Synthesis of Furan, Pyran, Pyrrolidine, and Piperidine Scaffolds *via* Tandem Prins Cyclization Reactions

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

Doctor of Philosophy in Chemistry

Submitted by

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August-2023

TH-3246_176122006

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STATEMENT

I do hereby declare that the matter embodied in this thesis entitled “**Synthesis of Furan, Pyran, Pyrrolidine, and Piperidine Scaffolds via Tandem Prins Cyclization Reactions**” 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 acknowledgement had been made wherever the work described is based on the findings of other investigators.

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CERTIFICATE

This is to certify that **Mr. Sudip Shit** has been working under my supervision since July 2017 as a regular registered Ph. D. student. I am forwarding his thesis entitled "**Synthesis of Furan, Pyran, Pyrrolidine, and Piperidine Scaffolds via Tandem Prins Cyclization Reactions**" 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.

17th August, 2023
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Prof. Anil K. Saikia
Supervisor

ACKNOWLEDGEMENTS

I want to thank my supervisor Prof. Anil K. Saikia, for his constant support and guidance throughout my Ph.D. tenure. His patience, immense knowledge and passion for research helped me to enhance my thought process and skills, which will be my lifelong assets. This thesis would not have been possible without his scientific advices, quick response and constructive criticism. I am forever indebted to him and consider myself lucky to have him my supervisor.

I would like to acknowledge my sincere gratitude to my doctoral committee members Prof. V. Manivannan, Prof. Siddhartha S. Ghosh and Dr. Pavan K. Kancharla for their valuable scientific suggestions.

I am also thankful to all the faculty members of Department of Chemistry, IIT Guwahati, for their encouragement and all the staff members of chemistry department for their valuable services, particularly, Mr. Imdadul Islam, Dr. Babulal Das and Mr. Diganta kumar Hira for their technical support.

I am very grateful to the Ministry of Education, Government of India for financial support and IIT Guwahati for all the facilities that were made available to me. I am also thankful to Central Instruments Facility (CIF) and Department of Chemistry, IIT Guwahati for providing the analytical facility.

I express my sincere gratitude to Mr. Sandip Tripathy, who concreted my basic education which helped me to pursue my career in science. I would also like to thank Dr. Tapan Kr. Lai for his constant encouragement and support.

Further, I would like to express my gratitude to all my past and present group members for their friendship and assistance. I especially thank Mr. Subhamoy Biswas for solving my crystals, and technical and general discussions. I express my thanks to Mr. Bipin Kumar Behera, for many discussions and his encouragement. I show my gratitude and thanks to Dr. Ngangbam Renubala Devi for helping me in my initial PhD year. I express my heartfelt thanks to Dr. Namita Devi, who directly helped me in my research work. I am thankful to Mr. Malay Das for introducing me with the analytical techniques, including column chromatography and TLC. I am also thankful to my past lab-members, Dr. Upasana Borthakur and Dr. Archana Kumari Sahu for their assistance in familiarizing with the work carried out in our lab.

I would like to take this opportunity to thank all of my lab juniors Ms. Bikoshita Porashar, Mr. Surjya Kumar Bora, Mr. Pallav Jyoti Arandhara, Ms. Archana Chutia, Ms. Chinmayee Choudhury, Mr. Hunmoina Phukon and Ms. Ankita Pradhan for being helpful in every step and for creating a pleasant work environment.

I am thankful to my dear friends Ms. Nikita Chakraborty, Mr. Avijit Mondal, Mr. Retwik Parui, Dr. Suman Manna, Dr. Shyamal Kanti Bera, Mr. Manojit Das and my seniors Dr. Aniruddha Das, Dr. Milan Pramanik, Mr. Arnab Das and Dr. Ankur Maji for being helpful in every possible way. I have been lucky to have been surrounded by such positive and creative individuals.

A special thanks to my fiancé Ms. Puja Sarkar for her encouragement and inspiration throughout this journey. I will forever remain in debt for her constant support and utmost care.

Finally, I feel a deep sense of gratitude to my family members for their sincere encouragement and lifting me uphill in this phase of my life. Specially I am thankful to my grandmother Smt. Radharani Shit for her innocent love and affection, which kept me motivated to achieve higher goals in life. I dedicate this thesis to her.

Sudip Shit

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LIST OF ABBREVIATIONS

Ac	*Acetyl*	LAH	*Lithium aluminium hydride*
Nu	*Nucleophile*	DBU	*1,8-Diazabicyclo[5.4. 0]undec-7-ene*
Ar	*Aryl*	LDA	*lithiumdiisopropyl amine*
		mp	*melting point*
Bn	*Benzyl*	MS	*molecular sieves*
Bu	*butyl*	m/z	*mass to charge ratio*
CCDC	*cambridge crystallographic data centre*	NMO	*N-methylmorpholine N-oxide*
Cy	*cyclohexyl*	NMR	*nuclear magnetic resonance*
DCE	*1,2-dichloroethane*	NOESY	*nuclear overhauser enhancement spectroscopy*
DCM	*dichloromethane*	ORTEP	*oak ridge thermal ellipsoid plot*
DFT	*Density function theory*	Ph	*phenyl*
DIAD	*diisopropylazodicarboxylate*	ppm	*parts per million*
DMAP	*4-dimethylaminopyridine*	Pr	*propyl*
DMF	*N, N-dimethylformamide*	*p*-TSA	*p-toluenesulfonic acid*
DMSO	*dimethylsulfoxide*	rt	*room temperature*
de	*diastereomeric excess*	THF	*tetrahydrofuran*
dr	*diastereomeric ratio*	TMSOTf	*Trimethylsilyl trifluoromethanesulfonate*
EDDA	*Ethylenediamine acetic acid*		
ee	*enantiomeric excess*	TFA	*trifluoroacetic acid*
HRMS	*high resolution mass spectrometry*	TLC	*thin layer chromatography*
IR	*infrared*	TMS	*trimethylsilyl*
LA	*Lewis acid*	Ts	*p-toluenesulfonyl*
Boc	*tert-butyloxycarbonyl*	PIDA	*Phenyliodine(III)diacetate*
	Tetra-n-butylammonium		

TBAI	*iodide*	TBAB	*Tetrabutylammonium bromide*
	N-Bromosuccinimide		
NBS		Q-TOF	*Quadrupole Time-of-Flight*

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

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

Abstract

The content of this thesis has been divided into five chapters on the basis of results of experimental work performed during the complete course of the PhD tenure. The chapter **1** describes the tandem Prins cyclization reactions and their mechanisms to construct Furan, Pyran, pyrrolidine and piperidine scafolds in brief. The chapter **2** deals with the stereoselective synthesis of hexahydrofuro[3,4-*b*] furan-4-ol and its dimer *via* tandem Prins and pinacol rearrangement. Chapter **3** describes synthesis of spiro[furan-2,1′-isoindolin]-3′-ones from 2-(4- hydroxybut-1-yn-1-yl)benzonitriles and aryl aldehydes under the action of triflic acid. In chapter **4**, nitrile stabilized synthesis of pyrrolidine and piperidine derivatives via tandem alkynyl aza-Prins-Ritter reactions. In chapter **5**, regio- and chemoselective synthesis of 3-(dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-imines *via* tandem alkynyl Prins- and intramolecular oxycyclization reaction is described.

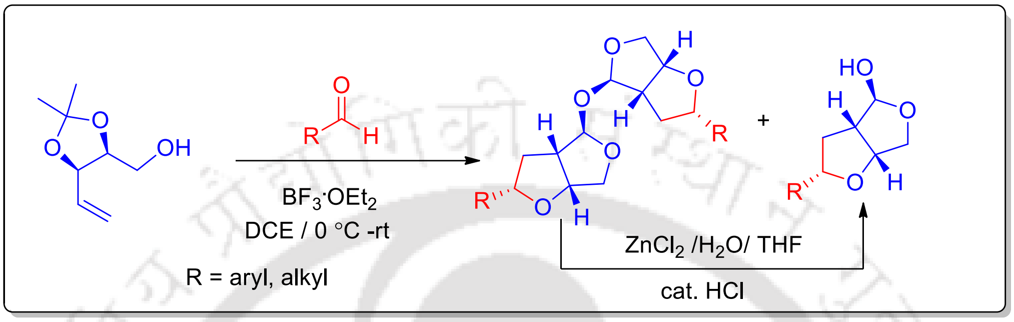
Chapter 1: Introduction to Tandem Prins Cyclization Reactions

Prins cyclization reactions is a versatile method for the synthesis of oxygen, nitrogen and sulphur containing heterocyclic scaffolds. Whereas, tandem Prins cyclization reaction is utilized for the fused, bi-cyclic, spiro and bridged heterocyclic motifs. There are several methods for the synthesis of heterocycles including hetero-Diels-Alder reactions, intramolecular Michael additions, epoxide opening, oxidative cyclizations, cross-coupling and Prins cyclizations. Among those, Prins cyclization reactions is a powerful tool for the stereoselective construction of the C-C, C-O, C-N and C-S bonds, due to its remarkable diastereoselectivity.

The nitrogen version of Prins reaction is called *aza*-Prins reaction, where the reaction goes through nitronium ion intermediate instead of oxo-carbenium ion formation. Similarly, thia-Prins reaction is also described in literature. There are many tandem Prins cyclizations reaction in literature including Prins-pinacol, Prins-Ritter reactions, Prins Friedel-Crafts, Prins Nazarov cyclizations etc. As we know, the heterocyclic compounds are widely spread in nature and conveniently used for the drugs, vitamins, perfumery, photochromic materials, plasticizers etc. Development of the new methodology for the organic synthesis is the motivations of an organic chemists. Prins cyclizations reactions can be utilized for the synthesis of heterocyclic scaffolds in a single step in stereoselective manner. This reaction can be used in total synthesis for the natural product synthesis in the cost-effective manner.

Chapter 2: Stereoselective Synthesis of Hexahydrofuro[3,4-*b*] furan-4-ol and its Dimer *via* Tandem Prins and Pinacol Rearrangement

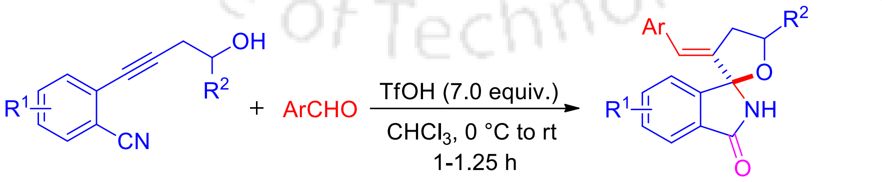
An efficient synthetic route for the cyclization of (4S,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)methanol with aldehyde to give hexahydrofuro[3,4-b]furan-4-ol and its dimer was developed. A variety of substituted furanol (up to 86%) and its bis-derivatives were obtained in good yields (up to 66%) with excellent diastereo- and enantio-selectivity mediated by borontrifluoride etherate. The dimer was conveniently converted to its corresponding monomer by aqueous zinc (II) chloride in THF in quantitative yields.



Org. Biomol. Chem. **2019**, *17*, 7398–7407.

Chapter 3: Synthesis of Spiro[furan-2,1′-isoindolin]-3′-ones from 2-(4- Hydroxybut-1-yn-1-yl)benzonitriles and Aryl Aldehydes under the Action of Triflic Acid

Synthesis of spiro[furan-2,1'-isoindolin]-3'-ones from 2-(4-hydroxybut-1-yn-1-yl)benzonitriles and aryl aldehydes is demonstrated, involving tandem reactions namely Prins, Ritter and tetrahydrofuran ring opening followed by nucleophilic attack of alcohol on *N*-acyliminium ion in moderate to good yields. It involves the initial formation of dihydrofuranylideneisoindolinone via intramolecular sequential Prins and Ritter reaction followed by ring opening of furanyl moiety to generate *N*-acyliminium ions and alcohols for the final cyclization reaction to give the spiro-cyclic compounds. Furthermore, late stage modifications of the compounds have been done using Sonogashira and click reactions.

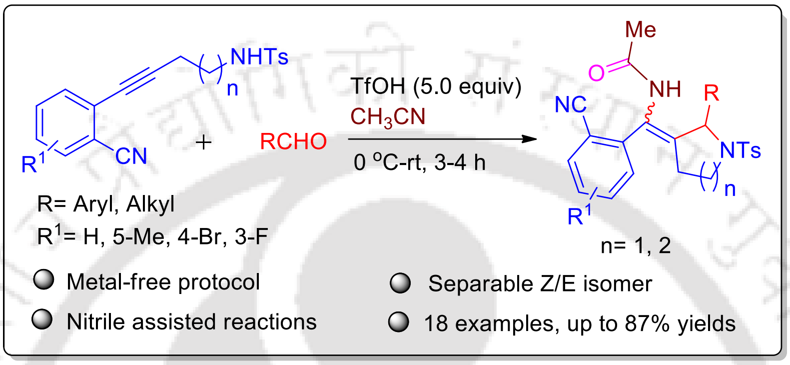


- Metal-free, one-pot tandem protocol
- One C-N, two C-O, and one C-C bond formation
- One newly formed quaternary carbon along with two five membered rings
- 20 examples, upto 76% yields

J. Org. Chem. **2022**, *87*, 11634−11643.

Chapter 4: Nitrile Stabilized Synthesis of Pyrrolidine and Piperidine Derivatives via Tandem Alkynyl aza-Prins-Ritter Reactions

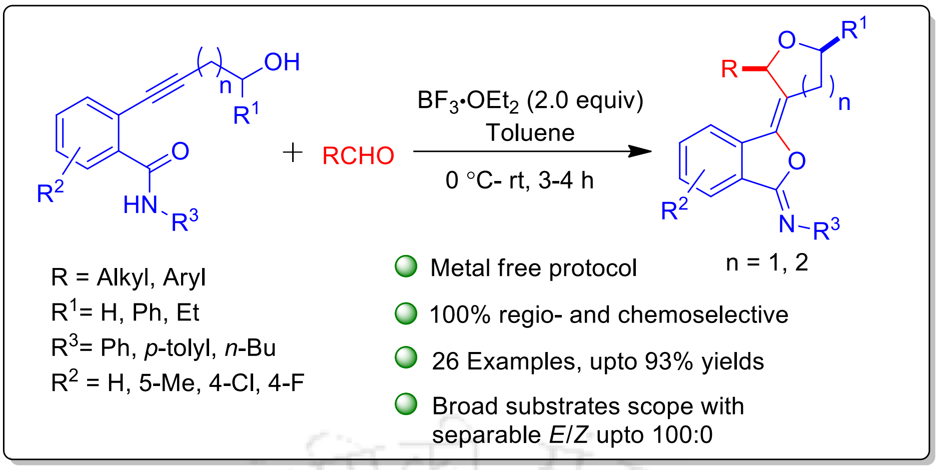
An efficient methodology for the synthesis of *N*-(pyrrolidine-3-ylidenemethyl)acetamides mediated by triflic acid has been demonstrated in good yields with high *Z/E* selectivity. The reaction involves the initial formation of pyrrolidin-3-ylidenemethylium carbocation *via* Prins cyclization reaction followed by Ritter reaction to produce *N*-(pyrrolidine-3-ylidenemethyl)acetamides. The methodology is also used for the synthesis of its piperidine derivatives. The amide functionality incorporated in the product comes from the solvent acetonitrile. The reaction occurs at room temperature within a short reaction time.



Manuscript under revision.

Chapter 5: Regio- and Chemoselective Synthesis of 3-(Dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-imines *via* Tandem Alkynyl Prins- and Intramolecular Oxycyclization Reactions

A metal-free Lewis acid initiated protocol for the synthesis of highly substituted 3-(dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-imines from 2-(4-hydroxybut-1-yn-1-yl)benzamides and aldehydes has been demonstrated. The reaction involves the initial formation of dihydrofuranylidene carbocation via Prins cyclization reaction using $BF_3{\cdot}OEt_2$, followed by intramolecular cyclization to produce 3-(dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-imines up to *E*/*Z*= 6:1 with moderate to good yields. The methodology can also be used for the synthesis of 3-(dihydro-2*H*-pyran-3(4*H*)-ylidene)-isobenzofuran-1(3*H*)-imines. Post synthetic application of the reaction was extended for the synthesis of furanylidene isobenzofuranones in excellent yields.



J. Org. Chem. **2023**, *88*, 10844−10857.

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Chapter 1:

1. Introduction to Tandem Prins Cyclization Reaction

1.1 General Background

Prins cyclization is a highly versatile reaction and important tool used for the synthesis of oxygen(O), nitrogen(N), and sulfur(S) containing heterocyclic scaffolds.[1a-b] On the other hand, tandem Prins cyclization reaction is employed to construct more complex structures, such as fused, bi-cyclic, spiro-, and bridged heterocyclic motifs.[1c] Several methods are reported for synthesizing heterocycles, including hetero-Diels-Alder reactions, intramolecular Michael additions, epoxide opening, oxidative cyclization, cross-coupling, Prins cyclization, and oxonium-ene cyclizations.[2a-d] Among these, Prins cyclization reaction is a effective tool for the stereoselective formation of C-C, C-O, C-N and C-S bonds, due to its remarkable diastereoselectivity.[2e-g] The cationic intermediate formed during the reaction can initiate a series of reactions in a tandem manner by trapping it with various nucleophiles, either by intermolecular or intramolecular fashion.[1,3] Due to its stereoselective nature, mild reaction conditions, and inexpensive reagents, Prins cyclization has become a key strategic method in natural products synthesis, complex heterocycles synthesis, and fragrance industry.

1.2 Tandem Reaction

Tandem reaction is a combined chemical process in which at least two successive reactions combine to result in one synthetic operation. The advantage of tandem reaction is the formation of several bonds without adding extra reagents or isolating any intermediate.[4a-b] On

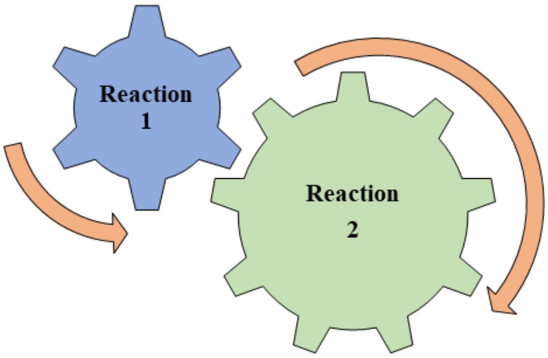


Figure 1.2.1: Schematic illustration of tandem reactions.

the contrary, in multistep transformations, the preparatory complexity increases with increase in the number of chemical transformations and several purification operations.[4c] Over the years, tandem reaction is gaining attraction in both academic and industrial research by reducing reaction time, cost, and by-products to effect given transformations. Designing of starting material subjected to the tandem reaction plays a pivotal role in the complex heterocycle synthesis.

1.3 Importance and applications of "O" heterocycles

1.3.1 Tetrahydro-furan and pyran scaffolds

Furan scaffold is the oxygen(O) containing five-membered heterocyclic ring, whereas pyran motif is the oxygen(O) containing six-membered heterocyclic ring. In general, the prefixes dihydro and tetrahydro are used to refer to the unsaturated molecules that are partly or entirely reduced. Dihydro-, tetrahydro-furan, and pyran motifs serve as fundamental building blocks in numerous bioactive compounds. These core subunits are prevalent in natural products and have garnered significant attention in drug discovery and pharmaceutical chemistry.[5a-b] Tetrahydrofuran motifs are present in separate classes of terrestrial and marine living being, such as Caloxilane A and Caloxilane B, both isolated form the Caribbean marine sponge, namely, *Calyx podatypa*.[5c-d] Corsifuran A, featuring a dihydrofuran moiety was isolated from the heartwood of the *Thespesia populnea* tree.[5e] Example of the lignin Fragransin C1, from the Fragransin family is used to treat type-2 diabetes and obesity, as well as other metabolic disorders.[5f] Similarly, tetrahydropyran containing natural product, (–)-centrolobine, isolated from the heartwood of *Centrolobium robustum* tree and stem of *Brosinum potabile* plants, which mostly found in Amazon forest. These natural product shows potent activity against Leishmania amazonensis promastigotes, a type of parasite associated leishmaniasis.[6a-b] Whereas, Diospongin A isolated from rhizhomes of *Discorea spongiosa*, shows anti-oesteopototic activity (*Figure 1.3.1.1*).[6c]

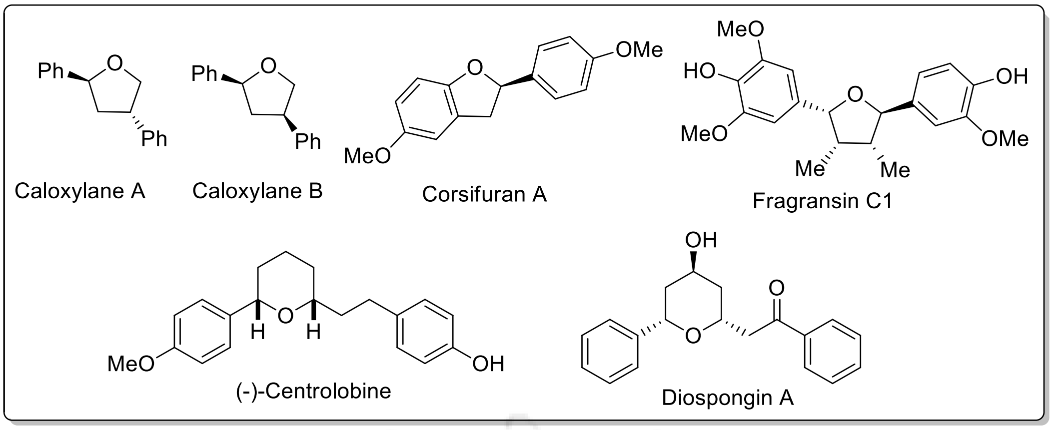


Figure 1.3.1.1: Some bio-active tetrahydrofurans.

1.3.2 Furofurans

Furofuran is the bicyclic compound having "O" on both rings. Numerous furofurans have been isolated from plants, and their bio-activity has been evaluated, such as sesamin shows cholesterol lowering effect in rat serum and liver,[7a] sesamolin exhibits antioxidant and neuroprotective activities. Sesaminol prevents neurodegenerative Parkinson's disease.[7b] Bis-tetrahydrofuran alcohol subunit containing compound darunavir shows potent activity against multidrug resistant HIV and is commercially available in the market (*Figure 1.3.2.1*).[7c-d]

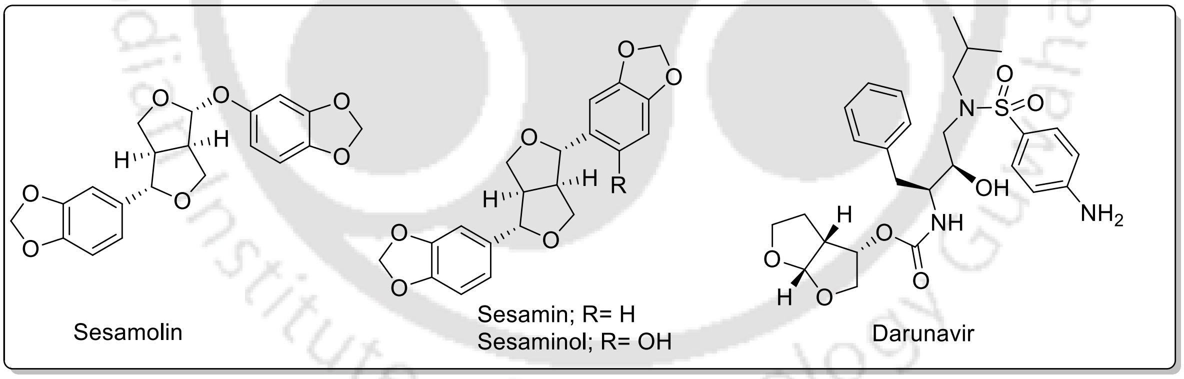


Figure 1.3.2.1: Some important furofurans.

1.4 Importance and applications of "N" heterocycles

1.4.1 Pyrrolidine and piperidine Scaffolds

Pyrrolidine and piperidines are five- and six-membered saturated nitrogen-containing heterocycles. Due to their immense presence in natural products and drug molecules, synthesis of these molecules is always highly demanding,[8a-e] for example, Hygrine is a class of pyrrolidine alkaloid, isolated from *Carl Liebermann* in 1889, can be used for the treatment of malaria.[9a] An antispasmodic drug procyclidine can be used in the treatment of various parkinson's disease and extrapyramidal symptoms.[9b] Pyrrolidine containing drug Captopril is used as an antihypertensive agent.[9c] In the same context, Pergolide exhibits clinical benefit in Parkinson's disease by stimulating dopamine D1 and D2 receptors.[9d-e] The alkaloid L-(-)-scopolamine prevent muscarinic receptors for a neurotransmitter acetylcholine. That can be used as a non-selective muscarinic antagonist.[10a] Morphine is commonly used as pain killer (*Figure 1.4.1.1*).[10b]

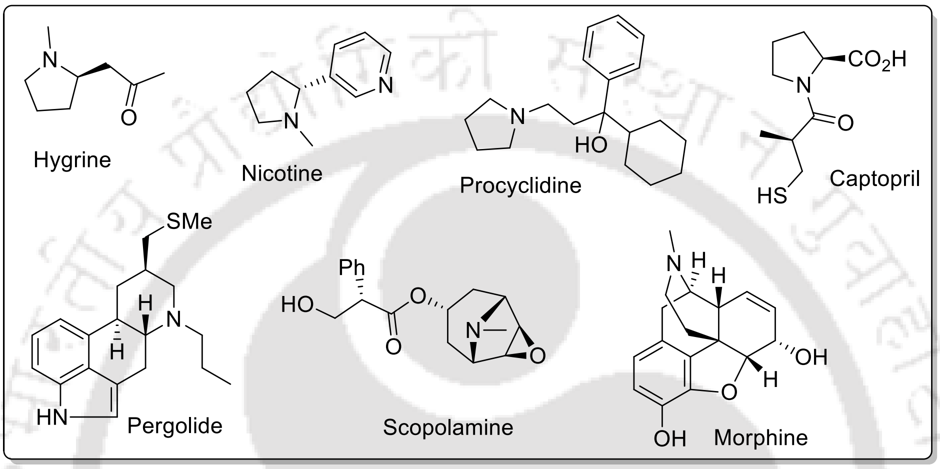


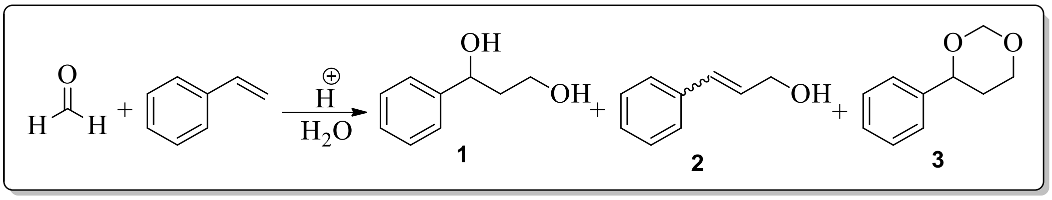
Figure 1.4.1.1: Some bio-active pyrrolidine and piperidine-containing molecules.

1.5 General approaches for "O" and "N" heterocycles synthesis

Several synthetic approaches are present in the literature, for the synthesis of oxygen and nitrogen-containing heterocycles, which mostly includes Prins cyclizations, oxonium-ene, Diels Alder reaction, reductive amination, transition metal catalyzed cyclization, radical cyclization reactions, etc.[11] Newer efficient methodologies with high regio- and stereocontrol approaches, which can be utilized for synthesis of complex molecular architect and natural products are always in demand. In search of newer methodologies for the development of complex heterocycles, Prins cyclization initiated tandem reactions have proven to be a reliable tool. Hence we focussed on tandem Prins cyclization reactions and discussed the several tandem protocols in this chapter.

1.5.1 Prins reaction

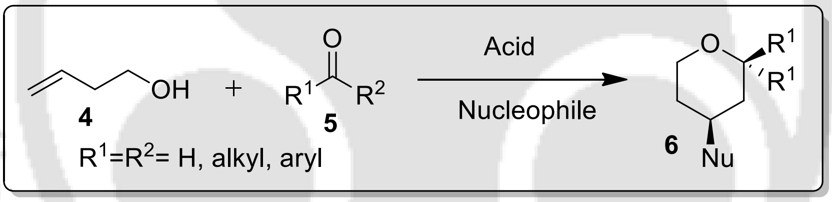
The condensation reaction of a homo-allylic alcohols and carbonyls in the presence of a Lewis/Brønsted acid is called Prins reaction. This reaction was first developed by H. J. Prins in 1919.[12a] He performed the condensation reaction of formaldehyde and styrene in water and resulted with the mixture of products, 1,3-butane diol **1**, unsaturated alcohols **2** along with some amount of 1,3-dioxane **3** (*Scheme 1.5.1.1*).



Scheme 1.5.1.1: Prins reaction invented by H. J. Prins.

1.5.2 Prins cyclization reaction

In 1955, Prins cyclization reaction was described by Hanschke, for the synthesis of tetrahydropyrans.[12b] The reaction was performed with homoallylic alcohol **4** with formaldehyde in the presence of hydrochloric acid in anhydrous condition. Surprisingly, tetrahydropyran **6** was formed instead of mixture of products (*Scheme 1.5.2.1*). Further investigation concluded that, homoallylic alcohol is the key intermediate of this reaction and day by day it became powerful tool for the synthesis of tetrahydropyran scaffolds.



Scheme 1.5.2.1: Prins cyclization reaction

1.5.3 Mechanism of Prins cyclization reaction

Lewis acid mediated condensation of aldehydes **7** and homoallylic alcohol **8** generate oxocarbenium ion intermediate **9**. The intermediate **9** is then cyclized via *6-endo-trig* fashion to give chair-like tetrahydropyranyl carbocation **10** (*Scheme 1.5.3.1*). The chair conformation of tetrahydropyran carbocation **10** is stabilized by stereoelectronic factors, which was confirmed by Alder's DFT calculations.[12c] The pseudo axial C-H bond at 4-position of the carbocation **10** directed the nucleophile towards equatorial attack to afford the final tetrahydropyran derivatives (*Scheme 1.5.3.1*).

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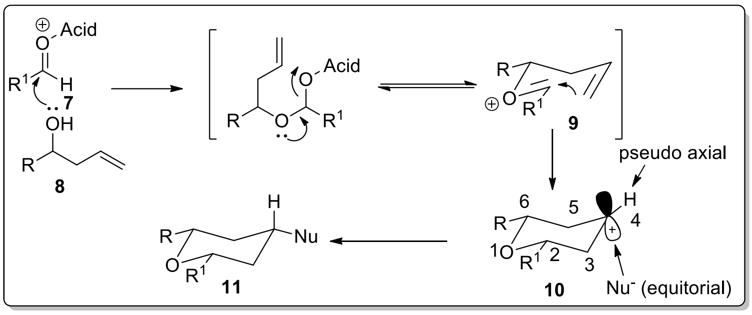


Scheme 1.5.3.1: Mechanism of Prins cyclization reaction.

Over the decades, a number of halogenated Lewis acids have been employed by various groups, in which tetrahydropyranyl carbocation is captured by halide nucleophiles.[1a] Trapping of the carbocations by various nucleophiles including, hydroxide(-OH), acetate(-OCOMe), azide(N_3) alkyne, and many sulfur nucleophiles is reported.[1-5, 15-17] To construct complex molecular structures, Prins reaction can be utilized as an initiator to promote several reactions in a tandem manner. This reaction can be utilized for natural product synthesis, due to its remarkable stereoselectivity.

1.5.4 A short bio-sketch of Hendrik Jacobus Prins

A short bio-sketch of Dutch chemist H. J. Prins is described below. He demonstrated the reaction first in 1919, and later it was named in his honour as Prins reaction.

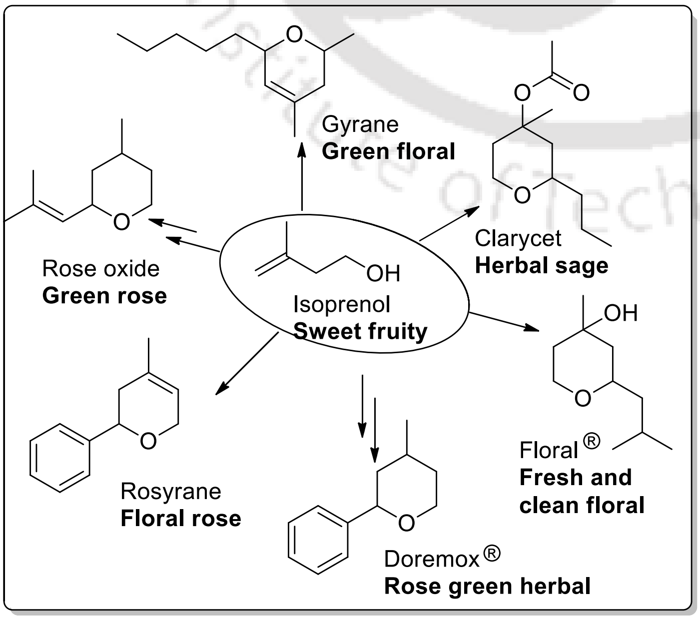
Figure 5. Picture of H. J. Prins at the entrance of his chemical laboratory

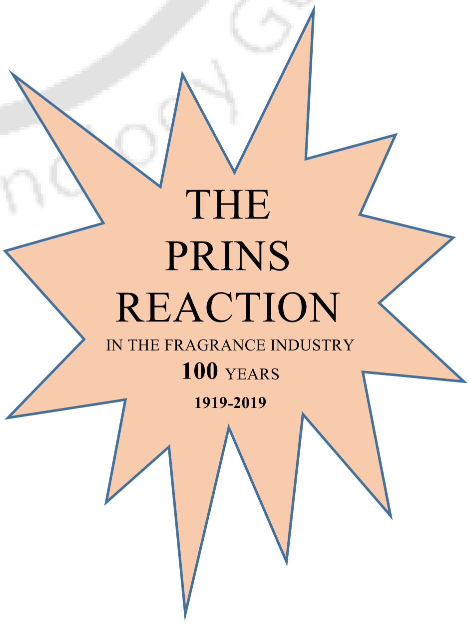
Hendrik Jacobus Prins: (1889–1958)- H. J. Prins worked at the company Polak and Schwarz(P&S), one of the parent companies of I. F. F (International Flavors and Fragrances) from 1912 to 1924. At the same time, he published his work on condensation of formaldehyde with styrene. Initially, he joined P&S in Zaandam as a chemist, and later established the first fragrance company in Hilversum. After completion of both the research site and the factory, Prins took over the role of research director at P&S in Hilversum.

Prins has contributed enormously in the area of fragrances beyond his famous name reaction and demonstrated the separation of isomeric compositions of terpenes. In 1924, Prins left the company P&S with few colleagues and established a company N.T.F (Nederlandse Thermochemische Fabrieken). Prins continued his research by working in a room in his house. Later, he converted that room into a chemical laboratory and funding his research expenses by himself. He explored the synthesis, analysis and characterizations of novel halo-hydrocarbon compounds, a research area he studied at the time of his doctoral research at Delft University. Along with his entrepreneurial and scientific spirit, he was fascinated with philosophy. Notably, the introduction chapter of his doctoral thesis is entitled “Philosophy as a critical factor in natural sciences”.[13]

1.5.5 Application of Prins reaction in flavours and fragrances

Fragrance ingredients are fascinating organic molecules that can be synthesized by utilizing Prins reaction. A short sketch of dihydro- or tetrahydro-pyran compounds synthesized from isoprenol is shown in scheme 4.[13] These Prins products are well known due to their unique odour properties, and synthesis of most of these compounds are revised and improved now. In 2017, List and co-workers described an organo-catalytic method for the synthesis of various dihydropyrans, the methodology was extensively used for the synthesis of enantiomerically pure form of unsaturated precursors of Doremox® and Rose oxide.[14a] Clarycet and Floral® were prepared by green and solvent-free Prins cyclization protocol.[14b] Apart from the Prins protocol, other chemical methods are also available for fragrance molecule synthesis (*Scheme 1.5.5.1*). For example, an industrial method for the preparation of Rose oxide, involved oxygenation of citronellol as an intermediate step.[14c]

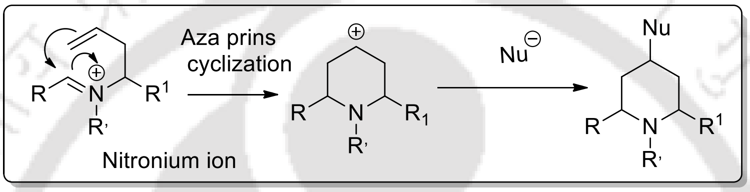




Scheme 1.5.5.1: Some examples of tetrahydro- and dihydro-furan fragrance compounds

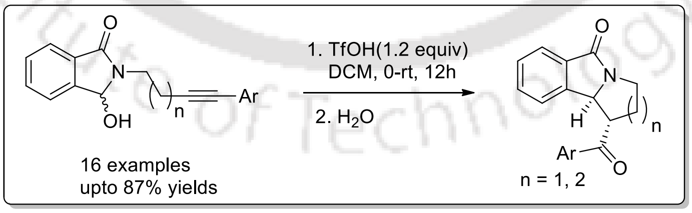
1.6 Aza-Prins cyclization reaction

Aza-Prins cyclization reaction is the coupling of homoallylic amines instead of homoallylic alcohols with aldehydes or ketones. There is formation of nitronium ion in place of oxo-carbenium ion, which after cyclization, followed by the capture of a nucleophile produced piperidine units instead of tetrahydropyran units (*Scheme 1.6.1*).[15a] In the same context, another type of aza-Prins reaction is also known, which is intramolecular cyclization to an *N*-acyliminium ion.[15b-c]



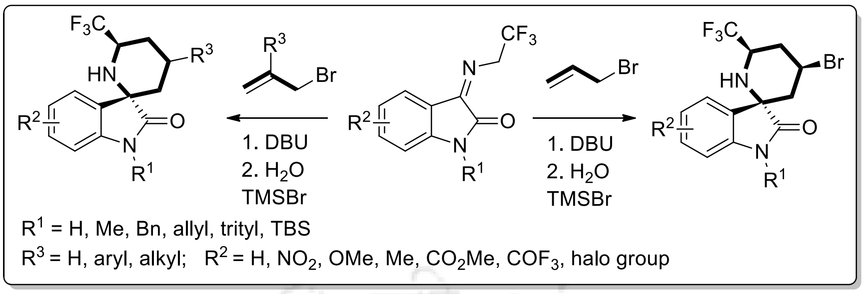
Scheme 1.6.1: Strategy of aza-Prins cyclization reaction

In 2018, Saikia and co-workers demonstrated a simple approach for the synthesis of functionalized pyrroloisoindolones and its six-membered analogues utilizing aza-Prins cyclization reaction. Cyclization of alkynyl part towards *in situ* formed *N*-acyliminium ion intermediate followed by aqueous workup furnished pyrroloisoindolones in excellent yields and diastereoselectivity. The synthetic methodology was utilized for the construction of pyrimidoisoindolone in good yields (*Scheme 1.6.2*).[16a]



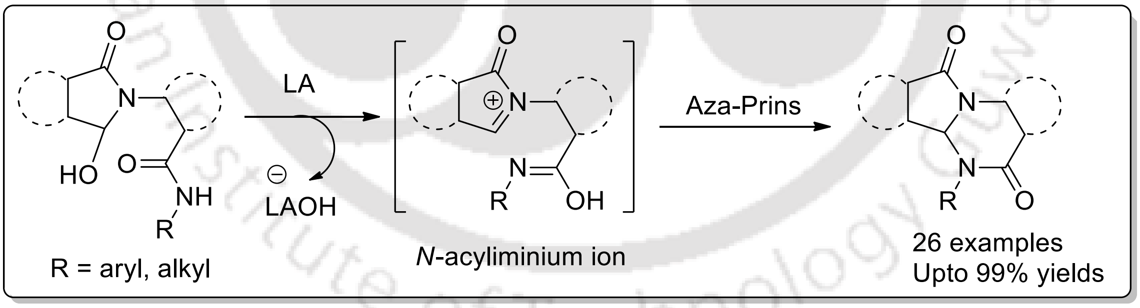
Scheme 1.6.2: Construction of pyrroloisoindolones and Pyridoisoindolones

In 2021, Ko and his group reported a umpolung allylation followed by aza-Prins cyclization reaction of *N*-2,2,2-trifluoroethylisatin ketimines. Although, aldehydes and amines are involved in the general aza-Prins reaction, this reaction utilizes the umpolung activity of *N*-2,2,2-trifluoroethylisatin ketimines in the presence of DBU. This metal-free one-pot synthetic protocol produced six-membered spirocyclic oxindole molecules in moderate to good yields (*Scheme 1.6.3*).[16b]



Scheme 1.6.3: Synthesis of functionalized spiro-oxindoles

In the same year, Saikia and co-workers demonstrated an aza-Prins type intramolecular cyclization reaction for the construction of pyrimido[2,1-*a*]isoindolones and isoindolo[2,1-*a*]quinazolinones in excellent yields. Designing and synthesis of the starting material plays an important role in this chemical transformation. The amido alcohol generates an *N*-acyliminium ion intermediate in the presence of $BF_3{\cdot}OEt_2$ followed by nucleophilic attack of "N" lone pair of amide *via* keto-enol type tautomerization to afford the final product. The methodology was further explored towards synthesis of isoindolo[2,1-*a*]quinazoline-5,11-diones in excellent yields (*Scheme 1.6.4*).[16c]

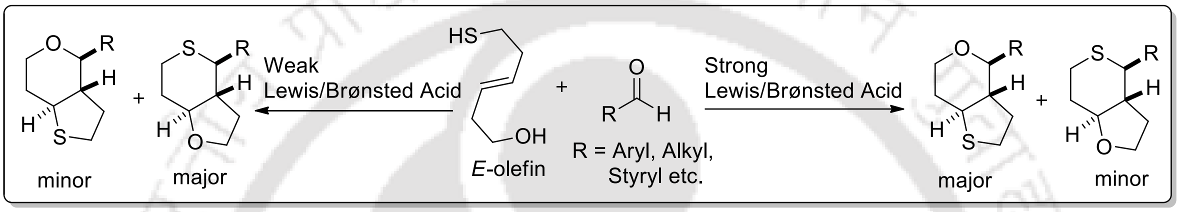


Scheme 1.6.4: Synthesis of pyrimido-isoindolones and isoindolo-quinazolinones

1.7 Thia-Prins reaction

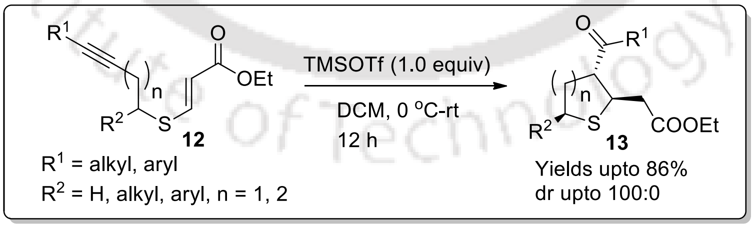
Lewis acid initiated condensation reaction of homoallylic thiol and carbonyls for the synthesis of thiopyrans is known as thia-Prins reaction. This reaction gained considerable attention for the synthesis of tetrahydro-thiophene, -thiopyran in a single step with excellent diastereoselectivity.[17a]

"O" versus "S" selectivity in Prins cyclization reaction has been observed and described by Reddy et al. in 2014.[17b] The reaction of 6-mercaptohex-3-en-1-ol and aldehydes produced hexahydro-2*H*-thieno[3,2-*c*]pyrans as a major product in the presence of strong Lewis or Brønsted acids (stoichiometric amount). Whereas, the same reaction in presence of catalytic amount of acids, produced hexahydro-2*H*-thiopyrano[4,3-*b*]furans predominately. The interaction and complexation of strong Lewis acids, such as borontrifluoroetherate with sulfur is favoured, and oxonium-Prins product formed predominately. On the other hand, the complexation of weak Lewis acids, such as $InCl_3$ with oxygen is favoured and thionium-Prins product was formed preferentially (*Scheme 1.7.1*).



Scheme 1.7.1: "O" versus "S" selectivity in Prins cyclization reaction

In 2015, Saikia and group described a thia-Prins cyclization reaction for the formation of functionalized tetrahydrothiophenes and –thiopyrans in good yields with remarkable diastereoselectivity.[17c] The reaction involves activation of ester functionality of thioacrylate **12** by TMSOTf, which after the formation of thiocarbenium ion followed by alkynyl cyclization and aqueous workup leads to the corresponding five- and six-membered sulfur heterocycles (*Scheme 1.7.2*).

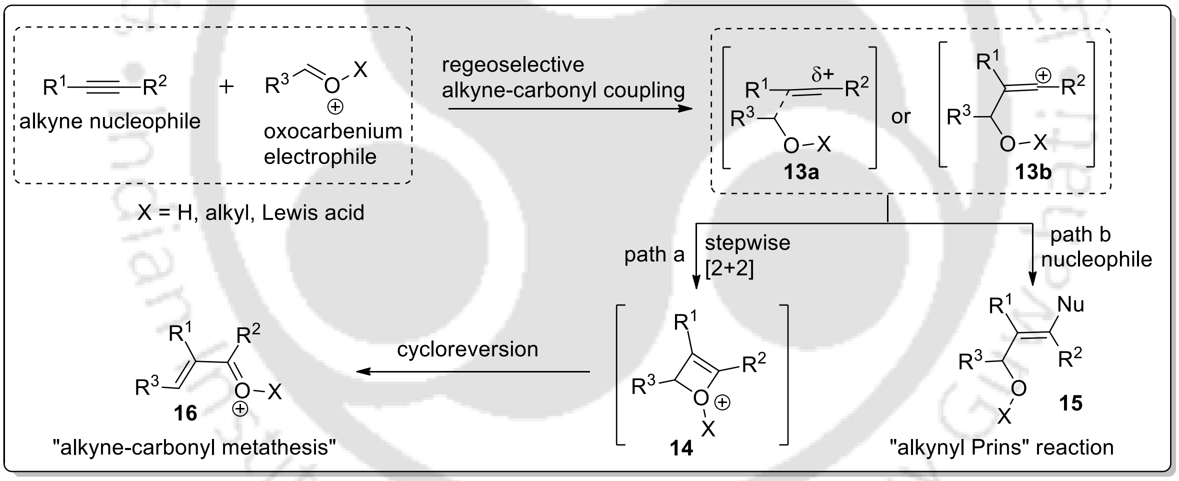


Scheme 1.7.2: Formation of functionalized tetrahydrothiophenes and –thiopyrans

1.8 Alkynyl Prins reaction

1.8.1 Alkyne-carbonyl coupling strategies

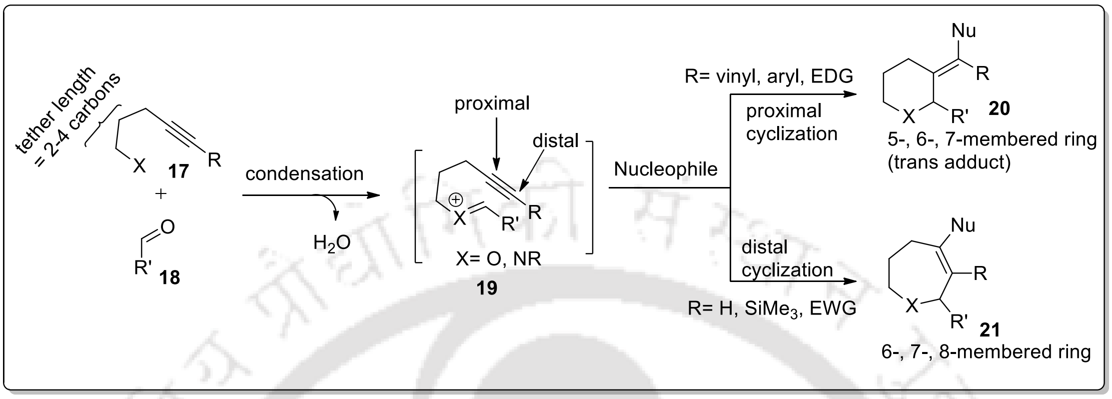
Lewis or Bronsted acid initiated intermolecular coupling of alkynes with carbonyls, including aldehydes, imines, acetals, and hemiketals are known in the literature.[18a-f] For the case of intramolecular reactions, ketone, and ketals also react with alkynes.[19a-b] The fate of the reaction initiated from the attack of the more nucleophilic centre of the alkyne to electrophilic oxocarbenium or iminium ions and subsequently, a vinyl cation is developed at other carbon centre of the alkyne (*Scheme 1.8.1.1*). The behaviour of the newly formed vinyl cation **13** is unpredictable and can undergo two different reaction pathways to provide the products **15** or **16**, but the regioselective nature of the process is quite impressive. The distinction of the reaction pathways can depend on the reagents, reactant, solvents, etc. In the case of path "a" the intramolecular attack of carbonyl oxygen to vinyl carbocation in a stepwise [2+2] cycloaddition followed by ring opening to afford enones **16** *via* oxetene ring **14** is described as "alkyne-carbonyl metathesis".[19c] On the other hand, in the case of path "b", the capture of vinyl cation **13a** or **13b** by nucleophile to afford the product **15** is called "alkynyl Prins reaction".



Scheme 1.8.1.1: Alkynyl-carbonyl coupling strategy

1.8.2 Cyclization cascades *via* alkynyl Prins reaction

By controlling the electronic and geometrical factors of a reaction, it can be possible to execute the alkynyl carbonyl coupling reaction that prefers the alkynyl Prins pathways. Lewis acid promoted condensation of aldehydes and alkyne **17** generates oxocarbenium or nitronium ion **19** intermediate, which after intramolecular alkynyl cyclization produced **20** and **21**. Attack of the proximal carbon centre of **17** to the cationic intermediate **19** leads to the formation of **20**, when R is π- electron donating group; thus helps to stabilize the positive charge generate on the distal carbon centre.[20a-b] On the other hand, regioselective cyclization through distal carbon centre of **17** produced compound **21**, when R= H, $SiMe_3$ and electron withdrawing groups; thus it can help to stabilize the positive charge formed in the proximal carbon (*Scheme 1.8.2.1*). [19b,20c]



Scheme 1.8.2.1: Alkynyl Prins annulations strategy

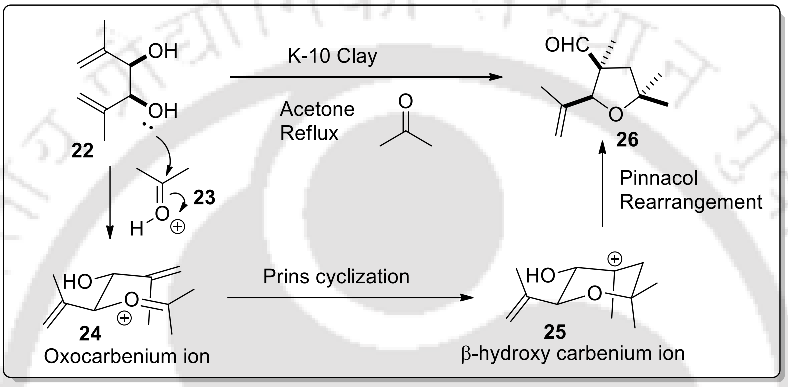
In the last two decades, there have been numerous development in alkynyl Prins cyclization reactions, including synthesis of dienes for [4+2] cycloadditions,[21a] synthesis of Nazarov cyclization adducts,[21b-c] tandem Prins carbocyclizations with aromatization,[21d-e] alkynyl aza-Prins cyclizations.[21c] This strategy is also used for the synthesis of several bio-active compounds and natural products such as carbacephem antibiotics, (-)-lycopodine, (±)-stemoamide, and aflavazole.[1a] Still, there is a scope on alkynyl Prins reaction for the progress of new synthetic methods as well as it can be used as a key step in the total synthesis.

1.9 Tandem Prins reaction

Prins reaction can be utilized as a powerful initiator for the tandem process, because of the cyclic carbocation generation during the reaction. Some examples of the tandem Prins reactions are discussed below.

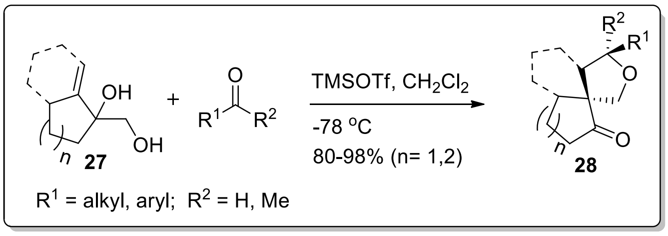
1.9.1 Tandem Prins pinacol rearrangement

In 1969, Mousset and co-workers first described the Prins pinacol reaction.[22a] To prepare the acetonide of meso allylic diol, they attempted the condensation reaction of allylic diol **22** and acetone under the action of an acidic clay catalyst, which resulted in a tetrahydrofuran **26** instead of the desired acetonide. Although the relative configuration of **26** and the mechanism of the reaction were wrongly assigned at the first attempt, after subsequent studies they corrected the structure of compound **26** with correct mechanism of the reaction. The condensation of meso allylic diol **22** and acetone initially form oxocarbenium ion **24**, which after Prins cyclization reaction formed β-hydroxy carbenium ion **25** and subsequent pinacol rearrangement produced tetrahydrofuran **26** (*Scheme 1.9.1.1*).[22b] Later, this methodology was harnessed by Overman for the highly efficient synthesis of numerous alkaloids, such as magellanine, magellaninone, etc., and it became a salient approach for the synthesis of complex molecular structures.[22c-d]

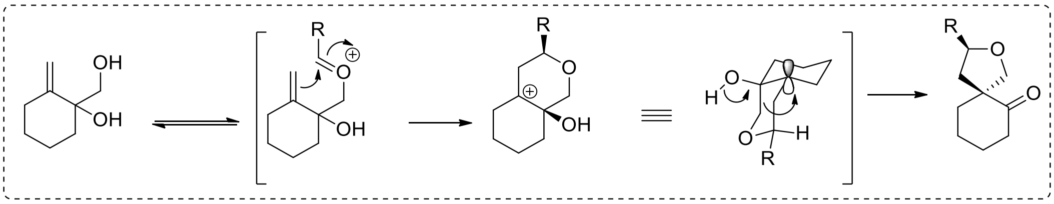


Scheme 1.9.1.1: First example of Pinacol terminated Prins cyclization reaction

In 2009, Cho et al. reported a Lewis acid initiated synthesis of oxaspirobicycles using a tandem Prins pinacol annulation reaction.[23a] Reaction of alkene diol **27** with numerous alkyl or aryl aldehydes and ketones produced 3-substituted oxaspiro-decanes/nonanes **28** in good yields with high diastereoselectivity (*Scheme 1.9.1.2*). 2-Oxaspiro-decanes/nonanes structural moiety has special attractions because these motifs are present in different natural products, including bakkenolide A, expansolide A, etc. The synthetic application of the reaction has been further extended for the synthesis of oxatricyclic compounds.

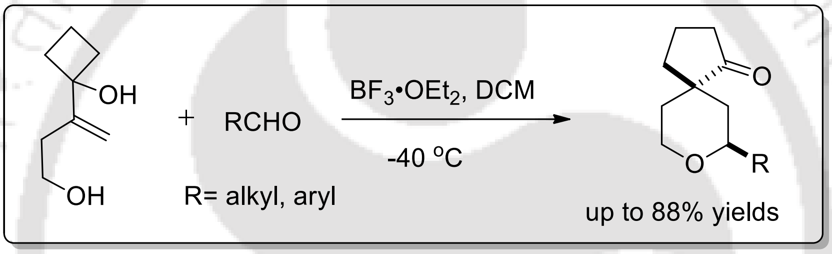


Scheme 1.9.1.2: Synthesis of oxaspirobicycles



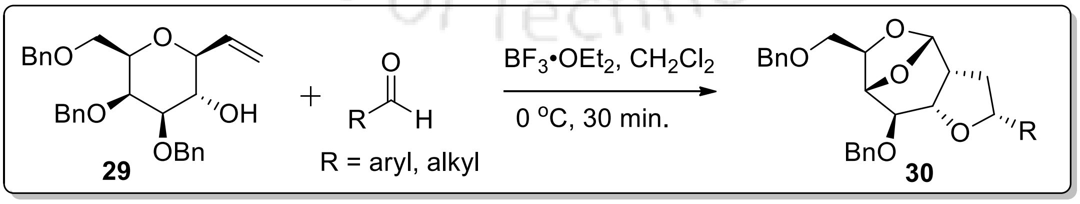
Scheme 1.9.1.3: Prins pinacol rearrangement mechanism for oxaspirobicycles synthesis

In 2014, Reddy and group described a methodology for the synthesis of oxaspirocycles by using Prins pinacol rearrangements.[23b] The reaction of aldehydes and 1-(4-hydroxybut-1-en-2-yl)cyclobutanol resulted with oxaspiro[4.5]decan-1-ones in high yields with excellent diastereoselectivity (*Scheme 1.9.1.4*). The reaction is highly adaptable with alkyl, aryl, hetero-aryl, and unsaturated aldehydes (*Scheme 1.9.1.4*).



Scheme 1.9.1.4: Synthesis of oxaspirocycles

In 2016, Vankar and co-workers described a tandem Prins and pinacol type rearrangement and subsequent intramolecular C4-OBn participation in the presence of $BF_3{\cdot}OEt_2$. The reaction of sugar originated homoallylic alcohols **29** with aldehydes furnished tetrahydrofuran fused bridged bicyclic ketals **30** in good yields (*Scheme 1.9.1.5*). The methodology was further used for the synthesis of tetrahydrofuranfused heptose compounds.[23c]

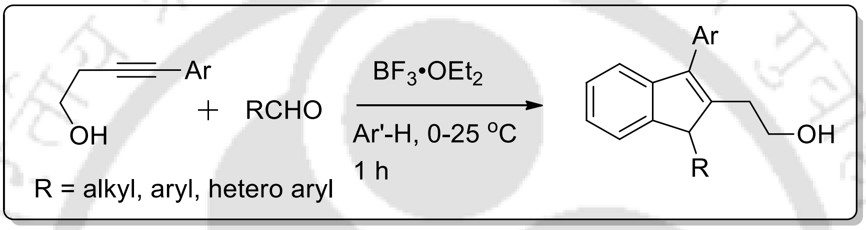


Scheme 1.9.1.5: Synthesis of fused bridged bicyclic ketals

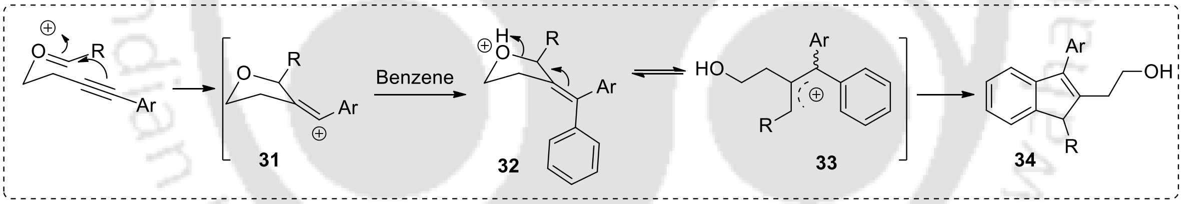
1.9.2 Tandem Prins Friedel-Crafts Reaction

Although the last two decades have seen an upsurge in the utilization of Prins Friedel-Crafts reaction towards the synthesis of various oxygen and nitrogen based heterocycles,[24a-b] we are briefly describing the recent developments in this area.

In 2018, Hou and co-workers demonstrated a Prins and Friedel-Crafts reaction sequence for the formation of functionalized indenes up to 90% yields under ambient conditions (*Scheme 1.9.2.1*).[24c] The reaction involves formation of carbocation **31** *via* Prins cyclization reaction of alkynyl alcohol and aldehydes, which after arene attack via Friedel-crafts reaction followed by ring opening generate carbocation **33**. Eventually, the carbocation **33** undergoes Friedel-Crafts arylation for the final cyclization to afford indene **34** (*Scheme 1.9.2.2*).

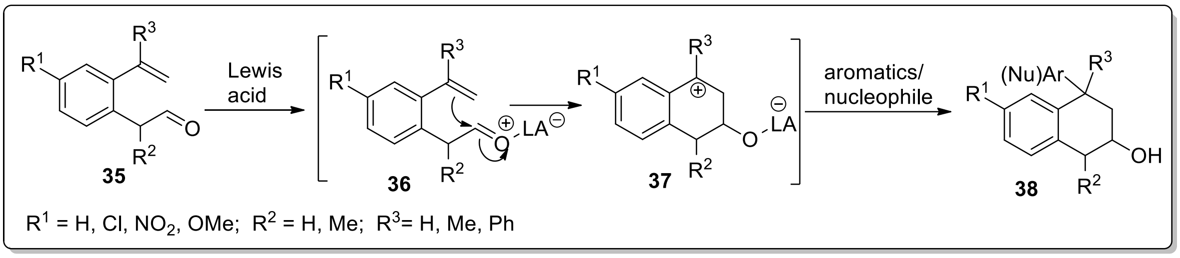


Scheme 1.9.2.1: Synthesis of functionalized indenes



Scheme 1.9.2.2: Prins Friedel-Crafts reaction mechanism for indene synthesis

In 2021, Wang and group reported an intramolecular Prins and Friedel-Crafts cascade reaction for synthesizing 4-aryl-tetralin-2-ols, 5-aryl-tetrahydro-5*H*-benzo[7]annulen-7-ols. Intramolecular Prins reaction of 2-(2-vinylphenyl)acetaldehyde **35** in the presence of $BF_3{\cdot}OEt_2$ formed benzyl carbocation intermediate **37** (*Scheme 1.9.2.3*). The carbocation **37** was then captured by various electron-rich arenes by Friedel-Crafts reaction to afford the final product **38**.[24d]

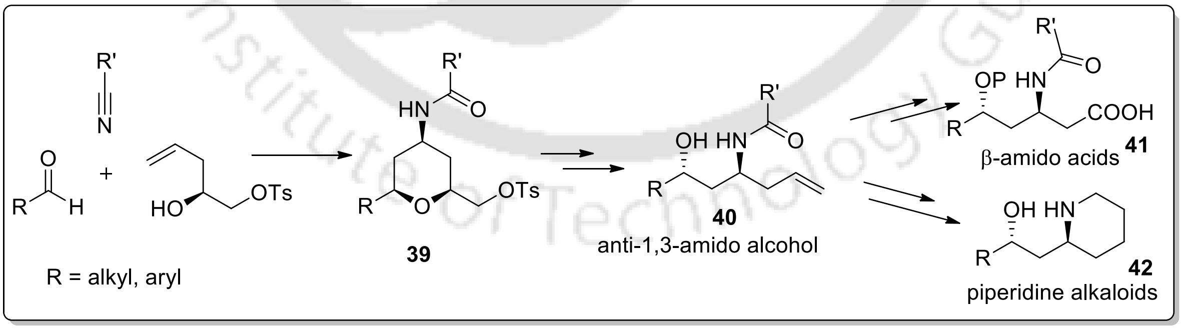


Scheme 1.9.2.3: Prins Friedel-Crafts annulation reaction

1.9.3 Tandem Prins-Ritter reaction

Ritter reaction is used for the synthesis of different nitrogen(N) containing heterocycles, including imidazolines, oxazolines, etc. In general, this reaction involves nucleophilic nitrile "N" lone pair attack towards carbocation followed by hydrolysis. This strategy can be applied in different reactions in tandem manner for the synthesis of piperidines, pyrrolidines, dihydroisoquinolines.[25a]

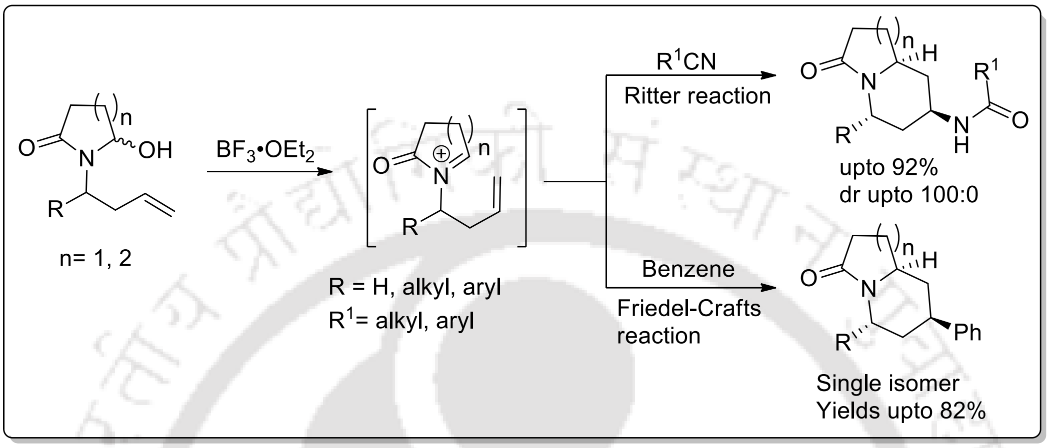
In 2013, Yadav and co-workers demonstrated a Prins Ritter reaction sequence for the synthesis of 4-amidotetrahydropyran **39**.[25b] The tosylated tetrahydropyran **39** was then converted to the corresponding iodide using NaI in refluxing acetone. The iodide compound is then converted to anti-1,3-amido alcohol **40** by reductive elimination using Zn dust in ethanol under reflux conditions. The synthetic methodology was further utilized for the total synthesis of β-amido acid and piperidine alkaloids (*Scheme 1.9.3.1*).



Scheme 1.9.3.1: Prins-Ritter strategy in total synthesis of β-amido acids and piperidine alkaloids

Saikia and co-workers reported a strategy for the synthesis of phenyl and amido azabicyclic scaffolds via tandem Prins Friedel-Crafts and Prins-Ritter reactions.[25c] In the presence of

BF_3•OEt_2, arenes have been utilized in tandem Prins and Friedel-Crafts reaction to capture the tetrahydropyranyl cation. Similarly, tandem Prins and Ritter reaction sequences have been used to capture the tetrahydropyranyl cation by nitrile group, and subsequent attack by water leads to the formation of amide functionality up to 92% yields with high stereoselectivity (*Scheme 1.9.3.2*).

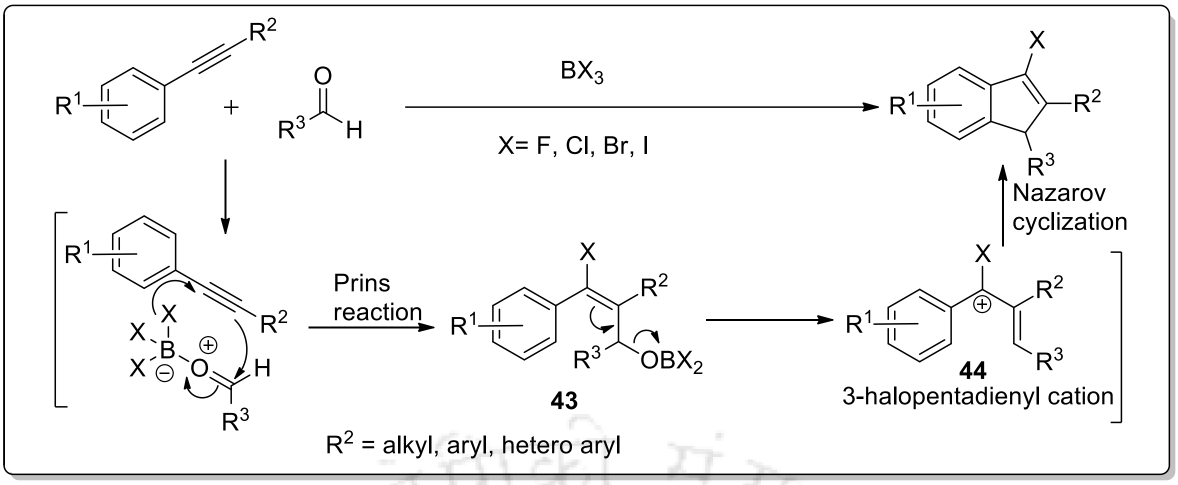


Scheme 1.9.3.2: Synthesis of phenyl and amido azabicyclic scaffolds

1.9.4 Prins Nazarov cyclization

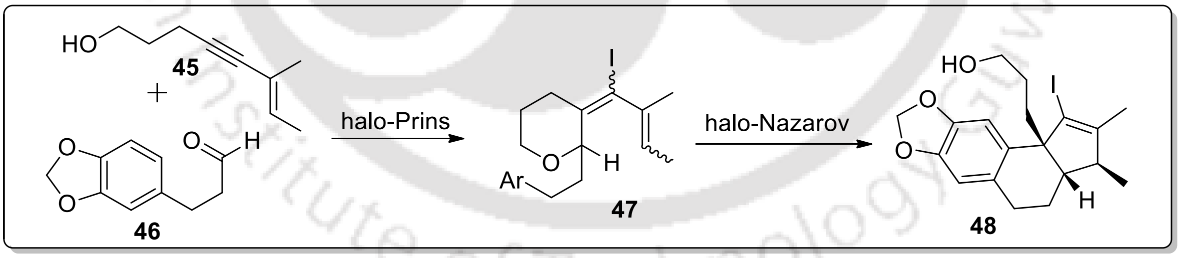
Nazarov reaction is an important tool in organic synthesis for the generation of cyclopentenones. Prins reaction can be conveniently used for the preparation of halo-adduct, which can be an efficient precursor for the Nazarov cyclization reaction.[21b-c, 25d]

In 2020, Lee and group demonstrated a tandem Prins Nazarov cyclization reaction for the synthesis of functionalized indenes.[21b] They used a special class of chromene carboxaldehyde, which was activated by BX_3. Subsequent Prins reaction generated 3-halopentadienyl cation **44**, which undergoes Nazarov cyclization to form the final halo-substituted indenes. In this reaction, BX_3 acts as both a carboxaldehyde activator and a halide source (*Scheme 1.9.4.1*).



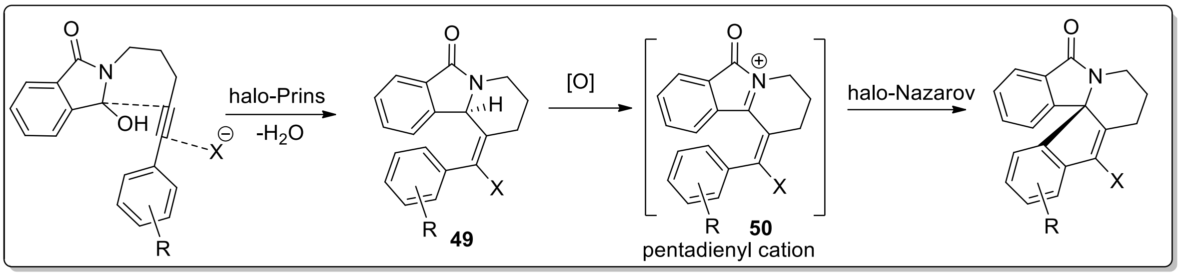
Scheme 1.9.4.1: Halo-indenes synthesis via Prins Nazarov cyclization reaction

In 2019, Frontier and co-workers demonstrated an efficient methodology for synthesizing functionalized polycyclic molecules using halo-Prins/halo-Nazarov strategy.[25d] In the presence of TfOH and TBAI, the reaction of alkynyl alcohol **45** with aldehyde **46** formed the iodo-adduct **47** through a halo-Prins reaction. In the same pot, acidic reaction condition promotes the cationic cascade via halo-Nazarov reaction followed by Friedel-Crafts allylation in highly diastereoselective manner. In the same year, they also reported functionalized haloindenes and indanones utilizing halo-Prins and subsequent aryl halo-Nazarov cyclizations (*Scheme 1.9.4.2*).



Scheme 1.9.4.2: Functionalized polycycles synthesis by Prins Nazarov cyclization reaction

In 2021, Frontier and co-workers again described a strategy for synthesizing spirocyclic isoindolones by employing alkynyl aza-Prins reaction followed by an oxidative halo-Nazarov cyclization reactions.[21c] The halo-Prins adduct **49** was oxidized at the 3-isoindolone position by activating the amide group using Tf_2NH and 2-chloropyridine to generate a pentadienyl cation, which undergoes a halo-Nazarov cyclization to form the final compound (*Scheme 1.9.4.3*).

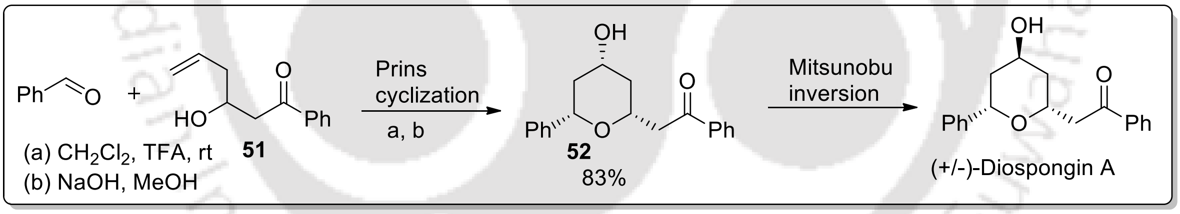


Scheme 1.9.4.3: Synthesis of spirocyclic isoindolones via Prins Nazarov cyclization

1.10 Prins reaction in the synthesis of natural products

1.10.1 Synthesis of diospongin A

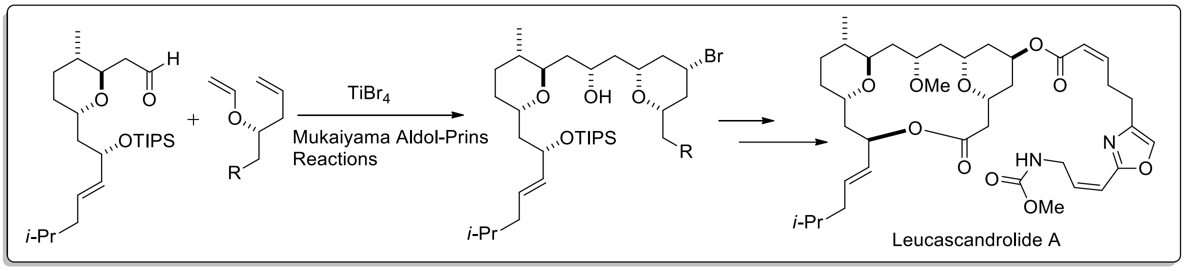
In 2007, Piva and group reported a simple synthetic strategy for the total synthesis of (+/−)-diospongin A with an overall yield of 23%.[6c] The transformations started from benzaldehyde and were converted to β-hydroxyketone **51** using different chemical reactions. Moreover, the reaction of unsaturated β-hydroxyketone **51** with benzaldehyde afforded 2,4,6-*cis*-trisubstituted tetrahydropyrans *via* Prins reaction and finally Mitsunobu reaction conditions, inverted the configuration of C4-hydroxyl group (*Scheme 1.10.1.1*).



Scheme 1.10.1.1: Synthesis of (+/-)-diospongin A by Prins cyclization reaction

1.10.2 Synthesis of Leucascandrolide A

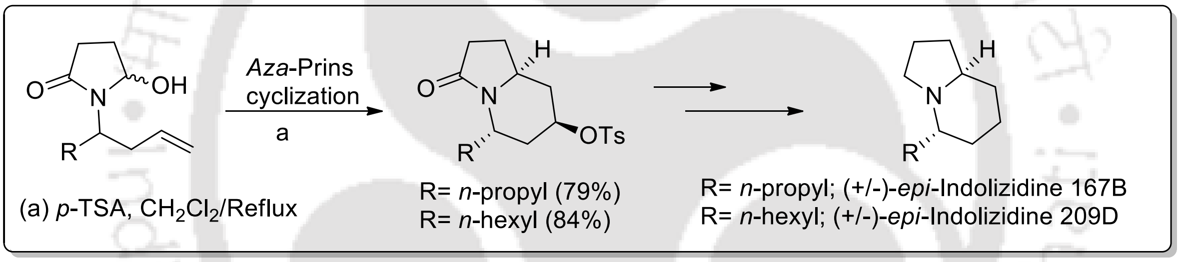
In 2007, Rychnovsky and co-workers demonstrated a total synthesis of Leucascandrolide A (a marine natural product) in overall 4.3% yields.[26a] $TiBr_4$ promoted Mukaiyama aldol Prins reaction has been utilized to assemble the core of the molecule in a stereoselective manner. The same group in 2008 reported a formal synthesis of (-)-Kendomycin using Prins cyclization to assemble the macrocycle in conformational preference (*Scheme 1.10.2.1*).[26b]



Scheme 1.10.2.1: MAP approach for the synthesis of leucascandrolide A

1.10.3 Synthesis of (±)-epi-indolizidine 167B and 209D

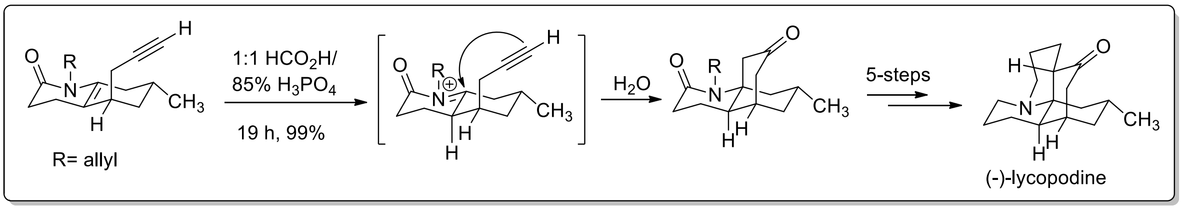
In 2014, Saikia and group also developed a methodology for synthesizing *o*-tosyl aza-bicyclic heterocycles using aza Prins cyclization reaction of endocyclic *N*-acyliminium ions.^{26c} The methodology was further extended for the synthesis of piperidine alkaloid (±)-epi-indolizidine 167B and (±)-epi-indolizidine 209D by manipulating the -OTs group (*Scheme 1.10.3.1*).



Scheme 1.10.3.1: Aza-Prins cyclization via endocyclic N-acyliminium ion

1.10.4 Synthesis of (-)-Lycopodine

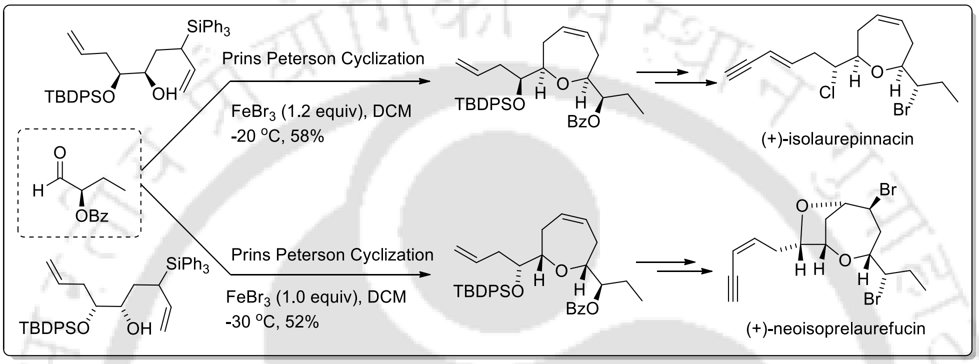
In 2016, She and co-workers reported a protecting group free strategy for the total synthesis of (−)-lycopodine alkaloid in eight steps from Wade's enone.^{26d} Phosphoric acid mediated stereocontrolled alkyne aza-Prins cyclization reaction plays a key role in this transformation (*Scheme 1.10.4.1*).



Scheme 1.10.4.1: Total synthesis of (-)-lycopodine via aza-Prins cyclization reaction

1.10.5 Synthesis of (+)-Isolaurepinnacin and (+)-Neoisoprelaurefucin

In 2022, Padrón and co-workers reported an enantioselective total synthesis of marine natural products (+)-isolaurepinnacin and (+)-neoisoprelaurefucin in 5 and 1.3% overall yields respectively.[27a] Prins-Peterson cyclization is utilized as a common synthetic pathway for the synthesis of these two natural products. These macroalgae show a large number of distinct metabolites, for example, lauroxanes, exhibit a wide range of bioactivity ranging from antitumor to antiepileptic properties (*Scheme 1.10.5.1*).[27b-c]



Scheme 1.10.5.1: Synthesis of (+)-isolaurepinnacin and (+)-neoisoprelaurefucin via Prins Peterson reaction

Apart from these, there are numerous complex natural products synthesized using Prins reaction, including arcutinidine, arcutine, arcutinine, (–)-pentazocine, (–)-eptazocine etc.[27d-e]

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Chapter 2:

Stereoselective Synthesis of Hexahydrofuro[3,4-*b*] furan-4-ol and its Dimer *via* Tandem Prins and Pinacol Rearrangement

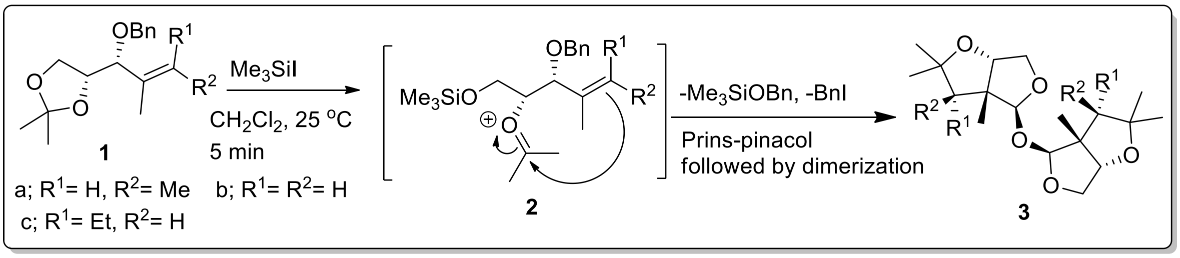
2.1 Importance and Applications

Tetrahydrofuran ring is an important motif in many natural products and biologically active molecules including, macrolides, polyether antibiotics, oxidized lipids or acetogenins.[1a-d] Natural products with a dihydro or perhydro furofuran moiety are often found to possess antifeedant activity against various insects and larvae.[1e] Recently, bis-tetrahydrofuran alcohol unit is found to be an prominent part of many multidrug resistant HIV agents viz. Darunavir, Brecanavir, GS-8374, SPI-256 etc.[2] Although there are several methods for the synthesis of hexahydrofuro[2,3-*b*]furan-3-ol in the literature,[3] but synthesis of hexahydrofuro[3,4-*b*]furan-4-ol is limited. In view of the importance of furofuran heterocyclic compounds, the construction of such unit in highly stereoselective manner is a challenge in synthetic organic chemistry.

2.2 An Overview of Relevant Synthetic Methods

An overview of Prins pinacol rearrangement reaction is discussed in chapter **1**, section **1.9.1**. Literature reports towards synthesis of hexahydrofuro[3,4-*b*] furan-4-ols in particular is described below.

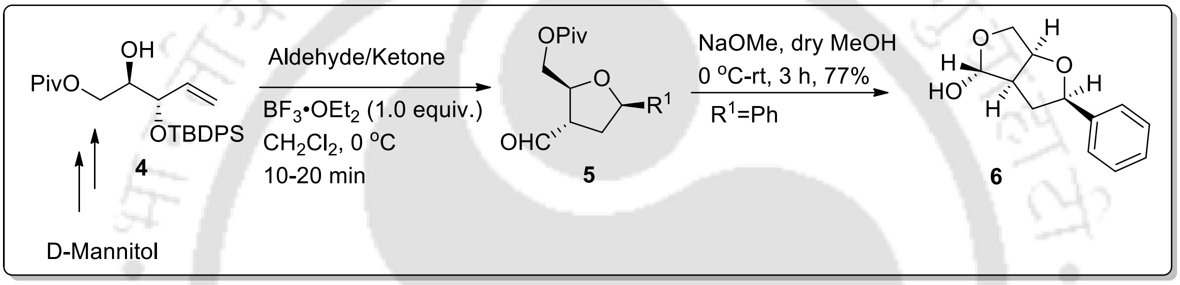
In 1993, Mulzer and co-workers reported a domino reaction of enetriol derivatives **1a-c** in the presence of Me_3SiI.[4] The acetonide ring of **1** was cleaved by trimethylsilyl iodide to generate oxocarbenium ion intermediate **2**, which further, intramolecular Prins pinacol rearrangement and subsequent dimerization to produce bis-furanoside derivatives **3** in moderate yields. The reaction was screened with different Lewis acids such as $AlCl_3$, $SnCl_4$, Me_3SiOTf, Me_3SiCN



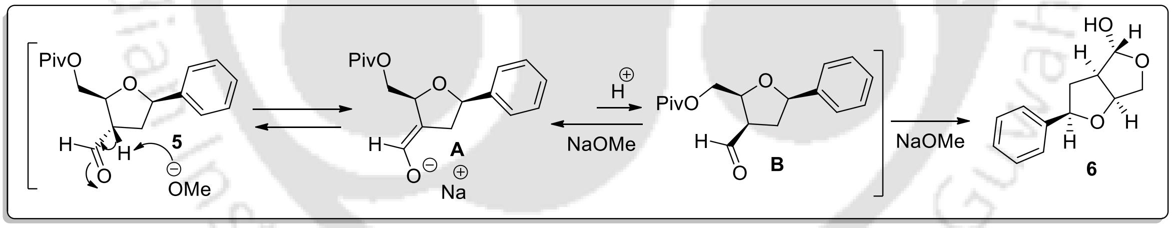
Scheme 2.2.1: Trimethylsilyl iodide promoted synthesis of bis-furanoside derivatives.

and Me_3SiCl, which failed to afford the desired products instead unreacted starting material or unidentified reaction mixture was observed (*Scheme 2.2.1*).

In 2018, Vankar and co-workers reported a Prins and pinacol type rearrangement reaction for the synthesis of 2,3-dideoxy-3C-formyl β-*C*-aryl furanosides **5** in good yields (*Scheme 2.2.2*).[5] Post-synthetic utility of the reaction was extended for the synthesis of **6**. The mechanism of formation of furanoside **6** was described as, base catalysed reaction of compound **5** undergoes in equilibrium condition with enolate **A**, which further make an equilibrium with compound **B** with inversion of configuration at C3 position. Finally, base catalysed hydrolysis to pivaloyl ester **B** in the presence of sodium methoxide in methanol and subsequent cyclization affords the final product **6** (*Scheme 2.2.3*).



Scheme 2.2.2: *Two step synthesis of hexahydrofuro[3,4-b] furan-4-ols*

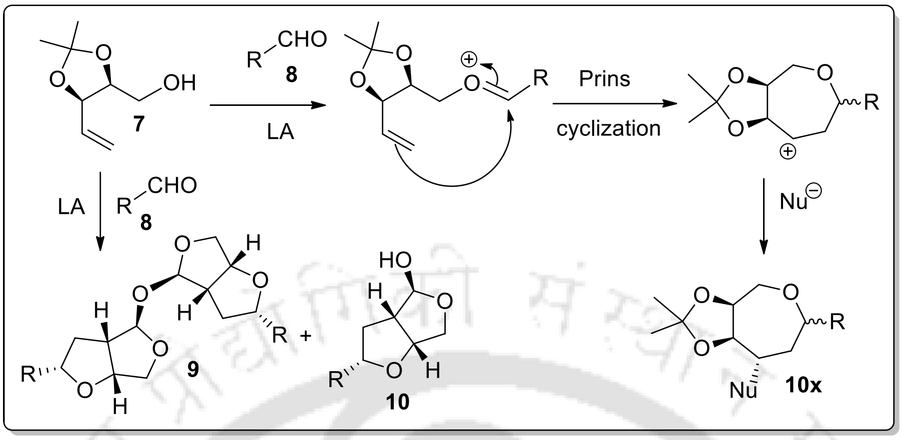


Scheme 2.2.3: *Plausible mechanism for the synthesis of hexahydrofuro[3,4-b] furan-4-ols*

2.3 Present Work

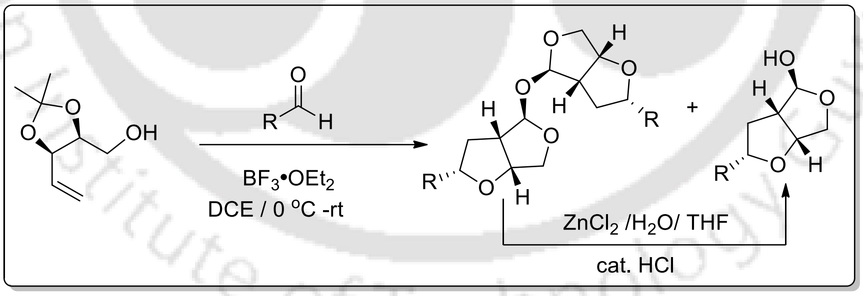
In continuation of our effort to synthesize oxacycles,[6] we envisioned that, the reaction of protected alcohol **7** with aldehyde under Prins cyclization conditions would provide seven membered oxygen heterocycles **10x** (*Scheme 2.3.1*), but to our surprise the proposed reaction provided hexahydrofuro[3,4-*b*]furan-4-ol (**10**) and its dimer **9**.

***Scheme 2.3.1:** Proposed reaction pathways.*



In this chapter, we described a method for the synthesis of hexahydrofuro[3,4-*b*]furan-4-ol, and its dimer in good yields with excellent diastereoselectivity. The Lewis acid mediated protocol followed tandem Prins cyclization reaction and pinacol rearrangement of (4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)methanol with aldehydes at 0 ˚C to room temperature. The dimer was conveniently converted to its corresponding monomer by aqueous zinc (II) chloride in THF in quantitative yields.

***Scheme 2.3.2:** Synthesis of furofurans.*



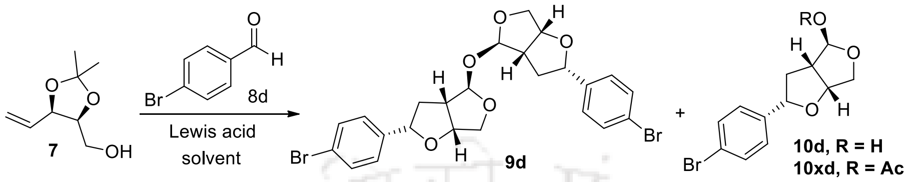
2.4 Results and Discussions

2.4.1 Optimization of the Reaction

Considering 4-bromobenzaldehyde **(8d)** and chiral alcohol ((4S,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)methanol (**7**) as model substrates, they were subjected to react with 1.2 equivalents of borontriflouride etherate ($BF_3{\cdot}OEt_2$) in dichloromethane at 0 ˚C to room temperature for 2 h (entry 1, Table 1) and to our surprise the proposed reaction provided dimer **9d** and monomeric unit **10d** with 20% (actual yield 40%) and 19%

yields, respectively. To suppress the yield of dimer, the reaction was performed at -40 °C (entry 2, Table 1), but obtained a mixture of dimer and monomer with 10% (actual yield 20%) and 12% yields, respectively (entry 2, Table 1).

Table 1 Optimization of reaction condition



entry	Substrate ratio 7:8d	Acid/(equiv)	Solvent	Temp/ °C	Time/ h	Yield (%)[a] 9d+10d+10xd
1	1:1	$BF_3•OEt_2$ (1.2)	CH_2Cl_2	0 to rt	2	20 + 19 + 0
2	1:1	$BF_3•OEt_2$ (1.2)	CH_2Cl_2	-40	2	10 + 12 + 0
3	1:1	$BF_3•OEt_2$ (2.0)	CH_2Cl_2	0 to rt	2	20 + 17 + 0
4	**1:1**	**$BF_3•OEt_2$ (1.2)**	**DCE**	**0 to rt**	**2**	**25 + 28 + 0**
5	1:1.5	$BF_3•OEt_2$ (1.2)	DCE	0 to rt	2	24 + 28 + 0
6	1:1	$BF_3•OEt_2$ (1.0)	DCE	0 to rt	2	21 + 24 + 0
7	1:1	$BF_3•OEt_2$ (1.2)	AcOH	0 to rt	2	5 + 19 + 40
8	1:1	$BF_3•OEt_2$ (1.2)	Toluene	0 to rt	2	19 + 21 + 0
9	1:1	$InCl_3$ (0.3)	CH_2Cl_2	0 to rt	3	0
10	1:1	$InCl_3$ (0.3)	CH_2Cl_2	40	12	0
11	1:1	$FeCl_3$ (0.1)	CH_2Cl_2	0 to rt	12	0
12	1:1	$FeCl_3$ (0.1)	CH_2Cl_2	40	12	0
13	1:1	$Sc(OTf)_3$ (0.2)	DCE	0 to rt	12	-
14	1:1	$Bi(OTf)_3$ (0.2)	DCE	0 to rt	24	-
15	1:1	TMSOTf (0.25)	CH_2Cl_2	0 to rt	1	17 + 19 + 0
16	1:1	TfOH (1.0)	CH_2Cl_2	0 to rt	2	d
17	1:1	PTSA (1.0)	CH_2Cl_2	0 to rt	24	0
18	1:1	TMSI (0.3)	CH_2Cl_2	0 to rt	5	0

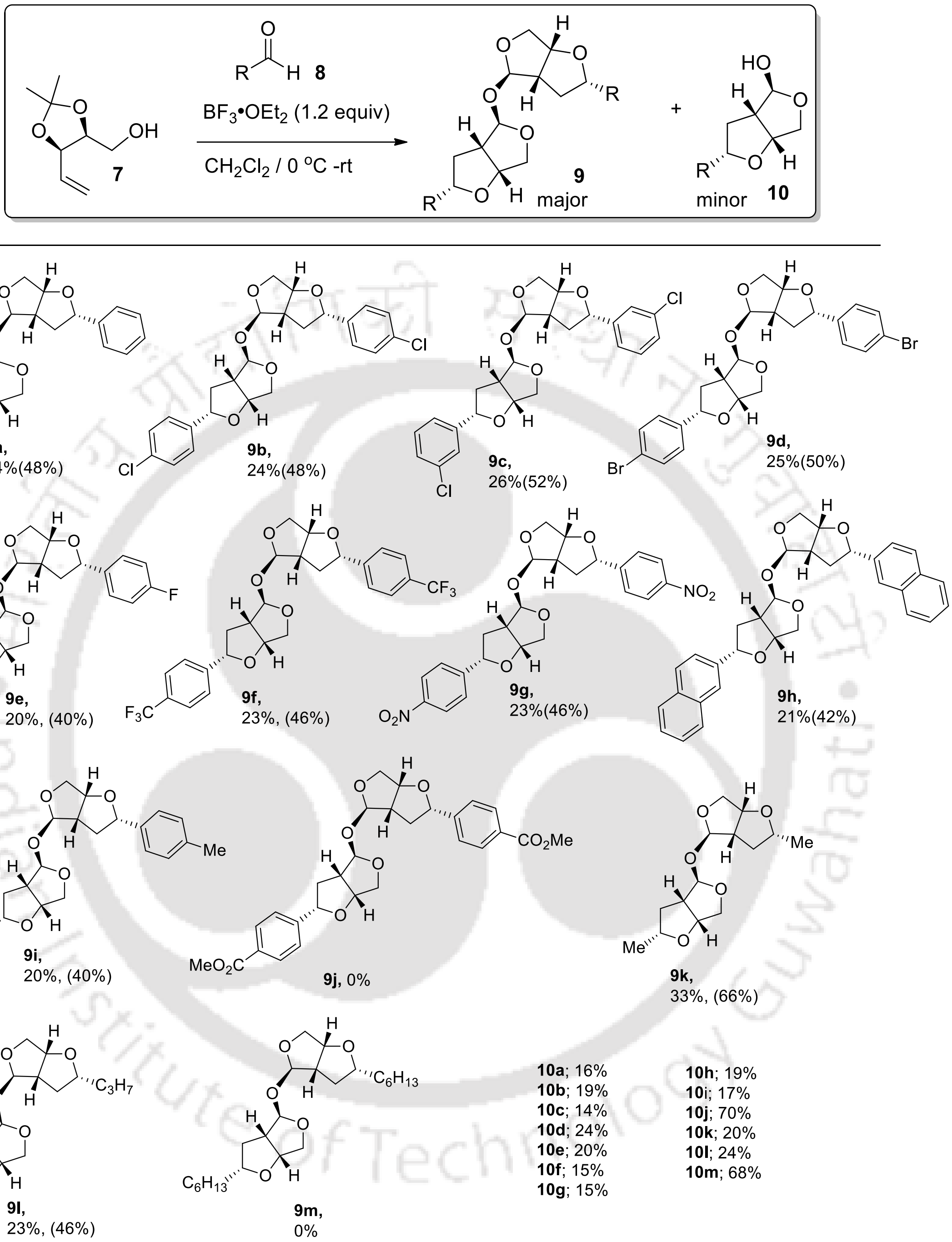
Reaction conditions: 7 (1.0 equiv), 8 (1.0 equiv), [a]yields refer to isolated yield.

Increase in concentration of $BF_3•OEt_2$ to two equivalents (entry 3, Table 1), the reaction has little effect on the selectivity and yield; whereas decreasing the concentration of Lewis acid (entry 6, Table 1), has adverse effect on the yield of **9d** (21%, actual yield 42%) and **10d** (24%). An enhanced yield 25% (actual yield 50%) of **9d** and 28% of **10d** were obtained, when the reaction was performed in dichloroethane (DCE) as solvent (entry 4, table 1). When the reaction was performed in acetic acid, it gave **9d**, **10d** and its acetate **10xd** in 5% (actual yield 10%), 19 and 40% yields, respectively (entry 7, Table 1). Toluene was found to be not a good solvent for the reaction (entry 8, Table 1). Other Lewis acids such as $InCl_3$, $FeCl_3$, $Sc(OTf)_3$, and $Bi(OTf)_3$, etc. were found to be inefficient for the reaction (entries 9-10, 11-14, Table 1). Trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave compounds **9d** and **10d**, with 17% (actual yield 34%) and 19% yields, respectively (entry 15, Table 1). On the other hand, Børnsted acids such as triflic acid and *p*-toluenesulfonic acids failed to give any products (entries 16-17, Table 1). Trimethylsilyliodide was also found to be inappropriate reagent for this reaction (entry 18, Table 1). The dimer **9** was converted into its monomer **10** by reacting with 2.0 equivalents of aqueous $ZnCl_2$ in presence of catalytic amount of concentrated HCl in good yields (*Scheme 2.4.2.2*). Therefore, 1.2 equivalents of $BF_3{\cdot}OEt_2$ in DCE and hydrolysis of **9** with aqueous $ZnCl_2$ are the optimum conditions for the synthesis of **10**.

2.4.2 Substrates Scope of the Reaction

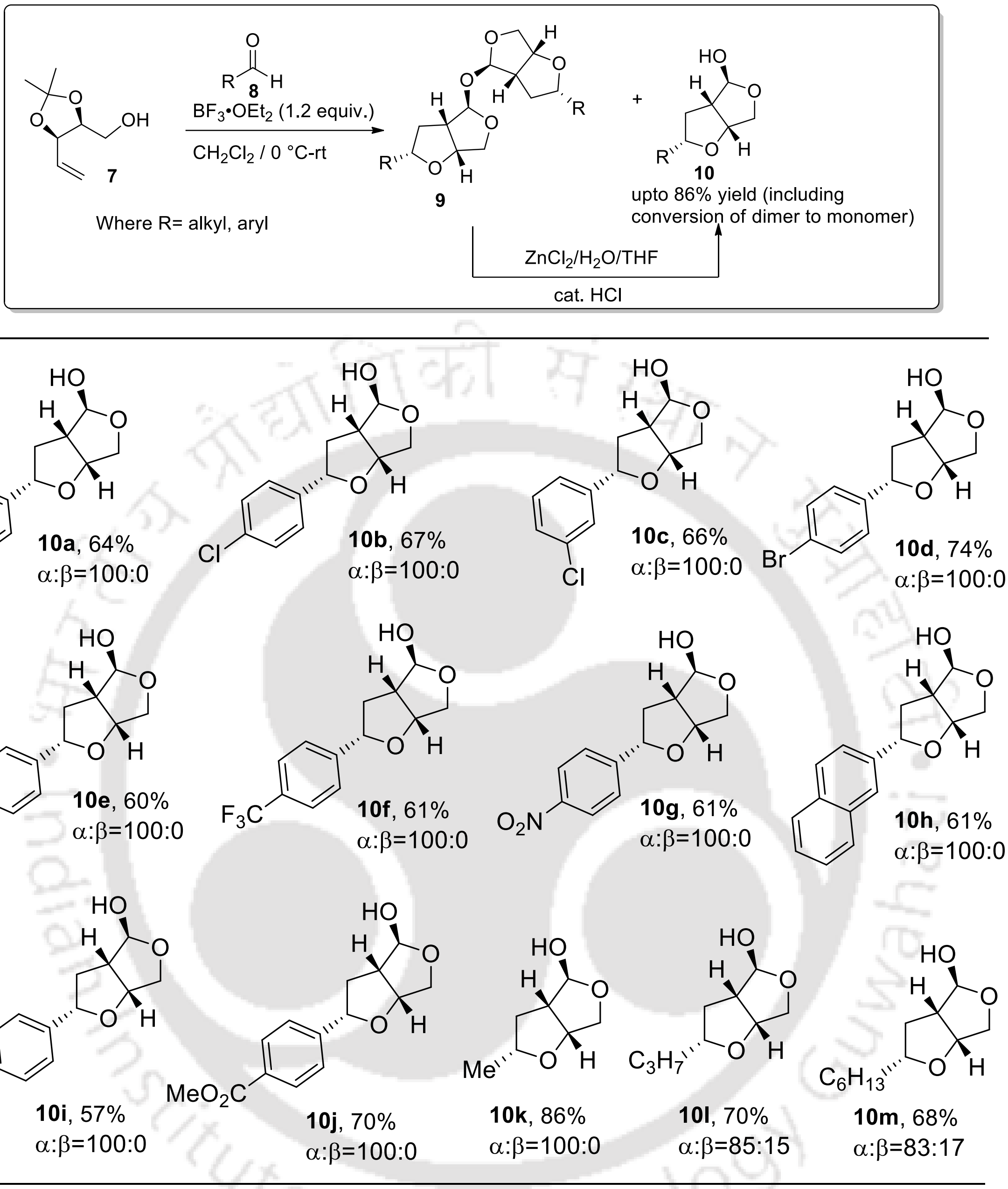
With this optimum condition in hand the reaction was generalized with different substrates and the results are shown in *Scheme 2.4.2.1* and *2.4.2.2*. It was observed that both aromatic and aliphatic aldehydes work well under the reaction conditions giving moderate to good yields. Electron-donating and electron- withdrawing groups on the aromatic ring does not have any role in yields. However, aliphatic aldehydes gave better yields than the aromatic aldehydes. Aromatic aldehyde with an ester group on the aromatic ring **8j** gave only monomer **10j** with 70% yield. Similarly, heptaldehyde **8m** yielded only monomer **10m** but an anomeric mixture with a ratio of α:β::83:17. Butanal also gave an anomeric mixture with a ratio of α:β::85:15. The formation of anomeric mixture in case of butanal and heptanal may be attributed to the steric effect of alkyl chain. As both alkyl chain and lactal ring are cis to each other, the lactal ring experiences a repulsive force from alkyl chain for which the lactal ring opens up giving anomeric mixture. This is supported by the fact that the anomeric mixture was not observed in case of acetaldehyde (*Scheme 2.4.2.2*). The stereochemistry and structure of **9** and **10** were determined by NMR spectroscopy and finally by X-ray crystallographic analysis of compounds **9d** and **10d**. It may be noted that the actual yield for all dimer is calculated on the basis that two equivalents of compound **7** is involved for generation of one equivalent of **9**. Same is true for conversion of **9** to **10**.

Scheme 2.4.2.1: *Synthesis of synthesis of hexahydrofuro[3,4-b] furan-4-ol and its dimer*[a]



[a]Reaction conditions: **7** (1.0 mmol, 1.0 equiv), **8** (1.0 mmol, 1.0 equiv), BF_3·OEt_2 (1.2 mmol, 1.2 equiv), DCE (4.0 mL), 0 °C-rt, [b]Yields refer to the isolated yield. Yields within parenthesis refer to the actual yield.

Scheme 2.4.2.2: *Conversion of dimer to its monomeric unit*[a]

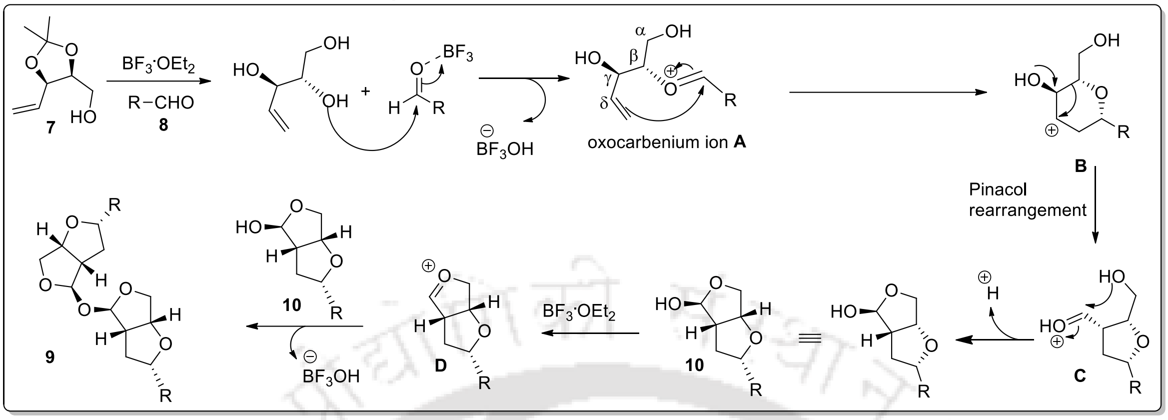


[a]Reaction conditions: **9** (0.1 mmol), saturated aq. solution of $ZnCl_2$ (1 mL), THF (3 mL), cat. Conc. HCl [b]Yields refer to the isolated combined yield.

2.5 Plausible Mechanism of the Reaction

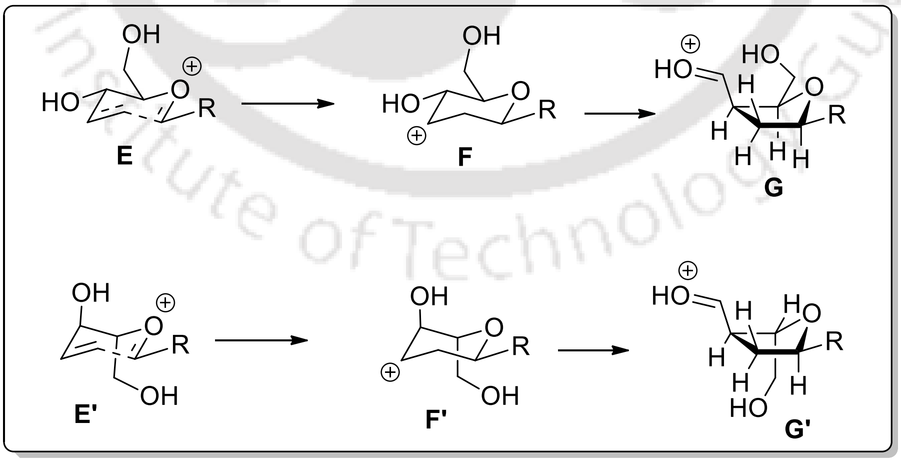
The mechanism of the reaction can be explained by considering previous Prins cyclization reactions[6] and illustrated in the literature.[4] The protected triol **7** under the influence of BF_3•OEt_2 forms oxocarbenium ion **A.** Prins cyclization and subsequent Pinacol type rearrangement forms furan ring **C** with a protonated aldehyde group in the side chain which reacts with alcoholic group to form second furan ring to give hexahydrofuro[3,4-*b*]furan-4-ol (**10**). BF_3•OEt_2 removes α-hydroxy group of compound **10** to produce oxocarbenium ion **D** which reacts with another hexahydrofuro[3,4-*b*]furan-4-ol (**10**) to give dimer **9** (*Scheme 2.5.1*).

***Scheme 2.5.1:** Mechanism of the reaction*



In the entire process the stereogenic center at C_β remains unchanged during the transformations and the six membered transition state **E** is responsible for the configurations at other stereogenic centers as $–CH_2OH$ and R groups will acquire the equatorial position of the six membered transition state **E** (*Scheme 2.5.2*). Suprafacial Pinacol rearrangement produced intermediate **G**, which forms second furan ring. Transition state **E′** is not a preferred conformation due to the 1,3-diaxial interactions experienced by both primary and secondary alcoholic groups. It would produce intermediate **G′**, which cannot form second furan ring as both the ring forming groups are in *trans* arrangement (*Scheme 2.5.2*).

***Scheme 2.5.2:** Model for the formation of single diastereomer*



2.6 Conclusion

In conclusion we have demonstrated a methodology for the synthesis of hexahydrofuro[3,4-*b*]furan-4-ol and its dimer with high enantio- and diastereo-selectivity. The reported method is faster and proceeds well under mild reaction condition to obtain desired products in good to high yield. The dimer can be conveniently converted into its monomer by hydrolysis with aqueous $ZnCl_2$ solution in THF without by-products.

2.7 Experimental Section

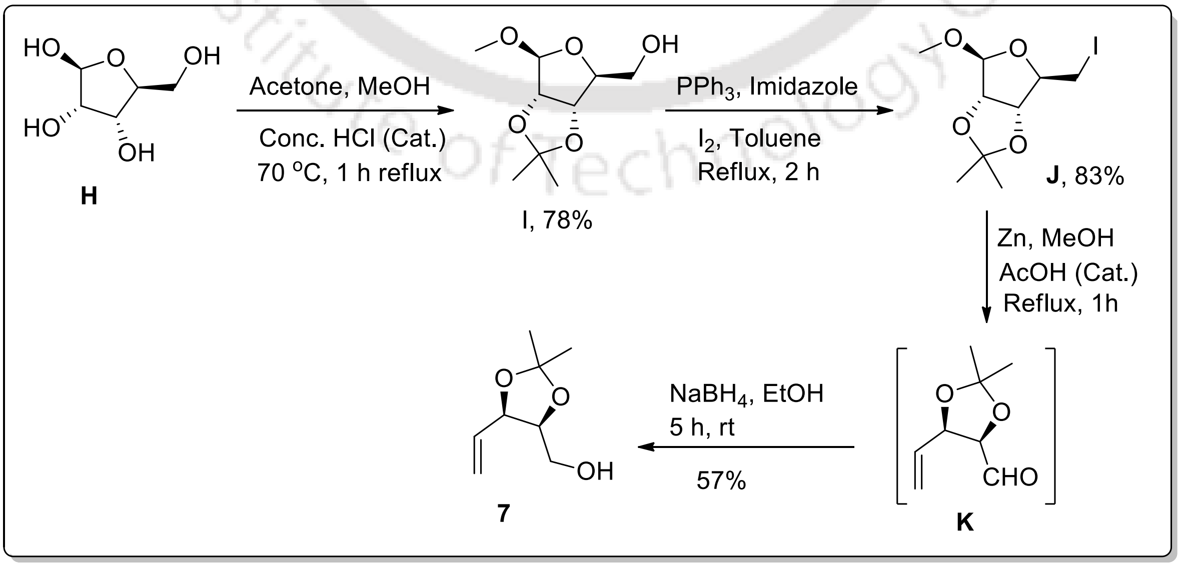
2.7.1 Instrumentations and Characterization

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

2.7.2 Preparation of Starting Material

The starting material alcohol **7** was prepared as per the literature procedure and the spectroscopic data are in good agreement with the literature one.[7] D-ribose **H** was transformed to ketal **I** in 78% yields using refluxing methanol and acetone in the presence of catalytic amount of conc. HCl. Ketal **I** was then converted to its iodo compound **J**, which was further reduced to **K** using Zn powder and addition of $NaBH_4$ in ethanol to afford the protected triol **7** (*Scheme 2.7.2.1*).

Scheme 2.7.2.1: *Synthesis of protected triol 7*



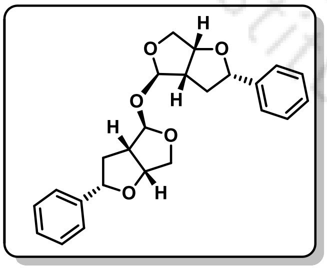
2.7.3 General Procedure for the Synthesis of (9a-9l, 10a-10m)

To a solution of chiral alcohol **7** (1.0 mmol) and aldehyde **8** (1.0 mmol) in dry DCE (4 mL), was added $BF_3.OEt_2$ (1.2 mmol) dropwise at 0 °C under nitrogen atmosphere. The reaction mixture was then stirred at room temperature for 2 h and progress of the reaction was monitored through TLC (EA: Hexane = 3:7). After completion of the reaction, the organic components were extracted with dichloromethane (2x10 mL) and washed with saturated sodium bicarbonate and brine solutions. The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4) and evaporated to get the crude dimer and monomer which were purified by column chromatography using ethyl acetate and hexane as eluents.

The hydrolysis of the dimer **9** (0.1 mmol) to its monomeric units **10** were accomplished by treating the dimer with aqueous saturated solution of $ZnCl_2$ (1 mL) and THF (3 mL) at room temperature in presence of catalytic amount of conc. HCl. After full conversion (monitored through TLC), the reaction mixture was neutralized by sodium bicarbonate, washed with brine and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to get the crude product which was purified by column chromatography to provide pure hexahydrofuro[3,4-*b*]furan-4-ol, **10** in high yield.

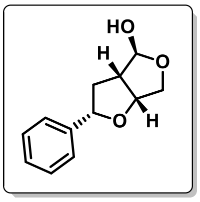
2.7.4 Characterization Data

(2S,2'S,3aS,3a'S,4R,4'R,6aR,6a'R)-4,4'-Oxybis(2-phenylhexahydrofuro[3,4-b]furan) (9a):



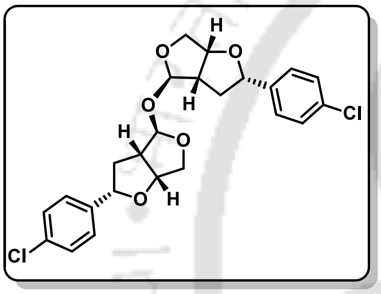
Colourless solid, yield 95 mg ((48)24%). mp 108–110 °C; *R*$_f$ = 0.60 (7:3 hexane/ethyl acetate); $[\alpha]^{25}_D$ +80.7 (c 0.30 $CHCl_3$); IR (KBr, neat) ν 2990, 2885, 1693, 1604, 1451, 1366, 1265, 1097, 1056, 924, 755, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.38–7.33 (m, 8 H), 7.31–7.27 (m, 2 H), 5.26 (s, 2 H), 4.78–4.73 (m, 4 H), 4.14 (d, *J* = 10.2 Hz, 2 H), 3.96 (dd, *J* = 10.2 and 4.2 Hz, 2 H), 2.93 (q, *J* = 9.0 Hz, 2 H), 2.58–2.50 (m, 2 H), 1.69–1.59 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 140.5, 128.7, 128.1, 126.3, 104.5, 83.3, 83.2, 72.6, 51.5, 39.9. HRMS (ESI) calcd. for $C_{24}H_{26}NaO_5$ $(M+Na)^+$: m/z 417.1672. Found 417.1687.

(2S,3aS,4S,6aR)-2-Phenylhexahydrofuro[3,4-b]furan-4-ol (10a):



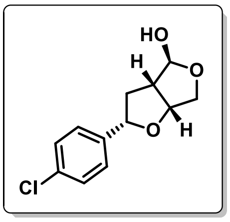
Colourless solid, yield (132 mg, 64%). mp 101-103 °C; R_f = 0.40 (7:3 hexane/ethyl acetate); $[\alpha]^{25}_D$ -10.5 (c 0.21 CHCl$_3$); IR (KBr, neat) ν 3418, 2927, 2882, 1643, 1455, 1367, 1215, 1103, 1066, 1028, 969, 759, 700 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ (ppm) 7.40–7.34 (m, 4 H), 7.31–7.28 (m, 1 H), 5.40 (s, 1 H), 4.82–4.77 (m, 2 H), 4.21–4.15 (m, 2 H), 3.01 (q, J = 7.8 Hz, 1 H), 2.79 (brs, 1 H), 2.60–2.55 (m, 1 H),1.68–1.62 (m, 1 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm) 140.6, 128.6, 128.0, 126.3, 103.7, 83.4, 83.1, 72.5, 52.3, 39.9. HRMS (ESI) Calcd for $C_{12}H_{14}NaO_3$ (M+Na)$^+$: m/z 229.0835. Found 229.0865.

(2S,2'S,3aS,3a'S,4R,4'R,6aR,6a'R)-4,4'-Oxybis(2-(4-chlorophenyl)hexahydrofuro[3,4-b]furan) (9b):



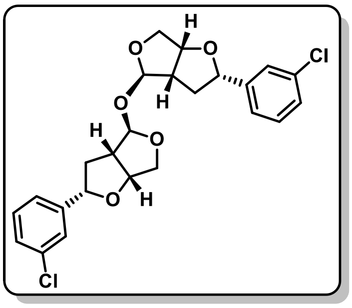
Colourless solid, yield (112 mg, (48)24%). mp 176-178 °C; R_f = 0.60 (7:3 hexane/ethyl acetate); $[\alpha]^{25}_D$ + 72.9 (c 0.26 CHCl$_3$); IR (KBr, neat) ν 2978, 2875, 1637, 1492, 1345, 1107, 1040, 1014, 967, 820, 693 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.33–7.23 (m, 8 H), 5.23 (s, 2 H), 4.77–4.70 (m, 4 H), 4.12 (d, J = 10.2 Hz, 2 H), 3.94 (dd, J = 10.2 and 4.2 Hz, 2 H), 2.91 (q, J = 8.8 Hz, 2 H), 2.56–2.49 (m, 2 H), 1.60–1.54 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm) 139.1, 133.7, 128.8, 127.6, 104.3, 83.3, 82.4, 72.5, 51.5, 40.0. HRMS (ESI) Calcd for $C_{24}H_{24}Cl_2KO_5$ (M + K)$^+$: m/z 501.0632. Found 501.0636.

(2S,3aS,4S,6aR)-2-(4-Chlorophenyl)hexahydrofuro[3,4-b]furan-4-ol (10b):



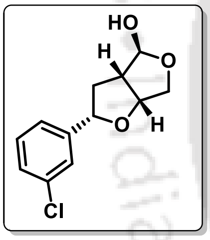
Colourless solid, yield (160 mg, 67%). mp 73-75 °C; R_f = 0.40 (7:3 hexane/ethyl acetate); $[\alpha]^{25}_D$ -16.0 (c 0.20 CHCl$_3$); IR (KBr, neat) ν 3404, 2924, 2853, 1647, 1493, 1364, 1214, 1092, 1068, 1033, 968, 819, 772 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.36–7.25 (m, 4 H), 5.37 (d, J = 1.6 Hz, 1 H), 4.79 (d, J = 7.2 Hz, 1 H), 4.74 (dd, J = 10.6 and 5.2 Hz, 1 H), 4.15 (d, J = 2.3 Hz, 2 H), 2.99 (q, J = 8.8 Hz, 1 H), 2.58–2.52 (m, 1 H), 2.50 (brs, 1 H), 1.58–1.52 (m, 1 H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm) 139.2, 133.7, 128.8, 127.6, 103.7, 83.5, 82.3, 72.5, 52.3, 39.9. HRMS (ESI) Calcd for $C_{12}H_{13}ClNaO_3$ (M + Na)$^+$ m/z 263.0445. Found 263.0447.

(2S,2'S,3aS,3a'S,4R,4'R,6aR,6a'R)-4,4'-Oxybis(2-(3-chlorophenyl)hexahydrofuro[3,4-b]furan) (9c):



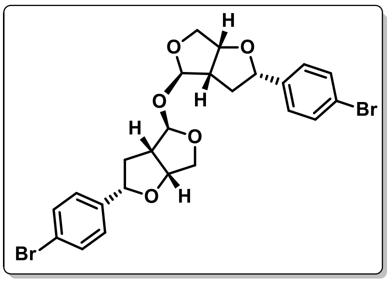
Colourless solid, yield (120 mg, (52) 26%). mp 103-105 °C; R_f = 0.50 (7:3 hexane/ethyl acetate); $[\alpha]^{25}_{D}$ + 76.5 (c 0.23 $CHCl_3$); IR (KBr, neat) ν 2932, 2876, 1633, 1477, 1347, 1214, 1105, 1039, 1017, 965, 785, 711 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.38 (s, 2 H), 7.28–7.24 (m, 6 H), 5.26 (s, 2 H), 4.78 (dd, *J* = 7.3 and 4.0 Hz, 2 H), 4.74 (dd, *J* = 10.2 and 5.0 Hz, 2 H), 4.16 (d, *J* = 10.2 Hz, 2 H), 3.98 (dd, *J* = 10.2 and 4.2 Hz, 2 H), 2.94 (q, *J* = 8.9 Hz, 2 H), 2.58–2.55 (m, 2 H), 1.64–1.59 (m, 2 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 142.8, 134.5, 129.9, 128.2, 126.4, 39.9, 124.4, 104.3, 83.4, 82.3, 72.5, 51.5, HRMS (ESI) Calcd for $C_{24}H_{24}Cl_2NaO_5$ $(M + Na)^+$ m/z 485.0893. Found 485.0914.

(2S,3aS,4S,6aR)-2-(3-Chlorophenyl)hexahydrofuro[3,4-b]furan-4-ol (10c):



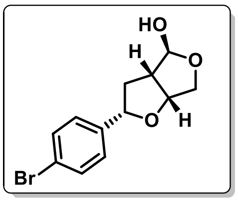
Colourless gum, yield (156 mg, 66%). R_f = 0.40 (hexane/ethyl acetae); $[\alpha]^{25}_{D}$ - 17.1 (c 0.26 $CHCl_3$); IR (KBr, neat) ν 3416, 29325, 2853, 1641, 1475, 1365, 1266, 1104, 1068, 1032, 982, 753, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37 (s, 1 H), 7.26–7.23 (m, 3 H), 5.37 (d, *J* = 2.0 Hz, 1 H), 4.80 (dd, *J* = 7.2 and 1.4 Hz, 1 H), 4.74 (dd, *J* = 10.6 and 5.2 Hz, 1 H), 4.18–4.11 (m, 2 H), 3.0 (q, *J* = 8.8 Hz, 1 H), 2.60–2.53 (m, 1 H), 2.41 (brs, 1 H), 1.62–1.54 (m, 1 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 142.8, 134.5, 129.9, 128.1, 126.3, 124.4, 103.7, 83.6, 82.3, 72.5, 52.2, 39.9. HRMS (ESI) Calcd for $C_{12}H_{13}ClNaO_3$ $(M + Na)^+$: m/z 263.0445. Found 263.0472.

(2S,2'S,3aS,3a'S,4R,4'R,6aR,6a'R)-4,4'-Oxybis(2-(4-bromophenyl)hexahydrofuro[3,4-b]furan) (9d):



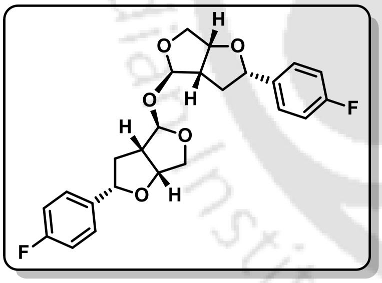
Colourless solid, yield (139 mg, (50)25%). mp 187-189 °C; R_f = 0.40 (7:3 hexane/ethyl aceytate); $[\alpha]^{25}_{D}$ + 61.5 (c 0.27 $CHCl_3$); IR (KBr, neat) ν 2978, 2863, 1642, 1488, 1349, 1214, 1100, 1068, 1010, 921, 739, 675 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.47 (d, *J* = 8.2 Hz, 4 H), 7.25 (d, *J* = 8.2 Hz, 4 H), 5.25 (s, 2 H), 4.77 (dd, *J* = 7.2 and 4.0 Hz, 2 H), 4.73 (dd, *J* = 10.6 and 4.0 Hz, 2 H), 4.14 (d, *J* = 10.2 Hz, 2 H), 3.97 (dd, *J* = 10.2 and 4.0 Hz, 2 H), 2.93 (q, *J* = 8.6 Hz, 2 H), 2.57–2.52 (m, 2 H), 1.65-1.57 (m, 2 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 139.7, 131.7, 128.0, 121.8, 104.3, 83.4, 82.4, 72.5, 51.5, 39.9. HRMS (ESI) Calcd for $C_{24}H_{24}Br_2NaO_5$ (M + Na)$^+$: m/z 574.9863. Found 574.9879.

(2S,3aS,4S,6aR)-2-(4-Bromophenyl)hexahydrofuro[3,4-b]furan-4-ol (10d):



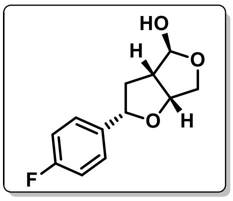
Colourless solid, yield (210 mg, 74%). mp 84-86 °C; R_f (7:3 hexane/ethyl acetate); $[\alpha]^{25}_D$ - 16.6 (c 0.33 $CHCl_3$); IR (KBr, neat) ν 3423, 2960, 2928, 1638, 1489, 1380, 1261, 1101, 1011, 804, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45 (d, *J* = 8.2 Hz, 2 H), 7.22 (d, *J* = 8.2 Hz, 2 H), 5.34 (s, 1 H), 4.78 (dt, *J* = 7.2 and 2.2 Hz, 1 H), 4.71 (dd, *J* = 10.6 and 5.0 Hz, 1 H), 4.13 (d, *J* = 2.2 Hz, 2 H), 2.98 (q, *J* = 8.6 Hz, 1 H), 2.92 (brs, 1 H), 2.57-2.50 (m, 1 H), 1.59–1.50 (m, 1 H), $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 139.7, 131.7, 127.9, 121.7, 103.6, 83.5, 82.3, 72.4, 52.2, 39.8. HRMS (ESI) Calcd for $C_{12}H_{14}BrO_3$ (M + H)$^+$: m/z 285.0121. Found 285.0134.

(2S,2'S,3aS,3a'S,4R,4'R,6aR,6a'R)-4,4'-Oxybis(2-(4-fluorophenyl)hexahydrofuro[3,4-b]furan) (9e):



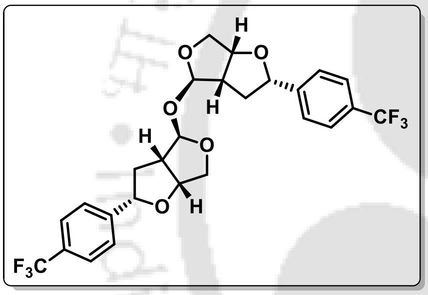
Colourless solid, yield (95 mg, (44)22%). mp 157-159 °C; R_f =0.40 (7:3 hexane/ethyl acetate); $[\alpha]^{25}_D$ + 67.3 (c 0.30 $CHCl_3$); IR (KBr, neat) ν 2980, 2875, 1605, 1513, 1350, 1227, 1107, 1063, 1016, 926, 839, 774, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35–7.31 (m, 4 H), 7.04–7.6.99 (m, 4 H), 5.25 (s, 2 H), 4.76–4.70 (m, 4 H), 4.12 (d, *J* = 10.0 Hz, 2 H), 3.95 (dd, *J* = 10.2 and 4.0 Hz, 2 H), 2.92 (q, *J* = 9.0 Hz, 2 H), 2.56–2.48 (m, 2 H), 1.64–1.56(m, 2 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 162.6 (d, *J* = 244.1 Hz), 136.2 (d, *J* = 3.0 Hz), 128.0 (d, *J* = 8.1 Hz), 115.5 (d, *J* = 21.3 Hz), 104.3, 83.2, 82.5, 72.5, 51.5, 40.0. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ (ppm) 47; HRMS (ESI) Calcd for $C_{24}H_{24}F_2NaO_5$ (M + Na)$^+$ m/z 453.1484. Found 453.1499.

(2S,3aS,4S,6aR)-2-(4-Fluorophenyl)hexahydrofuro[3,4-b]furan-4-ol (10e):



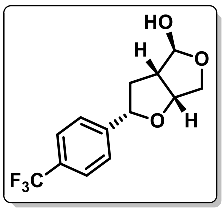
Colourless gum, yield (135 mg, 60%). R_f = 0.30 (7:3 hexane/ethyl acetate); $[\alpha]^{25}_{D}$ - 4.0 (c 0.20 $CHCl_3$); IR (KBr, neat) ν 3405, 2933, 2880, 1607, 1509, 1365, 1223, 1104, 1030, 922, 834, 797 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35–7.31 (m, 2 H), 7.04-6.99 (m, 2 H), 5.38 (s, 1 H), 4.79 (d, J = 7.2 Hz, 1 H), 4.74 (dd, J = 10.7 and 5.0 Hz, 1 H), 4.15 (d, J = 2.2 Hz, 2 H), 3.00 (q, J = 9.0 Hz, 1 H), 2.62 (brs, 1 H), 2.58–2.50 (m, 1 H), 1.66–1.54 (m, 1 H).$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 162.6 (d, J = 244.1 Hz), 136.4 (d, J = 3.0 Hz), 127.9 (d, J = 8.0 Hz), 115.5 (d, J = 21.3 Hz), 103.7, 83.4, 82.4, 72.5, 52.3, 40.0. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ (ppm) 47.3; HRMS (ESI) Calcd for $C_{12}H_{13}FNaO_3$ $(M + Na)^+$: m/z 247.0741. Found 247.0735.

(2S,2'S,3aS,3a'S,4R,4'R,6aR,6a'R)-4,4'-oxybis(2-(4-(Trifluoromethyl)phenyl)hexahydrofuro[3,4-b]furan)(9f):



Colourless solid, yield (120 mg, (46)23%). Mp 207-209 °C; R_f = 0.60 (7:3 hexane/ethyl acetate); $[\alpha]^{25}_{D}$ + 17.1 (c 0.35 $CHCl_3$); IR (KBr, neat) ν 2927, 2878, 1621, 1421, 1326, 1164, 1124, 1017, 968, 832, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58 (d, J = 8.0 Hz, 4 H), 7.47 (d, J = 8.0 Hz, 4 H), 5.23 (s, 2 H), 4.83–4.77 (m, 4 H), 4.14 (d, J = 10.2 Hz, 2 H), 3.96 (dd, J = 10.2 and 4.0 Hz, 2 H), 2.94 (q, J = 8.8 Hz, 2 H), 2.62–2.55 (m, 2 H), 1.64–1.56 (m, 2 H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 144.8, 130.2 (q, J = 32.2 Hz), 128.4, 125.6 (q, J = 3.6 Hz), 124.4 (q, J = 267.6 Hz), 104.5, 83.6, 82.3, 72.6, 51.5, 39.9. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ (ppm) 99.2; HRMS (ESI) Calcd for $C_{26}H_{24}F_6NH_4O_5$ $(M + NH_4)^+$: m/z 548.1867. Found 548.1893.

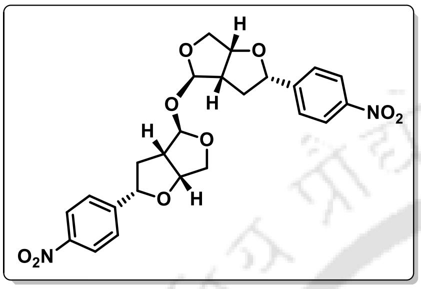
(2S,3aS,4S,6aR)-2-(4-(Trifluoromethyl)phenyl)hexahydrofuro[3,4-b]furan-4-ol (10f):



Colourless gum, yield (173 mg, 63%). R_f = 0.40 (hexane/ethyl acetate); $[\alpha]^{25}_{D}$ +2.9 (c 0.21 $CHCl_3$); IR (KBr, neat) ν 3442, 2925, 2856, 1621, 1417, 1326, 1164, 1124, 1067, 1018, 832, 739 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.60 (d, J = 8.0 Hz, 2 H), 7.48 (d, J = 8.0 Hz, 2 H), 5.35 (s, 1 H), 4.85–4.82 (m, 2 H), 4.19–4.14 (m, 2 H), 3.58 (brs, 1 H), 3.02 (q, J = 8.6 Hz, 1 H), 2.62–2.57 (m, 1 H), 1.61–1.55 (m, 1 H). $^{13}C\{^1H\}$ NMR

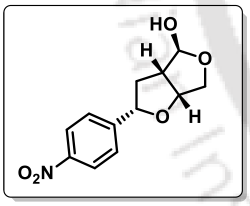
(150 MHz, $CDCl_3$) δ (ppm) 144.9, 130.1 (q, *J* = 32.1 Hz), 126.3 (q, *J* = 11.1 Hz), 125.6, 125.5, 124.4 (q, *J* = 270.3 Hz), 103.6, 83.7, 82.2, 72.3, 39.8, 52.2. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ (ppm) 99.2; HRMS (ESI) Calcd for $C_{13}H_{14}F_3O_3$ $(M + H)^+$: m/z 275.0890. Found 275.0907.

(2S,2'S,3aS,3a'S,4R,4'R,6aR,6a'R)-4,4'-Oxybis(2-(4-nitrophenyl)hexahydrofuro[3,4-b]furan) (9g):



Pale yellow solid, yield (110 mg, (46)23%). Mp 220-222 °C; *R*f = 0.40 (3: 2 hexane/ethyl acetate); $[\alpha]^{25}_D$ + 35.8 (c 0.27 $CHCl_3$); IR (KBr, neat) ν 2926, 2852, 1636, 1513, 1454, 1335, 1266, 1034, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.19 (d, *J* = 8.6 Hz, 4 H), 7.52 (d, *J* = 8.6 Hz, 4 H), 5.22 (s, 2 H), 4.86 (dd, *J* = 10.5 and 5.2 Hz, 2 H), 4.81(dd, *J* = 7.2 and 4.0 Hz, 2 H), 4.15 (d, *J* = 10.2 Hz, 2 H), 3.96 (dd, *J* = 10.2 and 4.0 Hz, 2 H), 2.96 (q, *J* = 8.7 Hz, 2 H), 2.66–2.59 (m, 2 H), 1.63–1.55 (m, 2 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 148.3, 147.7, 126.8, 124.0, 104.3, 83.8, 81.9, 72.5, 52.5, 40.0. HRMS (ESI) Calcd for $C_{24}H_{24}N_2NaO_9$ $(M + Na)^+$: m/z 507.1375. Found 507.1388.

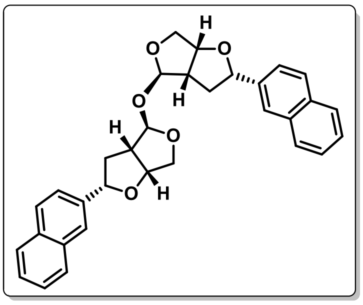
(2S,3aS,4S,6aR)-2-(4-Nitrophenyl)hexahydrofuro[3,4-b]furan-4-ol (10g):



Pale yellow gum, yield (156 mg, 61%). *R*f = 0.40 (3:2 hexane/ethyl acetate); $[\alpha]^{25}_D$ - 10.2 (c 0.32 $CHCl_3$); IR (KBr, neat) ν 2925, 2855, 1607, 1518, 1459, 1351, 1215, 1104, 1031, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.18 (d, *J* = 8.6 Hz, 2 H), 7.52 (d, *J* = 8.6 Hz, 2 H), 5.35 (s, 1 H), 4.89–4.83 (m, 2 H), 4.17 (d, *J* = 2.2 Hz, 1 H), 3.04 (q, *J* = 8.8 Hz, 2 H), 2.89 (brs, 1 H), 2.68–2.61 (m, 1 H), 1.61–1.52 (m, 1 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 148.4, 147.6, 126.8, 123.9, 103.6, 83.9, 81.8, 72.4, 52.2, 39.9, HRMS (ESI) Calcd for $C_{12}H_{14}NO_5$$(M + H)^+$: m/z 252.0866. Found 252.0815.

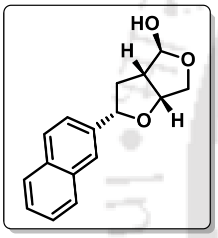
(2S,2'S,3aS,3a'S,4R,4'R,6aR,6a'R)-4,4'-oxybis(2-(naphthalen-2-yl)hexahydrofuro[3,4-b]furan) (9h):

Colourless solid, yield (104 mg, (42)21%). mp 186-188 °C; *R*f = 0.40 (7:3 hexane/ethyl acetate); $[\alpha]^{25}_D$ + 14.4 (c 0.19 $CHCl_3$); IR (KBr, neat) ν 2972, 2925, 2868, 1633, 1438,



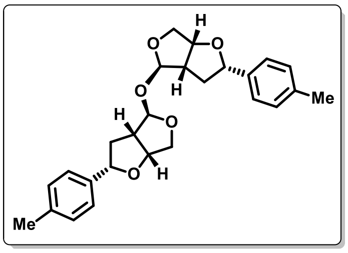
1338, 1274, 1100, 1039, 966, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (d, *J* = 8.0 Hz, 2 H), 7.84 (d, *J* = 8.0 Hz, 2 H), 7.76 (d, *J* = 8.0 Hz, 2 H), 7.56 (t, *J* = 8.0 Hz, 2 H), 7.50 (t, *J* = 8.0 Hz, 2 H), 7.29 (d, *J* = 18.4 Hz, 2 H), 6.05 (d, *J* = 6.6 Hz, 2 H), 5.05 (d, *J* = 5.4 Hz, 2 H), 4.83 (dd, *J* = 5.4 and 3.6 Hz, 2 H), 4.15 (dd, *J* = 10.2 and 4.0 Hz, 2 H), 3.50 (dd, *J* = 10.2 and 1.4 Hz, 2 H), 3.38–3.34 (m, 2 H), 2.36–2.30 (m, 2 H), 1.99 (d, *J* = 11.6 Hz, 2 H), 1.30–1.25 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 140.7, 134.2, 132.6, 129.4, 128.9, 126.9, 126.0, 124.4, 83.5, 77.83, 77.8, 76.6, 74.5, 45.4, 36.3. HRMS (ESI) Calcd for $C_{32}H_{30}NaO_5$ $(M + Na)^+$: m/z 517.1986. Found 517.1993.

(2S,3aS,4S,6aR)-2-(Naphthalen-2-yl)hexahydrofuro[3,4-b]furan-4-ol (10h):



Colourless gum, yield (154 mg, 61%); R_f = 0.30 (hexane/ethyl acetate); $[\alpha]^{25}_{D}$ + 15.3 (c 0.27 $CHCl_3$); IR (KBr, neat) ν 3440, 2938, 2881, 1616, 1445, 1364, 1215, 1170, 1095, 1019, 815, 784, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.83–7.81 (m, 4 H), 7.50–7.40 (m, 3 H), 5.41 (d, *J* = 1.8 Hz, 1 H), 4.93 (d, *J* = 10.6 and 5.2 Hz, 1 H), 4.86 (dd, *J* = 7.2 and 3.8 Hz, 1 H), 4.24 (d, *J* = 10.2 Hz, 1 H), 4.19 (dd, *J* = 10.2 and 4.0 Hz, 1 H), 3.09–3.02 (m, 1 H), 2.65–2.60 (m, 1 H), 2.45 (brs, 1 H), 1.75–1.67 (m, 1 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 138.1, 133.5, 133.4, 128.5, 128.2, 127.9, 126.3, 126.1, 125.0, 124.3, 103.8, 83.6, 83.2, 72.6, 52.4, 39.9. HRMS (ESI) Calcd for $C_{16}H_{16}NaO_3$ $(M + Na)^+$: m/z 279.0992. Found 279.0997.

(2S,2'S,3aS,3a'S,4R,4'R,6aR,6a'R)-4,4'-Oxybis(2-(*p*-tolyl)hexa -hydrofuro[3,4-*b*]furan)(9i):



Colourless solid, yield (84 mg, (40)20%). mp 178-180 °C; R_f = 0.50 (7:3 hexane/ethyl acetate); $[\alpha]^{25}_{D}$ + 75.2 (c 0.29 $CHCl_3$); IR (KBr, neat) ν 2990, 2924, 2861, 1617, 1445, 1365, 1266, 1098, 1067, 1020, 972, 804, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.25 (d, *J* = 7.8 Hz, 4 H), 7.13 (d, *J* = 7.8 Hz, 4 H), 5.25 (s, 2 H), 4.76–4.69 (m, 4 H), 4.13 (d, *J* = 10.2 Hz, 2 H), 3.95 (dd, *J* = 10.2 and 4.2 Hz, 2 H), 2.94–2.87 (m, 2 H), 2.51–2.48 (m, 2 H), 2.33 (s, 6 H), 1.67–1.59 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 137.8, 137.5, 129.3,

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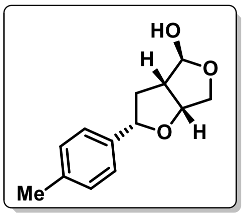
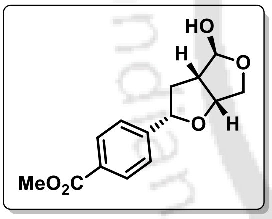
126.3, 104.4, 83.2, 83.1, 72.6, 51.5, 39.8, 21.4. HRMS (ESI) Calcd for $C_{26}H_{30}NaO_5$ $(M + Na)^+$: m/z 445.1986. Found 445.1988.

(2S,3aS,4S,6aR)-2-(*p*-Tolyl)hexahydrofuro[3,4-*b*]furan-4-ol (10i):



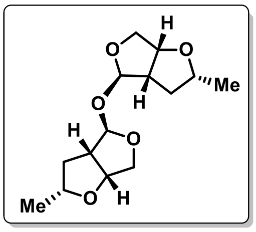
Colourless solid, yield (122 mg, 57%). mp 86-88 °C; $R_f = 0.40$ (7:3 hexane/ethyl acetate); $[\alpha]^{25}_D$ - 14.6 (c 0.21 $CHCl_3$). IR (KBr, neat) ν 3408, 2928, 2879, 1617, 1446, 1307, 1215, 1101, 1069, 1021, 922, 814, 785 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.25 (d, *J* = 7.8 Hz, 2 H), 7.13 (d, *J* = 7.8 Hz, 2 H), 5.38 (d, *J* = 1.8 Hz, 1 H), 4.78 (dd, *J* = 7.2 and 2.8 Hz, 1 H), 4.73 (dd, *J* = 10.6 and 1.8 Hz, 1 H), 4.16 (s, 2 H), 3.02–2.96 (m, 1 H), 2.56–2.49 (m, 1 H), 2.42 (brs, 1 H), 2.33 (s, 3 H), 1.66–1.57 (m, 1 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 137.8, 137.5, 129.3, 126.3, 103.8, 83.3, 83.0, 72.6, 52.3, 39.8, 21.4. HRMS (ESI) Calcd for $C_{13}H_{16}NaO_3$ $(M + H)^+$: m/z 243.0997. Found 243.0992.

Methyl 4-((2S,3aS,4S,6aR)-4-hydroxyhexahydrofuro[3,4-b]furan-2-yl)benzoate (10j):



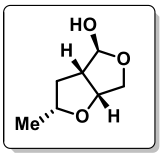
Colourless solid, yield (153 mg, 58%). Mp 106-108 °C; $R_f = 0.40$ (7:3 hexane/ethyl acetate); $[\alpha]^{25}_D$ - 21.3 (c 0.15 $CHCl_3$); IR (KBr, neat) ν 3423, 2924, 2852, 1790, 1613, 1437, 1277, 1105, 1068, 1019, 766 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.00 (d, *J* = 7.8 Hz, 2 H), 7.43 (d, *J* = 7.8 Hz, 2 H), 5.37 (s, 1 H), 4.82 (dd, *J* = 10.8 and 6.0 Hz, 2 H), 4.20–4.15 (m, 2 H), 3.91 (s, 3 H), 3.02 (q, *J* = 8.4 Hz, 1 H), 2.62 (brs, 1 H), 2.61–2.59 (m, 1 H), 1.62–1.56 (m, 1 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 167.2, 146.0, 130.0, 129.7, 126.0, 103.7, 83.7, 82.5, 72.5, 52.4, 52.3, 39.9. HRMS (ESI) Calcd for $C_{14}H_{16}NaO_5$ $(M + Na)^+$: m/z 287.0890. Found 287.0899.

(2R,2'R,3aS,3a'S,4R,4'R,6aR,6a'R)-4,4'-Oxybis(2-methylhexahydrofuro[3,4-b]furan) (9k):



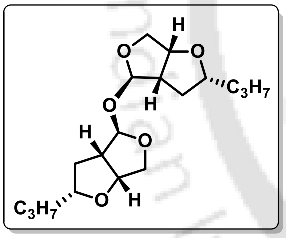
Colourless solid, yield (89 mg, (66)33%). mp 103-105 °C; $[\alpha]^{25}_D$ + 145.0 (c 0.32 $CHCl_3$); $R_f = 0.50$ (7:3 hexane/ethyl acetate); IR (KBr, neat) ν 2976, 2877, 1641, 1456, 1385, 1224, 1141, 1011, 985, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.19 (s, 2 H), 4.56 (dd, *J* = 7.0 and 4.2 Hz, 2 H), 3.97 (d, *J* = 10.0 Hz, 2 H), 3.85 (dd, J = 10.0 and 4.6 Hz, 4 H), 2.75 (q, J = 8.0 Hz, 2 H), 2.27–2.20 (m, 2 H), 1.26 (d, J = 6.0 Hz, 6 H), 1.28–1.24 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 104.6, 83.0, 77.4, 72.5, 51.6, 38.8, 19.8. HRMS (ESI) Calcd for $C_{14}H_{22}NaO_5$ (M + Na)$^+$: m/z 293.1360. Found 293.1364.

(2R,3aS,4S,6aR)-2-Methylhexahydrofuro[3,4-b]furan-4-ol (10k):



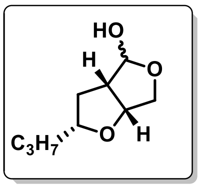
Colourless oil, yield (123 mg, 86%). R_f = 0.40 (6:4 hexane/ethyl acetate); [α]$^{25}_D$ + 10.0 (c 0.10 $CHCl_3$); IR (KBr, neat) ν 3417, 2962, 2852, 1643, 1453, 1388, 1260, 1102, 1012, 999, 800 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.34 (s, 1 H), 4.61 (dd, J = 4.8 and 2.6 Hz, 1 H), 4.06 (dd, J = 6.8 and 2.6 Hz, 1 H), 3.99 (d, J = 6.8 Hz, 1 H), 3.88–3.84 (m, 1 H), 2.86 (q, J = 5.8 Hz, 1 H), 2.34 (s, 1 H), 2.29–2.25 (m, 1 H), 1.26 (d, J = 4.0 Hz, 3 H), 1.27–1.24 (m, 1 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 104.0, 83.3, 77.5, 72.4, 52.5, 38.8, 19.8. HRMS (ESI) Calcd for $C_7H_{12}KO_3$ (M$^+$ + K): m/z 183.0419. Found 183.0407.

(2R,2'R,3aS,3a'S,4R,4'R,6aR,6a'R)-4,4'-Oxybis(2-propylhexahydrofuro[3,4-b]furan) (9l):



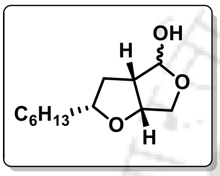
Colourless solid, yield (74 mg, (46)23%). Mp 87-89 °C; R_f = 0.50 (7:3 hexane/ethyl acetate); [α]$^{25}_D$ + 84.4 (c 0.27 $CHCl_3$); IR (KBr, neat) ν 2957, 2872, 1493, 1456, 1226, 1107, 1045, 1004, 929, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.17 (s, 2 H), 4.56 (dd, J = 7.2 and 4.0 Hz, 2 H), 3.96 (d, J = 10.0 Hz, 2 H), 3.84 (dd, J = 10.0 and 4.2 Hz, 2 H), 3.75–3.67 (m, 2 H), 2.73 (q, J = 8.6 Hz, 2 H), 2.25–2.18 (m, 2 H), 1.65–1.58 (m, 2 H), 1.47–1.40 (m, 4 H), 1.33–1.27 (m, 4 H), 0.92 (t, J = 7.2 Hz, 6 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 104.7, 82.9, 81.5, 72.5, 51.1, 37.1, 36.9, 19.8, 14.4. HRMS (ESI) Calcd for $C_{18}H_{30}NaO_5$ (M + Na)$^+$: m/z 349.1991. Found 349.2013.

(2R,3aS,4S,6aR)-2-Propylhexahydrofuro[3,4-b]furan-4-ol (4l, anomeric mixture, α:β=85:15) (10l):



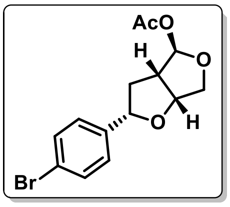
Colourless solid, yield (119 mg, 70%). Mp 103-105 °C; R_f = 0.40 (7:3 hexane/ethyl acetate); [α]$^{25}_D$ + 23.1 (c 0.13 $CHCl_3$); IR (KBr, neat) ν 3416, 2959, 2873, 1642, 1461, 1376, 1214, 1165, 1061, 1007, 927, 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.32 (s, 1 H, major), 5.26 (d, *J* = 5.4 Hz, 1 H, minor), 4.61 (dd, *J* = 7.2 and 4.0 Hz, 1 H), 4.44 (d, *J* = 10.8 Hz, 1 H, minor), 4.35 (dd, *J* = 10.8 and 4.2 Hz, 1 H, minor), 4.05 (dd, *J* = 10.0 and 4.0 Hz, 1 H, major), 4.00 (d, *J* = 10.0 Hz, 1 H, major), 3.95–3.85 (m, 1 H, minor), 3.77–3.69 (m, 1 H, major), 3.18–3.12 (m, 1 H, minor), 2.83 (q, *J* = 8.4 Hz, 1 H, major), 2.48–2.40 (m, 1 H, minor), 2.88–2.22 (m, 1 H, major), 1.50–1.22 (5 H), 1.66–1.59 (m, 1 H), 0.92 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 104.0, 99.0, 83.7, 83.0, 81.5, 81.3, 72.5, 72.2, 52.0, 37.5, 37.1, 36.9, 19.8, 19.5, 14.4, 14.2. HRMS (ESI) Calcd for $C_9H_{16}NaO_3$ $(M + Na)^+$: m/z 195.0992. Found 195.1020.

(2R,3aS,4S,6aR)-2-Hexylhexahydrofuro[3,4-b]furan-4-ol (4m, anomeric mixture, α:β=83:17) (10m):



Colourless oil, yield (146 mg, 68%); R_f = 0.60 (7:3 hexane/ethyl acetate); $[\alpha]^{25}_D$ + 12.0 (c 0.15 $CHCl_3$); IR (KBr, neat) ν 3405, 2927, 2856, 1640, 1459, 1366, 1223, 1109, 1033, 992, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.33 (s, 1 H), 4.62–4.58 (m, 1 H), 4.44 (d, *J* = 10.8 Hz, 1 H, minor), 4.35 (dd, *J* = 10.8 and 4.2 Hz, 1 H, minor), 4.06 (dd, *J* = 10.0 and 4.0 Hz, 1 H, major), 4.00 (d, *J* = 10.0 Hz, 1 H, major), 3.95–3.89 (m, 1 H, minor), 3.75–3.68 (m, 1 H, major), 3.18–3.12 (m, 1 H, minor), 2.83 (q, *J* = 8.2 Hz, 1 H, major), 2.53 (s, 1 H), 2.48–2.40 (m, 1 H, minor), 2.28–2.23 (m, 1 H, major), 2.05–2.00 (m, 1 H, minor), 1.91–1.86 (m, 1 H, minor), 1.66–1.61 (m, 1 H, major), 1.50–1.46 (m, 1 H, major), 1.42–1.36 (m, 1 H), 1.33–1.25 (m, 8 H), 0.88 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 104.1, 83.0, 81.8, 81.6, 79.2, 72.5, 72.3, 52.0, 45.1, 37.0, 35.8, 35.4, 35.2, 34.8, 32.0, 29.9, 29.6, 26.6, 26.4, 26.2, 22.8, 14.3. HRMS (ESI) Calcd for $C_{12}H_{22}NaO_3$ $(M + Na)^+$: 237.1462. Found 237.1482.

(2S,3aS,4R,6aR)-2-(4-Bromophenyl)hexahydrofuro[3,4-b]furan-4-yl acetate (10xd):

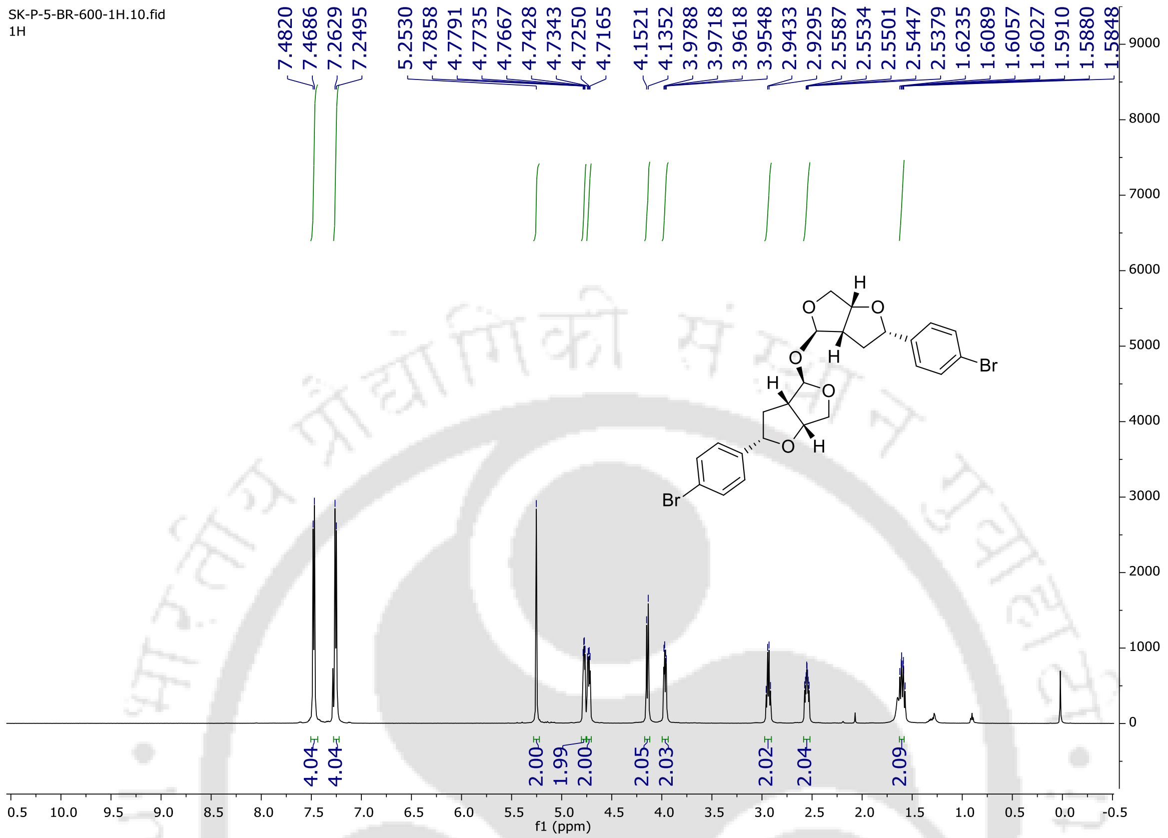


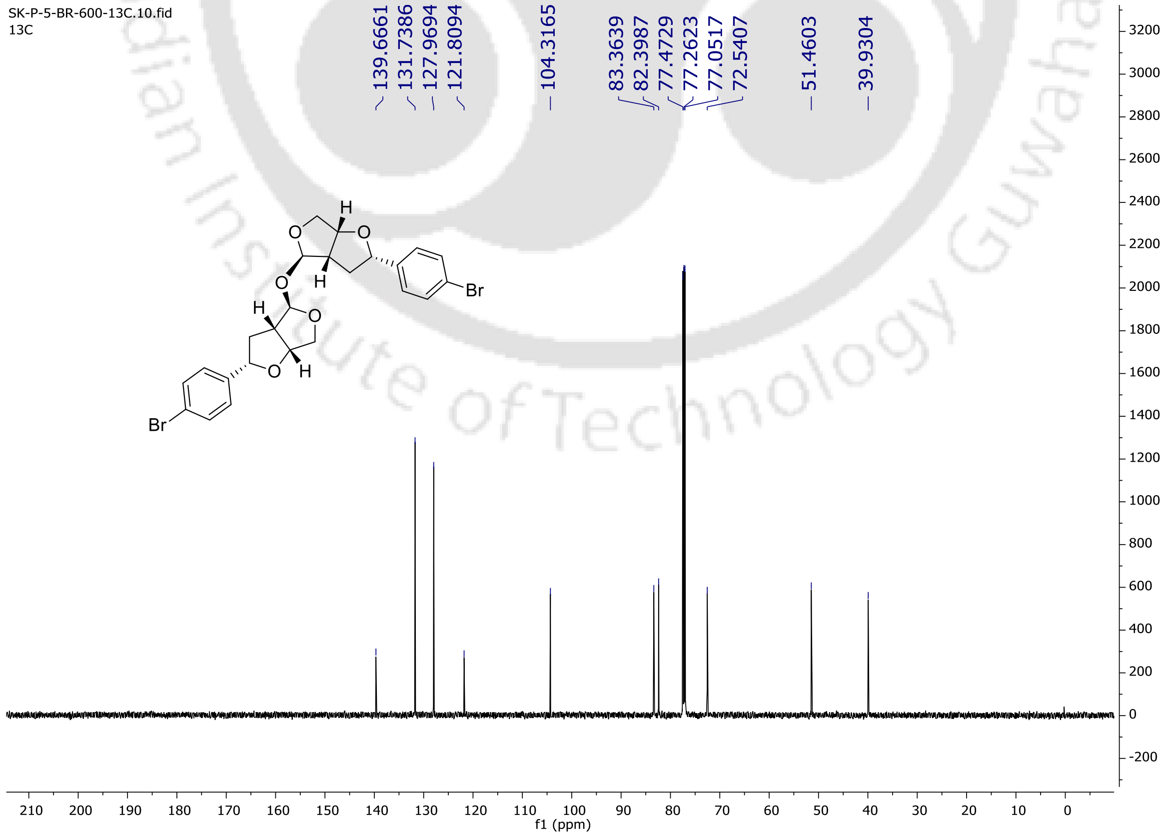
Colourless solid, yield (131 mg, 40%). mp 164-166 °C; R_f = 0.60 (4:1 hexane/ethyl acetate); $[\alpha]^{25}_D$ +55.2 (c 0.33 $CHCl_3$). IR (KBr, neat) ν 2926, 2854, 1740, 1643, 1489, 1366, 1238, 1106, 1071, 1010, 923, 817, 777, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46 (d, *J* = 8.4 Hz, 2 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 6.12 (s, 1 H), 4.79 ((dd, *J* = 7.2 and 4.0 Hz, 1 H), 4.73 (dd, *J* = 10.5 and 5.2 Hz, 1 H), 4.25 ((d, *J* = 10.4 and 4.2 Hz, 1 H), 4.06 ((dd, *J* = 10.4 and 4.2 Hz, 1 H), 3.06 (q, *J* = 8.6 Hz, 1

H), 2.65–2.58 (m, 1 H), 2.05 (s, 3 H), 1.67–1.59 (m, 1 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm) 170.3, 139.4, 131.7, 127.9, 103.4, 82.8, 82.4, 74.2, 51.5, 39.9, 21.4. HRMS (ESI) Calcd for $C_{14}H_{15}BrNaO_4$ (M + Na)$^+$: m/z 349.0046. Found 349.0065.

2.7.5 Representative spectra and crystal parameter

^{1}H (600 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100 MHz, $CDCl_3$) NMR spectra of **9d**





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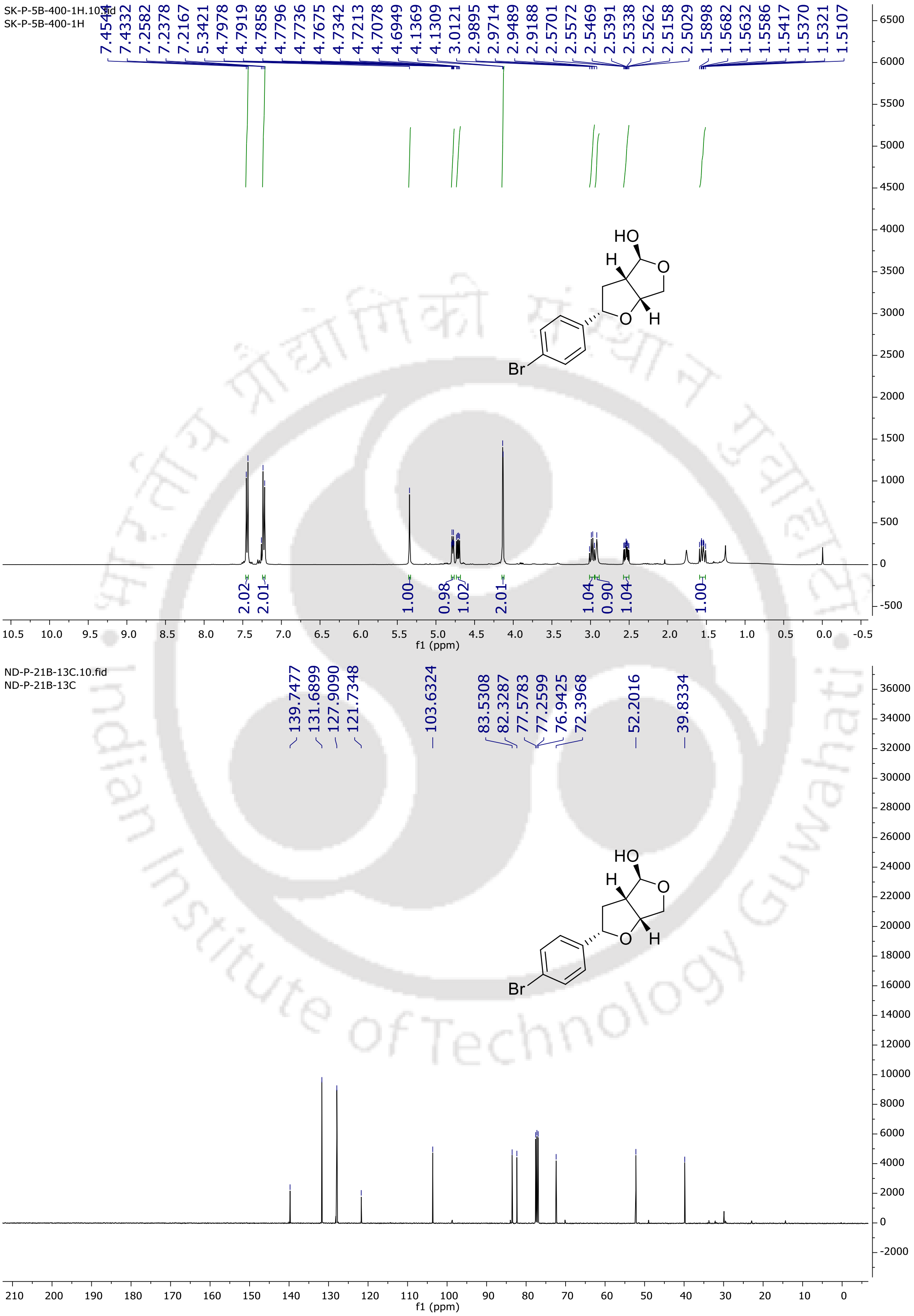
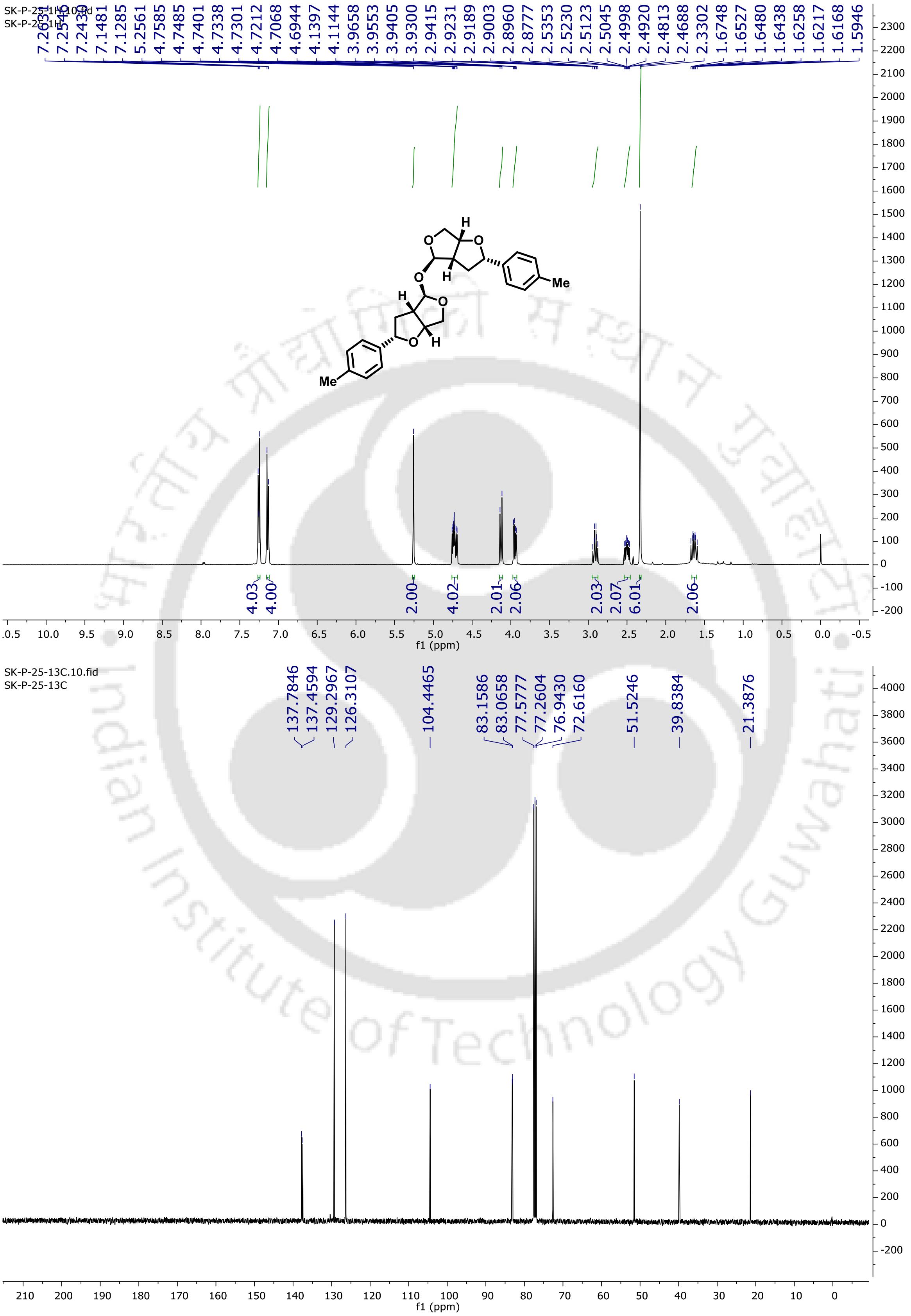
^{1}H (400 MHz, CDCl$_3$) and ^{13}C{^{1}H} (100 MHz, CDCl$_3$) NMR spectra of **10d**



^{1}H (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100 MHz, $CDCl_3$) NMR spectra of **9i**



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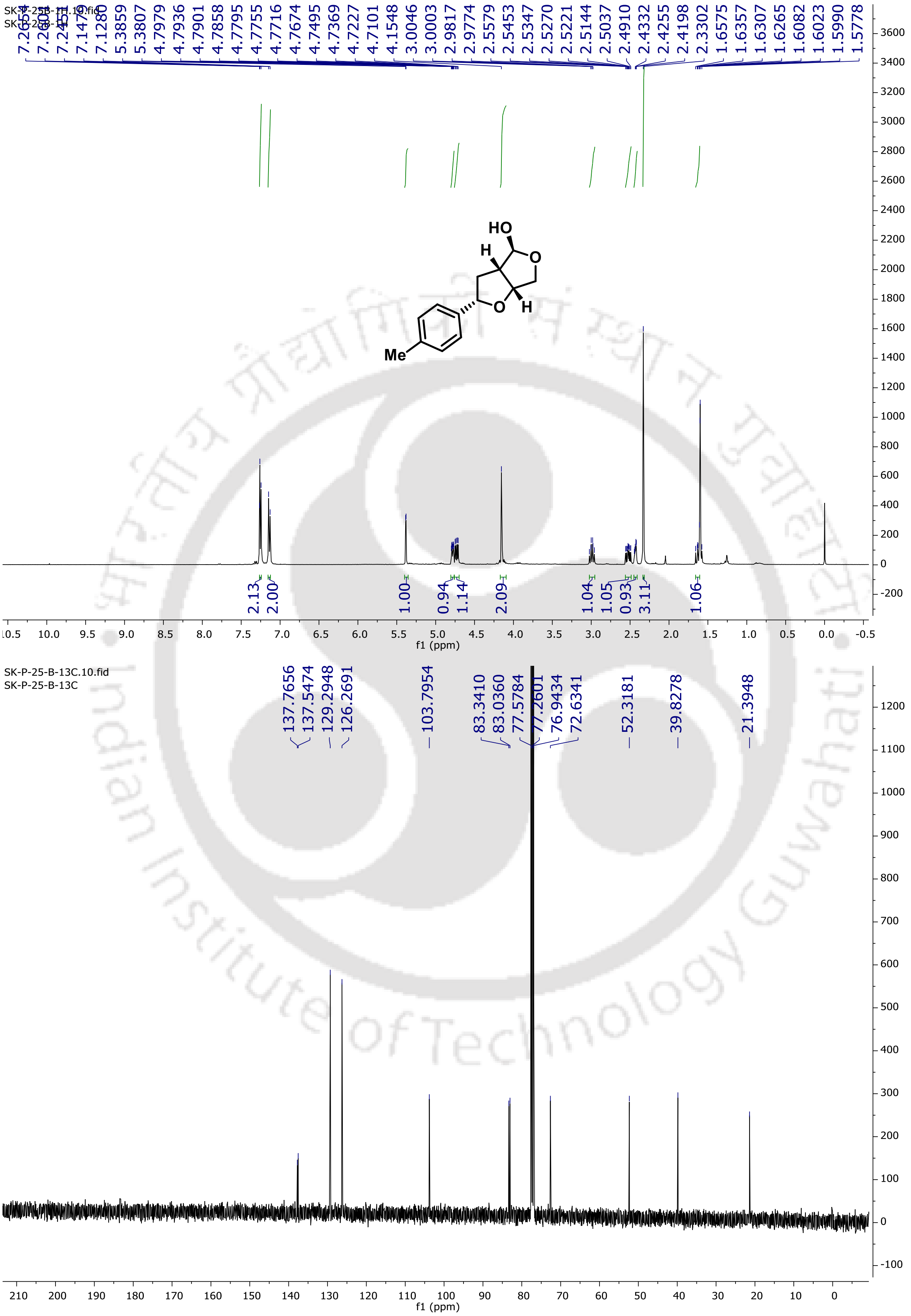
^{1}H (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100 MHz, $CDCl_3$) NMR spectra of **10i**



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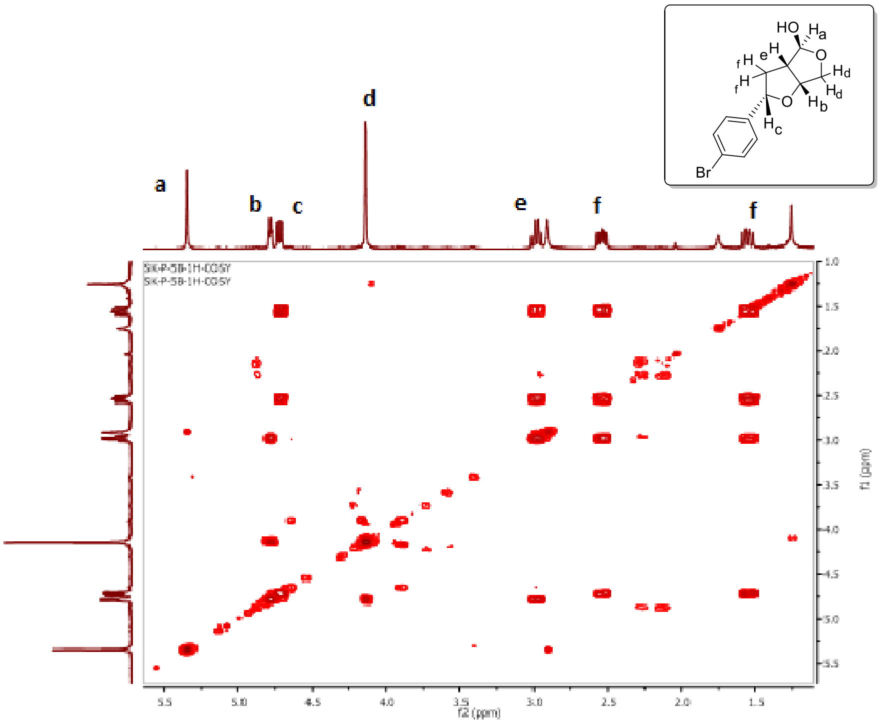
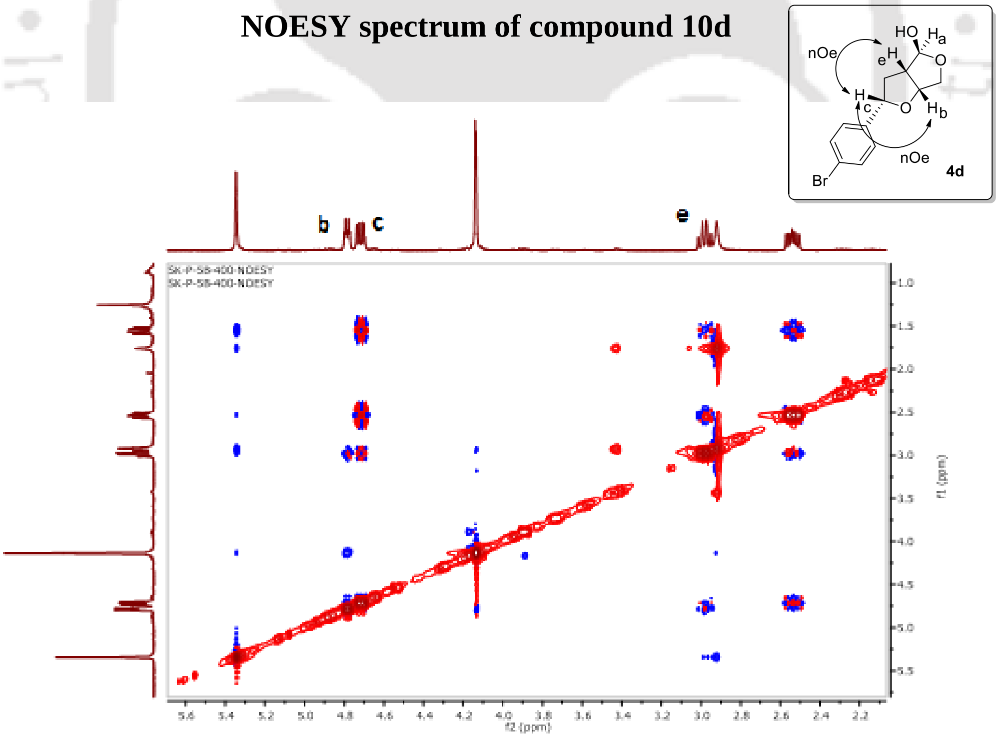
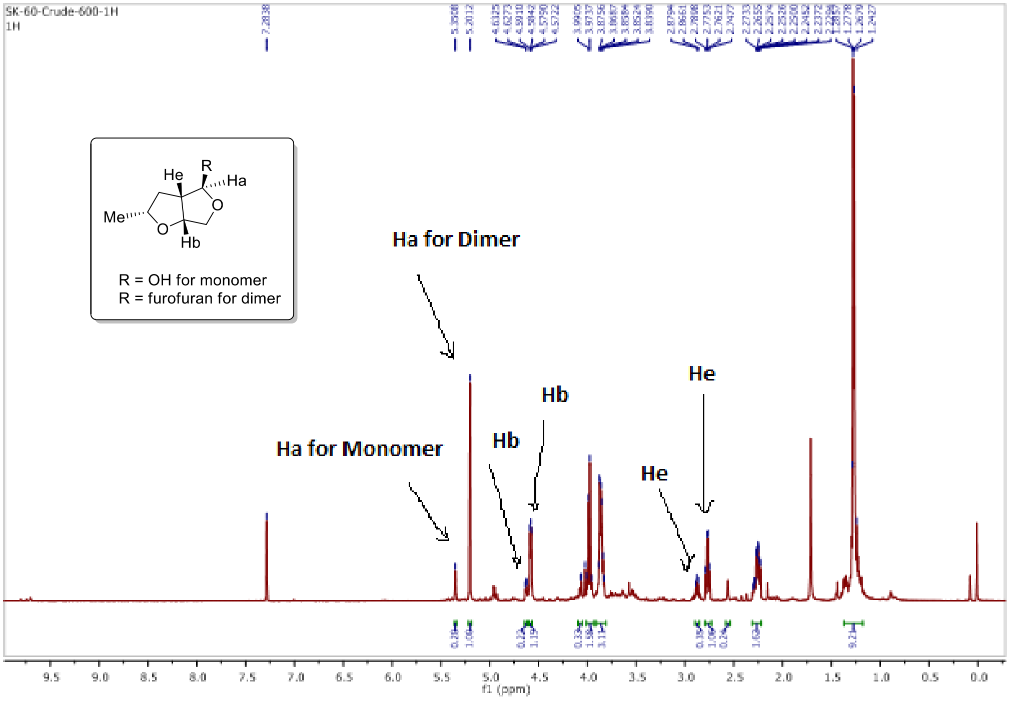
COSY spectrum of compound 10d



NOESY spectrum of compound 10d



Crude ^{1}H NMR spectrum of **10K**



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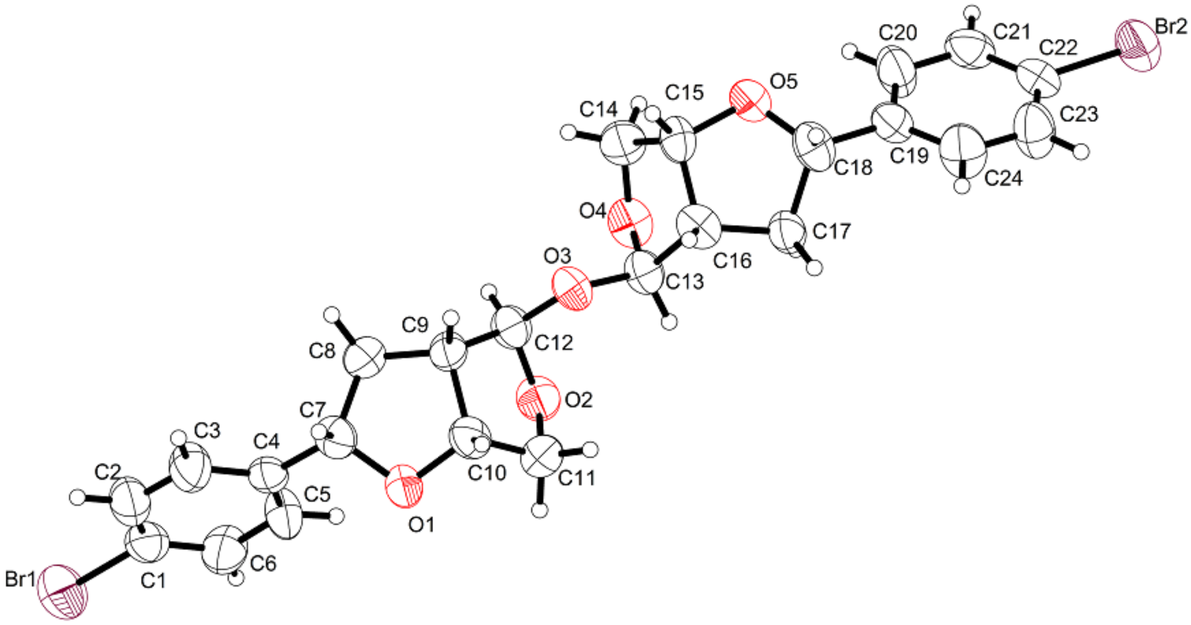
The crystal parameters:

The crystal parameters of compound **9d**

	CCDC 1888883
Formula	$C_{24} H_{24} Br_2 O_5$
Formula weight	552.25
T/K	293(2)
Crystal system	Orthorhombic
Space group	P212121
a/Å	17.353(5)
b/Å	24.435(8)
c/Å	5.4165(17)
α/°	90.00
β/°	90.00
γ/°	90.00
V/Å^3	2296.7(12)
Z	4
Abs. Coeff./mm^{-1}	3.562
Abs. Correction	none
GOF on F^2	0.974
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0605
	$wR2$ = 0.1377
R indices [all data]	$R1$ = 0.1571
	$wR2$ = 0.1942

ORTEP Diagram of compound **9d** with 30% probability:



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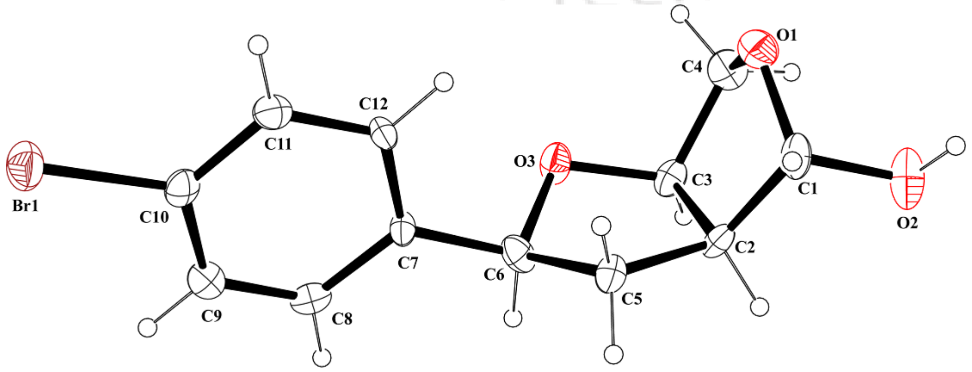
The crystal parameters of compound **10d**

	CCDC 1914873
Formula	$C_{12}H_{13}BrO_3$
Formula weight	285.13
T/K	293(2)
Crystal system	monoclinic
Space group	P1211
a/Å	5.8450(5)
b/Å	7.6852(6)
c/Å	12.8843(10)
α/°	90.00
β/°	100.457(8)
γ/°	90.00
V/Å^3	569.15(8)
Z	2
Abs. Coeff./mm^{-1}	3.600
Abs. Correction	multi-scan
GOF on F^2	1.029
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0437
	wR2 = 0.0851
R indices [all data]	*R1* = 0.0541
	wR2 = 0.0930

ORTEP Diagram of compound **10d** with 30% probability:



2.8 References

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Chapter 3:

Synthesis of Spiro[furan-2,1′-isoindolin]-3′-ones from 2-(4- Hydroxybut-1-yn-1-yl)benzonitriles and Aryl Aldehydes under the Action of Triflic Acid

3.1 Importance and Applications

Spirocycles are the bi- or poly-cyclic molecules with identical or different ring connected through a single atom. The connected atom is called "spiro" atom, most likely a quaternary carbon.[1a] These compounds can be used as photochromic materials, plasticizers, in perfumery industry and spiro form of lactones and oxazines as leuco dyes.[1b-e] The 3–spiroisoindolinone units are privileged motifs in biologically active molecules and natural products.[2] For example, spiropachysine an alkaloid isolated from *Pachysandra procumbens*,[2a] and impatien A an alkaloid isolated from *Corydalis impatiens*[2b] are natural products; many spiroisoindolinone compounds have biological activity such as aldose reductase inhibitor,[2c] histamine H3 receptor antagonist,[2d] potent human farnesyltransferase inhibitor,[2e] and anticancer agent.[2f] Apart from this, spiroisoindolinone containing compounds are fluorescent chemosensor.[3] The spiro[furan-2,1'-isoindolin]-3'-one unit is found in biologically active molecules and natural products.[4] For example, spirocollequins A (**I**) and B (**II**) are alkaloids[4] featuring spirocyclic isoindolinone core, isolated from *Colletotrium boninense* AM-12-2; pratensilin A (**III**) and pratensilin D (**IV**) alkaloids isolated from a marine *Streptomyces* sp. are natural products (*Figure 3.1*).[5] Spirocollequins A and B exhibit antiplasmodial activity,[4] whereas pratensilin A[5a] shows moderate cytotoxic activities against human cancer cells and compound **IV**[5b] exhibits antibacterial and cytotoxic activities. Therefore, synthesis of these molecules is important in material chemistry and drug discovery.

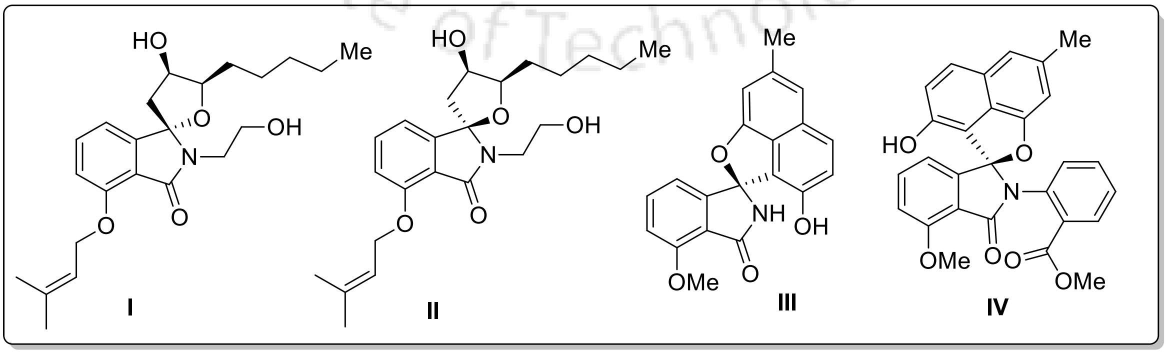


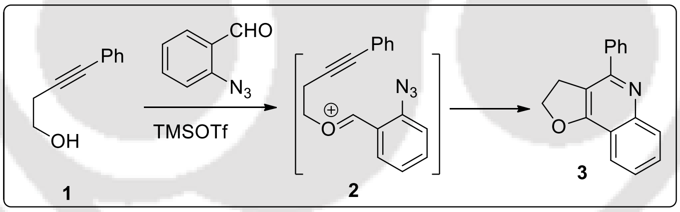
Figure 3.1: *Biologically active molecules.*

3.2 An Overview of Relevant Synthetic Methods

Alkyne Prins cyclization is well known for the synthesis of various heterocyclic compounds. Ritter reaction in which nitrile reacts with secondary carbocation is well established,[6] but Ritter reaction with a vinyl carbocation is limited.[7] In this work, synthesis of spiro[furan-2,1′-isoindolin]-3′-ones via alkynyl Prins cyclization followed by Ritter reaction with vinyl carbocation is disclosed. The basic overview of alkynyl Prins reaction and Prins-Ritter reaction is described in chapter **1**, section **1.8** and **1.9.3**. The recent development on cyclization strategy of alkynols and synthesis of spirocycles is described briefly.

3.2.1 Reaction of Alkynols

In 2017, Gharpure et al. reported an oxocarbenium ion initiated carboamination of alkynes for the synthesis of cyclic ether fused quinolones.[8a] The reaction of alkynol **1** with 2-azidobenzaldehyde forms carbenium ion intermediate **2** in presence of TMSOTf, which further underwent Prins cyclization followed by carboamination reaction to produce ether fused quinolines **3** (*Scheme 3.2.1.1*). The reaction is also used for the synthesis of 4-alkoxy quinolines. The synthetic utility of the methodology was extended for the synthesis of potent drug molecules including, Graveoline and ERβ ligand.



Scheme 3.2.1.1: *Oxocarbenium ion driven carboamination reaction of alkynes.*

In the same year, they demonstrated Lewis/Brønsted acid promoted hydroalkoxylation and subsequent formal [4+2] cycloaddition reaction for the synthesis of tetrahydrofurano/pyrano-chromenes.[8b] For the case of internal alkynes, alkynol formed heteroannular ketals via 5- or 6-endo-dig cyclization fashion. In case of terminal alkynes, the reaction underwent through 5-exo-dig fashion to afford the corresponding spiro-ketals (*Scheme 3.2.1.2*).

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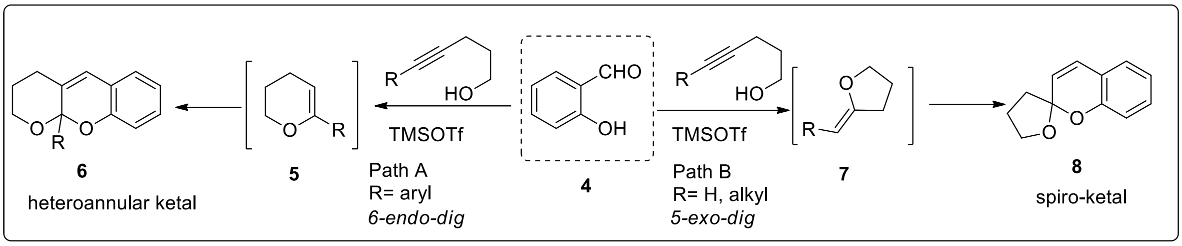
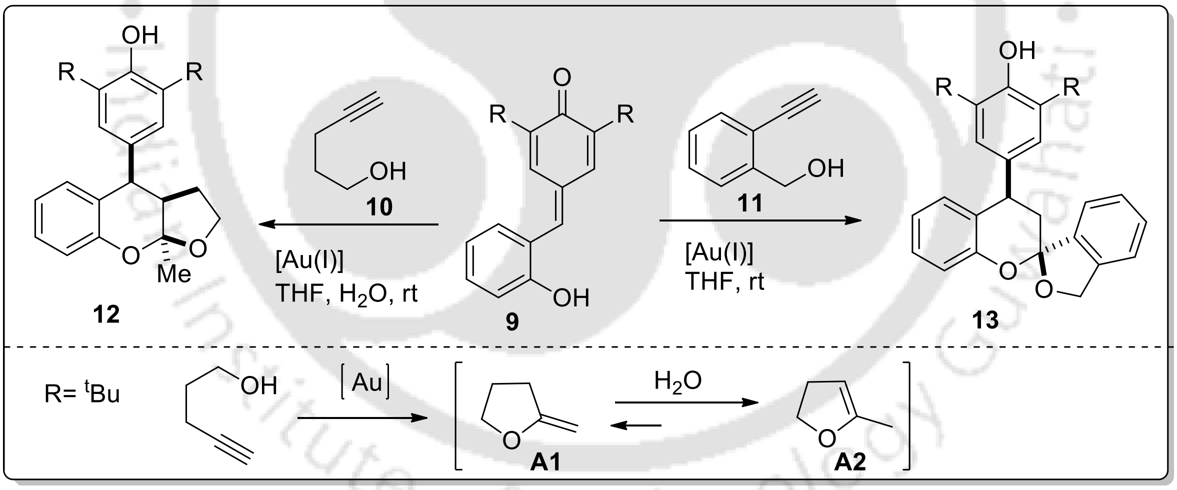


Scheme 3.2.1.2: *Hydroalkoxylation and formal [4+2] cycloaddition of various alkynols.*

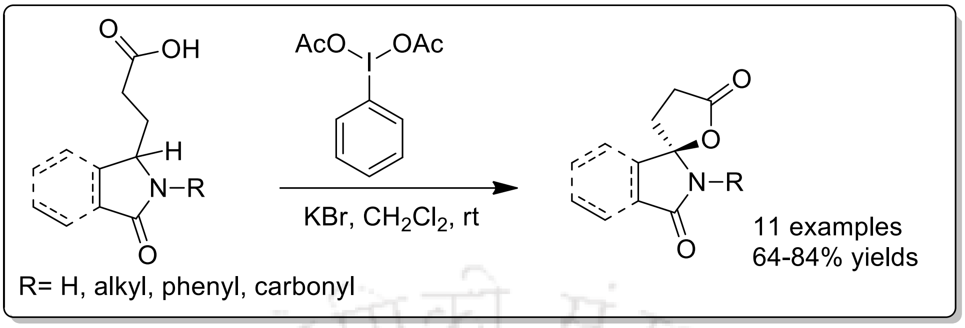
In 2020, Xu and co-workers reported a domino reaction for the synthesis of fused- and spiro-ketals from alkynols and *p*-quinone methides in the presence of JohnphosAuNTf$_2$.[9a] The spirocyclic ketal **13** was formed by the reaction of exocyclic enol ether **A1** with alkynol **11**. In the presence of trace amount of H_2O, enol ether **A1** isomerized to its stabilized form **A2** and which underwent cycloaddition reaction with alkynol **10** to afford fused ketal **12**. The reaction shows poor selectivity with alkynol **10**, both fused- and spiro-ketals are formed with trace amount of water. In case of benzene tethered alkynol **11,** only spiro ketal **13** was formed, because there was no possibility of isomerization due to the phenyl ring present in **11**.



Scheme 3.2.1.3: *Gold catalysed cycloisomerization for the synthesis of fused- and spiro-ketals.*

3.2.2 Oxidative *C-H* Spirocyclization

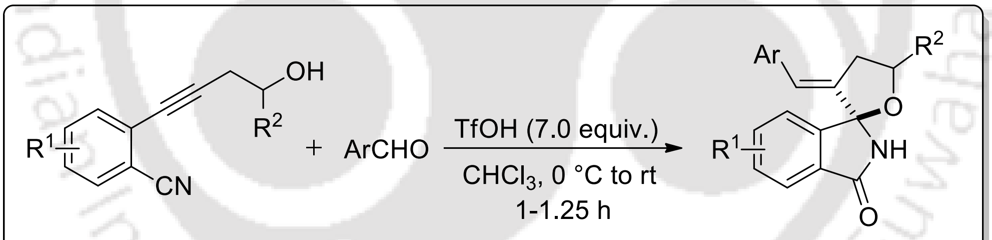
In 2019, Yoda and co-workers reported a new synthetic methodology for the synthesis of azaspiro-γ-lactones via C-H spirolactonization.[9b] The oxidizing agent PIDA and potassium bromide accomplished the transformations with yields. This protocol was also used for the synthesis of bislactone compounds and alicyclic azaspiro-γ-lactones.



Scheme 4: *Synthesis of spirolactones via oxidative C-H spirocyclizations.*

3.3 Present Work

A new efficient methodology for the synthesis of spiro[furan-2,1'-isoindolin]-3'-ones from 2-(4-hydroxybut-1-yn-1-yl)benzonitriles and aryl aldehydes *via* tandem reactions namely Prins, Ritter and tetrahydrofuranyl ring opening followed by nucleophilic addition of alcohol on *N*-acyliminium ion is disclosed.



- Metal-free, one-pot tandem protocol
- One C-N, two C-O, and one C-C bond formation
- One newly formed quaternary carbon along with two five membered rings
- 20 examples, upto 76% yields

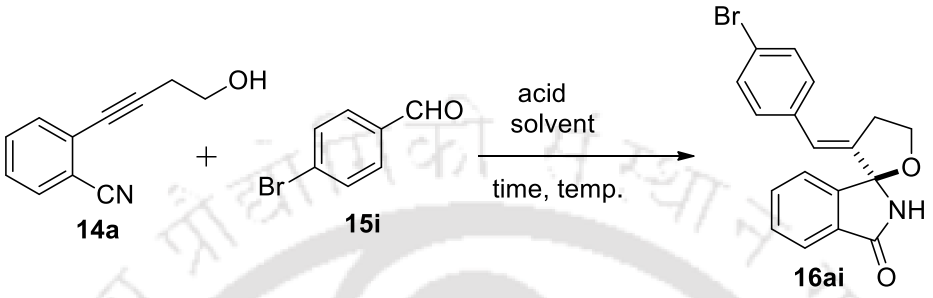
3.3.1 Results and Discussions

3.3.2 Optimization of the Reaction

In this study, homopropargylic alcohol 2-(4-hydroxybut-1-yn-1-yl)benzonitrile (**14a**) and 4-bromobenzaldehyde (**15i**) were considered as model substrates. Initially, **14a** (0.6 mmol, 1.0 equiv.) was reacted with **15i** (0.72 mmol, 1.2 equiv.) in the presence of 1.5 equiv. of borontrifluoride etherate ($BF_3 \cdot OEt_2$) in acetonitrile at 0 °C to room temperature. The product

(*E*)-3-(4-bromobenzylidene)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (**16ai**) was obtained with 10% yield in 1.5 h. Increase in loading of $BF_3{\cdot}OEt_2$ to 5.0 equiv. provided only 24% yield (entry 2, Table 1). Encouraged by the result, the reaction was then screened with different reaction conditions as shown in Table 1. Brønsted acids Tf_2NH (1.5 equiv.), *p*-TSA

Table 1: Optimization of the reaction



Entry	Acid (equiv.)	Solvent	Temp.	Time/h	%Yield[a]
1	$BF_3{\cdot}OEt_2$ (1.5)	CH_3CN	0 °C-rt	1.5	10
2	$BF_3{\cdot}OEt_2$ (5.0)	CH_3CN	0 °C-rt	1.5	24
3	Tf_2NH (1.5)	CH_3CN	rt	24	0
4	*p*-TSA (1.5)	CH_3CN	0 °C-rt	24	0
5	TMSOTf (1.5)	CH_3CN	0 °C-rt	16	-[b]
6	TfOH (1.5)	CH_3CN	0 °C-rt	1.5	22
7	TfOH (1.5)	CH_3CN	0 °C	1.5	trace
8	TfOH (5.0)	CH_3CN	0 °C-rt	1.5	38
9	TfOH (7.0)	CH_3CN	0 °C-rt	1.0	43
10	TfOH (10.0)	CH_3CN	0 °C-rt	1.0	40
11	TfOH (10.0)	CH_2Cl_2	0 °C-rt	2.0	10
12	TfOH (7.0)	CH_2Cl_2	0 °C-rt	1.0	trace
13	TfOH (7.0)	DCE	0 °C-rt	1.0	15
14	TfOH (7.0)	$CHCl_3$	0 °C-rt	1.0	65
15	**TfOH (7.0)**	**$CHCl_3$**	**0 °C-rt**	**1.25**	**72**
16	TfOH (7.0)	$CHCl_3$	0 °C -rt	2.00	69
17	TfOH (5.0)	$CHCl_3$	0 °C-rt	1.25	54
18	TfOH (2.0)	$CHCl_3$	0 °C-rt	1.25	20
19	TfOH (10.0)	$CHCl_3$	0 °C-rt	1.25	70
20	TfOH (10.0)	Neat	0 °C-rt	1.25	61

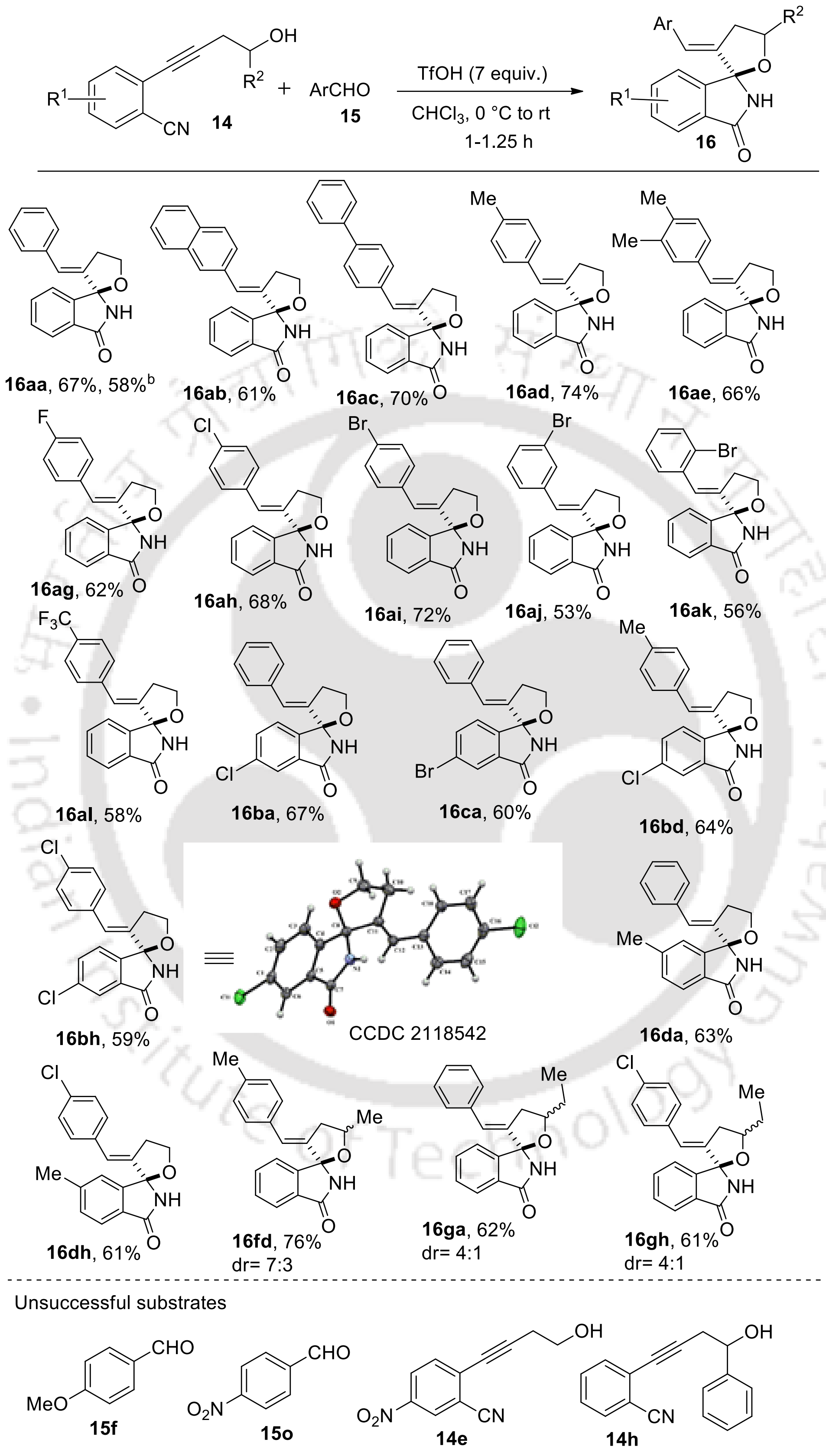
Reaction Conditions: **14a** (0.6 mmol, 1.0 equiv.), **15i** (0.72 mmol, 1.2 equiv.), [a]Yield refers to isolated yield, [b]Complex mixture

(1.5 equiv.) and Lewis acid TMSOTf (1.5 equiv.) failed to give the desired product (entries 3-5, Table 1). On the other hand, 1.5 equiv. of triflic acid (TfOH) in acetonitrile at 0 °C to room temperature gave the desired product in 22% yield (entry 6, Table 1), while the same at 0 °C trace amount of the product was obtained (entry 7, Table 1). Increasing the amount of TfOH to 5.0 equiv., produced the product in 38% yield (entry 8, Table 1). Furthermore, increasing the amount of TfOH to 7.0 and 10.0 equiv., provided the product in 43% and 40% yields, respectively (entry 9-10, Table 1). While changing the solvent from CH_3CN to CH_2Cl_2 (DCM), keeping TfOH as 10.0 equiv. furnished 10% of the desired product with a mixture of side products (entry 11, Table 1). The reaction in dichloromethane (DCM) with 7.0 equiv. of TfOH gave only trace amount of the expected product (entry 12, Table 1). While changing the solvent from DCM to 1,2-dichloroethane (DCE) only 15% of the product was formed (entry 13, Table 1). Fortunately, 7.0 equiv. of TfOH in chloroform provided 65% yield at 0 °C–rt in 1 h (entry 14, Table 1), whereas the same reaction in 1.25 h provided 72% yield (entry 15, Table 1). Increasing the time from 1.25 h to 2 h resulted in 69% yield (entry 16, Table 1). On the other hand, lower TfOH loadings such as 5 equiv. and 2 equiv. gave 54% and 20% yields, respectively (entries 17-18). Again, increasing the amount of TfOH to 10.0 equiv. in chloroform ($CHCl_3$) yielded 70% of the desired product (entry 19, Table 1). The reaction with neat TfOH (10.0 equiv.) resulted in 61% of the product (entry 20, Table 1). Therefore, 7.0 equiv. of TfOH in $CHCl_3$ at 0 °C to rt are the optimum conditions for the reaction.

3.3.3 Substrates Scope of the Reaction:

With this optimal conditions in hand, the reaction is generalized with different substrates as depicted in Scheme 3.3.3.1. It was observed from Scheme 3.3.3.1 that both electron-donating (4-Me, 3,4-diMe) as well as electron-withdrawing halo- groups in the aromatic ring of the aldehydes produced the desired products in good yields. But the highly electron-donating –OMe and electron-withdrawing $–NO_2$ groups in the aromatic ring of the aldehyde did not produce the desired products, instead resulted in decomposed products. In the case of secondary alcohols (**14f-14g**) gave diastereomeric mixture with a ratio of 7:3, 4:1 and 4:1, respectively. Unfortunately, secondary alcohol **14h** with phenyl ring did not produce desired product, instead decomposed under the reaction conditions. This might be due to the formation of stable carbocation under this strong acidic condition. Similarly, moderately electron-withdrawing groups in the aromatic ring of the homopropargylic alcohols (**14b-14c**) and

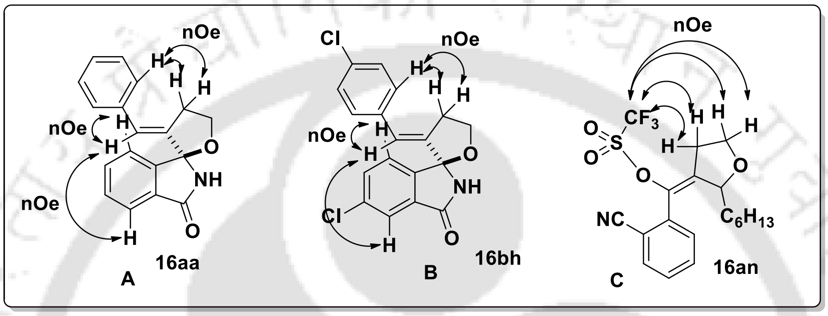
Scheme 3.3.3.1: Synthesis of spiro[furan-2,1'-isoindolin]-3'-ones[a]



[a]Reaction conditions: **14** (0.6 mmol, 1 equiv.), **15** (0.72 mmol, 1.2 equiv.), TfOH (7 equiv.), $CHCl_3$ (2 mL), temp. (0 °C - rt), dr for **16fd-16gh** was deterimned by ^1H NMR, b= reaction with 5.58 mmol, 1 g scale

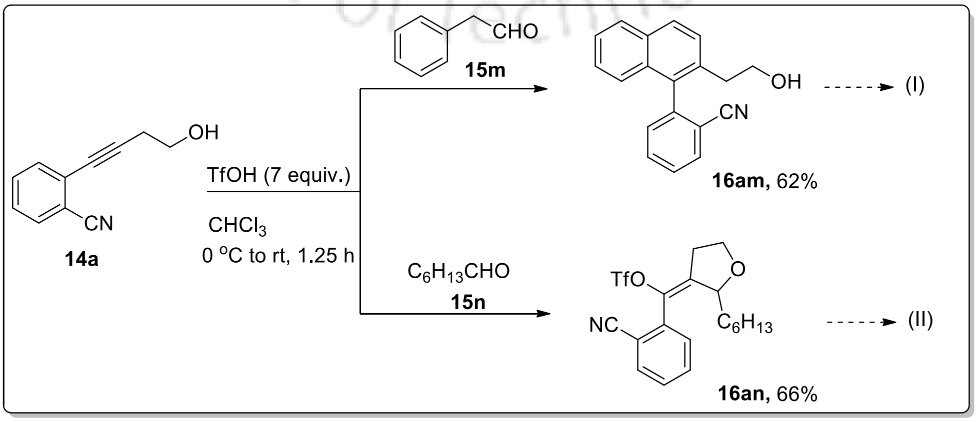
electron-donating groups in the aromatic ring (**14d**) yielded desired product in good yields, but strong electron-withdrawing –NO_2 group in aromatic ring (**14e**) again failed to give desired product. The reaction is highly stereoselective and produced exclusively "*E*"- isomer, which is due to the less steric interaction between the "Ar" group and phthalimide group (*Scheme 3.3.4.2*). The structure of the compounds was determined by ^{1}H, ^{13}C NMR, mass spectrometry, nOe experiment (*Figure 3.3.3.1. A-C*) and finally by X-ray crystallographic analysis of the compound **16bh** (see ESI).[14]

Figure 3.3.3.1.** nOe of compounds **16aa**, **16bh** and **16an



However, when phenyl acetaldehyde was used, instead of the desired product a polysubstituted naphthalene compound **16am** was formed in 62% yield. The product **16am** was formed by nucleophilic attack of alkyne with activated carbonyl group of aldehyde and subsequent Friedel-Crafts and aromatization reactions similar to the work reported in the literature (Scheme 3.3.3.2, equation I).[12b] On the other hand, aliphatic aledehyde such as heptaldehyde **15n** gave only Prins cyclization product **16an** with 66% yield with "*E*" configuration (Scheme 2, equation II), which was determined by ^{19}F-^{1}H heteronuclear nOe (HOESY) experiment (*Figure 3.3.3.1 C*).

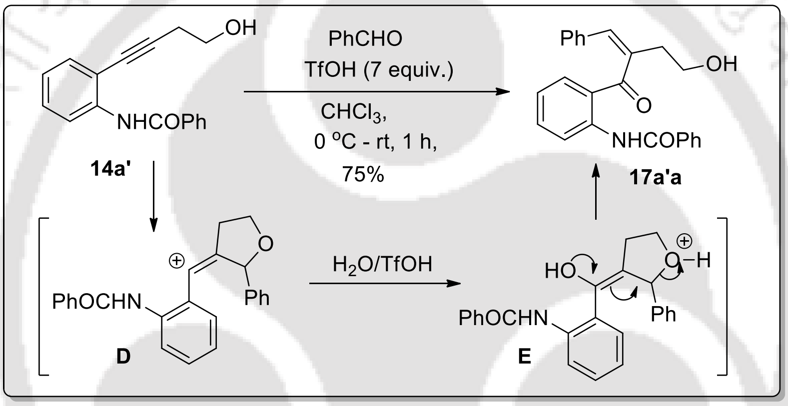
***Scheme 3.3.3.2**. Reaction with phenyl acetaldehyde and heptanal*



3.3.4. Possible mechanism of the reaction

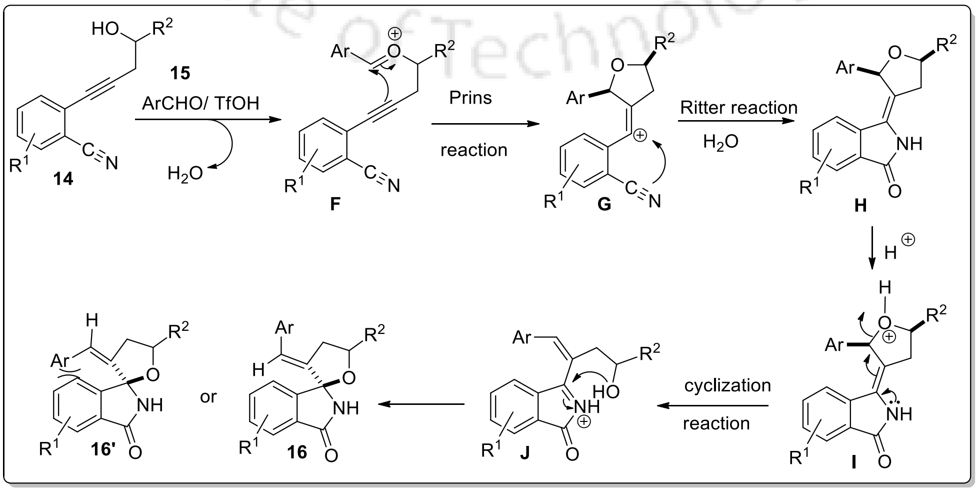
In order to get information about the mechanism of the reaction the following controlled experiment was performed. The substrate **14a′** was prepared where the cyanide group was replaced with amide group in the aromatic ring using literature procedure.[10] Compound **14a′** was then subjected to standard reaction conditions and it was observed that compound **17a′a** was obtained in 75% yield. Formation of **17a′a** indicated that the reaction proceeds *via* Prins type reaction to give intermediate carbocation **D**, which after attack by water molecule under acidic condition gave intermediate **E**. The protonated furanyl ring of the intermediate **E** opened up to give homoallylic alcohol **17a′a** (*Scheme 3.3.4.1*).

Scheme 3.3.4.1. *Controlled Experiment*



A plausible mechanism was proposed on the basis of our findings and literature evidence[11] as shown in scheme 3.3.4.2. Initially, under acidic conditions, alcohol **14** reacts with aldehyde **15** to form *oxo*-carbenium ion intermediate **F**, which after Prins cyclization reaction produced

Scheme 3.3.4.2. *Plausible Mechanism of the Reaction*

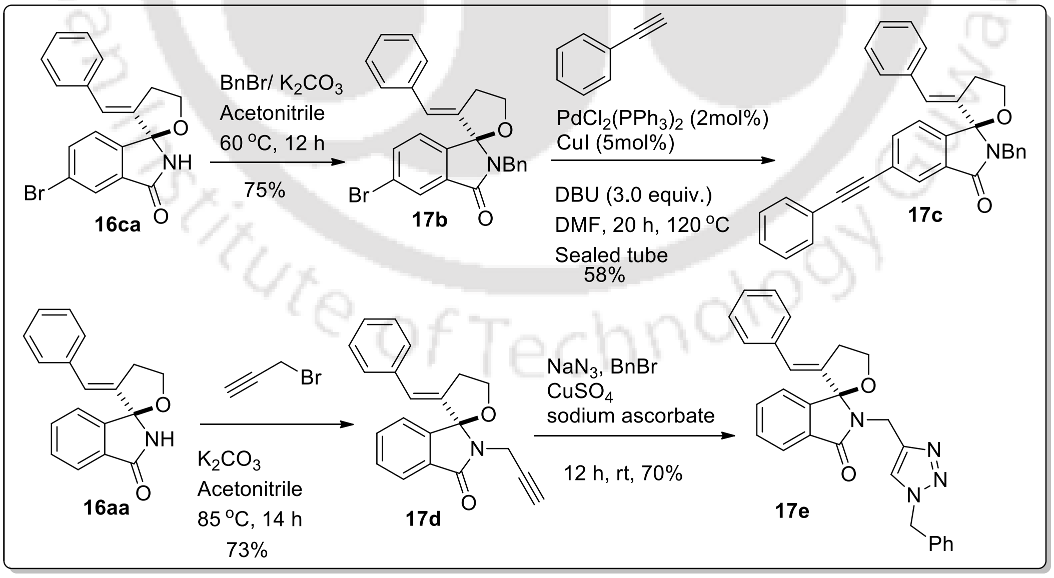


carbocation **G,** which is attacked by cyanide group to produce Ritter product **H**. The furanyl ring, under acidic conditions, is opened up to generate acyliminium ion **J** with a side chain alcoholic group, which after cyclization gives final compound **16** exclusively as structure **16′** is not stable due to the steric interaction between the "Ar" group and phthalimide group.

3.3.5. Post Synthetic Utility of the Reaction:

Post synthetic transformation of compounds **16ca** and **16aa** was carried out as shown in Scheme 3.3.5.1. Thus, the reaction of **16ca** with benzyl bromide gave (*E*)-2'-benzyl-3-benzylidene-5'-bromo-4,5-dihydro- 3*H*-spiro[furan-2,1'-isoindolin]-3'-one (**17b**) in 75% yield, which was then converted into (*E*)-2'-benzyl-3-benzylidene-5'-(phenylethynyl)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (**17c**) using Sonogashira reaction with 58% yield. Similarly, compound **16aa** was reacted with propargyl bromide to give (*E*)-3-benzylidene-2'-(prop-2-yn-1-yl)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (**17d**) in 73% yield, which was further converted to its triazole derivative (*E*)-2'-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-benzylidene-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (**17e**) in 70 % yield using click reaction.

Scheme 3.3.5.1 *Post synthetic application of spiro[furan-2,1'-isoindolin]-3'-ones*



3.4 Conclusion

An efficient methodology for the synthesis of spiro[furan-2,1'-isoindolin]-3'-ones has been developed in good yields. The metal free, one pot protocol provides the spiro-isoindolinone *via* tandem reactions from easily available starting material within a short period of reaction time. Furthermore, late stage modifications of the compounds have been done using Sonogashira and click reactions. The synthesized product possesses *exo*-cyclic double bond and amide functionality, which can be utilized for the synthesis of useful molecules.

3.5 Experimental Section

3.5.1 General Information

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

The starting material 2-(4-hydroxybut-1-yn-1-yl)benzonitrile (**14a, 14f and 14h**)[12a] and (**14a′**)[10] were synthesized according to the modified literature report. The spectroscopic data of these compounds are in good agreement with the literature one. The experimental procedure and characterization data for the unknown starting material (**14b-14e, 14g**) is given as follows:

3.5.2 General Procedure for the Preparation of Starting Materials (14b-14e, 14g):

To a stirred solution of 2-aminobenzonitrile derivatives (10 mmol, 1.0 equiv.**)** in a 100 mL round bottomed flask was added 15 mL 4M conc. HCl at 0 °C temperature. After 5 minutes, $NaNO_2$ (12 mmol, 1.2 equiv.) dissolved in water (4.0 mL) was added to the reaction mixture and allowed to stir for an hour. Finally, KI (20 mmol, 2.0 equiv.) dissolved in water (4.0 mL) was added to it dropwise at 0 °C and the reaction mixture was allowed to stir for over-night at room temperature. After completion of the reaction, the reaction mixture was diluted with saturated $Na_2S_2O_3$, $NaHCO_3$ solution, ethyl acetate and washed with brine. The organic layer was extracted with (3×20 mL) ethyl acetate. The combined organic layer was dried over Na_2SO_4 and concentrated by rotary evaporator. The crude was subjected to column chromatography over silica gel to afford the iodo-arene derivatives in 78-86% yields.

To a stirred suspension of $PdCl_2(PPh_3)_2$ (0.06 mmol, 2 mol%) and CuI (0.15 mmol, 5 mol%) in of triethylamine (15.0 mmol, 5.0 equiv.) under nitrogen atmosphere, Iodo arene derivative (3.3 mmol, 1.1 equiv.) was added and the reaction was allowed to stir for 10 minutes. Atlast, alkyne (3.0 mmol, 1.0 equiv.) was added to the reaction mixture dropwise via syringe and the reaction was stirred at room temperature for 16 hours. After completion of the reaction, the solvent was removed by rotary evaporator and diluted with saturated NH_4Cl solution and brine then the organic layer was extracted with ethyl acetate (3×20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in a rotary evaporator. The crude was subjected to column chromatography to get the corresponding product **14b-14e, 14g** in 74-82% yield.

3.5.3 General procedure for the synthesis of (16aa-16an, 16ba, 16ca, 16bd, 16bh, 16da, 16dh, 16fd, 16ga, 16gh):

To a stirred solution of 2-(4-hydroxybut-1-yn-1-yl)benzonitrile (0.6 mmol, 1.0 equiv.) and aldehydes (0.72 mmol, 1.2 equiv.) in chloroform (2.0 mL) was added TfOH (4.2 mmol, 7.0 equiv.) slowly *via* syringe at 0 ^{o}C under nitrogen atmosphere. The reaction was stirred at room temperature for 1-1.25 h and progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was washed with saturated sodium bicarbonate solution and brine. The organic layer was extracted by ethyl acetate(3×20mL), dried over Na_2SO_4 and evaporated by rotary evaporator. The corresponding product was obtained by column chromatography over silica gel using hexane and ethyl acetate as eluent in 53-76% yields.

3.5.4. Experimental procedure for the synthesis of 17aa':

N-(2-(4-hydroxybut-1-yn-1-yl)phenyl)benzamide (158 mg, 0.6 mmol) and benzaldehyde (76.4 mg, 0.72 mmol) were taken in an oven dried round bottomed flak with magnetic bar to which chloroform (2 mL) was added. Subsequently, Triflic acid (0.37 mL, 4.2 mmol) was added to the reaction mixture dropwise under nitrogen atmosphere and the reaction was stirred for 1.5 h. After completion of the reaction, the reaction mixture was washed with saturated $NaHCO_3$ solution and brine. The organic layer was extracted with ethyl acetate (2×20 mL) and dried over Na_2SO_4. Then the product was separated using column chromatography, with hexane and ethyl acetate as eluent to afford compound **17aa'**.

3.5.5 Experimental procedure for the synthesis of 17c

To a stirring suspension of finely powdered K_2CO_3 (232 mg, 1.68 mmol) and (*E*)-3-benzylidene-5'-bromo-4,5-dihydro-3H-spiro[furan-2,1'-isoindolin]-3'-one **16ca** (200 mg, 0.56 mmol) in acetonitrile (3.0 mL) was added benzyl bromide (0.1 mL, 0.84 mmol) under nitrogen atmosphere and the reaction was stirred at 60 °C for 12 h in an oil bath. After completion of the reaction, K_2CO_3 was filtered and the organic layer was extracted by ethyl acetate (2× 20 mL) and washed by water. The extracted layer was then dried over Na_2SO_4 and concentrated by rotary evaporator. Compound **17b** was obtained by column chromatography over silica gel using ethyl acetate in hexane as eluent in 75% (187 mg, colorless gum) yields.

To a magnetic bar containing oven dried pressure tube (15mL, 10.2 cm, 25.4 mm) was added $PdCl_2(PPh_3)_2$ (4.0 mg, 0.005 mmol,), CuI (3 mg, 0.0112 mmol), (*E*)-2'-benzyl-3-benzylidene-5'-bromo-4,5-dihydro-3H-spiro[furan-2,1'-isoindolin]-3'-one **17b** (100 mg, 0.224 mmol), phenylacetylene (0.027 mL, 0.246 mmol), DBU (0.1 mL, 0.672 mmol), DMF (2 mL) and the reaction was stirred for 20 h at 120 °C in an oil bath. After completion of the reaction, the reaction mixture was filtered and organic layer was washed with ice cold water and extracted by (3× 15mL) ethyl acetate and dried over Na_2SO_4. The solvent was then evaporated by rotary evaporator and the compound **17c** was obtained by column chromatography using hexane and ethyl acetate as eluent in 58% (60 mg, colourless gum) yields.

3.5.6 Experimental procedure for the synthesis of 17e

To a stirred suspension of K_2CO_3 (298 mg, 2.16 mmol) was added (E)-3-benzylidene-4,5-dihydro-3H-spiro[furan-2,1'-isoindolin]-3'-one **16aa** (200 mg, 0.722 mmol) in acetonitrile (4mL) was added propargyl bromide (0.1 mL, 1.08 mmol, 80% w/w in toluene) under nitrogen atmosphere. The reaction was stirred at 85 °C for 14 h in an oil bath. After completion of the reaction the K_2CO_3 was filtered, extracted with (2×20 mL) ethyl acetate and washed with brine solution. The crude was then concentrated with rotary evaporator and compound **17d** was obtained by column chromatography over silica gel using hexane and ethyl acetate as eluent in 73% (colourless gum, 166 mg) yields.

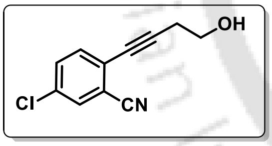
To a stirred solution of benzyl bromide (79 mg, 0.454 mmol) in water (1 mL)/ t-BuOH (1 mL) under nitrogen atmosphere, sodium azide (27 mg, 0.413 mmol) and Et_3N (54 mg, 0.53 mmol) were added. After 1 hour, (E)-3-benzylidene-2'-(prop-2-yn-1-yl)-4,5-dihydro-3H-spiro[furan-2,1'-isoindolin]-3'-one **17d** (130 mg, 0.413 mmol), sodium ascorbate (44 mg, 0.22 mmol) and $CuSO_4$ (10 mg, 0.063 mmol) were added to the freshly prepared benzyl azide. The reaction was stirred for 12 h at room temperature. After completion of the reaction, the reaction mixture was diluted with saturated $NaHCO_3$ solution. The crude was then extracted with (2×20 mL) ethyl acetate and washed with brine solution. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in rotary evaporator, which was then subjected to column chromatography over silica gel to get the corresponding product **17e** in 70% (129 mg, colorless gum) yield.

3.5.7 Experimental procedure for the gram scale reaction

To a stirred solution of 2-(4-hydroxybut-1-yn-1-yl)benzonitrile **14a** (1.0 g, 5.85 mmol) and benzaldehyde (0.72 mL, 7.02 mmol) in chloroform (15 mL) was added TfOH (3.6 mL, 41 mmol) slowly *via* syringe at 0 °C under nitrogen atmosphere. The reaction was stirred at room temperature for 1.5 h and progress of the reaction was monitored by TLC. After completion of the reaction the organic layer was extracted by ethyl acetate (3×30mL), saturated sodium bicarbonate solution and brine. The extracted organic layer was dried over sodium sulphate and evaporated by rotary evaporator. The product **16aa** was obtained by column chromatography over silica gel using hexane and ethyl acetate as eluent in 58% (936 mg, white solid) yields.

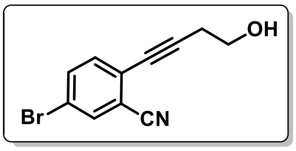
3.5.8 Characterization Data

5-Chloro-2-(4-hydroxybut-1-yn-1-yl)benzonitrile (14b):



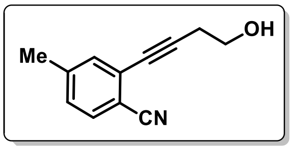
Brown liquid; R_f (hexane/ethyl acetate, 7:3) 0.40; yield 504 mg, 82%; IR (KBr, neat) ν 3394, 3064, 2884, 2231, 1475, 1040, 832, 505 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (q, J = 2.4 Hz, 1 H), 7.49 – 7.46 (m, 1 H), 7.44–7.41 (m, 1 H), 3.86 (q, J = 5.9 Hz, 2 H), 2.76–2.73 (m, 2 H), 2.42 (s, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 134.2, 133.4, 133.1, 132.2, 126.4, 117.1, 116.9, 96.1, 78.1, 60.9, 24.2. HRMS (ESI) calcd. For $C_{11}H_9ClNO$ $(M+H)^+$ 206.0367, found 206.0370.

5-Bromo-2-(4-hydroxybut-1-yn-1-yl)benzonitrile (14c):



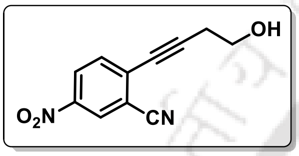
Brown liquid; R_f (hexane/ethyl acetate, 7:3) 0.40; yield 592 mg, 79%; IR (KBr, neat) ν 3409, 2946, 2886, 2233, 1475, 1048, 830, 505 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 2.1 Hz, 1 H), 7.65–7.63 (m, 1 H), 7.36 (d, J = 8.5 Hz, 1 H), 3.86 (t, J = 6.2 Hz, 2 H), 2.74 (t, J = 6.1 Hz, 2 H), 2.31 (s, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 136.0, 135.1, 133.5, 126.8, 121.8, 117.3, 116.8, 96.3, 78.3, 61.0, 24.3. HRMS (ESI) calcd. for $C_{11}H_8BrNNaO$ $(M + Na)^+$ 271.9681, found 271.9692.

2-(4-Hydroxybut-1-yn-1-yl)-4-methylbenzonitrile (14d):



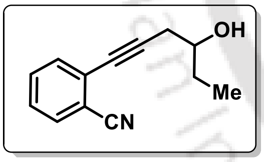
Brown liquid; R_f (hexane/ethyl acetate, 7:3) 0.40; yield 417 mg, 75%; IR (KBr, neat) ν 3422, 2946, 2881, 2226, 1600, 1043, 822, 587 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.49–7.46 (m, 1 H), 7.30 (s, 1 H), 7.15 (d, *J* = 7.9 Hz, 1 H), 3.85 (q, *J* = 5.8, 4.3 Hz, 2 H), 2.72 (t, *J* = 6.0 Hz, 2 H), 2.54 (s, 1 H), 2.36 (s, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 143.7, 132.8, 132.3, 129.1, 127.6, 118.6, 112.6, 94.1, 79.1, 61.1, 24.1, 21.8. HRMS (ESI) calcd. for $C_{12}H_{12}NO$ $(M + H)^+$ 186.0913, found 186.0931.

2-(4-Hydroxybut-1-yn-1-yl)-5-nitrobenzonitrile(14e):



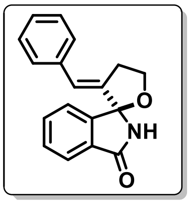
Brown liquid; R_f (hexane/ethyl acetate, 1:1) 0.40; yield 479 mg, 74%; IR (KBr, neat) ν 3417, 3096, 2943, 2233, 1600, 1578, 1523, 1348, 1048, 745, 502 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1 H), 8.38–8.35 (m, 1 H), 7.70–6.68 (m, 1 H), 3.90 (t, *J* = 6.0 Hz, 2 H), 2.82 (t, *J* = 5.3 Hz, 2 H), 2.32 (s, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 146.5, 134.0, 133.4, 127.7, 127.4, 117.0, 116.2, 101.6, 78.1, 60.8, 24.4. HRMS (ESI) calcd. for $C_{11}H_9N_2O_3$ $(M + H)^+$ 217.0608, found 217.0601.

2-(4-Hydroxyhex-1-yn-1-yl)benzonitrile(14g):



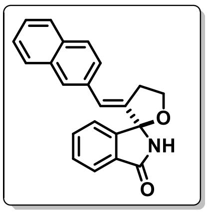
Brown gum; R_f (hexane/ethyl acetate, 7:3) 0.40; yield 443 mg, 74%; IR (KBr, neat) ν 3427, 2966, 2879, 2231, 1483, 1108, 977, 762, 512 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.8 Hz, 1 H), 7.53–7.49 (m, 2 H), 7.38–7.35 (m, 1 H), 3.85 – 3.80 (m, 1 H), 2.75 – 2.70 (m, 1 H), 2.65–2.60 (m, 1 H), 2.30 (s, 1 H), 1.71–1.64 (m, 2 H), 1.00 (t, *J* = 7.4 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 132.6, 132.5, 132.3, 128.2, 127.9, 118.3, 115.8, 94.5, 79.5, 71.7, 29.5, 28.3, 10.2. HRMS (ESI) calcd. for $C_{13}H_{13}KNO$ $(M + K)^+$ 238.0629, found 238.0604.

(*E*)-3-Benzylidene-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16aa):



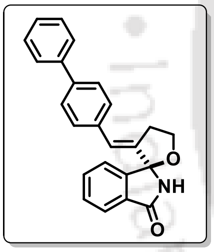
White Solid; R_f (hexane/ethyl acetate, 7:3) 0.40; mp 153-155 °C, yield 112 mg, 67%; IR (KBr, neat) ν 3057, 2879, 1701, 1610, 1468, 1040, 690, 515 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.5 Hz, 1 H), 7.56-7.53 (m, 1 H), 7.49 – 7.45 (m, 2 H), 7.37 (d, *J* = 7.5 Hz, 1 H), 7.33 – 7.29 (m, 2 H), 7.26 – 7.21 (m, 3 H), 6.24 (t, *J* = 2.7 Hz, 1 H), 4.35-4.31 (m, 1 H), 4.17 (q, *J* = 7.9 Hz, 1 H), 3.20–3.17 (m, 2 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.1, 148.3, 139.4, 136.4, 133.1, 130.9, 129.9, 128.7, 128.6, 127.8, 125.6, 123.7, 122.9, 97.0, 67.2, 31.4. HRMS (ESI) calcd. for $C_{18}H_{16}NO_2$ $(M + H)^+$ 278.1176, found 278.1179.

(*E*)-3-(Naphthalen-2-ylmethylene)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16ab):



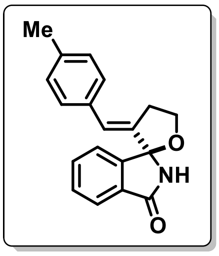
Colourless gum; R_f (hexane/ethyl acetate, 7:3) 0.40; yield 120 mg, 61%; IR (KBr, neat) ν 3057, 2924, 1701, 1610, 1468, 1040, 760, 475 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.5 Hz, 1 H), 7.80–7.76 (m, 3 H), 7.69 (s, 1 H), 7.57 (t, *J* = 7.4 Hz, 1 H), 7.51 – 7.44 (m, 3 H), 7.43 – 7.39 (m, 2 H), 7.33 (s, 1 H), 6.41 (s, 1 H), 4.40–4.35 (m, 1 H), 4.20 (q, *J* = 7.8 Hz, 1 H), 3.31–3.27 (m, 2 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.1, 148.4, 139.8, 133.9, 133.5, 133.2, 132.8, 130.9, 129.9, 128.3, 128.2, 127.8, 126.6, 126.5, 126.3, 125.7, 123.7, 123.0, 97.1, 67.3, 31.6. HRMS (ESI) calcd. for $C_{22}H_{18}NO_2$ $(M + H)^+$ 328.1332, found 328.1340.

(*E*)-3-([1,1'-Biphenyl]-4-ylmethylene)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16ac):



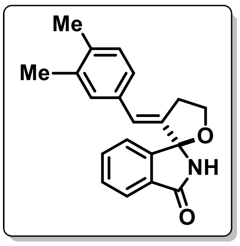
White Solid; R_f (hexane/ethyl acetate, 7:3) 0.40; mp 174–176 ºC, yield 148 mg, 70%; IR (KBr, neat) ν 3051, 2924, 1698, 1613, 1468, 1040, 755, 692, 505 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.5 Hz, 1 H), 7.57 (t, *J* = 7.4 Hz, 5 H), 7.49 (t, *J* = 7.5 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 7.38 (d, *J* = 7.6 Hz, 1 H), 7.35–7.33 (m, 3 H), 7.02 (s, 1 H), 6.30 (s, 1 H), 4.38–4.34 (m, 1 H), 4.19 (q, *J* = 7.9 Hz, 1 H), 3.25–3.22 (m, 2 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 148.4, 140.6, 135.4, 133.2, 129.9, 129.2, 129.1, 127.7, 127.4, 127.2, 125.3, 123.7, 123.0, 97.1, 67.2, 31.6. HRMS (ESI) calcd. for $C_{24}H_{19}NNaO_2$ $(M + Na)^+$ 376.1308, found 376.1296.

(*E*)-3-(4-Methylbenzylidene)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16ad):



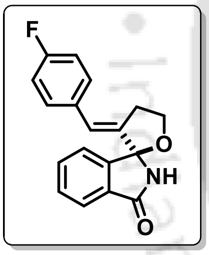
White Solid; R_f (hexane/ethyl acetate, 7:3) 0.40; mp 171–173 ºC, yield 129 mg, 74%; IR (KBr, neat) ν 3082, 2916, 1701, 1613, 1465, 1040, 757, 517 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.5 Hz, 1 H), 7.57–7.54 (m, 1 H), 7.50 – 7.47 (m, 1 H), 7.37 (d, *J* = 7.5 Hz, 1 H), 7.27 (s, 1 H), 7.14 (q, *J* = 8.2 Hz, 4 H), 6.22 (t, *J* = 2.6 Hz, 1 H), 4.35–4.31 (m, 1 H), 4.16 (q, *J* = 7.9 Hz, 1 H), 3.21 – 3.16 (m, 2 H), 2.33 (s, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.1, 148.5, 138.1, 137.8, 133.6, 133.1, 130.8, 129.8, 129.4, 128.7, 125.5, 123.7, 122.9, 97.0, 67.2, 31.4, 21.4. HRMS (ESI) calcd. for $C_{19}H_{18}NO_2$ $(M + H)^+$ 292.1332, found 292.1327.

(*E*)-3-(3,4-Dimethylbenzylidene)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16ae):



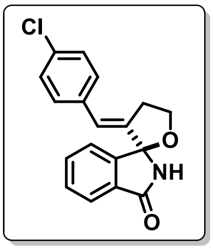
Colorless gum; R_f (hexane/ethyl acetate, 7:3) 0.40; yield 120 mg, 66%; IR (KBr, neat) ν 2923, 2883, 1702, 1613, 1468, 1041, 761, 537, 420 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, J = 7.5 Hz, 1 H), 7.57–7.55 (m, 1 H), 7.51–7.48 (m, 1 H), 7.37 (d, J = 7.6 Hz, 1 H), 7.10 (d, J = 8.3 Hz, 1 H), 7.04 – 7.02 (m, 2 H), 6.59 (s, 1 H), 6.22 (t, J = 2.6 Hz, 1 H), 4.36–4.32 (m, 1 H), 4.17–4.13 (m, 1 H), 3.21–3.18 (m, 2 H), 2.24 (d, J = 5.3 Hz, 6 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.8, 148.6, 137.8, 136.9, 136.7, 133.9, 133.2, 130.6, 130.2, 130.0, 129.9, 126.0, 125.8, 123.7, 122.9, 96.9, 67.2, 31.5, 20.0, 19.8. HRMS (ESI) calcd. for $C_{20}H_{20}NO_2$ $(M + H)^+$ 306.1489, found 306.1466.

(*E*)-3-(4-Fluorobenzylidene)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16ag):



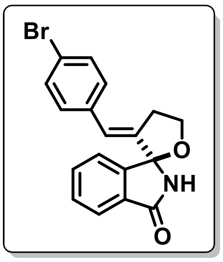
White Solid; R_f (hexane/ethyl acetate, 7:3) 0.40; mp 175–177 °C, yield 109 mg, 62%; IR (KBr, neat) ν 3062, 2874, 1698, 1600, 1228, 1040, 730, 520 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 7.5 Hz, 1 H), 7.56 (t, J = 7.5 Hz, 1 H), 7.51 – 7.45 (m, 2 H), 7.37 (d, J = 7.5 Hz, 1 H), 7.22 (dd, J = 8.5, 5.4 Hz, 2 H), 7.00 (t, J = 8.7 Hz, 2 H), 6.20 (d, J = 2.7 Hz, 1 H), 4.34 (dt, J = 8.6, 6.3 Hz, 1 H), 4.18 (q, J = 7.9 Hz, 1 H), 3.15 (td, J = 6.9, 6.5, 2.5 Hz, 2 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.2, 162.0 (d, J =247 Hz), 148.2, 139.1, 133.2, 132.6, 130.9, 130.4, 129.9, 124.4, 123.7, 122.9, 115.7(d, J = 21.4), 97.0, 67.2, 31.3. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ 48.25; HRMS (ESI) calcd. For $C_{18}H_{15}FNO_2$ $(M+H)^+$ 296.1081, found 296.1054.

(*E*)-3-(4-Chlorobenzylidene)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16ah):



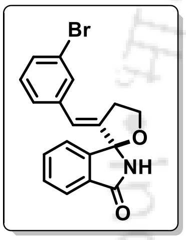
White Solid; R_f (hexane/ethyl acetate, 7:3) 0.40; mp 216–218 °C, yield 127 mg, 68%; IR (KBr, neat) ν 3082, 2881,1703, 1613, 1488, 1043, 760, 515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.5 Hz, 1 H), 7.5–7.55 (m, 1 H), 7.51–7.47 (m, 1 H), 7.37 (d, J = 7.5 Hz, 1 H), 7.30–7.26 (m, 3 H), 7.20 – 7.17 (m, 2 H), 6.20 (t, J = 2.7 Hz, 1 H), 4.37 – 4.32 (m, 1 H), 4.21 – 4.15 (m, 1 H), 3.18 – 3.14 (m, 2 H).$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.9, 148.2, 140.1, 134.8, 133.7, 133.3, 130.6, 130.1, 129.9, 128.9, 124.6, 123.8, 122.9, 96.9, 67.2, 31.4. HRMS (ESI) calcd. for $C_{18}H_{15}ClNO_2$ $(M + H)^+$ 312.0786, found 312.0790.

(*E*)-3-(4-Bromobenzylidene)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16ai):



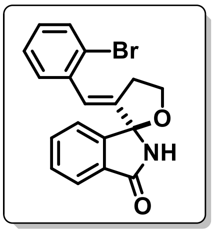
White Solid; R_f (hexane/ethyl acetate, 7:3) 0.40; mp 173–175 °C, yield 153 mg, 72%; IR (KBr, neat) ν 3084, 2879, 1703, 1610, 1488, 1043, 755, 512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.4 Hz, 1H), 7.58–7.54 (m, 1 H), 7.50–7.46 (m, 1 H), 7.44 – 7.41 (m, 3 H), 7.36 (d, J = 7.5 Hz, 1 H), 7.12 – 7.09 (m, 2 H), 6.17 (s, 1 H), 4.36 – 4.31 (m, 1 H), 4.20 – 4.15 (m, 1 H), 3.16 – 3.12 (m, 2 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 170.0, 148.1, 140.3, 135.3, 133.3, 131.9, 130.7, 130.2, 130.0, 124.6, 123.8, 122.9, 121.9, 96.9, 67.2, 31.4. HRMS (ESI) calcd. for $C_{18}H_{15}BrNO_2$ $(M + H)^+$ 356.0281, found 356.0282.

(*E*)-3-(3-Bromobenzylidene)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16aj):



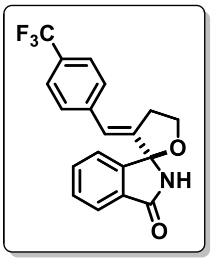
Colourless gum; R_f (hexane/ethyl acetate, 7:3) 0.40; yield 113 mg, 53%; IR (KBr, neat) ν 3079, 2881, 1700, 1614, 1468, 1043, 760, 555 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.85 (s, 1 H), 7.79 (d, J = 7.5 Hz, 1 H), 7.55 (t, J = 7.5 Hz, 1 H), 7.48 (t, J = 7.5 Hz, 1 H), 7.39 (s, 1 H), 7.37 – 7.30 (m, 2 H), 7.17–7.14 (m, 2 H), 6.15 (t, J = 2.7 Hz, 1 H), 4.35–4.32 (m, 1 H), 4.19 (q, J = 7.9 Hz, 1 H), 3.18–3.16 (m, 2 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.1, 148.0, 141.3, 138.5, 133.3, 131.4, 130.8, 130.7, 130.2, 130.0, 127.4, 124.2, 123.8, 122.9, 122.8, 96.9, 67.2, 31.4. HRMS (ESI) calcd. for $C_{18}H_{15}BrNO_2$ $(M + H)^+$ 356.0281, found 356.0256.

(*E*)-3-(2-Bromobenzylidene)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16ak):



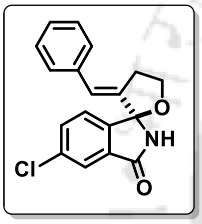
White Solid; R_f (hexane/ethyl acetate, 7:3) 0.40; mp 105–107 °C, yield 120 mg, 56%; IR (KBr, neat) ν 3082, 2881, 1701, 1613, 1465, 1040, 757, 537 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 7.5 Hz, 1 H), 7.60 (t, J = 7.5 Hz, 1 H), 7.53–7.50 (m, 2 H), 7.45 (d, J = 7.6 Hz, 1 H), 7.41 (s, 1 H), 7.33 – 7.26 (m, 2 H), 7.12–7.08 (m, 1 H), 6.45 (t, J = 2.6 Hz, 1 H), 4.29–4.25 (m, 1 H), 4.17 (q, J = 7.8 Hz, 1 H), 3.06–3.03 (m, 2 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.9, 147.9, 141.9, 136.5, 133.2, 133.0, 130.9, 130.0, 129.6, 129.3, 127.4, 125.2, 124.6, 123.8, 123.1, 96.4, 67.0, 30.8. HRMS (ESI) calcd. for $C_{18}H_{14}BrNNaO_2$ $(M + Na)^+$ 378.0100, found 378.0109.

(*E*)-3-(4-(Trifluoromethyl)benzylidene)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16al):



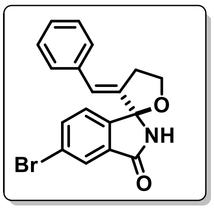
White Solid; Rf (hexane/ethyl acetate, 7:3) 0.40; mp 192–194 °C, yield 120 mg, 58%; IR (KBr, neat) ν 2926, 2854, 1703, 1613, 1323, 1068, 757, 515 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.4 Hz, 1 H), 7.59 – 7.55 (m, 3 H), 7.52–7.48 (m, 1 H), 7.46 (s, 1 H), 7.39 – 7.35 (m, 3 H), 6.28 (t, *J* = 2.7 Hz, 1 H), 4.39 – 4.34 (m, 1 H), 4.23 – 4.18 (m, 1 H), 3.23–3.19 (m, 2 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.3, 147.8, 142.5, 139.9, 133.3, 130.9, 130.1, 129.5 (q, *J* =32.3 Hz), 128.8, 125.6 (q, *J* = 3.7 Hz), 124.3, 124.2 (q, *J* = 270.4 Hz), 123.7, 123.0, 97.0, 67.2, 31.4. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ 99.19; HRMS (ESI) calcd. for $C_{19}H_{15}F_3NO_2$ $(M + H)^+$ 346.1049, found 346.1050.

(*E*)-3-Benzylidene-5'-chloro-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16ba):



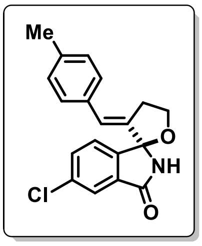
White Solid; Rf (hexane/ethyl acetate, 7:3) 0.40; mp 191–193 °C, yield 125 mg, 67%; IR (KBr, neat) ν 3056, 2879, 1711, 1433, 1320, 1045, 692, 550 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (s, 1 H), 7.54–7.53 (m, 1 H), 7.36–7.32 (m, 4 H), 7.28 (d, *J* = 7.6 Hz, 3 H), 6.25 (t, *J* = 2.6 Hz, 1 H), 4.37–4.33 (m, 1 H), 4.18 (q, *J* = 7.9 Hz, 1 H), 3.22–3.19 (m, 2 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 168.6, 146.4, 138.8, 136.2, 136.1, 133.3, 132.7, 128.8, 128.7, 128.1, 125.9, 124.4, 123.9, 96.7, 67.4, 31.4. HRMS (ESI) calcd. for $C_{18}H_{15}ClNO_2$ $(M + H)^+$ 312.0786, found 312.0781.

(*E*)-3-Benzylidene-5'-bromo-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16ca):



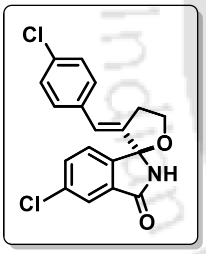
Colourless gum; Rf (hexane/ethyl acetate, 7:3) 0.40; yield 128 mg, 60%; IR (KBr, neat) ν 3056, 2886, 1708, 1605, 1428, 1043, 735, 552 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$/ DMSO-d_6) δ 7.90 – 7.88 (m, 1 H), 7.68–7.66 (m, 1 H), 7.33 (t, *J* = 7.6 Hz, 2 H), 7.28–7.23 (m, 4 H), 6.19 (t, *J* = 3.1 Hz, 1 H), 4.33–4.28 (m, 1 H), 4.18 (q, *J* = 7.9 Hz, 1 H), 3.19–3.15 (m, 2 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$/ DMSO-d_6) δ 167.7, 146.4, 139.2, 135.9, 135.3, 133.3, 128.3, 128.2, 127.4, 126.1, 124.7, 124.5, 123.4, 96.4, 66.9, 31.0. HRMS (ESI) calcd. for $C_{18}H_{15}BrNO_2$ $(M + H)^+$ 356.0281, found 356.0280.

(*E*)-5'-Chloro-3-(4-methylbenzylidene)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16bd):



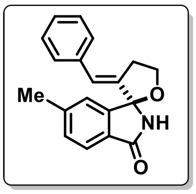
White Solid; R_f (hexane/ethyl acetate, 7:3) 0.40; mp 222–224 °C, yield 124 mg, 64%; IR (KBr, neat) ν 3091, 2881, 1711, 1433, 1318, 1043, 822, 517 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1 H), 7.67–7.65 (m, 2 H), 7.51 (d, J = 8.6 Hz, 1 H), 7.25 (d, J = 7.9 Hz, 2 H), 7.17 (d, J = 7.9 Hz, 2 H), 6.09 (t, J = 2.6 Hz, 1 H), 4.27–4.22 (m, 1 H), 4.07 (q, J = 7.8 Hz, 1 H), 3.25–3.16 (m, 1 H), 3.11 – 3.03 (m, 1 H), 2.28 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 166.8, 146.6, 139.2, 136.8, 134.4, 133.3, 133.2, 132.5, 129.1, 128.2, 124.9, 123.4, 122.3, 96.2, 66.4, 30.8, 20.7. HRMS (ESI) calcd. for $C_{19}H_{17}ClNO_2$ $(M + H)^+$ 326.0942, found 326.0930.

(*E*)-5'-Chloro-3-(4-chlorobenzylidene)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16bh):



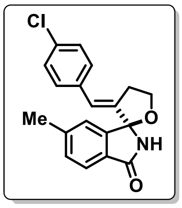
White Solid; R_f (hexane/ethyl acetate, 7:3) 0.40; mp 242–244 °C, yield 122 mg, 59%; IR (KBr, neat) ν 3076, 2884, 1706, 1593, 1433, 1045, 822, 512 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$/ DMSO-d_6) δ 7.93 (s, 1 H), 7.74 (s, 1 H), 7.54 – 7.51 (m, 1 H), 7.33 – 7.29 (m, 3 H), 7.21–7.19 (m, 2 H), 6.15 (t, J = 2.8 Hz, 1 H), 4.34 – 4.29 (m, 1 H), 4.20–4.15 (m, 1 H), 3.16-3.11 (m, 2 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$/ DMSO-d_6) δ 168.0, 146.0, 140.1, 135.9, 134.7, 133.5, 133.1, 132.9, 129.7, 128.8, 124.3, 124.1, 123.6, 96.5, 67.1, 31.2. HRMS (ESI) calcd. for $C_{18}H_{13}Cl_2NNaO_2$ $(M + Na)^+$ 368.0216, found 368.0224.

(*E*)-3-Benzylidene-6'-methyl-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16da):



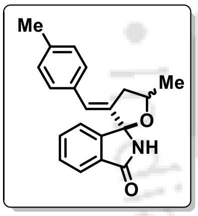
White Solid; R_f (hexane/ethyl acetate, 7:3) 0.40; mp 142–145 °C, yield 110 mg, 63%; IR (KBr, neat) ν 3056, 2879, 1695, 1620, 1410, 1040, 735, 515 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, J = 7.7 Hz, 1 H), 7.33 (t, J = 7.6 Hz, 2 H), 7.30 – 7.23 (m, 4 H), 7.17 (s, 1 H), 6.95 (s, 1 H), 6.27 (t, J = 2.6 Hz, 1 H), 4.36–4.33 (m, 1 H), 4.15 (q, J = 7.9 Hz, 1 H), 3.22 – 3.18 (m, 2 H), 2.42 (s, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 170.2, 148.8, 144.1, 139.4, 136.4, 130.8, 128.7, 128.7, 128.1, 127.9, 125.7, 123.5, 123.4, 96.8, 67.2, 31.6, 22.2. HRMS (ESI) calcd. for $C_{19}H_{18}NO_2$ (M + H)$^+$ 292.1332, found 292.1348.

(*E*)-3-(4-Chlorobenzylidene)-6'-methyl-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (16dh):



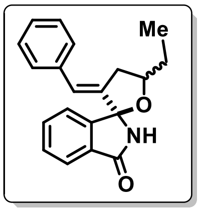
White Solid; R_f (hexane/ethyl acetate, 7:3) 0.40; mp 249–251 °C, yield 119 mg, 61%; IR (KBr, neat) ν 2954, 2921, 1698, 1615, 1488, 1043, 782, 515 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.68 (d, *J* = 7.8 Hz, 1 H), 7.29 (d, *J* = 8.7 Hz, 3 H), 7.20 (d, *J* = 8.6 Hz, 2 H), 7.16 (s, 1 H), 6.97 (s, 1 H), 6.21 (t, *J* = 2.7 Hz, 1 H), 4.37–4.33 (m, 1 H), 4.16 (q, *J* = 7.6 Hz, 1 H), 3.17–3.14 (m, 2 H), 2.43 (s, 3 H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 170.1, 148.7, 144.2, 140.3, 134.9, 133.7, 130.9, 129.9, 128.9, 128.1, 124.5, 123.6, 123.4, 96.8, 67.1, 31.5, 22.2. HRMS (ESI) calcd. for $C_{19}H_{17}ClNO_2$ (M + H)$^+$ 326.0942, found 326.0948.

(*E*)-5-Methyl-3-(4-methylbenzylidene)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (diastereomeric mixture, ratio= 7:3) **(16fd):**



White Solid; R_f (hexane/ethyl acetate, 7:3) 0.40; mp 160–162 °C, yield 140 mg, 76%; IR (KBr, neat) ν 3056, 2965, 1701, 1615, 1468, 1310, 1033, 695, 515 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.80 (d, J = 7.6 Hz, 1 H), 7.58–7.53 (m, 1 H), 7.48 (t, *J* = 7.5 Hz, 1 H), 7.39–7.36 (m, 1 H), 7.15 – 7.12 (m, 5 H), 6.26 (t, *J* =2.5 Hz, 1 H, minor) 6.18 (t, *J* = 2.5 Hz, 1 H, major), 4.61–4.56 (m, 1 H, minor) 4.38–4.34 (m, 1 H, major), 3.35–3.29 (m, 1H, minor), 3.29–3.24 (m, 1 H, major), 2.83–2.78 (m, 1 H, minor), 2.76–2.73 (m, 1 H, major) 2.33 (s, 3 H), 1.49 (d, *J* = 5.9 Hz, 2 H), 1.43 (d, *J* = 6.1 Hz, 1 H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 170.1, 149.2, 148.3, 139.6, 137.7, 133.6, 133.2, 129.8, 129.7, 129.4, 128.7, 128.7, 125.6, 125.4, 123.7, 123.5, 123.2, 122.7, 97.3, 75.2, 74.7, 39.6, 38.4, 22.1, 21.4, 21.2. HRMS (ESI) calcd. for $C_{20}H_{20}NO_2$ (M + H)$^+$ 306.1489, found 306.1495.

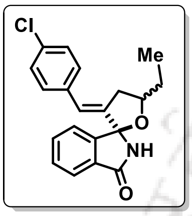
(*E*)-3-Benzylidene-5-ethyl-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (diastereomeric mixture, ratio= 4:1) **(16ga):**



Colourless gum; R_f (hexane/ethyl acetate, 7:3) 0.40; yield 114 mg, 62%; IR (KBr, neat) ν 3055, 2971, 2880, 1698, 1610, 1468, 1040, 757, 515 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.80 (d, *J* = 7.4 Hz, 1 H), 7.59–7.54 (m, 1 H), 7.49 (t, *J* = 7.4 Hz, 1 H), 7.38 (d, *J* = 7.6 Hz, 1 H), 7.35 – 7.32 (m, 2

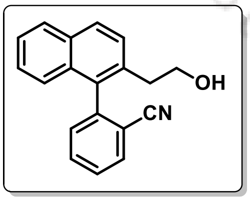
H), 7.27–7.23 (m, 3 H), 6.66 (s, 1 H), 6.29 (t, *J* =2.7 Hz, 1 H, minor), 6.23 (t, *J* = 2.5 Hz, 1 H, major), 4.41–4.35 (m, 1 H, minor), 4.20 – 4.15 (m, 1 H, major), 3.34–3.28 (m, 1 H, minor), 3.25–3.20 (m, 1 H, major), 2.86–2.81 (m, 1 H, minor), 2.81–2.75 (m, 1 H, major), 1.90–7.83 (m, 1 H), 1.80 – 1.74 (m, 1 H), 1.69 – 1.65 (m, 1 H), 1.06-1.01 (m, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, CDCl3) δ 169.9, 149.2, 148.4, 140.5, 139.5, 136.4, 133.3, 130.6, 129.9, 129.8, 128.7,127.9, 125.7, 123.8, 123.6, 123.1, 122.7, 97.0, 80.4, 80.0, 37.3, 36.5, 29.5, 28.6, 10.2, 10.0. HRMS (ESI) calcd. For $C_{20}H_{20}NO_2$ $(M+H)^+$ 306.1489, found 306.1483.

(*E*)-3-(4-Chlorobenzylidene)-5-ethyl-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (diastereomeric ratio= 4:1) **(16gh):**



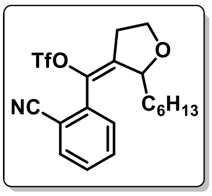
Colourless gum; R_f (hexane/ethyl acetate, 7:3) 0.40; yield 125 mg, 61%; IR (KBr, neat) ν 3084, 2964, 1701, 1613, 1490, 1088, 755, 515 cm^{-1}; ^{1}H NMR (500 MHz, CDCl3) δ 7.78 (d, *J* = 7.5 Hz, 1 H), 7.58–7.54 (m, 2 H), 7.48 (t, *J* = 7.5 Hz, 1 H), 7.37 (d, *J* = 7.5 Hz, 1 H), 7.29–7.26 (m, 2 H), 7.17–7.15 (m, 2 H), 6.22 (t, *J* =2.6 Hz, 1 H, minor), 6.15 (t, *J* = 2.6 Hz, 1 H, major), 4.40–4.35 (m, 1 H, minor), 4.25–4.20 (m, 1 H, major), 3.28–3.23 (m, 1 H, minor), 3.22–3.17 (m, 1 H, major), 2.84–2.79 (m, 1 H, minor), 2.76–2.70 (m, 1 H, major), 1.88–1.83 (m, 1 H), 1.79–1.73 (m, 1 H, major), 1.69–1.64 (m, 1 H, minor), 1.05–0.99 (m, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, CDCl3) δ 170.1, 169.9, 149.0,148.1, 141.4, 140.5, 134.9, 133.5, 133.2, 130.9, 129.9, 129.8, 128.8, 124.3, 123.7, 123.6, 123.2, 122.7, 97.1, 97.0, 80.3, 80.0, 37.2, 36.3, 29.4, 28.6, 10.2, 9.9. HRMS (ESI) calcd. for $C_{20}H_{19}ClNO_2$ $(M + H)^+$ 340.1099, found 340.1096.

2-(2-(2-Hydroxyethyl)naphthalen-1-yl)benzonitrile (16am):



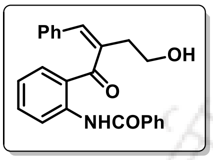
Colourless gum; R_f (hexane/ethyl acetate, 7:3) 0.40; yield 102 mg, 62%; IR (KBr, neat) ν 3412, 3061, 2954, 2875, 2226, 1725, 1598, 1387, 1043, 761, 555 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92–7.87 (m, 2 H), 7.85–7.83 (m, 1 H), 7.74–7.70 (m, 1 H), 7.58–7.54 (m, 1 H), 7.51 (d, *J* = 8.4 Hz, 1 H), 7.48–7.45 (m, 1 H), 7.42 (d, *J* = 7.7 Hz, 1 H), 7.39–7.36 (m, 1 H), 7.13 (d, *J* = 8.5 Hz, 1 H), 3.78–3.75 (m, 2 H), 2.84–2.79 (m, 1 H), 2.77–2.71 (m, 1 H), 1.66 (s, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 143.6, 134.9, 134.4, 133.2, 132.9, 132.6, 132.4, 131.9, 129.3, 128.3, 127.7, 126.8, 125.8, 125.5, 117.9, 114.5, 63.2, 37.0. HRMS (ESI) calcd. for $C_{19}H_{15}NNaO$ $(M + Na)^+$ 296.1046, found 296.1026.

(*E*)-(2-Cyanophenyl)(2-hexyldihydrofuran-3(2*H*)-ylidene)methyl trifluoromethanesulfo-nate (16an):



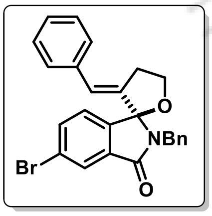
Colourless gum; R_f (hexane/ethyl acetate, 9:1) 0.60; yield 165 mg, 66%; IR (KBr, neat) ν 2929, 2859, 2232, 1730, 1414, 1208, 1136, 827, 604, 507 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.7 Hz, 1 H), 7.67 (t, *J* = 7.7 Hz, 1 H), 7.59–7.55 (m, 2 H), 4.63 (s, 1 H), 4.08 – 3.92 (m, 2 H), 3.01 (s, 2 H), 1.25–1.13 (m, 5 H), 1.09 – 0.98 (m, 5 H), 0.80 (t, *J* = 7.3 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.7, 135.7, 134.9, 133.7, 133.2, 131.3, 130.9, 118.3 (q, *J* = 318.2 Hz), 78.9, 66.3, 31.6, 28.9, 24.8, 22.6, 14.2. ^{19}F NMR (377 MHz, $C_6F_6/CDCl_3$) δ 86.97. HRMS (ESI) calcd. For $C_{19}H_{22}F_3KNO_4S$ $(M+K)^+$ 456.0853, found 456.0824.

(*E*)-*N*-(2-(2-benzylidene-4-hydroxybutanoyl)phenyl)benzamide (17a):



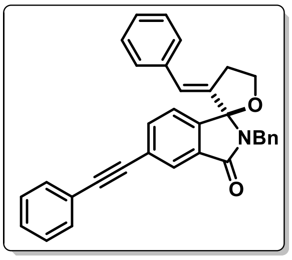
Light yellow solid; R_f (hexane/ethyl acetate, 1:1) 0.50; mp 117-119 °C, yield 166 mg, 75%; IR (KBr, neat) ν 3323, 2897, 1687, 1578, 1526, 1446, 1244, 1025, 749, 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.51 (s, 1 H), 8.77-8.74 (m, 1 H), 8.01 (d, *J* = 8.2 Hz, 2 H), 7.84 (d, *J* = 7.8 Hz, 1 H), 7.61–7.54 (m, 1 H), 7.52 – 7.48 (m, 3 H), 7.44 – 7.33 (m, 5 H), 7.15 – 7.12 (m, 1 H), 7.09 (s, 1 H), 3.90-3.86 (m, 2 H), 3.04 (t, *J* = 6.4 Hz, 2 H), 2.24 (brs, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 203.1, 166.1, 142.8, 140.8, 139.7, 135.2, 134.8, 134.5, 133.6, 132.3, 129.5, 129.1, 129.0, 128.9, 127.6, 124.7, 122.7, 122.0, 61.8, 31.5. HRMS (ESI) calcd. For $C_{24}H_{21}NNaO_3$ $(M+Na)^+$ 394.1414, found 394.1419.

(*E*)-2'-Benzyl-3-benzylidene-5'-bromo-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (17b):



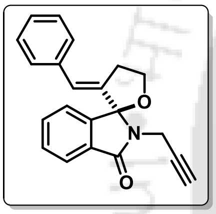
Colourless gum; R_f (hexane/ethyl acetate, 8:2) 0.40; yield 187 mg, 75%; IR (KBr, neat) ν 3061, 2923, 1705, 1425, 1053, 695, 550 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 1.9 Hz, 1 H), 7.65 (dd, *J* = 8.0, 1.8 Hz, 1 H), 7.34 – 7.28 (m, 4 H), 7.25 – 7.19 (m, 4 H), 7.17 – 7.14 (m, 1 H), 7.07 (d, *J* = 7.3 Hz, 2 H), 5.98 (s, 1 H), 4.77 (d, *J* = 15.8 Hz, 1 H), 4.50 (d, *J* = 15.8 Hz, 1 H), 4.19–4.15 (m, 1 H), 4.07–4.03 (m, 1 H), 3.12–3.07 (m, 2 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.8, 147.0, 137.8, 137.2, 135.9, 135.7, 132.8, 128.7, 128.6, 128.5, 128.1, 127.9, 127.3, 127.2, 126.7, 124.0, 123.8, 100.5, 68.1, 43.7, 31.6. HRMS (ESI) calcd. for $C_{25}H_{21}BrNO_2$ $(M + H)^+$ 446.0750, found 446.0741.

(*E*)-2'-Benzyl-3-benzylidene-5'-(phenylethynyl)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one(17c):



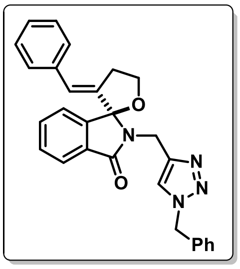
Colourless gum; R$_f$ (hexane/ethyl acetate, 7:3) 0.40; yield 60 mg, 58%; IR (KBr, neat) ν 2956, 2923, 2855, 1705, 1438, 1379, 1056, 756, 407 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.01 (d, *J* = 1.6 Hz, 1 H), 7.66 (dd, *J* = 7.8, 1.5 Hz, 1 H), 7.57 – 7.55 (m, 2 H), 7.41 (d, *J* = 6.8 Hz, 2 H), 7.38–7.37 (m, 3 H), 7.32 (t, *J* = 7.2 Hz, 2 H), 7.30 – 7.27 (m, 1 H), 7.21 (d, *J* = 7.8 Hz, 1 H), 7.18 – 7.15 (m, 3 H), 6.71 (dd, *J* = 7.7, 1.8 Hz, 2 H), 5.74 (t, *J* = 1.7 Hz, 1 H), 4.75–4.68 (m, 2 H), 4.59 (d, *J* = 15.3 Hz, 1 H), 4.45 (d, *J* = 15.3 Hz, 1 H), 2.62 – 2.54 (m, 2 H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3) δ 167.1, 144.5, 139.5, 138.2, 137.6, 135.8, 131.9, 129.2, 128.9, 128.7, 128.6, 128.1, 127.6, 126.7, 126.6, 125.5, 123.0, 122.7, 105.1, 91.1, 88.6, 74.9, 43.1, 32.5. HRMS (ESI) calcd. for $C_{33}H_{26}NO_2$ $(M + H)^+$ 468.1958, found 468.1939.

(*E*)-3-Benzylidene-2'-(prop-2-yn-1-yl)-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one(17d):



Colourless gum; R$_f$ (hexane/ethyl acetate, 7:3) 0.40; yield 166 mg, 73%; IR (KBr, neat) ν 2926, 2881, 1721, 1611, 1394, 1048, 758, 697, 511 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.85 (d, *J* = 7.5 Hz, 1 H), 7.58–7.55 (m, 1 H), 7.51–7.49 (m, 1 H), 7.39 – 7.34 (m, 3 H), 7.29–7.27 (m, 3 H), 6.18 (t, *J* = 2.6 Hz, 1 H), 4.49–4.45 (m, 1 H), 4.39–4.35 (m, 1 H), 4.28–4.27 (m, 2 H), 3.37–3.32 (m, 1 H), 3.29 – 3.24 (m, 1 H), 2.12 (t, *J* = 2.5 Hz, 1 H). ^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$) δ 167.4, 148.2, 137.2, 136.3, 133.0, 130.3, 129.7, 128.8, 128.7, 127.9, 127.1, 123.7, 122.4, 100.2, 79.3, 70.8, 68.3, 31.7, 28.2· HRMS (ESI) calcd. for $C_{21}H_{18}NO_2$ $(M + H)^+$ 316.1332, found 316.1326.

(*E*)-2'-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-benzylidene-4,5-dihydro-3*H*-spiro[furan-2,1'-isoindolin]-3'-one (17e):

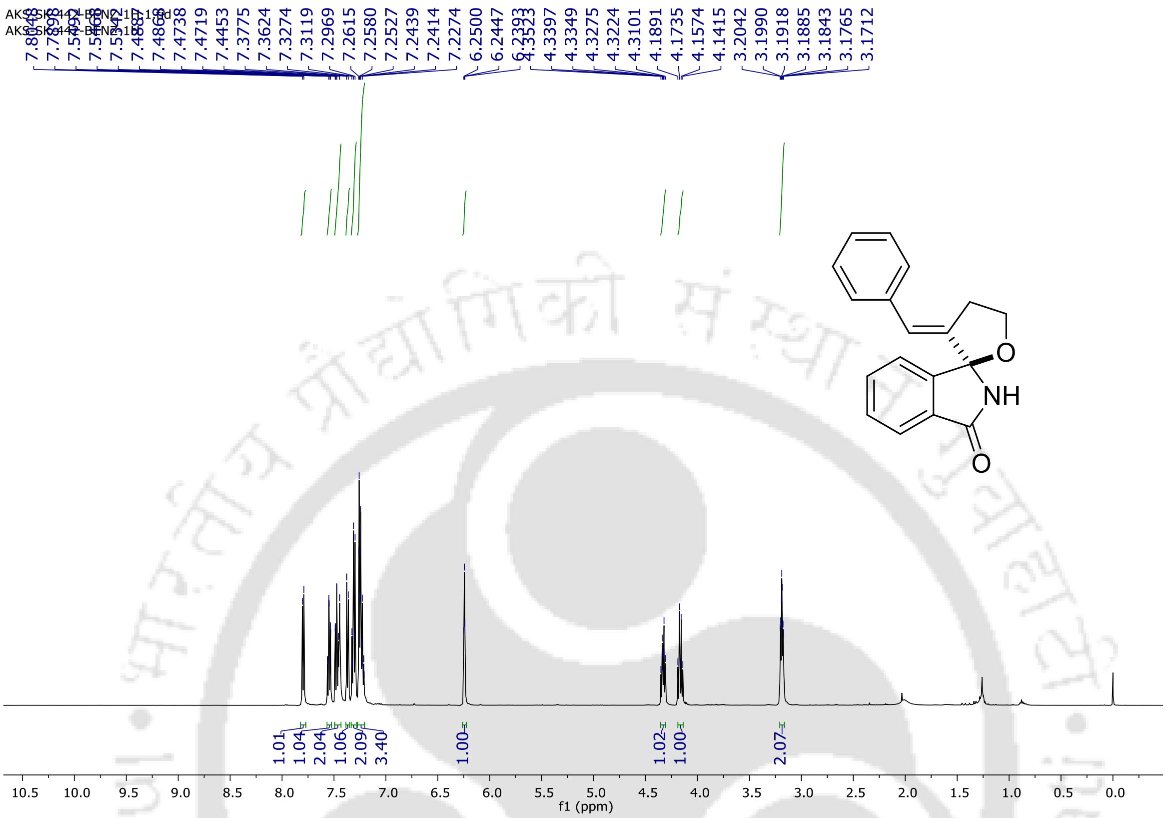


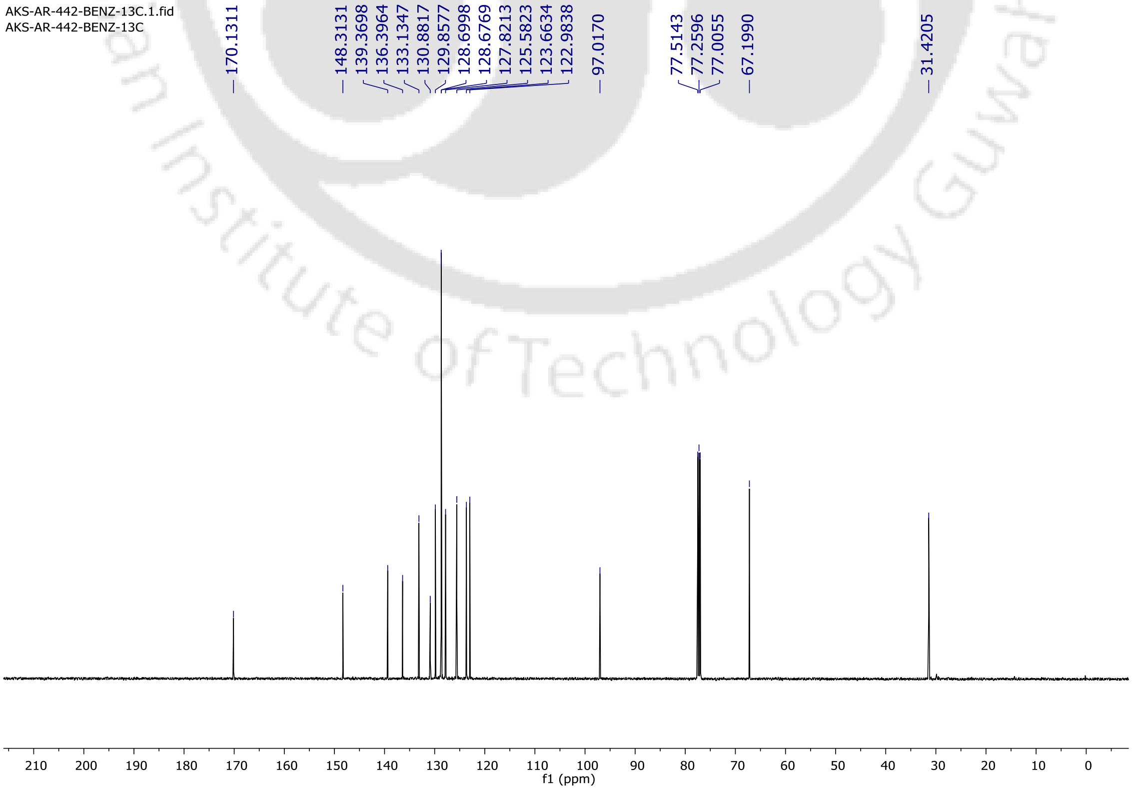
Colourless gum; R$_f$ (hexane/ethyl acetate, 7:3) 0.40; yield 129 mg, 70%; IR (KBr, neat) ν 3030, 2880, 1697, 1374, 1046, 697, 514 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.81 (d, *J* = 7.5 Hz, 1 H), 7.55–7.53 (m, 1 H), 7.50 – 7.46 (m, 2 H), 7.34 – 7.31 (m, 3 H), 7.27 – 7.23 (m, 4 H), 7.14 (d, *J* = 7.2 Hz, 2 H), 7.07 (d, *J* = 6.4 Hz, 2 H), 5.89 (t, *J* = 2.6 Hz, 1 H), 5.30 (d, *J* = 1.9 Hz, 2 H), 4.85 (d, *J* = 16.0 Hz, 1 H), 4.68 (d, *J* = 16.0 Hz, 1 H), 4.39–4.35 (m, 1 H), 4.22–4.18 (m, 1 H), 3.41–3.36 (m, 1 H), 3.15–3.09 (m, 1 H). ^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$) δ 167.8, 148.2, 145.7, 138.3, 136.2, 134.6, 133.0, 130.7, 129.7, 129.2, 128.8, 128.7, 128.2, 128.0, 126.6, 123.5, 122.9, 122.6, 100.4, 68.4, 54.3, 35.1, 31.7. HRMS (ESI) calcd. for $C_{28}H_{25}N_4O_2$ (M + H)$^+$ 449.1973, found 449.1963.

TH-3246_176122006

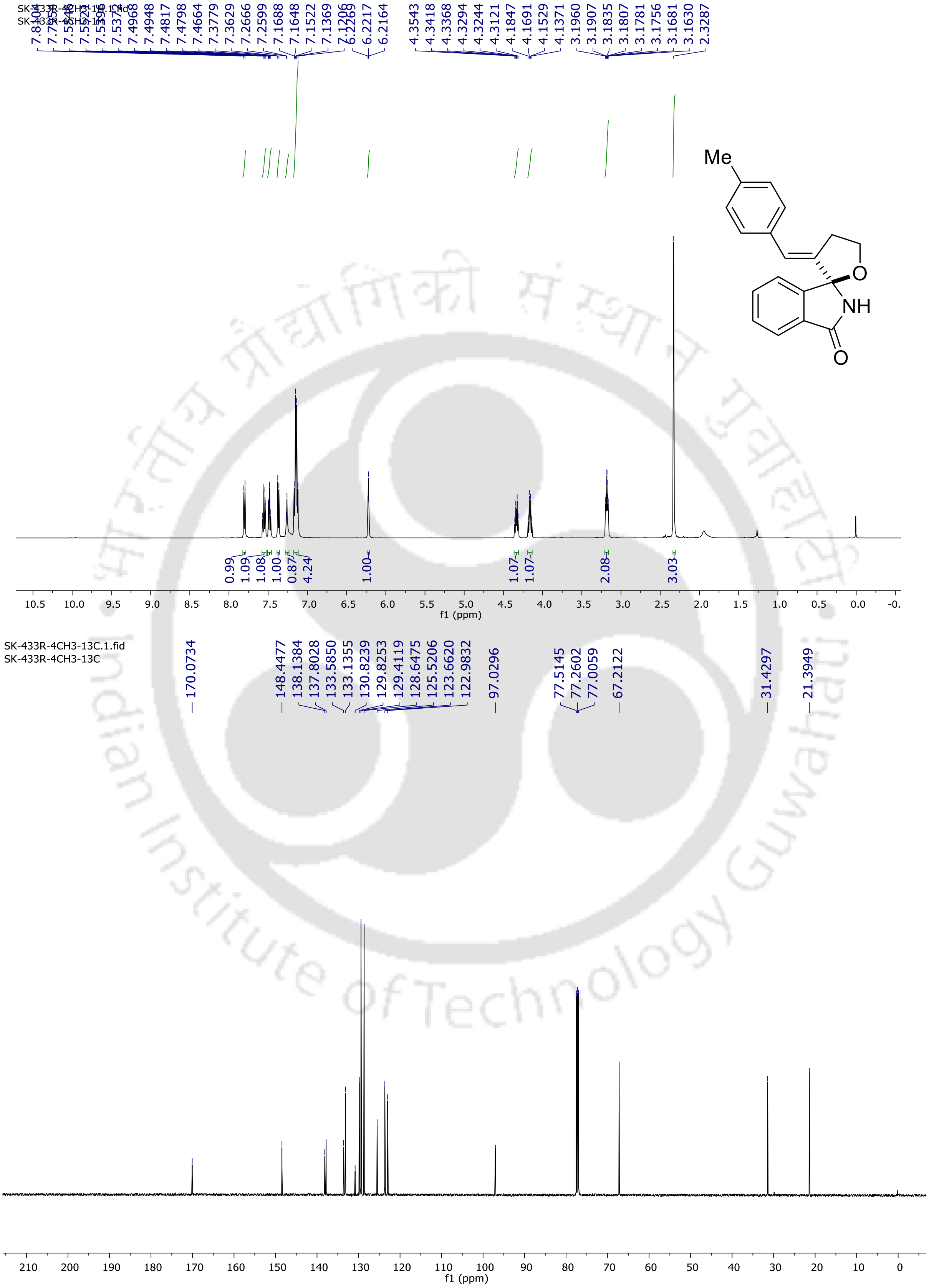
3.5.9 Representative Spectra and crystal parameter

^{1}H(500 MHz, CDCl$_3$) and ^{13}C{^{1}H} (125 MHz, CDCl$_3$) spectra of **16aa**





^{1}H (500 MHz, CDCl$_3$) and ^{13}C{^{1}H} (125 MHz, CDCl$_3$) spectra of **16ad**



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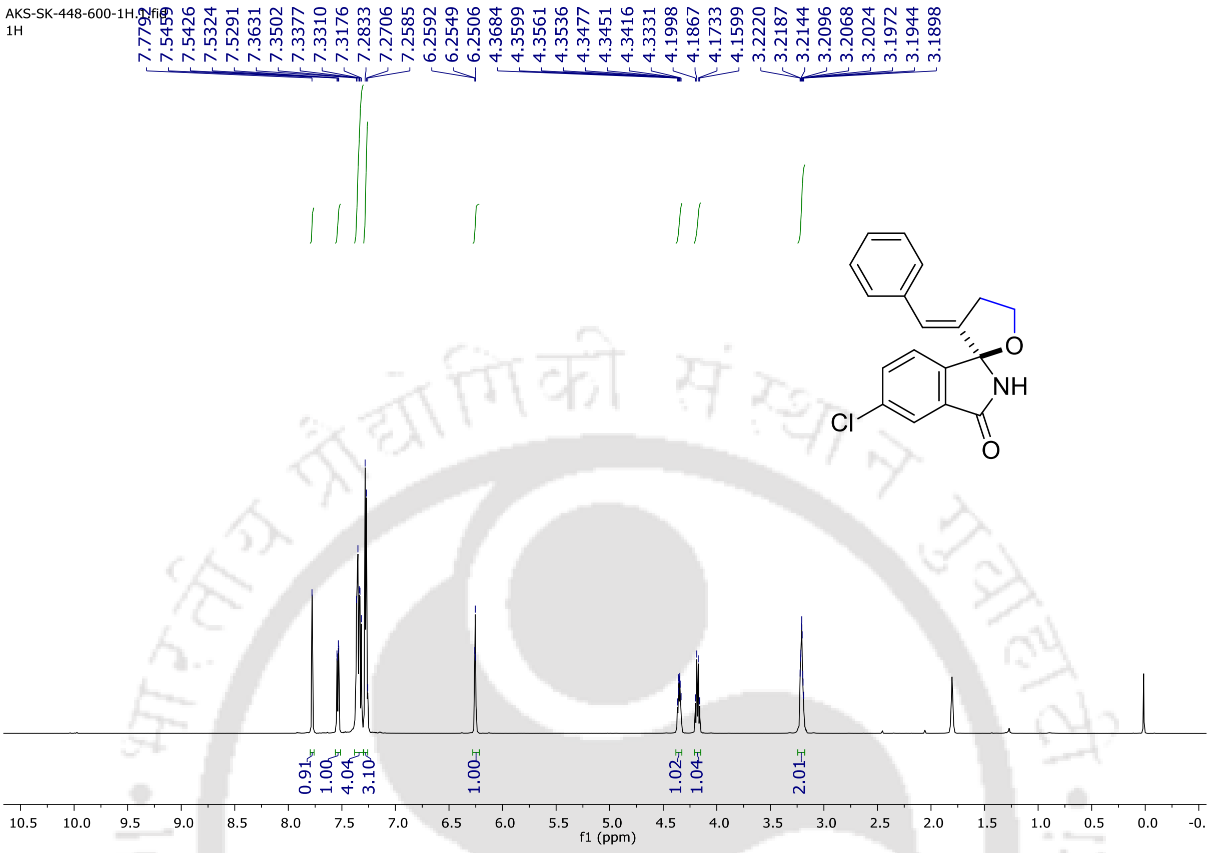
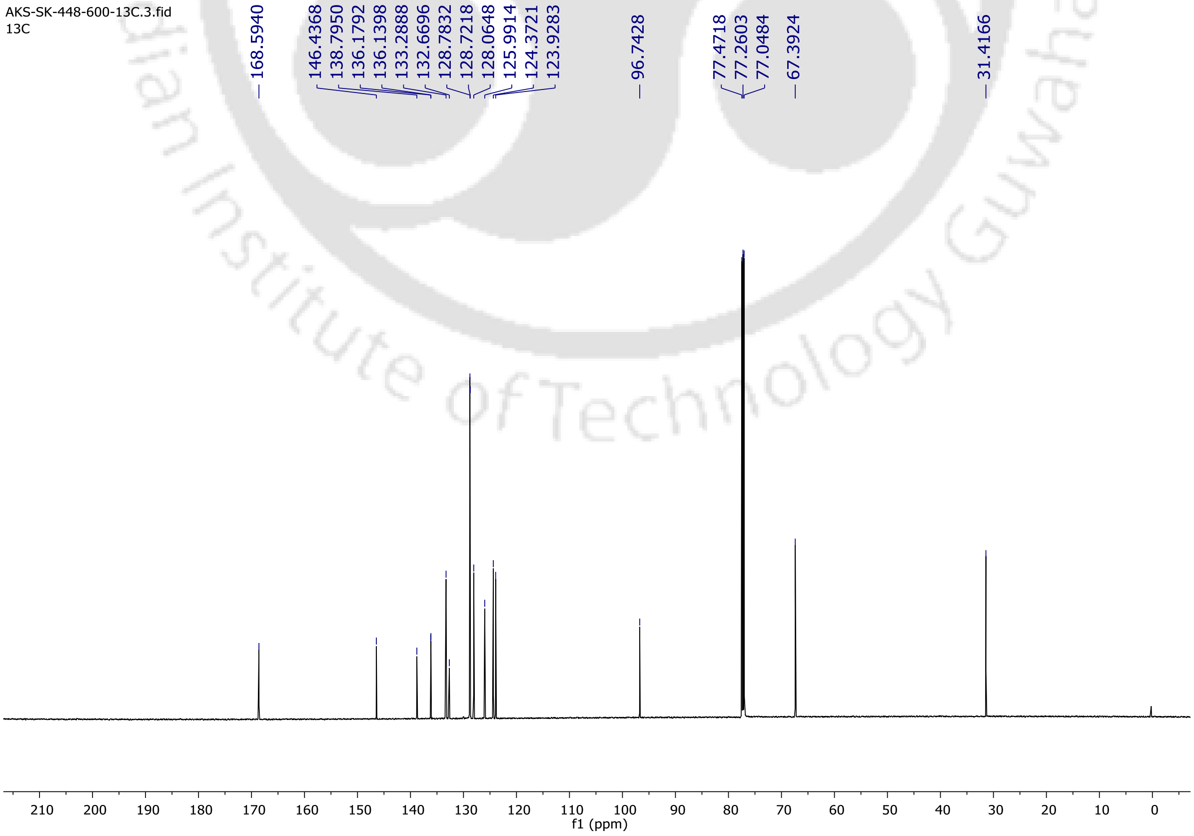
^{1}H (600 MHz, CDCl$_3$) and ^{13}C{^{1}H} (150 MHz, CDCl$_3$) spectra of **16ba**





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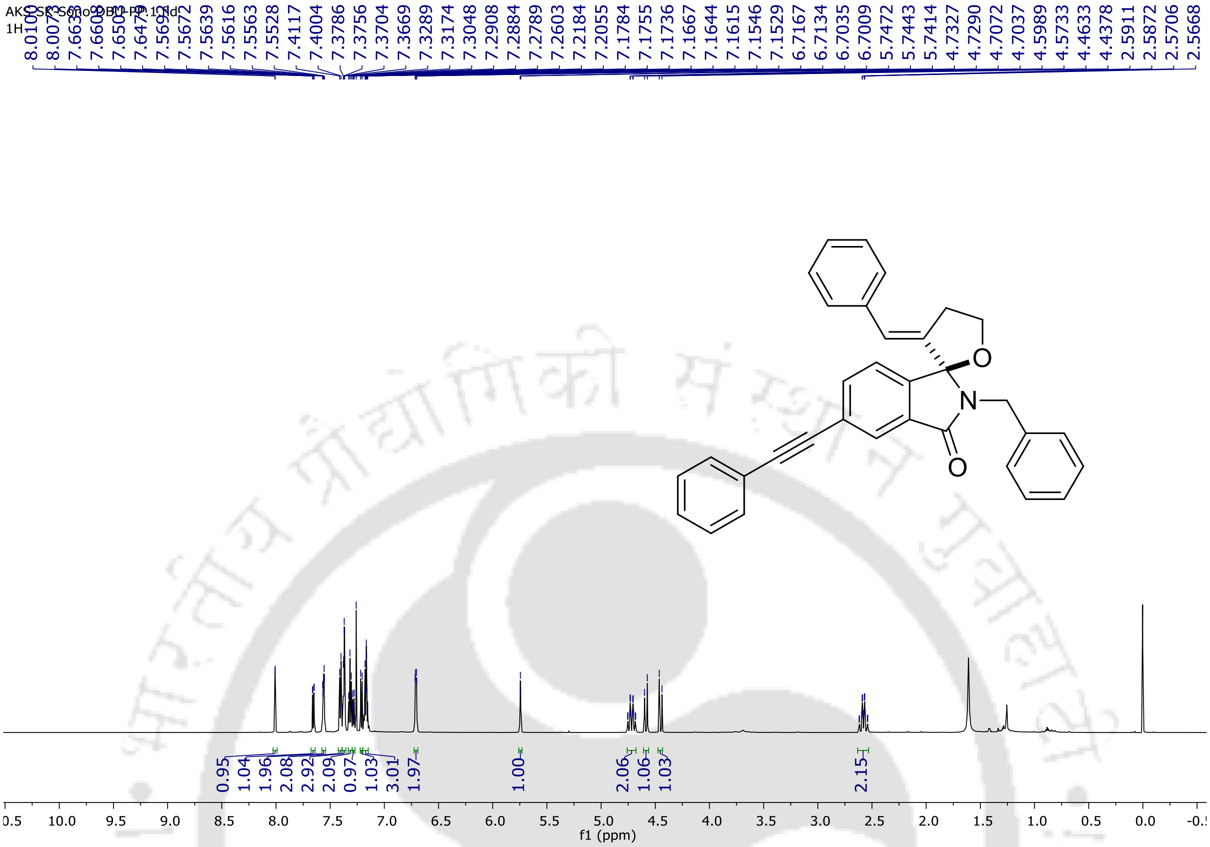
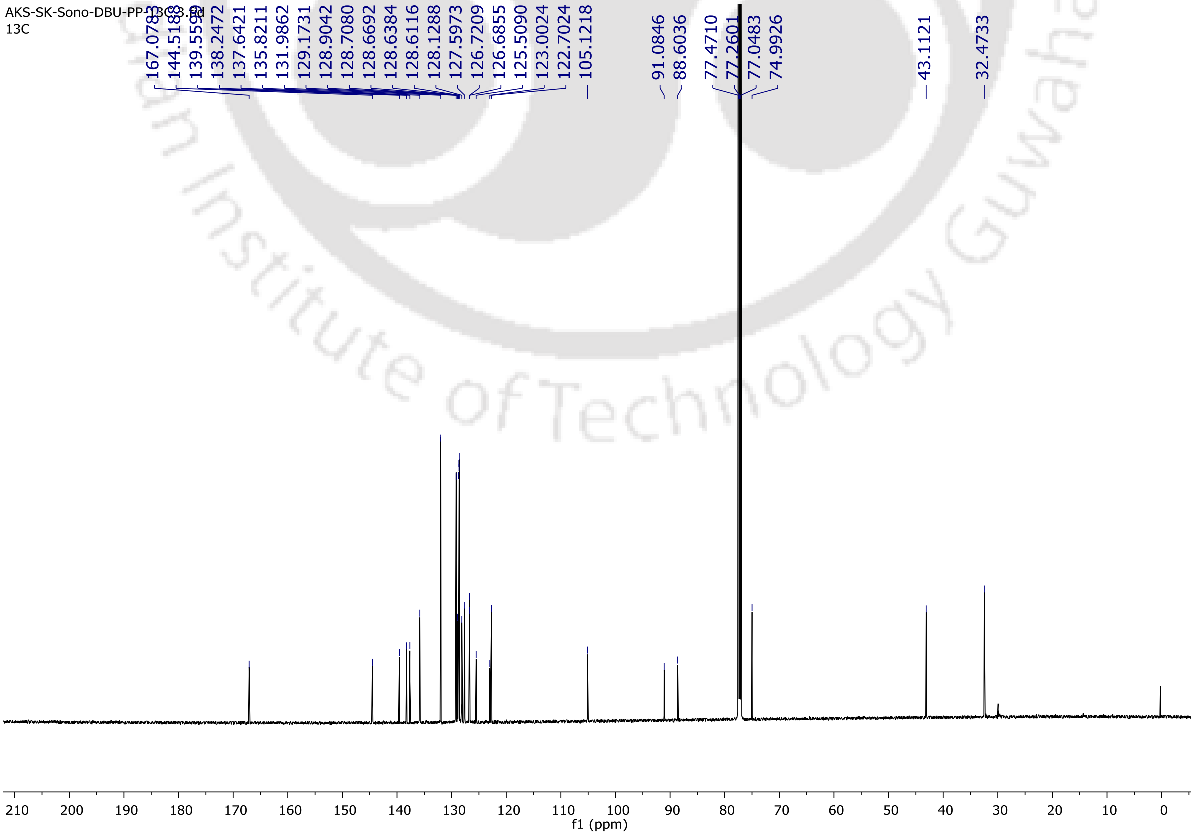
^{1}H (600 MHz, CDCl$_3$) and ^{13}C{^{1}H} (150 MHz, CDCl$_3$) spectra of **17c**





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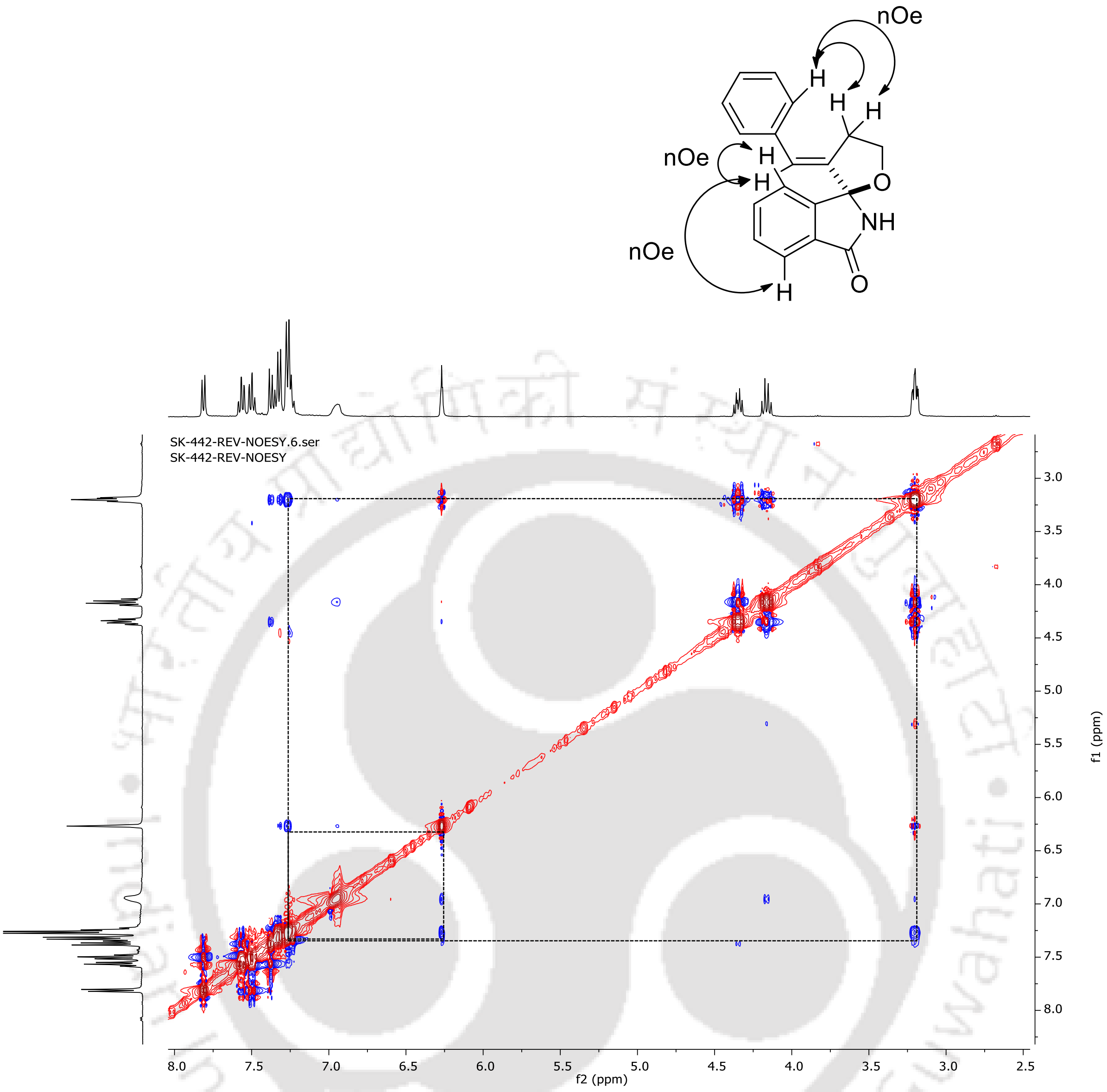
NOESY spectrum of compound **16aa** (400 MHz, $CDCl_3$)



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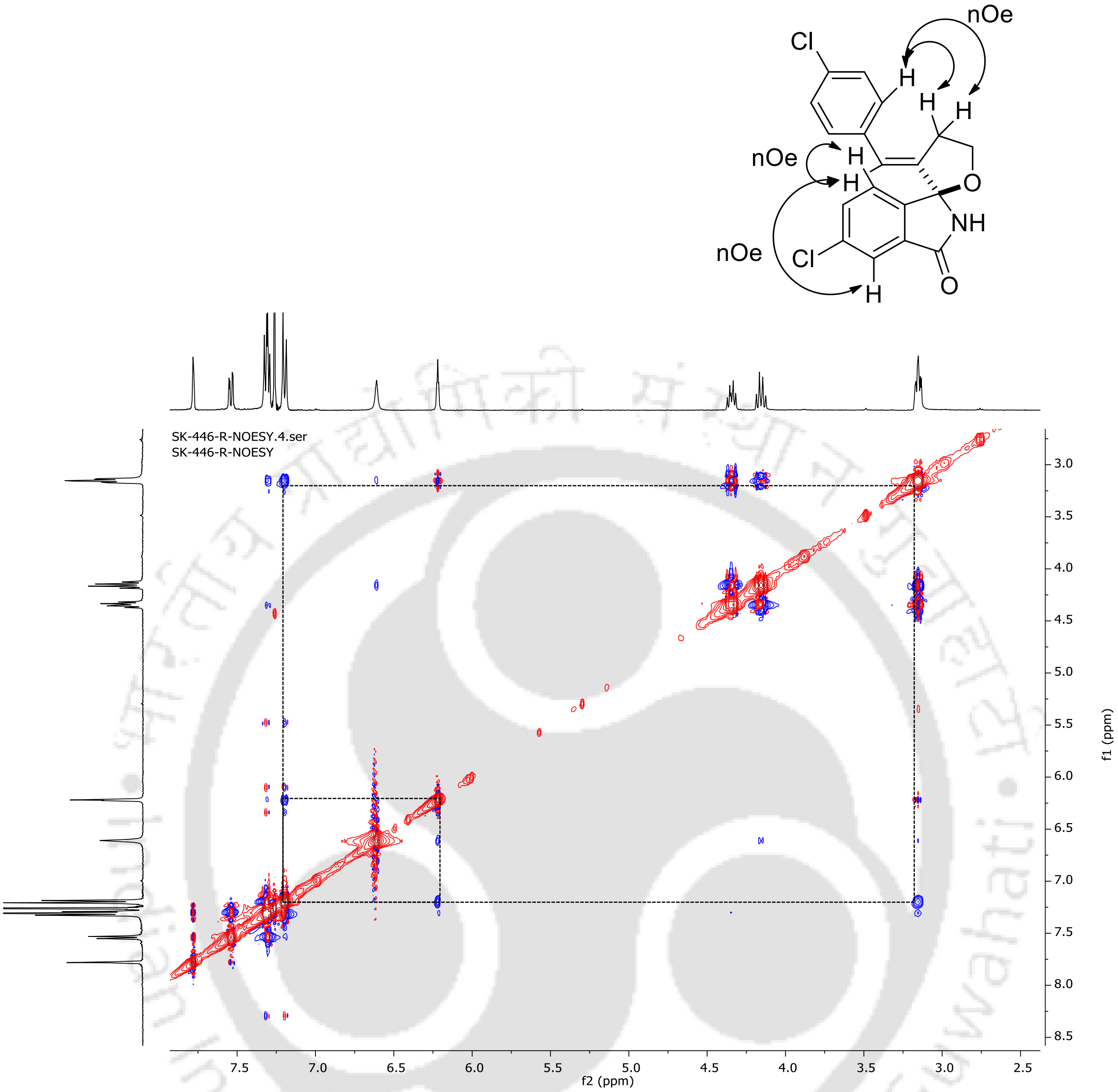
NOESY spectrum of compound **16bh** (400 MHz, $CDCl_3$)



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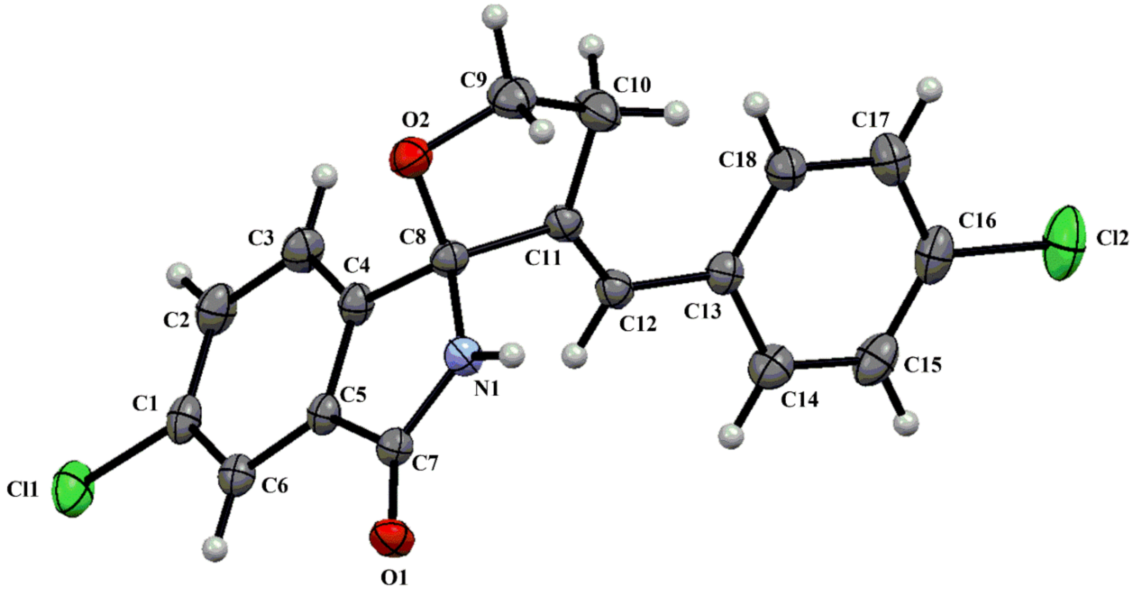
The crystal parameters of compound 16bh

	CCDC 2118542
Formula	$C_{18}H_{13}Cl_2NO_2$
Formula weight	346.2073
T/K	296(2)
Crystal system	monoclinic
Space group	P 21/n
a/Å	8.0474(10)
b/Å	12.2908(16)
c/Å	16.153(2)
α/^{o}	90
β/^{o}	91.621(4)
γ/^{o}	90
V/Å^3	1597.0(3)
Z	4
Abs. Coeff./mm^{-1}	0.415
Abs. Correction	none
GOF on F^2	1.358
Final R indices [I> 2σ(I)]	$R1$ = 0.0479 $wR2$ = 0.1625
R indices [all data]	$R1$ = 0.0656 $wR2$ = 0.1816

ORTEP diagram of compound (**16bh**) with 30% probability



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Chapter 4:

Nitrile Stabilized Synthesis of Pyrrolidine and Piperidine Derivatives via Tandem Alkynyl aza-Prins-Ritter Reactions

4.1 Importance and Applications

Pyrrolidine and piperidine scaffolds are the five- and six-membered heterocycles, present in a range of pheromones, many drug molecules and alkaloids such as, (+)-preussin, a hydroxyl containing pyrrolidine derivative, isolated from marine sponge related fungus *Aspergillus candidus* KUFA 0062, which exhibits anti-fungal activity, growth inhibitory and cytotoxic effect.[1] Ramipril is an angiotensin-converting enzyme (ACE) inhibitor used for the high blood pressure and congestive heart failure treatment.[2] ABT-418 is a cholinergic antagonist can be used in Alzheimer's disease and in ADHT (attention deficient hyperactivity treatment) in adults.[3] In the same contest, piperidine containing drug naratriptan is a class of selective serotonin receptor agonists, can be used for severe migraine headaches.[4a] Donepezil exhibits considerable activity against severe Alzheimer's disease, a neurodegenerative disorder.[4b] Ibrutinib shows remarkable activity against chronic lymphocytic leukemia (CLL).[4c]

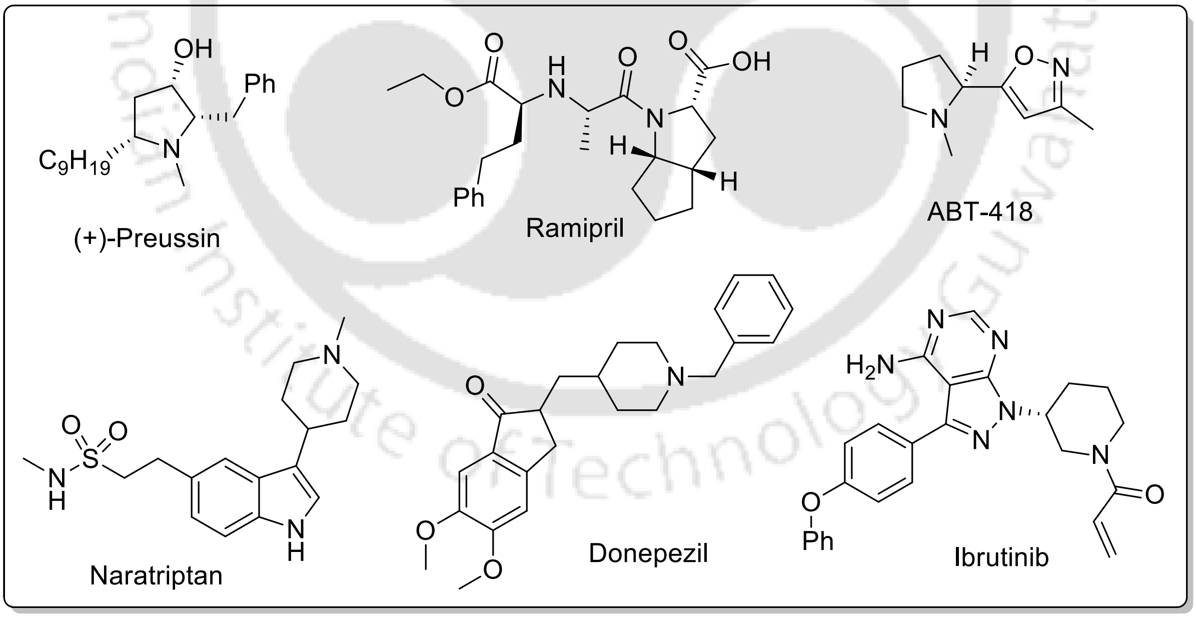
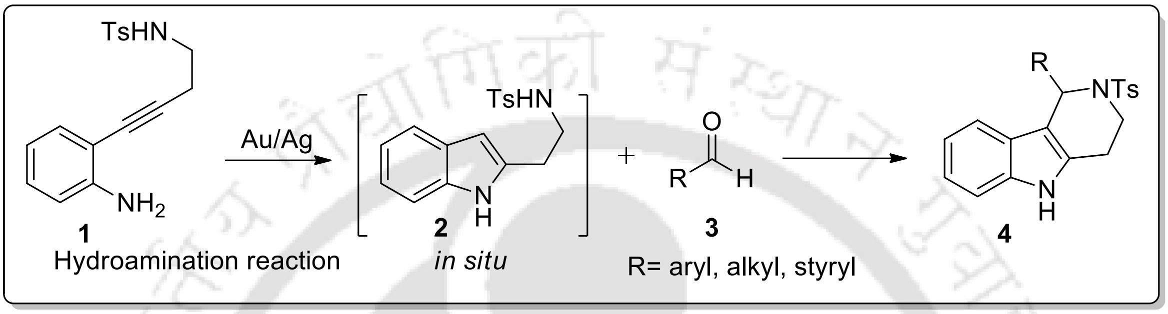


Figure 4.1.1: Bio-active molecules containing pyrrolidine and piperidine scaffolds.

4.2 An Overview of Relevant Synthetic Methods

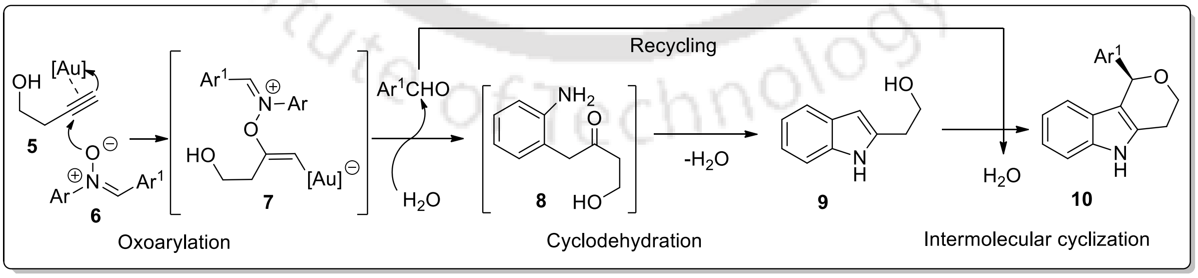
4.2.1 Metal Mediated Alkyne Functionalization

In 2012, Reddy and co-workers reported a gold(I) catalysed alkyne functionalization reaction for the synthesis of tetrahydropyrido[4,3-*b*]indole motif.[5] Initially, 2-(4-aminobut-1-yn-1-yl)anilines **1** underwent intramolecular hydroamination reaction via 5-endo-dig cyclization followed by Pictet-Spengler reaction to afford the final annulated product **4** (*Scheme 4.2.1.1*).



Scheme 4.2.1.1: Gold(I) catalysed alkyne functionalization.

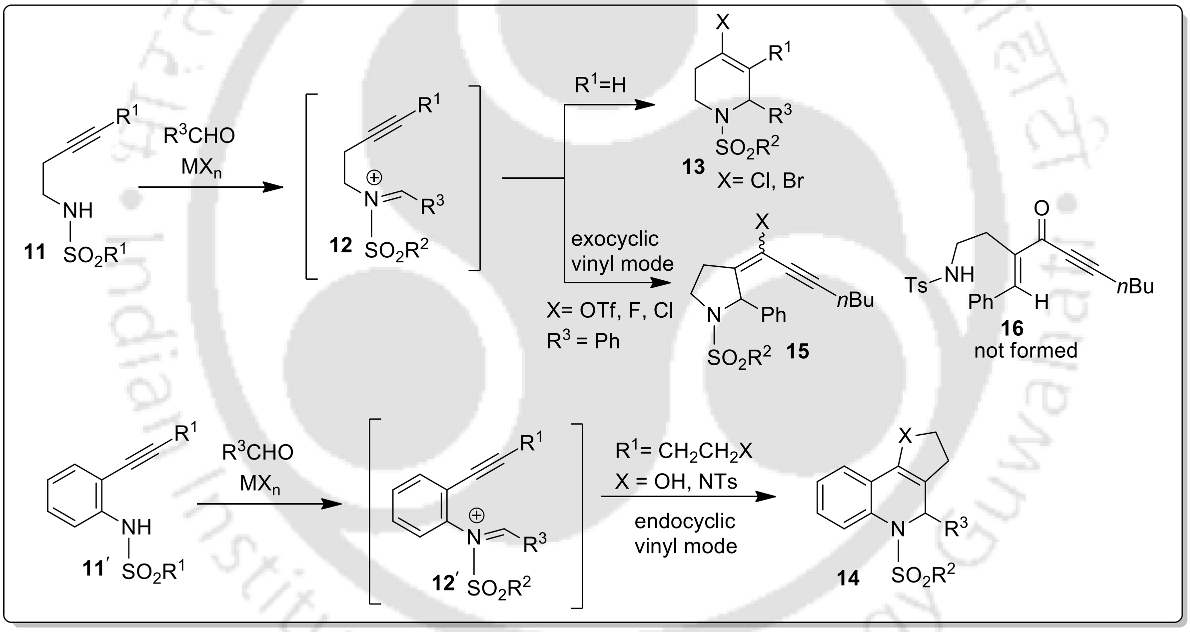
In 2019, Xu and co-workers demonstrated a gold catalysed annulation of homopropargyl alcohols with nitrones for the synthesis of tetrahydropyrano[4,3-*b*]indoles.[6] The propargyl alcohol **5** and nitrone **6** involved in oxoarylation reaction to form **8**, which after cyclodehydration generate **9**, the newly formed 2-(1*H*-indol-2-yl)ethanol (**9**) reacted with aldehydes which was a leaving species in the early step of this tandem process (*Scheme 4.2.1.2*). Water played an important role in this cascade process, which was confirmed by the controlled experiment using 4 Å molecular sieves.



Scheme 4.2.1.2: Annulations of homopropargylic alcohols with nitrones.

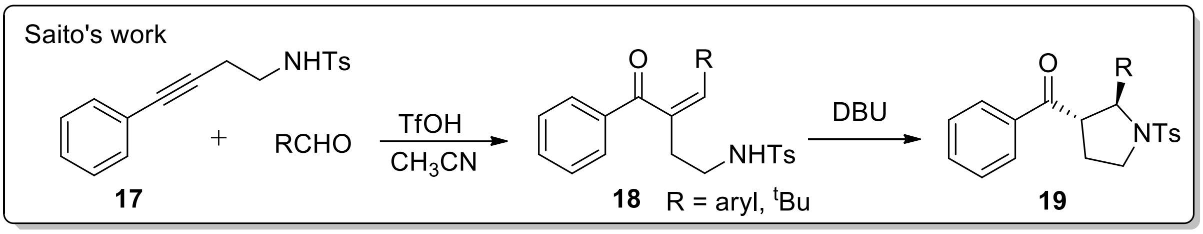
4.2.2 Alkyne *aza*-Prins Cyclization Reactions

Intramolecular addition of alkynes to iminium ions is called alkyne aza-Prins cyclization reaction.[7-8] Different strategies of aza-Prins cyclizations are described by various groups which is depicted in scheme 4.2.2.1. In 2006, Padrón and co-workers reported a Fe(III) mediated aza-Prins cyclization strategy for the synthesis of six-membered azacycles **13** (*Scheme 4.2.2.1*).[7a] The intramolecular cyclization of alkyne to iminium ion **12** took place via *6-endo-trig* fashion. In 2014, Ma and co-workers described an annulation reaction of *o*-alkynylanilines with aldehydes, to afford 1,2-dihydroquinoline derivatives **14**.[7b] In this work, initially, homopropargylic alcohol/amine self-cyclized and subsequent alkyne attack to iminium ion intermediate for the final bicyclic product **14**. Saito and co-workers demonstrated an aza-Prins cyclization reaction of f 3,5-diynyl amides and aldehydes in 2019.[8] The cyclization took place via *5-endo-trig* mode, which generated corresponding exocyclic vinyl cation and subsequent attack by triflate to afford 2,3-dialkylidenetetrahydrofurans **15**.



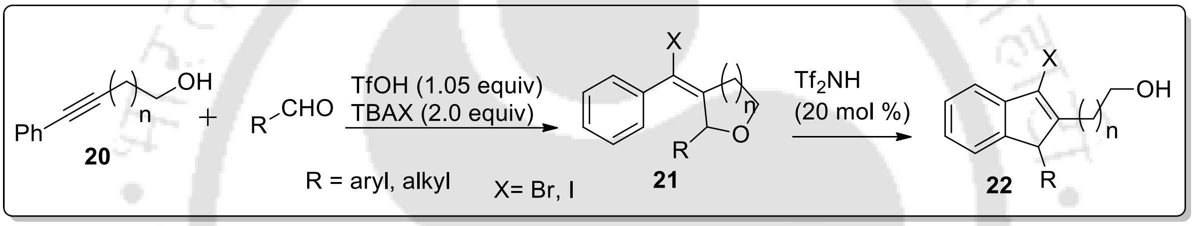
Scheme 4.2.2.1: Different strategies of alkyne aza-Prins cyclizations reaction.

In 2021, Saito and co-workers reported an alkyne aza-Prins reaction of aryl-substituted homopropargyl sulphonamides **17** and aldehydes for the synthesis of α-(aminoethyl)-α, β-enones **18**, which was further cyclized via *5-endo-trig* fashion by DBU to give the pyrrolidine derivatives **19** (*Scheme 4.2.2.2*).[9]



Scheme 4.2.2.2: Two steps synthesis of pyrrolidine derivatives.

In 2019, Frontier and co-workers reported a halo- alkyne Prins cyclization reaction for the two step synthesis of functionalized haloindenes and indenes.[10] In the presence of TfOH, homopropargyl alcohol **20** reacted with aldehydes to afford the halo- adduct **21**, TBAI or TBAB is the halogen source in this reaction. Finally, halo adduct **21** underwent halo-Nazarov cyclization to give the indene **22** (*Scheme 4.2.2.3*).

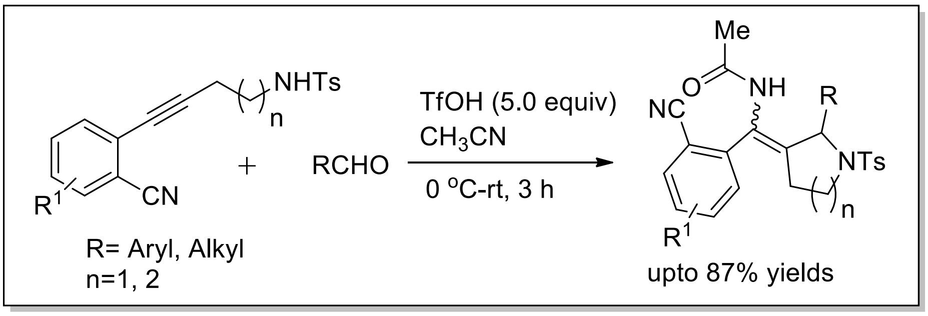


Scheme 4.2.2.3 halo-Prins reaction for indene synthesis

However, there are no direct report in literature for the synthesis of *N*-(pyrrolidine-3-ylidenemethyl)acetamide. We have demonstrated a simple nitrile assisted methodology for the synthesis of *N*-(pyrrolidine-3-ylidenemethyl)acetamides in moderate to good yields.

4.3 This Work

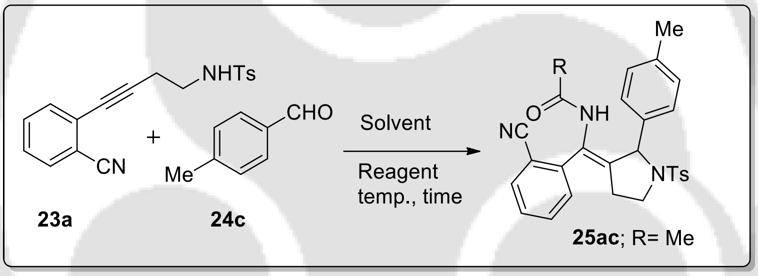
In this chapter, we have described an efficient methodology for the synthesis of *N*-(pyrrolidine-3-ylidenemethyl)acetamides mediated by triflic acid in good yields with high *Z*/*E* selectivity. The reaction involves the initial formation of pyrrolidin-3-ylidenemethylium carbocation *via* Prins cyclization reaction followed by Ritter reaction to produce *N*-(pyrrolidine-3-ylidenemethyl)acetamides. The amide functionality incorporated in the product comes from the solvent acetonitrile. The reaction occurs at room temperature within a short reaction time.



4.3.1 Results and discussion

In this study, *N*-(4-(2-cyanophenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide **23a** and *p*-tolualdehyde **24c** were taken as model substrates. First, the reaction was carried out with **23a** (0.2 mmol, 65 mg) and **24c** (0.24 mmol, 29 mg) in the presence of 2.0 equiv of BF_3•OEt_2 in acetonitrile (entry 1, table 1). Only unreacted starting material was recovered after 16 h. The reaction was carried out with $FeCl_3$ and Brønsted acid *p*-TSA, which also does not produce any desired product, rather unreacted starting material was recovered (entries 2&3, table 1). When the reaction was screened with 2.0 equiv of Brønsted acid (TfOH) in acetonitrile at 0 ˚C-rt, *N*-((2-cyanophenyl)(2-(p-tolyl)-1-tosylpyrrolidin-3-ylidene)methyl)acetamide **(25ac)** was obtained in 54% yield with *Z*/*E*=2.3:1 (entry 4, table 1). On increasing the amount of TfOH to

Table 1: Optimization of the reaction[a]:



Entry	Reagent(equiv)	Solvent	Temp.	Time(h)	**25ac** (%)/(Z:E)
1	BF_3•OEt_2 (2.0)	CH_3CN	0 ˚C-rt	16	0^b
2	$FeCl_3$ (2.0)	CH_3CN	0 ˚C-rt	16	0^b
3	*p*-TSA (2.0)	CH_3CN	0 ˚C-rt	14	0^b
4	TfOH (2.0)	CH_3CN	0 ˚C-rt	4	54 (2.3:1)
5	TfOH (3.0)	CH_3CN	0 ˚C-rt	4	59(2.3:1)
6	TfOH (5.0)	CH_3CN	0 ˚C-rt	3	87 (2.3:1)
7	TfOH (5.0)	CH_3CN	0 ˚C	5	44 (2.3:1)
8	TfOH (5.0)	benzonitrile	0 ˚C-rt	4	$-^c$
9	TfOH (5.0)	acrylonitrile	0 ˚C-rt	3	$-^d$
10	TMSOTf (5.0)	CH_3CN	0 ˚C-rt	5	81(2.1:1)

[a]Reaction conditions: **23a** (0.2 mmol, 65mg), **24c** (0.24 mmol, 29 mg), CH_3CN (2.0 mL), Nitrogen atmosphere, [b]starting material recovered, [c]Desired product not formed, [d]Decomposed product, yield refer to isolated yields

3.0 equiv and 5.0 equiv, resulted in 59 % and 87 % yields of the desired product, respectively (entries 5&6, table 1). Reaction at 0 ˚C gave only 44% of the expected product with *Z*/*E*= 2.3:1, along with some unreacted starting material (entry 7, table 1). Further, the reaction was tested with benzonitrile but the desired product was not formed (entry 8, table 1). Similarly, the reaction was also screened with acrylonitrile, which produced decomposed products. Furthermore, the reaction was carried out with 5.0 equiv of TMSOTf at 0 ˚C to rt, which produce the desired product in 81% yields with *Z*/*E*= 2.1:1. Therefore, 5.0 equiv of TfOH in acetonitrile at 0 ˚C to rt is the optimized condition for the reaction.

4.3.2 substrates scope of the reaction

With these optimal condition in hand, substrate scope of the reaction was investigated and depicted in scheme 4.3.1.1 and 4.3.1.2. Electron donating group in the aromatic ring of aldehydes (**24c**-**24e**) gave good yields of the corresponding products (**25ac**-**25ae**) with *Z*-selectivity. Electron withdrawing 2-Br and 4-CO_2Me group in the aromatic ring of aldehyde (**24f** and **24g**) produced the desired products **25af** and **25ag** in 66 and 87 % yields respectively, with *E*-selectivity (*Scheme 4.3.1.1*). Reaction with bulky 1-naphthaldehyde failed to give desired product instead unreacted starting material was recovered.

Scheme 4.3.1.1: *Synthesis of N-(Pyrrolidine-3-ylidenemethyl)acetamides*

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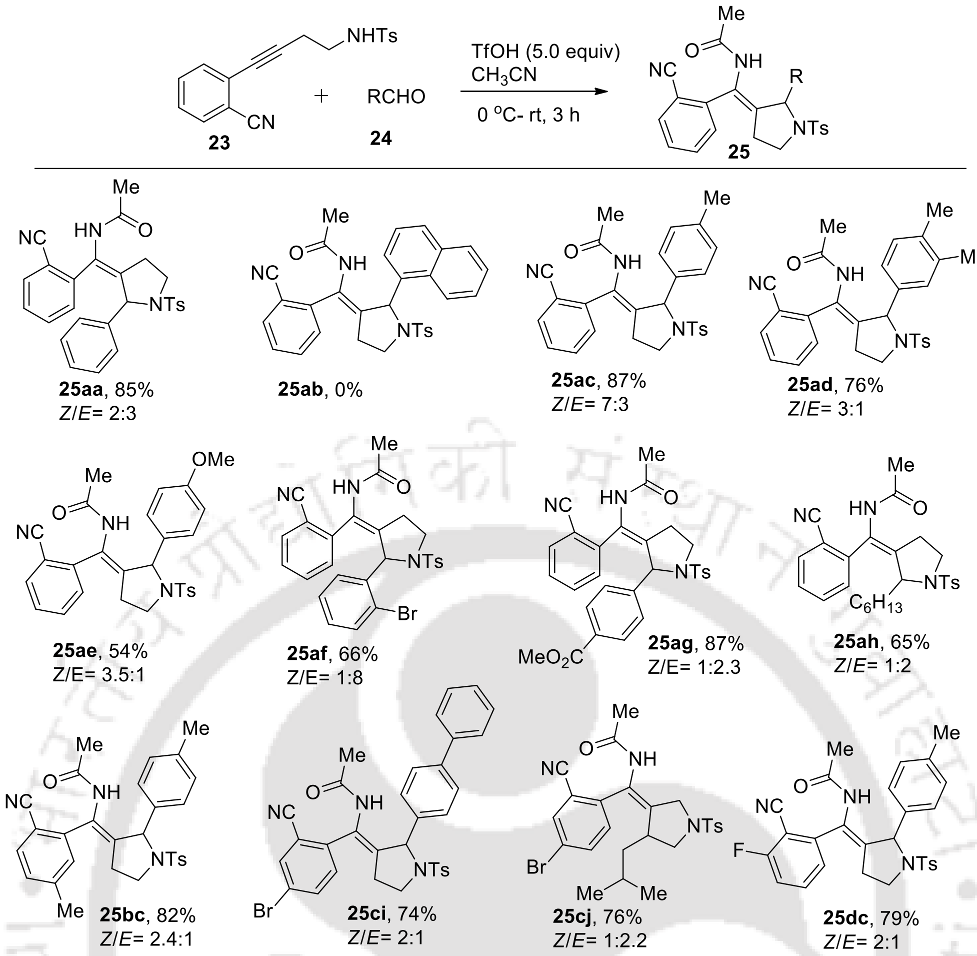
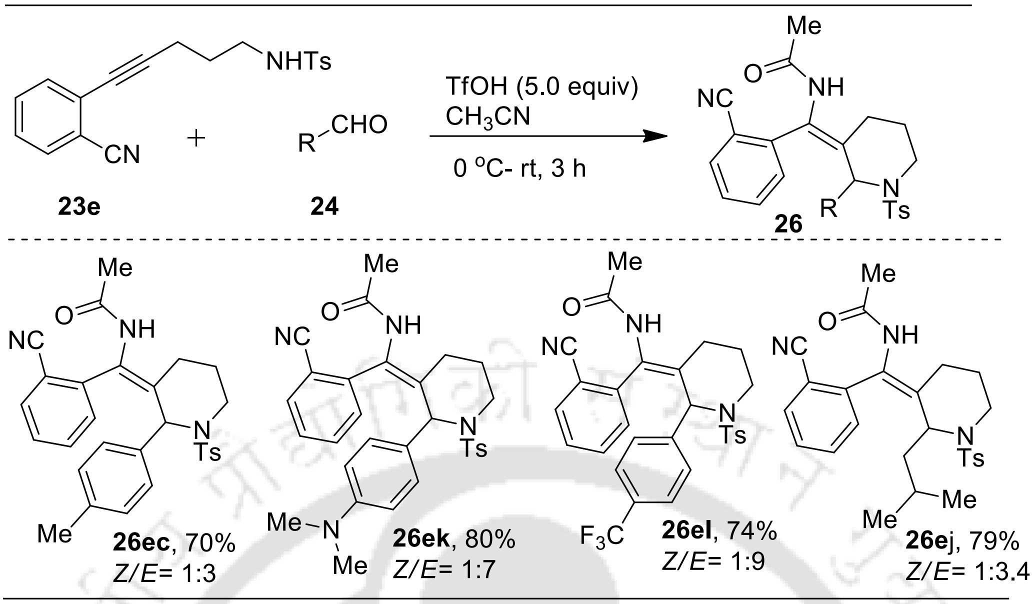


[a]Reaction conditions: **23** (0.2 mmol, 1.0 equiv), **24** (0.24 mmol, 1.2 equiv), TfOH (1.0 mmol, 5.0 equiv), CH_3CN (2.0 mL), N_2 atm. Reaction temperature= 0 °C-rt, *Z*/*E* ratio was calculated by crude ^{1}H NMR, Formula of the major isomer is shown in the scheme.

The reaction was further explored with aliphatic aldehyde **24h** to afford the desired product **25ah** in 65 % yields with *E*-selectivity. Alkynyl sulphonamide **23b** bearing the –Me group at 5- position gave the desired product **25bc** in 82 % yields with *Z*/*E*=2.4:1 (*Scheme 5.3.1.1*). On the other hand, moderately electron-withdrawing halo group at 4- and 6- position of alkynyl sulphonamide (**23c**, **23d**) gave the corresponding products in 74 and 79% yields respectively. Reaction of isovaleraldehyde with **23c** gave the desired product **25cj** with 76% yields with *Z*/*E*= 1:2.2(*Scheme 4.3.1.1*).

Further, the scope of the reaction was extended to the synthesis of its piperidine analogue. Reaction of **23e** with aryl and hetero-aryl aldehydes (**24c**, **24k**) produced the desired product (**26ec** and **26ek)** in 70 and 80 % yields respectively, with *E*-selectivity (*Scheme 4.3.1.2*). Similarly, the aliphatic aldehyde **24j** gave the expected piperidine derivative **26ej** in 79% yield with *Z*/*E*= 1:3.4. The electron–withdrawing aldehyde **24l** give good yields with excellent *E*-selectivity (1:9) (*Scheme 4.3.1.2*).

Scheme 4.3.1.2: Synthesis of Piperidine Derivatives

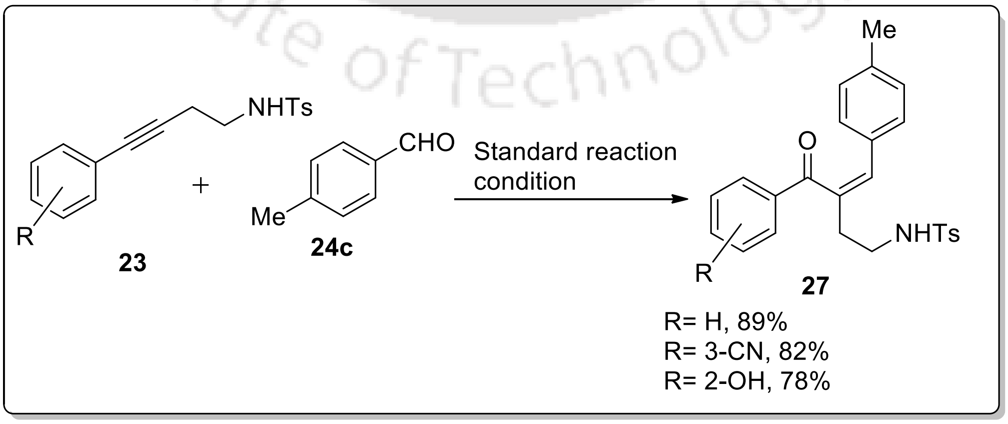


[a]Reaction conditions: **23** (0.2 mmol, 1.0 equiv), **24** (0.24 mmol, 1.2 equiv), TfOH (1.0 mmol, 5.0 equiv), CH_3CN (2.0 mL), N_2 atmosphere. Reaction temperature= 0 °C-rt, *Z*/*E* ratio was calculated by crude ^{1}H NMR, Formula of the major isomer is shown in the scheme.

4.3.3 Plausible mechanism of the reaction

To understand the role of –CN at 2-position of the alkynyl sulphonamide, few controlled experiments with were performed. Homoallylic sulfonamide without -CN group, -CN at 3-position and -OH group at -2 position was performed. The outcome of these reactions was depicted in scheme 5.3.2.1. When –CN functionality was removed from 2-position of the alkynyl sulphonamide, open chain unsaturated carbonyl compounds were formed (*Scheme 4.3.2.1*). Which indicated that the –CN group at 2-position of the alkynyl sulphonamide played an important role for the stabilization of the carbocation formed in the Prins reaction.

Scheme 4.3.2.1: Controlled Experiments



Initially, the reaction of homoallylic sulphonamide **23a** and aldehyde **24a** formed pyrrolidin-3-ylidenemethylium carbocation **A** and **A′** *via* Prins cyclization reaction. The carbocation **A**

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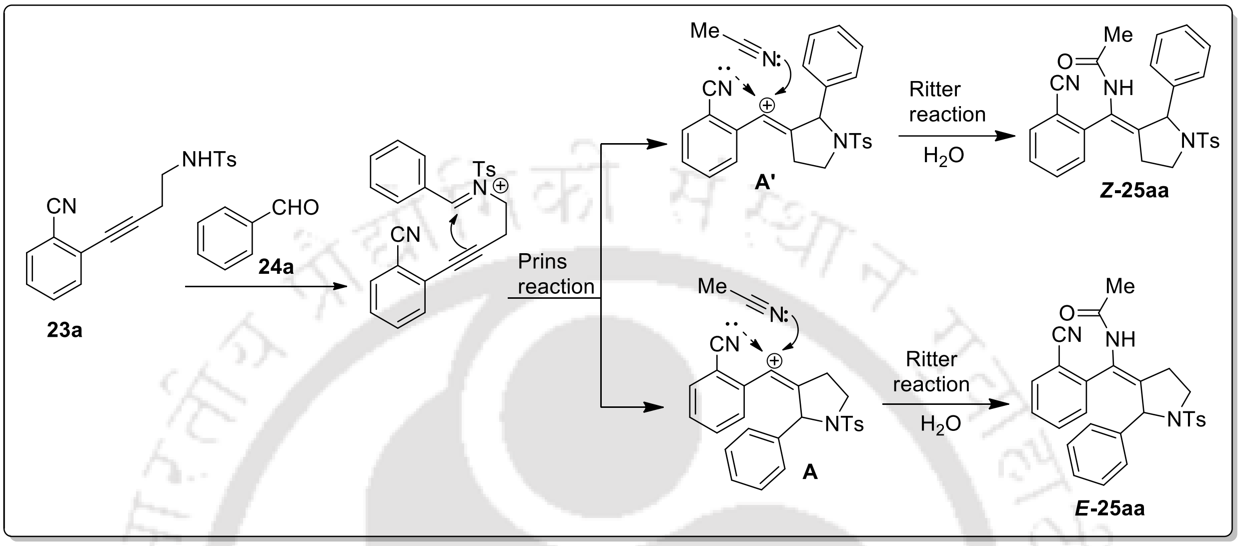
and **A′** were then stabilized by lone pair of –CN group at the 2-position of the aromatic ring. The acetonitrile was then involved in the nucleophilic attack to the carbocation **A** and **A′** followed by hydrolysis via Ritter reaction to afford the final product **25aa** and **25aa′** (*Scheme 4.3.2.2*).

Scheme 4.3.2.2: *Plausible mechanism of the reaction*



4.4 Conclusion

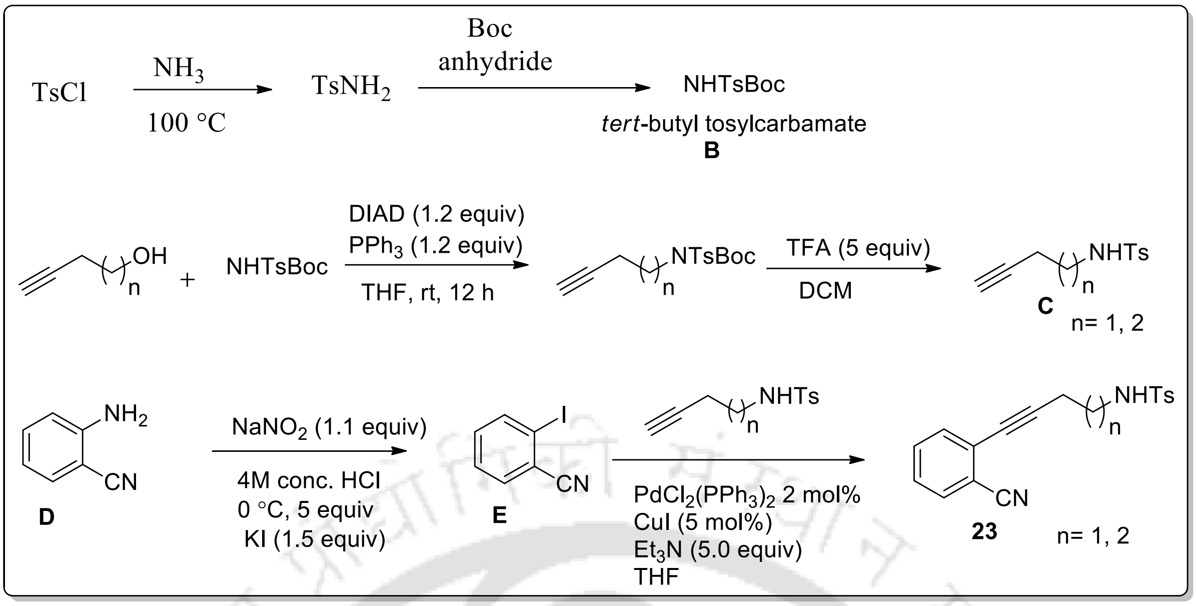
In conclusion, a nitrile stabilized efficient methodology for the synthesis of *N*-(pyrrolidine-3-ylidenemethyl)acetamides at 0 ˚C to room temperature is demonstrated. The methodology was utilized for the synthesis of its piperidine analogues in good yields. The amide functionality incorporated in the product comes from the solvent acetonitrile.

4.5 Experimental section

4.5.1 General Information

General information of instrumentation and characterization of data is described in chapter 3, section 3.5.1.

4.5.2 General procedure for the preparation of starting material



The compound **B** and **C** were prepared according to the literature procedure.[9] To a stirred solution of 2-aminobenzonitrile **D** (4.0 mmol, 1.0 equiv.) in a 50 mL round bottomed flask was added 6.0 mL of 4M conc. HCl at 0 ˚C. After 10 minutes, $NaNO_2$ (0.48 mmol, 1.2 equiv) dissolved in water (1.6 mL) was added to the reaction mixture and the reaction mixture was allowed to stir at least 1 h. Eventually, KI (8.0 mmol, 2.0 equiv) in water (1.6 mL) was added to the reaction mixture and allowed to stir at room temperature for 12 h. After completion of the reaction, the reaction mixture was diluted with saturated $Na_2S_2O_3$, $NaHCO_3$ solutions and brine. The organic layer was extracted by ethyl acetate (2x15 mL) and then evaporated by rotary evaporator and subjected to column chromatography using hexane and ethyl acetate as eluent to afford the product **E**.

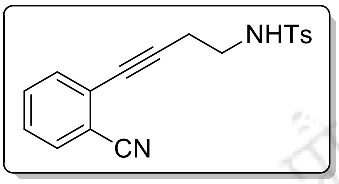
To a stirred suspension of $PdCl_2(PPh_3)_2$ (0.02 mmol, 2 mol%) and CuI (0.5 mmol, 5 mol %) in Et_3N (5.0 mmol, 5.0 equiv) under a nitrogen atmosphere was added to iodo-arene **E** (1.1 mmol, 1.1 equiv). The reaction was stirred for 10 minutes and alkyne **C** (1.0 mmol, 1.0 equiv) was added with 5.0 mL of dry THF to the reaction mixture. The reaction was allowed to stir for 12 h at room temperature. After completion of the reaction, the reaction mixture was filtered, washed with EtOAc and filtrate was taken for the further process. The excess Et_3N and THF were evaporated by rotary evaporator and subjected to column chromatography using hexane and ethyl acetate as eluent to get the corresponding product **1** in quantitative yields.

4.5.3 General procedure for the preparation of 25aa-25ah, 25bc, 25ci, 25cj, 25dc, 26ec, 26ek, 26ej, 27fc and 27ga

To a stirred solution of **23** (0.2 mmol, 1.0 equiv) and aldehyde (0.24 mmol, 1.2 equiv) in acetonitrile (2.0 mL) was added TfOH (1.0 mmol, 5.0 equiv) under nitrogen atmosphere *via* syringe at 0 ˚C temperature. The reaction was stirred at room temperature for 3 h and monitored by TLC (hexane and ethyl acetate as eluent). After completion of the reaction, the reaction mixture was diluted by saturated $NaHCO_3$ solution and brine. The organic layer was extracted by ethyl acetate and evaporated by rotary evaporator. The crude was subjected to column chromatography to afford the corresponding final product with separable *Z/E* up to 87% yields.

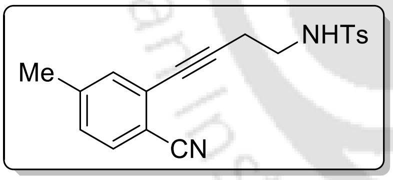
4.5.4 Characterization data

***N*-(4-(2-Cyanophenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (23a)**



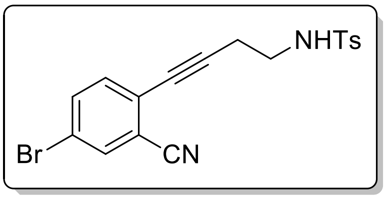
Brown Solid; R_f (hexane/ethyl acetate, 3:2) 0.50; mp 92-94 ºC, yield 272 mg, 84%; IR (KBr, neat) ν 3282, 3066, 2229, 1595, 1325, 1154, 762, 660, 548 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 7.53 (t, *J* = 7.7 Hz, 1 H), 7.46 (d, *J* = 7.8 Hz, 1 H), 7.39 (t, *J* = 7.7 Hz, 1 H), 7.29 (d, *J* = 7.8 Hz, 2 H), 5.21 (q, *J* = 6.1 Hz, 1 H), 3.25 (q, *J* = 6.4 Hz, 2 H), 2.66 (t, *J* = 6.3 Hz, 2 H), 2.41 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 137.4, 132.7, 132.5, 132.2, 130.0, 128.5, 127.5, 127.3, 118.4, 115.8, 93.8, 79.5, 42.0, 21.7, 21.4. HRMS (ESI) calcd. for $C_{18}H_{17}N_2O_2S$ $(M + H)^+$ 325.1005, found 325.1013.

***N*-(4-(2-Cyano-5-methylphenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (23b)**



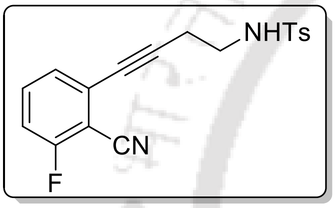
White Solid; R_f (hexane/ethyl acetate, 3:2) 0.50; yield 227 mg, 67%; IR (KBr, neat) ν 3284, 3065, 2918, 2878, 2226, 1594, 1482, 1324, 1155, 1087, 764, 661, 549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2 H), 7.49 (d, *J* = 7.9 Hz, 1 H), 7.29 (d, *J* = 8.3 Hz, 3 H), 7.18 (d, *J* = 7.9 Hz, 1 H), 5.26 (s, 1 H), 3.24 (q, *J* = 6.3 Hz, 2 H), 2.64 (t, *J* = 6.2 Hz, 2 H), 2.40 (s, 3 H), 2.38 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 143.7, 137.4, 132.8, 132.3, 129.9, 129.4, 127.3, 127.2, 118.7, 112.7, 93.1, 79.6, 42.0, 21.8, 21.7, 21.4. HRMS (ESI) calcd. for $C_{19}H_{19}N_2O_2S$ $(M + H)^+$ 339.1162, found 339.1172.

***N*-(4-(4-Bromo-2-cyanophenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (23c)**



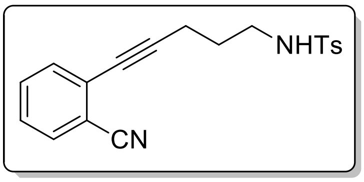
White Solid; R_f (hexane/ethyl acetate, 3:2) 0.50; yield 301 mg, 75%; IR (KBr, neat) ν 3285, 3068, 2920, 2233, 1599, 1479, 1329, 1159, 1089, 817, 662, 549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2 H), 7.74 (d, *J* = 1.8 Hz, 1 H), 7.66 – 7.64 (m, 1 H), 7.31 (dd, *J* = 13.4, 8.4 Hz, 3 H), 5.15 (s, 1 H), 3.24 (q, *J* = 6.4 Hz, 2 H), 2.66 (t, *J* = 6.3 Hz, 2 H), 2.41 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 137.4, 136.1, 135.0, 133.4, 130.0, 127.3, 126.4, 122.1, 117.3, 116.9, 95.2, 78.7, 41.9, 21.8, 21.6. HRMS (ESI) calcd. for $C_{18}H_{16}BrN_2O_2S$ $(M + H)^+$ 403.0110, found 403.0115.

N-(4-(2-Cyano-3-fluorophenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (23d)



Brown Solid; R_f (hexane/ethyl acetate, 3:2) 0.50; mp 95-97 °C, yield 260 mg, 76%; IR (KBr, neat) ν 3285, 2925, 2236, 1604, 1561, 1471, 1326, 1159, 1094, 797, 662, 552 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.2 Hz, 2 H), 7.47–7.41 (m, 1 H), 7.24–7.19 (m, 3 H), 7.07 (t, *J* = 8.6 Hz, 1 H), 5.20 (q, *J* = 7.5 Hz, 1 H), 3.17 (q, *J* = 6.4 Hz, 2 H), 2.60 (t, *J* = 6.4 Hz, 2 H), 2.34 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2 (d, *J* = 133.2 Hz), 143.8, 137.3, 134.5 (d, *J* = 9.3 Hz), 130.03, 129.99, 129.1 (d, *J* = 1.9 Hz), 128.1, 127.3, 127.2, 116.0 (d, J = 19.5 Hz), 113.5, 95.0, 78.6, 41.8, 21.7, 21.4. HRMS (ESI) calcd. for $C_{18}H_{16}FN_2O_2S$ $(M + H)^+$ 343.0911, found 343.0919.

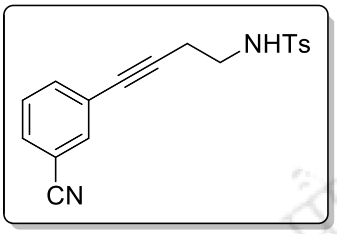
N-(5-(2-Cyanophenyl)pent-4-yn-1-yl)-4-methylbenzenesulfonamide (23e)



White Solid; R_f (hexane/ethyl acetate, 3:2) 0.50; yield 294 mg, 87%; IR (KBr, neat) ν 3283, 3066, 2948, 2878, 2229, 1594, 1482, 1324, 1155, 1088, 765, 663, 547 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2 H), 7.60 (dd, *J* = 7.8, 1.3 Hz, 1 H), 7.51 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.46 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.36 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.29 (d, *J* = 7.9 Hz, 2 H), 4.82 (s, 1 H), 3.17 (t, *J* = 7.0 Hz, 2 H), 2.56 (t, *J* = 6.7 Hz, 2 H), 2.40 (s, 3 H), 1.87–1.80

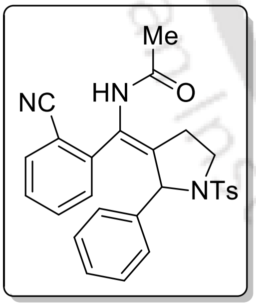
(m, 2 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.6, 137.2, 132.65, 132.59, 132.3, 129.9, 128.1, 127.9, 127.4, 118.2, 115.6, 96.2, 78.5, 42.1, 28.34, 21.7, 16.9. HRMS (ESI) calcd. for $C_{19}H_{19}N_2O_2S$ (M + H)$^+$ 339.1162, found 339.1185.

N-(4-(3-Cyanophenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (23f)



Brown gum; R$_f$ (hexane/ethyl acetate, 3:2) 0.50; yield 275 mg, 85%; IR (KBr, neat) ν 3282, 3066, 2929, 2880, 2228, 1597, 1486, 1326, 1154, 1087, 764, 662, 546 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.77 (d, *J* = 8.2 Hz, 2 H), 7.58 – 7.53 (m, 3 H), 7.40–7.36 (m, 1 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 5.18 (s, 1 H), 3.19 (qd, *J* = 6.5, 1.9 Hz, 2 H), 2.60 (td, *J* = 6.6, 1.8 Hz, 2 H), 2.41 (s, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.9, 137.2, 136.0, 135.2, 131.5, 130.0, 129.4, 127.3, 124.9, 118.3, 112.9, 88.9, 80.7, 41.9, 21.7, 21.1. HRMS (ESI) calcd. for $C_{18}H_{17}N_2O_2S$ (M + H)$^+$ 325.1005, found 325.1029.

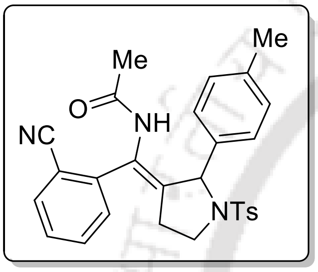
N-((2-Cyanophenyl)(2-phenyl-1-tosylpyrrolidin-3-ylidene)methyl)acetamide (25aa):



Combined yield 80 mg, 85%; (*Z/E*=1.1). For the minor *Z*-3aa: white solid; R$_f$ (hexane/ethyl acetate, 1:1) 0.40; mp 158-160 °C, IR (KBr, neat) ν 3318, 3031, 2225, 1662, 1493, 1339, 1156, 734, 665, 582 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53 (d, *J* = 7.8 Hz, 1 H), 7.48 (d, *J* = 8.0 Hz, 2 H), 7.43 (dd, *J* = 7.7, 1.3 Hz, 1 H), 7.36 (d, *J* = 7.0 Hz, 2 H), 7.29–7.25 (m, 3 H), 7.22 – 7.15 (m, 4 H), 6.61 (s, 1 H), 5.47 (s, 1 H), 3.52–3.41 (m, 2 H), 2.62–2.54 (m, 1 H), 2.33 (s, 3 H), 2.29 – 2.21 (m, 1 H), 1.68 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.2, 143.8, 141.3, 139.2, 137.2, 135.3, 133.1, 132.7, 130.6, 129.9, 129.1, 128.5, 128.2, 127.6, 126.8, 118.1, 111.5, 65.7, 47.4, 29.9, 22.9, 21.7. For the major *E*-3aa: colorless gum; R$_f$ (hexane/ethyl acetate, 1:1) 0.30; IR (KBr, neat) ν 3301, 3031, 2226, 1665, 1494, 1340, 1156, 732, 697 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37 (d, *J* = 8.0 Hz, 3 H), 7.32 (dd, *J* = 7.8, 1.4

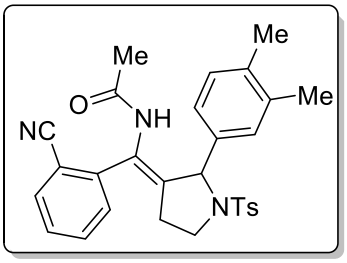
Hz, 1 H), 7.24 – 7.19 (m, 1 H), 7.14 (t, *J* = 5.4 Hz, 3 H), 7.08 (d, *J* = 7.7 Hz, 1 H), 7.03 – 6.99 (m, 1 H), 6.94 (t, *J* = 7.5 Hz, 2 H), 6.67 (d, *J* = 7.2 Hz, 2 H), 5.11 (s, 1 H), 3.64–3.58 (m, 1 H), 3.46 (q, *J* = 9.8 Hz, 1 H), 2.86–2.78 (m, 1 H), 2.69–2.62 (m, 1 H), 2.33 (s, 3 H), 1.86 (s, 3 H), 1.75 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 143.8, 141.0, 140.3, 137.8, 134.9, 132.8, 131.2, 129.7, 128.4, 128.3, 127.62, 127.58, 127.5, 127.0, 117.6, 111.4, 65.1, 47.3, 29.7, 23.1, 21.7. HRMS (ESI) calcd. for $C_{27}H_{25}N_3NaO_3S$ $(M + Na)^+$ 494.1509, found 494.1518.

_N_-((2-Cyanophenyl)(2-(_p_-tolyl)-1-tosylpyrrolidin-3-ylidene)methyl)acetamide (25ac):



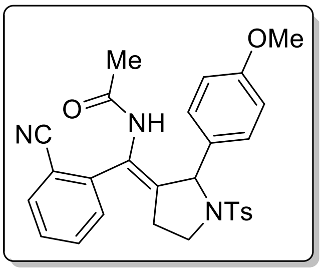
Combined yield 84 mg, 87%; (*Z*/*E*=7:3). For the major *Z*-3ac: yellowish gum; R_f (hexane/ethyl acetate, 1:1) 0.50; IR (KBr, neat) ν 3330, 3055, 2985, 2226, 1669, 1509, 1339, 1264, 1159, 732, 662, 549 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.7 Hz, 1 H), 7.49 (d, *J* = 7.9 Hz, 2 H), 7.43 (t, *J* = 7.7 Hz, 1 H), 7.28–7.22 (m, 3 H), 7.19 (t, *J* = 3.6 Hz, 1 H), 7.16 (d, *J* = 7.9 Hz, 2 H), 7.06 (d, *J* = 7.7 Hz, 2 H), 6.67 (s, 1 H), 5.44 (s, 1 H), 3.48 – 3.41 (m, 2 H), 2.58–2.52 (m, 1 H), 2.33 (s, 3 H), 2.26 (m, 3 H), 2.25–2.20 (m, 1 H), 1.69 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 143.7, 141.3, 138.4, 137.0, 136.0, 135.3, 133.1, 132.7, 130.6, 129.9, 129.8, 128.4, 128.1, 127.7, 126.7, 118.1, 111.4, 65.4, 47.4, 29.8, 22.9, 21.7, 21.4. HRMS (ESI) calcd. for $C_{28}H_{27}N_3NaO_3S$ $(M + Na)^+$ 508.1665, found 508.1679. For the minor *E*-3ac: brown gum; R_f (hexane/ethyl acetate, 1:1) 0.40; IR (KBr, neat) ν 3328, 3023, 2920, 2226, 1666, 1512, 1336, 1157, 1092, 817, 669, 545 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.2 Hz, 2 H), 7.37 – 7.34 (m, 2 H), 7.23 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.08 (d, *J* = 7.7 Hz, 1 H), 7.01 (s, 1 H), 6.77 (d, *J* = 7.8 Hz, 2 H), 6.60 (d, *J* = 7.9 Hz, 2 H), 5.09 (s, 1 H), 3.62–3.57 (m, 1 H), 3.48–3.42 (m, 1 H), 2.85–2.77 (m, 1 H), 2.67–2.60 (m, 1 H), 2.34 (s, 3 H), 2.16 (s, 3 H), 1.89 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 143.8, 141.0, 138.3, 137.4, 137.3, 135.0, 132.8, 132.7, 131.3, 129.8, 129.0, 128.5, 127.6, 127.4, 126.7, 117.7, 111.3, 64.8, 47.2, 29.8, 23.2, 21.8, 21.3.

_N_-((2-Cyanophenyl)(2-(3,4-dimethylphenyl)-1-tosylpyrrolidin-3-ylidene)methyl)acetamide (25ad):



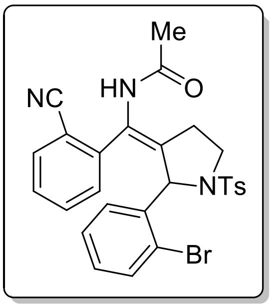
Combined yield 76 mg, 76%; (*Z/E*=3:1). For the major *Z*-3ad: brown gum; R$_f$ (hexane/ethyl acetate, 1:1) 0.50; IR (KBr, neat) ν 3228, 2923, 2226, 1664, 1500, 1337, 1156, 728, 664, 585 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 (d, *J* = 7.6, 1 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 7.42 (td, *J* = 7.8, 1.3 Hz,1 H), 7.26 (t, *J* = 7.6 Hz, 1 H), 7.19–7.14 (m, 3 H), 7.09–7.01 (m, 3 H), 6.59 (s, 1 H), 5.40 (s, 1 H), 3.46 (t, *J* = 7.1 Hz, 2 H), 2.54–2.46 (m, 1 H), 2.34 (s, 3 H), 2.28 – 2.22 (m, 1 H), 2.17 (s, 3 H), 2.14 (s, 3 H), 1.69 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.1, 143.6, 141.3, 137.5, 137.0, 136.9, 136.2, 135.5, 133.1, 132.7, 130.7, 130.3, 129.8, 129.2, 128.4, 127.7, 126.6, 125.6, 118.1, 111.4, 65.5, 47.4, 29.8, 22.97, 21.7, 19.8, 19.7. HRMS (ESI) calcd. for $C_{29}H_{29}N_3NaO_3S$ (M + Na)$^+$ 522.1822, found 522.1822. For the minor *E*-3ad: colourless solid; R$_f$ (hexane/ethyl acetate, 1:1) 0.40; IR (KBr, neat) ν 3298, 2924, 2227, 1665, 1503, 1339, 1156, 729, 585 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47 – 7.44 (m, 3 H), 7.41 (t, *J* = 4.9 Hz, 1 H), 7.30 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.16 (d, *J* = 7.8 Hz, 1 H), 6.97 (s, 1 H), 6.79 (d, *J* = 7.7 Hz, 1 H), 6.52 (dd, *J* = 7.8, 2.0 Hz, 1 H), 6.43 (s, 1 H), 5.13 (s, 1 H), 3.71 – 3.66 (m, 1 H), 3.57 – 3.50 (m, 1 H), 2.90 – 2.82 (m, 1 H), 2.74–2.66 (m, 1 H), 2.41 (s, 3 H), 2.13 (s, 3 H), 2.02 (s, 3 H), 1.96 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.5, 143.7, 141.0, 138.3, 137.5, 136.3, 135.9, 135.0, 133.0, 132.7, 131.4, 129.7, 129.5, 128.7, 128.4, 127.7, 126.6, 124.9, 117.7, 111.4, 64.9, 47.2, 29.6, 23.2, 21.7, 19.7, 19.6.

_N_-((2-Cyanophenyl)(2-(4-methoxyphenyl)-1-tosylpyrrolidin-3-ylidene)methyl)acetamide (25ae):



Combined yield 54 mg, 54%; (*Z*/*E*=3.5:1). For the major *Z*-3ae: brown gum; R_f (hexane/ethyl acetate, 1:1) 0.50; IR (KBr, neat) ν 3323, 2923, 2845, 2226, 1664, 1509, 1247, 1157, 729, 664, 544 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.7 Hz, 1 H), 7.49 – 7.42 (m, 3 H), 7.30–7.26 (m, 3 H), 7.21 – 7.16 (m, 3 H), 6.79 (d, *J* = 8.3 Hz, 2 H), 6.56 (s, 1 H), 5.42 (s, 1 H), 3.73 (s, 3 H), 3.47–3.42 (m, 2 H), 2.58–2.50 (m, 1 H), 2.34 (s, 3 H), 2.29 – 2.23 (m, 1 H), 1.71 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 159.8, 143.7, 141.4, 137.2, 135.4, 133.1, 132.8, 131.0, 130.7, 129.9, 129.5, 128.5, 127.7, 126.7, 118.2, 114.5, 111.5, 65.2, 55.5, 47.3, 29.9, 23.0, 21.7. HRMS (ESI) calcd. for $C_{28}H_{27}N_3NaO_4S$ $(M + Na)^+$ 524.1614, found 524.1626. For the minor *E*-3ae: brown gum; R_f (hexane/ethyl acetate, 1:1) 0.40; IR (KBr, neat) ν 3330, 3055, 2923, 2848, 2231, 1674, 1599, 1509, 1247, 1157, 1029, 729, 552 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, *J* = 8.3 Hz, 4 H), 7.30 (t, *J* = 7.4 Hz, 1 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.15 (d, *J* = 7.7 Hz, 1 H), 6.92 (s, 1 H), 6.73 (d, *J* = 8.6 Hz, 2 H), 6.57 (d, *J* = 8.7 Hz, 2 H), 5.17 (s, 1 H), 3.72 (s, 3 H), 3.69 – 3.63 (m, 1 H), 3.57 – 3.51 (m, 1 H), 2.93–2.85 (m, 1 H), 2.75–2.68 (m, 1 H), 2.40 (s, 3 H), 1.98 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 159.1, 143.7, 141.0, 138.8, 135.2, 132.83, 132.77, 132.5, 131.3, 129.8, 128.9, 128.5, 127.6, 126.6, 117.8, 113.8, 111.3, 64.6, 55.5, 47.1, 29.9, 23.3, 21.8.

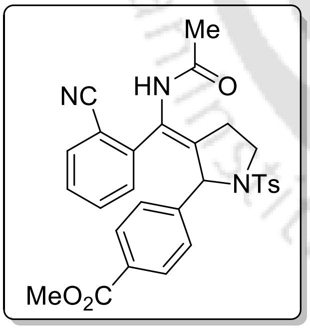
N-((2-(2-Bromophenyl)-1-tosylpyrrolidin-3-ylidene)(2-cyanophenyl)methyl)acetamide (25af):



Combined yield 73 mg, 66%; (*Z*/*E*=1:8). For the minor *Z*-3af: brown gum; R_f (hexane/ethyl acetate, 1:1) 0.50; IR (KBr, neat) ν 3295, 3063, 2925, 2226, 1726, 1471, 1346, 1157, 1092, 657, 549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.1 Hz, 2 H), 7.59 (d, *J* = 7.7 Hz, 1 H), 7.54 – 7.50 (m, 2 H), 7.44 (dd, *J* = 7.9, 1.7 Hz, 1 H), 7.37 (d, *J* = 7.6 Hz, 1 H), 7.34 – 7.28 (m, 3 H), 7.17 – 7.12 (m, 1 H), 6.71 (s, 1 H), 5.62 (s, 1 H), 3.87–3.82

(m, 1 H), 3.27–3.21 (m, 1 H), 3.04–2.96 (m, 1 H), 2.42 (s, 3 H), 2.41 – 2.35 (m, 2 H), 1.84 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.1, 144.1, 141.1, 139.5, 136.8, 133.7, 133.3, 132.7, 132.5, 131.0, 130.4, 130.0, 129.9, 129.0, 128.5, 128.3, 127.7, 123.8, 118.1, 111.6, 63.9, 48.6, 30.2, 23.0, 21.8. For the major *E*-3af: brown gum; R$_f$ (hexane/ethyl acetate, 1:1) 0.40; IR (KBr, neat) ν 3335, 3060, 2850, 2228, 1671, 1511, 1346, 1266, 1159, 1092, 732, 582, 547 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 (d, *J* = 7.9 Hz, 2 H), 7.37 – 7.31 (m, 2 H), 7.24 (d, *J* = 7.7 Hz, 1 H), 7.19 (d, *J* = 8.1 Hz, 2 H), 7.11 – 7.02 (m, 3 H), 7.00 (s, 2 H), 6.89–6.85 (m, 1 H), 5.51 (s, 1 H), 3.87–3.82 (m, 1 H), 3.48 (q, *J* = 8.7 Hz, 1 H), 3.11–3.03 (m, 1 H), 2.78–2.71 (m, 1 H), 2.38 (s, 3 H), 1.91 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.3, 143.8, 140.5, 139.6, 139.2, 134.3, 132.9, 132.7, 131.4, 129.6, 128.9, 128.4, 127.9, 127.8, 127.2, 123.8, 117.6, 111.5, 64.0, 48.0, 30.5, 23.3, 21.7. HRMS (ESI) calcd. for $C_{27}H_{24}BrN_3NaO_3S$ $(M + Na)^+$ 572.0614, found 572.0601.

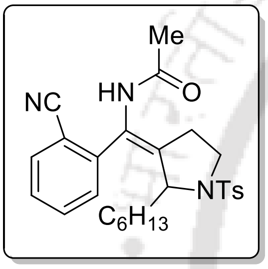
Methyl 4-(3-(acetamido(2-cyanophenyl)methylene)-1-tosylpyrrolidin-2-yl)benzoate (25ag):



Combined yield 92 mg, 87%; (*Z*/*E*=1:2.3). For the minor *Z*-3ag: Orange gum; R$_f$ (hexane/ethyl acetate, 1:1) 0.50; IR (KBr, neat) ν 3328, 3000, 2918, 2853, 2226, 1719, 1434, 1281, 1159, 732, 662, 552 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 (d, *J* = 7.9 Hz, 2 H), 7.58–7.53 (m, 3 H), 7.51–7.46 (m, 3 H), 7.33 (t, *J* = 7.6 Hz, 1 H), 7.22 (t, *J* = 6.3 Hz, 3 H), 6.61 (s, 1 H), 5.52 (s, 1 H), 3.87 (s, 3 H), 3.61 – 3.55 (m, 1 H), 3.46–3.39 (m, 1 H), 2.78–2.69 (m, 1 H), 2.37 (s, 3 H), 2.31–2.23 (m, 1 H), 1.75 (s, 3 H). ^{13}C NMR (150 MHz, CDCl$_3$) δ 168.1, 166.9, 144.6, 144.1, 141.2, 138.1, 134.9, 133.2, 132.9, 130.6, 130.2, 130.1, 130.0, 128.8, 128.3, 127.8, 126.7, 118.1, 111.6, 65.3, 52.4, 47.7, 30.1, 23.0, 21.7.For the major *E*-3ag: orange gum; R$_f$ (hexane/ethyl acetate, 1:1) 0.40; IR (KBr, neat) ν 3325, 3053, 2955, 2226, 1719, 1434, 1264, 1159, 1097, 729, 702, 547 cm^{-1}; ^{1}H NMR (400

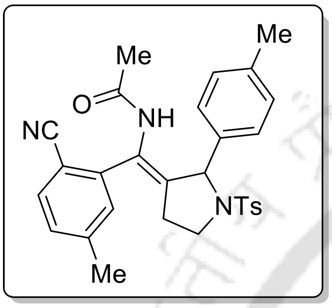
MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.2 Hz, 2 H), 7.48 – 7.40 (m, 4 H), 7.32 (t, *J* = 7.6 Hz, 1 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.14 (d, *J* = 7.8 Hz, 1 H), 7.04 (s, 1 H), 6.79 (d, *J* = 8.3 Hz, 2 H), 5.20 (s, 1 H), 3.88 (s, 3 H), 3.77–3.72 (m, 1 H), 3.51 (q, *J* = 8.2 Hz, 1 H), 2.97–2.88 (m, 1 H), 2.79–2.72 (m, 1 H), 2.40 (s, 3 H), 1.95 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 166.9, 145.5, 144.2, 140.7, 137.6, 134.6, 132.9, 131.1, 129.9, 129.6, 129.4, 128.8, 127.7, 127.5, 127.3, 117.4, 111.5, 64.7, 52.3, 47.6, 29.9, 23.3, 21.8. HRMS (ESI) calcd. for $C_{29}H_{27}N_3NaO_5S$ $(M + Na)^+$ 552.1564, found 552.1581.

N-((2-Cyanophenyl)(2-hexyl-1-tosylpyrrolidin-3-ylidene)methyl)acetamide (25ah):



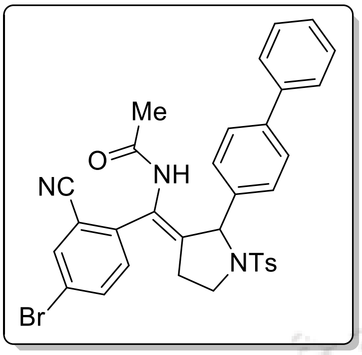
Combined yield 62 mg, 65%; (*Z/E*=1:2). For the minor *Z*-3ah: yellowish gum; R_f (hexane/ethyl acetate, 1:1) 0.50; IR (KBr, neat) ν 3307, 2925, 2855, 2226, 1660, 1502, 1443, 1156, 667, 547 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2 H), 7.59 (dd, *J* = 7.8, 1.3 Hz, 1 H), 7.49 (td, *J* = 7.7, 1.4 Hz, 1 H), 7.35–7.30 (m, 3 H), 7.24 (s, 1 H), 7.16 (s, 1 H), 4.77 (t, *J* = 6.2 Hz, 1 H), 3.50–3.44 (m, 1 H), 3.37–3.31 (m, 1 H), 2.54 – 2.45 (m, 1 H), 2.43 (s, 3 H), 2.04 (s, 3 H), 1.90 – 1.83 (m, 1 H), 1.79 – 1.68 (m, 2 H), 1.48 (t, *J* = 7.6 Hz, 2 H), 1.30–1.25 (m, 6 H), 0.88 (d, *J* = 6.4 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 144.1, 141.9, 138.8, 135.5, 133.1, 132.7, 130.7, 130.2, 128.4, 127.7, 125.2, 118.3, 111.4, 62.8, 46.9, 34.4, 32.0, 29.4, 29.1, 25.4, 23.1, 22.9, 21.8, 14.3. ^{19}F NMR (471 MHz, $CDCl_3$) δ -105.8. For the major *E*-3ah: yellowish gum; R_f (hexane/ethyl acetate, 1:1) 0.40; IR (KBr, neat) ν 3290, 2926, 2857, 2226, 1665, 1515, 1339, 1157, 734, 663, 547 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2 H), 7.63 (dd, *J* = 7.7, 1.4 Hz, 1 H), 7.55 (td, *J* = 7.7, 1.4 Hz, 1 H), 7.40 (td, *J* = 7.7, 1.2 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 8.1 Hz, 1 H), 7.08 (s, 1 H), 4.34 (t, *J* = 5.6 Hz, 1 H), 3.60–3.54 (m, 1 H), 3.39–3.32 (m, 1 H), 2.64–2.55 (m, 1 H), 2.45 (s, 3 H), 2.44 – 2.340 (m, 1 H), 1.96 (s, 3 H), 1.47–1.42 (m, 1 H), 1.20–1.15 (m, 4 H), 1.10 – 1.05 (m, 4 H), 1.00-0.95 (m, 1 H), 0.81 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 144.1, 141.2, 137.1, 134.8, 133.1, 133.0, 131.1, 130.0, 128.7, 127.8, 125.2, 117.8, 111.6, 61.5, 47.3, 35.2, 31.7, 29.4, 29.0, 24.5, 23.1, 22.7, 21.8, 14.2. HRMS (ESI) calcd. for $C_{27}H_{34}N_3O_3S$ $(M + H)^+$ 480.2315, found 480.2332.

N-((2-Cyano-5-methylphenyl)(2-(p-tolyl)-1-tosylpyrrolidin-3-ylidene)methyl)acetamide (25bc):



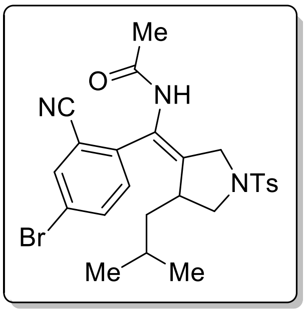
Combined yield 82 mg, 82%; (*Z/E*=2.4:1). For the major *Z*-3bc: Orange solid; R_f (hexane/ethyl acetate, 1:1) 0.50; mp 99-101 °C, IR (KBr, neat) ν 3343, 3050, 2855, 2223, 1666, 1491, 1339, 1264, 1154, 817, 729, 664, 545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2 H), 7.47 (d, *J* = 7.9 Hz, 1 H), 7.30 (d, *J* = 7.8 Hz, 2 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 7.13 (d, *J* = 7.7 Hz, 3 H), 7.04 (s, 1 H), 6.68 (s, 1 H), 5.50 (s, 1 H), 3.54 – 3.48 (m, 2 H), 2.65–2.57 (m, 1 H), 2.41 (s, 3 H), 2.34 (d, *J* = 6.4 Hz, 6 H), 2.29–2.23 (m, 2 H), 1.77 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 143.70, 143.68, 141.2, 138.3, 137.2, 136.1, 135.3, 133.0, 131.2, 129.9, 129.7, 129.3, 128.1, 127.7, 126.7, 118.4, 108.4, 65.5, 47.4, 29.9, 23.0, 22.0, 21.72, 21.4. HRMS (ESI) calcd. for $C_{29}H_{29}N_3NaO_3S$ $(M + Na)^+$ 522.1822, found 522.1826. For the minor *E*-3bc: brown gum; R_f (hexane/ethyl acetate, 1:1) 0.40; IR (KBr, neat) ν 3320, 3048, 2923, 2226, 1666, 1509, 1339, 1264, 1157, 729, 667, 542 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 7.9 Hz, 1 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.08 (t, *J* = 7.9 Hz, 2 H), 6.84 (t, *J* = 7.8 Hz, 3 H), 6.68 (d, *J* = 7.7 Hz, 2 H), 5.12 (s, 1 H), 3.69 – 3.63 (m, 1 H), 3.54 – 3.47 (m, 1 H), 2.91–2.83 (m, 1 H), 2.72–2.64 (m, 1 H), 2.40 (s, 3 H), 2.24 (d, *J* = 2.7 Hz, 6 H), 1.94 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 143.8, 143.7, 140.8, 138.2, 137.7, 137.3, 134.96, 132.6, 132.0, 129.8, 129.2, 129.0, 127.6, 127.5, 126.7, 118.1, 108.2, 65.0, 47.2, 29.8, 23.2, 21.9, 21.7, 21.2.

N-((2-([1,1'-Biphenyl]-4-yl)-1-tosylpyrrolidin-3-ylidene)(4-bromo-2-cyanophenyl)-methyl)acetamide (25ci):



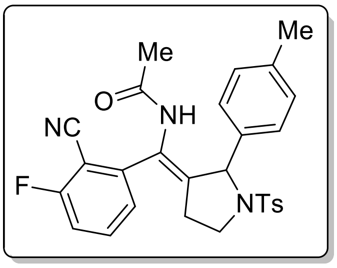
Combined yield 93 mg, 74%; (*Z/E*=2:1). For the major *Z*-3ci: colourless gum; R$_f$ (hexane/ethyl acetate, 1:1) 0.50; IR (KBr, neat) ν 3295, 3064, 2924, 2226, 1728, 1613, 1506, 1471, 1348, 1158, 1092, 654, 549 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.72 (d, *J* = 2.1 Hz, 1 H), 7.62 (dd, *J* = 8.4, 2.1 Hz, 1 H), 7.55 (t, *J* = 7.6 Hz, 6 H), 7.45 (dd, *J* = 14.2, 7.3 Hz, 4 H), 7.36 (t, *J* = 7.2 Hz, 1 H), 7.18 (dd, *J* = 16.3, 8.0 Hz, 3 H), 6.92 (s, 1 H), 5.65 (s, 1 H), 3.60–3.56 (m, 2 H), 2.72–2.64 (m, 1 H), 2.37 (s, 3 H), 2.30 (dd, *J* = 16.6, 8.1 Hz, 1 H), 1.78 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.5, 143.9, 141.4, 140.5, 140.2, 137.7, 137.3, 136.1, 135.6, 135.3, 132.0, 129.9, 129.0, 128.6, 127.8, 127.7, 127.6, 127.2, 126.1, 122.1, 116.8, 113.3, 65.3, 47.4, 29.9, 22.9, 21.7. HRMS (ESI) calcd. for $C_{33}H_{28}BrN_3NaO_3S$ (M + Na)$^+$ 648.0927, found 648.0943. For the minor *E*-3ci: colorless gum; R$_f$ (hexane/ethyl acetate, 1:1) 0.40; IR (KBr, neat) ν 3294, 3065, 2922, 2227, 1726, 1614, 1504, 1472, 1348, 1159, 1092, 655, 548 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 – 7.50 (m, 2 H), 7.48 – 7.41 (m, 6 H), 7.35 (t, *J* = 7.2 Hz, 1 H), 7.25 (d, *J* = 5.7 Hz, 2 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 7.10 (s, 1 H), 7.03 (d, *J* = 8.3 Hz, 1 H), 6.82 (d, *J* = 7.9 Hz, 2 H), 5.15 (s, 1 H), 3.74–3.69 (m, 1 H), 3.60–3.53 (m, 1 H), 2.96–2.87 (m, 1 H), 2.79–2.72 (m, 1 H), 2.37 (s, 3 H), 1.95 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.7, 143.9, 140.7, 139.9, 139.0, 138.7, 135.9, 135.1, 134.8, 132.7, 129.8, 129.0, 128.2, 127.6, 127.2, 127.1, 126.3, 122.1, 116.3, 113.1, 64.8, 47.4, 29.9, 23.2, 21.7.

N-((4-Bromo-2-cyanophenyl)(2-isobutyl-1-tosylpyrrolidin-3-ylidene)methyl)acetamide (25cj):



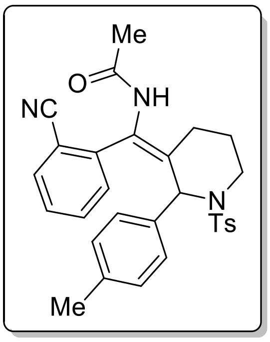
Combined yield 81 mg, 76%; (*Z/E*=1:2.2). For the minor ***Z*-3cj**: yellow gum; R_f (hexane/ethyl acetate, 1:1) 0.50; IR (KBr, neat) ν 3328, 2955, 2923, 2853, 2231, 1661, 1499, 1336, 1157, 1089, 817, 732, 667, 549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 2.0 Hz, 1 H), 7.69 (t, *J* = 8.3 Hz, 3 H), 7.35 (d, *J* = 7.9 Hz, 2 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 4.36 (dd, *J* = 8.8, 4.9 Hz, 1 H), 3.58 – 3.49 (m, 2 H), 2.60–2.52 (m, 1 H), 2.45 (s, 3 H), 2.38 – 2.27 (m, 1 H), 1.95 (s, 3 H), 1.61–1.55 (m, 1 H), 1.40–1.32 (m, 1 H), 1.00–0.93 (m, 1 H), 0.60 (d, *J* = 6.5 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 144.2, 140.8, 140.5, 136.0, 135.7, 135.5, 132.1, 130.3, 127.7, 123.9, 121.9, 116.8, 113.1, 61.5, 46.2, 43.2, 28.6, 24.8, 23.5, 23.0, 22.0, 21.8. For the major *E*-3cj: orange gum; R_f (hexane/ethyl acetate, 1:1) 0.40; IR (KBr, neat) ν 3338, 2955, 2918, 2231, 1664, 1516, 1336, 1157, 1094, 734, 662, 549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.9 Hz, 2 H), 7.70 (d, *J* = 2.1 Hz, 1 H), 7.58 (dd, *J* = 8.4, 2.1 Hz, 1 H), 7.34 (d, *J* = 7.9 Hz, 2 H), 7.27 (s, 1 H), 7.06 (d, *J* = 8.4 Hz, 1 H), 4.85 (dd, *J* = 9.8, 4.2 Hz, 1 H), 3.54–3.48 (m, 1 H), 3.46 – 3.39 (m, 1 H), 2.43 (s, 3 H), 2.38–2.35 (m, 1 H), 2.04 (s, 3 H), 1.95–1.88 (m, 1 H), 1.74 – 1.66 (m, 1 H), 1.63 – 1.56 (m, 1 H), 1.38 – 1.31 (m, 1 H), 1.04 (d, *J* = 6.5 Hz, 3 H), 0.97 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 144.3, 140.1, 137.5, 136.2, 135.6, 135.4, 132.8, 130.2, 127.7, 124.4, 122.1, 116.6, 113.2, 60.1, 46.4, 44.6, 29.0, 24.4, 23.1, 23.0, 21.8. HRMS (ESI) calcd. for $C_{25}H_{29}BrN_3NaO_3S$ $(M + Na)^+$ 553.1005, found 553.0981.

***N*-((2-Cyano-3-fluorophenyl)(2-(*p*-tolyl)-1-tosylpyrrolidin-3-ylidene)methyl)acetamide (25dc):**



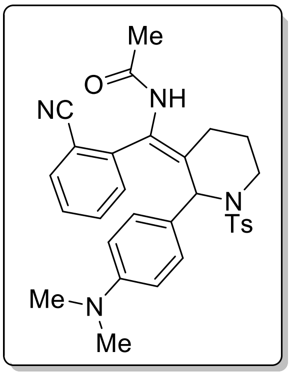
Combined yield 80 mg, 79%; (*Z*/*E*=2:1). For the major *Z*-3dc: yellowish gum; R_f (hexane/ethyl acetate, 1:1) 0.50; IR (KBr, neat) ν 3335, 3053, 2915, 2850, 2233, 1666, 1514, 1334, 1159, 1092, 809, 734, 662, 582 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 (d, J = 7.9 Hz, 2 H), 7.53–7.46 (m, 1 H), 7.30 (d, J = 7.8 Hz, 2 H), 7.25 (d, J = 8.0 Hz, 2 H), 7.15 (d, J = 7.7 Hz, 2 H), 7.12–7.07 (m, 2 H), 6.86 (s, 1 H), 5.55 (s, 1 H), 3.58–3.51 (m, 2 H), 2.70 – 2.62 (m, 1 H), 2.42 (s, 3 H), 2.37–2.32 (m, 4 H), 1.79 (s, 3 H). ^{13}C NMR (150 MHz, CDCl$_3$) δ 168.4, 164.6, 162.8, 143.5 (d, J = 100.6 Hz), 138.5, 137.3, 135.8, 135.3, 134.4 (d, J = 8.8 Hz), 129.9, 129.8, 128.0, 127.6, 126.2 (d, J = 3.2 Hz), 125.90, 115.5 (d, J = 19.6 Hz), 113.1, 100.8 (d, J = 15.4 Hz), 65.4, 47.3, 29.8, 22.8, 21.7, 21.3. ^{19}F NMR (471 MHz, CDCl$_3$) δ -105.8. HRMS (ESI) calcd. for $C_{28}H_{27}FN_3NaO_3S$ $(M + Na)^+$ 527.1649, found 527.1633. For the minor *E*-3dc: orange gum; R_f (hexane/ethyl acetate, 1:1) 0.40; IR (KBr, neat) ν 3318, 2920, 2855, 2236, 1671, 1509, 1329, 1254, 1154, 1092, 807, 732, 662, 545 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45–7.39 (m, 3 H), 7.19 (d, J = 6.8 Hz, 3 H), 7.05 – 6.98 (m, 2 H), 6.85 (d, J = 7.6 Hz, 2 H), 6.67 (d, J = 7.7 Hz, 2 H), 5.13 (s, 1 H), 3.69–3.63 (m, 1 H), 3.52 (q, J = 7.8 Hz, 1 H), 2.91–2.83 (m, 1 H), 2.75–2.68 (m, 1 H), 2.40 (s, 3 H), 2.24 (s, 3 H), 1.95 (s, 3 H). ^{13}C NMR (150 MHz, CDCl$_3$) δ 168.7, 164.4, 162.7, 143.9, 142.8, 138.7, 137.3 (d, J = 79.8 Hz), 134.9, 134.4 (d, J = 8.8 Hz), 129.7, 129.1, 127.6, 127.4, 126.9 (d, J = 3.1 Hz), 125.9 (d, J = 2.1 Hz), 115.5 (d, J = 19.5 Hz), 112.8, 100.5 (d, J = 15.1 Hz), 64.8, 47.1, 29.8, 23.1, 21.7, 21.2. ^{19}F NMR (471 MHz, CDCl$_3$) δ -106.3.

***N*-((2-Cyanophenyl)(2-(*p*-tolyl)-1-tosylpiperidin-3-ylidene)methyl)acetamide (26ec):**



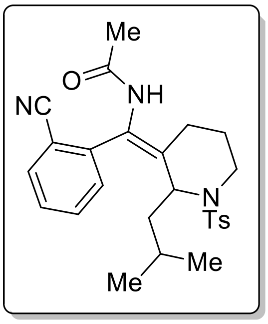
Combined yield 70 mg, 70%; (*Z*/*E*=1:3). For the minor *Z*-4ec: colorless gum; R_f (hexane/ethyl acetate, 1:1) 0.50; IR (KBr, neat) ν 3325, 2923, 2848, 2228, 1684, 1496, 1324, 1154, 949, 734, 654, 547 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.9 Hz, 2 H), 7.67 (d, *J* = 7.7 Hz, 1 H), 7.54 (t, *J* = 7.7 Hz, 1 H), 7.45 (s, 1 H), 7.39 (t, *J* = 7.7 Hz, 3 H), 7.34 (d, *J* = 7.8 Hz, 2 H), 7.23 (d, *J* = 7.9 Hz, 2 H), 6.28 (s, 1 H), 3.78 (d, *J* = 14.6 Hz, 1 H), 3.10–3.04 (m, 1 H), 2.47 (s, 3 H), 2.35 (s, 3 H), 2.08–1.97 (m, 5 H), 1.91 – 1.82 (m, 1 H), 1.31 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 143.8, 141.3, 138.3, 137.8, 133.3, 133.1, 132.4, 131.6, 130.3, 130.2, 129.4, 128.4, 127.5, 126.9, 118.6, 112.2, 56.9, 41.5, 29.9, 26.6, 25.0, 23.3, 21.8, 21.2. For the major *E*-4ec: yellowish gum; R_f (hexane/ethyl acetate, 1:1) 0.40; IR (KBr, neat) ν 3263, 3030, 2923, 2855, 2226, 1666, 1512, 1319, 1157, 954, 767, 659, 542 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.6 Hz, 1 H), 7.57 – 7.51 (m, 3 H), 7.47 (t, *J* = 7.5 Hz, 1 H), 7.41 – 7.34 (m, 4 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.19 (d, *J* = 7.8 Hz, 2 H), 5.70 (s, 1 H), 3.69–3.63 (m, 1 H), 3.03–2.96 (m, 1 H), 2.71–2.66 (m, 1 H), 2.42 (s, 3 H), 2.34 (s, 3 H), 2.23–2.15 (m, 1 H), 2.10 (s, 3 H), 1.86–1.73 (s, 1 H), 1.53 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 143.6, 140.9, 137.8, 137.6, 134.5, 133.6, 133.0, 130.1, 129.9, 128.7, 128.4, 127.6, 127.3, 118.8, 111.2, 57.8, 41.2, 25.5, 24.5, 23.2, 21.8, 21.2. HRMS (ESI) calcd. for $C_{29}H_{30}N_3O_3S$ $(M + H)^+$ 500.2002, found 500.2022.

N-((2-Cyanophenyl)(2-(4-(dimethylamino)phenyl)-1-tosylpiperidin-3-ylidene)methyl)-acetamide (26ek):



Combined yield 85 mg, 80%; (*Z/E*=1:7). For the minor *Z*-4ek: yellowish gum; R_f (hexane/ethyl acetate, 1:1) 0.50; IR (KBr, neat) ν 3317, 2923, 2852, 2796, 2225, 1684, 1613, 1522, 1324, 1156, 948, 760, 656, 572 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2 Hz, 2 H), 7.67 (dd, *J* = 7.7, 1.4 Hz, 1 H), 7.55 – 7.51 (m, 1 H), 7.40 – 7.36 (m, 4 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 6.77 (d, *J* = 8.8 Hz, 2 H), 6.23 (s, 1 H), 3.77 (d, *J* = 14.5 Hz, 1 H), 3.13 – 3.05 (m, 1 H), 2.95 (s, 6 H), 2.47 (s, 3 H), 2.04 (s, 5 H), 1.66 (s, 1 H), 1.33 – 1.26 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 150.4, 143.6, 141.4, 133.0, 132.3, 131.7, 130.3, 129.1, 128.3, 127.9, 127.5, 123.2, 118.7, 113.3, 112.1, 56.8, 41.3, 40.8, 29.9, 25.4, 24.9, 23.3, 21.8. For the major *E*-4ek: yellowish gum; R_f (hexane/ethyl acetate, 1:1) 0.40; IR (KBr, neat) ν 3261, 2923, 2857, 2801, 2225, 1666, 1613, 1517, 1319, 1154, 953, 811, 770, 539 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.6 Hz, 1 H), 7.54 (d, *J* = 8.7 Hz, 3 H), 7.47 (t, *J* = 7.4 Hz, 1 H), 7.38 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.33–7.27 (m, 4 H), 7.21 (s, 1 H), 6.74 (d, *J* = 8.4 Hz, 2 H), 5.66 (s, 1 H), 3.66 (d, *J* = 13.6 Hz, 1 H), 3.07–3.00 (m, 1 H), 2.95 (s, 6 H), 2.67–2.64 (m, 1 H), 2.43 (s, 3 H), 2.27–2.20 (m, 1 H), 2.09 (s, 3 H), 1.55 – 1.45 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 150.1, 143.5, 141.0, 138.1, 133.6, 133.1, 130.1, 128.7, 128.0, 127.3, 124.6, 119.0, 113.0, 111.2, 57.6, 41.0, 40.7, 25.5, 24.6, 23.2, 21.8. HRMS (ESI) calcd. for $C_{30}H_{32}N_4NaO_3S$ $(M + Na)^+$ 551.2088, found 551.2083.

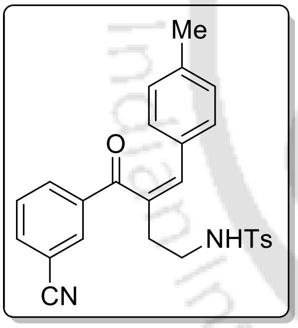
N-((2-Cyanophenyl)(2-isobutyl-1-tosylpiperidin-3-ylidene)methyl)acetamide (26ej):



Combined yield 74 mg, 79%; (*E/Z*=1:3.4). For the minor *Z*-4ej: white solid; R_f (hexane/ethyl acetate, 1:1) 0.50; mp 114-116 °C, IR (KBr, neat) ν 3215, 3155, 2925, 2853, 2228, 1634, 1516, 1329, 1149, 717, 659, 545 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.9 Hz, 2 H), 7.63 (d, *J* = 7.6 Hz, 1 H), 7.54 – 7.50 (m, 2 H), 7.37–7.30 (m, 4 H), 5.09 (t, *J* = 7.5 Hz, 1 H), 3.73 (d, *J* = 14.2 Hz, 1 H), 3.24–3.16 (m, 1 H), 2.44 (s, 3 H), 2.34 –

2.26 (m, 1 H), 2.06 (s, 4 H), 1.70 – 1.61 (m, 2 H), 1.54 – 1.46 (m, 2 H), 1.33 – 1.28 (m, 1 H), 0.92 (dd, *J* = 14.7, 6.2 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 143.7, 141.4, 138.2, 132.9, 132.4, 130.1, 128.2, 127.4, 126.4, 118.4, 52.4, 40.4, 39.8, 29.9, 26.0, 24.5, 24.4, 23.1, 22.9, 22.5, 21.8. For the major *E*-4ej: yellowish gum; R_f (hexane/ethyl acetate, 1:1) 0.40; IR (KBr, neat) ν 3325, 3058, 2958, 2228, 1676, 1491, 1264, 1149, 1087, 732, 577 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 5 H), 7.44 (t, *J* = 8.4 Hz, 1 H), 7.29–7.26 (m, 3 H), 4.62 (t, *J* = 6.8 Hz, 1 H), 3.70 – 3.64 (m, 1 H), 3.15 (td, *J* = 13.2, 3.0 Hz, 1 H), 2.68–2.63 (m, 1 H), 2.42 (s, 3 H), 2.28 – 2.20 (m, 1 H), 2.04 (s, 3 H), 1.72 – 1.69 (m, 1 H), 1.58 (s, 1 H), 1.42 (s, 1 H), 1.36–1.29 (m, 2 H), 0.58 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 143.4, 141.2, 137.9, 133.2, 132.8, 129.8, 128.6, 127.5, 118.4, 111.6, 53.2, 40.1, 25.3, 24.3, 23.6, 23.2, 22.1, 21.7. HRMS (ESI) calcd. for $C_{26}H_{32}N_3O_3S$ $(M + H)^+$ 466.2159, found 466.2172.

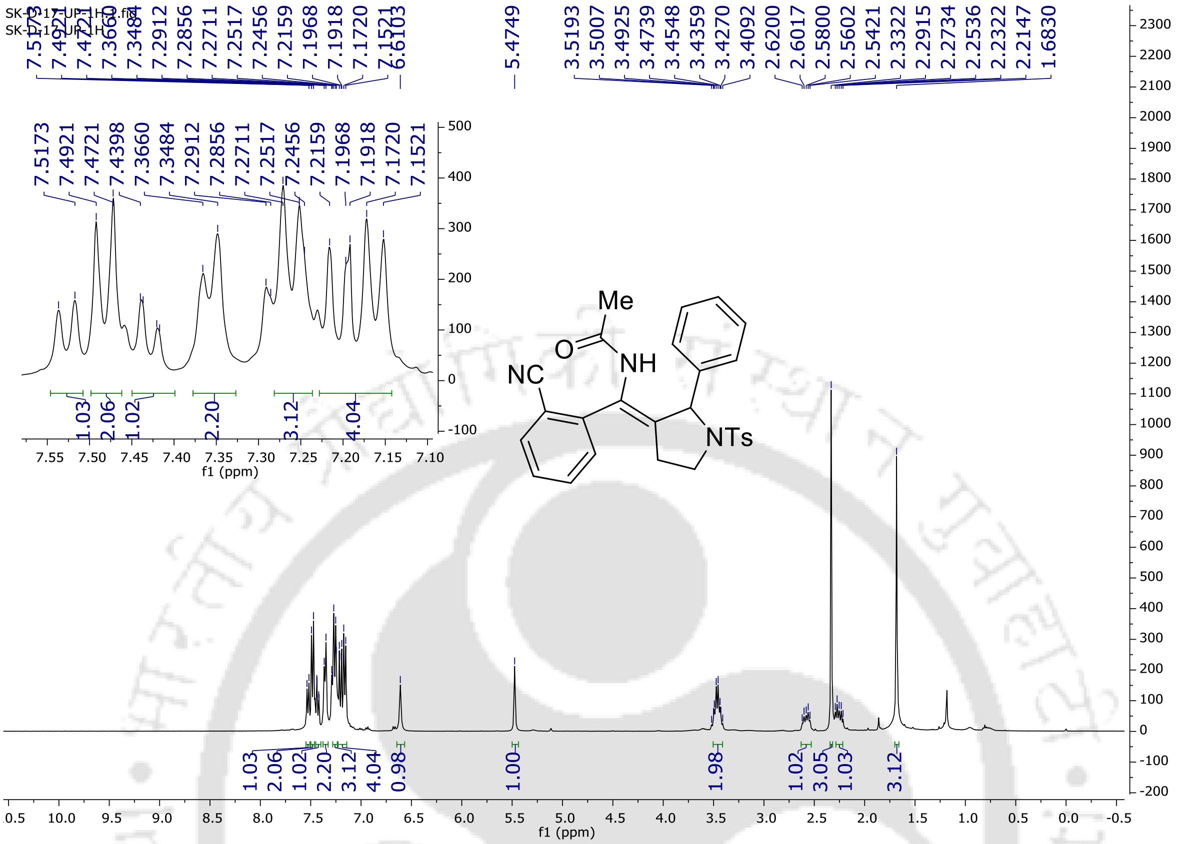
(*Z*)-*N*-(3-(3-cyanobenzoyl)-4-(*p*-tolyl)but-3-en-1-yl)-4-methylbenzenesulfonamide (27fc)

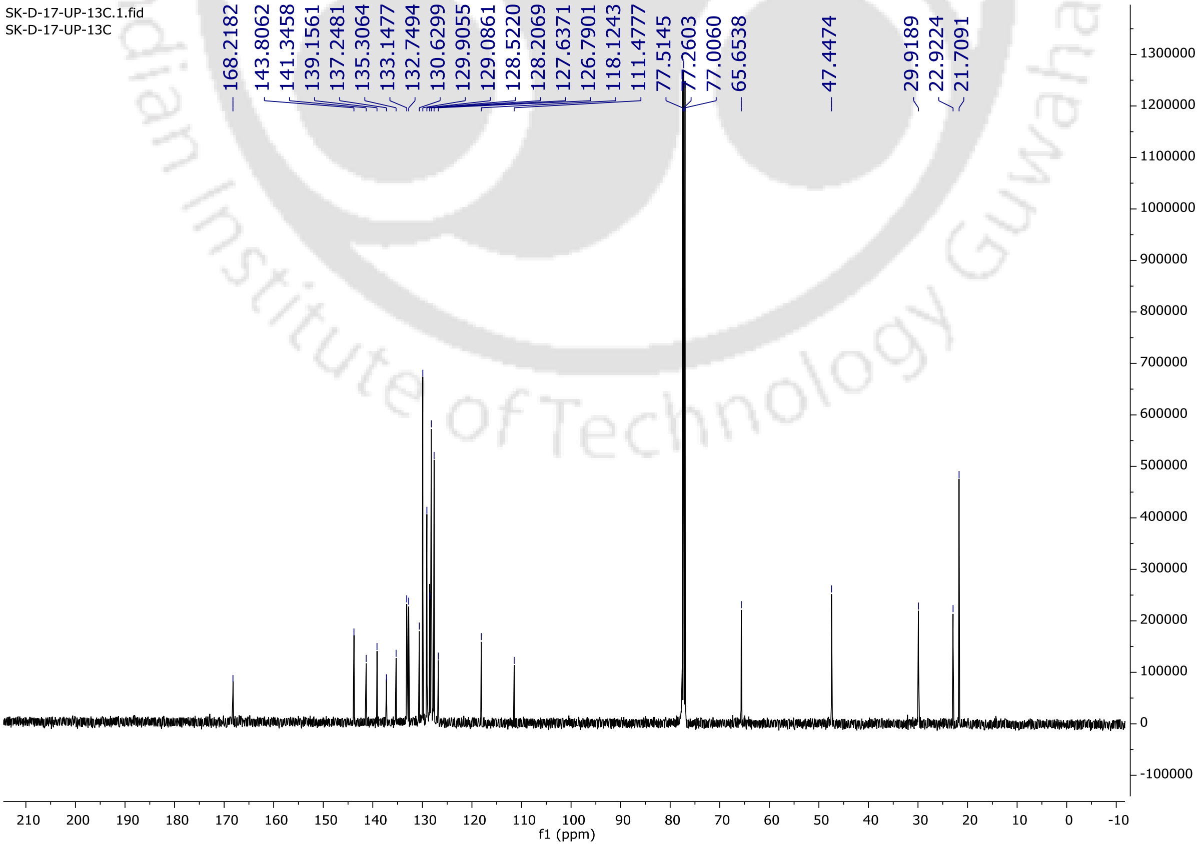


Pale yellow gum; R_f (hexane/ethyl acetate, 7:3) 0.50; yield 89 mg, 82%; IR (KBr, neat) ν 3280, 2925, 2233, 1646, 1599, 1322, 1157, 1094, 812, 664, 549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.84 (m, 2 H), 7.72 (d, *J* = 7.8 Hz, 1 H), 7.61 (d, *J* = 8.1 Hz, 2 H), 7.49 (t, *J* = 7.7 Hz, 1 H), 7.20–7.11 (m, 6 H), 7.05 (s, 1 H), 5.18 (t, *J* = 6.2 Hz, 1 H), 3.12 (q, *J* = 6.8 Hz, 2 H), 2.84 (t, *J* = 7.0 Hz, 2 H), 2.29 (d, *J* = 3.9 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.4, 146.7, 143.4, 140.2, 139.5, 137.1, 136.5, 135.0, 133.8, 133.0, 131.5, 129.8, 129.76, 129.68, 129.4, 127.1, 118.2, 112.8, 42.0, 27.9, 21.6, 21.5. HRMS (ESI) calcd. for $C_{26}H_{25}N_2O_3S$ $(M + H)^+$ 545.1580, found 545.1587.

4.5.5 Representative spectra and crystal parameter

^{1}H (400 MHz, CDCl$_3$) and ^{13}C{^{1}H} (125 MHz, CDCl$_3$) NMR spectra of ***Z*-25aa**





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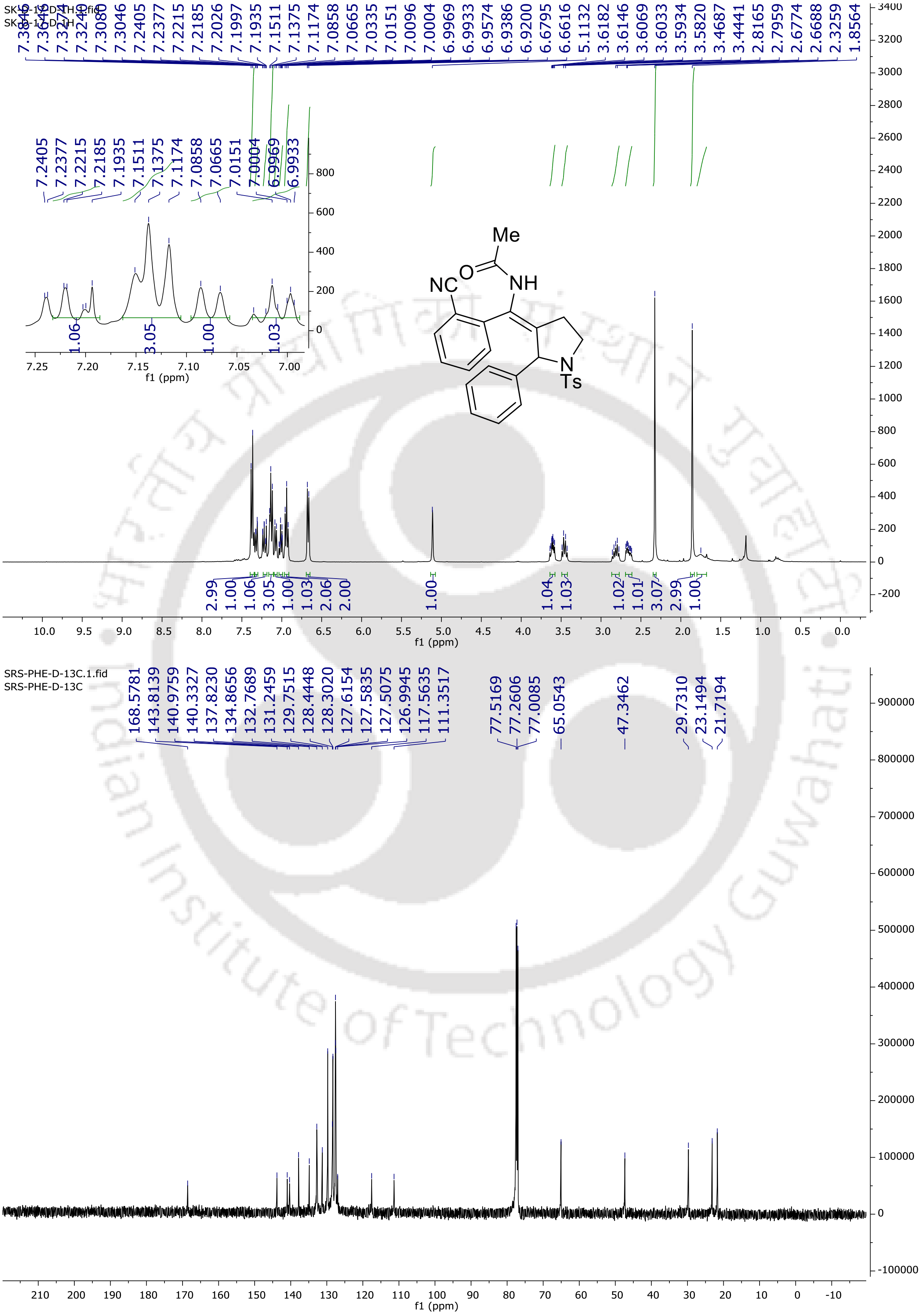
^{1}H (400 MHz, CDCl$_3$) and ^{13}C{^{1}H} (125 MHz, CDCl$_3$) NMR spectra of ***E*-25aa**



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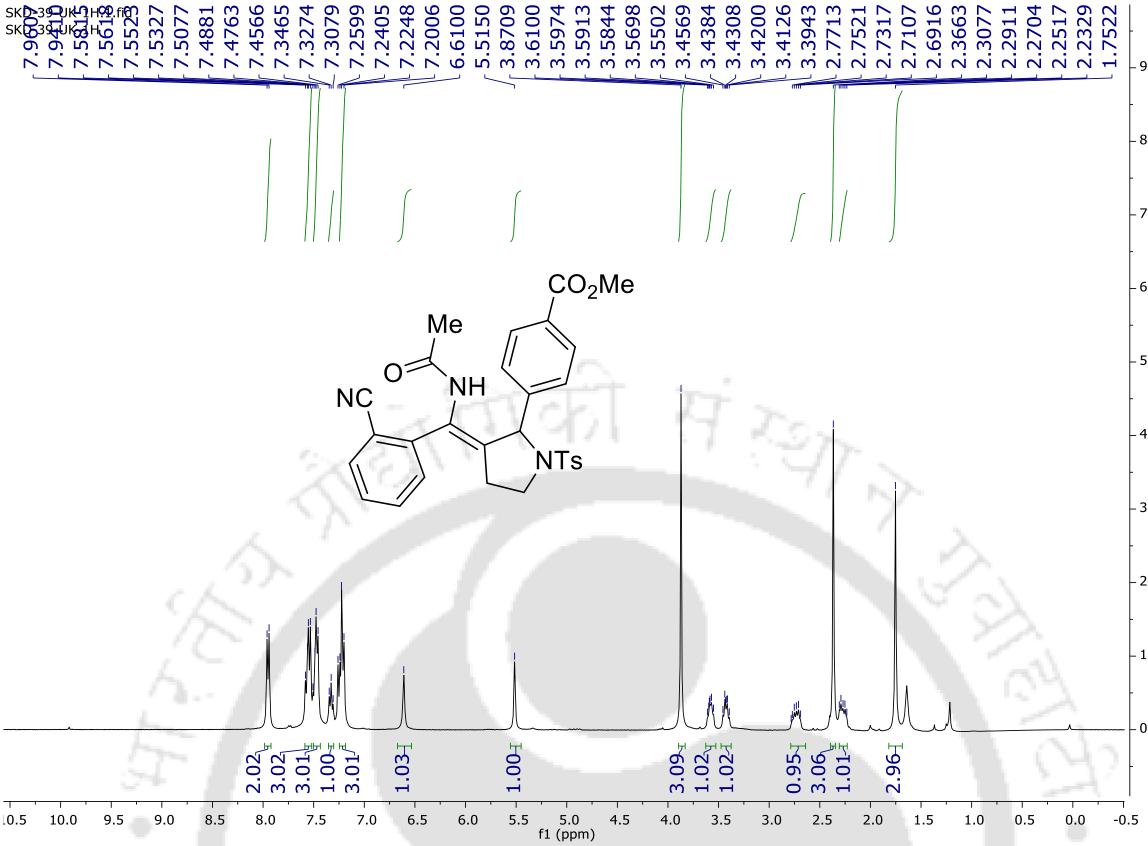
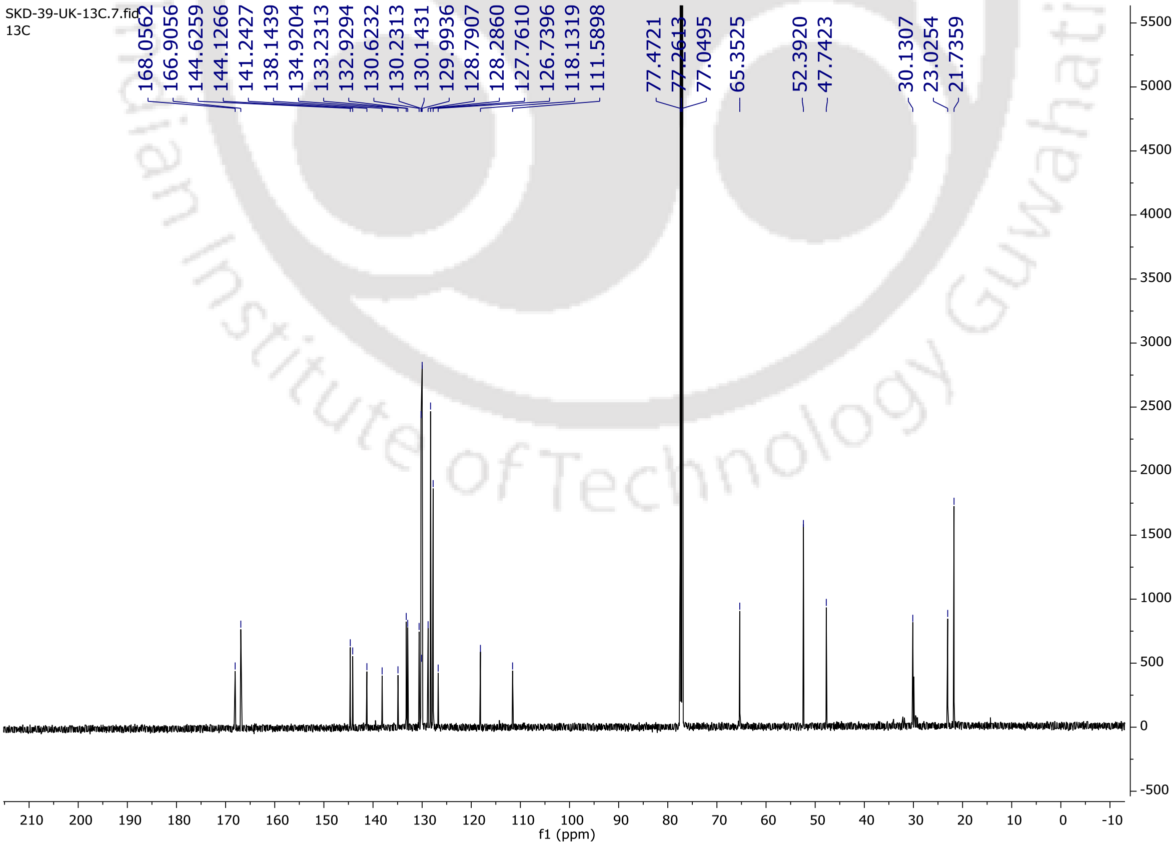
^{1}H (400 MHz, CDCl$_3$) and ^{13}C{^{1}H} (150 MHz, CDCl$_3$) NMR spectra of ***Z*-25ah**





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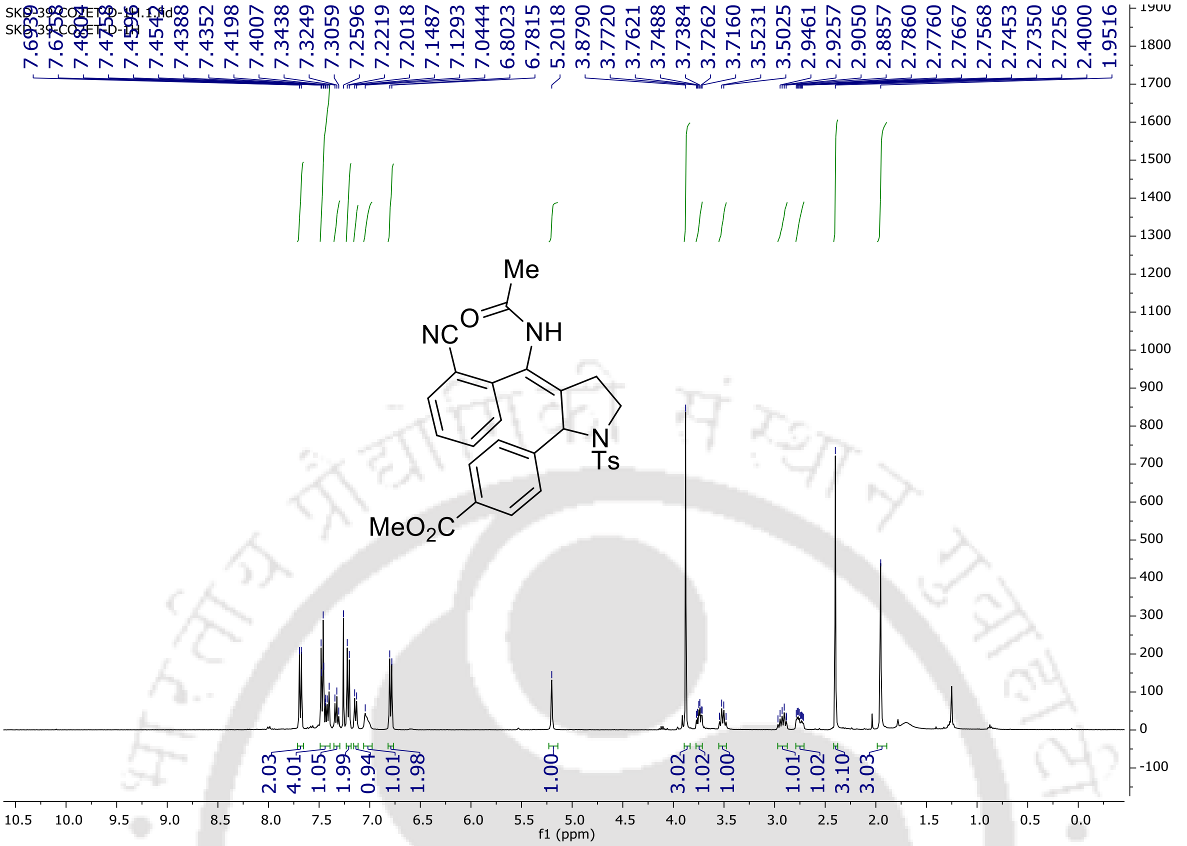
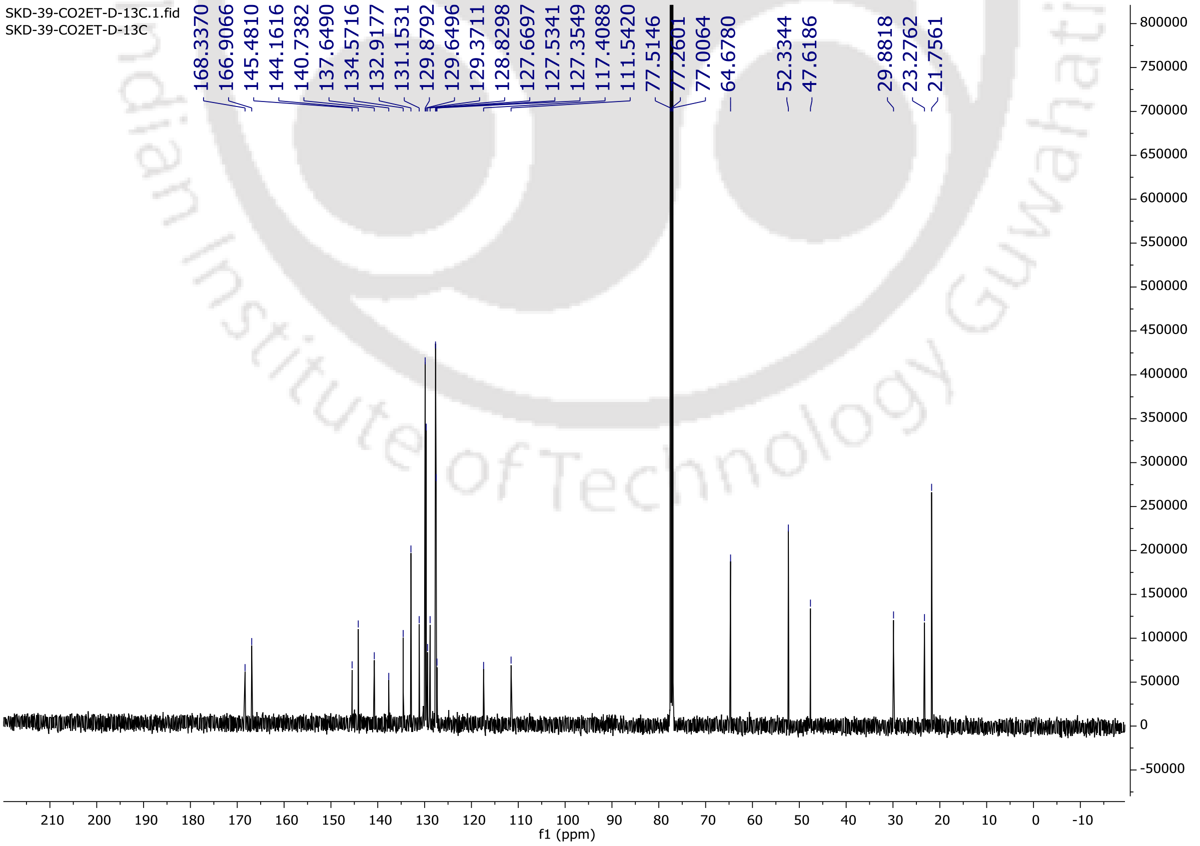
^{1}H (400 MHz, CDCl$_3$) and ^{13}C{^{1}H} (125 MHz, CDCl$_3$) NMR spectra of ***E*-25ah**





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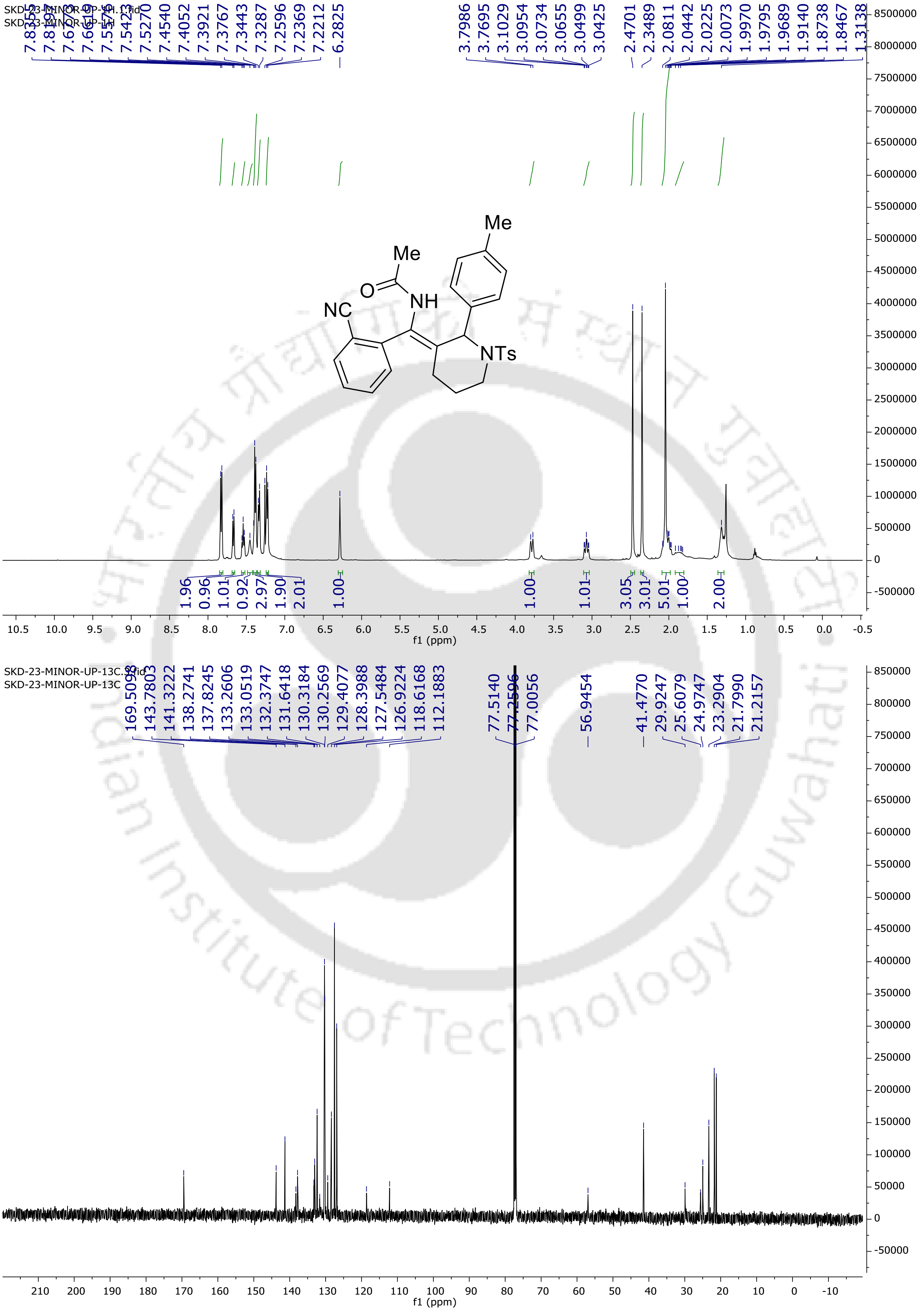
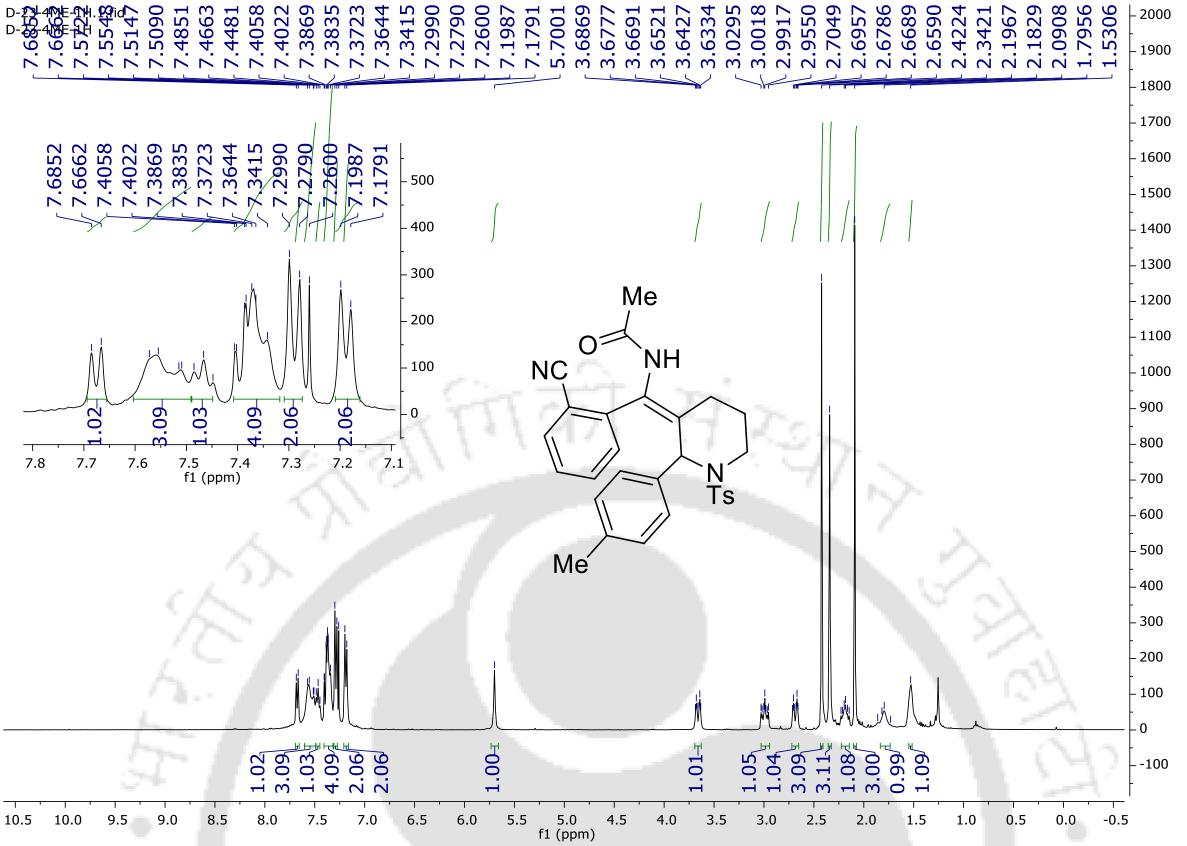
^{1}H (500 MHz, CDCl$_3$) and ^{13}C{^{1}H} (125 MHz, CDCl$_3$) NMR spectra of ***Z*-26ec**



^{1}H (400 MHz, CDCl$_3$) and ^{13}C{^{1}H} (125 MHz, CDCl$_3$) NMR spectra of ***E*-26ec**



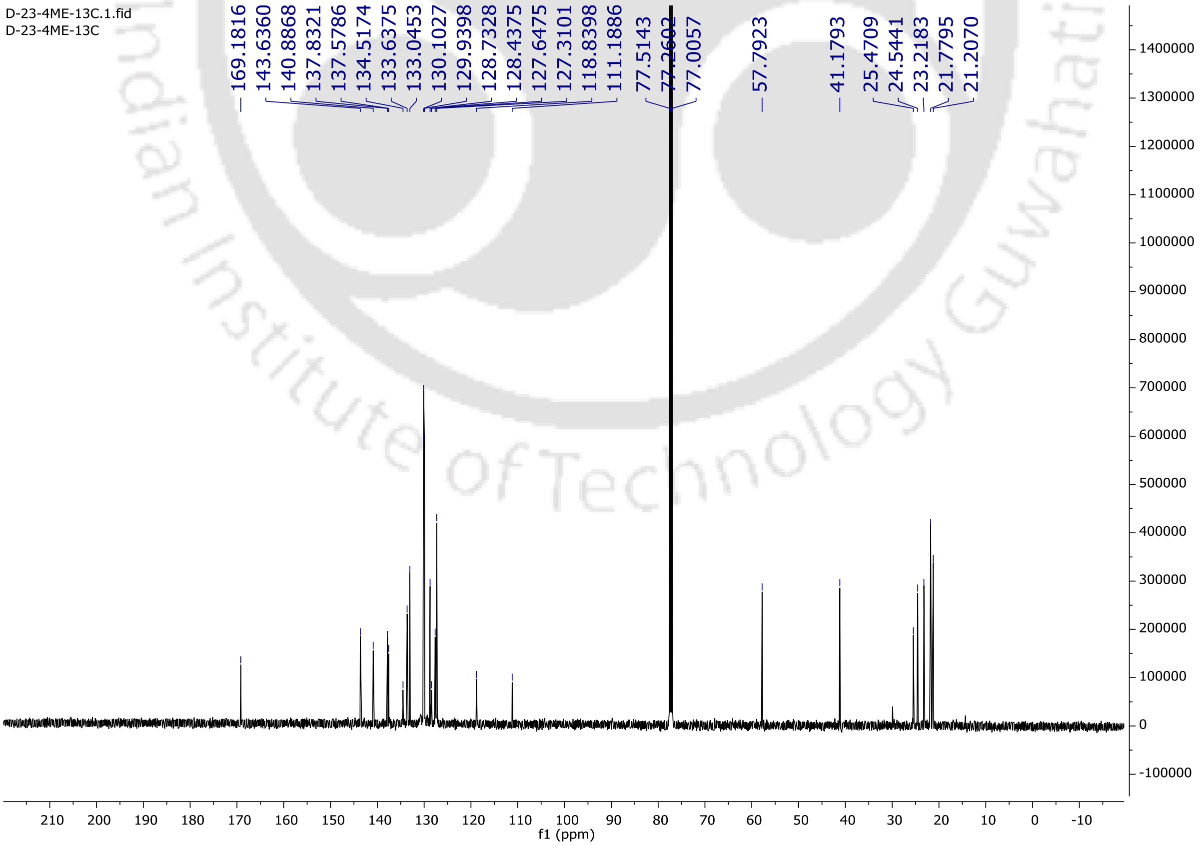
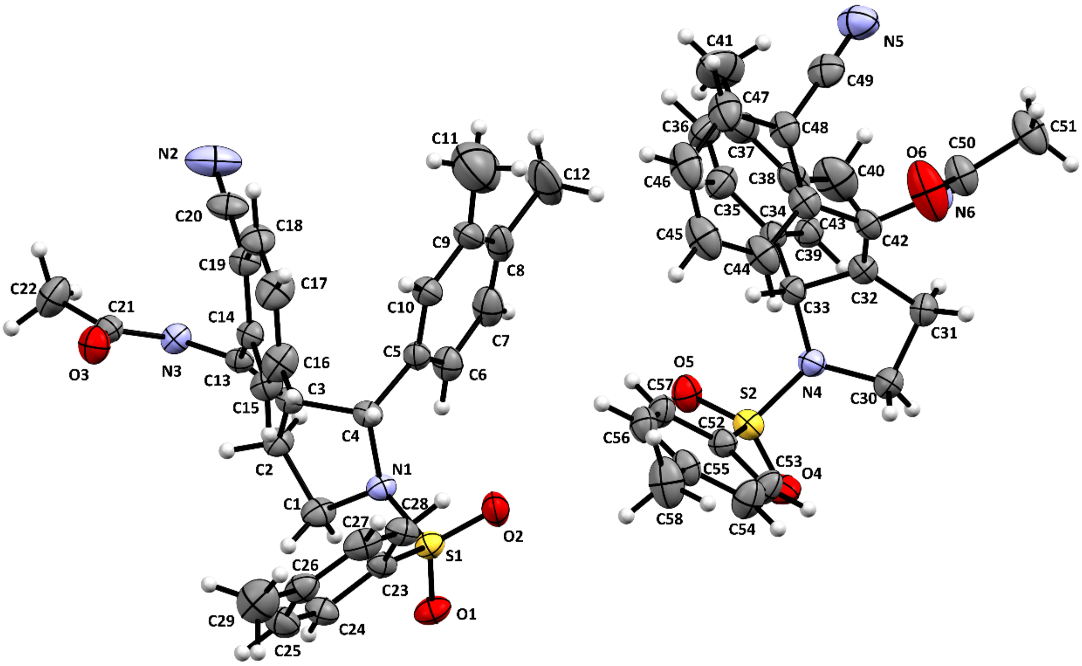


Table S1: The crystal parameters of compound *E*-25ad

	CCDC 2287207
Formula	$C_{29}H_{29}N_3O_3S$
Formula weight	499.61
T/K	297(2)
Crystal system	monoclinic
Space group	'P 21/n'
a/Å	22.290(2)
b/Å	11.2327(11)
c/Å	22.560(2)
α/º	90
β/º	108.847(3)
γ/º	90
V/Å^3	5345.7(9)
Z	8
Abs. Coeff./mm^{-1}	0.156
Abs. Correction	'none'
GOF on F^2	1.016
Final *R* indices [*I*> 2σ(I)]	*R1* = 0.0701 *wR2* = 0.1815
R indices [all data]	*R1* = 0.1221 *wR2* = 0.2074

XRD structure of ***E*-25ad** with 30% probability



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4.6 References

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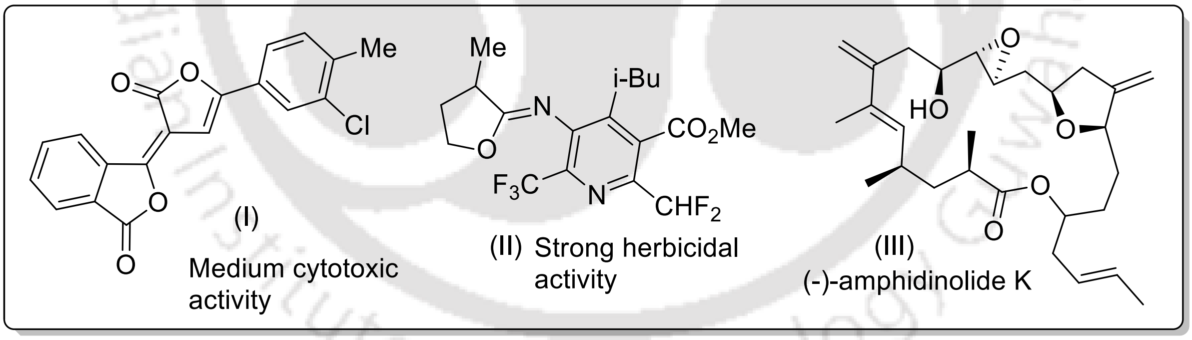
Chapter 5:

Regio- and Chemoselective Synthesis of 3-(Dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-imines *via* Tandem Alkynyl Prins- and Intramolecular Oxycyclization Reactions

5.1 Importance and Applications

Tetrahydrofuran moiety serves as a fundamental building block in the synthesis of various natural products. 3-Methylenetetrahydrofuran, in particular, plays a pivotal role in the formation of important natural products like amphidinolides C, C2, C3, and F, as well as (–)-Amphidinolide K, Halaven, E–7389, and Halichondrin.[1,2] These molecules exhibit remarkable biological activities, including potent cytotoxicity, anti-cancer, anti-tumour, tubulin assembly inhibitor, which makes them valuable targets for pharmaceutical research and drug development. Furthermore, incorporation of a 1,3-dihydroisobenzofuran moiety into molecules have been identified with significant biological activity as antimicrobial, antioxidant, and antitumor agents, highlighting their potential for the development of new pharmaceuticals.[3a] On a different note, cyclic imidate (II) compounds have showed substantial herbicidal activity, which can be further utilized in the agricultural industry (*Figure 5.1.1*).[3b]



(I) Medium cytotoxic activity

(II) Strong herbicidal activity

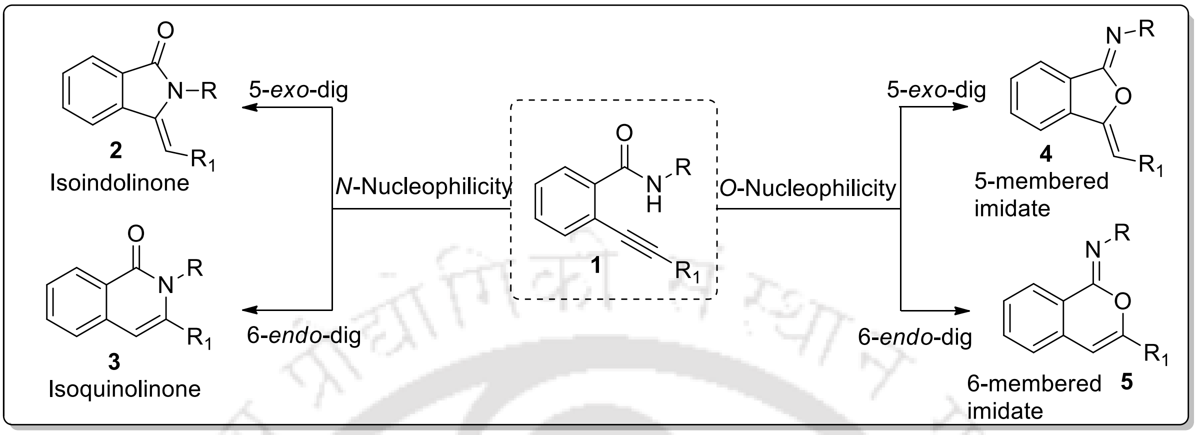
(III) (-)-amphidinolide K

Figure 5.1.1: *Biologically active molecules*

5.2 An Overview of Relevant Synthetic Methods

5.2.1 Metal Mediated Intramolecular Reactions

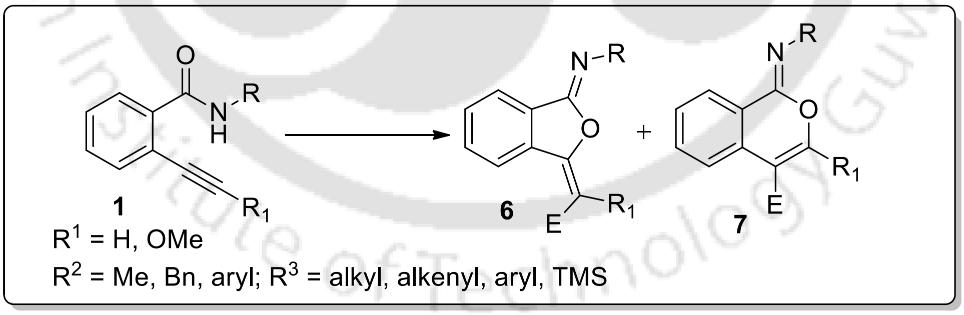
Over the past two decades, 2-(1-alkynyl)benzamide motifs are used for regio- and chemoselective synthesis of oxa- and aza-cycles utilizing amide oxygen (O) or nitrogen (N) as the nucleophiles.[4,5] Metal mediated cyclization of 2-(1-alkynyl)benzamides for the synthesis of cyclic imidates,[4] isoindolinones[5b-c] and isoquinolinones[5d] has already been established by various groups. The five-membered imidates and isoindolinones are formed by *5-exo-dig* cyclization fashion, on the other hand six-membered imidates and isoquinolinones are formed *via 6-endo-dig* fashion (*Scheme 5.2.1.1*).



Scheme 5.2.1.1: *Metal mediated intramolecular cyclization of 2-(1-alkynyl)benzamides*

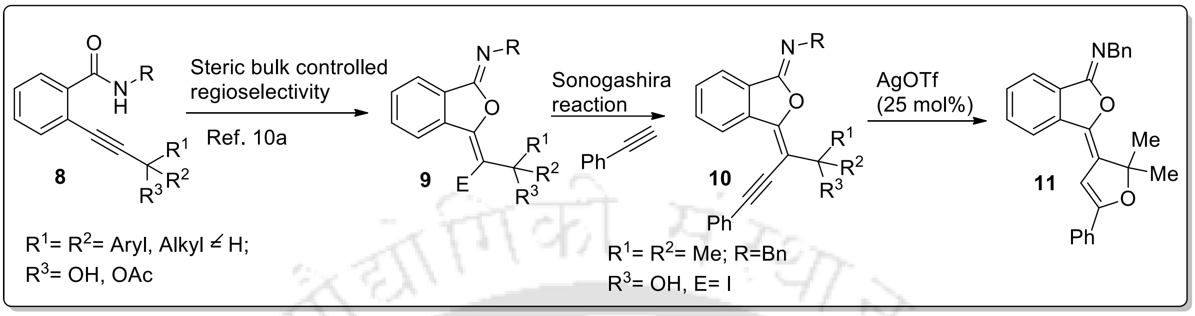
5.2.2 Metal-free Intramolecular Reactions

In 2012, Larock and co-workers reported an electrophile induced cyclization of 2-(1-alkynyl)-benzamides by employing various electrophiles including, I_2, ICl, NBS, etc. The metal-free protocol showed poor regioselectivity by forming both the five- and six-membered cyclic imidates in most of the cases via *5-exo-dig* and *6-endo-dig* oxycyclization process. (*Scheme 5.2.2.1*).[6]



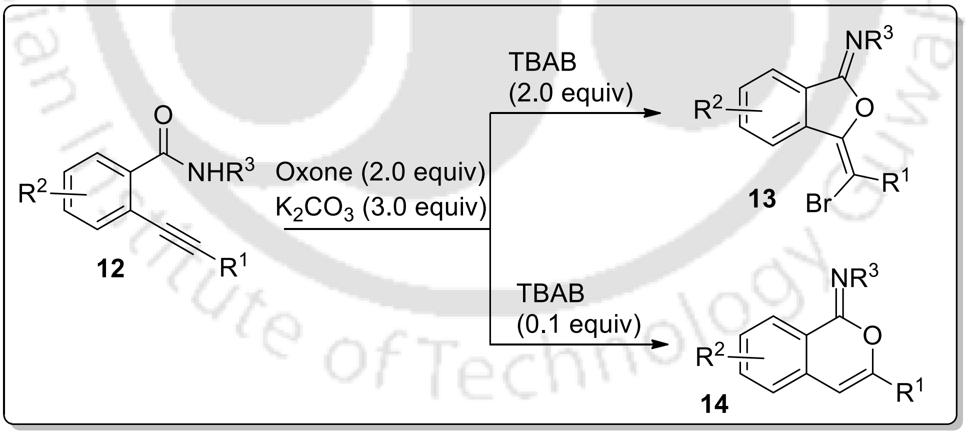
Scheme 5.2.2.1: *Larock's metal-free cyclizations of 2-(1-alkynyl)- benzamides*

In 2018, Baire and co-workers demonstrated a highly regioselective electrophilic cyclization of 2-(1-alkynyl)benzamides **8** for the synthesis of five-membered haloimidates **9**.[7] To afford the excellent regioselectivity, the steric bulk substituent at the terminal position of propargylic group played a pivotal role. The steric bulk group inhibited the generation of six-membered halonium ion intermediate and which directed the formation of five-membered halonium ion intermediates to afford the five-membered cyclized products **9** exclusively. Replacement of the tertiary bulky group at the propargylic terminal by phenyl substituent, produced both five- as well as six-membered imidates. The methodology was extended for two step synthesis of furanylidine-isobenzofuran derivatives **11** using Ag(I) salts (*Scheme 5.2.2.2*).



***Scheme 5.2.2.2:** Three step synthesis of furanylidine-isobenzofuran*

Liu and co-workers reported the methodologies for the synthesis of isobenzofuran-1-imines **13** and isocoumarin-1-imines **14** by utilizing oxycyclization of 2-alkynylbenzamide **12** *via* radical pathway.[8] Two equivalents of TBAB was used for the formation of five-membered halo imidates **13**, whereas, catalytic amount of TBAB initiated the reaction towards formation of six-membered imidates **14**. The bromide anion was oxidized to bromide radical by Oxone, and subsequent formation of bromine via bromide radical combination (*Scheme 5.2.2.3*).

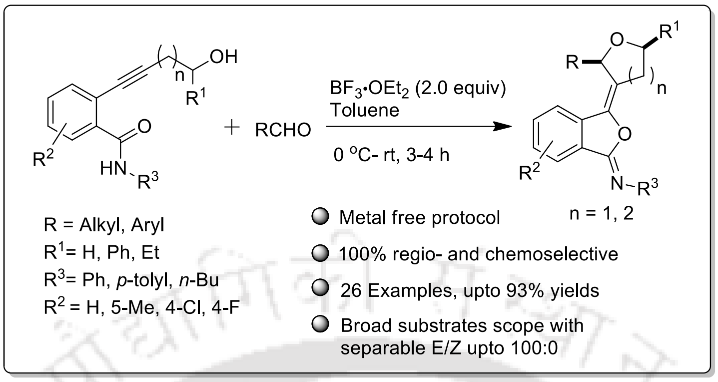


***Scheme 5.2.2.3:** Radical cyclizations of 2-(1-alkynyl)benzamides*

5.3 Present Work

There are no direct reports in the literature for the synthesis of 3-methylenetetrahydrofuran connected to isobenzofuran. In this chapter, we have demonstrated a metal-free approach for the regio- and chemoselective synthesis of 3-(dihydrofuran-3(2*H*)-ylidene)isobenzofuran-

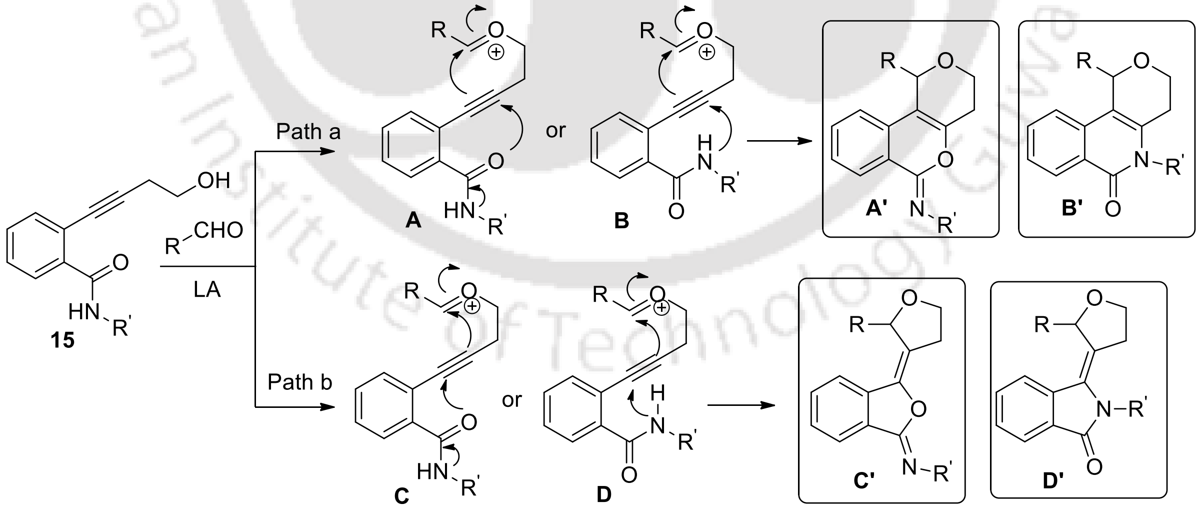
1(3*H*)-imines under mild reaction conditions with moderate to good yields within a short reaction time. Furthermore, the reaction was extended for the synthesis of furanylidene isobenzofuranones in excellent yields.



5.3.1 Results and Discussion

Initially, we envisioned that the reaction of 2-(4-hydroxybut-1-yn-1-yl)benzamides and aldehydes *via* tandem Prins cyclization and *oxy*- or *aza*-cyclization will furnish pyranoisochromene **A′** or pyranoisoquinolinone **B′** (*path a, Scheme 5.3.1.1*). However, the reaction produced furanylidine- isobenzofuran **C'** *via O*-cyclization of amide (*path b, Scheme 5.3.1.1*).

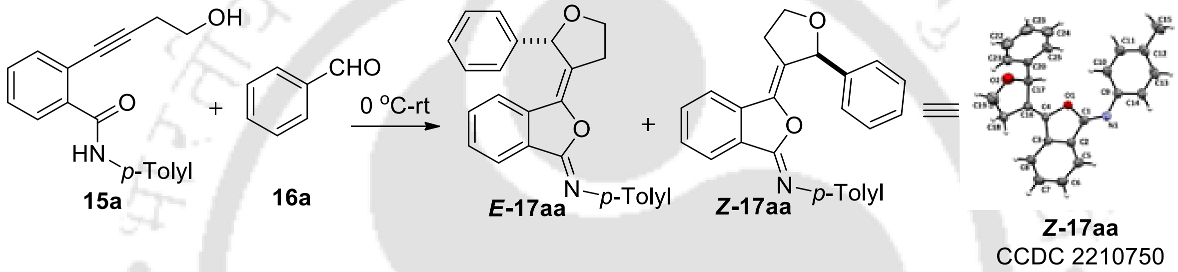
Scheme 5.3.1.1: *Proposed Reaction Pathways*



5.3.2 Optimization of the Reaction

The reaction condition was optimized using 2-(4-hydroxybut-1-yn-1-yl)-*N*-(*p*-tolyl)benzamide (**15a**) and benzaldehyde (**16a**) as model substrates. When 2-(4-hydroxybut-1-yn-1-yl)-*N*-(*p*-tolyl)benzamide (**15a**) was subjected to react with 1.2 equiv of benzaldehyde (**16a**) in the presence of 1.5 equiv of $BF_3{\cdot}OEt_2$ in dichloromethane, the reaction produced (*Z*)-4-methyl-*N*-((*E*/*Z*)-3-(2-phenyldihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)aniline (**17aa**) in 69% yields with *E*/*Z*=2:1 in 2 h (entry 1, Table 1). On increasing the amount of $BF_3{\cdot}OEt_2$ to 2.0 equiv, the reaction gave 77% yield of the product (entry 2, Table 1). However, further increase in the reagent load to 3.0 equiv did not lead to any significant improvement of the yield (entry 3, Table 1). Therefore, all further reactions were carried out with 2.0 equiv of the reagent. Switching the solvent to toluene resulted in the expected product in 78% yield within 2 h (entry 4, Table 1). An increase in the duration of the reaction up to 3 and 4 h, resulted in 83 and 80% yields respectively (entries 5 and 6, Table1). Reaction at 0 °C gave only 38% yields

Table 1: Optimization of the Reaction



S. No	Reagent (equiv)	Solvent	Time(h)	*E*:*Z*	Yield^b
1	$BF_3{\cdot}OEt_2$ (1.5)	DCM	2.0	2:1	69
2	$BF_3{\cdot}OEt_2$ (2.0)	DCM	2.0	2:1	77
3	$BF_3{\cdot}OEt_2$ (3.0)	DCM	2.0	2:1	76
4	$BF_3{\cdot}OEt_2$ (2.0)	Toluene	2.0	3:1	78
5	$BF_3{\cdot}OEt_2$ (2.0)	Toluene	3.0	3:1	83
6	$BF_3{\cdot}OEt_2$ (2.0)	Toluene	4.0	3:1	80
7	$BF_3{\cdot}OEt_2$ (2.0)	Toluene	4.0	3:1	38^c
8	$BF_3{\cdot}OEt_2$ (2.0)	Benzene	3.0	3:1	82
9	$BF_3{\cdot}OEt_2$ (2.0)	Acetonitrile	3.0	3:1	46
10	$FeCl_3$ (2.0)	Toluene	8.0	-	NR
11	TfOH (2.0)	Toluene	3.0	3:1	56
12	*p*-TSA (2.0)	Toluene	18.0	-	NR
13	TMSOTf (2.0)	Toluene	3.0	2:1	68
14	TMSOTf(2.0)	DCM	3.0	2:1	74

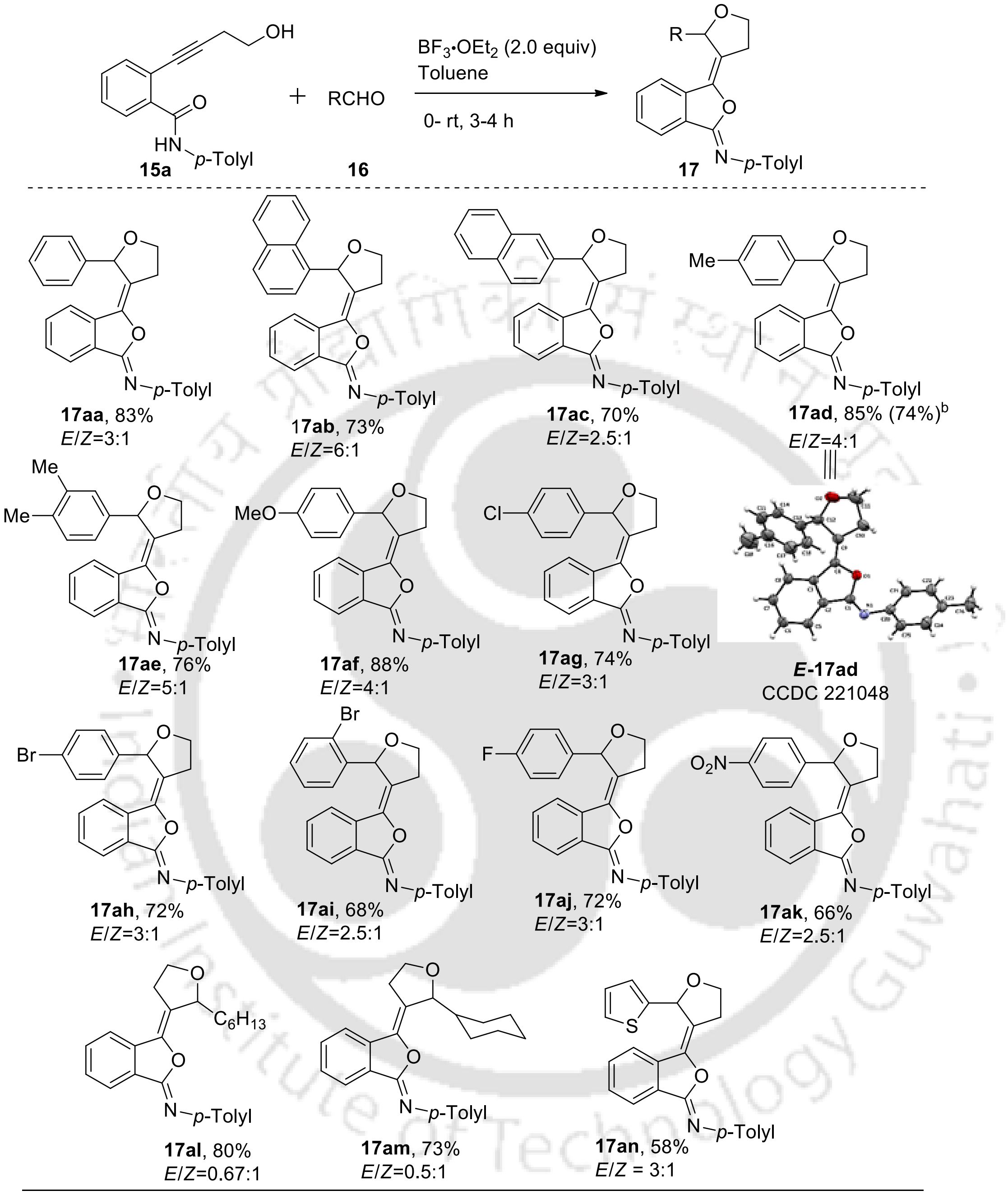
^{a}Reaction condition: **15a** (0.29 mmol, 1.0 equiv), **16a** (0.35 mmol, 1.2 equiv), N_2 atmosphere, ^{b}Yields refer to isolated yield, Reaction temperature= 0 °C-rt, ^{c}Reaction at 0 °C, NR= No reaction.

with *E*/*Z* = 3:1 and the unreacted starting material was recovered (entry 7, Table 1). Furthermore, the reaction was screened in benzene and acetonitrile solvent which resulted in 82 and 46% yields of the desired products, respectively, with *E*/*Z* = 3:1 (entries 8 and 9, Table 1). Similarly, other Lewis acids like $FeCl_3$ failed to give any product whereas TMSOTf in toluene yielded 68% of the product with *E*/*Z*=2:1 (entries 10 and 13, Table 1). When the reaction was treated with Brønsted acid TfOH in toluene, only 56% of the desired product was obtained (entry 11, Table 1), whereas *p*-TSA failed to produce the expected product (entry 12, Table 1). TMSOTf (2.0 equiv.) in dichloromethane produced 74% of the desired product with *E*/*Z*=2:1 (entry 14). Therefore, 2.0 equiv of $BF_3{\cdot}OEt_2$ in toluene at 0 ˚C to rt are the optimized conditions of the reaction.

5.3.3 Substrates Scope of the Reaction

With these optimal conditions in hand, the reaction was investigated with different substrates as depicted in Schemes 5.3.3.1 and 5.3.3.2. The reaction of 2-(4-hydroxybut-1-yn-1-yl)-N-(p-tolyl)benzamide (**15a**) with electron-donating groups in the aromatic ring of aldehydes (**16d**, **16e**) provided the corresponding products in good yields with *E*/*Z* ratio of 4:1 and 5:1, respectively. On the other hand, moderately electron-withdrawing halo- groups in the phenyl ring of aldehydes produced the expected product (**17ag**- **17aj**) in good yields. Moreover, the highly electron-donating (–OMe) group and highly electron-withdrawing nitro (–NO_2) group in the aromatic ring of aldehyde furnished 88 and 66% yields, respectively, of the corresponding products (*Scheme 5.3.3.1*). The reaction was also tested with bulky aromatic aldehydes **16b, 16c** which produced the corresponding products **17ab**, **17ac** in 73% and 70% yields, respectively (*Scheme 5.3.3.1*). Interestingly, with 1-naphthaldehyde (**16b**), the reaction gave higher *E*-selectivity up to *E*/*Z*= 6:1, whereas 2-naphthaldehyde (**16c**) furnished the product with *E*/*Z*= 2.5:1. It is noteworthy that *E*-selectivity for aromatic aldehydes is due to π-π interaction between aryl group and the 2-aminocarbonylphenyl group. The methodology was further explored with aliphatic aldehydes **16l** and **16m** to obtain the corresponding products **17al** and **17am** with 80 and 73% yields, respectively (*Scheme 5.3.3.1*). The reaction is *Z*-selective for aliphatic aldehydes and *Z*-isomer was obtained as the major product owing to the steric repulsion between the aliphatic group and 2-aminocarbonylphenyl group. Heteroaromatic aldehyde **16n** also compatible under the reaction conditions and resulted in 58% yield with *E*/*Z* = 3:1 (*Scheme 5.3.3.1*).

Scheme 5.3.3.1: Scope of Aldehydes for the Synthesis of 3-(Dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-imines[a]



[a]Reaction conditions: **15a** (0.29 mmol, 1.0 equiv), **16** (0.35 mmol, 1.2 equiv), BF_3•OEt_2 (0.58 mmol, 2.0 equiv), Toluene (2.0 mL), N_2 atm. Reaction temperature= 0 °C-rt, *E*/*Z* ratio was calculated by crude ^{1}H NMR, [b]Yield reported for 3.6 mmol scale. Formula of the major isomer is shown in the scheme.

In addition, secondary alcohols **15b** and **15c** gave the corresponding product **17ba** and **17ca** with 78 and 62% yields, respectively (*Scheme 5.3.3.2*). The formation of 2,5-disubstituted tetrahydrofuran ring is *cis*-selective which was determined by NOE experiment of **17ba**. The benzamide **15d** bearing electron donating group –Me at 5-position of the aromatic ring

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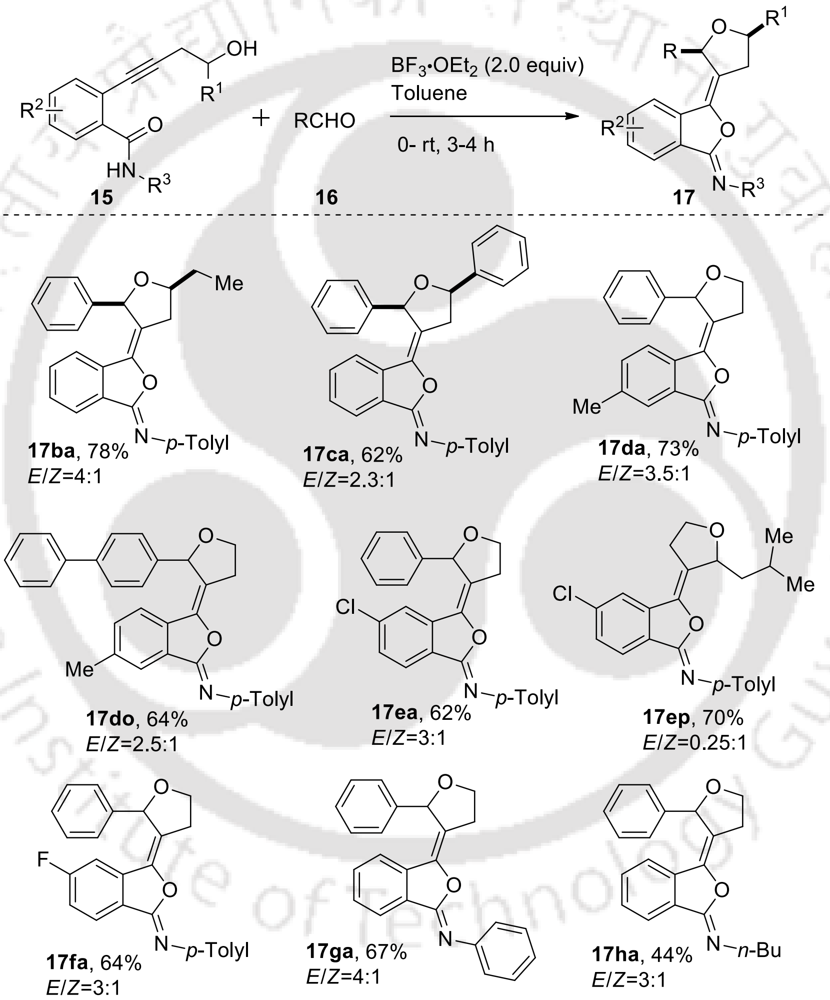
provided the desired product **17da** and **17do** in good yields. On the other hand, incorporating electron withdrawing halo- group at the 4-position of the aromatic ring of the benzamide resulted in the corresponding products **17ea**, **17ep** and **17fa** in good yields (Scheme 5.3.3.2). In the case of **17ep** the stereoselectivity is changed from *E* to *Z* (*E*/*Z*= 1:4) as stated earlier. Furthermore, the substrate scope of the reaction was explored by changing the amine part of the benzamide ($PhNH_2$ and *n*-$BuNH_2$) and the desired products **17ga** and **17ha** were obtained in 67 and 44% yields, respectively (*Scheme 5.3.3.2*).

Scheme 5.3.3.2: Scope of 2-(4-Hydroxybut-1-yn-1-yl)benzamides[a]



[a]Reaction conditions: **15** (0.29 mmol, 1.0 equiv), **16** (0.35 mmol, 1.2 equiv), $BF_3{\bullet}OEt_2$ (0.58 mmol, 2.0 equiv), Toluene (2.0 mL), N_2 atmosphere, Reaction temperature= 0 °C-rt, *E*/*Z* ratio was calculated by crude ^{1}H NMR analysis. Formula of the major isomer is shown in the scheme.

The scope of the reaction was further extended to the synthesis of its pyran analogues in good yields (*Scheme 5.3.3.3*). Thus, the treatment of **15i** with **16a-b** and **16l** under the standard reaction conditions provided corresponding pyran analogues in 93, 89 and 90% yields, respectively. Interestingly, an improved *E/Z* ratio was found compared to its furan counterpart.

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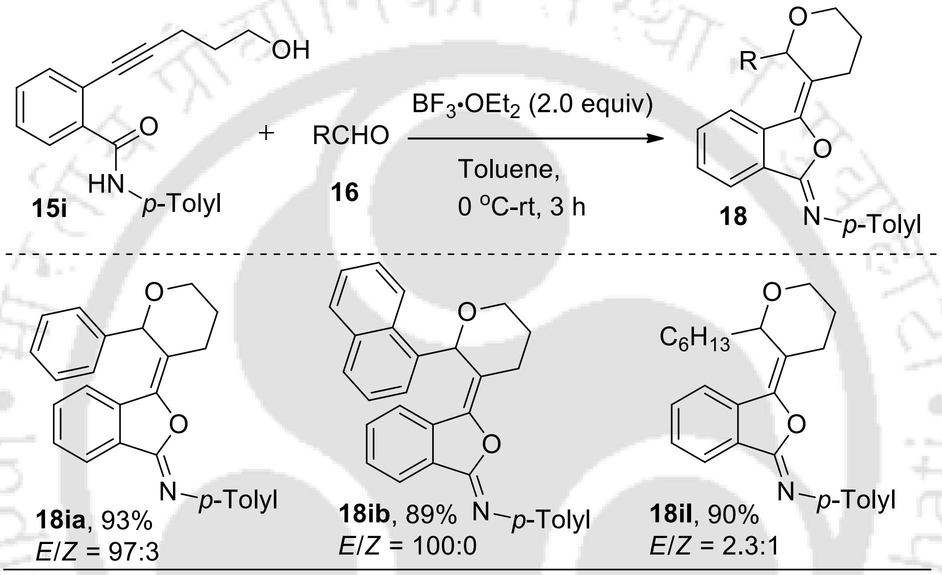
The *E/Z* ratio for **18ia** and **18il** was found to be 97:3 and 2.3:1, respectively, whereas **18ib** was obtained with 100% *E*-selectivity, which might be due to π-π interaction between bulky 1-naphthyl group with 2-aminocarbonylphenyl group. Interestingly, in the case of six membered tetrahydropyran ring with alkyl side chain of **18il**, the selectivity was changed to *E*. This is due to the steric repulsion between alkyl chain and tolyl group in the expanded six membered pyran ring compared to five membered furan ring.

Scheme 5.3.3.3: Synthesis of 3-(Dihydro-2*H*-pyran-3(4*H*)-ylidene)isobenzofuran-1(3*H*)-imines[a]



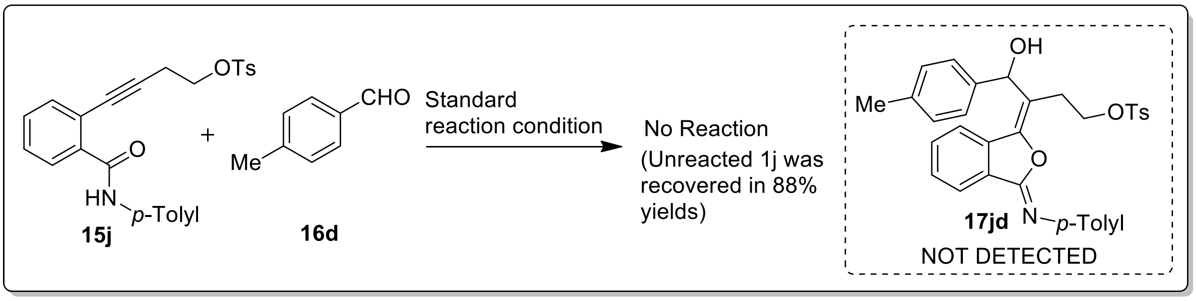
[a]Reaction conditions: **15i** (0.20 mmol, 1.0 equiv), **16** (0.24 mmol, 1.2 equiv). BF_3•OEt_2 (0.40 mmol, 2.0 equiv), Toluene (2.0 mL), N_2 atmosphere, Reaction temperature= 0 °C-rt, *E/Z* ratio was calculated by crude ^1H NMR analysis. Formula of the major isomer is shown in the scheme.

The structure of the compounds was determined by ^1H, ^{13}C spectroscopy, NOESY, mass spectrometry and finally by X-ray crystallographic analysis of compounds *Z*-**17aa**, *E*-**17ad** and **19aa**.

5.3.4. Controlled Experiments

To gather the information about the mechanism of the reaction, we had performed a controlled experiment with **15j** in which, –OH group was protected with tosyl group. The reaction of **15j** with **16d** under standard reaction conditions failed to produce **17jd** and the unreacted starting material was recovered (*Scheme 5.3.4.1*). This indicates that in absence of homopropargylic alcohol moiety, BF_3•OEt_2 is not efficient for the oxycyclization reaction.

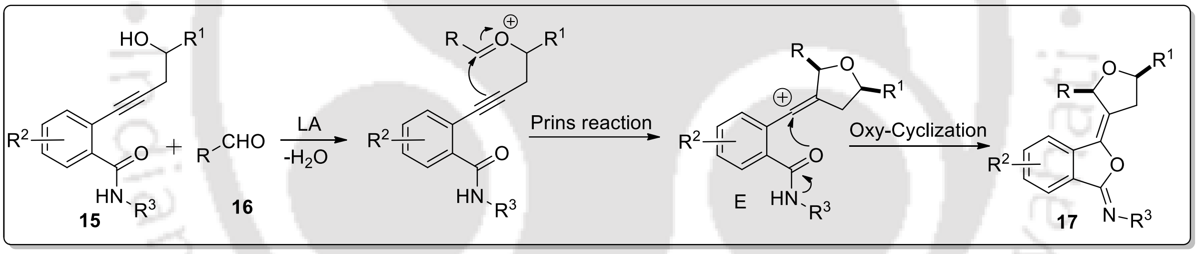
Scheme 5.3.4.1: *Control experiment*



5.3.5 Mechanism of the Reaction

As per the controlled experiment and literature reports,[7,9] a plausible mechanism of the reaction is depicted in Scheme 5.3.5.1. The reaction involves the initial formation of dihydrofuranylidene carbocation **E** *via* Prins cyclization reaction, which undergoes oxy-cyclization of amide functionality through keto-enol type tautomerism to produce the desired product **17** exclusively. Notably, both the isomers are separable by column chromatography.

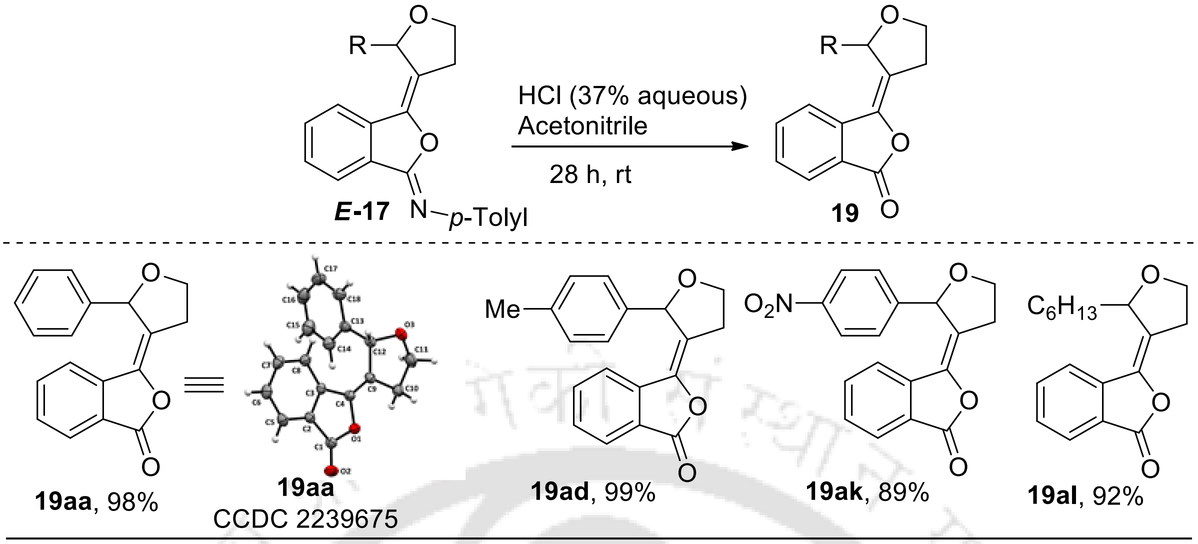
Scheme 5.3.5.1: *Plausible mechanism of the reaction*



5.3.6 Post Synthetic Utility of the Reaction

The strategy was further extended for the synthesis of furanylidene isobenzofuranones. Treatment of ***E*-17aa**, ***E*-17ad**, ***E*-17ak** and ***E*-17al** with conc. HCl in acetonitrile for 28 h resulted in the corresponding products up to 99% yields (*Scheme 5.3.6.1*).

Scheme 5.3.6.1: *Synthesis of furanylidene isobenzofuranones*



5.4 Conclusion

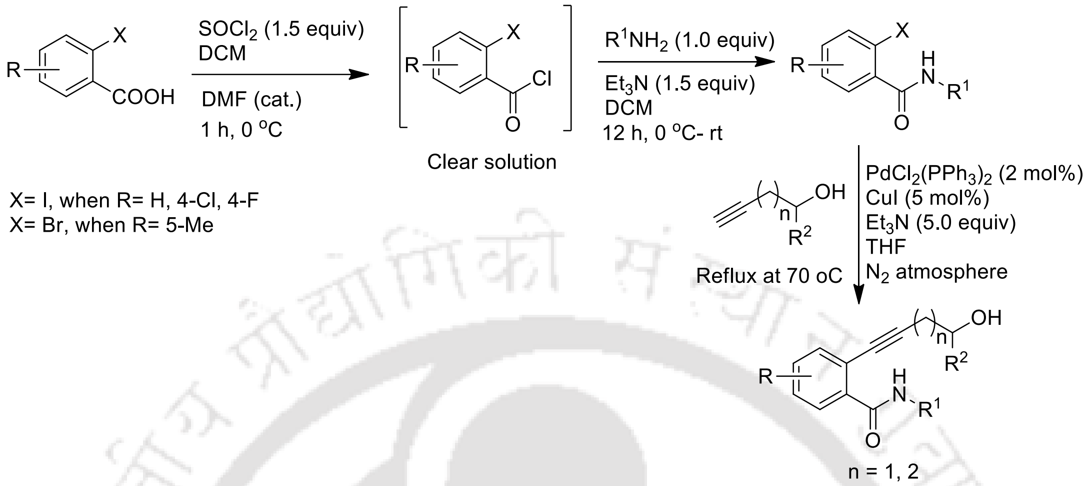
An expedient methodology for the synthesis of 3-(dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-imines mediated by $BF_3{\cdot}OEt_2$ has been developed. The diverse functionalized metal-free protocol furnished the desired compounds in moderate to good yields within a short reaction time *via* tandem Prins- and intramolecular oxy-cyclization reaction. The reaction is stereoselective as well as regio- and chemo-selective (~100%) in nature. The methodology was further extended for the synthesis of furanylidene isobenzofuranones with excellent stereoselectivity and yields.

5.5 Experimental Section

5.5.1 General information

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (600 MHz, 500 MHz and 400 MHz) or ^{13}C (150 MHz, 125 MHz and 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. Structural assignments were made with additional information from NOESY and single crystal XRD experiments. HRMS spectra were recorded using Q-TOF and micrOTOF-Q II mass spectrometer. Aldehydes **16a-16p** were purchased from Sigma-Aldrich and used without further purification.

5.5.2 General Procedure for the Preparation of Starting Materials (15a-15i)



The starting material (**15a-15i**) were prepared according to the modified literature methods.[10] To an oven dried round bottomed flask, the corresponding 2-halobenzoic acid (2.0 mmol, 1.0 equiv) was taken followed by addition of thionyl chloride (3.0 mmol, 1.5 eqiv), dichloromethane (10 mL) and catalytic amount of *N*, *N*-Dimethylformamide (4-5 drops) in ice cold conditions under nitrogen atmosphere. The reaction mixture was stirred for an hour until the reaction mixture becomes clear solution. After 1 h, the excess thionyl chloride was evaporated by using rotary evaporator and the residue was cooled to 0 ˚C using ice bath. Then the primary amine (2.0 mmol, 1.0 equiv) was added to the reaction mixture followed by triethylamine (3.0 mmol, 1.5 equiv) and stirred for overnight. After completion of the reaction, the excess triethylamine was evaporated using rotary evaporator and the reaction mixture was washed using saturated NH_4Cl and brine solution. The organic layer was extracted by ethyl acetate (3x15 mL), dried over Na_2SO_4 and evaporated by a rotary evaporator. The crude was then subjected to column chromatography over silica get using ethyl acetate and hexane as eluent to get the corresponding *N*- substituted 2-halobenzamide in white solid.

To a stirred suspension of $PdCl_2(PPh_3)_2$ (0.02 mmol, 2 mol %) and CuI (0.05 mmol, 5 mol %) in trimethylamine (5.0 mmol, 5.0 equiv) under nitrogen atmosphere was added the *N*-substituted 2-halobenzamide (1.1 mmol, 1.1 equiv) followed by freshly dried THF (10 mL), then the reaction mixture was stirred for 10 minutes. Eventually, alkyne (1.0 mmol, 1.0 equiv) was added to the reaction mixture and refluxed for 12 h at 70 ˚C in an oil bath and monitored by TLC (using Hexane: Ethyl acetate = 7:3 as eluent). After completion of the reaction, the excess triethylamine was evaporated by using rotary evaporator and the reaction mixture was washed by saturated NH_4Cl and brine solution. The organic layer was extracted by ethyl acetate (3x15 mL), dried over Na_2SO_4 and evaporated by a rotary evaporator. The crude was then subjected to column chromatography using hexane and ethyl acetate as eluent to afford the *N*-substituted 2-(4-Hydroxybut-1-yn-1-yl)-benzamide (**15a-15i**).

5.5.3 Experimental procedure for the preparation of 15j

To a stirred solution of 2-(4-hydroxybut-1-yn-1-yl)-*N*-(*p*-tolyl)benzamide (**15a**) (280 mg, 1 mmol), 4-dimethylaminopyridine (12.0 mg, 0.1 mmol) in CH_2Cl_2 (5.0 mL) was added triethylamine (0.28 mL, 2.0 mmol) at 0 ˚C. Eventually, TsCl (286 mg, 1.5 mmol) was added to the reaction mixture and stirred at room temperature for 4 hours. After completion of the reaction, the progress of the reaction was checked by TLC. The excess solvent was evaporated by using rotary evaporator and washed by saturated NH_4Cl solution and brine. The organic layer was extracted by ethyl acetate (2x15 mL), dried over Na_2SO_4 and evaporated by rotary evaporator. The crude was then subjected to column chromatography using ethyl acetate and hexane as eluent to give the corresponding product in 78% yields (colourless gum, 338 mg).

5.5.4 General procedure for the synthesis of 17aa-17an, 17ba, 17ca, 17da, 17do, 17ea, 17ep, 17fa, 17ga, 17ha

To a stirred solution of *N*-substituted 2-(4-hydroxybut-1-yn-1-yl)-benzamide (0.29 mmol, 1.0 equiv) and aldehydes (0.35 mmol, 1.2 equiv) in toluene (2.0 mL) was added $BF_3{\cdot}OEt_2$ (0.58 mmol, 2.0 equiv) *via* syringe at 0 ˚C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3-4 h, and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was washed by saturated sodium bicarbonate solution and brine. The organic layer was extracted by ethyl acetate (3x15 mL), dried over Na_2SO_4 and evaporated by a rotary evaporator. The crude was then subjected by column chromatography using ethyl acetate and hexane as eluent to get the corresponding products ***E*-17** and ***Z*-17**.

5.5.5 General procedure for the synthesis of 18ia, 18ib and 18il

To a stirred solution of 2-(5-hydroxypent-1-yn-1-yl)-*N*-(*p*-tolyl)benzamide (0.20 mmol, 1.0 equiv) and aldehydes (0.24 mmol, 1.2 equiv) in toluene (2.0 mL) was added $BF_3{\cdot}OEt_2$ (0.4 mmol, 2.0 equiv) *via* syringe at 0 ˚C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 h, and the progress of the reaction was monitored by TLC.

After completion of the reaction, the reaction mixture was washed by saturated sodium bicarbonate and brine. The organic layer was extracted by ethyl acetate (3x15 mL), dried over Na_2SO_4 and evaporated by a rotary evaporator. The crude was then subjected by column chromatography using ethyl acetate and hexane as eluent to get the corresponding ***E*-18** and ***Z*-18.**

5.5.6 General Procedure for the Synthesis of 19aa, 19ad, 19ak, 19al

To a stirred solution of 3-(dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-imines (0.1 mmol) in acetonitrile (2.0 mL) was added conc. HCl (37% aqueous, 25 µL) dropwise. The reaction was stirred at room temperature for 28 h, and was monitored *via* TLC. After completion of the reaction, the reaction mixture was washed with saturated sodium bicarbonate and brine solution. Then the organic layer was extracted with ethyl acetate (3x10 mL), dried over Na_2SO_4 and evaporated by a rotary evaporator. The crude was subjected to column chromatography via silica gel using hexane and ethyl acetate as eluent to get the corresponding products in 89-99% yields.

5.5.7 Experimental procedure of the gram scale reaction

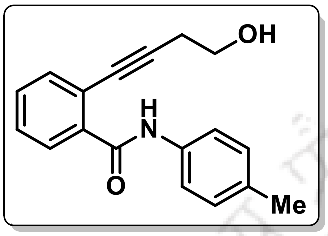
To a stirred solution of 2-(4-hydroxybut-1-yn-1-yl)-*N*-(*p*-tolyl)benzamide (**15a**) (1.0 g, 3.58 mmol) and *p*-tolualdehyde (**16d**) (0.51 mL, 4.30 mmol) in toluene (15 mL) was added $BF_3{\cdot}OEt_2$ (0.88 mL, 7.16 mmol) slowly *via* syringe at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3.5 h, and the progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was washed by saturated sodium bicarbonate solution, and brine. The organic layer was extracted with ethyl acetate (3 × 30 mL), dried over Na_2SO_4 and evaporated by a rotary evaporator. The product 3ab was obtained in a 74% (1.01 g, white solid) with *E*/*Z* = 3:1 yield by column chromatography over silica gel using hexane and ethyl acetate as eluents.

5.5.8 Experimental procedure of the controlled experiment

To a stirred solution of 4-(2-(*p*-tolylcarbamoyl)phenyl)but-3-yn-1-yl 4-methylbenzenesulfonate (**15j**) (108 mg, 0.25 mmol) and *p*-tolualdehyde (**16d**) (36 mg, 0.3 mmol) in toluene (2.0 mL) was added $BF_3{\cdot}OEt_2$ (0.06 mL, 0.5 mmol) slowly by a syringe at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 4 h, and the progress of the reaction was monitored by TLC, but no new spot was observed in TLC. To collect the unreacted starting material, the reaction mixture was washed by saturated sodium bicarbonate solution, and brine. The organic layer was extracted with ethyl acetate (2 × 20 mL), dried over Na_2SO_4 and evaporated by a rotary evaporator. The unreacted starting material **15j** was obtained in 88% yield (95 mg, colourless gum) by column chromatography over silica gel using hexane and ethyl acetate as eluents.

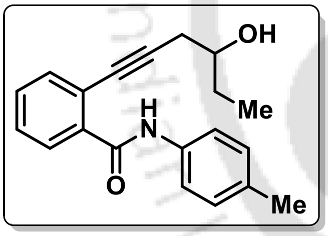
5.9 Characterization data

2-(4-Hydroxybut-1-yn-1-yl)-*N*-(*p*-tolyl)benzamide (15a):



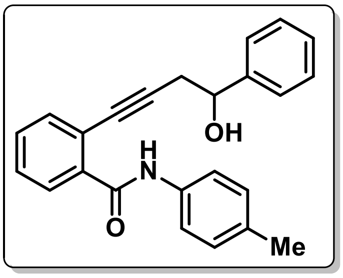
Pale yellow solid; R_f (hexane/ethyl acetate, 7:3) 0.40; mp 118-120 °C, yield 221 mg, 79%; IR (KBr, neat) ν 3335, 2920, 2878, 2228, 1649, 1601, 1516, 1321, 1047, 817, 757, 509 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.85 (s, 1 H), 7.97 – 7.94 (m, 1 H), 7.55–7.50 (m, 3 H), 7.42 – 7.39 (m, 2 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 3.78 (t, *J* = 6.7 Hz, 2 H), 2.72 (t, *J* = 6.1 Hz, 2 H), 2.43 (s, 1 H), 2.33 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 165.1, 136.7, 135.6, 134.5, 133.7, 130.9, 129.9, 129.6, 128.7, 120.4, 94.6, 80.8, 61.1, 24.2, 21.1. HRMS (ESI) calcd. for $C_{18}H_{18}NO_2$ $(M + H)^+$ 280.1337, found 280.1330.

2-(4-Hydroxyhex-1-yn-1-yl)-*N*-(*p*-tolyl)benzamide (15b):



Pale yellow gum; R_f (hexane/ethyl acetate, 7:3) 0.40; yield 240 mg, 78%; IR (KBr, neat) ν 3345, 2963, 2927, 1650, 1599, 1512, 1322, 978, 815, 754, 512 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, 1 H), 7.97 – 7.95 (m, 1 H), 7.55 (d, *J* = 8.1 Hz, 2 H), 7.52 – 7.50 (m, 1 H), 7.43–7.39 (m, 2 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 3.77–3.72 (m, 1 H), 2.70 (dd, *J* = 17.0, 4.6 Hz, 1 H), 2.59 (dd, *J* = 16.9, 6.6 Hz, 1 H), 2.33 (s, 3 H), 1.73 (s, 1 H), 1.63 – 1.55 (m, 2 H), 0.92 (t, *J* = 7.4 Hz, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 165.0, 136.7, 135.6, 134.4, 133.8, 130.9, 129.8, 129.6, 128.7, 120.5, 120.4, 94.3, 81.2, 71.7, 29.6, 28.3, 21.1, 10.1. HRMS (ESI) calcd. for $C_{20}H_{22}NO_2$ $(M + H)^+$ 308.1650, found 308.1645.

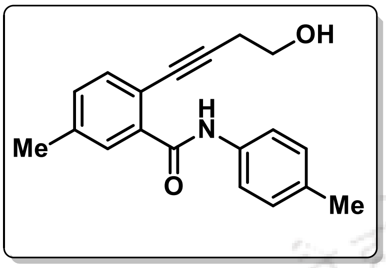
2-(4-Hydroxy-4-phenylbut-1-yn-1-yl)-*N*-(*p*-tolyl)benzamide (15c):



Orange gum; R_f (hexane/ethyl acetate, 7:3) 0.40; yield 267 mg, 75%; IR (KBr, neat) ν 3338, 3030, 2913, 2223, 1649, 1601, 1516, 1321, 1052, 814, 754, 699, 512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1 H), 7.96 – 7.94 (m, 1 H), 7.50 – 7.46 (m, 3 H), 7.40 – 7.25 (m, 7 H), 7.14 (d, *J* = 8.1 Hz, 2 H), 4.93 (d, *J* = 6.9 Hz, 1 H), 2.94 (s, 1 H), 2.89 (d, *J* = 6.2 Hz, 2 H), 2.32 (s, 3

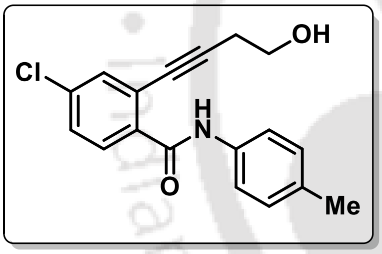
H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.0, 142.9, 136.6, 135.6, 134.4, 133.8, 130.9, 129.8, 129.7, 128.8, 128.7, 128.2, 125.9, 120.5, 94.1, 81.4, 72.7, 30.9, 21.1. HRMS (ESI) calcd. for $C_{24}H_{22}NO_2$ $(M + H)^+$ 356.1650, found 356.1642.

2-(4-Hydroxybut-1-yn-1-yl)-5-methyl-*N*-(*p*-tolyl)benzamide (15d):



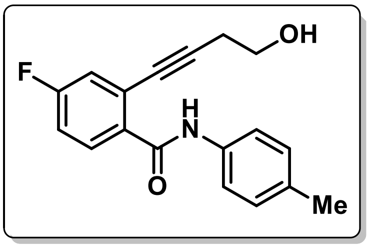
Orange gum; R_f (hexane/ethyl acetate, 7:3) 0.40; yield 165 mg, 56%; IR (KBr, neat) ν 3345, 2923, 2870, 1651, 1601, 1519, 1321, 1047, 918, 512 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1 H), 7.76 (s, 1 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.38 (d, *J* = 7.8 Hz, 1 H), 7.20 (dd, *J* = 7.9, 2.0 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 3.76 (t, *J* = 6.2 Hz, 2 H), 2.69 (t, *J* = 6.2 Hz, 2 H), 2.64 (s, 1 H), 2.37 (s, 3 H), 2.32 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 165.2, 139.0, 136.3, 135.6, 134.4, 133.7, 131.7, 130.2, 129.8, 120.4, 117.4, 93.7, 80.8, 61.1, 24.2, 21.5, 21.1. HRMS (ESI) calcd. for $C_{19}H_{20}NO_2$ $(M + H)^+$ 294.1494, found 294.1486.

4-Chloro-2-(4-hydroxybut-1-yn-1-yl)-*N*-(*p*-tolyl)benzamide (15e):



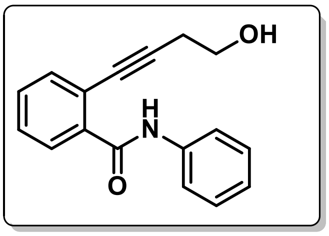
Orange solid; R_f (hexane/ethyl acetate, 7:3) 0.40; mp 105-107 °C, yield 179 mg, 57%; IR (KBr, neat) ν 3339, 2920, 2883, 2230, 1648, 1514, 1320, 1048, 815, 512 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.00 (s, 1 H), 7.84 (d, *J* = 8.5 Hz, 1 H), 7.50 (d, *J* = 8.1 Hz, 2 H), 7.44 (d, *J* = 2.2 Hz, 1 H), 7.31 (dd, *J* = 8.4, 2.2 Hz, 1 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 3.76 (t, *J* = 7.2 Hz, 2 H), 2.80 (s, 1 H), 2.69 (t, *J* = 6.1 Hz, 2 H), 2.31 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.2, 136.9, 135.3, 134.8, 134.7, 133.3, 131.1, 129.8, 128.9, 122.1, 120.5, 96.2, 79.6, 60.8, 24.1, 21.1. HRMS (ESI) calcd. for $C_{18}H_{17}ClNO_2$ $(M + H)^+$ 314.0948, found 314.0937.

4-Fluoro-2-(4-hydroxybut-1-yn-1-yl)-*N*-(*p*-tolyl)benzamide (15f):



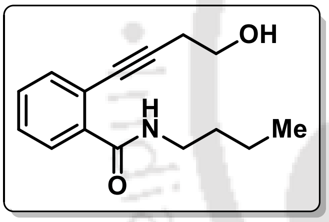
Colourless gum; R_f (hexane/ethyl acetate, 7:3) 0.40; yield 178 mg, 60%; IR (KBr, neat) ν 3344, 2927, 2883, 2230, 1650, 1514, 1322, 1259, 1172, 1051, 815, 609 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.94 (s, 1 H), 7.94 (dd, *J* = 8.8, 5.8 Hz, 1 H), 7.51 (d, *J* = 8.0 Hz, 2 H), 7.19 – 7.13 (m, 3 H), 7.08–7.04 (m, 1 H), 3.77 (t, *J* = 6.1 Hz, 2 H), 2.70 (t, *J* = 6.1 Hz, 3 H), 2.32 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.2, 163.7 (d, *J* = 250.8 Hz), 135.4, 134.6, 132.9 (d, *J* = 3.4 Hz), 132.2 (d, *J* = 9.3 Hz), 129.8, 122.7 (d, J = 10.0 Hz), 120.5, 120.2 (d, J = 23.3 Hz), 116.2 (d, J = 21.4 Hz), 96.1, 79.7 (d, J = 2.8 Hz), 60.8, 24.1, 21.1. ^{19}F NMR (471 MHz, $CDCl_3$) δ 52.6. HRMS (ESI) calcd. for $C_{18}H_{17}FNO_2$ $(M + H)^+$ 298.1238, found 298.1222.

2-(4-Hydroxybut-1-yn-1-yl)-*N*-phenylbenzamide (15g):



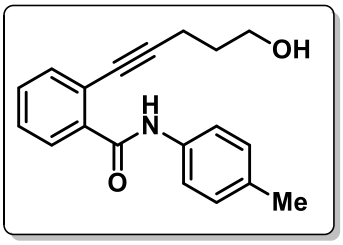
Pale yellow gum; R$_f$ (hexane/ethyl acetate, 7:3) 0.40; yield 217 mg, 82%; IR (KBr, neat) ν 3288, 3060, 2880, 2233, 1649, 1596, 1534, 1439, 1044, 752, 692, 507 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.08 (s, 1 H), 7.87 (dd, J = 7.4, 1.9 Hz, 1 H), 7.64 (d, J = 7.9 Hz, 2 H), 7.46 (dd, J = 7.3, 1.8 Hz, 1 H), 7.38 – 7.30 (m, 4 H), 7.11 (t, J = 7.4 Hz, 1 H), 3.72 (t, J = 6.3 Hz, 2 H), 3.13 (s, 1 H), 2.65 (t, J = 6.2 Hz, 2 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.4, 138.0, 136.4, 133.7, 130.9, 129.4, 129.2, 128.6, 124.8, 120.5, 120.4, 94.7, 80.5, 60.9, 24.1. HRMS (ESI) calcd. for $C_{17}H_{16}NO_2$ $(M + H)^+$ 266.1176, found 266.1158.

***N*-Butyl-2-(4-hydroxybut-1-yn-1-yl)benzamide (15h):**



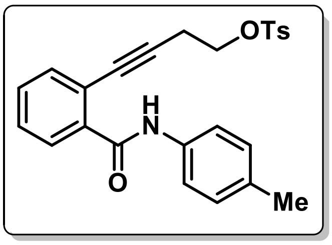
Orange gum; R$_f$ (hexane/ethyl acetate, 7:3) 0.40; yield 208 mg, 85%; IR (KBr, neat) ν 3366, 3286, 2932, 1631, 1536, 1305, 1046, 754, 531 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, J = 6.9, 2.1 Hz, 1 H), 7.44 (d, J = 7.1 Hz, 1 H), 7.38 – 7.29 (m, 3 H), 3.80 (s, 2 H), 3.66 (s, 1 H), 3.42 (q, J = 6.7 Hz, 2 H), 2.67 (t, J = 6.1 Hz, 2 H), 1.60–1.54 (m, 2 H), 1.43–1.36 (m, 2 H), 0.93 (t, J = 7.4 Hz, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 167.3, 136.5, 133.4, 130.3, 129.1, 128.3, 120.5, 93.9, 80.8, 60.8, 40.0, 31.7, 24.1, 20.3, 13.9. HRMS (ESI) calcd. for $C_{15}H_{20}NO_2$ $(M + H)^+$ 246.1489, found 246.1471.

2-(5-Hydroxypent-1-yn-1-yl)-*N*-(*p*-tolyl)benzamide (15i):



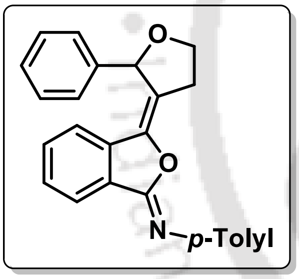
Orange gum; R$_f$ (hexane/ethyl acetate, 7:3) 0.40; yield 220 mg, 75%; IR (KBr, neat) ν 3336, 2922, 2868, 2228, 1650, 1600, 1513, 1322, 1053, 814, 753, 509 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.11 (s, 1 H), 8.06–8.03 (m, 1 H), 7.55 (d, J = 7.9 Hz, 2 H), 7.50 (dd, J = 5.5, 2.5 Hz, 1 H), 7.42–7.40 (m, 2 H), 7.17 (d, J = 7.9 Hz, 2 H), 3.73 (t, J = 6.1 Hz, 2 H), 2.63 (t, J = 6.8 Hz, 2 H), 2.33 (s, 3 H), 1.85–1.80 (m, 2 H), 1.70 (s, 1 H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 164.7, 136.2, 135.7, 134.4, 133.8, 130.9, 130.2, 129.8, 128.7, 120.4, 120.3, 97.4, 79.7, 61.5, 31.3, 21.1, 16.4. HRMS (ESI) calcd. for $C_{19}H_{19}NNaO_2$ $(M + Na)^+$ 316.1308, found 316.1313.

4-(2-(*p*-Tolylcarbamoyl)phenyl)but-3-yn-1-yl 4-methylbenzenesulfonate (15j):



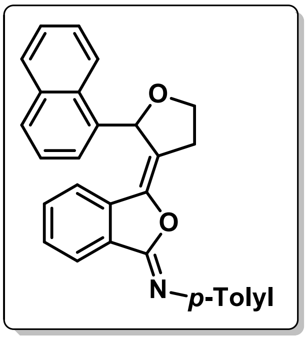
Colorless gum; R_f (hexane/ethyl acetate, 4:1) 0.40; yield 338 mg, 78%; IR (KBr, neat) ν 3362, 3029, 2921, 2246, 1659, 1515, 1358, 1173, 975, 812, 729, 551 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1 H), 7.98 – 7.96 (m, 1 H), 7.71 (d, J = 8.2 Hz, 2 H), 7.51 (d, J = 8.1 Hz, 2 H), 7.44–7.38 (m, 3 H), 7.23 (d, J = 8.0 Hz, 2 H), 7.15 (d, J = 8.0 Hz, 2 H), 4.15 (t, J = 6.7 Hz, 2 H), 2.83 (t, J = 6.7 Hz, 2 H), 2.34 (d, J = 7.9 Hz, 6 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.5, 145.3, 136.6, 135.5, 134.3, 133.9, 132.8, 130.7, 130.1, 129.9, 129.8, 129.0, 127.98, 120.1, 119.4, 91.5, 81.1, 67.5, 21.7, 21.1, 20.8. HRMS (ESI) calcd. for $C_{25}H_{23}NNaO_4S$ $(M + Na)^+$ 456.1240, found 456.1252.

(*NZ*)-4-Methyl-*N*-(3-(2-phenyldihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)aniline (17aa):



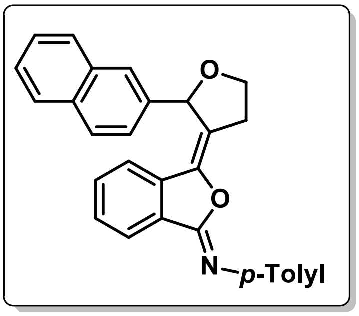
Combined yield 88 mg, 83%; (*E*/*Z*=3:1). For the major *E*-17aa: Orange solid; R_f (hexane/ethyl acetate, 9:1) 0.50; mp 134-136 °C, IR (KBr, neat) ν 3029, 2866, 1670, 1507, 1264, 1048, 1017, 733, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 7.6 Hz, 1 H), 7.46 – 7.40 (m, 5 H), 7.37–7.32 (m, 4 H), 7.21 (d, J = 8.1 Hz, 2 H), 7.04 (d, J = 7.7 Hz, 1 H), 5.99 (s, 1 H), 4.05–3.97 (m, 2 H), 3.23–3.17 (m, 1 H), 3.09 – 3.03 (m, 1 H), 2.39 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.6, 143.6, 143.1, 139.2, 134.9, 134.7, 132.1, 131.5, 129.6, 129.3, 129.1, 128.7, 127.9, 124.6, 123.9, 122.4, 119.7, 80.3, 66.2, 31.9, 21.3. HRMS (ESI) calcd. for $C_{25}H_{22}NO_2$ $(M + H)^+$ 368.1650, found 368.1651. For the minor *Z*-17aa: White Solid; R_f (hexane/ethyl acetate, 9:1) 0.40; mp 158-160 °C, IR (KBr, neat) ν 3028, 2860, 1669, 1504, 1172, 1017, 759, 732, 697, 672, 527 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 7.7 Hz, 1 H), 7.63–7.59 (m, 2 H), 7.50 (t, J = 7.2 Hz, 1 H), 7.40 – 7.30 (m, 5 H), 7.06 (dd, J = 8.3, 3.7 Hz, 2 H), 6.98-6.95 (m, 2 H), 5.80 (s, 1 H), 4.38 (q, J = 6.5 Hz, 1 H), 4.07 (q, J = 7.8 Hz, 1 H), 3.17 (t, J = 6.8 Hz, 2 H), 2.36 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.2, 142.9, 142.2, 141.1, 136.2, 134.5, 132.2, 131.3, 129.5, 129.4, 128.6, 128.2, 128.1, 124.4, 124.1, 121.9, 120.1, 82.9, 68.4, 30.5, 21.3. HRMS (ESI) calcd. for $C_{25}H_{22}NO_2$ $(M + H)^+$ 368.1650, found 368.1648.

(*NZ*)-4-Methyl-N-(3-(2-(naphthalen-1-yl)dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)aniline (17ab):



Combined yield 89 mg, 73% (*E/Z*=6:1). For the major *E*-17ab: White Solid; R$_f$ (hexane/ethyl acetate, 4:1) 0.40; mp 208-210 °C, IR (KBr, neat) ν 3050, 2918, 2863, 1669, 1504, 1042, 1017, 927, 774, 759, 732, 527 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.43 (d, *J* = 8.5 Hz, 1 H), 7.89 (d, *J* = 7.8 Hz, 1 H), 7.85 (d, *J* = 8.2 Hz, 1 H), 7.74 (d, *J* = 8.2 Hz, 1 H), 7.61–7.58 (m, 1 H), 7.51 (t, *J* = 7.6 Hz, 1 H), 7.39 (d, *J* = 8.1 Hz, 2 H), 7.31 – 7.25 (m, 2 H), 7.21 (t, *J* = 7.6 Hz, 1 H), 7.16 (t, *J* = 6.3 Hz, 2 H), 7.08 (t, *J* = 7.6 Hz, 1 H), 6.66 (s, 1 H), 6.59 (d, *J* = 7.8 Hz, 1 H), 4.03–3.98 (m, 1 H), 3.84 (q, *J* = 7.6 Hz, 1 H), 3.23–3.17 (m, 1 H), 3.12 – 3.06 (m, 1 H), 2.32 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 153.6, 143.9, 143.1, 134.8, 134.7, 134.6, 133.5, 132.3, 132.2, 131.4, 129.7, 129.6, 129.2, 129.0, 126.9, 126.2, 125.3, 124.7, 124.67, 124.66, 124.5, 123.8, 122.4, 118.9, 77.6, 66.4, 32.1, 21.3. HRMS (ESI) calcd. for $C_{29}H_{24}NO_2$ $(M + H)^+$ 418.1802, found 418.1815. For the minor *Z*-17ab:Pale yellow gum; R$_f$ (hexane/ethyl acetate, 4:1) 0.40; IR (KBr, neat) ν 2923, 2853, 1671, 1509, 1469, 1042, 1009, 777, 672 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.34 – 8.32 (m, 1 H), 8.01 – 7.95 (m, 2 H), 7.87 (dd, J = 7.7, 1.8 Hz, 1 H), 7.72 (d, J = 7.7 Hz, 1 H), 7.67 – 7.64 (m, 1 H), 7.57 – 7.51 (m, 3 H), 7.44 – 7.39 (m, 2 H), 6.61 (d, J = 8.3 Hz, 2 H), 6.57 (s, 1 H), 6.43 (d, J = 8.2 Hz, 2 H), 4.32 – 4.28 (m, 1 H), 4.21 – 4.17 (m, 1 H), 3.37– 3.26 (m, 2 H), 2.11 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 152.9, 142.25, 142.18, 135.9, 135.2, 134.5, 134.4, 132.4, 132.2, 131.6, 129.5, 129.3, 128.97, 128.91, 126.6, 126.0, 125.9, 125.4, 124.6, 124.4, 124.1, 121.9, 119.2, 80.1, 68.1, 30.8, 21.1.

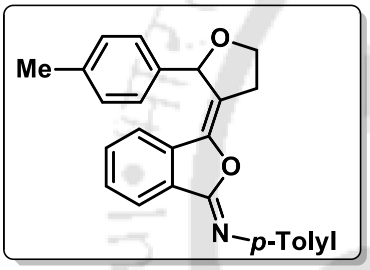
(*NZ*)-4-Methyl-*N*-(3-(2-(naphthalen-2-yl)dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)aniline (17ac):



Combined yield 85 mg, 70% (*E/Z*=2.5:1). For the major *E*-17ac: White Solid; R$_f$ (hexane/ethyl acetate, 4:1) 0.50; mp 174-176 °C, IR (KBr, neat) ν 3053, 2864, 1670, 1507, 1468, 1046, 1017, 817, 754, 672 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89 (d, *J* = 7.7 Hz, 1 H), 7.78–7.67 (m, 4 H), 7.51 (d, *J* = 8.3 Hz, 1 H), 7.39 – 7.34 (m, 4 H), 7.28 (t, *J* = 7.4 Hz, 1 H), 7.19 (t, *J* = 7.7 Hz, 1 H), 7.13 (d, *J* = 8.2 Hz, 2 H), 6.97 (d, *J* = 7.8 Hz, 1 H), 6.06 (s, 1 H), 3.99–3.94 (m, 1 H), 3.88 (q, *J* = 7.6 Hz, 1 H), 3.18–3.10 (m, 1 H), 3.06 – 2.98 (m, 1 H), 2.29 (s, 3 H); ^{13}C{^{1}H} NMR (125

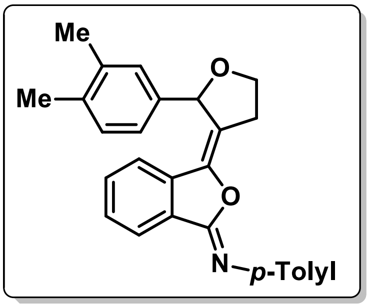
MHz, $CDCl_3$) δ 153.6, 143.8, 143.1, 136.4, 134.9, 134.7, 133.5, 133.4, 132.2, 131.5, 129.6, 129.3, 129.1, 128.4, 127.9, 126.7, 126.6, 126.5, 125.8, 124.6, 123.9, 122.4, 119.4, 80.4, 66.2, 31.9, 21.3. HRMS (ESI) calcd. for $C_{29}H_{24}NO_2$ $(M + H)^+$ 418.1802, found 418.1813. For the minor *Z*-17ac: White Solid; R_f (hexane/ethyl acetate, 4:1) 0.40; mp 149-151 °C, IR (KBr, neat) ν 3053, 2923, 2850, 1672, 1506, 1471, 1024, 817, 759, 479 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.7 Hz, 1 H), 7.86 – 7.77 (m, 4 H), 7.66 – 7.60 (m, 2 H), 7.52–7.47 (m, 4 H), 6.80 (d, *J* = 7.9 Hz, 2 H), 6.70 (d, *J* = 7.9 Hz, 2 H), 5.91 (s, 1 H), 4.47–4.42 (m, 1 H), 4.12 (q, *J* = 7.9 Hz, 1 H), 3.27–3.22 (m, 2 H), 2.25 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.2, 142.6, 142.3, 138.4, 136.2, 134.3, 133.6, 133.5, 132.3, 131.2, 129.5, 129.3, 128.6, 128.5, 127.9, 127.5, 126.3, 126.1, 125.6, 124.1, 122.0, 119.9, 83.1, 68.5, 30.7, 21.2.

(*NZ*)-4-Methyl-*N*-(3-(2-(p-tolyl)dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)aniline (17ad):



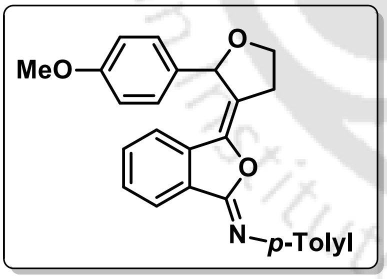
Combined yield 94 mg, 85% (*E/Z*= 4:1). For the major *E*-17ad: White Solid; R_f (hexane/ethyl acetate, 9:1) 0.50; mp 170-172 °C, IR (KBr, neat) ν 2920, 2863, 1779, 1671, 1506, 1049, 1019, 817, 759, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.5 Hz, 1 H), 7.44 – 7.34 (m, 4 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.16 (d, *J* = 7.9 Hz, 2 H), 7.05 (d, *J* = 7.7 Hz, 1 H), 5.96 (s, 1 H), 4.04 – 3.94 (m, 2 H), 3.23–3.15 (m, 1 H), 3.09–3.01 (m, 1 H), 2.38 (s, 3 H), 2.33 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.7, 143.4, 143.1, 138.5, 136.2, 134.9, 134.7, 132.2, 131.5, 129.8, 129.6, 129.2, 127.8, 124.6, 123.9, 122.5, 120.0, 80.2, 66.1, 32.0, 21.4, 21.3. HRMS (ESI) calcd. for $C_{26}H_{24}NO_2$ $(M + H)^+$ 382.1802, found 382.1811. For the minor *Z*-17ad: Pale yellow solid; R_f (hexane/ethyl acetate, 9:1) 0.40; mp 104-106 °C, IR (KBr, neat) ν 2917, 2859, 1776, 1670, 1507, 1269, 1019, 810, 762, 735, 529 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.7 Hz, 1 H), 7.62 – 7.58 (m, 2 H), 7.51–7.48 (m, 1 H), 7.26 (d, *J* = 7.8 Hz, 2 H), 7.14 (d, *J* = 7.8 Hz, 2 H), 7.04 (d, *J* = 8.1 Hz, 2 H), 6.97 (d, *J* = 8.3 Hz, 2 H), 5.73 (s, 1 H), 4.38–4.34 (m, 1 H), 4.05 (q, *J* = 7.8 Hz, 1 H), 3.18 – 3.14 (m, 2 H), 2.35 (d, *J* = 3.4 Hz, 6 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.4, 142.7, 142.1, 138.1, 137.9, 136.2, 134.5, 132.2, 131.2, 129.5, 129.4, 129.3, 127.9, 124.5, 124.1, 121.9, 120.4, 82.7, 68.2, 30.5, 21.5, 21.3.

(*NZ*)-*N*-(3-(2-(3,4-Dimethylphenyl)dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)-4-methylaniline (17ae):



Combined yield 87 mg, 76% (*E/Z*= 5:1). For the major *E*-17ae: Orange solid; R$_f$ (hexane/ethyl acetate, 9:1) 0.50; mp 128-130 °C, IR (KBr, neat) ν 2924, 2859, 1670, 1507, 1264, 1046, 733, 526 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.99 (d, *J* = 7.6 Hz, 1 H), 7.47 – 7.36 (m, 4 H), 7.22 (d, *J* = 7.7 Hz, 3 H), 7.15 (dd, *J* = 7.8, 2.0 Hz, 1 H), 7.11 – 7.06 (m, 2 H), 5.94 (s, 1 H), 4.04–3.97 (m, 2 H), 3.23–3.17 (m, 1 H), 3.10–3.04 (m, 1 H), 2.39 (s, 3 H), 2.25 (d, *J* = 4.4 Hz, 6 H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 153.7, 143.4, 143.1, 137.4, 137.1, 136.6, 135.0, 134.6, 132.1, 131.4, 130.2, 129.6, 129.2, 129.1, 125.2, 124.6, 123.8, 122.5, 120.0, 80.3, 66.1, 32.0, 21.3, 20.1, 19.7. HRMS (ESI) calcd. for $C_{27}H_{26}NO_2$ (M + H)+ 396.1959, found 396.1964. For the minor *Z*-17ae: Orange gum; R$_f$ (hexane/ethyl acetate, 9:1) 0.40; IR (KBr, neat) ν 2920, 2859, 1776, 1670, 1507, 1267, 1024, 730, 519 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98 (d, J = 7.7 Hz, 1 H), 7.63 – 7.59 (m, 2 H), 7.52–7.48 (m, 1 H), 7.15 (s, 1 H), 7.10 (d, J = 1.3 Hz, 2 H), 7.04–6.98 (m, 4 H), 5.73 (s, 1 H), 4.39–4.35 (m, 1 H), 4.06 (q, J = 7.8 Hz, 1 H), 3.19–3.16 (m, 2 H), 2.35 (s, 3 H), 2.24 (d, J = 16.0 Hz, 6 H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 153.4, 142.8, 142.0, 138.6, 136.8, 136.6, 136.3, 134.4, 132.2, 131.3, 129.8, 129.4, 129.3, 129.1, 125.4, 124.5, 124.1, 121.9, 120.4, 82.8, 68.2, 30.5, 21.3, 20.1, 19.8.

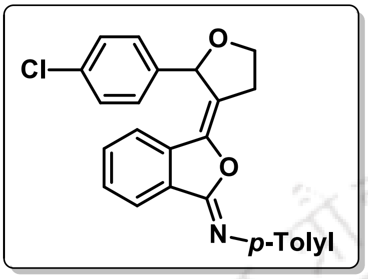
(*NZ*)-*N*-(3-(2-(4-Methoxyphenyl)dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)-4-methylaniline (17af):



Combined yield 102 mg, 88% (*E/Z*= 4:1). For the major *E*-17af: Pale yellow solid; R$_f$ (hexane/ethyl acetate, 4:1) 0.50; mp 167-169 °C, IR (KBr, neat) ν 2920, 2856, 1706, 1670, 1509, 1245, 1024, 825, 762, 529 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98 (d, *J* = 7.6 Hz, 1 H), 7.44–7.40 (m, 3 H), 7.37–7.35 (m, 3 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.03 (d, *J* = 7.8 Hz, 1 H), 6.88 (d, *J* = 8.3 Hz, 2 H), 5.94 (s, 1 H), 4.03–3.95 (m, 2 H), 3.78 (s, 3 H), 3.21–3.15 (m, 1 H), 3.09 – 3.02 (m, 1 H), 2.38 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 159.9, 153.7, 143.4, 143.1, 134.9, 134.7, 132.1, 131.5, 131.4, 129.6, 129.2, 124.6, 123.9, 122.5, 120.1, 114.4, 80.0, 66.1, 55.5, 32.1, 21.3. HRMS (ESI) calcd. for $C_{26}H_{24}NO_3$ (M + H)$^+$ 398.1751, found 398.1747. For the minor *Z*-17af: Pale yellow gum; R$_f$ (hexane/ethyl acetate, 4:1) 0.40; IR (KBr, neat) ν 2922, 2866, 1670, 1507, 1245, 1019, 822, 733, 575 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98 (d, *J* = 7.7 Hz, 1 H), 7.63 – 7.59 (m, 2 H), 7.52–7.48 (m, 1 H), 7.31 – 7.28 (m, 2 H), 7.05 (d, *J* = 8.1 Hz, 2 H), 6.97 (d, *J* = 8.4 Hz, 2 H), 6.88–6.85 (m, 2 H), 5.72 (s, 1 H), 4.38–4.34 (m, 1

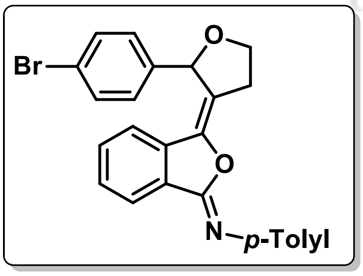
H), 4.04 (q, *J* = 7.8 Hz, 1 H), 3.80 (s, 3 H), 3.18–3.15 (m, 2 H), 2.36 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.6, 153.3, 142.8, 142.1, 136.2, 134.5, 133.3, 132.2, 131.2, 129.5, 129.4, 129.3, 124.5, 124.1, 121.9, 120.4, 114.0, 82.5, 68.1, 55.5, 30.6, 21.3.

(*NZ*)-*N*-(3-(2-(4-Chlorophenyl)dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)-4-methylaniline (17ag):



Combined yield 86 mg, 74% (*E/Z*= 3:1). For the major *E*-17ag: White Solid; R_f (hexane/ethyl acetate, 9:1) 0.50; mp 168-170 °C, IR (KBr, neat) ν 2869, 1670, 1505, 1267, 1048, 1014, 820, 733, 526 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 7.6 Hz, 1 H), 7.46 – 7.40 (m, 3 H), 7.38 (d, J = 8.9 Hz, 3 H), 7.32 (d, J = 8.2 Hz, 2 H), 7.21 (d, J = 7.9 Hz, 2 H), 7.01 (d, J = 7.8 Hz, 1 H), 5.95 (s, 1 H), 4.02 (q, J = 7.5 Hz, 1 H), 3.94 (q, J = 7.5 Hz, 1 H), 3.22–3.15 (m, 1 H), 3.05–3.00 (m, 1 H), 2.38 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.4, 143.8, 142.9, 137.7, 134.8, 134.7, 134.6, 132.2, 131.6, 129.6, 129.5, 129.3, 124.6, 124.1, 122.3, 119.1, 79.5, 66.3, 31.8, 21.3. HRMS (ESI) calcd. for $C_{25}H_{21}ClNO_2$ (M + H)$^+$ 402.1261, found 402.1257. For the minor *Z*-17ag: Orange gum; R_f (hexane/ethyl acetate, 9:1) 0.40; IR (KBr, neat) ν 2924, 2859, 1776, 1706, 1670, 1509, 1269, 1014, 759, 733, 524 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.8 Hz, 1 H), 7.60 (s, 2 H), 7.53–7.50 (m, 1 H), 7.29–7.23 (m, 4 H), 7.07 (d, *J* = 7.9 Hz, 2 H), 6.94 (d, *J* = 7.9 Hz, 2 H), 5.68 (s, 1 H), 4.38–4.34 (m, 1 H), 4.05 (q, *J* = 7.9 Hz, 1 H), 3.14 (s, *J* = 6.3 Hz, 2 H), 2.37 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.4, 142.8, 142.3, 139.4, 136.1, 134.6, 133.9, 132.4, 131.0, 129.7, 129.5, 129.4, 128.7, 124.2, 123.9, 121.9, 119.7, 82.1, 68.5, 30.3, 21.3.

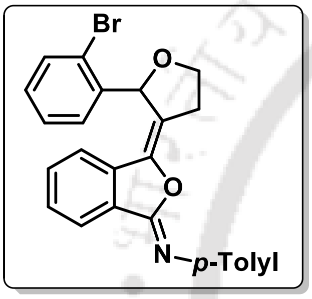
(*NZ*)-*N*-(3-(2-(4-Bromophenyl)dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)-4-methylaniline (17ah):



Combined yield 93 mg, 72% (*E/Z*= 3:1). For the major *E*-17ah. Orange solid; R_f (hexane/ethyl acetate, 9:1) 0.50; mp 134-136 °C, IR (KBr, neat) ν 2924, 2869, 1670, 1507, 1264, 1048, 1012, 733, 526 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.6 Hz, 1 H), 7.49 – 7.38 (m, 6 H), 7.31 (d, *J* = 8.5 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.01 (d, *J* = 7.7 Hz, 1 H), 5.94 (s, 1 H), 4.04–4.00 (m, 1 H), 3.96 – 3.91 (m, 1 H), 3.21–3.15 (m, 1 H), 3.05 – 2.98 (m, 1 H), 2.38 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.4, 143.8, 142.9, 138.2, 134.8, 134.7, 132.3, 132.2, 131.6, 129.6, 129.5, 124.6, 124.1, 122.8, 122.3, 118.9, 79.6, 66.3, 31.8, 21.3. HRMS (ESI) calcd. for $C_{25}H_{21}BrNO_2$ (M +

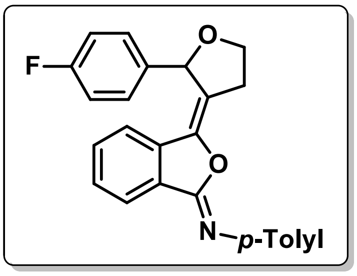
H)$^+$ 446.0755, found 446.0752. For the minor *Z*-17ah: Orange solid; R$_f$ (hexane/ethyl acetate, 9:1) 0.40; mp 112-114 °C, IR (KBr, neat) ν 2927, 2859, 1776, 1708, 1672, 1509, 1264, 1012, 733, 519 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98 (d, *J* = 7.7 Hz, 1 H), 7.62–7.60 (m, 2 H), 7.53–7.50 (m, 1 H), 7.41 (d, *J* = 8.4 Hz, 2 H), 7.21 (d, *J* = 8.4 Hz, 2 H), 7.08 (d, *J* = 8.0 Hz, 2 H), 6.94 (d, *J* = 8.3 Hz, 2 H), 5.67 (s, 1 H), 4.39–4.36 (m, 1 H), 4.05 (q, *J* = 8.0 Hz, 1 H), 3.16 – 3.13 (m, 2 H), 2.37 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 153.2, 142.9, 142.3, 140.0, 136.1, 134.5, 132.4, 131.7, 131.1, 129.7, 129.6, 129.5, 124.2, 123.9, 122.1, 121.9, 119.5, 82.2, 68.5, 30.3, 21.3.

(*NZ*)-*N*-(3-(2-(2-Bromophenyl)dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)-4-methylaniline (17ai):



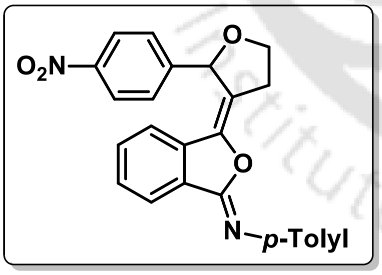
Combined yield 88 mg, 68% (*E/Z*= 2.5:1). For the major *E*-17ag. Pale yellow solid; R$_f$ (hexane/ethyl acetate, 9:1) 0.50; mp 188-190 °C, IR (KBr, neat) ν 2922, 2864, 1670, 1507, 1468, 1043, 1019, 754, 669, 529 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.96 (d, *J* = 7.5 Hz, 1 H), 7.71 – 7.69 (m, 1 H), 7.45 – 7.35 (m, 4 H), 7.24 – 7.16 (m, 5 H), 6.86 (d, *J* = 7.6 Hz, 1 H), 6.35 (s, 1 H), 4.08 – 3.99 (m, 2 H), 3.28 – 3.22 (m, 1 H), 3.20–3.14 (m, 1 H), 2.39 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 153.4, 143.7, 142.9, 138.1, 134.8, 134.5, 133.8, 132.3, 131.4, 130.5, 129.6, 129.4, 129.2, 128.0, 125.6, 124.6, 123.9, 122.1, 119.1, 79.8, 66.5, 32.5, 21.3. HRMS (ESI) calcd. for $C_{25}H_{21}BrNO_2$ (M + H)$^+$ 446.0755, found 446.0756. For the minor *Z*-17ag: Pale yellow solid; R$_f$ (hexane/ethyl acetate, 9:1) 0.40; mp 92-94 °C, IR (KBr, neat) ν 2920, 2866, 1779, 1706, 1672, 1509, 1271, 1021, 757, 529 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.97 (d, *J* = 7.7 Hz, 1 H), 7.67–7.62 (m, 3 H), 7.52 (t, *J* = 7.4 Hz, 1 H), 7.27 – 7.22 (m, 2 H), 7.19 – 7.16 (m, 1 H), 6.98 (d, *J* = 7.9 Hz, 2 H), 6.87 (d, *J* = 8.0 Hz, 2 H), 6.19 (s, 1 H), 4.36–4.31 (m, 1 H), 4.12 (d, *J* = 8.0 Hz, 1 H), 3.31–3.19 (m, 2 H), 2.33 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 152.7, 142.4, 142.3, 139.1, 135.8, 134.8, 133.4, 132.2, 131.6, 130.2, 130.1, 129.6, 129.4, 127.8, 125.3, 124.9, 124.1, 121.9, 118.9, 82.4, 68.4, 31.1, 21.4.

(*NZ*)-*N*-(3-(2-(4-Fluorophenyl)dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)-4-methylaniline (17aj):



Combined yield 81 mg, 72% (*E/Z*= 3:1). For the major *E*-17aj. Orange solid; R_f (hexane/ethyl acetate, 9:1) 0.50; mp 137-139 °C, IR (KBr, neat) ν 2920, 2869, 1670, 1504, 1223, 1046, 1017, 825, 733, 563 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.7 Hz, 1 H), 7.44 – 7.35 (m, 6 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 7.05 – 6.98 (m, 3 H), 5.95 (s, 1 H), 4.03 – 3.93 (m, 2 H), 3.21 – 3.15 (m, 1 H), 3.06–2.99 (m, 1 H), 2.37 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.9 (d, *J* =245.8 Hz), 153.5, 143.7, 142.9, 135.1 (d, *J* =3.2 Hz) 134.8 (d, *J* = 5.9 Hz), 132.2, 131.6, 129.7 (d, *J* = 5.2), 129.6, 129.4, 124.6, 124.0, 122.3, 119.5, 116.0 (d, *J* = 21.4 Hz), 79.6, 66.2, 31.9, 21.3. ^{19}F NMR (377 MHz, $C_6F_6/CDCl_3$) δ 48.28; HRMS (ESI) calcd. for $C_{25}H_{21}FNO_2$ $(M + H)^+$ 386.1556, found 386.1552. For the minor *Z*-17aj: Pale yellow solid; R_f (hexane/ethyl acetate, 9:1) 0.40; mp 101-103 °C, IR (KBr, neat) ν 2922, 2864, 1776, 1672, 1507, 1225, 1019, 733, 529 cm^{-1}; ^1H NMR (500 MHz, CDCl3) δ 7.98 (d, *J* = 7.8 Hz, 1 H), 7.61 (d, *J* = 4.2 Hz, 2 H), 7.53–7.49 (m, 1 H), 7.33 – 7.29 (m, 2 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 7.01 – 6.94 (m, 4 H), 5.71 (s, 1 H), 4.39–4.35 (m, 1 H), 4.05 (q, *J* = 7.9 Hz, 1 H), 3.17–3.14 (m, 2 H), 2.37 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.7 (d, *J* = 244.7 Hz), 153.3, 142.9, 142.3, 136.8 (d, *J* = 3.2 Hz), 136.1, 134.5, 132.3, 131.2, 129.8 (d, *J* = 8.2 Hz), 129.6, 129.4, 124.2, 124.1, 121.9, 119.9, 115.4 (d, *J* = 21.3 Hz), 82.2, 68.4, 30.4, 21.3. ^{19}F NMR (377 MHz, $C_6F_6/CDCl_3$) δ 47.41.

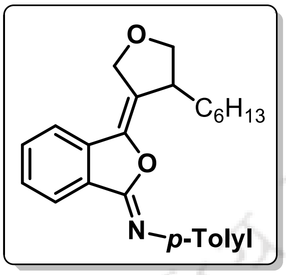
(*NZ*)-4-Methyl-*N*-(3-(2-(4-nitrophenyl)dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)aniline (17ak):



Combined yield 79 mg, 66% (*E/Z*= 2.5:1). For the major *E*-17ak. Pale yellow solid; R_f (hexane/ethyl acetate, 4:1) 0.40; mp 152-154 °C, IR (KBr, neat) ν 2923, 2865, 1671, 1514, 1342, 1047, 1017, 817, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.7 Hz, 2 H), 8.03 (d, *J* = 7.5 Hz, 1 H), 7.62 (d, *J* = 8.7 Hz, 2 H), 7.49 – 7.39 (m, 4 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 7.00 (d, *J* = 7.6 Hz, 1 H), 6.06 (s, 1 H), 4.13–4.05 (m, 1 H), 3.96 – 3.89 (m, 1 H), 3.26–3.18 (m, 1 H), 3.06–2.97 (m, 1 H), 2.38 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.0, 148.2, 146.3, 144.2, 142.8, 135.0, 134.5, 132.4, 131.8, 129.9, 129.7, 129.6, 128.7, 124.6, 124.4, 124.3, 121.9, 117.9, 79.1, 66.6, 31.4, 21.3. HRMS (ESI) calcd. for $C_{25}H_{21}N_2O_4$ $(M + H)^+$ 413.1501, found 413.1502. For the minor *Z*-17ak: Pale yellow solid; R_f (hexane/ethyl acetate, 4:1) 0.40; mp 161-163 °C, IR (KBr, neat) ν 2862, 1672, 1514, 1342, 1017, 764, 699, 524 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2 H), 7.97 (d, *J* = 7.7 Hz, 1 H), 7.64 – 7.59 (m, 2 H), 7.54 – 7.51 (m, 1 H), 7.44

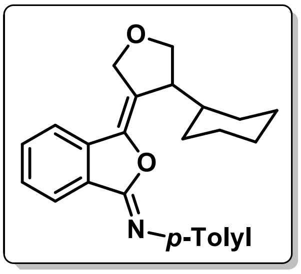
(d, *J* = 8.4 Hz, 2 H), 7.11 (d, *J* = 8.1 Hz, 2 H), 6.93 (d, *J* = 8.0 Hz, 2 H), 5.76 (s, 1 H), 4.46–4.42 (m, 1 H), 4.10 (q, *J* = 8.6 Hz, 1 H), 3.18–3.14 (m, 2 H), 2.40 (s, 3 H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 153.2, 148.1, 147.6, 143.3, 142.6, 135.9, 134.5, 132.5, 130.9, 129.9, 129.5, 128.7, 124.2, 123.7, 123.3, 122.0, 118.8, 81.7, 69.0, 30.0, 21.3.

(*NZ*)-*N*-(3-(2-Hexyldihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)-4-methylaniline (17al):



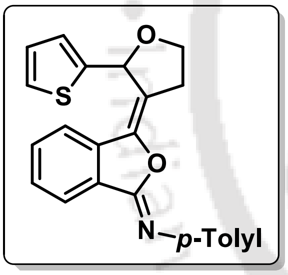
Combined yield 87 mg, 80% (*E/Z*= 0.67:1). For the minor *E*-17al. White Solid; R$_f$ (hexane/ethyl acetate, 9:1) 0.50; mp 82-84 °C, IR (KBr, neat) ν 2924, 2856, 1672, 1507, 1468, 1029, 759, 672, 529 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.7 Hz, 1 H), 7.60 (t, *J* = 7.6 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.39 (d, *J* = 7.9 Hz, 3 H), 7.18 (d, *J* = 7.9 Hz, 2 H), 5.04 (s, *J* = 5.2 Hz, 1 H), 4.08–4.04 (m, 1 H), 3.94 (q, *J* = 7.5 Hz, 1 H), 3.04 – 2.98 (m, 1 H), 2.93 – 2.86 (m, 1 H), 2.36 (s, 3 H), 1.71 – 1.66 (m, 2 H), 1.60 – 1.51 (m, 2 H), 1.35 – 1.30 (m, 6 H), 0.89 (t, *J* = 7.0 Hz, 3 H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 153.7, 143.2, 141.6, 135.1, 134.5, 132.2, 131.6, 129.5, 129.1, 124.5, 124.2, 123.0, 121.9, 78.4, 66.2, 33.9, 32.1, 30.9, 29.4, 26.2, 22.8, 21.3, 14.3. For the major *Z*-17al:Orange gum; R$_f$ (hexane/ethyl acetate, 9:1) 0.40; IR (KBr, neat) ν 2953, 2925, 2858, 1776, 1701, 1516, 1374, 1272, 1022, 812, 767, 692 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.8 Hz, 1 H), 7.52 – 7.46 (m, 2 H), 7.41 (t, *J* = 7.5 Hz, 1 H), 7.24 (d, *J* = 7.8 Hz, 2 H), 7.08 (d, *J* = 8.1 Hz, 2 H), 4.74 (d, *J* = 8.3 Hz, 1 H), 4.13–4.08 (m, 1 H), 3.86 (q, *J* = 7.7 Hz, 1 H), 2.92 – 2.83 (m, 2 H), 2.28 (s, 3 H), 1.87–1.80 (m, 1 H), 1.66–1.58 (m, 1 H), 1.38–1.34 (m, 2 H), 1.25 – 1.18 (m, 6 H), 0.80 (t, *J* = 7.2 Hz, 3 H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 153.8, 143.2, 140.9, 136.4, 134.5, 132.2, 131.0, 129.5, 129.2, 124.3, 124.1, 121.8, 121.4, 81.1, 67.5, 33.8, 32.1, 30.1, 29.5, 25.9, 22.9, 21.2, 14.3. HRMS (ESI) calcd. for $C_{25}H_{30}NO_2$ $(M + H)^+$ 376.2276, found 376.2298.

(*NZ*)-*N*-(3-(2-Cyclohexyldihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)-4-methylaniline (17am):



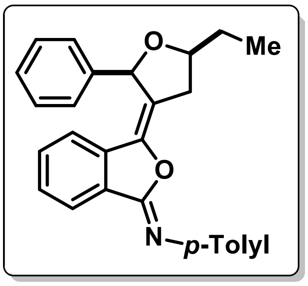
Combined yield 79 mg, 73% (*E/Z*= 0.5:1). For the minor *E*-17am. White Solid; R$_f$ (hexane/ethyl acetate, 9:1) 0.50; mp 144-146 °C, IR (KBr, neat) ν 2922, 2852, 1670, 1502, 1026, 934, 759, 733, 672, 527 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.7 Hz, 1 H), 7.60 (t, *J* = 7.6 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 7.43 (d, *J* = 7.8 Hz, 1 H), 7.39 (d, *J* = 8.0 Hz, 2 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 4.89 (t, *J* = 2.8 Hz, 1 H), 4.15–4.11 (m, 1 H), 3.86 (q, *J* = 8.0 Hz, 1 H), 3.09–3.04 (m, 1 H), 2.85 – 2.78 (m, 1 H), 2.36 (s, 3 H), 1.82 – 1.65 (m, 6 H), 1.48 – 1.39 (m, 1 H), 1.28 – 1.20 (m, 2 H), 1.18 – 1.11 (m, 2 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.7, 143.2, 142.1, 135.2, 134.6, 132.2, 131.7, 129.6, 129.1, 124.5, 124.2, 122.3, 122.2, 82.3, 67.3, 43.1, 31.4, 30.6, 27.2, 26.9, 26.5, 26.4, 21.3. For the major *Z*-17am: Pale yellow gum; R_f (hexane/ethyl acetate, 9:1) 0.40; IR (KBr, neat) ν 2927, 2852, 1774, 1670, 1509, 1264, 1019, 733, 512 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.7 Hz, 1 H), 7.62 – 7.57 (m, 2 H), 7.52–7.49 (m, 1 H), 7.32 (d, *J* = 8.3 Hz, 2 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 4.67 (t, *J* = 3.0 Hz, 1 H), 4.24–4.20 (m, 1 H), 3.89 (q, *J* = 7.0 Hz, 1 H), 3.04–2.98 (m, 1 H), 2.91–2.84 (m, 1 H), 2.37 (s, 3 H), 2.05–1.99 (m, 1 H), 1.83 – 1.65 (m, 6 H), 1.59–1.56 (m, 1 H), 1.40 – 1.33 (m, 1 H), 1.27 – 1.20 (m, 2 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.9, 143.3, 141.0, 136.5, 134.5, 132.3, 131.0, 129.4, 129.2, 124.3, 124.1, 121.9, 120.6, 85.4, 68.1, 41.9, 30.8, 30.4, 27.1, 26.8, 26.7, 26.6, 21.3. HRMS (ESI) calcd. for $C_{25}H_{28}NO_2$ (M + H)$^+$ 374.2120, found 374.2122.

(*NZ*)-4-Methyl-*N*-(3-(2-(thiophen-2-yl)dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)aniline (17an)



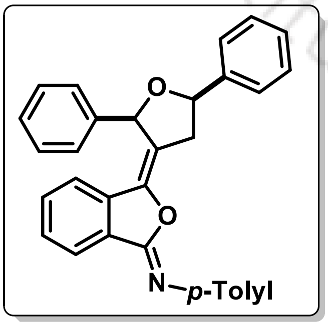
Combined yield 63 mg, 58% (*E*/*Z*= 3:1). For the major *E*-17an. Pale yellow gum; R_f (hexane/ethyl acetate, 9:1) 0.40; IR (KBr, neat) ν 2919, 2866, 1778, 1668, 1506, 1231, 1043, 1012, 761, 702, 529 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 6.5 Hz, 1 H), 7.47 – 7.41 (m, 4 H), 7.29 (d, *J* = 5.1 Hz, 1 H), 7.22–7.19 (m, 3 H), 7.06 (d, *J* = 3.6 Hz, 1 H), 6.95 (dd, *J* = 4.8 Hz, 3.2 Hz, 1 H), 6.21 (s, 1 H), 4.12–4.07 (m, 1 H), 4.04 (q, *J* = 7.9 Hz, 1 H), 3.17 – 3.06 (m, 2 H), 2.38 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.5, 143.8, 143.2, 142.9, 134.8, 134.7, 132.2, 131.5, 129.6, 129.5, 127.2, 126.6, 126.5, 124.6, 123.9, 122.5, 119.9, 75.5, 66.3, 31.2, 21.3. HRMS (ESI) calcd. for $C_{23}H_{20}NO_2S$ (M + H)$^+$ 374.1209, found 374.1215. For the minor *Z*-17an. Pale yellow gum; R_f (hexane/ethyl acetate, 9:1) 0.40; IR (KBr, neat) ν 2917, 2866, 1778, 1671, 1506, 1470, 1228, 1015, 763, 700, 527 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.8 Hz, 1 H), 7.63–7.61 (m, 2 H), 7.54–7.51 (m, 1 H), 7.29 (d, *J* = 5.1 Hz, 1 H), 7.07 (s, 5 H), 7.00 (dd, *J* = 5.0, 3.4 Hz, 1 H), 6.10 (s, 1 H), 4.33 (q, *J* = 6.1 Hz, 1 H), 4.14 (q, *J* = 8.4 Hz, 1 H), 3.21 – 3.09 (m, 2 H), 2.35 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.5, 144.6, 142.7, 142.3, 136.0, 134.9, 132.4, 131.2, 129.7, 129.5, 126.8, 126.4, 125.9, 124.6, 124.3, 122.0, 119.8, 77.7, 67.9, 29.8, 21.3.

(*NZ*)-*N*-(3-((2*R*,5*S*)-5-Ethyl-2-phenyldihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)-4-methylaniline (17ba):



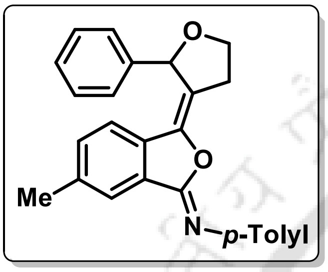
Combined yield 90 mg, 78% (*E/Z*= 4:1). For the major *E*-17ba. Pale yellow gum; R_f (hexane/ethyl acetate, 9:1) 0.40; IR (KBr, neat) ν 2966, 2876, 1774, 1706, 1512, 1267, 1014, 735, 694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.7 Hz, 1 H), 7.46–7.40 (m, 4 H), 7.38 – 7.34 (m, 3 H), 7.32–7.29 (m, 2 H), 7.22 (d, *J* = 7.9 Hz, 2 H), 6.96 (d, *J* = 7.9 Hz, 1 H), 5.86 (s, 1 H), 4.05–3.99 (m, 1 H), 3.31 (dd, *J* = 16.1, 5.1 Hz, 1 H), 2.71–2.65 (m, 1 H), 2.39 (s, 3 H), 1.82–1.73 (m, 1 H), 1.69–1.62 (m, 1 H), 0.99 (t, *J* = 7.5 Hz, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.6, 143.2, 143.1, 140.4, 134.7, 134.6, 132.0, 131.6, 129.6, 129.2, 129.1, 128.7, 128.3, 124.5, 123.8, 122.7, 121.8, 81.0, 80.9, 38.1, 28.4, 21.3, 10.5. HRMS (ESI) calcd. for $C_{27}H_{26}NO_2$ $(M + H)^+$ 396.1963, found 396.1962. For the minor *Z*-17ba. Pale yellow gum; R_f (hexane/ethyl acetate, 9:1) 0.40; IR (KBr, neat) ν 2963, 2873, 1776, 1708, 1517, 1269, 1019, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.6 Hz, 1 H), 7.62 – 7.57 (m, 2 H), 7.48 (t, *J* = 7.5 Hz, 1 H), 7.38 – 7.29 (m, 5 H), 7.08 (d, *J* = 7.9 Hz, 2 H), 6.92 (d, *J* = 7.8 Hz, 2 H), 5.68 (s, 1 H), 4.09–4.04 (m, 1 H), 3.22 (dd, *J* = 15.3, 5.2 Hz, 1 H), 2.81 – 2.75 (m, 1 H), 2.37 (s, 3 H), 1.97 – 1.92 (m, 1 H), 1.84 – 1.79 (m, 1 H), 1.09 (t, *J* = 7.5 Hz, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.3, 142.9, 141.9, 141.4, 136.3, 134.4, 132.2, 131.2, 129.4, 129.3, 128.5, 128.4, 128.2, 124.3, 124.0, 121.9, 121.5, 83.2, 81.7, 36.3, 28.2, 21.3, 10.5.

(*NZ*)-*N*-(3-(2,5-Diphenyldihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)-4-methylaniline (17ca)



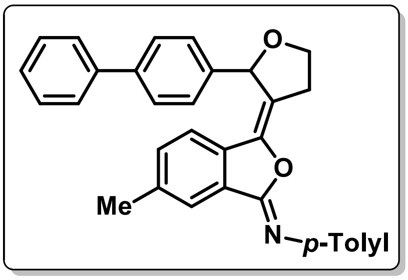
Combined yield 80 mg, 62% (*E/Z*= 2.3:1), Pale yellow gum; R_f (hexane/ethyl acetate, 9:1) 0.40; IR (KBr, neat) ν 3028, 2919, 2858, 1778, 1673, 1506, 1045, 1012, 748, 700, 527 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.7, 4.7 Hz, 1 H), 7.52 – 7.48 (m, 1 H), 7.45 (d, *J* = 7.5 Hz, 2 H), 7.40–7.37 (m, 1 H), 7.32 – 7.28 (m, 5 H), 7.27–7.24 (m, 3 H), 7.21 – 7.17 (m, 1 H), 7.10 (d, *J* = 8.0 Hz, 1 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 6.87 (d, *J* = 8.1 Hz, 1 H), 5.94 (d, *J* = 2.6 Hz, 1 H, major), 5.76 (d, *J* =2.8 Hz, 1 H, minor), 5.10 (dd, *J* = 10.6, 5.4 Hz, 1 H, minor), 5.00 (dd, *J* = 10.8, 5.2 Hz, 1 H, major), 3.53 (dd, *J* = 16.0, 5.2 Hz, 1 H, major), 3.46 (dd, *J* = 15.5, 5.4 Hz, 1 H, minor), 3.06–3.01 (m, 1 H, minor), 2.95–2.89 (m, 1 H, major), 2.30 (s, 1 H, minor), 2.27 (s, 2 H, major); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.5, 153.2, 143.3, 143.1, 142.8, 142.1, 141.1, 140.7, 140.0, 136.2, 134.7, 134.6, 134.5, 132.2, 132.0, 131.7, 131.2, 129.6, 129.5, 129.4, 129.3, 129.2, 128.85, 128.83, 128.7, 128.6, 128.5, 128.4, 128.39, 128.34, 128.2, 126.6, 126.4, 124.5, 124.4, 124.1, 123.9, 122.8, 121.9, 121.0, 120.7, 83.5, 81.7, 81.3, 81.2, 41.7, 39.6, 21.4, 21.3. HRMS (ESI) calcd. for $C_{31}H_{26}NO_2$ $(M + H)^+$ 444.1963, found 444.1964.

(*NZ*)-4-Methyl-*N*-(6-methyl-3-(2-phenyldihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)aniline (17da):



Combined yield 81 mg, 73% (*E/Z*= 3.5:1). For the major *E*-17da. White Solid; R_f (hexane/ethyl acetate, 9:1) 0.50; mp 145-147 °C, IR (KBr, neat) ν 2924, 2871, 1771, 1703, 1514, 1371, 1274, 1053, 820, 701, 514 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1 H), 7.43 (d, J = 6.4 Hz, 4 H), 7.37 – 7.29 (m, 3 H), 7.19 (dd, *J* = 16.8, 8.0 Hz, 3 H), 6.91 (d, *J* = 8.0 Hz, 1 H), 5.96 (s, 1 H), 4.04 – 3.96 (m, 2 H), 3.22–3.15 (m, 1 H), 3.07–3.01 (m, 1 H), 2.39 (d, *J* = 11.7 Hz, 6 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.8, 143.6, 143.1, 139.8, 139.3, 134.6, 133.4, 132.5, 131.8, 129.6, 129.0, 128.6, 127.9, 124.6, 123.9, 122.2, 118.6, 80.3, 66.3, 31.9, 21.6, 21.3 HRMS (ESI) calcd. for $C_{26}H_{24}NO_2$ $(M + H)^+$ 382.1807, found 382.1805. For the minor *Z*-17da: Pale yellow gum; R_f (hexane/ethyl acetate, 9:1) 0.40; IR (KBr, neat) ν 2915, 2861, 1776, 1703, 1670, 1509, 1269, 1024, 817, 735, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.41 (d, *J* = 8.4 Hz, 1 H), 7.38 – 7.30 (m, 5 H), 7.04 (d, *J* = 8.0 Hz, 2 H), 6.94 (d, *J* = 8.2 Hz, 2 H), 5.75 (s, 1 H), 4.39 – 4.35 (m, 1 H), 4.06 (q, *J* = 8.0 Hz, 1 H), 3.17 – 3.14 (m, 2 H), 2.47 (s, 3 H), 2.35 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.4, 142.9, 142.2, 141.2, 140.0, 134.4, 133.8, 133.5, 131.5, 129.4, 128.6, 128.2, 128.1, 124.4, 124.1, 121.7, 119.0, 82.8, 68.4, 30.5, 21.7, 21.3.

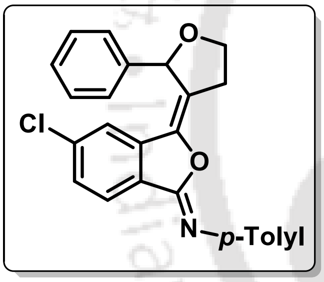
(*NZ*)-*N*-(3-(2-([1,1'-Biphenyl]-4-yl)dihydrofuran-3(2*H*)-ylidene)-6-methylisobenzofuran-1(3*H*)-ylidene)-4-methylaniline (17do):



Combined yield 85 mg, 64% (*E/Z*= 2.5:1). For the major *E*-17do: White Solid; R_f (hexane/ethyl acetate, 9:1) 0.40; mp 225-227 °C, IR (KBr, neat) ν 2922, 2856, 1774, 1672, 1509, 1487, 1053, 820, 762, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1 H), 7.58–7.56 (m, 4 H), 7.50 (d, *J* = 8.2 Hz, 2 H), 7.45 – 7.41 (m, 4 H), 7.36 – 7.32 (m, 1 H), 7.22–

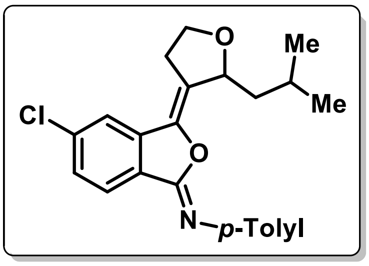
7.19 (m, 3 H), 6.99 (d, *J* = 8.0 Hz, 1 H), 6.01 (s, 1 H), 4.07 – 4.00 (m, 2 H), 3.24–3.18 (m, 1 H), 3.10 – 3.04 (m, 1 H), 2.40 (d, *J* = 13.1 Hz, 6 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.8, 143.7, 143.1, 141.5, 140.8, 139.9, 138.3, 134.7, 133.5, 132.6, 131.8, 129.6, 129.0, 128.3, 127.8, 127.7, 127.3, 124.6, 124.0, 122.3, 118.6, 80.1, 66.4, 31.9, 21.6, 21.3. HRMS (ESI) calcd. for $C_{32}H_{28}NO_2$ $(M + H)^+$ 458.2120, found 458.2115. For the minor *Z*-17do: Pale yellow gum; R_f (hexane/ethyl acetate, 9:1) 0.40; IR (KBr, neat) ν 2922, 2859, 1777, 1670, 1485, 1274, 1026, 820, 735, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1 H), 7.58 – 7.51 (m, 5 H), 7.45 – 7.41 (m, 5 H), 7.36 – 7.33 (m, 1 H), 7.03 (d, *J* = 8.1 Hz, 2 H), 6.99 (d, *J* = 8.3 Hz, 2 H), 5.80 (s, 1 H), 4.42 – 4.38 (m, 1 H), 4.09 (q, *J* = 8.0 Hz, 1 H), 3.19–3.16 (m, 2 H), 2.48 (s, 3 H), 2.32 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.5, 143.0, 142.3, 141.2, 141.1, 140.1, 140.0, 134.4, 133.8, 133.5, 131.5, 129.4, 128.9, 128.4, 127.5, 127.4, 124.3, 124.2, 121.7, 118.9, 82.5, 68.4, 30.4, 21.7, 21.3.

(*NZ*)-*N*-(5-Chloro-3-(2-phenyldihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)-4-methylaniline (17ea):



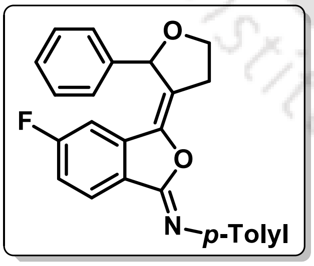
Combined yield 73 mg, 62% (*E/Z*= 3:1). For the major *E*-17ea: White Solid; R_f (hexane/ethyl acetate, 9:1) 0.50; mp 153-155 °C, IR (KBr, neat) ν 2920, 2864, 1670, 1504, 1429, 1264, 1048, 1021, 825, 735, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.2 Hz, 1 H), 7.44 – 7.40 (m, 4 H), 7.38 – 7.33 (m, 4 H), 7.20 (d, *J* = 8.1 Hz, 2 H), 6.97 (s, 1 H), 5.91 (s, 1 H), 4.03 (t, *J* = 7.4 Hz, 2 H), 3.23–3.17 (m, 1 H), 3.11–3.04 (m, 1 H), 2.38 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 152.4, 142.7, 142.4, 138.9, 138.4, 136.1, 135.0, 130.0, 129.8, 129.6, 129.3, 129.0, 127.9, 125.0, 124.7, 122.5, 121.7, 80.5, 66.3, 32.3, 21.3. HRMS (ESI) calcd. for $C_{25}H_{21}ClNO_2$ $(M + H)^+$ 402.1261, found 402.1259. For the minor *Z*-17ea: Pale yellow solid; R_f (hexane/ethyl acetate, 9:1) 0.40; mp 142-144 °C, IR (KBr, neat) ν 2924, 2859, 1779, 1672, 1507, 1429, 1170, 1024, 832, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 1 H), 7.59 (s, 1 H), 7.47 (dd, *J* = 8.3, 1.8 Hz, 1 H), 7.38 – 7.31 (m, 5 H), 7.04 (d, *J* = 8.0 Hz, 2 H), 6.93 (d, *J* = 8.0 Hz, 2 H), 5.74 (s, 1 H), 4.41 – 4.37 (m, 1 H), 4.10–4.04 (m, 1 H), 3.19–3.15 (m, 2 H), 2.35 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 152.0, 142.4, 141.2, 140.7, 138.5, 137.6, 134.8, 129.9, 129.8, 129.5, 128.7, 128.4, 128.1, 125.2, 124.5, 122.0, 121.6, 83.0, 68.3, 30.6, 21.3.

(*NZ*)-*N*-(5-Chloro-3-(2-isobutyldihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)-4-methylaniline (17ep):



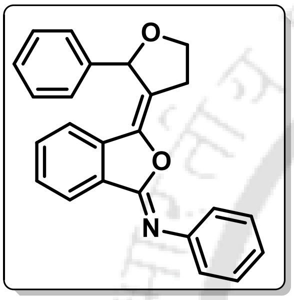
Combined yield 78 mg, 70% (*E/Z*= 0.25:1). For the minor *E*-17ep: Pale yellow solid; R_f (hexane/ethyl acetate, 9:1) 0.50; mp 99-101 °C, IR (KBr, neat) ν 2965, 2866, 1779, 1706, 1672, 1606, 1509, 1072, 1029, 825, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.8 Hz, 1 H), 7.46 (d, *J* = 7.2 Hz, 1 H), 7.41 – 7.36 (m, 3 H), 7.18 (d, *J* = 7.4 Hz, 2 H), 5.10 (d, *J* = 11.1 Hz, 1 H), 4.05 (q, *J* = 7.5 Hz, 1 H), 3.96 (q, *J* = 7.3 Hz, 1 H), 3.03 – 2.88 (m, 2 H), 2.37 (s, 3 H), 2.04–1.97 (m, 1 H), 1.69–1.62 (m, 1 H), 1.39 – 1.32 (m, 1 H), 1.16 (d, *J* = 6.6 Hz, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 152.6, 142.8, 140.3, 138.5, 136.4, 134.9, 130.0, 129.6, 129.5, 125.3, 124.9, 124.6, 122.1, 76.5, 65.9, 42.2, 30.8, 25.4, 24.0, 21.5, 21.3. For the major *Z*-17ep: Pale yellow solid; R_f (hexane/ethyl acetate, 9:1) 0.40; mp 137-139 °C, IR (KBr, neat) ν 2963, 2869, 1779, 1670, 1507, 1427, 1284, 1070, 1036, 825, 735, 514 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 1 H), 7.51 (s, 1 H), 7.45 (dd, *J* = 8.2, 1.8 Hz, 1 H), 7.37 – 7.34 (m, 2 H), 7.16 (d, *J* = 8.2 Hz, 2 H), 4.91 (d, *J* = 10.4 Hz, 1 H), 4.20–4.16 (m, 1 H), 3.01–3.96 (m, 1 H), 2.96–2.93 (m, 2 H), 2.36 (s, 3 H), 1.91–1.85 (m, 1 H), 1.72 – 1.67 (m, 1 H), 1.60–1.54 (m, 1 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.7 Hz, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 152.5, 142.8, 139.8, 138.5, 137.7, 134.9, 129.6, 129.5, 125.2, 124.6, 123.5, 121.8, 79.5, 67.3, 42.3, 29.9, 25.4, 24.1, 21.6, 21.3. HRMS (ESI) calcd. for $C_{23}H_{25}ClNO_2$ $(M + H)^+$ 382.1574, found 382.1571.

(*NZ*)-*N*-(5-Fluoro-3-(2-phenyldihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)-4-methylaniline (17fa):



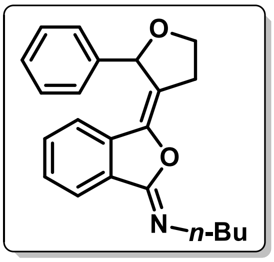
Combined yield 72 mg, 64% (*E/Z*= 3:1). For the major *E*-17fa: White Solid; R_f (hexane/ethyl acetate, 9:1) 0.50; mp 158-160 °C, IR (KBr, neat) ν 2920, 2864, 1672, 1478, 1269, 1220, 1048, 1022, 827, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.5, 4.9 Hz, 1 H), 7.44 – 7.32 (m, 7 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 7.11 (td, *J* = 8.7, 2.2 Hz, 1 H), 6.66 (dd, *J* = 8.6, 2.2 Hz, 1 H), 5.91 (s, 1 H), 4.02 (td, *J* = 6.8, 2.1 Hz, 2 H), 3.23 – 3.17 (m, 1 H), 3.11–3.04 (m, 1 H), 2.38 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 165.3 (d, *J* = 249.9 Hz), 152.4, 142.9, 142.6 (d, *J* = 4.2 Hz), 138.8, 136.8 (d, *J* = 10.5 Hz), 134.8, 129.6, 129.3, 128.9, 127.9, 125.96, 125.9 (d, *J* = 9.9 Hz), 124.6, 121.5, 117.4 (d, *J* = 24.2 Hz), 109.3 (d, *J* = 25.6 Hz), 80.4, 66.3, 32.2, 21.3. ^{19}F NMR (471 MHz, $CDCl_3$) δ 55.4. HRMS (ESI) calcd. for $C_{25}H_{21}FNO_2$ $(M + H)^+$ 386.1556, found 386.1551. For the minor *Z*-17fa: White Solid; R_f (hexane/ethyl acetate, 9:1) 0.40; mp 130-132 °C, IR (KBr, neat) ν 2920, 2859, 1776, 1670, 1507, 1478, 1021, 827, 730, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.5, 4.9 Hz, 1 H), 7.37 – 7.31 (m, 5 H), 7.28 (d, *J* = 2.2 Hz, 1 H), 7.20 (td, *J* = 8.7, 2.2 Hz, 1 H), 7.04 (d, *J* = 8.0 Hz, 2 H), 6.92 (d, *J* = 8.3 Hz, 2 H), 5.74 (s, 1 H), 4.41–4.37 (m, 1 H), 4.07 (q, *J* = 7.9 Hz, 1 H), 3.17 – 3.10 (m, 2 H), 2.35 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.5 (d, *J* = 250.1 Hz), 152.1, 142.6, 141.3 (d, *J* = 4.2 Hz), 140.7, 138.1 (d, *J* = 10.4 Hz), 134.6, 129.4, 128.7, 128.4, 128.0, 127.3, 126.1 (d, *J* = 9.9 Hz), 124.3, 121.5, 117.5 (d, *J* = 24.0 Hz), 108.8 (d, *J* = 25.1 Hz), 82.9, 68.3, 30.5, 21.3. ^{19}F NMR (471 MHz, $CDCl_3$) δ 55.2.

(*NZ*)-*N*-(3-(2-Phenyldihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)aniline (17ga):



Combined yield 69 mg, 67% (*E/Z*= 4:1). For the major *E*-17ga: Pale yellow gum; R_f (hexane/ethyl acetate, 4:1) 0.50; IR (KBr, neat) ν 3060, 2870, 1776, 1709, 1674, 1591, 1491, 1276, 1052, 1024, 757, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.7 Hz, 1 H), 7.48 (dd, *J* = 8.4, 1.3 Hz, 2 H), 7.44 – 7.29 (m, 9 H), 7.17 (t, *J* = 7.3 Hz, 1 H), 7.04 (d, *J* = 7.7 Hz, 1 H), 5.98 (s, 1 H), 4.03 – 3.95 (m, 2 H), 3.20 – 3.14 (m, 1 H), 3.06–3.00 (m, 1 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 154.0, 145.9, 143.5, 139.1, 135.0, 132.3, 131.4, 129.3, 129.1, 128.9, 128.7, 127.9, 124.9, 124.4, 124.0, 122.4, 120.1, 80.3, 66.2, 31.9. HRMS (ESI) calcd. for $C_{24}H_{20}NO_2$ $(M + H)^+$ 354.1489, found 354.1465. For the minor *Z*-17ga: Orange solid; R_f (hexane/ethyl acetate, 4:1) 0.40; mp 151-153 °C, IR (KBr, neat) ν 3055, 2864, 1672, 1592, 1485, 1269, 1022, 752, 694, 512 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.7 Hz, 1 H), 7.62 – 7.59 (m, 2 H), 7.52–7.49 (m, 1 H), 7.33–7.28 (m, 5 H), 7.25 (t, *J* = 7.4 Hz, 2 H), 7.10 (t, *J* = 7.4 Hz, 1 H), 7.01 (d, *J* = 7.8 Hz, 2 H), 5.73 (s, 1 H), 4.40–4.36 (m, 1 H), 4.06 (q, *J* = 7.9 Hz, 1 H), 3.18 – 3.15 (m, 2 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.7, 145.6, 142.1, 141.0, 136.3, 132.4, 131.0, 129.5, 128.8, 128.6, 128.2, 128.0, 124.7, 124.2, 121.9, 120.5, 82.9, 68.4, 30.5.

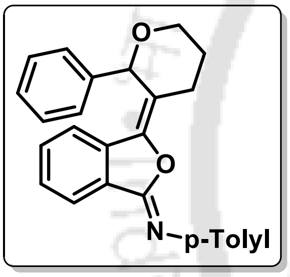
(*NZ*)-*N*-(3-(2-Phenyldihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)butan-1-amine (17ha):



Combined yield 43 mg, 44% (*E/Z*= 3:1). For the major *E*-17ha: Orange gum; R_f (hexane/ethyl acetate, 9:1) 0.40; IR (KBr, neat) ν 2958, 2869, 1776, 1701, 1655, 1373, 1267, 1054, 1017, 730, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.6 Hz, 1 H), 7.45 – 7.43 (m, 2 H), 7.37 – 7.28 (m, 5 H), 7.00 (d, *J* = 7.7 Hz, 1 H), 5.96 (s, 1 H), 4.06 –

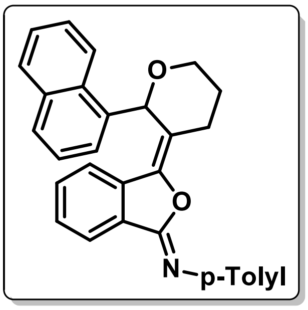
3.96 (m, 2 H), 3.68–3.64 (m, 2 H), 3.22–3.16 (m, 1 H), 3.06–2.99 (m, 1 H), 1.72 (q, *J* = 7.4 Hz, 2 H), 1.51–1.43 (m, 2 H), 0.99 (t, *J* = 7.4 Hz, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 155.2, 143.3, 139.3, 135.3, 131.6, 130.9, 129.1, 129.0, 128.6, 127.9, 123.3, 122.4, 117.9, 80.3, 66.2, 47.7, 33.2, 31.6, 20.9, 14.2. HRMS (ESI) calcd. for $C_{22}H_{24}NO_2$ $(M + NH_4)^+$ 351.2067, found 351.2044. For the minor *Z*-17ha: Orange gum; R_f (hexane/ethyl acetate, 9:1) 0.40; IR (KBr, neat) ν 2958, 2873, 1771, 1699, 1390, 1267, 1051, 733, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.3 Hz, 1 H), 7.52–7.43 (m, 3 H), 7.36 – 7.31 (m, 4 H), 7.27 (s, 1 H), 6.10 (t, *J* = 2.7 Hz, 1 H), 4.36–4.32 (m, 2 H), 3.64–3.58 (m, 1 H), 3.28–3.24 (m, 2 H), 3.19 – 3.13 (m, 1 H), 1.73–1.65 (m, 2 H), 1.38 (q, *J* = 7.4 Hz, 2 H), 0.91 (t, *J* = 7.4 Hz, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 168.1, 148.4, 138.2, 136.4, 132.5, 131.1, 129.6, 128.8, 128.7, 128.0, 126.2, 123.4, 122.1, 100.9, 67.9, 40.2, 31.9, 31.6, 20.8, 14.1.

(*Z*)-4-Methyl-*N*-((*E*)-3-(2-phenyldihydro-2H-pyran-3(4*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)aniline (18ia):



Combined yield 71 mg, 93% (*E*/*Z*= 97:3). Pale yellow gum; R_f (hexane/ethyl acetate, 9:1) 0.40; IR (KBr, neat) ν 2927, 2858, 1689, 1658, 1503, 1086, 1012, 725, 524 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 – 8.05 (m, 1 H), 7.49 – 7.43 (m, 6 H), 7.39 (q, *J* = 7.4 Hz, 3 H), 7.32 (t, *J* = 7.3 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 6.29 (s, 1 H), 3.81–3.77 (m, 1 H), 3.67 (td, *J* = 11.7, 2.7 Hz, 1 H), 3.21 – 3.17 (m, 1 H), 2.39 (s, 3 H), 2.30–2.24 (m, 1 H), 1.99-1.91 (m, 1 H), 1.71-1.68 (m, 1 H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 153.4, 145.5, 143.2, 138.1, 134.9, 134.6, 132.4, 132.3, 129.6, 129.4, 129.1, 128.0, 127.4, 124.5, 124.1, 122.9, 116.7, 73.4, 61.7, 26.6, 22.9, 21.3. HRMS (ESI) calcd. for $C_{26}H_{24}NO_2$ $(M + H)^+$ 382.1802, found 382.1807.

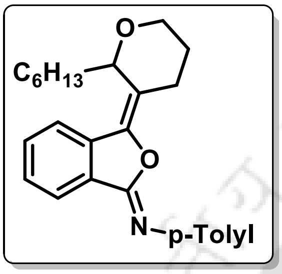
(*Z*)-4-Methyl-*N*-((*E*)-3-(2-(naphthalen-1-yl)dihydro-2*H*-pyran-3(4*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)aniline (18ib):



Combined yield 77 mg, 89% (*E*/*Z*= 100:0). White solid; R_f (hexane/ethyl acetate, 9:1) 0.40; mp 206-208 °C, IR (KBr, neat) ν 3049, 2922, 2856, 1689, 1658, 1506, 1084, 1015, 783, 735, 527 cm^{-1}; ^1H NMR (500 MHz,$CDCl_3$) δ 8.52 (d, *J* = 8.5 Hz, 1 H), 7.90 (d, *J* = 7.7 Hz, 1 H), 7.84 (d, *J* = 8.1 Hz, 1 H), 7.75 (d, *J* = 8.1 Hz, 1 H), 7.58–7.55 (m, 1 H), 7.51 – 7.48 (m, 1 H), 7.38–7.33 (m, 3 H), 7.29–7.24 (m, 2 H), 7.17 – 7.13 (m, 3 H), 6.91 (d, *J* = 8.0 Hz, 1 H), 6.74 (s, 1 H), 3.62–3.58

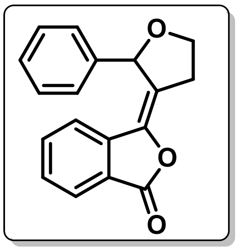
(m, 1 H), 3.42 – 3.37 (m, 1 H), 3.32–3.27 (m, 1 H), 2.70–2.63 (m, 1 H), 2.32 (s, 3 H), 1.92–1.85 (m, 1 H), 1.76–1.72 (m, 1 H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 153.5, 145.7, 143.3, 134.63, 134.62, 134.60, 133.9, 132.60, 132.36, 132.09, 129.6, 129.2, 129.1, 126.8, 126.7, 126.2, 125.3, 125.0, 124.5, 124.0, 122.9, 116.2, 72.7, 61.7, 25.5, 23.7, 21.3. HRMS (ESI) calcd. for $C_{30}H_{26}NO_2$ $(M + H)^+$ 432.1958, found 432.1964.

(*NZ*)-*N*-(3-(2-Hexyldihydro-2*H*-pyran-3(4*H*)-ylidene)isobenzofuran-1(3*H*)-ylidene)-4-methylaniline (18il):



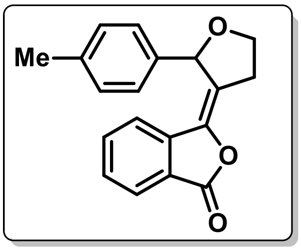
Combined yield 70 mg, 90% (*E/Z*= 2.3:1). Pale yellow gum; R_f (hexane/ethyl acetate, 9:1) 0.40; IR (KBr, neat) ν 2924, 2853, 1686, 1658, 1503, 1465, 1078, 1015, 758, 672, 529 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.8, 2.9 Hz, 1 H), 7.79 (d, 7.9 Hz, 2 H, minor),7.60–7.54 (m, 2 H, major), 7.47 (t, *J* = 7.4 Hz, 1 H), 7.38 (d, *J* = 7.9 Hz, 1 H), 7.34 (d, *J* = 7.9 Hz, 1 H), 7.19 (d, *J* = 7.9 Hz, 1 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 5.11 (dd, *J* = 9.5, 4.0 Hz, 1 H, major), 4.92 (dd, *J* = 9.1, 5.4 Hz, 1 H, minor), 3.89–3.82 (m, 1 H), 3.69–3.64 (m, 1 H), 3.13–3.05 (m, 1 H), 2.61–2.55 (m, 1 H, minor), 2.35–2.31 (m, 1 H, major), 2.37 (s, 3 H, major), 2.36 (s, 3 H, minor), 2.14–2.05 (m, 1 H), 1.88–1.83 (m, 1 H), 1.64–1.55 (m, 2 H), 1.45–1.38 (m, 1 H), 1.33–1.26 (m, 6 H), 0.91–0.86 (m, 3 H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 153.6, 153.4, 143.3, 143.2, 143.1, 142.3, 135.9, 135.1, 134.4, 134.3, 132.2, 132.1, 132.0, 129.5, 129.4, 128.99, 129.0, 128.9, 124.4, 124.3, 124.1, 124.0, 122.75, 122.70, 120.5, 119.9, 73.2, 72.5, 60.9, 32.1, 32.0, 31.6, 31.4, 29.4, 29.2, 26.3, 26.0, 25.9, 22.85, 22.81, 21.8, 21.3, 21.2, 21.1, 14.3. HRMS (ESI) calcd. for $C_{26}H_{31}NNaO_2$ $(M + Na)^+$ 412.2247, found 412.2253.

(*E*)-3-(2-Phenyldihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-one (19aa):



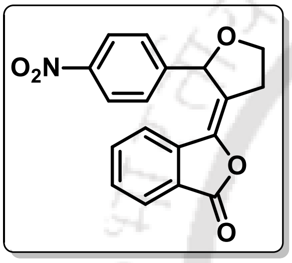
Colourless solid, R_f (hexane/ethyl acetate, 9:1) 0.40; mp 178-180 °C, yield 27 mg, 98%; IR (KBr, neat) ν 2922, 2859, 1777, 1703, 1017, 762, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.90 (m, 1 H), 7.51–7.45 (m, 2 H), 7.44 – 7.40 (m, 2 H), 7.39 – 7.30 (m, 3 H), 7.08 (d, *J* = 7.0 Hz, 1 H), 5.99 (d, *J* = 2.1 Hz, 1 H), 4.09 – 3.97 (m, 2 H), 3.31–3.24 (m, 1 H), 3.16 – 3.08 (m, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.1, 140.3, 138.6, 137.8, 134.6, 129.6, 129.2, 128.9, 127.9, 125.9, 125.3, 125.0, 122.9, 80.4, 66.2, 32.2. HRMS (ESI) calcd. for $C_{18}H_{15}O_3$ $(M + H)^+$ 279.1016, found 279.1015.

(*E*)-3-(2-(*p*-Tolyl)dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-one (19ad):



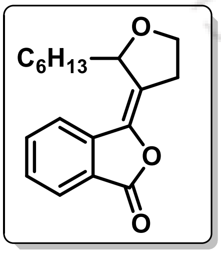
White Solid; R_f (hexane/ethyl acetate, 9:1) 0.40; mp 156-158 °C, yield 29 mg, 99%; IR (KBr, neat) ν 2920, 2868, 1771, 1699, 1471, 1264, 1047, 1014, 762, 687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 7.4 Hz, 1 H), 7.51 – 7.43 (m, 2 H), 7.30 (d, J = 7.9 Hz, 2 H), 7.16 (d, J = 7.9 Hz, 2 H), 7.09 (d, J = 7.7 Hz, 1 H), 5.96 (s, 1 H), 4.06 – 3.97 (m, 2 H), 3.29–3.23 (m, 1 H), 3.15–3.08 (m, 1 H), 2.33 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.1, 140.1, 138.7, 137.8, 135.6, 134.6, 129.8, 129.5, 127.8, 125.8, 125.3, 125.2, 122.9, 80.3, 66.1, 32.2, 21.4. HRMS (ESI) calcd. for $C_{19}H_{16}KO_3$ $(M + K)^+$ 331.0732, found 331.0736.

(*E*)-3-(2-(4-Nitrophenyl)dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-one (19ak):



Pale yellow solid; R_f (hexane/ethyl acetate, 4:1) 0.40; mp 192-194 °C, yield 29 mg, 89%; IR (KBr, neat) ν 2923, 2870, 1779, 1519, 1344, 1019, 767, 695 cm^{-1}; ^1H NMR (400 MHz, DMSO–d_6/$CDCl_3$) δ 8.22 (d, J = 8.2 Hz, 2 H), 7.95 (d, J = 7.0 Hz, 1 H), 7.61 (d, J = 8.1 Hz, 2 H), 7.57–7.50 (m, 2 H), 7.05 (d, J = 7.1 Hz, 1 H), 6.07 (s, 1 H), 4.14–4.08 (m, 1 H), 3.95 (q, J = 7.8 Hz, 1 H), 3.33 – 3.25 (m, 1 H), 3.12–3.04 (m, 1 H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO–d_6/$CDCl_3$) δ 166.7, 148.2, 145.6, 140.8, 137.3, 134.8, 130.1, 128.7, 126.2, 125.5, 124.3, 123.1, 122.3, 79.1, 66.5, 31.7. HRMS (ESI) calcd. for $C_{18}H_{14}NO_5$ $(M + H)^+$ 324.0867, found 324.0871.

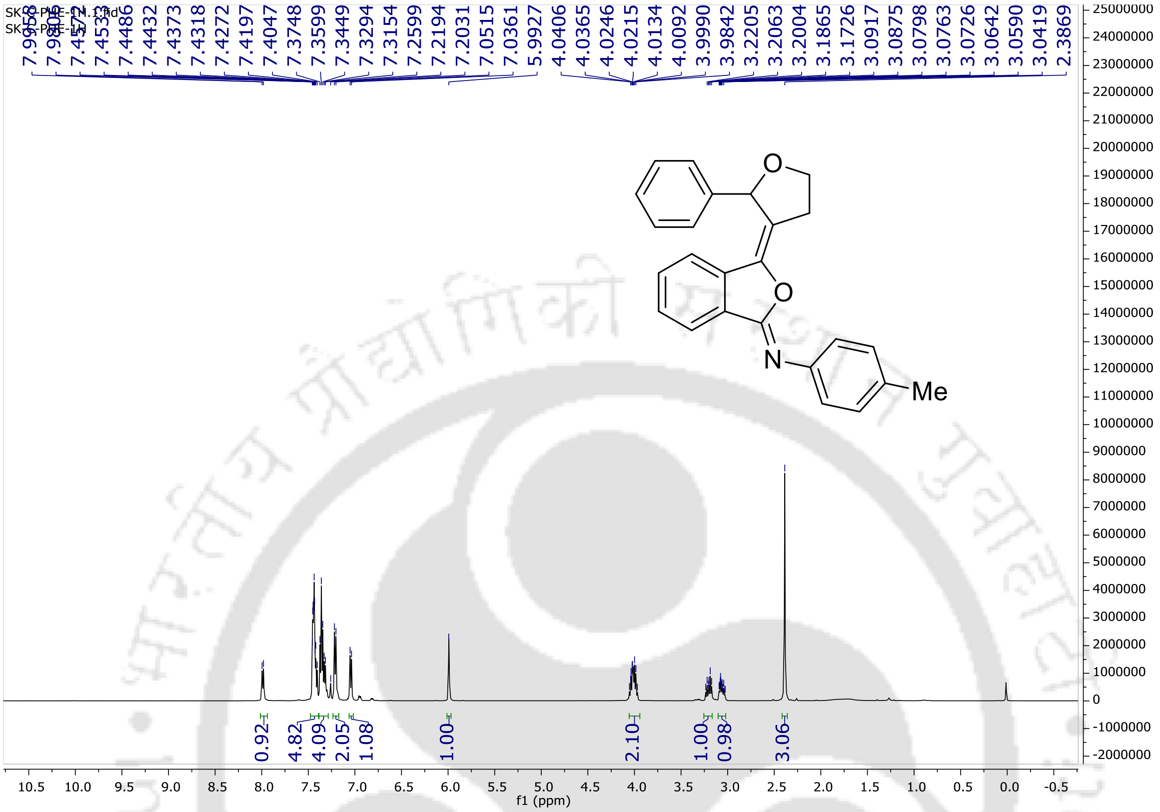
(*E*)-3-(2-Hexyldihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-one (19al):

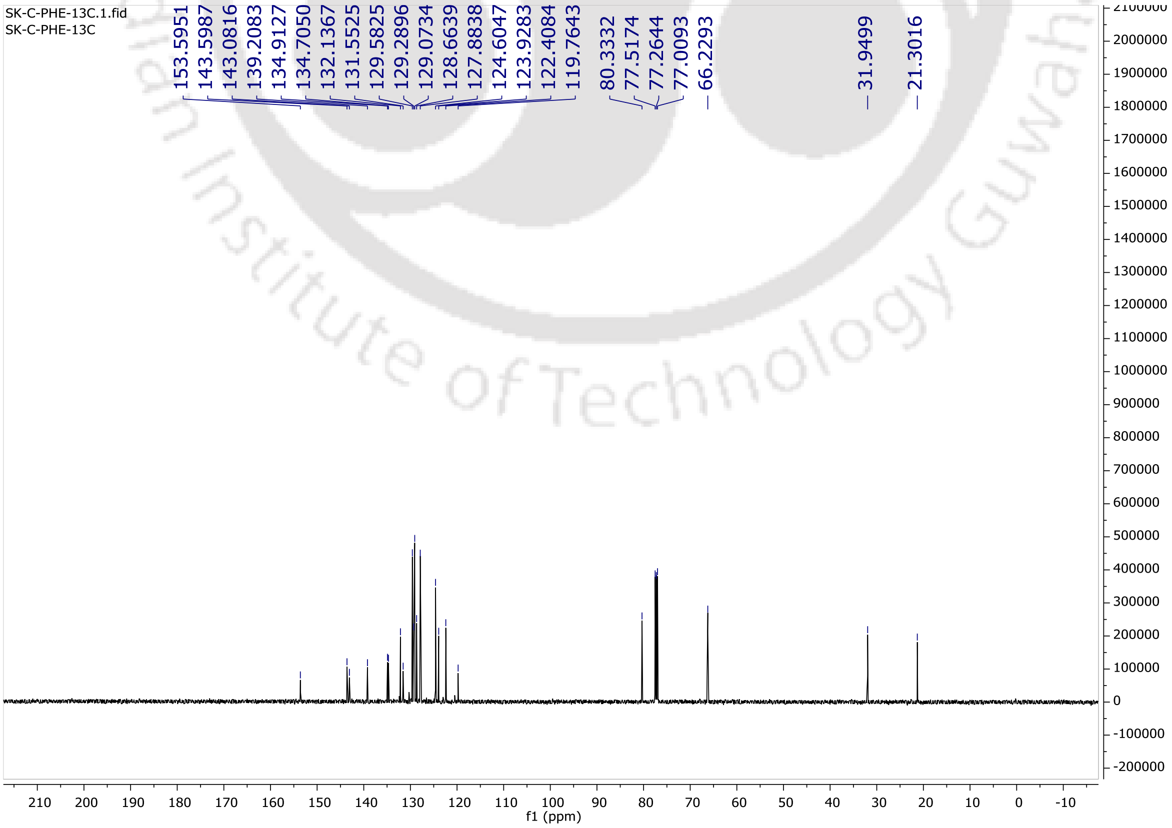


Pale yellow gum; R_f (hexane/ethyl acetate, 9:1) 0.40; yield 26 mg, 92%; IR (KBr, neat) ν 2924, 2854, 1776, 1473, 1267, 1017, 764, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 7.7 Hz, 1 H), 7.73 (t, J = 7.6 Hz, 1 H), 7.53 (t, J = 7.6 Hz, 1 H), 7.44 (d, J = 7.9 Hz, 1 H), 5.06–5.03 (m, 1 H), 4.10–4.05 (m, 1 H), 3.97 (q, J = 7.5 Hz, 1 H), 3.11–3.05 (m, 1 H), 2.99–2.94 (m, 1 H), 1.71 – 1.65 (m, 2 H), 1.61–1.52 (m, 2 H), 1.41 – 1.36 (m, 1 H), 1.35–1.28 (m, 5 H), 0.88 (t, J = 6.5 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.2, 138.3, 137.9, 134.7, 129.3, 128.3, 126.1, 125.4, 122.3, 78.4, 66.1, 33.7, 32.0, 31.1, 29.3, 26.2, 22.8, 14.3. HRMS (ESI) calcd. for $C_{18}H_{23}O_3$ $(M + H)^+$ 287.1642, found 287.1641.

5.10 Representative Spectra and crystal parameter

^{1}H (500 MHz, CDCl$_3$) and ^{13}C{^{1}H} (125 MHz, CDCl$_3$) spectra of ***E*-17aa**





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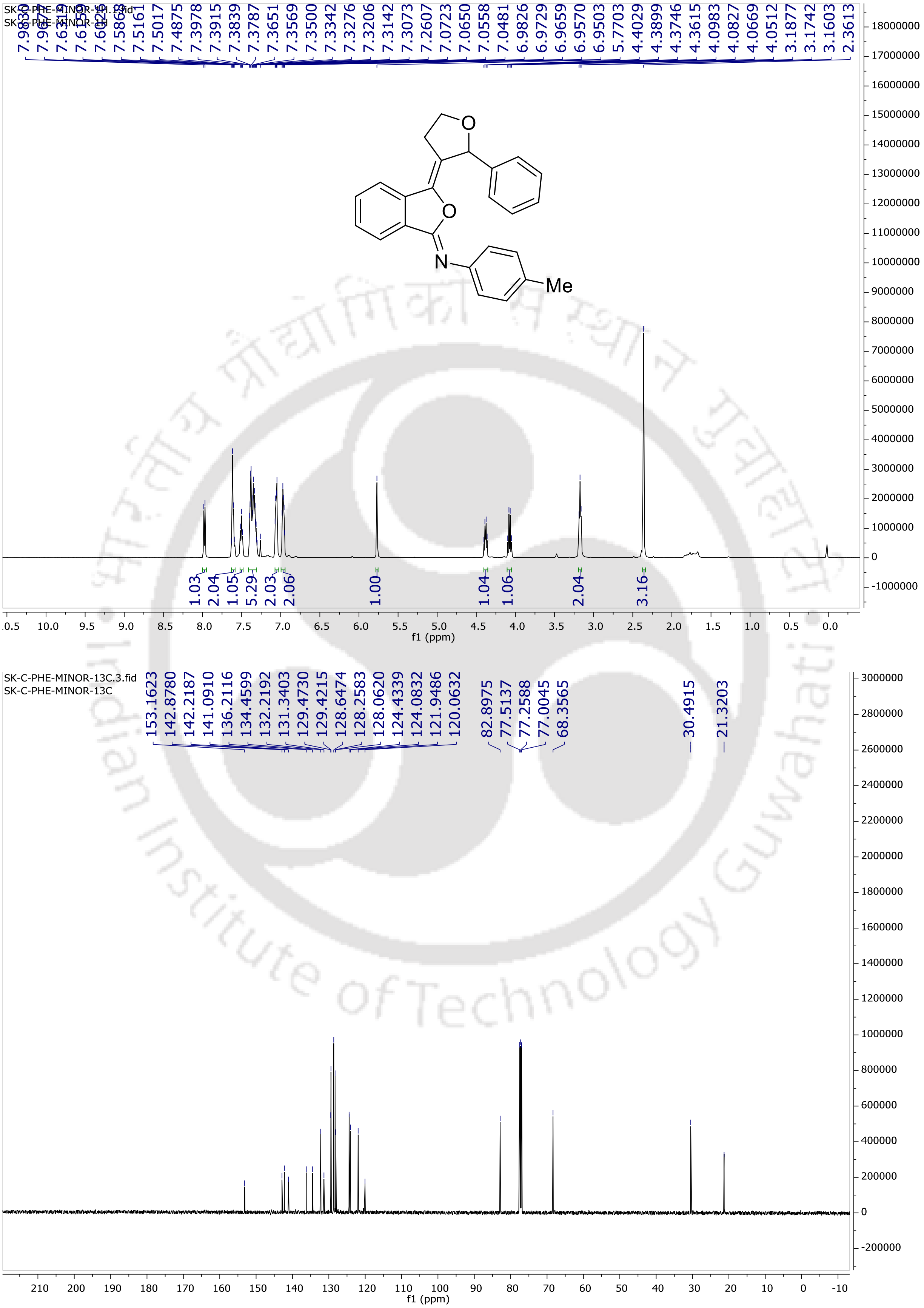
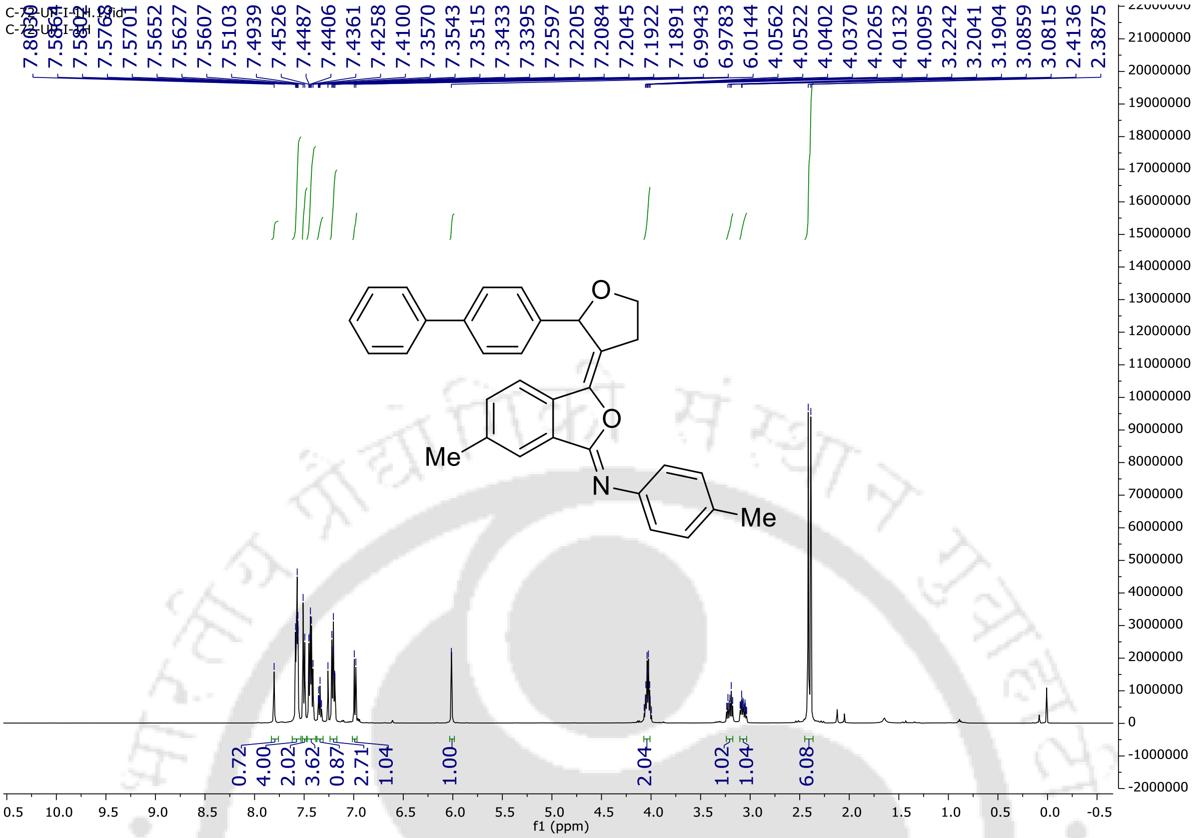
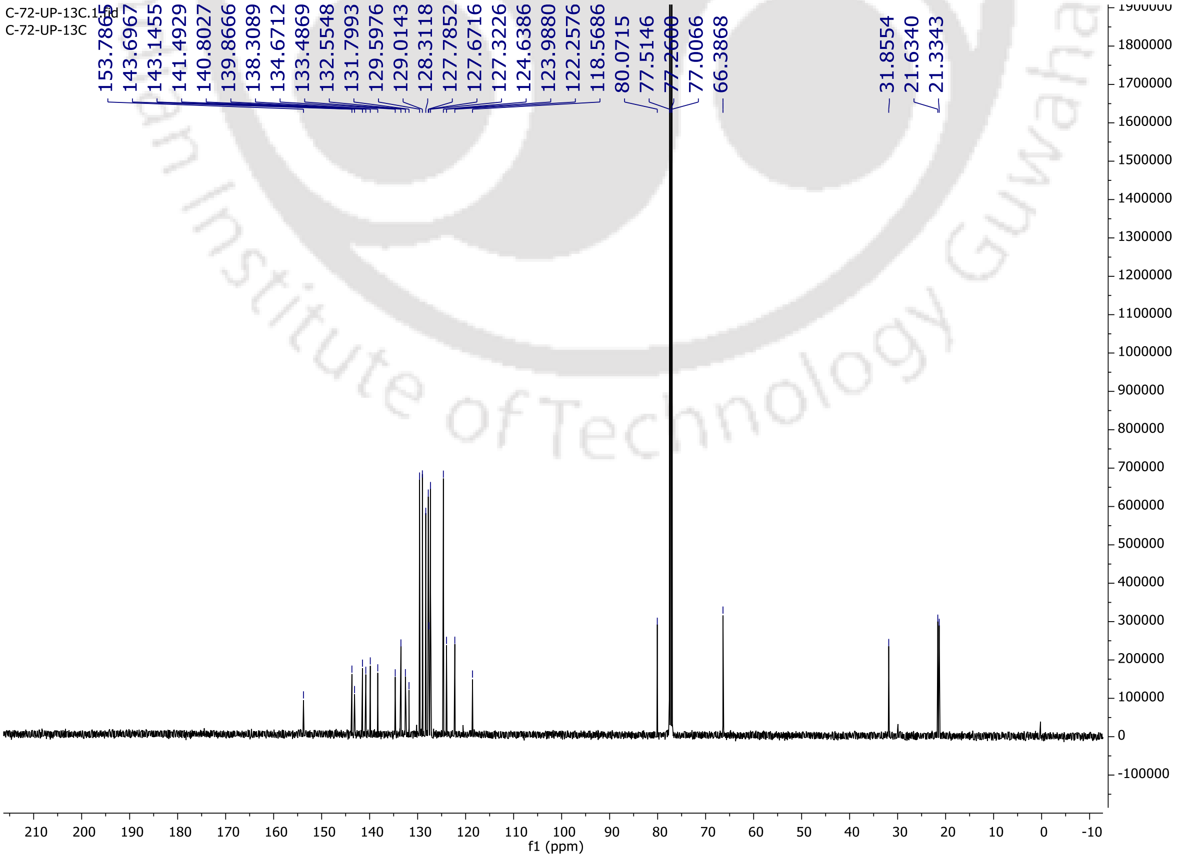
^{1}H (500 MHz, CDCl$_3$) and ^{13}C{^{1}H} (125 MHz, CDCl$_3$) spectra of ***Z*-17aa**



^{1}H (500 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (125 MHz, $CDCl_3$) spectra of ***E*-17do**





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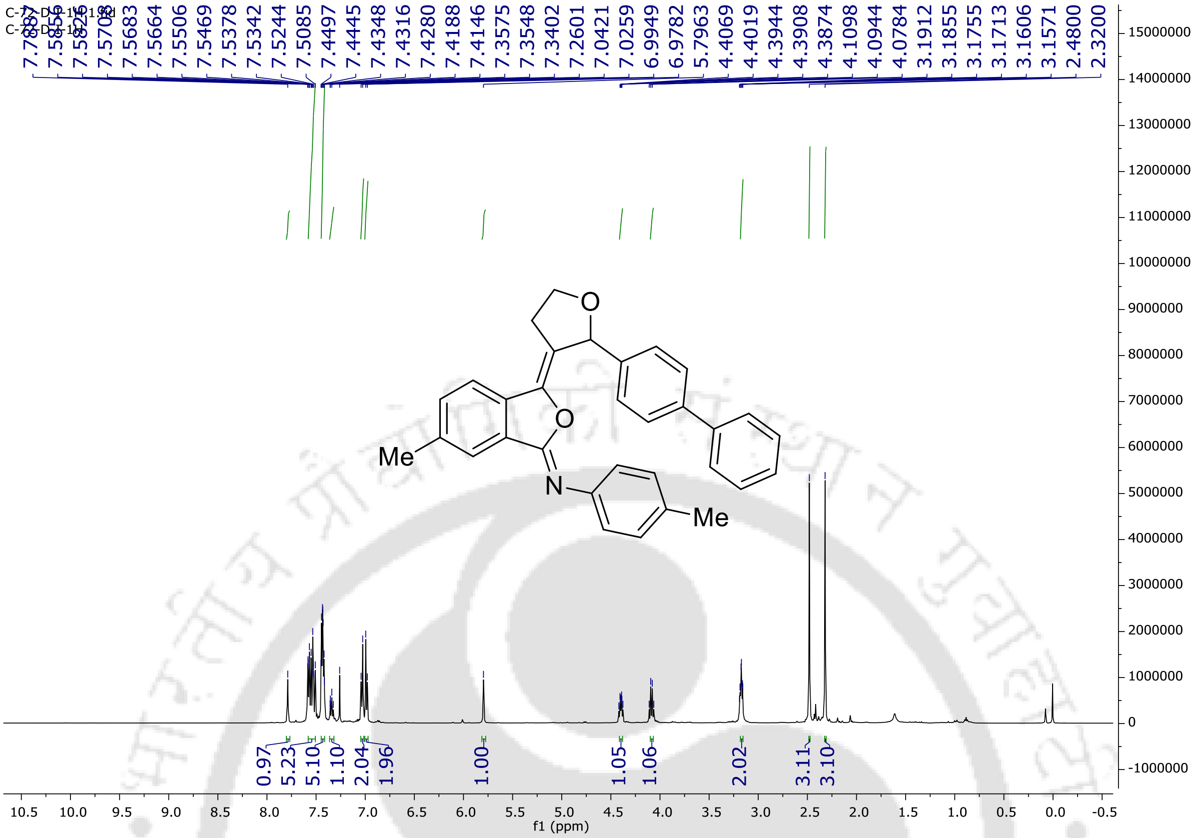
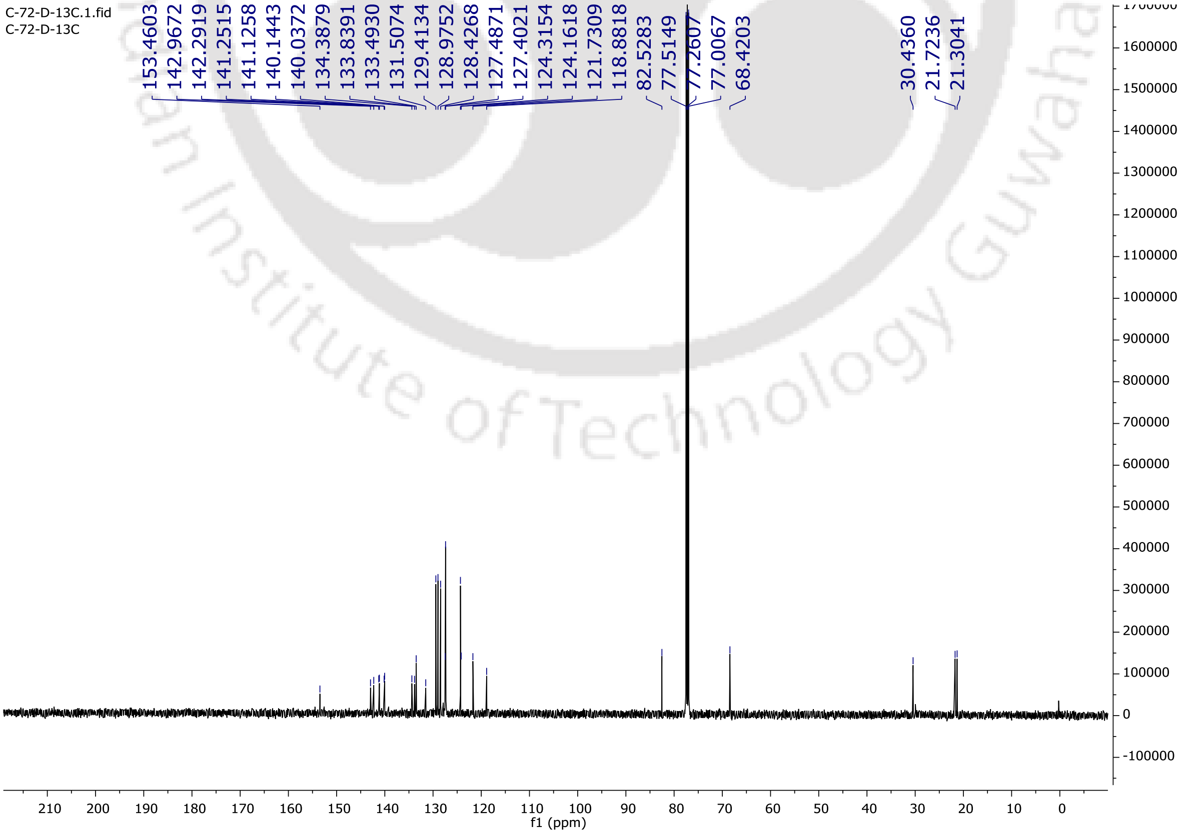
^{1}H (500 MHz, CDCl$_3$) and ^{13}C{^{1}H} (125 MHz, CDCl$_3$) spectra of ***Z*-17do**





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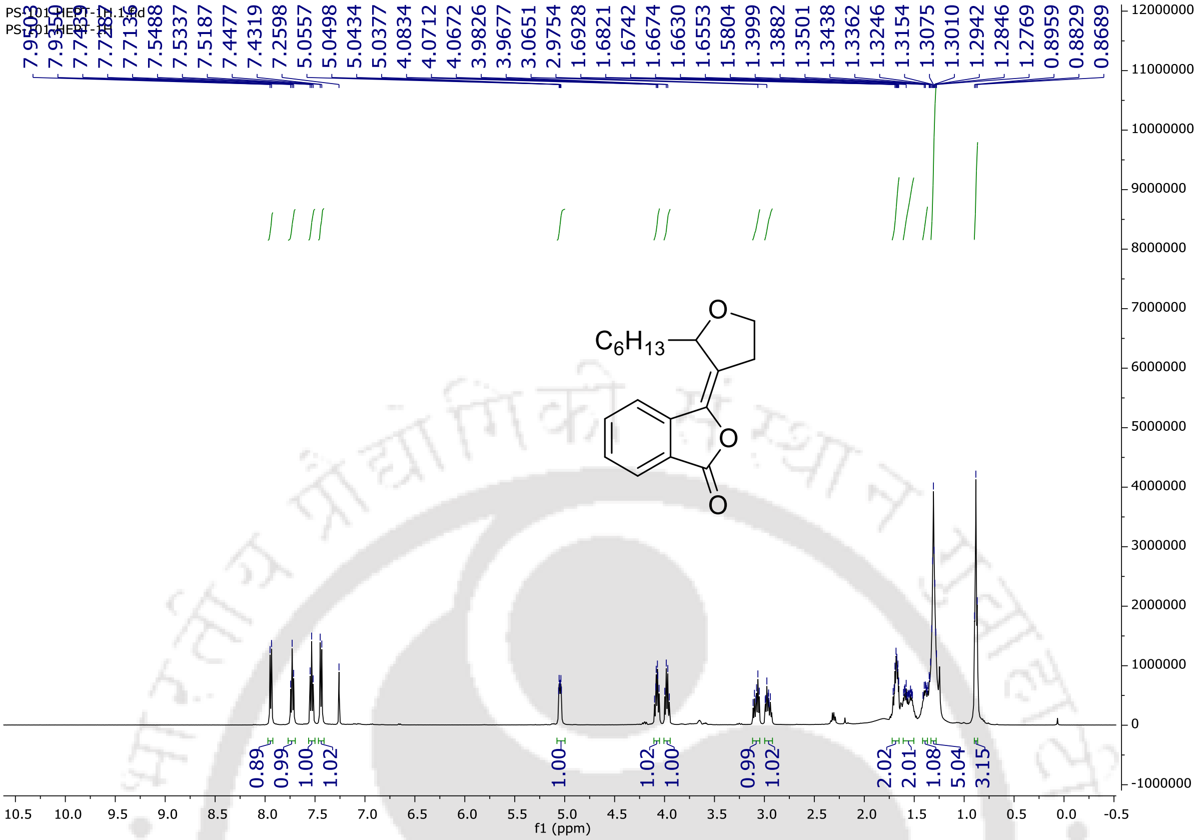
^{1}H (500 MHz, CDCl$_3$) and ^{13}C{^{1}H} (100 MHz, CDCl$_3$) spectra of **19al**



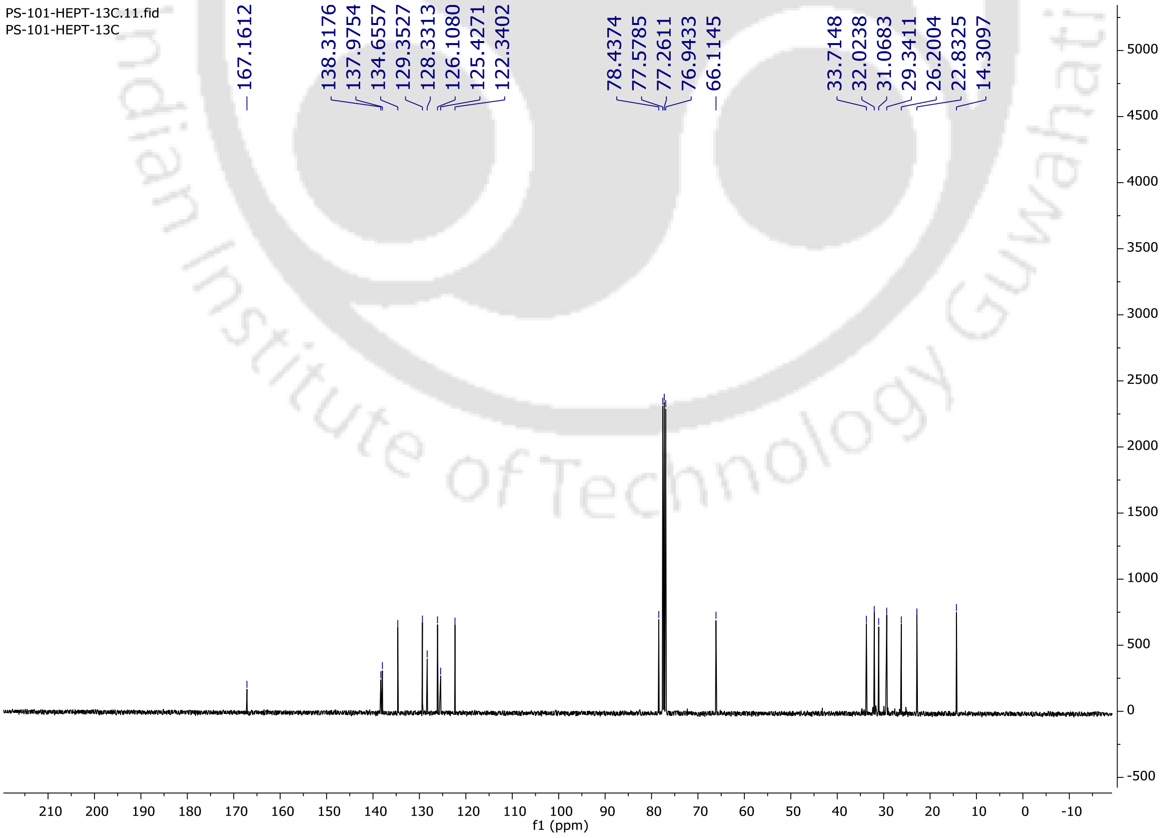


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Figure **S1**: NOESY (400 MHz, $CDCl_3$) spectrum of ***E*-17ep**

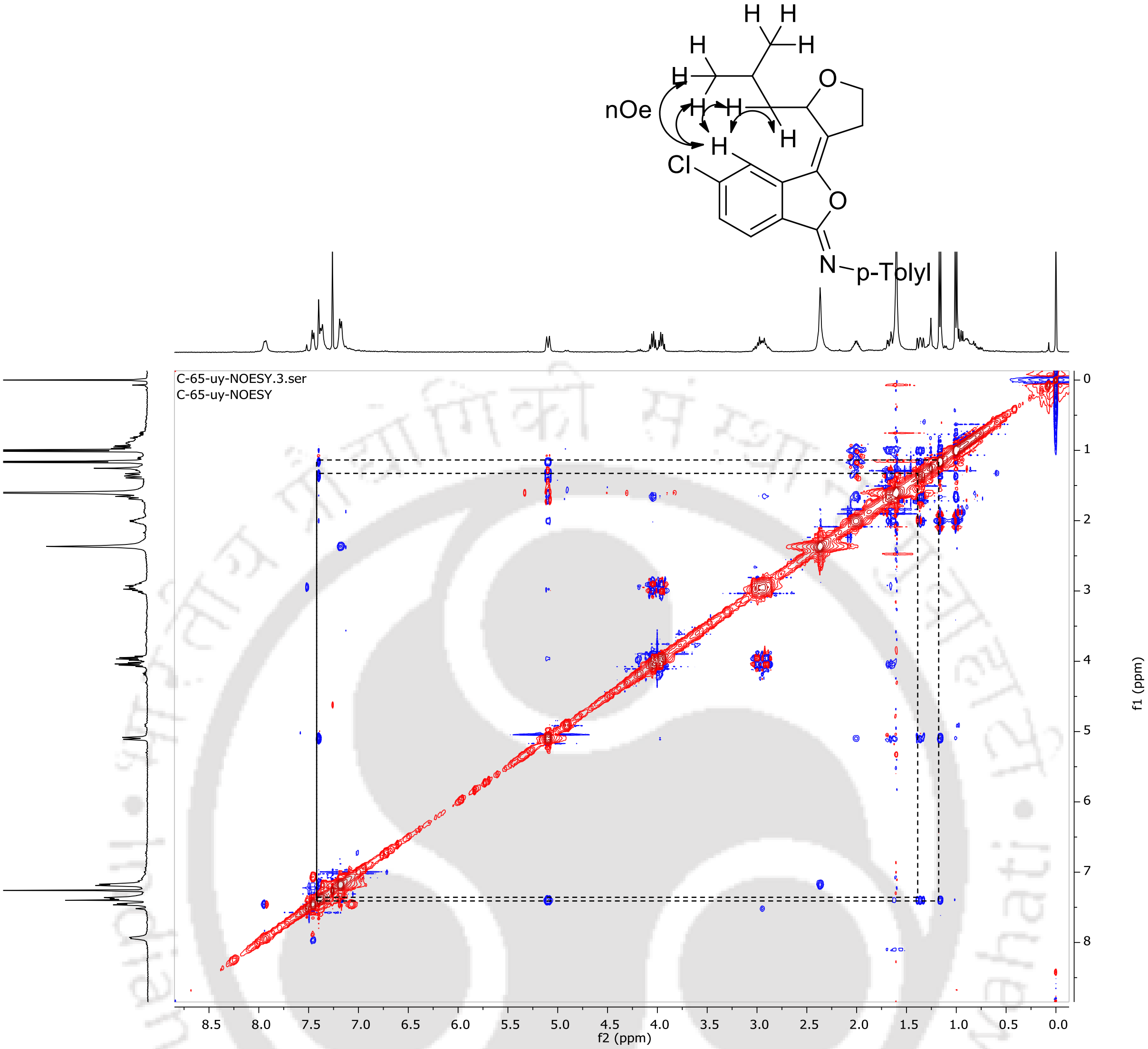

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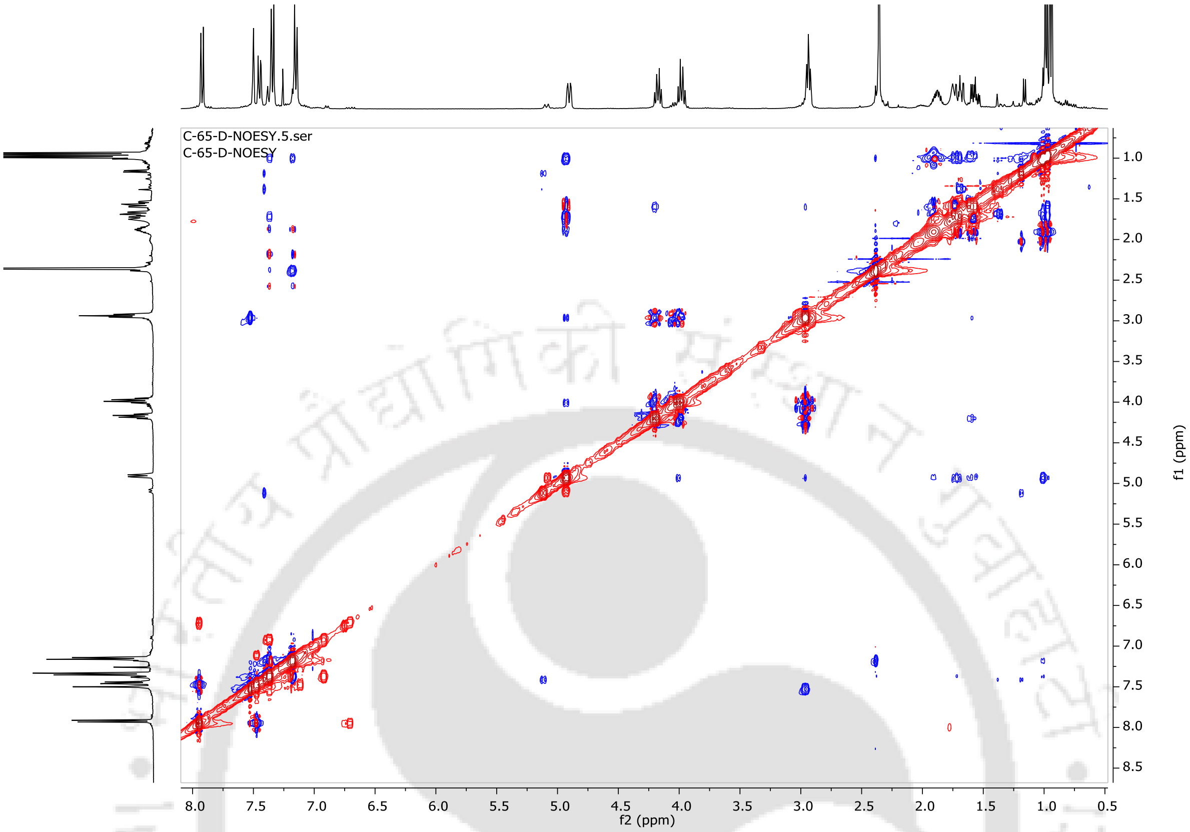
Figure **S2**: NOESY (400 MHz, $CDCl_3$) spectrum of ***Z*-17ep**



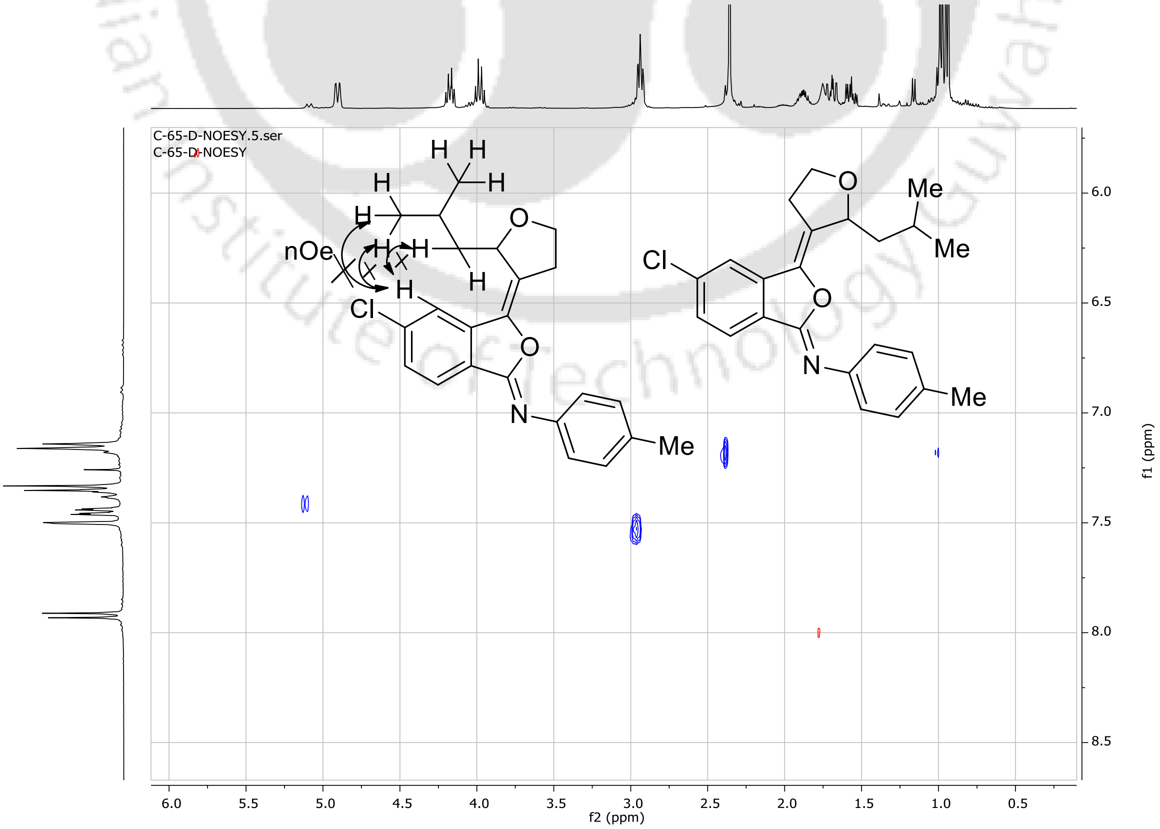


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Figure **S3**: NOESY (400 MHz, CDCl3) spectrum of ***E*-17ba**

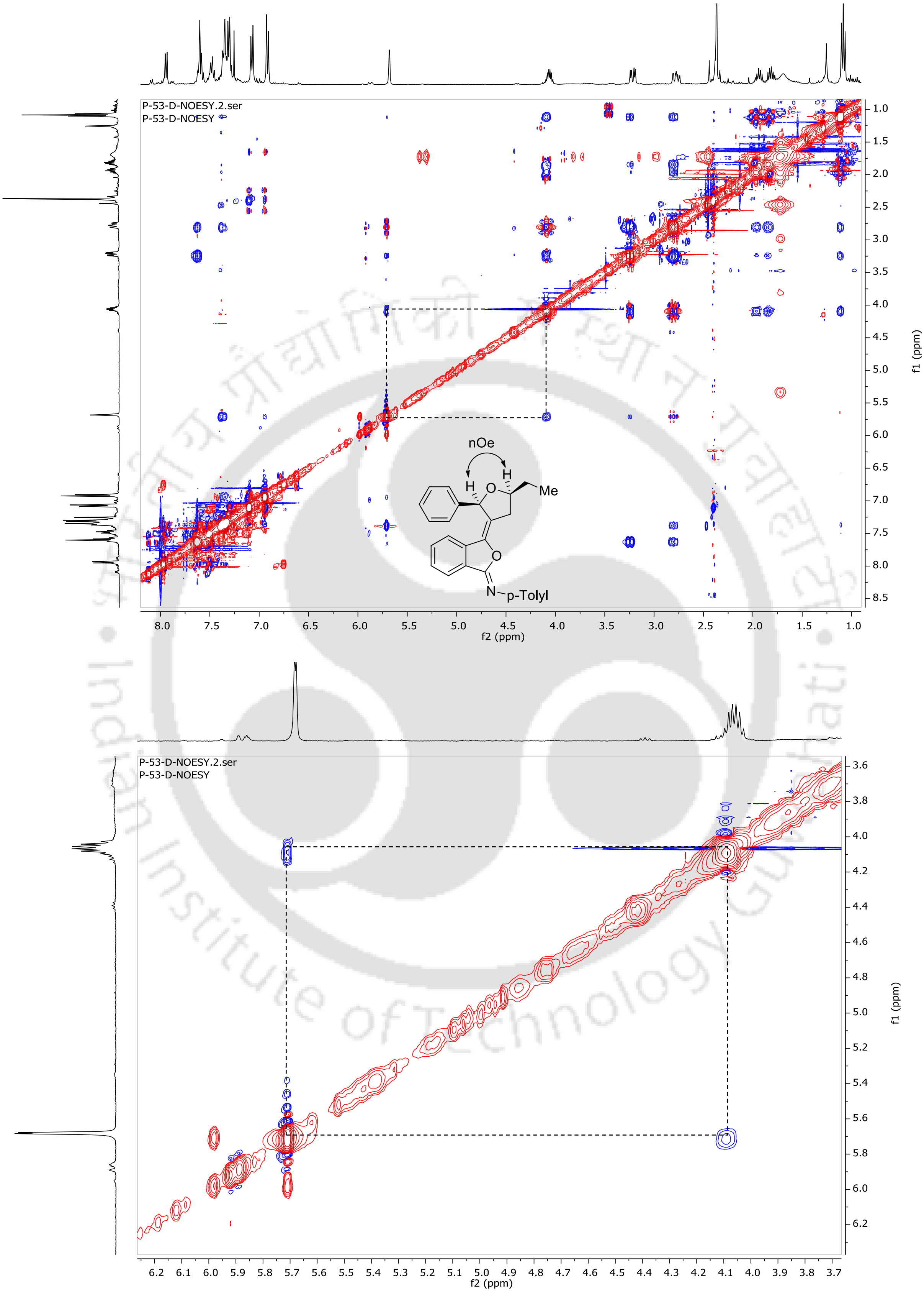

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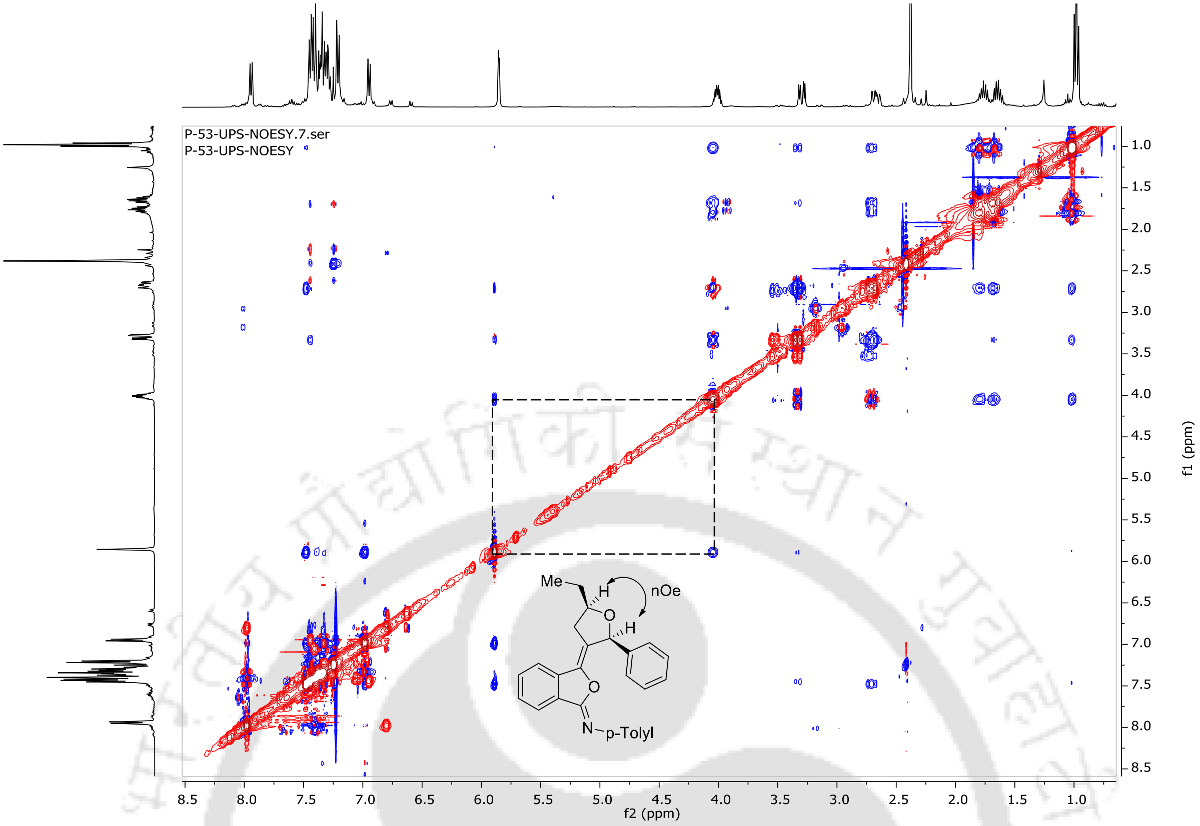
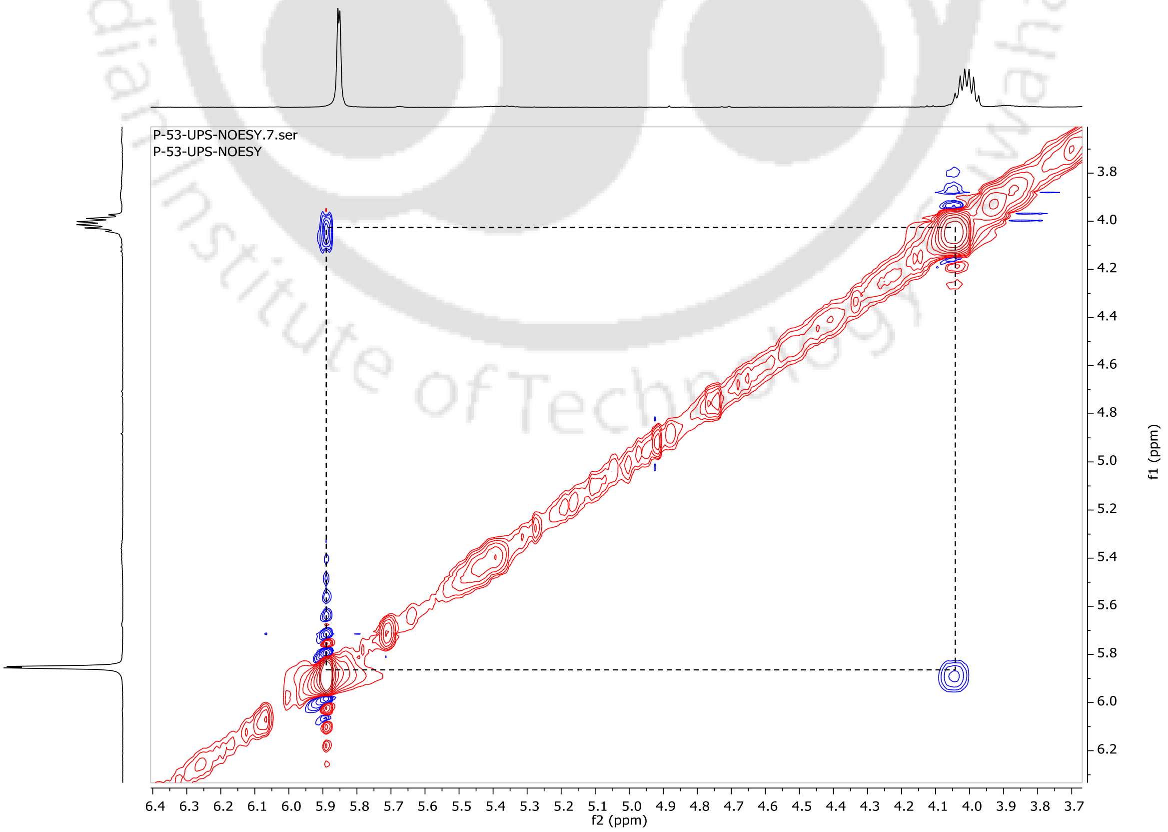
Figure **S4**: NOESY (400 MHz, $CDCl_3$) spectrum of ***Z*-17ba**





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Crude ^1H (400 MHz, $CDCl_3$) NMR spectrum of **17aa**

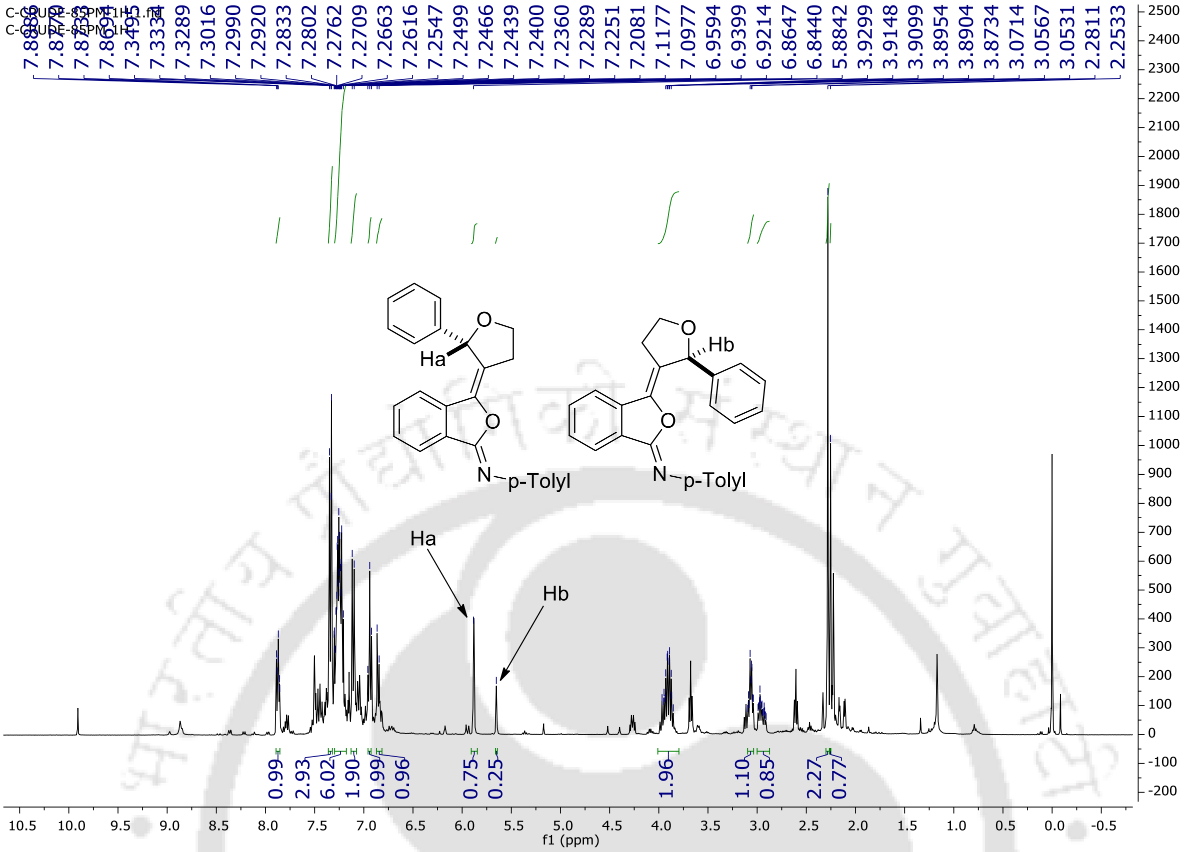

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Table S1: The crystal parameters of compound *E*-17ad

	CCDC 2210748
Formula	$C_{26}H_{23}NO_2$
Formula weight	381.45
T/K	297(2)
Crystal system	monoclinic
Space group	P c
a/Å	11.4325(15)
b/Å	10.1625(13)
c/Å	9.6490(13)
α/°	90
β/°	114.811(3)
γ/°	90
V/Å^3	1017.6(2)
Z	2
Abs. Coeff./mm^{-1}	0.078
Abs. Correction	‘none’
GOF on F^2	1.051
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0415 *wR2* = 0.1193
R indices [all data]	*R1* = 0.0511 *wR2* = 0.1347

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Table S2: The crystal parameters of compound *Z*-17aa

	CCDC 2210750
Formula	$C_{25}H_{21}NO_2$
Formula weight	367.43
T/K	293(2)
Crystal system	triclinic
Space group	P -1
a/Å	7.5875(8)
b/Å	14.7095(16)
c/Å	18.565(2)
α/°	72.069(4)
β/°	83.599(4)
γ/°	82.918(4)
V/Å^3	1950.4(4)
Z	4
Abs. Coeff./mm^{-1}	0.079
Abs. Correction	‘none’
GOF on F^2	1.019
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0581 $wR2$ = 0.1254
R indices [all data]	$R1$ = 0.1260 $wR2$ = 0.1522

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Table S3: The crystal parameters of compound 19aa

	CCDC 2239675
Formula	$C_{18}H_{14}O_3$
Formula weight	278.29
T/K	298(2)
Crystal system	trigonal
Space group	R -3 :H
a/Å	30.1762(14)
b/Å	30.1762(14)
c/Å	7.9395(4)
α/°	90
β/°	90
γ/°	120
V/Å^3	6261.1(7)
Z	18
Abs. Coeff./mm^{-1}	0.090
Abs. Correction	'none'
GOF on F^2	1.336
Final R indices [I> 2σ(I)]	$R1$ = 0.0404 $wR2$ = 0.1476
R indices [all data]	$R1$ = 0.0487 $wR2$ = 0.1639

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5.11 References

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1. **Shit, S.**; Devi, N.; Devi, N. R.; Saikia, A. K. Stereoselective Synthesis of Hexahydrofuro[3,4-*b*] furan-4-ol and its Dimer *via* Tandem Prins and Pinacol Rearrangement. *Org. Biomol. Chem.* **2019**, *17*, 7398–7407.
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   >*Highlighted in "Synfacts".*
3. **Shit, S.**; Behera, B. K.; Biswas, S.; Saikia, A. K. Regio- and Chemoselective Synthesis of 3-(Dihydrofuran-3(2*H*)-ylidene)isobenzofuran-1(3*H*)-imines via Tandem Alkynyl Prins- and Intramolecular Oxycyclization Reactions. *J. Org. Chem.* **2023**, *88*, 10844−10857.
4. **Shit, S.**; Choudhury, C.; Saikia, A. K. Nitrile Stabilized Synthesis of Pyrrolidine and Piperidine Derivatives via Tandem Alkynyl aza-Prins-Ritter Reactions. (*Manuscript under revision*).
5. Devi, N. R.; **Shit, S.**; Behera, B. K.; Saikia, A. K. Synthesis of 4-Vinyl-1,2,3,4-tetrahydroisoquinoline from *N*-Tethered Benzyl-Alkenol Catalyzed by Indium(III) Chloride: Formal Synthesis of (±)-Isocyclocelabenzine. *Synthesis* **2020**, *52*, 1425–1434.
6. Sahu, A. K.; Unnava, R.; **Shit, S.**; Saikia, A. K. In(OTf)3-Catalyzed One-Pot Tandem Mannich and Conia-Ene Cyclization Reaction of N-Propargyl Amido Alcohols with 1,3-Dicarbonyl Compounds: An Approach To Construct Tetrahydro-1H-pyrrolo[2,1-a]isoindolone-1,1-dicarboxylate and Its Application. *J. Org. Chem.* **2020**, *85*, 1961−1971.
7. Behera, B. K.; **Shit, S.**; Biswas, S.; Saikia, A. K. Synthesis of Thiazole-2(3*H*)-ones *via* [3,3]-Sigmatropic Rearrangement/5-exo-dig Cyclization of *N*-Propargylamines. *J. Org. Chem.* **2022**, *87*, 9259−9269.
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9. Biswas, S.; **Shit. S.**; Behere, B. K.; Sahu, A. K.; Saikia, A. K. Leveraging Cascade Alkynyl Prins Cyclization Towards the Stereoselective Synthesis of Spiro-furan quinazolinone Scaffolds, *Chem. Commun*. **2023**, *59*, 14301–14304.