
Synthesis of *N/O*-Heterocycles *via* Prins Cyclization, Hydroalkoxylation and Intramolecular Oxycyclization Reactions

A dissertation submitted in partial fulfillment for the degree of

Doctor of Philosophy



Submitted by

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DEDICATED WITH LOVE

To Mom, Dad and My Little Sister, For Their Endless
Love, Support and Encouragement





INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
DEPARTMENT OF CHEMISTRY

STATEMENT

I hereby declare that the matter embodied in this thesis, titled “**Synthesis of N/O-Heterocycles via Prins Cyclization, Hydroalkoxylation and Intramolecular Oxycyclization Reactions**” is the result of my own investigations in the Department of Chemistry, Indian Institute of Technology Guwahati, India, under the supervision of Prof. Anil K. Saikia. I have submitted this thesis to the Department of Chemistry, Indian Institute of Technology Guwahati for the award of the degree of Doctor of Philosophy.

In accordance with the standard scientific reporting practices, I have duly acknowledged the contributions of other researchers wherever their findings are referenced in this work. I also declare that, to the best of my knowledge, this work has not been submitted elsewhere for any degree, diploma, associateship, or membership at any institute or university.

Date: 30th January 2025

Subhamoy Biswas

Place: IIT Guwahati





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CERTIFICATE

This is to certify that Subhamoy Biswas has been working under my supervision as a regular registered Ph. D. student since January 2018. His thesis, entitled “**Synthesis of N/O-Heterocycles via Prins Cyclization, Hydroalkoxylation and Intramolecular Oxycyclization Reactions**”, is an authentic record of the results obtained from the research work performed in the Department of Chemistry, Indian Institute of Technology Guwahati, Assam, India. I am forwarding his thesis for submission towards the Ph.D. (Science) degree at 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.

Date: 30th January 2025

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Subhamoy Biswas



List of Abbreviations:

Ac	Acetyl	LA	Lewis acid
AcOH	Acetic acid	Me	Methyl
Ar	Aryl	mp	Melting point
Boc	tert-butyloxycarbonyl	MS	Molecular sieves
BF ₃ ·OEt ₂	Boron trifluoride etherate	m/z	Mass to charge ratio
Bn	Benzyl	NMR	Nuclear magnetic resonance
n-Bu	n-Butyl	Nu	Nucleophile
CCDC	Cambridge Crystallographic Data Centre	NBS	N-Bromosuccinimide
CH ₃ CN	Acetonitrile	NIS	N-Iodosuccinimide
Cy	Cyclohexyl	ORTEP	Oak ridge thermal ellipsoid plot
Et	Ethyl	Ph	Phenyl
DABCO	1,4-Diazabicyclo[2.2.2]octane	ppm	Parts per million
DCE	1,2-Dichloroethane	Pr	Propyl
DCM	Dichloromethane	rt	Room temperature
DFT	Density function theory	TFA	Trifluoroacetic acid
DMSO	Dimethylsulfoxide	TfOH	Triflic acid
dr	Diastereomeric ratio	THF	Tetrahydrofuran
ee	Enantiomeric excess	TLC	Thin layer chromatography
H ₂ O ₂	Hydrogenperoxide	TMS	Trimethylsilyl
HRMS	High resolution mass spectrometry	TMSOTf	Trimethylsilyl trifluoromethanesulfonate
IR	Infrared	p-TsOH	p-toluenesulfonic acid

Abbreviations for intensities of ¹H-NMR signals:

s	Singlet	dd	Doublet of doublets
d	Doublet	dt	Doublet of triplets
t	Triplet	td	Triplet of doublets
q	Quartet	tt	Triplet of triplets
p	Pentate(quintet)	Hz	Hertz
m	Multiplet	Mhz	Mega hertz



SYNOPSIS

The thesis, titled “Synthesis of *N/O*-Heterocycles *via* Prins Cyclization, Hydroalkoxylation and Intramolecular Oxycyclization Reactions,” is divided into six chapters, each based on the results of experimental work performed throughout the research period.

- Chapter I provides a concise overview of cascade reactions, with a primary focus on Prins cyclization, hydroalkoxylation reactions and Intramolecular oxycyclization reactions.
- Chapter II covers the synthesis of pyrimido[2,1-*a*]isoindolone and isoindolo[2,1-*a*]quinazolinone scaffolds using aza-Prins type cyclization reactions.
- Chapter III describes the stereoselective cascade alkynyl Prins cyclization for the synthesis of spiro-furan quinazolinone scaffolds.
- Chapter IV showcases the advancements in the synthesis of pyrano- and isochromeno-quinolines utilizing cascade aza-Prins and hydroalkoxylation reactions.
- Chapter V highlights regioselective nature of the hydroalkoxylation reaction within alkynol ureas, to produce spiro furan/pyran quinazolinone frameworks.
- Chapter VI discusses regioselective intramolecular oxycyclization, followed by a [2+2] cycloaddition reaction of *o*-alkynol benzamides for the construction of spiro-isobenzofuran cyclobutanes.

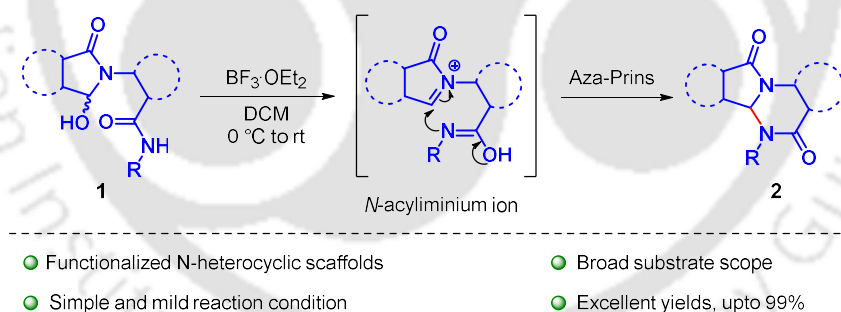
Chapter I: Cascade Reactions, Prins Cyclization, Hydroalkoxylation, and Intramolecular Oxycyclization Strategies for Complex Heterocycle Synthesis.

This chapter offers a concise overview of cascade reactions, primarily emphasizing Prins cyclization, hydroalkoxylation and intramolecular oxycyclization reactions. It includes a brief discussion about cascade strategy and its application in synthesizing various heterocycles. The chapter then explores different types of Prins cyclization reaction, highlighting their utility in developing fused, bi-cyclic, spiro and bridged heterocyclic motifs. Additionally, it also discusses the aspects of hydroalkoxylation

processes and intramolecular oxycyclization strategies in the advancement of complicated heterocycles. The chapter aims to deliver a comprehensive understanding of the approaches and their importance in the development of complex molecular frameworks in contemporary synthetic chemistry.

Chapter II: Synthesis of Pyrimido[2,1-*a*]isoindolone and Isoindolo[2,1-*a*]quinazolinone *via* Intramolecular Aza-Prins Type Reaction.

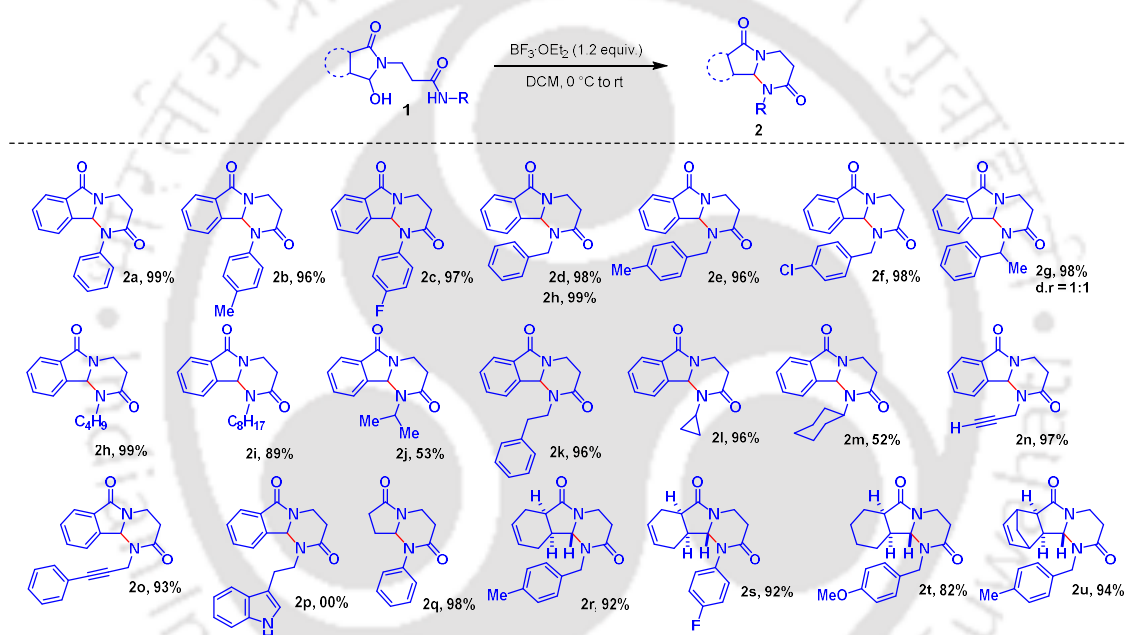
This chapter outlines a highly efficient protocol for the synthesis of tetrahydropyrimido[2,1-*a*]isoindole-2,6-dione and 6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione derivatives through intramolecular aza-Prins type cyclization reaction of *N*-acyliminium ions and amides. The resulting products are obtained in excellent yields with a broad substrate scope. Notably, the strategy operates under metal-free conditions and utilizes inexpensive reagents to provide functionalized N-heterocyclic frameworks. Furthermore, post-synthetic modification results in the unprecedented formation of its triazole, tetracyclic diazacyclopenta[*def*]phenanthrene-1,4(9*a*1*H*)-dione and carbonyl derivatives (Scheme 1).



Scheme 1. Aza-Prins cyclization of *N*-acyliminium ion and amides.

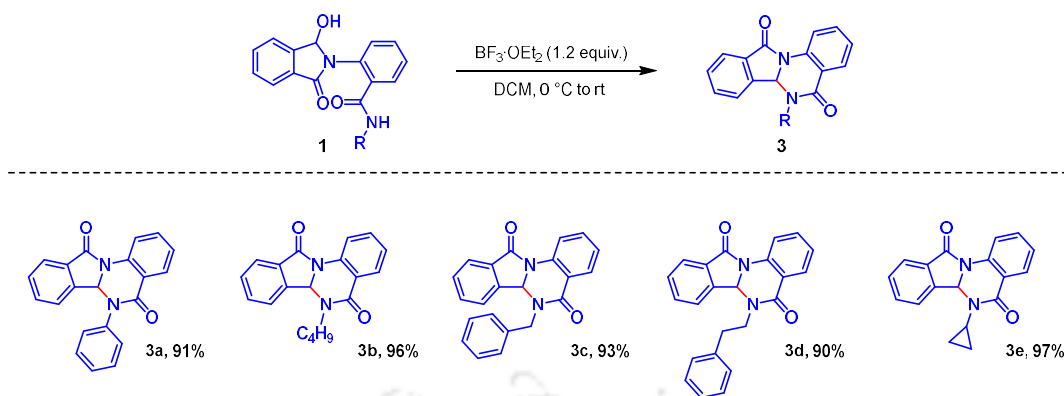
Considering 3-(1-hydroxy-3-oxoisoindolin-2-yl)-*N*-phenylpropanamide as model substrate, the reaction was performed with 1.0 equivalent of $\text{BF}_3\cdot\text{OEt}_2$ in DCM under nitrogen atmosphere. To our delight, the desired compound was obtained in 92% yield. Encouraged by the result, the reaction was screened in solvents like toluene, DCE, acetonitrile, along with various Lewis and Brønsted acids. Finally, $\text{BF}_3\cdot\text{OEt}_2$ (1.2 equiv.) in DCM at 0 °C to room temperature are found to be the optimized conditions for the reaction.

With these optimum conditions in hand, the substrate scope of the reaction was investigated (Scheme 2). Amides with electron-donating and electron-withdrawing groups gave their respective products in excellent yields. Additionally, aliphatic amides were also found to be compatible with the reaction conditions. However, heterocyclic amide failed to afford any product. Next, the imide part of the starting material was explored, and the results were very appealing with the products obtained in high yields. The structure of all compounds was determined with the help of ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR, and mass spectrometry. Finally, the structure of the compound was determined by single crystal X-ray analysis of **2a**.



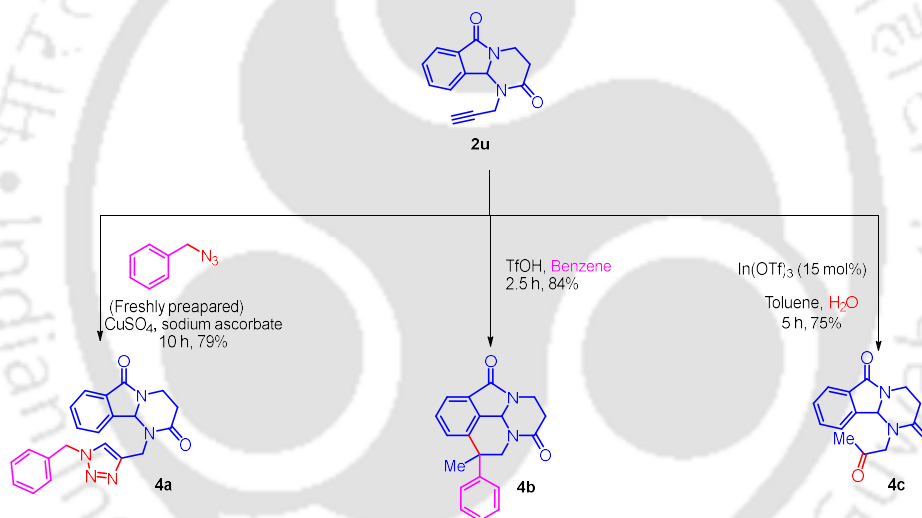
Scheme 2. Synthesis of tetrahydropyrimido[2,1-a]isoindole-2,6-dione derivatives.

Furthermore, the strategy was expanded for the synthesis of isoindolo[2,1-a]quinazoline-5,11-dione derivatives (Scheme 3).



Scheme 3. Synthesis of Isoindolo[2,1-a]quinazoline-5,11-dione derivatives.

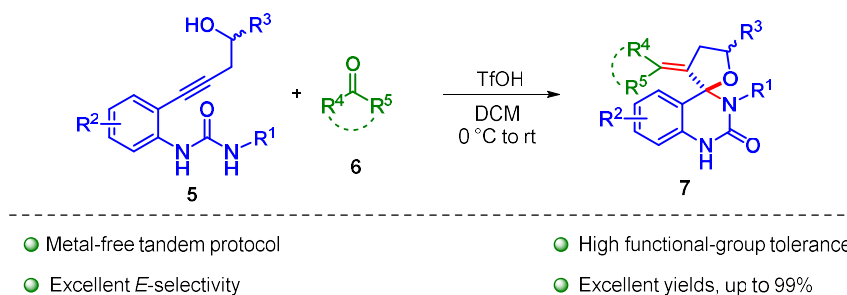
Utility of the reaction can be extended to the synthesis of its triazole, tetracyclic diazacyclopenta[def]phenanthrene-1,4(9a1H)-dione and carbonyl derivatives (Scheme 4).



Scheme 4. Post synthetic transformations.

Chapter III: Leveraging Cascade Alkynyl Prins Cyclization Towards the Stereoselective Synthesis of Spiro-Furan Quinazolinone Scaffolds

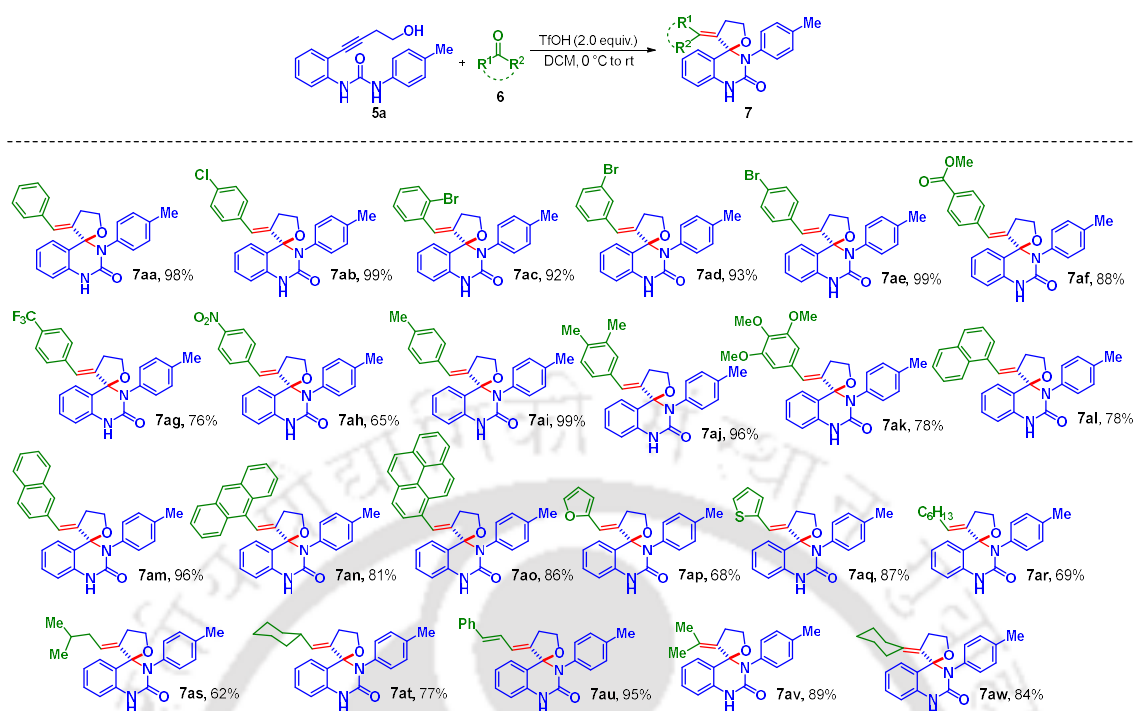
This chapter describes a metal-free protocol for the synthesis of spiro-furan quinazolinones utilizing cascade alkynyl Prins cyclization reaction. The strategy features highly functionalized spiro-heterocycles in excellent yields with exclusive *E*-selectivity under ambient conditions. Furthermore, post synthetic modifications includes bromination and acetylation of the synthesized spiro-heterocycles (Scheme 5).



Scheme 5. Cascade alkyne Prins cyclization towards the synthesis of spiroquinoxalinone scaffolds.

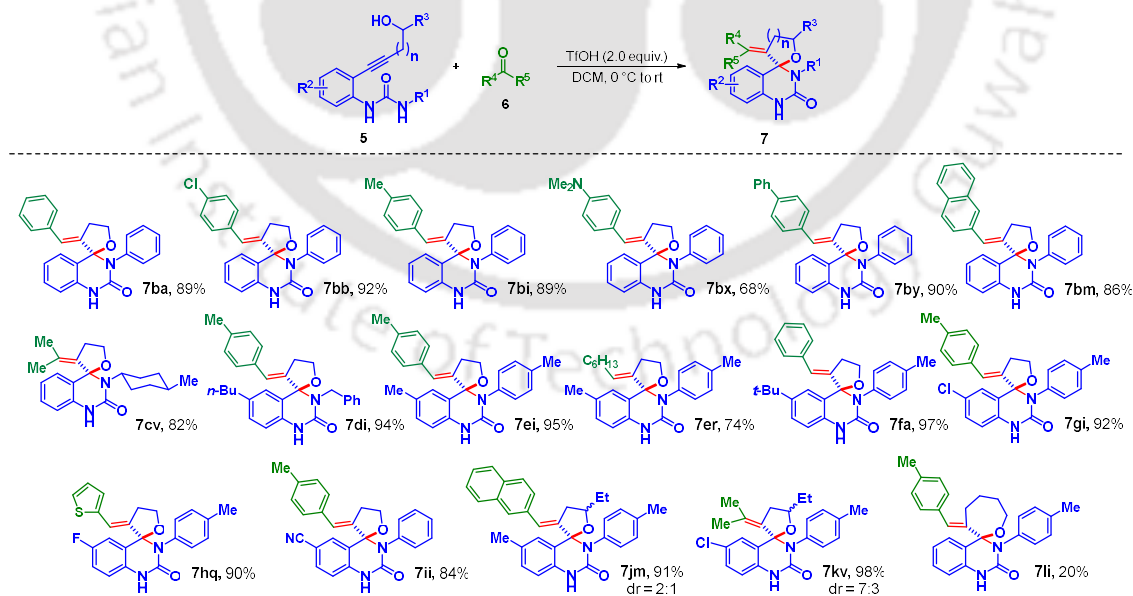
A preliminary investigation was carried out between 1-(2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-phenylurea and *p*-chlorobenzaldehyde in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ in DCM at 0 °C to room temperature. The reaction endowed the desired spiro-furan quinoxalinone product **7** within 2 h in a good yield of 86%. However, a mixture of geometrical isomers in the ratio *E*:*Z* = 7:3 was obtained. Spectroscopic evidence (^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR) and HRMS values revealed the structure of the product to be 3-(4-chlorobenzylidene)-3'-phenyl-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,4'-quinoxalin]-2'(3'*H*)-one (**7bb**). However, the exact structure of the product was fully ascertained by single-crystal X-ray diffraction of one of its derivatives **7ai**. Further screening of the reaction parameters was done to enhance the selectivity and productivity of the reaction. Finally, the use of 2.0 equiv. of TfOH in DCM at 0 °C to room temperature are found to be the optimized condition for this transformation.

With the optimized condition in hand, the substrate scope for the transformation was studied with various aldehydes and ketones (Scheme 6). Electron-donating and electro-withdrawing benzaldehydes efficaciously furnished their respective product in high yields with excellent diastereoselectivity. Polyaromatic and heterocyclic aldehydes were also well tolerated in the transformation. Aliphatic aldehydes also proved to be effective, resulting the products in high yields. Furthermore, the strategy was successfully extended to ketones, resulting in high-yielding products as well.



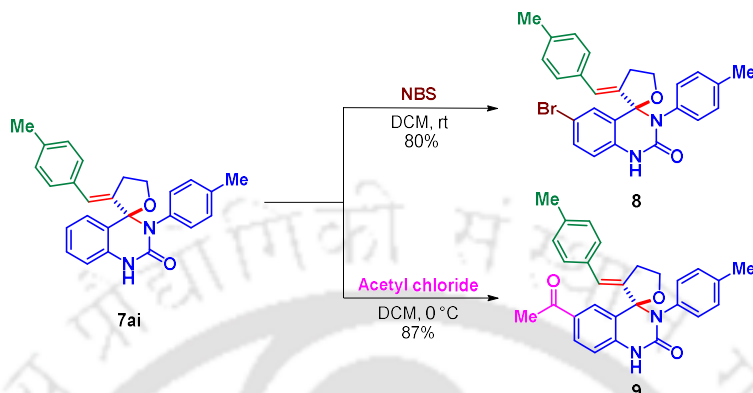
Scheme 6. Scope of the aldehydes.

Next, the alkynol urea was varied with different electron-donating and electron-withdrawing substituents. Remarkably, all variations proved to be effective, yielding fruitful results (Scheme 7).



Scheme 7. Scope of the alkynol ureas.

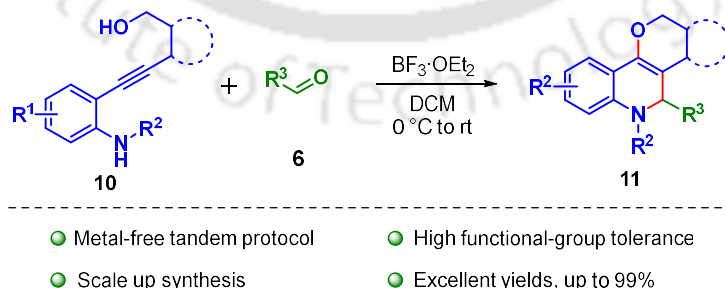
To investigate the synthetic utility of the spirocyclic product, bromination and acetylation reaction were performed. Both transformations resulted in the formation of their respective products with high yields (Scheme 8).



Scheme 8. Post synthetic transformations.

Chapter IV: Cascade Aza-Prins Cyclization and Hydroalkoxylation Reaction: *En Route* to Stereoselective Pyrano- and Isochromeno-Quinoline Scaffolds

The chapter highlights a Lewis acid mediated protocol for the stereoselective synthesis of pyranoquinoline scaffolds. The reaction goes *via* aza-Prins cyclization and hydroalkoxylation in a concerted manner. The strategy has also been expanded to synthesize isochromenoquinoline frameworks in high yields. Furthermore, post synthetic modification includes Rh(III)-catalyzed oxidative C-H bond activation, followed by N-annulation of pyrano[3,2-*c*]quinoline derivatives with diphenylacetylene, which results in isoquinolino[2,1-*a*]pyrano[3,2-*c*]quinolinium salts in excellent yields (Scheme 9).

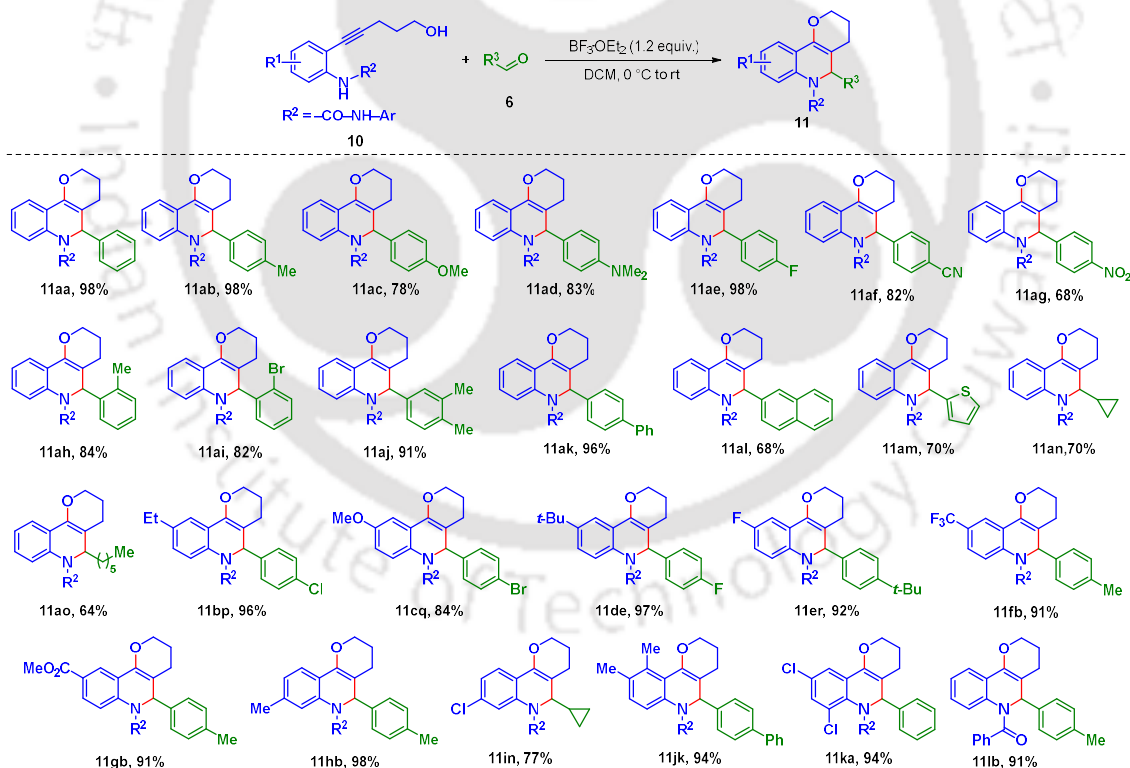


Scheme 9. Aza-Prins cyclization-hydroalkoxylation of alkynol ureas and aldehydes.

To start with 1-(2-(5-hydroxypent-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea and *p*-tolualdehyde were reacted in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ in DCM at 0 °C to room

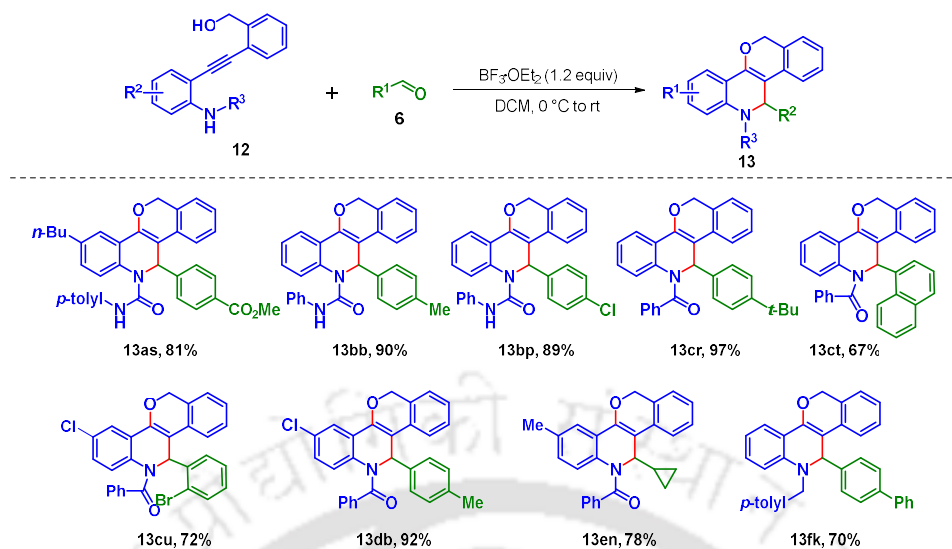
temperature. To our delight, a new product (*S*)-*N*,5-di-*p*-tolyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinoline-6(5*H*)-carboxamide was isolated with a yield of 99%. The structure of the compound was determined with the help of ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR, and mass spectrometry. Finally, the structure of the compound was determined by single crystal X-ray analysis. The reaction was investigated with various reagents and solvents. $\text{BF}_3\cdot\text{OEt}_2$ in DCM 0 °C to room temperature turned out to be the optimized reaction conditions for this transformation.

With the established optimum condition, the scope of the reaction was investigated (Scheme 10). Electron-donating and electro-withdrawing aromatic aldehydes provide the products in high yields. Polyaromatic, heterocyclic and aliphatic aldehydes were also tolerated in this transformation. Next, the urea substituted alkynol was varied with various electron-donating and electron-withdrawing substituents. The products were obtained in high yields.



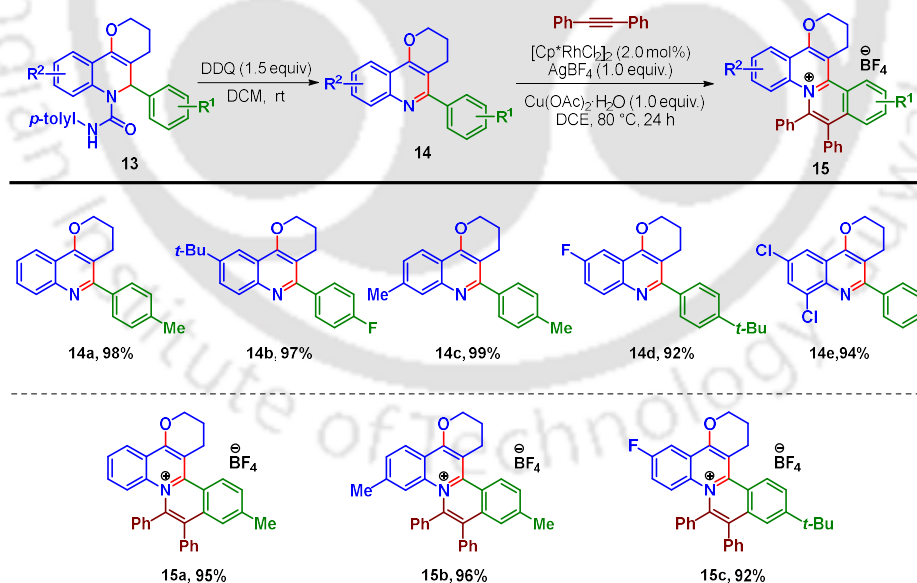
Scheme 10. Synthesis of dihydropyrano[3,2-*c*]quinoline derivatives.

Furthermore, the strategy was extended to encompass the synthesis of isochromenoquinoline derivatives (Scheme 11).



Scheme 11. Synthesis of dihydro isochromenoquinoline derivatives.

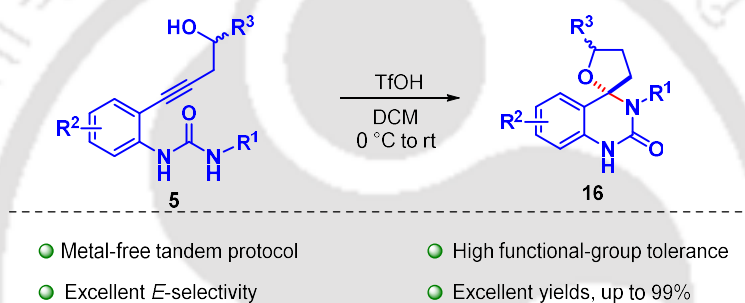
For post synthetic modifications, the dihydro-2*H*-pyrano[3,2-*c*]quinoline-6(5*H*)-carboxamide derivatives were oxidized to pyrano[3,2-*c*]quinoline frameworks, which were further reacted with diphenyl acetylene in presence of $[\text{Cp}^*\text{RhCl}_2]_2$ to give the isoquinolino[2,1-*a*]pyrano[3,2-*c*]quinolinium salts (Scheme 12).



Scheme 12. Post synthetic transformations.

Chapter V: Regioselective Synthesis of Spiro Quinazolinones *via* Sequential Hydroalkoxylation and Intramolecular Amide-Cyclization of Alkynol Ureas

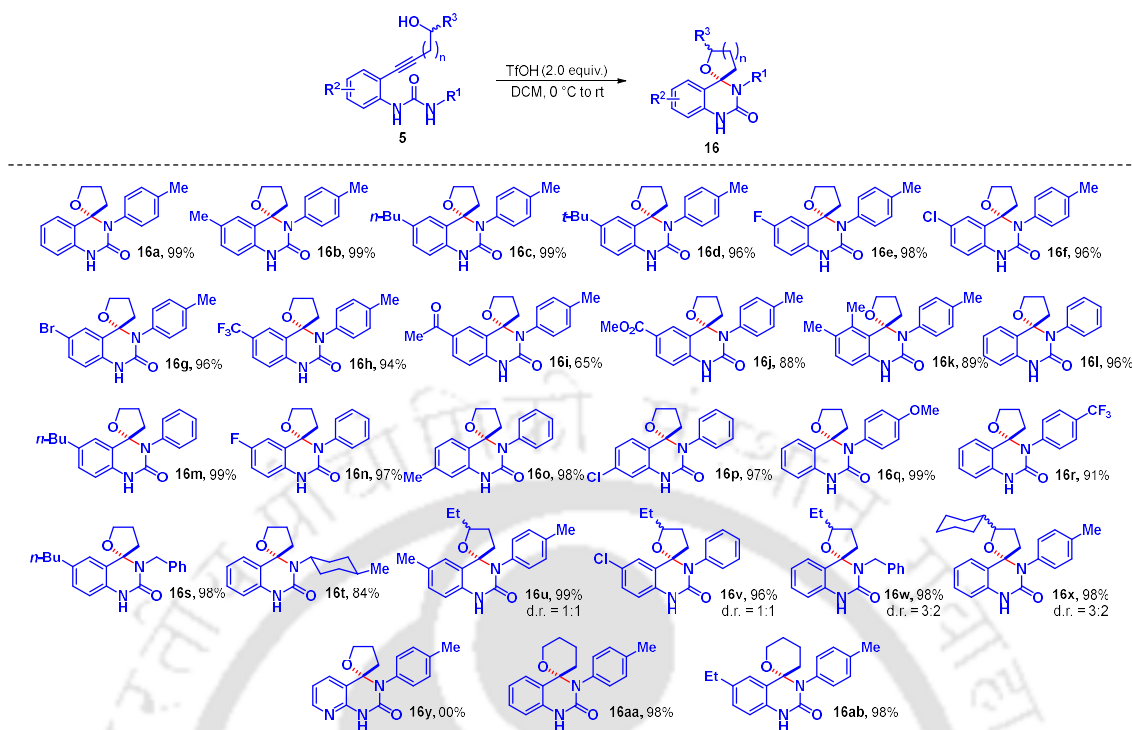
The chapter outlines the synthesis of spiro-furan/pyran quinazolinones *via* a cascade hydroalkoxylation and intramolecular amide-cyclization reaction of alkynol ureas. This TfOH acid mediated protocol enables the production of highly functionalized spiro-heterocycles with impressive yields and exclusive regioselectivity. Moreover, this strategy can also be employed for the synthesis of spiro-pyrrolidine quinazolinones. Additionally, post-synthetic modification allows the incorporation of bromide functionality into the synthesized spiro-heterocycle (Scheme 13).



Scheme 13. Regioselective synthesis of spiroquinazolinones.

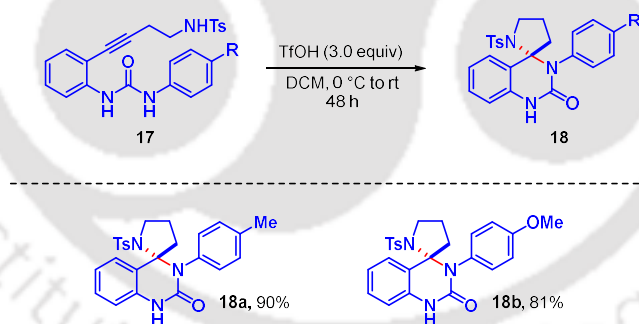
Considering 1-(2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-phenylurea as model substrate, a preliminary investigation was conducted in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ in DCM at 0°C to room temperature. The reaction resulted in a new spiro-furan quinazolinone derivative. Spectroscopic data (^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR) and HRMS, established the product as 3'-phenyl-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one. Subsequently, the precise structure was confirmed through single-crystal X-ray diffraction on one of its derivatives, **16a**. To enhance the efficiency of the transformation, the reaction was systematically explored with various reagents and solvents.

With the optimized condition in hand, the generality of the reaction was checked with various electron-donating and electron-withdrawing alkynol substituted ureas (Scheme 14). The products obtained were in high yields. The methodology was also applied to secondary alkynol ureas. Although, the yield of the products was high, the diastereoselectivity was relatively low.



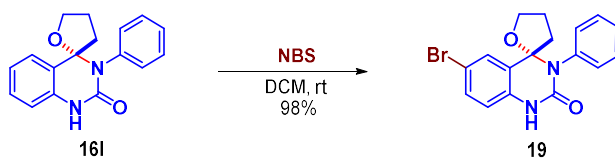
Scheme 14. Synthesis of spiroquinazolinone derivatives.

Additionally, the strategy was extended to synthesize spiro-pyrrolidine quinazolinone derivatives (Scheme 15).



Scheme 15. Synthesis of spiro-pyrrolidine quinazolinones.

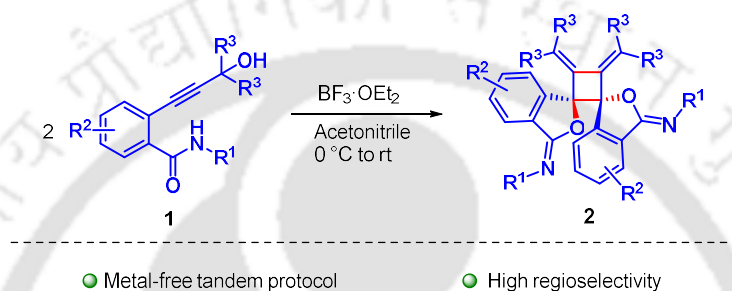
Post synthetic modification includes incorporation of bromide substituent in the spirocyclic framework (Scheme 16).



Scheme 16. Post synthetic transformation.

Chapter VI: Regioselective Synthesis of Spiro-Isobenzofuran Cyclobutanes from *o*-Alkynol Benzamides *via* Oxycyclization and [2+2] Cycloaddition Reaction

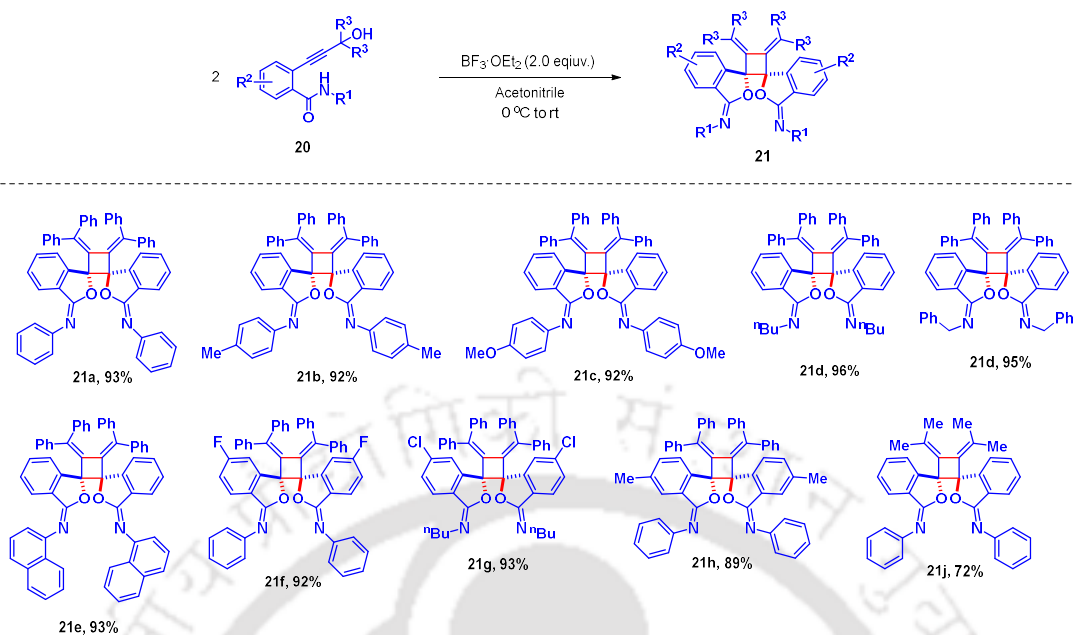
This chapter describes a Lewis acid-mediated protocol to synthesize dispiro-[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-diamine derivatives in high yields utilizing propargyl alcohol substituted benzamides. A notable aspect of this strategy is its emphasis on highly regioselective synthesis of polysubstituted cyclobutanes *via* [2+2] cycloaddition of allenes (Scheme 17).



Scheme 17. Synthesis of spiro-siobenzofuran cyclobutanes.

To begin with, 2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)-N-phenylbenzamide was subjected to 1.2 equiv. of $\text{BF}_3 \cdot \text{OEt}_2$ in DCM at 0 °C to rt. To our surprise, a new product in 72% yield was isolated. Later, spectroscopic data (^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR and HRMS) revealed the product to be (3*E*,3''*E*)-3',4'-bis(diphenylmethylene)-*N*3,*N*3''-diphenyl-3*H*,3''*H*-dispiro[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine. Single-crystal X-ray diffraction analysis of one of its derivatives confirmed the structure. Further, in search of optimized conditions, the reaction was screened with various reagents and solvents. Finally, 2.0 equiv. of $\text{BF}_3 \cdot \text{OEt}_2$ in acetonitrile turned out to be the optimized reaction conditions for the transformation.

With the optimized reaction conditions, the substrate scope of the reaction was investigated (Scheme 18). Electron-donating and electron-withdrawing amides furnished their respective spirocyclobutane in high yields. Aliphatic amides also performed well under the reaction condition.



Scheme 18. Synthesis of functionalized spiro-isobenzofuranimine cyclobutanes.



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CHAPTER I

**Cascade Reaction, Prins Cyclization,
Hydroalkoxylation, and Intramolecular Oxy-
Cyclization Strategies for Complex Heterocycle
Synthesis**



Chapter I

Cascade Reaction, Prins Cyclization, Hydroalkoxylation, and Intramolecular Oxy-Cyclization Strategies for Complex Heterocycle Synthesis

1.1. Cascade Reaction

Nature, as we know it today, has undergone eons of evolution to create a sustainable environment for life on Earth with invaluable natural resources. Modern organic chemistry now offers a myriad of efficient processes for synthesizing numerous natural products. Organic chemistry, with its roots, dates to the early 1800s, a time when humans heavily relied on nature for organic chemicals. Even today, natural feedstocks remain a significant source of pharmaceuticals.¹ Early chemists used to isolate natural products for their use in medications while simultaneously trying to synthesize these compounds using conventional methods.² They soon realized the intricate complexities of the process and learned to mimic the proficiency displayed in nature's biosynthetic processes. The remarkable efficiency of these biosynthetic reactions is partly linked with nature's extensive use of cascade reactions. This efficiency can be further enhanced by combining cascade reactions with the exclusion of protecting groups.³

With the increase in structural and stereochemical complexities of organic molecule, target-oriented synthesis has become a significant intellectual challenge for the chemists. This impressive activity requires expertise in regioselectivity, chemoselectivity, diastereoselectivity, and enantioselectivity to achieve an effective outcome. The traditional process of synthesizing a targeted molecule involves the stepwise generation of individual bonds to construct the desired compound. However, this stepwise process is associated with several reaction solvents, workup procedures, and purification steps for each reaction. Thus, developing a strategy to carry out several transformations in a single sequence without isolating the intermediates would be more efficient and beneficial, as it would require fewer reagents, solvents, energy, and labour.⁴ Reducing waste in a chemical process and conserving the Earth's natural resources through this approach would address some

of society's major concerns. This one step process has been documented in various context and different terms have been used to refer them.

Type I processes, often called 'domino' or 'cascade' reactions, consist of a well-planned series of tightly integrated reactions to facilitate the one-pot construction of several bonds. The steps involved in this process are inseparable and difficult to perform independently. Therefore, the intermediates formed between these steps are unstable, and their isolation and characterization are elusive (Figure 1.1.1).

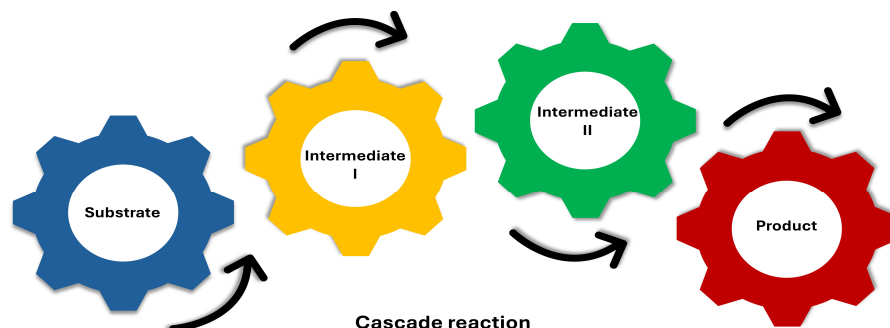


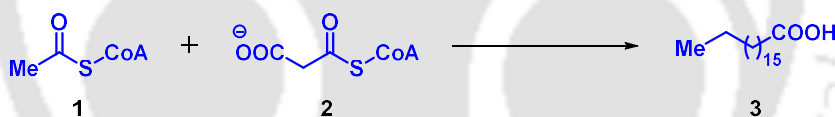
Figure 1.1.1. Cascade or domino reaction.

In contrast, *type II processes* involve 'sequential' or 'tandem' reactions that proceed consecutively, with each step capable of being completely independent. The intermediates associated with these steps are relatively stable and can be isolated for further characterization.

The efficiency of a reaction is contingent upon its capacity to establish chemical bonds, enhance structural intricacy, and possess broad applicability. Bond forming efficacy is a measure of the quantity of bonds that are created in a consecutive sequence. The production of palytoxin is a remarkable example of a cascade reaction. The structural complexity of palytoxin is emphasized by the presence of 64 stereogenic sites, resulting in more than 10^{19} possible stereoisomers.⁵ The development of these cascade reactions has delivered a considerable impact on the field of total synthesis, by strengthening both the practical efficiency and wide application of the process. Furthermore, they have also added to the aesthetic attractiveness of synthetic planning.

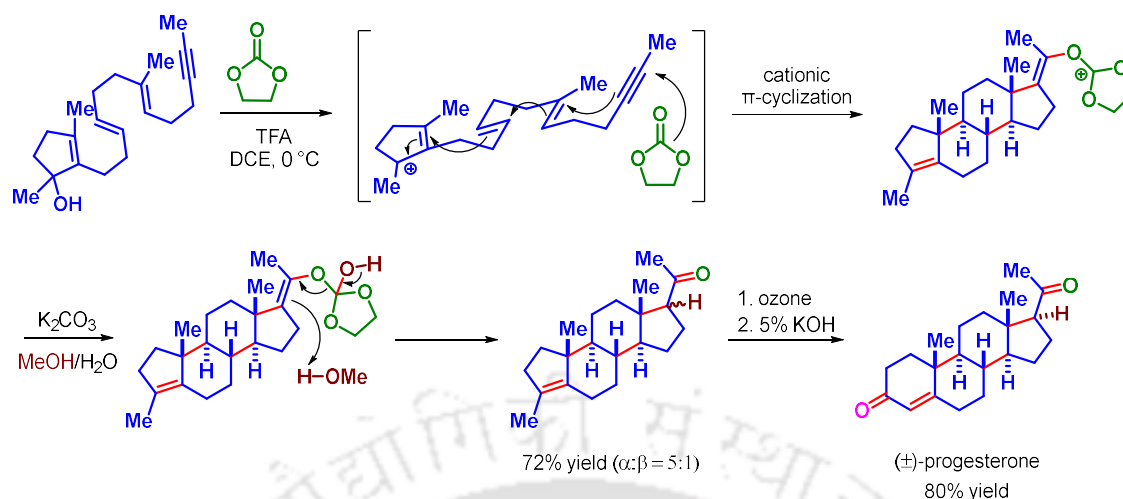
1.1.1. Historical Background

Domino reactions are very common in nature, as evidenced by the synthesis of diverse compounds such as fatty acids from acetate, steroids, progesterone, daphnilactone A, and (+)-codaphniphylline through cascade processes.⁶ Natural forces have selectively developed and improved the characteristics of biological macromolecules to aid the survival of the host organism. These adaptive forces have equipped enzymes with the ability to catalyze reactions at astonishing speeds, sometimes up to 10^{17} times faster. A direct comparison of the complexity and rapidity of these multi-enzyme reactions to lab-based synthetic methodologies is neither feasible nor justifiable. An exceptional instance of a natural cascade reaction is the biosynthesis of fatty acids from acetate. Remarkably, the process halts after mixing acetate **1** with 7.0 or 8.0 equiv. of malonyl-S-CoA (**2**), providing palmitic acid or stearic acid (**3**). Achieving such exact control in a laboratory environment is very challenging (Scheme 1.1.1.1).⁷ Another such example is the production of steroids from squalene epoxide, which is preferentially transformed into lanosterol, establishing four carbon-carbon bonds with the generation of six stereogenic centers.⁸



Scheme 1.1.1.1. Biosynthesis of fatty acids.

Cascade or domino reactions, whether anticipated or stumbled upon, have always intrigued synthetic organic chemists from the early days of total synthesis. One of the earliest and most significant discoveries in this area was made by Schöpf and Robinson in 1917. The combination of succinaldehyde, acetone dicarboxylic acid, and methylamine using double Mannich reactions, resulted in the formation of tropinone.⁹ This pioneering work established the Mannich reaction as the earliest known cascade reaction in the scientific literature.¹⁰ Following this, Johnson and his team developed a method to synthesize progesterone *via* cationic polyolefin cyclization, inspired by the Stork-Eschenmoser hypothesis (Scheme 1.1.1.2).^{6c,d}



Scheme 1.1.1.2. Total synthesis of ($\pm$)-progesterone *via* polyolefin cyclization.

1.1.2. Classification of Cascade Reactions

Due to the varied nature of the steps involved in a cascade reaction, classifying them is a very challenging task. According to L. F. Tietze, a cascade reaction is a sequence of bond-forming transformation that occur under the same conditions without the need for additional reagents or catalysts, with each subsequent reaction directed by the functional groups formed in the preceding step.^{3a} L. F. Tietze classified the cascades reactions based on the nature of the first step in the mechanism into the following categories:

- Anionic Cascade Reactions
- Cationic Cascade Reactions
- Pericyclic Cascade Reactions
- Radical Cascade Reactions
- Transition-Metal-Induced Cascade Reactions
- Enzymatic Cascade Reactions
- Photochemical-Induced Cascade Reactions
- Cascade Reactions Induced by Oxidation/Reduction

A crucial aspect to highlight in cascade reaction is that at least two transformations need to occur, with each step in the sequence relying on the outcome of the preceding one. Despite the challenges in developing cascades to produce molecules with specific

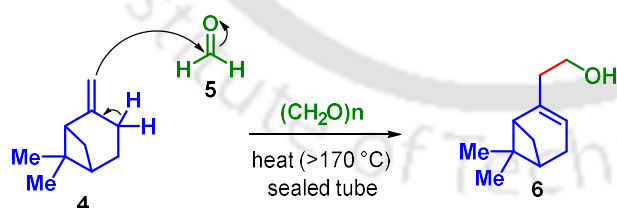
structural and stereochemical properties, these reactions remain one of the most powerful tools in organic chemistry.

In the following section of this chapter, we will explore Prins cyclization, hydroalkoxylation, and intramolecular oxycyclization. Each of these reactions will be examined in detail, with a particular focus on their cascade approaches. We will discuss how these cyclizations function individually and in concert, highlighting the innovative strategies that enhance their efficiency and versatility in synthetic chemistry.

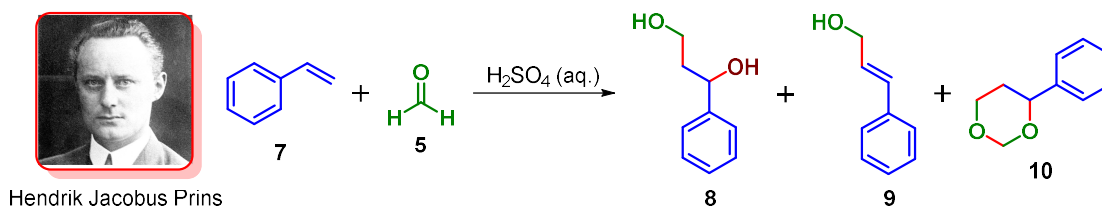
1.2. Prins Reaction

In 1899, Kriewitz first described a method to synthesize unsaturated pinene alcohol **6** by reacting β -pinene (**4**) and paraformaldehyde (**5**) at temperatures above 170 °C.¹¹ This reaction follows an ene-type concerted route to produce the unsaturated pinene alcohol (Scheme 1.2.1.a). However, the strategy faced severe drawbacks in attaining the high temperature, thus opening an opportunity for further improvement among the chemists. Nearly twenty years after its release, a Dutch chemist, Hendrik Jacobus Prins, modified the process, allowing it to be performed at a milder temperature with the help of an acid catalyst. In 1919, Prins reported a condensation reaction of styrene (**7**) and paraformaldehyde (**5**) in the presence of aqueous H_2SO_4 , which enabled the synthesis of diglycol **8**, unsaturated alcohol **9**, and ortho-oxane **10** (Scheme 1.2.1.b).¹²

(a) Kriewitz reaction (1899)



(b) Prins reaction (1919)



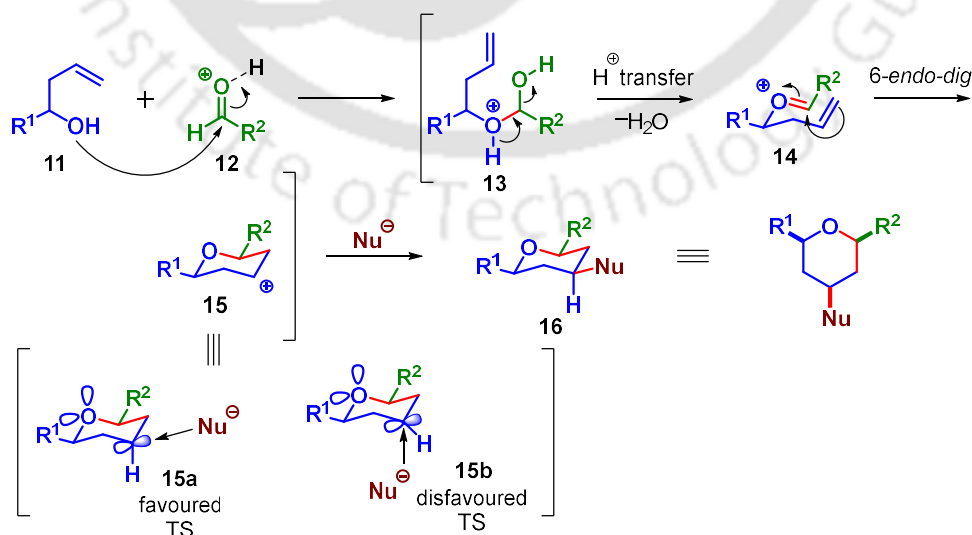
Scheme 1.2.1. (a) Kriewitz reaction and (b) Prins reaction.

This acid-catalyzed reaction proceeds *via* a stepwise mechanism with a carbenium ion intermediate. Initially, the Prins reaction was of less interest to the chemists. Nevertheless, in the late 1930s, with the advancements in the petroleum-cracking processes, the production of olefins also peaked. Consequently, the Prins reaction, which received less attention, was now reconsidered as an effective strategy for transforming the olefins into oxygenated organic compounds.¹³

1.2.1. Prins Cyclization Reaction

The Prins cyclization, as we know it today, gained worldwide attention thanks to Hanschke's groundbreaking study in 1955. His work on the selective formation of the tetrahydropyran ring through an acid-catalyzed Prins reaction between 3-butene-1-ol (**11**) and various aldehydes **12** marked a significant improvement (Scheme 1.2.1.1).¹⁴

Compared to Kriewitz's reaction, which follows a thermal ene-rearrangement, Prins cyclization generally proceeds *via* the formation of an oxocarbenium ion. This oxocarbenium ion **14** undergoes a 6-*endo* cyclization with the alkene moiety to produce a stereoselective tetrahydropyranyl carbocation **15**, which is trapped by various nucleophiles to give 4-substituted tetrahydropyran derivatives **16**. The exclusive *cis*-stereoselectivity of the Prins cyclization can be attributed to the most favourable conformation of the oxocarbenium ion, in which the 2,6-substituents adopt an equatorial orientation (Scheme 1.2.1.1).



Scheme 1.2.1.1. Stereochemical outcome of the Prins cyclization.

The formation of all-*cis*-2,4,6-trisubstituted tetrahydropyrans was explained by Alder's group using density functional theory (DFT). They reported that in the presence of an external nucleophile, the stabilization of the carbenium ion is greatly influenced by stereoelectronic effects.¹⁵ The equatorial approach of the nucleophile allows the efficient overlap of its HOMO with the vacant p-orbital of the C4 atom in TS **15a**. Additionally, the presence of the pseudoaxial C4 hydrogen atom in TS **15a** results in an optimal overlap of the σ and σ^* orbitals of C2–C3 and C5–C6 with the coplanar equatorial lone pair of the oxygen atom and the vacant p-orbital at C4. The combined effect of these orbital stabilizations, along with the absence of 1,3-diaxial interaction for the incoming nucleophile (mostly halide), results in a preferential equatorial attack, affording all-*cis*-2,4,6-trisubstituted tetrahydropyrans (Scheme 1.2.1.1).

1.2.2. Classification of Prins Cyclization

Prins cyclization has gained considerable attention owing to its potential in constructing complex molecular frameworks, which are often found in numerous natural products and biologically active compounds.¹⁶ The reaction's flexibility and ability to adjust to different substrates and conditions have led to the development of its various adaptations. In this discussion, we explore the three primary categories of Prins cyclization: classical Prins cyclization, aza-Prins cyclization, and thia-Prins cyclization. Each variant has its unique advantages and broadens the scope of applications in synthetic chemistry.

1.2.3. Classical Prins Cyclization

It is a condensation reaction between a homoallylic alcohol and carbonyl compounds in the presence of an acid catalyst to form oxygen heterocycles. Prins cyclization had played a major role in the synthesis of various natural products. For instance, Dallavalle's group employed Prins cyclization strategy for the synthesis of (+)-spiroloxine methyl ether, a metabolite of the fungus *Sporotrichum laxum*.¹⁷ Overman's group utilized a Prins–pinacol reaction sequence for the total synthesis of sclerophytin A.¹⁸ Furthermore, the application of Prins cyclization extends to the flavour and fragrance industries in synthesizing various fragrance ingredients (Figure

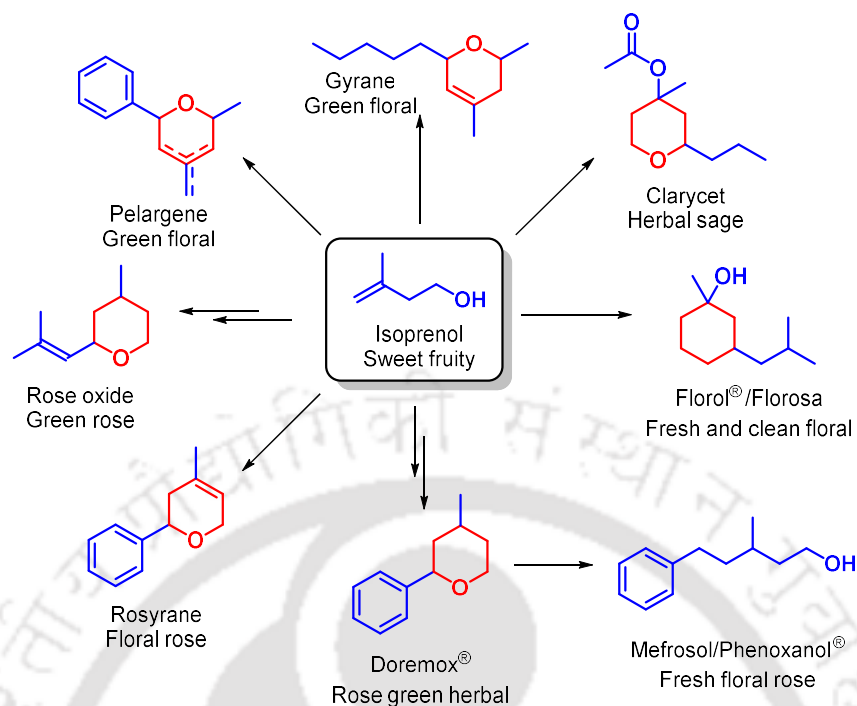


Figure 1.2.3.1. Fragrance ingredients derived from isoprenol utilizing Prins cyclization.

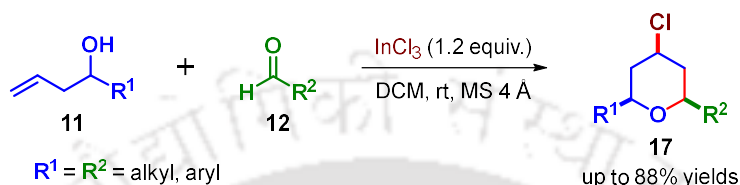
1.2.3.1).^{16a} With the growing popularity of the reaction, various modifications were implanted for the starting materials and nucleophiles, as listed below.

1.2.3.1. Modification of the Nucleophiles

Alterations of nucleophiles in Prins cyclization have increased the range and adaptability of the reaction, thereby enabling it to accept varied functional groups. By modifying the characteristics of the Lewis acid and adjusting the nucleophiles involved, it is possible to influence the reaction outcome and create a wide variety of cyclized products with various oxygenated functional groups like alcohols, ethers, or esters, as well as nitrogen-containing functional groups like amides or azides, at C4 position. This modification of the reaction to satisfy the individual synthetic needs and enhance the yields is of vital significance. Based on the types of nucleophiles incorporated for the reaction, Prins cyclization can be further classified into the followings.

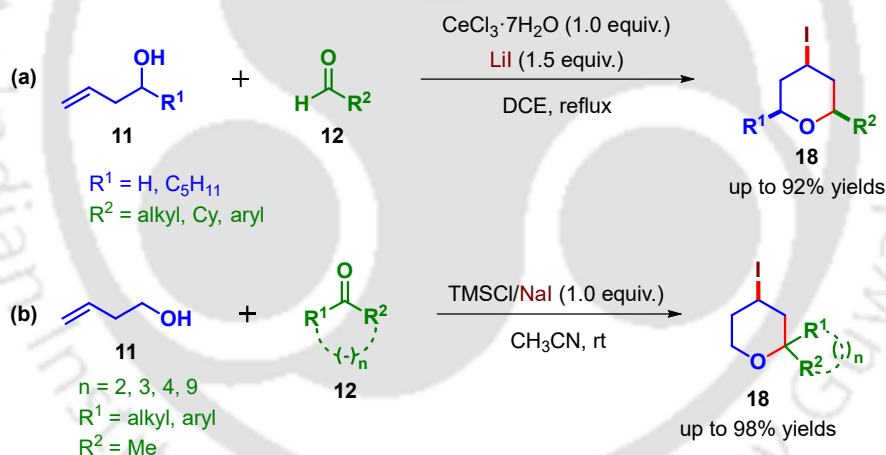
1.2.3.1.1. Trapping with Halogen Nucleophiles (Halo-Prins Cyclization)

Li's group reported an indium trichloride mediated synthesis of symmetrical 2,6-dialkyl-4-chlorotetrahydropyrans **17** from homo allylic alcohols **11** and aldehydes **12**. The tetrahydropyrans were achieved in high yields, with high stereoselectivity (Scheme 1.2.3.1.1.1.).¹⁹



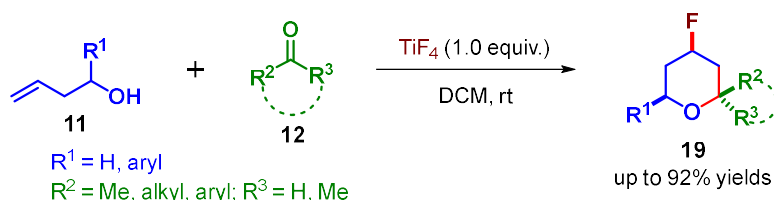
Scheme 1.2.3.1.1.1. InCl₃-promoted synthesis of 4-chlorotetrahydropyrans.

Yadav's group demonstrated various strategies to synthesize 4-iodo-tetrahydropyrans **18** *via* Prins cyclization utilizing any of the following system: CeCl₃·7H₂O/LiI (Scheme 1.2.3.1.1.2.a)^{20a} or TMSCl/NaI (Scheme 1.2.3.1.1.2.b).^{20b}



Scheme 1.2.3.1.1.2. Synthesis of 4-iodotetrahydropyrans.

The use of fluorides as nucleophiles in the Prins cyclization is quite rare. However, a few works have been documented using fluorides to capture the intermediate



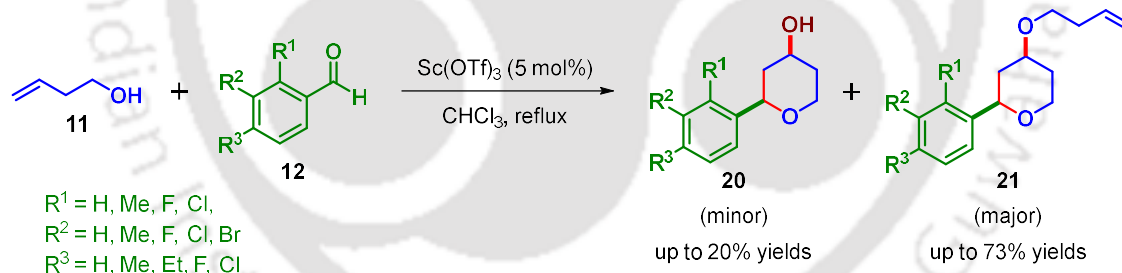
Scheme 1.2.3.1.1.3. TiF₄-mediated synthesis of 4-fluorotetrahydropyrans.

carbocation of the Prins cyclization. In this context, Saikia's group has effectively utilized titanium tetrafluoride, as the fluoride source for the stereoselective synthesis of 4-fluorotetrahydropyrans (Scheme 1.2.3.1.1.3).²¹

1.2.3.1.2. Trapping with Oxygen Nucleophiles

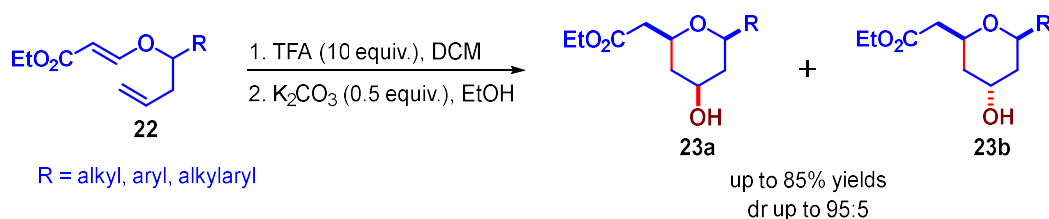
Various examples of Prins cyclization have been documented where the tetrahydropyranyl cation is captured by oxygen-centered nucleophiles. The formation of tetrahydropyrans with an oxygen atom in C4 position can be achieved by replacing the more reactive halide ligands in the Lewis acid by the oxygenated ligands of lower nucleophilicity.

Li's group described a scandium triflate-catalyzed Prins cyclization of 3-buten-1-ol (**11**) with aromatic aldehydes **12**. However, the reaction provided 4-hydroxy-tetrahydropyrans **20** in minor quantities, while their corresponding ethers **21** turned out to be the major product. This outcome was due to the excess use of homoallylic alcohol, which trapped the in situ generated tetrahydropyranyl cation, resulting in ethers being the main Prins product (Scheme 1.2.3.1.2.1).²²



Scheme 1.2.3.1.2.1. $\text{Sc}(\text{OTf})_3$ -catalyzed synthesis of 4-oxy-substituted tetrahydropyrans.

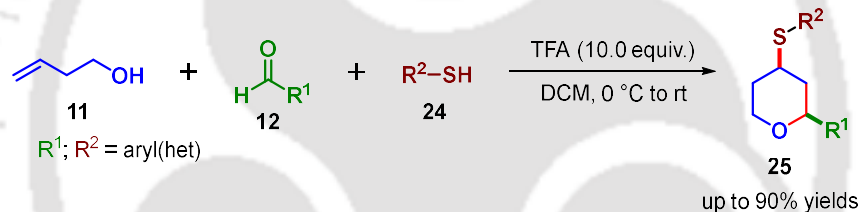
Enol ethers **22** have been efficiently cyclized by Hart's group into their corresponding 4-hydroxytetrahydropyrans **23** using trifluoroacetic acid as a promoter. The acid mediated Prins cyclization, followed by basic workup provides the pyranols **23a** and **23b** in a combined yield of 42–85%, with stereoselectivities at C4 atom ranging from 95:5 to 50:50 (Scheme 1.2.3.1.2.2).²³



Scheme 1.2.3.1.2.2. TFA-promoted synthesis of 4-hydroxytetrahydropyrans.

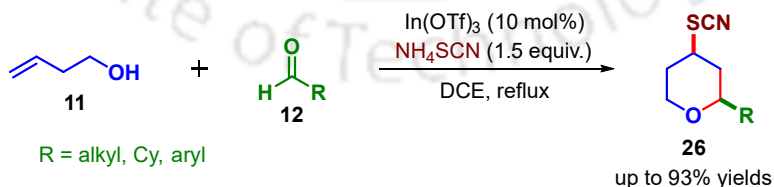
1.2.3.1.3. Trapping with Sulfur Nucleophiles

Yadav's group described a one-pot, three component strategy to synthesize 4-arylthiotetrahydropyrans **25**. The trifluoroacetic acid mediated Prins cyclization involves the reaction of a homoallylic alcohol **11** with an aromatic aldehyde **12** in presence of an aromatic or heteroaromatic thiol **24**, acting as nucleophile. The products are obtained in good yields with all-*cis*-selectivity (Scheme 1.2.3.1.3.1).²⁴



Scheme 1.2.3.1.3.1. TFA-mediated synthesis of 4-arylthiotetrahydropyrans.

The same group also developed a three-component strategy for the synthesis of 4-thiocyanotetrahydropyrans **26**. By changing the catalyst to In(OTf)₃ and the nucleophile to ammonium thiocyanate, they achieved the Prins product with all-*cis*-selectivity in excellent yields (Scheme 1.2.3.1.3.2).²⁵

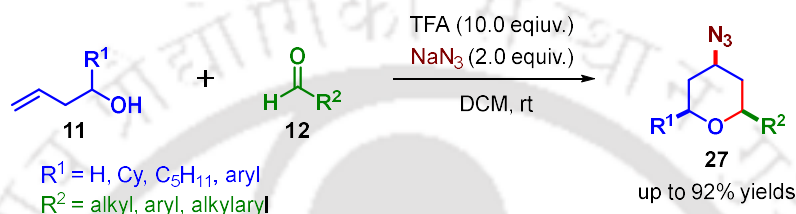


Scheme 1.2.3.1.3.2. In(OTf)₃-catalyzed synthesis of 4-thiocyanotetrahydropyrans.

1.2.3.1.4. Trapping with Nitrogen Nucleophiles

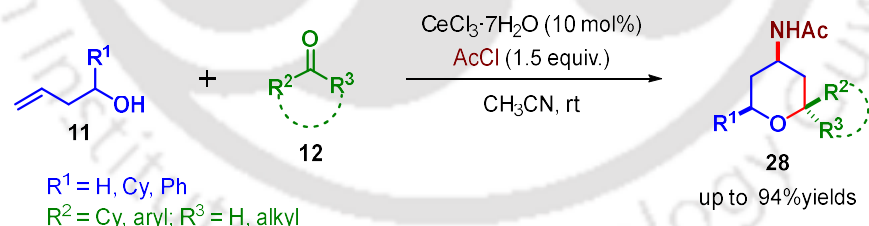
A multicomponent Prins cyclization for the synthesis 4-azidotetrahydropyran derivatives **27** was developed by Yadav's group. The trifluoroacetic acid promoted

condensation reaction between homoallylic alcohol, aldehyde and sodium azide furnished the product with all-*cis*-selectivity. It is to be noted that, under the acid-mediated condition, sodium azide transforms into hydrazoic acid, which is responsible for the capturing of the tetrahydropyranyl carbocation to give the azide substituted Prins product (Scheme 1.2.3.1.4.1).^{26a} Later, the methodology was modified to a milder version by using trimethylsilyl azide instead of explosive sodium azide in a relatively weaker acidic medium achieved by phosphomolybdic acid.^{26b}



Scheme 1.2.3.1.4.1. TFA-promoted synthesis of 4-azidotetrahydropyrans.

Yadav demonstrated that the Prins–Ritter reaction for the synthesis of 4-amido tetrahydropyrans **28** can be mediated by $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$. However, this method requires acetyl chloride to proceed successfully. This system proved effective where other Lewis acids, such as InCl_3 , InBr_3 , BiCl_3 , and ZrCl_4 failed. Under the same experimental conditions, ketones furnished spirocyclic amido tetrahydropyrans in high yields (Scheme 1.2.3.1.4.2).²⁷

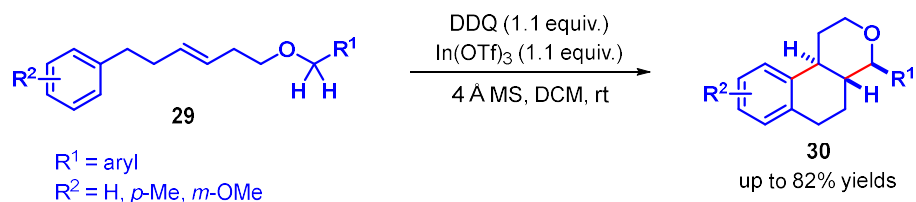


Scheme 1.2.3.1.4.2. Prins–Ritter reaction for the synthesis of 4-amido tetrahydropyrans.

1.2.3.1.5. Trapping with Carbon Nucleophiles

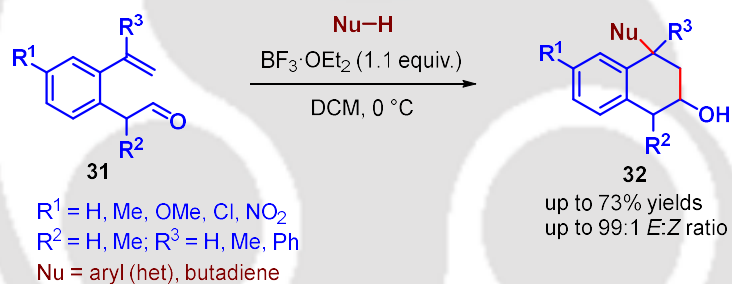
Reddy's group demonstrated a versatile protocol to efficiently synthesize oxatricycles in a single step. The reaction proceeds *via* DDQ promoted benzylic C–H activation of compound **29**, followed by intramolecular Prins cyclization reaction to

provide *trans*-fused hexahydro-benzoisochromenes **30** in good yields with excellent stereoselectivity (Scheme 1.2.3.1.5.1).²⁸



Scheme 1.2.3.1.5.1. Oxidative Prins cyclization for the synthesis of hexahydro-benzoisochromenes.

Wang's group reported a Lewis acid promoted intramolecular Prins reaction of 2-(2-vinylphenyl)acetaldehydes **31** to synthesize 4-aryl-tetralinols **32**. The reaction proceeds *via* the generation of benzyl carbenium ion, which gets trapped by variety of electron rich benzene or heteroaromatic systems to yield the final product (Scheme 1.2.3.1.5.2).²⁹



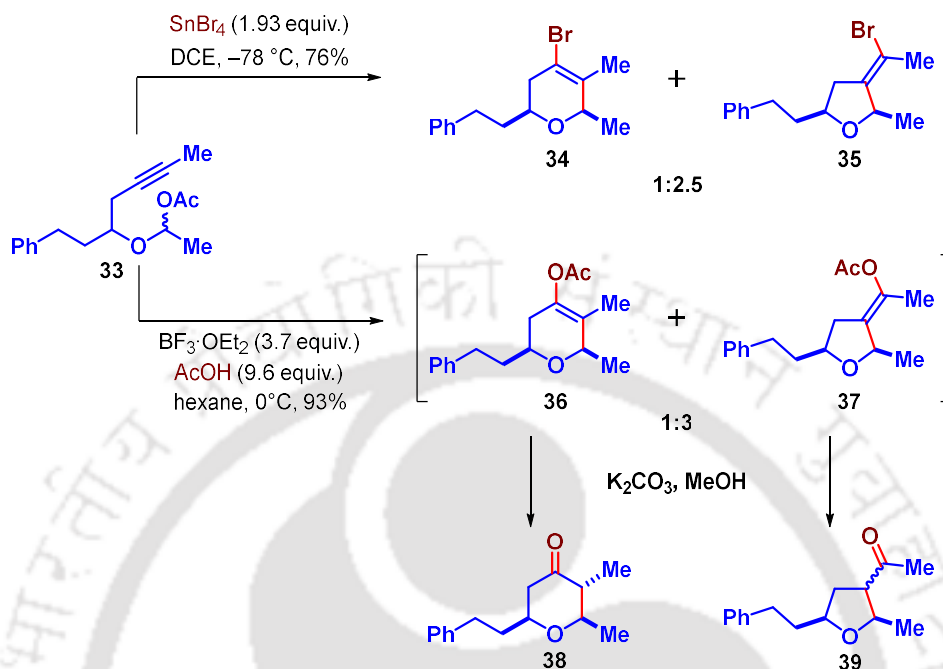
Scheme 1.2.3.1.5.2. Intramolecular Prins cyclization for the synthesis of aryl-tetrahydrobenzoannulenols.

1.2.3.2. Modification of the Starting Materials

1.2.3.2.1. Alkynyl Prins Cyclization

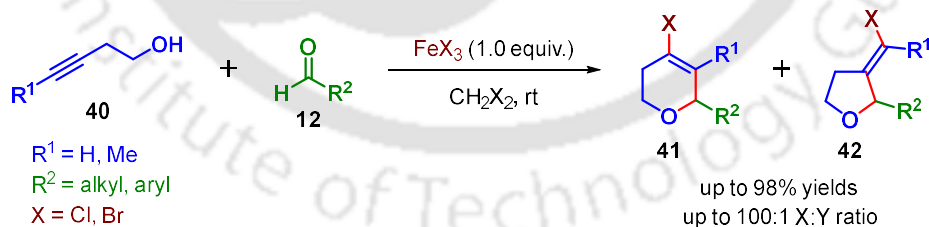
In 2001, Rychnovsky's group reported a SnBr_4 or $\text{BF}_3 \cdot \text{OEt}_2$ promoted alkynyl Prins cyclization of α -acetoxy ethers. When compound **33** was subjected to SnBr_4 in DCM at -78 °C, it furnished the cyclized products **34** and **35** in 76% yield, with a 1:2.5 ratio of distal to proximal bromine incorporation. However, when the reagent was replaced with a mixture of acetic acid and $\text{BF}_3 \cdot \text{OEt}_2$, a regioisomeric acetate-trapped cyclized products **36** and **37** were obtained in a ratio of 1:3. Basic workup of the reaction

mixtures **36** and **37** produced the *endo*- and *exo*-cyclic ketones **38** and **39**, respectively, in 93% yield (Scheme 1.2.3.2.1.1).³⁰



Scheme 1.2.3.2.1.1. Alkynyl Prins cyclization of α -acetoxy ethers.

In 2003, Martin's group employed the alkynyl Prins cyclization strategy to synthesize halo-dihydropyrans. The FeX_3 ($\text{X} = \text{Cl}, \text{Br}$) mediated cyclization between homopropargylic alcohol **40** and aldehydes **12** resulted the halo-Prins product **41** and **42** in good yields (Scheme 1.2.3.2.1.2).³¹

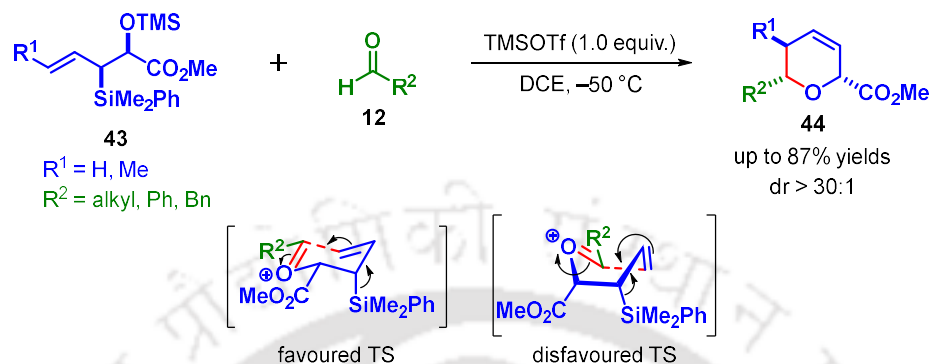


Scheme 1.2.3.2.1.2. Alkynyl Prins cyclization synthesis of halo-dihydropyrans.

1.2.3.2.2. Silyl Prins Cyclization

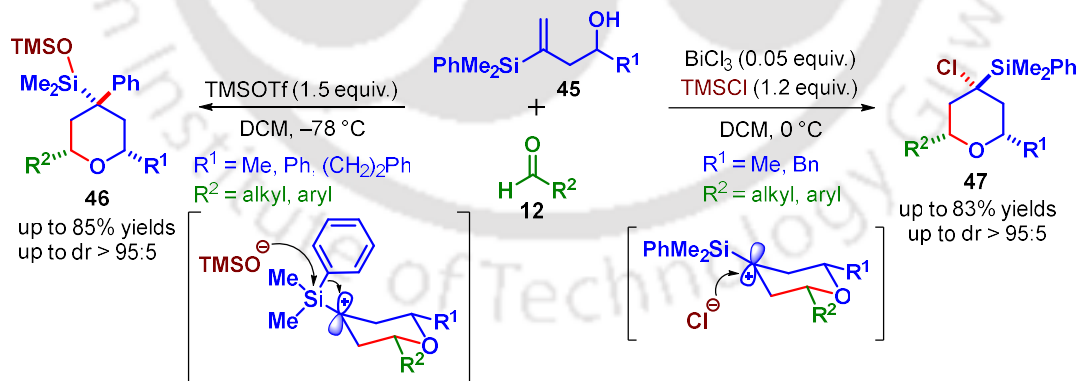
Panek's group described an interesting protocol to synthesize polysubstituted dihydropyrans from allylsilyl alcohols. The process involves the acid-promoted cyclization of chiral *syn*-allylsilyl ethers **43** with aldehydes **12**, to selectively produce the *cis*-2,5,6-trisubstituted dihydropyrans **44**. The key feature of this protocol is its

ability to dictate the configuration of the C2 and C6 substituents in the final tetrahydropyran product by manipulating the stereochemical orientations of the silyl and hydroxy groups on the allylsilane (Scheme 1.2.3.2.2.1).³²



Scheme 1.2.3.2.2.1. Silyl Prins cyclization synthesis of dihydropyrans.

Barbero's group demonstrated an attractive reagent-tunable silyl-Prins cyclization for the stereoselective synthesis of polysubstituted tetrahydropyrans from vinylsilyl alcohols **45** and aldehydes **12**. With TMSOTf as the activator, the reaction generated an α -silyl carbocation, which underwent a tandem silicon-to-carbon aryl-migration to give compound **46**. In contrast, when BiCl_3 was used, the α -silyl carbocation was subsequently captured by the counter anion of the Lewis acid to produce compound **47** (Scheme 1.2.3.2.2.2).³³

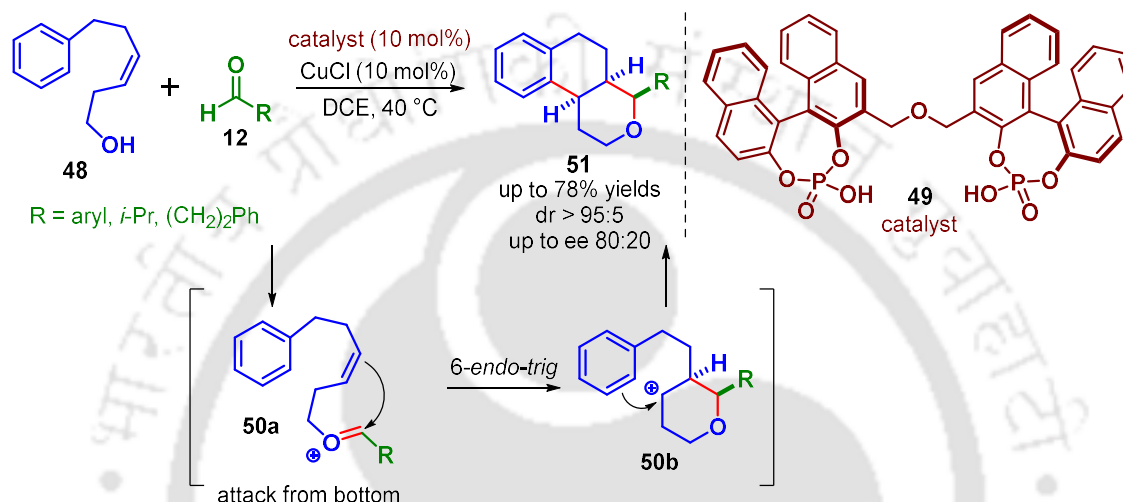


Scheme 1.2.3.2.2.2. Reagent-tunable silyl-Prins cyclization synthesis of polysubstituted tetrahydropyrans.

1.2.3.3. Enantioselective Prins Cyclization

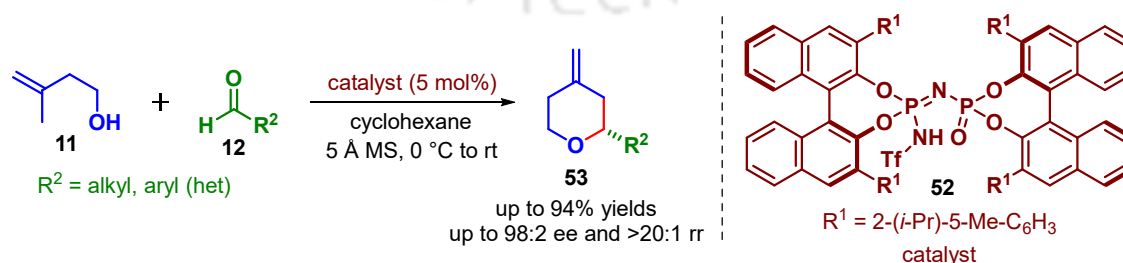
One of the first enantioselective form of the Prins cyclization was published by

Lalli's group. They reported that a combination of a Lewis acid (CuCl) and a chiral Brønsted bis-phosphoric acid derived from BINOL **49** turned out as the most effective catalytic system for the transformation. The reaction involves a sequential Prins-intramolecular Friedel-Crafts type alkylation, for the formation of a series of benzo[*f*]-isochromenes **51** with high yields and diastereoselectivities, as well as moderate enantioselectivities (Scheme 1.2.3.3.1).³⁴



Scheme 1.2.3.3.1. CuCl/BINOL-derived diphenylphosphoric acid catalyzed Prins cyclization.

List's group have proposed a more comprehensive method for conducting a catalytic enantioselective Prins cyclization. This approach enables the direct synthesis of tetrahydropyrans **53** by the reaction of a simple homoallylic alcohol **11** with an aliphatic or (hetero)aromatic aldehyde **12**. The iminoimidodiphosphate catalyst **52** plays a crucial role in the reaction by promoting the process in a confined environment, resulting in efficient transfer of stereochemical information from the



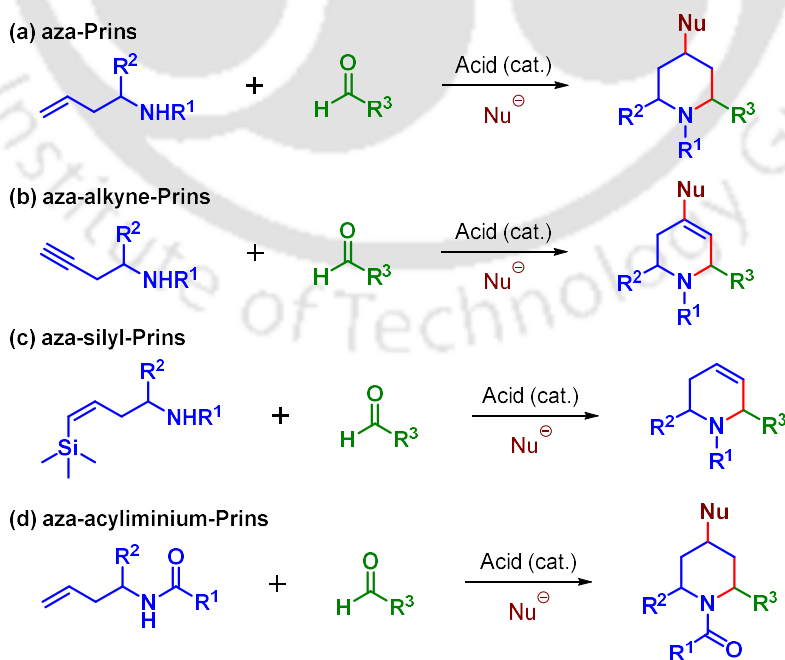
Scheme 1.2.3.3.2. BINOL-derived imino-imidodiphosphate catalyzed Prins cyclization.

catalyst to the product. The exocyclic double bond has been hydrogenated to produce a variety of scents using this procedure (Scheme 1.2.3.3.2).³⁵

1.2.4. Aza-Prins Cyclization

Considering the success of the Prins cyclization reaction, it was only a matter of time before a similar process involving amines would be developed. The aza-Prins cyclization, as its name suggests, is the nitrogen analogue of the Prins cyclization reaction. This reaction enables the direct formation of the piperidine skeleton, typically with good stereocontrol. Nevertheless, although the aza-Prins reaction allows for the rapid generation of many important heterocycles, especially piperidines, it is not as extensively studied or documented as the Prins cyclization. This may be attributed to the need of a protecting group for N-atom, particularly N-tosyl (R = Ts, Ns, Bs), to achieve the aza-Prins products in high yields. Removal of the protecting group has proven to be quite problematic, especially in the presence of other functional groups in the heterocyclic product.

The development of aza-Prins cyclization can be categorized into two groups: cyclization onto an iminium ion intermediate, which is often produced from a single molecule precursor, or a similar reaction to the Prins reaction, in which, a homoallylic



Scheme 1.2.4.1. Classification of aza-Prins cyclization.

amine under acidic conditions reacts with a carbonyl compound (Scheme 1.2.4.1.a). The latter definition has been crucial in the recent advancements of the aza-Prins reaction and can be further divided into four subclasses namely, aza-Prins reaction, aza-alkyne-Prins reaction, aza-silyl-Prins reaction, and aza-acyliminium Prins reaction (Scheme 1.2.4.1).

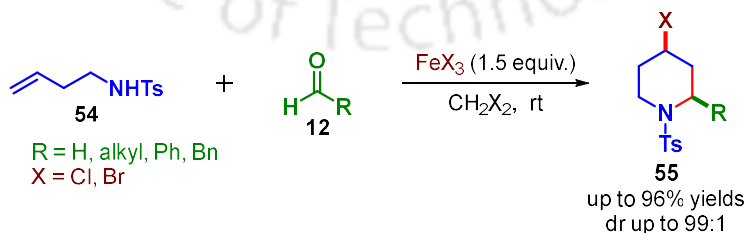
1.2.4.1. Normal Aza-Prins Cyclization

A significant amount of research has focused on using various acids in the aza-Prins cyclization to control the outcome of the reaction, primarily in terms of the nucleophile trapping. Majority of the work in the aza-Prins cyclization has concentrated on trapping of the carbocation intermediate formed during the process with various nucleophiles. Some of the approaches are discussed below.

1.2.4.1.1. Trapping with Halogen Nucleophiles

There have been many works documented to encompass all the halogens being incorporated at C4 position of piperidines during the aza-Prins cyclization. However, chloride and bromide have been found to be the most widely integrated nucleophiles from various Lewis acids.

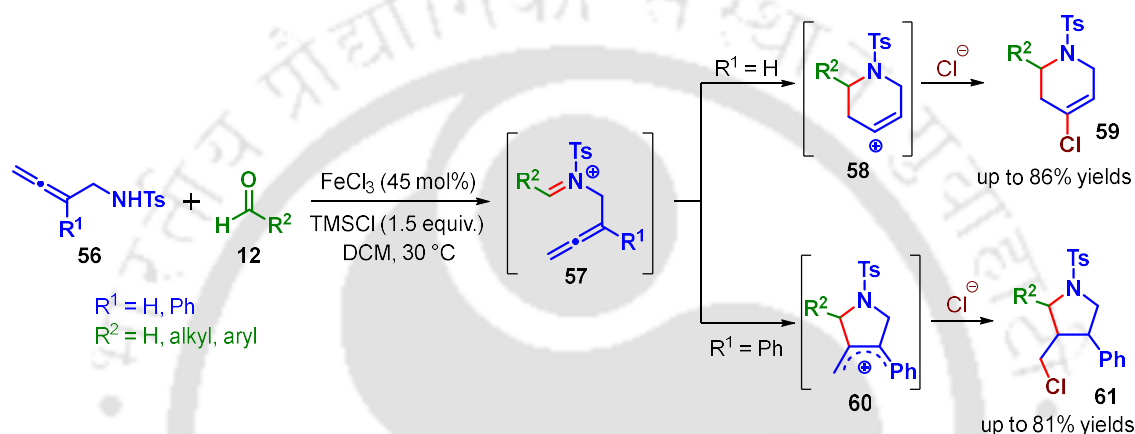
Martín and Padrón have identified Fe(III)-halides as an effective catalyst for the aza-Prins cyclization to synthesize 4-halopiperidines in good yields. The coupling reaction between homoallyl tosylamines **54** and aldehydes **12** proceeds *via* the in situ generation of γ -unsaturated-iminium ion, followed by the nucleophilic trapping of the intermediate to furnish the product *trans*-2-alkyl-4-halo-tosylpiperidines **55** with good diastereoselectivity (Scheme 1.2.4.1.1.1).^{36a} Furthermore, they have modified their



Scheme 1.2.4.1.1.1. Fe(III)-promoted aza-Prins cyclization to synthesize 4-halo-tosylpiperidines.

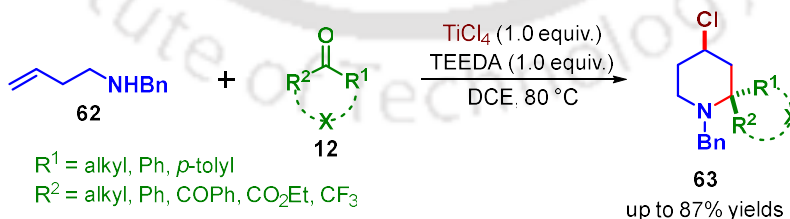
methodology to encompass 4-iodopiperidines by employing FeI_3 and TMSI as the catalytic system.^{36b}

Ma's group has demonstrated a highly regioselective synthesis of FeCl_3 -catalyzed aza-Prins cyclization of α -sulfonamido-allenes **56** with aldehydes to produce tetrahydropyridines **59** or dihydro-pyrrole derivatives **61** in moderate to good yields. The change in regioselectivity of the reaction may be attributed to the stabilizing factor of the R^1 substituent on the allylic intermediate **57** (Scheme 1.2.4.1.1.2).³⁷



Scheme 1.2.4.1.1.2. FeCl_3 -catalyzed aza-Prins cyclization of α -sulfonamido-allenes with aldehydes.

Lalli's group developed a titanium-TEEDA mediated aza-Prins cyclization reaction of benzyl protected homoallyl amines **62** with various aldehydes and ketones **12**. The strategy features an easy access to piperidines with tetrasubstituted or spiranic carbon centers at C2 position **63** (Scheme 1.2.4.1.1.3).³⁸

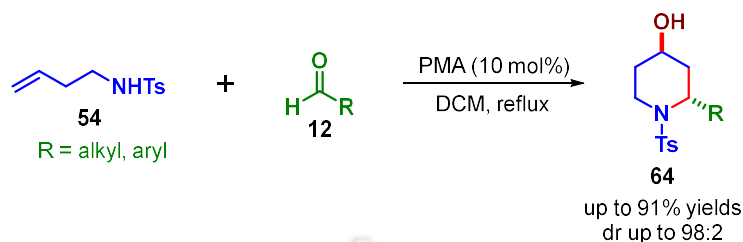


Scheme 1.2.4.1.1.3. TiCl_4 -mediated synthesis of tetrasubstituted piperidines.

1.2.4.1.2. Trapping with Oxygen Nucleophiles

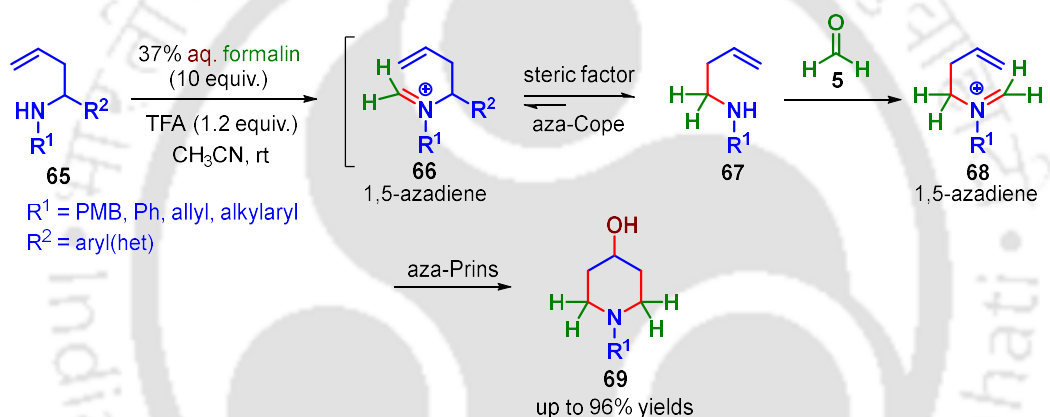
The first report on the preparation of 4-hydroxypiperidines was reported by Yadav's group. Phosphomolybdic acid (PMA) has been successfully utilized to

catalyze the aza-Prins reaction to generate high yields of 4-hydroxypiperidines **64** with exclusive *trans*-selectivity (Scheme 1.2.4.1.2.1).³⁹



Scheme 1.2.4.1.2.1. PMA-catalyzed synthesis of 4-hydroxypiperidines.

Fernandes's group reported an aza-cope/aza-Prins cyclization strategy for the preparation of 4-hydroxypiperidines **69** in good yields (Scheme 1.2.4.1.2.2).⁴⁰

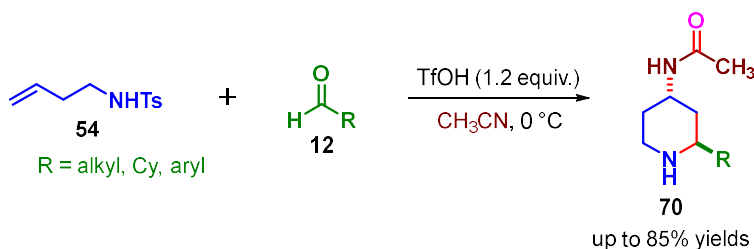


Scheme 1.2.4.1.2.2. Aza-cope/aza-Prins protocol to synthesize 4-hydroxypiperidines.

1.2.4.1.3. Trapping with Nitrogen Nucleophiles

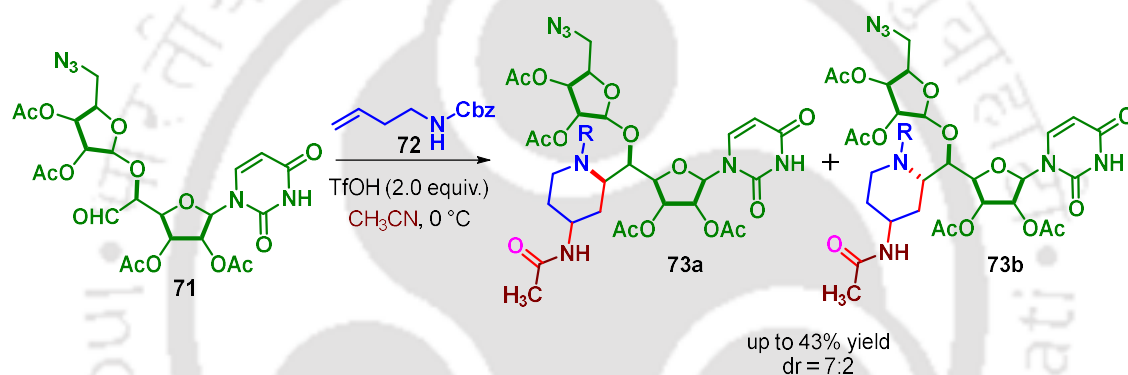
The widely used approach to capture a secondary Prins carbocation using a nitrogen nucleophile is typically achieved through a Ritter reaction. Although the usage of this method in the Prins reaction to produce 4-amido-tetrahydropyrans is well-established, its utilization in aza-Prins reactions has been somewhat limited.

Reddy's group reported a triflic acid mediated synthesis of substituted 4-amidopiperidine derivatives **70** through an aza-Prins–Ritter cyclization strategy (Scheme 1.2.4.1.3.1).⁴¹



Scheme 1.2.4.1.3.1. Triflic acid-promoted aza-Prins-Ritter reaction.

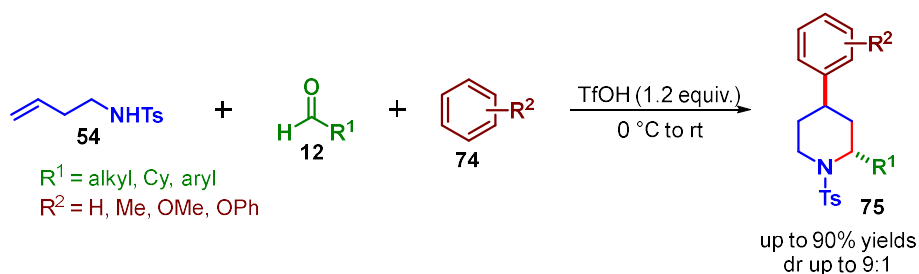
The synthesis of a series of 5'-C-piperidinyl-5'-O-aminoribosyluridine derivatives **73** has been achieved using the same reaction sequence (Scheme 1.2.4.1.3.2).⁴² Ichikawa's group deliberately designed these molecules as simpler versions of caprazamycins and tested them for their potential antibacterial activity.



Scheme 1.2.4.1.3.2. Aza-Prins strategy to synthesize aminoribosyluridine derivatives.

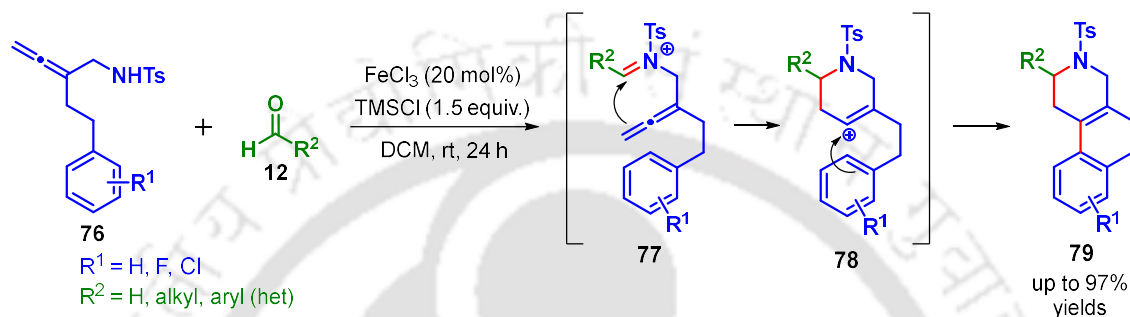
1.2.4.1.4. Trapping with Carbon Nucleophiles

Yadav's group reported a one-pot three component synthesis of 4-arylpiperidines **75**. The process involves an intermolecular trapping of the piperidinyl carbocation using an excess of the aromatic compound **74**, which serves as both the solvent and the trapping agent (Scheme 1.2.4.1.4.1).⁴³



Scheme 1.2.4.1.4.1. TfOH-mediated synthesis of 4-arylpiperidines.

Ma's group described an efficient protocol to synthesize hexahydrobenzo[*f*]-isoquinolines **79** from 2-arylethyl-2,3-butadienyl tosylamides **76** and aldehydes **12**. The Fe(III)-catalyzed cascade reaction proceeds through an aza-Prins cyclization to give the tetrahydropyridinium intermediate **78**, which is subsequently trapped by the proximal aryl group to deliver the product **79** in moderate to excellent yields (Scheme 1.2.4.1.4.2).⁴⁴

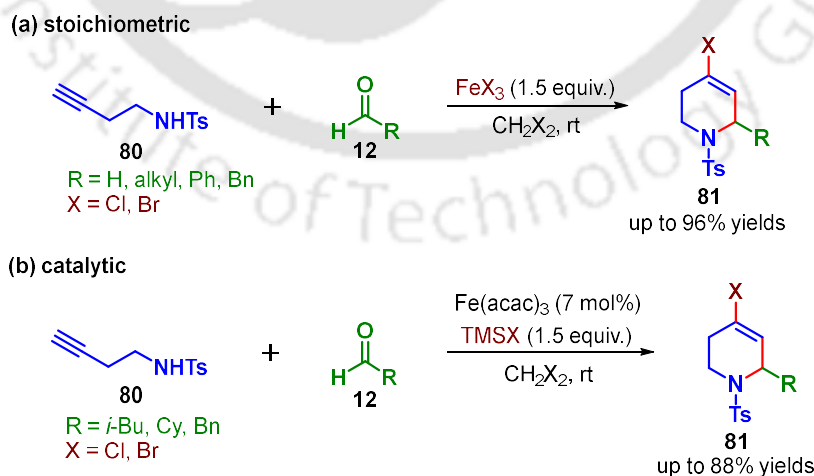


Scheme 1.2.4.1.4.2. Fe(III)-catalyzed cascade aza-Prins cyclization.

1.2.4.2. Aza-Alkyne-Prins Cyclization

In 2006, Martín and Padrón reported a strategy to synthesize 4-halo-tetrahydropyridine derivatives **81** using an alkyne aza-Prins cyclization. This process involves the reaction between *N*-tosyl homopropargylamines **80** and aldehydes **12** in the presence of stoichiometric amounts of Fe(III) halides (Scheme 1.2.4.2.1.a).^{36a}

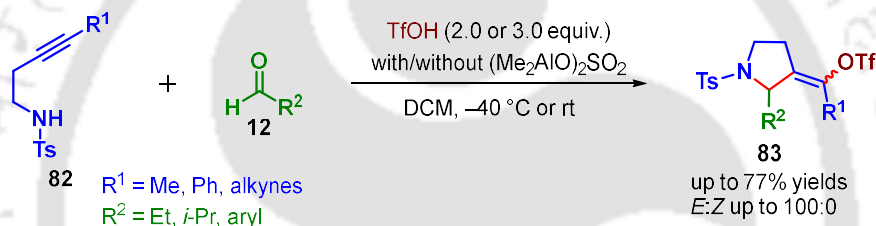
In 2007, the same group revealed a modified version of this reaction to efficiently



Scheme 1.2.4.2.1. Fe(III)-promoted alkyne aza-Prins synthesis of 4-halo-tetrahydropyridines.

produce nitrogen-containing heterocycles using an $\text{Fe}(\text{acac})_3$ system with trimethylsilyl halide as the nucleophilic source. With these mild reaction conditions, it is quite easy to introduce chloride, bromide, and iodide into the aza-Prins products with satisfactory to excellent yields (Scheme 1.2.4.2.1.b).^{36b} Catalytic FeX_3 also results in similar yields. However, $\text{Fe}(\text{acac})_3$, due to its lower hygroscopicity, is much easier to handle.

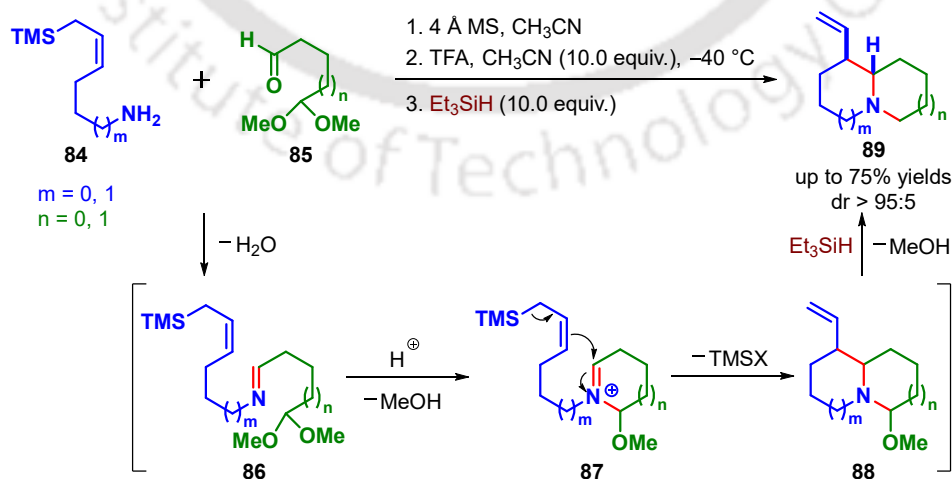
Saito's group was the first to incorporate triflates as the nucleophile in the aza-Prins cyclization. The TfOH-mediated alkyne aza-Prins cyclization of 3,5-diynyl amides **82** and aldehydes **12** with/without $(\text{Me}_2\text{AlO})_2\text{SO}_2$ afforded the TfO-substituted pyrrolidines **83** with *E*-selectivity and exclusive regioselectivity. Moreover, the strategy also works well with homopropargyl amides (Scheme 1.2.4.2.2).⁴⁵



Scheme 1.2.4.2.2. TfOH-mediated synthesis of TfO-substituted pyrrolidines.

1.2.4.3. Aza-Silyl-Prins Cyclization

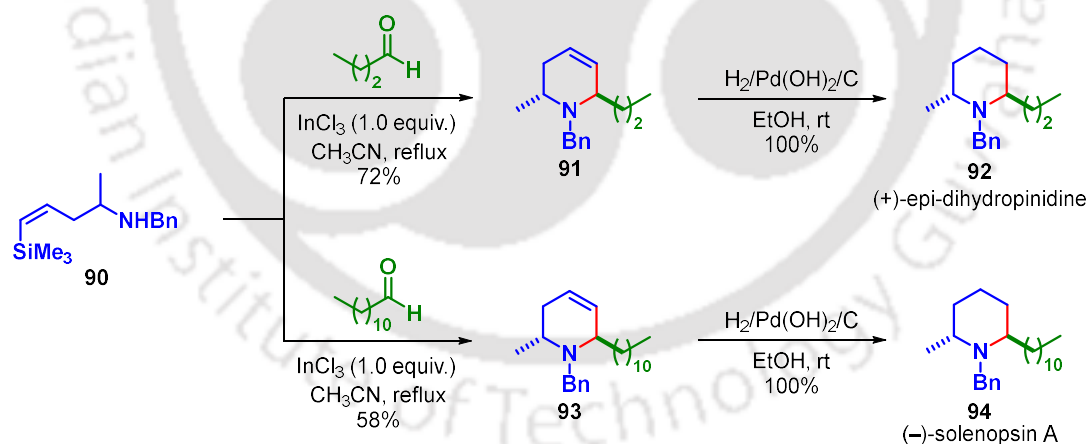
Martin's group described an intriguing approach for producing quinolizidines and indolizines through the reaction of (*Z*)-allylsilyl-free amines **84** with dialdehydes



Scheme 1.2.4.3.1. Aza-Silyl-Prins synthesis of quinolizidines.

containing a dimethyl acetal protecting group at one of the carbonyl groups **85**. Initially, they formed the expected imine **86** in the presence of molecular sieves, and subsequently, upon treatment with TFA at low temperature, a cascade reaction took place. The resulting cyclic N,O-acetal **88** generated a second iminium ion that could be intercepted by a nucleophile, with the simplest being hydride. Quinolizidines **89** were obtained in moderate yields, yet with outstanding diastereoselectivity (Scheme 1.2.4.3.1).⁴⁶

Dobbs's group has developed an InCl_3 mediated silyl aza-Prins cyclization strategy from silylated homoallylic amines **90** and aldehydes. Tetrahydropyridines **91** and **93** are obtained with *trans*-configuration, which is opposite to that observed in the cyclization of their corresponding alcohols. The authors proposed that the reaction proceeds *via* a chair-like transition state that includes a Z-iminium cation, where the axial position is occupied by the -Me substituent.^{47a-b} The strategy also features the synthesis of the natural products (+)-epi-dihydropinidine **92** and (-)-solenopsin A **94** (Scheme 1.2.4.3.2).^{47c} They have further broadened their strategy to produce various CF_3 -containing dihydropyrans and tetrahydropyridines.^{47d}

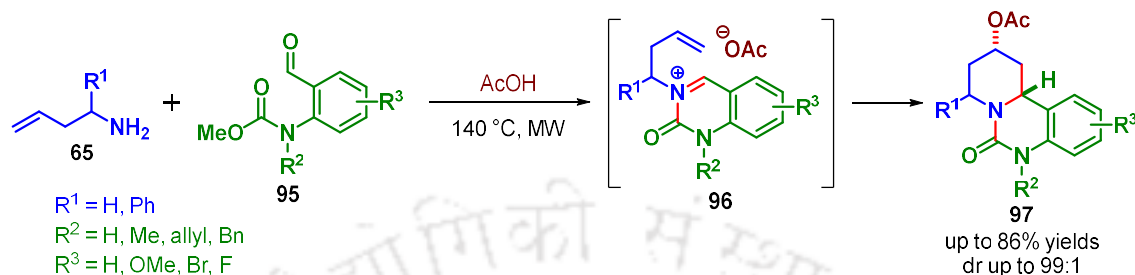


Scheme 1.2.4.3.2. InCl_3 -mediated silyl aza-Prins cyclization.

1.2.4.4. Aza-Acyliminium Prins Cyclization

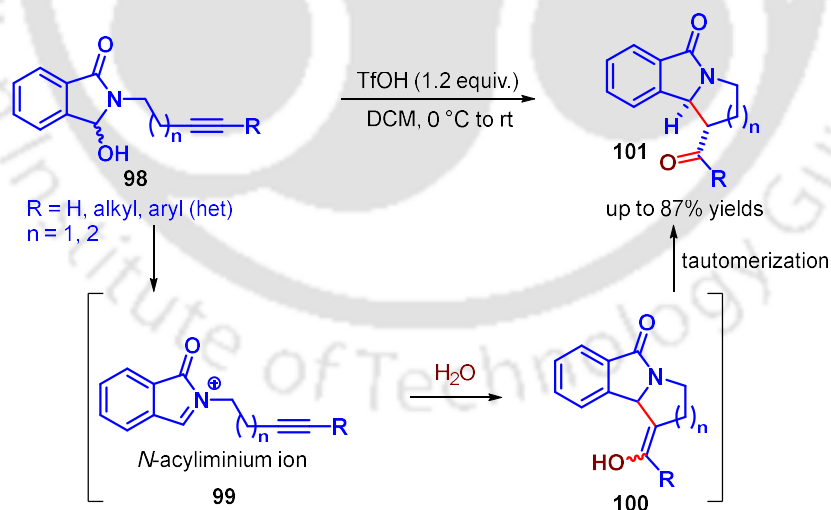
Odell's group has disclosed an acetic acid promoted metal-free strategy for the formation of masked *cis*-hydroxyhexahydropyrido[1,2-*c*]quinazolinones in good yields. The reaction between homoallylic amines **65** and o-formyl carbamates **95**

generates *N*-acyliminium ion intermediate **96**, which subsequently undergoes an aza-Prins cyclization reaction to afford highly functionalized fused tricyclic 3,4-dihydroquinazolinones **97** with excellent diastereoselectivity (Scheme 1.2.4.4.1).⁴⁸



Scheme 1.2.4.4.1. Aza-acyliminium Prins synthesis of pyrido[1,2-*c*]quinazolinones.

Saikia's group has successfully achieved the synthesis of pyrrolo- and pyridoisoindolone skeletons **101** via an intramolecular alkynyl aza-Prins cyclization of *N*-acyliminium ion. Carbinol lactams **98** generates an in-situ *N*-acyliminium ion **99**, which is then attacked by the proximal alkyne to create a vinyl cation. This cation is subsequently trapped with water to form the enol ether intermediate **100**. Subsequent tautomerization leads to the selective formation of various diastereoselective aza-Prins products (Scheme 1.2.4.4.2).⁴⁹



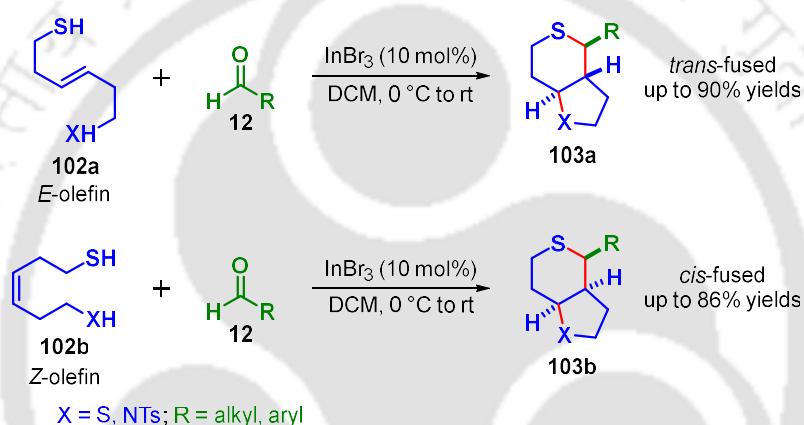
Scheme 1.2.4.4.2. *N*-Acyliminium ion cyclization followed by trapping with water.

1.2.5. Thia-Prins Cyclization

Thia-Prins cyclization, the sulfur version of the Prins cyclization, can be defined as

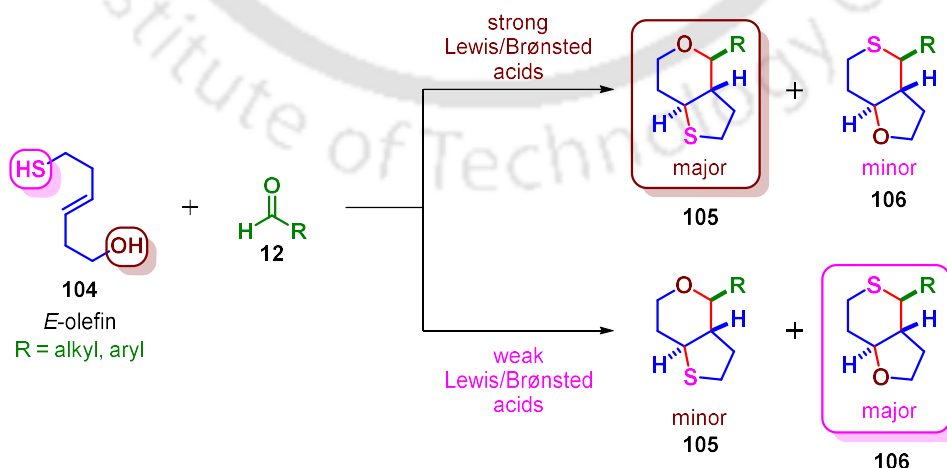
the acid mediated coupling reaction of homoallylic thiols and carbonyl compounds for the synthesis of sulfur heterocycles.

Reddy's group has developed an InBr_3 -catalyzed thia-Prins strategy for the stereoselective synthesis of hexahydro-thieno[3,2-*c*]thiopyrans **103**. This approach involves the cyclization of homoallylic mercaptans **102** with aldehydes **12**. Additionally, the strategy has been extended to include the synthesis of *N*-tosyloctahydrothiopyrano[4,3-*b*]pyrroles. The protocol is highly stereoselective, producing *trans*-fused products **103a** from *E*-homoallylic mercaptans **102a** and *cis*-fused products **103b** from *Z*-homoallylic mercaptans **102b** (Scheme 1.2.5.1).⁵⁰



Scheme 1.2.5.1. InBr_3 -catalyzed synthesis of thieno[3,2-*c*]thiopyrans.

In a study carried out by Reddy's group on the oxa- *vs* thia-selectivity in Prins cyclization using 6-mercaptohex-3-enol **104** and aldehydes **12**, they uncovered some



Scheme 1.2.5.2. Tunable selectivity in Prins cyclization.

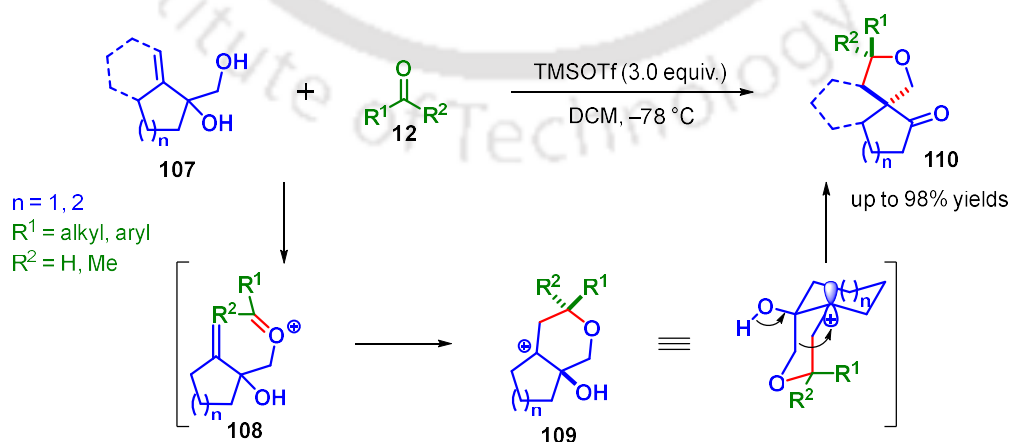
intriguing results. Reactions performed with stoichiometric amounts of strong acids (either Lewis or Brønsted acids) predominantly resulted the classical Prins product, hexahydro-thieno[3,2-*c*]pyrans **105**. In contrast, catalytic amount of weak acid favoured the formation of hexahydro-thiopyrano[4,3-*b*]furans **106** through the thia-Prins pathway. Furthermore, the reactions exhibited good stereoselectivity, providing respective *cis*- and *trans*-products from *Z*- and *E*-mercaptohex-3-enols (Scheme 1.2.5.2).⁵¹

1.2.6. Cascade Prins and Aza-Prins Cyclization Reactions

Cascade Prins cyclization represents a versatile and powerful approach in organic chemistry for creating complex molecular frameworks. This method is particularly valuable for the stereoselective synthesis of structurally diverse O/N-fused, bridged, and spiro heterocycles. Cascade strategies outperform their multistep and traditional counterparts in terms of efficacy. The major benefit of cascade Prins cyclization is its capacity to generate several bonds (C-C, C-O, and C-N) and rings simultaneously in a single process. This feature renders it a useful tool for synthesizing complex structures, including natural products and biologically active molecules. Among the various cascade Prins strategies, some notable approaches are discussed below.

1.2.6.1. Prins-Pinacol Reaction

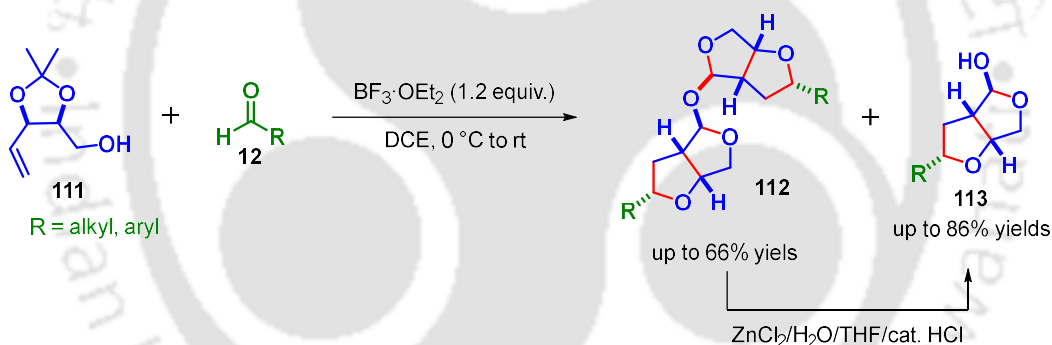
Oxaspirodecane and oxaspirononane frameworks are prevalent in many natural products, such as bakkenolide A, expansolide A, and withaphysalin F.⁵² Cho's group



Scheme 1.2.6.1.1. Prins-pinacol annulation strategy for oxaspiro compounds.

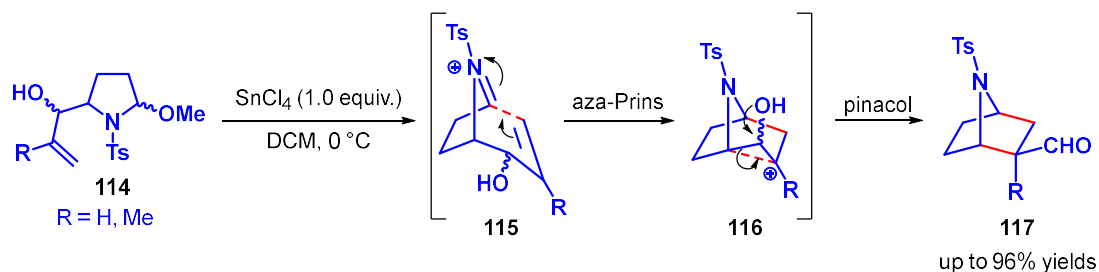
developed a Prins–pinacol annulation strategy for the stereoselective synthesis of 2-oxaspiro[4,5]decanes and [4,4]nonanes from olefinic diols and carbonyl compounds. This process involves the formation of the carbocation **109** from methylene diols **107** and aldehydes **12** *via* Prins cyclization, followed by a pinacol rearrangement to produce the 3-substituted 2-oxaspiro compounds **110**. Additionally, this strategy also facilitates the production of oxatricyclic compounds, showcasing its effectiveness in building intricate molecules (Scheme 1.2.6.1.1).⁵³

Saikia's group reported a Lewis acid catalyzed synthesis of hexahydrofuro[3,4-*b*]furanols with high enantio- and diastereoselectivity. The Prins–pinacol cascade strategy of (dimethyl-5-vinyl-1,3-dioxolan-4-yl)methanol **111** with various aldehydes **12** afforded both furanols **113** and their dimers **112**. Nevertheless, the dimers were subsequently converted to their corresponding monomers in high yields using an aqueous ZnCl_2 solution (Scheme 1.2.6.1.2).⁵⁴



Scheme 1.2.6.1.2. Prins–pinacol cascade strategy for hexahydrofuro[3,4-*b*]furanols.

Armstrong's group outlined a concise method for synthesizing the bicyclic alkaloid ($\pm$)-epibatidine and its analog ($\pm$)-epiboxidine, poisons derived from frog skin. Their approach utilizes 7-azabicyclo[2.2.1]heptane skeleton **117** as a key intermediate, which

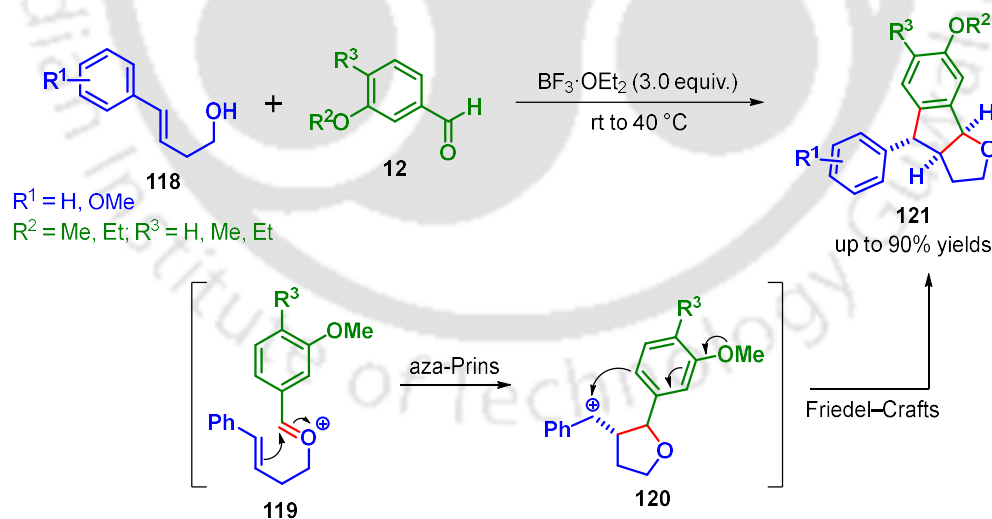


Scheme 1.2.6.1.3. Aza-Prins–pinacol strategy.

is obtained from a substituted pyrrolidine **114** in the presence of a stoichiometric amount of SnCl_4 . The exclusive diastereoselective formation of the *exo*-product (relative to the aldehyde function) can be attributed to a typical aza-Prins–pinacol sequence (Scheme 1.2.6.1.3).⁵⁵

1.2.6.2. Prins–Fridel–Crafts Reaction

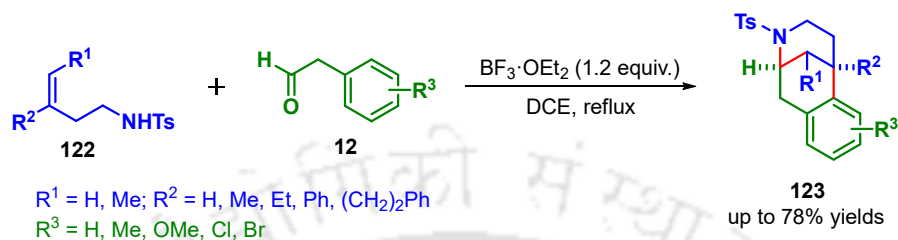
Nagumo's group has described a cascade reaction sequence for synthesizing indeno-tetrahydrofuran derivatives using a Prins/Friedel–Crafts cyclization. The reaction involves homocinnamyl alcohol **118** and aromatic aldehyde **12** in presence of $\text{BF}_3 \cdot \text{OEt}_2$, leading to the formation of the indeno-tetrahydrofuran derivatives **121**. This cascade sequence proceeds with the construction of a five-membered ring **120** through a Prins cyclization, which involves the oxocarbenium ion **119** produced from the homocinnamyl alcohol and aromatic aldehyde. The stereoselective cyclization forms both *cis*- and *trans*-benzyl cations, which exist in equilibrium during the reaction. However, only the *cis*-benzyl cation undergoes a five-membered Friedel–Crafts cyclization resulting in the desired product because of the ring strain in the *trans*-fused bicyclo[3.3.0] system (Scheme 1.2.6.2.1).⁵⁶



Scheme 1.2.6.2.1. Prins–Fridel–Crafts strategy for the synthesis of indeno-tetrahydrofurans.

Maison's group reported a Lewis/Brønsted acid-promoted synthesis of substituted benzomorphans, which form the core structure of several opioid compounds. This

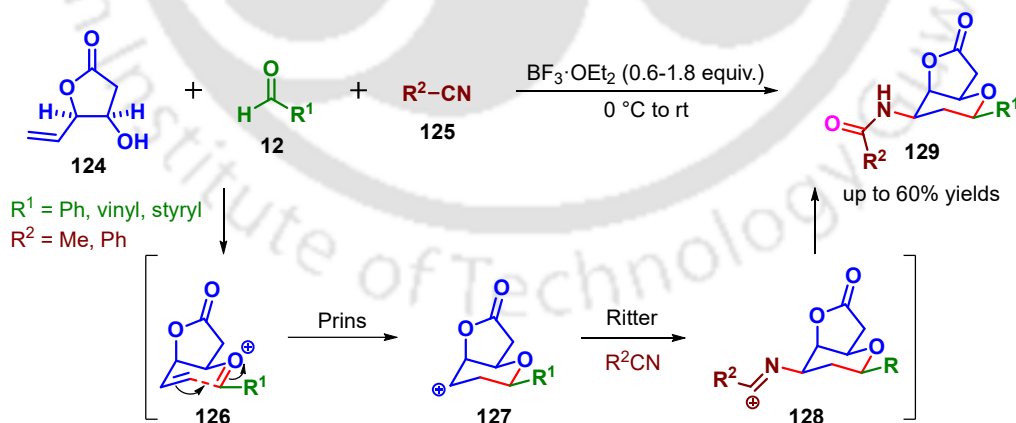
method utilizes a domino aza-Prins–Friedel–Crafts sequence involving *N*-tosyl homoallylic amines **122** and phenylacetaldehyde derivatives **12**. The process offers a straightforward route to benzoannulated azabicyclononanes **123**, yielding them in good quantities (Scheme 1.2.6.2.2).⁵⁷



Scheme 1.2.6.2.2. Aza-Prins–Friedel–Crafts sequence to synthesize benzomorphans.

1.2.6.3. Prins–Ritter Reaction

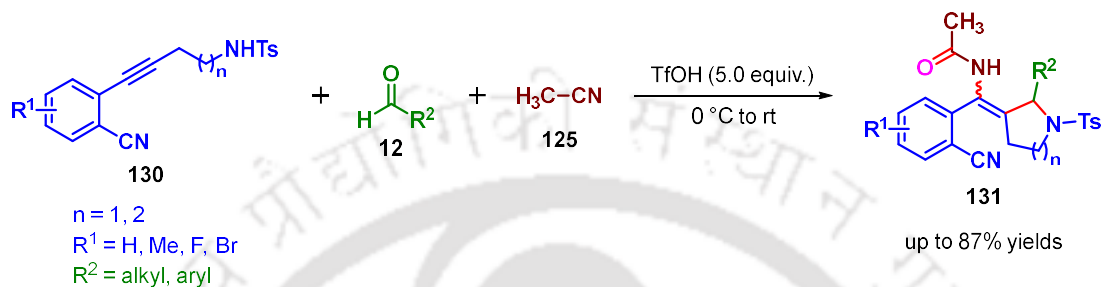
Oikawa's group developed a one-pot, three-component strategy featuring the Prins–Ritter protocol for the synthesis of tetra-*cis*-substituted 4-amidotetrahydropyrans **129**. The coupling reaction of homoallylic alcohols **124** and aldehydes **12** in the presence of nitriles **125** afforded the product with high *cis*-diastereoselectivity at the newly formed stereogenic centers. The strategy, initially applied to carbohydrate-based heterobicycles, was successfully extended to more complex heterotricycles (Scheme 1.2.6.3.1).⁵⁸



Scheme 1.2.6.3.1. Prins–Ritter synthesis of 4-amidotetrahydropyrans.

Saikia's group demonstrated a TfOH-mediated synthesis of *N*-(pyrrolidine-3-ylidenemethyl)acetamides **131** using a cascade aza-Prins–Ritter reaction. In this process, the Prins cyclization of *o*-cyanophenyl-substituted alkyne-benzene-

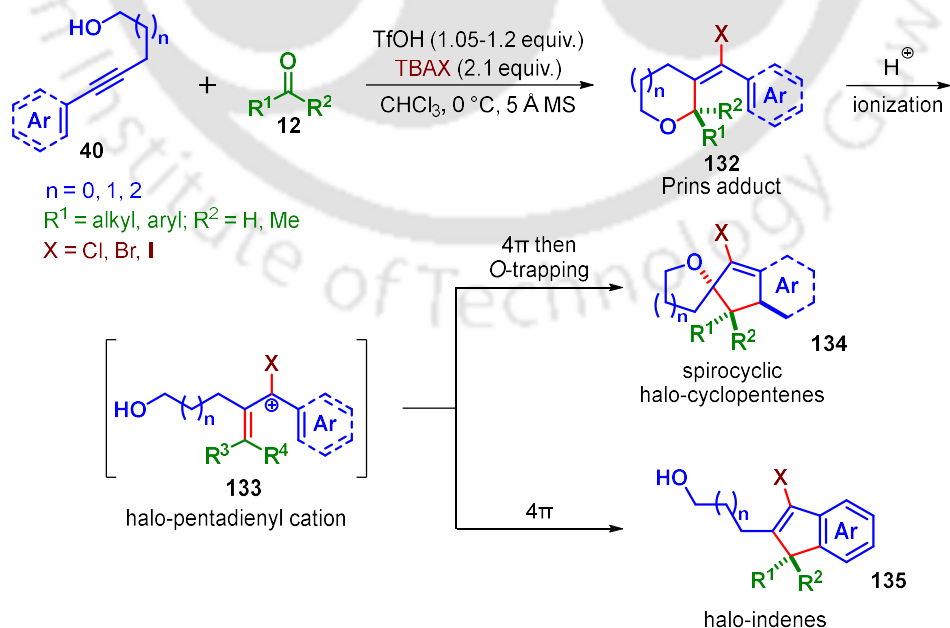
sulfonamide **130** and aldehydes **12** generates the pyrrolidin-3-ylidenemethylm cation, which is then trapped by solvent molecules (acetonitrile) through a Ritter reaction, yielding the product with separable *Z/E*-isomers. This strategy has also been successfully applied to synthesize piperidine analogues in good yields (Scheme 1.2.6.3.2).⁵⁹



Scheme 1.2.6.3.2. Cascade aza-Prins-Ritter protocol.

1.2.6.4. Prins-Nazarov Cyclization

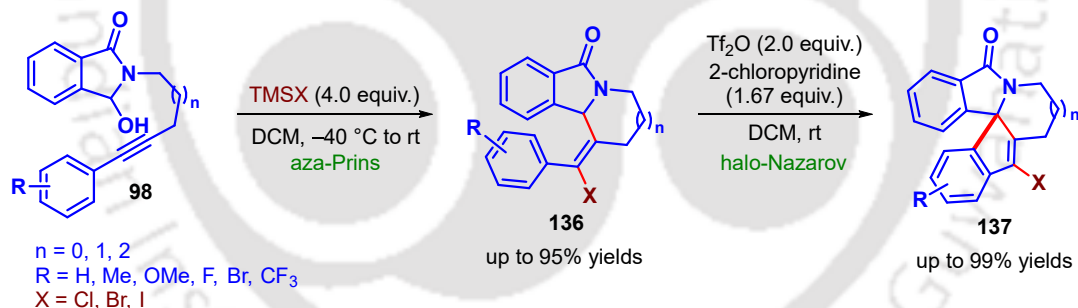
Frontier's group showed that alkynyl Prins adducts **132** can serve as a foundation for halo-Nazarov-initiated cascade reactions to synthesize intricate molecules. The ring opening of the Prins product results in the formation of halopentadienyl cation **133**, which may be effectively used to construct diverse molecular frameworks, depending on the choice of starting materials. In one scenario, the halopentadienyl



Scheme 1.2.6.4.1. Alkynyl Prins-halo-Nazarov strategy.

cation **133** experience a 4π -conrotatory (halo-Nazarov) electrocyclization, followed by capture by the adjacent alcohol to produce spirocyclic halo-cyclopentenones **134** with high diastereoselectivity.^{60a} In another scenario, when R^3/R^4 are aryl groups, the 4π -electrocyclization readily yields halo-indenes **135** (Scheme 1.2.6.4.1). Additionally, it allows the diastereoselective synthesis of indanones, presenting a mild and convenient alternative to the traditional Nazarov cyclization of aryl enones.^{60b}

The same group also describe a tandem reaction sequence to synthesize spirocyclic isoindolones **137** from arenyne and enyne 3-hydroxyisoindolone **98**. This process involves an alkynyl halo-aza-Prins cyclization reaction to provide the Prins product isoindolones **136**. The amide group of the Prins adduct after activation by triflic anhydride and 2-chloropyridine undergoes oxidation at the 3-isoindolone position to generate a pentadienyl cation, which can undergo a halo-Nazarov cyclization. This methodology enables the generation of angular-fused N-heterocyclic small molecules with two new rings, two new carbon-carbon bonds, a vinyl halide, and an aza-tertiary stereocenter in satisfactory yields (Scheme 1.2.6.4.2).⁶¹

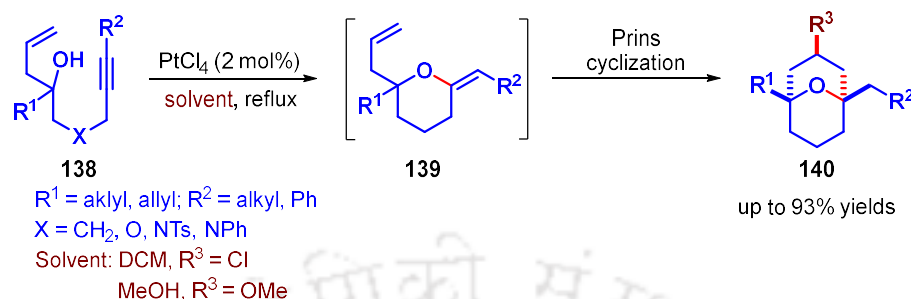


Scheme 1.2.6.4.2. Alkynyl halo-aza-Prins-halo-Nazarov cyclization protocol.

1.2.6.5. Prins-Hydroalkoxylation

In 2009, Barluenga's group developed a Pt-catalyzed protocol for the synthesis of complex bicyclic compounds from alkynol derivatives **138**. An intramolecular hydroalkoxylation reaction of the triple bond, followed by a Prins type cyclization afforded the highly substituted [3.3.1]bicyclic compounds **140**. By varying the structure of the starting alkynol, or modifying the nucleophile, a library of new bicyclic compounds was synthesized, including some enantiomerically pure

products. This strategy also enabled the synthesis of enantiomerically pure compounds derived from α -amino acids and lactic acids (Scheme 1.2.6.5.1).⁶²



Scheme 1.2.6.5.1. Pt-catalyzed cascade Prins-hydroalkoxylation strategy.

1.3 Hydroalkoxylation

Hydrofunctionalization of C–C multiple bonds provide a streamlined and efficient way for integrating both structural and stereochemical complexity into important chemicals and drugs molecules. This approach allows for the precise addition of functional groups like alcohols, carboxylic acids, and water to C–C multiple bonds, resulting in the synthesis of stereochemically enriched compounds.⁶³ These reactions (hydroalkoxylation, hydroacyloxylation, and hydration) offer a redox-neutral pathway to synthesize a diverse range of functionalized molecules, including ethers, acetals, esters, lactones, and alcohols, with high stereochemical control.⁶⁴ Among these, hydroalkoxylation, where alcohols are added to C–C multiple bonds stand out due to its ability to produce highly stereoselective products. This reaction not only simplifies synthetic routes but also enhances the creation of complex molecules with significant bioactivity, making it a valuable tool in medicinal chemistry and natural product synthesis.⁶⁵

Recently, alkynol-based cascade reactions have garnered significant attention for their potential to efficiently generate complex molecular architectures, sparking renewed interest in this promising area of synthetic chemistry.⁶⁶ Numerous approaches have been developed to achieve diastereo- and enantioselective hydroalkoxylation and cascade reactions of alkynes, enabling the synthesis of complex oxygen-bearing heterocycles. Extensive research has focused on the transition-metal-catalyzed activation of alkynes, enabling their capture by oxygen

nucleophiles like alcohols to form enol ethers.⁶⁷ In the case of terminal alkyne, the attack of the alcohol on the more substituted carbon atom (Path A) is favored because

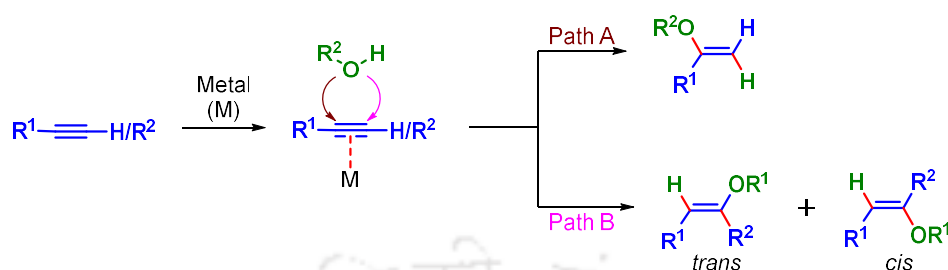


Figure 1.3.1. Modes of intermolecular hydroalkoxylation of alkynes.

of the formation of a more stable vinyl carbocation intermediate (Figure 1.3.1). Similarly, internal alkynes undergo selective nucleophilic attack by alcohols, yielding *cis/trans*-enol ethers through the preferential formation of a stable vinyl carbocation.

1.3.1. Metal-Based Hydroalkoxylation of Alkynes

Nolan's group developed a gold-catalyzed alkyne hydroalkoxylation,^{68a} while Kakiuchi's group independently reported rhodium-catalyzed hydroalkoxylation,^{68b} both using alkyne substrates to produce enol ethers. Transition-metal-catalyzed hydroalkoxylation, combined with cascade reactions, enables the formation of valuable scaffolds. A one-pot process merging hydroalkoxylation with Claisen rearrangement converts allyl alcohols and alkynes into γ,δ -unsaturated ketones *via* allyl enol ether intermediates. Numerous researchers have independently developed tandem reaction protocols, combining intermolecular hydroalkoxylation and Claisen rearrangement.⁶⁹

Intramolecular hydroalkoxylation proceeds more smoothly compared to the intermolecular process, as the associated strain decreases the entropy and enthalpy barriers. However, regioselectivity challenges in intramolecular hydroalkoxylation remain, particularly regarding *endo*- versus *exo-dig* modes (Figure 1.3.1.1). According to the literature, preferred hydroalkoxylation pathway is typically determined by the stability of the vinyl carbocation intermediate, rather than the influence of the catalyst. However, when a reaction can proceed *via* both *endo*- and *exo-dig* modes, the selectivity of the reaction is dictated by the catalyst system. Employing this principle, several

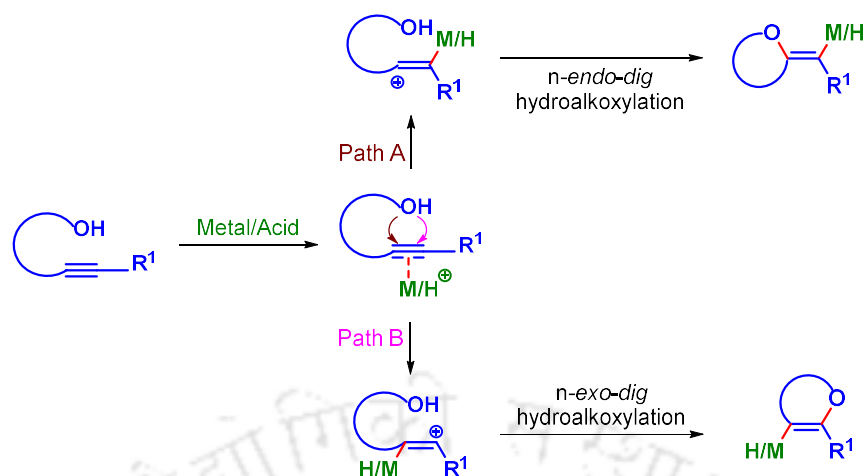
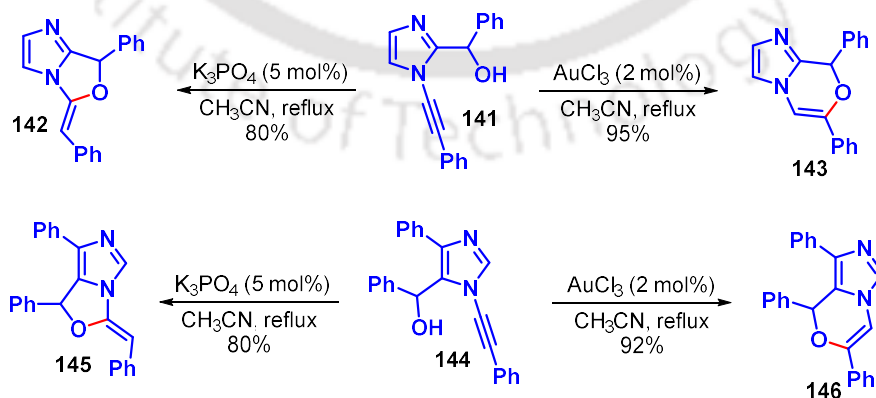


Figure 1.3.1.1. *Endo-vs exo-mode* in intramolecular hydroalkoxylation.

groups have attempted to synthesize products through *endo-* and *exo-dig* hydroalkoxylation modes. For instance, Blacquiere's group described an Fe-catalyzed regioselective synthesis of enol ethers from an intramolecular hydroalkoxylation of alkynols through an *endo-dig* cyclization mode.^{70a} In contrast, Sanchez's group showed that the use of yttrium (Y) or lutetium (Lu) based rare-earth catalyst takes the hydroalkoxylation route to the opposite pathway, leading to an *exo-dig* favoured mode of cyclization.^{70b} Thus, the exposure of the same alkynols to this rare-earth catalytic system provides an easy access to several exocyclic enol ethers.

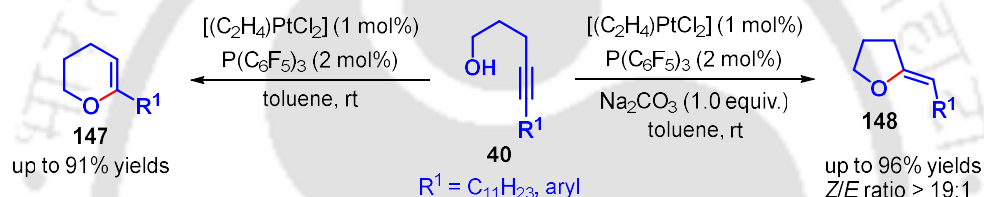
In their study of the cyclization of 1-alkynyl imidazole derivatives using various catalytic systems, Kerwin's group discovered distinct cyclization modes. When treated with K_3PO_4 , the alkynyl-imidazoles **141** and **144** produced exocyclic enol



Scheme 1.3.1.1. Reagent-controlled regioselective hydroalkoxylation.

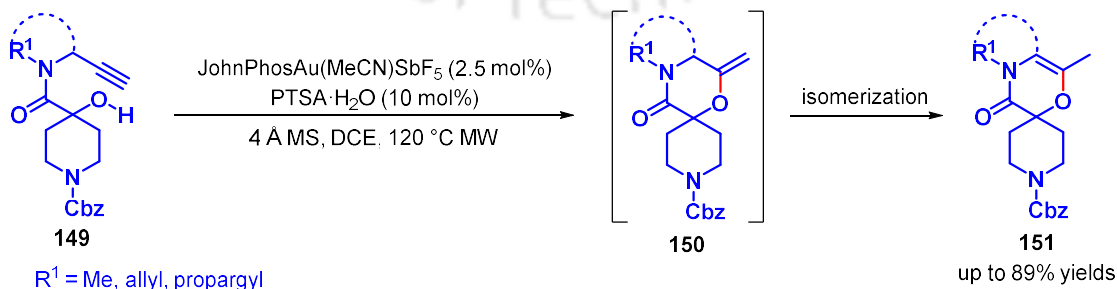
ethers **142** and **145**, respectively. Conversely, using AuCl_3 as the catalyst, resulted in the formation of endocyclic enol ethers **143** and **146** (Scheme 1.3.1.1).⁷¹

Ferreira's group reported a tunable Pt-catalyzed synthesis of regioselective cyclic ethers from alkynols. The key feature of this protocol is the strategic use of Na_2CO_3 as a directing additive, which toggles the reaction between *exo*- and *endo*-dig cyclization pathway. The reaction with only Pt-catalyst follows an *endo*-dig mode of cyclization to yield dihydropyran derivatives **147**, whereas incorporation of Na_2CO_3 in the reaction system favours *exo*-dig hydroalkoxylation to afford tetrahydrofuran derivatives **148** (Scheme 1.3.1.2).⁷² Additionally, electron-withdrawing groups on the aromatic ring leads to *exo*-dig hydroalkoxylated products, while electron-releasing group results in *endo*-dig hydroalkoxylated products.



Scheme 1.3.1.2. Pt-catalyzed regioselective synthesis of enol ether.

Ple and co-workers reported a sophisticated approach for constructing O,N-containing spiro-heterocycles using gold-catalyzed hydroalkoxylation and hydroamination of *O,N*-tethered alkynyl amides **149**.⁷³ The mechanism involves an intramolecular 6-*exo*-dig hydroalkoxylation to form an exocyclic enol ether **150**. Further isomerization of the double bond leads to an endocyclic enol ether **151**. However, the use of Brønsted acid as an additive facilitates the double bond isomerization for the exclusive formation of the same endocyclic enol ether **151**.



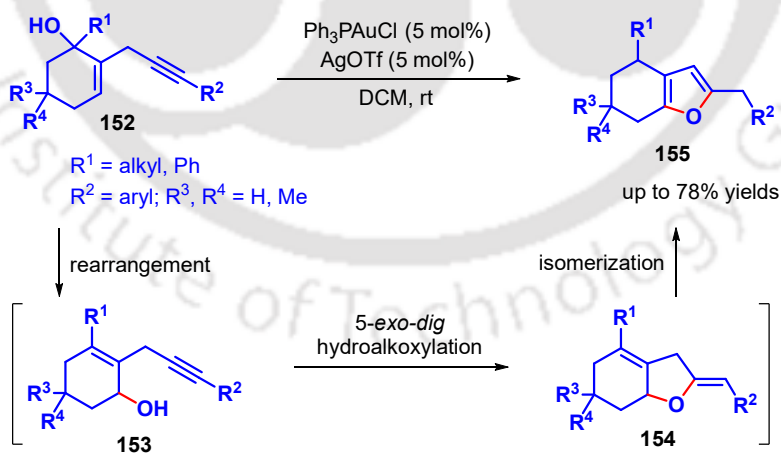
Scheme 1.3.1.3. Gold catalyzed hydroalkoxylation-isomerization.

(Scheme 1.3.1.3). This optimized route was successfully implemented in hydroamination of terminal alkynols to produce nitrogen-containing spiro-heterocycles in excellent yields.

Chemists have found innovative strategies for synthesizing heterocyclic compounds, including the work of Manzo who employed Au-catalysis to cyclize 2-alkynyl phenols into benzo-oxazines,⁷⁴ while Porcel utilized gold and silver catalysts to convert cyclic acids into alkylidene lactones through intramolecular hydroalkoxylation,⁷⁵ and another team harnessed iron catalysis to facilitate the cyclization of quinoline-tethered alkynols *via* 6-*endo-dig* hydroalkoxylation.

1.3.1.1. Cascade Hydroalkoxylation

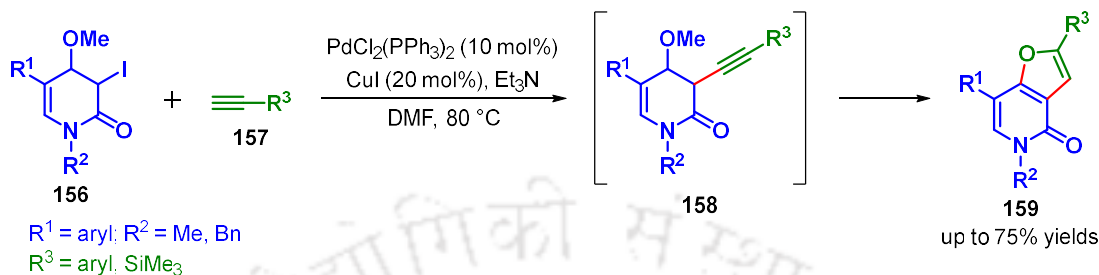
Yeh's group developed a tandem hydroalkoxylation-isomerization sequence using a gold-silver catalyst to synthesize tri-substituted furans **155** from enynols **152**, with reduced yields observed for substrates bearing alkyl or electron-poor aryl groups. The process initially involves a 1,3-hydroxy shift to form allyl alcohol **153**, followed by a 5-*exo-dig* hydroalkoxylation to produce **154**. This is followed by a double isomerization of the exocyclic double bond, resulting in the formation of trisubstituted furans **155** (Scheme 1.3.1.1.1).⁷⁶



Scheme 1.3.1.1.1. Cascade hydroalkoxylation-isomerization synthesis of furans.

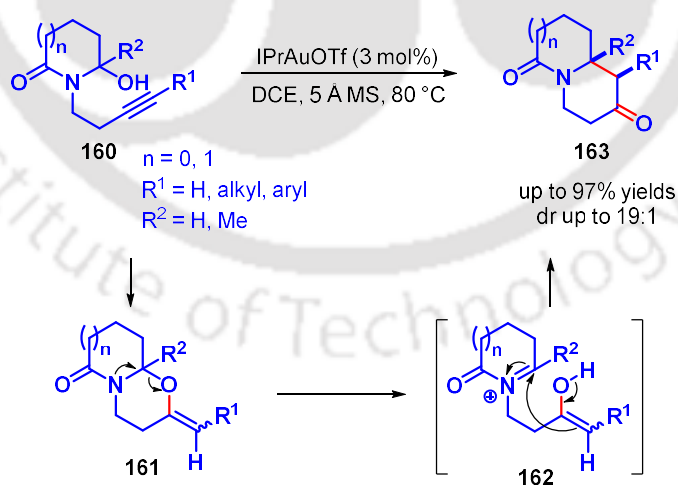
Balme's group developed a tandem Sonogashira coupling and hydroalkoxylation to efficiently synthesize furan-fused heterocycles. The process involves the Sonogashira coupling of iodo-pyridin-2-ones **156** with terminal alkynes **157** to form

furan-fused heterocycles **158** in good yields. This alkynone intermediate **158**, then undergoes a 5-*endo-dig* hydroalkoxylation and subsequent demethylation to produce the desired furan-fused heterocycles **159** (Scheme 1.3.1.1.2).⁷⁷



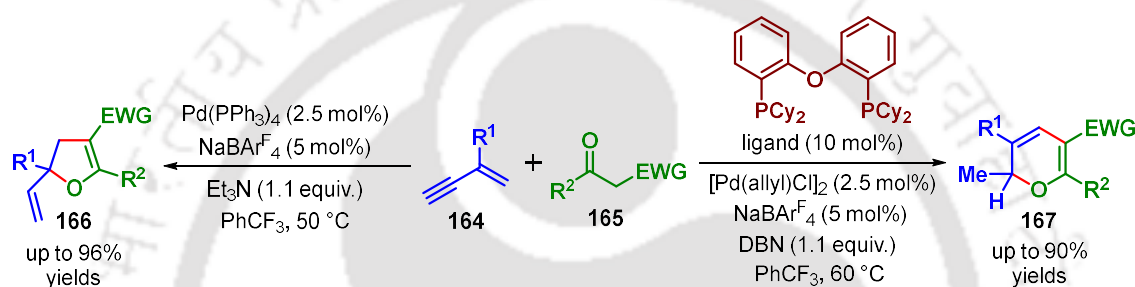
Scheme 1.3.1.1.2. One-pot Sonogashira-hydroalkoxylation-demethylation sequence for the synthesis of furans.

Patil's group employed gold catalysts in a cascade hydroalkoxylation–Petasis–Ferrier rearrangement to stereoselectively synthesize nitrogen-containing heterocycles. The process involves the reaction of alkynes tethered amins **160** with IPrAuOTf , resulting in the formation of bicyclic lactams **163** with moderate to high diastereoselectivity (Scheme 1.3.1.1.3).⁷⁸ The reaction was effective with aromatic, aliphatic, and terminal alkynes. However, amins featuring benzylic linkages did not yield the desired products.



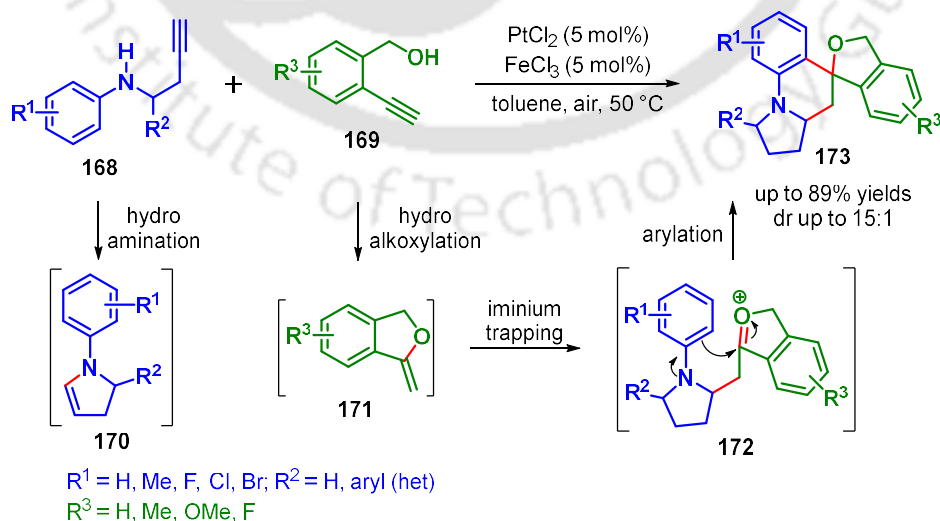
Scheme 1.3.1.1.3. Hydroalkoxylation-Petasis-Ferrier rearrangement cascade sequence for the synthesis of bicyclic lactams.

Carbonyl compounds have favoured carbon-based nucleophilicity over oxygen-based in transition metal-catalyzed reactions, leaving the hydroalkenoxylation pathway largely uninvestigated. Nevertheless, He's group reported a versatile protocol for this challenging reaction. The strategic use of palladium catalysts with varied ligands enables the selective execution of both *exo*-trig and *endo*-trig hydroalkenoxylation pathways involving 1,3-enynes **164** and ketoesters **165** (Scheme 1.3.1.1.4).⁷⁹ Mechanistic insights suggested a novel ligand-to-ligand hydrogen transfer step for the efficient and selective formation of polysubstituted hydrofurans **166** and hydropyrans **167**.



Scheme 1.3.1.1.4. Ligand control palladium-catalyzed synthesis of oxygenated heterocycles.

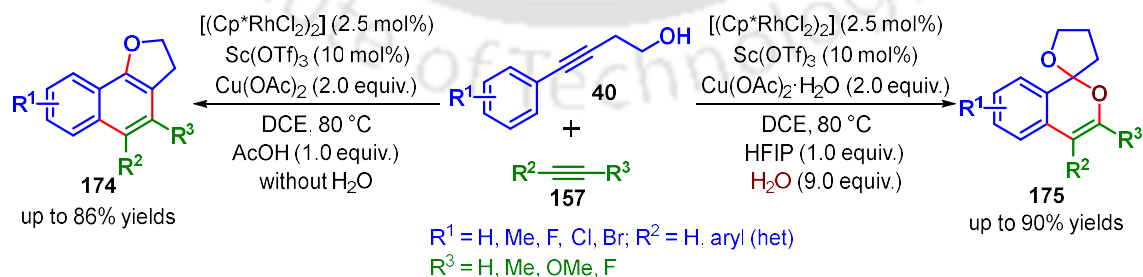
Platinum metal has also been exploited as a catalyst in hydroalkoxylation cascade reactions. Notably, Barluenga's group developed a Pt-catalyzed hydroalkoxylation-cationic cyclization cascade reaction, offering a highly efficient route to furo-



Scheme 1.3.1.1.5. Cascade hydroalkoxylation/hydroamination-Povarov strategy.

quinolines.⁸⁰ Additionally, Li and co-workers reported a Pt-catalyzed tandem reaction, in the presence of FeCl_3 , which involves the reaction of arylalkynols **169** with N-arylhomopropargylic amines **168** to produce complex polycyclic spiro-derivatives.⁸¹ This reaction sequence consists of two intramolecular cyclizations: a 5-*endo-dig* hydroamination of homopropargylic amines to form cycloiminium ions **170**, and a 5-*exo-dig* hydroalkoxylation of arylalkynols to produce isobenzofurans **171** with an exocyclic double bond. These intermediates then undergo an unconventional Povarov-type reaction, facilitated by the catalytic system, to form spiro-heterocycles, specifically spiro-isobenzofuran- β -pyrroloquinolines **173**, with moderate diastereoselectivity (Scheme 1.3.1.1.5).

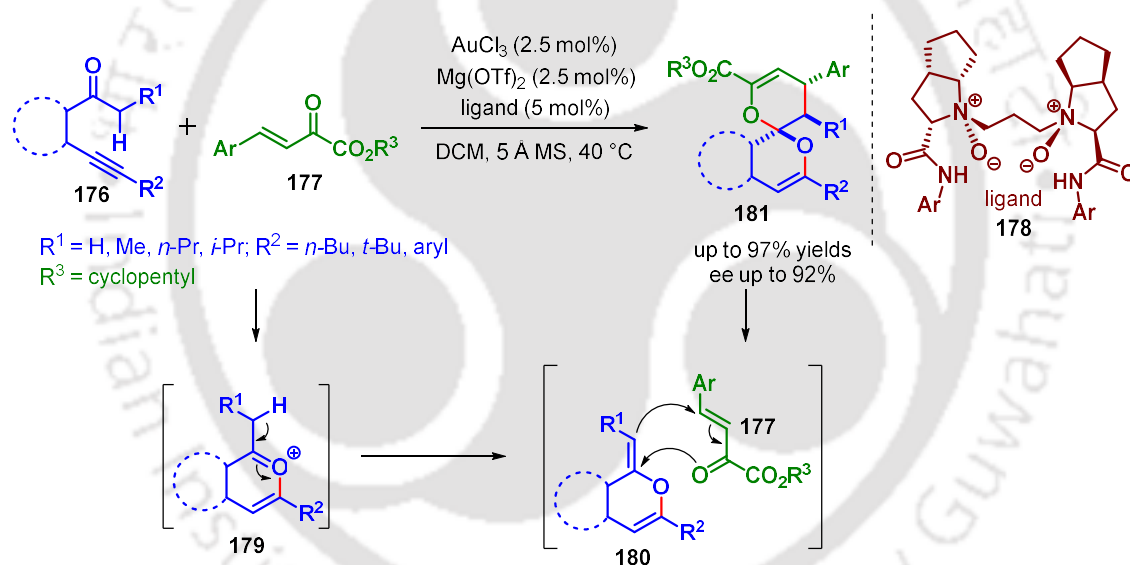
Li's group developed a versatile domino reaction using a novel catalytic system that combines rhodium and $\text{Sc}(\text{OTf})_3$ to synthesize spiro-cyclic heterocycles (Scheme 1.3.1.1.6).⁸² The presence or absence of water influences the reaction pathway: in the absence of water, the process favors *endo*-cycloisomerization and C-H activation to produce 2,3-dihydronaphtho[1,2-*b*]furans **174**. On the contrary, with water present in the system, the reaction proceeds *via* hydroalkoxylation pathway followed by C-H activation, resulting in spiro-derivatives **175** with good yields. The key feature of this reaction is the in situ generation of a ketal directing group, formed *via* intramolecular C-H bond activation and oxonium ion trapping with water. This directing group plays a crucial role in facilitating subsequent C-H bond activation. The reaction transforms alkynols and 7-oxabenzonorbornadienes into spiro-cyclic heterocycles through a multi-step process, including rhodium-catalyzed hydroalkoxylation, water



Scheme 1.3.1.1.6. Tunable Cascade Reactions under combined scandium and rhodium catalysis.

trapping, Rh-insertion, and reductive elimination, ultimately yielding the desired products in good to excellent yields.

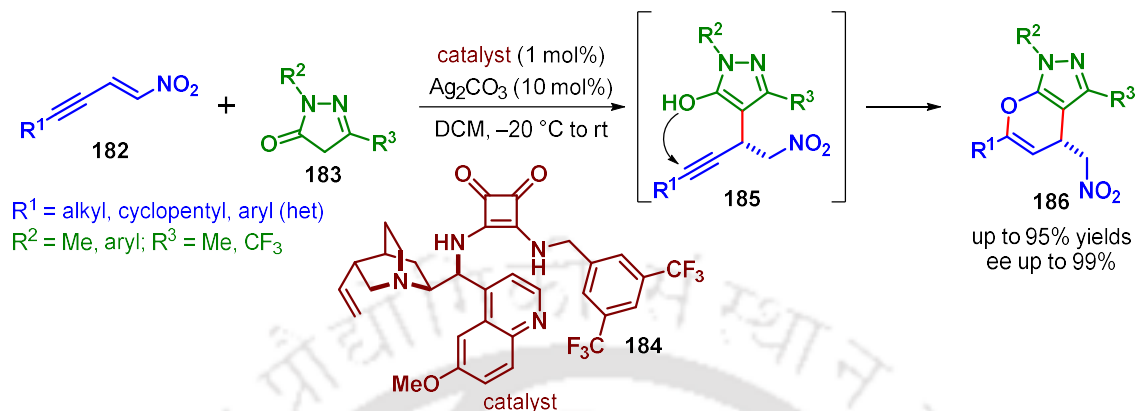
Enantioselective synthesis of 6,6-spiro-ketals was successfully accomplished by Feng's group using a bimetallic catalytic system. The asymmetric tandem reaction involves reaction of *o*-alkynyl ketone **176** and α,β -unsaturated esters **177** with AuCl_3 (2.5 mol%), $\text{Mg}(\text{OTf})_2$ (2.5 mol%), and a chiral N,N-dioxide ligand **178** (5 mol%) to deliver the corresponding spiro-ketals **181**. The reaction mechanism encompassed hydroalkoxylation followed by elimination of α -hydrogen to yield the exocyclic enol ether **180**, which on subsequent hetero-Diels-Alder cycloaddition with **177** afforded the desired spiro-ketal with good to excellent diastereo- and enantioselectivity (Scheme 1.3.1.1.7).⁸³



Scheme 1.3.1.1.7. Enantioselective synthesis of spiro-ketals.

Enders's group devised an efficient protocol which consists of an enantioselective intermolecular Michael addition along with a subsequent intramolecular 6-*endo-dig* hydroalkoxylation process, as detailed in Scheme 1.3.1.1.8.⁸⁴ By employing squaramide **184** for the asymmetric Michael addition, they have effectively coupled pyrazoles **183** with alkynes-linked α,β -unsaturated nitro olefins **182**, resulting in the production of the Michael adduct **185**. Further treatment of the intermediate **185** with silver carbonate, successfully yielded chiral pyrano-pyrazoles **186** with impressive

efficiency through a 6-*endo-dig* hydroalkoxylation process. This method has been successfully employed to synthesize a variety of chiral pyrano-pyrazoles.



Scheme 1.3.1.1.8. Tandem enantioselective Michael addition and hydroalkoxylation.

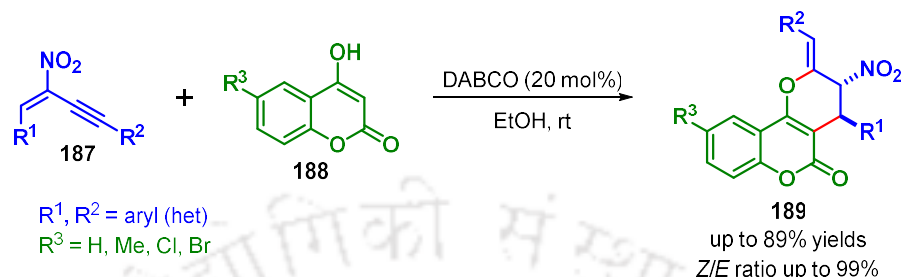
The discussion so far has comprehensively covered various metal-catalyzed synthetic pathways for hydrofunctionalization-cascade reactions of alkynes, with a notable focus on the transition metal-mediated hydroalkoxylation of alkyne derivatives to produce O-incorporated compounds. In response to challenges such as the high cost of transition metals and the hazardous nature of some reaction conditions, researchers have been focused on developing metal-free hydroalkoxylation of alkynes. A recent review by S. K. Nanda has delved into the topic of metal-free intramolecular hydroalkoxylation and the cascade reactions propelled by intramolecular hydroalkoxylation.⁸⁵

1.3.2. Non-Metal Based Hydroalkoxylation of Alkynes

1.3.2.1. Organocatalytic Hydroalkoxylation

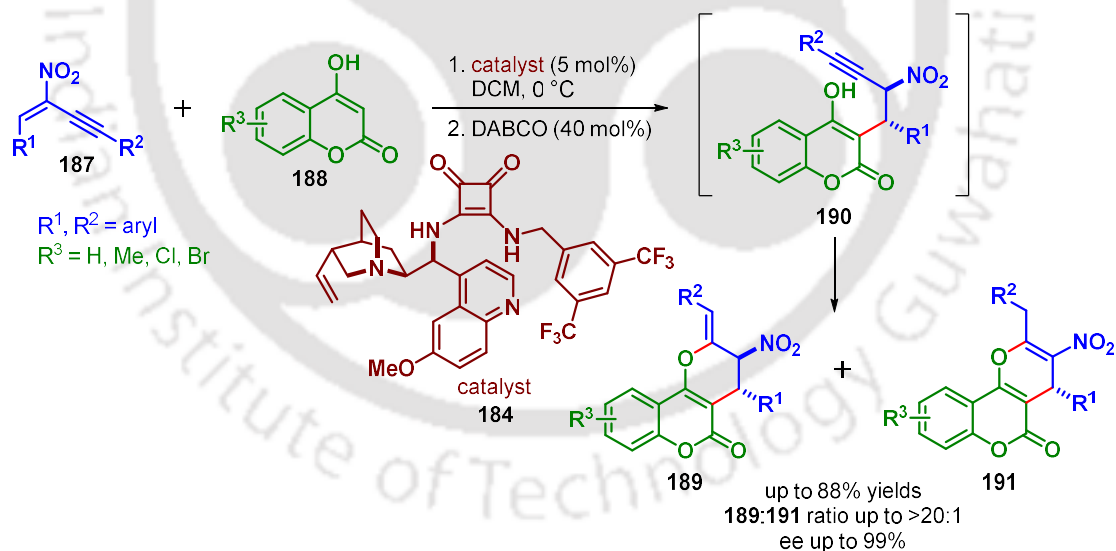
The utilization of organocatalytic Michael addition reactions has become one of the powerful approaches for creating C-C, C-N, and C-O bonds. Nitroenynes, in particular, have been widely utilized in diverse cascade reactions, which mostly includes a tandem organocatalytic Michael addition followed by transition metal-catalyzed alkyne activation sequence.⁸⁶ However recent advancements have demonstrated that these reactions can indeed occur without requiring a metal catalyst. This can be achieved with high selectivity by employing cascade reactions, involving tandem Michael addition and alkyne activation. For example, Biswas's group

reported a DABCO-catalyzed tandem Michael addition–hydroalkoxylation reaction involving alkyne-tethered nitroalkenes **187** with cyclic β -keto esters or 1,3-dicarbonyls **188** to synthesize pyrano-fused heterocyclic derivatives **189** (Scheme 1.3.2.1.1).⁸⁷



Scheme 1.3.2.1.1. Michael addition–hydroalkoxylation synthesis of fused pyrans.

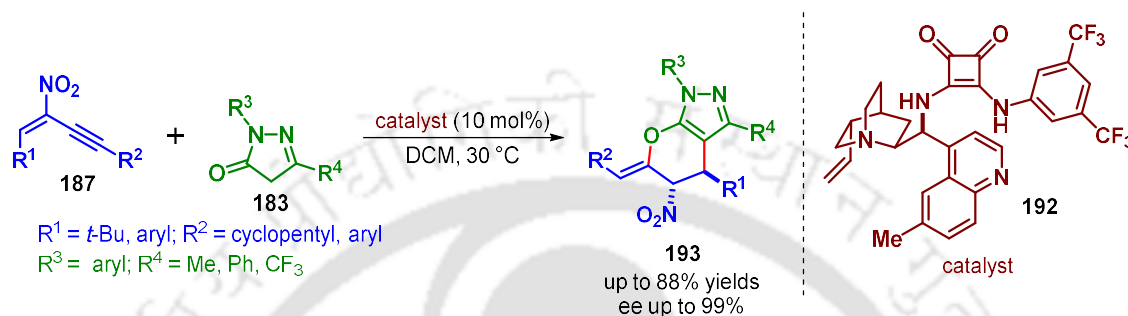
In this direction, Chen and colleagues demonstrated a useful approach to the enantioselective construction of pyrano-chromene or its derivatives **189** and **191** by using squaramide **184** as a catalyst along with DABCO. The reaction proceeds *via* a sequential cascade of conjugate addition followed by Michael addition-6-*endo-dig* hydroalkoxylation, yielding up to 88% with excellent selectivity (Scheme 1.3.2.1.2).⁸⁸



Scheme 1.3.2.1.2. Enantioselective Michael addition–hydroalkoxylation cascade synthesis of pyrano-chromenes.

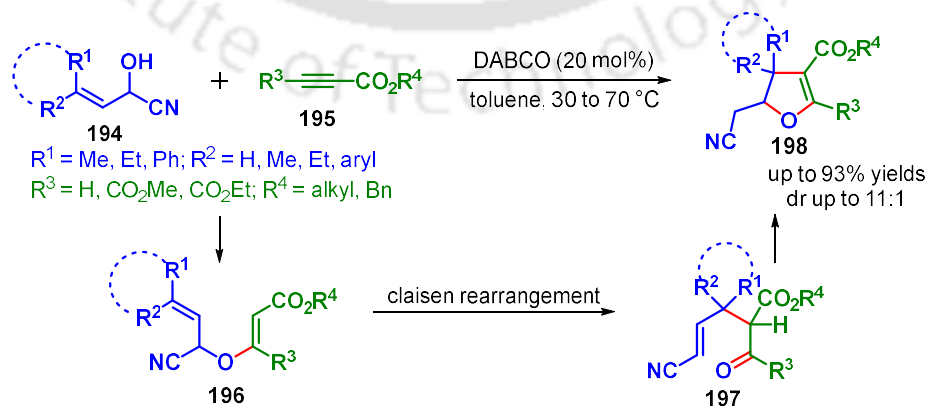
Singh's group extended this concept by developing an enantioselective domino Michael–hydroalkoxylation reaction to synthesize tetrahydropyrano[2,3-*c*]pyrazole derivatives **193** using a chiral cinchona derived squaramide catalyst **192**.⁸⁹ By

leveraging alkyne-tethered nitro olefins **187** as acceptors and N-arylpyrazolinones **183** as substrates, they efficiently synthesized a diverse array of pyrano[2,3-*c*]pyrazoles bearing an exocyclic alkene at the C6 position with high enantio- and diastereoselectivity (Scheme 1.3.2.1.3). However, its scope is currently limited to aryl alkynes, warranting further exploration with aliphatic and terminal alkynes.



Scheme 1.3.2.1.3. Enantioselective domino Michael-hydroalkoxylation synthesis of pyrano[2,3-*c*]pyrazoles.

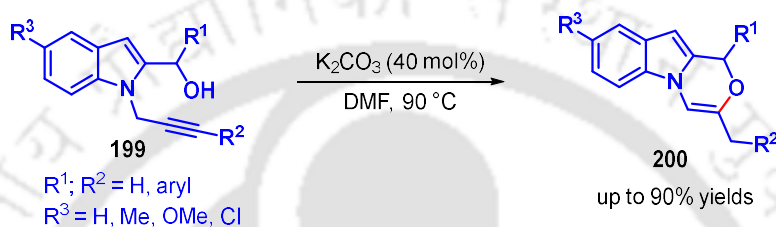
Numerous studies have pointed out the use of metal catalysts in cascade reactions involving Claisen rearrangement. On the contrary, the organocatalytic cascade hydroalkoxylation-Claisen rearrangement reaction of allylic alcohols and alkyne remains underdeveloped. In this context, Liao and colleagues demonstrated a metal-free approach for the synthesis of dihydropyran derivatives utilizing DABCO as a catalyst. The process involves the generation of intermediate **196**, which readily undergoes Claisen rearrangement to give **197**. Finally, a 5-*exotrig* intramolecular oxa-Michael addition reaction produced the dihydrofurans **198** in good to excellent yields (Scheme 1.3.2.1.4).⁹⁰



Scheme 1.3.2.1.4. Hydroalkoxylation-Claisen rearrangement-Michael addition.

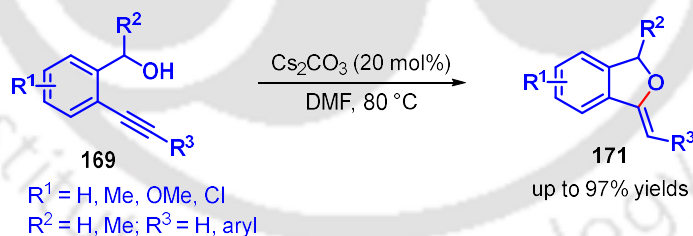
1.3.2.2. Base-Mediated Hydroalkoxylation

Wang's group developed a base-catalyzed protocol for the synthesis of indole-fused-1,4-oxazines **200** from N-propargyl indolyl alcohols **199**. This strategy involves a 6-*exo-dig* hydroalkoxylation reaction, followed by a double bond isomerization to yield the of indole-fused-oxazines in good yields (Scheme 1.3.2.2.1).⁹¹ Furthermore, a novel, single-step amination reaction was discovered to occur that exhibit chemical and positional selectivity, yielding indole-fused azlactones under these conditions.



Scheme 1.3.2.2.1. Base catalyzed intramolecular hydroalkoxylation for the synthesis of pyrrole-fused-oxazines.

Yu's group reported a base catalyzed hydroalkoxylation of *o*-alkynyl benzyl alcohols **169** to synthesize isobenzofurans **171**. This Cs_2CO_3 catalyzed hydroalkoxylation reaction proceeds *via* 5-*exo-dig* mode to furnish isobenzofuran derivatives in good yields (Scheme 1.3.2.2.2).⁹²



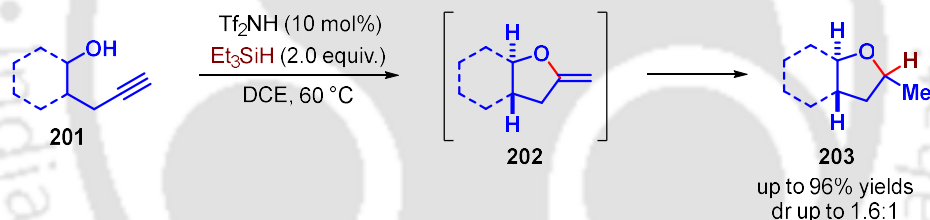
Scheme 1.3.2.2.2. Base catalyzed intramolecular hydroalkoxylation for the synthesis of isobenzofurans.

1.3.2.3. Acid-Mediated Hydroalkoxylation

Comprehensive literature reports on metal-catalyzed hydroalkoxylation of alkyne highlighted the need for complementary Lewis/Brønsted acids to achieve the effective transformational changes.⁸⁵ This prompts the question: can these acids alone facilitate the desired reactions? Although the transition metal-free catalysis mostly

remained unexplored, recent advancement indicate that Lewis/Brønsted acids can indeed independently drive complex hydroalkoxylation and cascade reactions, challenging the conventional reliance on transition metal catalysts.

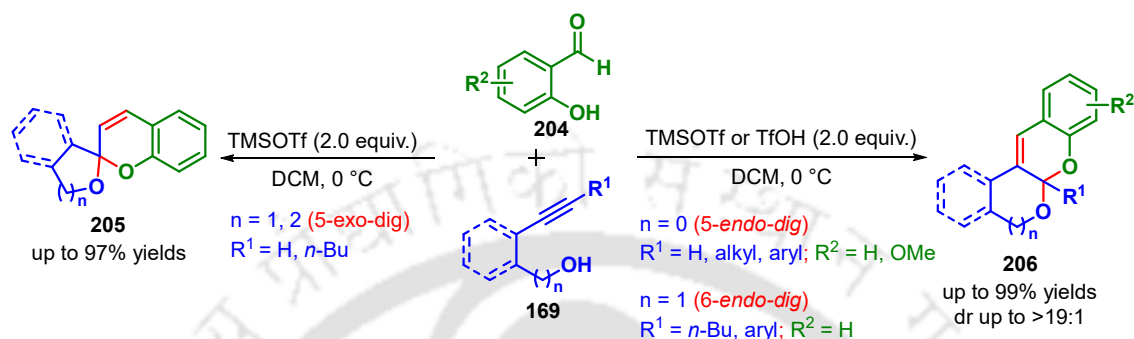
Building on this concept, Shibuya's group developed an innovative approach to synthesize cyclic ethers through the use of a silane-iodine catalytic system, which facilitates the intramolecular hydroalkoxylation of unactivated alkenes, offering a novel and efficient pathway for constructing these heterocyclic compounds.⁹³ Later, they modified their technique by utilizing a combination of Brønsted acid with silanes to achieve the desired cyclic ethers. They demonstrated that a range of terminal alkynols **201** could be efficiently converted into cyclic ethers **203** using a $\text{ Tf}_2\text{NH-Et}_3\text{SiH}$ catalytic system. The unactivated alkynes are electrophilically activated by the Brønsted acid to furnish reactive exocyclic enol ethers *via* 5-*exo-dig* intramolecular hydroalkoxylation. These intermediates are then reduced by Et_3SiH to produce the corresponding saturated cyclic ethers (Scheme 1.3.2.3.1).⁹⁴



Scheme 1.3.2.3.1. $\text{ Tf}_2\text{NH-Et}_3\text{SiH}$ mediated intramolecular hydroalkoxylation.

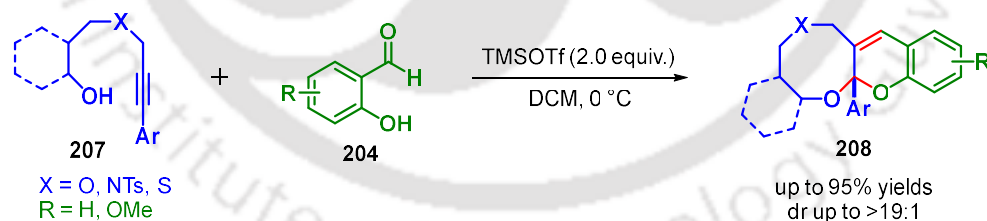
Numerous strategies have been devised for the synthesis of chromene ketal scaffolds due to their presence in various complex natural products. Gharpure's group reported a transition metal-free protocol for the stereoselective synthesis of tetrahydrofurano- and pyrano-chromenes, and spiroketals. This cascade hydroalkoxylation-formal [4+2] cycloaddition protocol of alkynols **169** with salicylaldehyde derivatives **204** under the influence of TMSOTf provides the cyclic ketals in good yields. The regioselectivity of hydroalkoxylation in alkynols was investigated, revealing distinct preferences based on alkyne topology. Internal alkynes exhibit a strong preference for 5/6-*endo-dig* cyclization that led to production of heteroannular ketals **206** (Scheme 1.3.2.3.2).⁹⁵ In contrast, terminal alkynols favour *exo-dig* cyclization, resulting in spiroketal products **205**. Additionally, complex

scaffolds like bis-chromene, quinoline-fused chromene, core of xyloketal and paecilospirone natural products could be assembled using this strategy. This study sheds light on the key factors influencing the regioselectivity of hydroalkoxylation reactions, enabling a deeper understanding of the underlying mechanisms.



Scheme 1.3.2.3.2. TMSOTf-promoted synthesis of fused-chromenes and spiroketals.

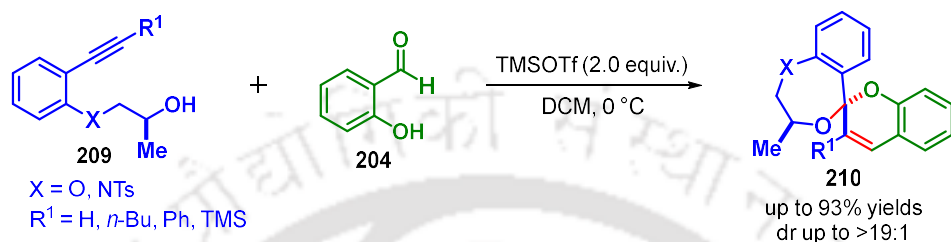
The strategy was further explored by the same group to encompass the synthesis of 1,4-heterocycle-fused chromene **208** and spiro chromene derivatives **210** with excellent regio- and stereoselectivity. Notably, the reaction consistently proceeded through an *endo-dig* hydroalkoxylation mode. Treatment of various N/O/S-tethered alkynols **207** with salicylaldehyde derivatives **204** in the presence of 2.0 equiv. of TMSOTf yielded the corresponding chromenes **208** as single diastereomers (Scheme 1.3.2.3.3).⁹⁶



Scheme 1.3.2.3.3. TMSOTf-mediated intramolecular hydroalkoxylation of N/O/S-tethered alkynols and salicylaldehyde.

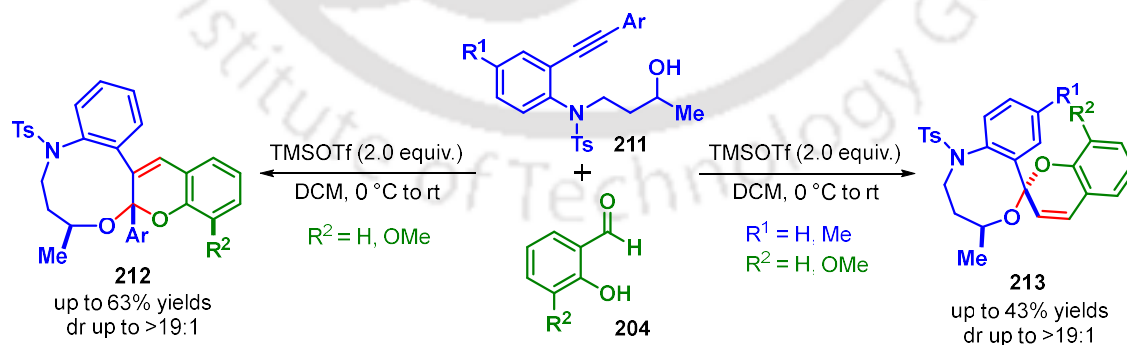
Interestingly, when aryl-tethered alkynol or its derivatives **209** were reacted with salicylaldehyde (**204**) under the same set of reagents, the desired products were the spiro chromene derivatives **210**, afforded in moderate to good yields along with good diastereoselectivity (Scheme 1.3.2.3.4).⁹⁶ The dominant factor behind this remarkable regioselectivity, consistently yielding spiro-ketals as the sole products, is the Lewis

acid-mediated 7-*exo-dig* hydroalkoxylation of alkynols, which takes precedence over 8-*endo-dig* hydroalkoxylation because of the enhanced stability of the vinyl cation intermediate. This stability facilitates the production of an exocyclic vinyl ether, which subsequently undergoes a [4+2] cycloaddition with salicylaldehyde to produce the corresponding spiro-ketal compounds.



Scheme 1.3.2.3.4. Stereoselective synthesis of *spiro*-cyclic ketals.

In a report, the aforementioned group extended the same method to synthesize medium-ring heterocycle-fused chromenes, featuring a diastereoselective tandem hydroalkoxylation-formal [4+2] cycloaddition reaction (Scheme 1.3.2.3.5).⁹⁷ This synthetic strategy enables the construction of complex chromene structures, including spiro-cyclic and linearly-fused ladder-like polyethers, as well as bridged tricyclic ketals through subsequent carbene-insertion-[2,3]-sigmatropic shift. Notably, the use of TMSOTf promotes *endo-dig* hydroalkoxylation, leading to the stereoselective formation of 9-membered 1,4-heterocycle fused-chromene ketals **212** in good yields and high diastereomeric purity. However, in case of terminal alkynols, the stability of



Scheme 1.3.2.3.5. Hydroalkoxylation-formal [4+2] cycloaddition protocol to synthesize fused chromene and spiroketals.

the internal/benzylic vinyl cation favours *exo*-selectivity, subsequently generating the spiro ketals **213** with excellent diastereoselectivity.

In an approach by combining Lewis acid-promoted tandem hydroalkoxylation and reduction, Gharpure's group achieved the stereoselective construction of cyclic ethers, offering an efficient and selective method for synthesizing the valuable heterocyclic compounds.⁹⁸

Despite the significant progress in hydroalkoxylation, there are still challenges that need to be addressed. One such challenge is the regioselectivity between *exo-dig* and *endo-dig* modes, which can lead to the formation of mixed products. Additionally, aliphatic alkynes have low reactivity, and successful cyclization typically involve electron-rich alkynes. Metal-free hydroalkoxylation is not as advanced as its metal-catalyzed counterpart, and there are unresolved issues concerning the reactivity of terminal and aliphatic alkynols. To overcome these challenges, there is an urgent need for efficient and broadly applicable methods for metal-free enantioselective hydroalkoxylation cascades to expand the scope of this synthetic strategy.

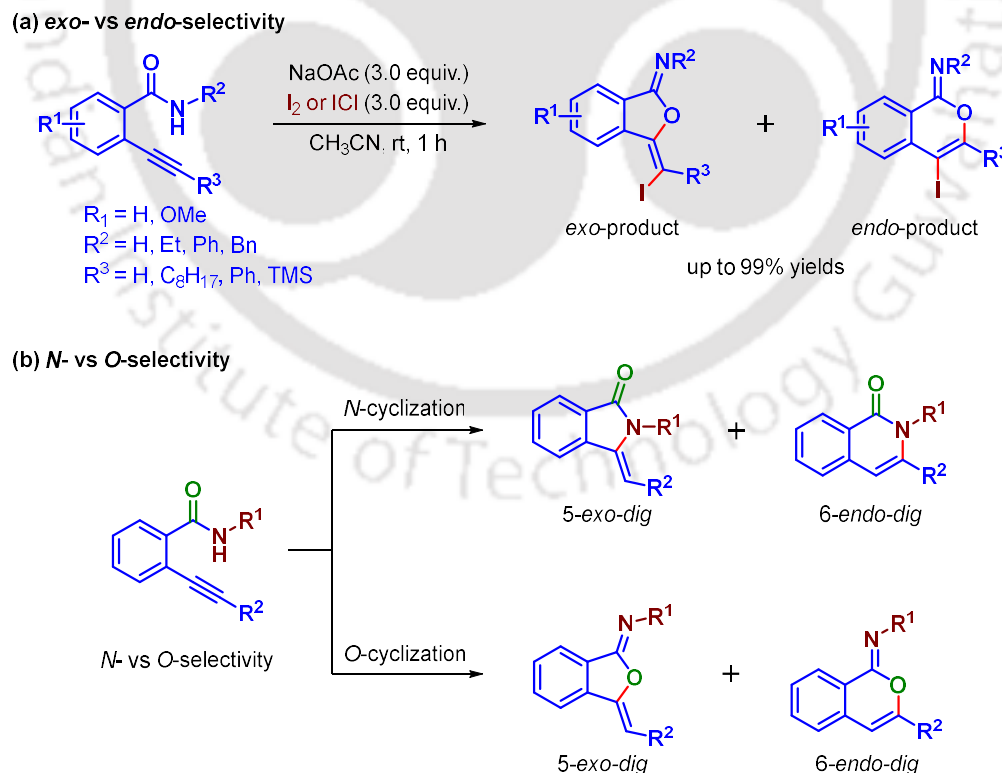
1.4. Intramolecular Oxycyclization

Intramolecular oxycyclization is an intriguing aspect of organic chemistry, where oxygen-containing molecules cyclize within themselves, forming cyclic ethers or lactones. This process plays a crucial role in producing a wide range of complex organic compounds, including natural products and bioactive molecules.⁹⁹ One classic example of intramolecular oxycyclization is the creation of tetrahydropyrans, which serve as essential structural components in numerous natural products. Likewise, intramolecular oxycyclization of amides represents a specific and powerful class of transformations in organic synthesis. Given the prevalence of amides in pharmaceuticals, natural products, and material science, the ability to efficiently transform these functional groups into more complex structures through oxycyclization has consistently been highly valued in the synthetic chemistry community.

The fundamental mechanism of intramolecular oxycyclization involves the

nucleophilic attack of an oxygen atom, typically part of the amide group, on an electrophilic carbon atom within the same molecule. This process involves the generation of a new oxygen heterocycle with a neighbouring imine moiety (Scheme 1.4.1). The driving force behind this transformation can be attributed to the formation of a stable cyclic structure, often facilitated by the release of strain in the starting material or the formation of a thermodynamically favoured ring size.

While intramolecular oxycyclization of amides are powerful tools in organic synthesis, these reactions navigate through a labyrinth of challenges. One of the major concerns is the inherently low nucleophilicity of amides, which hampers the reaction kinetics and outcomes. Additionally, these reactions often encounter unpredictable regioselectivity issue, oscillating between *exo*- and *endo*-pathways in complex molecular structures (Scheme 1.4.1.a).^{100a} This unpredictability is further exacerbated by the potential formation of undesired stereoisomers. Moreover, the dilemma of competing O- vs N-cyclization of amides introduces an extra dimension of complexity for the intramolecular nucleophilic addition of amides (Scheme 1.4.1.b).^{100b-e} These



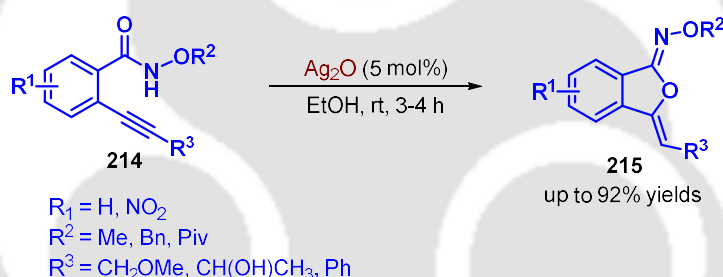
Scheme 1.4.1. (a) *exo*- vs *endo*-oxycyclization and (b) N- vs O-selectivity of amides.

overlapping challenges highlight the need for strategic approaches for the utilization of intramolecular oxycyclization in advanced organic synthesis.

Oxycyclization reactions are initiated under acidic or basic conditions, which activate the electrophilic center or deprotonate the nucleophilic oxygen, respectively, for further transformation. Few examples of acidic and basic conditions for the transformation are listed below.

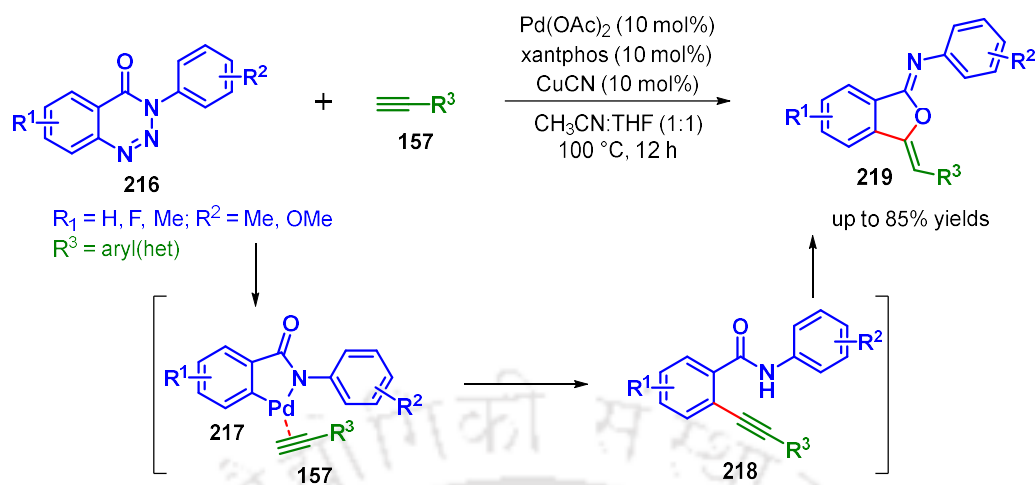
1.4.1. Oxycyclization Synthesis of Isobenzofurans

Belmont's group described a silver-catalyzed cycloisomerization reaction of *o*-alkynylbenzohydroxamic acids **214** for the synthesis of isobenzofuranone oximes **215** in moderate to good yields. The reaction proceeds *via* 5-*exo-dig* mode of cyclization from the oxygen atom of the amide group to the silver activated alkynyl moiety to furnish the desired oxygenated heterocycle (Scheme 1.4.1.1).^{100d}



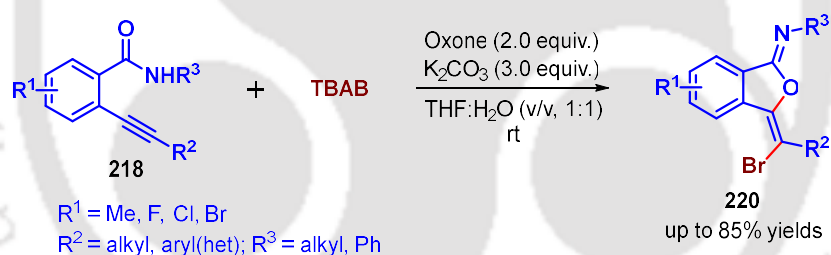
Scheme 1.4.1.1. Silver-catalyzed oxycyclization reaction.

Mannathan's group reported an efficient denitrogenative tandem alkynylation/cyclization strategy to synthesize benzyldene(imino)isobenzofuranones **219** from benzotriazin-4(3*H*)-ones **216** and aromatic terminal alkynes **157**. The reaction proceeds *via* the generation of a five-membered aza-palladacyclic intermediate **217** with the extrusion of a nitrogen molecule, followed by the chemoselective addition of the proximal amide group through the O-atom to form the desired products (Scheme 1.4.1.2).^{100e}



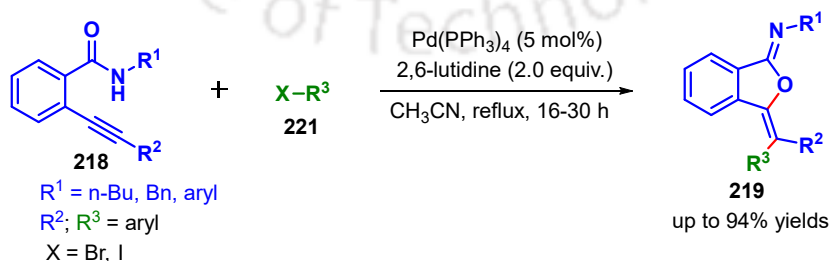
Scheme 1.4.1.2. Tandem alkynylation/cyclization synthesis of isobenzo-furanones.

Qiu's group developed a TBAB-mediated brominative oxycyclization of *o*-alkynylbenzamide **218** for the synthesis of bromide substituted isobenzofuranimines **220**. This reaction proceeds smoothly with a high preference for 5-*exo-dig* cyclization to furnish the functionalized isobenofuranimines in good yields (Scheme 1.4.1.3).¹⁰¹



Scheme 1.4.1.3. TBAB-mediated brominative oxycyclization of *o*-alkynylbenzamides.

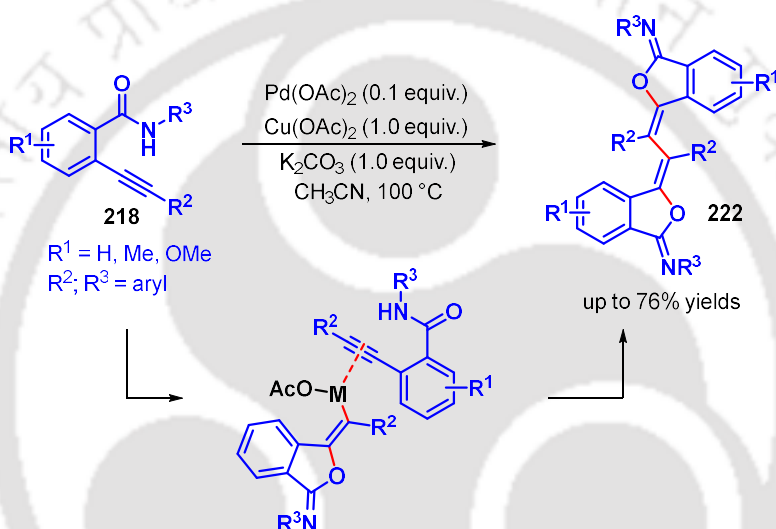
Wang's group reported a palladium-catalyzed synthesis of isobenzofuranylidene-benzenamines **219** from *o*-alkynylbenzamides **218** and arylhalides **221**. The process



Scheme 1.4.1.4. Palladium-catalyzed synthesis of isobenzofuranylidene-benzenamines.

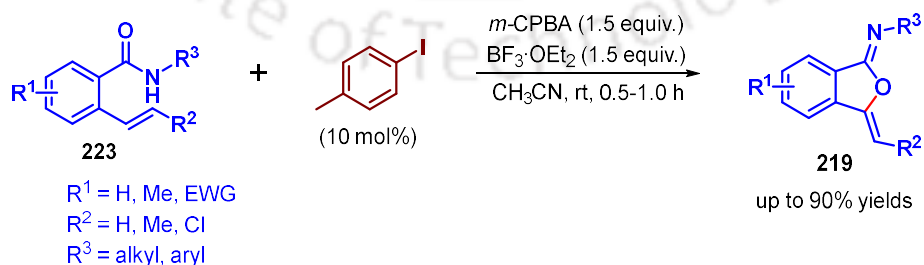
exhibits high regioselectivity for synthesizing functionalized isobenzofuranylidene-benzenamines in good yields (Scheme 1.4.1.4).¹⁰²

Zhu's group developed a $\text{Pd}(\text{OAc})_2/\text{Cu}(\text{OAc})_2$ co-catalyzed method for the dimerization of *o*-alkynylbenzamides **218**, producing axially chiral *E,E*-1,3-diene **222**. The key feature of this reaction is the concurrent formation of vinylpalladium and vinylcopper intermediates, followed by transmetalation step. Notably, $\text{Cu}(\text{OAc})_2$ plays a dual role, acting not only as an oxidant but also as an active participant in C–C and C–O bond formation alongside $\text{Pd}(\text{OAc})_2$ (Scheme 1.4.1.5).¹⁰³



Scheme 1.4.1.5. Pd/Cu co-catalyzed dimerization of *o*-alkynylbenzamides.

He and co-workers developed an aryl iodide-catalyzed intramolecular oxycyclization strategy to synthesize various benzoiminolactones **219** in good to excellent yields (Scheme 1.4.1.6).¹⁰⁴ Here, *m*-CPBA functions as both oxidant and ligand at the

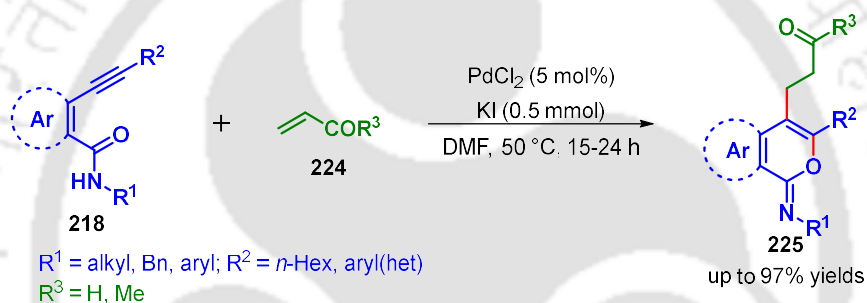


Scheme 1.4.1.6. Aryl iodide-catalyzed intramolecular oxycyclization strategy for the synthesis of benzoiminolactones.

I(III) center, while $\text{BF}_3 \cdot \text{OEt}_2$ facilitates ligand exchange and promotes reductive elimination during the catalytic cycle.

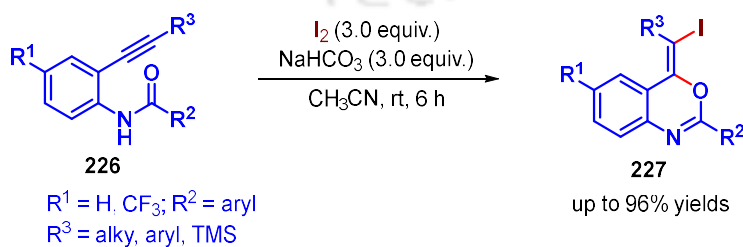
1.4.2. Oxycyclization Synthesis of Isochromenes

Aurrecoechea's group described a palladium catalyzed cyclization–coupling cascade sequence for the regio- and chemoselective synthesis of isochromenimines **225** from *o*-alkynylarylcarboxamides **218** and methyl vinyl ketone or acrylaldehyde **224**. The process involves an initial 6-*endo*-oxypalladation of the alkyne moiety, followed by a C–C coupling to furnish isochromenimine-type products with an alkyl-type exocyclic side chain derived from the α,β -unsaturated carbonyl compound (Scheme 1.4.2.1).¹⁰⁵



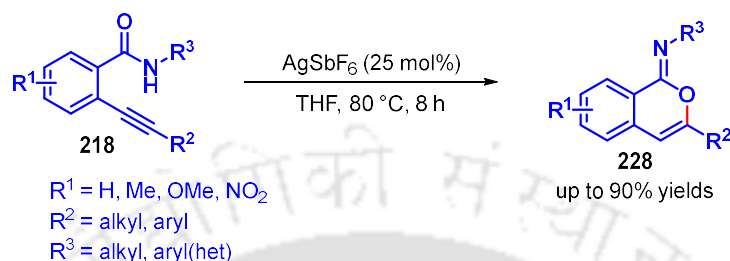
Scheme 1.4.2.1. Palladium-catalyzed coupling cascade synthesis of isochromenimines.

Wang's group demonstrated a base-mediated intramolecular 6-*exo-dig* cyclization strategy of compound **226** for the regio- and chemoselective synthesis of 1,3-benzoxazines **227**. Interestingly, DFT calculations revealed that the *Z*-isomer of the product was found to be more stable than the *E*-isomer by 3.5 kcal mol⁻¹ (Scheme 1.4.2.2).¹⁰⁶



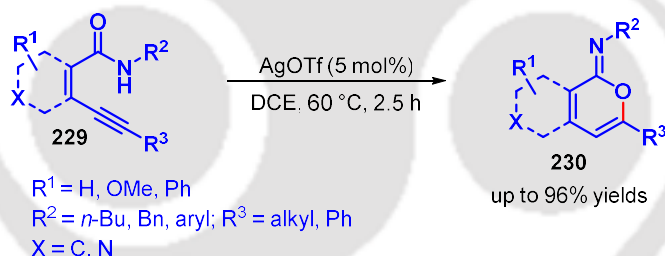
Scheme 1.4.2.2. Base-mediated synthesis of 1,3-benzoxazines.

Liu's group reported the first Ag(I)-catalyzed regiocontrolled intramolecular addition of the amide group towards an alkyne. The process involves a 6-*endo-dig* attack from the O-atom of the amide group to the alkyne moiety of the *o*-alkynylbenzamides **218** to give isochromenimines **228** (Scheme 1.4.2.3).¹⁰⁷



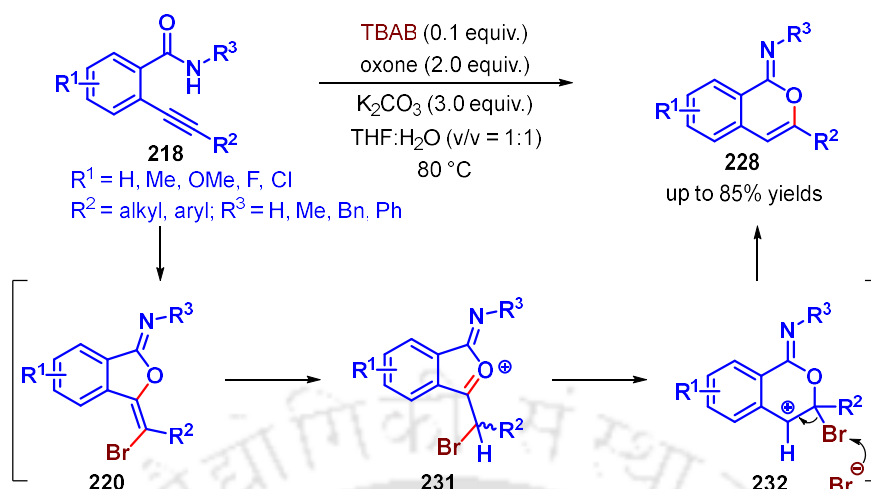
Scheme 1.4.2.3. Silver-catalyzed synthesis of isochromenimines.

Ma's group developed a highly efficient AgOTf-catalyzed intramolecular oxycyclization reaction of *o*-(1-alkynyl)benzamide or (*Z*)-alk-2-en-4-ynamides **229** to synthesize iminoisocoumarin and R-iminopyrone derivatives **230** in good yields. The process involves a selective 6-*endo-dig* type, O-nucleophilic attack of the amide group onto the tethered C–C triple bond (Scheme 1.4.2.4).¹⁰⁸



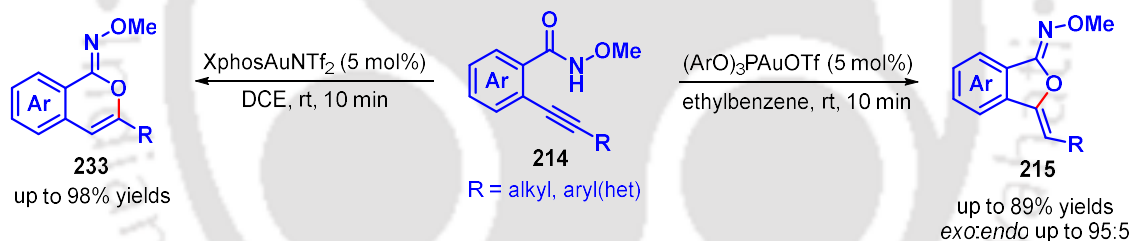
Scheme 1.4.2.4. AgOTf-catalyzed intramolecular oxycyclization *o*-alkynylbenzamides.

Liu's group extended their radical strategy of synthesizing isobenzofuranimines to encompass the synthesis of isocoumarinimines **228**. Initially, TBAB-catalyzed oxycyclization of *o*-alkynylbenzamides **218** generates the 5-*exo-dig* cyclized product, isobenzofuranimines **220**. Subsequently, protonation of the isobenzofuranimine intermediate **220**, followed a 1,2-HAT of the carbon cation and sequential 1,2-migration of the C–O bond forms the isocoumarinimine cation **232**. Finally, elimination of the bromide functionality furnishes the desired isocoumarinimines **228** (Scheme 1.4.2.5).¹⁰⁹



Scheme 1.4.2.5. Radical synthesis of isocoumarinimines.

Jiang's group developed a chemo- and regioselective approach for the construction of benzoheterocycles. The protocol effectively illustrates the impact of ligands in gold catalysis, enabling regioselective cyclization of *o*-alkynyl-N-methoxyl-benzamides **214** to give the 5-*exo-dig* **215** and 6-*endo-dig* **233** products (Scheme 1.4.2.6).¹¹⁰



Scheme 1.4.2.6. Ligand controlled gold catalysis for the synthesis of benzoheterocycles.

1.5. Objective of the Present Work

The primary objective of this research is to investigate and define new approaches for synthesizing complex heterocyclic frameworks through the strategic use of cascade reactions, including Prins cyclization, hydroalkoxylation, and intramolecular oxycyclization. This study seeks to advance the synthesis of structurally unique frameworks, such as isoindoloquinazolinones, pyrimidoisoindolones, pyranoquinolines, and various spirocyclic scaffolds, by employing stereoselective and regioselective strategies. The research aims to provide a comprehensive understanding of the effective use of these methodologies for constructing intricate

heterocyclic compounds. The insights gained from this work are expected to contribute to drug discovery, offering a reliable platform for the development of new therapeutic agents.

1.6. References

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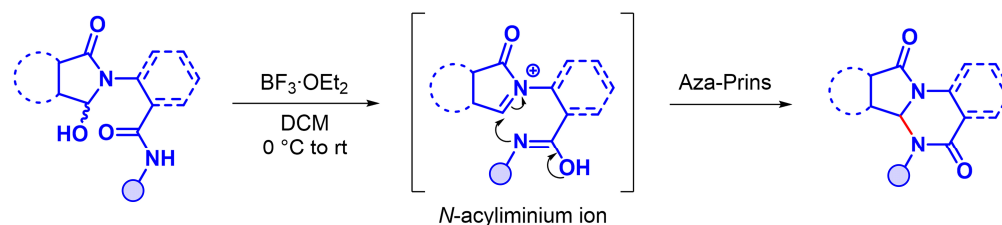
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Synthesis of Pyrimido[2,1-*a*]isoindolone and Isoindolo[2,1-*a*]quinazolinone *via* Intramolecular Aza-Prins Type Reaction



- Functionalized N-heterocyclic scaffolds
- Broad substrate scope
- Simple and mild reaction condition
- Excellent yields, up to 99%

Abstract: A novel aza-Prins type cyclization reaction involving N-acyliminium ions and amides is reported for the synthesis of tetrahydropyrimido[2,1-*a*]isoindole-2,6-dione and 6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione derivatives in excellent yields. The strategy features inexpensive reagents, mild reaction conditions, and metal-free synthesis of N-heterocyclic frameworks. Further, post-synthetic modification results in the unprecedented formation of its triazole, tetracyclic diazacyclopenta[*def*]phenanthrene-1,4(9a1*H*)-dione and carbonyl derivatives.



Chapter II

Synthesis of Pyrimido[2,1-*a*]isoindolone and Isoindolo[2,1-*a*]quinazolinone *via* Intramolecular Aza-Prins Type Reaction

2.1. Introduction

Aza-Prins cyclization, the nitrogen variant of the traditional Prins cyclization, has emerged as a highly reliable strategy for constructing complex and diverse nitrogenous heterocycles.¹ Scientists worldwide have effectively leveraged this strategy to synthesize numerous bioactive molecules, prevalent in many natural products and pharmaceuticals. The utilization of iminium and acyliminium ion ring closure strategies to synthesize piperidines scaffolds is well-documented. However, the investigation into the aza-Prins reaction as a viable pathway for such syntheses has yet to be adequately explored.

Isoindolinone scaffolds are versatile chemical structures found in various natural products and synthetic compounds.² These scaffolds exhibit various biological and pharmaceutical activities, which makes them valuable assets in medicinal chemistry. Researchers worldwide have harnessed its potential, tweaking the isoindolinone moiety to synthesize a wide range of promising drug candidates. Fused isoindolinones, by virtue of their versatile nature, serve as antimalarial,^{3a} antimicrobial,^{3b} antibacterial,^{3c} anticancer,^{3d} anticonvulsant,^{3e} antiplasmodial,^{3f} antiangiogenic^{3g} and urotensin-II receptor antagonists agents.^{3h} They also serve as potent Cdk4 inhibitor,^{4a} topoisomerase II inhibitors,^{4b} cyclin-dependent kinase 5 (Cdk5) and glycogen synthase kinase 3 (GSK3) dual inhibitors,^{4c} show cytotoxicity,^{4d} and poses anti-HIV activity.^{4e} A pyrimidoisoindole derivative of Mazindol inhibits the reverse capture of dopamine more efficiently than cocaine and Mazindol.⁵ They also serve as key intermediates to synthesize highly useful organic compounds and natural products.⁶

Similarly, quinazolinones, owing to their immense biological applications, hold significant in the field of chemical and pharmaceutical research.⁷ They act as potent inhibitors of PDE 7A (phosphodiesterase 7A),^{8a} TNF- α ^{8b} and cancer cell proliferation,^{8c} and are therefore utilized in the treatment of several inflammatory disorders like

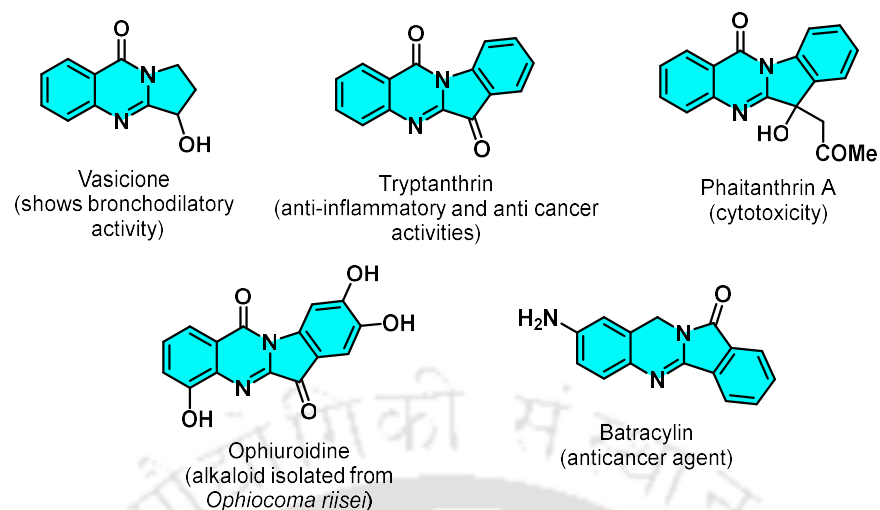
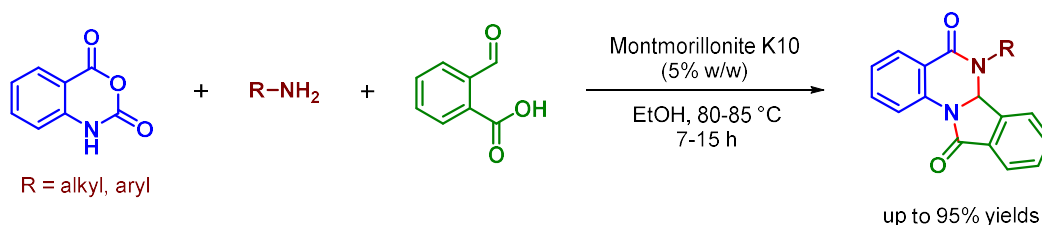


Figure 2.1.1. Representative examples of bioactive indoloquinazolinones.⁹

rheumatoid arthritis, Crohn's disease, and ulcerative colitis.^{8d} Isoindoloquinazolinone-based compounds could serve as a potent and selective inhibitor targeting hepatitis B virus.¹⁰ Moreover, isoindoloquinazolinones are used as stabilizers against the degradation of organic materials due to heat, light, or oxidation.¹¹

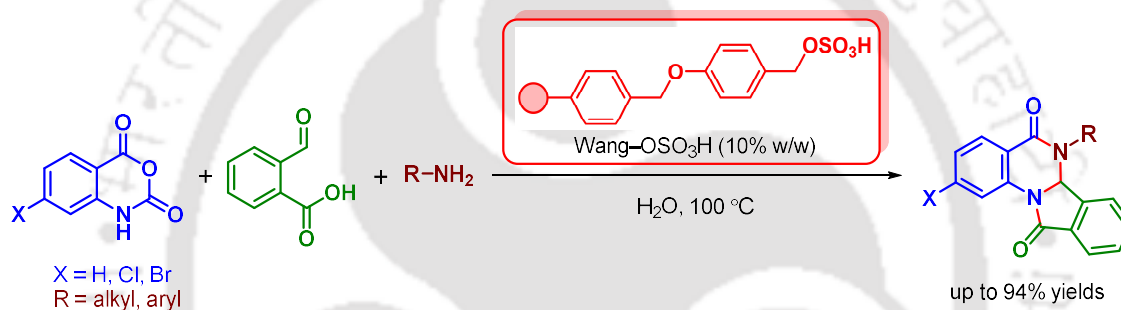
2.2. Differential Strategies Towards the Synthesis of Pyrimido[2,1-*a*]isoindolones and Isoindolo[2,1-*a*]quinazolinones

TNF- α (Tumor Necrosis Factor-alpha), one of the significant cytokine mediators associated with the inflammatory responses, acts as a marker for various inflammatory disorders.^{12a} While several large compounds are known to exhibit inhibitory effects, inhibition of TNF- α by small molecules is less prevalent in the literature.^{12b} In 2011, Pal's group demonstrated a simple and efficient green approach for the synthesis of isoindolo[2,1-*a*]quinazolinones, a potent TNF- α inhibitor. The three-component reaction involves the *in situ* formation of a 2-amino-*N*-arylbenzamide intermediate through the reaction of isatoic anhydride with an amine. This intermediate subsequently undergoes an intramolecular concurrent cyclization with 2-formyl benzoic acid to produce the desired product (Scheme 2.2.1).^{8b}



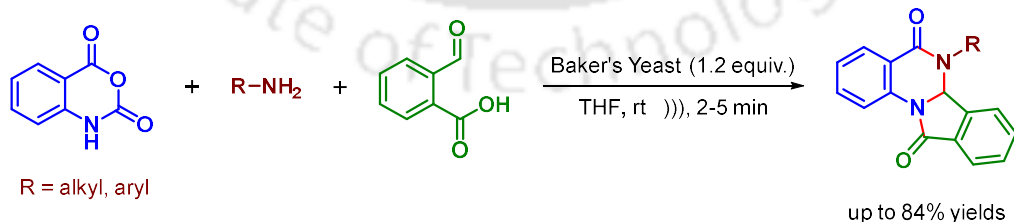
Scheme 2.2.1. Montmorillonite catalyzed green synthesis of isoindoloquinazolinones.

The same group utilized sulphonic acid-functionalized Wang resin (Wang-OSO₃H) as a polymeric, recoverable acidic catalyst for synthesizing functionalized isoindolo[2,1-*a*]quinazolinone derivatives. The catalyst can be recycled numerous times without significant loss of its catalytic activity (Scheme 2.2.2).¹³



Scheme 2.2.2. Wang resin catalyzed green synthesis of isoindoloquinazolinones.

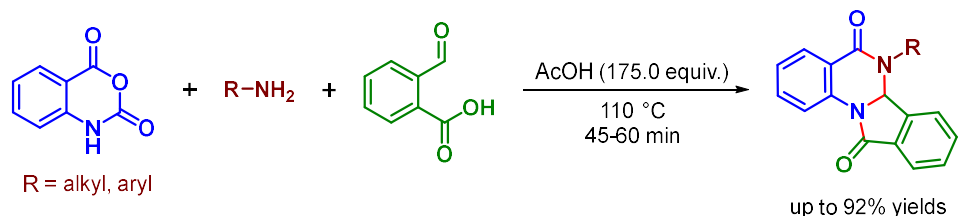
To expedite the synthesis of isoindolo[2,1-*a*]quinazolinones, Raval's group used *Saccharomyces cerevisiae* (baker's yeast) as a catalyst. The use of baker's yeast as the whole cell biocatalyst and ultrasound irradiation have significantly reduced the reaction time to just 2-5 mins. This acceleration in the process can be attributed to the synergetic effect of baker's yeast and ultrasound (Scheme 2.2.3).¹⁴



Scheme 2.2.3. Baker's yeast mediated synthesis of isoindoloquinazolinones.

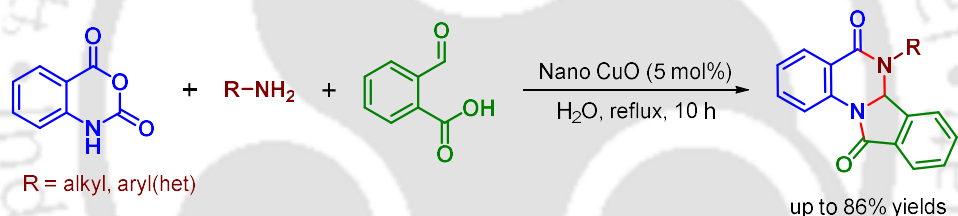
Following these developments, several groups have modified the reaction by adjusting various parameters of the transformation. Sashidhara's group, for instance,

developed a highly efficient catalyst-free protocol to synthesize isoindolo[2,1-*a*]quinazolinones in excellent yields (Scheme 2.2.4).¹⁵



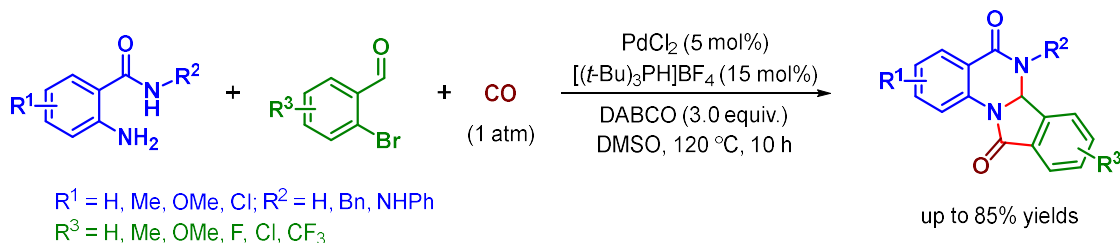
Scheme 2.2.4. AcOH promoted synthesis of isoindoloquinazolinones.

In pursuit of more sustainable synthetic methodologies, Hajra's group developed a nano CuO-catalyzed "on-water" strategy that efficaciously produces isoindolo[2,1-*a*]quinazolines in good yields. Water plays a crucial role in accelerating the reaction through hydrogen bond mediated 'electrophile-nucleophile dual activation'. Additionally, the catalyst exhibits robust reusability without significant loss of catalytic activity (Scheme 2.2.5).¹⁶



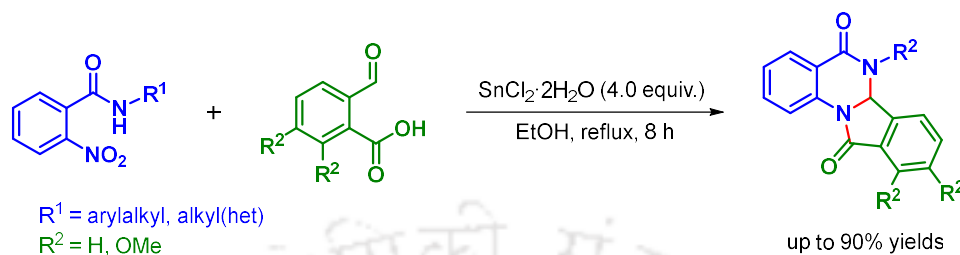
Scheme 2.2.5. Nano CuO-catalyzed "on-water" synthesis of isoindoloquinazolinones.

Fan's group has devised a palladium-catalyzed method for the selective construction of isoindolo[2,1-*a*]quinazolinone derivatives. This one-pot three-component approach involves the carbonylative cyclization of 2-aminobenzamides with 2-bromobenzaldehydes under an atmospheric pressure of carbon monoxide. The protocol provides easy access to a diverse array of functionalized isoindolo[2,1-*a*]quinazolinones in high yields with excellent regioselectivity (Scheme 2.2.6).¹⁷



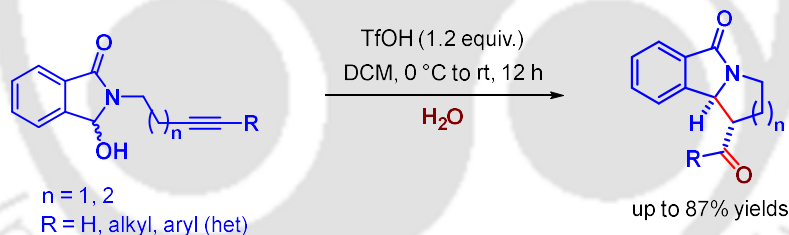
Scheme 2.2.6. Palladium-catalyzed cascade synthesis of isoindoloquinazolinones.

With a different approach, Foroumadi's group reported a $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ promoted direct synthesis of isoindolo[2,1-*a*]quinazolinones through a reductive reaction of *N*-substituted 2-nitrobenzamides and 2-formyl benzoic acid (Scheme 2.2.7).¹⁸



Scheme 2.2.7. Reductive one-pot strategy to synthesize isoindoloquinazolinones.

Saikia's group demonstrated a TfOH -mediated protocol for the synthesis of functionalized pyrroloisoindolone and pyridoisoindolones *via* aza-Prins cyclization reaction. This process involves the intramolecular cyclization of the alkynyl group to the *in situ* generated *N*-acyliminium ion, followed by an aqueous workup that affords the desired products in high yields with exclusive diastereoselectivity. Additionally, the methodology can be extended to synthesize pyrimido[2,1-*a*]isoindolones scaffolds (Scheme 2.2.8).¹⁹



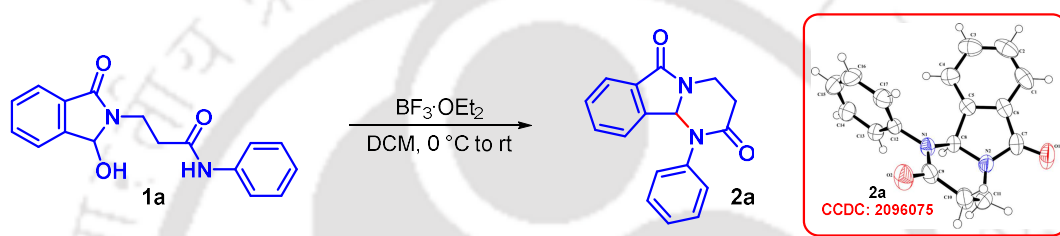
Scheme 2.2.8. Aza-Prins cyclization for the synthesis of isoindolones scaffolds.

2.3 Present Work

The literature reveals that several methodologies have been introduced for the synthesis of isoindolo[2,1-*a*]quinazolinones. However, most developments have primarily focused on catalyst improvements, leaving alternative synthetic strategies unexplored. While the use of Prins cyclization for the construction of piperidine, indoline, isoindolone, pyrrolizidinone and indolizidinones scaffolds is well documented, the synthesis of pyrimido[2,1-*a*]isoindolone and isoindolo[2,1-*a*]quinazolinone has not yet been reported. We anticipated to synthesize these

heterocycles from propanamide substituted imidoalcohols **1** using aza-Prins cyclization strategy (Scheme 2.3.1).

To synchronize our assumption, a preliminary reaction was performed with 3-(1-hydroxy-3-oxoisindolin-2-yl)-*N*-phenylpropanamide (**1a**) in DCM with an equivalent of $\text{BF}_3 \cdot \text{OEt}_2$. A new product was isolated in 92% yield. Spectroscopic data (^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR) and HRMS value revealed the product to be 1-phenyl-1,3,4,10b-tetrahydropyrimido[2,1-*a*]isoindole-2,6-dione (**2a**) (Scheme 2.3.1). Finally, single-crystal X-ray diffraction re-established its structure to be 1-phenyl-1,3,4,10b-tetrahydropyrimido[2,1-*a*]isoindole-2,6-dione.

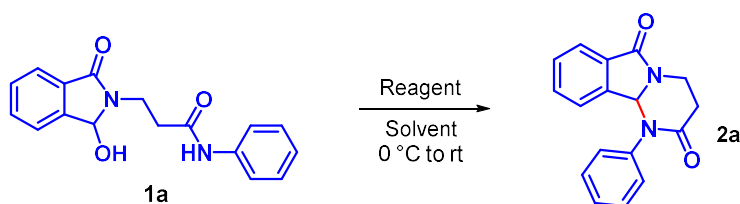


Scheme 2.3.1. Synthesis of pyrimido[2,1-*a*]isoindolones and isoindolo[2,1-*a*]quinazolinones.

2.4. Results and Discussion

2.4.1. Optimization of the Reaction Conditions

Highly intrigued by the result, further optimizations were carried out to maximize the yield of the product. Increasing the stoichiometry of $\text{BF}_3 \cdot \text{OEt}_2$ (1.2 equiv.) led to an escalated yield of 99% within 15 minutes (0.25 h) of the reaction (Table 2.4.1.1, entry 2). Solvents like toluene, DCE and acetonitrile were found to be equally effective, affording the product in 93, 92 and 96% yields, respectively (Table 2.4.1.1, entries 3-5). Additionally, the influence of various reagents on the reaction was studied. TMSOTf furnished the product in 91% yield (Table 2.4.1.1, entry 6). While $\text{Bi}(\text{OTf})_3$ and $\text{In}(\text{OTf})_3$ gave the desired product in 85 and 80% yields, respectively (Table 2.4.1.1, entries 10 and 11), other metal triflates such as $\text{Zn}(\text{OTf})_2$, $\text{Cu}(\text{OTf})_2$ and $\text{Sc}(\text{OTf})_3$ remained completely silent in the transformation (Table 2.4.1.1, entries 7-9). Metal halides were also incapable of producing a superior yield (Table 2.4.1.1, entries 12-14). In contrast, the reaction with Bronsted acids performed relatively well (Table 2.4.1.1, entries 15-

Table 2.4.1.1. Optimization of the reaction conditions.

Entry ^a	Reagent	Equivalent	Solvent	Time (h)	Yield ^b (%)
1	BF ₃ ·OEt ₂	1.0	DCM	24	92
2	BF₃·OEt₂	1.2	DCM	0.25	99
3	BF ₃ ·OEt ₂	1.2	Toluene	14	93
4	BF ₃ ·OEt ₂	1.2	DCE	0.25	92
5	BF ₃ ·OEt ₂	1.2	CH ₃ CN	0.25	96
6	TMSOTf	1.2	DCM	24	91
7	Zn(OTf) ₂	0.1	DCM	24	– ^c
8	Cu(OTf) ₂	0.1	DCM	24	– ^c
9	Sc(OTf) ₃	0.1	DCM	24	– ^c
10	Bi(OTf) ₃	0.1	DCM	24	85
11	In(OTf) ₃	0.1	DCM	24	80
12	InCl ₃	0.1	DCM	24	– ^c
13	InBr ₃	0.1	DCM	24	– ^c
14	FeCl ₃	1.2	DCM	05	75
15	TFA	1.2	DCM	04	94
16	TfOH	1.2	DCM	24	69
17	<i>p</i> -TsOH·H ₂ O	1.2	DCM	24	72

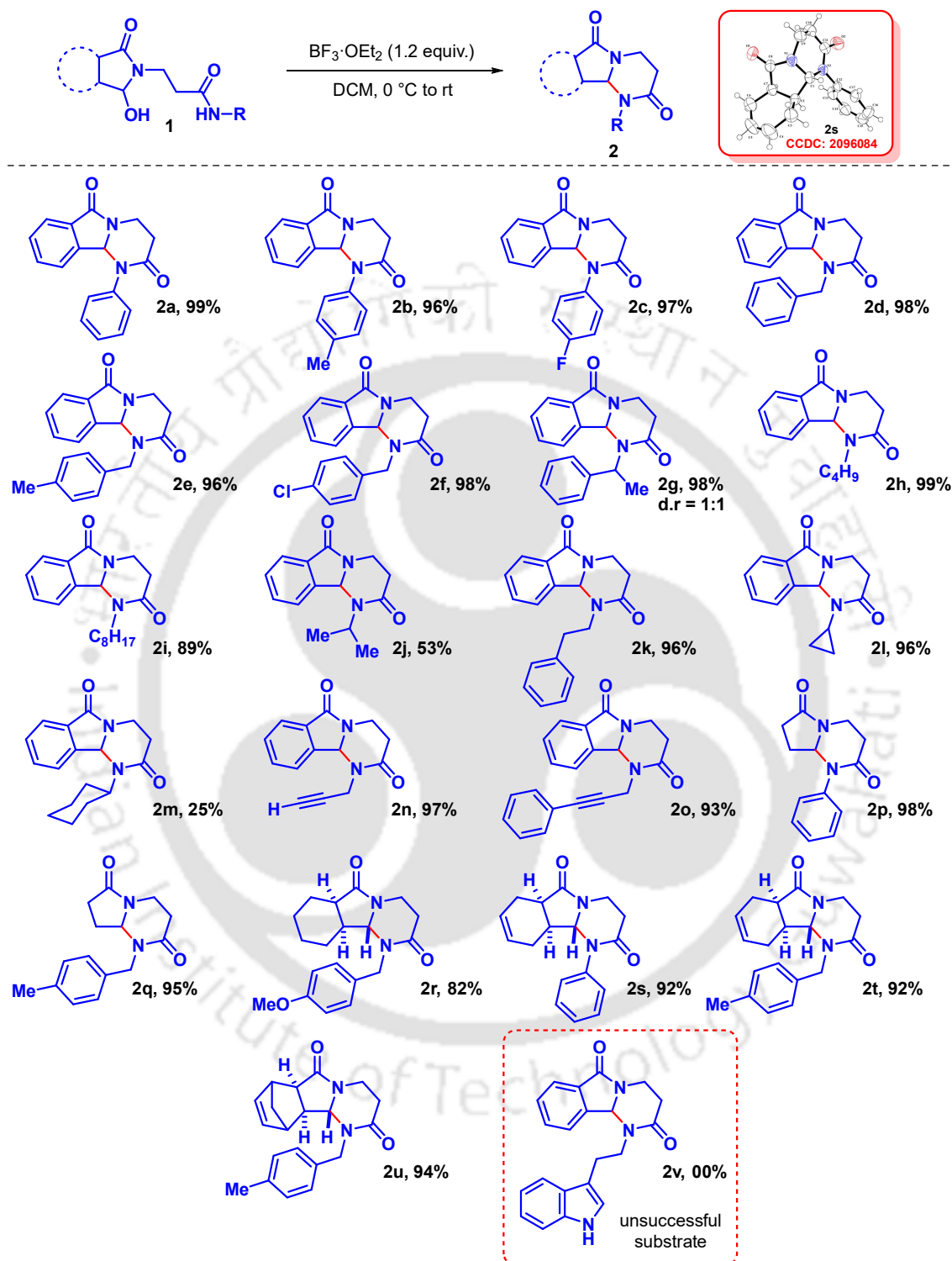
^aReaction conditions: **1a** (0.2 mmol), solvent (2.0 mL), 0 °C to rt, N₂ atmosphere.

^bIsolated yields. ^cNo reaction.

17), achieving a maximum yield of 94%. Finally, the use of BF₃·OEt₂ (1.2 equiv.) in DCM at 0 °C to room temperature are found to be the optimized conditions for this transformation.

2.4.2. Substrate Scope

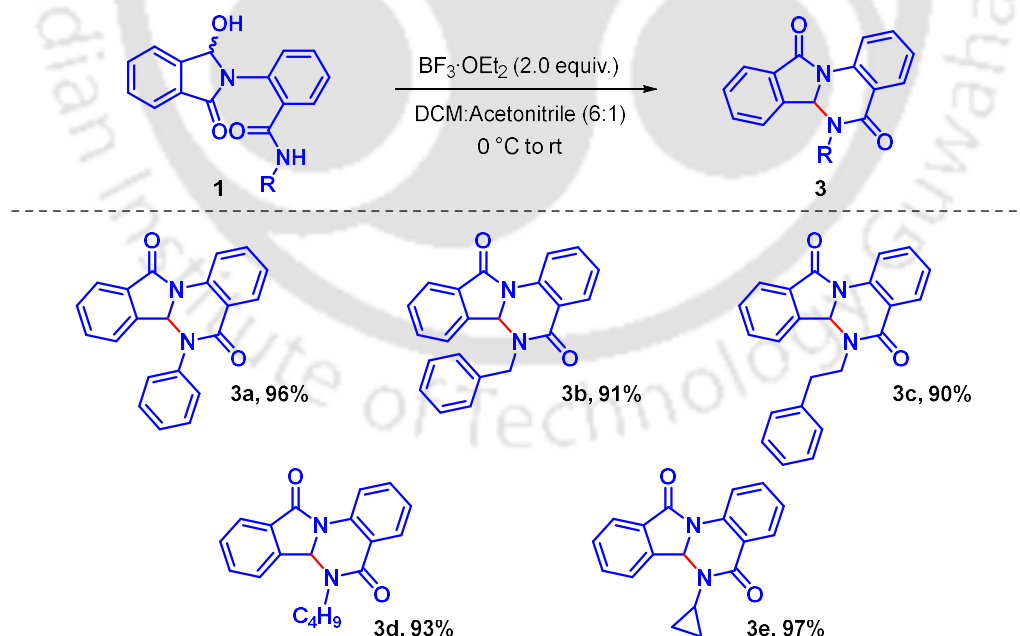
With these optimized conditions, the scope of the transformation was evaluated (Scheme 2.4.2.1). Variations in the “R” substituent of the *N*-substituted imido-alcohol **1** with phenyl group bearing electron-neutral, electron-donating and electron-

Scheme 2.4.2.1. Synthesis of tetrahydropyrimido[2,1-*a*]isoindole-2,6-diones.

^aReaction conditions: **1** (0.5 mmol), $\text{BF}_3 \cdot \text{OEt}_2$ (1.2 equiv.), DCM (3.0 mL), 0 °C to rt, N_2 atmosphere. ^bIsolated yields.

withdrawing substituents gave the anticipated products **2a**, **2b** and **2c** in excellent yields. Benzyl group with *para*-substituents such as *p*-H, *p*-Me and *p*-Cl furnished their respective products **2d**, **2e** and **2f** in 98, 96 and 98% yields. In contrast, benzyl group with α -Me substitution gave the product **2g** in a diastereomeric ratio of 1:1. The reaction was screened with aliphatic and alicyclic groups as well. Small chain, long chain and branched aliphatic groups afforded the expected product in 99, 89 and 53% yields. Cyclopropyl and cyclohexyl groups were also well tolerated in the transformation. Arylalkyl (phenylethyl) substituted imido alcohol also gave the product **2k** in 96% yield. Propargyl and phenyl-substituted propargyl groups were also introduced in the system, and the products obtained **2n** and **2o** were in high yields. However, the reaction failed miserably in the case of a hetero-aliphatic substituent **1u**. The feasibility of the transformation was evaluated by modifying the imide portion of the *N*-substituted imido-alcohol **1**. Alterations of the imide with succinimide, hexahydro-phthalimide, tetrahydro-phthalimide, and norbornene dicarboximide moiety resulted in the products **2p-2t** in good to excellent yields.

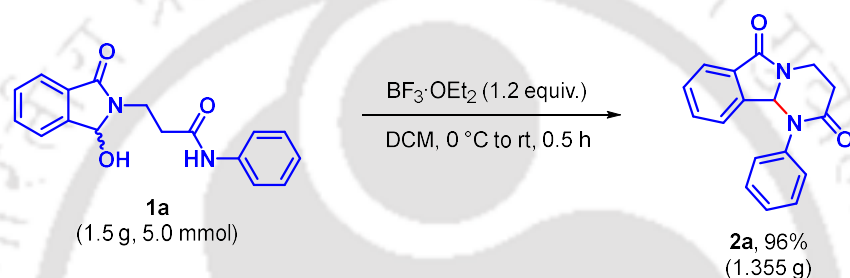
Scheme 2.4.2.2. Synthesis of tetrahydropyrimido[2,1-*a*]isoindole-2,6-diones.



^aReaction conditions: **1** (0.5 mmol), $\text{BF}_3 \cdot \text{OEt}_2$ (2.0 equiv.), DCM (3.0 mL), Acetonitrile (0.5 mL), $0\text{ }^\circ\text{C}$ to rt, N_2 atmosphere. ^bIsolated yields.

After successfully demonstrating the present strategy for pyrimido[2,1-*a*]isoindolones, the scope of this protocol was broadened to encompass isoindolo[2,1-*a*]quinazolinones. Substituting the “R” portion of the amido alcohol **1** with phenyl, benzyl, phenylethyl, *n*-butyl, and cyclopropyl groups furnished their respective isoindoloquinazolinone derivatives **3a-c** in excellent yields (Scheme 2.4.2.2).

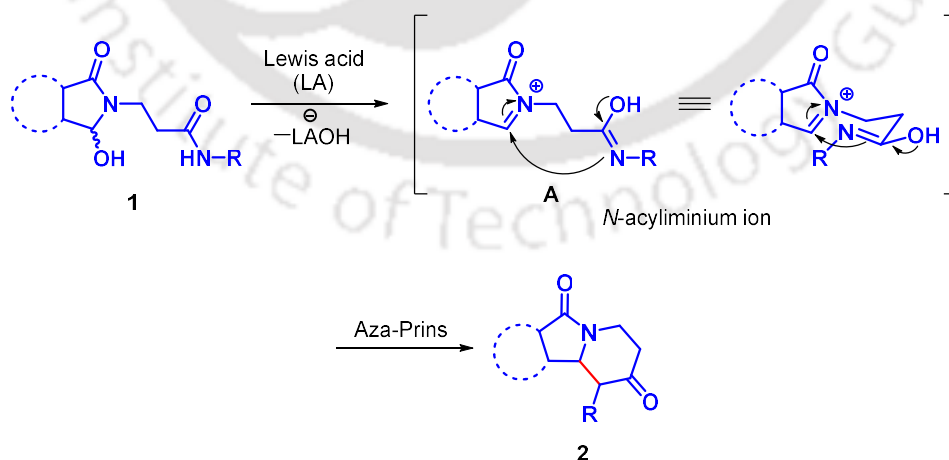
To demonstrate the scalability of this strategy, a scale-up synthesis with 3-(1-hydroxy-3-oxoisoindolin-2-yl)-*N*-phenylpropanamide (**1a**) (1.5 g, 5.0 mmol) was performed. Under the standard reaction conditions, the desired product **2a** was isolated in 96% yield (1.355 g) (Scheme 2.4.2.3).



Scheme 2.4.2.3. Scale-up experiment.

2.4.3. Plausible Mechanism

Based on established literature precedents, a plausible mechanism for this strategy is proposed in Scheme 2.4.3.1. Under the influence of Lewis acid ($\text{BF}_3 \cdot \text{OEt}_2$), the *N*-substituted amido alcohol **1** generates the corresponding *N*-acyliminium ion **A**.

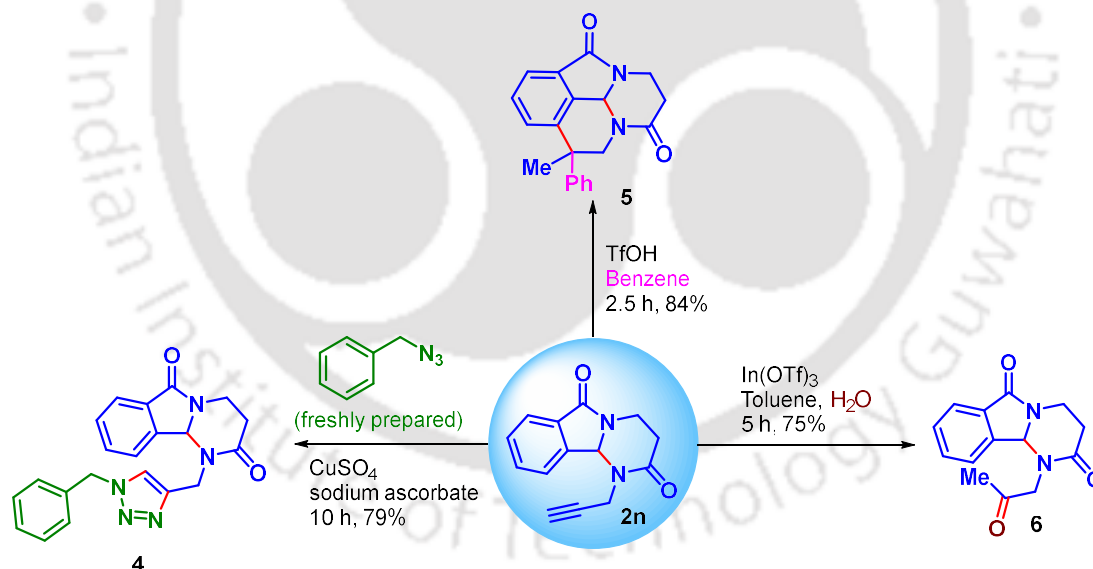


Scheme 2.4.3.1. Plausible mechanism for the synthesis of pyrimido-isoindolones and isoindolo-quinazolinones.

Simultaneously, the amide group of **1** undergoes an amide-iminol tautomerization, facilitating a rapid 6-*endo*-trig cyclization to the *N*-acyliminium carbon centre to produce pyrimido-isoindolone and isoindolo-quinazolinone derivatives.

2.4.4. Synthetic Transformation

To illustrate the synthetic utility of this protocol, several transformation reactions were performed (Scheme 2.4.4.1). The click reaction of pyrimido[2,1-*a*]isoindoline containing an active alkynyl group **2n** with freshly prepared benzyl azide successfully afforded its triazole derivative **4** in 79% yield. Additionally, the compound **2n**, under the influence of TfOH in benzene, resulted in the unprecedented formation of a tetracyclic diazacyclopenta[*def*]phenanthrene-1,4(9*a*1*H*)-dione derivative **5** in 84% yield. This selective six-membered ring formation proceeds *via* intramolecular cyclization at the propargyl group, followed by the addition of a benzene molecule. Finally, the reaction of **2n** with In(OTf)₃ produced the functionalized carbonyl derivative **6** in 75% yield.



Scheme 2.4.4.1. Synthetic transformations of pyrimido-isoindolone **2n**.

2.5. Conclusions

In conclusion, an efficient strategy for the synthesis of tetrahydropyrimido[2,1-*a*]isoindolinones and dihydroisoindolo[2,1-*a*]quinazolinones in high yields and with excellent selectivity has been developed. This protocol involves the *in situ* formation

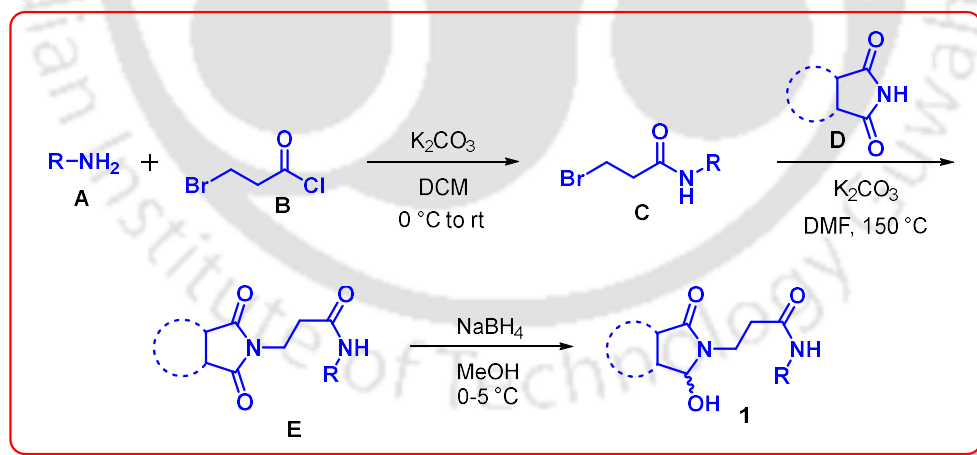
of *N*-acyliminium ion, which subsequently undergoes an intramolecular aza-Prins type cyclization with amides to furnish the desired products. The reaction tolerates a wide range of substrates, and its utility extends to the synthesis of its triazole, tetracyclic and carbonyl derivatives.

2.6. Experimental Section

2.6.1. 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 CDCl₃ with tetramethylsilane as the internal standard for ¹H (600, 500, and 400 MHz) or ¹³C{¹H} (150, 125, and 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

2.6.2. General procedure for the synthesis of starting materials 1a-1v:



To an ice-cold suspension of substituted amine **A** (5.0 mmol, 1.0 equiv.) and K₂CO₃ (1.2 equiv.) in DCM under N₂ atmosphere, 3-bromopropanoyl chloride (**B**) (1.2 equiv.) was added dropwise. The reaction mixture was allowed to stir at 0 °C for 5 minutes, which was then warmed to room temperature. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, the reaction mixture was

quenched with saturated NaHCO_3 solution. The organic layer was extracted with DCM (2×15 mL), and the combined organic layers were further washed with brine, followed by drying over anhydrous Na_2SO_4 . The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the desired product **C**.

To a stirred suspension of imide **D** (1.2 equiv.) and K_2CO_3 (1.5 equiv.) in DMF under N_2 atmosphere, *N*-substituted bromo propanamide **C** (3.0 mmol, 1.0 equiv.) dissolved in DMF was added. The reaction was heated at 150°C in a pre-heated oil bath until the starting material was fully consumed, monitored by TLC analysis. The reaction mixture was diluted with ice-cold water and the organic layer was extracted with ethyl acetate (20 mL). The organic layer was further washed with brine (2×20 mL), followed by drying over anhydrous Na_2SO_4 . The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the desired product **E**.

To an ice-cold solution of imide substituted *N*-alkyl/aryl propanamide **E** (1.0 mmol, 1.0 equiv.) in methanol, NaBH_4 (1.5 equiv.) was added. The reaction was allowed to stir at the same temperature (0°C) until the starting material was entirely consumed as evident by TLC analysis. After completion of the reaction, the solvent was removed under reduced pressure and diluted with saturated NaHCO_3 solution. The organic layer was extracted with DCM (2×20 mL), and the combined organic layers were further washed with brine, followed by drying over anhydrous Na_2SO_4 . The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the desired product **1**.

2.6.3. General procedure for the synthesis of compounds **2a-2u**:

To an ice-cold solution of *N*-alkyl/aryl propanamide amido alcohol **1** (0.5 mmol, 1.0 equiv.) in DCM (3.0 mL), $\text{BF}_3 \cdot \text{OEt}_2$ (1.2 equiv.) was added under N_2 atmosphere. The reaction was stirred at room temperature until all the starting material was consumed, as evident by TLC. Then it was treated with saturated NaHCO_3 solution, and the organic layer was extracted with DCM (2×10 mL). The combined organic layers were

further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product.

2.6.4. Experimental procedure for scale-up synthesis of compound 2a:

To an ice-cold solution of 3-(1-hydroxy-3-oxoisindolin-2-yl)-*N*-phenylpropanamide (**1a**) (1.5 g, 5.0 mmol, 1.0 equiv.) in DCM (15.0 mL), BF₃·OEt₂ (0.74 mL, 6.0 mmol, 1.2 equiv.) was added slowly under N₂ atmosphere. The reaction was stirred at room temperature until all the starting material was consumed, as evident by TLC. Then it was treated with saturated NaHCO₃ solution, and the organic layer was extracted with DCM (2 x 30 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **2a** as a white solid in 96% yield (1.35 g).

2.6.5. General procedure for the synthesis of compound 3a-3e:

To an ice-cold solution of *N*-alkyl/aryl benzamide amido alcohol **1** (0.5 mmol, 1.0 equiv.) in DCM (3.0 mL) and acetonitrile (0.5 mL), BF₃·OEt₂ (2.0 equiv.) was added under N₂ atmosphere. The reaction was stirred at room temperature until all the starting material was consumed, as evident by TLC. Then it was treated with saturated NaHCO₃ solution, and the organic layer was extracted with DCM (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **3**.

2.6.6. Experimental procedure for the synthesis of compound 4:

To a stirred solution of benzyl bromide (56 mg, 0.33 mmol) in H₂O (2 mL)/*t*-BuOH (2 mL) under N₂ atmosphere, sodium azide (20 mg, 0.3 mmol) and Et₃N (40 mg, 0.39 mmol) were added. The reaction was allowed to stir at room temperature for an hour. Later, 1-(prop-2-yn-1-yl)-1,3,4,10*b*-tetrahydropyrimido[2,1-*a*]isoindole-2,6-dione (**2n**) (72 mg, 0.3 mmol), sodium ascorbate (30 mg, 0.15 mmol), and CuSO₄ (5.0 mg, 0.03

mmol) were added to the freshly prepared benzyl azide. The reaction mixture was then stirred at room temperature for 10 h. Upon completion of the reaction (checked by TLC analysis), the reaction mixture was diluted with saturated NaHCO_3 solution. The crude product was extracted with ethyl acetate (2×10 mL). The combined organic layers were further washed with brine and dried over anhydrous Na_2SO_4 . The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the corresponding product **4**.

2.6.7. Experimental procedure for the synthesis of compound **5**:

To an ice-cold solution of 1-(prop-2-yn-1-yl)-1,3,4,10*b*-tetrahydropyrimido[2,1-*a*]isoindole-2,6-dione (**2n**) (96 mg, 0.4 mmol) in benzene (0.5 mL) under N_2 atmosphere, triflic acid (1.5 mL) was added. The reaction was then refluxed at 80°C in an oil bath for 2.5 h. Upon completion of the reaction (checked by TLC analysis), the reaction mixture was made basic with 50% NaOH solution and extracted with ethyl acetate (2×10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the corresponding product **5**.

2.6.8. Experimental procedure for the synthesis of compound **6**:

To a stirred solution of 1-(prop-2-yn-1-yl)-1,3,4,10*b*-tetrahydropyrimido[2,1-*a*]isoindole-2,6-dione (**2n**) (96 mg, 0.4 mmol) in toluene (3.0 mL) under inert atmosphere, $\text{In}(\text{OTf})_3$ (34 mg, 0.06 mmol) was added. The reaction mixture was refluxed in an oil bath for 5 h. Upon completion of the reaction (checked by TLC analysis), the solvent was removed under reduced pressure and diluted with saturated NaHCO_3 solution. The organic layer was extracted with ethyl acetate (2×10 mL). The combined organic layers were further washed with brine and dried over anhydrous Na_2SO_4 . The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the corresponding product **6**.

2.7. References

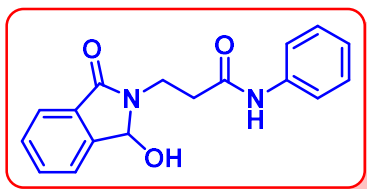
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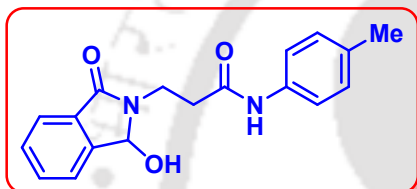
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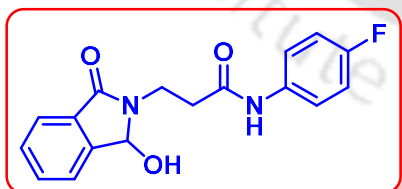
2.8. Characterization Data

3-(1-Hydroxy-3-oxoisindolin-2-yl)-*N*-phenylpropanamide (1a):

White solid; R_f (Hexane:EtOAc, 1:4) 0.5; mp 176–178 °C. Yield 253 mg, 85%. ^1H NMR (400 MHz, $\text{CDCl}_3/\text{DMSO-d}_6$) δ 2.46–2.90 (m, 2H), 3.91–3.99 (m, 2H), 5.89 (s, 1H), 6.12 (s, 1 H), 7.06 (t, $J = 7.2$ Hz, 1 H), 7.28–7.33 (m, 2 H), 7.46 (t, $J = 7.2$ Hz, 1H), 7.53–7.60 (m, 4H), 7.74 (d, $J = 7.2$ Hz, 1H), 9.22 (brs, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO-d_6) δ 35.8, 36.4, 82.2, 119.9, 122.7, 123.2, 123.8, 128.6, 129.2, 131.6, 131.9, 138.3, 144.3, 167.6, 170.2. IR (KBr, neat) ν 3251, 1661, 1543, 1316, 1193, 1064, 743 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{NaO}_3$ ($\text{M} + \text{Na}$) $^+$ 319.1053, found 319.1053.

3-(1-Hydroxy-3-oxoisindolin-2-yl)-*N*-(*p*-tolyl)propanamide (1b):

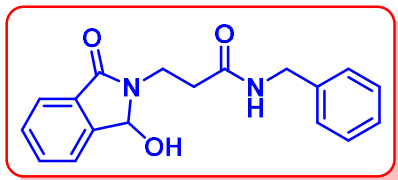
White solid; R_f (Hexane EtOAc, 1:4) 0.5; mp 189–191 °C. Yield 220 mg, 71%. ^1H NMR (400 MHz, $\text{CDCl}_3/\text{MeOH-d}_4$) δ 2.26 (s, 3H), 2.71–2.74 (m, 4H), 3.80–3.88 (m, 2H), 5.85 (s, 1H), 7.07 (t, $J = 7.2$ Hz, 2H), 7.36–7.38 (m, 2H), 7.43–7.46 (m, 1H), 7.52–7.55 (m, 2H), 7.70 (d, $J = 7.2$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{CDCl}_3/\text{MeOH-d}_4$) δ 20.8, 36.4 (2C), 82.2, 120.1, 120.2, 122.9, 123.4, 129.4, 129.6, 131.3, 132.4, 134.1, 135.2, 144.0, 168.5, 170.4. IR (KBr, neat) ν 3395, 1687, 1653, 1543, 1302, 1116, 1065, 747 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 311.1390, found 311.1389.

***N*-(4-fluorophenyl)-3-(1-hydroxy-3-oxoisindolin-2-yl)propanamide (1c):**

White solid; R_f (Hexane:EtOAc, 1:4) 0.5; mp 182–184 °C. Yield 198 mg, 63%. ^1H NMR (600 MHz, $\text{CDCl}_3/\text{MeOH-d}_4$) δ 2.72–2.75 (m, 2H), 3.79–3.89 (m, 2H), 5.85 (s, 1H), 6.94–6.97 (m, 2H), 7.45–7.48 (m, 3H), 7.54–7.55 (m, 2H), 7.69 (d, $J = 7.2$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{CDCl}_3/\text{MeOH-d}_4$) δ 36.2, 36.4, 82.2, 115.4 (d, $J = 22.2$ Hz), 121.7, 121.8, 122.9, 123.4, 129.6, 132.4, 133.9 (d, $J = 2.8$ Hz), 144.0, 159.3 (d, $J = 241.9$ Hz), 168.5, 170.4. ^{19}F NMR (564 MHz, $\text{CDCl}_3/\text{MeOH-d}_4/\text{C}_6\text{F}_6$) δ -121.09 (m, -CF-). IR (KBr, neat) ν 3249, 2936, 1659, 1618,

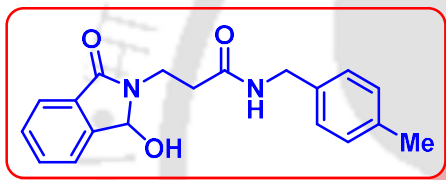
1504, 1381, 1209, 1062, 784 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{15}\text{FN}_2\text{NaO}_3$ ($\text{M} + \text{Na}$)⁺ 337.0959, found 337.0959.

N-benzyl-3-(1-hydroxy-3-oxoisindolin-2-yl)propanamide (1d):



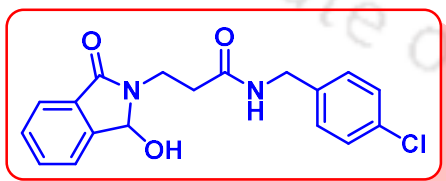
White solid; R_f (EtOAc, 100%) 0.5; mp 158–160 °C. Yield 248 mg, 80%. ^1H NMR (400 MHz, CDCl_3) δ 2.59–2.74 (m, 2H), 3.75–3.90 (m, 2H), 4.28–4.40 (m, 2H), 5.80–5.85 (m, 2H), 6.91 (t, J = 5.8 Hz, 1H), 7.16–7.22 (m, 5H), 7.39–7.45 (m, 1H), 7.51–7.56 (m, 2H), 7.59 (d, J = 7.4 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 35.3, 36.2, 43.8, 82.7, 123.0, 123.4, 127.5, 127.8, 128.7, 129.5, 131.4, 132.3, 137.7, 144.1, 168.1, 172.2. IR (KBr, neat) ν 3286, 2934, 1673, 1632, 1413, 1386, 1047, 747 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 311.1390, found 311.1389.

3-(1-Hydroxy-3-oxoisindolin-2-yl)-N-(4-methylbenzyl)propanamide (1e):



White solid; R_f (EtOAc, 100%) 0.5; mp 157–159 °C. Yield 247 mg, 76%. ^1H NMR (400 MHz, CDCl_3) δ 2.25 (s, 3H), 2.63 (t, J = 6.4 Hz, 2H), 3.71–3.85 (m, 2H), 4.18–4.30 (m, 2H), 5.78 (s, 1H), 6.23 (brs, 1H), 6.97 (d, J = 7.8 Hz, 2H), 7.02 (d, J = 7.8 Hz, 2H), 7.22–7.28 (m, 1H), 7.35–7.39 (m, 1H), 7.49–7.52 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 21.1, 35.2, 36.2, 43.5, 82.6, 123.0, 123.4, 127.8, 129.3, 129.4, 131.4, 132.2, 134.7, 137.1, 144.1, 168.1, 172.1. IR (KBr, neat) ν 3338, 2856, 1670, 1634, 1546, 1385, 1051, 745 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{NaO}_3$ ($\text{M} + \text{Na}$)⁺ 347.1366, found 347.1377.

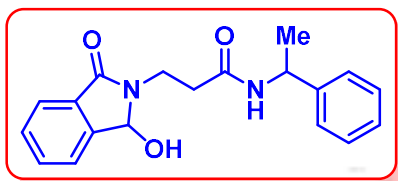
N-(4-chlorobenzyl)-3-(1-hydroxy-3-oxoisindolin-2-yl)propanamide (1f):



White solid; R_f (EtOAc, 100%) 0.6; mp 147–149 °C. Yield 241 mg, 70%. ^1H NMR (400 MHz, CDCl_3) δ 2.61–2.75 (m, 2H), 3.74–3.80 (m, 1H), 3.83–3.90 (m, 1H), 4.22–4.34 (m, 2H), 5.69 (d, J = 6.2 Hz, 1H), 5.78 (d, J = 6.2 Hz, 1H), 7.07–7.10 (m, 3H), 7.13–7.16 (m, 2H), 7.41–7.46 (m, 1H), 7.52–7.57 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 35.3, 36.3, 43.0, 82.8, 122.9, 123.4, 128.8, 129.1, 129.6, 131.3, 132.4, 133.3, 136.4, 144.0, 168.2, 172.3. IR (KBr, neat) ν 3393, 2944,

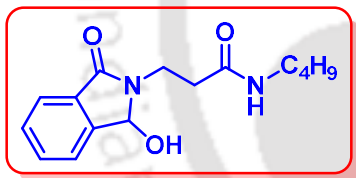
1688, 1621, 1571, 1062, 746 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{NaO}_3$ ($\text{M} + \text{Na}$)⁺ 367.0820, found 367.0825.

3-(1-Hydroxy-3-oxoisindolin-2-yl)-N-(1-phenylethyl)propanamide (diastereomeric mixture, 1:1, 1g):



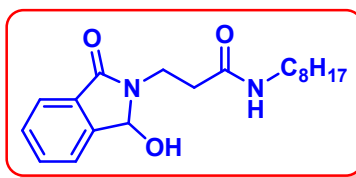
White solid; R_f (Hexane:EtOAc, 1:4) 0.4; mp 148–150 °C. Yield 266 mg, 82%. ^1H NMR (400 MHz, CDCl_3) δ 1.38 (d, $J = 7.0$ Hz, 3H), 1.40 (d, $J = 7.0$ Hz, 3H), 2.58–2.63 (m, 2H), 3.70–3.83 (m, 2H), 4.94–5.04 (m, 1H), 5.65 (d, $J = 5.2$ Hz, 1H), 5.82 (d, $J = 5.6$ Hz, 1H), 6.08 (brs, 1H), 7.14–7.24 (m, 5H), 7.38–7.43 (m, 1H), 7.46–7.50 (m, 2H), 7.52–7.62 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 21.7, 21.8, 35.3, 34.0, 36.1, 49.1, 49.2, 82.4, 82.6, 122.8, 122.9, 123.3, 123.4, 126.0, 126.1, 127.1, 127.2, 128.4, 128.5, 129.4, 129.5, 132.2, 143.0, 143.2, 144.1, 168.0, 168.1, 171.1, 171.2. IR (KBr, neat) ν 3292, 2881, 1681, 1641, 1067, 744 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 325.1547, found 325.1546.

N-butyl-3-(1-hydroxy-3-oxoisindolin-2-yl)propanamide (1h):



White semi-solid; R_f (EtOAc, 100%) 0.6. Yield 260 mg, 94%. ^1H NMR (600 MHz, CDCl_3) δ 0.84 (t, $J = 7.4$ Hz, 3H), 1.22–1.28 (m, 2H), 1.38–1.43 (m, 2H), 2.58–2.69 (m, 2H), 3.11–3.19 (m, 2H), 3.77–3.82 (m, 1H), 3.84–3.88 (m, 1H), 5.86 (d, $J = 6.4$ Hz, 1H), 6.25 (d, $J = 6.6$ Hz, 1H), 6.71 (t, $J = 5.6$ Hz, 1H), 7.42 (t, $J = 7.4$ Hz, 1H), 7.52 (t, $J = 7.4$ Hz, 1H), 7.55 (d, $J = 7.4$ Hz, 1H), 7.65 (t, $J = 7.4$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) δ 13.7, 20.0, 31.3, 35.3, 36.2, 39.5, 82.6, 122.9, 123.4, 129.5, 131.4, 132.3, 144.1, 168.1, 172.1. IR (KBr, neat) ν 3303, 2932, 1683, 1636, 1462, 1208, 1054, 737 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 277.1547, found 277.1547.

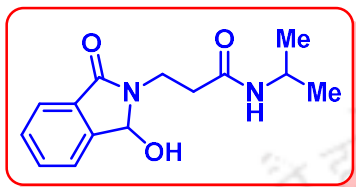
3-(1-Hydroxy-3-oxoisindolin-2-yl)-N-octylpropanamide (1i):



White semi-solid; R_f (EtOAc, 100%) 0.6. Yield 249 mg, 75%. ^1H NMR (400 MHz, CDCl_3) δ 0.86 (t, $J = 7.0$ Hz, 3H), 1.20–1.25 (m, 10H), 1.40–1.43 (m, 2H), 2.59–2.63 (m, 1H), 2.65–2.68 (m, 1H), 3.14–3.19 (m, 2H), 3.78–3.90 (m, 2H), 5.86 (d, $J = 6.2$ Hz, 1H), 6.01 (d, $J = 6.8$ Hz, 1H), 6.47 (brs, 1H), 7.44 (t, $J = 7.2$ Hz, 1H),

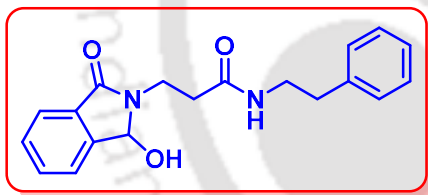
7.52–7.59 (m, 2H), 7.68 (d, $J = 7.2$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) δ 14.1, 22.6, 26.9, 29.1, 29.2, 29.3, 31.8, 35.4, 36.1, 39.9, 82.6, 123.0, 123.4, 129.5, 131.5, 132.3, 144.1, 168.1, 172.3. IR (KBr, neat) ν 3258, 2856, 1660, 1629, 1449, 1061, 738 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{29}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 333.2173, found 333.2174.

3-(1-Hydroxy-3-oxoisindolin-2-yl)-*N*-isopropylpropanamide (1j):



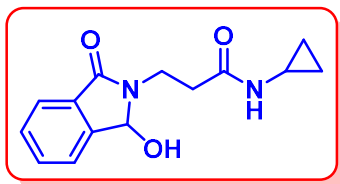
White solid; R_f (EtOAc, 100%) 0.4; mp 127–129 °C. Yield 236 mg, 90%. ^1H NMR (600 MHz, CDCl_3) δ 1.07 (d, $J = 7.4$ Hz, 3H), 1.08 (d, $J = 7.4$ Hz, 3H), 2.55–2.66 (m, 2H), 3.76–3.81 (m, 1H), 3.83–3.88 (m, 1H), 3.93–3.99 (m, 1H), 5.86 (d, $J = 6.2$ Hz, 1H), 6.22–6.32 (m, 1H), 6.45–6.58 (m, 1H), 7.44 (t, $J = 7.2$ Hz, 1H), 7.45–7.58 (m, 2H), 7.64–7.68 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) δ 22.5, 22.51, 35.5, 36.0, 41.8, 82.7, 123.0, 123.4, 129.5, 131.5, 132.3, 144.0, 168.1, 171.5. IR (KBr, neat) ν 3295, 2872, 1680, 1642, 1549, 1057, 751 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 263.1390, found 263.1384.

3-(1-Hydroxy-3-oxoisindolin-2-yl)-*N*-phenethylpropanamide (1k):



White solid; R_f (EtOAc, 100%) 0.4; mp 138–140 °C. Yield 190 mg, 59%. ^1H NMR (500 MHz, CDCl_3) δ 2.52–2.65 (m, 2H), 2.75 (t, $J = 7.2$ Hz, 2H), 3.41–3.47 (m, 2H), 3.74–3.79 (m, 1H), 3.80–3.85 (m, 1H), 5.82 (d, $J = 6.6$ Hz, 1H), 6.08 (brs, 1H), 6.69 (brs, 1H), 7.11 (d, $J = 7.5$ Hz, 2H), 7.14 (d, $J = 7.2$ Hz, 1H), 7.21 (t, $J = 7.5$ Hz, 2H), 7.44 (t, $J = 7.2$ Hz, 1H), 7.51–7.57 (m, 2H), 7.65 (d, $J = 7.5$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 35.3, 35.4, 36.1, 40.9, 82.6, 123.0, 123.4, 126.5, 128.6, 128.7, 129.5, 131.4, 132.3, 138.6, 144.1, 168.1, 172.3. IR (KBr, neat) ν 3293, 2867, 1676, 1646, 1550, 1055, 748 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 325.1547, found 325.1548.

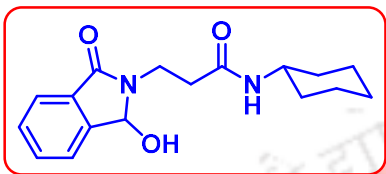
N-cyclopropyl-3-(1-hydroxy-3-oxoisindolin-2-yl)propanamide (1l):



White semi-solid; R_f (EtOAc, 100%) 0.4. Yield 184 mg, 71%. ^1H NMR (600 MHz, CDCl_3) δ 0.45–0.47 (m, 2H), 0.67–0.69 (m, 2H), 2.58–2.63 (m, 3H), 3.74–3.78 (m, 1H), 3.82–3.88 (m, 1H), 5.86 (d, $J = 6.0$ Hz, 1H), 6.24–6.26 (m, 1H), 7.08–7.15

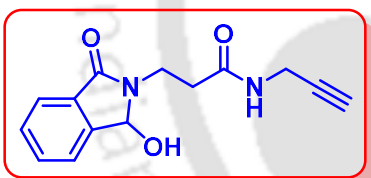
(m, 1H), 7.42 (t, $J = 7.4$ Hz, 1H), 7.51–7.53 (m, 1H), 7.56 (d, $J = 7.4$ Hz, 1H), 7.62–7.64 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) δ 6.3, 6.4, 22.8, 35.3, 36.1, 82.7, 123.0, 123.4, 129.6, 131.4, 132.4, 144.1, 168.2, 173.9. IR (KBr, neat) ν 3255, 2857, 1673, 1638, 1454, 1020, 741 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 261.1234, found 261.1235.

N-cyclohexyl-3-(1-hydroxy-3-oxoisindolin-2-yl)propanamide (1m):



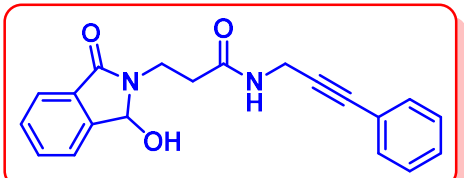
White solid; R_f (EtOAc, 100%) 0.6; mp 158–160 °C. Yield 189 mg, 63%. ^1H NMR (400 MHz, CDCl_3) δ 1.06–1.13 (m, 3H), 1.23–1.29 (m, 2H), 1.54–1.58 (m, 1H), 1.62–1.68 (m, 2H), 1.76–1.82 (m, 2H), 2.53–2.67 (m, 2H), 3.60–3.69 (m, 1H), 3.74–3.88 (m, 2H), 5.85 (d, $J = 5.8$ Hz, 1H), 6.27–6.31 (m, 1H), 6.53–7.59 (m, 1H), 7.41 (t, $J = 7.2$ Hz, 1H), 7.44–7.56 (m, 2H), 7.65 (d, $J = 7.2$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 24.8, 25.4, 32.8, 35.5, 36.1, 48.6, 82.5, 122.9, 123.4, 129.4, 131.4, 132.2, 144.1, 168.1, 171.2. IR (KBr, neat) ν 3280, 2927, 1671, 1838, 1550, 1059, 742 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 303.1703, found 303.1708.

3-(1-Hydroxy-3-oxoisindolin-2-yl)-N-(prop-2-yn-1-yl)propanamide (1n):



White solid; R_f (Hexane:EtOAc,1:4) 0.4; mp 146–147 °C. Yield 190 mg, 74%. ^1H NMR (400 MHz, $\text{CDCl}_3/\text{MeOH}-d_4$) δ 2.14 (t, $J = 2.4$ Hz, 1H), 2.53–2.66 (m, 2H), 2.89 (brs, 1H), 3.73–3.83 (m, 2H), 3.86–3.99 (m, 2H), 5.81 (s, 1H), 7.39–7.43 (m, 1H), 7.49–7.54 (m, 2H), 7.64–7.68 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{CDCl}_3/\text{MeOH}-d_4$) δ 29.0, 35.2, 36.3, 71.3, 79.1, 82.2, 122.9, 123.3, 129.5, 131.3, 132.3, 144.1, 168.3, 171.9. IR (KBr, neat) ν 3287, 2924, 1657, 1421, 1313, 1058, 745 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 259.1077, found 259.1077.

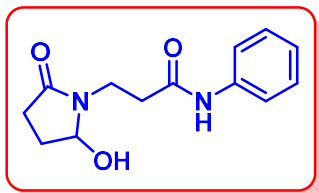
3-(1-Hydroxy-3-oxoisindolin-2-yl)-N-(3-phenylprop-2-yn-1-yl)propanamide (1o):



White semi-solid; R_f (Hexane:EtOAc,1:4) 0.4. Yield 272 mg, 81%. ^1H NMR (500 MHz, CDCl_3) δ 2.64–2.76 (m, 2H), 3.80–3.92 (m, 2H), 4.16 (dd, $J = 17.6$ and 5.0 Hz, 1H), 4.24 (dd, $J = 17.6$ and 5.2 Hz, 1H), 5.67 (brs, 1H), 5.85 (d, $J = 6.2$ Hz, 1H), 7.05 (brs, 1H), 7.22–7.28 (m, 3H), 7.32–7.38 (m, 3H), 7.46–7.51 (m, 2H), 7.66 (d, $J = 7.4$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3)

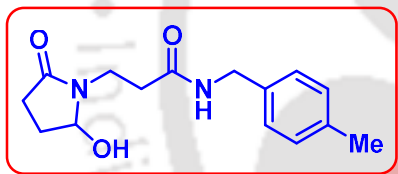
δ 30.2, 35.2, 36.1, 82.7, 83.4, 84.5, 122.5, 123.1, 123.4, 128.3, 128.5, 129.5, 131.4, 131.8, 132.3, 144.1, 168.2, 172.1. IR (KBr, neat) ν 3288, 2923, 1678, 1649, 1443, 1237, 1060, 748 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 335.1390, found 335.1370.

3-(2-Hydroxy-5-oxopyrrolidin-1-yl)-N-phenylpropanamide (1p):



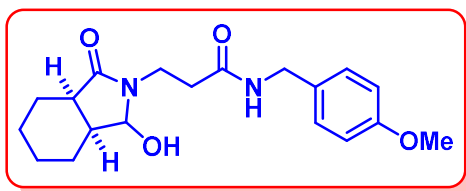
White solid; R_f (CH_2Cl_2 :MeOH, 23:2) 0.4; mp 79–81 °C. Yield 144 mg, 58%. ^1H NMR (600 MHz, CDCl_3) δ 1.89–1.93 (m, 1H), 2.24–2.30 (m, 2H), 2.55–2.61 (m, 1H), 2.68–2.73 (m, 1H), 2.79–2.85 (m, 1H), 3.58–3.63 (m, 1H), 3.71–3.77 (m, 1H), 5.29 (d, J = 5.6 Hz, 1H), 5.55 (brs, 1H), 7.08 (t, J = 8.2 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 9.08 (brs, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 27.9, 29.3, 35.8, 37.1, 84.6, 120.2, 124.5, 127.8, 128.9, 129.7, 137.8, 171.0, 176.0. IR (KBr, neat) ν 3280, 2927, 1671, 1638, 1550, 1059, 742 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 249.1234, found 249.1229.

3-(2-Hydroxy-5-oxopyrrolidin-1-yl)-N-(4-methylbenzyl)propanamide (1q):



White solid; R_f (CH_2Cl_2 :MeOH, 23:2) 0.5; mp 113–115 °C. Yield 169 mg, 61%. ^1H NMR (400 MHz, CDCl_3) δ 1.85–1.92 (m, 1H), 2.16–2.24 (m, 2H), 2.32 (s, 3H), 2.44–2.57 (m, 2H), 2.64–2.72 (m, 1H), 3.48–3.56 (m, 1H), 3.64–3.69 (m, 1H), 4.29–4.41 (m, 2H), 5.21 (d, J = 5.2 Hz, 1H), 5.49 (brs, 1H), 6.52 (brs, 1H), 7.10–7.15 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 21.1, 27.8, 29.2, 34.7, 37.1, 43.6, 84.5, 127.9, 129.4, 134.6, 137.5, 172.6, 175.6. IR (KBr, neat) ν 3292, 2852, 1652, 1157, 1070, 752 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{NaO}_3$ ($\text{M} + \text{Na}$)⁺ 299.1366, found 299.1366.

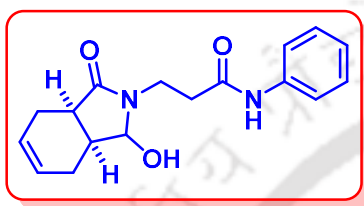
3-(1-Hydroxy-3-oxohexahydro-1H-isoindol-2(3H)-yl)-N-(4-methoxybenzyl)propanamide (1r, diastereomeric mixture, 9:1; only major isomer is considered):



White semi-solid; R_f (EtOAc, 100%) 0.4. Yield 219 mg, 63%. ^1H NMR (500 MHz, CDCl_3) δ 0.94–1.04 (m, 2H), 1.16–1.19 (m, 1H), 1.43–1.51 (m, 3H), 1.72–1.75 (m, 1H), 1.86–1.90 (m, 1H), 2.16–2.18 (m, 1H), 2.45–2.50 (m, 1H), 2.64–2.70 (m, 1H), 2.72–2.76 (m, 1H), 3.41–3.46 (m, 1H),

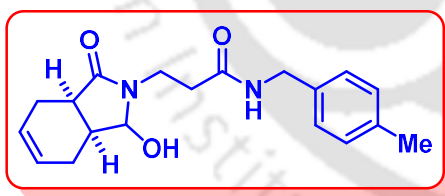
3.65–3.71 (m, 1H), 3.76 (s, 3H), 4.25–4.71 (m, 2H), 4.71 (s, 1H), 5.41 (s, 1H), 6.82 (d, J = 6.5 Hz, 2H), 6.91 (s, 1H), 7.15 (d, J = 6.5 Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 23.0, 23.1, 23.3, 26.2, 34.7, 38.0, 39.1, 41.0, 43.3, 55.3, 88.4, 114.1, 129.2, 130.0, 159.1, 172.6, 177.3. IR (KBr, neat) ν 3294, 2855, 1650, 1513, 1246, 1027, 745 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{27}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 347.1965, found 347.1974.

3-(1-Hydroxy-3-oxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl)-N-phenylpropanamide (1s, diastereomeric mixture, 9:1; only major isomer is considered):



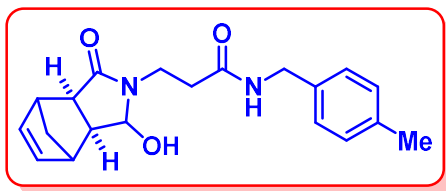
White semi-solid; R_f (EtOAc, 100%) 0.5. Yield 188 mg, 63%. ^1H NMR (400 MHz, CDCl_3) δ 1.74–1.82 (m, 1H), 2.14–2.30 (m, 3H), 2.38–2.44 (m, 1H), 2.67–2.73 (m, 1H), 2.82–2.89 (m, 1H), 2.98–3.03 (m, 1H), 3.54–3.61 (m, 1H), 3.72–3.78 (m, 1H), 4.84 (d, J = 6.0 Hz, 1H), 5.43–5.56 (m, 1H), 5.62–5.78 (m, 2H), 7.09 (t, J = 7.2 Hz, 1H), 7.28 (t, J = 7.2 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 9.04 (brs, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 22.0, 24.3, 35.8, 37.7, 37.72, 38.4, 89.7, 120.3, 124.6, 125.4, 126.2, 128.9, 137.8, 171.0, 178.1. IR (KBr, neat) ν 3301, 2850, 1667, 1601, 1545, 1038, 755 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{NaO}_3$ ($\text{M} + \text{Na}$) $^+$ 323.1366, found 323.1366.

3-(1-hydroxy-3-oxo-1,3,3a,4,7,7a-hexahydro-2H-isoindol-2-yl)-N-(4-methylbenzyl)propanamide (1t):



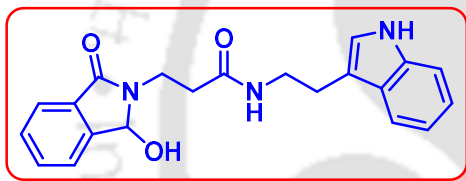
White semi-solid; R_f (EtOAc, 100%) 0.4. Yield 188 mg, 57%. ^1H NMR (400 MHz, CDCl_3) δ 1.69–1.76 (m, 1H), 1.90–1.98 (m, 1H), 2.14–2.30 (m, 2H), 2.32 (s, 3H), 2.33–2.38 (m, 1H), 2.42–2.49 (m, 1H), 2.64–2.71 (m, 1H), 2.89–2.94 (m, 1H), 3.43–3.50 (m, 1H), 3.64–3.71 (m, 1H), 4.28–4.39 (m, 2H), 4.76 (t, J = 2.6 Hz, 1H), 5.47 (brs, 1H), 5.64–5.72 (m, 2H), 6.68 (brs, 1H), 7.09–7.13 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 21.1, 21.9, 24.3, 34.7, 37.4, 37.7, 38.2, 43.6, 89.5, 125.2, 126.4, 127.9, 129.4, 134.6, 137.4, 172.6, 177.6. IR (KBr, neat) ν 3297, 2850, 1652, 1459, 1050, 740 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 329.1860, found 329.1858.

3-(1-Hydroxy-3-oxo-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindol-2(3H)-yl)-N-(4-methylbenzyl)propanamide (1u):



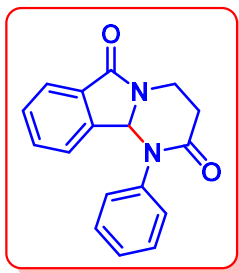
White solid; R_f (CH_2Cl_2 :MeOH, 23:2) 0.4; mp 139–141 °C. Yield 248 mg, 73%. ^1H NMR (400 MHz, CDCl_3) δ 1.31 (d, J = 10.5 Hz, 1H), 1.51 (d, J = 10.5 Hz, 1H), 2.30 (s, 3H), 2.36–2.41 (m, 1H), 2.42–2.52 (m, 1H), 2.59–2.63 (m, 1H), 3.03–3.10 (m, 3H), 3.32–3.39 (m, 1H), 3.43–3.50 (m, 1H), 4.29 (d, J = 5.6 Hz, 2H), 4.55 (d, J = 4.8 Hz, 1H), 5.68 (d, J = 5.0 Hz, 1H), 5.93–5.98 (m, 2H), 7.07–7.16 (m, 5H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 21.1, 34.6, 36.7, 43.4, 44.7, 44.8, 46.3, 49.3, 51.1, 85.8, 127.8, 129.3, 133.7, 134.9, 135.7, 137.2, 172.0, 176.3. IR (KBr, neat) ν 3289, 2887, 1651, 1546, 1057, 722 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_3$ ($M + \text{H}$) $^+$ 341.1860, found 341.1872.

N-(2-(1H-indol-3-yl)ethyl)-3-(1-hydroxy-3-oxoisindolin-2-yl)propanamide (1v):



Brown solid; R_f (EtOAc, 100%) 0.5; mp 68–70 °C. Yield 252 mg, 69%. ^1H NMR (600 MHz, CDCl_3) δ 2.44–2.49 (m, 1H), 2.54–2.59 (m, 1H), 2.90 (t, J = 6.8 Hz, 2H), 3.48–3.57 (m, 2H), 3.72–3.76 (m, 1H), 3.80–3.84 (m, 1H), 5.78 (brs, 1H), 5.87 (brs, 1H), 6.28 (t, J = 5.8 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 7.05 (t, J = 7.0 Hz, 1H), 7.14 (t, J = 7.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 7.2 Hz, 1H), 7.50–7.56 (m, 3H), 7.66 (d, J = 7.2 Hz, 1H), 8.25 (s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) δ 25.0, 35.3, 36.1, 39.9, 82.6, 111.3, 112.5, 118.6, 119.4, 122.1, 122.2, 123.0, 123.4, 127.2, 129.6, 131.4, 132.3, 136.3, 144.0, 168.0, 172.4. IR (KBr, neat) ν 3281, 2854, 1642, 1540, 1042, 740 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{22}\text{N}_3\text{O}_3$ ($M + \text{H}$) $^+$ 364.1656, found 364.1655.

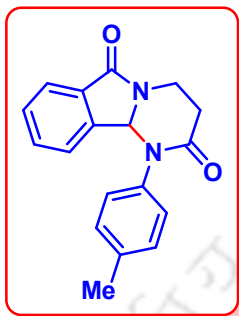
1-Phenyl-1,3,4,10b-tetrahydropyrimido[2,1-a]isoindole-2,6-dione (2a):



White solid; R_f (EtOAc, 100%) 0.6; mp 168–170 °C. Yield 139 mg, 99%. ^1H NMR (400 MHz, CDCl_3) δ 2.69 (ddd, J = 17.0, 4.8 and 2.2 Hz, 1H), 2.80 (ddd, J = 18.4, 9.8 and 7.2 Hz, 1H), 3.60 (ddd, J = 16.2, 11.2 and 4.8 Hz, 1H), 4.63 (ddd, J = 13.6, 7.0 and 2.4 Hz, 1H), 6.12 (d, J = 7.6 Hz, 1H), 6.22 (s, 1H), 7.15–7.18 (m, 2H), 7.24 (t, J = 7.6

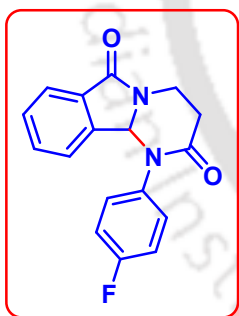
Hz, 1H), 7.43–7.50 (m, 4H), 7.85 (dt, $J = 7.6$ and 1.0 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 32.2, 35.6, 72.4, 124.0, 124.5, 128.7, 129.0, 129.6, 130.0, 131.6, 131.7, 138.4, 140.6, 167.3, 167.7. IR (KBr, neat) ν 2877, 1713, 1658, 1121, 732 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 279.1128, found 279.1129.

1-(*p*-Tolyl)-1,3,4,10b-tetrahydropyrimido[2,1-*a*]isoindole-2,6-dione (2b):



White semi-solid; R_f (EtOAc, 100%) 0.6. Yield 141 mg, 96%. ^1H NMR (400 MHz, CDCl_3) δ 2.42 (s, 3H), 2.68 (ddd, $J = 17.2$, 3.0 and 1.2 Hz, 1H), 2.78 (ddd, $J = 17.2$, 11.2 and 7.2 Hz, 1H), 3.59 (ddd, $J = 16.2$, 11.2 and 4.8 Hz, 1H), 4.61 (ddd, $J = 13.4$, 6.8 and 1.4 Hz, 1H), 6.19 (s, 1H), 6.20 (d, $J = 7.6$ Hz, 1H), 7.03 (d, $J = 7.8$ Hz, 2H), 7.27–7.29 (m, 3H), 7.46 (t, $J = 7.6$ Hz, 1H), 7.84 (dd, $J = 7.8$ and 1.2 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 21.2, 32.2, 35.5, 72.3, 123.9, 124.6, 128.6, 129.9, 130.2, 131.6, 131.7, 135.6, 138.6, 140.6, 167.2, 167.8. IR (KBr, neat) ν 2854, 1693, 1646, 1426, 1149, 729 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 293.1285, found 293.1286.

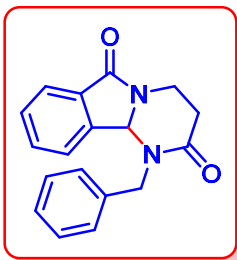
1-(4-Fluorophenyl)-1,3,4,10b-tetrahydropyrimido[2,1-*a*]isoindole-2,6-dione (2c):



White solid; R_f (EtOAc, 100%) 0.6; mp 152–154 $^{\circ}\text{C}$. Yield 144 mg, 97%. ^1H NMR (600 MHz, CDCl_3) δ 2.70 (ddd, $J = 17.4$, 4.8 and 2.6 Hz, 1H), 2.75 (ddd, $J = 17.6$, 11.2 and 2.2 Hz, 1H), 3.60 (ddd, $J = 16.2$, 11.4 and 4.8 Hz, 1H), 4.62 (ddd, $J = 13.6$, 7.2 and 4.2 Hz, 1H), 6.18 (s, 1H), 6.20 (d, $J = 7.6$ Hz, 1H), 7.11–7.18 (m, 4H), 7.29 (t, $J = 7.6$ Hz, 1H), 7.48 (t, $J = 7.6$ Hz, 1H), 7.86 (d, $J = 7.6$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) δ 32.2, 35.6, 72.5, 116.7 (d, $J = 22.5$ Hz), 124.2, 124.4, 130.2, 130.8, 131.7 (d, $J = 3.8$ Hz), 134.3, 140.4, 162.2 (d, $J = 247.4$ Hz), 167.3, 167.9. ^{19}F NMR (564 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -115.3. IR (KBr, neat) ν 2856, 1696, 1640, 1434, 727 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{13}\text{FN}_2\text{NaO}_2$ ($\text{M} + \text{Na}$) $^+$ 319.0853, found 319.0855.

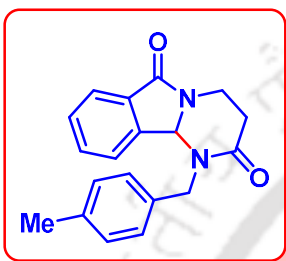
1-Benzyl-1,3,4,10b-tetrahydropyrimido[2,1-*a*]isoindole-2,6-dione (2d):

White solid; R_f (Hexane:EtOAc, 1:4) 0.4; mp 149–151 $^{\circ}\text{C}$. Yield 144 mg, 98%. ^1H NMR (400 MHz, CDCl_3) δ 2.74 (ddd, $J = 13.4$, 10.0 and 7.0 Hz, 2H), 3.48 (ddd, $J = 15.6$, 9.2 and 6.2 Hz, 1H), 4.46 (ddd, $J = 13.4$, 6.2 and 2.2 Hz, 1H), 4.55 (d, $J = 16.2$ Hz, 1H), 5.44



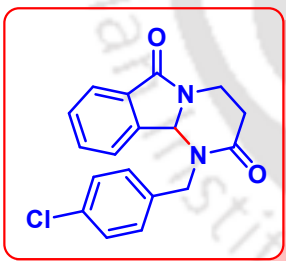
(d, $J = 16.2$ Hz, 1H), 5.86 (s, 1H), 7.20 (d, $J = 7.4$ Hz, 2H), 7.25 (t, $J = 7.2$ Hz, 1H), 7.27–7.35 (m, 2H), 7.51–7.55 (m, 3H), 7.85–7.88 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 32.3, 35.8, 46.0, 70.1, 124.5, 124.7, 127.0, 127.5, 129.0, 130.3, 132.0, 132.3, 136.1, 140.5, 167.5, 168.5. IR (KBr, neat) ν 2857, 1699, 1633, 1402, 740 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 293.1285, found 293.1285.

1-(4-Methylbenzyl)-1,3,4,10b-tetrahydropyrimido[2,1-a]isoindole-2,6-dione (2e):



White solid; R_f (Hexane:EtOAc, 1:4) 0.4; mp 141–143 °C. Yield 151 mg, 98%. ^1H NMR (400 MHz, CDCl_3) δ 2.32 (s, 3H), 2.71 (ddd, $J = 11.6, 7.6$ and 2.0 Hz, 2H), 3.44 (ddd, $J = 15.6, 9.4$ and 6.2 Hz, 1H), 4.42 (d, $J = 16.0$ Hz, 1H), 4.45 (ddd, $J = 13.4, 6.0$ and 4.2 Hz, 1H), 5.47 (d, $J = 16.0$ Hz, 1H), 5.83 (s, 1H), 7.09–7.15 (m, 4H), 7.51–7.55 (m, 3H), 7.84–7.87 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 21.1, 32.3, 35.7, 45.7, 69.9, 124.4, 124.7, 127.0, 129.6, 130.2, 132.0, 132.3, 132.9, 137.2, 140.6, 167.5, 168.3. IR (KBr, neat) ν 2921, 1685, 1660, 1422, 1091, 796 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 307.1441, found 307.1442.

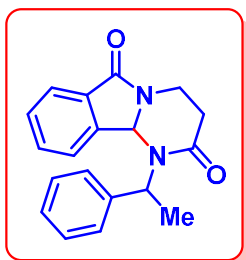
1-(4-Chlorobenzyl)-1,3,4,10b-tetrahydropyrimido[2,1-a]isoindole-2,6-dione (2f):



White solid; R_f (EtOAc, 100%) 0.6; mp 172–174 °C. Yield 161 mg, 98%. ^1H NMR (400 MHz, CDCl_3) δ 2.74 (ddd, $J = 15.0, 9.8$ and 6.6 Hz, 2H), 3.48 (ddd, $J = 15.4, 9.8$ and 5.8 Hz, 1H), 4.47 (ddd, $J = 13.5, 6.4$ and 3.8 Hz, 1H), 4.65 (d, $J = 16.2$ Hz, 1H), 5.22 (d, $J = 16.2$ Hz, 1H), 5.85 (s, 1H), 7.08 (d, $J = 8.2$ Hz, 2H), 7.27 (d, $J = 8.2$ Hz, 2H), 7.44–7.57 (m, 3H), 7.87 (d, $J = 7.0$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 32.2, 35.7, 45.8, 70.4, 124.5, 124.6, 128.2, 129.1, 130.4, 132.0, 132.3, 133.3, 134.9, 140.2, 167.4, 168.6. IR (KBr, neat) ν 2940, 1697, 1646, 1418, 1212, 737 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{16}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 327.0895, found 327.0895.

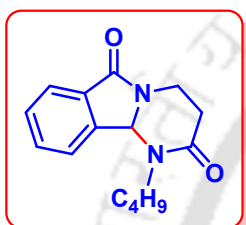
1-(1-Phenylethyl)-1,3,4,10b-tetrahydropyrimido[2,1-a]isoindole-2,6-dione (diastereomeric mixture, 1:1, 2g):

White solid; R_f (EtOAc, 100%) 0.5; mp 131–133 °C. Yield 151 mg, 98%. ^1H NMR (400 MHz, CDCl_3) δ 1.40 (d, $J = 6.4$ Hz, 3H), 1.41 (d, $J = 6.4$ Hz, 3H), 2.56–2.68 (m, 2H), 3.73–



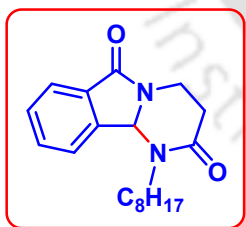
3.84 (m, 2H), 4.99–5.03 (m, 1H), 5.66 (d, $J = 4.2$ Hz, 0.5H), 5.83 (s, 1H), 5.90 (d, $J = 4.2$ Hz, 0.5H), 6.93–7.00 (m, 1H), 7.16–7.25 (m, 5H), 7.42–7.45 (m, 1H), 7.48–7.55 (m, 2 H), 7.62–7.65 (m, 1 H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 21.7, 21.8, 35.3, 35.4, 35.9, 36.1, 49.2, 49.3, 82.5, 82.6, 122.9, 123.0, 123.4, 123.5, 126.0, 126.2, 127.2, 127.3, 128.5, 128.6, 129.4, 129.5, 131.4, 131.5, 132.2, 132.3, 142.9, 143.0, 144.0, 144.1, 168.1, 168.2, 171.2, 171.4. IR (KBr, neat) ν 2926, 1681, 1637, 1557, 1285, 741 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 307.1441, found 307.1441.

1-Butyl-1,3,4,10b-tetrahydropyrimido[2,1-a]isoindole-2,6-dione (2h):



White semi-solid; R_f (EtOAc, 100%) 0.5. Yield 128 mg, 99%. ^1H NMR (600 MHz, CDCl_3) δ 0.92 (t, $J = 6.6$ Hz, 3H), 1.31–1.39 (m, 3H), 1.63–1.70 (m, 1H), 2.55 (ddd, $J = 14.2$, 5.8 and 2.8 Hz, 2H), 2.62 (ddd, $J = 17.0$, 7.4 and 6.2 Hz, 1H), 3.41 (ddd, $J = 15.8$, 10.4 and 5.0 Hz, 1H), 3.59 (ddd, $J = 14.2$, 9.2 and 5.2 Hz, 1H), 4.38–4.44 (m, 1H), 5.82 (s, 1H), 7.56–7.63 (m, 3H), 7.88 (d, $J = 7.2$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 13.8, 20.1, 29.8, 32.0, 35.6, 43.4, 70.3, 124.2, 124.4, 130.2, 132.0, 132.3, 140.6, 167.1, 167.8. IR (KBr, neat) ν 2930, 1700, 1639, 1430, 732 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 259.1441, found 259.1435.

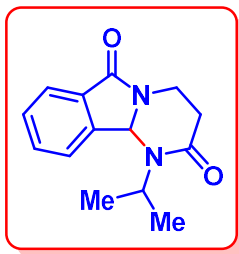
1-Octyl-1,3,4,10b-tetrahydropyrimido[2,1-a]isoindole-2,6-dione (2i):



White semi-solid; R_f (EtOAc, 100%) 0.5. Yield 140 mg, 89%. ^1H NMR (400 MHz, CDCl_3) δ 0.87 (t, $J = 6.6$ Hz, 3H), 1.22–1.33 (m, 11H), 1.64–1.71 (m, 1H), 2.52–2.67 (m, 2H), 3.42 (ddd, $J = 15.6$, 10.2 and 5.4 Hz, 1H), 3.57–3.70 (m, 2H), 4.41 (ddd, $J = 13.4$, 6.6 and 3.6 Hz, 1H), 5.83 (s, 1H), 7.60–7.63 (m, 3H), 7.89 (d, $J = 7.6$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 14.1, 22.6, 26.9, 27.8, 29.1, 29.2, 31.8, 32.1, 35.7, 43.8, 70.4, 124.2, 124.6, 130.3, 132.1, 132.5, 140.7, 167.2, 167.8. IR (KBr, neat) ν 2855, 1705, 1646, 1427, 1208, 730, cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{27}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 315.2067, found 315.2066.

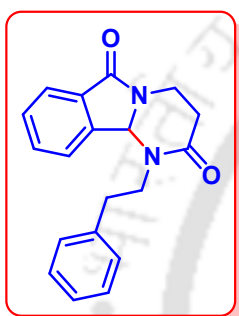
1-Isopropyl-1,3,4,10b-tetrahydropyrimido[2,1-a]isoindole-2,6-dione (2j):

White solid; R_f (EtOAc, 100%) 0.5; mp 96–98 $^{\circ}\text{C}$. Yield 65 mg, 53%. ^1H NMR (600 MHz,



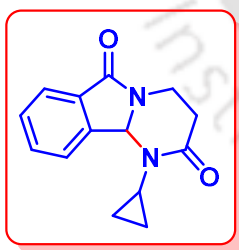
CDCl₃) δ 1.41 (d, J = 7.0 Hz, 3H), 1.58 (d, J = 7.0 Hz, 3H), 2.42–2.46 (m, 1H), 2.47–2.54 (m, 1H), 3.29 (ddd, J = 16.0, 11.4 and 3.0 Hz, 1H), 3.83–3.88 (m, 1H), 4.42 (ddd, J = 13.4, 6.4 and 2.2 Hz, 1H), 5.77 (s, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.70 (d, J = 7.4 Hz, 1H), 7.89 (d, J = 7.4 Hz, 1H). ¹³C{¹H} NMR (150 MHz, CDCl₃) δ 19.4, 20.3, 33.8, 35.6, 51.5, 71.6, 123.8, 124.5, 130.2, 132.3, 132.4, 141.9, 167.6, 167.7. IR (KBr, neat) ν 2926, 1697, 1640, 1410, 735 cm⁻¹. HRMS (ESI) calcd. for C₁₄H₁₇N₂O₂ (M + H)⁺ 245.1285, found 245.1285.

1-Phenethyl-1,3,4,10b-tetrahydropyrimido[2,1-a]isoindole-2,6-dione (2k):



White solid; R_f (EtOAc, 100%) 0.5; mp 115–117 °C. Yield 146 mg, 95%. ¹H NMR (400 MHz, CDCl₃) δ 2.55–2.67 (m, 3H), 3.06 (ddd, J = 16.5, 13.4 and 8.2 Hz, 1H), 3.33 (ddd, J = 13.4, 10.2 and 5.2 Hz, 1H), 4.89 (t, J = 7.8 Hz, 2H), 4.36 (ddd, J = 10.3, 6.8 and 3.6 Hz, 1H), 5.61 (s, 1H), 7.20–7.25 (m, 3H), 7.31 (t, J = 7.4 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.61–7.66 (m, 2H), 7.88 (d, J = 7.4 Hz, 1H). ¹³C{¹H} NMR (150 MHz, CDCl₃) δ 32.3, 34.0, 35.7, 45.5, 70.8, 124.3, 124.6, 126.8, 128.7, 128.8, 130.3, 132.1, 132.5, 138.6, 140.7, 167.2, 168.1. IR (KBr, neat) ν 2860, 1704, 1647, 1427, 734 cm⁻¹. HRMS (ESI) calcd. for C₁₉H₁₉N₂O₂ (M + H)⁺ 307.1441, found 307.1452.

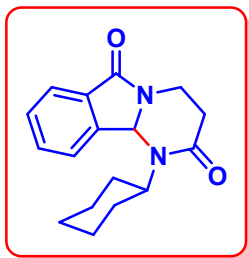
1-Cyclopropyl-1,3,4,10b-tetrahydropyrimido[2,1-a]isoindole-2,6-dione (2l):



White semi-solid; R_f (EtOAc, 100%) 0.4. Yield 184 mg, 71%. ¹H NMR (400 MHz, CDCl₃) δ 0.86–0.93 (m, 1H), 1.02–1.09 (m, 2H), 1.22–1.28 (m, 1H), 2.45–2.50 (m, 1H), 2.55–2.65 (m, 2H), 3.29 (ddd, J = 16.0, 11.8 and 6.8 Hz, 1H), 4.45 (dd, J = 13.6 and 6.8 Hz, 1H), 5.79 (s, 1H), 7.55–7.62 (m, 2H), 7.89 (d, J = 7.0 Hz, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 7.05, 11.0, 26.6, 32.8, 35.4, 70.9, 124.3, 124.4, 130.2, 132.0, 132.2, 141.5, 167.8, 168.8. IR (KBr, neat) ν 2856, 1695, 1645, 1412, 729 cm⁻¹. HRMS (ESI) calcd. for C₁₄H₁₅N₂O₂ (M + H)⁺ 243.1128, found 243.1128.

1-Cyclohexyl-1,3,4,10b-tetrahydropyrimido[2,1-a]isoindole-2,6-dione (2m):

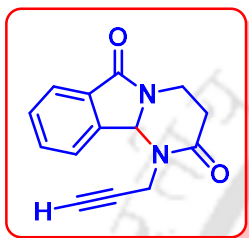
White solid; R_f (EtOAc, 100%) 0.5; mp 219–221 °C. Yield 36 mg, 25%. ¹H NMR (400 MHz, CDCl₃) δ 1.25–1.33 (m, 2H), 1.49–1.55 (m, 1H), 1.62–1.68 (m, 2H), 1.75–1.84 (m,



2H), 1.90–1.95 (m, 1H), 2.34–2.49 (m, 2H), 2.51–2.61 (m, 2H), 3.25–3.36 (m, 2H), 4.42 (ddd, $J = 13.4, 6.2$ and 2.4 Hz, 1H), 5.78 (s, 1H), 7.59–7.62 (m, 2H), 7.67 (d, $J = 7.4$ Hz, 1H), 7.89 (d, $J = 7.4$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 25.2, 26.5, 26.8, 28.7, 29.9, 33.9, 35.7, 60.4, 71.7, 123.6, 124.5, 130.2, 132.3, 132.4, 142.1, 167.6, 167.7.

IR (KBr, neat) ν 2854, 1692, 1640, 1405, 733 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 285.1598, found 285.1599.

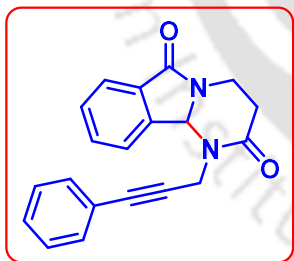
1-(Prop-2-yn-1-yl)-1,3,4,10b-tetrahydropyrimido[2,1-a]isoindole-2,6-dione (2n):



White solid; R_f (Hexane:EtOAc, 1:4) 0.6; mp 159–161 $^{\circ}\text{C}$. Yield 116 mg, 97%. ^1H NMR (500 MHz, CDCl_3) δ 2.44 (t, $J = 2.6$ Hz, 1H), 2.57–2.64 (m, 2H), 3.41–3.47 (m, 1H), 3.81 (dd, $J = 17.8$ and 2.5 Hz, 1H), 4.45–4.50 (m, 1H), 5.32 (dd, $J = 17.8$ and 2.6 Hz, 1H), 6.12 (s, 1H), 7.56–7.61 (m, 2H), 7.62–7.65 (m, 1H), 7.86–7.90 (m, 1H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 31.7, 32.0, 35.4, 69.7, 74.3, 77.8, 124.6, 124.7, 130.4, 132.2, 132.3, 140.1, 167.4. IR (KBr, neat) ν 2931, 1705, 1652, 1436, 1092, 734 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 241.0972, found 241.0972.

1-(3-Phenylprop-2-yn-1-yl)-1,3,4,10b-tetrahydropyrimido[2,1-a]isoindole-2,6-dione (2o):

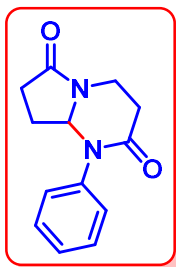


White semi-solid; R_f (Hexane:EtOAc, 1:4) 0.5. Yield 148 mg, 93%. ^1H NMR (500 MHz, CDCl_3) δ 2.58–2.71 (m, 2H), 3.44–3.50 (m, 1H), 4.06 (d, $J = 17.8$ Hz, 1H), 4.47–4.53 (m, 1H), 5.56 (dd, $J = 17.8$ and 2.1 Hz, 1H), 6.21 (s, 1H), 7.29–7.34 (m, 3H), 7.44 (d, $J = 7.0$ Hz, 2H), 7.60 (t, $J = 7.4$ Hz, 1H), 7.66 (t, $J = 7.4$

Hz, 1H), 7.91 (d, $J = 7.8$ Hz, 1H), 7.98 (d, $J = 7.8$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 32.0, 32.5, 35.4, 69.8, 82.9, 86.2, 122.1, 124.6, 124.7, 128.4, 128.9, 130.4, 131.8, 132.2, 132.3, 140.3, 167.3, 167.4. IR (KBr, neat) ν 2928, 1710, 1654, 1438, 732 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 317.1285, found 317.1264.

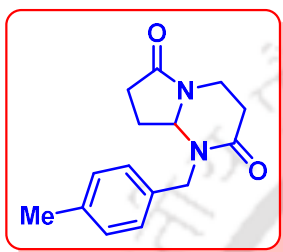
1-Phenylhexahydropyrrolo[1,2-a]pyrimidine-2,6-dione (2p):

White semi-solid; R_f (EtOAc, 100%) 0.4. Yield 112 mg, 97%. ^1H NMR (400 MHz, CDCl_3) δ 1.80–1.86 (m, 1H), 2.02–2.08 (m, 1H), 2.38–2.48 (m, 2H), 2.59 (ddd, $J = 16.8, 4.7$ and



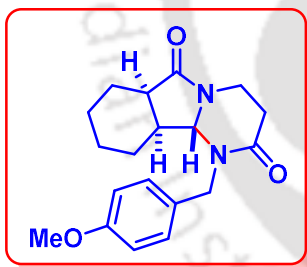
1.8 Hz, 1H), 2.74 (ddd, $J = 17.4, 10.8$ and 7.4 Hz, 1H), 3.23–3.32 (m, 1H), 4.30–4.35 (m, 1H), 5.49 (t, $J = 5.7$ Hz, 1 H), 7.18 (d, $J = 7.6$ Hz, 2 H), 7.34 (t, $J = 7.6$ Hz, 1 H), 7.44 (t, $J = 7.6$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 25.7, 29.1, 31.9, 35.7, 72.8, 127.9, 128.1, 129.7, 137.9, 168.0, 173.2. IR (KBr, neat) ν 2857, 1686, 1645, 1396, 758 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 231.1128, found 231.1128.

1-(4-Methylbenzyl)hexahydropyrrolo[1,2-a]pyrimidine-2,6-dione (2q):



White semi-solid; R_f (EtOAc, 100%) 0.4. Yield 123 mg, 95%. ^1H NMR (400 MHz, CDCl_3) δ 1.83–1.91 (m, 1H), 2.27–2.37 (m, 1H), 2.31 (s, 3H), 2.38–2.48 (m, 2H), 2.51–2.65 (m, 2H), 2.98–3.06 (m, 1H), 4.22 (d, $J = 15.2$ Hz, 1H), 4.21–4.27 (m, 1H), 4.92 (t, $J = 6.2$ Hz, 1H), 5.04 (d, $J = 15.2$ Hz, 1H), 7.12–7.15 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 21.1, 26.2, 29.5, 32.0, 35.2, 45.2, 70.5, 127.8, 129.6, 133.4, 137.5, 167.6, 172.4. IR (KBr, neat) ν 2856, 1691, 1643, 1420, 1012, 790 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 259.1441, found 259.1443

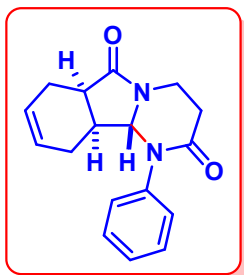
1-(4-Methoxybenzyl)decahydropyrimido[2,1-a]isoindole-2,6-dione (2r):



White solid; R_f (EtOAc, 100%) 0.5; mp 124–126 $^{\circ}\text{C}$. Yield 135 mg, 82%. ^1H NMR (400 MHz, CDCl_3) δ 1.02–1.21 (m, 3H), 1.41–1.57 (m, 3H), 1.61–1.66 (m, 1H), 2.01–2.08 (m, 1H), 2.40–2.47 (m, 3H), 2.57–2.67 (m, 1H), 3.06 (ddd, $J = 17.4, 12.6$ and 4.8 Hz, 1H), 3.77 (s, 3H), 4.21 (ddd, $J = 13.0, 8.6$ and 7.0 Hz, 1H), 4.43 (d, $J = 15.0$ Hz, 1H), 4.45 (s, 1H), 4.81 (d, $J = 15.0$ Hz, 1H), 6.84 (d, $J = 8.6$ Hz, 2H), 7.12 (d, $J = 8.4$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 22.5, 23.0, 23.3, 27.4, 31.8, 34.9, 36.5, 39.4, 45.5, 55.2, 75.6, 114.2, 128.7, 128.9, 159.0, 168.9, 176.6. IR (KBr, neat) ν 2855, 1706, 1649, 1422, 1249, 753 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 329.1860, found 329.1834.

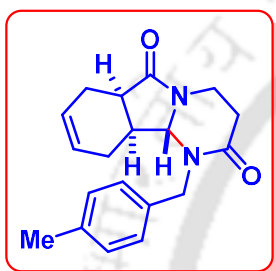
1-Phenyl-1,3,4,6a,7,10,10a,10b-octahydropyrimido[2,1-a]isoindole-2,6-dione (2s):

White solid; R_f (EtOAc, 100%) 0.4; mp 136–138 $^{\circ}\text{C}$. Yield 130 mg, 92%. ^1H NMR (600 MHz, CDCl_3) δ 1.52–1.58 (m, 1H), 1.85–1.93 (m, 1H), 2.25–2.28 (m, 1H), 2.37–2.44 (m, 2H), 2.53–2.55 (m, 1H), 2.58–2.73 (m, 1H), 2.80–2.84 (m, 1H), 3.25 (ddd, $J = 16.2, 8.4$ and



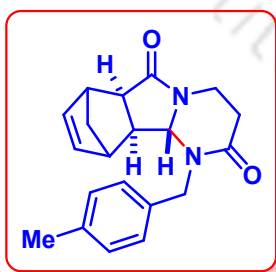
1.4 Hz, 1H), 4.35 (ddd, $J = 16.2, 9.0$ and 2.4 Hz, 1H), 5.06 (d, $J = 3.6$ Hz, 1H), 5.64–5.69 (m, 1H), 5.80–5.84 (m, 1H), 7.20 (d, $J = 8.4$ Hz, 2H), 7.38 (t, $J = 8.4$ Hz, 1H), 7.45 (t, $J = 8.4$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 23.1, 25.3, 31.9, 35.8, 36.0, 39.0, 78.7, 125.8, 127.6, 128.0, 128.2, 129.8, 138.3, 168.2, 176.2. IR (KBr, neat) ν 2848, 1693, 1658, 1459, 753 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{NaO}_2$ ($\text{M} + \text{Na}$) $^+$ 305.1260, found 305.1240.

1-(4-Methylbenzyl)-1,3,4,6a,7,10,10a,10b-octahydropyrimido[2,1-a]isoindole-2,6-dione (2t):



White solid; R_f (EtOAc, 100%) 0.5; mp 112–114 $^\circ\text{C}$. Yield 143 mg, 92%. ^1H NMR (400 MHz, CDCl_3) δ 1.86–1.94 (m, 1H), 2.11–2.23 (m, 2H), 2.32 (s, 3H), 2.36–2.42 (m, 1H), 2.49 (dd, $J = 17.0$ and 4.8 Hz, 1H), 2.58–2.73 (m, 3H), 3.06 (ddd, $J = 17.0, 12.5$ and 4.8 Hz, 1H), 4.24 (dd, $J = 13.4$ and 7.2 Hz, 1H), 4.46 (d, $J = 15.4$ Hz, 1H), 4.54 (s, 1H), 4.88 (d, $J = 15.4$ Hz, 1H), 5.70–5.75 (m, 1H), 5.80–5.85 (m, 1H), 7.09–7.15 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 21.1, 22.9, 26.0, 32.0, 34.7, 36.0, 39.0, 45.6, 125.7, 127.3, 127.8, 129.6, 133.7, 137.3, 168.5, 176.3. IR (KBr, neat) ν 2850, 1698, 1647, 1428, 753 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 311.1754, found 311.1755.

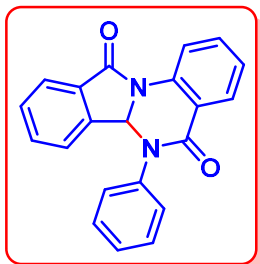
(6a,10a,10b)-1-(4-methylbenzyl)-1,3,4,6a,7,10,10a,10b-octahydro-7,10-methanopyrimido[2,1-a]isoindole-2,6-dione (2u):



White solid; R_f (EtOAc, 100%) 0.4; mp 122–124 $^\circ\text{C}$. Yield 152 mg, 94%. ^1H NMR (400 MHz, CDCl_3) δ 1.34–1.41 (m, 1H), 1.56–1.62 (m, 1H), 2.33 (s, 3H), 2.42 (ddd, $J = 17.0, 4.7$ and 1.6 Hz, 1H), 2.51 (ddd, $J = 17.0, 12.0$ and 7.0 Hz, 1H), 2.81 (dd, $J = 16.8$ and 4.8 Hz, 1H), 2.85–2.90 (m, 1H), 3.01–3.05 (m, 1H), 3.13 (dd, $J = 9.4$ and 4.4 Hz, 1H), 3.22–3.25 (m, 1H), 4.11 (ddd, $J = 13.2, 7.0$ and 1.8 Hz, 1H), 4.26 (s, 1H), 4.30 (d, $J = 15.2$ Hz, 1H), 5.07 (d, $J = 15.2$ Hz, 1H), 5.96 (dd, $J = 5.8$ and 3.0 Hz, 1H), 6.16 (dd, $J = 5.8$ and 3.0 Hz, 1H), 7.12–7.17 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 21.1, 32.4, 35.2, 43.7, 44.7, 45.2, 45.4, 50.2, 51.5, 72.9, 127.8, 129.6, 133.6, 133.8, 136.8,

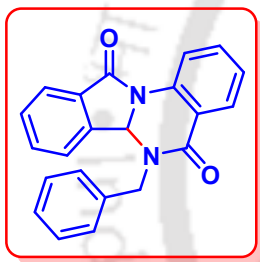
137.4, 168.0, 173.6. IR (KBr, neat) ν 2870, 1693, 1648, 1427, 754 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2\text{K}$ ($\text{M} + \text{K}$)⁺ 361.1313, found 361.1309.

6-Phenyl-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (3a):



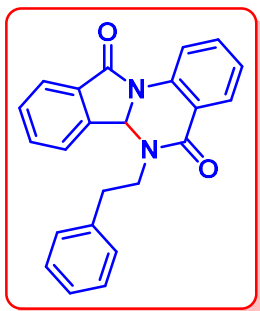
White solid; R_f (EtOAc, 100%) 0.7; mp 200–202 °C. Yield 156 mg, 96%. ^1H NMR (400 MHz, CDCl_3) δ 6.15 (d, J = 7.6 Hz, 1H), 6.54 (s, 1H), 7.26 (t, J = 7.4 Hz, 2H), 7.35 (d, J = 7.6 Hz, 2H), 7.45–7.53 (m, 4H), 7.68 (t, J = 7.6 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 8.18–8.21 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 72.3, 120.3, 120.33, 124.5, 125.3, 125.4, 129.2, 129.5, 129.8, 130.3, 132.1, 132.2, 133.9, 137.1, 138.2, 138.7, 164.2, 165.3. IR (KBr, neat) ν 2926, 1716, 1665, 1404, 739 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{15}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 327.1128, found 327.1118.

6-Benzyl-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (3b):



White solid; R_f (Hexane:EtOAc, 1:4) 0.7; mp 153–155 °C. Yield 154 mg, 91%. ^1H NMR (600 MHz, CDCl_3) δ 4.62 (d, J = 16.6 Hz, 1H), 5.51 (d, J = 16.6 Hz, 1H), 6.36 (s, 1H), 7.20 (d, J = 7.6 Hz, 2H), 7.25 (d, J = 7.6 Hz, 1H), 7.32–7.38 (m, 3H), 7.41 (d, J = 7.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 7.4 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.96 (d, J = 7.4 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 8.22 (t, J = 7.6 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) δ 46.6, 70.7, 120.1, 120.2, 125.0, 125.3, 125.4, 126.3, 127.3, 129.1, 129.5, 130.6, 132.5, 132.6, 133.8, 136.1, 136.9, 137.7, 164.1, 164.9. IR (KBr, neat) ν 2854, 1717, 1657, 1410, 735 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{17}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 341.1285, found 341.1286.

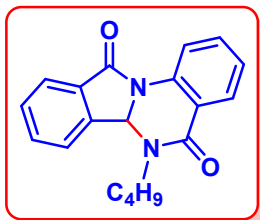
6-Phenethyl-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (3c):



White solid; R_f (Hexane:EtOAc, 1:1) 0.6; mp 145–147 °C. Yield 157 mg, 88%. ^1H NMR (500 MHz, CDCl_3) δ 2.62–2.68 (m, 1H), 2.91–2.97 (m, 1H), 3.92–3.99 (m, 1H), 4.05–4.12 (m, 1H), 6.17 (s, 1H), 7.10–7.12 (m, 2H), 7.18–7.20 (m, 1H), 7.22–7.26 (m, 2H), 7.32–7.35 (m, 1H), 7.61–7.71 (m, 4H), 7.97–7.99 (m, 1H), 8.07–8.10 (m, 1H), 8.15–8.17 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 34.5, 44.8, 70.8, 120.2, 120.6, 125.3, 125.33, 125.4, 126.6, 128.7, 128.8, 129.0, 130.7, 132.6,

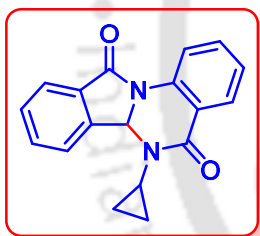
133.1, 133.5, 136.8, 138.1, 138.3, 163.8, 164.7. IR (KBr, neat) ν 2856, 1716, 1653, 1411, 735 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{19}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 355.1441, found 355.1461.

6-Butyl-6,6a-dihydroisindolo[2,1-a]quinazoline-5,11-dione (3d):



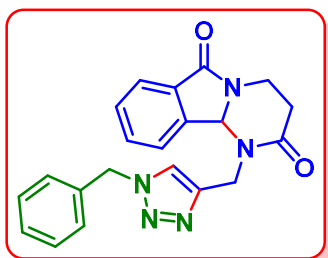
White solid; R_f (Hexane:EtOAc, 1:4) 0.6; mp 136–138 °C. Yield 142 mg, 93%. ^1H NMR (400 MHz, CDCl_3) δ 0.91 (t, J = 7.2 Hz, 3H), 1.28–1.37 (m, 2H), 1.41–1.50 (m, 1H), 1.52–1.60 (m, 1H), 3.69 (ddd, J = 15.0, 7.6 and 5.6 Hz, 1H), 3.88 (ddd, J = 14.2, 10.2 and 5.6 Hz, 1H), 6.21 (s, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.64–7.69 (m, 1H), 7.70–7.73 (m, 2H), 8.01 (d, J = 7.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 13.8, 20.1, 30.4, 42.9, 70.6, 120.1, 120.6, 125.0, 125.1, 125.2, 129.1, 130.6, 132.7, 130.0, 133.3, 136.7, 138.3, 163.7, 164.8. IR (KBr, neat) ν 2868, 1717, 1657, 1416, 756 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 307.1441, found 307.1416.

6-Cyclopropyl-6,6a-dihydroisindolo[2,1-a]quinazoline-5,11-dione (3e):



White solid; R_f (Hexane:EtOAc, 2:3) 0.6; mp 160–162 °C. Yield 142 mg, 97%. ^1H NMR (500 MHz, CDCl_3) δ 0.03–0.08 (m, 1H), 0.65–0.71 (m, 1H), 0.84–0.90 (m, 1H), 1.11–1.17 (m, 1H), 2.68–2.72 (m, 1H), 6.17 (s, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.65–7.70 (m, 2H), 7.91 (d, J = 7.2 Hz, 1H), 7.99 (d, J = 7.2 Hz, 1H), 8.13–8.17 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 9.6, 11.6, 26.2, 72.1, 119.6, 120.5, 124.7, 125.0, 126.6, 129.1, 130.3, 132.0, 132.6, 133.6, 137.1, 138.4, 164.9, 165.6. IR (KBr, neat) ν 2923, 2853, 1714, 1664, 1409, 756 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 291.1128, found 291.1140.

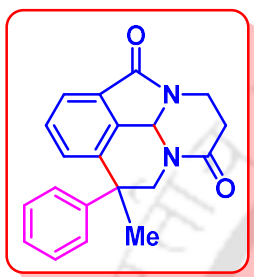
1-((2-Benzyl-2H-1,2,3-triazol-4-yl)methyl)-1,3,4,10b-tetrahydropyrimido[2,1-a]isoindole-2,6-dione (4):



White solid; R_f (EtOAc, 100%) 0.4; mp 198–200 °C. Yield 89 mg, 79%. ^1H NMR (400 MHz, CDCl_3) δ 2.49–2.56 (m, 1H), 2.60–2.68 (m, 1H), 3.32–3.40 (m, 1H), 4.37–4.44 (m, 1H), 4.65 (d, J = 15.6 Hz, 1H), 5.19 (d, J = 15.6 Hz, 1H), 5.40 (d, J = 14.8 Hz, 1H), 5.52 (d, J = 14.8 Hz, 1H), 6.02 (s, 1H), 7.20–

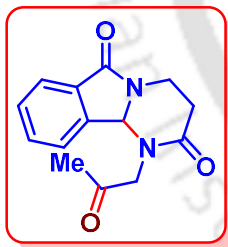
7.23 (m, 2H), 7.33–7.35 (m, 3H), 7.45 (s, 1H), 7.51–7.60 (m, 2H), 7.85 (d, $J = 7.2$ Hz, 1H), 8.15 (d, $J = 7.2$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 32.1, 35.5, 38.2, 54.3, 70.5, 123.2, 124.3, 125.8, 128.1, 128.8, 129.1, 130.2, 132.1, 134.4, 140.5, 144.2, 167.5, 168.4. IR (KBr, neat) ν 2927, 1705, 1650, 1425, 1294, 730 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{19}\text{N}_5\text{NaO}_2$ ($\text{M} + \text{Na}$) $^+$ 396.1431, found 396.1432.

8-Methyl-8-phenyl-2,3,8,9a¹-tetrahydro-1H-3a,9a-diazacyclopenta[def]phenanthrene-1,4(9H)-dione (5):



White semi-solid; R_f (Hexane:EtOAc, 2:3) 0.5. Yield 108 mg, 84%. ^1H NMR (500 MHz, CDCl_3) δ 2.21 (s, 3H), 2.88–2.94 (m, 1H), 3.03–3.10 (m, 1H), 3.29–3.35 (m, 1H), 4.21–4.27 (m, 1H), 5.43 (s, 1H), 6.57 (t, $J = 1.4$ Hz, 1H), 7.08–7.10 (m, 2H), 7.11–7.13 (m, 1H), 7.28–7.34 (m, 3H), 7.40–7.45 (m, 2H), 7.84–7.88 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 10.8, 27.4, 38.1, 64.8, 122.6, 123.1, 123.5, 127.6, 128.3, 128.7, 129.1, 131.3, 131.8, 136.8, 146.4, 148.8, 160.8, 168.7. IR (KBr, neat) ν 2926, 1692, 1403, 1217, 740 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 319.1441, found 319.1438.

1-(2-Oxopropyl)-1,3,4,10b-tetrahydropyrimido[2,1-a]isoindole-2,6-dione (6):



White solid; R_f (EtOAc, 100%) 0.4; mp 159–161 $^{\circ}\text{C}$. Yield 78 mg, 75%. ^1H NMR (500 MHz, CDCl_3) δ 2.16 (s, 3H), 2.69 (dd, $J = 7.4$ and 5.8 Hz, 2H), 3.59 (dt, $J = 13.2$ and 7.4 Hz, 1H), 4.08 (d, $J = 18.2$ Hz, 1H), 4.36 (dt, $J = 11.5$ and 5.8 Hz, 1H), 4.81 (d, $J = 18.2$ Hz, 1H), 6.00 (s, 1H), 7.37–7.41 (m, 1H), 7.56–7.59 (m, 2H), 7.87–7.91 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 27.3, 31.6, 35.8, 53.0, 70.7, 123.8, 124.8, 130.5, 132.1, 132.7, 140.0, 167.2, 169.0, 203.2. IR (KBr, neat) ν 2925, 1702, 1650, 1412, 1295, 735 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 259.1077, found 259.1102.

2.8.1. Crystallographic Description

Table 2.8.1.1. Crystal parameters of compound **2a**

Compound 2a	CCDC 2096075
Formula	C ₁₇ H ₁₄ N ₂ O ₂
Formula weight	278.30
T/K	296(2)
Crystal system	monoclinic
Space group	P 2 ₁ /n
<i>a</i> /Å	9.5567(6)
<i>b</i> /Å	9.7212(6)
<i>c</i> /Å	15.0352(9)
<i>a</i> /°	90
<i>β</i> /°	93.695(2)
<i>γ</i> /°	90
<i>V</i> /Å ³	1393.91(15)
<i>Z</i>	4
Abs. Coeff./mm ⁻¹	0.089
Abs. Correction	multi-scan
GOF on <i>F</i> ²	1.048
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.0499 <i>wR</i> ₂ = 0.1424
<i>R</i> indices [all data]	<i>R</i> ₁ = 0.0800 <i>wR</i> ₂ = 0.1768

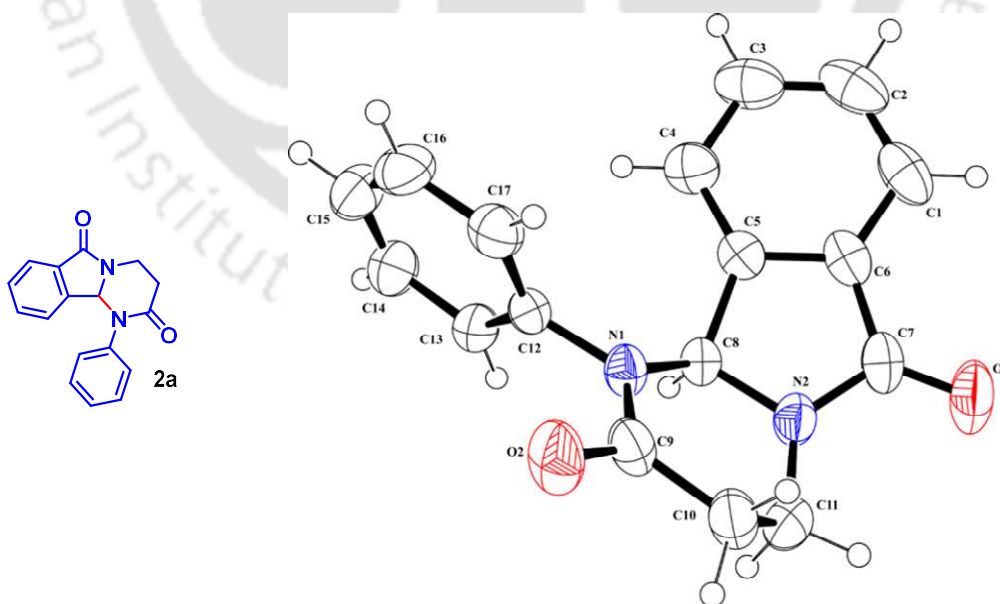
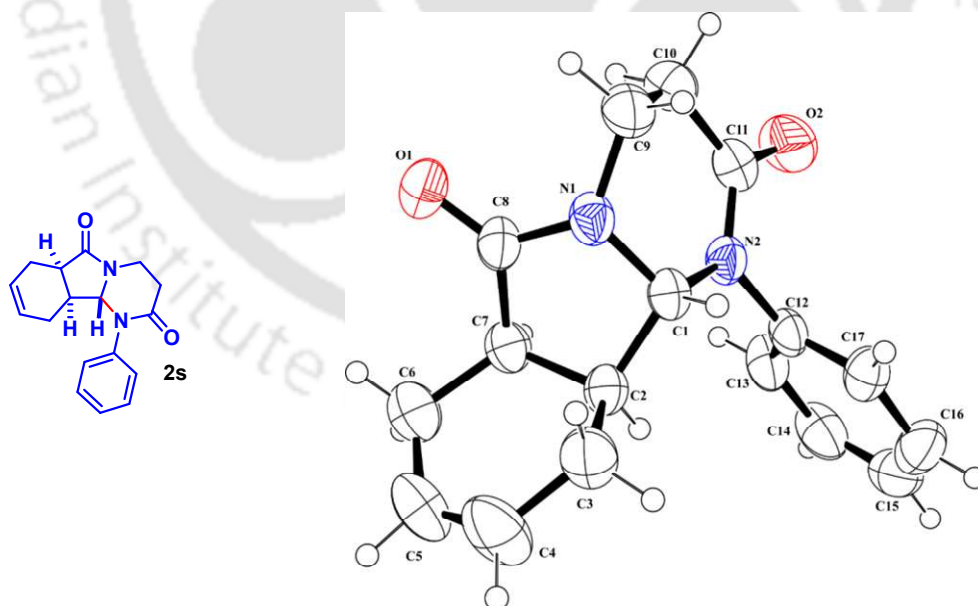


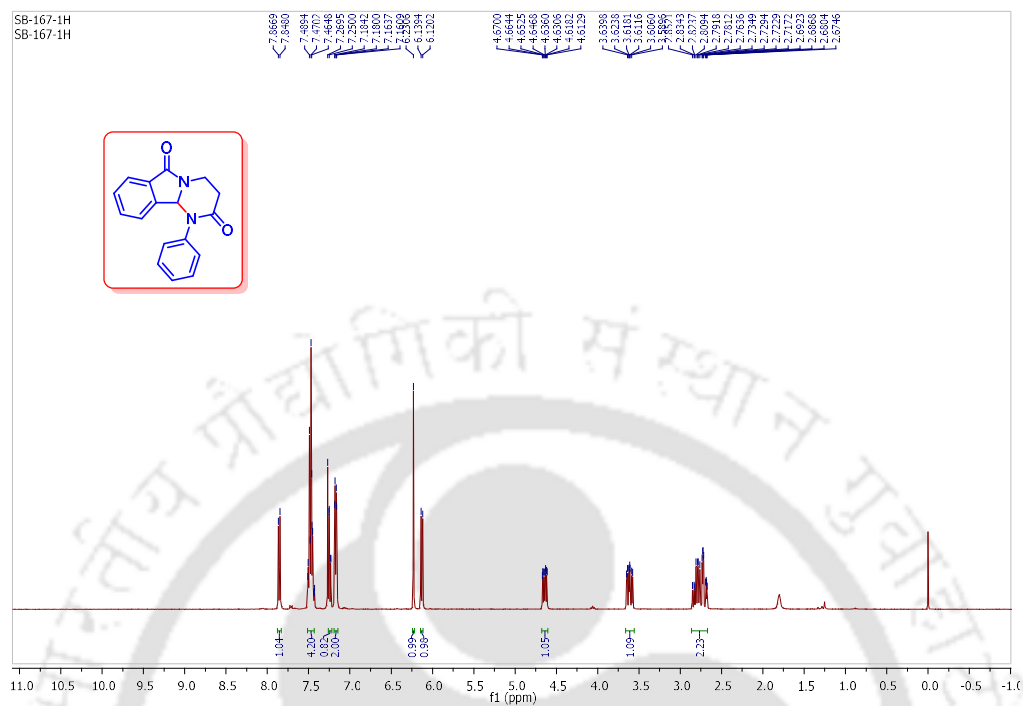
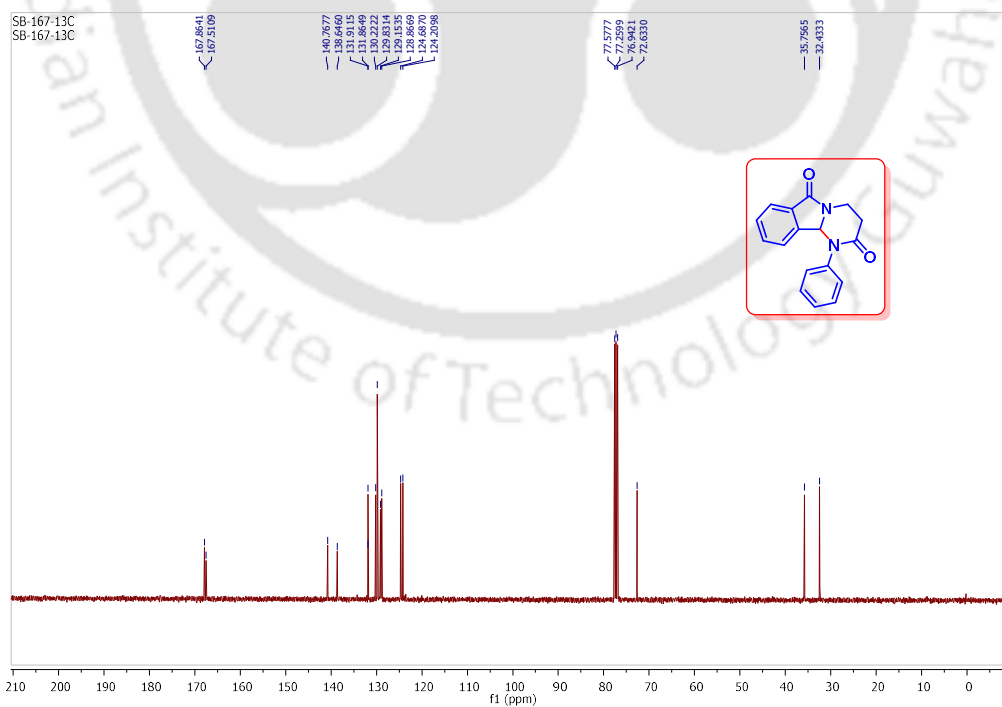
Figure 2.8.1.1. ORTEP diagram of compound **2a** with thermal ellipsoid of 30% probability.

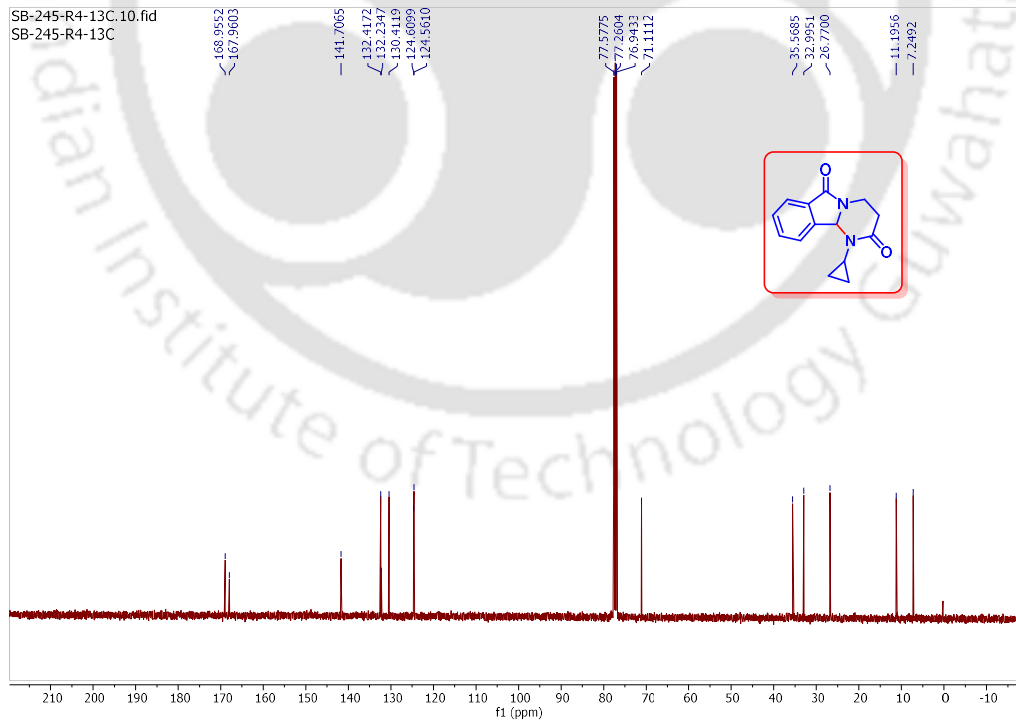
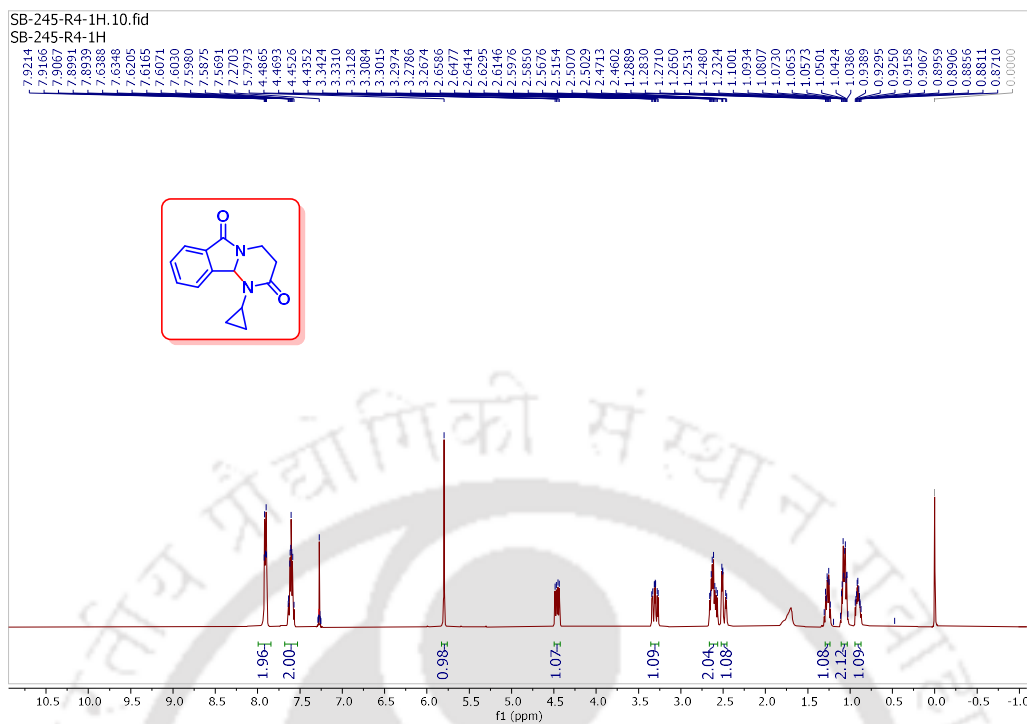
Table 2.8.1.2. Crystal parameters of compound **2s**

Compound 2s	CCDC 2096084
Formula	C ₁₇ H ₁₈ N ₂ O ₂
Formula weight	282.33
<i>T</i> /K	296(2)
Crystal system	orthorhombic
Space group	P21 21 21
<i>a</i> /Å	8.9929(8)
<i>b</i> /Å	9.6220(10)
<i>c</i> /Å	17.0576(19)
<i>a</i> /°	90
<i>β</i> /°	90
<i>γ</i> /°	90
<i>V</i> /Å ³	1476.0(3)
<i>Z</i>	4
Abs. Coeff./mm ⁻¹	0.084
Abs. Correction	none
GOF on <i>F</i> ²	0.866
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> 1 = 0.0426 <i>wR</i> 2 = 0.1245
<i>R</i> indices [all data]	<i>R</i> 1 = 0.0512 <i>wR</i> 2 = 0.1334

Figure 2.8.1.2. ORTEP diagram of compound **2s** with thermal ellipsoid of 30% probability.

2.9. Representative Spectra

Figure 2.9.1. ¹H NMR spectrum of compound **2a** (400 MHz, CDCl₃).Figure 2.9.2. ¹³C{¹H} NMR spectrum of compound **2a** (100 MHz, CDCl₃).



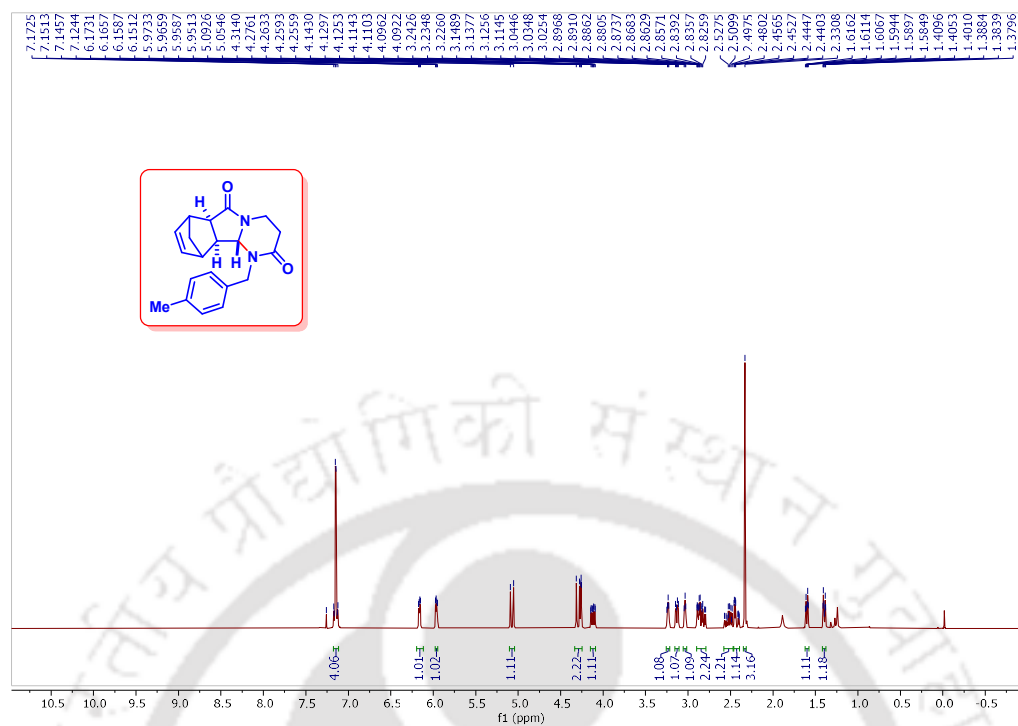


Figure 2.9.5. ^1H NMR spectrum of compound **2u** (400 MHz, CDCl_3).

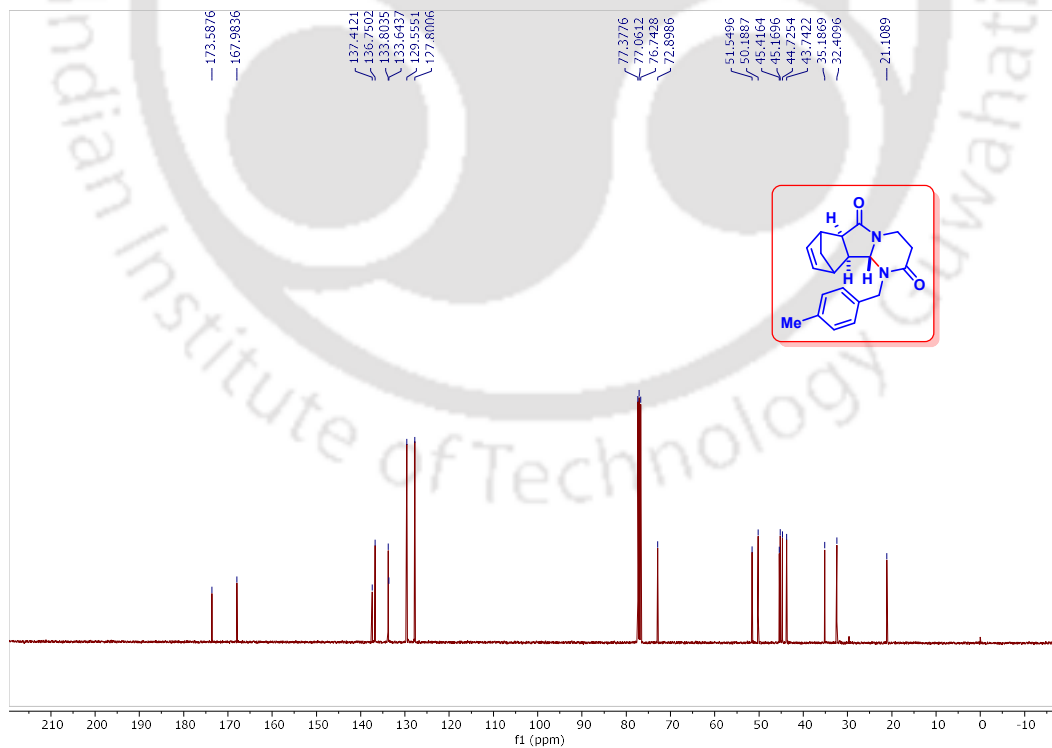


Figure 2.9.6. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of compound **2u** (100 MHz, CDCl_3).

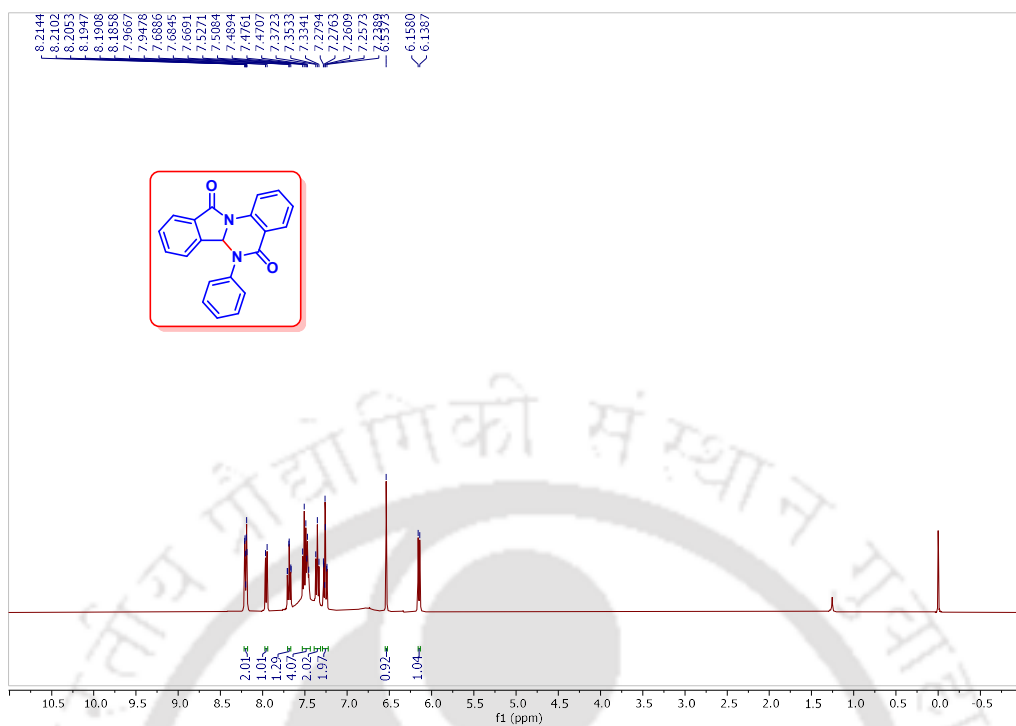


Figure 2.9.7. ¹H NMR spectrum of compound **3a** (400 MHz, CDCl₃).

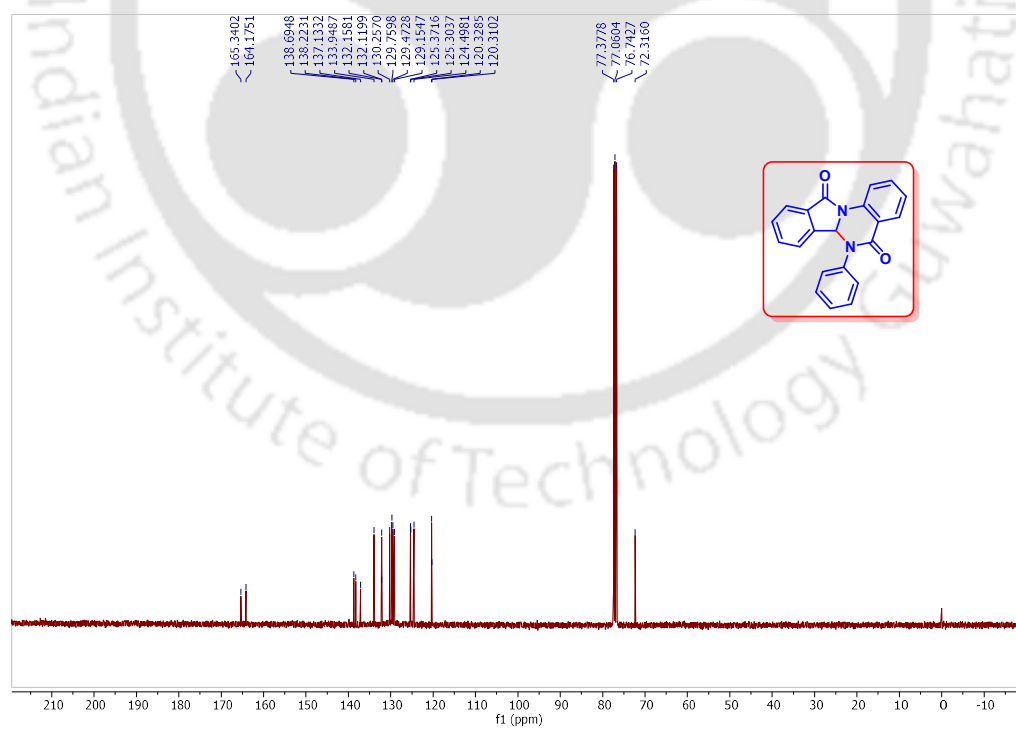


Figure 2.9.8. ¹³C{¹H} NMR spectrum of compound **3a** (100 MHz, CDCl₃).

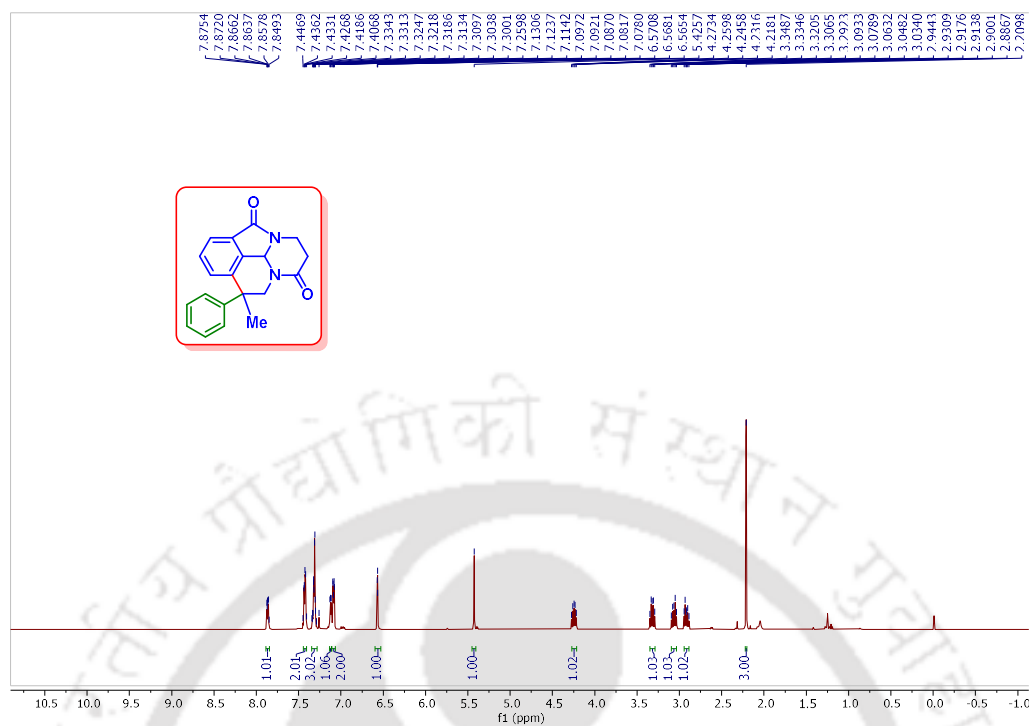


Figure 2.9.9. ¹H NMR spectrum of compound 5 (500 MHz, CDCl₃).

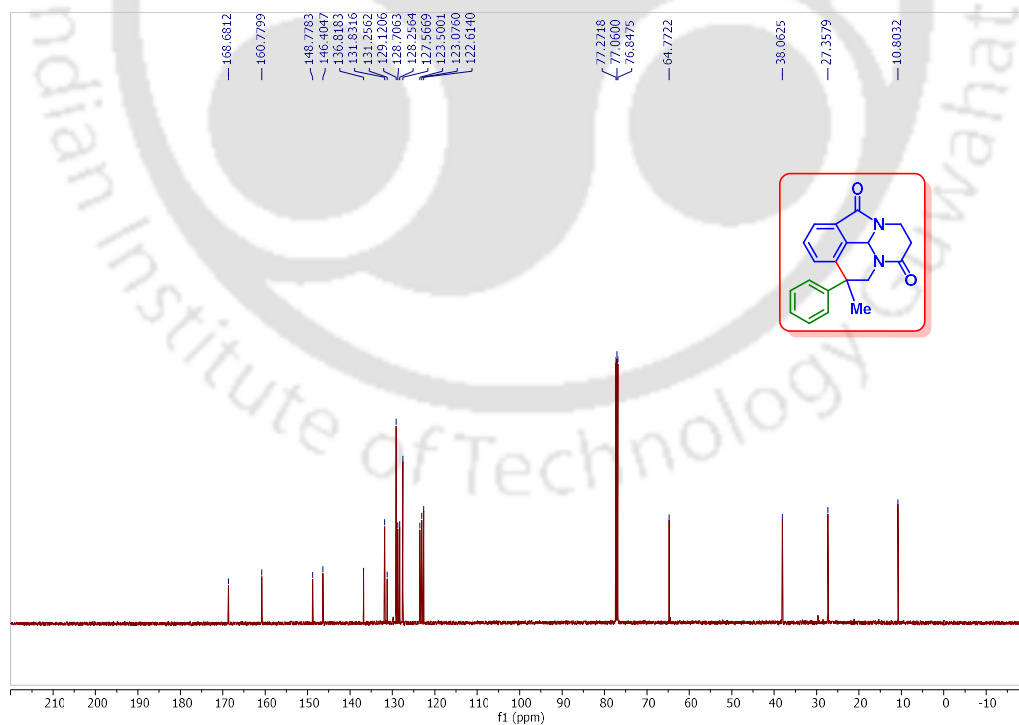
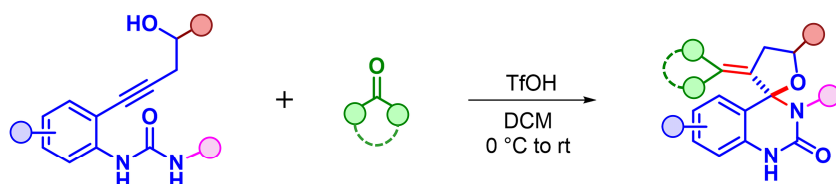


Figure 2.9.10. ¹³C{¹H} NMR spectrum of compound 5 (125 MHz, CDCl₃).



Leveraging Cascade Alkynyl Prins Cyclization Towards the Stereoselective Synthesis of Spiro-Furan Quinazolinone Scaffolds



- Metal-free tandem protocol
- Excellent *E*-selectivity
- High functional-group tolerance
- Excellent yields, up to 99%

Abstract: A TfOH-promoted, metal-free protocol has been unveiled for the synthesis of spiro-furan quinazolinones employing alkynol urea derivatives utilizing alkynyl Prins cyclization reaction. This methodology produces highly functionalized spiro-heterocycles in excellent yields with exclusive *E*-selectivity under ambient conditions. Furthermore, late-stage modifications incorporate bromide and acetyl functionalities into the synthesized spiro-heterocycles.



Chapter III

Leveraging Cascade Alkynyl Prins Cyclization Towards the Stereoselective Synthesis of Spiro-Furan Quinazolinone Scaffolds

3.1 Introduction

Prins cyclization has proven to be a reliable tool, providing an efficient and convenient method to synthesize intricate structures, facilitating the synthesis of bioactive molecules, and contributing to the total synthesis of natural products.¹ Likewise, alkynyl Prins cyclization holds exciting potential for the construction of crucial intermediates, which are prevalent in natural product synthesis.^{2,3} Over time, several works in alkynyl Prins cyclization have been documented for the formation of complex cyclic compounds.³

Spirocycles are characterized as fused ring systems where two or more rings share a single common atom. They are of prime interest to the scientific community due to their unique structural features and numerous biological activities.⁴ Various natural products, alkaloids, and bioactive molecules comprise these spirocyclic cores.^{4c} Consequently, developing regio- and stereo controlled spirocyclic frameworks is highly important among synthetic organic researchers.⁵ In particular, spiro-quinazolinones, because of their diverse biological applications, have emerged as a crucial heterocyclic substructure in medicinal chemistry. Their bioactivities primarily include anticancer,^{6a} antifungal,^{6b} antitumor,^{6a} anticonvulsant,^{6c} antidiabetic,^{6d} antifibrillatory,^{6e} anti-inflammatory and analgesic properties.^{6f} Additionally, spiro-quinazolinones exhibit cytotoxic and apoptosis-inducing properties^{7a} and serve as

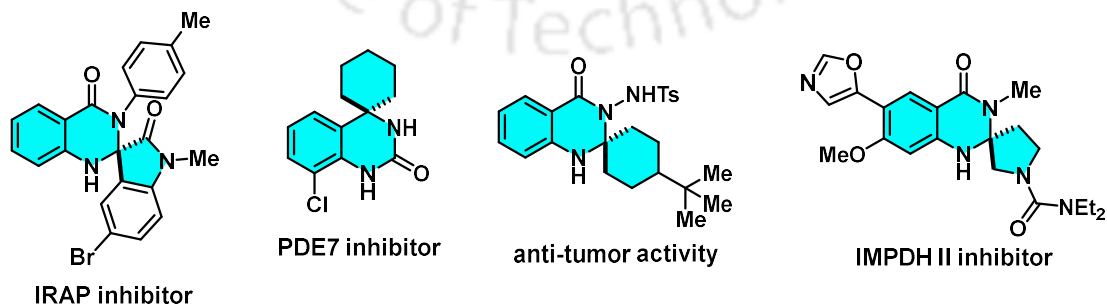
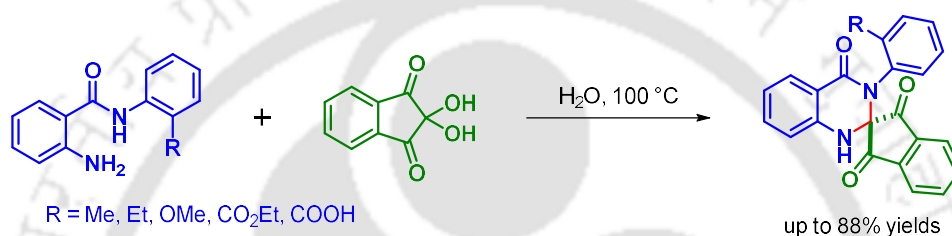


Figure 3.1.1. Representative examples of biologically active spiro-quinazolinones.

phosphodiesterase 7 inhibitors,^{7b} chitin synthase inhibitors,^{6b} IRAP inhibitors,^{7c} chorismate mutase inhibitors,^{7d} IMPDH II inhibitors,^{7e} and dual SENP1 and SENP2 inhibitors (Figure 3.1.1).^{7f} Furthermore, they are actively involved in material sciences and agrochemicals.⁸

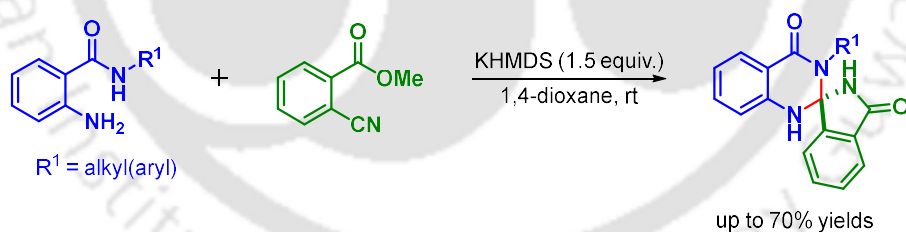
3.2 Differential Strategies Towards the Synthesis of Spiro-Quinazolinones

Bhate's group developed a catalyst-free and environmentally benign strategy for the synthesis of spiro-indene quinazolinones from aminobenzamides bearing an ortho substituent and ninhydrin (Scheme 3.2.1).⁹



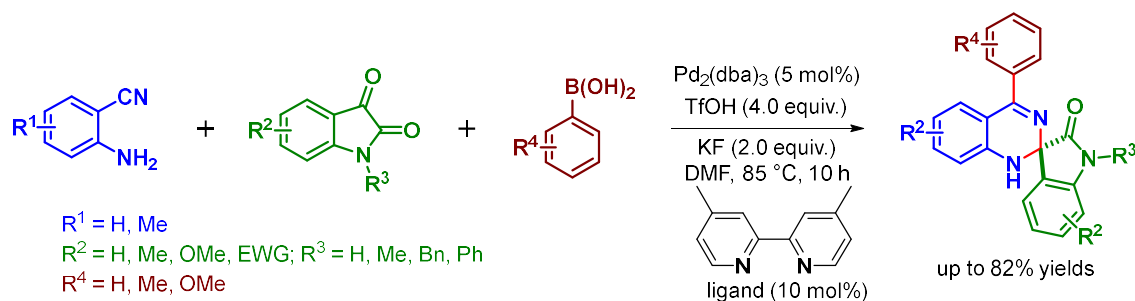
Scheme 3.2.1. Green synthesis of spiro-indene quinazolinones.

Raghunadh's group has demonstrated a base mediated synthesis of spiro-isoindolinone dihydroquinazolinones from *o*-aminobenzamide and *o*-cyanomethyl benzoate in moderate yields (Scheme 3.2.2).¹⁰



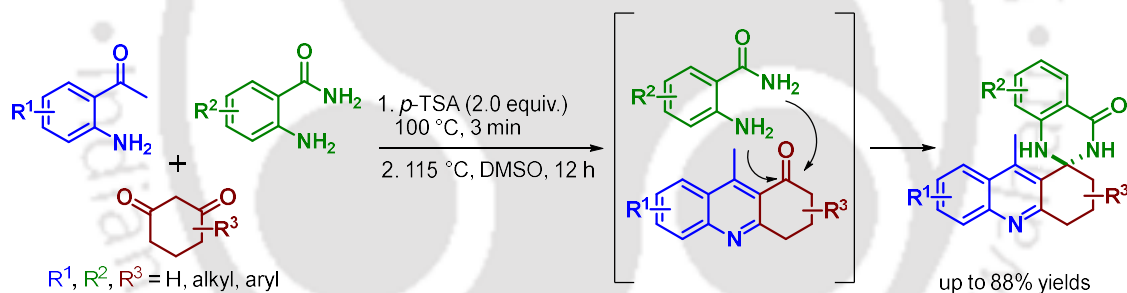
Scheme 3.2.2. Base mediated synthesis of spiro-isoindolinone dihydroquinazolinones.

Gogoi's group devised a palladium-catalyzed cascade protocol for one-pot synthesis of functionalized spiro(indoline-3,2'-quinazolin)-2-one derivatives from 2-aminobenzonitriles, arylboronic acids and isatins (Scheme 3.2.3).¹¹



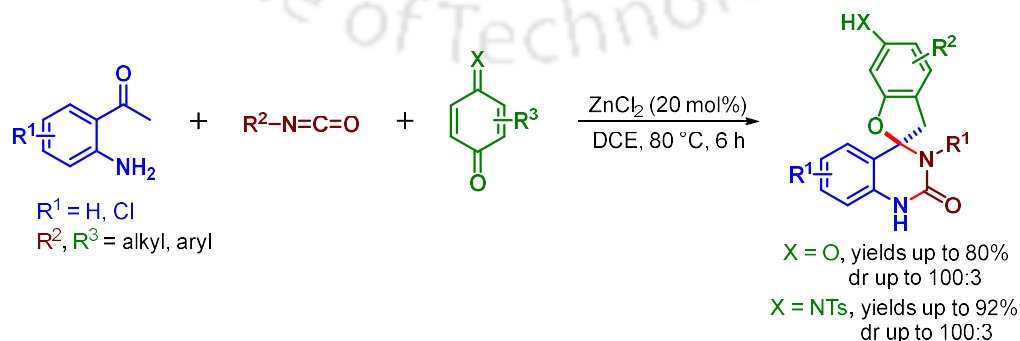
Scheme 3.2.3. Palladium-catalyzed synthesis of spiro-indoline quinazolinones.

Sathananthan's group described a one-pot synthesis of quinoline-appended quinazolinone derivatives from *o*-aminoacetophenones, cyclohexanediones and anthranilamides. The strategy features a Friedländer condensation between *o*-aminoacetophenones and cyclohexanediones, followed by imine formation between the intermediate and anthranilamide. Finally, nucleophilic amide N-attack on the imine provides the quinoline-fused dihydro-spiro-quinazolinones derivatives (Scheme 3.2.4).¹²



Scheme 3.2.4. One-pot synthesis of quinoline-appended quinazolinone derivatives.

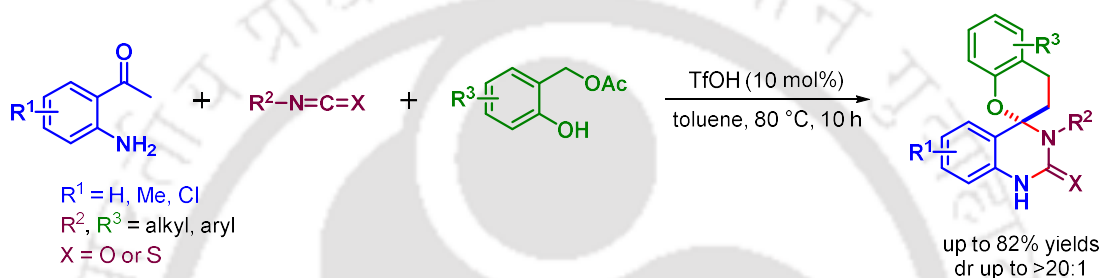
Xu's group reported a ZnCl_2 -catalyzed in situ cyclization-spiroannulation strategy to synthesize spiro-2,3-dihydrobenzofurans. The process involves a cyclization



Scheme 3.2.5. ZnCl_2 -catalyzed cyclization-spiroannulation strategy.

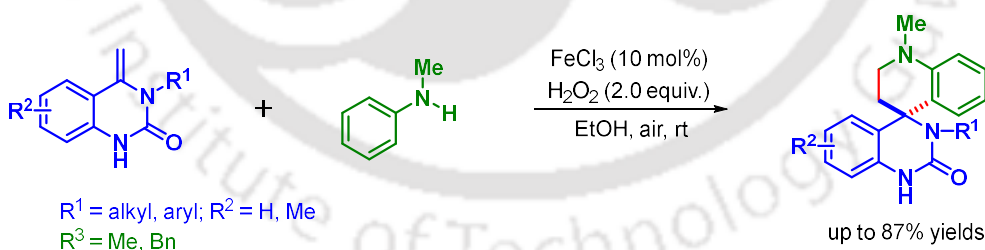
between *o*-aminoacetophenones and isocyanates, followed by a spiroannulation of the intermediate with 1,4-benzoquinones or quinone monoimines to successfully yield the spiro-heterocycles in moderate to good yields (Scheme 3.2.5).¹³

Ma's group developed a three-component domino double (4+2) annulation strategy for the synthesis of chroman-spiroquinazolin(thi)ones. The process involves the condensation reaction between aminoacetophenones and iso(thio)cyanates, followed by a hetero-Diels-Alder annulation with 2-hydroxybenzyl alcohol derivatives to afford the spirocyclic product in good yields (Scheme 3.2.6).¹⁴



Scheme 3.2.6. Domino double (4+2) annulation synthesis of chroman-spiroquinazolin(thi)ones.

The same group further developed a Fe(III)-catalyzed cross-dehydrogenative coupling (4+2) annulation of secondary anilines with quinazolinones to synthesize quinoline-spiroquinazolinones (Scheme 3.2.7).¹⁵



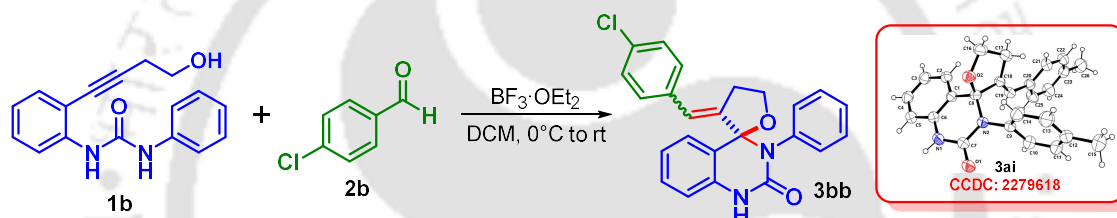
Scheme 3.2.7. Fe(III)-catalyzed cross-dehydrogenative coupling (4+2) annulation strategy.

3.3. Present Work

Although various methodologies have been developed for the synthesis of spiro-quinazolinones, the application of Prins cyclization in this context remains less explored.^{16a} However, recently our group introduced a method to synthesize spiro-

furan isoindolinones through a cascade alkynyl Prins–Ritter sequence, followed by an intramolecular oxycyclization step.^{16b} Building on this, we have developed a simple approach using TfOH to efficiently synthesize of spiro-furan quinazolinones.

Initially, a preliminary reaction was performed between 1-(2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-phenylurea (**1b**) and *p*-chlorobenzaldehyde (**2b**) in presence of $\text{BF}_3 \cdot \text{OEt}_2$ in DCM at 0 °C to room temperature (Table 3.4.1.1, entry 1). To our delight, a new compound was isolated in 86% yield in an *E/Z* ratio of 7:3. Spectroscopic evidence (^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR) and HRMS value revealed the product to be 3-(4-chlorobenzylidene)-3'-phenyl-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (**3bb**). The exact structure of the product was fully ascertained by single-crystal X-ray diffraction of one of its derivatives **3ai** (Scheme 3.3.1).



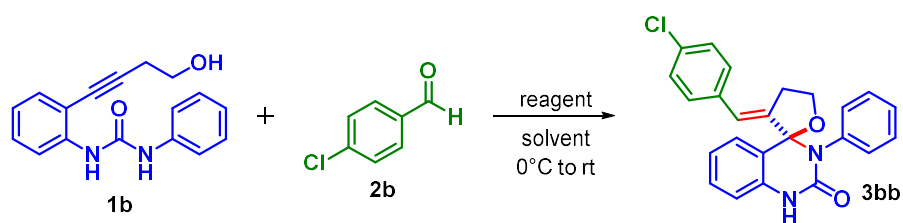
Scheme 3.3.1. Synthesis of spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one.

3.4. Results and Discussion

3.4.1. Optimization of the Reaction Conditions

Albeit the reaction endowed the desired spiro-furan quinazolinone product **3bb** within 2 h in a good yield of 86%, it gave a mixture of geometrical isomers in the ratio *E/Z* = 7:3. Hence, further optimization of the reaction parameters was tuned to enhance the selectivity and productivity of the reaction. Initially, we began our investigation by varying different reagents in place of $\text{BF}_3 \cdot \text{OEt}_2$. Gratifyingly, the reaction, when performed with 2.0 equiv. of TMSOTf, exclusively delivered *E*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one within 3 h in 80% yield (Table 3.4.1.1, entry 2). Under the influence of metal halides like FeCl_3 and InCl_3 , the reaction afforded the desired *E*-selective product in significantly low yields (Table 3.4.1.1, entries 3 and 4). Metal triflates also failed to show any remarkable effect on yield and time (Table 3.4.1.1, entries 5-7). Moreover, the reaction was screened in the presence of different

Table 3.4.1.1. Optimization of the reaction conditions



Entry ^a	Reagent	Equiv.	Solvent	Time (h)	Yield ^b (%)	E/Z ratio ^d
1	BF ₃ ·OEt ₂	2.0	DCM	2.0	86	7:3
2	TMSOTf	2.0	DCM	3.0	80	100:0
3	FeCl ₃	2.0	DCM	24	33	9:1
4	InCl ₃	0.3	DCM	24	20	100:0
5	Bi(OTf) ₃	0.3	DCM	24	32	100:0
6	In(OTf) ₃	0.3	DCM	24	24	100:0
7	Cu(OTf) ₂	0.3	DCM	24	18	100:0
8	<i>p</i> -TsOH·H ₂ O	2.0	DCM	24	– ^c	–
9	CSA	2.0	DCM	24	– ^c	–
10	TfOH	2.0	DCM	0.5	92	100:0
11	TfOH	1.5	DCM	4.0	89	100:0
12	TfOH	3.0	DCM	0.5	90	100:0
13	TfOH	2.0	DCE	0.5	88	100:0
14	TfOH	2.0	Toluene	8.0	29	100:0
15	TfOH	2.0	CH ₃ CN	2.0	43	100:0

^aReaction conditions: **1b** (0.2 mmol), **2b** (0.24 mmol), solvent (2.0 mL), 0 °C to rt, N₂ atmosphere. ^bIsolated yields. ^cNo reaction. ^dE/Z ratio was analyzed by crude ¹H NMR analysis.

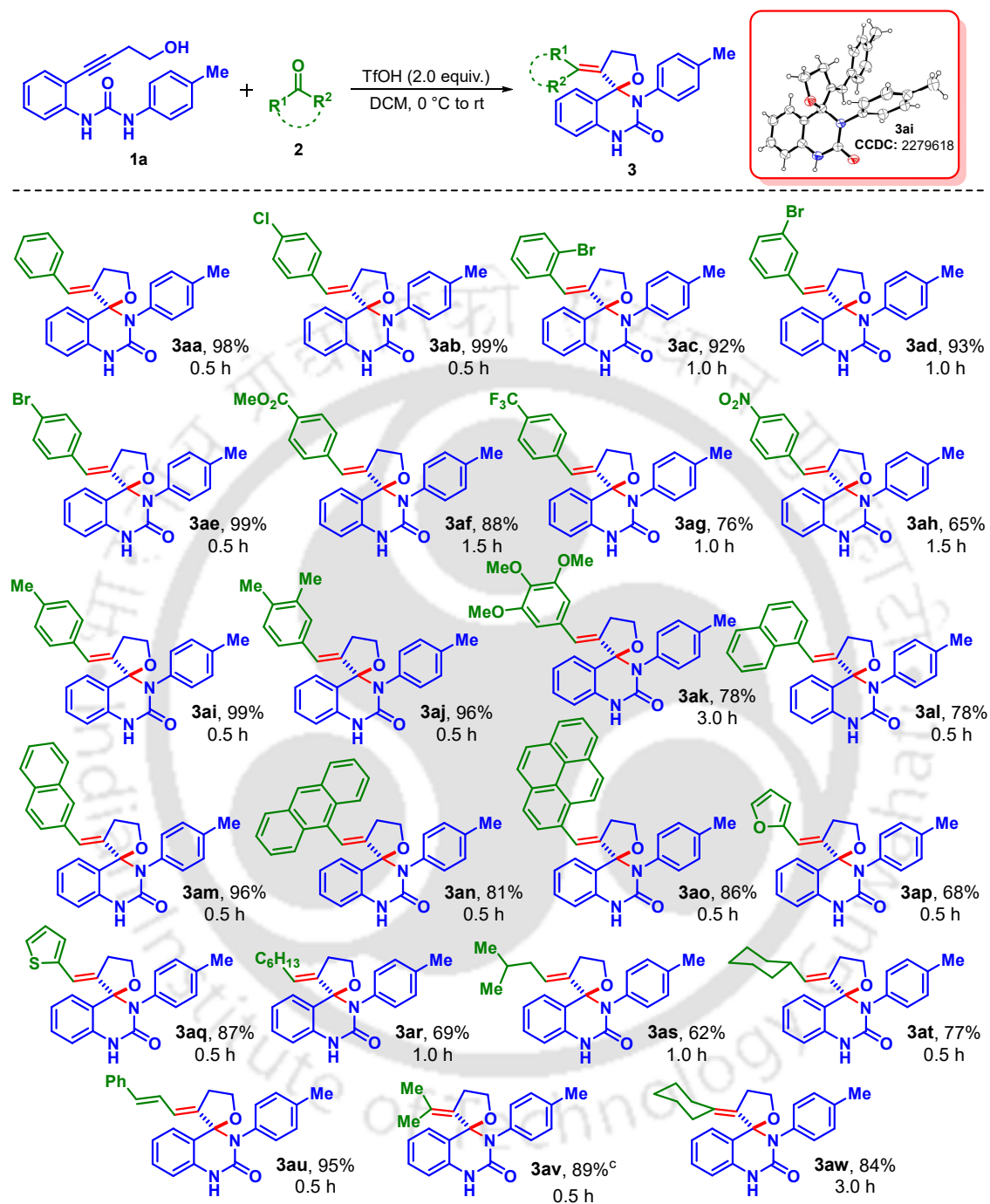
Brønsted acids as well. *p*-TsOH and CSA were found to be ineffective for the transformation (Table 3.4.1.1, entries 8 and 9). Nonetheless, the use of 2.0 equiv. of TfOH acid has exclusively resulted the *E*-selective product in an escalated yield of 92%, within 0.5 h of the reaction (Table 3.4.1.1, entry 10). Altering the stoichiometry of TfOH to 1.5 equiv. and 3.0 equiv. furnished the *E*-selective product in 89% and 90% yield, respectively (Table 3.4.1.1, entries 11 and 12). Furthermore, we explored the influence of solvents on the reaction outcome. In contrast to less efficacious solvents like toluene and acetonitrile (Table 3.4.1.1, entries 14 and 15), DCE delivered the *E*-selective product with an admirable yield of 88% (Table 3.4.1.1, entry 13). Finally, the

use of 2.0 equiv. of TfOH in DCM at 0 °C to room temperature are found to be the optimized conditions for this transformation.

3.4.2. Substrate Scope

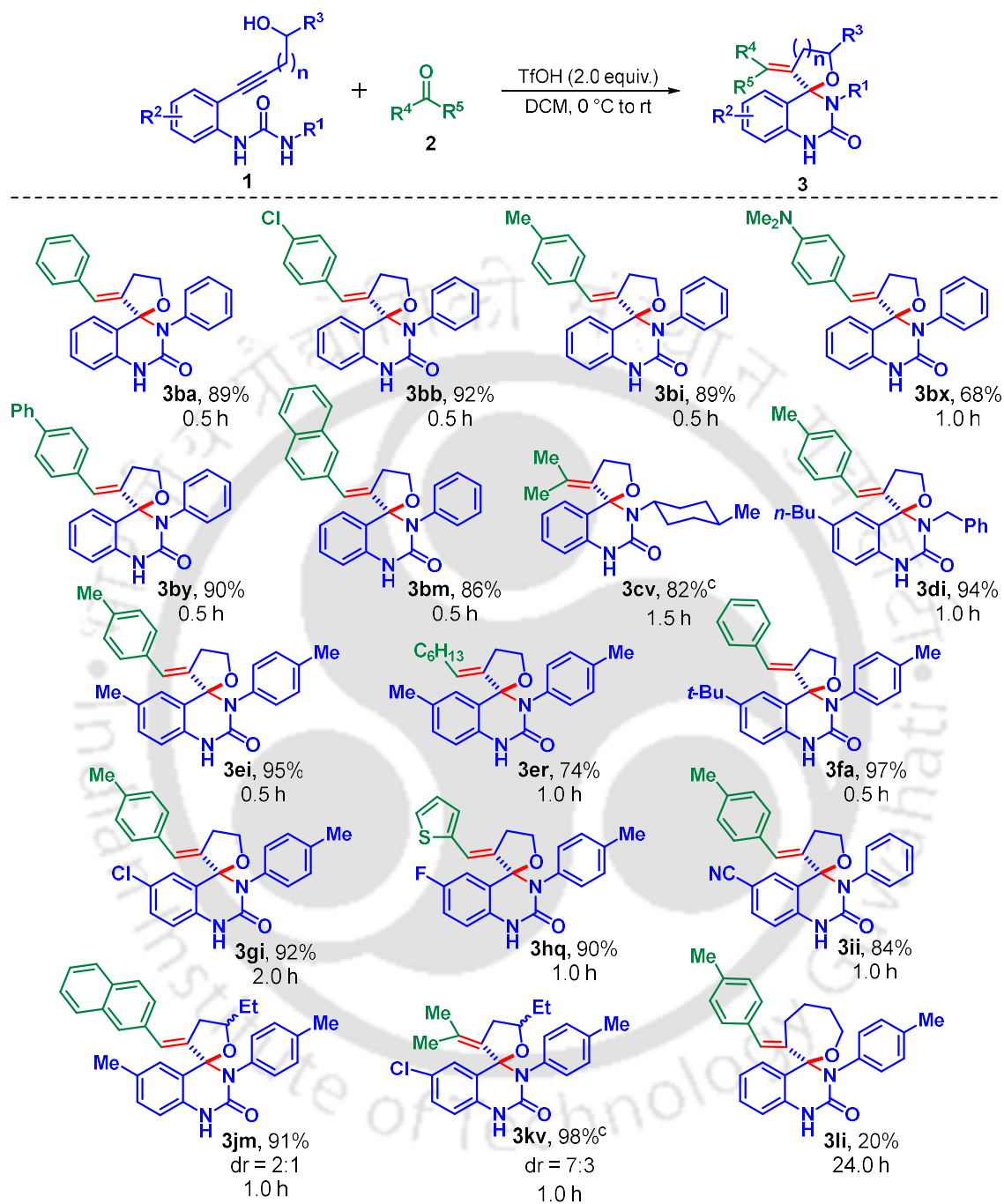
Intrigued by the outcome, the generality of the transformation was evaluated with alkynol substituted diphenyl urea **1a** and various aldehydes **2** (Scheme 3.4.2.1). Reaction of benzaldehyde (**2a**) with **1a** furnished the spiro-product **3aa** in an excellent yield of 98%. Benzaldehydes bearing weak electron-withdrawing groups such as *p*-Cl and *p*-Br, afforded the spirocycles **3ab** and **3ae**, respectively in 99% yields. To address the steric congestion in this transformation, bromine functionality at *o*- and *m*-positions of the benzaldehyde was introduced into the system. The products **3ac** and **3ad** obtained from *o*- and *m*-bromobenzaldehyde, respectively were in admirable yields of 92 and 93%. However, the transformation required some additional time to achieve the full conversion of the starting materials. Strong electron-withdrawing groups like -CO₂Me, -CF₃, and -NO₂ at the *para*-position of the benzaldehyde gave their respective products **3af**, **3ag** and **3ah** in moderate to good yields (65-88%). The current protocol was also screened for benzaldehyde with electron-donating groups. Weak electron-donating group (*p*-Me) showed similar result with 99% of the desired spirocycle **3ai**. Polysubstituted electron-donating benzaldehydes **2j** and **2k** resulted in the functionalized spirocycles **3aj** and **3ak** in 96 and 78% yields, respectively. The response of polyaromatic aldehydes towards the newly developed strategy was also investigated. β -naphthaldehyde (**2m**) proceeded more efficiently compared to α -naphthaldehyde (**2l**), providing 96% of the desired product **3am**. 9-Anthracenecarboxaldehyde (**2n**) and 1-pyrenecarboxaldehyde (**2o**) also advanced efficaciously affording the desired spirocycles in 81 and 86% yields, respectively. Heterocyclic aldehydes, such as furfural (**2p**) and 2-thiophenecarboxaldehyde (**2q**) also delivered their respective products in good to excellent yields. To further validate our protocol, the strategy was investigated with aliphatic aldehydes. Long chain aldehyde, heptanal (**2r**), furnished the desired product **3ar** in 69% yields, whereas isovaleraldehyde (**2s**) gave only 62% yield. Alicyclic aldehyde, cyclohexanecarboxaldehyde (**2t**), was also well tolerated in the transformation, with a

Scheme 3.4.2.1. Synthesis of spiro-furan quinazolinones.



^aReaction conditions: **1a** (0.4 mmol, 1.0 equiv.), **2** (0.48 mmol, 1.2 equiv.), TfOH (0.8 mmol, 2.0 equiv.), DCM (4 mL), 0 °C to rt, N₂ atmosphere. ^bIsolated yields. ^c2.0 Equiv. of **2v** used.

Scheme 3.4.2.2. Scope of functionalized alkynol substituted diphenyl urea.

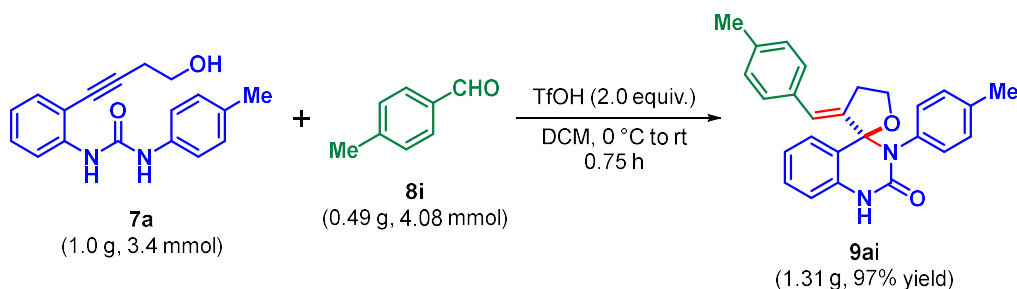


^aReaction conditions: **1** (0.4 mmol, 1.0 equiv.), **2** (0.48 mmol, 1.2 equiv.), TfOH (0.8 mmol, 2.0 equiv.), DCM (4 mL), 0 °C to rt, N₂ atmosphere. ^bIsolated yields. ^c2.0 Equiv. of **2v** used.

product yield of 62%. α,β -Unsaturated aldehyde, (*E*)-cinnamaldehyde (**2u**), advanced well under the reaction conditions, affording the product **3au** in 95% yield. The strategy was also expanded to encompass ketones. Acetone (**2v**) and cyclohexanone (**2w**) delivered the products **3av** and **3aw** in 89 and 84% yields, respectively.

The strategy was further investigated by altering the “R¹” group of the alkynol-substituted phenyl urea **1** (Scheme 3.4.2.2). Reaction of benzaldehyde with **1b** resulted in the product **3ba** with 89% yield. Electron-donating and electron-withdrawing benzaldehydes when reacted with **1b** exhibited similar reactivity affording the product in good to excellent yields (68-92%). Biphenyl-4-carboxaldehyde (**2y**) and β -naphthaldehyde (**2m**) also advanced efficaciously in the transformation. Incorporation of aliphatic substituents like 4-methylcyclohexyl, and benzyl into the “R¹” position resulted in the products **3cv** and **3di** in 82 and 94% yields, respectively. Variation of “R²” group of the alkynol-substituted diphenyl urea **1** with weak and bulky electron-donating substituents like methyl and *t*-butyl, gave the products **3ei**, **3er** and **3fa** in 74-97% yields. Similarly, electron-withdrawing substituents like chloro, fluoro and cyano in the “R²” position showered the products **3gi**, **3hq** and **3ii** in yields ranging from 84-92%. However, switching the alcohol functionality of **1** from primary to secondary alcohol furnished the products **3jm** and **3kv** with diastereomeric ratio of 2:1 and 7:3, respectively. Additionally, the protocol was utilized to synthesize spiro-oxepane quinazolinone scaffold **3li** with 20% yield.

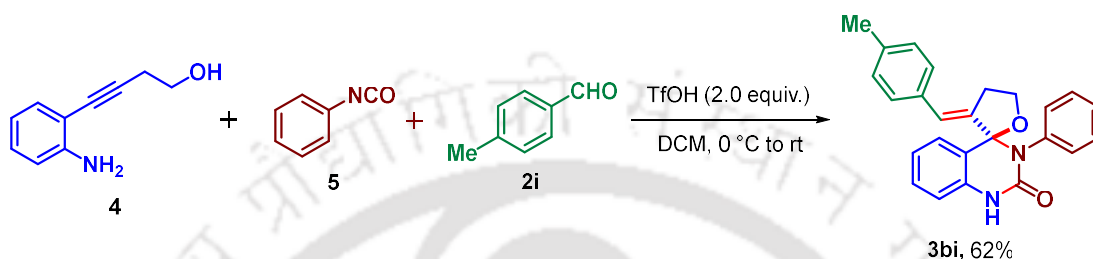
To demonstrate the scalability of this protocol, a scaleup synthesis was performed with 1-(2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea (**1a**) (1.0 g, 3.4 mmol) and *p*-tolualdehyde (**2i**) (0.49 g, 4.08 mmol). Under the standard reaction conditions, the spirocycle **3ai** was obtained in 97% yield (1.31 g) (Scheme 3.4.2.3).



Scheme 3.4.2.3. Scale-up experiment.

3.4.3. One-Pot Synthesis

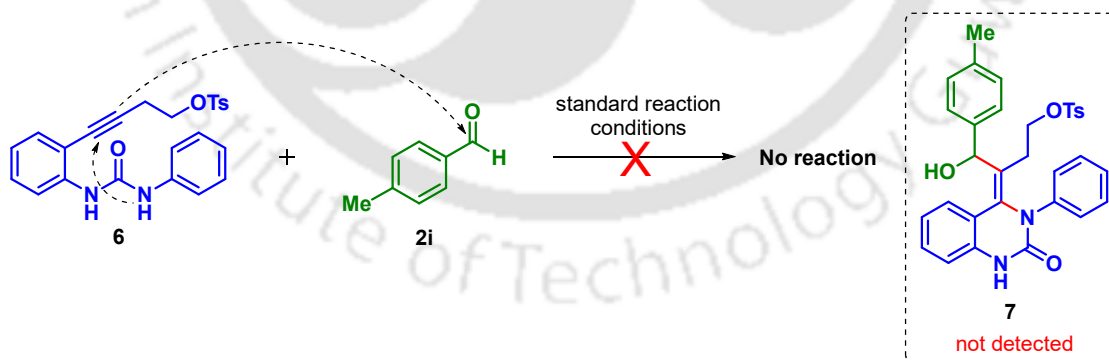
A one-pot three-component reaction was carried out with substituted alkynol **4**, phenyl isocyanate (**5**), and *p*-tolualdehyde (**2i**). Under the same set of reaction conditions, the spiro-furan quinazolinone product **3bi** was achieved in 62% yield (Scheme 3.4.3.1).



Scheme 3.4.3.1. One-pot synthesis of spiro-furan quinazolinone.

3.4.4. Control Experiment

A control experiment was performed to ascertain the mechanism of the transformation (Scheme 3.4.4.1). The reaction of tosyl-protected substituted alkynol **6** with *p*-tolualdehyde (**2i**) under the standard reaction conditions failed to produce any product. This observation indicates that the reaction initially proceeds *via* alkynyl Prins cyclization rather than the urea group attacking the alkyne to form intermediate **7**.

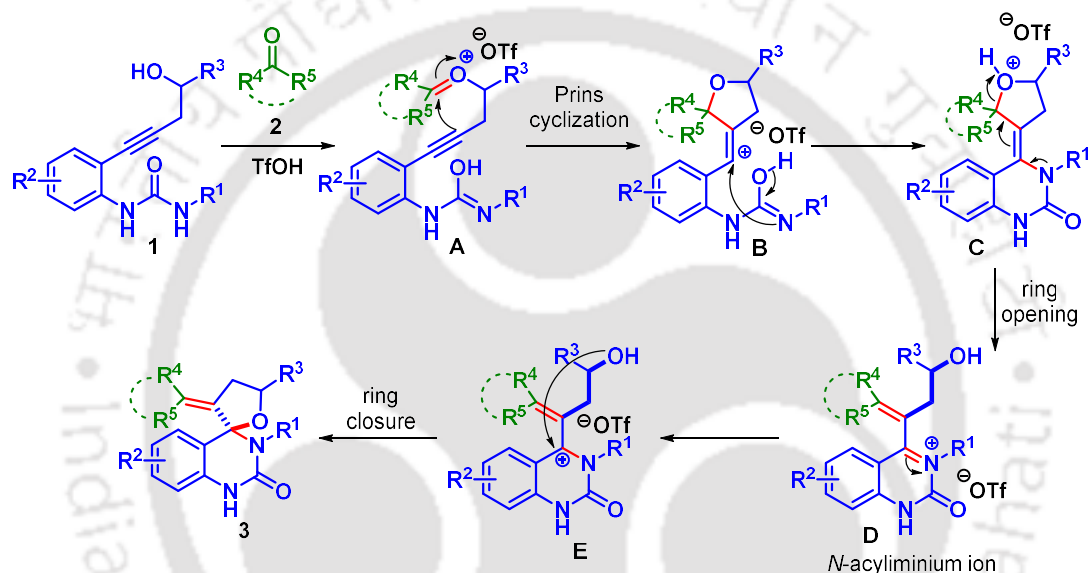


Scheme 3.4.4.1. Control experiment.

3.4.5. Plausible Mechanism

From the earlier reports and our experimental findings, a plausible mechanism has been delineated in Scheme 3.4.5.1. Triflic acid promoted alkynyl Prins cyclization

reaction of alkynol **1** and aldehyde **2** generates a dihydrofuran intermediate **B**. Concurrently, the urea moiety of **1** experience an amide-iminol tautomerization for a smooth nucleophilic addition to the dihydrofuran moiety for the formation of a dihydrofuran-substituted quinazolinone scaffold **C**. Subsequent ring opening of the protonated dihydrofuran moiety, through nitrogen's electron delocalization results in a new carbocation intermediate **E**. Carbocation **E** exists as an ion pair with the triflate anion, thus preventing the alkyl/aryl group from acquiring Z-orientation. This may be attributed to the strong interaction between the two groups. Finally, an

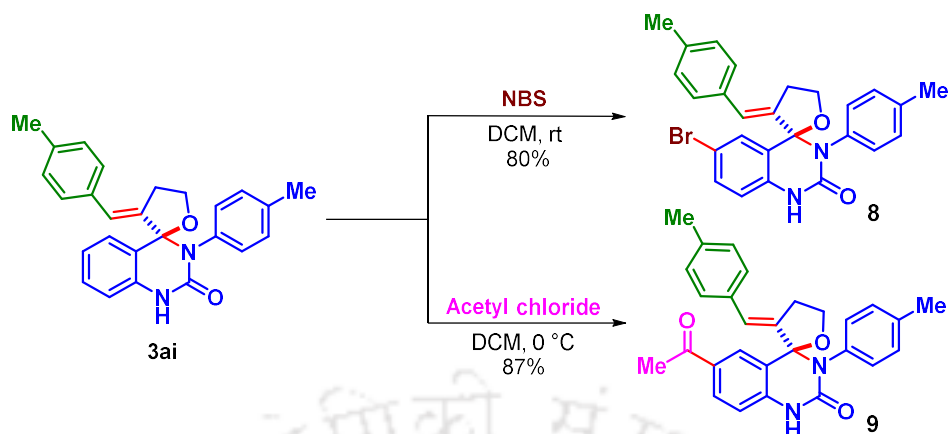


Scheme 3.4.5.1. Plausible mechanism for the synthesis of spiro-furan quinazolinones.

intramolecular nucleophilic attack of the hydroxy group on the electrophilic carbon of intermediate **E** results in the exclusive formation of *E*-spiro-furan quinazolinones **3**. In case of $\text{BF}_3 \cdot \text{OEt}_2$ and FeCl_3 , the formation of *E/Z*-mixture can be attributed to their smaller size and weaker ion pair interaction in comparison to the triflate anion.

3.4.6. Synthetic Transformation

To explore the utility of the spiro-furan quinazolinones, a few synthetic transformation reactions were carried out (Scheme 3.4.6.1). Spirocycle **3ai** when subjected to a bromination reaction with NBS in DCM resulted in the successful formation of its brominated derivative **8** in 80% yield. Subsequently, acetylation reaction of **3ai** afforded the acetylated spirocycle **9** in 87% yield.



Scheme 3.4.6.1. Synthetic transformations of spiro-furan quinazolinone **3ai**.

3.5. Conclusions

In conclusion, an effective strategy for the synthesis of spiro-heterocycles utilizing cascade alkynyl Prins cyclization has been demonstrated. This TfOH-promoted, metal-free protocol produces an easy access to a diverse functionalized spiro-furan quinazolinone scaffolds. The quinazolinone framework bears an exocyclic double bond and a urea functionality which may be useful in different fields of research. Moreover, late-stage modifications involve bromination and acetylation of the spiro-furan quinazolinone scaffold.

3.6. Experimental Section

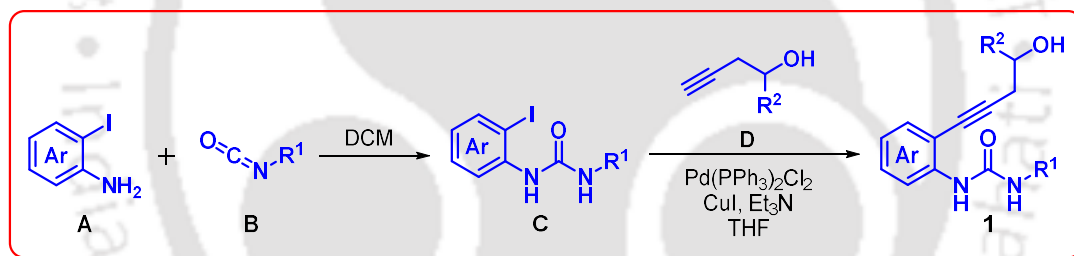
3.6.1. General Information

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 (500 and 400 MHz) or $^{13}\text{C}\{^1\text{H}\}$ (150, 125, and 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

Trifluoromethanesulfonic acid (reagent grade, 100 mL bottle) was purchased from Spectrochem and used without further purification. It is highly advisable to handle trifluoromethanesulfonic acid using glass(micro) syringes and steel needles. Disposable plastic syringes and needles should be avoided, as they may dissolve/melt in the presence of TfOH. After using triflic acid, two layers of PTFE tape were applied, followed by a layer of parafilm, to seal the bottle cap, and it was stored in the freezer at -5 °C.

To synthesize the starting materials **1j** and **1k**, homopropargyl alcohol derivative (5-hexyn-3-ol) used was directly purchased from Sigma-Aldrich. The starting material, 4-(2-aminophenyl)but-3-yn-1-ol (**4**) was synthesized according to a literature report, and the spectroscopic data of the compound is in good agreement with the literature data.¹⁷

3.6.2. General procedure for the synthesis of the starting materials 1a-1k:



To a solution of substituted 2-iodoaniline **A** (2.0 mmol, 1.0 equiv.) in DCM under N_2 atmosphere, substituted phenyl isocyanate **B** (2.2 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was stirred overnight at room temperature to obtain a white precipitate, which was then filtered and washed with n-hexane to obtain a substituted 1,3-diphenyl urea **C**.

To a mixture of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.04 mmol, 0.04 equiv.), CuI (0.02 mmol, 0.02 equiv.) and iodo substituted 1,3-diphenyl urea derivatives **C** (1.0 mmol, 1.0 equiv.) in dry THF (5.0 mL) under N_2 atmosphere, triethylamine (5.0 mmol, 5.0 equiv.) was added. The reaction mixture was stirred for 10 minutes at room temperature, after which substituted homo propargylic alcohol **D** (1.2 mmol, 1.2 equiv.) was added dropwise over a period of 5 minutes. The reaction mixture was stirred for 3.0 hours (monitored

by TLC analysis) before filtering through a pad of celite. The solids were washed with ethyl acetate, and the combined filtrates were concentrated in a rotary evaporator. The crude product was then purified by column chromatography to provide the corresponding product **1**.

3.6.3. General procedure for the synthesis of compounds **3aa–3aw**, **3ba**, **3bb**, **3bi**, **3bx**, **3by**, **3bm**, **3cv**, **3di**, **3ei**, **3er**, **3fa**, **3gi**, **3hq**, **3ii**, **3jm**, **3kv** and **3li**:

To an ice-cold suspension of alkynol substituted diphenyl urea **1** (0.4 mmol, 1.0 equiv.) and aldehyde or ketone **2** (0.48 mmol, 1.2 equiv.) in DCM (3.0 mL), triflic acid (0.8 mmol, 2.0 equiv.) was added under N₂ atmosphere. The reaction was continued to stir at room temperature till all the starting material was consumed, as evident by TLC. It was then treated with saturated NaHCO₃ solution, and the organic layer was extracted with DCM (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product.

3.6.4. Experimental procedure for scale-up synthesis of compound **3ai**:

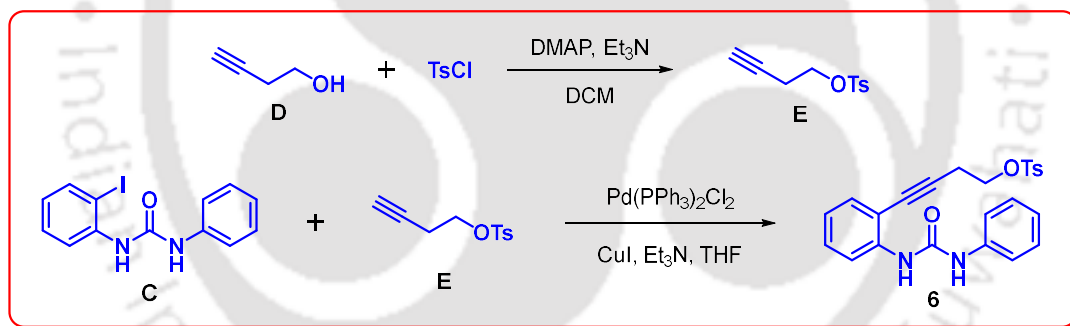
To an ice-cold suspension of 1-(2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea (**1a**) (1.0 g, 3.4 mmol, 1.0 equiv.) and *p*-tolualdehyde (**2i**) (490 mg, 4.08 mmol, 1.2 equiv.) in DCM (15.0 mL), triflic acid (0.6 mL, 6.8 mmol, 2.0 equiv.) was added slowly under N₂ atmosphere. The reaction was continued to stir for 0.75 h at room temperature, and the progress of the reaction was monitored by TLC. It was then treated with saturated NaHCO₃ solution, and the organic layer was extracted with DCM (2 x 30 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **3ai** as a white solid in 97% yield (1.31 g).

3.6.5. Experimental procedure for one-pot strategy:

To a solution of 4-(2-aminophenyl)but-3-yn-1-ol (**4**) (161 mg, 1.0 mmol, 1.0 equiv.) in DCM (3 mL), phenyl isocyanate (**5**) (0.12 mL, 1.1 mmol, 1.1 equiv.) was added under

N₂ atmosphere. The reaction was stirred at room temperature for 3 h, and the progress of the reaction was monitored by TLC. Meanwhile, a white solid precipitate started to form in the reaction mixture, which indicated the formation of the desired diphenyl urea compound. When all the alkynol substituted aniline was consumed, *p*-tolualdehyde (**2i**) (0.14 mL, 1.2 mmol, 1.2 equiv.) was introduced into the system, along with some more DCM solvent (3.0 mL). The reaction was then cooled to 0 °C and triflic acid (0.18 mL, 2.0 mmol, 2.0 equiv.) was added slowly. The reaction mixture was further stirred for 8 h at room temperature before quenching with a saturated NaHCO₃ solution. The organic layer was extracted with DCM (2 x 10 mL), and the combined organic layers were further washed with brine and dried over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **3bi** in 62% yield (237 mg).

3.6.6. Experimental procedure for the synthesis of compound 6:



To an ice-cold solution of 3-butyn-1-ol (**D**) (2.0 mmol, 1.0 equiv.), DMAP (0.2 mmol, 0.1 equiv.) and Et₃N (2.4 mmol, 1.2 equiv.) in DCM under N₂ atmosphere, tosyl chloride (2.4 mmol, 1.2 equiv.) in DCM was added dropwise over a period of 5 minutes. The reaction was allowed to stir at room temperature for 2 h and then quenched with saturated NH₄Cl solution. The organic layer was extracted with DCM (2 x 10 mL). The combined organic layers were further washed with brine, dried over anhydrous Na₂SO₄, and concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide product **E** in 98% yield.

To a mixture of $\text{Pd(PPh}_3)_2\text{Cl}_2$ (0.04 mmol, 0.04 equiv.), CuI (0.02 mmol, 0.02 equiv.) and 1-(2-iodophenyl)-3-phenylurea (**C**) (1.0 mmol, 1.0 equiv.) in dry THF (5.0 mL) under N_2 atmosphere, triethylamine (5.0 mmol, 5.0 equiv.) was added. The reaction mixture was stirred for 10 minutes at room temperature, after which tosyl protected homo propargylic alcohol **E** (1.2 mmol, 1.2 equiv.) was added dropwise over a period of 5 minutes. The reaction mixture was stirred for 5.0 hours (monitored by TLC analysis) before filtering through a pad of celite. The solids were washed with ethyl acetate, and the combined filtrates were concentrated in a rotary evaporator. The crude product was then purified by column chromatography to provide the corresponding product **6** in 65% yield (282 mg).

3.6.7. Experimental procedure for control experiment:

To an ice-cold suspension of 4-(2-(3-phenylureido)phenyl)but-3-yn-1-yl 4-methylbenzenesulfonate (**6**) (174 mg, 0.4 mmol, 1.0 equiv.) and *p*-tolualdehyde (**2i**) (58 mg, 0.48 mmol, 1.2 equiv.) in DCM (5.0 mL), triflic acid (0.07 mL, 0.8 mmol, 2.0 equiv.) was added slowly under N_2 atmosphere. The reaction was continued to stir for 5 h at room temperature, and the progress of the reaction was monitored by TLC. Although no new spot was formed, to collect the starting material, the reaction mixture was treated with saturated NaHCO_3 solution, and the organic layer was extracted with DCM (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na_2SO_4 . The organic phase was concentrated in a rotary evaporator which was then subjected to column chromatography over silica gel to get the unreacted starting material **6** in 87% yield.

3.6.8. Experimental procedure for the synthesis of compound **8**:¹⁸

To an ice-cold solution of spiro-furan quinazolinone derivative **3ai** (159 mg, 0.4 mmol, 1.0 equiv.) in DCM (3.0 mL), N-Bromosuccinimide (NBS) (85 mg, 0.48 mmol, 1.2 equiv.) was added portion wise over a period of 5 minutes. The reaction was stirred for 1.0 hour at room temperature, and the progress of the reaction was monitored by TLC. It was then treated with saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution, and the organic layer was extracted with DCM (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na_2SO_4 . The organic phase was

concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **8** as a white solid in 80% yield (152 mg).

3.6.9. Experimental procedure for the synthesis of compound **9**:¹⁹

To an ice-cold mixture of aluminum trichloride (134 mg, 1.0 mmol, 2.5 equiv.) in DCM (3.0 mL), spiro-furan quinazolinone derivative **3ai** (159 mg, 0.4 mmol, 1.0 equiv.) was added slowly under N₂ atmosphere at 0 °C, followed by the dropwise addition of acetyl chloride (0.06 mL, 0.8 mmol, 2.0 equiv.). The reaction mixture was stirred at 0 °C for about an hour, and the progress of the reaction was monitored by TLC. Upon completion of the reaction, it was quenched with ice-cold saturated NaHCO₃ solution, and the organic layer was extracted with DCM (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **9** as a white solid in 87% yield (153 mg).

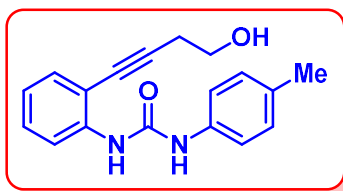
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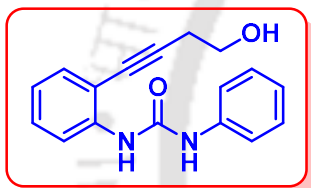
3.8. Characterization Data

1-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea (1a):

White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 160–162 °C.

Yield 277 mg, 94%. ^1H NMR (400 MHz, CDCl_3) δ 8.25 (dd, $J = 8.7, 1.1$ Hz, 1H), 7.98 (s, 1H), 7.58 (s, 1H), 7.25–7.22 (m, 4H), 7.03 (d, $J = 8.0$ Hz, 2H), 6.89 (td, $J = 7.6, 1.2$ Hz, 1H),

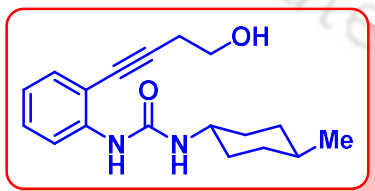
3.84 (t, $J = 5.6$ Hz, 2H), 2.98 (s, 1H), 2.61 (t, $J = 5.7$ Hz, 2H), 2.25 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 153.2, 140.9, 135.9, 133.2, 130.1, 129.6, 129.3, 121.7, 120.5, 118.0, 111.6, 94.9, 78.9, 61.5, 23.9, 20.8. IR (KBr, neat) ν 3317, 3050, 2922, 1661, 1511, 1445, 1293, 1201, 1040, 751, 735, 507 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_2$ ($M + \text{H}$) $^+$ 295.1441, found 295.1440.

1-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)-3-phenylurea (1b):

White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 136–138 °C.

Yield 258 mg, 92%. ^1H NMR (400 MHz, CDCl_3) δ 8.24 (dd, $J = 8.7, 1.5$ Hz, 1H), 8.07 (s, 1H), 7.83 (d, $J = 5.6$ Hz, 1H), 7.37 (d, $J = 7.9$ Hz, 2H), 7.25–7.20 (m, 4H), 6.99 (t, $J = 7.3$ Hz, 1H),

6.88 (t, $J = 7.5$ Hz, 1H), 3.89–3.84 (m, 2H), 3.22–3.13 (m, 1H), 2.63 (td, $J = 5.7, 1.7$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 153.0, 140.8, 138.7, 130.0, 129.2, 129.0, 123.2, 121.7, 119.8, 117.9, 111.7, 95.2, 78.9, 61.5, 23.9. IR (KBr, neat) ν 3330, 3057, 2887, 1677, 1539, 1447, 1305, 1249, 1044, 752, 593 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_2$ ($M + \text{H}$) $^+$ 281.1285, found 281.1282.

1-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)-3-(4-methylcyclohexyl)urea (1c):

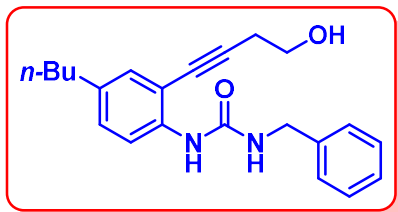
White solid; R_f (Hexane:EtOAc, 7:3) 0.5; mp 139–141 °C.

Yield 280 mg, 93%. ^1H NMR (400 MHz, CDCl_3) δ 8.13 (d, $J = 8.3$ Hz, 1H), 7.78 (s, 1H), 7.26–7.19 (m, 2H), 6.86 (t, $J = 7.5$ Hz, 1H), 5.65 (s, 1H), 3.86 (q, $J = 5.6$ Hz, 2H),

3.72 (s, 1H), 3.55–3.45 (m, 1H), 2.68 (t, $J = 5.7$ Hz, 2H), 1.93 (d, $J = 10.4$ Hz, 2H), 1.60 (d, $J = 12.3$ Hz, 2H), 1.25–1.17 (m, 1H), 1.06 (qd, $J = 12.4, 3.1$ Hz, 2H), 0.95 (t, $J = 12.0$ Hz, 2H), 0.81 (d, $J = 6.2$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 155.1, 141.4, 130.4, 129.1, 121.3, 118.1, 111.6, 94.9, 78.9, 61.3, 49.1, 33.9, 33.6, 31.9, 24.0, 22.2. IR (KBr, neat) ν 3332,

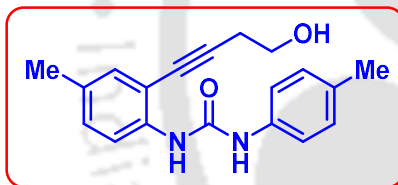
2926, 2850, 1659, 1547, 1448, 1306, 1217, 1042, 752, 542 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 301.1911, found 301.1916.

1-Benzyl-3-(4-butyl-2-(4-hydroxybut-1-yn-1-yl)phenyl)urea (1d):



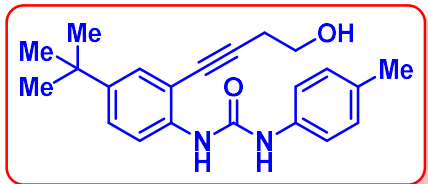
White solid; R_f (Hexane:EtOAc, 7:3) 0.5; mp 100–102 °C. Yield 316 mg, 90%. ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, $J = 8.4$ Hz, 1H), 7.64 (s, 1H), 7.29–7.18 (m, 5H), 7.09 (d, $J = 2.1$ Hz, 1H), 7.04 (dd, $J = 8.5, 2.2$ Hz, 1H), 5.87 (t, $J = 6.0$ Hz, 1H), 4.36 (d, $J = 5.7$ Hz, 2H), 3.78 (q, $J = 5.7$ Hz, 2H), 3.11 (t, $J = 6.2$ Hz, 1H), 2.62 (t, $J = 5.7$ Hz, 2H), 2.48 (t, $J = 7.7$ Hz, 2H), 1.56–1.49 (m, 2H), 1.36–1.26 (m, 2H), 0.90 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 156.0, 139.2, 138.7, 136.5, 130.3, 129.3, 128.5, 127.3, 127.1, 118.8, 112.3, 94.4, 79.0, 61.2, 43.9, 34.7, 33.5, 23.9, 22.2, 13.9. IR (KBr, neat) ν 3329, 3032, 2956, 2931, 2860, 1661, 1550, 1522, 1420, 1301, 1050, 697 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 351.2067, found 351.2071.

1-(2-(4-Hydroxybut-1-yn-1-yl)-5-methylphenyl)-3-(*p*-tolyl)urea (1e):



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 97–99 °C. Yield 299 mg, 97%. ^1H NMR (400 MHz, CDCl_3) δ 8.08 (d, $J = 9.1$ Hz, 1H), 7.84 (s, 1H), 7.49 (s, 1H), 7.24 (d, $J = 8.4$ Hz, 2H), 7.05–7.03 (m, 4H), 3.83 (q, $J = 5.8$ Hz, 2H), 3.01 (t, $J = 6.6$ Hz, 1H), 2.60 (t, $J = 5.8$ Hz, 2H), 2.26 (s, 3H), 2.21 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.2, 138.4, 136.0, 133.1, 131.3, 130.6, 130.0, 129.6, 120.5, 118.3, 111.8, 94.4, 78.9, 61.5, 23.9, 20.8, 20.5. IR (KBr, neat) ν 3317, 2921, 1660, 1509, 1291, 1200, 1040, 815, 734, 507 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 309.1598, found 309.1598.

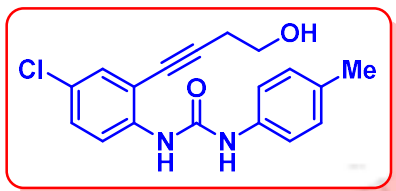
1-(4-(tert-Butyl)-2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea (1f):



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 117–119 °C. Yield 308 mg, 88%. ^1H NMR (400 MHz, CDCl_3) δ 8.00 (d, $J = 8.6$ Hz, 1H), 7.84 (s, 1H), 7.61 (s, 1H), 7.19–7.13 (m, 4H), 6.91 (d, $J = 7.9$ Hz, 2H), 3.72 (t, $J = 5.8$ Hz, 2H), 3.41 (s, 1H), 2.50 (t, $J = 5.8$ Hz, 2H), 2.14 (s, 3H), 1.16 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.5, 144.7, 138.2, 135.9, 133.0, 129.5, 127.1, 126.3,

120.4, 118.1, 111.7, 94.3, 79.2, 61.3, 34.1, 31.3, 23.9, 20.8. IR (KBr, neat) ν 3323, 2958, 1664, 1509, 1289, 1202, 1042, 817, 734, 507 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}_2$ ($M + H$)⁺ 351.2067, found 351.2075.

1-(5-Chloro-2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea (1g):



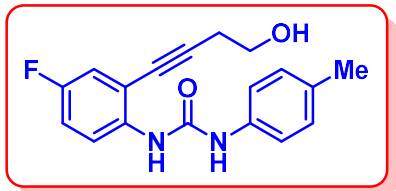
White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 176–178 °C. Yield 312 mg, 95%. ^1H NMR (400 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.27–8.21 (m, 3H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.22–7.16 (m, 2H), 7.04 (d, $J = 8.3$ Hz, 2H), 4.84 (s, 1H), 3.88–3.83 (m, 2H), 2.69–2.65 (m, 2H), 2.26 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 152.7, 139.8, 136.3, 132.3, 129.7, 129.3, 128.9, 125.9, 119.3, 119.1, 113.0, 96.8, 77.5, 60.7, 23.9, 20.7. IR (KBr, neat) ν 3300, 2917, 1639, 1598, 1546, 1511, 1402, 1292, 1210, 1040, 816, 505 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{18}\text{ClN}_2\text{O}_2$ ($M + H$)⁺ 329.1051, found 329.1054.

1-(5-Cyano-2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea (1h):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 175–177 °C. Yield 259 mg, 85%. ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.58 (dd, $J = 20.5, 5.5$ Hz, 2H), 8.44 (t, $J = 7.5$ Hz, 1H), 7.48–7.41 (m, 4H), 7.23 (q, $J = 7.2$ Hz, 2H), 6.97 (q, $J = 6.9$ Hz, 1H), 3.86 (q, $J = 5.9$ Hz, 2H), 3.72 (s, 1H), 2.68 (q, $J = 5.8$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 152.0, 145.0, 138.6, 133.5, 132.6, 128.8, 123.0, 119.1, 118.7, 117.6, 112.1, 104.0, 98.3, 60.6, 24.0. IR (KBr, neat) ν 3325, 2944, 2887, 2226, 1713, 1553, 1520, 1307, 1250, 1197, 1041, 751, 694 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_3\text{O}_2$ ($M + H$)⁺ 306.1237, found 306.1237.

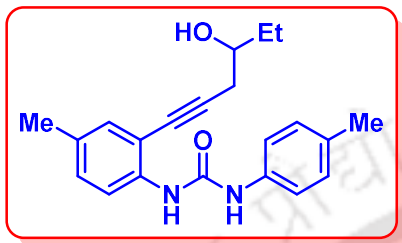
1-(4-Fluoro-2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea (1i):



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 179–181 °C. Yield 281 mg, 90%. ^1H NMR (400 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.32–8.26 (m, 1H), 8.19 (dd, $J = 8.8, 5.2$ Hz, 1H), 8.12 (s, 1H), 7.29 (d, $J = 8.2$ Hz, 2H), 7.01 (d, $J = 8.1$ Hz, 2H), 6.93–6.87 (m, 2H), 5.09 (s, 1H), 3.81 (q, $J = 5.8$ Hz, 2H), 2.64 (t, $J = 5.5$, 2H), 2.22 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 156.9 (d, $J = 239.3$),

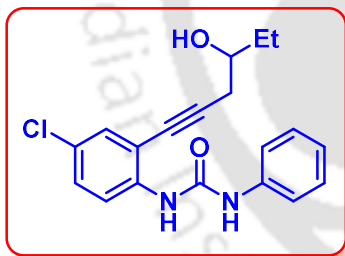
152.8, 137.5, 136.7, 132.0, 129.2, 119.44 (d, $J = 8.2$ Hz), 119.1, 116.4 (d, $J = 3.4$ Hz), 116.2, 115.6 (d, $J = 25.3$ Hz), 112.8 (d, $J = 8.8$ Hz), 96.77, 60.6, 24.0, 20.6. ^{19}F NMR (470 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -124.5. IR (KBr, neat) ν 3307, 2924, 1674, 1605, 1537, 1427, 1167, 806, 688, 507 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{18}\text{FN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 313.1347, found 313.1356.

1-(2-(4-Hydroxyhex-1-yn-1-yl)-5-methylphenyl)-3-(*p*-tolyl)urea (1j):



White solid; R_f (Hexane:EtOAc, 7:3) 0.5; mp 134–136 °C. Yield 303 mg, 90%. ^1H NMR (500 MHz, CDCl_3) δ 8.01 (d, $J = 8.3$ Hz, 1H), 7.90 (s, 1H), 7.62 (s, 1H), 7.14 (d, $J = 7.8$ Hz, 2H), 6.90 (d, $J = 6.7$ Hz, 4H), 3.67 (s, 1H), 2.84 (s, 1H), 2.52 (dd, $J = 17.1, 4.0$ Hz, 1H), 2.33 (dd, $J = 17.0, 6.7$ Hz, 1H), 2.13 (s, 3H), 2.08 (s, 3H), 1.57–1.43 (m, 2H), 0.85 (t, $J = 7.4$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.1, 138.7, 136.3, 132.4, 130.9, 130.1, 129.8, 129.5, 119.6, 117.7, 111.6, 94.3, 79.3, 72.7, 29.3, 27.9, 20.7, 20.5, 10.3. IR (KBr, neat) ν 3316, 2969, 2923, 1662, 1509, 1292, 1198, 816, 508 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 337.1911, found 337.1912.

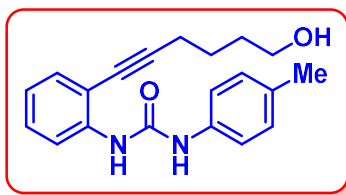
1-(5-Chloro-2-(4-hydroxyhex-1-yn-1-yl)phenyl)-3-phenylurea (1k):



White solid; R_f (Hexane:EtOAc, 7:3) 0.5; mp 163–165 °C. Yield 329 mg, 96%. ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.53 (s, 1H), 8.41 (s, 1H), 8.24 (dd, $J = 8.8, 3.5$ Hz, 1H), 7.44–7.42 (m, 2H), 7.23–7.19 (m, 2H), 7.18–7.13 (m, 2H), 6.95–6.92 (m, 1H), 5.19–5.17 (m, 1H), 3.84–3.78 (m, 1H), 2.72 (dt, $J = 17.1, 3.9$ Hz, 1H), 2.54–2.48 (m, 1H), 1.71–1.63 (m, 1H), 1.62–1.53 (m, 1H), 0.95 (td, $J = 7.1, 3.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 152.4, 140.0, 139.2, 129.2, 128.75, 128.73, 125.7, 122.4, 118.7, 118.6, 112.9, 96.8, 77.8, 71.9, 29.1, 27.8, 10.3. IR (KBr, neat) ν 3328, 2960, 2928, 1692, 1601, 1549, 1524, 1499, 1306, 1209, 749, 692 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{20}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 343.1208, found 343.1211.

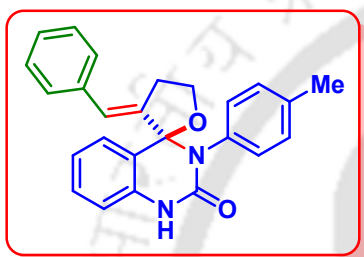
1-(2-(6-hydroxyhex-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea (1l):

White semi-solid; R_f (Hexane:EtOAc, 3:2) 0.4. Yield 319 mg, 99%. ^1H NMR (400 MHz, CDCl_3) δ 8.60–8.53 (m, 1H), 8.23 (d, $J = 8.3$ Hz, 1H), 7.76 (d, $J = 6.7$ Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.30 (dd, $J = 7.7, 1.5$ Hz, 1H), 7.23 (t, $J = 7.8$ Hz, 1H), 7.08 (d, $J = 8.1$ Hz,



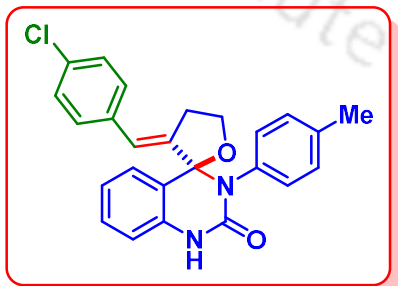
2H), 6.90 (td, $J = 7.6, 1.2$ Hz, 1H), 3.93 (s, 1H), 3.75 (t, $J = 5.6$ Hz, 2H), 2.51 (t, $J = 6.3$ Hz, 2H), 2.28 (s, 3H), 1.81–1.69 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 153.0, 140.4, 136.4, 132.4, 131.4, 129.3, 128.6, 121.6, 120.0, 118.7, 112.1, 96.9, 61.6, 31.2, 24.8, 20.7, 19.2. IR (KBr, neat) ν 3330, 2934, 1665, 1533, 1513, 1446, 1297, 1249, 1208, 1055, 817, 752 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2$ ($M + H$) $^+$ 323.1754, found 323.1754.

(E)-3-Benzylidene-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3aa):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 136–138 °C. Yield 150 mg, 98%. ^1H NMR (500 MHz, CDCl_3) δ 8.77–8.56 (m, 1H), 7.36 (s, 1H), 7.25 (t, $J = 7.6$ Hz, 2H), 7.18–7.13 (m, 3H), 7.07 (d, $J = 7.6$ Hz, 2H), 7.04 (d, $J = 7.8$ Hz, 1H), 7.01–7.00 (m, 1H), 6.96 (s, 1H), 6.89 (t, $J = 7.5$ Hz, 1H), 6.71 (d, $J = 8.0$ Hz, 1H), 6.42 (t, $J = 2.6$ Hz, 1H), 3.81–3.74 (m, 2H), 2.73–2.67 (m, 1H), 2.29 (s, 3H), 2.18–2.11 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.6, 143.8, 137.5, 136.6, 135.7, 135.5, 131.5, 129.4, 129.2, 128.5, 128.47, 128.41, 127.5, 127.3, 123.1, 122.0, 114.3, 99.2, 67.1, 31.3, 21.3. IR (KBr, neat) ν 3212, 3055, 2980, 1671, 1601, 1402, 1264, 1038, 731, 509 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{23}\text{N}_2\text{O}_2$ ($M + H$) $^+$ 383.1754, found 383.1759.

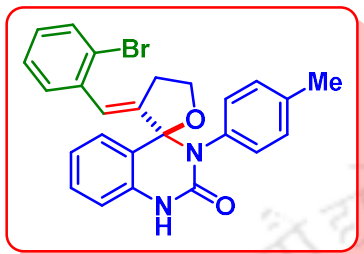
(E)-3-(4-Chlorobenzylidene)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3ab):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 136–138 °C. Yield 165 mg, 99%. ^1H NMR (400 MHz, CDCl_3) δ 8.60 (s, 1H), 7.43 (s, 1H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.23 (d, $J = 7.2$ Hz, 2H), 7.11–7.06 (m, 4H), 6.97 (t, $J = 7.6$ Hz, 2H), 6.80 (d, $J = 7.9$ Hz, 1H), 6.45 (s, 1H), 3.91–3.82 (m, 2H), 2.77–2.71 (m, 1H), 2.37 (s, 3H), 2.24–2.15 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.4, 144.6, 137.6, 135.6, 135.5, 135.0, 133.3, 131.4, 129.7, 129.6, 129.2, 128.7, 127.3, 127.2, 122.9, 122.1, 114.3, 99.2, 67.1, 31.3, 21.3. IR

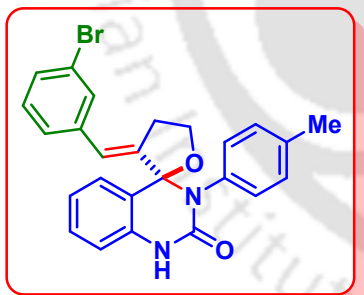
(KBr, neat) ν 3237, 3060, 2919, 1675, 1602, 1493, 1403, 1040, 754, 514 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{22}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 417.1364, found 417.1360.

(E)-3-(2-Bromobenzylidene)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazoli-n]-2'(3'H)-one (3ac):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 114–116 °C. Yield 170 mg, 92%. ^1H NMR (500 MHz, CDCl_3) δ 8.43 (s, 1H), 7.59 (dd, J = 8.0, 1.2 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.33–7.27 (m, 4H), 7.20–7.12 (m, 3H), 7.06 (t, J = 7.6 Hz, 1H), 6.94 (dd, J = 7.6, 1.7 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.72 (t, J = 2.6 Hz, 1H), 3.94–3.90 (m, 1H), 3.84–3.79 (m, 1H), 2.60–2.55 (m, 1H), 2.44 (s, 3H), 2.14–2.06 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 152.5, 145.5, 137.7, 136.9, 135.7, 135.6, 132.7, 131.9, 131.4, 129.6, 129.5, 129.4, 129.2, 128.9, 128.1, 127.7, 127.2, 124.4, 122.6, 122.0, 114.2, 98.5, 66.6, 31.0, 21.3. IR (KBr, neat) ν 3214, 3057, 2917, 1671, 1600, 1398, 1263, 1033, 731, 508 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{22}\text{BrN}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 461.0859, found 461.0858.

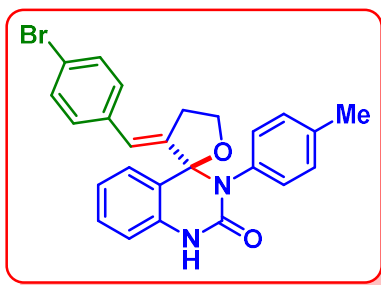
(E)-3-(3-Bromobenzylidene)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazoli-n]-2'(3'H)-one (3ad):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 209–211 °C. Yield 172 mg, 93%. ^1H NMR (400 MHz, CDCl_3) δ 8.46 (s, 1H), 7.43 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.29–7.23 (m, 3H), 7.19 (t, J = 7.8 Hz, 1H), 7.10–7.05 (m, 3H), 7.00–6.96 (m, 2H), 6.80 (d, J = 8.0 Hz, 1H), 6.43 (t, J = 2.7 Hz, 1H), 3.9–3.82 (m, 2H), 2.81–2.73 (m, 1H), 2.38 (s, 3H), 2.28–2.19 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.4, 145.6, 138.7, 137.7, 135.6, 135.4, 131.4, 131.2, 130.4, 130.0, 129.6, 129.2, 127.3, 127.1, 127.0, 122.9, 122.7, 122.1, 114.3, 99.2, 67.0, 31.3, 21.3. IR (KBr, neat) ν 3214, 3058, 2919, 1668, 1600, 1400, 1267, 1033, 751, 558, 507 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{22}\text{BrN}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 461.0859, found 461.0857.

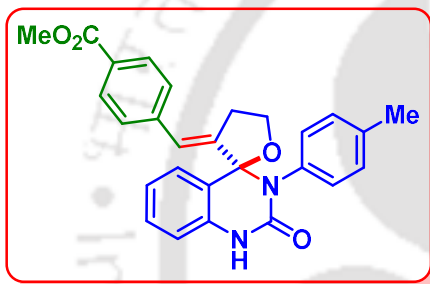
(E)-3-(4-Bromobenzylidene)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazoli-n]-2'(3'H)-one (3ae):

White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 152–154 °C. Yield 183 mg, 99%. ^1H NMR



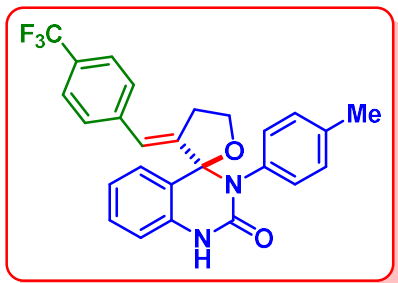
(500 MHz, CDCl_3) δ 8.46 (s, 1H), 7.44 (d, $J = 8.2$ Hz, 2H), 7.42 (s, 1H), 7.26–7.21 (m, 2H), 7.09 (d, $J = 7.8$ Hz, 1H), 7.07 (s, 1H), 7.01–6.96 (m, 4H), 6.79 (d, $J = 8.0$ Hz, 1H), 6.43 (t, $J = 2.8$ Hz, 1H), 3.90–3.83 (m, 2H), 2.76–2.70 (m, 1H), 2.36 (s, 3H), 2.22–2.15 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.3, 144.7, 137.7, 135.6, 135.5, 135.4, 131.7, 131.4, 130.0, 129.6, 129.2, 127.3, 122.9, 122.2, 121.5, 114.3, 99.2, 67.1, 31.3, 21.3. IR (KBr, neat) ν 3224, 3059, 2916, 1672, 1602, 1495, 1401, 1039, 754, 512 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{22}\text{BrN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 461.0859, found 461.0862.

Methyl (E)-4-((2'-oxo-3'-(*p*-tolyl)-2',3',4,5-tetrahydro-1'*H*,3*H*-spiro[furan-2,4'-quinazolin]-3-ylidene)methyl)benzoate (3af):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 248–250 $^{\circ}\text{C}$. Yield 155 mg, 88%. ^1H NMR (500 MHz, CDCl_3) δ 8.52 (s, 1H), 7.91 (d, $J = 8.0$ Hz, 2H), 7.36 (s, 1H), 7.19–7.16 (m, 2H), 7.13 (d, $J = 8.2$ Hz, 2H), 7.03 (d, $J = 7.9$ Hz, 1H), 7.00 (s, 1H), 6.93 (s, 1H), 6.90 (t, $J = 7.6$ Hz, 1H), 6.73 (d, $J = 8.0$ Hz, 1H), 6.46 (t, $J = 2.7$ Hz, 1H), 3.83 (s, 3H), 3.82–3.76 (m, 2H), 2.75–2.69 (m, 1H), 2.29 (s, 3H), 2.22–2.15 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 166.7, 152.5, 146.6, 141.0, 137.7, 135.6, 135.5, 131.4, 129.7, 129.6, 129.2, 128.9, 128.3, 127.5, 127.2, 122.8, 122.1, 114.4, 99.2, 67.0, 52.2, 31.5, 21.2. IR (KBr, neat) ν 3224, 3058, 2919, 1717, 1671, 1601, 1399, 1275, 1108, 1037, 733, 510 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{25}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 441.1809, found 441.1808.

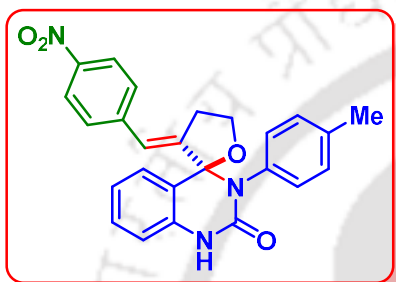
(E)-3'-(*p*-Tolyl)-3-(4-(trifluoromethyl)benzylidene)-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (3ag):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 246–248 $^{\circ}\text{C}$. Yield 137 mg, 76%. ^1H NMR (400 MHz, CDCl_3) δ 9.11 (s, 1H), 7.63 (d, $J = 8.0$ Hz, 2H), 7.51 (d, $J = 7.9$ Hz, 1H), 7.29 (d, $J = 8.3$ Hz, 4H), 7.14 (d, $J = 7.6$ Hz, 2H), 7.07–7.00 (m, 2H), 6.84 (d, $J = 8.1$ Hz, 1H), 6.59 (s, 1H),

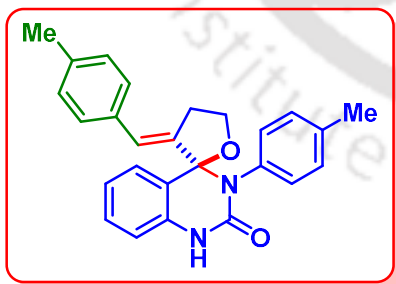
3.95–3.91 (m, 2H), 2.86–2.79 (m, 1H), 2.43 (s, 3H), 2.35–2.25 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.4, 146.7, 140.0, 137.8, 135.6, 135.5, 131.4, 129.7, 129.5, 129.2, 128.6, 127.3, 127.1, 125.4 (q, $J = 3.7$ Hz), 124.1 (q, $J = 270.4$ Hz), 122.8, 122.2, 114.4, 99.2, 67.0, 31.4, 21.3. ^{19}F NMR (470 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -65.8. IR (KBr, neat) ν 3220, 2955, 2923, 2855, 1676, 1604, 1407, 1324, 1122, 1069, 754 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 451.1628, found 451.1631.

(E)-3-(4-Nitrobenzylidene)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3ah):



Yellow solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 135–137 °C. Yield 111 mg, 65%. ^1H NMR (400 MHz, CDCl_3) δ 8.90 (s, 1H), 8.20 (d, $J = 8.8$ Hz, 2H), 7.46 (s, 1H), 7.31–7.25 (m, 4H), 7.10 (dd, $J = 7.9, 1.4$ Hz, 2H), 7.01 (t, $J = 7.4$ Hz, 2H), 6.82 (d, $J = 8.0$ Hz, 1H), 6.59 (t, $J = 2.7$ Hz, 1H), 3.97–3.88 (m, 2H), 2.86–2.78 (m, 1H), 2.39 (s, 3H), 2.34–2.25 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.5, 148.9, 146.6, 142.9, 137.9, 135.5, 131.3, 129.7, 129.2, 129.0, 127.1, 126.5, 123.8, 122.5, 122.2, 114.6, 99.2, 67.0, 31.5, 21.2. IR (KBr, neat) ν 3238, 3062, 2922, 1672, 1599, 1513, 1342, 1040, 754, 510 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{22}\text{N}_3\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 428.1605, found 428.1605.

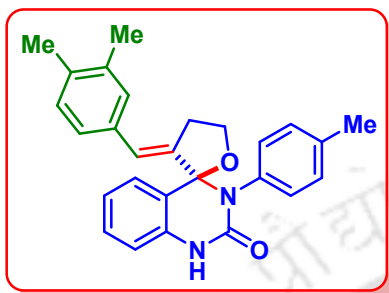
(E)-3-(4-Methylbenzylidene)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3ai):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 133–135 °C. Yield 157 mg, 99%. ^1H NMR (500 MHz, CDCl_3) δ 8.46–8.26 (m, 1H), 7.43 (s, 1H), 7.27–7.21 (m, 2H), 7.13 (t, $J = 9.0$ Hz, 3H), 7.08 (s, 1H), 7.06 (d, $J = 8.0$ Hz, 2H), 7.02 (s, 1H), 6.97 (td, $J = 7.6, 1.3$ Hz, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 6.47 (t, $J = 2.7$ Hz, 1H), 3.89–3.82 (m, 2H), 2.81–2.75 (m, 1H), 2.36 (s, 3H), 2.34 (s, 3H), 2.25–2.18 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.4, 142.7, 137.52, 137.49, 135.7, 135.4, 133.8, 131.5, 131.4, 129.4, 129.2, 128.5, 128.3, 127.4, 123.2, 122.1, 114.2, 99.3, 67.2, 31.3, 21.3, 21.2. IR (KBr, neat) ν 3220, 3056,

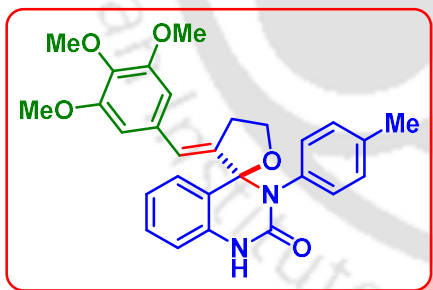
2919, 1670, 1601, 1399, 1263, 1038, 752, 734, 505 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 397.1911, found 397.1914.

(E)-3-(3,4-Dimethylbenzylidene)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3aj):



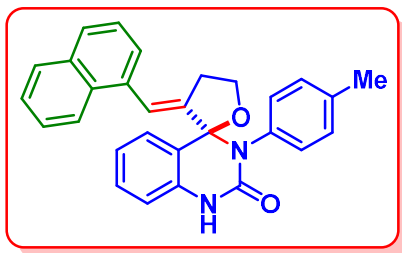
White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 230–232 °C. Yield 158 mg, 96%. ^1H NMR (400 MHz, CDCl_3) δ 9.28 (s, 1H), 7.47 (s, 1H), 7.30–7.25 (m, 1H), 7.22 (t, J = 7.7 Hz, 1H), 7.13 (d, J = 7.7 Hz, 3H), 7.08 (s, 1H), 6.98 (s, 1H), 6.95 (t, J = 7.5 Hz, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.48 (t, J = 2.6 Hz, 1H), 3.92–3.83 (m, 2H), 2.86–2.78 (m, 1H), 2.40 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H), 2.24–2.20 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.7, 142.7, 137.3, 136.6, 136.1, 135.8, 135.5, 134.3, 131.5, 130.0, 129.7, 129.3, 129.1, 128.3, 127.3, 125.8, 123.2, 121.9, 114.4, 99.3, 67.1, 31.3, 21.2, 19.8, 19.5. IR (KBr, neat) ν 3210, 3055, 2923, 1669, 1602, 1399, 1264, 1039, 732, 502 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{27}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 411.2067, found 411.2071.

(E)-3'-(p-Tolyl)-3-(3,4,5-trimethoxybenzylidene)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3ak):



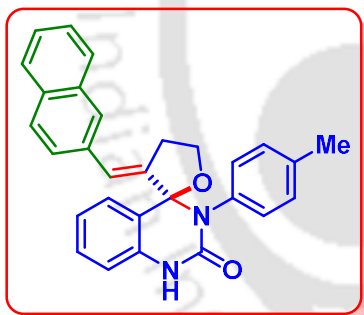
White solid; R_f (Hexane:EtOAc, 1:4) 0.5; mp 142–144 °C. Yield 148 mg, 78%. ^1H NMR (400 MHz, CDCl_3) δ 8.89 (s, 1H), 7.00 (t, J = 7.7 Hz, 1H), 6.92–6.86 (m, 5H), 6.68 (d, J = 7.5 Hz, 1H), 6.65 (d, J = 7.5 Hz, 1H), 6.47 (d, J = 7.8 Hz, 1H), 6.33 (s, 1H), 6.16 (s, 1H), 3.76 (s, 6H), 3.67–3.60 (m, 2H), 3.42 (s, 3H), 2.70–2.62 (m, 1H), 2.41–2.33 (m, 1H), 2.17 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 154.7, 154.3, 152.6, 149.7, 140.2, 137.5, 137.4, 137.0, 135.5, 134.5, 128.7, 128.5, 126.8, 124.8, 121.6, 118.6, 114.6, 100.6, 60.7, 60.5, 59.6, 56.0, 30.4, 21.0. IR (KBr, neat) ν 3223, 3057, 2932, 1663, 1599, 1406, 1109, 732, 504 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{28}\text{H}_{29}\text{N}_2\text{O}_5$ ($\text{M} + \text{H}$)⁺ 473.2071, found 473.2074.

(E)-3-(Naphthalen-1-ylmethylene)-3'-(*p*-tolyl)-4,5-dihydro-1*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3*H*)-one (3al):



Yellow solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 180–182 °C. Yield 135 mg, 78%. ^1H NMR (500 MHz, CDCl_3) δ 9.06 (s, 1H), 7.85 (d, $J = 8.1$ Hz, 1H), 7.77 (d, $J = 8.2$ Hz, 1H), 7.56–7.51 (m, 2H), 7.48 (t, $J = 7.5$ Hz, 1H), 7.42 (q, $J = 7.4$ Hz, 2H), 7.34–7.28 (m, 3H), 7.20 (s, 1H), 7.13 (s, 1H), 7.11–7.05 (m, 3H), 6.90 (d, $J = 8.0$ Hz, 1H), 3.96 (td, $J = 8.7, 2.7$ Hz, 1H), 3.76 (q, $J = 8.3$ Hz, 1H), 2.53–2.48 (m, 1H), 2.45 (s, 3H), 2.20–2.12 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.8, 145.6, 137.6, 136.0, 135.9, 133.9, 133.4, 131.8, 131.5, 131.1, 129.6, 128.5, 128.0, 127.2, 126.5, 126.2, 126.0, 125.6, 125.2, 124.3, 123.1, 121.9, 114.7, 98.4, 66.4, 31.4, 21.3. IR (KBr, neat) ν 3301, 3055, 2922, 1665, 1601, 1509, 1401, 1237, 1033, 753, 507 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 433.1911, found 433.1909.

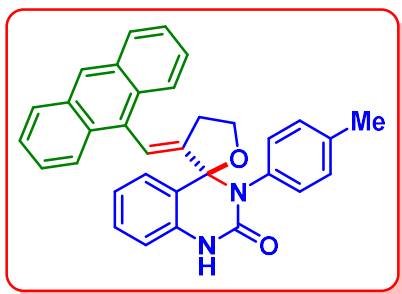
(E)-3-(Naphthalen-2-ylmethylene)-3'-(*p*-tolyl)-4,5-dihydro-1*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3*H*)-one (3am):



White solid; R_f (Hexane:EtOAc, 1:1) 0.6; mp 124–126 °C. Yield 166 mg, 96%. ^1H NMR (500 MHz, CDCl_3) δ 8.94 (s, 1H), 7.71–7.66 (m, 3H), 7.50 (s, 1H), 7.40–7.35 (m, 3H), 7.21 (d, $J = 8.5$ Hz, 1H), 7.17–7.12 (m, 2H), 7.06 (d, $J = 7.7$ Hz, 1H), 6.99 (s, 2H), 6.89 (t, $J = 7.5$ Hz, 1H), 6.72 (d, $J = 8.0$ Hz, 1H), 6.57 (t, $J = 2.7$ Hz, 1H), 3.84–3.76 (m, 2H), 2.83–2.77 (m, 1H), 2.28 (s, 3H), 2.27–2.23 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.7, 144.3, 137.5, 135.8, 135.6, 134.1, 133.3, 132.5, 131.5, 129.4, 129.2, 128.4, 128.1, 128.0, 127.8, 127.6, 127.3, 126.4, 126.3, 126.2, 123.1, 122.0, 114.5, 99.3, 67.1, 31.4, 21.2. IR (KBr, neat) ν 3217, 3055, 2921, 1670, 1600, 1400, 1264, 1038, 732, 479 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 433.1911, found 433.1914.

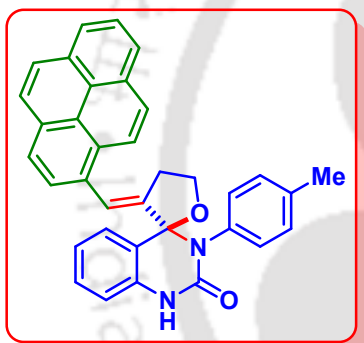
(E)-3-(Anthracen-9-ylmethylene)-3'-(*p*-tolyl)-4,5-dihydro-1*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3*H*)-one (3an):

Yellow solid; R_f (Hexane:EtOAc, 1:1) 0.6; mp 290–292 °C. Yield 156 mg, 81%. ^1H NMR (400 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 9.42 (s, 1H), 8.35 (s, 1H), 7.96 (s, 2H), 7.83 (s, 1H), 7.73



(s, 1H), 7.43–7.36 (m, 5H), 7.35 (s, 1H), 7.30 (s, 2H), 7.22 (s, 1H), 7.14 (td, $J = 7.6, 1.3$ Hz, 1H), 7.10 (d, $J = 8.1$ Hz, 1H), 7.04 (s, 1H), 6.48 (s, 1H), 4.05 (td, $J = 9.0, 2.2$ Hz, 1H), 3.69–3.63 (m, 1H), 2.51 (s, 3H), 2.29–2.19 (m, 1H), 1.97–1.91 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 152.8, 146.6, 137.3, 137.1, 135.9, 131.8, 130.8, 130.5, 129.7, 129.4, 129.1, 128.4, 126.7, 126.6, 126.3, 126.1, 125.4, 124.9, 123.2, 121.2, 114.5, 97.9, 64.5, 31.9, 21.1. IR (KBr, neat) ν 3243, 3057, 2923, 1676, 1601, 1401, 1034, 754, 510 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{33}\text{H}_{27}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 483.2067, found 483.2067.

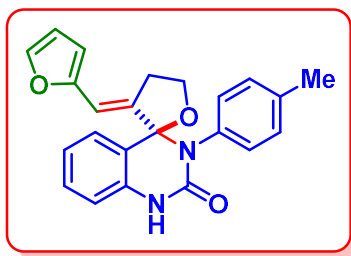
(E)-3-(Pyren-1-ylmethylene)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazoli-n]-2'(3'H)-one (3ao):



Yellow solid; R_f (Hexane:EtOAc, 1:1) 0.4; mp 268–270 °C. Yield 174 mg, 86%. ^1H NMR (400 MHz, CDCl_3) δ 8.91 (s, 1H), 8.15 (t, $J = 8.3$ Hz, 2H), 8.07–7.97 (m, 4H), 7.94 (d, $J = 9.2$ Hz, 1H), 7.69 (d, $J = 9.3$ Hz, 1H), 7.61 (s, 1H), 7.57 (d, $J = 8.0$ Hz, 1H), 7.40–7.35 (m, 4H), 7.25 (s, 2H), 7.15 (td, $J = 7.6, 1.2$ Hz, 1H), 6.94 (d, $J = 7.9$ Hz, 1H), 3.97 (td, $J = 8.7, 3.1$ Hz, 1H), 3.81 (td, $J = 8.9, 6.9$ Hz, 1H), 2.59–2.52 (m, 1H), 2.49 (s, 3H), 2.33–2.24 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.3, 146.0, 137.7, 136.1, 136.0, 131.9, 131.3, 131.2, 130.8, 130.7, 129.7, 129.4, 128.8, 127.7, 127.6, 127.30, 127.27, 127.0, 126.1, 125.7, 125.4, 125.2, 124.7, 124.4, 123.6, 123.3, 122.0, 114.7, 98.7, 66.5, 31.5, 21.4. IR (KBr, neat) ν 3225, 3043, 2923, 2853, 1672, 1601, 1404, 1262, 1034, 845, 734, 509 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{35}\text{H}_{27}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 507.2067, found 507.2067.

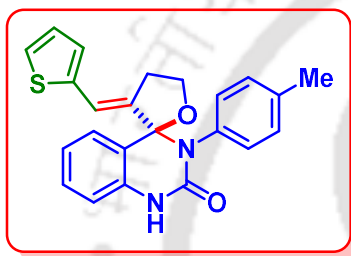
(E)-3-(Furan-2-ylmethylene)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazoli-n]-2'(3'H)-one (3ap):

White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 137–139 °C. Yield 101 mg, 68%. ^1H NMR (400 MHz, CDCl_3) δ 8.90 (s, 1H), 7.40 (s, 2H), 7.20 (t, $J = 7.5$ Hz, 2H), 7.10 (d, $J = 7.8$ Hz, 2H), 7.02 (d, $J = 7.4$ Hz, 1H), 6.95 (t, $J = 7.6$ Hz, 1H), 6.76 (d, $J = 8.0$ Hz, 1H), 6.40 (dd, J



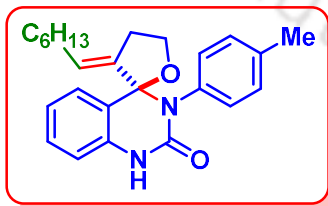
= 3.3, 1.8 Hz, 1H), 6.32 (t, J = 2.7 Hz, 1H), 6.21 (d, J = 3.4 Hz, 1H), 3.95 (q, J = 7.8 Hz, 1H), 3.76 (td, J = 8.5, 4.9 Hz, 1H), 3.00–2.92 (m, 1H), 2.36 (s, 3H), 2.34–2.29 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.6, 152.3, 142.6, 142.1, 137.5, 135.6, 135.2, 131.2, 129.4, 127.2, 123.0, 122.0, 116.2, 114.4, 111.5, 110.2, 99.0, 67.4, 31.5, 21.2. IR (KBr, neat) ν 3216, 3057, 2919, 1668, 1600, 1399, 1264, 1037, 731, 508 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 373.1547, found 373.1548.

(E)-3-(Thiophen-2-ylmethylene)-3'-(*p*-tolyl)-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (3aq):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 210–212 $^{\circ}\text{C}$. Yield 136 mg, 87%. ^1H NMR (400 MHz, CDCl_3) δ 8.77 (s, 1H), 7.41 (s, 1H), 7.33 (d, J = 5.1 Hz, 1H), 7.22 (t, J = 7.7 Hz, 2H), 7.10 (d, J = 7.8 Hz, 2H), 7.04 (t, J = 4.5 Hz, 1H), 7.00–6.94 (m, 3H), 6.78 (d, J = 8.0 Hz, 1H), 6.69 (s, 1H), 3.98 (q, J = 7.8 Hz, 1H), 3.81 (td, J = 8.6, 4.7 Hz, 1H), 2.90–2.82 (m, 1H), 2.36 (s, 3H), 2.27–2.18 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.5, 142.0, 140.5, 137.6, 135.6, 135.3, 131.3, 129.5, 127.9, 127.4, 127.3, 126.4, 123.0, 122.1, 121.5, 114.3, 99.3, 67.4, 31.5, 21.2. IR (KBr, neat) ν 3212, 3056, 2921, 1671, 1601, 1401, 1264, 1038, 732, 701, 508 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}_2\text{S}$ ($\text{M} + \text{H}$) $^+$ 389.1318, found 389.1316.

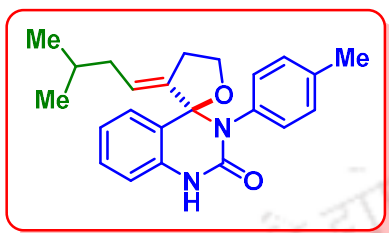
(E)-3-Heptylidene-3'-(*p*-tolyl)-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (3ar):



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 145–147 $^{\circ}\text{C}$. Yield 108 mg, 69%. ^1H NMR (500 MHz, CDCl_3) δ 8.16 (s, 1H), 7.38 (s, 1H), 7.22 (t, J = 7.7 Hz, 1H), 7.18 (s, 1H), 7.13 (s, 1H), 7.08 (d, J = 7.7 Hz, 1H), 6.99 (s, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 5.50–5.46 (m, 1H), 3.83–3.77 (m, 2H), 2.54–2.48 (m, 1H), 2.37 (s, 3H), 2.01–1.90 (m, 3H), 1.31–1.16 (m, 8H), 0.88 (t, J = 7.1 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.7, 141.4, 137.3, 136.0, 135.3, 131.6, 130.8, 129.8, 129.4, 129.2, 129.0, 127.2, 123.7, 121.8, 114.0, 97.7, 66.4, 31.7, 30.2, 29.4, 29.1, 28.7, 22.6, 21.2,

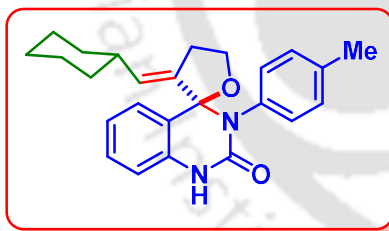
14.1. IR (KBr, neat) ν 3227, 3059, 2923, 1672, 1601, 1395, 1035, 751, 655, 508 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{31}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 391.2380, found 391.2380.

(E)-3-(3-Methylbutylidene)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazol-in]-2'(3'H)-one (3as):



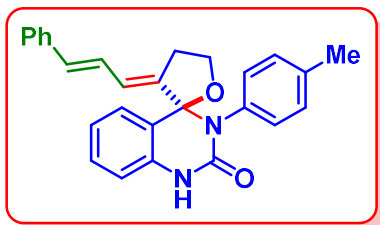
White semi-solid; R_f (Hexane:EtOAc, 3:2) 0.5. Yield 90 mg, 62%. ^1H NMR (500 MHz, CDCl_3) δ 8.38 (s, 1H), 7.39 (s, 1H), 7.21 (td, $J = 7.7, 1.4$ Hz, 1H), 7.17 (s, 1H), 7.13 (s, 1H), 7.08 (d, $J = 7.8$ Hz, 1H), 7.03–6.98 (m, 1H), 6.95 (td, $J = 7.7, 1.2$ Hz, 1H), 6.76 (d, $J = 7.9$ Hz, 1H), 5.50 (tt, $J = 7.5, 2.6$ Hz, 1H), 3.84–3.77 (m, 2H), 2.54–2.49 (m, 1H), 2.36 (s, 3H), 1.99–1.91 (m, 1H), 1.85 (t, $J = 7.2$ Hz, 2H), 1.60–1.52 (m, 1H), 0.81 (d, $J = 6.6$ Hz, 3H), 0.78 (d, $J = 6.6$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.8, 142.2, 137.3, 136.0, 135.3, 131.5, 130.7, 129.2, 128.7, 127.2, 123.7, 121.7, 114.1, 97.8, 66.3, 39.5, 29.6, 28.4, 22.6, 22.4, 21.2. IR (KBr, neat) ν 3224, 3057, 2918, 1717, 1671, 1601, 1398, 1275, 1108, 752, 512 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 363.2067, found 363.2067.

(E)-3-(Cyclohexylmethylene)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazoli-n]-2'(3'H)-one (3at):



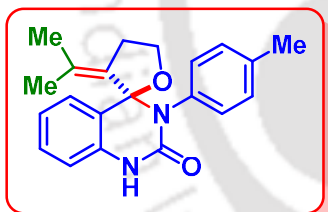
White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 104–106 $^{\circ}\text{C}$. Yield 120 mg, 77%. ^1H NMR (500 MHz, CDCl_3) δ 8.44 (s, 1H), 7.39 (d, $J = 7.9$ Hz, 1H), 7.20 (td, $J = 7.7, 1.5$ Hz, 1H), 7.17 (s, 1H), 7.12 (d, $J = 8.0$ Hz, 1H), 7.07 (d, $J = 7.7$ Hz, 1H), 7.01–6.98 (m, 1H), 6.94 (t, $J = 7.5$ Hz, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 5.31 (dt, $J = 9.5, 2.6$ Hz, 1H), 3.84 (td, $J = 8.7, 3.9$ Hz, 1H), 3.77 (q, $J = 8.2$ Hz, 1H), 2.55–2.49 (m, 1H), 2.37 (s, 3H), 2.01–1.90 (m, 2H), 1.69–1.64 (m, 2H), 1.63–1.57 (m, 2H), 1.42 (d, $J = 12.9$ Hz, 1H), 1.24–1.11 (m, 3H), 1.05–0.93 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.8, 139.4, 137.3, 136.0, 135.5, 135.2, 132.0, 130.8, 129.3, 129.1, 128.9, 127.2, 123.6, 121.7, 114.1, 97.7, 66.3, 39.7, 32.3, 31.6, 29.3, 25.9, 25.8, 25.7, 21.2. IR (KBr, neat) ν 3221, 3058, 2922, 2851, 1671, 1600, 1398, 1256, 1035, 732, 509 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 389.2224, found 389.2225.

(E)-3-((E)-3-Phenylallylidene)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3au):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 152–154 °C. Yield 155 mg, 95%. ^1H NMR (400 MHz, CDCl_3) δ 8.60 (s, 1H), 7.33 (s, 1H), 7.30 (d, $J = 7.6$ Hz, 2H), 7.23 (t, $J = 7.5$ Hz, 2H), 7.16 (d, $J = 7.8$ Hz, 1H), 7.13 (d, $J = 7.3$ Hz, 2H), 7.05 (s, 1H), 7.01 (d, $J = 8.0$, 1H), 6.94 (s, 1H), 6.88 (t, $J = 7.5$ Hz, 1H), 6.70 (d, $J = 8.0$ Hz, 1H), 6.61 (dd, $J = 15.6, 10.8$ Hz, 1H), 6.45 (d, $J = 15.6$ Hz, 1H), 6.15 (d, $J = 10.8$ Hz, 1H), 3.83 (q, $J = 7.9$ Hz, 1H), 3.70 (td, $J = 8.5, 4.5$ Hz, 1H), 2.73–2.66 (m, 1H), 2.28 (s, 3H), 2.13–2.04 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.7, 144.4, 137.5, 136.9, 135.7, 135.3, 134.4, 131.3, 129.4, 128.7, 128.0, 127.7, 127.2, 126.5, 125.3, 123.0, 122.0, 114.3, 98.3, 66.9, 29.9, 21.2. IR (KBr, neat) ν 3209, 3057, 2919, 1670, 1600, 1398, 1264, 1031, 749, 509 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 409.1911, found 409.1911.

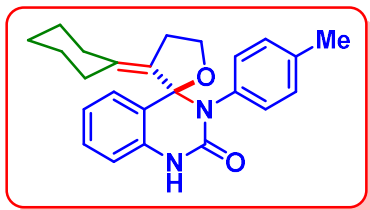
3-(Propan-2-ylidene)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3av):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 238–240 °C. Yield 119 mg, 89%. ^1H NMR (500 MHz, CDCl_3) δ 8.49 (s, 1H), 7.44 (s, 1H), 7.20 (td, $J = 7.6, 1.4$ Hz, 1H), 7.17 (s, 1H), 7.12 (s, 1H), 7.07 (d, $J = 7.8$ Hz, 1H), 6.94 (t, $J = 7.4$ Hz, 2H), 6.75 (d, $J = 7.8$ Hz, 1H), 3.86 (td, $J = 8.7, 3.4$ Hz, 1H), 3.75 (q, $J = 8.3$, 1H), 2.56–2.51 (m, 1H), 2.37 (s, 3H), 2.02–1.94 (m, 1H), 1.59 (s, 3H), 1.46 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.9, 137.3, 136.2, 134.9, 134.2, 130.5, 130.0, 129.2, 129.0, 126.3, 122.7, 121.9, 114.2, 96.7, 65.7, 31.9, 22.9, 21.2, 21.1. IR (KBr, neat) ν 3211, 3058, 2915, 1670, 1600, 1397, 1264, 1038, 753, 734, 510 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 335.1754, found 335.1754.

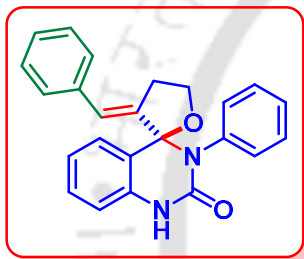
3-Cyclohexylidene-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3aw):

White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 204–206 °C. Yield 126 mg, 84%. ^1H NMR (500 MHz, CDCl_3) δ 8.74 (s, 1H), 7.45 (d, $J = 8.1$ Hz, 1H), 7.18 (t, $J = 7.8$ Hz, 2H), 7.13



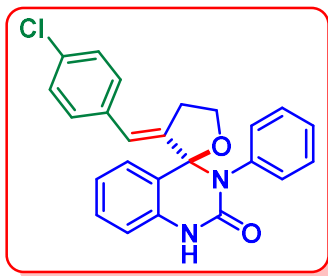
(d, $J = 7.7$ Hz, 1H), 7.11 (s, 1H), 6.99 (d, $J = 8.0$ Hz, 1H), 6.94 (t, $J = 7.5$ Hz, 1H), 6.74 (d, $J = 8.0$ Hz, 1H), 3.87 (td, $J = 8.7, 3.2$ Hz, 1H), 3.74 (q, $J = 8.4$ Hz, 1H), 2.61–2.56 (m, 1H), 2.37 (s, 3H), 2.15–2.10 (m, 1H), 2.07–1.98 (m, 2H), 1.86–1.79 (m, 2H), 1.59–1.54 (m, 1H), 1.50–1.46 (m, 1H), 1.43–1.33 (m, 3H), 1.04–0.96 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.0, 137.2, 137.1, 136.2, 134.7, 131.1, 130.3, 129.9, 129.1, 129.0, 128.7, 126.4, 123.1, 121.6, 114.3, 96.3, 65.5, 33.1, 31.2, 31.0, 27.2, 26.0, 25.9, 21.2. IR (KBr, neat) ν 3212, 3055, 2927, 1672, 1600, 1400, 1265, 1037, 732, 512 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 375.2067, found 375.2067.

(E)-3-Benzylidene-3'-phenyl-4,5-dihydro-1H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3ba):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 187–189 °C. Yield 131 mg, 89%. ^1H NMR (400 MHz, CDCl_3) δ 9.09 (s, 1H), 7.59 (s, 1H), 7.46–7.41 (m, 1H), 7.38–7.29 (m, 4H), 7.27–7.21 (m, 2H), 7.19 (s, 1H), 7.13 (t, $J = 6.4$ Hz, 3H), 6.97 (t, $J = 7.6$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.53 (t, $J = 2.6$ Hz, 1H), 3.86 (dd, $J = 8.6, 5.6$ Hz, 2H), 2.82–2.74 (m, 1H), 2.23–2.14 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.7, 143.6, 138.5, 136.6, 135.6, 132.0, 131.7, 129.5, 128.6, 128.47, 128.46, 127.8, 127.5, 127.2, 122.9, 122.0, 114.5, 99.2, 67.0, 31.3. IR (KBr, neat) ν 3227, 3057, 2922, 1669, 1600, 1399, 1264, 1034, 734, 696, 549 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{21}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 281.1285, found 281.1285.

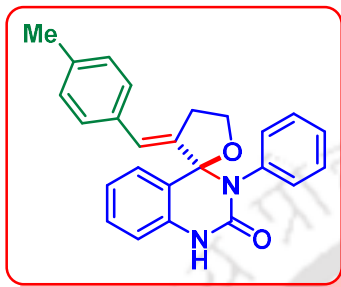
(E)-3-(4-Chlorobenzylidene)-3'-phenyl-4,5-dihydro-1H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3bb):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 208–210 °C. Yield 148 mg, 92%. ^1H NMR (400 MHz, CDCl_3) δ 9.03 (s, 1H), 7.58 (s, 1H), 7.44 (s, 1H), 7.35 (t, $J = 7.2$ Hz, 1H), 7.32–7.27 (m, 3H), 7.23 (td, $J = 7.6, 1.4$ Hz, 1H), 7.13 (m, 1H), 7.10 (d, $J = 7.8$ Hz, 1H), 7.05 (d, $J = 8.5$ Hz, 2H), 6.98 (d, $J = 7.5$ Hz, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 6.46 (t, $J = 2.6$ Hz, 1H), 3.86 (dd, $J = 8.5, 5.6$ Hz, 2H), 2.76–2.69 (m, 1H), 2.19–2.10 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 152.5, 144.4,

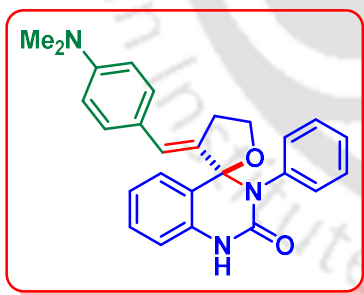
138.4, 135.5, 134.5, 133.4, 131.8, 129.7, 129.6, 128.7, 128.5, 127.9, 127.4, 127.2, 122.8, 122.1, 114.5, 99.2, 67.0, 31.3. IR (KBr, neat) ν 3206, 3052, 2919, 1673, 1599, 1395, 1032, 756, 702, 555 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{20}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 403.1208, found 403.1213.

(E)-3-(4-Methylbenzylidene)-3'-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3bi):



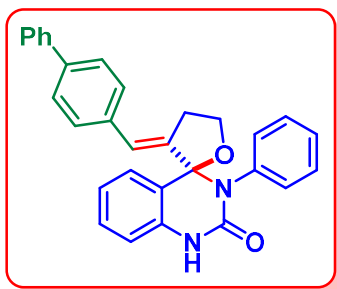
White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 190–192 °C. Yield 136 mg, 89%. ^1H NMR (500 MHz, CDCl_3) 9.58 (s, 1H), 7.64 (s, 1H), 7.48 (s, 1H), 7.38 (t, $J = 7.2$ Hz, 1H), 7.33 (s, 1H), 7.21 (t, $J = 7.7$ Hz, 2H), 7.17 (d, $J = 7.8$ Hz, 2H), 7.14 (d, $J = 7.7$ Hz, 1H), 7.08 (d, $J = 7.8$ Hz, 2H), 6.98 (t, $J = 7.6$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.52 (t, $J = 2.6$ Hz, 1H), 3.88 (dd, $J = 8.9, 5.6$ Hz, 2H), 2.82–2.76 (m, 1H), 2.37 (s, 3H), 2.23–2.16 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.8, 142.6, 138.5, 137.4, 135.6, 133.7, 131.9, 131.7, 129.3, 129.1, 128.5, 128.4, 127.6, 127.1, 122.9, 121.8, 114.6, 99.2, 66.9, 31.2, 21.1. IR (KBr, neat) ν 3227, 3057, 2920, 1669, 1601, 1398, 1265, 1038, 753, 704, 551 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{23}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 383.1754, found 383.1756.

(E)-3-(4-(Dimethylamino)benzylidene)-3'-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3bx):



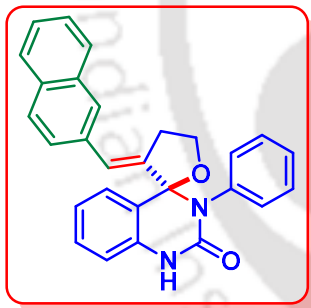
Yellow solid; R_f (Hexane:EtOAc, 1:1) 0.4; mp 212–214 °C. Yield 112 mg, 68%. ^1H NMR (400 MHz, CDCl_3) δ 8.62 (s, 1H), 7.57 (s, 1H), 7.42 (s, 1H), 7.33 (t, $J = 7.2$ Hz, 1H), 7.28 (s, 1H), 7.23 (t, $J = 7.8$ Hz, 1H), 7.17 (s, 1H), 7.14 (d, $J = 7.7$ Hz, 1H), 7.06 (d, $J = 8.4$ Hz, 2H), 6.96 (t, $J = 7.6$ Hz, 1H), 6.79 (d, $J = 8.0$ Hz, 1H), 6.68 (d, $J = 8.4$ Hz, 2H), 6.40 (t, $J = 2.6$ Hz, 1H), 3.89–3.80 (m, 2H), 2.97 (s, 6H), 2.81–2.74 (m, 1H), 2.19–2.10 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 152.5, 149.6, 138.8, 138.6, 135.5, 132.0, 131.7, 129.7, 129.3, 128.5, 127.6, 127.5, 123.4, 122.0, 114.2, 112.1, 99.5, 67.2, 40.4, 31.3. IR (KBr, neat) ν 3214, 3055, 2906, 1669, 1602, 1400, 1164, 1036, 732, 701, 550 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}_2$ ($\text{M} + \text{H}$)⁺ 412.2020, found 412.2025.

(E)-3-([1,1'-Biphenyl]-4-ylmethylene)-3'-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3by):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 239–241 °C. Yield 160 mg, 90%. ^1H NMR (500 MHz, CDCl_3) δ 8.92 (s, 1H), 7.52 (s, 1H), 7.48 (t, J = 9.1 Hz, 4H), 7.35 (t, J = 7.6 Hz, 3H), 7.27–7.22 (m, 3H), 7.14 (t, J = 8.8 Hz, 3H), 7.10 (s, 1H), 7.04 (d, J = 7.8 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.46 (s, 1H), 3.79 (t, J = 6.9 Hz, 2H), 2.76–2.70 (m, 1H), 2.17–2.10 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.6, 143.7, 140.4, 140.3, 138.5, 135.5, 131.7, 129.5, 129.0, 128.9, 128.5, 128.2, 127.8, 127.5, 127.3, 127.2, 127.0, 123.0, 122.1, 114.5, 99.3, 67.0, 31.4. IR (KBr, neat) ν 3220, 3057, 2922, 1670, 1600, 1401, 1263, 1036, 734, 698, 551 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 445.1911, found 445.1908.

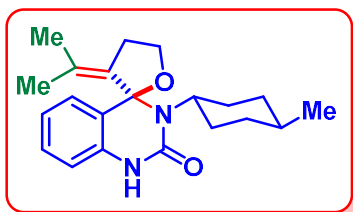
(E)-3-(Naphthalen-2-ylmethylene)-3'-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3bm):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 134–136 °C. Yield 144 mg, 86%. ^1H NMR (500 MHz, CDCl_3) δ 9.14 (s, 1H), 7.81 (d, J = 5.1 Hz, 1H), 7.80–7.77 (m, 2H), 7.63 (s, 1H), 7.59 (s, 1H), 7.49–7.46 (m, 3H), 7.37 (t, J = 7.2 Hz, 1H), 7.32 (s, 1H), 7.30 (d, J = 8.5 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.23 (s, 1H), 7.18 (d, J = 7.8 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.69 (t, J = 2.6 Hz, 1H), 3.94–3.87 (m, 2H), 2.92–2.86 (m, 1H), 2.36–2.28 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 152.7, 144.1, 138.5, 135.6, 134.1, 133.2, 132.5, 131.8, 129.5, 128.6, 128.1, 128.0, 127.8, 127.7, 127.6, 127.2, 126.4, 126.3, 126.1, 123.0, 122.0, 114.6, 99.3, 67.0, 31.4. IR (KBr, neat) ν 3218, 3056, 2903, 1669, 1600, 1399, 1264, 1037, 731, 702, 550 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{28}\text{H}_{23}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 419.1754, found 419.1757.

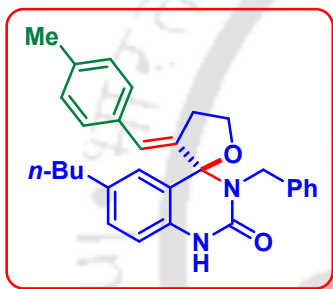
3'-(4-Methylcyclohexyl)-3-(propan-2-ylidene)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3cv):

White solid; R_f (Hexane:EtOAc, 4:1) 0.5; mp 224–226 °C. Yield 112 mg, 82%. ^1H NMR



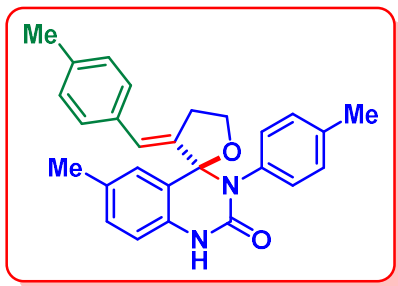
(400 MHz, CDCl_3) δ 8.81–8.44 (m, 1H), 7.17 (td, $J = 7.7$, 1.5 Hz, 1H), 6.98 (d, $J = 7.8$ Hz, 1H), 6.87 (t, $J = 7.6$ Hz, 1H), 6.73 (dd, $J = 8.2$, 4.4 Hz, 1H), 4.15–4.09 (m, 1H), 3.94 (q, $J = 8.1$ Hz, 1H), 3.00–2.88 (m, 3H), 2.68–2.51 (m, 2H), 1.86–1.72 (m, 7H), 1.47 (s, 1H), 1.37 (s, 3H), 0.98–0.79 (m, 5H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.2, 135.0, 134.7, 130.0, 128.8, 126.4, 122.2, 121.3, 113.3, 97.7, 65.3, 59.3, 36.0, 35.9, 32.8, 31.9, 30.2, 29.7, 23.1, 22.5, 20.5. IR (KBr, neat) ν 3192, 3063, 2918, 1666, 1606, 1441, 1372, 1042, 750, 582 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 341.2224, found 341.2229.

(E)-3'-Benzyl-6'-butyl-3-(4-methylbenzylidene)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3di):



White solid; R_f (Hexane:EtOAc, 7:3) 0.6; mp 110–112 $^{\circ}\text{C}$. Yield 170 mg, 94%. ^1H NMR (400 MHz, CDCl_3) δ 9.33 (s, 1H), 7.36 (d, $J = 7.5$ Hz, 2H), 7.21 (t, $J = 7.4$ Hz, 2H), 7.16–7.13 (m, 3H), 7.04 (d, $J = 8.2$ Hz, 2H), 7.01 (s, 1H), 6.85 (s, 1H), 6.68 (d, $J = 8.1$ Hz, 1H), 6.30 (s, 1H), 4.81 (d, $J = 15.9$ Hz, 1H), 4.65 (d, $J = 16.0$ Hz, 1H), 4.16 (q, $J = 7.4$ Hz, 1H), 4.03 (q, $J = 7.8$ Hz, 1H), 3.15 (t, $J = 7.4$ Hz, 2H), 2.51 (t, $J = 7.7$ Hz, 2H), 2.35 (s, 3H), 1.51 (p, $J = 8.0$ Hz, 2H), 1.36–1.26 (m, 2H), 0.89 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 154.2, 140.1, 139.8, 137.4, 136.3, 133.6, 132.9, 129.4, 129.1, 128.4, 128.2, 128.0, 127.2, 126.3, 126.2, 122.9, 114.2, 99.1, 66.3, 47.6, 35.1, 33.8, 31.8, 22.2, 21.2, 13.9. IR (KBr, neat) ν 3200, 3030, 2954, 2928, 2860, 1669, 1514, 1443, 1052, 1042, 712, 519 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{33}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 453.2537, found 453.2540.

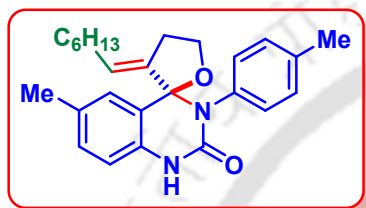
(E)-7'-Methyl-3-(4-methylbenzylidene)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3ei):



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 217–219 $^{\circ}\text{C}$. Yield 156 mg, 95%. ^1H NMR (400 MHz, CDCl_3) δ 8.65 (s, 1H), 7.43 (d, $J = 8.0$ Hz, 1H), 7.25–7.20 (m, 1H), 7.16 (d, $J = 7.9$ Hz, 2H), 7.09 (d, $J = 7.9$ Hz, 3H), 7.04 (dd, $J = 8.1$, 1.9 Hz, 2H), 6.90 (s, 1H), 6.70 (d, $J = 8.1$

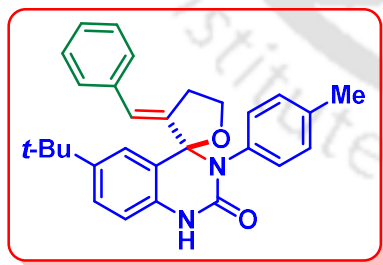
Hz, 1H), 6.47 (t, $J = 2.7$ Hz, 1H), 3.89 (q, $J = 8.0$ Hz, 1H), 3.81 (td, $J = 8.5, 4.3$ Hz, 1H), 2.84–2.76 (m, 1H), 2.37 (s, 3H), 2.36 (s, 3H), 2.26 (s, 3H), 2.23–2.18 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.6, 142.9, 137.4, 137.3, 135.8, 133.9, 133.1, 131.5, 131.3, 130.2, 129.4, 129.2, 128.5, 128.1, 127.4, 123.0, 114.2, 99.4, 67.2, 31.3, 21.23, 21.20, 20.9. IR (KBr, neat) ν 3206, 3047, 2923, 1669, 1512, 1417, 1264, 1037, 732, 514 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{27}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 411.2067, found 411.2065.

(E)-3-Heptylidene-7'-methyl-3'-(*p*-tolyl)-4,5-dihydro-1*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3*H*)-one (3er):



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 134–136 °C. Yield 120 mg, 74%. ^1H NMR (500 MHz, CDCl_3) δ 7.95 (s, 1H), 7.37 (s, 1H), 7.17 (s, 1H), 7.12 (s, 1H), 7.03 (d, $J = 7.7$ Hz, 1H), 7.00 (s, 1H), 6.86 (s, 1H), 6.65 (d, $J = 8.0$ Hz, 1H), 5.47 (t, $J = 6.4$ Hz, 1H), 3.84–3.75 (m, 2H), 2.54–2.49 (m, 1H), 2.36 (s, 3H), 2.27 (s, 3H), 2.01–1.91 (m, 3H), 1.31–1.17 (m, 8H), 0.88 (t, $J = 7.0$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.0, 141.7, 137.0, 136.1, 133.0, 131.7, 130.8, 129.8, 129.5, 129.2, 128.8, 127.1, 123.3, 114.2, 97.8, 66.4, 31.7, 30.1, 29.3, 29.0, 28.6, 22.5, 21.2, 20.9, 14.0. IR (KBr, neat) ν 3217, 3039, 2924, 2857, 1671, 1512, 1414, 1033, 819, 733, 514 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{33}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 405.2537, found 405.2537.

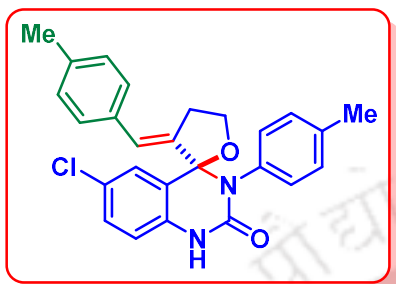
(E)-3-Benzylidene-6'-(*tert*-butyl)-3'-(*p*-tolyl)-4,5-dihydro-1*H*,3*H*-spiro[furan-2,4'-quin-azolin]-2'(3*H*)-one (3fa):



White solid; R_f (Hexane:EtOAc, 1:1) 0.6; mp 208–210 °C. Yield 170 mg, 97%. ^1H NMR (500 MHz, CDCl_3) δ 8.40 (s, 1H), 7.46 (s, 1H), 7.34 (t, $J = 7.6$ Hz, 2H), 7.30 (dd, $J = 8.4, 2.1$ Hz, 1H), 7.26 (t, $J = 7.5$ Hz, 1H), 7.23 (s, 1H), 7.13 (d, $J = 7.8$ Hz, 3H), 7.10 (s, 1H), 7.03 (d, $J = 7.6$ Hz, 1H), 6.75 (d, $J = 8.4$ Hz, 1H), 6.53 (t, $J = 2.7$ Hz, 1H), 3.89–3.82 (m, 2H), 2.80–2.74 (m, 1H), 2.38 (s, 3H), 2.24–2.16 (m, 1H), 1.26 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.6, 144.8, 143.9, 137.4, 136.8, 135.9, 133.2, 131.6, 129.4, 128.5, 128.4, 128.3, 127.4, 126.6, 123.9, 122.4, 113.9, 99.3, 67.0, 34.3, 31.4, 31.3, 21.3. IR (KBr, neat) ν 3218, 3050, 2958,

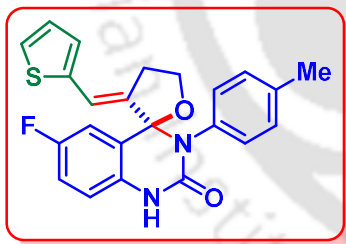
1672, 1512, 1389, 1264, 1037, 732, 697, 514 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{31}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 439.2380, found 439.2380.

(E)-7'-Chloro-3-(4-methylbenzylidene)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3gi):



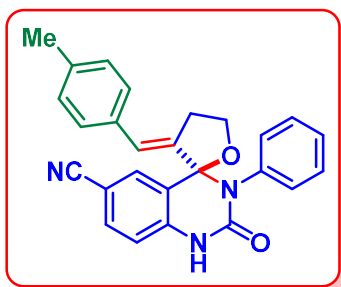
White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 226–228 °C. Yield 159 mg, 92%. ^1H NMR (500 MHz, CDCl_3) δ 9.34 (s, 1H), 7.41 (d, $J = 7.9$ Hz, 1H), 7.23 (d, $J = 7.6$ Hz, 1H), 7.16 (d, $J = 7.8$ Hz, 2H), 7.13 (dd, $J = 8.5, 2.3$ Hz, 1H), 7.08 (d, $J = 7.2$ Hz, 4H), 7.01 (d, $J = 8.1$ Hz, 1H), 6.69 (d, $J = 8.5$ Hz, 1H), 6.46 (s, 1H), 3.88 (q, $J = 7.9$ Hz, 1H), 3.80 (td, $J = 8.6, 4.3$ Hz, 1H), 2.82–2.76 (m, 1H), 2.38 (s, 3H), 2.35 (s, 3H), 2.26–2.18 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.5, 142.5, 137.7, 137.6, 135.5, 134.3, 133.6, 131.4, 129.5, 129.2, 128.55, 128.52, 126.9, 126.7, 124.6, 116.0, 98.9, 67.4, 31.1, 21.3, 21.2. IR (KBr, neat) ν 3223, 3049, 2925, 1672, 1497, 1381, 1263, 1039, 731, 513 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{24}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 431.1521, found 431.1521.

(E)-6'-Fluoro-3-(thiophen-2-ylmethylene)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3hq):



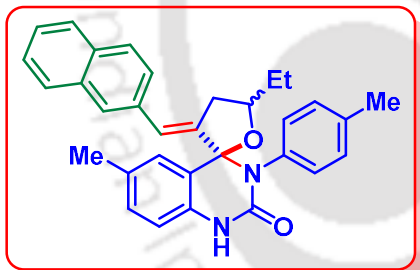
White solid; R_f (Hexane:EtOAc, 2:3) 0.5; mp 239–241 °C. Yield 146 mg, 90%. ^1H NMR (400 MHz, CDCl_3) δ 9.05 (s, 1H), 7.38 (s, 1H), 7.34 (d, $J = 5.0$ Hz, 1H), 7.21 (s, 1H), 7.09–7.04 (m, 2H), 6.99 (s, 1H), 6.96 (d, $J = 3.6$ Hz, 1H), 6.92 (td, $J = 8.4, 2.9$ Hz, 1H), 6.79 (dd, $J = 9.1, 2.8$ Hz, 1H), 6.72 (dd, $J = 8.8, 4.6$ Hz, 1H), 6.68 (t, $J = 2.7$ Hz, 1H), 3.97 (q, $J = 7.8$ Hz, 1H), 3.77 (td, $J = 8.6, 4.9$ Hz, 1H), 2.89–2.81 (m, 1H), 2.35 (s, 3H), 2.27–2.18 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 157.9 (d, $J = 238.5$ Hz), 152.5, 141.5, 140.3, 137.7, 135.4, 131.68 (d, $J = 2.1$ Hz), 131.3, 131.1, 129.6, 129.4, 128.1, 127.4, 126.7, 124.1 (d, $J = 6.9$ Hz), 121.7, 116.8 (d, $J = 23.2$ Hz), 115.81 (d, $J = 7.8$ Hz), 113.5 (d, $J = 24.1$ Hz), 98.9, 67.6, 31.4, 21.2. ^{19}F NMR (470 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -123.6. IR (KBr, neat) ν 3232, 3054, 2964, 1671, 1508, 1418, 1387, 1263, 1037, 732, 700, 513 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{20}\text{FN}_2\text{O}_2\text{S}$ ($\text{M} + \text{H}$)⁺ 407.1224, found 407.1224.

(E)-3-(4-Methylbenzylidene)-2'-oxo-3'-phenyl-2',3',4,5-tetrahydro-1'H,3H-spiro[furan-2,4'-quinazoline]-7'-carbonitrile (3ii):



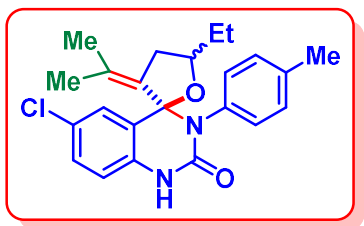
White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 265–267 °C. Yield 137 mg, 84%. ^1H NMR (400 MHz, CDCl_3) δ 10.10 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.48 (t, J = 7.0 Hz, 1H), 7.43–7.39 (m, 2H), 7.34–7.29 (m, 2H), 7.16 (d, J = 7.8 Hz, 2H), 7.13 (s, 1H), 7.04 (d, J = 7.8 Hz, 2H), 6.58 (d, J = 8.4 Hz, 1H), 6.42 (t, J = 2.6 Hz, 1H), 3.90–3.79 (m, 2H), 2.84–2.76 (m, 1H), 2.35 (s, 3H), 2.22–2.13 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.1, 141.9, 139.4, 138.0, 137.9, 133.1, 133.0, 131.9, 131.8, 131.6, 129.3, 129.2, 128.9, 128.6, 128.5, 128.2, 123.9, 119.1, 115.6, 104.8, 98.5, 67.5, 31.1, 21.2. IR (KBr, neat) ν 3234, 3064, 2941, 2224, 1678, 1612, 1414, 1389, 1036, 709, 515 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 408.1707, found 408.1710.

(E)-5-Ethyl-7'-methyl-3-(naphthalen-2-ylmethylene)-3'-(*p*-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (3jm):



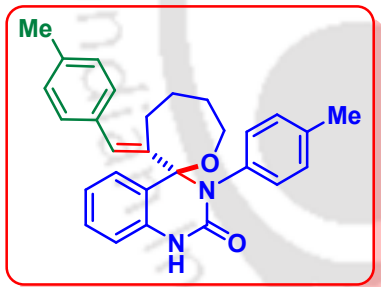
White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 133–135 °C. Yield 173 mg, 91% (d.r. = 2:1). ^1H NMR (500 MHz, CDCl_3) δ 8.40 (s, 1H, minor), 8.30 (s, 1H, major), 7.72–7.68 (m, 4H, major), 7.59 (s, 4H, minor), 7.46–7.30 (m, 3H), 7.18–7.13 (m, 2H), 7.07 (d, J = 7.9 Hz, 1H), 7.00–6.87 (m, 3H), 6.66–6.59 (m, 2H, major), 6.52 (d, J = 3.2 Hz, 2H, minor), 3.84–3.78 (m, 1H, minor), 3.34–3.28 (m, 1H, major), 2.82 (dd, J = 16.0, 5.4 Hz, 2H, minor), 2.62–2.49 (m, 2H, major), 2.28 (d, J = 10.4 Hz, 3H), 2.20 (s, 3H), 1.67–1.58 (m, 1H), 1.47–1.34 (m, 1H), 0.84–0.80 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.8, 152.5, 146.6, 144.5, 137.6, 137.4, 135.7, 134.3, 134.2, 133.4, 133.33, 133.29, 132.52, 132.48, 132.1, 131.8, 131.5, 131.3, 130.2, 129.6, 129.3, 129.0, 128.6, 128.1, 128.02, 127.97, 127.83, 127.78, 127.6, 127.4, 127.3, 127.2, 126.4, 126.3, 126.2, 123.7, 123.2, 114.3, 114.2, 99.7, 99.0, 80.9, 79.4, 37.5, 36.9, 29.5, 28.3, 21.3, 21.2, 21.0, 10.3, 10.0. IR (KBr, neat) ν 3209, 3046, 2962, 2925, 1669, 1604, 1511, 1416, 1388, 1265, 1017, 817, 738, 476 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{32}\text{H}_{31}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 475.2380, found 475.2380.

7'-Chloro-5-ethyl-3-(propan-2-ylidene)-3'-(*p*-tolyl)-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (3kv):



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 240–242 °C. Yield 150 mg, 98% (d.r. = 7:3). ^1H NMR (500 MHz, CDCl_3) δ 9.00 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.36–7.30 (m, 2H), 7.14 (dd, J = 8.5, 2.3 Hz, 1H), 7.06 (dd, J = 2.3 Hz, 1H), 7.04–7.00 (m, 1H), 6.67 (d, J = 8.5 Hz, 1H), 3.77–3.72 (m, 1H), 2.57 (dd, J = 15.0, 5.7 Hz, 1H), 1.72–1.64 (m, 1H), 1.56 (s, 3H), 1.46 (d, J = 2.7 Hz, 3H), 1.44–1.38 (m, 2H), 0.86 (t, J = 7.6 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.0, 138.5, 133.8, 133.6, 131.3, 130.7, 129.4, 129.1, 128.1, 127.8, 126.6, 125.6, 124.4, 116.0, 96.0, 77.7, 37.6, 28.1, 22.7, 21.5, 10.2. IR (KBr, neat) ν 3245, 2960, 2928, 1681, 1599, 1491, 1409, 1379, 1257, 982, 707, 557 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{24}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 383.1521, found 383.1521.

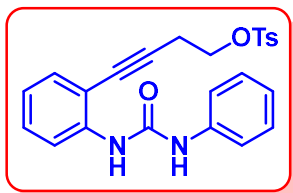
(*E*)-3-(4-methylbenzylidene)-3'-(*p*-tolyl)-1'*H*-spiro[oxepane-2,4'-quinazolin]-2'(3'*H*)-one (3li):



White semi-solid; R_f (Hexane:EtOAc, 3:2) 0.5. Yield 34 mg, 20%. ^1H NMR (400 MHz, CDCl_3) δ 7.38 (d, J = 8.0 Hz, 2H), 7.25 (s, 1H), 7.23–7.19 (m, 2H), 7.16 (s, 1H), 7.13–6.99 (m, 5H), 6.86 (td, J = 7.1, 2.0 Hz, 1H), 6.60 (d, J = 7.5 Hz, 1H), 6.44 (t, J = 1.9 Hz, 1H), 3.59 (t, J = 6.2 Hz, 2H), 2.32–2.26 (m, 4H), 2.23 (s, 3H), 2.20–2.15 (m, 1H), 1.71–1.62 (m, 2H), 1.61–1.54 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 151.6, 151.5, 148.2, 141.7, 138.8, 136.2, 135.9, 132.5, 130.0, 129.5, 129.2, 127.7, 124.4, 123.8, 123.4, 123.1, 122.7, 120.6, 119.4, 91.0, 62.6, 32.4, 26.5, 23.4, 21.4, 20.8. IR (KBr, neat) ν 3283, 2924, 2858, 1634, 1585, 1519, 1478, 1409, 1227, 1029, 908, 816, 760, 730, 648, 504 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{28}\text{H}_{29}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 425.2224, found 425.2225.

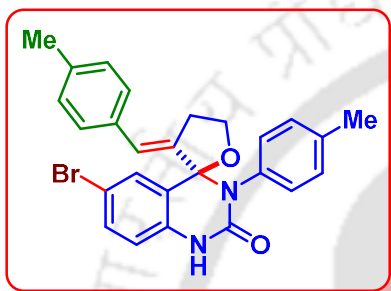
4-(2-(3-Phenylureido)phenyl)but-3-yn-1-yl 4-methylbenzenesulfonate (6):

White semi-solid; R_f (Hexane:EtOAc, 7:3) 0.6. Yield 282 mg, 65%. ^1H NMR (500 MHz, CDCl_3) δ 8.22 (d, J = 8.3 Hz, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.62–7.58 (m, 1H), 7.47 (s, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.25–7.17 (m, 6H), 6.95 (t, J = 7.4 Hz, 1H), 6.85 (t, J = 7.5 Hz,



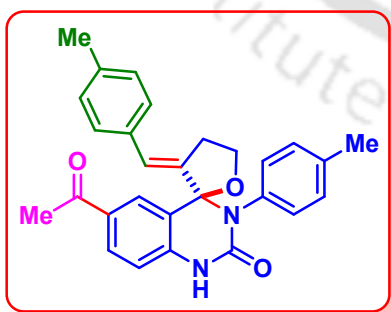
1H), 4.18 (t, $J = 5.7$ Hz, 2H), 2.77 (t, $J = 5.6$ Hz, 2H), 2.34 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.6, 145.7, 140.4, 138.8, 132.3, 131.8, 130.2, 130.0, 129.4, 128.9, 128.0, 127.8, 123.3, 121.9, 120.1, 119.0, 111.2, 91.1, 78.7, 68.3, 21.7, 21.1. IR (KBr, neat) ν 3340, 2954, 2926, 2852, 1682, 1601, 1496, 1446, 1187, 1174, 1029, 757, 552 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{23}\text{N}_2\text{O}_4\text{S}$ ($\text{M} + \text{H}$) $^+$ 435.1373, found 435.1381.

(E)-6'-Bromo-3-(4-methylbenzylidene)-3'-(*p*-tolyl)-4,5-dihydro-1*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (8):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 216–218 $^{\circ}\text{C}$. Yield 152 mg, 80%. ^1H NMR (400 MHz, CDCl_3) δ 9.35 (s, 1H), 7.32 (d, $J = 8.0$ Hz, 1H), 7.17–7.12 (m, 2H), 7.11 (d, $J = 1.9$ Hz, 1H), 7.07 (d, $J = 8.0$ Hz, 2H), 6.99 (d, $J = 7.9$ Hz, 3H), 6.92 (d, $J = 8.2$ Hz, 1H), 6.53 (d, $J = 8.5$ Hz, 1H), 6.37 (t, $J = 2.7$ Hz, 1H), 3.79 (q, $J = 8.0$ Hz, 1H), 3.70 (td, $J = 8.5, 4.4$ Hz, 1H), 2.74–2.66 (m, 1H), 2.29 (s, 3H), 2.27 (s, 3H), 2.17–2.08 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.5, 142.5, 137.7, 137.6, 135.4, 134.7, 133.5, 132.3, 131.4, 129.8, 129.5, 129.2, 128.55, 128.53, 125.0, 116.4, 113.9, 98.8, 67.4, 31.1, 21.3, 21.2. IR (KBr, neat) ν 3235, 2923, 2870, 1676, 1599, 1411, 1379, 1259, 1039, 814, 512 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{24}\text{BrN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 475.1016, found 475.1037.

(E)-6'-Acetyl-3-(4-methylbenzylidene)-3'-(*p*-tolyl)-4,5-dihydro-1*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (9):



White solid; R_f (Hexane:EtOAc, 7:3) 0.5; mp 218–220 $^{\circ}\text{C}$. Yield 153 mg, 87%. ^1H NMR (400 MHz, CDCl_3) δ 9.34 (s, 1H), 8.23 (d, $J = 8.4$ Hz, 1H), 7.37 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.31 (t, $J = 7.9$ Hz, 1H), 7.13 (d, $J = 7.8$ Hz, 3H), 7.03 (d, $J = 8.0$ Hz, 2H), 6.95 (d, $J = 6.7$ Hz, 2H), 6.92 (s, 1H), 6.84 (t, $J = 7.5$ Hz, 1H), 4.18 (t, $J = 6.6$ Hz, 2H), 2.89 (t, $J = 6.7$ Hz, 2H), 2.20 (s, 3H), 2.13 (s, 3H), 1.79 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 201.0, 171.4, 153.2, 144.7, 140.4, 139.5, 136.9, 135.6, 133.1, 131.9, 131.8, 129.6, 129.5, 129.4, 125.1, 121.6, 121.1, 120.9, 62.9, 27.3, 21.4, 20.9, 20.8. IR (KBr, neat) ν

3213, 2958, 2923, 1739, 1686, 1506, 1386, 1234, 1037, 814, 754 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{28}\text{H}_{27}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 439.2016, found 439.2031.

3.8.1. Crystallographic Description

Table 3.8.1.1. Crystal parameters of compound **3ai**

Compound 3ai	CCDC 2279618
Formula	$\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_2$
Formula weight	396.47
T/K	298(2)
Crystal system	monoclinic
Space group	P 21/n
$a/\text{\AA}$	12.1441(13)
$b/\text{\AA}$	10.4866(11)
$c/\text{\AA}$	21.897(2)
$\alpha/^\circ$	90
$\beta/^\circ$	97.791(3)
$\gamma/^\circ$	90
$V/\text{\AA}^3$	2762.9(5)
Z	4
Abs. Coeff./ mm^{-1}	0.061
Abs. Correction	none
GOF on F^2	1.061
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0528$ $wR_2 = 0.1520$
R indices [all data]	$R_1 = 0.0675$ $wR_2 = 0.1771$

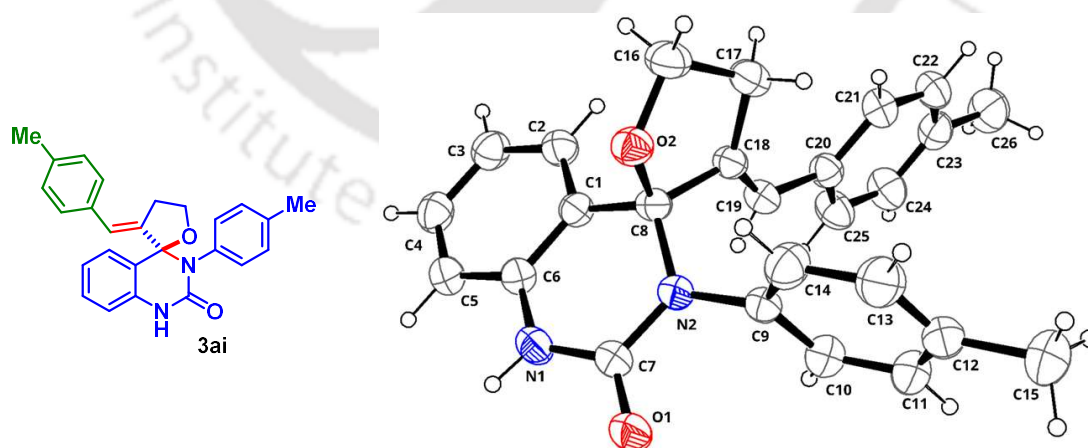
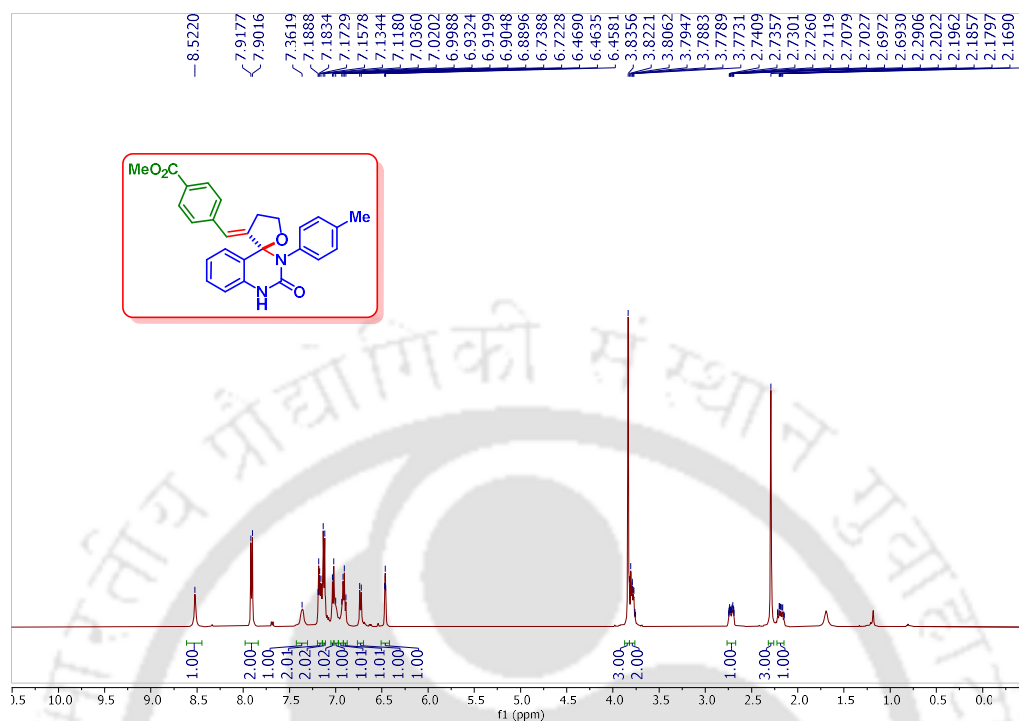
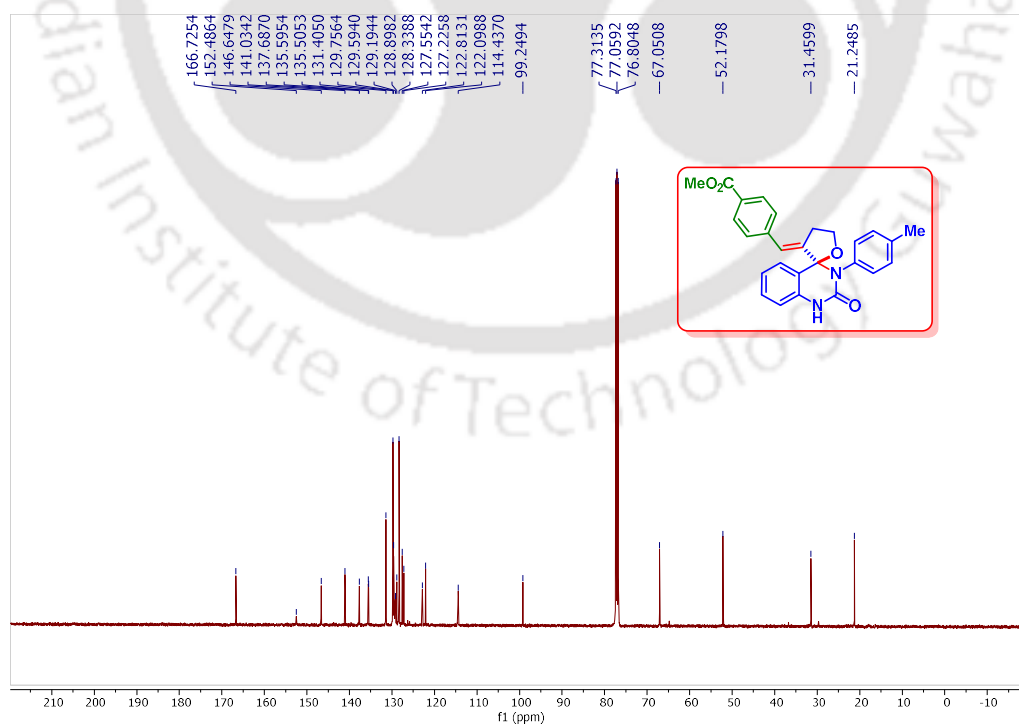


Figure 3.8.1.1. ORTEP diagram of compound **3ai** with thermal ellipsoid of 30% probability.

3.9. Representative Spectra

Figure 3.9.1. ¹H NMR spectrum of compound 3af (500 MHz, CDCl₃).Figure 3.9.2. ¹³C{¹H} NMR spectrum of compound 3af (125 MHz, CDCl₃).

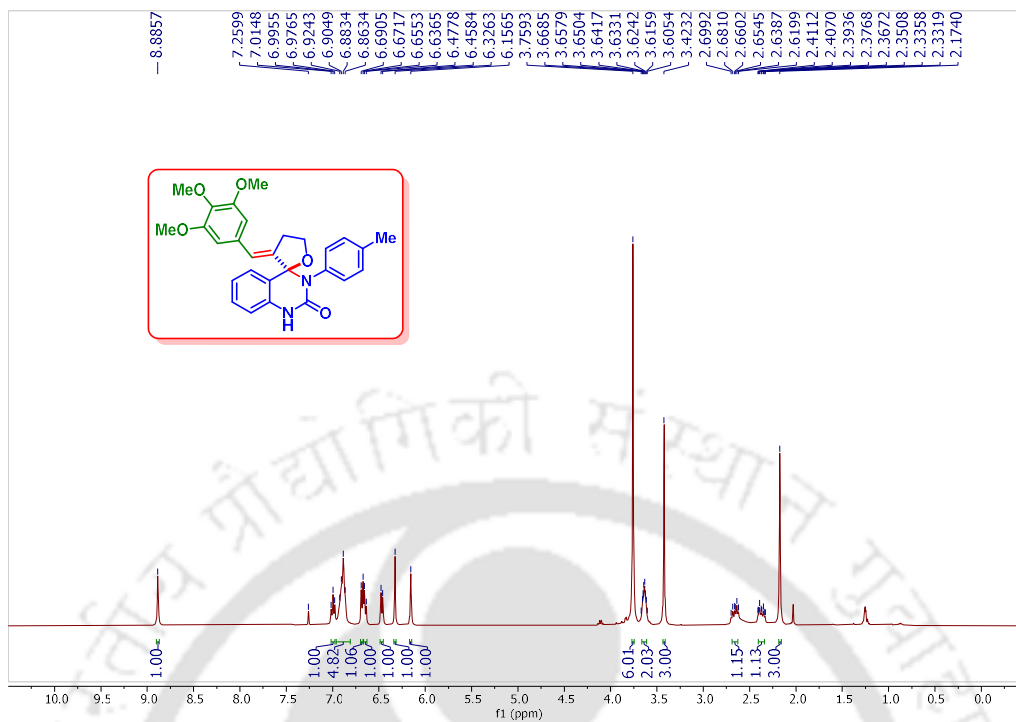


Figure 3.9.3. ^1H NMR spectrum of compound **3ak** (400 MHz, CDCl_3).

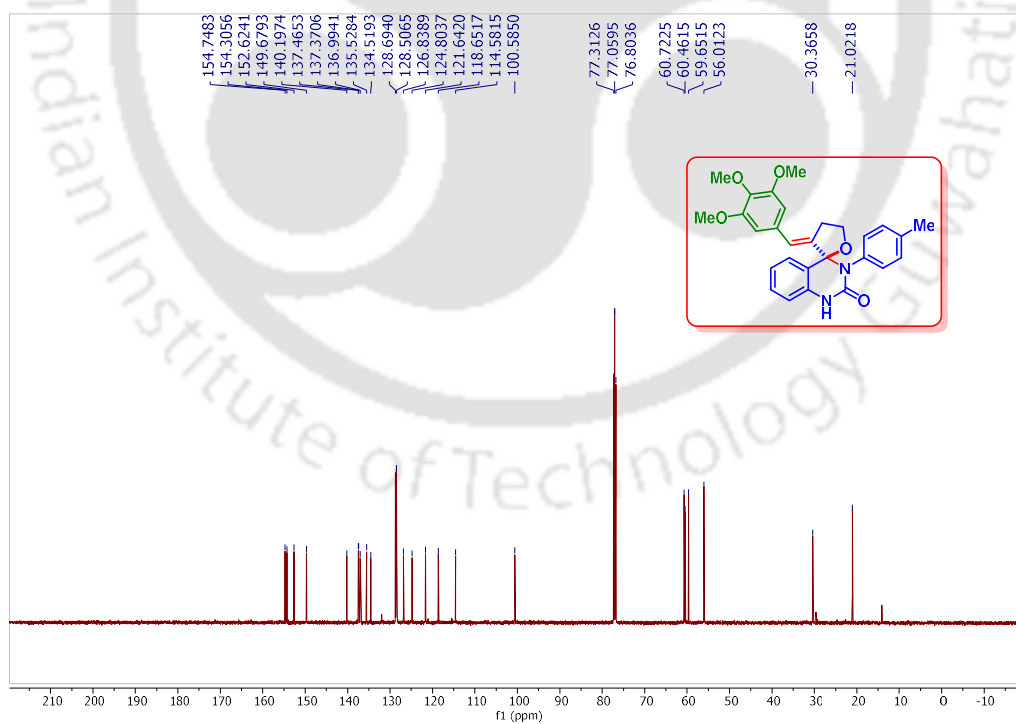


Figure 3.9.4. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of compound **3ak** (125 MHz, CDCl_3).

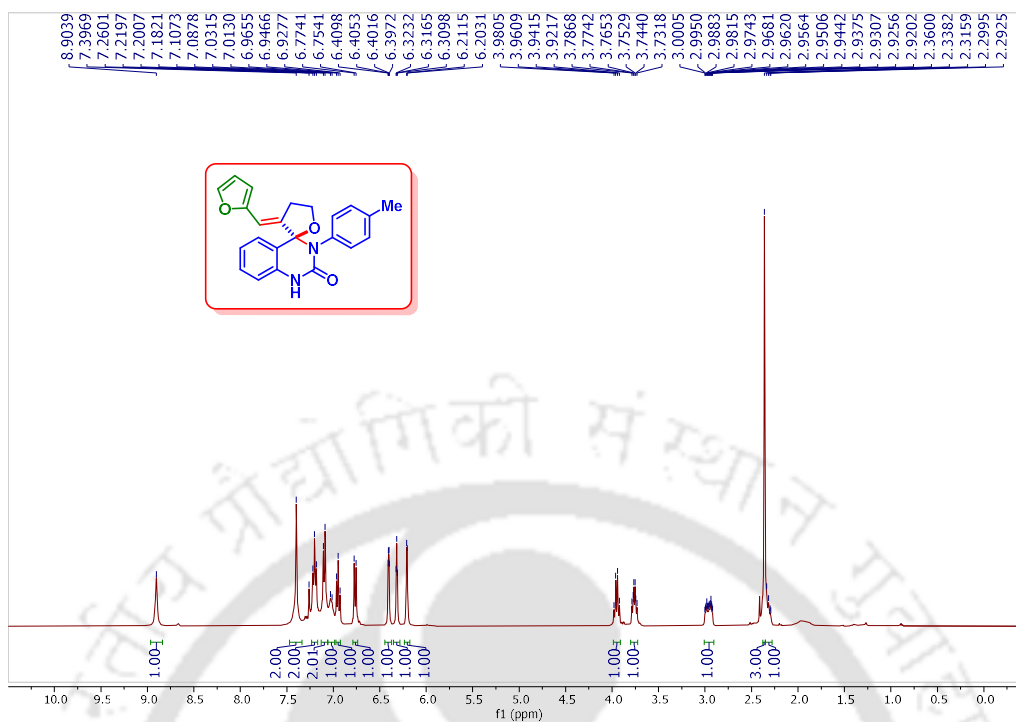


Figure 3.9.5. ¹H NMR spectrum of compound **3ap** (400 MHz, CDCl₃).

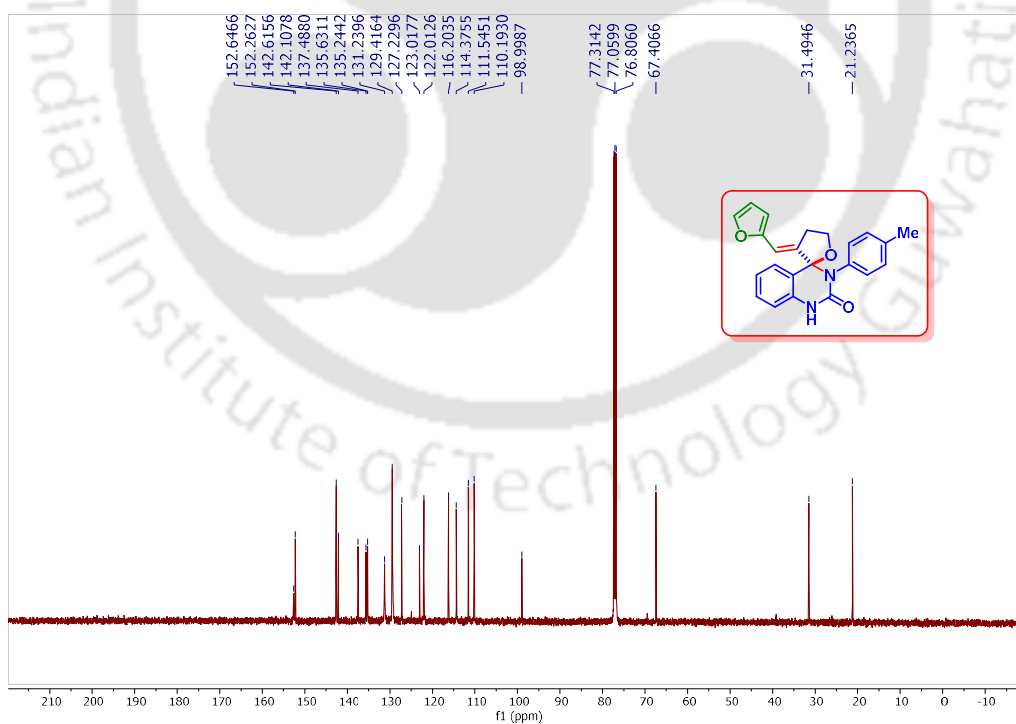


Figure 3.9.6. ¹³C{¹H} NMR spectrum of compound **3ap** (125 MHz, CDCl₃).

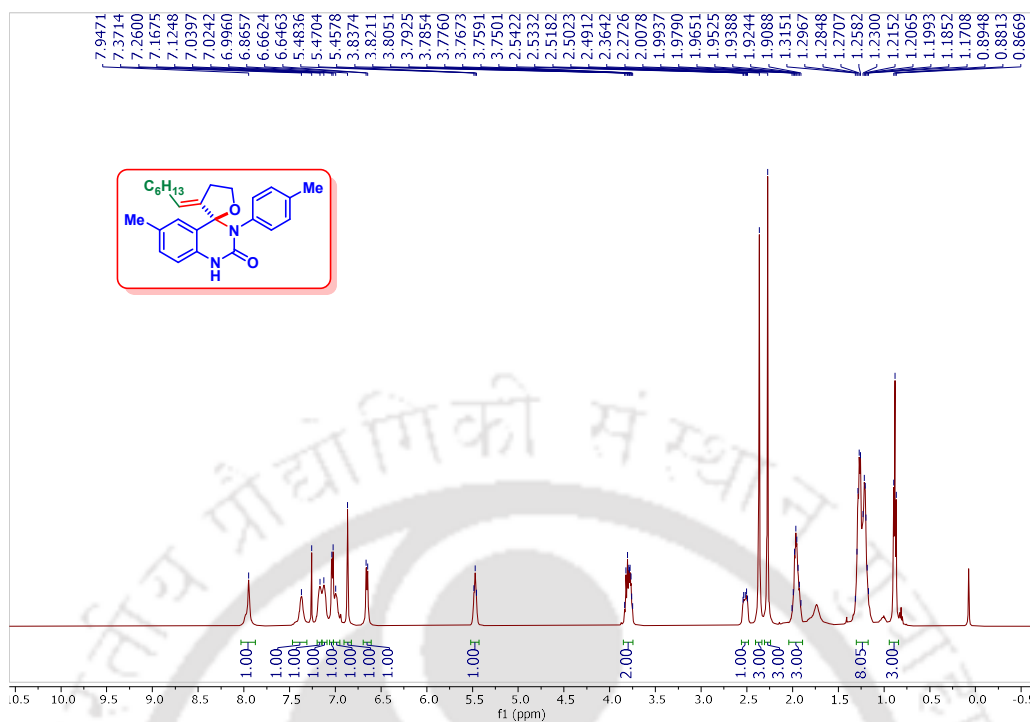


Figure 3.9.7. ¹H NMR spectrum of compound 3er (500 MHz, CDCl₃).

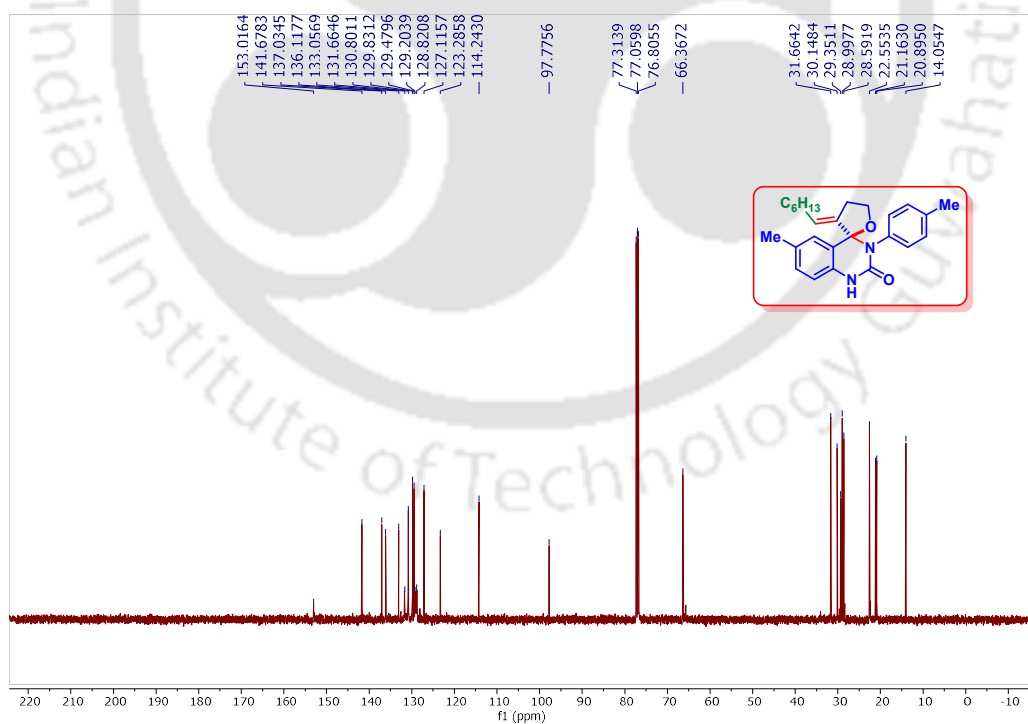


Figure 3.9.8. ¹³C{¹H} NMR spectrum of compound 3er (125 MHz, CDCl₃).

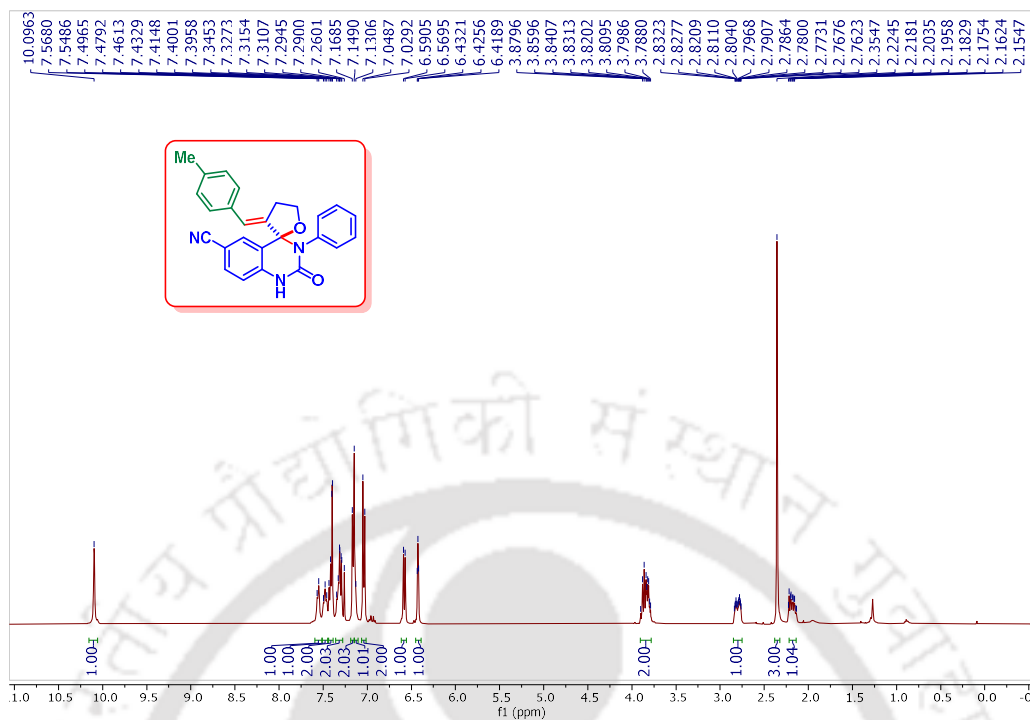


Figure 3.9.9. ¹H NMR spectrum of compound 3ii (400 MHz, CDCl₃).

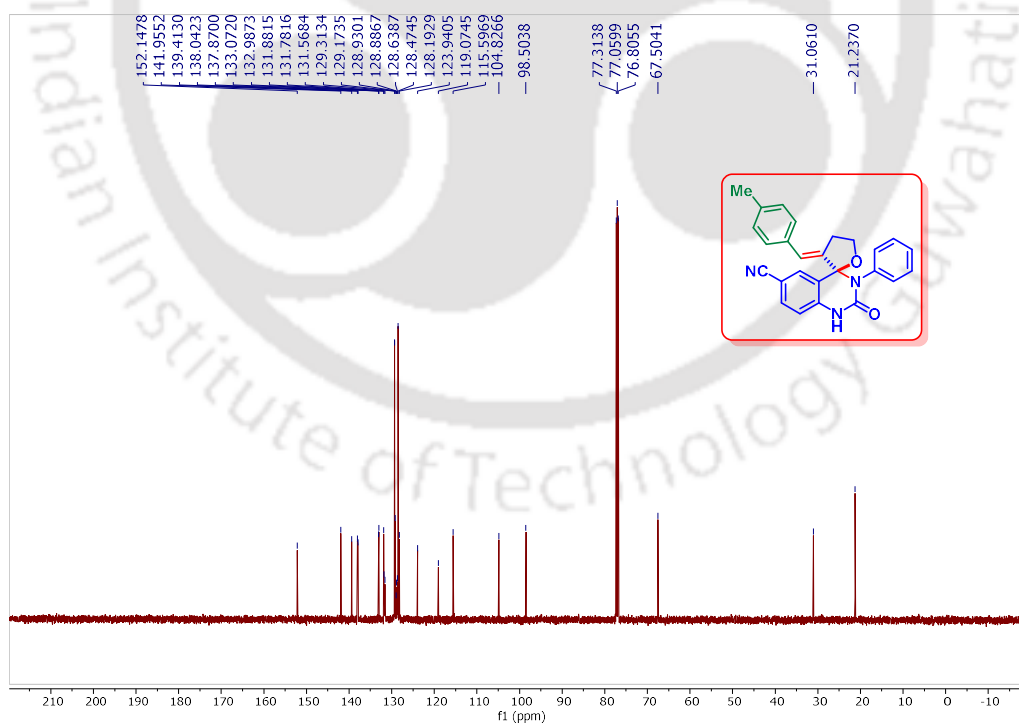


Figure 3.9.10. ¹³C{¹H} NMR spectrum of compound 3ii (125 MHz, CDCl₃).

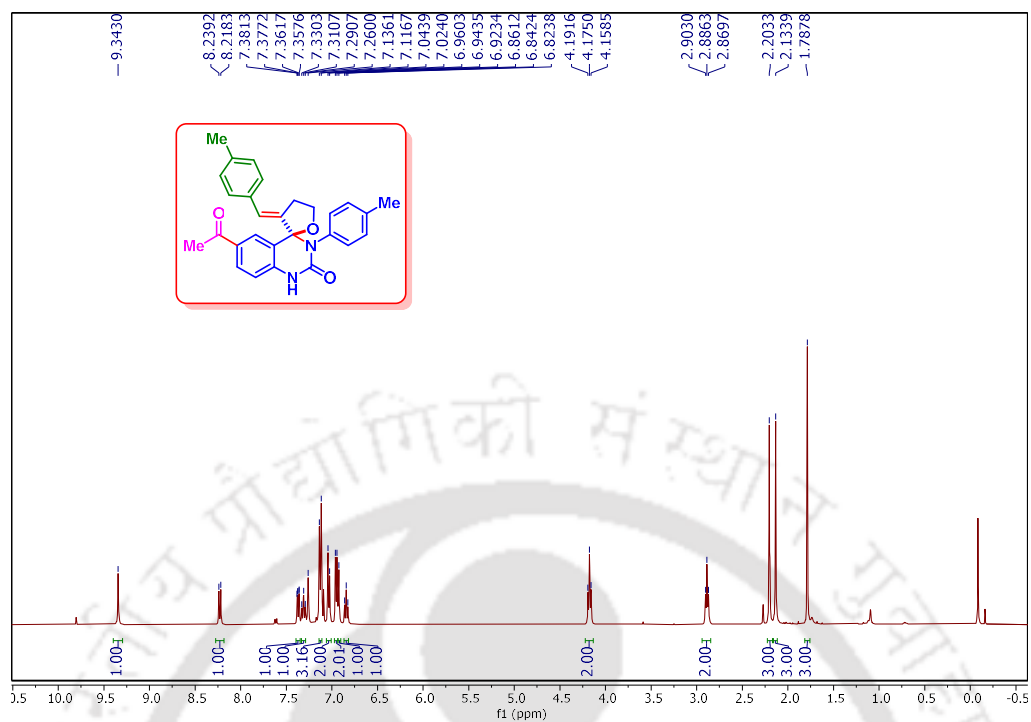


Figure 3.9.11. ^1H NMR spectrum of compound **9** (400 MHz, CDCl_3).

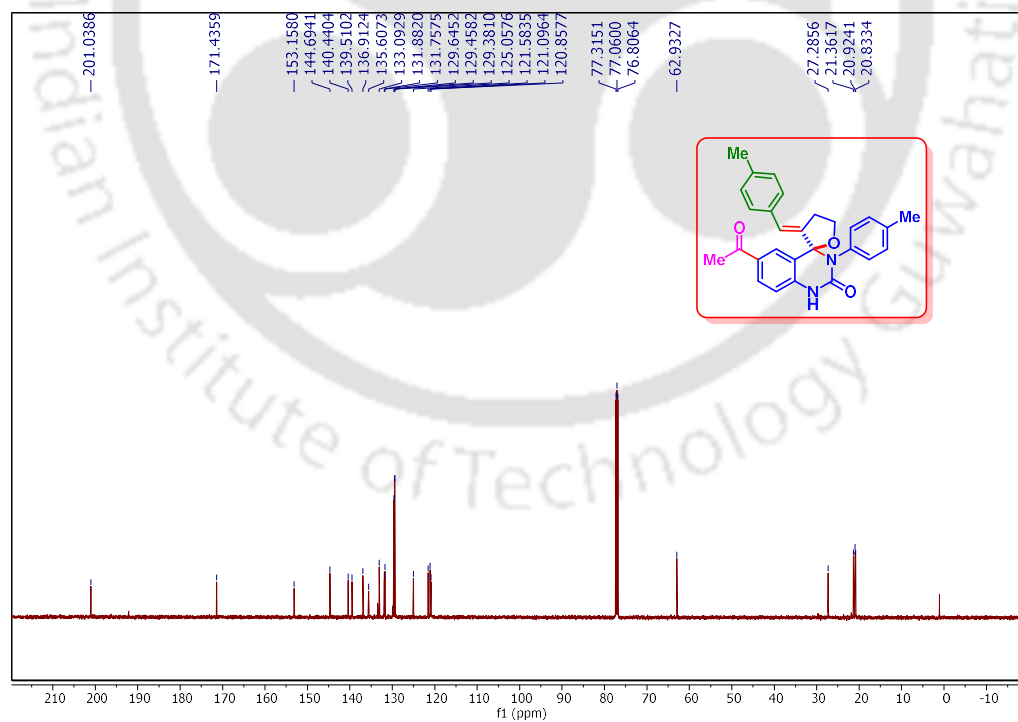
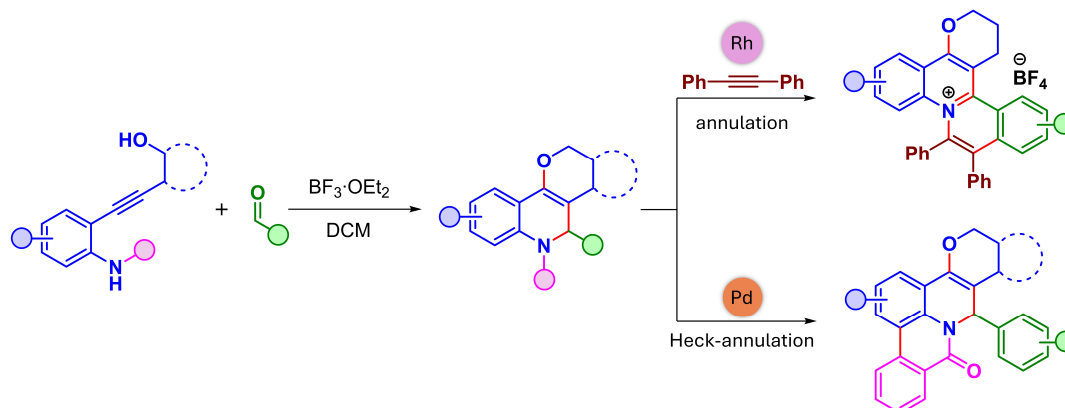


Figure 3.9.12. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of compound **9** (125 MHz, CDCl_3).





Cascade Alkynyl Prins Cyclization and Aza-Michael Reaction: *En Route* to Regioselective Pyrano- and Isochromenoquinoline Scaffolds



- Metal-free cascade protocol
- Polycyclic annulated products
- High functional-group tolerance
- Excellent yields, up to 98%

Abstract: A metal-free, Lewis acid approach for the regioselective synthesis of dihydropyranoquinoline scaffolds has been unveiled. The methodology employs a cascade aza-Prins–hydroalkoxylation protocol in a concerted manner. The strategy features mild reaction conditions, broad substrate scope, and high functional group tolerance. The protocol has been further extended to include isochromenoquinoline derivatives. The utility of the reaction lies in the synthesis of highly fused polycyclic N,O-heterocycles via intramolecular Heck coupling. Additionally, a Rh(III)-catalyzed annulation results in the formation of highly fluorescent pentacyclic ammonium salts in excellent yields. Photophysical studies reveal that these pentacyclic ammonium salts exhibit strong emission in the green region (500–550 nm).



Chapter IV

Cascade Alkynyl Prins Cyclization and Aza-Michael Reaction: *En Route* to Regioselective Pyrano- and Isochromenoquinoline Scaffolds

4.1 Introduction

Quinolines and related moieties are unique among nitrogen-containing heterocycles due to their exceptional pharmacological attributes.¹ Their widespread occurrence in alkaloids and natural products highlights their evolutionary significance and influence on conventional medical practices. Similarly, pyrans and their derivatives have been pivotal in propelling the advancement of modern pharmaceuticals.² Their diverse pharmacological profiles have spurred substantial growth in the pharmaceutical sector and facilitated the development of innovative drugs and therapeutic solutions. The rich pharmacophoric features of quinolines, combined with the advantageous pharmacokinetic properties of pyrans, provide a versatile framework for the development of novel pharmaceutical agents targeting various ailments, ranging from infectious diseases to cancer and neurodegenerative disorders.³

Pyrano[3,2-*c*]quinolines serve as a fundamental core unit in numerous naturally occurring alkaloids, including zanthosimuline, melicobisquinolinone-B, flindersine, veprisine, and oricine (Figure 4.1.1).^{3c,4} Many of these alkaloids have been reported to show cytotoxicity against several cancer cell lines, making them a promising target for potential anticancer agents. Some of their derivatives can inhibit migration, cellular growth, proliferation and induce apoptosis of MCF7 and MDA-MB-231 cell lines.⁵

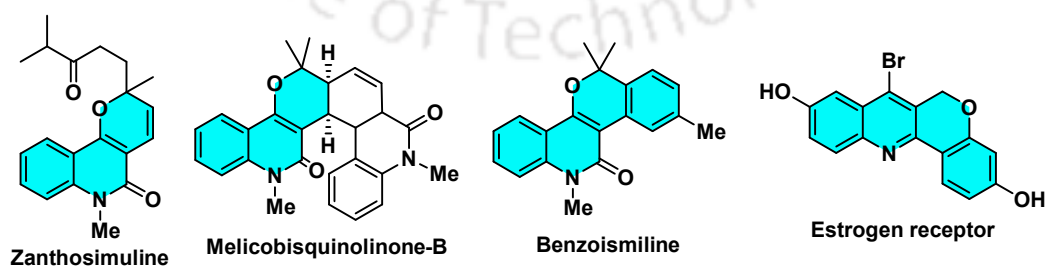


Figure 4.1.1. Representative examples of biologically active pyrano- and isochromeno-quinolines.

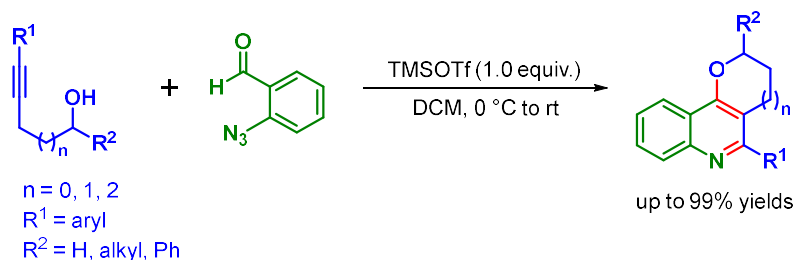
Moreover, pyrano[3,2-*c*]quinoline derivatives exhibit notable antiproliferative activity on leukemia and breast cancer cell lines.^{3b} They also display a broad spectrum of pharmacological effects, encompassing antibacterial,^{6a} antimicrobial,^{6a} anti-inflammatory,^{6b} α -glucosidase^{6c} and TNF- α inhibitory effects.^{6d} They act as antitubulin agents and show efficacy as antischistosomal and antihypertensive agents.⁷ Additionally, they can modulate critical physiological processes such as calcium signaling,^{8a} platelet aggregation,^{8b} and nitric oxide production.^{8c} Furthermore, these compounds are promising candidates for anti-Alzheimer's therapy.⁹ Beyond their medicinal applications, pyrano[3,2-*c*]quinolines extend their contribution to agrochemicals and material sciences for producing azo dyes and photodiodes, respectively.¹⁰ Likewise, the combination of chromene and quinoline scaffolds facilitates exploring diverse biological activities, along with extended branches in dye synthesis for bacteria and cell imaging.¹¹

Hydroalkoxylation reactions, characterized as the addition of alcohol across a C-C multiple bonds, have gained significant attention. Recent developments with alkynol scaffolds have re-established their participation in the hydroalkoxylation reaction of alkynes.¹² However, hydroalkoxylation of alkynes suffers from regioselectivity issues, mainly between *exo-dig* and *endo-dig* modes.¹³ Prins cyclization has established itself in contemporary chemistry because of its versatile and widespread application in the construction of complex molecules.¹⁴ Aza-Prins cyclization, its nitrogen variant, plays a crucial role in the synthesis of nitrogenous bioactive compounds and natural products.¹⁵ Despite its enormous potential for the synthesis of complex nitrogen heterocycles, aza-Prins cyclization has been less explored.

4.2. Differential Strategies Towards the Synthesis of Fused Quinoline Frameworks

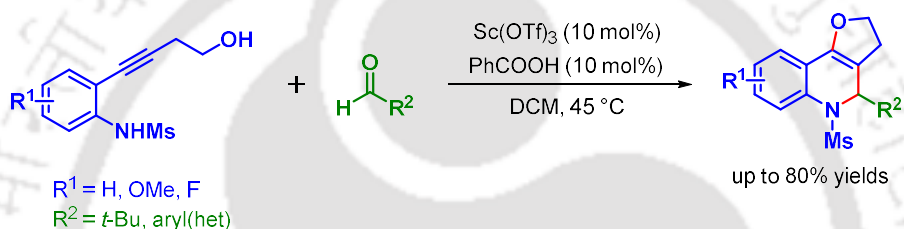
4.2.1. Synthesis of Pyrano-Quinolines

Gharpure's group described a metal-free, Lewis acid-promoted multi-segment, cascade coupling strategy for the chemoselective synthesis of cyclic ether fused-quinolines. The process involves the reaction of substituted alkynols and 2-azidobenzaldehydes through an oxonium ion triggered alkyne carboamination sequence to furnish the ether fused quinoline products (Scheme 4.2.1.1).¹⁶



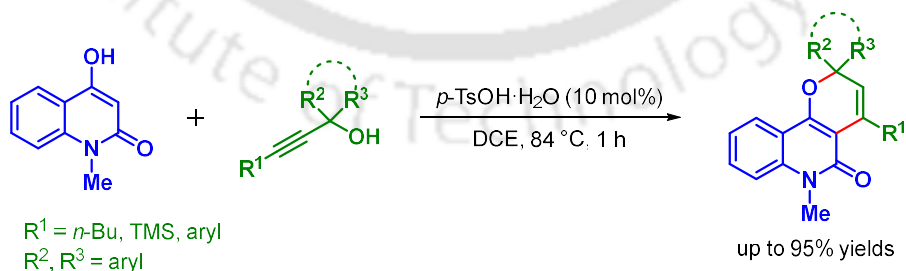
Scheme 4.2.1.1. Lewis acid promoted chemoselective synthesis of cyclic ether fused-quinolines

Ma's group described a $\text{Sc}(\text{OTf})_3$ -catalyzed Prins-type cyclization reaction of *o*-alkynylanilines with aldehydes to construct cyclic ether fused quinoline scaffolds in moderate to good yields (Scheme 4.2.1.2).¹⁷



Scheme 4.2.1.2. Prins-type cyclization for the synthesis of cyclic ether fused quinolines.

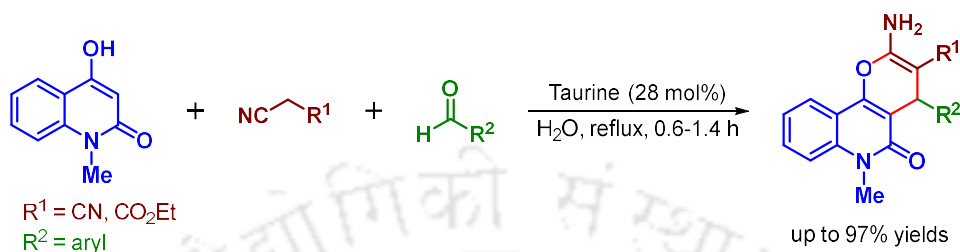
Wang's group reported a *p*-TsOH-catalyzed synthesis of pyrano[3,2-*c*]quinolones in moderate to good yields. The reaction proceeds through a Friedel-Crafts-type allenylation reaction between 4-hydroxymethylquinolinone and propargylic alcohols, followed by 6-*endo-dig* cyclization to afford the pyrano[3,2-*c*]quinolones derivatives (Scheme 4.2.1.3).¹⁸



Scheme 4.2.1.3. *p*-TsOH-catalyzed synthesis of pyrano[3,2-*c*]quinolones.

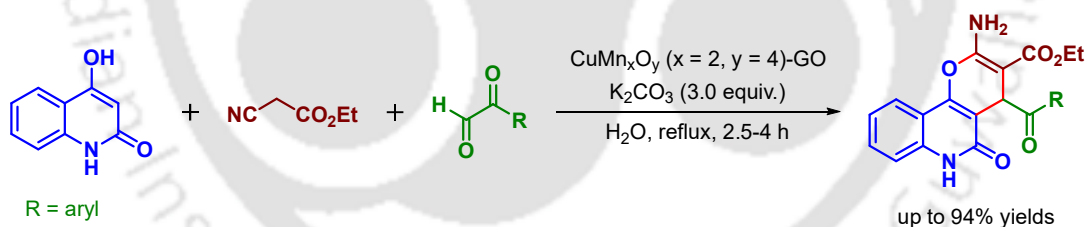
Guleria's group developed an efficient protocol for the green synthesis of pyrano-quinolones using taurine as a bio-organic catalyst and water as the solvent. This

tandem three-component reaction between malononitrile/ethylcyanoacetate, aldehydes, and 4-hydroxy-1-methyl-2(1*H*)-quinolone produces pyrano-quinolones in high yields, involves a straightforward workup procedure with simple filtration and no need for additional purification (Scheme 4.2.1.4).¹⁹



Scheme 4.2.1.4. Bio-organic catalyzed synthesis of pyrano-quinolones.

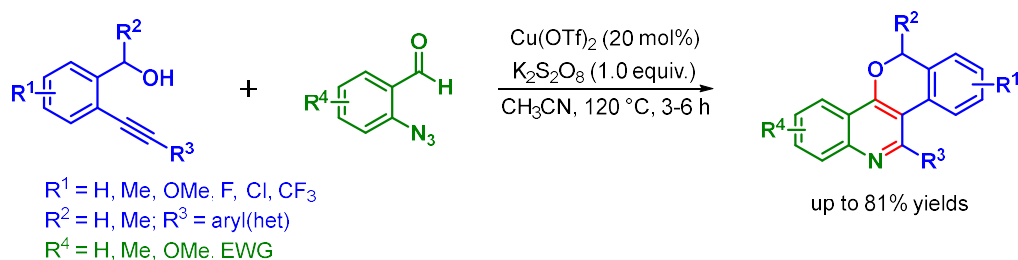
In response to the need for more eco-friendly approaches, Marjani's group developed a CuMn_xO_y -GO nano catalyst to synthesize pyrano-quinoline derivatives *via* an environmentally benign method. This one-pot multicomponent reaction of aryl glyoxal, 4-hydroxyquinolinone, and ethyl cyanoacetate, catalyzed by CuMn_xO_y -GO nano catalyst in the presence of K_2CO_3 and water furnished the desired pyrano-quinolines in high yields. The key features of this protocol are easy workup, recyclability of nanocatalyst, and high yields of products (Scheme 4.2.1.5).²⁰



Scheme 4.2.1.5. CuMn_xO_y -GO nano-catalyzed synthesis of pyrano-quinoline derivatives.

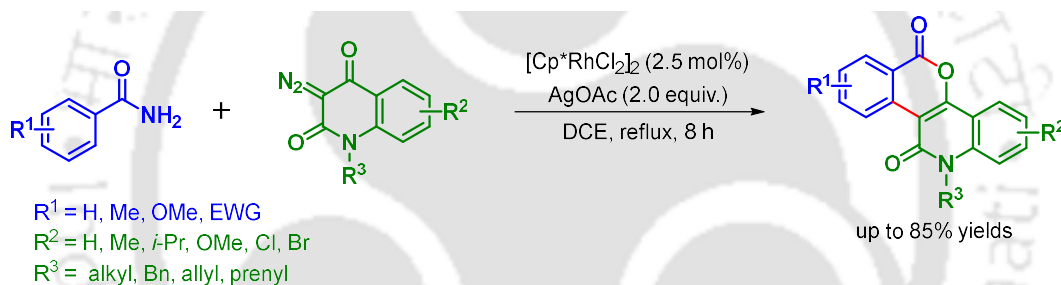
4.2.2. Synthesis of Isochromeno-Quinolines

Liu's group developed a copper-catalyzed cascade annulation protocol to synthesize isochromeno-quinolines from alkynols and 2-azidobenzaldehydes. The first step of this protocol is the intermolecular addition, which is entropically unfavourable, rather than the traditional intramolecular cycloisomerization. Subsequent intramolecular cyclization of the hemiacetal intermediate, followed by aromatization yields the desired N,O-heterocycle (Scheme 4.2.2.1).²¹



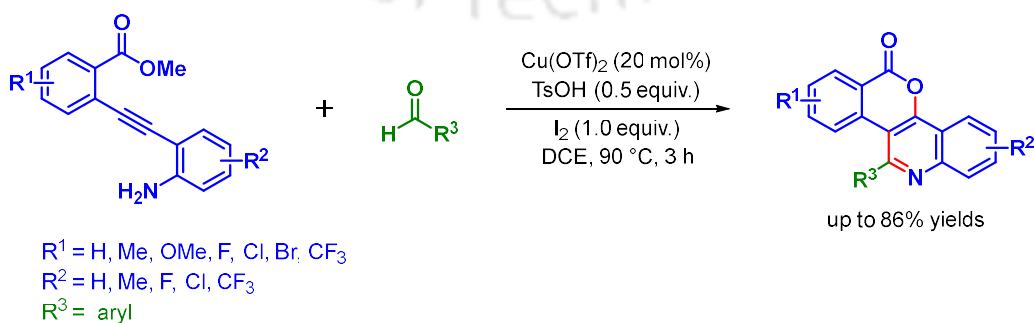
Scheme 4.2.2.1. Cu(II)-catalyzed synthesis of isochromeno-quinolines.

Lee's group established an efficient Rh(III)-catalyzed annulation strategy for the construction of a wide variety of highly functionalized isochromeno-quinolinediones. This reaction proceeds through a cascade C-H activation of arylamides, followed by carbene insertion of 3-diazoquinolinediones, and concludes with an intramolecular lactonization to afford the isochromeno-quinolinediones in good yields (Scheme 4.2.2.2).²²



Scheme 4.2.2.2. Rh(III)-catalyzed annulation strategy for the synthesis of isochromeno-quinolinediones.

Liu's group demonstrated a Cu(OTf)₂-catalyzed intramolecular radical domino reaction for the efficient synthesis of a variety of diverse quinoline-annulated polyheterocyclic compounds from diarylacetylenes and aromatic aldehydes (Scheme 4.2.2.3).²³

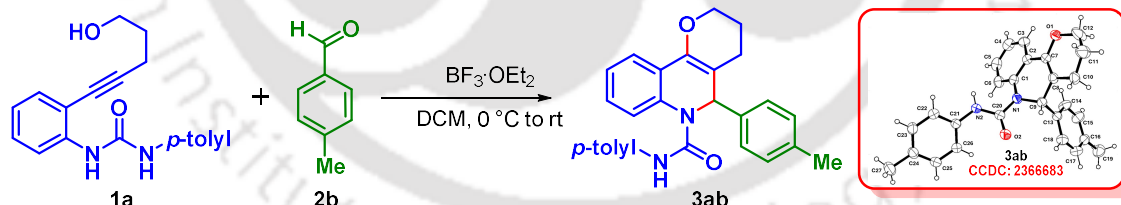


Scheme 4.2.2.3. Radical domino synthesis of isochromeno-quinolines.

4.3. Present Work

Several approaches have been documented for the synthesis of pyrano-quinoline and isochromeno-quinoline scaffolds. However, most of them either rely on metals or high temperature, leaving metal-free strategies underexplored. As highlighted in chapter I, while aza-Prins cyclization is a powerful tool to synthesize N-heterocycles, its application for the same remains limited. Furthermore, the use of cascade sequences incorporating the aza-Prins reaction has been sparsely investigated. We have developed a simple cascade sequence that enables the formation of fused pyrano-quinoline and isochromeno-quinoline scaffolds by employing aza-Prins-hydroalkoxylation strategy.

To begin with, an initial investigation was conducted between 1-(2-(5-hydroxypent-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea (**1a**) and *p*-tolualdehyde (**2b**) in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ (2.0 equiv.) in DCM at 0 °C to rt (Table 4.4.1.1, entry 1). To our delight, a new product was isolated in 98% yield within 30 minutes of the reaction. Spectroscopic evidence (^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR) and HRMS values revealed the structure of the product to be *N*,5-di-*p*-tolyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinoline-6(5*H*)-carboxamide (**3ab**). Finally, the exact structure of the synthesized compound was fully ascertained by single crystal X-ray diffraction of **3ab** (Scheme 4.3.1).



Scheme 4.3.1. Synthesis of dihydro-pyrano-quinoline.

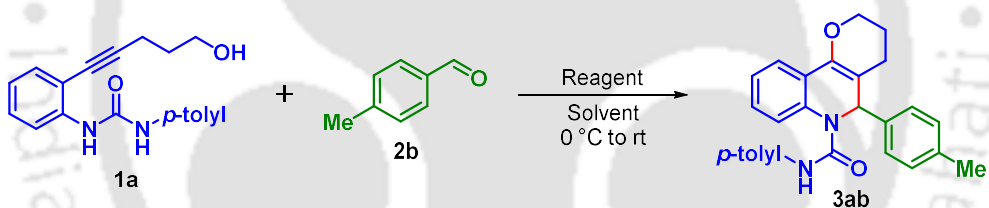
4.4. Results and Discussion

4.4.1. Optimization of the Reaction Conditions

In the pursuit of achieving optimal reaction conditions for this transformation, a series of optimization studies involving various reagents and solvents were conducted. When the reaction was performed with 1.2 and 0.5 equiv. of $\text{BF}_3 \cdot \text{OEt}_2$, the

desired product was obtained in 98 and 92% yields, respectively (Table 4.4.1.1, entries 2 and 3). However, the latter condition required a significantly prolonged reaction time for completion. A similar trend was observed with TMSOTf as the reagent, endowing the desired product in 98% yield within 1.0 h of the reaction (Table 4.4.1.1, entry 4). Furthermore, the reaction was screened with Brønsted acids. Whilst camphor sulfonic acid (CSA) and trifluoro acetic acid (TFA) fell short of expectations (Table 4.4.1.1, entries 7 and 8), TfOH and *p*-TsOH·H₂O efficiently facilitated the transformation, affording the product in 76 and 75% yields, respectively (Table 4.4.1.1, entries 5 and 6). Additionally, the reaction was also tuned with solvents like acetonitrile and toluene. However, the outcomes were less promising, with the desired product obtained in only 25% yield for acetonitrile (Table 4.4.1.1, entry 9) and 18% for toluene (Table 4.4.1.1, entry 10). Finally, 1.2 equiv. of BF₃·OEt₂ in DCM at 0 °C to rt are found to be the optimized conditions for the required transformation.

Table 4.4.1.1. Optimization of the reaction conditions.



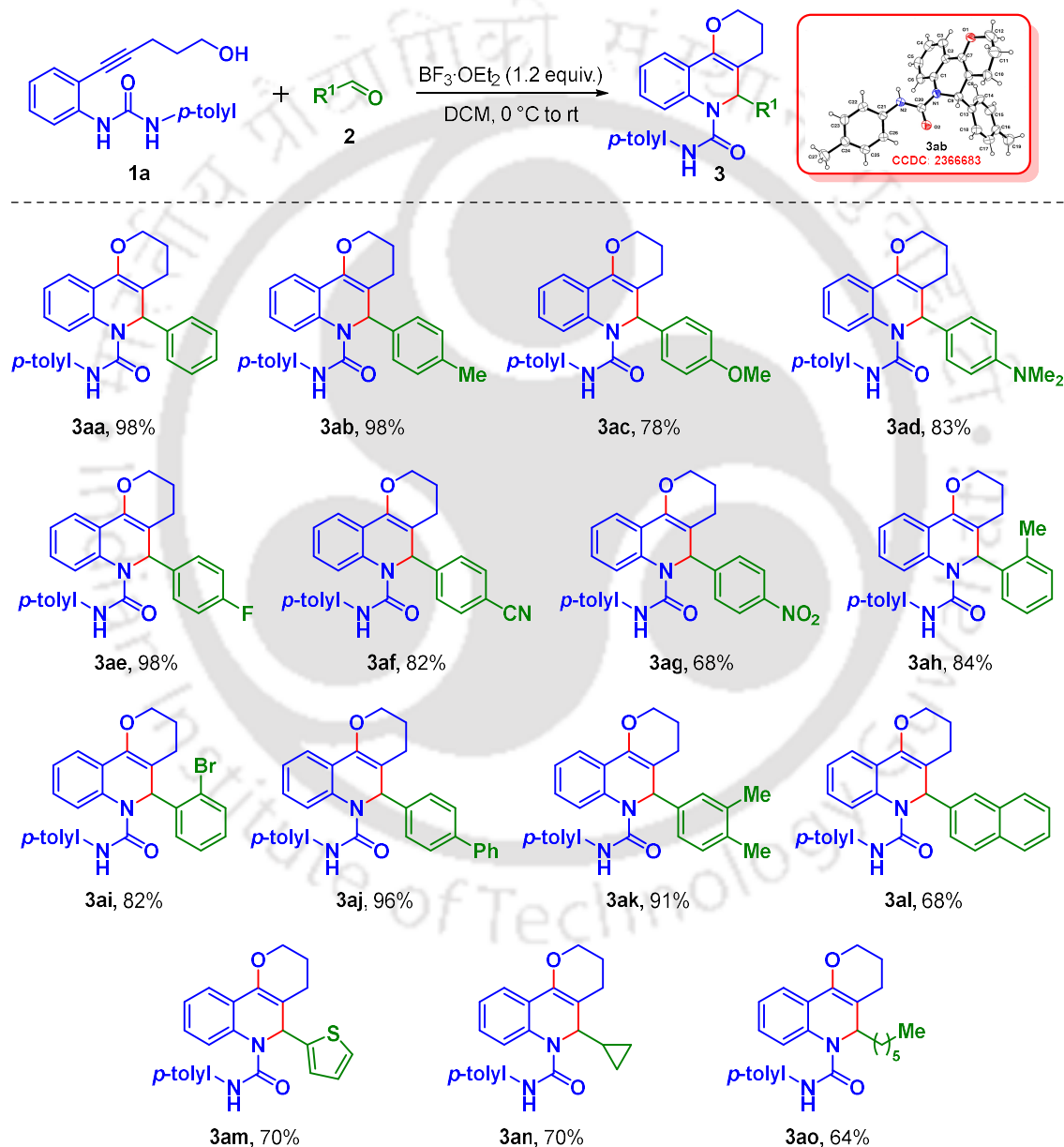
Entry ^a	Reagent	Equivalent	Solvent	Time (h)	Yield ^b (%)
1	BF ₃ ·OEt ₂	2.0	DCM	0.5	98
2	BF₃·OEt₂	1.2	DCM	0.5	98
3	BF ₃ ·OEt ₂	0.5	DCM	5.0	92
4	TMSOTf	1.2	DCM	1.0	98
5	TfOH	1.2	DCM	0.5	76
6	<i>p</i> -TsOH·H ₂ O	1.2	DCM	02	75
7	CSA	1.2	DCM	24	44
8	TFA	1.2	DCM	03	48
9	BF ₃ ·OEt ₂	1.2	CH ₃ CN	1.5	25
10	BF ₃ ·OEt ₂	1.2	Toluene	04	18

^aReaction conditions: **1a** (0.25 mmol, 1.0 equiv.), **2b** (0.30 mmol, 1.2 equiv.), solvent (4.0 mL), 0 °C to rt, N₂ atmosphere. ^bIsolated yields.

4.4.2. Substrate Scope

The generality of the transformation was explored to include various substrates. Initially, aldehydes **2** were changed (Scheme 4.4.2.1), followed by the *o*-alkynol diphenyl urea **1** (Scheme 4.4.2.2). Reaction of **1a** with benzaldehyde (**2a**) readily furnished the dihydro pyrano[3,2-*c*]quinoline carboxamide scaffold **3aa** in an

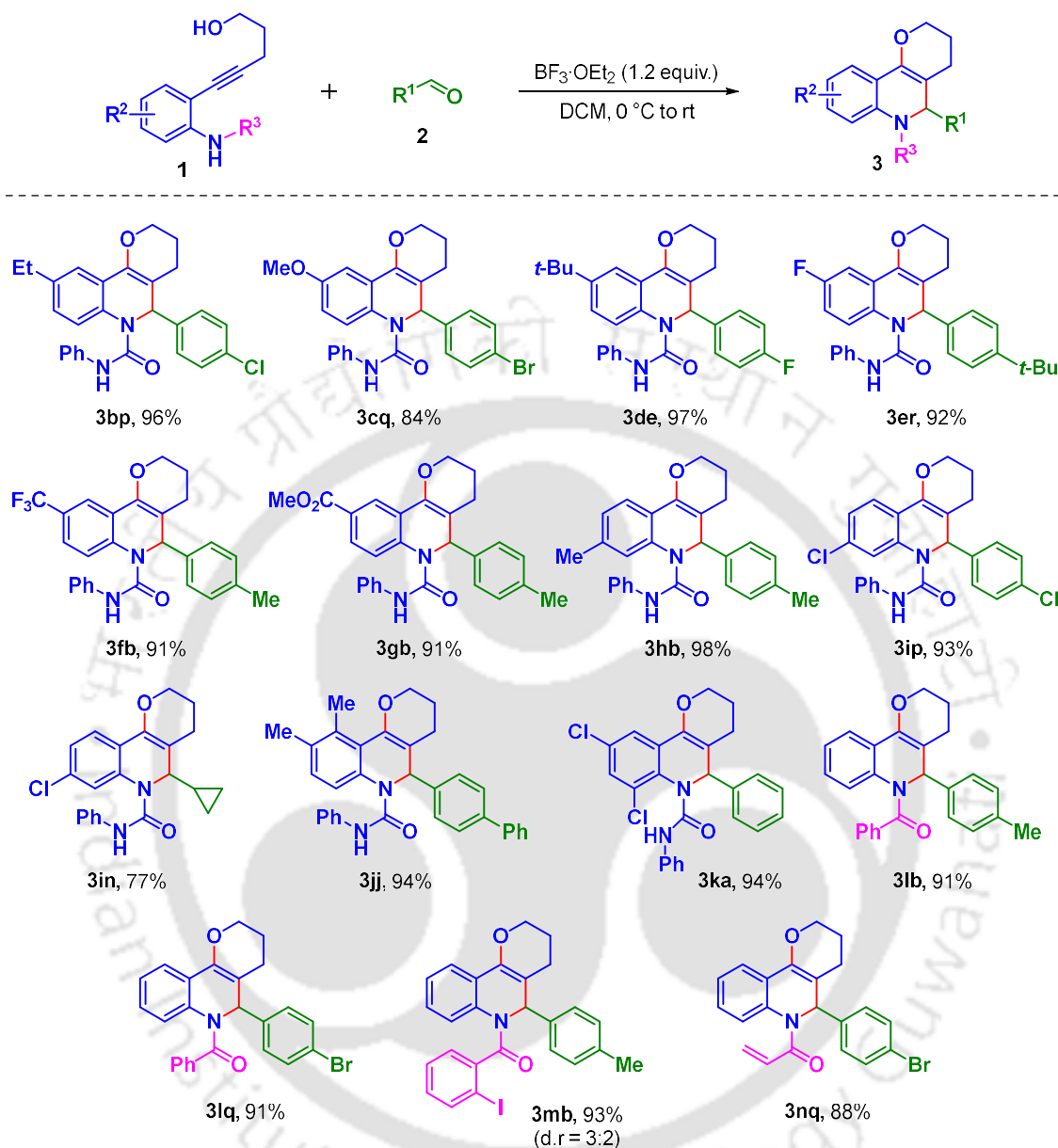
Scheme 4.4.2.1. Synthesis of dihydro-2*H*-pyrano[3,2-*c*]quinolines.



^aReaction conditions: **1a** (0.4 mmol), **2** (0.48 mmol), DCM (6 mL), 0 °C to rt, N_2 atmosphere. ^bIsolated Yields.

exceptional yield of 98%. When *p*-tolualdehyde (**2b**) was employed, the product **3ab** was obtained in a remarkable 98% yield within just 0.5 h of the reaction. Benzaldehydes bearing strong electron-donating groups like *p*-OMe and *p*-NMe₂ were equally compatible in the transformation, enduring their respective products **3ac** and **3ad** in 78 and 83% yields, respectively. The strategy worked equally well with strong electron-withdrawing groups. Benzaldehydes with *p*-F, *p*-CN and *p*-NO₂ groups furnished their respective products **3ae**, **3af** and **3ag** in 98, 82 and 68% yields. To account for the steric congestion during the transformation, *o*-methyl and *o*-bromobenzaldehydes were introduced into the system. The resulting products **3ah** and **3ai** from these sterically hindered aldehydes demonstrated good yields of 84% and 82%, respectively. Biphenyl-4-carboxaldehyde also furnished its product **3aj** in 96% yield. 3,4-dimethyl benzaldehyde advanced efficaciously with the protocol, resulting in the functionalized product **3ak** in 91% yield. Reaction with β -naphthaldehyde successfully produced the functionalized product **3al** in 68% yield. The behaviour of heterocyclic aldehyde towards the developed strategy was also explored. 2-Thiophenecarboxaldehyde provided the product **3am** in 70% yield. Long chain aldehyde (heptanal) and alicyclic aldehyde (cyclopropanecarboxaldehyde) afforded their respective products **3an** and **3ao** in 70 and 64% yields.

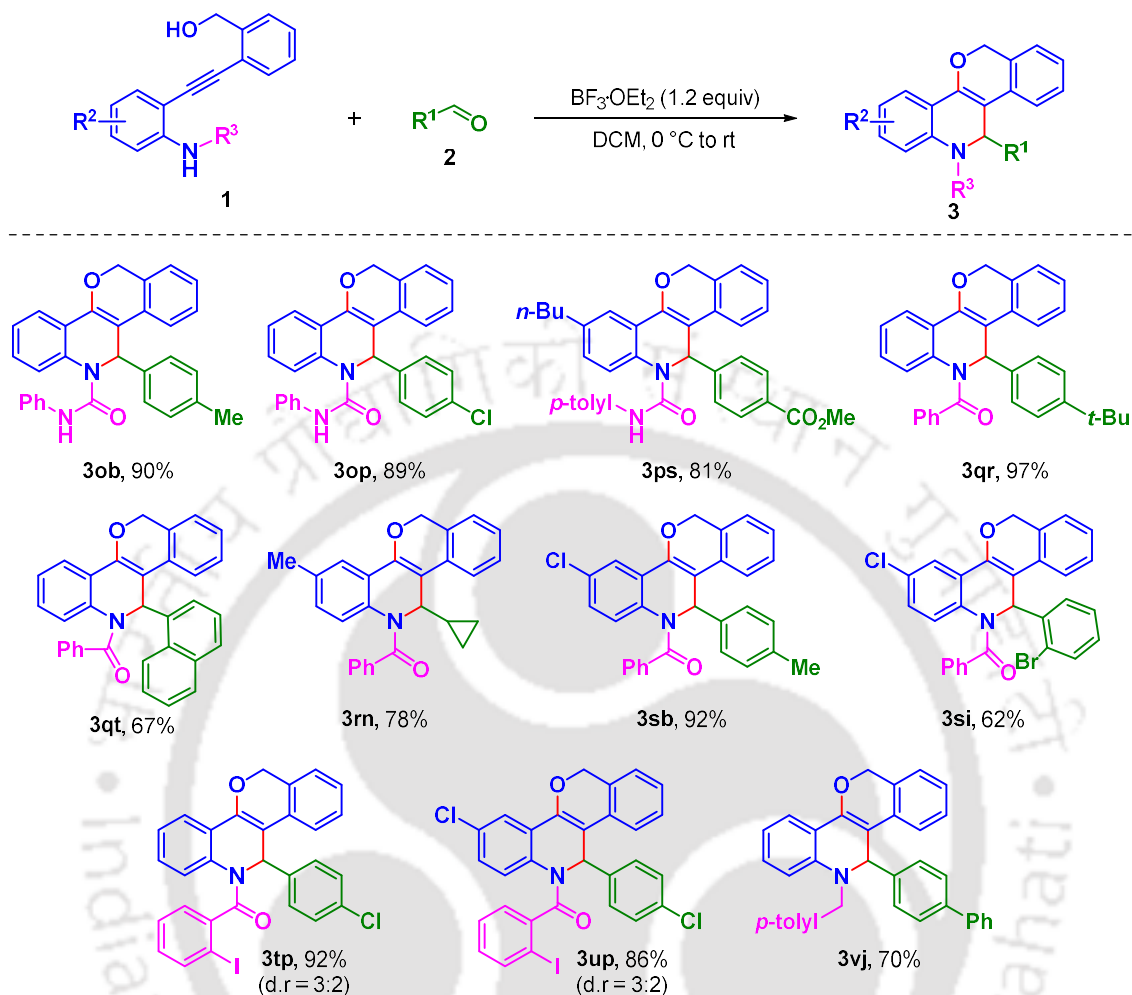
Further, to enhance the applicability of the transformation, various functionalities were incorporated into the *o*-alkynol diphenyl urea (Scheme 4.4.2.2). Initially, the “R²” group of the urea was varied with different types of electron-donating substituents. *o*-Alkynol diphenyl urea **1** equipped with weak, strong and bulky electron-donating substituents provided the dihydro pyrano[3,2-*c*]quinoline carboxamide derivatives **3bp**, **3cq** and **3de** in 96, 84 and 97% yields, respectively. Similarly, the *o*-alkynol urea was altered with strong electron-withdrawing substituents like F, CF₃ and CO₂Me, which furnished the products **3er**, **3fb** and **3gb** in 92, 91 and 91% yields, respectively. Steering the electron-donating and electron-withdrawing substituent of the *o*-alkynol ureas to the 5-position resulted the desired products **3hb**, **3ip** and **3in** in 98, 93 and 77% yields, respectively. Difunctionalized methyl and chloro *o*-alkynol ureas efficaciously afforded the products **3jj** and **3ka** in excellent yields. Changing the “R³” group furnished the products **3lb**, **3lq**, **3mb** and **3nq** in 88–91% yields.

Scheme 4.4.2.2. Synthesis of functionalized pyrano[3,2-*c*]quinolines.

^aReaction conditions: **1** (0.4 mmol), **2** (0.48 mmol), DCM (6 mL), 0 °C to rt, N₂ atmosphere.

^bIsolated Yields.

This protocol was further extended to synthesize isochromeno[4,3-*c*]quinoline derivatives (Scheme 4.4.2.3). Reaction of electron-donating and electron-withdrawing benzaldehydes **2** with **1** readily afforded the isochromeno[4,3-*c*]quinoline scaffolds **3** in moderate to good yields. α -Naphthaldehyde (**2t**) and cyclopropanecarboxaldehyde (**2n**) also furnished their respective products **3qt** and **3rn** in 67 and 78% yields,

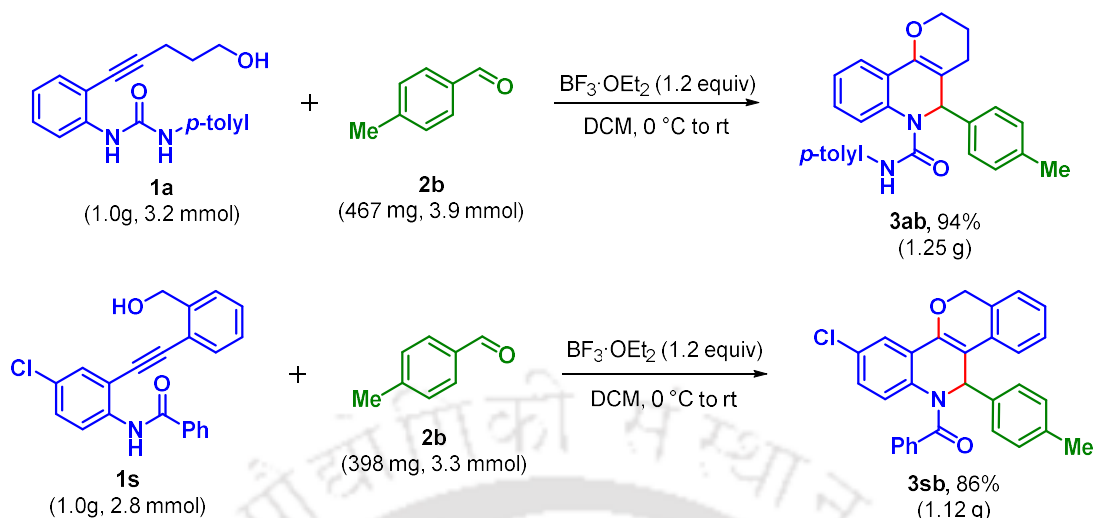
Scheme 4.4.2.3. Synthesis of isochromeno[4,3-*c*]quinolines.

^aReaction conditions: **1** (0.4 mmol), **2** (0.48 mmol), DCM (6 mL), 0 °C to rt, N_2 atmosphere.

^bIsolated Yields.

respectively. Changing the “ R^3 ” part of **1** resulted in the isochromeno[4,3-*c*]quinolines **3tp**, **3up** and **3vj** in 92, 86 and 70% yields, respectively.

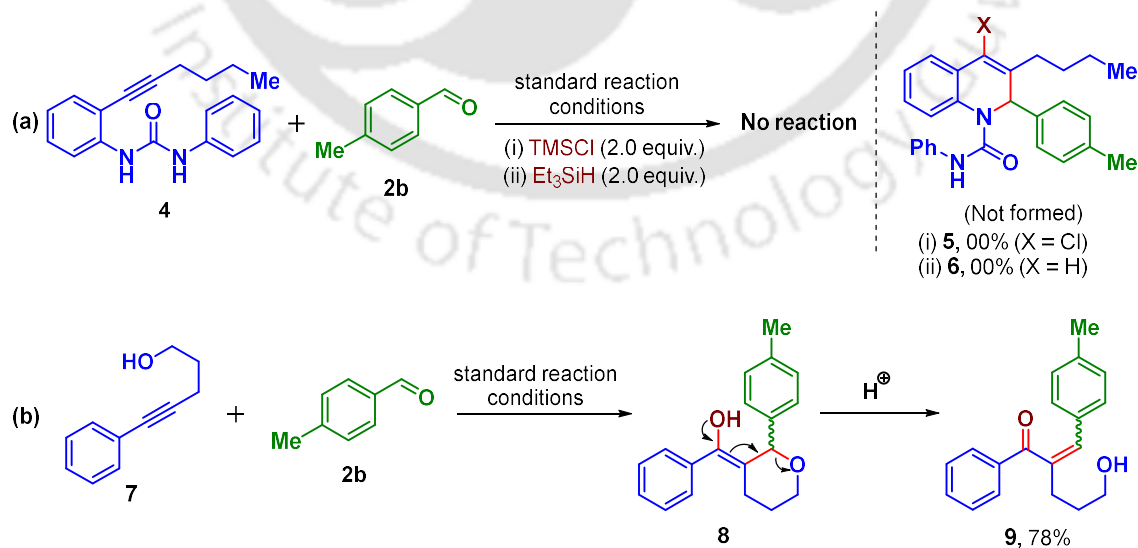
To demonstrate the scalability of this methodology, two scale-up synthesis were performed (Scheme 4.4.2.4). Under the standard reaction protocol, the resulting pyrano[3,2-*c*]quinoline **3ab** and isochromeno[4,3-*c*]quinoline **3sb** were obtained in good yields of 94% (1.25 g) and 86% (1.12 g), respectively.



Scheme 4.4.2.4. Scale-up experiment.

4.4.3. Control Experiment

To comprehend the mechanistic steps involved in the reaction, several control experiments were conducted (Scheme 4.4.3.1). The reaction of alkyne-substituted diphenyl urea **4** and *p*-tolualdehyde (**2a**) in presence of TMSCl was completely silent and did not provide any product (Scheme 4.4.3.1.a(i)). Likewise, when Et_3SiH was used as a nucleophile, the reaction failed to give any product (Scheme 4.4.3.1.a(ii)). Nevertheless, when phenyl substituted alkynol **7** was employed, the reaction did not furnish the anticipated hydroalkoxylated product. Rather a dihydropyranylidene

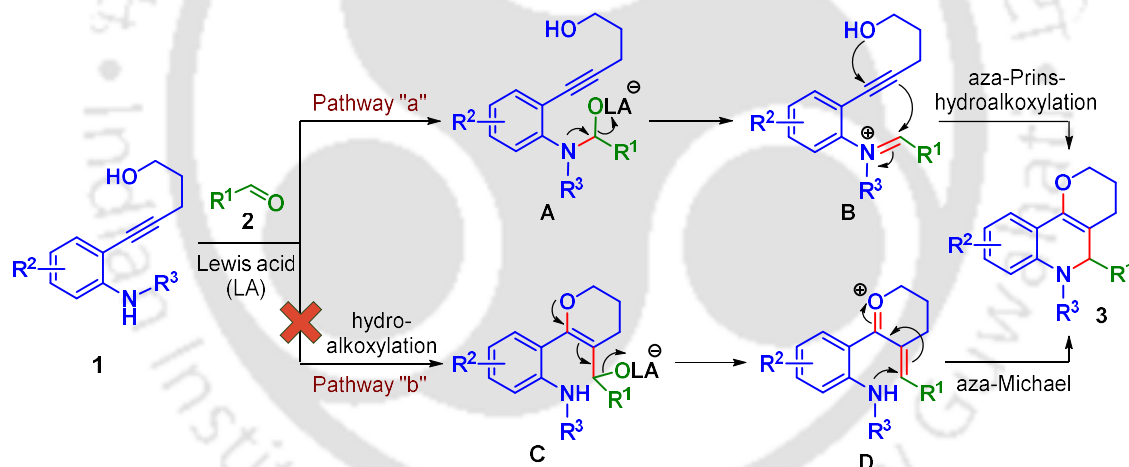


Scheme 4.4.3.1. Control experiment.

intermediate **8** was produced, which subsequently rearranged to a more stable α,β -unsaturated carbonyl compound **9** in 78% yield ((Scheme 4.4.3.1.b). When aza-Prins cyclization of **4** and hydroalkoxylation of **7** were performed in isolation, both the reactions failed to provide their conventional products. These experiments indicate that the aza-Prins cyclization and hydroalkoxylation reactions proceed through a concerted route rather than a stepwise mechanism.

4.4.4. Plausible Mechanism

The mechanism can be represented in pathways "a" and "b" (Scheme 4.4.4.1). Pathway "b" proceeds *via* a hydroalkoxylation route,²⁴ followed by an aza-Michael reaction. While pathway "a" involves the generation of iminium ion intermediate **B**, which readily undergoes aza-Prins cyclization-hydroalkoxylation reaction to form the product **3**. Control experiments suggest that the transformation follows pathway "a" rather than pathway "b".

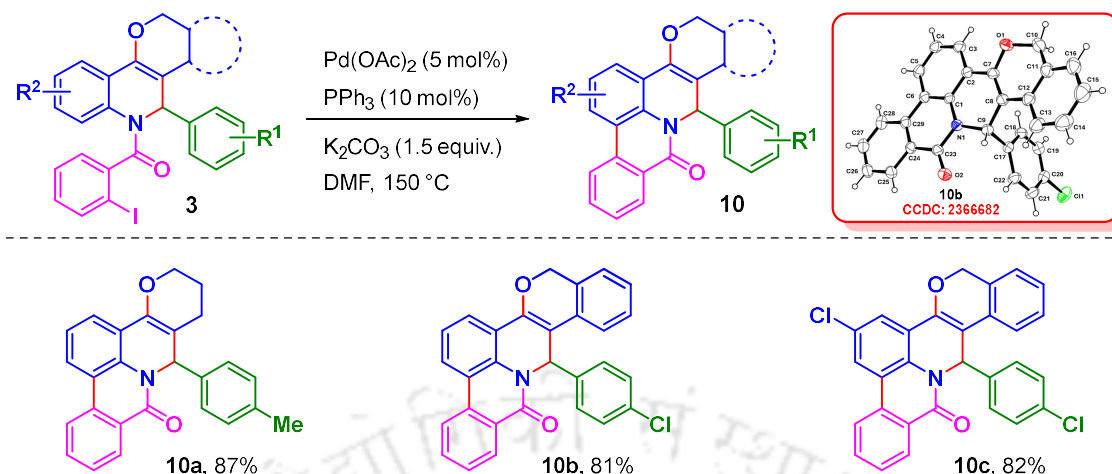


Scheme 4.4.4.1. Plausible mechanism for the synthesis of cyclic ether fused quinolines.

4.4.5. Synthetic Transformation

4.4.5.1. Intramolecular Heck Coupling of Cyclic Ether Fused Quinolines (**3**)

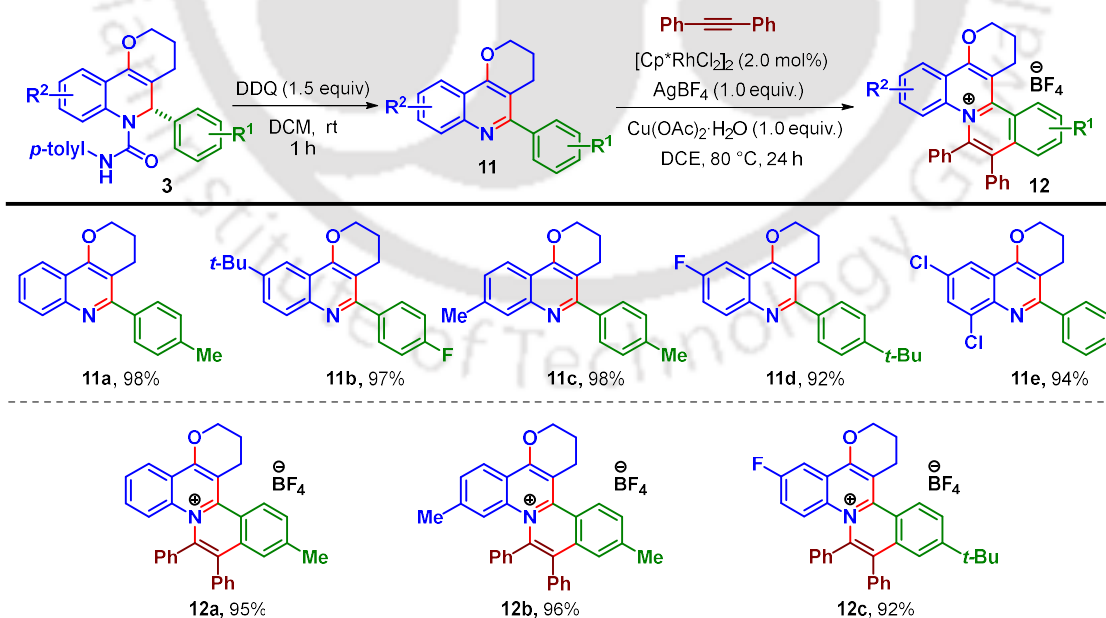
To check the utility of the compound **3**, several synthetic modifications were made. Compound **3** when subjected to intramolecular Heck coupling reaction, furnished the annulated polycyclic N,O-heterocycles **10** in good yields (Scheme 4.4.5.1.1).



Scheme 4.4.5.1.1. Synthesis of polycyclic N,O-heterocycles through intramolecular Heck coupling.

4.4.5.2. Oxidation and N-Annulation of Cyclic Ether Fused Quinolines (3)

Aromatization of compounds **3** with DDQ afforded the dihydropyrano[3,2-*c*]quinoline derivatives **11a–11e** in 92–98% yields (Scheme 4.4.5.2.1). Furthermore, these compounds were utilized to synthesize highly fluorescent annulated pentacyclic ammonium salts (Scheme 4.4.5.2.1).²⁵ Rh(III)-catalyzed oxidative C–H bond activation, coupled with *N*-annulation of compounds **11** with diphenyl acetylene



Scheme 4.4.5.2.1. Oxidation reaction and N-annulation for the construction of pentacyclic ammonium salts.

successfully provided the isoquinolino[2,1-*a*]pyrano[3,2-*c*]quinolinium salts **12a-12c** in excellent yields.

4.4.5.2.1. Photophysical Studies of Pentacyclic Ammonium Salts (12)

Quinolinium salts **12** displays a variety of potential applications, including fluorescent dyes, ionic liquids, photocatalysts, and optoelectronic materials.²⁶ Their promising utility in the photoelectronic field has prompted us to evaluate the absorption and emission spectra of the synthesized quinolinium salts **12a-12c**, and the results are summarized in Table 4.4.5.2.1.1. The compounds emit strong fluorescence in the green region (500–550 nm), which can be attributed to the π -expansion provided by the diphenyl-isoquinolino[2,1-*a*]pyrano[3,2-*c*]quinolinium framework (Figure 4.4.5.2.1.1). Their fluorescence properties allow them to achieve exciting applications in material science.

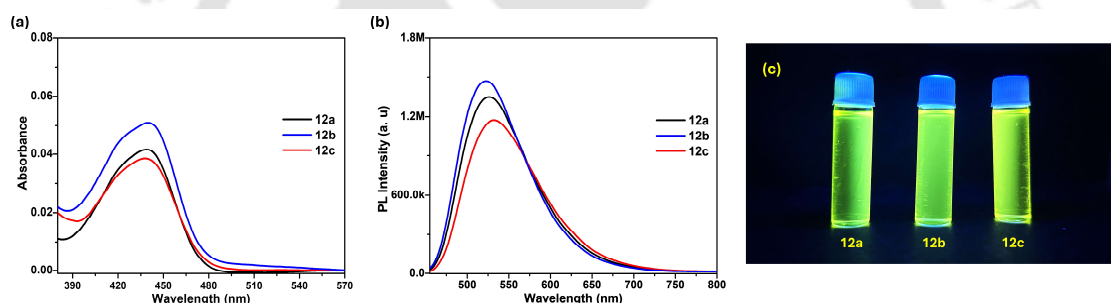


Figure 4.4.5.2.1.1. (a) Ultraviolet-visible, (b) fluorescence spectra and (c) UV irradiation of compounds **12a**, **12b** and **12c** at 365 nm.

Photophysical studies such as ultraviolet-visible and photoluminescence were conducted on compounds **12a-12c**. The absorption $\lambda_{\max}$ and the emission λ_{em} spectra

Table 4.4.5.2.1.1. Ultraviolet-visible and photoluminescence parameters

Entry	Compd.	$\lambda_{\max}$ (nm) ^a	Absorbance at $\lambda_{\max}$	ϵ ($1 \times 10^4 \text{ M}^{-1}\text{cm}^{-1}$)	λ_{em} (nm) ^b
1	12a	439	0.041	1.234196267	527
2	12b	440	0.051	1.535219747	523
3	12c	438	0.038	1.143889223	532

^aAbsorption wavelengths. ^bEmission wavelengths in DCM at a concentration of $3.32 \times 10^{-6} \text{ M}$.

of the compounds were measured in 3.32 μ M dichloromethane solution. The ultraviolet-visible and fluorescence emission spectra of these compounds (**12a**, **12b** and **12c**) are presented in Figure 4.4.5.2.1.1 and their results are described in Table 4.4.5.2.1.1.

4.5. Conclusions

In conclusion, this work describes the construction of functionalized pyrano- and isochromeno-quinolines in excellent yields *via* a tandem alkynyl aza-Prins-hydroalkoxylation strategy. This metal-free protocol withstands a broad substrate scope with exceptional functional group tolerance. The synthetic utility includes intramolecular Heck coupling, which provides fused polycyclic *N,O*-heterocycles. Furthermore, Rh(III)-catalyzed annulation of pyranoquinolines with diphenylacetylene produces isoquinolinopyrano-quinolinium salts, known for their exceptional photophysical properties.

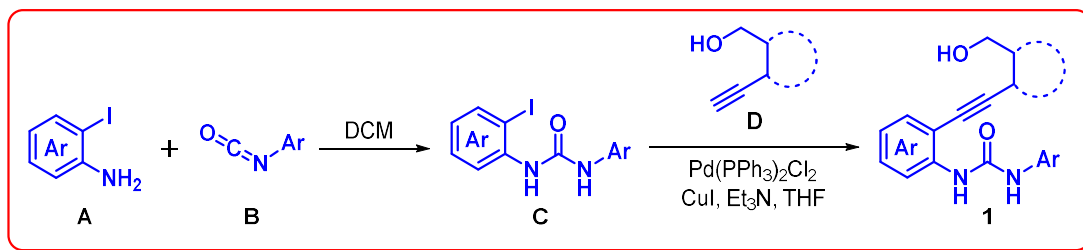
4.6. Experimental Section

4.6.1. 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 (500 MHz and 400 MHz) or $^{13}\text{C}\{^1\text{H}\}$ (126 MHz) NMR. Chemical shifts (δ) are reported in ppm with abbreviations, s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, tt = triplet of triplets, q = quartet, qd = quartet of doublets, p = quintet, m = multiplet and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

The starting material **1a**, was synthesized according to a literature report, and the spectroscopic data of the compound is in good agreement with the literature data.²⁷

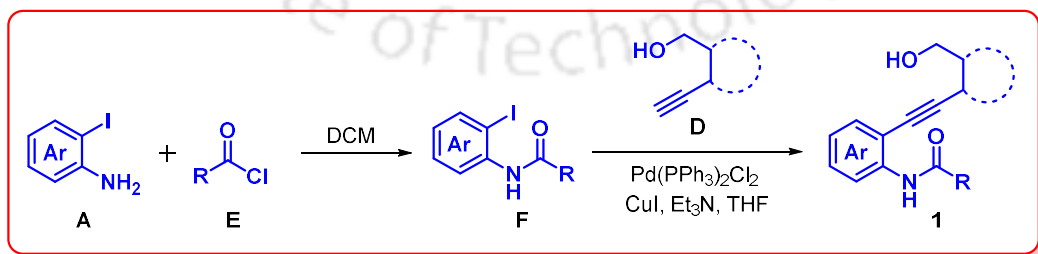
4.6.2. General procedure for the synthesis of the starting materials 1b-1k, 1o and 1p:



To a solution of substituted 2-iodoaniline **A** (2.0 mmol, 1.0 equiv.) in DCM (5.0 mL) under N₂ atmosphere, substituted phenyl isocyanate **B** (2.2 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was stirred overnight at room temperature to obtain a white precipitate, which was then filtered and washed with n-hexane to obtain a substituted 1,3-diphenyl urea **C**.

To a mixture of Pd(PPh₃)₂Cl₂ (0.04 mmol, 0.04 equiv.), CuI (0.06 mmol, 0.06 equiv.) and iodo substituted 1,3-diphenyl urea derivatives **C** (1.0 mmol, 1.0 equiv.) in dry THF (5.0 mL) under N₂ atmosphere, triethylamine (5.0 mmol, 5.0 equiv.) was added. The reaction mixture was stirred for 10 minutes at room temperature, after which alkynol **D** (1.2 mmol, 1.2 equiv.) was added dropwise over a period of 5 minutes. The reaction mixture was stirred for 3.0 hours (monitored by TLC analysis) before filtering through a pad of celite. The solids were washed with ethyl acetate, and the combined filtrates were concentrated in a rotary evaporator. The crude product was then purified by column chromatography to provide the corresponding product **1**.

4.6.3. General procedure for the synthesis of the starting materials 1l, 1n, 1q-1s and 1v:

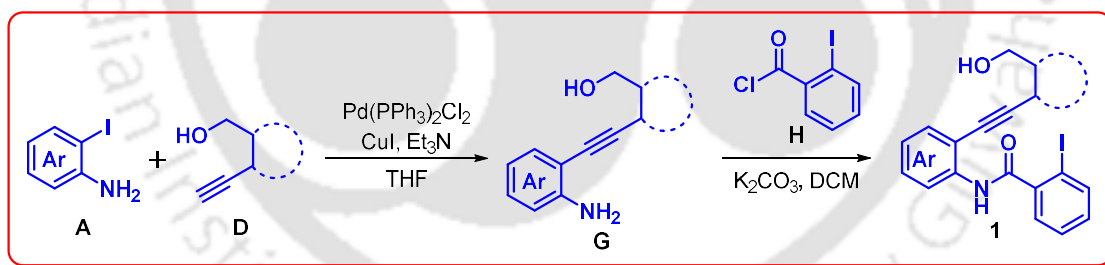


To a solution of substituted 2-iodoaniline **A** (2.0 mmol, 1.0 equiv.) and Et₃N (2.4 mmol, 1.2 equiv.) in DCM (5.0 mL) under N₂ atmosphere, acyl chloride **E** (2.4 mmol,

1.2 equiv.) was added dropwise. The reaction mixture was stirred for 12 h (monitored by TLC analysis). It was then treated with saturated NH_4Cl solution, and the organic layer was extracted with DCM (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na_2SO_4 . The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the amide **F**.

To a mixture of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.04 mmol, 0.04 equiv.), CuI (0.06 mmol, 0.06 equiv.) and iodo-substituted amide derivatives **F** (1.0 mmol, 1.0 equiv.) in dry THF (5.0 mL) under N_2 atmosphere, triethylamine (5.0 mmol, 5.0 equiv.) was added. The reaction mixture was stirred for 10 minutes at room temperature, after which alkynol **D** (1.2 mmol, 1.2 equiv.) was added dropwise over a period of 5 minutes. The reaction mixture was stirred for 3.0 hours (monitored by TLC analysis) before filtering through a pad of celite. The solids were washed with ethyl acetate, and the combined filtrates were concentrated in a rotary evaporator. The crude product was then purified by column chromatography to provide the corresponding product **1**.

4.6.4. General procedure for the synthesis of the starting materials **1m**, **1t** and **1u**:



To a mixture of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.08 mmol, 0.04 equiv.), CuI (0.12 mmol, 0.06 equiv.) and substituted 2-iodoaniline **A** (2.0 mmol, 1.0 equiv.) in dry THF (5.0 mL) under N_2 atmosphere, triethylamine (10.0 mmol, 5.0 equiv.) was added. The reaction mixture was stirred for 10 minutes at room temperature, after which alkynol **D** (2.4 mmol, 1.2 equiv.) was added dropwise over a period of 5 minutes. The reaction mixture was stirred for 3.0 hours (monitored by TLC analysis) before filtering through a pad of celite. The solids were washed with ethyl acetate, and the combined filtrates were

concentrated in a rotary evaporator. The crude product was then purified by column chromatography to provide the corresponding product **G**.

To a suspension of compound **G** (1.0 mmol, 1.0 equiv.) and K_2CO_3 (1.2 mmol, 1.2 equiv.) in DCM (5.0 mL) under N_2 atmosphere, 2-iodobenzoyl chloride (**H**) (1.2 mmol, 1.2 equiv.) in DCM (2 mL) was added dropwise. The reaction mixture was stirred for 24 h (monitored by TLC analysis). It was then treated with saturated NH_4Cl solution, and the organic layer was extracted with DCM (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na_2SO_4 . The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the product **1**.

4.6.5. General procedure for the synthesis of compounds 3ab–3ao, 3bp, 3cq, 3de, 3er, 3fb, 3gb, 3hb, 3ip, 3in, 3jj, 3ka, 3lb, 3lq, 3mb, 3nq, 3ob, 3op, 3ps, 3qr, 3qt, 3rn, 3sb, 3si, 3tp, 3up and 3vj:

To an ice-cold suspension of alkynol substituted urea or amide **1** (0.4 mmol, 1.0 equiv.) and aldehyde (0.48 mmol, 1.2 equiv.) in DCM (6.0 mL), $BF_3 \cdot OEt_2$ (0.48 mmol, 1.2 equiv.) was added under N_2 atmosphere. The reaction was continued to stir at room temperature till all the starting material was consumed, as evident by TLC. It was then treated with saturated $NaHCO_3$ solution, and the organic layer was extracted with DCM (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na_2SO_4 . The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product.

4.6.6. Experimental procedure for scale-up synthesis of compound 3ab:

To an ice-cold suspension of 1-(2-(5-hydroxypent-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea (**1a**) (1.0 g, 3.2 mmol, 1.0 equiv.) and *p*-tolualdehyde (**2b**) (467mg, 3.9 mmol, 1.2 equiv.) in DCM (20 mL), $BF_3 \cdot OEt_2$ (0.48 mL, 3.9 mmol, 1.2 equiv.) was added slowly under N_2 atmosphere. The reaction was continued to stir for 1.0 h at room temperature, and the progress of the reaction was monitored by TLC. It was then treated with saturated $NaHCO_3$ solution, and the organic layer was extracted with DCM (2 x 20 mL). The

combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **3ab** as a white solid in 94% yield (1.25 g).

4.6.7. Experimental procedure for scale-up synthesis of compound **3sb**:

To an ice-cold suspension of *N*-(4-chloro-2-((2-(hydroxymethyl)phenyl)ethynyl)-phenyl)benzamide (**1s**) (1.0 g, 2.8 mmol, 1.0 equiv.) and *p*-tolualdehyde (**2b**) (398 mg, 3.3 mmol, 1.2 equiv.) in DCM (20 mL), BF₃·OEt₂ (0.41 mL, 3.3 mmol, 1.2 equiv.) was added slowly under N₂ atmosphere. The reaction was continued to stir for 1.0 h at room temperature, and the progress of the reaction was monitored by TLC. It was then treated with saturated NaHCO₃ solution, and the organic layer was extracted with DCM (2 x 20 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **3sb** as a white solid in 86% yield (1.12 g).

4.6.8. Experimental procedure for control experiment:

4.6.8.1. Experimental procedure for scheme 4.4.3.1.a(i):

To an ice-cold suspension of 1-(2-(hex-1-yn-1-yl)phenyl)-3-phenylurea (**4**) (117 mg, 0.4 mmol, 1.0 equiv.), *p*-tolualdehyde (**2b**) (58 mg, 0.48 mmol, 1.2 equiv.) and TMSCl (0.10 mL, 0.8 mmol, 2.0 equiv.) in DCM (6.0 mL), BF₃·OEt₂ (0.06 mL, 0.48 mmol, 1.2 equiv.) was added slowly under N₂ atmosphere. The reaction was continued to stir for 24 h at room temperature, and the progress of the reaction was monitored by TLC. To collect the starting material, the reaction mixture was treated with saturated NaHCO₃ solution, and the organic layer was extracted with DCM (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator which was then subjected to column chromatography over silica gel to get the unreacted starting material **4** in 92% yield.

4.6.8.2. Experimental procedure for scheme 4.4.3.1.a(ii):

To an ice-cold suspension of 1-(2-(hex-1-yn-1-yl)phenyl)-3-phenylurea (**4**) (117 mg, 0.4 mmol, 1.0 equiv), *p*-tolualdehyde (**2b**) (58 mg, 0.48 mmol, 1.2 equiv.) and Et₃SiH (0.13 mL, 0.8 mmol, 2.0 equiv.) in DCM (6.0 mL), BF₃·OEt₂ (0.06 mL, 0.48 mmol, 1.2 equiv.) was added slowly under N₂ atmosphere. The reaction was continued to stir for 24 h at room temperature, and the progress of the reaction was monitored by TLC. To collect the starting material, the reaction mixture was treated with saturated NaHCO₃ solution, and the organic layer was extracted with DCM (2 × 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator which was then subjected to column chromatography over silica gel to get the unreacted starting material **4** in 94% yield.

4.6.8.3. Experimental procedure for scheme 4.4.3.1.b:

To an ice-cold suspension of 5-phenylpent-4-yn-1-ol (**7**) (96 mg, 0.6 mmol, 1.0 equiv) and *p*-tolualdehyde (**2b**) (86 mg, 0.72 mmol, 1.2 equiv.) in DCM (6.0 mL), BF₃·OEt₂ (0.09 mL, 0.72 mmol, 1.2 equiv.) was added slowly under N₂ atmosphere. The reaction was continued to stir for 1.0 h at room temperature, and the progress of the reaction was monitored by TLC. It was then treated with saturated NaHCO₃ solution, and the organic layer was extracted with DCM (2 × 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **9** as a white semi-solid in 78% yield (131 mg).

4.6.9. General experimental procedure for the synthesis of compounds 10a-10c:

To an oven-dried 25 mL two neck round bottom flask fitted with a condenser, compound **3** (0.2 mmol, 1.0 equiv.), K₂CO₃ (0.3 mmol, 1.5 equiv.), Pd(OAc)₂ (0.01 mmol, 5 mol%) and PPh₃ (0.02 mmol, 10 mol%) in DMF (3.0 mL) was refluxed under N₂ atmosphere in a pre-heated oil bath at 150 °C for 4 h. The progress of the reaction was monitored by TLC. Upon completion of the reaction, it was cooled and diluted with ice-cold brine solution. The organic layer was extracted with ethyl acetate (10

mL). The organic layer was further washed with brine (2 x 10 mL), followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the desired product **10**.

4.6.10. General experimental procedure for the synthesis of compounds 11a-11e:

To a solution of DDQ (0.45 mmol, 1.5 equiv.) in DCM (3.0 mL), compound **3** (0.3 mmol, 1.0 equiv.) was added slowly under N₂ atmosphere. The reaction was continued to stir for 1.0 h at room temperature, and the progress of the reaction was monitored by TLC. It was then treated with brine solution, and the organic layer was extracted with DCM (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **11**.

4.6.11. General experimental procedure for the synthesis of compounds 12a-12c:

To an oven-dried sealed tube, compound **11** (0.2 mmol, 1.0 equiv.), diphenyl acetylene (0.2 mmol, 1.0 equiv.), [Cp*RhCl₂]₂ (0.004 mmol, 2 mol%), AgBF₄ (0.2 mmol, 1.0 equiv.) and Cu(OAc)₂·H₂O (0.2 mmol, 1.0 equiv.) in DCE (2.0 mL) was refluxed in a pre-heated oil bath at 80 °C. The reaction mixture was refluxed for 24 h (monitored by TLC analysis) before filtering through a short pad of celite. The solids were washed with MeOH, and the combined filtrates were concentrated in a rotary evaporator. The crude product was then purified by column chromatography to provide the corresponding product **12**.

4.7. References

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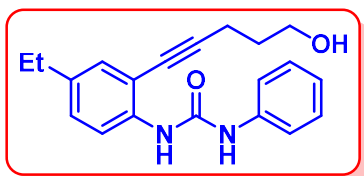
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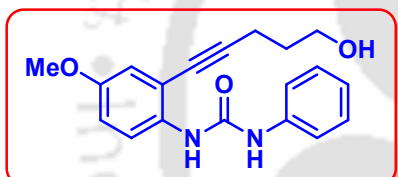
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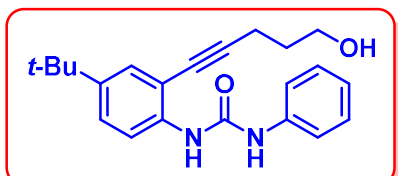
4.8. Characterization Data

1-(4-Ethyl-2-(5-hydroxypent-1-yn-1-yl)phenyl)-3-phenylurea (1b):

White solid; R_f (Hexane:EtOAc, 3:2) 0.4; mp 128–130 °C. Yield 313 mg, 97%. ^1H NMR (500 MHz, CDCl_3) δ 8.13 (d, J = 8.5 Hz, 1H), 8.00 (s, 1H), 7.89 (s, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.23 (t, J = 7.7 Hz, 2H), 7.09 (d, J = 1.6 Hz, 1H), 7.04 (dd, J = 8.5, 2.1 Hz, 1H), 6.99 (t, J = 7.4 Hz, 1H), 3.92 (t, J = 5.3 Hz, 2H), 2.78 (s, 1H), 2.56 (t, J = 6.4 Hz, 2H), 2.51 (t, J = 7.6 Hz, 2H), 1.83 (p, J = 5.9 Hz, 2H), 1.17 (t, J = 7.6 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.2, 138.9, 138.6, 137.7, 129.9, 129.0, 128.6, 123.0, 119.7, 118.3, 112.0, 96.3, 77.5, 63.1, 30.5, 28.0, 17.3, 15.5. IR (KBr, neat) ν 3326, 2961, 1668, 1591, 1524, 1498, 1441, 1299, 1252, 1211, 1058, 749, 693, 505 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 323.1754, found 323.1761.

1-(2-(5-Hydroxypent-1-yn-1-yl)-4-methoxyphenyl)-3-phenylurea (1c):

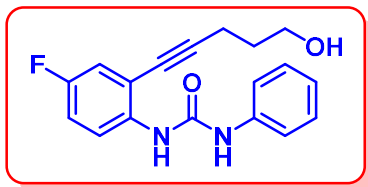
White solid; R_f (Hexane:EtOAc, 1:1) 0.4; mp 153–155 °C. Yield 279 mg, 86%. ^1H NMR (500 MHz, CDCl_3) δ 8.11–8.09 (m, 1H), 7.78 (s, 1H), 7.71 (s, 1H), 7.40 (d, J = 7.9 Hz, 2H), 7.28–7.25 (m, 2H), 7.01 (t, J = 7.3 Hz, 1H), 6.83–6.80 (m, 2H), 3.95 (t, J = 5.3 Hz, 2H), 3.74 (s, 3H), 2.58 (t, J = 6.3 Hz, 2H), 1.95 (s, 1H), 1.86 (p, J = 5.9 Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 154.4, 153.2, 139.0, 134.5, 129.0, 123.1, 120.1, 119.8, 115.6, 115.1, 113.4, 96.5, 63.2, 55.6, 30.6, 17.3. IR (KBr, neat) ν 3314, 2935, 1649, 1598, 1528, 1499, 1442, 1314, 1209, 1171, 1034, 802, 693 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 325.1547, found 325.1548.

1-(4-(*tert*-Butyl)-2-(5-hydroxypent-1-yn-1-yl)phenyl)-3-phenylurea (1d):

White solid; R_f (Hexane:EtOAc, 3:2) 0.4; mp 133–135 °C. Yield 315 mg, 90%. ^1H NMR (500 MHz, CDCl_3) δ 8.12 (dt, J = 8.9, 2.8 Hz, 1H), 7.92–7.83 (m, 2H), 7.38–7.35 (m, 2H), 7.24–7.19 (m, 4H), 6.99–6.95 (m, 1H), 3.92 (p, J = 6.0 Hz, 2H), 2.58–2.54 (m, 2H), 1.85–1.79 (p, J = 5.4 Hz, 2H), 1.23 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.1, 144.7, 138.9, 138.4, 129.0, 127.6, 126.3, 123.1, 119.8, 118.0, 111.5, 96.0, 77.8, 63.2, 34.2, 31.3, 30.6, 17.3. IR (KBr, neat) ν 3325, 2956, 1669, 1597,

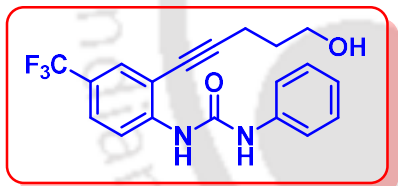
1549, 1524, 1498, 1441, 1306, 1257, 1210, 1043, 736, 692, 506 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 351.2067, found 351.2068.

1-(4-Fluoro-2-(5-hydroxypent-1-yn-1-yl)phenyl)-3-phenylurea (1e):



White solid; R_f (Hexane:EtOAc, 3:2) 0.4; mp 157–159 °C. Yield 300 mg, 96%. ^1H NMR (500 MHz, CDCl_3) δ 8.21 (dd, $J = 8.9, 5.2$ Hz, 1H), 8.01 (s, 1H), 7.90 (s, 1H), 7.37 (dd, $J = 8.5, 1.3$ Hz, 2H), 7.26–7.22 (m, 2H), 7.01 (t, $J = 7.3$ Hz, 1H), 6.94–6.90 (m, 2H), 3.96 (t, $J = 5.3$ Hz, 2H), 2.58 (t, $J = 6.3$ Hz, 2H), 2.11 (s, 1H), 1.86 (q, $J = 5.8$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 157.2 (d, $J = 241.5$ Hz), 153.0, 138.8, 137.4 (d, $J = 2.6$ Hz), 129.0, 123.2, 119.7, 119.4 (d, $J = 8.0$ Hz), 117.0 (d, $J = 23.9$ Hz), 115.9 (d, $J = 22.0$ Hz), 113.1 (d, $J = 9.4$ Hz), 97.7, 76.5 (d, $J = 3.0$ Hz), 63.4, 30.4, 17.5. ^{19}F NMR (471 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -124.7. IR (KBr, neat) ν 3314, 2964, 2231, 1677, 1599, 1549, 1499, 1442, 1308, 1254, 1209, 1167, 1049, 871, 751, 691 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{18}\text{FN}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 313.1347, found 313.1352.

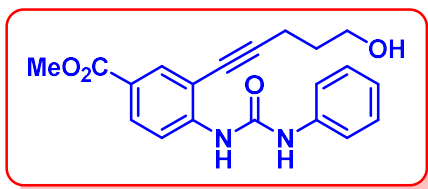
1-(2-(5-Hydroxypent-1-yn-1-yl)-4-(trifluoromethyl)phenyl)-3-phenylurea (1f):



White solid; R_f (Hexane:EtOAc, 3:2) 0.4; mp 153–155 °C. Yield 337 mg, 93%. ^1H NMR (400 MHz, CDCl_3) δ 8.41 (d, $J = 8.8$ Hz, 1H), 8.24 (s, 1H), 8.21 (s, 1H), 7.44 (s, 1H), 7.40 (dd, $J = 8.9, 2.2$ Hz, 1H), 7.34 (d, $J = 7.8$ Hz, 2H), 7.22 (t, $J = 7.8$ Hz, 2H), 7.00 (t, $J = 7.3$ Hz, 1H), 3.99 (q, $J = 5.4$ Hz, 2H), 2.92 (t, $J = 5.9$ Hz, 1H), 2.60 (t, $J = 6.16$ Hz, 2H), 1.89 (p, $J = 5.9$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 152.5, 144.0, 138.5, 129.1, 127.7 (q, $J = 3.8$ Hz), 125.9 (q, $J = 3.5$ Hz), 124.0 (q, $J = 272.0$ Hz), 123.44 (q, $J = 32.8$ Hz), 123.39, 119.5, 117.3, 111.6, 98.1, 76.2, 63.9, 30.4, 17.7. ^{19}F NMR (471 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -65.3. IR (KBr, neat) ν 3332, 2929, 1687, 1591, 1534, 1499, 1328, 1259, 1117, 1074, 751, 693, 506 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 363.1315, found 363.1314.

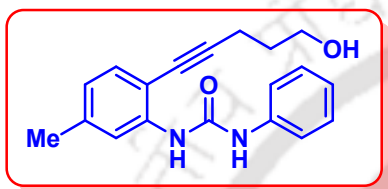
Methyl 3-(5-hydroxypent-1-yn-1-yl)-4-(3-phenylureido)benzoate (1g):

White solid; R_f (Hexane:EtOAc, 1:1) 0.4; mp 121–123 °C. Yield 345 mg, 98%. ^1H NMR (500 MHz, CDCl_3) δ 8.41 (s, 1H), 8.31 (d, $J = 8.8$ Hz, 1H), 8.22 (s, 1H), 7.87 (d, $J = 2.1$ Hz, 1H), 7.81 (dd, $J = 8.8, 2.1$ Hz, 1H), 7.36 (d, $J = 7.8$ Hz, 2H), 7.22 (t, $J = 7.9$ Hz, 2H),



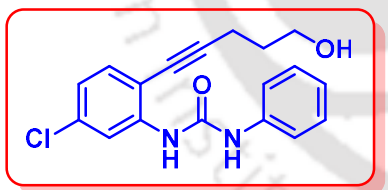
6.99 (t, $J = 7.4$ Hz, 1H), 3.96 (t, $J = 5.2$ Hz, 2H), 3.83 (s, 3H), 2.57 (t, $J = 6.2$ Hz, 2H), 1.99 (s, 1H), 1.86 (p, $J = 5.6$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 166.7, 152.6, 145.0, 138.6, 132.3, 130.4, 129.0, 123.2, 122.7, 119.4, 116.7, 111.4, 97.7, 76.3, 63.5, 52.0, 30.3, 17.6. IR (KBr, neat) ν 3333, 2950, 1715, 1582, 1525, 1499, 1438, 1293, 1252, 1197, 1128, 753, 695 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 353.1496, found 353.1496.

1-(2-(5-Hydroxypent-1-yn-1-yl)-5-methylphenyl)-3-phenylurea (1h):



White solid; R_f (Hexane:EtOAc, 3:2) 0.4; mp 178–180 $^{\circ}\text{C}$. Yield 284 mg, 92%. ^1H NMR (500 MHz, CDCl_3) δ 8.15 (s, 1H), 7.91 (d, $J = 10.8$ Hz, 2H), 7.43 (d, $J = 8.0$ Hz, 2H), 7.28 (t, $J = 7.8$ Hz, 2H), 7.16 (d, $J = 7.7$ Hz, 1H), 7.03 (t, $J = 7.3$ Hz, 1H), 6.72 (d, $J = 7.7$ Hz, 1H), 4.00 (t, $J = 5.3$ Hz, 2H), 2.61 (t, $J = 6.3$ Hz, 2H), 2.32 (s, 3H), 1.88 (p, $J = 5.8$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 152.8, 140.9, 139.5, 139.0, 130.5, 129.0, 123.1, 122.6, 119.7, 118.6, 108.8, 95.8, 77.5, 63.5, 30.6, 22.0, 17.5. IR (KBr, neat) ν 3332, 2926, 1672, 1600, 1547, 1499, 1440, 1320, 1255, 1212, 750, 694 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 309.1598, found 309.1598.

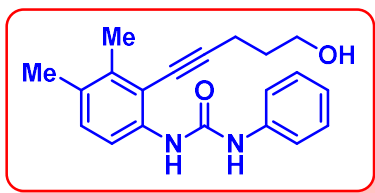
1-(5-Chloro-2-(5-hydroxypent-1-yn-1-yl)phenyl)-3-phenylurea (1i):



White solid; R_f (Hexane:EtOAc, 3:2) 0.4; mp 165–167 $^{\circ}\text{C}$. Yield 322 mg, 98%. ^1H NMR (500 MHz, CDCl_3) δ 8.42 (d, $J = 2.2$ Hz, 1H), 8.05 (s, 1H), 8.04 (s, 1H), 7.37–7.35 (m, 2H), 7.26–7.22 (m, 2H), 7.12 (d, $J = 8.3$ Hz, 1H), 7.00 (t, $J = 7.0$ Hz, 1H), 6.85 (dd, $J = 8.3, 2.1$ Hz, 1H), 4.03 (t, $J = 5.4$ Hz, 2H), 2.63 (t, $J = 6.2$ Hz, 2H), 2.56 (s, 1H), 1.92 (p, $J = 5.6$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 152.6, 142.1, 138.7, 134.8, 131.3, 129.0, 123.2, 121.6, 119.4, 117.8, 109.8, 97.6, 76.5, 63.9, 30.5, 17.8. IR (KBr, neat) ν 3329, 2926, 1683, 1610, 1554, 1523, 1499, 1417, 1250, 1210, 750, 693 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{18}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 329.1051, found 329.1053.

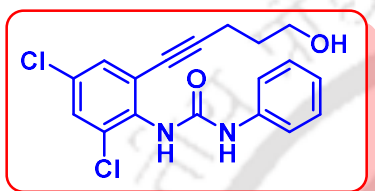
1-(2-(5-Hydroxypent-1-yn-1-yl)-3,4-dimethylphenyl)-3-phenylurea (1j):

White solid; R_f (Hexane:EtOAc, 3:2) 0.4; mp 146–148 $^{\circ}\text{C}$. Yield 264 mg, 82%. ^1H NMR (400 MHz, CDCl_3) δ 8.03 (s, 1H), 7.95 (s, 1H), 7.80 (s, 1H), 7.39 (d, $J = 7.6$ Hz, 2H), 7.27–



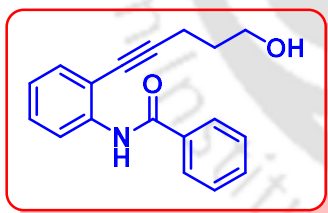
7.22 (m, 2H), 7.03–6.97 (m, 2H), 3.94 (t, $J = 5.3$ Hz, 2H), 2.68 (s, 1H), 2.56 (t, $J = 6.3$ Hz, 2H), 2.21 (s, 3H), 2.13 (s, 3H), 1.84 (p, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.2, 139.0, 138.6, 137.9, 131.4, 130.0, 128.9, 122.9, 119.6, 119.5, 109.4, 95.6, 77.4, 63.2, 30.6, 20.2, 18.9, 17.4. IR (KBr, neat) ν 3329, 2924, 1665, 1599, 1551, 1524, 1499, 1444, 1311, 1212, 1048, 880, 694 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 323.1754, found 323.1760.

1-(2,4-Dichloro-6-(5-hydroxypent-1-yn-1-yl)phenyl)-3-phenylurea (1k):



White solid; R_f (Hexane:EtOAc, 3:2) 0.4; mp 190–192 °C. Yield 320 mg, 88%. ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.34 (s, 1H), 7.65 (s, 1H), 7.41–7.38 (m, 2H), 7.28–7.26 (m, 2H), 7.22–7.17 (m, 3H), 6.94–6.90 (m, 1H), 3.65–3.62 (m, 2H), 2.47–2.43 (m, 2H), 1.72–1.66 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 152.6, 139.3, 135.6, 132.2, 130.8, 130.1, 128.8, 128.7, 124.3, 122.3, 118.5, 97.4, 76.4, 60.8, 30.7, 16.3. IR (KBr, neat) ν 3325, 946, 1702, 1600, 1551, 1497, 1438, 1314, 1174, 1120, 1057, 723, 694, 541 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{17}\text{Cl}_2\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 363.0662, found 363.0663.

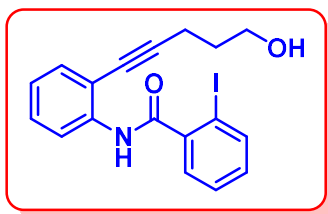
N-(2-(5-Hydroxypent-1-yn-1-yl)phenyl)benzamide (1l):



White solid; R_f (Hexane:EtOAc, 3:2) 0.4; mp 72–74 °C. Yield 274 mg, 98%. ^1H NMR (500 MHz, CDCl_3) δ 8.82 (s, 1H), 8.53 (d, $J = 8.3$ Hz, 1H), 7.90 (d, $J = 7.4$ Hz, 2H), 7.55–7.51 (m, 1H), 7.48 (t, $J = 7.5$ Hz, 2H), 7.39 (d, $J = 7.6$ Hz, 1H), 7.33 (t, $J = 7.9$ Hz, 1H), 7.03 (t, $J = 7.5$ Hz, 1H), 3.76 (t, $J = 6.1$ Hz, 2H), 2.64 (t, $J = 7.0$ Hz, 2H), 2.34 (s, 1H), 1.87 (p, $J = 6.6$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 165.3, 139.0, 134.9, 132.0, 131.5, 129.1, 128.8, 127.0, 123.5, 119.1, 112.9, 97.5, 76.4, 61.3, 31.4, 16.1. IR (KBr, neat) ν 3390, 2945, 1676, 1605, 1578, 1522, 1449, 1310, 1252, 1070, 756, 706 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{18}\text{NO}_2$ ($\text{M} + \text{H}$) $^+$ 280.1332, found 280.1332.

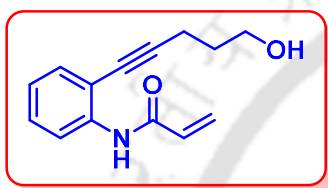
N-(2-(5-Hydroxypent-1-yn-1-yl)phenyl)-2-iodobenzamide (1m):

White solid; R_f (Hexane:EtOAc, 1:1) 0.4; mp 88–90 °C. Yield 389 mg, 96%. ^1H NMR (400 MHz, CDCl_3) δ 8.53 (d, $J = 7.7$ Hz, 1H), 8.38 (s, 1H), 7.94 (dd, $J = 7.8, 2.1$ Hz, 1H),



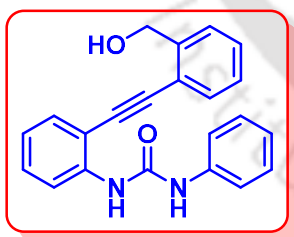
7.56 (d, $J = 7.6$ Hz, 1H), 7.45 (t, $J = 6.9$ Hz, 1H), 7.39 (d, $J = 7.9$ Hz, 1H), 7.36 (t, $J = 7.7$ Hz, 1H), 7.18–7.13 (m, 1H), 7.07 (t, $J = 7.6$ Hz, 1H), 3.68–3.64 (m, 2H), 2.57–2.53 (m, 2H), 1.88–1.74 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 167.1, 142.1, 140.3, 138.6, 131.6, 129.1, 128.5, 128.4, 127.9, 123.9, 119.4, 113.2, 97.6, 92.3, 76.3, 61.5, 31.1, 16.3. IR (KBr, neat) ν 3387, 2946, 1675, 1602, 1575, 1518, 1452, 1310, 1255, 1074, 750, 704 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{17}\text{NO}_2$ ($\text{M} + \text{H}$) $^+$ 406.0298, found 406.0300.

N-(2-(5-Hydroxypent-1-yn-1-yl)phenyl)acrylamide (1n):



White solid; R_f (Hexane:EtOAc, 1:1) 0.4; mp 71–73 °C. Yield 190 mg, 83%. ^1H NMR (500 MHz, CDCl_3) δ 8.39 (d, $J = 8.4$ Hz, 1H), 8.19 (s, 1H), 7.31 (d, $J = 7.6$ Hz, 1H), 7.24 (d, $J = 6.6$ Hz, 1H), 6.97 (t, $J = 7.6$ Hz, 1H), 6.39–6.26 (m, 2H), 5.72 (d, $J = 9.9$ Hz, 1H), 3.79 (t, $J = 5.7$ Hz, 2H), 2.59 (t, $J = 6.8$ Hz, 2H), 2.28 (s, 1H), 1.84 (p, $J = 6.4$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 163.6, 138.8, 131.5, 131.4, 128.9, 127.7, 123.6, 119.4, 112.9, 97.3, 76.3, 61.6, 31.2, 16.4. IR (KBr, neat) ν 3378, 2936, 2225, 1671, 1577, 1518, 1446, 2403, 1317, 1183, 964, 754, 607 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{16}\text{NO}_2$ ($\text{M} + \text{H}$) $^+$ 230.1176, found 230.1177.

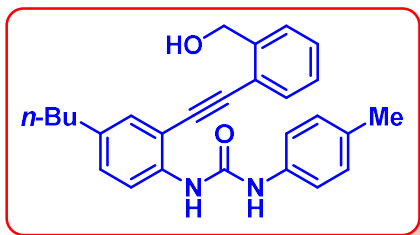
1-(2-((2-(Hydroxymethyl)phenyl)ethynyl)phenyl)-3-phenylurea (1o):



White solid; R_f (Hexane:EtOAc, 3:2) 0.6; mp 185–187 °C. Yield 308 mg, 90%. ^1H NMR (400 MHz, CDCl_3) δ 8.45 (d, $J = 8.4$ Hz), 8.43 (s, 1H), 8.18 (s, 1H), 7.63 (d, $J = 7.4$ Hz, 1H), 7.50–7.43 (m, 3H), 7.42–7.33 (m, 4H), 7.32–7.29 (m, 1H), 7.28 (s, 1H), 7.02–6.95 (m, 2H), 4.95 (s, 2H), 2.51 (s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 152.7, 141.6, 139.8, 139.3, 135.3, 132.6, 131.2, 130.3, 130.2, 129.5, 129.2, 129.0, 128.7, 123.6, 122.7, 121.6, 119.0, 118.2, 110.5, 93.7, 90.5, 66.0. IR (KBr, neat) ν 3326, 2922, 1687, 1603, 1580, 1553, 1532, 1499, 1447, 1304, 1260, 1224, 1009, 753, 691 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 343.1441, found 343.1442.

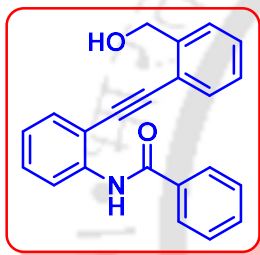
1-(4-Butyl-2-((2-(hydroxymethyl)phenyl)ethynyl)phenyl)-3-(p-tolyl)urea (1p):

White solid; R_f (Hexane:EtOAc, 1:1) 0.6; mp 172–174 °C. Yield 379 mg, 92%. ^1H NMR



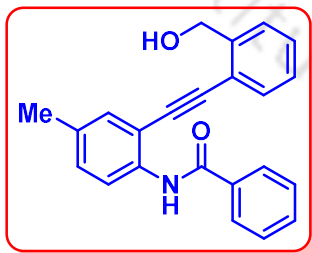
(400 MHz, CDCl_3) δ 8.29 (s, 1H), 8.24 (d, $J = 8.5$ Hz, 1H), 8.02 (s, 1H), 7.55 (d, $J = 7.4$ Hz, 1H), 7.35–7.31 (m, 1H), 7.30–7.26 (m, 4H), 7.24 (d, $J = 2.2$ Hz, 1H), 7.09 (dd, $J = 8.6, 2.2$ Hz, 1H), 7.01 (d, $J = 8.1$ Hz, 2H), 4.83 (s, 2H), 3.05 (s, 1H), 2.52 (t, $J = 7.7$ Hz, 2H), 2.22 (s, 3H), 1.62–1.54 (m, 2H), 1.41–1.31 (m, 2H), 0.94 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.1, 140.0, 139.4, 136.6, 136.0, 132.4, 132.1, 130.6, 130.3, 129.39, 129.36, 128.9, 128.4, 123.5, 119.1, 118.1, 110.5, 93.4, 90.7, 65.6, 34.7, 33.5, 22.3, 20.7, 14.0. IR (KBr, neat) ν 3328, 2926, 2859, 1684, 1586, 1513, 1294, 1226, 1010, 817, 755, 693, 519 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 413.2224, found 413.2228.

***N*-(2-((2-(Hydroxymethyl)phenyl)ethynyl)phenyl)benzamide (1q):**



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 135–137 $^{\circ}\text{C}$. Yield 295 mg, 90%. ^1H NMR (400 MHz, CDCl_3) δ 8.87 (s, 1H), 8.56 (d, $J = 8.4$ Hz, 1H), 7.95–7.92 (m, 2H), 7.57–7.52 (m, 3H), 7.49–7.44 (m, 3H), 7.43–7.37 (m, 2H), 7.31 (td, $J = 7.5, 1.4$ Hz, 1H), 7.13 (td, $J = 7.5, 1.2$ Hz, 1H), 4.81 (s, 2H), 1.98 (s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 165.7, 142.3, 139.1, 135.1, 132.2, 132.1, 131.9, 130.1, 129.3, 128.8, 127.7, 127.6, 127.2, 123.8, 120.8, 119.9, 112.5, 94.2, 89.2, 63.9. IR (KBr, neat) ν 3396, 3062, 1665, 1578, 1521, 1443, 1308, 1255, 1042, 756, 708, 574 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{18}\text{NO}_2$ ($\text{M} + \text{H}$) $^+$ 328.1332, found 328.1330.

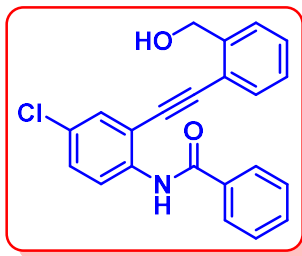
***N*-(2-((2-(Hydroxymethyl)phenyl)ethynyl)-4-methylphenyl)benzamide (1r):**



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 137–139 $^{\circ}\text{C}$. Yield 314 mg, 92%. ^1H NMR (500 MHz, CDCl_3) δ 8.78 (s, 1H), 8.41 (d, $J = 8.5$ Hz, 1H), 7.92 (d, $J = 7.5$ Hz, 2H), 7.52 (t, $J = 7.5$ Hz, 2H), 7.49–7.44 (m, 3H), 7.38 (t, $J = 7.5$ Hz, 1H), 7.35 (s, 1H), 7.30 (t, $J = 7.5$ Hz, 1H), 7.22 (d, $J = 8.5$ Hz, 1H), 4.81 (d, $J = 5.0$ Hz, 2H), 2.34 (s, 3H), 2.04 (t, $J = 5.9$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 165.6, 142.3, 136.7, 135.1, 133.4, 132.08, 132.07, 131.9, 130.8, 129.2, 128.8, 127.7, 127.6, 127.2, 120.8, 119.9, 112.4, 93.8, 89.4, 63.9, 20.7. IR (KBr, neat) ν 3397, 3061, 2921,

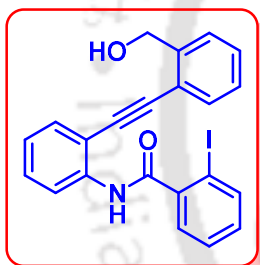
1663, 1517, 1308, 1254, 892, 821, 758, 706, 573 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{20}\text{NO}_2$ ($\text{M} + \text{H}$)⁺ 342.1489, found 342.1489.

***N*-(4-Chloro-2-((2-(hydroxymethyl)phenyl)ethynyl)phenyl)benzamide (1s):**



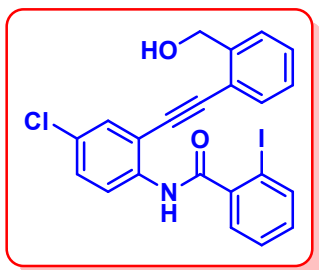
White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 151-153 °C. Yield 318 mg, 88%. ^1H NMR (500 MHz, CDCl_3) δ 8.84 (s, 1H), 8.53 (d, J = 8.9 Hz, 1H), 7.91 (d, J = 7.4 Hz, 2H), 7.57–7.50 (m, 3H), 7.49–7.46 (m, 3H), 7.41 (t, J = 7.6 Hz, 1H), 7.37 (dt, J = 9.0, 2.2 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 4.80 (s, 2H), 1.79 (s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 165.8, 142.4, 137.8, 134.8, 132.3, 132.2, 131.2, 130.0, 129.7, 128.9, 128.6, 127.9, 127.7, 127.3, 121.1, 120.4, 114.0, 95.2, 87.9, 63.9. IR (KBr, neat) ν 3409, 1682, 1575, 1515, 1402, 1304, 1033, 822, 759, 695, 542 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{17}\text{ClNO}_2$ ($\text{M} + \text{H}$)⁺ 362.0942, found 362.0943.

***N*-(2-((2-(Hydroxymethyl)phenyl)ethynyl)phenyl)-2-iodobenzamide (1t):**



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 148–150 °C. Yield 399 mg, 88%. ^1H NMR (500 MHz, CDCl_3) δ 8.73 (s, 1H), 8.59 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.56–7.51 (m, 2H), 7.49 (d, J = 7.4 Hz, 1H), 7.45–7.40 (m, 2H), 7.32 (d, J = 4.4 Hz, 2H), 7.30–7.26 (m, 1H), 7.15 (t, J = 7.6 Hz, 2H), 4.58 (s, 2H), 1.45 (s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 167.7, 142.6, 141.9, 139.9, 139.1, 132.2, 131.8, 131.3, 129.9, 129.0, 128.3, 128.2, 127.9, 127.7, 124.1, 121.4, 120.2, 112.7, 94.2, 92.6, 89.3, 64.2. IR (KBr, neat) ν 3379, 3064, 1673, 1572, 1509, 1401, 1305, 1100, 1016, 905, 821, 758 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{17}\text{INO}_2$ ($\text{M} + \text{H}$)⁺ 454.0298, found 454.0297.

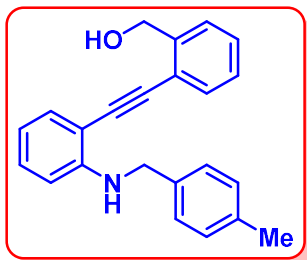
***N*-(4-Chloro-2-((2-(hydroxymethyl)phenyl)ethynyl)phenyl)-2-iodobenzamide (1u):**



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 153–155 °C. Yield 434 mg, 89%. ^1H NMR (400 MHz, CDCl_3) δ 8.79 (s, 1H), 8.57 (d, J = 9.0 Hz, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.53–7.47 (m, 3H), 7.43 (dt, J = 7.4, 1.1 Hz, 1H), 7.41–7.37 (m, 1H), 7.36–7.28 (m, 3H), 7.16 (t, J = 7.7 Hz, 1H), 4.56 (s, 2H), 1.74 (s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 167.8, 142.4, 142.0, 139.8, 137.8, 132.3, 131.4, 131.2, 129.9, 129.3, 128.9, 128.3, 128.2, 128.0, 127.9, 121.4, 121.1, 114.3, 95.2, 92.6, 88.1,

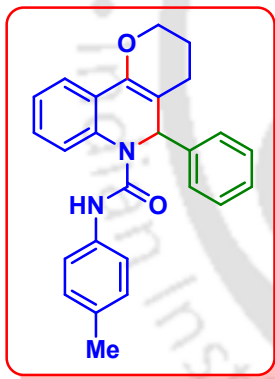
64.3. IR (KBr, neat) ν 3377, 3059, 2925, 1664, 1572, 1506, 1400, 1302, 1040, 1015, 905, 821, 757, 740 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{16}\text{ClINO}_2$ ($\text{M} + \text{H}$) $^+$ 487.9909, found 487.9908.

(2-((2-((4-Methylbenzyl)amino)phenyl)ethynyl)phenyl)methanol (1v):



White solid; R_f (Hexane:EtOAc, 3:2) 0.6; mp 63–65 °C. Yield 233 mg, 71%. ^1H NMR (500 MHz, CDCl_3) δ 7.53 (d, J = 7.3 Hz, 1H), 7.40 (d, J = 7.6 Hz, 2H), 7.34–7.28 (m, 4H), 7.21–7.18 (m, 3H), 6.68 (t, J = 7.5 Hz, 1H), 6.63 (d, J = 8.3 Hz, 1H), 5.43 (s, 1H), 4.75 (d, J = 3.7 Hz, 2H), 4.41 (s, 2H), 2.37 (s, 3H), 1.73 (s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 149.2, 141.6, 136.9, 136.2, 132.0, 131.9, 130.3, 129.4, 128.4, 127.75, 127.72, 127.4, 122.2, 116.4, 109.9, 107.3, 92.8, 91.2, 64.4, 47.5, 21.1. IR (KBr, neat) ν 3357, 3022, 2919, 2855, 2203, 1896, 1598, 1571, 1508, 1454, 1321, 1159, 745, 556 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{22}\text{NO}$ ($\text{M} + \text{H}$) $^+$ 328.1696, found 328.1698.

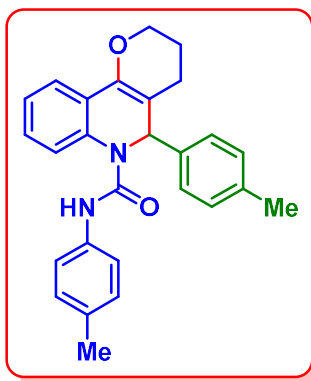
5-Phenyl-*N*-(*p*-tolyl)-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinoline-6(5*H*)-carboxamide (3aa):



White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 173–175 °C. Yield 155 mg, 98%. ^1H NMR (500 MHz, CDCl_3) δ 7.60–7.58 (m, 1H), 7.33 (d, J = 6.7 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 7.23–7.18 (m, 3H), 7.17–7.13 (m, 3H), 7.08 (d, J = 8.1 Hz, 2H), 6.93 (s, 1H), 6.09 (s, 1H), 4.29–4.25 (m, 1H), 4.21–4.16 (m, 1H), 2.29 (s, 3H), 2.24 (dt, J = 17.6, 6.8 Hz, 1H), 2.11 (dt, J = 17.5, 5.9 Hz, 1H), 2.03–1.92 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.3, 143.9, 139.6, 135.8, 134.5, 132.9, 129.5, 128.4, 127.84, 127.77, 127.7, 126.4, 124.8, 122.8, 122.2, 119.5, 111.0, 66.4, 58.1, 23.4, 22.4, 20.8. IR (KBr, neat) ν 3416, 3030, 2926, 2872, 1670, 1516, 1488, 1316, 1221, 1154, 1103, 963, 810, 733, 699, 503 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 397.1911, found 397.1911.

***N*,5-Di-*p*-tolyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinoline-6(5*H*)-carboxamide (3ab):**

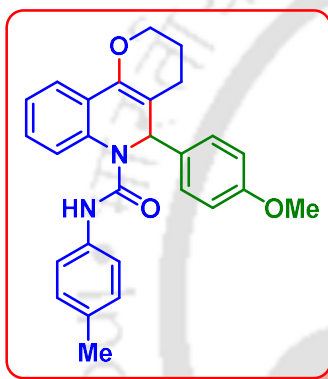
White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 154–156 °C. Yield 161 mg, 98%. ^1H NMR (400 MHz, CDCl_3) δ 7.60–7.57 (m, 1H), 7.25 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.18–7.13 (m, 3H), 7.08 (d, J = 8.1 Hz, 2H), 7.02 (d, J = 7.8 Hz, 2H), 6.92 (s, 1H), 6.05 (s,



1H), 4.29–4.24 (m, 1H), 4.20–4.14 (m, 1H), 2.28 (s, 3H), 2.25 (s, 3H), 2.23–2.18 (m, 1H), 2.09 (dt, $J = 17.5, 5.7$ Hz, 1H), 2.01–1.92 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.3, 143.8, 137.3, 136.6, 135.9, 134.5, 132.8, 129.4, 129.1, 127.8, 127.7, 126.4, 124.8, 122.8, 122.1, 119.5, 111.1, 66.4, 57.9, 23.3, 22.4, 21.1, 20.8. IR (KBr, neat) ν 3419, 2924, 1673, 1517, 1489, 1316, 1222, 1155, 1104, 811, 767, 734, 505 cm^{-1} . HRMS (ESI) calcd.

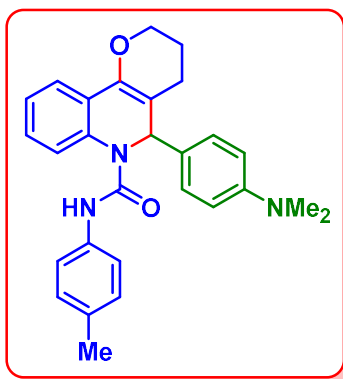
for $\text{C}_{27}\text{H}_{27}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 411.2067, found 411.2072.

5-(4-Methoxyphenyl)-N-(p-tolyl)-3,4-dihydro-2H-pyrano[3,2-c]quinoline-6(5H)-carboxamide (3ac):



White solid; R_f (Hexane:EtOAc, 4:1) 0.5; mp 154–156 $^{\circ}\text{C}$. Yield 133 mg, 78%. ^1H NMR (500 MHz, CDCl_3) δ 7.62–7.60 (m, 1H), 7.27 (d, $J = 8.3$ Hz, 4H), 7.20–7.15 (m, 3H), 7.10 (d, $J = 8.0$ Hz, 2H), 6.93 (s, 1H), 6.76 (d, $J = 8.5$ Hz, 2H), 6.05 (s, 1H), 4.30–4.26 (m, 1H), 4.21–4.17 (m, 1H), 3.74 (s, 3H), 2.30 (s, 3H), 2.23 (dt, $J = 17.5, 6.8$ Hz, 1H), 2.10 (dt, $J = 17.5, 5.8$ Hz, 1H), 2.04–1.93 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 159.1, 153.3, 143.7, 135.9, 134.4, 132.8, 131.7, 129.5, 129.0, 127.8, 126.3, 124.8, 122.8, 122.1, 119.5, 113.8, 111.2, 66.4, 57.6, 55.2, 23.2, 22.4, 20.8. IR (KBr, neat) ν 3416, 2928, 1670, 1595, 1489, 1366, 1316, 1222, 1155, 1104, 811, 764, 734, 506 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{27}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 427.2016, found 427.2021.

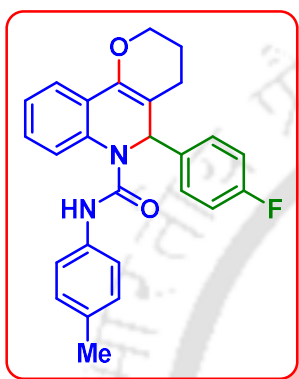
5-(4-(Dimethylamino)phenyl)-N-(p-tolyl)-3,4-dihydro-2H-pyrano[3,2-c]quinoline-6(5H)-carboxamide (3ad):



Yellow solid; R_f (Hexane:EtOAc, 4:1) 0.5; mp 187–189 $^{\circ}\text{C}$. Yield 146 mg, 83%. ^1H NMR (500 MHz, CDCl_3) δ 7.62–7.59 (m, 1H), 7.27 (d, $J = 5.4$ Hz, 2H), 7.21 (d, $J = 8.4$ Hz, 2H), 7.18–7.14 (m, 3H), 7.10 (d, $J = 8.1$ Hz, 2H), 6.93 (s, 1H), 6.60 (d, $J = 8.3$ Hz, 2H), 6.02 (s, 1H), 4.30–4.25 (m, 1H), 4.21–4.16 (m, 1H), 2.89 (s, 6H), 2.30 (s, 3H), 2.22 (dt, $J = 17.5, 6.9$ Hz, 1H), 2.12 (dt, $J = 17.5, 5.9$ Hz, 1H), 2.03–

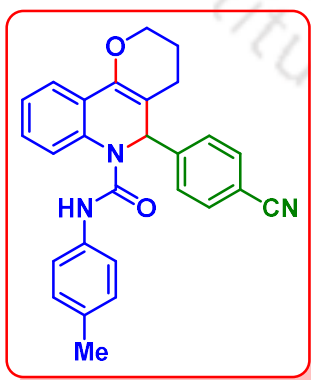
1.91 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.3, 150.0, 143.4, 136.0, 134.6, 132.7, 129.4, 128.7, 127.7, 127.3, 126.4, 124.6, 122.9, 122.0, 119.5, 112.3, 111.6, 66.4, 57.9, 40.5, 23.2, 22.4, 20.8. IR (KBr, neat) ν 3418, 2923, 1670, 1595, 1489, 1366, 1316, 1223, 1158, 1105, 1107, 814, 765, 741, 509 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{28}\text{H}_{30}\text{N}_3\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 440.2333, found 440.2333.

5-(4-Fluorophenyl)-N-(*p*-tolyl)-3,4-dihydro-2H-pyrano[3,2-*c*]quinoline-6(5H)-carboxamide (3ae):



White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 181–183 °C. Yield 162 mg, 98%. ^1H NMR (500 MHz, CDCl_3) δ 7.54–7.50 (m, 1H), 7.24–7.22 (m, 2H), 7.18 (d, J = 8.1 Hz, 2H), 7.12–7.06 (m, 3H), 7.01 (d, J = 8.1 Hz, 2H), 6.84 (s, 1H), 6.81 (t, J = 8.7 Hz, 2H), 5.99 (s, 1H), 4.22–4.18 (m, 1H), 4.13–4.09 (m, 1H), 2.21 (s, 3H), 2.15 (dt, J = 17.4, 6.8 Hz, 1H), 1.99 (dt, J = 17.5, 5.9 Hz, 1H), 1.95–1.84 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 163.3 (d, J = 246.3 Hz), 153.2, 144.0, 135.7, 135.3 (d, J = 3.2 Hz), 134.2, 133.0, 129.55, 129.50, 128.0, 126.2, 124.9, 122.7, 122.3, 119.6, 115.2 (d, J = 21.2 Hz), 110.7, 66.4, 57.3, 23.3, 22.3, 20.8; ^{19}F NMR (470 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -118.0. IR (KBr, neat) ν 3419, 2927, 1672, 597, 1518, 1505, 1490, 1318, 1221, 1156, 1104, 764, 740, 506 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{24}\text{FN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 415.1816, found 415.1816.

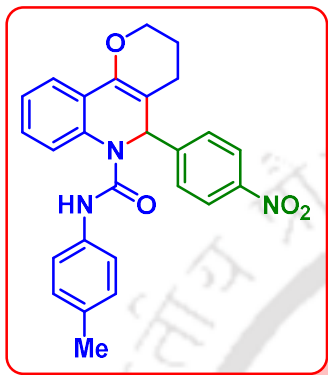
5-(4-Cyanophenyl)-N-(*p*-tolyl)-3,4-dihydro-2H-pyrano[3,2-*c*]quinoline-6(5H)-carboxamide (3af):



White solid; R_f (Hexane:EtOAc, 4:1) 0.5; mp 209–211 °C. Yield 138 mg, 82%. ^1H NMR (500 MHz, CDCl_3) δ 7.53 (dd, J = 7.0, 2.1 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 3.0 Hz, 1H), 7.29 (s, 1H), 7.23 (td, J = 7.0, 2.2 Hz, 2H), 7.20–7.18 (m, 1H), 7.14 (d, J = 8.1 Hz, 2H), 6.99 (s, 1H), 6.15 (s, 1H), 4.35–4.31 (m, 1H), 4.27–4.23 (m, 1H), 2.34 (s, 3H), 2.32–2.27 (m, 1H), 2.14–2.09 (m, 1H), 2.08–2.00 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.2, 145.0, 144.6, 135.5, 134.1, 133.3, 132.3, 129.5, 128.5, 128.3, 125.9, 125.1, 122.6, 122.5, 119.6, 118.8, 111.5, 109.3, 66.4, 57.6, 23.4,

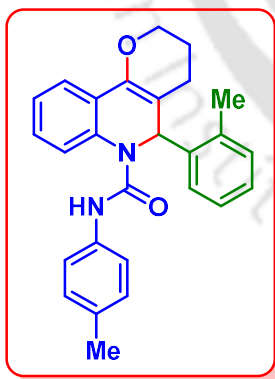
22.2, 20.8. IR (KBr, neat) ν 3319, 2925, 2228, 1670, 1516, 1489, 1317, 1223, 1155, 812, 733, 699, 556, 507 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{24}\text{N}_3\text{O}_2$ ($\text{M} + \text{H}$)⁺ 422.1863, found 422.1866.

5-(4-Nitrophenyl)-N-(*p*-tolyl)-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinoline-6(5*H*)-carboxamide (3ag):



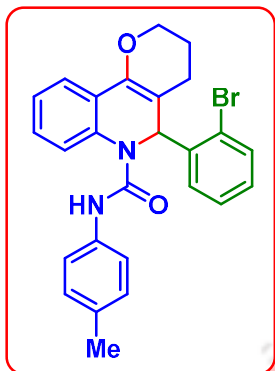
Yellow solid; R_f (Hexane:EtOAc, 4:1) 0.5; mp 201–203 °C. Yield 120 mg, 68%. ^1H NMR (400 MHz, CDCl_3) δ 8.08 (d, J = 8.7 Hz, 2H), 7.63–7.59 (m, 1H), 7.52 (d, J = 8.6 Hz, 2H), 7.27–7.25 (m, 2H), 7.23–7.18 (m, 2H), 7.17–7.14 (m, 1H), 7.11 (d, J = 8.1 Hz, 2H), 6.94 (s, 1H), 6.16 (s, 1H), 4.33–4.28 (m, 1H), 4.25–4.20 (m, 1H), 2.30 (s, 3H), 2.29–2.24 (m, 1H), 2.12–1.97 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.2, 147.5, 147.0, 144.8, 135.5, 134.1, 133.4, 129.6, 128.7, 128.3, 125.9, 125.3, 123.8, 122.63, 122.60, 119.7, 109.4, 66.5, 57.4, 23.5, 22.3, 20.8. IR (KBr, neat) ν 341, 2926, 1672, 1516, 1489, 1344, 1318, 1223, 1156, 1105, 810, 735, 707, 506 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{24}\text{N}_3\text{O}_4$ ($\text{M} + \text{H}$)⁺ 442.1761, found 442.1765.

5-(*o*-Tolyl)-N-(*p*-tolyl)-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinoline-6(5*H*)-carboxamide (3ah):



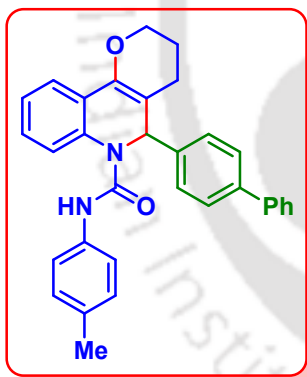
White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 168–170 °C. Yield 138 mg, 84%. ^1H NMR (500 MHz, CDCl_3) δ 7.63 (d, J = 7.1 Hz, 1H), 7.24–7.19 (m, 4H), 7.17–7.15 (m, 2H), 7.10 (d, J = 7.1 Hz, 1H), 7.07 (d, J = 8.2 Hz, 2H), 6.93–6.88 (m, 3H), 6.37 (s, 1H), 4.29–4.24 (m, 1H), 4.18–4.14 (m, 1H), 2.69 (s, 3H), 2.33–2.22 (m, 4H), 2.02–1.96 (m, 2H), 1.94–1.87 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.7, 143.6, 137.22, 137.17, 135.8, 134.9, 132.9, 130.8, 129.4, 127.8, 127.7, 127.5, 127.2, 125.9, 125.7, 124.1, 122.1, 119.8, 113.2, 66.3, 55.1, 22.8, 22.3, 20.8, 20.0. IR (KBr, neat) ν 3419, 2927, 1673, 1517, 1488, 1264, 1219, 1156, 1102, 810, 765, 732, 701, 505 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{27}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 411.2067, found 411.2068.

5-(2-Bromophenyl)-N-(*p*-tolyl)-3,4-dihydro-2H-pyrano[3,2-*c*]quinoline-6(5H)-carboxamide (3ai):



White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 209–211 °C. Yield 156 mg, 82%. ^1H NMR (500 MHz, CDCl_3) δ 7.58 (dd, $J = 7.5, 1.7$ Hz, 1H), 7.53 (dd, $J = 7.5, 1.8$ Hz, 1H), 7.25–7.24 (m, 2H), 7.23 (d, $J = 3.8$ Hz, 2H), 7.21–7.17 (m, 1H), 7.05–7.00 (m, 4H), 6.98 (td, $J = 7.5, 2.0$ Hz, 1H), 6.91 (s, 1H), 6.48 (s, 1H), 4.18–4.09 (m, 2H), 2.33–2.28 (m, 1H), 2.25 (s, 3H), 2.04–1.98 (m, 1H), 1.97–1.91 (m, 1H), 1.87–1.79 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.5, 142.9, 140.0, 135.8, 135.5, 133.1, 132.9, 129.42, 129.40, 128.7, 128.1, 127.9, 126.1, 125.0, 123.3, 122.8, 122.2, 119.7, 112.6, 66.3, 58.3, 22.6, 22.3, 20.8. IR (KBr, neat) ν 3420, 2926, 1678, 1517, 1316, 1222, 1157, 1103, 1022, 806, 759, 737, 507 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{24}\text{BrN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 475.1016, found 475.1018.

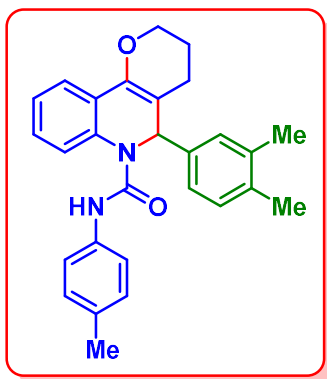
5-([1,1'-Biphenyl]-4-yl)-N-(*p*-tolyl)-3,4-dihydro-2H-pyrano[3,2-*c*]quinoline-6(5H)-carboxamide (3aj):



White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 218–220 °C. Yield 181 mg, 96%. ^1H NMR (400 MHz, CDCl_3) δ 7.65–7.62 (m, 1H), 7.52 (d, $J = 7.2$ Hz, 2H), 7.48–7.46 (m, 2H), 7.43–7.38 (m, 4H), 7.33–7.28 (m, 3H), 7.22–7.17 (m, 3H), 7.12 (d, $J = 8.2$ Hz, 2H), 6.98 (s, 1H), 6.15 (s, 1H), 4.34–4.29 (m, 1H), 4.25–4.19 (m, 1H), 2.32 (s, 3H), 2.29–2.25 (m, 1H), 2.17 (dt, $J = 17.5, 5.9$ Hz, 1H), 2.08–1.98 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.3, 143.9, 140.8, 140.5, 138.6, 135.8, 134.5, 132.9, 129.5, 128.7, 128.2, 127.9, 127.2, 127.0, 126.3, 124.9, 122.8, 122.2, 119.5, 110.9, 66.4, 57.9, 23.4, 22.4, 20.8. IR (KBr, neat) ν 3416, 225, 1672, 1517, 1487, 1316, 1222, 1155, 1104, 810, 761, 734, 697, 505 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{32}\text{H}_{29}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 473.2224, found 473.2225.

5-(3,4-Dimethylphenyl)-N-(*p*-tolyl)-3,4-dihydro-2H-pyrano[3,2-*c*]quinoline-6(5H)-carboxamide (3ak):

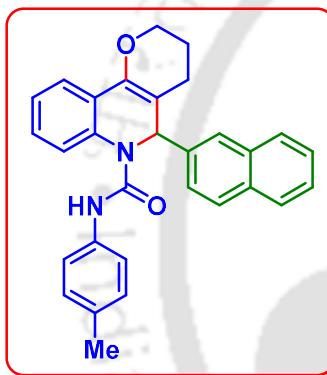
White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 153–155 °C. Yield 154 mg, 91%. ^1H NMR (400 MHz, CDCl_3) δ 7.60–7.56 (m, 1H), 7.24 (d, $J = 2.4$ Hz, 2H), 7.17–7.13 (m, 4H), 7.08



(d, $J = 8.2$ Hz, 2H), 7.00–6.94 (m, 2H), 6.92 (d, $J = 4.4$ Hz, 1H), 6.02 (s, 1H), 4.29–4.24 (m, 1H), 4.20–4.14 (m, 1H), 2.28 (s, 3H), 2.25–2.19 (m, 1H), 2.17 (s, 3H), 2.16 (s, 3H), 2.09 (dt, $J = 17.5, 5.7$ Hz, 1H), 2.00–1.92 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.3, 143.6, 137.0, 136.6, 136.1, 135.9, 134.6, 132.8, 129.6, 129.5, 129.3, 127.8, 126.4, 124.85, 124.79, 122.9, 122.1, 119.5, 111.3, 66.4, 58.0, 23.3, 22.4, 20.8, 19.9, 19.5. IR

(KBr, neat) ν 3418, 2924, 1671, 1517, 1490, 316, 1221, 1155, 811, 764, 732, 701, 506 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{28}\text{H}_{29}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 425.2224, found 425.2225.

5-(Naphthalen-2-yl)-N-(p-tolyl)-3,4-dihydro-2H-pyrano[3,2-c]quinoline-6(5H)-carboxamide (3al):

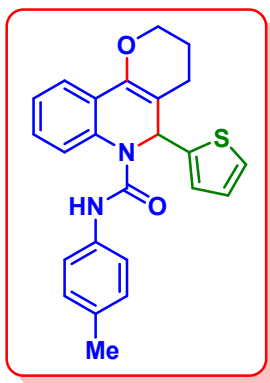


White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 195–197 $^{\circ}\text{C}$. Yield 121 mg, 68%. ^1H NMR (500 MHz, CDCl_3) δ 7.77–7.71 (m, 4H), 7.67–7.63 (m, 1H), 7.56–7.52 (m, 1H), 7.44–7.39 (m, 2H), 7.31–7.28 (m, 2H), 7.20–7.14 (m, 3H), 7.13–7.10 (m, 2H), 6.99–6.97 (m, 1H), 6.30–6.27 (m, 1H), 4.37–4.32 (m, 1H), 4.26–4.21 (m, 1H), 2.35–2.27 (m, 4H), 2.21–2.15 (m, 1H), 2.06–2.00 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ

153.4, 144.2, 137.0, 135.8, 134.5, 133.2, 133.05, 132.98, 129.5, 128.4, 128.2, 127.9, 127.6, 126.5, 126.4, 126.2, 125.9, 125.0, 122.9, 122.3, 119.6, 110.8, 66.5, 58.2, 23.5, 22.4, 20.8. IR (KBr, neat) ν 3416, 3053, 2926, 1671, 1516, 1489, 1317, 1222, 1157, 1103, 762, 734, 701, 478 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{27}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 447.2067, found 447.2067.

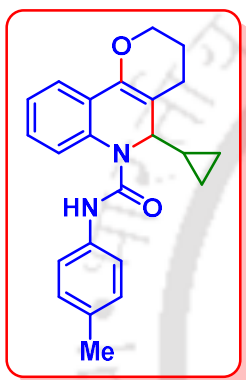
5-(Thiophen-2-yl)-N-(p-tolyl)-3,4-dihydro-2H-pyrano[3,2-c]quinoline-6(5H)-carboxamide (3am):

White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 162–164 $^{\circ}\text{C}$. Yield 113 mg, 70%. ^1H NMR (500 MHz, CDCl_3) δ 7.61 (d, $J = 7.3$ Hz, 1H), 7.28 (d, $J = 8.2$ Hz, 2H), 7.24–7.21 (m, 2H), 7.20–7.16 (m, 1H), 7.11–7.09 (m, 3H), 6.99 (d, $J = 3.5$ Hz, 1H), 6.95 (s, 1H), 6.85 (t, $J = 4.2$ Hz, 1H), 6.31 (s, 1H), 4.29–4.24 (m, 1H), 4.21–4.17 (m, 1H), 2.30 (s, 3H), 2.27 (t, $J = 6.4$



Hz, 2H), 2.05–1.94 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 152.8, 143.8, 143.7, 135.7, 134.0, 133.0, 129.5, 128.0, 126.5, 125.9, 125.7, 125.2, 124.8, 122.5, 122.4, 119.5, 111.4, 66.4, 53.9, 23.2, 22.4, 20.8. IR (KBr, neat) ν 3415, 2926, 1671, 1516, 1489, 1318, 1221, 115, 1104, 811, 761, 735, 703, 507 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{23}\text{N}_2\text{O}_2\text{S}$ ($\text{M} + \text{H}$) $^+$ 403.1475, found 403.1480.

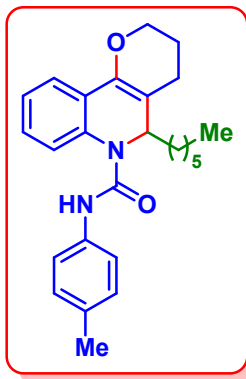
5-Cyclopropyl-N-(p-tolyl)-3,4-dihydro-2H-pyrano[3,2-c]quinoline-6(5H)-carboxamide (3an):



White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 147–149 °C. Yield 101 mg, 70%. ^1H NMR (500 MHz, CDCl_3) δ 7.53 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.25–7.21 (m, 3H), 7.17 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 8.0 Hz, 2H), 6.87 (s, 1H), 4.27 (d, J = 9.0 Hz, 1H), 4.14 (t, J = 5.1 Hz, 2H), 2.44 (dt, J = 17.5, 6.7 Hz, 1H), 2.27 (s, 3H), 2.16 (dt, J = 17.6, 6.0 Hz, 1H), 1.95 (p, J = 6.0 Hz, 2H), 0.89–0.82 (m, 1H), 0.56–0.47 (m, 2H), 0.45–0.40 (m, 1H), 0.31–0.25 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$

NMR (126 MHz, CDCl_3) δ 153.0, 142.4, 136.0, 135.1, 132.7, 129.4, 127.6, 126.4, 124.7, 122.8, 122.3, 119.4, 113.0, 66.3, 60.1, 24.1, 22.5, 20.8, 14.5, 4.1, 1.9. IR (KBr, neat) ν 3420, 2927, 1672, 1517, 1489, 1318, 1223, 1160, 1104, 765, 736, 508 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 361.1911, found 361.1915.

5-Hexyl-N-(p-tolyl)-3,4-dihydro-2H-pyrano[3,2-c]quinoline-6(5H)-carboxamide (3ao):

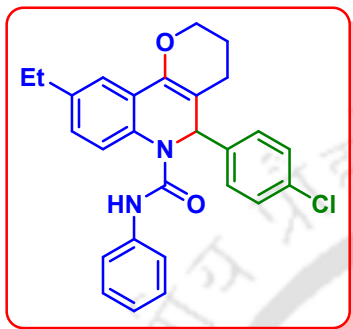


White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 92–94 °C. Yield 103 mg, 64%. ^1H NMR (400 MHz, CDCl_3) δ 7.51 (d, J = 7.5 Hz, 1H), 7.29 (dd, J = 7.8, 1.5 Hz, 1H), 7.24–7.20 (m, 3H), 7.18 (td, J = 7.4, 1.6 Hz, 1H), 7.05 (d, J = 8.2 Hz, 2H), 6.85 (s, 1H), 4.90 (dd, J = 9.7, 3.9 Hz, 1H), 4.12 (t, J = 5.3 Hz, 2H), 2.27 (s, 3H), 2.24–2.14 (m, 2H), 1.97–1.89 (m, 2H), 1.48–1.42 (m, 1H), 1.39–1.33 (m, 2H), 1.32–1.24 (m, 3H), 1.23–1.17 (m, 4H), 0.82 (t, J = 6.7 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR

(126 MHz, CDCl_3) δ 153.3, 142.4, 136.0, 134.4, 132.6, 129.4, 127.5, 126.7, 125.0, 123.3,

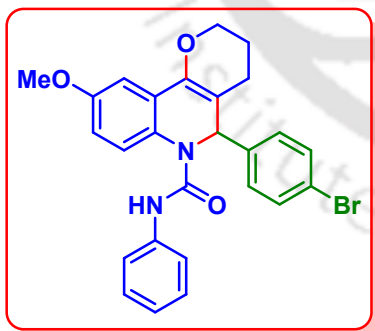
122.2, 119.4, 113.5, 66.2, 55.6, 32.0, 31.7, 29.2, 25.9, 23.5, 22.6, 22.5, 20.7, 14.1. IR (KBr, neat) ν 3422, 2925, 2855, 1674, 1516, 1488, 1317, 1221, 1156, 1103, 809, 761, 507 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{33}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 405.2537, found 405.2542.

5-(4-Chlorophenyl)-9-ethyl-N-phenyl-3,4-dihydro-2H-pyrano[3,2-c]quinoline-6(5H)-carboxamide (3bp):



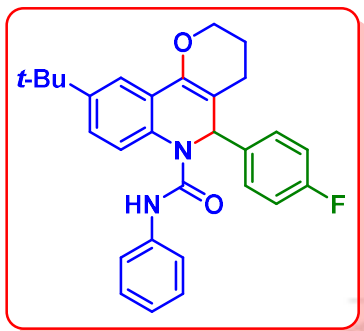
White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 163–165 °C. Yield 1, 71 mg, 96%. ^1H NMR (500 MHz, CDCl_3) δ 7.43 (s, 1H), 7.37 (d, J = 7.9 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 7.27–7.24 (m, 2H), 7.18 (d, J = 8.3 Hz, 2H), 7.07–7.03 (m, 2H), 7.02–6.98 (m, 2H), 6.06 (s, 1H), 4.30–4.26 (m, 1H), 4.20–4.16 (m, 1H), 2.65 (q, J = 7.6 Hz, 2H), 2.23 (dt, J = 17.5, 6.8 Hz, 1H), 2.07 (dt, J = 17.4, 5.8 Hz, 1H), 2.02–1.92 (m, 2H), 1.25 (t, J = 7.6 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.2, 144.3, 141.3, 138.4, 138.1, 133.4, 131.7, 129.3, 129.0, 128.6, 127.5, 126.1, 123.4, 122.7, 121.6, 119.4, 110.3, 66.4, 57.3, 28.5, 23.4, 22.3, 15.4. IR (KBr, neat) ν 3413, 2963, 2930, 1671, 1522, 1491, 1439, 1221, 1192, 1114, 1088, 735, 691, 576 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{26}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 445.1677, found 445.1678.

5-(4-Bromophenyl)-9-methoxy-N-phenyl-3,4-dihydro-2H-pyrano[3,2-c]quinoline-6(5H)-carboxamide (3cq):



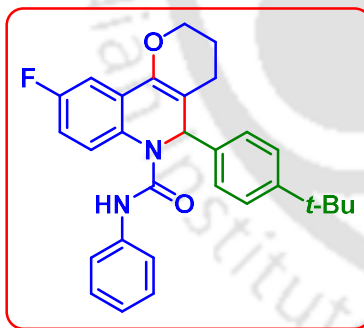
White solid; R_f (Hexane:EtOAc, 4:1) 0.5; mp 220–222 °C. Yield 165 mg, 84%. ^1H NMR (500 MHz, CDCl_3) δ 7.32 (t, J = 9.0 Hz, 4H), 7.26 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 4.7 Hz, 1H), 7.16 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 2.9 Hz, 1H), 7.03–6.99 (m, 2H), 6.88 (s, 1H), 6.70 (dd, J = 8.7, 2.9 Hz, 1H), 6.03 (s, 1H), 4.27–4.23 (m, 1H), 4.18–4.13 (m, 1H), 3.81 (s, 3H), 2.21 (dt, J = 17.5, 6.8 Hz, 1H), 2.04 (dt, J = 17.4, 5.7 Hz, 1H), 1.99–1.89 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 157.2, 153.4, 144.2, 138.4, 138.4, 131.6, 129.6, 129.0, 127.6, 126.8, 124.3, 123.4, 121.7, 119.4, 114.0, 111.1, 107.0, 66.5, 57.3, 55.6, 23.4, 22.3. IR (KBr, neat) ν 3419, 2927, 1671, 1596, 1525, 1494, 1441, 1222, 1178, 1012, 811, 736, 693 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{24}\text{BrN}_2\text{O}_3$ ($\text{M} + \text{H}$)⁺ 491.0965, found 491.0965.

9-(*tert*-Butyl)-5-(4-fluorophenyl)-*N*-phenyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinoline-6(5*H*)-carboxamide (3de):



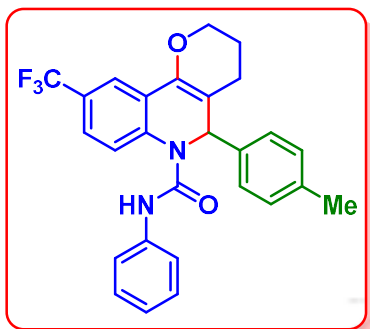
White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 202–204 °C. Yield 177 mg, 97%. ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J = 2.3$ Hz, 1H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.25–7.21 (m, 3H), 7.18 (d, $J = 6.2$ Hz, 1H), 7.13 (dd, $J = 8.4, 2.3$ Hz, 1H), 7.00 (d, $J = 8.4$ Hz, 1H), 6.97 (d, $J = 7.4$ Hz, 1H), 6.94 (s, 1H), 6.82 (t, $J = 8.6$ Hz, 2H), 5.99 (s, 1H), 4.25–4.20 (m, 1H), 4.14–4.09 (m, 1H), 2.16 (dt, $J = 17.3, 6.7$ Hz, 1H), 2.00 (dt, $J = 17.5, 5.6$ Hz, 1H), 1.95–1.87 (m, 2H), 1.27 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 162.3 (d, $J = 246.1$ Hz), 153.3, 148.1, 144.3, 138.5, 135.4 (d, $J = 3.2$ Hz), 131.5, 129.6 (d, $J = 8.2$ Hz), 129.0, 125.6, 125.0, 123.3, 122.3, 119.5, 119.1, 115.2 (d, $J = 21.3$ Hz), 110.3, 66.4, 57.4, 34.7, 31.4, 23.4, 22.4. ^{19}F NMR (471 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -118.14. IR (KBr, neat) ν 3360, 2927, 1671, 1596, 1525, 1494, 1441, 1222, 1178, 1012, 811, 736, 693 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{30}\text{FN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 457.2286, found 457.2285.

5-(4-(*tert*-Butyl)phenyl)-9-fluoro-*N*-phenyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinoline-6(5*H*)-carboxamide (3er):



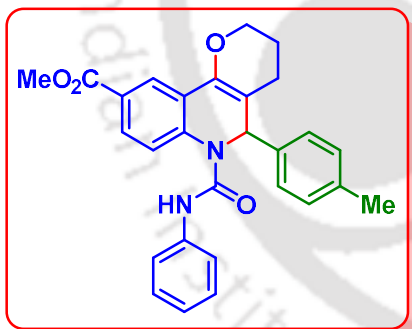
White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 210–212 °C. Yield 168 mg, 92%. ^1H NMR (500 MHz, CDCl_3) δ 7.41 (d, $J = 7.9$ Hz, 2H), 7.36–7.32 (m, 3H), 7.31 (s, 1H), 7.28 (d, $J = 6.2$ Hz, 3H), 7.19 (dd, $J = 8.7, 4.6$ Hz, 1H), 7.09 (t, $J = 7.1$ Hz, 1H), 6.92 (td, $J = 8.4, 2.9$ Hz, 1H), 6.89 (s, 1H), 6.12 (s, 1H), 4.33–4.29 (m, 1H), 4.25–4.21 (m, 1H), 2.27 (dt, $J = 17.7, 6.8$ Hz, 1H), 2.17 (dt, $J = 17.7, 5.9$ Hz, 1H), 2.08–1.97 (m, 2H), 1.30 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 160.0 (d, $J = 245.0$ Hz), 153.2, 150.7, 143.2 (d, $J = 2.2$ Hz), 138.4, 136.0, 130.3 (d, $J = 2.8$ Hz), 129.0, 128.4 (d, $J = 8.4$ Hz), 127.3, 125.5, 124.5 (d, $J = 8.3$ Hz), 123.4, 119.4, 114.3 (d, $J = 23.2$ Hz), 112.7, 109.3 (d, $J = 24.8$ Hz), 66.5, 58.1, 34.5, 31.3, 23.3, 22.3. ^{19}F NMR (471 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -119.52. IR (KBr, neat) ν 3420, 2960, 1673, 1522, 1490, 1440, 1316, 1221, 1176, 1102, 820, 735, 692, 578 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{30}\text{FN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 457.2286, found 457.2287.

***N*-Phenyl-5-(*p*-tolyl)-9-(trifluoromethyl)-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinoline-6(5*H*)-carboxamide (3fb):**



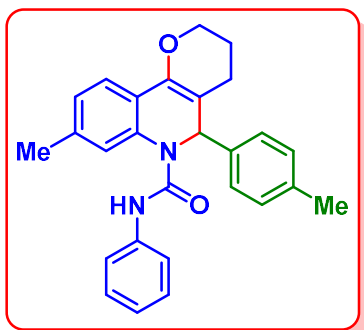
White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 208–210 °C. Yield 169 mg, 91%. ^1H NMR (400 MHz, CDCl_3) δ 7.87 (s, 1H), 7.42 (dd, $J = 8.4, 2.2$ Hz, 1H), 7.38 (d, $J = 7.8$ Hz, 2H), 7.33–7.28 (m, 3H), 7.23 (d, $J = 7.8$ Hz, 2H), 7.11–7.05 (m, 3H), 6.86 (s, 1H), 6.00 (s, 1H), 4.32–4.27 (m, 1H), 4.24–4.18 (m, 1H), 2.29 (s, 3H), 2.25–2.19 (m, 1H), 2.12 (dt, $J = 17.5, 5.9$ Hz, 1H), 2.05–1.93 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 152.9, 142.9, 138.0, 137.9, 137.6, 136.2, 129.4, 129.1, 127.5, 126.5 (q, $J = 33.0$ Hz), 126.3, 124.6 (q, $J = 3.6$ Hz), 124.0 (q, $J = 272.5$ Hz), 123.8, 122.4, 119.55, 119.51 (q, $J = 4.0$ Hz), 112.3, 66.5, 58.7, 23.2, 22.2, 21.1. ^{19}F NMR (471 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -65.48. IR (KBr, neat) ν 2927, 1677, 1596, 1524, 1499, 1441, 1328, 1272, 1223, 1117, 1075, 835, 750 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 465.1784, found 465.1784.

Methyl 6-(phenylcarbamoyl)-5-(*p*-tolyl)-3,4,5,6-tetrahydro-2*H*-pyrano[3,2-*c*]quinoline-9-carboxylate (3gb):



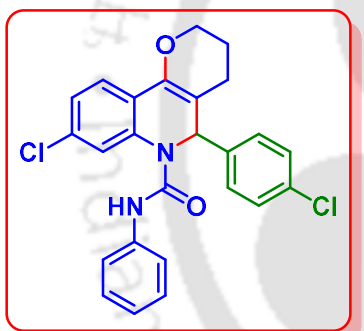
White solid; R_f (Hexane:EtOAc, 4:1) 0.5; mp 202–204 °C. Yield 165 mg, 91%. ^1H NMR (500 MHz, CDCl_3) δ 8.27 (s, 1H), 7.86 (d, $J = 8.0$ Hz, 1H), 7.41 (d, $J = 7.5$ Hz, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 7.28 (d, $J = 4.0$ Hz, 1H), 7.25 (d, $J = 7.8$ Hz, 2H), 7.10 (d, $J = 7.2$ Hz, 1H), 7.07 (d, $J = 8.0$ Hz, 2H), 7.04–6.98 (m, 1H), 6.00 (s, 1H), 4.33–4.29 (m, 1H), 4.25–4.21 (m, 1H), 3.93 (s, 3H), 2.30 (s, 3H), 2.24 (dt, $J = 17.6, 6.8$ Hz, 1H), 2.12 (dt, $J = 17.5, 5.9$ Hz, 1H), 2.06–1.95 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 166.5, 152.8, 143.2, 138.8, 138.2, 137.8, 136.3, 129.30, 129.27, 129.1, 127.6, 126.0, 125.7, 123.6, 122.1, 119.5, 111.5, 66.4, 58.8, 52.2, 23.2, 22.3, 21.1. IR (KBr, neat) ν 3343, 2950, 1677, 1527, 1440, 1311, 1261, 1219, 1121, 757, 693 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{28}\text{H}_{27}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 455.1965, found 455.1964.

8-Methyl-*N*-phenyl-5-(*p*-tolyl)-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinoline-6(5*H*)-carboxamide (3hb):



White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 116–118 °C. Yield 161 mg, 98%. ^1H NMR (500 MHz, CDCl_3) δ 7.48 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 7.9 Hz, 2H), 7.30 (t, J = 7.7 Hz, 2H), 7.24 (d, J = 7.8 Hz, 2H), 7.06 (d, J = 7.2 Hz, 2H), 7.03 (d, J = 9.7 Hz, 2H), 6.98 (d, J = 7.3 Hz, 2H), 6.05 (s, 1H), 4.28–4.24 (m, 1H), 4.20–4.16 (m, 1H), 2.28 (s, 6H), 2.22 (dt, J = 17.4, 6.8 Hz, 1H), 2.09 (dt, J = 17.4, 5.9 Hz, 1H), 2.03–1.92 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.3, 143.9, 138.6, 137.9, 137.3, 136.6, 134.4, 129.1, 129.0, 127.8, 125.7, 123.8, 123.4, 123.3, 122.0, 119.4, 109.8, 66.4, 58.0, 23.3, 22.4, 21.5, 21.1. IR (KBr, neat) ν 3414, 2924, 1673, 1522, 1502, 1439, 1308, 1222, 1154, 1114, 8147, 734, 691, 500 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{27}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 411.2067, found 411.2067.

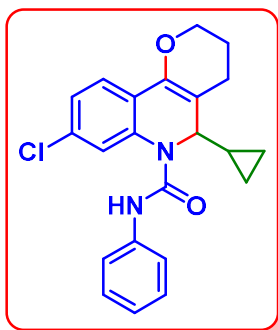
8-Chloro-5-(4-chlorophenyl)-N-phenyl-3,4-dihydro-2H-pyrano[3,2-c]quinoline-6(5H)-carboxamide (3ip):



White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 181–183 °C. Yield 168 mg, 93%. ^1H NMR (400 MHz, CDCl_3) δ 7.53 (d, J = 8.3 Hz, 1H), 7.39 (dd, J = 8.6, 1.4 Hz, 2H), 7.34–7.30 (m, 2H), 7.28 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 2.0 Hz, 1H), 7.14 (dd, J = 8.3, 2.0 Hz, 1H), 7.09 (tt, J = 7.2, 1.2 Hz, 1H), 6.90 (s, 1H), 6.03 (s, 1H), 4.30–4.25 (m, 1H), 4.22–4.16 (m, 1H), 2.22 (dt, J = 17.8, 6.7 Hz, 1H), 2.10–1.92 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 152.8, 143.7, 138.0, 137.6, 135.3, 133.8, 133.3, 129.2, 129.1, 128.8, 125.1, 124.5, 123.9, 123.5, 122.6, 119.8, 110.5, 66.5, 57.8, 23.2, 22.2. IR (KBr, neat) ν 3414, 2931, 162, 1596, 1522, 1486, 439, 1304, 1219, 1153, 1088, 733, 691, 442 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{21}\text{Cl}_2\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 451.0975, found 451.0975.

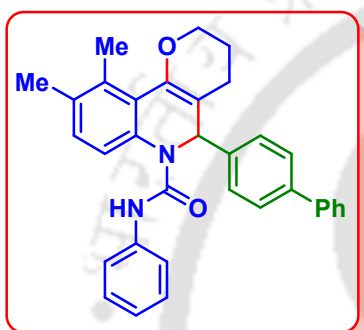
8-Chloro-5-cyclopropyl-N-phenyl-3,4-dihydro-2H-pyrano[3,2-c]quinoline-6(5H)-carboxamide (3in):

White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 158–160 °C. Yield 117 mg, 77%. ^1H NMR (500 MHz, CDCl_3) δ 7.47 (d, J = 8.3 Hz, 1H), 7.36–7.39 (m, 3H), 7.30 (t, J = 7.8 Hz, 2H), 7.16 (dd, J = 8.4, 2.0 Hz, 1H), 7.06 (t, J = 7.3 Hz, 1H), 6.86 (s, 1H), 4.26 (d, J = 9.2 Hz, 1H), 4.16 (t, J = 5.1 Hz, 2H), 2.45 (dt, J = 17.6, 6.8 Hz, 1H), 2.16 (dt, J = 17.6, 6.0 Hz, 1H),



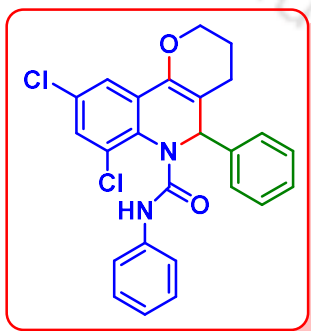
1.97 (p, $J = 6.0$ Hz, 2H), 0.90–0.83 (m, 1H), 0.59–0.52 (m, 2H), 0.47–0.42 (m, 1H), 0.35–0.30 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 152.6, 141.9, 138.3, 136.1, 132.8, 129.0, 124.8, 123.5, 123.5, 122.6, 119.6, 113.1, 66.4, 60.5, 24.0, 22.4, 14.5, 4.2, 2.0. IR (KBr, neat) ν 3417, 2931, 1667, 1595, 1518, 1486, 1438, 1219, 159, 1111, 733, 691, 504 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{22}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 381.1364, found 381.1365.

5-([1,1'-Biphenyl]-4-yl)-9,10-dimethyl-N-phenyl-3,4-dihydro-2H-pyrano[3,2-c]quinoline-6(5H)-carboxamide (3jj):



White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 206–208 $^{\circ}\text{C}$. Yield 183 mg, 94%. ^1H NMR (500 MHz, CDCl_3) δ 7.53 (dd, $J = 7.2, 1.0$ Hz 2H), 7.48–7.45 (m, 2H), 7.43–7.38 (m, 7H), 7.33–7.29 (m, 3H), 7.08–7.04 (m, 2H), 6.98 (s, 1H), 6.13 (s, 1H), 4.32–4.27 (m, 1H), 4.23–4.19 (m, 1H), 2.30–2.23 (m, 4H), 2.20 (s, 3H), 2.15 (dt, $J = 17.4, 5.7$ Hz, 1H), 2.06–1.97 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.4, 144.1, 140.9, 140.4, 138.8, 138.6, 136.6, 133.5, 132.1, 129.0, 128.7, 128.3, 127.20, 127.18, 127.0, 124.03, 124.01, 123.25, 123.19, 119.4, 109.7, 66.5, 57.9, 23.4, 22.5, 20.0, 19.4. IR (KBr, neat) ν 33411, 2925, 1672, 1521, 1499, 1439, 1223, 1154, 1072, 734, 693, 503 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{33}\text{H}_{31}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 487.2380, found 487.2380.

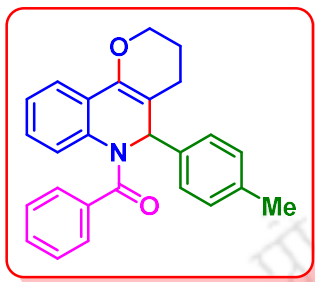
7,9-Dichloro-N,5-diphenyl-3,4-dihydro-2H-pyrano[3,2-c]quinoline-6(5H)-carboxamide (3ka):



White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 163–165 $^{\circ}\text{C}$. Yield 170 mg, 94%. ^1H NMR (400 MHz, CDCl_3) δ 7.43 (d, $J = 2.4$ Hz, 1H), 7.32 (d, $J = 8.1$ Hz, 2H), 7.25–7.21 (m, 4H), 7.20–7.17 (m, 2H), 7.16–7.13 (m, 2H), 7.00 (t, $J = 7.3$ Hz, 1H), 6.31 (d, $J = 6.3$ Hz, 1H), 6.09 (s, 1H), 4.27–4.22 (m, 1H), 4.18–4.12 (m, 1H), 2.28 (dt, $J = 18.1, 6.8$ Hz, 1H), 2.17 (dt, $J = 18.0, 5.9$ Hz, 1H), 1.99–1.93 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.0, 143.6, 138.1, 138.1, 132.0, 130.4, 130.3, 129.9, 129.0, 128.7, 128.4, 127.98, 127.5, 123.9, 121.0, 119.9, 114.2, 66.7,

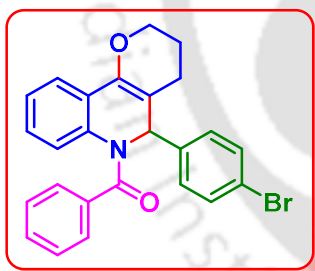
58.3, 23.8, 22.1. IR (KBr, neat) ν 3314, 3058, 2932, 1667, 1519, 1457, 1440, 1262, 1236, 1196, 1147, 733, 694, 566 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{21}\text{Cl}_2\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 451.0975, found 451.0976.

Phenyl(5-(*p*-tolyl)-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinolin-6(5*H*)-yl)methanone (3lb):



White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 196–198 °C. Yield 139 mg, 91%. ^1H NMR (400 MHz, CDCl_3) δ 7.52 (dd, J = 7.7, 1.6 Hz, 1H), 7.34–7.30 (m, 3H), 7.28–7.25 (m, 2H), 7.23–7.19 (m, 2H), 7.05–7.00 (m, 3H), 6.71 (td, J = 7.7, 1.6 Hz, 1H), 6.26 (d, J = 8.0 Hz, 1H), 6.17 (s, 1H), 4.34–4.22 (m, 2H), 2.34–2.26 (s, 4H), 2.14–1.96 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 169.4, 144.0, 137.6, 135.8, 135.7, 135.2, 130.2, 129.3, 129.2, 128.0, 127.9, 126.5, 125.6, 125.1, 124.6, 121.0, 110.5, 66.4, 58.7, 23.1, 22.4, 21.1. IR (KBr, neat) ν 2927, 2873, 1640, 1573, 1489, 1377, 1333, 1273, 1137, 967, 761, 739, 705, 656, 522 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{24}\text{NO}_2$ ($\text{M} + \text{H}$)⁺ 382.1802, found 382.1804.

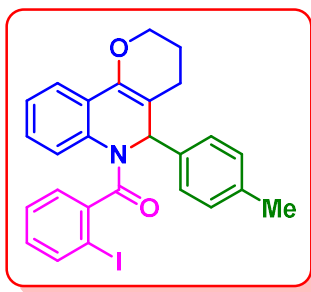
(5-(4-Bromophenyl)-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinolin-6(5*H*)-yl)(phenyl)-methanone (3lq):



White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 178–180 °C. Yield 162 mg, 91%. ^1H NMR (400 MHz, CDCl_3) δ 7.44 (dd, J = 7.7, 1.6 Hz, 1H), 7.30–7.21 (m, 5H), 7.20–7.15 (m, 3H), 7.13 (d, J = 7.9 Hz, 1H), 6.94 (td, J = 7.6, 1.2 Hz, 1H), 6.64 (td, J = 7.8, 1.6 Hz, 1H), 6.15 (d, J = 8.0 Hz, 1H), 6.07 (s, 1H), 4.26–4.13 (m, 2H), 2.27–2.18 (m, 1H), 2.02–1.88 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 169.5, 144.4, 137.7, 135.4, 134.9, 131.6, 130.4, 129.9, 129.3, 128.0, 126.8, 125.5, 124.9, 124.8, 121.9, 121.2, 109.6, 66.4, 58.2, 23.0, 22.4. IR (KBr, neat) ν 3057, 2928, 2875, 1639, 1487, 135, 1332, 1272, 1137, 1100, 1070, 1009, 761, 736, 700, 652 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{21}\text{BrNO}_2$ ($\text{M} + \text{H}$)⁺ 446.0750, found 446.0724.

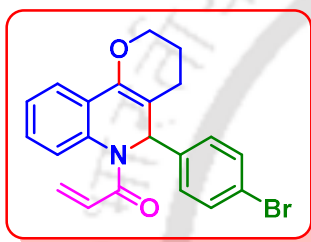
(2-Iodophenyl)(5-(*p*-tolyl)-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinolin-6(5*H*)-yl)methanone (3mb):

White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 186–188 °C. Yield 189 mg, 93% (d.r = 3:2). ^1H NMR (400 MHz, CDCl_3) δ 7.95–7.74 (m, 1H), 7.55–7.40 (m, 2H), 7.32–7.23 (m, 2H),



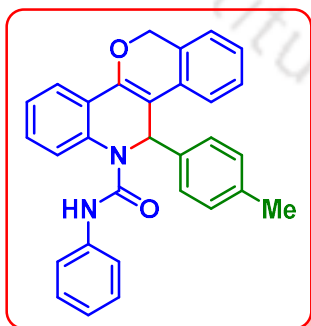
7.10–6.91 (m, 5H), 6.69 (s, 1H), 6.45 (s, 1H), 6.33 (s, 1H, major), 6.19 (s, 1H, minor), 4.36–4.16 (m, 2H), 2.39–2.00 (m, 7H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 169.4, 168.8, 144.4, 142.3, 141.7, 139.7, 139.1, 137.5, 135.7, 135.2, 134.0, 133.4, 130.8, 130.2, 129.2, 128.2, 127.9, 127.5, 126.8, 126.2, 125.5, 125.1, 124.9, 121.1, 121.0, 109.9, 108.9, 95.9, 92.2, 66.5, 57.4, 56.6, 23.3, 22.4, 21.1. IR (KBr, neat) ν 2927, 1645, 1491, 1381, 1335, 1276, 1144, 1101, 968, 762, 521 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{23}\text{INO}_2$ ($\text{M} + \text{H}$) $^+$ 508.0768, found 508.0769.

1-(5-(4-Bromophenyl)-3,4-dihydro-2H-pyrano[3,2-c]quinolin-6(5H)-yl)prop-2-en-1-one (3nq):



White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 96–98 °C. Yield 139 mg, 88%. ^1H NMR (500 MHz, CDCl_3) δ 7.54 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 8.5 Hz, 2H), 7.19–7.15 (m, 3H), 7.11 (t, J = 7.8 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 6.49–6.47 (m, 2H), 6.17 (s, 1H), 5.71 (d, J = 6.7, 5.5 Hz, 1H), 4.29–4.25 (m, 1H), 4.19–4.15 (m, 1H), 2.23 (dt, J = 17.7, 6.8 Hz, 1H), 2.05–1.92 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 165.2, 144.3, 137.7, 133.5, 131.6, 129.8, 129.4, 128.6, 127.2, 125.6, 125.5, 124.5, 121.9, 121.5, 109.9, 66.4, 57.2, 23.1, 22.3. IR (KBr, neat) ν 3061, 2930, 2875, 1652, 1614, 1487, 1404, 1229, 1154, 1067, 978, 764, 735, 520 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{19}\text{BrNO}_2$ ($\text{M} + \text{H}$) $^+$ 396.0594, found 396.0597.

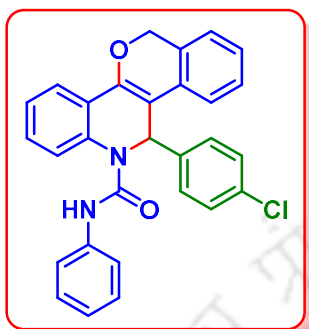
N-phenyl-11-(*p*-tolyl)-6H-isochromeno[4,3-*c*]quinoline-12(11H)-carboxamide (3ob):



White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 98–100 °C. Yield 160 mg, 90%. ^1H NMR (500 MHz, CDCl_3) δ 7.73 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.33–7.28 (m, 4H), 7.26–7.21 (m, 2H), 7.21–7.17 (m, 2H), 7.11 (dd, J = 11.0, 7.2 Hz, 2H), 7.06 (t, J = 7.4 Hz, 1H), 7.01 (s, 2H), 7.00 (s, 1H), 6.96 (s, 1H), 5.31 (s, 2H), 2.24 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.0, 146.2, 138.3, 137.4, 136.1, 135.2, 129.9, 129.7, 129.1, 129.0, 128.9, 128.5, 128.3, 127.6, 127.2, 125.8, 125.2, 124.1, 123.5, 123.3, 123.2, 121.2, 119.5, 113.1, 68.9, 53.1, 21.1. IR (KBr,

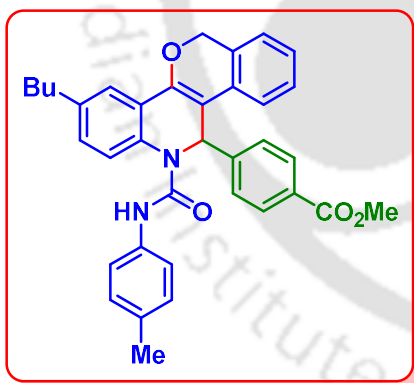
neat) ν 3414, 3053, 2849, 1672, 1597, 1522, 1486, 1435, 1219, 1155, 1093, 732, 693, 542, 501 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 445.1911, found 445.1911.

11-(4-Chlorophenyl)-N-phenyl-6H-isochromeno[4,3-c]quinoline-12(11H)-carboxamide (3op):



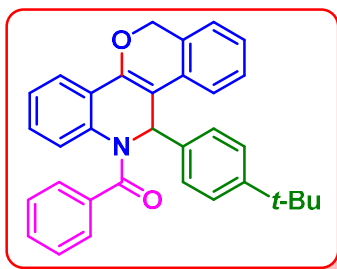
White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 170–172 °C. Yield 165 mg, 89%. ^1H NMR (500 MHz, CDCl_3) δ 7.73 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 7.9 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.30 (t, J = 7.7 Hz, 2H), 7.25–7.24 (m, 2H), 7.23–7.19 (m, 3H), 7.16 (d, J = 8.2 Hz, 2H), 7.12–7.10 (m, 1H), 7.08–7.05 (m, 2H), 7.01 (s, 1H), 6.93 (s, 1H), 5.31 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.0, 146.5, 138.2, 137.7, 134.9, 133.5, 129.6, 129.15, 129.09, 129.06, 128.6, 128.2, 127.4, 125.6, 125.4, 124.2, 123.7, 123.5, 123.1, 121.0, 119.5, 112.4, 68.9, 52.6. IR (KBr, neat) ν 3414, 3058, 2847, 1673, 1597, 1523, 1486, 1439, 1319, 1220, 1091, 1015, 752, 693, 551 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{22}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 465.1364, found 465.1364.

Methyl 4-(3-butyl-12-(*p*-tolylcarbamoyl)-11,12-dihydro-6H-isochromeno[4,3-c]quinolin-11-yl)benzoate (3ps):



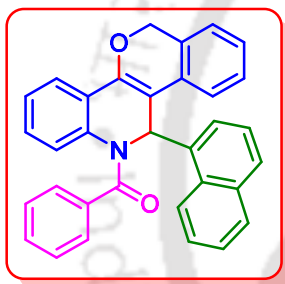
White solid; R_f (Hexane:EtOAc, 4:2) 0.5; mp 95–97 °C. Yield 181 mg, 81%. ^1H NMR (400 MHz, CDCl_3) δ 7.86 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.21–7.16 (m, 3H), 7.13–7.05 (m, 5H), 7.00 (d, J = 8.2 Hz, 2H), 5.32 (s, 2H), 3.84 (s, 3H), 2.61 (dd, J = 8.9, 6.8 Hz, 2H), 2.31 (s, 3H), 1.66–1.59 (m, 2H), 1.43–1.34 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 166.9, 153.3, 146.9, 144.7, 140.3, 135.6, 133.2, 132.7, 129.9, 129.7, 129.5, 129.4, 129.2, 128.6, 128.2, 127.7, 127.3, 125.3, 124.2, 123.2, 123.0, 120.9, 119.7, 112.2, 69.0, 52.8, 52.0, 35.3, 33.4, 22.5, 20.8, 14.0. IR (KBr, neat) ν 3415, 2930, 1719, 1673, 1519, 1492, 1264, 1223, 1109, 731, 704, 507 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{36}\text{H}_{35}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$)⁺ 559.2591, found 559.2590.

(11-(4-(*tert*-Butyl)phenyl)-6H-isochromeno[4,3-c]quinolin-12(11H)-yl)(phenyl)-methanone (3qr):



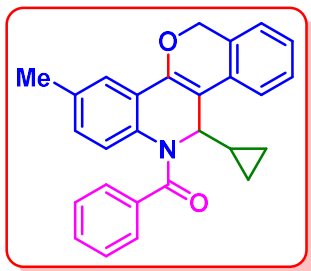
White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 170–172 °C. Yield 183 mg, 97%. ^1H NMR (500 MHz, CDCl_3) δ 7.73 (d, J = 7.7 Hz, 1H), 7.46–7.40 (m, 5H), 7.33 (d, J = 8.1 Hz, 2H), 7.31–7.27 (m, 4H), 7.25 (d, J = 7.3 Hz, 1H), 7.21 (d, J = 7.1 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.10 (s, 1H), 6.88 (t, J = 7.7 Hz, 1H), 6.50 (s, 1H), 5.46–5.40 (m, 2H), 1.30 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 169.6, 150.5, 146.5, 136.2, 135.45, 135.40, 130.4, 129.9, 129.3, 128.53, 128.47, 128.1, 127.6, 127.4, 127.1, 125.9, 125.4, 124.8, 124.4, 124.2, 122.3, 121.1, 112.5, 69.0, 54.0, 34.4, 31.3. IR (KBr, neat) ν 3058, 2960, 2865, 1643, 1487, 1382, 1331, 1272, 1097, 1055, 1021, 756, 699, 558 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{33}\text{H}_{30}\text{NO}_2$ ($\text{M} + \text{H}$) $^+$ 472.2271, found 472.2273.

(11-(Naphthalen-1-yl)-6H-isochromeno[4,3-c]quinolin-12(11H)-yl)(phenyl)-methanone (3qt):



White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 95–97 °C. Yield 125 mg, 67%. ^1H NMR (400 MHz, CDCl_3) δ 9.37 (d, J = 8.6 Hz, 1H), 7.93 (s, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.82–7.78 (m, 1H), 7.73–7.69 (m, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.30–7.26 (m, 1H), 7.21–7.16 (m, 5H), 7.14–7.05 (m, 5H), 6.91 (d, J = 7.6 Hz, 1H), 6.69 (td, J = 7.7, 1.5 Hz, 1H), 6.16 (d, J = 8.0 Hz, 1H), 5.41 (q, J = 12.9 Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 169.3, 147.4, 135.9, 135.8, 134.3, 132.1, 131.7, 129.7, 129.5, 129.2, 128.7, 128.5, 128.4, 128.2, 127.8, 127.6, 127.2, 127.0, 126.8, 126.4, 126.3, 125.8, 125.1, 124.8, 124.1, 121.4, 120.9, 114.5, 68.9, 50.8. IR (KBr, neat) ν 3054, 2923, 2850, 1642, 1599, 1487, 1326, 1269, 1123, 1097, 1026, 784, 757, 732, 698, 549 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{33}\text{H}_{24}\text{NO}_2$ ($\text{M} + \text{H}$) $^+$ 466.1802, found 466.1800.

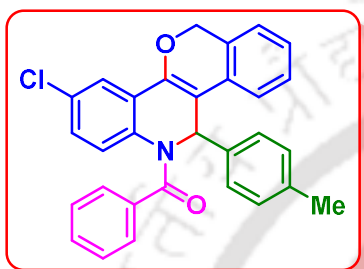
(11-Cyclopropyl-3-methyl-6H-isochromeno[4,3-c]quinolin-12(11H)-yl)(phenyl)-methanone (3rn):



White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 199–201 °C. Yield 123 mg, 78%. ^1H NMR (400 MHz, CDCl_3) δ 7.43 (d, J = 2.0 Hz, 1H), 7.36–7.29 (m, 5H), 7.26–7.20 (m, 3H), 7.12 (dt, J = 7.3, 1.0 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 6.50 (s, 1H), 5.60 (d, J = 7.8 Hz, 1H), 5.31 (d, J = 12.8 Hz, 1H), 5.19 (d, J = 12.8

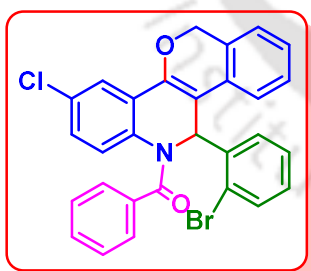
Hz, 1H), 2.30 (s, 3H), 1.18–1.09 (m, 1H), 0.52–0.31 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 169.2, 145.9, 135.7, 134.5, 134.3, 130.4, 130.2, 129.2, 128.7, 128.5, 128.4, 128.1, 126.9, 125.3, 124.4, 123.53, 123.49, 120.9, 112.1, 69.1, 21.0, 14.4, 3.5, 2.6. IR (KBr, neat) ν 3401, 2923, 2852, 1636, 1490, 1447, 1329, 1278, 1135, 820, 754, 721, 700, 649, 619 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{24}\text{NO}_2$ ($\text{M} + \text{H}$) $^+$ 394.1802, found 394.1803.

(3-Chloro-11-(*p*-tolyl)-6*H*-isochromeno[4,3-*c*]quinolin-12(11*H*)-yl)(phenyl)-methanone (3sb):



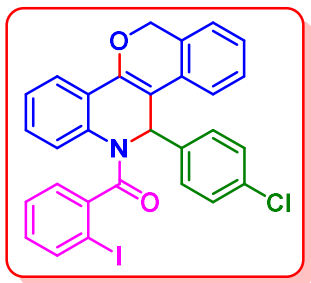
White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 215–217 °C. Yield 171 mg, 92%. ^1H NMR (500 MHz, CDCl_3) δ 7.50 (d, J = 1.5 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 7.8 Hz, 2H), 7.16 (s, 1H), 7.14 (d, J = 8.3 Hz, 2H), 7.10–7.06 (m, 2H), 7.02–6.97 (m, 2H), 6.91–6.88 (m, 3H), 6.61 (d, J = 8.4 Hz, 1H), 6.17 (d, J = 6.9 Hz, 1H), 5.23 (s, 2H), 2.12 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 169.4, 145.6, 137.8, 135.0, 134.5, 130.7, 130.5, 129.35, 129.31, 129.2, 128.6, 128.5, 128.3, 127.7, 127.6, 127.5, 126.8, 125.9, 124.2, 122.2, 121.3, 113.4, 69.0, 54.1, 21.1. IR (KBr, neat) ν 3058, 2851, 1646, 1483, 1328, 1275, 1138, 1106, 987, 818, 759, 614, 519 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{23}\text{ClNO}_2$ ($\text{M} + \text{H}$) $^+$ 464.1412, found 464.1412.

(11-(2-Bromophenyl)-3-chloro-6*H*-isochromeno[4,3-*c*]quinolin-12(11*H*)-yl)(phenyl)-methanone (3si):



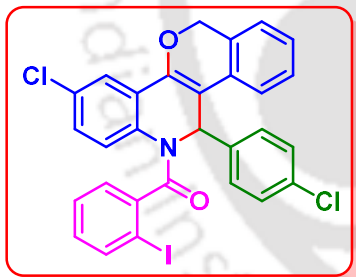
White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 227–229 °C. Yield 131 mg, 62%. ^1H NMR (400 MHz, CDCl_3) δ 7.69 (d, J = 2.4 Hz, 1H), 7.61 (dd, J = 7.9, 1.3 Hz, 1H), 7.37–7.32 (m, 2H), 7.32–7.26 (m, 4H), 7.26–7.23 (m, 2H), 7.23–7.20 (m, 1H), 7.12 (d, J = 6.4 Hz, 1H), 7.08–7.03 (m, 1H), 7.02–6.95 (m, 2H), 6.83 (dd, J = 8.5, 2.5 Hz, 1H), 6.45 (d, J = 8.5 Hz, 1H), 5.32 (d, J = 3.5 Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 169.5, 145.9, 136.6, 135.3, 134.5, 134.0, 131.1, 130.2, 130.0, 129.3, 128.8, 128.64, 128.62, 128.4, 128.1, 127.8, 127.7, 127.61, 127.59, 126.6, 124.3, 123.4, 122.1, 121.4, 115.3, 68.9, 54.3. IR (KBr, neat) ν 3071, 2923, 2852, 1661, 1483, 1325, 1274, 1134, 1106, 1025, 986, 755, 699 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{20}\text{BrClNO}_2$ ($\text{M} + \text{H}$) $^+$ 528.0360, found 528.0351.

(11-(4-Chlorophenyl)-6H-isochromeno[4,3-c]quinolin-12(11H)-yl)(2-iodophenyl)-methanone (3tp):



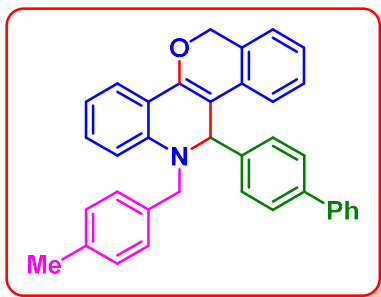
White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 97–99 °C. Yield 212 mg, 92% (d.r = 3:2). ^1H NMR (500 MHz, CDCl_3) δ 7.91 (d, J = 7.3 Hz, 1H, major), 7.69–7.47 (m, 2H), 7.46–7.37 (m, 2H), 7.37–7.32 (m, 1H, minor), 7.28 (s, 1H), 7.25–7.22 (m, 2H), 7.19 (d, J = 8.3 Hz, 2H), 7.16 (s, 1H), 7.11 (d, J = 7.0 Hz, 1H), 7.07–7.00 (m, 2H), 6.99–6.95 (m, 1H, minor), 6.84–6.77 (m, 1H, major), 6.77–6.71 (m, 1H), 6.46 (d, J = 8.0 Hz, 1H, major), 6.27 (d, J = 8.1 Hz, 1H, minor), 5.37–5.27 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 171.6, 169.0, 141.1, 139.8, 139.2, 136.5, 134.6, 133.7, 130.9, 130.6, 129.9, 129.7, 129.6, 129.3, 128.8, 128.72, 128.69, 128.1, 127.6, 127.5, 127.2, 125.6, 125.2, 124.3, 122.2, 121.0, 111.5, 95.9, 92.3, 69.0, 52.5, 51.8. IR (KBr, neat) ν 3059, 2846, 1647, 1488, 1383, 1332, 1278, 1145, 1091, 1015, 757, 734, 669 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{20}\text{ClINO}_2$ ($\text{M} + \text{H}$) $^+$ 576.0222, found 576.0214.

(3-Chloro-11-(4-chlorophenyl)-6H-isochromeno[4,3-c]quinolin-12(11H)-yl)(2-iodophenyl)methanone (3up):



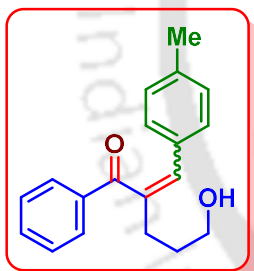
White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 99–101 °C. Yield 210 mg, 86% (d.r = 3:2). ^1H NMR (500 MHz, CDCl_3) δ 7.82 (d, J = 7.9 Hz, 1H, minor), 7.56–7.50 (m, 1H), 7.48 (s, 1H, major), 7.40–7.35 (m, 1H, major), 7.32–7.22 (m, 2H), 7.18 (s, 1H), 7.17 (s, 1H), 7.16 (s, 1H, minor), 7.15 (s, 1H), 7.12 (d, J = 8.1 Hz, 2H), 7.08–6.98 (m, 3H), 6.97–6.91 (m, 1H), 6.66–6.59 (m, 1H), 6.28 (d, J = 8.1 Hz, 1H, major), 6.09 (d, J = 8.2 Hz, 1H, minor), 5.30–5.18 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 169.4, 168.9, 146.3, 145.8, 141.3, 140.7, 139.9, 139.3, 136.5, 136.2, 134.0, 133.0, 132.4, 131.3, 130.9, 130.8, 129.2, 129.1, 128.9, 128.8, 128.7, 128.5, 128.2, 128.0, 127.9, 127.7, 127.6, 127.3, 126.3, 126.1, 126.0, 124.4, 122.3, 121.25, 121.18, 112.6, 111.4, 95.7, 92.3, 69.0, 52.5, 51.8. IR (KBr, neat) ν 3062, 2847, 1651, 1485, 1383, 1330, 1279, 1144, 1108, 1015, 987, 826, 758, 738 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{19}\text{Cl}_2\text{INO}_2$ ($\text{M} + \text{H}$) $^+$ 609.9832, found 609.9809.

11-([1,1'-Biphenyl]-4-yl)-12-(4-methylbenzyl)-11,12-dihydro-6H-isochromeno[4,3-c]quinoline (3vj):



White solid; R_f (Hexane:EtOAc, 19:1) 0.5; mp 152–154 °C. Yield 138 mg, 70%. ^1H NMR (400 MHz, CDCl_3) δ 7.62 (dd, J = 7.6, 1.7 Hz, 1H), 7.53–7.49 (m, 2H), 7.46–7.38 (m, 6H), 7.34–7.29 (m, 1H), 7.23 (d, J = 7.7 Hz, 2H), 7.18–7.11 (m, 4H), 7.10–7.02 (m, 3H), 6.74 (t, J = 7.4 Hz, 1H), 6.50 (d, J = 8.3 Hz, 1H), 5.70 (s, 1H), 5.27 (d, J = 12.8 Hz, 1H), 5.14 (d, J = 12.8 Hz, 1H), 4.62 (d, J = 16.2 Hz, 1H), 4.31 (d, J = 16.1 Hz, 1H), 2.35 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 146.7, 144.5, 140.8, 140.7, 140.6, 136.8, 134.3, 130.5, 130.3, 129.4, 129.2, 128.7, 128.0, 127.38, 127.35, 127.2, 127.1, 127.0, 126.2, 124.1, 122.8, 119.5, 117.5, 116.7, 111.3, 108.3, 68.6, 61.2, 51.5, 21.1. IR (KBr, neat) ν 2960, 2924, 1721, 1594, 1487, 1259, 1042, 803, 752, 696, 521, 450 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{36}\text{H}_{30}\text{NO}$ ($\text{M} + \text{H}$) $^+$ 492.2322, found 492.2300.

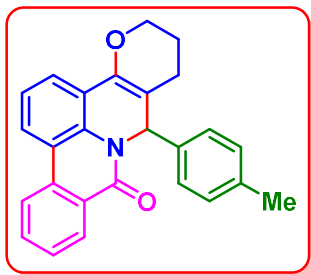
5-Hydroxy-2-(4-methylbenzylidene)-1-phenylpentan-1-one (9):



White semi-solid; R_f (Hexane:EtOAc, 3:2) 0.50. Yield 131 mg, 78%. ^1H NMR (500 MHz, CDCl_3) δ 7.75 (d, J = 7.7 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 7.8 Hz, 2H), 7.16 (s, 1H), 3.65 (t, J = 6.1 Hz, 2H), 2.87 (t, J = 7.4 Hz, 2H), 2.38 (s, 3H), 2.35–2.30 (m, 1H), 1.85 (p, J = 6.8 Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 200.3, 143.4, 140.1, 139.2, 138.6, 132.5, 131.9, 129.7, 129.5, 129.4, 128.2, 61.8, 31.5, 23.5, 21.4. IR (KBr, neat) ν 3416, 2923, 1639, 1604, 1445, 1319, 1255, 1056, 951, 815, 716, 702, 654, 499 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 281.1536, found 281.1537.

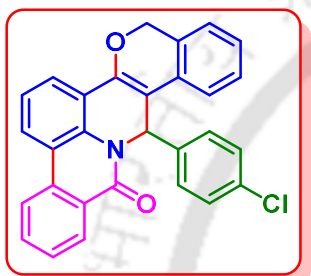
8-(*p*-Tolyl)-6,7-dihydro-5H,8H,10H-pyrano[2',3':4,5]pyrido[3,2,1-*de*]phenanthridin-10-one (10a):

White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 104–106 °C. Yield 66 mg, 87%. ^1H NMR (500 MHz, CDCl_3) δ 8.44 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H), 8.12 (d, J = 8.1 Hz, 1H), 7.71–7.68 (m, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.31–7.27 (m, 3H), 7.02 (d, J = 7.9 Hz, 2H), 6.46 (s, 1H), 4.26–4.22 (m, 1H), 4.13–4.09 (m, 1H), 2.24 (s, 3H), 2.17–2.11 (m, 1H),



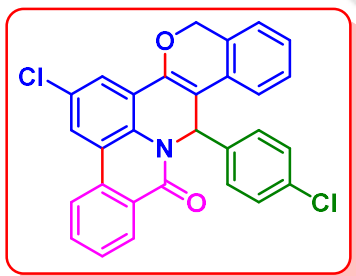
2.05–1.99 (m, 2H), 1.94–1.88 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 161.0, 141.3, 138.7, 137.4, 133.5, 133.0, 132.4, 129.1, 128.8, 127.7, 127.3, 125.5, 122.32, 122.26, 121.7, 121.6, 120.2, 118.1, 107.7, 66.2, 60.3, 22.7, 22.3, 21.1. IR (KBr, neat) ν 3055, 2926, 2870, 1682, 1649, 1609, 1586, 1426, 1313, 1266, 1146, 1066, 758, 736, 694 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{22}\text{NO}_2$ ($\text{M} + \text{H}$) $^+$ 380.1645, found 380.1643.

10-(4-Chlorophenyl)-5H,10H,12H-isochromeno[3',4':4,5]pyrido[3,2,1-de]phenanthridin-12-one (10b):



Lemon green solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 218–220 $^{\circ}\text{C}$. Yield 72 mg, 81%. ^1H NMR (500 MHz, CDCl_3) δ 8.50 (d, J = 8.0 Hz, 1H), 8.23 (d, J = 8.1 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.75 (t, J = 7.6 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.51 (d, J = 8.5 Hz, 2H), 7.49 (s, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 7.14 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 7.4 Hz, 1H), 5.31 (d, J = 12.7 Hz, 1H), 5.17 (d, J = 12.7 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 161.2, 144.8, 139.4, 133.7, 133.4, 133.1, 132.8, 129.2, 129.1, 128.9, 128.7, 128.5, 128.2, 127.5, 125.4, 124.4, 123.8, 123.2, 122.7, 121.8, 120.2, 119.1, 118.6, 108.9, 68.9, 53.9. IR (KBr, neat) ν 3063, 2924, 2853, 1713, 1653, 1590, 1487, 1304, 1260, 1088, 1014, 797, 755, 689, 569 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{19}\text{ClNO}_2$ ($\text{M} + \text{H}$) $^+$ 448.1099, found 448.1098.

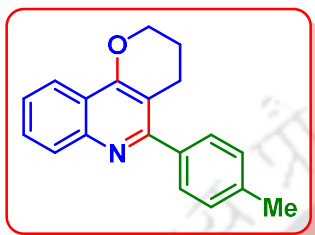
2-Chloro-10-(4-chlorophenyl)-5H,10H,12H-isochromeno[3',4':4,5]pyrido[3,2,1-de]phenanthridin-12-one (10c):



Lemon green solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 186–188 $^{\circ}\text{C}$. Yield 79 mg, 82%. ^1H NMR (500 MHz, CDCl_3) δ 8.46 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 8.1 Hz, 1H), 8.05 (s, 1H), 7.79 (s, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 7.0 Hz, 2H), 7.41 (d, J = 8.1 Hz, 1H), 7.40 (s, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 7.3 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 7.3 Hz, 1H), 5.28 (d, J = 12.7 Hz, 1H), 5.15 (d, J = 12.8 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126

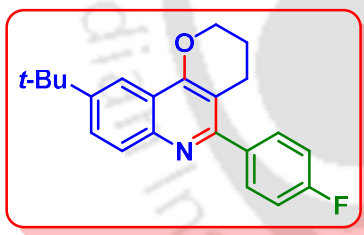
MHz, CDCl₃) δ 160.8, 143.6, 139.0, 133.9, 133.0, 132.2, 131.5, 129.3, 129.1, 129.0, 128.8, 128.77, 128.70, 128.6, 128.5, 127.9, 125.6, 124.5, 123.1, 123.0, 121.8, 120.7, 120.5, 120.0, 110.0, 68.9, 54.0. IR (KBr, neat) ν 3065, 2923, 2853, 1697, 1655, 1487, 1430, 1303, 1139, 1090, 1061, 997, 759, 740, 683 cm⁻¹. HRMS (ESI) calcd. for C₂₉H₁₈Cl₂NO₂ (M + H)⁺ 482.0709, found 482.0706.

5-(*p*-Tolyl)-3,4-dihydro-2H-pyrano[3,2-*c*]quinoline (11a):



White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 112–114 °C. Yield 81 mg, 98%. ¹H NMR (400 MHz, CDCl₃) δ 8.12 (d, *J* = 8.32, 0.96 Hz, 1H), 8.04 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.66–7.62 (m, 1H), 7.50–7.44 (m, 3H), 7.28 (d, *J* = 7.8 Hz, 2H), 4.45 (t, *J* = 5.2 Hz, 2H), 2.77 (t, *J* = 6.3 Hz, 2H), 2.42 (s, 3H), 2.06–2.00 (m, 2H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 161.0, 157.4, 147.3, 138.0, 137.7, 129.1, 129.0, 128.9, 128.7, 125.2, 121.2, 120.0, 110.7, 67.0, 23.9, 22.0, 21.3. IR (KBr, neat) ν 2946, 1746, 1586, 1491, 1407, 1324, 1157, 1114, 985, 825, 765, 451 cm⁻¹. HRMS (ESI) calcd. for C₁₉H₁₈NO (M + H)⁺ 276.1383, found 276.1384.

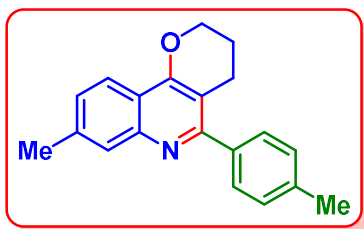
9-(*tert*-Butyl)-5-(4-fluorophenyl)-3,4-dihydro-2H-pyrano[3,2-*c*]quinoline (11b):



White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 206–208 °C. Yield 98 mg, 97%. ¹H NMR (500 MHz, CDCl₃) δ 8.06 (d, *J* = 1.6 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.75 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.57–7.53 (m, 2H), 7.15 (t, *J* = 8.6 Hz, 2H), 4.47 (t, *J* = 5.2 Hz, 2H), 2.74 (t, *J* = 6.3 Hz, 2H), 2.05 (p, *J* = 5.8 Hz, 2H), 1.43 (s, 9H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 162.8 (d, *J* = 247.5 Hz), 159.1, 157.5, 148.5, 145.7, 136.7, 130.7 (d, *J* = 8.2 Hz), 128.6, 128.2, 119.4, 116.1, 115.2 (d, *J* = 21.4 Hz), 110.4, 67.1, 35.1, 31.4, 23.9, 22.0. ¹⁹F NMR (471 MHz, CDCl₃/C₆F₆) δ -117.1. IR (KBr, neat) ν 2958, 1585, 1511, 1401, 1274, 1163, 1133, 991, 833, 586, 558 cm⁻¹. HRMS (ESI) calcd. for C₂₂H₂₃FN (M + H)⁺ 336.1758, found 336.1760.

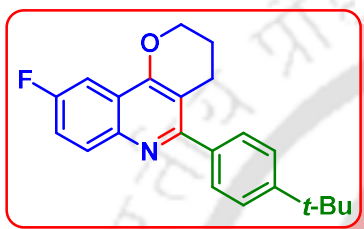
8-Methyl-5-(*p*-tolyl)-3,4-dihydro-2H-pyrano[3,2-*c*]quinoline (11c):

White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 108–110 °C. Yield 85 mg, 98%. ¹H NMR (500 MHz, CDCl₃) δ 8.00 (d, *J* = 8.4 Hz, 1H), 7.82 (s, 1H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.29 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 2H), 4.44 (t, *J* = 5.1 Hz, 2H), 2.76 (t, *J* = 6.3



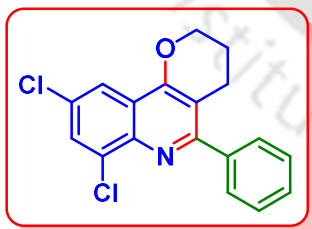
Hz, 2H), 2.52 (s, 3H), 2.42 (s, 3H), 2.02 (p, $J = 5.6$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 160.9, 157.3, 147.6, 139.2, 137.89, 137.86, 128.9, 128.7, 128.1, 127.4, 120.9, 117.8, 109.9, 67.0, 23.9, 22.0, 21.8, 21.3. IR (KBr, neat) ν 3032, 2921, 1625, 1591, 1497, 1418, 1350, 1329, 1170, 1126, 1066, 987, 823, 780, 731 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{20}\text{NO}$ ($\text{M} + \text{H}$) $^+$ 290.1539, found 290.1537.

5-(4-(*tert*-Butyl)phenyl)-9-fluoro-3,4-dihydro-2H-pyrano[3,2-*c*]quinoline (11d):



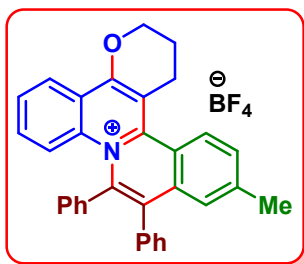
White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 156–158 $^{\circ}\text{C}$. Yield 93 mg, 92%. ^1H NMR (500 MHz, CDCl_3) δ 8.02 (dd, $J = 9.3, 5.2$ Hz, 1H), 7.71 (dd, $J = 9.6, 2.3$ Hz, 1H), 7.52–7.47 (m, 4H), 7.39 (td, $J = 8.6, 2.2$ Hz, 1H), 4.46 (t, $J = 4.9$ Hz, 2H), 2.81 (t, $J = 6.3$ Hz, 2H), 2.04 (p, $J = 5.8$ Hz, 2H), 1.37 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 160.3 (d, $J = 2.5$ Hz), 160.1 (d, $J = 246.0$ Hz), 156.9 (d, $J = 4.8$ Hz), 151.3, 144.4, 137.4, 131.5 (d, $J = 8.9$ Hz), 128.5, 125.3, 120.5 (d, $J = 9.7$ Hz), 119.0 (d, $J = 25.6$ Hz), 111.3, 105.0 (d, $J = 23.5$ Hz), 67.1, 34.7, 31.4, 23.9, 21.9. ^{19}F NMR (471 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -118.0. IR (KBr, neat) ν 2958, 1628, 1594, 1494, 1454, 1041, 1354, 1268, 1235, 1183, 1105, 989, 937, 829, 785, 574 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{23}\text{FNO}$ ($\text{M} + \text{H}$) $^+$ 336.1758, found 336.1756.

7,9-Dichloro-5-phenyl-3,4-dihydro-2H-pyrano[3,2-*c*]quinoline (11e):



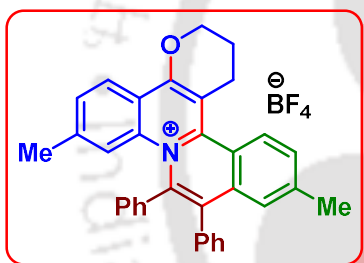
White solid; R_f (Hexane:EtOAc, 9:1) 0.4; mp 173–175 $^{\circ}\text{C}$. Yield 93 mg, 94%. ^1H NMR (500 MHz, CDCl_3) δ 8.03 (s, 1H), 7.73 (s, 1H), 7.66 (d, $J = 7.5$ Hz, 2H), 7.49–7.42 (m, 3H), 4.47 (t, $J = 5.1$ Hz, 2H), 2.83 (t, $J = 6.2$ Hz, 2H), 2.02 (p, $J = 5.5$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 161.2, 156.9, 142.2, 139.9, 134.4, 130.3, 129.8, 129.3, 128.7, 128.2, 121.5, 119.7, 112.4, 67.3, 24.1, 21.7. IR (KBr, neat) ν 3058, 2954, 2891, 1580, 1464, 1350, 1321, 1157, 1029, 986, 864, 765, 700, 571 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{14}\text{Cl}_2\text{NO}$ ($\text{M} + \text{H}$) $^+$ 330.0447, found 330.0436.

9-Methyl-6,7-diphenyl-13,14-dihydro-12H-isoquinolino[2,1-*a*]pyrano[3,2-*c*]quinolin-5-ium tetrafluoroborate (12a):



Yellow solid; R_f (DCM:MeOH, 9:1) 0.4; mp 290–292 °C. Yield 102 mg, 95%. ^1H NMR (400 MHz, CDCl_3) δ 8.64 (d, J = 8.6 Hz, 1H), 8.33 (dd, J = 8.6, 1.3 Hz, 1H), 7.69 (dd, J = 8.7, 1.8 Hz, 1H), 7.60 (d, J = 8.9 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.43 (s, 1H), 7.37–7.32 (m, 3H), 7.29–7.27 (m, 1H), 7.23–7.19 (m, 2H), 7.12–7.03 (m, 3H), 6.9–6.95 (m, 2H), 4.92 (t, J = 5.3 Hz, 2H), 3.67 (t, J = 5.9 Hz, 2H), 2.50 (s, 3H), 2.42 (p, J = 5.6 Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 161.2, 153.9, 146.1, 139.3, 136.8, 136.5, 134.33, 134.30, 132.9, 130.84, 130.80, 130.7, 130.0, 129.8, 128.8, 128.52, 128.50, 128.2, 128.0, 126.5, 124.3, 123.5, 122.8, 120.9, 112.7, 70.0, 27.7, 22.3, 21.9. IR (KBr, neat) ν 3059, 2922, 1612, 1587, 152, 14223, 1315, 1185, 1053, 1002, 786, 765, 699, 643 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{33}\text{H}_{26}\text{NO}$ ($\text{M} - \text{BF}_4$) $^+$ 452.2009, found 452.2009.

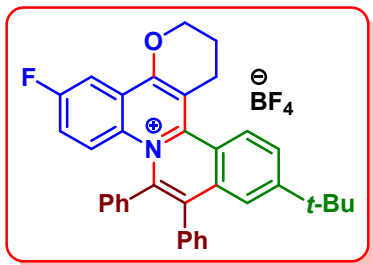
3,9-Dimethyl-6,7-diphenyl-13,14-dihydro-12H-isoquinolino[2,1-a]pyrano[3,2-c]quinolin-5-ium tetrafluoroborate (12b):



Yellow solid; R_f (DCM:MeOH, 9:1) 0.4; mp 315–317 °C. Yield 106 mg, 96%. ^1H NMR (500 MHz, CDCl_3) δ 8.61 (d, J = 8.6 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 16.9 Hz, 2H), 7.36–7.32 (m, 4H), 7.22–7.20 (m, 2H), 7.13–7.09 (m, 1H), 7.08–7.05 (m, 2H), 6.96 (d, J = 7.1 Hz, 2H), 4.90 (t, J = 5.3 Hz, 2H), 3.65 (t, J = 5.9 Hz, 2H), 2.49 (s, 3H), 2.40 (p, J = 5.6 Hz, 2H), 2.11 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 161.4, 153.5, 145.9, 141.7, 139.2, 136.9, 136.5, 134.3, 134.1, 132.6, 130.80, 130.77, 130.74, 129.8, 129.7, 128.7, 128.5, 128.4, 128.2, 126.4, 124.4, 123.3, 122.8, 118.9, 112.1, 69.9, 27.6, 22.3, 22.0, 21.7. IR (KBr, neat) ν 3026, 2930, 1614, 1583, 1505, 1427, 1316, 1187, 1139, 1054, 827, 764, 703 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{34}\text{H}_{28}\text{NO}$ ($\text{M} - \text{BF}_4$) $^+$ 466.2166, found 466.2166.

9-(tert-Butyl)-2-fluoro-6,7-diphenyl-13,14-dihydro-12H-isoquinolino[2,1-a]pyrano[3,2-c]quinolin-5-ium tetrafluoroborate (12c):

Yellow solid; R_f (DCM:MeOH, 9:1) 0.4; mp 267–269 °C. Yield 110 mg, 92%. ^1H NMR (500 MHz, CDCl_3) δ 8.69 (d, J = 8.9 Hz, 1H), 7.93–7.90 (m, 2H), 7.66–7.63 (m, 2H), 7.37–7.32 (m, 3H), 7.23–7.21 (m, 2H), 7.14–7.07 (m, 3H), 7.01 (d, J = 7.4 Hz, 2H), 7.00–6.96 (m, 1H), 4.91 (t, J = 5.1 Hz, 2H), 3.68 (t, J = 5.8 Hz, 2H), 2.41 (p, J = 5.6 Hz, 2H), 1.29 (s,



9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 160.5 (d, J = 254.2 Hz), 160.3 (d, J = 3.2 Hz), 158.8, 153.5, 139.2, 136.4, 134.4, 134.2, 133.7, 133.4 (d, J = 1.5 Hz), 130.9, 130.6, 129.7, 128.9, 128.7, 128.5, 128.3, 127.5, 126.9 (d, J = 8.4 Hz), 122.79, 122.78, 122.7, 118.9 (d, J = 25.2 Hz), 113.4, 108.3 (d, J = 24.4 Hz), 70.0, 35.8, 30.7, 27.7, 21.8. ^{19}F NMR (471 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -112.1, -157.2. IR (KBr, neat) ν 2963, 1594, 1527, 1503, 1431, 1367, 1276, 1218, 1055, 826, 763, 709 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{36}\text{H}_{31}\text{FNO}$ ($\text{M} - \text{BF}_4$) $^+$ 512.2385, found 512.2390.



4.8.1. Crystallographic Description

Table 4.8.1.1. Crystal parameters of compound **3ab**

Compound 3ab	CCDC 2366683
Formula	C ₂₇ H ₂₆ N ₂ O ₂
Formula weight	410.50
T/K	295(2)
Crystal system	monoclinic
Space group	C 2/c
<i>a</i> /Å	21.0914(8)
<i>b</i> /Å	14.5976(6)
<i>c</i> /Å	17.1365(11)
<i>a</i> /°	90
<i>β</i> /°	123.3360(10)
<i>γ</i> /°	90
<i>V</i> /Å ³	4407.9(4)
<i>Z</i>	8
Abs. Coeff./mm ⁻¹	0.078
Abs. Correction	none
GOF on <i>F</i> ²	1.032
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.0604 <i>wR</i> ₂ = 0.1416
<i>R</i> indices [all data]	<i>R</i> ₁ = 0.0800 <i>wR</i> ₂ = 0.1632

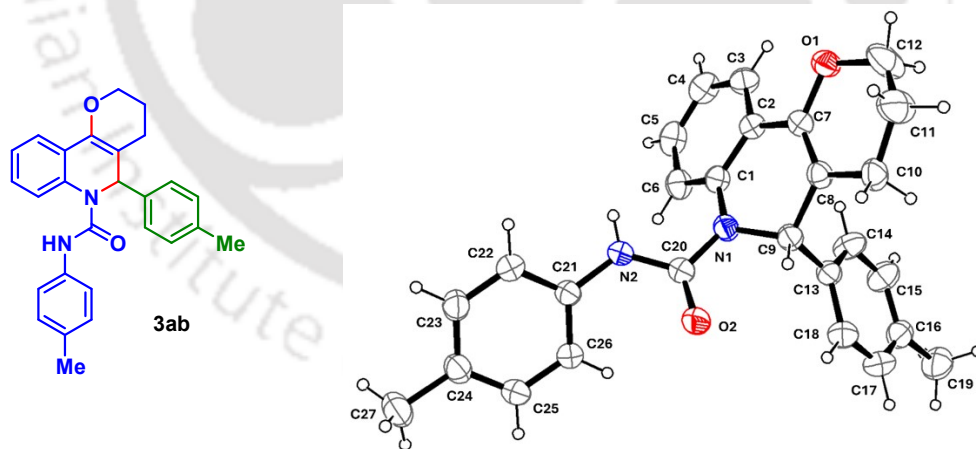
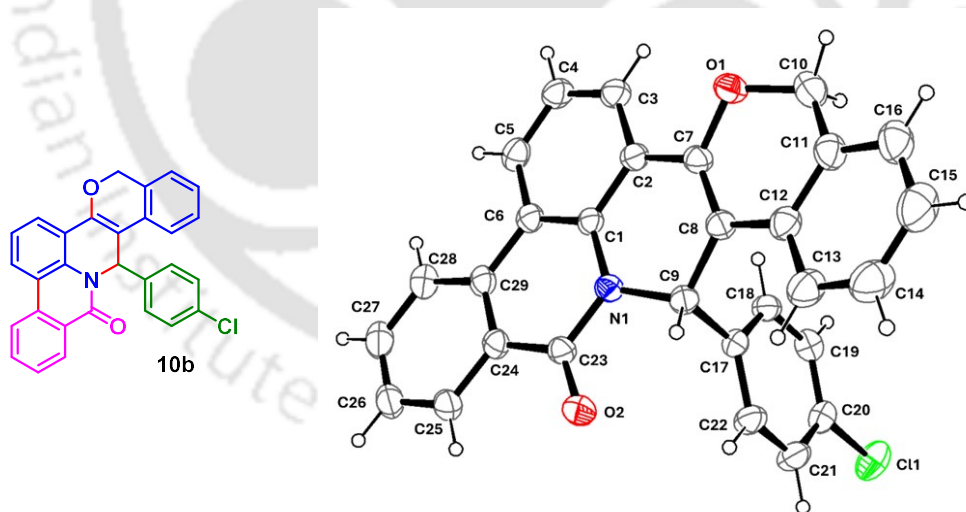
Figure 4.8.1.1. ORTEP diagram of compound **3ab** with thermal ellipsoid of 30% probability.

Table 4.8.1.2. Crystal parameters of compound **10b**

Compound 10b	CCDC 2366682
Formula	C ₂₉ H ₁₈ ClNO ₂
Formula weight	447.89
T/K	296
Crystal system	monoclinic
Space group	C 1 2/c 1
a/Å	28.691(6)
b/Å	11.105(2)
c/Å	16.340(3)
α/°	90
β/°	97.595(5)
γ/°	90
V/Å ³	5160.6(17)
Z	8
Abs. Coeff./mm ⁻¹	0.172
Abs. Correction	none
GOF on F ²	1.033
Final R indices [I > 2σ(I)]	R ₁ = 0.0791 wR ₂ = 0.2154
R indices [all data]	R ₁ = 0.0960 wR ₂ = 0.2399

Figure 4.8.1.2. ORTEP diagram of compound **10b** with thermal ellipsoid of 30% probability.

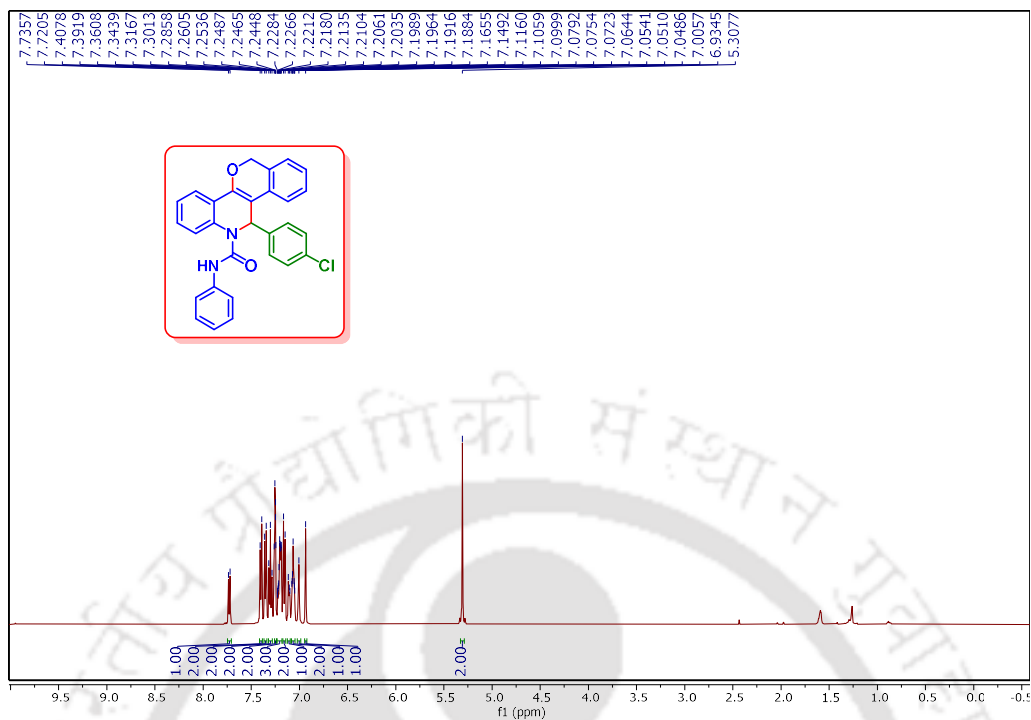


Figure 4.9.3. ¹H NMR spectrum of compound **3op** (500 MHz, CDCl₃).

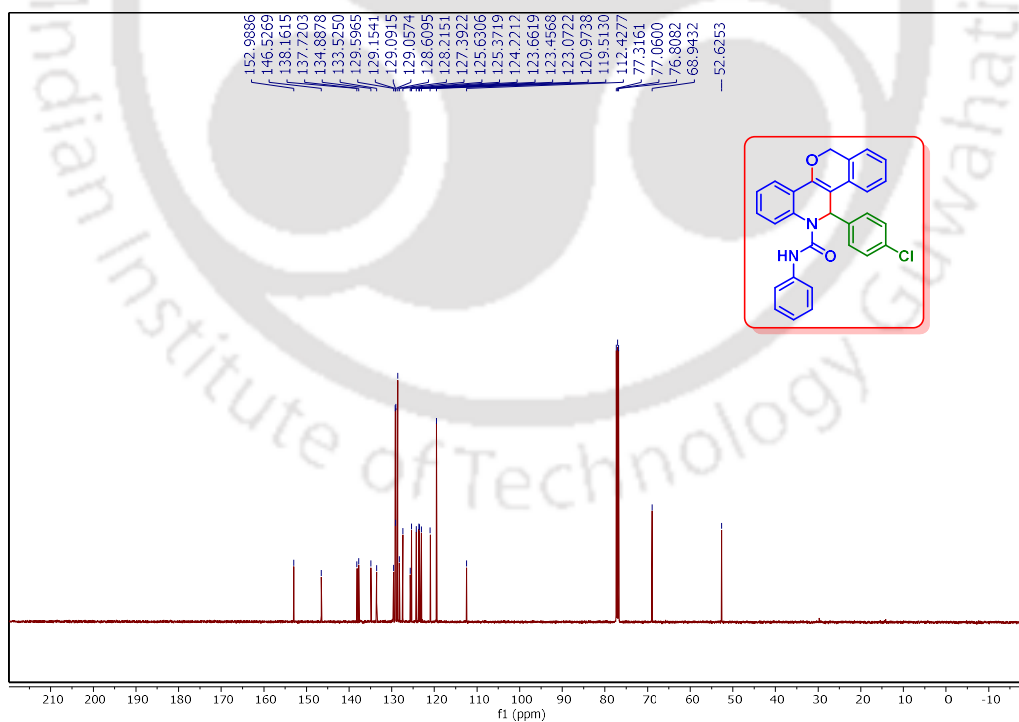


Figure 4.9.4. ¹³C{¹H} NMR spectrum of compound **3op** (126 MHz, CDCl₃).

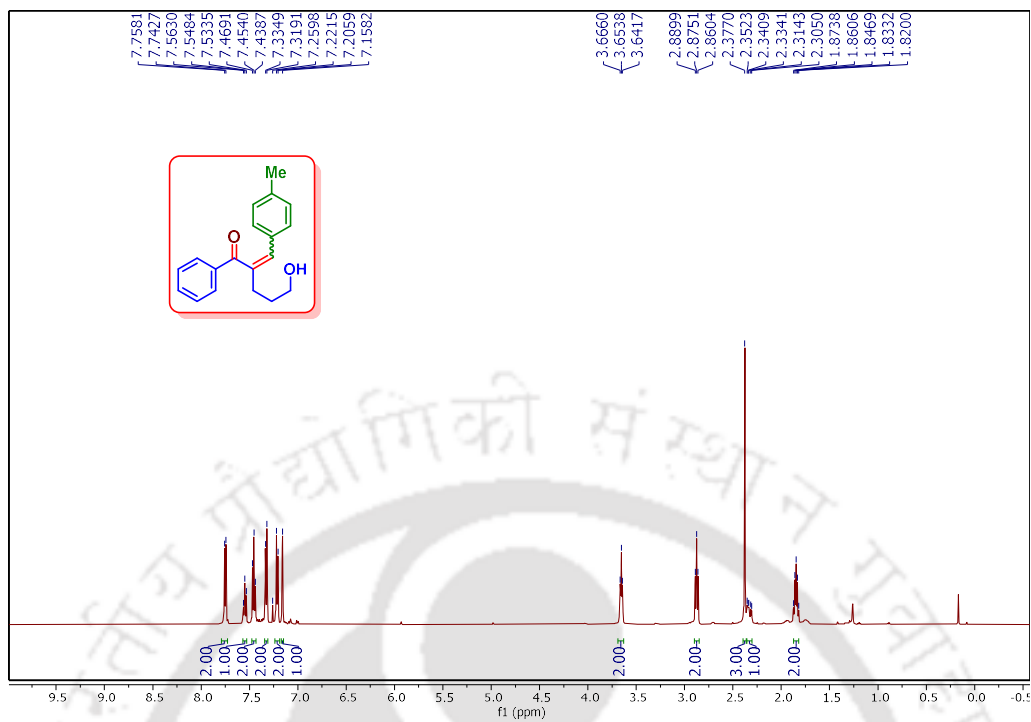


Figure 4.9.5. ¹H NMR spectrum of compound 9 (500 MHz, CDCl₃).

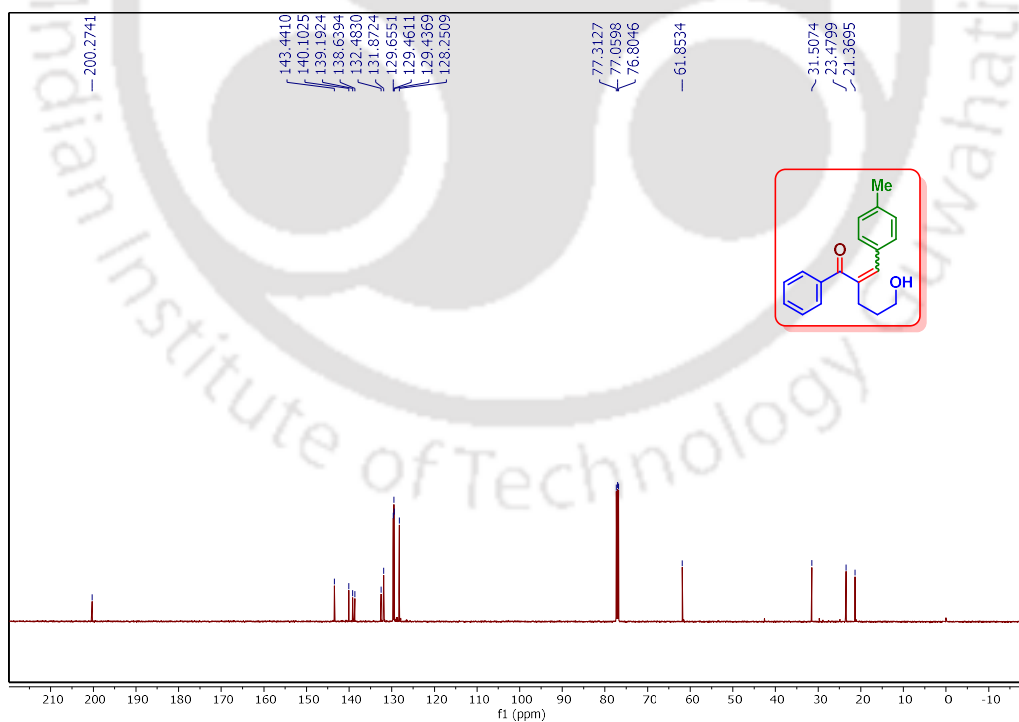


Figure 4.9.6. ¹³C{¹H} NMR spectrum of compound 9 (126 MHz, CDCl₃).

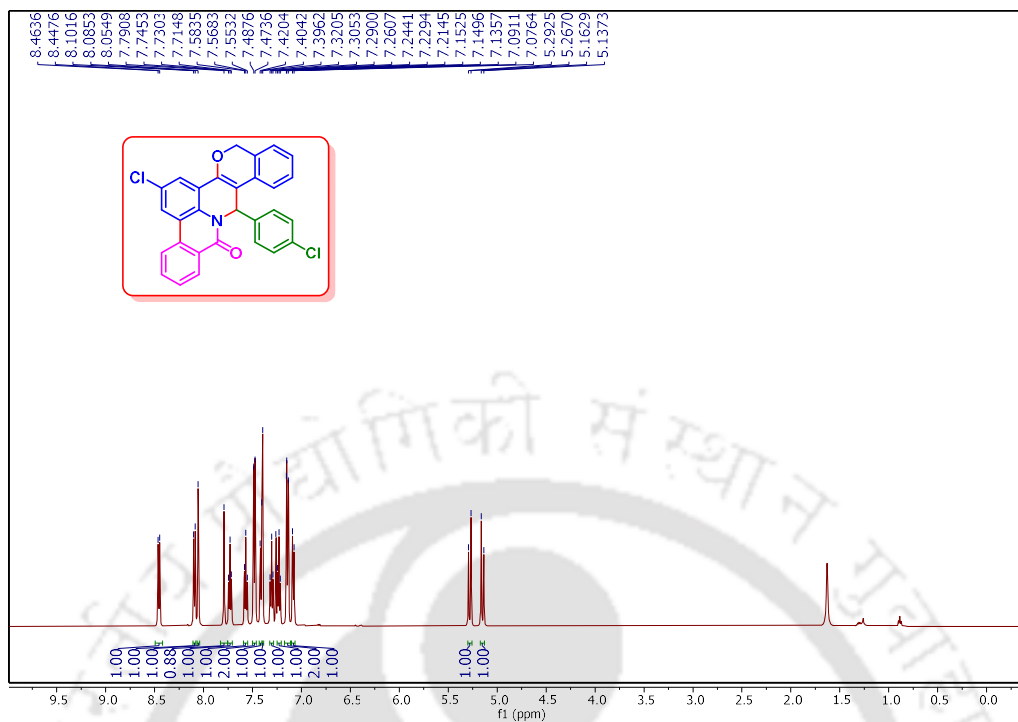


Figure 4.9.7. ¹H NMR spectrum of compound 10c (500 MHz, CDCl₃).

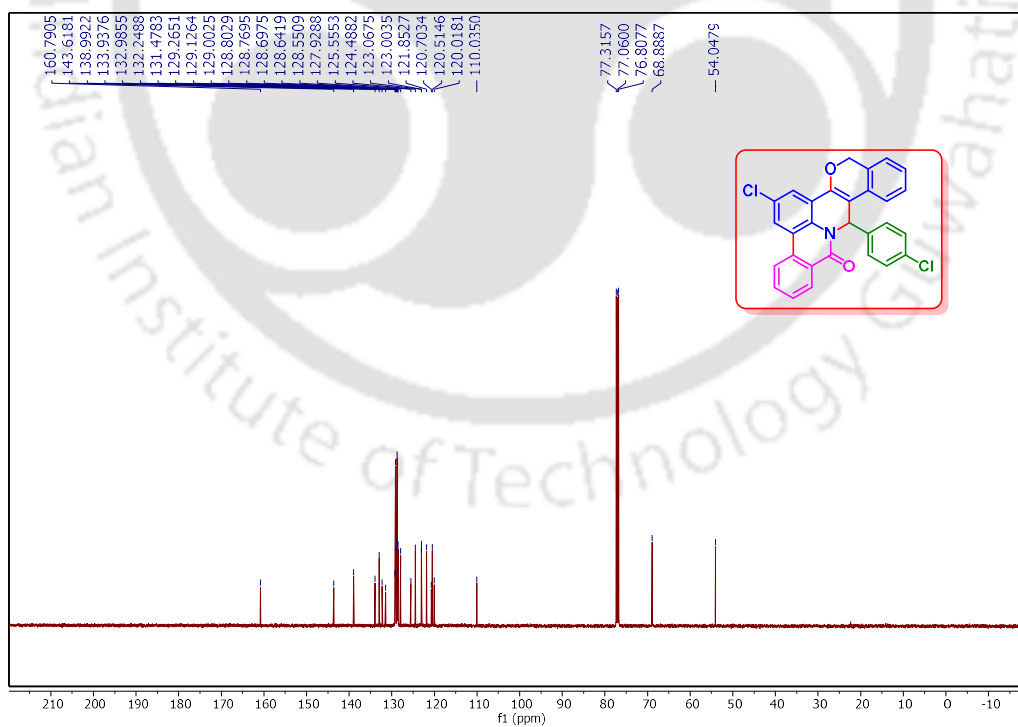


Figure 4.9.8. ¹³C{¹H} NMR spectrum of compound 10c (126 MHz, CDCl₃).

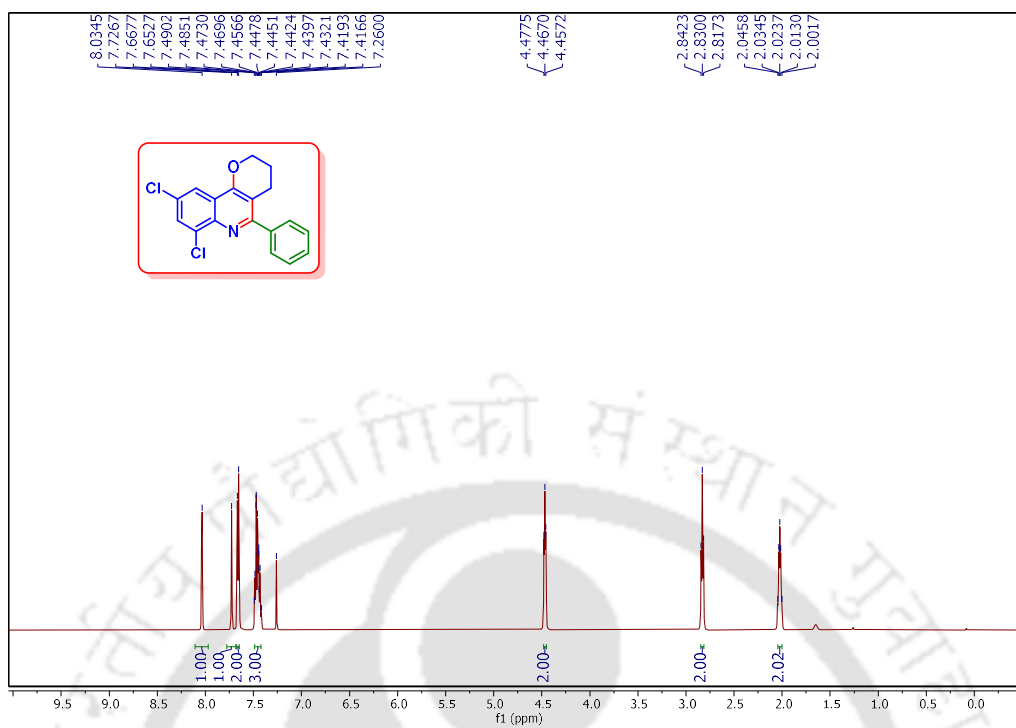


Figure 4.9.9. ¹H NMR spectrum of compound **11e** (500 MHz, CDCl₃).

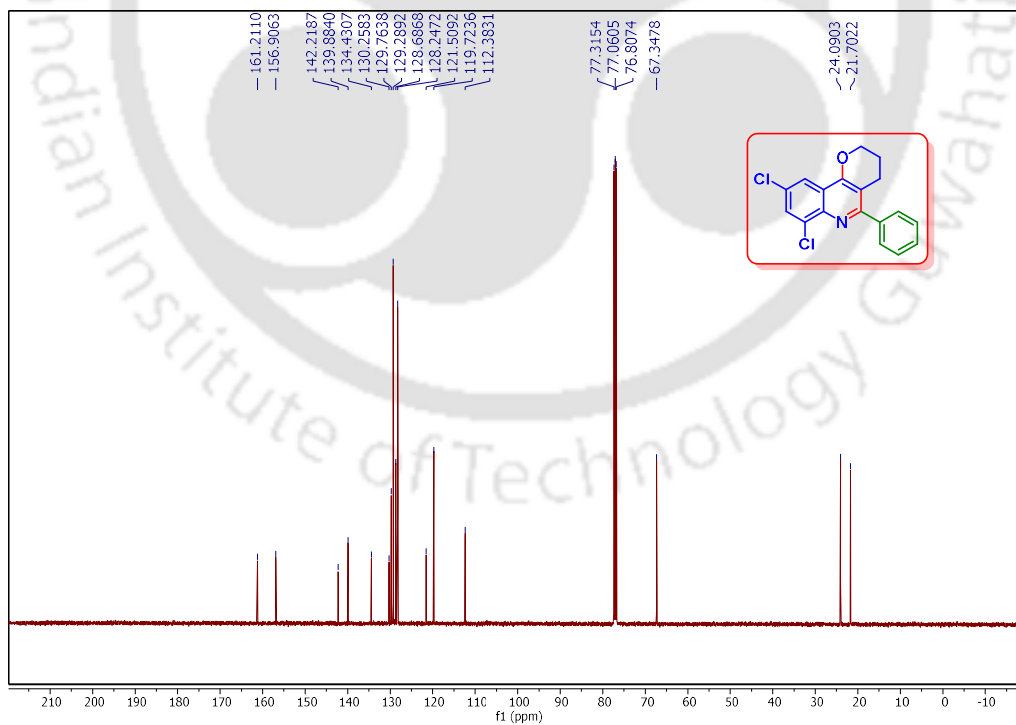


Figure 4.9.10. ¹³C{¹H} NMR spectrum of compound **11e** (126 MHz, CDCl₃).

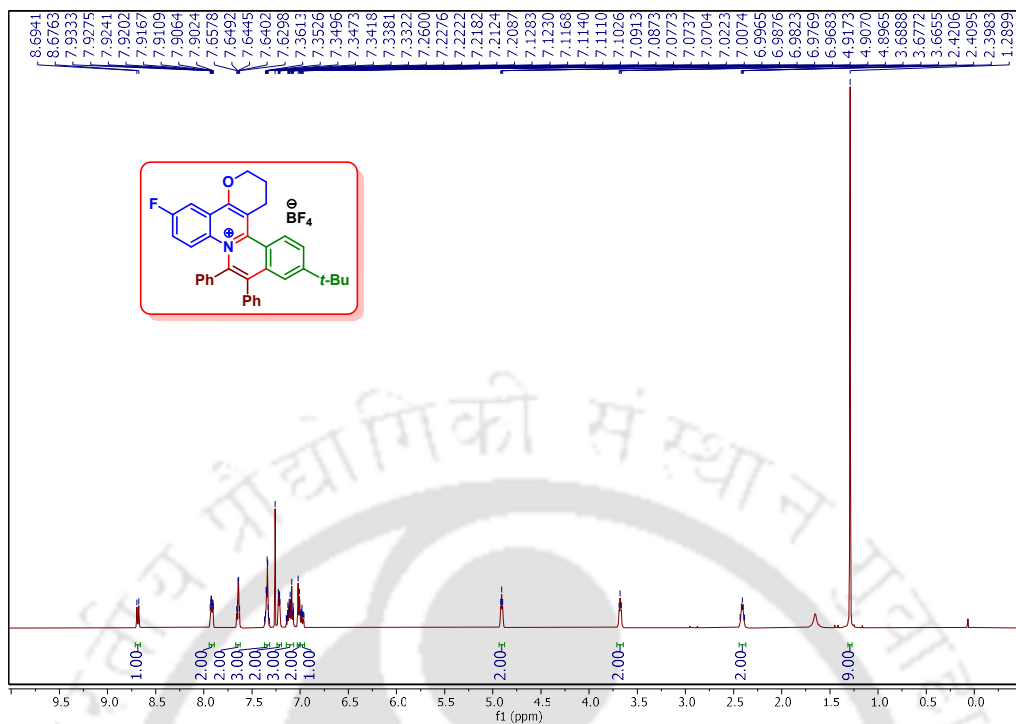


Figure 4.9.11. ^1H NMR spectrum of compound 12c (500 MHz, CDCl_3).

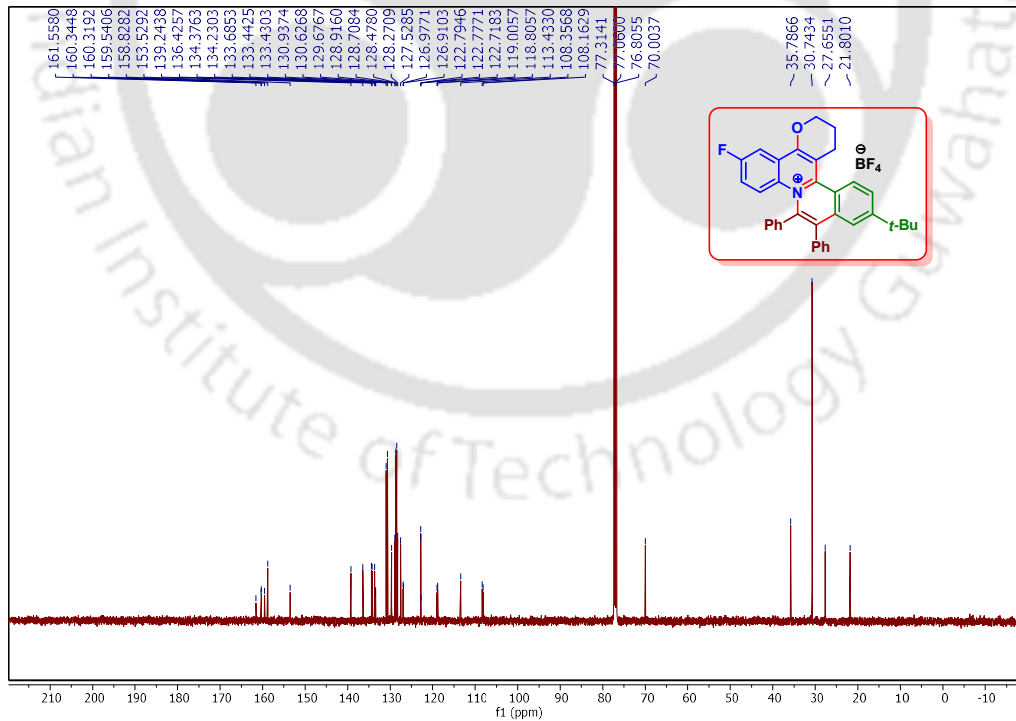
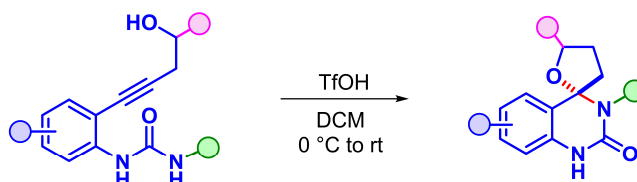


Figure 4.9.12. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of compound 12c (126 MHz, CDCl_3).



Regioselective Synthesis of Spiro-Quinazolinones *via* Sequential Hydroalkoxylation and Intramolecular Amide-Cyclization of Alkynol Ureas



- Metal-free tandem protocol
- Functionalized spirocycles
- High regioselectivity
- Excellent yields, up to 99%

Abstract: A TfOH-mediated, metal-free protocol for the synthesis of spiro-furan/pyran quinazolinones through a cascade hydroalkoxylation and intramolecular amide-cyclization reaction of alkynol ureas has been unveiled. This methodology facilitates the generation of highly functionalized spiro-heterocycles with remarkable yields and exclusive regioselectivity. Furthermore, the applicability of the strategy extends to the synthesis of spiro-pyrrolidine quinazolinones. Finally, post-synthetic modification incorporates bromide functionality into the synthesized spiro-heterocycle.



Chapter V

Regioselective Synthesis of Spiro-Quinazolinones *via* Sequential Hydro-Alkoxylation and Intramolecular Amide-Cyclization of Alkynol Ureas

5.1. Introduction

Spirocycles, known for their diverse biological applications, have gained considerable attention from scientists around the world.¹ Their unique balance between conformational constraints and flexibility enables them to circumvent absorption and permeability issues, rendering them suitable for various biological targets in drug discovery projects.² Over the years, their reputation in the medical field has witnessed a substantial growth, as evidenced by the increasing number of publications on the subject.^{1a} Many marketed drugs feature these spirocyclic scaffolds, demonstrating their potential for drug development.³ They are also utilized in perfume and dye industries.⁴ In this context, spiro quinazolinones exhibit exceptional pharmacological properties including anticancer,^{5a} antibacterial,^{5b} antidiabetic,^{5c} anticonvulsant,^{5d} antifibrillatory,^{5e} cytotoxic, and apoptosis-inducing properties.^{5f} Additionally, these compounds are crucial as inhibitors for various enzymes, including phosphodiesterase 7 (PDE 7),^{6a} insulin-regulated aminopeptidase (IRAP),^{6b} chorismate mutase,^{6c} chitin synthase,^{6d} and inosine monophosphate dehydrogenase II (IMPDH II)^{6e} (Figure 5.1.1). Beyond their medical applications, they have proven valuable in agrochemical industry.⁷

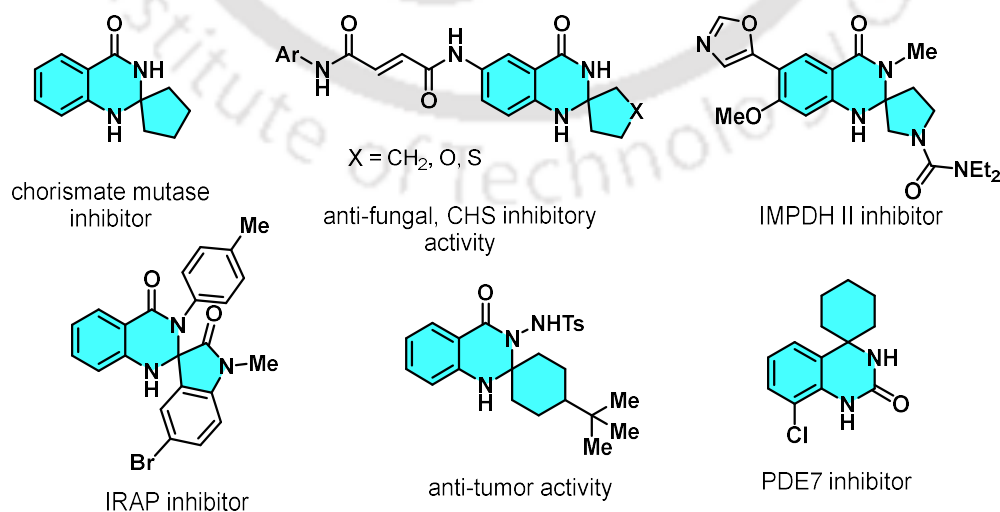
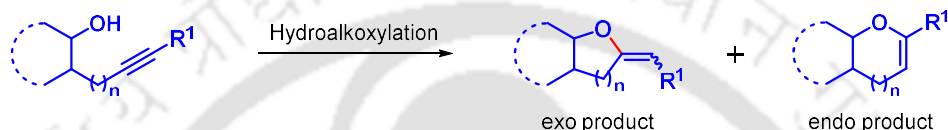


Figure 5.1.1. Representative examples of biologically active spiroquinazolinones.^{5,6}

The insertion of alcohols (RO-H) across a C-C multiple bonds to produce ether compounds is known as hydroalkoxylation reaction (Scheme 5.1.1).⁸ This process offers an atom- and step-economic route to generate ether compounds from relatively inexpensive and ubiquitous starting materials. Despite significant progress in intramolecular hydroalkoxylation reactions, the issues related to regioselectivity between the *exo-dig* and *endo-dig* modes remain a concern.^{8a} The primary factor dictating the mode of the hydroalkoxylation reaction depends on the stability of the *in situ* generated vinyl carbocation and not on the influence of the catalysts.

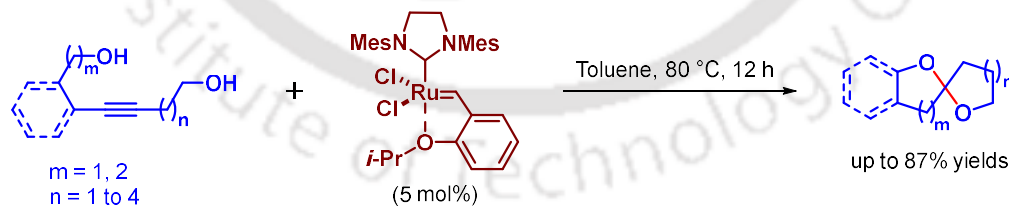


Scheme 5.1.1. Intramolecular hydroalkoxylation reaction of substituted alkynols.

5.2. Tandem Hydroalkoxylation Strategies Towards the Synthesis of Spirocycles

5.2.1. Synthesis of Spiro-O,O-Heterocycles

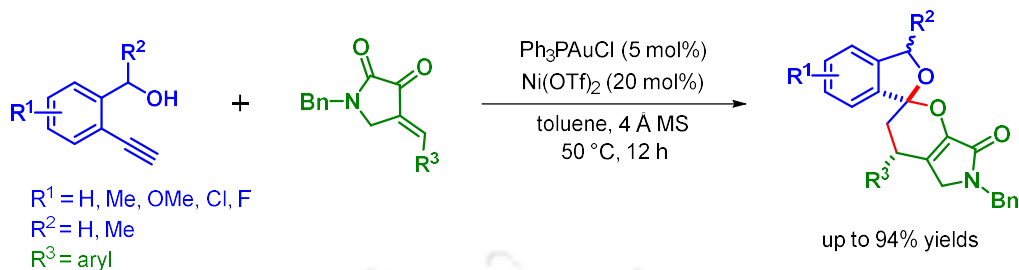
Fuwas's group reported a dual intramolecular hydroalkoxylation strategy using a Grubbs-type ruthenium carbene complex to synthesize spiroacetals. This process involves the intramolecular *trans* addition of the hydroxy group to the internal alkyne, followed by an intramolecular addition of the second hydroxy group to the newly generated oxocarbenium ion to produce the spiroacetals in high yields (Scheme 5.2.1.1).⁹



Scheme 5.2.1.1. Dual intramolecular hydroalkoxylation synthesis of spiroacetals.

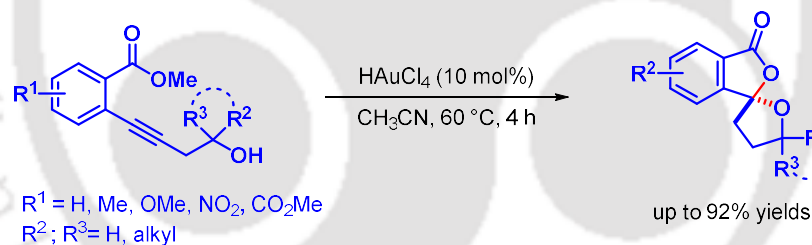
Li's group developed an Au(I)/Ni(OTf)₂-catalyzed protocol for the synthesis of spiroketals from arylalkynols and dioxopyrrolidienes. This cocatalyst-driven cascade cycloaddition strategy involves an intramolecular hydroalkoxylation of arylalkynols, followed by an inverse electron demand [2+4]-cycloaddition of Ni(OTf)₂ activated

dioxopyrrolidienes to generate the spiroketals in high yields with good stereoselectivity (Scheme 5.2.1.2).¹⁰



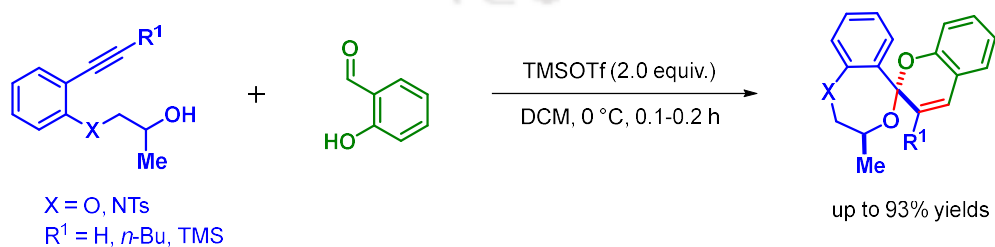
Scheme 5.2.1.2. Intramolecular hydroalkoxylation and inverse electron demand [2+4]-cycloaddition strategy for the synthesis of spiroketals.

An unprecedented Au(III)-catalyzed cascade cyclization of 2-(4-hydroxyalkynyl)-benzoates for the construction of benzannulated oxaspirolactones has been disclosed by Reddy's group. This protocol features a biologically active isobenzofuranone moiety. The reaction proceeds via hydroalkoxylation of the alkynol segment, followed by the addition of carboxylate to the oxocarbenium, facilitating the oxaspirolactone scaffold in good to excellent yields (Scheme 5.2.1.3).¹¹



Scheme 5.2.1.3. Au(III)-catalyzed synthesis of oxaspirolactones.

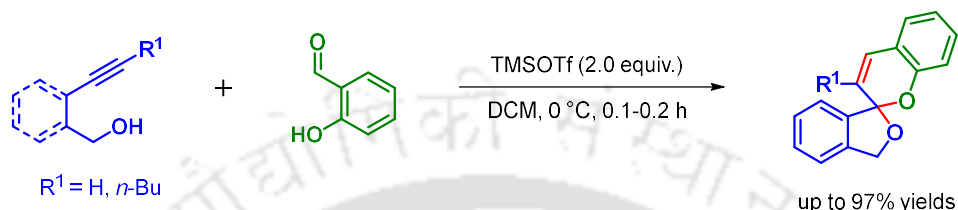
Gharpure's group devised a transition metal-free, Lewis acid promoted domino hydroalkoxylation-formal-[4+2]-cycloaddition strategy for the synthesis of spirocyclic 1,4-heterocycle-fused chromene ketals. This sequential hydroalkoxylation



Scheme 5.2.1.4. Domino hydroalkoxylation-formal-[4+2]-cycloaddition strategy for the synthesis of spirocyclic chromene ketals.

approach provides a rapid access to the spirocyclic [6-6-7-6] tetracyclic core of cytorhizhins B-D with the appropriate relative configuration (Scheme 5.2.1.4).¹²

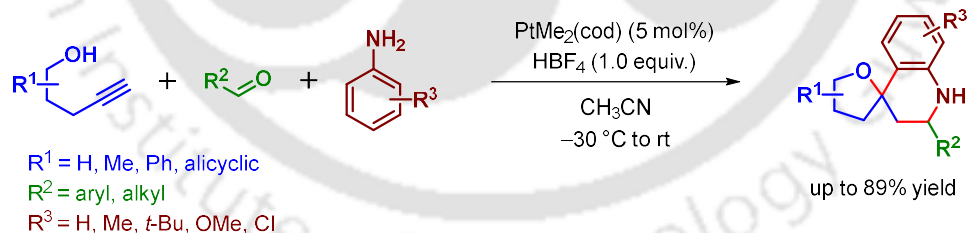
The same group further extended this cascade hydroalkoxylation-formal-(4+2)-cycloaddition strategy to construct spirocyclic chromene derivatives from readily available alkynols and salicylaldehyde (Scheme 5.2.1.5).¹³



Scheme 5.2.1.5. A domino hydroalkoxylation-formal-[4+2]-cycloaddition strategy for the synthesis of spirocyclic chromene.

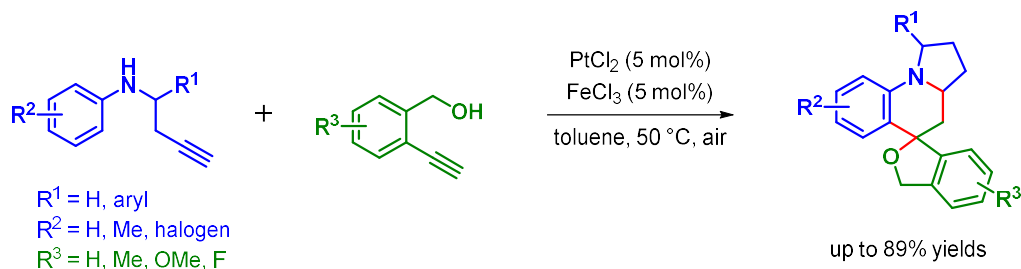
5.2.2. Synthesis of Spiro-N,O-Heterocycles

Barluenga's group reported the first Povarov reaction with exocyclic enol ethers to produce the functionalized spirocyclic quinoline derivatives in high yields. This one-pot, three-component coupling reaction of an alkynol derivative, an aldehyde, and an aromatic amine utilizes a combination of Pt-complex and a Brønsted acid to generate the enol ether and N-aryl aldimine required for the Povarov reaction (Scheme 5.2.2.1).¹⁴



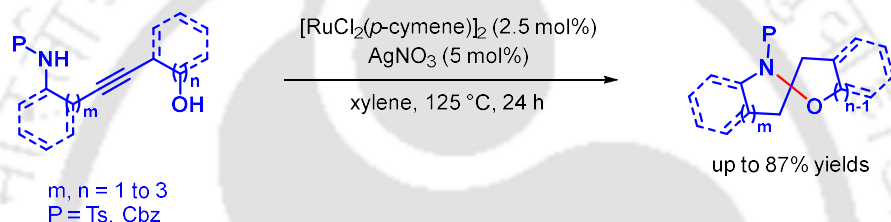
Scheme 5.2.2.1. Povarov reaction for the synthesis of spirocyclic quinoline.

The Povarov strategy was further explored by Li's group, whereby a cascade reaction of arylalkynols and homopropargyl amines led to the successful synthesis of spiroisobenzofuran-*b*-pyrroloquinolines. The reaction features the one-pot formation of four new bonds and two new stereocenters (Scheme 5.2.2.2).¹⁵



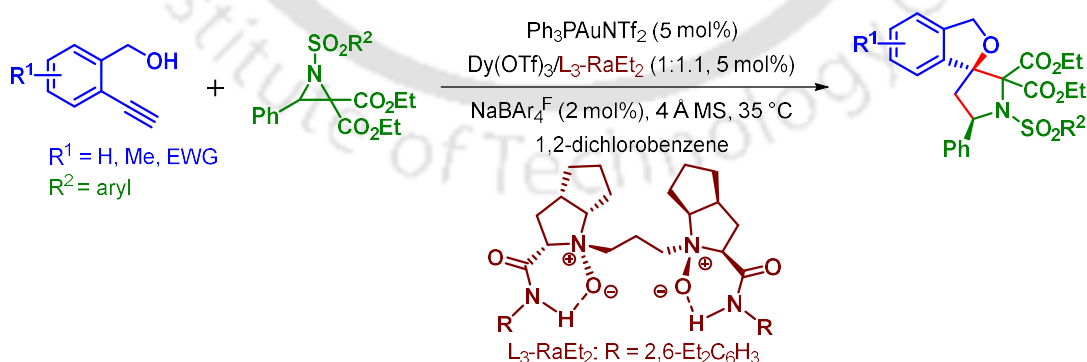
Scheme 5.2.2.2. Povarov reaction for the synthesis of spirocyclic spiroisobenzofuran-*b*-pyrroloquinolines.

Fuwas's group demonstrated a Ru/Ag-catalyzed intramolecular double hydrofunctionalization of internal alkynes to synthesize diverse spirocyclic hemiaminal ether derivatives in good to excellent yields (Scheme 5.2.2.3).¹⁶



Scheme 5.2.2.3. A double hydrofunctionalization strategy for the synthesis of spirocyclic hemiaminal ethers.

An asymmetric catalytic tandem reaction of diester aziridines and ethynyl benzyl alcohols, catalyzed by Au(I) and a chiral *N,N'*-dioxide-Dy(III) complex was studied by Feng's group. The cycloisomerization/[3+2]-cycloaddition protocol successfully furnished various enantioenriched spiroisobenzofuran pyrrolidine scaffolds in



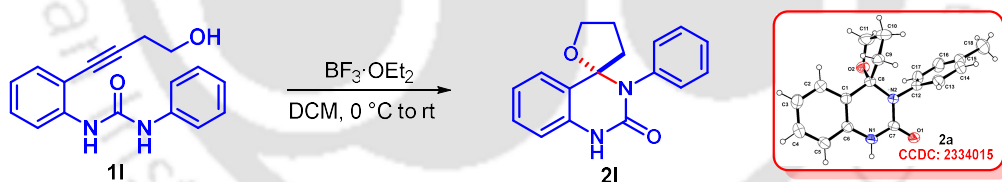
Scheme 5.2.2.4. Cycloisomerization/[3+2]-cycloaddition strategy for the synthesis of enantioenriched spiroisobenzofuran pyrrolidines.

moderate to good yields with high diastereo- and enantioselectivity (up to 81% yield, >19:1 dr, 95% ee) (Scheme 5.2.2.4).¹⁷

5.3 Present Work

Despite the numerous methodologies developed for cascade hydroalkoxylation of alkynes, there are relatively fewer reports on the synthesis of N,O-spirocycles compared to linearly fused products. We have introduced a straightforward approach employing Brønsted acid, which facilitates the efficient synthesis of spiroquinazolinones. This method involves a hydroalkoxylation step followed by nucleophilic addition of amides to alkynol ureas.

An initial reaction was conducted using 1-(2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-phenylurea (**11**) in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ in DCM at 0 °C to room temperature (Table 5.4.1.1, entry 1). To our delight, a new spiro-furan quinazolinone derivative **21** was isolated in 88% yield. The structural elucidation was confirmed through spectroscopic data (^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR) and HRMS, establishing the product as 3'-phenyl-4,5-dihydro-1*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3*H*)-one (**21**). Subsequently, the precise structure was confirmed by employing single-crystal X-ray diffraction on one of its derivatives, **2a** (Scheme 5.3.1).

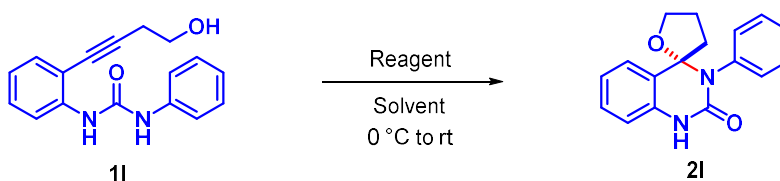


Scheme 5.3.1. Synthesis of spirofuran quinazolinone.

5.4. Results and Discussion

5.4.1. Optimization of the Reaction Conditions

To enhance the efficiency of the transformation, the reaction was systematically explored with various reagents and solvents. The reaction with 2.0 equiv. of $\text{BF}_3 \cdot \text{OEt}_2$ in acetonitrile delivered the product in 86% yield (Table 5.4.1.1, entry 2), whilst the same reaction in toluene and chloroform resulted in 75 and 63% yields (Table 5.4.1.1, entries 3 and 4), respectively. Intrigued by the results, the reaction was

Table 5.4.1.1. Optimization of the reaction conditions

Entry ^a	Reagent	Equivalent	Solvent	Time (h)	Yield ^b (%)
1	BF ₃ ·OEt ₂	2.0	DCM	16	88
2	BF ₃ ·OEt ₂	2.0	Acetonitrile	24	86
3	BF ₃ ·OEt ₂	2.0	Toluene	24	75
4	BF ₃ ·OEt ₂	2.0	Chloroform	24	63
5	TMSOTf	2.0	DCM	24	78
6	Bi(OTf) ₃	0.2	DCM	24	70
7	In(OTf) ₃	0.2	DCM	24	58
8	Cu(OTf) ₂	0.2	DCM	24	15
9	InCl ₃	0.2	DCM	24	– ^c
10	FeCl ₃	0.2	DCM	24	30
11	TfOH	2.0	DCM	04	96
12	CSA	2.0	DCM	24	65
13	TFA	2.0	DCM	24	10
14	<i>p</i> -TsOH·H ₂ O	2.0	DCM	24	88
15	TfOH	1.5	DCM	24	91
16	TfOH	3.0	DCM	02	88
17 ^d	TfOH	0.2	DCE	10	82

^aReactions conditions: **11** (0.2 mmol), Solvent (2.0 mL), 0 °C to rt, N₂ atmosphere.

^bIsolated yields. ^cNo reaction. ^dReaction at 80 °C.

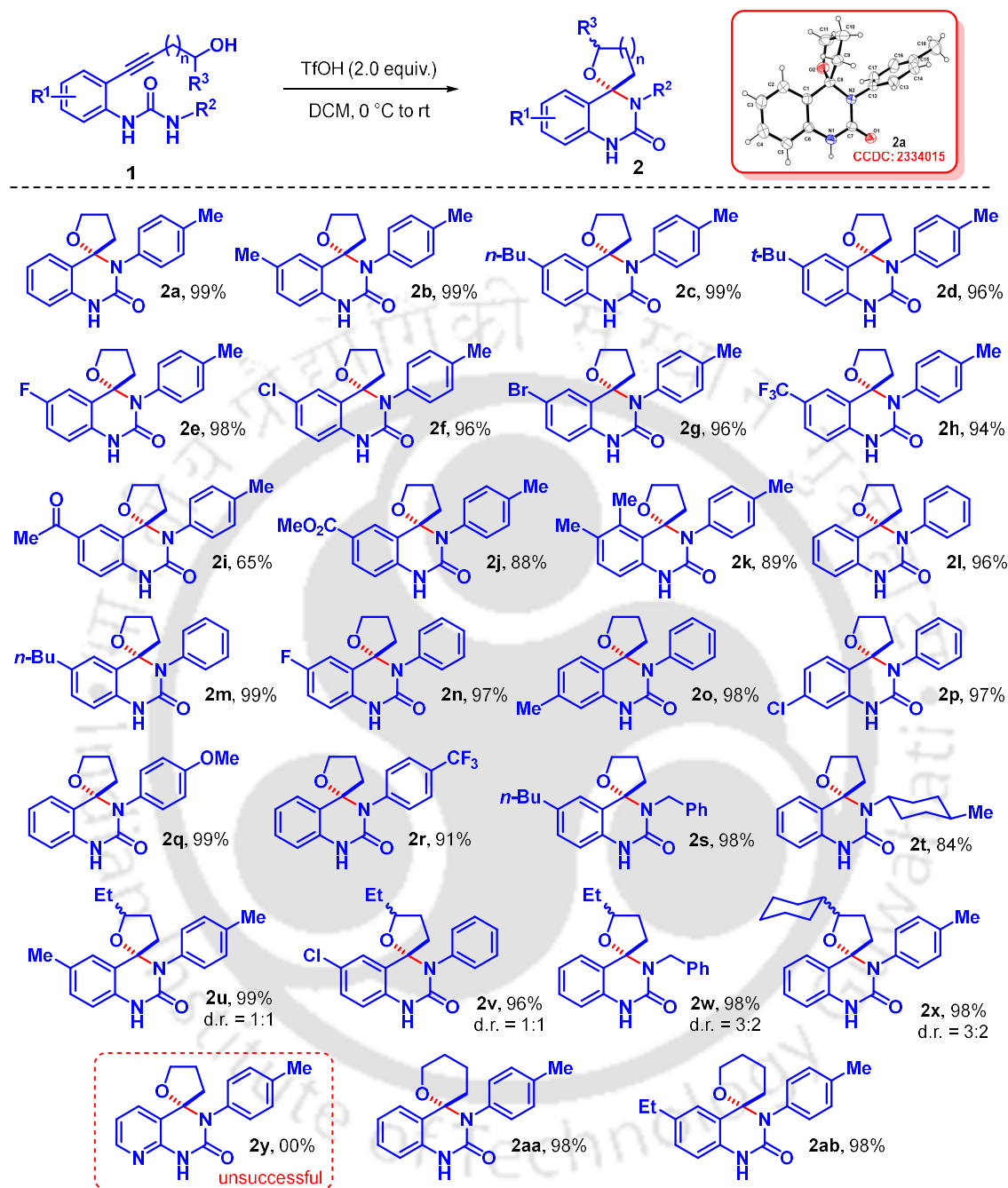
explored with different reagents. TMSOTf in DCM endowed the product in 78% yield (Table 5.4.1.1, entry 5). Metal triflates like Bi(OTf)₃, In(OTf)₃, and Cu(OTf)₂ furnished the product in 70, 63, and 15% yields (Table 5.4.1.1, entries 6–8), respectively. InCl₃ did not respond to the reaction, whereas FeCl₃ gave the product in 30% yield (Table 5.4.1.1, entries 9 and 10). The reaction was screened with Brønsted acids as well. TfOH astonishingly furnished the product within 4 h of the reaction with a remarkable yield of 96% (Table 5.4.1.1, entry 11). CSA and TFA fell short of our expectations and gave the product in 65 and 10% yields (Table 5.4.1.1, entries 12 and 13), respectively. However, *p*-TsOH exhibited comparatively better reactivity and endowed the product in 88% yield (Table 5.4.1.1, entry 14). Furthermore, adjusting the stoichiometry of

TfOH to 1.5 and 3.0 equiv. had minimal impact on the yield, resulting in the products in 91 and 88% yields (Table 5.4.1.1, entries 15 and 16), respectively. Additionally, 0.2 equiv. of TfOH at 80 °C in DCE afforded the product in 82% yield (Table 5.4.1.1, entry 17). Finally, employing 2.0 equiv. of TfOH in DCM at 0 °C to room temperature proved to be the optimized condition for this transformation.

5.4.2. Substrate Scope

With the establishment of the optimal parameters, the validation of the strategy was investigated with different functional groups. Changing the substituent “R¹” of the alkynol-substituted diphenyl urea **1** to H provided a spirocycle **2a** in 99% yield. Introduction of electron-donating substituents such as Me, *n*-Bu and *t*-Bu in the “R¹” position furnished their respective functionalized spiro-furan quinazolinones **2b**, **2c** and **2d** in excellent yields. Similarly, electron-withdrawing substituents proceeded well with the protocol, affording the products **2e-2j** in 65-98% yields, with an extended reaction time. This delay in the reaction period can be attributed to the destabilization caused by the electron-withdrawing substituents on the benzylic vinyl carbocation **A** throughout the transformation (Scheme 5.4.4.1). Di-substituted methyl alkynol urea delivered the spirocycle **2k** in 89% yield. Switching the “R²” group of the alkynol urea with a phenyl substituent afforded the products **2l**, **2m** and **2n** in 96, 99, and 97% yields, respectively. Moreover, shifting the “R¹” substituents to a different position (5-position) delivered their respective spirocyclic products **2o** and **2p** in 98 and 97% yields. Electron-rich (OMe) and electron-deficient (CF₃) phenyl groups in the “R²” position furnished their respective products **2q** and **2r** in 99 and 91% yields. Alkylaryl (benzyl) **1s** and alicyclic (4-methylcyclohexyl) **1t** groups were well-tolerated in the protocol, with a 98 and 84% product yield. The methodology was also expanded to include racemic secondary alkynol ureas. As anticipated, the racemic secondary alkynol ureas furnished their respective diastereomeric spirocycles **2u-2x** in high yields. Unfortunately, the strategy was utterly silent in the case of heterocyclic alkynol urea **1y**. The lack of reactivity of **1y** might be due to an acid-base reaction between the pyridine moiety and TfOH. Furthermore, higher homologues of the alkynols were

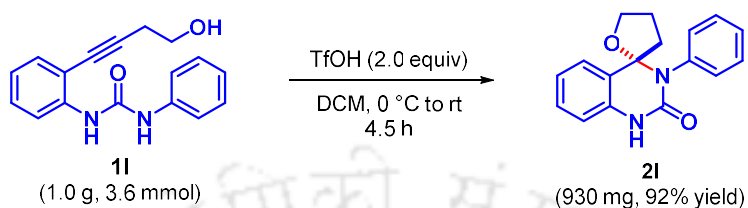
Scheme 5.4.2.1. Synthesis of spiro-furan/pyran quinazolinones.



^aReaction conditions: **1** (0.4 mmol, 1.0 equiv.), TfOH (2.0 equiv.), DCM (4.0 mL), 0 °C to rt, N₂ atmosphere. ^bIsolated yields.

introduced in the system. Under the optimized conditions, spiro-pyran quinazolinones **2aa** and **2ab** were achieved in 98% yields.

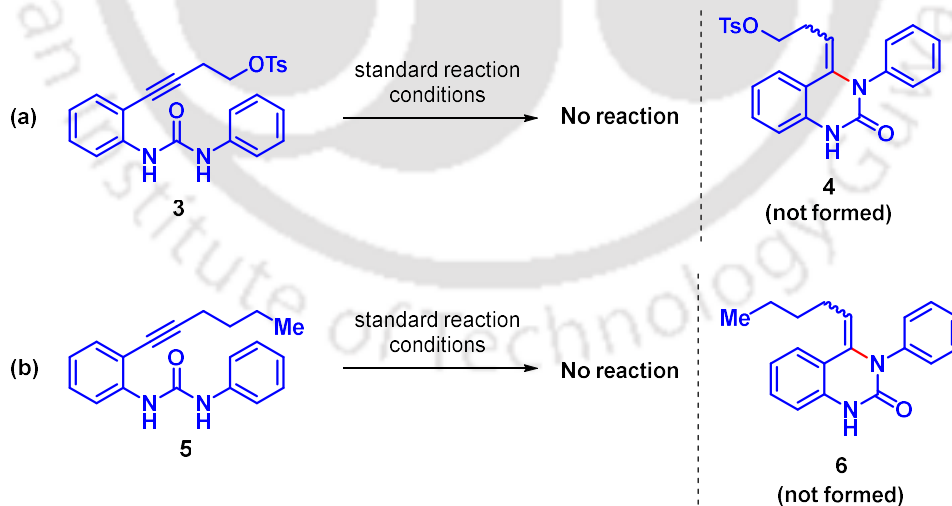
To demonstrate the scalability of this protocol, a scale-up synthesis was performed with 1-(2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-phenylurea (**11**) (1.0 g, 3.6 mmol). Under the standard reaction conditions, the resulting spiro-furan quinazolinone **21** was obtained in a high yield of 92% (930 mg) (Scheme 5.4.2.2).



Scheme 5.4.2.2. Scale-up experiment.

5.4.3. Control Experiment

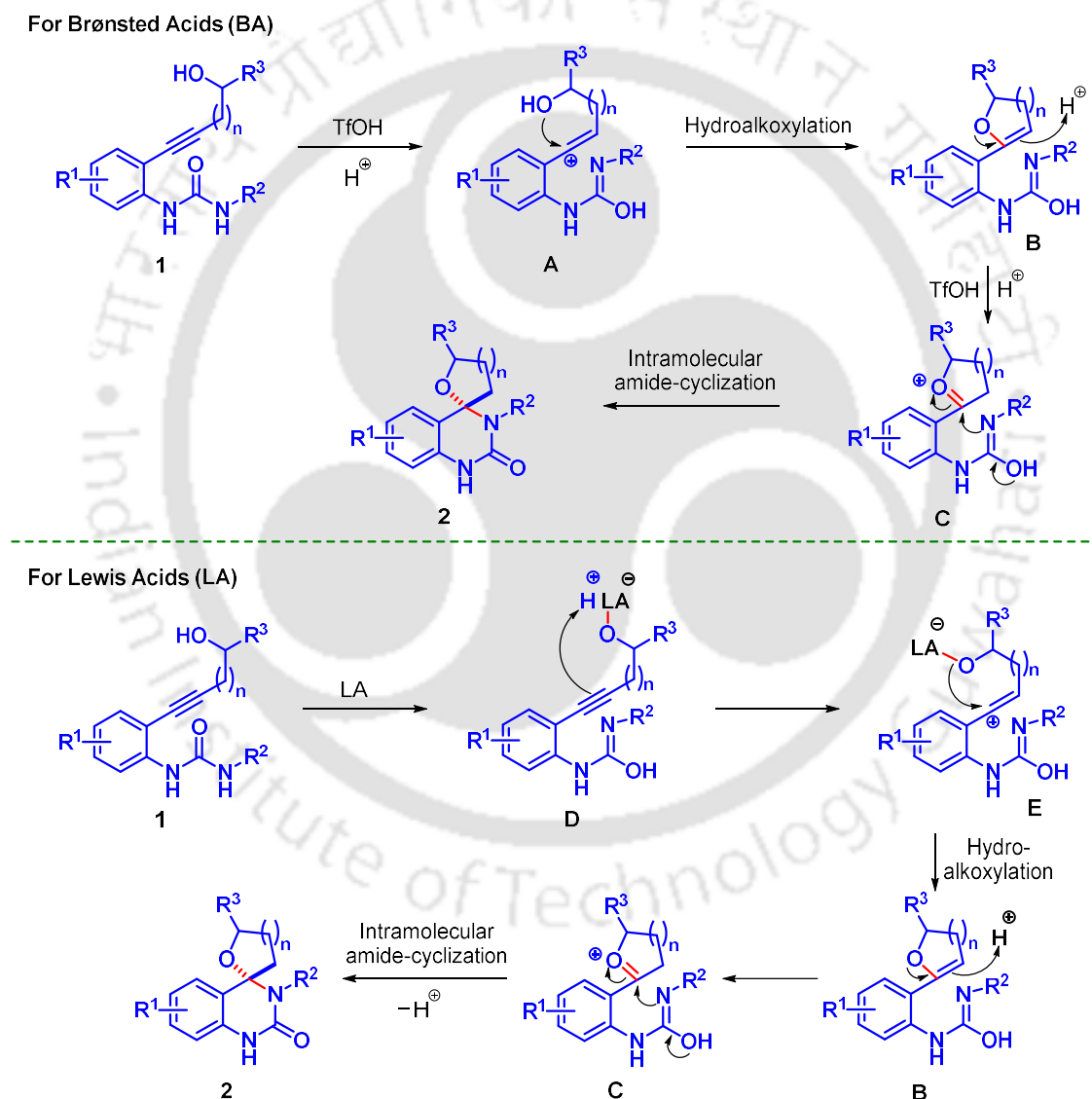
A few control experiments were conducted to understand the reaction sequence of this protocol. Under the standard reaction conditions, both the tosyl-protected alkynol urea **3** and alkyne-substituted urea **5** did not exhibit any reactivity and failed to produce their respective amidated products **4** and **6**. Moreover, it is well-established that alkynols, under acidic conditions, readily undergo hydroalkoxylation reactions to form oxygen heterocycles. Therefore, it is likely that the strategy follows a hydroalkoxylation-intramolecular amide-cyclization pathway (Scheme 5.4.3.1).



Scheme 5.4.3.1. Control experiment.

5.4.4. Plausible Mechanism

From the experimental findings and precedent works of literature, a plausible mechanism has been proposed in Scheme 5.4.4.1. For Brønsted acids, the initial step involves the protonation of the alkyne moiety of the alkynol urea **1**, which subsequently undergoes a hydroalkoxylation reaction to form the intermediate **B**. Further protonation of the intermediate **B** and an intramolecular amide-cyclization reaction ascending from the amide-iminol tautomerized urea functionality finally



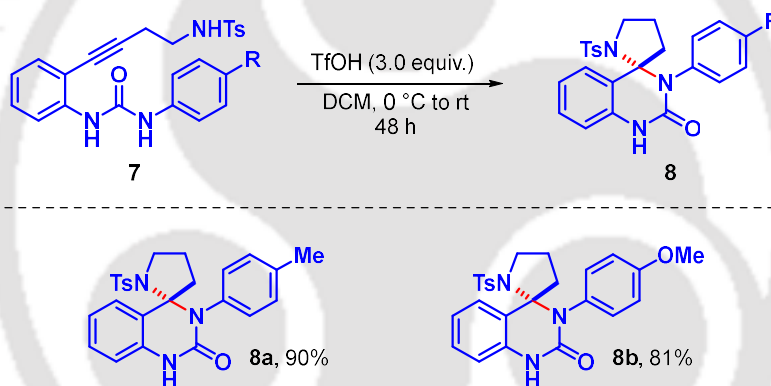
Scheme 5.4.4.1. Plausible mechanism for the synthesis of spiro-furan/pyran quinazolinones.

produces the desired spiroquinazolinones **2**. In contrast, the process for Lewis acid begins with the interaction of the Lewis acid and the hydroxy group of the alkynol urea **1**. Subsequent protonation of the alkyne group, leading to an intramolecular hydroalkoxylation reaction, produces intermediate **B**. This intermediate **B** further undergoes an intramolecular amide-cyclization reaction, which delivers spirocycle **2**.

5.4.5. Synthesis of Spiro-Pyrrolidine Quinazolinones

The strategy was extended to encompass the nitrogen variant **7** of the alkynol urea. Utilizing a tandem hydroamidation–intramolecular amide-cyclization protocol, spiro-pyrrolidine quinazolinones **8a** and **8b** were synthesized efficaciously in 90 and 81% yields, respectively (Scheme 5.4.5.1).

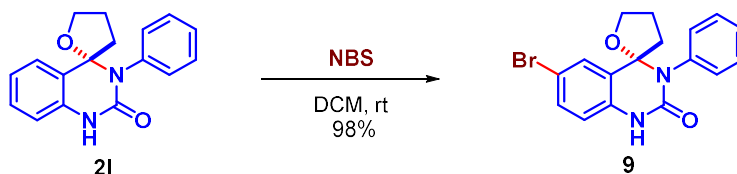
Scheme 5.4.5.1. Spiro-pyrrolidine quinazolinones.



^aReaction conditions: **7** (0.4 mmol), TfOH (3.0 equiv.), DCM (4.0 mL), 0 °C to rt, N₂ atmosphere. ^bIsolated yields.

5.4.6. Synthetic Transformation

A synthetic transformation reaction was performed to explore the utility of the spirocyclic product. Compound **21**, when treated with N-bromosuccinimide (NBS) in



Scheme 5.4.6.1. Bromination of spiro-furan quinazolinone **21**.

DCM successfully synthesized its brominated derivative **9** in 98% yield (Scheme 5.4.6.1).

5.5. Conclusions

In conclusion, a highly efficient method for the regioselective synthesis of spiro-quinazolinones has been developed. This approach utilizes a cascade hydroalkoxylation–intramolecular amide-cyclization reaction to obtain the spiro-quinazolinone derivatives in high yields. The strategy exhibits excellent tolerance to various functional groups. Moreover, the methodology has been extended to include the nitrogen analogue of the alkynol urea, allowing the synthesis of spiro-pyrrolidine quinazolinones. Late-stage modifications involve the bromination of the spiro-furan quinazolinone framework.

5.6. Experimental Section

5.6.1. General Information

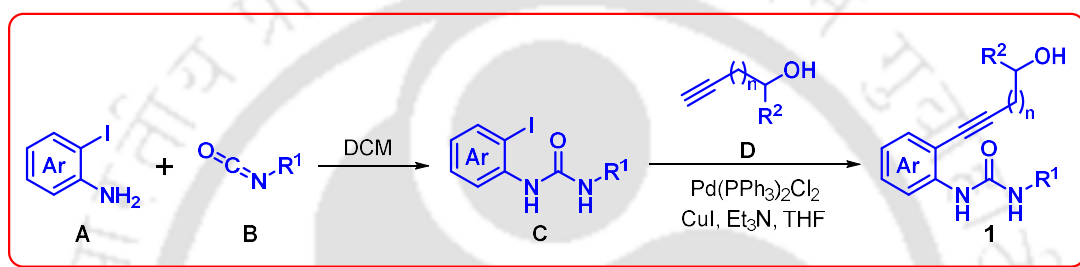
All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in CDCl₃ with tetramethylsilane as the internal standard for ¹H (500 MHz and 400 MHz) or ¹³C{¹H} (125 MHz) NMR. Chemical shifts (δ) are reported in ppm with abbreviations, s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, tt = triplet of triplets, q = quartet, qd = quartet of doublets, p = quintet, h = sextet, m = multiplet and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

Trifluoromethanesulfonic acid (reagent grade, 100 mL bottle) was purchased from Spectrochem and used without further purification. It is highly advisable to handle trifluoromethanesulfonic acid using glass(micro) syringes and steel needles. Disposable plastic syringes and needles should be avoided, as they may dissolve/melt

in the presence of TfOH. After using triflic acid, two layers of PTFE tape were applied, followed by a layer of parafilm, to seal the bottle cap, and it was stored in the freezer at -5 °C.

The starting materials, **1a**, **1b**, **1d**, **1e**, **1f**, **1l**, **1s**, **1t**, **1u**, **1v** and **3** were synthesized according to the literature report, and the spectroscopic data of the compounds are in good agreement with the literature data.¹⁸

5.6.2. General procedure for the synthesis of the starting materials **1c**, **1g-1k**, **1m-1r**, **1w-1y**, **1aa** and **1ab**:



To a solution of substituted 2-iodoaniline **A** (2.0 mmol, 1.0 equiv.) in DCM (5.0 mL) under N_2 atmosphere, substituted phenyl isocyanate **B** (2.2 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was stirred overnight at room temperature to obtain a white precipitate, which was then filtered and washed with n-hexane to obtain a substituted 1,3-diphenyl urea **C**.

To a mixture of $\text{Pd(PPh}_3)_2\text{Cl}_2$ (0.04 mmol, 0.04 equiv.), CuI (0.02 mmol, 0.02 equiv.) and iodo substituted 1,3-diphenyl urea derivatives **C** (1.0 mmol, 1.0 equiv.) in dry THF (5.0 mL) under N_2 atmosphere, triethylamine (5.0 mmol, 5.0 equiv.) was added. The reaction mixture was stirred for 10 minutes at room temperature, after which the substituted alkynol **D** (1.2 mmol, 1.2 equiv.) was added dropwise over a period of 5 minutes. The reaction mixture was stirred for 3.0 hours (monitored by TLC analysis) before filtering through a pad of celite. The solids were washed with ethyl acetate, and the combined filtrates were concentrated in a rotary evaporator. The crude product was then purified by column chromatography to provide the corresponding product **1**.

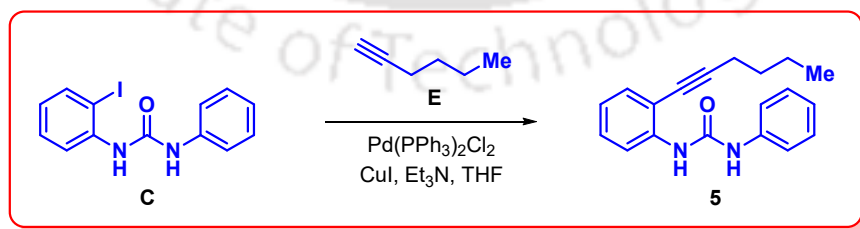
5.6.3. General procedure for the synthesis of compounds 2a-2x, 2aa, 2ab:

To an ice-cold suspension of alkynol substituted diphenyl urea **1** (0.4 mmol, 1.0 equiv.) in DCM (4.0 mL), triflic acid (0.8 mmol, 2.0 equiv.) was added under N₂ atmosphere. The reaction was continued to stir at room temperature till all the starting material was consumed, as evident by TLC. It was then treated with saturated NaHCO₃ solution, and the organic layer was extracted with DCM (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **2**.

5.6.4. Experimental procedure for scale-up synthesis of compound 2l:

To an ice-cold suspension of 1-(2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-phenylurea (**11**) (1.0 g, 3.6 mmol, 1.0 equiv.) in DCM (15.0 mL), triflic acid (0.6 mL, 7.2 mmol, 2.0 equiv.) was added slowly under N₂ atmosphere. The reaction was continued to stir for 4.5 h at room temperature, and the progress of the reaction was monitored by TLC. It was then treated with saturated NaHCO₃ solution, and the organic layer was extracted with DCM (2 x 30 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **2l** as a white solid in 92% yield (930 mg).

5.6.5. Experimental procedure for the synthesis of compound 5:



To a mixture of Pd(PPh₃)₂Cl₂ (0.04 mmol, 0.04 equiv.), CuI (0.02 mmol, 0.02 equiv.) and 1-(2-iodophenyl)-3-phenylurea (**C**) (1.0 mmol, 1.0 equiv.) in dry THF (5.0 mL) under N₂ atmosphere, triethylamine (5.0 mmol, 5.0 equiv.) was added. The reaction

mixture was stirred for 10 minutes at room temperature, after which 1-hexyne (**E**) (1.2 mmol, 1.2 equiv.) was added dropwise over a period of 5 minutes. The reaction mixture was stirred for 5.0 hours (monitored by TLC analysis) before filtering through a pad of celite. The solids were washed with ethyl acetate, and the combined filtrates were concentrated in a rotary evaporator. The crude product was then purified by column chromatography to provide the corresponding product **5** in 96% yield (281 mg).

5.6.6. Experimental procedure for control experiment:

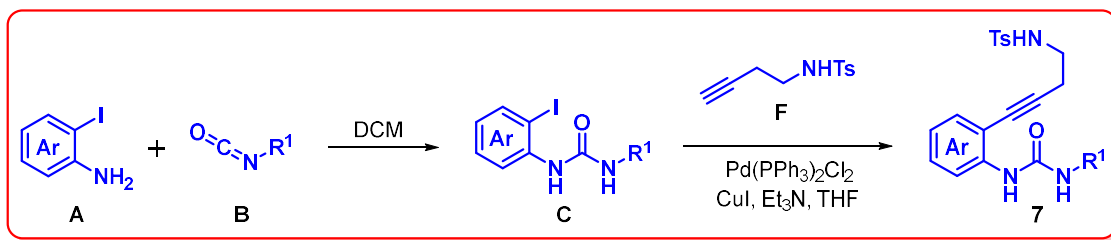
5.6.6.1. Experimental procedure for scheme 5.4.3.1.a:

To an ice-cold solution of 4-(2-(3-phenylureido)phenyl)but-3-yn-1-yl 4-methylbenzene-sulfonate (**3**) (174 mg, 0.4 mmol, 1.0 equiv) in DCM (4.0 mL), triflic acid (0.07 mL, 0.8 mmol, 2.0 equiv.) was added slowly under N₂ atmosphere. The reaction was continued to stir for 5 h at room temperature, and the progress of the reaction was monitored by TLC. To collect the starting material, the reaction mixture was treated with saturated NaHCO₃ solution, and the organic layer was extracted with DCM (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator which was then subjected to column chromatography over silica gel to get the unreacted starting material **3** in 86% yield.

5.6.6.2. Experimental procedure for scheme 5.4.3.1.b:

To an ice-cold solution of 1-(2-(hex-1-yn-1-yl)phenyl)-3-phenylurea (**5**) (117 mg, 0.4 mmol, 1.0 equiv) in DCM (4.0 mL), triflic acid (0.07 mL, 0.8 mmol, 2.0 equiv.) was added slowly under N₂ atmosphere. The reaction was continued to stir for 5 h at room temperature, and the progress of the reaction was monitored by TLC. To collect the starting material, the reaction mixture was treated with saturated NaHCO₃ solution, and the organic layer was extracted with DCM (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator which was then subjected to column chromatography over silica gel to get the unreacted starting material **5** in 83% yield.

5.6.7. General procedure for the synthesis of compounds 7a and 7b:



To a solution of substituted 2-iodoaniline **A** (2.0 mmol, 1.0 equiv.) in DCM (5.0 mL) under N₂ atmosphere, substituted phenyl isocyanate **B** (2.2 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was stirred overnight at room temperature to obtain a white precipitate, which was then filtered and washed with n-hexane to obtain a substituted 1,3-diphenyl urea **C**.

To a mixture of Pd(PPh₃)₂Cl₂ (0.04 mmol, 0.04 equiv.), CuI (0.02 mmol, 0.02 equiv.) and iodo substituted 1,3-diphenyl urea derivatives **C** (1.0 mmol, 1.0 equiv.) in dry THF (5.0 mL) under N₂ atmosphere, triethylamine (5.0 mmol, 5.0 equiv.) was added. The reaction mixture was stirred for 10 minutes at room temperature, after which sulfonamide **F** (1.2 mmol, 1.2 equiv.) in dry THF (1.0 mL) was added dropwise over a period of 5 minutes. The reaction mixture was stirred for 3.0 hours (monitored by TLC analysis) before filtering through a pad of celite. The solids were washed with ethyl acetate, and the combined filtrates were concentrated in a rotary evaporator. The crude product was then purified by column chromatography to provide the corresponding product **7**.

5.6.8. General procedure for the synthesis of compounds 8a and 8b:

To an ice-cold suspension of alkynyl-benzenesulfonamide substituted diphenyl urea **7** (0.4 mmol, 1.0 equiv.) in DCM (4.0 mL), triflic acid (1.2 mmol, 3.0 equiv.) was added under N₂ atmosphere. The reaction was continued to stir at room temperature for 48 h. It was then treated with saturated NaHCO₃ solution, and the organic layer was extracted with DCM (2 × 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **8**.

5.6.9. Experimental procedure for the synthesis of compound 9:¹⁹

To an ice-cold solution of spiro-furan quinazolinone derivative **21** (113 mg, 0.4 mmol, 1.0 equiv.) in DCM (3.0 mL), N-Bromo succinimide (NBS) (85 mg, 0.48 mmol, 1.2 equiv.) was added portion wise over a period of 5 minutes. The reaction was stirred for 1.0 hour at room temperature, and the progress of the reaction was monitored by TLC. It was then treated with saturated Na₂S₂O₃ solution, and the organic layer was extracted with DCM (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **9** as a white solid in 98% yield (141 mg).

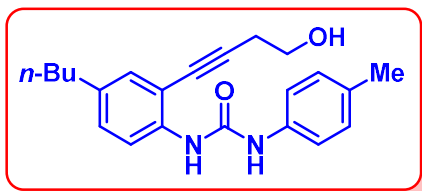
5.7. References

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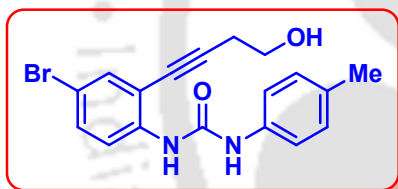
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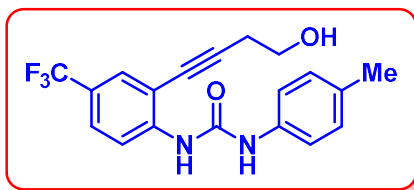
5.8. Characterization Data

1-(4-Butyl-2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea (1c):

White solid; R_f (Hexane:EtOAc, 3:2) 0.6; mp 137–139 °C. Yield 315 mg, 90%. ^1H NMR (400 MHz, CDCl_3) δ 8.09 (d, J = 8.2 Hz, 1H), 7.85 (s, 1H), 7.49 (s, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 10.7 Hz, 3H), 7.02 (s, 1H), 3.82 (q, J = 5.9 Hz, 2H), 3.07 (s, 1H), 2.59 (t, J = 5.7 Hz, 2H), 2.48 (t, J = 7.7 Hz, 2H), 2.26 (s, 3H), 1.57–1.49 (m, 2H), 1.32 (h, J = 7.4 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.4, 138.6, 136.5, 136.1, 133.2, 130.1, 129.7, 129.5, 120.7, 118.4, 111.9, 94.5, 79.1, 61.5, 34.8, 33.6, 24.0, 22.3, 20.9, 14.1. IR (KBr, neat) ν 3321, 2955, 2926, 2859, 1666, 1589, 1529, 1509, 1414, 1310, 1292, 1250, 1207, 1042, 936, 895, 815, 736, 507 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}_2$ ($M + \text{H}$) $^+$ 351.2067, found 351.2070.

1-(4-Bromo-2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea (1g):

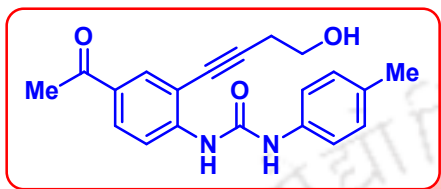
White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 183–185 °C. Yield 328 mg, 88%. ^1H NMR (400 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.37 (s, 1H), 8.27 (s, 1H), 8.24 (d, J = 8.9 Hz, 1H), 7.40 (d, J = 2.3 Hz, 1H), 7.37–7.32 (m, 3H), 7.09 (d, J = 8.0 Hz, 2H), 5.10 (s, 1H), 3.89 (q, J = 5.1 Hz, 2H), 2.72 (t, J = 5.7 Hz, 2H), 2.29 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 152.6, 140.4, 136.4, 132.5, 132.2, 131.8, 129.4, 119.4, 119.2, 113.4, 113.1, 97.2, 77.4, 60.7, 24.1, 20.7. IR (KBr, neat) ν 3311, 1680, 1600, 1571, 1549, 1512, 1403, 1295, 1208, 1039, 811, 752, 690, 573, 508 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{18}\text{BrN}_2\text{O}_2$ ($M + \text{H}$) $^+$ 373.0546, found 373.0540.

1-(2-(4-Hydroxybut-1-yn-1-yl)-4-(trifluoromethyl)phenyl)-3-(*p*-tolyl)urea (1h):

White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 156–158 °C. Yield 341 mg, 94%. ^1H NMR (400 MHz, CDCl_3) δ 8.43 (d, J = 8.6 Hz, 1H), 8.21 (s, 1H), 7.67 (s, 1H), 7.46 (d, J = 9.9 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 7.9 Hz, 2H), 3.93 (t, J = 5.7 Hz, 2H), 2.88 (s, 1H), 2.67 (t, J = 5.7 Hz, 2H), 2.26 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.8, 143.9, 135.6, 133.4, 129.7, 126.9, 126.1 (q,

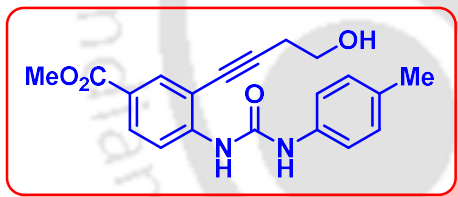
$J = 3.9$ Hz), 124.1 (q, $J = 270.5$ Hz), 123.5 (q, $J = 32.7$ Hz), 120.1, 117.1, 111.5, 96.7, 78.0, 61.5, 24.0, 20.8. IR (KBr, neat) ν 3318, 2891, 1685, 1610, 1590, 1539, 1514, 1427, 1334, 1315, 1260, 1203, 1166, 1118, 1074, 1039, 897, 839, 813, 705, 643, 508 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{N}_2\text{O}_2$ ($M + H$)⁺ 363.1315, found 363.1315.

1-(4-Acetyl-2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea (1i):



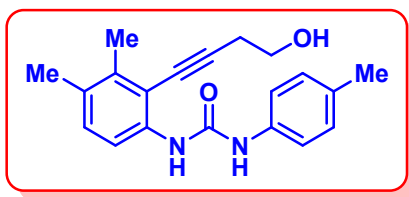
White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 175–177 °C. Yield 296 mg, 88%. ^1H NMR (500 MHz, CDCl_3) δ 8.40 (d, $J = 8.7$ Hz, 1H), 8.27 (s, 1H), 7.84–7.81 (m, 2H), 7.77 (s, 1H), 7.28 (d, $J = 8.3$ Hz, 2H), 7.07 (d, $J = 8.0$ Hz, 2H), 3.93 (t, $J = 5.6$ Hz, 2H), 3.04 (s, 1H), 2.68 (t, $J = 5.7$ Hz, 2H), 2.50 (s, 3H), 2.28 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 196.9, 152.5, 145.3, 135.8, 133.4, 130.4, 130.3, 130.0, 129.7, 120.2, 116.7, 111.3, 96.1, 78.4, 61.7, 26.4, 24.0, 20.9. IR (KBr, neat) ν 3339, 2927, 2885, 1669, 1577, 1512, 1409, 1359, 1289, 1253, 1196, 1143, 1044, 819, 729 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_3$ ($M + H$)⁺ 337.1547, found 337.1547.

Methyl 3-(4-hydroxybut-1-yn-1-yl)-4-(3-(*p*-tolyl)ureido)benzoate (1j):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 152–154 °C. Yield 300 mg, 85%. ^1H NMR (400 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.56 (s, 1H), 8.51–8.46 (m, 1H), 8.42–8.36 (m, 1H), 7.95–7.91 (m, 1H), 7.89–7.84 (m, 1H), 7.37–7.31 (m, 2H), 7.08–7.02 (m, 2H), 5.26 (s, 1H), 3.89–3.82 (m, 5H), 2.73–2.66 (m, 2H), 2.28–2.23 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 166.2, 152.2, 145.1, 136.2, 132.2, 131.6, 130.4, 129.3, 122.5, 119.1, 116.7, 111.1, 96.7, 77.7, 60.7, 51.8, 24.0, 20.6. IR (KBr, neat) ν 3325, 2951, 1708, 1606, 1581, 1511, 1435, 1286, 1249, 1193, 1116, 1038, 815, 764, 734, 541, 507 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_4$ ($M + H$)⁺ 353.1496, found 353.1496.

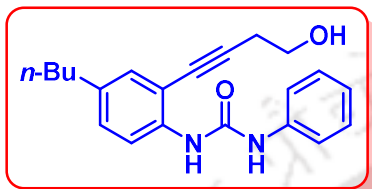
1-(2-(4-Hydroxybut-1-yn-1-yl)-3,4-dimethylphenyl)-3-(*p*-tolyl)urea (1k):



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 191–193 °C. Yield 277 mg, 86%. ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.63 (s, 1H), 8.30 (s, 1H), 8.28 (s, 1H), 7.59–7.56 (m, 3H), 7.27 (d, $J = 8.2$ Hz, 2H), 5.27

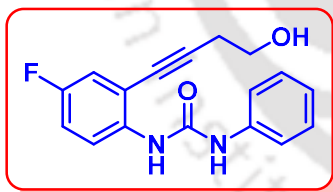
(t, $J = 6.2$ Hz, 1H), 4.06 (q, $J = 5.9$ Hz, 2H), 2.90 (t, $J = 5.8$ Hz, 2H), 2.49 (s, 3H), 2.45 (s, 3H), 2.36 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 152.8, 138.7, 137.6, 136.7, 131.6, 130.9, 129.4, 129.1, 119.3, 118.9, 108.9, 94.5, 78.5, 60.7, 24.0, 20.6, 20.1, 18.7. IR (KBr, neat) ν 3342, 2926, 1664, 1599, 1513, 1436, 1275, 1266, 1047, 753, 724, 696, 541 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2$ ($M + H$) $^+$ 323.1754, found 323.1754.

1-(4-Butyl-2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-phenylurea (1m):



White solid; R_f (Hexane:EtOAc, 3:2) 0.6; mp 135–137 °C. Yield 289 mg, 86%. ^1H NMR (400 MHz, CDCl_3) δ 8.07 (d, $J = 8.3$ Hz, 1H), 7.95 (s, 1H), 7.78–7.73 (m, 1H), 7.36 (d, $J = 7.8$ Hz, 2H), 7.21 (t, $J = 7.6$ Hz, 2H), 7.06 (s, 1H), 7.04 (d, $J = 8.7$ Hz, 1H), 6.98 (t, $J = 7.4$ Hz, 1H), 3.83 (q, $J = 4.6$ Hz, 2H), 3.31 (s, 1H), 2.61 (t, $J = 5.6$ Hz, 2H), 2.46 (t, $J = 7.6$ Hz, 2H), 1.52 (p, $J = 7.3$ Hz, 2H), 1.31 (h, $J = 7.5$ Hz, 2H), 0.91 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.3, 138.8, 138.5, 136.7, 130.0, 129.4, 129.1, 123.3, 120.0, 118.4, 112.1, 94.7, 79.2, 61.6, 34.8, 33.6, 24.0, 22.3, 14.0. IR (KBr, neat) ν 3324, 2926, 2856, 1690, 1588, 1550, 1526, 1498, 1442, 1303, 1257, 1214, 1036, 824, 746, 692, 505 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_2$ ($M + H$) $^+$ 337.1911, found 337.1917.

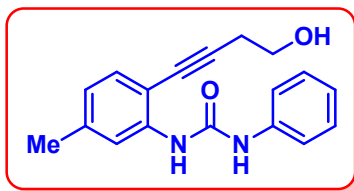
1-(4-Fluoro-2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-phenylurea (1n):



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 175–177 °C. Yield 283 mg, 95%. ^1H NMR (400 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.36 (s, 1H), 8.23–8.19 (m, 2H), 7.44 (d, $J = 7.8$ Hz, 2H), 7.25 (d, $J = 4.0$ Hz, 1H), 7.22 (d, $J = 8.2$ Hz, 1H), 7.00–6.90 (m, 3H), 5.10–5.00 (m, 1H), 3.85 (q, $J = 5.9$ Hz, 2H), 2.67 (t, $J = 5.6$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 157.1 (d, $J = 239.0$ Hz), 152.8, 139.3, 137.6 (d, $J = 2.3$ Hz), 128.9, 122.6, 119.6 (d, $J = 8.3$ Hz), 119.0, 116.4 (d, $J = 23.6$ Hz), 116.0, 115.8, 96.9, 78.0, 60.8, 24.1. ^{19}F NMR (470 MHz, $\text{CDCl}_3/\text{DMSO}-d_6/\text{C}_6\text{F}_6$) δ -125.0. IR (KBr, neat) ν 3231, 2927, 1667, 1599, 1534, 1499, 440, 1311, 1255, 1201, 1166, 0144, 940, 869, 751, 693, 510 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{16}\text{FN}_2\text{O}_2$ ($M + H$) $^+$ 299.1190, found 299.1190.

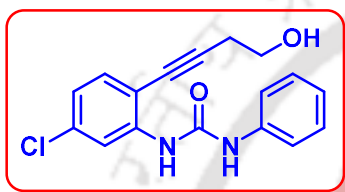
1-(2-(4-Hydroxybut-1-yn-1-yl)-5-methylphenyl)-3-phenylurea (1o):

White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 143–145 °C. Yield 265 mg, 90%. ^1H NMR



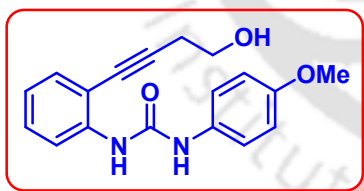
(500 MHz, CDCl_3) δ 8.09 (s, 1H), 8.00 (s, 1H), 7.77 (s, 1H), 7.39 (d, $J = 7.9$ Hz, 2H), 7.24 (t, $J = 7.8$ Hz, 2H), 7.13 (d, $J = 7.8$ Hz, 1H), 7.00 (t, $J = 7.3$ Hz, 1H), 6.71 (d, $J = 7.8$ Hz, 1H), 3.87 (t, $J = 5.5$ Hz, 2H), 2.64 (t, $J = 5.7$ Hz, 2H), 2.31 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.1, 140.8, 139.8, 138.9, 129.8, 129.1, 123.3, 122.8, 119.8, 118.8, 108.9, 94.5, 79.2, 61.7, 24.1, 22.1. IR (KBr, neat) ν 3314, 2928, 1679, 1603, 1542, 1498, 1475, 1433, 1317, 1294, 1250, 1213, 1047, 839, 805, 745, 690, 504 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 295.1441, found 295.1442.

1-(5-Chloro-2-(4-hydroxybut-1-yn-1-yl)phenyl)-3-phenylurea (1p):



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 150–152 $^{\circ}\text{C}$. Yield 293 mg, 93%. ^1H NMR (400 MHz, CDCl_3) δ 8.39 (d, $J = 2.1$ Hz, 1H), 8.12 (s, 1H), 7.73 (s, 1H), 7.37–7.34 (m, 2H), 7.25–7.20 (m, 2H), 7.11 (d, $J = 8.2$ Hz, 1H), 7.01 (t, $J = 7.4$ Hz, 1H), 6.85 (dd, $J = 8.2, 2.1$ Hz, 1H), 3.94 (q, $J = 5.9$ Hz, 2H), 2.79 (t, $J = 6.7$ Hz, 1H), 2.69 (t, $J = 5.6$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.6, 142.1, 138.6, 135.2, 130.5, 129.2, 123.4, 121.8, 119.7, 117.8, 109.7, 96.1, 78.5, 61.8, 24.1. IR (KBr, neat) ν 3324, 2930, 1680, 1601, 1569, 1551, 1523, 1499, 1441, 1417, 1314, 1246, 1208, 1043, 809, 749, 692, 504 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{16}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 315.0895, found 315.0896.

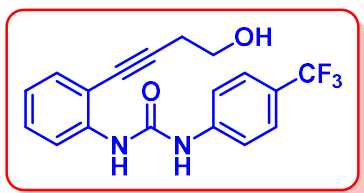
1-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)-3-(4-methoxyphenyl)urea (1q):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 154–156 $^{\circ}\text{C}$. Yield 264 mg, 85%. ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.31 (d, $J = 8.3$ Hz, 1H), 8.17 (s, 1H), 8.04 (s, 1H), 7.37 (d, $J = 9.0$ Hz, 2H), 7.31–7.27 (m, 2H), 6.92 (td, $J = 7.6, 1.2$ Hz, 1H), 6.84 (d, $J = 8.8$ Hz, 2H), 4.53 (s, 1H), 3.88 (t, $J = 5.1$ Hz, 2H), 3.78 (s, 3H), 2.68 (t, $J = 5.7$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 155.8, 153.3, 141.2, 132.0, 130.2, 129.1, 121.8, 121.5, 118.0, 114.3, 111.6, 95.6, 78.8, 61.1, 55.6, 24.1. IR (KBr, neat) ν 3318, 2944, 1668, 1608, 1578, 1537, 1509, 1447, 1301, 1241, 1215, 1177, 1036, 830, 753, 521 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 311.1390, found 311.1396.

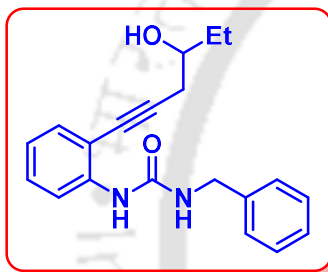
1-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)-3-(4-(trifluoromethyl)phenyl)urea (1r):

White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 171–173 $^{\circ}\text{C}$. Yield 293 mg, 84%. ^1H NMR



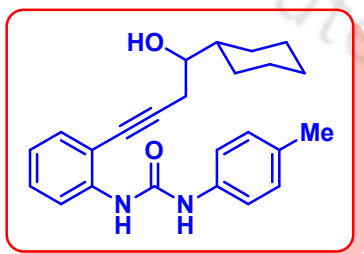
(400 MHz, CDCl_3) δ 8.28 (d, $J = 8.4$ Hz, 1H), 8.22 (s, 1H), 8.05 (s, 1H), 7.50 (d, $J = 8.6$ Hz, 2H), 7.45 (d, $J = 8.7$ Hz, 2H), 7.29 (td, $J = 7.9, 1.1$ Hz, 1H), 7.24 (dd, $J = 7.8, 1.0$ Hz, 1H), 6.93 (td, $J = 7.5, 1.1$ Hz, 1H), 4.02 (q, $J = 5.7$ Hz, 2H), 2.75 (t, $J = 5.6$ Hz, 2H), 2.70 (t, $J = 6.5$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.4, 142.4, 140.8, 129.9, 129.5, 126.3 (q, $J = 3.7$ Hz), 124.5 (q, $J = 32.3$ Hz), 124.4 (q, $J = 269.7$ Hz), 122.1, 118.2, 117.8, 111.6, 95.3, 79.3, 62.1, 24.2. ^{19}F NMR (470 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -65.0. IR (KBr, neat) ν 3328, 2927, 2858, 1661, 1605, 1584, 1534, 1450, 1411, 1321, 1257, 1164, 1115, 1067, 842, 752, 701, 592 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 349.1158, found 349.1158.

1-Benzyl-3-(2-(4-hydroxyhex-1-yn-1-yl)phenyl)urea (1w):



White solid; R_f (Hexane:EtOAc, 7:3) 0.6; mp 125–127 °C. Yield 313 mg, 97%. ^1H NMR (400 MHz, CDCl_3) δ 8.26 (d, $J = 8.3$ Hz, 1H), 8.12 (s, 1H), 7.30–7.27 (m, 4H), 7.25–7.18 (m, 3H), 6.85 (td, $J = 7.5, 1.2$ Hz, 1H), 6.41 (s, 1H), 4.39 (d, $J = 5.7$ Hz, 2H), 3.97–3.71 (m, 2H), 2.70 (dd, $J = 17.1, 4.0$ Hz, 1H), 2.50 (dd, $J = 17.1, 6.3$ Hz, 1H), 1.64–1.51 (m, 2H), 0.88 (t, $J = 7.4$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 155.6, 141.7, 139.6, 130.0, 129.1, 128.6, 127.6, 127.1, 121.1, 117.9, 111.4, 94.9, 79.2, 72.1, 43.9, 29.2, 28.0, 10.3. IR (KBr, neat) ν 3325, 2965, 2930, 1669, 1545, 1450, 1305, 1245, 1217, 1100, 1025, 979, 840, 752, 697, 477 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 323.1754, found 323.1757.

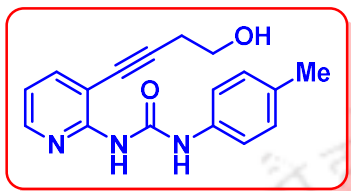
1-(2-(4-Cyclohexyl-4-hydroxybut-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea (1x):



White solid; R_f (Hexane:EtOAc, 7:3) 0.6; mp 133–135 °C. Yield 301 mg, 80%. ^1H NMR (500 MHz, CDCl_3) δ 8.27 (d, $J = 8.3$ Hz, 1H), 8.16 (s, 1H), 7.86 (s, 1H), 7.24 (d, $J = 7.9$ Hz, 2H), 7.21 (d, $J = 7.8$ Hz, 1H), 7.17 (d, $J = 8.3$ Hz, 1H), 6.98 (d, $J = 8.0$ Hz, 2H), 6.83 (t, $J = 7.5$ Hz, 1H), 3.58–3.53 (m, 1H), 2.96 (d, $J = 7.8$ Hz, 1H), 2.62 (dd, $J = 17.1, 3.6$ Hz, 1H), 2.48 (dd, $J = 17.1, 8.1$ Hz, 1H), 2.21 (s, 3H), 1.97–1.92 (m, 1H), 1.73 (d, $J = 12.5$ Hz, 2H), 1.64 (t, $J = 13.4$ Hz, 2H), 1.48–1.41 (m, 1H), 1.27–1.08 (m, 3H), 1.04–0.95 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz,

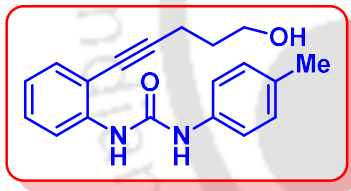
CDCl₃) δ 153.2, 141.5, 136.4, 132.4, 129.6, 129.5, 129.1, 121.3, 119.4, 117.5, 111.6, 95.6, 79.2, 76.0, 43.2, 29.2, 29.0, 26.3, 26.0, 25.95, 25.93, 20.8. IR (KBr, neat) ν 3320, 3039, 2923, 2852, 161, 1603, 1578, 1534, 1512, 1448, 1406, 1309, 1293, 1247, 1204, 1106, 1031, 815, 748, 703, 507 cm⁻¹. HRMS (ESI) calcd. for C₂₄H₂₉N₂O₂ (M + H)⁺ 377.2224, found 377.2225.

1-(3-(4-Hydroxybut-1-yn-1-yl)pyridin-2-yl)-3-(*p*-tolyl)urea (1y):



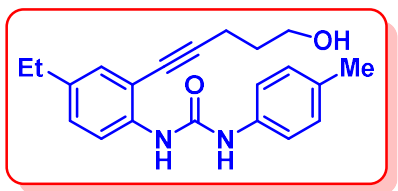
White solid; *R_f* (Hexane:EtOAc, 3:2) 0.5; mp 128–130 °C. Yield 266 mg, 90%. ¹H NMR (500 MHz, CDCl₃) δ 11.67 (s, 1H), 8.15 (d, *J* = 5.3 Hz, 1H), 7.91 (s, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.87 (dd, *J* = 7.3, 5.1 Hz, 1H), 3.90 (t, *J* = 6.2 Hz, 2H), 2.92 (s, 1H), 2.78 (t, *J* = 6.1 Hz, 2H), 2.32 (s, 3H). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 153.2, 152.5, 144.9, 140.6, 135.8, 133.3, 129.6, 120.5, 116.5, 107.3, 97.7, 75.6, 60.8, 24.0, 21.0. IR (KBr, neat) ν 3393, 2948, 2231, 1679, 1610, 1582, 1556, 1478, 1409, 1315, 1258, 1226, 1048, 814, 749, 510 cm⁻¹. HRMS (ESI) calcd. for C₁₇H₁₈N₃O₂ (M + H)⁺ 296.1394, found 296.1394.

1-(2-(5-Hydroxypent-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea (1aa):



White solid; *R_f* (Hexane:EtOAc, 1:1) 0.5; mp 146–148 °C. Yield 284 mg, 92%. ¹H NMR (500 MHz, CDCl₃) δ 8.33 (d, *J* = 8.3 Hz, 1H), 8.03 (s, 1H), 8.00 (s, 1H), 7.32 (d, *J* = 8.5 Hz, 3H), 7.28 (t, *J* = 7.9 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 2H), 6.95 (t, *J* = 7.5 Hz, 1H), 3.96 (t, *J* = 4.8 Hz, 2H), 2.91 (s, 1H), 2.60 (t, *J* = 5.8 Hz, 2H), 2.32 (s, 3H), 1.91–1.86 (m, 2H). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 153.4, 141.1, 136.1, 133.0, 130.9, 129.6, 129.0, 121.6, 120.3, 119.0, 111.9, 96.8, 77.2, 63.1, 30.6, 20.9, 17.4. IR (KBr, neat) ν 3326, 2932, 1672, 1605, 1579, 1537, 1513, 1448, 1297, 1252, 1208, 1046, 816, 752, 508 cm⁻¹. HRMS (ESI) calcd. for C₁₉H₂₁N₂O₂ (M + H)⁺ 309.1598, found 309.1598.

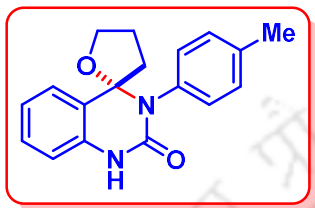
1-(4-Ethyl-2-(5-hydroxypent-1-yn-1-yl)phenyl)-3-(*p*-tolyl)urea (1ab):



White solid; *R_f* (Hexane:EtOAc, 1:1) 0.5; mp 131–133 °C. Yield 306 mg, 91%. ¹H NMR (500 MHz, CDCl₃) δ 8.14 (d, *J* = 8.5 Hz, 1H), 7.79 (s, 1H), 7.75 (s, 1H), 7.27 (s, 1H), 7.25 (s, 1H), 7.09 (s, 1H), 7.07–7.04 (m, 3H), 3.90 (t, *J* = 5.5 Hz, 2H), 2.65 (s, 1H), 2.55–2.50 (m, 4H), 2.27 (s, 3H), 1.82 (p, *J* = 5.9 Hz, 2H),

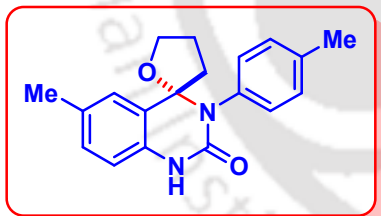
1.17 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.4, 138.7, 137.7, 136.2, 133.0, 130.1, 129.7, 128.7, 120.5, 118.4, 112.0, 96.2, 77.6, 63.1, 30.7, 28.1, 20.9, 17.3, 15.7. IR (KBr, neat) ν 3307, 2961, 1672, 1610, 1583, 1511, 1413, 1293, 1252, 1201, 1061, 894, 812, 750, 507 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 337.1911, found 337.1911.

(S)-3'-(*p*-Tolyl)-4,5-dihydro-1*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (2a):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 239–241 °C. Yield 117 mg, 99%. ^1H NMR (500 MHz, CDCl_3) δ 8.57–8.39 (m, 1H), 7.28 (d, $J = 7.9$ Hz, 2H), 7.25–7.18 (m, 4H), 7.00 (t, $J = 7.6$ Hz, 1H), 6.71 (d, $J = 7.9$ Hz, 1H), 3.87 (q, $J = 7.6$ Hz, 1H), 3.69 (td, $J = 7.9, 5.3$ Hz, 1H), 2.50–2.44 (m, 1H), 2.40–2.35 (m, 4H), 1.90–1.83 (m, 1H), 1.43–1.34 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.9, 137.8, 135.4, 134.9, 131.2, 129.6, 129.3, 125.1, 124.3, 122.2, 114.4, 97.2, 69.6, 39.2, 26.1, 21.3. IR (KBr, neat) ν 3202, 3060, 2922, 2855, 1668, 1600, 1502, 1404, 1271, 1189, 1025, 932, 786, 748, 661, 507 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 295.1441, found 295.1441.

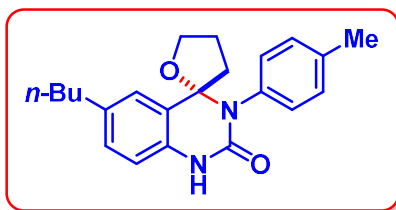
(S)-6'-Methyl-3'-(*p*-tolyl)-4,5-dihydro-1*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (2b):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 241–243 °C. Yield 122 mg, 99%. ^1H NMR (400 MHz, CDCl_3) δ 8.51 (s, 1H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.23 (d, $J = 8.2$ Hz, 2H), 7.07 (s, 1H), 7.02 (dd, $J = 8.0, 1.9$ Hz, 1H), 6.63 (d, $J = 8.1$ Hz, 1H), 3.89 (q, $J = 7.6$ Hz, 1H), 3.68 (td, $J = 7.9, 5.2$ Hz, 1H), 2.51–2.44 (m, 1H), 2.41 (s, 3H), 2.40–2.34 (m, 1H), 2.31 (s, 3H), 1.91–1.83 (m, 1H), 1.41–1.34 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.9, 137.7, 135.5, 132.5, 131.5, 131.2, 130.0, 129.5, 125.2, 124.1, 114.3, 97.2, 69.6, 39.3, 26.1, 21.3, 21.1. IR (KBr, neat) ν 3197, 3058, 2916, 1663, 1605, 1501, 1438, 1375, 1268, 1041, 935, 750, 654, 578, 465 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 309.1598, found 309.1598.

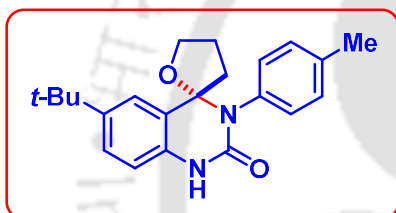
(S)-6'-Butyl-3'-(*p*-tolyl)-4,5-dihydro-1*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (2c):

White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 184–186 °C. Yield 139 mg, 99%. ^1H NMR



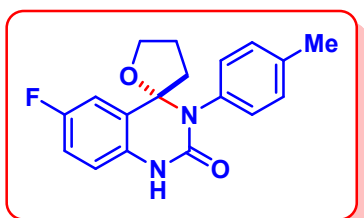
(400 MHz, CDCl_3) δ 8.35–8.29 (m, 1H), 7.29 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 7.07 (s, 1H), 7.03 (dd, J = 8.2, 1.9 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 3.89 (q, J = 7.6 Hz, 1H), 3.69 (td, J = 7.9, 5.1 Hz, 1H), 2.57 (t, J = 7.8 Hz, 2H), 2.51–2.44 (m, 1H), 2.40 (s, 3H), 2.39–2.35 (m, 1H), 1.91–1.83 (m, 1H), 1.61–1.53 (m, 2H), 1.42–1.31 (m, 3H), 0.93 (t, J = 7.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.9, 137.7, 136.8, 135.6, 132.6, 131.2, 129.6, 129.3, 124.7, 124.1, 114.2, 97.3, 69.6, 39.2, 35.4, 34.0, 26.2, 22.4, 21.3, 14.1. IR (KBr, neat) ν 3195, 3041, 2925, 2869, 1671, 1604, 1510, 1423, 1395, 1268, 1194, 1102, 1055, 1025, 815, 736, 642, 512 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 351.2067, found 351.2067.

(S)-6'-(tert-Butyl)-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (2d):



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 211–213 $^{\circ}\text{C}$. Yield 135 mg, 96%. ^1H NMR (400 MHz, CDCl_3) δ 8.37 (s, 1H), 7.22–7.17 (m, 3H), 7.17–7.14 (m, 3H), 6.58 (d, J = 8.3 Hz, 1H), 3.82 (q, J = 7.6 Hz, 1H), 3.61 (td, J = 7.8, 5.2 Hz, 1H), 2.44–2.37 (m, 1H), 2.32 (s, 3H), 2.31–2.26 (m, 1H), 1.85–1.76 (m, 1H), 1.38–1.29 (m, 1H), 1.22 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.9, 145.0, 137.7, 135.5, 132.4, 131.2, 129.5, 126.5, 123.6, 121.3, 114.0, 97.4, 69.6, 39.3, 34.5, 31.5, 26.2, 21.3. IR (KBr, neat) ν 3228, 3049, 2956, 2869, 1671, 1605, 1510, 1388, 1261, 1146, 1106, 1032, 954, 886, 824, 732, 644, 513 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 351.2067, found 351.2078.

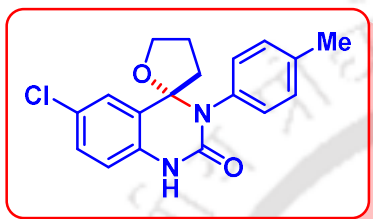
(S)-6'-Fluoro-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (2e):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 236–238 $^{\circ}\text{C}$. Yield 122 mg, 98%. ^1H NMR (500 MHz, CDCl_3) δ 9.03 (s, 1H), 7.28–7.20 (m, 4H), 6.97 (dd, J = 9.3, 2.8 Hz, 1H), 6.89 (td, J = 8.5, 2.8 Hz, 1H), 6.65 (dd, J = 8.8, 4.7 Hz, 1H), 3.87 (q, J = 7.6 Hz, 1H), 3.65 (td, J = 7.9, 5.3 Hz, 1H), 2.51–2.45 (m, 1H), 2.40 (s, 3H), 2.34–2.28 (m, 1H), 1.91–1.82 (m, 1H), 1.47–1.33 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ

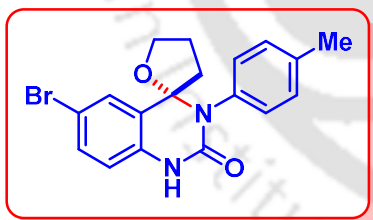
158.2 (d, $J = 238.0$ Hz), 153.0, 137.9, 135.1, 131.2, 131.1, 129.6, 125.6 (d, $J = 6.8$ Hz), 116.3 (d, $J = 23.1$ Hz), 115.8 (d, $J = 7.8$ Hz), 111.6 (d, $J = 24.2$ Hz), 96.8 (d, $J = 1.8$ Hz), 69.8, 39.3, 26.1, 21.4. ^{19}F NMR (470 MHz, CDCl_3) δ -124.2. IR (KBr, neat) ν 3205, 2982, 2924, 2870, 1671, 1610, 1506, 1417, 1390, 1264, 1171, 1051, 1024, 862, 815, 753, 642, 513 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{18}\text{FN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 313.1347, found 313.1359.

(S)-6'-Chloro-3'-(*p*-tolyl)-4,5-dihydro-1*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (2f):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 229–231 $^{\circ}\text{C}$. Yield 126 mg, 96%. ^1H NMR (400 MHz, CDCl_3) δ 9.13 (s, 1H), 7.27–7.22 (m, 5H), 7.11 (dd, $J = 8.5, 2.3$ Hz, 1H), 6.61 (d, $J = 8.5$ Hz, 1H), 3.88 (q, $J = 7.5$ Hz, 1H), 3.65 (td, $J = 7.9, 5.4$ Hz, 1H), 2.51–2.44 (m, 1H), 2.41 (s, 3H), 2.35–2.27 (m, 1H), 1.91–1.82 (m, 1H), 1.45–1.34 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.9, 138.0, 135.1, 133.6, 131.2, 129.6, 129.2, 126.9, 125.8, 124.9, 116.0, 96.8, 69.8, 39.5, 26.0, 21.3. IR (KBr, neat) ν 3209, 2935, 1675, 1600, 1495, 1417, 1385, 1269, 1054, 880, 817, 751, 726, 645, 509 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{18}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 329.1051, found 329.1051.

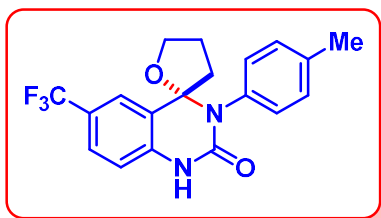
(S)-6'-Bromo-3'-(*p*-tolyl)-4,5-dihydro-1*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (2g):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 239–241 $^{\circ}\text{C}$. Yield 143 mg, 96%. ^1H NMR (400 MHz, CDCl_3) δ 8.98 (s, 1H), 7.37 (d, $J = 2.2$ Hz, 1H), 7.29–7.22 (m, 5H), 6.57 (d, $J = 8.5$ Hz, 1H), 3.89 (q, $J = 7.6$ Hz, 1H), 3.65 (td, $J = 7.9, 5.4$ Hz, 1H), 2.52–2.45 (m, 1H), 2.41 (s, 3H), 2.35–2.28 (m, 1H), 1.92–1.82 (m, 1H), 1.45–1.34 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.8, 138.0, 135.0, 134.1, 132.1, 131.1, 129.7, 127.9, 126.3, 116.3, 114.2, 96.7, 69.9, 39.6, 26.0, 21.4. IR (KBr, neat) ν 3239, 3080, 2928, 2873, 1672, 1596, 1494, 1417, 1379, 1262, 1032, 941, 873, 820, 752, 642, 510 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{18}\text{BrN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 373.0546, found 373.0547.

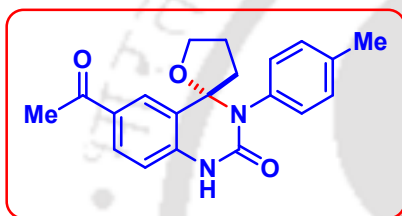
(S)-3'-(*p*-Tolyl)-6'-(trifluoromethyl)-4,5-dihydro-1*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (2h):

White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 184–186 $^{\circ}\text{C}$. Yield 136 mg, 94%. ^1H NMR



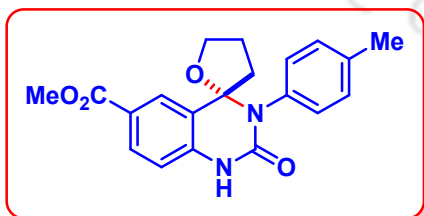
(500 MHz, CDCl_3) δ 9.34 (s, 1H), 7.50 (s, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.31–7.23 (m, 4H), 6.73 (d, J = 8.3 Hz, 1H), 3.91 (t, J = 7.9 Hz, 1H), 3.67 (q, J = 7.3 Hz, 1H), 2.57–2.48 (m, 1H), 2.42 (s, 3H), 2.37–2.29 (m, 1H), 1.93–1.86 (m, 1H), 1.47–1.39 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.7, 138.2, 137.8, 134.8, 131.1, 129.7, 126.4 (q, J = 3.6 Hz), 124.6, 124.3 (q, J = 269.7 Hz), 124.2 (q, J = 32.6 Hz), 122.5 (q, J = 3.9 Hz), 114.9, 96.8, 70.0, 39.9, 26.0, 21.3. IR (KBr, neat) ν 3245, 2956, 2878, 1676, 1607, 1512, 1429, 1393, 1322, 1261, 1163, 1113, 1077, 1033, 836, 667, 509 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 363.1315, found 363.1315.

(S)-6'-Acetyl-3'-(p-tolyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (2i):



White solid; R_f (Hexane:EtOAc, 2:3) 0.5; mp 240–242 °C. Yield 87 mg, 65%. ^1H NMR (400 MHz, CDCl_3) δ 9.50 (s, 1H), 7.94 (d, J = 1.9 Hz, 1H), 7.76 (dd, J = 8.4, 1.9 Hz, 1H), 7.34–7.23 (m, 4H), 6.72 (d, J = 8.4 Hz, 1H), 3.93 (q, J = 7.7 Hz, 1H), 3.70 (td, J = 8.0, 5.1 Hz, 1H), 2.55 (s, 3H), 2.51–2.44 (m, 1H), 2.42 (s, 3H), 2.40–2.37 (m, 1H), 1.94–1.89 (m, 1H), 1.43–1.33 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 196.5, 152.7, 139.2, 138.1, 135.0, 131.5, 131.1, 130.2, 129.7, 126.0, 124.3, 114.5, 96.9, 69.9, 39.6, 26.4, 26.1, 21.4. IR (KBr, neat) ν 3243, 2958, 2925, 1674, 1604, 1512, 1424, 1390, 1357, 1326, 1288, 1243, 1151, 1032, 829, 753, 642, 506 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 337.1547, found 337.1547.

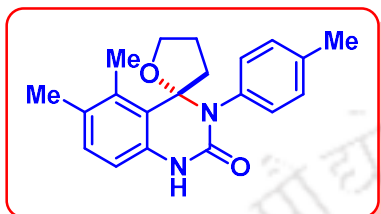
Methyl (S)-2'-oxo-3'-(p-tolyl)-2',3',4,5-tetrahydro-1'H,3H-spiro[furan-2,4'-quinazolin]-6'-carboxylate (2j):



White solid; R_f (Hexane:EtOAc, 2:3) 0.5; mp 258–260 °C. Yield 124 mg, 88%. ^1H NMR (400 MHz, CDCl_3) δ 9.41 (s, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.83 (dd, J = 8.4, 1.9 Hz, 1H), 7.27–7.23 (m, 4H), 6.68 (d, J = 8.4 Hz, 1H), 3.95–3.87 (m, 4H), 3.71 (td, J = 8.0, 5.0 Hz, 1H), 2.53–2.37 (m, 5H), 1.97–1.87 (m, 1H), 1.44–1.31 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 166.7, 152.7, 139.0, 138.1, 135.0, 131.1, 130.8, 129.7, 127.4, 124.0, 123.8, 114.5, 96.9, 69.8, 52.1, 39.5, 26.1, 21.3.

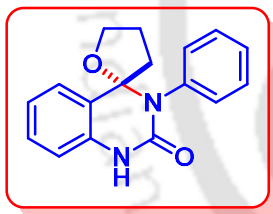
IR (KBr, neat) ν 3250, 2951, 2877, 1716, 1676, 1614, 1513, 1422, 1389, 1293, 1244, 1110, 1033, 897, 846, 767, 667, 644, 514 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$)⁺ 353.1496, found 353.1497.

(S)-5',6'-Dimethyl-3'-(*p*-tolyl)-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (2k):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 180–182 °C. Yield 115 mg, 89%. ^1H NMR (400 MHz, CDCl_3) δ 9.41 (s, 1H), 7.97 (d, $J = 1.8$ Hz, 1H), 7.83 (dd, $J = 8.4, 1.9$ Hz, 1H), 7.27–7.23 (m, 4H), 6.68 (d, $J = 8.4$ Hz, 1H), 3.95–3.87 (m, 4H), 3.71 (td, $J = 8.0, 5.0$ Hz, 1H), 2.53–2.37 (m, 5H), 1.97–1.87 (m, 1H), 1.44–1.31 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) 152.9, 138.0, 137.7, 135.7, 132.7, 131.2, 130.4, 129.6, 125.8, 121.6, 115.3, 97.2, 69.5, 39.1, 26.2, 21.3, 19.6, 19.5. IR (KBr, neat) ν 3197, 2923, 2867, 1665, 1599, 1510, 1414, 1379, 1265, 1199, 1033, 867, 819, 732, 656, 565, 524, 463 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 323.1754, found 323.1759.

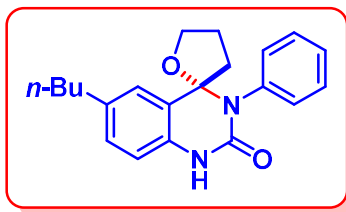
(S)-3'-Phenyl-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (2l):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 198–200 °C. Yield 108 mg, 96%. ^1H NMR (400 MHz, CDCl_3) δ 8.83–8.57 (m, 1H), 7.46–7.37 (m, 5H), 7.29 (d, $J = 7.8$ Hz, 1H), 7.23–7.18 (m, 1H), 7.01 (t, $J = 7.6$ Hz, 1H), 6.72 (d, $J = 7.9$ Hz, 1H), 3.88 (q, $J = 7.6$ Hz, 1H), 3.68 (td, $J = 8.0, 5.1$ Hz, 1H), 2.52–2.44 (m, 1H), 2.43–2.35 (m, 1H), 1.90–1.82 (m, 1H), 1.38–1.31 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.8, 138.1, 134.8, 131.6, 129.3, 128.9, 128.0, 125.0, 124.3, 122.2, 114.4, 97.2, 69.6, 39.3, 26.1. IR (KBr, neat) ν 3204, 3057, 2977, 2925, 2873, 1664, 1600, 1491, 1407, 1323, 1269, 1191, 1033, 989, 809, 752, 704, 642, 546 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 281.1285, found 281.1303.

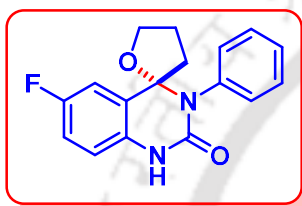
(S)-6'-Butyl-3'-phenyl-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (2m):

White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 156–158 °C. Yield 133 mg, 99%. ^1H NMR (500 MHz, CDCl_3) δ 8.57–8.42 (m, 1H), 7.47–7.37 (h, $J = 7.0, 6.0$ Hz, 5H), 7.07 (s, 1H), 7.03 (d, $J = 7.85$ Hz, 1H), 6.65 (d, $J = 8.1$ Hz, 1H), 3.89 (q, $J = 7.7$ Hz, 1H), 3.67 (td, $J = 8.0, 5.1$ Hz, 1H), 2.57 (t, $J = 7.8$ Hz, 2H), 2.50–2.44 (m, 1H), 2.42–2.36 (m, 1H), 1.91–1.83



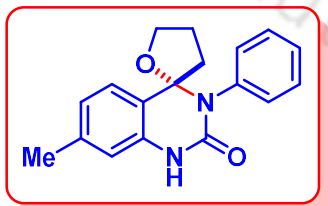
(m, 1H), 1.61–1.54 (m, 2H), 1.40–1.31 (m, 3H), 0.93 (t, J = 7.4 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.8, 138.3, 136.8, 132.6, 131.6, 129.4, 128.8, 128.0, 124.6, 124.1, 114.3, 97.3, 69.6, 39.3, 35.4, 33.9, 26.1, 22.4, 14.0. IR (KBr, neat) ν 3209, 3050, 2955, 2928, 2866, 1669, 1607, 1514, 1423, 1392, 1266, 1192, 1030, 828, 734, 703, 646, 550 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 337.1911, found 337.1911.

(S)-6'-Fluoro-3'-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (2n):



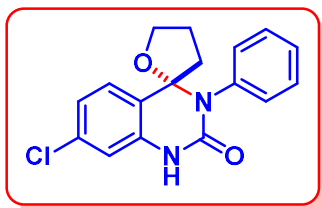
White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 247–249 °C. Yield 116 mg, 97%. ^1H NMR (400 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.95 (s, 1H), 7.41–7.32 (m, 5H), 6.95 (dd, J = 9.4, 2.7 Hz, 1H), 6.90 (td, J = 8.4, 2.7 Hz, 1H), 6.74 (dd, J = 8.8, 4.7 Hz, 1H), 3.84 (q, J = 7.7 Hz, 1H), 3.64–3.58 (m, 1H), 2.48–2.41 (m, 1H), 2.34–2.26 (m, 1H), 1.88–1.78 (m, 1H), 1.39–1.28 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 158.1 (d, J = 238.1 Hz), 152.5, 137.9, 131.5, 131.3, 128.8, 128.0, 125.5 (d, J = 6.8 Hz), 116.2 (d, J = 22.9 Hz), 115.6 (d, J = 7.8 Hz), 111.5 (d, J = 24.3 Hz), 96.8, 69.6, 39.2, 25.9. ^{19}F NMR (470 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -123.9. IR (KBr, neat) ν 3202, 2923, 2853, 1663, 1506, 1425, 1393, 1262, 1191, 1034, 794, 754, 707, 645, 552 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{16}\text{FN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 299.1190, found 299.1191.

(S)-7'-Methyl-3'-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (2o):



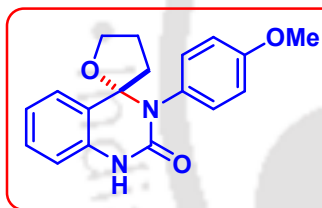
White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 218–220 °C. Yield 115 mg, 98%. ^1H NMR (400 MHz, CDCl_3) δ 8.10 (s, 1H), 7.49–7.33 (m, 5H), 7.19 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.56 (s, 1H), 3.77 (s, 2H), 2.42 (t, J = 7.8 Hz, 2H), 2.30 (s, 3H), 2.08–1.71 (m, 1H), 1.52–1.20 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.7, 139.7, 138.2, 134.7, 131.5, 128.9, 128.1, 125.1, 123.4, 121.5, 114.6, 69.4, 39.0, 26.2, 21.2. IR (KBr, neat) ν 3209, 2974, 2872, 1667, 1595, 489, 1411, 1270, 1189, 1031, 871, 805, 702, 523 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 295.1441, found 295.1447.

(S)-7'-Chloro-3'-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (2p):



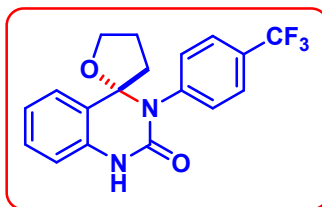
White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 245–247 °C. Yield 122 mg, 97%. ^1H NMR (400 MHz, CDCl_3) δ 8.91 (s, 1H), 7.48–7.34 (m, 5H), 7.20 (d, J = 8.4 Hz, 1H), 6.97 (dd, J = 8.4, 2.1 Hz, 1H), 6.73 (d, J = 2.1 Hz, 1H), 3.87 (q, J = 7.6 Hz, 1H), 3.65 (td, J = 8.0, 5.3 Hz, 1H), 2.52–2.45 (m, 1H), 2.32 (dt, J = 14.1, 8.3 Hz, 1H), 1.90–1.80 (m, 1H), 1.41–1.30 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.7, 137.7, 136.0, 134.9, 131.4, 129.0, 128.3, 126.4, 122.9, 122.3, 114.3, 96.9, 69.8, 39.5, 26.0. IR (KBr, neat) ν 3211, 2961, 2872, 1674, 1596, 1493, 1413, 1377, 1315, 1251, 1087, 1035, 953, 865, 803, 764, 701, 575, 487, 447 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{16}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 315.0895, found 315.0895.

(S)-3'-(4-Methoxyphenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (2q):



White solid; R_f (Hexane:EtOAc, 3:7) 0.4; mp 267–269 °C. Yield 123 mg, 99%. ^1H NMR (400 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 8.37 (s, 1H), 7.38–7.27 (m, 3H), 7.23 (td, J = 7.6, 1.4 Hz, 1H), 7.02 (td, J = 7.6, 1.2 Hz, 1H), 6.94 (dt, J = 9.1, 1.4 Hz, 2H), 6.78 (dd, J = 8.1, 1.2 Hz, 1H), 3.88 (q, J = 7.7 Hz, 1H), 3.84 (s, 3H), 3.71 (td, J = 7.9, 5.1 Hz, 1H), 2.51–2.36 (m, 2H), 1.93–1.84 (m, 1H), 1.45–1.34 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 159.1, 152.7, 134.9, 132.4, 130.7, 129.3, 125.1, 124.2, 122.1, 114.2, 114.1, 97.2, 69.6, 55.5, 39.2, 26.1. IR (KBr, neat) ν 3189, 2919, 1660, 1602, 1506, 1429, 1243, 1171, 1033, 821, 756, 667, 538 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 311.1390, found 311.1391.

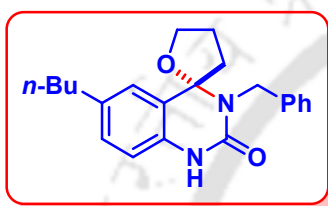
(S)-3'-(4-(Trifluoromethyl)phenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (2r):



White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 268–270 °C. Yield 127 mg, 91%. ^1H NMR (400 MHz, CDCl_3) δ 8.67 (s, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 7.9 Hz, 1H), 7.24 (td, J = 7.7, 1.4 Hz, 1H), 7.05 (td, J =

7.6, 0.9 Hz, 1H), 6.73 (d, $J = 7.9$ Hz, 1H), 3.91 (q, $J = 7.4$ Hz, 1H), 3.66 (td, $J = 7.8, 5.3$ Hz, 1H), 2.42 (d, $J = 6.3$ Hz, 1H), 2.40 (d, $J = 7.0$ Hz, 1H), 1.96–1.87 (m, 1H), 1.44–1.33 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.6, 141.6, 134.5, 132.1, 130.2 (q, $J = 32.4$ Hz), 129.5, 125.9 (q, $J = 3.7$ Hz), 124.9, 124.3, 124.2 (q, $J = 270.5$ Hz), 122.6, 114.5, 97.3, 69.7, 39.4, 26.0. ^{19}F NMR (470 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -65.7. IR (KBr, neat) ν 3209, 3066, 2925, 1671, 1601, 1501, 1403, 1321, 1269, 1162, 1064, 1022, 934, 748, 704, 640, 584 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 349.1158, found 349.1158.

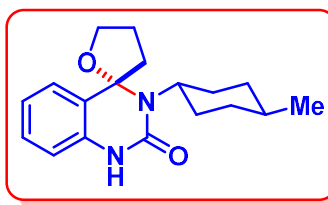
(S)-3'-Benzyl-6'-butyl-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (2s):



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 156–158 °C. Yield 137 mg, 98%. ^1H NMR (500 MHz, CDCl_3) δ 9.05 (s, 1H), 7.39 (d, $J = 7.6$ Hz, 2H), 7.29 (t, $J = 7.6$ Hz, 2H), 7.21 (t, $J = 7.4$ Hz, 1H), 7.00 (s, 1H), 6.97 (d, $J = 8.2$ Hz, 1H), 6.53 (d, $J = 8.0$ Hz, 1H), 4.80 (d, $J = 15.5$ Hz, 1H), 4.65 (d, $J = 15.5$ Hz, 1H), 4.25–4.17 (m, 2H), 2.56 (t, $J = 7.8$ Hz, 2H), 2.33–2.27 (m, 1H), 2.23–2.17 (m, 1H), 2.14–2.03 (m, 2H), 1.57 (p, $J = 7.5$ Hz, 2H), 1.36 (h, $J = 7.4$ Hz, 2H), 0.93 (t, $J = 7.4$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 154.2, 139.9, 136.6, 132.2, 129.1, 128.3, 127.3, 126.7, 125.0, 124.0, 114.0, 96.9, 70.2, 45.4, 39.1, 35.3, 34.0, 25.6, 22.5, 14.1. IR (KBr, neat) ν 3194, 3042, 2927, 2867, 1663, 1605, 1511, 1436, 1401, 1354, 1263, 1050, 953, 825, 707, 643, 599, 506 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 351.2067, found 351.2070.

(S)-3'-((1*r*,4*S*)-4-Methylcyclohexyl)-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (2t):

White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 203–205 °C. Yield 101 mg, 84%. ^1H NMR (500 MHz, CDCl_3) δ 8.13 (s, 1H), 7.20–7.17 (m, 2H), 6.95 (t, $J = 7.6$ Hz, 1H), 6.71 (d, $J =$

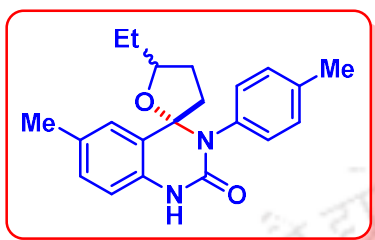


8.1 Hz, 1H), 4.23–4.24 (m, 2H), 3.27 (s, 1H), 2.82 (q, $J = 12.6$ Hz, 1H), 2.43 (qd, $J = 12.5, 3.6$ Hz, 1H), 2.38–2.31 (m, 1H), 2.21–2.12 (m, 3H), 1.84–1.75 (m, 2H), 1.74–1.71 (m, 1H), 1.69–1.65 (m, 1H), 1.53–1.43 (m, 1H), 1.04–0.95 (m, 2H), 0.90 (d, $J = 6.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.4, 134.7, 129.0, 125.5, 124.6, 121.7, 113.2, 97.7, 70.8, 55.6, 41.0, 36.0, 35.8, 31.9, 30.7, 30.6, 25.8, 22.6. IR (KBr,

neat) ν 3195, 3058, 2916, 1663, 1605, 1501, 1438, 1375, 1268, 1041, 750, 578, 465 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 301.1911, found 301.1919.

5-Ethyl-6'-methyl-3'-(*p*-tolyl)-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,4'-quinazolin]-

2'(3'*H*)-one (2u):



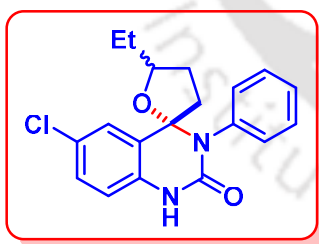
White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 214–216 °C.

Yield 133 mg, 99% (d.r. = 1:1). ^1H NMR (500 MHz, CDCl_3) δ 8.46 (d, J = 13.5 Hz, 0.5H), 8.37 (d, J = 13.2 Hz, 0.5H), 7.29 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.10 (s, 1H), 7.01 (t, J = 6.9 Hz, 1H), 6.62 (t, J = 7.9 Hz,

1H), 3.96–3.90 (m, 0.5H), 3.38–3.33 (m, 0.5H), 2.58–2.53 (m, 0.5H), 2.51–2.47 (m, 1H), 2.41 (s, 3H), 2.33 (s, 1.5H), 2.32 (s, 1.5H), 2.30–2.23 (m, 0.5H), 1.89–1.83 (m, 0.5H), 1.77–1.39 (m, 3H), 1.27–1.19 (m, 0.5H), 0.87 (t, J = 7.4 Hz, 1.5H), 0.84 (t, J = 7.5 Hz, 1.5H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.1, 153.0, 137.8, 137.6, 135.5, 135.1, 132.5, 132.2, 131.7, 131.5, 131.4, 129.9, 129.8, 129.4, 129.3, 125.3, 125.2, 125.0, 124.5, 114.4, 114.2, 97.1, 96.5, 82.6, 40.2, 39.3, 31.5, 31.4, 28.7, 28.0, 21.3, 21.2, 10.6, 10.4. IR (KBr, neat) ν 3212, 3037, 2962, 2925, 1671, 1605, 1512, 1421, 1390, 1266, 1024, 820, 756, 641, 515, 437 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 337.1911, found 337.1913.

6'-Chloro-5-ethyl-3'-phenyl-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,4'-quinazolin]-

2'(3'*H*)-one (2v):



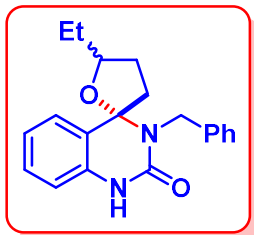
White solid; R_f (Hexane:EtOAc, 1:1) 0.6; mp 152–154 °C.

Yield 132 mg, 96% (d.r. = 1:1). ^1H NMR (500 MHz, CDCl_3) δ 9.28–9.24 (m, 0.5H), 9.18–9.15 (m, 0.5H), 7.46–7.36 (m, 5H), 7.26–7.24 (m, 1H), 7.12–7.09 (m, 1H), 6.61 (dd, J = 8.5, 3.8 Hz, 1H), 3.96–3.90 (m, 0.5H), 3.29–3.24 (m, 0.5H), 2.57–

2.48 (m, 1H), 2.43–2.36 (m, 0.5H), 2.29–2.24 (m, 0.5H), 1.97–1.82 (m, 1H), 1.72–1.67 (m, 0.5H), 1.66–1.60 (m, 0.5H), 1.59–1.52 (m, 0.5H), 1.48–1.38 (m, 1H), 1.22–1.13 (m, 0.5H), 0.86 (t, J = 7.4 Hz, 2H), 0.82 (t, J = 7.5 Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.0, 152.9, 137.9, 137.3, 133.6, 133.4, 132.0, 129.2, 129.1, 128.8, 128.7, 128.3, 128.1, 127.1, 126.9, 126.8, 126.3, 124.8, 116.1, 115.9, 96.6, 96.1, 83.1, 83.0, 40.4, 39.7, 31.3, 31.2, 28.6, 27.9, 10.6, 10.4. IR (KBr, neat) ν 3250, 2964, 2930, 2873, 1673, 1597, 1494, 1415, 1381, 1261, 1086,

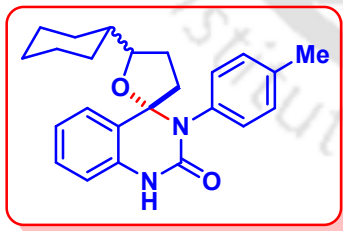
981, 943, 822, 753, 702, 639, 554 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{20}\text{ClN}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 343.1208, found 343.1211.

3'-Benzyl-5-ethyl-4,5-dihydro-1*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (2w):



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 205–207 °C. Yield 126 mg, 98% (d.r. = 3:2). ^1H NMR (400 MHz, CDCl_3) δ 9.16–9.04 (m, 1H, minor), 8.97–8.85 (m, 1H, major), 7.41 (d, J = 7.3 Hz, 2H, major), 7.35 (d, J = 7.4 Hz, 2H, minor), 7.30–7.25 (m, 3H), 7.22–7.17 (m, 1H), 7.17–7.11 (m, 1H), 6.99–6.94 (m, 1H), 6.61 (d, J = 7.9, 1H, minor), 6.58 (d, J = 7.9, 1H, major), 4.96 (d, J = 16.0 Hz, 1H, minor), 4.88 (d, J = 15.3 Hz, 1H), 4.63 (d, J = 16.0 Hz, 1H, minor), 4.53 (d, J = 15.3 Hz, 1H, major), 4.25–4.13 (m, 1H), 2.44–2.28 (m, 3H, minor), 2.20–2.04 (m, 3H, major), 1.89–1.75 (m, 1H), 1.70–1.56 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H, major), 0.95 (t, J = 7.4 Hz, 3H, minor). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 154.0, 153.8, 139.9, 134.5, 134.4, 129.1, 129.0, 128.4, 128.3, 127.7, 127.0, 126.7, 126.6, 125.8, 125.0, 124.7, 124.6, 122.0, 114.3, 113.9, 96.5, 96.4, 83.8, 82.4, 45.4, 45.3, 40.5, 38.9, 31.2, 31.1, 28.7, 28.6, 10.7, 10.5. IR (KBr, neat) ν 3198, 3122, 3057, 2965, 2922, 2873, 1664, 1501, 1494, 1435, 1404, 1355, 1321, 1266, 1174, 1061, 1027, 944, 848, 807, 754, 735, 698, 653, 601, 503 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 323.1754, found 323.1758.

5-Cyclohexyl-3'-(*p*-tolyl)-4,5-dihydro-1*H*,3*H*-spiro[furan-2,4'-quinazolin]-2'(3'*H*)-one (2x):

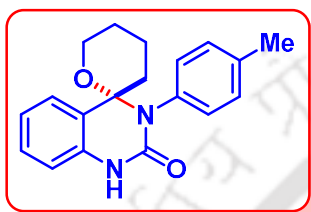


White solid; R_f (Hexane:EtOAc, 7:3) 0.5; mp 226–228 °C. Yield 148 mg, 98% (d.r. = 3:2). ^1H NMR (500 MHz, CDCl_3) δ 8.63 (s, 1H, minor), 8.57 (s, 1H, major), 7.32 (d, J = 7.7 Hz, 3H, minor), 7.29 (d, J = 7.8 Hz, 3H, major), 7.23 (d, J = 7.7 Hz, 2H), 7.19 (t, J = 7.7 Hz, 1H), 7.02–6.98 (m, 1H), 6.72 (t, J = 7.5 Hz, 1H), 3.67–3.62 (m, 1H, minor), 3.07–3.03 (m, 1H, major), 2.55–2.45 (m, 1H), 2.42 (s, 3H), 2.40–2.35 (m, 1H, minor), 2.30–2.25 (m, 1H, major), 1.97–1.92 (m, 1H), 1.85–1.79 (m, 1H, minor), 1.72–1.61 (m, 4H), 1.49 (d, J = 13.0 Hz, 1H, major), 1.42–1.34 (m, 1H), 1.26–1.07 (m, 3H), 1.03–0.75 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.1, 153.0, 137.8, 137.6, 135.5, 134.9, 134.8, 134.5, 131.8, 129.4, 129.3, 129.0, 128.9, 125.5, 125.1,

125.0, 124.9, 122.1, 122.0, 114.4, 114.2, 96.5, 96.2, 85.6, 85.5, 43.0, 42.9, 40.2, 39.4, 30.6, 30.1, 29.9, 29.8, 29.0, 28.8, 26.6, 26.5, 26.1, 26.0, 25.8, 25.7, 21.4, 21.3. IR (KBr, neat) ν 3211, 3057, 2922, 2852, 1669, 1600, 1503, 1403, 1322, 1265, 1175, 1106, 1025, 866, 814, 786, 750, 702, 658, 508 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 377.2224, found 377.2225.

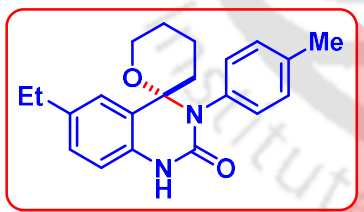
(S)-3'-(*p*-Tolyl)-3,4,5,6-tetrahydro-1*H*-spiro[pyran-2,4'-quinazolin]-2'(3*H*)-one

(2aa):

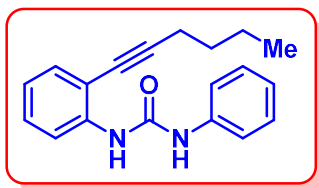


White solid; R_f (Hexane:EtOAc, 2:3) 0.4; mp 168–170 °C. Yield 121 mg, 98%. ^1H NMR (400 MHz, CDCl_3) δ 7.84 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 7.7 Hz, 2H), 7.34 (t, J = 7.7 Hz, 1H), 7.30–7.27 (m, 3H), 7.09 (t, J = 7.7 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 4.35 (dd, J = 13.1, 6.2 Hz, 1H), 3.68–3.62 (m, 1H), 3.54 (td, J = 11.5, 2.9 Hz, 1H), 2.91–2.80 (m, 1H), 2.53–2.33 (m, 5H), 1.81–1.66 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.5, 138.5, 135.9, 134.6, 131.0, 129.9, 129.7, 127.7, 120.6, 119.5, 115.1, 89.5, 62.1, 34.6, 29.5, 27.9, 21.5. IR (KBr, neat) ν 3222, 3061, 2941, 1675, 1597, 1495, 1401, 1266, 1166, 1073, 1025, 870, 753, 704, 567 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 309.1598, found 309.1598.

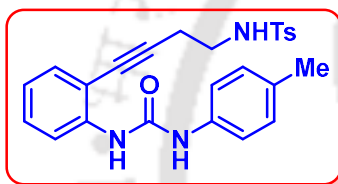
(S)-6'-Ethyl-3'-(*p*-tolyl)-3,4,5,6-tetrahydro-1*H*-spiro[pyran-2,4'-quinazolin]-2'(3*H*)-one (2ab):



White solid; R_f (Hexane:EtOAc, 2:3) 0.4; mp 154–156 °C. Yield 132 mg, 98%. ^1H NMR (500 MHz, CDCl_3) δ 7.54 (s, 1H), 7.33 (s, 1H), 7.23–7.09 (m, 4H), 7.06 (dd, J = 8.1, 1.8 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 3.45–3.41 (m, 1H), 3.29–3.22 (m, 1H), 2.60 (q, J = 7.6 Hz, 2H), 2.32 (s, 3H), 2.03–1.91 (m, 2H), 1.86–1.77 (m, 1H), 1.67–1.61 (m, 1H), 1.55–1.50 (m, 1H), 1.46–1.37 (m, 1H), 1.19 (t, J = 7.6 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 154.4, 137.8, 137.4, 136.1, 133.7, 131.0, 129.7, 128.6, 124.6, 123.7, 114.7, 87.2, 62.6, 30.3, 28.7, 24.0, 21.4, 20.2, 16.1. IR (KBr, neat) ν 2960, 2931, 2870, 1671, 1601, 1510, 1423, 1391, 1265, 1074, 1029, 1006, 823, 757, 658, 515 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 337.1911, found 337.1911.

1-(2-(Hex-1-yn-1-yl)phenyl)-3-phenylurea (5):

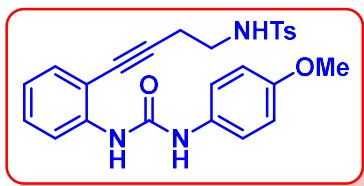
White solid; R_f (Hexane:EtOAc, 4:1) 0.6; mp 142–144 °C. Yield 281 mg, 96%. ^1H NMR (400 MHz, CDCl_3) δ 8.13 (d, J = 8.3 Hz, 1H), 7.44 (s, 1H), 7.33–7.29 (m, 4H), 7.25 (dd, J = 7.7, 1.6 Hz, 1H), 7.22–7.16 (m, 2H), 7.15–7.08 (m, 1H), 6.88 (t, J = 7.5 Hz, 1H), 2.17 (t, J = 6.8 Hz, 2H), 1.41–1.28 (m, 4H), 0.84 (t, J = 7.1 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.2, 139.6, 137.7, 137.7, 131.9, 129.6, 129.0, 125.30, 125.27, 123.1, 122.5, 118.9, 118.8, 112.9, 97.6, 76.1, 30.8, 22.2, 19.3, 13.7. IR (KBr, neat) ν 3327, 2957, 2928, 2870, 1657, 1600, 1579, 1549, 1499, 1446, 1303, 1250, 1214, 751, 693, 508 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ 293.1648, found 293.1647.

4-Methyl-N-(4-(2-(3-(*p*-tolyl)ureido)phenyl)but-3-yn-1-yl)benzenesulfonamide (7a):

White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 154–156 °C. Yield 439 mg, 98%. ^1H NMR (500 MHz, CDCl_3) δ 8.25 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 11.7 Hz, 1H), 7.75 (d, J = 7.8 Hz, 2H), 7.65 (s, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 7.7 Hz, 1H), 7.26 (d, J = 8.2 Hz, 3H), 7.06 (d, J = 8.0 Hz, 2H), 6.92 (t, J = 7.6 Hz, 1H), 5.56–5.46 (m, 1H), 3.15–3.10 (m, 2H), 2.64–2.59 (m, 2H), 2.40 (s, 3H), 2.28 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.3, 144.1, 140.5, 136.6, 136.2, 133.0, 132.0, 130.1, 129.6, 129.3, 127.0, 122.1, 120.7, 119.4, 120.0, 92.9, 78.6, 41.9, 21.7, 21.6, 20.9. IR (KBr, neat) ν 3359, 2922, 1677, 1600, 1578, 1531, 1515, 1446, 1301, 1247, 1202, 1154, 1092, 917, 814, 753, 662, 548, 507 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_3\text{S}$ ($\text{M} + \text{H}$) $^+$ 448.1689, found 448.1689.

N-(4-(2-(3-(4-Methoxyphenyl)ureido)phenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (7b):

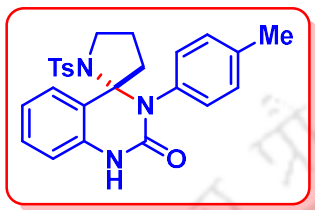
White solid; R_f (Hexane:EtOAc, 1:1) 0.4; mp 120–122 °C. Yield 445 mg, 96%. ^1H NMR



(400 MHz, CDCl_3) δ 8.19 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 7.9 Hz, 3H), 7.57 (s, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.24–7.18 (m, 4H), 6.87 (t, J = 7.5 Hz, 1H), 6.76 (d, J = 8.3 Hz, 2H), 5.62 (s, 1H), 3.72 (s, 3H), 3.06 (s, 2H), 2.54 (t, J = 5.8

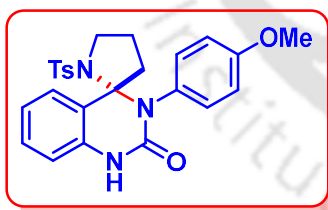
Hz, 2H), 2.36 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 156.2, 153.6, 144.0, 140.4, 136.6, 132.0, 131.5, 130.0, 129.9, 129.2, 127.1, 127.0, 123.1, 122.0, 119.2, 114.4, 111.9, 92.9, 78.5, 55.6, 41.9, 21.6, 21.5. IR (KBr, neat) ν 3361, 2932, 1674, 1601, 1579, 1532, 1508, 1445, 1301, 1241, 1211, 1153, 1091, 1035, 813, 753, 735, 661, 547 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_4\text{S}$ ($\text{M} + \text{H}$) $^+$ 464.1639, found 464.1636.

(S)-3'-(*p*-Tolyl)-1-tosyl-1'*H*-spiro[pyrrolidine-2,4'-quinazolin]-2'(3'*H*)-one (8a):



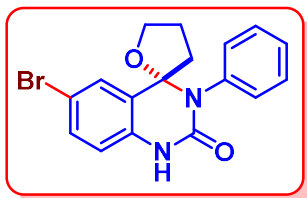
White solid; R_f (Hexane:EtOAc, 2:3) 0.5; mp 220–222 °C. Yield 161 mg, 90%. ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO-d}_6$) δ 9.05 (s, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.25–7.23 (m, 1H), 7.14 (d, J = 8.2 Hz, 1H), 7.06 (t, J = 7.8 Hz, 2H), 6.90 (d, J = 7.3 Hz, 2H), 6.85–6.78 (m, 3H), 6.45–6.35 (m, 2H), 3.60 (t, J = 8.7 Hz, 1H), 3.09 (q, J = 8.2 Hz, 1H), 2.61 (dd, J = 14.1, 8.1 Hz, 1H), 2.52–2.46 (m, 1H), 2.42–2.37 (m, 1H), 2.32 (s, 3H), 2.25 (s, 3H), 0.81–0.71 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $\text{CDCl}_3/\text{DMSO-d}_6$) δ 151.7, 142.3, 137.8, 137.1, 136.5, 135.5, 131.4, 131.1, 130.1, 129.4, 129.0, 128.8, 126.5, 126.4, 121.1, 120.0, 114.5, 83.8, 49.6, 45.1, 22.2, 21.3, 21.2. IR (KBr, neat) ν 3068, 2988, 2922, 1676, 1602, 1509, 1413, 1340, 1226, 1215, 1155, 1112, 1059, 1004, 980, 885, 817, 753, 671, 595, 572, 549, 529 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_3\text{S}$ ($\text{M} + \text{H}$) $^+$ 448.1689, found 448.1689.

(S)-3'-(4-Methoxyphenyl)-1-tosyl-1'*H*-spiro[pyrrolidine-2,4'-quinazolin]-2'(3'*H*)-one (8b):



White solid; R_f (Hexane:EtOAc, 3:7) 0.5; mp 220–222 °C. Yield 150 mg, 81%. ^1H NMR (400 MHz, $\text{CDCl}_3/\text{Methanol-d}_4$) δ 7.82 (dd, J = 8.8, 2.6 Hz, 1H), 7.18–7.12 (m, 2H), 7.05 (dd, J = 8.9, 3.0 Hz, 1H), 6.96 (d, J = 8.1 Hz, 2H), 6.92 (dd, J = 8.8, 3.0 Hz, 1H), 6.88 (d, J = 8.1 Hz, 2H), 6.80 (d, J = 8.0 Hz, 1H), 6.49–6.44 (m, 2H), 3.83 (s, 3H), 3.66 (t, J = 8.4 Hz, 1H), 3.15 (td, J = 9.5, 6.7 Hz, 1H), 2.69–2.53 (m, 2H), 2.31 (s, 3H), 1.57–1.49 (m, 1H), 0.90–0.78 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, $\text{CDCl}_3/\text{DMSO-d}_6$) δ 158.9, 151.6, 142.3, 137.1, 136.4, 132.6, 132.2, 130.7, 129.3, 128.9, 128.8, 126.6, 126.4, 126.3, 120.9, 119.8, 114.4, 114.3, 114.1, 83.8, 55.2, 49.6, 45.1, 22.1, 21.2. IR (KBr, neat) ν 3065, 2928, 1675, 1603, 1511, 1413, 1339, 1249, 1157, 1113, 1008, 980, 836, 752, 672, 573, 548 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_4\text{S}$ ($\text{M} + \text{H}$) $^+$ 464.1639, found 464.1639.

(S)-6'-Bromo-3'-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,4'-quinazolin]-2'(3'H)-one (9):

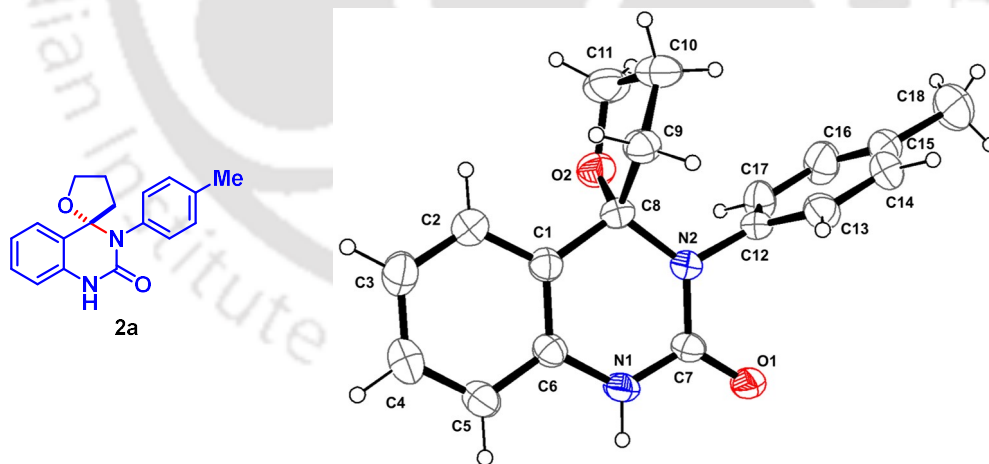


White solid; R_f (Hexane:EtOAc, 1:1) 0.5; mp 194–196 °C. Yield 141 mg, 98%. ^1H NMR (400 MHz, CDCl_3) δ 9.28 (s, 1H), 7.47–7.44 (m, 1H), 7.43–7.38 (m, 4H), 7.37–7.37 (d, J = 1.6 Hz, 1H), 7.25 (dd, J = 8.5, 2.2 Hz, 1H), 6.55 (d, J = 8.5 Hz, 1H), 3.93–3.83 (m, 1H), 3.67–3.57 (m, 1H), 2.52–2.42 (m, 1H), 2.37–2.26 (m, 1H), 1.91–1.80 (m, 1H), 1.41–1.31 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 152.7, 137.7, 134.0, 132.2, 131.5, 129.0, 128.2, 127.9, 126.3, 116.4, 114.4, 96.8, 69.9, 39.7, 26.0. IR (KBr, neat) ν 3224, 2958, 1774, 1705, 1670, 1595, 1491, 1418, 1380, 1262, 1181, 1031, 817, 702, 641, 549, 510 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{16}\text{BrN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 359.0390, found 359.0390.

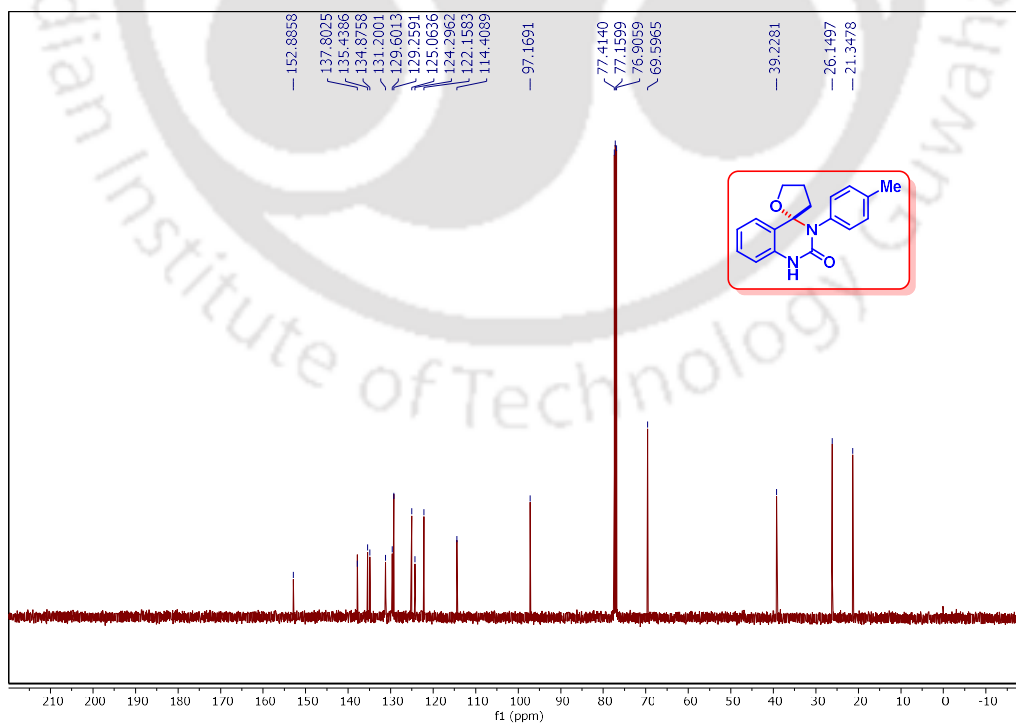
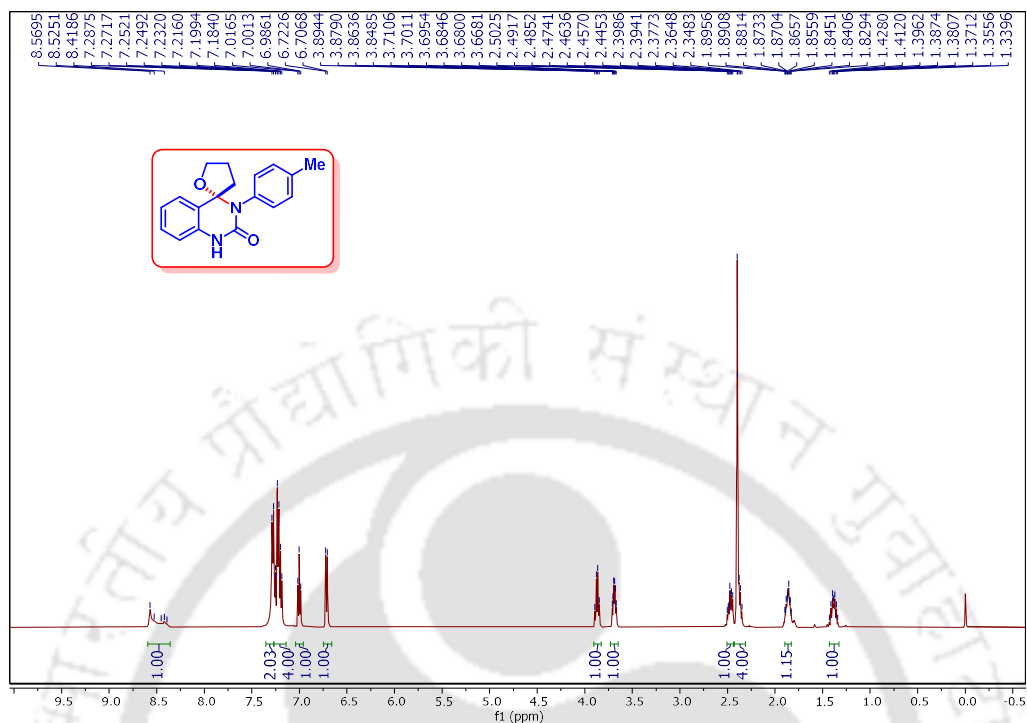
5.8.1. Crystallographic Description

Table 5.8.1.1. Crystal parameters of compound **2a**

Compound 2a	CCDC 2334015
Formula	C ₁₈ H ₁₈ N ₂ O ₂
Formula weight	294.34
T/K	297(2)
Crystal system	monoclinic
Space group	P 2 ₁ /n
<i>a</i> /Å	12.5261(6)
<i>b</i> /Å	7.3772(4)
<i>c</i> /Å	16.8208(9)
<i>a</i> /°	90
<i>β</i> /°	98.222(2)
<i>γ</i> /°	90
<i>V</i> /Å ³	1538.39(14)
<i>Z</i>	4
Abs. Coeff./mm ⁻¹	0.084
Abs. Correction	none
GOF on <i>F</i> ²	1.189
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.0730 <i>wR</i> ₂ = 0.1298
<i>R</i> indices [all data]	<i>R</i> ₁ = 0.1141 <i>wR</i> ₂ = 0.1506

Figure 5.8.1.1. ORTEP diagram of compound **2a** with thermal ellipsoid of 30% probability.

5.9. Representative Spectra



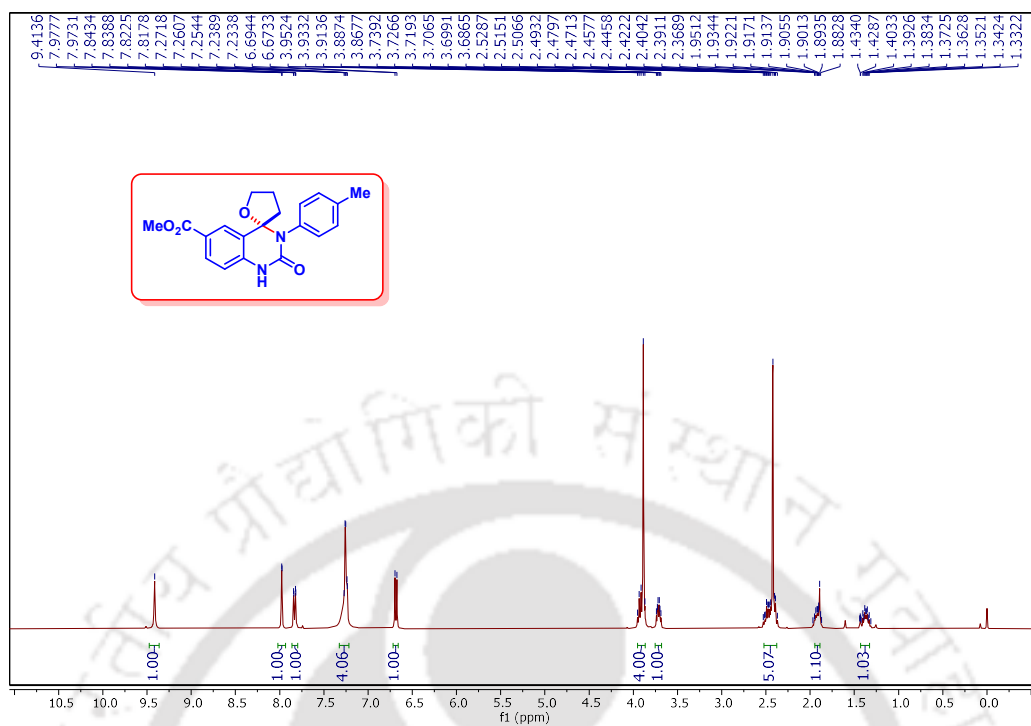


Figure 5.9.3. ¹H NMR spectrum of compound **2j** (400 MHz, CDCl₃).

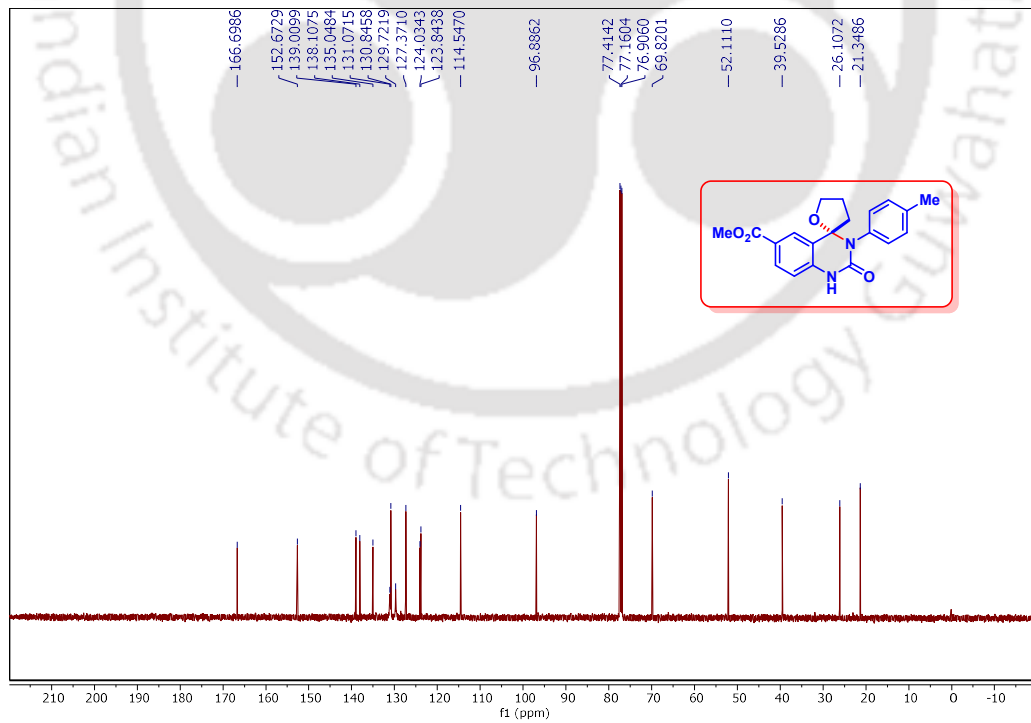


Figure 5.9.4. ¹³C{¹H} NMR spectrum of compound **2j** (125 MHz, CDCl₃).

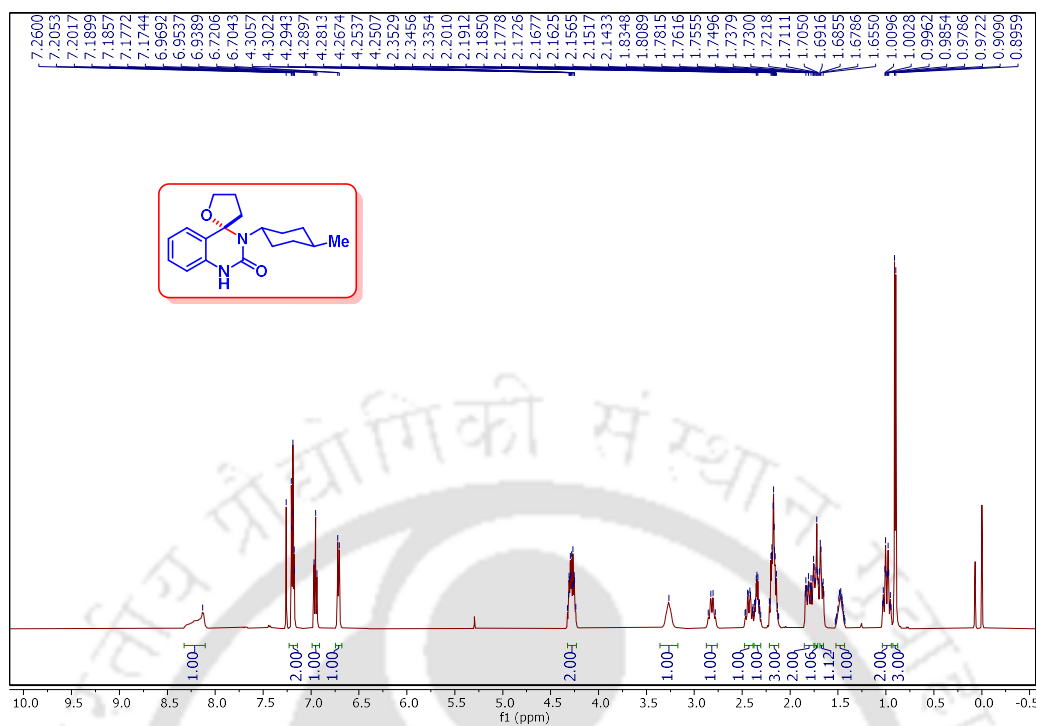


Figure 5.9.5. ¹H NMR spectrum of compound 2t (500 MHz, CDCl₃).

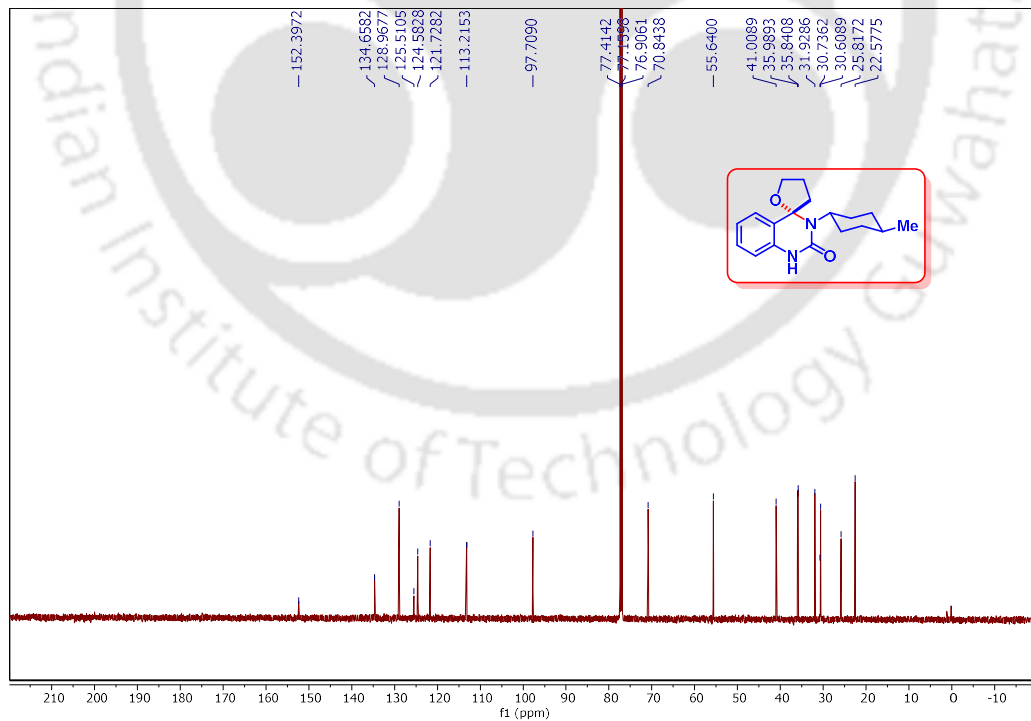


Figure 5.9.6. ¹³C{¹H} NMR spectrum of compound 2t (125 MHz, CDCl₃).

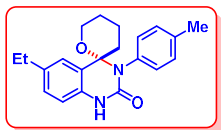


Figure 5.9.7. ^1H NMR spectrum of compound **2ab** (500 MHz, CDCl_3).

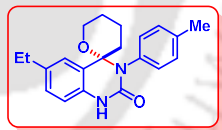


Figure 5.9.8. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of compound **2ab** (125 MHz, CDCl_3).

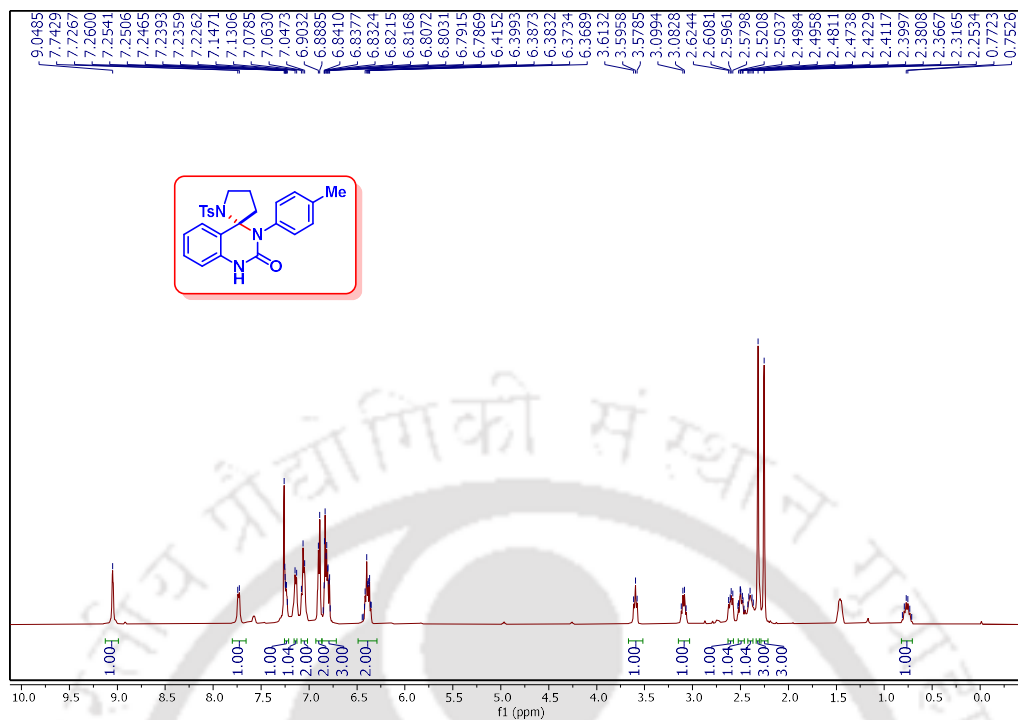


Figure 5.9.9. ¹H NMR spectrum of compound 8a (500 MHz, CDCl₃/DMSO-d₆).

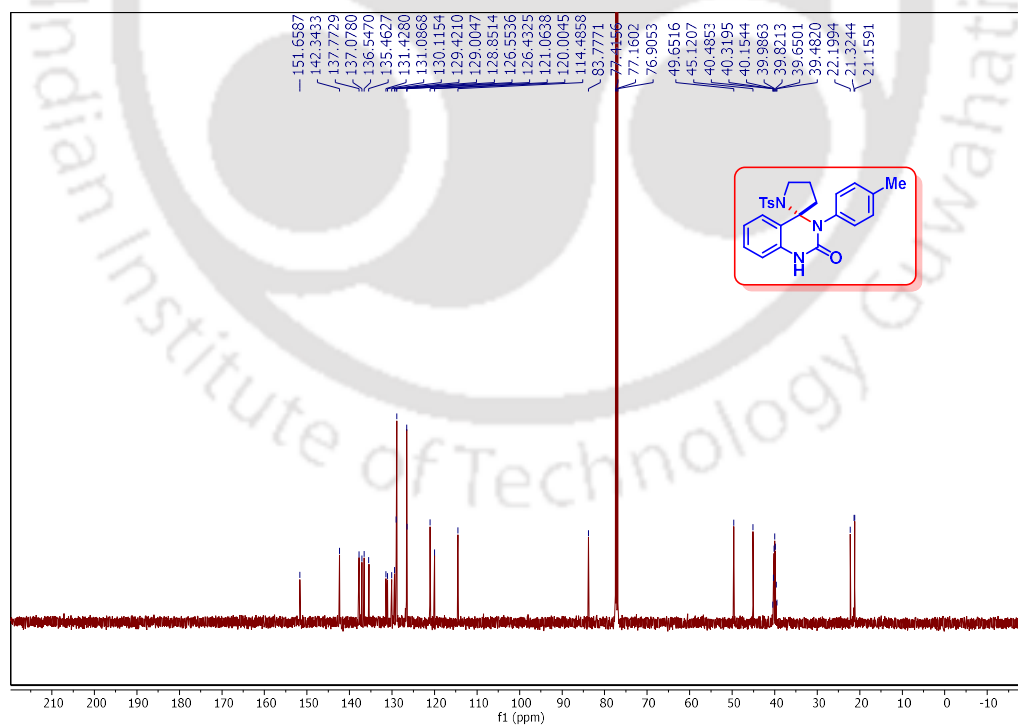


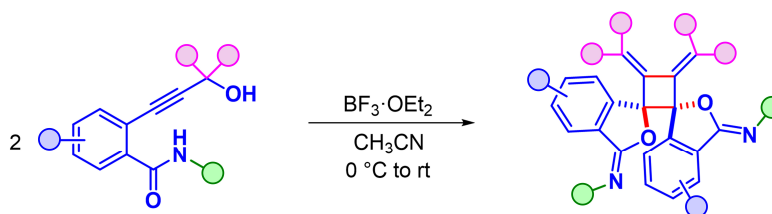
Figure 5.9.10. ¹³C{¹H} NMR spectrum of compound 8a (125 MHz, CDCl₃/DMSO-d₆).





CHAPTER VI

Regioselective Synthesis of Spiro-Isobenzofuran-Cyclobutanes from *o*-Alkynol Benzamides *via* Oxycyclization and [2+2] Cycloaddition Reaction



- Metal-free cascade protocol
- Highly strained dispiro-compound
- High regioselectivity
- Yields up to 96%

Abstract: A metal-free, highly regioselective synthesis of spiro-isobenzofuranimine-cyclobutanes has been unveiled. The strategy involves a cascade intramolecular oxycyclization followed by a [2+2] cycloaddition reaction sequence to deliver the highly strained functionalized spirocycle in good yields. The protocol's scalability is demonstrated through a scale-up experiment, and ongoing investigations are underway in the laboratory.



Chapter VI

Regioselective Synthesis of Spiro-Isobenzofuran Cyclobutanes from *o*-Alkynol Benzamides *via* Oxycyclization and [2+2] Cycloaddition Reaction

6.1 Introduction

Electrophile activated cyclization of alkynes has been well-established to be an indispensable tool for the construction of structurally divergent heterocyclic systems.¹ This protocol has been utilized in the synthesis of numerous biologically active heterocyclic scaffolds such as furans,^{2a} benzofurans,^{2b} indoles,^{2c} quinolines,^{2d} carbazoles,^{2e} benzothiophenes,^{2f} etc.

o-Alkynylbenzamides are highly versatile molecules that serve as fundamental building blocks in the regiodivergent synthesis of various heterocyclic systems. The intrinsic diversity of this synthesis stems from the unique mode of cyclization exhibited by the alkyne moiety (*exo* vs *endo*), combined with the chemoselective nucleophilicity facilitated by the N- or O-atom of the amide group (Figure 6.1.1).³ This regio- and chemoselective cyclization of *o*-alkynylbenzamides endures four possible isomers, with most studied conditions displaying significant selectivity for isobenzofuranimines. In this context, intramolecular oxycyclization plays a pivotal role in the formation of isobenzofuranimines derivatives.⁴ While sometimes the approach may lead to regioisomers but it can be modified by tweaking the catalytic system to selectively afford one particular isomer.

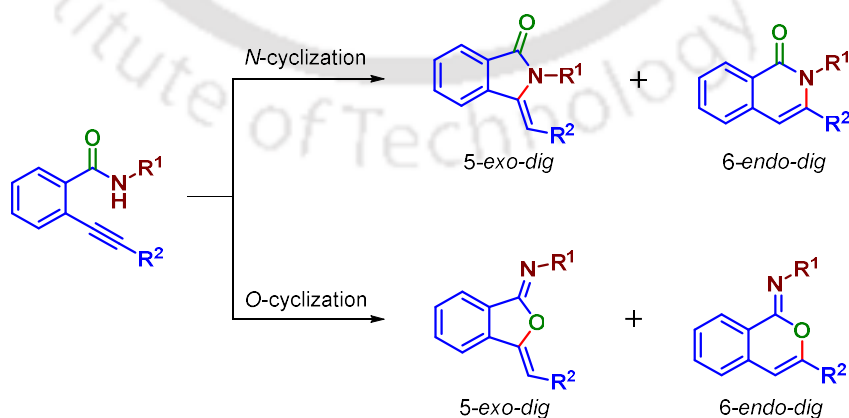
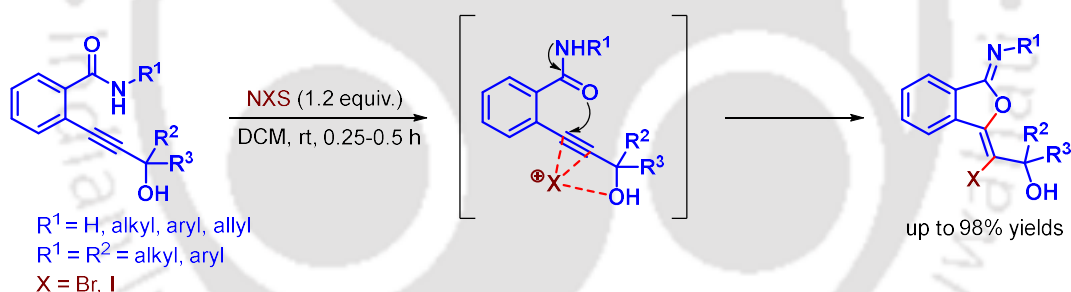


Figure 6.1.1. *Exo- vs endo*-mode of cyclization and *N- vs O*-selectivity.

Isobenzofuran derivatives constitute a significant class of organic compounds known for their extensive bioactive properties. These compounds are prevalent in various natural products and plant sources, where they contribute to the chemical diversity.⁵ Recent studies have highlighted the pharmacological potential of isobenzofuran derivatives, emphasizing their roles in cytotoxicity, anti-inflammatory, antifungal, and anticancer activities. Additionally, these compounds have shown promise in neuroprotective and antioxidant applications, further expanding their therapeutic relevance.⁶

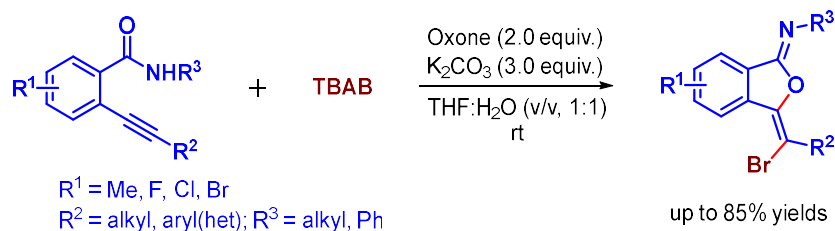
6.2. Differential Strategies Towards the Synthesis of Isobenzofuran Derivatives

Baire's group developed a NXS (X = Br and I) promoted intramolecular oxycyclization approach for the highly regioselective synthesis of halogenated isobenzofuranimines from *o*-alkynylbenzamides. The steric bulk and neighbouring group assistance of the substituent at the propargylic carbon of the alkyne were found to be crucial for achieving this regioselectivity (Scheme 6.2.1).⁷



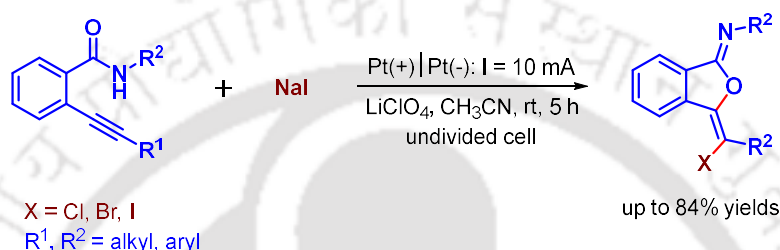
Scheme 6.2.1. NXS-promoted oxycyclization of *o*-alkynylbenzamides.

Qiu's group reported a TBAB-mediated 5-*exo-dig* oxycyclization of *o*-alkynylbenzamides for the synthesis of brominated isobenzofuranimines (Scheme 6.2.2).^{4c}



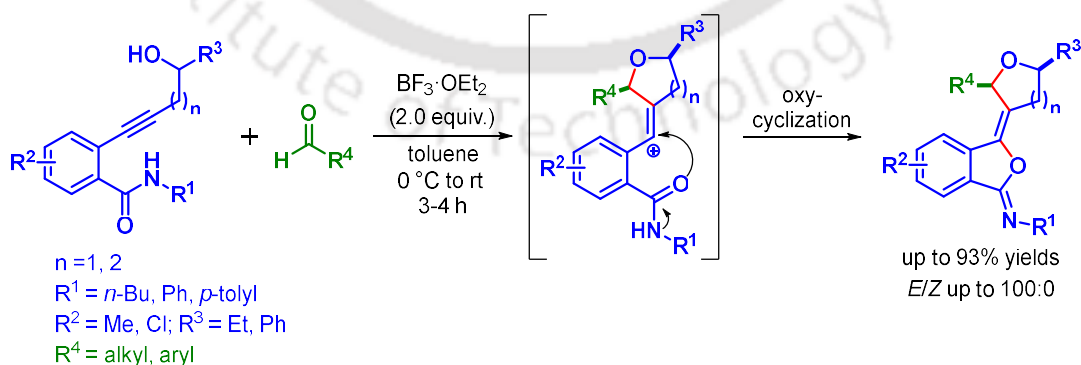
Scheme 6.2.2. TBAB-mediated oxycyclization of *o*-alkynylbenzamides.

Anandhan's group described an electrochemical oxidative 5-*exo-dig*-oxy-halocyclization of *o*-alkynylbenzamides for the synthesis of halogenated isobenzofuranimines using NaX (X = Cl, Br and I) as the halide source. Unlike other approaches where there is a need for stoichiometric amounts of oxidants and transition metal catalysts, this electrochemical approach demonstrates high regioselectivity and efficient conversion of starting materials to isobenzofuranimines in good yields (Scheme 6.2.3).⁸



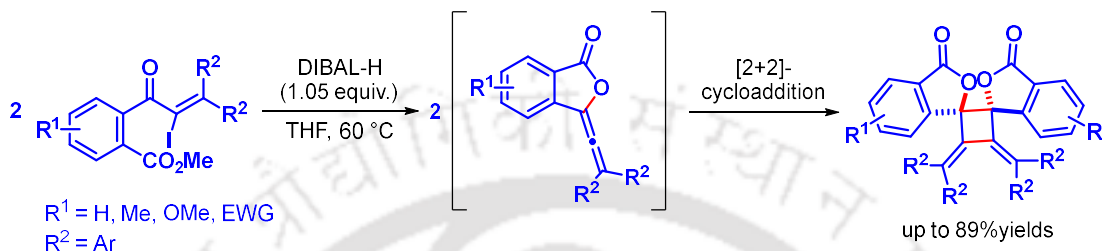
Scheme 6.2.3. Electrochemical oxidative oxy-halocyclization of *o*-alkynylbenzamides.

Saikia's group reported a metal-free protocol to synthesize dihydrofuranylidene-isobenzofuranimines from *o*-alkynolbenzamides and aldehydes. This process involves the formation of dihydrofuranylidene carbocation through an alkynyl Prins cyclization reaction followed by an intramolecular oxycyclization to furnish the desired product in moderate to good yields with an *E/Z* ratio up to 6:1. The strategy has also been extended to synthesize dihydropyranylidene-isobenzofuranimines in high yields (Scheme 6.2.4).⁹



Scheme 6.2.4. Cascade alkynyl Prins-intramolecular oxycyclization strategy.

Zhu's group reported an intermolecular [2+2]-cycloaddition of α -iodo-unsaturated ketones to synthesize trispirocyclic derivatives containing a cyclobutane ring. This process proceeds *via* lactonization of α -iodo-unsaturated ketones to an allenylic ester intermediate, followed by an intermolecular [2+2]-cycloaddition of the intermediate to afford the trispirocyclic derivatives (Scheme 6.2.5).¹⁰

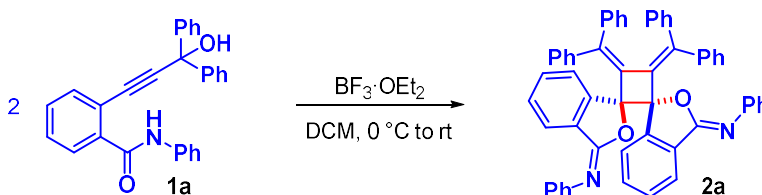


Scheme 6.2.5. Sequential lactonization-[2+2]-cycloaddition strategy.

6.3. Present Work

While there have been many reports on intramolecular oxycyclization strategies for constructing isobenzofuranimine scaffolds, cascade reactions in this context remain scarce. To address this gap, we aim to develop a cascade intramolecular oxycyclization-[2+2]-cycloaddition sequence of *o*-alkynolbenzamides, leading to the synthesis of spiro-isobenzofuranimine cyclobutane.

Initially, *o*-alkynolbenzamide **1a** was subjected to 2.0 equiv. of $\text{BF}_3 \cdot \text{OEt}_2$ in DCM under N_2 atmosphere. Gratifyingly, a new product was isolated in 88% yields within 2 h of the reaction (Table 6.4.1.1, entry 1). From the spectroscopic (^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR), HRMS and single crystal X-ray diffraction analysis of one of its derivatives **2j**, the structure of the isolated product was established to be 3',4'-bis(diphenylmethylene)- $\text{N}^3, \text{N}^{3''}$ -diphenyl-3*H*,3''*H*-dispiro[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (**2a**) (Scheme 6.3.1).



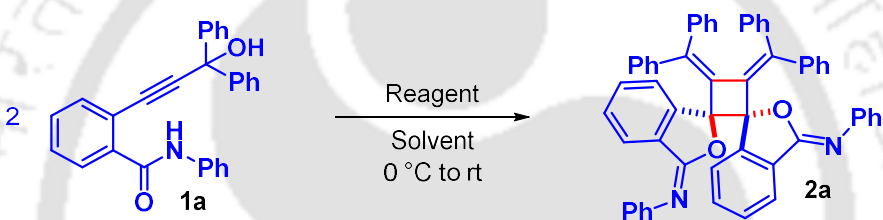
Scheme 6.3.1. Synthesis of spiro-isobenzofuranimine cyclobutene.

6.4. Results and Discussion

6.4.1. Optimization of the Reaction Conditions

Intrigued by the result, several optimizations were implemented to enhance the reaction outcomes. Changing the stoichiometry of $\text{BF}_3 \cdot \text{OEt}_2$ to 1.2 and 3.0 equiv. resulted the product in 71 and 87% yields, respectively (Table 6.4.1.1, entries 2 and 3). Solvent optimization revealed that the reaction in DCE, toluene, and CH_3CN afforded the product in 86, 25, and 93% yields, respectively (Table 6.4.1.1, entries 4-6). Further investigation into the effects of various reagents showed that metal triflates like $\text{Bi}(\text{OTf})_3$ and $\text{In}(\text{OTf})_3$ furnished the product in 71% and 80% yields, respectively

Table 6.4.1.1. Optimization of the reaction conditions



Entry ^a	Reagent	Equivalent	Solvent	Time (h)	Yield ^b (%)
1	$\text{BF}_3 \cdot \text{OEt}_2$	2.0	DCM	02	88
2	$\text{BF}_3 \cdot \text{OEt}_2$	1.2	DCM	24	72
3	$\text{BF}_3 \cdot \text{OEt}_2$	3.0	DCM	01	87
4	$\text{BF}_3 \cdot \text{OEt}_2$	2.0	DCE	01	86
5	$\text{BF}_3 \cdot \text{OEt}_2$	2.0	toluene	24	25
6	$\text{BF}_3 \cdot \text{OEt}_2$	2.0	CH_3CN	01	93
7	$\text{Bi}(\text{OTf})_3$	0.3	CH_3CN	24	71
8	$\text{In}(\text{OTf})_3$	0.3	CH_3CN	24	80
9	$\text{Cu}(\text{OTf})_2$	0.3	CH_3CN	24	31
10	$\text{Zn}(\text{OTf})_2$	0.3	CH_3CN	24	10
11	InCl_3	0.3	CH_3CN	24	10
12	FeCl_3	2.0	CH_3CN	04	74
13	$p\text{-TsOH} \cdot \text{H}_2\text{O}$	2.0	CH_3CN	24	31
14	CSA	2.0	CH_3CN	24	25

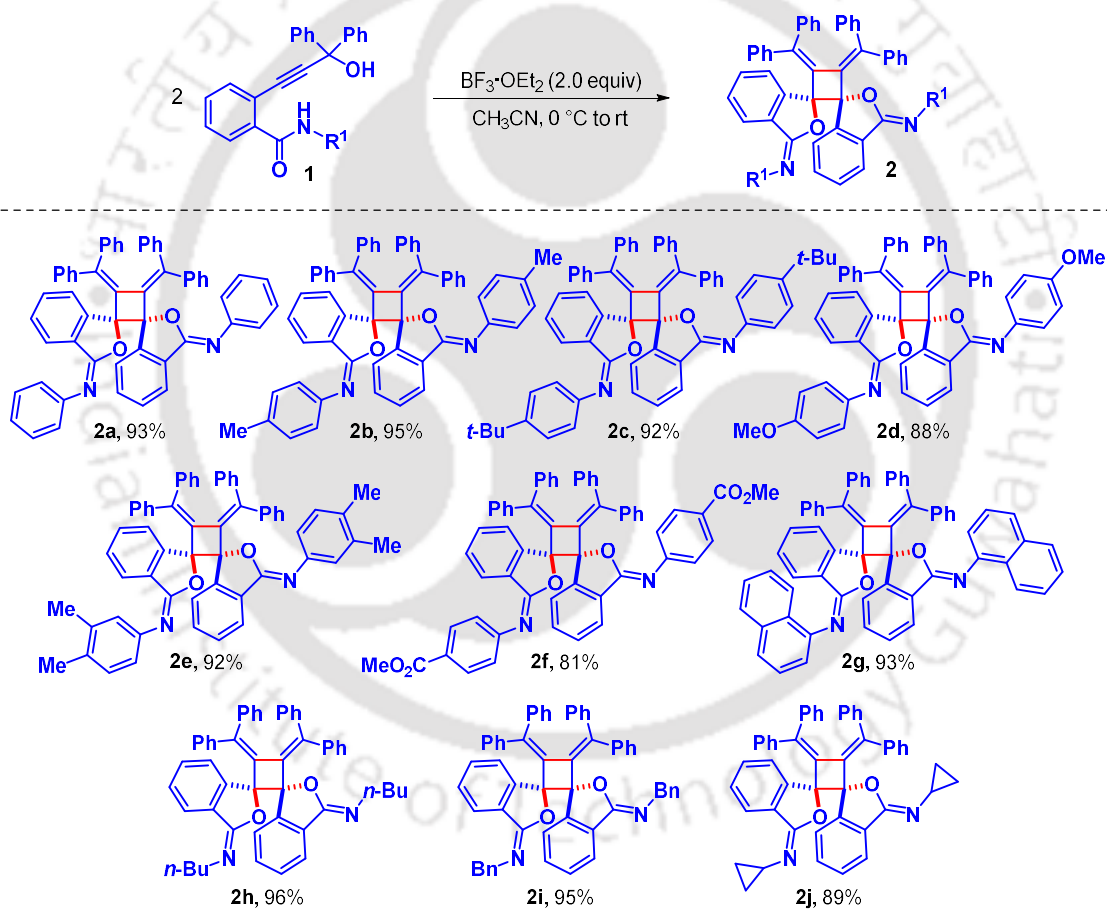
^aReactions conditions: **1a** (0.2 mmol), solvent (2.0 mL), 0 °C to rt, N_2 atmosphere.

^bIsolated yields.

(Table 6.4.1.1, entries 7 and 8), while $\text{Cu}(\text{OTf})_2$ and $\text{Zn}(\text{OTf})_2$ did not significantly improve the yields (Table 6.4.1.1, entries 9 and 10). Among metal halides, FeCl_3 produced 74% yield, whereas InCl_3 resulted in only 10% of the product (Table 6.4.1.1, entries 11 and 12). Brønsted acids, such as *p*-TsOH·H₂O and camphor sulfonic acid (CSA), had minimal influence on the reaction (Table 6.4.1.1, entries 13 and 14). Consequently, 2.0 equiv. of $\text{BF}_3\cdot\text{OEt}_2$ in CH_3CN at 0 °C to room temperature are determined to be the optimized condition for the reaction.

6.4.2. Substrate Scope

Scheme 6.4.2.1. Substrate scope of amides.

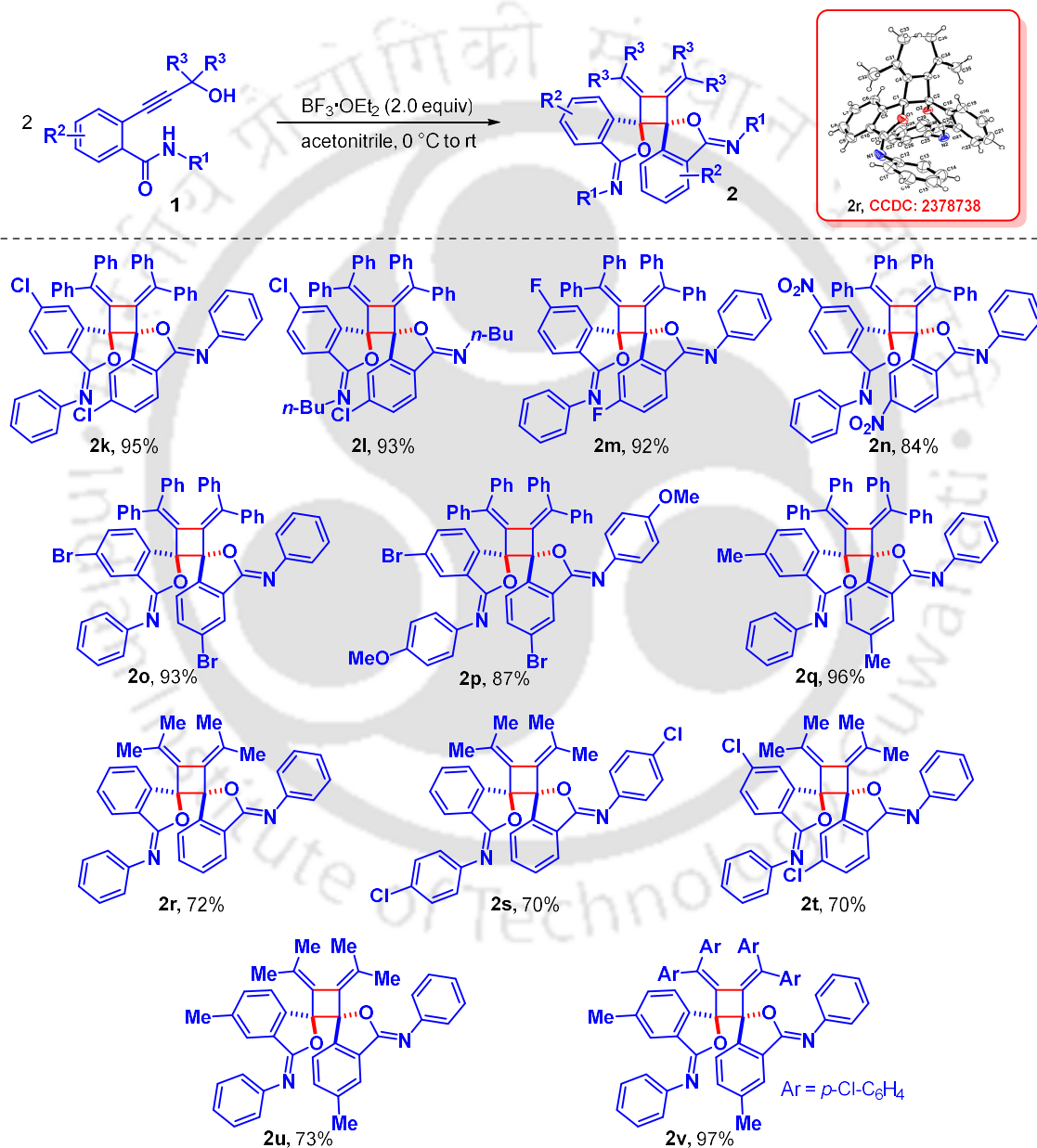


^aReaction conditions: **1** (0.4 mmol, 1.0 equiv.), $\text{BF}_3\cdot\text{OEt}_2$ (0.8 mmol, 2.0 equiv.), CH_3CN (4.0 mL), 0 °C to rt, N₂ atmosphere. ^bIsolated yields.

Having established the optimized condition for the transformation, the generality of the reaction was investigated with various functional groups in the amide part of the *o*-alkynolbenzamide **1** (Scheme 6.4.2.1). Altering the “R¹” substituent with a

phenyl group resulted the product **2a** in 93% yields. Incorporation of electron-donating aromatic groups like *p*-Me-C₆H₄, *p*-*t*-Bu-C₆H₄ and *p*-OMe-C₆H₄ in the “R¹” position delivered the products **2b**, **2c** and **2d** in 95, 92 and 88% yields, respectively. Dimethyl functionalized aromatic group furnished the product **2e** in 92% yield. Electron-withdrawing aromatic group (*p*-CO₂Me-C₆H₄) afforded **2f** in 81% yield.

Scheme 6.4.2.2. Synthesis of spiro-isobenzofuranimine cyclobutanes.

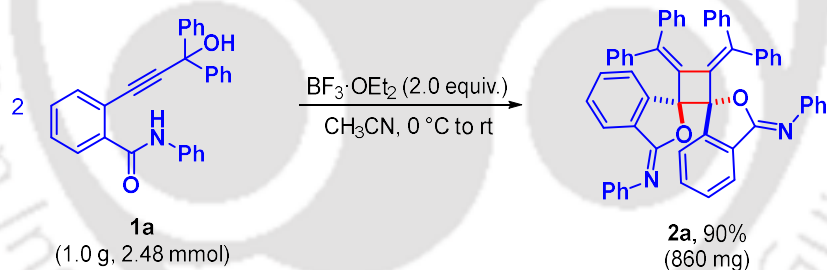


^aReaction conditions: **1** (0.4 mmol, 1.0 equiv.), $\text{BF}_3 \cdot \text{OEt}_2$ (0.8 mmol, 2.0 equiv.), CH_3CN (4.0 mL), 0 °C to rt, N_2 atmosphere. ^bIsolated yields.

α -Naphthyl group was also well-tolerated in the transformation, providing the product **2g** in 93% yield. Aliphatic (*n*-Bu), alkylaryl (benzyl) and alicyclic (cyclopropyl) groups endowed their corresponding products **2h**, **2i** and **2j** in 96, 95 and 89% yields, respectively.

To investigate the applicability of the transformation, a spectrum of functionalities was integrated at the “R²” position of *o*-alkynolbenzamide **1** (Scheme 6.4.2.2). Electron-withdrawing groups such as F, Cl, and NO₂ at the 4-position resulted their respective products **2k-2n** in 84-95% yields. Further, steering the substituents at the 5-position gave the products **2o**, **2p** and **2q** in 93, 87 and 96% yields, respectively. Switching the “R³” substituent of the benzamide **1** with Me and *p*-Cl-C₆H₄ groups, furnished the products **2r-2v** in 70-97% yields.

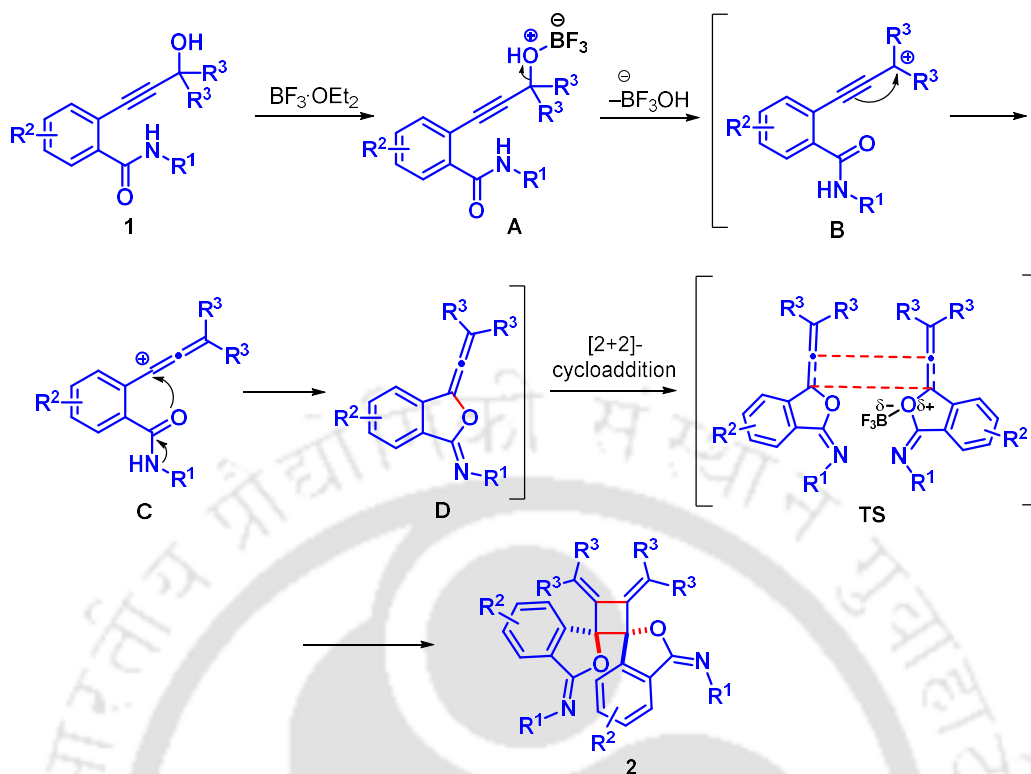
To demonstrate the scalability of this strategy, a scale-up synthesis with 2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)-*N*-phenylbenzamide (**1a**) (1.0 g, 2.48 mmol) was performed. Under the standard reaction conditions, the desired product **2a** was isolated in 90% yield (860 mg).



Scheme 6.4.2.2. Scale-up experiment.

6.4.3. Plausible Mechanism

With the established literature precedents,^{9,10} a plausible mechanism for this strategy is proposed in Scheme 6.4.3.1. In the presence of the Lewis acid (BF₃·OEt₂), the propargyl alcohol group of *o*-alkynolbenzamide **1** generates an allenic carbocation **C**. This carbocation **C** readily gets trapped by the O-atom of the proximal amide group through an intramolecular oxycyclization, leading to the formation of diarylvinyldiene-isobenzofuranimine **D**. Finally, a [2+2] cycloaddition between two molecules of intermediate **D** affords the dispirocyclic compound **2**.



Scheme 6.4.3.1. Plausible mechanism.

6.5. Conclusion

In conclusion, we have developed a metal-free, highly regio- and chemoselective approach for synthesizing spiro-isobenzofuranimines cyclobutanes from *o*-alkynolbenzamides. This strategy employs a cascade intramolecular oxycyclization followed by a [2+2] cycloaddition to construct the spirocyclic heterocycle. The method demonstrates excellent tolerance to various functional groups and delivers the product in good yields.

6.6. Experimental Section

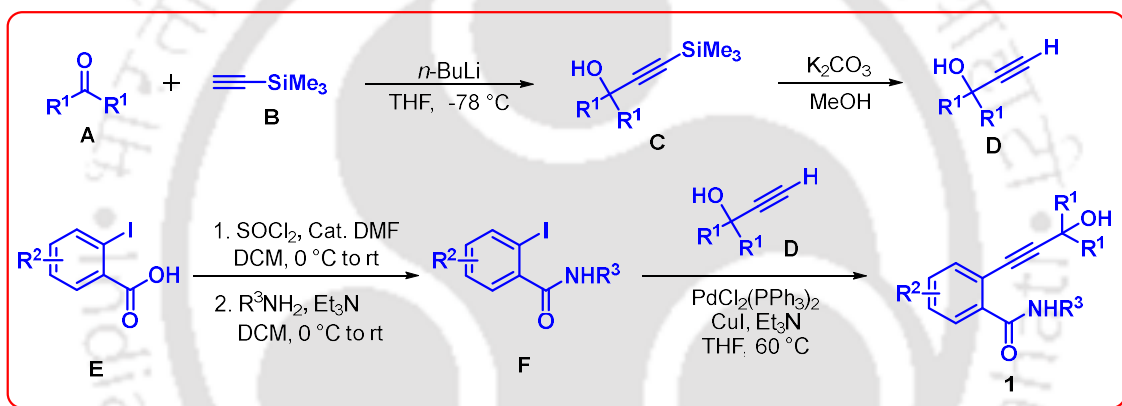
6.6.1. General Information

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

(500 MHz and 400 MHz) or $^{13}\text{C}\{^1\text{H}\}$ (126 MHz and 100 MHz) NMR. Chemical shifts (δ) are reported in ppm with abbreviations, s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, m = multiplet and spin-spin coupling constants (J) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

The starting materials, **1i**, **1s** and **1u** were synthesized according to the literature report, and the spectroscopic data of the compounds are in good agreement with the literature data.⁷

6.6.2. General procedure for the synthesis of starting materials 1a-1h, 1j-1r, 1t and 1v:



To a solution of ethynyltrimethylsilane **B** (5.0 mmol, 1.0 equiv.) in dry THF (10 mL) under N_2 atmosphere, $n\text{-BuLi}$ (5.5 mmol, 1.1 equiv.) was added dropwise at -78°C . After stirring the reaction for 0.5 h at -78°C , ketones **A** (5.0 mmol, 1.0 equiv.) in dry THF (2.0 mL) was added dropwise over a period of 5 minutes. The mixture was kept at the same temperature for 1.0 h and then it was brought to room temperature. The reaction was continued to stir at room temperature till all the starting material was consumed, as evident by TLC. It was then treated with saturated NH_4Cl solution, and the organic layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na_2SO_4 . The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the product **C**.

To an ice-cold solution of compound **C** (1.0 equiv.) in MeOH (10 mL), K_2CO_3 (3.0 equiv.) was added portion wise over a period of 5 minutes. The reaction was then warmed to room temperature and the progress of the reaction was monitored using TLC analysis. After completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl solution. The organic layer was extracted with EtOAc (2 x 15 mL), and the combined organic layers were further washed with brine, followed by drying over anhydrous Na_2SO_4 . The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the desired product **D**.

To an ice-cold stirred suspension of substituted 2-iodobenzoic acid **E** (4.0 mmol, 1.0 equiv.) in DCM (10 mL) in the presence of catalytic amount of DMF (5-7 drops per gram) under N_2 atmosphere, thionyl chloride (6.0 mmol, 1.5 equiv.) was added dropwise. The reaction was stirred for 1.0 h until the mixture became transparent. Excess thionyl chloride was then removed using a rotary evaporator to give a semi-solid residue. This residue was reacted with a primary amine (4.0 mmol, 1.0 equiv.) in DCM in the presence of triethylamine (6.0 mmol, 1.5 equiv.). The reaction mixture was stirred at 0 °C for 5 minutes, then allowed to warm to room temperature. The progress of the reaction was monitored by TLC analysis. Upon completion, the reaction mixture was quenched with saturated NH_4Cl solution. The organic layer was extracted with DCM (2 x 15 mL), and the combined organic layers were further washed with brine, followed by drying over anhydrous Na_2SO_4 . The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the desired product **F**.

To a mixture of $Pd(PPh_3)_2Cl_2$ (0.04 mmol, 0.04 equiv.), CuI (0.02 mmol, 0.02 equiv.) and substituted 2-iodobenzamides **F** (1.0 mmol, 1.0 equiv.) in dry THF (5.0 mL) under N_2 atmosphere, triethylamine (5.0 mmol, 5.0 equiv.) was added. The reaction mixture was stirred for 10 minutes at room temperature, after which the substituted propargyl alcohol **D** (1.2 mmol, 1.2 equiv.) was added dropwise over a period of 5 minutes. The reaction mixture was stirred for 24 hours (monitored by TLC analysis) before filtering through a pad of celite. The solids were washed with ethyl acetate, and the combined

filtrates were concentrated in a rotary evaporator. The crude product was then purified by column chromatography to provide the corresponding product **1**.

6.6.3. General procedure for the synthesis of compounds **2a-2j**:

To an ice-cold solution of alkynol substituted benzamide **1** (0.4 mmol, 1.0 equiv.) in CH₃CN (4.0 mL), BF₃·OEt₂ (0.8 mmol, 2.0 equiv.) was added under N₂ atmosphere. The reaction was continued to stir at room temperature till all the starting material was consumed, as evident by TLC. It was then treated with saturated NaHCO₃ solution, and the organic layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **2**.

6.6.4. Experimental procedure for scale-up synthesis of compound **2a**:

To an ice-cold solution of 2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)-*N*-phenylbenzamide (**1a**) (1.0 g, 2.48 mmol, 1.0 equiv.) in CH₃CN (10.0 mL), BF₃·OEt₂ (0.61 mL, 4.96 mmol, 2.0 equiv.) was added slowly under N₂ atmosphere. The reaction was continued to stir for 1.0 h at room temperature, and the progress of the reaction was monitored by TLC. It was then treated with saturated NaHCO₃ solution, and the organic layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na₂SO₄. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **2a** in 90% yield (860 mg).

6.7. References

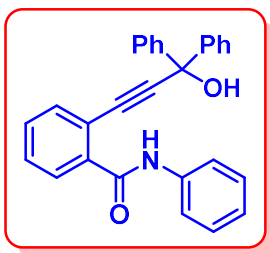
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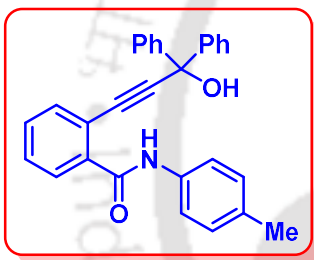
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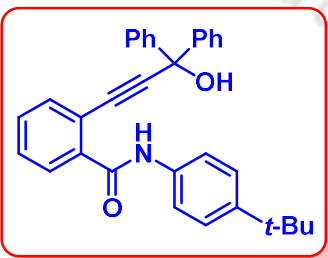
6.8. Characterization Data

2-(3-Hydroxy-3,3-diphenylprop-1-yn-1-yl)-N-phenylbenzamide (1a):

White semi-solid; R_f (Hexane:EtOAc, 3:2) 0.5. Yield 315 mg, 78%. ^1H NMR (500 MHz, CDCl_3) δ 8.74 (s, 1H), 8.02–7.98 (m, 1H), 7.61–7.56 (m, 5H), 7.45–7.41 (m, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.28–7.23 (m, 6H), 7.19 (t, J = 7.8 Hz, 2H), 7.05 (t, J = 7.3 Hz, 1H), 3.42–3.35 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 164.5, 144.4, 137.7, 136.3, 133.8, 130.8, 130.1, 129.4, 128.9, 128.5, 128.0, 126.0, 124.5, 120.3, 118.9, 99.1, 84.7, 75.0. IR (KBr, neat) ν 3351, 3060, 1651, 1599, 1537, 1489, 1447, 1324, 1249, 1177, 992, 892, 752, 697, 644 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{28}\text{H}_{21}\text{KNO}_2$ ($\text{M} + \text{K}$) $^+$ 442.1204, found 442.1203.

2-(3-Hydroxy-3,3-diphenylprop-1-yn-1-yl)-N-(*p*-tolyl)benzamide (1b):

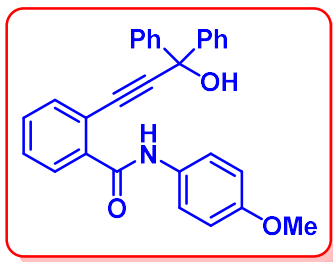
White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 136–138 °C. Yield 317 mg, 76 %. ^1H NMR (400 MHz, CDCl_3) δ 8.75 (s, 1H), 7.96 (s, 1H), 7.63–7.56 (m, 4H), 7.52 (s, 1H), 7.41–7.36 (m, 2H), 7.30–7.20 (m, 8H), 6.95 (d, J = 8.0 Hz, 2H), 3.76–3.58 (m, 1H), 2.26 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 164.4, 144.5, 136.1, 135.1, 134.0, 133.8, 130.6, 130.0, 129.3, 129.2, 128.4, 127.9, 126.0, 120.3, 118.9, 99.1, 84.6, 74.9, 20.9. IR (KBr, neat) ν 3351, 3059, 2922, 1646, 1597, 1514, 1448, 1320, 1246, 1032, 991, 815, 751, 696, 643 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{23}\text{NaNO}_2$ ($\text{M} + \text{Na}$) $^+$ 440.1621, found 440.1611.

N-(4-(*tert*-Butyl)phenyl)-2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)benzamide (1c):

White semi-solid; R_f (Hexane:EtOAc, 2:3) 0.5. Yield 354 mg, 77%. ^1H NMR (400 MHz, CDCl_3) δ 8.72 (s, 1H), 8.05–7.99 (m, 1H), 7.68–7.55 (m, 5H), 7.47–7.43 (m, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.30–7.23 (m, 8H), 3.62–3.33 (m, 1H), 1.34 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 164.5, 147.4, 144.4, 136.5, 135.1, 133.8, 130.7, 130.0, 129.3, 128.4, 127.9, 126.0, 125.7, 120.0, 118.9, 98.9, 84.7, 75.0, 34.4, 31.4. IR (KBr, neat) ν 3352, 2960, 1649, 1597, 1519, 1449, 1324, 1269, 1032,

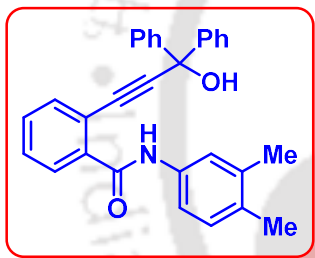
992, 834, 754, 698, 645, 608 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{32}\text{H}_{29}\text{NaNO}_2$ ($\text{M} + \text{Na}$)⁺ 482.2091, found 482.2079.

2-(3-Hydroxy-3,3-diphenylprop-1-yn-1-yl)-N-(4-methoxyphenyl)benzamide (1d):



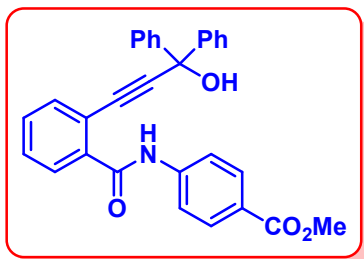
White solid; R_f (Hexane:EtOAc, 2:3) 0.4; mp 153–155 °C. Yield 363 mg, 82%. ^1H NMR (400 MHz, CDCl_3) δ 8.72 (s, 1H), 7.98–7.94 (m, 1H), 7.59–7.54 (m, 4H), 7.52–7.49 (m, 1H), 7.39–7.35 (m, 2H), 7.26–7.19 (m, 8H), 6.67–6.63 (m, 2H), 3.71 (s, 3H), 3.64 (s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 164.2, 156.4, 144.5, 136.0, 133.8, 130.8, 130.6, 130.1, 129.3, 128.5, 128.0, 126.0, 122.0, 118.8, 114.0, 99.2, 84.7, 74.9, 55.4. IR (KBr, neat) ν 3352, 3060, 2933, 2835, 1645, 1600, 1510, 1449, 1242, 1177, 1032, 992, 828, 754, 686 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{23}\text{NaNO}_3$ ($\text{M} + \text{Na}$)⁺ 456.1570, found 456.1560.

N-(3,4-Dimethylphenyl)-2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)benzamide (1e):



White solid; R_f (Hexane:EtOAc, 2:3) 0.5; mp 163–165 °C. Yield 349 mg, 81%. ^1H NMR (500 MHz, CDCl_3) δ 8.66 (s, 1H), 8.01 (s, 1H), 7.65–7.55 (m, 5H), 7.47–7.42 (m, 2H), 7.29–7.22 (m, 7H), 7.14 (d, J = 8.2 Hz, 1H), 6.96 (d, J = 8.1 Hz, 1H), 3.35–3.27 (m, 1H), 2.19 (s, 3H), 2.15 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 164.4, 144.4, 137.1, 136.5, 135.4, 133.7, 132.9, 130.6, 130.0, 129.9, 129.4, 128.5, 128.0, 126.0, 121.6, 118.8, 117.8, 98.9, 84.8, 75.0, 19.9, 19.2. IR (KBr, neat) ν 3354, 3062, 1650, 1595, 1533, 1449, 1403, 1317, 1175, 993, 893, 753, 698 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{25}\text{NaNO}_2$ ($\text{M} + \text{Na}$)⁺ 454.1778, found 454.1757.

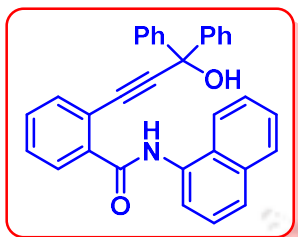
Methyl 4-(2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)benzamido)benzoate (1f):



White solid; R_f (Hexane:EtOAc, 2:3) 0.4, mp 108–110 °C. Yield 360 mg, 78%. ^1H NMR (500 MHz, CDCl_3) δ 9.13 (s, 1H), 8.06–8.01 (m, 1H), 7.82 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 7.2 Hz, 4H), 7.61–7.58 (m, 1H), 7.48–7.44 (m, 2H), 7.41 (d, J = 8.8 Hz, 2H), 7.33–7.27 (m, 6H), 3.90 (s, 3H), 3.88–3.78 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 166.7, 164.4, 144.3, 141.8, 135.2, 134.0, 131.2, 130.6, 130.4, 129.5, 128.5, 128.1, 126.0, 125.6, 119.4, 118.8, 99.9, 84.4, 74.9, 52.0. IR

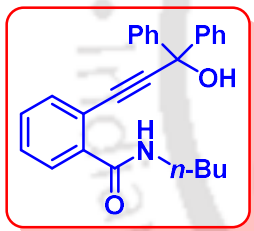
(KBr, neat) ν 3342, 3060, 2951, 1714, 1595, 1525, 1435, 1406, 1228, 1175, 1110, 1033, 992, 753, 696, 643 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{23}\text{NaNO}_4$ ($\text{M} + \text{Na}$) $^{+}$ 484.1519, found 484.1501.

2-(3-Hydroxy-3,3-diphenylprop-1-yn-1-yl)-N-(naphthalen-1-yl)benzamide (1g):



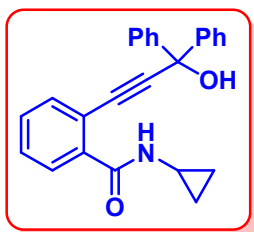
White solid; R_f (Hexane:EtOAc, 3:2) 0.6, mp 142–144 $^{\circ}\text{C}$. Yield 326 mg, 72%. ^1H NMR (500 MHz, CDCl_3) δ 9.04 (s, 1H), 8.12–8.07 (m, 1H), 7.83 (t, $J = 8.4$ Hz, 3H), 7.70 (d, $J = 8.2$ Hz, 1H), 7.68–7.65 (m, 1H), 7.51–7.40 (m, 8H), 7.27–7.23 (m, 1H), 7.12–7.05 (m, 6H), 3.18–2.98 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 165.4, 144.1, 136.4, 134.2, 133.9, 132.3, 130.9, 130.2, 129.4, 128.6, 128.2, 127.8, 127.7, 126.35, 126.26, 126.0, 125.8, 125.7, 121.6, 121.2, 119.2, 99.0, 85.1, 74.9. IR (KBr, neat) ν 3290, 3058, 1651, 1494, 1448, 1395, 1265, 1032, 993, 792, 756, 696, 643, 606 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{32}\text{H}_{23}\text{NaNO}_2$ ($\text{M} + \text{Na}$) $^{+}$ 476.1621, found 476.1611.

N-Butyl-2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)benzamide (1h):



White semi-solid; R_f (Hexane:EtOAc, 3:2) 0.5. Yield 280 mg, 73%. ^1H NMR (400 MHz, CDCl_3) δ 7.98–7.93 (m, 1H), 7.66–7.61 (m, 4H), 7.53–7.49 (m, 1H), 7.41–7.37 (m, 3H), 7.36–7.33 (m, 3H), 7.31–7.27 (m, 2H), 7.09 (s, 1H), 3.73–3.57 (m, 1H), 3.15 (q, $J = 6.6$ Hz, 2H), 1.27–1.16 (m, 4H), 0.81 (t, $J = 7.0$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 166.2, 144.6, 136.1, 133.6, 130.3, 129.9, 129.2, 128.5, 128.0, 126.1, 118.8, 98.2, 85.2, 74.8, 40.0, 31.3, 20.2, 13.7. IR (KBr, neat) ν 3300, 3060, 2957, 2869, 1631, 1534, 1448, 1305, 1265, 2033, 992, 751, 695, 643, 607 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{25}\text{NaNO}_2$ ($\text{M} + \text{Na}$) $^{+}$ 406.1778, found 406.1773.

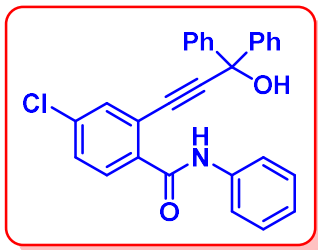
N-Cyclopropyl-2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)benzamide (1j):



White semi-solid; R_f (Hexane:EtOAc, 3:2) 0.5. Yield 323 mg, 88%. ^1H NMR (400 MHz, CDCl_3) δ 7.71–7.64 (m, 1H), 7.48–7.39 (m, 4H), 7.28–7.21 (m, 1H), 7.17–7.11 (m, 6H), 7.10–7.05 (m, 3H), 3.93 (s, 1H), 2.61–2.48 (m, 1H), 0.44–0.35 (m, 2H), 0.15–0.08 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 167.8, 144.7, 135.5, 133.5, 130.4, 129.8, 129.1, 128.4, 127.9, 126.0, 118.8, 98.4, 84.8, 74.8, 23.3, 6.3. IR (KBr, neat) ν 3369,

3063, 1638, 1593, 1527, 1489, 1450, 1277, 1176, 1048, 994, 894, 751, 698, 644 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{22}\text{NO}_2$ ($\text{M} + \text{H}$)⁺ 368.1645, found 368.1640.

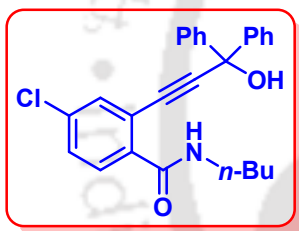
4-Chloro-2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)-N-phenylbenzamide (1k):



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 159–161 °C. Yield 359 mg, 82%. ^1H NMR (400 MHz, CDCl_3) δ 8.84 (s, 1H), 8.00–7.91 (m, 1H), 7.64–7.51 (m, 5H), 7.42–7.34 (m, 3H), 7.33–7.25 (m, 6H), 7.19 (t, J = 7.6 Hz, 2H), 7.08 (t, J = 7.3 Hz, 1H), 3.73 (s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

δ 163.5, 144.1, 137.3, 137.0, 134.2, 133.3, 131.7, 129.6, 128.9, 128.5, 128.4, 128.12, 128.08, 126.1, 126.0, 124.7, 120.43, 120.37, 100.5, 83.3, 74.9. IR (KBr, neat) ν 3358, 3063, 2925, 2854, 1656, 1598, 1538, 1490, 1447, 1323, 1177, 1091, 1031, 893, 753, 697, 643 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{28}\text{H}_{20}\text{ClNaNO}_2$ ($\text{M} + \text{Na}$)⁺ 460.1075, found 460.1066.

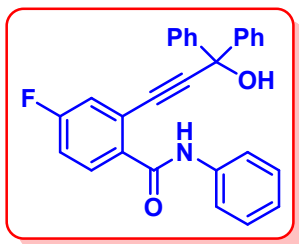
N-Butyl-4-chloro-2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)benzamide (1l):



White semi-solid; R_f (Hexane:EtOAc, 3:2) 0.5. Yield 301 mg, 72%. ^1H NMR (500 MHz, CDCl_3) δ 7.81 (d, J = 8.5 Hz, 1H), 7.63–7.59 (m, 4H), 7.39 (d, J = 2.2 Hz, 1H), 7.37–7.33 (m, 4H), 7.32–7.27 (m, 3H), 7.18 (t, J = 5.8 Hz, 1H), 4.38 (s, 1H), 3.12 (q, J = 6.8 Hz, 2H), 1.26–1.15 (m, 4H), 0.81 (t, J = 7.2 Hz, 3H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 165.2, 144.5, 136.5, 134.0, 132.9, 131.7, 129.4, 128.5, 128.0, 126.0, 120.3, 99.7, 83.6, 74.7, 40.1, 31.2, 20.1, 13.7. IR (KBr, neat) ν 3298, 3060, 2959, 2870, 2635, 1586, 1537, 1449, 1264, 1043, 1000, 875, 766, 735, 696, 643 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{24}\text{ClNaNO}_2$ ($\text{M} + \text{Na}$)⁺ 440.1388, found 440.1379.

4-Fluoro-2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)-N-phenylbenzamide (1m):

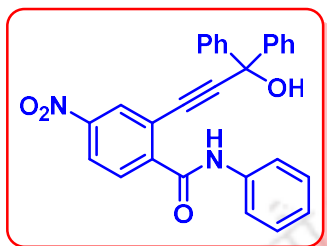


White semi-solid; R_f (Hexane:EtOAc, 3:2) 0.5. Yield 312 mg, 74%. ^1H NMR (500 MHz, CDCl_3) δ 8.78 (s, 1H), 8.02–7.97 (m, 1H), 7.60–7.56 (m, 4H), 7.33 (d, J = 8.0 Hz, 2H), 7.29–7.24 (m, 6H), 7.23–7.20 (m, 1H), 7.17 (t, J = 7.6 Hz, 2H), 7.12–7.08 (m, 1H), 7.05 (t, J = 7.4 Hz, 1H), 3.73–3.61 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR

(126 MHz, CDCl_3) δ 163.49, 163.47 (d, J = 253.5 Hz), 144.1, 137.5, 132.8 (d, J = 9.4 Hz), 132.3, 128.9, 128.5, 128.1, 126.0, 124.6, 121.0 (d, J = 10.1 Hz), 120.4, 120.2, 116.9 (d, J =

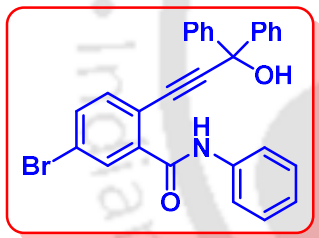
21.3 Hz), 100.3, 83.5, 74.9. ^{19}F NMR (471 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -111.8. IR (KBr, neat) ν 3324, 3063, 2952, 2874, 1688, 1590, 1528, 1472, 1456, 1323, 1176, 1090, 1032, 890, 751, 697, 642 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{28}\text{H}_{20}\text{FNaNO}_2$ ($\text{M} + \text{Na}$) $^+$ 444.1370, found 444.1375.

2-(3-Hydroxy-3,3-diphenylprop-1-yn-1-yl)-4-nitro-N-phenylbenzamide (1n):



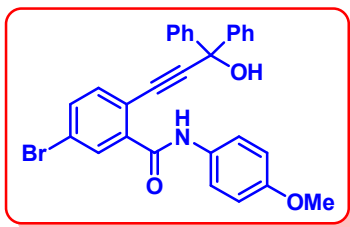
White solid; R_f (Hexane:EtOAc, 3:2) 0.4; mp 173–175 $^{\circ}\text{C}$. Yield 327 mg, 73%. ^1H NMR (400 MHz, CDCl_3) δ 8.65 (s, 1H), 8.36 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.6 Hz, 1H), 7.58–7.47 (m, 4H), 7.37 (d, J = 8.0 Hz, 2H), 7.28–7.18 (m, 8H), 7.08 (t, J = 7.4 Hz, 1H), 3.27 (s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 162.6, 148.7, 143.7, 141.6, 137.1, 131.5, 129.1, 128.7, 128.5, 128.4, 126.0, 125.2, 123.8, 120.7, 120.4, 101.4, 82.6, 75.1. IR (KBr, neat) ν 3522, 3359, 3059, 2923, 1659, 1599, 1530, 1444, 1352, 1320, 1245, 1042, 1005, 882, 753, 734, 693, 610, 508 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{28}\text{H}_{20}\text{NaN}_2\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 471.1315, found 471.1290.

5-Bromo-2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)-N-phenylbenzamide (1o):



White semi-solid; R_f (Hexane:EtOAc, 3:2) 0.5. Yield 381 mg, 79%. ^1H NMR (500 MHz, CDCl_3) δ 8.70 (s, 1H), 8.06 (s, 1H), 7.52–7.48 (m, 4H), 7.46 (dd, J = 8.3, 2.1 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.27–7.23 (m, 2H), 7.21–7.16 (m, 6H), 7.09 (t, J = 7.6 Hz, 2H), 6.98 (t, J = 7.2 Hz, 1H), 3.54 (s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 163.0, 144.1, 137.5, 137.3, 135.1, 133.9, 133.1, 128.9, 128.5, 128.4, 128.1, 126.1, 126.0, 124.7, 123.8, 120.4, 117.8, 100.3, 83.7, 75.0. IR (KBr, neat) ν 3351, 3058, 1651, 1598, 1538, 1489, 1444, 1321, 1275, 1261, 1031, 894, 825, 750, 697 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{28}\text{H}_{20}\text{BrKNO}_2$ ($\text{M} + \text{K}$) $^+$ 520.0309, found 520.0293.

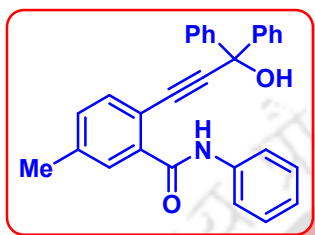
5-Bromo-2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)-N-(4-methoxyphenyl)benzamide (1p):



White solid; R_f (Hexane:EtOAc, 3:2) 0.4; 136–138 $^{\circ}\text{C}$. Yield 461 mg, 90%. ^1H NMR (400 MHz, CDCl_3) δ 8.77 (s, 1H), 8.10 (s, 1H), 7.59–7.52 (m, 4H), 7.47 (dd, J = 8.2, 2.2 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.27–7.19 (m, 6H), 7.15 (d, J = 8.9 Hz, 2H), 6.60 (d, J = 9.0 Hz, 2H), 4.07–3.91 (m, 1H),

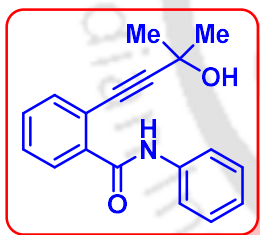
3.70 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 162.6, 156.5, 144.3, 144.2, 137.2, 135.1, 133.7, 133.1, 130.4, 128.5, 128.0, 126.0, 123.7, 122.1, 117.7, 114.0, 100.4, 83.7, 74.9, 55.4. IR (KBr, neat) ν 343, 3060, 2833, 1634, 1539, 1509, 1450, 1238, 1175, 1030, 994, 825, 771, 749, 697, 642 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{22}\text{BrNaNO}_3$ ($\text{M} + \text{Na}$) $^+$ 534.0675, found 534.0670.

2-(3-Hydroxy-3,3-diphenylprop-1-yn-1-yl)-5-methyl-N-phenylbenzamide (1q):



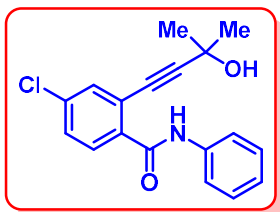
White semi-solid; R_f (Hexane:EtOAc, 3:2) 0.5. Yield 351 mg, 84%. ^1H NMR (400 MHz, CDCl_3) δ 8.75 (s, 1H), 7.84 (s, 1H), 7.59–7.56 (m, 4H), 7.48 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 7.9 Hz, 2H), 7.27–7.21 (m, 7H), 7.18 (t, J = 7.6 Hz, 2H), 7.04 (t, J = 7.3 Hz, 1H), 3.16 (s, 1H), 2.38 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 164.6, 144.4, 140.0, 137.7, 136.0, 133.9, 131.6, 130.7, 128.9, 128.5, 128.0, 126.0, 124.4, 120.2, 115.8, 98.4, 84.9, 75.0, 21.5. IR (KBr, neat) ν 3355, 3057, 1656, 1598, 1537, 1490, 1444, 1319, 1177, 1030, 751, 696, 541 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{23}\text{NaNO}_2$ ($\text{M} + \text{Na}$) $^+$ 440.1621, found 418.1790.

2-(3-Hydroxy-3-methylbut-1-yn-1-yl)-N-phenylbenzamide (1r):



White solid; R_f (Hexane:EtOAc, 3:2) 0.5, mp 111–113 $^{\circ}\text{C}$. Yield 229 mg, 82%. ^1H NMR (500 MHz, CDCl_3) δ 8.93 (s, 1H), 8.05–8.02 (m, 1H), 7.72 (d, J = 7.9 Hz, 2H), 7.51–7.46 (m, 1H), 7.45–7.40 (m, 2H), 7.34 (t, J = 7.3 Hz, 2H), 7.13 (t, J = 7.4 Hz, 1H), 2.69–2.44 (m, 1H), 1.58 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 164.6, 137.9, 136.1, 133.6, 130.8, 130.0, 129.1, 129.0, 124.6, 120.2, 119.1, 101.2, 80.2, 65.7, 31.4. IR (KBr, neat) ν 3354, 2981, 1654, 1600, 1539, 1499, 1446, 1325, 1258, 1164, 963, 910, 753, 692 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{17}\text{KNO}_2$ ($\text{M} + \text{K}$) $^+$ 318.0891, found 318.0892.

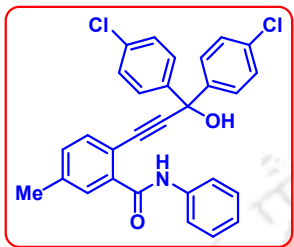
4-Chloro-2-(3-hydroxy-3-methylbut-1-yn-1-yl)-N-phenylbenzamide (1t):



White solid; R_f (Hexane:EtOAc, 3:2) 0.5; mp 96–98 $^{\circ}\text{C}$. Yield 267 mg, 85%. ^1H NMR (500 MHz, CDCl_3) δ 9.01 (s, 1H), 7.98–7.93 (m, 1H), 7.68 (d, J = 7.9 Hz, 2H), 7.43–7.39 (m, 1H), 7.38–7.34 (m, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.12 (t, J = 7.4 Hz, 1H), 2.90 (s, 1H), 1.57 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 163.6, 137.6, 137.0, 134.0, 133.1,

131.6, 129.3, 129.1, 124.8, 120.7, 120.3, 102.6, 79.0, 65.6, 31.2. IR (KBr, neat) ν 3353, 2981, 2928, 1720, 1650, 1599, 1540, 1443, 1325, 1274, 1168, 1080, 929, 887, 752, 690 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{16}\text{ClNaNO}_2$ ($\text{M} + \text{Na}$)⁺ 336.0762, found 336.0752.

2-(3,3-bis(4-Chlorophenyl)-3-hydroxyprop-1-yn-1-yl)-5-methyl-N-phenylbenzamide (1v):



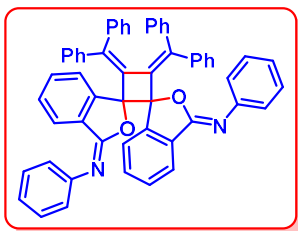
White semi-solid; R_f (Hexane:EtOAc, 3:2) 0.5. Yield 404 mg, 83%. ^1H NMR (500 MHz, CDCl_3) δ 8.45 (s, 1H), 7.67 (s, 1H), 7.46 (d, J = 8.7 Hz, 4H), 7.38 (dd, J = 8.1, 2.8 Hz, 1H), 7.32 (d, J = 7.9 Hz, 2H), 7.22–7.14 (m, 7H), 7.09 (t, J = 7.3 Hz, 1H), 4.16–4.05 (m, 1H), 2.37 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 165.0, 142.8, 140.0, 137.4, 136.5, 133.9, 133.7, 131.6, 130.1, 128.9, 128.6, 127.4, 124.7, 120.1, 115.7, 96.9, 85.1, 73.9, 21.4. IR (KBr, neat) ν 3322, 3059, 2923, 2222, 1906, 1649, 1597, 1533, 1487, 1442, 1401, 1322, 1249, 1174, 1091, 1047, 1013, 993, 902, 821, 780, 751, 736, 690, 604, 532, 509 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{21}\text{Cl}_2\text{NaNO}_2$ ($\text{M} + \text{Na}$)⁺ 508.0842, found 508.0823.

General procedure for the synthesis of compounds 2a-2v:

To an ice-cold solution of alkynol substituted benzamide **1** (0.4 mmol, 1.0 equiv.) in acetonitrile (4.0 mL), $\text{BF}_3 \cdot \text{OEt}_2$ (0.8 mmol, 2.0 equiv.) was added under N_2 atmosphere. The reaction was continued to stir at room temperature till all the starting material was consumed, as evident by TLC. It was then treated with saturated NaHCO_3 solution, and the organic layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were further washed with brine, followed by drying over anhydrous Na_2SO_4 . The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the final product **2**.

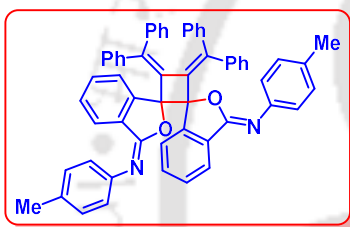
Characterization data of compounds 2a-2v:

(3Z,3''E)-3',4'-bis(Diphenylmethylene)-N³,N^{3''}-diphenyl-3H,3''H-dispiro[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2a):



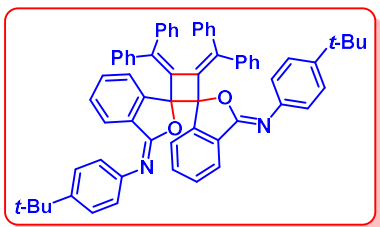
Yellow solid; R_f (Hexane:EtOAc, 9:1) 0.5, mp 150–152 °C. Yield 143 mg, 93%. ^1H NMR (500 MHz, CDCl_3) δ 7.74 (dd, J = 10.6, 7.7 Hz, 4H), 7.57 (t, J = 7.5 Hz, 2H), 7.50 (t, J = 7.5 Hz, 2H), 7.14 (t, J = 7.5 Hz, 2H), 7.07 (t, J = 7.7 Hz, 4H), 6.97–6.91 (m, 12H), 6.79 (t, J = 7.6 Hz, 4H), 6.69 (d, J = 7.6 Hz, 4H), 6.50 (d, J = 7.8 Hz, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 156.2, 145.9, 145.8, 140.4, 140.4, 139.4, 133.3, 131.6, 130.7, 129.3, 129.2, 129.0, 128.1, 127.9, 127.78, 127.76, 127.4, 123.5, 123.39, 123.37, 95.0. IR (KBr, neat) ν 3081, 3055, 3022, 1690, 1590, 1488, 1467, 1443, 1293, 1276, 1205, 1096, 1073, 1038, 986, 752, 692, 670 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{56}\text{H}_{39}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 771.3006, found 771.2999.

(3Z,3'E)-3',4'-bis(Diphenylmethylene)- $N^3,N^{3''}$ -di-*p*-tolyl-3H,3''H-dispiro[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2b):



Yellow solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 199–201 °C. Yield 152 mg, 95%. ^1H NMR (400 MHz, CDCl_3) δ 7.80 (d, J = 7.6 Hz, 2H), 7.71 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.5 Hz, 2H), 7.49 (t, J = 7.4 Hz, 2H), 7.12 (t, J = 7.4 Hz, 2H), 6.97–6.91 (m, 10H), 6.88 (d, J = 8.0 Hz, 4H), 6.78 (t, J = 7.6 Hz, 4H), 6.70 (d, J = 7.3 Hz, 4H), 6.47 (d, J = 8.0 Hz, 4H), 2.28 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 155.8, 145.8, 143.0, 140.4, 140.3, 139.3, 133.5, 133.0, 131.4, 131.0, 129.3, 129.1, 129.0, 128.4, 128.0, 127.9, 127.7, 127.4, 123.5, 123.5, 123.3, 95.0, 21.0. IR (KBr, neat) ν 3024, 2920, 2347, 1777, 1685, 1607, 1571, 1506, 1491, 1467, 1443, 1291, 1264, 1201, 1095, 1072, 1040, 983, 812, 768, 734, 695, 668, 613, 581, 529 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{58}\text{H}_{43}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 799.3319, found 799.3317.

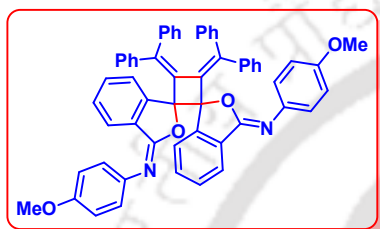
(3Z,3'E)- $N^3,N^{3''}$ -bis(4-(*tert*-Butyl)phenyl)-3',4'-bis(diphenylmethylene)-3H,3''H-dispiro-[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2c):



Yellow solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 202–204 °C. Yield 162 mg, 92%. ^1H NMR (400 MHz, CDCl_3) δ 7.78 (d, J = 7.6 Hz, 2H), 7.71 (d, J = 7.6 Hz, 2H), 7.53 (td, J = 7.5, 1.2 Hz, 2H), 7.46 (td, J = 7.5, 1.1 Hz, 2H), 7.12–7.06 (m, 6H), 6.97 (d, J = 8.1 Hz, 4H), 6.93 (t, J = 7.6

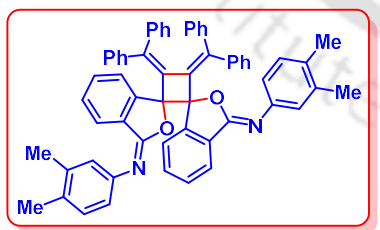
Hz, 6H), 6.79 (t, $J = 7.7$ Hz, 4H), 6.71 (d, $J = 7.6$ Hz, 4H), 6.54 (d, $J = 8.6$ Hz, 4H), 1.31 (s, 18H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 155.8, 146.4, 145.6, 142.8, 140.4, 140.3, 139.3, 133.7, 131.3, 131.0, 129.3, 129.1, 129.0, 128.0, 127.9, 127.7, 127.4, 124.5, 123.5, 123.3, 95.0, 34.3, 31.5. IR (KBr, neat) ν 3053, 2960, 2903, 2866, 1778, 1688, 1603, 1508, 1467, 1292, 1265, 1095, 983, 832, 767, 736, 693, 668, 579, 557 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{64}\text{H}_{55}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 883.4258, found 883.4248.

(3Z,3''E)-3',4'-bis(Diphenylmethylene)-N³,N^{3''}-bis(4-methoxyphenyl)-3H,3''H-dispiro-[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2d):



Yellow solid; R_f (Hexane:EtOAc, 4:1) 0.5; mp 236–238 °C. Yield 146 mg, 88%. ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, $J = 7.7$ Hz, 2H), 7.73 (d, $J = 7.6$ Hz, 2H), 7.61 (td, $J = 7.5, 1.1$ Hz, 2H), 7.49 (td, $J = 7.5, 1.0$ Hz, 2H), 7.10 (tt, $J = 7.5, 1.3$ Hz, 2H), 6.97 (d, $J = 7.9$ Hz, 4H), 6.94 (t, $J = 7.7$ Hz, 6H), 6.80 (t, $J = 7.6$ Hz, 4H), 6.71 (d, $J = 7.3$ Hz, 4H), 6.63–6.57 (m, 8H), 3.77 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 156.0, 155.3, 145.8, 140.4, 140.0, 139.3, 138.6, 133.4, 131.3, 131.1, 129.2, 128.9, 128.0, 127.9, 127.7, 127.4, 125.2, 123.5, 123.1, 112.9, 94.9, 55.3. IR (KBr, neat) ν 3356, 3052, 2950, 2834, 1682, 1604, 1504, 1466, 1442, 1240, 1201, 1034, 982, 833, 769, 733, 694, 667 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{58}\text{H}_{43}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 831.3217, found 831.3219.

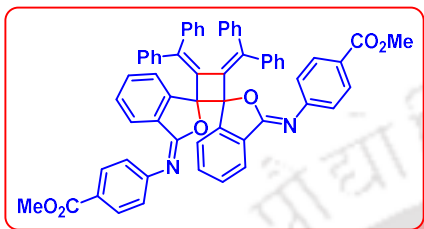
(3Z,3''E)-N³,N^{3''}-bis(3,4-Dimethylphenyl)-3',4'-bis(diphenylmethylene)-3H,3''H-dispiro-[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2e):



Yellow solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 272–274 °C. Yield 152 mg, 92%. ^1H NMR (500 MHz, CDCl_3) δ 7.81 (d, $J = 7.7$ Hz, 2H), 7.73 (d, $J = 7.7$ Hz, 2H), 7.58 (t, $J = 7.4$ Hz, 2H), 7.49 (t, $J = 7.5$ Hz, 2H), 7.13 (t, $J = 7.4$ Hz, 2H), 6.97–6.91 (m, 10H), 6.84 (d, $J = 8.0$ Hz, 2H), 6.78 (t, $J = 7.7$ Hz, 4H), 6.69 (d, $J = 7.6$ Hz, 4H), 6.42 (s, 2H), 6.34 (d, $J = 7.5$ Hz, 2H), 2.19 (s, 6H), 2.12 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 155.6, 145.8, 143.3, 140.4, 140.1, 139.3, 135.6, 133.6, 131.6, 131.4, 131.1, 129.3, 129.1, 128.9, 128.9, 128.0, 127.9, 127.8, 127.4, 124.7, 123.5, 123.2, 121.0, 94.9, 19.8, 19.3. IR (KBr, neat) ν 3052, 2921, 2854, 1777, 1686, 1602,

1499, 1467, 1444, 1295, 1091, 981, 823, 766, 735, 696, 668 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{60}\text{H}_{48}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 827.3632, found 827.3596.

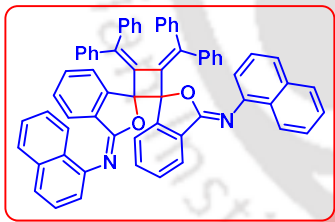
Methyl 4-(((3Z,3''E)-3'-((4-acetoxyphenyl)imino)-3',4'-bis(diphenylmethylene)-3H,3''H-dispiro[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3-ylidene)amino)benzoate (2f):



Brown solid; R_f (Hexane:EtOAc, 4:1) 0.5; mp 215–217 °C. Yield 144 mg, 81%. ^1H NMR (400 MHz, CDCl_3) δ 7.77–7.71 (m, 8H), 7.63 (t, J = 7.4 Hz, 2H), 7.56 (t, J = 7.5 Hz, 2H), 7.16 (t, J = 7.6 Hz, 2H), 6.96 (t, J = 7.7 Hz, 4H), 6.93–6.88 (m, 6H), 6.78 (t, J = 7.7

Hz, 4H), 6.65 (d, J = 7.6 Hz, 4H), 6.41 (d, J = 8.2 Hz, 4H), 3.89 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 167.2, 157.1, 150.5, 146.4, 140.6, 140.1, 139.3, 132.4, 132.3, 130.1, 129.6, 129.5, 129.2, 128.9, 128.2, 128.1, 127.8, 127.5, 125.1, 123.8, 123.2, 123.0, 95.1, 51.9. IR (KBr, neat) ν 3351, 3060, 2960, 2867, 1649, 1597, 1519, 1449, 1324, 1169, 1031, 833, 753, 697, 644 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{60}\text{H}_{43}\text{N}_2\text{O}_6$ ($\text{M} + \text{H}$)⁺ 887.3116, found 887.3116.

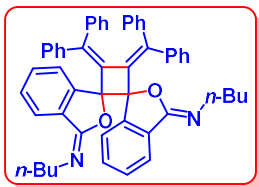
(3Z,3''E)-3',4'-bis(Diphenylmethylene)-N³,N^{3''}-di(naphthalen-1-yl)-3H,3''H-dispiro[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2g):



Brown solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 219–221 °C. Yield 162 mg, 93%. ^1H NMR (500 MHz, CDCl_3) δ 7.87 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 7.8 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 7.6 Hz, 2H), 7.51 (d, J = 8.1 Hz, 2H), 7.45 (t, J = 7.4 Hz, 2H), 7.42–7.36 (m, 4H), 7.30 (t, J = 7.6 Hz, 2H),

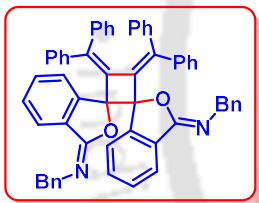
7.20 (t, J = 7.7 Hz, 2H), 7.02 (t, J = 7.4 Hz, 2H), 6.90–6.87 (m, 4H), 6.86–6.82 (m, 6H), 6.74 (t, J = 7.6 Hz, 4H), 6.63 (d, J = 7.5 Hz, 4H), 6.41 (d, J = 7.3 Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 156.5, 145.5, 142.3, 140.7, 140.4, 139.3, 133.8, 133.5, 131.6, 130.8, 129.3, 129.2, 129.0, 128.5, 128.2, 127.9, 127.6, 127.3, 125.5, 125.3, 124.8, 124.4, 123.6, 123.5, 123.4, 117.5, 95.3. IR (KBr, neat) ν 3053, 2924, 1688, 1573, 1491, 1468, 1443, 1393, 1293, 1259, 1223, 1094, 985, 949, 796, 770, 718, 698, 576 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{64}\text{H}_{43}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 871.3319, found 871.3320.

(3Z,3''E)-N³,N^{3''}-Dibutyl-3',4'-bis(diphenylmethylene)-3H,3''H-dispiro[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2h):



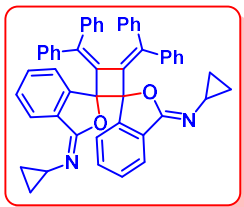
Yellow solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 155–157 °C. Yield 140 mg, 96%. ^1H NMR (500 MHz, CDCl_3) δ 7.86 (d, J = 7.6 Hz, 2H), 7.61 (d, J = 7.7 Hz, 2H), 7.57 (t, J = 7.6 Hz, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.14 (t, J = 7.6 Hz, 2H), 7.03–6.98 (m, 8H), 6.95 (t, J = 7.5 Hz, 2H), 6.83 (t, J = 7.5 Hz, 4H), 6.75 (d, J = 7.5 Hz, 4H), 2.75–2.69 (m, 2H), 2.66–2.61 (m, 2H), 1.04–0.91 (m, 8H), 0.67 (t, J = 6.8 Hz, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 157.0, 146.1, 140.6, 139.8, 139.4, 134.3, 130.8, 130.6, 129.2, 129.0, 128.9, 128.0, 127.8, 127.7, 127.5, 122.9, 93.8, 46.8, 32.1, 20.5, 13.9. IR (KBr, neat) ν 3056, 2956, 2929, 2869, 1776, 1698, 1657, 1491, 1443, 1264, 1073, 985, 734, 698, 614 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{52}\text{H}_{47}\text{N}_2\text{O}_2$ ($M + \text{H}$)⁺ 731.3632, found 731.3634.

(3Z,3''E)-N³,N^{3''}-Dibenzyl-3',4'-bis(diphenylmethylene)-3H,3''H-dispiro[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2i):



Yellow solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 213–215 °C. Yield 152 mg, 95%. ^1H NMR (500 MHz, CDCl_3) δ 7.94 (d, J = 7.6 Hz, 2H), 7.69 (d, J = 7.7 Hz, 2H), 7.60 (t, J = 7.5 Hz, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.18 (t, J = 7.4 Hz, 2H), 7.12–7.08 (m, 6H), 7.07–7.01 (m, 8H), 6.97 (t, J = 7.4 Hz, 2H), 6.92–6.88 (m, 4H), 6.84 (t, J = 7.6 Hz, 4H), 6.79 (d, J = 7.6 Hz, 4H), 3.97 (d, J = 14.7 Hz, 2H), 3.75 (d, J = 14.7 Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 157.5, 146.2, 140.5, 140.3, 139.7, 139.5, 133.9, 131.3, 130.6, 129.2, 129.1, 128.1, 128.11, 128.07, 127.92, 127.88, 127.5, 126.3, 123.4, 122.8, 94.1, 51.0. IR (KBr, neat) ν 3056, 3027, 2926, 1449, 1778, 1697, 1605, 1492, 1467, 1444, 1292, 1072, 975, 730, 695 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{58}\text{H}_{43}\text{N}_2\text{O}_2$ ($M + \text{H}$)⁺ 799.3319, found 799.3318.

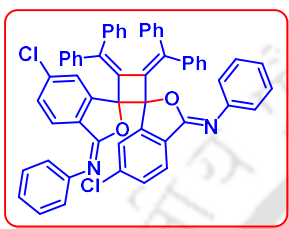
(3Z,3''E)-N³,N^{3''}-Dicyclopropyl-3',4'-bis(diphenylmethylene)-3H,3''H-dispiro[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2j):



Yellow solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 211–213 °C. Yield 124 mg, 89%. ^1H NMR (500 MHz, CDCl_3) δ 7.84 (d, J = 7.6 Hz, 2H), 7.56–7.48 (m, 4H), 7.37 (t, J = 7.5 Hz, 2H), 7.15 (t, J = 7.3 Hz, 2H), 7.05–6.99 (m, 8H), 6.95 (t, J = 7.4 Hz, 2H), 6.82 (t, J = 7.6 Hz, 4H),

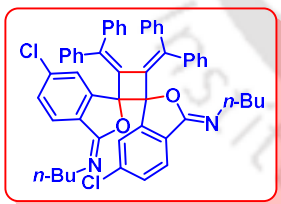
6.78 (d, $J = 7.6$ Hz, 4H), 2.61–2.55 (m, 2H), 0.49–0.44 (m, 2H), 0.43–0.30 (m, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 158.0, 145.2, 140.6, 139.6, 139.5, 134.6, 130.8, 130.5, 129.3, 129.0, 128.8, 127.9, 127.7, 127.4, 123.0, 122.5, 94.1, 29.2, 7.6, 7.5. IR (KBr, neat) ν 3054, 2925, 2853, 1777, 1694, 1491, 1467, 1290, 1153, 1037, 986, 761, 735, 696, 663 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{50}\text{H}_{39}\text{N}_2\text{O}_2$ ($M + \text{H}$) $^+$ 699.3006, found 699.3000.

(3Z,3'E)-6,6''-Dichloro-3',4'-bis(diphenylmethylene)-N³,N^{3''}-diphenyl-3H,3''H-dispiro-[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2k):



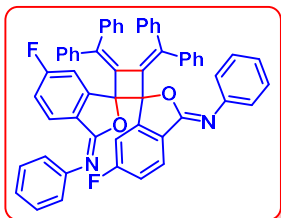
Brown solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 116–118 °C. Yield 160 mg, 95%. ^1H NMR (500 MHz, CDCl_3) δ 7.53 (s, 2H), 7.48 (d, $J = 8.2$ Hz, 2H), 7.32 (dd, $J = 8.2, 1.8$ Hz, 2H), 7.17–7.14 (m, 4H), 7.03 (t, $J = 7.3$ Hz, 2H), 6.96 (t, $J = 7.4$ Hz, 2H), 6.88 (t, $J = 7.6$ Hz, 4H), 6.84 (d, $J = 7.3$ Hz, 2H), 6.78 (d, $J = 7.7$ Hz, 4H), 6.69–6.64 (m, 8H), 6.62 (d, $J = 7.8$ Hz, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 154.6, 146.2, 145.4, 141.8, 140.0, 139.0, 137.8, 132.8, 129.9, 129.7, 129.5, 128.9, 128.34, 128.28, 128.2, 127.8, 127.3, 124.6, 124.1, 123.8, 123.2, 95.0. IR (KBr, neat) ν 3058, 2925, 1688, 1590, 1489, 1444, 1421, 1321, 1278, 1204, 1106, 1037, 991, 870, 830, 756, 694, 663, 543 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{56}\text{H}_{37}\text{Cl}_2\text{N}_2\text{O}_2$ ($M + \text{H}$) $^+$ 839.2227, found 839.2214.

(3Z,3'E)-N³,N^{3''}-Dibutyl-6,6''-dichloro-3',4'-bis(diphenylmethylene)-3H,3''H-dispiro-[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2l):



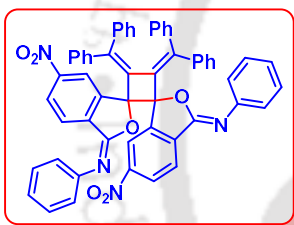
Yellow solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 163–165 °C. Yield 149 mg, 93%. ^1H NMR (500 MHz, CDCl_3) δ 7.69 (d, $J = 1.2$ Hz, 2H), 7.47 (d, $J = 8.2$ Hz, 2H), 7.34 (dd, $J = 8.3, 1.8$ Hz, 2H), 7.13 (t, $J = 7.4$ Hz, 2H), 7.02 (t, $J = 7.6$ Hz, 4H), 6.99–6.94 (m, 6H), 6.85–6.80 (m, 8H), 2.94–2.83 (m, 4H), 1.21–1.06 (m, 8H), 0.76 (t, $J = 7.0$ Hz, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 155.7, 146.3, 140.9, 140.2, 139.4, 136.9, 133.5, 129.6, 129.4, 129.4, 128.2, 128.2, 127.8, 127.5, 124.0, 123.5, 93.9, 47.1, 32.2, 20.6, 13.9. IR (KBr, neat) ν 3056, 2956, 2929, 2868, 1779, 1700, 1646, 1579, 1463, 1265, 1099, 1074, 990, 828, 735, 696, 659 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{52}\text{H}_{45}\text{Cl}_2\text{N}_2\text{O}_2$ ($M + \text{H}$) $^+$ 799.2853, found 799.2854.

(3Z,3'E)-3',4'-bis(Diphenylmethylene)-6,6''-difluoro-N³,N^{3''}-diphenyl-3H,3''H-dispiro-[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2m):



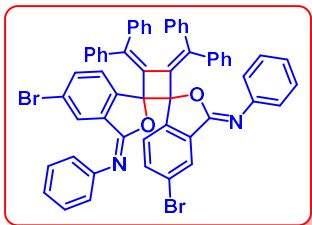
Yellow solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 124–126 °C. Yield 148 mg, 92%. ^1H NMR (500 MHz, CDCl_3) δ 7.69 (s, 2H), 7.31 (dd, J = 8.0, 2.2 Hz, 2H), 7.19–7.13 (m, 8H), 7.03 (t, J = 7.3 Hz, 2H), 6.99 (t, J = 7.5 Hz, 4H), 6.94 (t, J = 7.4 Hz, 2H), 6.87 (d, J = 7.8 Hz, 4H), 6.77 (d, J = 7.6 Hz, 4H), 6.74 (d, J = 8.2 Hz, 4H), 6.62 (d, J = 7.8 Hz, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 165.1 (d, J = 253.2 Hz), 155.0, 147.3 (d, J = 9.6 Hz), 145.4, 141.7, 140.0, 139.0, 132.5, 129.4, 129.0, 128.29, 128.27, 128.1, 127.8, 127.4, 126.8, 125.6, 124.1, 123.0, 117.4 (d, J = 24.1 Hz), 110.7 (d, J = 24.7 Hz), 94.8. ^{19}F NMR (471 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ -119.5. IR (KBr, neat) ν 3057, 1781, 1689, 1592, 1488, 1442, 1263, 1073, 993, 828, 737, 693, 664, 555 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{56}\text{H}_{37}\text{F}_2\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 807.2818, found 807.2820.

(3Z,3'E)-3',4'-bis(Diphenylmethylene)-6,6''-dinitro- $N^3,N^{3''}$ -diphenyl-3H,3''H-dispiro-[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2n):



Yellow solid; R_f (Hexane:EtOAc, 4:1) 0.4; mp 199–201 °C. Yield 145 mg, 84%. ^1H NMR (400 MHz, CDCl_3) δ 8.41 (d, J = 2.0 Hz, 2H), 8.21 (dd, J = 8.4, 2.0 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.22 (t, J = 7.7 Hz, 4H), 7.12–7.06 (m, 4H), 7.01–6.94 (m, 6H), 6.89 (d, J = 7.4 Hz, 4H), 6.85–6.81 (m, 8H), 6.79 (t, J = 7.8 Hz, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 152.9, 149.8, 144.6, 144.4, 143.2, 139.6, 138.9, 136.7, 132.2, 129.6, 129.1, 128.7, 128.52, 128.47, 127.9, 127.4, 125.3, 124.7, 124.4, 123.3, 119.4, 95.5. IR (KBr, neat) ν 3057, 2924, 2853, 1787, 1689, 1592, 1531, 1488, 1443, 1345, 1292, 1202, 1118, 1070, 1036, 991, 893, 755, 692, 656, 581 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{56}\text{H}_{37}\text{N}_4\text{O}_6$ ($\text{M} + \text{H}$) $^+$ 861.2708, found 861.2708.

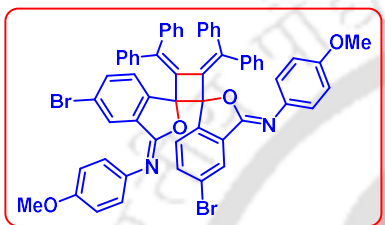
(3Z,3'E)-5,5''-Dibromo-3',4'-bis(diphenylmethylene)- $N^3,N^{3''}$ -diphenyl-3H,3''H-dispiro-[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2o):



Yellow solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 240–242 °C. Yield 173 mg, 93%. ^1H NMR (500 MHz, CDCl_3) δ 7.87 (s, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.18–7.12 (m, 6H), 7.03–6.98 (m, 6H), 6.94 (t, J = 7.5 Hz, 2H), 6.90 (d, J = 7.8 Hz, 4H), 6.78 (t, J = 7.6 Hz, 4H), 6.72 (d, J = 7.6 Hz, 4H), 6.53

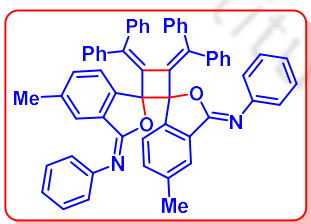
(d, $J = 7.7$ Hz, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 154.3, 145.3, 144.1, 141.1, 140.0, 139.1, 134.7, 132.9, 132.5, 129.3, 128.9, 128.3, 128.2, 128.0, 127.9, 127.4, 126.6, 124.8, 124.1, 123.3, 123.2, 94.9. IR (KBr, neat) ν 3056, 2963, 2924, 1784, 1688, 1591, 1488, 1421, 1258, 1202, 1094, 1026, 985, 799, 756, 691, 612 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{56}\text{H}_{37}\text{Br}_2\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 929.1196, found 929.1162.

(3Z,3'E)-5,5''-Dibromo-3',4'-bis(diphenylmethylene)-N³,N^{3''}-bis(4-methoxyphenyl)-3H,3''H-dispiro[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2p):



Yellow solid; R_f (Hexane:EtOAc, 4:1) 0.5; mp 150–152 °C. Yield 172 mg, 87%. ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, $J = 1.2$ Hz, 2H), 7.67 (dd, $J = 8.1, 1.7$ Hz, 2H), 7.64 (d, $J = 8.0$ Hz, 2H), 7.12 (tt, $J = 7.4, 1.3$ Hz, 2H), 6.97 (d, $J = 7.8$ Hz, 4H), 6.95–6.90 (m, 6H), 6.80 (dd, $J = 8.5, 7.1$ Hz, 4H), 6.74–6.69 (m, 4H), 6.68–6.64 (m, 4H), 6.62–6.57 (m, 4H), 3.79 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 156.5, 153.2, 144.0, 140.6, 140.0, 139.1, 138.2, 134.3, 133.3, 132.7, 129.2, 128.9, 128.3, 128.2, 127.9, 127.5, 126.5, 125.2, 124.4, 123.3, 113.2, 94.8, 55.4. IR (KBr, neat) ν 3007, 2834, 1686, 1600, 1505, 1464, 1443, 1424, 1275, 1259, 1242, 1200, 1036, 983, 828, 764, 750, 699 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{58}\text{H}_{41}\text{Br}_2\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 989.1408, found 989.1407.

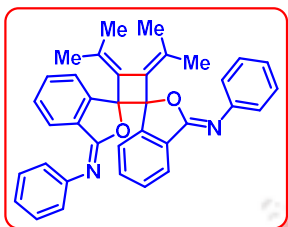
(3Z,3'E)-3',4'-bis(Diphenylmethylene)-5,5''-dimethyl-N³,N^{3''}-diphenyl-3H,3''H-dispiro-[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2q):



Yellow solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 187–189 °C. Yield 153 mg, 96%. ^1H NMR (400 MHz, CDCl_3) δ 7.62 (d, $J = 7.8$ Hz, 2H), 7.56 (s, 2H), 7.37 (d, $J = 7.7$ Hz, 2H), 7.13 (t, $J = 7.4$ Hz, 2H), 7.05 (t, $J = 7.6$ Hz, 4H), 6.97 (d, $J = 7.7$ Hz, 4H), 6.95–6.90 (m, 8H), 6.79 (t, $J = 7.6$ Hz, 4H), 6.70 (d, $J = 7.2$ Hz, 4H), 6.49 (d, $J = 7.7$ Hz, 4H), 2.49 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 156.5, 145.8, 143.5, 140.4, 140.0, 139.4, 139.3, 133.4, 132.8, 130.8, 129.2, 129.0, 128.0, 127.8, 127.73, 127.70, 127.4, 123.6, 123.51, 123.48, 122.9, 94.9, 21.4. IR (KBr, neat) ν 3057, 2927, 1684,

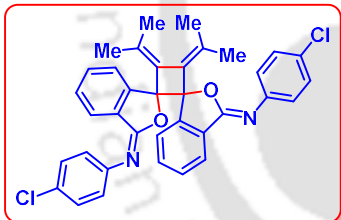
1593, 1489, 1444, 1295, 1210, 1038, 987, 899, 755, 694 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{58}\text{H}_{43}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 799.3319, found 799.3307.

(3Z,3'E)-N³,N^{3'}-Diphenyl-3',4'-di(propan-2-ylidene)-3H,3''H-dispiro[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2r):



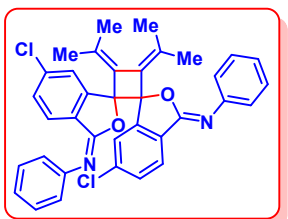
White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 173–175 °C. Yield 75 mg, 72%. ^1H NMR (400 MHz, CDCl_3) δ 7.89 (d, J = 7.3 Hz, 2H), 7.59–7.55 (m, 2H), 7.54 (dd, J = 7.3, 1.4 Hz, 2H), 7.50 (d, J = 7.1 Hz, 2H), 7.16 (t, J = 7.7 Hz, 4H), 7.03 (t, J = 7.2 Hz, 2H), 6.79 (d, J = 7.3 Hz, 4H), 1.94 (s, 6H), 1.49 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 156.9, 146.0, 144.1, 131.7, 131.0, 130.6, 130.3, 129.2, 128.3, 123.9, 123.7, 123.6, 123.4, 94.9, 23.8, 20.6. IR (KBr, neat) ν 3355, 2974, 2925, 2854, 1770, 1682, 1590, 1488, 1440, 1293, 1204, 1097, 973, 737, 753, 692 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{36}\text{H}_{31}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 523.2380, found 523.2378.

(3Z,3'E)-N³,N^{3'}-bis(4-Chlorophenyl)-3',4'-di(propan-2-ylidene)-3H,3''H-dispiro[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2s):



White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 143–145 °C. Yield 83 mg, 70%. ^1H NMR (400 MHz, CDCl_3) δ 7.86 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 7.4 Hz, 2H), 7.54 (t, J = 7.5 Hz, 2H), 7.50 (d, J = 7.6 Hz, 2H), 7.10 (d, J = 8.6 Hz, 4H), 6.71 (d, J = 8.5 Hz, 4H), 1.96 (s, 6H), 1.49 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 157.2, 144.5, 144.1, 131.9, 131.2, 130.3, 130.1, 129.4, 129.1, 128.4, 125.0, 123.6, 123.5, 95.1, 23.8, 20.6. IR (KBr, neat) ν 2979, 2925, 2854, 1774, 1681, 1488, 1470, 1288, 1204, 1092, 1009, 976, 824, 770, 736, 504 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{36}\text{H}_{29}\text{Cl}_2\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 591.1601, found 591.1588.

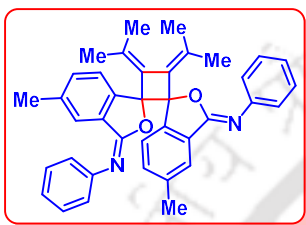
(3Z,3'E)-6,6''-Dichloro-N³,N^{3'}-diphenyl-3',4'-di(propan-2-ylidene)-3H,3''H-dispiro[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2t):



White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 210–212 °C. Yield 83 mg, 70%. ^1H NMR (500 MHz, CDCl_3) δ 7.82 (d, J = 8.1 Hz, 2H), 7.54–7.46 (m, 4H), 7.29–7.24 (m, 4H), 7.09 (t, J = 7.4 Hz, 2H), 6.88 (d, J = 7.5 Hz, 4H), 1.96 (s, 6H), 1.50 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$

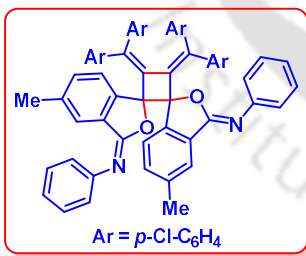
NMR (126 MHz, CDCl_3) δ 155.2, 145.4, 145.2, 138.2, 132.3, 130.0, 129.9, 129.1, 128.6, 124.6, 124.5, 123.9, 123.6, 94.5, 24.0, 20.7. IR (KBr, neat) ν 2924, 2853, 1777, 1690, 1607, 1591, 1489, 1465, 1419, 1368, 1263, 1126, 1105, 1072, 1014, 983, 862, 832, 763, 746, 719, 694, 662, 501 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{36}\text{H}_{29}\text{Cl}_2\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 591.1601, found 591.1596.

(3Z,3''E)-5,5''-Dimethyl-N³,N^{3''}-diphenyl-3',4'-di(propan-2-ylidene)-3H,3''H-dispiro[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2u):



White solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 174–176 °C. Yield 80 mg, 73%. ^1H NMR (500 MHz, CDCl_3) δ 7.69 (s, 2H), 7.37 (s, 4H), 7.15 (t, J = 7.6 Hz, 4H), 7.03 (t, J = 7.2 Hz, 2H), 6.80 (d, J = 7.8 Hz, 4H), 2.49 (s, 6H), 1.93 (s, 6H), 1.48 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 157.1, 146.1, 141.5, 139.3, 132.9, 130.8, 130.5, 128.2, 123.8, 123.7, 123.5, 123.3, 94.9, 23.8, 21.4, 20.6. IR (KBr, neat) ν 2988, 2917, 2857, 1771, 1678, 1591, 1489, 1442, 1367, 1291, 1263, 1208, 1170, 1103, 1072, 1009, 973, 896, 800, 757, 736, 692, 553, 508 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{38}\text{H}_{35}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 551.2693, found 551.2691

(3Z,3''E)-3',4'-bis(bis(4-Chlorophenyl)methylene)-5,5''-dimethyl-N³,N^{3''}-diphenyl-3H,3''H-dispiro[isobenzofuran-1,1'-cyclobutane-2',1''-isobenzofuran]-3,3''-diimine (2v):



Yellow solid; R_f (Hexane:EtOAc, 9:1) 0.5; mp 294–296 °C. Yield 182 mg, 97%. ^1H NMR (500 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 7.62 (s, 2H), 7.49 (d, J = 7.8 Hz, 2H), 7.40 (d, J = 7.8 Hz, 2H), 7.04 (t, J = 7.5 Hz, 4H), 6.94 (t, J = 7.4 Hz, 2H), 6.88 (d, J = 7.8 Hz, 4H), 6.78 (d, J = 8.4 Hz, 4H), 6.74 (d, J = 8.6 Hz, 4H), 6.50 (d, J = 8.0 Hz, 4H), 6.45 (d, J = 7.8 Hz, 4H), 2.50 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 156.6, 145.1, 142.8, 140.1, 138.1, 137.9, 137.0, 134.6, 134.5, 133.9, 133.2, 130.3, 130.1, 130.0, 128.1, 127.85, 127.81, 123.9, 123.2, 122.7, 94.4, 21.4. IR (KBr, neat) ν 2924, 2853, 1693, 1596, 1489, 1441, 1275, 1260, 1091, 1015, 833, 767, 750, 696 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{58}\text{H}_{39}\text{Cl}_4\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 935.1760, found 935.1739.

6.8.1. Crystallographic Description

Table 6.8.1.1. Crystal parameters of compound **2r**

Compound 2r	CCDC 2378738
Formula	C ₃₆ H ₃₀ N ₂ O ₂
Formula weight	522.62
<i>T</i> /K	297(2)
Crystal system	Triclinic
Space group	P -1
<i>a</i> /Å	9.9036(16)
<i>b</i> /Å	11.8774(19)
<i>c</i> /Å	13.099(2)
α /°	83.336(5)
β /°	71.897(4)
γ /°	79.790(5)
<i>V</i> /Å ³	1438.3(4)
<i>Z</i>	2
Abs. Coeff./mm ⁻¹	0.075
Abs. Correction	none
GOF on <i>F</i> ²	1.150
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.0724 <i>wR</i> ₂ = 0.1407
<i>R</i> indices [all data]	<i>R</i> ₁ = 0.1212 <i>wR</i> ₂ = 0.1729

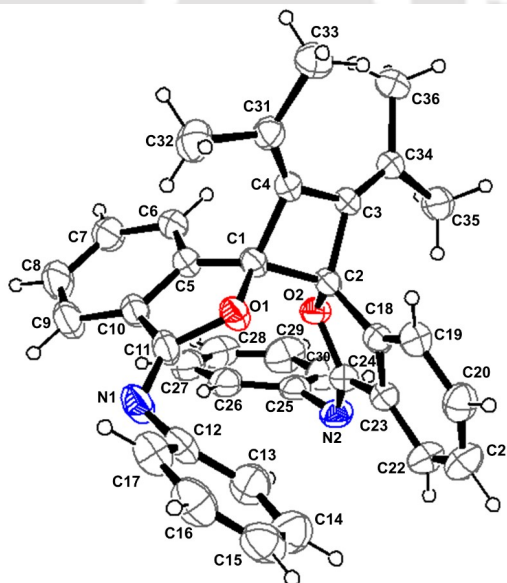
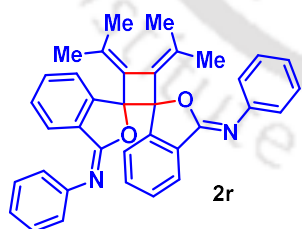
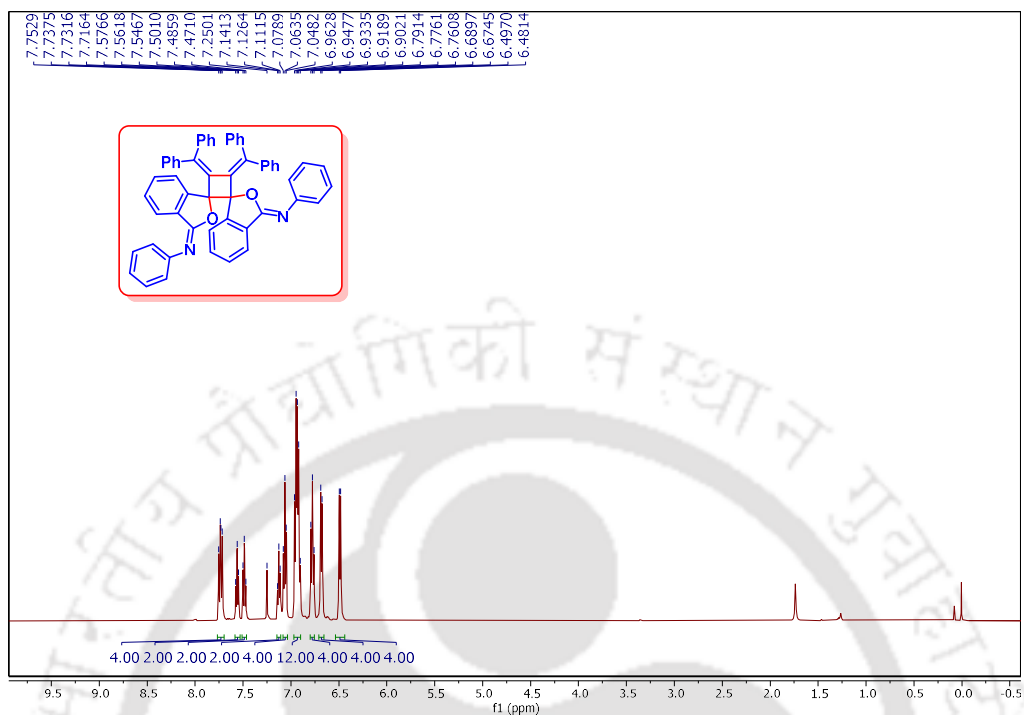
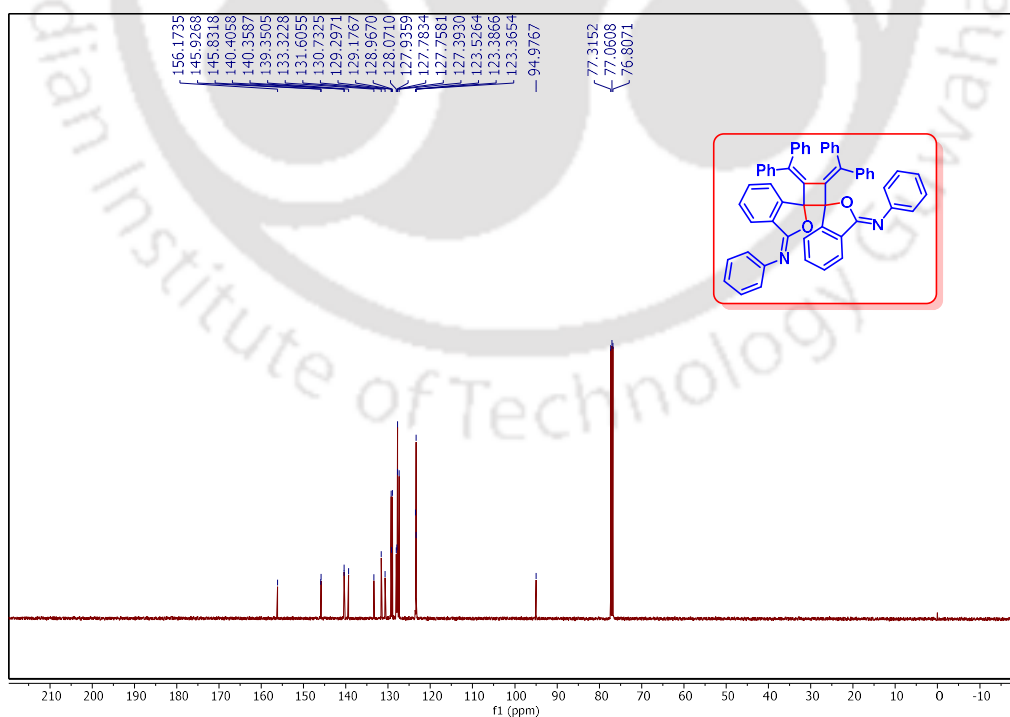


Figure 6.8.1.1. ORTEP diagram of compound **2r** with thermal ellipsoid of 30% probability.

6.9. Representative Spectra

Figure 6.9.1. ^1H NMR spectrum of compound **2a** (500 MHz, CDCl_3).Figure 6.9.2. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of compound **2a** (126 MHz, CDCl_3).

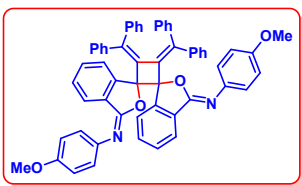


Figure 6.9.3. ^1H NMR spectrum of compound **2d** (400 MHz, CDCl_3).

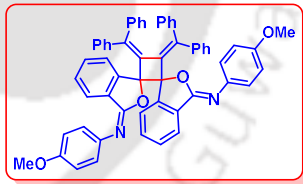
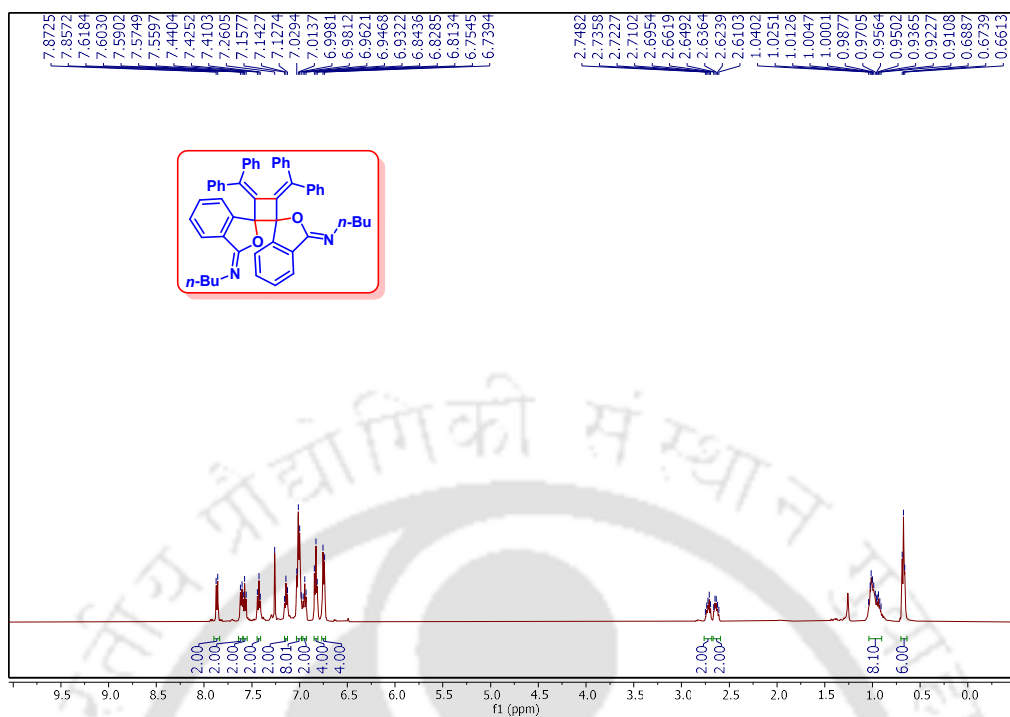


Figure 6.9.4. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of compound **2d** (126 MHz, CDCl_3).



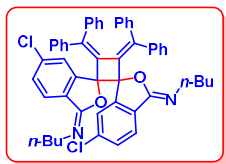


Figure 6.9.7. ^1H NMR spectrum of compound **21** (500 MHz, CDCl_3).

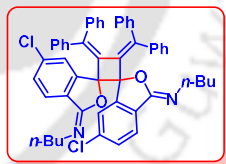


Figure 6.9.8. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of compound **21** (126 MHz, CDCl_3).

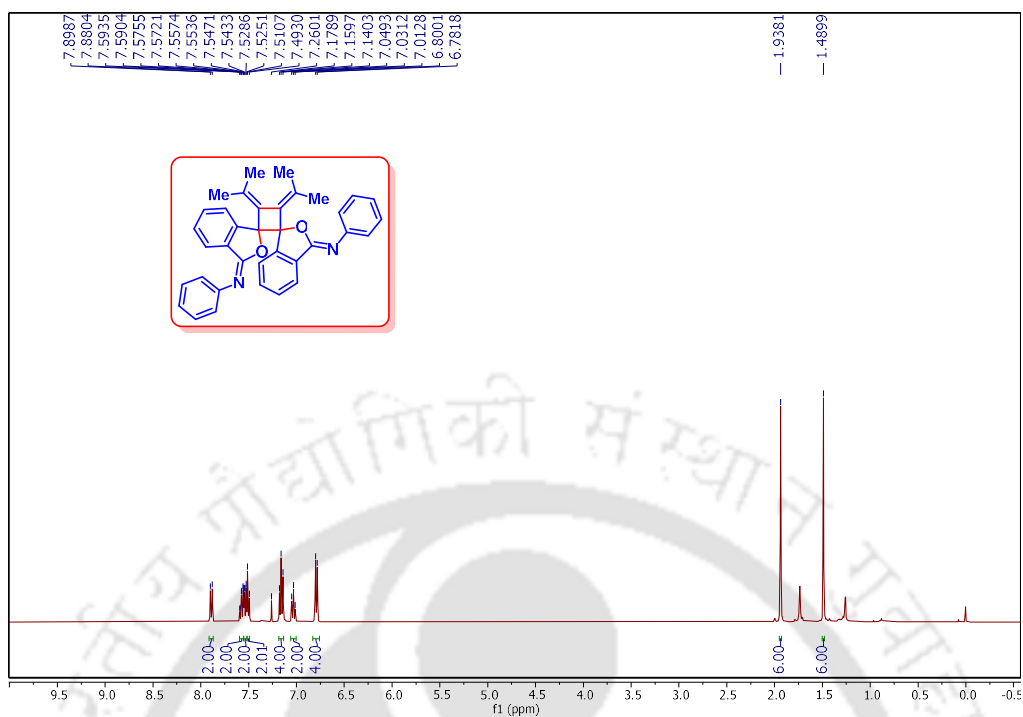


Figure 6.9.9. ¹H NMR spectrum of compound **2r** (400 MHz, CDCl₃).

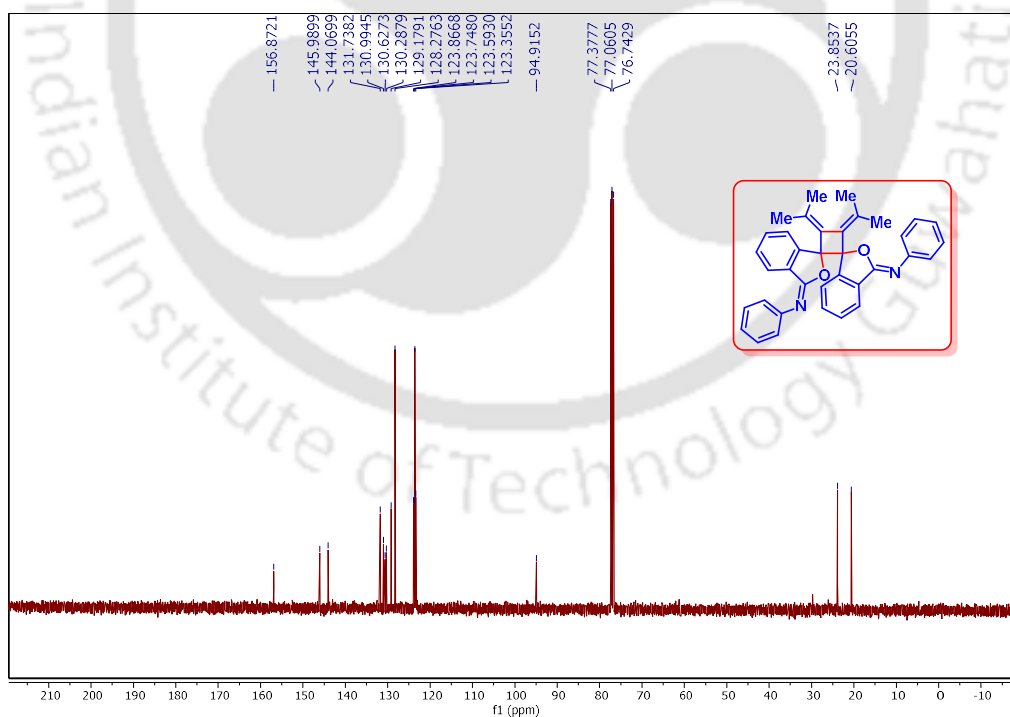


Figure 6.9.10. ¹³C{¹H} NMR spectrum of compound **2r** (100 MHz, CDCl₃).

List of Publications:

- (1) Synthesis of Pyrimido[2,1-*a*]isoindolone and Isoindolo[2,1-*a*]quinazolinone *via* Intramolecular Aza-Prins Type Reaction.
S. Biswas, B. Porashar, P. J. Arandhara and A. K. Saikia, *Chem. Commun.*, 2021, **57**, 11701–11704.
- (2) Leveraging Cascade Alkynyl Prins Cyclization Towards the Stereoselective Synthesis of Spiro-Furan Quinazolinone Scaffolds.
S. Biswas, S. Shit, B. K. Behera, A. K. Sahu and A. K. Saikia, *Chem. Commun.*, 2023, **59**, 14301–14304.
- (3) Cascade Alkynyl Prins Cyclization and Aza-Michael Reaction: En Route to Regioselective Pyrano- and Isochromenoquinoline Scaffolds.
S. Biswas and A. K. Saikia, *J. Org. Chem.*, 2024, **89**, 14454–14471.
- (4) Regioselective Synthesis of Spiro Quinazolinones *via* Sequential Hydroalkoxylation and Intramolecular Amide-Cyclization of Alkynol Ureas.
S. Biswas, S. K. Bora, P. J. Arandhara and A. K. Saikia, *New J. Chem.*, 2024, **48**, 10756–10761.
- (5) Regioselective Synthesis of Spiro-Isobenzofuran Cyclobutanes from *o*-Alkynol Benzamides *via* Oxycyclization and [2+2] Cycloaddition Reaction.
S. Biswas, G. Kumar, C. Choudhury and A. K. Saikia, *manuscript under communication*.
- (6) Vinylsilanes in Highly Diastereo- and Regio-Selective Synthesis of Dihydropyrans.
U. Borthakur, **S. Biswas** and A. K. Saikia, *ACS Omega*, 2019, **4**, 2630–2636.
- (7) Synthesis of 3C-Alkylated Active Methylene Substituted 2*H*-Indazole Derivatives *via* Sequential Ring Opening of Donor–Acceptor Cyclopropanes and Reductive Cyclization Reaction.
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- (8) Synthesis of Thiazole-2(3*H*)-ones *via* [3,3]-Sigmatropic Rearrangement/5-*exo-dig* Cyclization of N-Propargylamines.

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