 Hz, 2 H), 7.39 (d, J = 8.4 Hz, 2 H), 7.29 (d, J = 4.2 Hz, 1 H), 2.49 (3 H); ¹³C NMR (150 MHz, CDCl₃): δ 149.0, 147.3, 146.9, 137.3, 137.1, 132.3, 132.1, 131.3, 129.5, 124.5,

123.1, 121.5, 22.1; IR (KBr, neat) 3180, 2985, 1510, 1492, 1448, 1344, 1110, 980, 778, 670 cm⁻¹; HRMS (ESI) calcd. for $C_{16}H_{13}BrN$ ($M + H$)⁺ 298.0226, found 298.0266.

N-(3-(4-Bromophenyl)prop-2-yn-1-yl)-N-(p-tolyl)nitrous amide (41):

Dark red solid; mp 70-72 °C; R_f (hexane/EtOAc 9:1) 0.60; yield 77 mg, 75%; ¹H NMR (400

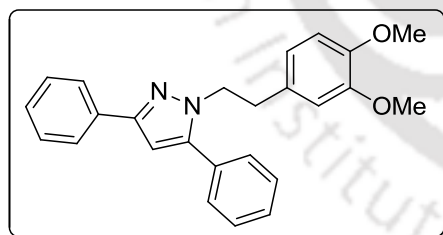


MHz, CDCl₃): δ 7.55 (d, J = 8.0 Hz, 2 H), 7.42 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 7.22 (d, J = 7.2 Hz, 2 H), 4.91 (s, 2 H), 2.42 (s, 3 H); ¹³C NMR (150 MHz, CDCl₃): δ 138.7, 137.9, 133.4, 131.7, 130.2, 123.2, 121.2, 120.1, 82.7, 82.5, 33.8, 21.2;

IR (KBr, neat) 2960, 2924, 2852, 1629, 1532, 1406, 1283, 1136, 1011, 915, 819, 527 cm⁻¹; HRMS (ESI) calcd. for $C_{16}H_{14}N_2O$ ($M + H$)⁺ 329.0824, found 329.0288.

1-(3,4-Dimethoxyphenethyl)-3,5-diphenyl-1H-pyrazole (42a):

Light yellow solid; mp 73-75 °C; R_f (hexane/EtOAc 4:1) 0.50; yield 55 mg, 96%; ¹H NMR

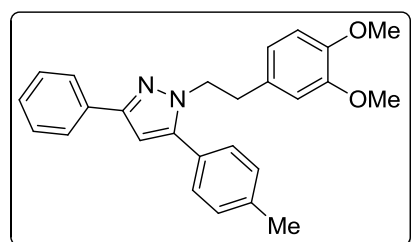


(600 MHz, CDCl₃): δ 7.87 (d, J = 7.8 Hz, 2 H), 7.44 (t, J = 7.2 Hz, 2 H), 7.36-7.32 (m, 4 H), 7.08 (s, 1 H), 7.07 (s, 1 H), 6.68 (d, J = 8.4 Hz, 1 H), 6.51 (d, J = 7.2 Hz, 1 H), 6.50 (s, 1 H), 6.38 (s, 1 H), 4.34 (t, J = 7.2 Hz, 2 H), 3.83 (s, 3 H), 3.67 (s, 3 H), 3.12 (t, J = 6.6 Hz, 2 H); ¹³C

NMR (150 MHz, CDCl₃): δ 151.0, 148.9, 147.9, 145.8, 133.7, 130.9, 130.8, 129.1, 128.8, 128.6, 127.8, 125.8, 120.9, 112.0, 111.2, 103.4, 56.1, 55.8, 51.1, 36.6; IR (KBr, neat) 3058, 2999, 2935, 2834, 1604, 1515, 1461, 1369, 1236, 1139, 1078, 1030, 919, 804, 735, 697 cm⁻¹;

HRMS (ESI) calcd. for $C_{25}H_{25}N_2O_3$ ($M + H$)⁺ 385.1919, found 385.1919.

1-(3,4-Dimethoxyphenethyl)-3-phenyl-5-(p-tolyl)-1H-pyrazole (42b):

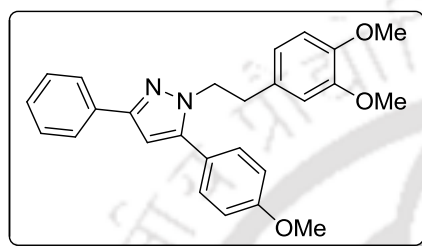


Pale yellow solid; mp 75-77 °C; R_f (hexane/EtOAc 4:1) 0.50; yield 56 mg, 94%; ¹H NMR (600 MHz, CDCl₃): δ 7.87 (d, J = 7.8 Hz, 2 H), 7.43 (t, J = 7.8 Hz, 2 H), 7.33 (t, J = 7.2 Hz, 1 H), 7.17 (d, J = 7.2 Hz, 2 H), 6.97 (d, J = 7.8

Hz, 2 H), 6.70 (d, $J = 8.4$ Hz, 1 H), 6.53 (d, $J = 8.4$ Hz, 1 H), 6.48 (s, 1 H), 6.40 (s, 1 H), 4.33 (t, $J = 6.6$ Hz, 2 H), 3.84 (s, 3 H), 3.68 (s, 3 H), 3.13 (t, $J = 7.2$ Hz, 2 H), 2.39 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3): δ 150.9, 148.9, 147.8, 145.8, 138.5, 133.8, 130.9, 129.2, 129.0, 128.8, 127.8, 127.7, 125.7, 120.9, 112.0, 111.2, 103.2, 56.0, 55.7, 51.0, 36.5, 21.4; IR (KBr, neat) 3056, 2936, 2834, 1593, 1515, 1492, 1460, 1368, 1263, 1154, 1030, 958, 823, 766, 695 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 399.2067, found 399.2076.

1-(3,4-Dimethoxyphenethyl)-5-(4-methoxyphenyl)-3-phenyl-1H-pyrazole (42c):

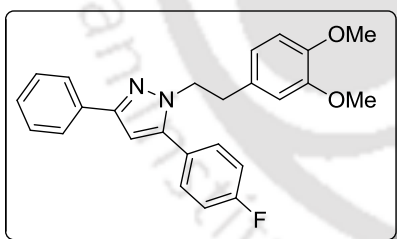
Light yellow solid; mp 95-97 $^{\circ}\text{C}$; R_f (hexane/EtOAc 4:1) 0.51; yield 58 mg, 94%; ^1H NMR



(600 MHz, CDCl_3): δ 7.86 (d, $J = 7.2$ Hz, 2 H), 7.42 (t, $J = 7.2$ Hz, 2 H), 7.31 (t, $J = 7.2$ Hz, 1 H), 6.97 (d, $J = 7.8$ Hz, 2 H), 6.86 (d, $J = 7.8$ Hz, 2 H), 6.69 (d, $J = 7.8$ Hz, 1 H), 6.52 (d, $J = 8.4$ Hz, 1 H), 6.45 (s, 1 H), 6.38 (s, 1 H), 4.29 (t, $J = 7.2$ Hz, 2 H), 3.83 (s, 6 H), 3.67 (s, 3 H), 3.11

(t, $J = 7.2$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 160.1, 148.9, 147.8, 133.6, 130.0, 129.9, 129.9, 128.7, 128.6, 128.4, 126.4, 121.6, 121.0, 114.2, 111.9, 111.2, 98.6, 56.0, 55.6, 55.4, 45.8, 33.9; IR (KBr, neat) 3055, 3000, 2937, 2836, 1612, 1554, 1492, 1406, 1369, 1260, 1141, 1032, 838, 767, 605 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 415.2016, found 415.2021.

1-(3,4-Dimethoxyphenethyl)-5-(4-fluorophenyl)-3-phenyl-1H-pyrazole (42d):

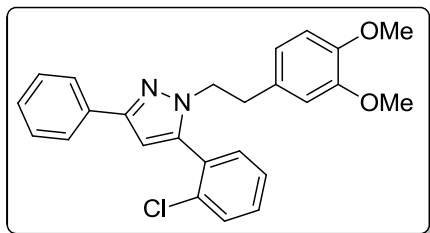


Light yellow semi solid; R_f (hexane/EtOAc 4:1) 0.50; yield 57 mg, 95%; ^1H NMR (600 MHz, CDCl_3): δ 7.87 (d, $J = 7.2$ Hz, 2 H), 7.42 (t, $J = 7.8$ Hz, 2 H), 7.32 (t, $J = 7.2$ Hz, 1 H), 7.02 (t, $J = 7.8$ Hz, 2 H), 6.96 (t, $J = 5.4$ Hz, 2 H), 6.68 (d, $J = 7.8$ Hz, 1 H), 6.47 (d, $J = 7.8$ Hz, 1 H), 6.45 (s, 1 H),

6.33 (s, 1 H), 4.28 (t, $J = 6.6$ Hz, 2 H), 3.83 (s, 3 H), 3.65 (s, 3 H), 3.10 (t, $J = 6.6$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 162.9 (d, $J = 247.5$ Hz), 151.0, 148.9, 147.9, 144.9, 133.7, 131.0 (d, $J = 9.0$ Hz), 130.9, 128.9, 127.9, 126.9, 125.8, 120.9, 115.5 (d, $J = 22.5$ Hz), 112.0, 111.3, 103.4, 56.1, 55.8, 51.1, 36.5; ^{19}F NMR (376 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ 48.90 (s, C-F); IR (KBr, neat) 3060, 2933, 2834, 2215, 1683, 1594, 1508, 1486, 1256, 1207, 1148, 1071, 861, 756, 690 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{24}\text{FN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 403.1816, found 403.1814.

5-(2-Chlorophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-1H-pyrazole (42e):

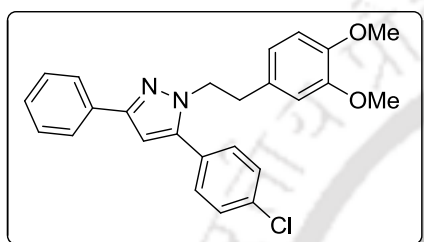
Light yellow solid; mp 85-87 $^{\circ}\text{C}$; R_f (hexane/EtOAc 4:1) 0.50; yield 58 mg, 92%; ^1H NMR (400 MHz, CDCl_3): δ 7.89 (d, $J = 7.2$ Hz, 2 H), 7.46-7.41 (m, 3 H), 7.34-7.29 (m, 2 H), 7.17 (t, $J = 7.6$ Hz, 1 H), 6.72 (d, $J = 7.6$ Hz, 1 H), 6.67 (d, $J = 8.4$ Hz, 1 H), 6.49 (s, 1 H), 6.44 (d, $J = 8.0$ Hz, 1 H), 6.34 (s, 1 H), 4.16 (t, $J = 7.2$ Hz, 2 H), 3.83 (s, 3 H), 3.65 (s, 3 H), 3.09 (t, J



= 6.8 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 150.8, 148.8, 147.7, 142.1, 134.1, 133.6, 132.3, 130.9, 130.3, 129.8, 129.6, 128.8, 127.8, 126.6, 125.7, 120.8, 111.8, 111.2, 103.9, 56.0, 55.7, 51.4, 36.3; IR (KBr, neat) 3061, 2936, 2833, 1594, 1515, 1463, 1263, 1238, 1190, 1156, 1072, 1030, 956, 804, 765 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{24}\text{ClN}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 419.1521, found 419.1521.

5-(4-Chlorophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-1H-pyrazole (42f):

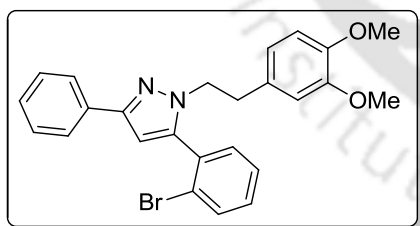
Light yellow semisolid; mp 73-75 $^{\circ}\text{C}$; R_f (hexane/EtOAc 4:1) 0.50; yield 59 mg, 94%; ^1H



NMR (600 MHz, CDCl_3): δ 7.86 (d, J = 7.8 Hz, 2 H), 7.42 (t, J = 7.2 Hz, 2 H), 7.32 (t, J = 7.2 Hz, 1 H), 7.28 (d, J = 7.8 Hz, 2 H), 6.90 (d, J = 7.8 Hz, 2 H), 6.65 (d, J = 8.4 Hz, 1 H), 6.47-6.45 (m, 2 H), 6.30 (s, 1 H), 4.28 (t, J = 6.0 Hz, 2 H), 3.82 (s, 3 H), 3.64 (s, 3 H), 3.09 (t, J = 6.6 Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 151.0, 148.8, 147.8, 144.7, 134.6, 133.5, 130.7, 130.2, 129.1, 128.8, 128.7, 128.5, 127.9, 125.7, 120.8, 111.9, 111.1, 103.4, 56.0, 55.6, 51.1, 36.4; IR (KBr, neat) 3060, 2998, 2937, 2834, 1595, 1514, 1461, 1420, 1368, 1263, 1238, 1189, 1155, 1030, 956, 804, 764, 696 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{24}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 419.1521, found 419.1524.

5-(2-Bromophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-1H-pyrazole (42g):

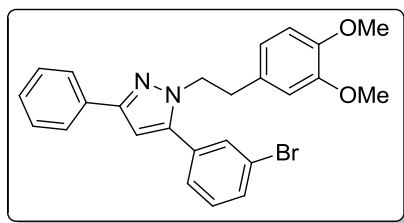
Light yellow solid; mp 91-93 $^{\circ}\text{C}$; R_f (hexane/EtOAc 4:1) 0.51; yield 63 mg, 91%; ^1H NMR



(400 MHz, CDCl_3): δ 7.88 (d, J = 7.6 Hz, 2 H), 7.62 (t, J = 7.2 Hz, 1 H), 7.41 (t, J = 7.6 Hz, 2 H), 7.31 (t, J = 7.6 Hz, 1 H), 7.25-7.18 (m, 2 H), 6.65 (d, J = 8.0 Hz, 2 H), 6.47 (s, 1 H), 6.43 (d, J = 8.0 Hz, 1 H), 6.34 (s, 1 H), 4.14 (t, J = 6.4 Hz, 2 H), 3.83 (s, 3 H), 3.64 (s, 3 H), 3.09 (t, J = 6.4 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 150.6, 148.7, 147.6, 143.6, 133.5, 132.7, 132.3, 131.8, 130.8, 130.4, 128.7, 127.7, 127.0, 125.6, 124.2, 120.8, 111.8, 111.1, 103.6, 55.9, 55.6, 51.3, 36.2; IR (KBr, neat) 3056, 2998, 2930, 2833, 1639, 1515, 1401, 1419, 1366, 1263, 1237, 1190, 1156, 1029, 955, 803, 763, 695 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{24}\text{BrN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 463.1016, found 463.1015.

5-(3-Bromophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-1H-pyrazole (42h):

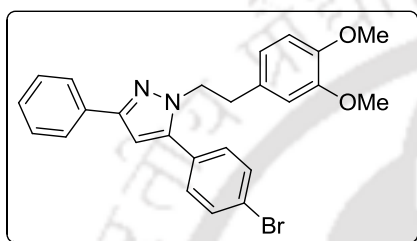
Light yellow semisolid; R_f (hexane/EtOAc 4:1) 0.51; yield 64 mg, 93%; ^1H NMR (600 MHz, CDCl_3): δ 7.87 (d, J = 7.8 Hz, 2 H), 7.46 (d, J = 7.6 Hz, 1 H), 7.43 (t, J = 7.2 Hz, 2 H), 7.34 (t, J = 7.8 Hz, 1 H), 7.19 (t, J = 7.8 Hz, 1 H), 6.99 (s, 1 H), 6.98 (d, J = 8.4 Hz, 1 H), 6.49 (d, J =



8.4 Hz, 1 H), 6.50 (d, $J = 7.8$ Hz, 1 H), 6.6 Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 151.1, 148.8, 147.8, 144.4, 133.5, 132.6, 131.9, 131.5, 130.6, 129.9, 128.8, 127.9, 127.7, 125.7, 122.5, 120.8, 111.8, 111.2, 103.2, 56.0, 55.7, 51.1, 36.4; IR (KBr, neat) 3060, 2998, 2935, 2833, 1560, 1546, 1515, 1462, 1420, 1334, 1263, 1189, 1077, 1029, 958, 887, 765, 695 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{24}\text{BrN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 463.1016, found 463.1020.

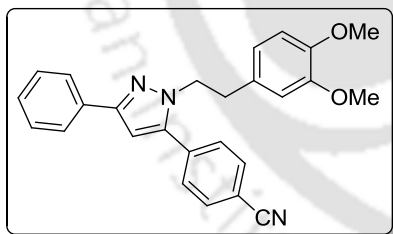
5-(4-Bromophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-1H-pyrazole (42i):

Light yellow semisolid; R_f (hexane/EtOAc 4:1) 0.51; yield 65 mg, 94%; ^1H NMR (600 MHz,



CDCl_3): δ 7.86 (d, $J = 7.2$ Hz, 2 H), 7.46-7.41 (m, 4 H), 7.33 (t, $J = 7.2$ Hz, 1 H), 6.84 (d, $J = 7.8$ Hz, 2 H), 6.67 (d, $J = 8.4$ Hz, 1 H), 6.48-6.45 (m, 2 H), 6.31 (s, 1 H), 4.29 (t, $J = 6.6$ Hz, 2 H), 3.83 (s, 3 H), 3.65 (s, 3 H), 3.10 (t, $J = 6.6$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 151.1, 148.9, 147.9, 144.8, 133.5, 131.7, 130.7, 130.6, 129.6, 128.9, 127.9, 125.8, 122.9, 120.9, 111.9, 111.2, 101.4, 56.1, 55.7, 51.1, 36.5; IR (KBr, neat) 3057, 2999, 2935, 2834, 1596, 1515, 1461, 1263, 1238, 1188, 1155, 1074, 1029, 831, 767, 696 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{24}\text{BrN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 463.1016, found 463.1018.

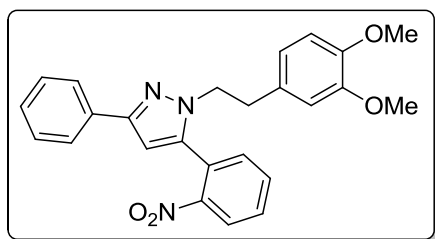
4-(1-(3,4-Dimethoxyphenethyl)-3-phenyl-1H-pyrazol-5-yl)benzonitrile (42j):



Light yellow semisolid; R_f (hexane/EtOAc 9:1) 0.50; yield 56 mg, 92%; ^1H NMR (600 MHz, CDCl_3): δ 7.86 (d, $J = 7.8$ Hz, 2 H), 7.59 (d, $J = 7.8$ Hz, 2 H), 7.43 (t, $J = 7.2$ Hz, 2 H), 7.34 (t, $J = 7.2$ Hz, 1 H), 7.06 (d, $J = 7.8$ Hz, 2 H), 6.65 (d, $J = 8.4$ Hz, 1 H), 6.50 (s, 1 H), 6.44 (d, $J = 7.8$ Hz, 1 H), 6.26 (s, 1 H), 4.31 (t, $J = 6.0$ Hz, 2 H), 3.82 (s, 3 H), 3.62 (s, 3 H), 3.10 (t, $J = 6.6$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 151.4, 148.9, 147.9, 144.1, 135.1, 133.2, 132.2, 130.5, 129.5, 128.9, 128.1, 125.7, 120.8, 118.4, 112.1, 111.9, 111.2, 103.8, 56.0, 55.7, 51.4, 36.4; IR (KBr, neat) 3060, 2933, 2834, 2215, 1683, 1594, 1508, 1486, 1256, 1207, 1148, 1071, 861, 756, 690 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{24}\text{BrN}_3\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 410.1863, found 410.1861.

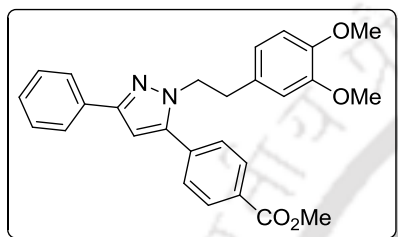
1-(3,4-Dimethoxyphenethyl)-5-(2-nitrophenyl)-3-phenyl-1H-pyrazole (42k):

Light yellow solid; mp 112-114 $^\circ\text{C}$; R_f (hexane/EtOAc 7:3) 0.52; yield 58 mg, 90%; ^1H NMR (600 MHz, CDCl_3): δ 7.95 (d, $J = 7.8$ Hz, 1 H), 7.85 (d, $J = 7.8$ Hz, 2 H), 7.46 (t, $J = 7.8$ Hz, 1 H), 7.43-7.28 (m, 3 H), 7.31 (t, $J = 7.2$ Hz, 1 H), 6.65 (d, $J = 8.4$ Hz, 1 H), 6.61 (d, $J = 7.2$ Hz,



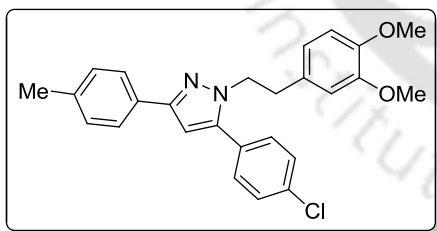
1 H), 6.45-6.42 (m, 2 H), 6.35 (s, 1 H), 4.06 (t, $J = 6.0$ Hz, 2 H), 3.81 (s, 3 H), 3.62 (s, 3 H), 3.09 (t, $J = 6.0$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 150.8, 148.7, 148.6, 147.7, 139.9, 133.3, 133.1, 132.6, 130.8, 130.0, 128.6, 127.7, 125.6, 125.0, 124.2, 120.8, 111.9, 111.0, 103.4, 55.9, 55.6, 51.4, 35.9; IR (KBr, neat) 3064, 3000, 2937, 2834, 1610, 1525, 1461, 1420, 1348, 1263, 1156, 1084, 1028, 958, 854, 737, 696 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{24}\text{N}_3\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 430.1761, found 430.1766.

1-(3,4-Dimethoxyphenethyl)-5-(4-(methoxycarbonyl)phenyl)-3-phenyl-1H-pyrazole (42l):



Light yellow solid; mp 93-95 $^{\circ}\text{C}$; R_f (hexane/EtOAc 7:3) 0.51; yield 60 mg, 91%; ^1H NMR (600 MHz, CDCl_3): δ 8.01 (d, $J = 8.4$ Hz, 2 H), 7.86 (d, $J = 7.8$ Hz, 2 H), 7.43 (t, $J = 7.2$ Hz, 2 H), 7.34 (t, $J = 7.2$ Hz, 1 H), 7.10 (d, $J = 7.8$ Hz, 2 H), 6.67 (d, $J = 7.8$ Hz, 1 H), 6.53 (s, 1 H), 6.47 (d, $J = 7.8$ Hz, 1 H), 6.30 (s, 1 H), 4.34 (t, $J = 6.6$ Hz, 2 H), 3.94 (s, 3 H), 3.83 (s, 3 H), 3.64 (s, 3 H), 3.12 (t, $J = 6.6$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 166.8, 151.3, 148.9, 147.9, 145.0, 135.2, 133.5, 130.7, 130.0, 129.8, 129.0, 128.9, 128.0, 125.8, 120.9, 112.0, 111.2, 103.7, 56.1, 55.8, 52.5, 51.4, 36.5; IR (KBr, neat) 3061, 2999, 2951, 2835, 1722, 1611, 1515, 1460, 1439, 1279, 1239, 1185, 1109, 1028, 961, 804, 768, 698 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{27}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 443.1965, found 443.1973.

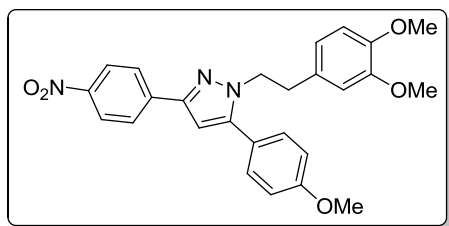
5-(4-Chlorophenyl)-1-(3,4-dimethoxyphenethyl)-3-(p-tolyl)-1H-pyrazole (42m):



Light yellow solid; mp 102-104 $^{\circ}\text{C}$; R_f (hexane/EtOAc 4:1) 0.51; yield 60 mg, 93%; ^1H NMR (600 MHz, CDCl_3): δ 7.75 (d, $J = 7.8$ Hz, 2 H), 7.29 (d, $J = 7.8$ Hz, 2 H), 7.24 (d, $J = 7.8$ Hz, 2 H), 6.91 (d, $J = 7.2$ Hz, 2 H), 6.67 (d, $J = 7.8$ Hz, 1 H), 6.47 (d, $J = 7.8$ Hz, 1 H), 6.43 (s, 1 H), 6.31 (s, 1 H), 4.29 (t, $J = 6.6$ Hz, 2 H), 3.84 (s, 3 H), 3.65 (s, 3 H), 3.10 (t, $J = 6.6$ Hz, 2 H), 2.39 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3): δ 151.2, 148.9, 147.8, 144.6, 137.7, 134.6, 130.8, 130.7, 130.4, 129.5, 129.2, 128.7, 125.6, 120.9, 111.9, 111.2, 103.2, 56.0, 55.7, 51.1, 36.5, 21.4; IR (KBr, neat) 3058, 3000, 2934, 2833, 1606, 1515, 1482, 1452, 1418, 1355, 1263, 1237, 1187, 1092, 1029, 957, 831, 794, 638 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{26}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 433.1677, found 433.1676.

1-(3,4-Dimethoxyphenethyl)-5-(4-methoxyphenyl)-3-(4-nitrophenyl)-1H-pyrazole (42n):

Pale red; mp 112-114 °C; R_f (hexane/EtOAc 7:3) 0.51; yield 62 mg, 91%; $^1\text{H NMR}$ (400

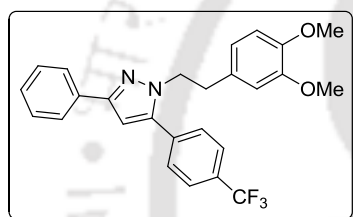


MHz, CDCl_3): δ 8.26 (d, $J = 9.2$ Hz, 2 H), 8.00 (d, $J = 8.0$ Hz, 2 H), 6.98 (d, $J = 8.8$ Hz, 2 H), 6.89 (d, $J = 9.6$ Hz, 2 H), 6.70 (d, $J = 8.0$ Hz, 1 H), 6.54 (s, 1 H), 6.51 (d, $J = 8.4$ Hz, 1 H), 6.38 (s, 1 H), 4.33 (t, $J = 7.2$ Hz, 2 H), 3.84 (s, 3 H), 3.68 (s, 3 H), 3.11 (s, 3 H), 3.11 (t, $J = 7.2$

Hz, 2 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 160.1, 148.9, 148.4, 147.9, 147.1, 146.2, 140.2, 130.6, 130.4, 126.0, 124.3, 122.4, 120.9, 114.1, 111.9, 111.3, 104.1, 56.1, 55.7, 55.1, 51.3, 36.5; **IR** (KBr, neat) 3001, 2834, 2837, 1603, 1516, 1491, 1458, 1341, 1288, 1254, 1180, 1154, 1010, 958, 856, 758, cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}_5$ ($\text{M} + \text{H}$) $^+$ 460.1867, found 460.1864.

1-(3,4-Dimethoxyphenethyl)-3-phenyl-5-(4-(trifluoromethyl)phenyl)-1H-pyrazole (42o):

Light yellow solid; mp 79-81 °C; R_f (hexane/EtOAc 4:1) 0.51; yield 61 mg, 91%; $^1\text{H NMR}$

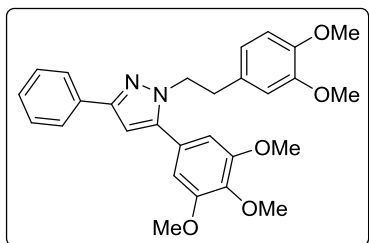


(600 MHz, CDCl_3): δ 7.87 (d, $J = 7.8$ Hz, 2 H), 7.58 (d, $J = 7.8$ Hz, 2 H), 7.44 (t, $J = 7.8$ Hz, 2 H), 7.35 (t, $J = 7.2$ Hz, 1 H), 7.09 (d, $J = 7.8$ Hz, 2 H), 6.65 (d, $J = 8.4$ Hz, 1 H), 6.51 (s, 1 H), 6.46 (d, $J = 8.4$ Hz, 1 H), 6.29 (s, 1 H), 4.33 (t, $J = 6.6$ Hz, 2 H), 3.83 (s, 3 H), 3.63 (s, 3 H), 3.12 (t, $J = 6.6$ Hz, 2 H); $^{13}\text{C NMR}$ (150

MHz, CDCl_3): δ 151.3, 149.0, 148.0, 144.6, 134.4, 133.5, 130.7, 130.5 (q, $J = 34.5$ Hz), 129.4, 128.9, 128.0, 125.8, 125.5, 124.1 (q, $J = 271.5$ Hz), 120.9, 112.0, 111.3, 103.7, 56.1, 55.7, 51.3, 36.5; $^{19}\text{F NMR}$ (376 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ 99.6 (s, C-F); **IR** (KBr, neat) 3061, 3001, 2939, 2836, 1620, 1515, 1461, 1326, 1263, 1239, 1128, 1068, 1028, 958, 849, 767, 695 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 453.1784, found 453.1784.

1-(3,4-Dimethoxyphenethyl)-3-phenyl-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (42p):

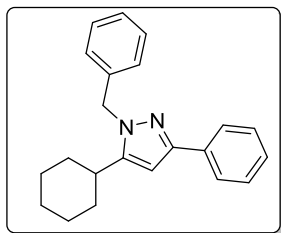
Orange red semi solid; R_f (hexane/EtOAc 13:7) 0.51; yield 66 mg, 93%; $^1\text{H NMR}$ (600 MHz,



CDCl_3): δ 7.87 (d, $J = 7.8$ Hz, 2 H), 7.43 (t, $J = 7.2$ Hz, 2 H), 7.33 (t, $J = 7.2$ Hz, 1 H), 6.66 (d, $J = 7.8$ Hz, 1 H), 6.51 (d, $J = 8.4$ Hz, 1 H), 6.48 (s, 1 H), 6.33 (s, 1 H), 6.25 (s, 2 H), 4.35 (t, $J = 6.6$ Hz, 2 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 3.78 (s, 6 H), 3.65 (s, 3 H), 3.16 (t, $J = 6.6$ Hz, 2 H); $^{13}\text{C NMR}$ (150 MHz,

CDCl_3): δ 153.3, 151.0, 148.8, 147.7, 146.0, 138.4, 133.7, 131.0, 128.9, 128.8, 127.9, 126.2, 125.8, 120.9, 112.1, 111.2, 106.4, 103.3, 61.0, 56.3, 55.9, 55.7, 51.0, 36.4; **IR** (KBr, neat) 3059, 2999, 2934, 2835, 1584, 1550, 1515, 1462, 1323, 1238, 1128, 1029, 1006, 960, 804, 768 697 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{28}\text{H}_{31}\text{N}_2\text{O}_5$ ($\text{M} + \text{H}$) $^+$ 475.2227, found 475.2231.

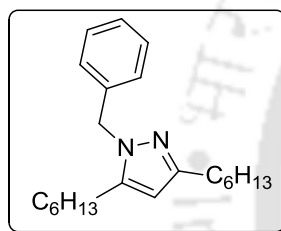
1-Benzyl-5-cyclohexyl-3-phenyl-1H-pyrazole (42s):



Yellow solid; mp 48-50 °C; R_f (hexane/EtOAc 9:1) 0.51; yield 44 mg, 93%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.81 (d, J = 8.0 Hz, 2 H), 7.37 (t, J = 7.2 Hz, 2 H), 7.30-7.21 (m, 4 H), 7.09 (d, J = 7.6 Hz, 2 H), 6.38 (s, 1 H), 5.36 (s, 2 H), 2.48 (t, J = 7.2 Hz, 1 H), 1.79-1.65 (m, 4 H), 1.40-1.120 (m, 6 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 150.6, 150.4, 137.8, 134.0, 128.8, 128.7, 127.6, 127.5, 126.7, 125.7, 100.2, 53.1, 35.6, 33.5, 26.5, 26.0; **IR** (KBr, neat) 3061, 3031, 2929, 2853, 1605, 1544, 1503, 1449, 1369, 1313, 1199, 0015, 1029, 959, 795, 765, 695 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{22}\text{H}_{25}\text{N}_2$ ($\text{M} + \text{H}$) $^+$ 317.2012, found 317.2018.

1-Benzyl-3,5-dihexyl-1H-pyrazole (42u):

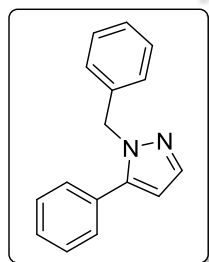
Pale orange liquid; R_f (hexane/EtOAc 9:1) 0.51; yield 44 mg, 92%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.28 (t, J = 7.8 Hz, 2 H), 7.23 (t, J = 7.2 Hz, 1 H), 7.02 (d, J = 7.2 Hz, 2 H), 5.88 (s, 1 H), 5.23 (s, 2 H), 2.59 (t, J = 7.8 Hz, 2 H), 2.44 (t, J = 7.8 Hz, 2 H), 1.66-1.61 (m, 2 H),



1.55-1.50 (m, 2 H), 1.37-1.33 (m, 2 H), 1.31-1.21 (m, 10 H), 0.89-0.84 (m, 6 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 152.7, 144.3, 137.8, 128.8, 127.5, 126.6, 103.3, 52.7, 31.9, 31.7, 30.0, 29.3, 29.1, 28.5, 25.7, 22.8, 22.7, 14.3, 14.2; **IR** (KBr, neat) 3064, 3031, 2928, 2856, 1606, 1547, 1460, 1391, 1356, 1309, 1180, 1093, 1027, 782, 725,

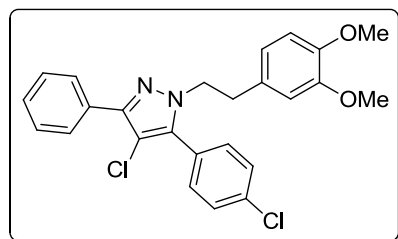
700, 578 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{22}\text{H}_{35}\text{N}_2$ ($\text{M} + \text{H}$) $^+$ 327.2795, found 327.2797.

1-Benzyl-5-phenyl-1H-pyrazole (42v):



Pale yellow solid; mp 58-60 °C; R_f (hexane/EtOAc 19:1) 0.51; yield 31 mg, 90%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.61 (s, 1 H), 7.39-7.35 (m, 3 H), 7.33-7.29 (m, 2 H), 7.28-7.23 (m, 2 H), 7.23 (d, J = 7.2 Hz, 1 H), 7.04 (d, J = 7.2 Hz, 2 H), 6.35 (s, 1 H), 5.35 (s, 2 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 144.2, 139.5, 137.8, 130.8, 129.1, 128.8, 128.7 (2C), 127.6, 126.9, 106.6, 53.2; **IR** (KBr, neat) 3062, 3032, 2929, 2853, 1605, 1488, 1458, 1397, 1302, 1120, 1074, 1029, 985, 952, 925, 760, 698 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{16}\text{H}_{15}\text{N}_2$ ($\text{M} + \text{H}$) $^+$ 235.1230, found 235.1237.

4-Chloro-5-(4-chlorophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-1H-pyrazole (43f):



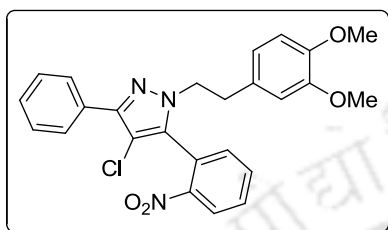
Pale yellow semisolid; R_f (hexane/EtOAc 3:1) 0.53; yield 49 mg, 73%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.97 (d, J = 7.8 Hz, 2 H), 7.48 (t, J = 8.0 Hz, 2 H), 7.40 (t, J = 7.6 Hz, 1 H), 7.35 (d, J = 8.8 Hz, 2 H), 6.89 (d, J = 8.4 Hz, 2 H), 6.69 (d, J = 8.0 Hz, 1 H), 6.54 (d, J = 8.4 Hz, 1 H), 6.27 (s, 1

H), 4.24 (t, J = 6.4 Hz, 2 H), 3.85 (s, 3 H), 3.68 (s, 3 H), 3.07 (t, J = 6.8 Hz, 2 H); $^{13}\text{C NMR}$

(100 MHz, CDCl₃): δ 149.0, 148.0, 147.0, 141.0, 131.3, 130.4, 128.9, 128.7, 128.4, 127.5, 120.9, 111.8, 111.2, 106.6, 56.1, 55.7, 52.0, 36.3; **IR** (KBr, neat) 3045, 3008, 2981, 2912, 1638, 1515, 1459, 1360, 1264, 1155, 1088, 1030, 913, 805, 751, 688 cm⁻¹; **HRMS** (ESI) calcd. for C₂₅H₂₃Cl₂N₂O₂ (M + H)⁺ 453.1131, found 453.1133.

4-Chloro-1-(3,4-dimethoxyphenethyl)-5-(2-nitrophenyl)-3-phenyl-1H-pyrazole (43k)

Pale orange red semisolid; R_f (hexane/EtOAc 7:3) 0.51; yield 46 mg, 66%; **¹H NMR** (400

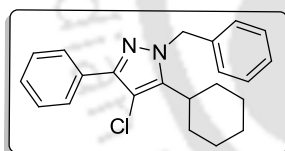


MHz, CDCl₃): δ 8.11 (d, *J* = 8.0 Hz, 1 H), 7.99 (d, *J* = 8.4 Hz, 2 H), 7.58 (t, *J* = 7.2 Hz, 1 H), 7.52 (t, *J* = 8.4 Hz, 1 H), 7.40 (t, *J* = 7.2 Hz, 2 H), 7.40-7.35 (m, 1 H), 6.70 (d, *J* = 8.0 Hz, 1 H), 6.58 (d, *J* = 7.6 Hz, 1 H), 6.48 (d, *J* = 8.4 Hz, 1 H), 6.36 (s, 1 H), 4.33-4.28 (m, 1 H), 3.91-3.82 (m, 1 H), 3.83

(s, 3 H), 3.66 (s, 3 H), 3.32-3.24 (m, 1 H), 2.95-2.89 (m, 1 H); **¹³C NMR** (100 MHz, CDCl₃): δ 148.9, 148.5, 147.8, 146.6, 137.6, 133.5, 133.3, 131.7, 130.8, 130.5, 128.6, 128.3, 127.3, 124.8, 122.7, 120.9, 111.8, 111.2, 106.7, 56.0, 55.6, 52.3, 35.7; **IR** (KBr, neat) 3064, 2999, 2936, 2835, 1733, 1607, 1574, 1516, 1464, 1419, 1349, 1263, 1179, 1158, 1030, 854, 789, 697 cm⁻¹; **HRMS** (ESI) calcd. for C₂₅H₂₃ClN₂O₄ (M + H)⁺ 464.1372, found 464.1373.

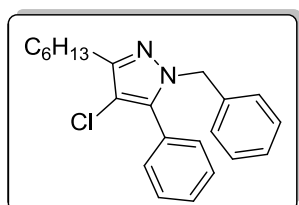
1-Benzyl-4-chloro-5-cyclohexyl-3-phenyl-1H-pyrazole (43s)

Pale yellow semisolid; R_f (hexane/EtOAc 19:1) 0.49; yield 38 mg, 72%; **¹H NMR** (400



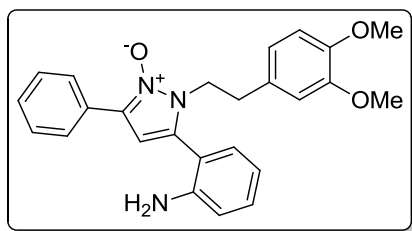
MHz, CDCl₃): δ 7.92 (d, *J* = 6.8 Hz, 2 H), 7.40 (d, *J* = 7.6 Hz, 2 H), 7.34-7.20 (m, 4 H), 7.11 (d, *J* = 7.2 Hz, 2 H), 5.34 (s, 2 H), 2.69-2.63 (m, 1 H), 1.95-1.86 (m, 3 H), 1.76-1.59 (m, 2 H), 1.49-1.41 (m, 2 H), 1.27-1.12 (m, 4 H); **¹³C NMR** (100 MHz, CDCl₃): δ 146.8, 143.9, 137.1, 132.1, 128.8, 128.4, 128.0, 127.8, 127.7, 126.7, 105.8, 54.7, 36.6, 29.4, 27.0, 25.7; **IR** (KBr, neat) 3063, 3031, 2931, 2854, 1638, 1496, 1449, 1354, 1310, 1269, 1189, 1075, 1016, 914, 799, 696 cm⁻¹; **HRMS** (ESI) calcd. for C₂₂H₂₄ClN₂ (M + H)⁺ 351.1623, found 351.1625.

1-Benzyl-4-chloro-3-hexyl-5-phenyl-1H-pyrazole (43t)



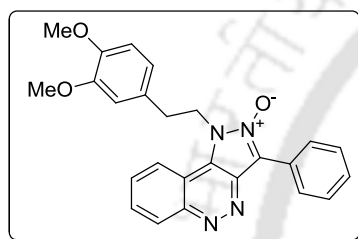
Pale yellow semisolid; R_f (hexane/EtOAc 19:1) 0.51; yield 36 mg, 69%; **¹H NMR** (400 MHz, CDCl₃): δ 7.40-7.37 (m, 3 H), 7.30-7.27 (m, 2 H), 7.26-7.19 (m, 3 H), 6.98 (d, *J* = 8.0 Hz, 2 H), 5.21 (s, 2 H), 2.70 (t, *J* = 7.6 Hz, 2 H), 1.78-1.69 (m, 2 H), 1.40-1.26 (m, 6 H), 0.88 (t, *J* = 6.4 Hz, 3 H); **¹³C NMR** (100 MHz, CDCl₃): δ 149.8, 140.4, 137.4, 129.7, 129.2, 128.8, 128.7, 128.5, 127.6, 126.8, 110.1, 108.0, 53.9, 31.8, 29.2, 28.8, 26.4, 22.8, 14.3; **IR** (KBr, neat) 3063, 2954, 2927, 2855, 1638, 1494, 1458, 1383, 1305, 1158, 1086, 1010, 967, 763, 699 cm⁻¹; **HRMS** (ESI) calcd. for C₂₂H₂₆ClN₂ (M + H)⁺ 353.1779, found 353.1782.

5-(2-Aminophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-1H-pyrazole 2-oxide (44):



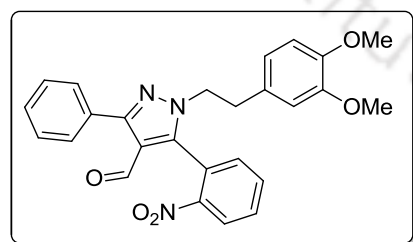
Dark brown oil; R_f (hexane/EtOAc 3:2) 0.61; yield 81 mg, 65%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 8.23 (d, $J = 7.2$ Hz, 2 H), 7.47 (t, $J = 7.2$ Hz, 2 H), 7.37 (t, $J = 7.8$ Hz, 1 H), 7.21-7.18 (m, 1 H), 6.18 (d, $J = 7.2$ Hz, 3 H), 6.65 (d, $J = 7.8$ Hz, 1 H), 6.47 (d, $J = 7.8$ Hz, 1 H), 6.38 (s, 2 H), 4.34 (t, $J = 7.2$ Hz, 2 H), 3.82 (s, 3 H), 3.64 (s, 3 H), 3.02 (d, $J = 7.2$ Hz, 2 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 148.6, 147.5, 145.2, 130.9, 130.4, 130.0, 129.8, 128.4 (2C), 128.1, 126.0 (2C), 120.8, 117.7, 115.3, 113.4, 111.5, 110.9, 99.4, 55.7, 55.4, 45.7, 33.4; **IR** (KBr, neat) 3346, 3026, 2983, 2813, 1533, 1501, 1487, 1280, 1208, 832, 750 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 416.1969, found 416.1967.

1-(3,4-Dimethoxyphenethyl)-3-phenyl-1H-pyrazolo[4,3-c]cinnoline 2-oxide (45):



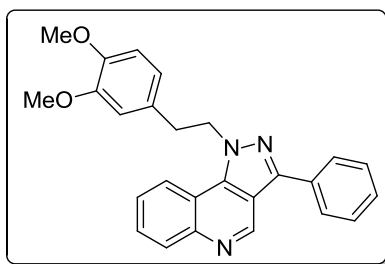
Brown red solid; mp 138-140 $^{\circ}\text{C}$; R_f (hexane/EtOAc 7:3) 0.51; yield 52 mg, 76%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 9.06 (d, $J = 7.8$ Hz, 2 H), 8.67 (d, $J = 8.4$ Hz, 1 H), 8.04 (d, $J = 7.8$ Hz, 1 H), 7.86 (t, $J = 7.8$ Hz, 1 H), 7.79 (t, $J = 7.8$ Hz, 1 H), 7.62 (t, $J = 7.8$ Hz, 2 H), 7.52 (d, $J = 7.2$ Hz, 1 H), 6.66-6.68 (m, 3 H), 5.05 (t, $J = 7.2$ Hz, 2 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.18 (t, $J = 7.2$ Hz, 2 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 149.4, 148.4, 146.9, 134.9, 131.5, 131.4, 129.8, 129.4, 129.1, 128.8, 128.1, 126.8, 121.7, 121.1, 119.9, 119.8, 112.1, 111.7, 110.1, 56.1, 56.0, 46.2, 34.4; **IR** (KBr, neat) 2983, 2854, 1549, 1502, 1404, 1379, 1250, 1207, 831, 707 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{23}\text{N}_4\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 427.1765, found 427.1765.

1-(3,4-Dimethoxyphenethyl)-5-(2-nitrophenyl)-3-phenyl-1H-pyrazole-4-carbaldehyde (46):



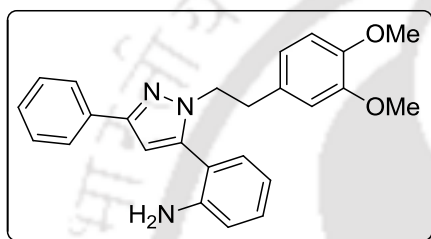
Light yellow semisolid; R_f (hexane/EtOAc 3:2) 0.55; yield 43 mg, 63%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 9.74 (s, 1 H), 8.18 (d, $J = 8.4$ Hz, 1 H), 7.79 (d, $J = 8.0$ Hz, 2 H), 7.62 (t, $J = 8.4$ Hz, 1 H), 7.55-7.48 (m, 4 H), 6.72 (d, $J = 8.4$ Hz, 1 H), 6.48 (d, $J = 7.8$ Hz, 2 H), 6.42 (s, 1 H), 7.34-4.28 (m, 1 H), 3.94-3.89 (m, 1 H), 3.88 (s, 3 H), 3.69 (s, 3 H), 3.80-3.30 (m, 1 H), 3.01-2.95 (m, 1 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 185.1, 154.4, 149.0, 148.3, 148.0, 143.5, 133.3, 132.7, 131.5, 131.0, 130.2, 129.3, 129.1, 128.8, 124.9, 123.7, 121.0, 117.7, 111.9, 111.3, 56.0, 55.7, 51.5, 35.3; **IR** (KBr, neat) 3002, 293.2, 2835, 2740, 1646, 1528, 1480, 1262, 1238, 1159, 1028, 854, 698 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{24}\text{N}_3\text{O}_5$ ($\text{M} + \text{H}$) $^+$ 458.1710, found 458.1713.

1-(3,4-Dimethoxyphenethyl)-3-phenyl-1H-pyrazolo[4,3-c]quinoline (47):



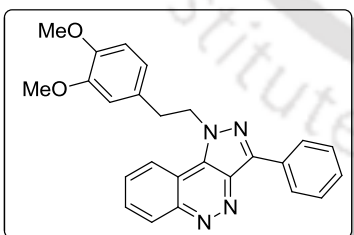
Light red solid; mp 119-121 °C; R_f (hexane/EtOAc 7:3) 0.48; yield 42 mg, 68%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 9.43 (s, 1 H), 8.31 (t, $J = 6.4$ Hz, 2 H), 7.95 (d, $J = 8.0$ Hz, 2 H), 7.78 (t, $J = 6.8$ Hz, 1 H), 7.68 (t, $J = 7.6$ Hz, 1 H), 7.57 (t, $J = 6.8$ Hz, 2 H), 7.5-7.46 (m, 1 H), 6.79 (s, 2 H), 6.71 (s, 1 H), 5.06 (t, $J = 8.0$ Hz, 2 H), 3.84 (s, 3 H), 3.31 (s, 3 H), 3.18 (t, $J = 8.0$ Hz, 2 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 149.2, 148.2, 146.3, 146.1, 145.1, 140.0, 132.2, 130.3, 130.0, 129.4, 129.1, 128.1 (2C), 127.2, 121.6, 120.9, 116.5, 116.0, 112.1, 111.6, 56.1, 56.0, 54.3, 36.0; **IR** (KBr, neat) 2924, 2852, 1585, 1516, 1459, 1418, 1365, 1262, 1238, 1142, 1074, 1027, 913, 807, 764, 695, 668 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{24}\text{N}_3\text{O}_2$ ($M + \text{H}$) $^+$ 410.1863, found 410.1863.

2-(1-(3,4-Dimethoxyphenethyl)-3-phenyl-1H-pyrazol-5-yl)aniline (48):



Dark brown oil; R_f (hexane/EtOAc 7:3) 0.51; yield 93 mg, 78%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.87 (d, $J = 6.8$ Hz, 2 H), 7.43 (t, $J = 7.2$ Hz, 2 H), 7.33 (t, $J = 7.6$ Hz, 1 H), 7.19 (t, $J = 7.6$ Hz, 1 H), 6.73-6.66 (m, 4 H), 6.52-6.49 (m, 2 H), 6.39 (s, 1 H), 4.22 (t, $J = 7.8$ Hz, 2 H), 3.82 (s, 3 H), 3.67 (s, 3 H), 3.60 (br, 2 H), 3.08 (t, $J = 7.2$ Hz, 2 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 151.2, 148.8, 147.7, 145.1, 141.8, 133.6, 131.1, 130.9, 130.3, 128.8, 127.8, 125.7, 121.0, 118.0, 115.5, 115.3, 111.8, 111.1, 103.6, 56.0, 55.7, 51.1, 36.5; **IR** (KBr, neat) 3026, 2983, 2884, 1531, 1502, 1457, 1250, 1208, 945, 860 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_2$ ($M + \text{H}$) $^+$ 400.2020, found 400.2020.

1-(3,4-Dimethoxyphenethyl)-3-phenyl-1H-pyrazolo[4,3-c]cinnoline (49):

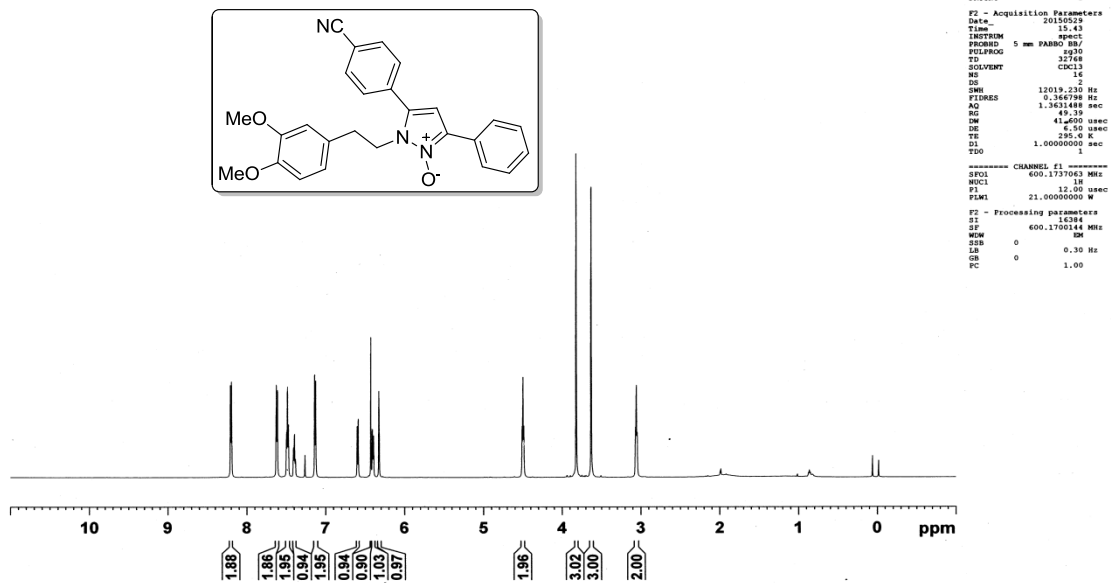


Light yellow solid; mp 132-134 °C; R_f (hexane/EtOAc 7:3) 0.51; yield 51 mg, 80%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.68 (d, $J = 7.2$ Hz, 3 H), 8.05 (d, $J = 8.4$ Hz, 1 H), 7.80 (t, $J = 7.2$ Hz, 1 H), 7.73 (t, $J = 7.6$ Hz, 1 H), 7.53 (t, $J = 7.6$ Hz, 2 H), 7.45 (t, $J = 7.2$ Hz, 1 H), 6.70-6.45 (m, 2 H), 6.57 (s, 1 H), 4.91 (t, $J = 7.2$ Hz, 2 H), 3.74 (s, 3 H), 3.68 (s, 3 H), 3.324 (t, $J = 7.2$ Hz, 2 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 149.1, 148.0, 145.8, 144.9, 131.4, 131.0, 129.8, 129.3, 129.2, 128.9, 128.0 (2C), 127.6, 120.9, 120.4, 113.1, 112.0, 111.4, 56.0, 55.9, 55.8, 54.1, 36.0; **IR** (KBr, neat) 3068, 2993, 2931, 2834, 1591, 1516, 1495, 1461, 1416, 1263, 1238, 1182, 1158, 1028, 930, 808, 767, 693 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{23}\text{N}_4\text{O}_3$ ($M + \text{H}$) $^+$ 411.1816, found 411.1816.

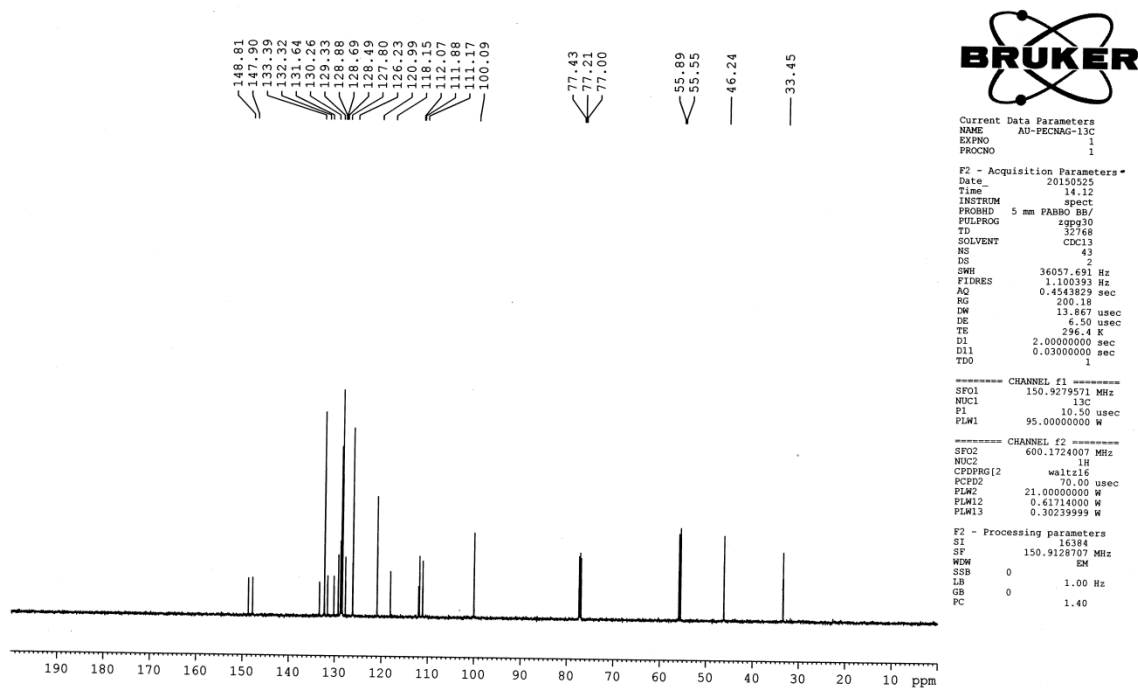
3.9. Selected spectra

5-(4-cyanophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-1*H*-pyrazole 2-oxide (39j)

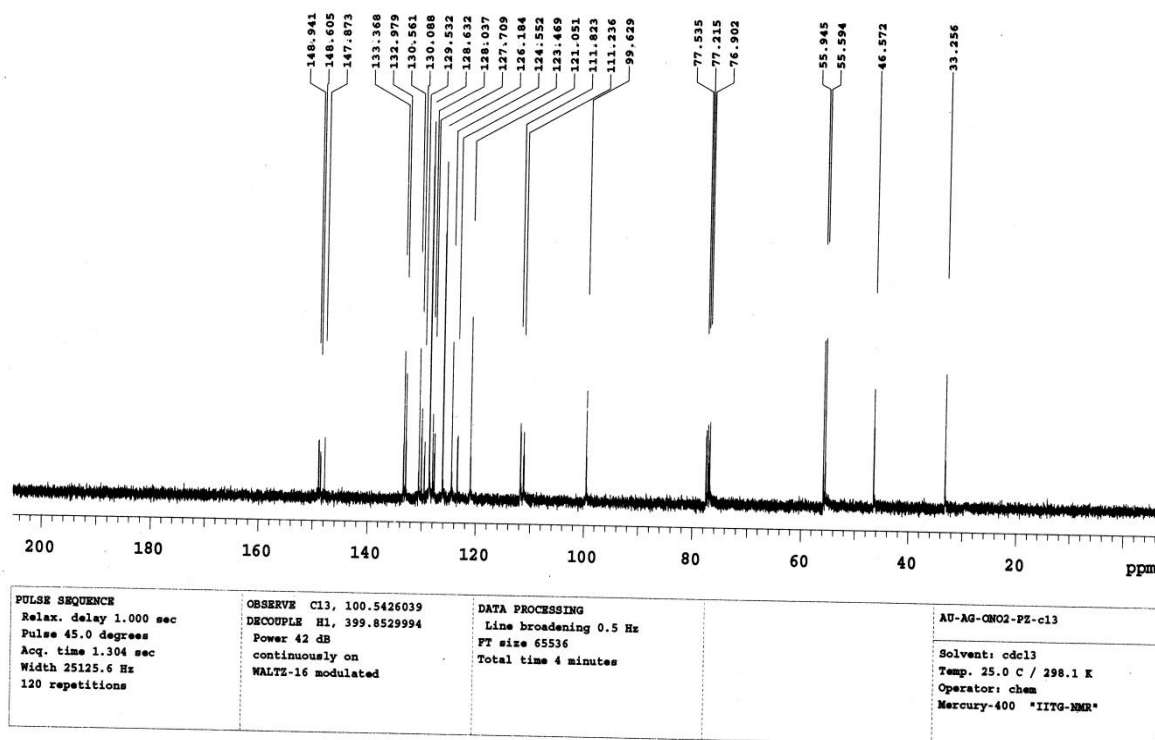
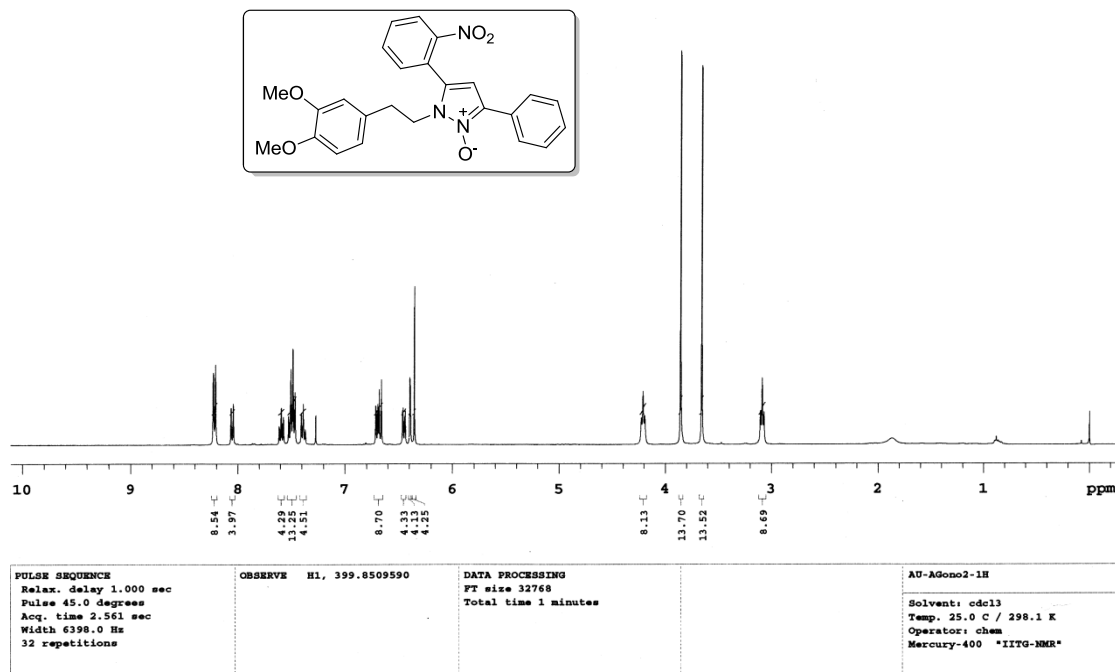
AU_AG_CNP_1H



AU-PECNAG-13C

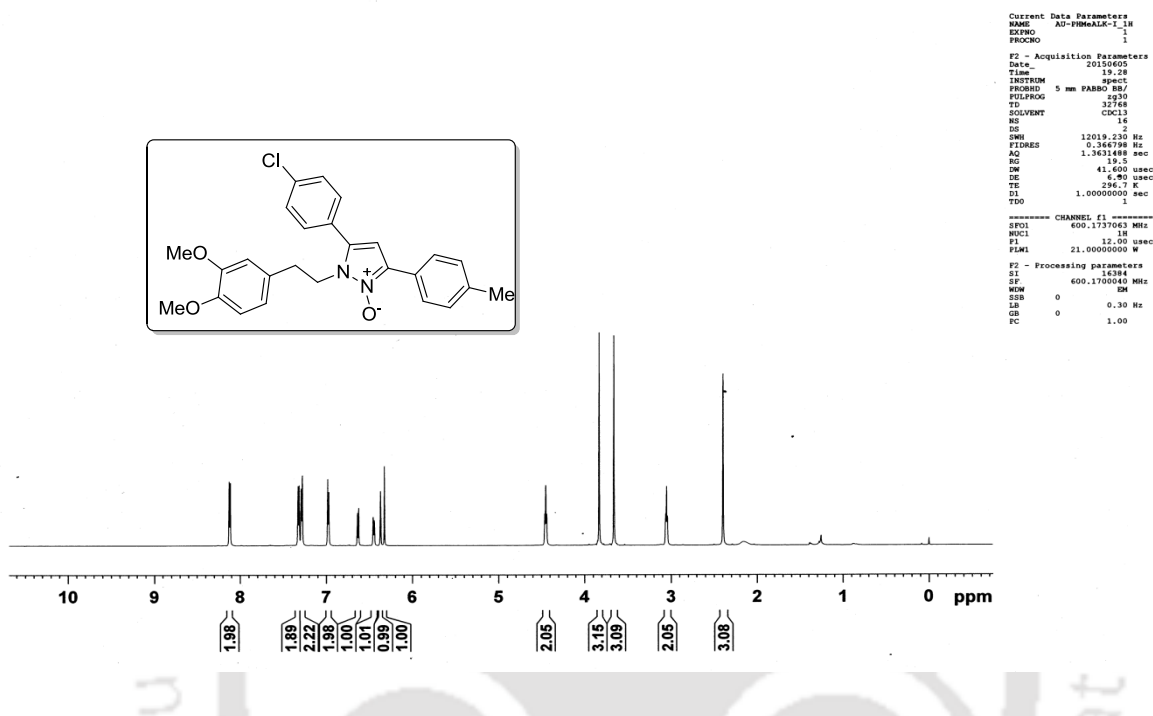


^1H , ^{13}C NMR spectra of 1-(3,4-dimethoxyphenethyl)-5-(2-nitrophenyl)-3-phenyl-1H-pyrazole 2-oxide (39k)

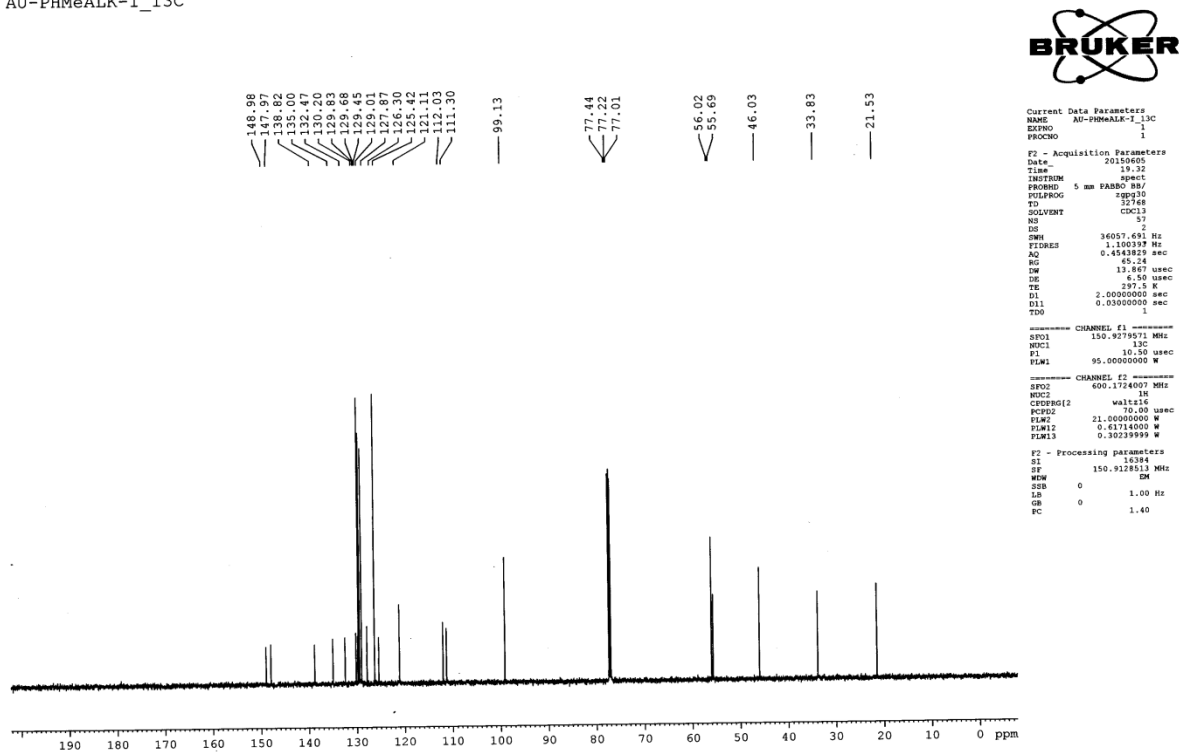


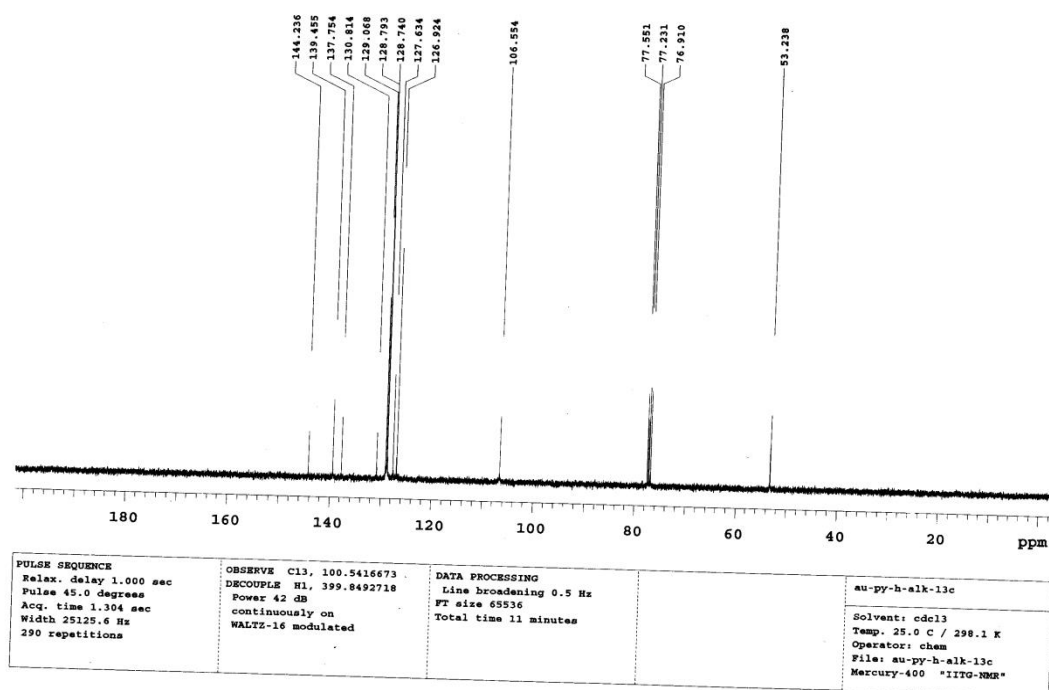
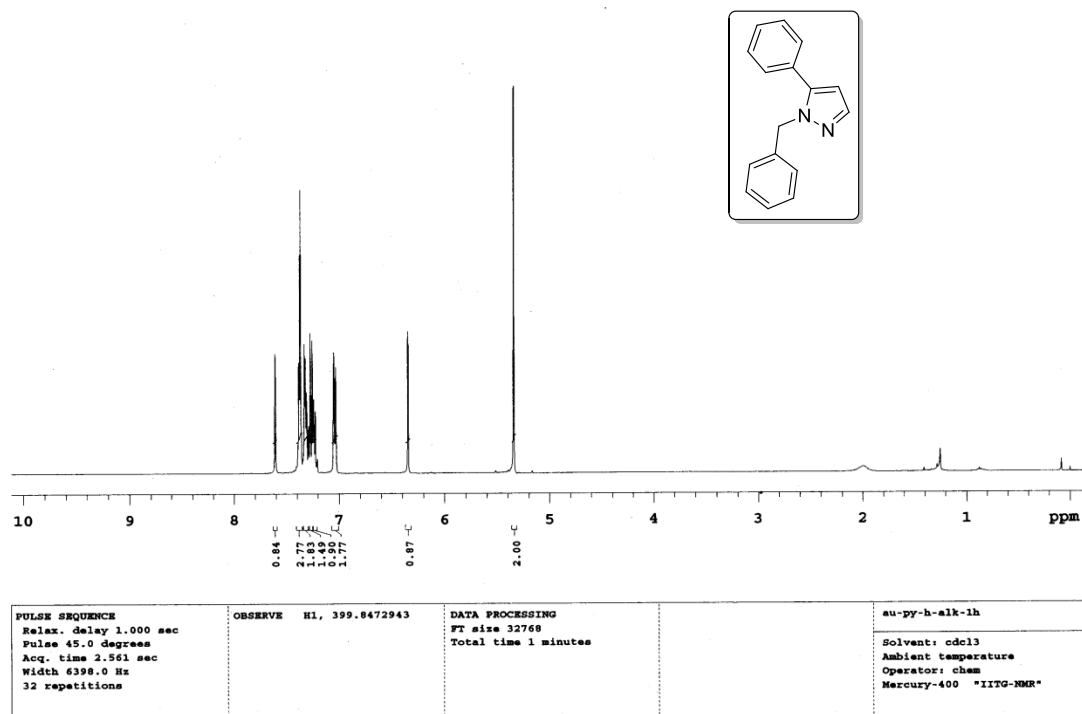
^1H , ^{13}C NMR spectra of 5-(4-chlorophenyl)-1-(3,4-dimethoxyphenethyl)-3-(*p*-tolyl)-1*H*-pyrazole 2-oxide (39m)

AU-PHMeALK-I_1H



AU-PHMeALK-I_13C



^1H , ^{13}C NMR spectra of 1-benzyl-5-phenyl-1H-pyrazole (42v)

CHAPTER 4

Synthesis of Highly Substituted 4-Iodopyrazole *N*-Oxides and Pyrazoles from Propargylamines

4.1. Importance of molecular iodine in organic transformations

In recent years, simple molecular iodine is employed as one of the most important reagents in organic synthesis and several transformations have been executed including iodination of unsaturated bonds.¹ In addition, molecular iodine is inexpensive and ideal for achieving environmental friendly reactions.² Due to the great advantages of molecular iodine, it has been particularly used for the electrophilic cyclization of tethered hetero atom bearing alkynes in order to synthesize highly substituted heterocycles such as furan,³ pyrrole,⁴ thiophene,⁵ indole,⁶ benzofurans⁷ and benzothiophene.⁸ Furthermore the iodinated products can also be manipulated to introduce new functionalities.⁹ Similarly, synthesis of iodinated pyrazoles is an intriguing subject for synthetic organic chemists. In particular, regiospecifically synthesized *C*-arylated pyrazoles possess high biological activities.¹⁰ To achieve such goals, iodinated pyrazoles have added advantages in converting iodo functionality into *C*-arylated pyrazoles. Some of the iodopyrazole literature methods are discussed below.

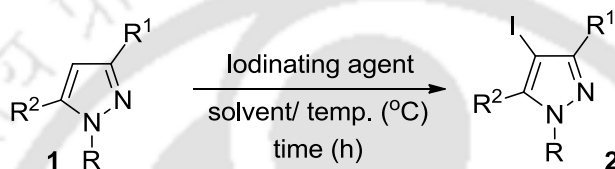
4.2. Literature methods for the synthesis of iodopyrazoles

Iodopyrazoles are generally synthesized by direct iodination of pyrazoles using an iodine source. In the same way, conversion of aminopyrazoles into iodopyrazoles *via* Sandmeyer reaction conditions is also well studied. In contemporary research, a very few of highly substituted 4-iodopyrazole derivatives have been developed *via* electrophilic cyclization reactions using iodine source in synthetic organic chemistry. Some of the important examples of 4-iodopyrazoles are described below.

4.2.1. Direct iodination of pyrazoles

4-Iodopyrazoles **2** are appreciable starting materials for the synthesis of highly substituted pyrazoles using cross-coupling reactions. To synthesize such 4-iodopyrazole derivatives, regioselective iodination of *N*-substituted pyrazoles **1** has been carried out using different

iodinating agents in combination with a variety of catalysts. For example, molecular iodine with oxidants such as $\text{PhI}(\text{OAc})_2$,^{11a} HIO_3 ,^{11b} H_2O_2 ,^{11c} CAN ¹² and $\text{I}_2/(\text{NaI}^{13a}$ or $\text{KI}^{13b})$ have been used as direct iodination of pyrazoles. Similarly, molecular iodine in presence of silver salts like AgOAc^{14a} and AgOOCF_3 ^{14b} has also been studied for conversion of pyrazoles into 4-iodopyrazoles in excellent yields. Other than molecular iodine, the combinations such as *N*-iodosuccinimide (NIS)/ultrasonic^{15a} and NIS/TFA have also been reported.^{15b} On other hand, iodine monochloride (ICl) combination with base (K_2CO_3)¹⁶ has been implemented for the synthesis of pyrazoles to 4-iodopyrazole derivatives **2**. The details of the reaction conditions are represented in Table 4.2.1.1.



Scheme 4.2.1.1.

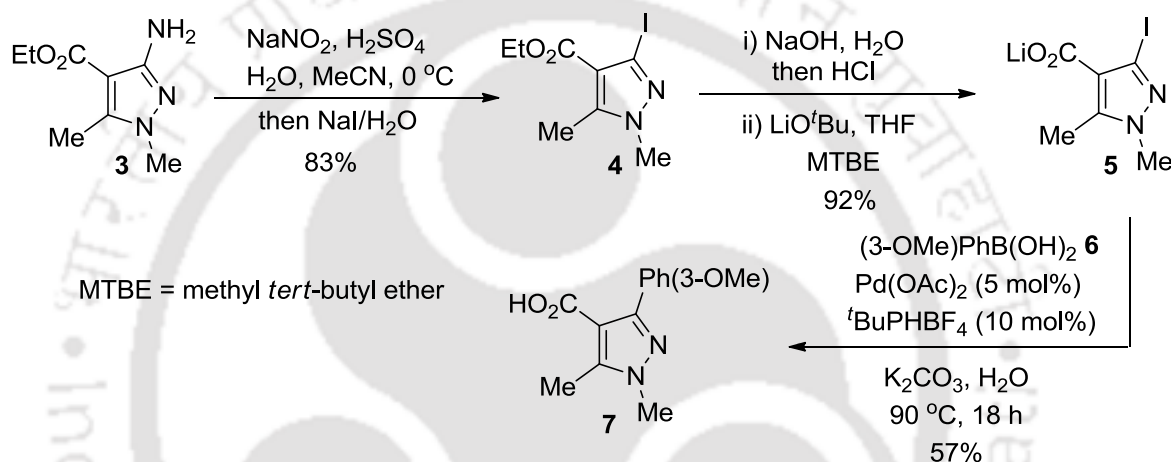
Table 4.2.1.1. Reaction conditions for the synthesis of 4-iodopyrazoles from pyrazoles

Ref No.	Reaction conditions	R	R ¹	R ²	Yield (%)
11a	I_2/IBD , CH_2Cl_2 , rt, 15 min.	H	Me	Me	90
11b	I_2/HIO_3 , AcOH, reflux, 4.0 h	Ph	Me	Cl	62
11c	$\text{I}_2/\text{H}_2\text{O}_2$, H_2O , 52.0 h	Ph	Me	H	100
12	I_2/CAN , CH_3CN , rt, 3.0 h	H	Me	H	90
13a	$\text{I}_2/\text{NaI}/\text{K}_2\text{CO}_3$, EtOH- H_2O , 25 $^\circ\text{C}$, 1.5 h	H	OiPr	Me	82
13b	I_2/KI , EtOH- H_2O , rt, overnight	$(\text{CH}_2)_2\text{S}$	Me	Me	94
14a	I_2/AgOAc , CH_2Cl_2 , 110 $^\circ\text{C}$, 20 min.	Et	Me	Me	88
14b	$\text{I}_2/\text{CF}_3\text{COOAg}$, CH_2Cl_2 , -15 $^\circ\text{C}$ -rt, 4.0 h	H	CHF_2	CHF_2	98
15a	NIS/ Ultrasonic, acetone, 30 $^\circ\text{C}$, 20 min.	H	Me	Me	85
15b	NIS/ TFA/ MW, CH_3CN , rt, 20 min.	Ph	MIDA	H	95
16	$\text{ICl}/\text{K}_2\text{CO}_3$, CHCl_3 , rt, 12 h	OBn	H	H	81

MIDA = *N*-methyliminodiacetic acid boronate

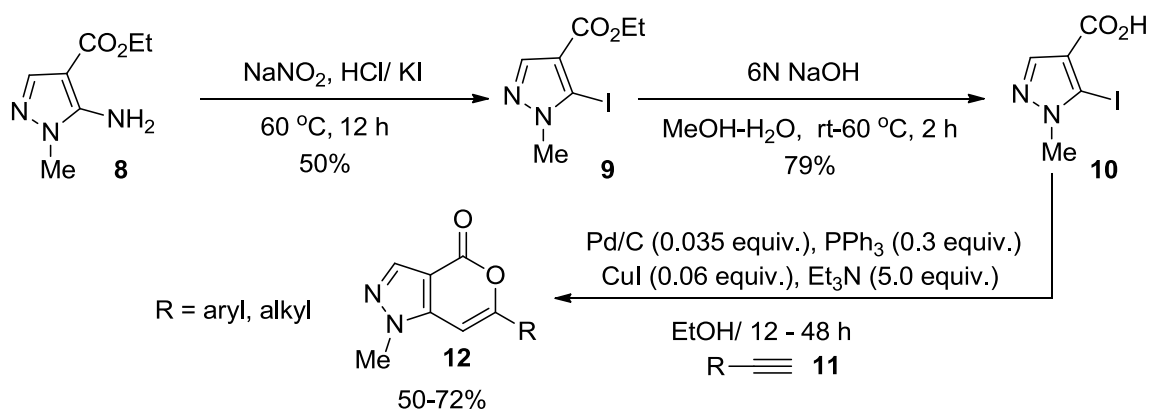
4.2.2. Synthesis of 4-iodo pyrazoles using Sandmeyer reaction conditions

Fandrick and coworkers effectively converted 3-aminopyrazole **3** into 3-iodopyrazole **4** under Sandmeyer reaction conditions. 3-Amino pyrazole **3** was subjected to treatment with sodium nitrite in presence of sulfuric acid followed by iodination with sodium iodide resulted 3-iodopyrazole **4** in 83% yield. Ester hydrolysis of compound **4** and then subsequent lithiation with LiO^tBu afforded compound **5**. In addition, the iodo compound **5** was successfully used in Suzuki-Miyaura cross-coupling reaction with 3-methoxyphenylboronic acid **6** to obtain highly substituted 3-arylpyrazole-4-carboxylic acid **7** in 57% yield (Scheme 4.2.2.1).¹⁷



Scheme 4.2.2.1.

Gorja *et al.* described a two-step procedure for the synthesis of 5-iodo-pyrazole-4-carboxylic acid **10** from 5-amino-pyrazole-4-carboxylate **8**. Initially, ethyl-5-amino-1*H*-pyrazole-4-carboxylate was converted to ethyl-5-iodo-pyrazole-4-carboxylate **9** under Sandmeyer reaction conditions in 50% yield. Further compound **9** was treated with base to obtain a hydrolysis product, 5-iodo-pyrazole-4-carboxylic acid **10** in 79% yield.



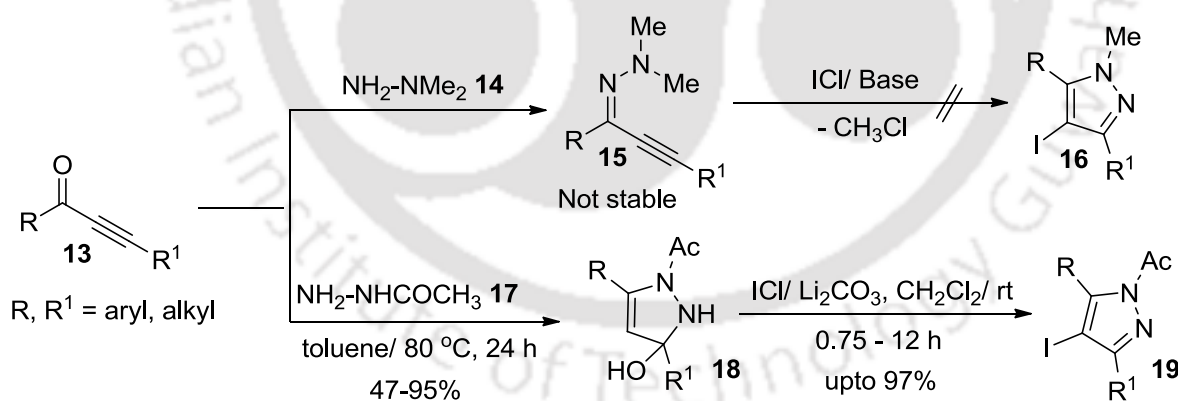
Scheme 4.2.2.2.

In addition, 5-iodo-pyrazole-4-carboxylic acid **10** was involved in tandem cyclization process using Pd/C and CuI bis-catalyzed Sonogashira coupling reaction with terminal alkynes **11**, to give pyrano[4,3-*c*]pyrazol-4(1*H*)-ones **12** in good yields (Scheme 4.2.2.2).¹⁸

4.2.3. Electrophilic cyclization towards 4-iodopyrazoles synthesis

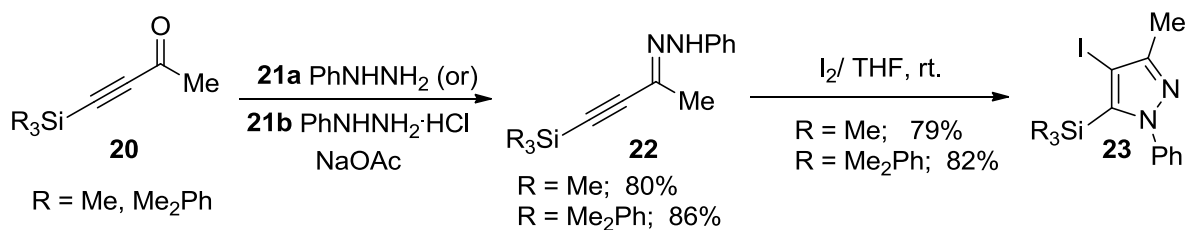
In the past decades, a very less number of reports have been reported in the literature for electrophilic cyclization of alkynes towards the synthesis of 4-iodopyrazoles using the iodine and they are discussed below.

Larock and coworkers demonstrated a concise protocol for the synthesis of highly substituted 1-acyl-4-iodo-1*H*-pyrazoles from alkynones and hydrazine derivatives. At first they assumed that, ICl/base mediated electrophilic cyclization of hydrazones **15** would produce *N*-methyl-4-iodopyrazole **16**. However, the reaction failed to achieve the desired products **16** because of its unstable hydrazones **15**. Alternatively, propargylic ketones **13** reacted with *N*-acyl hydrazine **17** to afford dihydropyrazoles **18** via intramolecular cyclization process in 45-95% yields. Then, the compound **18** was subjected to dehydration followed by iodination in presence of ICl/Li₂CO₃ yielded 1-acyl-4-iodo-pyrazoles **19** (Scheme 4.2.3.1).¹⁹



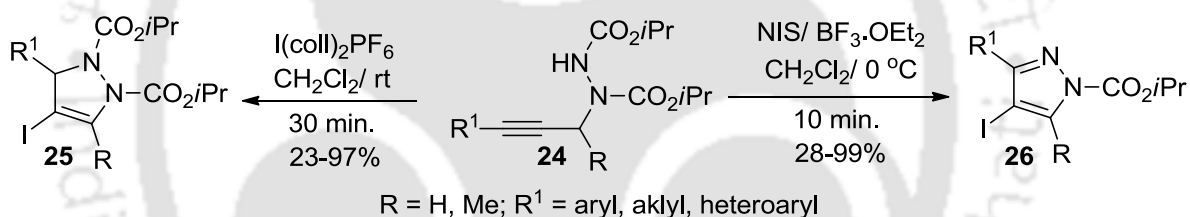
Scheme 4.2.3.1.

Molecular iodine promoted electrophilic cyclization of silylated acetylenic ketones **20** with hydrazines (**21a/b**) to afford 4-iodo-5-silylpyrazoles **23** was reported by González-Nogal and his group (Scheme 4.2.3.2).²⁰ However, this study was restricted to two derivatives of 4-iodo-5-silylpyrazoles **23** due to the difficulty in the preparation of condensation products **22** and also preferable risk of desilylation process under acidic conditions.



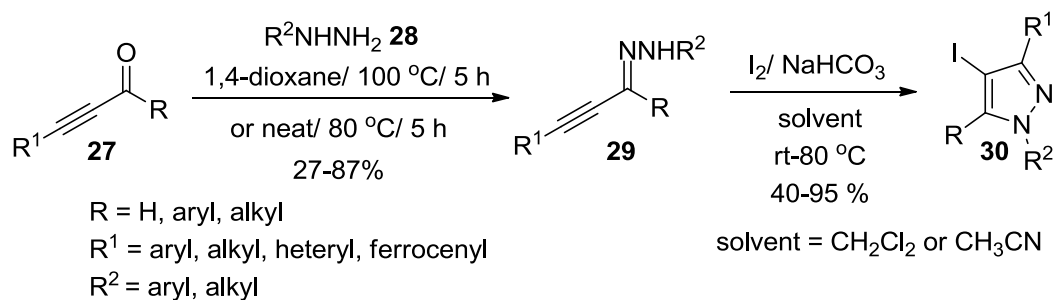
Scheme 4.2.3.2.

Wada and his group established a reagent controlled oxidative iodocyclization of propargylic hydrazides **24** to afford 4-iodo-2,3-dihydropyrazole **25** and 4-iodopyrazoles **26** (Scheme 4.2.3.3).²¹ The electrophilic cyclization of hydrazides with bis(2,4,6-collidine)-iodonium(I) hexafluorophosphate (I(coll)₂PF₆) selectively formed 4-iodo-2,3-dihydro pyrazole derivatives **25** in 23-97% yields. Whereas, the treatment of hydrazides with *N*-iododsuccinimide in the presence of boron trifluoride etherate led to exclusive formation of 4-iodopyrazoles **26** in 28-99% yields.



Scheme 4.2.3.3.

Zora and coworkers investigated a mild and efficient approach for the synthesis of highly substituted 4-iodopyrazoles **30** in good yields via electrophilic cyclization of α,β -alkynic hydrazones **29** using I₂/NaHCO₃ system (Scheme 4.2.3.4).²² The α,β -alkynic hydrazones **29** were readily prepared by the reaction of propargylic aldehydes and ketones **27** with hydrazines **28**.

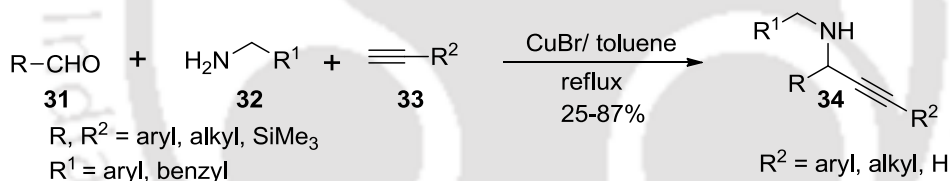


Scheme 4.2.3.4.

4.3. Results and discussion

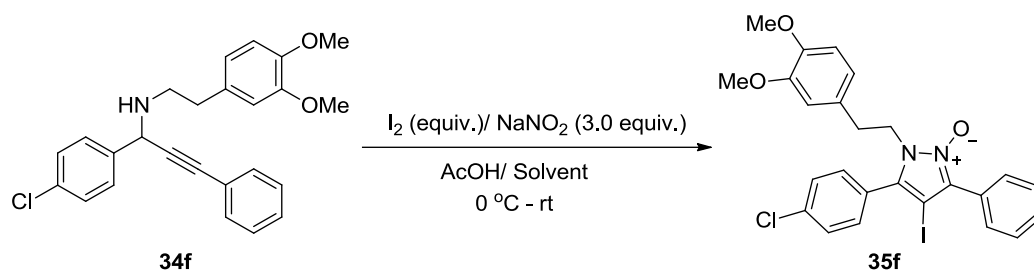
In our previous chapter, we have described an efficient methodology for the synthesis of 1,5 and 1,3,5-substituted pyrazole *N*-oxides and pyrazoles from propargylamines using AgOTf and NaNO₂/AcOH. In the same chapter, we were also able to prepare a few derivatives of highly substituted 4-chloropyrazoles from 1,3,5-trisubstituted pyrazole *N*-oxides by treating with POCl₃. These results encouraged us to develop a direct route for the synthesis 4-iodopyrazole *N*-oxides *via* halogen mediated electrophilic cyclization reaction. To the best of our knowledge, till date there is no literature methods found for the synthesis 4-iodopyrazole *N*-oxide from propargylamines. This chapter demonstrates the one-pot synthesis of highly substituted 4-iodopyrazole *N*-oxides and pyrazoles from propargylamines using NaNO₂/AcOH and molecular iodine *via* 5-*endo-dig*-cyclization fashion.

First, propargylamine **34** were easily synthesized in one step *via* A³ coupling reaction of aldehydes **31**, amines **32** and alkynes **33** catalyzed by copper(I) bromide and the results are presented below (Scheme 4.3.1).²³



Scheme 4.3.1. Synthesis of propargylamines

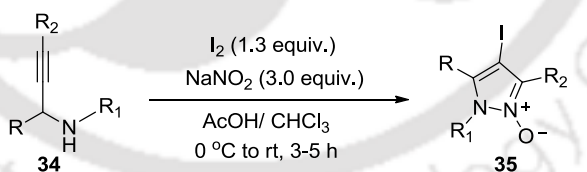
Under initial investigation of the reaction 1.0 equivalent of propargylamine **34f** was treated with 1.1 equivalents of iodine and 3.0 equivalents of sodium nitrite with acetic acid (0.6 mL) in CHCl₃ (2 mL) at 0 °C. The reaction mixture was slowly warmed to room temperature and continued for 3.5 h. 5-(4-Chlorophenyl)-1-(3,4-dimethoxyphenethyl)-4-iodo-3-phenyl-1*H*-pyrazole 2-oxide **35f** was obtained in 70 % yield (Table 4.3.1.; entry 1). When the amount of molecular iodine was increased to 1.3 equivalents under the similar conditions the yield of the product slightly increased to 76% (entry 2). The same reaction in dichloromethane and acetonitrile gave 72% and 45% yields, respectively (entries 3-4). From these observations we conclude that, 1.3 equivalents of iodine, 3.0 equivalents of sodium nitrite and acetic acid in chloroform is the best optimum condition of the reaction.

Table 4.3.1. Optimisation of the reaction conditions^a

Entry	Iodine (eq.)	Solvent	Time (h)	Yield(%) ^b
1	I ₂ (1.1)	CHCl ₃	3.5	70
2	I ₂ (1.3)	CHCl ₃	3.5	76
3	I ₂ (1.3)	CH ₂ Cl ₂	4.0	72
4	I ₂ (1.3)	CH ₃ CN	4.0	45

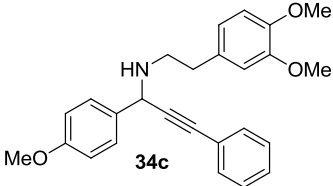
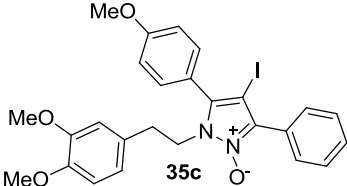
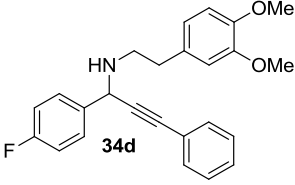
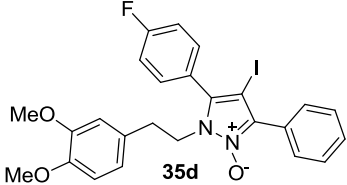
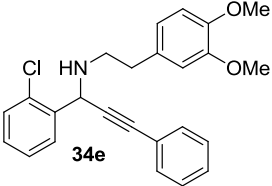
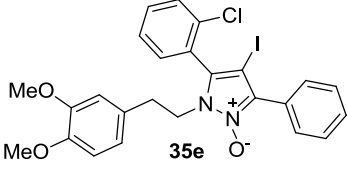
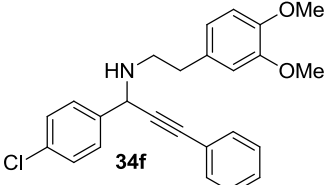
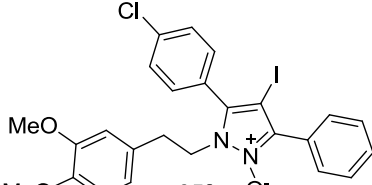
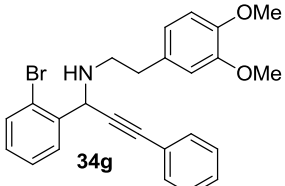
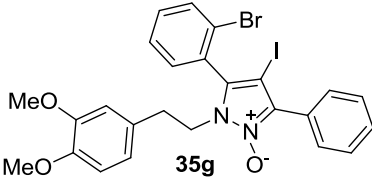
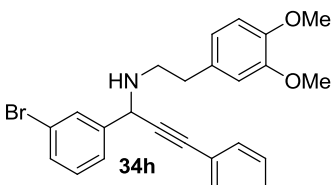
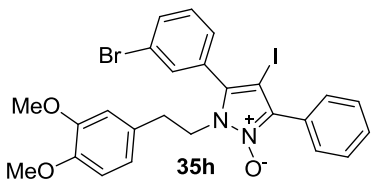
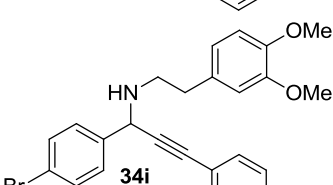
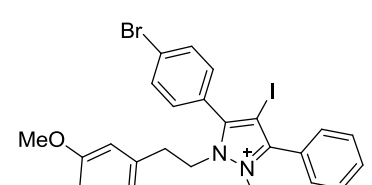
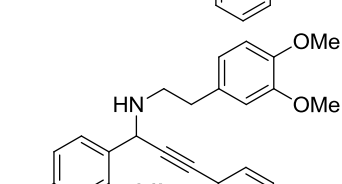
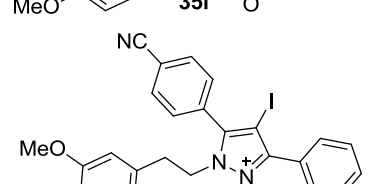
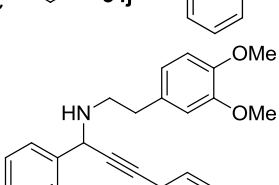
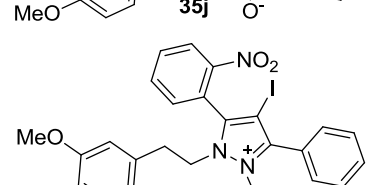
^aReaction conditions: Propargylamine **34f** (0.3 mmol), NaNO₂ (0.9 mmol), Iodine (0.4 mmol), Acetic acid (0.6 mL), Solvent (1 mL). ^bRefers to isolated yield.

With this optimum condition in hand, the scope of the reaction was examined with a variety of substrates (Table 4.3.2). It was observed that both alkyl and aryl substituents in the alkyne side chain gave the desired pyrazole *N*-oxides **35a-35w** in good yields (Table 4.3.2).

Table 4.3.2. Synthesis of 4-iodopyrazole *N*-oxides^a

Entry	Substrate (34)	Product (35)	Time (h)	Yield (%) ^b
1	 34a	 35a	3.0	85
2	 34b	 35b	3.0	81

Continuation....

Entry	Substrate (34)	Product (35)	Time (h)	Yield (%) ^b
3	 34c	 35c	3.0	78
4	 34d	 35d	3.0	72
5	 34e	 35e	3.5	72
6	 34f	 35f	3.5	76
7	 34g	 35g	3.5	72
8	 34h	 35h	3.5	73
9	 34i	 35i	3.5	75
10	 34j	 35j	3.5	71
11	 34k	 35k	4.5	65

Continuation...

Entry	Substrate (34)	Product (35)	Time (h)	Yield (%) ^b
12	 34l	 35l	4.5	68
13	 34m	 35m	3.0	75
14	 34n	 35n	4.5	62
15	 34o	 35o	3.5	71
16	 34p	 35p	3.5	51
17	 34q	 35q	3.5	77
18	 34r	 35r	3.0	86
19	 34s	 35s	3.5	70
20	 34t	 35t	3.5	70

Continuation.....

Entry	Substrate (34)	Product (35)	Time (h)	Yield (%) ^b
21			3.0	74
22			3.5	68
23			3.5	65
24			8.0	d
25			10.0	d

^aReaction conditions: Propargylamine **34** (0.3 mmol), NaNO₂ (0.9 mmol), Iodine (0.4 mmol), Acetic acid (0.6 mL), Solvent (1 mL). ^bRefers to isolated yield. Compounds are characterised by ¹H, ¹³C NMR, IR and Mass spectrometry.

Similarly, different functional groups having substituted propargylamines (*Table 4.3.2.*; **34a-34w**) gave the desired products (*Table 4.3.2.*; **35a-35w**) in 51-85% yields. On the other hand, terminal alkyne **34x** failed to give the desired product **35x**. In case of *N*-aryl propargylamine **34y** we didn't observe the formation of desired product **35y** rather the starting material got decomposed. The structure of the compounds was determined by NMR and mass spectrometry. It was further confirmed by X-ray crystallographic analysis of **35q** (*Figure 4.3.1*).²⁴

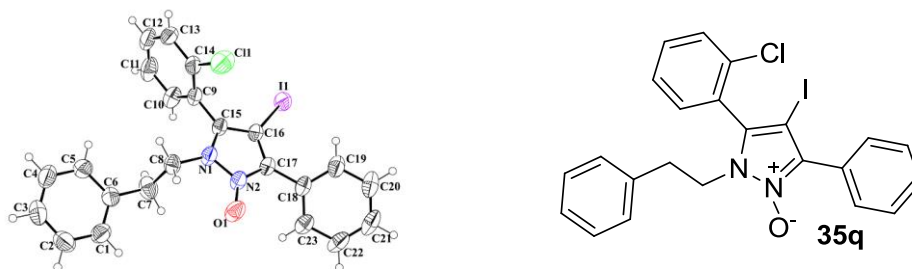
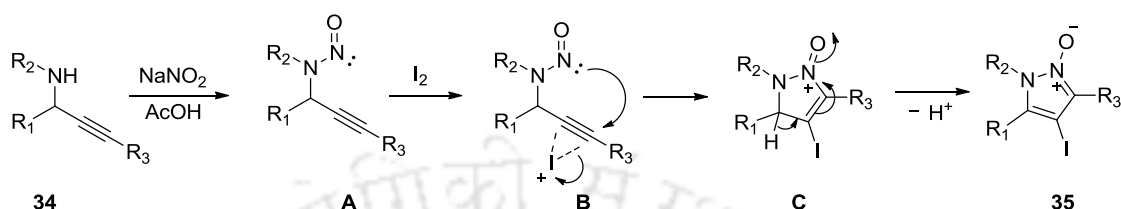


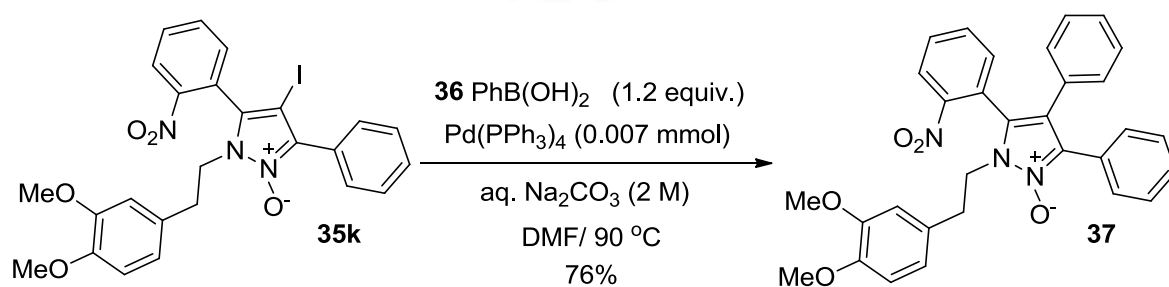
Figure 4.3.1. ORTEP diagram of compound 5-(2-chlorophenyl)-4-iodo-1-phenylethyl-3-phenyl-1H-pyrazole 2-oxide **35q**.

The mechanism of the reaction can be explained as follows. The reaction of amine **34** with sodium nitrite in acetic acid generates *N*-nitrosamine **A**. The alkyne group of **A** is activated by iodine to form iodonium ion **B**, which undergoes 5-*endo-dig* cyclization to give an intermediate **C**. Finally removal of proton from **C** gives the final product **35** (Scheme 4.3.2).

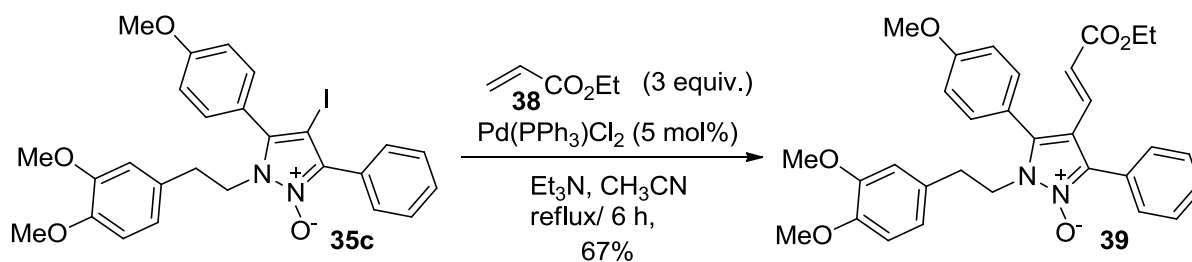


Scheme 4.3.2. Plausible mechanism of the reaction

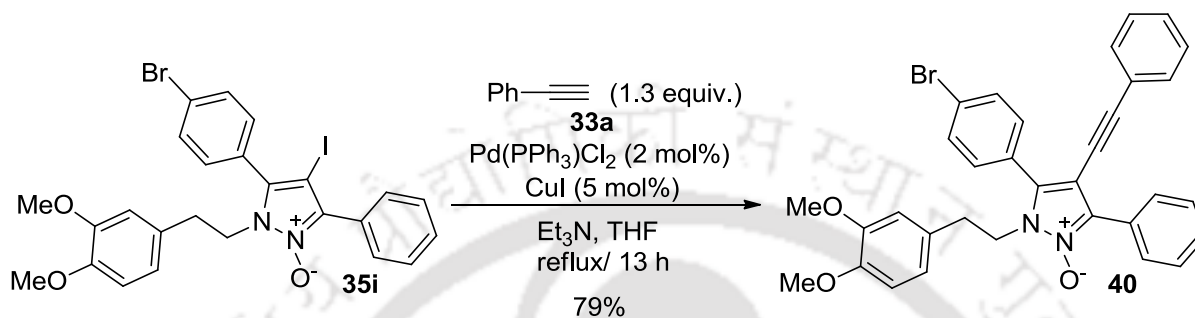
To investigate the further applicability of the pyrazole *N*-oxide, the iodo functionality was used for the Suzuki, Heck and Sonogashira cross coupling reactions. Thus the reaction of 1-(3,4-dimethoxyphenethyl)-4-iodo-5-(2-nitrophenyl)-3-phenyl-1*H*-pyrazole 2-oxide **35k** with phenylboronic acid **36** under Suzuki coupling condition gave 1-(3,4-dimethoxyphenethyl)-5-(2-nitrophenyl)-3,4-diphenyl-1*H*-pyrazole 2-oxide **37** in 76% yield (Scheme 4.3.3.1). Similarly, Heck coupling of 1-(3,4-dimethoxyphenethyl)-4-iodo-5-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazole 2-oxide **35c** with ethyl acrylate **38** produced (*E*)-1-(3,4-dimethoxyphenethyl)-4-(3-ethoxy-3-oxoprop-1-en-1-yl)-5-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazole 2-oxide **39** in 67% yield (Scheme 4.3.3.2). On the other hand, Sonogashira coupling of 5-(4-bromophenyl)-1-(3,4-dimethoxyphenethyl)-4-iodo-3-phenyl-1*H*-pyrazole 2-oxide **35i** with phenylacetylene **33a** afforded the product 5-(4-bromophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-4-(phenylethynyl)-1*H*-pyrazole 2-oxide **40** in 79% yield (Scheme 4.3.3.3).



Scheme 4.3.3.1. Suzuki cross coupling reaction with 4-iodo pyrazole *N*-oxide



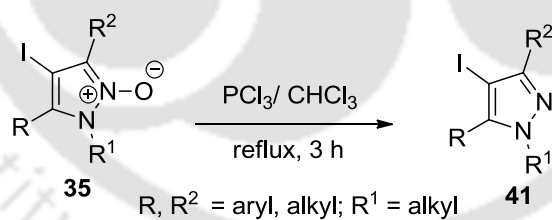
Scheme 4.3.3.2. Heck cross coupling reaction with 4-iodo pyrazole *N*-oxide



Scheme 4.3.3.3. Sonogashira cross coupling reaction with 4-iodo pyrazole *N*-oxide

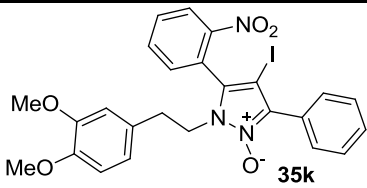
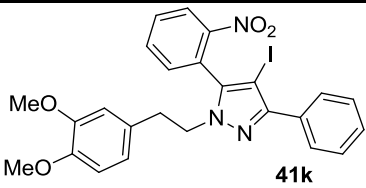
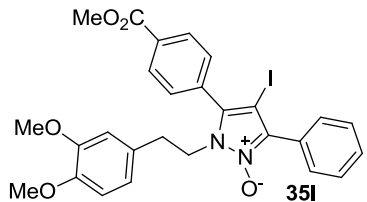
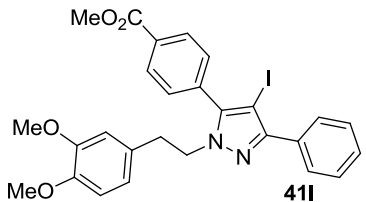
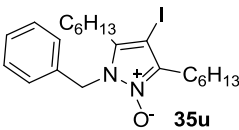
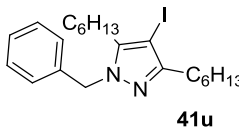
The reduction of pyrazole *N*-oxides to pyrazoles was performed by the treatment with phosphorous trichloride in chloroform at refluxing temperatures and the results are depicted in Table 4.3.3.

Table 4.3.3. Reduction of *N*-oxide bond^a



Entry	Substrate (35)	Substrate (41)	Yield (%) ^b
1			90
2			87

Continuation....

Entry	Substrate (35)	Substrate (41)	Yield (%) ^b
3	 35k	 41k	85
4	 35l	 41l	87
5	 35u	 41u	88

^aReaction conditions: 4-Iodopyrazole *N*-oxide **35** (0.2 mmol), PCl₃ (1.2 mmol), Solvent (1.5 mL).

^bRefers to isolated yield. Products are characterized by ¹H, ¹³C NMR, IR and Mass spectrometry.

The cleavage of *N*-oxide observed with different substituents such as bromo (**35h**), nitrile (**35j**), nitro (**35k**), ester (**35l**) and alkyl groups (**35u**) having pyrazole *N*-oxides and the resultant highly substituent 4-iodopyrazoles **41** (Table 4.3.3; entries 1-5) were obtained in 85-90% yields.

Conclusions

In conclusion, a mild and efficient method has been developed for the synthesis of iodo substituted pyrazole *N*-oxides from propargyl amines in good yields. The reaction is compatible with a wide range of functional groups such as ester, ether, -NO₂, nitrile and halides. The iodo functionality was also successfully applied for Suzuki, Heck and Sonogashira cross-coupling reactions. Some of the pyrazole *N*-oxides were converted to pyrazoles by the treatment with phosphorous trichloride in refluxing chloroform.

4.4. Experimental section

4.4.1. Instrumentation and characterization

As described in chapter 2 section 2.5.1.

4.4.2. General experimental procedure for the synthesis of propargylamines **34**:

As described in chapter 3 section 3.5.2.

4.4.3. General experimental procedure for the synthesis of 4-iodopyrazole *N*-oxides (35):

In general, propargylamine **34** (0.3 mmol) was stirred with (0.4 mmol) of I_2 in a dry $CHCl_3$ (1 mL) kept at 0 °C followed by slow addition of 0.9 mmol of $NaNO_2$ and acetic acid and then reaction mixture was stirred at room temperature for 2-5 h. After completion of the reaction quenched with saturated $Na_2S_2O_3$ solution and then extracted with dichloromethane. The organic layer was further washed with saturated $NaHCO_3$ solution for 2-3 times. The combined organic layers 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 **35**.

4.4.4. Experimental procedure for the synthesis of compound (37) (Suzuki coupling):

Compound **35j** (0.15 mmol, 86 mg) in DMF (0.8 mL) was added to phenylboronic acid **36** (0.18 mmol, 22 mg) and $Pd(PPh_3)_4$ (8 mg, 0.007 mmol) under strict N_2 atmosphere. Na_2CO_3 (0.45 mmol, 2 M) was also added. The reaction mixture was stirred at 90 °C for 6 h. After completion of reaction, the reaction mixture was diluted with ice-cold water (10 ml) and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to furnish a residue. The residue was purified by column chromatography over silica gel to give **37**.

4.4.5. Experimental procedure for the synthesis of compound (39) (Heck coupling):

Compound **35c** (89 mg, 0.16 mmol) in anhydrous CH_3CN (2.50 mL) was added to $PdCl_2(PPh_3)_2$ (0.008 mmol) under N_2 atmosphere. Ethyl acrylate **38** (0.48 mmol) and Et_3N (0.48 mmol) were also added. The reaction mixture was refluxed for 7 h. After completion of reaction, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by column chromatography on silica gel by elution with hexane/ EtOAc to give **39**.

4.4.6. Experimental procedure for the synthesis of compound (40) (Sonogashira coupling):

Compound **35h** (90 mg, 0.15 mmol) in THF (1.5 mL) was added to $PdCl_2(PPh_3)_2$ (2.1 mg, 2 mol%) and CuI (2 mg, 5 mol%) under N_2 atmosphere. Phenyl acetylene **33a** (20 mg, 0.2 mmol) and Et_3N (1 mL) were also added. The reaction mixture was refluxed for 13 h. After completion of reaction, the reaction mixture was quenched with saturated aqueous

solution of NH_4Cl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by column chromatography on silica gel by elution with hexane/ EtOAc to give **40**.

4.4.7. General procedure for the synthesis of 4-iodopyrazoles (**41**):

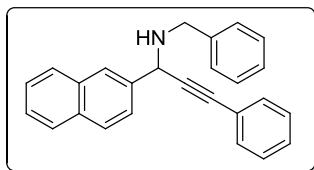
To a stirred solution of compound **35** (120 mg, 0.2 mmol) in CHCl_3 (1.5 mL) phosphorus trichloride (0.1 mL, 1.2 mmol) was added and the reaction mixture was heated to 60 °C. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into ice-cold water. The aqueous layer basified with NaOH and the product was extracted with DCM. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography by elution with hexane/ EtOAc to give **41**.

4.5. References

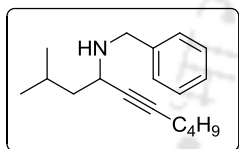
1. (a) Jereb, M.; Vrazic, D.; Zupan, M. *Tetrahedron*. **2011**, 67, 1355-1387. (b) Banerjee, A. K.; Vera, W.; Mora, H.; Laya, M. S.; Bedoya, L.; Cabrera, E. V. *JSCI and Res*. **2006**, 65, 299-308.
2. (a) French, A. N.; Bissmire, S.; Wirth, T. *Chem. Soc. Rev.* **2004**, 33, 354-362. (b) Togo, H.; Iida, S. *Synlett*. **2006**, 2159-2175. (c) Mphahlele, M. J. *Molecules*. **2009**, 14, 4814-4837. (d) Aggarwal, T.; Kumar S.; Verma, A. K. *Org. Biomol. Chem.* **2016**, 14, 7639-7653.
3. (a) Knight, D. W.; Redfern A. L.; Gilmore, J. *Chem. Commun.* **1998**, 2207-2208. (b) Spinaa, R.; Colacinoa, E.; Gabrieleb, B.; Salernoc, G.; Martineza, J.; Lamaty, F. *Synlett*. **2012**, 23, 1481-1484. (c) Bharathiraja, G.; Sakthivel, S.; Sengoden, M.; Punniyamurthy, T. *Org. Lett.* **2013**, 15, 4996-4999.
4. (a) Liu, Y.; Zhou, S. *Org. Lett.* **2005**, 7, 4609-4611. (b) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, 70, 7679-7685. (c) Bew, S. P.; El-Taeb, G. M. M.; Jones, S.; Knight, D. W.; Tan W.-F. *Eur. J. Org. Chem.* **2007**, 5759-5770.
5. (a) Flynn, B. L.; Flynn, G. P.; Hamelb, E.; M. Jung K. *Bioorg. Med. Chem. Lett.* **2001**, 11, 2341-2343. (b) Mancuso, R.; Pomelli, C. S.; Chiappe, C.; Larockc. R. C.; Gabriele, B. *Org. Biomol. Chem.* **2014**, 12, 651-659. (c) Gabriele, B.; Mancuso, R.; Salerno, G.; Larock, R. C. *J. Org. Chem.* **2012**, 77, 7640-7645.
6. (a) Yue, D.; Larock, R.C. *Org. Lett.* **2004**, 6, 1037-1040. (b) Shi, W.; Colemanb R. S.; Lowary, T. L.; *Org. Biomol. Chem.* **2009**, 7, 3709-3722. (c) Danilkinaa, N. A.; Bräse, S.; Balova, I. A. *Synlett*. **2011**, 517-520.
7. (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett*. **1999**, 1432-1434. (b) Gay, R. M.; Manarin, F.; Brandão R.; Zeni, G. *J. Braz. Chem. Soc.* **2010**, 21, 1635-1641. (c) Jung Y.; Kim, I. *Org. Biomol. Chem.* **2016**, 14, 10454-10472.
8. (a) Yue, D.; Larock, R.C. *J. Org. Chem.* **2002**, 67, 1905-1909. (b) Aurelio, L.; Volpe, R.; Halim, R.; Scammells, P. J.; Flynn, B. L. *Adv. Synth. Catal.* **2014**, 356, 1974-1978. (c) Hessian, K.O.; Flynn, B. L. *Org. Lett.* **2003**, 5, 4377-4380.
9. Manarin, F.; Roehrs, J. A.; Gay, R. M.; Brandão, R.; Menezes, P. H.; Nogueira, C. W.; Zeni, G. *J. Org. Chem.* **2009**, 74, 2153-2162.
10. (a) Stauffer, S. R.; Huang, Y. R.; Coletta, C. J.; Tedesco, R.; Katzenellenbogen, J. A. *Bio. Med. Chem.* **2001**, 9, 141-150. (b) Eskildsen, J.; Vedsø, P.; Begtrup, M. *Synthesis*.

- 2001**, 1053-1056. (c) Goikhman, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 3042-3048.
11. (a) Cheng, D.-P.; Chen, Z.-C.; Zheng, Q.-G. *Synth Commun.* **2003**, *33*, 2671-2676. (b) Eller, G. A.; Vilkauskaitė, G.; Arbačiauskienė, E.; Šačkus, A.; Holzer, W. *Synthetic Commun.* **2011**, *41*, 541-547. (c) Kim, M. M.; Ruck, R. T.; Zhao, D.; Huffman, M. A. *Tetrahedron Lett.* **2008**, *49*, 4026-4028.
12. (a) Rodríguez-Franco, M. I.; Dorronsoro, I.; Hernández-Higueras A. I.; Antequera, G. *Tetrahedron Lett.* **2001**, *42*, 863-865.
13. (a) Guillou, S.; Bonhomme, F. J.; Janin, Y. L. *Tetrahedron.* **2009**, *65*, 2660-2668. (b) Potapov, A. S.; Chernova, N. P.; Ogorodnikov, V. D.; Petrenko, T. V.; Khlebnikov, A. I. *Beilstein J. Org. Chem.* **2011**, *7*, 1526-1532.
14. (a) Iglesias, M.; Schuster, O.; Albrecht, M. *Tetrahedron Lett.* **2010**, *51*, 5423-5425. (b) Schmitt, E.; Panossian, A.; Vors, J.-P.; Funke, C.; Lui, N.; Pazenok, S.; Leroux, F. R. *Chem. Eur. J.* **2016**, *22*, 11239-11244.
15. (a) Stefani, H. A.; Pereira, C. M. P.; Almeida, R. B.; Braga, R. C.; Guzenb, K. P.; Cella, R. *Tetrahedron Lett.* **2005**, *46*, 6833-6837. (b) Delaunay, T.; Es-Sayed, M.; Vors, J.-P.; Monteiro, N.; Balme G. *Chem. Lett.* **2011**, *40*, 1434-1436.
16. Felding, J.; Kristensen, J.; Bjerregaard, T.; Sander, L.; Vedso, P.; Begtrup, M. *J. Org. Chem.* **1999**, *64*, 4196-4198.
17. Fandrick, D. R.; Sanyal, S.; Kaloko, J.; Mulder, J. A.; Wang, Y.; Wu, L.; Lee, H.; Roschangar, Frank.; Hoffmann, M.; Senanayake, C. H. *Org. Lett.* **2015**, *17*, 2964-2967.
18. Gorja1, D. R.; Batchu, V. R.; Ettam, A.; Pal, M. *Beilstein J. Org. Chem.* **2009**, *5*, 64-69.
19. Waldo, J. P.; Mehta, S.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 6666-6670.
20. Caudrado, P.; González-Nogal, A. M.; Valero, R. *Tetrahedron.* **2002**, *58*, 4975-4980.
21. Okitsu, T.; Sato, K.; Wada, A. *Org. Lett.* **2010**, *12*, 3506-3509.
22. Zora, M.; Kivrak, A.; Yazici, C. *J. Org. Chem.* **2011**, *76*, 6726-6742.
23. Unnava, R.; Saikia, A. K. *Chemistry Select.* **2016**, *1*, 1816-1823.
24. CCDC 1419355 (**35q**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

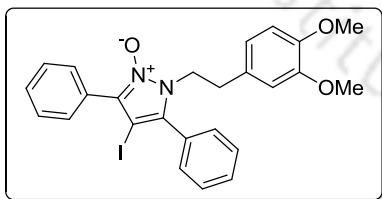
4.6. Characterization data

N-Benzyl-1-(naphthalen-2-yl)-3-phenylprop-2-yn-1-amine (34s):

Orange gum; R_f (hexane/EtOAc 9:1) 0.51; yield 415 mg, 60%; ^1H NMR (600 MHz, CDCl_3): δ 8.08 (s, 1 H), 7.89 (d, $J = 7.8$ Hz, 2 H), 7.86 (d, $J = 8.4$ Hz, 1 H), 7.77 (d, $J = 7.8$ Hz, 1 H), 7.58-7.50 (m, 2 H), 7.50-7.44 (m, 4 H), 7.39-7.35 (m, 5 H), 7.31-7.28 (m, 1 H), 5.01 (s, 1 H), 4.05 (s, 2 H), 1.87 (brs, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 140.0, 137.9, 133.5, 133.2, 132.0, 128.6, 128.5, 128.4, 128.2, 127.8, 127.3, 126.5, 126.3, 126.2, 126.0, 123.3, 89.4, 86.2, 54.0, 51.3; IR (KBr, neat) 3349, 3058, 1600, 1504, 1275, 1172, 1086, 1023, 838, 756, 694 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{22}\text{N}$ ($M + \text{H}$) $^+$ 348.1747, found 348.1747.

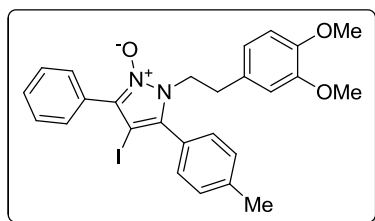
N-Benzyl-2-methyldec-5-yn-4-amine (34u):

Pale yellow oil; R_f (hexane/EtOAc 19:1) 0.51; yield 231 mg, 45%; ^1H NMR (400 MHz, CDCl_3): δ 7.37-7.30 (m, 4 H), 7.23 (d, $J = 6.8$ Hz, 1 H), 4.03 (d, $J = 12.8$ Hz, 1 H), 3.79 (d, $J = 12.8$ Hz, 1 H), 3.39 (t, $J = 7.2$ Hz, 1 H), 2.23 (t, $J = 6.8$ Hz, 2 H), 1.94-1.83 (m, 1 H), 1.55-1.39 (m, 7 H), 0.93 (t, $J = 7.2$ Hz, 3 H), 0.88 (d, $J = 6.0$ Hz, 6 H); ^{13}C NMR (100 MHz, CDCl_3): δ 140.5, 128.5, 128.5, 127.0, 84.0, 81.7, 51.6, 48.2, 45.8, 31.3, 25.4, 23.2, 22.3, 22.1, 18.6, 13.8; IR (KBr, neat) 3026, 2868, 1626, 1529, 1501, 1368, 1219, 1166, 1058, 1008, 786, 680 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{28}\text{N}$ ($M + \text{H}$) $^+$ 258.2216, found 258.2216.

1-(3,4-Dimethoxyphenethyl)-4-iodo-3,5-diphenyl-1H-pyrazole 2-oxide (35a):

Orange red solid; mp 116-118 $^{\circ}\text{C}$; R_f (hexane/EtOAc 3:2) 0.51; yield 134 mg, 85 %; ^1H NMR (400 MHz, CDCl_3): δ 7.90 (d, $J = 7.6$ Hz, 2 H), 7.51 (t, $J = 7.6$ Hz, 2 H), 7.45-7.38 (m, 4 H), 7.05 (d, $J = 7.2$ Hz, 2 H), 6.68 (d, $J = 8.4$ Hz, 1 H), 6.44 (d, $J = 7.6$ Hz, 1 H), 6.35 (s, 1 H), 4.38 (t, $J = 7.2$ Hz, 2 H), 3.84 (s, 3 H), 3.69 (s, 3 H), 3.00 (t, $J = 7.2$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 149.1, 148.1, 136.2, 131.8, 130.3, 129.8, 129.7, 129.7, 129.5, 128.9, 128.8, 128.4, 127.6, 121.1, 112.0, 111.4, 57.2, 56.1, 55.8, 47.5, 33.9; IR (KBr, neat) 2956, 2833, 1516, 1466, 1263, 1237, 1157, 1028, 852, 763, 696 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{24}\text{IN}_2\text{O}_3$ ($M + \text{H}$) $^+$ 527.0826, found 527.0829.

1-(3,4-Dimethoxyphenethyl)-4-iodo-3-phenyl-5-(p-tolyl)-1H-pyrazole 2-oxide (35b):



Orange red solid; mp 120-122 °C; R_f (hexane/EtOAc 3:2) 0.51; yield 131 mg, 81%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.90 (d, $J = 7.6$ Hz, 2 H), 7.51 (t, $J = 7.6$ Hz, 2 H), 7.44 (t, $J = 7.2$ Hz, 1H), 7.22 (d, $J = 7.6$ Hz, 2 H), 6.95 (d, $J = 7.2$ Hz, 2 H), 6.70 (d, $J = 8.0$ Hz, 1 H), 6.47 (d, $J = 8.0$ Hz, 1 H), 6.38 (s, 1 H), 4.38 (t, $J = 6.8$ Hz, 2 H), 3.86 (s, 3 H), 3.70 (s, 3 H), 3.01 (t, $J = 6.8$ Hz, 2 H), 2.42 (s, 3 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 149.2, 148.1, 140.0, 136.3, 131.8, 130.2, 129.9, 129.8, 129.6, 129.5, 128.5, 127.8, 126.0, 121.2, 112.0, 111.4, 57.1, 56.2, 55.8, 47.5, 34.0, 21.6; **IR** (KBr, neat) 2994, 2833, 1515, 1417, 1262, 1157, 1026, 822, 766, 737, 681 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{26}\text{IN}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 541.0983, found 541.0980.

1-(3,4-Dimethoxyphenethyl)-4-iodo-5-(4-methoxyphenyl)-3-phenyl-1H-pyrazole-2-oxide (35c):

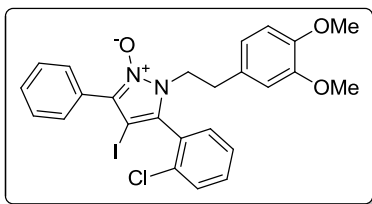
Orange red solid; mp 136-138 °C; R_f (hexane/EtOAc 3:2) 0.51; yield 130 mg, 78 %; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.88 (d, $J = 8.0$ Hz, 2 H), 7.49 (t, $J = 7.2$ Hz, 2 H), 7.40 (t, $J = 6.8$ Hz, 1 H), 6.96 (d, $J = 8.4$ Hz, 2 H), 6.91 (d, $J = 8.8$ Hz, 2 H), 6.68 (d, $J = 8.4$ Hz, 1 H), 6.46 (d, $J = 8.4$ Hz, 1 H), 6.36 (s, 1 H), 4.35 (t, $J = 6.4$ Hz, 2 H), 3.83 (s, 6 H), 3.67 (s, 3 H), 3.00 (t, $J = 6.8$ Hz, 2 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 160.4, 149.0, 147.9, 135.7, 131.6, 131.2, 129.8, 129.7, 129.2, 128.3, 127.7, 121.0, 120.9, 114.1, 111.8, 111.2, 57.0, 56.0, 55.7, 55.4, 47.2, 33.8; **IR** (KBr, neat) 3025, 2995, 1501, 1277, 1230, 1126, 1015, 822, 752, 715, 681 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{26}\text{IN}_2\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 557.0932, found 557.0937.

1-(3,4-Dimethoxyphenethyl)-5-(4-fluorophenyl)-4-iodo-3-phenyl-1H-pyrazole 2-oxide (35d):

Orange red gum; R_f (hexane/EtOAc 3:2) 0.52; yield 117 mg, 72 %; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.89 (d, $J = 7.6$ Hz, 2 H), 7.51 (t, $J = 7.6$ Hz, 2 H), 7.43 (t, $J = 7.6$ Hz, 1 H), 7.09 (t, $J = 8.4$ Hz, 2 H), 6.99-6.94 (m, 2 H), 6.69 (d, $J = 8.0$ Hz, 1 H), 6.44 (d, $J = 8.4$ Hz, 1 H), 6.34 (s, 1 H), 4.35 (t, $J = 6.4$ Hz, 2 H), 3.85 (s, 3 H), 3.70 (s, 3 H), 3.01 (t, $J = 6.8$ Hz, 2 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 163.3 (d, $J = 250.1$ Hz), 149.2, 148.2, 134.9, 132.4 (d, $J = 9.0$ Hz), 131.4, 129.8, 129.5, 128.5, 127.7, 125.1, 125.0, 121.2, 116.0 (d, $J = 22.1$ Hz), 112.0, 111.5, 57.3, 55.9, 55.8, 47.5, 33.7; $^{19}\text{F NMR}$ (376 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$): 51.52; **IR** (KBr, neat) 2994, 2834, 1609, 1515, 1489, 1417, 1236, 1157, 1026, 843, 767, 737, 682 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{23}\text{FIN}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 545.0732, found 545.0735.

5-(2-Chlorophenyl)-1-(3,4-dimethoxyphenethyl)-4-iodo-3-phenyl-1H-pyrazole 2-oxide (35e):

Orange red gum; R_f (hexane/EtOAc 3:2) 0.52; yield 121 mg, 72 %; $^1\text{H NMR}$ (400 MHz,

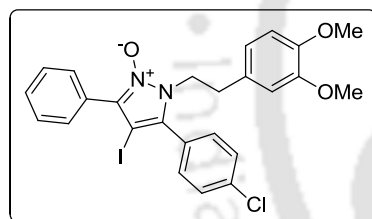


CDCl_3): δ 7.96 (d, $J = 7.2$ Hz, 2 H), 7.51 (t, $J = 7.6$ Hz, 3 H), 7.45-7.39 (m, 2 H), 7.24 (t, $J = 7.2$ Hz, 1 H), 6.70 (d, $J = 8.0$ Hz, 2 H), 6.46 (d, $J = 8.0$ Hz, 1 H), 6.38 (s, 1 H), 4.61-4.55 (m, 1 H), 3.98-3.91 (m, 1 H), 3.85 (s, 3 H), 3.69 (s, 3 H), 3.25-

3.17 (m, 1 H), 2.89-2.83 (m, 1 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 149.1, 148.0, 134.7, 133.2, 132.8, 131.5, 130.9, 129.9, 129.6, 129.2, 128.3, 128.1, 127.5, 127.0, 121.0, 111.9, 111.4, 57.7, 56.1, 55.7, 47.6, 33.5; **IR** (KBr, neat) 2982, 2881, 2816, 1627, 1562, 1501, 1271, 1123, 1060, 996, 850, 753, 576 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{23}\text{ClIN}_2\text{O}_3$ ($M + H$) $^+$ 561.0436, found 561.0433.

5-(4-Chlorophenyl)-1-(3,4-dimethoxyphenethyl)-4-iodo-3-phenyl-1H-pyrazole 2-oxide (35f):

Orange red semisolid; R_f (hexane/EtOAc 3:2) 0.51; yield 127 mg, 76 %; $^1\text{H NMR}$ (400 MHz,

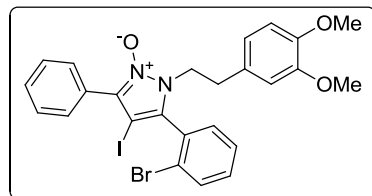


CDCl_3): δ 7.89 (d, $J = 7.6$ Hz, 2 H), 7.50 (t, $J = 7.6$ Hz, 2 H), 7.44 (t, $J = 6.8$ Hz, 1 H), 7.35 (d, $J = 7.6$ Hz, 2 H), 6.90 (d, $J = 7.2$ Hz, 2 H), 6.68 (d, $J = 8.0$ Hz, 1 H), 6.43 (d, $J = 7.6$ Hz, 1 H), 6.32 (s, 1 H), 4.36 (t, $J = 6.0$ Hz, 2 H), 3.85 (s, 3 H), 3.69 (s, 3 H), 3.00 (t, $J = 6.0$ Hz, 2 H); $^{13}\text{C NMR}$ (100 MHz,

CDCl_3): δ 149.1, 148.1, 135.9, 134.7, 131.6, 131.5, 129.7, 129.6, 129.4, 129.0, 128.4, 127.6, 127.3, 121.1, 111.9, 111.4, 57.3, 56.1, 55.7, 47.5, 33.7; **IR** (KBr, neat) 3042, 2938, 2835, 1612, 1528, 1465, 1347, 1264, 1157, 1026, 853, 737 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{23}\text{ClIN}_2\text{O}_3$ ($M + H$) $^+$ 561.0436, found 561.0436.

5-(2-Bromophenyl)-1-(3,4-dimethoxyphenethyl)-4-iodo-3-phenyl-1H-pyrazole 2-oxide (35g):

Pale yellow semi solid; R_f (hexane/EtOAc 3:2) 0.51; yield 130 mg, 72 %; $^1\text{H NMR}$ (400



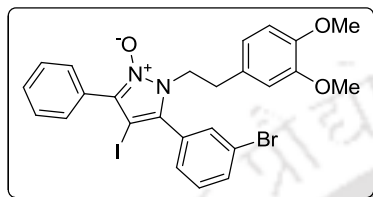
MHz, CDCl_3): δ 7.96 (d, $J = 7.6$ Hz, 2 H), 7.68 (d, $J = 8.0$ Hz, 1 H), 7.51 (t, $J = 7.6$ Hz, 2 H), 7.43 (t, $J = 7.6$ Hz, 1 H), 7.34 (t, $J = 7.6$ Hz, 1 H), 7.28 (d, $J = 7.6$ Hz, 1 H), 6.70 (d, $J = 8.0$ Hz, 1 H), 6.65 (d, $J = 7.6$ Hz, 1 H), 6.46 (d, $J = 8.4$ Hz, 1 H),

6.39 (s, 1 H), 4.58 (ddd, $J = 12.4, 7.6$ and 4.0 Hz, 1 H), 3.91 (ddd, $J = 15.2, 7.6$ and 4.0 Hz, 1 H), 3.85 (s, 3 H), 3.69 (s, 3 H), 3.22 (ddd, $J = 14.0, 8.0$ and 5.6 Hz, 1 H), 2.87 (ddd, $J = 13.6, 8.4$ and 5.6 Hz, 1 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 149.1, 148.0, 134.4, 133.3, 133.1,

131.7, 130.9, 130.3, 129.9, 129.6, 129.3, 128.3, 127.6, 124.9, 121.1, 112.0, 111.4, 57.6, 56.1, 55.8, 47.7, 33.6; **IR** (KBr, neat) 3060, 3001, 2927, 2836, 1637, 1515, 1467, 1390, 1264, 1151, 1027, 970, 855, 758, 733, 694 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{23}\text{BrIN}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 604.9931, found 604.9933.

5-(3-Bromophenyl)-1-(3,4-dimethoxyphenethyl)-4-iodo-3-phenyl-1H-pyrazole 2-oxide (35h):

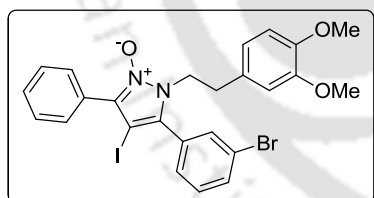
Pale yellow solid; mp 140-142 °C; R_f (hexane/EtOAc 3:2) 0.51; yield 132 mg, 73 %; **¹H NMR**



(400 MHz, CDCl_3): δ 7.90 (d, J = 7.6 Hz, 2 H), 7.56-7.49 (m, 3 H), 7.43 (t, J = 7.2 Hz, 1 H), 7.24 (t, J = 7.2 Hz, 1 H), 7.01 (s, 1 H), 6.95 (d, J = 7.6 Hz, 1 H), 6.71 (d, J = 7.6 Hz, 1 H), 6.45 (d, J = 8.0 Hz, 1 H), 6.33 (s, 1 H), 4.37 (t, J = 6.0 Hz, 2 H), 3.86 (s, 3 H), 3.70 (s, 3 H), 3.05 (t, J = 6.4 Hz, 2 H); **¹³C NMR** (100 MHz, CDCl_3): δ 149.0, 148.0, 134.0, 132.8, 132.6, 131.1, 130.7, 130.0, 129.6, 129.4, 129.3, 128.8, 128.3, 127.5, 122.5, 121.0, 111.8, 111.3, 57.2, 55.9, 55.7, 47.5, 33.4; **IR** (KBr, neat) 3050, 3000, 2833, 1600, 1594, 1514, 1416, 1268, 1154, 1071, 1029, 854, 795, 735, 632 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{23}\text{BrIN}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 604.9931, found 604.9929.

5-(4-Bromophenyl)-1-(3,4-dimethoxyphenethyl)-4-iodo-3-phenyl-1H-pyrazole 2-oxide (35i):

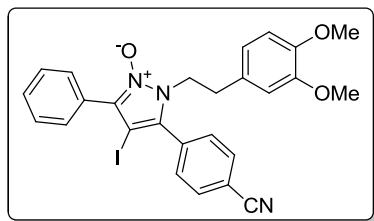
Orange red solid; mp 158-160 °C; R_f (hexane/EtOAc 3:2) 0.51; yield 136 mg, 75 %; **¹H NMR**



(400 MHz, CDCl_3): δ 7.88 (d, J = 7.6 Hz, 2 H), 7.51 (t, J = 7.6 Hz, 4 H), 7.42 (t, J = 7.2 Hz, 1 H), 6.83 (d, J = 7.6 Hz, 2 H), 6.68 (d, J = 8.0 Hz, 1 H), 6.43 (d, J = 8.0 Hz, 1 H), 6.31 (s, 1 H), 4.36 (t, J = 6.8 Hz, 2 H), 3.85 (s, 3 H), 3.69 (s, 3 H), 3.00 (t, J = 6.4 Hz, 2 H); **¹³C NMR** (100 MHz, CDCl_3): δ 149.0, 148.0, 134.5, 131.9, 131.7, 131.2, 129.6, 129.5, 129.3, 128.3, 127.7, 127.5, 124.0, 121.1, 111.8, 111.3, 57.1, 56.0, 55.7, 47.3, 33.6; **IR** (KBr, neat) 2982, 2881, 2815, 1627, 1531, 1500, 1476, 1307, 1281, 1187, 1010, 869, 781 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{23}\text{BrIN}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 604.9931, found 604.9929.

5-(4-Cyanophenyl)-1-(3,4-dimethoxyphenethyl)-4-iodo-3-phenyl-1H-pyrazole 2-oxide: (35j):

Pale yellow solid; mp 155-157 °C; R_f (hexane/EtOAc 3:2) 0.51; yield 117 mg, 71 %; **¹H NMR**

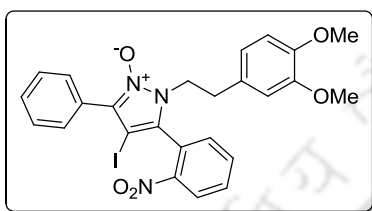


(400 MHz, CDCl_3): δ 7.88 (d, J = 7.6 Hz, 2 H), 7.64 (d, J = 8.0 Hz, 2 H), 7.53 (t, J = 7.2 Hz, 2 H), 7.46 (t, J = 7.2 Hz, 1 H), 7.08 (d, J = 7.6 Hz, 2 H), 6.68 (d, J = 8.0 Hz, 1 H), 6.39 (d, J = 8.4 Hz, 1 H), 6.29 (s, 1 H), 4.40 (t, J = 6.0 Hz, 2 H),

3.88 (s, 3 H), 3.70 (s, 3 H), 3.03 (d, $J = 6.4$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 149.2, 148.3, 133.8, 133.4, 132.4, 131.9, 130.9, 129.8, 129.7, 129.4, 128.6, 127.4, 121.2, 118.2, 113.3, 112.0, 111.5, 57.8, 56.2, 55.8, 47.8, 33.5; IR (KBr, neat) 3045, 2834, 2229, 1609, 1516, 1465, 1262, 1141, 1027, 845, 766, 738 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{23}\text{IN}_3\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 552.0779, found 552.0783.

1-(3,4-Dimethoxyphenethyl)-4-iodo-5-(2-nitrophenyl)-3-phenyl-1H-pyrazole 2-oxide (35k):

Brown red semisolid; R_f (hexane/EtOAc 1:1) 0.51; yield 111 mg, 65 %; ^1H NMR (400 MHz,

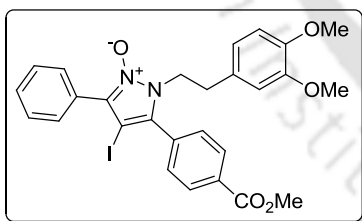


CDCl_3): δ 8.05 (d, $J = 8.0$ Hz, 1 H), 7.84 (d, $J = 7.6$ Hz, 2 H), 7.56 (t, $J = 7.2$ Hz, 1 H), 7.49 (t, $J = 7.2$ Hz, 1 H), 7.41 (t, $J = 7.2$ Hz, 2 H), 7.33 (t, $J = 7.2$ Hz, 1 H), 6.64 (d, $J = 8.4$ Hz, 1 H), 6.54 (d, $J = 7.6$ Hz, 1 H), 6.41 (d, $J = 8.0$ Hz, 1 H), 6.33 (s,

1 H), 4.50-4.21 (m, 1 H), 3.86-3.75 (m, 1 H), 3.78 (s, 3 H), 3.59 (m, 3 H), 3.29-3.19 (m, 1 H), 2.79-2.61 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 148.9, 148.4, 147.8, 133.8, 133.4, 131.5, 131.2, 130.8, 129.7, 129.3, 129.1, 128.1, 127.1, 124.8, 123.4, 121.0, 111.7, 111.2, 56.9, 55.8, 55.5, 48.0, 33.1; IR (KBr, neat) 3057, 2936, 2836, 1610, 1530, 1348, 1235, 1153, 1029, 969, 856, 734, 630 cm^{-1} ; HRMS (ESI) calcd. For $\text{C}_{25}\text{H}_{23}\text{IN}_3\text{O}_5$ ($\text{M} + \text{H}$) $^+$ 572.0677, found 572.0679.

1-(3,4-Dimethoxyphenethyl)-4-iodo-5-(4-(methoxycarbonyl)phenyl)-3-phenyl-1H-pyrazole 2-oxide (35l):

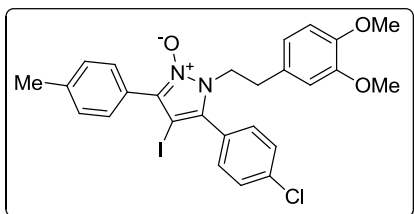
Orange red semisolid; R_f (hexane/EtOAc 1:1) 0.51; yield 119 mg, 68 %; ^1H NMR (400 MHz,



CDCl_3): δ 8.01 (d, $J = 8.4$ Hz, 2 H), 7.85 (d, $J = 7.6$ Hz, 2 H), 7.48 (t, $J = 7.2$ Hz, 2 H), 7.40 (t, $J = 7.2$ Hz, 1 H), 7.06 (d, $J = 8.4$ Hz, 2 H), 6.61 (d, $J = 7.6$ Hz, 1 H), 6.37 (d, $J = 8.0$ Hz, 1 H), 6.28 (s, 1 H), 4.37 (t, $J = 6.8$ Hz, 2 H), 3.91 (s, 3 H), 3.82 (s, 3 H), 3.65 (s, 3 H), 2.97 (t, $J = 6.4$ Hz, 2 H); ^{13}C NMR (100

MHz, CDCl_3): δ 166.3, 148.9, 147.9, 134.7, 133.1, 131.7, 130.9, 130.1, 129.7, 129.6, 129.4, 129.3, 128.3, 127.4, 120.9, 111.8, 111.3, 57.3, 56.0, 55.6, 52.5, 47.5, 33.5; IR (KBr, neat) 3057, 2999, 2836, 1733, 1610, 1520, 1419, 1103, 1026, 966, 856, 778, 637 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{26}\text{IN}_2\text{O}_5$ ($\text{M} + \text{H}$) $^+$ 585.0881, found 585.0891.

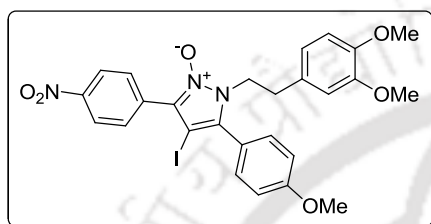
5-(4-Chlorophenyl)-1-(3,4-dimethoxyphenethyl)-4-iodo-3-(p-tolyl)-1H-pyrazole 2-oxide (35m):



Pale yellow solid; mp 160-162 $^{\circ}\text{C}$; R_f (hexane/EtOAc 3:2) 0.51; yield 129 mg, 75 %; ^1H NMR (400 MHz, CDCl_3): δ 7.79 (d, $J = 7.6$ Hz, 2 H), 7.33 (t, $J = 8.8$ Hz, 4 H), 6.90 (d,

$J = 8.4$ Hz, 2 H), 6.68 (d, $J = 8.0$ Hz, 1 H), 6.44 (d, $J = 8.0$ Hz, 1 H), 6.31 (s, 1 H), 4.36 (t, $J = 6.0$ Hz, 2 H), 3.85 (s, 3 H), 3.69 (s, 3 H), 3.01 (t, $J = 6.4$ Hz, 2 H), 2.41 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 149.0, 148.0, 139.4, 135.7, 134.4, 131.5, 131.4, 129.6, 129.5, 129.0, 128.9, 127.4, 124.6, 121.1, 111.9, 111.3, 57.2, 56.0, 55.7, 47.4, 33.6, 21.6; **IR** (KBr, neat) 3050, 2956, 2834, 1592, 1520, 1266, 1157, 1088, 1029, 813, 766, 738 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{25}\text{ClIN}_2\text{O}_3$ ($M + H$) $^+$ 575.0593, found 575.0591.

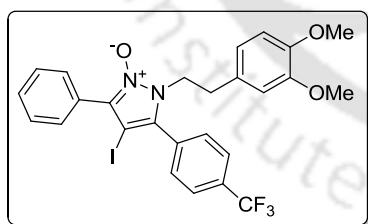
1-(3,4-Dimethoxyphenethyl)-4-iodo-5-(4-methoxyphenyl)-3-(4-nitrophenyl)-1H-pyrazole 2-oxide (35n):



Brown red semisolid; R_f (hexane/EtOAc 3:2) 0.51; yield 93 mg, 62 %; ^1H NMR (400 MHz, CDCl_3): δ 8.35 (d, $J = 8.4$ Hz, 2 H), 8.20 (d, $J = 8.4$ Hz, 2 H), 6.99 (d, $J = 8.4$ Hz, 2 H), 6.95 (d, $J = 8.4$ Hz, 2 H), 6.70 (d, $J = 8.0$ Hz, 1 H), 6.47 (d, $J = 8.4$ Hz, 1 H), 6.37 (s, 1 H), 4.38 (t, $J = 6.8$ Hz, 2 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.70 (s, 3 H), 3.00 (t, $J = 7.2$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.7, 149.0, 148.0, 147.5, 136.2, 134.2, 131.5, 130.3, 129.4, 128.8, 123.4, 120.4, 114.2, 113.8, 111.7, 111.3, 56.3, 56.0, 55.7, 55.4, 47.3, 33.7; **IR** (KBr, neat) 2969, 2836, 1610, 1573, 1520, 1464, 1344, 1256, 1157, 1026, 767, 738 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{25}\text{IN}_3\text{O}_6$ ($M + H$) $^+$ 602.0783, found 602.0783.

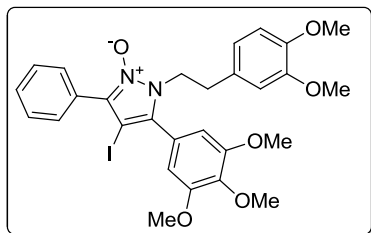
1-(3,4-Dimethoxyphenethyl)-4-iodo-3-phenyl-5-(4-(trifluoromethyl)phenyl)-1H-pyrazole 2-oxide (35o):

Pale yellow semisolid; R_f (hexane/EtOAc 3:2) 0.51; yield 105 mg, 71 %; ^1H NMR (600 MHz,



CDCl_3): δ 7.90 (d, $J = 7.6$ Hz, 2 H), 7.64 (d, $J = 8.4$ Hz, 2 H), 7.53 (t, $J = 7.2$ Hz, 2 H), 7.45 (t, $J = 6.8$ Hz, 1 H), 7.10 (d, $J = 8.4$ Hz, 2 H), 6.67 (d, $J = 8.0$ Hz, 1 H), 6.41 (d, $J = 7.6$ Hz, 1 H), 6.30 (s, 1 H), 4.40 (t, $J = 6.4$ Hz, 2 H), 3.87 (s, 3 H), 3.67 (s, 3 H), 3.03 (t, $J = 6.4$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 149.1, 148.2, 134.2, 132.5, 131.6, 131.5 (q, $J = 32.8$ Hz), 129.7, 129.5, 129.4, 128.5, 127.9, 127.5, 125.6, 125.5, 125.2, 123.8 (q, $J = 270.8$ Hz), 121.1, 111.9, 111.4, 110.4, 57.4, 56.1, 55.7, 47.6, 33.6; ^{19}F NMR (376 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$): 98.90; **IR** (KBr, neat) 2932, 2835, 1619, 1516, 1466, 1324, 1238, 1126, 1066, 1027, 847, 762, 694 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{26}\text{H}_{23}\text{F}_3\text{IN}_2\text{O}_3$ ($M + H$) $^+$ 595.0700, found 595.0709.

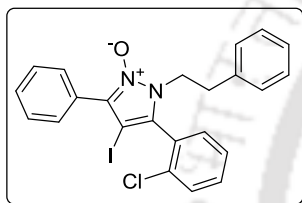
1-(3,4-Dimethoxyphenethyl)-4-iodo-3-phenyl-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole 2-oxide (35p):



Pale yellow solid; mp 157-159 °C; R_f (hexane/EtOAc 1:1) 0.51; yield 94 mg, 51%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.90 (d, $J = 7.6$ Hz, 2 H), 7.52 (t, $J = 7.6$ Hz, 2 H), 7.44 (t, $J = 7.2$ Hz, 1 H), 6.68 (d, $J = 8.4$ Hz, 1 H), 6.47 (d, $J = 8.4$ Hz, 1 H), 6.40 (s, 1 H), 6.30 (s, 2 H), 4.45 (t, $J = 6.4$ Hz, 2 H), 3.92 (s, 3 H), 3.85 (s, 6 H), 3.83 (s, 3 H), 3.73 (s, 3 H), 3.06 (t, $J = 6.4$ Hz, 2 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 153.3, 153.2, 148.9, 147.8, 139.0, 135.8, 131.4, 129.7, 129.4, 128.4, 127.7, 124.1, 121.1, 112.0, 111.3, 107.3, 61.0, 57.0, 56.4, 56.3(2C), 55.8, 47.4, 33.7; **IR** (KBr, neat) 2928, 2853, 1624, 1515, 1457, 1263, 1129, 1028, 761 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{28}\text{H}_{30}\text{IN}_2\text{O}_6$ ($M + \text{H}$) $^+$ 617.1143, found 617.1145.

5-(2-Chlorophenyl)-4-iodo-1-phenethyl-3-phenyl-1H-pyrazole 2-oxide (35q):

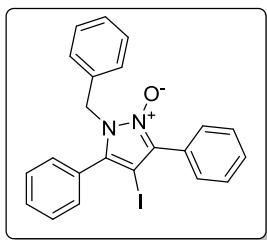
Pale yellow solid; mp 126-128 °C; R_f (hexane/EtOAc 3:2) 0.52; yield 115 mg, 77 %; $^1\text{H NMR}$



(400 MHz, CDCl_3): δ 7.96 (d, $J = 7.6$ Hz, 2 H), 7.52 (t, $J = 7.2$ Hz, 3 H), 7.44 (t, $J = 6.8$ Hz, 2 H), 7.28-7.24 (m, 1 H), 7.22-7.18 (m, 3 H), 6.95-6.91 (m, 2 H), 6.78 (d, $J = 7.2$ Hz, 1 H), 4.57-4.50 (m, 1 H), 4.03-3.95 (m, 1 H), 3.24-3.16 (m, 1 H), 2.97-2.90 (m, 1 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 137.5, 135.0, 133.3, 132.9, 131.8, 131.2, 130.1, 129.8, 129.4, 129.2, 128.9, 128.4, 128.3, 127.7, 127.3, 127.0, 58.0, 47.4, 34.2; **IR** (KBr, neat) 2996, 2834, 1612, 1526, 1464, 1346, 1263, 1157, 1027, 855, 737 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{23}\text{H}_{19}\text{ClIN}_2\text{O}$ ($M + \text{H}$) $^+$ 501.0225, found 501.0227.

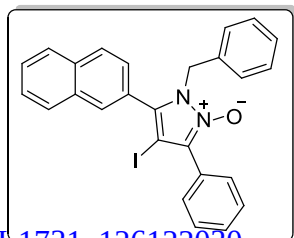
1-Benzyl-4-iodo-3,5-diphenyl-1H-pyrazole 2-oxide (35r):

Red brown solid; mp 137-139 °C; R_f (hexane/EtOAc 13:7) 0.48; yield 116 mg, 86 %; $^1\text{H NMR}$



(400 MHz, CDCl_3): δ 7.91 (d, $J = 7.2$ Hz, 2 H), 7.51-7.38 (m, 6 H), 7.30 (d, $J = 6.4$ Hz, 2 H), 7.22-7.24 (m, 3 H), 7.08-7.10 (m, 2 H), 5.39 (s, 2 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 135.5, 135.4, 131.1, 130.5, 130.0, 129.8, 129.3, 129.1, 129.0, 128.8, 128.3, 128.1, 127.9, 127.8, 57.6, 48.1; **IR** (KBr, neat) 2925, 2852, 1602, 1515, 1473, 1429, 1236, 1149, 1074, 945, 758, 696 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{22}\text{H}_{18}\text{IN}_2\text{O}$ ($M + \text{H}$) $^+$ 453.0458, found 453.0459.

1-Benzyl-4-iodo-5-(naphthalen-2-yl)-3-phenyl-1H-pyrazole 2-oxide (35s):

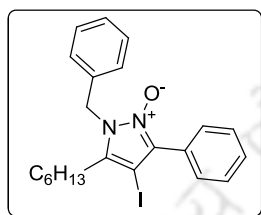


Orange red solid; mp 147-149 °C; R_f (hexane/EtOAc 3:2) 0.52; yield 105 mg, 70 %; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.95 (d, $J = 7.6$ Hz, 2 H), 7.88 (t, $J = 8.8$ Hz, 2 H), 7.78-7.74 (m, 2 H), 7.56-7.49 (m, 4 H), 7.41-7.35 (s, 2 H), 7.22-7.19 (m, 3 H), 7.10-7.08 (m, 2 H), 5.40 (s, 2

H); ^{13}C NMR (100 MHz, CDCl_3): δ 135.6, 135.5, 133.5, 132.9, 131.0, 130.6, 129.8, 129.2, 128.9, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.5, 127.0, 126.9, 126.3, 57.9, 48.3; IR (KBr, neat) 3055, 2976, 1635, 1533, 1496, 1459, 1431, 1229, 1147, 1094, 950, 863, 820, 725, 698 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{20}\text{IN}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 503.0615, found 503.0618.

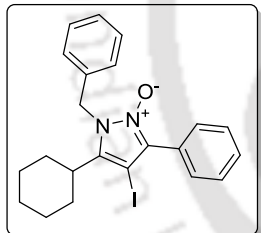
1-Benzyl-5-hexyl-4-iodo-3-phenyl-1H-pyrazole 2-oxide (35t):

Dark red semi solid; R_f (hexane/EtOAc 13:7) 0.49; yield 102 mg, 74 %; ^1H NMR (400 MHz, CDCl_3): δ 7.44-7.38 (m, 3 H), 7.25-7.20 (m, 5 H), 6.99-7.02 (m, 2 H), 5.33 (s, 2 H), 2.78 (t, $J = 7.6$ Hz, 2 H), 1.76-1.68 (m, 2 H), 1.42-1.37 (m, 2 H), 1.36-1.30 (m, 4 H), 0.89 (t, $J = 7.2$ Hz, 3 H); ^{13}C NMR (150 MHz, CDCl_3): δ 135.7, 134.5, 133.8, 130.1, 129.7, 128.9, 128.8, 128.7, 127.9, 127.5, 58.6, 47.9, 31.6, 29.0, 26.6, 26.0, 22.6, 14.2; IR (KBr, neat) 2954, 2855, 1497, 1458, 1422, 1235, 1045, 765, 699 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{26}\text{IN}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 461.1084, found 461.1084.



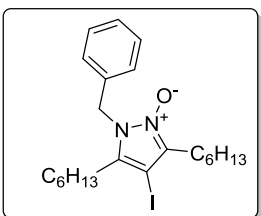
1-Benzyl-5-cyclohexyl-4-iodo-3-phenyl-1H-pyrazole 2-oxide (35u):

Pale yellow semisolid; R_f (hexane/EtOAc 3:2) 0.52; yield 96 mg, 70 %; ^1H NMR (400 MHz, CDCl_3): δ 7.79 (d, $J = 7.2$ Hz, 2 H), 7.47 (t, $J = 7.6$ Hz, 2 H), 7.40 (t, $J = 6.8$ Hz, 1 H), 7.34 (d, $J = 7.2$ Hz, 2 H), 7.29 (d, $J = 7.6$ Hz, 1 H), 7.25 (d, $J = 6.8$ Hz, 2 H), 5.56 (s, 2 H), 2.85-2.76 (m, 1 H), 1.99-1.90 (m, 2 H), 1.81-1.66 (m, 2 H), 1.54-1.46 (m, 2 H), 1.26-1.19 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3): δ 137.4, 135.8, 131.2, 130.2, 129.2, 129.0, 128.3, 128.2, 128.1, 127.9, 127.1, 53.3, 46.5, 38.4, 30.0, 29.9, 26.6, 25.5; IR (KBr, neat) 2934, 2852, 1606, 1524, 1496, 1412, 1219, 1116, 1063, 947, 804, 763, 738 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{24}\text{IN}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 459.0928, found 459.0933.

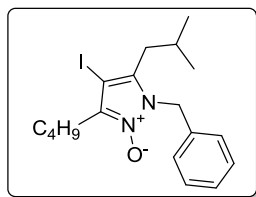


1-Benzyl-3,5-dihexyl-4-iodo-1H-pyrazole 2-oxide (35v):

Pale yellow semi solid; R_f (hexane/EtOAc 13:7) 0.51; yield 84 mg, 68 %; ^1H NMR (400 MHz, CDCl_3): δ 7.32-7.26 (m, 3 H), 7.17 (d, $J = 7.2$ Hz, 2 H), 5.42 (s, 2 H), 2.71 (t, $J = 7.6$ Hz, 2 H), 2.51 (t, $J = 7.2$ Hz, 2 H), 1.71-1.63 (m, 2 H), 1.39-1.32 (m, 8 H), 1.28-1.19 (m, 6 H), 0.90-0.84 (m, 6 H); ^{13}C NMR (100 MHz, CDCl_3): δ 135.6, 134.7, 133.1, 128.9, 128.1, 127.1, 57.4, 46.7, 31.6, 31.4, 29.0, 28.8, 28.4, 27.3, 26.6, 25.8, 22.6, 22.4, 14.2, 14.1; IR (KBr, neat) 3095, 2956, 1652, 1522, 1491, 1413, 1228, 1169, 1048, 789, 724, 681 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{34}\text{IN}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 469.1710, found 469.1714.



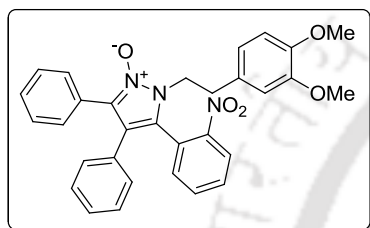
1-Benzyl-3-butyl-4-iodo-5-isobutyl-1H-pyrazole 2-oxide (35w):



Yellow gum; R_f (hexane/EtOAc 13:7) 0.52; yield 80 mg, 65 %; ^1H NMR (400 MHz, CDCl_3): δ 7.34-7.26 (m, 3 H), 7.15 (d, $J = 7.6$ Hz, 2 H), 5.42 (s, 2 H), 2.73 (t, $J = 7.6$ Hz, 2 H), 2.40 (d, $J = 7.2$ Hz, 2 H), 1.91-1.80 (m, 1 H), 1.70-1.62 (s, 2 H), 1.45-1.36 (m, 2 H), 0.96 (t, $J = 7.6$ Hz, 3 H), 0.90 (d, $J = 6.0$ Hz, 6 H); ^{13}C NMR (100 MHz, CDCl_3): δ 135.5, 133.7, 133.1, 129.0, 128.1, 127.1, 58.8, 46.7, 35.8, 28.8, 28.7, 25.7, 22.6, 22.4, 14.0; IR (KBr, neat) 3033, 2959, 2869, 1606, 1524, 1497, 1464, 1224, 1091, 1074, 770, 734 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{26}\text{IN}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 413.1084, found 413.1089.

1-(3,4-Dimethoxyphenethyl)-5-(2-nitrophenyl)-3,4-diphenyl-1H-pyrazole 2-oxide (37):

Pale yellow semisolid; R_f (hexane/EtOAc 3:2) 0.51; yield 59 mg, 76 %; ^1H NMR (600 MHz,

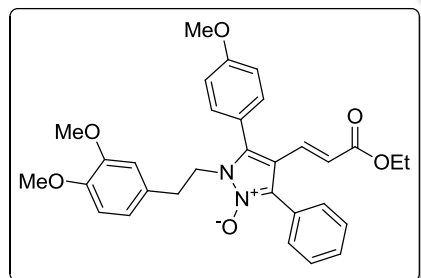


CDCl_3): δ 7.95 (d, $J = 7.8$ Hz, 1 H), 7.67-7.62 (m, 3 H), 7.53-7.48 (m, 1 H), 7.44 (t, $J = 7.2$ Hz, 1 H), 7.40 (t, $J = 7.8$ Hz, 1 H), 7.32-7.27 (m, 2 H), 7.11 (d, $J = 7.2$ Hz, 1 H), 7.08 (t, $J = 7.2$ Hz, 1 H), 6.85 (d, $J = 7.2$ Hz, 2 H), 6.71 (d, $J = 7.8$ Hz, 1 H), 6.60 (d, $J = 7.8$ Hz, 1 H), 6.54 (d, $J = 7.8$ Hz, 1 H), 6.49 (s, 1 H),

4.56-4.50 (m, 1 H), 3.94-3.89 (m, 1 H), 3.83 (s, 3 H), 3.71 (s, 3 H), 3.44-3.39 (m, 1 H), 2.90-2.84 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 149.5, 149.1, 148.0, 134.3, 133.0, 132.2, 132.1, 130.6, 130.5, 130.4, 129.9, 129.4, 128.6, 128.5, 128.2, 127.5, 125.0, 124.7, 123.1, 121.2, 115.6, 112.1, 111.3, 56.1, 55.8, 46.8, 33.5; IR (KBr, neat) 2956, 1653, 1528, 1517, 1478, 1346, 1262, 1158, 1027, 793, 752, 696 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{31}\text{H}_{28}\text{N}_3\text{O}_5$ ($\text{M} + \text{H}$) $^+$ 522.2023, found 522.2020.

(E)-1-(3,4-Dimethoxyphenethyl)-4-(3-ethoxy-3-oxoprop-1-en-1-yl)-5-(4-methoxy-phenyl)-3-phenyl-1H-pyrazole 2-oxide (39):

Pale yellow semisolid; R_f (hexane/EtOAc 3:2) 0.48; yield 53 mg, 67 %; ^1H NMR (600 MHz,

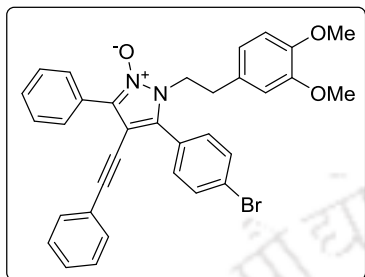


CDCl_3): δ 7.71 (d, $J = 7.8$ Hz, 2 H), 7.54 (t, $J = 7.8$ Hz, 2 H), 7.48 (t, $J = 7.2$ Hz, 2 H), 7.27 (d, $J = 10.8$ Hz, 1 H), 6.95-6.91 (m, 4 H), 6.70 (d, $J = 7.8$ Hz, 1 H), 6.47 (d, $J = 7.2$ Hz, 1 H), 6.39 (s, 1 H), 5.63 (d, $J = 16.2$ Hz, 1 H), 4.32 (t, $J = 6.6$ Hz, 2 H), 4.08 (q, $J = 7.2$ Hz, 2 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.71 (s, 3 H), 3.03 (t, $J = 6.6$ Hz, 2 H), 1.19

(t, $J = 7.2$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.2, 161.0, 149.3, 148.2, 133.7, 132.2, 131.7, 130.1, 129.8, 129.7, 129.1, 128.8, 127.3, 121.2, 119.0, 118.3, 114.7, 112.0, 111.5, 109.1, 60.5, 56.2, 55.8, 55.6, 46.4, 33.9, 14.4; IR (KBr, neat) 2927, 2853, 1706, 1632, 1516, 1492, 1261, 1154, 1029, 841, 765, 698 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{31}\text{H}_{33}\text{N}_2\text{O}_6$ ($\text{M} + \text{H}$) $^+$ 529.2333, found 529.2334.

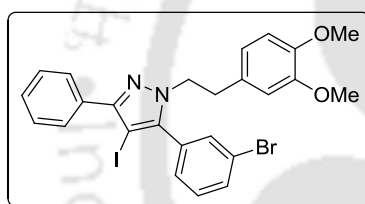
5-(4-Bromophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-4-(phenylethynyl)-1*H*-pyrazole 2-oxide (40):

Dark red gum; R_f (hexane/EtOAc 3:2) 0.61; yield 68 mg, 79 %; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 8.40 (d, $J = 7.8$ Hz, 2 H), 7.57-7.51 (m, 4 H), 7.44 (t, $J = 7.8$ Hz, 1 H), 7.28 (s, 5 H), 7.07 (d, $J = 8.4$ Hz, 2 H), 6.65 (d, $J = 8.4$ Hz, 1 H), 6.45 (d, $J = 7.8$ Hz, 1 H), 6.34 (s, 1 H), 4.50 (t, $J =$



6.6 Hz, 2 H), 3.84 (s, 3 H), 3.69 (s, 3 H), 3.06 (d, $J = 6.0$ Hz, 2 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 149.1, 148.1, 134.8, 131.9, 131.7, 131.2, 130.9, 129.8, 129.5, 129.3, 128.5, 128.4, 128.2, 127.4, 126.5, 123.8, 122.9, 121.1, 111.9, 111.4, 96.8, 93.2, 80.5, 56.1, 55.7, 46.6, 33.7; **IR** (KBr, neat) 3060, 2933, 2834, 2215, 1683, 1594, 1508, 1486, 1256, 1207, 1148, 1071, 1012, 861, 756, 690 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{33}\text{H}_{28}\text{BrN}_2\text{O}_3$ ($M + H$) $^+$ 579.1278, found 579.1277.

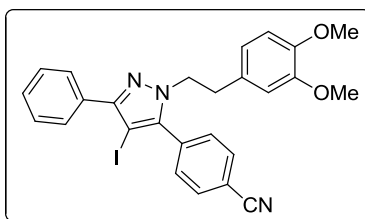
5-(3-Bromophenyl)-1-(3,4-dimethoxyphenethyl)-4-iodo-3-phenyl-1*H*-pyrazole (41h):



Pale yellow gum; R_f (hexane/EtOAc 9:1) 0.50; yield 79 mg, 90 %; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.89 (d, $J = 7.6$ Hz, 2 H), 7.51 (t, $J = 8.4$ Hz, 1 H), 7.48 (d, $J = 8.0$ Hz, 2 H), 7.41 (t, $J = 8.0$ Hz, 1 H), 7.24 (t, $J = 8.0$ Hz, 1 H), 6.90 (d, $J = 8.0$ Hz, 1 H), 6.83 (s, 1 H), 6.75 (d, $J = 8.0$ Hz, 1 H), 6.48 (d, $J = 8.8$ Hz, 1 H), 6.24 (s, 1 H), 4.24 (t, $J = 6.4$ Hz, 2 H), 3.87 (s, 3 H), 3.68 (s, 3 H), 3.08 (t, $J = 6.8$ Hz, 2 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 152.1, 149.0, 148.0, 146.0, 133.1, 132.4, 131.9, 130.4, 130.0, 129.2, 128.6, 128.4, 128.4, 122.5, 120.9, 111.8, 111.4, 60.4, 56.1, 55.8, 52.4, 36.3; **IR** (KBr, neat) 2932, 2834, 2228, 1611, 1516, 1488, 1263, 1238, 1159, 1028, 1006, 847, 767, 696 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{23}\text{BrIN}_2\text{O}_2$ ($M + H$) $^+$ 588.9982, found 588.9994.

4-(1-(3,4-Dimethoxyphenethyl)-4-iodo-3-phenyl-1*H*-pyrazol-5-yl)benzonitrile (41j)

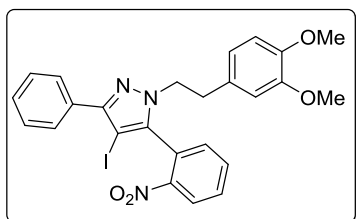
Pale yellow solid; mp 155-157 $^{\circ}\text{C}$; R_f (hexane/EtOAc 9:1) 0.50; yield 69 mg, 87 %; $^1\text{H NMR}$



(400 MHz, CDCl_3): δ 7.88 (d, $J = 7.2$ Hz, 2 H), 7.63 (d, $J = 8.4$ Hz, 2 H), 7.49 (t, $J = 7.2$ Hz, 2 H), 7.42 (t, $J = 7.2$ Hz, 1 H), 6.96 (d, $J = 8.4$ Hz, 2 H), 6.70 (d, $J = 7.6$ Hz, 1 H), 6.42 (d, $J = 8.4$ Hz, 1 H), 6.18 (d, $J = 2.0$ Hz, 1 H), 4.25 (t, $J = 6.4$ Hz, 2 H), 3.87 (s, 3 H), 3.67 (s, 3 H), 3.06 (t, $J = 6.8$ Hz, 2 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 152.5, 149.1, 148.2, 145.6, 134.6, 132.9, 132.3, 131.2, 130.3, 128.7, 128.6, 128.5, 121.0, 118.4, 113.1, 111.9, 111.4, 60.5, 56.2, 55.8, 52.6, 36.4; **IR** (KBr, neat) 2926, 2857, 2237, 1611, 1516, 1462, 1375, 1293, 1149, 1028, 753 cm^{-1} ; **HRMS** (ESI)

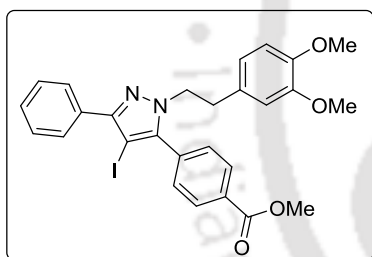
calcd. for $C_{26}H_{23}IN_3O_2$ ($M + H$)⁺ 536.0829, found 536.0839.

1-(3,4-Dimethoxyphenethyl)-4-iodo-5-(2-nitrophenyl)-3-phenyl-1*H*-pyrazole (41k):



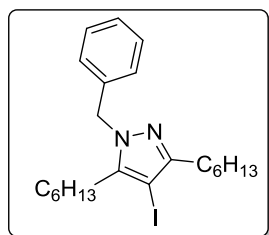
Pale yellow solid; mp 123-125 °C; R_f (hexane/EtOAc 17:3) 0.50; yield 71 mg, 85 %; 1H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.4 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 2 H), 7.61 (t, J = 7.6 Hz, 1 H), 7.53 (t, J = 7.2 Hz, 1 H), 7.47 (t, J = 7.6 Hz, 2 H), 7.40 (t, J = 7.6 Hz, 1 H), 6.72 (d, J = 8.4 Hz, 1 H), 6.52 (d, J = 7.2 Hz, 1 H), 6.48 (d, J = 8.0 Hz, 1 H), 6.35 (s, 1 H), 4.36 (ddd, J = 13.2, 6.8 and 4.0 Hz, 1 H), 3.90 (ddd, J = 13.2, 7.2 and 4.0 Hz, 1 H), 3.86 (s, 3 H), 3.68 (s, 3 H), 3.30 (ddd, J = 13.6, 8.8 and 4.8 Hz, 1 H), 2.93 (ddd, J = 13.2, 7.2 and 5.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 151.8, 149.0, 148.8, 148.0, 143.3, 133.9, 133.3, 132.9, 130.9, 130.7, 128.5, 128.4, 128.3, 125.1, 124.8, 121.0, 112.0, 111.3, 60.1, 56.2, 55.8, 52.9, 35.9; IR (KBr, neat) 2929, 2854, 1526, 1459, 1349, 1264, 1238, 1155, 1029, 973, 740 cm^{-1} ; HRMS (ESI) calcd. for $C_{25}H_{23}IN_3O_4$ ($M + H$)⁺ 556.0728, found 556.0736.

Methyl 4-(1-(3,4-dimethoxyphenethyl)-4-iodo-3-phenyl-1*H*-pyrazol-5-yl)benzoate (41i):



Pale yellow solid; mp 121-123 °C; R_f (hexane/EtOAc 17:3) 0.50; yield 72 mg, 87 %; 1H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 8.0 Hz, 2 H), 7.89 (d, J = 7.2 Hz, 2 H), 7.48 (t, J = 7.2 Hz, 2 H), 7.41 (t, J = 7.6 Hz, 1 H), 7.00 (d, J = 8.4 Hz, 2 H), 6.70 (d, J = 7.6 Hz, 1 H), 6.44 (d, J = 8.0 Hz, 1 H), 6.24 (s, 1 H), 4.26 (t, J = 6.4 Hz, 2 H), 3.95 (s, 3 H), 3.86 (s, 3 H), 3.67 (s, 3 H), 3.06 (t, J = 6.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.7, 152.2, 149.0, 148.1, 146.4, 134.5, 133.1, 130.8, 130.5, 130.4, 129.8, 128.6, 128.5, 125.8, 120.9, 111.8, 111.4, 60.4, 56.2, 55.8, 52.6, 52.5, 36.4; IR (KBr, neat) 2925, 2852, 1723, 1515, 1432, 1276, 1239, 1154, 1108, 1028, 971, 768 cm^{-1} ; HRMS (ESI) calcd. for $C_{27}H_{26}IN_2O_4$ ($M + H$)⁺ 569.0932, found 569.0935.

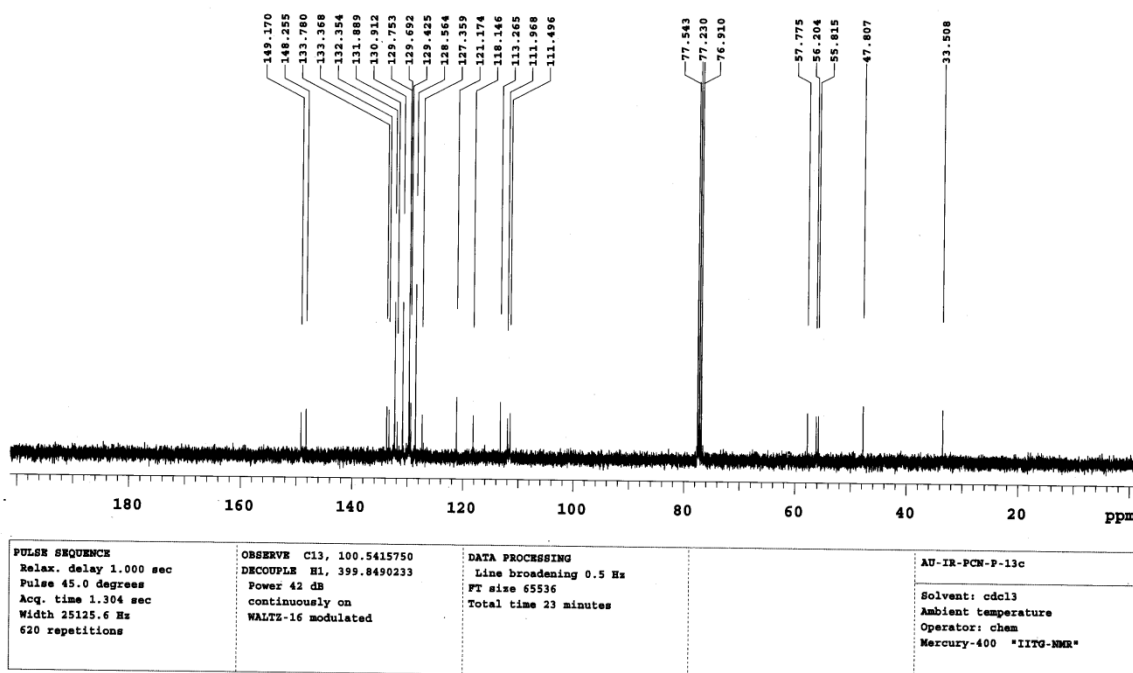
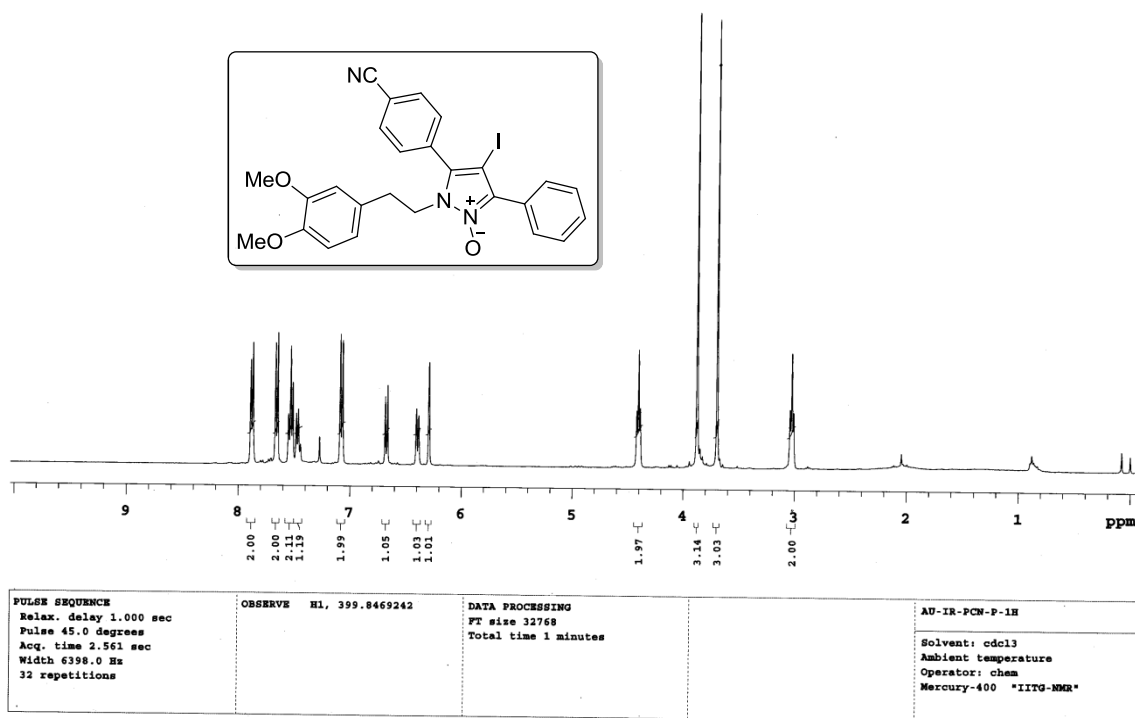
1-Benzyl-3,5-dihexyl-4-iodo-1*H*-pyrazole (41v):

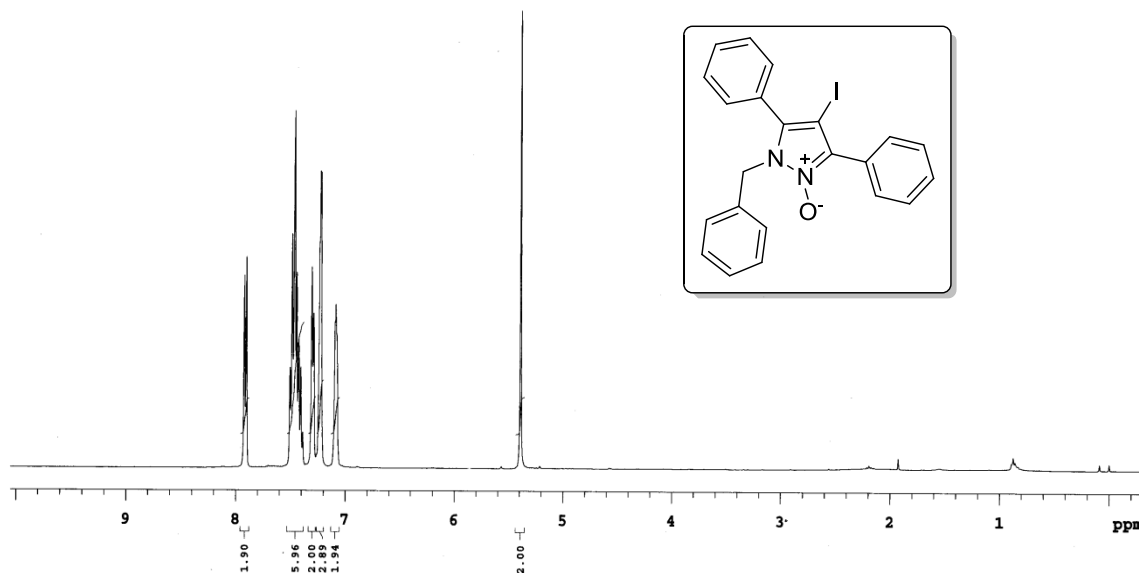


Pale yellow gum; R_f (hexane/EtOAc 9:1) 0.50; yield 59 mg, 88 %; 1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.23 (m, 3 H), 7.05 (d, J = 7.2 Hz, 2 H), 5.29 (s, 2 H), 2.58 (t, J = 8.0 Hz, 2 H), 2.53 (t, J = 7.2 Hz, 2 H), 1.67-1.62 (m, 2 H), 1.41-1.22 (m, 14 H), 0.90-0.84 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 144.8, 137.4, 128.9, 127.8, 126.7, 62.4, 54.1, 31.8, 31.5, 29.3, 29.2, 28.6, 26.3, 22.8, 22.7, 14.3, 14.2; IR (KBr, neat) 2926, 2856, 1606, 1525, 1467, 1379, 1100, 1076, 1029, 724, 699 cm^{-1} ; HRMS (ESI) calcd. for $C_{22}H_{34}IN_2$ ($M + H$)⁺ 453.1761, found 453.1761.

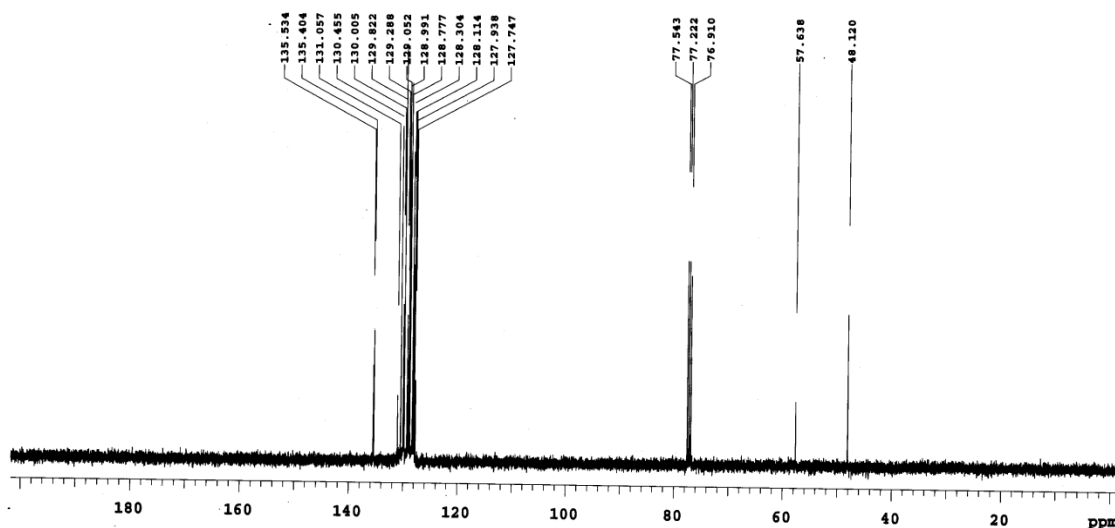
4.7. Selected spectra

^1H , ^{13}C NMR spectra of 5-(4-cyanophenyl)-1-(3,4-dimethoxyphenethyl)-4-iodo-3-phenyl-1*H*-pyrazole 2-oxide (35j)



^1H , ^{13}C NMR spectra of 1-benzyl-4-iodo-3,5-diphenyl-1H-pyrazole 2-oxide (35r)

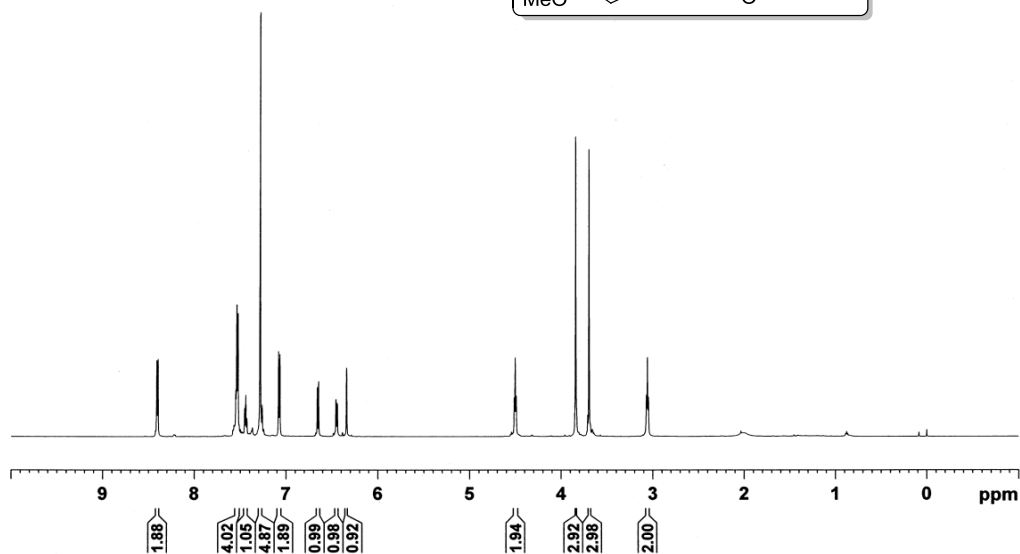
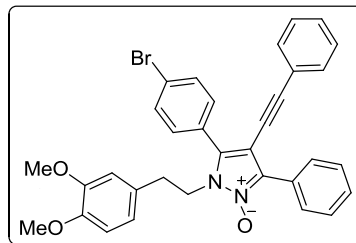
PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 2.563 sec Width 10000.0 Hz 44 repetitions	OBSERVE H1, 399.8470643	DATA PROCESSING FF size 65536 Total time 2 minutes	AU-ir-PH-PH-BN-1H Solvent: cdcl3 Ambient temperature Operator: chem Mercury-400 "IITG-NMR"
--	--------------------------------	---	---



PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 1.304 sec Width 25125.6 Hz 220 repetitions	OBSERVE C13, 100.5416172 DECOUPLE H1, 399.8490233 Power 42 dB continuously on WALTZ-16 modulated	DATA PROCESSING Line broadening 0.5 Hz FF size 65536 Total time 8 minutes	AU-ir-PH-PH-BN-13c Solvent: cdcl3 Ambient temperature Operator: chem Mercury-400 "IITG-NMR"
---	--	---	--

^1H , ^{13}C NMR spectra of 5-(4-bromophenyl)-1-(3,4-dimethoxyphenethyl)-3-phenyl-4-(phenylethynyl)-1*H*-pyrazole 2-oxide (40)

AU_SG_1H



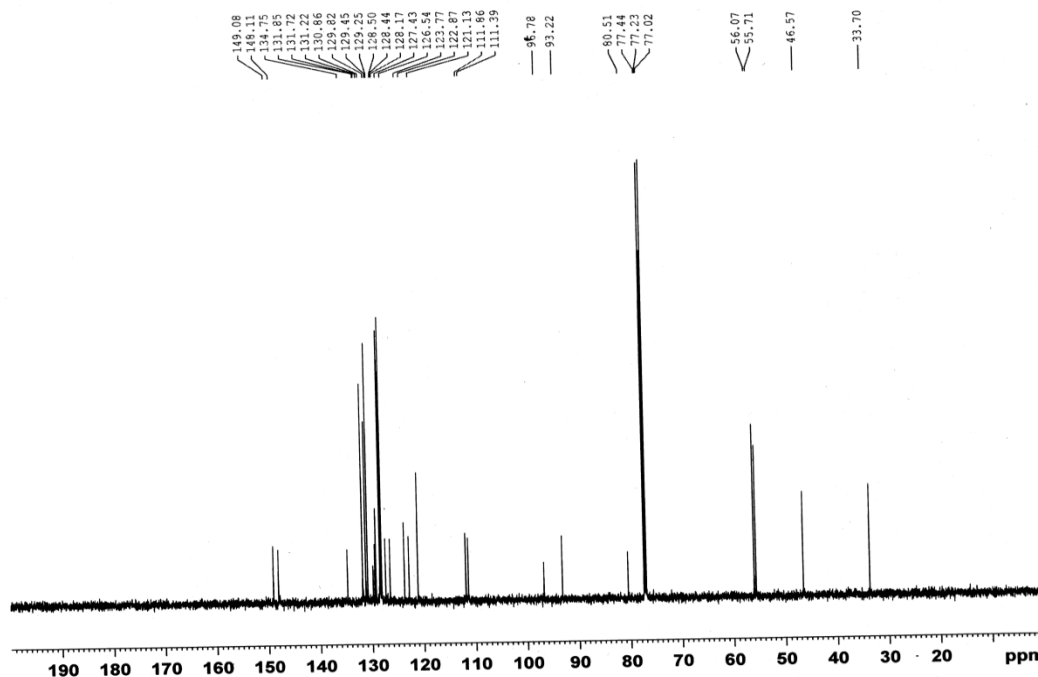
Current Data Parameters
NAME AU_SG_1H
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150529
Time 15.52
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 1.3631489 sec
RG 38.54
DW 41.800 usec
DE 6.50 usec
TE 295.0 K
D1 1.00000000 sec
TDO

CHANNEL f1
SFO1 600.1737063 MHz
NUC1 1H
P1 12.00 usec
PLM1 21.00000000 W

F2 - Processing parameters
SI 16384
SF 600.1700137 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

AU_SG_13C



BRUKER

Current Data Parameters
NAME AU_SG_13C
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150529
Time 17.12
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 107
DS 2
SWH 36051.691 Hz
FIDRES 1.100393 Hz
AQ 0.4543859 sec
RG 65.24
DW 13.967 usec
DE 6.50 usec
TE 295.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1

CHANNEL f1
SFO1 150.9279571 MHz
NUC1 13C
P1 10.00 usec
PLM1 95.00000000 W

CHANNEL f2
SFO2 600.1724007 MHz
NUC2 1H
CPDPRG2 waltz16
PCPDG 10.00 usec
PLM2 21.00000000 W
PLM12 0.61714000 W
PLM13 0.30239999 W

F2 - Processing parameters
SI 16384
SF 150.9128518 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

4.8. Crystal parameters

The crystal parameters of compound **35q**

	CCDC 1419355
Formula	C ₂₃ H ₁₈ Cl I N ₂ O
Formula weight	500.74
<i>T</i> /K	296(2)
Crystal system	Triclinic
Space group	P-1
<i>a</i> /Å	7.9899(2)
<i>b</i> /Å	8.7928(3)
<i>c</i> /Å	15.7992(5)
α /°	76.616(2)
β /°	77.925(2)
γ /°	78.763(2)
<i>V</i> /Å ³	1043.33(6)
<i>Z</i>	2
Abs. Coeff./mm ⁻¹	1.678
Abs. Correction	None
GOF on <i>F</i> ²	1.097
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> 1 = 0.0308 <i>wR</i> 2 = 0.0806
<i>R</i> indices [all data]	<i>R</i> 1 = 0.0385 <i>wR</i> 2 = 0.0857

CHAPTER 5

Intramolecular Pictet-Spengler Reaction of Cyclic Iminium Ions: A Novel Access to Benzo[1,4]oxazepine Fused Tetrahydroisoquinoline and Tetrahydro- β -Carboline Analogous

5.1. Importance of seven membered fused tetrahydroisoquinoline and tetrahydro- β -carboline analogous

Seven membered fused tetrahydroisoquinoline (THIQ) and tetrahydro- β -carboline (THBC) motifs are privileged architectures and they have gained considerable attention due to their presence in wide range of biologically active compounds. For example, homoprotoberberine alkaloid (**1**) (Figure 5.1.1.) having tetrahydroisoquinoline skeleton displays antibacterial and antimalarial properties.¹ Similarly, kopsiunnanine K (**2**) and eudistomins (**3**) are tetrahydro- β -carboline framework alkaloids. Among these, kopsiunnanine K (**2**) is a unique monoterpene alkaloid having azepine fused tetrahydro- β -carboline core unit and it was isolated from *Kopsia arborea* tree species, which are found in the Yunnan Province of China.² Another kind of alkaloids in this class are eudistomins, isolated from a Caribbean tunicate (*Eudistoma olivaceum*) by Rinehart and coworkers in 1984. They exhibit potent antiviral activities against DNA and RNA viruses as well as shows antitumor and antimicrobial activities.³

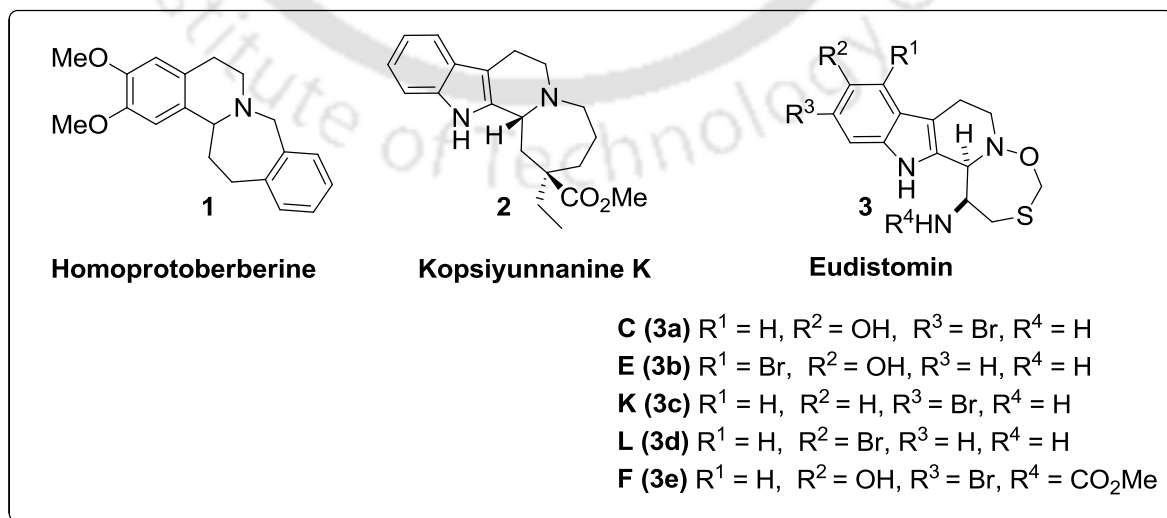
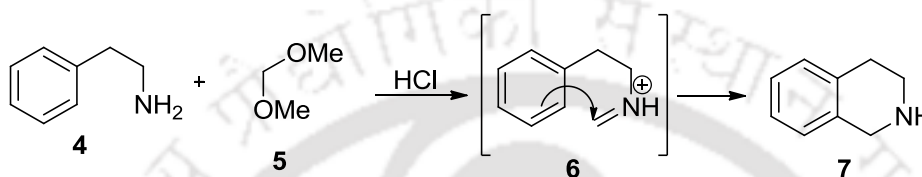


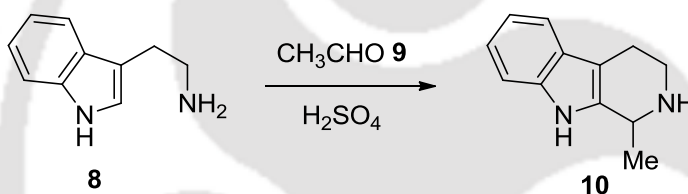
Figure 5.1.1. Biologically active compounds having fused THIQ, THBC scaffolds

5.2. Literature methods of Pictet-Spengler reaction

Pictet-Spengler reaction is one of the most important methods for the preparation of valuable nitrogen containing heterocyclic compounds. It was discovered in 1911 by Am  e Pictet and Theodor Spengler. They achieved tetrahydroisoquinoline **7** from the cyclization of iminium ion **6**, which was obtained from condensation of phenethylamine **4** with methylal **5** in presence of hydrochloric acid (Scheme 5.2.1).^{4a} Later on Tatsui and coworkers tried same reaction with tryptamine **8** and acetaldehyde **9** to furnish tetrahydro- -carboline **10** (Scheme 5.2.2).^{4b}



Scheme 5.2.1.



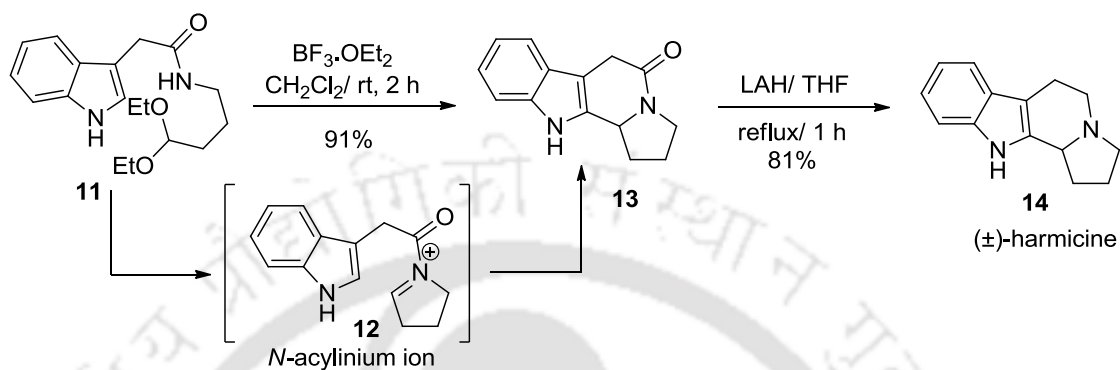
Scheme 5.2.2.

Since the discovery of this reaction, a large number of reports have been published for the synthesis of tetrahydroisoquinoline and tetrahydro- -carboline derivatives in pharmaceuticals, natural products and biologically active compounds.⁵ Moreover, intramolecular version of this reaction using in situ generated cyclic *N*-acyliminium ion intermediates has also been well studied to achieve fused heterocyclic compounds.⁶ However, some methods have been investigated to construct a fused tetrahydroisoquinoline and tetrahydro- -carboline scaffolds via an acid promoted intramolecular Pictet-Spengler reaction plays a key step in double cyclization of cascade reaction sequence. Few of them are discussed below.

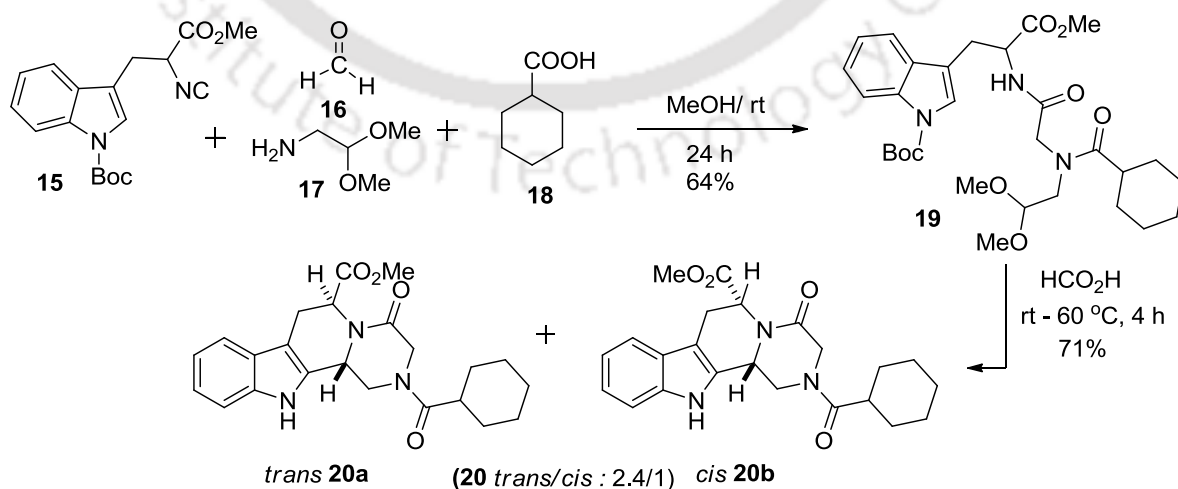
5.2.1. Pictet-Spengler reaction via intramolecular *N*-acyliminium ion intermediates:

King and coworkers reported a novel approach for the synthesis of fused tetrahydro- -carboline **13**, via BF₃·OEt₂ mediated Pictet-Spengler reaction of *N*-tethered acetal **11**. The

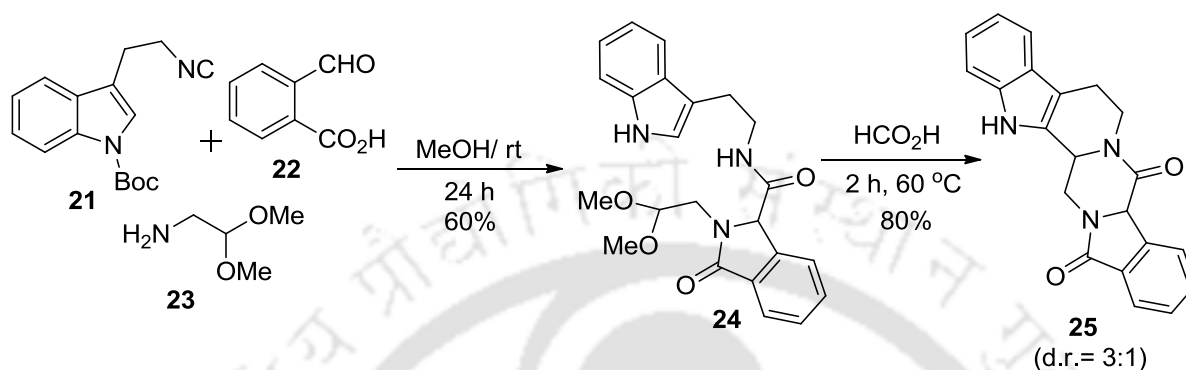
reaction mechanism suggests that, the formation of *N*-acyliminium ion intermediate **12** is a key step in order to obtain cyclized products in excellent yields. This methodology was successfully applied for the synthesis of pyrrolidine fused to tetrahydro- β -carboline alkaloid ($\pm$)-harmicine (**14**) in 81% yield (Scheme 5.2.1.1).⁷



Dömling and coworkers demonstrated a two-step reaction sequence for the diastereoselective synthesis of highly substituted fused tetrahydro- β -carbolines **20** in yields 71%. First they prepared *N*-tethered acetal **19** using Ugi multicomponent reaction and then subjected them to an acid mediated intramolecular Pictet-Spengler ring closure to achieve the two cyclized products **20a/b**. The major advantage of this method is that various substituted end products were obtained with *trans* isomer as the major product, starting from diverse starting materials. The ratio of diastereomeric mixture of compound **20** is *trans/cis*: 2.4/1 (Scheme 5.2.1.2).⁸

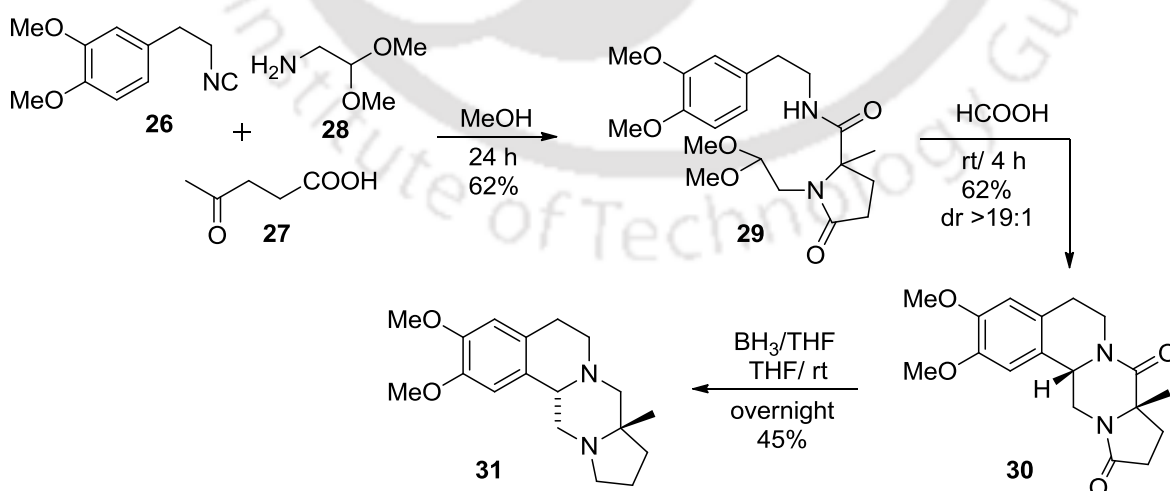


The same group in 2010 developed a similar protocol for the synthesis of complex polycyclic tetrahydro- β -carboline core skeleton **25** via tandem Ugi **24** and intramolecular Pictet-Spengler reaction, starting from 2-isocyanoethylindole **21** with a bifunctional oxocarboxylic acid **22** and an aminoacetaldehyde dimethyl acetal **23** (Scheme 5.2.1.3).⁹



Scheme 5.2.1.3.

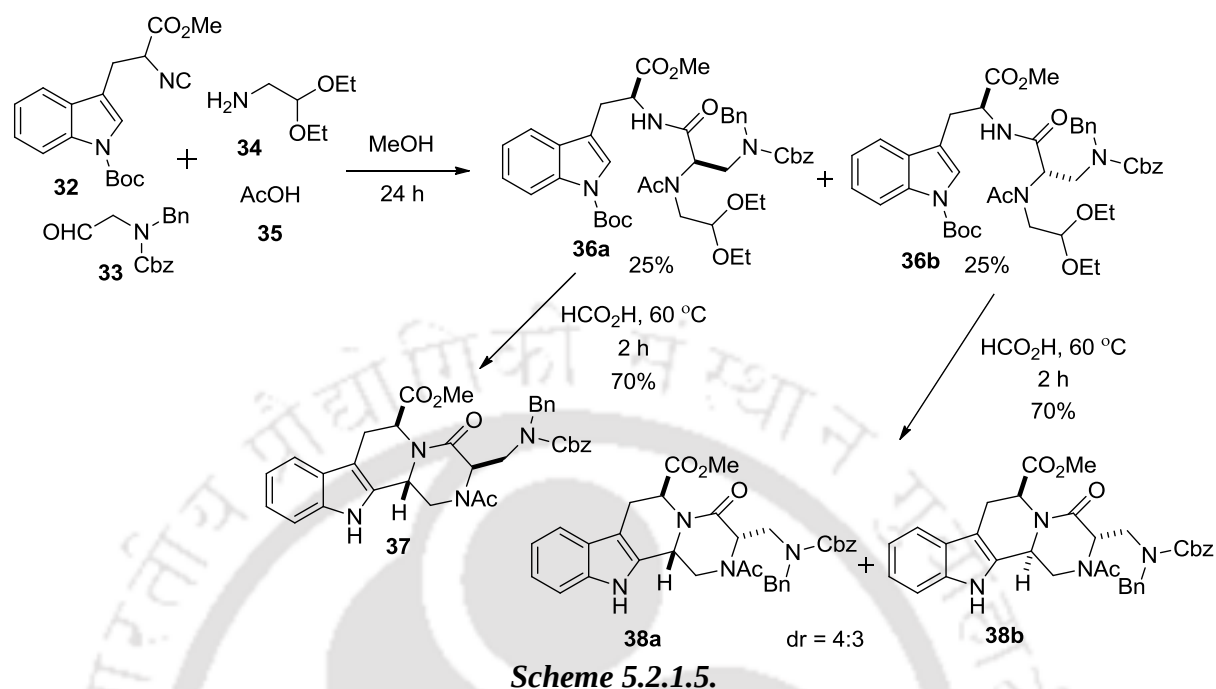
Later on, they further designed a similar two-step procedure to access highly stereoselective fused tetrahydroisoquinoline polycyclic architecture **30**. The reaction sequence initiated with Ugi transformation between phenylethylamine-derived isocyanide **26**, oxocarboxylic acid **27** and aminoacetaldehyde dimethylacetal **28** gives an intermediate **29**, which was further involved in acid mediated Pictet-Spengler reaction, to give polycyclic compound **30**. The resulting product is fully reduced to their tertiary amine **31** (Scheme 5.2.1.4).¹⁰



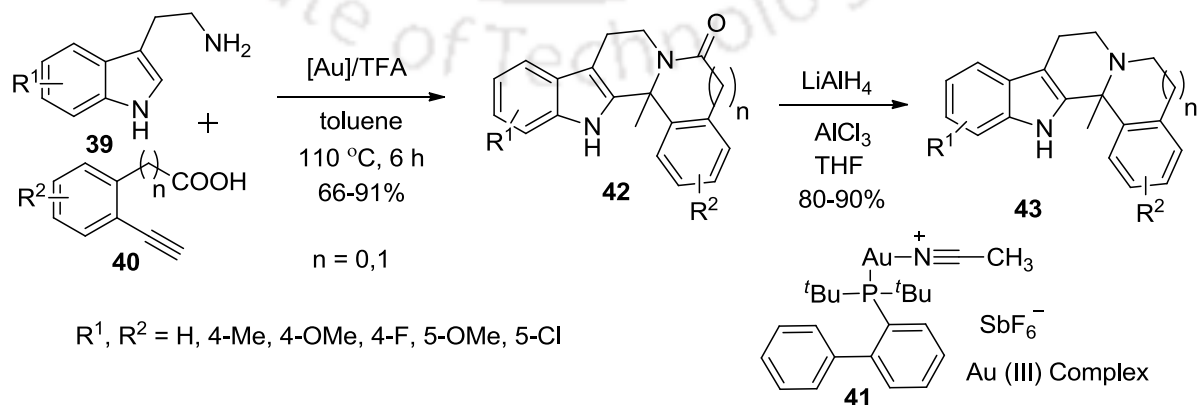
Scheme 5.2.1.4.

Lesma and coworkers reported a facile approach for the diastereoselective synthesis of tetrahydro- β -carboline based tetracyclic peptidomimetics (**38**, **39a&b**) via Ugi 4-CR followed

by Pictet-Spengler reaction under mild acidic conditions (Scheme 5.2.1.5).¹¹



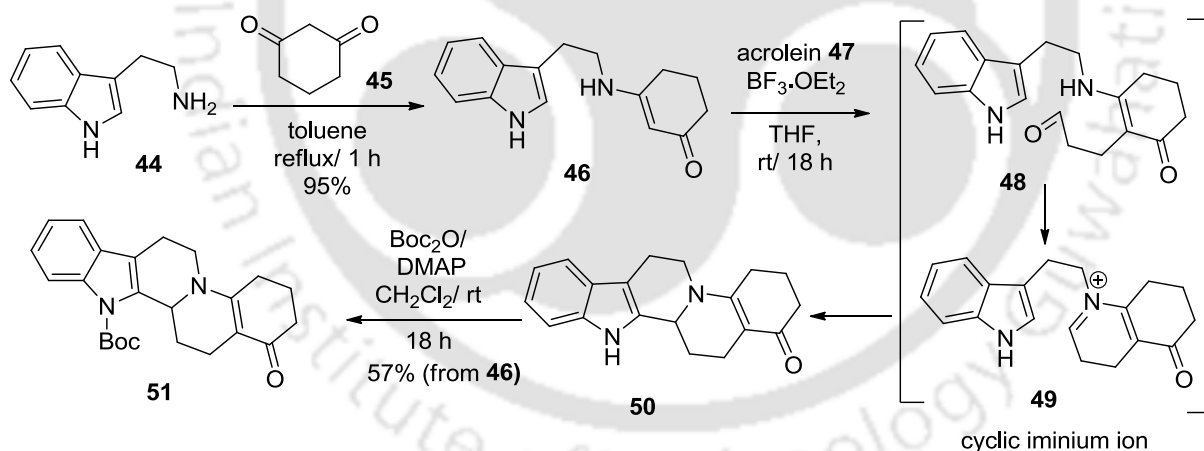
Tryptamine-fused polycyclic structures have been observed as potent α_1 -adrenergic receptors antagonists. To achieve these kind of biologically active tryptamine-fused polycyclic compounds **43**, Liu and coworkers developed a novel one-pot cascade approach by reacting tryptamines **39** with 2-ethynylbenzoicacids (or) 2-ethynylphenylacetic acids **40** in the presence of catalytic amount of Au(III) complex **41** and TFA gave an intermediated compounds **42** in good yields. These are further reduced to tertiary amine **43** using $\text{LiAlH}_4/\text{AlCl}_3$ (Scheme 5.2.1.6).¹²



5.2.2. Intramolecular Pictet-Spengler reaction of cyclic iminium ion intermediates:

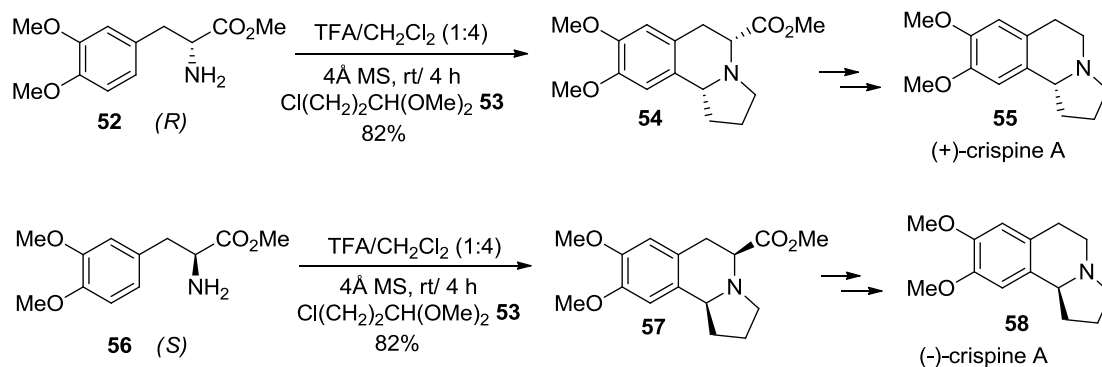
Intramolecular Pictet-Spengler reaction of cyclic iminium ion intermediates are also useful to construct tetrahydroisoquinoline and tetrahydro- β -carboline frame works.¹³ But intramolecular Pictet-Spengler reaction of cyclic iminium ions are less studied compared to cyclic *N*-acyliminium ions. This is due to less electrophilic character of cyclic iminium ions over *N*-acyliminium ions. However, a few of them are listed below.

Zhai and coworkers described a fast assemble tandem cyclization towards the synthesis of benz[*f*]indolo[2,3-*a*]quinolizidine intermediate **51** in three step process. The synthesis starts from a simple condensation reaction between tryptamine **44** and 1,3-cyclohexanedione **45** to give enamine **46**. The intermediate **46** could participate in [3+3] cycloaddition/Pictet-Spengler reaction with acrolein **47** promoted by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to install an unprotected pentacyclic compound **50**. Finally, the Boc protection of compound **50** under standard conditions gave a *N*-Boc protected pentacyclic benz[*f*]indolo[2,3-*a*]quinolizidine **51** (Scheme 5.2.2.1).¹⁴



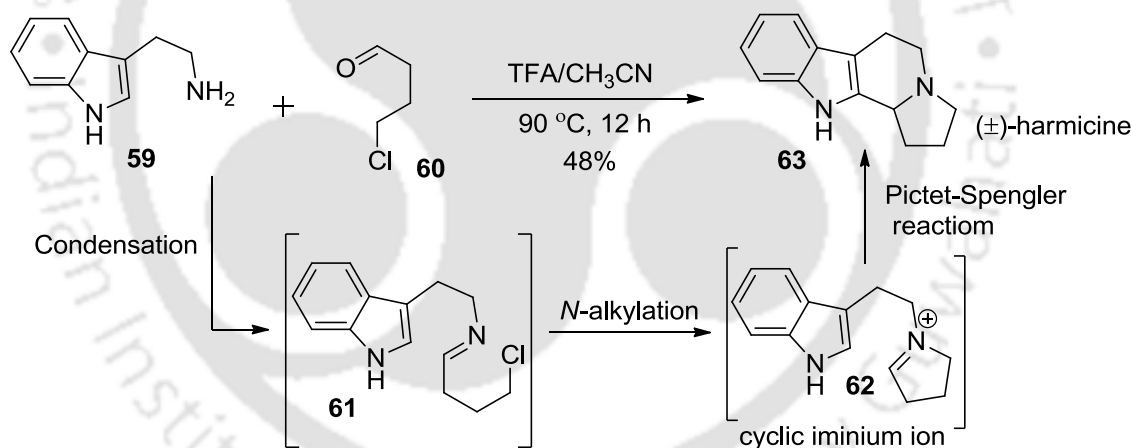
Scheme 5.2.2.1.

Herr *et al.*¹⁵ employed a TFA mediated asymmetric Pictet-Spengler reaction between commercially available (*R*)-(-)-methyl-2-amino-3-(3,4-dimethoxyphenyl)-propanoate **52** and 4-chloro-1,1-dimethoxybutane **53** to afford a tricyclic compound **54** in 82% yield. This reaction is of particular interest, since the resulting tricyclic compound **54** could be used in the synthesis of enantiopure natural product (+)-crispine A **55** by manipulating the ester group. Similarly, the unnatural antipode (-)-crispine A **58** was obtained, starting from (*S*)-(+)- amino acid **56**.



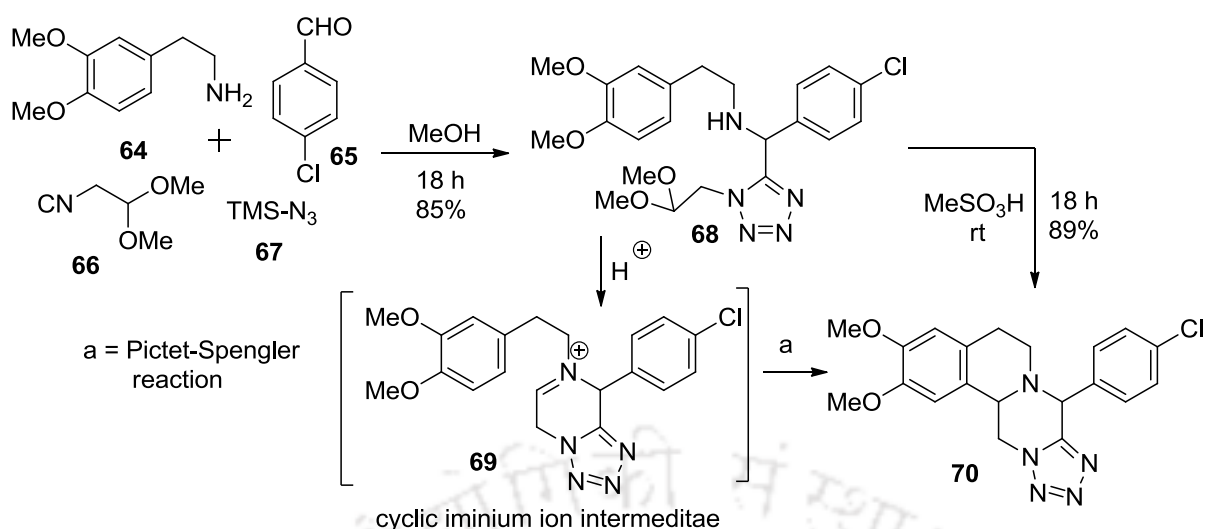
Scheme 5.2.2.2.

Jana and coworkers reported a one-pot reaction for the total synthesis of indole alkaloid (±)-harmicine **63** derived from tryptamine **59** and 4-chlorobutanal **60** in presence of TFA using acetonitrile as solvent. The reaction mechanism suggested that, it proceeds *via* condensation/*N*-alkylation of in situ generated cyclic iminium ion **62** mediated intra molecular Pictet-Spengler reaction in 48% yield (Scheme 5.2.2.3).¹⁶



Scheme 5.2.2.3.

Dömling and his group developed a short route for the synthesis of tetracyclic tetrazole motif **70** *via* Ugi-Pictet-Spengler reaction (Scheme 5.2.2.4).¹⁷ The reaction was initiated through a classical Ugi tetrazole MCR using phenylethylamine **64**, 4-chlorobenzaldehyde **65**, isocyanoacetaldehyde dimethyl acetal **66** and trimethylsilyl azide **67**. Later on Ugi product **68** participated in bis-cyclization of intramolecular cyclic iminium ion intermediated **69** Pictet-Spengler reactions under acidic conditions to afford the target compound **70**.

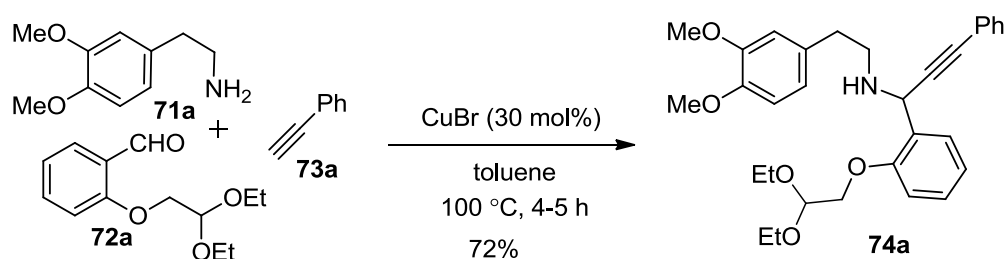


Scheme 5.2.2.4.

5.3. Present work

In our previous chapters, we have synthesized a few of substituted nitrogen heterocycles from either in situ generated secondary propargylamine or secondary propargylamine as a starting precursor by using copper(I) bromide catalyzed A^3 -coupling reaction. Our current interest is developing a new class of complex polyheterocyclic compounds with privileged architectures by using intramolecular Pictet-Spengler reaction. In this chapter, we describes a simple and efficient approach for the synthesis of benzo[1,4]oxazepino-fused tetrahydroisoquinoline and tetrahydro- β -carboline derivatives *via* one-pot cascade reaction sequence. This reaction involves the intramolecular Pictet-Spengler reaction of cyclic iminium ion, which was generated in situ *via* trifluoroacetic acid mediated deprotection of acetal derived from β -arylethylamine and 2-(2,2-diethoxyethoxy)benzaldehyde.

Initially, we synthesized a secondary propargylamine **74a** using known reported methods *via* copper(I) bromide catalysed A^3 -coupling reaction of 3,4-dimethoxyphenylethylamine **71a**, 2-(2,2-diethoxyethoxy)benzaldehyde **72a** and phenylacetylene **73a** in 72% yield (Scheme 5.3.1).¹⁸



Scheme 5.3.1. Synthesis of propargylamine

Table 5.3.1: Optimization of the reaction conditions.^a

Entry	Acid (Eq.)	Solvent	Temperature (°C)	Time (h)	Yield (%) ^b
1	TFA (6.0)	CHCl ₃	rt	6.0	52
2	TFA (6.0)	CHCl ₃	reflux	6.0	58
3	TFA (6.0)	CH ₂ Cl ₂	rt	6.0	41
4	TFA (6.0)	DCE	rt	5.0	62
5	TFA (6.0)	1,4-dioxane	rt	9.0	30
6	TFA (6.0)	toluene	rt	10.0	41
7	TFA (6.0)	DCE	reflux	5.0	69
8	TFA (6.0)	1,4-dioxane	reflux	10.0	36
9	TFA (6.0)	CCl ₄	reflux	5.5	60
10	TFA (10.0)	DCE	reflux	5.0	80
11	TFA (15.0)	DCE	reflux	5.0	85
12	TFA (20.0)	DCE	reflux	5.0	85
13	<i>p</i> -TsOH (2.0)	toluene	reflux	24.0	NR ^c
14	BF ₃ ·Et ₂ O (2.0)	CH ₂ Cl ₂	rt	7.0	35
15	HCl	DCE	rt	24.0	44
16	H ₂ SO ₄	DCE	rt	24.0	31

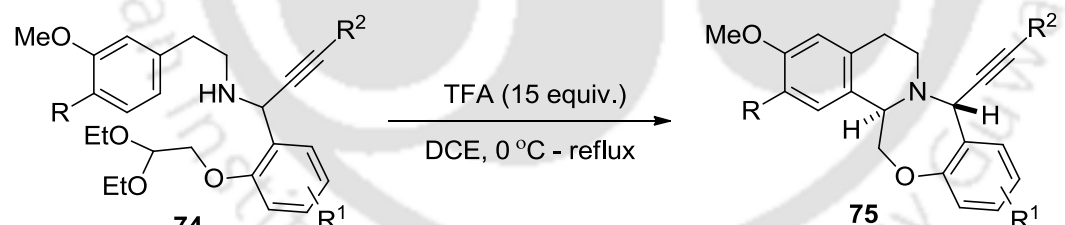
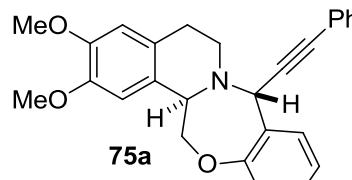
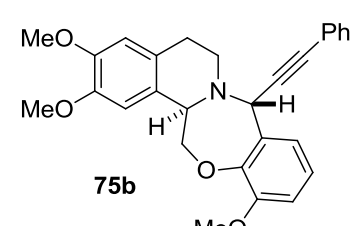
^aReaction conditions: Propargylamine **74a** (0.3 mmol), Solvent (1.0 mL) and Acid. ^bRefers to isolated yield.^cNo reaction.

Under initial investigation, 1.0 equivalent of propargylamine **74a** was treated with 6.0 equivalents of TFA in CHCl₃ (1 mL) at 0 °C and allowed the reaction to ambient temperature. After 5 h, 2,3-dimethoxy-8-(phenylethynyl)-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-a]isoquinoline **75a** was obtained in 52% of yield (Table 5.3.1; entry 1). Whereas, a little increment in the yield 58% was observed at reflux temperature (entry 2). The reaction was also carried out with other solvents like, CH₂Cl₂, DCE, 1,4-dioxane and toluene (1 mL) under similar conditions at room temperature which resulted in 41%, 62%, 30% and 41%

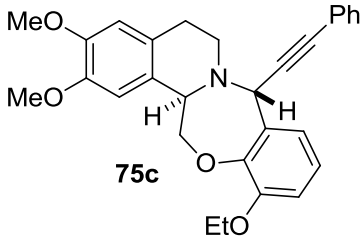
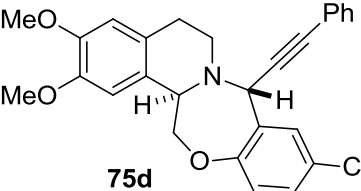
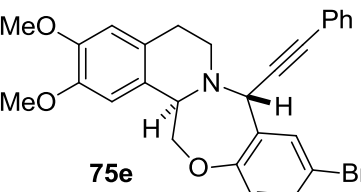
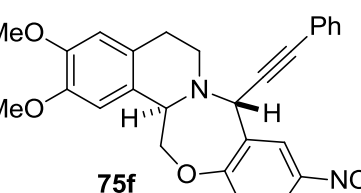
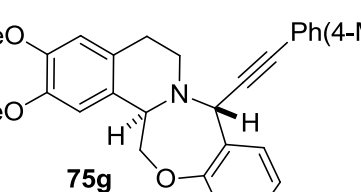
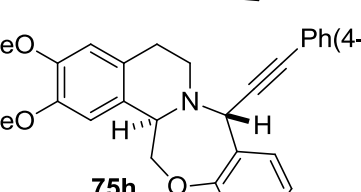
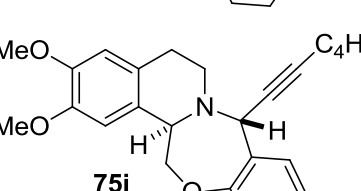
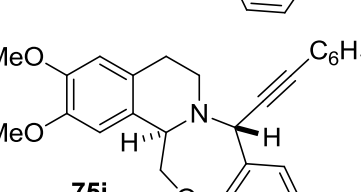
yields, respectively (entries 3-6). The reaction in DCE and 1,4-dioxane at their reflux temperatures gave the desired product in 69% and 36% yields, respectively (entries 7-8). The reaction was also performed in CCl_4 at reflux temperature, which resulted in 60% yield (entry 9). When the amount of TFA was increased from 6.0 equivalents to 10.0 and 15.0 equivalents the yield were increased to 80% and 85%, respectively (entries 10-11). However, with 20.0 equivalents of TFA (entry 12), the reaction didn't show any increment in the yield. Other Brønsted acid, like 2.0 equivalents of *p*-TsOH in toluene failed to give the desired product even after a prolonged reaction time, instead starting material was recovered in 88% yield (entry 13). The reaction was also screened with strong Lewis acid like $\text{BF}_3 \cdot \text{OEt}_2$ (2.0 equivalents), but resulted in 35% yield (entry 14). Moreover, the use of mineral acids such as, HCl and H_2SO_4 in DCE (1 mL) were ineffective for this reaction and gave low yields (31-44%; entries 15-16). From these observations, it was concluded that 15.0 equivalents of TFA in DCE at reflux temperature is the optimum condition for the respective transformation (entry 11).

With this optimized conditions in hand, the scope of the reaction was examined with variety of substrates having substitutions on aryl rings and obtained the desired tetracyclic products **75** in good to excellent yields.

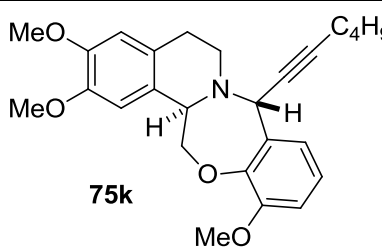
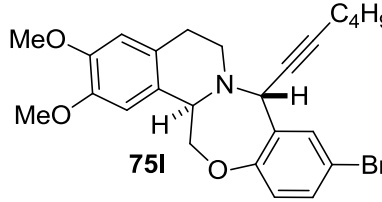
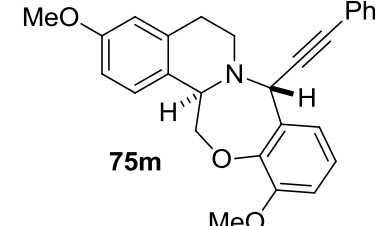
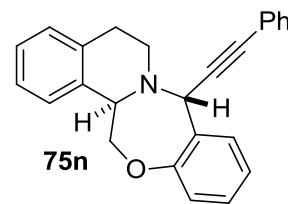
Table 5.3.2. Substrate Scope of the reaction.^a

			
Entry	Product (75)	Time (h)	Yield (%) ^b
1	 75a	5.0	85
2	 75b	5.5	83

Continuation....

Entry	Product (75)	Time (h)	Yield (%) ^b
3	 75c	5.5	82
4	 75d	5.5	85
5	 75e	5.0	83
6	 75f	5.5	81
7	 75g	5.0	84
8	 75h	5.0	82
9	 75i	5.0	83
10	 75j	5.0	82

Continuation....

Entry	Product (75)	Time (h)	Yield (%) ^b
11	 75k	5.5	81
12	 75l	5.0	82
13	 75m	6.0	82
14	 75n	24.0	0

^aReaction conditions; Propargylamine **74** (0.3 mmol) and TFA (4.5 mmol) in 1 mL DCE at reflux. ^bYields refers to isolated. Compounds are characterized by ¹H, ¹³C NMR, IR and mass spectrometry.

The reaction proceeds smoothly with highly electron rich phenylethylamine derivatives such as 3,4-dimethoxyphenylethylamine (Table 5.3.2.; products **75a-75l**) and 3-methoxyphenyl ethylamine (**75m**) derivatives. In case of simple phenylethylamine we were unable to isolate the desired product (**75n**), but the starting material decomposed. The reaction was also tried with different aromatic aldehydes having ether, halo and nitro functional groups in aromatic ring and it was observed that the reaction worked well in all the cases (Table 5.3.2). Similarly the reaction with alkynes having aryl (**75a-75h** and **75m**) and alkyl (**75i-75l**) side chains gave in good to excellent yields. The structure of the compounds was determined by NMR and mass spectrometry. The *trans* stereochemistry of compounds **75a-75m** was confirmed by X-ray crystallographic analysis of **75a** (Figure 5.3.1).¹⁹

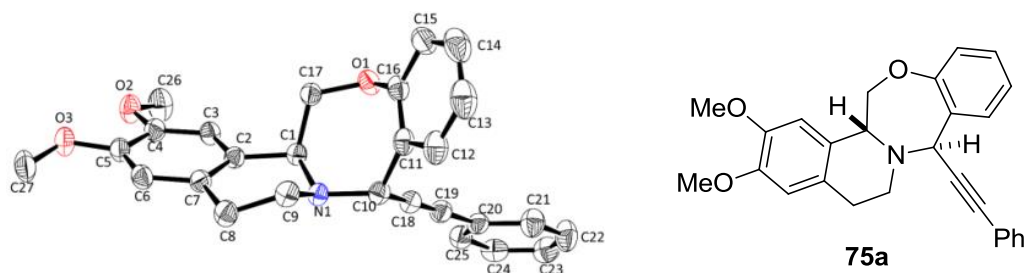
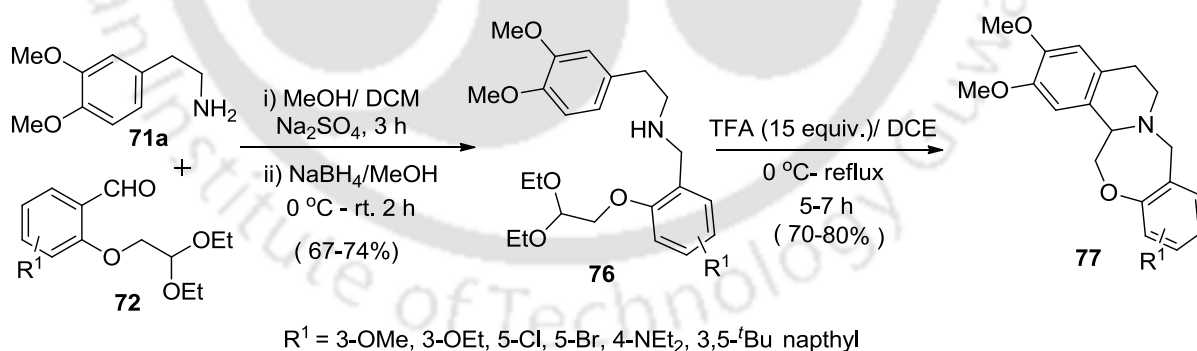


Figure 5.3.1. ORTEP diagram of compound (8*R**,14*aR**)-2,3-dimethoxy-8-(phenylethynyl)-6,8,14,14*a*-tetrahydro-5*H*-benzo[6,7][1,4]oxazepino[3,4-*a*]isoquinoline **75a**.

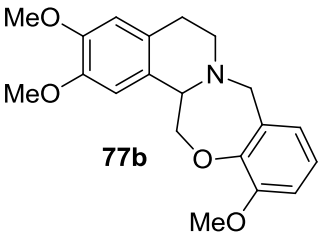
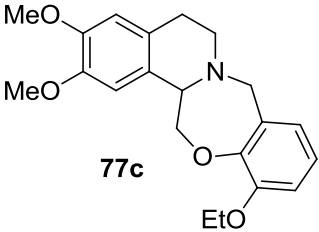
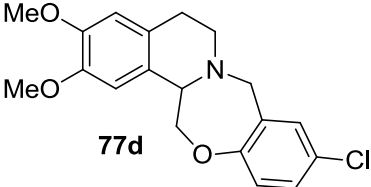
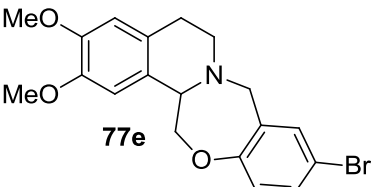
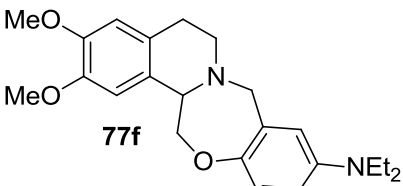
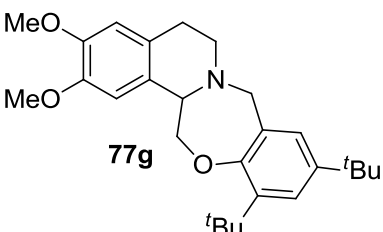
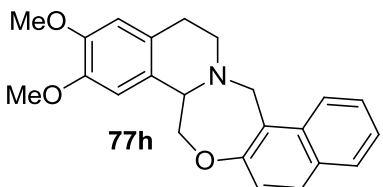
Further the reaction was also performed in absence of alkyne substituents in secondary amine. The condensation of 3,4-dimethoxyphenylethylamine **71a** with 2-(2,2-diethoxyethoxy) benzaldehyde derivatives **72** gives imine which is subsequently reduced with NaBH₄ in ethanol to give secondary amines **76**. The resultant amines **76** were cyclized under similar conditions to give rise to 2,3-dimethoxy-6,8,14,14*a*-tetrahydro-5*H*-benzo[6,7][1,4]oxazepino[3,4-*a*] isoquinoline derivatives **77a-77h** and the results are depicted in (Table 5.3.3).

Table 5.3.3. Synthesis of 2,3-dimethoxy-6,8,14,14*a*-tetrahydro-5*H*-benzo[6,7][1,4]oxazepino[3,4-*a*]isoquinoline derivatives.^a



Entry	Product (77)	Time(h)	Yield(%) ^b
1		5.5	80

Continuation...

Entry	Product (77)	Time(h)	Yield(%) ^b
2	 77b	5.5	78
3	 77c	5.5	76
4	 77d	5.5	79
5	 77e	5.5	76
6	 77f	6.0	75
7	 77g	5.5	73
8	 77h	6.5	70

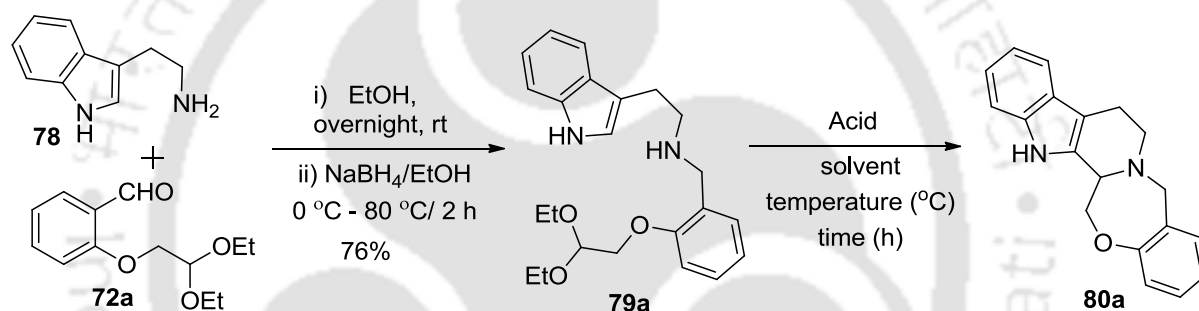
^aReaction conditions: Compound **76** (0.3 mmol) and TFA (4.5 mmol) in 1 mL DCE at reflux. ^bYields refers to isolated. Compounds are characterized by ¹H, ¹³C NMR, IR and mass spectrometry.

This reaction was also examined with variety of 2-(2,2-diethoxyethoxy)benzaldehyde derivatives such as ether, halo, amine and bulky alkyl groups in aromatic ring. The resultant products were obtained in 73-80% yields (Table 5.3.3.; products **77a-77g**). Similarly, the

reaction with 2-(2,2-diethoxyethoxy)naphthaldehyde derivative gave the corresponding pentacyclic product in 70% yield **77h**.

The scope of the reaction was also investigated with heteroarylethylamines like tryptamine **78**. Initially, condensation of tryptamine **78**, with 2-(2,2-diethoxyethoxy)benzaldehyde **72a** followed by reduction with NaBH₄ in ethanol at 0 °C to 80 °C gave *N*-(2-(2,2-diethoxyethoxy)benzyl)-2-(1*H*-indol-3-yl)ethanamine **79a**, which was subjected to double cyclization with 15.0 equivalents of TFA in DCE (1.0 mL) at 0 °C to room temperature to obtain 8,13,13*b*,14-tetrahydro-5*H*,7*H*-benzo[6',7']-[1,4]oxazepino[4',3':1,2] pyrido[3,4-*b*]indole **80a** in 39% yield (Table 5.3.4; entry 1).

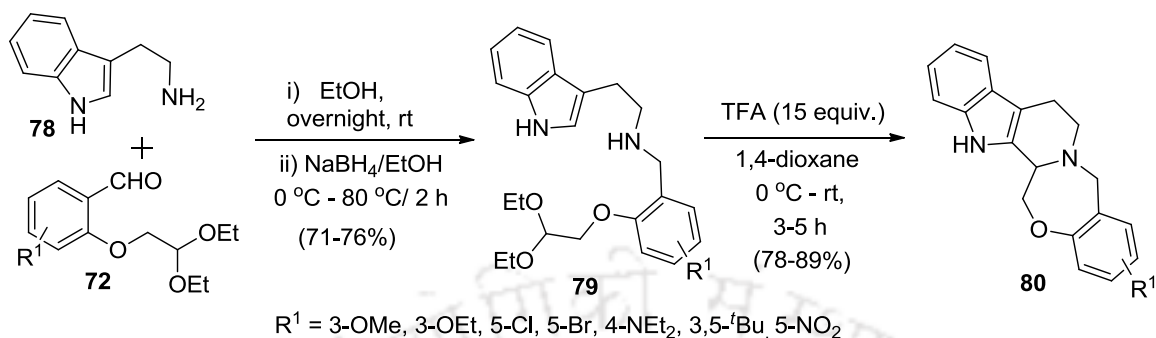
Table 5.3.4: Optimization of the reaction conditions.^a



Entry	Acid (equiv.)	Solvent	Temperature (°C)	Time (h)	Yield(%) ^b
1	TFA (15.0)	DCE	rt	4.0	39
2	TFA (15.0)	DCE	reflux	4.0	51
3	TFA (15.0)	1,4-dioxane	rt	3.0	89

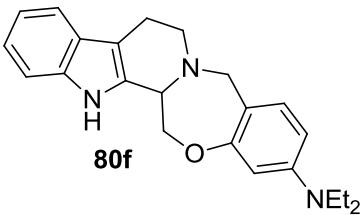
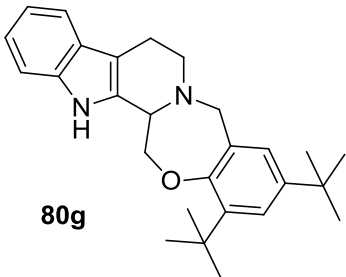
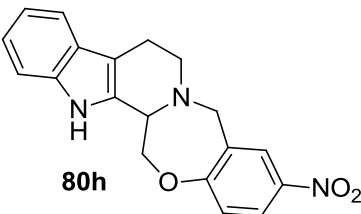
^aReaction conditions: Compound **79a** (0.3 mmol), Solvent (1.0 mL) and Acid. ^bRefers to isolated yield.

Upon increasing the temperature from room temperature to reflux conditions did not give the satisfactory result (entry 2). Surprisingly, use of 1,4-dioxane with the same amount of TFA at 0 °C to room temperature gave in 89% of yield (entry 3) respectively. With this optimized conditions in hand the reaction was screened with various secondary amines **79** which we were synthesized using differently substituted 2-(2,2-diethoxyethoxy)benzaldehyde derivatives leading to formation of corresponding products **80a-80h** and the results are depicted in (Table 5.3.5).

Table 5.3.5. Synthesis of 8,13,13*b*,14-tetrahydro-5*H*,7*H*-benzo[6',7']-[1,4]oxazepino[4',3':1,2]pyrido[3,4-*b*]indole derivatives.^a

Entry	Product (80)	Time(h)	Yield(%) ^b
1		3.0	89
2		3.0	87
3		3.5	84
4		3.0	86
5		3.0	84

Continuation....

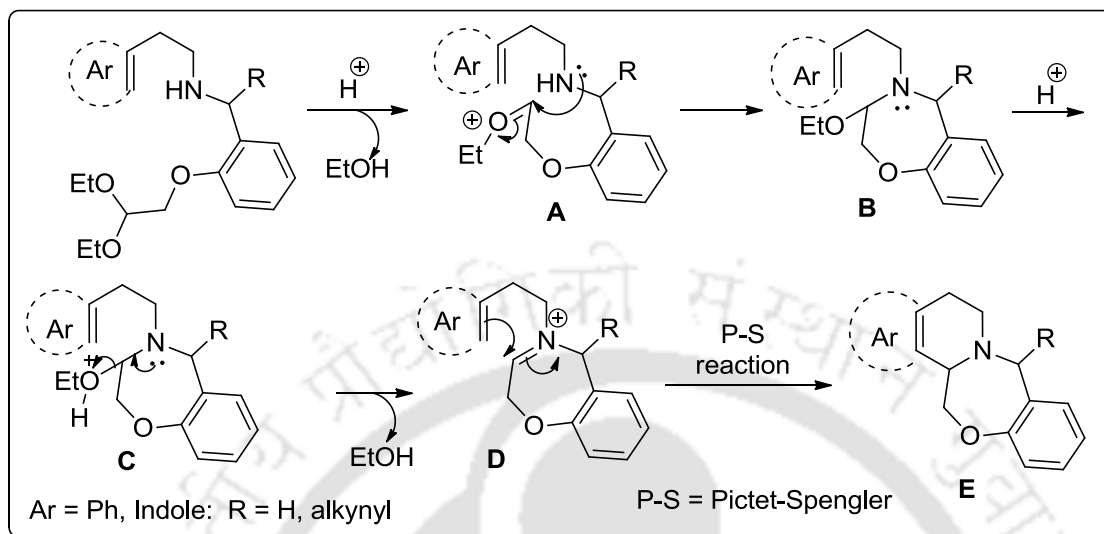
Entry	Product (80)	Time(h)	Yield(%) ^b
6	 80f	3.5	82
7	 80g	3.5	78
8	 80h	3.5	82

^aReaction conditions: Compound **79** (0.3 mmol) and TFA (4.5 mmol) in 1 mL of 1,4-dioxane at reflux conditions. ^bYields refers to isolated. Compounds are characterised by ¹H, ¹³C NMR, IR and mass spectrometry.

This reaction was examined with variety 2-(2,2-diethoxyethoxy)benzaldehyde derivatives having electron donating and electron withdrawing groups in aromatic ring. When the reaction was performed with strong electron donating groups (such as 3-methoxy and 3-ethoxy) in the aromatic ring of 2-(2,2-diethoxyethoxy)benzaldehyde derivatives, the resulting products were obtained in 87-84% yields (Table 5.3.5.; products **80b-80c**). Similarly, the reaction with bulky substituents, 2-(2,2-diethoxyethoxy)-4-(diethylamino) benzaldehyde **80f** 3,5-di-*tert*-butyl-2-(2,2-diethoxyethoxy)benzaldehyde **80g** and gave in 82% and 78% yields, respectively. Halogenated substituents like 5-chloro **80d** and 5-bromo **80f** derivatives gave 84% and 86% yields, respectively. Finally with strong electron withdrawing group having 5-nitro **80h** substituent also didn't show much difference, and the resulted in 82% yield (Table 5.3.5).

The mechanism of the reaction can be explained as follows. Brønsted acid generates oxocarbenium ion **A** by the elimination of ethanol, which under goes nucleophilic attack followed by cyclization gives an intermediate **B**. Excess of acid further reacted with intermediate **B** to produce an iminium ion intermediate **D** via intermediate **C**. Finally,

intermediate **D** participated in Pictet-Spengler reaction to give the corresponding polycyclic products (Scheme 5.3.2).



Scheme 5.3.2: Plausible mechanism of the reaction

Conclusions

In conclusion, a straight forward synthesis of a new class of benzo[1,4]oxazepino fused tetrahydroisoquinoline and tetrahydro- β -carboline frameworks has been achieved in good yields. The synthetic strategy features an efficient generation of cyclic iminium ion to construct the benzo[1,4]oxazepino unit, and an intramolecular Pictet-Spengler reaction to install the tetrahydroisoquinoline or tetrahydro- β -carboline rings as the key steps.

5.4. Experimental section

5.4.1. Instrumentation and characterisation

As described in chapter 2 section 2.5.1

5.4.2. General experimental procedure for the synthesis of propargylamines (74):

To a mixture of CuBr (30 mol%), 2-(2,2-diethoxyethoxy)benzaldehyde derivative **72** (2.0 mmol), and phenyl ethyl amine derivative **71** (2.1 mmol), acetylenes **73** (4 mmol) dissolved in 3 mL of dry toluene, was added and the reaction mixture was stirred at 100 °C for 4-6 h. After

completion of reaction, the reaction mixture was cooled and the solvent was removed on a rotary evaporator. The residue was treated with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with brine solution for three times. The organic layer was dried over Na_2SO_4 and concentrated in a rotary evaporator. The crude product was subjected to column chromatography over silica gel using hexane/ EtOAc (7:3) to give the corresponding product.

5.4.3. Typical procedure for the synthesis of substituted benzo[1,4]oxazepine fused tetrahydroisoquinoline derivatives (75):

Trifluoroacetic acid (4.5 mmol) was slowly added to a stirring solution of amine **74** (0.3 mmol) in DCE (1 mL) at 0 °C and then brought to room temperature. Later on the reaction mixture was stirred at reflux temperature for 5-7 h. After completion of reaction, the reaction was cooled to room temperature and solvent was removed under reduced pressure, diluted with saturated NaHCO_3 and extracted with ethyl acetate (3x6 mL). The organic layer was washed with brine solution for 2-3 times. The combined organic layers were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude mixture was subjected to column chromatography over silica gel using hexane/ EtOAc (4:1) to give the corresponding product.

5.4.4. General procedure for the synthesis of secondary amines (76):

Two compounds 2-(2,2-Diethoxyethoxy)benzaldehyde **72** (1.05 mmol), and 3,4-dimethoxy phenyl ethyl amine **71** (1.0 mmol) were dissolved in 3 mL of dry DCM followed by addition of anhydrous Na_2SO_4 (5.0 mmol). The reaction mixture was stirred at room temperature for 2-3 h. After completion of reaction, the mixture was filtered off and the solvent was removed under reduced pressure to give corresponding imine without any further purification. The imine was dissolved in methanol followed by addition of NaBH_4 (1.5 mmol) slowly (approx. 5 min) at 0 °C. After completion of reaction, the reaction mixture was diluted with saturated ammonium chloride and then extracted with ethyl acetate. The organic layer was further washed with brine solution 2-3 times. The combined organic layers were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude mixture was subjected to column chromatography over silica gel using DCM/ MeOH (9:1) to give the respected product.

5.4.5. Typical procedure for the synthesis of benzo[1,4]oxazepine fused tetrahydro-isoquinoline derivatives (77):

Trifluoroacetic acid (4.5 mmol) was slowly added to a stirring solution of amine **76** (0.3 mmol) in DCE (1 mL) at 0 °C and then brought to room temperature and successively stirred at reflux for 6-7 h. After completion of reaction, the reaction was cooled to room temperature and solvent was removed under reduced pressure, diluted with saturated NaHCO₃ and extracted with ethyl acetate (3x6 mL). The organic layer was washed with brine solution for 2-3 times. The combined organic layers were dried over Na₂SO₄ and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel using hexane/ EtOAc (3:2) to give the expected product.

5.4.6. Experimental procedure for the synthesis of secondary amines (79):

Two compounds 2-(2,2-Diethoxyethoxy)benzaldehyde **72** (1.05 mmol) and tryptamine **78** (1.0 mmol) were dissolved in 3 mL of ethanol followed by addition of anhydrous Na₂SO₄ (3.0 mmol) and the reaction mixture was stirred at room temperature for overnight. After completion of reaction, the mixture was filtered off and the solvent was removed under reduced pressure to give corresponding imine without any further purification. The imine was dissolved in ethanol (3 mL), subsequently addition of NaBH₄ (3.0 mmol) done slowly (approx. 5 min) at 0 °C and stirring continued for 0.5 h at same temperature. Later on reaction mixture was refluxed for 2-3 h. After completion of reaction, the reaction mixture was cooled to room temperature and diluted with saturated ammonium chloride and extracted with DCM (3x7 mL). The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over Na₂SO₄ and concentrated in rotary evaporator. The crude mixture was subjected to column chromatography over silica gel using DCM/ MeOH (9:1) to give the desired product.

5.4.7. Typical procedure for the synthesis of benzo[1,4]oxazepine fused tetrahydro-β-carboline derivatives (80):

Trifluoroacetic acid (4.5mmol) was slowly added to a stirring solution of amine **79a** (0.3 mmol) in 1,4-dioxane (1 mL) at 0 °C and then the reaction mixture was stirred at room temperature for 3-4 h. After completion of reaction, solvent was removed under reduced pressure, diluted with saturated NaHCO₃ and extracted with dichloromethane (DCM) (3x6 mL). The organic layer was washed with brine solution 2-3 times. The combined organic layers were dried over Na₂SO₄ and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel using DCM/ MeOH (9:1) to give the resultant product **80**.

5.5. References:

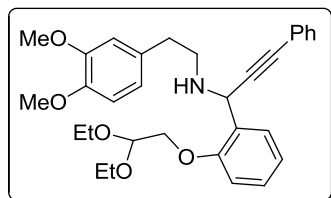
- (a) Suau, R.; López-Romero, J. M.; Ruiz, A.; Rico, R. *Tetrahedron*. **2000**, 56, 993-998.
(b) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudeon, P. *Synthesis*. **2012**, 44, 1410-1416. (c) Shi, Z.; Grohmann, C.; Glorius, F. *Angew. Chem. Int. Ed.* **2013**, 52, 5393-5397. (d) Wang, W.-J.; Zhao, X.; Tong, L.; Chen, J.-H.; Zhang, X.-J.; Yan, M. *J. Org. Chem.* **2014**, 79, 8557-8565. (e) Shamma, M.; Hillman, M. J. *Tetrahedron*. **1971**, 27, 1363-1374. (f) Miyata, J.; Nakashima, H.; Nemoto, H.; Kim, H.-S.; Wataya, Y.; Ihara, M. *Heterocycles*. **1998**, 49, 101-104.
- Tokuda, R.; Okamoto, Y.; Koyama, T.; Kogure, N.; Kitajima, M.; Takayama, H. *Org. Lett.* **2016**, 18, 3490-3493.
- (a) Rinehart, K. L. Jr.; Kobayashi, J.; Harbour, C. G.; Gilmore, J.; Mascal, M.; Holt, T. G.; Shield, L. S.; Lafargue, F. *J. Am. Chem. Soc.* **1987**, 109, 3378-3387. (b) van Maarseveen, J. H.; Hermkens, P. H. H.; Clercq, E. D.; Balzarini, J.; Scheeren, H. W.; Kruse, C. G. *J. Med. Chem.* **1992**, 35, 3223-3230. (c) Nakagawa, M.; Liu, J.-J.; Hino, T. *J. Am. Chem. Soc.* **1989**, 111, 2721-2722. (d) Nakagawa, M.; Liu, J.-J.; Hino, T.; Tsuruoka, A.; Harada, N.; Ariga, M.; Asada, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3477-3494. (e) Still, I. W. J.; Strautmanis, J. R. *Can. J. Chem.* **1990**, 68, 1408-1044. (f) Yamashita, T.; Kawai, N.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2005**, 127, 15038-15039.
- (a) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, 44, 2030-2036. (b) Tatsui, G. J. *Pharm. Soc. Jpn.* **1928**, 48, 92.
- (a) Cox E. D.; Coe, J. M. *Chem. Rev.* **1995**, 95, 1797-1842. (b) Laine, A. E.; Lood C.; Koskinen, A. M. P. *Molecules*. **2014**, 19, 1544-1567. (c) Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angew. Chem. Int. Ed.* **2011**, 50, 8538-8564. (d) Luk, L.Y.P.; Bunn, S.; Liscombe, D. K.; Facchini, P. J.; Tanner, M. E. *Biochemistry*. **2007**, 46, 10153-10161. (e) Nuhant, P.; Raikar, S. B.; Wypych, J.-C.; Delpech, B.; Marazano, C. *J. Org. Chem.* **2009**, 74, 9413-9421. (f) Herlé, B.; Wanner, M. J.; Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2011**, 76, 8907-8912. (g) Gurram, M.; Gyimóthy, B.; Wang, R.; Lam, S. Q.; Ahmed, F.; Herr, R. J. *J. Org. Chem.* **2011**, 76, 1605-1613. (h) Zheng, Y.; Liu, Y.; Wang, Q. *J. Org. Chem.* **2014**, 79, 3348-3357. (i) Gobé, V.; Retailleau, P.; Guinchard, X. *Chem. Eur. J.* **2015**, 21, 17587-17590. (j) Jida, M.; Poorten, O. V.; Guillemin, K.; Urbanczyk-Lipkowska, Z.; Tourwé, D.; Ballet, S. *Org. Lett.* **2015**, 17, 4482-4485.
- (a) Wang H.; Ganesan, A. *Org. Lett.* **1999**, 1, 1647-1649. (b) Marson, C. M. *ARKIVOC*.

- 2001**, 1, 1-16. (c) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, 104, 1431-1628. (d) Yang, J.-E.; In, J.-K.; Lee, M.-S.; Kwak, J.-H.; Lee, H.; Lee, S. J.; Kang, H.-Y.; Suh, Y.-G.; Jung, J.-K. *Bull. Korean Chem. Soc.* **2007**, 28, 1401-1404. (e) Kaim, L. E.; Gageat, M.; Gaultier, L.; Grimaud, L. *Synlett.* **2007**, 3, 500-502. (f) Juma, B.; Adeel, M.; Villinger, A.; Reinke, H.; Spannenberg, A.; Fischer, C.; Langer, P. *Adv. Synth. Catal.* **2009**, 351, 1073-1079. (g) Znabet, A.; Zonneveld, J.; Janssen, E.; De Kanter, F. J. J.; Helliwell, M.; Turner, N. J.; Ruijter, E.; Orru, R. V. A. *Chem Commun.* **2010**, 46, 7706-7708. (h) Rao, R. N.; Maiti, B.; Chanda K.; *ACS Comb. Sci.* **2017**, 19, 199-228.
7. King, F. D. *J. Heterocyclic Chem.* **2007**, 44, 1459-1463.
8. Liu, H.; Dömling, A. *J. Org. Chem.* **2009**, 74, 6895-6898.
9. Wang, W.; Herdtweck, E.; Dömling, A. *Chem. Commun.* **2010**, 46, 770-772.
10. Wang, W.; Ollio, S.; Herdtweck, E.; Dömling, A. *J. Org. Chem.* **2011**, 76, 637-644.
11. Lesma, G.; Cecchi, R.; Crippa, S.; Giovanelli, P.; Meneghetti, F.; Musolino, M.; Sacchetti, A.; Silvani, A. *Org. Biomol. Chem.* **2012**, 10, 9004-9012.
12. Li, Z.; Li, J.; Yang, N.; Chen, Y.; Zhou, Y.; Ji, X.; Zhang, L.; Wang, J.; Xie, X.; Liu, H. *J. Org. Chem.* **2013**, 78, 10802-10811.
13. (a) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra H. *J. Org. Chem.* **2008**, 73, 6405-6408. (b) Zein, A. L.; Dawe, L. N.; Georghiou, P. E. *J. Nat. Prod.* **2010**, 73, 1427-1430. (c) Ghislieri, D.; Green, A. P.; Pontini, M.; Willies, S. C.; Rowles, I.; Frank, A.; Grogan, G.; Turner, N. J. *J. Am. Chem. Soc.* **2013**, 135, 10863-10869. (d). Bailey, P. D.; Hollinshead, S. P.; Dauter, Z. *J. Chem. Soc. Chem. Commun.* **1985**, 1507-1509.
14. Luo, S.; Zhao, J.; Zhai, H. *J. Org. Chem.* **2004**, 69, 4548-4550.
15. Gurram, M.; Gyimóthy, B.; Wang, R.; Lam, S. Q.; Ahmed, F.; Herr, R. J. *J. Org. Chem.* **2011**, 76, 1605-1613.
16. Sanaboina, C.; Jana, S.; Chidara, S.; Patro, B.; Raolji, G. B.; Eppakayala, L. *Tetrahedron Lett.* **2012**, 53, 5027-5029.
17. Patil, P.; Khoury, K.; Herdtweck, E.; Dömling, A. *Bioorg. Med. Chem.* **2015**, 23, 2699-2715.
18. (a) Unnava, R.; Deka, M. J.; Saikia, A. K. *Asian. J. Org. Chem.* **2016**, 5, 2188-2190. (b) Unnava, R.; Saikia, A. K. *Chemistry Select.* **2016**, 1, 1816-1823.
19. The crystallographic data for compound **75a** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 1528350.

5.6. Characterization data

1-(2-(2,2-Diethoxyethoxy)phenyl)-*N*-(3,4-dimethoxyphenethyl)-3-phenylprop-2-yn-1-amine (74a):

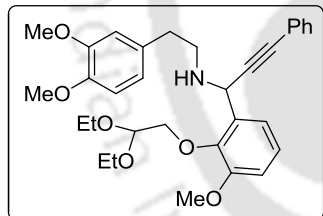
Brown gummy oil; R_f (hexane/EtOAc 7:3) 0.49; yield 784 mg, 78%; $^1\text{H NMR}$ (400 MHz,



CDCl_3): δ 7.61 (d, $J = 7.6$ Hz, 1 H), 7.47-7.43 (m, 2 H), 7.31-7.23 (m, 4 H), 6.98 (t, $J = 7.6$ Hz, 1 H), 6.87 (d, $J = 8.0$ Hz, 1 H), 6.78-6.70 (m, 3 H), 5.12 (s, 1 H), 4.74 (t, $J = 5.6$ Hz, 1 H), 3.99 (d, $J = 5.2$ Hz, 2 H), 3.84 (s, 3 H), 3.79 (s, 3 H), 3.75-3.69 (m, 2 H), 3.65-3.56 (m, 2 H), 3.07-2.93 (m, 2 H), 2.87-2.73 (m, 2 H), 2.17 (brs, 1 H), 1.12 (t, $J = 7.2$ Hz, 6 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 155.6, 148.8, 147.6, 131.6, 130.8, 130.3, 129.9, 129.7, 128.6, 128.4, 126.2, 121.0, 120.9, 118.3, 111.9, 111.8, 111.1, 100.7, 99.6, 69.3, 63.3, 55.9, 55.6, 46.2, 33.6, 15.3; **IR** (KBr, neat) 3387, 2975, 2932, 1599, 1516, 1451, 1374, 1262, 1140, 1070, 1028, 930, 807, 758, 693 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{31}\text{H}_{38}\text{NO}_5$ ($M + \text{H}$) $^+$ 504.2744 found 504.2740.

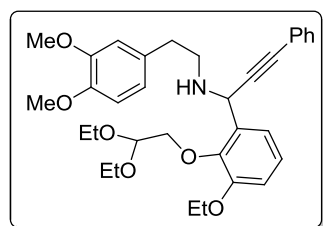
1-(2-(2,2-Diethoxyethoxy)-3-methoxyphenyl)-*N*-(3,4-dimethoxyphenethyl)-3-phenylprop-2-yn-1-amine (74b):

Orange red gummy oil; R_f (hexane/EtOAc 7:3) 0.47; yield 767 mg, 72%; $^1\text{H NMR}$ (600 MHz,



CDCl_3): δ 7.35-7.32 (m, 2 H), 7.19-7.16 (m, 3 H), 7.08 (t, $J = 7.8$ Hz, 1 H), 6.95 (t, $J = 7.8$ Hz, 1 H), 6.76 (d, $J = 8.4$ Hz, 1 H), 6.69-6.64 (m, 3 H), 5.20 (s, 1 H), 4.77 (t, $J = 5.4$ Hz, 1 H), 4.12-4.09 (m, 1H), 4.02-3.98 (m, 1 H), 3.75 (s, 6 H), 3.72 (s, 3 H), 3.68-3.60 (m, 2 H), 3.54-3.48 (m, 2 H), 2.99-2.94 (m, 1 H), 2.87-2.75 (m, 1 H), 2.74-2.66 (m, 2 H), 1.99 (brs, 1 H), 1.14 (t, $J = 7.2$ Hz, 6 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 152.5, 148.9, 147.4, 145.5, 134.3, 132.7, 131.7, 128.3, 128.1, 124.1, 123.4, 120.7, 120.5, 112.0, 111.9, 111.3, 100.9, 90.1, 84.3, 72.8, 62.3, 62.1, 56.0, 55.8, 49.3, 48.7, 35.9, 15.5, 15.4; **IR** (KBr, neat) 3339, 2974, 2934, 2835, 1589, 1516, 1480, 1417, 1373, 1237, 1139, 1069, 962, 851, 758, 693 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{32}\text{H}_{40}\text{NO}_6$ ($M + \text{H}$) $^+$ 534.2850 found 534.2859.

1-(2-(2,2-Diethoxyethoxy)-3-ethoxyphenyl)-*N*-(3,4-dimethoxyphenethyl)-3-phenylprop-2-yn-1-amine (74c):

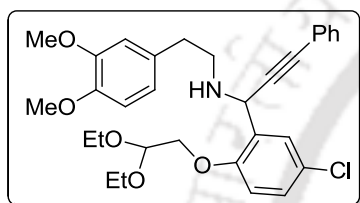


Deep orange gummy oil; R_f (hexane/EtOAc 7:3) 0.48; yield 776 mg, 71%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.34-7.32 (m, 2 H), 7.19-7.16 (m, 3 H), 7.06 (d, $J = 7.8$ Hz, 1 H), 6.92 (t, $J = 8.4$ Hz, 1 H), 6.76 (d, $J = 7.8$ Hz, 1 H), 6.70-6.64 (m, 3 H), 5.19 (s, 1 H), 4.78

(t, $J = 6.6$ Hz, 1 H), 4.13-4.10 (m, 1 H), 4.04-4.01 (m, 1 H), 3.97-3.93 (m, 2 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.67-3.64 (m, 2 H), 3.52-3.48 (m, 2 H), 2.99-2.95 (m, 1 H), 2.89-2.75 (m, 1 H), 2.76-2.67 (m, 2 H), 2.45 (brs, 1 H), 1.35 (t, $J = 6.6$ Hz, 3 H), 1.14 (t, $J = 7.2$ Hz, 6 H); ^{13}C NMR (150 MHz, CDCl_3): δ 151.8, 148.9, 147.4, 145.6, 134.1, 132.7, 131.7, 128.3, 128.1, 124.0, 123.4, 120.7, 120.4, 113.0, 112.1, 111.4, 100.9, 90.0, 84.3, 72.6, 64.2, 62.5, 62.2, 62.0, 56.0, 55.8, 49.4, 48.7, 35.8, 15.5, 15.4, 15.0; IR (KBr, neat) 3325, 3057, 2976, 2933, 2835, 1590, 1516, 1470, 1394, 1269, 1138, 1061, 1027, 946, 852, 758, 693cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{33}\text{H}_{42}\text{NO}_6(\text{M} + \text{H})^+$ 548.3007 found 548.3014.

1-(5-Chloro-2-(2,2-diethoxyethoxy)phenyl)-N-(3,4-dimethoxyphenethyl)-3-phenylprop-2-yn-1-amine (74d):

Pale yellow gummy oil; R_f (hexane/EtOAc 7:3) 0.47; yield 805 mg, 75%; ^1H NMR (600

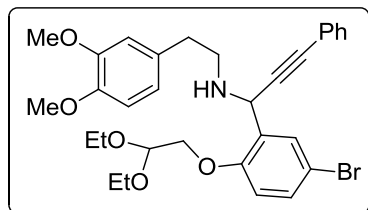


MHz, CDCl_3): δ 7.46 (s, 1 H), 7.37-7.34 (m, 2 H), 7.19-7.17 (m, 3 H), 7.11 (d, $J = 9.0$ Hz, 1 H), 6.70 (t, $J = 8.4$ Hz, 2 H), 6.64-6.60 (m, 2 H), 5.07 (s, 1 H), 4.61 (t, $J = 5.4$ Hz, 1 H), 3.85

(d, $J = 5.4$ Hz, 2 H), 3.74 (s, 3 H), 3.70 (s, 3 H), 3.63-3.60 (m, 2 H), 3.52-3.48 (m, 2 H), 2.93-2.84 (m, 2 H), 2.76-2.69 (m, 1 H), 2.74-2.64 (m, 1 H), 2.20 (brs, 1 H), 1.25 (t, $J = 7.2$ Hz, 6 H); ^{13}C NMR (150 MHz, CDCl_3): δ 154.4, 148.9, 147.4, 132.5, 131.8, 130.5, 128.8, 128.6, 128.3, 128.2, 126.1, 123.0, 120.6, 113.3, 111.9, 111.3, 100.4, 88.5, 84.9, 69.2, 62.8, 55.9, 55.8, 49.2, 48.2, 35.8, 15.4 (2C); IR (KBr, neat) 3330, 3057, 2975, 2933, 2834, 2065, 1656, 1594, 1516, 1463, 1415, 1374, 1261, 1128, 1071, 1029, 915, 807, 758cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{31}\text{H}_{37}\text{ClNO}_5(\text{M} + \text{H})^+$ 538.2355 found 538.2339.

1-(5-Bromo-2-(2,2-diethoxyethoxy)phenyl)-N-(3,4-dimethoxyphenethyl)-3-phenylprop-2-yn-1-amine (74e):

Deep orange gummy oil; R_f (hexane/EtOAc 7:3) 0.47; yield 849 mg, 73%; ^1H NMR (600

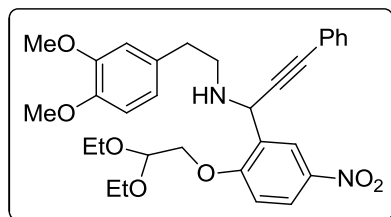


MHz, CDCl_3): δ 7.60 (s, 1 H), 7.34 (s, 2 H), 7.24 (m, 1 H), 7.19-7.17 (m, 3 H), 6.68-6.60 (m, 4 H), 5.13 (s, 1 H), 4.60 (t, $J = 4.8$ Hz, 1 H), 3.85 (d, $J = 4.8$ Hz, 2 H), 3.73 (s, 3 H), 3.69 (s, 3 H), 3.65-3.59 (m, 2 H), 3.51-3.47 (m, 2 H), 2.89-2.67 (m, 4

H), 2.22 (brs, 1 H), 1.15 (t, $J = 7.2$ Hz, 6 H); ^{13}C NMR (150 MHz, CDCl_3): δ 154.8, 148.9, 147.4, 132.4, 131.7, 131.6, 128.2, 128.1, 123.0, 120.6, 113.7, 113.5, 111.9, 111.3, 100.3, 88.4, 84.9, 69.1, 62.8, 55.9, 55.7, 35.7, 15.4, 15.3; IR (KBr, neat) 3324, 3058, 2975, 2934, 2834, 2251, 1591, 1516, 1489, 1417, 1374, 1263, 1125, 1070, 1028, 931, 807, $758, 692\text{cm}^{-1}$; HRMS (ESI) calcd. for $\text{C}_{31}\text{H}_{37}\text{BrNO}_5(\text{M} + \text{H})^+$ 582.1850, found 582.1840.

1-(2-(2,2-Diethoxyethoxy)-5-nitrophenyl)-N-(3,4-dimethoxyphenethyl)-3-phenylprop-2-yn-1-amine (74f):

Yellow gummy oil; R_f (hexane/EtOAc 7:3) 0.45; yield 756 mg, 69%; $^1\text{H NMR}$ (600 MHz,

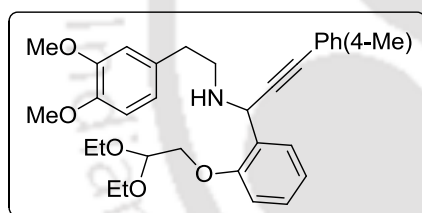


CDCl_3): δ 8.51 (s, 1 H), 8.17 (d, $J = 9.0$ Hz, 1 H), 7.45-7.43 (m, 2 H), 7.30-7.28 (m, 3 H), 6.94 (d, $J = 9.0$ Hz, 1 H), 6.77 (d, $J = 7.8$ Hz, 1 H), 6.75-6.69 (m, 2 H), 5.17 (s, 1 H), 4.75 (t, $J = 5.4$ Hz, 1 H), 4.06 (d, $J = 5.4$ Hz, 2 H), 3.83 (s, 3 H), 3.78

(s, 3 H), 3.75-3.70 (m, 2 H), 3.62-3.58 (m, 2 H), 3.03-2.95 (m, 2 H), 2.85-2.81 (m, 1 H), 2.78-2.73 (m, 1 H), 2.40 (brs, 1 H), 1.22 (t, $J = 7.2$ Hz, 6 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 160.7, 149.1, 147.6, 141.7, 132.4, 131.9, 130.0, 128.6, 128.4, 125.3, 124.8, 122.8, 120.7, 112.1, 111.7, 111.4, 100.2, 87.7, 85.6, 69.5, 63.2, 63.1, 56.0, 55.9, 49.3, 48.4, 35.8, 15.5; **IR** (KBr, neat) 3335, 3110, 2921, 2874, 1591, 1516, 1451, 1341, 1275, 1262, 1138, 1026, 965, 835, 764, 669 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{31}\text{H}_{37}\text{N}_2\text{O}_7$ ($\text{M} + \text{H}$) $^+$ 549.2595 found 549.2584.

1-(2-(2,2-Diethoxyethoxy)phenyl)-N-(3,4-dimethoxyphenethyl)-3-(p-tolyl)prop-2-yn-1-amine (74g):

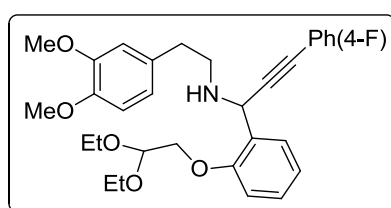
Red gummy oil; R_f (hexane/EtOAc 7:3) 0.50; yield 723 mg, 70%; $^1\text{H NMR}$ (400 MHz,



CDCl_3): δ 7.60 (d, $J = 7.6$ Hz, 1 H), 7.35 (d, $J = 8.0$ Hz, 2 H), 7.24 (t, $J = 8.0$ Hz, 1 H), 7.09 (d, $J = 7.6$ Hz, 2 H), 6.97 (t, $J = 7.6$ Hz, 1 H), 6.86 (d, $J = 8.0$ Hz, 1 H), 6.77-6.69 (m, 3 H), 5.20 (s, 1 H), 4.72 (t, $J = 5.2$ Hz, 1 H), 3.98

(d, $J = 5.2$ Hz, 2 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.76-3.69 (m, 2 H), 3.65-3.56 (m, 2 H), 3.07-2.92 (m, 2 H), 2.87-2.73 (m, 2 H), 2.34 (brs, 1 H), 2.31 (s, 3 H), 1.22 (t, $J = 7.2$ Hz, 6 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 155.6, 148.7, 147.2, 138.0, 132.5, 131.5, 128.9, 128.5, 121.0, 120.5, 120.2, 111.8, 111.1, 100.5, 88.3, 84.7, 68.7, 62.7, 55.8, 55.7, 49.5, 48.2, 35.7, 21.4, 15.4, 15.3; **IR** (KBr, neat) 3324, 2975, 2932, 2835, 1600, 1514, 1452, 1417, 1375, 1262, 1140, 1070, 1028, 941, 852, 817, 756 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{32}\text{H}_{40}\text{NO}_5$ ($\text{M} + \text{H}$) $^+$ 518.2901 found 518.2910.

1-(2-(2,2-Diethoxyethoxy)phenyl)-N-(3,4-dimethoxyphenethyl)-3-(4-fluorophenyl)prop-2-yn-1-amine (74h):

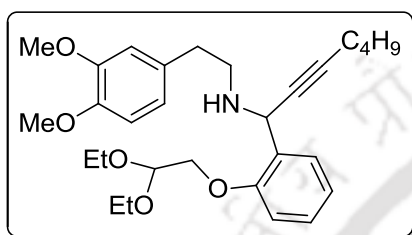


Orange gummy oil; R_f (hexane/EtOAc 7:3) 0.47; yield 698 mg, 67%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.42 (d, $J = 7.8$ Hz, 1 H), 7.30 (t, $J = 8.4$ Hz, 2 H), 7.13 (t, $J = 7.8$ Hz, 1 H), 6.87-6.84 (m, 3 H), 6.76 (d, $J = 7.8$ Hz, 1 H), 6.66-6.58 (m, 3 H), 5.09 (s, 1 H), 4.61 (t, $J = 5.4$ Hz, 1 H), 3.88 (d, $J = 5.4$ Hz, 2 H), 3.71 (s, 3 H), 3.68 (s, 3

H), 3.64-3.59 (m, 2 H), 3.51-3.47 (m, 2 H), 2.93-2.83 (m, 2 H), 2.75-2.64 (m, 2 H), 2.33 (brs, 1 H), 1.18 (t, $J = 7.2$ Hz, 6 H); ^{13}C NMR (150 MHz, CDCl_3): δ 163.1, 161.4, 155.6, 148.8, 147.3, 133.5, 133.4, 132.5, 129.0, 128.8, 128.3, 121.0, 120.5, 119.4, 119.3, 115.5, 115.3, 111.9, 111.8, 111.2, 100.4, 88.8, 83.4, 68.7, 62.6, 55.8, 55.6, 49.5, 48.2, 35.6, 15.4, 15.3; IR (KBr, neat) 3328, 3060, 2975, 2933, 2835, 1600, 1516, 1464, 1375, 1263, 1138, 1028, 938, 839, 755 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{31}\text{H}_{37}\text{FNO}_5$ ($M + \text{H}$) $^+$ 522.2650 found 522.2655.

1-(2-(2,2-Diethoxyethoxy)phenyl)-N-(3,4-dimethoxyphenethyl)hept-2-yn-1-amine (74i):

Deep orange gummy oil; R_f (hexane/EtOAc 3:1) 0.51; yield 492 mg, 51%; ^1H NMR (400

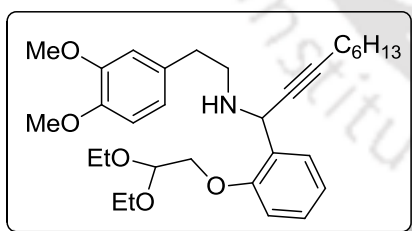


MHz, CDCl_3): δ 7.54 (d, $J = 8.0$ Hz, 1 H), 7.21 (t, $J = 7.6$ Hz, 1 H), 6.95 (t, $J = 7.2$ Hz, 1 H), 6.82 (d, $J = 8.4$ Hz, 1 H), 6.77 (d, $J = 8.0$ Hz, 1 H), 6.70-6.66 (m, 2 H), 4.98 (s, 1 H), 4.69 (t, $J = 5.2$ Hz, 1 H), 3.94 (d, $J = 5.2$ Hz, 2 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.75-3.67 (m, 2 H), 3.63-3.56 (m, 2

H), 2.87-2.72 (m, 4 H), 2.23 (t, $J = 6.8$ Hz, 2 H), 2.13 (brs, 1 H), 1.54-1.47 (m, 2 H), 1.45-1.21 (m, 2 H), 1.22 (t, $J = 7.2$ Hz, 6 H), 0.89 (t, $J = 6.8$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 155.5, 148.7, 147.3, 132.6, 128.9, 128.7, 120.9, 120.5, 111.9, 111.6, 111.1, 100.4, 85.1, 79.1, 68.6, 62.7, 62.6, 55.8, 55.6, 48.8, 47.8, 35.5, 30.9, 21.9, 18.5, 15.3, 13.6; IR (KBr, neat) 3325, 2958, 2834, 2240, 1589, 1517, 1464, 1375, 1263, 1028, 937, 854, 807, 752 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{42}\text{NO}_5$ ($M + \text{H}$) $^+$ 484.3057 found 484.3066.

1-(2-(2,2-Diethoxyethoxy)phenyl)-N-(3,4-dimethoxyphenethyl)non-2-yn-1-amine (74j):

Orange gummy oil; R_f (hexane/EtOAc 3:1) 0.51; yield 512 mg, 50%; ^1H NMR (400 MHz,

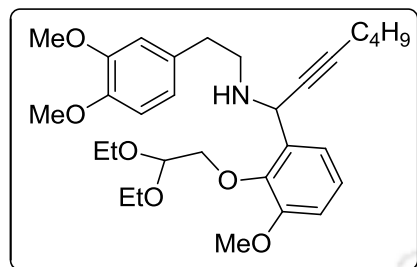


CDCl_3): δ 7.53 (d, $J = 7.2$ Hz, 1 H), 7.18 (t, $J = 7.6$ Hz, 1 H), 6.92 (t, $J = 7.6$ Hz, 1 H), 6.80 (d, $J = 8.4$ Hz, 1 H), 6.75 (d, $J = 8.0$ Hz, 1 H), 6.68-6.49 (m, 2 H), 4.97 (s, 1 H), 4.66 (t, $J = 4.8$ Hz, 1 H), 3.92 (d, $J = 4.8$ Hz, 2 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.75-3.65 (m, 2 H), 3.61-3.54 (m, 2 H), 2.92-2.85

(m, 2 H), 2.81-2.65 (m, 2 H), 2.21 (t, $J = 6.0$ Hz, 2 H), 2.13 (brs, 1 H), 1.54-1.46 (m, 2 H), 1.40-1.29 (m, 2 H), 1.26-1.19 (m, 10 H), 0.85 (t, $J = 6.4$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 155.6, 148.9, 147.3, 132.8, 129.1, 128.9, 128.7, 120.9, 120.6, 111.9, 111.6, 111.1, 100.5, 85.1, 79.5, 68.7, 62.8, 62.7, 55.9, 55.7, 48.8, 48.0, 35.8, 31.4, 28.9, 28.6, 22.6, 18.9, 15.5, 15.4, 14.1; IR (KBr, neat) 3347, 2930, 2857, 2361, 1590, 1515, 1453, 1417, 1375, 1261, 1139, 1072, 1029, 937, 805, 754 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{31}\text{H}_{46}\text{NO}_5$ ($M + \text{H}$) $^+$ 512.3371 found 512.3377.

1-(2-(2,2-Diethoxyethoxy)-3-methoxyphenyl)-N-(3,4-dimethoxyphenethyl)hept-2-yn-1-amine (74k):

Orange gummy oil; R_f (hexane/EtOAc 3:1) 0.49; yield 461 mg, 45%; $^1\text{H NMR}$ (600 MHz,

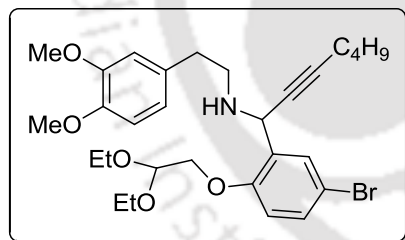


CDCl_3): δ 7.07 (d, $J = 7.8$ Hz, 1 H), 6.96 (t, $J = 7.8$ Hz, 1 H), 6.77 (d, $J = 7.8$ Hz, 1 H), 6.72 (d, $J = 8.4$ Hz, 1 H), 6.67-6.60 (m, 2 H), 5.02 (s, 1 H), 4.77 (t, $J = 5.4$ Hz, 1 H), 4.10-4.07 (m, 1 H), 3.98-3.96 (m, 1 H), 3.78-3.75 (m, 9 H), 3.69-3.66 (m, 2 H), 3.57-3.53 (m, 2 H), 2.91-2.87 (m, 1 H), 2.83-2.79 (m, 1 H), 2.75-2.68 (m, 2 H), 2.37 (brs, 1 H),

2.17 (m, 2 H), 1.45-1.42 (m, 2 H), 1.36-1.32 (m, 2 H), 1.20-1.13 (m, 6 H), 0.83 (t, $J = 7.2$ Hz, 3 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 152.2, 148.7, 147.2, 145.2, 134.5, 132.6, 123.9, 120.5, 120.3, 111.9, 111.6, 111.2, 100.7, 84.6, 80.0, 72.6, 62.2, 62.0, 61.9, 55.8, 55.6 (2C), 48.4, 48.3, 35.6, 30.8, 21.9, 18.5, 15.3, 15.2, 15.1, 13.5; **IR** (KBr, neat) 3329, 2932, 2837, 2238, 1691, 1588, 1517, 1481, 1265, 1156, 1126, 1024, 930, 851, 762 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{30}\text{H}_{44}\text{NO}_6$ ($M + \text{H}$) $^+$ 514.3163 found 514.3162.

1-(5-Bromo-2-(2,2-diethoxyethoxy)phenyl)-N-(3,4-dimethoxyphenethyl)hept-2-yn-1-amine (74l):

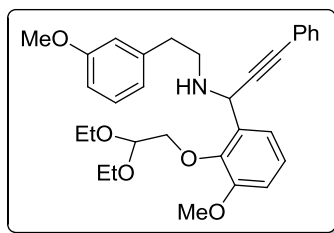
Yellow gummy oil; R_f (hexane/EtOAc 3:1) 0.51; yield 527 mg, 47%; $^1\text{H NMR}$ (600 MHz,



CDCl_3): δ 7.63 (s, 1 H), 7.31 (d, $J = 7.8$ Hz, 1 H), 6.78 (d, $J = 7.8$ Hz, 1 H), 6.69 (t, $J = 7.2$ Hz, 3 H), 4.94 (s, 1 H), 4.67 (t, $J = 5.4$ Hz, 1 H), 3.92-3.88 (m, 2 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.74-3.68 (m, 2 H), 3.62-3.56 (m, 2 H), 2.87 (t, $J = 6.0$ Hz, 2 H), 2.80-2.76 (m, 1 H), 2.73-2.69 (m, 1 H), 2.25 (t, $J =$

7.2 Hz, 2 H), 1.99 (brs, 1 H), 1.54-1.49 (m, 2 H), 1.46-1.40 (m, 2 H), 1.24-1.21 (m, 6 H), 0.92 (t, $J = 7.2$ Hz, 3 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 154.7, 148.8, 147.3, 132.6, 131.7, 131.4, 131.3, 120.5, 113.4, 113.3, 111.8, 111.1, 100.3, 85.6, 78.7, 68.9, 62.8, 62.7, 55.8, 55.7, 48.5, 47.8, 35.7, 30.8, 22.0, 18.5, 15.4, 13.6; **IR** (KBr, neat) 3328, 2956, 2932, 2872, 1590, 1517, 1463, 1375, 1319, 1260, 1139, 1072, 1029, 934, 853, 806, 764 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{29}\text{H}_{41}\text{BrNO}_5$ ($M + \text{H}$) $^+$ 562.2163 found 562.2166.

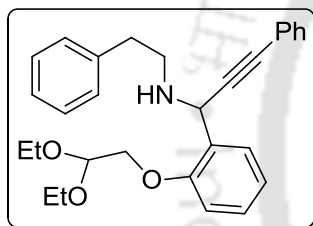
1-(2-(2,2-Diethoxyethoxy)-3-methoxyphenyl)-N-(3-methoxyphenethyl)-3-phenylprop-2-yn-1-amine (74m):



Yellow gummy oil; R_f (hexane/EtOAc 3:1) 0.55; yield 714 mg, 71%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.35-7.30 (m, 2 H), 7.18-7.13 (m, 3 H), 7.08 (t, $J = 7.8$ Hz, 2 H), 6.94 (t, $J = 7.8$ Hz, 1 H), 6.74 (d, $J = 8.4$ Hz, 1 H), 6.71 (d, $J = 7.2$ Hz, 2 H), 6.66 (s, 1 H), 6.62 (d, $J = 8.4$ Hz, 1 H), 5.20 (s, 1 H), 4.77 (t, $J = 4.8$ Hz, 2 H), 4.11-4.08 (m, 1 H), 4.02-3.98 (m, 1 H), 3.71 (s, 3 H), 3.66-3.58 (m, 5 H), 3.53-3.45 (m, 2 H), 3.00-2.95 (m, 1 H), 2.88-2.85 (m, 1 H), 2.79-2.69 (m, 2 H), 2.02 (brs, 1 H), 1.14 (t, $J = 5.4$ Hz, 6 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 159.6, 152.4, 145.4, 141.7, 134.1, 131.7, 129.4, 128.2, 128.0, 124.1, 123.3, 121.1, 12.0.4, 114.3, 111.9, 111.5, 100.8, 89.9, 84.2, 72.7, 62.3, 62.0, 55.7, 55.0, 49.3, 48.5, 36.4, 15.4; **IR** (KBr, neat) 3328, 3053, 2975, 2836, 1585, 1491, 1373, 1346, 1212, 1511, 1072, 927, 874, 757, 692 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{31}\text{H}_{33}\text{NO}_5$ ($M + \text{H}$) $^+$ 504.2744 found 504.2754.

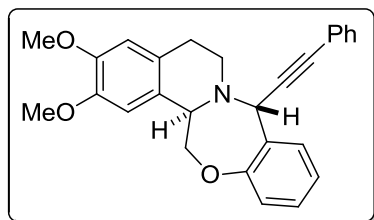
1-(2-(2,2-Diethoxyethoxy)phenyl)-N-phenethyl-3-phenylprop-2-yn-1-amine (74n):

Orange gummy oil; R_f (hexane/EtOAc 3:1) 0.55; yield 575 mg, 65%; $^1\text{H NMR}$ (400 MHz,



CDCl_3): δ 7.61 (d, $J = 7.2$ Hz, 1 H), 7.46-7.43 (m, 2 H), 7.31-7.20 (m, 6 H), 7.18 (d, $J = 6.8$ Hz, 3 H), 6.97 (d, $J = 7.6$ Hz, 1 H), 6.87 (d, $J = 8.0$ Hz, 1 H), 5.52 (s, 1 H), 4.73 (t, $J = 5.6$ Hz, 1 H), 4.00 (d, $J = 5.2$ Hz, 2 H), 3.76-3.3.69 (m, 2 H), 3.65-3.58 (m, 2 H), 3.07-2.91 (m, 2 H), 2.90-2.79 (m, 2 H), 2.17 (brs, 1 H), 125-121 (m, 6 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 155.8, 140.2, 131.8, 129.1, 129.0, 128.8, 128.6, 128.5, 128.3, 128.1, 126.2, 121.2, 111.9, 100.6, 89.3, 84.7, 68.9, 62.9, 62.8, 49.8, 48.5, 36.4, 15.6, 15.5; **IR** (KBr, neat) 3048, 3061, 2975, 2929, 1600, 1533, 1491, 1451, 1374, 1289, 1247, 1132, 1071, 1028, 934, 821, 754 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{29}\text{H}_{34}\text{NO}_3$ ($M + \text{H}$) $^+$ 444.2533 found 444.2525.

(8*R,14*aR**)-2,3-Dimethoxy-8-(phenylethynyl)-6,8,14,14*a*-tetrahydro-5*H*-benzo[6,7][1,4]oxazepino[3,4-*a*]isoquinoline (75a):**

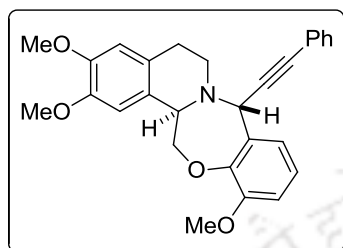


Light yellow solid; mp 140-142 $^{\circ}\text{C}$; R_f (hexane/EtOAc 4:1) 0.51; yield 104 mg, 85%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.46-7.41 (m, 2 H), 7.28-7.23 (m, 5 H), 7.08 (t, $J = 8.0$ Hz, 2 H), 6.85 (s, 1 H), 6.57 (s, 1 H), 5.09 (d, $J = 10.0$ Hz, 1 H), 5.02 (s, 1 H), 4.40 (d, $J = 12.8$ Hz, 1 H), 4.02 (dd, $J = 10.0$ & 2.8 Hz, 1 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.04-2.96 (m, 1 H), 2.95-2.83 (m, 2 H), 2.78-2.72 (m, 1 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 158.6, 148.2, 147.4, 132.5, 132.1, 130.3, 129.7, 128.3, 128.2, 127.5, 125.9, 124.1, 123.2, 121.9, 111.6, 110.4, 86.6, 73.5, 61.9, 59.1, 56.2, 56.0, 45.6, 29.5; **IR** (KBr, neat) 3060, 3001,

2922, 2843, 1582, 1519, 1453, 1411, 1356, 1259, 1220, 1106, 1070, 898, 859, 758 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{27}\text{H}_{26}\text{NO}_3$ ($\text{M} + \text{H}$)⁺ 412.1907, found 412.1899.

(8R*,14aR*)-2,3,12-Trimethoxy-8-(phenylethynyl)-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-a]isoquinoline (75b):

Light yellow solid; mp 160-162 °C; R_f (hexane/EtOAc 4:1) 0.50; yield 109 mg, 83%; ¹H

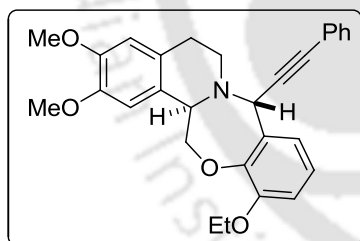


NMR (600 MHz, CDCl_3): δ 7.35-7.33 (m, 2 H), 7.13 (t, J = 8.4 Hz, 3 H), 6.91 (t, J = 7.8 Hz, 1 H), 6.76 (t, J = 8.4 Hz, 2 H), 6.57 (s, 1 H), 6.46 (s, 1 H), 4.99 (d, J = 10.2 Hz, 1 H), 4.92 (s, 1 H), 4.45 (d, J = 12.6 Hz, 1 H), 4.02 (dd, J = 13.2 & 2.4 Hz, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 2.91-2.86 (m, 1 H),

2.83-2.75 (m, 2 H), 2.67-2.63 (m, 1 H); ¹³C **NMR** (150 MHz, CDCl_3): δ 151.9, 147.9, 147.6, 147.2, 133.6, 131.9, 128.1, 127.4, 125.7, 123.8, 123.1, 121.5, 112.4, 111.4, 110.1, 86.4, 86.3, 73.6, 61.6, 58.9, 56.2, 55.9, 55.8, 45.5, 29.4; **IR** (KBr, neat) 3055, 3000, 2933, 2835, 2229, 1585, 1522, 1385, 1334, 1127, 1080, 1005, 968, 898, 859, 785 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{28}\text{H}_{28}\text{NO}_4$ ($\text{M} + \text{H}$)⁺ 442.2013, found 442.2009.

(8R*,14aR*)-12-Ethoxy-2,3-dimethoxy-8-(phenylethynyl)-6,8,14,14a-tetrahydro-5H-benzo [6,7][1,4]oxazepino[3,4-a]isoquinoline (75c):

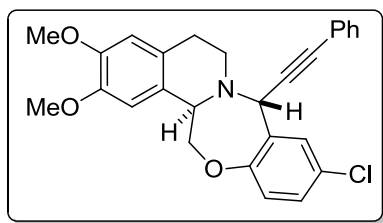
Light yellow solid; mp 133-135 °C; R_f (hexane/EtOAc 4:1) 0.51; yield 111 mg, 82%; ¹H



NMR (600 MHz, CDCl_3): δ 7.35-7.33 (m, 2 H), 7.15 (t, J = 8.4 Hz, 3 H), 6.90 (t, J = 7.8 Hz, 1 H), 6.79 (d, J = 7.8 Hz, 1 H), 6.77 (d, J = 7.8 Hz, 1 H), 6.59 (s, 1 H), 6.47 (s, 1 H), 5.01 (d, J = 9.0 Hz, 1 H), 4.92 (s, 1 H), 4.43 (d, J = 12.6 Hz, 1 H), 4.02-3.94 (m, 2 H), 3.58 (d, J = 12.6 Hz, 1 H), 3.75 (s, 3 H), 3.72 (s,

3 H), 2.93-2.87 (m, 1 H), 2.84-2.75 (m, 2 H), 2.67-2.64 (m, 1 H), 1.33 (t, J = 7.2 Hz, 3 H); ¹³C **NMR** (150 MHz, CDCl_3): δ 151.3, 148.1, 148.0, 147.2, 133.8, 132.0, 128.2, 127.4, 125.8, 123.8, 123.2, 121.6, 114.1, 111.5, 110.2, 86.5, 86.4, 73.5, 64.8, 61.8, 59.0, 56.0, 55.9, 45.5, 29.5, 15.0; **IR** (KBr, neat) 3056, 2977, 2930, 2834, 1598, 1519, 1488, 1443, 1385, 1334, 1268, 1126, 1044, 1005, 866, 783, 756 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{29}\text{H}_{30}\text{NO}_4$ ($\text{M} + \text{H}$)⁺ 456.2169 found 456.2182.

(8R*,14aR*)-10-Chloro-2,3-dimethoxy-8-(phenylethynyl)-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-a]isoquinoline (75d):

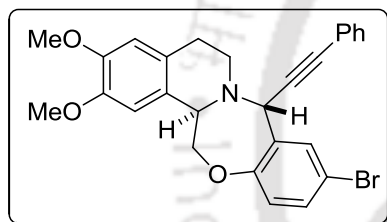


Orange solid; mp 178-180 °C; R_f (hexane/EtOAc 4:1) 0.52; yield 112 mg, 84%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.35-7.33 (m, 2 H), 7.17-7.15 (m, 4 H), 7.10 (d, $J = 8.4$ Hz, 1 H), 6.90 (d, $J = 9.0$ Hz, 1 H), 6.58 (s, 1 H), 6.48 (s, 1 H), 4.97 (d, $J = 10.2$ Hz, 1 H), 4.86 (s, 1 H), 4.29 (d, $J = 13.2$ Hz, 1 H),

3.88 (dd, $J = 13.2$ & 3.0 Hz, 1 H), 3.75 (s, 3 H), 3.73 (s, 3 H), 2.92-2.87 (m, 1 H), 2.83-2.73 (m, 2 H), 2.67-2.63 (m, 1 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 157.2, 148.1, 147.3, 134.1, 132.0, 129.6, 129.3, 128.8, 128.4, 128.3, 127.4, 125.5, 123.2, 122.9, 111.5, 110.3, 86.9, 85.8, 73.4, 61.4, 58.8, 56.1, 55.9, 45.4, 29.4; **IR** (KBr, neat) 3056, 2999, 2930, 2834, 1519, 1486, 1403, 1357, 1295, 1227, 1174, 1127, 1007, 858, 789, 757 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{27}\text{H}_{25}\text{ClNO}_3(\text{M} + \text{H})^+$ 446.1517, found 446.1520.

(8R*,14aR*)-10-Bromo-2,3-dimethoxy-8-(phenylethynyl)-6,8,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-a]isoquinoline (75e):

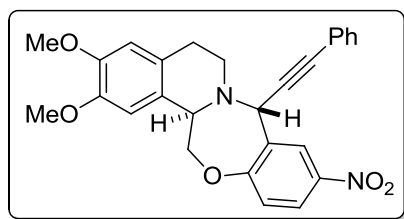
Brown semi solid; R_f (hexane/EtOAc 4:1) 0.52; yield 122 mg, 83%; $^1\text{H NMR}$ (600 MHz,



CDCl_3): δ 7.35-7.33 (m, 2 H), 7.31 (d, $J = 7.8$ Hz, 1 H), 7.25 (d, $J = 8.4$ Hz, 1 H), 7.18-7.16 (m, 3 H), 6.86 (d, $J = 9.0$ Hz, 1 H), 6.58 (s, 1 H), 6.49 (s, 1 H), 4.98 (d, $J = 10.2$ Hz, 1 H), 4.86 (s, 1 H), 4.30 (d, $J = 13.2$ Hz, 1 H), 3.89 (dd, $J = 13.2$ &

3.0 Hz, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 2.93-2.87 (m, 1 H), 2.83-2.74 (m, 2 H), 2.68-2.64 (m, 1 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 157.7, 148.2, 147.4, 134.6, 132.5, 132.3, 132.0, 128.4, 128.3, 127.4, 125.5, 123.7, 122.9, 116.4, 111.5, 110.3, 86.9, 85.8, 73.4, 61.4, 58.8, 56.1, 55.9, 45.4, 29.4; **IR** (KBr, neat) 3055, 2999, 2931, 2843, 1572, 1520, 1411, 1385, 1336, 1296, 1171, 1126, 1070, 1006, 901, 875, 787, 692 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{27}\text{H}_{25}\text{BrNO}_3(\text{M} + \text{H})^+$ 490.1012, found 490.1016.

(8R*,14aR*)-2,3-Dimethoxy-10-nitro-8-(phenylethynyl)-6,8,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-a]isoquinoline (75f):



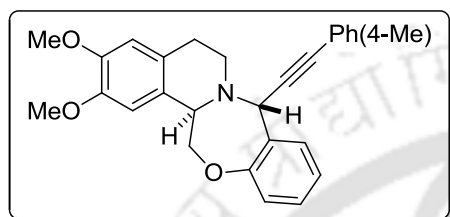
Brown solid; mp 125-127 °C; R_f (hexane/EtOAc 4:1) 0.48; yield 110 mg, 81%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 8.15 (s, 1 H), 8.07 (d, $J = 8.4$ Hz, 1 H), 7.36-7.34 (m, 2 H), 7.21-7.19 (m, 3 H), 7.09 (d, $J = 9.0$ Hz, 1 H), 6.62 (s, 1 H), 6.52 (s, 1 H), 5.01 (s, 1 H), 4.98 (d, $J = 9.6$ Hz, 1 H), 4.46 (d, $J =$

13.2 Hz, 1 H), 4.01 (dd, $J = 13.2$ & 3.6 Hz, 1 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 2.93-2.87 (m, 3 H), 2.75-2.71 (m, 1 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 164.0, 148.4, 147.5, 143.7, 133.4, 132.0, 128.7, 128.4, 127.6, 125.7, 125.3, 125.1, 122.8, 122.6, 111.7, 110.2, 87.7, 84.9, 74.5,

61.7, 58.7, 56.2, 56.0, 46.3, 29.5; **IR** (KBr, neat) 3063, 2931, 2835, 1589, 1521, 1488, 1413, 1344, 1256, 1127, 1091, 1001, 918, 847, 757 3061, 2999, 2892, 2835, 1608, 1514, 1487, 1413, 1356, 1262, 1125, 1011, 857, 818, 736 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{27}\text{H}_{25}\text{N}_2\text{O}_5$ ($\text{M} + \text{H}$)⁺ 457.1758, found 457.1769.

(8R*,14aR*)-2,3-dimethoxy-8-(*p*-tolylethynyl)-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-*a*]isoquinoline (75g):

Brown solid; mp 142-144 °C; R_f (hexane/EtOAc 4:1) 0.52; yield 107 mg, 84%; **¹H NMR** (400

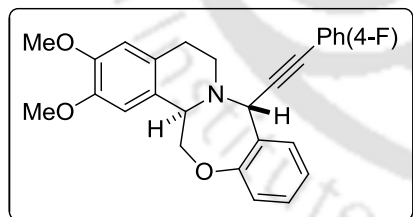


MHz, CDCl_3): δ 7.33 (d, J = 8.0 Hz, 2 H), 7.27-7.22 (m, 2 H), 7.09-7.04 (m, 4 H), 6.68 (s, 1 H), 6.57 (s, 1 H), 5.08 (d, J = 10.0 Hz, 1 H), 5.01 (s, 1 H), 4.40 (d, J = 12.8 Hz, 1 H), 4.02 (dd, J = 10.0 & 2.8 Hz, 1 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.04-2.97 (m, 1 H), 2.96-2.83 (m, 2 H), 2.78-

2.72 (m, 1 H), 2.30 (s, 3 H); **¹³C NMR** (100 MHz, CDCl_3): δ 158.6, 148.1, 147.3, 138.3, 132.5, 131.9, 130.0, 129.5, 129.0, 127.5, 125.9, 124.0, 121.8, 111.6, 110.4, 86.7, 85.8, 73.4, 61.9, 59.0, 56.1, 56.0, 45.5, 29.4, 21.6; **IR** (KBr, neat) 3033, 2999, 2929, 2835, 1608, 1509, 1464, 1413, 1356, 1262, 1180, 1125, 1043, 1011, 942, 857, 818, 736 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{28}\text{H}_{28}\text{NO}_3$ ($\text{M} + \text{H}$)⁺ 426.2064, found 456.2065.

(8R*,14aR*)-8-((4-Fluorophenyl)ethynyl)-2,3-dimethoxy-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-*a*]isoquinoline (75h):

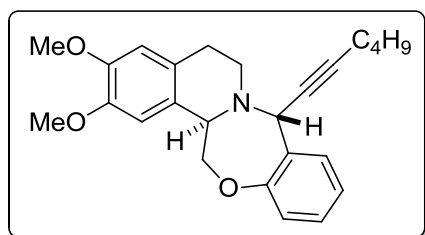
Brown solid; mp 159-161 °C; R_f (hexane/EtOAc 4:1) 0.51; yield 105 mg, 82%; **¹H NMR**



(600 MHz, CDCl_3): δ 7.41-7.39 (s, 2 H), 7.27 (d, J = 7.2 Hz, 2 H), 7.09-7.06 (m, 2 H), 6.94 (m, 2 H), 6.68 (s, 1 H), 6.57 (s, 1 H), 5.06 (d, J = 10.2 Hz, 1 H), 5.01 (s, 1 H), 4.40 (d, J = 12.6 Hz, 1 H), 4.02 (dd, J = 12.6 & 3.6 Hz, 1 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.03-2.98 (m, 1 H), 2.93-2.83 (m, 2 H),

2.77-2.73 (m, 1 H); **¹³C NMR** (150 MHz, CDCl_3): δ 163.4, 161.7, 158.6, 148.1, 147.3, 133.9, 133.8, 132.4, 130.0, 129.7, 127.5, 125.8, 124.1, 121.9, 119.2, 115.6, 115.4, 111.5, 110.3, 86.3, 85.5, 73.3, 61.8, 59.0, 56.1, 56.0, 45.4, 29.5; **IR** (KBr, neat) 3059, 3001, 2931, 2835, 1601, 1507, 1452, 1384, 1356, 1261, 1179, 1155, 1044, 1010, 899, 797, 736 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{27}\text{H}_{25}\text{FNO}_3$ ($\text{M} + \text{H}$)⁺ 430.1813, found 430.1804.

(8R*,14aR*)-8-(Hex-1-yn-1-yl)-2,3-dimethoxy-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-*a*]isoquinoline (75i):

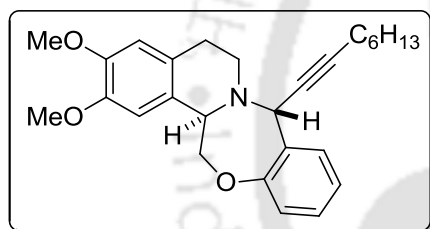


Brown solid; mp 110-112 °C; R_f (hexane/EtOAc 4:1) 0.56; yield 97 mg, 83%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.23 (d, $J = 8.4$ Hz, 2 H), 7.03 (t, $J = 7.6$ Hz, 2 H), 6.67 (s, 1 H), 6.55 (s, 1 H), 5.03 (d, $J = 10.0$ Hz, 1 H), 4.79 (s, 1 H), 4.37 (d, $J = 9.2$ Hz, 1 H), 3.98 (dd, $J = 10.0$ & 2.8 Hz, 1 H),

3.83 (s, 3 H), 3.81 (s, 3 H), 3.01-2.93 (m, 1 H), 2.87-2.67 (m, 3 H), 2.21 (t, $J = 7.2$ Hz, 2 H), 1.50-1.43 (m, 2 H), 1.40-1.31 (m, 2 H), 0.86 (t, $J = 7.2$ Hz, 3 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 158.2, 148.0, 147.2, 132.9, 129.8, 129.3, 127.5, 125.9, 123.9, 121.6, 111.4, 110.2, 87.1, 73.1, 61.4, 58.5, 56.0, 55.9, 45.2, 30.9, 29.3, 22.1, 18.8, 13.7; **IR** (KBr, neat) 3059, 2998, 2930, 2858, 2853, 1581, 1519, 1465, 1384, 1357, 1295, 1219, 1122, 1045, 1012, 898, 856, 765, 702 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{30}\text{NO}_3$ ($M + \text{H}$) $^+$ 392.2220, found 392.2219.

(8R*,14aR*)-2,3-Dimethoxy-8-(oct-1-yn-1-yl)-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-a]isoquinoline (75j):

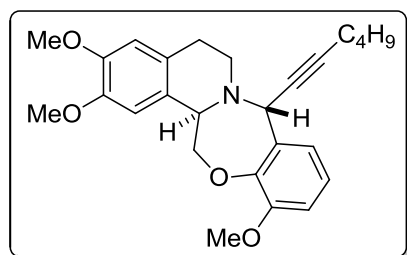
Yellow solid; mp 95-97 °C; R_f (hexane/EtOAc 4:1) 0.56; yield 103 mg, 82%; $^1\text{H NMR}$ (400



MHz, CDCl_3): δ 7.22 (d, $J = 7.6$ Hz, 2 H), 7.04 (t, $J = 8.0$ Hz, 2 H), 6.67 (s, 1 H), 6.56 (s, 1 H), 5.03 (d, $J = 10.0$ Hz, 1 H), 4.80 (s, 1 H), 4.37 (d, $J = 13.2$ Hz, 1 H), 3.98 (dd, $J = 12.8$ & 2.8 Hz, 1 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.01-2.93 (m, 1 H), 2.88-2.68 (m, 3 H), 2.21 (t, $J = 7.2$ Hz,

2 H), 1.52-1.45 (m, 2 H), 1.39-1.29 (m, 2 H), 1.27-1.21 (s, 4 H), 0.85 (t, $J = 9.8$ Hz, 3 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 158.3, 148.0, 147.2, 133.0, 129.8, 129.2, 127.5, 126.0, 123.8, 121.6, 111.4, 110.2, 87.2, 73.2, 61.4, 58.6, 56.0, 55.9, 45.3, 31.4, 29.4, 28.7, 28.6, 22.7, 19.1, 14.1; **IR** (KBr, neat) 2997, 2929, 2856, 1581, 1488, 1384, 1333, 1252, 1220, 1184, 1123, 1044, 1011, 898, 856, 764 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{27}\text{H}_{34}\text{NO}_3$ ($M + \text{H}$) $^+$ 420.2533, found 420.2531.

(8R*,14aR*)-8-(Hex-1-yn-1-yl)-2,3,12-trimethoxy-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-a]isoquinoline (75k):



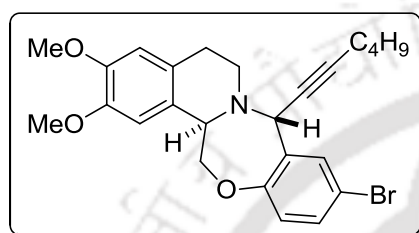
Orange solid; mp 100-102 °C; R_f (hexane/EtOAc 4:1) 0.52; yield 104 mg, 81%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 6.91 (d, $J = 8.4$ Hz, 1 H), 6.79 (d, $J = 7.2$ Hz, 1 H), 6.73 (d, $J = 7.8$ Hz, 1 H), 6.57 (s, 1 H), 6.48 (s, 1 H), 4.93 (d, $J = 9.6$ Hz, 1 H), 4.70 (s, 1 H), 4.40 (d, $J = 12.6$ Hz, 1 H), 3.69-

3.83 (m, 1 H), 3.76 (s, 6 H), 3.74 (s, 3 H), 2.90-2.85 (m, 1 H), 2.80-2.76 (m, 1 H), 2.74-2.70 (m, 1 H), 2.67-2.62 (m, 1 H), 2.13 (t, $J = 12.6$ Hz, 2 H), 1.43-1.37 (m, 2 H), 1.33-1.27 (m, 2

H), 0.79 (t, $J = 7.2$ Hz, 3 H); ^{13}C NMR (150 MHz, CDCl_3): δ 151.9, 148.0, 147.5, 147.3, 134.2, 127.6, 126.0, 123.8, 121.6, 112.3, 111.5, 110.2, 87.1, 76.8, 73.7, 61.3, 58.6, 56.3, 56.1, 55.9, 45.5, 30.9, 29.5, 22.2, 18.8, 13.7; IR (KBr, neat) 3016, 2956, 2930, 2859, 2834, 1610, 1520, 1481, 1357, 1252, 1175, 1123, 1042, 1010, 900, 832, 737 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{32}\text{BrNO}_3 (\text{M} + \text{H})^+$ 422.2326, found 422.2327.

(8R*,14aR*)-10-Bromo-8-(hex-1-yn-1-yl)-2,3-dimethoxy-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-a]isoquinoline (75l):

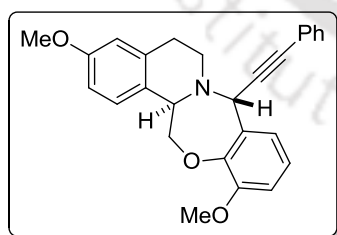
Orange solid; mp 105–107 °C; R_f (hexane/EtOAc 4:1) 0.54; yield 115 mg, 82%; ^1H NMR (600



MHz, CDCl_3): δ 7.33–7.29 (m, 2 H), 6.91 (d, $J = 8.4$ Hz, 1 H), 6.66 (s, 1 H), 6.58 (s, 1 H), 4.99 (d, $J = 10.2$ Hz, 1 H), 4.72 (s, 1 H), 4.34 (d, $J = 13.2$ Hz, 1 H), 3.92 (t, $J = 10.8$ Hz, 1 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 2.98–2.93 (m, 1 H), 2.86–2.77 (m, 1 H), 2.73–2.70 (s, 1 H), 2.22 (t, $J = 6.6$ Hz, 1 H), 1.50–1.45 (m, 2 H), 1.40–1.34 (m, 2 H), 1.29–1.23 (m, 2 H), 0.87 (t, $J = 7.8$ Hz, 3 H); ^{13}C NMR (150 MHz, CDCl_3): δ 157.5, 148.1, 147.3, 135.2, 132.4, 132.0, 127.5, 125.7, 123.5, 116.3, 111.5, 110.2, 87.7, 73.3, 61.0, 58.4, 56.1, 55.9, 45.3, 30.8, 29.4, 22.1, 18.8, 13.7; IR (KBr, neat) 3043, 2976, 2913, 2853, 1613, 1592, 1507, 1492, 1456, 1341, 1267, 1133, 1073, 972, 861, 807, 703 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{29}\text{BrNO}_3 (\text{M} + \text{H})^+$ 470.1325, found 470.1331.

(8R*,14aR*)-3,12-dimethoxy-8-(phenylethynyl)-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-a]isoquinoline (75m):

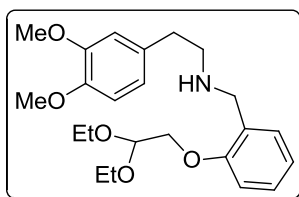
Pale yellow solid; mp 165–167 °C; R_f (hexane/EtOAc 3:1) 0.56; yield 101 mg, 82%; ^1H NMR



(600 MHz, CDCl_3): δ 7.35–7.23 (m, 2 H), 7.16–7.13 (m, 3 H), 7.02 (d, $J = 9.0$ Hz, 1 H), 6.92 (t, $J = 7.8$ Hz, 1 H), 6.77 (t, $J = 7.8$ Hz, 2 H), 6.64 (d, $J = 8.4$ Hz, 1 H), 6.52 (s, 1 H), 5.03 (d, $J = 9.6$ Hz, 1 H), 4.92 (s, 1 H), 4.39 (d, $J = 11.4$ Hz, 1 H), 3.86 (t, $J = 10.8$ Hz, 1 H), 3.74 (s, 3 H), 3.65 (s, 1 H), 2.98–2.92 (m, 1 H), 2.85–2.76 (m, 1 H), 2.73–2.69 (m, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 158.3, 152.0, 147.6, 136.6, 133.6, 132.0, 128.5, 128.2, 126.2, 123.9, 123.2, 121.6, 113.5, 112.4, 112.2, 86.5, 86.3, 73.6, 61.6, 58.7, 56.2, 55.3, 45.4, 30.2; IR (KBr, neat) 2998, 2924, 2853, 2835, 1610, 1584, 1503, 1487, 1442, 1386, 1336, 1265, 1121, 1136, 1082, 934, 813, 756, 692 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{26}\text{NO}_3 (\text{M} + \text{H})^+$ 412.1907, found 412.1906.

N-(2-(2,2-Diethoxyethoxy)benzyl)-2-(3,4-dimethoxyphenyl)ethanamine (76a):

Brown gummy oil; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.47; yield 371 mg, 91%; ^1H NMR (600 MHz,

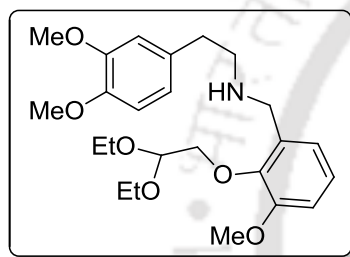


CDCl_3): δ 7.21-7.16 (m, 2 H), 6.85 (t, $J = 7.2$ Hz, 1 H), 6.77 (d, $J = 8.4$ Hz, 1 H), 6.69 (t, $J = 8.4$ Hz, 1 H), 6.23 (t, $J = 12.6$ Hz, 1 H), 6.60 (s, 1 H), 4.67 (t, $J = 5.4$ Hz, 1 H), 4.57 (brs, 1 H), 3.89 (t, $J = 4.8$ Hz, 3 H), 3.79 (d, $J = 8.4$ Hz, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H),

3.68-3.63 (m, 2 H), 3.55-3.50 (m, 2 H), 2.86-2.78 (m, 4 H), 1.15 (t, $J = 7.2$ Hz, 6 H); ^{13}C NMR (150 MHz, CDCl_3): δ 156.8, 149.1, 147.8, 131.3, 131.1, 129.6, 121.3, 120.8, 112.1, 111.7, 111.4, 100.4, 68.5, 62.9, 56.0, 55.9, 49.2, 48.3, 34.2, 15.5; IR (KBr, neat) 3451, 3062, 3027, 2976, 2930, 1603, 1589, 1495, 1454, 1375, 1347, 1290, 1245, 1125, 1070, 1029, 937, 857, 752, 701cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{34}\text{NO}_5$ ($M + H$) $^+$ 404.2431, found 404.2436.

N-(2-(2,2-Diethoxyethoxy)-3-methoxybenzyl)-2-(3,4-dimethoxyphenyl)ethanamine (76b):

Orange gummy oil; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.49; yield 376 mg, 87%; ^1H NMR (600 MHz,

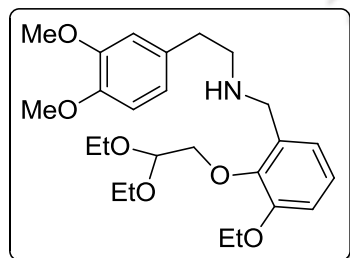


CDCl_3): δ 6.82-6.78 (m, 1 H), 6.69 (d, $J = 7.8$ Hz, 1 H), 6.64 (t, $J = 6.0$ Hz, 1 H), 6.61-6.58 (m, 1 H), 6.57-6.54 (m, 2 H), 4.61 (t, $J = 6.0$ Hz, 1 H), 3.88 (d, $J = 4.8$ Hz, 2 H), 3.75 (s, 2 H), 3.65 (s, 3 H), 3.63 (s, 6 H), 3.56-3.54 (m, 2 H), 3.44-3.40 (m, 2 H), 3.27 (brs, 1 H), 2.69-2.63 (m, 4 H), 1.07 (t, $J = 7.8$ Hz, 6 H); ^{13}C

NMR (150 MHz, CDCl_3): δ 151.8, 148.4, 146.9, 145.7, 132.1, 131.9, 123.4, 121.6, 120.2, 111.5, 111.2, 110.9, 100.4, 72.1, 61.8, 55.4, 55.3, 55.2, 49.7, 48.1, 35.0, 14.9; IR (KBr, neat) 3440, 2974, 2935, 2836, 1588, 1517, 1418, 1374, 1263, 1140, 1069, 1028, 944, 852, 750cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{36}\text{NO}_6$ ($M + H$) $^+$ 434.2537, found 434.2535.

N-(2-(2,2-Diethoxyethoxy)-3-ethoxybenzyl)-2-(3,4-dimethoxyphenyl)ethanamine (76c):

Brown gummy oil; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.51; yield 384 mg, 86%; ^1H NMR (600 MHz,

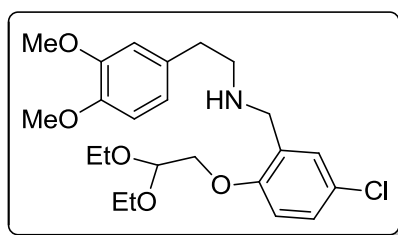


CDCl_3): δ 6.84-6.80 (m, 1 H), 6.72 (d, $J = 7.2$ Hz, 1 H), 6.67 (t, $J = 6.0$ Hz, 1 H), 6.64-6.21 (m, 1 H), 6.61-6.658 (m, 2 H), 4.67 (t, $J = 4.8\text{Hz}$, 1 H), 3.94 (t, $J = 4.2$ Hz, 2 H), 3.90-3.86 (m, 2 H), 3.79 (s, 2 H), 3.70-3.68 (m, 6 H), 3.60-3.58 (m, 1 H), 3.48-3.45 (m, 4 H), 2.73-2.68 (m, 4 H), 1.30 (t, $J = 8.4$ Hz, 3 H), 1.10 (t, J

$= 7.2$ Hz, 6 H); ^{13}C NMR (150 MHz, CDCl_3): δ 151.1, 148.5, 147.1, 146.0, 131.9, 131.8, 123.5, 121.7, 120.3, 112.4, 111.6, 111.0, 100.5, 72.1, 63.7, 61.8, 55.5, 55.4, 49.7, 48.2, 35.0, 15.1, 14.6; IR (KBr, neat) 3416, 2976, 2933, 2834, 1588, 1519, 1469, 1393, 1262, 1213, 1140, 946, 852, 752cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{38}\text{NO}_6$ ($M + H$) $^+$ 448.2694, found 448.2708.

N-(5-Chloro-2-(2,2-diethoxyethoxy)benzyl)-2-(3,4-dimethoxyphenyl)ethanamine (76d):

Pale yellow gummy oil; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.52; yield 388 mg, 89%; $^1\text{H NMR}$ (600

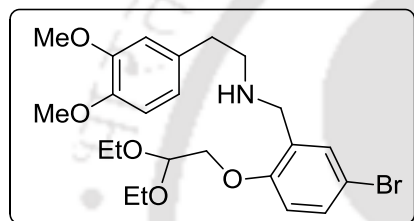


MHz, CDCl_3): δ 7.14 (s, 1 H), 6.85 (d, $J = 7.2$ Hz, 1 H), 6.74 (d, $J = 7$ Hz, 1 H), 6.71-6.65 (m, 3 H), 4.65 (t, $J = 6.0$ Hz, 1 H), 3.88-3.86 (m, 2 H), 3.80 (s, 6 H), 3.75 (s, 2 H), 3.71-3.65 (s, 2 H), 3.57-3.52 (m, 2 H), 2.80-2.71 (m, 5 H), 1.18 (t, $J = 7.8$ Hz, 6 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 155.2, 148.9,

147.5, 132.4, 129.9, 129.7, 127.9, 125.7, 120.6, 112.6, 111.9, 111.3, 100.4, 68.8, 62.8, 55.9, 55.8, 50.1, 48.7, 35.7, 15.4; **IR** (KBr, neat) 3439, 2975, 2932, 2834, 1592, 1518, 1491, 1417, 1374, 1236, 1182, 1029, 943, 877, 806, 763 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{23}\text{H}_{33}\text{ClNO}_5$ ($\text{M} + \text{H}$) $^+$ 438.2402, found 438.2050.

***N*-(5-Bromo-2-((2,2-diethoxyethoxy)methyl)phenyl)-2-(3,4-dimethoxyphenyl)ethanamine (76e):**

Yellow gummy oil; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.52; yield 428 mg, 89%; $^1\text{H NMR}$ (600 MHz,

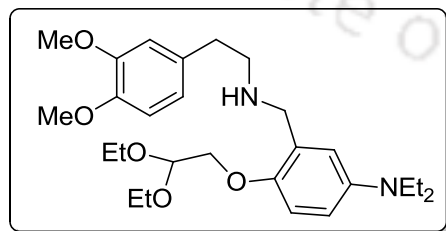


CDCl_3): δ 7.30 (s, 1 H), 7.24 (d, $J = 8.4$ Hz, 1 H), 6.74 (d, $J = 7.8$ Hz, 1 H), 6.66-6.63 (m, 3 H), 4.66 (t, $J = 6.0$ Hz, 1 H), 3.87-3.83 (m, 2 H), 3.80-3.72 (m, 8 H), 3.69-3.64 (m, 3 H), 3.56-3.50 (m, 2 H), 2.82-2.69 (m, 4 H), 1.17 (t, $J = 6.6$ Hz, 6 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 155.7, 148.9,

147.5, 132.8, 131.9, 131.3, 129.0, 120.6, 113.1, 111.9, 111.3, 100.2, 68.6, 62.7, 55.8, 55.7, 49.8, 48.2, 35.1, 15.4; **IR** (KBr, neat) 3440, 2975, 2933, 2834, 1591, 1518, 1487, 1417, 1374, 1236, 1132, 1070, 942, 854, 806, 735 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{23}\text{H}_{33}\text{BrNO}_5$ ($\text{M} + \text{H}$) $^+$ 482.1537, found 482.1518.

4-(2,2-Diethoxyethoxy)-3-(((3,4-dimethoxyphenethyl)amino)methyl)-*N,N*-diethylaniline (76f):

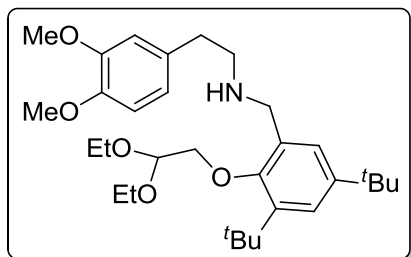
Brown gummy oil; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.48; yield 379 mg, 80%; $^1\text{H NMR}$ (600 MHz,



CDCl_3): δ 7.04 (d, $J = 8.4$ Hz, 1 H), 6.64-6.59 (m, 3 H), 6.09 (d, $J = 8.4$ Hz, 1 H), 5.99 (s, 1 H), 5.75 (brs, 1 H), 4.68 (t, $J = 4.8$ Hz, 1 H), 3.86-3.79 (s, 4 H), 3.69 (s, 6 H), 3.64-3.58 (m, 2 H), 3.52-3.46 (m, 2 H), 3.18-3.14 (m, 4 H), 2.85 (s, 4 H), 1.10 (t, $J = 8.4$ Hz, 6 H), 0.99 (t, $J = 7.2$

Hz, 6 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 157.9, 149.3, 148.7, 147.4, 132.1, 130.6, 120.5, 111.8, 111.1, 108.4, 104.1, 100.2, 95.2, 68.0, 62.6, 55.6, 55.5, 47.8, 46.6, 44.2, 33.0, 15.2, 12.3; **IR** (KBr, neat) 3472, 2974, 2834, 1620, 1556, 1520, 1464, 1376, 1356, 1260, 1209, 1122, 1066, 1026, 963, 853, 808, 765 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{27}\text{H}_{43}\text{N}_2\text{O}_5$ ($\text{M} + \text{H}$) $^+$ 475.3166, found 475.3161.

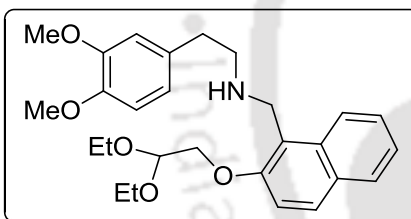
***N*-(3,5-Di-*tert*-butyl-2-(2,2-diethoxyethoxy)benzyl)-2-(3,4-dimethoxyphenyl)ethanamine (76g):**



Pale yellow gummy oil; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.50; yield 396 mg, 77%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.25 (s, 1 H), 7.13 (s, 1 H), 6.79 (d, $J = 8.4$ Hz, 1 H), 6.74 (d, $J = 9.6$ Hz, 2 H), 4.81 (t, $J = 4.8$ Hz, 1 H), 3.93-3.91 (m, 4 H), 3.85 (s, 6 H), 3.79-3.75 (m, 2 H), 3.66-3.61 (m, 2 H), 2.88-2.86 (m, 2 H), 2.81-2.77 (m, 2 H), 1.18 (brs, 1 H), 1.41 (s, 9 H), 1.28 (s, 9 H), 1.25 (t, $J = 7.2$ Hz, 6 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 153.7, 149.0, 147.6, 146.1, 142.1, 132.7, 132.3, 125.4, 120.7, 112.2, 111.5, 101.6, 74.4, 63.2, 56.1, 55.9, 50.8, 49.5, 35.9, 35.5, 34.6, 31.7, 31.4, 15.6; **IR** (KBr, neat) 3425, 2982, 2945, 2834, 1588, 1520, 1456, 1337, 1264, 1184, 1104, 1073, 945, 842, 834, 756 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{31}\text{H}_{50}\text{NO}_5$ ($M + \text{H}$) $^+$ 516.3684, found 516.3682.

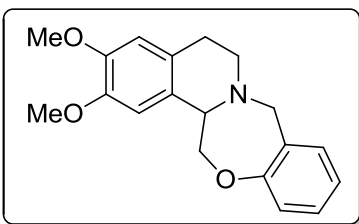
***N*-((2-(2,2-Diethoxyethoxy)naphthalen-1-yl)methyl)-2-(3,4-dimethoxyphenyl)ethanamine (76h):**

Brown gummy oil; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.51; yield 380 mg, 84%; $^1\text{H NMR}$ (600 MHz,



CDCl_3): δ 7.921 (d, $J = 9.0$ Hz, 1 H), 7.68 (d, $J = 8.4$ Hz, 2 H), 7.39 (t, $J = 7.2$ Hz, 1 H), 7.25 (t, $J = 7.2$ Hz, 1 H), 7.15 (d, $J = 9.0$ Hz, 1 H), 6.64 (d, $J = 8.4$ Hz, 1 H), 6.61 (d, $J = 8.4$ Hz, 1 H), 6.57 (s, 1 H), 4.67 (t, $J = 4.8$ Hz, 1 H), 4.29 (s, 2 H), 4.06 (d, $J = 5.4$ Hz, 2 H), 3.74 (s, 3 H), 3.72-3.67 (m, 6 H), 3.59-3.54 (m, 2 H), 2.90 (t, $J = 7.2$ Hz, 2 H), 2.75 (d, $J = 7.2$ Hz, 2 H), 1.19 (d, $J = 7.2$ Hz, 6 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 154.1, 148.6, 147.2, 133.0, 131.8, 129.4, 129.1, 128.4, 126.8, 123.5, 122.7, 120.4, 119.5, 113.8, 111.7, 111.0, 100.4, 69.3, 62.6, 55.6, 55.5, 50.0, 42.6, 34.9, 15.2; **IR** (KBr, neat) 3418, 2975, 2934, 2834, 1594, 1518, 1464, 1347, 1236, 1184, 1063, 1027, 945, 855, 807, 750 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{27}\text{H}_{36}\text{NO}_5$ ($M + \text{H}$) $^+$ 454.2588, found 454.2587.

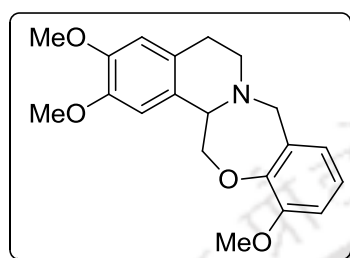
2,3-Dimethoxy-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-a]isoquinoline (77a):



Brown semi solid; R_f (hexane/EtOAc 3:2) 0.49; yield 74 mg, 80%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.23-7.19 (m, 2 H), 7.06-7.00 (m, 2 H), 6.60 (s, 1 H), 6.56 (s, 1 H), 4.54 (d, $J = 14.4$ Hz, 1 H), 4.43 (d, $J = 10.2$ Hz, 1 H), 4.27 (d, $J = 12.6$ Hz, 1 H), 3.96 (t, $J = 12.6$ Hz, 1 H), 3.90 (d, $J = 15.0$ Hz, 1 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.04-2.98 (m, 2 H), 2.78-2.73 (m, 1 H), 2.65-2.60 (m, 1H); $^{13}\text{C NMR}$ (150

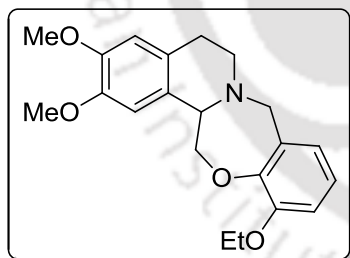
MHz, CDCl₃): δ 159.6, 148.3, 147.4, 131.6, 130.6, 129.1, 127.2, 125.5, 124.0, 120.8, 111.7, 110.2, 72.1, 63.9, 59.0, 56.2, 56.0, 43.0, 28.9; **IR** (KBr, neat) 3006, 2981, 2920, 2834, 1610, 1582, 1520, 1464, 1411, 1383, 1330, 1263, 1220, 1188, 1133, 1102, 1042, 1010, 989, 856, 735 cm⁻¹; **HRMS** (ESI) calcd. for C₁₉H₂₂NO₃ (M + H)⁺ 312.1594, found 312.1592.

2,3,12-Trimethoxy-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-a]isoquinoline (77b):



Brown semi solid; R_f (hexane/EtOAc 3:2) 0.47; yield 80 mg, 78%; **¹H NMR** (600 MHz, CDCl₃): δ 6.94 (t, J = 7.8 Hz, 1 H), 6.81 (d, J = 12.6 Hz, 1 H), 6.76 (d, J = 7.8 Hz, 1 H), 6.56 (s, 1 H), 6.52 (s, 1 H), 4.51 (d, J = 15.0 Hz, 1 H), 4.38-4.32 (m, 2 H), 3.90 (t, J = 12.6 Hz, 1 H), 3.83 (d, J = 13.8 Hz, 1 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 2.96-2.90 (m, 1 H), 2.74-2.66 (m, 2 H), 2.60-2.55 (m, 1 H); **¹³C NMR** (150 MHz, CDCl₃): δ 151.3, 148.4, 147.9, 147.1, 133.3, 127.2, 125.7, 123.7, 122.1, 111.9, 111.5, 109.9, 72.2, 63.8, 58.9, 56.1, 55.9, 55.8, 42.9, 29.0; **IR** (KBr, neat) 3021, 2927, 2834, 1611, 1584, 1520, 1486, 1411, 1383, 1357, 1270, 1134, 1070, 1011, 925, 856, 748 cm⁻¹; **HRMS** (ESI) calcd. for C₂₀H₂₄NO₄ (M + H)⁺ 342.1700, found 342.1698.

12-Ethoxy-2,3-dimethoxy-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-a]isoquinoline (77c):



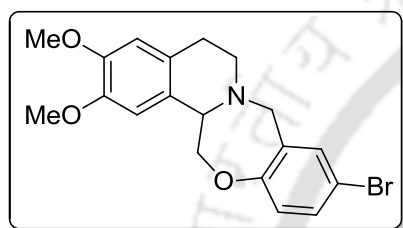
Brown semi solid; R_f (hexane/EtOAc 3:2) 0.47; yield 81 mg, 76%; **¹H NMR** (600 MHz, CDCl₃): δ 6.94 (t, J = 7.8 Hz, 1 H), 6.83 (d, J = 7.8 Hz, 1 H), 6.77 (d, J = 7.8 Hz, 1 H), 6.58 (s, 1 H), 6.54 (s, 1 H), 4.53 (d, J = 15.0 Hz, 1 H), 4.39-4.34 (m, 2 H), 4.06-4.02 (m, 2 H), 3.90 (t, J = 12.6 Hz, 1 H), 3.84 (d, J = 13.8 Hz, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 2.98-2.93 (m, 1 H), 2.76-2.69 (m, 2 H), 2.64-2.58 (m, 1 H), 1.39 (t, J = 4.8 Hz, 3 H); **¹³C NMR** (150 MHz, CDCl₃): δ 150.7, 148.9, 148.0, 147.1, 133.5, 127.3, 125.8, 123.7, 122.3, 113.6, 111.5, 110.0, 72.2, 64.7, 63.9, 59.0, 56.0, 55.9, 43.0, 29.1, 15.0; **IR** (KBr, neat) 2999, 2909, 2834, 1611, 1520, 1465, 1408, 1383, 1330, 1257, 1222, 1177, 1136, 1109, 1101, 993, 891, 775, 735, cm⁻¹; **HRMS** (ESI) calcd. for C₂₁H₂₆NO₄ (M + H)⁺ 356.1856, found 356.1858.

10-Chloro-2,3-dimethoxy-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-a]isoquinoline (77d):

Brown semi solid; R_f (hexane/EtOAc 3:2) 0.52; yield 82 mg, 79%; **¹H NMR** (600 MHz, CDCl₃): δ 7.15 (s, 1 H), 7.13 (d, J = 8.4 Hz, 1 H), 6.93 (d, J = 8.4 Hz, 1 H), 6.57 (s, 1 H), 6.55 (s, 1 H), 4.47 (d, J = 14.4 Hz, 1 H), 4.37 (d, J = 10.2 Hz, 1 H), 4.22 (d, J = 13.2 Hz, 1 H), 3.90

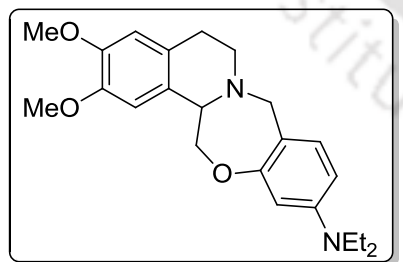
(t, $J = 13.2$ Hz, 1H), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.78 (d, $J = 15.0$ Hz, 1 H), 2.99-2.93 (m, 1 H), 2.75-2.68 (m, 2 H), 2.64-2.59 (m, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 158.2, 148.2, 147.3, 134.0, 130.1, 128.8, 128.6, 127.3, 125.5, 122.1, 111.6, 110.1, 72.2, 63.7, 58.7, 56.1, 55.9, 42.9, 29.0; **IR** (KBr, neat) 3000, 2909, 2834, 1520, 1465, 1383, 1330, 1257, 1222, 1177, 1136, 1070, 1101, 928, 891, 829, 775, 735 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{ClNO}_3$ ($\text{M} + \text{H}$) $^+$ 346.1204, found 346.1200.

10-Bromo-2,3-dimethoxy-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-a]isoquinoline (77e):



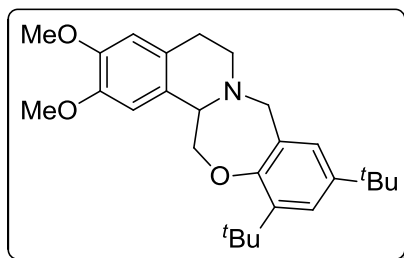
Pale yellow semi solid; R_f (hexane/EtOAc 3:2) 0.52; yield 89 mg, 76%; ^1H NMR (600 MHz, CDCl_3): δ 7.32 (s, 1 H), 7.30 (d, $J = 8.4$ Hz, 1 H), 6.89 (d, $J = 8.4$ Hz, 1 H), 6.58 (s, 1 H), 6.57 (s, 1 H), 4.49 (d, $J = 15.0$ Hz, 1 H), 4.37 (d, $J = 10.2$ Hz, 1 H), 4.24 (d, $J = 13.2$ Hz, 1 H), 3.94-3.91 (m, 1 H), 3.87-3.78 (s, 1 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 2.99-2.94 (m, 1 H), 2.78-2.69 (m, 2 H), 2.65-2.61 (m, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 158.8, 148.3, 147.3, 134.6, 133.1, 131.7, 127.4, 125.6, 122.7, 116.5, 111.7, 110.2, 72.2, 63.8, 58.8, 56.2, 56.0, 43.1, 29.1; **IR** (KBr, neat) 3026, 3000, 2929, 2834, 1610, 1519, 1479, 1383, 13358, 1258, 1136, 1109, 1072, 1011, 863, 826, 751 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{BrNO}_3$ ($\text{M} + \text{H}$) $^+$ 390.0699, found 390.0702.

***N,N*-Diethyl-2,3-dimethoxy-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-a]isoquinolin-10-amine (77f):**



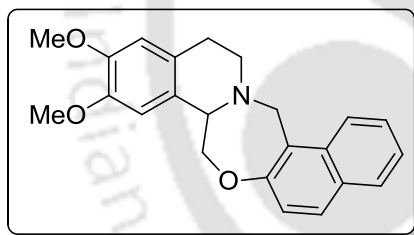
Brown semi solid; R_f (hexane/EtOAc 7:3) 0.45; yield 86 mg, 75%; ^1H NMR (600 MHz, CDCl_3): δ 7.01 (d, $J = 8.4$ Hz, 1 H), 6.61 (s, 1 H), 6.56 (s, 1 H), 6.36 (s, 1 H), 6.35 (d, $J = 7.8$ Hz, 1 H), 4.52 (d, $J = 15.0$ Hz, 1 H), 4.37 (d, $J = 10.2$ Hz, 1 H), 4.21 (d, $J = 13.2$ Hz, 1 H), 4.00 (d, $J = 13.2$ Hz, 1 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.77 (d, $J = 15.0$ Hz, 1 H), 3.33-3.26 (m, 4 H), 3.01-2.95 (m, 1 H), 2.83-2.78 (m, 1 H), 2.71-2.68 (s, 1 H), 2.65-2.61 (m, 1 H), 1.14 (t, $J = 6.6$ Hz, 6 H); ^{13}C NMR (150 MHz, CDCl_3): δ 160.7, 148.9, 148.1, 147.2, 131.2, 127.5, 126.2, 118.1, 111.6, 110.3, 106.8, 103.9, 72.3, 64.0, 58.6, 56.1, 55.9, 44.5, 42.8, 29.1, 12.7; **IR** (KBr, neat) 2996, 2927, 2833, 1617, 1561, 1517, 1465, 1378, 1329, 1262, 1196, 1135, 1067, 1020, 991, 822, 789, 753 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{21}\text{H}_{31}\text{NO}_4$ ($\text{M} + \text{H}$) $^+$ 383.2329, found 383.2316.

10,12-Di-*tert*-butyl-2,3-dimethoxy-6,8,14,14a-tetrahydro-5H-benzo[6,7][1,4]oxazepino[3,4-*a*]isoquinoline (77g):



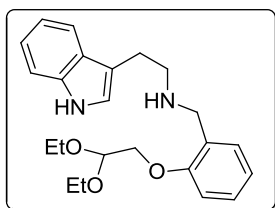
Yellow semi solid; R_f (hexane/EtOAc 7:3) 0.52; yield 96 mg, 73%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.25 (s, 1 H), 7.07 (s, 1 H), 6.65 (s, 1 H), 6.58 (s, 1 H), 4.57 (d, $J = 14.4$ Hz, 1 H), 4.44 (d, $J = 10.2$ Hz, 1 H), 4.26 (d, $J = 12.6$ Hz, 1 H), 3.89-3.81 (m, 8 H), 3.02-2.78 (m, 1 H), 2.78-2.76 (m, 2 H), 2.68-2.64 (m, 1 H), 1.39 (s, 9 H), 1.32 (s, 9 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 156.6, 148.2, 147.3, 145.7, 140.4, 132.2, 127.5, 126.1, 125.8, 123.4, 111.7, 110.2, 72.4, 63.7, 60.0, 56.2, 56.0, 43.1, 35.3, 34.6, 31.8, 30.7, 29.2; **IR** (KBr, neat) 2954, 2865, 2834, 1611, 1519, 1464, 1383, 1329, 1269, 1203, 1135, 1014, 930, 855, 757 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{27}\text{H}_{38}\text{NO}_3$ ($M + H$) 424.2846, found 424.2840.

10,11-Dimethoxy-8a,13,14,16-tetrahydro-8H-naphtho[1',2':6,7][1,4]oxazepino[3,4-*a*]isoquinoline (77h):



Orange semi solid; R_f (hexane/EtOAc 3:2) 0.49; yield 76 mg, 70%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 8.14 (d, $J = 8.4$ Hz, 1 H), 7.77 (d, $J = 8.4$ Hz, 1 H), 7.66 (d, $J = 8.4$ Hz, 1 H), 7.46 (t, $J = 7.8$ Hz, 1 H), 7.34 (t, $J = 7.8$ Hz, 1 H), 7.18 (d, $J = 8.4$ Hz, 1 H), 6.63 (s, 1 H), 6.57 (s, 1 H), 4.85 (d, $J = 15.0$ Hz, 1 H), 4.51 (d, $J = 15.0$ Hz, 1 H), 4.70 (d, $J = 10.2$ Hz, 1 H), 4.29-4.26 (m, 1 H), 3.96 (t, $J = 12.6$ Hz, 1 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 2.97-2.91 (m, 1 H), 2.81-2.77 (m, 1 H), 2.71-2.66 (m, 1 H), 2.53-2.50 (m, 1 H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 157.9, 148.2, 147.3, 133.6, 131.2, 129.3, 129.0, 127.4, 126.7, 125.9, 125.1, 124.4, 123.1, 121.5, 111.7, 110.1, 71.9, 63.7, 56.2, 56.0, 51.4, 42.7, 29.0; **IR** (KBr, neat) 2974, 2934, 2834, 1625, 1594, 1515, 1464, 1417, 1418, 1374, 1236, 1184, 1133, 1063, 945, 855, 807, 750 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{23}\text{H}_{24}\text{NO}_3$ ($M + H$) 362.1751, found 362.1751.

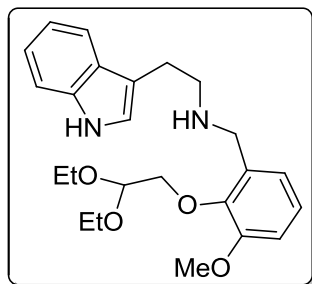
***N*-(2-(2,2-Diethoxyethoxy)benzyl)-2-(1H-indol-3-yl)ethanamine (79a):**



Orange gummy oil; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.51; yield 328 mg, 86%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 9.43 (brs, 1 H), 7.38-7.35 (m, 2 H), 7.30 (d, $J = 7.2$ Hz, 1 H), 7.20 (t, $J = 7.2$ Hz, 1 H), 7.07 (t, $J = 8.0$ Hz, 1 H), 6.97-6.92 (m, 2 H), 6.85 (t, $J = 7.2$ Hz, 1 H), 6.73 (d, $J = 8.4$ Hz, 1 H), 4.58 (t, $J = 4.8$ Hz, 1 H), 4.80 (s, 2 H), 3.80 (d, $J = 4.8$ Hz, 2 H), 3.64-3.56 (m, 2 H), 3.51-3.43 (m, 2 H), 3.17 (t, $J = 4.8$ Hz, 2 H), 3.01 (t, $J = 4.8$ Hz, 2 H), 1.14 (t, $J = 6.8$ Hz, 6 H); $^{13}\text{C NMR}$

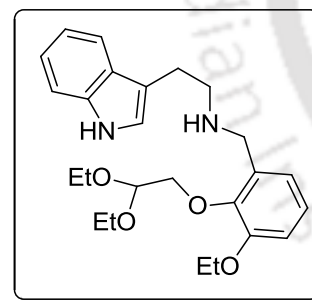
NMR (100 MHz, CDCl_3): δ 156.6, 136.5, 131.9, 130.9, 126.7, 123.4, 121.9, 121.6, 119.7, 119.3, 118.3, 111.8, 111.7, 109.7, 100.0, 68.1, 63.0, 47.0, 46.7, 22.6, 15.4; **IR** (KBr, neat) 3641, 3046, 2984, 2857, 1604, 1561, 1497, 1457, 1290, 1244, 1146, 1052, 928, 849, 746, cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{23}\text{H}_{31}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 383.2329, found 383.2325.

N-(2-(2,2-Diethoxyethoxy)-3-methoxybenzyl)-2-(1H-indol-3-yl)ethanamine (79b):



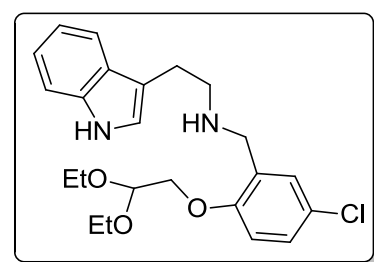
Yellow gummy oil; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.47; yield 343 mg, 83%; **^1H NMR** (600 MHz, CDCl_3): δ 9.20 (brs, 1 H), 7.41 (d, $J = 7.8$ Hz, 1 H), 7.16 (d, $J = 7.8$ Hz, 1 H), 6.98 (t, $J = 7.2$ Hz, 1 H), 6.90 (t, $J = 7.2$ Hz, 1 H), 6.79 (t, $J = 7.8$ Hz, 1 H), 6.75 (s, 1 H), 6.67 (d, $J = 7.8$ Hz, 1 H), 6.64 (d, $J = 7.8$ Hz, 1 H), 4.58 (t, $J = 4.8$ Hz, 1 H), 3.91 (d, $J = 4.8$ Hz, 2 H), 3.79 (s, 2 H), 3.65 (brs, 1 H), 3.62 (s, 3 H), 3.56-3.51 (m, 2 H), 3.43-3.37 (m, 2 H), 2.89-2.82 (m, 4 H), 1.06 (t, $J = 5.4$ Hz, 6 H); **^{13}C NMR** (150 MHz, CDCl_3): δ 152.0, 145.9, 136.4, 131.7, 127.2, 123.9, 122.4, 121.9, 121.4, 118.7, 118.4, 112.3, 111.8, 111.3, 100.8, 62.3, 55.5, 48.8, 48.4, 25.1, 15.2; **IR** (KBr, neat) 3314, 3055, 2975, 2929, 1586, 1480, 1458, 1373, 1342, 1277, 1245, 1131, 1070, 1021, 927, 782, 743 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{24}\text{H}_{33}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$)⁺ 413.2435, found 413.2443.

N-(2-(2,2-Diethoxyethoxy)-3-ethoxybenzyl)-2-(1H-indol-3-yl)ethanamine (79c):



Brown gummy oil; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.49; yield 349 mg, 83%; **^1H NMR** (600 MHz, CDCl_3): δ 9.36 (brs, 1 H), 7.41 (d, $J = 7.8$ Hz, 1 H), 7.14 (d, $J = 7.8$ Hz, 1 H), 6.97 (t, $J = 7.2$ Hz, 1 H), 6.89 (t, $J = 7.2$ Hz, 1 H), 6.75 (t, $J = 7.8$ Hz, 1 H), 6.72 (s, 1 H), 6.65 (d, $J = 7.2$ Hz, 1 H), 6.61 (d, $J = 8.4$ Hz, 1 H), 4.59 (t, $J = 4.8$ Hz, 1 H), 3.93 (d, $J = 4.8$ Hz, 2 H), 3.84-3.76 (m, 4 H), 3.62 (brs, 1 H), 3.57-3.51 (m, 2 H), 3.42-3.36 (m, 2 H), 2.90-2.79 (m, 4 H), 1.12 (t, $J = 6.6$ Hz, 3 H), 1.06 (t, $J = 5.4$ Hz, 6 H); **^{13}C NMR** (150 MHz, CDCl_3): δ 151.2, 146.0, 136.3, 131.8, 127.1, 123.7, 122.4, 121.7, 121.3, 118.6, 118.4, 112.6, 112.2, 111.3, 100.7, 72.2, 63.9, 62.1, 48.8, 48.4, 25.1, 15.2, 14.7; **IR** (KBr, neat) 3415, 3055, 2975, 2883, 1586, 1486, 1393, 1273, 1213, 1020, 954, 924, 850, 746 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{25}\text{H}_{35}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$)⁺ 427.2591, found 427.2595.

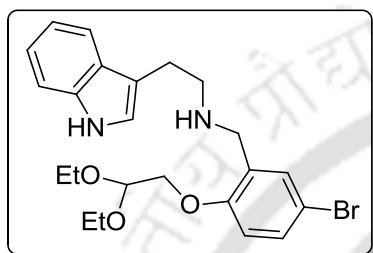
N-(5-chloro-2-(2,2-diethoxyethoxy)benzyl)-2-(1H-indol-3-yl)ethanamine (79d):



Brown gummy oil; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.50; yield 353 mg, 85%; **^1H NMR** (400 MHz, CDCl_3): δ 8.80 (brs, 1 H), 7.51 (d, $J = 7.8$ Hz, 1 H), 7.33 (d, $J = 7.8$ Hz, 1 H), 7.18-7.12 (m, 3 H), 7.06 (t, $J = 7.2$ Hz, 1 H), 6.97 (s, 1 H), 6.67 (d, $J = 8.4$ Hz, 1

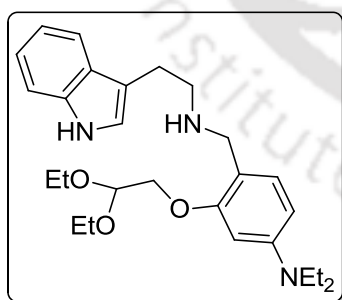
H), 4.55 (t, $J = 5.4$ Hz, 1 H), 4.47 (brs, 1 H), 3.84 (s, 2 H), 3.80 (d, $J = 4.8$ Hz, 2 H), 3.68-3.63 (m, 2 H), 3.56-3.49 (m, 2 H), 3.03 (t, $J = 7.2$ Hz, 2 H), 2.96 (t, $J = 7.2$ Hz, 2 H), 1.20 (t, $J = 7.2$ Hz, 6 H); ^{13}C NMR (150 MHz, CDCl_3): δ 155.3, 136.6, 130.2, 128.5, 127.3, 125.9, 122.7, 122.0, 119.3, 118.7, 112.7, 112.6, 111.4, 100.4, 68.8, 63.1, 48.4, 25.1, 15.5; IR (KBr, neat) 3413, 3056, 2976, 2882, 1599, 1491, 1457, 1375, 1343, 1248, 1183, 1131, 1067, 950, 878, 808, 742 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{30}\text{ClN}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 417.1939, found 417.1945.

***N*-(5-Bromo-2-(2,2-diethoxyethoxy)benzyl)-2-(1*H*-indol-3-yl)ethanamine (79e):**



Orange semi solid; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.50; yield 377 mg, 82%; ^1H NMR (400 MHz, CDCl_3): δ 8.74 (brs, 1 H), 7.41 (d, $J = 7.8$ Hz, 1 H), 7.21-7.14 (m, 3 H), 7.04 (t, $J = 7.2$ Hz, 1 H), 6.95 (t, $J = 7.8$ Hz, 1 H), 6.84 (s, 1 H), 6.51 (s, 1 H), 4.45 (t, $J = 4.8$ Hz, 1 H), 4.15 (brs, 1 H), 3.73 (s, 2 H), 3.70 (d, $J = 5.4$ Hz, 2 H), 3.56-3.53 (m, 2 H), 3.44-3.39 (m, 2 H), 2.92 (t, $J = 7.2$ Hz, 2 H), 2.86 (t, $J = 7.2$ Hz, 2 H), 1.09 (t, $J = 7.2$ Hz, 6 H); ^{13}C NMR (150 MHz, CDCl_3): δ 155.7, 136.5, 133.0, 131.5, 128.5, 127.3, 122.6, 121.9, 119.2, 118.7, 113.2, 113.1, 112.4, 111.4, 100.4, 68.7, 63.0, 62.9, 62.8, 48.5, 48.3, 25.0, 15.4; IR (KBr, neat) 3340, 3057, 2974, 2930, 1587, 1491, 1455, 1322, 1285, 1248, 1195, 1129, 1061, 1028, 920, 852, 804, 704 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{30}\text{BrN}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 461.1434, found 461.1432.

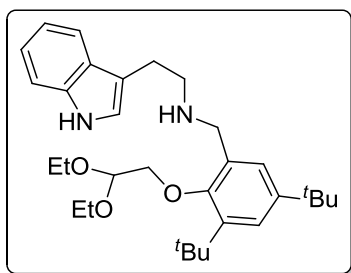
4-(((2-(1*H*-Indol-3-yl)ethyl)amino)methyl)-3-(2,2-diethoxyethoxy)-*N,N*-diethylaniline (79f):



Brown red gummy oil; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.47; yield 340 mg, 75%; ^1H NMR (600 MHz, CDCl_3): δ 9.34 (brs, 1 H), 7.43 (d, $J = 8.4$ Hz, 1 H), 7.37 (d, $J = 7.8$ Hz, 1 H), 7.11 (t, $J = 7.2$ Hz, 1 H), 7.01-6.98 (m, 3 H), 6.17 (d, $J = 8.4$ Hz, 1 H), 6.01 (s, 1 H), 4.52 (t, $J = 4.8$ Hz, 1 H), 3.93 (s, 2 H), 3.77 (d, $J = 5.4$ Hz, 2 H), 3.66-3.61 (m, 2 H), 3.54-3.49 (m, 2 H), 3.11 (t, $J = 7.2$ Hz, 2 H), 3.03 (t, $J = 7.2$ Hz, 2 H), 1.19 (t, $J = 7.2$ Hz, 6 H), 1.11 (t, $J = 7.2$ Hz, 6 H); ^{13}C NMR (150 MHz, CDCl_3): δ 157.9, 149.7, 136.6, 132.2, 127.0, 123.3, 121.9, 119.2, 118.5, 111.7, 110.8, 108.3, 104.4, 100.4, 95.6, 68.1, 63.0, 62.8, 47.7, 46.8, 44.5, 29.8, 23.6, 15.5, 15.4, 12.7, 12.6; IR (KBr, neat) 3042, 3056, 2968, 2924, 2851, 1619, 1562, 1519, 1452, 1358, 1325, 1265, 1195, 1130, 1024, 943, 873, 739 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{35}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 454.3064, found 454.3063.

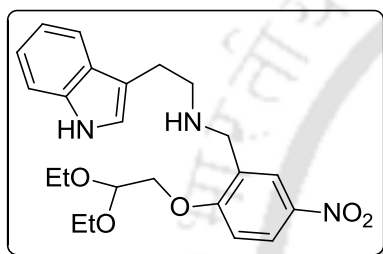
***N*-(3,5-Di-*tert*-butyl-2-(2,2-diethoxyethoxy)benzyl)-2-(1*H*-indol-3-yl)ethanamine (79g):**

Yellow gummy oil; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.47; yield 390 mg, 79%; $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 8.62 (brs, 1 H) 7.41 (d, $J = 6.6\text{ Hz}$, 1 H), 7.19 (d, $J = 8.4\text{ Hz}$, 2 H), 7.04-7.01 (m, 2 H), 6.94 (t, $J = 7.8\text{ Hz}$, 1 H), 6.85 (s, 1 H), 4.68 (t, $J = 4.8\text{ Hz}$, 1 H), 3.88 (d, $J = 7.8\text{ Hz}$, 2 H), 3.83 (m, 2 H), 3.66-3.64 (m, 2 H), 3.63-3.50 (m, 2 H), 3.48 (brs, 1 H), 2.91-2.86 (m, 4 H), 1.31 (t, $J = 2.4\text{ Hz}$, 6 H), 1.19 (s, 18 H);



$^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 153.6, 146.3, 142.2, 136.5, 131.5, 127.5, 125.7, 123.9, 122.4, 121.9, 119.2, 118.8, 113.2, 111.4, 101.5, 74.2, 63.4, 49.4, 49.2, 35.5, 34.6, 31.6, 31.4, 25.4, 15.5; **IR** (KBr, neat) 3416, 2960, 2857, 1573, 1476, 1458, 1360, 1225, 1125, 1068, 1024, 954, 826, 740 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{31}\text{H}_{47}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 495.3581, found 495.3579.

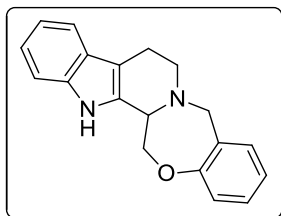
***N*-(2-(2,2-Diethoxyethoxy)-5-nitrobenzyl)-2-(1*H*-indol-3-yl)ethanamine (79h):**



Brown solid; mp 86-88 °C; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.47; yield 341 mg, 80%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.46 (brs, 1 H), 8.14 (s, 1 H), 8.08 (d, $J = 9.0\text{ Hz}$, 1 H), 7.54 (d, $J = 7.8\text{ Hz}$, 1 H), 7.33 (d, $J = 7.8\text{ Hz}$, 1 H), 7.17 (t, $J = 7.2\text{ Hz}$, 1 H), 7.06 (t, $J = 7.2\text{ Hz}$, 1 H), 7.00 (s, 1 H), 6.79 (t, $J = 9.0\text{ Hz}$, 1 H), 4.61 (t, $J = 5.4\text{ Hz}$, 1 H), 3.93 (t, $J = 5.4\text{ Hz}$, 2 H), 3.84 (s, 2 H), 3.72-3.68 (m, 2 H), 3.58-3.53 (m, 2 H), 3.00 (t, $J = 7.2\text{ Hz}$, 2 H), 2.95 (t, $J = 7.2\text{ Hz}$, 2 H), 2.10 (brs, 1 H), 1.22 (t, $J = 7.2\text{ Hz}$, 6 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 161.5, 141.4, 136.5, 129.9, 127.5, 125.1, 124.7, 122.4, 122.1, 119.3, 118.9, 113.6, 111.3, 110.8, 100.3, 69.1, 63.3, 49.1, 48.5, 25.9, 15.5; **IR** (KBr, neat) 3413, 3056, 2976, 2928, 1591, 1516, 1492, 1456, 1373, 1340, 1272, 1132, 1071, 931, 816, 744 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{23}\text{H}_{30}\text{N}_3\text{O}_5$ ($\text{M} + \text{H}$) $^+$ 428.2180, found 428.2175.

5,7,8,13,13*b*,14-Hexahydrobenzo[6',7']-[1,4]oxazepino[4',3':1,2]pyrido[3,4-*b*]indole (80a):

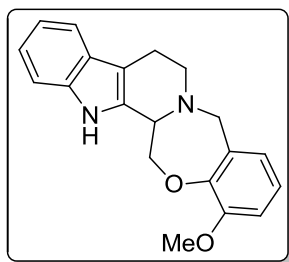
Brown solid; mp 135-137 °C; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.51; yield 77 mg, 89%; $^1\text{H NMR}$ (400



MHz, CDCl_3): δ 8.23 (brs, 1 H), 7.45 (d, $J = 7.6\text{ Hz}$, 1 H), 7.22-7.09 (m, 7 H), 4.40 (d, $J = 14.4\text{ Hz}$, 1 H), 4.37 (d, $J = 10.0\text{ Hz}$, 1 H), 4.28 (d, $J = 12.8\text{ Hz}$, 1 H), 3.94 (t, $J = 10.4\text{ Hz}$, 2 H), 2.92-2.84 (m, 3 H), 2.77-2.68 (m, 1 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 159.5, 136.4, 131.8, 130.8, 129.1, 127.1, 124.2, 122.0, 120.7, 119.5, 118.4, 111.2, 109.9, 71.9, 60.9, 59.4, 45.5, 21.8; **IR** (KBr, neat) 3041, 3057, 2923, 2851, 1583, 1488, 1362, 1325, 1221, 1162, 1100, 1043, 1010, 881, 742, 667 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 291.1492, found 291.1493.

1-Methoxy-5,7,8,13,13*b*,14-hexahydrobenzo[6',7']-[1,4]oxazepino[4',3':1,2]pyrido[3,4-*b*]indole (80b):

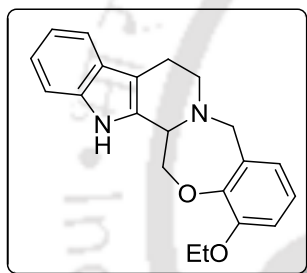
Pale yellow solid; mp 260-262 °C; R_f (CH₂Cl₂/MeOH 9:1) 0.49; yield 83 mg, 87%; ¹H NMR



(600 MHz, CDCl₃/MeOH): δ 7.36 (d, J = 7.8 Hz, 1 H), 7.25 (t, J = 7.8 Hz, 1 H), 7.06 (t, J = 7.2 Hz, 1 H), 6.98-6.93 (s, 2 H), 6.82 (d, J = 7.8 Hz, 1 H), 6.78 (d, J = 7.2 Hz, 1 H), 4.37 (t, J = 10.8 Hz, 2 H), 4.40 (d, J = 14.4 Hz, 1 H), 3.87-3.84 (m, 2 H), 3.79 (s, 3 H), 2.83-2.80 (m, 3 H), 2.74-2.69 (m, 1 H); ¹³C NMR (150 MHz, CDCl₃/MeOH): δ 151.0, 148.3, 136.5, 132.6, 130.5, 126.8, 124.1, 122.5, 121.5, 119.0, 118.0, 112.0, 111.1, 108.8, 71.8, 61.0, 58.8, 56.1, 45.6, 21.6; IR (KBr, neat) 3364, 2950, 2930, 1581, 1480, 1324, 1264, 1199, 1136, 1079, 1038, 1000, 939, 863, 778, 743, 692 cm⁻¹; HRMS (ESI) calcd. for C₂₀H₂₁N₂O₂ (M + H)⁺ 321.1598, found 321.1605.

1-Ethoxy-5,7,8,13,13b,14-hexahydrobenzo[6',7']-[1,4]oxazepino[4',3':1,2]pyrido[3,4-b]indole (80c):

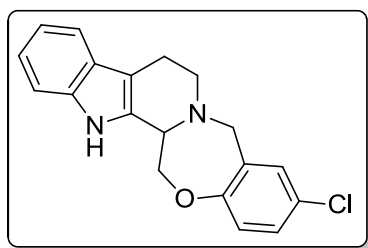
Brown solid; mp 198-200 °C; R_f (CH₂Cl₂/MeOH 9:1) 0.52; yield 84 mg, 84%; ¹H NMR (600



MHz, CDCl₃): δ 8.68 (brs, 1 H), 7.51 (d, J = 7.8 Hz, 1 H), 7.24 (d, J = 8.4 Hz, 1 H), 7.15 (t, J = 6.6 Hz, 1 H), 7.14 (t, J = 7.2 Hz, 1 H), 7.06 (t, J = 8.4 Hz, 1 H), 6.95 (d, J = 7.8 Hz, 1 H), 6.90 (d, J = 7.2 Hz, 1 H), 4.60-4.55 (m, 3 H), 4.17-4.09 (m, 2 H), 4.04 (t, J = 9.6 Hz, 1 H), 3.99 (d, J = 15.0 Hz, 1 H), 2.96 (m, 3 H), 2.84-2.79 (m, 1 H), 1.39 (t, J = 7.2 Hz, 3 H); ¹³C NMR (150 MHz, CDCl₃): δ 150.5, 148.8, 136.5, 133.5, 131.0, 127.1, 124.1, 122.6, 121.7, 119.3, 118.3, 113.7, 111.2, 109.5, 72.0, 64.9, 61.0, 59.3, 45.3, 21.9, 14.9; IR (KBr, neat) 3366, 3056, 2934, 2902, 2839, 1603, 1583, 1484, 1392, 1326, 1270, 1196, 1163, 1117, 1066, 998, 919, 889, 791, 741 cm⁻¹; HRMS (ESI) calcd. for C₂₁H₂₃N₂O₂ (M + H)⁺ 335.1754, found 335.1754.

3-Chloro-5,7,8,13,13b,14-hexahydrobenzo[6',7']-[1,4]oxazepino[4',3':1,2]pyrido[3,4-b]indole (80d):

Brown solid; mp 193-195 °C; R_f (CH₂Cl₂/MeOH 9:1) 0.53; yield 83 mg, 86%; ¹H NMR (600



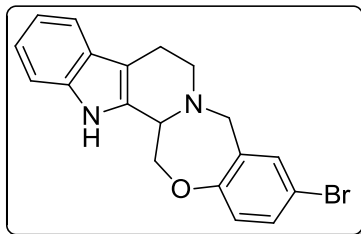
MHz, CDCl₃): δ 7.88 (brs, 1 H), 7.38 (d, J = 7.8 Hz, 1 H), 7.15 (t, J = 7.8 Hz, 1 H), 7.12 (s, 1 H), 7.08-7.05 (m, 2 H), 7.00 (t, J = 7.8 Hz, 1 H), 6.86 (d, J = 8.4 Hz, 1 H), 4.28 (t, J = 15.0 Hz, 2 H), 4.18 (d, J = 12.6 Hz, 1 H), 3.81 (t, J = 12.6 Hz, 1 H), 3.76 (d, J = 14.4 Hz, 1 H), 2.83-2.77 (m, 3 H), 2.67-2.63 (m, 1 H); ¹³C NMR (150 MHz, CDCl₃): δ 158.2, 136.4, 133.8, 130.6, 130.4, 129.0, 128.8, 127.1, 122.2, 122.1, 119.7, 118.5, 111.2, 110.1, 72.0, 60.8, 59.0, 45.5, 21.9; IR (KBr, neat) 3402, 2924,

2851, 1558, 1483, 1457, 1386, 1324, 1298, 1223, 1132, 1108, 1041, 1010, 879, 826, 742 cm^{-1} ;

HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{18}\text{ClN}_2\text{O}$ ($\text{M} + \text{H}$)⁺ 325.1102, found 325.1110.

3-Bromo-5,7,8,13,13b,14-hexahydrobenzo[6',7']-[1,4]oxazepino[4',3':1,2]pyrido[3,4-b]indole (80e):

Brown solid; mp 177-179 °C; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.53; yield 93 mg, 84%; ^1H NMR (600

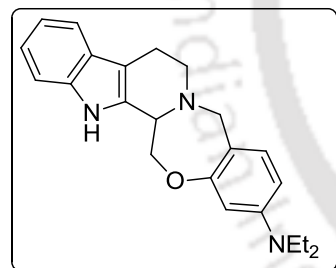


MHz, CDCl_3): δ 7.89 (brs, 1 H), 7.48 (d, $J = 7.8$ Hz, 1 H), 7.36 (s, 1 H), 7.33 (t, $J = 8.4$ Hz, 1 H), 7.28 (d, $J = 7.8$ Hz, 1 H), 7.17 (t, $J = 7.8$ Hz, 1 H), 7.09 (t, $J = 7.8$ Hz, 1 H), 6.92 (d, $J = 8.4$ Hz, 1 H), 4.43 (t, $J = 9.6$ Hz, 2 H), 4.34 (d, $J = 12.6$ Hz, 1

H), 3.39 (t, $J = 12.6$ Hz, 1 H), 3.87 (d, $J = 15.0$ Hz, 1 H), 2.91-2.86 (m, 3 H), 2.80-2.74 (m, 1 H); ^{13}C NMR (150 MHz, $\text{CDCl}_3/\text{MeOH}$): δ 158.8, 136.4, 134.4, 133.3, 131.8, 130.6, 127.2, 122.6, 122.2, 119.8, 118.5, 116.7, 111.2, 110.3, 72.1, 60.9, 59.1, 45.7, 21.9; **IR** (KBr, neat) 3401, 3056, 2925, 2850, 1594, 1482, 1457, 1362, 1325, 1251, 1178, 1134, 1010, 872, 810, 743 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{19}\text{H}_{18}\text{BrN}_2\text{O}$ ($\text{M} + \text{H}$)⁺ 369.0597, found 369.0572.

***N,N*-Diethyl-5,7,8,13,13b,14-hexahydrobenzo[6',7']-[1,4]oxazepino[4',3':1,2]pyrido[3,4-b]indol-2-amine (80f):**

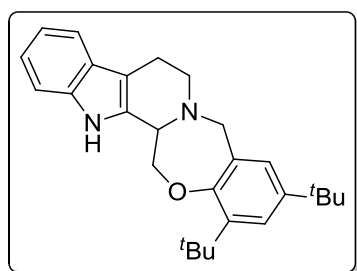
Brown semi solid; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.47; yield 88 mg, 82%; ^1H NMR (600 MHz,



CDCl_3): δ 8.22 (brs, 1 H), 7.36 (d, $J = 7.2$ Hz, 1 H), 7.12 (d, $J = 6.6$ Hz, 1 H), 7.01 (t, $J = 7.2$ Hz, 1 H), 6.95 (m, 2 H), 6.30 (s, 1 H), 6.25 (d, $J = 8.4$ Hz, 1 H), 4.28 (t, $J = 7.2$ Hz, 2 H), 4.22 (d, $J = 13.2$ Hz, 1 H), 3.90 (t, $J = 12.6$ Hz, 1 H), 3.73 (d, $J = 14.4$ Hz, 1 H), 3.23-3.19 (m, 4 H), 2.87-2.74 (m, 3 H), 2.67-2.62 (m, 1 H),

1.04 (t, $J = 6.6$ Hz, 6 H); ^{13}C NMR (150 MHz, CDCl_3): δ 160.6, 149.0, 136.4, 131.4, 131.3, 127.2, 121.8, 119.4, 118.4, 117.8, 111.2, 109.9, 107.0, 103.8, 72.0, 61.1, 58.9, 45.3, 44.5, 21.9, 12.7; **IR** (KBr, neat) 3402, 2969, 2927, 2846, 1617, 1561, 1514, 1451, 1375, 1346, 1277, 1196, 1129, 1043, 1024, 943, 872, 748 cm^{-1} ; **HRMS** (ESI) calcd. for $\text{C}_{23}\text{H}_{28}\text{N}_3\text{O}$ ($\text{M} + \text{H}$)⁺ 362.2227, found 362.2225.

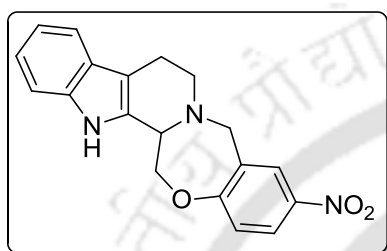
1,3-Di-*tert*-butyl-5,7,8,13,13b,14-hexahydrobenzo[6',7']-[1,4]oxazepino[4',3':1,2]pyrido[3,4-b]indole (80g):



Brown solid; mp 213-215 °C; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.52; yield 88 mg, 78%; ^1H NMR (600 MHz, CDCl_3): δ 7.89 (brs, 1 H), 7.46 (d, $J = 7.8$ Hz, 1 H), 7.29 (d, $J = 7.8$ Hz, 1 H), 7.59 (d, $J = 7.2$ Hz, 1 H), 7.14 (d, $J = 7.8$ Hz, 1 H), 7.10-7.07 (m, 2 H),

4.84-4.08 (m, 3 H), 3.89-3.83(m, 2 H), 2.95-2.88 (m, 3 H), 2.85-2.78 (m, 1 H), 1.38 (s, 9 H), 1.31 (s, 9 H); ^{13}C NMR (150 MHz, CDCl_3): δ 156.7, 145.9, 140.5, 136.4, 132.1, 131.1, 127.3, 126.0, 123.5, 122.1, 119.7, 118.5, 111.1, 110.2, 72.2, 61.1, 60.5, 46.3, 35.3, 34.7, 31.8, 30.7, 22.0; IR (KBr, neat) 3400, 3056, 2956, 2867, 1599, 1479, 1460, 1391, 3400, 3056, 2955, 2867, 1599, 1479, 1460, 1391, 1361, 1325, 1299, 1243, 1167, 1120, 1045, 1012, 924, 881, 793, 740 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{35}\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 403.2744, found 403.2754.

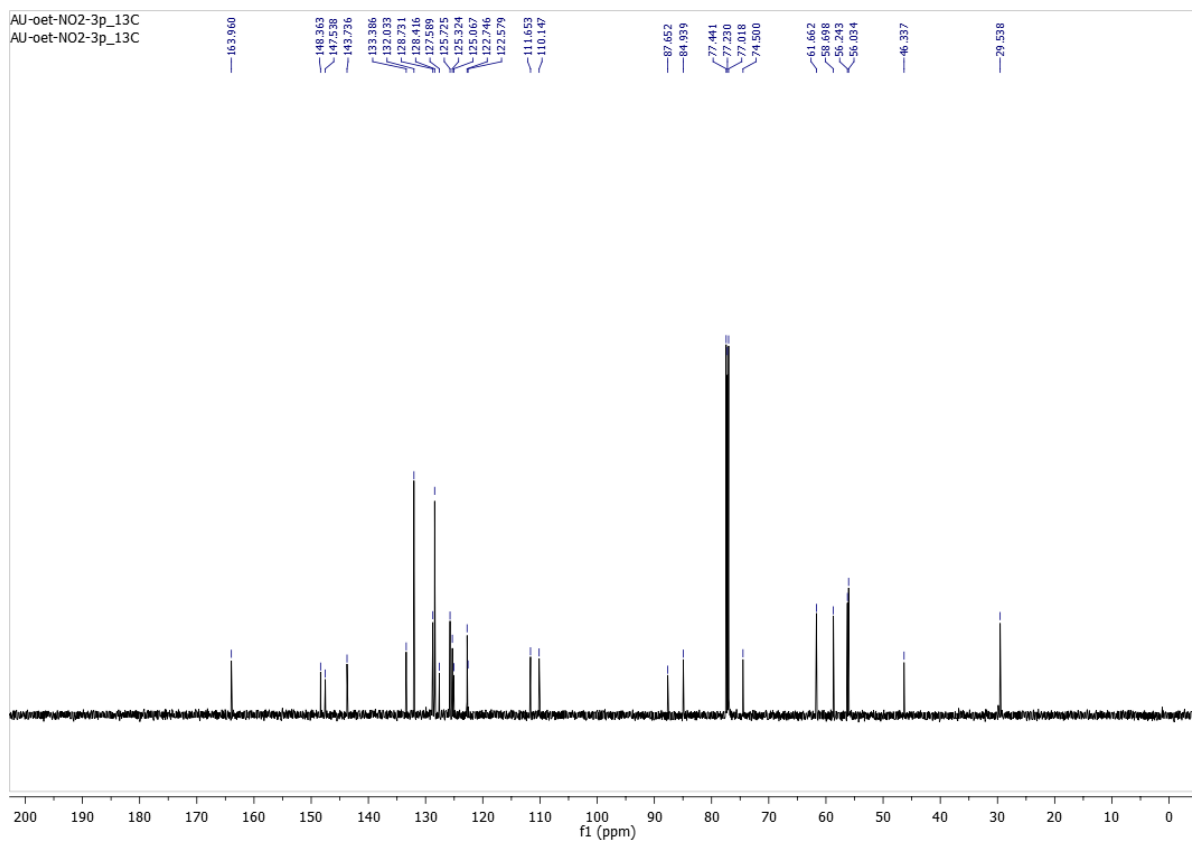
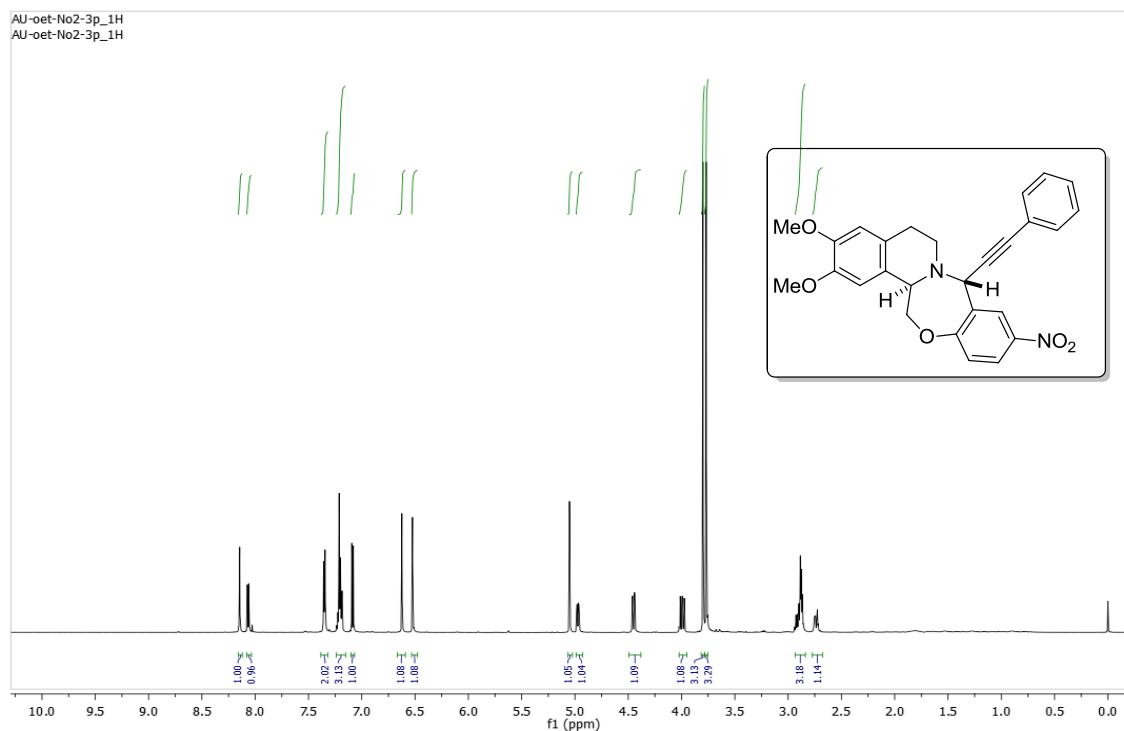
3-Nitro-5,7,8,13,13b,14-hexahydrobenzo[6',7']-[1,4]oxazepino[4',3':1,2]pyrido[3,4-b]indole(80h):



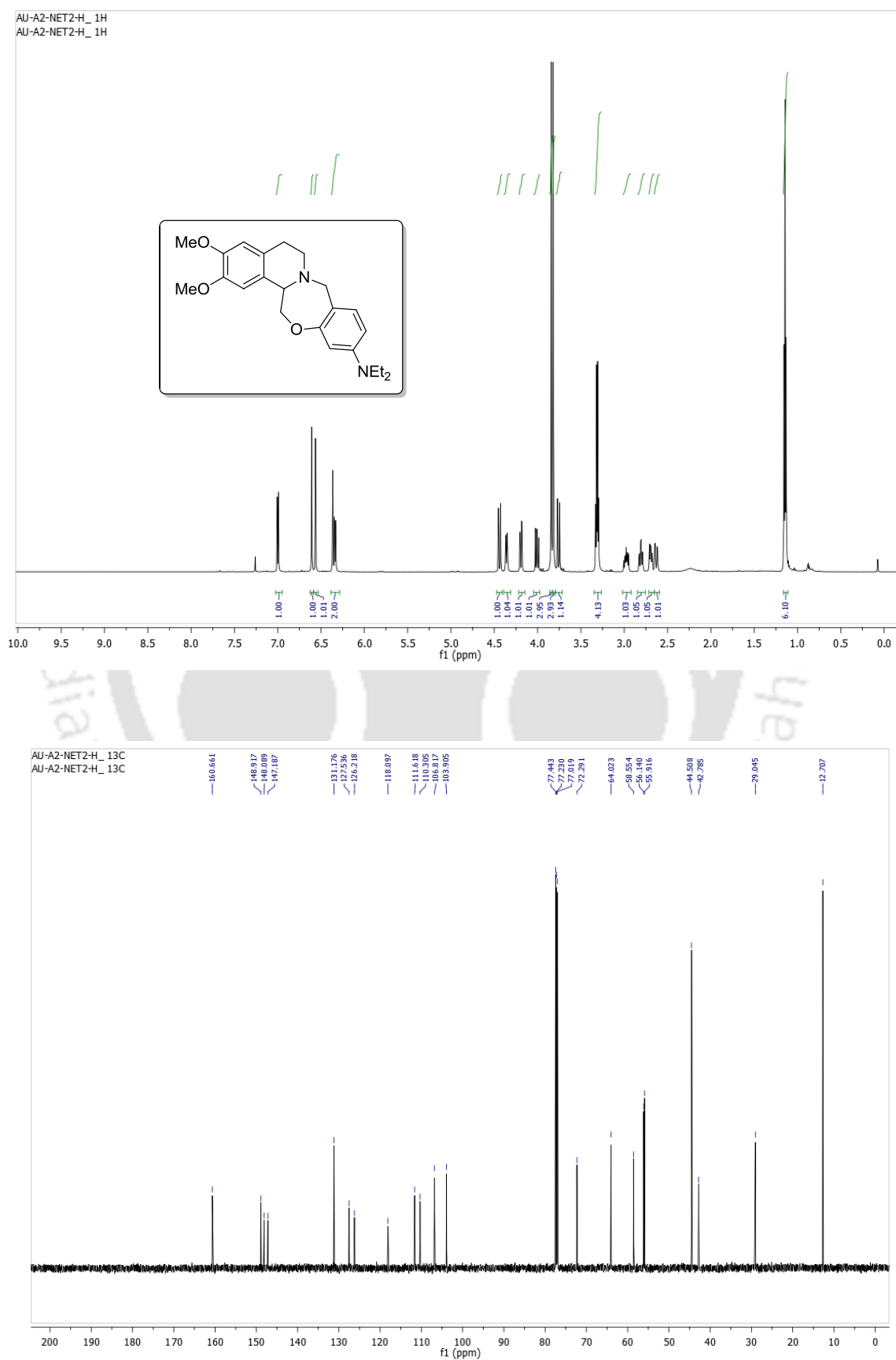
Orange solid; mp 230-232 $^{\circ}\text{C}$; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.50; yield 81 mg, 81%; ^1H NMR (600 MHz, $\text{CDCl}_3/\text{MeOH}$): δ 8.09 (s, 1 H), 8.03 (t, $J = 8.4\text{ Hz}$, 1 H), 7.38(t, $J = 7.2\text{ Hz}$, 1 H), 7.25(t, $J = 7.2\text{ Hz}$, 1 H), 7.07-7.03 (m, 2 H), 6.99-6.96 (m, 1 H), 4.53 (t, $J = 15.0\text{ Hz}$, 1 H), 4.46 (d, $J = 8.4\text{ Hz}$, 1 H), 4.29 (d, $J = 15.0\text{ Hz}$, 1 H), 3.99-3.91 (m, 2 H), 2.90 (s, 2 H), 2.84-2.74 (m, 2 H); ^{13}C NMR (150 MHz, $\text{CDCl}_3/\text{MeOH}$): δ 164.8, 143.6, 136.5, 132.2, 129.8, 126.7, 126.1, 124.8, 121.7, 121.4, 119.1, 118.1, 111.1, 72.3, 60.4, 58.4, 49.0, 48.8, 46.7, 21.3; IR (KBr, neat) 3399, 3059, 2923, 2850, 1586, 1517, 1486, 1343, 1230, 1088, 1009, 961, 826, 747 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_3\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 336.1343, found 336.1342.

5.7. Selected spectra

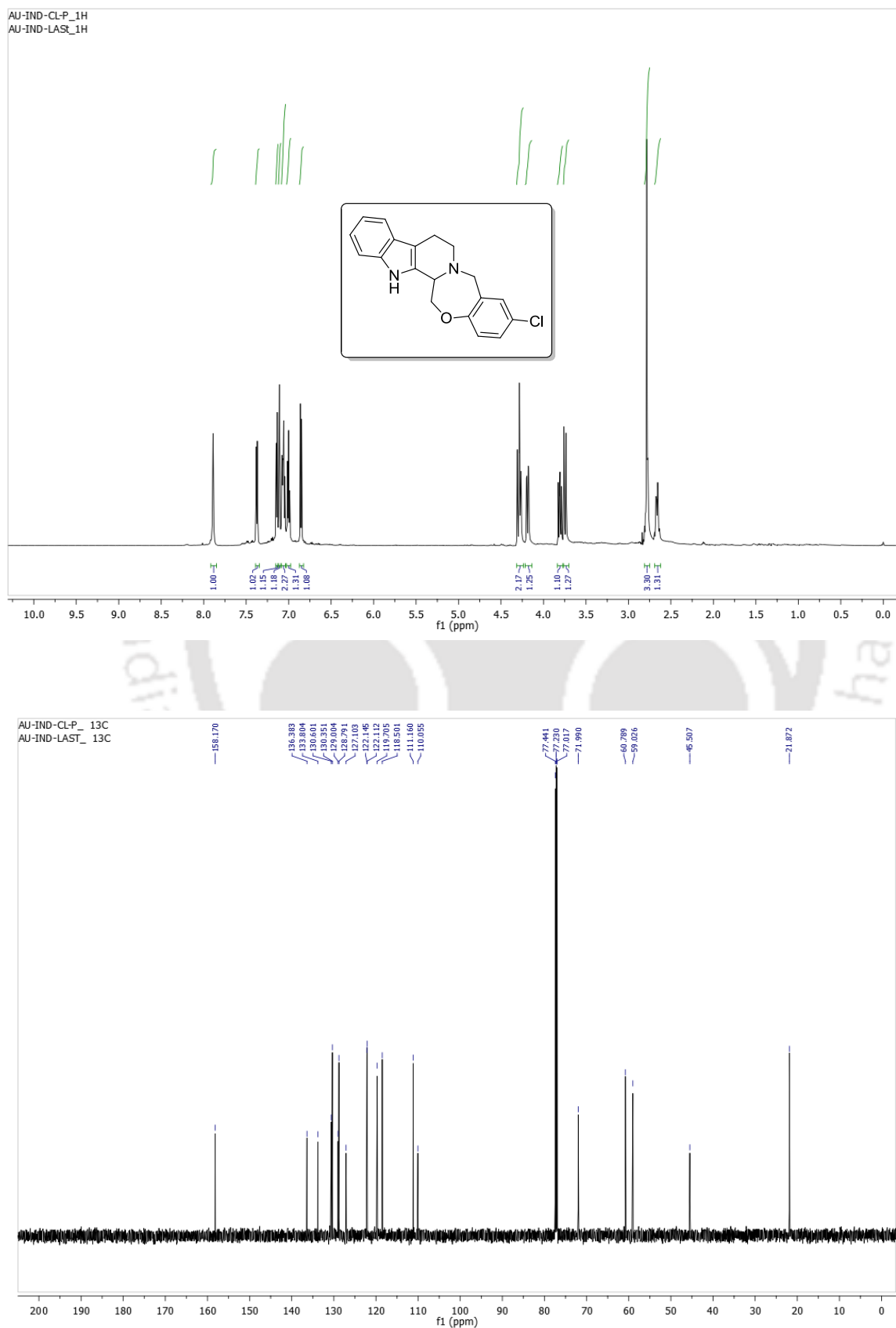
^1H , ^{13}C NMR spectra of compound **(8*R**,14*aR**)-2,3-dimethoxy-10-nitro-8-(phenylethynyl)-6,8,14,14*a*-tetrahydro-5*H*-benzo[6,7][1,4]oxazepino[3,4-*a*]isoquinoline (75f)**



^1H , ^{13}C NMR spectra of compound *N,N*-diethyl-2,3-dimethoxy-6,8,14,14a-tetrahydro-5*H*-benzo[6,7][1,4]oxazepino[3,4-*a*]isoquinolin-11-amine (77f)



^1H , ^{13}C NMR spectra of compound **3-chloro-5,7,8,13,13b,14-hexahydrobenzo[6',7']-[1,4]oxazepino[4',3':1,2]pyrido[3,4-b]indole (80d)**



5.8. Crystal parameters

The crystal parameters of compound **75a**

	CCDC 1528350
Formula	C ₂₇ H ₂₅ NO ₃
Formula weight	411.48
<i>T</i> /K	296(2)
Crystal system	Monoclinic
Space group	P 2 ₁ /n
<i>a</i> /Å	15.367(3)
<i>b</i> /Å	9.068(2)
<i>c</i> /Å	16.092(4)
α /°	90.00
β /°	108.582(14)
γ /°	90.00
<i>V</i> /Å ³	2125.5(8)
<i>Z</i>	4
Abs. Coeff./mm ⁻¹	0.083
Abs. Correction	Multi-scan
GOF on <i>F</i> ²	1.107
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> 1 = 0.0423 <i>wR</i> 2 = 0.1037
<i>R</i> indices [all data]	<i>R</i> 1 = 0.0622 <i>wR</i> 2 = 0.1144

List of Publications

1. "Intramolecular Pictet-Spengler Reaction of Cyclic Iminium Ions: A Novel Access to Benzo[1,4]oxazepine Fused Tetrahydroisoquinoline and Tetrahydro- β -carboline Analogous" **Unnava, R.**; Sahu, A. K.; Saikia, A. K. *Asian J. Org. Chem.* **2017**, 6, 1003-1007.
2. "Synthesis of Substituted Pyrazole *N*-Oxide and Pyrazole from Propargylamine" **Unnava, R.**; Saikia, A. K. *Chemistry Select.* **2016**, 01, 1816-1823.
3. "Synthesis of Isochroman Derivatives via Oxa-Pictet-Spengler Reaction of Vinylogous Esters" Sarkar, S.; Sultana, S.; Indukuri, K.; **Unnava, R.**; Saikia, A. K. *Synthesis.* **2016**, 48, 1727-1733.
4. "Synthesis of Highly Substituted 4-Iodopyrazole *N*-Oxide and Pyrazole from Propargyl amine" **Unnava, R.**; Deka, M. J.; Saikia, A. K. *Asian J. Org. Chem.* **2016**, 05, 528-536.
5. "Regioselective One-Pot, Three-Component Synthesis of Substituted 2*H*-Indazoles from 2-Nitroarylaldehyde, Alkyne and Amine Catalyzed by CuBr/Zn(OTf)₂ System" Saikia, A. K.; **Unnava, R.**; Indukuri, K.; Sarkar, S. *RSC Adv.* **2014**, 04, 55296-55299.
6. "Stereoselective Synthesis of Amido and Phenyl Azabicyclic Derivatives via A Tandem Aza Prins-Ritter/Friedel-Crafts Type Reaction of Endocyclic *N*-Acyliminium Ions" Indukuri, K.; **Unnava, R.**; Deka, M. J.; Saikia, A. K. *J. Org. Chem.* **2013**, 78, 10629-10641.