Structural entities with arenes and heteroarenes represents a privileged chemical space in synthetic chemistry and medicinal chemistry. These aryl or heteroaryl moieties are quite ubiquitous in numerous biologically active natural products and billion-dollar pharmaceutical drugs such as Nilotinib, Apixaban etc. (Figure **1A**). Owing to the appearance of the arylated scaffolds in other important areas like agro-chemical sciences, material sciences and polymer chemistry; devising novel synthetic methodologies to incorporate aromatic rings have been considered as a fundamental research interest in organic synthesis.

As arylation chemistry denotes the add-on of an aryl moiety into nucleophilic centre and construction of the C-aryl or heteroatom-aryl bonds, the strategies to architect an arylation reaction depends on the classes of the nucleophile and the choice of the arylating partner. The past legacy of the arylation reactions e.g., i) aryl halide based: Ullmann coupling (1901) and Goldberg coupling (1906) to Buchwald-Hartwig reaction (1995); or ii) aryl boronic acid based: Chan-Lam-Evans coupling (1997) are well-explored and still relevant for arylation reactions. In the realm of arylating sources, diaryliodonium salts have recently emerged as an effective and versatile aryl precursor and their fascinating arylation strategies have been acknowledged from the perspective of sustainable organic synthesis.

Diaryliodonium salts ($Ar^1Ar^2I^+X^-$) are one of the well-known hypervalent iodine(III) compounds like (diacetoxyiodo)benzene (DIB or PIDA) and [bis(trifluoroacetoxy)iodo]benzene (BTI or PIFA) and these organoiodine compounds play a key role as aryl-transfer reagents in modern organic synthesis. These aryl-transferring reagents are mild, stable, non-toxic, and easily preparable. The structural features and X-ray crystallography reveals that the actual geometry around the iodine centre is pseudo-trigonal bipyramidal or T-shape where the bond angle between Ar-I-Ar is 90° and the counter-anion and iodine atom possess secondary interaction. Due to the presence of electrophilic hypervalent bond, it exhibits remarkable reactivity behaviors and have been utilized in arylation chemistry with diverse nucleophilic atoms (C, N, O, F, S, P etc.) (Figure **1B**). As diaryliodonium salts are useable under both metal-free and metal-catalyzed conditions; however, the most appreciable achievement of this aryl source is their utilization in metal-free arylation from the perspective of pharmaceutical interest, as it could mitigate the requirement of heavy transition metals

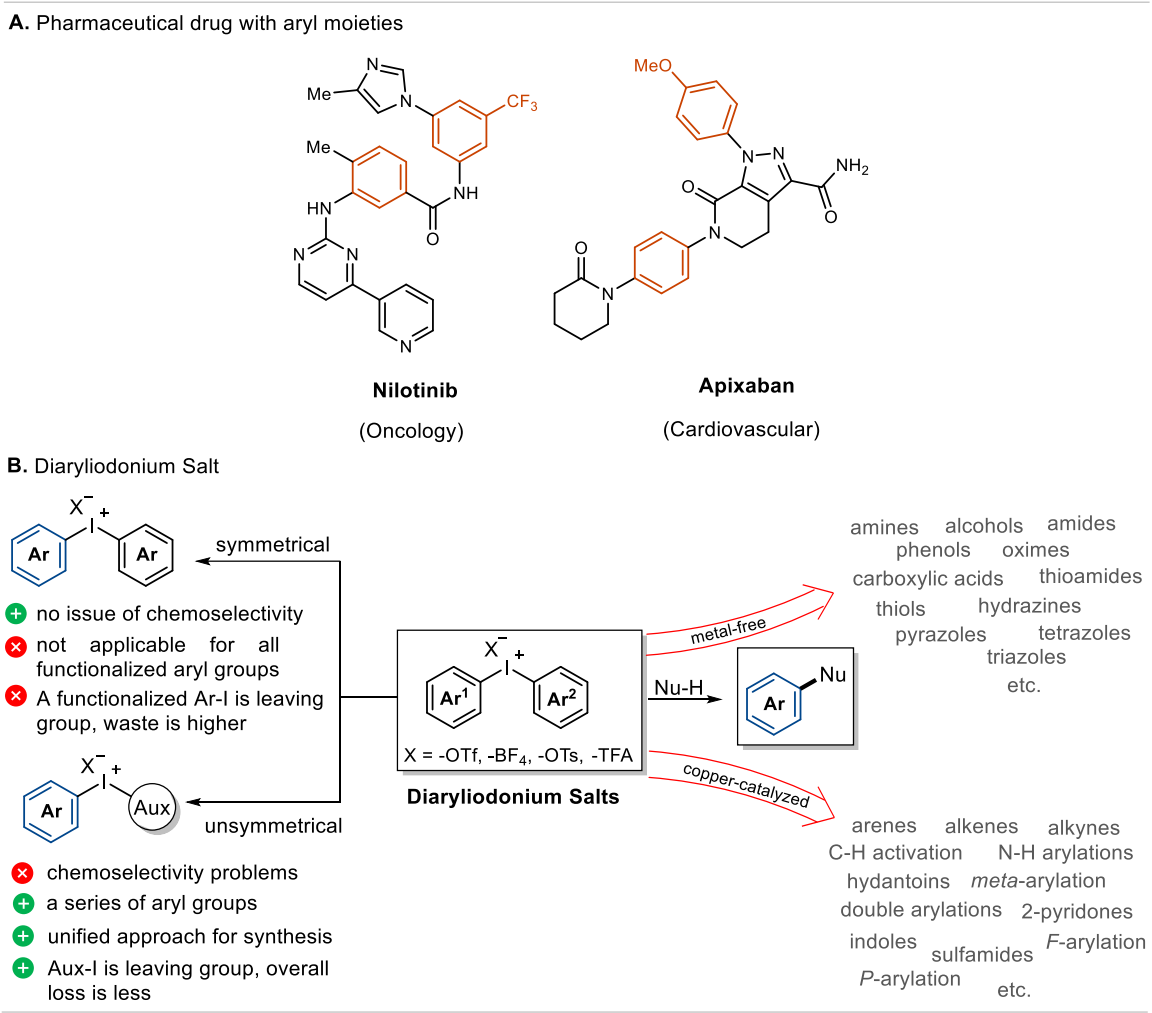


Figure **1**. **A)** Structure of Nilotinib and Apixaban, **B)** classification of diaryliodonium salts and their various applications in organic synthesis

(Pd, Ru, Rh etc.). In general, the most convenient way to prepare diaryliodonium salts is from aryl iodides and arenes with an appropriate oxidant. As both symmetrical and unsymmetrical iodonium salts are utilized depending on the reaction conditions, however; the arylation chemistry with unsymmetrical diaryliodonium salts with an electron-rich auxiliary group {such as 1,3,5-trimethoxyphenyl (TMP), anisyl (An) or mesityl (Mes)} are more advantageous than symmetrical iodonium salts as the former (i) reduces the cost of synthesis, (ii) provides aryl sources with a range of functional groups, (iii) has high chemoselectivity, and (iv) has a minimum potential waste generation factor (Figure **1B**). Notably, the synthesis of functionalized symmetrical iodonium salt requires the usage of aryl iodides and aryl boronic acids together containing a similar functional group in each half, which ultimately increases the cost of synthesis and potential waste. Unsymmetrical iodonium salts

with electron-rich auxiliaries like the An and TMP groups exhibit higher selectivity in metal-free reactions, while the sterically hindered mesityl group is a better auxiliary in metal-catalyzed reactions.

A plethora of metal-free arylation methods with valuable organic scaffolds, such as amines, alcohols, carboxylic acids, amides, and thiols have been reported under mild conditions with both symmetrical and unsymmetrical iodonium salts without the use of transition metals. In addition, arylation of various biologically active heterocyclic molecules have been achieved with diaryliodonium salts. In addition to metal-free arylations, diaryliodonium salts have been utilized in numerous C–H functionalizations and hetero-atom arylations with transition-metal catalysts such as palladium, copper, nickel, ruthenium etc. Among the transition-metal catalyzed methodologies, the combination of copper-catalyzed reactions with diaryliodonium salts is well-known because of numerous other challenging arylation methods. For example, Guant's group utilized diaryliodonium salts to achieve direct *meta*-selective C–H bond arylation of acetanilide derivatives under mild copper-catalyzed conditions without using any expensive and complicated directing group or heavy transition-metal. In the concurrent period, this versatile reagent has been employed in numerous arylation reactions of total synthesis of drug molecules and used as an effective synthon in benzyne reactions.

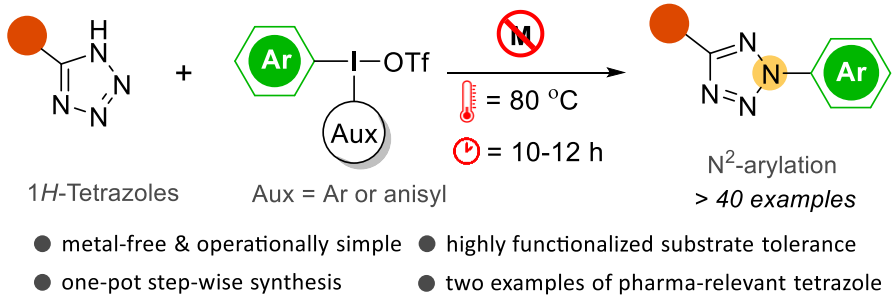
The Thesis

To fulfill the mentioned aims in the proposed objectives, the work is planned and carried out accordingly. The thesis comprises total of **six chapters**. Chapters **2** and **3** of the thesis discuss the development of two metal-free methods with diaryliodonium salts for the *N*-arylation of tetrazoles and *S*-arylation of heterocylic thiols respectively, while the subsequent chapters (Chapters **4** and **5**) describe the utilization of diaryliodonium salts under copper-catalysis for the *N*-arylation of two important heterocycles i.e., hydantoins and isatoic anhydrides respectively. To bring clarity in expression, each work is systematically organized and discussed in the thesis.

Chapter 1: The first chapter delivers detailed introduction of diaryliodonium salts and their earlier applications. The bonding pattern, reactivity, and classification of the diaryliodonium salts are included in this chapter. Different types of synthesis routes for both symmetrical and unsymmetrical iodonium salts are mentioned too.

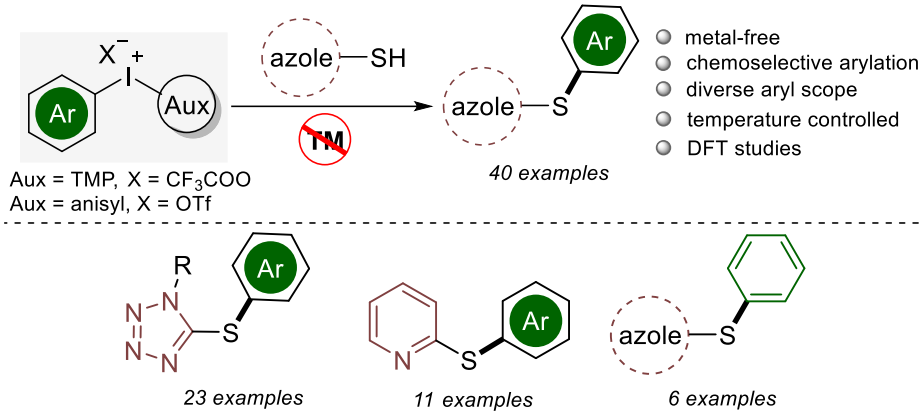
Finally, an extensive literature background for metal-free arylation methodologies with diaryliodonium salts and copper-catalyzed arylation methods for heterocyclic molecules are discussed. The objectives of the thesis are also outlined towards the end.

Chapter 2: This chapter describes the development of metal-free methodology for regioselective N^2-arylation of 5-substituted-1*H*-tetrazoles with diaryliodonium salts (Scheme **1**). As the previous symmetrical iodonium salt-based methods for *N*-arylation of tetrazoles depend on transition-metal involved conditions, this methodology provides an effective alternative path to achieve series of 2-aryl-5-substituted tetrazole scaffolds under very mild conditions. The developed method requires a mild basic medium and the aryl group from the diaryliodonium salts smoothly transfers to the N^2-position of the tetrazole with high regioselectivity without showing any presence of N^1-arylated product. Examination of various unsymmetrical iodonium salts reveal that the anisyl-iodonium salt is the most suitable auxiliary in comparison to the mesityl- and TMP-iodonium salts. The optimized metal-free protocol is tested with a series of functionalized 5-substituted-1*H*-tetrazoles having alkyl and electronically variant aryl groups and affording its corresponding N^2-arylated products in moderate to good yields. Diaryliodonium salts of symmetrical and unsymmetrical (anisyl-auxiliary) could be applicable with this protocol; however, majority of the functionalized aryl groups are derived from aryl(anisyl)iodonium triflates except few symmetrical types. Variety of aryl groups with electron-rich and electron-withdrawing functional groups work well with the methodology and demonstrates the robustness of the method. *Ortho*-substituted and sterically congested aryl groups are also suitable. The method is easily scalable and can be performed up to gram-scale. The N^2-arylation of two tetrazolic pharma-relevant molecules demonstrates the possibility of the method for late-stage modifications (Scheme **1**). Furthermore, one-pot system has devised where the tetrazole are prepared *in-situ* from nitriles followed by the addition of diaryliodonium salts to obtain N^2-arylation; a series of 2,5-diaryl-tetrazoles have been synthesized with the strategy. Mechanistic investigations with various radical-trapping reagents confirm that the mechanism is ionic and proceeds *via* conventional T-shaped intermediate.



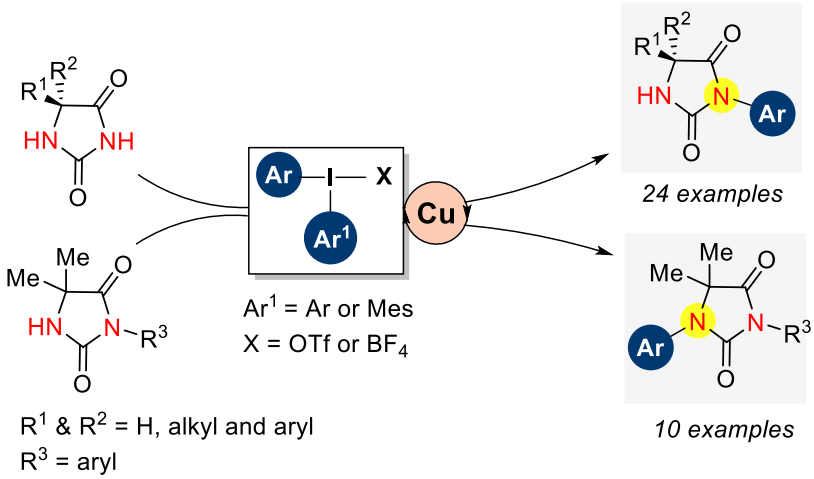
Scheme **1.** Regioselective *N*[2]-arylation of 1*H*-tetrazoles with diaryliodonium salts

Chapter 3: Inspired by the unsymmetrical iodonium salts due to their unified approach for chemoselective arylation for all patterns of functionalized aryl groups and easy access for preparation; this chapter highlights *S*-arylation of heterocyclic thiols or mercapto-azoles (especially previously less-explored 5-mecaptotetrazoles and 2-mercaptopyridine) using two types of unsymmetrical iodonium salts; aryl(TMP)iodonium trifluoroacetate and aryl(anisyl)iodonium triflate (Scheme **2**). The developed reaction conditions are metal-free and temperature dependent; and the arylation is easily feasible under basic conditions. A detailed study on unsymmetrical iodonium salts reveals that TMP-iodonium salt with trfiluoroacetate as counter-anion is suitable for 5-mercaptotetrazoles and other mecapto-azoles; however, in case of 2-mercaptopyridine, anisyl-iodonium triflate exhibits better conversion. With the proper auxiliary-iodonium salts selection, aryl(TMP)iodonium salts demonstrates the unified selectivity for the transfer of functionalized aryl groups (electron-rich, sterically congested *ortho*-substituted, electron-poor etc.) to the sulphur nucleophile and affords diverse di(hetero)aryl thiethers in moderate to good yields. The generality of the method is further established by reacting tetrazole-5-thiol with different alkyl and aryl groups in the *N*[1]-position. Moreover, the methodology is equally applicable to other mercapto-azoles (azoles such as triazole, pyrimidine, imidazole etc.). As disulphide bond (S-S) formation is witnessed in case of 2-mercaptopyridine, the re-investigation of the reaction conditions reveal that this moiety demands slight change in reaction conditions for arylation i.e., temperature and auxiliary of the unsymmetrical iodonium salts. The reaction conditions are further established with diverse examples of aryl groups derived from aryl(anisyl)iodonium triflate by chemoselective arylation with 2-mercaptopyridine. The density functional theory (DFT) calculations also validate the chemoselective *S*-phenylation of 2-mercaptopyridine with phenyl(anisyl)iodonium triflate.



Scheme **2**. *S*-arylation of mercapto-azoles by exploring unsymmetrical iodonium salts

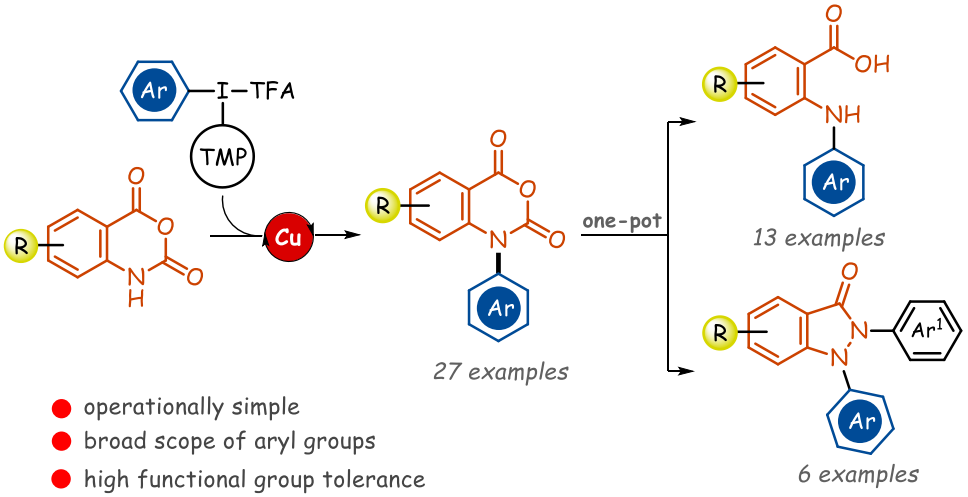
Chapter 4: This chapter describes that diaryliodonium salts can be used as an effective arylating source to achieve previously challenged Cu-catalysed arylation method for the *N*-arylation of hydantoins (Scheme **3**). The optimized reaction condition is performable at room temperature under mild conditions without using excess amount of reagents. In addition, the catalytic conditions are ligand-free, easily scalable and highly regioselective at the N^3-position of the hydantoin. With the developed catalytic conditions, the methodology explores the synthesis of valuable synthetic building blocks of arylated hydantoins in moderate to good yields. The robustness of the protocol is tested with the varied examples of hydantoins including C^5-H and N^1-H unprotected hydantoins. Hydantoin having a chiral centre at C^5-position works smoothly under this method without affecting the chirality of the compound. Though symmetrical iodonium salts can be easily utilized for N^3-arylation; however, the extensive examination of electronically and sterically variable unsymmetrical iodonium salts shows that aryl(mesityl)iodonium salts is the best choice among other auxiliaries and this mesityl version of iodonium salt show chemoselective transfer of the functionalized aryl groups. Diverse aryl substrates possessing electron-neutral, electron-rich and electron-withdrawing functionalized groups from diaryliodonium salts are incorporated in the hydantoin nucleus in this methodology. As the previous arylation methods were unsuccessful with *ortho*-substituted aryl groups for the N^3-arylation; *ortho*-substituted aryl iodonium salts also exhibit good conversion in this method. In addition to N^3-arylation, this strategy can also be effectively extended to N^1-arylation of the N^3-protected hydantoins.



Scheme **3**. Utilizing diaryliodonium salts for N^1- and N^3-arylations of hydantoins

Chapter 5: This chapter describes the investigation of the innate reactivity and chemoselectivity of the TMP-iodonium salts under copper-catalyzed conditions for the *N*-arylation of isatoic anhydrides (Scheme **4**). Though, few previous methodologies for this important *N*-arylation are available in literature; however, the methodologies to access the *N*-arylated compounds have the limitations on the arylation scope. Thorough optimizations with various bases, solvents and temperature reveal that the reaction cannot be accomplished under metal-free conditions. The *N*-arylation requires mild catalytic condition i.e., copper (5 mol%) at room temperature. This TMP-iodonium salt-based reaction strategy can be applied to symmetrical iodonium salts and mesityl-iodonium salts. As the formed *N*-arylated product exhibits silica-sensitivity and is prone to decarboxylation; the proper selection of chromatographic technique is standardized for purification of the desired product. The applicability of the present *N*-arylation scheme is supported by tolerance of wide variety of functional groups in the aryl part derived from aryl(TMP)iodonium salts under reaction conditions and in all cases, the aryl group is transferred selectively. Aryl groups possessing the electron-rich and electron-deficient groups, and *ortho*-substitution are demonstrated in the arylation scope and affords a series of *N*-arylated isatoic anhydrides in moderate to good yields. Along the arylation scope, the reaction efficacy has been checked with other substituted isatoic anhydrides and most of the examples work smoothly in this protocol. As isatoic anhydride plays a vital role as a synthon for other heterocycles and organic building blocks, this work further provides the alternative path to synthesize two

biologically privileged scaffolds such as fenamic acids and *N,N'*-diarylindazole-3-ones. In each case, one-pot methodology is devised where *N*-arylation of isatoic anhydrides is the intermediate step and affords a library of fenamic acid derivatives (including flufenamic acid, an anti-inflammatory drug) and *N,N'*-diarylindazole-3-ones by showcasing a variety of functionalized aryl groups.



Scheme **4**. *N*-arylation of isatoic anhydrides and its application as an intermediate

Chapter 6: This chapter summaries the significant results of all the above works mentioned from chapter 2 to chapter 5. This chapter also includes the future prospect of the synthesis and application of diaryliodonium salts.