Expeditious Strategies Towards the Construction of C–C and C–Heteroatom Bonds

A dissertation submitted in partial fulfilment for the degree of

Doctor of Philosophy

Submitted by

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September, 2018

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MY PARENTS

&

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STATEMENT

I do hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India, under the guidance of Professor Bhisma K. Patel. This thesis has been submitted by me to the Department of Chemistry, Indian Institute of Technology Guwahati for the award of the degree of Doctor of Philosophy

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators. I further declare that this work has not been submitted anywhere else for any degree, diploma, associateship or membership etc. of any Institute or University to the best of my knowledge

September, 2018 **Anju Modi**
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CERTIFICATE

This is to certify that Anju Modi has been working under my supervision since January, 2014 as a regular Ph.D. student. Her thesis entitled **"Expeditious Strategies Towards the Construction of C–C and C–Heteroatom Bonds"** is an authentic record of the results obtained from the research work in the Department of Chemistry, Indian Institute of Technology Guwahati, Assam, India. I am forwarding her thesis to submit for the Ph.D. (Science) degree from this institute. I certify that she has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in her thesis and this work has not been submitted elsewhere for a degree.

September, 2018

Prof. Bhisma K. Patel
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ACKNOWLEDGEMENT

It is my great pleasure to take this opportunity to express my gratitude and thanks to all the people around me who have helped and encouraged me during my Ph.D. studies. Nothing in this thesis would have been possible without each and every one of you. Thanks a lot!

First and foremost, I want to express my deepest respect and most sincere gratitude to my supervisor, Prof. Bhisma K. Patel, for offering me the great opportunity to be his Ph.D. student. His guidance, continuous support, scientific ideas, patience, and motivation helped me a lot to explore the domain of work assembled in this thesis. I am grateful to him for his faith in me and giving me the right direction during the entire journey.

I would also like to extend my heartiest thanks to the doctoral committee members, Dr. Subhas C. Pan, Dr. Tapas K Mandal and Dr. Krishna P. Bhabak for their timely evaluation of my Ph.D. work and insightful suggestions, which helped me a lot in the betterment of my thesis. Thanks to the Chemistry department staff members, for their co-operative nature. I would like to thank Dr. Babulal Das for the help he has rendered me with the Single Crystal XRD studies during the course of my Ph.D. My sincere thanks to the staffs of Central Instrument Facility, for their help and in hand guidance to several analytical instruments, required during my research work.

I wish to express sincere gratitude to IIT Guwahati for all the facilities that were made available to me and the Council of Scientific and Industrial Research (CSIR), India for the financial support.

Besides I have been fortunate that I came across wonderful lab seniors like Srimanta da, Saroj da, Arghya da, Nilufa di, Anupal da, Ganesh bhai, Sourav bhai and Wajid bhai. I thank them all for their enormous help and support during my initial days and providing precious suggestions and mentoring me even when they are miles away. I also feel lucky to have shared most of my moments with my batch mate Ahalya and extraordinary juniors Prakash, Suresh, Bilal, Prasenjit, Amitava, Anjali, Subhendu, Tipu, Ashish and Nikita. You all have been fabulous and cooperative under all circumstances. I am also thankful to the postdoctoral fellows Sutapa Mam, Joy da, Suman da, Ritush bhai and Gaurav bhai. I also had the opportunity to work with some dedicated summer and M.Sc. trainees like Debapratim, Saayak, Anwesha, Vandana.

A very special mention of my MSc. batch mate cum best friend Bharath who has been a support system during my Ph.D. journey. He has always been a push factor for me get my things done at proper time. My heartiest thanks to him for being there by my side during highs and lows of my life. Without his continuous encouragement and motivation, I would not have achieved this.

I would like to thank my friends, Ahalya, Mahmuda, Gaurangi, Sumona, Soumita, Jyoti, Srinu, Subhra, Ravindra, Madhurjya, Amlan, Dhriti, Titli, Abhishek, Tanmoy, Soumendra, Arup, for their help, support and joyful moments shared with them at IITG. I would also like to thank my seniors and colleagues here in IITG Sattavisha di, Surojit da, Manas da, Anindya da, Hiranya da, Kuldeep da, Hemanta da, Krupa bhai, Kobirul da, Arindam da, Karuna, Nibedita, Upasana, Renu, Nimisha, Baishakhi, Asha, Soumi, Karabi, Munendra, Biswajit, Rupinder, Tushar, Suzane, Tapasi, Rajat and others for their help and moral support.

I would also like to thank my friends here in IITG Konku, Bikash, Sumit, Gagan, Violina di, Deepika, Ruchika, Shruti, Ila, Arvin, Nayan, Sarthak, Garima, Harsha, Rishi, and many others for being a part of my journey. I would like to thank Arsha, Papuli, Shweta and Richa di for coming in my life during this journey though for a short period.

I am grateful to my brother Rahul for his support, affection and deep concern for my career. Thank you for motivating me. Special thanks to my beloved cousins Diksha, Hemadree, Vivek and Nick for giving me breaks from my normal routine and having stress-free weekends with me.

Finally, my Ph. D. endeavour could not have been completed without the endless love, unending support, tolerance and blessings from my family. My deepest gratitude especially to my Mom and Dad who stood against all odds just to support me. Their enormous sacrifices and unconditional love in every stage of my life motivated me to overcome all the challenges and I owe my entire life to them.

Last but not the least; I am thankful to Almighty for His continuous blessing during my research carrier to accomplish this remarkable journey.

ANJU MODI

SYNOPSIS

The contents of this thesis has been divided into five chapters based on the results of experimental works performed during the complete course of the research period. The introductory chapter of the thesis presents an overview of cascade reactions for heterocycle synthesis, different aspect of C–H functionalization and the oxirane chemistry for the construction of C–C and C–heteroatom bonds. All other chapters' highlight on C–C, C–N, C–O, and C–S bond forming reactions via cascade strategy involving reactions of 2-halobenzamides with (aryl)methanamines and *o*-alkynylanilines with aroyl isothiocyanates, C–H functionalization strategies like directing-group assisted C–H activation followed by annulation and cross-dehydrogenative coupling and lastly oxirane ring opening with aroyl/acyl isothiocyanates.

Chapter II demonstrates a CuO nano particle catalyzed domino synthesis of 2,3-disubstituted quinazolinones from 2-halobenzamides and (aryl)methanamines.

Chapter III describes a base promoted cascade synthesis of quinoline-4(1*H*)-thiones via an in situ generated *o*-alkynylthiourea obtained by reacting *o*-alkynylanilines with aroyl/acyl isothiocyanates.

Chapter IV illustrates a Ru(II)-catalyzed regiospecific C–H/S–H annulation of quinoline-4(1*H*)-thiones with alkynes leading to the synthesis of thiopyrano[2,3,4-*de*]quinolines.

Chapter V elucidates a Cu(II)-catalyzed oxidative methylene-bridged dimerization of two analogous imidazo[1,2-*a*]pyridine using *N*,*N*-dimethylacetamide (DMA) as solvent cum methylene source.

Chapter VI describes a regioselective and concomitant transfer of thiocyanate (–SCN) and aroyl/acyl (–COR) group from aroyl/acyl isothiocyanate onto oxiranes giving thiocyanato benzoates.

Each of these chapters comprises of introduction, previous work, present work, experimental section, references, spectral data and few representative spectra.

CHAPTER I: An Overview of Cascade Reactions, Metal-Catalyzed C–H Functionalization and Oxirane Chemistry for the Construction of C–C and C–Heteroatom Bonds

First part of this chapter gives an overview about the cascade reactions towards the synthesis of heterocyclic molecule.

Molecules containing heterocyclic substructures have always attracted the synthetic chemists since they often exhibit diverse and important biological properties. Consequently, developing novel methods for the stereoselective synthesis of hetero-polycyclic ring systems have gained considerable attention in the field of synthetic organic chemistry. The efficiency with which the heterocyclic molecules can be constructed is more important from the economic and ecological point of view. The increase in molecular complexity as one progresses from simple starting material to the final product can give a measure of the competency of reaction. The number of steps required to achieve the desired target, avoidance of toxic reagents, reduction of waste and responsible treatment of resources is also crucial. In this regard, sequential reactions have evolved as powerful synthetic tool in modern organic chemistry. In comparison to traditional stepwise reaction, sequential reactions (such as cascade, domino and tandem reaction) are characterized by their great elegance, high stereoselectivity, few steps and reduction in the amount of undesired by-products. Cascade reactions are sequence of transformations where the product of the first step serves as the substrate for the second step, whose product is again the substrate for the next step and so on. This process repeats until a stable product is formed under the same reaction condition. L. F. Tietze, defines domino/cascade reactions as:

"*A process where two or more bond-forming transformations occur under the same reaction conditions, without the addition of auxiliary reagents or catalysts and in which the subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step.*"

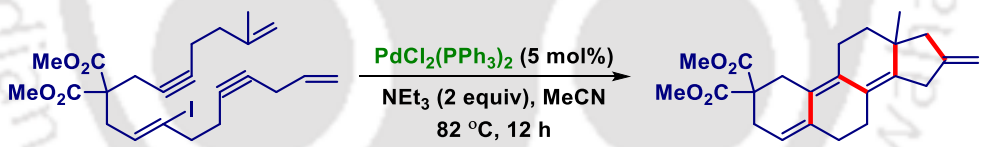
Cascade reactions can be considered to fall under the banner of 'green chemistry' because single reaction solvent, workup procedure, and purification step may be required to provide a desired product that would otherwise be synthesized over the course of several individual steps. Cascade reactions require a combination of highly selective transformations compatible with different functional groups, which can be challenging to

chemists. Consequently, a good understanding of the combined processes is required in order to develop such combinations.

Domino/cascade reactions can be classified based on the nature of the mechanism involved in each step as:

1. Cationic 2. Anionic 3. Radical 4. Pericyclic 5. Photochemical 6. Transition metal-catalyzed 7. Nucleophilic/electrophilic initiated. 8. Oxidation or Reduction initiated. 9. Enzyme assisted.

During cascade reactions preserving the functional group in a molecule is one of the challenging tasks for synthetic organic chemists. As a result, to address such issue a good synthetic combination is required. In last few decades use of transition metals in organic transformation has increased tremendously. Transition metals have been found as of immense importance in cascade reactions. Various transition metals such as Cu, Pd, Ru, Rh, Ir, Mn, Fe, Ag, Co, and Au have been employed in the cascade reactions. However, the chemistry of palladium, silver and copper are versatile and quite well understood. Therefore, there are numerous reports on palladium, silver and copper-catalyzed cascade reactions in recent time. Negishi developed a Pd(II)-catalyzed formation of a polycyclic compound that display a good example of metal-catalyzed cascade reaction (Scheme I.1).



Scheme I.1. *Formation of polycyclic compound*

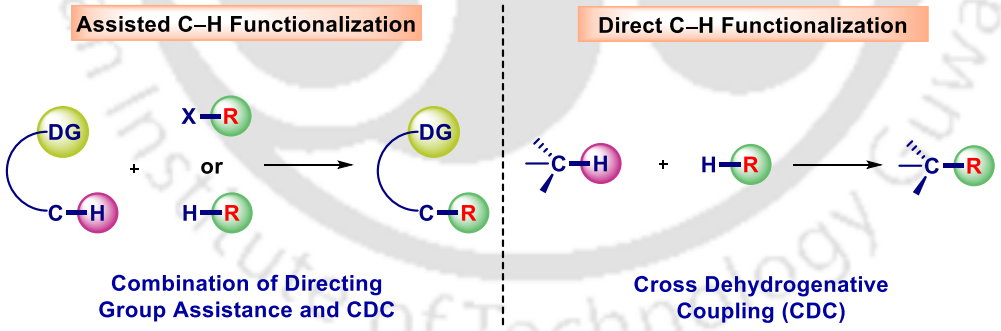
The second part of this chapter gives an outline on the history of C–H activation, various tactics implemented in modern days, their advantages, challenges and application in organic synthesis.

Coupling chemistry is an important synthetic approach towards the construction of C–C and C–heteroatom bonds that has been widely explored in industry and academia. The traditional coupling reactions involves the use of pre-functionalized starting materials and stoichiometric organometallic reagents. Over the past few decades there has been extensive progress in this area of research and this methodology has been successfully implemented for the synthesis of many commercially important molecules. Conversely, the use of pre-functionalized substrates adds extra steps to the overall method and is a major concern for the synthetic chemists from an atom-economic and environmental

perspective. This issues can be addressed by using un-functionalized starting materials and direct functionalization of C–H bonds.

The C–H bonds are considered as dormant functional groups. They are highly stable and resistant to reaction with acids and bases or electrophiles and nucleophiles. Due to the ubiquitous nature of C–H bonds in an organic molecule, selective functionalization of a desired C–H bond and preserving the existing functionality in the molecule is quiet challenging. With this features in mind, it is clear that if the balance between the reactivity and selectivity is achieved it could potentially constitute the most broadly relevant and powerful class of transformations in organic synthesis.

With the aim to enhance this revolutionary field of organic synthesis, more systematic and concerted efforts have been made towards C–H activation and its application in coupling chemistry in recent years. As a consequence, remarkably useful methods have been developed and transition-metal catalyzed C–H bond functionalization is one such tactic to achieve C–C and C–X (X = heteroatom) bond formation. The two most common approach towards C–H activation are: (i) chelation assisted C–H bond functionalization and (ii) cross dehydrogenative coupling (Scheme I.2). In this regard, our group has been involved in the development of new methodologies towards the functionalization of inert C–H bonds.



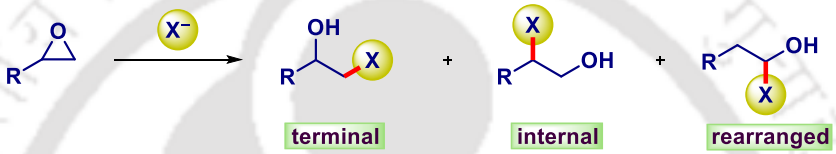
Scheme I.2. *Diverse C–H functionalization route*

The third section of this chapter gives a brief account on exploring the chemistry of oxirane towards the formation of C–C and C–heteroatom bonds.

The oxirane ring, one of the simplest heterocycle, is a vital functional group in organic chemistry. Due to their ease of formation they are widely utilized as versatile starting material and synthetic intermediates in organic synthesis. The inherent ring strain along with the polarization of the carbon–oxygen bonds generates a significant reactivity profile

for oxiranes. The ring-opening reactions of oxiranes with a variety of nucleophilic reagents (such as acids, bases, reducing and oxidizing agents) can be attributed to the electrophilic nature of this heterocycle leading to the synthesis of multi-functionalized organic compounds. Generally, the ring-opening of epoxides is an atom-economical process, generating highly regio- and stereoselective products under suitable reaction conditions.

The stereoselectivity of oxirane ring opening is usually *anti* and the regioselectivity depends on the oxirane structure and reaction conditions. The three major possibilities for nucleophilic substitution is depicted in Scheme I.3 under suitable reaction conditions. With these characteristic features of oxirane in mind we set to explore its reactivity towards the construction of C–C and C–heteroatom bonds.



Scheme I.3. *Three major possibilities of nucleophilic attack*

CHAPTER II: CuO Nanoparticle Catalyzed Synthesis of 2,3-Disubstituted Quinazolinones via Sequential *N*-Arylation and Oxidative C–H Amidation

This chapter focuses on CuO nanoparticle catalyzed synthesis of 2,3-disubstituted quinazolinones from 2-halobenzamides and (aryl)methanamines under an air atmosphere. This cascade synthesis involves Ullmann coupling between 2-halobenzamide and (aryl)methanamine, oxidation of the *in situ* generated secondary amine to imine followed by an intramolecular nucleophilic attack of the amidic N–H on to the imine carbon (C–N bond formation) resulting in the synthesis of 2,3-disubstitued quinazolinones.

In last few decades, synthesis of nitrogen containing polyheterocycles via domino approach and the reaction involving the direct C–H bond functionalization has emerged as one of the powerful tools for their synthesis. A significant attention has been paid to nitrogen bearing heterocycles, as they are the integral part of many natural products and biologically and pharmaceutically active molecules. Among nitrogen containing heterocycles, quinazolinones represent a class of very important structural motifs as they form the core skeleton of many natural products like luotonine A, rutaecarpine, bouchardatine. They are also the major building blocks of many drugs having anti-

hypertensive, anti-inflamatory, anti-bacterial, anti-cancer and anti-tuberculosis activities. Therefore, there is substantial interest to develop novel, efficient and practical approach for their synthesis. Since quinazolinones are assigned as privileged structure in drug development, a number of methods have been developed for their synthesis. The conventional synthesis of quinazolinones involves coupling of *o*-aminobenzamides or *o*-nitrobenzamides with aldehydes, alcohols and other coupling reagents. However, benzoic acid derivatives bearing *o*-amino or *o*-nitro groups are not readily available and are difficult to prepare. With the advancement of Cu catalyzed *N*–arylation strategies for the synthesis of *N*–heterocycles Fu group reported the synthesis of quinazolinones using 2-halobenzamide and benzylamine using copper(I) in an air atmosphere. So far many methods have been reported using various transition metal catalysts. However, due to homogeneous nature of the reaction mixture further use of the catalyst for the next catalytic cycle is rarely studied as the separation of catalyst and product is often difficult. Heterogeneous catalytic systems have several advantages in terms of good dispersion of their active site, easy separation of reaction mixture and catalyst recyclability over homogeneous systems.

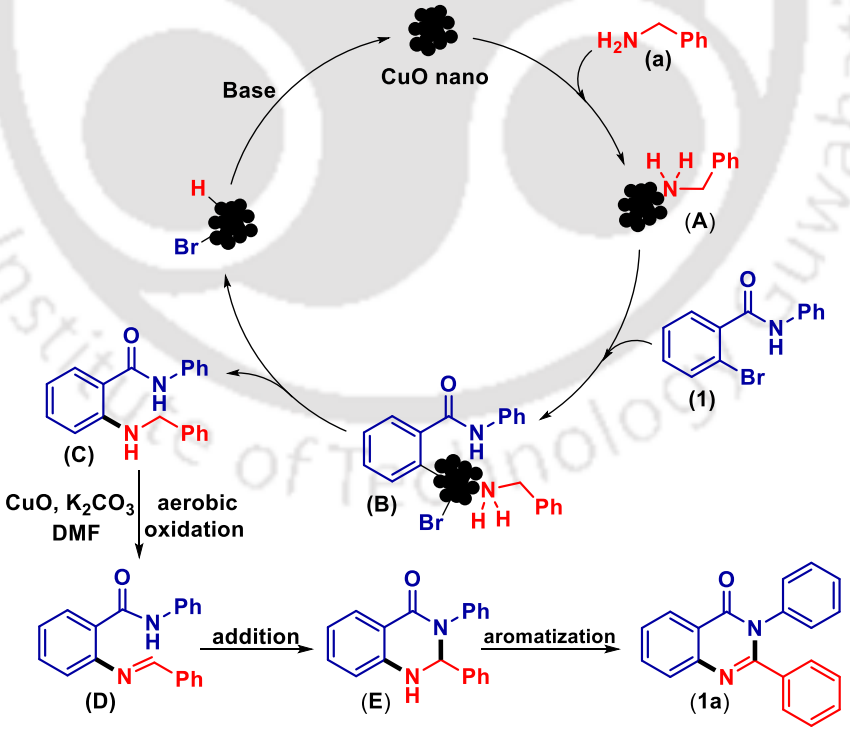
In modern era of organic synthesis, nanoparticle catalyzed reactions has been one of the most progressive research areas. Owing to the advantage of heterogeneous catalyst, nano-crystalline metal oxides have always tempted the synthetic chemists. They are advantageous over conventional metal catalyst in terms of large surface area, high reactivity, high thermal resistance giving higher yields with better atom economy. Several *N, O* and *S*-arylation reactions using CuO nano particle are already reported. To the best of our knowledge, nano CuO catalyzed domino reaction for the synthesis of quinazolinones have not been explored. Herein, we report a simple and efficient method for the synthesis of a diverse array of quinazolinones via the Ullmann coupling of various *o*-halobenzamides and (aryl)methanamines followed by an intramolecular aerobic oxidative C–H amidation.

To reach the suitable reaction condition for the synthesis of quinazolinones various reaction parameters such as catalyst, base, solvent and temperature were scrutinized. After a series of optimization, it was found that the use of 5 mol% CuO nano, 3 equiv K_2CO_3 in DMF at 120 ^oC to be the optimal reaction condition. With this optimized conditions in hand, we investigated the scope of this transformation with various 2-halobenzamides and (aryl)methanamines. Most of the substrates provided good to moderate yields of products

regardless of their electronic environment. Maximum yields were obtained when the substituents in the aryl ring of benzylamine and *N*-aryl ring of benzamides were both electron-donating. Slightly lower yields were obtained when any one of the ring is substituted with electron-donating groups and the other ring with electron-neutral and electron-withdrawing groups. The reaction also went efficiently with heterocyclic analogues of benzylamines and *N*-aryl benzamides.

Several control experiments were performed to understand the possible reaction mechanism. Based on the observation of these experiments and previous related literature reports, a plausible reaction mechanism has been proposed (Scheme II.1).

To check the efficacy of the catalyst for the next catalytic cycle, the catalyst was recovered. The catalytic efficiency of the recovered catalyst was examined upto three cycles. It was found that the catalytic activity of the recovered CuO was slightly lower in subsequent cycles. After third cycle the reaction mixture containing the catalyst was centrifuged and its surface morphology was analyzed and compared with that of fresh catalyst using TEM, which shows agglomeration of the catalyst during the course of the reaction.



Scheme II.1. *Plausible mechanism for CuO nanoparticle catalyzed synthesis of quinazolinones*

In conclusion, we have developed a CuO nanoparticle catalyzed simple and efficient method for the synthesis of 2,3-disubstituted quinazolinones by coupling of 2-halobenzamides and (aryl)methanamines. This reaction operates through sequential C–N bond formation, aerobic oxidation and intramolecular cyclization without the requirement of ligand and additives. The method is advantageous as it offers low catalyst loading, high yield, and recyclability of the catalyst and tolerance of a wide range of functional groups.

CHAPTER III: Base-Promoted Synthesis of Quinoline-4(1*H*)-thiones from *o*-Alkynylanilines and Aroyl Isothiocyanates

This chapter demonstrate a base-promoted synthesis of quinoline-4(1*H*)-thiones from the *in situ* generated *o*-alkynylthiourea, obtained by reacting *o*-alkynylanilines with aroyl/acyl isothiocyanates. A 6-*exo*-dig *S*-cyclization of the *in situ* generated thiourea is followed by a rearrangement to give quinoline-4(1*H*)-thiones.

Construction of heterocycles with privileged scaffolds, which exhibit various biological activities, is in great demand in the field of chemical genetics. Among numerous efforts devoted towards the development of these compounds, cascade reactions have emerged as a powerful synthetic tool in modern synthetic organic chemistry. Compared to the traditional stepwise synthesis, cascade reactions have the advantage of sequential incorporation of multiple C–C and C–hetero atom bonds in one-pot, thereby increasing the overall synthetic efficiency. Taking advantage of this strategy, several alkyne-based substrates, possessing internal nucleophiles at appropriate positions, are often utilized for the construction of interesting heterocycles. Among various alkynes, *o*-alkynylanilines have been extensively employed for the construction of molecular frameworks such as indole, quinoline, quinazolinone, benzoxazine, 4*H*-benzo[*d*][1,3]thiazine using various metal salts such as palladium, copper and silver.

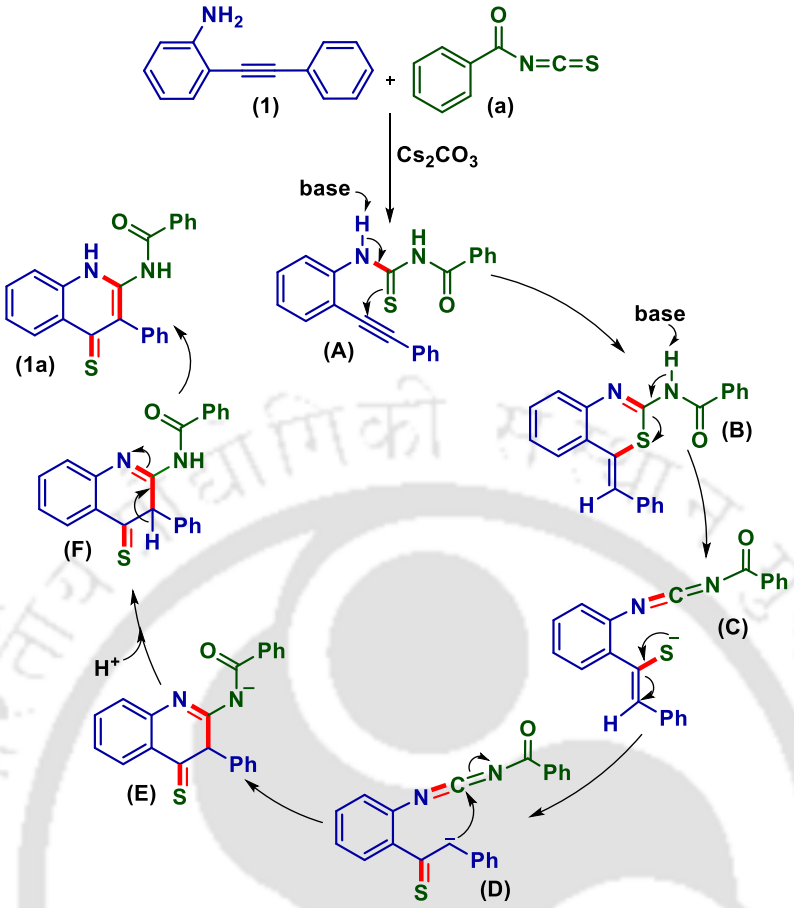
Recently, our group reported the synthesis of indolo[2,3-*b*]quinolines from *o*-alkynylanilines and aryl isothiocyantes in presence of Ag_2CO_3 under microwave heating. Interestingly, replacement of aryl isothiocyante with an aroyl isothiocyante completely changed the course of reaction and the product outcome, giving a quinoline-4(1*H*)-thione. We carried out an initial investigations by reacting 2-(phenylethynyl)aniline and benzoyl isothiocyanate in the presence of CuI (10 mol %) and K_2CO_3 (4 equiv) in 1,4-dioxane at 110 ^oC. The reaction gave a completely new product i.e. *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide which was analyzed by spectroscopic methods and

further confirmed by single-crystal X-ray diffraction of one of its derivative. Interestingly, the benzoyl thiourea generated *in situ* underwent a 6-*exo*-dig *S*-attack onto the internal alkyne, followed by rearrangement giving thequinoline-4(1*H*)-thione moiety in 100% atom economy.

Based on recent studies, quinoline-4(1*H*)-thione derivatives are found to be inhibitors of virulence factor elastase of the human pathogen *Pseudomonas aeruginosa*. Some of the quinoline-4(1*H*)-thione derivatives are reported to form oxovanadium complexes with $VO(acac)_2$, exhibiting cytotoxic activity and apoptosis in human malignant cell lines. Despite the importance of the quinoline-4(1*H*)-thione framework, there are only a few reports of their synthesis which mainly involve thioketolization of the preformed quinolin-4(1*H*)-ones with phosphorus pentasulfide (P_4S_{10}) or with Lawesson's reagent. To the best of our knowledge, there is no report at this date for the synthesis of quinoline-4(1*H*)-thiones from *o*-alkynylanilines and aroyl isothiocyanate in the presence of base.

Various reaction parameters such as catalysts, base, solvent and temperature were screened to obtain the optimal conditions for this reaction and it was found that the reaction in the absence of any catalyst and merely in the presence of Cs_2CO_3 (2 equiv) and CH_3CN solvent at 80 ^oC under air is the most suitable conditions. With this optimized condition the scope of this transformation was extended to a variety of *o*-alkynylanilines and aroyl isothiocyanates. Aroyl isothiocyanates having electron-donating (EDG) or electron-withdrawing (EWG) substituents and acyclic as well as heterocyclic carbonyl isothiocyanates all reacted competently giving good yields of their respective products. The presence of different substituents on the phenyl rings of *o*-alkynylanilines also gave good to excellent yields of the product on reaction with various aroyl isothiocyanates.

Based on the literature reports, a plausible pathway has been proposed for the base-promoted cascade reaction (Scheme III.1).



Scheme III.1. *Plausible mechanism for the synthesis of quinoline-4(1H)-thiones*

In conclusion, we have demonstrated a metal-free approach for the synthesis of quinoline-4(1*H*)-thione derivatives. This is the first example of a base promoted synthesis of quinoline-4(1*H*)-thiones from *o*-alkynylanilines and aroyl isothiocyanate. Through the cascade process, simultaneous formation of three C–C, C–N and C–S bonds has been accomplished. This protocol shows wide functional group tolerance with good to excellent yields of the product in 100% atom economy.

CHAPTER IV: A Thiocarbonyl Directed Regiospecific C–H/S–H Annulation of Quinoline-4(1*H*)-thiones with Alkynes

This chapter gives a unique illustration of regiospecific C–H/S–H annulation of quinoline-4(1*H*)-thiones with alkynes directed via a C=S group using a Ru(II)-catalyst. Here, preferential annulation takes place at the sterically hindered position even in the presence of three other competing sites *viz.* two C–H/N–H and one C–H/O–H leading to the synthesis of thiopyrano[2,3,4-*de*]quinolines.

The evolution of C–H bond activation is emerging as one of the most powerful tools in synthetic chemistry and has streamlined the construction and functionalization of complex molecules in the past decade. Among various transition metals, ruthenium catalyzed chelation directed C–H bond activation, followed by annulation with alkynes, has led to the synthesis of a wide range of fused polyheterocycles. To accomplish this, diverse N- and O- based directing groups such as amines, anilides, imines, amides, ketones, esters, carboxylic acids, and alcohols have been well studied. The coordination of heteroatom to the metal centre is assumed to be the key step in these transformations, thereby directing the metal centre to the proximal C–H bond and thus achieving the desired functionalization. In the midst of several directing groups, sulfur containing compounds such as thiols, thioethers, sulfoxides have not been utilized for any metal directed annulations. Nevertheless, arylation, alkenylation and heterocycle synthesis have been reported. Remarkably, organosulfur compounds are important chemical entities because of its occurrence in many biological systems, synthetic drugs and functional materials. However, the susceptibility of sulfur to easy oxidation and its affinity towards metal ions poisons the catalyst thereby hampering its usage in C–H activation reactions. Any sulfur directed annulation is hitherto unprecedented and thus developing novel routes for the synthesis of complex molecules with concurrent sulphur incorporation is highly desirable.

Quinoline-4(1*H*)-thione i.e., *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide moiety reported in our previous chapter have four directing sites *viz.* two C–H/N–H, and one each of C–H/S–H and C–H/O–H susceptible for possible annulation with alkyne. Previously our group reported a Ru(II)-catalyzed oxidative C–H/O–H annulation of 2-arylquinolinone with internal alkynes wherein, annulation is via the more favourable phenolic form of quinone over other possible pathways (C–H/N–H and C–H/C–H). In this case, the metal coordinates to the weaker carbonyl oxygen in the presence of stronger nitrogen-directing group giving a regiospecific annulated product. Thus, we were inquisitive to see whether annulation reaction in quinoline-4(1*H*)-thione will proceed via the thiophenolic form (C–H/S–H) or other competing sites (C–H/N–H or C–H/O–H) will dictate?

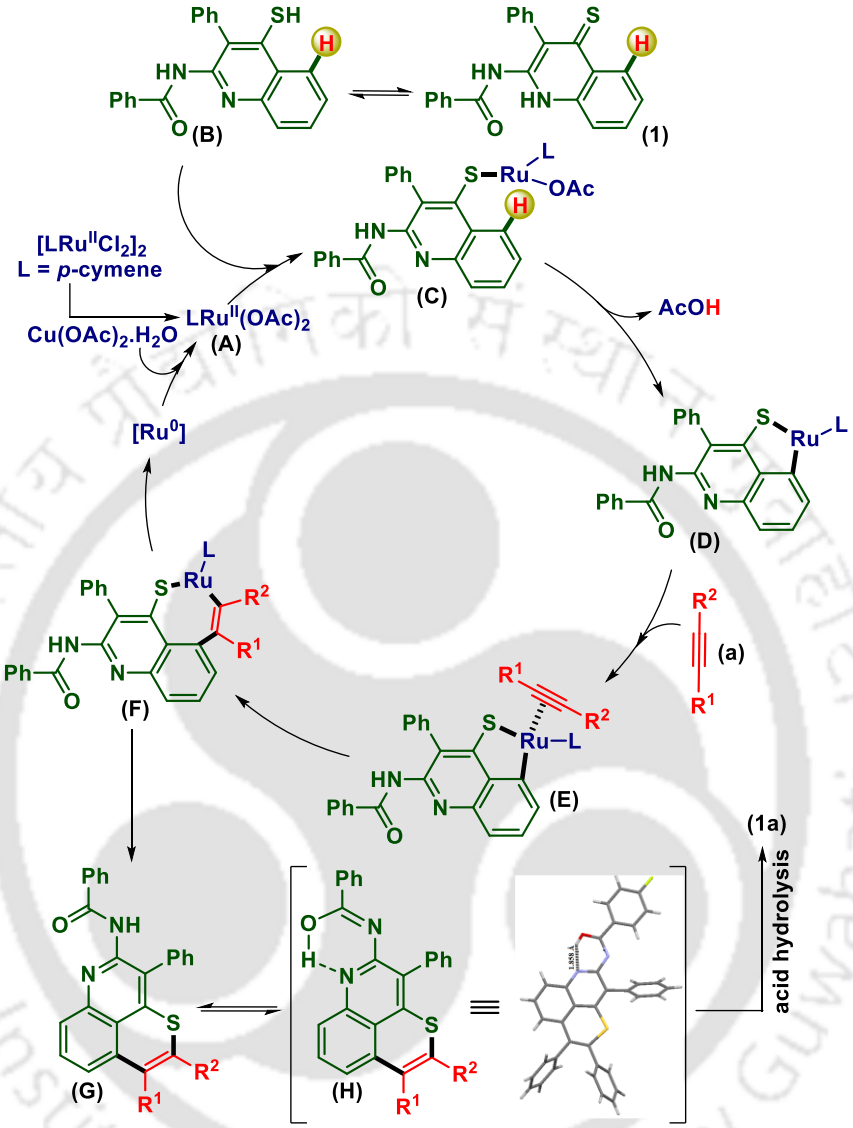
With this motivation, we commenced our exploration by reacting *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide and diphenylacetylene with the well investigated catalyst $[RuCl_2(p\text{-cymene})]_2$ (2 mol%), AgOAc (1 equiv) as the oxidant in

AcOH under air at 110 ^{o}C. A new product was isolated in 55% yield after 12 h. Spectroscopic analysis (^{1}H NMR and ^{13}C NMR) revealed its structure to be 3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine, which was reconfirmed by single crystal X-ray diffraction. The analysis of the product confirms a [4 + 2] annulation of alkyne via oxidative C–H/S–H bond cleavage over other competing annulations (C–H/N–H or C–H/O–H). This process is however associated with the loss of –COPh group possibly via a hydrolytic path. Thus the question arises, whether the amide bond cleavage takes place before the annulation or after? Subsequently, crystal structure of one of the isolated intermediate (after 30 minutes) confirms that the annulation precedes over the amidic bond cleavage. It is worthy to mention that, the alkyne annulations reported till date often involves C–H/N–H, C–H/O–H, and C–H/N–O bond cleavages. To the best of our knowledge, this is the only example of alkyne annulation via C–H/S–H bond functionalization leading to the first synthesis of thiopyrano[2,3,4-*de*]quinolines.

Quinoline and quinoline-fused polyheterocycles are important building blocks in natural products, agrochemicals, material chemistry, and also useful as chiral ligands. Among various quinoline derivatives, thiopyranoquinoline are of considerable interest as they exhibit significant pharmaceutical activities. Molecules having thiopyranoquinoline framework are reported to function as inhibitors of telomerase and are valuable for the treatment of cellular proliferation disorders. Considering the importance of quinoline-fused thiopyran ring system, the present synthetic protocol would render the generation of thiopyrano[2,3,4-*de*]quinoline moiety with potential application in diverse field of research.

To find out the appropriate optimized condition a series of experiments have been carried out and it was found that the use of $[RuCl_2(p\text{-cymene})]_2$ (2 mol%), $Cu(OAc)_2.H_2O$ (2 equiv) in AcOH under air at 110 ^{o}C is the best condition for the present transformation. After establishing the optimized annulation strategy, we probed the diversity of this oxidative annulation by employing various decorated quinoline-4(1*H*)-thiones with variety of symmetrical internal alkynes. Gratifyingly, the present protocol proceeded well with a variety of *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamides derivative giving good to excellent yields of the product. Interestingly, the reaction with asymmetric alkynes as well as terminal alkynes gave a single regioisomeric product.

Based on literature reports a plausible reaction mechanism has been proposed as depicted in Scheme IV.1.



Scheme IV.1. *Plausible mechanism for annulation of quinoline-4(1H)-thiones*

In summary, we have demonstrated the first thiocarbonyl directed regiospecific annulation of alkynes with quinoline-4(1*H*)-thiones. In a multi-directed sites *viz.* C–H/N–H and C–H/O–H, the C–H/S–H annulation is preferred even under a constraint environment. Terminal and unsymmetrical alkynes, gave single regioisomeric product. Thus, thiopyrano[2,3,4-*de*]quinolines could be conveniently synthesized via the coupling of quinoline-4(1*H*)-thiones with internal or terminal alkynes.

CHAPTER V: *N,N*-Dimethylacetamide (DMA) as a Methylene Synthon for Regioselective Linkage of Imidazo[1,2-*a*]pyridine

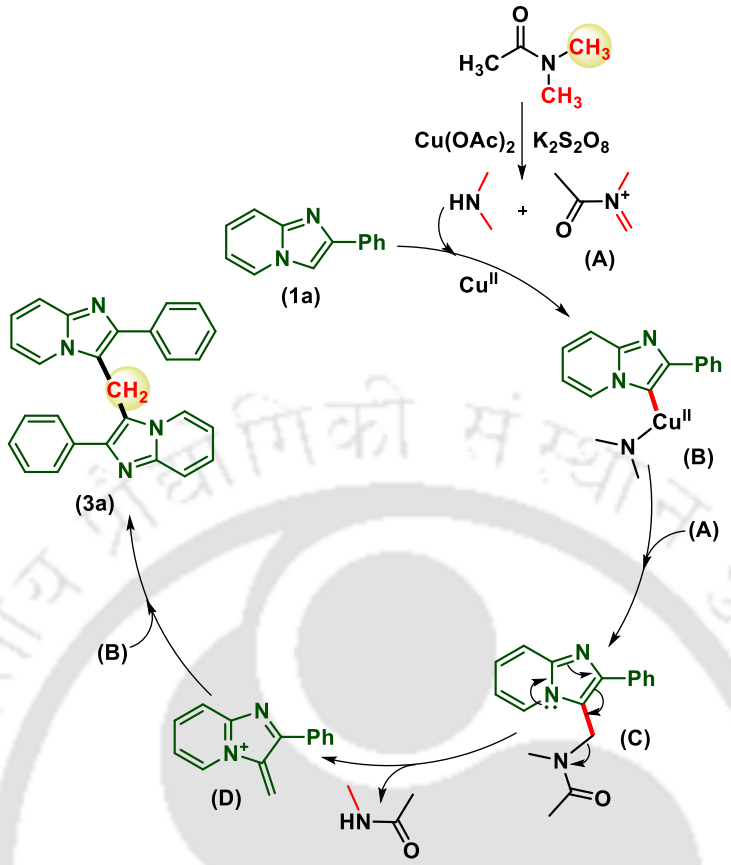
This chapter demonstrates a Cu(II)-catalyzed oxidative methylene-bridged dimerization of two analogous imidazo[1,2-*a*]pyridine using *N,N*-dimethylacetamide (DMA) as solvent cum methylene source.

Cross-dehydrogenative coupling (CDC) under oxidative conditions is one of the most efficient and straightforward tools for the construction of C–C bonds. This strategy is now so powerful that, even the commonly used organic solvents such as formamides and sulfoxides are utilized as the source of various functional groups. *N,N*-dimethylformamide (DMF), a well-known solvent, has turned out to be a multipurpose reagent widely used in organic chemistry as building block of various units such as -O, -CO, -NMe_2, -$CONMe_2$, -Me, -CHO, etc. Similarly, dimethyl sulfoxide (DMSO) is also utilized as the source of -SMe, -CN, -CHO, -Me, etc. *N,N*-dimethylacetamide (DMA), although chemically inert compared to DMF, has been successfully explored as a one-carbon synthon for the synthesis of terminal alkenes and heterocycles *via* sp^3–sp^3 and sp^2–sp^3 C–H couplings, respectively. However, the use of DMA as the source of a one-carbon linker between two analogous imidazo[1,2-*a*]pyridines *via* cross-dehydrogenative coupling of sp^2 C−H of arene and sp^3 C−H bond of DMA is unfamiliar so far.

Among the *N*-heterocycles, imidazo[1,2-*a*]pyridines represent an important structural motif because of their prevalence in the field of medicinal and material chemistry. The derivatives are reported to have a diverse array of biological activities such as antiviral, antibacterial, antifungal, antiulcer, and antihelminthics. They also form the core skeleton of many pharmaceutically important drugs such as necopidem, saripidem, alpidem, zolpidem and zolimidine. Owing to the ubiquity of imidazo[1,2-*a*]pyridine framework in various fields, substantial attention has been paid to their synthesis and further functionalizations. Of late, many methods have been explored for the C-3 functionalization of imidazo[1,2-*a*]pyridines, *viz*. trifluoromethylation, sulfenylation, fluorination, cyanation, thiocyanation, dicarbonylation, aminomethylation as well as oxidative homocoupling of two imidazo[1,2-*a*]pyridine moieties. Although there have been significant developments toward the regioselective functionalization at the C-3 carbon, the quest for the further derivatizations is still ongoing.

With the aim to functionalize the C-3 position of imidazo[1,2-*a*]pyridine, it was treated with DMA (solvent cum reagent) in the presence of catalyst CuI (20 mol%) and oxidant $K_2S_2O_8$ (1 equiv.). Formation of an unexpected product was observed in 50% yield. The product showed a singlet at 4.99 ppm in its ^{1}HNMR and a peak at 19.9 ppm in its ^{13}CNMR spectra, which may be due to the presence of a methylene carbon in the product. Furthermore, from the single crystal X-ray diffraction study of one of its derivative, its structure was established to be a C-3 methylene bridge bis-heterocycle. To ascertain the source of the methylene carbon in the product, a similar reaction was carried out separately with *N*,*N*-dimethylformamide (DMF) and *N*,*N*-diethylacetamide (DEA) in lieu of DMA under otherwise identical conditions. Formation of product was observed only with DMF (and not with DEA), thereby suggesting that the methylene carbon possibly originates from the *N*-methyl group of DMA/DMF and not from the acetyl group of DMA. When the reaction was carried out with DMF-d_7, insertion of a deuterated methylene group was observed, which was confirmed from the HR-MS analysis of the reaction mixture. This result unequivocally confirms that the *N*-Me group of DMA/DMF is the source of methylene carbon in the product. There are reports where the *N*-methyl of DMA served as a one-carbon surrogate for the synthesis of terminal alkenes. The group of Xu and Wang have independently reported vinylation of 2-methylazaarenes using iron(III) catalyst. Recently, Miura *et al.* have developed a copper(II) catalyzed α-methylenation of benzylpyridines. Lately, DMF and DMA both were employed as a one-carbon source by Lei and Li using copper(II) and iron(III) catalysts respectively. Herein, we report DMA as a one-carbon source, i.e. as a methylene linker for coupling of two imidazo[1,2-*a*]pyridines.

Encouraged by the above unprecedented result, further optimizations of the reaction parameters such as catalysts, oxidants and reaction temperature were screened to find the optimal reaction condition to achieve the maximum yield of the product. After a series of experiments, the best condition was found as $Cu(OAc)_2$ (20 mol%), $K_2S_2O_8$ (2 equiv) in DMA under air at 120 ^{o}C. The scope and generality of this methodology was then extended to a range of imidazo[1,2-*a*]pyridines. Irrespective of the nature of the substituent on the phenyl ring of 2-phenylimidazo[1,2-*a*]pyridine moiety and substituents on the pyridine ring of imidazo[1,2-*a*]pyridine moiety all gave moderate to good yields of the products.



Scheme V.1. *Plausible mechanistic pathway*

To gain an insight into the reaction mechanism, a number of control experiments were carried out. On the basis of the results obtained from these experiments and literature precedence a plausible reaction mechanism has been proposed as shown in Scheme V.1.

In conclusion, we have developed a copper(II)-catalyzed dimerization of two imidazo[1,2-*a*]pyridine moieties with a methylene linkage in the presence of an external oxidant. Use of cheaper reagents, regioselectivity, and broad substrate scope are the notable features of this methodology. The synthesized methylene bridged dimeric imidazo[1,2-*a*]pyridine derivatives may find applications in the field of medicinal and material chemistry.

CHAPTER VI: Organocatalytic Regioselective Concomitant Thiocyanation and Acylation of Oxiranes Using Aroyl Isothiocyanates

This chapter describes a regioselective and concomitant transfer of thiocyanate (–SCN) and aroyl/acyl (–COR) groups from aroyl/acyl isothiocyanates onto oxiranes,

giving thiocyanato benzoates in 100% atom economy. In this biomimetic organocatalytic process, one part (–SCN) of aroyl/acyl isothiocyanates acts as the nucleophile whereas the other half (–COR) serves as an electrophilc partner.

The desire to develop newer methodology for the construction of C–C and C–X (X = heteroatom) bonds has brought about many appealing results in the field of synthetic chemistry. Compared to the traditional electrophiles, epoxides have emerged as attractive coupling partners. The ring strain in epoxides makes them susceptible to ring opening with a range of nucleophiles such as alcohols, amines, thiols and other strong nucleophilic organometallic reagents like Grignard or organolithium. Recently, there have been many reports on transition-metal-catalyzed coupling of epoxides with aryl halides, arenes, alkenes, alkynes and boronic acids, resulting in the construction of a variety of alcohols. However, these transition-metal-catalyzed reactions are not universally acceptable due to their high cost and toxicity.

From our previous work on biomimetic thiocyanate group transfer from aroyl isothiocyanate onto α-haloketones, a nucleophilic substitution product was observed in the absence of any real nucleophile. In this process, the α-haloketone serves as an electrophile and the aroyl isothiocyanate as the source of nucleophile (–SCN). Thus, it will be interesting to see if an oxirane can act as the electrophilic partner for this nucleophile-less nucleophilic substitution. Furthermore, if the ring opens up, what will be the fate of the resultant alkoxy ion? Will it form an alcohol (via protonation), or will it undergo further nucleophilic attack onto a suitable electrophile?

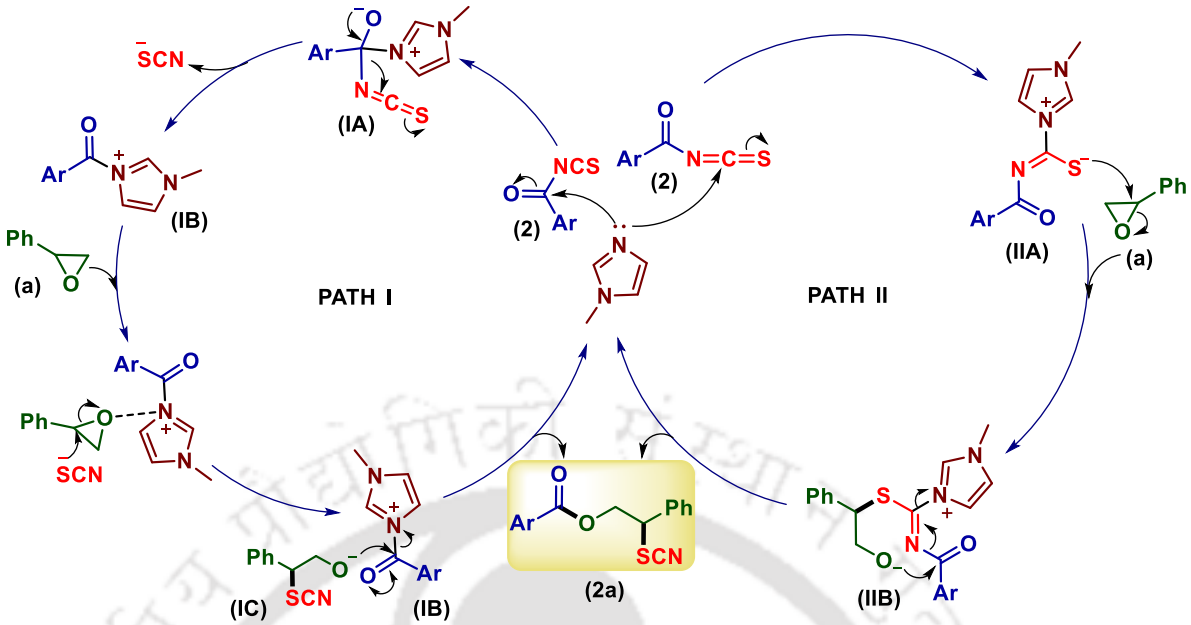
To find answers to the above queries, a reaction was carried out with benzoyl isothiocyanate (1 equiv) and 2-phenyloxirane (1 equiv) in the presence of *N*-methylimidazole (NMI) (1 equiv) in acetonitrile (2 mL) at room temperature, under a reaction condition identical to that reported in our previous work. Both reactants were completely consumed (as indicated by TLC) giving a new product. The IR spectra of newly formed product showed a characteristic peak at 2154 cm^{-1} suggesting the incorporation of a –SCN group. Another peak at 1705 cm^{-1} may be due to the presence of a carbonyl group in the resultant product. Further, ^{1}H and ^{13}C NMR of the isolated product revealed the presence of an ester functionality. Finally, the structure of the product was confirmed by single-crystal X-ray diffraction study of one of its derivative, which revealed the presence of a thiocyanate as well as an ester functionality. As anticipated, the thiocyanate acts as a

nucleophile and attacks at the Aα position of the epoxide. The resultant alkoxy species obtained by the ring opening of epoxide possibly undergoes benzoylation, giving 2-phenyl-2-thiocyanatoethyl benzoate. Here, the reaction gave a single regioisomeric product in 67% isolated yield. In the absence of NMI, the reaction did not proceed at all, suggesting its definite involvement during this simultaneous electrophilc-nucleophilic process. This unprecedented outcome showing the transfer of both halves (i.e., thiocyanate (–SCN) and the acyl (–COPh) group from aroyl/acyl isothiocyanate to oxirane) results in the formation of a product having new C–S and C–O bonds in 100% atom economy.

Organic thiocyanates are prevalent subunits in bioactive compounds possessing antimicrobial and antiproliferative activity and are versatile precursors for the synthesis of many sulfur-containing heterocycles. Aryl esters are also a ubiquitous functionality found in pharmaceuticals, agrochemicals and polymers and are important building blocks for organic synthesis. The presence of both of these important functionalities, viz. thiocyanate and ester, in a single molecule derived from readily available starting material is a boon to synthetic chemists.

Encouraged by this double functional group transfer, further optimizations were carried out to improve the yield of the *bis*-functionalized product. Various other organic bases, solvents and temperature were scrutinized and it was found that the reaction gave the best yield with 20 mol% of NMI at room temperature in the absence of any solvent. The scope of this methodology was further extended to a range of aroyl/acyl isothiocyanates and oxirane derivatives. The presence of electron donating substituent on the phenyl ring of aroyl isothiocyanate gave better yield with 2-phenyloxirane derivatives compared to electron withdrawing substituents. In the case of glycidic epoxide, the –SCN attack takes place at the Aα (benzylic carbon) site, giving single regioisomeric products. In the case of non-benzylic oxiranes the attack of –SCN takes place at the less sterically hindered carbon (Aβ).

To ascertain the nucleophilic (S_N2) path of oxirane ring opening in glycidic epoxide systems reactions were conducted with chiral epoxides and the isolated products were found to be optically active. Based on our previous work and from literature reports a plausible reaction mechanism has been proposed (Scheme VI.1).



Scheme VI.1. *Plausible reaction mechanism*

In conclusion, we have demonstrated a biomimetic organocatalytic bis-functionalization of oxiranes from aroyl/acyl isothiocyanates in the presence of NMI. In this simultaneous electrophilic–nucleophilic reaction, the thiocyanate (–SCN) of aroyl/acyl serves as the nucleophile, whereas the aroyl part acts as the electrophilic partners, giving products in 100% atom economy. In this metal free process, C–S and C–O bonds are simultaneously constructed in the presence of NMI under solvent free conditions.

CONTENTS

CHAPTER I

An Overview of Cascade Reactions, Metal-Catalyzed C–H Functionalization and Oxirane Chemistry for the Construction of C–C and C–Heteroatom Bonds

CHAPTER IA

IA. An Overview of Cascade Reactions

IA.1. Introduction

Synthetic organic chemistry has evolved in a fascinating way over the past fifty years. In earlier days, the synthesis of complex molecules with high selectivity was quite tedious. But gradually with time, various methodologies have been developed which allow the preparation of complex molecules efficiently with excellent regio-, chemo-, diastereo-, and enantioselectivity. Some incredible examples of such molecules are palytoxin,[1] brevetoxine A,[2] and gambierol.[3] Regardless of this inordinate success and the importance of chemistry to our civilization, its public image has declined. This is due to the growing concern of environmental issues to our society and the distress of negative influence of chemistry to the ecological balance. However, a change of paradigm in chemical synthesis has been observed in the past decade. Certainly, the question today is not only what can we synthesize but also how do we accomplish it in a sustainable manner?

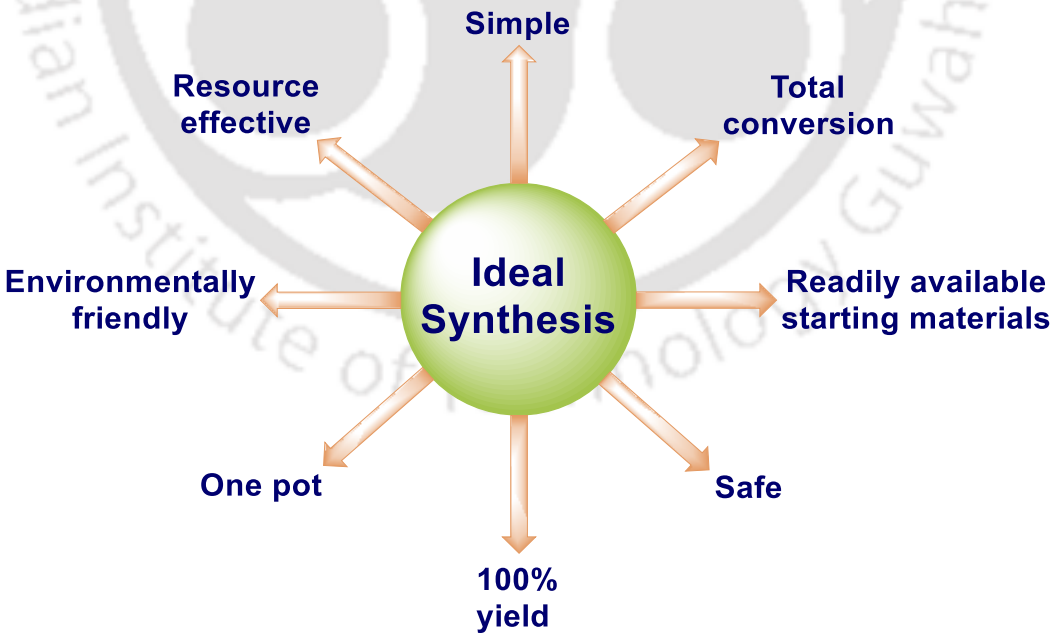


Figure IA.1.1. *The ideal chemical synthesis proposed by Wender et al.*

The major challenge in the present scenario is the efficiency of a chemical synthesis which is defined by the increase in the complexity of the molecule after each

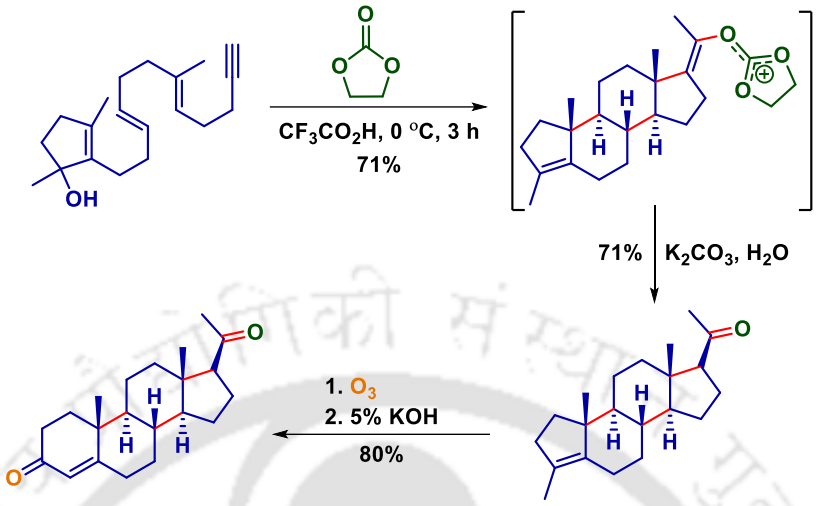
transformation and the needs of our environment such as preservation of resources and the avoidance of toxic reagents and solvents.[4] If these issues are overcome, it will not only be beneficial for nature but also advantageous from economic point of view as it will reduce the production time as well as the amount of waste generated. Other important issues which organic chemists have to deal with has been summarized in the ideal synthesis proposed by Wender *et al.* (Figure IA.1.1).[5]

Until now, the normal procedure for the synthesis of organic compound has been a stepwise formation of individual bonds in the target molecules, with work-up and isolation stage after each transformation. In contradiction, modern synthesis seeks for strategies that allow the formation of several bonds such as C–C, C–N, C–O, C–S, in one sequence. Ideally, the entire transformation should take place without the isolation of any intermediates and without addition of any reagents or catalysts and changing the reaction conditions.[6] Hence, this kind of transformations minimizes the waste thereby avoiding waste management and cutting down the labour. Such type of transformations is defined as "domino reaction" or "domino process." It is also termed as cascade reaction or cascade transformation with few exceptions. These reactions involve the transformation of two or more bond-forming reactions under identical conditions, in which the latter transformations take place at the functionalities obtained in the former-bond forming reactions. The eminence of this strategy can be associated to the number of bonds formed in one sequence, increasing the molecular intricacy and its suitability for a general application.

IA.2. Historical Background

Cascade reactions in nature are quiet common, however its direct comparison to the reactions performed in laboratory is unfeasible as the former involves multi-enzymes which can allow the catalysis of different steps. Biosynthesis of fatty acids from acetate,[7] lanosterols from (*S*)-2,3-oxidosqualene[8] and uroporphyrinogen (III) from cyclotetramerization of the monomer porphobilinogen[9], progesterone,[10] daphnilactone A[11] and (+)-codaphniphylline[12] are some of the examples of the naturally synthesized compounds catalyzed by enzyme via domino reaction. These natural processes led to many biomimetic approaches, the first example being described by van Tamelen[13] and Corey for steroid synthesis.[14] Later, Johnson developed a more efficient method towards the

synthesis of progesterone by an acid catalyzed polycyclization of monocyclic trieneyne (Scheme IA.2.1).[10]



Scheme IA.2.1. *Biomimetic cascade synthesis of progesterone*

Robinson[15] described a domino process for the synthesis of tropinone which was later improved by Schöpf[16] using succinaldehyde, methylamine and acetonedicarboxylic acid without isolating any intermediate. The synthesis is based on a double Mannich process with iminium ions as intermediate. Mannich reaction[17] is the first domino reaction developed by humankind.

IA.3. Classification of Cascade Reactions

L. F. Tietze, defined domino/cascade reactions as "*a process where two or more bond-forming transformations occur under the same reaction conditions, without the addition of auxiliary reagents or catalysts and in which the subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step.*" However, many reactions do not fall under this category as they fail to meet the requirement as per the given definition. A substrate with several functionalities which undergoes individual transformation in the same pot is not a domino reaction. Likewise, the initial formation of reactive intermediates such as a carbocation or a carbanion is not counted as a reaction step. Whereas, the formation of a diene by a retro-Diels-Alder reaction with a consequent cycloaddition would be considered as a domino reaction. It is highly anticipated to categorize different types of domino reactions which will not give a better understanding of the existing strategies but will also facilitate the

invention of new domino reactions. Therefore, based on the mechanism of the first step, cascade reactions are classified into the following categories:

1. Cationic domino reaction
2. Anionic domino reaction
3. Radical domino reaction
4. Pericyclic domino reaction
5. Photochemically-induced domino reaction
6. Transition-metal catalyzed domino reaction
7. Domino reaction initiated by oxidation or reduction
8. Enzyme-induced domino reaction
9. Domino reaction initiated by nucleophiles or electrophiles

Combination of reactions of the same mechanism is called homo-domino reactions such as cationic-cationic, anionic-anionic, radical-radical, pericyclic-pericyclic and transition-metal catalyzed and they are more frequently reported in literature. Whereas, a sequence of reaction with different mechanisms are called hetero-domino reactions. Some very powerful hetero-domino reactions such as anionic-pericyclic sequence or even anionic-pericyclic-pericyclic sequence are well investigated.

Since the work reported in this thesis solely belongs to cascade synthesis of *N*-heterocycles from the readily available starting materials, below descriptions are based on copper catalyzed cascade synthesis of *N*-heterocycles and few representative examples of heterocycle synthesis from *o*-alkynylanilines.

IA.4. Copper-Mediated Cascade Synthesis of Heterocycles

Transition-metal mediated cascade reactions have drawn significant attention of synthetic chemists for several decades and is one of the most vibrant areas of research.[18] The efficiency of a catalytic system in cascade reaction is evaluated by the number and diversity of individual transformations involved and the number of new bonds that can be formed by the catalyst. These factors are typically proportional to the complexity of the final products. From this perspective, various transition metals Cu, Pd, Ru, Rh, Ir, Mn, Fe, Ag, Au, Co and Ni have been explored for several bond breaking/making processes. Though each metals have their own advantages, copper-mediated reactions[19] are more promising due to the low cost of copper-based catalytic systems, high natural abundance,

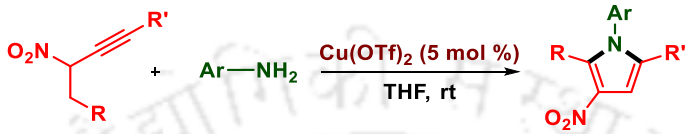
high catalyst activity, low toxicity, easy recyclability, and excellent tolerance to different reaction conditions as well as functional groups.

The foundation of modern copper-mediated chemistry lies in the pioneering and remarkable works of Ullmann,[20] Goldberg,[21] and Hurtley.[22] Their contribution clearly delivered some of the most useful methods for the formation of C–C, C–O, and C–N bonds for more than a century and paved the way for today's development. However, it was only in the late 1990s that the full potential of these classical transformation began to be unveiled with the development of more efficient copper/ligand catalytic systems operating under much milder reaction conditions.[23] Ullmann-type coupling reactions have become increasingly popular for the cascade synthesis of heterocycles in which two individual catalytic transformations are directly mediated by copper salts. Since one of the chapter in the thesis mainly focus on copper catalyzed *N*-heterocycle synthesis via cascade process, only descriptions relevant to heterocycle synthesis via copper-mediated cascade strategy have been discussed.

Heterocycles are ubiquitous units found in many natural products. The myriad biological and pharmacological activities exhibited by these heterocycles make them attractive candidates in drug discovery programs. A number of novel, efficient and well-established methods are now available for their synthesis. Among these, transition-metal catalyzed strategies have gained considerable attention as they allow direct and straightforward formation of various heterocycles.[24] Owing to the various advantages of copper catalysts and their remarkable efficiency for C–X (X = C, N, O, S) bond formation, they have been widely explored towards heterocycle synthesis. Among various heterocyclic systems, *N*-heterocycles are more relevant as they form the core skeleton of many natural products and biologically active molecules.[25] They are capable of forming salts thereby increasing the solubility of a molecule which are important for oral absorption and bioavailability.[26] Thus most of the drugs incorporate at least one nitrogen heterocycle within their structures and are considered as privileged targets by pharmaceutical industries and medicinal chemists. Below few examples of copper-catalyzed cascade synthesis of *N*-heterocycles have been discussed. Although there are numerous reports in literature towards the synthesis of these heterocycles only one representative example of a few *N*-heterocycle is being shown.

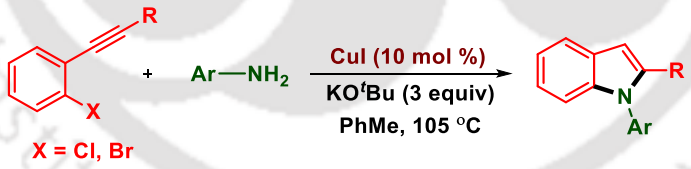
IA.4.1. Synthesis of *N*-Heterocycles

Pyrrole derivatives are important components in many pharmacophores such as heme, vitamin B_{12}, and cytochromes.[27] Punniyamurthy *et al.* reported the synthesis of tetrasubstituted pyrroles/pyrazoles from nitro-substituted 1,3-enynes with aromatic amines/hydrazines via copper-catalyzed aza-Michael addition, cyclization and aromatization at room temperature using air as the oxidant (Scheme IA.4.1.1).[28]



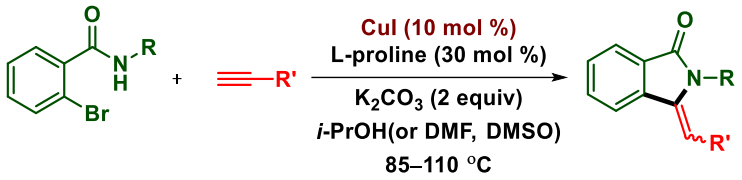
Scheme IA.4.1.1. *Copper-catalyzed synthesis of tetrasubstituted pyrroles*

Indole derivatives occur widely in nature[29a] and are essential structural motif for the development of pharmaceuticals,[29b] agrochemicals,[29c] materials[29d,e] and perfumes.[29f] The synthesis of indole has been a key area of focus for organic chemists since centuries and numerous methods are available in literature for their synthesis. Ackermann and co-workers reported a copper-catalyzed domino *N*-arylation/hydroamination syntheses of indole derivatives from *o*-alkynylbromoarenes (Scheme IA.4.1.2).[30] The broad scope of this methodology was illustrated with the synthesis of diversely functionalized indoles and azaindoles along with an efficient preparation of the pharmacophore Chek1/KDR inhibitor.



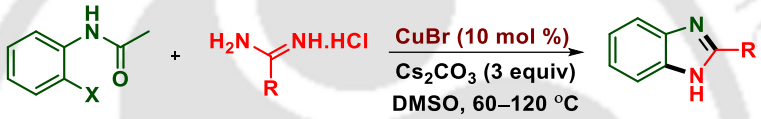
Scheme IA.4.1.2. *Copper-catalyzed synthesis of N-arylindoles*

Isoindolinone units are found in a muscaric receptor ligand[31a] and an influenza endonuclease inhibitor[31b] and are important versatile synthetic blocks in organic synthesis[31c] and dyes.[31d] Ma, Jiang and co-workers developed a copper(I) iodide and L-proline catalyzed route for the synthesis of isoindolinone (Scheme IA.4.1.3).[32] The cascade reaction proceeded via Sonogashira coupling of 2-bromobenzamides with terminal alkynes in isopropyl alcohol (or DMF and DMSO) at 85–110 °C followed by subsequent additive cyclization.



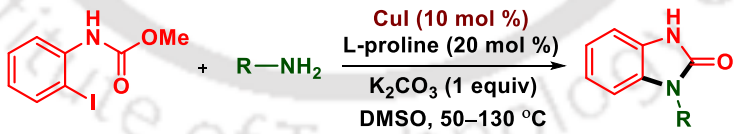
Scheme IA.4.1.3. *Copper-catalyzed synthesis of isoindolinone*

Benzimidazole moieties appear in pharmaceutical molecules exhibiting anti-viral activity[33a] and are used as non-peptide thrombin inhibitors[33b] and anti-allergic agents.[33c] Fu group reported an efficient synthesis of 2-substituted benzimidazole via copper-catalyzed cascade reaction of *o*-haloacetoanilide derivatives with amidine hydrochlorides (Scheme IA.4.1.4).[34] The coupling between the two results into an amide intermediate which on intramolecular cyclization gives 2-substituted 1*H*-benzimidazole with the loss of NH_3.



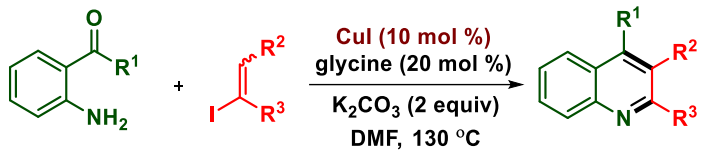
Scheme IA.4.1.4. *Copper-catalyzed synthesis of 2-substituted benzimidazole*

Benzimidazolone derivatives are found in molecules that are used as inhibitors of potent anti-retroviral activity against HIV strains,[35a] potassium channel regulators[35b] and progesterone receptor antagonists.[35c] Ma and co-workers demonstrated the assembly of *N*-substituted 1,3-dihydrobenzimidazol-2-ones via a CuI/amino acid catalyzed coupling of methyl *o*-haloarylcarbamates and amines followed by subsequent condensative cyclization showing wide functional group tolerance (Scheme IA.4.1.5).[36]



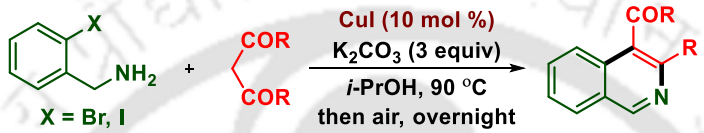
Scheme IA.4.1.5. *Copper-catalyzed synthesis of benzimidazolone*

Compounds having quinoline skeleton are known to exhibit various biological activities such as anti-mitotic,[37a] anti-viral,[37b] and anti-platelet functions.[37c] Liu, Li and co-workers reported an efficient cascade copper-catalyzed intermolecular Ullmann-type C–N coupling/enamine condensation between *o*-acylanilines and alkenyl iodides giving multi-substituted quinolines in good to excellent yields (Scheme IA.4.1.6).[38]



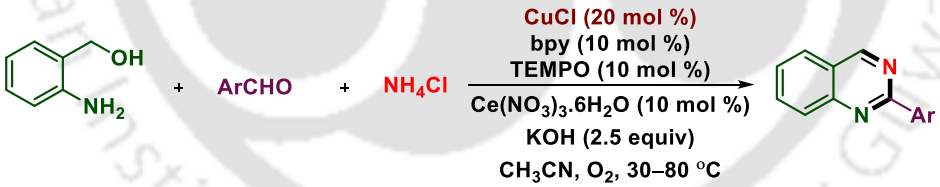
Scheme IA.4.1.6. *Copper-catalyzed synthesis of quinoline*

The isoquinoline unit is often found in natural products, and these alkaloids display unique biological activity.[39] Ma and co-workers developed a Cu(I)-catalyzed cascade method for the synthesis of substituted isoquinoline from *o*-halobenzylamines and β-keto esters (Scheme IA.4.1.7).[40] The protocol shows wide functional group tolerance.



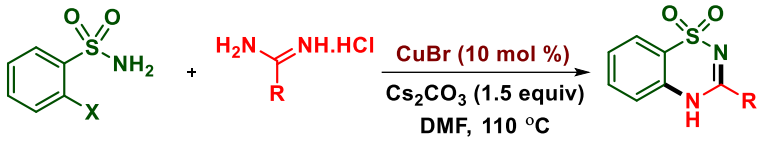
Scheme IA.4.1.7. *Copper-catalyzed synthesis of isoquinoline*

Quinazoline motifs form the core skeleton of molecules exhibiting anti-cancer,[41a] anti-viral,[41b,c] anti-tubercular,[41d] and anti-malarial properties.[41e] Wu group reported a Cu-catalyzed cascade reaction of (2-aminophenyl)methanols with aldehydes using the combination of cerium nitrate hexahydrate and ammonium chloride leading to a wide range of 2-substituted quinazolines (Scheme IA.4.1.8).[42] The procedure exhibits wide functional group tolerance.



Scheme IA.4.1.8. *Copper-catalyzed synthesis of quinazoline*

Benzothiadiazine 1,1-doixide derivatives are used as ATP-sensitive potassium channel openers[43a,b] and reduce the AMPA receptor desensitization[43c] and improve the impaired synaptic transmission of functions useful in the treatment of Alzheimer's disease.[43d,e] Fu, Hu and co-workers developed the synthesis of benzothiadiazine 1,1-dioxide derivatives via coupling of 2-halobenzenesulfonamides with amidine (Scheme IA.4.1.9).[44] The reaction takes place in the presence of an inexpensive catalyst (CuBr) and in the absence of any ligand or any additive.

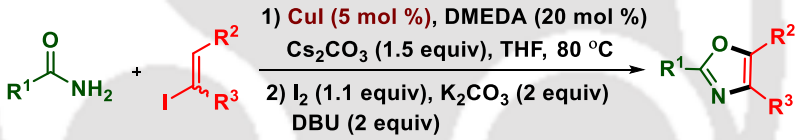


Scheme IA.4.1.9. *Copper-catalyzed synthesis of benzothiadiazine 1,1-dioxide*

The importance and the different strategies for quinazolinone synthesis have been discussed elaborately in Chapter II.

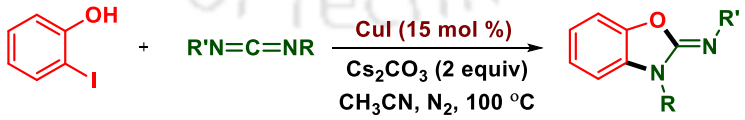
IA.4.2. Synthesis of *N,O*-Heterocycles

Oxazoles are found in a wide variety of natural products and biologically active molecules such as estrogen receptor agonists,[45a] melatonin receptor agonists,[45b] and 5-HT3 receptor agonists.[45c] In 2007, Buchwald group demonstrated the synthesis of highly substituted oxazoles. The transformation consists of sequential copper-catalyzed amidation of vinyl halides followed by cyclization promoted by iodine (Scheme IA.4.2.1).[46] The readily available precursors and functional group tolerance makes the method attractive.



Scheme IA.4.2.1. *Copper-catalyzed synthesis of oxazole*

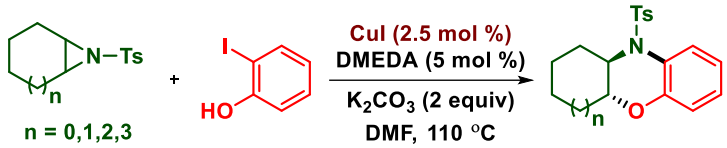
Benzoxazole derivatives are important heterocycles used as fluorescent probes[47a] and heat-resistant polymers.[47b] Bao and co-workers reported a novel and efficient synthesis of benzoxale via a ligand-free, copper(I)-catalyzed cascade process by coupling carbodiimides with *o*-halophenols (Scheme IA.4.2.2).[48] The strategy gives moderate to excellent yields of benzoxazole derivatives under a mild reaction condition.



Scheme IA.4.2.2. *Copper-catalyzed synthesis of benzoxazole derivative*

1,4-Benzoxazine derivatives display various biological activities such as they are used as potential intracellular calcium antagonist, vasodilator agents, and potassium channel activators.[49] Sekar group developed a novel, economical, and practical method for the synthesis of *trans*-3,4-dihydro-2*H*-1,4-benzoxazine (Scheme IA.4.2.3).[50] The method

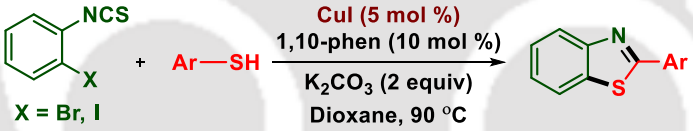
involves a domino ring-opening of aziridine ring with *o*-iodophenols, followed by Goldberg coupling cyclization using ethylenediamine–CuI complex as catalyst and K_2CO_3 as base.



Scheme IA.4.2.3. *Copper-catalyzed synthesis of 1,4-benzoxazine*

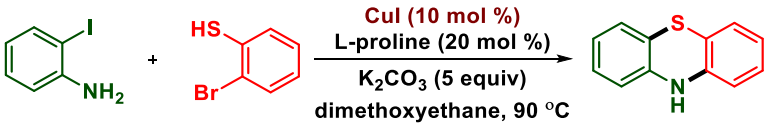
IA.4.3. Synthesis of *N,S*-Heterocycles

Benzothiazole scaffold are active pharmacological agents and ubiquitous in natural products. They act as potent heat shock protein-90 inhibitors[51a] and as an inhibitor of cathepsin-D.[51b] Our group reported an efficient cascade process for the synthesis of 2-subsituted 1,3-benzothiazoles (Scheme IA.4.3.1).[52] The thiocarbamate or dithiocarbamate generated *in situ* by the reaction of *o*-haloaryl isothiocyanates and S-nucleophiles undergoes CuI–L (L = ligand i.e., 1,10-phenanthroline) catalyzed intramolecular C–S bond formation giving substituted benzothiazoles.



Scheme IA.4.3.1. *Copper-catalyzed synthesis of benzothiazole*

Phenothiazine an important class of heterocycle are used as drugs such as promazine used for psychotropic medication,[53a] quaternized trifluoropromazine derivative that has antitubercular activity,[53b] cholinesterase inhibitor,[53c] histamine H_1 antagonist,[53d] and MDR (multiple drug resistance) reverting agent.[53e] Ma and co-workers reported the assembly of substituted phenothiazine by a sequentially controlled CuI/L-proline catalyzed cascade C–S and C–N bond formation between 2-haloanilines and 2-halobenzenethiols (Scheme IA.4.3.2).[54]

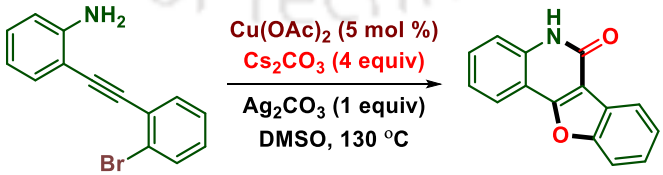


Scheme IA.4.3.2. *Copper-catalyzed synthesis of phenothiazine*

IA.5. Representative Examples of Heterocycle Synthesis from *o*-Alkynylanilines

In modern organic chemistry developing new reactions from readily available starting materials with high product selectivity is the most promising challenge. As a consequence, organic chemists have started the synthesis of different heterocyclic skeleton from the same set of starting substrate.[55] Alkyne and its derivatives are most valuable chemical entities because of its easy availability and versatile reactivity. They have been utilized as molecular building blocks for the designing of novel organic reactions and assembly of functional materials.[56] With the recent development in transition-metal catalyzed transformations, they have been employed for the rapid access to complex molecular scaffold.[57] Among alkyne derivatives, 2-alkynylaniline and its derivatives are useful synthetic intermediates to assemble *N*-heterocycles and polycyclic scaffolds. 2-Alkynyl derivatives can be easily prepared via classical Sonogashira reaction between 2-iodo/bromoaniline and terminal alkynes which are employed for the synthesis of various heterocycles having privileged molecular skeleton.[58] Several transition metals such as Pd, Cu, Ru, Rh, Ag and Au are known to activate the internal alkyne which undergo transformation into various heterocycles. In recent years, heterocycle synthesis from 2-alkynylaniline via transition-metal catalyzed cascade strategy has emerged as a powerful synthetic tool.[59] Few representative examples are discussed below.

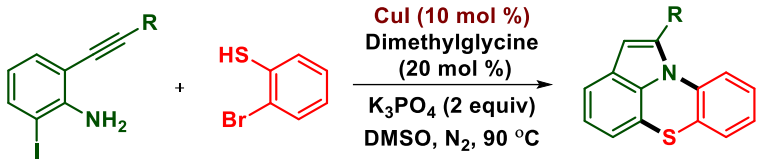
Our group reported a copper catalyzed cascade synthesis of benzofuran[3,2-*c*] quinoline-6[5-*H*]ones from 2-((2-bromophenyl)ethynyl)aniline (Scheme IA.5.1).[60] The protocol involves a simultaneous construction of three types of bonds *viz.* C–C, C–O, and C–N bonds. In this carbonylation-etherification cascade process both carbonyl and ethereal oxygen originates from Cs_2CO_3.



Scheme IA.5.1. *Copper catalyzed synthesis of benzofuran[3,2-c] quinoline-6[5-H]ones*

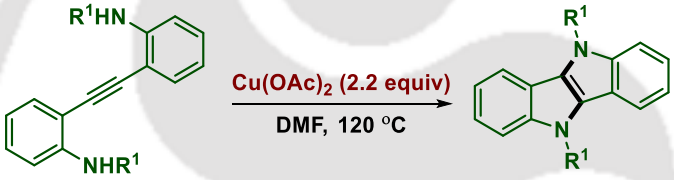
Lv group reported a novel and efficient Cu(I)-catalyzed C–S coupling/double cyclization leading to the synthesis of pyrrolo[3,2,1-*kl*]phenothiazines. The reaction

involves coupling of 2-alkynyl-6-iodoanilines with *o*-bromobenzenethiols (Scheme IA.5.2).[61]



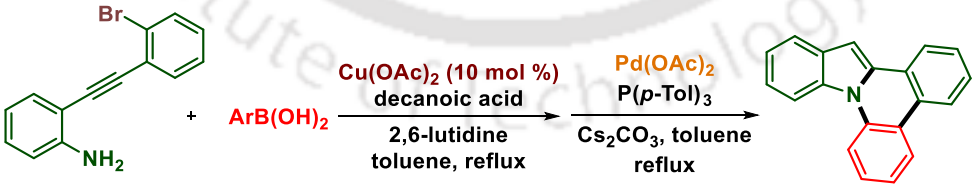
Scheme IA.5.2. *Copper catalyzed synthesis of pyrrolo[3,2,1-kl]phenothiazines*

Du and co-workers reported an unusual Cu(II)-promoted cascade reaction featuring annulation of diarylalkyne sulphonamides to form 5,10-dihydroindolo[3,2-*b*]indoles (Scheme IA.5.3).[62] This unprecedented process incorporates two sequential C–N bond formation, resulting into an efficient synthesis of biologically important indoloindole derivatives. In this process $Cu(OAc)_2$ serves as a catalyst in the first step and an oxidant in the second step.



Scheme IA.5.3. *Copper promoted synthesis of 5,10-dihydroindolo[3,2-b]indoles*

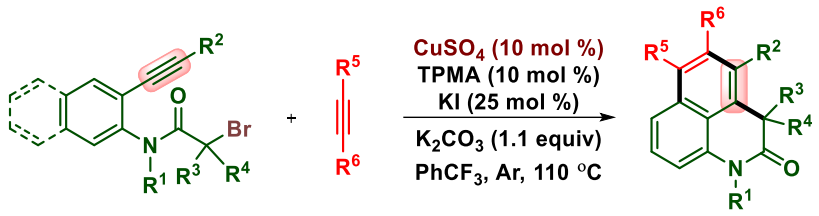
Wang, Lv and co-workers developed a one pot bimetallic (Cu/Pd)-catalyzed cascade synthesis of polycyclic indole derivatives (Scheme IA.5.4).[63] Initially, the 1,2-disubstituted indole is formed via a Cu-catalyzed domino coupling cyclization process under an aerobic condition followed by a Pd-catalyzed intramolecular direct C(sp^2)–H arylation in the same pot.



Scheme IA.5.4. *Cu/Pd-catalyzed synthesis of polycyclic indoles*

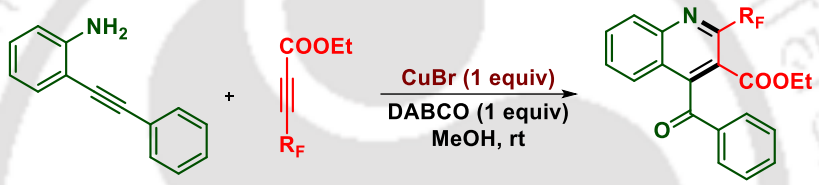
Recently, Li *et al.* described a new Cu-catalyzed annulation cascade of alkyne-tethered α-bromocarbonyls with alkynes giving various heteropolycyclic frameworks including 1*H*-benzo[*de*]quinolin-2(3*H*)-ones, 4*H*-dibenzo[*de,g*]quinolin-5(6*H*)-one, and benzo[*de*]chromen-2(3*H*)-one (Scheme IA.5.5).[64] The protocol involves two-component

annulation cascades via C–Br bond split, intramolecular cyclization, intermolecular [4 + 2] annulation, and aryl C(sp^2)–H functionalization.



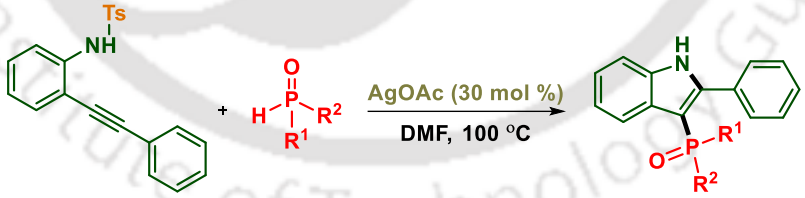
Scheme IA.5.5. *Cu-catalyzed synthesis of heteropolycyclic framework*

Cao *et al*. developed a Cu(II)-promoted aerobic cascade cyclization of *o*-alkynylanilines and methylperfluoroalk-2-ynoates for the synthesis of 4-carbonyl-2-perfluoroalkylquinolines (Scheme IA.5.6).[65] The reaction affords quinoline derivatives in good to excellent yield with the tolerance of a wide range of functional group.



Scheme IA.5.6. *Cu-mediated synthesis of substituted quinolines*

A silver-mediated cycloaddition between *N*-Ts-2-alkynylaniline derivatives and H-phosphine oxides for the synthesis of 3-phosphinoylindole derivatives was developed by Tang *et al.* (Scheme. IA.5.7).[66] This transformation offers a straightforward route to the formation of C–P bond, indole ring, and desulfonylation in one step.

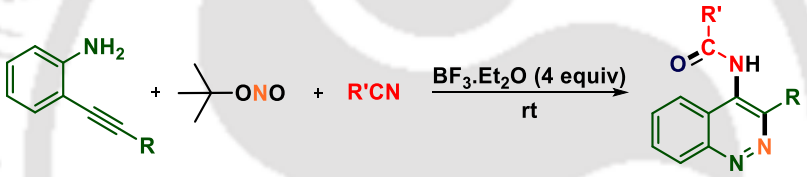


Scheme IA.5.7. *Cu-mediated synthesis of 3-phosphinoylindole derivatives*

A Pd-catalyzed cascade arene/alkyne annulation reaction for the synthesis of fluorene-benzoxaine derivatives was developed by Wang, Ji and co-workers (Scheme IA.5.8).[67] Control experiments and kinetic isotopic studies reveals that the reaction involves a 6-*exo-dig* cyclization, a 1,3-oxazine vinylpalladium intermediate, and a C–H bond activation. The cascade reaction is operationally simple, is compatible with a broad substrate scope, and represent an efficient, step- and atom-economic way for the construction of scarcely known fluorene-benzoxazine derivatives.

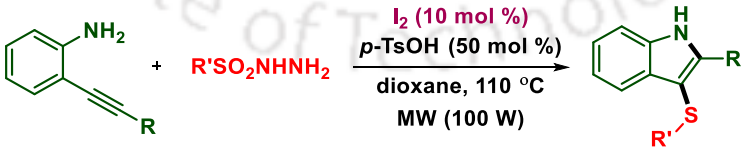
Scheme IA.5.8. *Pd-catalyzed synthesis of fluorene-benzoxazine derivatives*

Wang group demonstrated a BF_3-etherate promoted cascade assembly of 4-amido-cinnolines by reacting nitriles with 2-alkynylanilines (Scheme IA.5.9).[68] The transformation achieves the formation of two C–N bonds via a reaction sequence of diazotization with *t*-BuONO, nucleophilic addition of the alkyne to the BF_3-coordinated diazonium ion, followed by nitrile addition to the intermediary vinyl cation and hydrolysis. The notable feature of the method includes broad functional group tolerance and avoidance of transition metals.



Scheme IA.5.9. *BF_3.Et_2O-promoted synthesis of 4-amido-cinnolines*

Pardasani *et al.* established a metal-/oxidant-free protocol for the synthesis of 3-sulfenylindoles based on electrophilic cyclization of 2-alkynylanilines under microwave irradiation (Scheme IA.5.10).[69] The protocol involves catalytic amount of iodine and stoichiometric amount of sulfonyl hydrazides as electrophile to induce 5-*endo-dig* cyclization of 2-alkynylanilines. The strategy shows good functional group tolerance and wide substrate scope.

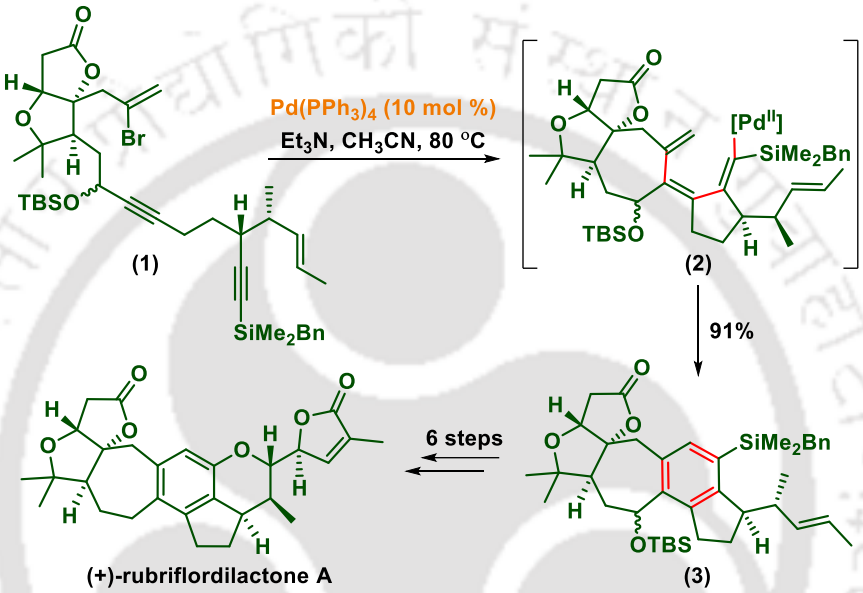


Scheme IA.5.10. *Metal-free synthesis of 3-sulfenylindoles*

IA.6. Cascade Reaction in Natural Product Synthesis

Total synthesis of natural products exemplifies a great accomplishment and ambition in organic chemistry and is essential for the commercial development of natural products or their derivatives as bioactive agents. The combination of new catalytic processes (such

as C–H activation, organocatalysis, and photoredox chemistry) along with the evergreen creativity of the synthetic organic chemist, concise and efficient routes to complex bioactive natural products can be designed. Among the most efficient synthetic tools of modern synthetic chemists are cascade/domino reactions that not only increases the molecular complexity and reduces the overall step, but also demonstrate synthetic elegance and creativity.[70] An example of metal-catalyzed cascade synthesis of rubriflordilactone A by Anderson group is described below.[71]



Scheme IA.6.1. *Carbopalladation cascades in the synthesis of rubriflordilactone A*

The transformation involves cascade cyclization of a complex bromoendiyne (**1**). A sequence of two carbo-palladations leads to intermediate trienylpalladium complex (**2**). A 6π-elecrocyclization/β-hydride elimination, or alkene electrophilic palladation/reductive elimination of (**2**) gives the pentacyclic structure (**3**), which on further 6 steps gives the product rubriflordilactone A (**4**).

IA.7. References

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CHAPTER IB

IB. An Outline of Transition Metal-Catalyzed C–H Functionalization

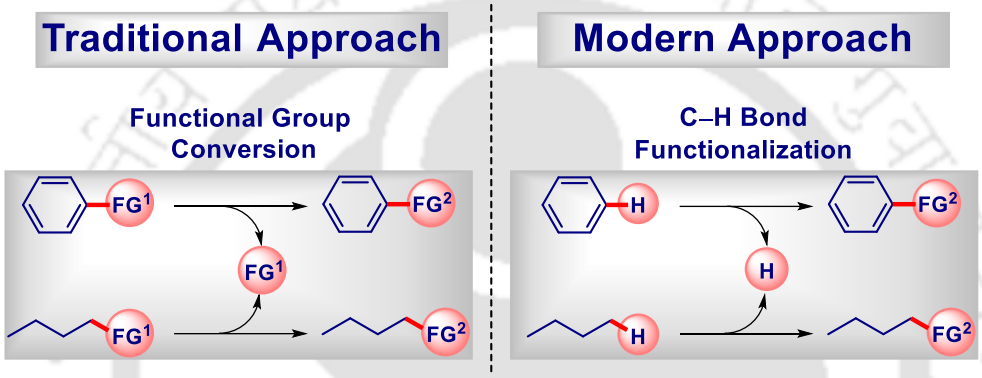
IB.1. Introduction

The evolution of cross-coupling chemistry over the past decades have considerably improved the strategies for the construction of carbon–carbon and carbon–heteroatom bonds in both industry as well as academia.[1] The advance form of cross coupling strategy has been successfully implemented for the production of commercially important molecules.[2] Regardless of the significant progress made in this area, the methodology suffers from some major drawbacks. First, the pre-functionalization of the substrate undergoing coupling (via halogenation, metalation or other measures), which increases the number of synthetic steps and second, is the use of stoichiometric organometallic reagents thereby resulting in the chemical waste in the overall process. These issues can be overcome by the direct functionalization of the un-activated carbon–hydrogen bonds.[3] The method is reliable as it is highly step- and atom-economic and uses readily available starting materials.

Organic compounds mainly consist of chains or rings of consecutive carbon atoms, each capped with one or more hydrogen atoms. This C–H bonds are regarded as un-functionalized and taking advantage of the myriad of C–H groups as functional handles they can be explored for several bond making as well as bond breaking processes. Of late, extensive studies on transition-metal catalyzed C–H activation reaction has impressively enhanced our understanding of how to selectively functionalize the inert C–H bonds competently. Evidently, direct functionalization of C–H bonds to carbon–carbon and carbon–heteroatom bonds has matured to the point where it can be contemplated as a viable strategy for the synthesis of complex targets by means of shortest possible route. The strategy embraces enormous potential of further development in the field of chemical synthesis.

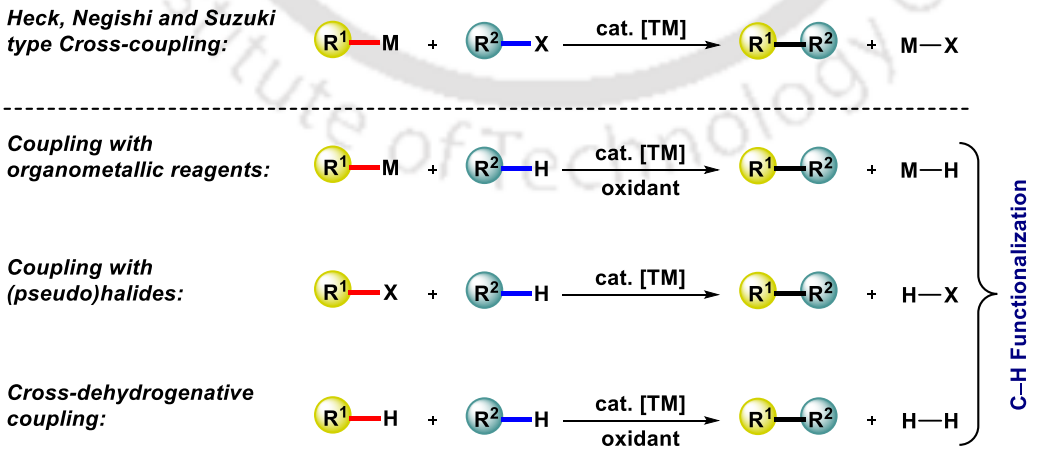
IB.2. Traditional Vs Modern Approach

Traditional organic reactions mainly involve the exchange of an existing functional group (FG) with a new one (Scheme IB.2.1). To achieve this, the starting material needs to be pre-functionalized i.e. a functional group (FG^1) is first installed and then removed in the subsequent step as byproduct (Scheme IB.2.1). Consequently, the efficiency and atom economy of the process decreases and it also adds extra step and cost to the overall transformation. On the contrary, modern C–H functionalization strategy does not require any prefunctionalized starting materials (Scheme IB.2.1).



Scheme IB.2.1. *Traditional vs modern approach*

The invention of transition metal-catalyzed coupling reactions has set the stage for new developments in the field of synthetic organic chemistry. In 2010 *R. F. Heck*, *E. Negishi* and *A. Suzuki* were awarded with Noble Prize in chemistry for their significant contribution to the development of palladium-catalyzed cross-coupling reactions.[4]

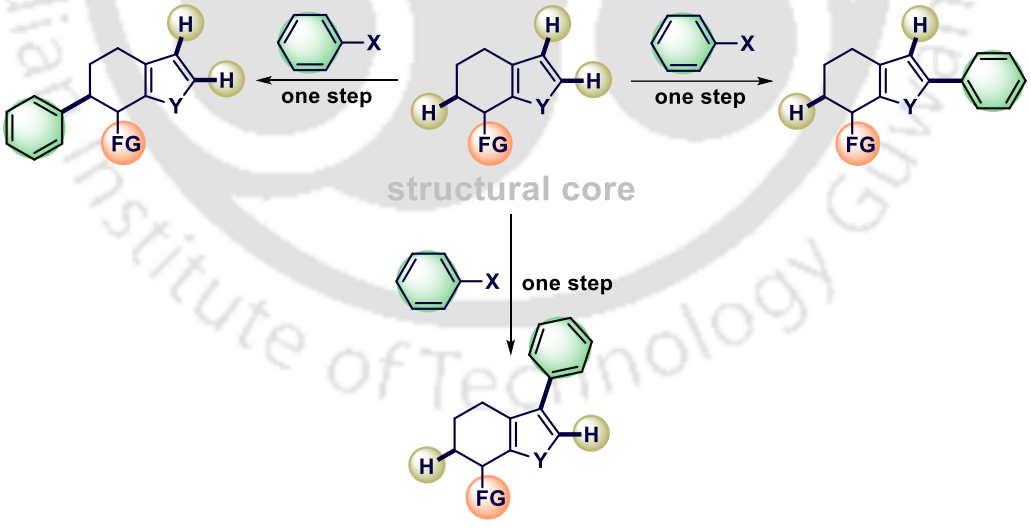


Scheme IB.2.2. *Developing algorithm in organic synthesis*

Gradually with time, chemists developed new ideas on transition metal-catalyzed C–H bond functionalization in order to circumvent the pre-functionalization of starting materials. The Scheme IB.2.2 shows how transition metal-catalyzed cross-coupling reactions have evolved starting from the traditional coupling to the modern C–H bond functionalization approach.

The ubiquitous nature of C–H bonds makes it quiet challenging for a chemist to selectively functionalize every C–H bonds. If this problem is resolved, the area of chemical synthesis and drug discovery would be revolutionized forever. Just like natural enzymes, which have specific structure to achieve site selective C–H oxidations, organic chemists need to develop selective catalyst or substrates to achieve any predictable site selectivity in a target molecule. Molecules isolated from nature are the renewable sources of simple organic molecules. Therefore, selective diversification of these readily available molecules exemplifies the progress towards sustainable drug discovery and production of useful chemicals.

In addition to the assembly of specific target molecules, C–H bond functionalization also re-shapes synthetic strategies for preparation of series of compounds [“structural core diversification” (Scheme IB.2.3)].



Scheme IB.2.3. *Structural core diversification by means of C–H functionalization*

The potential to selectively target a number of different C–H bonds in a complex molecule gives privilege of direct access to multiple analogues from a common structural precursor which were earlier not feasible via traditional coupling strategy. Hence, treating

C–H bonds as "ubiquitous functionality", a new chapter is being opened in organic synthesis with many exciting opportunities.

IB.3. Challenges to C–H Functionalization

C–H functionalization has emerged as an ideal synthetic strategy from the step and atom economy point of view. However, the most important challenges that a chemist have to face is the selectivity and reactivity due to the ubiquitous nature and relative bond energies of C–H bonds. Inherent low reactivity, regio-, chemo-, and stereo-selectivity are the four major challenges in C–H functionalization.

✓ **Inherent Low Reactivity:**

The organic compounds that are readily available mainly have sp^2 or sp^3 hybridized C–H bonds with pK_a values in the range of 45–50. These bonds are associated with huge kinetic barriers and large amount of energy is required to cleave these bonds which is difficult to achieve via homolytic and heterolytic pathways.

✓ **Regioselectivity:**

Selectively functionalizing a preferred C–H bond while leaving all other C–H bonds intact is a difficult task. For example, the pharmaceutical drug Cinacalcet, sold as "Sensipar" or "Mimpara" shown in Figure IB.3.1, possess multiple distinct C–H bonds.

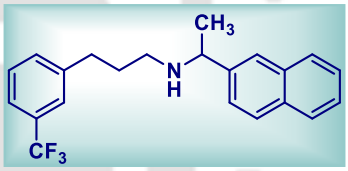
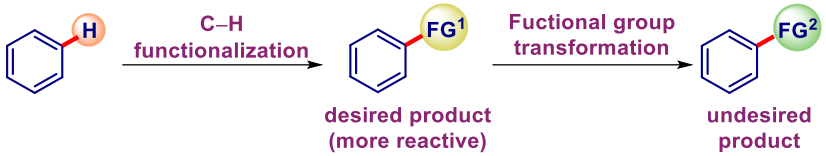


Figure IB.3.1. *Drug molecule 'Sensipar' having multiple unique C–H bonds.*

Site-selective functionalization of anyone of these various sites could be highly desirable for structure-activity relationship studies in search of new drug derivatives or to study the pharmacokinetics.

✓ **Chemoselectivity:**

Chemoselectivity means the selective reactivity of one of the functional group in the presence of others. Suppose during C–H functionalization, if the desired product formed is more reactive than the starting material, there is the possibility for it to undergo further functional group transformation giving undesired products (Scheme IB.3.1).



Scheme IB.3.1. *Chemoselectivity issue in C–H functionalization*

✓ **Stereoselectivity:**

The C–H functionalization reactions generally demands harsh reaction conditions and elevated temperature to overcome the inertness of the C–H bonds. Consequently, it might have adverse effects on the stability of the chiral complexes and the efficiency of asymmetric induction. Therefore, introducing new stereogenic centre with high diastereo- or enantio-selective isomer is the most challenging task in C–H functionalization process.

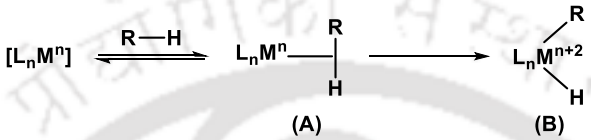
Preserving the existing functionality in the precursor molecules during transformation as well as controlling the competing side reactions such as homo-and hetero-coupling are few more concerns related to C–H functionalization process. Hence, resolving the *reactivity* and *selectivity* issues minimizes these effects also.

IB.4. Mechanisms of C–H Functionalization

Two different mechanistic pathways have been proposed by Sanford *viz.* 'inner sphere mechanism' and 'outer sphere mechanism'.[5] In inner sphere mechanism, the transition metal undergoes insertion into a C–H bond forming a discrete organometallic intermediate having C–M bond. This *in situ* generated species converts to a new functional group by reacting with an external reagent or an organic ligand attached to the metal centre.[6] Whereas in outer sphere mechanism the C–H bond of the substrate does not interact directly with the metal centre but instead react with the ligand coordinated to the metal centre.[6] However, these mechanisms were restricted to saturated C–H bonds only. Later, Bercaw gave a more elaborate classification as: (i) oxidative addition; (ii) σ-bond metathesis; (iii) electrophilic activation; (iv) metalloradical activation; and (v) 1,2-addition.[7] Out of these five distinct mechanisms involved in the formation of stable organometallic species, three of these are quite common, while the other two are rare.

(a) Oxidative Addition

During oxidative addition the transition metal coordinates to a C–H σ-bond and donates the electron density into the σ* orbital of the C–H bond (Scheme IB.4.1, complex **A**). This reduces the bond order and weakens the C–H bond resulting into the formation of a new metal-carbon bond (Scheme IB.4.1, complex **B**). Thus, the cleavage of the C–H bond by transition metal ion leads to an increase in the oxidation state of the transition metal.



Scheme IB.4.1. *Oxidative addition mechanism*

A qualitative molecular orbital diagram showing only the C–H–M π interaction (M = metal) is shown in Figure IB.4.1. The resulting organometallic intermediate can then be further manipulated to release different carbon–X bonds, where X is carbon, nitrogen, oxygen, halogen etc. Oxidative addition reactions are typical for electron-rich, low-valent complexes of the "late transition metals" such as Re, Fe, Ru, Os, Rh, Ir, and Pt.

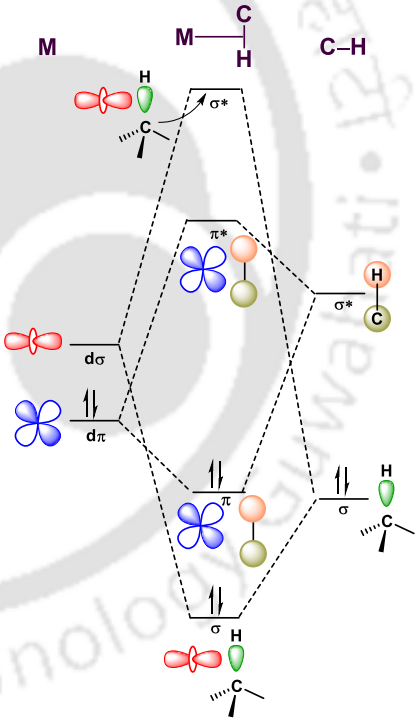
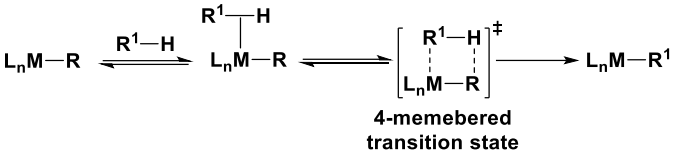


Figure. IB.4.1. *A qualitative MO diagram for oxidative addition*

(b) Sigma Bond Metathesis



Scheme IB.4.2. *A σ-bond metathesis mechanism*

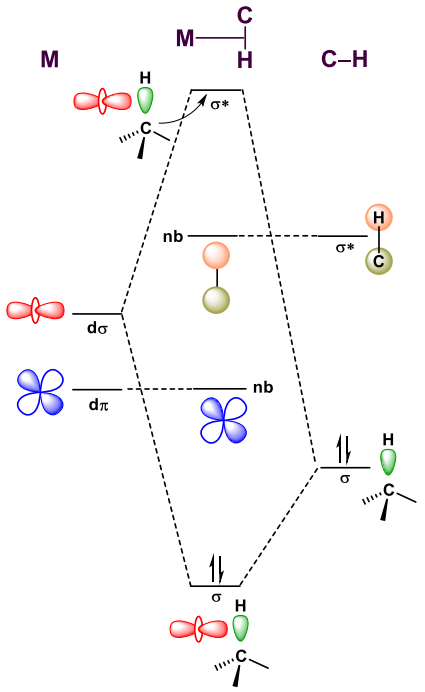
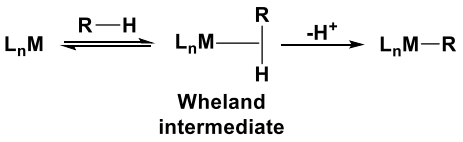


Figure. IB.4.2. *A qualitative MO diagram for σ-bond*

In this mechanism the cleavage and formation of σ-bond is catalyzed by alkyl or hydride complexes of "early transition metals" with d^0 electronic configuration such as scandium, lanthanides and actinides. These metals mostly belong to group III of the periodic tables. However, some examples of transition metals from groups IV and V are also known. Extensive experimental and theoretical studies have led to the theory of a four-centre transition state (Scheme IB.4.2). A qualitative molecular orbital diagram of this reaction specifies that there is no π interaction because of the absence of any d-electrons (Figure IB.4.2).

(c) Electrophilic Activation



Scheme IB.4.3. *An electrophilic activation mechanism*

Electrophilic activation mechanism mainly involves late transition metals with higher oxidation state. In aromatic nucleus the reaction proceeds via two stages: (i) the electrophilic species adds to the arene forming a Wheland intermediate, (ii) loss of a proton giving a discrete σ-organyl complex (Scheme IB.4.3).

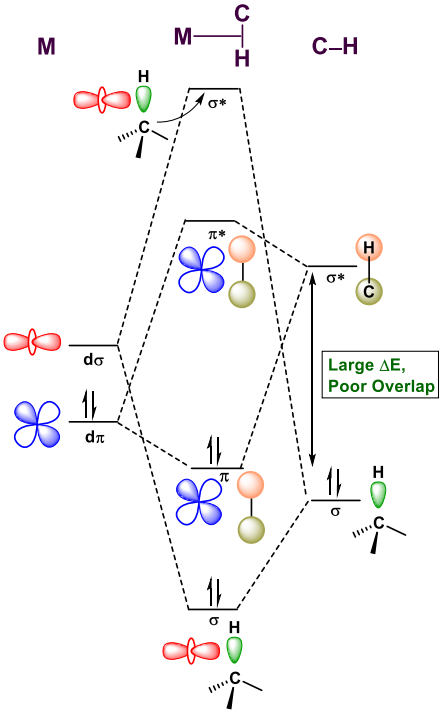
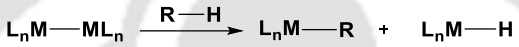


Figure. IB.4.3. *A qualitative MO diagram for electrophilic activation*

In case of saturated hydrocarbons, an analogous intermediate might be formed with an electrophilic metal-containing species. A qualitative molecular orbital diagram (Figure IB.4.3) for this reaction shows that it usually involves late or post-transition metals (Pd^{2+}, Pt^{2+}/Pt^{4+}, Hg^{2+} and Tl^{3+}) where d orbitals energy is dropped.

(d) Metalloradical Activation

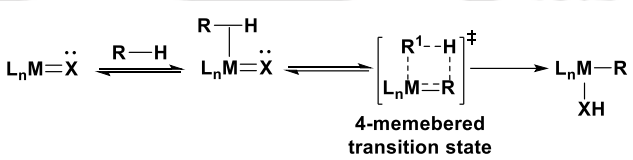
The metalloradical C–H activation is mainly shown by alkane C–H bonds. The transition metal complex exists in monomer–dimer equilibrium that reversibly break alkane C–H bonds and the two fragments are attached to two different halves of the metal complex (Scheme IB.4.4). Rhodium and ruthenium complexes are usually employed for this activation reactions.



Scheme IB.4.4. *C–H activation mechanism via metalloradical pathway*

(e) 1,2-Addition

In 1,2-addition, the alkane C–H bond adds to a metal–non-metal double bond forming a 4-memebered transition state as depicted in Scheme IB.4.5. Addition of the C–H bond across metal-nitrogen and metal-carbon double bonds of early and middle transition-metal are known, but the scope and its potentiality still remain uncertain.



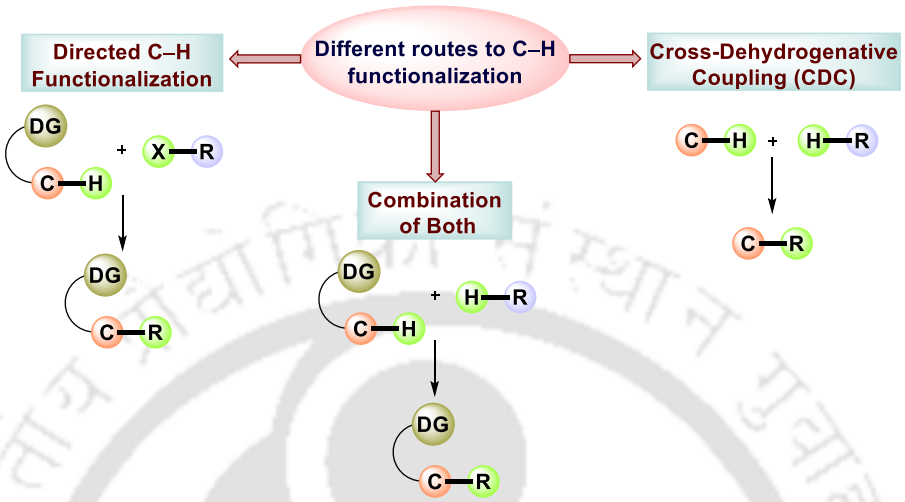
Scheme IB.4.5. *1,2-Addition mechanism*

The mechanistic pathways for C–H bond activation categorized above takes place in the presence of a transition metal complex. The metal insertion into the C–H bond is called "true" activation as the C–H bond containing substrates enter into the coordination sphere of the metal complex forming an σ-organyl ligand. Therefore, there is a close interaction between the metal ion and the C–H bond (i.e. a normal σ-bond between metal and carbon).

IB.5. Modern Approach to C–H Functionalization

The "golden period" of C–H bond functionalization flourished during early 1990's in which numerous metal salts and complexes were scrutinized for catalytic C–H activation process. The methodology generally implements two major strategies *viz.* (i) directing

group assisted C–H functionalization and (ii) cross-dehydrogenative coupling (CDC) (Scheme IB.5.1). Furthermore, there are approaches which are based on the combination of both the strategies (Scheme IB.5.1).



Scheme IB.5.1. *Different routes to C–H functionalization*

IB.5.1. Directing Group Assisted C–H Functionalization

Controlling the positional selectivity of C–H bond cleavage in a molecule containing multiple C–H bonds and to outwit their inert nature is an outstanding challenge that need to be addressed. These problems are overcome by the predominant use of directing groups (DGs). Directing groups are generally σ-coordinating functional groups containing electronegative atoms such as nitrogen (N), oxygen (O), and sulfur (S), which by pre-coordination place the metal catalyst in close proximity to the specific C–H bond that has to be functionalized. The key step in directing group-assisted C–H functionalization is the formation of a five- or a six-membered cyclometallated intermediate which is both thermodynamically and kinetically favoured. This intermediate than leads to the construction of new C–C or C–heteroatom bonds via C–H functionalization. Directed metalation is a powerful approach for selective functionalization of C–H bonds in substrates possessing a variety of C–H bonds.[8] In addition to *ortho*-functionalization,[9] employing suitable DGs has led the chemists to achieve functionalization even at *meta*-[10] and *para*-positions.[11] The strategy is also useful for functionalization at various positions (α, β, γ and δ) of diverse aliphatic systems.[12]

Despite the extensive utility of DG-assisted C–H functionalization, the installation and removal of these DGs adds additional steps thereby compromising the step- and atom-economical nature of the overall C–H activation strategy. However, in recent years these problems have been resolved either by using a transient directing group[13] or by implementation of a traceless directing group.[14] In other cases, the DG is an intrinsic functional group in the substrate and serves as an essential component in products. Hence, there is no need for extra installation or cleavage steps. The transition-metals commonly employed in this methodology are Ru, Rh, Pd, and Cu. Other transition metals such as Mn, Fe, Co, Ni, Re, Ir, Pt, Ag, Au are also being explored. With the evolution of this methodology over the past two decades, the strategy has been successfully implemented for the diverse functionalization of the C–H bonds *viz.*

(i) arylation,[15] alkylation,[16] alkenylation,[17] alkynylation,[18] carbonylation,[19] trifluomethylation,[20] cyanation[21] via C–C bond formation.

(ii) acetoxylation,[22] benzoxylation,[23] hydroxylation,[24] alkoxylation[25] via C–O bond formation.

(iii) amination,[26] amidation,[27] nitration[28] via C–N bond formation.

(iv) sulfonylation,[29] sulfenylation[30] via C–S bond formation.

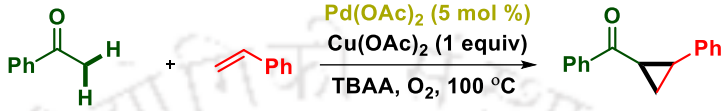
(v) halogenation,[31] borylation,[32] silylation,[33] and selenation[34] via C–X bond formation where (X = F, Cl, Br, I, B, Si, Se) etc.

In addition to the above-mentioned C–H bond functionalization reactions, recent years have witnessed an upsurge in metal-catalyzed cycloaddition processes or annulation. These transformations are highly appealing from synthetic perspective as it allows the conversion of readily available substrates into highly valuable cyclic molecules. Most annulation strategy requires the presence of a heteroatom (as DG) in the substrate that enhances the reactivity and controls the regioselectivity by driving the metal complex to the reacting C–H site. The heteroatom can either be a part of the final ring or may get eliminated.

As one of the chapter in the thesis focuses on thiocarbonyl directed C–H activation and annulation, below are some representative examples of heteroatom directed annulation that has been classified based on the number of atoms involved in annulation. The notation used here is described by Huisgen with parentheses and with number referring to the atoms involved in the ring formation.[35]

(a) [2 + 1] Annulations

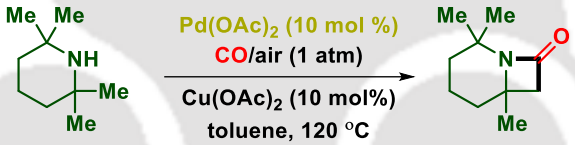
In 2014, Cotugno *et al.* described a [2 + 1] annulation between aryl methyl ketones and styrene giving cyclopropanes (Scheme IB.5.1.1).[36] The reaction involves the cleavage of two C–H bonds at the α-position of ketone. The reaction is catalyzed by $Pd(OAc)_2$ and utilizes stoichiometric amount of $Cu(OAc)_2$ as the oxidant and molten TBAA (tetrabutylammomnium acetate) as the solvent under O_2 atmosphere.



Scheme IB.5.1.1. *Pd(II)-catalyzed assembly of cyclopropane*

(b) [3 + 1] Annulations

Gaunt group demonstrated a Pd-catalyzed C–H carbonylation of aliphatic amines to construct β-lactames (Scheme IB.5.1.2).[37] The transformation can be considered as a [3 + 1] annulation and the use of hindered amines is crucial for the accomplishment of the reaction.

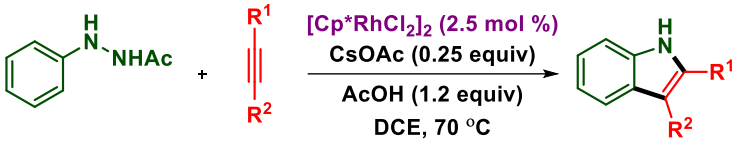


Scheme IB.5.1.2. *Pd(II)-catalyzed carbonylation of aliphatic amine*

(c) [3 + 2] Annulations

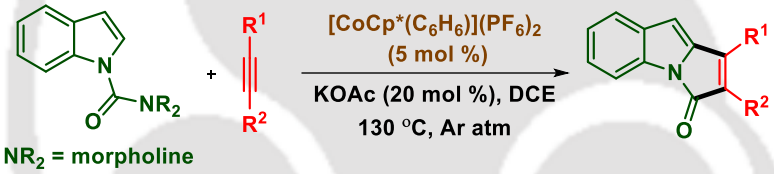
A few examples of [3 + 2] annulation is the formation of heterocycles such as indoles, pyrroles and benzofurans. Fagnou and co-workers reported the synthesis of indole from anilides and alkynes catalyzed by Rh(III) complex. Initially, the reaction employed stoichiometric amount of $Cu(OAc)_2$ as the oxidant and high reaction temperature.[38a] However, consequent studies led to the use of molecular oxygen as the oxidant and milder reaction conditions.[38b-d] Gradually, with the innovation of redox-neutral C–H functionalization where an oxidizing functional group serves both as a directing group and an internal oxidant,[39] alternative methods have been developed for the synthesis of indoles. These methods involve the use of anilide derivatives such as arylhydrazines, hydrazones or nitrosoaniline, where N–N bond functions as an internal oxidant.[40] Based on this, Glorius group reported a mild and efficient Rh(III)-catalyzed redox-neutral C–H

activation/cyclization reaction for the formation of indoles from *N*-acetyl-1-arylydrazines and alkynes (Scheme IB.5.1.3).[41] The reaction does not require any external oxidant.



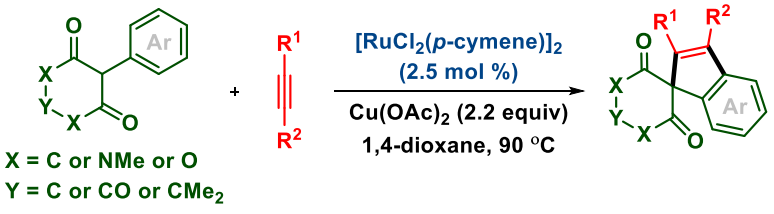
Scheme IB.5.1.3. *Annulation between N-acetyl-1-arylydrazines and alkyne*

In 2014, Matsunaga, Kanai and co-workers disclosed a C-2 selective *N*-carbamoyl indoles alkenylation/annulation reaction with internal alkynes to synthesize pyrroloindolones using $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ complex and KOAc as the additive (Scheme IB.5.1.4).[42] Glorius *et al.* also developed a Co(III)-catalyzed redox-neutral synthesis of indoles by the reaction of *N*-BOC hydrazine derivative with alkynes showing wide range of functional group tolerance.[43] After this report, Jiao and Zhu groups independently reported the indole synthesis by reacting alkyne with *N*-nitroso aniline[44] and arylhydrazine[45] respectively.



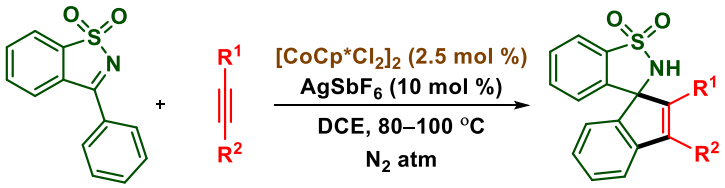
Scheme IB.5.1.4. *Cobalt-catalyzed synthesis of pyrroloindolones*

Using enamides instead of anilides provided pyrroles[46] and utilizing phenols instead of aniline derivatives generated benzofurans.[47] Apart from the heterocycle synthesis, [3 + 2] cycloaddition was also used to generate carbocycles. Lam group reported his finding in numerous articles on the synthesis of spiroindenes from 2-aryl-1,3-carbonylic compounds and alkynes using Ru(II) or Pd(II) complexes (Scheme IB.5.1.5).[48] Luan and co-workers also demonstrated related Ru-catalyzed annulation using 2-phenylnaphthols or electron-rich phenylphenols as substrates.[49]



Scheme IB.5.1.5. *Ru-catalyzed synthesis of spiroindenes from phenyldiones and alkyne*

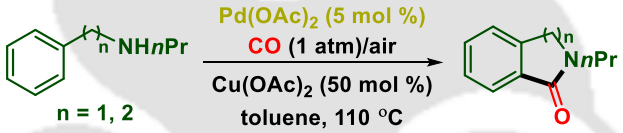
Wang *et al.* reported an efficient Cp*Co(III)-catalyzed synthesis of spiro indenyl benzosultams via directed C–H alkenylation/annulation of *N*-sulfonyl ketimine with alkynes (Scheme IB.5.1.6).[50]



Scheme IB.5.1.6. *Co-catalyzed synthesis of spiro indenyl sultams*

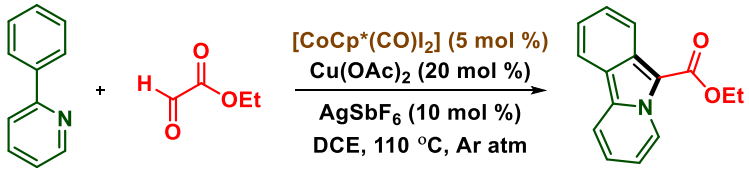
(d) [4 + 1] Annulations

Orito *et al.* demonstrated a Pd(II)-catalyzed direct aromatic carbonylation of *N*-mono-alkylated benzylamines with CO resulting into the synthesis of five- or six-membered benzolactams (Scheme IB.5.1.7)[51] representing an example of formal [4 + 1] annulation. Later, using similar approach Yu and co-workers reported several related annulation involving C(sp^3)–H bond activation in α-substituted amides.[52]



Scheme IB.5.1.7. *Carbonylation of C(sp^2)–H and C(sp^3)–H bonds*

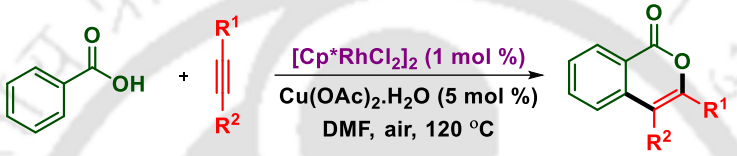
Ellman group described the first Co(III)-catalyzed azobenzene and α,β-unsaturated oxime directed sp^2 C–H activation followed by addition reaction with aldehydes to furnish indazoles and furans respectively.[53] Li and co-workers established a cooperative Co(III)/Cu(II) catalyzed C–H activation of imidate esters and oxidative coupling with anthranils resulting into an efficient synthesis of 1*H*-indazoles.[54] Zeng *et al.* uncovered a Co(III)-catalyzed [4 + 1] dehydrative cyclization of 2-arylpyridine or 2-alkenylpyridines with activated aldehydes such as ethyl oxoacetate giving diverse indolizines (Scheme IB.5.1.8).[55]



Scheme IB.5.1.8. *Synthesis of indolizine via Co-catalyzed dehydrative annulation*

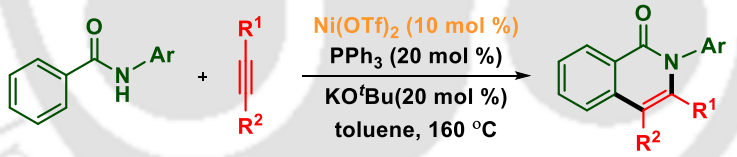
(e) [4 + 2] Annulations

In 2007, Miura e*t al.* made a significant breakthrough in formal [4 + 2] annulation by demonstrating the synthesis of isocoumarins by heating benzoic acids with internal alkynes in the presence of catalytic amount of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2.H_2O$ as the oxidant (Scheme IB.5.1.9).[56] It was later found that acrylic acids can also undergo similar transformation involving the cleavage of vinylic C–H bond.[57] Ackermann group reported similar reaction with Ru(II) catalyst using oxygen as the sole oxidant.[58] Sundararaju and co-workers established a Co-catalyzed synthesis of isocoumarins and pyrones through the oxidative cyclization of benzoic acid and acrylic acid derivatives with alkynes.[59]



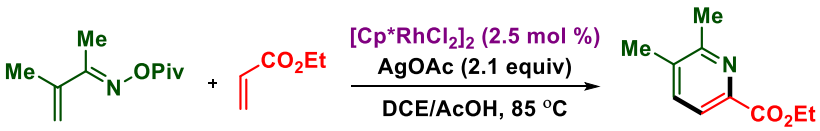
Scheme IB.5.1.9. *Rh-catalyzed synthesis of isocoumarins*

Similar annulation reactions were reported from benzamide derivatives and alkynes affording isoquinolones using Rh[60] or Ru[61] or Co[62] catalysts. Recently, Chatani *et al.* reported a Ni(II)-catalyzed production of isoquinolones from benzamides and alkynes (Scheme IB.5.1.10).[63]



Scheme IB.5.1.10. *Ni-catalyzed synthesis of isoquinolones*

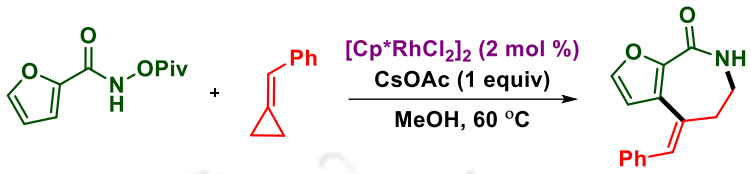
Rovis *et al.* reported [4 + 2] annulation with activated alkenes and *O*-pivaloyloximes resulting into the assembly of substituted pyridines (Scheme IB.5.1.11).[64] The reaction is catalyzed by $[Cp^*RhCl_2]_2$ and is exceptionally regioselective giving high yields.



Scheme IB.5.1.11. *Synthesis of pyridine derivatives from pivaloyloxime and alkene*

(f) [4 + 3] Annulations

Cui group reported the synthesis of furan-fused azepinones via [4 + 3] annulation of furancarboxyamides with benzylidenecyclopropanes catalyzed by Rh complex (Scheme IB.5.1.12).[65]

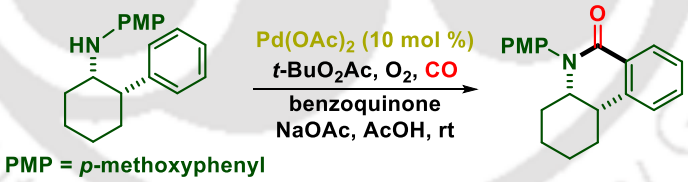


Scheme IB.5.1.12. *Rh-catalyzed annulation of furancarboxyamide and alkylidenecyclopropane*

The same group later reported the synthesis of azepinones from benzamides and vinylcarbenoids as three-carbon component via Rh(III)-catalyzed C–H activation / [4 + 3] cycloaddition.[66]

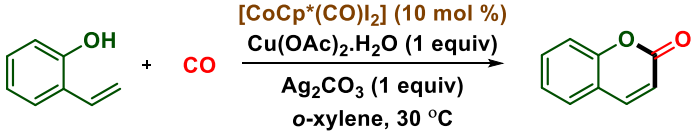
(g) [5 + 1] Annulations

Gaunt and co-workers accomplished the synthesis of six-membered lactams from β-arylethylamines and CO catalyzed by Pd(II) complex at room temperature (Scheme IB.5.1.13).[67] The Shi research group reported a related carbonylation of 2-arylphenols giving lactones using Pd(II) catalyst.[68] Similar carbonylation process was described by Inamoto *et al.* promoted by Ru(II) catalyst.[69]



Scheme IB.5.1.13. *Carbonylation of secondary amines*

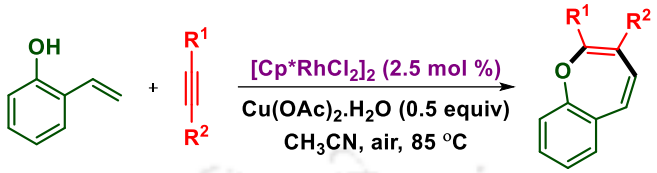
A Cp*Co(III)-catalyzed annulation of 2-alkenylphenols with CO was reported by Wang group affording coumarin derivatives. Mild reaction conditions, broad substrate scope, and good functional group tolerance are the notable features of the reaction (Scheme IB.5.1.14).[70]



Scheme IB.5.1.14. *Oxidative cyclization of 2-vinylphenols with carbon monoxide*

(h) [5 + 2] Annulations

In 2014, Mascareñas, Gulías and co-workers reported a [5 + 2] annulation between *o*-vinylphenols and alkynes producing benzoxepines in an atom economical manner (Scheme IB.5.1.15).[71]



Scheme IB.5.1.15. *Synthesis of benzoxepines from o-vinylphenols and alkynes*

In all the above mentioned annulations, the mechanism involves the C–H bond cleavage leading to the formation of an organometallic complex. Than the migratory insertion of the unsaturated partner followed by reductive elimination gives the desired cyclic product.

IB.5.2. Cross-Dehydrogenative Coupling (CDC)

Cross-dehydrogenative coupling exemplifies one of the most powerful tool and advance form of C–H functionalization. This strategy generally implies the formation of C–C or C–X bonds by reacting two C–H bonds or C–H and X–H (X = heteroatom) bonds.[72] This methodology has an inherent advantage of higher atom economy, shorter synthetic routes, low cost and less waste. However, irrespective of the name, H_2 gas is not usually the byproduct of these transformation and generally requires an external driving force mainly a suitable sacrificial oxidant. These oxidants may be in the form of oxygen such as hydrogen peroxides or organic peroxides like *tert*-butyl hydrogen peroxide (TBHP) or *tert*-butyl peroxide (TBP), and *N*-halosuccinimides such as *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) which accepts the hydrogen generated during the course of the reaction. Transition metal catalysts commonly employed for the CDC reactions are Fe, Cu, Pd, Zn, Ni, Mn. With the growing development in this area, more sustainable and environmentally benign methods have been reported which are performed in the absence of any metal salts, in aqueous medium and even using photocatalysts.

Advantages:

- ✓ No need of pre-functionalized starting materials or any directing group.
- ✓ Ambient reaction conditions and simple starting materials.
- ✓ High degree of C–H bond activation.

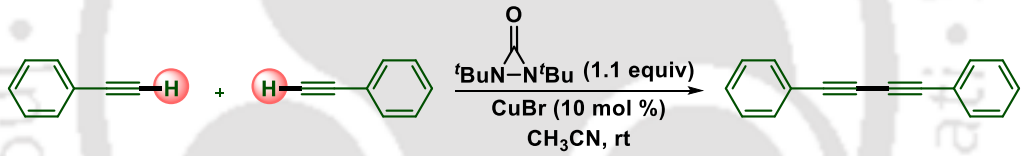
Limitations:

- ✓ Regioselectivity issues as functionalization can occur at any of the C–H's.
- ✓ Lacking of chemoselectivity due to over-functionalization.

Representative Examples of CDC Reactions

➢ **$C_{(sp)}$–$C_{(sp)}$ Bond Formation**

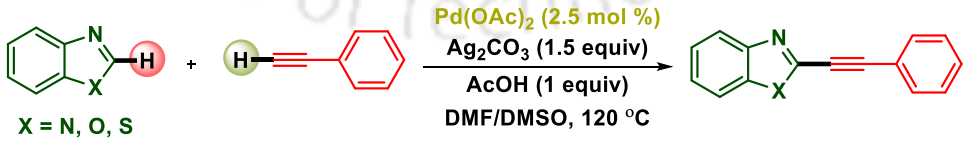
A mild and efficient Cu(I)-catalyzed oxidative homocoupling of terminal alkynes was reported by Shi *et al.* in the presence of diaziridinone as an oxidant (Scheme IB.5.2.1).[73] Various terminal alkynes were effectively coupled to give 1,4-disubstituted 1,3-diynes in good yields.



Scheme IB.5.2.1. *Cu(I)-catalyzed homocoupling of terminal alkynes*

➢ **$C_{(sp)}$–$C_{(sp2)}$ Bond Formation**

An oxidative coupling of heteroarenes such as imidazole, benzimidazole, imidazo[1,5-*a*]pyridine, oxazole, benzoxazole, thiazole, and benzothiazole with terminal alkynes was developed by Murai *et al.* (Scheme IB.5.2.2).[74] They used a combination of palladium and silver salts in polar solvents like DMF or DMSO at 120 °C.

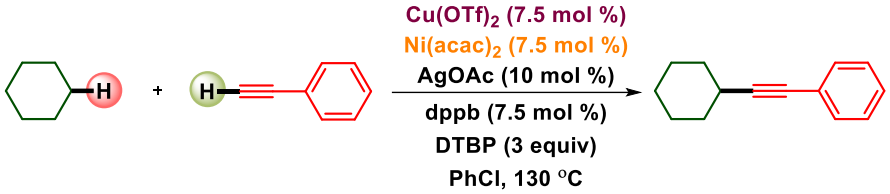


Scheme IB.5.2.2. *Pd(II)-catalyzed direct alkynylation of heteroarenes*

➢ **$C_{(sp)}$–$C_{(sp3)}$ Bond Formation**

Lei group developed a combined Cu/Ni/Ag catalytic system to achieve the oxidative C(sp^3)–H/C(sp)–H cross coupling of unactivated alkanes with terminal alkynes (Scheme

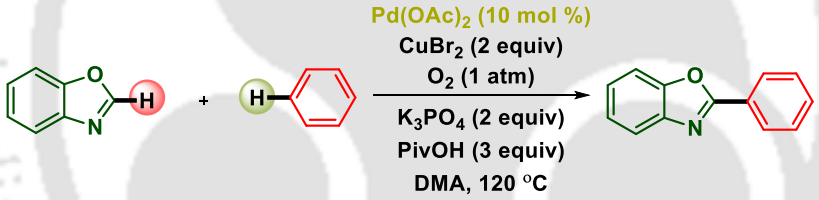
IB.5.2.3).[75] The utilization of multi-metallic catalysis was the key for controlling the reaction selectivity toward $C_{(sp)}$–$C_{(sp3)}$ bond formation.



Scheme IB.5.2.3. *Multimetallic catalyzed direct alkynylation of unactivated alkanes*

➢ **$C_{(sp2)}$–$C_{(sp2)}$ Bond Formation**

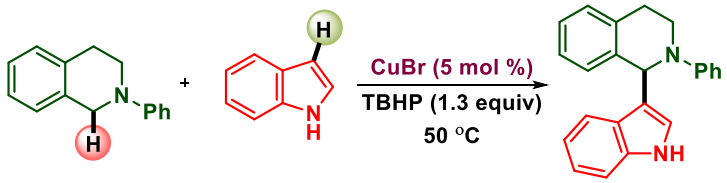
Su *et al.* developed a palladium-catalyzed intermolecular sp^2 C–H/C–H cross coupling of benzoxazoles with unactivated simple arenes (Scheme IB.5.2.4).[76] In this reaction $CuBr_2$ is used as an additive and K_3PO_4 as the base in O_2 atmosphere. Homocoupling was successfully suppressed such that no traces of bis-heteroaryls were obtained through the selective cleavage of C–H bonds in both the substrates without the requirement of pre-functionalized substrate.



Scheme IB.5.2.4. *Pd(II)-catalyzed oxidative sp^2 C–H/sp^2 C–H coupling*

➢ **$C_{(sp2)}$–$C_{(sp3)}$ Bond Formation**

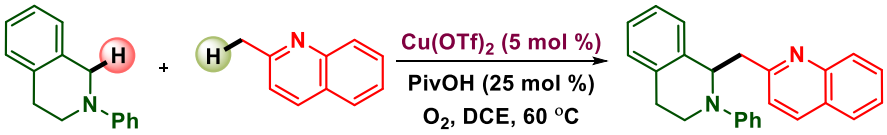
Li and co-workers reported a Cu(I)-catalyzed direct indolation of tetrahydroquinoline by dehydrogenative coupling between sp^3 C–H and sp^2 C–H (Scheme IB.5.2.5).[77] Relatively mild reaction condition, use of free (NH) indoles, tolerance of various functional group, high regioselectivity and use of relatively cheap metal as the catalyst are the remarkable features of this protocol.



Scheme IB.5.2.5. *Cu(I)-catalyzed indolation of tetrahydroquinoline*

➢ **$C_{(sp3)}$–$C_{(sp3)}$ Bond Formation**

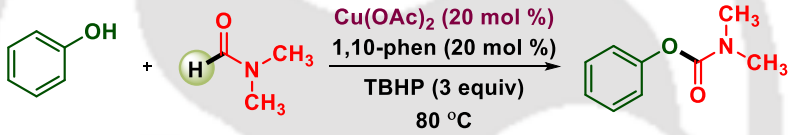
A copper/Brønsted acid dual-catalyst promoted oxidative dehydrogenative coupling of alkylazaarenes with tertiary amines was developed by Yang group (Scheme IB.5.2.6).[78] The reaction utilizes dioxygen as the terminal oxidant under mild reaction conditions.



Scheme IB.5.2.6. *Dual-catalyst promoted coupling of alkylazaarenes and tertiary amines*

➢ **$C_{(sp2)}$–O Bond Formation**

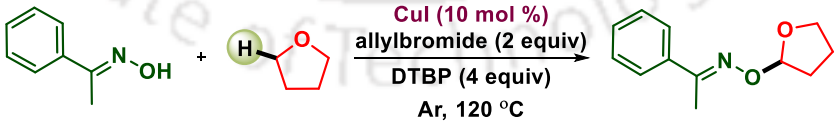
A novel phosgene free route to carbamates via copper-catalyzed oxidative C–O bond formation of formamide with phenols was demonstrated by Reddy and co-workers (Scheme IB.5.2.7).[79] 1,10-Phenanthroline as ligand was used along with TBHP as the external oxidant in this transformation.



Scheme IB.5.2.7. *Cu(II)-catalyzed synthesis of carbamates via C–O bond formation*

➢ **$C_{(sp3)}$–O Bond Formation**

Ren, Guan and co-workers reported a novel and efficient copper(I)-catalyzed oxidative coupling of oximes with THF resulting into the synthesis of tetrahydrofuran-2-yl oximes ethers (Scheme IB.5.2.8).[80] Allyl bromide acts as an additive and DTBP as the oxidant. The reaction shows good functional group tolerance.

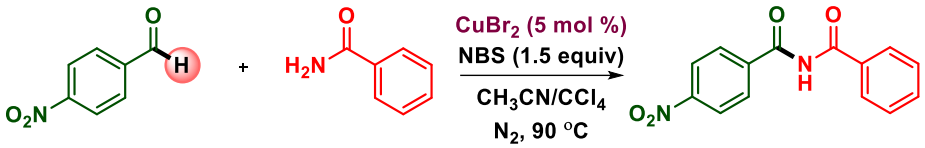


Scheme IB.5.2.8. *Cu(I)-catalyzed oxidative C–O coupling of oximes and THF*

➢ **$C_{(sp2)}$–N Bond Formation**

Fu group developed a cross-dehydrogenative coupling reaction for the synthesis of imides from aldehydes and secondary or tertiary amides (Scheme IB.5.2.9).[81] The reaction takes place in the presence of catalyst $CuBr_2$ and NBS as the oxidant. The reaction gave

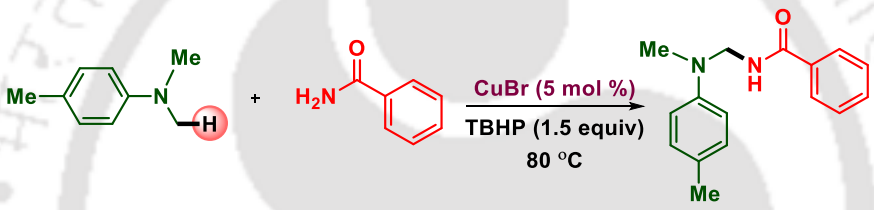
good to excellent yields of the product and showed wide functional group tolerance under mild conditions.



Scheme IB.5.2.9. *Cu(II)-catalyzed synthesis of imides via sp^2 C–H amidation*

➢ **$C_{(sp3)}$–N Bond Formation**

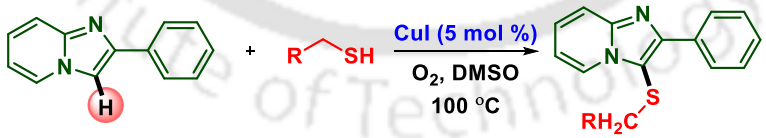
A novel copper-catalyzed amidation of unactivated sp^3 C–H bonds adjacent to a nitrogen atom was established by Fu group (Scheme IB.5.2.10).[82] The transformation takes place in the presence of inexpensive catalyst-oxidant (CuBr/t-BuOOH) system under mild reaction conditions.



Scheme IB.5.2.10. *Cu(I)-catalyzed amidation of sp^3 C–H bonds*

➢ **$C_{(sp2)}$–S Bond Formation**

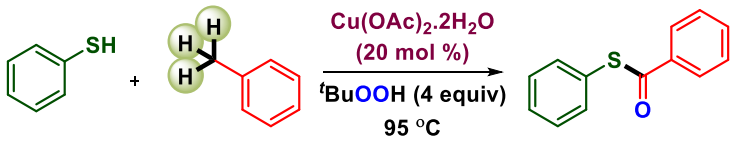
A highly regioselective C–H/S–H cross-coupling of imidazo[1,2-*a*]pyridine with thiols was developed by Cao *et al.* (Scheme IB.5.2.11).[83] The reaction takes place in the presence of copper catalyst and molecular oxygen and proceed smoothly giving broad range of substrate scope.



Scheme IB.5.2.11. *Cu(I)-catalyzed thiolation of imidazo[1,2-a]pyridine*

➢ **$C_{(sp3)}$–S Bond Formation**

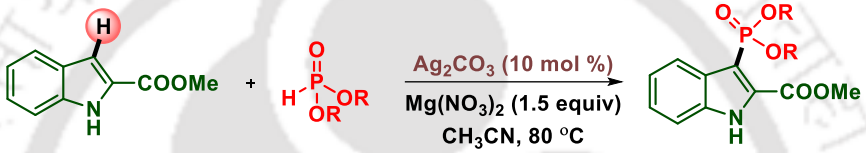
A unique Cu(II)-catalyzed cross-dehydrogenative coupling (CDC) of thiols and alkylbenzene has been developed by our group for the synthesis of thioesters without the assistance of any directing group (Scheme IB.5.2.12).[84] A thioester moiety is created via successive C–S and C–O bond formation at the expense of three sp^3 C–H bonds of the alkylbenzene and one sp^3 S–H bond of the thiol.



Scheme IB.5.2.12. *Cu(II)-catalyzed synthesis of thioesters*

➢ **$C_{(sp2)}$–P Bond Formation**

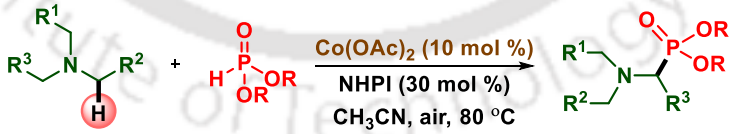
Zou and co-workers developed a silver-catalyzed direct sp^2 C–H phosphorylation of indoles in the presence of magnesium nitrate as the oxidant (Scheme IB.5.2.13).[85] The reaction affords selectively phosphonoindoles in moderate to good yields. The protocol provides an efficient and general method for the preparation of 2- and 3- phosphorylated indoles.



Scheme IB.5.2.13. *Ag(I)-catalyzed phosphorylation of indoles*

➢ **$C_{(sp3)}$–P Bond Formation**

Recently, the first oxidative $C(sp^3)$–H phosphonylation of tertiary aliphatic amines has been developed by Tang group (Scheme IB.5.2.14).[86] The transformation involves the use of cobalt acetate as the catalyst, *N*-hydroxypthalimide (NHPI) as the co-catalyst, and air as the oxidant which enables the conversion of tertiary aromatic and aliphatic amines into α-aminophosphonates. The protocol gives moderate to excellent yield of the product under mild reaction conditions via cross-dehydrogenative coupling.



Scheme IB.5.2.14. *Co(II)-catalyzed synthesis of α-aminophosphonates*

IB.5.3. Directing Group Assisted Cross-Dehydrogenative Coupling

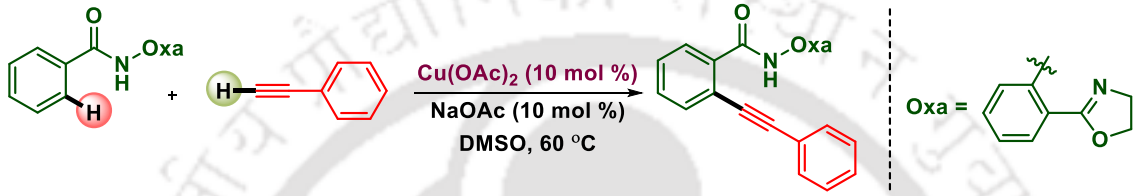
The operation of directing group and cross-dehydrogenative coupling strategy together gives the most powerful and appealing results. This approach provides selective functionalization of *ortho*-C–H bonds to form C–C and C–X (X= heteroatom) bonds. This

strategy has advantage both in terms of regioselectivity and chemoselectivity and offers higher degree of C–H bond cleavages.

Representative Examples of Directed Cross-Dehydrogenative Coupling Reactions

➢ ***Ortho*-Alkynylation**

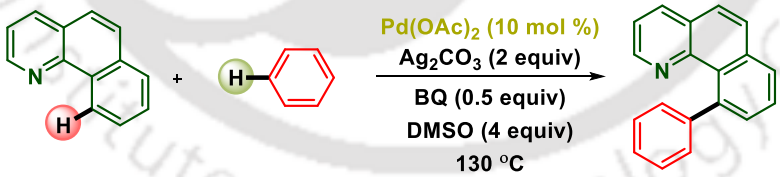
Dai, Yu and co-workers reported a Cu(II)-promoted alkynylation of arenes and heteroarenes with terminal alkynes giving aryl alkynes (Scheme IB.5.3.1).[87] The protocol serves as an alternative synthetic disconnection to Sonogashira coupling.



Scheme IB.5.3.1. *Cu(II)-catalyzed directing group assisted ortho-alkynylation of arenes*

➢ ***Ortho*-Arylation**

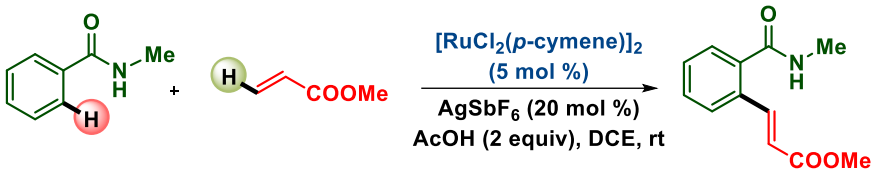
Pd-catalyzed oxidative cross-coupling of aromatic C−H bonds were achieved with high chemo- and regioselectivity by Sanford *et al.* Various directing arenes such as benzo[*h*]quinoline, 2-arylpyridine, 1-arylpyrazole, 2-arylpyrimidine and 8-methylquinoline derivatives were effectively employed under this reaction condition providing similar cross-coupled products using Ag_2CO_3 and *p*-benzoquinone as terminal oxidants (Scheme IB.5.3.2).[88]



Scheme IB.5.3.2. *Pd(II)-catalyzed ortho-arylation of benzo[h]quinoline*

➢ ***Ortho*-Alkenylation**

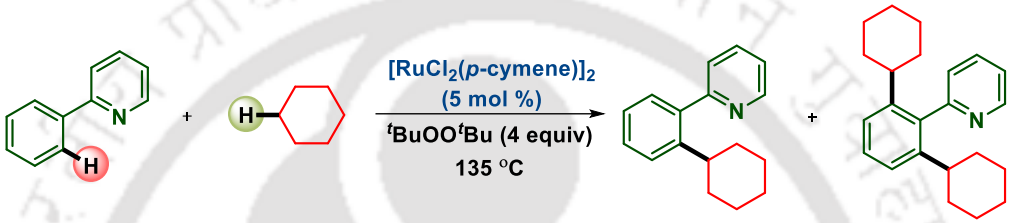
A Ru-catalyzed highly regioselective *ortho*-alkenylation of aromatic compounds such as aromatic amides, ketoximes and anilides with alkenes has been demonstrated by Jeganmohan *et al.* (Scheme IB.5.3.3).[89] The reaction takes place in the presence of $AgSbF_6$ and acetic acid in DCE at room temperature. The *ortho*-alkenylated product is obtained with the evolution of H_2 gas. In the reaction no oxidant was used and the whole transformation occurred without changing the oxidation state of the metal.



Scheme IB.5.3.3. *Ru-catalyzed ortho-alkenylation of amides*

➢ **$C_{(sp2)}$–$C_{(sp3)}$ Bond Formation**

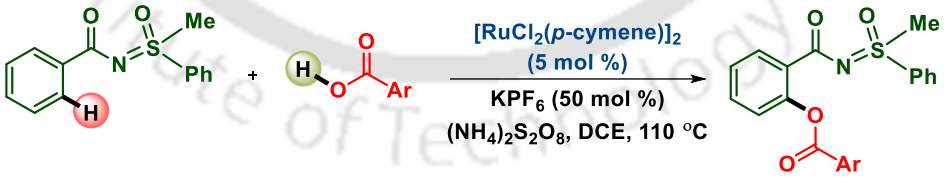
Li group developed a novel C–C bond formation based on the direct oxidative Csp^2–H/Csp^3–H coupling of directing arenes and cycloalkanes in the presence of Ru(II)-catalyst and di-*tert*-butyl peroxide (DTBP) as the oxidant (Scheme IB.5.3.4).[90]



Scheme IB.5.3.4. *Ru-catalyzed C–H cycloalkylation of 2-phenylpyridine*

➢ **$C_{(sp2)}$–O Bond Formation**

Ackermann and co-workers achieved C–H oxygenation of sulfoximine benzamides using Ru(II) catalyst (Scheme IB.5.3.5).[91] The catalytic system was characterized by excellent mono, chemo- and positional selectivity via facile base-assisted intramolecular electrophilic substitution-type C–H activation. The protocol shows high functional group tolerance and utilizes sulfoximine as the directing group that can be removed in a traceless fashion.

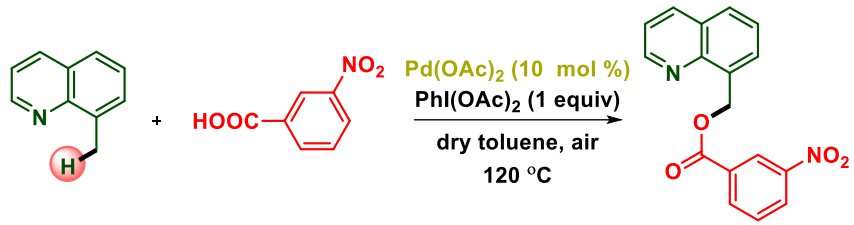


Scheme IB.5.3.5. *Ru-catalyzed C–H oxygenation of reusable sulfoximine benzamides*

➢ **$C_{(sp3)}$–O Bond Formation**

A chelation-assisted Pd-catalyzed acyloxylation of the sp^3 C–H bond of benzyl group with carboxylic acid employing $PhI(OAc)_2$ as a stoichiometric oxidant (Scheme IB.5.3.6) was demonstrated by Cheng group.[92a] The method tolerates a series of functional groups, providing the acyloxylated products in good to moderate yields. Later, Sahoo group reported a novel *S*-methyl-*S*-2-pyridyl-sulfoximine (MPyS) directed highly selective

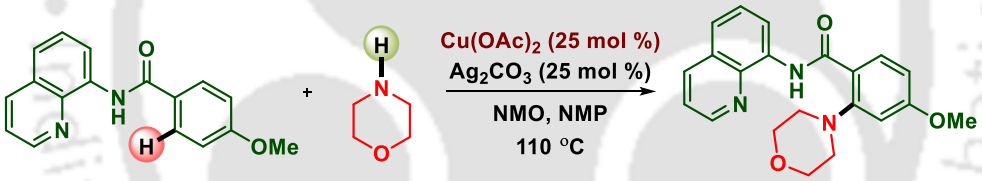
acetoxylation of the unactivated C(sp^3)–H bond.[92b] This method provides convenient access to α,α′-disubstituted-β-hydroxycarboxylic acids.



Scheme IB.5.3.6. *Pd(II)-catalyzed acyloxylation of the benzylic sp^3 C–H bond*

➢ ***Ortho*-Amination via C_{sp2}–H / N_{sp3}–H**

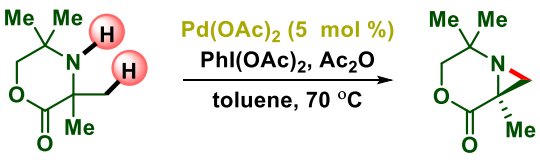
Daugulis and co-workers developed a direct amination of β-C_{sp2}–H bonds of benzoic acid derivatives and γ-C_{sp2}–H bonds of benzylamine derivatives by using aminoquinoline as the directing auxiliary (Scheme IB.5.3.7).[93] In the presence of $Cu(OAc)_2/Ag_2CO_3$ catalytic combinations reaction shows high generality and functional group tolerance, as well as providing a straightforward means for the preparation of *ortho*-aminobenzoic acid derivatives.



Scheme IB.5.3.7. *Aminoquinoline directed Cu(II)-catalyzed amination of arenes*

➢ **Amination via C_{sp3}–H / N_{sp3}–H**

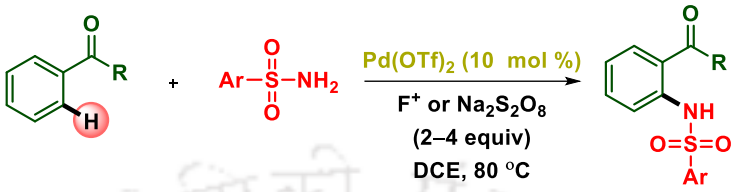
Gaunt *et al.* demonstrated a novel Pd-catalyzed intramolecular Csp^3–H amination that proceeds through an unusual four-membered-ring cyclopalladation pathway (Scheme IB.5.3.8).[37] Methyl group present adjacent to an unprotected secondary amine underwent intramolecular cyclization and transform into synthetically versatile nitrogen heterocycle such as aziridines and β-lactams via carbonylation processes.



Scheme IB.5.3.8. *Amine directed Pd(II)-catalyzed intramolecular sp^3 C–H amination*

➢ ***Ortho*-Amidation via C_{sp2}–H / N_{sp3}–H**

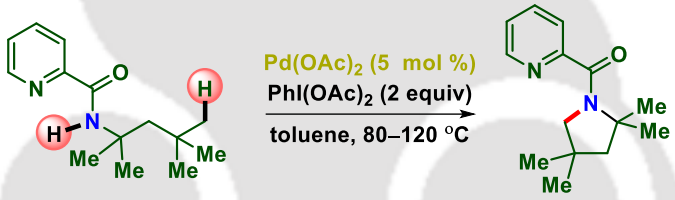
Liu group demonstrated a Pd-catalyzed directed *ortho* C–H amidation of aromatic ketones with both sulfonamides and amides (Scheme IB.5.3.9).[94] For the reaction to proceed, the use of an electron-deficient Pd complex i.e., $Pd(OTf)_2$ is highly crucial.



Scheme IB.5.3.9. *Ketone directed Pd(II)-catalyzed amidation of sulfonamides*

➢ **Amidation via C_{sp3}–H / N_{sp3}–H**

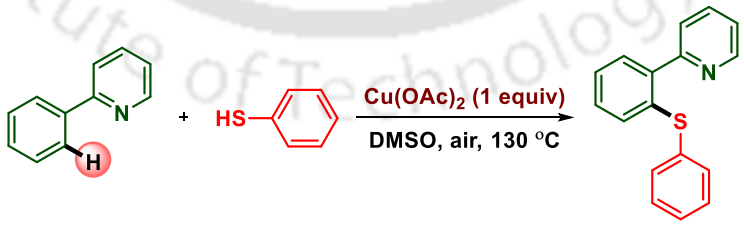
Daugulis group developed a Pd(II)-catalyzed intramolecular amidation of unactivated sp^3 carbon using picolinamides as directing auxiliary (Scheme IB.5.3.10).[95a] Later on a similar type of auxiliary directed intramolecular sp^3 C–H amidation methods were reported by Chen, Ge and Kanai groups.[95b-f]



Scheme IB.5.3.10. *Pd(II)-catalyzed intramolecular sp^3 C–H amidation*

➢ **C_{sp2}–S Bond Formation**

A Cu(II)-promoted direct sulfenylation at sp^2 C–H of 2-arylpyridine using benzene thiol as the coupling partner has been accomplished by Yu group (Scheme IB.5.3.11).[96]

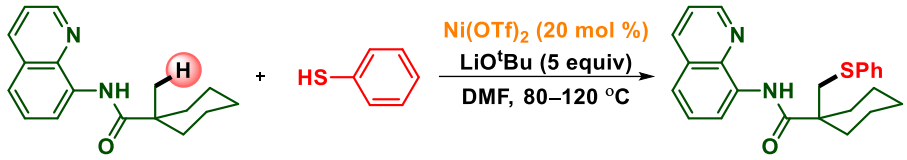


Scheme IB.5.3.11. *Cu(II)-catalyzed ortho-thiolation of arenes*

➢ **Sulfenylation via C_{sp3} / S_{sp3}–H**

Shi group reported a nickel-catalyzed directed sulfenylation of sp^3 C–H bond giving thioethers in good to excellent yields (Scheme IB.5.3.12).[97] The reaction did not take place

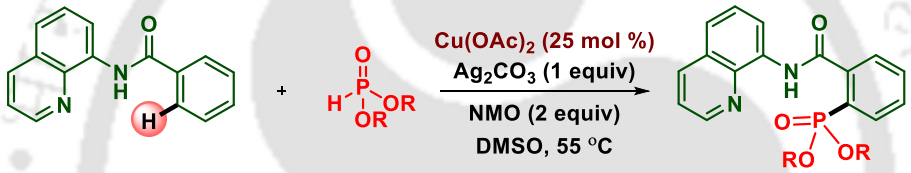
in the presence of any other metal catalysts such as Cu, Fe, Pd, Rh, Ru, and Co, highlighting the unique reactivity of Ni system.



Scheme IB.5.3.12. *Ni(II)-catalyzed sp^3 C–H sulfenylation*

➢ **C_{sp2}–P Bond Formation**

Yu group developed a Cu(II)-catalyzed phosphorylation of the *ortho* C–H bonds of benzamides using 8-aminoquinoline as a bidented directing group with H-phosphonate (Scheme IB.5.3.13).[98] This procedure shows high functional group compatibility and selectively giving mono-substituted products.



Scheme IB.5.3.13. *Cu(II)-catalyzed C–H phosphonation of benzamides*

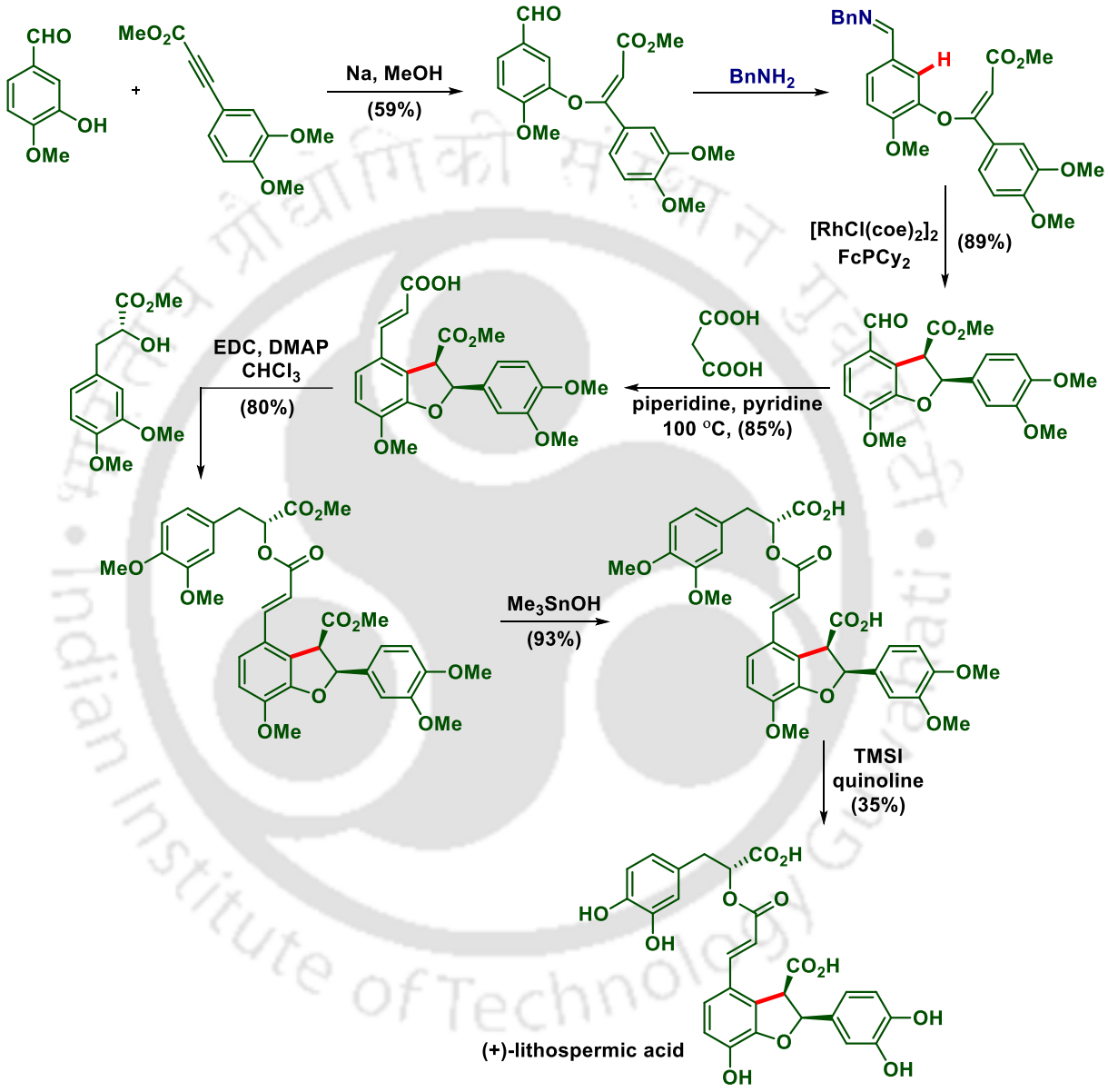
IB.6. C–H Activation: A New Archetype for Total Synthesis

The existing knowledge in the field of C–H functionalization has enabled its use as a reliable tool for natural product synthesis, even as a late-stage manipulation in complex targets.[99] Herein mentioned below is one example of total synthesis showcasing creative and ingenious incorporation of C–H activation as a strategic plan compared to the traditional methods, enlightening a new paradigm in strategic synthetic design.

IB.6.1. Total Synthesis of (+)-Lithospermic Acid

Lithospermic acid has been associated as an active component in Danshen, one of the most popular traditional herbs used in the treatment of cardiovascular disorders, cerebrovascular diseases, various types of hepatitis, chronic renal failure, and dysmenorrheal. Recent studies have shown that (+)-lithospermic acid has potent and nontoxic anti-HIV activity. The first total synthesis of this important natural product was reported by Bergman and Ellman (Scheme IB.6.1.1).[100] The synthesis features an asymmetric alkylation via C−H bond activation to assemble the dihydrobenzofuran core of the natural

product. This was accomplished via a chiral imine-directed C−H bond functionalization and represents the first application of this C−H activation method to natural product synthesis. Furthermore, a challenging deprotection of a late-stage permethylated lithospermic acid was achieved.



Scheme IB.6.1.1. *Total synthesis of (+)-lithospermic acid*

IB.7. References

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CHAPTER IC

IC. A Brief Account on Oxirane Chemistry

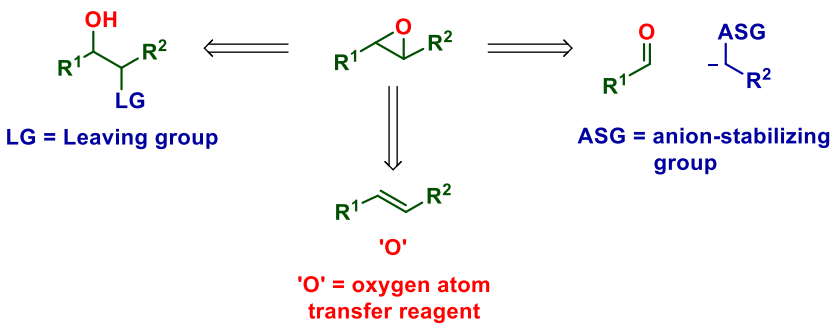
IC.1. Introduction

Three-membered heterocycles have gained significant attraction due to their apparent simplicity and rigid architecture. These heterocycles have played a dominant role in the history of organic synthesis.[1] Several evidences are available in literature about their diversity both in terms of preparation and subsequent transformations. These smallest heterocycles display a convenient balance between stability and reactivity and hence are employed as versatile synthetic intermediates. They have the ability to introduce two adjacent chiral centres with high atom economy.

Among these heterocycles, oxiranes are the simplest three-membered oxygen containing heterocycle that exists as fundamental functional group in organic chemistry. In a proverb by Dieter Seebach, he said: "*If carbonyl compounds have been said to be virtually the backbone of organic synthesis, the epoxides correspond to one of the main muscles.*"[2] Exploration into the current literature reveals that oxiranes are also designated as 1,2-epoxide or oxacyclopropane, or ethylene oxide. Oxiranes can be synthesized from simple starting materials using myriads of reagents by direct or indirect oxygenation methodologies. The importance of these compounds has inspired a number of protocols for their enantioselective preparation.[3]

IC.2. Synthesis of Oxiranes

The synthesis of oxirane usually follow one of the three possible routes (Scheme IC.2.1).

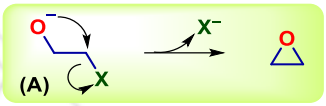


Scheme IC.2.1. *Possible retrosynthetic approaches towards oxirane synthesis*

The intramolecular displacement of a nucleofuge by an oxide such as in halohydrins is an important approach, while the most common technique involves oxygen atom transfer to a double bond. In addition, the transfer of a methylene equivalent to a carbonyl group is also frequently used.

IC.2.1. Oxiranes Synthesis by Intramolecular Substitution

The formation of oxiranes by intramolecular substitution is a straightforward approach for its synthesis. This route encompasses a critical intermediate (**A**) (Scheme IC.2.1.1) that can be attained in several ways such as:

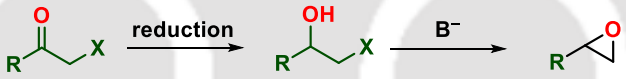


Scheme IC.2.1.1. *Intermediate in intramolecular substitution*

(i) Reaction of an alkene with hypohalous acid (Scheme IC.2.1.2).[4]

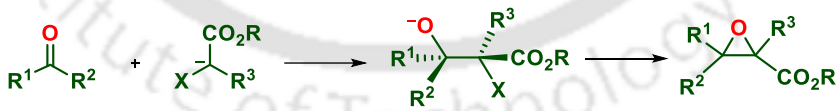
Scheme IC.2.1.2. *Epoxidation of alkenes*

(ii) Reduction of α-halocarbonyl compound followed by cyclization of halohydrin with base (Scheme IC.2.1.3).[5]



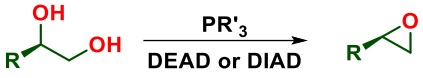
Scheme IC.2.1.3. *Epoxidation of carbonyl compounds*

(iii) Darzens reaction comprising of a nucleophilic attack on the carbonyl group of aldehyde or ketone with a α-halocarbanion (Scheme IC.2.1.4).[6]



Scheme IC.2.1.4. *Darzens synthesis of epoxides*

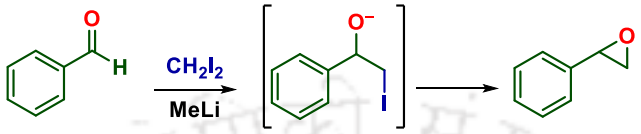
(iv) Mitsunobu reaction involving dehydration of 1,2-diols using PPh_3 and diethyl azodicarboxylate (DEAD) (Scheme IC.2.1.5).[7]



Scheme IC.2.1.5. *Epoxide synthesis by Mitsunobu reaction*

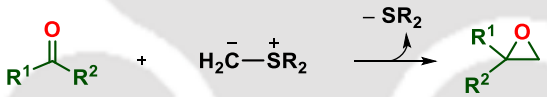
IC.2.2. Oxiranes from Carbonyl Compounds with $-CH_2$ Equivalent

A broad category of epoxides is synthesized by the reaction of carbonyl compounds with methylene equivalents such as diiodomethane and sulfur ylides. One of the most direct demonstration of this tactic is the conversion of benzaldehyde to styrene oxide in the presence of diiodomethane and methyllithium at 0 °C (Scheme IC.2.2.1).[8]



Scheme IC.2.2.1. *Synthesis of oxiranes from aldehyde and diiodomethane*

The use of sulfur ylide is another method adopted by many organic chemists for oxirane synthesis (Scheme IC.2.2.2).[9] Sulfur ylides can be produced by various methods like (i) desilylation of (trimethylsilyl)methylsulfonium salts using CsF in DMSO[10a] (ii) *in situ* generation by decarboxylation of a carboxymethylsulfonium betaine[10b] (iii) from trimethylsulfonium iodide and sodium hydride[10c] (iv) using Simmons-Smith reagent for the generation of sulfur ylides from sulfides.[10d]

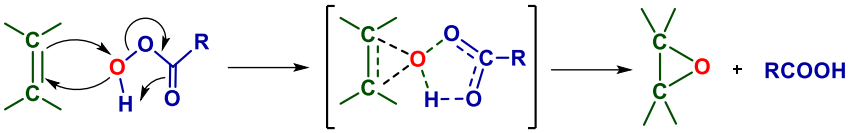


Scheme IC.2.2.2. *Oxirane synthesis using sulfur ylide*

IC.2.3. Oxiranes Synthesis from [2 + 1] Fragments

(a) Epoxidation with Percarboxylic Acids

The extensively used method for oxirane preparation is the Prilezhaev reaction which involves the epoxidation of alkenes with peracids via a cyclic transition state as shown in Scheme IC.2.3.1.[11] These reactions are highly exothermic. The presence of different substituents on the alkenes greatly influences the reaction rates. Electron-donating groups such as alkyl groups at the double bond of carbon atoms significantly enhances the reaction rate whereas electron-withdrawing groups have totally opposite effect.[12] The reactivity of peracids is also subject to electronic effects. Electron-withdrawing groups increases the rate of the reaction by enhancing its electrophilicity, whereas electron-donating groups reduces the reaction rate. The most commonly explored peroxy acid is *m*-chloroperbenzoic acid.[13]

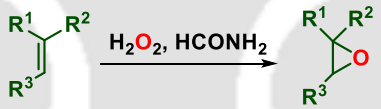


Scheme IC.2.3.1. *Mechanism of epoxidation with percarboxylic acids*

Solvents also play a crucial role in this reaction as the hydrophilic solvents retards the reaction rate by interfering with intramolecular hydrogen bonding of the peracids, while chlorinated and aromatic solvents gives faster reactions. The reaction is stereospecific with *cis* olefin giving *cis* epoxides and *trans* olefins giving *trans* product.[14]

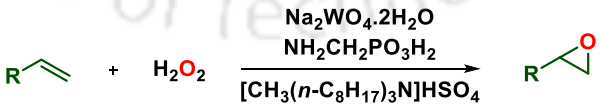
(b) Epoxidation with Hydrogen Peroxides

A number of studies have been reported for the use of hydrogen peroxide as a terminal oxidant in epoxidation reaction. Studies suggests that solvents provide a complementary charge template that stabilizes the transition state. Fluorinated alcohols[15a] and phenols[15b] as solvents enable the oxidation of alkenes using H_2O_2. The combination of formamide and hydrogen peroxide effectively oxidizes tri-and *cis*-disubstituted alkenes (Scheme IC.2.3.2).[16] Water-soluble alkenes can be epoxidized directly using bicarbonate-activated H_2O_2 in a mixed solvent system.[17]



Scheme IC.2.3.2. *Epoxidation of Z-disubstituted olefins*

An industrially applicable sodium tungstate-mediated epoxidation reaction using 30% H_2O_2 in the absence of any solvent was reported by Noyori and co-workers.[18] The technique involves the use of an (α-aminoalkyl)-phosphonic acid and a lipophilic ammonium hydrogen sulfate as the phase-transfer catalyst (Scheme IC.2.3.3).

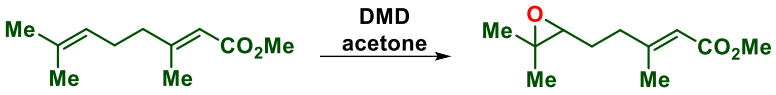


Scheme IC.2.3.3. *Epoxidation of terminal olefins*

(c) Epoxidation with Dioxiranes

Dioxiranes are the electrophilic oxidants utilized for a variety of oxidative transformations especially for the stereoselective epoxidation of alkenes.[19] Dioxiranes can be prepared and isolated or generated *in situ* using suitable ketone in the presence of

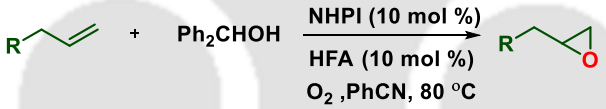
oxidant potassium monoperoxysulfate such as Oxone.[20] The most commonly used dioxiranes for epoxidation are dimethyl dioxirane (DMD) and methyl(trifluoromethyl)dioxirane (TFD). Both electron-rich as well as electron-deficient alkenes are epoxidized in good yields. In substrates having multiple double bonds, the most electron-rich double bond gets selectively epoxidized (Scheme IC.2.3.4).[21]



Scheme IC.2.3.4. *Epoxidation at electron-rich double bond*

(d) Epoxidation with Molecular Oxygen

Molecular oxygen is another attractive oxidant for conversion of alkenes to oxiranes. Terminal alkenes have been oxidized to epoxides using 2-ethylhexanal and oxygen in the absence of any catalyst or solvent.[22a] A metal-free approach has been reported towards the epoxidation of olefins via *in situ* generation of H_2O_2 from alcohols and O_2 under the influence of *N*-hydroxyphthalimide (NHPI) and hexafluoroacetone (HFA) (Scheme IC.2.3.5).[22b] However, the epoxidation of olefins by O_2 in the presence of aldehyde proceeds via the formation of an acyl peroxy radical.[22c]

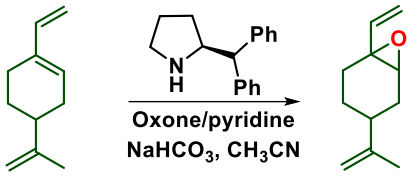


Scheme IC.2.3.5. *Epoxidation using molecular oxygen*

In the presence of metal complexes such as metalloprophyrins and metal cyclam epoxidation of alkene using oxygen and aldehyde proceeds via acyl peroxy radical as the primary oxidant.[23a] In the case of Mukaiyama reaction, the epoxidation of alkenes involving O_2, $Ni(acac)_2$, and aldehyde is via an acyl peroxy radical as well as peracid.[23b]

(e) Epoxidation with Amines

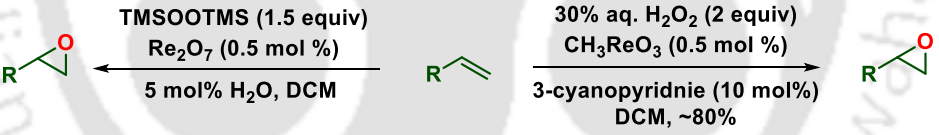
Simple amines in the presence of Oxone oxidize alkenes to oxiranes. For instance, Oxone, pyridine, 2-pyrrolidine derivative in the presence of CH_3CN selectively converts triene to a single epoxide (Scheme IC.2.3.6).[24] The mechanism is presumed to proceed via a single-electron transfer (SET) process involving radical cation intermediate.



Scheme IC.2.3.6. *Epoxidation with amines*

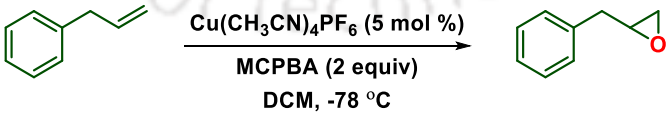
IC.2.4. Metal-Mediated Epoxidation

Metal-mediated epoxidation by oxygen-transfer reactions from hydrogen peroxide to organic substrates have been well explored.[25] Various catalytic systems have been developed for the synthesis of epoxides from alkenes and allyl alcohols. A Cu(I) system containing polypyrazolylborate ligands have been reported to convert alkenes into small-ring compounds.[26] New methods adopting Sharpless conditions ($VO(acac)_2$/TBHP) have been established for diastereoselective epoxidation of allylic alcohols.[27] A number of polyoxometallates have been discovered to catalyze the reaction between allyl alcohols and hydrogen peroxide to form epoxides.[28] Peroxide complexes derived from methylrhenium trioxide was used to convert styrenes to styrene oxide using hydrogen peroxide (Scheme IC.2.4.1).[29a] The use of bis(trimethylsilyl) peroxide as co-oxidant enabled the use of inorganic rhenium oxides as catalysts (Scheme IC.2.4.1).[29b,c]



Scheme IC.2.4.1. *Rhenium-catalyzed epoxidation*

An unusual copper(II)-catalyzed epoxidation has been reported using MCPBA as a terminal oxidant in DCM (Scheme IC.2.4.2).[30] Mixture of *cis* and *trans*-epoxides are obtained from a single stereoisomeric alkene via a stepwise radical mechanism.



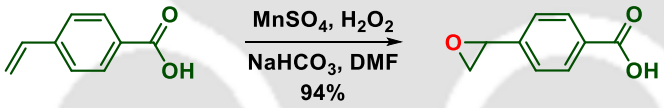
Scheme IC.2.4.2. *Copper-catalyzed epoxidation*

Catalytic epoxidation of alkenes using iron(III) porphyrin complexes and hydrogen peroxide in protic solvents have been testified.[31a] In yet another report, iron(IV) system ligated to an electron-deficient porphyrin ligand generated epoxides in a stereospecific manner.[31b]

A soluble PEG-supported ruthenium porphyrin catalyst exhibiting high reactivity and selectivity was utilized for alkene epoxidation.[32a,b] Another ruthenium complex i.e., ruthenium-terpyridine complex was used as an effective precatalyst along with H_2O_2 to generate epoxides from alkenes.[32c]

Vanadyl salen complexes have been explored to epoxidize cyclohexene via intermediate hydroperoxides formed by radical chain autoxidation.[33a,b] Reactions using vanadium complexes are also carried out in liquid CO_2.[33c]

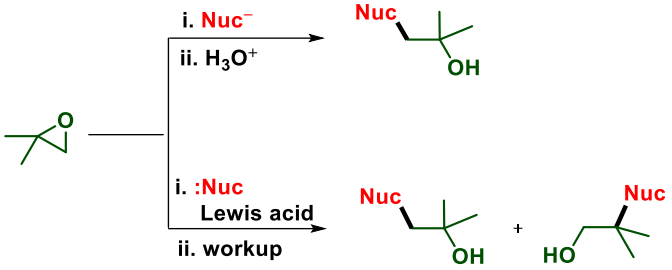
A Mn-porphyrin system was used for a diastereoselective epoxidation of allylic alcohols, amines and esters.[34a] Simple Mn(II) salts such as $MnSO_4$ provided an inexpensive, scalable and environmentally friendly approach for the large scale epoxidation using commercially available H_2O_2 solution (Scheme IC.2.4.3).[34b] A cationic Mn(II) complex catalyzed the peracid epoxidation of electron-deficient alkenes.[34c] A combination of nineteen ligand–Mn were examined in peracid oxidation of terminal alkenes.[34d] A non-heme Mn(IV) system was observed to catalyze the reaction via metallo-peracid complex as the intermediate rather than a metallo-oxo species.[34e]



Scheme IC.2.4.3. *Mn(II)-catalyzed epoxidation*

IC.3. Reactivity of Oxiranes

One of the most important characteristic feature exhibited by oxiranes are the ring-opening reactions with various nucleophiles. This reactivity of oxiranes can be attributed to (i) the ring strain, (ii) the polarization of the C–O bond, and (iii) the basicity of oxirane oxygen. The stereoselectivity of oxirane ring-opening is typically *anti* or *trans* and the regioselectivity depends on the oxirane structure and the reaction conditions as depicted in Scheme IC.3.1. Reaction with strong nucleophiles generally follow S_N2 mechanistic pathway with the nucleophiles attacking the least-substituted carbon atom due to steric reasons. However, in the presence of Brønsted or Lewis acids, the activation of the electrophile i.e., oxirane can lead to so called 'borderline S_N2' (i.e. bimolecular substitution having considerable S_N1 character in the transition state) or S_N1 processes. In these instances, reactions can occur at the more substituted carbon atom.



Scheme IC.3.1. *Regioselective ring-opening of oxiranes*

The regioselectivity in the case of 1,2-disubstituted oxiranes are even less predictable and the ring-opening reactions are affected by the nature of the nucleophile, the specific reaction conditions, and the structure of the oxirane electrophile (Figure IC.3.1). The electrophilic oxirane requires substituents that can either (i) activate one terminus via *in situ* coordination event or stabilization of the S_N2 transition state through resonance effect or (ii) deactivate one terminus by destabilization of the S_N2 transition state by inductive effect.

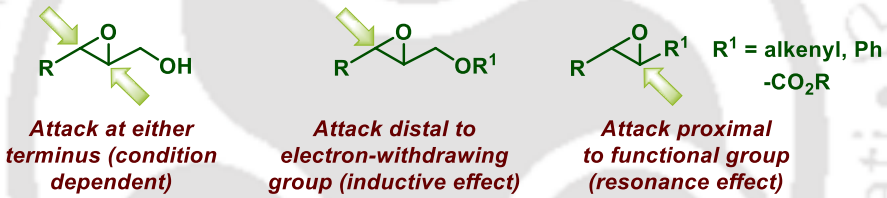


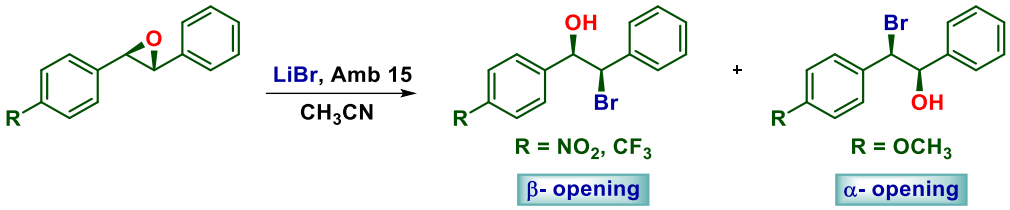
Figure IC.3.1. *Ring-opening in 1,2-disubstituted oxiranes*

Oxiranes participates in numerous reactions making them useful building blocks in organic synthesis and deliver industrially important products such as surfactants or detergents, anti-static or corrosion-protection agents, additives to laundry detergents, lubricating oils, textiles and cosmetics. Below are few examples of ring-opening reactions of oxiranes with different nucleophiles.

IC.3.1. Halides-Based Nucleophiles

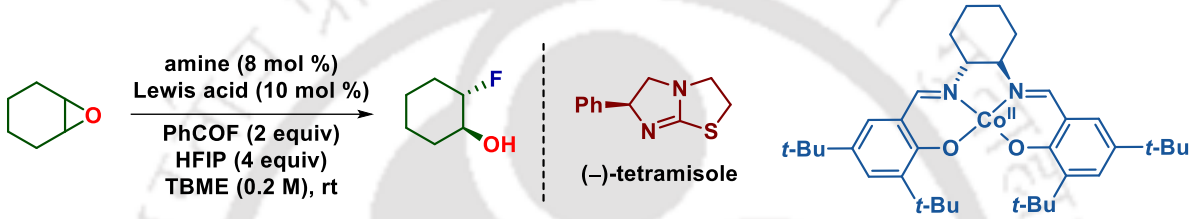
The ring-opening of oxiranes using halide ions is well established.[35] Lupattelli demonstrated a LiBr/Amberlyst 15 system for the regio- and stereoselective ring-opening of 2,3-diaryl oxiranes giving 1,2-diaryl-2-bromo alcohols (Scheme IC.3.1.1).[36] In case of symmetrical *trans*-stilbene oxide, the *syn* vs *anti*-bromohydrin ratio ranges between 88:12 and 30:70, by varying the temperature from 20 to -30 °C. Whereas, in the case of non-symmetrical *para*-substituted *trans*-2,3-diaryloxiranes, the regioselectivity is determined by electronic factors. If anyone of the phenyl ring bears strong electron-withdrawing

group, the nucleophilic attack is on the β-carbon with respect to the substituted phenyl ring.



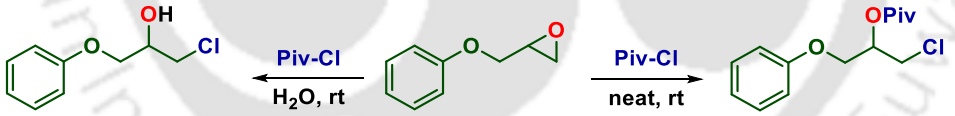
Scheme IC.3.1.1. *Regio- and stereoselective ring-opening of 2,3-diaryloxiranes*

Doyle group reported an enantioselective ring-opening of epoxides by fluoride anion promoted by a cooperative dual-catalytic system (Scheme IC.3.1.2).[37]



Scheme IC.3.1.2. *Enantioselective ring-opening of oxiranes*

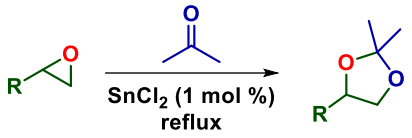
Venkateswarlu and co-workers demonstrated a protective ring-opening of epoxide with pivaloyl halides in the absence of any catalyst and under a solvent free condition (Scheme IC.3.1.3).[38] The protocol gives high yields and involves simple experimental procedures.



Scheme IC.3.1.3. *Protective ring-opening of epoxide with pivaloyl halides*

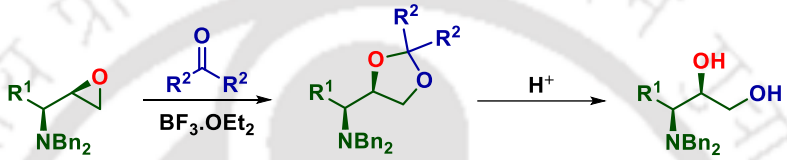
IC.3.2. Oxygen-Based Nucleophiles

One of the typical ring-opening reactions of oxirane is hydrolysis or alcoholysis. A number of catalyst have been developed to facilitate this process. Iranpoor *et al* reported an efficient and mild titanium salts [$TiCl_3(OTf)$ and $TiO(TFA)_2$] catalyzed alcoholysis, acetolysis and hydrolysis of epoxides.[39] Rao and co-workers developed an ammonium molybdate–H_2O_2 system for the conversion of epoxides to α-hydroxy ketones.[40] A Cu(II) tetrafluoroborate catalyzed ring-opening of oxiranes with alcohols was achieved by Barluenga group.[41] An anhydrous $SnCl_2$ catalyzed synthesis of 1,3-dioxolanes has been demonstrated by Vyvyan *et al.* in good to excellent yield (Scheme IC.3.2.1).[42]



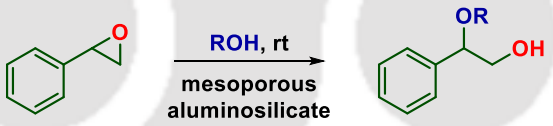
Scheme IC.3.2.1. *Sn(II)-catalyzed synthesis of 1,3-dioxolanes*

In yet another report, Concellon and co-workers achieved the transformation of enantiopure diastereoisomers of 2-(1-aminoalkyl)epoxides into the corresponding 4-(1-aminoalkyl)-1,3-dioxolanes by reacting different ketones in the presence of $BF_3.Et_2O$ (Scheme IC.3.2.2).[43] The obtained dioxolanes were further converted to 3-aminoalkano-1,2-diols using acid.



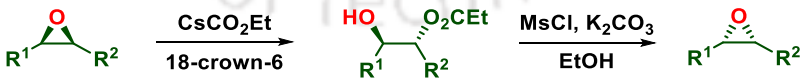
Scheme IC.3.2.2. *Brønsted acid-catalyzed synthesis of substituted 1,3-dioxolanes*

A mesoporous aluminosilicate promoted ring-opening of epoxide with alcohols was reported by Graham *et al.* to give β-alkoxyalcohols (Scheme IC.3.2.3).[44] Later, Nardi group developed an erbium(III) triflate catalyzed green, economically convenient and regioselective method for the alcoholysis under solvent free conditions.[45]



Scheme IC.3.2.3. *Mesoporous aluminosilicate promoted alcoholysis*

An epoxide inversion was demonstrated by Prieto and co-workers using cesium propionate as the epoxide cleaving agent, followed by treatment with methanesulfonyl chloride and K_2CO_3 producing inverted epoxide (Scheme IC.3.2.4).[46]

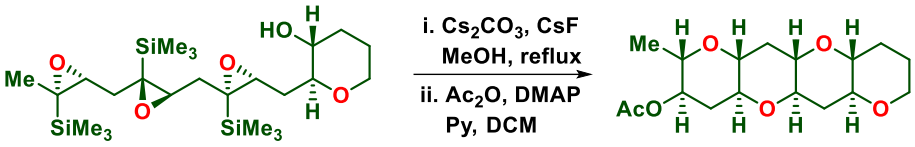


Scheme IC.3.2.4. *Inversion of epoxide*

Apart from the conventional oxygen nucleophiles, Iranpoor group reported the reaction of oxiranes in the presence of ceric ammonium nitrate or excess of nitrate ions giving β-nitrato alcohols in good to excellent yields.[47]

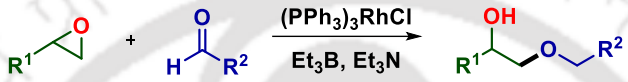
The addition of oxygen nucleophiles to epoxides in an intramolecular ring-forming process is also a useful protocol. Jamison group reported the construction of

tetrahydropyran tetrad via the combination of Me_3Si group, a Brønsted base, a fluoride source, and a hydroxylic solvent (Scheme IC.3.2.5).[48]



Scheme IC.3.2.5. *Polyether synthesis via cascade opening of epoxide*

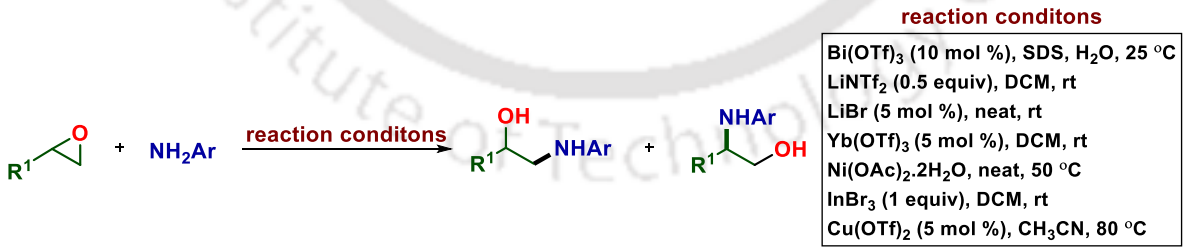
The same group reported the first reductive coupling of epoxides with aldehydes in the presence of Wilkinson's catalyst (Scheme IC.3.2.6).[49] Experimental studies suggest that epoxide-ring-opening occurs prior to the reduction of aldehyde.



Scheme IC.3.2.6. *Catalytic reductive coupling of epoxide and aldehyde*

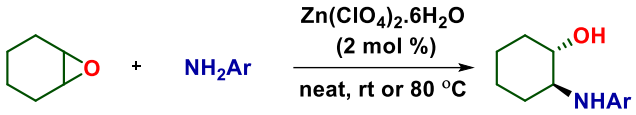
IC.3.3. Nitrogen-Based Nucleophiles

The electron-donating properties of nitrogen containing system make them excellent nucleophiles in the ring-opening reactions of oxiranes. In these processes, both steric and electronic effects of the substituents within oxirane and the nucleophile play a significant role. These reactions are promoted by a number of additives and different metals salts such as $Bi(OTf)_3$,[50a] $LiNTf_2$,[50b] LiBr,[50c] $Yb(OTf)_3$,[50d] $Ni(OAc)_2$,[50e] $InBr_3$,[50f] $Cu(OTf)_2$,[50g] $Sn(OTf)_2$,[50g] $ZrCl_4$,[50h] zinc salts,[50i] $Al(OTf)_3$,[50j] montmorillonite K10 clay[50k] (Scheme IC.3.3.1). Saidi *et al.* reported a metal-free aminolysis of epoxides with aliphatic and aromatic amines in water giving high yields of the products.[51]



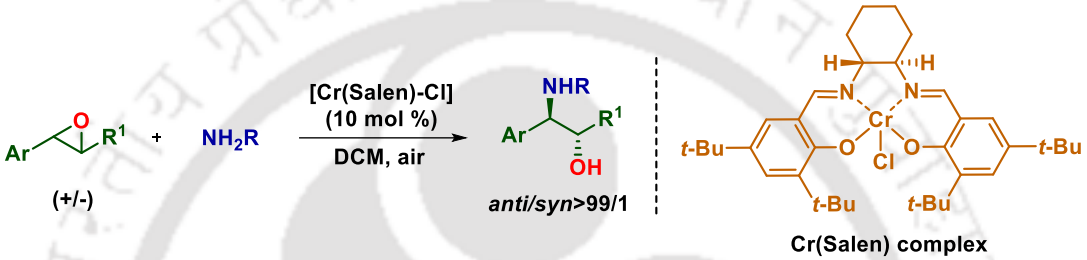
Scheme IC.3.3.1. *Ring-opening of oxirane with amines catalyzed by various metal salts*

Chakraborti group reported the reaction of epoxide with amines catalyzed by Zn(II) salt affording 2-aminoalcohols in high yields (Scheme IC.3.3.2).[52] The transformation takes place in the solvent-free condition with excellent chemo-, regio-, and stereoselectivites. For unsymmetrical oxiranes, the regioselectivity was influenced by electronic and steric factors of the epoxides and the amines.



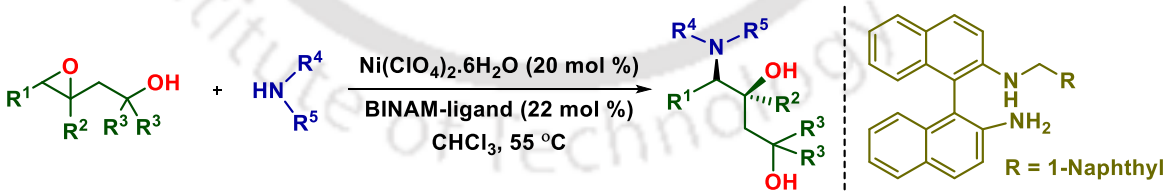
Scheme IC.3.3.2. *Zn(II)-catalyzed ring-opening of oxirane with amines*

Bartoli and co-workers reported the first asymmetric aminolysis of *trans*-aromatic epoxides with anilines in the presence of [Cr(Salen)Cl] as a Lewis acid catalyst, affording enantioenriched *anti*-β-amino alcohols in up to 99% ee (Scheme IC.3.3.3).[53] *cis*-Stilbene oxide gave (*S,S*)-amino alcohol under the same reaction condition whereas addition of a small quantity of Et_3N drastically increased the enantioselectivity.



Scheme IC.3.3.3. *Asymmetric aminolysis of epoxides with Cr(Salen) complex*

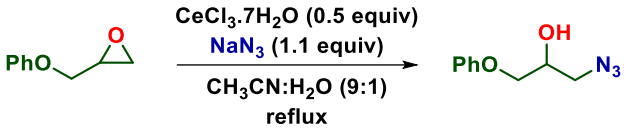
Yamamoto group reported tungsten-catalyzed highly C-3 selective and stereospecific ring-opening reaction of 2,3-epoxyalcohols affording the product in good to excellent yields.[54a,b] The same group later reported the aminolysis of 3,4-epoxy alcohols using Ni(II) catalyst providing γ-hydroxy-δ-amino alcohols (Scheme IC.3.3.4).[54c] The reaction proceeded in a stereospecific manner with high regioselectivity. Further, the enantioselectivity of aromatic 3,4-epoxy alcohols was efficiently promoted by (BINAM)-derived ligand.



Scheme IC.3.3.4. *Ni(II)-catalyzed aminolysis of 3,4-epoxy alcohols*

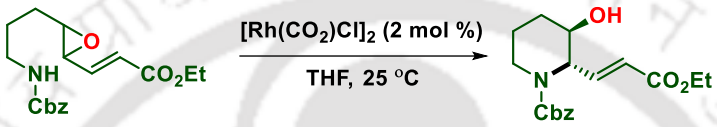
Another useful method of introducing nitrogen nucleophile is using azides. Das group demonstrated regioselective ring-opening of oxirane induced by $SnCl_2.2H_2O$–Mg–THF/NaN_3-H_2O system giving the corresponding 1,2-azido alcohol in good yield.[55a] Later, similar synthesis was reported by Sabitha and co-workers using $CeCl_3$ and NaN_3 in CH_3CN (Scheme IC.3.3.5).[55b] The transformation is highly regioselective

affording the desired product in good to excellent yields under mild and neutral reaction conditions.



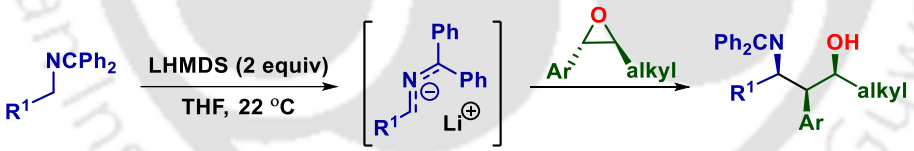
Scheme IC.3.3.5. *Ring-opening of oxiranes with azides*

A stereoselective 6-*endo* mode cyclization of vinyl epoxide was achieved by Ha group using catalytic amount of $[Rh(CO)_2Cl]_2$ resulting into a six-membered heterocyclic system such as piperidines and tetrahydropyrans (Scheme IC.3.3.6).[56]



Scheme IC.3.3.6. *Rh-catalyzed ring-opening of vinyl epoxides*

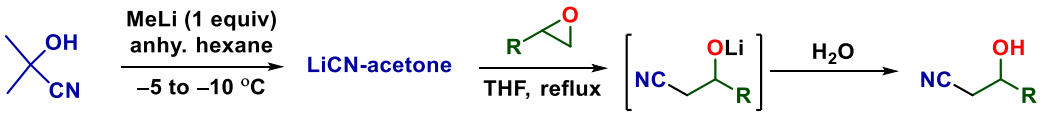
Recently, Malcolmson *et al.* reported the synthesis of 1,3-amino alcohols with three contiguous stereogenic centers by umpolung coupling of imines and epoxides (Scheme IC.3.3.7).[57] The reaction involves the stereoselective addition of nucleophilic 2-azaallyl anions generated from imines to epoxides to furnish 1,3-aminoalcohols after hydrolysis of imine. The transformation affords the product with >98% site selectivity with respect to both reaction partners with >98% yield and >20:1 dr.



Scheme IC.3.3.7. *Synthesis of 1,3-amino alcohols*

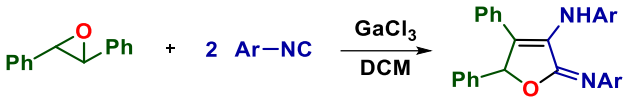
IC.3.4. Carbon-Based Nucleophiles

The addition of carbon nucleophiles to oxiranes are well explored. Benedetti group demonstrated a convenient route to β-hydroxy nitriles by ring-opening of epoxides with diethylaluminium cyanide.[58] A similar synthesis was achieved by Ciacccio *et al.* using LiCN-acetone complex that reacts with oxiranes affording the desired product (Scheme IC.3.4.1).[59]



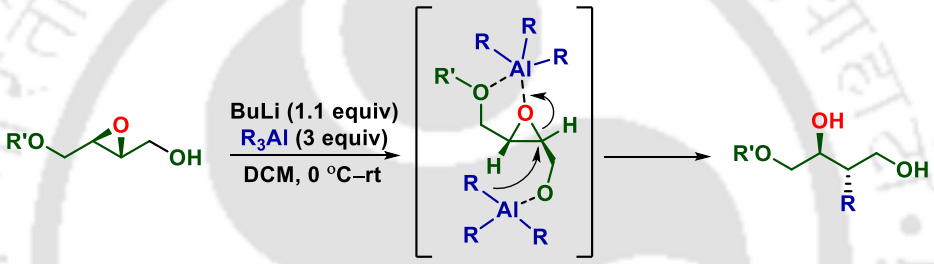
Scheme IC.3.4.1. *Synthesis of β-hydroxy nitriles*

Zhao and co-workers reported Ga(III)-catalyzed double insertion of aryl isocyanides into terminal and disubstituted epoxides giving 3-amino-2-imino-2,5-dihydrofurans in a single step (Scheme IC.3.4.2).[60]



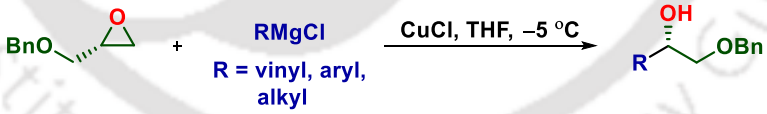
Scheme IC.3.4.2. *Insertion of isocyanides into epoxides*

An unprecedented nucleophilic substitution reaction of 2,3-epoxy-1-alkanols with alkyl- and alkynylaluminium ate complexes have been demonstrated by Miyashita group (Scheme IC.3.4.3).[61a] The reaction occurs at the C-2 position with high stereoselectivity in excellent yields. The same group later reported the use of R_3Al-R'_3SiOTf reagent system for one pot alkylation-silylation of epoxides.[61b]



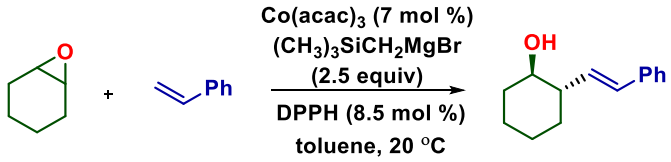
Scheme IC.3.4.3. *Regioselective alkyl and alkynyl substitution of epoxy alcohols*

Alam, Wise and co-workers described a Cu-catalyzed regioselective ring-opening of epoxides with Grignard reagents (Scheme IC.3.4.4).[62] The reaction gave the desired products in >90% yield with excellent regioselectivity and purity.



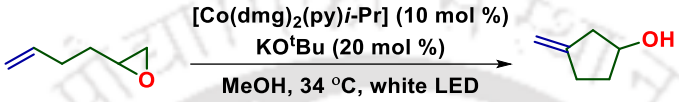
Scheme IC.3.4.4. *Ring-opening of epoxides with Grignard reagents*

A cobalt-mediated Mizoroki-Heck-type reaction of epoxides with styrene was reported by Oshima group affording homocinnamyl alcohols in good yields (Scheme IC.3.4.5).[63a] The reaction proceeds via ring-opening of epoxides by magnesium bromide to give 2-bromoethoxide followed by generation of radical by SET from electron-rich cobalt complex to 2-bromoethoxide. Recently, Zhou *et al.* demonstrated a Pd-catalyzed intermolecular Heck-type reaction of both cyclic and acyclic epoxides with styrene, conjugate dienes and electron-deficient olefins.[63b]



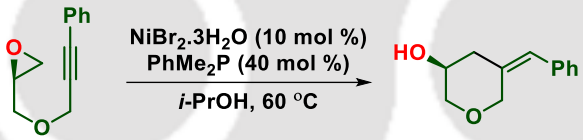
Scheme IC.3.4.5. *Co-mediated Mizoroki-Heck type reaction of epoxides with styrene*

Morandi and co-workers achieved a cobalt-catalyzed atom-economical and regioselective coupling of epoxides with alkenes affording homoallylic alcohols (Scheme IC.3.4.6).[64]



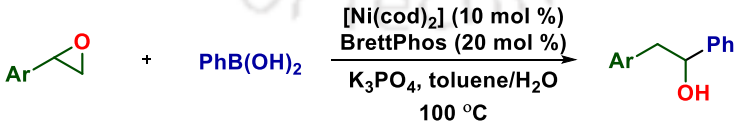
Scheme IC.3.4.6. *Co-catalyzed regioselective coupling of epoxide with alkenes*

Jamison group reported a nickel-catalyzed reductive coupling of epoxides with alkynes providing synthetically useful, chiral homoallylic alcohols.[65a] The same group later reported similar reaction with improved reaction condition i.e., the use of an air-stable and inexpensive Ni(II) precatalyst as the source of Ni(0) and simple alcohols as reducing agents (Scheme IC.3.4.7).[65b] The transformation takes place via oxidative addition of an epoxide C–O bond with inversion of configuration.



Scheme IC.3.4.7. *Ni-catalyzed coupling of oxiranes with alkynes*

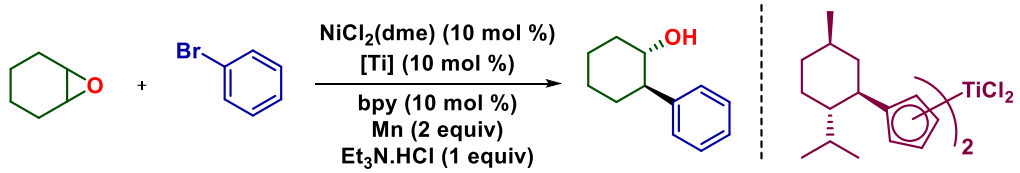
In yet another example, Doyle and co-workers described a nickel-catalyzed cross-coupling of epoxides with unstabilized carbon-centered nucleophiles (Scheme IC.3.4.8).[66] The reaction proceeds via a nickellaoxetane intermediate giving an isomerized product.



Scheme IC.3.4.8. *Ni-catalyzed coupling of oxiranes with boronic acids*

Weix group demonstrated a nickel/iodide and nickel/titanium catalytic systems for the ring-opening of epoxides with aryl bromide, vinyl bromide, and vinyl triflate.[67a] The regioselectivity in the case of terminal epoxides is governed by the co-catalyst employed. They later reported an enantioselective cross-electrophile coupling of aryl bromides with

meso-epoxides to form *trans*-β-arylcycloalkanols (Scheme IC.3.4.9).[67b] The reaction is catalyzed by a combination of (bpy)$NiCl_2$ and a chiral titanocene under reducing condition giving products in 57–99% yields with 78–95% ee.

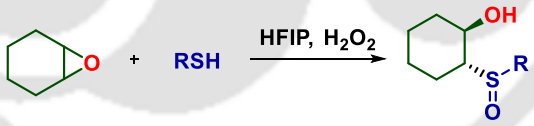


Scheme IC.3.4.9. *Enantioselective arylation of meso-epoxides*

IC.3.5. Sulfur, Selenium, Phosphorus-Based Nucleophiles

Sulfur nucleophiles are another successful species for the ring-opening of oxiranes giving β-hydroxy sulfides.[68a] These reactions can be achieved in an enantioselective manner using various metal complexes such as gallium-lithium binaphoxide complexes,[68b] salen complexes,[68c] Zn(II) catalyst,[68d] molybdate-based systems[68e] as well as ionic liquids.[68f]

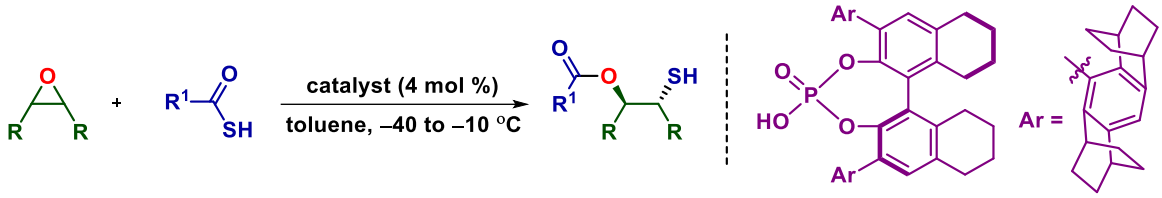
Bégué and co-workers demonstrated a one-pot synthesis of β-hydroxy sulfoxides by the ring-opening of oxiranes with thiols in hexafluoroisopropanol (HFIP) solvent followed by selective oxidation (Scheme IC.3.5.1).[69] The reaction takes place in the absence of any catalyst. It is assumed that the hydrogen bonding ability of HFIP helps in the activation of oxirane ring-opening.



Scheme IC.3.5.1. *Synthesis of β-hydroxy sulfoxides*

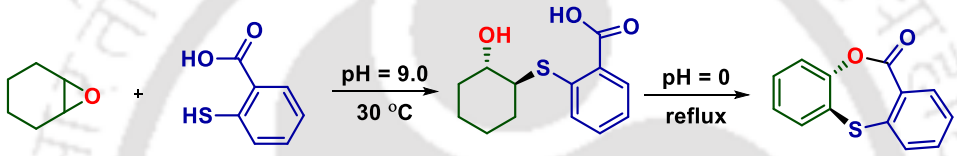
Enantioselective desymmetrization of *meso*-epoxides by thiols were achieved catalyzed by chiral Brønsted acid. Sun *et al.* reported the first chiral phosphoric acid catalyzed asymmetric nucleophilic ring-opening of *meso*-epoxides with aromatic thiols.[70] Later, Antilla and co-workers achieved similar reaction catalyzed by Li-BINOL phosphates.[71] The resulting β-hydroxy sulfides were obtained in excellent yield and enantioselectivity. List group demonstrated a novel method for the synthesis of enantiopure free thiols employing a chiral confined phosphoric acid catalyst (Scheme IC.3.5.2).[72] The reaction furnishes *O*-protected β-hydroxythiols with excellent

enantioselectivity. The transformation involves an asymmetric thiocarboxylysis of *meso*-epoxides, followed by an intramolecular *trans*-esterification reaction.



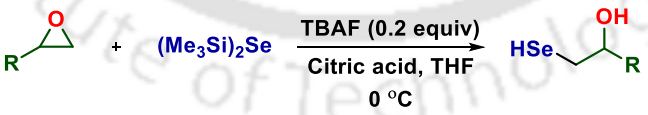
Scheme IC.3.5.2. *Enantioselective desymmetrization of meso-epoxides by thiols*

Conversion of oxiranes to many sulfur containing heterocycles such as 1,3-oxathiolane-2-thiones[73a] and thiiranes are also reported.[73b-e] Fringuelli, Pizzo and co-workers reported a one-pot synthesis of benzo[*e*]1,4-oxathiepin-5-ones under solvent free condition via self-promoted thiolysis of 1,2-epoxides (Scheme IC.3.5.3).[74]



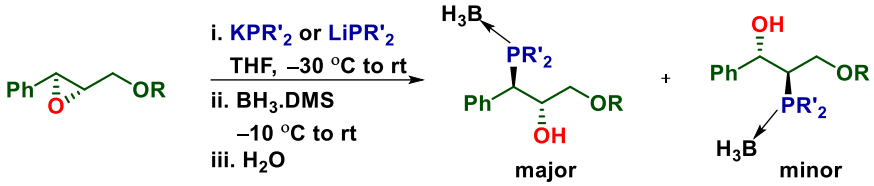
Scheme IC.3.5.3. *Synthesis of benzo[e]1,4-oxathiepin-5-ones*

Zhu group described the first enantioselective ring-opening of *meso*-epoxides with aryl selenols giving optically active β-arylseleno alcohols in up to 97% ee.[75] The reaction was performed using chiral Ti–Ga–Salen heterometallic catalyst. Recently, Tanini, Capperucci and co-workers reported the synthesis of β-hydroxy selenols by treating epoxides with bis(trimethylsilyl)-selenide (Scheme IC.3.5.4).[76] The DFT calculation shows unexpected stability of the product that can be ascribed to hydrogen bond interaction between SeH and OH group.



Scheme IC.3.5.4. *Synthesis of β-hydroxy selenols*

Reginato *et al.* reported the ring-opening of amino epoxides obtained from naturally occurring amino acids or dipeptides with lithium diphenylphosphido borane affording a new class of enantiomerically enriched multifunctional phosphines.[77] Later, Ferran and co-workers obtained 1,2- and 1,3-phosphino alcohols as stable borane complexes via ring-opening of oxiranes with phosphorus nucleophiles (Scheme IC.3.5.5).[78]



Scheme IC.3.5.5. *Ring-opening of oxirane with phosphorus nucleophile*

IC.4. References

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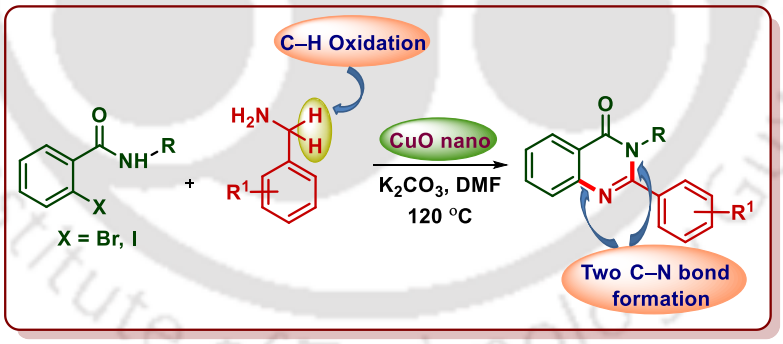
CHAPTER II

CuO Nanoparticle Catalyzed Synthesis of 2,3-Disubstituted Quinazolinones via Sequential N-Arylation and Oxidative C–H Amidation



ABSTARCT: *A CuO nano particle catalyzed synthesis of 2,3-disubstitued quinazolinones has been accomplished from 2-halobenzamides and (aryl)methanamines under an air atmosphere. This synthesis of N-heterocycle involves a sequential Ullmann coupling [between 2-halobenzamide and (aryl)methanamine], oxidation of the in situ generated secondary amine to imine. This is then followed by an intramolecular nucleophilic attack of the amidic N–H on to the imine carbon (C–N bond formation) resulting in the synthesis of 2,3-disubstitued quinazolinones. The recyclability of the catalyst and tolerance of a wide range of functional groups makes this method efficient and cost-effective.*

CHAPTER II

II. CuO Nanoparticle Catalyzed Synthesis of 2,3-Disubstituted Quinazolinones via Sequential *N*-Arylation and Oxidative C–H Amidation

II.1. Introduction

Transition metal catalyzed C–C and C–heteroatom bond forming reactions via cross coupling is a central theme in recent synthetic organic chemistry.[1] However, these traditional coupling reactions are associated with various issues such as requirement of additional functionalities in the starting materials and the use of stoichiometric metal based reagents. The direct C–H functionalization reactions have recently gained great interest as it obviates these requirements and significantly reduces the number of synthetic steps, thereby improving the atom economy of the process to access specific target molecules.[2] In last few years, synthesis of nitrogen containing polyheterocycles[3] via domino approach and the reaction involving the direct C–H bond functionalization has emerged as one of the most powerful tool for their synthesis.[4]

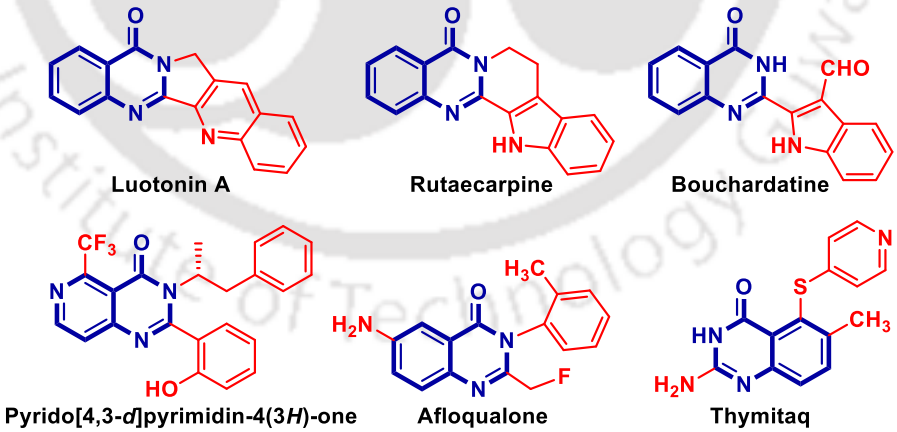


Figure II.1.1. *Natural products and drug compounds containing quinazolinone skeleton*

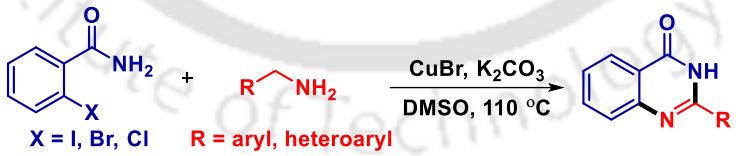
A significant attention has been paid to nitrogen bearing heterocycles, as they are the integral part of many natural products as well as biologically and pharmaceutically active molecules.[5] Among nitrogen containing heterocycles, quinazolinones represent a class of

very important structural motifs as they form the core skeleton of many natural products like luotonine A,[6a] rutaecarpine,[6b] bouchardatine,[6c] (Figure II.1.1). They are also the major building blocks of many drugs having anti-hypertensive,[6d] anti-inflamatory,[6e] anti-bacterial,[6f] anti-cancer[6g] and anti-tuberculosis[6h] activities. For example pyrido[4,3-*d*]pyrimidin-4(3*H*)-one[6i] are orally active calcium-sensing receptor antagonist, afloqualone[6j] is a GABAergic drug and thymitaq[6k] is a thymidylate synthase inhibitor used as anti-cancer agent for hepatocellular carcinoma (Figure II.1.1). Therefore, there is substantial interest to develop novel, efficient and practical methods for their synthesis.

II.2. Strategies for the Synthesis of Quinazolinones

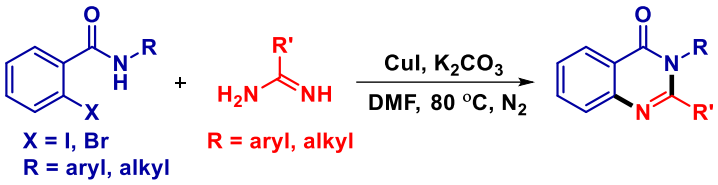
As quinazolinones are assigned as privileged structure in drug development, a number of methods have been developed for their synthesis.[7] The conventional synthesis of quinazolinones involves coupling of *o*-aminobenzamides or *o*-nitrobenzamides with aryl aldehydes,[8a] aryl carboxylic acids,[8b] aryl acid chlorides,[8c] and other coupling agents.[8d] However, benzoic acid derivatives bearing *o*-amino or *o*-nitro groups are not readily available and are difficult to prepare.

With the advancement of Cu catalyzed *N*–arylation strategies for the synthesis of *N*–heterocycles,[1a-c,9] Fu group reported the synthesis of quinazolinones via the coupling of 2-halobenzamide with benzylamine using Cu(I)-catalyst in an air atmosphere (Scheme II.2.1).[10] The domino reaction involves sequential copper-catalyzed Ullmann-type coupling followed by aerobic oxidative C–H amidation giving quinazolinones in good to moderate yields.



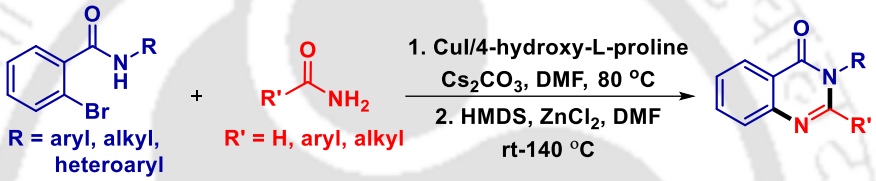
Scheme II.2.1. *Cu(I)-catalyzed synthesis of quinazolinones*

Prior to this report, Ding and co-workers reported a ligand-free CuI catalyzed coupling/condensative cyclization strategy for the synthesis of quinazolin-4(3*H*)-ones. The transformation involves the reaction of various *o*-haloarylcarboxamides with imidamides to generate versatile heterocycles in one-pot (Scheme II.2.2).[11]



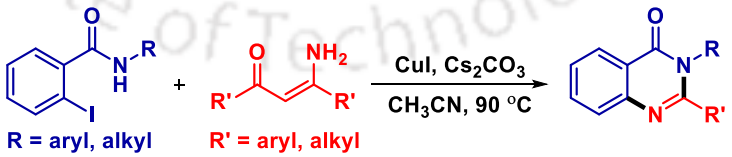
Scheme II.2.2. *Quinazolinone synthesis from o-halobenzamides and imidamides*

A CuI/4-hydroxy-L-proline catalyzed synthesis of 3-substituted quinazolinones from *N*-substituted *o*-bromobenzamides and formamides was demonstrated by Ma and co-workers (Scheme II.2.3).[12] The reaction was facilitated by aryl amidation followed by dehydration affording 3-substituted quinazolinones. However, other aliphatic and aromatic amides gave only simple coupling products which was further converted into 2,3-disubstituted quinazolinones via HMDS/$ZnCl_2$ mediated condensative cyclization.



Scheme II.2.3. *Synthesis of quinazolinones from o-bromobenzamides and formamides*

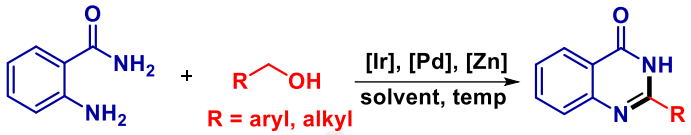
In a yet another report, Kaeobamrung group reported a copper-catalyzed cascade synthesis of quinazolinones from *N*-Substituted 2-iodobenzamides and enaminones (Scheme II.2.4).[13] The reaction involves an Ullmann-type coupling followed by intramolecular Michael addition and finally a retro-Mannich reaction. This domino process exhibited a unique stereochemical feature that the *Z*-enaminones underwent sequential reaction without any external ligands, whereas *E*-enaminones required the assistance of ligands.



Scheme II.2.4. *Quinazolinone synthesis from 2-iodobenzamides and enaminones*

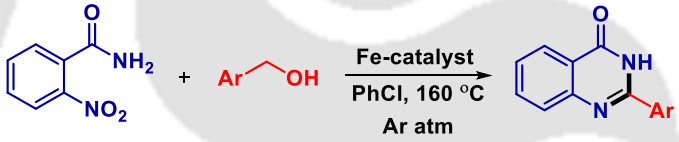
Apart from the copper-catalyzed reactions, various other transition metals such as Ir, Pd, Fe, Zn, have also been utilized for the synthesis of quinazolinones (Scheme II.2.5). In 2011, Zhou *et al* reported the first Ir-catalyzed synthesis of quinazolinones from primary alcohols and *o*-aminobenzamides.[14] The method utilizes catalytic amount of Ir complex,

$[Cp^*IrCl_2]_2$ which is air and water stable under base free condition giving H_2 and H_2O as the only by-products. Later, Yokoyama group also reported similar reaction but using palladium catalyst in water medium.[15] Also a Zn-catalyzed oxidative transformation of *o*-aminobenzamide with benzyl alcohol was achieved by Wu and co-workers.[16]



SchemeII.2.5. *Synthesis of quinazolinones from o-aminobenzamides and benzyl alcohol*

Further, Deng group described an Fe-catalyzed synthesis of 2,3-diarylquinazolinones from 2-nitro-*N*-arylbenzamides and benzylic alcohols (Scheme II.2.6).[17] The nitro group is reduced *in situ* by hydrogen transfer generated during alcohol oxidation to aldehyde and subsequent condensation and cyclization gave the desired quinazolinones.



Scheme II.2.6. *Fe-catalyzed synthesis of quinazolinones from o-nitrobenzamides and benzyl alcohols*

Although there are numerous reports in literature towards metal catalyzed synthesis of quinazolinones, these protocols are associated with a major drawback. The homogeneous nature of the reaction mixture makes the catalyst separation often difficult and further use of the catalyst for the next catalytic cycle is rarely studied. Whereas, heterogeneous catalytic systems have several advantages over homogeneous systems in terms of good dispersion of their active site, easy separation of reaction mixture and catalyst recyclability.

II.3. Present Work

In modern era of organic synthesis, nanoparticle catalyzed reactions has been one of the most progressive research areas.[18] Owing to the advantage of heterogeneous catalyst, nano-crystalline metal oxides have always tempted the synthetic chemists. They are advantageous over conventional metal catalyst in terms of large surface area, high reactivity, high thermal resistance giving higher yields with better atom economy. Several

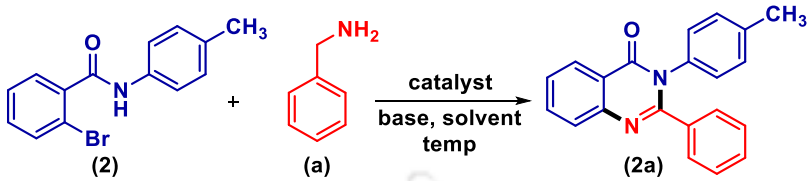
N, *O* and *S*-arylation reactions using CuO nano particle are already reported.[18,19] To the best of our knowledge, nano CuO catalyzed domino reaction for the synthesis of quinazolinones have not been explored. Herein, we report a simple and efficient method for the synthesis of a diverse array of quinazolinones via the Ullmann coupling of various *o*-halobenzamides and (aryl)methanamines followed by an intramolecular aerobic oxidative C–H amidation.

Optimization of Reaction Conditions:

Owing to the advantages of heterogeneous catalytic system (CuO nano), our initial investigation was intended towards the synthesis of quinazolinones. 2-Bromo-*N*-(*p*-tolyl)benzamide (**2**) (1 equiv) and benzylamine (**a**) (2 equiv), were chosen as the prototypical substrates, in the presence of catalyst CuO nano (5 mol%) and K_2CO_3 (3 equiv) in DMSO. As expected, the reaction with the above mentioned combinations at 120 ^oC resulted in the formation of 2-phenyl-3-(*p*-tolyl)quinazolin-4(3*H*)-one (**2a**) in 67% yield. With this positive outcome, further optimizations were carried out in order to improve the overall yield. Various other conventional copper salts such as CuI (43%), CuBr (55%), CuCl (32%), $Cu(OAc)_2$ (51%) examined were all found inferior to CuO nano (67%) (Table II.3.1, entries 1–5). A twofold decrease in the catalyst (CuO) loading (2.5 mol%) lowered the product yield (62%) (Table II.3.1, entry 6). However, an increase in the catalyst loading (10 mol%) had no substantial effect on this transformation (68%) (Table II.3.1, entry 7). The use of other inorganic bases such as Cs_2CO_3, Na_2CO_3 resulted in lower yields (Table II.3.1, entry 8 and 9) as compared to K_2CO_3 (Table II.3.1, entry 1). No further improvement in the yield (69%) was observed when the K_2CO_3 quantity was increased to 4 equivalents (Table1, entry 11). The yield decreased (54%) when the quantity of base was reduced to 2 equivalents (Table II.3.1, entry 10). A substantial improvement in the yield (78%) was observed when the reaction was performed in DMF (Table II.3.1, entry 12) in lieu of DMSO. Other solvents such as dimethyl acetamide (53%), chlorobenzene (30%) and acetonitrile (00%) did not give encouraging results (Table II.3.1, entries 13–15). An increase in the reaction temperature by 10 ^oC (130 ^oC) had no impact on the product yield (79%) (Table II.3.1, entry 16) while a lowering in the reaction temperature by 10 ^oC (110 ^oC) results in a slight decrease in the product formation (71%) (Table II.3.1, entry 17). Under otherwise identical conditions, control experiments either

in the absence of catalyst or base failed to provide the desired product signifying the requirements of both (Table II.3.1, entry 18 and 19).

Table II.3.1. *Screening of the reaction conditions*[a]



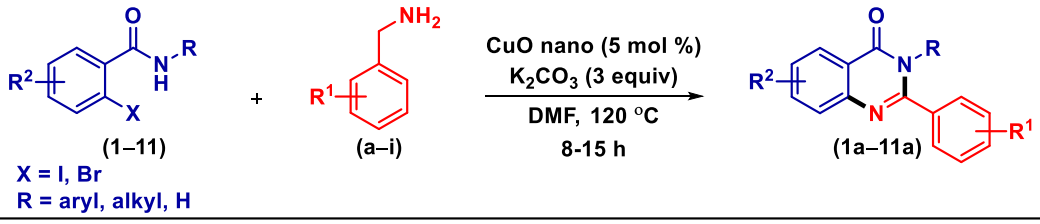
Entry	Catalyst (mol %)	Base (equiv)	Solvent	Temp (°C)	Yield (%)[b]
1	CuO nano (5)	K_2CO_3 (3)	DMSO	120	67
2	CuI (5)	K_2CO_3 (3)	DMSO	120	43
3	CuBr (5)	K_2CO_3 (3)	DMSO	120	55
4	CuCl (5)	K_2CO_3 (3)	DMSO	120	32
5	$Cu(OAc)_2$ (5)	K_2CO_3 (3)	DMSO	120	51
6	CuO nano (2.5)	K_2CO_3 (3)	DMSO	120	62
7	CuO nano (10)	K_2CO_3 (3)	DMSO	120	68
8	CuO nano (5)	Cs_2CO_3 (3)	DMSO	120	57
9	CuO nano (5)	Na_2CO_3 (3)	DMSO	120	32
10	CuO nano (5)	K_2CO_3 (2)	DMSO	120	54
11	CuO nano (5)	K_2CO_3 (4)	DMSO	120	69
12	**CuO nano (5)**	**K_2CO_3 (3)**	**DMF**	**120**	**78**
13	CuO nano (5)	K_2CO_3 (3)	DMA	120	53
14	CuO nano (5)	K_2CO_3 (3)	PhCl	120	30
15	CuO nano (5)	K_2CO_3 (3)	CH_3CN	120	00
16	CuO nano (5)	K_2CO_3 (3)	DMF	130	79
17	CuO nano (5)	K_2CO_3 (3)	DMF	110	71
18	-	K_2CO_3 (3)	DMF	120	00
19	CuO nano (5)	-	DMF	120	00

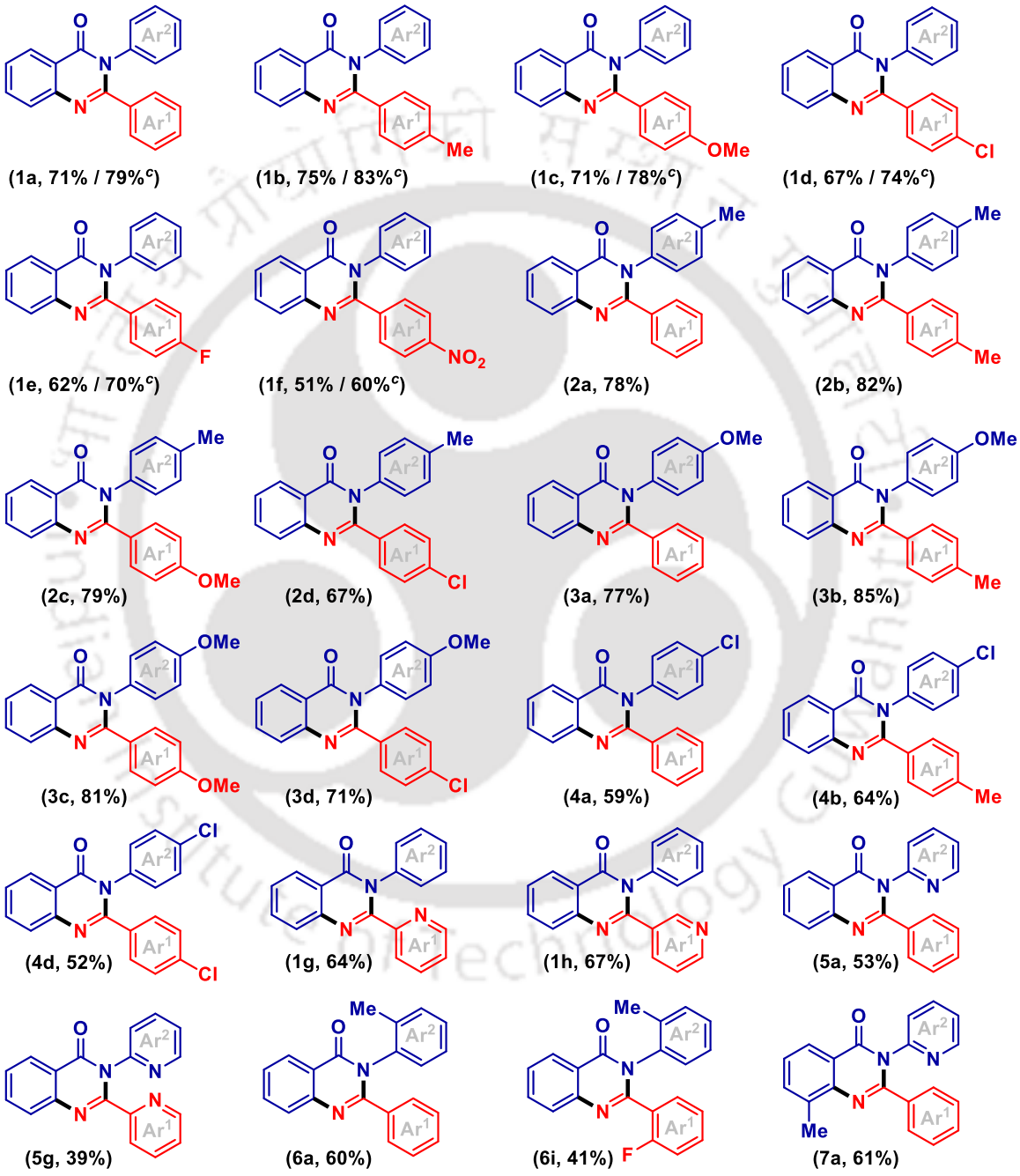
[a]Reaction conditions: 2-Bromo-*N*-(*p*-tolyl)benzamide **2** (0.25 mmol), benzylamine (**a**) (0.5 mmol), catalyst (mol %), base (equiv), solvent (2 mL) under air for 9 h. [b]Isolated yield.

Substrate Scope for the Synthesis of 2,3-Disubstituted Quinazolinones:

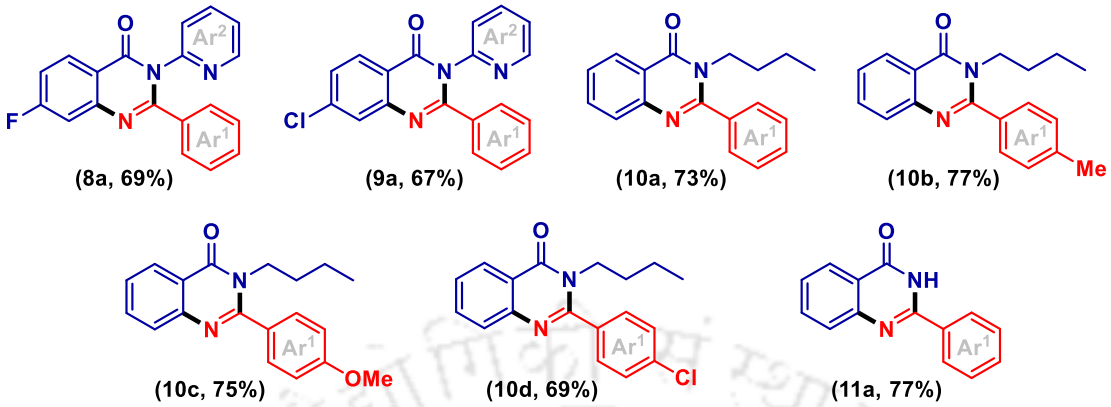
From the above screening experiments, it was found that the use of 5 mol% CuO nano, 3 equiv K_2CO_3 in DMF at 120 °C to be the optimal reaction condition (Table II.3.1, entry 12) which was used for rest of the investigations.

Scheme II.3.1. *Synthesis of various quinazolinones*[a,b]





Scheme II.3.1. contd...



[a]Reaction conditions: 2-bromobenzamide (**1**–**11**) (0.25 mmol), aryl methanamine (**a–i**) (0.5 mmol), CuO nano (0.0125 mmol), K_2CO_3 (0.75 mmol), DMF (2 mL) under air for 8–15 h. [b]Isolated yield. [c]Reaction performed with 2-iodo-*N*-phenylbenzamide.

As shown in Scheme II.3.1, most of the substrate studied provides good to moderate yields of products regardless of their electronic environment. Initially, the effect of substituents on the aryl ring of benzylamine (**a**–**i**) was examined by reacting them with 2-bromo-*N*-phenylbenzamide (**1**). Benzylamine bearing electron-donating substituents such as *p*-CH_3 (**b**), *p*-OCH_3 (**c**) all afforded their respective products (**1b**) and (**1c**) in good yields, 75% and 71% respectively (Scheme II.3.1). However, the presence of moderately electron-withdrawing groups such as *p*-Cl (**d**) and *p*-F (**e**) gave lower yields of their respective quinazolinones (**1d**) (67%) and (**1e**) (62%). While the presence of a strong electron withdrawing group like *p*-NO_2 (**f**) in benzylamine resulted into substantial drop (51%) in the product yield (**1f**). A comparative study in the reactivity of benzamides bearing *ortho*-iodo and *ortho*-bromo substituents, aryl iodides showed higher reactivity giving better yields than the corresponding bromides (Scheme II.3.1, **1a**–**1f**).

Further, the effects of substituents on *N*-aryl ring (Ar^2) of the benzamides (**2**–**4**) were examined. As can be seen from Scheme II.3.1, the presence of electron-donating groups in Ar^2 such as *p*-CH_3 (**2**) and *p*-OCH_3 (**3**) provided higher yields of products (**2a**–**2d** and **3a**–**3d**) irrespective of the substituents present in the Ar^1 ring. However, when the Ar^2 ring is substituted with an electron-withdrawing group such as *p*-Cl (**4**) and the Ar^1 ring with electron-neutral (-H) (**a**), electron-donating (*p*-CH_3) (**b**) and electron-withdrawing (*p*-Cl) (**d**) groups, all afforded their corresponding products (**4a**, 59%), (**4b**, 64%) and (**4d**, 52%) respectively. As can be seen from Scheme II.3.1, maximum yields of 2,3-disubstituted quinazolinones were obtained when both Ar^1 and Ar^2 possesses electron-donating groups

[(**2b**, 82%), (**2c**, 79%), (**3b**, 85%), and (**3c**, 81%)]. Slightly lower yields were obtained when any one of the ring is substituted with electron-donating groups and the other ring with electron-neutral [(**1b**, 75%), (**1c**, 71%), (**2a**, 78%), (**3a**, 77%)] and electron-withdrawing [(**2d**, 67%), (**3d**, 71%), (**4b**, 64%)] groups. Yields obtained were lowered further when both the rings are substituted with electron-withdrawing groups (**4d**, 52%). The structure of the product (**3b**) has been confirmed by the single X-ray crystallography (Figure II.3.1). Besides simple (aryl)methanamines, other heterocyclic methanamines like 2-picolylamine (**g**) and 3-picolylamine (**h**) were also investigated. Interestingly, they also serve as good coupling partners to provide products (**1g**) and (**1h**) in 64% and 67% yields respectively. Similarly 2-bromo-*N*-(pyridin-2-yl)benzamide (**5**) also participated in the reaction with benzylamine (**a**) to afford the corresponding product (**5a**) in modest yield (53%). Notably, a poor yield of 39% (**5g**) was obtain when 2-bromo-*N*-(pyridin-2-yl)benzamide (**5**) was coupled with 2-picolylamine (**g**). The poor yield obtained for (**5g**) is consistent with the observation for the substrate bearing electron-withdrawing groups in both Ar^1 and Ar^2 rings as was observed in (**4d**).

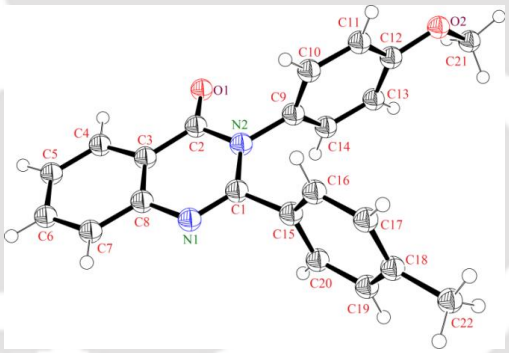


Figure II.3.1. *ORTEP view of (**3b**)*

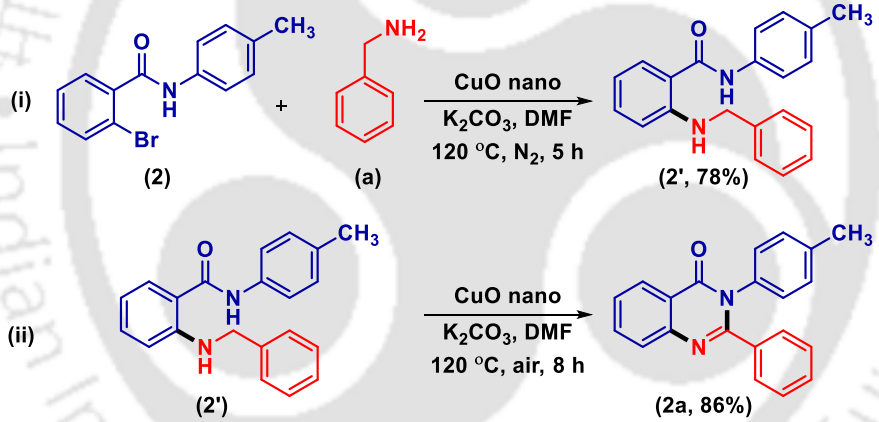
An *ortho* substituted *N*-aryl benzamide (**6**) gave comparatively lesser yield of 60% (**6a**) in contrast to its *para* analogue (**2a**, 78%), which may be due to the steric hindrance imparted by the *ortho* methyl group. A further decrease in the product (**6i**) yield (41%) was observed when *ortho* substituted amide (**6**) was treated with (2-fluorophenyl)methanamine (**i**). Similarly, 2-bromobenzamide substituted with -Me (**7**), -F (**8**) and -Cl (**9**) underwent efficient coupling with benzylamine (**a**) to afford their corresponding quinazolinones (**7a**), (**8a**) and (**9a**) respectively in good yields (Scheme II.3.1). Apart from *N*-aryl benzamide, *N*-alkyl (**10**) as well as unsubstituted amide (**11**) were also investigated. Gratifyingly, they provided their corresponding quinazolinones

(**10a**–**10d** and **11a**, Scheme II.3.1) in the range of 69% to 77% yields when reacted with various benzylamines (**a**–**d**).

Mechanistic Studies:

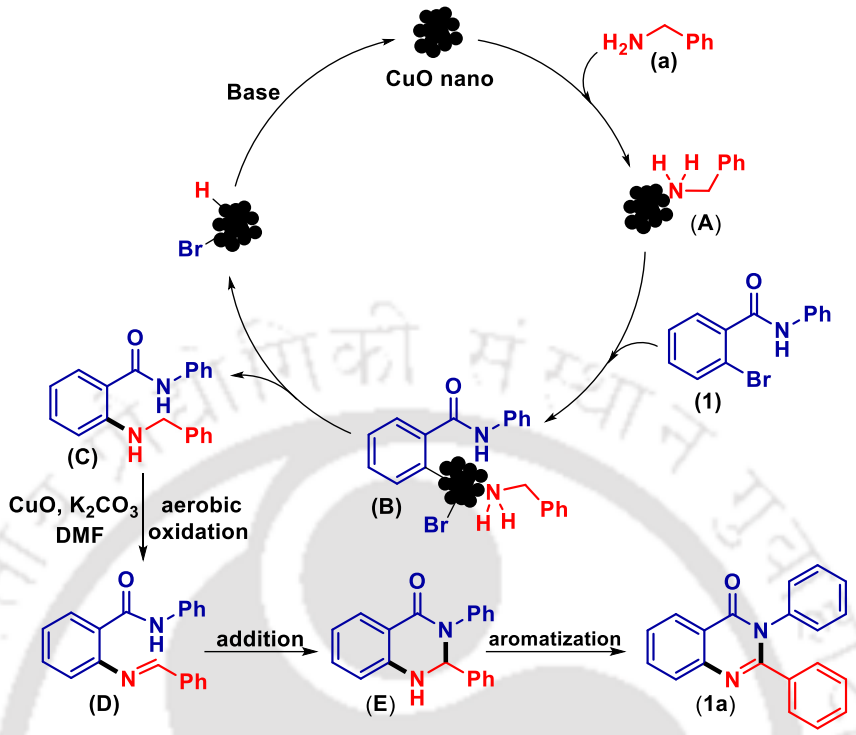
To understand the possible reaction mechanism, control experiments were performed which are depicted in Scheme II.3.2. A CuO nano catalyzed reaction of 2-bromo-*N*-(*p*-tolyl)benzamide (**2**) and benzylamine (**a**) in an atmosphere of N_2 under otherwise identical conditions afforded the Ullmann coupled product 2-(benzylamino)-*N*-(*p*-tolyl)benzamide (**2′**) in 78% [Scheme II.3.2 (i)] along with a trace (<5%) of cyclized product (**2a**). The isolated Ullmann product (**2′**) when subjected to the standard reaction condition was transformed to 2-phenyl-3-(*p*-tolyl)quinazolin-4(3*H*)-one (**2a**) in 86% yield [Scheme II.3.2 (ii)], suggesting its intermediacy during the course of the reaction.

Scheme II.3.2. *Mechanistic investigations*



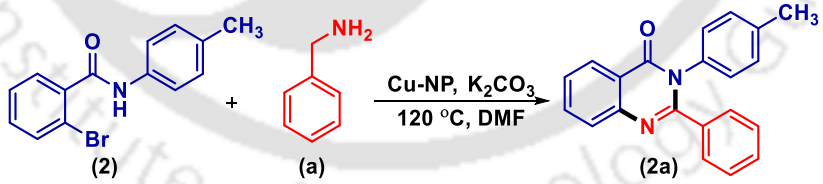
On the basis of the above results and from literature precedence a plausible mechanism for the formation of 2,3-disubstituted quinazolinones has been proposed as depicted in Scheme II.3.3. It is assumed that the mechanistic path goes via oxidative addition followed by reductive elimination (Scheme II.3.3). Benzylamine (**a**) stabilized active cluster of CuO nanoparticle (**A**) undergoes oxidative addition with 2-bromo-*N*-phenylbenzamide (**1**) to form intermediate (**B**), which on subsequent reductive elimination generates Ullmann-type coupled product (**C**). Removal of hydrogen halide with base regenerates the CuO nanoparticle which maintains the catalytic cycle (Scheme II.3.3). Copper catalyzed aerobic oxidation of (**C**) gives an imine intermediate (**D**). An intramolecular nucleophilic attack of the amidic N–H onto the imine carbon generates (**E**) which is finally oxidized to give product (**1a**) (Scheme II.3.3).

Scheme II.3.3. *Mechanistic pathway*



To check the efficacy of the catalyst for the next catalytic cycle, the catalyst was recovered from the reaction mixture by centrifugation and was washed thoroughly with ethyl acetate and water.

Table II.3.2. *Recyclability of CuO-nanoparticles*



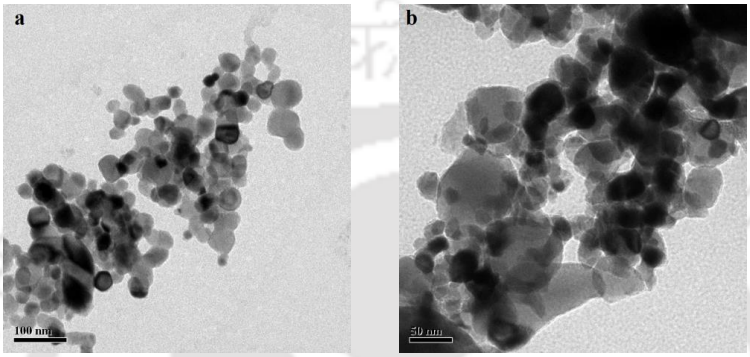
Run	Catalyst recovery (%)	Time (h)	Product yield (%)
1[a]	92	9	78
2[b]	87	13	72
3[b]	81	17	67

[a]2-bromo-*N*-(*p*-tolyl)benzamide (**2**) (0.25 mmol), benzylamine (**a**) (0.5 mmol), CuO-nanoparticle (0.0125 mmol), K_2CO_3 (0.75 mmol), DMF (2 mL) under air at 120 °C. [b]The recovered catalyst was used under identical reaction conditions as in the first run.

The catalytic efficiency of the recovered catalyst was examined up to three cycles by coupling (**2**) and (**a**) under standard reaction condition. It was found that the catalytic

activity of the recovered CuO was slightly lower in subsequent cycles (Table II.3.2). After third cycle the reaction mixture containing the catalyst was centrifuged and its surface morphology was analyzed and compared with that of fresh catalyst using TEM (Figure II.3.2), which shows agglomeration of the catalyst during the course of the reaction.

Figure II.3.2. *TEM Images of (a) fresh CuO nano catalyst and (b) CuO nano catalyst after third cycle*



In conclusion, we have developed a CuO nanoparticle catalyzed simple and efficient method for the synthesis of 2,3-disubstituted quinazolinones by coupling of 2-halobenzamides and (aryl)methanamines. This reaction operates through sequential C–N bond formation, aerobic oxidation and intramolecular cyclization without the requirement of ligand and additives. The method is advantageous as it offers low catalyst loading, high yield, and recyclability of the catalyst and tolerance of a wide range of functional groups.

II.4. Experimental Section

II.4.1. General Information: All the compounds were commercial grade and used without further purification. Organic extract was dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduce pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as internal standard for proton NMR (400 and 600 MHz) and $CDCl_3$ solvent as internal standard for ^{13}C NMR (100 and 150 MHz). HRMS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat.

II.4.2. Crystallographic Description

CCDC Number for Compound 3b: CCDC-1415275. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystallographic Description of 3-(4-Methoxyphenyl)-2-(*p*-tolyl)quinazolin-4(3*H*)-one (3b): $C_{22}H_{18}N_2O_2$, crystal dimensions 0.30 x 0.25 x 0.18mm, M_r = 342.38, Monoclinic, space group P 21 21 21, a = 14.455(3), b = 13.696(3), c = 18.362(4) Å, α = 90°, β = 99.906° (9), γ = 90°, V = 3581.0(13) Å^3, Z = 8, ρ_{calcd} = 1.270g/cm^3, μ = 0.082mm^{-1}, F(000) = 1440.0, reflection collected / unique = 6162 / 6283, refinement method = full-matrix least-squares on F^2, final R indices [I> 2σ(I)]: R_1 = 0.0456, wR_2 = 0.0456, R indices (all data): R_1 = 0.0918, wR_2 = 0.0740, goodness of fit = 1.020.

II.4.3. General Procedure for the Synthesis of 2-Phenyl-3-(*p*-tolyl)quinazolin-4(3*H*)-one (2a): To an oven dried round bottom flask charged with a stir bar, 2-bromo-*N*-(*p*-tolyl)benzamide (**2**) (0.25 mmol, 72.5 mg), benzylamine (**a**) (0.5 mmol, 53.5 mg), CuO nano (0.0125 mmol, 1 mg), K_2CO_3 (0.75 mmol, 103.5 mg) in DMF (2 mL), were taken and stirred on a preheated oil bath at 120 °C for 9 h. After the completion of the reaction (as indicated by the TLC), the reaction mixture was cooled to room temperature and admixed with water (10 mL) and the product was extracted with ethyl acetate (2 x 20 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The crude product was then purified by column chromatography (ethyl acetate:hexane, 1.2:8.7) to afford corresponding quinazolinone (**2a**) (61 mg, 78%).

II.5. References

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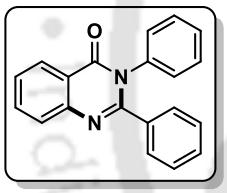
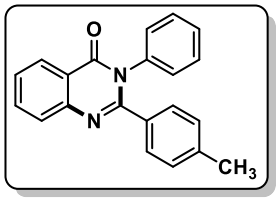
II.6. Spectral Data

2,3-Diphenylquinazolin-4(3*H*)-one (1a):



White solid (53 mg, 71%); mp 151–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.15 (d, 2H, *J* = 6.8 Hz), 7.22 (d, 2H, *J* = 7.6 Hz), 7.25–7.29 (m, 3H), 7.32–7.35 (m, 3H), 7.53–7.57 (m, 1H), 7.82–7.83 (m, 2H), 8.36 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 121.2, 127.4, 127.5, 127.6, 128.0, 128.2, 128.6, 129.2, 129.3, 129.5, 135.0, 135.6, 137.9, 147.7, 155.4, 162.5; IR (KBr): 3056, 2922, 2848, 1681, 1551, 1464, 1336, 1265, 1022, 774, 697 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{15}N_2O$ [M + H^+] 299.1179; found 299.1184.

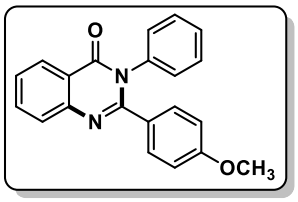
3-Phenyl-2-(*p*-tolyl)quinazolin-4(3*H*)-one (1b):



White solid (59 mg, 75%); mp 175–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.27 (s, 3H), 7.00 (d, 2H, *J* = 8.4 Hz), 7.15 (d, 2H, *J* = 6.8 Hz), 7.22 (d, 2H, *J* = 8.4 Hz), 7.25–7.35 (m, 3H), 7.50–7.54 (m, 1H), 7.79–7.81 (m, 2H), 8.34 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.5, 121.1, 127.3, 127.4, 127.9, 128.5, 128.8, 129.15, 129.18, 129.3, 132.8, 134.9, 138.0, 139.7,

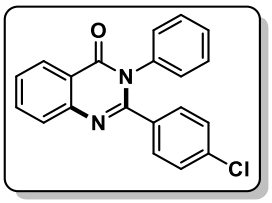
147.8, 155.5, 162.6; IR (KBr): 2979, 2923, 2853, 1680, 1544, 1464, 1334, 1263, 1107, 822, 770, 697 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{17}N_2O$ [M + H^+] 313.1335; found 313.1341.

2-(4-Methoxyphenyl)-3-phenylquinazolin-4(3*H*)-one (1c):



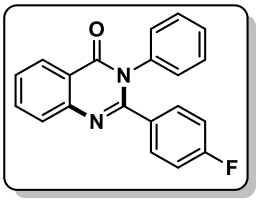
White solid (58 mg, 71%); mp 144–145 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.75 (s, 3H), 6.72 (d, 2H, *J* = 8.4 Hz), 7.16 (d, 2H, *J* = 7.8 Hz), 7.29 (q, 3H, *J* = 9.6 Hz), 7.35 (t, 2H, *J* = 7.8 Hz), 7.52 (s, 1H), 7.81 (s, 2H), 8.34 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.4, 113.5, 120.9, 127.2, 127.3, 127.7, 127.9, 128.5, 129.15, 129.23, 130.9, 134.9, 138.0, 147.7, 155.1, 160.4, 162.6; IR (KBr): 3529, 3061, 2927, 1678, 1602, 1546, 1464, 1336, 1254, 1179, 1026, 778, 699 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{17}N_2O_2$ [M + H^+] 329.1285; found 329.1292.

2-(4-Chlorophenyl)-3-phenylquinazolin-4(3*H*)-one (1d):



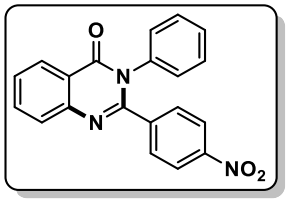
White solid (56 mg, 67%); mp 169–170 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.14 (d, 2H, *J* = 5.6 Hz), 7.18 (d, 2H, *J* = 7.2 Hz), 7.28 (d, 2H, *J* = 5.6 Hz), 7.30–7.35 (m, 3H), 7.52–7.55 (m, 1H), 7.81 (t, 2H, *J* = 4.0 Hz), 8.34 (d, 1H, *J* = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 121.1, 127.4, 127.7, 128.0, 128.5, 128.9, 129.2, 129.4, 130.6, 134.1, 135.0, 135.8, 137.7, 147.5, 154.2, 162.3; IR (KBr): 3251, 3047, 2924, 2843, 1681, 1544, 1464, 1333, 1262, 1085, 1013, 833, 770, 696 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{14}ClN_2O$ [M + H^+] 333.0789; found 333.0792.

2-(4-Fluorophenyl)-3-phenylquinazolin-4(3*H*)-one (1e):



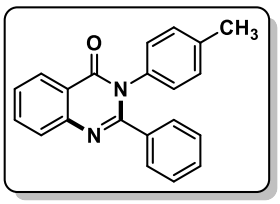
Yellow solid (49 mg, 62%); mp 163–165 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.90 (t, 2H, *J* = 8.4 Hz), 7.13 (d, 2H, *J* = 6.8 Hz), 7.29–7.36 (m, 5H), 7.51–7.55 (m, 1H), 7.81 (d, 2H, *J* = 5.6 Hz), 8.34 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 115.2, 115.5, 121.09, 121.13, 127.4, 127.6, 127.9, 128.7, 129.25, 129.31, 131.3, 131.4, 135.0, 137.8, 147.5, 154.4, 162.4, 164.4; IR (KBr): 3181, 3047, 2911, 1684, 1601, 1504, 1335, 1272, 1226, 1132, 1017, 842, 769, 694 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{14}FN_2O$ [M + H^+] 317.1085; found 317.1093.

2-(4-Nitrophenyl)-3-phenylquinazolin-4(3*H*)-one (1f):



Orange solid (44 mg, 51%); mp 163–165 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.05 (t, 1H, *J* = 7.6 Hz), 7.24 (t, 1H, *J* = 7.6 Hz), 7.49–7.42 (m, 3H), 7.64 (d, 1H, *J* = 8.0 Hz), 7.69 (d, 2H, *J* = 8.0 Hz), 8.17 (d, 2H, *J* = 8.8 Hz), 8.36 (d, 2H, *J* = 8.8 Hz), 8.65 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 121.2, 122.1, 123.4, 123.9, 124.2, 125.7, 128.8, 129.2, 129.5, 129.6, 130.4, 133.4, 137.3, 139.7, 140.4, 167.7; IR (KBr): 3300, 3228, 2922, 2852, 1654, 1600, 1523, 1438, 1338, 1251, 904, 760, 693 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{14}N_3O_3$ [M + H^+] 344.1030; found 344.1025.

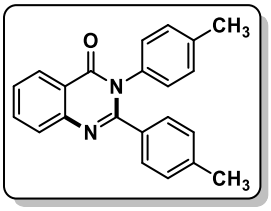
2-Phenyl-3-(*p*-tolyl)quinazolin-4(3*H*)-one (2a):



Yellow solid (62 mg, 78%); mp 172–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.30 (s, 3H), 7.01 (d, 2H, *J* = 8.4 Hz), 7.10 (d, 2H, *J* = 8.4 Hz), 7.19–7.25 (m, 3H), 7.34 (d, 2H, *J* = 6.8 Hz), 7.50–7.54 (m, 1H), 7.79–7.83 (m, 2H), 8.34 (d, 1H, *J* = 8.8 Hz,); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.3, 121.1, 127.4, 127.9, 128.1, 128.9,

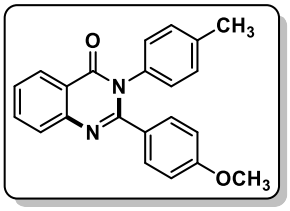
129.2, 129.4, 129.8, 134.8, 135.1, 135.7, 138.5, 147.7, 155.5, 162.6; IR (KBr): 3033, 2916, 2853, 1883, 1591, 1504, 1337, 1269, 1109, 1022, 771, 696 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{17}N_2O$ [M + H^+] 313.1335; found 313.1343.

2,3-Di-*p*-tolylquinazolin-4(3*H*)-one (2b):



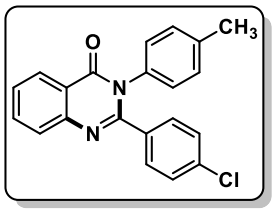
Yellow solid (67 mg, 82%); mp 168–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.28 (s, 3H), 2.32 (s, 3H), 7.02 (d, 4H, *J* = 8.4 Hz), 7.12 (d, 2H, *J* = 8.0 Hz), 7.25 (t, 2H, *J* = 5.2 Hz), 7.49–7.53 (m, 1H), 7.77–7.82 (m, 2H), 8.34 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.2, 21.3, 120.9, 127.0, 127.2, 127.6, 128.6, 128.7, 129.0, 129.1, 129.6, 134.6, 135.1, 138.3, 139.4, 147.6, 155.5, 162.5; IR (KBr): 3036, 2922, 2857, 1686, 1556, 1510, 1469, 1339, 1270, 1181, 1022, 818, 774 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{19}N_2O$ [M + H^+] 327.1492; found 327.1498.

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



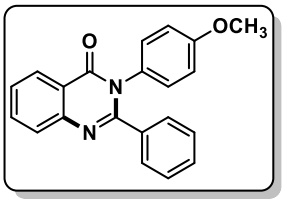
Yellow solid (68 mg, 79%); mp 155–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H), 3.75 (s, 3H), 6.72 (d, 2H, *J* = 9.2 Hz), 7.02 (d, 2H, *J* = 8.0 Hz), 7.13 (d, 2H, *J* = 8.4 Hz), 7.29 (d, 2H, *J* = 9.2Hz), 7.47–7.51 (m, 1H), 7.75–7.80 (m, 2H), 8.32 (d, 1H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 55.4, 113.5, 121.0, 127.1, 127.4, 127.7, 128.2, 128.9, 129.9, 130.9, 134.8, 135.4, 138.4, 147.8, 155.3, 160.4, 162.8; IR (KBr): 3060, 3022, 2957, 2836, 1685, 1589, 1507, 1463, 1333, 1245, 1025, 835, 773 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{19}N_2O_2$ [M + H^+] 343.1441; found 343.1449.

2-(4-Chlorophenyl)-3-(*p*-tolyl)quinazolin-4(3*H*)-one (2d):



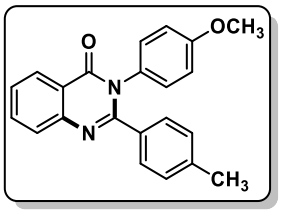
Yellow solid (58 mg, 67%); mp 183–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.31 (s, 3H), 6.99 (d, 2H, *J*= 8.0 Hz), 7.11 (d, 2H, *J* = 8.0 Hz), 7.17 (d, 2H, *J* = 8.8 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 7.48–7.52 (m, 1H), 7.73–7.81 (m, 2H), 8.31 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 121.1, 127.4, 127.6, 127.8, 128.4, 128.8, 129.1, 130.0, 130.6, 134.2, 134.9, 135.6, 138.8, 147.5, 154.4, 162.4; IR (KBr): 3055, 2922, 2843, 1680, 1546, 1333, 1263, 1123, 1012, 833, 766, 690 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{16}ClN_2O$ [M + H^+] 347.0946; found 347.0951.

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



Yellow solid (63 mg, 77%); mp 195–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.77 (s, 3H), 6.81 (d, 2H, *J* = 8.4 Hz), 7.05 (d, 2H, *J* = 9.2 Hz), 7.21–7.26 (m, 3H), 7.34 (d, 2H, *J* = 6.0 Hz), 7.49–7.55 (m, 1H), 7.80–7.83 (m, 2H), 8.35 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.6, 114.4, 121.2, 127.4, 127.9, 128.1, 128.2, 129.2, 129.4, 130.2, 130.5, 134.9, 135.8, 147.7, 155.7, 159.4, 162.8; IR (KBr): 3064, 2964, 2832, 1680, 1559, 1503, 1338, 1245, 1024, 830, 770, 699 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{17}N_2O_2$ [M + H^+] 329.1285; found 329.1291.

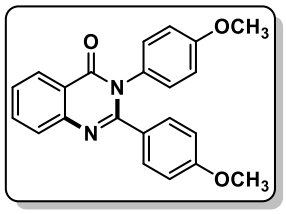
3-(4-Methoxyphenyl)-2-(*p*-tolyl)quinazolin-4(3*H*)-one (3b):



Yellow solid (73 mg, 85%); mp 237–239 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.28 (s, 3H), 3.77 (s, 3H), 6.82 (d, 2H, *J* = 8.8 Hz), 7.01–7.07 (m, 4H), 7.23 (d, 2H, *J* = 8.0 Hz), 7.48–7.52 (m, 1H), 7.73–7.81 (m, 2H), 8.33 (d, 1H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.5, 55.6, 114.4, 121.0, 127.2, 127.3, 127.8, 128.9,

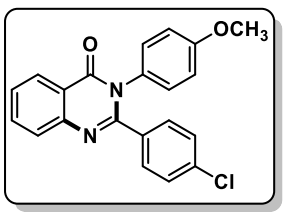
129.1, 130.2, 130.6, 132.9, 134.8, 139.5, 147.8, 155.8, 159.3, 162.8; IR (KBr): 3059, 3031, 2962, 2835, 1685, 1609, 1564, 1584, 1471, 1346, 1252, 1023, 817, 777, 619, 543 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{19}N_2O_2$ [M + H^+] 343.1441; found 343.1449.

2,3-Bis(4-methoxyphenyl)quinazolin-4(3*H*)-one (3c):



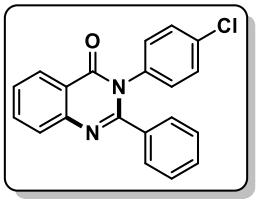
White solid (73 mg, 81%); mp 134–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.76 (s, 3H), 3.78 (s, 3H), 6.73 (d, 2H, *J* = 8.4 Hz), 6.84 (d, 2H, *J* = 8.8 Hz), 7.04–7.07 (m, 2H), 7.27–7.32 (m, 2H), 7.47–7.51 (m, 1H), 7.75–7.80 (m, 2H), 8.32 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.4, 55.6, 113.6, 114.5, 121.0, 127.1, 127.4, 127.8, 128.2, 130.2, 130.8, 130.9, 134.8, 147.8, 155.4, 159.3, 160.4, 162.9; IR (KBr): 3064, 2924, 2838, 1677, 1604, 1507, 1466, 1252, 1174, 1023, 827, 776 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{19}N_2O_3$ [M + H^+] 359.1390; found 359.1396.

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



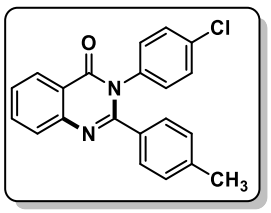
White solid (64 mg, 71%); mp 161–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.79 (s, 3H), 6.84 (d, 2H, *J* = 9.2 Hz), 7.04 (d, 2H, *J* = 9.2 Hz), 7.21 (d, 2H, *J* = 8.8 Hz), 7.29 (d, 2H, *J* = 8.8 Hz), 7.51–7.55 (m, 1H), 7.77–7.83 (m, 2H), 8.33 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.6, 114.6, 121.1, 127.5, 127.6, 127.9, 128.5, 130.16, 130.20, 130.6, 134.3, 135.0, 135.7, 147.6, 154.6, 159.5, 162.6; IR (KBr): 3328, 3052, 2928, 1676, 1505, 1330, 1244, 1176, 1022, 831, 777 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{16}ClN_2O_2$ [M + H^+] 363.0895; found 363.0901.

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



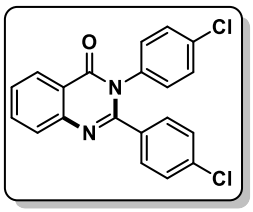
Yellow solid (49 mg, 59%); mp 190–196 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.07–7.10 (m, 2H), 7.22–7.34 (m, 7H), 7.51–7.56 (m, 1H), 7.81 (d, 2H, *J* = 4.0 Hz), 8.33 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 120.9, 127.4, 127.6, 128.0, 128.4, 129.1, 129.4, 129.8, 130.6, 134.5, 135.1, 135.3, 136.3, 147.5, 155.0, 162.3; IR (KBr): 3056, 3035, 1678, 1565, 1471, 1340, 1271, 1089, 1017, 838, 770, 699 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{14}ClN_2O$ [M + H^+] 333.0789; found 333.0795.

3-(4-Chlorophenyl)-2-(*p*-tolyl)quinazolin-4(3*H*)-one (4b):



Yellow solid (55 mg, 64%); mp 130–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.29 (s, 3H), 7.04 (d, 2H, *J* = 8.4 Hz), 7.09 (d, 2H, *J* = 8.8 Hz), 7.21 (d, 2H, *J* = 8.4 Hz), 7.29 (d, 2H, *J* = 8.8 Hz), 7.49–7.53 (m, 1H), 7.79 (d, 2H, *J* = 4.4 Hz), 8.31 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.5, 120.8, 127.3, 127.5, 127.9, 129.05, 129.09, 129.4, 130.6, 132.4, 134.4, 135.0, 136.5, 140.0, 147.6, 155.0, 162.4; IR (KBr): 3063, 2919, 2846, 1692, 1593, 1467, 1334, 1268, 1085, 1015, 815, 771 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{16}ClN_2O$ [M + H^+] 347.0946; found 347.0939.

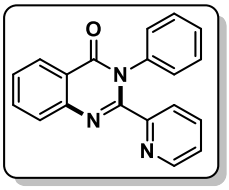
2,3-Bis(4-chlorophenyl)quinazolin-4(3*H*)-one (4d):



White solid (47.5 mg, 52%); mp 174–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.09 (d, 2H, *J* = 8.4 Hz), 7.22–7.33 (m, 6H), 7.55 (t, 1H, *J* = 6.8 Hz), 7.76–7.84 (m, 2H), 8.32 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 120.9, 127.4, 127.9, 128.0, 128.7, 129.7, 130.5, 130.6, 133.7, 134.8, 135.2, 136.07, 136.11, 147.4, 153.8, 162.2; IR (KBr): 3062, 2922, 2848, 1682, 1596,

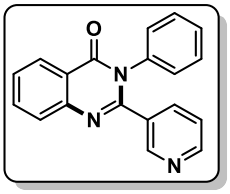
1486, 1336, 1268, 1086, 1012, 832, 764, 689 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{13}Cl_2N_2O$ [M + H^+] 367.0399; found 367.0390.

3-Phenyl-2-(pyridin-2-yl)quinazolin-4(3*H*)-one (1g):



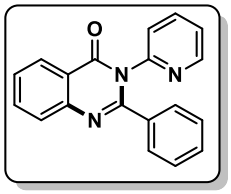
White solid (48 mg, 64%); mp 155–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.16 (t, 1H, *J* = 6.4 Hz), 7.20 (d, 2H, *J* = 8.0 Hz), 7.25–7.32 (m, 3H), 7.50 (d, 1H, *J* = 8.0 Hz), 7.57 (t, 1H, *J* = 6.8 Hz), 7.63 (d, 1H, *J* = 8.0 Hz), 7.81–7.87 (m, 2H), 8.37–8.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 121.6, 122.6, 123.9, 124.5, 127.4, 127.9, 128.1, 128.4, 128.9, 129.1, 134.9, 136.5, 137.5, 147.4, 149.0, 153.5, 162.2; IR (KBr): 3182, 3059, 2923, 2853, 1686, 1582, 1467, 1353, 1277, 775, 695 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}N_3O$ [M + H^+] 300.1131; found 300.1126.

3-Phenyl-2-(pyridin-3-yl)quinazolin-4(3*H*)-one (1h):



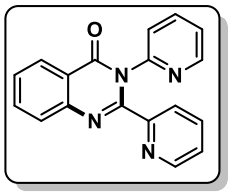
Brown solid (50 mg, 67%); mp 170–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.17 (d, 3H, *J* = 6.8 Hz), 7.30–7.38 (m, 3H), 7.55–7.62 (m, 2H), 7.81–7.86 (m, 2H), 8.36 (d, 1H, *J* = 7.2 Hz), 8.58 (bd, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 121.2, 127.5, 127.96, 128.01, 129.1, 129.3, 129.6, 135.1, 136.4, 137.3, 147.5, 149.9, 150.3, 152.7, 162.2; IR (KBr): 3041, 2923, 2854, 1677, 1591, 1469, 1338, 1276, 1022, 951 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}N_3O$ [M + H^+] 300.1131; found 300.1136.

2-Phenyl-3-(pyridin-2-yl)quinazolin-4(3*H*)-one (5a):



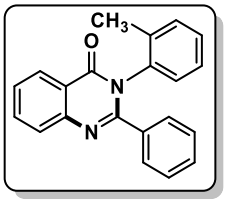
Brown solid (40 mg, 53%); mp 180–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.19–7.27 (m, 4H), 7.31 (d, 1H, *J* = 8.0 Hz), 7.38 (d, 2H, *J* = 6.8 Hz), 7.52–7.56 (m, 1H), 7.71–7.75 (m, 1H), 7.79–7.85 (m, 2H), 8.36 (d, 1H, *J* = 7.6 Hz), 8.45 (d, 1H, *J* = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 121.2, 123.9, 124.8, 127.3, 127.6, 128.1, 128.3, 129.0, 129.6, 135.1, 135.6, 138.2, 147.8, 149.6, 151.5, 154.7, 162.5; IR (KBr): 3063, 2923, 2848, 1682, 1556, 1463, 1336, 1080, 773, 697 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}N_3O$ [M + H^+] 300.1131; found 300.1127.

2,3-Di(pyridin-2-yl)quinazolin-4(3*H*)-one (5g):



Brown semisolid (29 mg, 39%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.14 (t, 1H, *J* = 4.0 Hz), 7.19 (t, 1H, *J* = 4.8 Hz), 7.54–7.58 (m, 1H), 7.71 (d, 1H, *J* = 7.6 Hz), 7.73–7.77 (m, 1H), 7.80–7.86 (m, 3H), 7.98 (d, 1H, *J* = 7.6 Hz), 8.18 (d, 2H, *J* = 13.2 Hz), 8.38 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 121.5, 123.2, 123.8, 125.1, 125.4, 127.4, 127.9, 128.1, 135.1, 136.9, 137.4, 147.4, 148.1, 148.5, 151.5, 152.7, 153.6, 162.2; IR (KBr): 3057, 2923, 2851, 2362, 1677, 1587, 1468, 1341, 1283, 770, 689 cm^{-1}; HRMS (ESI): calcd for $C_{18}H_{13}N_4O$ [M + H^+] 301.1084; found 301.1091.

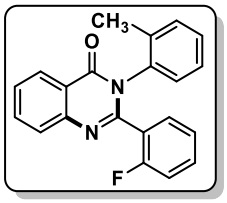
2-Phenyl-3-(*o*-tolyl)quinazolin-4(3*H*)-one (6a):



Yellow solid (47 mg, 60%); mp 142–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.14 (s, 3H), 7.06 (d, 1H, *J* = 7.6 Hz), 7.13 (t, 1H, *J* = 8.4 Hz), 7.18–7.28 (m, 5H), 7.34 (d, 2H, *J* = 6.8 Hz), 7.54 (t, 1H, *J* = 6.4 Hz), 7.80–7.86 (m, 2H), 8.37 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.1, 121.1, 126.8, 127.39,

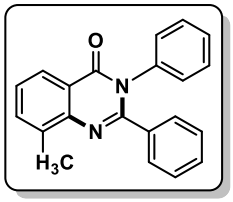
127.42, 127.9, 128.0, 128.8, 129.2, 129.6, 131.2, 134.9, 135.3, 135.8, 137.0, 147.9, 155.6, 162.0; IR (KBr): 3061, 2959, 1678, 1592, 1465, 1332, 1269, 1126, 1023, 947 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{17}N_2O$ [M + H^+] 313.1335; found 313.1329.

2-(2-Fluorophenyl)-3-(*o*-tolyl)quinazolin-4(3*H*)-one (6i):



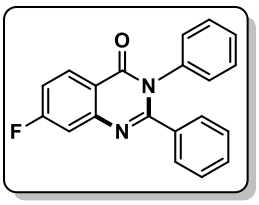
Yellow solid (34 mg, 41%); mp 117–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.16 (s, 3H), 6.88 (t, 1H, *J* = 9.6 Hz), 7.05 (t, 1H, *J* = 7.6 Hz), 7.08–7.13 (m, 2H), 7.16 (d, 2H, *J* = 4.0 Hz), 7.21–7.27 (m, 1H), 7.35 (t, 1H, *J* = 7.2 Hz), 7.55–7.59 (m, 1H), 7.80–7.85 (m, 2H), 8.39 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.9, 115.6, 115.9, 121.4, 124.03, 124.1, 126.5, 127.4, 127.8, 127.9, 129.0, 129.3, 129.7, 130.9, 131.7, 131.8, 134.9, 136.1, 147.6, 151.6, 157.7, 160.1, 161.5; IR (KBr): 3062, 2917, 1681, 1590, 1461, 1335, 1272, 1220, 1102, 947 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{16}FN_2O$ [M + H^+] 331.1241; found 331.1237.

8-Methyl-2,3-diphenylquinazolin-4(3*H*)-one (7a):



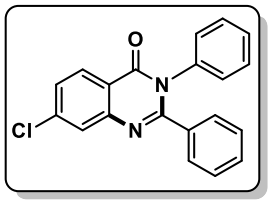
Yellow solid (48 mg, 61%); mp 123–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.67 (s, 3H), 7.14 (d, 2H, *J* = 7.6 Hz), 7.19 (d, 2H, *J* = 7.2 Hz), 7.24 (t, 1H, *J* = 4.4 Hz), 7.31 (q, 3H, *J* = 7.6 Hz), 7.35 (d, 2H, *J* = 8.0 Hz), 7.41 (d, 1H, *J* = 7.6 Hz), 7.64 (d, 1H, *J* = 7.6 Hz), 8.19 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.6, 121.0, 125.0, 127.0, 128.0, 128.5, 129.1, 129.2, 129.3, 129.4, 135.5, 135.9, 136.5, 138.1, 146.2, 153.7, 162.9; IR (KBr): 3052, 2932, 2748, 1679, 1555, 1434, 1346, 1285, 1012 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{16}N_2O$ [M + H^+] 313.1335; found 313.1341.

7-Fluoro-2,3-diphenylquinazolin-4(3*H*)-one (8a):



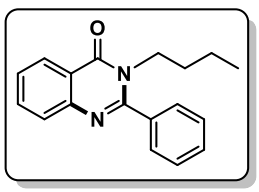
Yellow solid (55 mg, 69%); mp 207–209 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.13 (d, 2H, *J* = 7.2 Hz), 7.21 (t, 2H, *J* = 7.2 Hz), 7.25–7.28 (m, 3H), 7.31 (t, 4H, *J* = 7.8 Hz), 7.47 (d, 1H, *J* = 9.6 Hz), 8.35 (t, 1H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 113.2, 113.3, 116.2, 116.3, 117.8, 121.3, 125.5, 128.2, 128.7, 129.1, 129.7, 130.1, 130.2, 135.3, 137.6, 149.9, 156.7, 161.8, 166.1, 167.8; IR (KBr): 3042, 2952, 2778, 1682, 1515, 1444, 1346, 1285, 1012 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{13}FN_2O$ [M + H^+] 317.1085; found 317.1079.

7-Chloro-2,3-diphenylquinazolin-4(3*H*)-one (9a):



White solid (56 mg, 67%); mp 180–182 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.13 (d, 2H, *J* = 7.2 Hz), 7.21 (t, 2H, *J* = 7.8 Hz), 7.25–7.29 (m, 2H), 7.31 (bs, 4H), 7.48 (d, 1H, *J* = 8.4 Hz), 7.82 (s, 1H), 8.27 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 119.6, 121.2, 127.5, 127.6, 128.1, 128.2, 128.8, 128.9, 129.1, 129.13, 129.19, 129.2, 129.8, 137.6, 141.2, 156.6, 162.0; IR (KBr): 3032, 2912, 2758, 1672, 1565, 1134, 1006, 995 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{13}ClN_2O$ [M + H^+] 333.0789; found 333.0795.

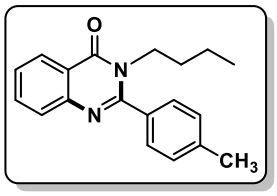
3-Butyl-2-phenylquinazolin-4(3*H*)-one (10a):



White solid (51 mg, 73%); mp 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.74 (t, 3H, *J* = 7.6 Hz), 1.11–1.18 (m, 2H), 1.54–1.61 (m, 2H), 3.96 (t, 2H, *J* = 7.6 Hz), 7.46–7.53 (m, 6H), 7.70–7.76 (m, 2H), 8.32 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.6, 20.0, 30.9, 45.9, 121.1, 126.9, 127.1, 127.6, 127.9, 128.9, 129.9, 134.4, 135.7, 147.3, 156.4, 162.3; IR (KBr): 3037, 2959, 2926, 2860, 1669, 1585, 1464, 1362, 1073, 772,

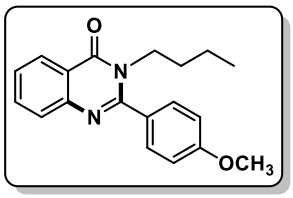
700 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{19}N_2O$ [M + H^+] 279.1492; found 279.1484.

3-Butyl-2-(*p*-tolyl)quinazolin-4(3*H*)-one (10b):



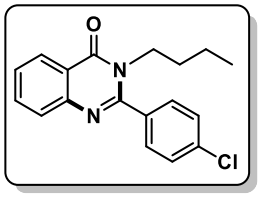
Yellow gummy (56 mg, 77%); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.77 (t, 3H, *J* = 7.2 Hz), 1.12–1.22 (m, 2H), 1.54–1.62 (m, 2H), 2.43 (s, 3H), 3.98 (t, 2H, *J* = 7.6 Hz), 7.30 (d, 2H, *J* = 8.0 Hz), 7.41 (d, 2H, *J* = 7.6 Hz), 7.46–7.50 (m, 1H),7.70–7.75 (m, 2H), 8.31 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.6, 20.1, 21.6. 30.9, 45.9, 121.0, 126.9, 127.0, 127.6, 127.9, 129.5, 132.9, 134.4, 140.0, 147.4, 156.6, 162.4; IR (KBr): 3342, 2959, 2927, 2867, 1680, 1561, 1468, 1373, 1233, 1176, 1079, 1023, 821, 776, 700 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{21}N_2O$ [M + H^+] 293.1648; found 293.1655.

3-Butyl-2-(4-methoxyphenyl)quinazolin-4(3*H*)-one (10c):



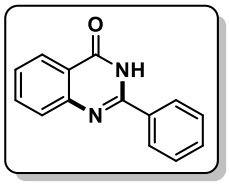
Yellow gummy (58 mg, 75%); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.77 (t, 3H, *J* = 7.6 Hz), 1.13–1.22 (m, 2H), 1.54–1.61 (m, 2H), 3.86 (s, 3H), 4.00 (t, 2H, *J* = 7.6 Hz), 7.01 (d, 2H, *J* = 8.8 Hz), 7.45–7.49 (m, 3H), 7.69–7.75 (m, 2H), 8.30 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.7, 20.1, 31.0, 45.9, 55.6, 114.2, 121.0, 126.9, 127.0, 127.5, 128.2, 129.6, 134.4, 147.4, 156.3, 160.8, 162.5; IR (KBr): 3070, 2959, 2929, 2867, 1676, 1609, 1512, 1466, 1294, 1251, 1176, 1029, 838, 776 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{21}N_2O_2$ [M + H^+] 309.1598; found 309.1607.

3-Butyl-2-(4-chlorophenyl)quinazolin-4(3*H*)-one (10d):



Yellow semisolid (54 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.78 (t, 3H, *J* = 7.6 Hz), 1.16–1.24 (m, 2H), 1.53–1.61 (m, 2H), 3.96 (t, 2H, *J* = 8.0 Hz), 7.50–7.53 (m, 5H), 7.70 (d, 1H, *J* = 8.0 Hz), 7.76 (t, 1H, *J* = 8.4 Hz), 8.32 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.7, 20.1, 31.0, 46.0, 121.1, 127.0, 127.4, 127.6, 129.3, 129.5, 134.2, 134.6, 136.2, 147.2, 155.3, 162.2; IR (KBr): 2960, 2927, 2864, 1684, 1599, 1466, 1366, 1231, 1083, 825, 786, 696 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{18}ClN_2O$ [M + H^+] 313.1102; found 313.1110.

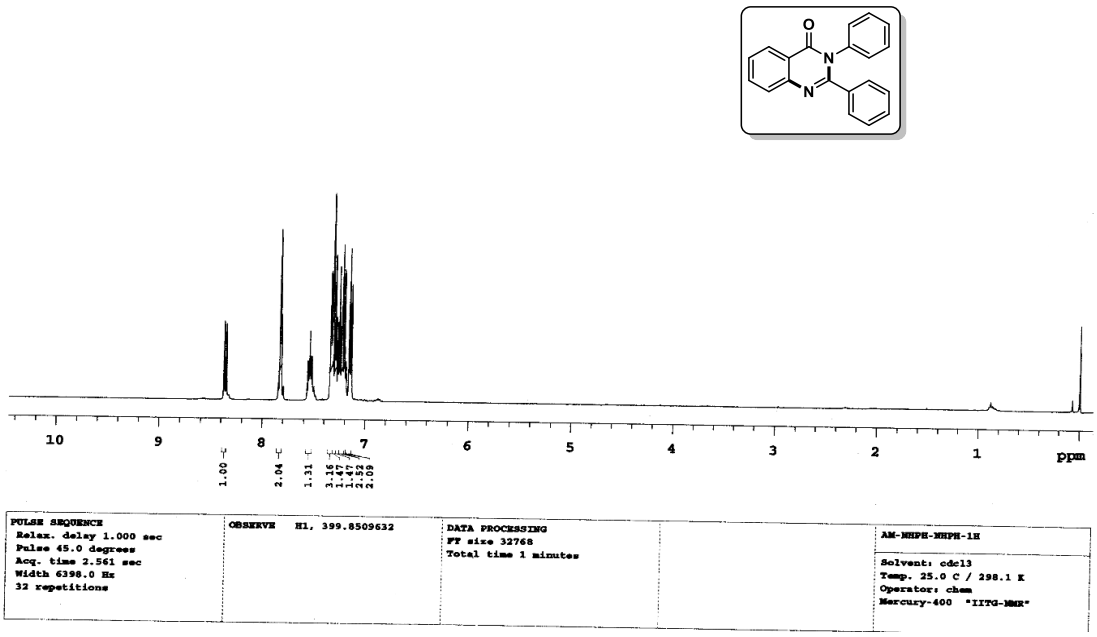
2-Phenylquinazolin-4(3*H*)-one (11a):



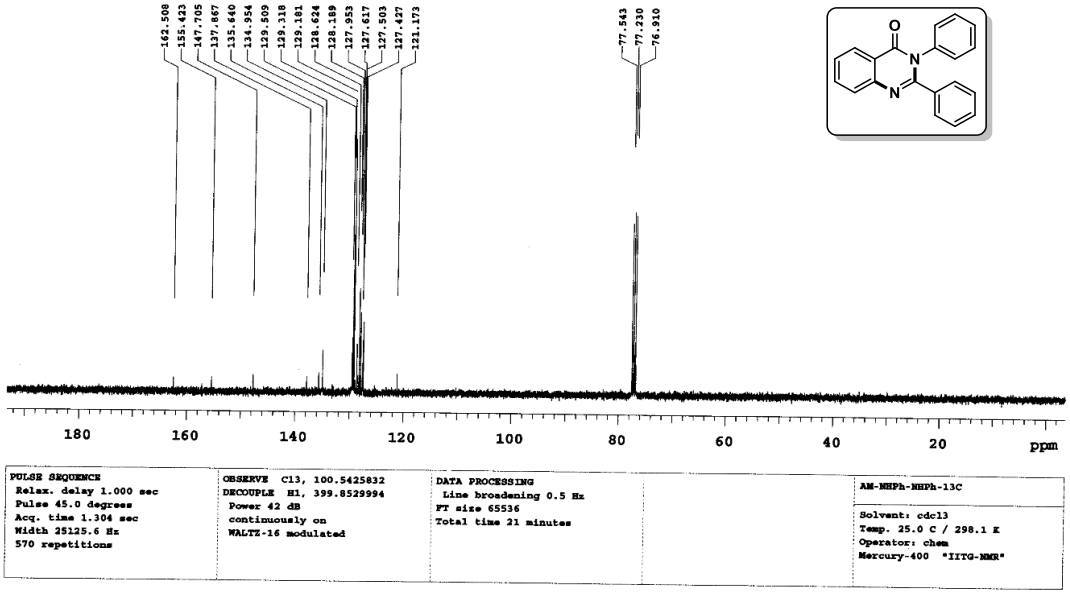
White solid (43 mg, 77%); mp 229–230 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.51 (t, 1H, *J* = 8.4 Hz), 7.59 (bs, 3H), 7.79–7.86 (m, 2H), 8.27 (bs, 2H), 8.33 (d, 1H, *J* = 7.6 Hz), 11.83 (s,1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 121.1, 126.6, 127.0, 127.6, 128.2, 129.2, 131.9, 133.0, 135.1, 149.7, 151.9, 164.1; IR (KBr): 3196, 3067, 2956, 1669, 1603, 1476, 1292, 1144 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{11}N_2O$ [M + H^+] 223.0866; found 223.0874.

II.7. Spectra

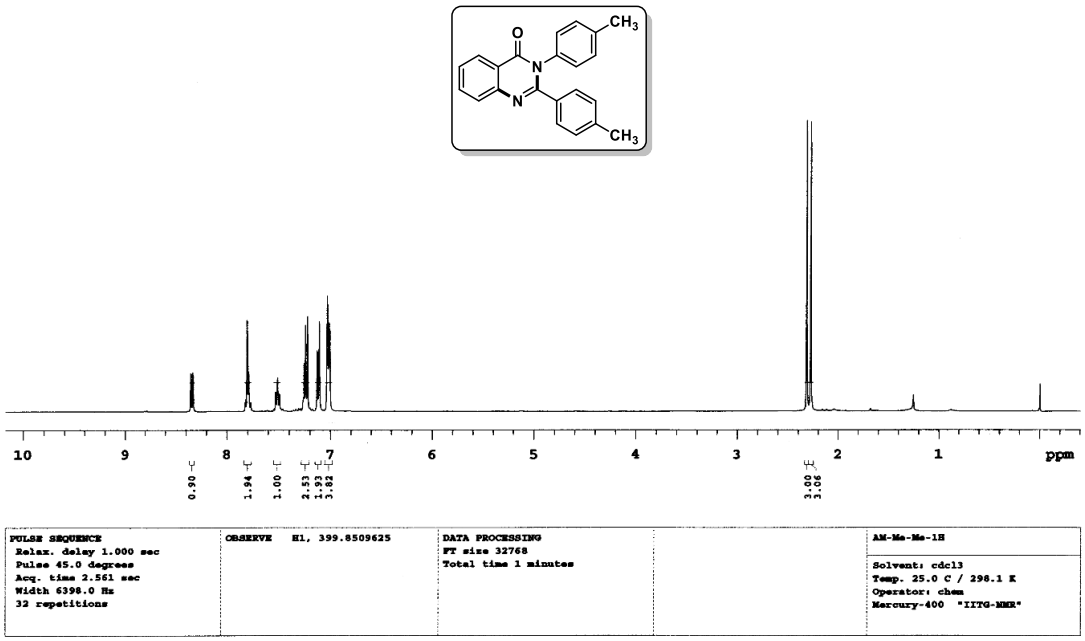
2,3-Diphenylquinazolin-4(3*H*)-one (1a): ^{1}HNMR (400 MHz, $CDCl_3$)



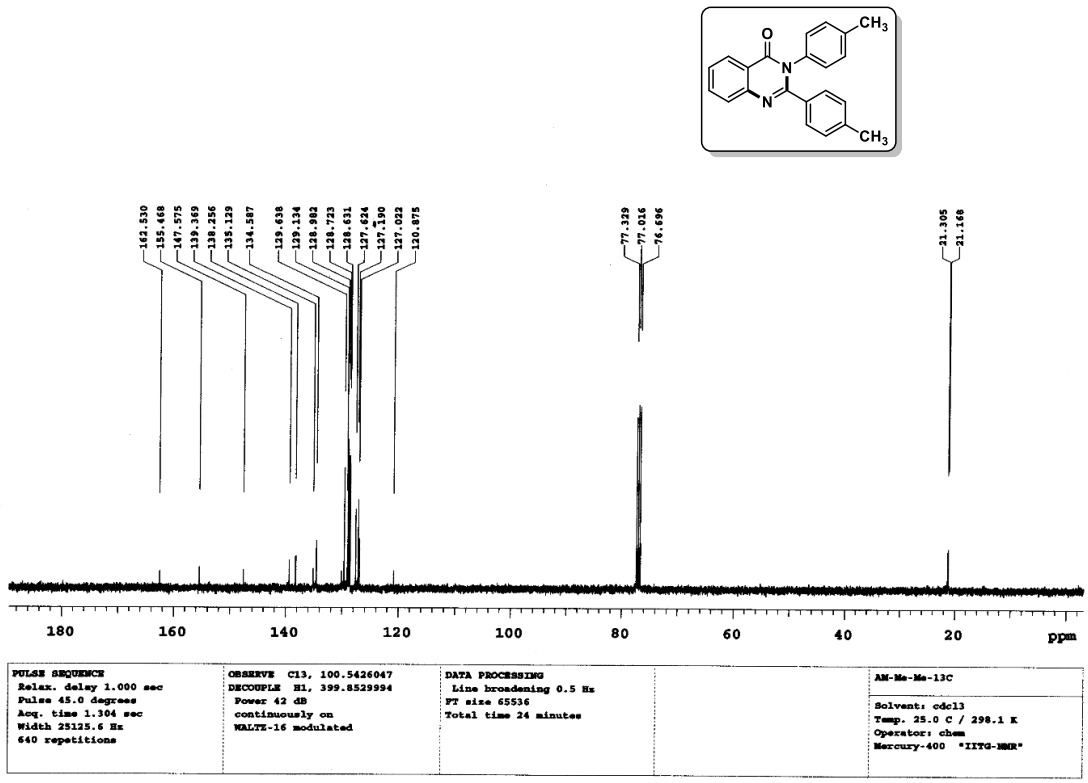
2,3-Diphenylquinazolin-4(3*H*)-one (1a): ^{13}CNMR (100 MHz, $CDCl_3$)



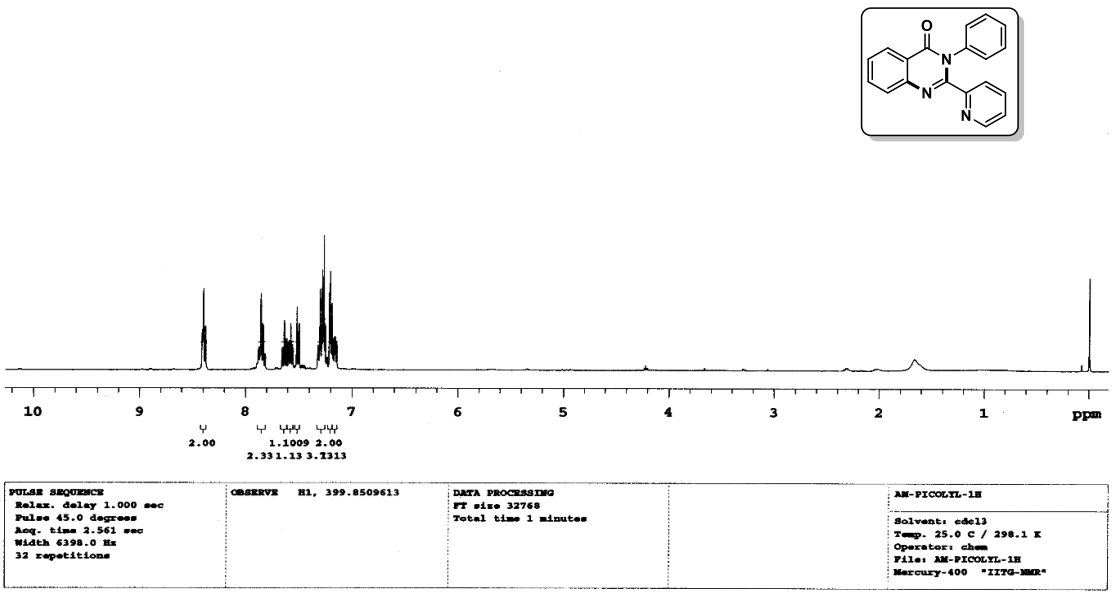
2,3-Di-*p*-tolylquinazolin-4(3*H*)-one (2b): ^{1}HNMR (400 MHz, $CDCl_3$)



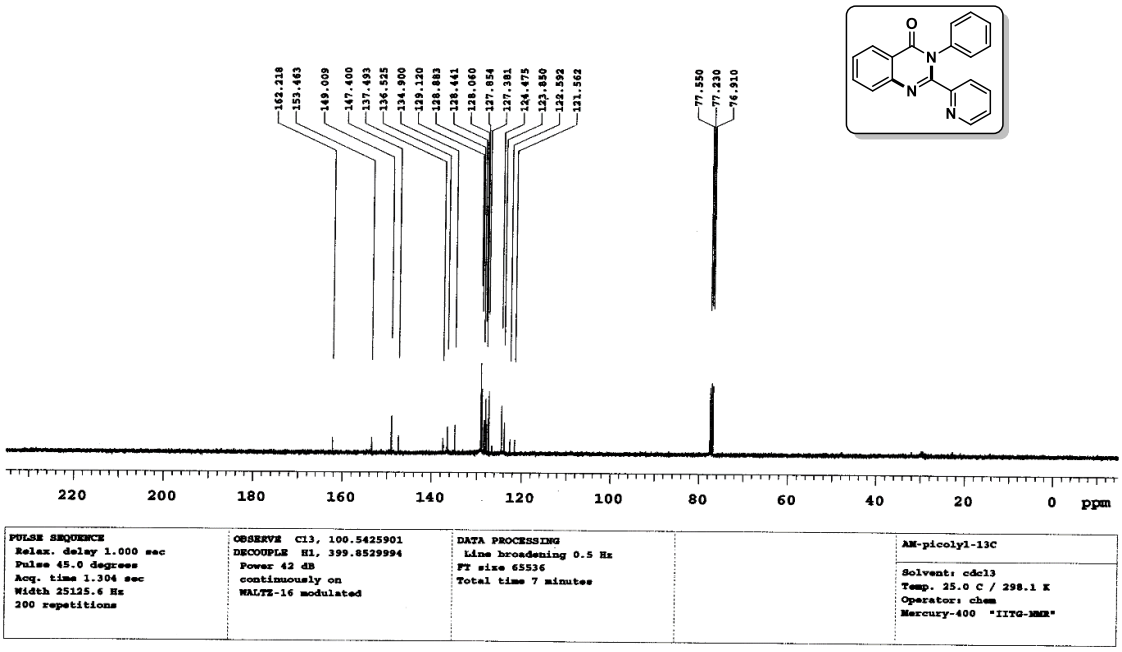
2,3-Di-*p*-tolylquinazolin-4(3*H*)-one (2b): ^{13}CNMR (100 MHz, $CDCl_3$)



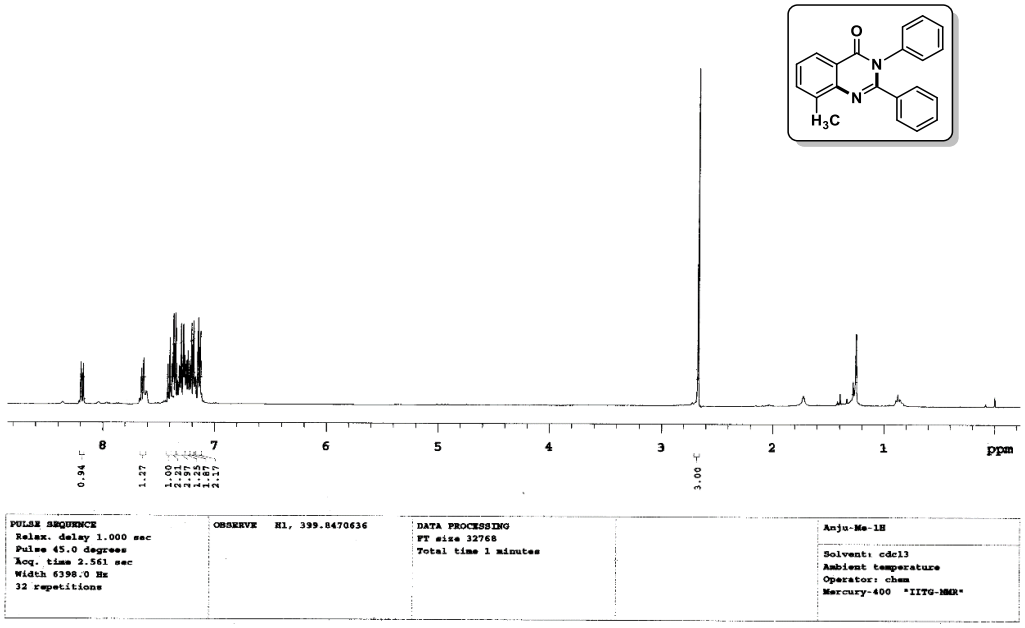
3-Phenyl-2-(pyridin-2-yl)quinazolin-4(3*H*)-one (1g): ^{1}HNMR (400 MHz, $CDCl_3$)



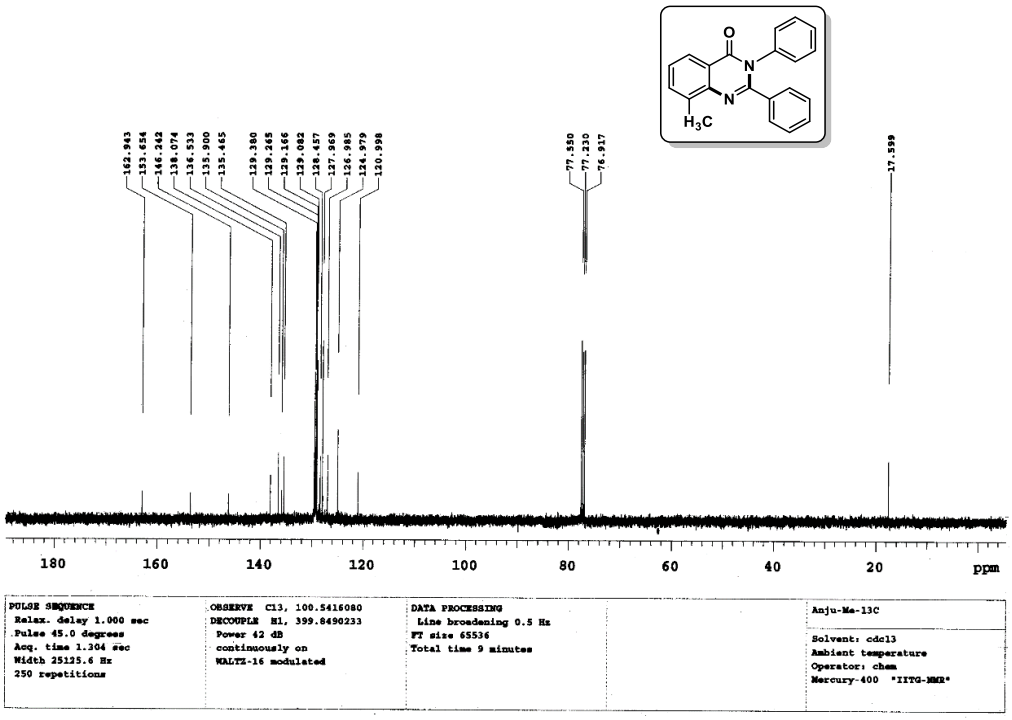
3-Phenyl-2-(pyridin-2-yl)quinazolin-4(3*H*)-one (1g): ^{13}CNMR (100 MHz, $CDCl_3$)



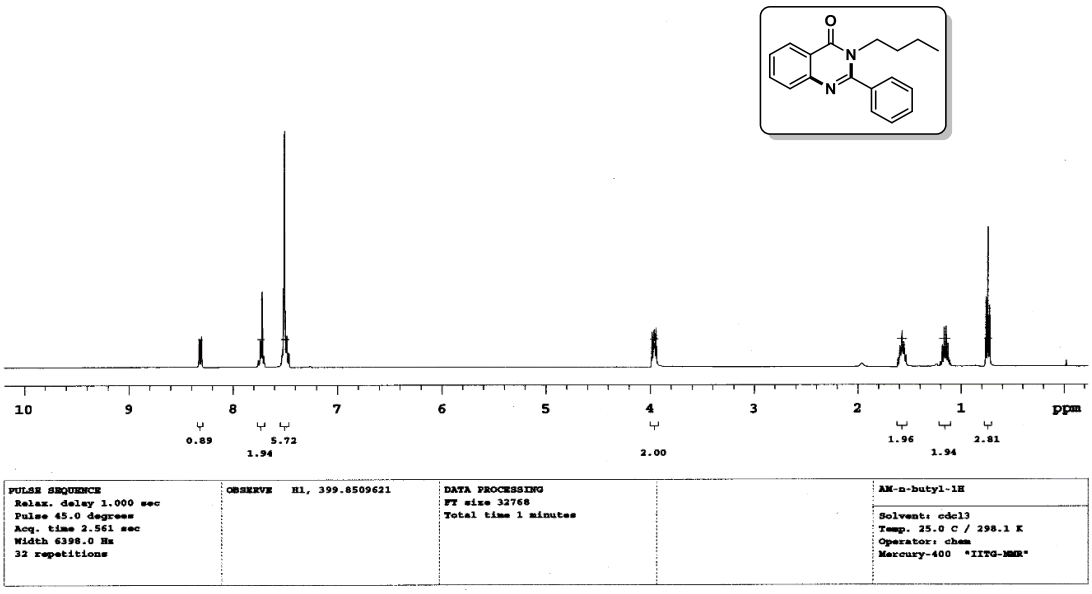
8-Methyl-2,3-diphenylquinazolin-4(3*H*)-one (7a): ^{1}HNMR (400 MHz, $CDCl_3$)



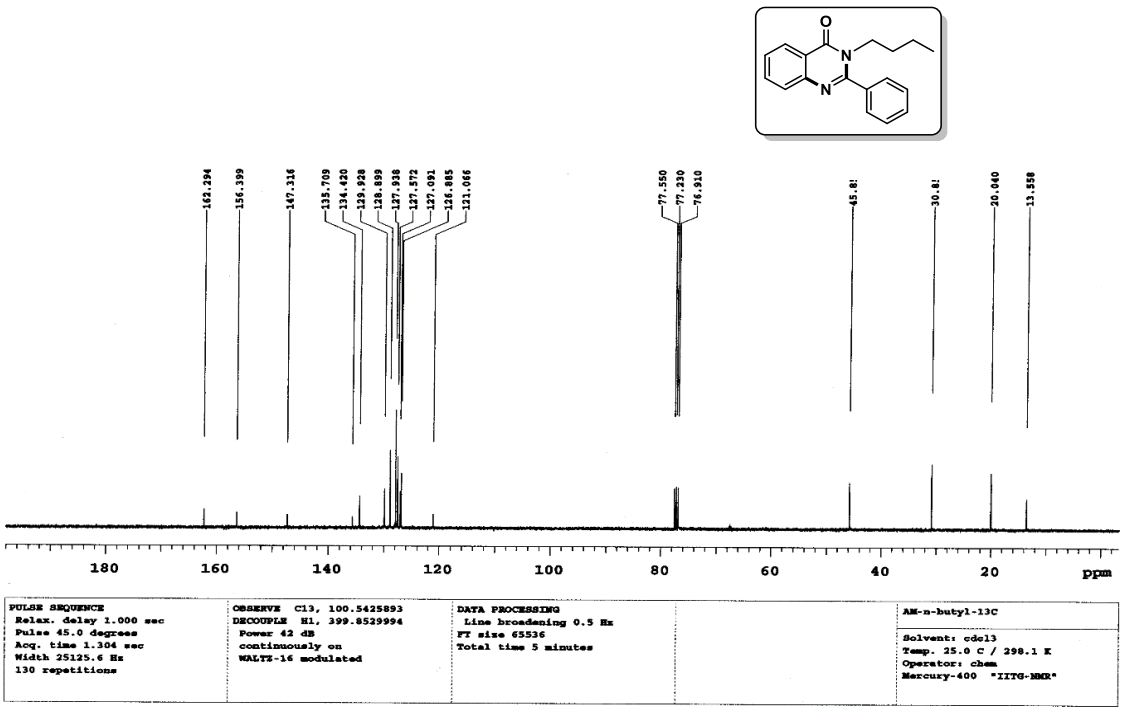
8-Methyl-2,3-diphenylquinazolin-4(3*H*)-one (7a): ^{13}CNMR (100 MHz, $CDCl_3$)



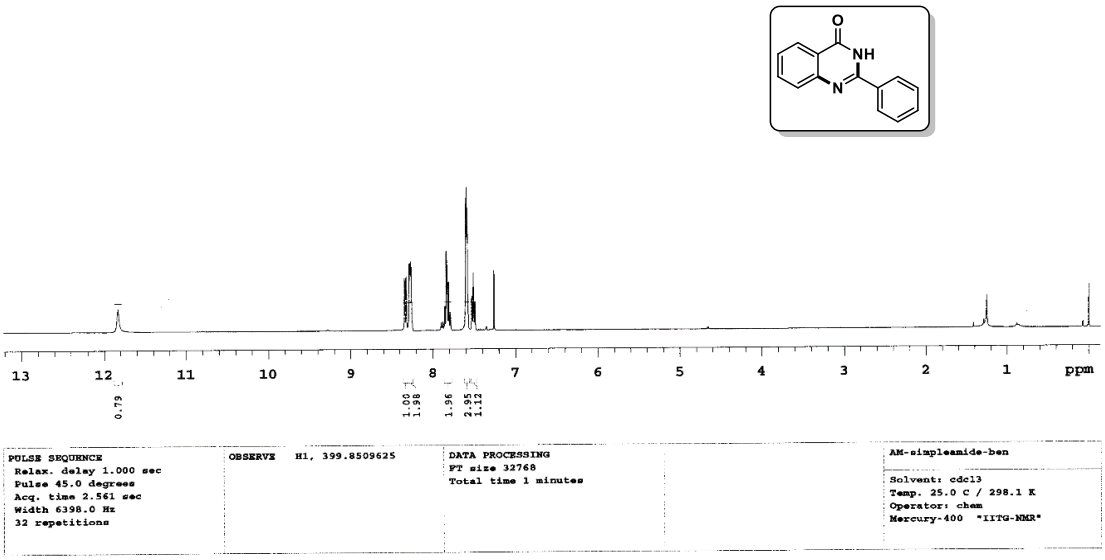
3-Butyl-2-phenylquinazolin-4(3*H*)-one (10a): ^{1}HNMR (400 MHz, $CDCl_3$)



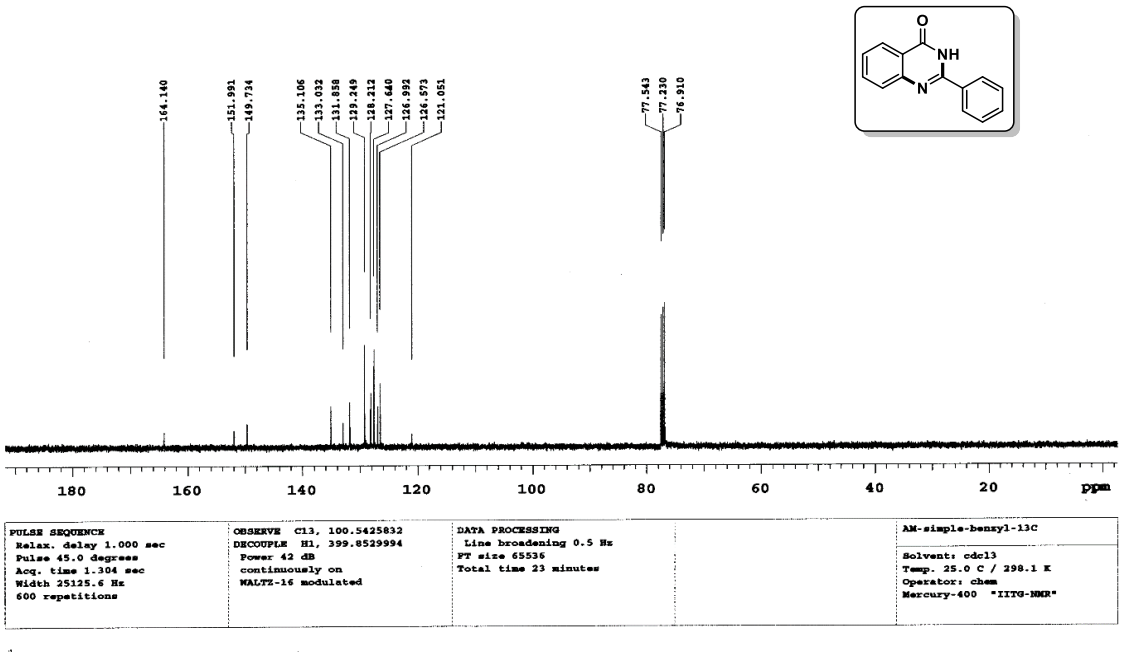
3-Butyl-2-phenylquinazolin-4(3*H*)-one (10a): ^{13}CNMR (100 MHz, $CDCl_3$)



2-Phenylquinazolin-4(3*H*)-one (11a): ^{1}HNMR (400 MHz, $CDCl_3$)

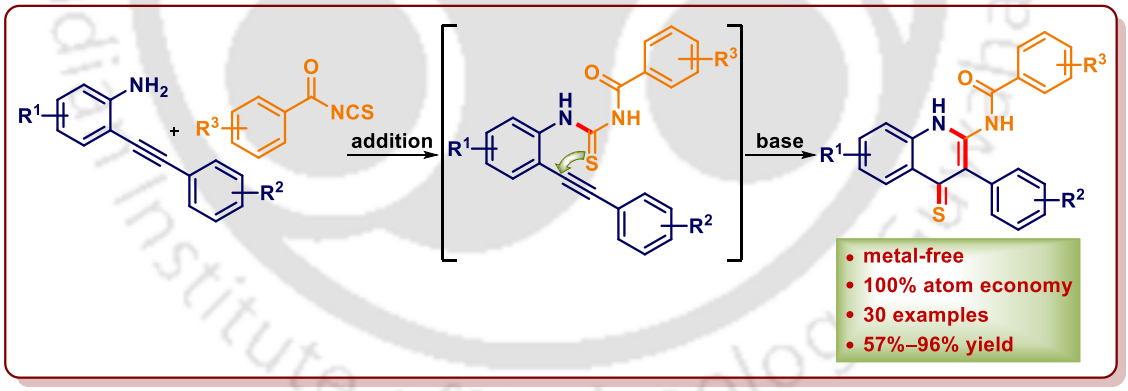


2-Phenylquinazolin-4(3*H*)-one (11a): ^{13}CNMR (100 MHz, $CDCl_3$)



CHAPTER III

Base-Promoted Synthesis of Quinoline-4(1H)-thiones from o-Alkynylanilines and Aroyl Isothiocyanates



ABSTARCT: *A base-promoted synthesis of quinoline-4(1H)-thiones has been accomplished from the in situ generated o-alkynylthiourea, obtained by reacting o-alkynylanilines with aroyl/acyl isothiocyanates. A 6-exo-dig S-cyclization of the in situ generated thiourea is followed by a rearrangement to give quinoline-4(1H)-thiones.*

CHAPTER III

III. Base-Promoted Synthesis of Quinoline-4(1*H*)-thiones from *o*-Alkynylanilines and Aroyl Isothiocyanates

III.1. Introduction

Construction of heterocycles with privileged scaffolds, which exhibit various biological activities, is in great demand in the field of chemical genetics.[1] Among numerous efforts devoted towards the development of these compounds, cascade reactions have emerged as a powerful synthetic tool in modern synthetic organic chemistry.[2] Compared to the traditional stepwise synthesis, cascade reactions have the advantage of sequential incorporation of multiple C–C and C–heteroatom bonds in one-pot, thereby increasing the overall synthetic efficiency. Taking advantage of this strategy, several alkyne-based substrates, possessing internal nucleophiles at appropriate positions, are often utilized for the construction of interesting heterocycles.[3] Among various alkynes, *o*-alkynylanilines have been extensively employed for the construction of molecular frameworks such as indole,[4] quinoline,[5] quinazolinone,[6] benzoxazine,[7] 4*H*-benzo[*d*][1,3]thiazine,[8] anthranils,[9] cinnolines,[10] using various metal salts such as palladium, copper and silver.

Nitrogen-containing heterocycles are found in a myriad of natural products and biologically active compounds. Therefore, construction and functionalization of such heterocyclic cores have always attracted the synthetic chemist. Among several *N*-heterocycles, quinoline-4(1*H*)-thione is also an important scaffold exhibiting significant biological properties. The derivatives of quinoline-4(1*H*)-thiones are found to be inhibitors of virulence factor elastase of the human pathogen *Pseudomonas aeruginosa* (Figure III.1.1, A).[11a,b] Some of the quinoline-4(1*H*)-thione derivatives (Figure III.1.1, B) are reported to form oxovanadium complexes with $VO(acac)_2$, exhibiting cytotoxic activity and apoptosis in human malignant cell lines.[11c] Despite the importance of the quinoline-4(1*H*)-thione framework, there are only a few reports of their synthesis which mainly involve thioketolization of the preformed quinolin-4(1*H*)-ones with phosphorus

pentasulfide (P_4S_{10}) or with Lawesson's reagent.[11,12] Owing to the importance of quinoline-4(1*H*)-thiones, development of synthetic strategy which are cost-effective and atom-economical is highly desirable.

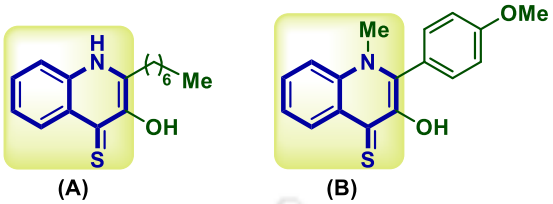


Figure III.1.1. *Active quinoline-4(1H)-thiones*

III.2. Idea Towards the Synthesis of Quinoline-4(1*H*)-thiones

Aroyl isothiocyanates are bifunctional compounds having an aroyl (–COAr) and a thiocyanate (–NSC) functionality. The reactivity of aroyl isothiocyanates are determined by four active centres *viz.* the nucleophilic nitrogen and sulfur atom, and the electrophilic carbon atoms of the carbonyl and thiocarbonyl groups (Figure. III.2.1). These compounds are easily accessible by reacting acid chlorides with salts of thiocyanate such as KSCN, NH_4SCN and $Pb(SCN)_2$. The presence of electron withdrawing acyl group makes them more reactive compared to aryl/alkyl isothiocyanate. They are also useful synthons in organic chemistry for the synthesis of many heterocycles such as functionalized thiazoles, thiadiazoles, triazoles, benzimidazoles, spiro-fused oxazolines, triazines and oxazines.[13]

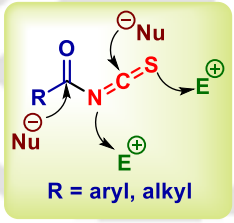
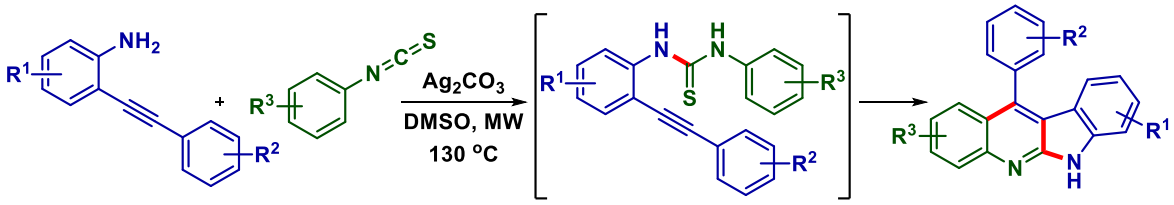


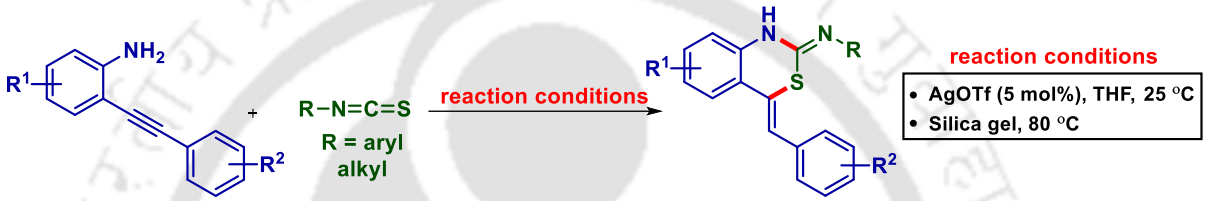
Figure. III.2.1. *Active sites in aroyl/acyl isothiocyanates*

Recently, our group reported the synthesis of indolo[2,3-*b*]quinolines from *o*-alkynylanilines and aryl isothiocyantes in presence of Ag_2CO_3 under microwave heating.[14] The reaction generates an *o*-alkynylthiourea intermediate via the coupling of *o*-alkynylanilines with aryl isothiocyanates. The intermediate undergoes desulfurization in the presence of Ag_2CO_3 and undergoes cascade cyclization to form indoloquinolines in good to moderate yields (Scheme III.2.1).



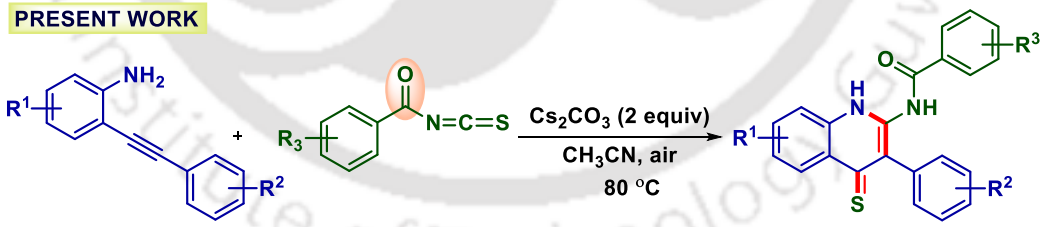
Scheme III.2.1. *Synthesis of indolo[2,3-b]quinolines*

In 2008, Wu group reported the synthesis of 2,4-dihydro-1*H*-benzo[*d*][1,3]thiazines via Lewis acid (AgOTf) catalyzed tandem addition-cyclization reaction of *o*-alkynylanilines and aryl isothiocyanates.[15a] Later Ding *et al.* reported similar reaction promoted by silica gel under metal- and solvent-free conditions (Scheme III.2.2).[15b]



Scheme III.2.2. *Synthesis of 2,4-dihydro-1H-benzo[d][1,3]thiazines*

Thus taking cues from literature and our recent work and further exploring the diverse reactivity of aroyl isothiocyanate, we reacted *o*-alkynylanilines with an aroyl isothiocyanate. Interestingly, replacement of aryl isothiocyante with an aroyl isothiocyante completely changed the course of reaction and the product outcome, giving a quinoline-4(1*H*)-thione (Scheme III.2.3).



Scheme III.2.3. *Synthesis of quinoline-4(1H)-thiones*

III.3. Present Work

We initiated our investigation by reacting 2-(phenylethynyl)aniline (**1**) (1 equiv) and benzoyl isothiocyanate (**a**) (1 equiv) in the presence of CuI (10 mol %) and K_2CO_3 (4 equiv) in 1,4-dioxane at 110 °C (Table III.3.1, entry 1). A product was isolated in 47% yield and the spectroscopic analysis (IR, ^{1}HNMR, ^{13}CNMR, and HRMS) of the product supported its structure to be *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide

(**1a**). However, the exact structure of the product was fully ascertained by single-crystal X-ray diffraction of one of its derivative (**3a**) (Figure III.3.1), thereby confirming its structure to be *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (**1a**). Interestingly, the benzoyl thiourea generated *in situ* underwent a 6-*exo*-dig *S*-attack onto the internal alkyne, followed by rearrangement giving quinoline-4(1*H*)-thione moiety in 100% atom economy.

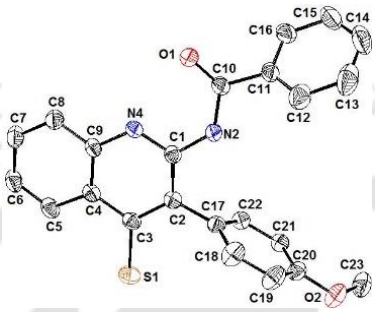
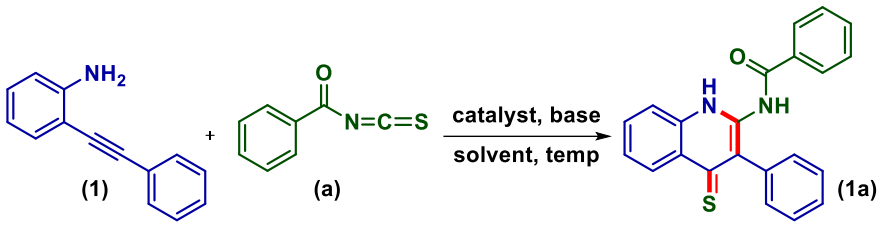


Figure III.3.1. *Ortep view of (**3a**)*

Optimization of Reaction Conditions:

Encouraged by the synthesis of quinoline-4(1*H*)-thiones, further optimization of the reaction parameters was tuned to enhance the productivity of the reaction. Initially, a range of other copper salts such as CuBr (52%), $Cu(OAc)_2$ (41%) and $Cu(OTf)_2$ (37%) were examined, among which CuBr gave better yield (52%) compared to CuI (47%) (Table III.3.1, entries 1–4). The use alkyne activating silver salt *viz.* Ag_2CO_3 (18%), in lieu of copper salt was not so effective (Table III.3.1, entry 5). Other inorganic bases such as Na_2CO_3 and Cs_2CO_3 (Table III.3.1, entries 6 and 7) and organic bases such as DBU and DABCO (Table III.3.1, entries 8 and 9) were tested. Except Cs_2CO_3 (68%, Table III.3.1, entry 7) none of the bases tested gave satisfactory results. Increasing the catalyst loading to 20 mol % was not beneficial (Table III.3.1, entry 10), while decreasing the catalyst loading to 5 mol % (Table III.3.1, entry 11) was equally effective to that of higher catalyst loading (10 mol %). A comparable yield of 66% was obtained when the amount of base used was reduced to 2 equiv (Table III.3.1, entry 12). Surprisingly, when the reaction was carried out in absence of the catalyst under otherwise identical condition, the product yield improved considerably (77%), while in the absence of base only a trace (13%) of the product was observed (Table III.3.1, entries 13 and 14). This result suggests the non-involvement of catalyst and the essential requirement of base for this cascade reaction.

Table III.3.1. *Screening of the reaction conditions*[a]

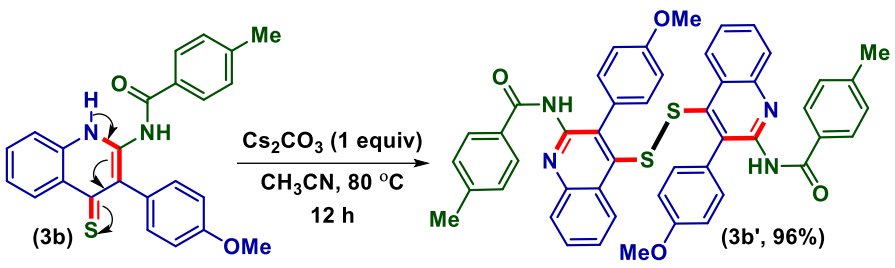


Entry	Catalyst (mol %)	Base (equiv)	Solvent	Yield (%)[d]
1	CuI (10)	K_2CO_3 (4)	dioxane	47
2	CuBr (10)	K_2CO_3 (4)	dioxane	52
3	$Cu(OAc)_2$ (10)	K_2CO_3 (4)	dioxane	41
4	$Cu(OTf)_2$ (10)	K_2CO_3 (4)	dioxane	37
5	Ag_2CO_3 (10)	K_2CO_3 (4)	dioxane	18
6	CuBr (10)	Na_2CO_3 (4)	dioxane	9
7	CuBr (10)	Cs_2CO_3 (4)	dioxane	68
8	CuBr (10)	DBU (4)	dioxane	29
9	CuBr (10)	DABCO (4)	dioxane	11
10	CuBr (20)	Cs_2CO_3 (4)	dioxane	64
11	CuBr (5)	Cs_2CO_3 (4)	dioxane	69
12	CuBr (5)	Cs_2CO_3 (2)	dioxane	66
13	-	Cs_2CO_3 (2)	dioxane	77
14	CuBr (5)	-	dioxane	13
15	-	Cs_2CO_3 (2)	CH_3CN	83
16	-	Cs_2CO_3 (2)	DMSO	48
17	-	Cs_2CO_3 (2)	DMF	53
18	-	Cs_2CO_3 (2)	DCE	00
19[b]	-	Cs_2CO_3 (2)	CH_3CN	71
20[c]	**-**	**Cs_2CO_3 (2)**	**CH_3CN**	**87**

[a]Reaction conditions: **1** (0.25 mmol), **a** (0.25 mmol), catalysts (mol %), base (equiv), solvent (2 mL) under air at 110 °C for 6 h. [b]Reaction at 130 °C. [c]Reaction at 80 °C. [d]Yield of the isolated product.

While screening different solvents such as CH_3CN, DMSO, DMF, DCE, solvent CH_3CN gave an improved yield of 83%, whereas, DMSO and DMF provided reduced yield of 48% and 53%, respectively (Table III.3.1, entries 15–17). No product formation was observed in DCE (Table III.3.1, entry 18). To check the effect of temperature, reactions were performed at an elevated temperature (130 °C) and at lower temperature (80 °C). Unexpectedly, here increase in the reaction temperature was detrimental in the product formation giving only 71% yield, whereas, lowering the temperature provided improved yield of 87% (Table III.3.1, entries 19 and 20). Lower yield at higher temperature may be due to the decomposition or dimerization of the product.

It may be noted that on prolonging the reaction time (12 h), the obtained product oxidized giving a dimeric (S–S bond) product (Scheme III.3.1).



Scheme III.3.1. *Oxidative dimerization of (**3b'**)*

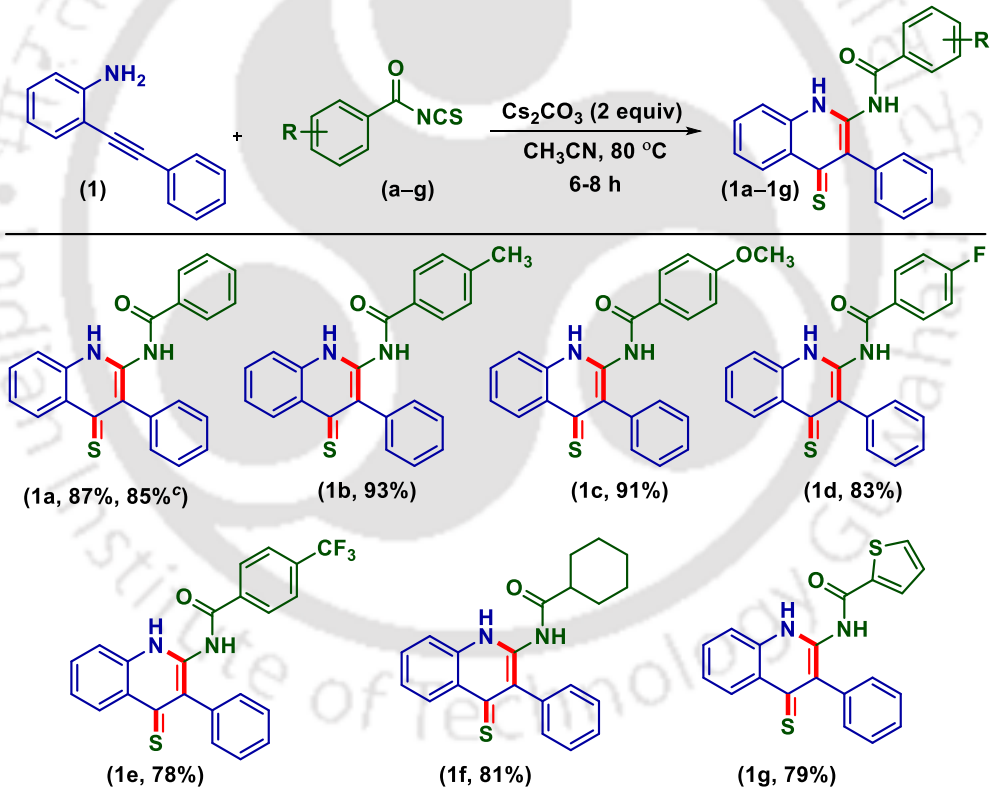
Substrate Scope for Quinoline-4(1*H*)-thiones Synthesis:

The scope and generality of the base promoted reaction was extended to a variety of *o*-alkynylanilines and aroyl isothiocyanates under the optimized reaction conditions (Table III.3.1, entry 20). At first, the effect of different aroyl/acyl isothiocyanates (**a**–**g**) on 2-(phenylethynyl)aniline (**1**) was examined and the results are summarized in Scheme III.3.2. The phenyl ring of benzoyl isothiocyanates bearing electron-donating groups such as [*p*-CH_3 (**b**) and *p*-OCH_3 (**c**)], provided excellent yields of **1b** (93%) and **1c** (91%) compared to the unsubstituted analogue **1a** (87%). However, lower yield of products **1d** (83%) and **1e** (78%) (Scheme III.3.2) were obtained when moderately electron-withdrawing *p*-F (**d**) and strongly electron-withdrawing *p*-CF_3 (**e**) groups were present on the phenyl ring of benzoyl isothiocyanates. Acyclic as well as heterocyclic carbonyl isothiocyanates such as cyclohexanecarbonyl isothiocyanate (**f**) and thiophene-2-carbonyl isothiocyanate (**g**) reacted competently with (**1**) giving good yields of the product **1f** (81%) and **1g** (79%), respectively. These results suggest that, irrespective of the substituents present on the aroyl isothiocyanates, all reacted well with (**1**) giving the corresponding products.

Next, the effect of the substituents R^2, present on the alkyne side of the phenyl ring in 2-(phenylethynyl)anilines (**2**–**14**) was tested by reacting them with various benzoyl isothiocyantes (**a**–**h**) (Scheme III.3.3). 2-(Phenylethynyl)aniline derivatives, bearing either electron-donating (*p*-CH_3 (**2**), *p*-OCH_3 (**3**) and *p*-^{t}Bu (**4**)) or electron-withdrawing (*p*-F (**5**), *p*-NO_2 (**6**)) groups on the alkyne side of phenyl ring, reacted efficiently with benzoyl isothiocyanate (**a**) giving good yields of their products (**2a**–**6a**) in the range of 89-95%. When both the substituents R^2 in alkynylanilines and R^3 in aroyl isothiocyanate were electron-donating, such as *p*-CH_3 (**2**)/*p*-CH_3 (**b**) and *p*-OCH_3 (**3**)/*p*-CH_3 (**b**), excellent yields of their product (**2b**, 93%) and (**3b**, 91%) were obtained. On the other hand, when

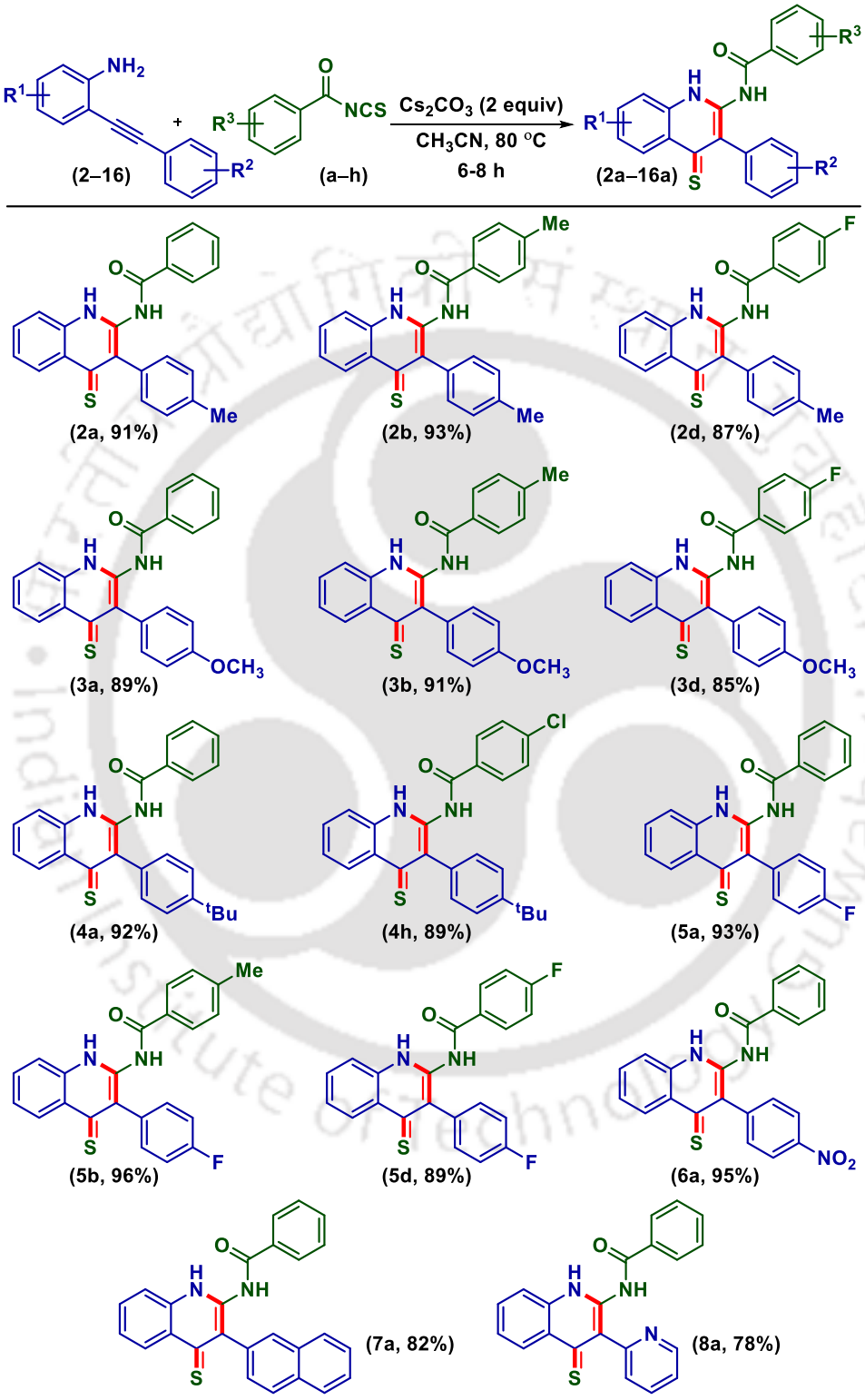
substituent R^2 was electron-donating and R^3 an electron-withdrawing combinations such as *p*-CH_3 (**2**)/*p*-F (**d**), *p*-OCH_3 (**3**)/*p*-F (**d**) and *p*-^{t}Bu (**4**)/*p*-Cl (**h**), the yields of their products were slightly lower (**2d**, 87%), (**3d**, 85%) and (**4h**, 89%). However, when R^2 was an electron-withdrawing group i.e. *p*-F (**5**) it gave comparatively higher yields of their products (**5b**, 96%), and (**5d**, 89%) irrespective of the nature of substituents R^3 (either electron-donating, *p*-CH_3 (**b**) or electron-withdrawing *p*-F (**d**)). Similarly, when R^2 was strongly electron-withdrawing such as *p*-NO_2 (**6**), higher yield of (**6a**, 95%) was obtained. 2-(Naphthalen-2-ylethynyl)aniline (**7**) and 2-(pyridin-2-ylethynyl)aniline (**8**) also reacted efficiently with benzoyl isothiocyanate (**a**) to give their respective product (**7a**) and (**8a**) in 82 and 78% yields.

Scheme III.3.2. *Substrate scope of 2-(phenylethynyl)aniline with aroyl isothiocyanates*[a,b,c]

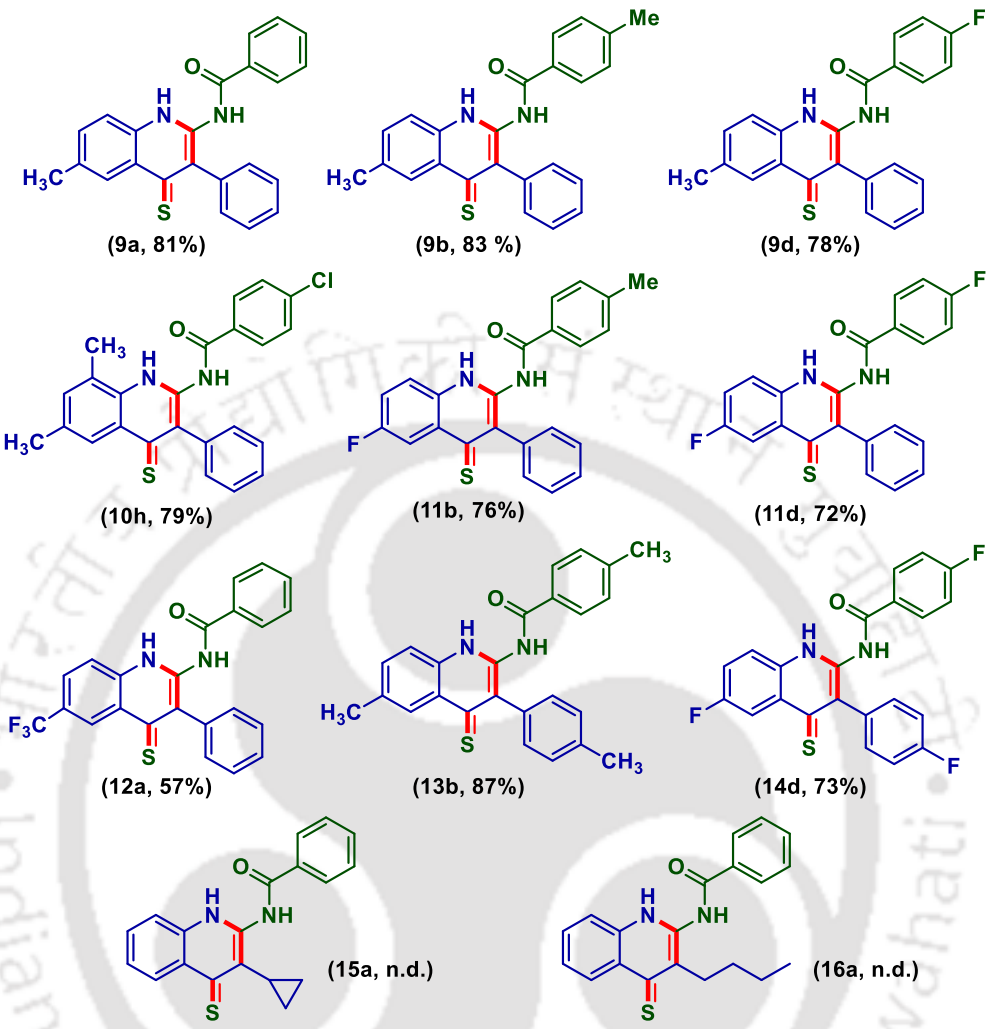


[a]Reaction conditions: 2-(phenylethynyl)aniline (**1**) (0.25 mmol), aroyl isothiocyanates (**a**–**g**) (0.25 mmol), Cs_2CO_3 (0.5 mmol) in CH_3CN (2 mL) under air at 80 °C for 6–8 h. [b]Isolated yield. [c]1 mmol scale.

Scheme III.3.3. *Substrate scope for substituted 2-(phenylethynyl)aniline and benzoyl isothiocyanates*[a,b]



Scheme III.3.3. contd…



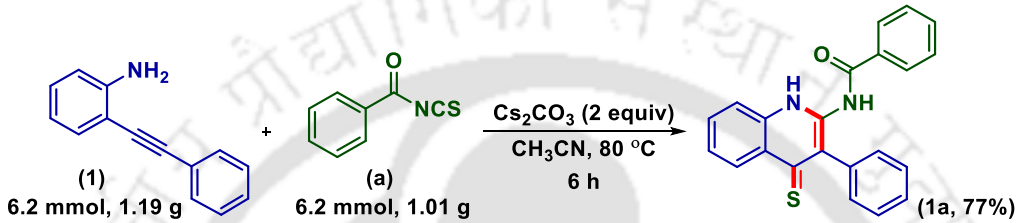
[a]Reaction conditions: 2-(phenylethynyl)aniline (**2**–**16**) (0.25 mmol), benzoyl isothiocyanates (**a**–**h**) (0.25 mmol), Cs_2CO_3 (0.5 mmol) in CH_3CN (2 mL) under air at 80 °C for 6–8 h. [b]Isolated yields.

Further, the effect of substituents R^1 present on the amine-bearing ring of 2-(phenylethynyl)anilines (**9**–**12**) was investigated (Scheme III.3.3). When the substituent R^1 was electron-donating, such as *p*-CH_3 (**9**) and 2,4-di-CH_3 (**10**) both gave good yields of their products (**9a**, 81%), (**9b**, 83%), (**9d**, 78%), and (**10h**, 79%) on reaction with benzoyl isothiocyantes (**a**, **b**, **d** and **h**). On the other hand, when R^1 was moderately electron-withdrawing such as *p*-F (**11**), the products (**11b**) and (**11d**) were obtained in 76% and 72% respectively. With strong electron-withdrawing group such as *p*-CF_3 (**12**), the yield dropped further to 57% (Scheme III.3.3). Moreover, when all the substituents R^1, R^2 and R^3 were either *p*-CH_3 (**13**) or *p*-F (**14**), both furnished their products (**13b**) and (**14d**) in 87% and 73% yields, respectively. When aliphatic groups like cyclopropyl (**15**) and n-butyl (**16**) were present instead of phenyl ring on the alkyne side of 2-

(phenylethynyl)aniline, the intermediate thiourea generated did not undergo any further reaction.

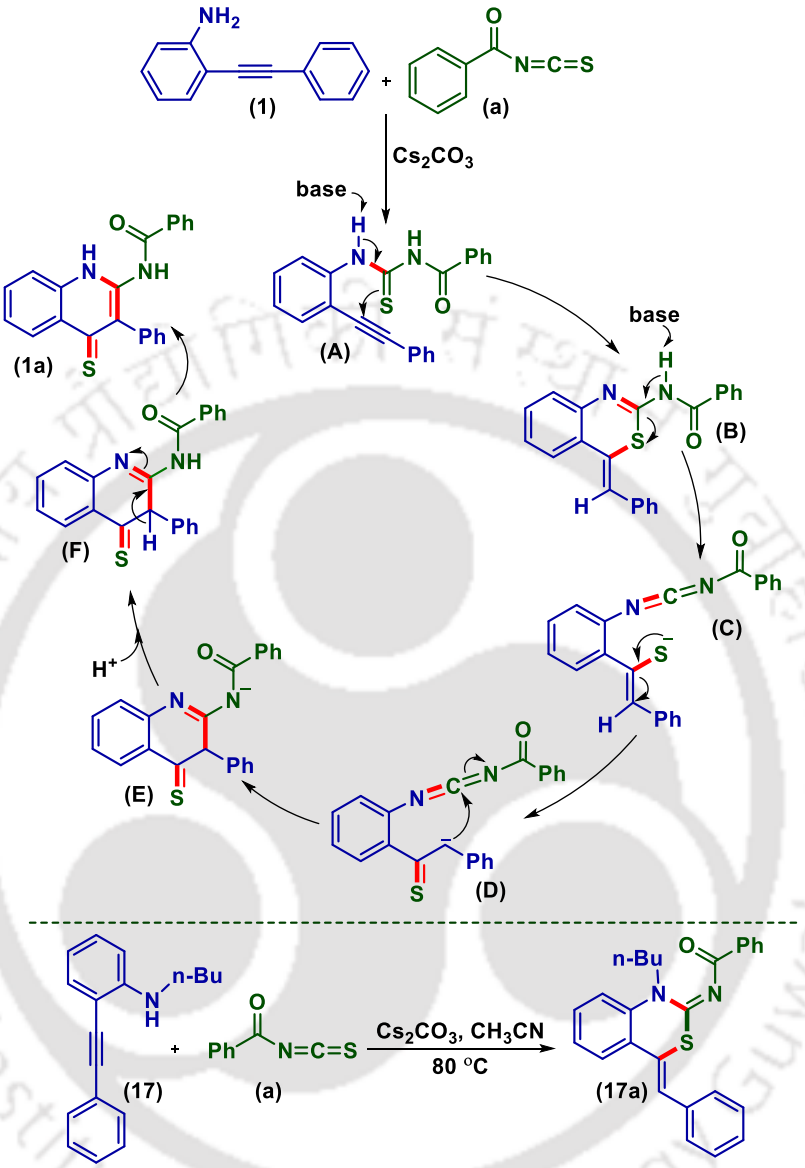
To demonstrate the potential application of the present method, a gram scale reaction was carried out with 2-(phenylethynyl)aniline (**1**) (6.2 mmol, 1.19 g) and benzoyl isothiocyanate (**a**) (6.2 mmol, 1.01 g) under the standard reaction condition (Scheme III.3.4). The reaction proceeded smoothly affording 77% isolated yield of (**1a**).

Scheme III.3.4. *Synthetic application of the base promoted cascade reaction*



Based on the literature reports, a plausible pathway has been proposed for the base-promoted cascade reaction (Scheme III.3.5). Reaction of 2-(phenylethynyl)aniline (**1**) and benzoyl isothiocyanate (**a**) generates an intermediate thiourea (**A**).[15a,b] A 6-*exo*-dig *S*-attack onto the internal alkyne is facilitated via the abstraction of a thioamidic nitrogen proton attached to the phenyl ring to give intermediate (**B**).[15a-c] Abstraction of a second proton from the intermediate (**B**) generates a carbodiimide intermediate (**C**). The thiolate (**C**) so generated undergoes thioketolization, giving a diphenylethane thione nucleophilic moiety (**D**).[15d,13d] Intramolecular nucleophilic attack of the heterocumulene generates a cyclic anionic intermediate (**E**), which upon protonation gave (**F**). Finally, a proton migration produces the desired quinoline-4(1*H*)-thiones product (**1a**). The reaction of aroyl isothiocyanate (**a**) with secondary amine based *o*-alkynylanilines (**17**) gave product (**17a**) in 92% yield (Scheme III.3.5), Inability of the product (**17a**) to undergo further ring opening cyclization is due to the absence second NH proton, there by supporting our proposed mechanism.

Scheme III.3.5. *Plausible reaction mechanism*



In conclusion, we have demonstrated a metal-free approach for the synthesis of quinoline-4(1*H*)-thione derivatives. This is the first example of a base promoted synthesis of quinoline-4(1*H*)-thiones from *o*-alkynylanilines and aroyl isothiocyanate. Through the cascade process, simultaneous formation of three C–C, C–N and C–S bonds has been accomplished. This protocol shows wide functional group tolerance with good to excellent yields of the product in 100% atom economy.

III.4. Experimental Section

III.4.1. General Information: All the compounds were commercial grade and used without further purification. Organic extract was dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduce pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as internal standard for proton NMR (400 and 600 MHz) and $CDCl_3$ solvent as internal standard for ^{13}C NMR (100 and 150 MHz). HRMS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat.

III.4.2. Crystallographic Description

CCDC Number for Compound 3a: CCDC-1575680. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystallographic Description of *N*-(3-(4-Methoxyphenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (3a): $C_{23}H_{18}N_2O_2S$, crystal dimensions 0.48 x 0.36 x 0.26 mm, M_r = 386.45, Triclinic, space group P -1, a = 10.8170(4), b = 11.6749(5), c = 16.4638(6)Å, α = 97.305º (2), β = 96.365º (2), γ = 108.875º (2), V = 1925.64(13)Å^3, Z = 4, ρ_{calcd} = 1.333g/cm^3, μ = 0.189 mm^{-1}, F(000)= 808.0, reflection collected / unique = 9714 / 5370, refinement method = full-matrix least-squares on F^2, final R indices [I> 2σ(I)]: R_1 = 0.1108, wR_2 = 0.1783, R indices (all data): R_1 = 0.0511, wR_2 = 0.1783, goodness of fit = 0.913.

III.4.3. General Procedure for the Synthesis of *N*-(3-Phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (1a): In an oven dried round bottom flask, 2-(phenylethynyl)aniline (**1**) (0.25 mmol) and benzoyl isothiocyanate (**a**) (0.25 mmol) were taken in CH_3CN (2 mL) and was stirred on a preheated oil bath at 80 ºC. After 3 h, when both the starting materials were completely consumed to give the thiourea intermediate (as indicated by TLC), Cs_2CO_3 (0.5 mmol) was added and the reaction mixture was further allowed to stir for 3 h. After the completion of the reaction (as indicated by the TLC), the crude mixture was evaporated in vacuum to remove CH_3CN solvent and the reaction mixture was admixed with ethyl acetate (20 mL). The organic layer was washed

successively with saturated solution of sodium bicarbonate (2 x 5 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuum. The crude product obtained was purified using column chromatography and eluted with ethyl acetate:hexane (1:4) to afford the corresponding product *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (**1a**) (77 mg, 87%).

III.4.4. General Procedure for the Synthesis of the Oxidative Dimerized product *N,N′*-(Disulfanediylbis(3-(4-methoxyphenyl)quinoline-4,2-diyl))bis(4-methylbenzamide) (3b′): The product *N*-(3-(4-Methoxyphenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)-4-methylbenzamide (**3b**) (0.25 mmol, 100 mg), was dissolved in CH_3CN (2 mL) to which Cs_2CO_3 (1 equiv) was added and the reaction mixture was heated at 80 ^oC for 12 h. During this period, complete conversion of (**3b**) to (**3b′**) was observed (as indicated by TLC). The crude mixture was evaporated in vacuum to remove CH_3CN solvent and the reaction mixture was admixed with ethyl acetate (20 mL). The organic layer was washed successively with water (2 x 5 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuum. The crude product so obtained was analyzed without further purification.

III.5. References

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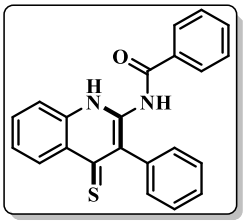
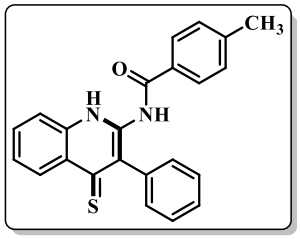
III.6. Spectral Data

_N_-(3-Phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (1a):



Orange solid (77 mg, 87%); mp 187–189 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.44–7.48 (m, 8H), 7.55 (t, 1H, *J* = 7.2 Hz), 7.58–7.61 (m, 1H), 7.64 (t, 2H, *J* = 7.2 Hz), 7.68 (t, 1H, *J* = 7.8 Hz), 8.26 (s, 1H), 9.07 (d, 1H, *J* = 8.4 Hz), 12.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 118.4, 122.9, 125.9, 127.1, 128.1, 129.2, 129.5, 130.2, 130.7, 131.0, 131.5, 132.4, 133.2, 134.1, 135.4, 139.9, 168.1, 192.8; IR (KBr): 3407, 2957, 2920, 2848, 1671, 1616, 1602, 1582, 1447, 1356, 1317, 1301, 1254, 1088, 1026, 848, 764, 694, 596 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{16}NO_2S^+$ [M + H^+] 357.1056; found 357.1061.

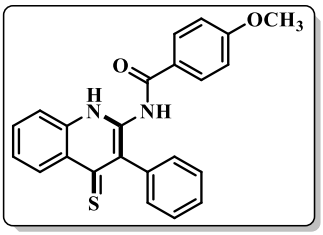
4-Methyl-_N_-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (1b):



Orange solid (86 mg, 93%); mp 212–215 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.39 (s, 3H), 7.24 (d, 2H, *J* = 7.8 Hz), 7.33 (d, 2H, *J* = 7.8 Hz), 7.45–7.48 (m, 4H), 7.54 (t, 1H, *J* = 7.8 Hz), 7.64 (t, 2H, *J* = 7.8 Hz), 7.68 (t, 1H, *J* = 7.8 Hz), 8.23 (s, 1H), 9.07 (d, 1H, *J* = 8.4 Hz), 13.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 118.4, 122.9, 125.9, 127.1, 128.7, 129.2, 129.7, 130.2, 130.8, 131.1, 131.8, 132.3, 132.5, 135.5, 140.1,

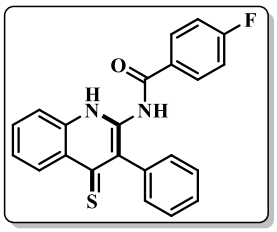
145.3, 168.2, 192.7; IR (KBr): 3406, 2957, 2850, 1670, 1604, 1578, 1444, 1284, 1256, 1094, 972, 757, 703, 584 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{18}N_2OS^+$ [M + H^+] 371.1213; found 371.1220.

4-Methoxy-*N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (1c):



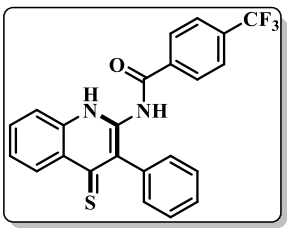
Orange solid (88 mg, 91%); mp 180–181 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.85 (s, 3H), 6.90 (d, 2H, *J* = 9.0 Hz), 7.34 (d, 2H, *J* = 9.0 Hz), 7.45–7.48 (m, 4H), 7.55 (t, 1H, *J* = 7.8 Hz), 7.63–7.69 (m, 3H), 8.16 (s, 1H), 9.07 (d, 1H, *J* = 8.4 Hz), 13.07 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 55.8, 114.2, 114.8, 118.4, 122.9, 123.6, 125.8, 129.2, 130.2, 130.4, 130.8, 131.1, 131.8, 132.3, 135.6, 140.3, 163.6, 164.3, 166.1, 167.6, 192.5; IR (KBr): 3406, 2956, 2917, 2853, 1664, 1611, 1571, 1314, 1246, 1169, 1096, 1025, 971, 841, 779, 758, 668, 584 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{18}N_2O_2S^+$ [M + H^+] 387.1162; found 387.1163.

4-Fluoro-*N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (1d):



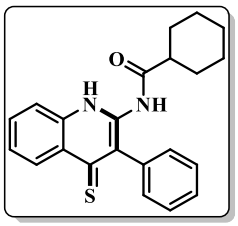
Yellow solid (78 mg, 83%); mp 200–203 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.13 (t, 2H, *J* = 8.4 Hz), 7.45–7.49 (m, 6H), 7.55 (t, 1H, *J* = 7.2 Hz), 7.65 (t, 2H, *J* = 7.2 Hz), 7.69 (t, 1H, *J* = 7.2 Hz), 8.18 (s, 1H), 9.07 (d, 1H, *J* = 8.4 Hz), 12.87(s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 116.9 (d, *J* = 22.2 Hz), 118.5, 123.0, 126.0, 127.8, 129.3, 129.8 (d, *J* = 9.1 Hz), 130.3, 130.8, 131.1, 131.9, 132.5, 135.4, 139.7, 164.9, 167.0, 193.1; ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -106.0 (s); IR (KBr): 3407, 2961, 2923, 2843, 1672, 1603, 1613, 1575, 1492, 1354, 1318, 1249, 1158, 1094, 969, 854, 763, 703, 668, 585, 552 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{15}FN_2OS^+$ [M + H^+] 375.0962; found 375.0964.

***N*-(3-Phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)-4-(trifluoromethyl)benzamide (1e):**



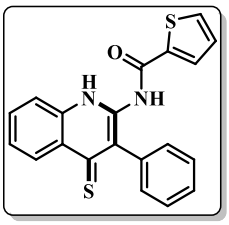
Orange solid (83 mg, 78%); mp 201–203 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.44–7.49 (m, 4H), 7.55–7.57 (m, 3H), 7.64 (t, 2H, *J* = 7.2 Hz), 7.69 (d, 1H, *J* = 8.4 Hz), 7.72 (d, 2H, *J* = 8.4 Hz), 8.26 (s, 1H), 9.04 (d, 1H, *J* = 8.4 Hz), 12.74 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 118.5, 123.1, 126.1, 126.56, 126.58, 126.6, 127.6, 129.3, 130.3, 130.7, 131.0, 132.0, 132.4, 132.5, 134.8, 135.2, 139.3, 166.7, 193.5; IR (KBr): 3406, 2957, 2921, 2850, 1684, 1680, 1604, 1576, 1495, 1451, 1362, 1326, 1254, 1166, 1133, 1100, 1065, 1011, 969, 865, 765, 599 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{15}F_3N_2OS^+$ [M + H^+] 425.0930; found 425.0940.

***N*-(3-Phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)cyclohexanecarboxamide (1f):**



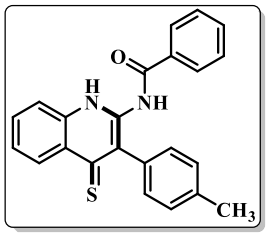
Yellow solid (74 mg, 81%); mp 170–172 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.20–1.28 (m, 5H), 1.64–1.66 (m, 1H), 1.73–1.76 (m, 4H), 2.11–2.15 (m, 1H), 7.36 (d, 2H, *J* = 7.2 Hz), 7.40 (d, 1H, *J* = 7.8 Hz), 7.45 (t, 1H, *J* = 8.4 Hz), 7.50 (t, 1H, *J* = 7.8 Hz), 7.53 (s, 1H), 7.60 (t, 2H, *J* = 7.8 Hz), 7.65 (t, 1H, *J* = 8.4 Hz), 9.05 (d, 1H, *J* = 8.4 Hz), 12.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.2, 25.4, 28.9, 46.1, 118.3, 122.6, 125.8, 129.0, 130.1, 130.7, 130.9, 131.7, 132.3, 132.4, 135.4, 139.9, 178.6, 192.8; IR (KBr): 3406, 2922, 2850, 1678, 1615, 1583, 1443, 1316, 1254, 1168, 1120, 977, 759, 705, 583 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{22}N_2OS^+$ [M + H^+] 363.1526; found 363.1536.

***N*-(3-Phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)thiophene-2-carboxamide (1g):**



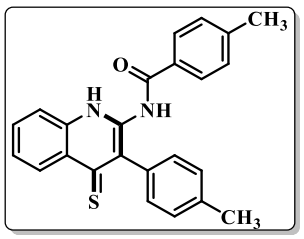
Orange solid (72 mg, 79%); mp 186–188 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.02 (d, 1H, *J* = 3.6 Hz), 7.08 (t, 1H, *J* = 4.2 Hz), 7.43–7.46 (m, 4H), 7.55 (t, 1H, *J* = 7.8 Hz), 7.63–7.68 (m, 4H), 8.05 (s, 1H), 9.05 (d, 1H, *J* = 8.4 Hz), 12.71 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 118.4, 122.8, 125.9, 128.3, 128.9, 129.2, 130.2, 130.4, 130.8, 131.2, 132.4, 132.5, 134.4, 135.4, 136.1, 139.7, 162.6, 193.1; IR (KBr): 3405, 2949, 2924, 2898, 1684, 1676, 1672, 1607, 1577, 1431, 1408, 1348, 1323, 1252, 1081, 1026, 967, 755, 735, 705, 592 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{14}N_2OS_2^+$ [M + H^+] 363.0620; found 363.0622.

***N*-(4-Thioxo-3-(*p*-tolyl)-1,4-dihydroquinolin-2-yl)benzamide (2a):**



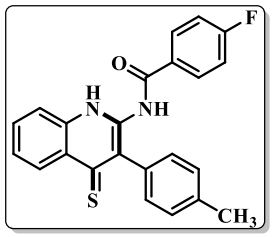
Yellow solid (85 mg, 91%); mp 190–192 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.48 (s, 3H), 7.34 (d, 2H, *J* = 7.8 Hz), 7.44 (d, 2H, *J* = 7.8 Hz), 7.46–7.49 (m, 6H), 7.61 (t, 1H, *J* = 7.2 Hz), 7.68 (t, 1H, *J* = 7.8 Hz), 8.35 (s, 1H), 9.07 (d, 1H, *J* = 8.4 Hz), 12.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.7, 118.4, 122.9, 125.8, 127.1, 127.5, 128.7, 129.5, 130.8, 130.9, 131.6, 131.8, 132.2, 132.4, 134.0, 138.9, 139.9, 168.2, 192.9; IR (KBr): 3405, 2950, 2923, 2854, 1684, 1670, 1654, 1615, 1602, 1577, 1447, 1355, 1282, 1252, 1087, 967, 764, 693, 596 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{18}N_2OS^+$ [M + H^+] 371.1213; found 371.1210.

4-Methyl-*N*-(4-thioxo-3-(*p*-tolyl)-1,4-dihydroquinolin-2-yl)benzamide (2b):



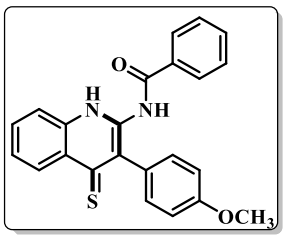
Orange solid (89 mg, 93%); mp 195–197 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.34 (s, 3H), 2.41 (s, 3H), 7.19 (d, 2H, *J* = 7.2 Hz), 7.26–7.30 (m, 4H), 7.37 (d, 2H, *J* = 7.8 Hz), 7.38–7.41 (m, 2H), 7.61 (t, 1H, *J* = 7.8 Hz), 8.24 (s, 1H), 9.01 (d, 1H, *J* = 8.4 Hz), 12.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.75, 21.83, 118.4, 122.9, 125.8, 127.2, 128.2, 128.8, 130.2, 130.8, 130.9, 131.8, 132.26, 132.33, 132.4, 138.9, 140.2, 145.2, 168.2, 192.8; IR (KBr): 3406, 2925, 2851, 1684, 1672, 1617, 1601, 1579, 1452, 1280, 1253, 1094, 1016, 974, 760, 669, 584 cm^{-1}; HRMS (ESI): calcd. for $C_{24}H_{20}N_2OS^+$ [M + H^+] 385.1369; found 385.1379.

4-Fluoro-*N*-(4-thioxo-3-(*p*-tolyl)-1,4-dihydroquinolin-2-yl)benzamide (2d):



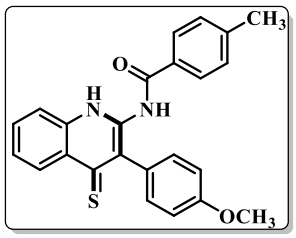
Orange solid (84 mg, 87%); mp 185–187 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.45 (s, 3H), 7.15 (t, 2H, *J* = 8.4 Hz), 7.34 (d, 2H, *J* = 8.4 Hz), 7.45 (d, 2H, *J* = 7.8 Hz), 7.46–7.51 (m, 4H), 7.68 (t, 1H, *J* = 7.8 Hz), 8.27 (s, 1H), 9.07 (d, 1H, *J* = 8.4 Hz), 12.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 116.9 (d, *J* = 22.2 Hz), 118.4, 122.9, 125.9, 127.9, 129.8 (d, *J* = 9.4 Hz), 130.8, 131.0, 131.9, 132.2, 132.4, 139.1, 139.8, 164.9, 167.1, 167.4, 193.1; ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -106.2 (s); IR (KBr): 3405, 2917, 2862, 1684, 1673, 1598, 1577, 1505, 1248, 1156, 1085, 970, 853, 763, 582 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{17}FN_2OS^+$ [M + H^+] 389.1118; found 389.1117.

***N*-(3-(4-Methoxyphenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (3a):**



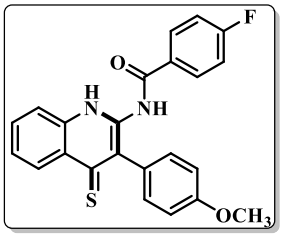
Orange solid (86 mg, 89%); mp 145–147 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.91 (s, 3H), 7.16 (d, 2H, *J* = 8.4 Hz), 7.38 (d, 2H, *J* = 8.4 Hz), 7.45–7.48 (m, 4H), 7.51 (d, 2H, *J* = 7.8 Hz), 7.61 (t, 1H, *J* = 7.2 Hz), 7.67 (t, 1H, *J* = 7.2 Hz), 8.38 (s, 1H), 9.07 (d, 1H, *J* = 8.4 Hz), 12.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.6, 115.7, 118.4, 122.7, 125.9, 127.2, 129.6, 130.9, 131.7, 131.9, 132.36, 132.44, 133.9, 134.1, 134.2, 140.2, 160.0, 168.3, 193.3; IR (KBr): 3407, 2953, 2923, 2851, 1684, 1676, 1600, 1580, 1507, 1448, 1280, 1241, 1170, 1026, 973, 762, 668, 595 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{18}N_2O_2S^+$ [M + H^+] 387.1162; found 387.1165.

***N*-(3-(4-Methoxyphenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)-4-methylbenzamide (3b):**



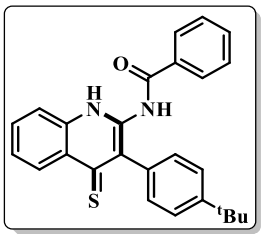
Orange solid (91 mg, 91%); mp 210–212 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.33 (s, 3H), 3.84 (s, 3H), 7.09 (d, 2H, *J* = 8.4 Hz), 7.18 (d, 2H, *J* = 7.2 Hz), 7.30–7.32 (m, 4H), 7.37–7.39 (m, 2H), 7.59 (t, 1H, *J* = 7.8 Hz), 8.27 (s, 1H), 8.99 (d, 1H, *J* = 8.4 Hz), 12.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 55.6, 115.6, 118.4, 122.6, 125.9, 127.17, 127.23, 128.8, 130.3, 130.9, 131.8, 132.29, 132.34, 132.4, 140.4, 145.3, 159.9, 168.3, 192.9; IR (KBr): 3387, 3005, 2954, 2926, 1684, 1676, 1613, 1601, 1539, 1514, 1343, 1317, 1249, 1184, 1090, 1016, 971, 827, 758, 668, 597 cm^{-1}; HRMS (ESI): calcd. for $C_{24}H_{20}N_2O_2S^+$ [M + H^+] 401.1318; found 401.1320.

4-Fluoro-*N*-(3-(4-methoxyphenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (3d):



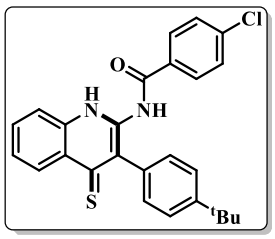
Orange solid (86 mg, 85%); mp 180–182 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.92 (s, 3H), 7.14–7.17 (m, 4H), 7.38 (d, 2H, *J* = 9.0 Hz), 7.46–7.49 (m, 2H), 7.51–7.54 (m, 2H), 7.68 (t, 1H, *J* = 7.2 Hz), 8.31 (s, 1H), 9.07 (d, 1H, *J* = 8.4 Hz), 12.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.6, 115.7, 116.9 (d, *J* = 22.2 Hz), 118.4, 122.7, 125.9, 127.1, 127.9, 129.8 (d, *J* = 9.4 Hz), 130.9, 131.8, 132.3, 132.4, 140.0, 160.0, 164.9, 167.1, 167.5, 193.3; ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -106.1 (s); IR (KBr): 3406, 2958, 2930, 1682, 1678, 1614, 1601, 1514, 1350, 1256, 1189, 1025, 956, 773, 656, 584 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{17}FN_2O_2S^+$ [M + H^+] 405.1068; found 405.1070.

***N*-(3-(4-(*tert*-Butyl)phenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (4a):**



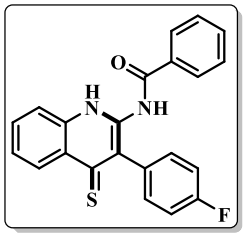
Orange solid (95 mg, 92%); mp 211–212 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.42 (s, 9H), 7.39–7.41 (m, 6H), 7.48 (d, 2H, *J* = 8.4 Hz), 7.58–7.61 (m, 1H), 7.66–7.70 (m, 3H), 8.24 (s, 1H), 9.09 (d, 1H, *J* = 8.4 Hz), 12.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 31.5, 35.0, 118.4, 123.1, 125.9, 127.1, 127.2, 128.1, 129.4, 130.6, 130.8, 131.5, 131.8, 132.3, 132.4, 134.1, 140.0, 151.9, 167.8, 192.5; IR (KBr): 3020, 2960, 2850, 1684, 1676, 1604, 1573, 1448, 1360, 1319, 1252, 1091, 969, 772, 668, 507 cm^{-1}; HRMS (ESI): calcd. for $C_{26}H_{24}N_2OS^+$ [M + H^+] 413.1682; found 413.1683.

_N_-(3-(4-(*tert*-Butyl)phenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)-4-chlorobenzamide (4h):



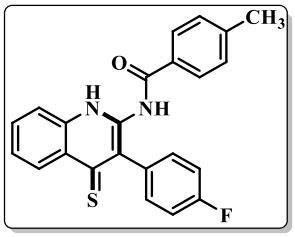
Yellow solid (100 mg, 89%); mp 203–205 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.42 (s, 9H), 7.32 (d, 2H, *J* = 8.4 Hz), 7.37 (t, 4H, *J* = 8.4 Hz), 7.44–7.48 (m, 2H), 7.65–7.69 (m, 3H), 8.17 (s, 1H), 9.06 (d, 1H, *J* = 8.4 Hz), 12.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 31.6, 35.1, 118.4, 123.1, 126.0, 127.3, 128.5, 129.3, 129.8, 129.9, 130.7, 130.8, 131.9, 132.4, 139.7, 140.8, 152.1, 166.7, 192.8; IR (KBr): 3407, 2960, 2900, 2863, 1684, 1604, 1575, 1435, 1362, 1320, 1248, 1098, 1012, 972, 841, 765, 696, 510 cm^{-1}; HRMS (ESI): calcd. for $C_{26}H_{23}ClN_2OS^+$ [M + H^+] 447.1292; found 447.1302.

_N_-(3-(4-Fluorophenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (5a):



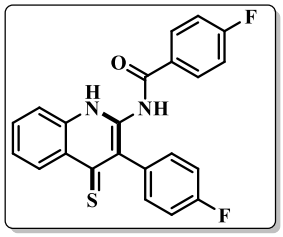
Orange solid (87 mg, 93%); mp 220–221 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.34 (t, 2H, *J* = 8.4 Hz), 7.43–7.46 (m, 2H), 7.47–7.49 (m, 6H), 7.62–7.65 (m, 1H), 7.70 (t, 1H, *J* = 7.8 Hz), 8.22 (s, 1H), 9.05 (d, 1H, *J* = 8.4 Hz), 13.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 117.4 (d, *J* = 21.4 Hz), 118.5, 121.8, 126.1, 127.1, 128.1, 129.1, 129.7, 130.7, 131.2, 131.5, 131.8, 132.5, 133.2 (d, *J* = 8.0 Hz), 134.3, 140.1, 161.7, 164.2, 168.3, 193.2; IR (KBr): 3410, 2947, 2920, 2840, 1684, 1672, 1613, 1577, 1509, 1319, 1250, 1217, 1087, 972, 827, 783, 701, 641, 593 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{15}FN_2OS^+$ [M + H^+] 375.0962; found 375.0965.

_N_-(3-(4-Fluorophenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)-4-methylbenzamide (5b):



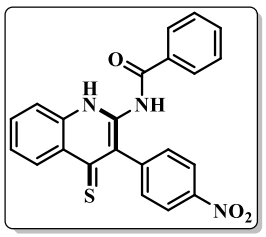
Yellow solid (93 mg, 96%); mp 221–223 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 7.28 (d, 2H, *J* = 7.8 Hz), 7.33 (t, 2H, *J* = 8.4 Hz), 7.37 (d, 2H, *J* = 8.4 Hz), 7.43–7.45 (m, 2H), 7.47–7.49 (m, 2H), 7.69 (t, 1H, *J* = 7.2 Hz), 8.17 (s, 1H), 9.05 (d, 1H, *J* = 7.8 Hz), 13.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 117.4 (d, *J* = 21.3 Hz), 118.5, 121.7, 126.0, 127.1, 128.7, 130.4, 130.8, 131.3, 131.8, 132.5, 133.2 (d. *J* = 6.2 Hz), 140.3, 145.5, 161.8, 164.2, 168.3, 193.1; IR (KBr): 3409, 2950, 2923, 2852, 1690, 1684, 1610, 1577, 1504, 1452, 1253, 1155, 1098, 965, 838, 762, 744, 668, 592 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{17}FN_2OS^+$ [M + H^+] 389.1118; found 389.1115.

4-Fluoro-_N_-(3-(4-fluorophenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (5d):



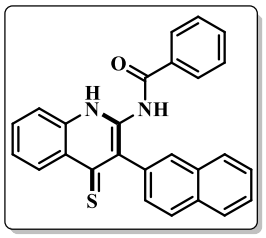
Orange solid (87 mg, 89%); mp 197–200 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.17 (t, 2H, *J* = 8.4 Hz), 7.34 (t, 2H, *J* = 8.4 Hz), 7.43–7.45 (m, 2H), 7.48 (d, 2H, *J* = 8.4 Hz), 7.50–7.52 (m, 2H), 7.70 (t, 1H, *J* = 8.4 Hz), 8.13 (s, 1H), 9.05 (d, 1H, *J* = 7.8 Hz), 12.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 116.9 (d, *J* = 22.3 Hz), 117.4 (d, *J* = 21.4 Hz), 118.5, 121.8, 126.1, 127.8, 129.7 (d, *J* = 9.4 Hz), 130.7, 131.1, 131.8, 132.5, 133.2 (d, *J* = 7.9 Hz), 139.9, 161.7, 164.2, 164.9, 167.1, 167.5, 193.3; ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -114.6 (s), -105.7 (s); IR (KBr): 3411, 2949, 2925, 2850, 1684, 1612, 1579, 1509, 1255, 1159, 1092, 963, 835, 766, 748, 670, 594 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{14}F_2N_2OS^+$ [M + H^+] 393.0868; found 393.0870.

***N*-(3-(4-Nitrophenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (6a):**



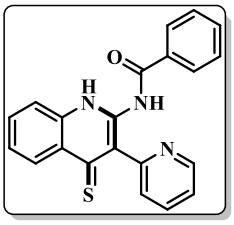
Orange solid (95 mg, 95%); mp 226–228 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.47–7.49 (m, 6H), 7.62–7.65 (m, 1H), 7.67 (d, 2H, *J* = 8.4 Hz), 7.71 (t, 1H, *J* = 7.8 Hz), 7.99 (s, 1H), 8.46 (d, 2H, *J* = 8.4 Hz), 8.99 (d, 1H, *J* = 8.4 Hz), 13.07 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 118.6, 120.6, 125.3, 126.4, 127.1, 129.8, 130.5, 131.4, 131.8, 132.5, 132.8, 132.9, 134.5, 139.7, 142.7, 148.1, 168.6, 193.2; IR (KBr): 3377, 3106, 3063, 2919, 2848, 1679, 1605, 1581, 1518, 1450, 1348, 1317, 1254, 1092, 972, 854, 778, 765, 643 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{15}N_3O_3S^+$ [M + H^+] 402.0907; found 402.0903.

***N*-(3-(Naphthalen-2-yl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (7a):**



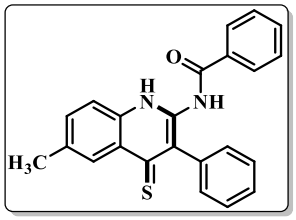
Orange solid (84 mg, 82%); mp 113–115 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.14 (d, 2H, *J* = 7.8 Hz), 7.31 (t, 2H, *J* = 8.4 Hz), 7.43 (t, 1H, *J* = 7.2 Hz), 7.51–7.55 (m, 4H), 7.60–7.62 (m, 1H), 7.68–7.74 (m, 3H), 7.87 (d, 1H, *J* = 7.8 Hz), 7.99 (d, 1H, *J* = 8.4 Hz), 8.05 (d, 1H, *J* = 8.4 Hz), 9.10 (d, 1H, *J* = 7.8 Hz), 13.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 118.5, 120.9, 125.2, 126.1, 126.5, 126.92, 126.98, 127.5, 128.1, 129.07, 129.14, 129.3, 129.4, 129.9, 130.7, 131.5, 131.9, 132.5, 132.7, 133.9, 134.5, 140.5, 168.3, 193.6; IR (KBr): 3411, 2960, 2925, 2850, 1680, 1617, 1605, 1589, 1450, 1358, 1320, 1302, 1256, 1090, 1030, 842, 765, 680, 590 cm^{-1}; HRMS (ESI): calcd. for $C_{26}H_{18}N_2OS^+$ [M + H^+] 407.1213; found 407.1215.

***N*-(3-(Pyridin-2-yl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (8a):**



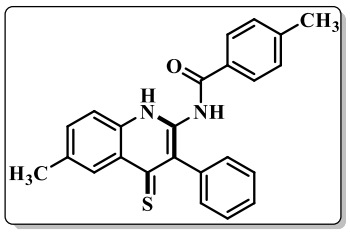
Orange solid (69 mg, 78%); mp 115–117 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.30 (t, 1H, *J* = 6.0 Hz), 7.43 (d, 1H, *J* = 8.4 Hz), 7.47 (t, 1H, *J* = 8.4 Hz), 7.56 (t, 2H, *J* = 7.8 Hz), 7.64–7.67 (m, 2H), 7.83 (t, 1H, *J* = 8.1 Hz), 7.93 (d, 2H, *J* = 7.8 Hz), 8.68 (d, 1H, *J* = 4.2 Hz), 8.92 (d, 1H, *J* = 8.4 Hz), 9.10 (d, 1H, *J* = 8.4 Hz), 13.49 (s, 1H), 13.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 117.7, 118.3, 122.7, 126.1, 127.8, 128.5, 129.0, 129.4, 131.5, 131.6, 132.3, 132.5, 133.9, 136.4, 142.9, 146.7, 156.6, 169.8, 192.1; IR (KBr): 2953, 2920, 2851, 1663, 1654, 1587, 1539, 1469, 1323, 1245, 1221, 1091, 1025, 971, 770, 744, 644, 567 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{15}N_3OS^+$ [M + H$^+$] 358.1009; found 385.1011.

***N*-(6-Methyl-3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (9a):**



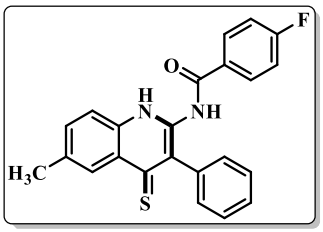
Orange solid (75 mg, 81%); mp 175–177 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.52 (s, 3H), 7.39 (d, 1H, *J* = 8.4 Hz), 7.44–7.46 (m, 6H), 7.52 (d, 1H, *J* = 8.4 Hz), 7.55 (d, 1H, *J* = 7.8 Hz), 7.58–7.61 (m, 1H), 7.64 (t, 2H, *J* = 7.2 Hz), 8.25 (s, 1H), 8.89 (s, 1H), 12.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.5, 118.3, 122.9, 127.1, 128.8, 129.2, 129.5, 130.1, 130.2, 130.4, 131.1, 131.6, 131.7, 134.1, 135.6, 136.2, 139.6, 168.1, 191.9; IR (KBr): 3409, 1920, 2954, 2853, 1682, 1614, 1580, 1447, 1280, 1258, 1090, 979, 747, 648, 584 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{18}N_2OS^+$ [M + H$^+$] 371.1213; found 371.1219.

4-Methyl-*N*-(6-methyl-3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (9b):



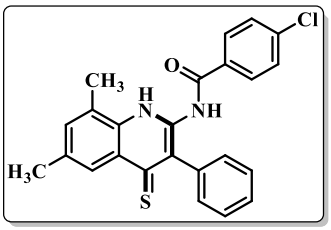
Yellow solid (80 mg, 83%); mp 214–216 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.40 (s, 3H), 2.52 (s, 3H), 7.24 (d, 2H, *J* = 7.8 Hz), 7.33 (d, 2H, *J* = 8.4 Hz), 7.39 (d, 1H, *J* = 8.4 Hz), 7.45 (d, 2H, *J* = 7.2 Hz), 7.51–7.55 (m, 2H), 7.64 (t, 2H, *J* = 7.8 Hz), 8.22 (s, 1H), 8.90 (s, 1H), 12.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.5, 21.8, 118.3, 122.9, 127.1, 128.8, 129.1, 129.5, 130.1, 130.2, 130.4, 131.1, 131.7, 134.0, 135.7, 136.2, 139.8, 145.2, 168.1, 191.8; IR (KBr): 3411, 2923, 2848, 1683, 1670, 1615, 1600, 1556, 1450, 1289, 1252, 1089, 1015, 970, 765, 678, 590 cm^{-1}; HRMS (ESI): calcd. for $C_{24}H_{20}N_2OS^+$ [M + H^+] 385.1369; found 385.1375.

4-Fluoro-*N*-(6-methyl-3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (9d):



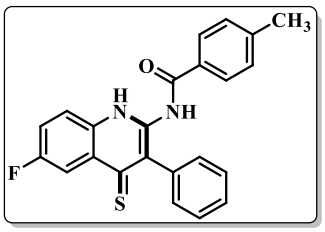
Orange solid (76 mg, 78%); mp 148–150 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.52 (s, 3H), 7.13 (t, 2H, *J* = 8.4 Hz), 7.39 (d, 1H, *J* = 8.4 Hz), 7.45–7.47 (m, 4H), 7.53 (d, 1H, *J* = 8.4 Hz), 7.55 (d, 1H, *J* = 7.2 Hz), 7.64 (t, 2H, *J* = 7.2 Hz), 8.17 (s, 1H), 8.88 (s, 1H), 12.86 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.5, 116.1 (d, *J* = 21.9 Hz), 116.8 (d, *J* = 22.2 Hz), 118.3, 122.9, 127.9, 129.2, 129.7 (d, *J* = 9.4 Hz), 130.0, 130.2, 130.4, 130.9 (d, *J* = 9.3 Hz), 131.1, 131.7, 134.0, 135.6, 136.2, 139.4, 165.3, 166.9, 192.1; ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -106.2 (s); IR (KBr): 3411, 2948, 2920, 2848, 1684, 1615, 1570, 1510, 1448, 1245, 1154, 1110, 978, 758, 738, 656, 584 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{17}FN_2OS^+$ [M + H^+] 389.1118; found 389.1115.

4-Chloro-*N*-(6,8-dimethyl-3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (10h):



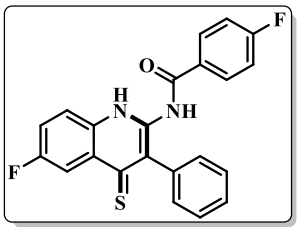
Orange solid (83 mg, 79%); mp 206–208 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.40 (s, 3H), 2.53 (s, 3H), 7.31 (d, 3H, *J* = 8.4 Hz), 7.35 (d, 2H, *J* = 9.0 Hz), 7.38 (d, 2H, *J* = 7.2 Hz), 7.46 (t, 1H, *J* = 7.2 Hz), 7.56 (t, 2H, *J* = 7.2 Hz), 8.14 (s, 1H), 8.67 (s, 1H), 12.97 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 16.8, 21.5, 122.7, 125.5, 128.1, 128.4, 129.0, 129.2, 129.7, 129.9, 130.1, 130.2, 131.1, 132.0, 134.9, 135.7, 139.0, 140.7, 167.2, 192.6; IR (KBr): 3409, 2954, 2919, 2855, 1684, 1663, 1585, 1489, 1312, 1254, 1167, 1107, 1014, 745, 698, 589 cm^{-1}; HRMS (ESI): calcd. for $C_{24}H_{19}ClN_2OS^+$ [M + H^+] 419.0979; found 419.0977.

***N*-(6-Fluoro-3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)-4-methylbenzamide (11b):**



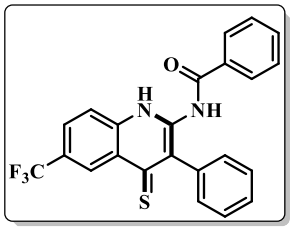
Orange solid (74 mg, 76%); mp 200–201 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.40 (s, 3H), 7.10 (d, 1H, *J* = 7.8 Hz), 7.24 (d, 2H, *J* = 7.8 Hz), 7.33 (d, 2H, *J* = 7.8 Hz), 7.44 (d, 2H, *J* = 7.2 Hz), 7.47–7.49 (m, 1H), 7.55 (t, 1H, *J* = 7.8 Hz), 7.64 (t, 2H, J = 7.8 Hz), 8.23 (s, 1H), 8.79 (dd, 1H, J_1 = 2.4 Hz, J_2 = 7.8 Hz), 13.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 115.5 (d, *J* = 24.7 Hz), 120.4 (d, *J* = 6.7 Hz), 120.9, 121.3, 122.9, 127.1, 127.2, 128.6, 128.8 (d, *J* = 4.9 Hz), 129.3, 129.5, 130.3, 130.9, 133.2, 135.3, 140.2, 145.4, 159.7, 162.1, 168.3, 191.4; IR (KBr): 3408, 2950, 2919, 2853, 1682, 1612, 1578, 1514, 1450, 1250, 1150, 1098, 975, 754, 735, 648, 596 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{17}FN_2OS^+$ [M + H^+] 389.1118; found 389.1117.

4-Fluoro-*N*-(6-fluoro-3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (11d):



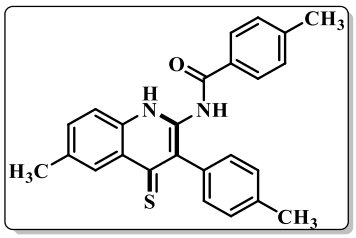
Orange solid (71 mg, 72%); mp 209–211 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.13 (t, 2H, *J* = 8.4 Hz), 7.44–7.50 (m, 6H), 7.56 (t, 1H, *J* = 7.2 Hz), 7.65 (t, 2H, *J* = 7.2 Hz), 8.19 (s, 1H), 8.78 (dd, 1H, J_1 = 2.4 Hz, J_2 = 7.8 Hz), 12.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 115.5 (d, *J* = 24.7 Hz), 116.9 (d, *J* = 22.2 Hz), 120.4 (d, *J* = 8.1 Hz), 121.1, 121.4, 122.9, 127.7, 128.8, 129.4, 129.8 (d, *J* = 9.4 Hz), 130.3, 130.9, 133.3 (d, *J* = 8.2 Hz), 135.2, 139.8, 159.8, 162.2, 164.9, 167.1, 167.5, 191.8; IR (KBr): 3402, 2952, 2930, 2845, 1682, 1610, 1568, 1512, 1248, 1160, 1087, 960, 825, 796, 723, 687, 568 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{14}F_2N_2OS^+$ [M + H$^+$] 393.0868; found 393.0867.

***N*-(3-Phenyl-4-thioxo-6-(trifluoromethyl)-1,4-dihydroquinolin-2-yl)benzamide (12a):**



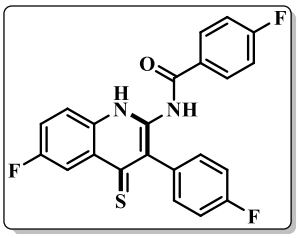
Orange solid (60 mg, 57%); mp 129–130 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.45–7.46 (m, 2H), 7.52 (t, 2H, *J* = 7.8 Hz), 7.56–7.58 (m, 1H), 7.61–7.63 (m, 2H), 7.66 (t, 2H, *J* = 7.8 Hz), 7.87 (d, 3H, *J* = 8.4 Hz), 8.28 (s, 1H), 9.36 (s, 1H), 13.09 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 119.5, 123.8, 127.1, 128.1, 128.7 (q, *J* = 4.0 Hz), 129.1, 129.5, 129.6, 130.4, 130.9, 131.3, 131.4, 133.3, 133.5, 134.3, 134.6, 134.9, 140.5, 166.6, 168.4, 193.5; IR (KBr): 3409, 2956, 2930, 2845, 1682, 1618, 1568, 1489, 1358, 1248, 1160, 1134, 1065, 978, 858, 763, 578 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{15}F_3N_2OS^+$ [M + H$^+$] 425.0930; found 425.0928.

4-Methyl-*N*-(6-methyl-4-thioxo-3-(*p*-tolyl)-1,4-dihydroquinolin-2-yl)benzamide (13b):



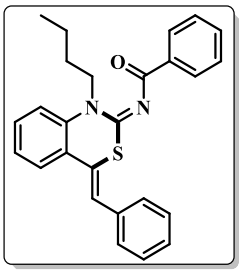
Orange solid (87 mg, 87%); mp 195–197 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.40 (s, 3H), 2.47 (s, 3H), 2.51 (s, 3H), 7.25 (d, 2H, *J* = 7.8 Hz), 7.33–7.38 (m, 5H), 7.43 (d, 2H, *J* = 7.8 Hz), 7.50 (d, 1H, *J* = 8.4 Hz), 8.29 (s, 1H), 8.88 (s, 1H), 12.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.5, 21.7, 21.8, 118.2, 122.9, 127.1, 128.9, 130.1, 130.2, 130.4, 130.85, 130.92, 131.6, 132.5, 133.9, 136.0, 138.9, 139.8, 145.1, 168.1, 191.8; IR (KBr): 3020, 2920, 2850, 1684, 1680, 1602, 1579, 1343, 1259, 1177, 1095, 971, 816, 739, 577 cm^{-1}; HRMS (ESI): calcd. for $C_{25}H_{22}N_2OS^+$ [M + H$^+$] 399.1526; found 399.1538.

4-Fluoro-*N*-(6-fluoro-3-(4-fluorophenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (14d):



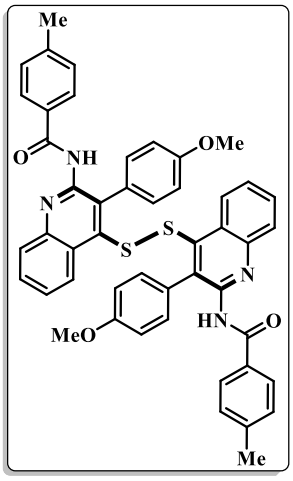
Orange solid (75 mg, 73%); mp 219–220 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.17 (t, 2H, *J* = 8.4 Hz), 7.33 (t, 2H, *J* = 8.4 Hz), 7.41–7.44 (m, 3H), 7.47–7.51 (m, 3H), 8.13 (s, 1H), 8.74 (dd, 1H, J_1 = 3.0 Hz, J_2 = 7.2 Hz), 13.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 115.6 (d, *J* = 24.8 Hz), 117.1 (d, *J* = 22.3 Hz), 117.5 (d, *J* = 21.4 Hz), 120.5 (d, *J* = 8.1 Hz), 121.3, 121.5, 121.7, 127.7 (d, *J* = 3.1 Hz), 128.8, 129.8 (d, *J* = 9.5 Hz), 131.0, 131.03, 133.1 (d, *J* = 8.1 Hz), 133.3 (d, *J* = 7.9 Hz), 139.9, 160.1, 162.0, 162.1, 164.1, 165.3, 167.2, 167.4, 192.3; ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -117.7 (s), -114.3 (s), -105.4 (s); IR (KBr): 3411, 2956, 2920, 2844, 1684, 1654, 1593, 1506, 1234, 1159, 1091, 938, 815, 748, 668, 578 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{13}F_3N_2OS^+$ [M + H$^+$] 411.0773; found 411.0773.

(*E*)-*N*-((Z)-4-Benzylidene-1-butyl-1*H*-benzo[*d*][1,3]thiazin-2(4*H*)-ylidene)benzamide (17a):



Gummy (95 mg, 92%); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.04 (t, 3H, *J* = 7.8 Hz), 1.49–1.56 (m, 2H), 1.96–2.01 (m, 2H), 4.42 (t, 2H, *J* = 7.2 Hz), 7.07 (s, 1H), 7.29–7.32 (m, 3H), 7.41 (t, 2H, *J* = 7.0 Hz), 7.44–7.47 (m, 3H), 7.51–7.53 (m, 1H), 7.55 (d, 3H, *J* = 7.8 Hz), 8.22 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 14.0, 20.5, 29.8, 50.5, 117.8, 125.0, 125.1, 126.2, 128.26, 128.29, 128.4, 128.7, 129.6, 129.91, 129.99, 130.9, 132.1, 135.2, 136.6, 138.2, 162.7, 174.6; IR (KBr): 2957, 2924, 2853, 1684, 1653, 1639, 1628, 1576, 1478, 1430, 1387, 1310, 1290, 1261, 1238, 1168, 1023, 899, 802, 752, 717, 693, 587 cm^{-1}; HRMS (ESI): calcd. for $C_{26}H_{24}N_2OS^+$ [M + H^+] 413.1682; found 413.1668.

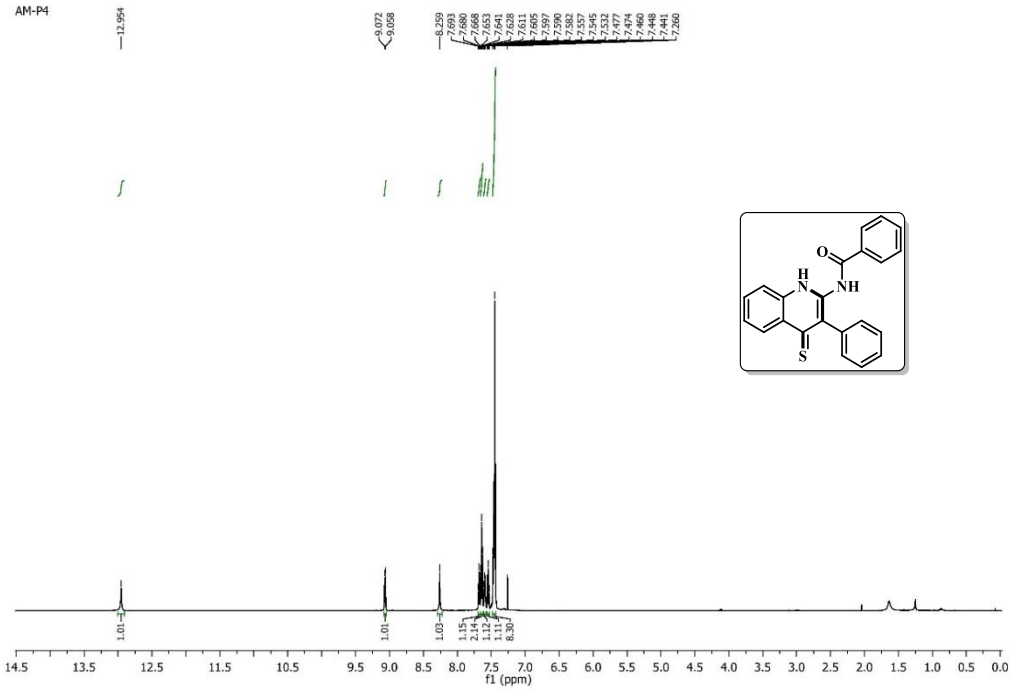
***N*,*N*'-(4,4'-Disulfanediylbis(3-(4-methoxyphenyl)quinoline-4,2-diyl))bis(4-methylbenzamide) (3b′):**



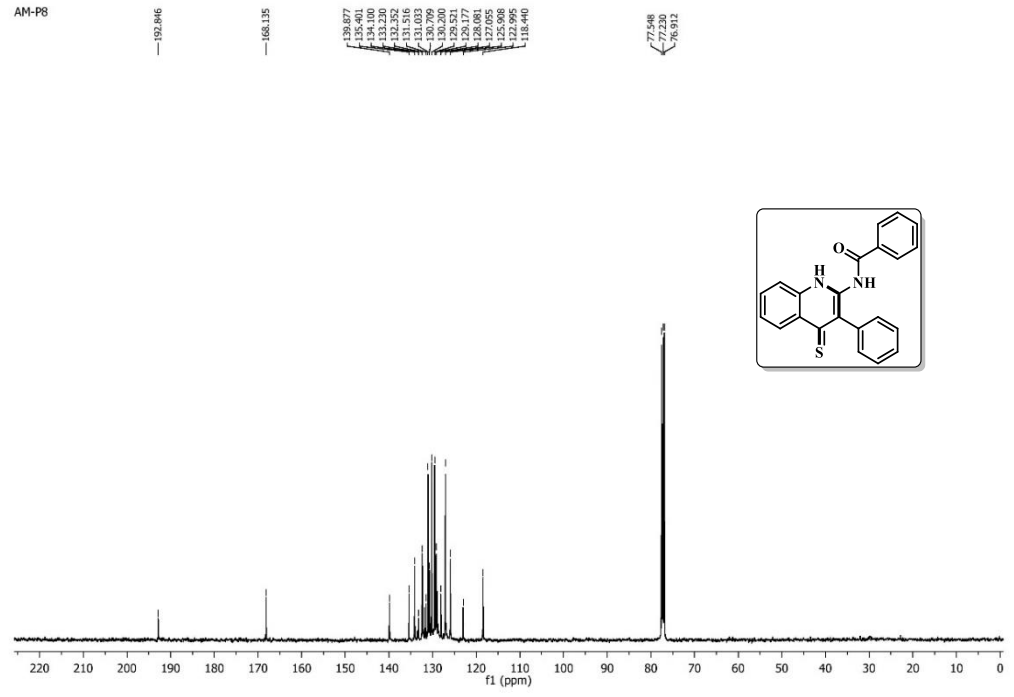
Gummy (96 mg, 96%); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.33 (s, 3H), 3.72 (s, 3H), 6.43 (bs, 2H), 6.61 (bs, 2H), 7.11 (d, 2H, *J* = 8.4 Hz), 7.35 (d, 3H, *J* = 7.2 Hz), 7.70 (t, 1H, *J* = 7.2 Hz), 7.97 (d, 2H, *J* = 7.8 Hz), 8.18 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.6, 55.4, 114.2, 126.2, 126.3, 126.6, 127.3, 129.5, 130.4, 131.01, 131.04, 131.5, 133.2, 142.9, 143.3, 147.2, 148.4, 159.5, 164.6. IR (KBr): 3418, 3061, 2924, 2853, 1666, 1610, 1570, 1512, 1496, 1469, 1394, 1247, 1178, 1028, 833, 748, 665, 581 cm^{-1}; HRMS (ESI): calcd. for $C_{48}H_{38}N_4O_4S_2^+$ [M + H^+] 799.2407; found 799.2390.

III.7. Spectra

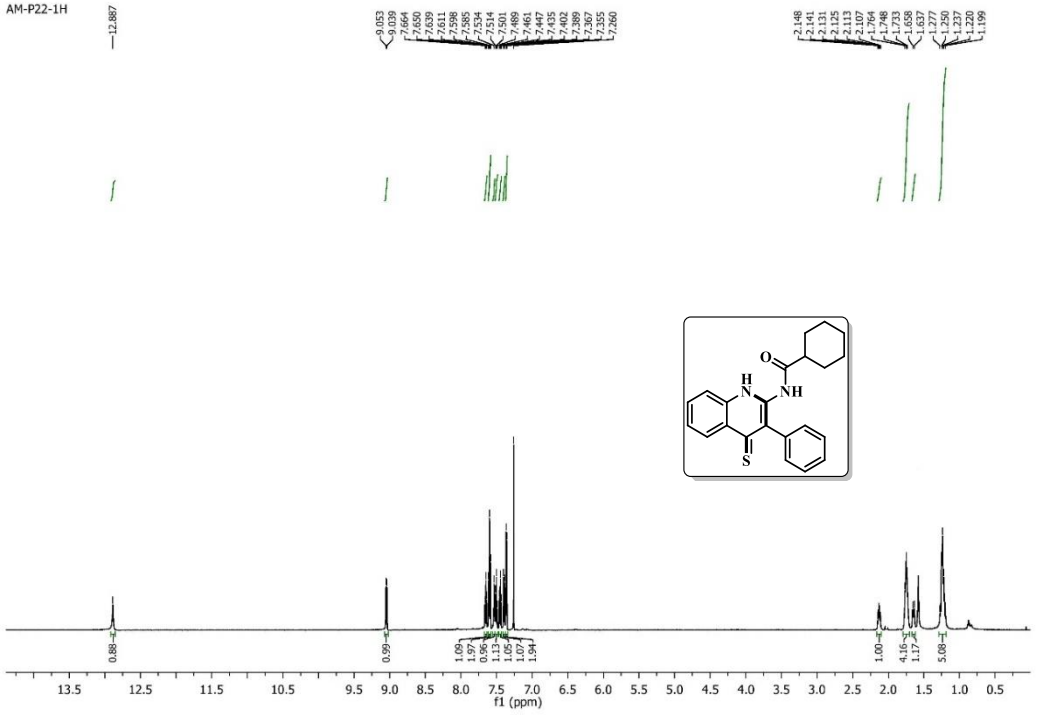
_N_-(3-Phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (1a): ^{1}HNMR (600 MHz, $CDCl_3$)



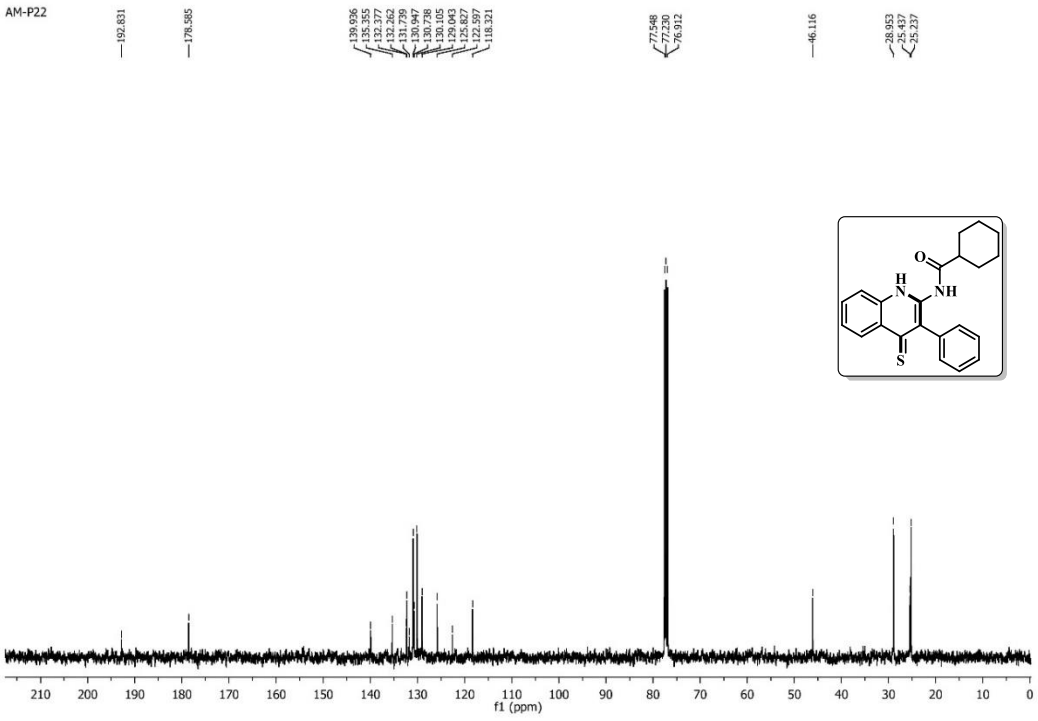
_N_-(3-Phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (1a): ^{13}CNMR (100 MHz, $CDCl_3$)



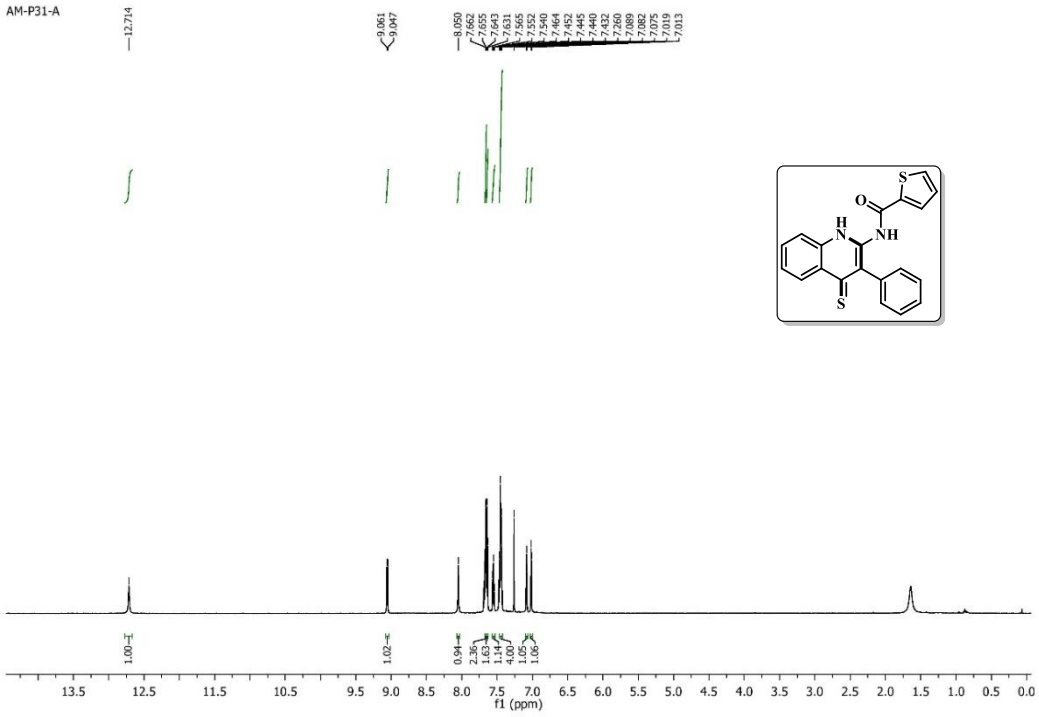
_N_-(3-Phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)cyclohexanecarboxamide (1f): ^{1}HNMR (600 MHz, $CDCl_3$)



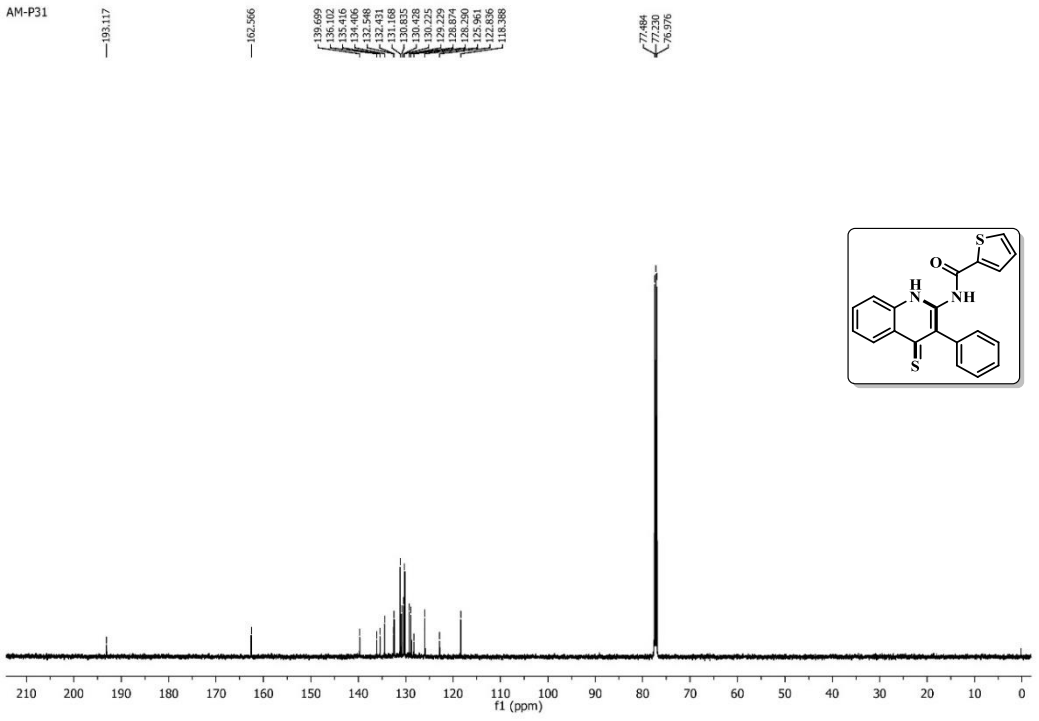
_N_-(3-Phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)cyclohexanecarboxamide (1f): ^{13}CNMR (100 MHz, $CDCl_3$)



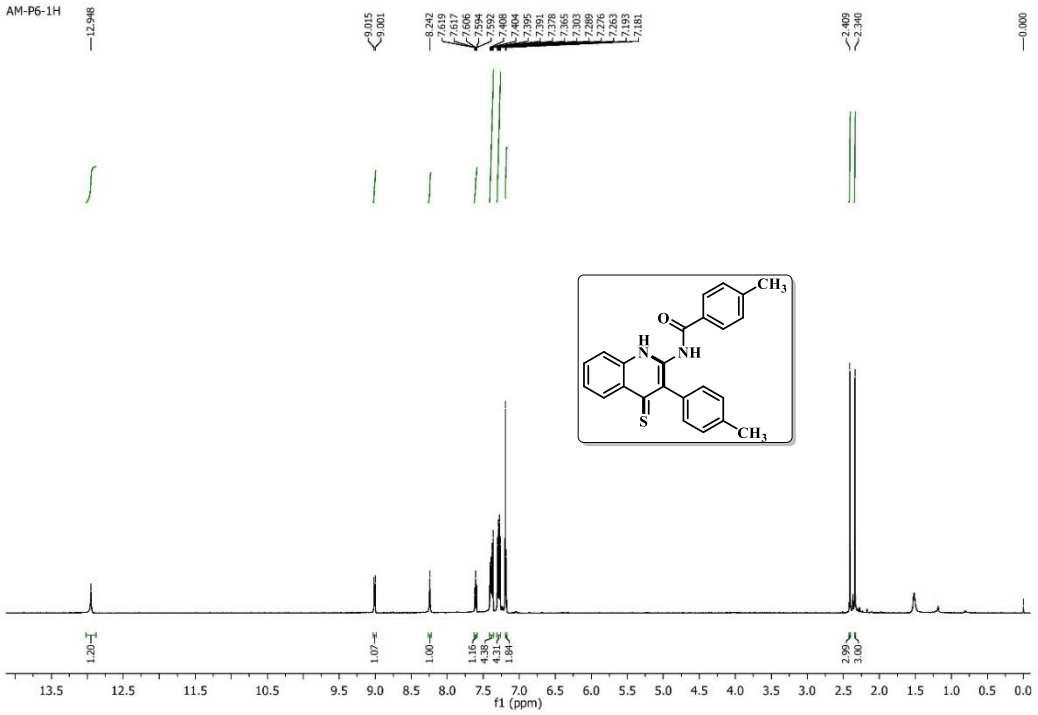
_N_-(3-Phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)thiophene-2-carboxamide (1g): ^{1}HNMR (600 MHz, $CDCl_3$)



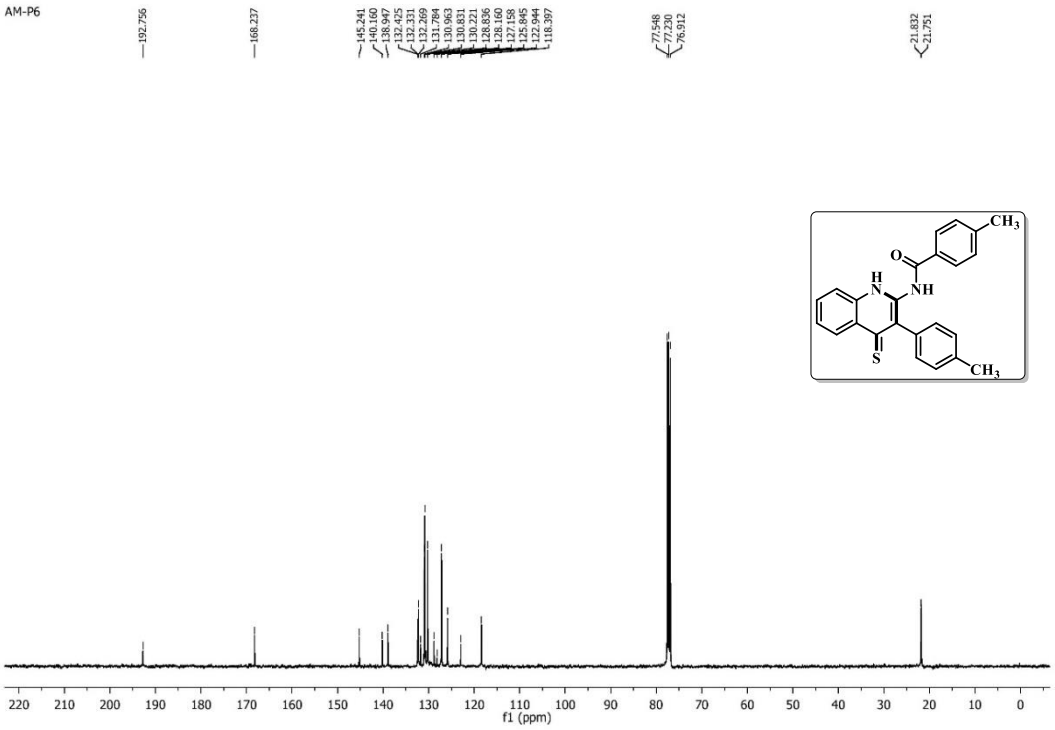
_N_-(3-Phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)thiophene-2-carboxamide (1g): ^{13}CNMR (125 MHz, $CDCl_3$)



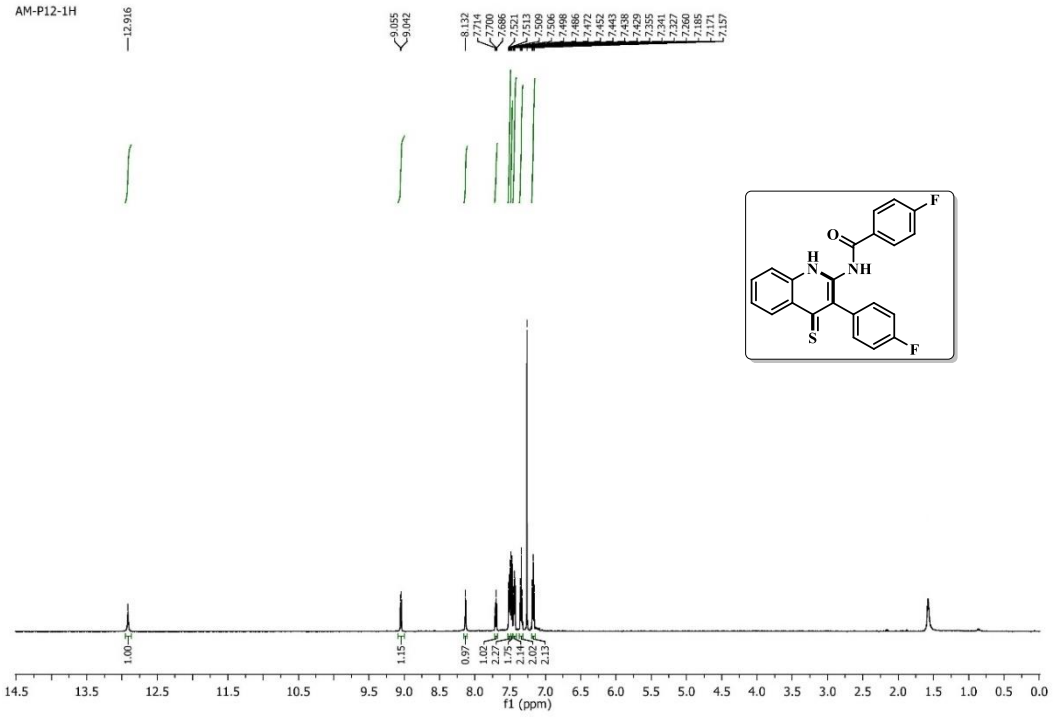
4-Methyl-*N*-(4-thioxo-3-(*p*-tolyl)-1,4-dihydroquinolin-2-yl)benzamide (2b): ^{1}HNMR (600 MHz, $CDCl_3$)



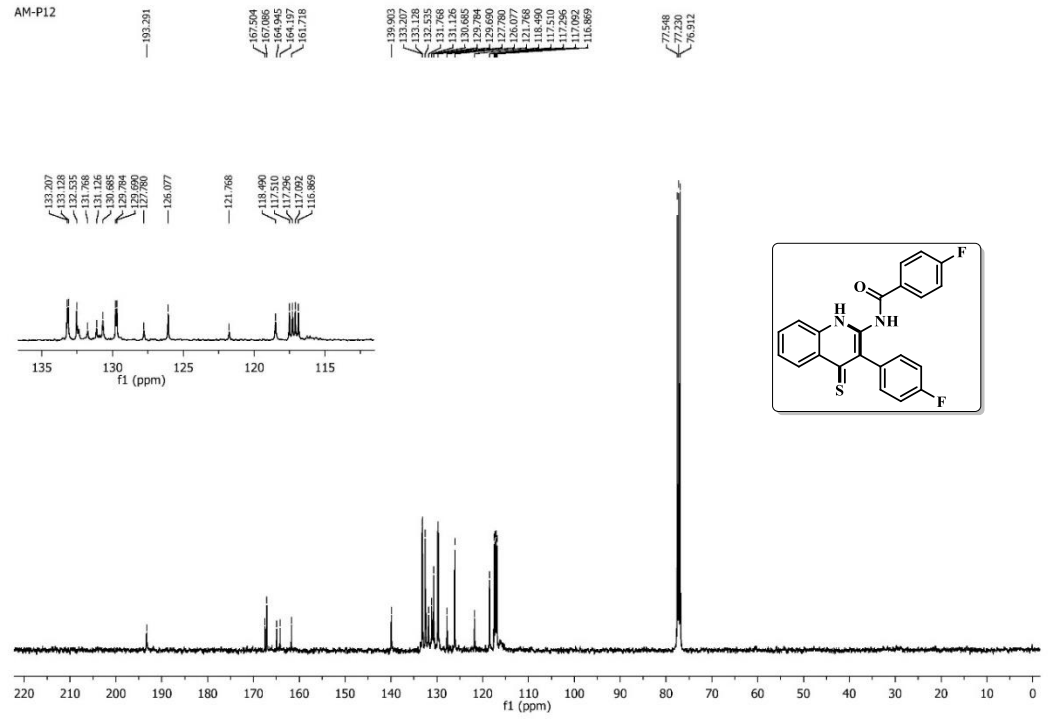
4-Methyl-*N*-(4-thioxo-3-(*p*-tolyl)-1,4-dihydroquinolin-2-yl)benzamide (2b): ^{13}CNMR (100 MHz, $CDCl_3$)



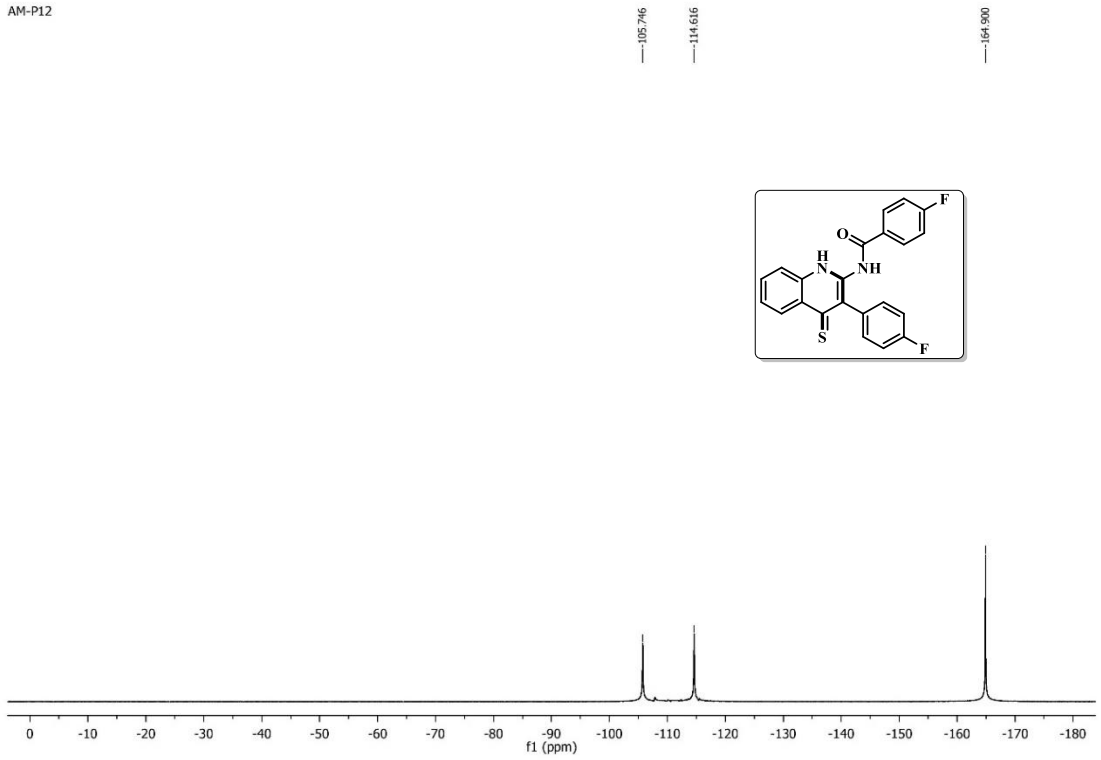
4-Fluoro-*N*-(3-(4-fluorophenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (5d): ^{1}HNMR (600 MHz, $CDCl_3$)



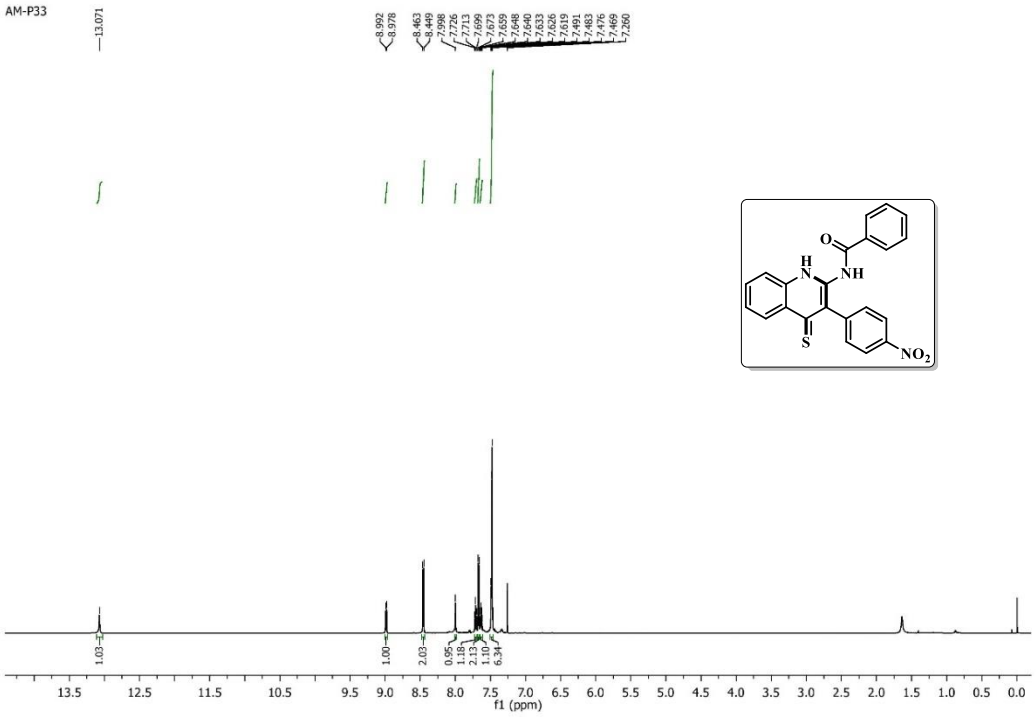
4-Fluoro-*N*-(3-(4-fluorophenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (5d): ^{13}CNMR (100 MHz, $CDCl_3$)



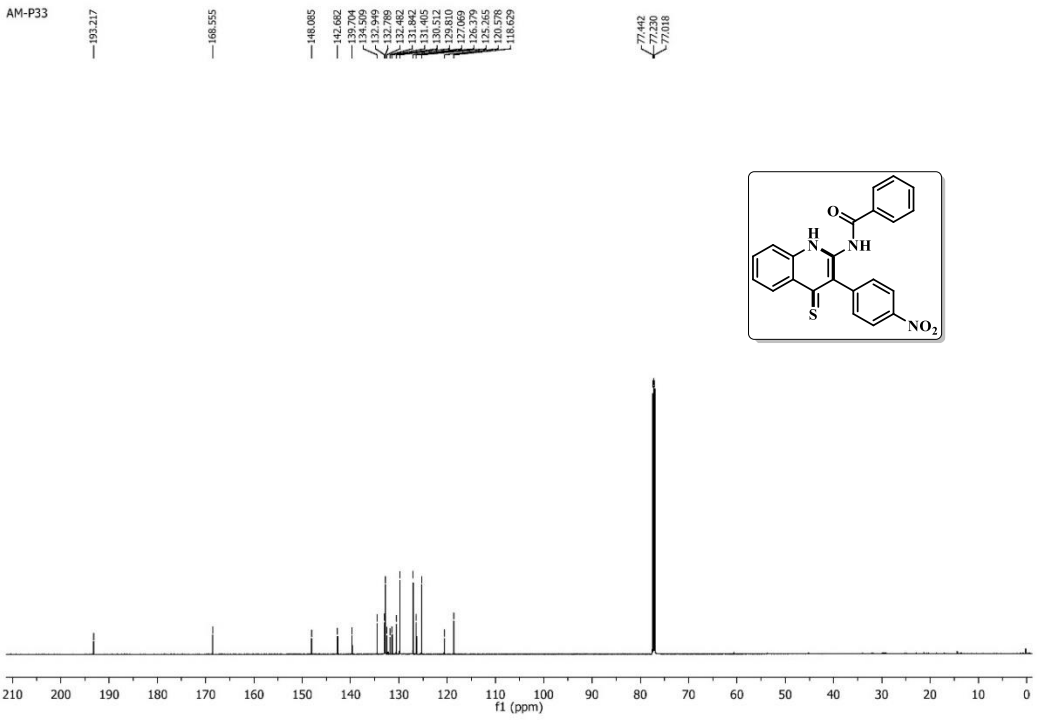
4-Fluoro-*N*-(3-(4-fluorophenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (5d): ^{19}FNMR ($CDCl_3$ + C_6F_6)



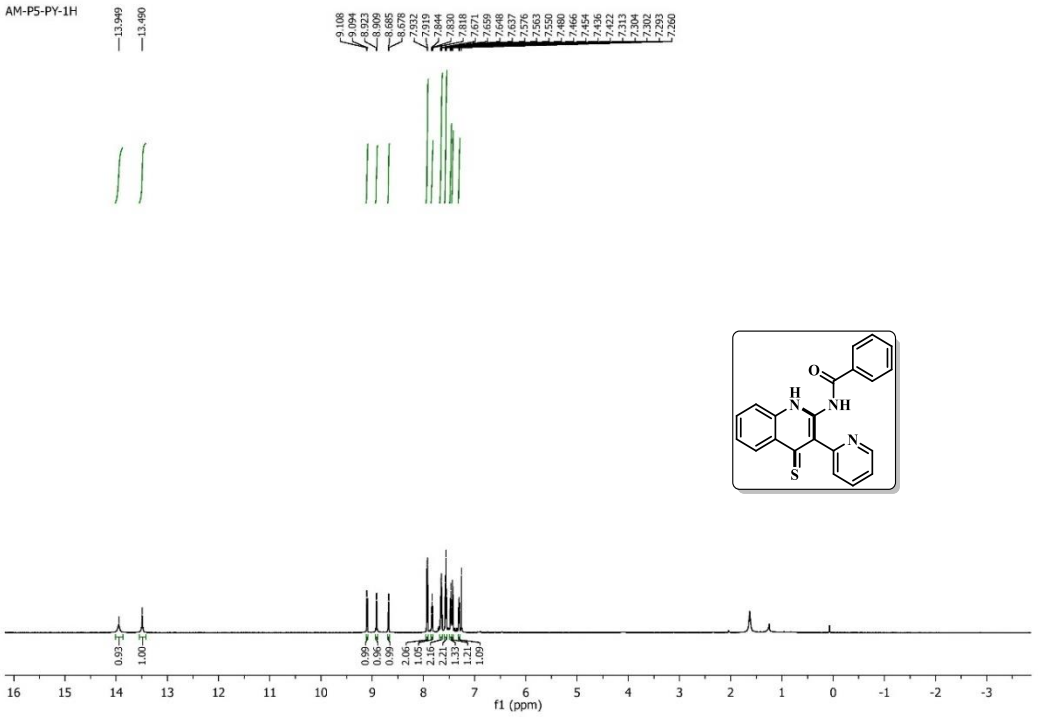
_N_-(3-(4-Nitrophenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (6a): ^{1}HNMR (600 MHz, $CDCl_3$)



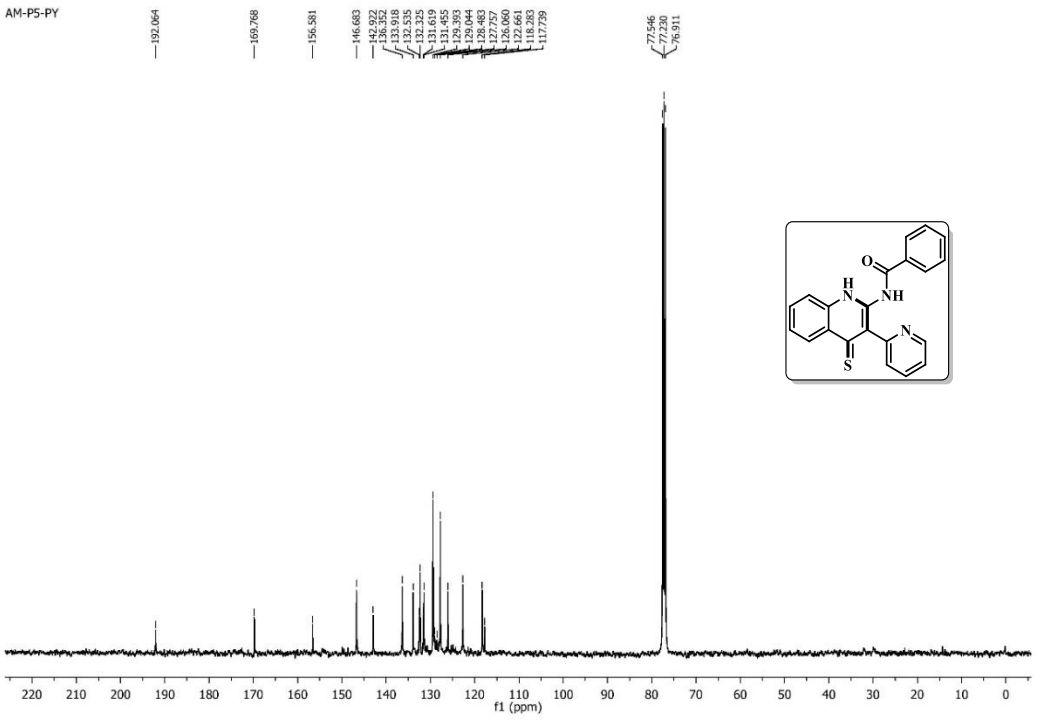
_N_-(3-(4-Nitrophenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (6a): ^{13}CNMR (150 MHz, $CDCl_3$)



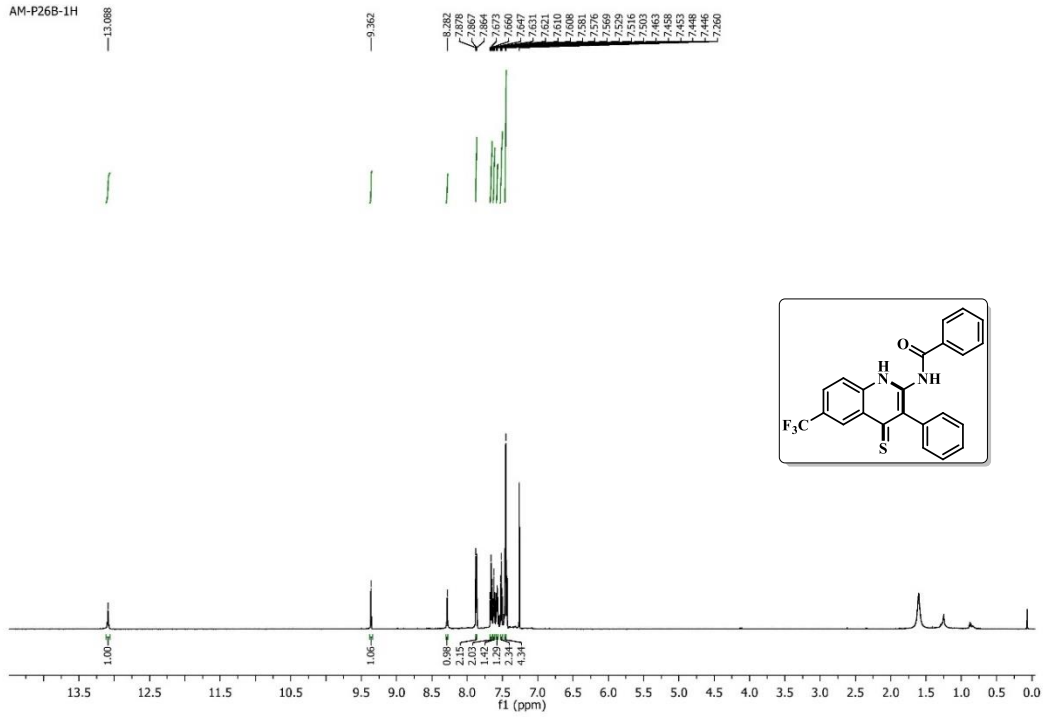
_N_-(3-(Pyridin-2-yl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (8a): ^{1}HNMR (600 MHz, $CDCl_3$)



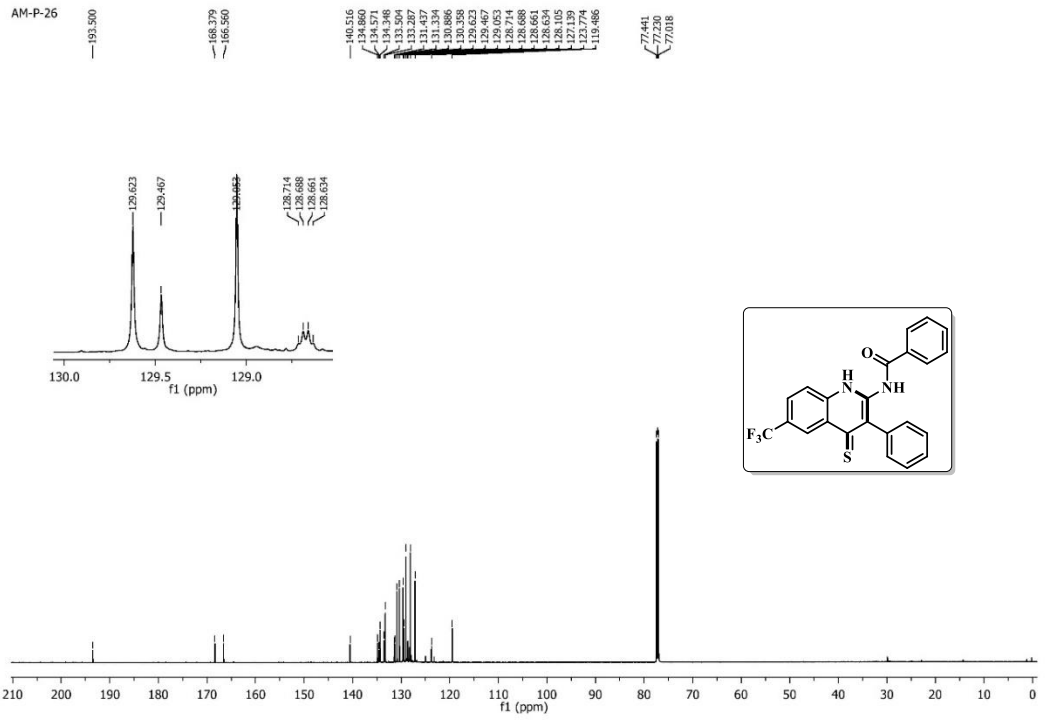
_N_-(3-(Pyridin-2-yl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (8a): ^{13}CNMR (100 MHz, $CDCl_3$)



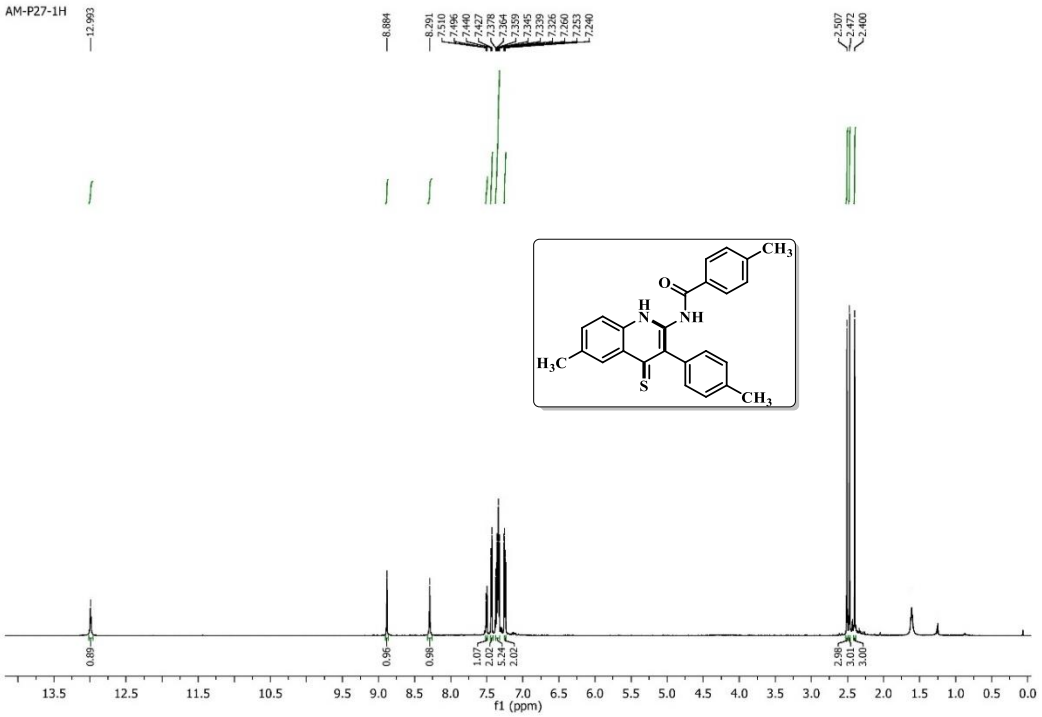
_N_-(3-Phenyl-4-thioxo-6-(trifluoromethyl)-1,4-dihydroquinolin-2-yl)benzamide (12a): ^{1}HNMR (600 MHz, $CDCl_3$)



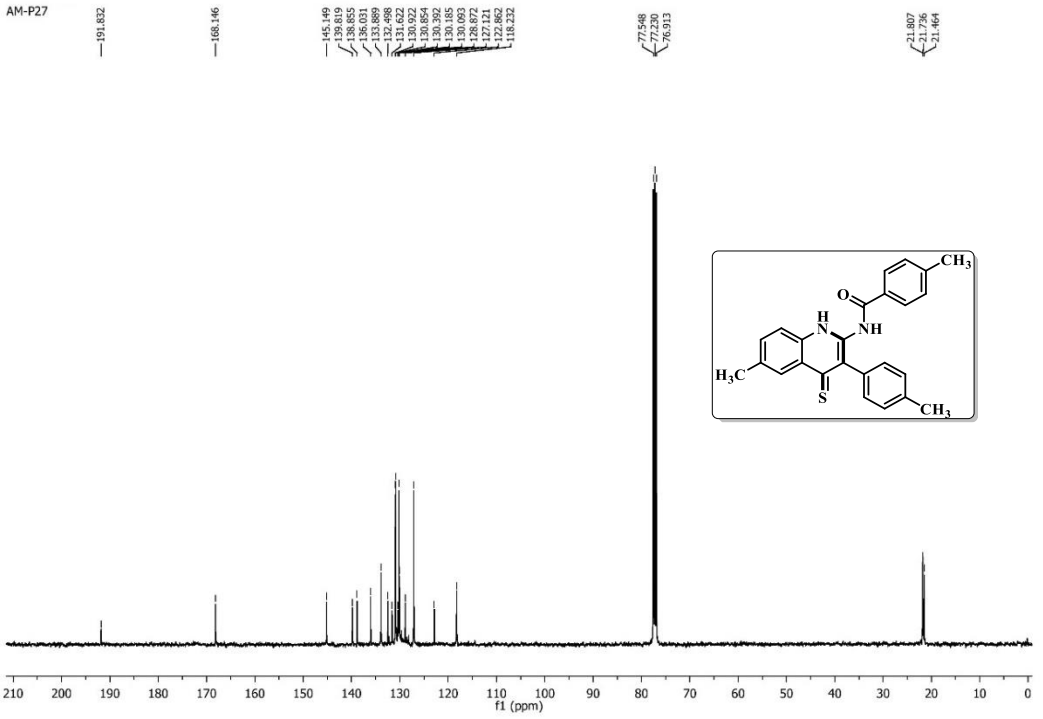
_N_-(3-Phenyl-4-thioxo-6-(trifluoromethyl)-1,4-dihydroquinolin-2-yl)benzamide (12a): ^{13}CNMR (150 MHz, $CDCl_3$)



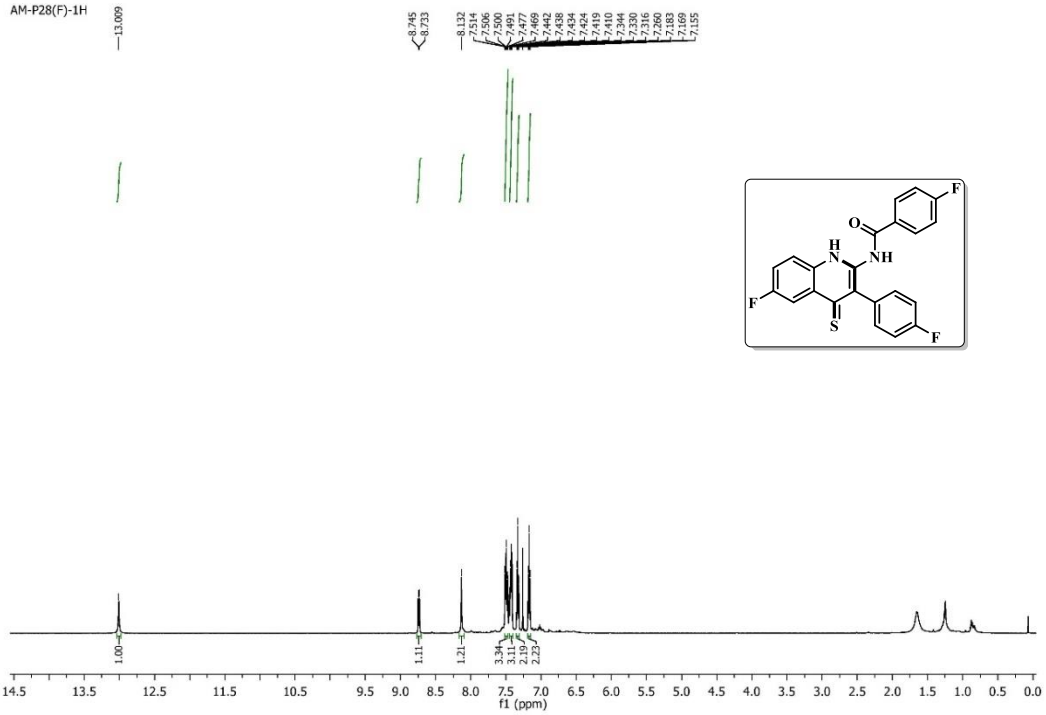
4-Methyl-*N*-(6-methyl-4-thioxo-3-(*p*-tolyl)-1,4-dihydroquinolin-2-yl)benzamide (13b): ^{1}HNMR (600 MHz, $CDCl_3$)



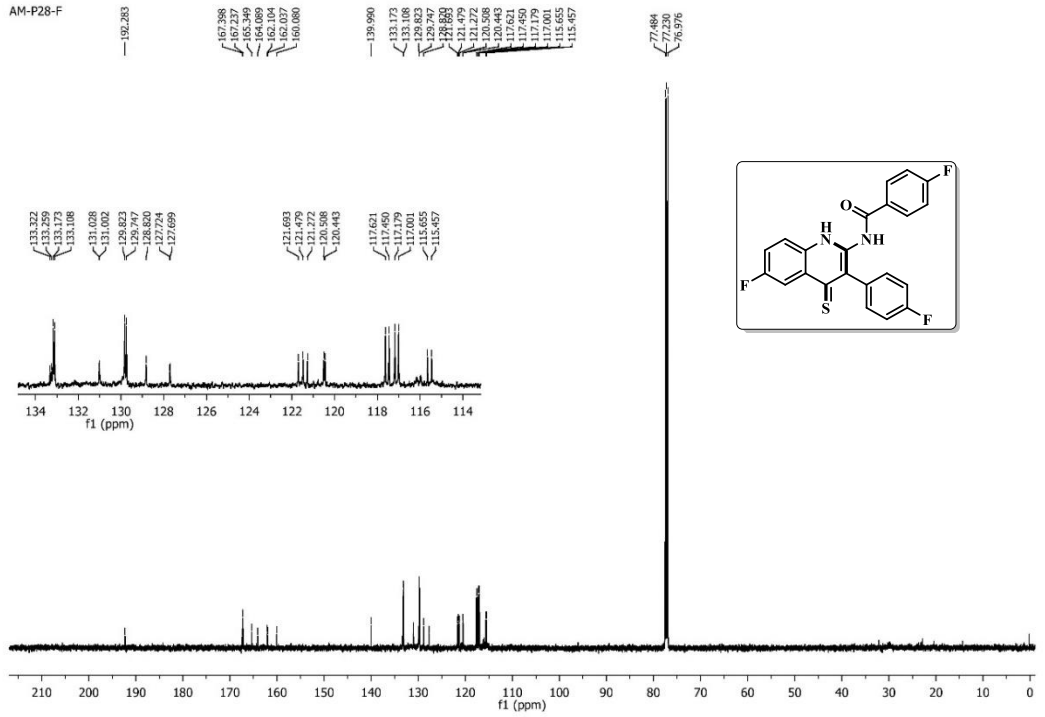
4-Methyl-*N*-(6-methyl-4-thioxo-3-(*p*-tolyl)-1,4-dihydroquinolin-2-yl)benzamide (13b): ^{13}CNMR (100 MHz, $CDCl_3$)



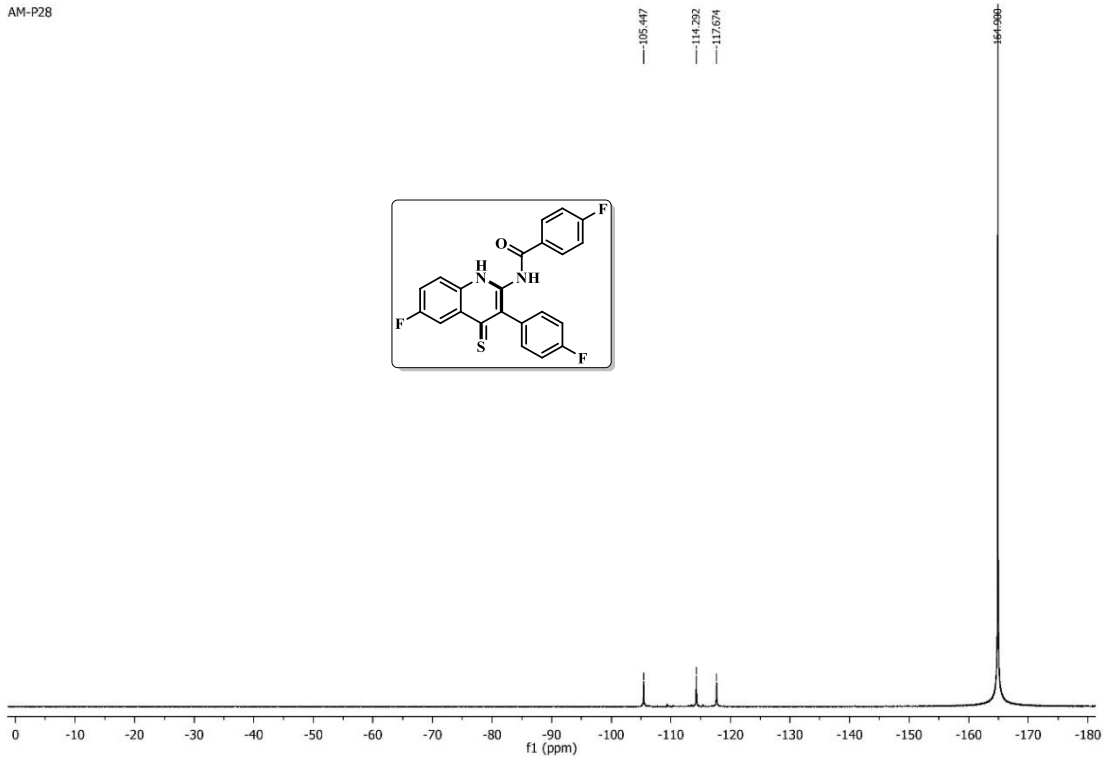
4-Fluoro-*N*-(6-fluoro-3-(4-fluorophenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (14d): **^{1}HNMR (600 MHz, $CDCl_3$)**



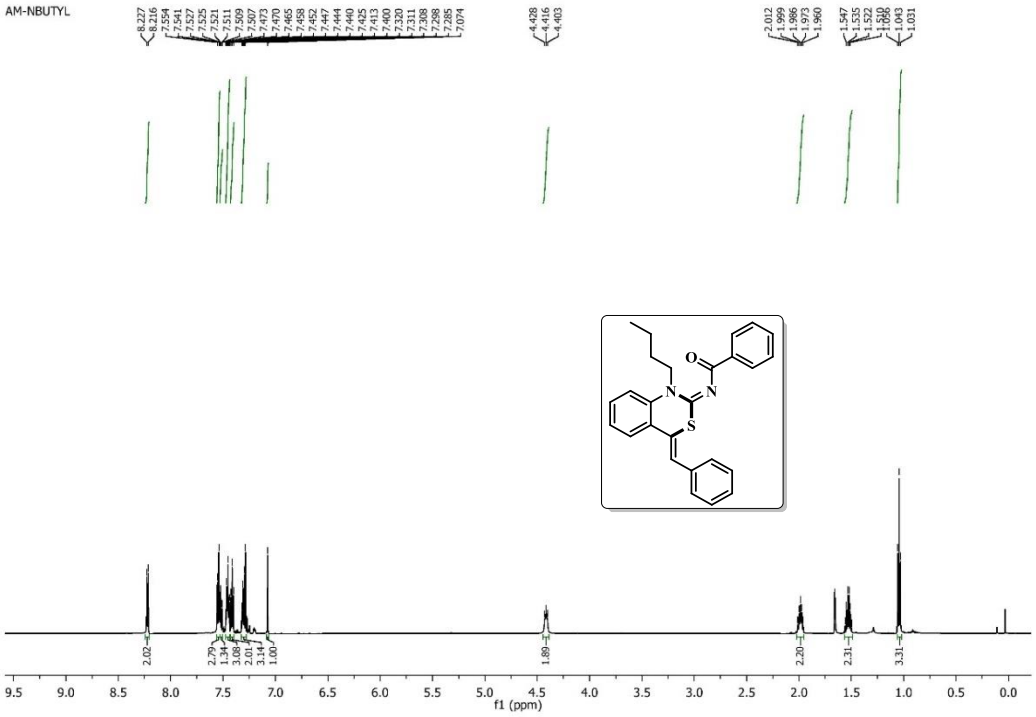
4-Fluoro-*N*-(6-fluoro-3-(4-fluorophenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (14d): **^{13}CNMR (125 MHz, $CDCl_3$)**



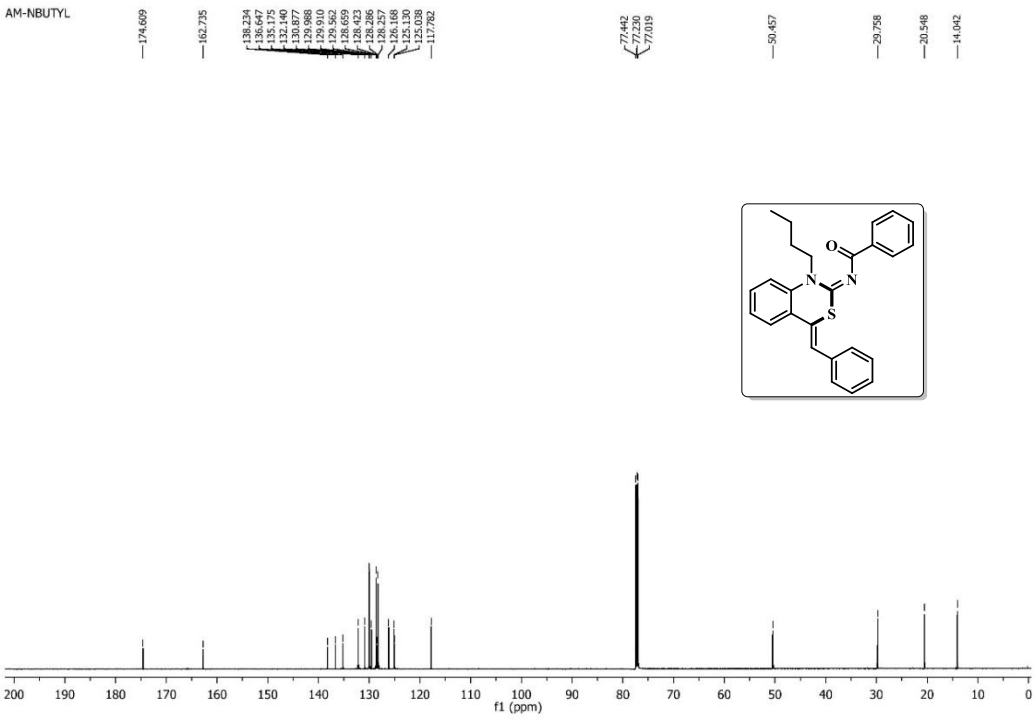
4-Fluoro-*N*-(6-fluoro-3-(4-fluorophenyl)-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (14d): **^{19}FNMR ($CDCl_3$ + C_6F_6)**



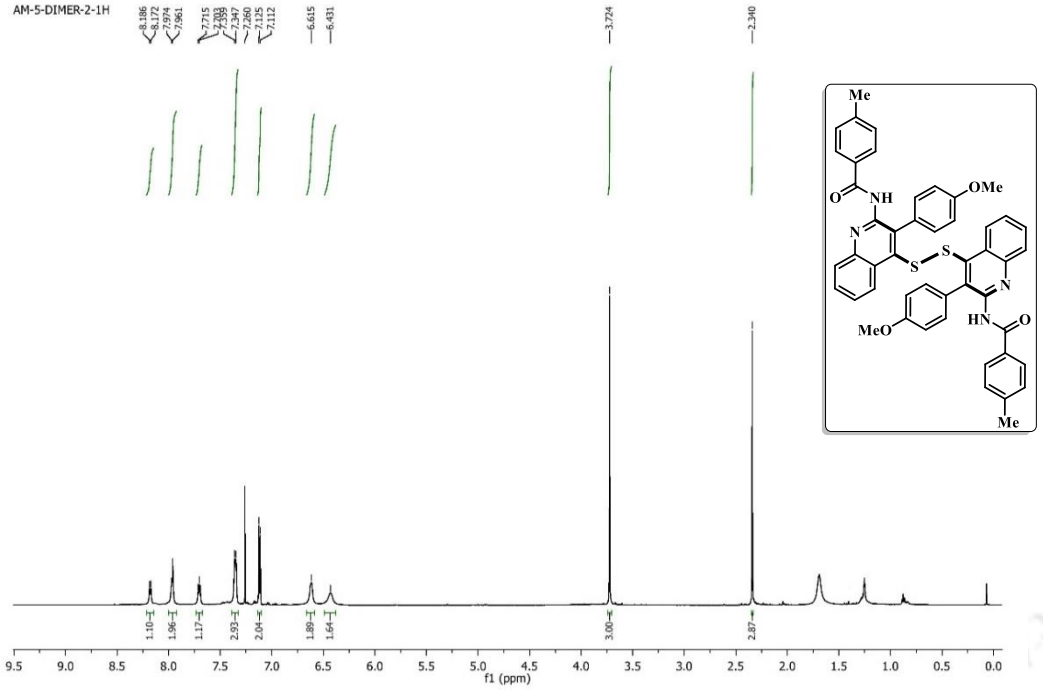
(*E*)-*N*-((Z)-4-Benzylidene-1-butyl-1*H*-benzo[*d*][1,3]thiazin-2(4*H*)-ylidene)benzamide (17a): **^{1}HNMR (600 MHz, $CDCl_3$)**



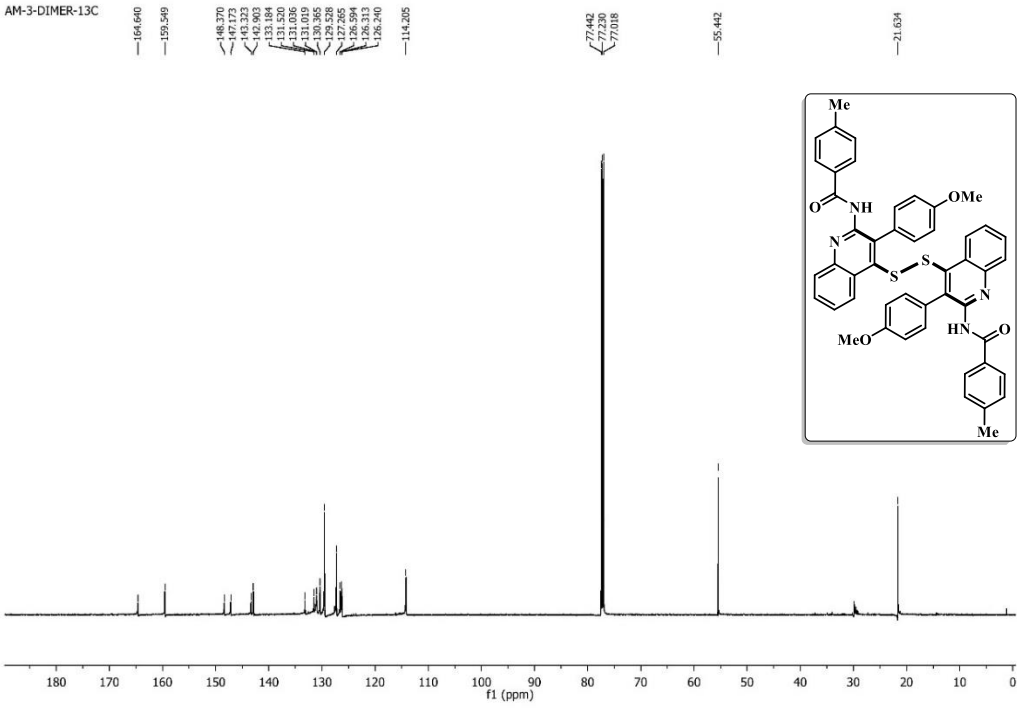
(*E*)-*N*-((Z)-4-Benzylidene-1-butyl-1*H*-benzo[*d*][1,3]thiazin-2(4*H*)-ylidene)benzamide (17a): **^{13}CNMR (150 MHz, $CDCl_3$)**



_N,N_'-(4,4'-Disulfanediylbis(3-(4-methoxyphenyl)quinoline-4,2-diyl))bis(4-methylbenzamide) (3b′): ^{1}HNMR (600 MHz, $CDCl_3$)

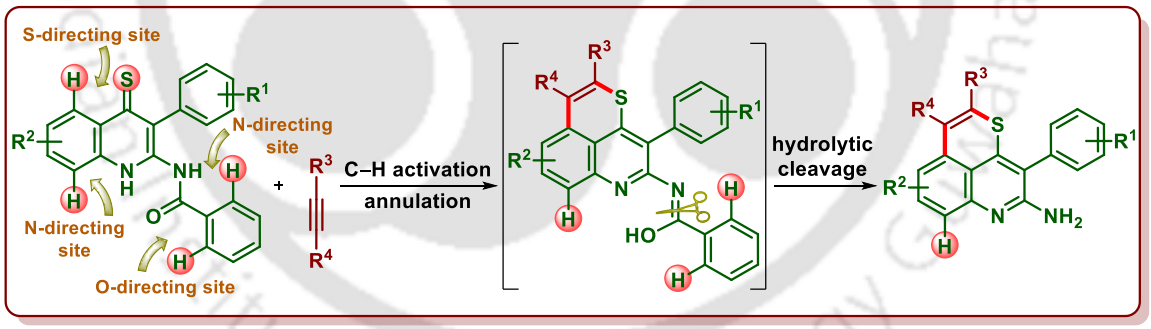


_N,N_'-(4,4'-Disulfanediylbis(3-(4-methoxyphenyl)quinoline-4,2-diyl))bis(4-methylbenzamide) (3b′): ^{13}CNMR (150 MHz, $CDCl_3$)



CHAPTER IV

A Thiocarbonyl Directed Regiospecific C–H/S–H Annulation of Quinoline-4(1H)-thiones with Alkynes



ABSTARCT: *A unique illustration of regiospecific C–H/S–H annulation of quinoline-4(1H)-thiones with alkynes have been demonstrated using a Ru(II)-catalyst. This is the first example of any C–H/S–H annulation directed via a C=S group. Here, preferential annulation takes place at the sterically hindered position even in the presence of three other competing sites viz. two C–H/N–H and one C–H/O–H leading to the synthesis of thiopyrano[2,3,4-de]quinolines.*

CHAPTER IV

IV. A Thiocarbonyl Directed Regiospecific C–H/S–H Annulation of Quinoline-4(1*H*)-thiones with Alkynes

IV.1. Introduction

The evolution of C–H bond activation[1] is emerging as one of the most powerful tools in synthetic chemistry and has streamlined the construction and functionalization of complex molecules in the past decade.[2] Among various transition metals, ruthenium catalyzed chelation directed C–H bond activation, followed by annulation with alkynes, has led to the synthesis of a wide range of fused polyheterocycles.[3] To accomplish this, diverse N- and O- based directing groups such as amines, anilides, imines, amides, ketones, esters, carboxylic acids, and alcohols have been well studied.[4] The coordination of heteroatom to the metal centre is assumed to be the key step in these transformations, thereby directing the metal centre to the proximal C–H bond and thus achieving the desired functionalization.

In the midst of several directing groups, sulfur containing compounds such as thiols, thioethers, sulfoxides have not been utilized for any metal directed annulations. Nevertheless, arylation, alkenylation and heterocycle synthesis have been reported.[5] Remarkably, organosulfur compounds are important chemical entities because of its occurrence in many biological systems,[6a] synthetic drugs and functional materials.[6b,c] However, the susceptibility of sulfur to easy oxidation and its affinity towards metal ions poisons the catalyst thereby hampering its usage in C–H activation reactions.[7] Any sulfur directed annulation is hitherto unprecedented and thus developing novel routes for the synthesis of complex molecules with concurrent sulphur incorporation is highly desirable.

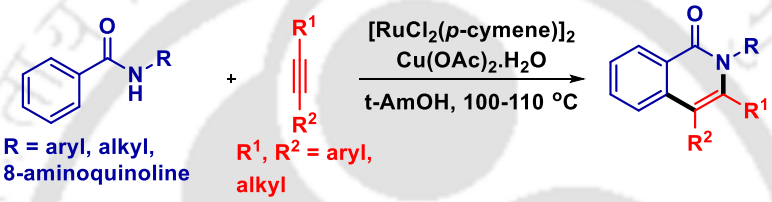
IV.2. Annulation Involving C–H/N–H, C–H/O–H, and C–H/N–O Bond Cleavages

The alkyne annulations reported till date often involves C–H/N–H, C–H/O–H, and C–H/N–O bond cleavages resulting into synthesis of many regioselectively decorated

heteroarenes.[2b] Below are some examples of ruthenium(II)-catalyzed oxidative annulation involving diverse directing groups with alkynes involving these cleavages.

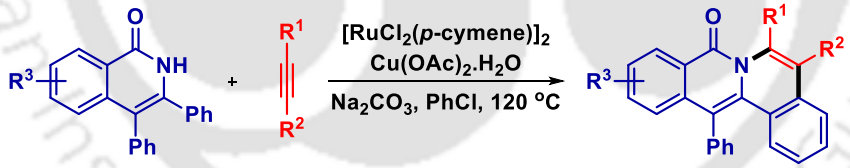
➢ **Annulation via C–H/N–H Bond Cleavage**

Ackermann group reported the first Ru(II)-catalyzed oxidative annulation reaction of alkynes with benzamides. The transformation occurs in a regioselective manner involving the functionalization of *ortho*-C–H and amide N–H bonds giving access to isoquinolones. The reaction utilizes $Cu(OAc)_2.H_2O$ as the oxidant in t-AmOH at 100 °C.[8a] In 2014, Swamy *et al.* demonstrated the synthesis of isoquinolones using 8-aminoquinolinyl moiety as a bidentate ligand under similar reaction conditions (Scheme IV.2.1).[8b]



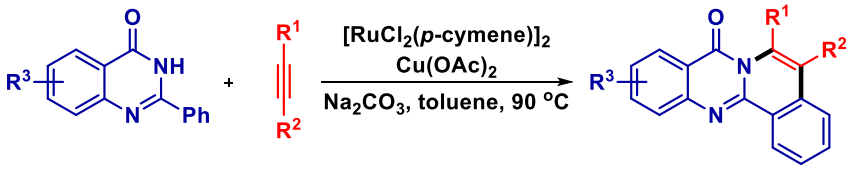
Scheme IV.2.1. *Annulation of alkynes with benzamide derivatives*

Li, Wang and co-workers developed a Ru-catalyzed oxidative coupling/cyclization of isoquinolones with alkynes resulting into the synthesis of dibenzo[*a*,*g*]quinolizin-8-one (Scheme IV.2.2).[9] The annulation takes place via the cleavage of C–H/N–H bonds.



Scheme IV.2.2. *Annulation of alkynes with isoquinolones*

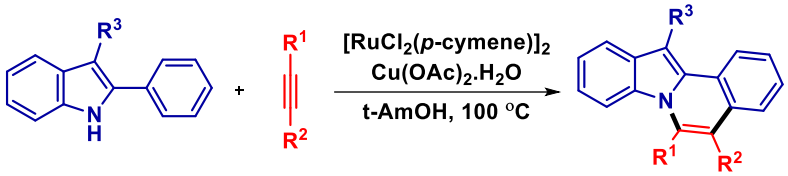
Peng group achieved annulation of alkynes with quinazolinones leading to the construction of fused tetracyclic heteroarenes (Scheme IV.2.3).[10]



Scheme IV.2.3. *Annulation of alkynes with quinazolones*

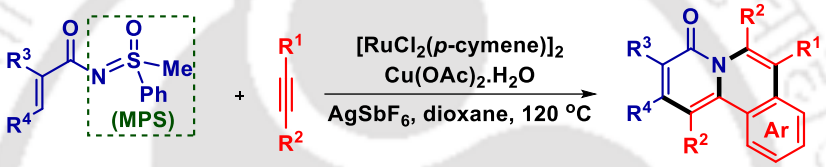
Ackermann group also reported Ru-catalyzed oxidative annulation of alkynes with 2-arylindoles using air as the ideal sacrificial oxidant. This aerobic annulation reaction was accomplished using co-catalytic amount of $Cu(OAc)_2.H_2O$ (Scheme IV.2.4).[11a] They later

achieved annulation of alkynes with various aryl-, heteroaryl-, and alkenyl-substituted 1*H*-pyrazoles via C–H/N–H bond functionalization. The reaction shows excellent chemo- and regioselectivities.[11b]



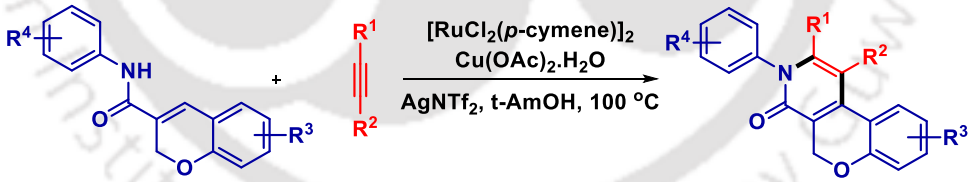
Scheme IV.2.4. *Oxidative annulation of alkynes with 2-arylindoles*

Sahoo *et al.* demonstrated a multiple annulation of acrylamides with alkynes in the presence of Ru(II) catalyst. This one-pot double annulation was achieved in the presence of methylphenyl sulfoximine (MPS) as transformable directing group. (Scheme IV.2.5)[12]



Scheme IV.2.5. *Multiple annulation of acrylamides*

Swamy and co-workers reported the synthesis of fused polyheterocycles 3,5-dihydro-4*H*-chromeno[3,4-*c*]pyridin-4-one from *N*-phenyl-2*H*-chromene-3-carboxamide as the directing arenes. This was also achieved via C–H/N–H bond cleavage (Scheme IV.2.6).[13]

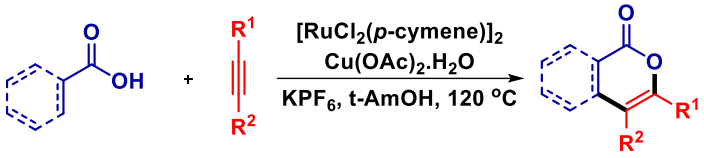


Scheme IV.2.6. *Annulation of alkynes with N-phenyl-2H-chromene-3-carboxamide*

➢ **Annulation via C–H/O–H Bond Cleavage**

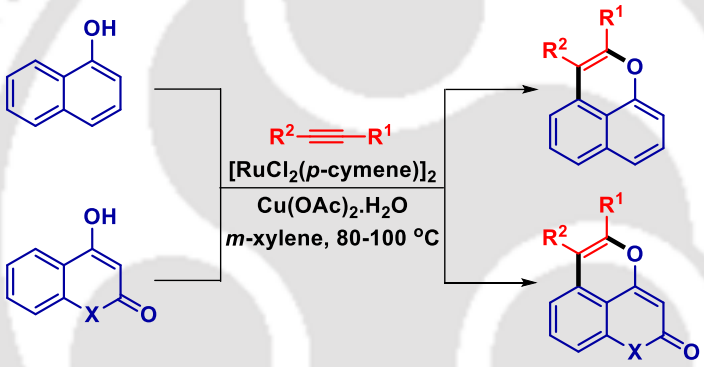
A Ru(II)-catalyzed oxidative annulation of alkynes with aromatic acids was demonstrated by Ackermann group as represented in Scheme IV.2.7.[14a] The reaction occurs in the presence of co-catalytic amount of additive i.e. KPF_6, involving the cleavage of C–H and O–H bonds. The method resulted into the synthesis of biologically important isocoumarins and α-pyrones. Jeganmohan group also reported similar reaction but used $AgSbF_6$ as the additive in DCE solvent.[14b] Gogoi and co-workers also demonstrated an oxidative annulation of cinnamic acids with disubstituted alkynes via C–H/O–H

functionalization strategy leading to the formation of α-pyrones. However, the reaction gave good yields in the absence of any additives.[14c]



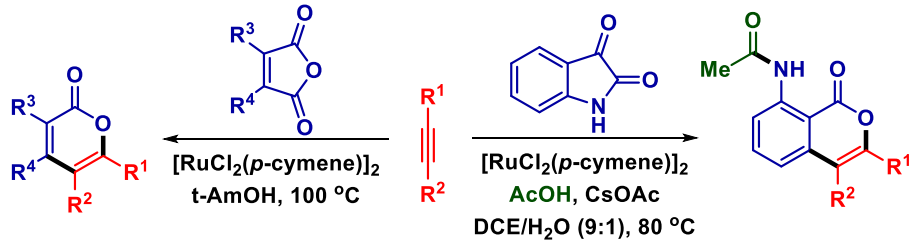
Scheme IV.2.7. *Annulation of alkynes with aromatic acids*

A hydroxyl-assisted oxidative annulations of alkynes with naphthols, 4-hydroxyquinolinone, and 4-hydroxycoumarins were accomplished by Ackermann group using the same ruthenium complex. The method delivers fluorescent annulated pyrans and diversely decorated coumarins and quinolin-2-ones via highly site selective as well as chemo- and regioselective C–H/O–H bond functionalization (Scheme IV.2.8).[15]



Scheme IV.2.8. *Hydroxyl group assisted annulation of alkynes*

Gogoi *et al.* demonstrated a ruthenium catalyzed decarbonylative addition reaction of anhydrides with alkynes to provide isocoumarins and α-pyrones (Scheme IV.2.9).[16a] The same group later employed isatins as novel substrates for external oxidant free Ru(II)-catalyzed C–H activation and annulation reaction with alkynes to prepare 8-amido isocoumarins.[16b]

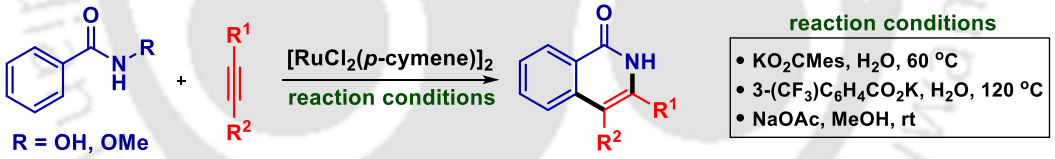


Scheme IV.2.9. *Annulation of alkynes with anhydrides and isatins*

➢ **Annulation via C–H/N–O Bond Cleavage**

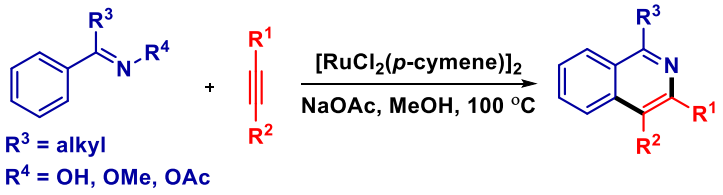
The annulations comprising of C–H/N–H and C–H/O–H bond cleavages often requires the use of an external oxidant to regenerate the catalyst. However, new strategies involving directing group that can also act as an (internal) oxidant has recently gained great attention in the field of C–H activation and annulation. These DGs obviates the need of an external co-oxidant, increases the reactivity and selectivity under mild reaction conditions, and reduces the amount of waste formed.

The first Ru-catalyzed annulation of alkynes with hydroxamic acids as a directing group cum internal oxidant was described by Ackermann *et al*. resulting into the formation of isoquinolones (Scheme IV.2.10).[17a] The reaction was accomplished via carboxylate assistance in the presence of a sterically hindered additive KO_2CMes in water as a green reaction medium at 60 °C. In 2014, they reported similar reaction using electron-deficient aromatic carboxylic acid 3-$(F_3C)C_6H_4CO_2H$ as the additive.[17b] Li and Wang group also reported similar Ru(II)-catalyzed strategy for isoquinolone synthesis using hydroxamic esters. They performed the reaction in MeOH using NaOAc as the additive at room temperature.[17c] In all these cases, annulation takes place via C–H/N–O bond cleavages (Scheme IV.2.10).



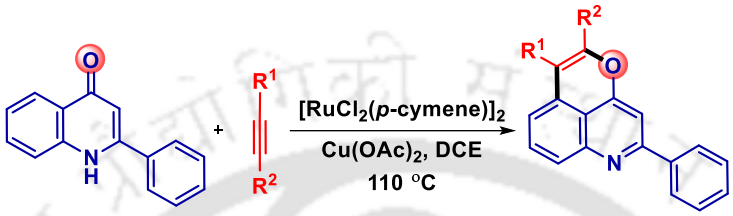
Scheme IV.2.10. *Annulation of alkynes with hydroxamic acid and ester*

Using the same concept, Jeganmohan group used oximes as directing groups cum internal oxidant leading to the synthesis of isoquinolines. The reaction took place in the presence of NaOAc as the additive in MeOH at 100 °C (Scheme IV.2.11).[18a] Similar work was reported by Ackermann and co-workers, however they used KPF_6 as the additive and the reaction was performed at 60 °C.[18b]



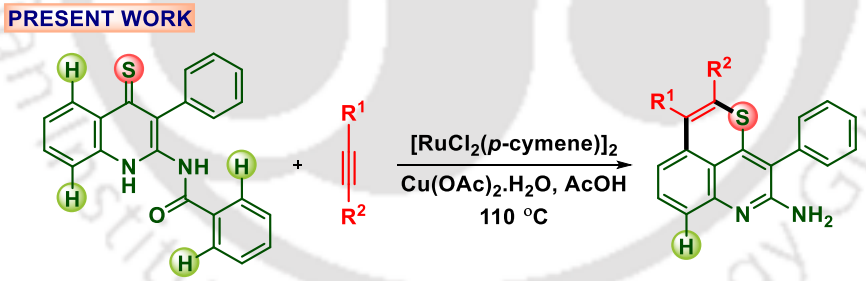
Scheme IV.2.11. *Annulation of alkynes with oximes*

In 2015, our group demonstrated a Ru(II)-catalyzed oxidative C–H/O–H annulation of 2-arylquinolinone with internal alkynes. In this case, the regiospecific annulation is via the more favourable phenolic form of quinolinone over other possible pathways (C–H/N–H and C–H/C–H). The metal coordinates to the weaker carbonyl oxygen in the presence of stronger nitrogen-directing group giving a regiospecific annulated product (Scheme IV.2.12).[19]



Scheme IV.2.12. *Annulation via weak coordinating group*

Inspired by our above work, we were inquisitive to see annulation in quinoline-4(1*H*)-thiones synthesized in previous chapter, wherein there are multiple directing sites *viz.* two C–H/N–H, one C–H/O–H, and one C–H/S–H. The reaction of quinoline-4(1*H*)-thiones with alkynes in the presence of a Ru(II) catalyst resulted into the synthesis of thiopyrano[2,3,4-*de*]quinolines via C–H/S–H bond functionalization as described here (Scheme IV.2.13).



Scheme IV.2.13. *Annulation in quinoline-4(1H)-thiones via C–H/S–H bond cleavage*

IV.3. Present Work

We commenced our exploration by reacting *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (**1**) (1 equiv) and diphenylacetylene (**a**) (1 equiv) with the well investigated catalyst $[RuCl_2(p\text{-cymene})]_2$ (2 mol%), AgOAc (1 equiv) as the oxidant in AcOH (2 mL) at 110 °C (Table IV.3.1, entry 1). A new product (**1a**) was isolated in 55% yield after 12 h. Spectroscopic analysis (^{1}H NMR and ^{13}C NMR) revealed its

structure to be 3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (**1a**), which was reconfirmed by single crystal X-ray diffraction study (Figure IV.3.1).

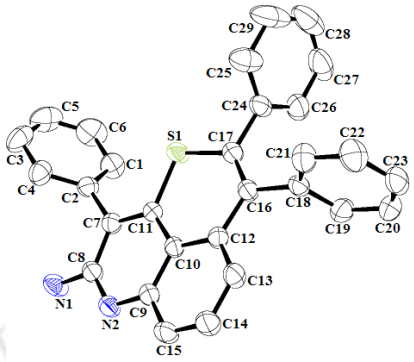


Figure IV.3.1. *Ortep view of* ***(1a)***

The analysis of the product confirms a [4 + 2] annulation of alkyne via oxidative C–H/S–H bond cleavage over other competing annulations (C–H/N–H or C–H/O–H). This process is however associated with the loss of –COPh group possibly via a hydrolytic path. Thus the question arises, whether the amide bond cleavage takes place before annulation or after? Subsequently, crystal structure of one of the isolated intermediate (**17a**) (after 30 minutes) confirms that the annulation precedes over the amidic bond cleavage (Figure IV.3.2). It is worthy to mention that, the alkyne annulations reported till date often involves C–H/N–H, C–H/O–H, and C–H/N–O bond cleavages.[2b] To the best of our knowledge, this is the only example of alkyne annulation via C–H/S–H bond functionalization leading to the first synthesis of thiopyrano[2,3,4-*de*]quinolines (Scheme IV.2.13).

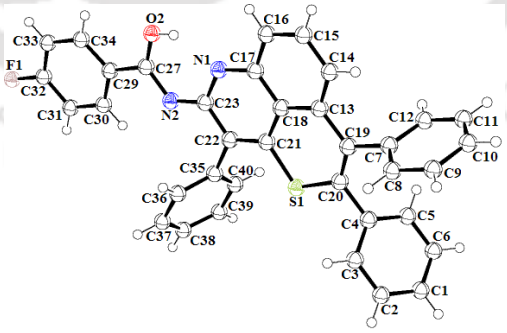


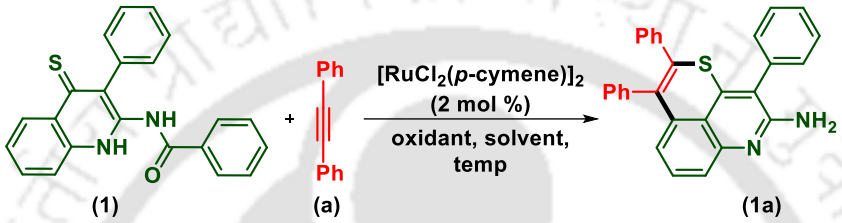
Figure IV.3.2. *Ortep view of* ***(17a)***

Quinoline and quinoline-fused polyheterocycles are important building blocks in natural products, agrochemicals, material chemistry, and also useful as chiral ligands.[20] Among various quinoline derivatives, thiopyranoquinoline are of considerable interest as they exhibit significant pharmaceutical activities.[21] Molecules having thiopyranoquinoline

framework are reported to function as inhibitors of telomerase and are valuable for the treatment of cellular proliferation disorders.[22] Considering the importance of quinoline-fused thiopyran ring system, the present synthetic protocol would render the generation of thiopyrano[2,3,4-*de*]quinoline moiety with potential application in diverse field of research.

Optimization of Reaction Conditions:

Table IV.3.1. *Screening of the reaction conditions*[a]



Entry	Oxidant (equiv)	Solvent	Yield (%)[e]
1	AgOAc (1)	AcOH	55
2	$AgSbF_6$ (1)	AcOH	45
3	Ag_2CO_3 (1)	AcOH	23
4	$CuBr_2$ (1)	AcOH	17
5	$Cu(OAc)_2$ (1)	AcOH	57
6	$Cu(OAc)_2.H_2O$ (1)	AcOH	69
7	**$Cu(OAc)_2.H_2O$ (2)**	**AcOH**	**81**
8	$Cu(OAc)_2.H_2O$ (2)	t-AmOH	21
9	$Cu(OAc)_2.H_2O$ (2)	DMF	00
10	$Cu(OAc)_2.H_2O$ (2)	DMSO	00
11	$Cu(OAc)_2.H_2O$ (2)	DCE	19
12[b]	$Cu(OAc)_2.H_2O$ (2)	AcOH	00
13	-	AcOH	9
14[c]	$Cu(OAc)_2.H_2O$ (2)	AcOH	78
15[d]	$Cu(OAc)_2.H_2O$ (2)	AcOH	57

[a]Reaction conditions: 0.25 mmol of (**1**), 0.25 mmol of (**a**), $[RuCl_2(p\text{-cymene})]_2$ (2 mol %), oxidant (equiv) and solvent (2 mL) under air at 110 °C for 12 h. [b]Reaction in the absence of catalyst. [c]Reaction at 130 °C. [d]Reaction at 90 °C. [e]Isolated yield.

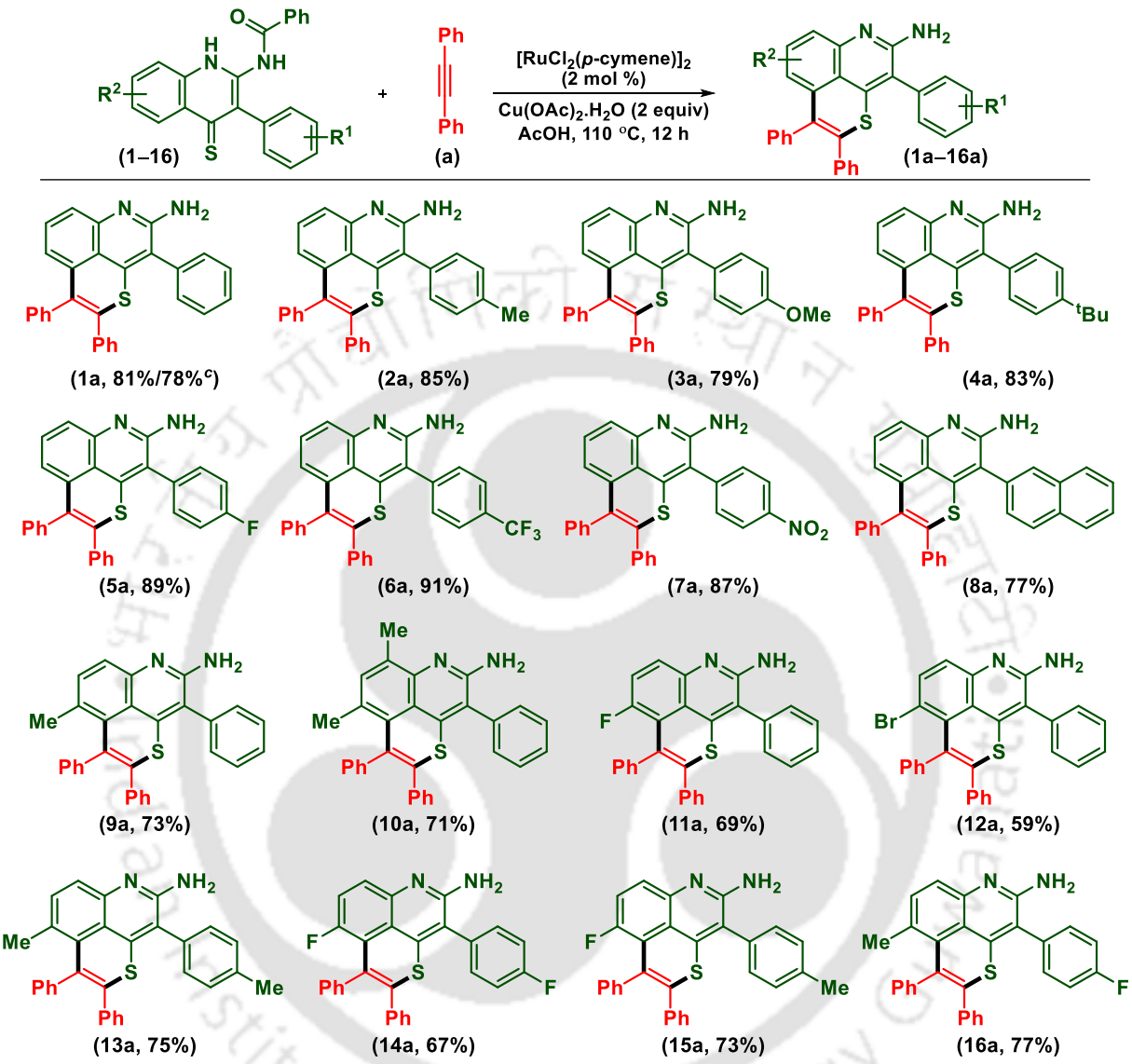
Encouraged by the unprecedented thiocarbonyl directed annulation via C–H/S–H bond cleavage, further optimizations were carried out to enhance the yield of the desired product. Among various oxidants, $Cu(OAc)_2.H_2O$ gave the best yield of 69% compared to other silver and copper salts such as AgOAc (55%), $AgSbF_6$ (45%), Ag_2CO_3 (23%), $CuBr_2$ (17%), $Cu(OAc)_2$ (57%) (Table IV.3.1, entries 1–6) examined. The product yield further improved to 81% by doubling the oxidant loading i.e. 2 equiv (Table IV.3.1, entry 7).

Screening of other polar [t-AmOH (21%), DMF (00%), DMSO (00%)] and non-polar [DCE (19%)] solvents (Table IV.3.1, entries 8–11), were all found to be less efficient to that of AcOH used initially. The reaction in the absence of $[RuCl_2(p\text{-cymene})]_2$ fail to give any trace of the product (Table IV.3.1, entry 12) whereas, in the absence of $Cu(OAc)_2.H_2O$ a meagre yield of 9% was obtained (Table IV.3.1, entry 13) suggesting the cooperative participation of both. Reactions performed at higher (130 ^oC) as well as lower temperature (90 ^oC) did not turn out to be beneficial (Table IV.3.1, entries 14 and 15).

Substrate Scope for C–H/S–H Annulation:

After establishing the optimized annulation strategy {$[RuCl_2(p\text{-cymene})]_2$ (2 mol%), $Cu(OAc)_2.H_2O$ (2 equiv) in AcOH (2 mL) under air at 110 ^oC}, we probed the diversity of this oxidative annulation by employing various decorated quinoline-4(1*H*)-thiones with diphenylacetylene (**a**). Gratifyingly, the present protocol proceeded well with a variety of *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamides (**1**–**16**) giving good to excellent yields of thiopyrano[2,3,4-*de*]quinolines (**1a**–**16a**) (Scheme IV.3.1). At first the effect of substituents R^1 present on the 3-aryl ring of quinoline-4(1*H*)-thiones (**1**–**7**) were examined (Scheme IV.3.1). 3-Aryl ring of quinoline-4(1*H*)-thiones bearing electron-donating groups such as *p*-Me (**2**), *p*-OMe (**3**), and *p*-^{t}Bu (**4**) all gave identical yields of their products (**2a**, 85%), (**3a**, 79%), and (**4a**, 83%) respectively, compared to that of electron-neutral substrate (**1a**, 81%). However, a marginally better yields of product (**5a**, 89%), (**6a**, 91%), and (**7a**, 87%) were obtained for electron-withdrawing substituents such as *p*-F (**5**), *p*-CF_3 (**6**) and *p*-NO_2 (**7**). A naphthyl analogue (**8**) at the C-3 position underwent efficient reaction giving the annulated product (**8a**) in 77% yield. Next the effect of substituents R^2 present on the phenyl ring attached to the pyridine-4(1*H*)-thione was evaluated (Scheme IV.3.1).

Scheme IV.3.1. *Substrate scope of various quinoline-4(1H)-thiones with diphenylacetylene*[a–c]

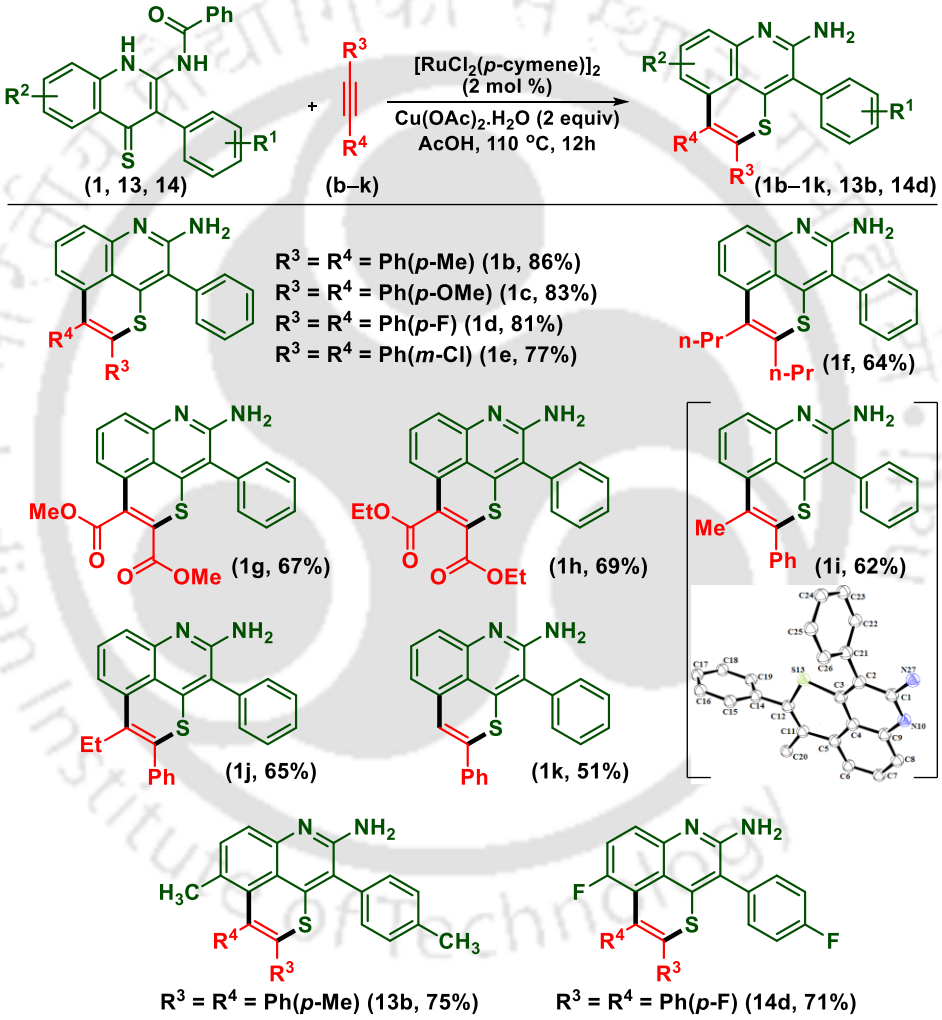


[a]Reaction conditions: 0.25 mmol of (**1**–**16**), 0.25 mmol of (**a**), $[RuCl_2(p\text{-cymene})]_2$ (2 mol %), $Cu(OAc)_2.H_2O$ (2 equiv) and AcOH (2 mL) under air at 110 °C for 12h. [b]Isolated yield. [c]1 mmol scale

The presence of electron-donating [6-Me (**9**) and 6,8-di-Me (**10**)] and electron-withdrawing [6-F (**11**) and 6-Br (**12**)] groups all gave moderate yields of their respective product (**9a**, 73%), (**10a**, 71%), (**11a**, 69%), and (**12a**, 59%). The lower yields of product obtained both for EDG and EWG could be due the steric hindrance imparted by these groups present at the C-6 position. Usually phenyl rings having *meta* substitutions undergo chelation from the sterically less hindered C–H sites. However, in the present scenario annulation takes place selectively at the more hindered site of quinoline-4(1*H*)-thione as

demonstrated for substrates **9**–**12** (Scheme IV.3.1). This result further endorses the preferential C–H/S–H annulation over other annulation pathway (C–H/N–H) even under constraint conditions. Reactions of quinoline-4(1*H*)-thiones (**13**–**16**) having substituents R^1 and R^2 in their respective rings were also examined with diphenylacetylene (**a**) as the annulating partner. Satisfyingly, all gave their products [**13a** (75%), **14a** (67%), **15a** (73%), and **16a** (77%)] in good yields (Scheme IV.3.1).

Scheme IV.3.2. *Substrate scope of quinoline-4(1H)-thiones with various alkynes*[a,b]



[a]Reaction conditions: 0.25 mmol of (**1**, **13**, **14**), 0.25 mmol of (**b–k**), $[RuCl_2(p\text{-cymene})]_2$ (2 mol %), $Cu(OAc)_2.H_2O$ (2 equiv) and AcOH (2 mL) under air at 110 °C for 12h. [b]Isolated yield.

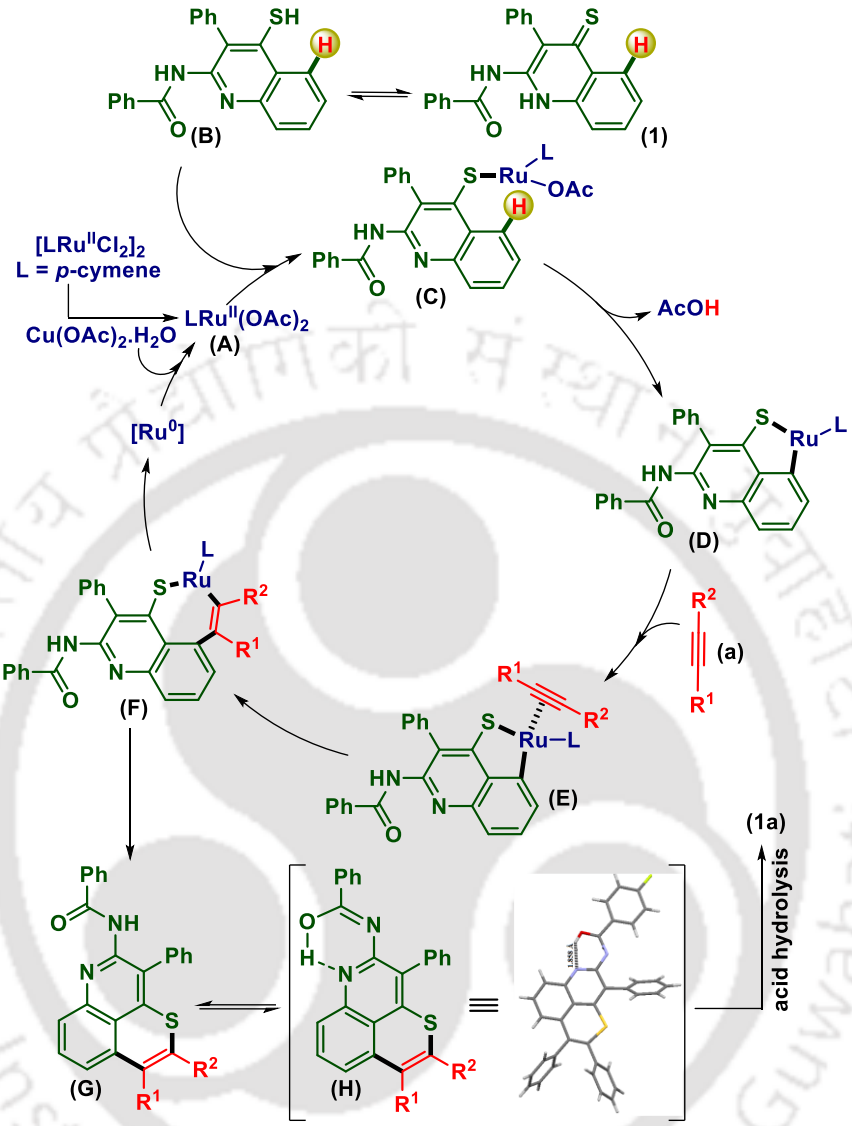
The scope of this thiocarbonyl directed annulation was than extended to other symmetrical alkynes (**b**–**h**) using *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (**1**) as the coupling partner (Scheme IV.3.2). Symmetrical 1,2-diarylacetylene bearing electron-donating substituents such as *p*-Me (**b**) and *p*-OMe (**c**)

gave good yields of their respective annulated product (**1b**, 86%) and (**1c**, 83%). Similarly, alkynes possessing electron-withdrawing substituents such as *p*-F (**d**) and *m*-Cl (**e**) furnished their corresponding annulated product (**1d**, 81%) and (**1e**, 77%) respectively in decent yields. Aliphatic symmetrical internal alkynes such as 4-octyne (**f**), dimethylacetylene dicarboxylate (**g**), and diethylacetylene dicarboxylate (**h**) underwent efficient coupling with (**1**) to produce their desired products (**1f**, 64%), (**1g**, 67%), and (**1h**, 69%) in moderate yields. All the alkynes examined in Scheme IV.3.1 and IV.3.2 are symmetrical in nature.

Now the question arises, whether unsymmetrical alkynes will give a mixture of regioisomeric products or will it provide exclusively a single regioisomer? To find an answer to this, coupling of (**1**) was performed with unsymmetrical alkyne 1-phenyl-1-propyne (**i**) under otherwise identical condition. A single regioisomeric product (**1i**) was isolated in 62% yield in which the benzylic carbon is attached to the sulfur atom (Scheme IV.3.2). The structure of the regioisomer (**1i**) was further confirmed by X-ray crystallography (Scheme IV.3.2). Similarly, another unsymmetrical alkyne, 1-phenyl-1-butyne (**j**) also afforded exclusively single regioisomeric product (**1j**) in 65% yield. Further, to check the feasibility of the present annulation with terminal alkynes, reaction of (**1**) was performed with phenylacetylene (**k**). To our delight, the reaction underwent smoothly giving (**1k)**, in a lesser yield of 51% (Scheme IV.3.2). Highly functionalized thiopyrano[2,3,4-*de*]quinolones (**13b**) and (**14d**) could be obtained in decent yields of 75% and 71% by coupling quinolone-4(1*H*)-thiones (**13**) and (**14**) with symmetrical electron-donating (*p*-Me) (**b**) and electron-withdrawing (*p*-F) (**d**) alkynes.

Based on literature reports,[3,19] a plausible reaction mechanism has been proposed in Scheme IV.3.3 for the formation of thiopyrano[2,3,4-*de*]quinolines (**1a**). At first, the active Ru(II) catalyst (**A**) originates via the exchange of chloride ligand from $[RuCl_2(p\text{-cymene})]_2$ with acetate ion of $Cu(OAc)_2.H_2O$. Quinoline-4(1*H*)-thione (**1**) undergoes aromatization in the reaction medium to form (**B**) for favourable metal coordination.

Scheme IV.3.3. *Plausible reaction mechanism*



The active Ru(II) catalyst (**A**) than binds to the S-directing site in (**B**) forming intermediate (**C**). Next, the proximal C–H in intermediate (**C**) forms a five-membered ruthenacycle intermediate (**D**) via C–H activation. The alkyne (**a**) gets attached to (**D**) forming intermediate (**E**). At this point, regioselective migratory insertion of the alkyne into C–Ru bond affords a seven-membered Ru(II) species (**F**). In order to account for the regioselectivity in unsymmetrical alkynes (**i**–**k**), the C–Ru bond formation is more likely to be at the carbon having higher electron density. The intermediate (**F**) undergoes reductive elimination to give the annulated product (**G**) and subsequently generates Ru(0). Further, Ru(0) is oxidized to Ru(II) in the presence of Cu(OAc)$_2$.H$_2$O. Interestingly, the amidic form (**G**) tautomerizes to its less stable imine form (**H**) due to the favourable

intramolecular H-bonding with the ring nitrogen. The structure of the intramolecular H-bonded intermediate (**H**) has been confirmed by X-ray crystallography analysis for one of the derivative (**17a**) (Scheme IV.3.3 and Figure IV.3.2). Finally, the imine form (**H**) which is more susceptible to hydrolysis undergoes acidic hydrolytic cleavage in the presence of AcOH to afford the annulated product (**1a**) via the loss of a –COPh group.

In summary, we have demonstrated the first thiocarbonyl directed regiospecific annulation of alkynes with quinoline-4(1*H*)-thiones. In a multi-directed sites *viz.* C–H/N–H and C–H/O–H, the C–H/S–H annulation is preferred even under a constraint environment. Terminal and unsymmetrical alkynes, gave single regioisomeric product. Thus, thiopyrano[2,3,4-*de*]quinolines could be conveniently synthesized via the coupling of quinoline-4(1*H*)-thiones with internal or terminal alkynes.

IV.4. Experimental Section

IV.4.1. General Information: All the compounds were commercial grade and used without further purification. Organic extract was dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduce pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as internal standard for proton NMR (400 and 600 MHz) and $CDCl_3$ solvent as internal standard for ^{13}C NMR (100 and 150 MHz). HRMS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat.

IV.4.2. Crystallographic Description

CCDC Number for Compounds (**1a**): CCDC-1845622; (**1i**): CCDC-1845623; (**17a**): CCDC-1845624. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystallographic Description of 3,5,6-Triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (1a): $C_{29}H_{20}N_2S$, crystal dimensions 0.28 x 0.21 x 0.16 mm, M_r = 428.53, Triclinic, space group P -1, a = 9.187(6), b = 9.949(6), c = 12.343(8)Å, α = 91.660^o (7), β = 98.507^o (7), γ = 98.502^o (5), V = 1101.9(12) Å^3, Z = 2, ρ_{calcd} = 1.291g/cm^3, μ = 0.166 mm^{-1}, F(000)= 448.0, reflection collected / unique = 3882 / 3167, refinement method = full-matrix least-

squares on F^2, final *R* indices [$I > 2\sigma(I)$]: R_1 = 0.0521, wR_2 = 0.1403, *R* indices (all data): R_1 = 0.0397, wR_2 = 0.1237, goodness of fit = 0.985.

Crystallographic Description of 6-Methyl-3,5-diphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (1i): $C_{24}H_{18}N_2S$, crystal dimensions 0.28 x 0.25 x 0.19 mm, M_r = 366.46, monoclinic, space group C 2/c, a = 20.9441(11), b = 10.3740(5), c = 18.3411(9) Å, α = 90°, β = 109.429° (6), γ = 90°, V = 3758.1(4) Å^3, Z = 8, ρ_{calcd} = 1.295g/cm^3, μ = 0.183 mm^{-1}, F(000)= 1536.0, reflection collected / unique = 4277 / 3018, refinement method = full-matrix least-squares on F^2, final *R* indices [$I > 2\sigma(I)$]: R_1 = 0.0759, wR_2 = 0.1464, *R* indices (all data): R_1 = 0.0501, wR_2 = 0.1264, goodness of fit = 1.067.

Crystallographic Description of 4-Fluoro-*N*-(3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-yl)benzamide (17a): $C_{36}H_{23}FN_2OS$, crystal dimensions 0.28 x 0.22 x 0.16 mm, M_r = 550.62, triclinic, space group P -1, a = 9.6192(4), b = 10.1084(4), c = 16.1049(6) Å, α = 92.110° (3), β = 90.093° (2), γ = 117.368° (2), V = 1389.43(10) Å^3, Z = 2, ρ_{calcd} = 1.316g/cm^3, μ = 0.156 mm^{-1}, F(000) = 572.0, reflection collected / unique = 4886 / 3374, refinement method = full-matrix least-squares on F^2, final *R* indices [$I > 2\sigma(I)$]: R_1 = 0.0741, wR_2 = 0.1685, *R* indices (all data): R_1 = 0.0494, wR_2 = 0.1497, goodness of fit = 1.081.

IV.4.3. General Procedure for the Synthesis of Starting Substrates: Compounds **1**–**17** were synthesized as per the following the method described in chapter III.

IV.4.4. General Procedure for the Synthesis of 3,5,6-Triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (1a): In an oven dried round bottom flask, *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (**1**) (0.25 mmol, 89 mg), diphenylacetylene (**a**) (0.25 mmol, 45 mg), [$RuCl_2$(*p*-cymene)]$_2$ (0.005 mmol, 3 mg), $Cu(OAc)_2.H_2O$ (0.5 mmol, 100 mg) were taken in 2 mL of AcOH and was stirred on a preheated oil bath at 110 °C for 12 h. After the completion of the reaction (as indicated by the TLC), the crude mixture was admixed with ethyl acetate (20 mL). The organic layer was washed successively with saturated solution of sodium bicarbonate (2 x 5 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuum. The crude product obtained was purified using column chromatography and eluted with 1:3 ethyl acetate:hexane to afford the corresponding product 3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (**1a**) (87 mg, 81%).

IV.4.5. General Procedure for the Synthesis and Isolation of Intermediate (*Z*)-4-Fluoro-*N*-(3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-yl)benzimidic acid (17a): To an oven dried round bottom flask, 4-fluoro-*N*-(4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (**17**) (0.25 mmol, 75 mg), diphenylacetylene (**a**) (0.25 mmol, 45 mg), $[RuCl_2(p\text{-cymene})]_2$ (0.005 mmol, 3 mg), $Cu(OAc)_2.H_2O$ (0.5 mmol, 100 mg) were taken in 2 mL of AcOH and was stirred on a preheated oil bath at 110 ^oC. The TLC was checked after an interval of 20 minutes which indicated the formation of an intermediate along with the traces of product (**1a**). After a further period of 10 minutes the reaction was stopped and the crude mixture was admixed with ethyl acetate (20 mL) and the organic layer was washed successively with saturated solution of sodium bicarbonate (2 x 5 mL). The organic layer was separated, dried over anhydrous sodium sulfate and the solvent was evaporated in vacuum. The crude product obtained was purified using column chromatography and eluted with 1:4 ethyl acetate:hexane to afford the corresponding product (*Z*)-4-fluoro-*N*-(3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-yl)benzimidic acid (**17a**) (82 mg, 59%).

IV.5. References

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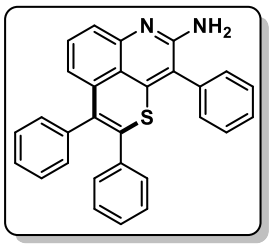
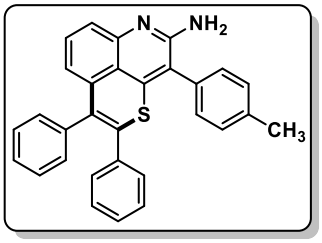
IV.6. Spectral Data

3,5,6-Triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (1a):



Brown solid (87 mg, 81%); mp 280–282 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 4.47 (s, 2H), 6.42 (d, 1H, *J* = 6.6 Hz), 6.95–6.99 (m, 7H), 7.08 (t, 1H, *J* = 7.2 Hz), 7.14 (t, 2H, *J* = 7.2 Hz), 7.19 (t, 1H, *J* = 7.8 Hz), 7.28 (d, 2H, *J* = 7.2 Hz), 7.31 (d, 1H, *J* = 8.4 Hz), 7.34 (t, 1H, *J* = 7.2 Hz), 7.45 (t, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 114.7, 119.3, 120.1, 124.9, 127.2, 128.0, 128.1, 128.6, 129.1, 129.6, 130.0, 130.5, 130.6, 130.9, 131.9, 133.2, 134.4, 134.9, 137.7, 138.1, 144.4, 148.4, 154.8; IR (KBr): 3485, 3288, 2925, 2849, 1632, 1548, 1477, 1413, 1341, 1072, 816, 744, 701 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{21}N_2S^+$ [M + H^+] 429.1420; found 429.1434.

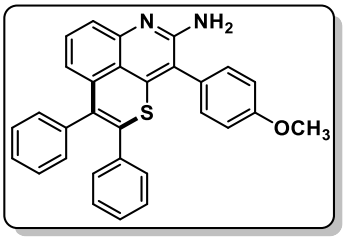
5,6-Diphenyl-3-(*p*-tolyl)thiopyrano[2,3,4-*de*]quinolin-2-amine (2a):



Brown solid (94 mg, 85%); mp 286–288 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 2.39 (s, 3H), 4.52 (s, 2H), 6.49 (d, 1H, *J* = 7.2 Hz), 7.03–7.07 (m, 7H), 7.16 (t, 1H, *J* = 7.2 Hz), 7.21–7.24 (m, 4H), 7.25–7.28 (m, 1H); 7.33 (d, 2H, *J* = 8.4 Hz), 7.38 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.6, 114.7, 119.3, 120.1, 124.9, 127.2, 127.9, 128.1, 128.6, 129.7, 129.8, 130.4, 130.9, 131.3, 131.8, 131.9 133.1, 134.4, 137.8, 138.1, 139.0, 144.4, 148.4, 154.9; IR (KBr): 3470, 3390, 3280, 2921, 2851, 1634, 1550, 1479, 1417, 1349, 1263, 814,

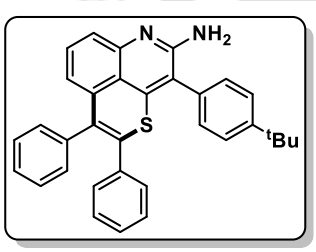
742, 699 cm^{-1}; HRMS (ESI): calcd. for $C_{30}H_{23}N_2S^+$ [M + H^+] 443.1576; found 443.1576.

3-(4-Methoxyphenyl)-5,6-diphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (3a):



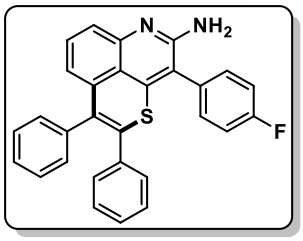
Brown solid (91 mg, 79%); mp 318–320 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 3.84 (s, 3H), 4.54 (s, 2H), 6.50 (d, 1H, *J* = 7.8 Hz), 7.03–7.07 (m, 9H), 7.16 (t, 1H, *J* = 7.2 Hz), 7.22 (t, 2H, *J* = 7.8 Hz), 7.27–7.28 (m, 3H); 7.39 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.5, 114.4, 116.1, 119.4, 120.1, 124.9, 126.8, 127.2, 128.0, 128.1, 128.6, 129.7, 130.5, 131.0, 131.3, 132.0, 133.1, 134.4, 137.8, 138.1, 144.9, 148.2, 155.1, 160.1; IR (KBr): 3491, 3286, 3146, 3044, 2927, 2832, 1626, 1604, 1563, 1546, 1509, 1479, 1419,1343, 1284, 1247, 1171, 1035, 1021, 814, 740, 693 cm^{-1}; HRMS (ESI): calcd. for $C_{30}H_{23}N_2OS^+$ [M + H^+] 459.1526; found 459.1520.

3-(4-(*tert*-Butyl)phenyl)-5,6-diphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (4a):



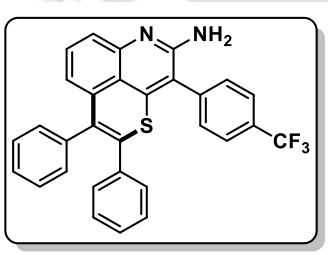
Brown solid (100 mg, 83%); mp 356–358 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.34 (s, 9H), 4.49 (s, 2H), 6.49 (d, 1H, *J* = 8.4 Hz), 7.05–7.08 (m, 7H), 7.16 (t, 1H, *J* = 7.2 Hz), 7.22 (t, 2H, *J* = 7.2 Hz), 7.26–7.28 (m, 3H), 7.38 (d, 1H, *J* = 9.0 Hz), 7.53 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 31.5, 34.9, 114.8, 119.4, 120.1, 124.9, 127.2, 127.5, 128.0, 128.2, 128.6, 129.5, 129.7, 130.4, 131.0, 131.7, 132.0, 133.2, 134.4, 137.9, 138.1, 144.5, 148.2, 152.1, 155.0; IR (KBr): 3480, 3286, 2923, 2850, 1631, 1552, 1478, 1345, 1075, 815, 743, 702, 645 cm^{-1}; HRMS (ESI): calcd. for $C_{33}H_{29}N_2S^+$ [M + H^+] 485.2046; found 485.2063.

3-(4-Fluorophenyl)-5,6-diphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (5a):



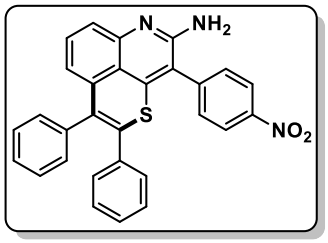
White solid (99 mg, 89%); mp 259–261 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 5.67 (s, 2H), 6.24 (dd, 1H, J_1 = 2.4 Hz, J_2 = 6.2 Hz), 7.05–7.08 (m, 3H), 7.09–7.13 (m, 4H), 7.18 (t, 1H, J = 7.2 Hz), 7.23–7.27 (m, 4H), 7.31–7.39 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 113.7, 117.2 (d, J = 33.2 Hz), 117.4, 118.6, 124.5, 127.1, 128.0, 128.1, 128.4, 129.1, 130.1, 130.5, 130.7 (d, J = 12.0 Hz), 130.8, 132.1 (d, J= 34.0 Hz), 132.4, 133.5, 137.1, 137.3, 142.0, 148.3, 155.3, 160.9, 163.4; ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -115.1 (s); IR (KBr): 3474, 3290, 2921, 2847, 1639, 1600, 1550, 1477, 1417, 1349, 1212, 1154, 1089, 818, 734, 699, 644 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{20}FN_2S^+$ [M + H$^+$] 447.1326; found 447.1346.

5,6-Diphenyl-3-(4-(trifluoromethyl)phenyl)thiopyrano[2,3,4-*de*]quinolin-2-amine (6a):



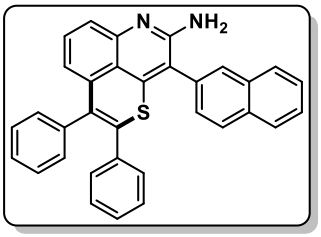
Yellow solid (113 mg, 91%); mp 324–326 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 4.48 (s, 2H), 6.54 (d, 1H, J = 7.8 Hz), 7.03–7.05 (m, 2H), 7.06–7.09 (m, 5H), 7.18 (t, 1H, J = 7.2 Hz), 7.23 (t, 2H, J = 7.2 Hz), 7.31 (t, 1H, J = 7.8 Hz), 7.40 (d, 1H, J = 7.8 Hz), 7.51 (d, 2H, J = 7.8 Hz), 7.80 (d, 2H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 120.4, 123.2, 124.9, 125.1, 127.4, 127.7 (q, J = 3.5 Hz), 128.20, 128.24, 128.6, 129.6, 130.86, 130.92, 131.2, 131.4, 131.5, 133.4, 134.3, 137.5, 137.8, 138.9, 144.7, 148.6, 154.2; ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -65.9 (s); IR (KBr): 3483, 3296, 2927, 2752, 2709, 1639, 1616, 1552, 1483, 1419, 1325, 1130, 1066, 1015, 908, 816, 738, 695 cm^{-1}; HRMS (ESI): calcd. for $C_{30}H_{20}F_3N_2S^+$ [M + H$^+$] 497.1294; found 497.1282.

3-(4-Nitrophenyl)-5,6-diphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (7a):



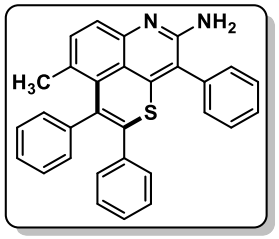
Orange solid (103 mg, 87%); mp 338–340 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 5.82 (s, 2H), 6.26 (d, 1H, *J* = 8.4 Hz), 7.05–7.15 (m, 7H), 7.19 (t, 1H, *J* = 7.6 Hz), 7.24–7.31 (m, 4H), 7.61 (d, 2H, *J* = 8.4 Hz), 8.37 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 112.9, 116.9, 118.8, 124.6, 125.5, 127.3, 127.4, 128.1, 128.2, 128.5, 129.2, 130.5, 131.8, 132.6, 133.5, 136.9, 137.2, 141.6, 141.8, 147.6, 148.6, 154.7; IR (KBr): 3489, 3380, 2925, 2855, 1606, 1557, 1513, 1470, 1415, 1345, 955, 818, 742, 697 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{20}N_3O_2S^+$ [M + H$^+$] 474.1271; found 474.1278.

3-(Naphthalen-2-yl)-5,6-diphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (8a):



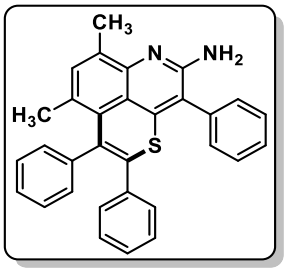
White solid (92 mg, 77%); mp 343–345 °C.^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 4.42 (s, 2H), 6.56 (d, 1H, *J* = 7.8 Hz), 6.94–6.97 (m, 2H), 6.98–7.00 (m, 3H), 7.08 (d, 2H, *J* = 7.8 Hz), 7.16 (t, 1H, *J* = 7.8 Hz), 7.21–7.23 (m, 2H), 7.34 (t, 1H, *J* = 7.8 Hz), 7.46–7.49 (m, 2H), 7.52–7.56 (m, 2H), 7.61 (t, 1H, *J* = 7.2 Hz), 7.75 (d, 1H, *J* = 8.4 Hz), 7.93 (t, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 112.6, 119.3, 120.2, 124.5, 124.9, 126.93, 126.98, 127.26, 127.32, 127.9, 128.1, 128.59, 128.62, 128.7, 129.0, 129.6, 129.8, 130.7, 130.9, 131.0, 132.1, 132.3, 133.2, 134.5, 134.8, 137.6, 138.1, 145.8, 148.6, 155.2; IR (KBr): 3497, 3384, 3060, 2929, 2853, 1591, 1548, 1477, 1415, 1384, 1343, 1072, 816, 765, 697 cm^{-1}; HRMS (ESI): calcd. for $C_{33}H_{23}N_2S^+$ [M + H$^+$] 479.1576; found 479.1585.

7-Methyl-3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (9a):



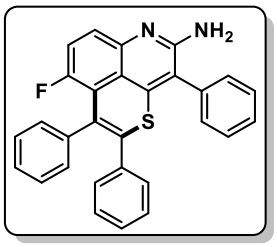
Brown solid (81 mg, 73%); mp 196–198 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.58 (s, 3H), 4.57 (s, 2H), 6.90–6.92 (m, 4H), 7.06–7.08 (m, 5H), 7.20 (d, 1H, *J* = 8.4 Hz), 7.32 (d, 2H, *J* = 7.2 Hz), 7.39 (t, 2H, *J* = 7.8 Hz), 7.50 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 23.8, 125.2, 126.5, 127.6, 127.86, 127.99, 128.2, 129.0, 129.39, 129.42, 130.0, 130.4, 130.8, 130.9, 131.9, 133.0, 133.6, 135.1, 136.5, 138.4, 140.9, 143.9, 146.2, 154.1; IR (KBr): 3471, 3389, 3278, 2924, 2850, 1630, 1555, 1478, 1415, 1350, 1070, 812, 745, 689 cm^{-1}; HRMS (ESI): calcd. for $C_{30}H_{23}N_2S^+$ [M + H^+] 443.1576; found 443.1599.

7,9-Dimethyl-3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (10a):



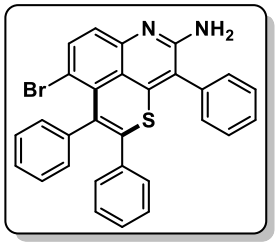
Yellow solid (81 mg, 71%); mp 246–248 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.58 (s, 3H), 2.54 (s, 3H), 4.48 (s, 2H), 6.91–6.93 (m, 4H), 7.06–7.08 (m, 6H), 7.12 (s, 1H), 7.33 (d, 2H, *J* = 7.2 Hz), 7.39 (t, 1H, *J* = 7.8 Hz), 7.50 (t, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 18.5, 23.7, 114.6, 121.5, 126.4, 127.4, 127.8, 128.1, 128.7, 128.9, 129.5, 129.9, 130.1, 130.3, 130.9, 131.6, 133.2, 133.7, 135.6, 136.7, 138.6, 141.3, 143.8, 145.0, 153.5; IR (KBr): 3477, 3376, 3284, 2919, 2853, 1602, 1542, 1483, 1423, 1029, 771, 717, 699 cm^{-1}; HRMS (ESI): calcd. for $C_{31}H_{25}N_2S^+$ [M + H^+] 457.1733; found 457.1753.

7-Fluoro-3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (11a):



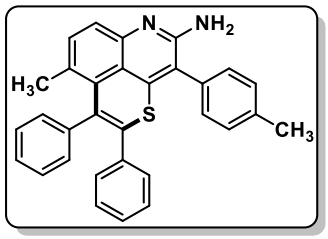
Brown solid (77 mg, 69%); mp 273–275 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 4.48 (s, 2H), 6.96–6.98 (m, 2H), 7.04–7.06 (m, 5H), 7.08–7.13 (m, 4H), 7.33 (d, 2H, *J* = 7.2 Hz), 7.39–7.43 (m, 2H), 7.53 (t, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 115.2, 119.2 (d, *J* = 7.2 Hz), 120.1 (d, *J* = 3.6 Hz), 121.5, 121.7, 126.6, 126.9 (d, *J* = 8.9 Hz), 127.6, 127.9, 128.1, 128.9 (d, *J* = 2.6 Hz), 129.3, 129.6, 129.79 (d, *J* = 4.4 Hz), 129.83, 130.6, 133.5, 134.7, 137.3, 139.8 (d, *J* = 4.7 Hz), 144.0 (d, *J* = 4.8 Hz), 145.1, 153.1, 154.3, 154.7; ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -114.5 (s); IR (KBr): 3470, 3327, 3210, 3050, 2927, 1618, 1569, 1485, 1433, 1368, 1200, 1025, 822, 740, 697 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{20}FN_2S^+$ [M + H^+] 447.1326; found 447.1344.

7-Bromo-3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (12a):



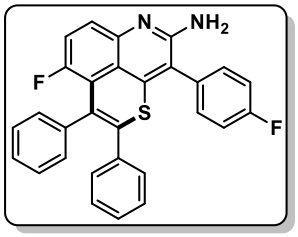
Yellow solid (75 mg, 59%); mp 246–248 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 4.54 (s, 2H), 6.89–6.92 (m, 4H), 7.06–7.09 (m, 6H), 7.29–7.33 (m, 3H), 7.41 (t, 1H, *J* = 7.2 Hz), 7.51 (t, 2H, *J* = 7.8 Hz), 7.58 (d, 1H, *J* = 9.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 114.7, 115.1, 122.9, 126.5, 126.7, 127.65, 127.69, 127.8, 128.1, 128.2, 129.22, 129.27, 129.31, 129.8, 130.6, 130.8, 131.6, 132.5, 132.8, 134.6, 135.3, 138.0, 138.3, 138.9, 143.3, 147.0, 154.6; IR (KBr): 3472, 3329, 3209, 3048, 2927, 2861, 1620, 1570, 1490, 1429, 1368, 1210, 1070, 825, 745, 694 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{20}BrN_2S^+$ [M + H^+] 507.0525; found 507.0544.

7-Methyl-5,6-diphenyl-3-(*p*-tolyl)thiopyrano[2,3,4-*de*]quinolin-2-amine (13a):



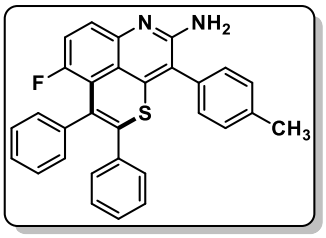
Yellow solid (86 mg, 75%); mp 243–245 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.58 (s, 3H), 2.37 (s, 3H), 4.52 (s, 2H), 6.91–6.93 (m, 4H), 7.06–7.08 (m, 6H), 7.19 (d, 1H, *J* = 9.0 Hz), 7.21 (d, 2H, *J* = 7.8 Hz), 7.30 (d, 2H, *J* = 7.8 Hz), 7.40 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.6, 23.8, 114.9, 121.8, 125.3, 126.5, 127.5, 127.8, 128.1, 129.2, 129.5, 129.8, 130.9, 131.1, 131.8, 132.1, 133.1, 133.5, 136.3, 138.5, 138.9, 141.0, 143.8, 146.4, 154.3; IR (KBr): 3478, 3378, 3284, 2920, 2854, 1612, 1564, 1485, 1070, 779, 698 cm^{-1}; HRMS (ESI): calcd. for $C_{31}H_{25}N_2S^+$ [M + H^+] 457.1733; found 457.1735.

7-Fluoro-3-(4-fluorophenyl)-5,6-diphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (14a):



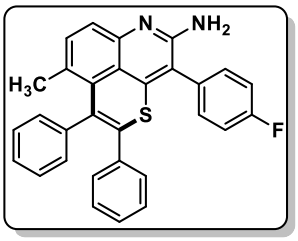
Brown solid (78 mg, 67%); mp 230–232 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 4.56 (s, 2H), 6.96–6.98 (m, 2H), 7.04 (d, 2H, *J* = 6.6 Hz), 7.07–7.08 (m, 3H), 7.10–7.13 (m, 2H), 7.22 (t, 2H, *J* = 9.0 Hz), 7.29–7.32 (m, 2H), 7.39–7.42 (m, 1H), 7.46 (t, 1H, *J* = 7.8 Hz), 7.82 (d, 1H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 114.1, 117.8, 117.9, 119.2 (d, *J* = 7.2 Hz), 121.7, 121.8, 126.6, 126.8 (d, *J* = 9.0 Hz), 127.5, 127.6, 128.0, 128.1, 128.8, 128.9, 129.6, 129.8 (d, *J* = 4.3 Hz), 130.4, 131.9 (d, *J* = 33.0 Hz), 132.2, 133.4, 137.2, 139.6 (d, *J* = 4.5 Hz), 144.9, 153.1, 154.3, 154.7, 162.3, 163.9; ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -114.8 (s), -114.2 (s); IR (KBr): 3475, 3288, 2924, 2875, 1642, 1610, 1556, 1480, 1420, 1350, 1158, 1090, 820, 750, 689 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{19}F_2N_2S^+$ [M + H^+] 465.1232; found 465.1229.

7-Fluoro-5,6-diphenyl-3-(*p*-tolyl)thiopyrano[2,3,4-*de*]quinolin-2-amine (15a):



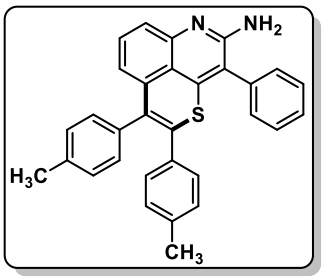
Orange solid (84 mg, 73%); mp 268–270 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 2.38 (s, 3H), 4.52 (s, 2H), 6.97–6.98 (m, 2H), 7.04–7.07 (m, 6H), 7.08–7.13 (m, 3H), 7.21 (d, 2H, *J* = 8.4 Hz), 7.33 (d, 2H, *J* = 7.8 Hz), 7.34–7.40 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.6, 115.2, 119.2 (d, *J* = 7.1 Hz), 120.1 (d, *J* = 3.8 Hz), 121.3, 121.5, 126.5, 126.9 (d, *J* = 9.0 Hz), 127.6, 127.9, 128.1, 128.8 (d, *J* = 2.7 Hz), 129.6 (d, *J* = 3.2 Hz), 129.8 (d, *J* = 4.4 Hz), 131.3, 131.6, 133.6, 137.3, 139.2, 139.8 (d, *J* = 4.5 Hz), 143.9 (d, *J* = 4.8 Hz), 145.1, 153.0, 154.5, 154.6; ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -114.6 (s); IR (KBr): 3485, 3294, 2923, 2855, 1634, 1571, 1544, 1454, 1407, 1195, 1019, 820, 742, 693 cm^{-1}; HRMS (ESI): calcd. for $C_{30}H_{22}FN_2S^+$ [M + H^+] 461.1482; found 461.1480.

3-(4-Fluorophenyl)-7-methyl-5,6-diphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (16a):



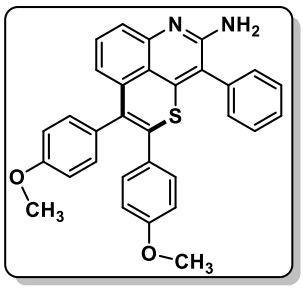
Yellow solid (89 mg, 77%); mp 248–250 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.58 (s, 3H), 4.47 (s, 2H), 6.90–6.92 (m, 4H), 7.07–7.09 (m, 6H), 7.18–7.21 (m, 3H), 7.29–7.32 (m, 2H), 7.41 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 23.8, 113.7, 117.5, 117.7, 121.7, 125.4, 126.6, 127.7, 127.9, 128.2, 129.4, 129.5, 130.9, 131.0 (d, *J* = 5.4 Hz), 131.8, 132.2 (d, *J* = 12.3 Hz), 132.8, 133.7, 136.6, 138.4, 140.9, 144.3, 146.5, 154.1, 161.8, 164.3; ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -115.3 (s); IR (KBr): 3470, 3288, 3058, 2972, 1634, 1604, 1571, 1491, 1435, 1228, 1157, 1029, 816, 742, 701, 609 cm^{-1}; HRMS (ESI): calcd. for $C_{30}H_{22}FN_2S^+$ [M + H^+] 461.1482; found 461.1484.

3-Phenyl-5,6-di-*p*-tolylthiopyrano[2,3,4-*de*]quinolin-2-amine (1b):



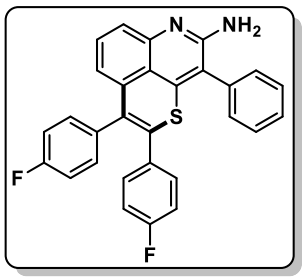
Brown solid (98 mg, 86%); mp 240–242 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 2.18 (s, 3H), 2.29 (s, 3H), 4.66 (s, 2H), 6.52 (d, 1H, *J* = 7.2 Hz), 6.88 (d, 2H, *J* = 7.8 Hz), 6.94–6.97 (m, 4H), 7.05 (d, 2H, *J* = 7.8 Hz), 7.35 (d, 3H, *J* = 7.8 Hz), 7.41 (t, 2H, *J* = 7.2 Hz), 7.52 (t, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.3, 21.4, 120.0, 124.6, 128.8, 128.9, 129.1, 129.2, 129.3, 129.4, 130.0, 130.4, 130.6, 130.8, 131.3, 131.7, 132.8, 134.7, 134.9, 135.1, 136.7, 137.7, 138.5, 139.4, 144.7, 148.3, 154.7; IR (KBr): 3470, 3290, 2960, 2918, 2835, 1620, 1602, 1544, 1510, 1460, 1410, 1285, 1250, 1168, 1020, 821, 745, 699 cm^{-1}; HRMS (ESI): calcd. for $C_{31}H_{25}N_2S^+$ [M + H^+] 457.1733; found 457.1735.

5,6-Bis(4-methoxyphenyl)-3-phenylthiopyrano[2,3,4-*de*]quinolin-2-amine (1c):



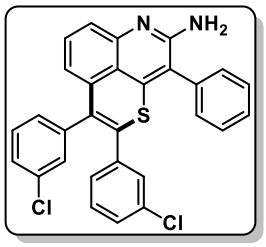
Orange solid (101 mg, 83%); mp 258–260 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 3.66 (s, 3H), 3.75 (s, 3H), 4.56 (s, 2H), 6.53 (d, 1H, *J* = 7.8 Hz), 6.59 (d, 2H, *J* = 9.0 Hz), 6.77 (d, 2H, *J* = 9.0 Hz), 6.96 (t, 4H, *J* = 9.0 Hz), 7.27 (t, 1H, *J* = 7.8 Hz), 7.34–7.36 (m, 3H), 7.41 (t, 1H, *J* = 7.8 Hz), 7.52 (t, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.26, 55.29, 113.5, 114.0, 114.6, 119.3, 119.9, 124.6, 129.1, 130.0, 130.2, 130.3, 130.5, 130.6, 130.8, 131.7, 132.0, 132.6, 134.85, 134.95, 144.6, 148.3, 154.8, 158.5, 159.0; IR (KBr): 3472, 3292, 2962, 2840, 1628, 1604, 1565, 1501, 1477, 1171, 1025, 813, 758, 736, 703 cm^{-1}; HRMS (ESI): calcd. for $C_{31}H_{25}N_2O_2S^+$ [M + H^+] 489.1631; found 489.1630.

5,6-Bis(4-fluorophenyl)-3-phenylthiopyrano[2,3,4-*de*]quinolin-2-amine (1d):



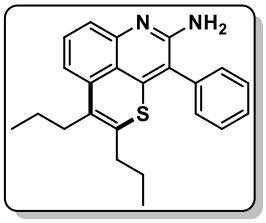
Yellow solid (94 mg, 81%); mp 303–305 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 4.55 (s, 2H), 6.46 (d, 1H, *J* = 7.8 Hz), 6.78 (t, 2H, *J* = 8.4 Hz), 6.94 (t, 2H, *J* = 9.0 Hz), 6.98–7.02 (m, 4H), 7.29 (t, 1H, *J* = 8.4 Hz), 7.34 (d, 2H, *J* = 7.2 Hz), 7.40–7.45 (m, 2H), 7.55 (t, 2H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 115.4 (d, *J* = 21.6), 115.8 (d, *J* = 21.3), 120.1, 125.2, 129.3, 129.9, 130.6, 130.7, 131.4, 131.5 (d, *J* = 8.3 Hz), 132.6 (d, *J* = 7.9 Hz), 133.5 (d, *J* = 3.3 Hz), 133.7 (d, *J* = 3.5 Hz), 134.1, 134.7, 144.1, 148.3, 154.8, 161.2, 161.4, 162.8, 163.1; ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -117.7 (s), -115.9 (s); IR (KBr): 3470, 3290, 2750, 2707, 1630, 1602, 1550, 1503, 1479, 1347, 1216, 1154, 1015, 964, 822, 738, 703, 549 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{19}F_2N_2S^+$ [M + H^+] 465.1232; found 465.1233.

5,6-Bis(3-chlorophenyl)-3-phenylthiopyrano[2,3,4-*de*]quinolin-2-amine (1e):



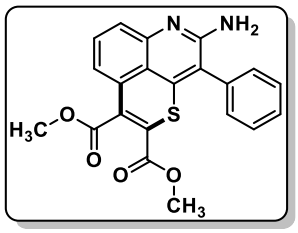
White solid (96 mg, 77%); mp 272–274 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 4.57 (s, 2H), 6.44 (d, 1H, *J* = 7.8 Hz), 6.89 (d, 1H, *J* = 7.8 Hz), 6.94–6.96 (m, 1H), 7.02 (t, 1H, *J* = 7.8 Hz), 7.06–7.09 (m, 3H), 7.18–7.19 (m, 2H), 7.29 (t, 1H, *J* = 7.8 Hz), 7.35 (t, 2H, *J* = 6.0 Hz), 7.41–7.46 (m, 2H), 7.55 (t, 2H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 120.2, 125.6, 127.8, 127.9, 128.5, 129.2, 129.3, 129.46, 129.56, 129.63, 129.88, 129.91, 130.1, 130.5, 130.7, 130.8, 131.1, 132.4, 133.5, 134.2, 134.5, 134.6, 138.9, 139.5, 143.6, 148.4, 154.9; IR (KBr): 3462, 3288, 2921, 2849, 1630, 1552, 1481, 1421, 1345, 1159, 818, 775, 701 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{19}Cl_2N_2S^+$ [M + H^+] 497.0641; found 497.0656.

3-Phenyl-5,6-dipropylthiopyrano[2,3,4-*de*]quinolin-2-amine (1f):



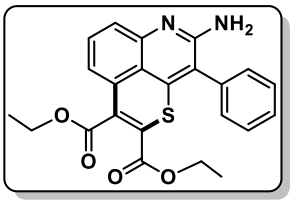
Brown solid (58 mg, 64%); mp 162–164 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 0.93 (t, 3H, *J* = 7.2 Hz), 1.04 (t, 3H, *J* = 7.2 Hz), 1.49–1.59 (m, 4H), 2.28 (t, 2H, *J* = 7.8 Hz), 2.54 (t, 2H, *J* = 7.8 Hz), 4.52 (s, 2H), 7.03 (d, 1H, *J* = 7.8 Hz), 7.31 (d, 2H, *J* = 6.6 Hz), 7.37 (d, 1H, *J* = 8.4 Hz), 7.43–7.48 (m, 2H), 7.56 (t, 2H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 14.2, 14.6, 21.8, 23.2, 31.1, 36.5, 114.3, 116.2, 119.5, 123.8, 128.4, 129.0, 130.1, 130.5, 130.7, 130.8, 133.1, 135.2, 144.6, 148.3, 154.3; IR (KBr): 3477, 3294, 2953, 2871, 1637, 1557, 1477, 1419, 1347, 1146, 1019, 814, 730, 695 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{25}N_2S^+$ [M + H^+] 361.1733; found 361.1734.

Dimethyl 2-amino-3-phenylthiopyrano[2,3,4-*de*]quinoline-5,6-dicarboxylate (1g):



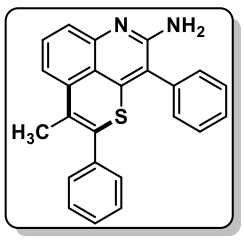
Orange solid (66 mg, 67%); mp 230–232 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 3.76 (s, 3H), 3.96 (s, 3H), 4.62 (s, 2H), 6.82 (d, 1H, *J* = 7.2 Hz), 7.30 (d, 2H, *J* = 7.2 Hz), 7.42 (t, 1H, *J* = 7.8 Hz), 7.48–7.51 (m, 2H), 7.59 (t, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 53.2, 53.5, 116.5, 119.4, 120.6, 122.7, 128.5, 128.6, 129.6, 129.7, 130.7, 130.9, 134.1, 136.9, 142.1, 148.2, 155.3, 162.4, 168.0; IR (KBr): 3458, 3284, 2947, 1745, 1721, 1632, 1595, 1479, 1431, 1243, 1210, 1171, 1118, 1033, 771, 707 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{17}N_2O_4S^+$ [M + H^+] 393.0904; found 393.0904.

Diethyl 2-amino-3-phenylthiopyrano[2,3,4-*de*]quinoline-5,6-dicarboxylate (1h):



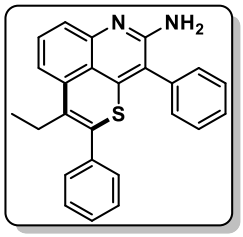
Yellow solid (72 mg, 69%); mp 195–197 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.25 (t, 3H, *J* = 7.2 Hz), 1.39 (t, 3H, *J* = 7.2 Hz), 4.23 (q, 2H, *J* = 7.2 Hz), 4.43 (q, 2H, *J* = 7.2 Hz), 4.68 (s, 2H), 6.85 (d, 1H, *J* = 7.8 Hz), 7.29 (d, 2H, *J* = 7.8 Hz), 7.41 (t, 1H, *J* = 7.8 Hz), 7.48 (d, 2H, *J* = 7.8 Hz), 7.58 (t, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 14.2, 62.3, 62.8, 116.4, 119.4, 120.4, 123.3, 128.2, 128.8, 129.5, 129.7, 130.7, 130.8, 134.1, 136.5, 142.3, 148.2, 155.3, 162.0, 167.5; IR (KBr): 3462, 3292, 3093, 2933, 1735, 1719, 1637, 1604, 1559, 1481, 1429, 1234, 1029, 814, 765, 699 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{21}N_2O_4S^+$ [M + H^+] 421.1217; found 421.1215.

6-Methyl-3,5-diphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (1i):



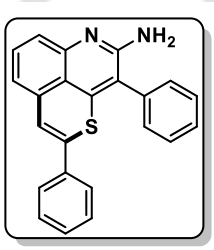
Brown solid (57 mg, 62%); mp 275–277 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.99 (s, 3H), 4.64 (s, 2H), 7.12 (d, 1H, *J* = 7.8 Hz), 7.25–7.27 (m, 2H), 7.31–7.37 (m, 5H), 7.41 (t, 1H, *J* = 7.2 Hz), 7.49–7.53 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 17.5, 114.3, 116.9, 119.1, 124.6, 125.1, 128.7, 128.8, 129.1, 129.7, 130.0, 130.4, 130.6, 130.8, 133.8, 134.8, 138.3, 144.7, 148.0, 154.5; IR (KBr): 3477, 3288, 2919, 2863, 2752, 1637, 1552, 1479, 1415, 1347, 1177, 1035, 812, 752, 695 cm^{-1}; HRMS (ESI): calcd. for $C_{24}H_{19}N_2S^+$ [M + H^+] 367.1263; found 367.1272.

6-Ethyl-3,5-diphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (1j):



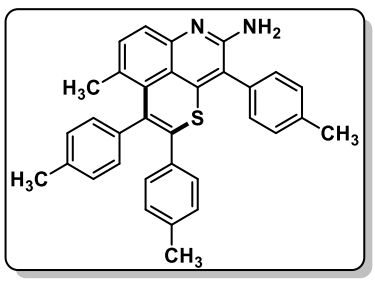
Brown solid (62 mg, 65%); mp 260–262 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.07 (t, 3H, *J* = 7.2 Hz), 2.44 (q, 2H, *J* = 7.8 Hz), 4.58 (s, 2H), 7.15 (d, 1H, *J* = 7.8 Hz), 7.25 (d, 2H, *J* = 6.6 Hz), 7.30 (d, 2H, *J* = 6.6 Hz), 7.32–7.36 (m, 3H), 7.39 (t, 1H, *J* = 7.2 Hz), 7.45 (d, 1H, *J* = 8.4 Hz), 7.50 (t, 3H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.6, 23.3, 116.9, 124.6, 128.6, 128.9, 129.1, 129.3, 130.0, 130.1, 130.4, 130.55, 130.59, 130.7, 131.2, 132.2, 134.9, 138.2, 144.6, 148.5, 154.5; IR (KBr): 3472, 3285, 2922, 2860, 2750, 1630, 1545, 1467, 1247, 1175, 1025, 801, 734, 694 cm^{-1}; HRMS (ESI): calcd. for $C_{25}H_{21}N_2S^+$ [M + H^+] 381.1420; found 381.1434.

3,5-Diphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (1k):



Brown solid (45 mg, 51%); mp 149–151 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 4.65 (s, 2H), 6.87 (d, 1H, *J* = 6.6 Hz), 6.91 (s, 1H), 7.33–7.36 (m, 5H), 7.37–7.42 (m, 2H), 7.44–7.48 (m, 3H), 7.57 (t, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 115.5, 118.4, 120.7, 121.9, 124.6, 126.1, 128.9, 129.25, 129.29, 129.9, 130.7, 131.1, 133.1, 133.9, 134.8, 137.5, 145.3, 147.6, 155.1; IR (KBr): 3472, 3280, 2915, 2864, 2754, 1625, 1555, 1477, 1247, 1077, 745, 715, 674 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{17}N_2S^+$ [M + H^+] 353.1107; found 353.1118.

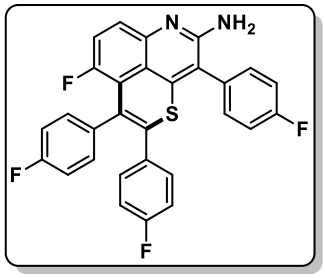
7-Methyl-3,5,6-tri-*p*-tolylthiopyrano[2,3,4-*de*]quinolin-2-amine (13b):



White solid (91 mg, 75%); mp 274–276 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.58 (s, 3H), 2.20 (s, 3H), 2.25 (s, 3H), 2.36 (s, 3H), 4.53 (s, 2H), 6.79 (t, 4H, *J* = 8.4 Hz), 6.88–6.89 (m, 4H), 7.18 (t, 3H, *J* = 7.8 Hz), 7.28 (d, 2H, *J* = 8.4 Hz), 7.39 (d, 1H, *J* = 9.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.39, 21.40, 21.6, 23.8, 114.7, 121.8,

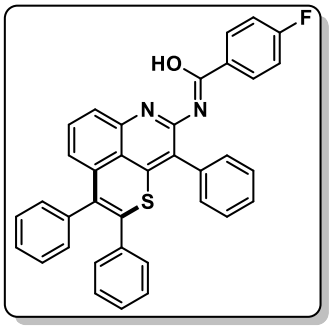
124.9, 128.6, 128.9, 129.2, 129.3, 129.8, 130.7, 131.1, 132.1, 132.3, 132.8, 133.3, 135.7, 135.9, 136.4, 137.2, 137.9, 138.8, 144.2, 146.1, 154.2; IR (KBr): 3475, 3278, 2957, 2919, 2840, 1615, 1555, 1520, 1462, 1400, 1278, 1245, 1170, 1015, 838, 750, 696 cm^{-1}; HRMS (ESI): calcd. for $C_{33}H_{29}N_2S^+$ [M + H^+] 485.2046; found 485.2052.

7-Fluoro-3,5,6-tris(4-fluorophenyl)thiopyrano[2,3,4-*de*]quinolin-2-amine (14d):



Brown solid (89 mg, 71%); mp 282–284 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 4.53 (s, 2H), 6.79 (t, 2H, *J* = 8.4 Hz), 6.83 (t, 2H, *J* = 9.0 Hz), 6.92–6.94 (m, 2H), 6.96–6.99 (m, 2H), 7.07–7.11 (m, 1H), 7.23 (t, 2H, *J* = 9.0 Hz), 7.29–7.31 (m, 2H), 7.39–7.42 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 114.3, 114.8 (d, *J* = 21.5 Hz), 115.5 (d, *J* = 21.6), 117.9 (d, *J* = 21.5), 118.9 (d, *J* = 7.1 Hz), 119.8, 121.8 (d, *J* = 27.6 Hz), 127.2 (d, *J* = 8.9 Hz), 128.5, 130.3 (d, *J* = 3.3 Hz), 131.2 (dd, J_1 = 7.8 Hz & J_2 = 4.4 Hz), 131.4 (d, *J* = 8.3 Hz), 131.9 (d, *J* = 8.3 Hz), 132.8, 132.9 (d, *J* = 3.5 Hz), 135.4 (t, *J* = 16 Hz), 144.0 (d, *J* = 4.8 Hz), 145.1, 153.1, 154.3, 154.7, 160.8, 161.4, 162.4 (d, *J* = 10.2 Hz), 163.0, 164.0; ^{19}F NMR ($CDCl_3$ + Hexafluorobenzene): δ -118.6 (s), -115.8 (s), -114.6 (s), -114.3 (s); IR (KBr): 3489, 3300, 2927, 2857, 1628, 1602, 1503, 1485, 1234, 1206, 1157, 1091, 818, 756, 668 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{17}F_4N_2S^+$ [M + H^+] 501.1043; found 501.1042.

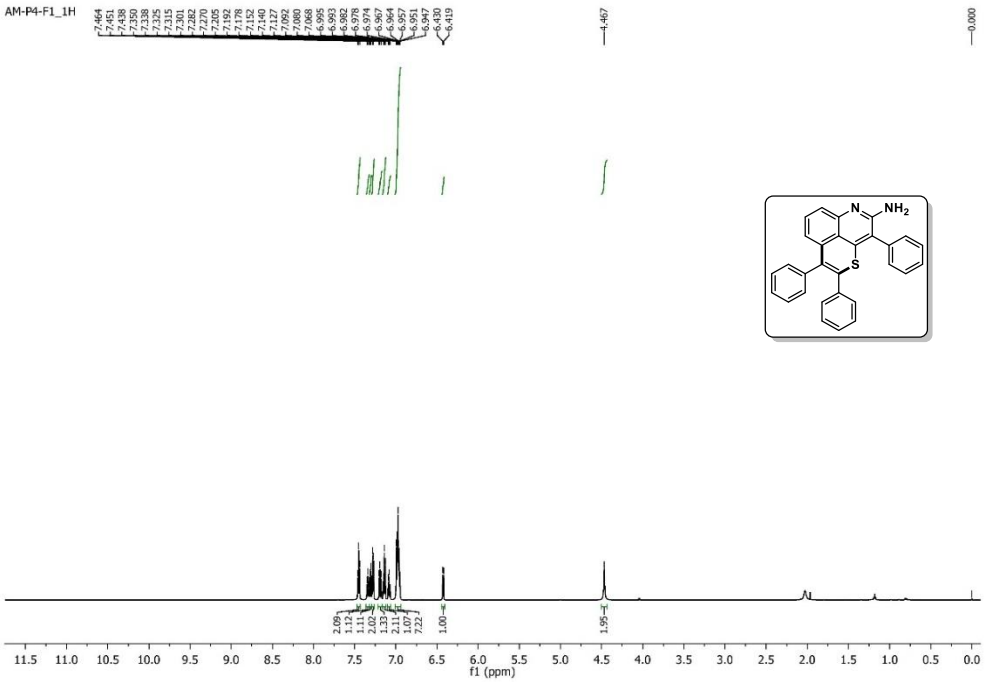
(*Z*)-4-Fluoro-*N*-(3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-yl)benzimidic acid (17a):



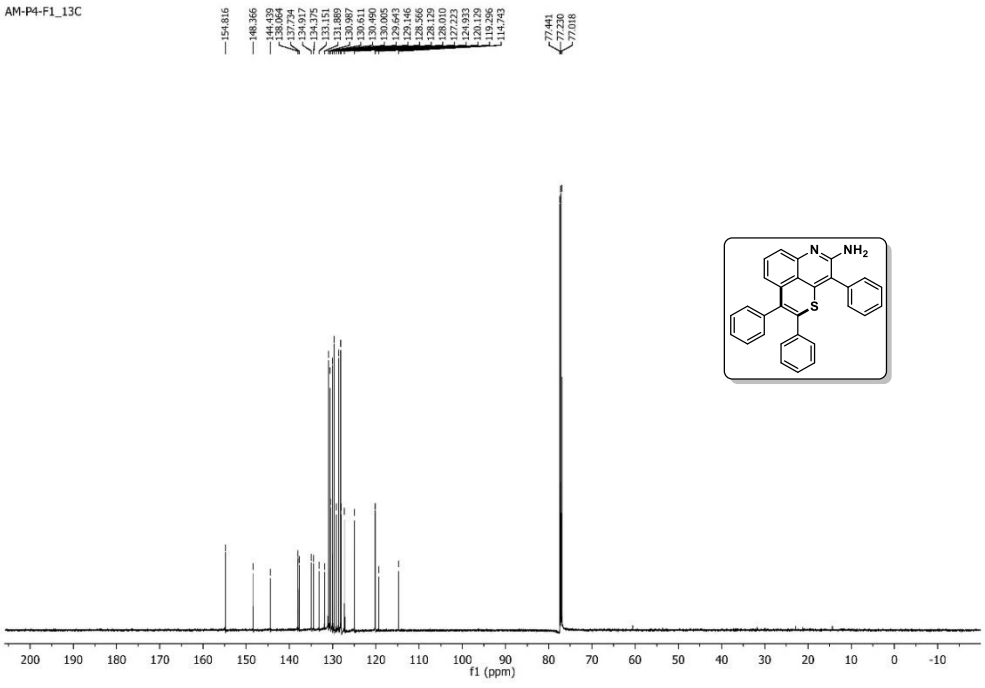
Yellow solid (82 mg, 59%); mp 253–255 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 6.72 (d, 1H, *J* = 7.8 Hz), 6.95 (t, 2H, *J* = 9.0 Hz), 7.04–7.08 (m, 7H), 7.18 (t, 1H, *J* = 7.2 Hz), 7.24 (t, 2H, *J* = 7.8 Hz), 7.38 (t, 1H, *J* = 8.4 Hz), 7.40–7.43 (m, 3H), 7.52 (t, 3H, *J* = 7.8 Hz), 7.69 (bs, 2H), 8.16 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 115.4 (d, *J* = 20.5 Hz), 122.3, 127.5, 128.2, 128.3, 128.8, 129.1, 129.5, 129.91, 129.98, 130.7, 131.2, 133.1, 134.5 (d, *J* = 25.0 Hz), 137.1, 137.3, 164.1, 165.8; IR (KBr): 3428, 2923, 2854, 1564, 1494, 1379, 1311, 1264, 1218, 1144, 850, 809, 699 cm^{-1}; HRMS (ESI): calcd. for $C_{36}H_{24}FN_2OS^+$ [M + H^+] 551.1588; found 551.1593.

IV.7. Spectra

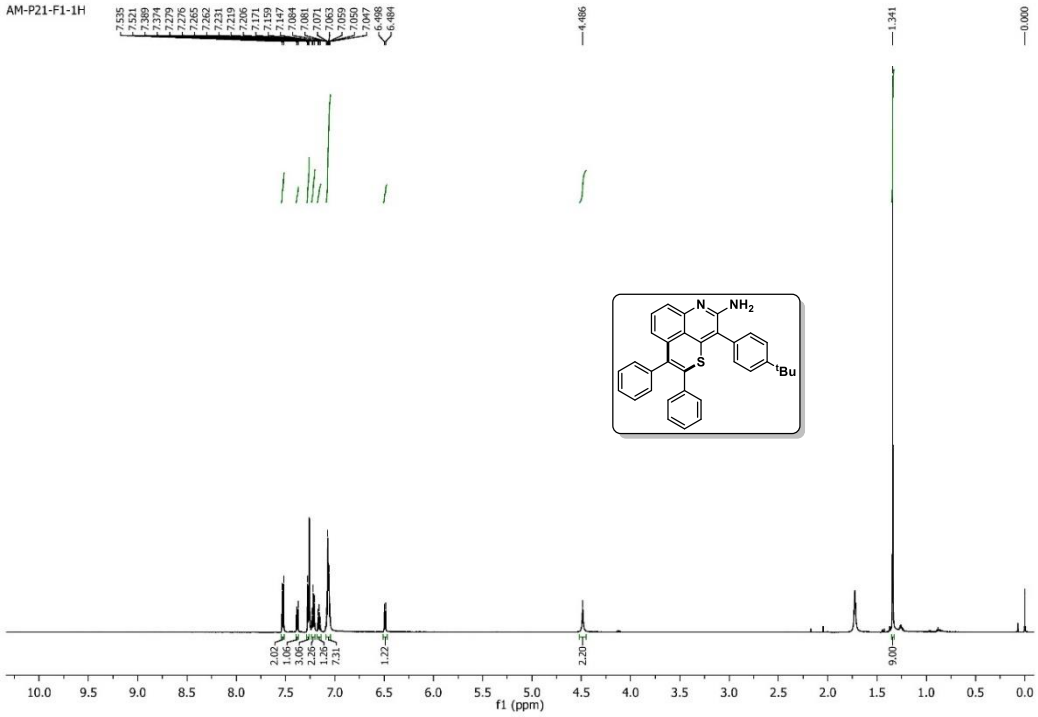
3,5,6-Triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (1a):^{1}HNMR (600 MHz, $CDCl_3$)



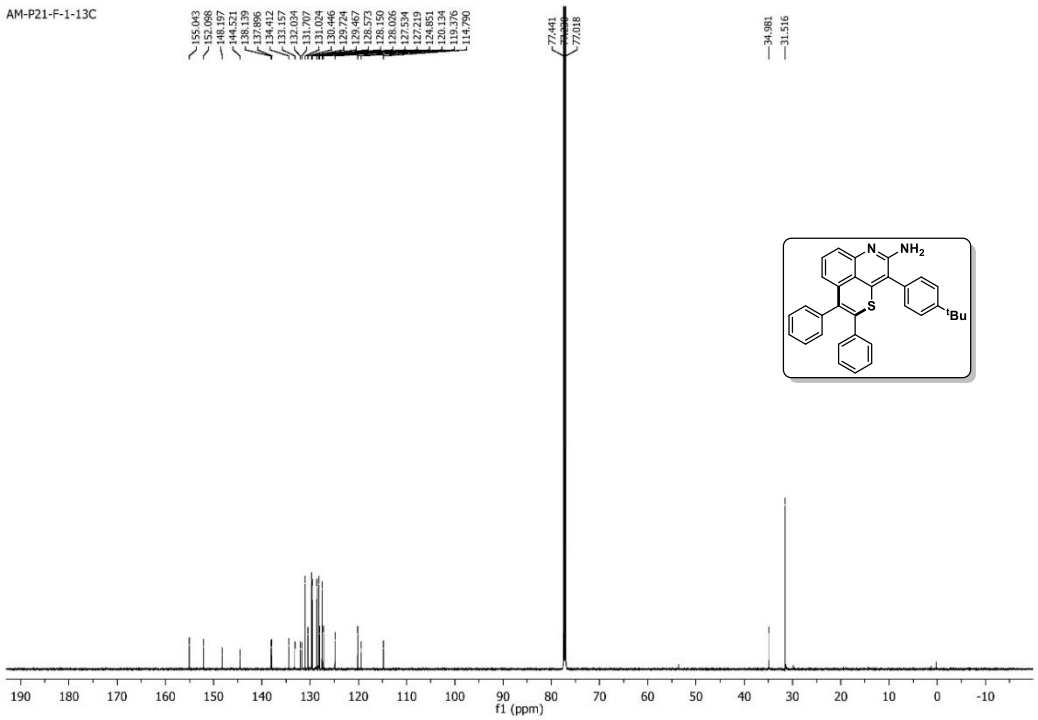
3,5,6-Triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (1a): ^{13}CNMR (150 MHz, $CDCl_3$)



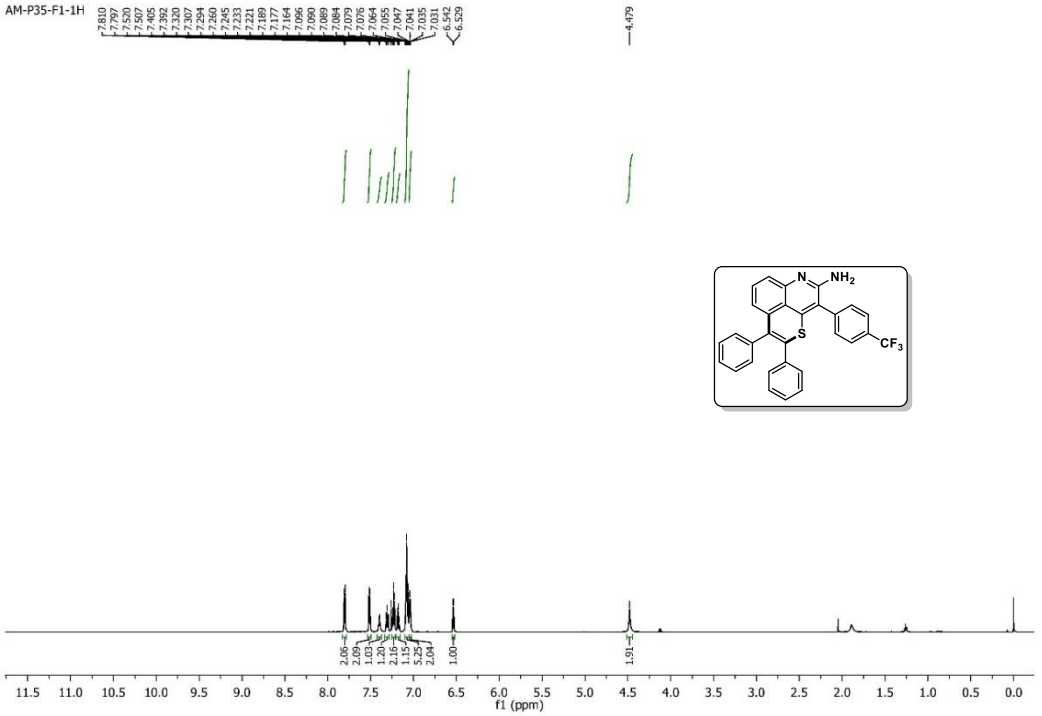
3-(4-(*tert*-Butyl)phenyl)-5,6-diphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (4a): ^{1}HNMR (600 MHz, $CDCl_3$)



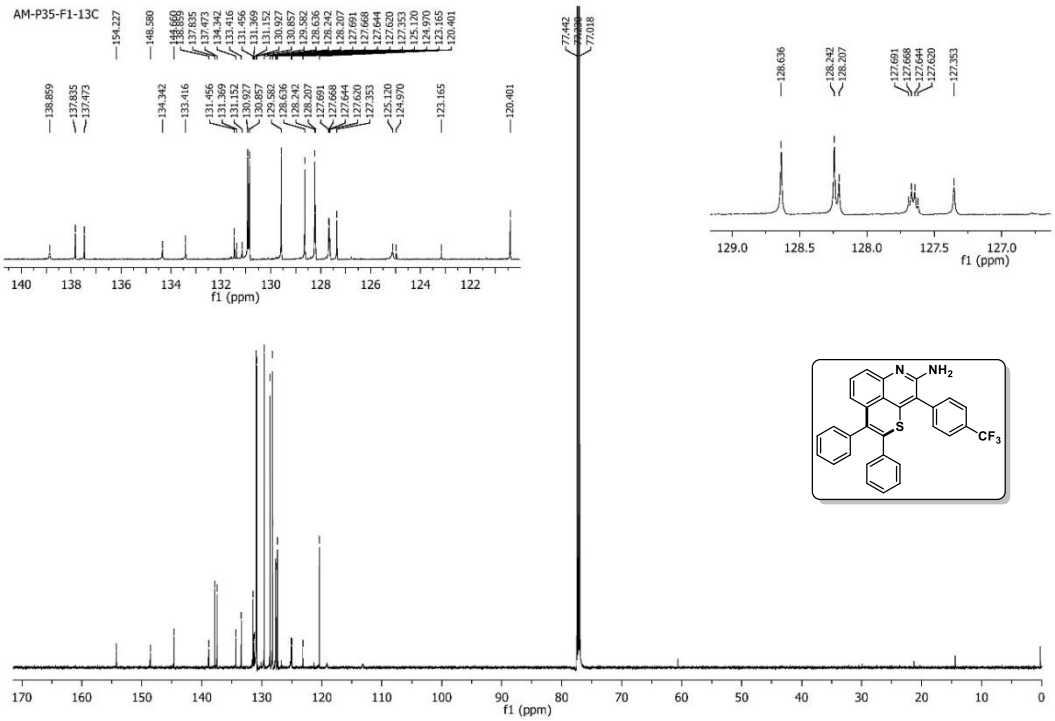
3-(4-(*tert*-Butyl)phenyl)-5,6-diphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (4a): ^{13}CNMR (150 MHz, $CDCl_3$)



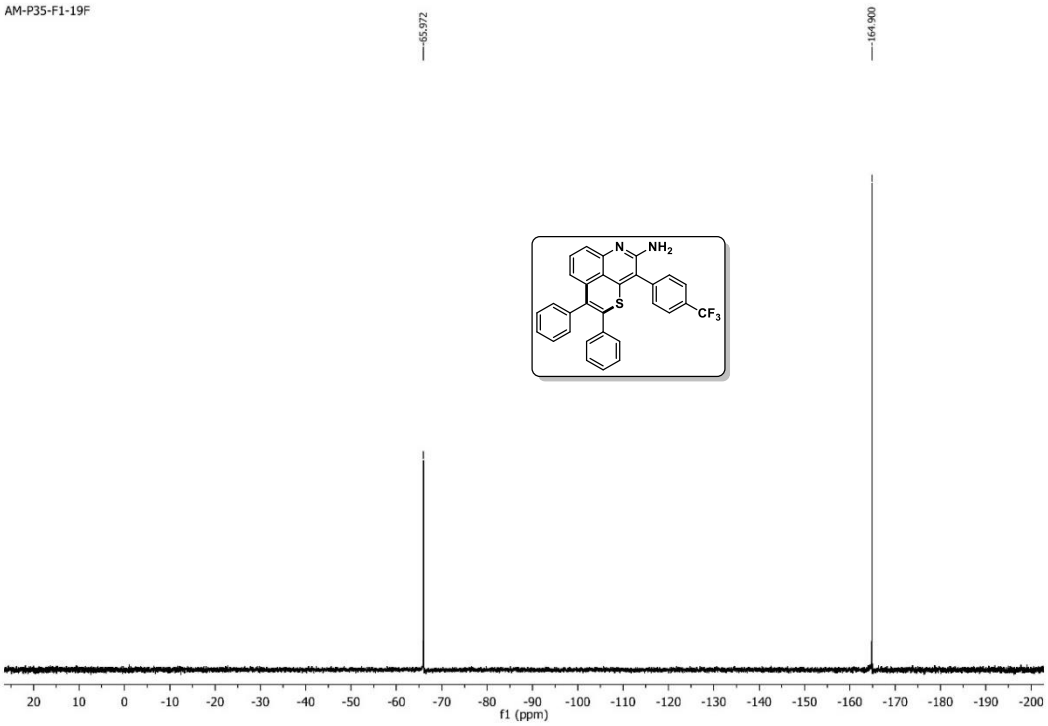
5,6-Diphenyl-3-(4-(trifluoromethyl)phenyl)thiopyrano[2,3,4-*de*]quinolin-2-amine (6a): ^{1}HNMR (600 MHz, $CDCl_3$)



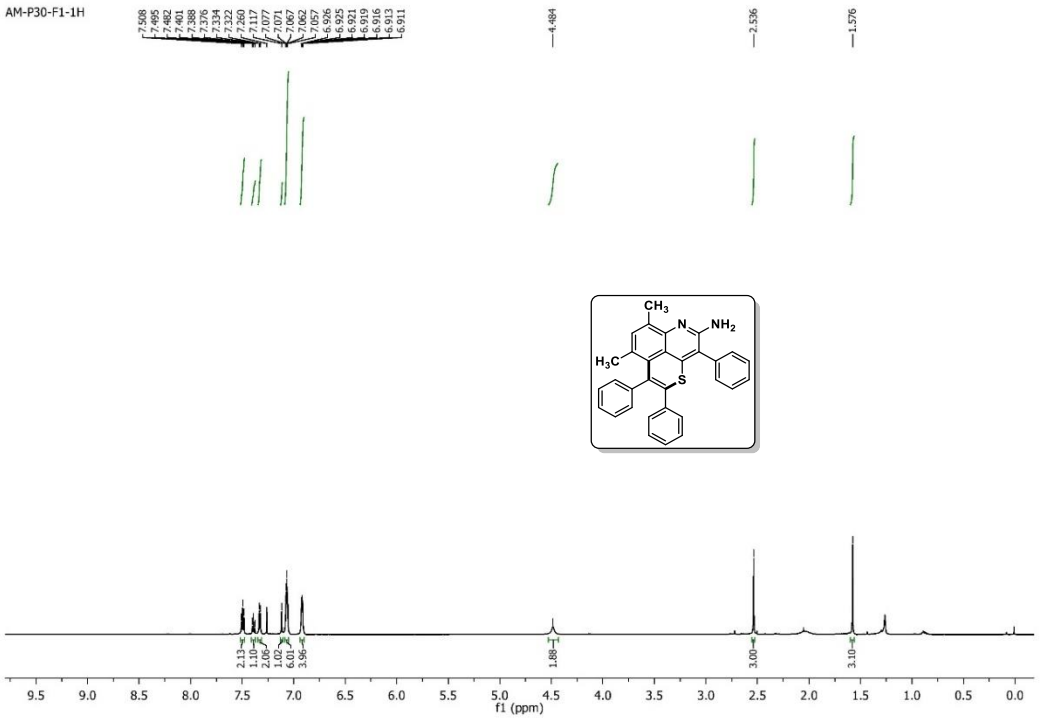
5,6-Diphenyl-3-(4-(trifluoromethyl)phenyl)thiopyrano[2,3,4-*de*]quinolin-2-amine (6a): ^{13}CNMR (150 MHz, $CDCl_3$)



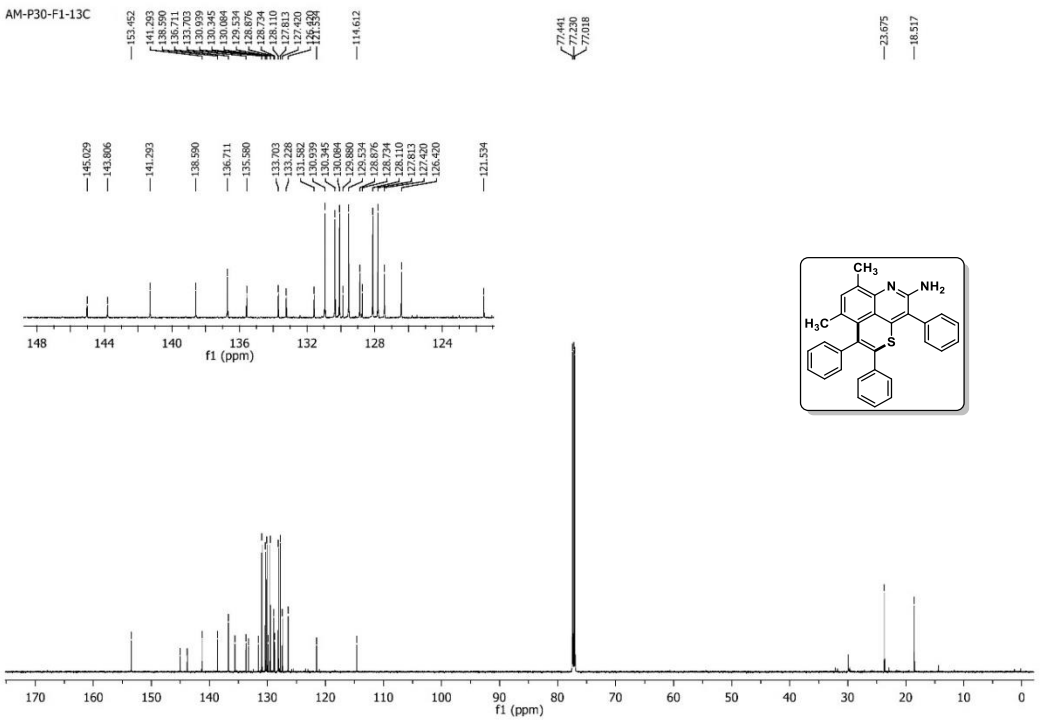
5,6-Diphenyl-3-(4-(trifluoromethyl)phenyl)thiopyrano[2,3,4-*de*]quinolin-2-amine (6a): ^{19}FNMR ($CDCl_3$ + C_6F_6)



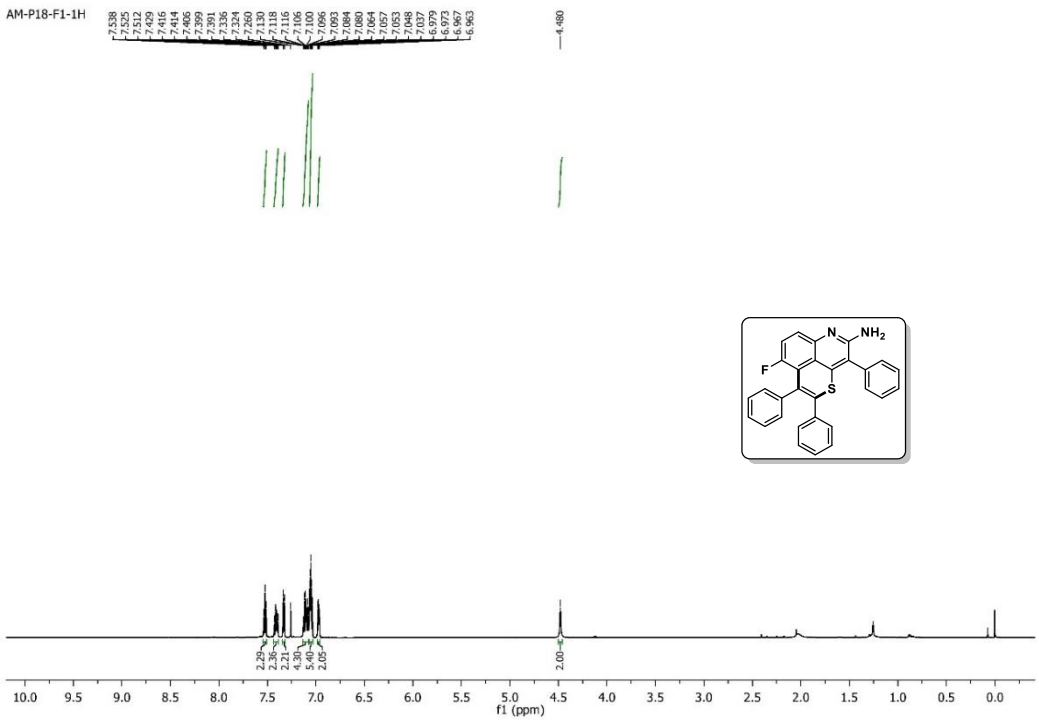
7,9-Dimethyl-3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (10a): ^{1}HNMR (600 MHz, $CDCl_3$)



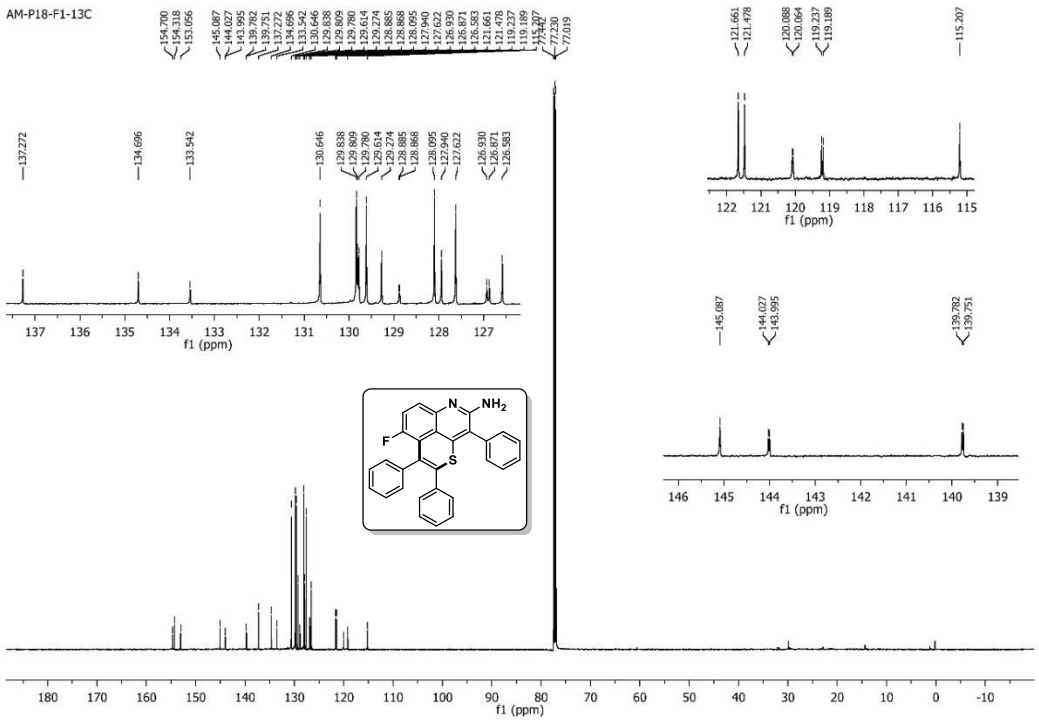
7,9-Dimethyl-3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (10a): ^{13}CNMR (150 MHz, $CDCl_3$)



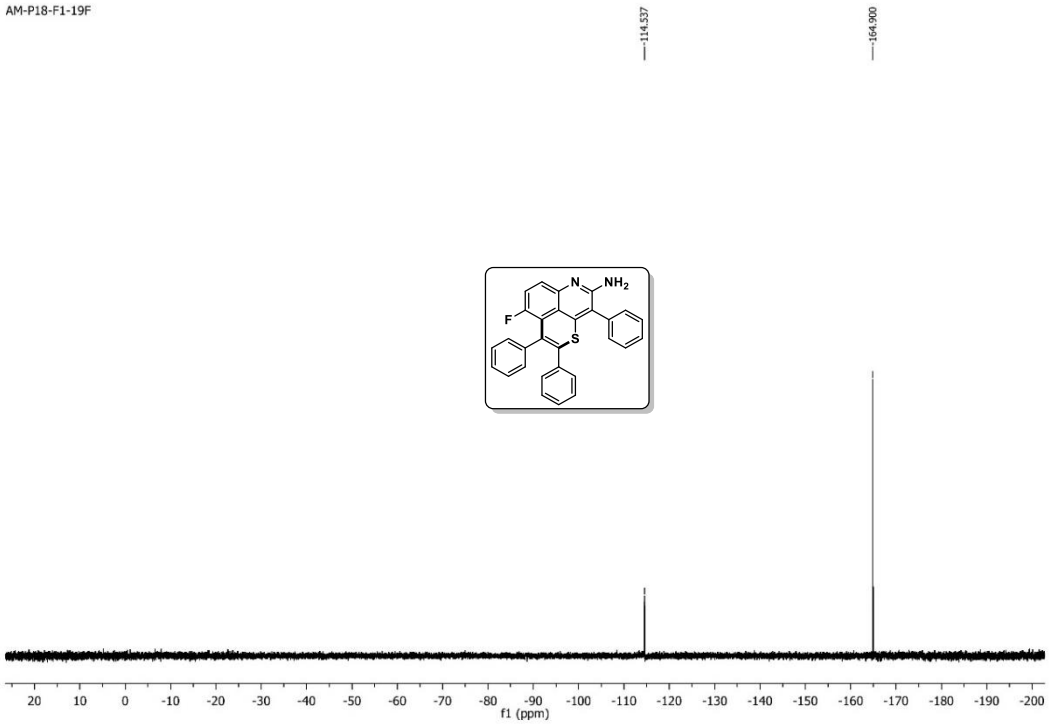
7-Fluoro-3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (11a): ^{1}HNMR (600 MHz, $CDCl_3$)



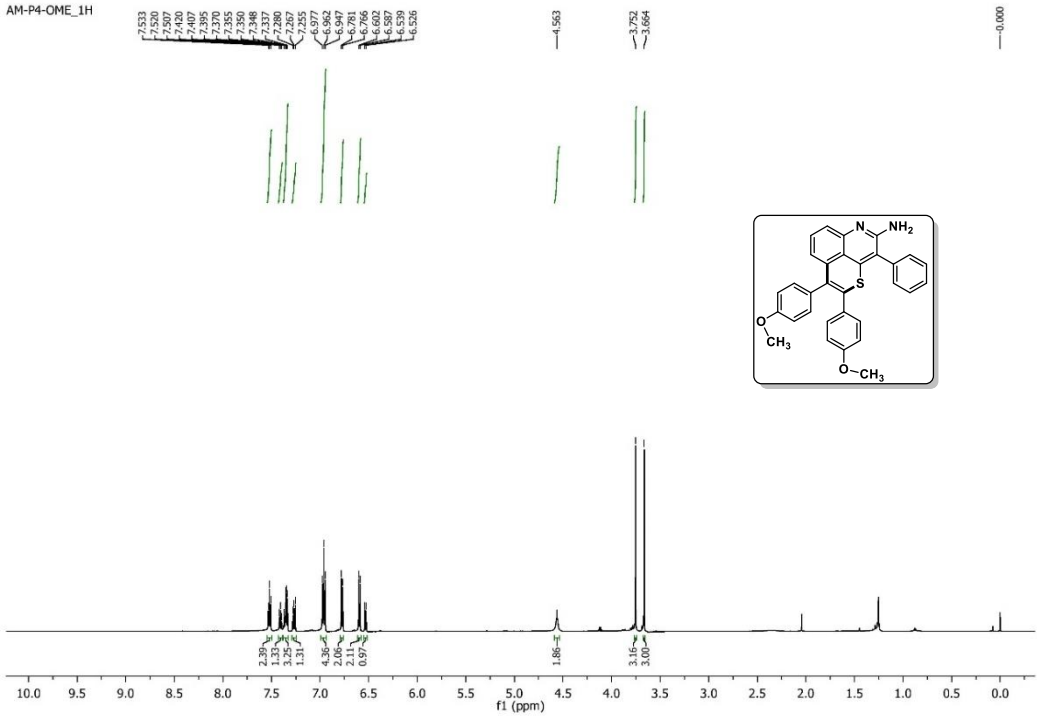
7-Fluoro-3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (11a): ^{13}CNMR (150 MHz, $CDCl_3$)



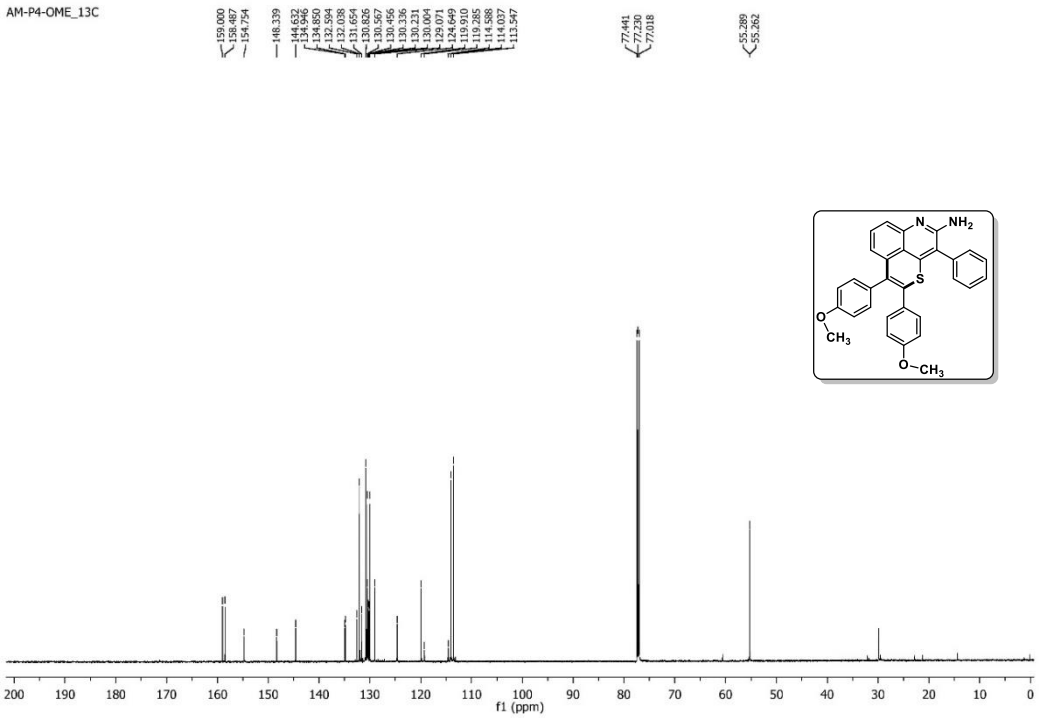
7-Fluoro-3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (11a): ^{19}FNMR ($CDCl_3$ + C_6F_6)



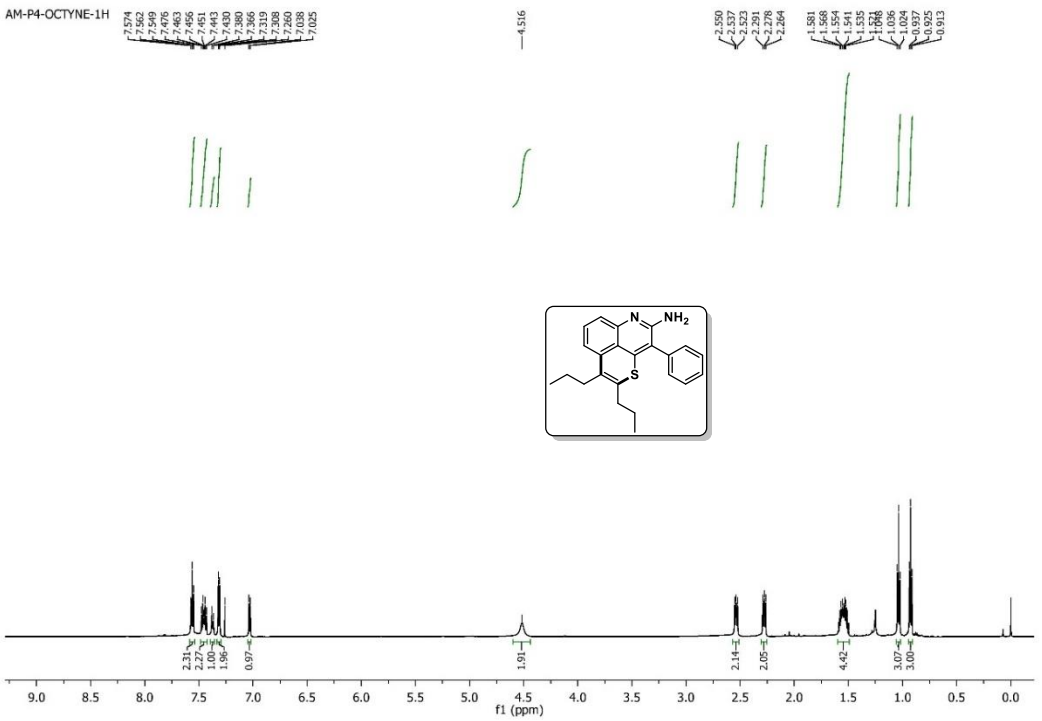
5,6-Bis(4-methoxyphenyl)-3-phenylthiopyrano[2,3,4-*de*]quinolin-2-amine (1c): ^{1}HNMR (600 MHz, $CDCl_3$)



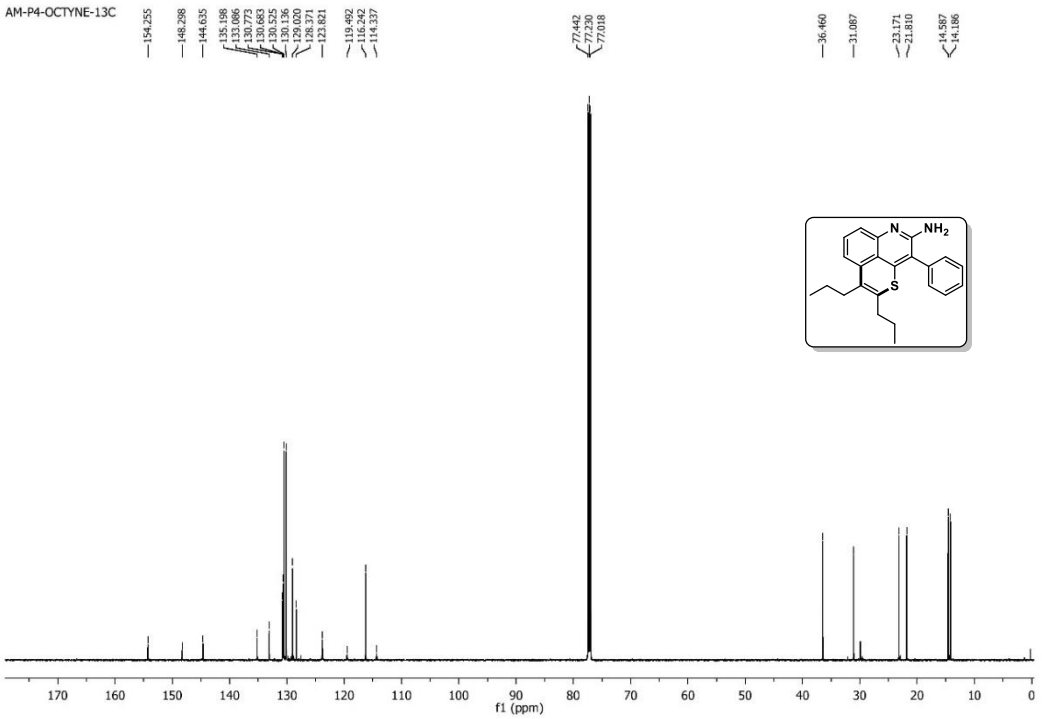
5,6-Bis(4-methoxyphenyl)-3-phenylthiopyrano[2,3,4-*de*]quinolin-2-amine (1c): ^{13}CNMR (150 MHz, $CDCl_3$)



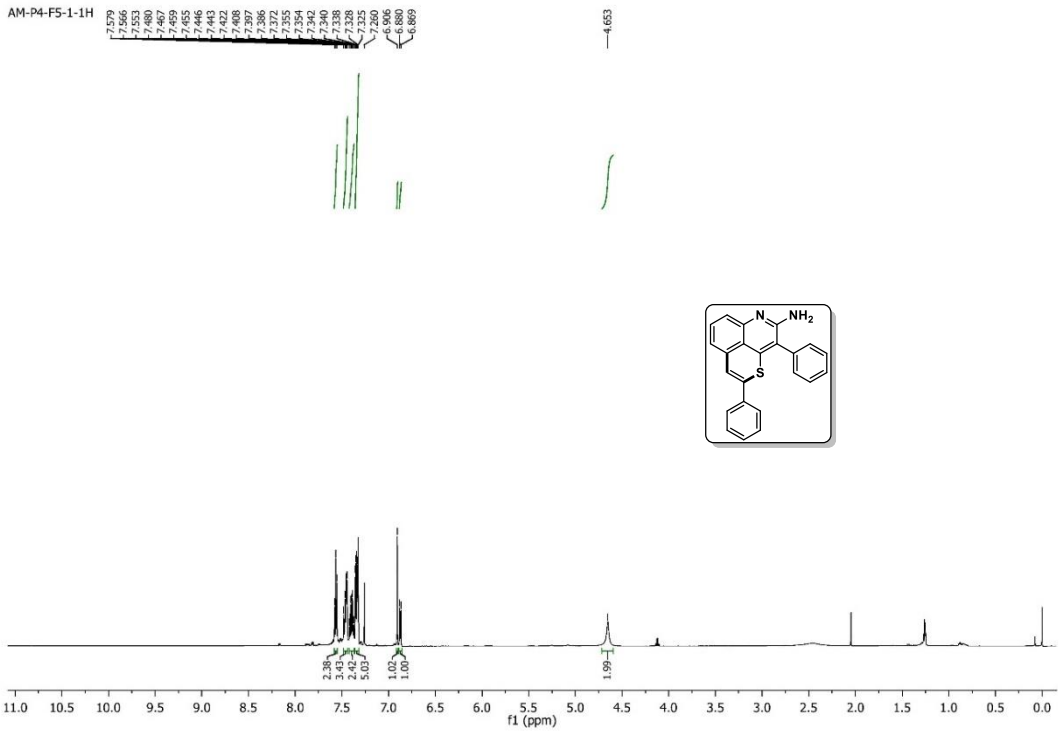
3-Phenyl-5,6-dipropylthiopyrano[2,3,4-*de*]quinolin-2-amine (1f): ^{1}HNMR (600 MHz, $CDCl_3$)



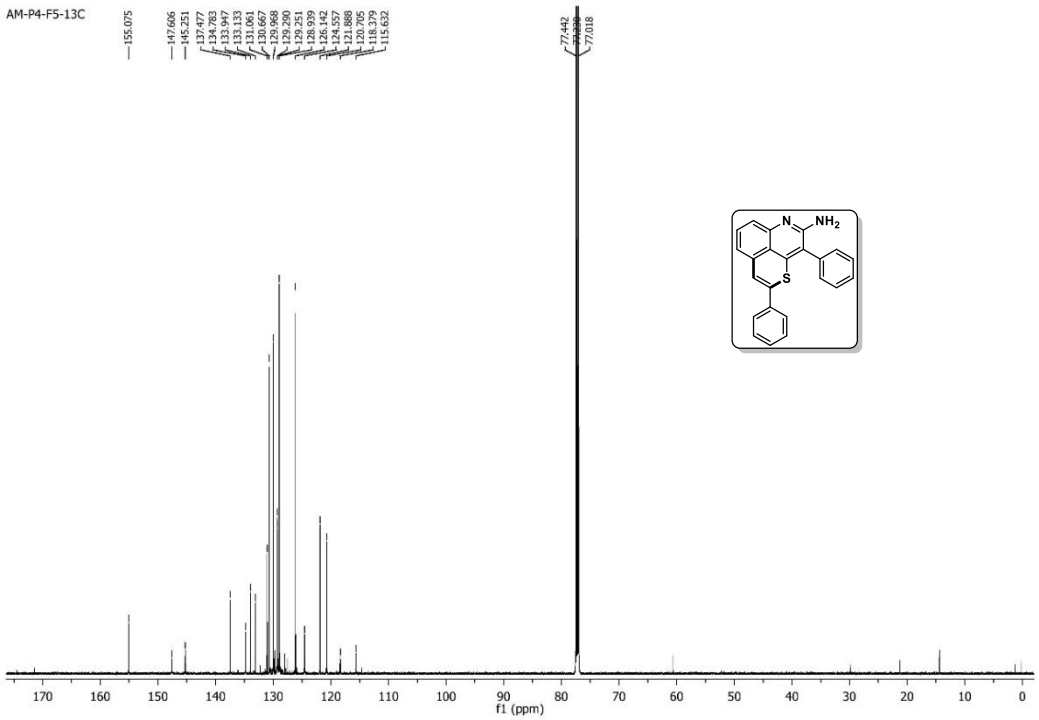
3-Phenyl-5,6-dipropylthiopyrano[2,3,4-*de*]quinolin-2-amine (1f): ^{13}CNMR (150 MHz, $CDCl_3$)



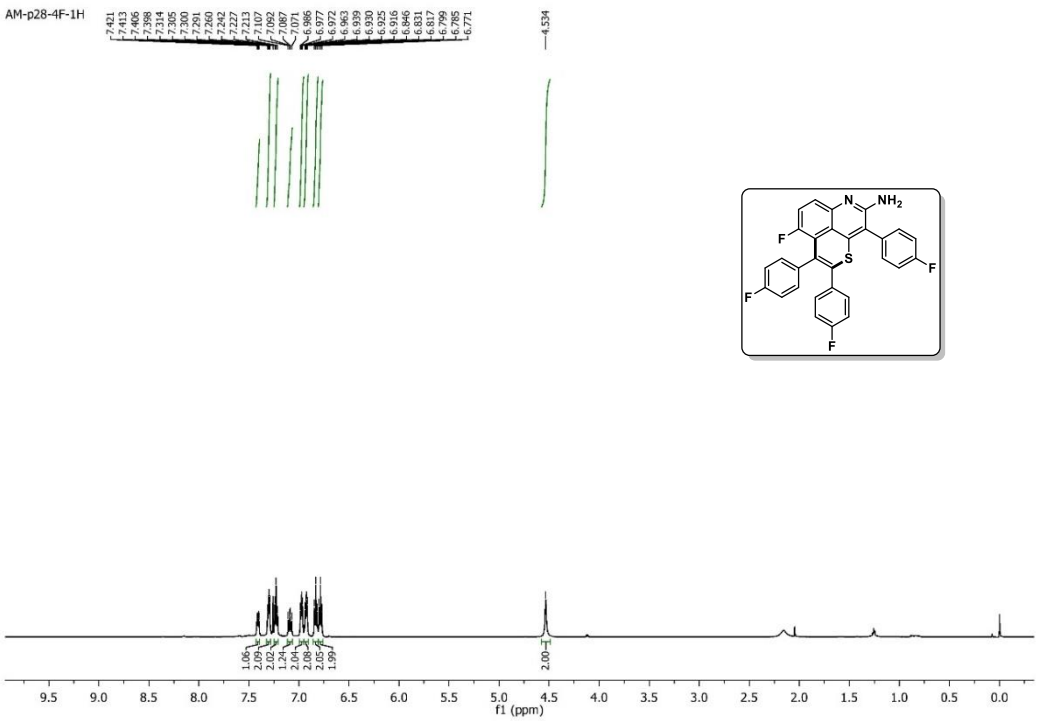
3,5-Diphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (1k): ^{1}HNMR (600 MHz, $CDCl_3$)



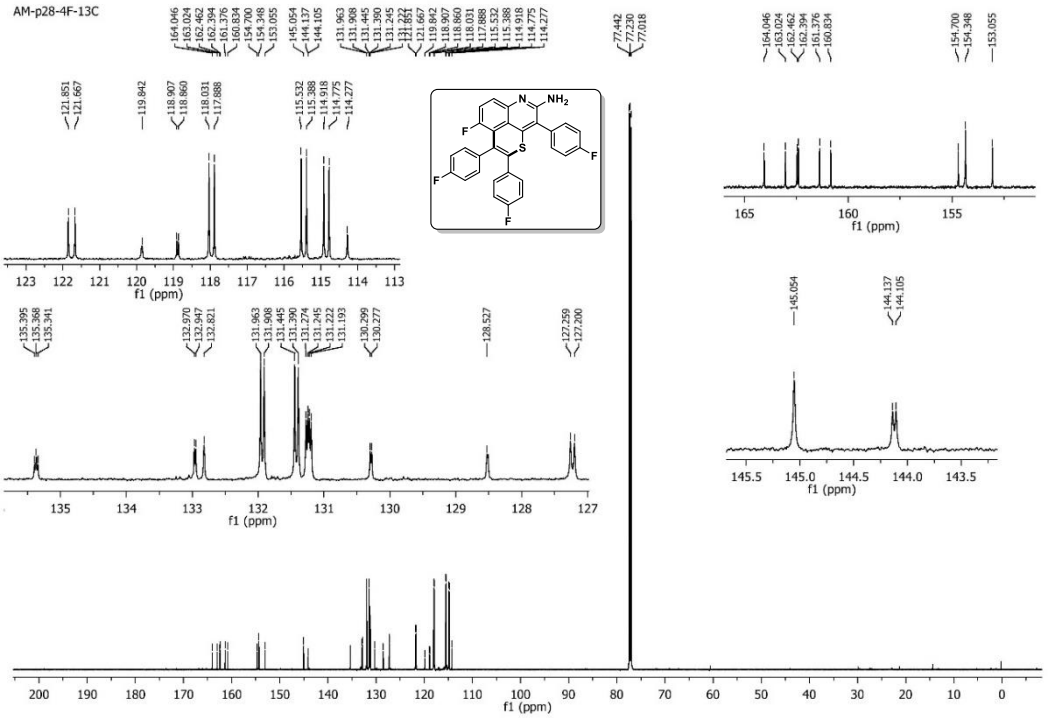
3,5-Diphenylthiopyrano[2,3,4-*de*]quinolin-2-amine (1k): ^{13}CNMR (150 MHz, $CDCl_3$)



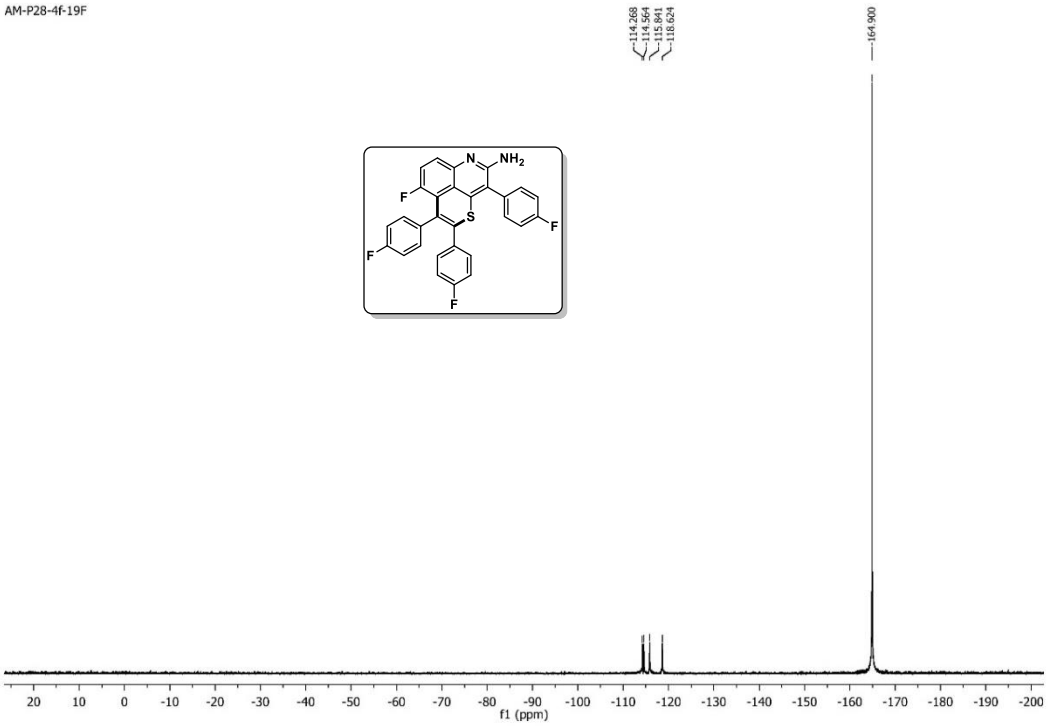
7-Fluoro-3,5,6-tris(4-fluorophenyl)thiopyrano[2,3,4-*de*]quinolin-2-amine (14d): ^{1}HNMR (600 MHz, $CDCl_3$)



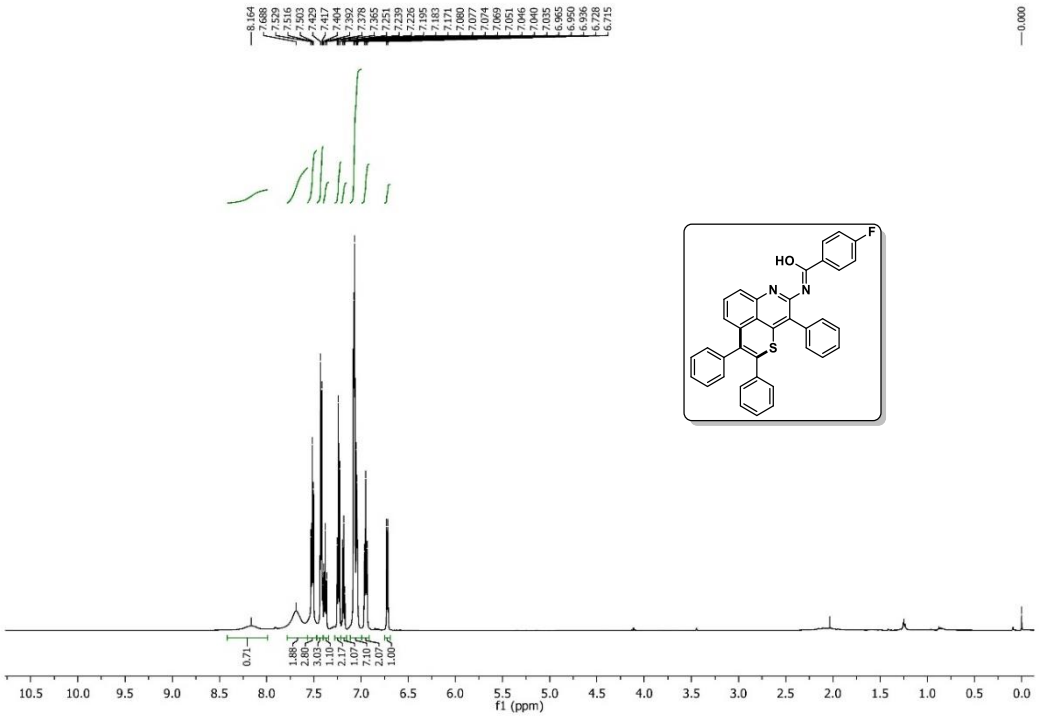
7-Fluoro-3,5,6-tris(4-fluorophenyl)thiopyrano[2,3,4-*de*]quinolin-2-amine (14d): ^{13}CNMR (150 MHz, $CDCl_3$)



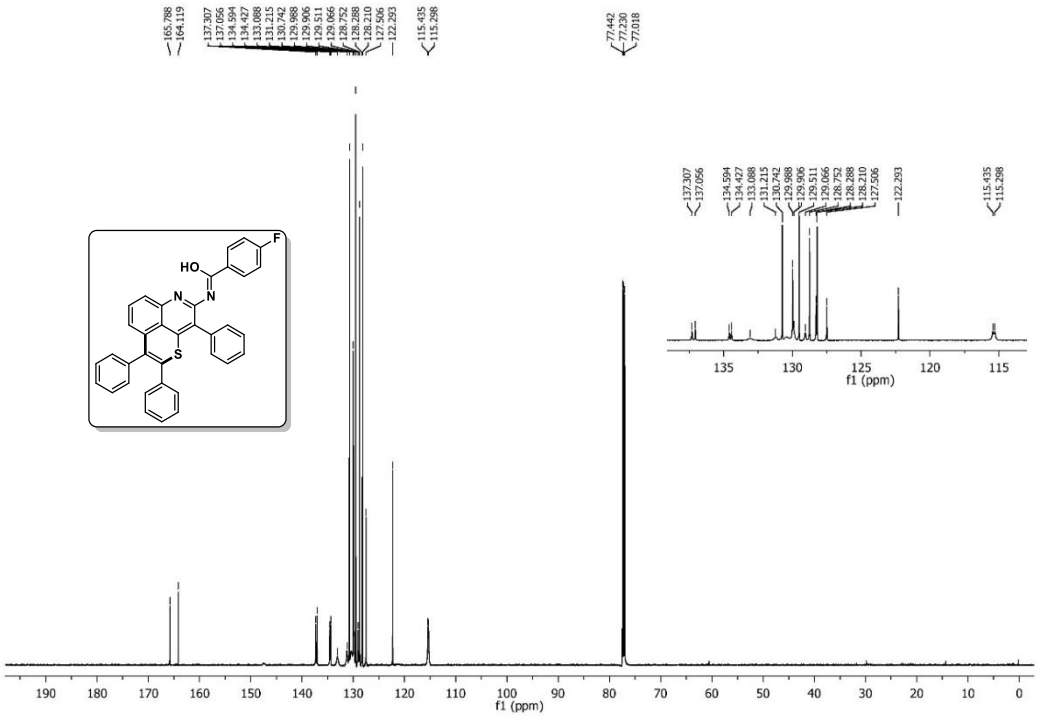
7-Fluoro-3,5,6-tris(4-fluorophenyl)thiopyrano[2,3,4-*de*]quinolin-2-amine (14d): ^{19}FNMR ($CDCl_3$ + C_6F_6)



(*Z*)-4-Fluoro-*N*-(3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-yl)benzimidic acid (17a): ^{1}HNMR (600 MHz, $CDCl_3$)

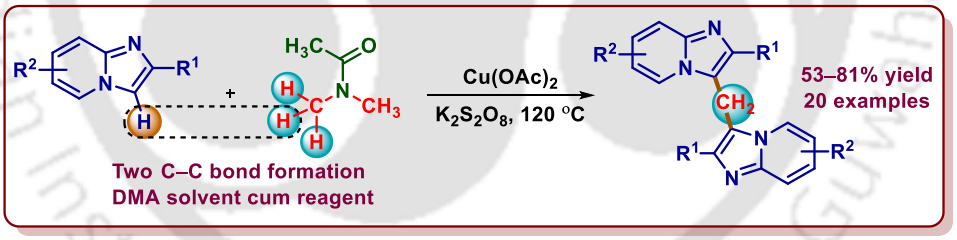


(*Z*)-4-Fluoro-*N*-(3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-yl)benzimidic acid (17a): ^{13}CNMR (150 MHz, $CDCl_3$)



CHAPTER V

N,N-Dimethylacetamide (DMA) as a Methylene Synthon for Regioselective Linkage of Imidazo[1,2-a]pyridine



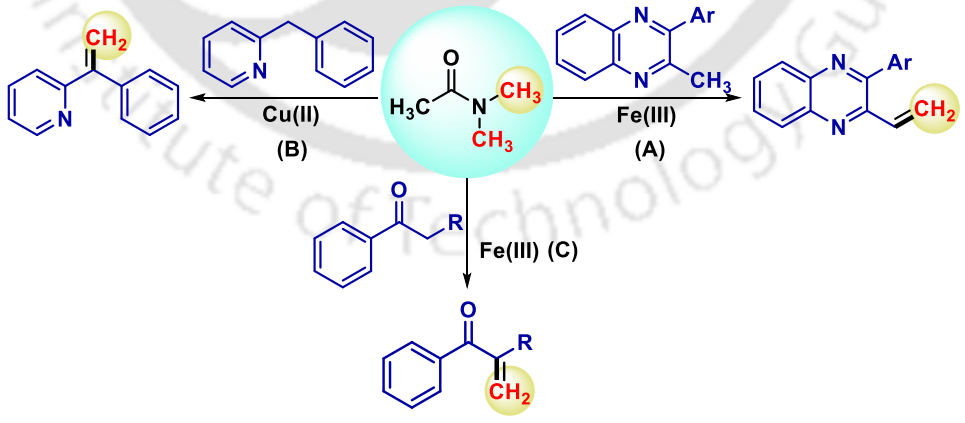
ABSTARCT: *A copper(II)-catalyzed oxidative methylene-bridged dimerization of two analogous imidazo[1,2-a]pyridine has been achieved using N,N-dimethylacetamide (DMA) as solvent cum methylene source. This reaction works with a variety of substituted imidazo[1,2-a]pyridines giving their products in moderate to good yields. Isotopic labeling experiments revealed that the methylene group in the product originates from the N,N-dimethyl moiety of DMA.*

CHAPTER V

V. *N*,*N*-Dimethylacetamide (DMA) as a Methylene Synthon for Regioselective Linkage of Imidazo[1,2-*a*]pyridine

V.1. Introduction

Cross-dehydrogenative coupling (CDC) under oxidative conditions is one of the most efficient and straightforward tool for the construction of C–C bonds.[1] This strategy is so powerful that, even the commonly used organic solvents such as formamides and sulfoxides are utilized as the source of various functional groups. *N*,*N*-Dimethylformamide (DMF), a well-known solvent, has turned out to be a multipurpose reagent widely used in organic chemistry as building block of various units such as -O, -CO, -NMe_2, -$CONMe_2$, -Me, -CHO, etc.[2] Similarly, dimethyl sulfoxide (DMSO) is also utilized as the source of -SMe,[3a,b] -CN,[3c] -CHO,[3d,e] -Me,[3f] etc. *N*,*N*-Dimethylacetamide (DMA), although chemically inert compared to DMF, has been successfully explored as a one-carbon synthon for the synthesis of terminal alkenes and heterocycles via sp^3–sp^3 and sp^2–sp^3 C–H couplings, respectively.[4]



Scheme V.1.1. *DMA as a methylene source*

There are reports where the *N*-methyl of DMA serves as a one-carbon surrogate for the synthesis of terminal alkenes such as Xu *et al.* reported an Fe(III)-catalyzed benzylic vinylation of 2-methylazaarenes generating 2-vinyl azaarenes (Scheme V.1.1, A).[4a] Miura

and co-workers developed a direct α-methylenation of benzylpyridines using DMA as the one-carbon source using Cu(II) catalyst (Scheme V.1.1, B).[4b] An Fe-catalyzed α-methylenation of ketones were achieved using DMA as the methylene source (Scheme V.1.1, C).[4e]

V.2. Strategies Towards the C-3 Functionalization of Imidazo[1,2-*a*]pyridines

Among the *N*-heterocycles, imidazo[1,2-*a*]pyridines represent an important structural motif because of their prevalence in the field of medicinal and material chemistry.[5] The derivatives are reported to have a diverse array of biological activities such as anti-viral,[6a] anti-bacterial,[6b,c] anti-fungal,[6d] anti-ulcer,[6e,f] and anti-helminthics.[6g] They also form the core skeleton of many pharmaceutically important drugs such as necopidem, saripidem, zolpidem, alpidem, zolimidine and miroprofen (Figure V.2.1).[7]

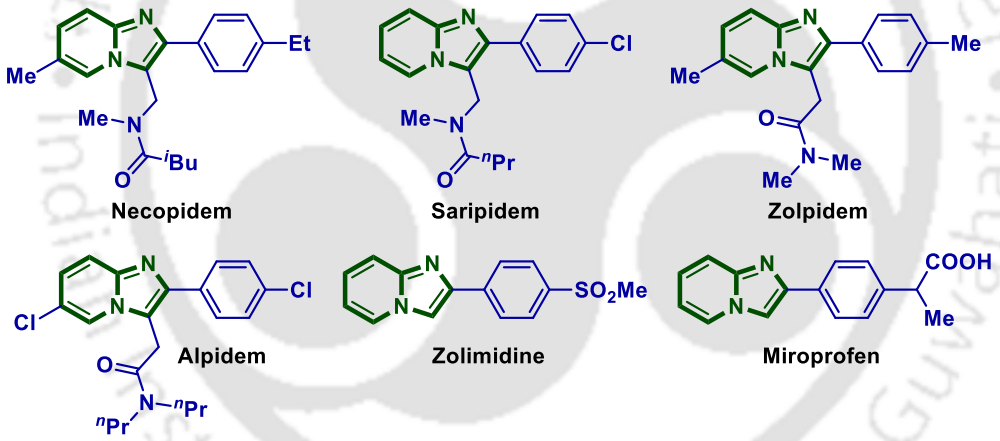
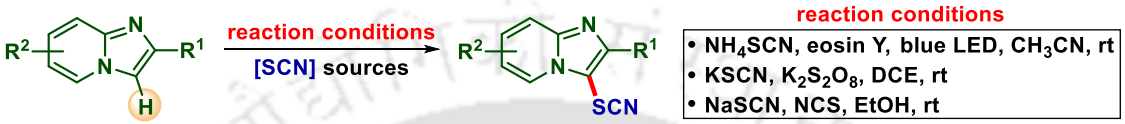


Figure V.2.1. *Examples of imidazo[1,2-a]pyridine-based therapeutics*

Owing to the ubiquity of imidazo[1,2-*a*]pyridine framework in various fields, substantial attention has been paid to their synthesis and further functionalizations.[8] Of late, many methods have been explored for the C-3 functionalization of imidazo[1,2-*a*]pyridines. Selected examples include (i) thiocyanation, (ii) sulfenylation, (iii) trifluoromethylation, (iv) cyanation, (v) halogenation (vi) aminomethylation (vii) dicarbonylation, (viii) phosphonation (ix) homocoupling, which have been discussed below:

➢ Thiocyanation of Imidazo[1,2-*a*]pyridine

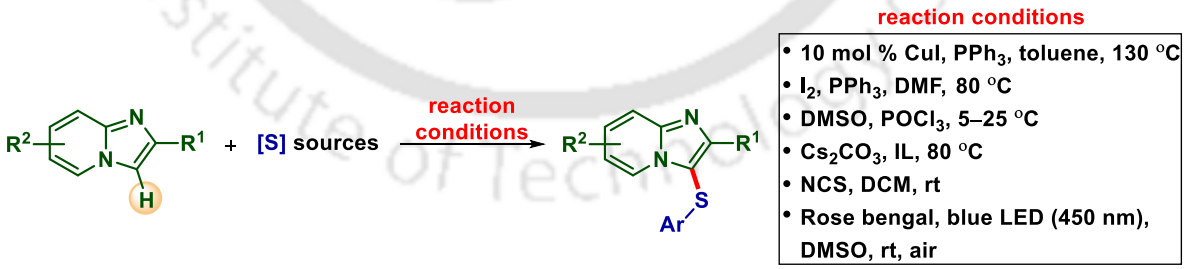
In 2015, Hajra *et al* have shown the first example of thiocyanation of imidazopyridines using photoredox catalyst (eosin Y) (Scheme V.2.1).[18a] Subsequently, Wang group disclosed the first catalyst-free regioselective C-3 thiocyanation of imidazopyridines using KSCN and $K_2S_2O_8$.[18b] Similar metal-free reaction was reported by Wang *et al*. using NCS/NaSCN combination.[18c]



Scheme V.2.1. *Thiocyanation of imidazo[1,2-a]pyridine*

➢ C-3 Sulfenylation of Imidazo[1,2-*a*]pyridine

Several strategies have been developed towards the sulfenylation of imidazo[1,2-*a*]pyridine under metal, metal-free and photo-induced conditions (Scheme V.2.2). These reactions have been accomplished using metals catalysts such as copper,[9] iodine derivatives,[10] hypervalent iodine,[11] strong acidic conditions,[12] ionic liquids,[13] silica supported $CeCl_3.7H_2O/NaI$,[14] NCS,[15] and NBS.[16] All these methods involve different thiolating agents such as thiols, disulfides, arylsulfonyl chlorides, sulfonyl hydrazides, sodium sulfinates, sulfur powder and sulfonothioate. Recently, Barman group reported C-3 sulfenylation of imidazo[1,2-*a*]pyridine with thiols at room temperature through a visible-light-promoted process in the presence of rose bengal.[17]

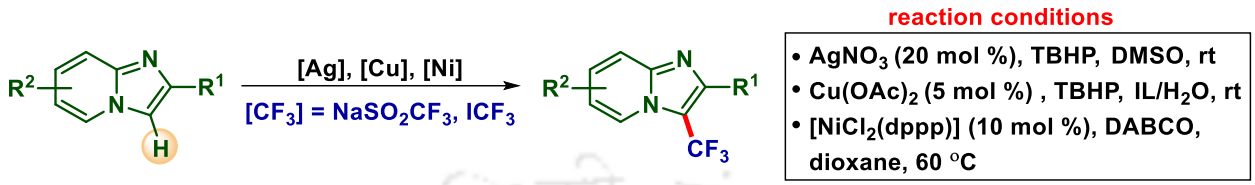


Scheme V.2.2. *Sulfenylation of imidazo[1,2-a]pyridine*

➢ Trifluoromethylation of Imidazo[1,2-*a*]pyridine

Owing to the importance of trifluoromethyl group in enhancing the physical, chemical and biological properties of a parent molecule, Hajra and Tang group independently reported trifluoromethylation of imidazo[1,2-*a*]pyridine using Langlois' reagent

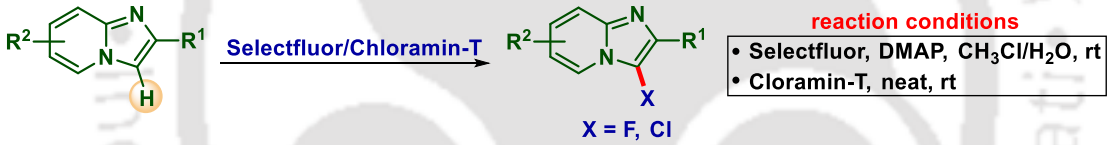
($NaSO_2CF_3$) in the presence of TBHP as $^{\bullet}CF_3$ radical source under different catalytic conditions (Scheme V.2.3). The former group[19a] used $AgNO_3$ as the catalyst and latter group[19b] used $Cu(OAc)_2$. Later, a Ni-catalyzed trifluoromethylation using iodotrifluoromethane (CF_3I) was demonstrated by Wang *et al.* (Scheme V.2.3).[19c]



Scheme V.2.3. *Trifluoromethylation of imidazo[1,2-a]pyridine*

➢ Halogenation of Imidazo[1,2-*a*]pyridine

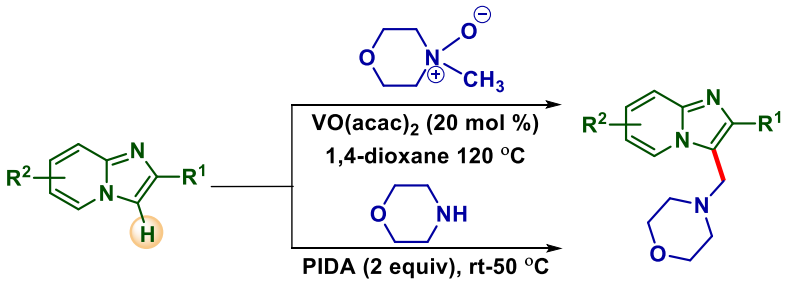
In 2015, Sun and co-workers described a regioselective synthesis of 3-fluorinated imidazo[1,2-*a*]pyridines using Selectfluor as the fluorinating reagent in aqueous condition (Scheme V.2.4).[20a] Recently, Hajra *et al* developed chlorination of imidazoheterocycle using chloramine-T as the chlorinating agent under a neat condition (Scheme V.2.4).[20b]



Scheme V.2.4. *Halogenation of imidazo[1,2-a]pyridine*

➢ Aminomethylation of Imidazo[1,2-*a*]pyridine

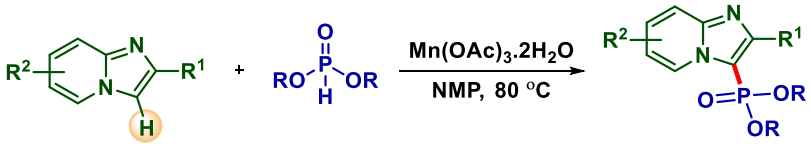
A vanadium-catalyzed aminomethylation at C-3 position of imidazo[1,2-*a*]pyridine has been reported by Kumar *et al.* using *N*-methylmorpholine oxide (NMO), which acts as the coupling partner as well as an oxidant at high temperature in 1,4-dioxane solvent (Scheme V.2.5).[21a] Another aminomethylation was achieved by Hajra group under a metal-free condition using morpholine as methylene source under neat condition (Scheme V.2.5).[21b]



Scheme V.2.5. *Aminomethylation of imidazo[1,2-a]pyridine*

➢ Phosphonation of Imidazo[1,2-*a*]pyridine

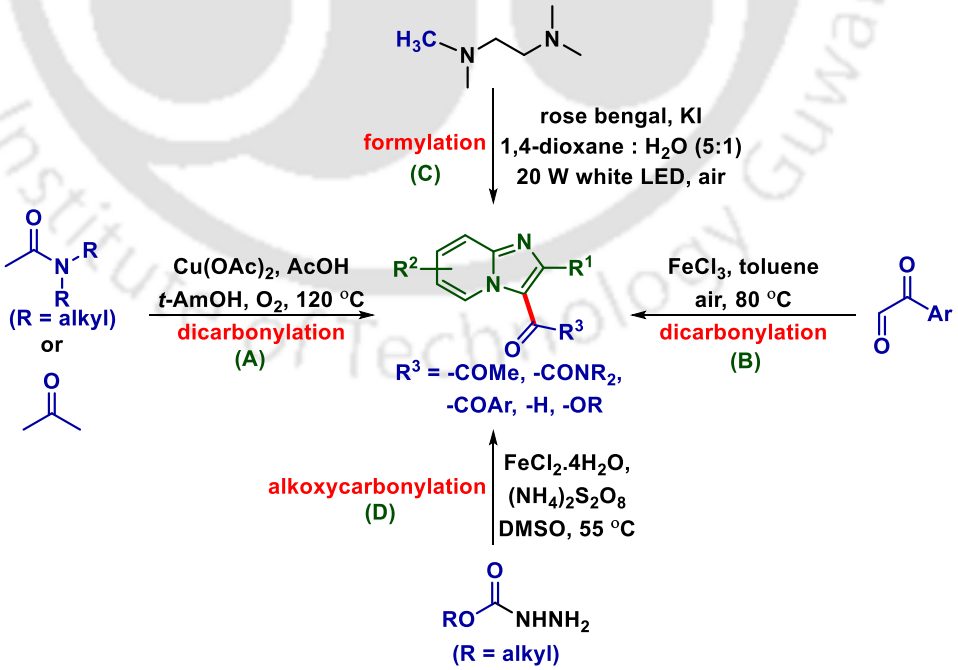
A Mn(III)-mediated regioselective direct C–H phosphonation of imidazo[1,2-*a*]pyridine has been described by Singh group using dialkylphosphites (Scheme V.2.6).[24]



Scheme V.2.6. *Phosphonation of imidazo[1,2-a]pyridine*

➢ Carbonylation of Imidazo[1,2-*a*]pyridine

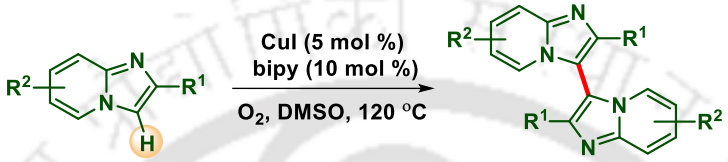
Cao *et al* reported a copper-catalyzed regioselective dicarbonylation of imidazo[1,2-*a*]pyridine with *N*,*N*-disubstituted acetamide or acetone using molecular oxygen (Scheme V.2.7, A).[22a] Later, Hajra group achieved similar reaction by coupling imidazo[1,2-*a*]pyridine with oxoaldehydes in the presence of Fe(III) catalyst (Scheme V.2.7, B).[22b] The same group recently reported a metal-free visible light induced C-3 formylation of imidazo[1,2-*a*]pyridine using tetramethylethylenediamine (TMEDA) as the one carbon source (Scheme V.2.7, C).[22c] Sun and co-workers also reported regioselective alkoxycarbonylation of imidazopyridine using carbazates as ester group source using Fe(II) catalyst and $(NH_4)_2S_2O_8$ as the oxidant (Scheme V.2.7, D).[22d]



Scheme V.2.7. *Different carbonylation strategy for imidazo[1,2-a]pyridine*

➢ **Homocoupling of Imidazo[1,2-*a*]pyridine**

The first regioselective homocoupling reaction of imidazo-[1,2-*a*]pyridine was demonstrated by Cao *et al.* using Cu-catalyst and 2,2'-bipyridine ligand in DMSO at 120 °C (Scheme V.2.8).[23a] Later, Sakhuja group also reported similar strategy but under metal-free condition using PIDA as the oxidant and $BF_3.OEt_2$ as additive.[23b] Recently, Han and co-workers achieved the first electrochemical homocoupling reaction of imidazo-[1,2-*a*]pyridine in good to excellent yields.[23c]



Scheme V.2.8. *Homocoupling of imidazo[1,2-a]pyridine*

Although there have been significant developments toward the regioselective functionalization of imidazo[1,2-*a*]pyridine at the C-3 position, the quest for further derivatizations is still ongoing.

V.3. Present Work

With the aim to functionalize the C-3 position of imidazo[1,2-*a*]pyridine (**1a**), it was treated with DMA (solvent cum reagent) in the presence of catalyst CuI (20 mol%) and oxidant $K_2S_2O_8$ (1 equiv) (Table V.3.1, entry 1). Formation of an unexpected product (**3a**) was observed in 50% yield. The product (**3a**) showed a singlet at 4.99 ppm in its ^{1}HNMR and a peak at 19.9 ppm in its ^{13}CNMR spectra, which may be due to the presence of a methylene carbon in the product. Furthermore, from the single crystal X-ray diffraction study of one of its derivative i.e., (**3b**) (Figure V.3.1), its structure was established to be a C-3 methylene bridge bis-heterocycle. To ascertain the source of the methylene carbon in the product (**3a**), a similar reaction was carried out separately with *N*,*N*-dimethylformamide (DMF) and *N*,*N*-diethylacetamide (DEA) in lieu of DMA under otherwise identical conditions. Formation of product (**3a**) was observed only with DMF (and not with DEA), thereby suggesting that the methylene carbon in (**3a**) possibly originates from the *N*-methyl group of DMA/DMF and not from the acetyl group of DMA. When the reaction was carried out with DMF-d_7, insertion of a deuterated methylene group was observed, which was confirmed from the HRMS analysis of the reaction mixture

(Figure.V.4.2). This result unequivocally confirms that the *N*-Me group of DMA/DMF to be the source of methylene carbon in the product (**3a**).

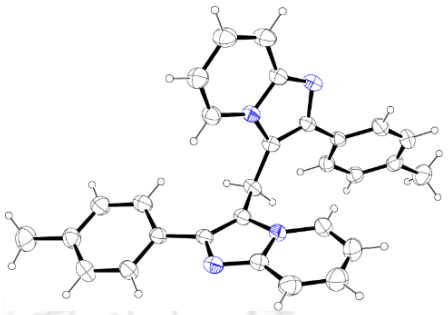


Figure V.3.1. *ORTEP view of* ***(3b)***

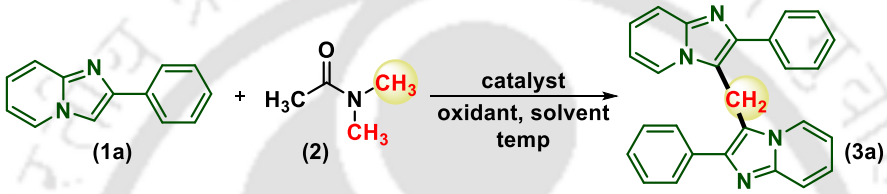
As already discussed earlier, *N*-methyl of DMA acts as a one-carbon surrogate for the synthesis of terminal alkenes. However, the use of DMA as the source of a one-carbon linker between two analogous imidazo[1,2-*a*]pyridines via cross-dehydrogenative coupling of sp^2 C−H of arene and sp^3 C−H bond of DMA is unfamiliar so far.

Optimization of Reaction Conditions:

Encouraged by the above unprecedented result, further optimizations were carried out to find the optimal reaction parameter to achieve the maximum yield of the product. A variety of copper salts in conjunction with different oxidants and solvents were examined, and the results are summarized in Table V.3.1. Among the various copper salts screened [CuBr (43%), CuCl (34%), $CuBr_2$ (56%), $CuCl_2$ (53%), $Cu(OTf)_2$ (31%)] (Table V.3.1, entries 2–6), $Cu(OAc)_2$ turn out to be superior, giving 64% yield (Table V.3.1, entry 7) of the expected product. The use of $FeCl_3.6H_2O$ as the catalyst instead of copper salts did not serve the purpose, affording the desired product in just 15% yield (Table V.3.1, entry 8). To further improve the yield, other oxidants [$Na_2S_2O_8$ (21%), $(NH_4)_2S_2O_8$ (39%)] (Table V.3.1, entry 9 and 10) were tested, but all were found inferior to $K_2S_2O_8$ (Table V.3.1, entry 7). A 5% improvement in the product yield was observed (Table V.3.1, entry 11), when the quantity of $K_2S_2O_8$ was increased by two-fold. The use of DMF in lieu of DMA resulted in an average yield (52%) of the product (Table V.3.1, entry 12). Further, the use of DMA in reagent quantity (5 equiv) along with other solvents such as DMSO (12%), chlorobenzene (00%), and *p*-xylene (00%) (Table V.3.1, entries 13–15) was not at all efficient. A lower yield (54%) of the product was observed when the catalyst loading was decreased to 10 mol% (Table V.3.1, entry 16), while an increase in the catalyst loading (30 mol%) resulted in a marginal improvement (71%) in the product yield (Table V.3.1,

entry 17). Further, increasing the reaction temperature to 130 °C (Table V.3.1, entry 18) had no impact on the product yield, whereas lowering the reaction temperature to 100 °C resulted in a slight decrease in the yield (61%) (Table V.3.1, entry 19). No improvement in the product yield was observed when the reaction was carried out in an atmosphere of N_2 (Table V.3.1, entry 20). In the absence of oxidant ($K_2S_2O_8$), the reaction was completely unproductive, while without the catalyst [$Cu(OAc)_2$] < 8% of product formation was observed. These observations clearly suggest the essential requirement of both the catalyst and oxidant in bringing about the above transformation (Table V.3.1, entry 21 and 22).

Table V.3.1. *Screening of the reaction conditions*[a]



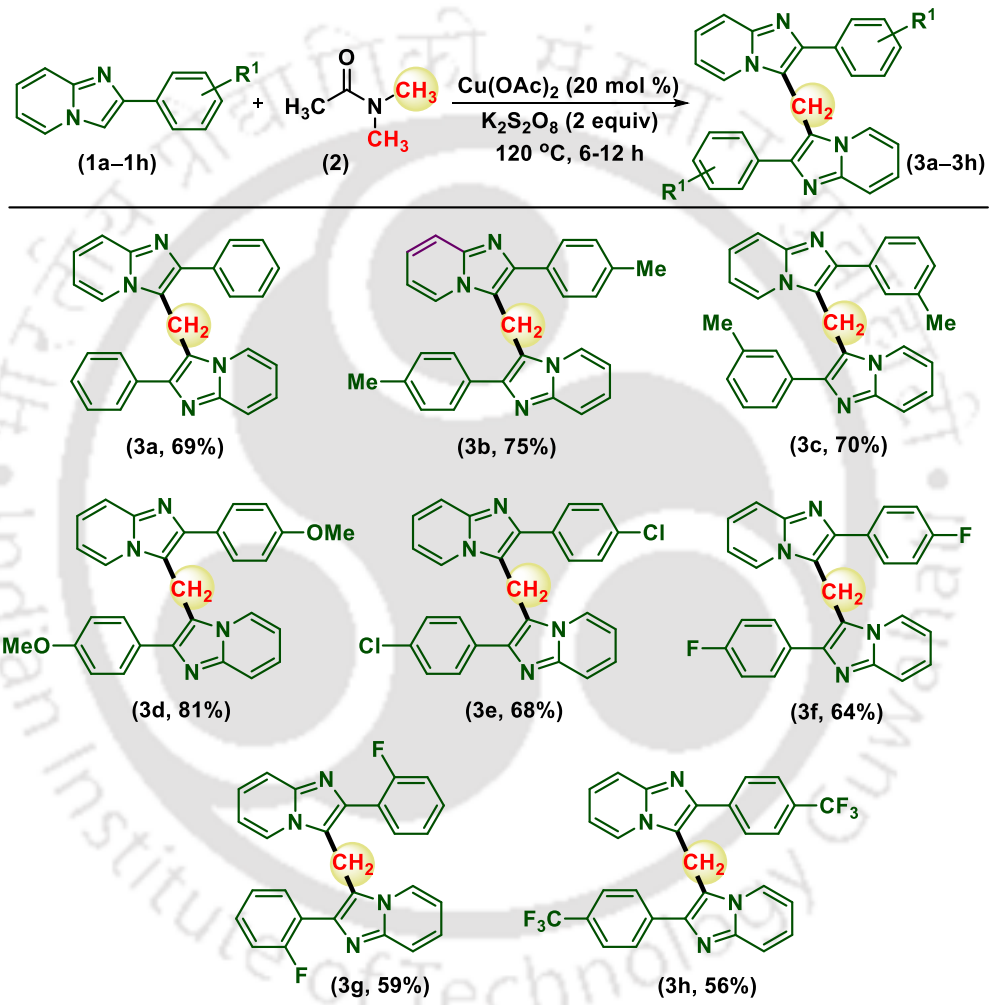
Entry	Catalyst (mol %)	Oxidant (equiv)	Solvent	Temp (°C)	Yield (%)[b]
1	CuI (20)	$K_2S_2O_8$ (1)	DMA	120	50
2	CuBr (20)	$K_2S_2O_8$ (1)	DMA	120	43
3	CuCl (20)	$K_2S_2O_8$ (1)	DMA	120	34
4	$CuBr_2$ (20)	$K_2S_2O_8$ (1)	DMA	120	56
5	$CuCl_2$ (20)	$K_2S_2O_8$ (1)	DMA	120	53
6	$Cu(OTf)_2$ (20)	$K_2S_2O_8$ (1)	DMA	120	31
7	$Cu(OAc)_2$ (20)	$K_2S_2O_8$ (1)	DMA	120	64
8	$FeCl_3.6H_2O$ (20)	$K_2S_2O_8$ (1)	DMA	120	15
9	$Cu(OAc)_2$ (20)	$Na_2S_2O_8$ (1)	DMA	120	21
10	$Cu(OAc)_2$ (20)	$(NH_4)_2S_2O_8$ (1)	DMA	120	39
11	**$Cu(OAc)_2$ (20)**	**$K_2S_2O_8$ (2)**	**DMA**	**120**	**69**
12	$Cu(OAc)_2$ (20)	$K_2S_2O_8$ (2)	DMF	120	52
13[c]	$Cu(OAc)_2$ (20)	$K_2S_2O_8$ (2)	DMSO	120	12
14[c]	$Cu(OAc)_2$ (20)	$K_2S_2O_8$ (2)	PhCl	120	00
15[c]	$Cu(OAc)_2$ (20)	$K_2S_2O_8$ (2)	*p*-Xylene	120	00
16	$Cu(OAc)_2$ (10)	$K_2S_2O_8$ (2)	DMA	120	54
17	$Cu(OAc)_2$ (30)	$K_2S_2O_8$ (2)	DMA	120	71
18	$Cu(OAc)_2$ (20)	$K_2S_2O_8$ (2)	DMA	130	69
19	$Cu(OAc)_2$ (20)	$K_2S_2O_8$ (2)	DMA	100	61
20[d]	$Cu(OAc)_2$ (20)	$K_2S_2O_8$ (2)	DMA	120	68
21	$Cu(OAc)_2$ (20)	-	DMA	120	00
22	-	$K_2S_2O_8$ (2)	DMA	120	< 8

[a]Reaction condition: 2-Phenylimidazo[1,2-*a*]pyridine (**1a**) (0.25 mmol), catalyst (mol %), oxidant (equiv), solvent (2.0 mL) under air for 6h. [b]Isolated yield. [c]DMA (5 equiv). [d]Reaction under an N_2 atmosphere.

Substrate Scope for Synthesis of Bisimidazo[1,2-*a*]pyridin-3-ylmethane Derivatives:

The scope and generality of this methodology was then extended to a range of imidazo[1,2-*a*]pyridines using $Cu(OAc)_2$ (20 mol%), $K_2S_2O_8$ (2 equiv) in DMA (2 mL) at 120 °C. At first, the effect of substituents (-Me, -OMe, -Cl, -F, $-CF_3$) on the phenyl ring of 2-phenylimidazo[1,2-*a*]pyridine moiety (**1a**–**1h**) were examined.

Scheme V.3.1. *Synthesis of bisimidazo[1,2-a]pyridin-3-ylmethane derivatives*[a,b]

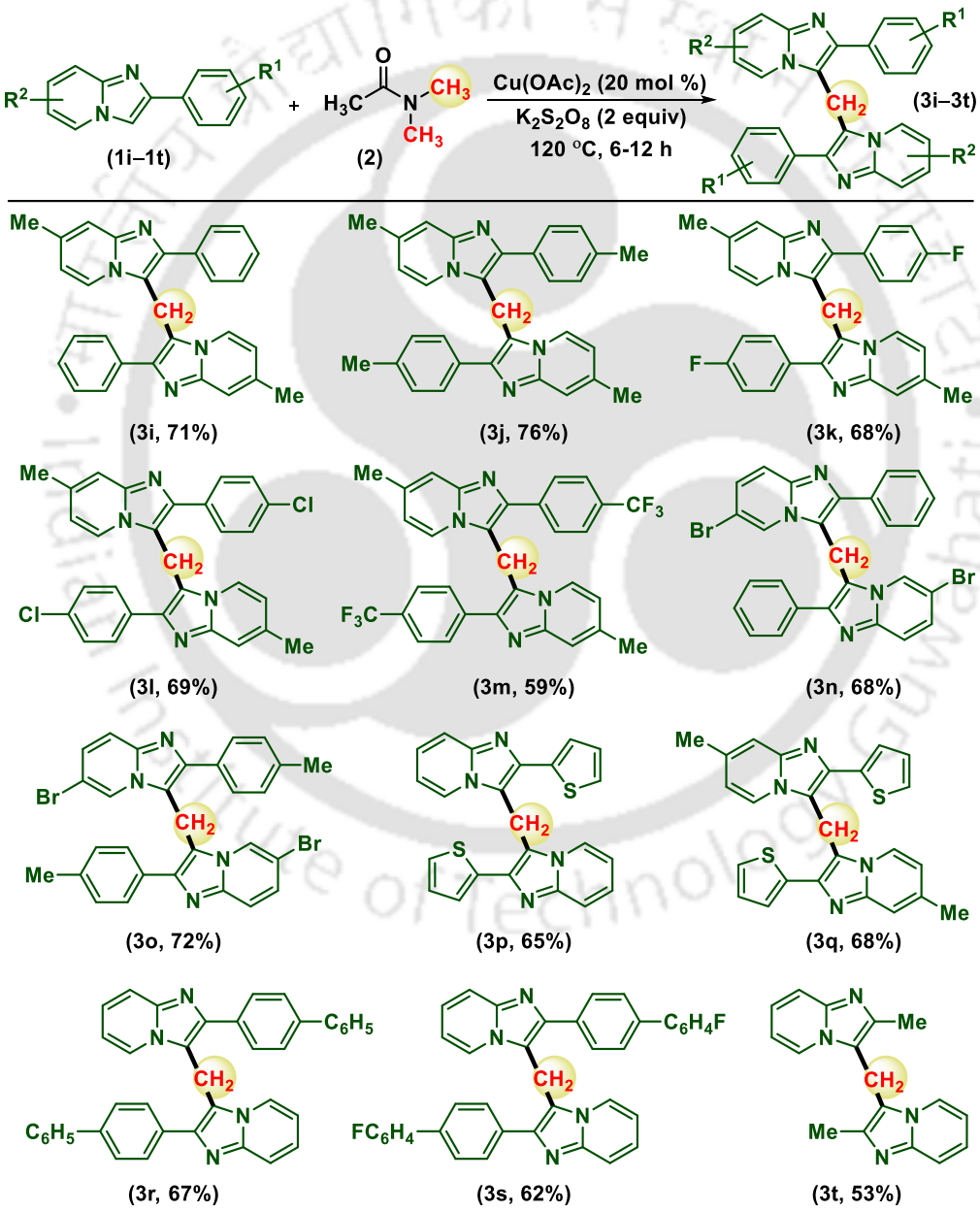


[a]Reaction conditions: Imidazo[1,2-*a*]pyridine (**1a**–**1h**) (0.25 mmol), $Cu(OAc)_2$ (20 mol %), $K_2S_2O_8$ (2 equiv) and DMA (2 mL) under air at 120 °C. [b]Isolated yield.

As can be seen from Scheme V.3.1, all afforded their corresponding products (**3a**–**3h**) in moderate to good yields. Relatively better yields of the product (**3b**, 75%) and (**3d**, 81%) were obtained when the phenyl ring is substituted with electron-donating groups such as *p*-Me (**1b**) and *p*-OMe (**1d**) compared to the electron-neutral 2-phenylimidazo[1,2-*a*]pyridine moiety (**1a**). However, the presence of a methyl group at the *meta* position in the phenyl ring of imidazo[1,2-*a*]pyridine (**1c**) did not show any significant effect on the

product yield (**3c**, 70%). The presence of moderately electron-withdrawing groups, such as *p*–Cl (**1e**) and *p*–F (**1f**) provided slightly lower yields of their product (**3e**, 68%) and (**3f**, 64%) respectively. When a moderately electron-withdrawing group (-F) (**1g**) is present at the *ortho* position of the phenyl ring, a further drop in the product yield (**3g**, 59%) was observed (Scheme V.3.1). Further, the presence of a strongly electron-withdrawing substituent *p*–CF_3 (**1h**) reduced the yield of the product (**3h**) to 56%.

Scheme V.3.2. *Synthesis of bisimidazo[1,2-a]pyridin-3-ylmethane derivatives*[a,b]

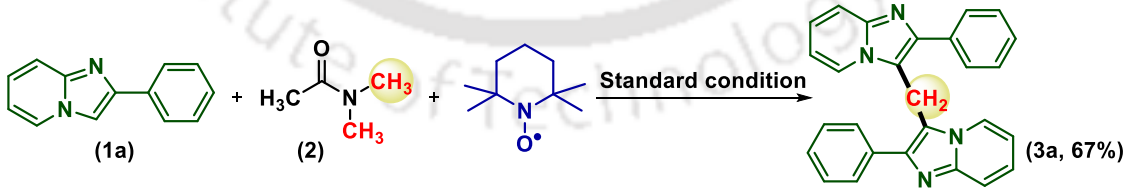


[a]Reaction conditions: Imidazo[1,2-*a*]pyridine (**1i**–**1t**) (0.25 mmol), $Cu(OAc)_2$ (20 mol %), $K_2S_2O_8$ (2 equiv) and DMA (2 mL) under air at 120 °C. [b]Isolated yield.

Next, electronic effects of substituents on the pyridine ring of imidazo[1,2-*a*]pyridine moiety were evaluated. In comparison to the electron-neutral analogue (**1a**), the presence of either a moderately electron-donating (-Me) or an electron-withdrawing group (-Br), irrespective of their positions of attachment, had negligible influence giving the corresponding products (**3i**–**3o**) in the yields ranging from 59–76% (Scheme V.3.2). Furthermore, a variety of imidazo[1,2-*a*]pyridine moieties having heterocycle, biphenyls as well as aliphatic groups (other than the phenyl derivatives) as C-2 substituents was explored (Scheme V.3.2, **3p**–**3t**). The reaction proceeded smoothly with all the substrates (**1p**–**1t**) giving the corresponding products in good to moderate yields under the optimized reaction conditions. Imidazo[1,2-*a*]pyridines bearing heterocycle substituent, 2-(thiophen-2-yl)imidazo[1,2-a]pyridine (**1p** and **1q**), gave their desired products (**3p**, 65%) and (**3q**, 68%), respectively, in comparable yields to that of electron-neutral substrate (**3a**, 69%). The biphenyl derivatives (**1r**) and (**1s**) had no influence on their product yields (**3r**, 67%) and (**3s**, 62%) relative to their phenyl analogues (**3a** and **3f**). However, the presence of a methyl group at C-2 position of imidazo[1,2-*a*]pyridine moiety (**1t**) resulted in a substantial drop in the product yield (**3t**, 53%), which may be due to the reduced nucleophilicity at the C-3 carbon (Scheme V.3.2).

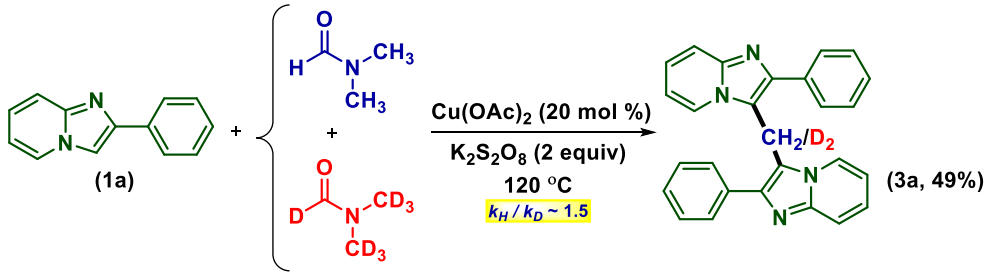
Mechanistic Studies:

To get an insight into the reaction mechanism, some experiments were carried out. Formation of the desired product (**3a**) even in the presence of a radical scavenger 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) (2 equiv) ruled out any possibility of a radical path (Scheme V.3.3).



Scheme V.3.3. *Reaction in the presence of radical scavenger TEMPO*

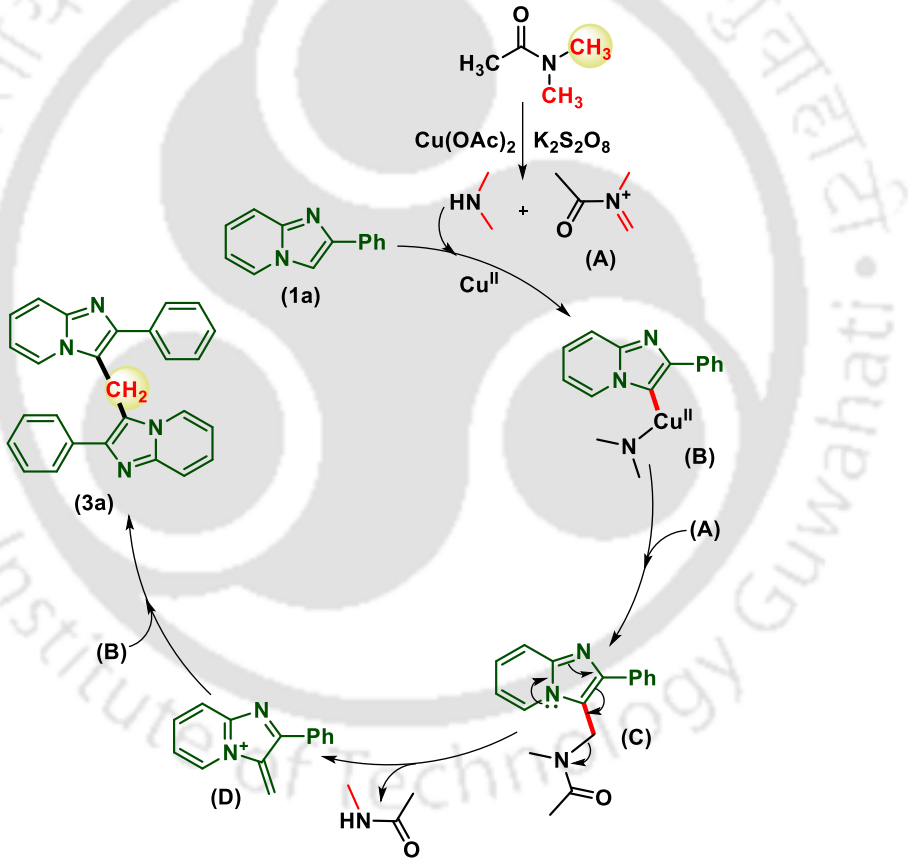
The observed KIE (k_H/k_D ~ 1.5) in an intermolecular competing reaction between DMF and DMF-d_7 with 2-phenylimidazo[1,2-*a*]pyridine (**1a**) suggests that the cleavage of the sp^3 C–H bond of DMA is possibly involved in the slow step of the reaction (Scheme V.3.4).



Scheme V.3.4. *KIE experiment with deuterated formamide*

On the basis of these observations, trends in the reaction yield and from the literature precedence, a plausible reaction mechanism is proposed in Scheme V.3.5.

Scheme V.3.5. *Plausible reaction mechanism*



Initially, an iminium cation (**A**)[25] and dimethylamine[26] are generated respectively by the oxidation and cleavage (C–N bond) of *N*,*N*-dimetylacetamide in the presence of $Cu(OAc)_2$ and $K_2S_2O_8$. The dimethylamine thus generated undergoes complexation with 2-phenylimidazo[1,2-*a*]pyridine (**1a**) and copper(II) salt generating species (**B**).[23a] The iminium cation (**A**) formed *in situ* undergoes subsequent nucleophilic addition with (**B**) forming an intermediate (**C**). Formation of intermediates (**B**) and (**C**) has been detected by

the HRMS analysis of the reaction aliquots after 0.5 and 1 h, respectively (Figure V.4.3 and V.4.4). The intermediate (**C**) is transformed to an intermediate (**D**), which finally reacts with the nucleophilic intermediate (**B**) to give the methylene linked product (**3a**) (Scheme V.3.5).

In conclusion, we have developed a copper(II)-catalyzed dimerization of two imidazo[1,2-*a*]pyridine moieties with a methylene linkage in the presence of an external oxidant. To the best of our knowledge, this is the first report on the utilization of DMA as a methylene source for the bridging of two analogous heterocycles. Use of cheaper reagents, regioselectivity, and broad substrate scope are the notable features of this methodology. The synthesized methylene bridged dimeric imidazo[1,2-*a*]pyridine derivatives may find applications in the field of medicinal and material chemistry.

V.4. Experimental Section

V.4.1. General Information: All the compounds were commercial grade and used without further purification. Organic extract was dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as internal standard for ^{1}HNMR (400 and 600 MHz) and $CDCl_3$ solvent as internal standard for ^{13}CNMR (100 and 150 MHz). HRMS spectra were recorded using ESI mode (Q-TOF type Mass Analyser). IR spectra were recorded in KBr or neat.

V.4.2. Crystallographic Description

CCDC Number for Compound 3b: CCDC-983611. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystallographic Description of Bis(2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3b): $C_{29}H_{24}N_4$, crystal dimensions 0.30 x 0.28 x 0.25mm, M_r = 428.52, Triclinic, space group P 21 21 21, a = 9.9914(7), b = 10.2478(7), c = 11.7303(8) Å, α = 75.234°, β = 84.071° (9), γ = 86.315°, V = 1154.29(14) Å^3, Z = 2, ρ_{calcd} = 1.233g/cm^3, μ = 0.074mm^{-1}, F(000)= 452.0, reflection collected / unique = 3918 / 4054, refinement method = full-

matrix least-squares on F^2, final *R* indices [$I > 2\sigma(I)$]: $R_1 = 0.0452$, $wR_2 = 0.1560$, *R* indices (all data): $R_1 = 0.0717$, $wR_2 = 0.1560$, goodness of fit = 1.031.

V.4.3. General Procedure for the Synthesis of Bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (3a): 2-Phenylimidazo[1,2-*a*]pyridine (**1a**) (0.25 mmol, 48.5 mg), $Cu(OAc)_2$ (0.05 mmol, 9 mg), $K_2S_2O_8$ (0.5 mmol, 135 mg), DMA (2 mL), were taken in an oven-dried round-bottom flask charged with a magnetic stir bar and stirred on a preheated oil bath at 120 ^oC for 6 h in an open air atmosphere. After completion of the reaction (as indicated by the TLC), the reaction mixture was cooled to room temperature and admixed with ethyl acetate (20 mL). The organic layer was washed successively with a saturated solution of sodium bicarbonate (2 x 5 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under vacuum. The crude product so obtained was purified using column chromatography and eluted with 2:3 ethyl acetate:hexane and triethylamine (1%) to afford the desired product (**3a**) in 69% (69 mg) yield.

V.4.4. Reaction of 2-Phenylimidazo[1,2-*a*]pyridine (1a) with DMA in the Presence of Radical Scavenger TEMPO: An oven-dried round bottom flask was charged with 2-phenylimidazo[1,2-*a*]pyridine (**1a**) (0.25 mmol, 48.5 mg), $Cu(OAc)_2$ (0.05 mmol, 9 mg), $K_2S_2O_8$ (0.5 mmol, 135 mg), TEMPO (0.5 mmol, 78 mg) and DMA (2 mL), and the mixture was stirred in a preheated oil bath at 120 ^oC for 6 h. The reaction after 6 h shows the formation of desired product (**3a**) in 67% yield.

V.4.5. Intermolecular Competing Kinetic Isotope Effect (KIE) Experiment with Deuterated Formamide: To a solution of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) (0.25 mmol, 48.5 mg) in DMF and DMF-d_7 (1:1, 2.0 mL) (**2**), catalyst $Cu(OAc)_2$ (20 mol %) and oxidant $K_2S_2O_8$ (2 equiv) were added and the resultant reaction mixture was put into a preheated oil bath at 120 ^oC for 8 h. After completion of the reaction (as indicated by the TLC), the reaction mixture was cooled to room temperature and admixed with ethyl acetate (20 mL). The organic layer was washed successively with saturated solution of sodium bicarbonate (2 x 5 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuum. The crude product so obtained was purified using column chromatography and eluted with 2:3 ethyl acetate:hexane in triethylamine (1%) to afford the corresponding deuterated and non-deuterated product. The product so obtained

was subjected to ^{1}HNMR analysis. The ratio of the deuterated and non-deuterated product was calculated on the basis of the integration ratio of the aromatic proton at 7.79 ppm and –CH_2 proton at 5.00 ppm by adopting the procedure of Huang *et al*.[27] The k_H/k_D calculated on the basis of ^{1}HNMR analysis of the pure product showed KIE (k_H/k_D = 1.5). This result suggests that the cleavage of the sp^3 C–H bond of DMA is possibly involved in the slow step of the reaction.

Calculation:

For four aromatic protons at 7.79, the integration value is 2.00.

Thus for a single proton the integration corresponds to 2.00 / 4 = 0.50.

Now for the integration value of the protons originating from formamide at 5.00 is 0.75.

Thus the number of protons corresponding to this integration value is 0.75 / 0.50 = 1.50.

Upon correlation with the aromatic proton the number of proton at 5.00 should be 2.

Hence the proton difference in this region is 2.00 – 1.50 = 0.50

Thus the k_H / k_D = 0.75 / 0.50 ~ 1.5.

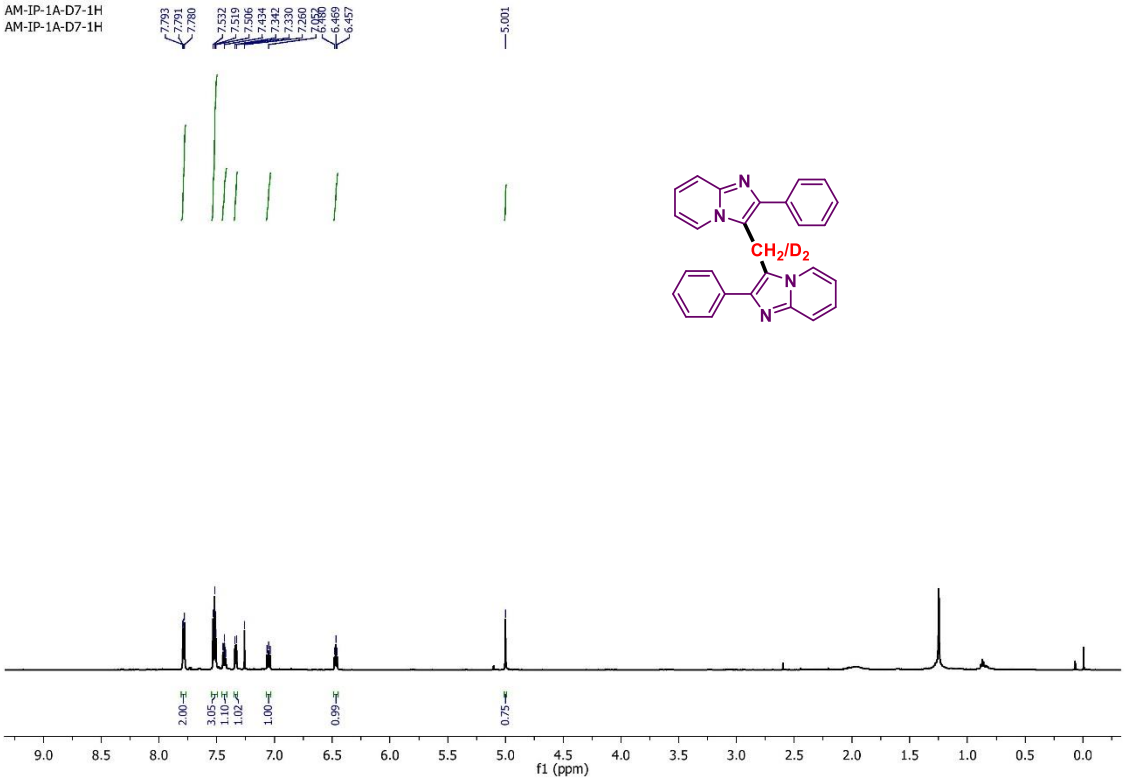


Figure V.4.1. *^{1}HNMR spectra of the deuterium inserted product*

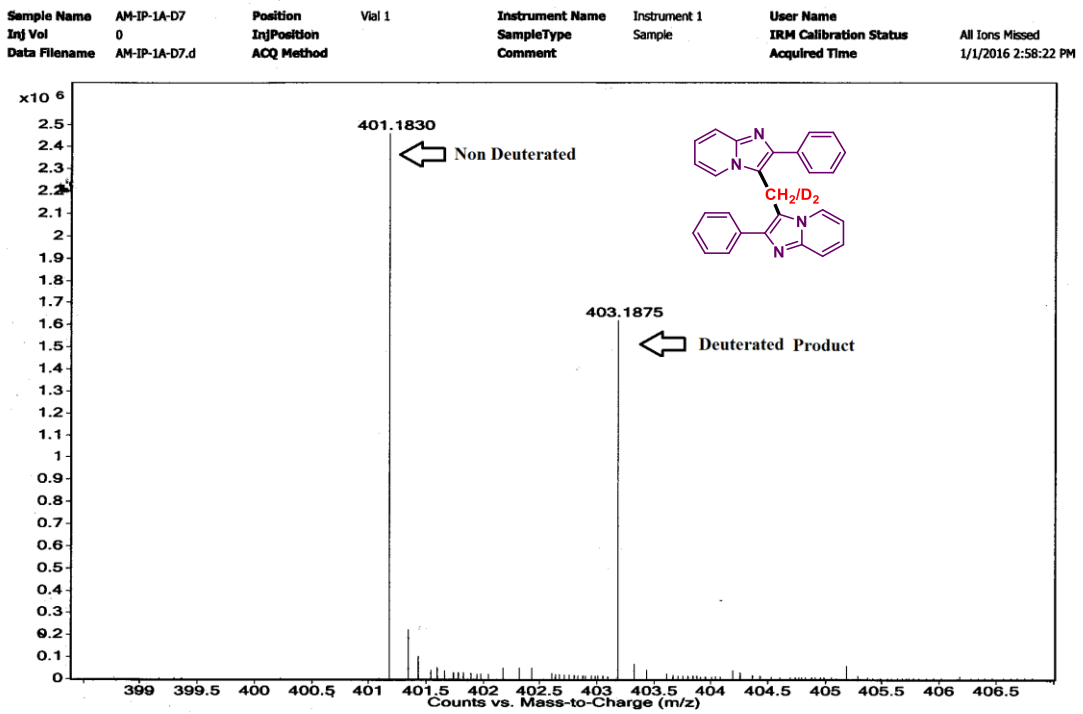


Figure V.4.2. *Mass spectra of the deuterium inserted product*

V.4.6. Identification of the Reaction Intermediates: In order to detect the intermediate species involved in the reaction mechanism, a HRMS analysis of crude reaction mixture was performed. After stirring the reaction for 30 minute, 20 µL reaction mixture was taken out and diluted with HPLC grade acetonitrile. The diluted solution was then injected to run ESI-MS analysis. Intermediate (**B**) was detected in the MS analysis as shown in Figure V.4.3. The reaction mixture injected after an interval of 1 h detected both the intermediates (**B**) and (**C**) (Figure V.4.4) along with the product mass.

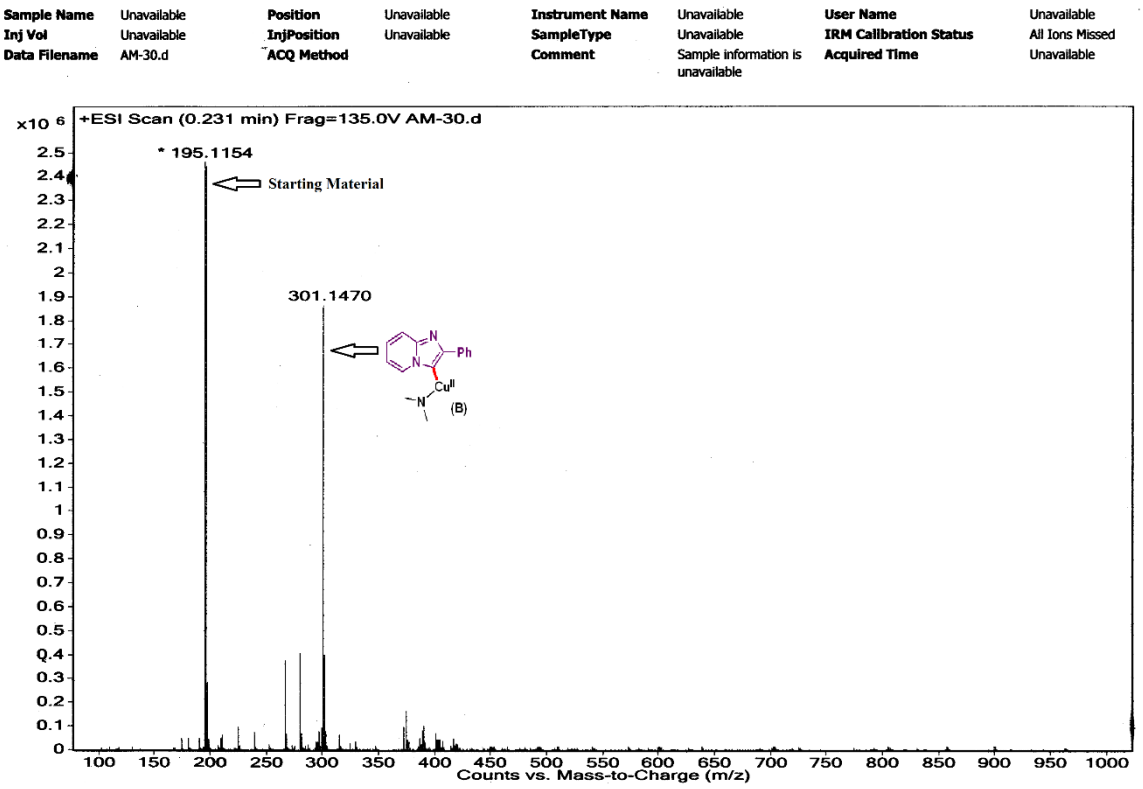


Figure V.4.3. *HRMS spectrum of the reaction mixture after 30 minutes*

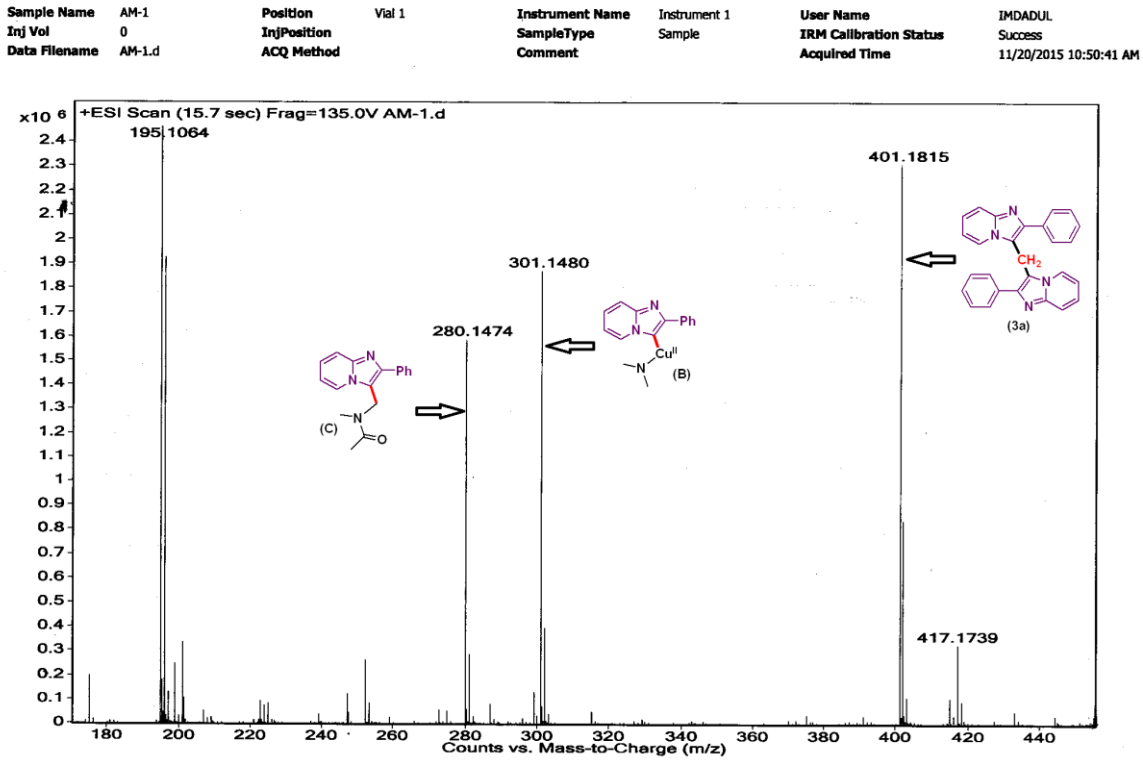


Figure V.4.4. *HRMS spectrum of the reaction mixture after 1 hour*

V.5. References

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(24) Yadav, M.; Dara, S.; Saikam, V.; Kumar, M.; Aithagani, S. K.; Paul, S.; Vishwakarma, R. A.; Singh, P. P. *Eur. J. Org. Chem.* **2015**, 6526.

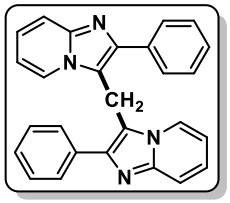
(25) (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (b) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997. (c) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (d) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (e) Baslé, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661. (f) Huang, L.; Zhang, X.; Zhang, Y. *Org. Lett.* **2009**, *11*, 3730.

(26) (a) Lao, Z.-Q.; Zhong, W.-H.; Lou, Q.-H.; Li, Z.-J.; Meng, X.-B. *Org. Biomol. Chem.* **2012**, *10*, 7869. (b) Xia, Q.; Chen, W. *J. Org. Chem.* **2012**, *77*, 9366.

(27) Xie, P.; Xie, Y.; Qian, B.; Zhou, H.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2012**, *134*, 9902.

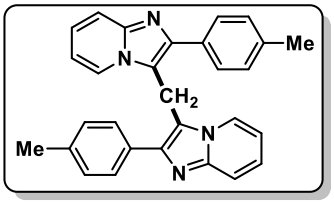
V.6. Spectral Data

Bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (3a):



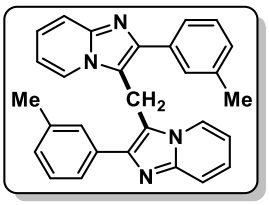
Brown solid (69 mg, 69%); mp 203–205 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 4.99 (s, 2H), 6.42 (t, 2H, *J* = 6.6 Hz), 7.04 (t, 2H, *J* = 7.2 Hz), 7.33 (d, 2H, *J* = 7.2 Hz), 7.43 (t, 2H. *J* = 7.2 Hz), 7.51 (t, 6H, *J* = 7.8 Hz), 7.78 (d, 4H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.9, 112.5, 114.5, 117.6, 124.0, 124.5, 128.4, 129.0, 129.1, 134.5, 144.4, 145.2; IR (KBr): 3070, 3037, 2924, 2847, 1630, 1618, 1501, 1479, 1353, 1259, 1218, 1069, 1023, 834, 751, 693 cm^{-1}; HRMS (ESI): calcd. for $C_{27}H_{20}N_4^+$ [M + H^+] 401.1761; found 401.1758.

Bis(2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3b):



White solid (80 mg, 75%); mp 252–255 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 6H), 4.97 (s, 2H), 6.44 (t, 2H, *J* = 6.8 Hz), 7.03 (t, 2H, *J* = 7.4 Hz), 7.32 (d, 6H, *J* = 7.6 Hz), 7.51 (d, 2H, *J* = 9.0 Hz), 7.68 (d, 4H, *J* = 8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.0, 21.6, 112.4, 114.3, 117.5, 124.1, 124.4, 129.0, 129.8, 131.6, 138.3, 144.4, 145.2; IR (KBr): 3067, 3038, 3026, 2918, 2850, 1631, 1499, 1354, 1268, 1233, 1173, 1114, 1014, 827, 739, 509 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{24}N_4^+$ [M + H^+] 429.2074; found 429.2084.

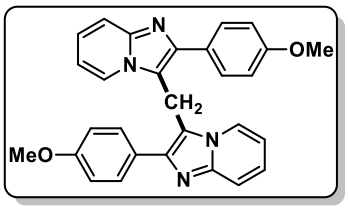
Bis(2-(*m*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3c):



Brown solid (75 mg, 70%); mp 101–103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.46 (s, 6H), 5.00 (s, 2H), 6.47 (t, 2H, *J* = 6.8 Hz), 7.05 (t, 2H, *J* = 8.0 Hz), 7.25 (d, 2H, *J* = 9.6 Hz), 7.36 (d, 2H, *J* = 6.8 Hz), 7.40 (t, 2H, *J* = 7.6 Hz), 7.53 (d, 2H, *J* = 8.8 Hz), 7.57 (d, 2H, *J* = 7.6 Hz), 7.63 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.0, 21.7, 112.5, 114.5, 117.6, 124.1, 124.5, 126.2, 128.9,

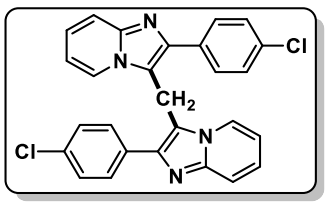
129.3, 129.9, 134.4, 138.8, 144.4, 145.1; IR (KBr): 3072, 3015, 2957, 2924, 2854, 1635, 1501, 1464, 1411, 1382, 1358, 1243, 1210, 1165, 1092, 1022, 785, 749, 691 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{24}N_4^+$ [M + H^+] 429.2074; found 429.2085.

Bis(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3d):



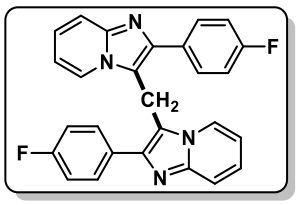
Brown gummy (93 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.88 (s, 6H), 4.93 (s, 2H), 6.46 (t, 2H, *J* = 6.8 Hz), 7.04 (d, 6H, *J* = 6.8 Hz) 7.34 (d, 2H, *J* = 6.8 Hz), 7.50 (d, 2H, *J* = 8.8 Hz), 7.71 (d, 4H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.0, 55.6, 112.4, 114.0, 114.5, 117.4, 124.0, 124.4, 126.9, 130.3, 144.1, 145.1, 159.8; IR (KBr): 3070, 3020, 2961, 2928, 2850, 1636, 1611, 1497, 1390, 1362, 1292, 1243, 1169, 1030, 834, 748, 732, 689 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{24}N_4O_2^+$ [M + H^+] 461.1972; found 461.1976.

Bis(2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3e):



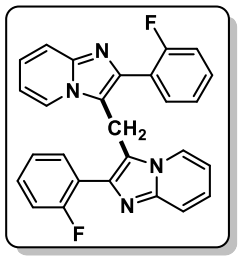
Brown solid (80 mg, 68%); mp 256–258 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.90 (s, 2H), 6.56 (t, 2H, *J* = 6.8 Hz), 7.10 (t, 2H, *J* = 7.6 Hz), 7.37 (d, 2H, *J* = 6.8 Hz), 7.42 (d, 4H, *J* = 8.4 Hz), 7.54 (d, 2H, *J* = 9.2 Hz), 7.64 (d, 4H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.2, 112.9, 114.2, 117.8, 123.6, 124.8, 129.1, 130.1, 132.8, 134.5, 143.3, 145.2; IR (KBr): 3119, 3031, 2919, 2847, 1623, 1500, 1479, 1402, 1351, 1274, 1228, 1172, 1090, 1013, 946, 823, 726, 511 cm^{-1}; HRMS (ESI): calcd. for $C_{27}H_{18}Cl_2N_4^+$ [M + H^+] 469.0981; found 469.0985.

Bis(2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3f):



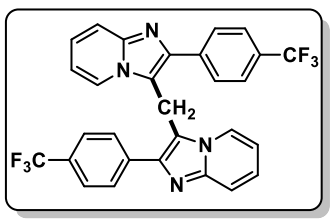
Pink solid (70 mg, 64%); mp 100–103 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 4.89 (s, 2H), 6.55 (t, 2H, *J* = 6.6 Hz), 7.10 (t, 2H, *J* = 6.9 Hz), 7.16 (t, 4H, *J* = 8.4 Hz), 7.37 (d, 2H, *J* = 7.2 Hz), 7.54 (d, 2H, *J* = 9.0 Hz), 7.68 (t, 4H, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.1, 112.8, 114.1, 115.9, 116.0, 117.7, 123.7, 124.8, 130.4, 130.6, 130.7, 143.4, 145.1, 162.1, 163.8; IR (KBr): 3071, 3028, 3015, 2924, 2852, 1633, 1615, 1495, 1387, 1351, 1223, 1151, 1182, 1095, 1008, 849, 752, 742, 687 cm^{-1}; HRMS (ESI): calcd. for $C_{27}H_{18}F_2N_4^+$ [M + H^+] 437.1572; found 437.1580.

Bis(2-(2-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3g):



Brown solid (64 mg, 59%); mp 175–177 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 4.71 (s, 2H), 6.57 (t, 2H, *J* = 6.6 Hz), 7.09 (t, 2H, *J* = 7.9 Hz), 7.18 (t, 2H, *J* = 9.6 Hz), 7.28 (t, 2H, *J* = 7.8 Hz), 7.40 (m, 2H), 7.48 (d, 2H, *J* = 7.2 Hz), 7.54 (d, 2H, *J* = 9.0 Hz), 7.66 (t, 2H, *J* = 7.5 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.2, 112.6, 116.1, 116.2, 117.8, 122.2, 122.3, 123.7, 124.4, 124.8, 130.5, 132.2, 138.9, 145.5, 159.0, 160.7; IR (KBr): 3068, 3030, 3017, 2930, 2850, 1634, 1618, 1489, 1380, 1361, 1225, 1149, 1192, 1090, 1010, 850, 742, 692 cm^{-1}; HRMS (ESI): calcd. for $C_{27}H_{18}F_2N_4^+$ [M + H^+] 437.1572; found 437.1582.

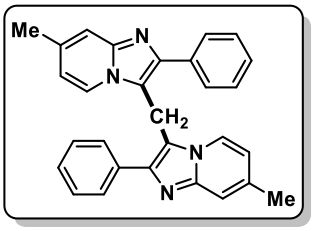
Bis(2-(4-(trifluoromethyl)phenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3h):



Brown solid (75 mg, 56%); mp 282–285 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.90 (s, 2H), 6.61 (t, 2H, *J* = 6.8 Hz), 7.13 (t, 2H, *J* = 7.6 Hz), 7.42 (d, 2H, *J* = 6.8 Hz), 7.54 (d, 2H, *J* = 9.2 Hz), 7.64 (d, 4H, *J* = 8.0 Hz), 7.74 (d, 4H, *J* = 8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm)

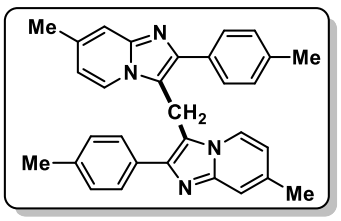
20.4, 113.1, 114.6, 118.0, 123.35, 123.41, 125.1, 125.2, 125.59, 125.62, 129.0, 129.9, 130.1, 130.3, 130.5, 137.8, 143.1, 145.3; IR (KBr): 3071, 3038, 2989, 2932, 1619, 1501, 1415, 1321, 1145, 1108 1071, 1006, 838, 736, 687 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{18}F_6N_4^+$ [M + H^+] 537.1508; found 537.1509.

Bis(7-methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (3i):



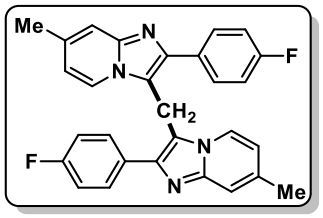
Brown gummy (76 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.26 (s, 6H), 4.95 (s, 2H), 6.28 (d, 2H, *J* = 6.8 Hz), 7.19 (d, 2H, *J* = 7.2 Hz), 7.26 (s, 2H), 7.43 (t, 2H, *J* = 7.6 Hz), 7.52 (t, 4H, *J* = 7.6 Hz), 7.80 (d, 4H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.9, 21.3, 114.1, 115.0, 115.9, 123.2, 128.2, 129.0, 129.1, 134.7, 135.5, 143.9, 145.6; IR (KBr): 3071, 3055, 2977, 2916, 2854, 1734, 1644, 1501, 1443, 1378, 1362, 1263, 1247, 1178, 1071, 1026, 920, 854, 773, 736 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{24}N_4^+$ [M + H^+] 429.2074; found 429.2079.

Bis(7-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3j):



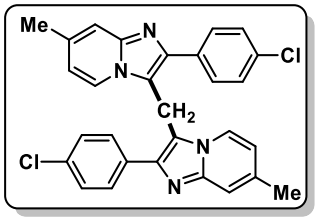
Orange gummy (87 mg, 76%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.25 (s, 6H), 2.43 (s, 6H), 4.91 (s, 2H), 6.27 (d, 2H, *J* = 7.2 Hz), 7.18 (d, 2H, *J* = 7.2 Hz), 7.27 (s, 2H), 7.32 (d, 4H, *J* = 8.0 Hz), 7.68 (d, 4H, *J* = 8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.8, 21.3, 21.5, 113.9, 115.0, 115.7, 123.3, 128.9, 129.7, 131.7, 135.4, 138.0, 143.8, 145.5; IR (KBr): 3065, 3051, 3030, 2961, 2920, 2859, 1644, 1619, 1558, 1497, 1443, 1378, 1353, 1243, 1174, 1108, 1026, 826, 777 cm^{-1}; HRMS (ESI): calcd. for $C_{31}H_{28}N_4^+$ [M + H^+] 457.2387; found 457.2390.

Bis(2-(4-chlorophenyl)-7-methylimidazo[1,2-*a*]pyridin-3-yl)methane (3k):



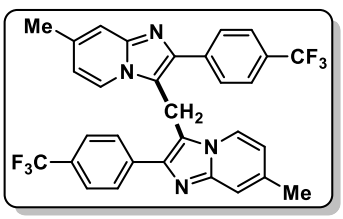
Brown solid (86 mg, 69%); mp 250–252 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.30 (s, 6H), 4.86 (s, 2H), 6.37 (d, 2H, *J* = 6.8 Hz), 7.22 (d, 2H, *J* = 6.8 Hz), 7.27 (d, 2H, *J* = 5.2 Hz), 7.45 (d, 4H, *J* = 8.4 Hz), 7.67 (d, 4H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.1, 21.4, 113.9, 115.5, 116.1, 122.9, 129.1, 130.1, 133.1, 134.3, 135.9, 142.8, 145.7; IR (KBr): 3064, 2964, 2920, 2850, 1644, 1480, 1403, 1374, 1239, 1169, 1088, 1010, 838, 777, 732 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{22}Cl_2N_4^+$ [M + H$^+$] 497.1294; found 497.1290.

Bis(2-(4-fluorophenyl)-7-methylimidazo[1,2-*a*]pyridin-3-yl)methane (3l):



Cream solid (79 mg, 68%); mp 245–248 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.29 (s, 6H), 4.85 (s, 2H), 6.35 (d, 2H, *J* = 6.8 Hz), 7.15–7.23 (m, 6H), 7.27 (s, 2H), 7.71 (t, 4H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.9, 21.3, 113.7, 115.2, 115.8, 115.9, 116.0, 122.9, 130.6, 130.7, 135.7, 143.0, 145.5, 161.6, 164.0; IR (KBr): 3063, 2952, 2916, 2859, 1644, 1607, 1497, 1382, 1223, 1157, 1092, 1010, 846, 773, 728, 650 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{22}F_2N_4^+$ [M + H$^+$] 465.1885; found 465.1889.

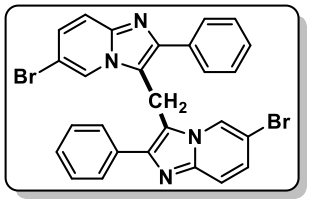
Bis(7-methyl-2-(4-(trifluoromethyl)phenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3m):



Brown solid (83 mg, 59%); mp 275–277 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 6H), 4.88 (s, 2H), 6.43 (d, 2H, *J* = 6.8 Hz), 7.28 (d, 4H, *J* = 7.6 Hz), 7.67 (d, 4H, *J* = 8.0 Hz), 7.78 (d, 4H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.4, 21.4, 114.3, 115.8, 116.3, 122.7, 123.4, 125.2, 125.7, 129.0, 129.8, 130.0, 130.2, 130.4, 136.2, 138.0, 142.7, 145.8; IR (KBr): 3060, 2965,

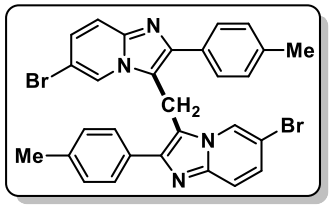
2920, 2846, 1636, 1505, 1411, 1321, 1169, 1116, 1071, 1010, 850, 767, 723 cm^{-1}; HRMS (ESI): calcd. for $C_{31}H_{22}F_6N_4^+$ [M + H^+] 565.1821; found 565.1827.

Bis(6-bromo-2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (3n):



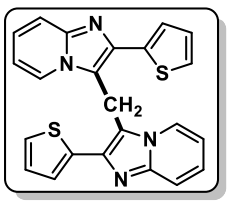
Cream solid (95 mg, 68%); mp 273–277 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.93 (s, 2H), 7.12 (d, 2H, *J* = 9.6 Hz), 7.41 (d, 4H, *J* = 10.4 Hz), 7.49 (t, 2H, *J* = 7.2 Hz), 7.58 (t, 4H, *J* = 7.2 Hz), 7.78 (d, 4H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.3, 107.3, 114.8, 118.3, 124.4, 128.2, 129.0, 129.3, 129.5, 133.9, 143.7, 145.4; IR (KBr): 3052, 2957, 2928, 2850, 1636, 1517, 1493, 1378, 1329, 1259, 1165, 1075, 1030, 777, 760, 699 cm^{-1}; HRMS (ESI): calcd. for $C_{27}H_{18}Br_2N_4^+$ [M + H^+] 556.9971; found 556.9990.

Bis(6-bromo-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3o):



Brown solid (105 mg, 72%); mp 275–278 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.45 (s, 6H), 4.87 (s, 2H), 7.09 (d, 2H, *J* = 9.6 Hz), 7.38 (t, 8H, *J* = 8.4 Hz), 7.64 (d, 4H, *J* = 7.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.2, 21.6, 107.1, 114.7, 118.1, 124.4, 128.0, 129.1, 130.1, 130.8, 138.8, 143.6, 145.3; IR (KBr): 3070, 3056, 2921, 2852, 1642, 1516, 1495, 1406, 1385, 1328, 1242, 1083, 1030, 821, 793 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{22}Br_2N_4^+$ [M + H^+] 585.0284; found 585.0270.

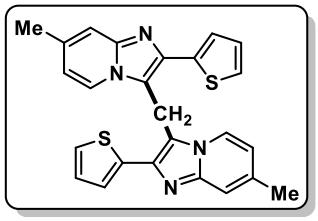
Bis(2-(thiophen-2-yl)imidazo[1,2-*a*]pyridin-3-yl)methane (3p):



Yellow solid (67 mg, 65%); mp 245–247 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 5.15 (s, 2H), 6.51 (t, 2H, *J* = 6.6 Hz), 7.07 (t, 2H, *J* = 7.8 Hz), 7.21 (t, 2H, *J* = 4.8 Hz), 7.48 (d, 2H, *J* = 5.4 Hz), 7.54 (t, 4H, *J* = 7.8 Hz), 7.59 (d, 2H, *J* = 3.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.5, 113.0, 113.7, 117.6, 124.0, 125.1, 126.0, 126.7,

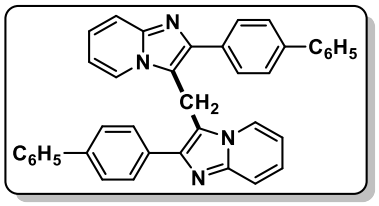
128.2, 137.1, 138.6, 145.4; IR (KBr): 3063, 2950, 2924, 2854, 1632, 1497, 1435, 1362, 1329, 1268, 1206, 1137, 740, 699 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{16}N_4S_2^+$ [M + H^+] 413.0889; found 413.0896.

Bis(7-methyl-2-(thiophen-2-yl)imidazo[1,2-*a*]pyridin-3-yl)methane (3q):



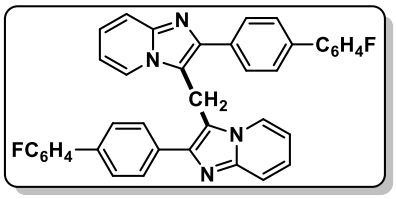
Brown solid (75 mg, 68%); mp 185–189 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.26 (s, 6H), 5.10 (s, 2H), 6.34 (d, 2H, *J* = 6.9 Hz), 7.21 (t, 2H, *J* = 4.2 Hz), 7.28 (s, 2H), 7.40 (d, 2H, *J* = 7.2 Hz), 7.46 (d, 2H, *J* = 5.4 Hz), 7.57 (d, 2H, *J* = 3.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.4, 21.4, 113.3, 115.6, 115.9, 123.3, 125.8, 126.4, 128.1, 136.1, 137.4, 138.2, 145.9; IR (KBr): 3062, 2957, 2928, 2850, 1640, 1558, 1497, 1435, 1378, 1341, 1247, 1214, 1161, 1022, 846, 707, 777 cm^{-1}; HRMS (ESI): calcd. for $C_{25}H_{20}N_4S_2^+$ [M + H^+] 441.1202; found 441.1209.

Bis(2-([1,1'-biphenyl]-4-yl)imidazo[1,2-*a*]pyridin-3-yl)methane (3r):



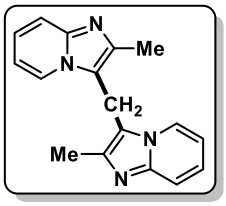
Black solid (92 mg, 67%); mp 233–235 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 5.05 (s, 2H), 6.50 (t, 2H, *J* = 6.6 Hz), 7.06 (t, 2H, *J* = 7.8 Hz), 7.38 (t, 2H, *J* = 7.2 Hz), 7.43 (d, 2H, *J* = 7.2 Hz), 7.48 (t, 4H, *J* = 7.2 Hz), 7.53 (d, 2H, *J* = 9.0 Hz), 7.68 (d, 4H, *J* = 7.2 Hz), 7.73 (d, 4H, *J* = 7.8 Hz), 7.86 (d, 4H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.3, 112.6, 114.5, 117.6, 123.9, 124.6, 127.3, 127.6, 127.7, 129.1, 129.4, 133.4, 140.7, 141.0, 144.1, 145.2; IR (KBr): 3051, 2922, 2852, 1634, 1484, 1447, 1384, 1358, 1273, 1242, 1148, 1179, 1007, 846, 734, 697 cm^{-1}; HRMS (ESI): calcd. for $C_{39}H_{28}N_4^+$ [M + H^+] 553.2387; found 553.2395.

Bis(2-(4'-fluoro-[1,1'-biphenyl]-4-yl)imidazo[1,2-a]pyridin-3-yl)methane (3s):



Brown solid (91 mg, 62%); mp 260–263 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.20 (s, 2H), 6.52 (t, 2H, *J* = 6.8 Hz), 7.07 (t, 2H, *J* = 7.6 Hz), 7.15 (t, 4H, *J* = 8.8 Hz), 7.44 (d, 2H, *J* = 6.8 Hz), 7.54 (d, 2H, *J* = 8.8 Hz), 7.61 (t, 4H, *J* = 7.0 Hz), 7.65 (d, 4H, *J* = 8.0 Hz), 7.83 (d, 4H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.4, 112.6, 114.4, 115.8, 116.0, 117.7, 123.8, 124.6, 127.4, 128.8, 128.9, 129.4, 133.3, 136.8, 140.0, 144.0, 145.2, 161.6, 164.0; IR (KBr): 3063, 2923, 2848, 1635, 1490, 1453, 1376, 1280, 1245, 1140, 1010, 773, 697 cm^{-1}; HRMS (ESI): calcd. for $C_{39}H_{26}F_2N_4^+$ [M + H^+] 589.2198; found 589.2209.

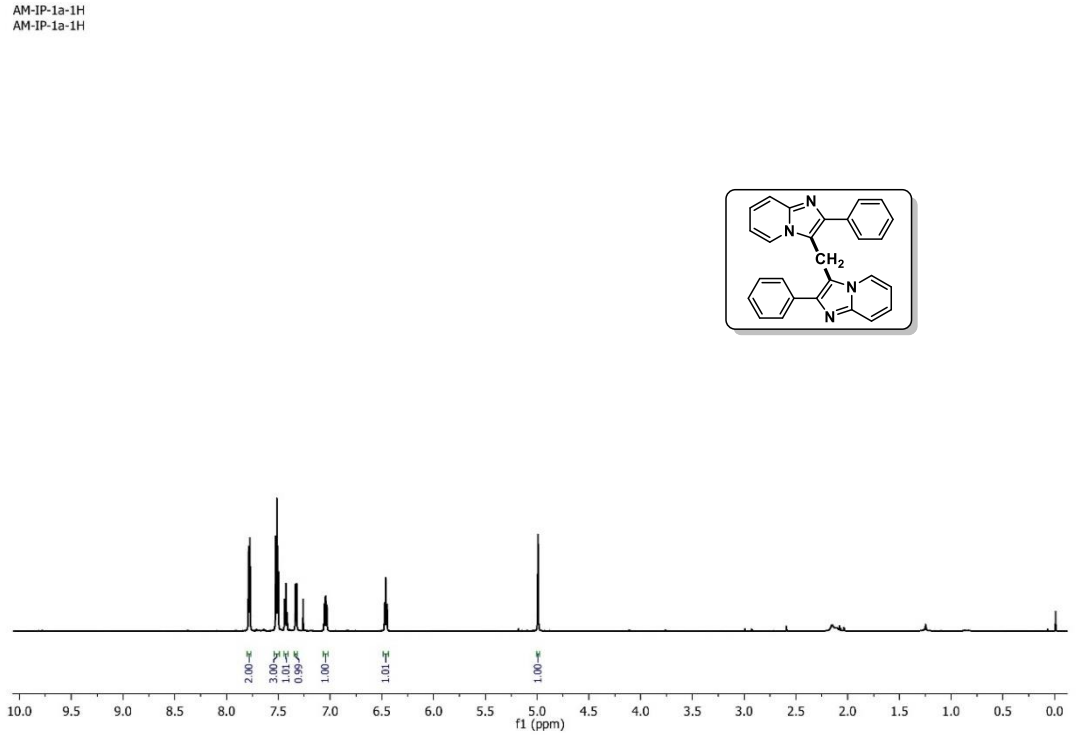
Bis(2-methylimidazo[1,2-*a*]pyridin-3-yl)methane (3t):



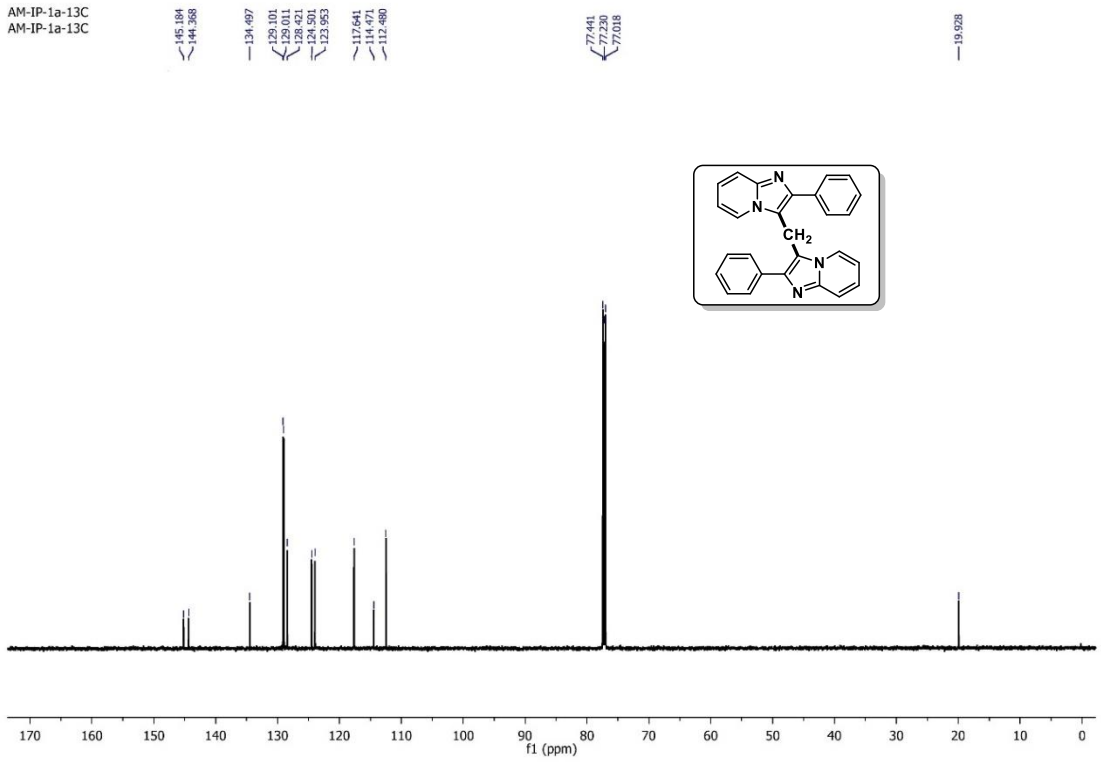
Brown solid (37 mg, 53%); mp 206–208 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 6H), 4.45 (s, 2H), 6.67 (t, 2H, *J* = 6.6 Hz), 7.10 (t, 2H, *J* = 7.2 Hz), 7.51 (d, 2H, *J* = 9.0 Hz), 7.62 (d, 2H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.7, 19.4, 112.4, 113.8, 117.1, 123.0, 123.9, 141.0, 144.8; IR (KBr): 3059, 2925, 2853, 1635, 1503, 1446, 1402, 1351, 1277, 1248, 1210, 1134, 751, 668 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{16}N_4^+$ [M + H^+] 277.1448; found 277.1460.

V.7. Spectra

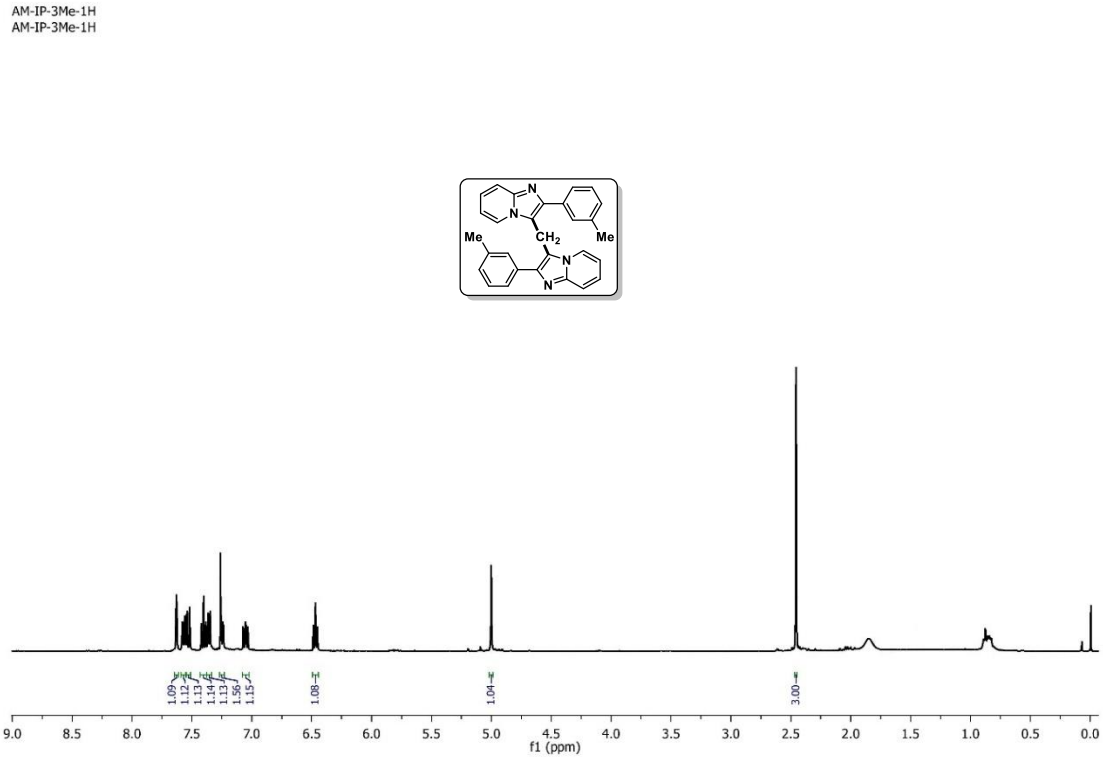
Bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (3a): ^{1}HNMR (600 MHz, $CDCl_3$)



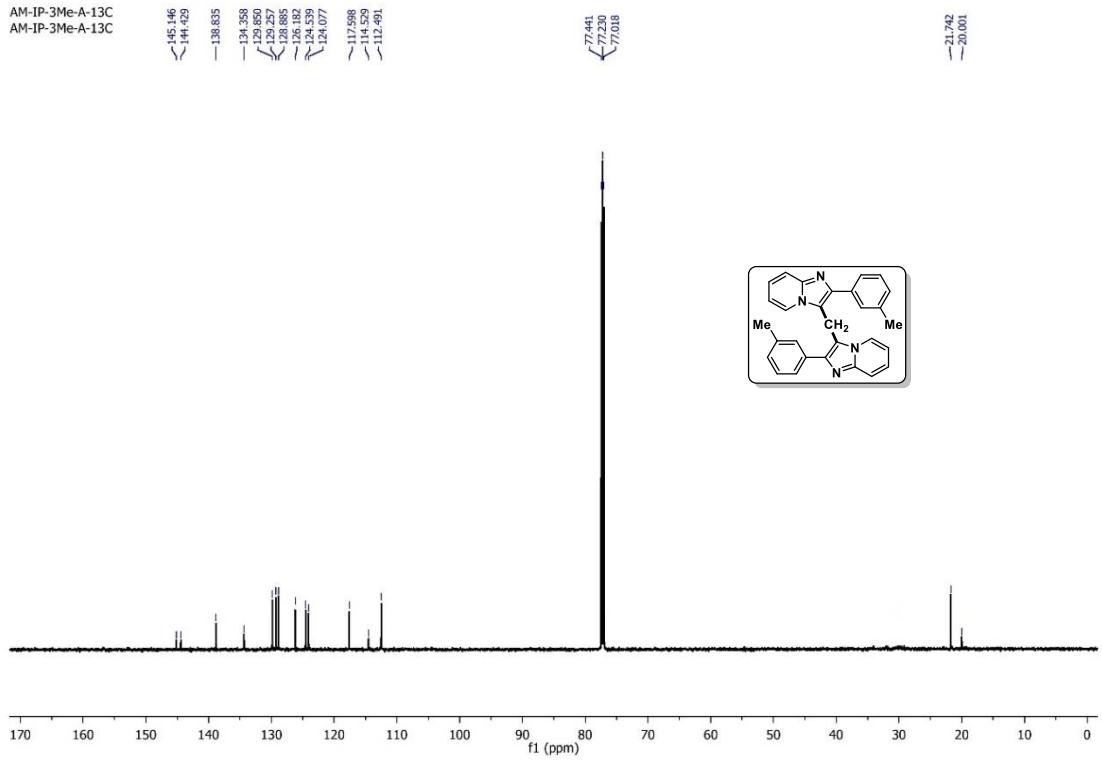
Bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (3a): ^{13}CNMR (150 MHz, $CDCl_3$)



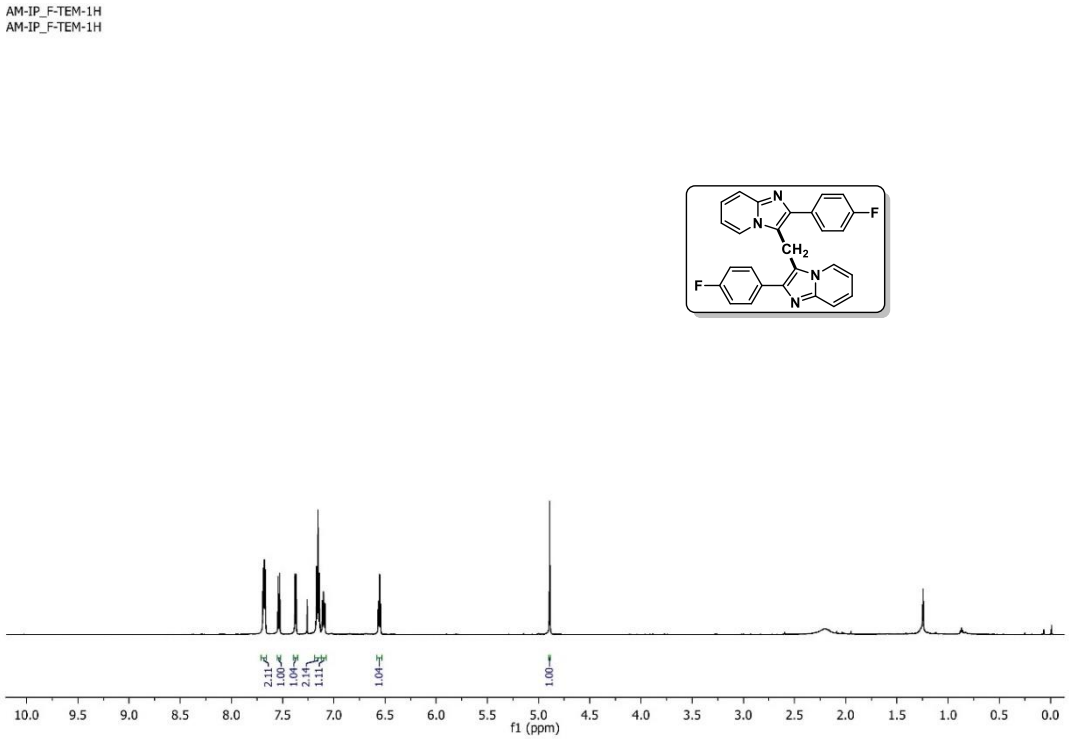
Bis(2-(*m*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3c): ^{1}HNMR (400 MHz, $CDCl_3$)



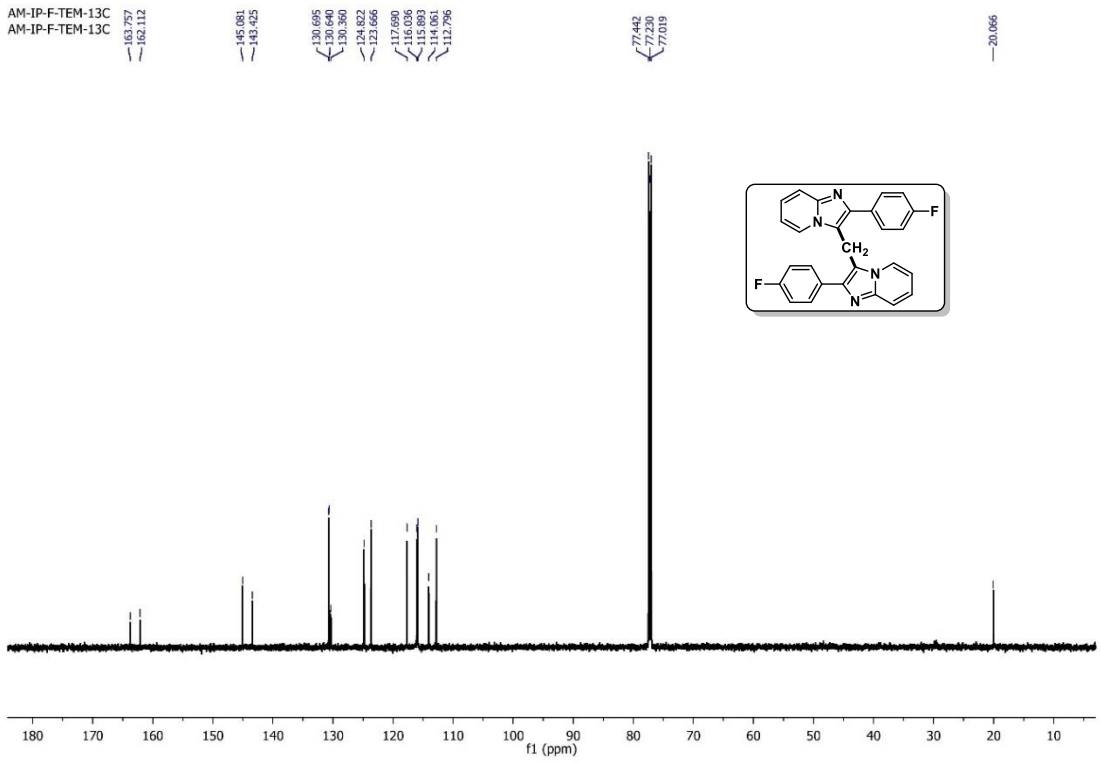
Bis(2-(*m*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3c): ^{13}CNMR (150 MHz, $CDCl_3$)



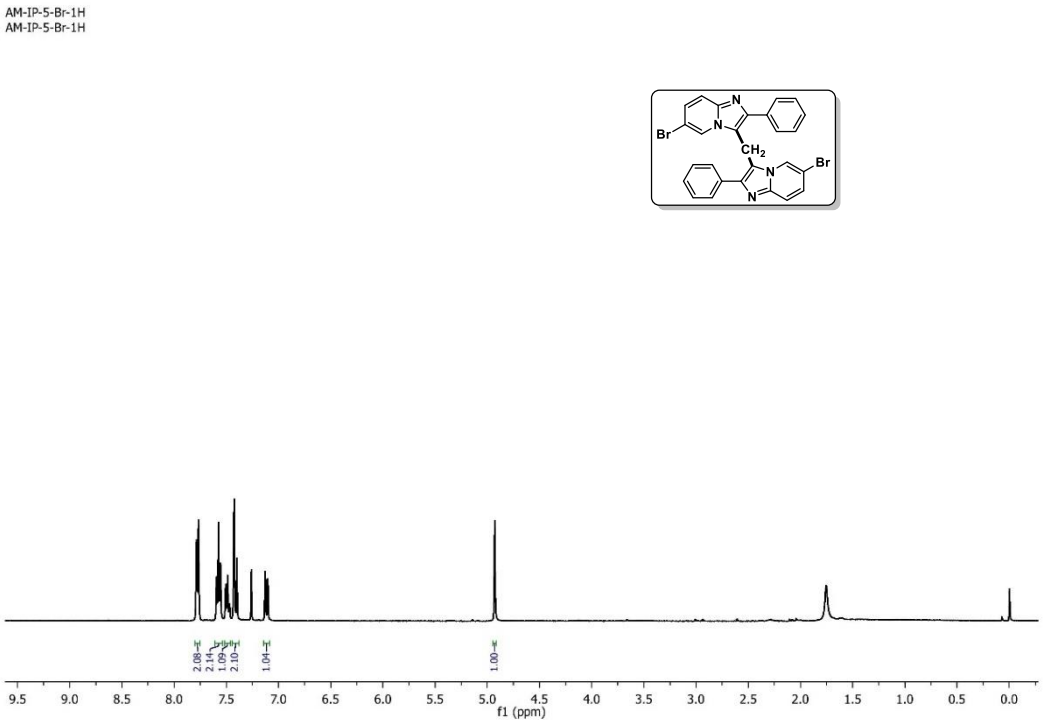
Bis(2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3f): ^{1}HNMR (600 MHz, $CDCl_3$)



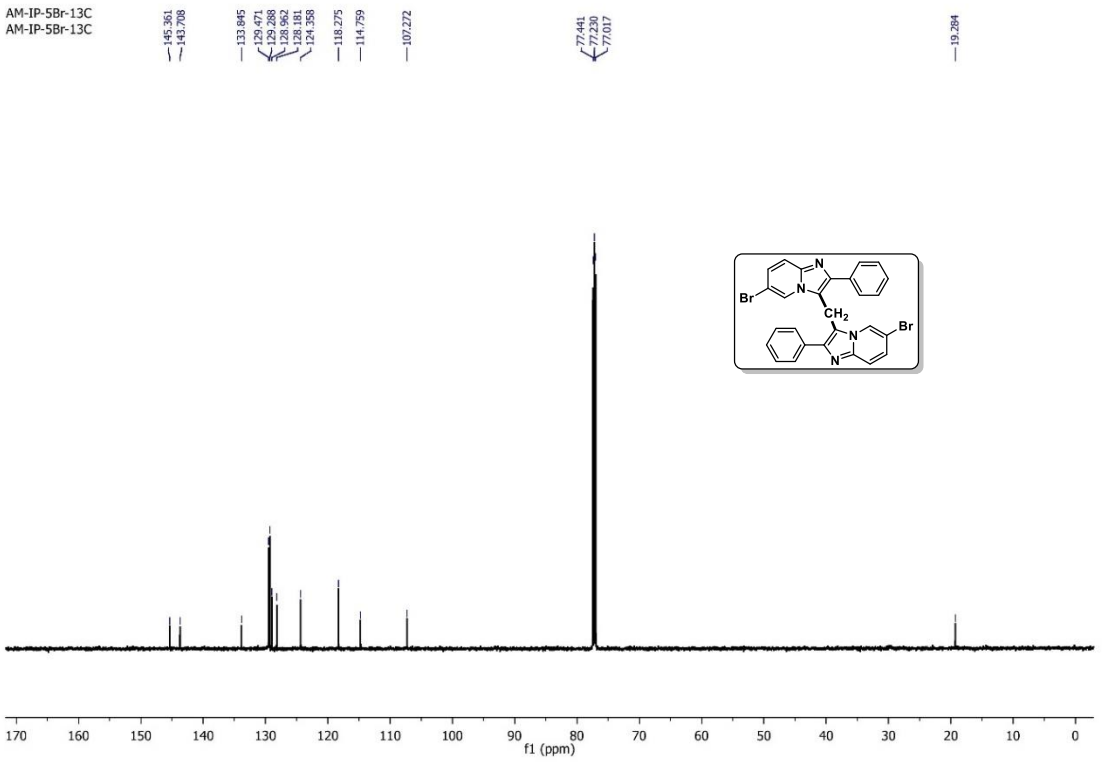
Bis(2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3f): ^{13}CNMR (150 MHz, $CDCl_3$)



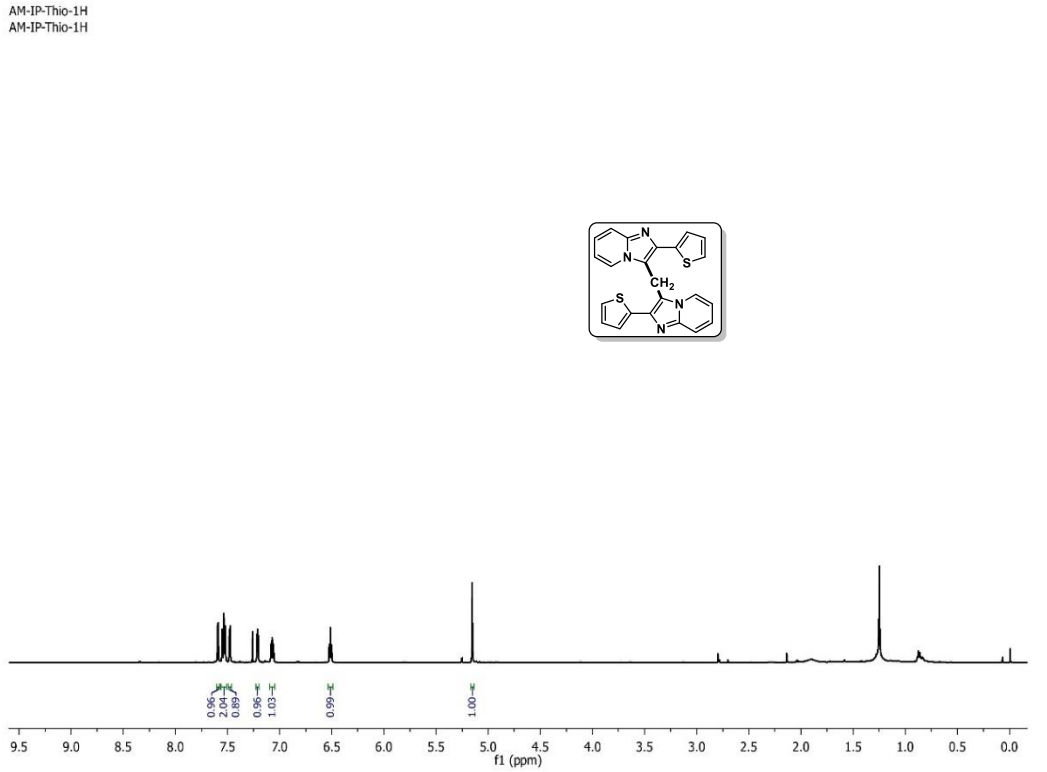
Bis(6-bromo-2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (3n): ^{1}HNMR (400 MHz, $CDCl_3$)



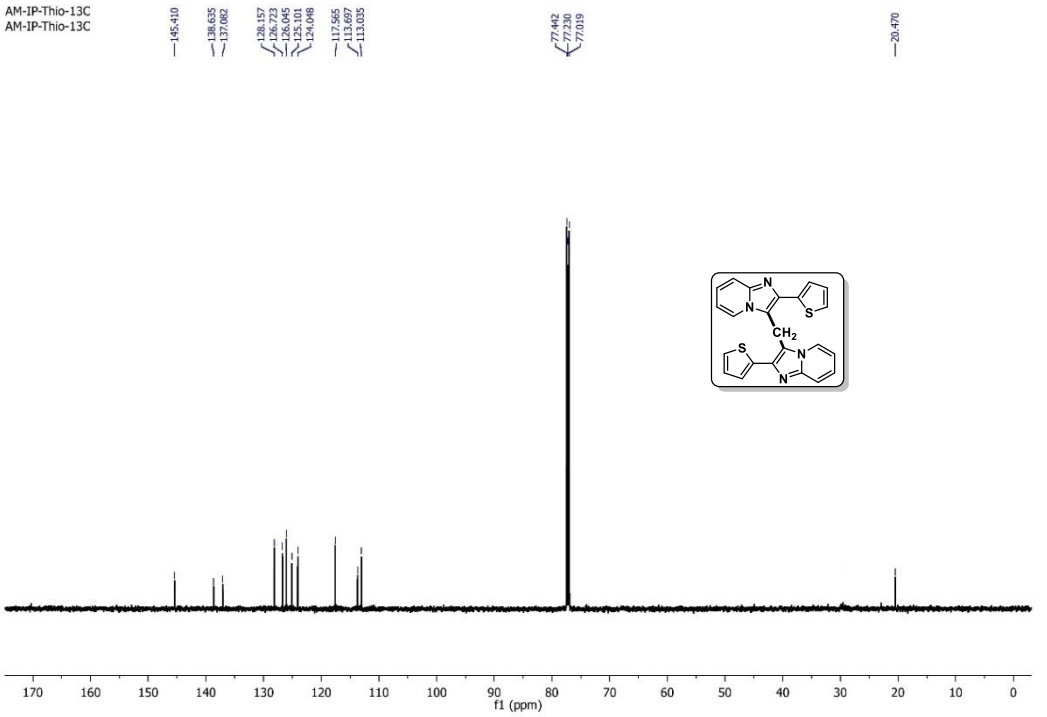
Bis(6-bromo-2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (3n): ^{13}CNMR (150 MHz, $CDCl_3$)



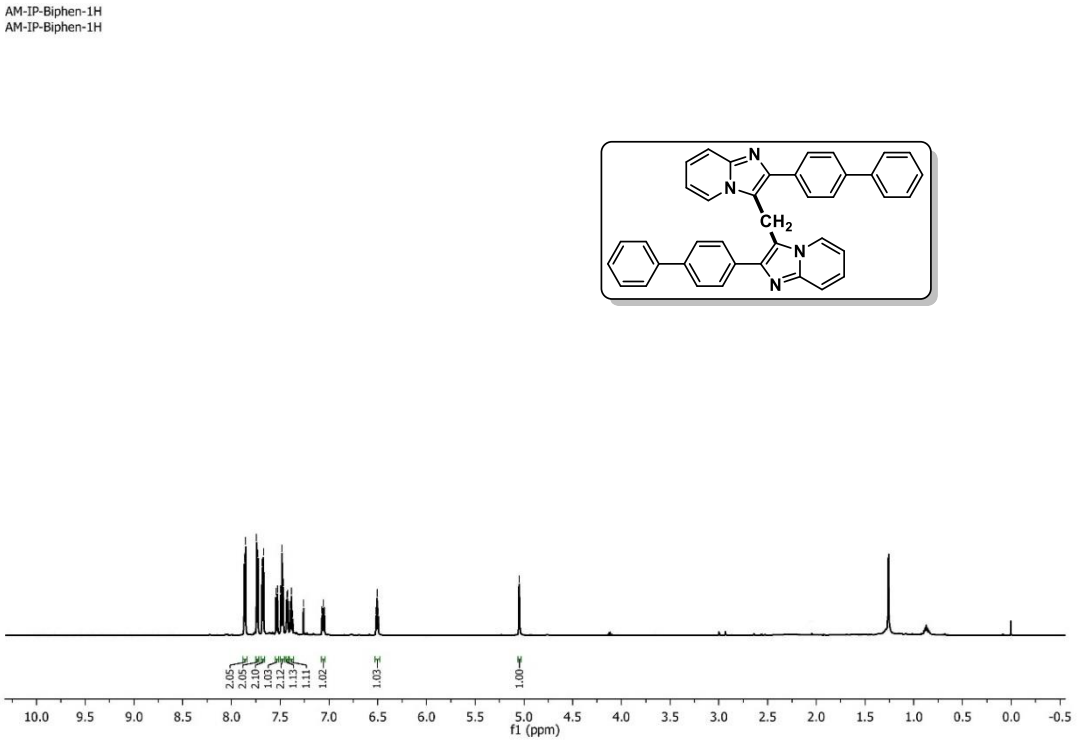
Bis(2-(thiophen-2-yl)imidazo[1,2-*a*]pyridin-3-yl)methane (3p): ^{1}HNMR (600 MHz, $CDCl_3$)



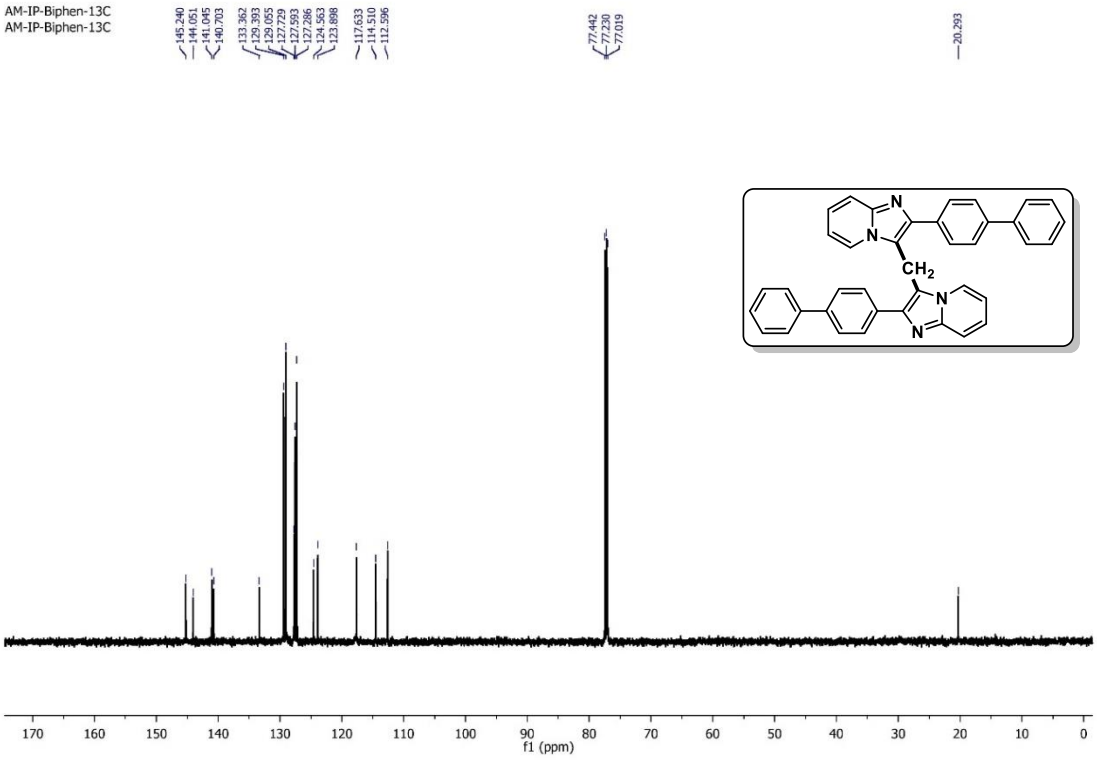
Bis(2-(thiophen-2-yl)imidazo[1,2-*a*]pyridin-3-yl)methane (3p): ^{13}HNMR (150 MHz, $CDCl_3$)



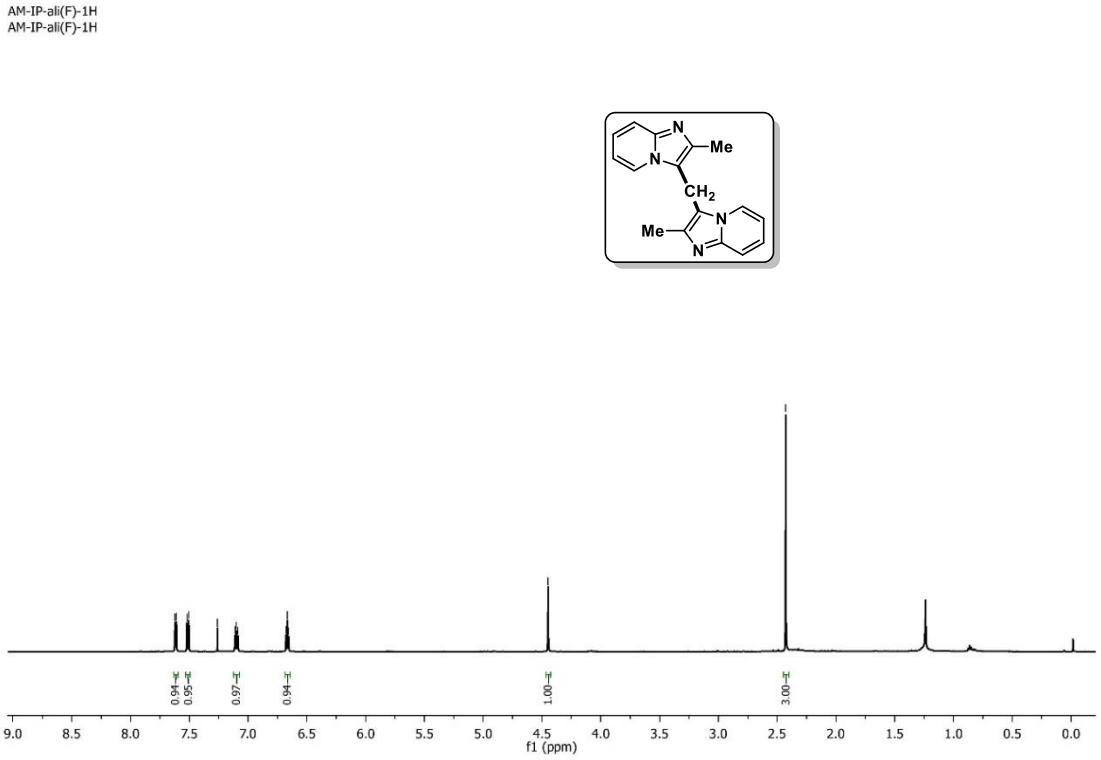
Bis(2-([1,1'-biphenyl]-4-yl)imidazo[1,2-*a*]pyridin-3-yl)methane (3r): ^{1}HNMR (600 MHz, $CDCl_3$)



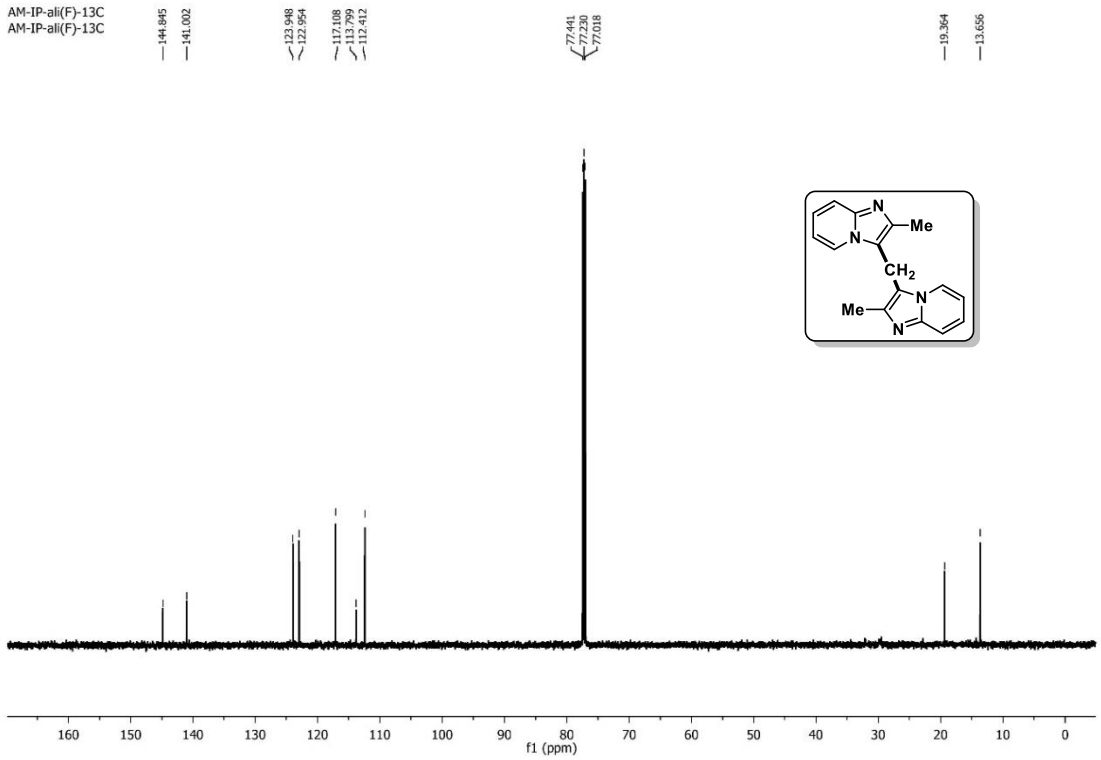
Bis(2-([1,1'-biphenyl]-4-yl)imidazo[1,2-*a*]pyridin-3-yl)methane (3r): ^{13}CNMR (150 MHz, $CDCl_3$)



Bis(2-methylimidazo[1,2-*a*]pyridin-3-yl)methane (3t): ^{1}HNMR (600 MHz, $CDCl_3$)

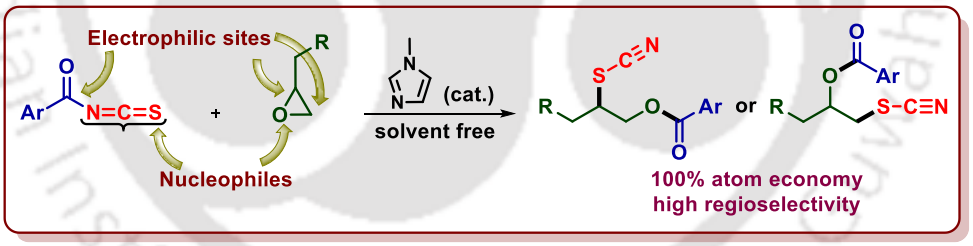


Bis(2-methylimidazo[1,2-*a*]pyridin-3-yl)methane (3t): ^{13}CNMR (150 MHz, $CDCl_3$)



CHAPTER VI

Organocatalytic Regioselective Concomitant Thiocyanation and Acylation of Oxirane Using Aroyl Isothiocyanates



ABSTARCT: *A regioselective and concomitant transfer of thiocyanate (–SCN) and aroyl/acyl (–COR) groups from aroyl/acyl isothiocyanates onto oxiranes was achieved, giving thiocyanato benzoates in 100% atom economy. In this biomimetic organocatalytic process, one part (–SCN) of aroyl/acyl isothiocyanates acts as the nucleophile whereas the other half (–COR) serves as an electrophilic partner.*

CHAPTER VI

VI. Organocatalytic Regioselective Concomitant Thiocyanation and Acylation of Oxiranes Using Aroyl Isothiocyanates

VI.1. Introduction

The desire to develop newer methodology for the construction of C–C and C–X (X = heteroatom) bonds has brought about many appealing results in the field of synthetic chemistry.[1] The establishment of C–SCN bond has recently received significant attention due to the fact that organic thiocyanates are efficient synthetic precursors to access various valuable sulfur-containing compounds such as $–SCF_3$, $–SCF_2H$, thiotetrazoles and 2-amino-1,3-thiazines.[2] The organic thiocyanates are also important functionality in natural products (Figure VI.1.1) and bioactive compounds possessing anti-microbial and anti-proliferative activities.[3]

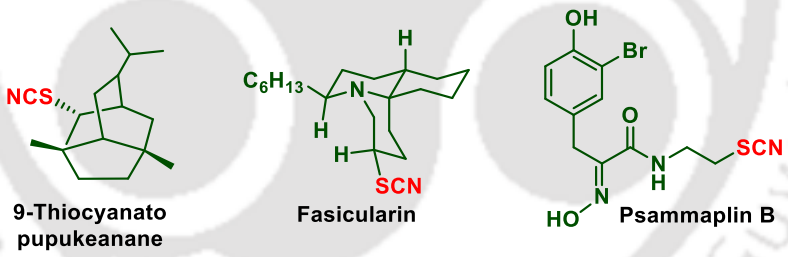
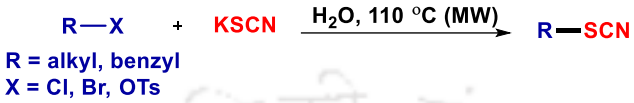


Figure VI.1.1. *Thiocyanate-containing natural products*

The organic thiocyanates are primarily synthesized either by using a thiocyanating agent or by reacting substrates bearing electrophilic or nucleophilic sulfur with cyanating agents. Thiocyanate salts such as potassium thiocyanate (KSCN), sodium thiocyanate (NaSCN) and ammonium thiocyanate (NH_4SCN) are generally used in nucleophilic substitutions to access alkyl thiocyanates. However, their combination with an oxidant or a transition metal is required for the preparation of aromatic counterparts via electrophilic reactions or cross-coupling reactions. Nucleophilic substitution approaches use easily accessible starting materials bearing leaving groups such as halides or activated hydroxyl group. The following section describes few strategies towards the synthesis of organic thiocyanates.

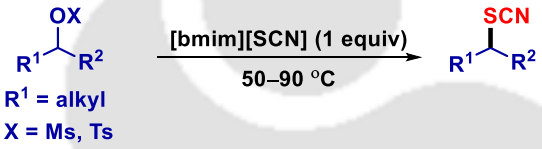
VI.2. Strategies for the Synthesis of Organic Thiocyanates

Varma and co-workers reported the synthesis of alkyl and benzyl isothiocyanates by reacting KSCN with mono or dihalides or tosylates in aqueous medium under microwave heating (Scheme VI.2.1).[4] The reaction occurred rapidly and efficiently in the absence of any phase transfer catalyst.



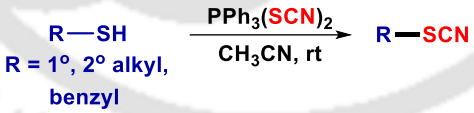
Scheme VI.2.1. *Microwave-promoted nucleophilic substitution with KSCN*

Chae *et al.* reported ionic liquid [bmim][SCN] as efficient reagent for nucleophilic substitution of sulfonate esters derived from primary and secondary alcohols, leading to the synthesis of thiocyanate products in excellent yield (Scheme VI.2.2).[5]



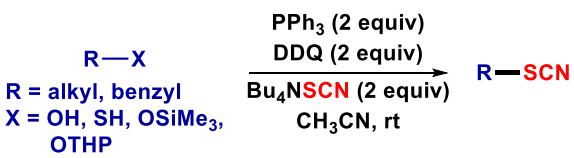
Scheme VI.2.2. *Nucleophilic substitution with [SCN]-based ionic liquid*

Iranpoor group achieved the conversion of aliphatic thiols to the corresponding thiocyanates using $PPh_3(SCN)_2$ as the thiocyanating agent (Scheme VI.2.3).[6] This reagent was generated *in situ* at room temperature from PPh_3, Br_2 and NH_4SCN in the ratio of 1.3:1:2.5 respectively. The sulfur in the resulting product originate from the "SCN" source rather than from thiol.



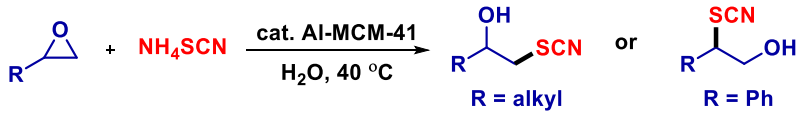
Scheme VI.2.3. *Conversion of thiols to thiocyanates using $PPh_3(SCN)_2$*

The same group later applied Mitsunobu reaction for the conversion of aliphatic alcohols, thiols, trimethylsilyl- and tetrahydropyranyl ethers to the corresponding thiocyanates. The reaction was performed using PPh_3, DDQ, and Bu_4NSCN giving their respective thiocyanate product in good to high yields (Scheme VI.2.4).[7]



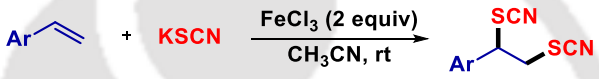
Scheme VI.2.4. *Synthesis of thiocyanates by Mitsunobu reaction*

Sayyahi and co-workers synthesized β-hydroxy thiocyanates by the regioselective ring opening of epoxides with NH_4SCN in water at 40 °C using mesoporous aluminosilicate (Al-MCM-41) as the catalyst (Scheme VI.2.5).[8] Phenyl epoxides opened with opposite regioselectivity compared to alkyl epoxides giving secondary thiocyanate.



Scheme VI.2.5. *Synthesis of thiocyanates by epoxide ring opening*

A simple, convenient and efficient protocol for dithiocyanation of alkenes using anhydrous $FeCl_3$ and KSCN has been proposed by Yadav *et al.* (Scheme VI.2.6).[9] During this reaction, $FeCl_3$ oxidizes KSCN to the corresponding radical and promotes subsequent addition to nucleophilic olefins to produce dithiocyanate derivatives in excellent yields.

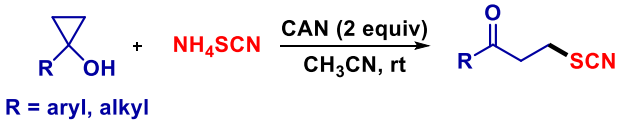


Scheme VI.2.6. *Dithiocyanation of alkenes*

In 2008, the same group achieved α-thiocyanation of enolizable ketones using anhydrous $FeCl_3$ and NH_4SCN to produce α-oxo thiocyanates in good yields with high selectivity (Scheme VI.2.7).[10]

Scheme VI.2.7. *Thiocyanation of enolizable ketones*

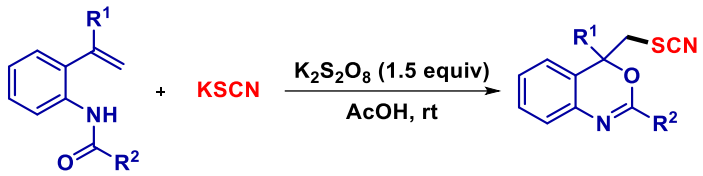
Flowers II and co-workers developed a novel and efficient approach towards the synthesis of β-functionalized ketones from substituted cyclopropyl alcohols (Scheme VI.2.8).[11] The reaction involves the oxidation of thiocyanate anion by ceric ammonium nitrate (CAN) to the corresponding radical generating β-thiocyanato ketones in good yields.



Scheme VI.2.8. *Synthesis of β-thiocyanato ketones*

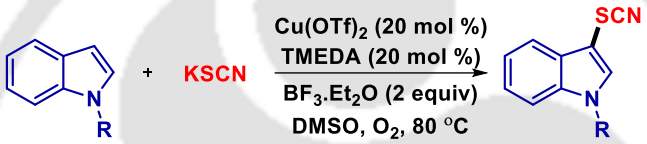
A unique transition-metal free tandem radical thiocyanooxygenation of olefinic amides with KSCN was accomplished by Guo group (Scheme VI.2.9).[12] The method gave

access to diverse SCN-containing heterocycles in good to excellent yields and showed wide range of functional group tolerance.



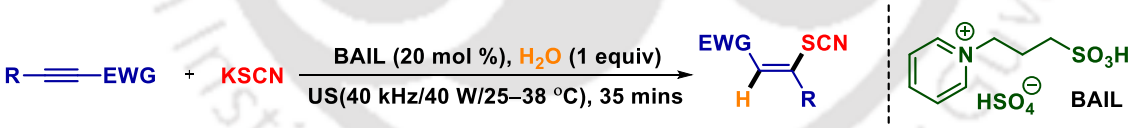
Scheme VI.2.9. *Thiocyanooxygenation of olefinic amides*

Recently, a Cu-catalyzed aerobic oxidative reaction of aromatic or heteroaromatic compounds with KSCN was reported by Jiang, Wu and co-workers (Scheme VI.2.10).[13] The transformation utilized $Cu(OTf)_2$, TMEDA, and $BF_3.Et_2O$ as the efficient catalytic system and molecular oxygen as the oxidant and the protocol showed wide functional group tolerance.



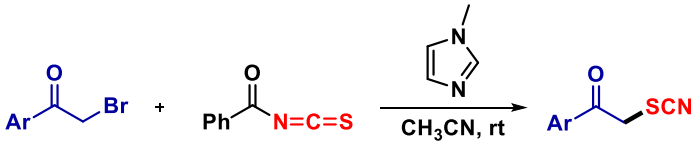
Scheme VI.2.10. *Thiocyanation of indoles*

An eco-friendly and practical approach for the synthesis of *Z*-vinyl thiocyanates was achieved by He *et al.* using ultrasound-promoted Brønsted acid ionic liquid-catalyzed (BAIL) hydrothiocyanation of activated alkynes with KSCN (Scheme VI.2.11).[14] The transformation takes place in the presence of water as the hydrogen source.



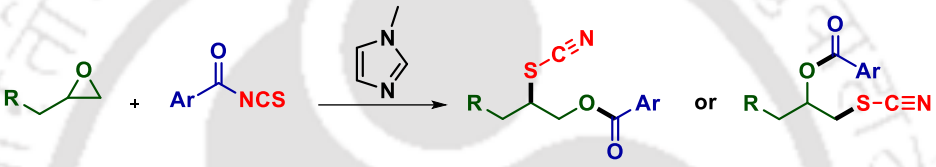
Scheme VI.2.11. *Thiocyanation of activated alkynes*

In 2009, our group reported a biomimetic thiocyanate group transfer from aroyl isothiocyanate onto α-haloketones in the presence of a tertiary amine, *N*-methylimidazole (NMI) at room temperature (Scheme VI.2.12).[15] In this reaction aroyl isothiocyanate acts as the –SCN source and a nucleophilic substitution product was obtained in the absence of any real nucleophile.



Scheme VI.2.12. *Synthesis of α-thiocyanatoketone using aroyl isothiocyanate*

Inspired by our work, we were curious to see the reactivity of aroyl isothiocyanate with epoxides as the coupling partner. As already discussed in chapter IC that epoxides are attractive coupling partners as the ring strain in epoxides makes them susceptible to ring-opening with variety of nucleophiles such as alcohols, amines, thiols and other strong nucleophilic organometallic reagents like Grignard or organolithium.[16] There have been many reports on transition-metal catalyzed coupling of epoxides with aryl halides, arenes, alkenes, alkynes and boronic acids, resulting in the construction of a variety of alcohols.[17] Further, the question arises if the ring opens up what will be the fate of the resultant alkoxy ion? Will it form an alcohol (via protonation), or will it undergo further nucleophilic attack onto a suitable electrophile? With all these queries we began our studies which is described here (Scheme VI.2.13).



Scheme VI.2.13. *Thiocyanation and acylation of epoxides*

VI.3. Present Work

With the ambition to further explore the reactivity of aroyl isothiocyanate with oxiranes, we carried out a reaction of benzoyl isothiocyanate (**1**) (1 equiv) and 2-phenyloxirane (**a**) (1 equiv) in the presence of *N*-methylimidazole (NMI) (1 equiv) in acetonitrile (2 mL) at room temperature, under a reaction condition identical to that reported in our previous work (Scheme. VI.2.12). Both reactants (**1**) and (**a**) were completely consumed (as indicated by TLC) giving a new product. The IR spectra of newly formed product showed a characteristic peak at 2154 cm^{-1} suggesting the incorporation of a –SCN group. Another peak at 1705 cm^{-1} may be due to the presence of a carbonyl group in the resultant product. Further, ^{1}H and ^{13}C NMR of the isolated product revealed the presence of an ester functionality. Finally, the structure of the product was confirmed by single-crystal X-ray diffraction study of one of its derivative (2-phenyl-2-thiocyanatoethyl 4-methylbenzoate(**2a**) (Figure VI.3.1), which revealed the presence of a thiocyanate as well as an ester functionality. As anticipated, the thiocyanate acts as a nucleophile and attacks at the Aα position of the epoxide.[18] The resultant alkoxy species obtained by the ring-opening of epoxide possibly undergoes benzoylation, giving 2-phenyl-2-

thiocyanatoethyl benzoate (**1a**). Here, the reaction gave a single regioisomeric product (**1a**) in 67% isolated yield. In the absence of NMI, the reaction did not proceed at all, suggesting its definite involvement during this simultaneous electrophilic-nucleophilic process. This unprecedented outcome showing the transfer of both halves [i.e., thiocyanate (–SCN) and the acyl (–COPh) group from (**1**) onto (**a**)] results in the formation of a product having new C–S and C–O bonds in 100% atom economy.

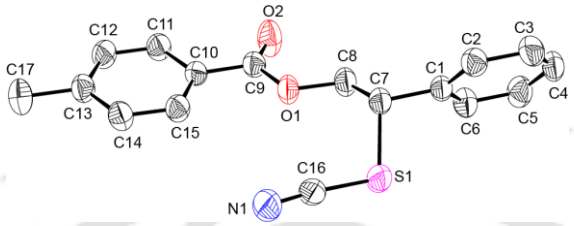


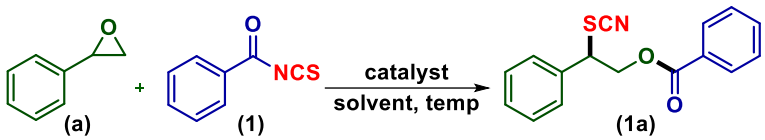
Figure VI.3.1. *ORTEP view of (**2a**)*

Aryl esters are also a ubiquitous functionality found in pharmaceuticals, agrochemicals and polymers and are important building blocks for organic synthesis.[19] The presence of both of these important functionalities, *viz.* thiocyanate and ester, in a single molecule derived from readily available starting material is a boon to the synthetic chemists.

Optimization of Reaction Conditions:

Encouraged by this double functional group transfer, we carried out further optimizations to improve the yield of the bis-functionalized product. Compounds (**1**) and (**a**) were chosen for this purpose. With the essential requirement of NMI (a tertiary amine) as the organocatalyst for the reaction to proceed, a set of other tertiary amines were screened. In comparison to NMI (67%), the use of imidazole and DMAP gave inferior yields, 45 and 15% respectively (Table VI.3.1, entries 1–3), whereas Et_3N, DBU and DABCO (Table VI.3.1, entries 4–6) resulted in no observable reactions. With NMI as the suitable promoter, increasing its loading from 1 to 1.5 equiv did not improve the yield significantly (69%, Table VI.3.1, entry 7).

Table VI.3.1. *Screening of the reaction conditions*[a]



Entry	Base (equiv)	Solvent	Yield (%)[b]
1	NMI (1)	CH_3CN	67
2	Imidazole (1)	CH_3CN	45
3	DMAP (1)	CH_3CN	15
4	Et_3N (1)	CH_3CN	00
5	DBU (1)	CH_3CN	00
6	DABCO(1)	CH_3CN	00
7	NMI (1.5)	CH_3CN	69
8	NMI (0.5)	CH_3CN	65
9	NMI (0.2)	CH_3CN	63
10	NMI (0.1)	CH_3CN	55
11	NMI (0.2)	DCM	42
12	NMI (0.2)	DMF	00
13	NMI (0.2)	DMSO	00
14	NMI (0.2)	Dioxane	00
15	NMI (0.2)	Toluene	00
16	NMI (0.2)	H_2O	15
17	**NMI (0.2)**	-	**89**
18[c]	NMI (0.2)	-	68
19[d]	NMI (0.2)	-	57

[a]Reaction conditions: Benzoyl isothiocyanate (**1**) (0.25 mmol), 2-phenyl oxirane (**a**) (0.25 mmol), tertiary amine (equiv) and solvent (2 mL) under air at room temperature for 3 h. [b]Isolated yield. [c]Reaction at 50 °C. [d]Reaction at 10 °C.

To check whether NMI acts as a promoter or a catalyst, a reaction was performed by decreasing the NMI loading. Interestingly, when the quantity of NMI was reduced to 0.5 and 0.2 equiv, the yield virtually remained unaltered (Table VI.3.1, entries 8 and 9). A reduction in the yield (55%) was observed when the NMI loading was decreased further to 0.1 equiv (Table VI.3.1, entry 10). This bis-functionalization route is truly a biomimetic organocatalytic process giving product in 100% atom economy. To see the effect of solvent if any, a range of other solvents such as DCM (42%), DMF (00%), DMSO (00%), dioxane (00%), toluene (00%), and H_2O (15%) (Table VI.3.1, entries 11–16) were screened and all were found inferior to that of acetonitrile. Since all the reactants are liquid, we thought of carrying out a neat reaction by mixing (**1**) (1 equiv), (**a**) (1 equiv), and NMI (0.2 equiv) at room temperature. Gratifyingly, an improvement in the yield of the isolated

product (**1a**, 89%) was observed (Table VI.3.1, entry 17). Thus, the nonrequirement of solvent makes the method even more green and sustainable, giving further advantage to the present protocol from synthetic point of view.[20] To see the effect of temperature, reactions were performed at elevated temperature (50 ^{o}C) and below room temperature (10 ^{o}C) under otherwise identical conditions, but both the reactions gave reduced yields, 68 and 57% respectively (Table VI.3.1, entries 18 and 19).

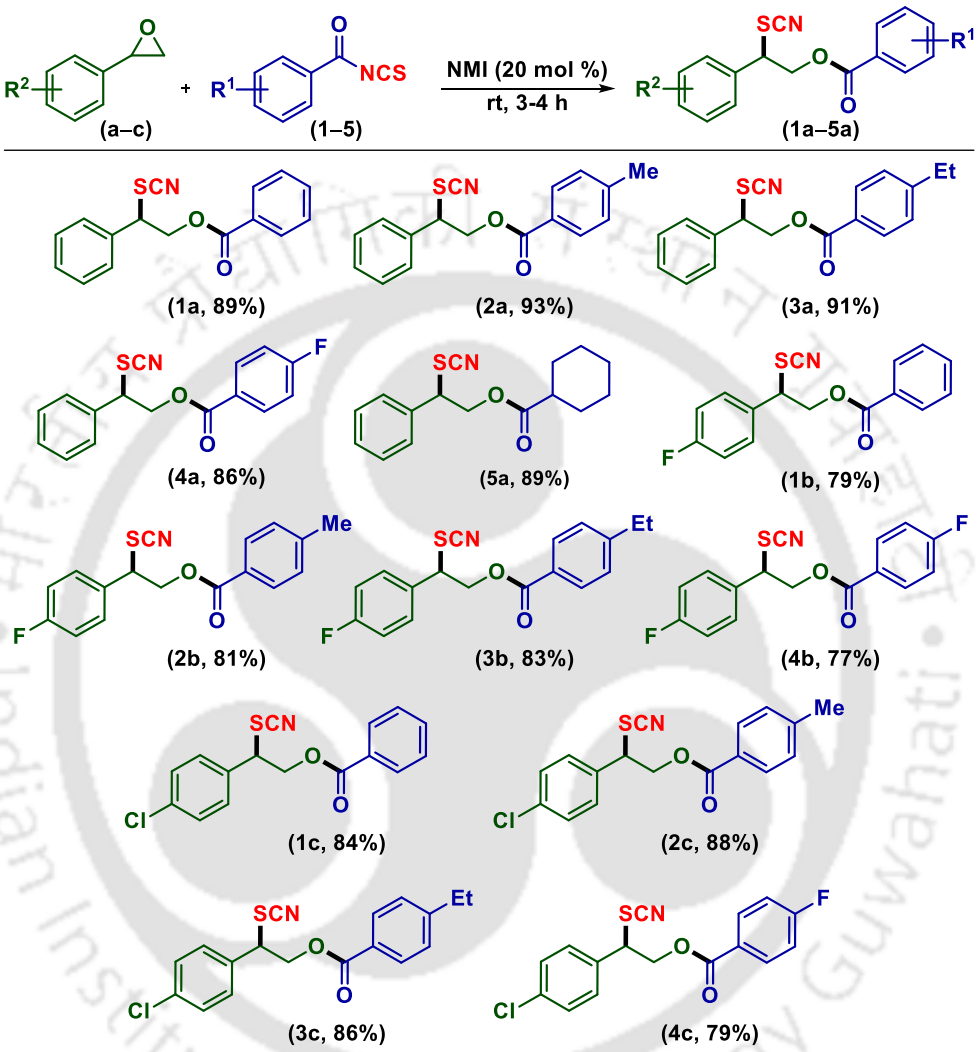
Substrate Scope for Thiocyanation and Acylation of Oxiranes:

With the optimized reaction condition [i.e., the use of benzoyl isothiocyanate (1 equiv), oxirane (1 equiv) and NMI (0.2 equiv) at room temperature], the scope of this methodology was further extended to a range of aroyl/acyl isothiocyanates and oxirane derivatives. At first, the influence of substituents on the phenyl ring of benzoyl isothiocyanates (**1**–**4**) was explored with (**a**) (Scheme VI.3.1). The presence of electron-donating groups such as *p*-Me (**2**) and *p*-Et (**3**) on the phenyl ring of benzoyl isothiocyanate gave corresponding products (**2a**) and (**3a**) in 93 and 91% yields, respectively, compared to the unsubstituted analogue (**1a**, 89%). A slight reduction in the yield of (**4a**) was noticed when a moderately electron-withdrawing group such as *p*-F (**4**) was present on the phenyl ring of benzoyl isothiocyanate. These observations suggest that the presence of either moderately electron-donating or electron-withdrawing groups on benzoyl isothiocyanate had no substantial influence on the product yield. Next, the influence of substituents such as *p*-F (**b**) and *p*-Cl (**c**) on the phenyl ring of 2-phenyloxirane was evaluated by reacting them separately with various benzoyl isothiocyanates (**1**–**4**) (Scheme VI.3.1). A slight reduction in the product yields (**1b**, 79%), (**2b**, 81%), (**3b**, 83%), and (**4b**, 77%) suggests the negative influence of electron-withdrawing *p*-F (**b**) substituent on the product outcome. Similar trends in the product yields were observed (**1c**, 84%), (**2c**, 88%), (**3c**, 86%), and (**4c**, 79%) when substituent *p*-Cl (**c**) is present on the phenyl ring of 2-phenyloxirane. This double functional group transfer strategy was also equally successful for aliphatic isothiocyanate, that is, cyclohexanecarbonyl isothiocyanate (**5**) giving the bis-functionalized product (**5a**) in 89% yield (Scheme VI.3.1).

All of the oxiranes tested in Scheme VI.3.1 open up via the attack of –SCN at the Aα (benzylic carbon) site, giving single regioisomeric products. If the reaction indeed proceeding via the nucleophilic attack of –SCN onto the epoxide, then the attack should be preferably at the less hindered (Aβ) site, giving the opposite regioisomer. Formation of

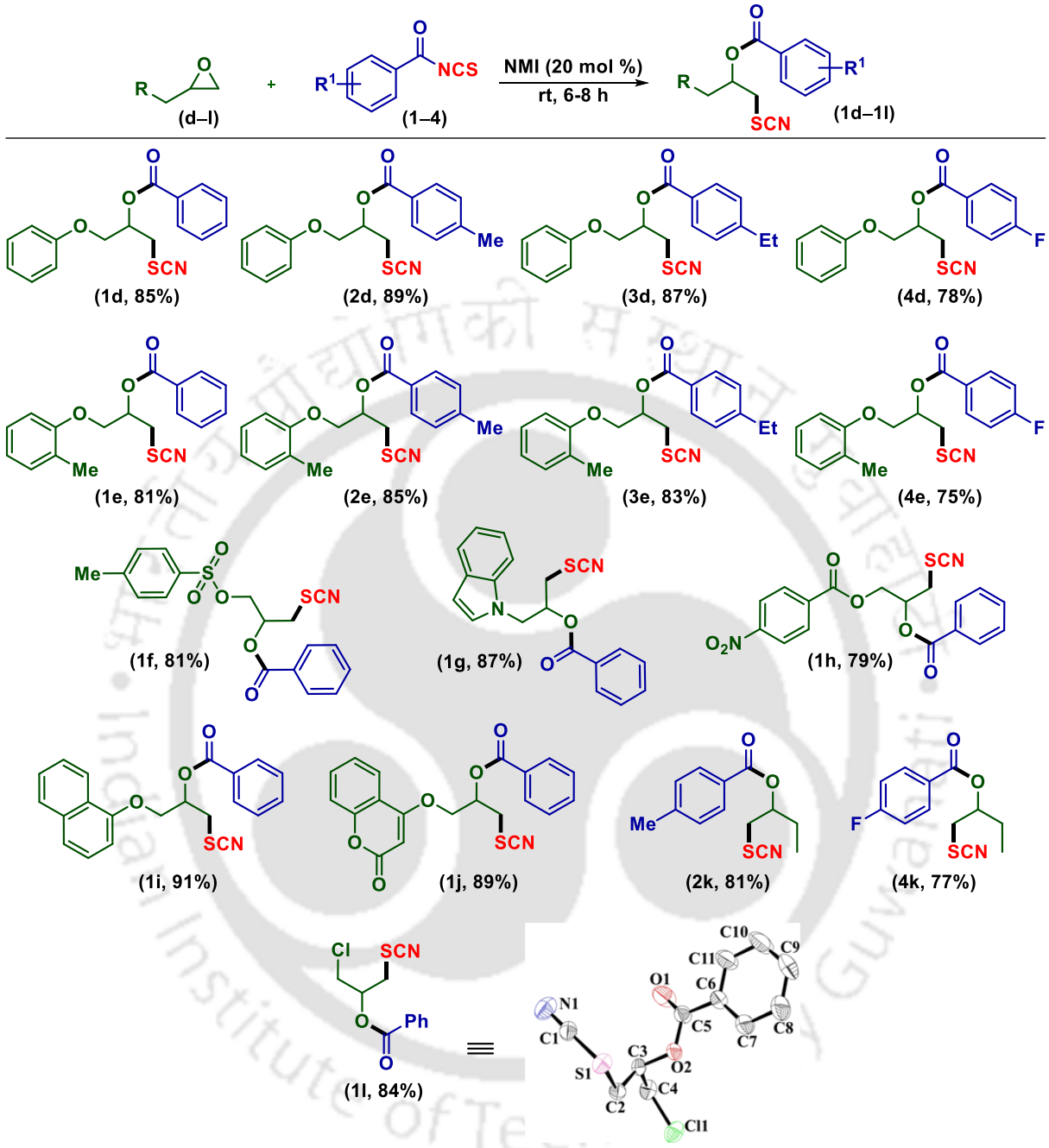
a single regioisomer in all cases (Scheme VI.3.1) is possibly due to the better stability of the incipient carbocation at the benzylic position.

Scheme VI.3.1. *Synthesis of 2-phenyl-2-thiocyanatoethyl benzoates*[a,b]



[a]Reaction conditions: Benzoyl isothiocyanate (**1**–**5**) (0.5 mmol), oxiranes (**a**–**c**) (0.5 mmol), NMI (0.1 mmol.) under air at room temperature for 3–4 h. [b]Isolated yield.

Scheme VI.3.2. *Synthesis of various thiocyanato benzoates*[a,b]



[a]Reaction conditions: Benzoyl isothiocyanate (**1**–**4**) (0.5 mmol), oxiranes (**d**–**l**) (0.5 mmol), NMI (0.1 mmol) under air at room temperature for 6–8 h. [b]Isolated yield.

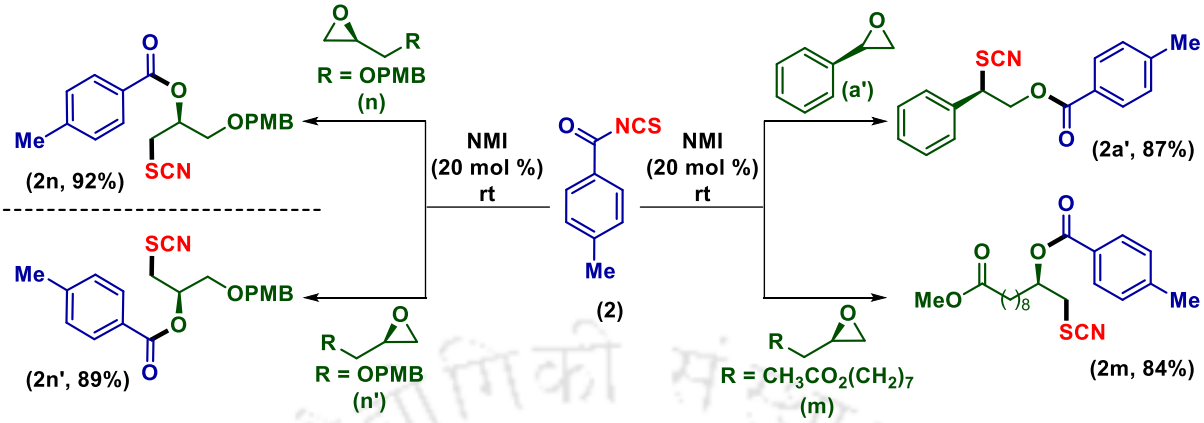
For non-benzylic oxiranes, it would be interesting to see if a single regioisomer is obtained or a mixture of isomeric products. To check this, a reaction was carried with 2-(phenoxymethyl)oxirane (**d**) and (**1**) under an otherwise identical reaction condition. Here again, a single regioisomer (**1d**) was observed but regioselectivity was opposite to that of 2-phenyloxirane derivatives (Scheme VI.3.2). The resultant product (**1d**, 85%) is obtained via the attack of –SCN at the less sterically hindered carbon (Aβ) in oxirane (**d**). This

observation is in contrast to the 2-phenyloxirane systems (Scheme VI.3.1), where the product is obtained via the attack at the more sterically hindered carbon (Aα). The glycidic epoxide (**d**) was than reacted with various other benzoyl isothiocyanates possessing electron-donating [*p*-Me (**2**), *p*-Et (**3**)] and electron-withdrawing [*p*-F (**4**)] groups, and all gave their single regioisomeric products (**2d**, 89%), (**3d**, 87 %), and (**4d**, 78%) (Scheme VI.3.2). Another glycidic epoxide, 2-((*o*-tolyloxy)methyl)oxirane (**e**), on treatment with bezoyl isothiocyanates (**1**–**4**) again gave their sole regioisomeric bis-functionalized products (**1e**, 81%), (**2e**, 85%), (**3e**, 83%), and (**4e**, 75%) (Scheme VI.3.2).

The utility of the present electrophilic–nucleophilic process was successfully demonstrated with a variety of other glycidic epoxides such as oxiran-2-ylmethyl 4-methylbenzenesulfonate (**f**), 1-(oxiran-2-ylmethyl)-1*H*-indole (**g**), oxiran-2-ylmethyl 4-nitrobenzoate (**h**), 2-((naphthalen-1-yloxy)methyl)oxirane (**i**), 4-(oxiran-2-ylmethoxy)-2*H*-chromen-2-one (**j**) (Scheme VI.3.2). All these oxiranes reacted well with (**1**) under the optimized reaction condition to afford their regioisomeric products (**1f**–**1j**) in yields ranging from 79 to 91%. Aliphatic oxirane such as 1,2-epoxy ethane (**k**) underwent reaction with (**2**) and 4-fluorobenzoyl isothiocyanate (**4**) to afford their corresponding products, (**2k**, 81%) and (**4k**, 77%), respectively. Similarly, 2-(chloromethyl)oxirane (**l**) underwent smooth bis-functionalization with (**1**), giving product (**1l**) in 84% yield. The structure of this regioisomeric product (**1l**) has been confirmed by single-crystal X-ray diffraction study (Scheme VI.3.2), reconfirming that the attack of –SCN nucleophile is at the less hindered site in glycidic epoxides (**d**–**l**) (Scheme VI.3.2).

To further ascertain the nucleophilic (S_N2) path of oxirane ring-opening in glycidic epoxide systems, a chiral epoxide (*R*)-methyl 9-(oxiran-2-yl)nonanoate (**m**) was reacted with (**2**). The bifunctionalized product (**2m**) obtained (84%) was found to be optically active {[α_D] = +23.73, $CHCl_3$} suggesting a S_N2 path of oxirane ring opening (Scheme VI.3.3). Similarly, chiral epoxide (*S*)-2-(4-methoxybenzyl)oxirane (**n**) when treated with isothiocyanate (**2**) gave an optically active bifunctionalized product (**2n**, 92%) {[α_D] = –55.10, $CHCl_3$}. Interestingly, its enantiomeric chiral epoxide (*R*)-2-(4-methoxybenzyl)oxirane (**n′**) yielded the opposite enantiomeric bifunctionalized product (**2n′**, 89%) {[α_D] = +56.32, $CHCl_3$}. This observation reconfirms that the nucleophilic attack on the epoxide is from the sterically less hindered Aβ carbon site (Scheme VI.3.3).

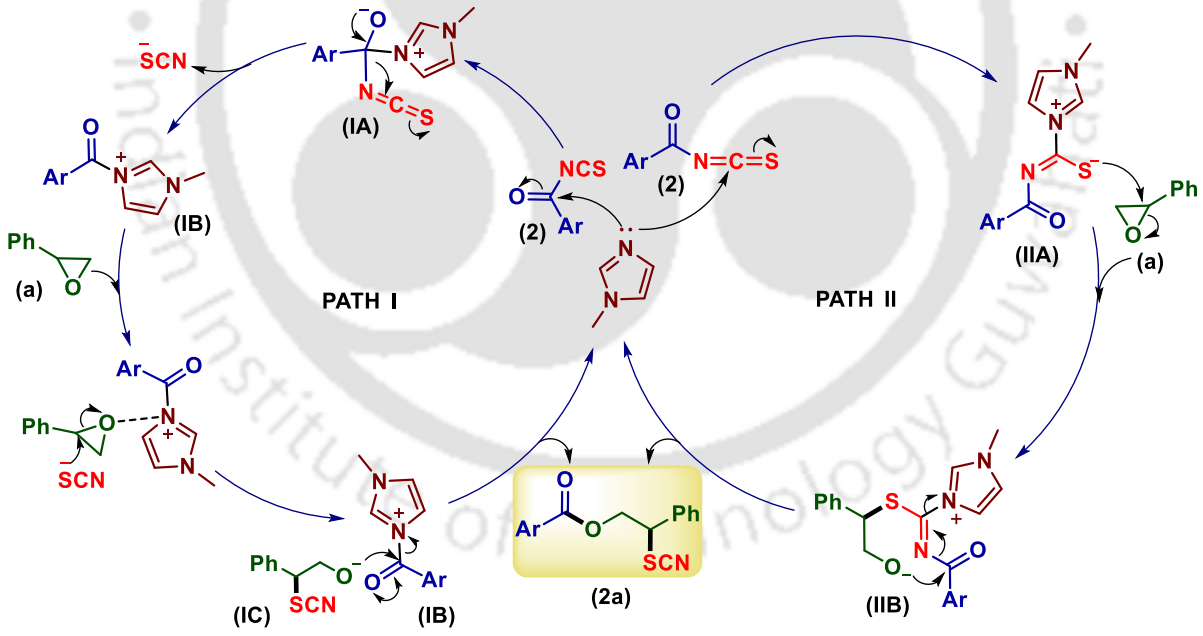
Scheme VI.3.3. *Synthesis of chiral thiocyanato benzoates*[a,b]



[a]Reaction conditions: 4-methylbenzoyl isothiocyanate (**2**) (0.5 mmol), oxirane (**m**, **n**, **n′** and **a′**) (0.5 mmol), NMI (0.1 mmol) under air at room temperature for 8 h. [b]Isolated yield

From our previous work and from the literature, a plausible reaction mechanism is proposed, as shown Scheme VI.3.4.[21]

Scheme VI.3.4. *Plausible reaction mechanism*



In path I, the NMI nitrogen attacks at the carbonyl carbon of (**2**), forming a negatively charged tetrahedral intermediate (**IA**). This active intermediate releases the nucleophilic thiocyanate (–SCN), forming a NMI aroylate species (**IB**). Epoxide (**a**) coordinates with the cationic species (**IB**), which is attacked by the nucleophilic –SCN, forming an alkoxy intermediate (**IC**). The nucleophilic alkoxy intermediate (**IC**) then attacks the electrophilic

aroyl intermediate (**IB**), giving the bis-functionalized product (**2a**) with concomitant release of NMI for further catalytic cycles. Formation of intermediate (**IB**) was detected by HRMS analysis of the reaction mixture (Figure VI.4.1). When an enantiopure 2-aryloxirane, (*R*)-styrene oxide (**a′**), was used, the obtained product (*R*)-2-phenyl-2-thiocyanatoethyl-4-methylbenzoate (**2a′**) was found to be optically active {[α_D] = +98.49, $CHCl_3$}, supporting the S_N2 reaction path (Scheme VI.3.3). Based on the concept of hard–soft nucleophilic character, an alternative mechanism as proposed previously[15] can also be envisaged for this transformation as shown in path II (Scheme VI.3.4). NMI attacks at the sp-hybridized carbon of benzoyl isothiocyanate (**2**), forming an activated thiolate species (**IIA**), which attacks the oxirane ring, giving an alkoxy intermediate (**IIB**). The intramolecular attack of the alkoxy anion at the carbonyl carbon gave product (**2a**) with the release of NMI (Scheme VI.3.4).

In conclusion, we have demonstrated a biomimetic organocatalytic bis-functionalization of oxiranes from aroyl/acyl isothiocyanates in the presence of NMI. In this simultaneous electrophilic–nucleophilic reaction, the thiocyanate (–SCN) of aroyl/acyl serves as the nucleophile, whereas the aroyl part acts as the electrophilic partners, giving products in 100% atom economy. In this metal free process, C–S and C–O bonds are simultaneously constructed in the presence of NMI under solvent free conditions.

VI.4. Experimental Section

VI.4.1. General Information: All the compounds were commercial grade and used without further purification. Organic extract was dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduce pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as internal standard for proton NMR (400 and 600 MHz) and $CDCl_3$ solvent as internal standard for ^{13}C NMR (100 and 150 MHz). HRMS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat.

VI.4.2. Crystallographic Description

CCDC Number for Compound 2a: CCDC-1524846 and **1l:** CCDC-1517630. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystallographic Description of 2-Phenyl-2-thiocyanatoethyl 4-methylbenzoate (2a): $C_{17}H_{15}NO_2S$, crystal dimensions 0.36 x 0.24 x 0.12mm, M_r = 297.36, Monoclinic, space group P 21/n, a = 8.2271(2), b = 10.0704(2), c = 19.1028(5) Å, α = 90°, β = 98.3640° (9), γ = 90°, V = 1565.84(6) Å^3, Z = 4, ρ_{calcd} = 1.261 g/cm^3, μ = 0.210 mm^{-1}, F(000)= 624.0, reflection collected / unique = 3898 / 3035, refinement method = full-matrix least-squares on F^2, final R indices [I> 2σ(I)]: R_1 = 0.0695, wR_2 = 0. 1722, R indices (all data): R_1 = 0.0568, wR_2 = 0.1609, goodness of fit = 1.060.

Crystallographic Description of 1-Chloro-3-thiocyanatopropan-2-yl benzoate (1l): $C_{11}H_{10}ClNO_2S$, crystal dimensions 0.38 x 0.28 x 0.22 mm, M_r = 255.71, Triclinic, space group P-1, a = 5.6654 (15), b = 8.296 (2), c = 13.194 (4) Å, α = 83.624° (18), β = 85.285° (16), γ = 79.966° (16), V = 605.6 (3) Å^3, Z = 2, ρ_{calcd} = 1.402 g/cm^3, μ = 0.471 mm^{-1}, F(000)= 264.0, reflection collected / unique = 2115 / 1877, refinement method = full-matrix least-squares on F^2, final R indices [I> 2σ(I)]: R_1 = 0.0412, wR_2 = 0.1329, R indices (all data): R_1 = 0.0372, wR_2 = 0.1329, goodness of fit = 1.037.

VI.4.3. General Procedure for the Synthesis of 2-Phenyl-2-thiocyanatoethyl benzoate (1a):

Benzoyl isothiocyanate (**1**) (0.5 mmol, 81.5 mg), 2-phenyloxirane (**a**) (0.5 mmol, 60.0 mg) and *N*-methylimidazole (NMI) (0.1 mmol, 8.2 mg), were taken in an oven dried 10 mL round bottom flask charged with a magnetic bar and stirred at room temperature for 3 h in open air atmosphere. After the completion of the reaction (as indicated by the TLC), the reaction mixture was admixed with ethyl acetate (20 mL). The organic layer was washed successively with saturated solution of sodium bicarbonate (2 x 5 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuum. The crude product obtained was purified using column chromatography and eluted with 5:95 ethyl acetate:hexane to afford the corresponding product 2-phenyl-2-thiocyanatoethyl benzoate (**1a**) (126 mg, 89%).

VI.4.4. Identification of the Reaction Intermediates: In order to detect the reaction intermediate if any an HRMS analysis of crude reaction mixture was performed. After stirring the reaction for 5 minutes, 5 µL of the reaction aliquot was taken and diluted with HPLC grade acetonitrile (1 mL), filtered through a syringe filter having pore size 0.2 µm. The diluted solution was then injected to run ESI-MS analysis. The peak at 201.1065 corresponding to the intermediate (**IB**) was detected.

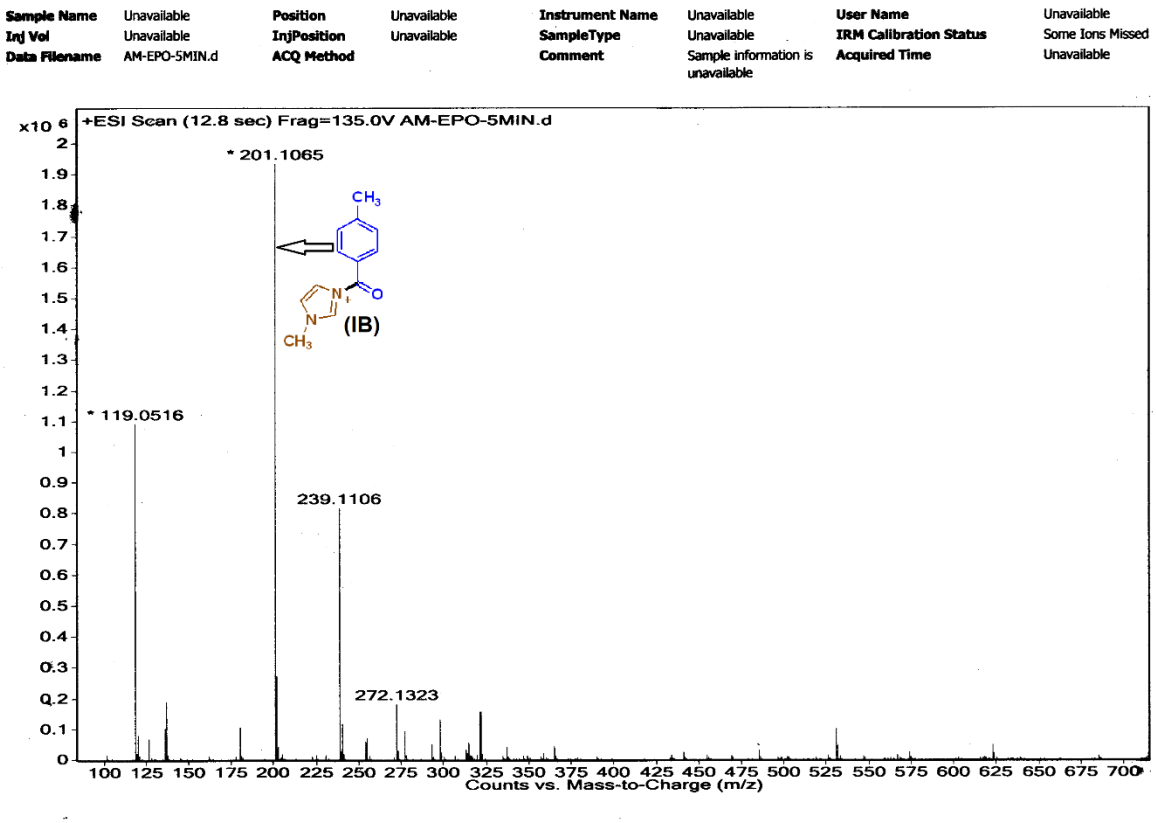


Figure VI.4.1. *HRMS spectrum of the reaction mixture after 5 minutes*

VI.5. References

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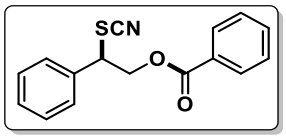
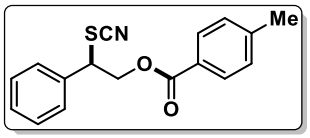
VI.6. Spectral Data

2-Phenyl-2-thiocyanatoethyl benzoate (1a):



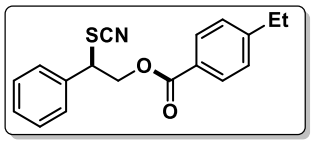
Cream solid (126 mg, 89%); mp 76–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.79–4.92 (m, 3H), 7.40–7.48 (m, 7H), 7.60 (t, 1H, *J* = 7.6 Hz), 8.06 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 51.8, 66.1, 111.0, 127.9, 128.7, 129.2, 129.6, 129.8, 130.0, 133.8, 134.9, 166.1; IR (KBr): 3062, 3027, 2948, 2890, 2154, 1705, 1600, 1491, 1451, 1383, 1318, 1269, 1120, 1024, 765 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{13}NO_2S^+$ [M + NH_4^+] 301.1005; found 301.1001.

2-Phenyl-2-thiocyanatoethyl 4-methylbenzoate (2a):



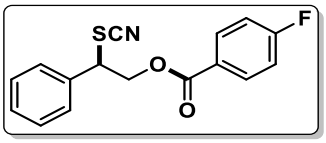
Cream solid (139 mg, 93%); mp 43–45 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.40 (s, 3H), 4.74–4.90 (m, 3H), 7.25 (d, 2H, *J* = 8.0 Hz), 7.41 (bs, 5H), 7.94 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.9, 51.9, 65.9, 111.0, 126.5, 127.9, 129.4, 129.5, 129.8, 130.1, 135.0, 144.6, 166.1; IR (KBr): 3064, 3028, 2950, 2892, 2845, 2156, 1708, 1601, 1585, 1453, 1385, 1270, 1123, 1070, 1026, 820, 756, 650 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{15}NO_2S^+$ [M + NH_4^+] 315.1162; found 315.1159.

2-Phenyl-2-thiocyanatoethyl 4-ethylbenzoate (3a):



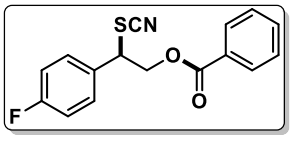
White solid (142 mg, 91%); mp 57–59 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.26 (t, 3H, *J* = 7.6 Hz), 2.71 (q, 2H, *J* = 7.6 Hz), 4.78–4.89 (m, 3H), 7.29 (d, 2H, *J* = 8.0 Hz), 7.40–7.44 (m, 5H), 7.98 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 15.4, 29.1, 51.9, 65.9, 111.0, 126.6, 127.9, 128.2, 129.5, 129.7, 130.1, 135.0, 150.7, 166.1; IR (KBr): 3063, 3030, 2952, 2895, 2850, 2156, 1708, 1615, 1607, 1497, 1460, 1382, 1272, 1160, 1098, 1055, 950, 846, 773, 710, 650 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{17}NO_2S^+$ [M + NH_4^+] 329.1318; found 329.1315.

2-Phenyl-2-thiocyanatoethyl 4-fluorobenzoate (4a):



White solid (129 mg, 86%); mp 84–86 °C . ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.79–4.91 (m, 3H), 7.13 (t, 2H, *J* = 8.4 Hz), 7.42 (bs, 5H), 8.07 (t, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 51.8, 66.3, 110.9, 115.9, 116.1, 125.5, 127.9, 129.6, 129.9, 132.66, 132.73, 134.8, 165.2, 165.5, 167.2; IR (KBr): 3065, 3030, 2950, 2895, 2156, 1715, 1610, 1495, 1456, 1385, 1320, 1265, 1115, 1025, 986, 765, 705, 660 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{12}FNO_2S^+$ [M + NH_4^+] 319.0911; found 319.0913.

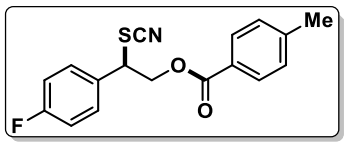
2-(4-Fluorophenyl)-2-thiocyanatoethyl benzoate (1b):



Cream solid (119 mg, 79%); mp 70–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.77–4.88 (m, 3H), 7.12 (t, 2H, *J* = 8.4 Hz), 7.40–7.48 (m, 4H), 7.60 (t, 1H, *J* = 7.6 Hz), 8.03 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 51.0, 65.8, 110.7, 116.6, 116.8, 128.8, 129.1, 129.8, 129.9, 130.0, 130.8, 130.9, 133.9, 162.1, 164.6, 166.0; IR (KBr): 3062, 3038, 2997, 2965, 2841, 2156,

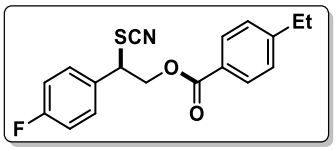
1718, 1601, 1508, 1451, 1396, 1266, 1105, 836, 709 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{12}FNO_2S^+$ [M + NH_4^+] 319.0911; found 319.0910.

2-(4-Fluorophenyl)-2-thiocyanatoethyl 4-methylbenzoate (2b):



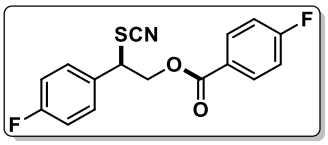
Yellow gummy (128 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.41 (s, 3H), 4.73–4.85 (m, 3H), 7.11 (t, 2H, *J* = 8.4 Hz), 7.25 (d, 2H, *J* = 8.8 Hz), 7.41 (t, 2H, *J* = 8.8 Hz), 7.92 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.9, 51.1, 65.6, 110.7, 116.5, 116.7, 126.3, 129.5, 129.8, 129.9, 130.0, 131.0, 144.6, 162.4, 164.1, 166.0; IR (KBr): 3068, 3035, 2995, 2964, 2850, 2156, 1720, 1603, 1510, 1455, 1422, 1269, 1225, 1163, 1110, 1070, 981, 840, 705, 652 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{14}FNO_2S^+$ [M + NH_4^+] 333.1068; found 333.1070.

2-(4-Fluorophenyl)-2-thiocyanatoethyl 4-ethylbenzoate (3b):



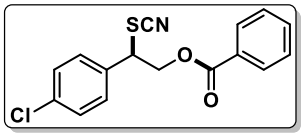
White solid (137 mg, 83%); mp 59–61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.26 (t, 3H, *J* = 7.6 Hz), 2.71 (q, 2H, *J* = 7.6 Hz), 4.76–4.86 (m, 3H), 7.12 (t, 2H, *J* = 8.4 Hz), 7.28 (d, 2H, *J* = 8.4 Hz), 7.42 (t, 2H, *J* = 8.8 Hz), 7.95 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 15.4, 29.2, 51.1, 65.7, 110.7, 116.6, 116.8, 126.5, 128.3, 129.85, 129.94, 130.2, 131.0, 150.9, 162.1, 164.6, 166.1; IR (KBr): 3060, 3035, 2989, 2965, 2846, 2156, 1720, 1636, 1505, 1421, 1321, 1269, 1225, 1169, 1116, 1071, 1030, 970, 840, 703, 682 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{16}FNO_2S^+$ [M + NH_4^+] 347.1224; found 347.1223.

2-(4-Fluorophenyl)-2-thiocyanatoethyl 4-fluorobenzoate (4b):



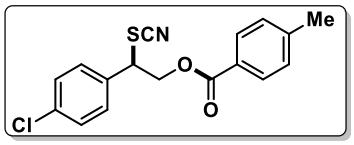
Orange gummy (123 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.77–4.87 (m, 3H), 7.12 (t, 4H, *J* = 8.8 Hz), 7.41 (t, 2H, *J* = 8.8 Hz), 8.05 (t, 2H, *J* = 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 51.0, 66.0, 110.7, 115.9, 116.1, 116.7, 116.8, 125.4, 129.8, 129.9, 130.7, 132.6, 132.7, 162.5, 164.2, 165.1, 165.5, 167.2; IR (KBr): 3060, 3032, 2994, 2958, 2854, 2156, 1723, 1610, 1505, 1460, 1428, 1270, 1223, 1165, 1105, 1072, 978, 850, 710, 657 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{11}F_2NO_2S^+$ [M + NH_4^+] 337.0817; found 337.0815.

2-(4-Chlorophenyl)-2-thiocyanatoethyl benzoate (1c):



White solid (130 mg, 84%); mp 80–82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.76–4.89 (m, 3H), 7.36–7.42 (m, 4H), 7.46 (t, 2H, *J* = 8.0 Hz), 7.60 (t, 1H, *J* = 7.6 Hz), 8.03 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 51.0, 65.6, 110.5, 128.8, 129.1, 129.3, 129.8, 130.0, 133.5, 133.9, 135.9, 166.0; IR (KBr): 3059, 3029, 2999, 2956, 2850, 2154, 1716, 1595, 1490, 1449, 1395, 1265, 1171, 1093, 1009, 850, 814, 708 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{12}ClNO_2S^+$ [M + NH_4^+] 335.0616; found 335.0614.

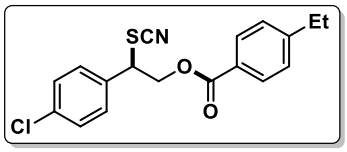
2-(4-Chlorophenyl)-2-thiocyanatoethyl 4-methylbenzoate (2c):



White solid (148 mg, 88%); mp 77–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.41 (s, 3H), 4.72–4.87 (m, 3H), 7.25 (d, 2H, *J* = 8.0 Hz), 7.38 (q, 4H, *J* = 8.8 Hz), 7.91 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.9, 51.0, 65.4, 110.5, 126.3, 129.3, 129.5, 129.8, 130.0, 133.6, 135.7, 144.7, 166.0; IR (KBr): 3062, 3030, 2998, 2962, 2915, 2848, 2154, 1718, 1560, 1485, 1445, 1390, 1316, 1263, 1175, 1113, 1078, 1012, 862, 709, 683 cm^{-1};

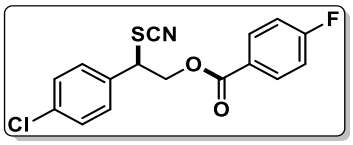
HRMS (ESI): calcd. for $C_{17}H_{14}ClNO_2S^+$ [M + NH_4^+] 349.0772; found 349.0769.

2-(4-Chlorophenyl)-2-thiocyanatoethyl 4-ethylbenzoate (3c):



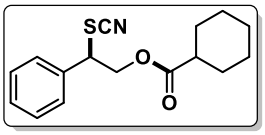
White solid (148 mg, 86%); mp 86–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.25 (t, 3H, *J* = 7.6 Hz), 2.71 (q, 2H, *J* = 7.6 Hz), 4.75–4.84 (m, 3H), 7.21 (t, 1H, *J* = 7.6 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 7.39 (q, 3H, *J* = 8.4 Hz), 7.94 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 15.4, 29.2, 51.1, 65.5, 110.6, 126.5, 128.3, 129.3, 129.8, 130.2, 133.6, 135.8, 150.9, 166.1; IR (KBr): 3052, 3031, 2997, 2970, 2920, 2862, 2154, 1715, 1595, 1495, 1452, 1412, 1387, 1329, 1270, 1165, 1075, 1010, 852, 709, 689 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{16}ClNO_2S^+$ [M + NH_4^+] 363.0929; found 363.0926.

2-(4-Chlorophenyl)-2-thiocyanatoethyl 4-fluorobenzoate (4c):



Cream solid (132 mg, 79%); mp 76–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.76–4.88 (m, 3H), 7.12 (t, 2H, *J* = 8.4 Hz), 7.38 (q, 4H, *J* = 8.4 Hz), 8.04 (t, 2H, *J* = 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 50.9, 65.7, 110.5, 115.9, 116.0, 125.3, 129.2, 129.8, 132.58, 132.64, 133.3, 135.8, 164.9, 165.4, 167.1; IR (KBr): 3065, 3028, 2990, 2968, 2920, 2845, 2156, 1720, 1566, 1480, 1450, 1392, 1320, 1265, 1180, 1110, 1085, 1019, 860, 710, 682 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{11}ClFNO_2S^+$ [M + NH_4^+] 353.0521; found 353.0519.

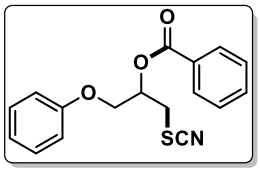
2-Phenyl-2-thiocyanatoethyl cyclohexanecarboxylate (5a):



Orange solid (129 mg, 89%); mp 62–64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.18–1.31 (m, 3H), 1.36–1.45 (m, 2H), 1.60–1.73 (m, 3H), 1.85–1.88 (m, 2H), 2.30–2.37 (m, 1H), 4.52–4.70 (m, 3H), 7.34–7.43 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 25.4, 25.8, 28.9, 43.0,

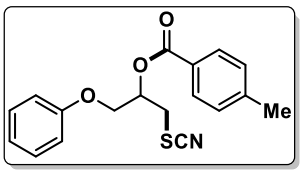
51.6, 65.1, 110.8, 127.9, 129.4, 129.7, 134.9, 175.5; IR (KBr): 3070, 3037, 2950, 2887, 2850, 2156, 1715, 1630, 1618, 1501, 1479, 1353, 1269, 1218, 1069, 1023, 834, 751, 693 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{19}NO_2S^+$ [M + NH_4^+] 307.1475; found 307.1472.

1-Phenoxy-3-thiocyanatopropan-2-yl benzoate (1d):



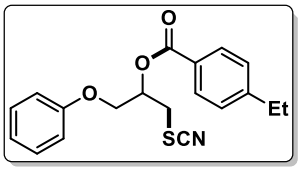
Orange gummy (133 mg, 85%); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.50–3.62 (m, 2H), 4.23–4.38 (m, 2H), 5.65–5.70 (m, 1H), 6.94 (d, 2H, *J* = 8.8 Hz), 7.00 (t, 1H, *J* = 7.2 Hz), 7.31 (t, 2H, *J* = 7.6 Hz), 7.47 (t, 2H, *J* = 7.6 Hz), 7.61 (t, 1H, *J* = 7.6 Hz), 8.10 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 35.0, 66.5, 70.7, 112.0, 114.7, 121.9, 128.8, 129.1, 129.9, 130.2, 133.9, 158.0, 165.8; IR (KBr): 3222, 3065, 2956, 2926, 2871, 2156, 1723, 1630, 1598, 1494, 1453, 1268, 1240, 1108, 1069, 753, 709 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{15}NO_3S^+$ [M + NH_4^+] 331.1111; found 331.1114.

1-Phenoxy-3-thiocyanatopropan-2-yl 4-methylbenzoate (2d):



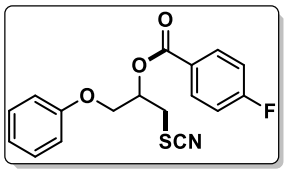
Gummy (146 mg, 89%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.41 (s, 3H), 3.47–3.58 (m, 2H), 4.25–4.36 (m, 2H), 5.61–5.67 (m, 1H), 6.93 (d, 2H, *J* = 7.6 Hz), 6.99 (t, 1H, *J* = 7.6 Hz), 7.26 (d, 2H, *J* = 8.0 Hz), 7.30 (t, 2H, *J* = 7.6 Hz), 7.98 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 34.9, 66.5, 70.4, 112.0, 114.7, 121.9, 126.2, 129.4, 129.8, 130.2, 144.7, 158.0, 165.8; IR (KBr): 3065, 3038, 2948, 2926, 2871, 2156, 1721, 1595, 1494, 1270, 1241, 1176, 1100, 1043, 839, 752, 690 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{17}NO_3S^+$ [M + NH_4^+] 345.1267; found 345.1271.

1-Phenoxy-3-thiocyanatopropan-2-yl 4-ethylbenzoate (3d):



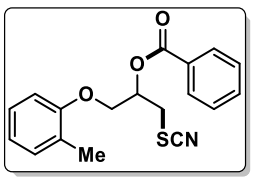
Yellow gummy (149 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.24 (t, 3H, *J* = 7.6 Hz), 2.69 (q, 2H, *J* = 7.6 Hz), 3.44–3.55 (m, 2H), 4.23–4.34 (m, 2H), 5.60–5.66 (m, 1H), 6.92 (d, 2H, *J* = 8.0 Hz), 6.98 (t, 1H, *J* = 7.2 Hz), 7.27 (q, 4H, *J* = 9.6 Hz), 8.01 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 15.3, 29.1, 34.9, 66.5, 70.4, 112.0, 114.7, 121.8, 126.5, 128.2, 129.7, 130.3, 150.8, 158.0, 165.7; IR (KBr): 3070, 3035, 2950, 2930, 2875, 2156, 1720, 1642, 1592, 1495, 1460, 1385, 1272, 1245, 1180, 1093, 1030, 952, 840, 750, 698, 611 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{19}NO_3S^+$ [M + NH_4^+] 359.1424; found 359.1423.

1-Phenoxy-3-thiocyanatopropan-2-yl 4-fluorobenzoate (4d):



Yellow gummy (129 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.47–3.58 (m, 2H), 4.26–4.36 (m, 2H), 5.62–5.68 (m, 1H), 6.93 (d, 2H, *J* = 8.0 Hz), 6.99 (t, 1H, *J* = 7.2 Hz), 7.12 (t, 2H, *J* = 8.8 Hz), 7.30 (t, 2H, *J* = 8.0 Hz), 8.11 (t, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 34.9, 66.5, 70.9, 112.0, 114.7, 115.9, 116.0, 122.0, 125.3, 129.7, 129.9, 132.8, 132.9, 158.0, 164.8, 165.5, 167.2; IR (KBr): 3062, 3032, 2945, 2925, 2863, 2154, 1720, 1592, 1495, 1265, 1240, 1120, 1105, 1050, 850, 750, 696 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{14}FNO_3S^+$ [M + NH_4^+] 349.1017; found 349.1020.

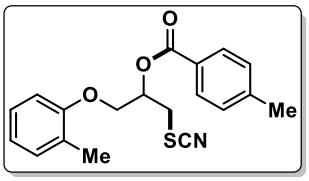
1-Thiocyanato-3-(*o*-tolyloxy)propan-2-yl benzoate (1e):



Gummy (132 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.23 (s, 3H), 3.51–3.63 (m, 2H), 4.28–4.39 (m, 2H), 5.70–5.75 (m, 1H), 6.85 (d, 1H, *J* = 8.0 Hz), 6.92 (t, 1H, *J* = 7.6 Hz), 7.16 (d, 2H, *J* = 7.6 Hz), 7.48 (t, 2H, *J* = 8.0 Hz), 7.61 (t, 1H, *J* = 7.2 Hz), 8.11 (d, 2H, *J* = 7.2 Hz);

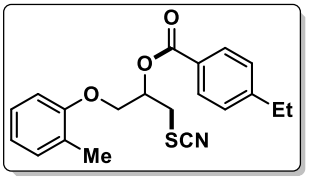
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.4, 35.1, 66.6, 70.8, 111.3, 111.9, 121.6, 127.0, 127.2, 128.8, 129.1, 130.2, 131.1, 133.9, 156.1, 165.8; IR (KBr): 3220, 3063, 3035, 2950, 2924, 2870, 2156, 1720, 1634, 1595, 1495, 1451, 1271, 1245, 1178, 1043, 886, 753, 691 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{17}NO_3S^+$ [M + NH_4^+] 345.1267; found 345.1270.

1-Thiocyanato-3-(*o*-tolyloxy)propan-2-yl 4-methylbenzoate (2e):



Gummy (145 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.22 (s, 3H), 2.41 (s, 3H), 3.48–3.59 (m, 2H), 4.25–4.36 (m, 2H), 5.66–5.71 (m, 1H), 6.84 (t, 1H, *J* = 7.6 Hz), 6.90 (t, 1H, *J* = 7.2 Hz), 7.15 (d, 2H, *J* = 7.6 Hz), 7.26 (d, 2H, *J* = 8.8 Hz), 7.99 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.4, 21.9, 35.0, 66.6, 70.5, 111.2, 112.0, 121.1, 121.6, 126.3, 127.1, 129.4, 130.2, 131.1, 144.7, 156.1, 165.8; IR (KBr): 3032, 2989, 2950, 2925, 2871, 2156, 1722, 1608, 1495, 1461, 1281, 1179, 1102, 1049, 840, 755, 689 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{19}NO_3S^+$ [M + NH_4^+] 359.1424; found 359.1420.

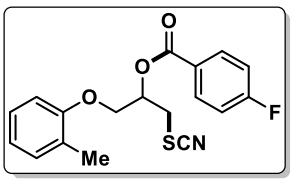
1-Thiocyanato-3-(*o*-tolyloxy)propan-2-yl 4-ethylbenzoate (3e):



Yellow gummy (147 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.24 (t, 3H, *J* = 7.2 Hz), 2.19 (s, 3H), 2.68 (q, 2H, *J* = 7.6 Hz), 3.25–3.30 (m, 1H), 3.54–3.58 (m, 1H), 4.25–4.30 (m, 2H), 5.64–5.72 (m, 1H), 6.80 (d, 1H, *J* = 8.0 Hz), 6.86 (t, 1H, *J* = 7.6 Hz), 7.12 (d, 2H, *J* = 7.6 Hz), 7.21–7.26 (m, 2H), 7.945 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 15.4, 16.5, 29.2, 35.1, 66.6, 70.5, 111.2, 112.0, 121.1, 121.6, 126.5, 127.2, 128.3, 130.3, 131.1, 150.9, 156.1, 165.8; IR (KBr): 3036, 2985, 2952, 2924, 2865, 2156, 1723, 1610, 1497, 1465,

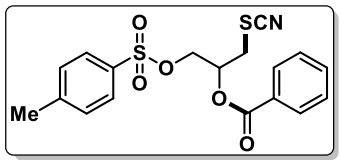
1285, 1180, 1110, 1050, 840, 760, 699 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{21}NO_3S^+$ [M + NH_4^+] 373.1580; found 373.1584.

1-Thiocyanato-3-(*o*-tolyloxy)propan-2-yl 4-fluorobenzoate (4e):



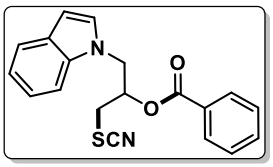
Yellow gummy (129 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.12 (s, 3H), 3.47–3.58 (m, 2H), 4.26–4.35 (m, 2H), 5.67–5.71 (m, 1H), 6.83 (d, 1H, *J* = 8.0 Hz), 6.90 (t, 1H, *J* = 7.6 Hz), 7.14 (q, 4H, *J* = 8.8 Hz), 8.11 (t, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 16.4, 34.9, 66.6, 70.9, 111.2, 111.9, 116.0, 121.1, 121.6, 126.9, 127.1, 127.2, 130.9, 131.1, 132.77, 132.84, 156.0, 164.8, 165.5, 167.2; IR (KBr): 3035, 2995, 2945, 2920, 2875, 2156, 1720, 1618, 1492, 1456, 1285, 1180, 1105, 1050, 848, 750, 690 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{16}FNO_3S^+$ [M + NH_4^+] 363.1173; found 363.1171.

1-Thiocyanato-3-(tosyloxy)propan-2-yl benzoate (1f):



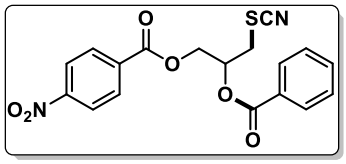
White solid (158 mg, 81%); mp 91–93 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 3H), 3.37 (d, 2H, *J* = 6.0 Hz), 4.34–4.39 (m, 2H), 5.43–5.46 (m, 1H), 7.27 (d, 2H, *J* = 7.8 Hz), 7.45 (t, 2H, *J* = 7.2 Hz), 7.61 (t, 1H, *J* = 7.2 Hz), 7.76 (d, 2H, *J* = 7.8 Hz), 7.99 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.8, 33.9, 67.7, 69.8, 111.3, 128.1, 128.6, 128.7, 130.2, 130.3, 132.1, 134.0, 145.7, 165.3; IR (KBr): 3043, 3005, 2955, 2934, 2855, 2151, 1714, 1599, 1454, 1383, 1351, 1263, 1177, 1109, 1012, 936, 810, 709, 663 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{17}NO_5S_2^+$ [M + NH_4^+] 409.0886; found 409.0883.

1-(1*H*-Indol-1-yl)-3-thiocyanatopropan-2-yl benzoate (1g):



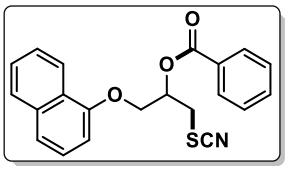
White solid (146 mg, 87%); mp 81–83 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.05–3.09 (m, 1H), 3.25–3.28 (m, 1H), 4.49–4.52 (m, 1H), 4.64–4.67 (m, 1H), 5.71–5.74 (m, 1H), 6.57 (d, 1H, *J* = 3.6 Hz), 7.12 (d, 1H, *J* = 3.6 Hz), 7.15 (t, 1H, *J* = 7.2 Hz), 7.26 (t, 1H, *J* = 8.4 Hz), 7.47–7.50 (m, 3H), 7.61–7.65 (m, 2H), 8.09 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 35.3, 47.3, 71.3, 103.3, 109.5, 111.6, 120.4, 121.5, 122.7, 128.0, 128.8, 128.9, 130.3, 134.1, 136.5, 165.8; IR (KBr): 3059, 3029, 3002, 2947, 2149, 1724, 1513, 1457, 1403, 1316, 1268, 1106, 1063, 883, 742, 700, 614 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}N_2O_2S^+$ [M + NH_4^+] 354.1271; found 354.1270.

2-(Benzoyloxy)-3-thiocyanatopropyl 4-nitrobenzoate (1h):



Yellow solid (152 mg, 79%); mp 67–69 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.41–3.54 (m, 2H), 4.68–4.82 (m, 2H), 5.73–5.78 (m, 1H), 7.46 (t, 2H, *J* = 7.6 Hz), 7.60 (t, 1H, *J* = 7.6 Hz), 8.07 (d, 2H, *J* = 7.2 Hz), 8.18 (d, 2H, *J* = 9.2 Hz), 8.27 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 34.8, 64.4, 70.0, 111.5, 123.9, 128.6, 128.8, 130.1, 130.3, 131.1, 134.0, 134.6, 150.9, 164.3, 165.6; IR (KBr): 3040, 3010, 2960, 2950, 2865, 2154, 1741, 1714, 1531, 1454, 1383, 1351, 1269, 1120, 810, 709, 668 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{14}N_2O_6S^+$ [M + NH_4^+] 404.0911; found 404.0913.

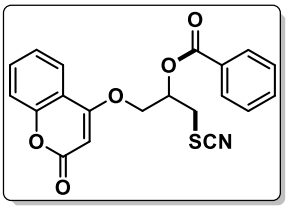
1-(Naphthalen-1-yloxy)-3-thiocyanatopropan-2-yl benzoate (1i):



Yellow gummy (165 mg, 91%); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.60–3.68 (m, 2H), 4.47–4.56 (m, 2H), 5.83–5.86 (m, 1H), 6.88 (d, 1H, *J* = 7.8 Hz), 7.39 (t, 1H, *J* = 7.8 Hz), 7.46–7.53 (m, 5H), 7.61 (t, 1H, *J* = 7.8 Hz),

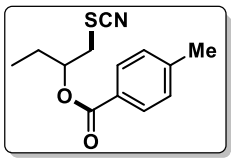
7.82 (d, 1H, *J* = 7.8 Hz), 8.14 (d, 2H, *J* = 7.2 Hz), 8.21 (d, 1H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 35.1, 67.0, 70.7, 105.3, 111.9, 121.6, 121.7, 125.5, 125.8, 125.9, 126.8, 127.8, 128.8, 129.1, 130.2, 133.9, 134.7, 153.7, 165.8; IR (KBr): 3792, 3400, 3059, 2929, 2877, 2156, 1721, 1630, 1579, 1453, 1396, 1264, 1240, 1176, 1102, 1069, 1023, 771, 710, 687 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{17}NO_3S^+$ [M + NH_4^+] 381.1267; found 381.1270.

1-((2-Oxo-2*H*-chromen-4-yl)oxy)-3-thiocyanatopropan-2-yl benzoate (1j):



Cream solid (170 mg, 89%); mp 111–113 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.53–3.62 (m, 2H), 4.49–4.54 (m, 2H), 5.77 (s, 1H), 5.84–5.87 (m, 1H), 7.27–7.32 (m, 2H), 7.48 (t, 2H, *J* = 7.8 Hz), 7.56 (t, 1H, *J* = 7.2 Hz), 7.61 (t, 1H, *J* = 7.2 Hz), 7.77 (d, 1H, *J* = 8.4 Hz), 8.11 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 34.7, 67.9, 69.8, 91.6, 111.4, 115.3, 117.1, 122.9, 124.4, 128.7, 128.9, 130.2, 133.0, 134.2, 153.5, 162.4, 164.8, 165.6; IR (KBr): 3610, 3375, 3138, 3010, 2915, 2847, 2155, 1724, 1624, 1566, 1452, 1379, 1269, 1240, 1183, 1107, 1026, 934, 819, 712, 683 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{15}NO_5S^+$ [M + NH_4^+] 399.1009; found 399.1007.

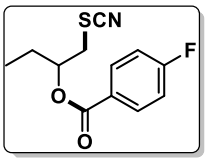
1-Thiocyanatobutan-2-yl 4-methylbenzoate (2k):



Yellow gummy (101 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.02 (t, 3H, *J* = 7.6 Hz), 1.81–1.98 (m, 2H), 2.42 (s, 3H), 3.23–3.28 (m, 1H), 3.35–3.40 (m, 1H), 5.28–5.33 (m, 1H), 7.27 (d, 2H, *J* = 8.0 Hz), 7.97 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 9.7, 21.9, 26.2, 37.6, 73.4, 112.3, 126.8, 129.4, 130.0, 144.4, 166.1; IR (KBr): 3035, 2971, 2937, 2877, 2155, 1720,

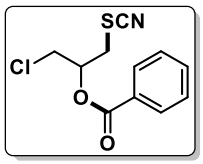
1611, 1459, 1310, 1269, 1177, 1102, 1019, 840, 752, 689 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{15}NO_2S^+$ [M + NH_4^+] 267.1162; found 267.1164.

1-Thiocyanatobutan-2-yl 4-fluorobenzoate (4k):



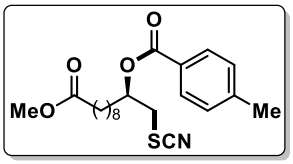
Yellow gummy (97 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.02 (t, 3H, *J* = 7.2 Hz), 1.83–1.96 (m, 2H), 3.21–3.26 (m, 1H), 3.35–3.40 (m, 1H), 5.28–5.34 (m, 1H), 7.13 (t, 2H, *J* = 8.4 Hz), 8.10 (t, 2H, *J* = 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 9.7, 26.2, 37.5, 73.8, 112.2, 115.8, 115.87, 115.95, 116.0, 125.8, 132.6, 132.7, 165.1, 165.4, 167.1; IR (KBr): 3032, 2970, 2945, 2875, 2156, 1723, 1615, 1460, 1315, 1265, 1175, 1192, 1022, 852, 750, 682 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{12}FNO_2S^+$ [M + NH_4^+] 271.0911; found 271.0913.

1-Chloro-3-thiocyanatopropan-2-yl benzoate (1l):



White solid (107 mg, 84%); mp 77–79 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.43–3.50 (m, 2H), 3.91 (d, 2H, *J* = 4.8 Hz), 5.52–5.56 (m, 1H), 7.48 (t, 2H, *J* = 7.8 Hz), 7.61 (t, 1H, *J* = 7.2 Hz), 8.10 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 35.0, 43.2, 71.3, 111.5, 128.79, 128.82, 130.2, 134.0, 165.5; IR (KBr): 3087, 3068, 3002, 2954, 2153, 1716, 1600, 1451, 1345, 1275, 1104, 1067, 1034, 966, 851, 706, 685 cm^{-1}; HRMS (ESI): calcd. for $C_{11}H_{10}ClNO_2S^+$ [M + NH_4^+] 273.0459; found 273.0457.

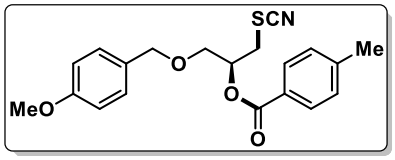
11-Methoxy-11-oxo-1-thiocyanatoundecan-2-yl 4-methylbenzoate (2m):



Yellow liquid (158 mg, 84%); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.28–1.36 (m, 10H), 1.59–1.61 (m, 2H), 1.76–1.81 (m, 1H), 1.85–1.91 (m, 1H), 2.29 (t, 2H, *J* = 7.2 Hz), 2.42 (s, 3H), 3.22–3.26 (m, 1H), 3.36–3.39 (m, 1H), 3.66 (s, 3H), 5.34–5.38 (m, 1H), 7.26 (d, 2H, *J* = 7.8

Hz), 7.96 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.8, 25.0, 25.2, 29.15, 29.19, 29.28, 29.30, 33.0, 34.2, 38.0, 51.6, 72.2, 112.3, 126.8, 129.35, 129.40, 130.0, 144.4, 166.0, 174.4; IR (KBr): 2995, 2926, 2854, 2155, 1734, 1718, 1611, 1463, 1409, 1356, 1268, 1205, 1177, 1100, 1019, 839, 752, 689 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{29}NO_4S^+$ [M + H^+] 392.1890; found 392.1893.

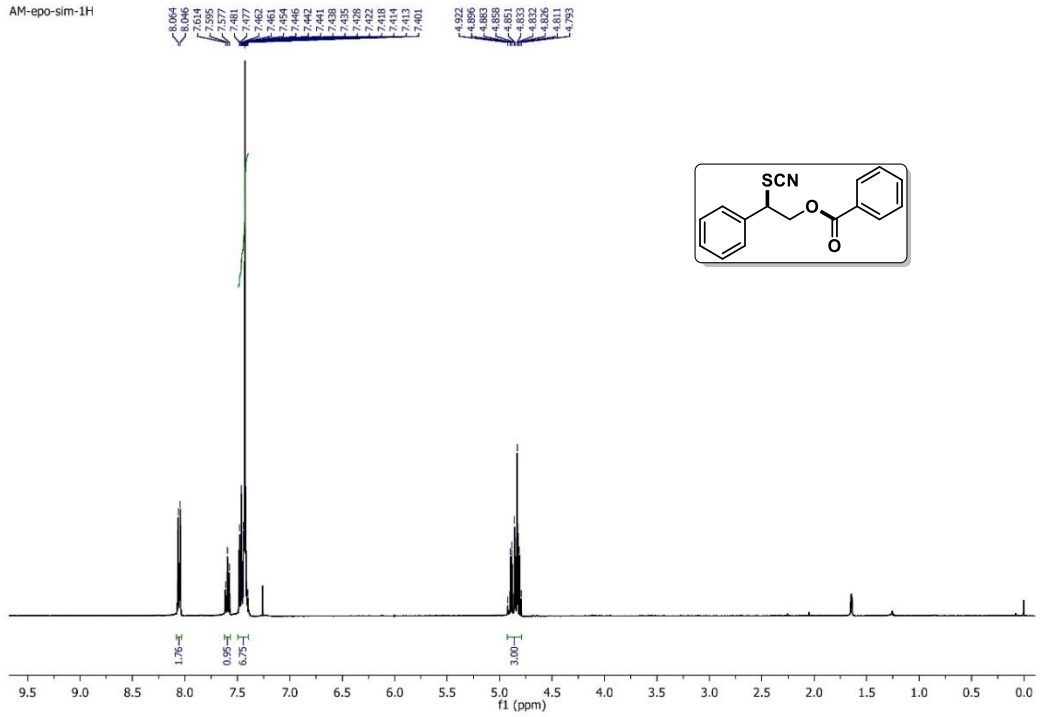
1-((4-Methoxybenzyl)oxy)-3-thiocyanatopropan-2-yl 4-methylbenzoate (2n):



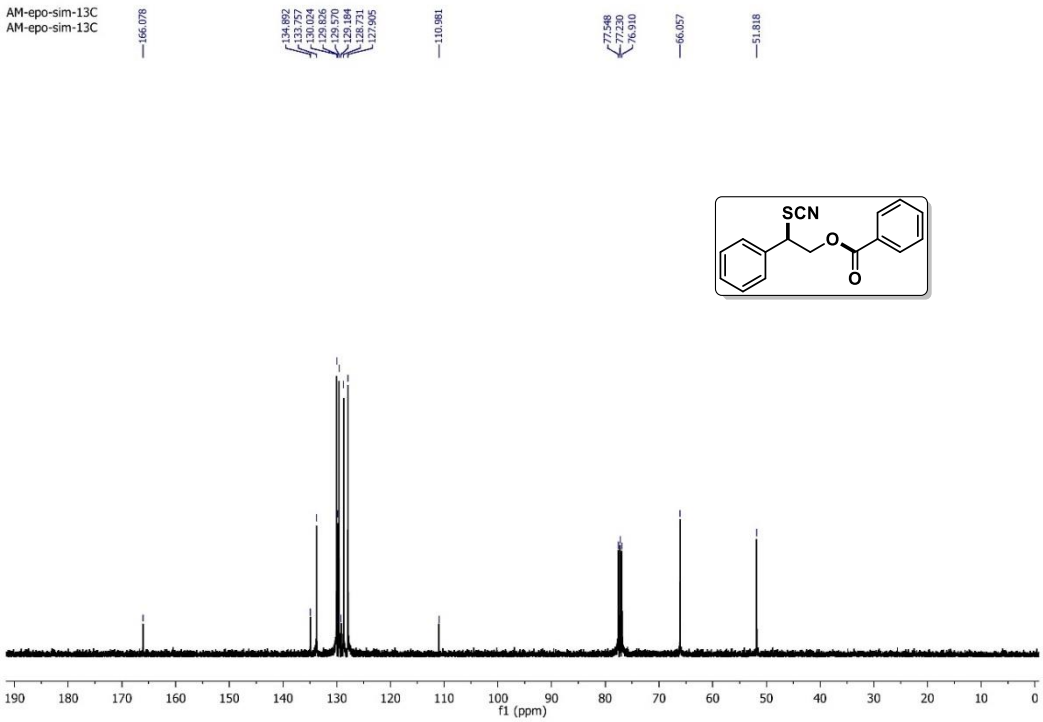
Yellow liquid (164 mg, 92%); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.41 (s, 3H), 3.36–3.46 (m, 2H), 3.71–3.80 (m, 5H), 4.48–4.59 (m, 2H), 5.43–5.46 (m, 1H), 6.87 (d, 2H, *J* = 8.4 Hz), 7.23 (dd, 4H, *J* = 6.0 Hz), 7.96 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.9, 35.2, 55.5, 68.2, 70.9, 73.4, 112.3, 114.1, 126.6, 129.4, 129.6, 129.7, 130.2, 144.6, 159.6, 165.8; IR (KBr): 2922, 2859, 2155, 1718, 1611, 1585, 1512, 1463, 1408, 1268, 1247, 1177, 1095, 1032, 816, 750, 689 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{21}NO_4S^+$ [M + NH_4^+] 389.1530; found 389.1532.

IV.7. Spectra

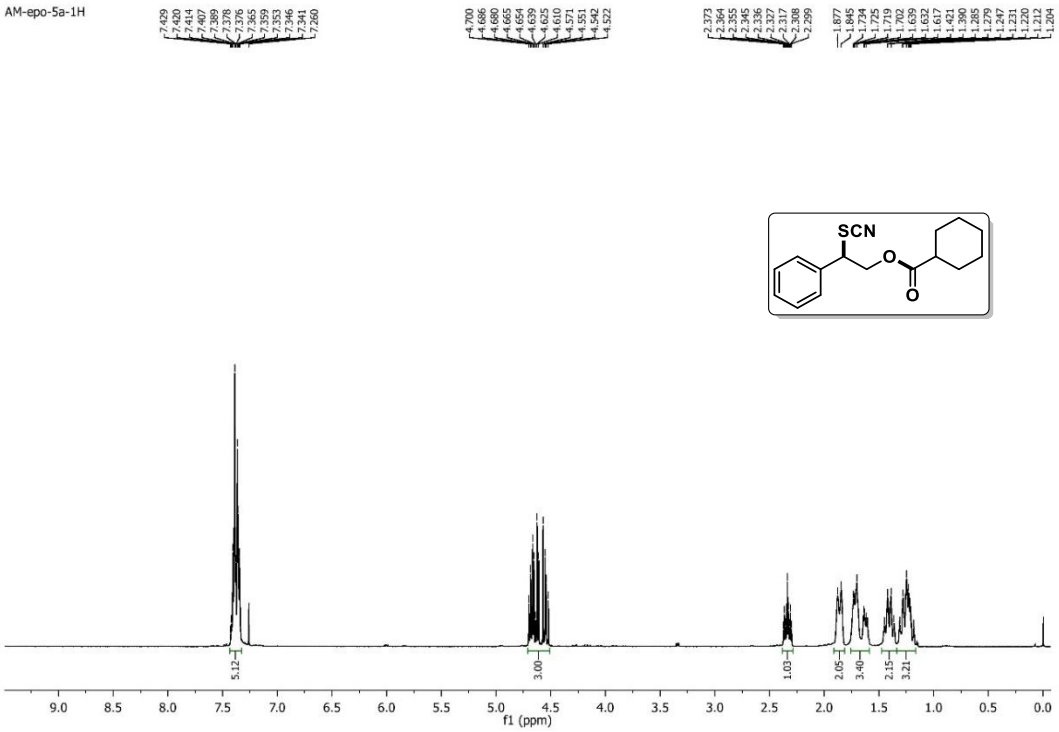
2-Phenyl-2-thiocyanatoethyl benzoate (1a): ^{1}HNMR (400 MHz, $CDCl_3$)



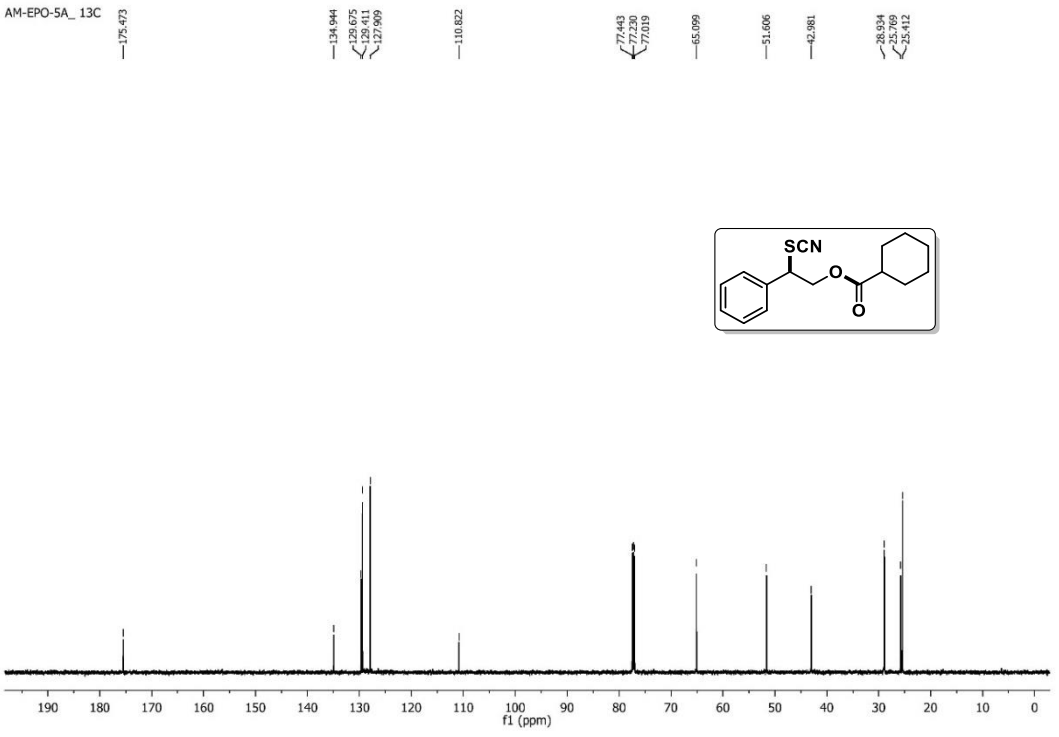
2-Phenyl-2-thiocyanatoethyl benzoate (1a): ^{13}CNMR (100 MHz, $CDCl_3$)



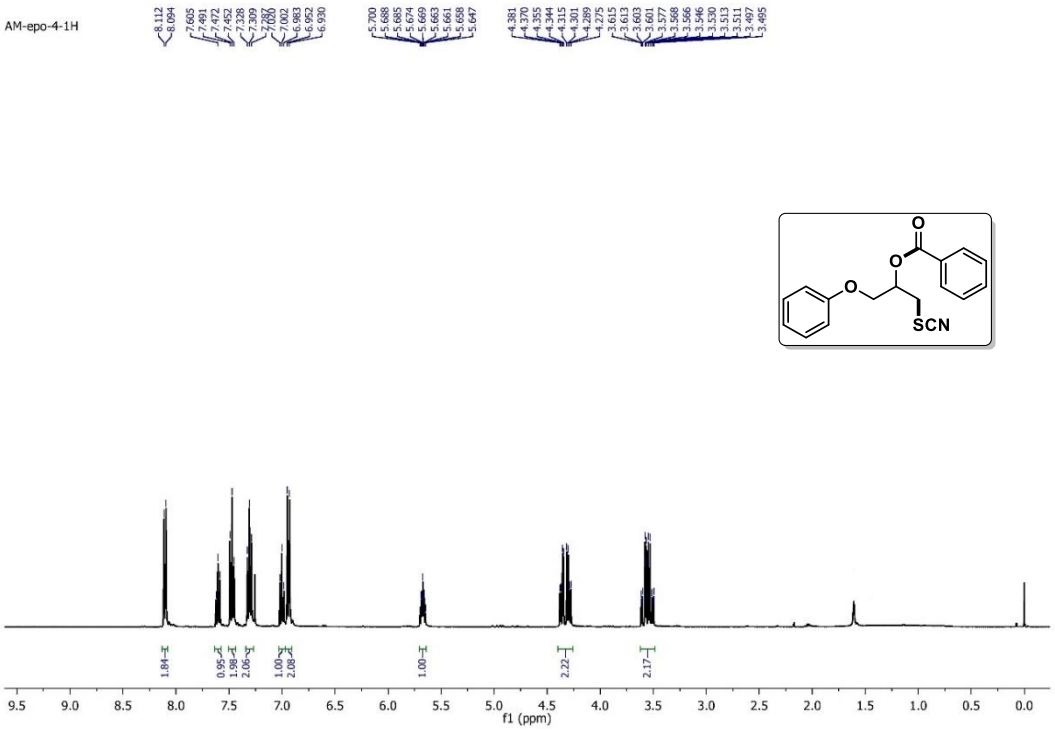
2-Phenyl-2-thiocyanatoethyl cyclohexanecarboxylate (5a): ^{1}HNMR (400 MHz, $CDCl_3$)



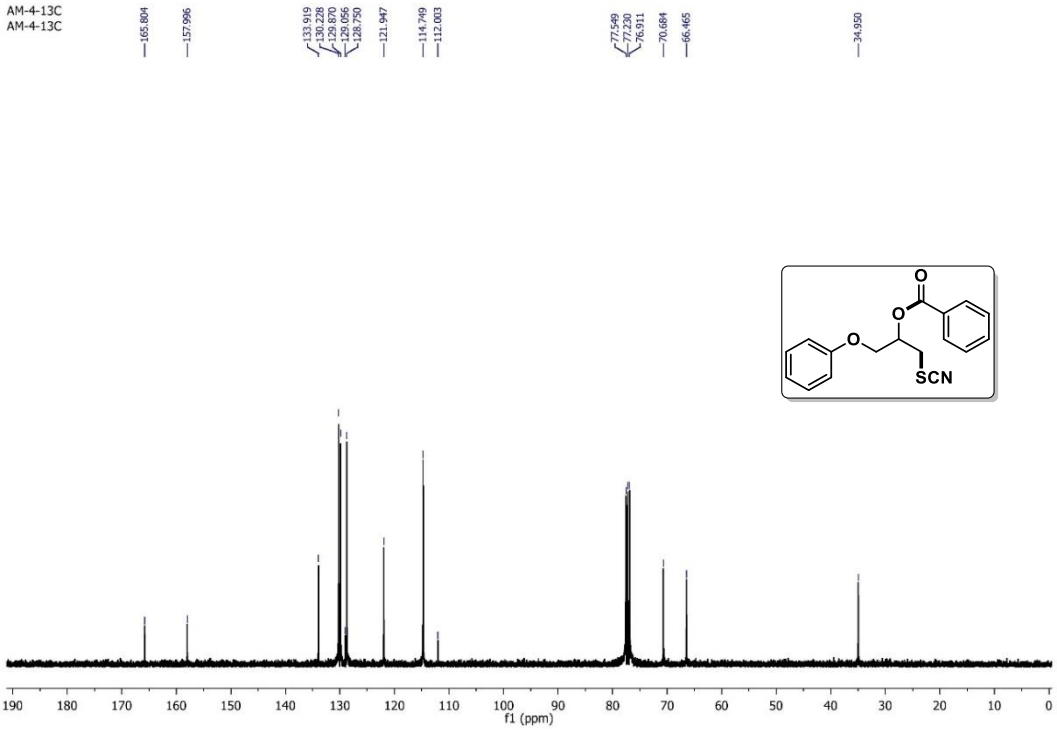
2-Phenyl-2-thiocyanatoethyl cyclohexanecarboxylate (5a): ^{13}CNMR (150 MHz, $CDCl_3$)



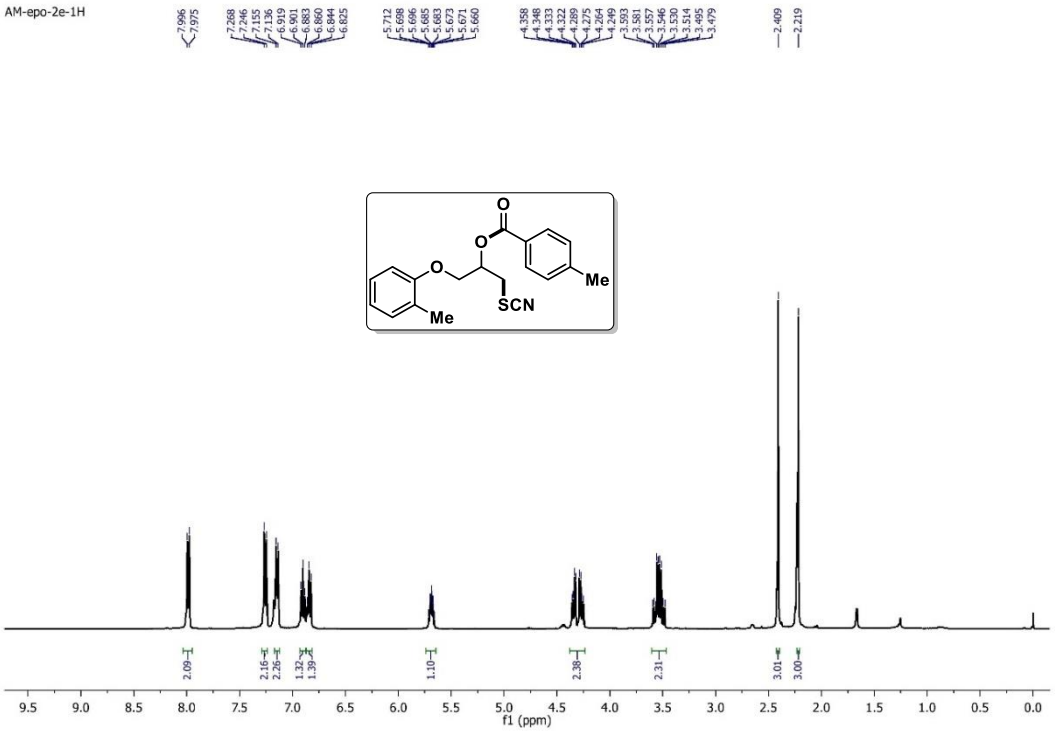
1-Phenoxy-3-thiocyanatopropan-2-yl benzoate (1d): ^{1}HNMR (400 MHz, $CDCl_3$)



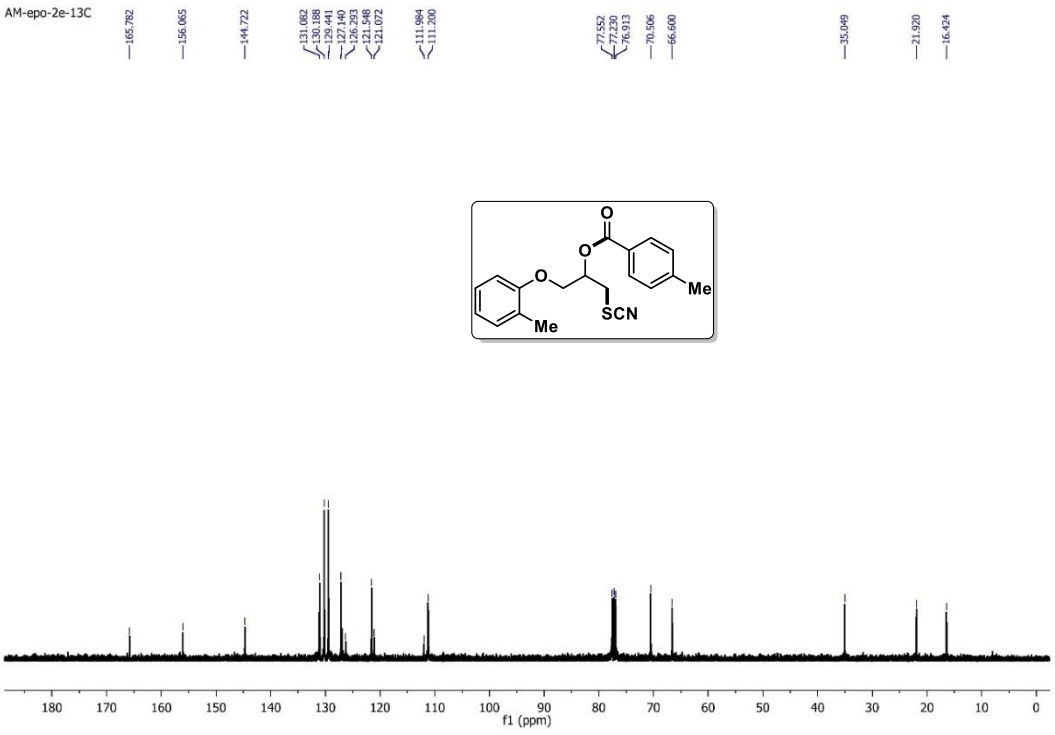
1-Phenoxy-3-thiocyanatopropan-2-yl benzoate (1d): ^{13}CNMR (100 MHz, $CDCl_3$)



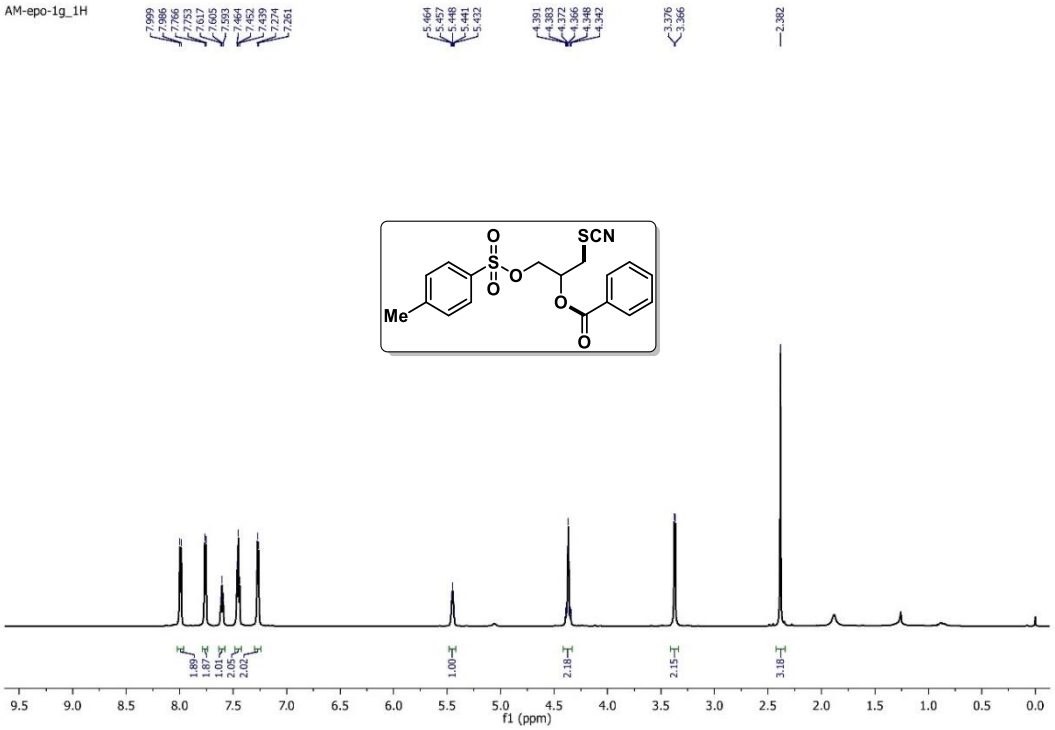
1-Thiocyanato-3-(*o*-tolyloxy)propan-2-yl 4-methylbenzoate (2e): ^{1}HNMR (400 MHz, $CDCl_3$)



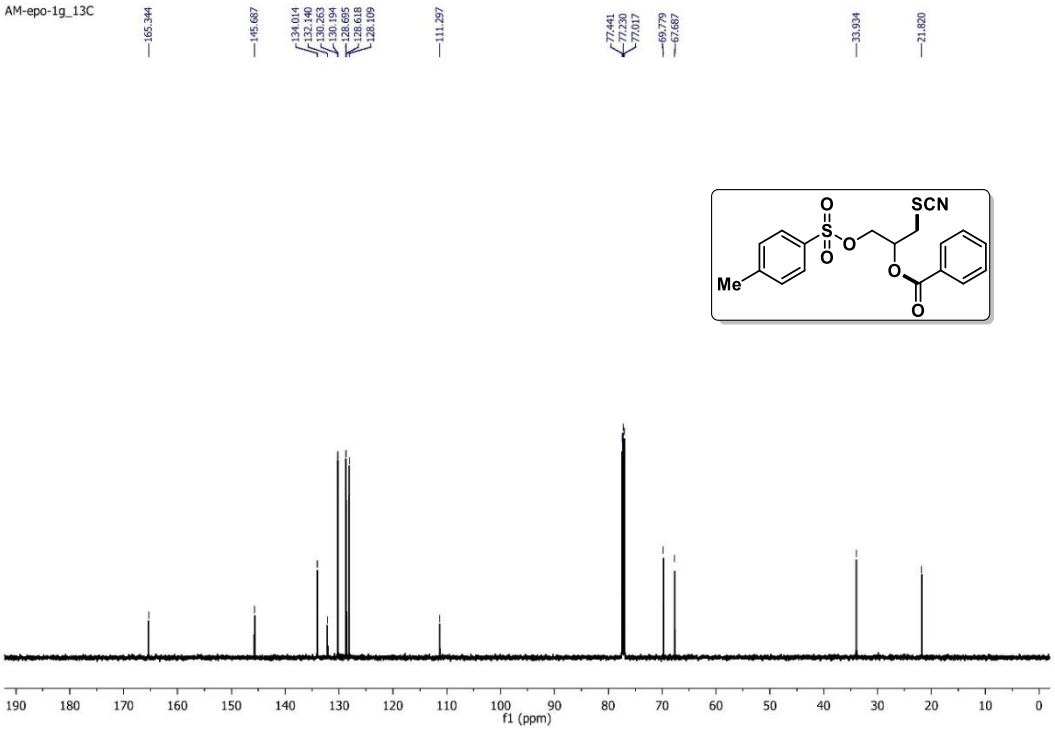
1-Thiocyanato-3-(*o*-tolyloxy)propan-2-yl 4-methylbenzoate (2e): ^{13}CNMR (100 MHz, $CDCl_3$)



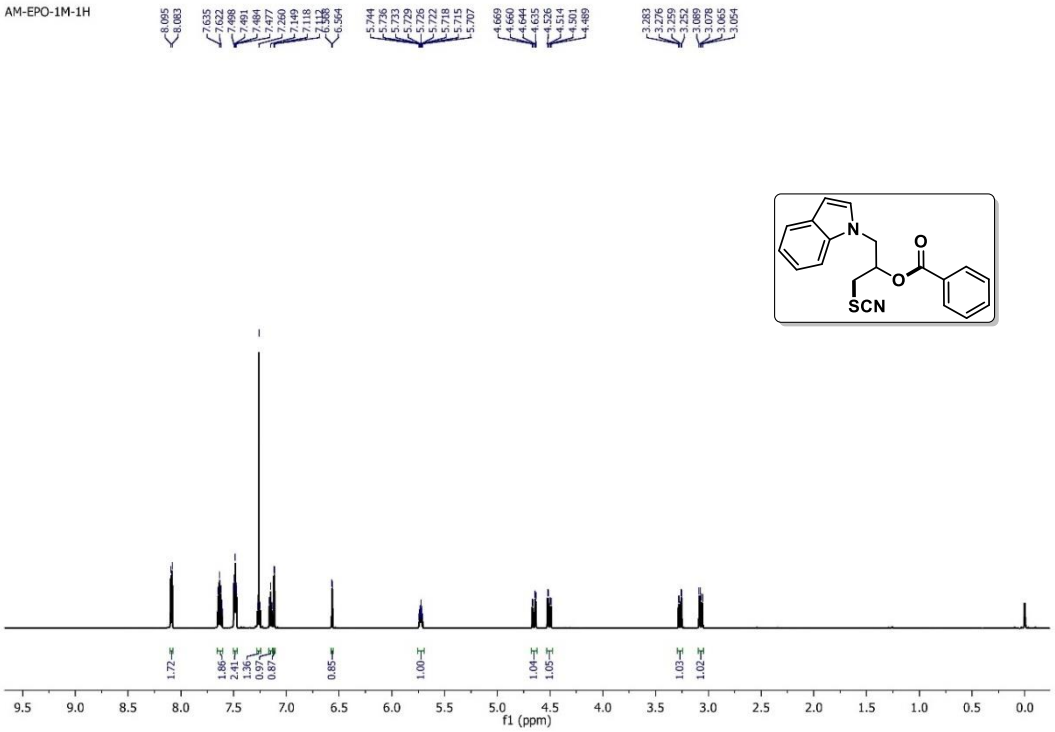
1-Thiocyanato-3-(tosyloxy)propan-2-yl benzoate (1f): ^{1}HNMR (600 MHz, $CDCl_3$)



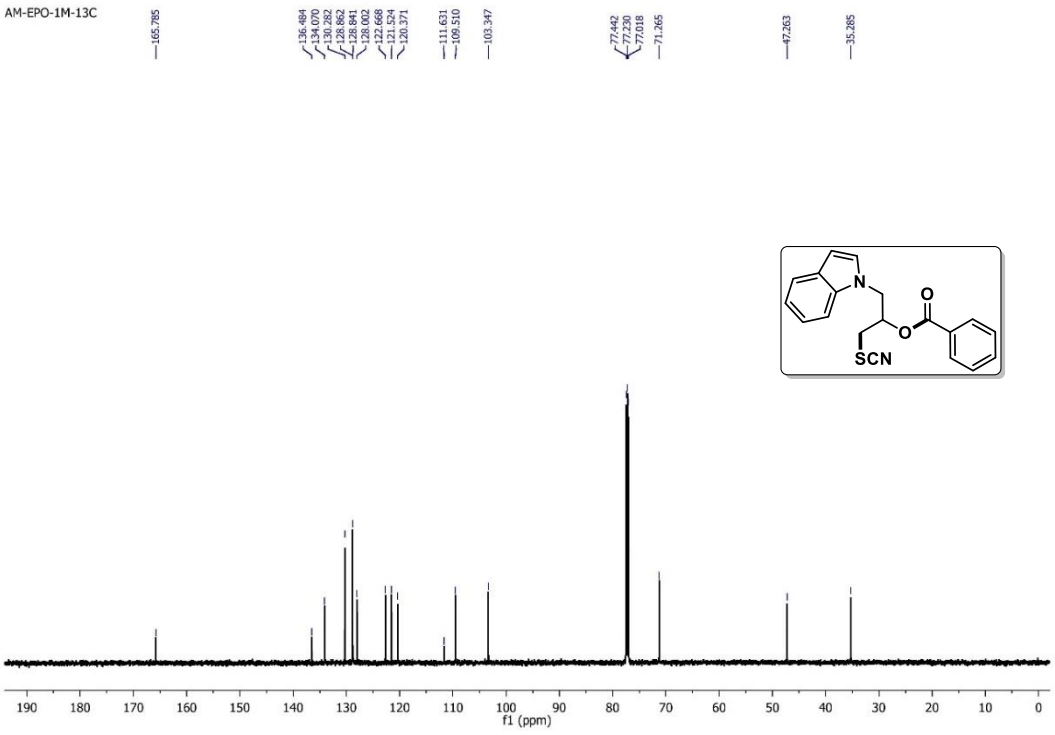
1-Thiocyanato-3-(tosyloxy)propan-2-yl benzoate (1f): ^{13}CNMR (150 MHz, $CDCl_3$)



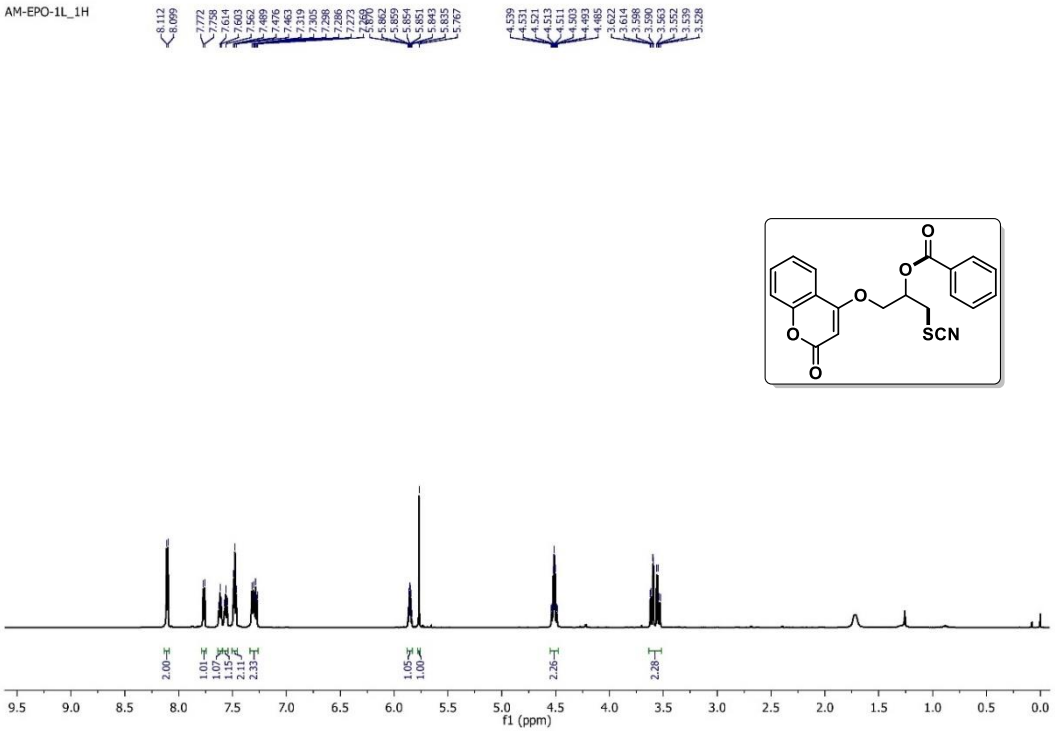
1-(1*H*-Indol-1-yl)-3-thiocyanatopropan-2-yl benzoate (1g): ^{1}HNMR (600 MHz, $CDCl_3$)



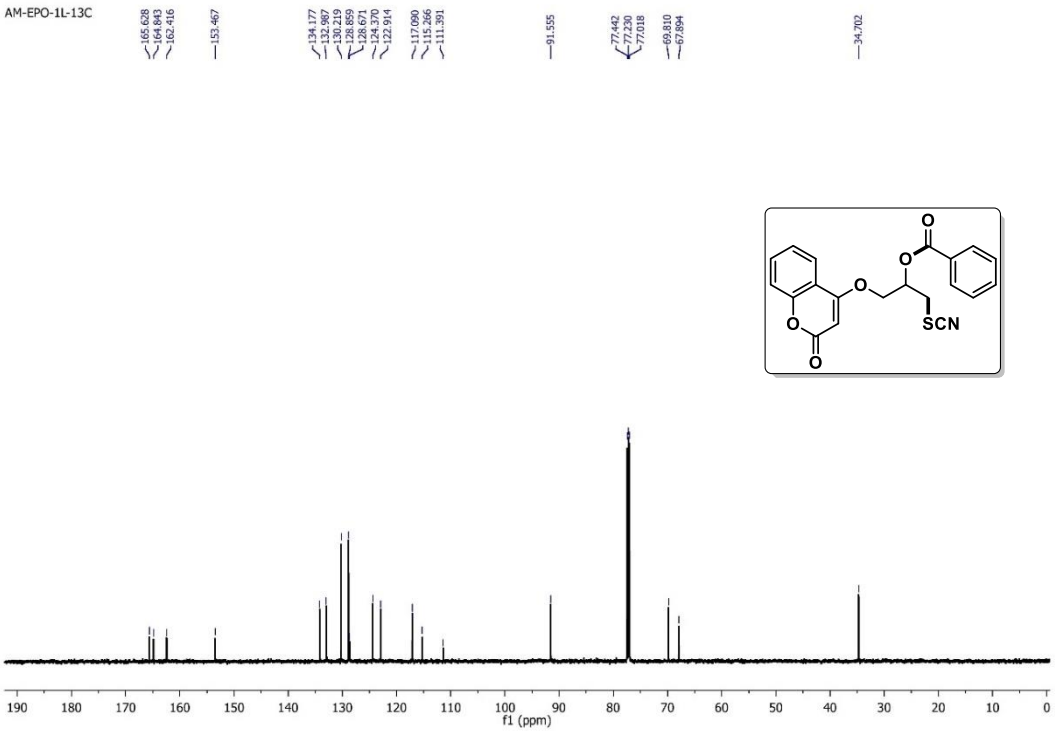
1-(1*H*-Indol-1-yl)-3-thiocyanatopropan-2-yl benzoate (1g): ^{13}CNMR (150 MHz, $CDCl_3$)



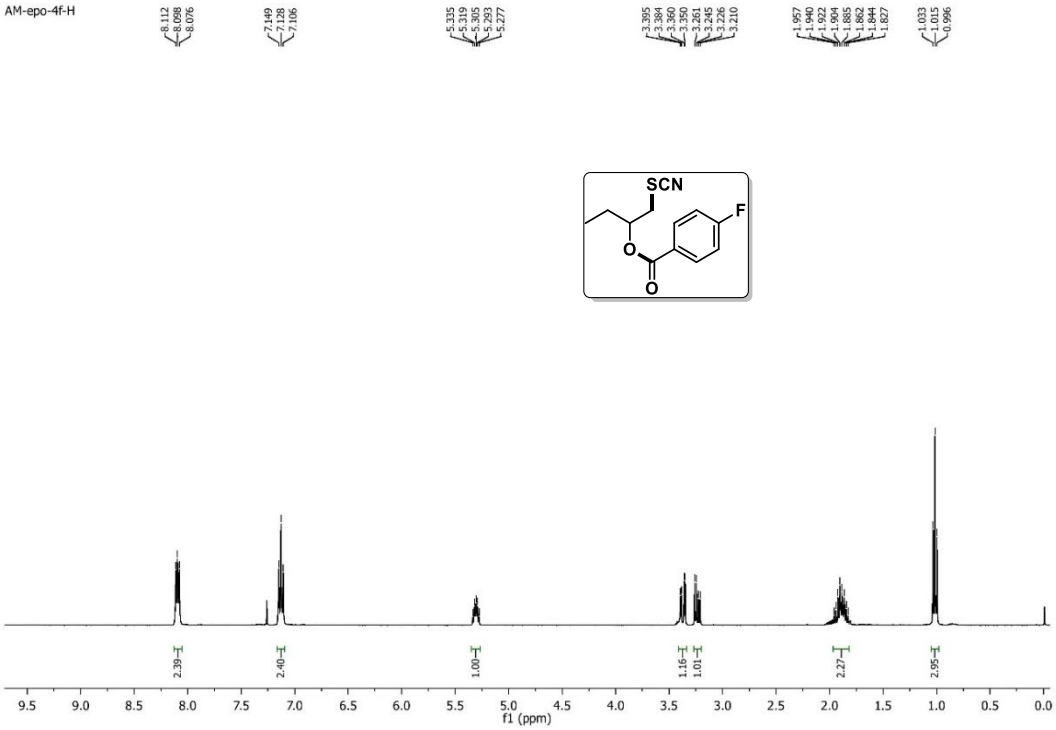
1-((2-Oxo-2*H*-chromen-4-yl)oxy)-3-thiocyanatopropan-2-yl benzoate (1j): ^{1}HNMR (600 MHz, $CDCl_3$)



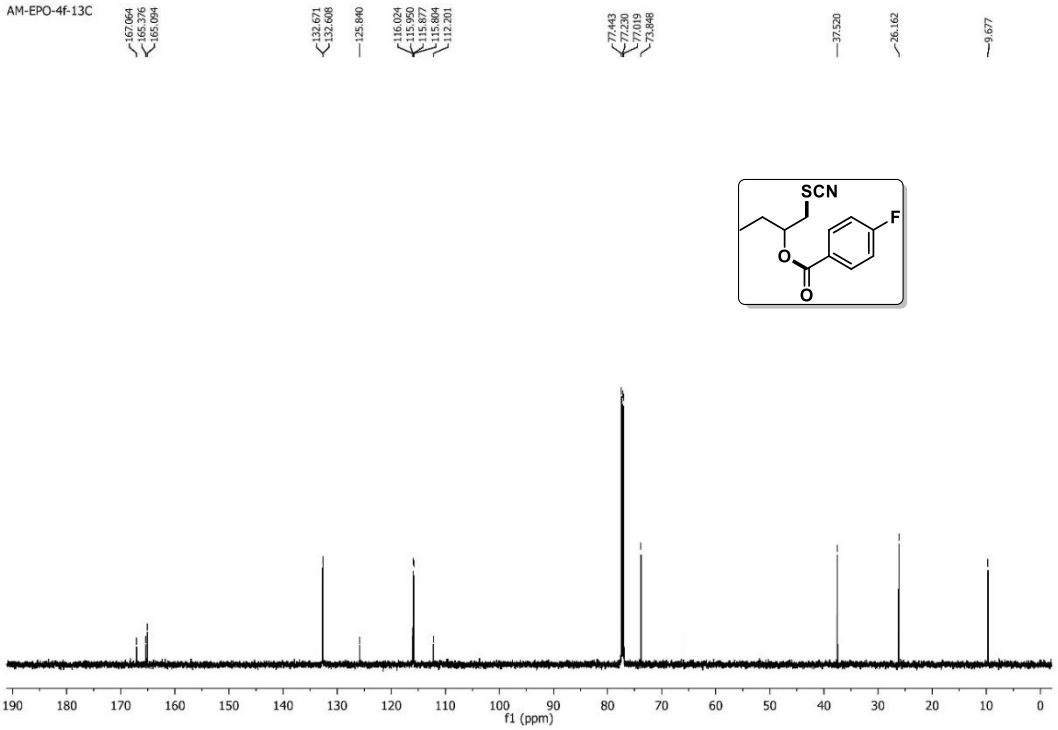
1-((2-Oxo-2*H*-chromen-4-yl)oxy)-3-thiocyanatopropan-2-yl benzoate (1j): ^{13}CNMR (150 MHz, $CDCl_3$)



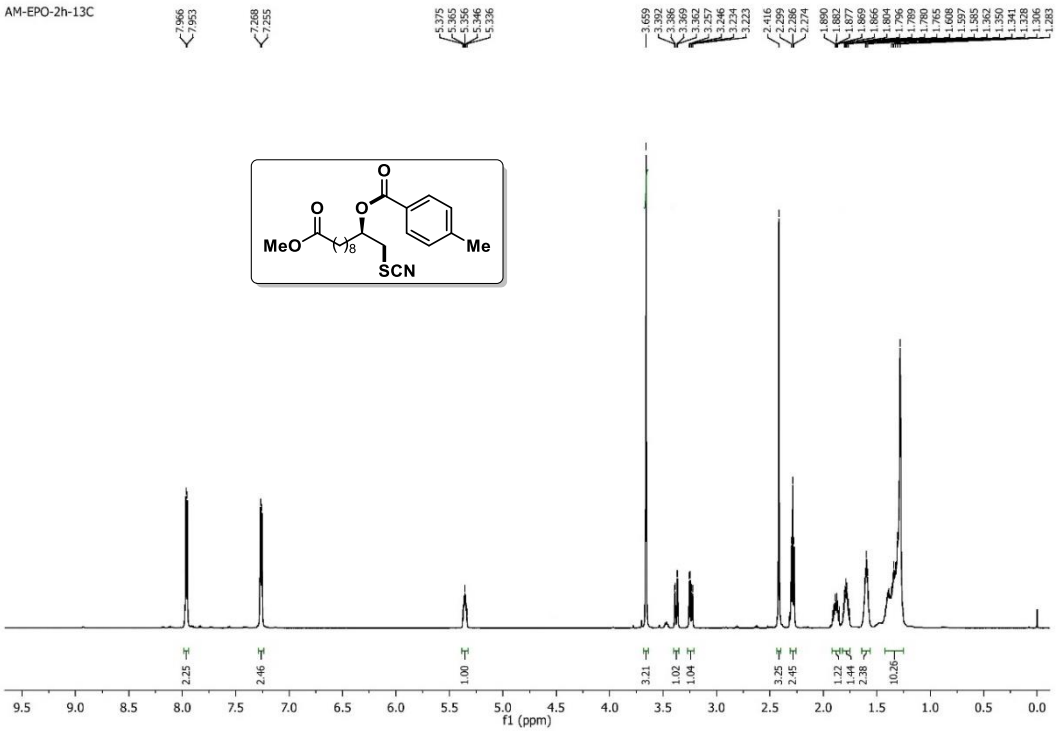
1-Thiocyanatobutan-2-yl 4-fluorobenzoate (4k): ^{1}HNMR (400 MHz, $CDCl_3$)



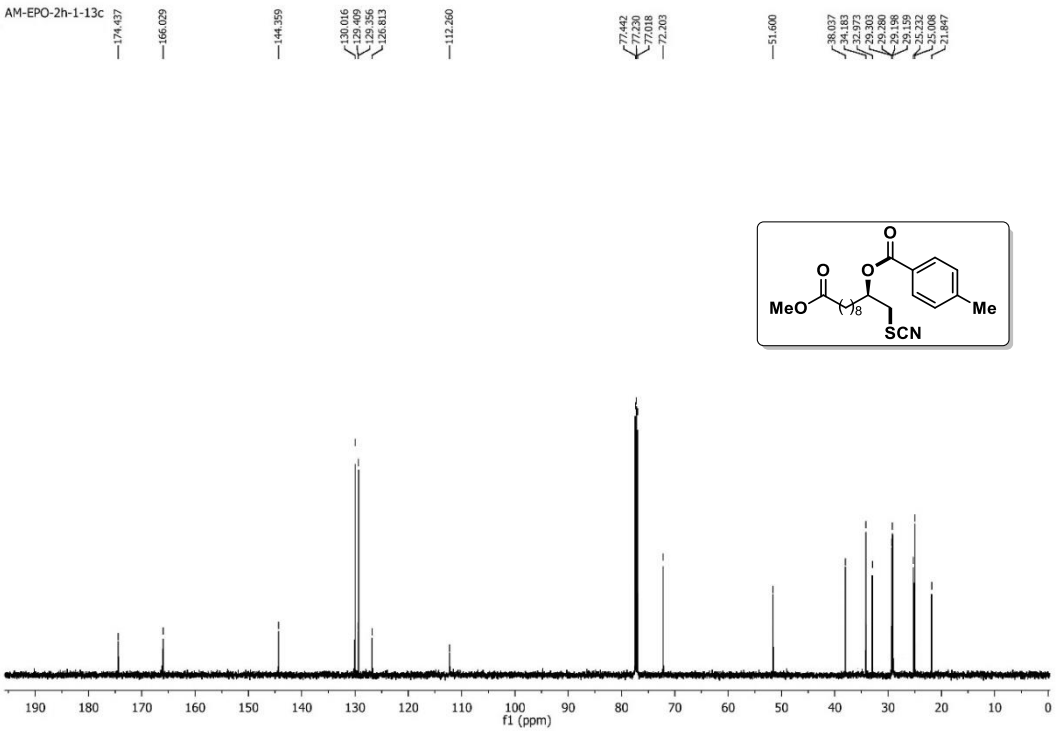
1-Thiocyanatobutan-2-yl 4-fluorobenzoate (4k): ^{13}CNMR (150 MHz, $CDCl_3$)



11-Methoxy-11-oxo-1-thiocyanatoundecan-2-yl 4-methylbenzoate (2m): ^{1}HNMR (600 MHz, $CDCl_3$)



11-Methoxy-11-oxo-1-thiocyanatoundecan-2-yl 4-methylbenzoate (2m): ^{13}CNMR (150 MHz, $CDCl_3$)



List of Publications:

(1) CuO Nanoparticle Catalyzed Synthesis of 2,3-Disubstituted Quinazolinones via Sequential *N*-Arylation and Oxidative C−H Amidation.
Modi, A.; Ali, W.; Mohanta, P. R.; Khatun, N.; Patel, B. K. *ACS Sustainable Chem. Eng.* **2015**, *3*, 2582.

(2) *N,N*-Dimethylacetamide (DMA) as a Methylene Synthon for Regioselective Linkage of Imidazo[1,2-*a*]pyridine.
Modi, A.; Ali, W.; Patel, B. K. *Adv. Synth. Catal.* **2016**, *358*, 2100.

(3) Organocatalytic Regioselective Concomitant Thiocyanation and Acylation of Oxiranes Using Aroyl Isothiocyanates
Modi, A.; Ali, W.; Patel, B. K. *Org. Lett.* **2017**, *19*, 432.

(4) Base-Promoted Synthesis of Quinoline-4(1*H*)-thiones from *o*-Alkynylanilines and Aroyl Isothiocyanates
Modi, A.; Sau, P.; Patel, B. K. *Org. Lett.* **2017**, *19*, 6128.

(5) A Thiocarbonyl Directed Regiospecific C–H/S–H Annulation of Quinoline-4(1*H*)-thiones with Alkynes
Modi, A.; Sau, P.; Patel, B. K. (*Manuscript under communication*).

(6) A metal free domino synthesis of 3-aroylindoles via two sp^3 C–H activation.
Gogoi, A.; **Modi, A.**; Guin, S.; Rout, S. K.; Das, D.; Patel, B. K. *Chem. Commun.* **2014**, *50*, 10445.

(7) Copper catalyzed Cross Dehydrogenative Coupling of *N,N*-Disubstituted Formamides and Phenols: A Direct Access to Carbamates.
Ali, W.; Rout, S. K.; Guin, S.; **Modi, A.**; Banerjee, A.; Patel, B. K. *Adv. Synth. Catal.* **2015**, *357*, 515.

(8) Palladium-Catalyzed Synthesis of 2-Aryl-*2H*-Benzotriazoles from Azoarenes and $TMSN_3$
Khatun, N.; **Modi, A.**; Ali, W.; Patel, B. K. *J. Org. Chem.* **2015**, *80*, 9662.

(9) Cs_2CO_3 as a source of carbonyl and ethereal oxygen in a Cu-catalyzed cascade synthesis of benzofuran[3,2-*c*] quinolin-6[5-*H*]ones
Ali, W.; **Modi, A.**; Behera, A.; Mohanta, P. R.; Patel, B. K. *Org. Biomol. Chem.* **2016**, *14*, 5940.

(10) Three sequential C−N bond formations: *tert*-butyl nitrite as a N1 synthon in a three component reaction leading to imidazo[*1,2-a*]quinolines and imidazo[*2,1-a*]isoquinolines
Sau, P.; Rakshit, A.; **Modi, A.**; Behera, A.; Patel, B. K. *J. Org. Chem*. **2018**, *83*, 1056.