CHAPTER I

I. Introduction to Transition Metal Catalysts and their Applications in Heterocyclic Chemistry

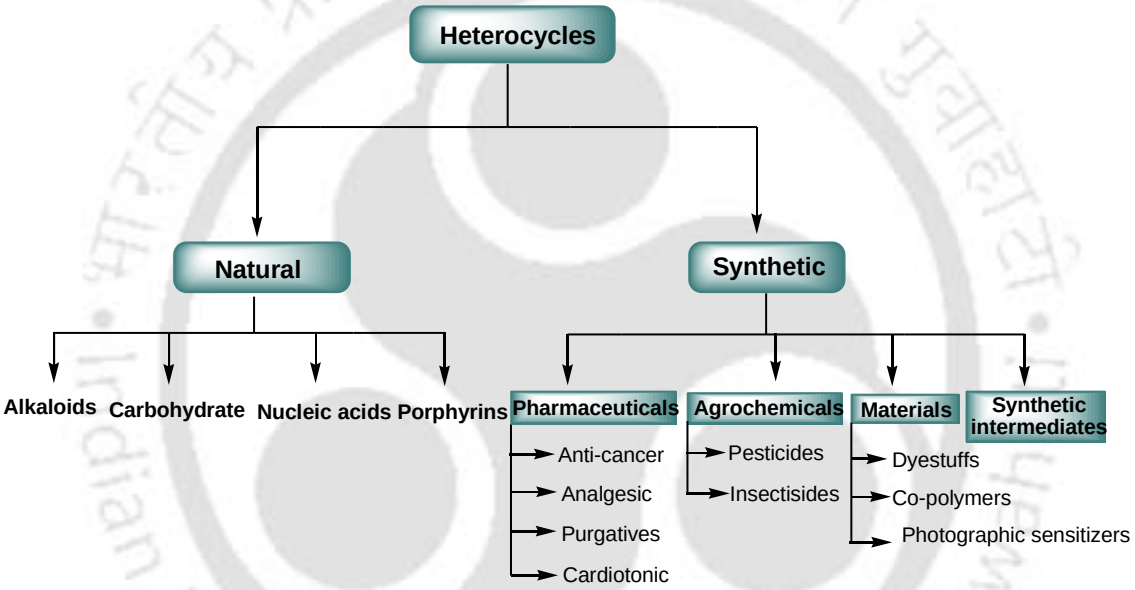
I.1. Introduction to Heterocyclic Chemistry

Most of the chemical compounds consist of molecules, which are classified based on their structure, type and number of atoms as well as their bonding patterns. In organic chemistry, there are two main types of frame work structures, namely cyclic and acyclic. Cyclic compounds in which the ring frame is made from only one element are called **isocyclic** compounds (e.g. S_8). If the building block is made from C-atoms they are term as **carbocyclic** compounds (e.g. cyclohexane, benzene). Cyclic compounds in which the ring frame is replaced by some other atom/atoms (hetero atom) are called **heterocyclic compounds**.[1] Atoms other than carbon in the ring are termed as **heteroatoms**. In nature, most commonly found hetero atoms are nitrogen, oxygen and sulfur. However, many other atoms can form stable covalent bonds for ring construction in heterocycles. Notable among are phosphorous, arsenic, antimony, silicon, tellurium, selenium, boron, and germanium.[1]

I.1.1. Heterocycles and their Importance

Heterocycles are the largest classical divisions of organic chemistry and more than half of all known drugs are heterocycles.[2] Almost all the compounds known as vitamins, co-enzymes, porphyrins (e.g.-hemoglobin), DNA, RNA and many other natural products are heterocycles.[1] This class also includes several other compounds of biological importance, such as nucleic acids, carbohydrates, hormones, and pigments. Their participation in a wide range of other areas cannot be underestimated. Consequently, researchers are on a continuous pursuit to design and produce better pharmaceuticals, pesticides, insecticides, rodenticides, and herbicides by following natural models. Other important practical applications of these compounds are used as a wide variety of industries including cosmetics, reprography, information storage, plastics, solvents, antioxidants,

and vulcanization accelerators. There are thousands of other heterocyclic compounds, both natural and synthetic, of major importance, not only in medicine but also in several other activities known to mankind (*Scheme I.1.1.1*). Finally, as an applied science, heterocyclic chemistry is an inexhaustible resource of novel bioactive compounds. A vast number of combinations of carbon, hydrogen, and hetero atoms can be designed, providing compounds with the most diverse physical, chemical, and biological properties.[2,3] It is, therefore, easy to understand why both the development of new methods and the strategic deployment of known methods for the synthesis of complex heterocyclic compounds continue to drive the field of synthetic organic chemistry.



Scheme I.1.1.1. *Various applications of heterocycles*

I.1.2. Pharmaceutical Applications of Heterocycles

Most of the heterocycles are fundamental to life processes (*Figure I.1.2.1*); for example, **Nelfinavir**[5a] is an antiretroviral drug used in the treatment of the human immunodeficiency virus (HIV). **Ceftobiprole** is a[5b] cephalosporin antibiotic, which is use for the treatment of skin and soft tissue infections. **LB-11058-Cephalosporin**[5c] is the most frequently prescribed class of antibiotics which is structurally and pharmacologically related to the penicillin. Like penicillin, cephalosporins have a beta-lactam ring structure that interferes with synthesis of the bacterial cell wall and so are bactericidal. **Ampicillin**[5d] is closely related to amoxicillin, another type of

penicillin, and both are used for the treatment against urinary tract infections, asthma, rash, kidney disease, a bleeding or blood clotting disorder. **Monobactam**[5e] is an antibiotic and its effects generally include diarrhea and nausea and vomiting. **Arylthioglycosides**[5f] is carbohydrate derived drug, currently used as antidiabetics, voglibose and acarbose. **Cathepsin D**[5g] is a protein, which in humans is encoded as gene. Mutations in this gene are involved in the pathogenesis of several diseases, including breast cancer and possibly alzheimer disease. **Cathepsin D** inhibitor is using for the treatment these diseases. The list and benefit of heterocyclic compound is uncountable and is beyond the scope of this thesis.

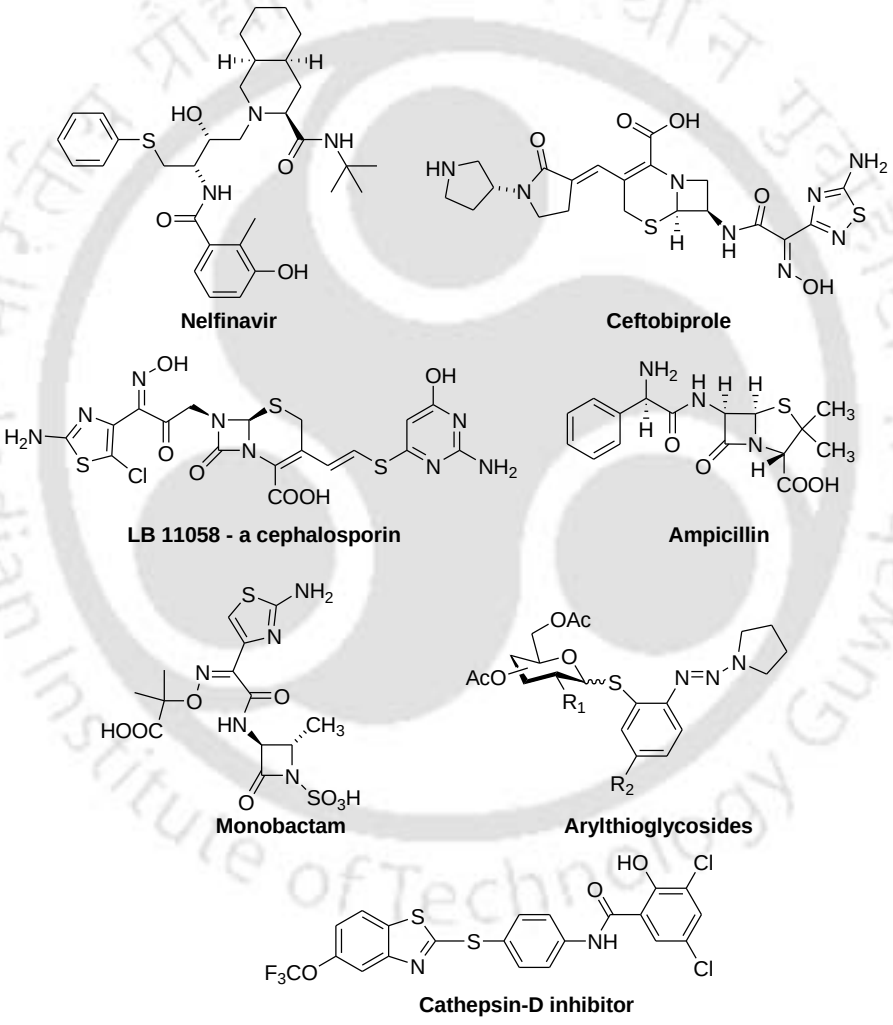


Figure I.1.2.1. *Examples of biologically active heterocycles*

I.1.3. Classification and Nomenclature

Heterocyclic compounds can be classified as mono, di- and tricyclic heterocyclic compounds *etc.* based on the number of rings present in the basic skeleton. Monocyclic heterocycles can be further sub-classified as:

(i) Heterocycloalkanes (saturated, e.g. aziridine, piperidine etc.).

(ii) Heterocycloalkenes (partially unsaturated, e.g. 2H-pyran, 4H-pyran etc.).

(iii) Heteroannulenes (systems with greatest possible number of non-cumulated double bonds, e.g. pyridine, pyrilium ion).

(iv) Heteroaromatics {systems posses (4n+2) π electrons, e.g. furan, thiophene}.

Chemists have been working with heterocycles for more than two centuries, and trivial names were often applied long before the structures of the compounds were known. As a result, many heterocycles continue to retain these names. Some common five- and six-membered heterocycles that contain one oxygen, nitrogen or sulfur atom are shown in *Figure I.1.3.1.*

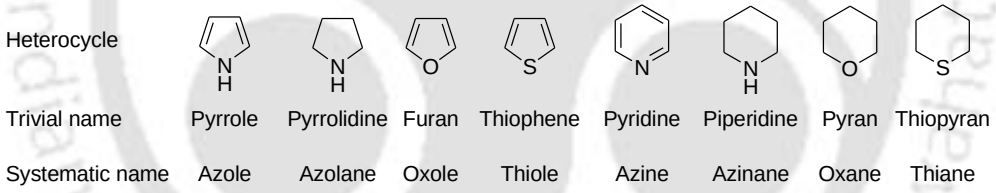


Figure I.1.3.1. *Trivial and systematic names of some common five and six membered heterocycles*

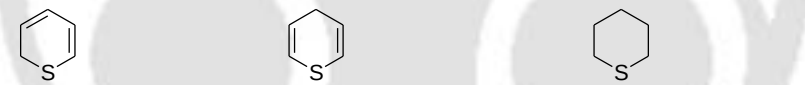
The most widely used systematic method for naming three to ten membered monocyclic heterocycles of various degree of unsaturation containing one or more heteroatoms is **Hantzsh-Widman** system.[6] This nomenclature specifies the ring size and the nature, type and position of the heteroatom and the degree of unsaturation in the ring. In this method the ring atoms are normally numbered such that the heteroatom carries the lowest number. Hetero monocyclic compounds are named by combining one or more prefixes for the heteroatoms with a stem indicating the size of the ring (*Table I.1.3.1 and 2*).

Table I.1.3.1. *Prefixes for heteroatoms (in decreasing order of priority)*

Heteroatom	**Symbol**	**Prefix**
Oxygen	O	Oxa
Sulfur	S	Thia
Nitrogen	N	Aza

Table I.1.3.2. *Stems for three to ten membered heterocycles*

Ring size	**Unsaturated**	**Saturated**
3	-irene	-irane
4	-ete	-etane
5	-ole	-olane
6	-ine	-ane
7	-epine	-epane
8	-ocine	-ocane
9	-onine	-onane
10	-ecine	-ecane



2H-Thiopyran 4H-Thiopyran 3,4,5,6-tetrahydro-2H-Thiopyran

Figure I.1.3.2. *Systematic names having sp^3 carbon atom in heterocyclic ring*

A problem arises with trivial names when a sp^3 hybridized atom is present in an unsaturated ring. A good example is thiopyran, a heterocycle that is formally the product of the addition of a single hydride ion to the thiopyrylium cation. However, as this addition could occur either at C-2 or C-4, two isomers of thiopyran are possible, which are called as 2H-thiopyran and 4H-thiopyran respectively. In these types of compounds, the position of the hydrogen/ sp^3 carbon is indicated by the number of the ring atom containing H (*Figure I.1.3.2*). This system of nomenclature works reasonably well in many related cases and is widely used in the literature.[7] It is also customary to use the prefixes di-, tetra-, hexahydro- etc instead of tri-, penta- or heptahydro- while referring to compounds that are partly (one or two double bonds) or fully reduced (three double bonds for six membered ring). It is important to note that the lowest

possible number is always selected for the locant (heteroatom); for example, the fully reduced thiopyrylium cation is referred to as 3,4,5,6-tetrahydro-2H-thiopyran (*Figure I.1.3.2*).

Many heterocycles are fused to other ring systems, notably benzene, giving in this case benzo derivatives such as benzothiazole, benzimidazole, benzoxazole etc. The basic heterocyclic nuclei investigated in this thesis along with their nomenclature are shown in *Figure I.1.3.3*.

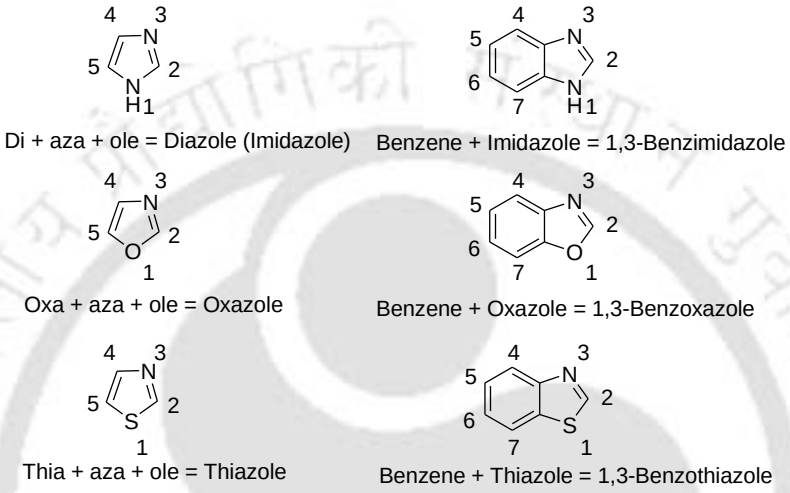


Figure I.1.1.3. *Some of the basic heterocyclic nuclei and their nomenclature*

I.1.4. General Approaches for the Construction of Aromatic Heterocycles

Generally, the following four major strategies are applied for the construction of aromatic heterocycles.

(i) Ring construction by ionic cyclizations.

(ii) Ring construction by pericyclic reactions.

(iii) Modification of existing rings by electrophilic or nucleophilic aromatic substitution or by lithiation followed by reaction with electrophiles.

(iv) Metal catalyzed cyclizations via C-heteroatom bond formation.

This thesis deals mainly with the construction of heterocycles involving transition metal catalyzed C–H activation, coupling (intra and intermolecular) and oxidative rearrangement / cyclization reactions. A brief summary of application involving these metal catalyzed reactions are discussed below.

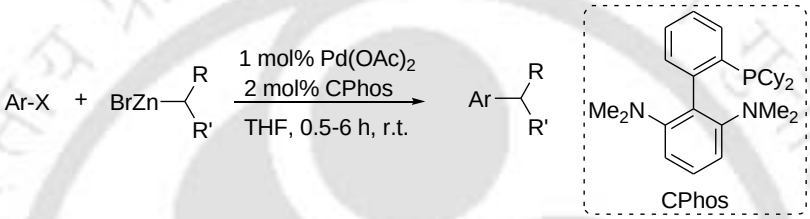
I.2. Transition Metal Catalysis and its Applications

There has been an upsurge of research in the area of catalysis by transition metal complexes since the 1940s. The demand for cheaper and more efficient processes in the industry necessitated a major explosion of research in the area of synthetic chemistry to develop new systems that can act as catalysts. This also resulted in a rapid development of newer process technologies relevant to industrial scale reactions for the production of organic compounds using transition metal complexes as catalysts. The most important thing about **catalysts** is that, they are recovered at the end of the reaction in their entirety; they are not used up during the reaction. They often undergo a temporary change during the reaction, but are turned back into the original chemical at the end of the reaction. As a result, transition metal-catalyzed couplings have become a reliable and indispensable tool for the synthesis of pharmaceuticals over the last two decades. These reactions provide new entries into pharmaceutical ingredients of continuously increasing complexity and catalysis with metals such as Pd, Ni, Cu, Zn, Co, Rh, Ru, and Mo have streamlined the syntheses of many marketed drugs or drug candidates under current development in laboratories around the world.[8,9] In the pharmaceutical industry, synthetic processes must also provide drug ingredients with very high purity. A consequence of implementing transition metal couplings is the need to purge residual metals from API (active pharmaceutical ingredient) to meet the stringent specifications for materials subjected to clinical testing.[10]

A catalyst is capable of accelerating a thermodynamically allowed reaction by lowering the energy barrier, however, it cannot favor a thermodynamically forbidden reaction. This is purely a kinetic effect. It has the essential characteristics of a cyclic process irrespective of whether the species acts as a homogeneous or a heterogeneous catalyst.

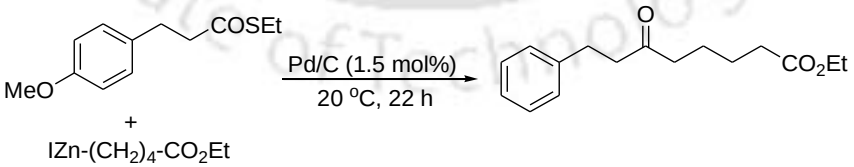
Homogeneous catalysts are those in the same physical phase as the other reactants e.g. all in solution together in the same solvent, or all are gases.[11] The reactions can be carried out at low temperatures and are accompanied by high specificities depending upon the catalyst employed. Their pioneering work is the stepping stone for the development of homogeneous catalysis. A great number of soluble metal complexes are now being employed in industry as catalysts for the

generation of a variety of useful compounds. More are being developed in order to find processes that would yield products in greater selectivity and purity and in high yields. With the advent of a variety of highly sophisticated and accurate spectroscopic techniques, the study of the mechanism of a homogenous catalytic process can be worked out much more easily; however the catalyst recovery is fraught of difficulties. A possible remedy to recovery problem is to attach a homogeneously active complex to a polymeric support and the process can be carried out. Therefore homogeneous catalysis reactions are more advantage procedures in academic as well as in industry. The work embedded in this thesis is based on the homogeneous catalysis reactions. Below is an example of homogeneous catalysis reactions (*Scheme I.2.1*).[11c]



Scheme I.2.1. *An example of homogeneous C-C cross coupling reaction*

Heterogeneous catalysts are those having different physical phase to the rest of the reactants. e.g. two different liquids in contact with the catalysis occurring at the interface between them, or more commonly a solid catalyst and a solution, or a solid and gases. The advantages and disadvantages of heterogeneous catalysis are as follows; in a heterogeneous catalytic process, the atoms or species that are catalytically active are only the surface ones, the reactions have to be carried out at relatively high temperatures and are often accompanied by low specificities. In addition, it is difficult to study the mechanistic aspects. However, the recovery of the catalyst is relatively easy in a heterogeneous process (*Scheme I.2.2.*).[12]



Scheme I.2.2. *An example of heterogeneous C-C cross coupling reaction*

I.2.1. Transition Metal Catalyzed Approaches to Heterocycles

The importance of heterocycles in many fields of science can hardly be overemphasized, and justifies a long lasting effort to work out new synthetic protocols for their production. A particularly attractive approach is based on transition-metal catalyzed heterocyclization reactions of suitably functionalized substrates, which can allow the regioselective and chemoselective synthesis of highly functionalized heterocycles starting from readily available precursors under mild and selective conditions. During the last few years, this approach to the synthesis of heterocycles has acquired a growing importance. Metal catalyzed C–H activation and cross-coupling reactions are now standard methods for the synthesis of heterocycles, but very innovative variations are still being discovered. The field is still wide-open for innovation and will continue to advance as even more versatile transformations are developed. Since this thesis mostly emphasized on palladium and copper catalyzed C–H functionalized cyclizations, intra- and inter-molecular (cascade) coupling, Ullmann reactions (IUCs) in particular for the synthesis of heterocycles, hence associated to those type reactions and mechanisms are discussed in section **I.3** and **I.4**.

I.3. Palladium Catalyzed Synthesis of Heterocycles

Transition metal catalyzed cross-coupling, intramolecular coupling, C–H activation reaction of organometallic reagents with organic halides or related electrophiles have become a powerful tool for a wide range of C–C, C–heteroatom (*N*, *O*, *S*) bond forming processes. In particular, Pd has emerged as the metal of choice for several transition metal catalyzed applications, despite its high cost relative to other non precious metals such as Cu, Ni, or Fe, due to several factors: (a) Pd can promote the couplings of low reactivity substrates (e.g., C–H activation); (b) Pd generally allows for reactions at lower temperatures; (c) Pd catalysts often provide high turnover numbers (TONs), which is of primary importance in large-scale applications where cost is the driving factor.[9a] The application of transition metal catalysis to large-scale synthesis requires technologies that are safe, robust, and scalable.[13a] Organometallic complexes derived from palladium display a variety of reactivity patterns such as transmetallation, β-hydride elimination

and reductive elimination.[13b] Various combinations of these individual steps constitute a catalytic cycle in which the organic substrate undergoes the desired transformation and the Pd catalyst is regenerated. Palladium catalyzed reactions are highly functional group tolerant. For example, hetero atoms (–NR_2, –OR, –SR), carbonyl groups and acid and basic functional groups are usually tolerated without the need for the protecting groups.[13b] In addition the commercial availability of palladium catalysts along with the development of new phosphine ligands further facilitates the use of Pd catalyzed reactions. The most popular palladium sources are $Pd(PPh_3)_4$, $Pd(dba)_2$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$ and $Pd(RCN)_2$. The most commonly used ligand is PPh_3. However, a number of new ligands which have different steric and electronic effects, have been designed and synthesized to attain high catalyst efficiency or selectivity and to expand the reaction scope (*Figure I.3.1*). Depending upon the nucleophilic partner of the palladium catalyzed coupling or C–H activation reaction C–C, C–N, C–O and C–S bond can be generated. This direct coupling of active C–H with organic halides has significant advantage in that they can be carried out without preparation of organometallic reagents in the presence of base and Pd catalyst. The strength of typical carbon–hydrogen bonds (which have bond dissociation energies between 85 and 105 kcal/mol) presents a first and very significant challenge in this area.[13c] The four major challenges associated with catalytic oxidative functionalization of C–H bonds of the complex organic molecules are (a) reactivity, (b) chemoselectivity, (c) regioselectivity, and (d) stereoselectivity.[13c] The recent developed Pd catalyzed hetero atom C–H activation reactions provides a revolutionary method to access aryl/alkenyl hetero atom (*N*, *O*, *S*) bonds, which are often difficult to form by other method.

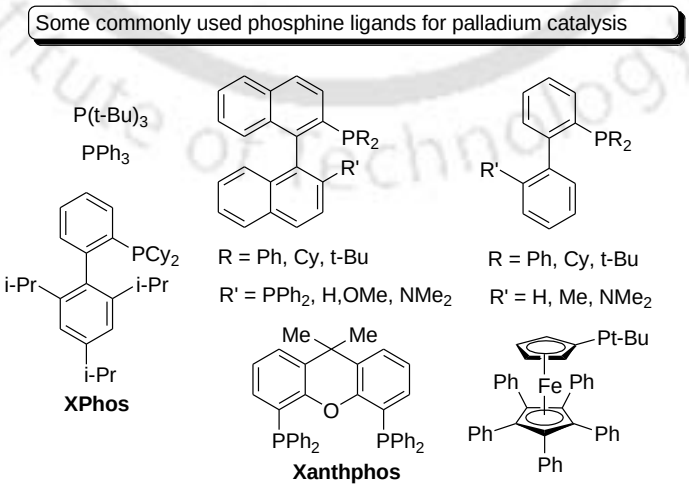


Figure I.3.1. *Typical ligands used in Pd-catalyzed hetero-arylations*

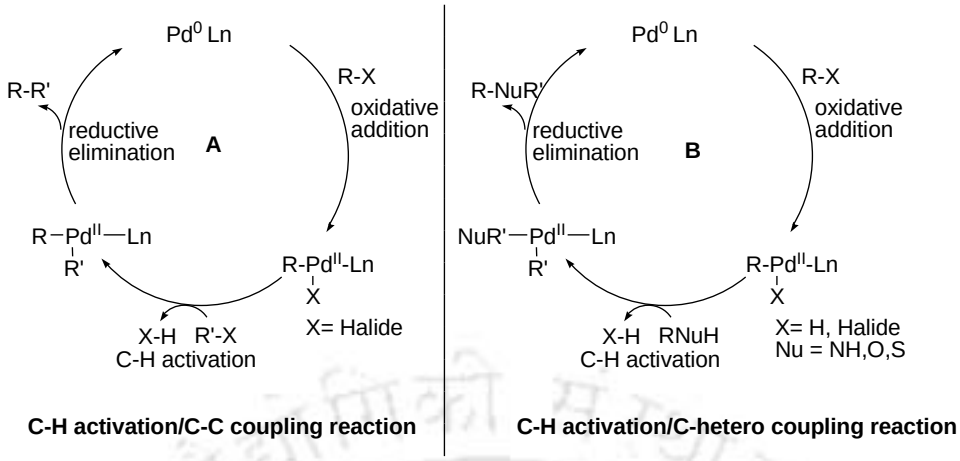
I.3.1. Mechanistic Aspects of Palladium-Catalyzed Inter- and Intramolecular Heteroarylations

It is a well accepted fact that palladium complexes exist in three oxidation states, Pd(0), Pd(II) and Pd(IV). The facile inter conversion between these oxidation states is responsible for the broad utility of palladium in organic chemistry, since each oxidation state exhibits different chemistries. To date, three plausible mechanisms for palladium coupling reactions have been described in the literature.

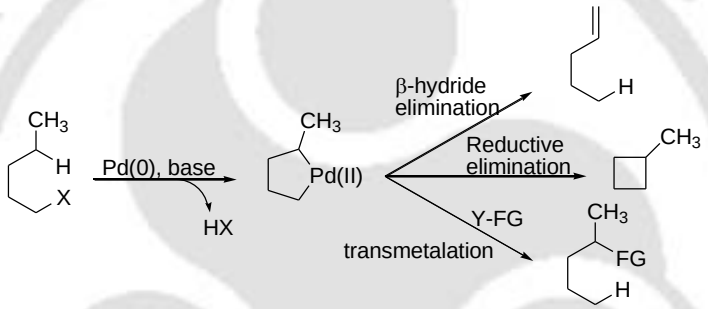
I.3.1.1. Pd(0)/Pd(II) Systems for C-H Activation/Coupling Reaction

Palladium(0) complexes are fairly nucleophilic and rather labile and are also easily oxidized, usually to the Pd(II) state. The most synthetically useful Pd(0) chemistry is based on the oxidative addition of aryl, vinylic, allylic halides or triflates to Pd(0).

Cyclization by palladium-catalyzed oxidative addition/reductive elimination is a powerful method for the construction of heterocycles. This process generally involves the addition of a covalent molecule to a Pd(0) complex, with cleavage of the covalent bond and oxidation of Pd(0) to Pd(II), to afford a σ–organopalladium(II) halide or triflate complex. The σ–bonded species, once formed, generally undergoes rapid insertion of an unsaturated species. Subsequent reductive elimination affords the desired heterocycle and Pd(0), which reenters the catalytic cycle directly, in contrast to Pd(II)-catalyzed reactions, which usually require an additional reoxidation step. The mechanistic details of these processes are shown in *Scheme I.3.1.1.1*.[14] Further, there are many possible ways for the formation of transition state/intermediate step during the course of reactions (*Scheme 1.3.1.1.2*).[14]



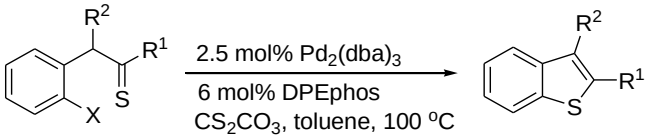
Scheme I.3.1.1.1. *Possible reaction mechanism of palladium(0) catalysis*



Scheme I.3.1.1.2. *Reaction pathways of palladium catalysis*

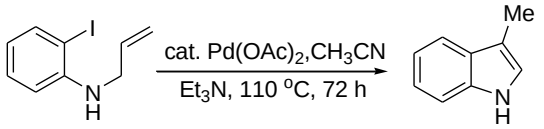
I.3.1.2. Representative Examples of Pd(0)–Catalyzed Intramolecular Hetero-arylations

Substituted benzothiophenes were prepared through the use of the intramolecular thio-enolate *S*-arylation reaction[15a] (*Scheme I.3.1.2.1*) using DPE-phos ligand. The enolates derived from *o*-haloaryl substituted thio-ketones underwent a cascade sequence under Pd-catalyzed conditions, and the products were formed in moderate to good yields.



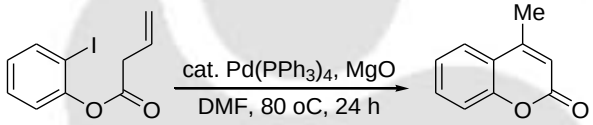
Scheme I.3.1.2.1. *Synthesis of benzothiophenes by intramolecular S-arylation reaction*

Hegedus and co-workers have reported the preparation of indoles using intramolecular Heck cyclization (*Scheme I.3.1.2.2*).[17b] Thus, the reaction of 2-iodoaniline with catalytic $Pd(OAc)_2$, Et_3N, and MeCN at 110 ^oC affords indole in good yields.



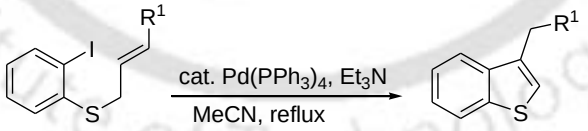
Scheme I.3.1.2.2. *Synthesis of indole using intra molecular Heck cyclization*

Catellani and co-workers have prepared 4-methylcoumarin in a quantitative yield from *o*-iodophenyl 3-butenoate (*Scheme I.3.1.2.3*).[17c] Isomerization of the carbon-carbon double bond in *o*-iodophenyl 3-butenoate to the internal position of 4-methylcoumarin was controlled by the appropriate choice of ligand, solvent, and base.



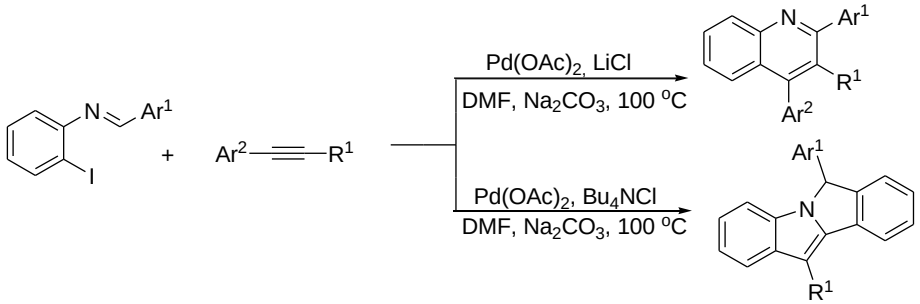
Scheme I.3.1.2.3. *Synthesis of coumarin using intra molecular Heck cyclization*

Aryl sulfide derived compounds are readily prepared from benzothiophene by an intramolecular Heck cyclization Thus, benzothiophene have been synthesized by the reaction of aryl halides bearing a neighboring olefin (*Scheme I.3.1.2.4*).[15d] The reaction of aryl iodide with a catalytic amount of $Pd(PPh_3)_4$ in the presence of Et_3N under reflux condition afforded the target product in a good yield.



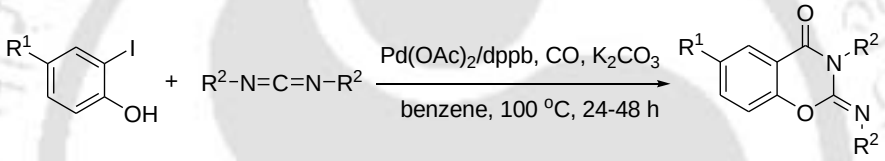
Scheme I.3.1.2.4. *Synthesis of benzothiophene using intra molecular Heck cyclization*

Larock *et. al.* have discovered that imines derived from *o*-iodoaniline and benzaldehyde react with internal aryl alkynes under the appropriate reaction conditions, to give either isoquinoline or more commonly the tetracyclic indoles depending upon the substituents present in alkynes (*Scheme I.3.1.2.5*).[17e,f] A variety of internal alkynes have been employed in this annulation process, in which the aromatic ring of the alkyne contains either a phenyl or a heterocyclic ring.



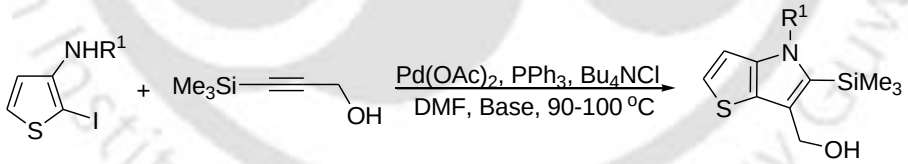
Scheme I.3.1.2.5. *Synthesis of chemoselective isoquinoline and indoles*

Alper and co-workers have shown that the *o*-iodophenols on reaction with carbodiimides in the presence of $Pd(OAc)_2$/dppb catalyst in benzene afforded benzo[*e*]-1,3-oxazinone derivatives in excellent yields (*Scheme I.3.1.2.6*).[17g,h] Both electron-donating and electron-withdrawing groups on the aromatic ring of the *o*-iodophenols afforded good yields.



Scheme I.3.1.2.6. *Synthesis of benzo-oxazinone hetrocycles*

Wensbo *et. al.* have prepared various heteroatom-substituted analogues, thienopyrroles using Pd(II) catalyst in presence of triphenylphosphine ligand. (*Scheme I.3.1.2.7*)[17i]



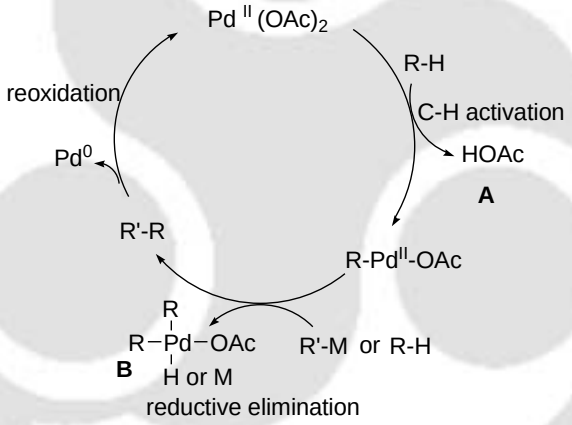
Scheme I.3.1.2.7. *Synthesis of thienopyrroles hetrocycles*

I.3.2.1. Pd(II)/Pd(0) Systems for C-H Activation Reaction

Complexes of Pd(II) are extremely important in organopalladium chemistry. They are typically electrophilic, soluble in most common organic solvents, and stable to air. Thus, they are easily stored and handled. The most common organic substrates for Pd(II) are electron-rich species, such as olefins, alkynes, and arenes. Some of the most useful Pd(II) chemistry is based on the fast and reversible formation of Pd(II) complexes with olefins and alkynes, which undergo

subsequent attack by nucleophiles. The most useful Pd(II) complexes are $PdCl_2(PPh_3)_2$,[16] $Pd(OAc)_2$,[17] and $PdCl_2(RCN)_2$.[18] Pd(II) complexes are often added to reactions as pre catalysts, since they are readily reduced by various species to Pd(0), which then catalyzes the desired process.

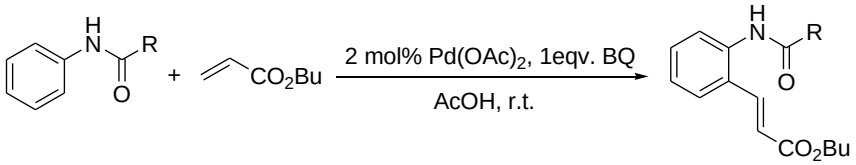
Being electrophilic species, Pd(II) salts tend to react with σ-nucleophiles such as olefins, alkynes, and arenes. For aromatic substrates, a different mechanism has been proposed that involves the electrophilic substitution of an aryl hydrogen by palladium to give **A**, and the subsequent formation of a σ-bonded aryl-Pd(II) complex **B** (*Scheme I.3.1.2.1*). This palladation intermediate can undergo a homo/hetero coupling reaction. Also in this case, elimination of Pd(0) is the final step. In general, palladium oxidation chemistry is dominated by ligand-free reaction conditions. In contrast, the use of O_2 generally requires a ligand for efficient catalysis, which introduces the possibility of making the reactions chemo- or stereoselective.



Scheme I.3.2.1.1. *Possible reaction mechanism of Pd(II)/Pd(0) catalysis*

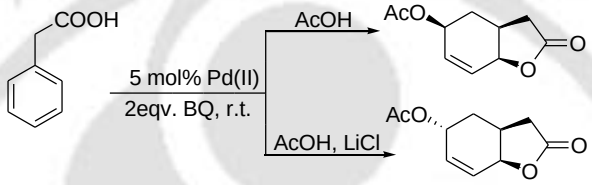
I.3.2.2. Representative Examples of Pd(II)/Pd(0) Catalyzed Intramolecular Heteroarylations

The benzene nucleus of anilides was particularly reactive toward electron-poor alkenes. In its coupling with butyl acrylate in the presence of $Pd(OAc)_2$ and BQ in AcOH at room temperature, alkenylation took place in the *ortho* position (*Scheme I.3.2.2.1*).[19a] No other isomer was formed because of the strong *ortho*-directing effect of the amide group. Simple anilines and *N*-methylacetanilides were not reactive under the tested conditions.



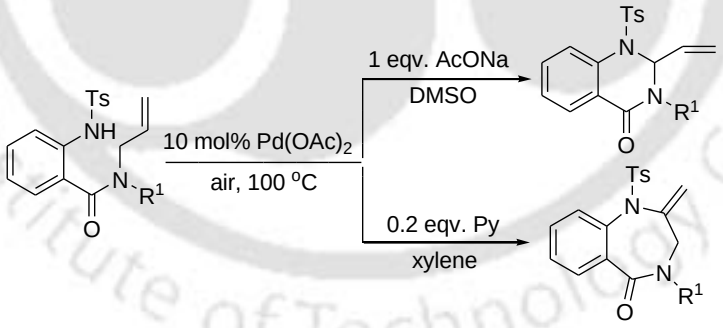
Scheme I.3.2.2.1. *Ortho functionalization of anilides*

Backvall and co-workers demonstrated an intramolecular cyclization of cyclohexa-dienylacetic acid to the corresponding acetoxylated *cis and trans*-fused γ-lactone (*Scheme I.3.2.2.2*).[19b] This reaction, which is highly regio- and stereoselective, takes place by successive intramolecular and intermolecular nucleophilic attacks.



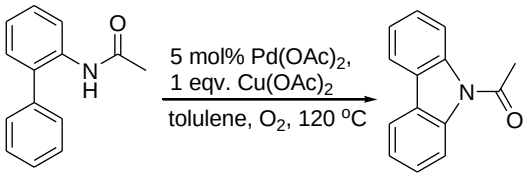
Scheme I.3.2.2.2. *Regio and stereoselective intra- and intermolecular C-H activation*

A divergent synthesis of quinazolin-4-ones and 1,4-benzodiazepin-5-ones by Pd(II)-catalyzed intramolecular amidation of tosylated *N*-allylanthranilamides was described (*Scheme I.3.2.2.3*).[19c]



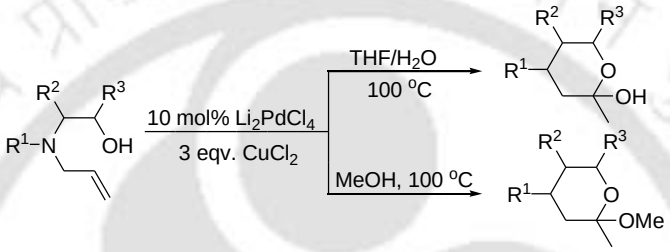
Scheme I.3.2.2.3. *Chemo selective synthesis of quinazolinones and benzodiazepinones*

Carbazoles were obtained from *o*-arylacetanilides by combined C–H functionalization and C–N bond formation (*Scheme I.3.2.2.4*).[19d] A plausible reaction pathway shows the formation of a six-membered palladacycle from which reductive elimination leads to product and Pd(0). The latter was reoxidized to Pd(II) by $Cu(OAc)_2$, and the reduced Cu species was in turn reoxidized to Cu(II) by oxygen.



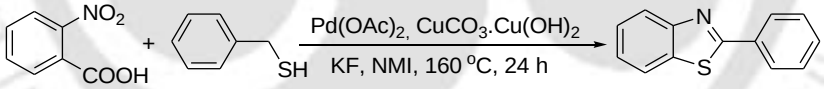
Scheme I.3.2.2.4. *Carbazoles obtained from o-arylacetanilides*

Dai *et. al.* demonstrated the synthesis of morpholine-type acetals,[19e] which were obtained in high yields from enantiopure *N*-allyl aminoalcohols by making slight changes in the $Li_2PdCl_4/CuCl_2$ reagent system, as depicted in *Scheme I.3.2.2.5*.



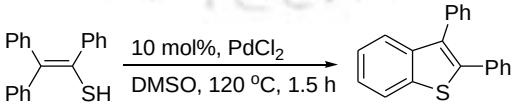
Scheme I.3.2.2.5. *Morpholine-type acetals from enantiopure N-allyl aminoalcohols*

In the case of *o*-nitrobenzoic acid, a catalytic decarboxylative coupling reaction was carried out in presence of Pd/Cu system accompanied by reduction of the $–NO_2$ group. The transformation of benzyl thiol led to the formation of benzothiazoles (*Scheme I.3.2.2.6*).[19f]



Scheme I.3.2.2.6. *Synthesis of benzothiazole by intramolecular S-arylation reaction*

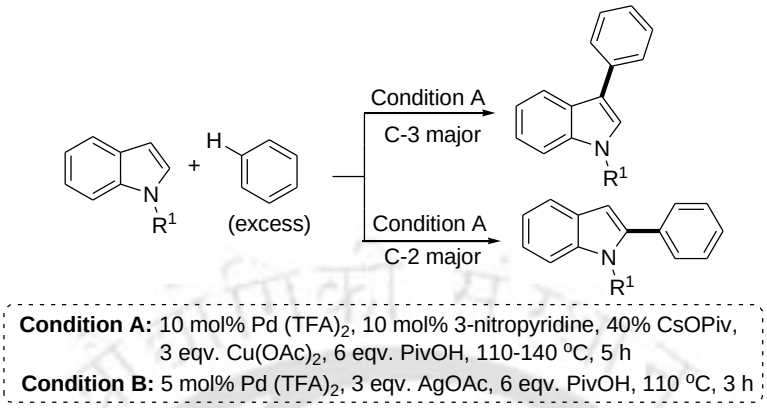
Inamoto *et al.* have discovered the one-pot conversion of thioenols into benzothiophenes by using a simple palladium catalyst such as $PdCl_2$ (*Scheme I.3.2.2.7*).[19g]



Scheme I.3.2.2.7. *Synthesis of benzothiophenes C–H activation reaction*

Fagnou *et al.* demonstrated that arylation at the C2 position of indole could be efficiently achieved with excellent selectivity (C2/C3, 25:1) when *N*-pivalyl indoles were employed as the

substrate and and benzenes as the aryl source and as a solvent in the presence of $Pd(TFA)_2$ as the catalyst, AgOAc (3 equiv.), and PivOH (6 equiv.) at 110 ^oC (*Scheme I.3.2.2.8*).[19h]

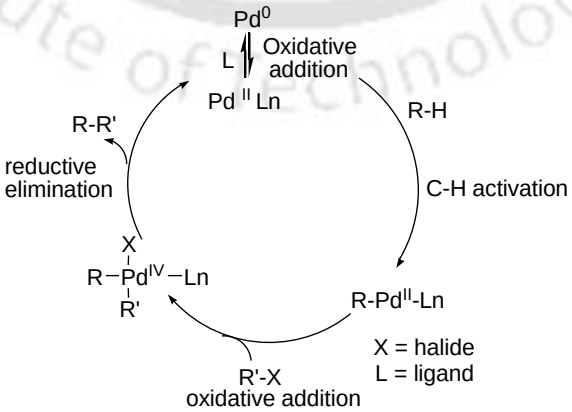


Scheme I.3.2.2.8. *Chemoselective C2 vs C3 arylation reaction*

I.3.3.1. Pd(II)/Pd(IV) Systems for C–H Activation Reaction

Pd(IV) complexes are quite rare, although a few complexes are known.[20] These complexes have been little explored, but transient Pd(IV) species have been increasingly implicated as intermediates in palladium catalyzed reactions. They appear to play little role in palladium catalyzed oxidative addition chemistry directed toward heterocyclic synthesis.

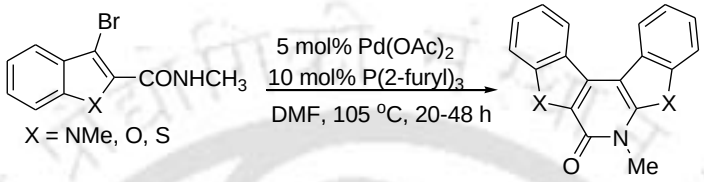
The key process of many palladium-catalyzed reactions, the oxidative addition of $C(sp^2)$-X bonds to Pd^0, is very well established, related reactions of Pd^{II} substrates with $C(sp^2)$-X bonds to form Pd^{IV} are much less documented. The complex mechanism mostly involves Pd^0, Pd^{II}, and Pd^{IV} species in a series[21] and some reactions involve Pd^{II}-Pd^{IV} catalytic cycles.[21d]



Scheme I.3.3.1.1. *Possible reaction mechanism of Pd(II)/Pd(IV) catalysis*

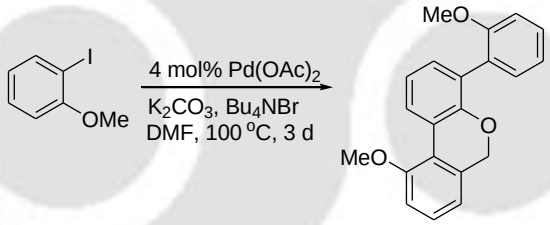
I.3.3.2. Representative Examples of Pd(II)/Pd(IV) Catalyzed Intramolecular Heteroarylations

Catellani and coworkers reported novel symmetrically condensed pyridones using $Pd(OAc)_2/P(2\text{-furyl})_3$ catalytic system, from *o*-bromoaromatic carboxamide (*Scheme I.3.3.2.1*).[22a]



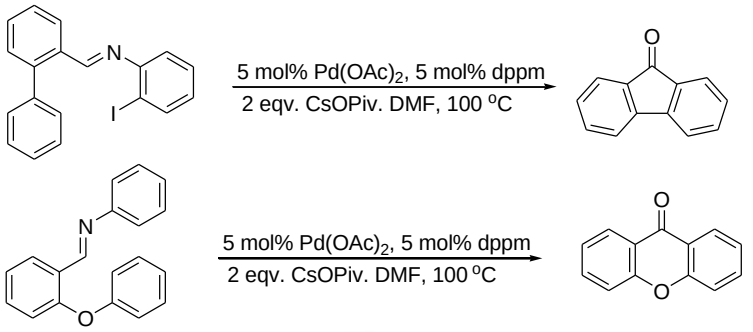
Scheme I.3.3.2.1. *Synthesis of pyridones from aromatic carboxamides*

Dyker *et. al.* have reported a novel type of palladium-catalyzed domino coupling reaction, where C–H activation at an aryl methoxy group occurs.[22b] The *o*-methoxy substituted iodobenzenes condense under palladium catalysis to give substituted dibenzopyrans (*Scheme I.3.3.2.2*).



Scheme I.3.3.2.2. *Synthesis of dibenzopyrans from o-methoxy substituted iodobenzenes*

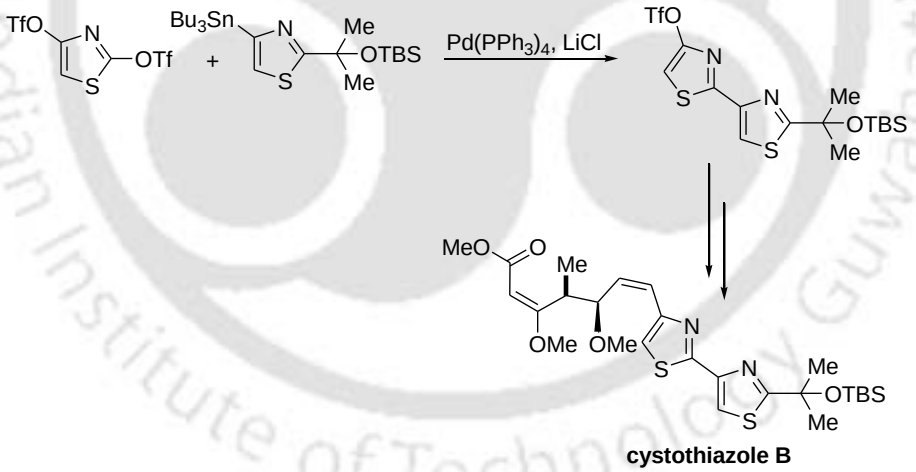
Larock group have demonstrated an aryl-imidoyl 1,4-Palladium migration followed by cyclization, a very efficient methodology for the synthesis of fluoren-9-ones and xanthones (*Scheme I.3.3.2.3*).[22c]



Scheme I.3.3.2.3. *Synthesis of fluoren-9-ones and xanthones from imines*

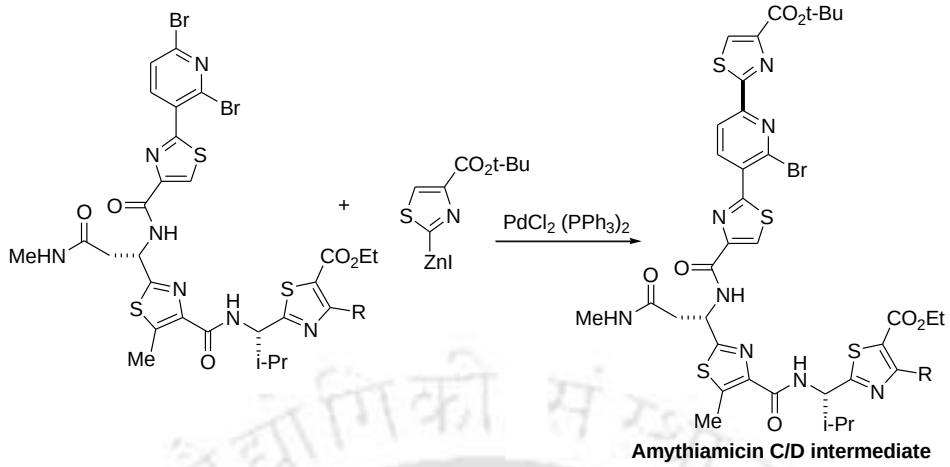
I.3.2. Application of Palladium Catalysis in Total Synthesis of Natural Products and Macrocycles

A regioselective Stille cross-coupling reaction was used in the total synthesis of the antifungal agent cystothiazole B[23a] The 4-tributylstannylthiazole was coupled with ditriflate which proceeds regioselectively to give bis-(thiazole) triflate. This triflate is converted into cystothiazole B in a few steps.



Scheme I.3.2.1. *Synthesis of cystothiazole B intermediate using Stille coupling*

Dibromopyridines derivative compound undergo regioselective Negishi cross-coupling reactions with the 2-zincated *tert*-butyl thiazole-5-carboxylate to give pyridyl tri(thiazoles), which serve as advanced intermediates to amythiamicin C/D[23b] respectively. The amythiamicins are members of the thiopeptide family of antibiotics, a class of sulfur-containing highly modified cyclic peptides.



Scheme I.3.2.2. *Synthesis of amythiamicin C/D intermediate using Negishi coupling*

I.4. Copper Catalyzed Synthesis of Heterocycles

Copper is another noteworthy metal that has been used for over a century in cross coupling reaction. The traditional copper mediated coupling reactions such as Ullman and Goldberg type reactions suffer several drawbacks[24]. The use of stoichiometric amount of copper reagents and harsh reaction conditions are the major limitations. Oflate, copper catalyzed heteroatom coupling reactions have received a significant amount of attention as an excellent complements to those transformation catalyzed by palladium due to the low cost of copper and functional group compatibility displayed in those reactions. The formation of aryl C–X bonds (X = *O*, *S*, *N* etc.) via copper-catalyzed coupling between aryl halides and hetero centered nucleophiles and by C–H activation strategy have drawn a great deal of attention in the past few years.[25-27] Many research groups have been actively involved in the development of more efficient copper/ligand combinations to widen the scope of such reactions in terms of substrate tolerance, copper loading, milder reaction conditions, enhanced chemoselectivity, and enantioselectivity.[27] The progress has been so spectacular that, in numerous cases, the use of copper systems is now a serious rival for the alternative palladium-catalyzed procedures. More recently, this methodology was successfully extended to the synthesis of various bioactive heterocycles and natural products.[28a]

I.4.1. Ligand Advantages in Cu-Catalyzed Intra-/Intermolecular Hetero-arylations

Several ligands are known to promote the copper-assisted coupling reactions. Possible explanations for the ligands effect in Cu-catalysis include (a) prevents the aggregation of intermediate complexes, (b) improve the solubility of *in-situ* formed complexes, (c) inhibition of catalyst decomposition and (d) prevents multiple ligation with substrates (nucleophiles), a process which might lead to the formation of inactive copper-complexes.

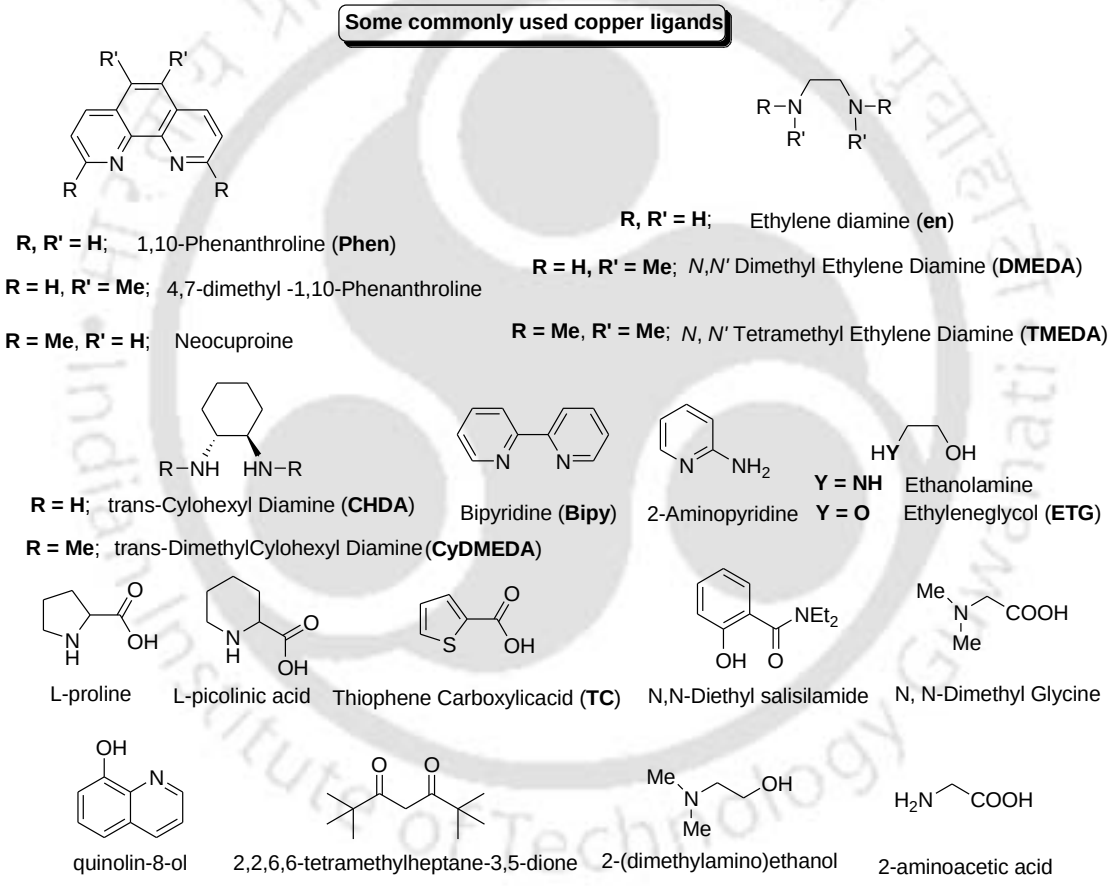
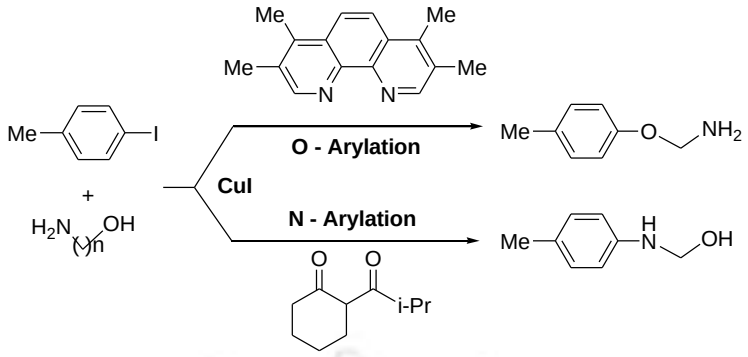


Figure I.4.1.1. *Typical ligands used in Cu-catalyzed hetero-arylations*

Below is an example which describes the tuning of reactivity of a metal catalyst by changing the ligand system. A selective *N*- or *O*-arylation can be achieved using 1,3-diketone or phenanthroline based ligands (*Scheme I.4.1.1*).[28b]



Scheme I.4.1.1. *Ligand assisted selective N- and O- arylations*

I.4.2. Mechanistic Aspects of Copper-Catalyzed Heteroarylations

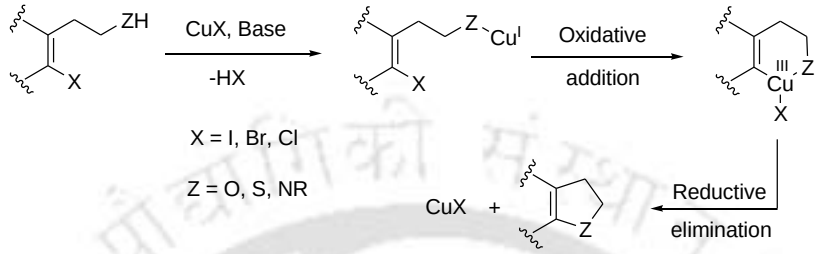
It is a well accepted fact that a reaction mechanism can never be proved, at the best, evidences can be given in the favor of or against it. The most important aspect of copper is its accessibility of four oxidation states from 0 to +3. Most likely the catalytic cycle of cross couplings with copper involves +1/+3 oxidation states. Copper catalyzed heteroarylations generally proceed via the C-hetero atom coupling by a C–H activation strategy.

I.4.2.1. Copper–Catalyzed Heteroarylations via Intramolecular Coupling Strategy

To date, three plausible mechanisms for Ullmann-type coupling reactions have been described in the literature.[29a-c] (a) Oxidative addition/reductive elimination mechanism proposed by Cohen in 1974.[29d] (b) π-complex mechanism proposed by Paine in 1987.[29e] (c) Radical or radical anion pathway.[29f,g]

However, oxidative addition/reductive elimination mechanism is most plausible for copper catalysis which is proposed by Cohen. The mechanism for the inter/intramolecular Cu^{I}-catalyzed C-heteroatom bond formation of aryl and vinyl halides with heteroatoms (*N*, *O*, *S*) is believed to proceed as shown in *Scheme I.4.2.1*. The heteroatom functional group co-ordinates with the Cu^{I}- which provides a new Cu^{I} intermediate which may then undergo oxidative addition into the aryl halide bond, thereby generating a Cu^{III} intermediate. Subsequent reductive elimination provides

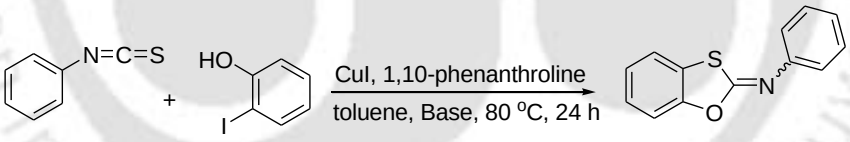
the target product and regenerates the Cu^{I} catalyst. However, various studies have shown that copper sources of different oxidation states (Cu^{0}-bronze, Cu^{I}, or Cu^{II}) are catalytically active, presumably a result of their conversion into the same active species during the course of reaction. It also seems likely that a Cu^{I}-Cu^{III} redox couple is involved in most of the reactions.[29d]



Scheme I.4.2.1. *Plausible mechanism for copper catalyzed C-hetero coupling reaction*

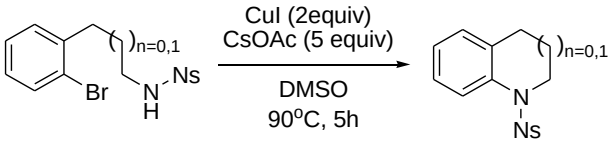
I.4.2.2. Representative Examples of Copper-Catalyzed Heteroarylations via Intramoleular Coupling Strategy

A novel and efficient formation of 2-iminobenzo-1,3-oxathioles from aryl isothiocyanates and 2-iodo phenol precursors via a Cu(I)-catalyzed one-pot cascade process has been reported by Bao *et al.* (*Scheme I.4.2.2.1*).[30a]



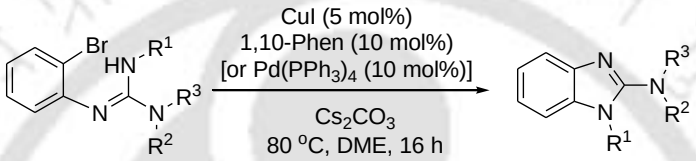
Scheme I.4.2.2.1. *Synthesis of 2-iminobenzo-1,3-oxathioles form isothiocyanates*

An intramolecular amination of aryl halides was found to be mediated by the combination of copper iodide and cesium acetate. The reaction works well at room temperature with primary or *N*-benzyl amines and at high temperature with other amines. The reaction has been applied to the formation of 5-, 6-, and 7-membered rings. In this experimental condition halogens at the *meta*-positions are unaffected providing an advantage over palladium-catalyzed systems (*Scheme I.4.2.2.2*).[30b]



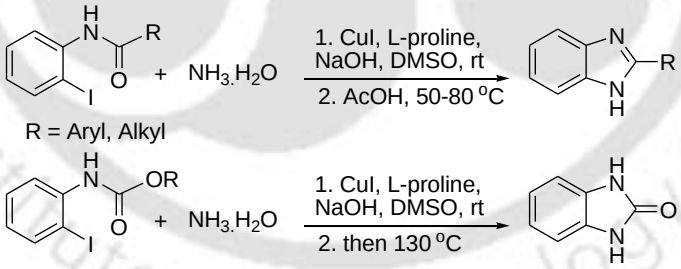
Scheme I.4.2.2.2. *Benzoquinolines using intramolecular amination*

Batey *et al.* have described an approach for the formation of 2-aminobenzimidazoles via an intramolecular C–N bond formation between an aryl halide and a guanidine moiety using either copper or palladium catalysis. Remarkably, inexpensive copper salt (CuI) is superior to the use of palladium catalysts for this transformation (*Scheme I.4.2.2.3*).[30c]



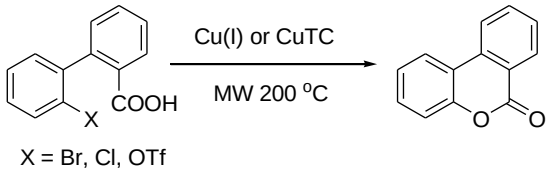
Scheme I.4.2.2.3. *Synthesis of 2-aminobenzimidazoles by intramolecular C-N coupling*

Ma *et al.* have reported CuI/L-proline-catalyzed intramolecular *N*-arylation of *o*-haloacetanilides and 2-halophenylcarbmamates in the presence of aqueous ammonia leading to the formation of benzimidazole and benzimidazolone derivative compounds. (*Scheme I.4.2.2.4*) [30d]



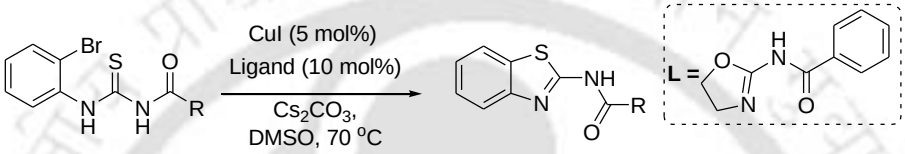
Scheme I.4.2.2.4. *Synthesis of benzimidazole and benzimidazolones*

A simple C–O carboxylic coupling reaction catalyzed by Cu(I) salts has been developed to synthesize benzopyranones by Ruchiravat *et al*. Various benzopyranones were synthesized using microwave irradiation. Furthermore, a new class of pyrroloisoquinoline alkaloid, isolamellarin, was also synthesized using this methodology (*Scheme I.4.2.2.5*).[30e]



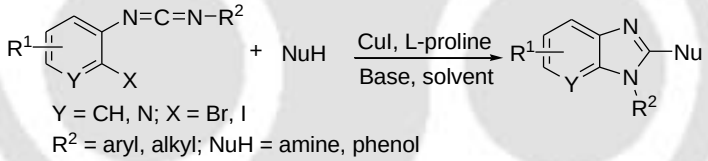
Scheme I.4.2.2.5. *Synthesis of benzopyranones using microwave irradiation process*

Pan and coworkers have reported a copper-catalyzed intramolecular cyclization of various substituted 1-acyl-3-(2-bromophenyl) thioureas to yield *N*-benzothiazol-2-yl-amides using *N*-(4,5-dihydrooxazol-2-yl) benzamide as the ligand (*Scheme I.4.2.2.6*).[30f]



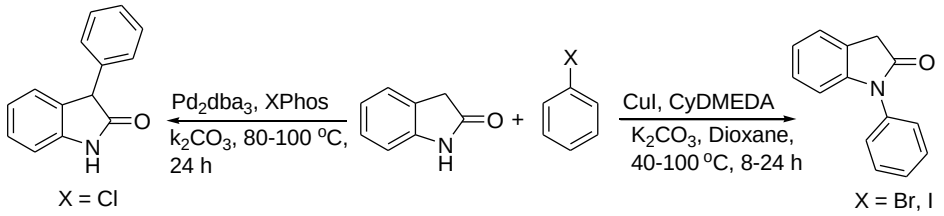
Scheme I.4.2.2.6. *Benzothiazole derivatives by intramolecular C-S coupling*

A novel and efficient one-pot 2-heterobenzimidazoles are synthesized from o-haloarylcarbodiimides and *N*- or *O*-nucleophiles through a Cu(I)-catalyzed cascade intermolecular addition/intramolecular C–N coupling process. (*Scheme I.4.2.2.7*).[30g]



Scheme I.4.2.2.7. *Synthesis of 2-heterobenzimidazoles from carbodiimides*

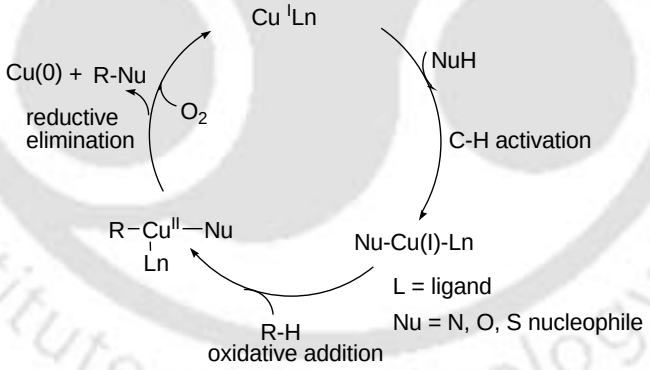
Buchwald *et al.* reported an orthogonal chemoselectively cross-coupling reaction of unprotected oxindoles with aryl halides, using Pd- and Cu-based catalytic systems. A Pd dialkylbiaryl-phosphine-based catalyst system arylated oxindole at the 3 position, while arylation occurred exclusively at the nitrogen using a Cu-diamine-based catalyst system (*Scheme I.4.2.2.8*).[30h]



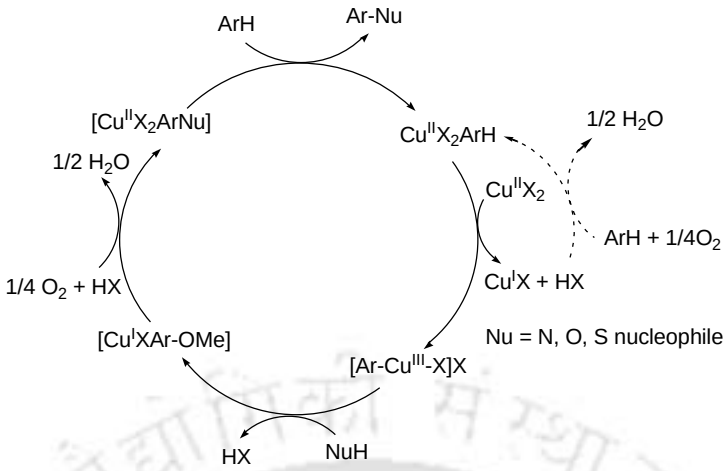
Scheme I.4.2.2.8. *Pd vs Cu catalyzed chemoselective coupling reaction*

I.4.3.1. Copper Catalyzed Heteroarylations via C–H Activation Strategy

Copper is a versatile oxidant, capable of promoting a wide range of oxidative coupling reactions initiated by single-electron transfer (SET) from electron-rich organic molecules. In some of these cases, evidence has been obtained for the involvement of organocopper(III) or copper(0) intermediates in the reaction mechanism. Organometallic C–H oxidation reactions of this type represent important new opportunities in the field of Cu-catalyzed aerobic oxidations. Now-a-days copper catalyzed C–H activation is a most challenging field in organic synthesis. However, mechanism of these reactions is not clear. Some possible reaction mechanism pathway of copper catalyzed reactions are shown below (*Scheme I.4.3.1.1 and I.4.3.1.2*).[31]



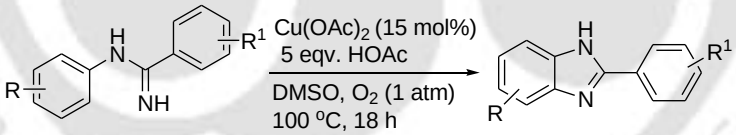
Scheme. I.4.3.1.1. *Plausible mechanism for Cu(I) catalyzed C-H activation*



Scheme. I.4.3.1.2. *Plausible mechanism for Cu(II) catalyzed C-H activation*

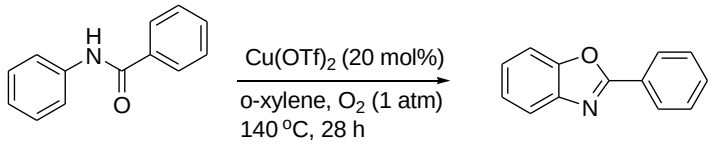
I.4.3.2. Representative Examples of Copper-Catalyzed Heteroarylations via C–H Activation Strategy

Buchwald and co-workers described the aerobic oxidative cyclization of amidines to give benzimidazoles using 15 mol% $Cu(OAc)_2$ and 5 equiv AcOH at 100 ^oC in DMSO under a dioxygen atmosphere (*Scheme I.4.3.2.1*).[32a] Cyclization was tolerant of both electron-donating and electron-withdrawing substituents.



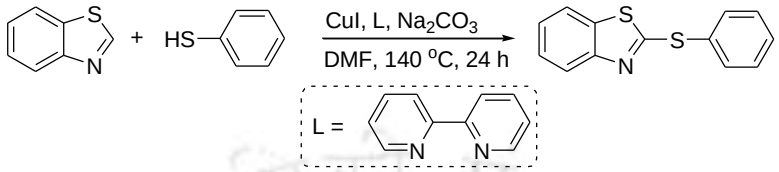
Scheme I.4.3.2.1. *Synthesis of benzimidazoles using Cu(II) catalyst*

The Nagasawa group have reported a similar protocol for the preparation of benzoxazoles.[32b] Various benzanilides underwent cyclization to their desired benzoxazole products in high yields using 20 mol% $Cu(OTf)_2$ at 140 ^oC in *o*-xylene under an oxygen atmosphere (*Scheme I.4.3.2.2*).



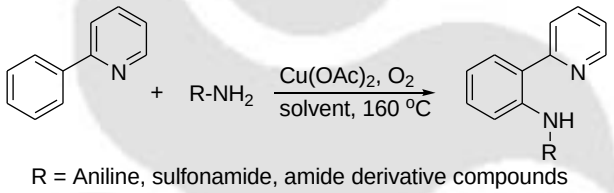
Scheme I.4.3.2.2. *Synthesis of benzoxazoles using Cu(II) catalyst*

Liu *et al.* reported the synthesis of a series of aryl- or alkylsubstituted 2-mercaptobenzothiazoles by the direct thiolation of benzothiazoles with aryl or alkyl thiols via copper-mediated aerobic C−H bond activation in the presence of stoichiometric CuI, 2,2′-bipyridine and Na_2CO_3. (*Scheme I.4.3.2.3*).[32c]



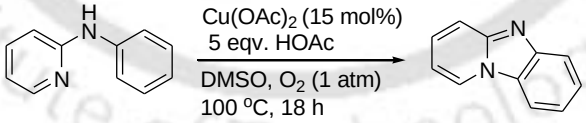
Scheme I.4.3.2.3. *Synthesis of benzothiazole using Cu(II) catalyst*

Nicholas group has reported the $Cu(OAc)_2$-catalyzed, O_2-mediated amidation of 2-phenylpyridine via C–H bond activation. A variety of nitrogen reagents including sulfonamides, carboxamides, and anilines participate in the reaction (*Scheme I.4.3.2.4*).[32d]



Scheme I.4.3.2.4. *Amidation of 2-phenylpyridine via C-H bond activation*

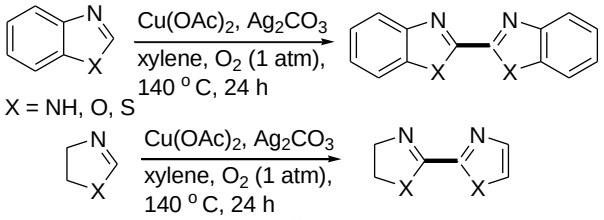
Zhu and co-workers demonstrated the oxidative annulations of *N*-aryl-2-aminopyridines using 20 mol% $Cu(OAc)_2$, with 10 mol% $Fe(NO_3)_3.9H_2O$, and 5 equivalent PivOH in DMF under O_2 at 130 °C (*Scheme I.4.3.2.5*).[32e]



Scheme I.4.3.2.5. *Synthesis of benzimidazoles derivatives via C-H bond activation*

Recently, Mori and co-workers demonstrated that oxidative homo dimerization of azoles can be achieved at the 2-position in the presence of $Cu(OAc)_2$ catalyst and Ag_2CO_3 additive under oxygen atmosphere. It was proposed that the reaction proceeds via reductive coupling of a Cu(II)–bisazole intermediate and that silver salt plays a dual role as a base to neutralize

generated acids and as the oxidant to regenerate Cu(II) species from Cu(0) with the aid of molecular oxygen (*Scheme I.4.3.2.6*).[32f,g]



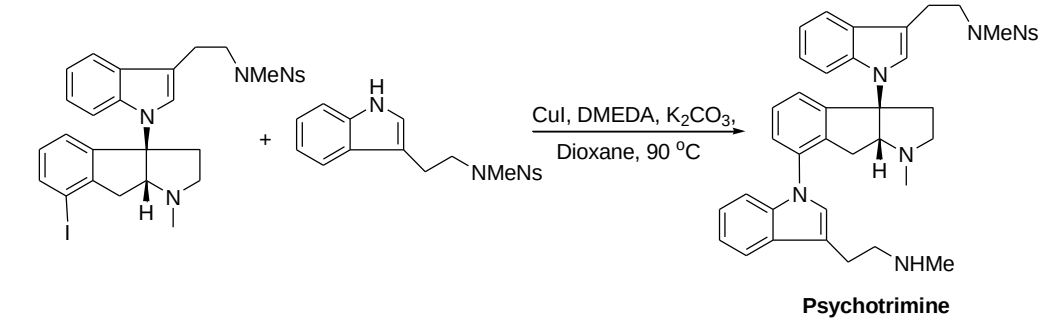
Scheme I.4.3.2.6. *Homo dimerization of azoles using Cu(II) catalyst*

I.4.3. Application of Copper Catalysis in Total Synthesis of Natural Products and Macrocycles

The dutasteride molecule has been synthesized by using catalytic amount of copper powder in the presence of *o*-xylene at a temperature of 140-150 ^{o}C. Dutasteride, a selective reductase inhibitor currently available as a drug for the treatment of various prostate diseases. It also used as anti cancer drug (*Scheme I.4.3.1*).[33a]

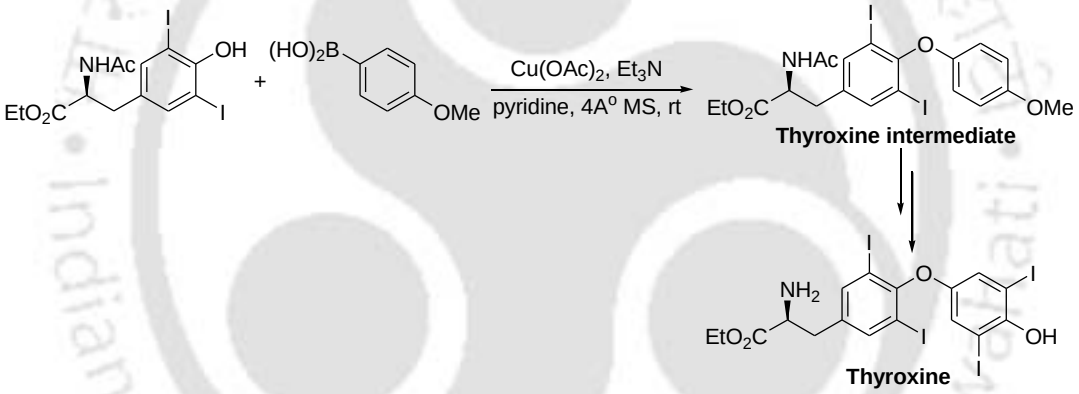
Scheme I.4.3.1. *Synthesis of dusteride using copper catalysis C-N cross coupling*

A ligand DMEDA assisted Cu(I) catalyzed C–N cross coupling method has been developed for the synthesis of psychotrimine in good yield (*Scheme I.4.3.2*). Psychotrimine is used as an antibacterial and antibiotic agent. This also shows activity against lung cancer.[33b]



Scheme I.4.3.2. *Psychotrimine synthesis using copper catalyzed C-N cross coupling*

Evans and co-workers have synthesized the thyroxine intermediate by using copper(II) acetate with pyridine and triethylamine at room temperature in dichloromethane. Thyroxine is used for nerve pain; diabetic patient is likely to be a requirement for increased dosage of insulin or oral anti-diabetic therapy (*Scheme I.4.3.3*).[33c]



Scheme I.4.3.3. *Synthesis of thyroxine intermediate using copper catalyzed C-O cross coupling*

I.5. References

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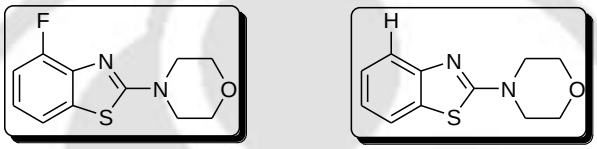
CHAPTER II

II. Regioselective Intramolecular Arylthiolations by Ligand Free Cu and Pd Catalyzed Reaction

II.1. Structure and Nomenclature

Details of nomenclature of heterocycles were discussed in CHAPTER I. This chapter deals with the regioselective synthesis of 2-aminobenzothiazoles using both Pd(II) and Cu(I) catalysts.



Via C–H activation (Pd catalysis) **Via dehalogenation (Cu catalysis)**

Synthesis of 2-aminobenzothiazoles from *in-situ* generated 2-fluoroaryl-sec-alkyl thiourea derived from 2-F phenylisothiocyanate and morpholine

II.2. Importance and Applications

Benzothiazoles are broadly found in bioorganic and medicinal chemistry with applications in drug discovery and for the treatment of diabetes,[1] epilepsy,[2] inflammation,[3a] amyotrophic lateral sclerosis,[3b] analgesia,[3c] tuberculosis,[3d] and viral infections.[3e] In particular, a variety of pharmacophores bearing 2-aminobenzothiazole have revealed broad spectrum of biological activities that encompass antimicrobial, anti-tumour, neuroprotective, anti-convulsant and anti-epileptic activities.[4] Some representative examples of biologically important aminobenzothiazoles (**I**–**VII**) are shown in *Figure II.2.1*. The bioactive molecules possessing the 2-aminobenzothiazole core include Riluzole (**I**) a glutamate neurotransmitor,[5a] R116010 (**II**) a potent inhibitor of retinoic acid metabolism,[4d] antibacterial compound (**III**).[5b] Some other pharmacophores possessing the 2-aminobenzothiazole as the core unit include the *N*-Myristoyltransferase (Nmr) inhibitor (**IV**),[5c-d] the PPAR agonist (**V**),[5e] the H3-receptor ligand (**VI**),[5f] the nicotinic-acetylcholine-receptor ligand (**VII**).[5g]

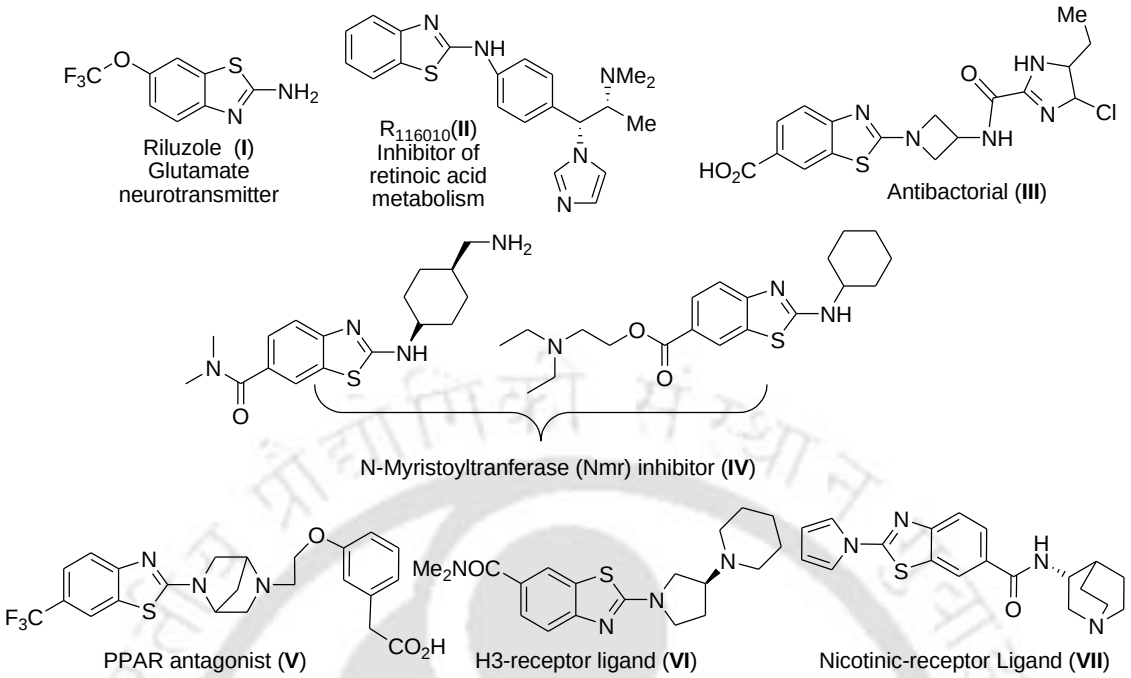
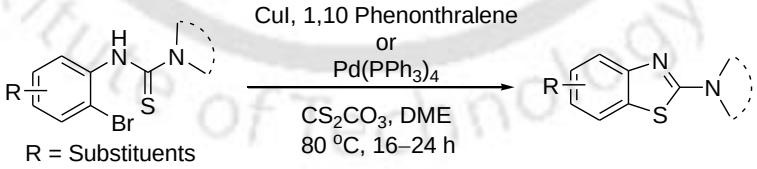


Figure II.2.1. *Structures of some biologically active substituted 2-aminobenzothiazoles*

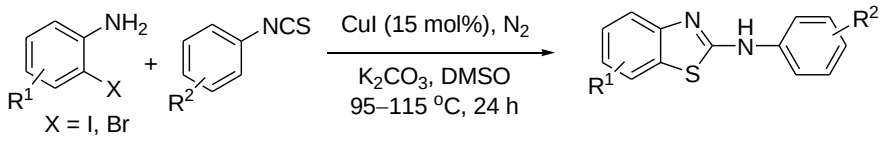
II.3. Existing Methods for the Synthesis of Benzothiazoles via Intramolecular *S*-Arylations Using Copper Catalyst

Copper and palladium-catalyzed intramolecular C–S bond formation by coupling between aryl halide and thiourea functionality has been demonstrated for the synthesis of 2-aminobenzothiazoles, wherein the Cu-catalyzed protocol is generally superior and more cost effective than the Pd-catalyzed protocol (*Scheme II.3.1*)[6a].



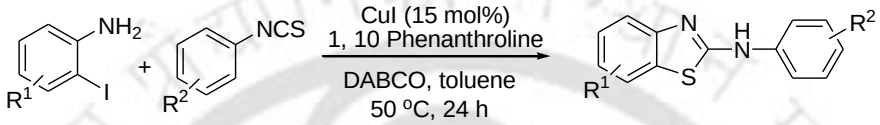
Scheme II.3.1. *Synthesis of 2-aminobenzothiazoles using Cu(I) and Pd(0) catalysts*

Bao *et al*. have reported *N*-substituted-2-aminobenzothiazoles by a ligand-free Cu(I)-catalyzed one-pot cascade process under nitrogen atmospher (*Scheme II.3.2*).[6b]



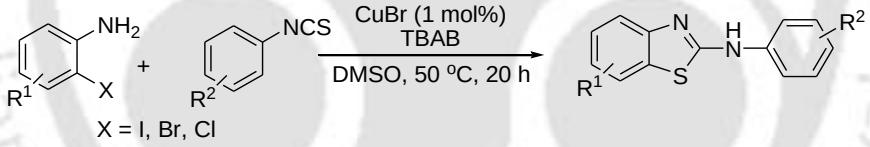
Scheme II.3.2. *Synthesis of N-substituted-2-aminobenzothiazoles using Cu(I) catalyst*

Wu *et al.* have developed a ligand assisted Cu(I)-catalyzed tandem reaction of 2-iodobenzenamine with isothiocyanate under mild conditions, which provides an efficient synthesis of 2-aminobenzothiazole (*Scheme II.3.3*).[6c]



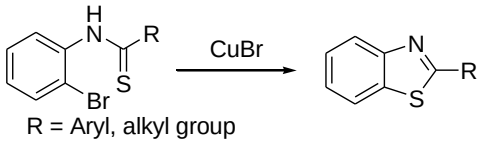
Scheme II.3.3. *Synthesis of 2-aminobenzothiazoles using ligand assisted Cu(I) catalyst*

A ligand-free copper-catalyzed reaction of 2-haloaniline with isothiocyanates has been developed for the synthesis of 2-aminobenzothiazoles by Guo *et.al.*[6d] The *in-situ* generated thiourea in the presence of CuBr and TBAB (tetra-*n*-butyl ammonium bromide, additive), at 40 °C, affords 2-aminobenzothiazoles (*Scheme II.3.4*).



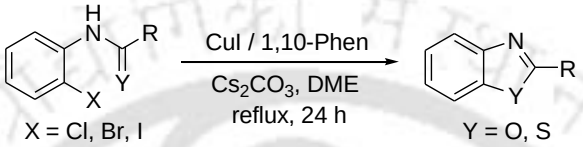
Scheme II.3.4. *Synthesis of 2-aminobenzothiazoles using Cu(I) catalyst*

Bowmann *et al.* have reported an intramolecular aromatic $S_{RN}1$ substitution for the preparation of 2-phenyl- and 2-methyl-1,3-benzothiazole from *ortho*-iodo thiobenzanilide and *ortho*-iodo thioacetanilide which however is found to be much more efficient under Cu(I)-catalyzed conditions (*Scheme II.3.5*).[6e]



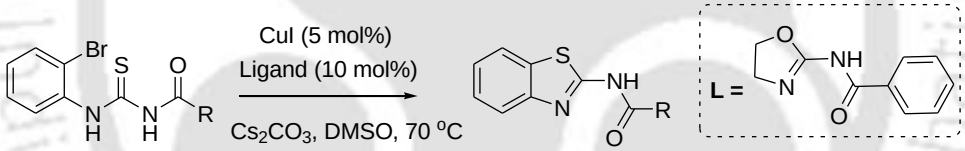
Scheme II.3.5. *Synthesis of 2-aryl/alkyl benzothiazole using Cu(I) salt*

Batey group have extensively studied the intramolecular *S*-arylation and *O*-arylaion of thioamides and amides. This approach complements the more commonly used strategies for benzoxazole and benzothiazole formation which require CuI, 1, 10-phenanthroline ligand, and base for acceleration / stabilization of reaction. Notably, the less active halides could also be applied successfully in the synthesis of benzoxazoles and benzothiazoles. The rate of reaction of the *o*-haloanilides follows the order I > Br > Cl, consistent with oxidative addition being the rate-determining step (*Scheme II.3.6*).[6f]



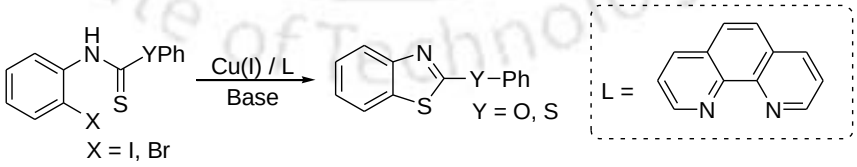
Scheme II.3.6. *Synthesis of 2-aryl/alkyl benzothiazole using Cu(I) salt*

A similar method has been reported using CuI/*N*-(4,5-dihydrooxazol-2-yl)benzamide as an efficient catalytic system for an intramolecular cyclization of substituted 1-aryl-acyl-3-(2-bromophenyl)thioureas to yield *N*-benzothiazol-2-yl-amides (*Scheme II.3.7*).[6g]



Scheme II.3.7. *Synthesis of N-benzothiazol-2-yl-amides using Cu(I) salt*

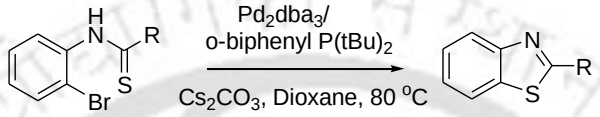
Recently, our group has demonstrated an intramolecular *S*-arylation for the synthesis of *S*-arylated and *O*-arylayed benzthiozoles using ligand (20 %) and CuI catalyst (10 %) in presence of dioxane solvent at 85 °C (*Scheme II.3.8*).[6h]



Scheme II.3.8. *Synthesis of S- and O-arylayed benzthiozoles using Cu(I) salt*

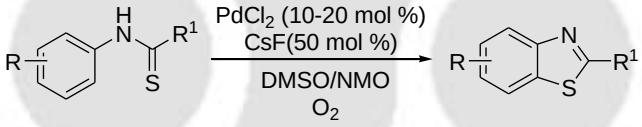
II.4. Existing Methods for the Synthesis of Benzothiazole via Intramolecular *S*-Arylations Using Palladium Catalyst

Castillon group have developed a palladium-catalyzed intramolecular cyclization of *o*-bromo-phenylthioureas and *o*-bromo-phenylthioamides for synthesizing 2-amino-, and 2-alkyl-benzothiazoles. Highly hindered alkyl monophosphines proved to be the most efficient ligands (*Scheme II.4.1*).[7a]



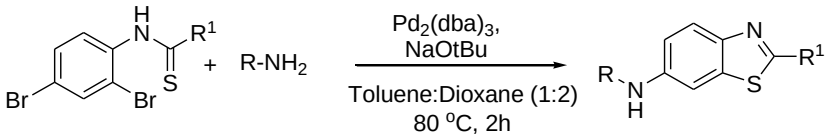
Scheme II.4.1. *Synthesis of 2-amino- and 2-alkyl-benzothiazoles using palladium catalyst*

Recently, Inamoto *et al.* have synthesized 2-arylbenzothiazoles and 2-aminobenzothiazoles using molecular oxygen (O_2) as a reoxidant through a palladium-catalyzed C–H functionalization/intramolecular C–S bond formation process. Addition of cesium fluoride (CsF) enhanced the reactions (*Scheme II.4.2*).[7b]



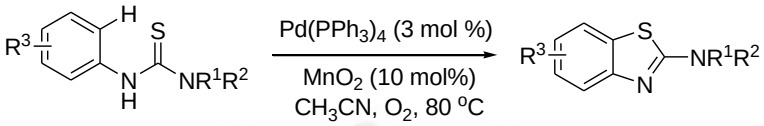
Scheme II.4.2. *Synthesis of 2-aryl-and 2-aminobenzothiazoles using C–H activation strategy*

A tandem palladium-catalyzed *S*- and *N*-arylation reaction of dibromothioamides to amino-substituted benzothiazoles has been developed in one-pot. Noteworthy, the immediate combination of all reagents at the outset of the reaction is preferable to stepwise addition in terms of product conversion, operational simplicity, and purification requirements (*Scheme II.4.3*).[7c]



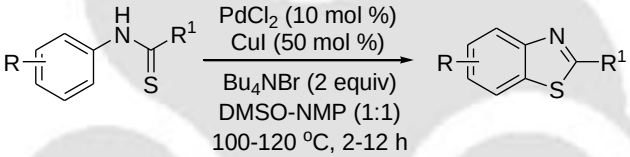
Scheme II.4.3. *S- and N-arylation using Pd(0) catalyst*

Batey *et al*. have demonstrated the construction of 2-aminobenzothiazoles[7d] from *N*-arylthioureas via an intramolecular C–S bond formation/C–H functionalization utilizing an unusual co-catalytic $Pd(PPh_3)_4/MnO_2$ system under an oxygen atmosphere at 80 °C (*Scheme II.4.4*).



Scheme II.4.4. *Synthesis of 2-aminobenzthiazole using Pd(0) catalyst*

Inamoto *et al.* have reported the synthesis of 2-substituted benzothiazoles from thiobenzanilides in the presence of a palladium catalyst through a C–H functionalization/C–S bond formation. This method features the use of a catalytic system consisting of 10 mol % of Pd(II), 50 mol % of Cu(I), and 2 equiv. of Bu_4NBr that produced variously substituted benzothiazoles (*Scheme II.4.5*).[7e]



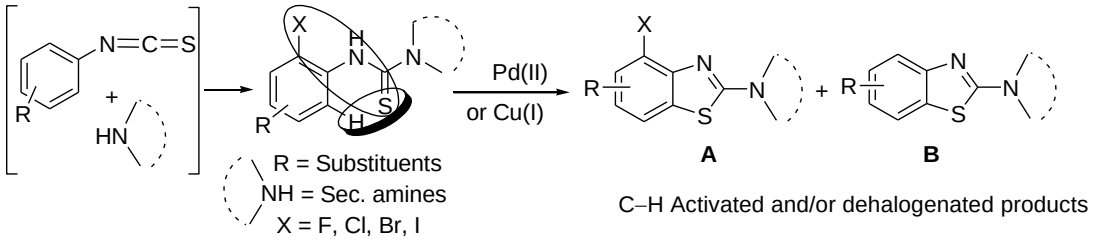
Scheme II.4.5. *Synthesis of 2-arylbenzothiazole using Pd(II) catalyst*

II.5. Present Work

II.5.1. Regioselective Intramolecular Arylthiolations by Ligand Free Cu and Pd Catalyzed Reaction

Great progresses have been made in the development of transition metal catalyzed reactions for the construction of C−N and C−O bonds, but until recently selective formation of C−S bonds remained relatively fewer in numbers because of the propensity of sulfur toward oxidative dimerization and their affinity for metals causing catalyst poisoning.[8] These problems have been overcome by the appropriate use of catalyst, ligand and additives through an inter and intra molecular C−H functionalizations. Although, the process of transition metal insertion into C−H bonds are known for several decades, however, this area of research has greatly been explored

only after the seminal contributions from Murai *et al.*[9] and others.[10] The C−H bonds can not only be envisioned as dormant synthetic equivalents of active functional groups but also these strategies improve atom economy and overall efficacy of synthetic processes. Among various transition metals, palladium and copper are most well explored.[10b,11] Despite of the high cost and difficulties associated with the removal of palladium-residues from polar reaction products, it is still the most preferred transition metal catalyst due to its high turnover number (TN) and selectivity. Relatively inexpensive and easily available copper has also been used for similar C−H functionalizations.[10b] Both palladium and copper have also been used as efficient catalyst toward carbon heteroatom bond formations via dehalogenative paths.[10c,12] Efficient catalytic methods for the formation of C−S bonds are in great demand in synthetic organic chemistry,[13] as well as in the material science[14] and pharmaceutical industries.[15] 2-Aminobenzothiazoles bearing C−S bonds are relevant in agrochemicals and pharmaceuticals.[16] Classical synthesis of 2-aminobenzothiazoles involves an intramolecular aromatic electrophilic substitution of thiobenzanilides using various oxidants, including Jacobson's and Hugerschoff methods.[17] These compounds have been prepared by intramolecular arylthiolation strategies using copper or palladium catalyzed cyclization of ortho-halo benzothioureas where the halides are invariably −Br or −I or at best −Cl but rarely with −F substituents.[6,7] All these reactions are carried out in the presence of catalyst, base, ligand and additives or their combinations. Intramolecular oxidative C−H bond activation of *N*-arylthioureas using $Pd(PPh_3)_4/MnO_2/O_2$, Pd−Cu/Bu_4NBr, catalytic system under an oxygen atmosphere[7b,d,e] and alternative strategies involving palladium catalyzed C−H activation[18] are atom economical. No doubt the latter methods (C−H activation) eliminate the need for ortho-halo (–Br, –I) substituents and a step forward in expanding the C−H activation, and requires 50 mol % of CuI for this methodology[7e] and large excess of additives such as Bu_4NBr. Instead of using expensive terminal oxidants such as para-benzoquinone, NMO, DMSO, MnO_2, Cu-salts, the cheap molecular oxygen has been employed many times.[11f,19] For Cu/Pd catalyzed intramolecular dehalogenative C−Z (*Z* = *O*, *S*, *N*) cross coupling of 2-halo ureas, guanidines and thioureas follows the order I > Br > Cl[6f,20] and very few reports using F substituents.[13d-i] Herein we made a systematic study to see how copper or palladium as catalyst behave toward various 2-halosubstituted thioureas. Second, in 2-fluoro or 2-chloro substituted thioureas whether a C−H activation product (**A**) or a dehalogenative product (**B**) would furnish by using Cu(I) and Pd(II) catalyst (*Scheme II.5.1.1*).



Scheme II.5.1.1. *Regioselective C–S bond formation using CuI and $PdCl_2$ catalysts*

In an attempt toward our study the intermediate thiourea (**1**) generated in situ upon mixing phenylisothiocyanate (**1′**) with morpholine (**a**) when treated with $PdCl_2$ (2 mol %) in DMF at 85 °C under an open atmosphere shows complete disappearance of the thiourea (**1**) with the formation of 2-aminobenzothiazole (**1a**) in excellent yield (91%) (*Table II.5.1.1*). It is noteworthy to mention here that similar transformations have been achieved using $Pd(PPh_3)_4/MnO_2/O_2$.[7d] Our results are advantageous as it uses commercially available relatively inexpensive robust catalyst, air (O_2) as the co-oxidant and under a ligand free condition in an air atmosphere. The catalyst $PdCl_2$ was found to be the best among various Pd salts screened in DMF in combination with either K_2CO_3 or Cs_2CO_3 as the base to give the desired product. Thioureas derived from phenyl isothiocyanate (**1′**) and secondary amines such as piperidine (**b**), 4-benzylpiperidine (**c**), 4-thiomorpholine (**d**), pyrrolidine (**e**), 4-cyclohexylpiperizine (**f**), 4-phenylpiperizine (**g**), and diethylamine (**h**) all gave corresponding 2-aminobenzothiazoles (**1b**–**1h**) in excellent yields (*Table II.5.1.1*).

Under this optimized reaction condition, thioureas (**2**−**7**) were subjected to catalytic combination of $PdCl_2$, K_2CO_3 in DMF at 85 °C under an open atmosphere and all underwent efficient conversion to 2-aminobenzothiazoles (**2a**−**7a**) through a C−H activation strategy. The substituents in the aromatic core ranges from activating −Me (**2**), n-Bu (**3**), moderately deactivating −F (**4**), −Br (**5**), and highly deactivating −CN (**6**), $-CF_3$ (**7**), and all gave their corresponding products in good to excellent yields (*Table II.5.1.2*). In general, the presence of electron-withdrawing substituents in the aromatic scaffolds gave better yields compared to electron rich ones. *meta*-Substituted substrates (**8**−**10**), regioselectively gave 5-substituted products (**8a**−**10a**). The exclusive formation of 5-substituted product is evident from the crystal X-ray crystallography of (**10a**) (*Figure II.5.1.1*). The disubstituted substrate (**11**) where one of

the substituent is meta to NH, also regioselectively gave 5-substituted product (**11a**). 1-Naphthylthiourea (**12**) yielded 2-aminobenzothiazole (**12a**) via a C−H activation path.

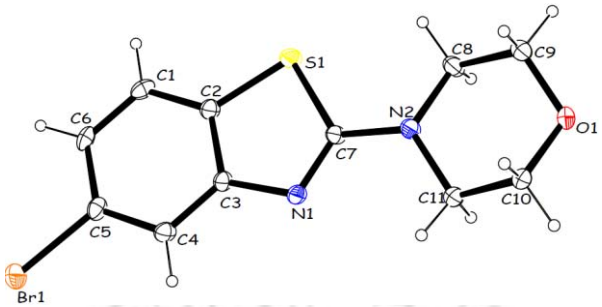
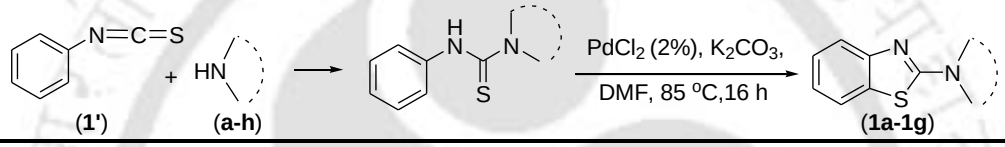
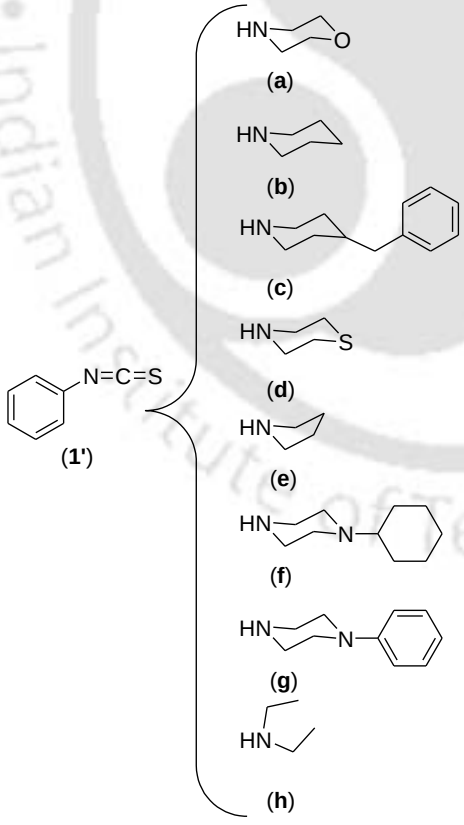
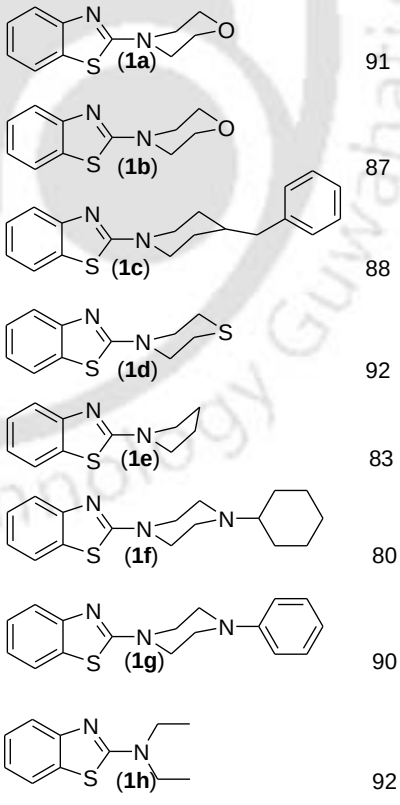


Figure II.5.1.1. *ORTEP diagram of* ***10a***

Table II.5.1. *Synthesis of 2-aminobenzothiazoles via C–H functionalization using* $PdCl_2$[a]

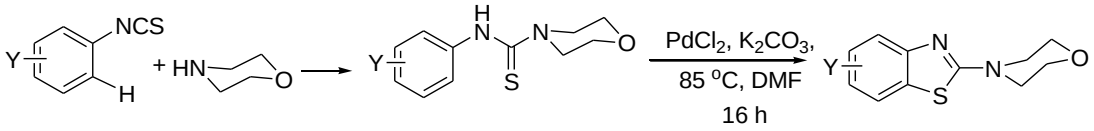


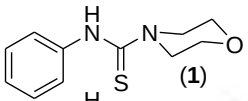
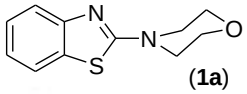
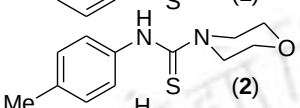
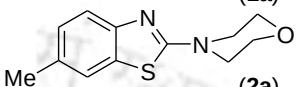
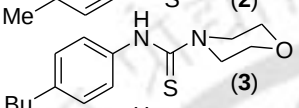
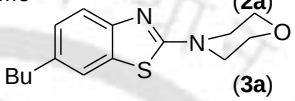
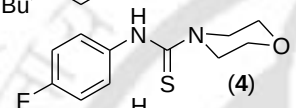
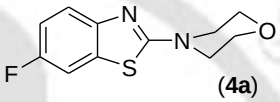
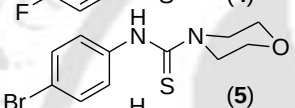
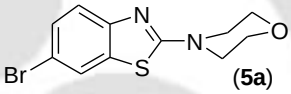
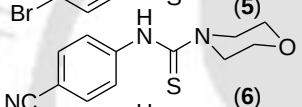
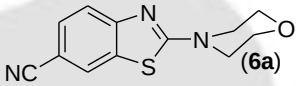
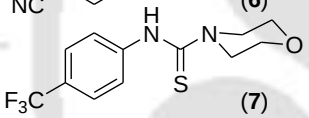
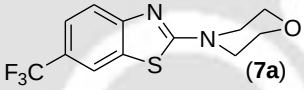
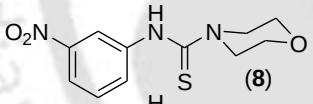
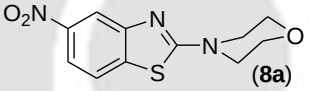
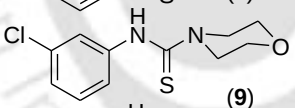
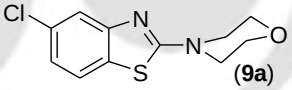
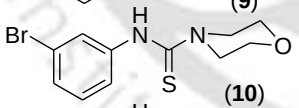
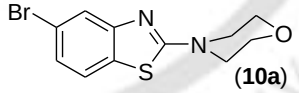
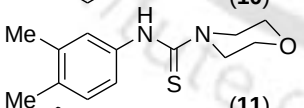
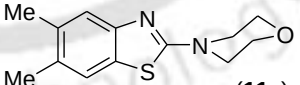
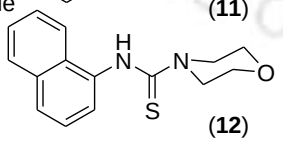
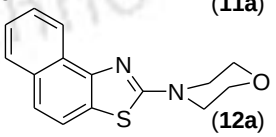
Substrate	Product	Yield%[b]
		91 87 88 92 83 80 90 92

[a]Confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. [b]Isolated yield.

Interestingly, 2-fluoro-substituted thiourea (**13**) also yielded 2-aminobenzothiazole (**13a**) in good yield under the identical condition but via a C−H functionalization strategy and not by a dehalogenative path (*Table II.5.1.3*). Structure of the product (**13a**) with retention of F-group has been confirmed by X-ray crystal structure (*Figure II.5.1.2*) as well as from ^{19}F-NMR. Thus, a Pd catalyzed reaction prefers C−H activation over dehalogenative arylthiolation, possibly because of the inertness of sp^2 C−F bond. Analogous 2-fluorothiourea (**13″**) gave 2-aminobenzothiazole (**13b**) via a C−H activation path. For partially fluorinated phenyl rings there is an intramolecular competition between C−H and C−F bond activation during intramolecular cyclization.[10] In the present system electronic effect was observed for disubstituted thioureas during the formation 2-aminobenzothiazole (*Table II.5.1.3*). Substrates bearing two fluoro groups in 2,4-positions (**15** and **15″**) gave exclusive/major dehaloganated products **4a** and **4c** which is in sharp contrast to observed nucleophilic C−H activated products for substrate **13** and **13″**. This observation supports the thermodynamic pathway of this intramolecular competitive cyclization.[21] In case of 4-methyl-2-fluoro substrate (**14**) the ring electron density is slightly increased with respect to difluoro substrates (**13**, **13″**, **17**) thus ruling out the possibility of nucleophilic C−H activated product and giving only dehalogenated (C−F bond cleavage) product (**2a**). The propensity of Pd toward C−H activation over defluorinative heteroarylation has been further demonstrated with other 2-fluoro thiourea (**16**) which gave benzothiazoles **16a** via C−H functionalization. It may be mentioned here that thiourea (**15″**) gave benzothiazole (**4′c**) as the minor product via defluorinative path (*Table II.5.1.3*). Instead of thiourea *N*-(2,4-difluorophenyl)morpholine-4-carbothioamide (**15**) when isomeric thiourea *N*-(2,5-difluorophenyl)-morpholine-4-carbothioamide (**17**) was used for the palladium catalyzed reaction in DMF solvent a completely unexpected product *N*-(2,4-difluorophenyl) acetamide (**17i**) was obtained. The crystal X-ray crystallography of product (**17i**) is shown in *Figure II.5.1.3*. The exact mechanism of this reaction is not clear at the moment but it seems the acetyl group is originating from solvent DMF. This is a very very substrate specific reaction and no other substrates examined (*Table II.5.1.1, II.5.1.2 and II.5.1.3*) gave similar product. Switching the solvent from DMF to DMSO gave the expected product (**17a′**) thus further supporting our assumption. Whereas regioisomeric substrate having two fluoro groups in 2,5-positions (**17**) exclusively gave nucleophilic C−H activation product (**17a′**) over dehalogenated (C−F bond cleavage) product which supports the kinetic pathway over thermodynamic pathway.[21]

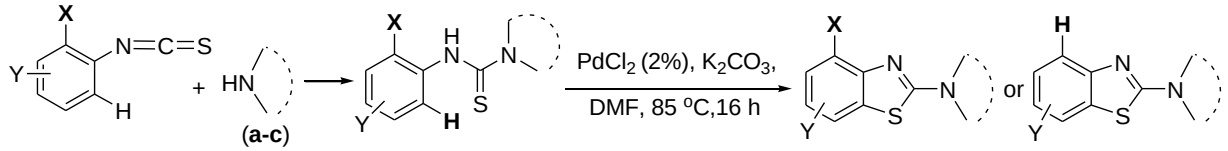
Table II.5.2. *Synthesis of 2-aminobenzothiazoles via C–H functionalization using* $PdCl_2$[a]

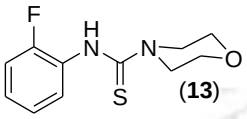
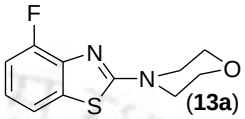
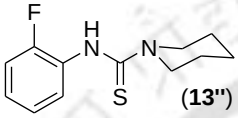
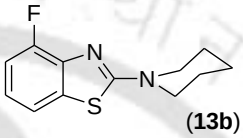
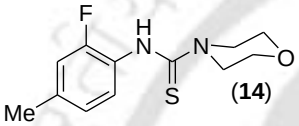
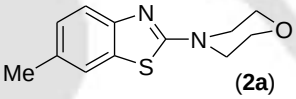
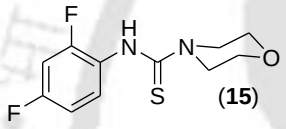
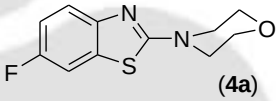
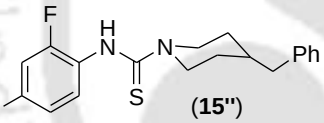
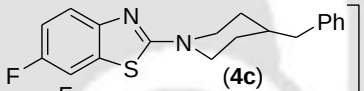
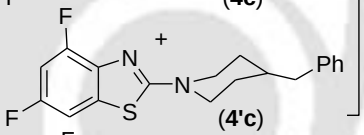
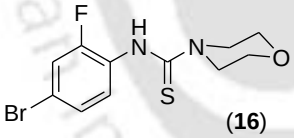
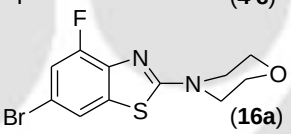
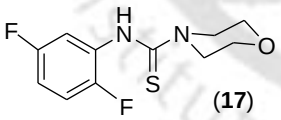
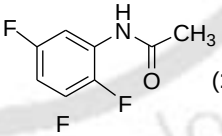
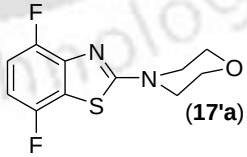


Substrate	Product	Yield%[b]
 (**1**)	 (**1a**)	91
 (**2**)	 (**2a**)	86
 (**3**)	 (**3a**)	82
 (**4**)	 (**4a**)	93
 (**5**)	 (**5a**)	93
 (**6**)	 (**6a**)	94
 (**7**)	 (**7a**)	91
 (**8**)	 (**8a**)	93
 (**9**)	 (**9a**)	94
 (**10**)	 (**10a**)	91
 (**11**)	 (**11a**)	80
 (**12**)	 (**12a**)	90

[a]Confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. [b]Isolated yield.

Table II.5.1.3. *Pd(II)-Catalyzed synthesis of 2-sminobenzothiazoles via C-H fuctinalization*[a]



Substrate	Product	Yield%[b]
 (**13**)	 (**13a**)	96
 (**13''**)	 (**13b**)	91
 (**14**)	 (**2a**)	93
 (**15**)	 (**4a**)	94
 (**15''**)	 (**4c**)	70
	 (**4'c**)	20
 (**16**)	 (**16a**)	80
 (**17**)	 (**17i**)	73
	 (**17'a**)	87c

[a]Confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. [b]Isolated yield.

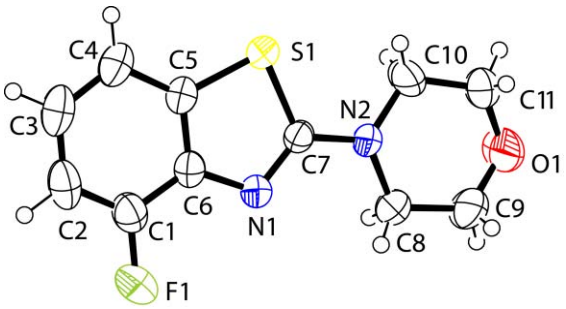


Figure II.5.1.2. *ORTEP diagram of* ***13a***

During Cu/Pd-catalyzed intramolecular dehalogenative cross coupling reaction of 2-halo ureas, guanidines, and thioureas follows the order I > Br > Cl > F. We wanted to see if −Cl a relatively more reactive halogen than −F prefer dehalogenation or C−H activation when subjected to palladium catalyzed reaction. A palladium catalyzed reaction of 2-chloro-substituted thioureas (**18**, **18″**, **19**, **19″**, and **20**) gave two types of benzothiazoles one via a dehalogenative process and the other follows a C−H activation path. Barring the case of (**18″**and **19″**) (*Table II.5.1.4*), the major product is obtained via a C−H activation path with the retention of –Cl group (**18a**, **19′a**, and **20a**), while the minor products (**1a**, **19a**, and **5a**) are obtained via a dehalogenative path. Not only the aryl ring but also the nature of the secondary amines present in thioureas also dictates the outcome of the regioselectivity. All other parameters remaining the same morpholino containing thioureas (**18**, **19**, and **20**) gave C−H activation as the major product while the analogous piperidine (**18″**) and 4-benzylpiperidine (**19″**) preferred dahalogenation over C−H activation giving (**1b**) and (**19c**) as the major product (*Table II.5.1.4*).

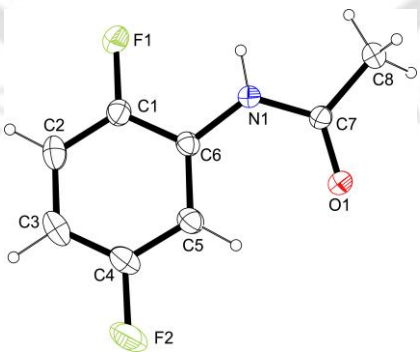
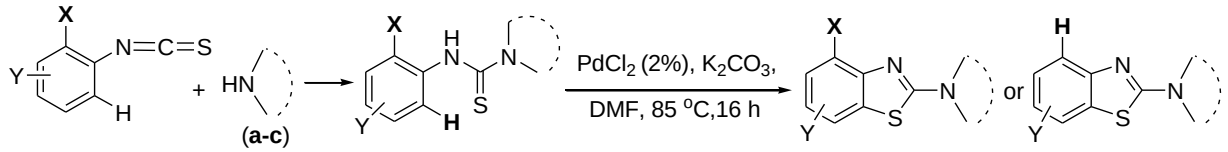
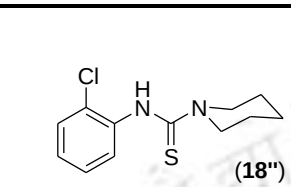
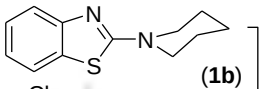
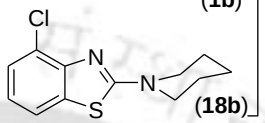
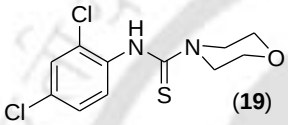
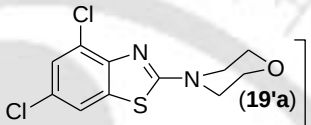
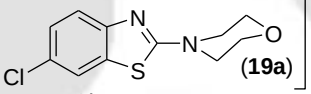
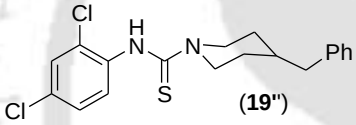
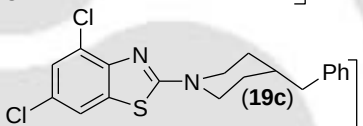
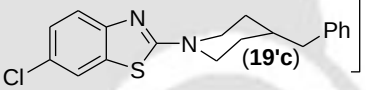
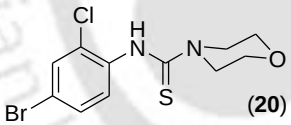
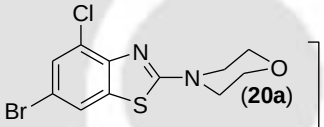
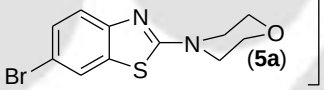


Figure II.5.1.3. *ORTEP diagram of* ***17i***

Table II.5.1.4. *Pd-Catalyzed synthesis of 2-aminobenzothiazoles via C–H functionalization*[a]



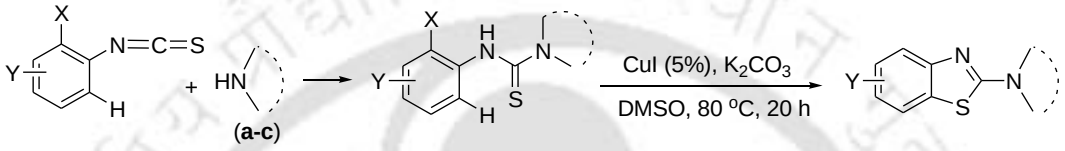
Substrate	Product	Yield%[b]
 (**18''**)	 (**1b**)	42
	 (**18b**)	33
 (**19**)	 (**19'a**)	51
	 (**19a**)	32
 (**19''**)	 (**19c**)	15
	 (**19'c**)	70
 (**20**)	 (**20a**)	72
	 (**5a**)	17

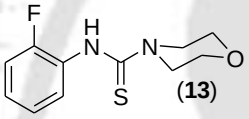
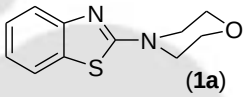
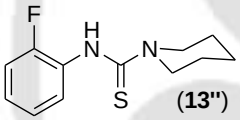
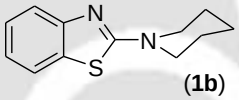
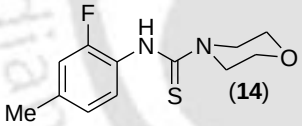
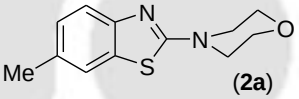
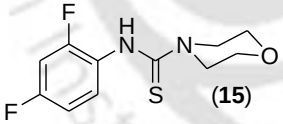
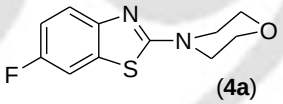
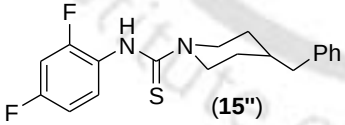
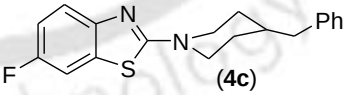
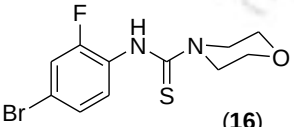
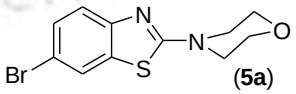
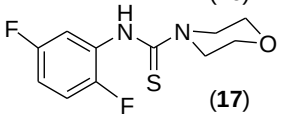
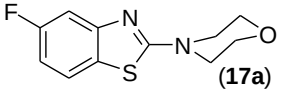
[a]Confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. [b]Isolated yield.

In general both Cu and Pd catalyst exhibits comparable selectivity and reactivity toward sp^2 C−H's activation and arylthiolation involving C−halogen bonds. In the study of thiourea (**13**) with CuI (2 mol %) as catalyst under an identical condition to that of palladium catalyzed reaction showed exclusive formation of dehalogenated product, benzothiazole (**1a**) sluggishly in moderate yield (50%). Using DMSO as the solvent and 5 mol % of catalyst gave benzothiazole (**1a**) in excellent yield (83%). These show preference for Cu toward dehalogenative path over C−H activation even with fluoro substituents. This assumption has been supported with the help of six other 2-fluoro substituted thioureas (**13″**, **14**, **15**, **15″**, **16**, and **17**) and all underwent

defluorinative path giving products (**1b**, **2a**, **4a**, **4c**, **5a**, and **17a**) respectively (*Table II.5.1.2.5*). Although *N*/*O*-arylation of fluoro substituted substrates with Cu and Fe salts have been reported.[22] However, an intramolecular *S*-arylation involving defluorinative path is yet to be explored. 2-Chloro substituted thioureas (**18**), (**18″**), (**19**), (**19″**), and (**20**) gave benzothiazoles (**1a**), (**1b**), (**19a**), (**19c**), and (**5a**) (*Table II.5.1.2.6*) via a dehalogenative path; an observation, in sharp contrast to the palladium catalyzed reactions (*Table II.5.1.2.4,5*).

Table II.5.1.5. *Cu-Catalyzed synthesis of 2-aminobenzothiazoles via dehalogenative Path*[a]

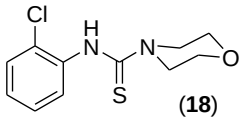
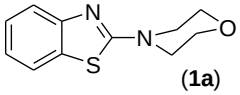
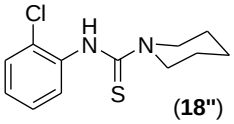
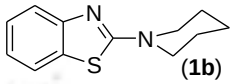
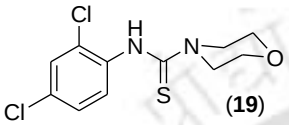
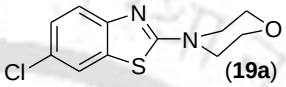
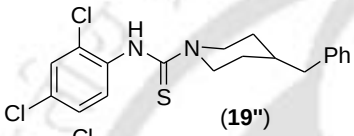
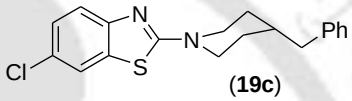
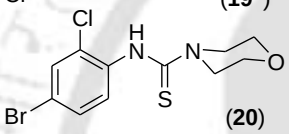
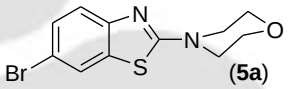


Substrate	Product	Yield %
 (**13**)	 (**1a**)	83
 (**13''**)	 (**1b**)	79
 (**14**)	 (**2a**)	79
 (**15**)	 (**4a**)	73
 (**15''**)	 (**4c**)	76
 (**16**)	 (**5a**)	81
 (**17**)	 (**17a**)	76

[a]Confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. [b]Isolated yield.

Continued…

Table II.5.1.5. *Continued…*

Substrate	Product	Yield %
 (**18**)	 (**1a**)	91
 (**18"**)	 (**1b**)	83
 (**19**)	 (**19a**)	81
 (**19"**)	 (**19c**)	83
 (**20**)	 (**5a**)	71

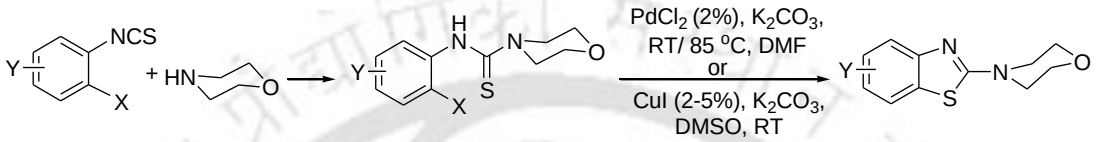
[a]Confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. [b]Isolated yield.

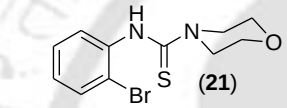
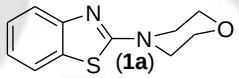
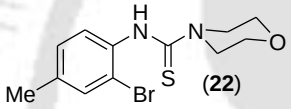
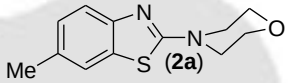
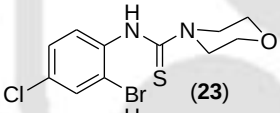
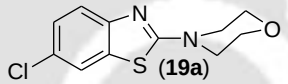
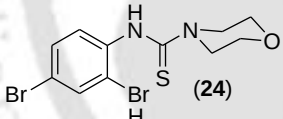
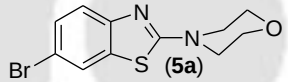
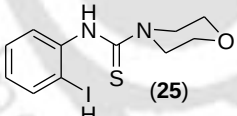
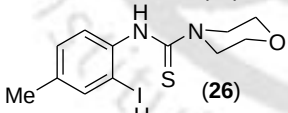
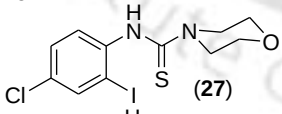
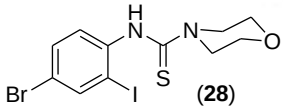
Copper and palladium catalyzed synthesis of 2-aminobenzthiazoles are reported for 2-Br and 2-I thioureas in the presence of ligand.[6,7] The same has been achieved under ligand and catalyst free condition[23] and in the presence of additives.[6d] But these procedure requires longer reaction times or high temperature.

From our present studies it is evident that Cu(I) prefers a dehalogenative path even with less reactive halogens such as –F and −Cl. In contrary Pd(II) gave exclusively C−H activated product with fluoro and a mixture of C−H activated and dehalogenated product in the case of −Cl substrates. Thus it is expected with reactive halogens such as –Br and −I both Pd(II) and Cu(I) should behave identically giving only dehalogenated products. To prove this assumption 2-bromo substituted thioureas (**21**−**24**) were reacted with $PdCl_2$ (2 mol %) and all gave corresponding benzothiazoles (*Table II.5.1.6*) via a dehalogenative path. It may be mentioned here that with a similar substrate (**21**) using ligand assisted Pd(0) salt only traces of dehalogenated product is reported along with the recovery of starting material.[7d] Identical results were also obtained using 2-iodo substituted thioureas (**25**−**28**). For 2-bromo substrates the

reaction works best using 2 mol % of the catalyst at 85 °C and iodo substrates goes at room temperature with 2 mol % of the catalyst. Identical results were obtained with Cu also but interestingly for 2-Br and 2-I thioureas the reaction goes at room temperature. The reaction works best with 5 mol % of the catalyst for −Br substrates whereas for –I substrates 2 mol % of catalyst was sufficient giving excellent yields of products (*Table II.5.1.6*).

Table II.5.1.6. *Pd / Cu Catalyzed synthesis of 2-aminobenzothiazoles*[a]

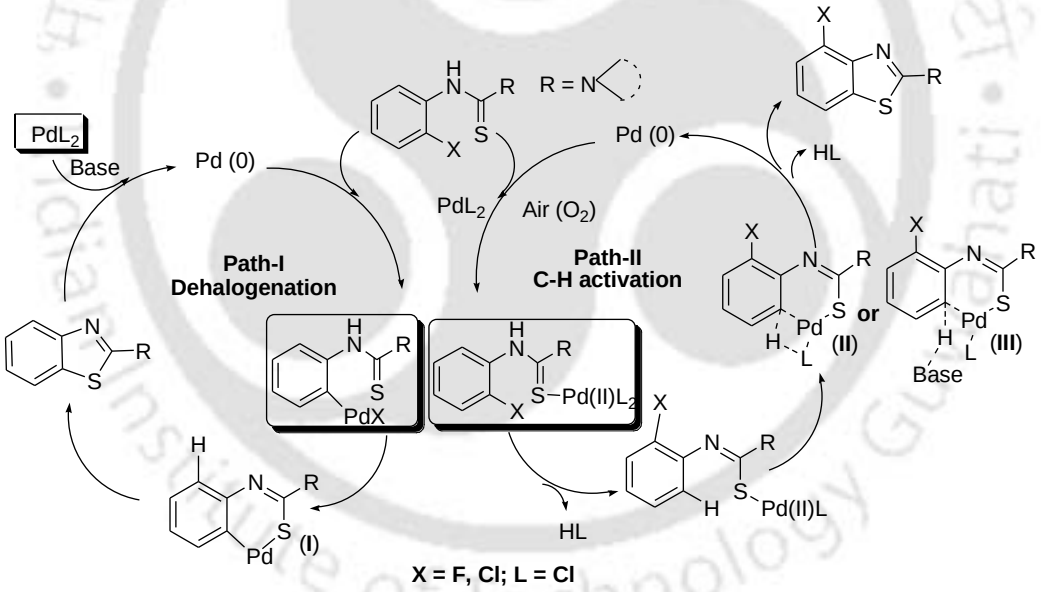


Substrate	Product	Yield%[b-d]
 (**21**)	 (**1a**)	91 / 96
 (**22**)	 (**2a**)	93 / 95
 (**23**)	 (**19a**)	94 / 97
 (**24**)	 (**5a**)	90 / 95
 (**25**)	(**1a**)	99 / 97
 (**26**)	(**2a**)	96 / 91
 (**27**)	(**19a**)	93 / 89
 (**28**)	(**5a**)	94 / 96

[a]Confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. [b]Isolated yield. [c]CuI (5 mol %), room temperature, 2 h. $PdCl_2$ (2 mol %), 85 °C, 1 h. [d]CuI (2 mol%), $PdCl_2$ (2 mol %), room temperature, 0.5 h.

A plausible mechanism for the formation of 2-aminobenzothiazole is shown in *Scheme II.5.1.2*. In path-I Pd(II) in the presence of base gets reduced to Pd(0).[24] This upon oxidative

insertion to halo group of thiourea followed by co-ordination with sulfur generates intermediate (I). Subsequent reductive elimination provides benzothiazoles with concomitant generation of Pd(0) which maintains the catalytic cycle (path I).[6a,24] In an alternative path (path II) substrates containing 2−F and −Cl substituents, precoordination of sulfur to palladium occur and the palladacycle is formed via σ bond metathesis giving intermediate (II) or via a base-assisted deprotonative metalation giving intermediate (III).[7d,e,25] Thus, benzothiazole is obtained via C−H activation path with the retention of 2-halo (−Cl, −F) substituents. The in situ generated Pd(0) in this path (Path II) gets oxidized to Pd(II) in air to take part in the next cycle.[7d,e] Depending on the nature of the substituents present they prefer to go either via path I or path II and in some cases two paths compete with each other giving both types of product. While, the copper catalyzed reaction involves an intramolecular C−S cross-coupling of ortho-halothioureas for the entire range of halogens (−F, −Cl, −Br, and −I) and is believed to proceed via an oxidative insertion/reductive elimination path through a Cu(I)/Cu(III) manifold.[6f]



Scheme II.5.1.2. *Plausible mechanism for the differential selectivity using Pd(II) catalyst*

In summary, we have demonstrated the regioselective intramolecular C−S bond formation during the formation of 2-aminobenzothiazole from 2-halo substituted thioureas using Cu(I) and Pd(II) catalyst. With few exceptions palladium prefers a C−H activation path over dehalogenative for less reactive halogens, such as fluoro. However, no satisfactory explanation on selectivity has emerged from the present study. For bromo and iodo a dehalogenative path is

favored while chloro substituted thioureas undergoes either of the paths giving both types of benzothiazoles. However, Cu(I) prefers dehalogenative path only for the entire range of halogens. These ligand free regioselective synthesis of 2-aminobenzothiazoles are advantageous over other reported methods in literature.

II.6. Experimental Section

II.6.1. Instrumentation and Characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. The solvents were of commercial grade and purified according to established procedures. Organic extracts were dried with anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Gas liquid chromatography was performed using HP 6890 series II instrument and using, a cross linked methyl silicon gum capillary column (30m x 0.32mm x 0.25μm) fitted with FID, and quantification was done using HP integrator.

Melting points were recorded with a Büchi B-540 melting point apparatus. Elemental analysis was performed with a Perkin-Elmer 2400 elemental analyzer. Fourier Transform-Infra Red (FT-IR) spectra were recorded on Nicolet Impact-410 instrument either as neat liquid or KBr pellets. Fast atom bombardments (FAB) mass were recorded using a JEOL SX-120/DA-6000 instrument using argon (6KV, 10mA) as the FAB gas. GC-MS were recorded using a capillary column (30 X 0.25 mm X 0.25 mμ) in EI mode. NMR spectra were recorded in $CDCl_3$ or [D_6] DMSO with tetramethylsilane as the internal standard for ^1H (400 MHz) or $CDCl_3$ or [D_6] DMSO solvent as the internal standard for ^{13}C (100 MHz). Crystal Data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoK_α radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied

with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F^2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

II.6.2. General Procedure for the Synthesis of Arylisothiocyanates

Arylisothiocyanates are prepared by using our greener procedures.[26]

II.6.3. General Procedure for the Synthesis of 4-Fluoro-2-morpholino-benzo[*d*]thiazole (13a) Using $PdCl_2$

To solution of 2-fluorophenyl isothiocyanate (**13'**) (2 mmol) in DMF (2 mL) was added morpholine (2 mmol) and stirred at room temperature complete formation of *N*-(2-fluoro phenyl) morpholine-4-carbothiamide **13** was observed within 15 minutes. To this was added K_2CO_3 (2 mmol), $PdCl_2$ (0.04 mmol) and the reaction was heated in an oil bath at 85 ^oC. Progress of the reaction was monitored by TLC. After 16 h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). Then the reaction mixture was filtered over Celite and washed with ethyl acetate (3 x 5 mL). The filtrate was washed successively with water (2 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product so obtained was purified over a short column of silica gel using EtOAc : hexane (1:9) as the eluents to give the product **13a** (0.457g) 96% isolated yield.

II.6.4. General Procedure for Preparation of 2-Morpholinobenzo[*d*]thiazole (1a) Using CuI

2-Fluorophenyl isothiocyanate (**13'**) (2 mmol) in DMSO (2 mL) was added morpholine (2 mmol) and stirred at room temperature complete formation of *N*-(2-Fluoro phenyl) morpholine-4-carbothiamide **13** was observed within 15 minutes. To this was added K_2CO_3 (2 mmol), CuI

(0.01 mmol) and the reaction mixture was heated in an oil bath at 80 ^{o}C. The progress of the reaction was monitored by TLC using ethyl acetate and hexane (2:8). After 20 h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). Then reaction mixture was filtered over Celite and washed with ethyl acetate (3 x 5 mL). The filtrate was washed successively with water (2 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified over a column of silica gel with EtOAc : hexane (2:8) as the eluents to give the product **1a** in (0.365g) 83% isolated yield.

II.6.5. Crystallographic Description

Crystal data of compound (10a): CCDC reference number 825877, $C_{11}H_{11}Br_1N_2O_1S_1$, M = 300.33, Monoclinic, space group $P_2(1)/n$, Z = 4, a = 13.1884(18) Å, b = 6.0953(8) Å, c = 15.447(2) Å, α = 90.00º, β = 112.049(7)º, γ = 90.00º, T = 296(2) K, Volume = 1150.9(3) Å^3, μ (Mo–Kα)= 3.372 mm^{-1}, (R_{int} = 0.0610). The final $R_1(I > 2\sigma(I))$ was 0.1641, GOF = 1.128.

Crystal data of compound (13a): CCDC reference number 821229, $C_{11}H_{11}N_2O_1F_1S_1$, M = 239.06, Monoclinic, space group $P_2(1)/n$, Z = 4, a = 10.0399(3) Å, b = 7.8357(2) Å, c = 13.7823(3) Å, α = 90.00º , β = 91.5910(10)º, γ = 90.00º, T = 296(2) K, Volume = 1083.83(5) Å^3, μ (Mo–Kα)= 0.291 mm^{-1}, (R_{int} = 00.0697). The final $R_1(I > 2\sigma(I))$ was 0.1671, GOF = 1.011.

Crystal data of compound (17i): CCDC reference number 848764, $C_8H_7N_1O_1F_2$, M = 171.15, Monoclinic, space group P 21/c, Z = 4, a = 7.3663(9) Å, b = 11.9295(13) Å, c = 9.5034(11) Å, α = 90.00º, β = 111.016(7)º, γ = 90.00º, T = 296(2) K, Volume = 779.57(16) Å^3, μ (Mo–Kα)= 0.129 mm^{-1}, (R_{int} = 0.0470). The final $R_1(I > 2\sigma(I))$ was 0.1067, GOF = 1.074.

II.7. References

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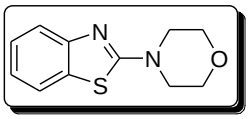
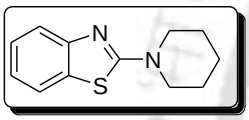
II.8. Spectral Data

2-Morpholinobenzo[*d*]thiazole (1a):



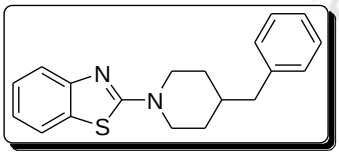
White solid; R_f = 0.55 (EtOAc : hexane (2:8); M.p. 120–122 ^{o}C (Lit.[58,60] 119–120 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.59 (t, 4H, *J* = 4.4 Hz), 3.80 (t, 4H., *J* = 4.4 Hz), 7.07 (t, 1H, *J* = 7.6 Hz), 7.28 (t, 1H, *J* = 8.0 Hz), 7.57 (dd, 1H, J_1 = 6.4 Hz, J_2 = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.5, 66.2, 119.4,120.8, 121.7, 126.1, 130.6, 152.5, 169.0 IR (KBr): 2918, 2854, 1591, 1537, 1441, 1377, 1289, 1229, 1113, 1067, 1032, 945, 859, 756 cm^{-1}; Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72; S, 14.56; Found C, 60.07; H, 5.55; N, 12.62; S, 14.48.

2-(Piperidin-1-yl)benzo[*d*]thiazole (1b):



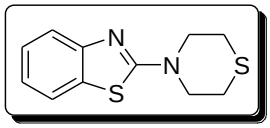
White solid; R_f = 0.50 (EtOAc : hexane (2:8); M.p. 96–97 ^{o}C (Lit.[102-103] 93 ^{o}C) [(102) Yella, R; Patel, B. K. *Org. Biomol. Chem*., ***2010***, *8*, 3389. (103) Jordan, A. D.; Luo, C.; Reitz, A. B. *J. Org. Chem*. ***2003***, *68*, 8693)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67 (s, 6H), 3.58 (s, 4H), 7.03 (t, 1H, *J* = 8.0 Hz), 7.26 (t, 1H, *J* = 8.0 Hz), 7.55 (dd, 2H, J_1 = 8.0 Hz, J_2 = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 25.4, 49.7, 118.9, 120.7, 121.1, 126.0, 130.8, 153.1, 169.0; IR (KBr): 2934, 2922, 2849, 1588, 1534, 1440, 1382, 1332, 1257, 1234, 1209, 1120, 1006, 760 cm^{-1}; Anal. Calcd for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83; S, 14.69; found C, 66.08; H, 6.50; N, 12.76; S, 14.55.

2-(4-Benzylpiperidin-1-yl)benzo[*d*]thiazole (1c):



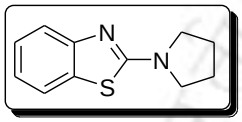
White solid; R_f = 0.5 (EtOAc : hexane (2:8); M.p. 113–115 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (m, 1H), 1.77 (d, 4H, *J* = 10.8 Hz), 2.59 (d, 2H, *J* = 7.2 Hz), 3.06 (t, 2H, *J* = 12.8 Hz), 4.15 (d, 2H, *J* = 13.2 Hz), 7.08 (t, 1H, *J* = 8.0 Hz), 7.18 (d, 2H, *J* = 8.0 Hz), 7.26 (d, 1H, *J* = 7.2 Hz), 7.32 (m, 3H), 7.60 (t, 2H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.5, 38.0, 43.0, 49.0, 118.9, 120.7, 121.2, 126.0, 126.2, 128.4, 129.2, 130.8, 139.9, 153.0, 168.7; IR (KBr): 3061, 3024,2937, 2920, 2851, 1595, 1539, 1492, 1444, 1388, 1324, 1278, 1258, 1172, 922, 752, 727 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{20}N_2S$ (M + H^{+}) 309.0955; found 309.0959.

2-Thiomorpholinobenzo[*d*]thiazole (1d):



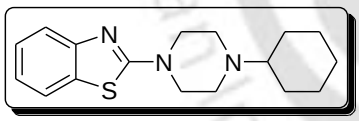
Yellow gum; R_f = 0.45 (EtOAc : hexane (2:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.71 (t, 4H, *J* = 5.2 Hz), 3.93 (t, 4H, *J* = 4.8), 7.06 (t, 1H, *J* = 7.2 Hz), 7.28 (t, 1H, *J* = 8.0 Hz), 7.52 (d, 1H, *J* = 8.0 Hz), 7.57 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.7, 51.3, 119.2, 120.8, 121.6, 126.2, 130.8, 152.7, 168.2; IR (KBr): 3059, 2936, 2858, 1599, 1531, 1444, 1385, 1359, 1313, 1218, 1054, 1020, 899, 750 cm^{-1}; Anal. Calcd for $C_{11}H_{12}N_2S_2$: C, 55.90; H, 5.12; N, 11.85; S, 27.13; found C, 55.94; H, 5.19; N, 11.77; S, 26.97.

2-(Pyrrolidin-1-yl)benzo[*d*]thiazole (1e):



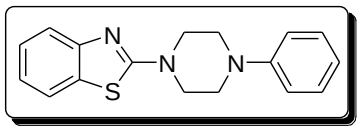
White solid; R_f = 0.50 (EtOAc : hexane (2:8); M.p. 101–103 ^{o}C (Lit.[102] 101 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (m, 4H), 3.57 (s, 4H), 7.02 (t, 1H, *J* = 7.6 Hz), 7.26 (t, 1H, *J* = 8.0 Hz), 7 57 (t, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.8, 48.8, 118.8, 120.8, 121.2, 126.1, 130.6, 153.1, 165.6; IR (KBr): 2924, 2851, 1604, 1544, 1442, 1363, 1314, 1278, 1166, 1119, 853 cm^{-1}; Anal. Calcd for $C_{11}H_{12}N_2S$: C, 64.67; H, 5.92; N, 13.61; S, 15.66; found C, 64.70; H, 5.96; N, 13.68; S, 15.73.

2-(4-Cyclohexylpiperazin-1-yl)benzo[*d*]thiazole (1f):



White solid; R_f = 0.55 (EtOAc : hexane (2:8); Mp. 129–131 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (m, 6H), 1.75 (m, 5H), 2.62 (t, 4H, *J* = 4.4 Hz), 3.56 (t, 4H, *J* = 4.4 Hz), 6.99 (t, 1H, *J* = 7.6 Hz), 7.21 (t, 1H, *J* = 8.0 Hz), 7.47 (d, 1H, *J* = 8.0 Hz), 7.51 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0, 26.4, 29.0, 48.5, 49.0, 63.8, 119.1, 120.8, 121.5, 126.1, 130.8, 152.9, 168.9; IR (KBr): 2922, 2851, 2814, 1595, 1541, 1443, 1387, 1341, 1250, 1125, 1016, 748 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{23}N_3S$ $(M + H)^+$ 302.1611; found 302.1617.

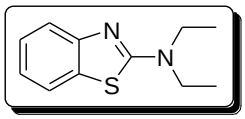
2-(4-Phenylpiperazin-1-yl)benzo[*d*]thiazole (1g):



White solid; R_f = 0.40 (EtOAc : hexane (2:8); M.p. 168–170 ^{o}C (Lit.[62] 162–163 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.29 (t, 4H, *J* = 5.2 Hz), 3.78 (t, 4H, *J* = 5.2 Hz), 6.94 (m, 3H), 7.10 (t, 1H, *J* = 8.0 Hz), 7.33 (m, 3H), 7.62 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.4, 49.1,

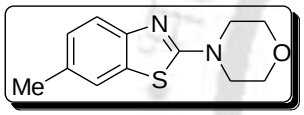
116.9, 119.3, 120.7, 120.8, 121.7, 126.2, 129.3, 130.9, 151.0, 152.8, 168.7; IR (KBr): 3026, 2861, 1594, 1560, 1539, 1503, 1443, 1384, 1347, 1293, 1249, 1229, 1194, 1158, 1024, 935, 755 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{17}N_3S$ $(M + H^+)$ 296.1154; found 296.1154.

_N_, _N_-Diethylbenzo[_d_]thiazole-2-amine (1h):



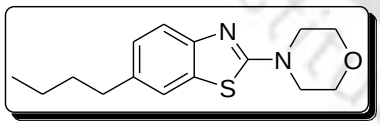
Gummy; R_f = 0.45 (EtOAc : hexane (2:8); ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (m, 6H), 3.55 (m, 4H), 7.03 (t, 1H, J = 8.0 Hz), 7.27 (t, 1H, J = 8.0 Hz), 7.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.9, 45.4, 118.5, 120.5, 120.7, 125.8, 130.6, 153.3, 167.3; IR (KBr): 3056, 2972, 2931, 2862, 1596, 1561, 1542, 1444, 1360, 1315, 1260, 1135, 1079, 1013, 750 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{14}N_2S$ $(M + H)^+$ 207.0687; found 207.0687.

6-Methyl-2-morpholinobenzo[_d_]thiazole (2a):



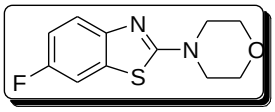
White solid; R_f = 0.50 (EtOAc : hexane (2:8); M.p. 134–136 °C (Lit.[103] 133–134 °C); ^1H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.56 (t, 4H, J = 4.8 Hz), 3.79 (t, 4H, J = 4.8 Hz), 7.09 (d, 1H, J = 8.0 Hz), 7.39 (s, 1H), 7.44 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 48. 6, 66.3, 119.0, 120.9, 127.4, 130.7, 131.6, 150.4, 168.6; IR (KBr): 2963, 2912, 2856, 1599, 1575, 1544, 1464, 1434, 1352, 1281, 1235, 1113, 1026, 943, 811 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{14}N_2OS$ $(M + H)^+$ 235.1035; found 235.1035.

6-Butyl-2-morpholinobenzo[_d_]thiazole (3a):



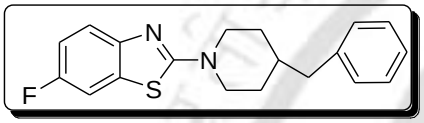
White solid; R_f = 0.5 (EtOAc : hexane (2:8); M.p. 61–63 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, J = 7.6 Hz), 1.33 (m, 2H), 1.58 (m, 2H), 2.61 (t, 2H, J = 8.0 Hz), 3.52 (t, 4H, J = 4.4 Hz), 3.74 (t, 4H, J = 4.4 Hz), 7.09 (d, 1H, J = 8.0 Hz), 7.38 (s, 1H), 7.47 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.2, 33.9, 35.4, 48.4, 66.1, 118.9, 120.1, 126.6, 130.6, 136.5, 150.5, 168.4; IR (KBr): 2953, 2920, 2856, 1538, 1462, 1375, 1340, 1290, 1231, 1110, 1072, 1032, 944, 877, 822, 658 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}N_2SO$ $(M + H)^+$ 277.0684; found 277.0687.

6-Fluoro-2-morpholinobenzo[*d*]thiazole (4a):



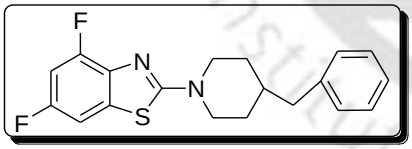
White solid; R_f = 0.42 (EtOAc : hexane (2:8); M.p. 157–158 ^oC (Lit.[62] 146–147.5 ^oC); ^1H NMR (400 MHz, $CDCl_3$): δ 3.51 (t, 4H, *J* = 4.8 Hz), 3.75 (t, 4H, *J* = 4.4 Hz), 6.97 (m, 1H), 7.25 (m, 1H), 7.44 (m, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 48.4, 66.1, 107.4, 107.6, 113.6, 113.9, 119.7, 119.8, 131.2, 131.4, 148.9, 157. 0, 159.4, 168.5; IR (KBr): 2982, 2901, 2863, 1673, 1597, 1538, 1459, 1376, 1343, 1287, 1234, 1181, 1111, 1073, 1029, 948, 920, 844 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}N_2OS$ F $(M + H)^+$ 239.0655; found 239.0662.

2-(4-Benzylpiperidin-1-yl)-6-fluorobenzo[*d*]thiazole (4c):



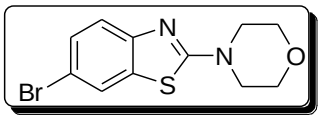
White solid; R_f = 0.43 (EtOAc : hexane (2:8); M.p. 108–109 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (m, 2H), 1.77 (m, 3H), 2.57 (d, 2H, *J* = 6.8 Hz), 3.03 (m, 2H), 4.06 (m, 2H), 7.02 (m, 1H), 7.17 (m, 2H), 7.29 (m, 4H), 7.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.4, 37.9, 42.9, 48.9, 107.2, 107.5, 113.3, 113.6, 119.2, 119.3, 126.1, 128.3, 129.1, 131.4, 131.6, 139.8, 149.4, 156.1, 159.1, 168.2; IR (KBr): 2924, 2850, 1606, 1545, 1457, 1380, 1327, 1240, 1155, 1097, 1053, 963, 817, 744 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{19}N_2S$ F $(M + H)^+$ 327.3331; found 327.3329.

2-(4-Benzylpiperidin-1-yl)-4,6-difluorobenzo[*d*]thiazole (4′c):



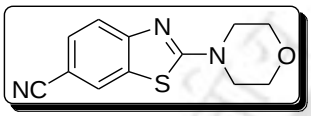
White solid; R_f = 0.45 (EtOAc : hexane (2:8); M.p. 123–124 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (m, 3H), 1.79 (m, 2H), 2.58 (d, 2H, *J* = 6.8 Hz), 3.06 (m, 2H), 4.10 (m, 2H), 6.80 (t, 1H, *J* = 7.2 Hz), 7.08 (d, 1H, *J* = 8.0 Hz), 7.14 (d, 2H, *J* = 7.2 Hz), 7.21 (d, 1H, *J* = 7.6 Hz), 7.29 (t, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.1, 37.5, 42.5, 48.7, 100.8, 101.1, 101.3, 102.9, 103.2, 116.5, 125.8, 128.1, 128.9, 133.1, 139.6, 150.7, 153.0, 156.2, 158.1, 167.9; IR (KBr): 3085, 3021, 2923, 2851, 1621, 1557, 1455, 1386, 1358, 1264, 1168, 1107, 1050, 992, 929, 828, 744,701 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}N_2S$ F_2 $(M + H)^+$ 345.1315; found 345.1312.

6-Bromo-2-morpholinobenzo[*d*]thiazole (5a):



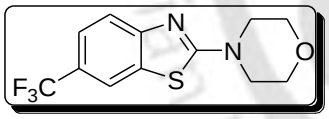
White solid; R_f = 0.43 (EtOAc : hexane (2:8); M.p. 165–167 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.57 (t, 4H, *J* = 4.8 Hz), 3.80 (t, 4H, *J* = 4.8 Hz), 7.37 (s, 2H), 7.68 (s, 1H); $^{13}CNMR$ (100 MHz, $CDCl_3$): δ 48.5, 66.3, 114.0, 120.5, 123.3, 129.4, 132.4, 151.6, 169.1; IR (KBr): 2918, 2857, 1591, 1535, 1443, 1372, 1280, 1258, 1229, 1110, 1026, 940, 863, 813 cm^{-1}. Anal. Calcd for $C_{11}H_{11}N_2OSBr$: C, 44.16; H, 3.71; N, 9.36; S, 10.72; found C, 44.23; H, 3.76; N, 9.28; S, 10.64.

2-Morpholinobenzo[d]thiazole-6-carbonitrile (6a):



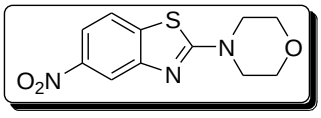
White solid; R_f = 0.30 (EtOAc : hexane (2:8); M.p. 173–175^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.57 (t, 4H, *J* = 4.8 Hz), 3.74 (t, 4H, *J* = 4.4 Hz), 7.42 (s, 2H), 7.75 (s, 1H);.^{13}C NMR (100 MHz, $CDCl_3$): δ 48.5, 66.0, 103.9, 119.2, 124.9, 130.0, 131.1, 155.9, 162.5, 171.0; IR (KBr): 2906, 2861, 2224, 1526, 1554, 1434, 1325, 1286, 1226, 1194, 1118, 1067, 1028, 949, 838 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{11}N_3OS$ $(M + H)^+$ 246.0702; found 246.0649.

6-(Trifluoromethyl)-2-morpholinobenzo[*d*]thiazole (7a):



White solid; R_f = 0.35 (EtOAc : hexane (2:8); Mp 118–120 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.57 (t, 4H, *J* = 4.8 Hz), 3.76 (t, 4H, *J* = 4.4 Hz), 7.48 (d, 1H, *J* = 8.4 Hz), 7.53 (d, 1H, *J* = 8.4 Hz, 7.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 48.5, 66.1, 118.2, 118.3, 119.0, 123.3, 123.4, 123.7, 126.0, 131.8, 155.2, 170.5 ^{19}F NMR ($CDCl_3$ + Hexafluoro Benzene); δ 100.7 (s); IR (KBr): 2973, 2949, 2921, 2898, 2863, 1571, 1541, 1378, 1321, 1291, 1232, 1161, 1115, 1085, 944, 832 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{11}F_3N_2OS$ $(M + H^+)$ 289.0629; found 289.0631.

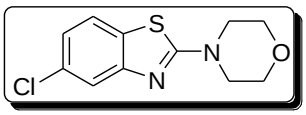
2-Morpholino-5-nitrobenzo[*d*]thiazole (8a):



Yellow solid; R_f = 0.35 (EtOAc : hexane (2:8); M.p. 172–174 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.60 (t, 4H, *J* = 4.8 Hz), 3.82 (t, 4H, *J* = 4.4 Hz), 7.64 (d, 1H, *J* = 8.4 Hz), 7.91 (d, 1H, *J* = 8.8 Hz), 8.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.5, 66.1, 113.9, 116.2, 120.8, 137.9, 146.9, 153.0, 154.1, 169.9, 170.3; IR (KBr):

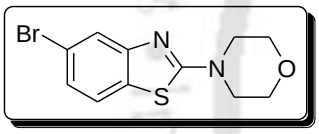
3095, 2972, 2914, 2865, 1602, 1579, 1528, 1508, 1449, 1428, 1343, 1282, 1233, 1119, 1068, 1022, 896, 873, 816 cm^{-1}; Anal. Calcd for $C_{11}H_{11}N_3O_3S$: C, 49.80; H, 4.18; N, 15.84; S, 12.09; found C, 49.83; H, 4.20; N, 15.82; S 12.12.

5-Chloro-2-morpholinobenzo[*d*]thiazole (9a):



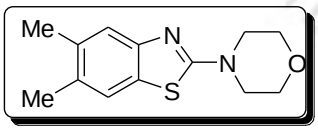
White solid; R_f = 0.40 (EtOAc : hexane (2:8); M.p. 122–124 ^oC ^1H NMR (400 MHz, $CDCl_3$): δ 3.56 (t, 4H, *J* = 4.8 Hz), 3.81 (t, 4H, *J* = 4.8 Hz), 7.18 (dd, 1H, J_1 = 8.4Hz, J_2 = 2.0 Hz), 7.43 (d, 1H, *J* = 8.4 Hz), 7.69 (d, 1H, *J* = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.5, 66.2, 119.3, 121.5, 121.8, 128.9, 132.0, 153.7, 170.1; IR (KBr): 3051, 2978, 2902, 2855, 1737, 1587, 1530, 147, 1375, 1325, 1279, 1234, 1142, 1116, 1070, 1035, 885, 872, 808, 678 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}N_2OSCl$ $(M + H)^+$ 255.0446; found 255.0446.

5-Bromo-2-morpholinobenzo[*d*]thiazole (10a):



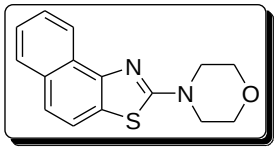
White solid; R_f = 0.45 (EtOAc : hexane (2:8); M.p. 118–120 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.56 (t, 4H, *J* = 4.8 Hz), 3.78 (t, 4H, *J* = 4.8 Hz), 7.01 (d, 1H, *J* = 8.4 Hz), 7.44 (d, 1H, *J* = 8.4 Hz), 7.50 (s 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.6, 66.3, 120.9, 121.9, 122.3, 124.6, 129.5, 154.1, 169.9; IR (KBr): 2924, 2853, 1526, 1443, 1338, 1230, 1110, 1068, 1030, 876, 800 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}N_2OSBr$ $(M + H)^+$ 300.9868; found 300.9870.

6,6-Dimethyl-2-morpholinobenzo[*d*]thiazole (11a):



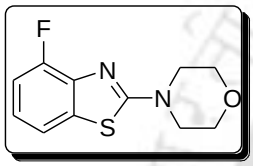
White solid; R_f = 0.55 (EtOAc : hexane (2:8); M.p. 156–158 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 3H), 2.28 (s, 3H), 3.55 (t, 4H, *J* = 4.4 Hz), 3.79 (t, 4H, *J* = 4.4 Hz), 7.34 (s, 1H), 7.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9, 20.2, 48.6, 66.4, 120.3, 121.2, 127.9, 130.7, 134.9, 151.0, 168.8; IR (KBr): 2966, 2916, 2857, 1612, 1537, 1444, 1375, 1343, 1283, 1227, 1140, 1114, 1069, 1042, 1020, 994, 899, 858 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{16}N_2OS$: $(M + H)^+$ 249.1161; found 249.1164.

2-Morpholinonaptho[1,2-*d*]thiazole (12a):



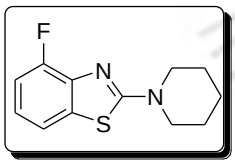
Pinkish solid; R_f = 0.5 (EtOAc : hexane (2:8); M.p 183–184 °C (Lit.[93] 183 –184 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (t, 4H, *J* = 4.8 Hz), 3.86.(t, 4H, *J* = 4.8 Hz), 7.58 (m, 3H), 7.98 (s, 1H), 8.23 (m, 1H), 8.57 (m, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 48.7, 66.4, 114.9, 122.4, 124.6, 125.5, 126.8, 126.7, 127.5, 127.9, 130.5, 148.5, 169; IR (KBr): 2961, 2844, 1568, 1531, 1496, 1451, 1393, 1351, 1278, 1226, 1156, 1112, 1080, 1035, 910, 758 cm^{-1}; Anal. Calcd for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36; S, 11.86; found C, 66.70; H, 5.24; N, 10.27; S, 11.79.

4-Fluoro-2-morpholinobenzo[*d*]thiazole (13a):



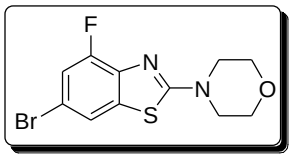
White solid; R_f = 0.45 (EtOAc : hexane (2:8); M.p. 122–123 °C (Lit.[58] 122–122.5 °C) ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.62 (t, 4H, *J* = 4.8 Hz), 3.80 (t, 4H, *J* = 4.8 Hz), 6.98–7.04 (m, 2H), 7.34–7.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.5, 66.2, 112.3($^2J_{CF}$ = 73.2 Hz), 116.5, 122.1 ($^2J_{CF}$ = 23.6 Hz), 133.1, 152.2, 154.7, 169.0; ^{19}F NMR ($CDCl_3$ + Hexafluoro Benzene) δ 35.6; IR (KBr): 2931, 2917, 2865, 1610, 1542, 1474, 1375, 1336, 1282, 12, 1121, 949, 927, 780 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}N_2OSF$ (M + H$^+$) 239.0616; found 239.0619.

4-Fluoro-2-(piperidin-1-yl)benzo[*d*]thiazole (13b):



White solid; R_f = 0.45 (EtOAc : hexane (2:8); M.p. 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (s, 6H), 3.54 (s, 4H), 6.88–6.98 (m, 2H), 7.26-7.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 25.3, 49.6, 111.8, 112.0, 116.2, 116.3, 121.1, 121.2, 133.3, 151.8, 154.3, 168.7; ^{19}F NMR ($CDCl_3$ + Hexafluoro Benzene) δ 35.1; IR (KBr): 2934, 2853, 1597, 1548, 1442, 1385, 1359, 1289, 1232, 1135, 1056, 1009, 911, 855, 771 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{13}N_2SF$ (M + H)$^+$ 237.0857; found 237.0857.

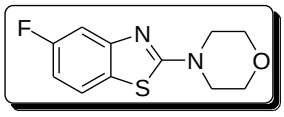
6-Bromo-4-fluoro-2-morpholinobenzo[*d*]thiazole (16a):



White solid; R_f = 0.45 (EtOAc : hexane (2:8); M.p. 103–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.61 (t, 4H, *J* = 4.8 Hz), 3.79 (t, 4H, *J* = 4.8 Hz), 6.98-7.18 (m, 1H,), 7.33–746 (m, 1H); ^{13}C NMR (100 MHz,

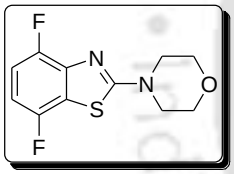
$CDCl_3$): δ 48.6, 66.3, 112.2, 112.4, 116.1, 16.3, 116.6, 119.3, 122.0, 122.1, 129.4, 154.8, 169.0; ^{19}F NMR ($CDCl_3$ + Hexafluoro Benzene) δ 35.7, 38.3; IR (KBr): 2922, 2857, 1608, 1544, 1445, 1375, 1283, 1232, 1232, 1114, 1031, 953, 805 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{10}FBrN_2OS$ $(M + H)^+$ 318.9728; found 318.9731.

5-Fluoro-2-morpholinobenzo[*d*]thiazole (17a):



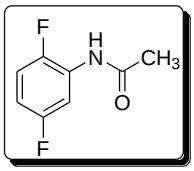
White solid; R_f = 0.45 (EtOAc : hexane (2:8); M.p. 110–111 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.50 (t, 4H, J = 4.4 Hz), 3.71 (t, 4H, J = 4.4 Hz), 6.73 (m, 1H), 7.17 (m, 1H), 7.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.5, 66.2, 106.0, 106.3, 109.3, 109.5, 121.2, 121.3, 125.8, 153.8, 153.9, 161.0, 163.4, 170.7; IR (KBr): 2971, 2918, 2852, 1610, 1528, 1446, 1339, 1286, 1231, 1117, 1033, 930, 899, 874, 806, 690 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}N_2OS\,F$ $(M + H)^+$ 239.0655; found 239.0662.

4,7-Difluoro-2-morpholinobenzo[*d*]thiazole (17′a):



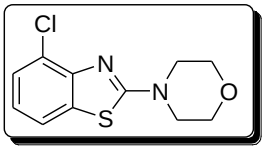
White solid; R_f = 0.40 (EtOAc : hexane (2:8); M.p. 159–160 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.57 (t, 4H, J = 4.8 Hz), 3.75 (t, 4H, J = 4.8 Hz), 6.66 (m, 1H), 6.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 48.5, 66.1, 107.0, 107.1, 107.2, 107.3, 112.3, 112.4, 112.5, 112.6, 118.9, 119.1, 142.5, 142.7, 148.4, 150.9, 151.4, 153.8, 169.3; IR (KBr): 3076, 2926, 1551, 1492, 1398, 1340, 1267, 1236, 1116, 1038, 947, 806, 750 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{10}N_2OS\,F_2$ $(M + H)^+$ 257.0579; found 257.0581.

***N*-(2,5-Diflurophenyl)acetamide (17i):**



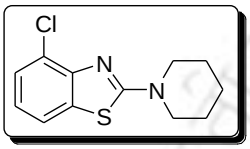
White solid; R_f = 0.50 (EtOAc : hexane (2:8); M.p. 131–133 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H), 6.71 (m, 1H), 7.00 (m, 1H), 7.78 (brs, 1H), 8.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6, 108.9, 109.2, 110.0, 110.1, 110.3, 115.1, 115.2, 115.3, 115.4, 127.3, 149.6, 157.4, 159.8, 168.8. IR (KBr): 3302, 3274, 2917, 1671, 1629, 1544, 1484, 1434, 1367, 1327, 1257, 1240, 1190, 1140, 1017, 971, 872, 804, 726 cm^{-1}; HRMS (ESI) calcd for $C_8H_7NO\,F_2$ $(M + H)^+$ 172.0541; found 172.0539.

4-Chloro-2-morpholinobenzo[*d*]thiazole (18a):



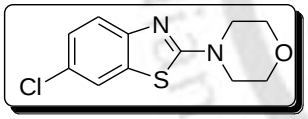
White solid; R_f = 0.50 (EtOAc : hexane (2:8); M.p. 101–102 ^oC (Lit.[58] 101-102 ^oC); ^1H NMR (400 MHz, $CDCl_3$): δ 3.57 (t, 4H, *J* = 4.4 Hz), 3.75 (t, 4H, *J* = 4.8 Hz), 6.92 (t, 1H, *J* = 8.0 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 7.41 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.5, 66.2, 119.3, 120.8, 122.0, 126.4, 131.8, 149.6, 169.0; IR (KBr): 2970, 2865, 1589, 1538, 1442, 1412, 1375, 1281, 1237, 1117, 1035, 945, 777 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}ClN_2OS$ $(M + H)^+$ 255.0446; found 255.0449.

4-Chloro-2-(piperidin-1-yl)benzo[*d*]thiazole (18b):



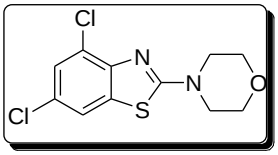
Gummy; R_f = 0.50 (EtOAc : hexane (2:8); ^1H NMR (400 MHz, $CDCl_3$): δ 1.67 (s, 6H), 3.60 (s, 4H), 6.92 (t, 1H, *J* = 8.0 Hz), 7.26 (d, 1H, *J* = 8.0 Hz), 7.43 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 25.5, 49.7, 119.2, 121.2, 121.4, 126.3, 132.0, 150.1, 168.9; IR (KBr): 2935, 2853, 1589, 1537, 1446, 1415, 1249, 1212, 1106, 1015 cm^{-1}; Anal. Calcd for $C_{12}H_{13}N_2SCl$: C, 57.02; H, 5.18; N, 11.08; S, 12.69; found C, 57.12; H, 5.26; N, 11.05; S, 12.71.

6-Chloro-2-morpholinobenzo[*d*]thiazole (19a):



White solid; R_f = 0.45 (EtOAc : hexane (2:8); M.p. 144–145 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.61 (t, 4H, *J* = 4.8 Hz), 3.81 (t, 4H, *J* = 5.2 Hz), 7.19 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.0 Hz), 7.39 (d, 1H, *J* = 8.8 Hz), 7.49 (d, 1H, *J* = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.4, 66.1, 119.9, 120.4, 126.5, 126.7, 131.8, 151.2, 169.0; IR (KBr): 2943, 2919, 2859, 1594, 1537, 1447, 1330, 1279, 1233, 1110, 1027, 940, 814 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}N_2OSCl$ $(M + H)^+$ 255.0446; found 255.0448.

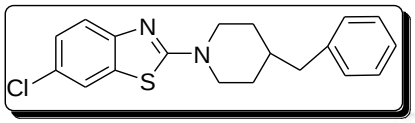
4, 6-Dichloro-2-morpholinobenzo[*d*]thiazole (19′a):



White solid; R_f = 0.42 (EtOAc : hexane (2:8); M.p. 141–142 ^oC ; ^1H NMR (400 MHz, $CDCl_3$): δ 3.51 (t, 4H, *J* = 4.4 Hz), 3.74 (t, 4H, *J* = 4.8 Hz), 7.30 (d, 1H, *J* = 2.0 Hz), 7.43 (d, 1H, *J* = 2.0 Hz); ^{13}C NMR (100

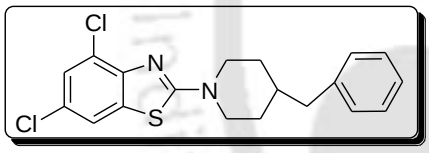
MHz, $CDCl_3$): δ 48.4, 66.2, 119.1, 123.9, 126.4, 126.5, 132.4, 148.4, 168.9; IR (KBr): 3060, 2856, 1587, 1536, 1431, 1380, 1336, 1275, 1231, 1115, 1070, 1026, 942 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{10}Cl_2N_2OS$ $(M + H)^+$ 289.0002; found 289.0002.

2-(4-Benzylpiperidin-1-yl)-6-chlorobenzo[*d*]thiazole (19c):



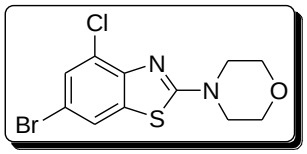
Gummy; R_f = 0.52 (EtOAc : hexane (2:8); ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (m, 3H), 1.75 (d, 2H, *J* = 11.2 Hz), 2.56 (d, 2H, *J* = 7.6 Hz), 3.05 (m, 2H), 4.07 (m, 2H), 7.13 (d, 2H, *J* = 8.4 Hz), 7.19 (m, 2H), 7.28 (m, 2H), 7.39 (d, 1H, *J* = 8.4 Hz), 7.51 (d, 1H, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.1, 37.5, 42.6, 48.6, 119.2, 120.0, 125.9, 126.0, 128.1, 128.9, 131.9, 139.5, 151.5, 168.4; IR (KBr): 2919, 2851, 1591, 1530, 1439, 1374, 1281, 1161, 1100, 1048, 965, 805, 699 cm^{-1}; HRMS (ESI) calcd for Anal. Calcd for $C_{19}H_{19}N_2S$ Cl: C, 66.55; H, 5.92; N, 8.17; S, 9.35; found C, 66.58; H, 5.96; N, 8.21; S, 9.38.

2-(4-Benzylpiperidin-1-yl)-4,6-dichlorobenzo[*d*]thiazole (19′c):



Gummy; R_f = 0.52 (EtOAc : hexane (2:8); ^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (m, 3H), 1.77 (m, 3H), 2.56 (d, 2H, *J* = 6.8 Hz), 3.06 (m, 1H), 4.09 (m, 2H), 7.15 (d, 2H, *J* = 7.2 Hz), 7.23 (m, 2H), 7.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.4, 37.8, 42.8, 48.9, 118.9, 120.3, 123.3, 125.6, 126.2, 128.4, 129.1, 132.7, 139.7, 148.9, 168.5; IR (KBr): 3076, 2926, 1551, 1492, 1398, 1340, 1267, 1236, 1116, 1038, 947, 806, 750 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}N_2S$ Cl_2 $(M + H)^+$ 379.0649; found 379.0649.

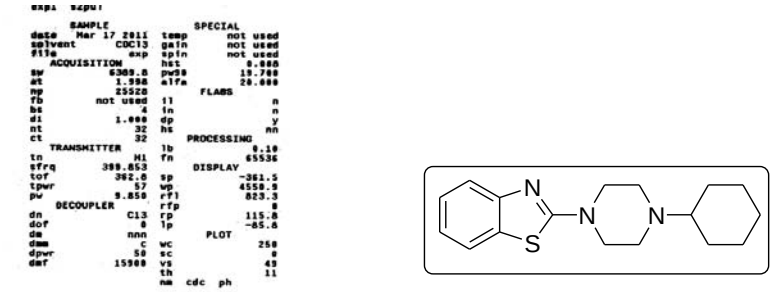
6-Bromo-4-chloro-2-morpholinobenzo[d]thiazole (20a):

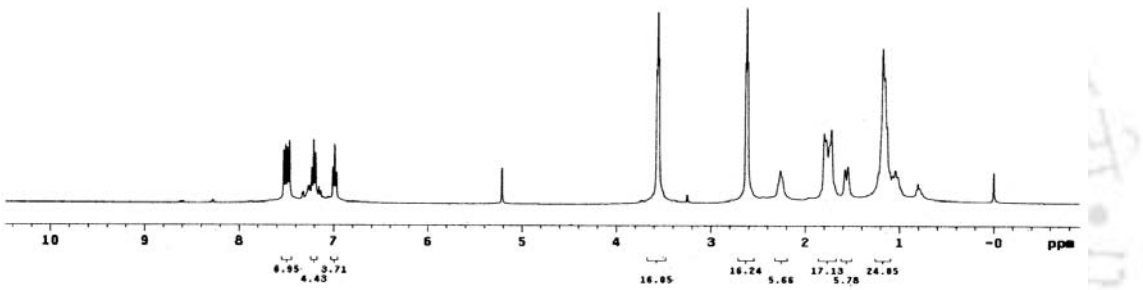


White solid; R_f = 0.45 (EtOAc : hexane (2:8); M.p. 158–159 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.57 (t, 4H, *J* = 4.8 Hz), 3.77 (t, 4H, *J* = 4.8 Hz), 7.39 (d, 1H, J_1 = 2.0 Hz), 7.52 (d, 1H, *J* = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.4, 66.1, 113.1, 121.8, 124.2, 129.0, 132.9, 148.8, 168.8; IR (KBr): 2922, 2857, 1637, 1589, 1533, 1429, 1375, 1333, 1230, 1115, 1031, 941, 835, 635 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{10}N_2OSClBr$ $(M + H)^+$ 334.9389; found 334.9384.

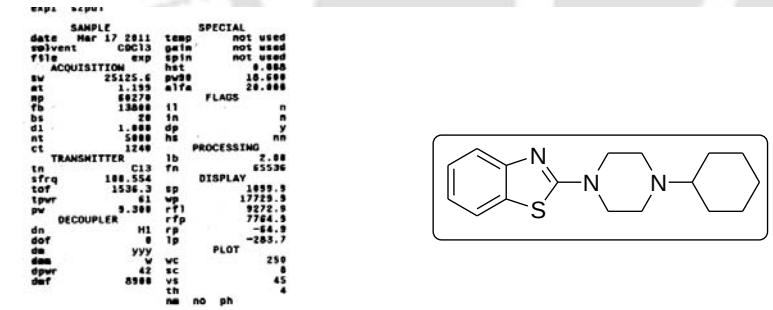
IV.9. Spectra

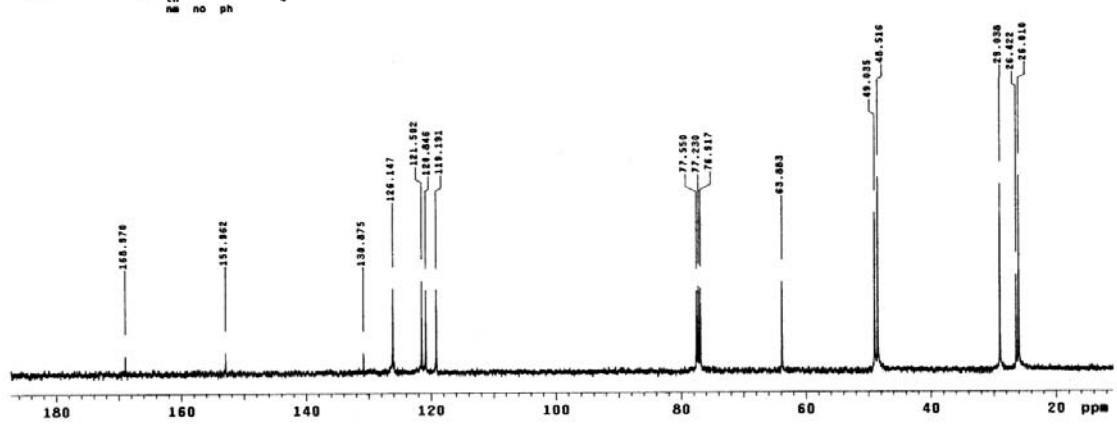
2-(4-Cyclohexylpiperazin-1-yl)benzo[*d*]thiazole (1f): ^{1}H NMR (400 MHz, $CDCl_3$):



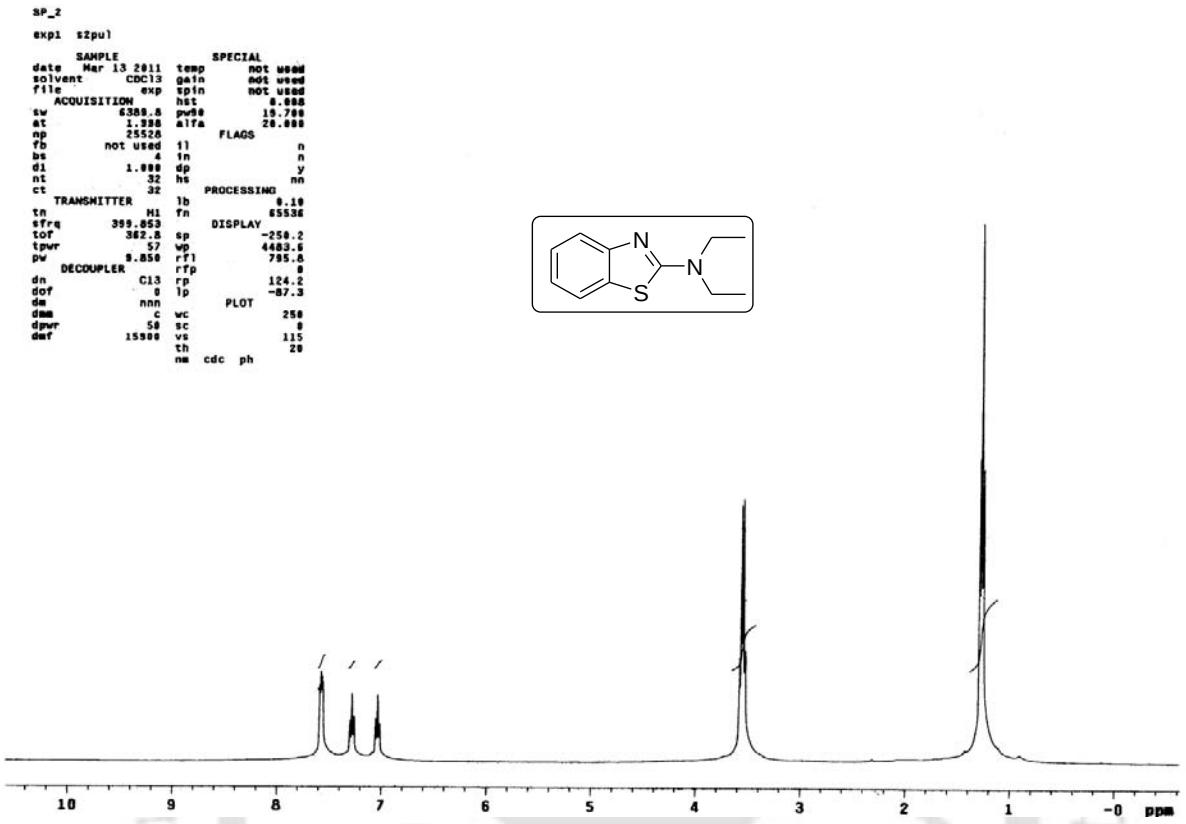


2-(4-Cyclohexylpiperazin-1-yl)benzo[*d*]thiazole (1f): ^{13}C NMR (100 MHz, $CDCl_3$):

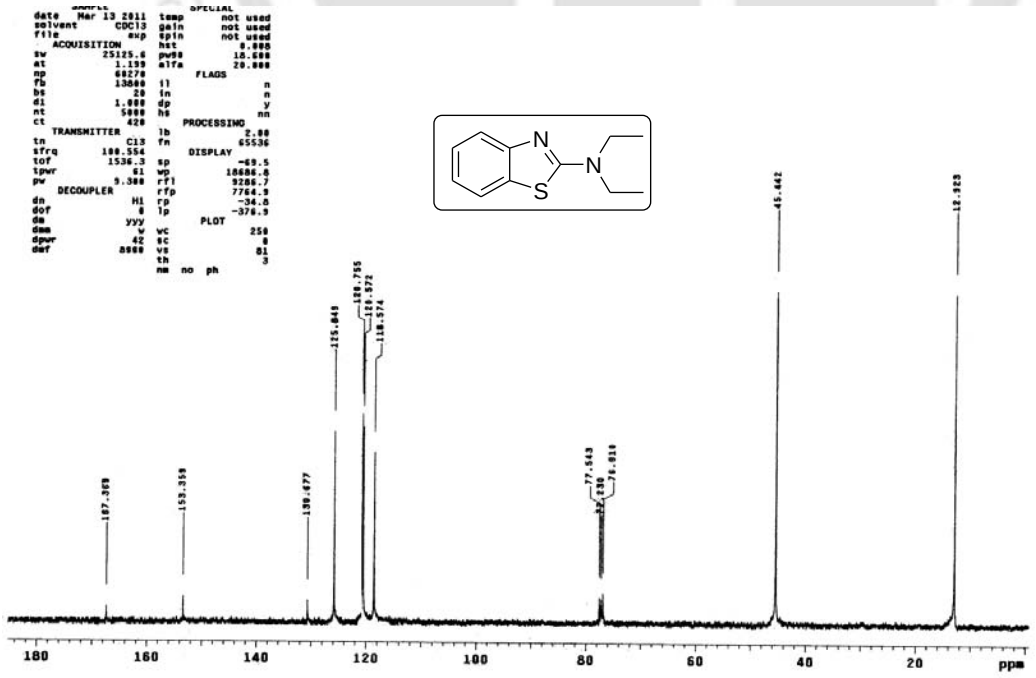




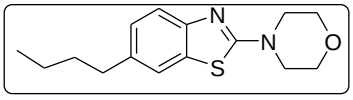
_N_, _N_-Diethylbenzo[_d_]thiazole-2-amine (1h): ^{1}H NMR (400 MHz, $CDCl_3$):

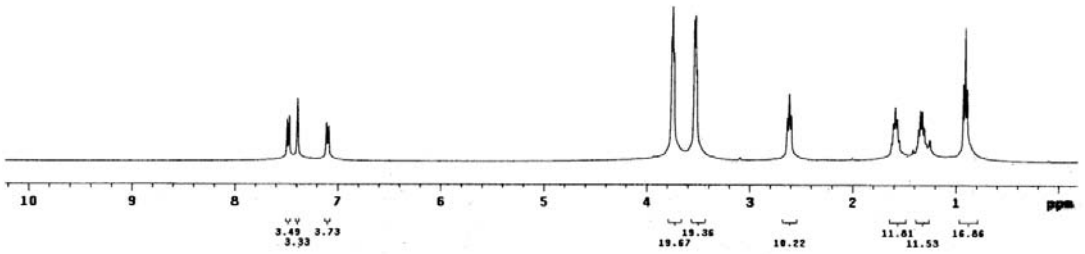


_N_, _N_-Diethylbenzo[_d_]thiazole-2-amine (1h): ^{13}C NMR (100 MHz, $CDCl_3$):

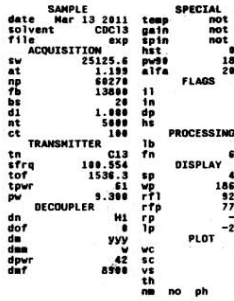


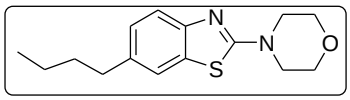
6-Butyl-2-morpholinobenzo[*d*]thiazole (3a):^{1}H NMR (400 MHz, $CDCl_3$):

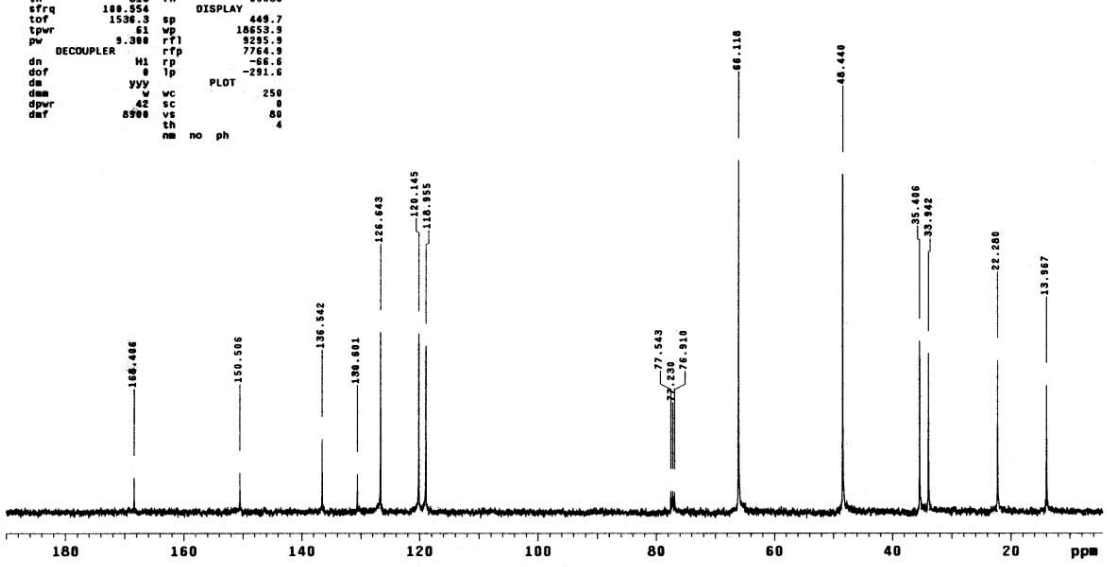




6-Butyl-2-morpholinobenzo[*d*]thiazole (3a):^{13}C NMR (100 MHz, $CDCl_3$):







CHAPTER III

III. Copper(II) Catalyzed Chemoselective Oxidative Transformation of Thiourea to Thioamidoguanidine / 2-Aminobenzothiazole

III.1. Structure and Nomenclature

Details of nomenclature of heterocycles were discussed in CHAPTER I.

III.2. Importance and Applications

The guanidine possessing molecules are capable of catalyzing organic reactions, used as a super base and exhibits a variety of co-ordination modes leading to compatibility with a wide range of metal ions.[1] Futher, the compound possessing thioamido and guanidine moieties might be act as herbicides.[2a] The compounds (**I**) and (**II**) can act as metal scavenger and may be used as vulcanising agent (*Figure III.2.1*).[2b] The detail applications of 2-aminobenzothiazoles are discussed in chapter II, section II.2.

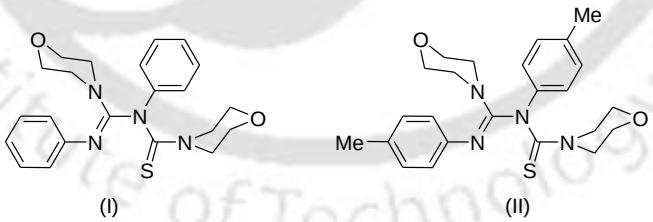
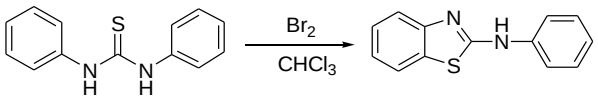


Figure III.2.1. *Synthetically important thiamidogunidino compounds*

III.3. Existing Synthetic Methods

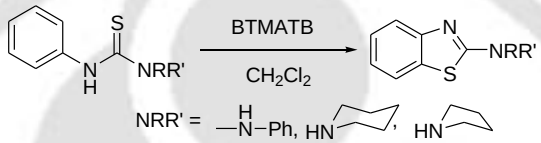
The classical Hugerschoff reaction known since 1901, involves the reaction of molecular bromine (Br_2) with 1,3-dirylthiourea in chloroform medium to produce 2-amino benzothiazole

(*Scheme III.3.1*).[3] This reaction essentially involves the intramolecular aromatic electrophilic substitution reaction of an aryl ring to the thiocarbonyl group of a thiourea is facilitated by thiophilic bromine.



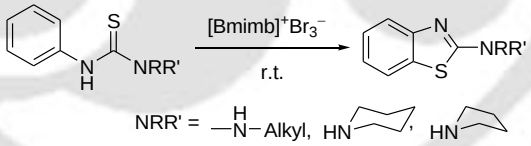
Scheme III.3.1. *Synthesis of 2-aminobenzothiazoles using Br_2*

Jordan *et al.* have been synthesized 2-aminobenzothiazole using benzyltrimethyl ammoniumtribromide ($PhCH_2NMe_3Br_3$), a bromine equivalent from secondary amine substituted thiourea (*Scheme III.3.2*).[4]



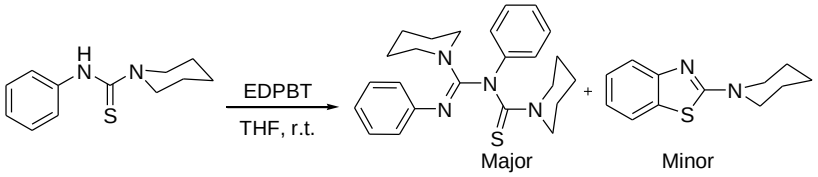
Scheme III.3.2. *Synthesis of 2-aminobenzothiazoles using Br_2 equivalent*

Further, Le *et al*. have also reported similar result, but a different bromine equivalent *i.e.* 1-butyl-3-methylimidazolium $[Bmim]^+Br_3^-$ (1-butyl-3-methylimidazolium tribromide) in the preparation of 2-aminobenzothiazoles from 1,3-diarylthiourea and aryl-*sec*-alkyl thioureas at room temperature (*Scheme III.3.3*).[5]



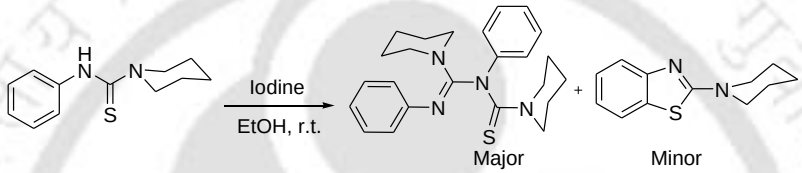
Scheme III.3.3. *Synthesis of 2-aminobenzothiazoles using brominating reagent*

Recently, our group have been demonstrated the synthesis of major thioamido- guanidino moiety and minor 2-aminobenzothiazole while using the similar kind of brominating reagents EDPBT[6] (1,1'(ethane-1,2-diyl)dipyridinium bistribromide) from secondary amine substituted thiourea (*Scheme III.3.4*). This methodology was sharp contrast to the recent reported by Jordan[4] and Le[5] *et al.* where 2-aminobenzothiazole is reported as the major product.



Scheme III.3.4. *Synthesis of thioamidoguanidino and 2-aminobenzothiazoles using EDPBT*

This same observation is consistent with our recent report on the formation of thioamido guanidino moiety rather than the expected 2-aminobenzothiazole (Hugerschoff product) when the *in situ* generated thiourea, aryl-*sec*-alkyl thiourea was treated with molecular iodine (*Scheme III.3.5*).[7]



Scheme III.3.5. *Synthesis of thioamidoguanidino and 2-aminobenzothiazoles using iodine*

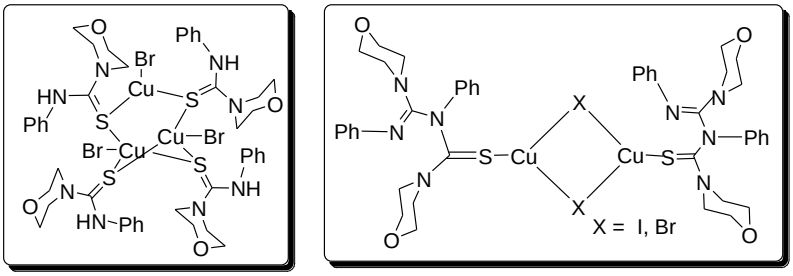
Regarding Cu-catalyzed synthesis of 2-aminobenzothiazoles has been discussed in chapter II and sections II.3.

III.4. Present Work

This chapter has been mainly divided into two parts. Part III.4.A highlights the mechanistic investigation of thioamidoguanidino (Tag) formation and redox activity of Cu(II) salts, where as part III.4.B describes the various substrates scope for the synthesis of thioamidoguanidine moieties and 2-aminobenzothiazoles from aryl-alkyl unsymmetrical thioureas using Cu(II) catalyst.

III.4.A. Stable Cu(I) Complexes with Thioamidoguanidine Possessing Halide-Bridge Structure

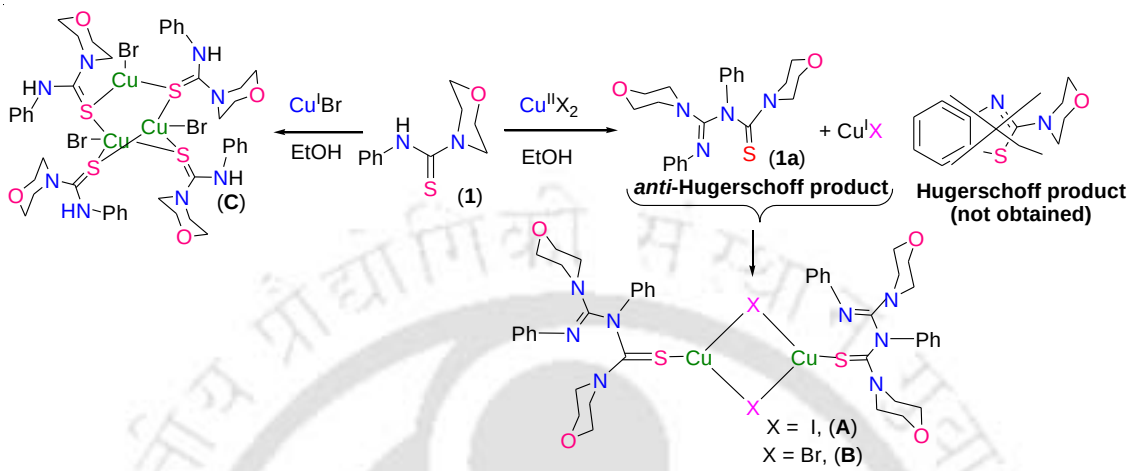
This part illustrate mainly the redox activity of Cu^{II} salt and formation of Cu^{I}(Tag) complex.



Formation of $[Cu_2^{I}(\mu{-}X)_2Tag_2]$ complex and $Cu^{I}_3S_4Br_3$ cluster from aryl-sec-alkyl unsymmetrical thiourea (Tu) using $Cu^{II}X_2$ and $Cu^{I}X$ salts

The classical Hugerschoff reaction known since 1901 involves the reaction of molecular bromine (Br2) with 1,3-diarylthiourea in chloroform to produce 2-aminobenzothiazole.[3] However, the products obtained by the reaction of aryl-sec-alkyl unsymmetrical thioureas (**1**) with bromine or its equivalents are different ones. While Jordan *et al.*[3] and Le *et al.*[4] have reported the formation of 2-aminobenzothiazole (Hugerschoff) as the exclusive product for certain substrates, we have reported the formation of thioamidoguanidine (Tag) (*anti*-Hugerschoff product) (**1a**) as the exclusive or major product.[6] The use of molecular iodine instead of bromine also gave an identical result, thus further supporting our proposition.[7] The formation of thioamidoguanidine (Tag) (**1a**) essentially involved an oxidative dimerization (S−S bond formation) of an unsymmetrical thiourea followed by an intramolecular iminedisulfide rearrangement.[6] During the formation of the Hugerschoff product the thiophilic bromine activates the sulfur of a thiourea toward an intramolecular aromatic electrophilic substitution reaction while it acts as a mere oxidizing (S−S bond forming) agent during the formation of a thioamidoguanidino (Tag) moiety. Taking clues from the above observations we thought of using another mild thiophilic environmentally benign redox-active metal which would only promote oxidative dimerization of thiourea leading to the exclusive formation of the thioamidoguanidine (Tag)/*anti*-Hugerschoff product (**1a**). If this strategy works, a competitive formation of Hugerschoff product could be avoided as was the case using bromine[6] and iodine[7] and only anti-Hugerschoff product could be achieved. Ideally salts of Cu^{II} suit the above envisaged strategy. Treatment of thiourea (Tu) with Cu^{II} salt gave our anticipated thioamidoguanidine (Tag) product along with the formation of an unprecedented Cu^{I} complex with Tag (**1a**). The reduction of Cu^{II} to Cu^{I} is at the expense of thiourea getting oxidized to

corresponding disulfide. Herein, we report the synthesis of a $[Cu_2^{I}(\mu\text{-}X)_2Tag_2]$ (**A** and **B**) complex and an air stable cluster $[Cu^{I}_3(\mu_2\text{–}S)_4Tu_4Br_3]$ (**C**) from thiourea (Tu) using $Cu^{II}X_2$ and $Cu^{I}Br$ salts, respectively (*Scheme III.4.A.1*).[8]



Scheme III.4.A.1. *Formation of $[Cu_2^{I}(\mu\text{–}X)_2Tag_2]$ complex (**A** and **B**) and cluster **C***

The in situ generated unsymmetrical thiourea (Tu) (**1**) obtained by reacting phenylisothiocyanate and morpholine in EtOH was treated with CuI_2. The greenish color of CuI_2 disappeared giving a pale yellow precipitate and leaving behind a pale yellow solution. A portion of this precipitate was dissolved in ethanol and was left aside for crystallization which gave a rod shaped pale yellow crystal **A**. The molecular structure of **A** was determined by X-ray crystallographic analysis (*Figure III.4.A.1*). As revealed from the structure, the ligand bound to the Cu centers is nothing but the thioamidoguanidine (Tag) product (**1a**). In keeping with our earlier observations,[6,7] it can be speculated that Cu^{II} being oxidizing in nature oxidizes thiourea in to a disulfide intermediately which then undergoes an imine disulfide rearrangement to give the Tag moiety; during the process, Cu^{II} gets reduced to Cu^{I}. The ligand (Tag) (**1a**) was isolated from the complex **A** by removing the Cu either using a disodium salt of ethylenediaminetetraacetic acid (EDTA) or an aqueous ammonia solution, and the product was characterized by spectroscopic analysis. No Hugerschoff product (2-aminobenzothiazole) was isolated from the reaction mixture (*Scheme III.4.A.1*). The ligand (**1a**) having a soft sulfur atom reacts with the soft Cu^{I} center to form complex **A** (*Scheme III.4.A.1*). The two Cu^{I} centers in the bimetallic complex A are held by two iodide ions. The EPR silence (*Figure III.4.A.2*),

diamagnetic nature ($\mu_{eff} = 0$), and the absence of d−d transition in the UV−vis spectrum (*Figure III.4.A.3*) support the existence of the (+1) oxidation state for copper in complex **A**.[9]

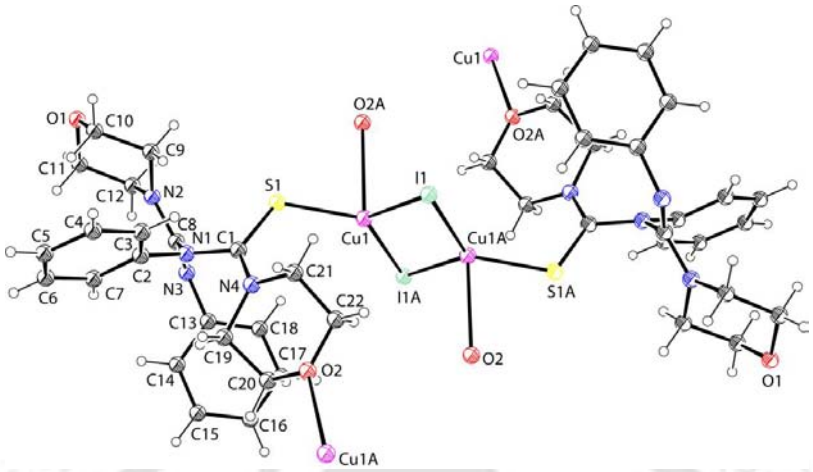


Figure III.4.A.1. *ORTEP view (30% probability ellipsoids) of compound **A***

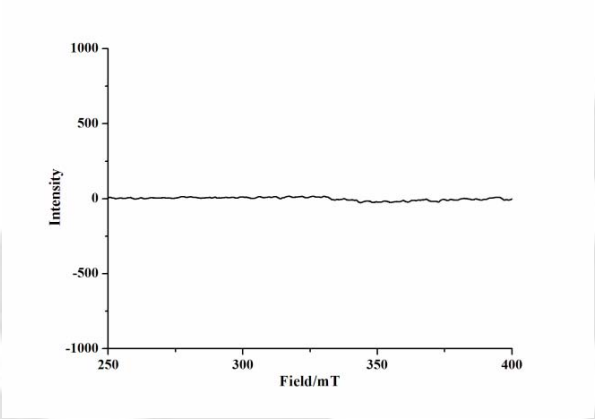


Figure III.4.A.2. *EPR Spectrum of complex **A***

Further, the reduction of Cu^{II} to Cu^{I} by the thiourea (Tu) has been independently confirmed by UV−vis titration. The d−d transition exhibited by green colored CuI_2 at λ_{max} = 804 nm in EtOH:H_2O (9:1) disappeared upon addition of an equivalent of thiourea (**1**) (*Figure III.4.A.3*). Encouraged by the presence of an interesting structural motif in complex **A**, the in situ generated thiourea (**1**) was then treated with $CuBr_2$ instead of CuI_2. Here, also similar observations were noticed (EPR silence; *Figure III.4.A.4*). The resultant compound **B** was crystallized from ethanol giving a rod shaped pale yellow crystal. X-ray crystallographic analysis of complex **B** showed an equally interesting structural motif to that of **A** (*Figure III.4.A.5*).

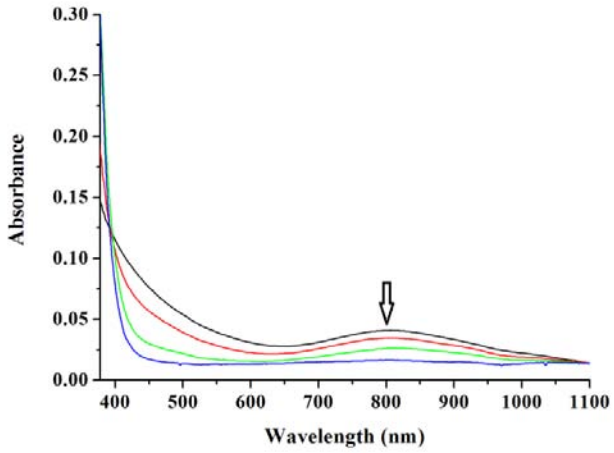


Figure III.4.A.3. *Supporting evidence for reduction of Cu(II) to Cu(I)*

UV−visible spectra of the reaction of CuI_2 solution (Black trace) (λ_{max} = 804 nm) in EtOH:H_2O (9:1) solvent at room temperature. Red, green and blue traces represent the spectral change at an intermediate stage and after complete reduction of Cu(II) to Cu(I), respectively. (i) Black line–CuI_2 solution spectra. (ii) Red line–CuI_2 solution + 0.25 equiv. Ligand **1**. (iii) Green line–CuI_2 solution + 0.5 equiv. Ligand **1**. (iv) Blue line–CuI_2 solution + 1 equiv. Ligand **1**.

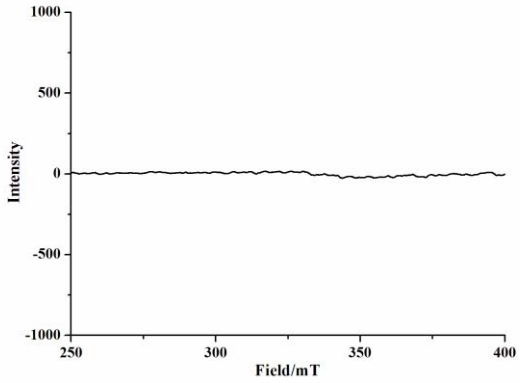


Figure III.4.A.4. *EPR Spectrum of complex* ***B***

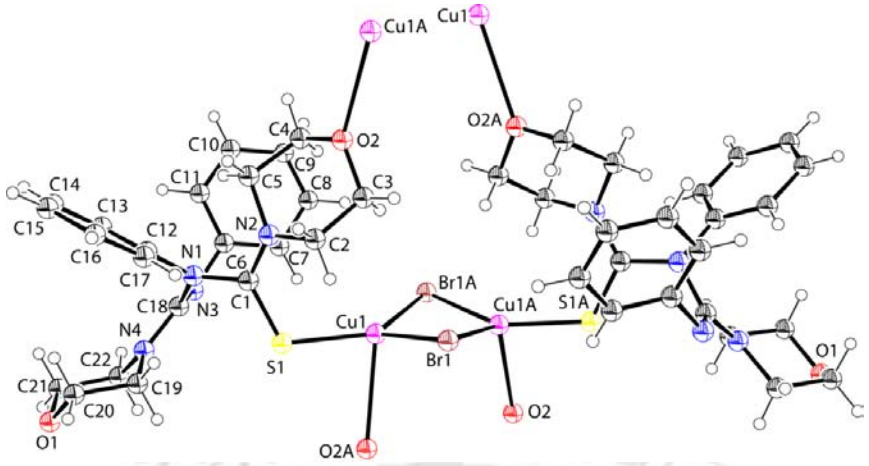


Figure III.4.A.5. *ORTEP view (30% probability ellipsoids) of complex* ***B***

A plethora of Cu^{I} complexes prepared in the literature is by the treatment of various ligands containing soft centers with salts of Cu^{I}, and there are only few examples where it is prepared from Cu^{II} salts. In the latter case Cu^{II} is reduced in situ to Cu^{I} in the presence of an external reducing agent.[9] In the present case, the complexes of Cu^{I}, **A** and **B** are prepared from their respective $Cu^{II}X_2$ (X = I, Br) salts which act as the source for Cu^{I} generated *in-situ* upon reduction by thiourea (Tu) (**1**). The thiourea get transformed to the Tag unit (**1a**) by an oxidative dimerization (S−S bond formation) followed by an imine-disulfide rearrangement. The Tag unit binds to the in situ generated Cu^{I} giving complexes **A** and **B**, a process not documented in the literature so far. Due to the presence of soft sulfur atom in thioureas and substituted thioureas, they are effective ligands for Cu^{I} salts.[10a] Unlike Cu^{II}, generally Cu^{I} centers can have variable coordination numbers ranging from 2 to 4.[10b]

The isolated thioamidoguanidino (Tag) (**1a**) ligand has no affinity for $Cu^{II}X_2$ (X = I, Br) salts whereas it has strong affinity toward Cu^{I} and forms complexes **A** and **B** when treated with CuI and CuBr, respectively. With the reduced form of Cu, i.e Cu^{I}, no transformation of thiourea (Tu) (**1**) to thioamidoguanidino (Tag) (**1a**) was observed thus supporting the redox mechanism. Interestingly, the in situ generated thiourea (**1**) forms a cluster with a $Cu^{I}_3S_4Br_3$ core **C** (*Figure III.4.A.6*) when treated with $Cu^{I}Br$ (EPR silence; *Figure III.4.A.7*). A vast array of Cu^{I} clusters are known where sulfur atom of thioureas behaves as SAB,[10a,11] but it is often difficult to predict as to when sulfur and halides behave as the SAB and when as monodentate.

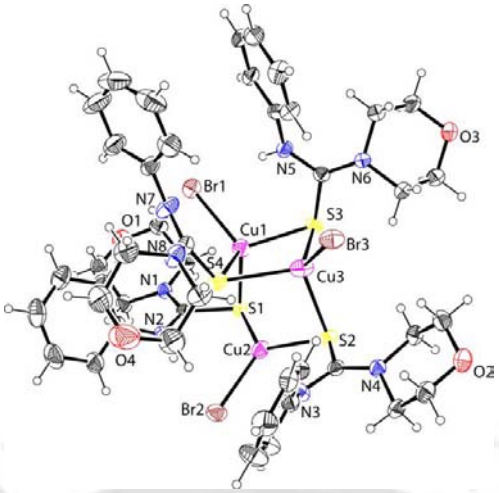


Figure III.4.A.6. *ORTEP view (30% probability ellipsoids) of complex* ***C***

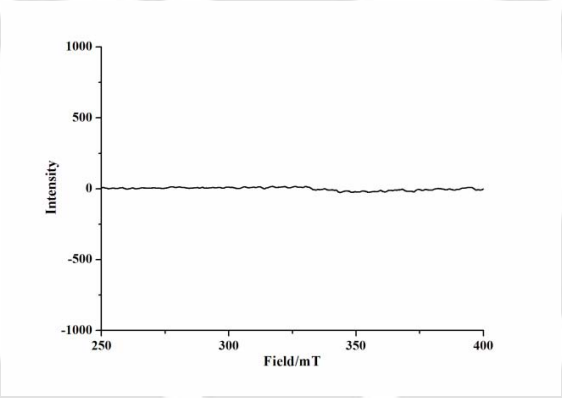


Figure III.4.A.7. *EPR Spectrum of complex* ***C***

Crystal structure of $[Cu_2^I(\mu\text{–}X)_2Tag_2]_n$ (X = I (A), Br (B): Compounds **A** and **B** are crystallized in space group C2/c and Pccn, respectively contains a dimeric core of $[Cu_2(\mu\text{–}X)_2]$. As shown in *Figure* (*III.4.A.1* and *III.4.A.*5), the asymmetric unit of compound **A** and **B** contains a distorted tetrahedral Cu^I centers bridged by two halogen atoms via $Cu_2(\mu\text{–}X)_2$ bridge and one mono-dentate sulfur atom (Tag moiety) in the basal plane and one morpholine–O atom of another Tag moiety directed axially. The axially coordinating morpholine–O atom is nearly perpendicular to the virtual $[Cu_2(\mu\text{–}X)_2Tag_2]$ plane. In compound **A** and **B**, the distortion form the regular tetrahedron geometry is evident from the bond angles around Cu^I centre (*Table III.4.A.1*). Compound **A** is centrosymmetric due to *trans* orientation of the two Tag unit whereas the compound **B** is non-centrosymmetric due to its *cis* orientation. As can be seen from the crystal structure of (**A**) and (**B**) despite the presence of several hard nitrogen atoms in the Tag-ligand (**1a**) only soft sulfur and halogen atoms are coordinating to the Cu^I centers. Such mono-

dentate sulfur co-ordination mode are rarely found in the literature.[12] Due to the presence of two or more lone pairs in a single atom, halogens (Cl, Br and I) and sulfur atoms are ideal candidates for single-atom-bridging (SAB), an efficient contributor to metal-organic networks (MONs). Similar type of four coordinated Cu^{I} bridge by a pair of iodide $[Cu_2(\mu\text{–}I)_2]$ and thiocarbonyl sulfur $[Cu_2(\mu\text{–}S_2)]$ atoms each acting as SAB's is reported.[13] In compounds **A** and **B**, comparison of bond angles around the Cu^{I} centers (*Table III.4.A.1.1*), indicates that the latter is more distorted than former. In both complexes **A** and **B**, the central $Cu_2(\mu\text{–}X)_2$ core is rhomboidal with a bridging bond distances of Cu–I (2.59 Å) and Cu–Br (2.45 Å) very close to their terminal Cu–I (2.58 Å) and Cu–Br (2.43 Å) bond distances. The angles in the core of (**A**) is 65.82(3)^{o} for Cu1–I1–Cu1A and 114.18(4)^{o} for I1–Cu1–I1A. Similar $Cu_2(\mu\text{–}I)_2$ motif where the copper is tetra-coordinated, the bond angles are 56.3^{o} for I1–Cu1–I1(A) and 123.7^{o} for Cu1–I1–Cu1A.[9b] The angles in the core of (**B**) are 103.14(4)^{o} for Br1–Cu1–Br1A and 74.50(3)^{o} for Cu1–Br1–Cu1A. Similar $Cu_2(\mu\text{–}Br)_2$ where the copper is tetra-coordinated the bond angles are opposite 50.6^{o} for Br1–Cu1–Br1A and 120.4^{o} for Cu1–Br1–Cu1A.[9b] The Cu–S bond distance is 2.259 Å and S1–Cu1–Cu1A atoms are not linear with an angle of 169.80^{o} in (**A**). However the Cu_2I_2 core is perfectly rhomboidal in shape (*Figure III.4.A.1*). The corresponding Cu_2Br_2 core in (**B**) is not perfectly rhomboidal (bowl shape) and the bromine atoms $(\mu\text{–}Br)_2$ are out of the plane by 20.45^{o} but the S1–Cu1–Cu1A atoms are nearly linear with an angle of 178.10^{o} (*Figure III.4.A.5*). This may be due to the *trans* orientation of iodine atoms in **A** and *cis* orientation of bromine atom in **B**.

In compound **A** and **B**, the axially coordinated morpholine–O atom of Tag extends the dimeric $[Cu_2(\mu\text{–}X)_2]$ core to a double standard 1D coordination polymer (*Figure III.4.A.8 and III.4.A.9*). In the double standard polymer, the centroid–centroid distances between two nearby $Cu_2(\mu\text{–}X)_2$ core are 7.37 Å (for compound **A**) and 7.33 Å (for compound B) respectively. It is interesting to note that although Tag moiety contains two morpholine–O atoms, only one morpholine–O atom (O2) extends the network whereas another morpholine–O atom (O1) exhibits C–H···O interactions (*Scheme III.4.A.2*). In compound **A**, C4–H4···O1 = 3.45(1) and C6–H6···I1 = 3.82(1), Å interactions between Tag moiety extends the 1D double standard chain to 2D ladder along *bc* plane (*Figure III.4.A.10*). Similarly, In compound **B**, non-covalent

interaction such as C15–H15···O1 = 3.37(1), C8–H8···N2 = 3.61(1) and C6–H6···Br1 = 3.65(1) Å extends the 1D double standard chain to 2D layer along *a* axis (*Figure III.4.A.11*).

Table III.4.A.1. *Selected bond distances (Å) and bond angles (°) in compound* ***A*** *and* ***B***

	Complex **A** (X = I)	Complex **B** (X = Br)
Cu(1)–X(1)	2.592(1)	2.457(1)
Cu(1)–X(1A)	2.560(1)	2.407(1)
Cu(1)–O(2)	2.635(1)	2.724(4)
Cu(1)–S(1)	2.259(2)	2.224(2)
Cu(1)–Cu(1A)	2.799(1)	2.945(1)
S(1)–Cu(1)–O(2)	79.2(1)	79.8(1)
S(1)–Cu(1)–X(1)	124.12(6)	128.45(5)
S(1)–Cu(1)–X(1A)	120.54(6)	126.69(5)
O(2)–Cu(1)–X(1)	93.6(1)	89.3(1)
O(2)–Cu(1)–X(1A)	109.2(1)	117.4(1)
X(1)–Cu(1)–X(1)	114.18(4)	103.14(4)

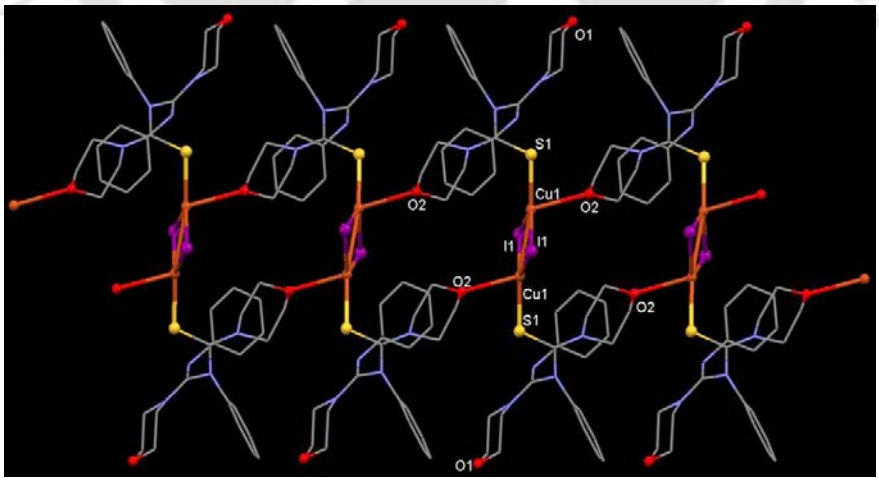
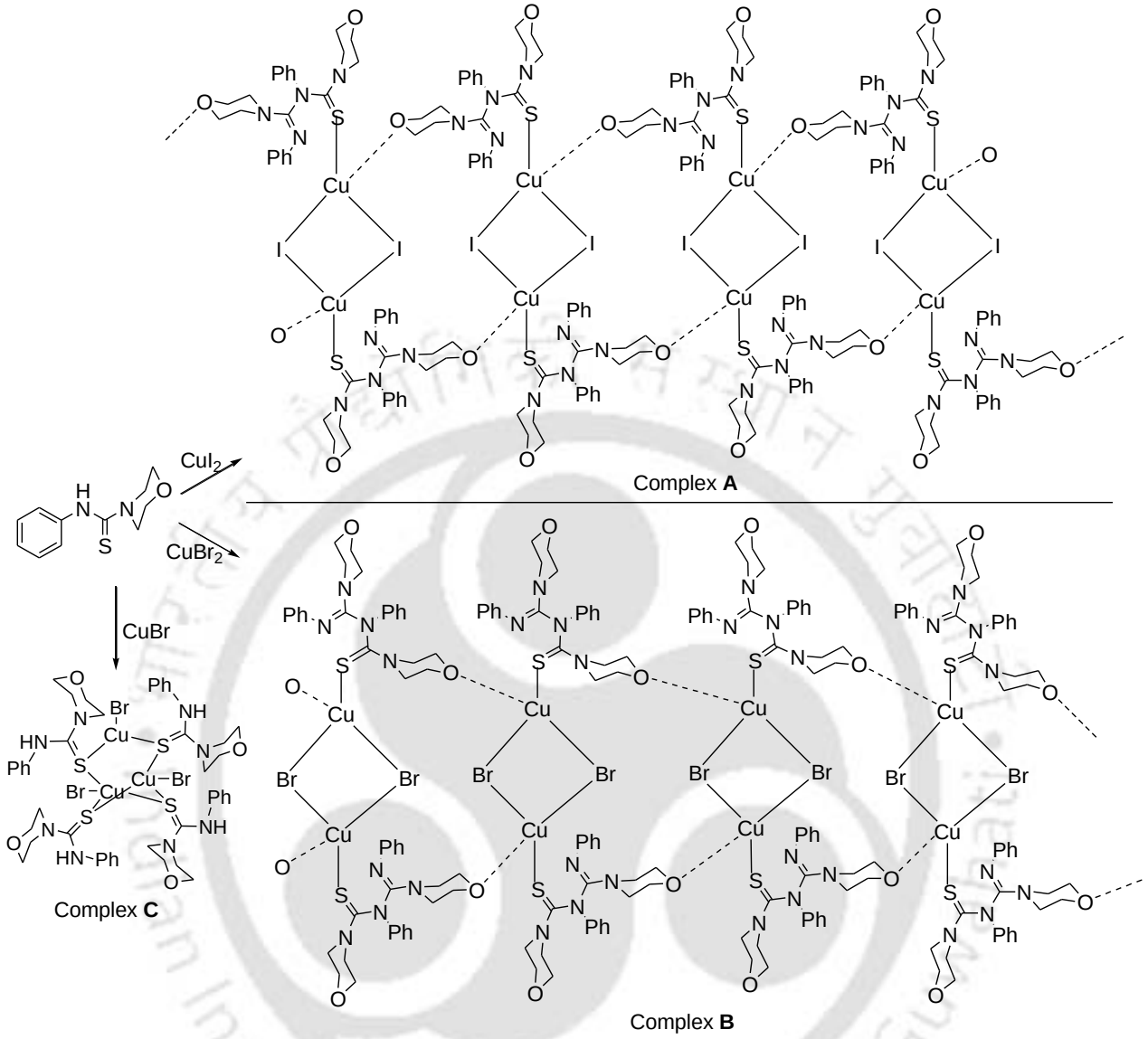


Figure III.4.A.8. *1D double standard coordination polymer of compound* ***A***



Scheme III.4.A.2. *Schematic diagram of coordination polymer of complex* ***A***, ***B*** *and cluster* ***C***

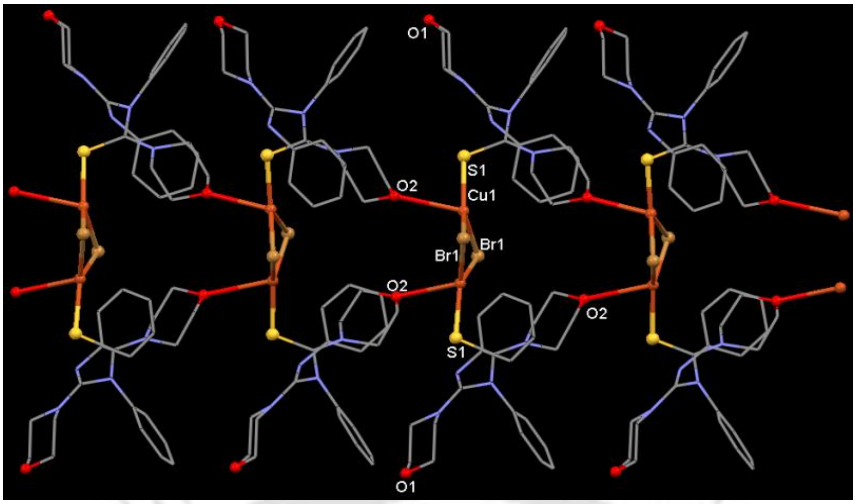


Figure III.4.A.9. *1D double standard coordination polymer of compound* ***B***

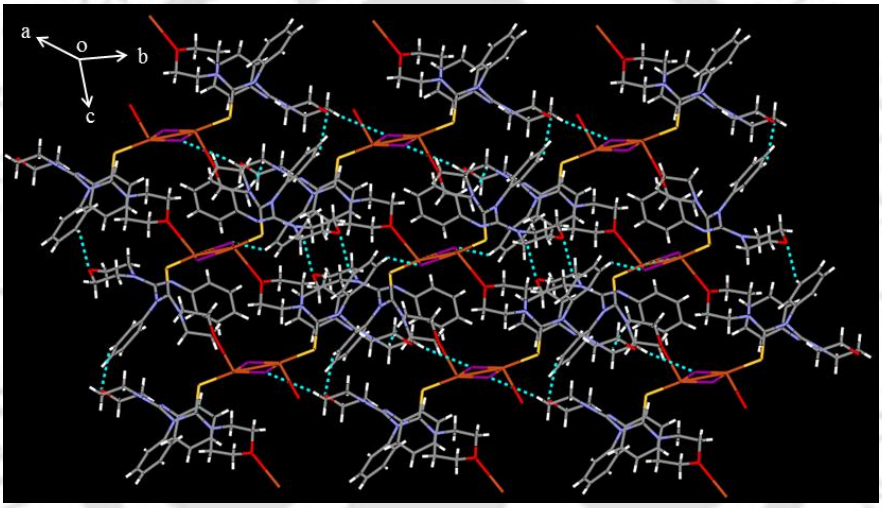


Figure III.4.A.10. *2D double ladder structure of compound* ***A*** *along bc plane*

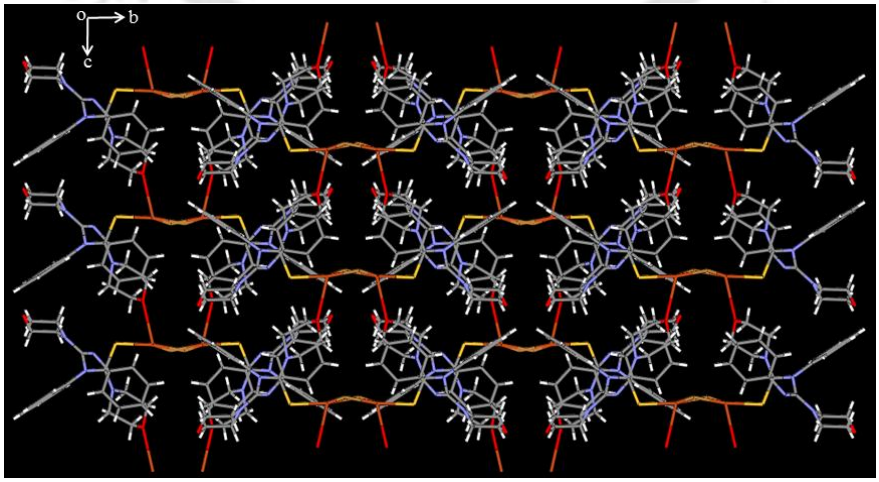


Figure III.4.A.11. *2D double layer structure of compound* ***B*** *along a axis*

Crystal structure of $[Cu_3^{I}Br_3(Tu)_4]$ (C): Complex C crystallized in P–1 space group and contains a $Cu^{I}_3S_4Br_3$ cluster. As shown in *Figure III.4.A.6*, the asymmetric unit of compound **C** contains one tri– and two tetra–coordinated Cu^{I} centers with four μ_2–thiourea bridging Tu ligands (μ_2–S) and three axially coordinating bromide atoms. Unlike compound **A** and **B** where two Cu^{I} centers are μ_2–X bridge and having a μ_1–S linkage, in compound (**C**) the linkages are opposite having four (μ_2–S) bridges and three μ_1–Br linkages (*Scheme III.4.A.2*) The tri–coordinated Cu^{I} center (Cu_2) forms bond from two S atoms of Tu (Cu2–S1 = 2.245(1) Å, Cu2–S2 = 2.261(1) Å) and one Br atom (Cu2–Br2 = 2.397(1) Å). The mean angle at Cu2 center is 119.85(3)°, which suggests almost trigonal planner geometry at Cu2. The coordination environment around the tetra-coordinated Cu1 and Cu3 centers are satisfied by three S atoms of Tu and one Br atom with a quasi-tetrahedral geometry. The Cu–S bond distances are in the range of (2.322(1)–2.487(1) Å) with an average bond distance of 2.414(1) Å around the Cu1 center and of 2.364(1) Å around Cu3 center. This may be compared with the Cu–S–Cys bonds in the range from 2.145–2.395 Å found in structurally characterized $Cu_8(CysS)_{10}$, (Cu_8–yeastMT) clusters.[14] The Cu–Br distances are of 2.361(1) and 2.459(1) Å around Cu1 and Cu3 centers respectively. The axially coordinating Br1 atom is nearly perpendicular to the virtual plane containing S1S3S4 atoms; similarly Br3 is nearly perpendicular to the plane containing S2S3S4 atoms. In $Cu^{I}_3S_4Br_3$ cluster, tetra-coordinated Cu1 center deviates by 1.052 Å from the plane containing S1S3S4 atoms whereas Cu3 center deviates by 0.870 Å from the plane containing S2S3S4 atoms. In compound **C**, comparison of bond angles (*Table III.4.A.2*) around Cu1 and Cu3 centers indicates that the former is more distorted than the latter.

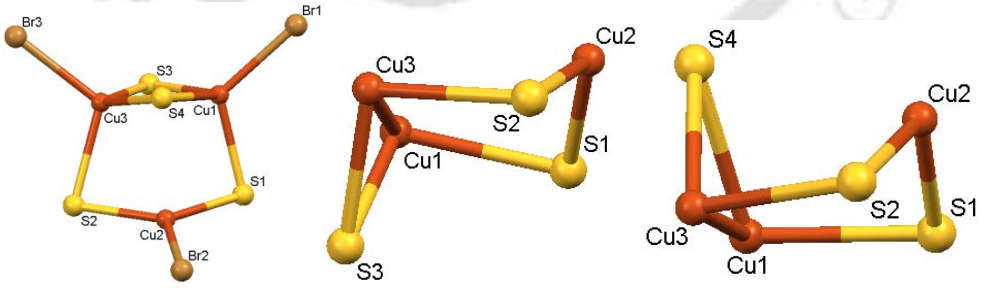


Figure III.4.A.12. *Ball-stick model of $Cu^{I}_3S_4Br_3$ cluster core (left) having both chair (middle) and boat form (right) of $Cu^{I}_3S_4$ cluster*

The central planer $Cu_2(\mu_2–S)_2$ core containing two tetrahedral copper center is rhomboidal with bridging bond distances of Cu1–S3; 2.392(1), Cu1–S4; 2.487(1), Cu2–S3; Cu2–S4;

2.350(1) Å respectively are shorter in comparisons to compound **A** and **B**. The angles in the $Cu_2(\mu_2–S)_2$ core are S3–Cu1–S4; 106.61(4), S3–Cu3–S4; 113.72(4), Cu1–S3–Cu3; 70.18(3), Cu1–S4–Cu3; 68.11(3)^o respectively. On carefully analysis of $Cu^I_3S_4Br_3$ cluster core (left), it was found that, both chair form (S3Cu3S2Cu2S1Cu1S3, middle) and boat form (S4Cu3S2Cu2S1Cu1S4, right) of $Cu^I_3S_3$ cluster exits (*Figure III.4.12*). The axially bridged Br atoms (Br2 and Br3) exhibits intermolecular H–bonding interactions with NH group of Tu (*Figure III.4.A.13*).[9b] The H–bonding distances are N1–H1···Br2 = 3.34(1), N3–H3···Br2 = 3.36(1), N7–H7···Br3 = 3.24(1) Å respectively.

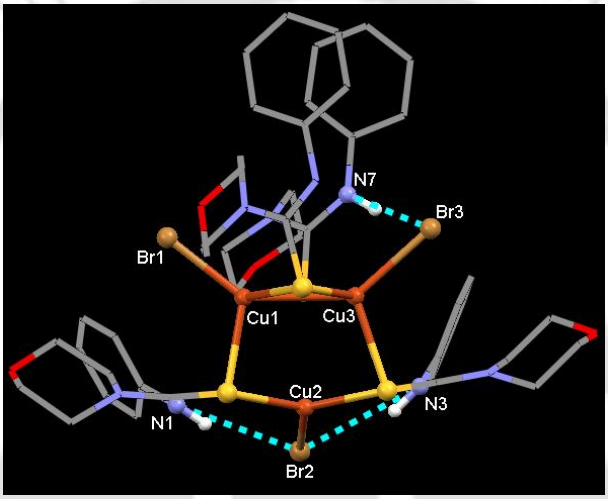


Figure III.4.A.13. *Mercury drawing representing intermolecular H–bonding interactions between axially coordinated Br atoms and NH group of Tu ligands in compound* ***C***

It is interesting to note that despite of four morpholine–O atoms from four Tu ligands, none of them extends the cluster to either 1D, 2D or 3D structures as found in compound **A** and **B** earlier. Compound **C** exhibits different non-covalent interactions such as C6–H6···O1 = 3.18(1), C43–H43···O2 = 3.44(1), C19–H19···O3 = 3.23(1), C8–H8···S3 = 3.70(1),C27–H27···Br1 = 3.76(1) and C31–H31···Br3 = 3.53(1) Å extending the Cu^I cluster to 2D sheet structure along *bc* plane as shown in (*Figure III.4.A.14*).

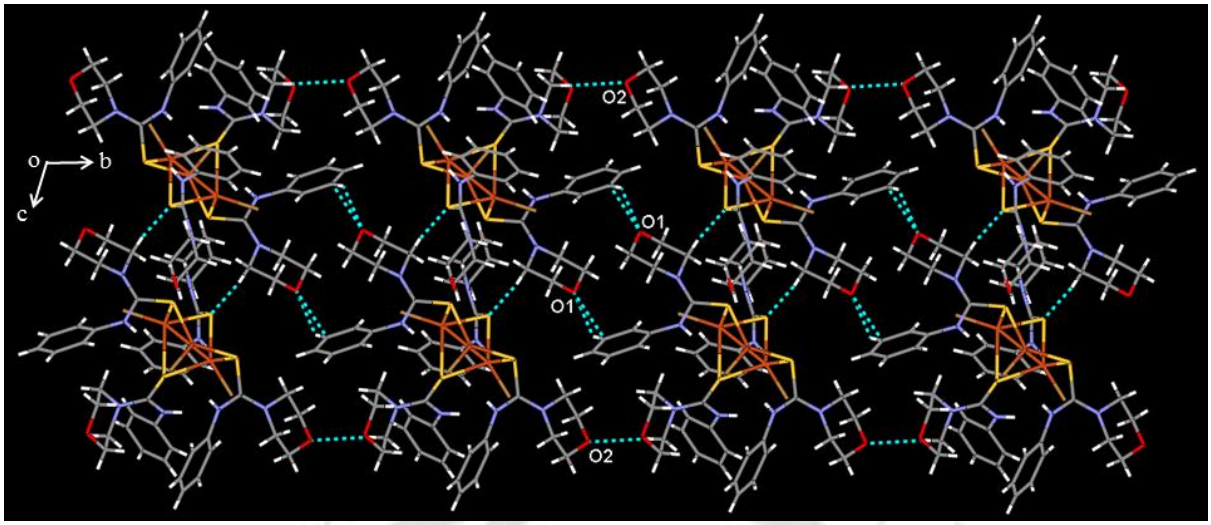


Figure III.4.A.14. *2D sheet structure of compound* ***C*** *along bc plane*

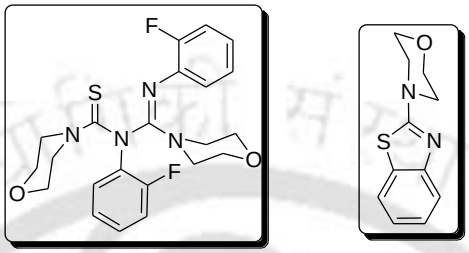
Table III.4.A.2. *Selected bond distances (Å) and bond angles (°) in compound* ***C***

Complex **C**			
Cu1–S1	2.3637(8)	Cu3–S2	2.4213(9)
Cu1–Br1	2.3603(7)	Cu3–Br3	2.4588(6)
Cu1–S3	2.392(1)	Cu3–S3	2.322(1)
Cu1–S4	2.487(1)	Cu3–S4	2.350(1)
Cu2–S1	2.245(1)	Cu1–Cu2	3.2197(7)
Cu2–Br2	2.3968(6)	Cu3–Cu1	2.7105(8)
Cu2–S2	2.261(1)	Cu3–Cu2	3.1196(6)
S1–Cu1–S3	97.96(3)	S2–Cu3–S3	104.61(3)
S1–Cu1–S4	102.52(3)	S2–Cu3–S4	103.15(3)
S1–Cu1–Br1	118.83(3)	S2–Cu3–Br3	113.40(3)
S3–Cu1–S4	106.61(3)	S3–Cu3–S4	113.72(4)
S3–Cu1–Br1	117.61(3)	S3–Cu3–Br3	111.18(3)
S4–Cu1–Br1	111.38(3)	S4–Cu3–Br4	110.47(3)

In conclusion we have developed a method where an aryl-sec-alkyl thiourea (Tu) undergoes an oxidative rearrangement in the presence of a redox active metal salt $Cu^{II}X_2$ to give a thioaminoguanidino moiety (Tag) and itself gets reduced to CuI. An interesting bimetallic CuI complex is formed from the resultant transformed ligand (Tag) and halide ions to form a $[Cu_2^I(\mu_2\text{-}X)_2Tag_2]$ complex. However in the presence of Cu^I, the thiourea forms a $[Cu^I_3(\mu_2\text{-}S)_4Tu_4Br_3]$ cluster. Compounds **A** and **B** contain only tetra-coordinated Cu^I centers whereas compound **C** contains one tri- and two tetra-coordinated Cu^I centers. Compounds **A** and **B** exhibit 1D chain structures with a $Cu_2(\mu_2\text{-}X)_2$ core whereas compound **C** is a $Cu^I_3S_4Br_3$ cluster. Compound **A** is centrosymmetric, whereas the compound **B** is ascentric. In compound A, the Cu_2I_2 core is perfectly rhomboidal, whereas in compound **B**, the Cu_2Br_2 core is bowl shaped. Thus the synergism of the potentially bridging ligands, the effectiveness of the halide ions as SAB and directional nature of noncovalent interactions provide complex connectivity patterns and a remarkable structural diversity. The occurrence of different noncovalent interactions between ligands and halide ions extend the networks to a 2D structure. These complexes are air stable, non−hygroscopic thus might find potential application as catalyst, in the construction of metal organic framework, in light-emitting diode (LED) technology and also understanding of metallothionenes.

III.4.B. Cu(II) Catalyzed Chemoselective Oxidative Transformation of Thiourea to Thioamidoguanidine / 2-Aminobenzothiazole

This chapter mainly focuses on the synthesis of thioamidoguanidino (Tag) and 2-amino-benzothiazole analogues.

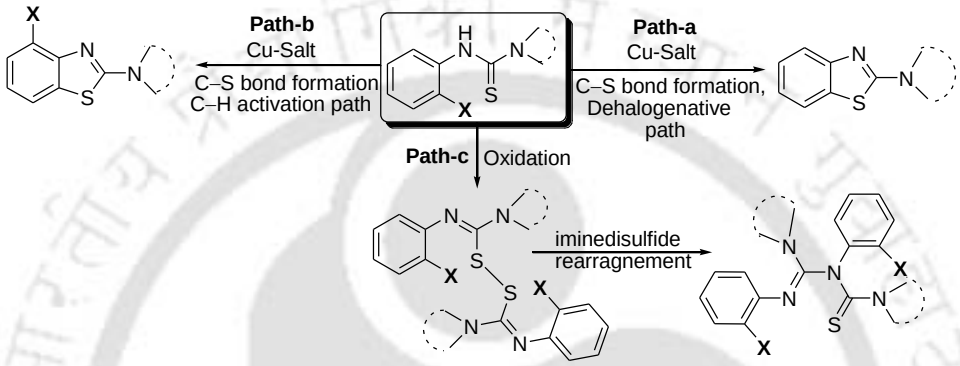


Thioamidoguanadino (Tag) **2-Aminobenzothiazole**

Synthesis of thioamidoguanidine/2-aminobenzothiazole from *in-situ* generated 2-fluoroaryl-sec-alkyl thiourea derived from 2-F phenylisothiocyanate and morpholine using Cu(II) catalyst

A competitive formation of 2-aminobenzothiazole (Hugerschoff product) and thioamidoguanidine (anti-Hugerschoff product) was observed for the moderately activated substrates.[6,7] The formation of the thioamidoguanidine (Tag) product from 2-aryl-sec-alkyl unsymmetrical thioureas goes via an oxidative dimerization (S−S bond formation) followed by an intramolecular imine-disulfide rearrangement.[6] On the other hand the formation of 2-aminobenzothiazole involves an intramolecular aromatic electrophilic substitution reaction (Hugerschoff path) facilitated by activation of the sulfur atom of the thiourea with a thiophilic reagent.[6,7] In order to circumvent the competitive formation of 2-aminobenzothiazole and allow exclusive formation of the Tag product, the redox active metal Cu(II) is expected to promote only oxidative dimerisation of thiourea (S−S bond formation). This is then followed by an intramolecular iminedisulfide rearrangement leading to the formation of Tag. Thiophilic redox active metal Cu(II) would not activate the sulphur atom of thiourea towards an intramolecular electrophilic substitution reaction (Hugerschoff path). Indeed this strategy was quite successful and the unsymmetrical thiourea (Tu) was transformed into a thioamidoguanidine (Tag) moiety with concomitant reduction of Cu(II) to Cu(I) which however formed a $[Cu_2^{I}(\mu_2\text{-}Br)_2Tag_2]$ complex.[8] Furthermore, we know that 2-halothioureas prefer a dehalogenative path during the formation of an intramolecular C−S bond formation giving 2-aminobenzothiazoles for the entire

range of halogens where as palladium favors a C−H activation path.[15] Recently, we have engineered a greener strategy for the synthesis of 2-aminobenzothiazole from ortho-halo (−F, −Cl, −Br and −I) substituted unsymmetrical thioureas using CuO nanoparticle.[16] In this strategy for ortho −I and −Br substituted thioureas the reaction affords 2-aminobenzothiazoles under metal free condition via a base promoted intramolecular nucleophilic aromatic substitution. However, base and Cu catalyst were essential for the relatively inert ortho −Cl and −F substrates.[16]

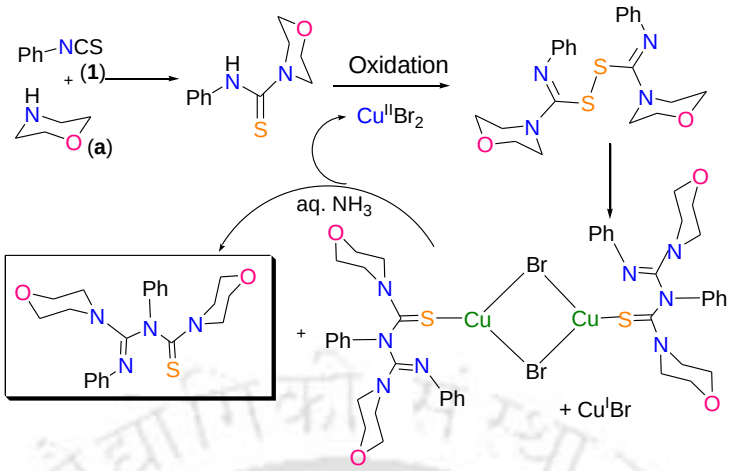


Scheme III.4.B.1. *Various possible reaction pathways of 2-halo thiourea*

2-Haloaryl-sec-alkyl unsymmetrical thioureas (Tu) on treatment with Cu(II) salts there exists several possible reaction pathways (*Scheme III.4.B.1*). In path-a, it can undergo an intramolecular C−S bond formation via a dehelogenative path giving 2-aminobenzothiazole. Depending on the nature of the 2- halo substituents, particularly inert halogens (−Cl, −F) or in the absence of any halo substituents it may furnish 2-aminobenzothiazole via a C−H activation strategy (path-b). The possibility of an oxidative dimerization (S−S bond formation) of a thiourea (Tu) in the presence of a redox active metal Cu(II) cannot be ruled out as shown in path-c which would eventually lead to the formation of a Tag moiety after an intramolecular imine-disulfide rearrangement. Thus we wish to investigate which of the above paths would operate when 2-haloaryl-secalkyl unsymmetrical thioureas (Tu) is treated with Cu(II) salt and also whether *o*-halogens would be any affect on the outcome of the product. For substrates without *o*-halo groups would path-b (C−H activation) or path-c (S−S bond formation) be followed when treated with a redox active Cu(II) salt? If path-c operates, then a library of guanidine class of molecules can be generated. The molecules containing guanidine moieties have shown number of biological and pharmaceutical applications. Furthermore, guanidine possessing molecules are

also capable of catalyzing organic reactions, can be used as a super base and their exhibits a variety of co-ordination modes leading to compatibility with a wide range of metal ions.[17]

We directly adopted our recently established procedure[8] for the preparation of Tag moiety from thiourea but the solvent system was switched to EtOAc : H_2O (3:1) instead of ethanol because of the convenience in work up at a later stage. The in situ generated unsymmetrical thiourea (Tu) obtained by reacting phenylisothiocyanate (**1**) with morpholine (**a**) (*Scheme III.4.B.2*) in EtOAc : H_2O (3:1) medium was treated with an aqueous solution of $CuBr_2$ (1 equiv). The green colour of $CuBr_2$ disappeared immediately giving a yellow solution along with yellow precipitate. From our earlier report we know that the yellow compound formed is a bimetallic $[Cu_2^{I}(\mu_2\text{-}Br)_2Tag_2]$ complex.[8] The co-ordinated copper was removed from the complex by treating the crude reaction mixture with an aqueous ammonia solution. The isolated ligand was found to be the expected thioamidoguanidino moiety (Tag) (**1a**) and no traces of 2-aminobenzothiazole (**11'a**) formation (*Table III.4.B.1*) was observed. It may be mentioned here that the use of bromine equivalent, 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) gave a mixture of thioamidoguanidino moiety (Tag) and 2-aminobenzothiazole (**11'a**). Thus our envisioned strategy was indeed successful in suppressing the formation of 2-aminobenzothiazole (**11'a**). From a green chemistry perspective it is desirable to have a catalytic quantity of Cu instead of stoichiometric amount for any transformations. The reaction when carried out with 10, 20, 30 and 40 mol % of $CuBr_2$ it was found that 30 mol % of $CuBr_2$ was optimum in converting the starting material into the product. As evident from our recent result when thiourea is treated with Cu(II) salt, it is first oxidized to its disulfide intermediate which then undergo an intramolecular rearrangement giving Tag and during the process the Cu(II) gets reduced to Cu(I). The in situ generated Cu(I) is reoxidised to Cu(II) by the atmospheric oxygen and the catalytic cycle continues. The amount of catalyst required is more (30 mol%) compared to any typical catalytic reactions because of the propensity of the *in-situ* generated Cu(I) species to form complex with the in situ generated Tag unit there by making part of the catalyst unavailable.[8] Other divalent Cu(II) salts like $CuSO_4.5H_2O$, $Cu(OAc)_2.2H_2O$, $Cu(NO_3)_2.3H_2O$, $CuCl_2.2H_2O$, CuI_2 were tested and gave the desired transformations, but were found to be inferior to $CuBr_2$.



Scheme III.4.B.2. *Formation of thioamidoguanidino moiety (**1a**) from thiourea (**1**)*

Despite their use as efficient vulcanizing and herbicide agents prior to our greener strategies there is only one synthetic method reported using 2−aryl-sec-alkyl unsymmetrical thioureas (Tu) and iodine in chloroform.[2b] Another report is on the crystal structure determination.[2a] Beside this report there are two more methods reported for the synthesis of thioamido guanidine in the literature. Both methods are from our group only, starting from aryl-sec-alkyl unsymmetrical thiourea using thiophilic reagents such as bromine or iodine.[6,7] Thus we wished to synthesize a series of thioamidoguanidine (Tag) moieties by varying the secondary aliphatic amines in thioureas keeping the aryl part constant. Thiomorpholine (**b**), *N*-phenyl piperazine (**c**), piperidine (**d**), 4-benzylpiperidine (**e**) and pyrrolydine (**f**) derived thioureas from phenyl isothiocyanate (**1**) all gave good yields of their corresponding Tag products (**1b**), (**1c**), (**1d**), (**1e**), and (**1f**), respectively (*Table III.4.B.1*). From the present study it was found that the aliphatic secondary amines in thioureas seem to have little or no effect on the outcome of the product yields. Thus we planned to investigate whether the substituents present in the aryl rings would influence the reaction path. Besides being an oxidizing agent, Cu(II) salts are also thiophilic in nature, so the presence of activated substituents in the aryl rings of thioureas (Tu) might promote an intramolecular aromatic electrophilic substitution (Hugerschoff path), path-b as was observed using bromine equivalent or iodine.[6,7] Alternatively, some of the substrates might exert C−H activation (path-b) giving 2-aminobenzothiazole. With this objective thioureas derived from *p*-methyl phenylisothiocyanate (**2**) and morpholine (**a**) was treated with $CuBr_2$ and the product isolated after an aqueous ammonia treatment was found to be the Tag product (**2a**) (*Table*

III.4.B.1) exclusively and no traces of corresponding 2-aminobenzothiazole was observed. Similarly thioureas derived from *p*-methyl phenylisothiocyanate (**2**) and other secondary amines such as thiomorpholine (**b**), *N*-phenyl piperazine (**c**) gave only their respective Tag products (**2b**) and (**2c**). Thioureas derived from aromatic isothiocyanate containing two weakly activating (methyl) substituents such as 3,4-dimethyl phenylisothiocyanate (**3**) and various secondary aliphatic amines like morpholine (**a**), thiomorpholine (**b**), *N*-phenyl piperazine (**c**) and piperidine (**d**) all afforded Tag products (**3a**), (**3b**), (**3c**), and (**3d**) respectively under the present reaction conditions. Structure of the product (**3d**) has been confirmed by single crystal X−ray crystallography (*Figure III.4.B.1*). It may be worth mentioning here that the same thiourea derived from 3,4-dimethylphenylisothiocyanate (**3**) and morpholine (**a**) gave a regioisomeric mixture of two 2-aminobenzothiazoles and no traces of Tag product (**3a**) was observed when bromine equivalent (EDPBT) was used as the thiophilic reagent (*Scheme III.4.B.3*).[6,7] Thus oxidizing ability (S−S bond formation) of Cu(II) predominates over its thiophilicity. Furthermore, the absence of any intramolecular aromatic electrophilic substitution product (2-aminobenzothiazole) using Cu(II) salt confirms its lower thiophilicity as compared to EDPBT. Thus, the use of Cu(II) as an oxidizing agent is advantageous over EDPBT in giving Tag products. Not surprisingly, thiourea derived from *p*-butyl phenylisothiocyante (**4**) and morpholine (**a**) yielded corresponding Tag product (**4a**).

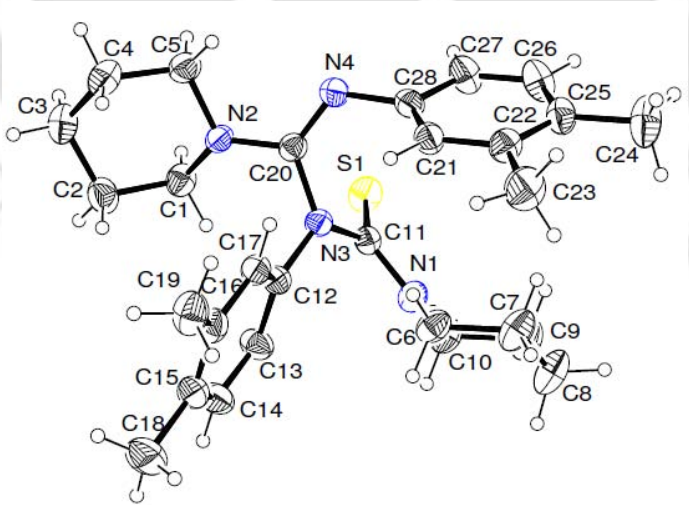
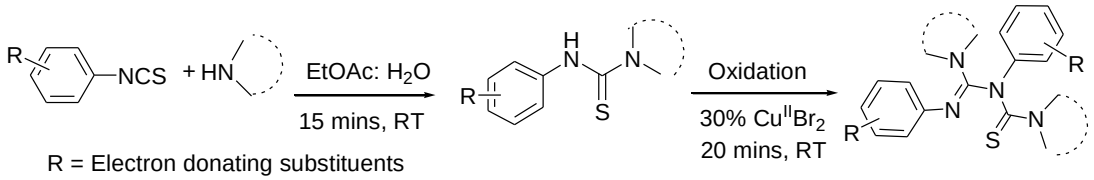
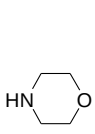
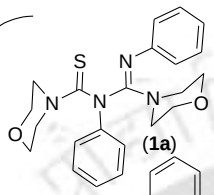
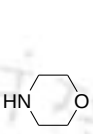
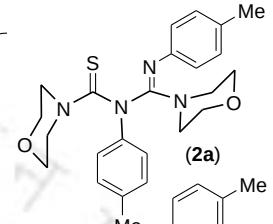
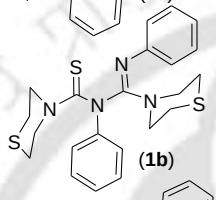
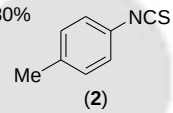
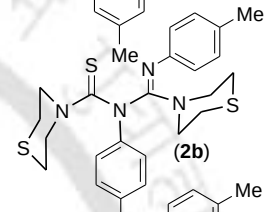
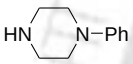
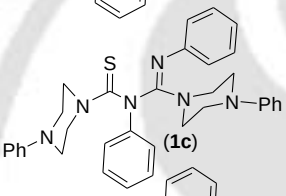
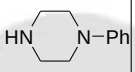
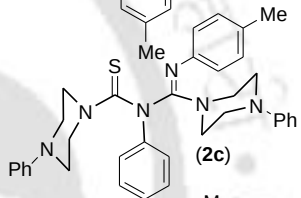
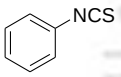
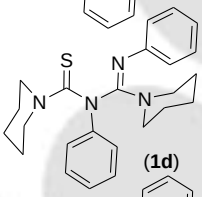
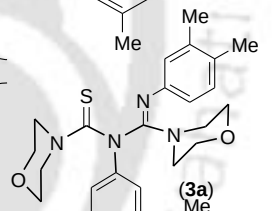
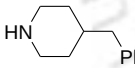
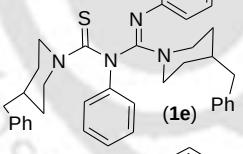
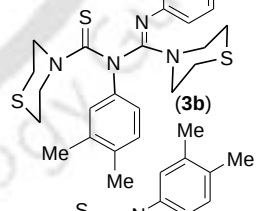
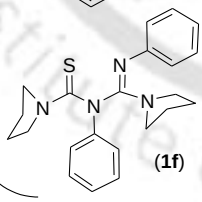
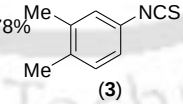
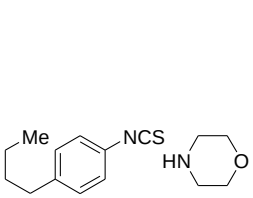
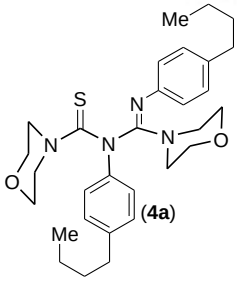
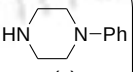
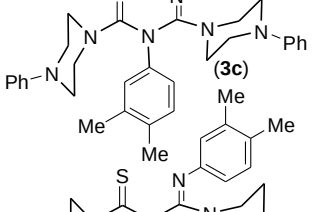
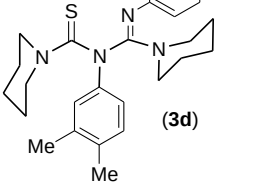


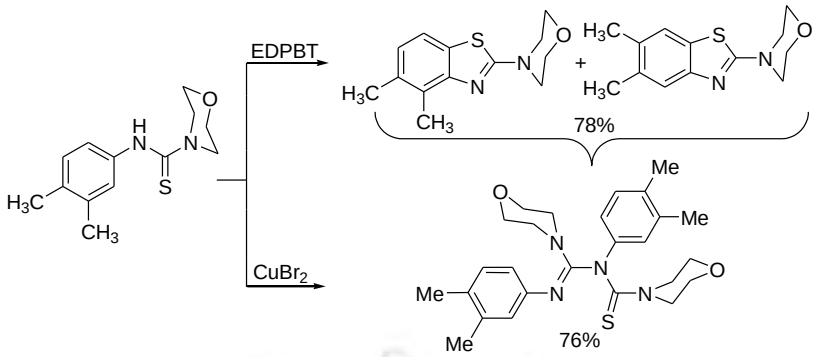
Figure III.4.B.1. *ORTEP view (30% probability ellipsoids) of compound* ***3d***

Table III.4.B.1. *Synthesis of thioamidoguanidino products from arylisothiocyanates and sec. amines*[a]



Substrate	Product	Yield	Substrate	Product	Yield
 (a)	 (1a)	89%	 (a)	 (2a)	86%
 (b)	 (1b)	80%	 (2)	 (2b)	71%
 (c)	 (1c)	83%	 (c)	 (2c)	73%
 (1)  (d)	 (1d)	88%	 (a)	 (3a)	86%
 (e)	 (1e)	85%	 (b)	 (3b)	73%
 (f)	 (1f)		 (3)		
 (4)	 (4a)	85%	 (c)	 (3c)	74%
			 (d)	 (3d)	83%

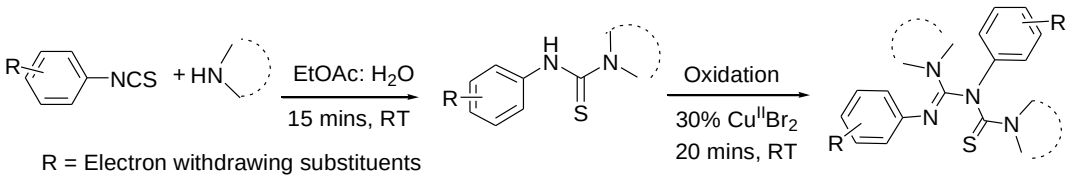
[a] Reaction monitored by TLC. [b] Confirmed by IR, ^{1}H, ^{13}C NMR spectra.

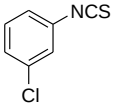
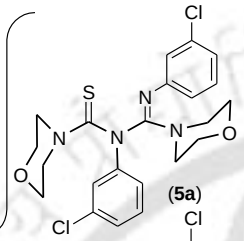
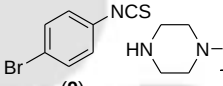
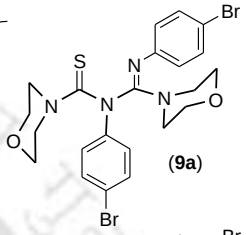
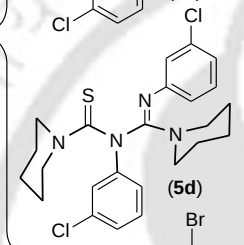
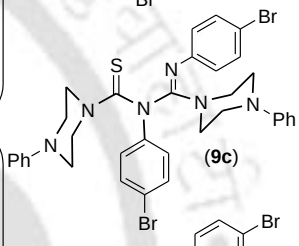
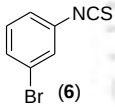
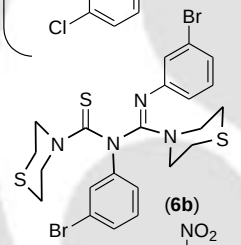
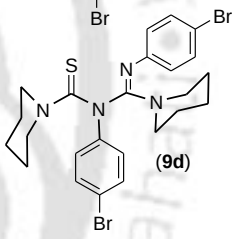
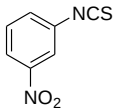
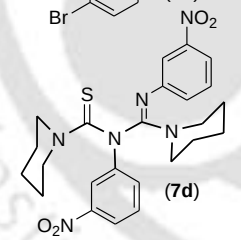
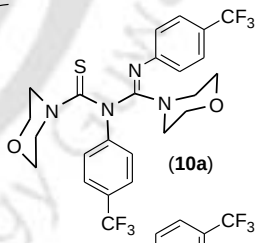
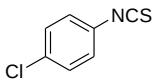
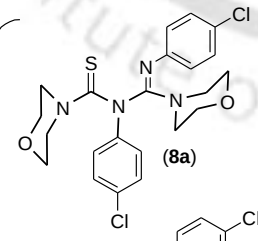
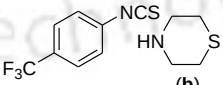
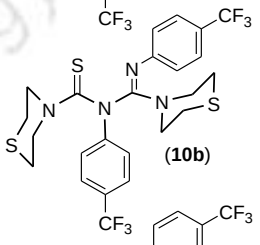
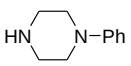
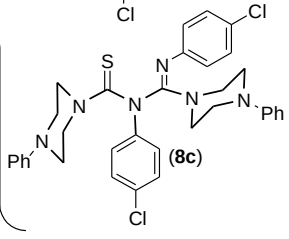
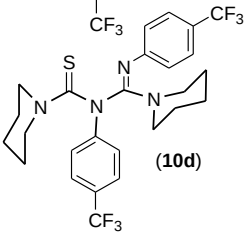


Scheme III.4.B.3. *Difference of thiophilicity between Cu(II) and EDPBT*

Unsymmetrical thioureas (Tu) possessing activating groups in the aryl rings are prone towards intramolecular aromatic electrophilic substitution reaction in the presence of a thiophilic reagent thereby enhancing the chances of forming 2-aminobenzothiazoles via a Hugerschoff path. However, the use of Cu(II) salt gave exclusively Tag products for substrates containing not only for deactivating substrates but also for activating substrates. However, the presence of weakly deactivating substituents in the aryl ring of the thiourea is more likely to give Tag products only. To verify this fact and demonstrate the versatility of the method thioureas derived from 3-chloro phenylisothiocyanate (**5**) and aliphatic secondary amines such as morpholine (**a**) and piperidine (**d**) on treatment with $CuBr_2$ gave exclusively Tag products (**5a**) and (**5d**) respectively in excellent yields (*Table III.4.B.2*). The treatment of the thiourea derived from 3-bromo phenylisothiocyanate (**6**) and thiomorpholine (**b**) with Cu(II) gave Tag product (**6b**) in a modest yield. Thioureas derived from sets of arylisothiocanates such as 3-nitro phenylisothiocyanate (**7**), 4-chloro phenylisothiocyanate (**8**), 4-bromo phenylisothiocyanate (**9**) and 4-trifluoromethyl phenylsiothiocyanate (**10**) and sets of aliphatic secondary amines (**a**−**d**) all gave their expected Tag products in good to excellent yield under the present reaction conditions (*Table III.4.B.2*).

Table III.4.B.2. *Synthesis of thioamidoguanidino products from arylisothiocyanates and sec. amines*[a]



Substrate	Product	Yield	Substrate	Product	Yield
 (5) +  (a)	 (5a)	91%	 (9) +  (a)	 (9a)	92%
(5) +  (d)	 (5d)	89%	(9) + (c)	 (9c)	78%
 (6) +  (b)	 (6b)	71%	 (d)	 (9d)	82%
 (7) +  (d)	 (7d)	79%	 (a)	 (10a)	85%
 (8) +  (a)	 (8a)	93%	 (10) + (b)	 (10b)	70%
(8) +  (c)	 (8c)	74%	 (d)	 (10d)	80%

[a] Reaction monitored by TLC. [b] Confirmed by IR, ^{1}H, ^{13}C NMR spectra.

2-Halo substituted thioureas undergoing copper catalysis are prone to intramolecular heteroarylation via a dehalogenative path.[15,16,18] All the substrates examined in *Table* (*III.4.B.1* and *III.4.B.2*) are devoid of 2-halosubstituents thus we wish to examine the effect of 2-halo substituents on the outcome of the products where all the three possibilities (path-a, path-b and path-c) exist equally (*Scheme III.4.B.1*). Recently, we have demonstrate that the use of Cu(I) gave 2-aminobenzothiazoles via a dehalogenative path for the entire range 2-halo (−F, −Cl, −Br, −I) substituted thioureas.[15] It is further demonstrated that the dehaloganative path is preferred even for less reactive halogens (−F, −Cl) using CuO nano particle in an aqueous medium at an elevated temperature.[16] In the present case thioureas derived from 2-fluoro phenylisothiocyanate with morpholine (**a**) and piperidine (**d**) when treated with Cu(II) salt gave Tag products (**11a**) and (**11d**) and not the expected 2-aminobenzothiazoles. Thus with lesser reactive halogens (−F, −Cl) Cu(II) behaves better as an oxidizing (S−S bond forming) agent at room temperature resulting in the formation of Tag. Formation of 2-aminobenzothiazoles were not observed either via an intramolecular C−S bond forming path (dehalogenation path-a, *Scheme III.4.B.1*) or via a C−H activation path (path-b, *Scheme III.4.B.1*). Thus, the thioureas derived from isothiocyanates (**12**), (**13**) and (**14**) and aliphatic secondary amines such as morpholine (**a**), thiomorpholine (**b**), *N*-phenyl piperazine (**c**) and piperidine (**d**) all gave only their corresponding Tag products (*Table III.4.B.3*) confirming the preferential oxidative path for 2-halo (−F, −Cl) possessing substrates.

The results in *Table III.4.B.3* are in contrast to our recent reports where Cu as a catalyst has more propensities towards intramolecular C−S bond formation via a dehalogenative path even for lesser activated halogens such as (2−F, 2−Cl).[15] A reaction temperature of 80 ^{o}C was used in our previous investigation with a catalyst loading of 5 mol% but in the present case the reaction is carried out at room temperature requiring 30 mol% of the catalyst. Thus an increase in the temperature to 80 ^{o}C might result in the formation of 2-aminobenzothiazoles from 2-halo (−F, −Cl) thioureas via a dehalogenative path as was observed earlier.[15] With this objective the in situ generated thiourea obtained by reacting 2-fluoro phenylisothiocyanate (**11**) and morpholine (**a**) when treated with a catalytic quantity (5 mol%) of CuBr2 at 80 ^{o}C gave 2-aminobenzothiazole (**11'a**) in a poor yield of 40% when EtOAc:H_2O was used as the solvent. Thus differential reactivity of 2-fluoro thiourea was observed at two different temperatures, at 80 ^{o}C path-a is followed and at room temperature path-c is followed (*Scheme III.4.B.1*). Further

experimentations revealed that the use of DMSO as the solvent gave superior yield 75% of (**11'a**) compared to other solvents such as CH_3CN, DMF, toluene, dioxane, EtOH and DMA tested. Similarly the thiourea generated from 2-fluoro phenylisothiocyanate (**11**) and piperidine (**d**) gave corresponding 2-aminobenzothiazole (**11'd**) in good yield. This dehalogenative strategy at higher temperature was also equally successful for other *in-situ* generated 2-fluoro thioureas (*Table III.4.B.4*). The structure of the product (**15'a**) has been further confirmed by crystal X−ray crystallography (*Figure III.4.B.2*). Not surprisingly the in situ generated 2-chloro thioureas underwent similar dehalogenative path giving corresponding 2-aminobenzothiazoles (*Table III.4.B.4*). From this study it is clear that using catalytic amount of $CuBr_2$ (5 mol%) and at higher temperatures a dehelogenative path is preferred giving 2-aminobenzothiazole, while a lower temperature favors an oxidative dimerization path giving Tag products. It is well documented that thioureas derived from more activated halogens such as 2–Br or 2−I undergo intramolecular C−S bond formation under ligand and catalyst free conditions at 130 ^oC in the presence of Cs_2CO_3.[19] For 2-bromo thiourea derived from 2-bromo phenylisothiocyanate (**17**) and morpholine (**a**) the reaction proceeded at room temperature with just 5 mol% of the catalyst. It may be mention here that the use of EDPBT gave exclusively the *anti*-Hugerschoff product (Tag) for the same substrate. Other 2-bromo substituted thioureas derived from respective isothiocyanates (**18**), (**19**) and (**20**) and secondary amines such as, morpholine (**a**) and piperidine (**d**) gave the respective 2-aminobenzothiazoles via a dehalogenetive path (*Table III.4.B.4*). 2-Iodo thioureas derived from respective arylisothiocyanates (**21**), (**22**) and (**23**) and secondary amines morpholine (**a**) and piperidine (**d**) were found to be much more reactive than their bromo analogues and the reaction goes at room temperature with just 2 mol% of the catalyst.

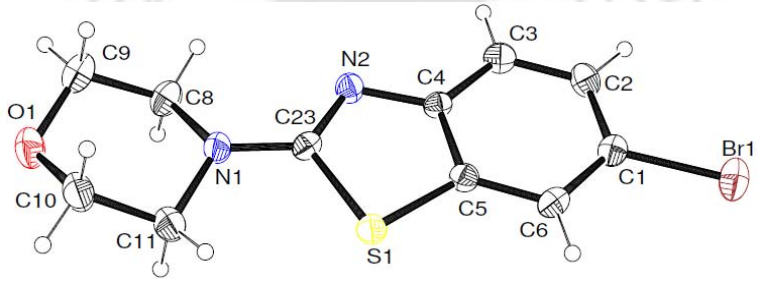
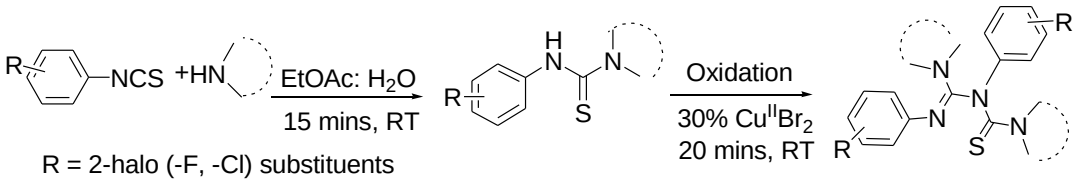
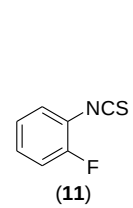
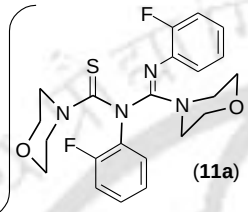
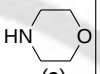
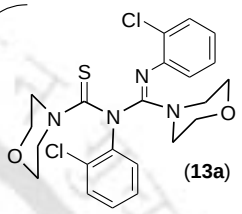
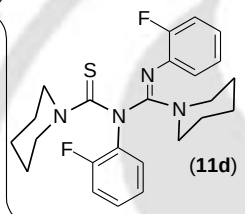
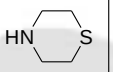
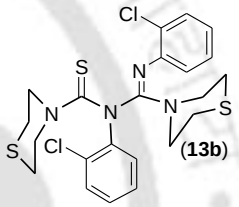
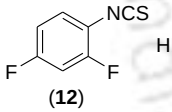
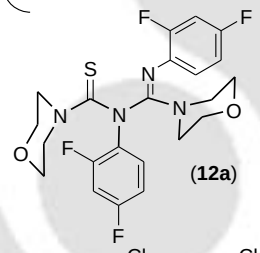
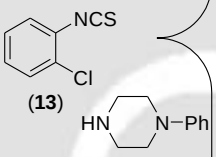
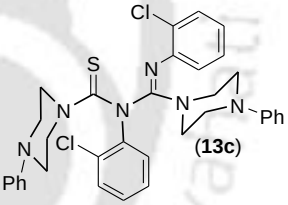
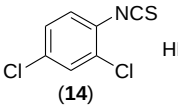
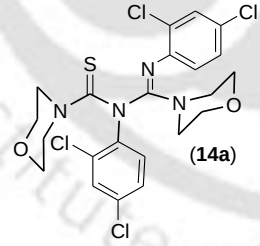
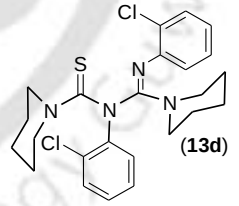


Figure III.4.B.2. *ORTEP view (30% probability ellipsoids) of compound* ***15'a***

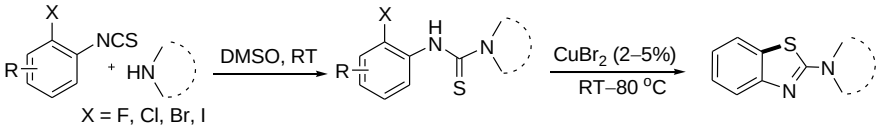
Table III.4.B.3. *Synthesis of thioamidoguanidino products from arylisothiocyanates and sec. amines*[a]

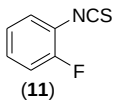
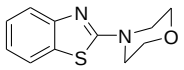
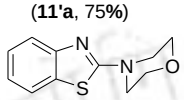
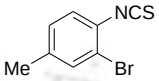
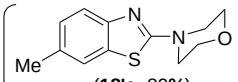
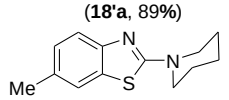
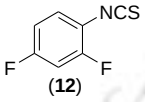
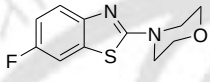
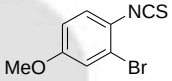
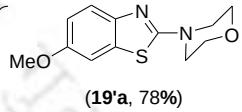
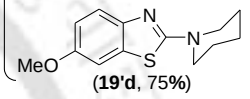
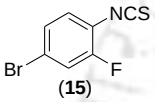
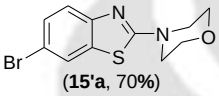
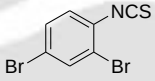
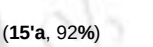
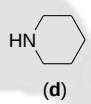
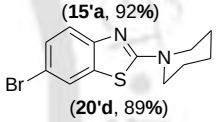
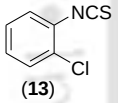
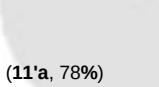
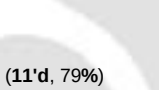
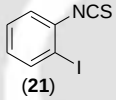
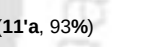
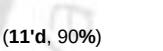
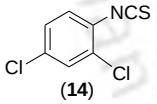
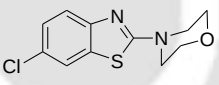


Substrate	Product	Yield	Substrate	Product	Yield
		92%			86%
		87%			73%
		81%			74%
		85%			83%

[a] Reaction monitored by TLC. [b] Confirmed by IR, ^{1}H, ^{13}C NMR spectra.

Table III.4.B.4. *Synthesis of 2-aminobenzothiazoles from 2-halo arylisothiocyanates and sec. amines*[a]

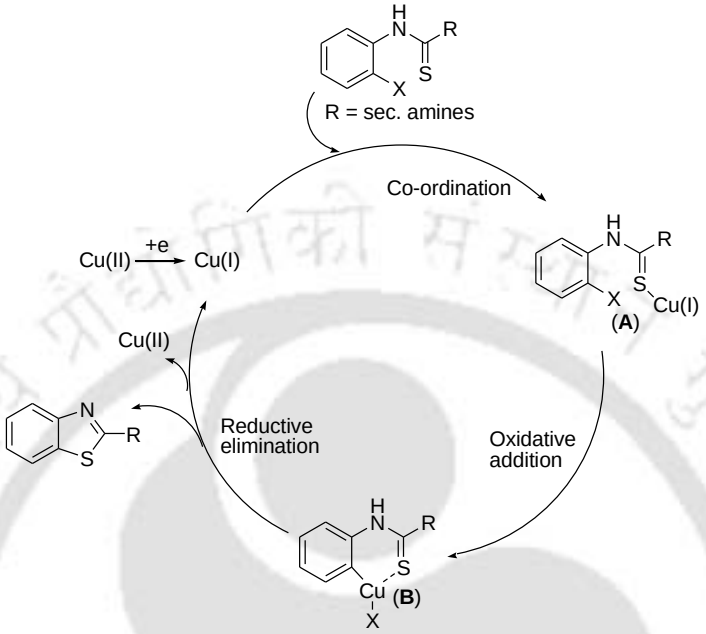


Substrate	Product	Substrate	Product
 (**11**)	 (**a**)  (**11'a**, 75%)  (**d**)  (**11'd**, 77%)	 (**18**)	 (**a**)  (**18'a**, 89%)  (**d**)  (**18'd**, 87%)
 (**12**)	 (**a**)  (**12'a**, 72%)	 (**19**)	 (**a**)  (**19'a**, 78%)  (**d**)  (**19'd**, 75%)
 (**15**)	 (**d**)  (**15'a**, 70%)	 (**20**)	 (**a**)  (**15'a**, 92%)  (**d**)  (**20'd**, 89%)
 (**13**)	 (**a**)  (**11'a**, 78%)  (**d**)  (**11'd**, 79%)	 (**21**)	 (**a**)  (**11'a**, 93%)  (**d**)  (**11'd**, 90%)
 (**14**)	 (**a**)  (**14'a**, 83%)	(**22**)	(**a**) (**18'a**, 91%) (**d**) (**18'd**, 89%)
(**16**)	(**a**) (**15'a**, 79%)	(**23**)	(**a**) (**15'a**, 95%) (**d**) (**20'd**, 94%)
(**17**)	(**a**) (**11'a**, 86%) (**d**) (**11'd**, 88%)		

[a]Isolated Yield. [b]Confirmed by IR, ^{1}H, ^{13}C NMR spectra. [c]$CuBr_2$ (5 mol %), Na_2CO_3 (1 equiv.), DMSO, 85 °C, 22 h, (when X = F, Cl). [d]$CuBr_2$ (2-5 mol %), 0.5–2 h, room temperature (when X = Br, I).

A proposed catalytic cycle for the synthesis of 2-aminobenzothiazole using Cu(II) can be envisaged taking cues from the literature (*Scheme III.4.B.4*). The copper(II) salt is initially reduced in situ to a copper(I) species by thiourea.[20] Co-ordination of thioureas with thiophilic

Cu(I) gives intermediate (**A**) which is then followed by an oxidative addition giving a copper (III) intermediate (**B**). Subsequent reductive elimination provides benzothiazole with concomitant regeneration of catalytic copper species for the next cycle (*Scheme III.4.B.4*).



Scheme III.4.B.4. *Proposed mechanism for the formation of 2-aminobenzothiazole*

In conclusion 2-haloaryl-sec-alkyl unsymmetrical thioureas (Tu) (halo = −F, −Cl) with a catalytic amount of Cu(II) salt at room temperature gives thioamidoguanidino (Tag) which is obtained via a oxidative dimerization followed by an iminedisulfide rearrangement. Changing the reaction temperature to 80 ^{o}C gives 2-aminobenzothiazole via a dehelogenative path and not by the Hugerschoff path involving an electrophilic substitution reaction. For thioureas containing reactive ortho halogens such as (−Br, −I) the reaction proceeds at room temperature giving 2-aminobenzothiazoles via a dehalogenative path. Failure to transform thiourea (Tu) to Tag with Cu(I) salts suggesting the requirement of oxidising Cu(II) salts for this oxidative transformation. Thus this method gives an easy access to a variety of Tag moiety using environmentally benign reagent. These Tag moieties might find application as metal scavenger and may be used as vulcanising agent. Mild reaction conditions, high yields, tolerance of various functional groups are some of the main attributes of this methodology.

III.5. Experimental Section

III.5.1. Instrumentation and Characterization

As described in Chapter II, Section II.6.1.

III.5.2. Experimental Procedure for the Synthesis of Thiourea (1)

To a stirred solution of phenylisothiocyanate (405 mg, 3 mmol) in ethanol (10 mL) was added drop wise morpholine (261 mg, 3 mmol). Formation of thiourea (**1**) was observed within 15 minutes as judged from TLC. This was used as such for the next step. For confirmation and characterization ethanol was evaporated under reduced pressure and dried by vacuum drier, a white solid compound was formed in quantitative yield.

III.5.3. Experimental Procedure for the Synthesis of Tag Product (1a)

Phenylisothiocyanate (**1'**) (3 mmol, 666 mg) in EtOAc/H_2O (25 mL, (3:1) was added morpholine (2 mmol) and stirred at room temperature complete formation of phenyl morpholine-4-carbothiamide (**1**) was observed within 15 minutes. To this was added an aqueous solution of $CuBr_2$ (0.9 mmol, 201 mg) and the resultant reaction mixture was stirred at room temperature for about 20 minutes. During this period a pale yellow solution along with yellow precipitate was obtained. After completion of the reaction, ethyl acetate (30 mL) was admixed to the reaction mixture. Aqueous ammonia (20%, 10 mL), was added to the above ethyl acetate suspended reaction mixture and the heterogeneous mixture was stirred at room temperature. During this time (10 min) the suspended insoluble yellow solid got dissolved into the ethyl acetate layer leaving the ammonical layer blue in color. The ethyl acetate layer was separated and dried over anhydrous Na_2SO_4 and concentrated under a reduced pressure. The product (**1a**) is further purified by recrystallization technique using ethyl acetate and hexane (9:1) (551 mg, 89%). Alternatively, the products can be purified by passing through silica gel column (saturated with 1% Et_3N) and eluted with hexane : ethylacetate (8:2) to give desire product (551 mg, 89%).

III.5.4. General Procedure for Preparation of Complexes

Method-1: $[Cu_2^{I}(\mu\text{–}I)_2Tag_2]$ (A). To a solution of thiourea (**1**) (1 mmol, 222 mg) dissolved in ethanol (15 mL) was added an ethanol solution of CuI_2 (1 mmol, 317.5 mg) and the resultant reaction mixture was stirred for 20 minutes. During this period a yellow colored solution along with yellow precipitate was formed. The precipitate was dissolved by warming the reaction mixture. Then resultant the solution was filtered under hot condition and kept for crystallization. A pale yellow crystalline solid were obtained upon standing. Yield of first crops 204 mg (68 %).

Method-2: $[Cu_2^{I}(\mu\text{–}I)_2Tag_2]$ (A). To a solution of thioamidoguanidino ligand (**1a**) (1 mmol, 410 mg) in acetonitrile (15 mL) was added CuI (1 mmol, 190 mg) dissolved in acetonitrile (15 mL) and the resultant reaction mixture was stirred for 20 minutes. A yellow color solution was formed along with yellow precipitate. The entire precipitate was dissolved by warming the reaction mixture in a water bath. Then the solution was filtered hot, redissolved by warming the filtrate and kept for crystallization, which deposited a pale yellow crystalline solid. Yield of first crops 535 mg (89 %). This compound prepared was found to be identical in all respect to that prepared following method-1.

Preparation of $[Cu_2^{I}(\mu\text{–}Br)_2Tag_2]$ (B). Prepared following method-1 and $CuBr_2$ was used instead of CuI_2. Yield 440 mg (80 %).

Preparation of $[Cu^{I}_3(\mu_2\text{–}S)_4Tu_4X_3]$ (C). To a solution of thiourea (**1**) (1 mmol, 222 mg) dissolved in ethanol (15 mL) was added a solution of CuBr (1 mmol, 143.5 mg) dissolved in ethanol (5 mL) and the resultant reaction mixture was stirred for 20 minutes. A yellow colored solution was formed which was filtered and kept for crystallization, which deposited a pale yellow crystalline solid after few days. Yield of first crops 250 mg (76 %).

III.5.5. General Procedure for Preparation of 2-Morpholinbenzo[*d*]thiazole (11'a) from *N*-(2-Fluoro phenyl)morpholine-4-carbothiamide (11a) using $CuBr_2$

2-Fluoro phenylisothiocyanate (**11'**) (2 mmol) in DMSO (2 mL) was added morpholine (2 mmol) and stirred at room temperature complete formation of *N*-(2-Fluoro phenyl) morpholine-4-carbothiamide (**11**) was observed within 15 minutes. To this was added Na_2CO_3 (2 mmol), $CuBr_2$ (0.01 mmol, 5 mol%) and the reaction mixture was heated in an oil bath at 80 ^oC. The progress of the reaction was monitored by TLC using ethyl acetate and hexane (2:8). After 22h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). Then reaction mixture was filtered over Celite and washed with ethyl acetate (3 x 5 mL). The filtrate was washed successively with water (2 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product (**11'a**) was purified over a column of silica gel with EtOAc : hexane (2:8) as the eluents to give the product 1a in (0.33g) 75% isolated yield.

III.5.6. Crystallographic Description

Crystal data of complex (A): CCDC reference number 8757778, $C_{22}H_{26}ICuN_4O_2S$, M = 600.99, Monoclinic, space group C 2/c, Z = 8, a = 22.3537(12) Å, b = 15.7364(10) Å, c = 14.7465(10) Å, $\alpha = \gamma = 90.0^o$, $\beta = 114.048(3)^o$, T = 293(2) K, Volume = 4737.1(5) $Å^3$, μ (Mo–Kα) = 2.340 mm^{-1}, 5953 reflections measured, 3286 unique (R_{int} = 0.0799).The final $R_1(I > 2\sigma(I))$ was 0.1177, GOF = 1.088.

Crystal data of complex (B): $C_{22}H_{26}BrCuN_4O_2S$, CCDC reference number 876074, M = 553.99, Orthorhombic, space group Pccn, Z = 8, a = 15.4710(8) Å, b = 20.2116(10) Å, c = 14.6730(8) Å, $\alpha = \beta = \gamma = 90.0^o$, T = 293(2) K, Volume = 553.99 $Å^3$, μ (Mo–Kα) = 2.811 mm^{-1}, 2919 reflections measured, 2316 unique (R_{int} = 0.0462). The final $R_1(I > 2\sigma(I))$ was 0.0567, GOF = 1.136.

Crystal data of complex (C): CCDC reference number 877794, $C_{44}H_{56}Br_3Cu_3N_8O_4S_4$, M = 1319.60, Triclinic, space group P –1, Z = 2, a = 12.8009(5) Å, b = 14.6565(6) Å, c = 14.8317(6)

Å, α = 81.033(2)º, β = 75.174(2)º, γ = 77.727(2)º, T = 293(2) K, Volume = 2613.34(18) $Å^3$, μ (Mo–Kα)= 3.711 mm^{-1}, 13060 reflections measured, 7046 unique (R_{int} = 0.0378). The final $R_1(I > 2\sigma(I))$ was 0.0905, GOF = 0.990.

Crystal data of compound (3d): CCDC reference number 894067, $C_{28}H_{38}N_4S$, M = 462.69, Monoclinic, space group P 21/c, Z = 4, a = 9.5021(13) Å, b = 11.2799(14) Å, c = 24.739(3) Å, α = 90.00º , β = 95.125(8)º, γ = 107.266(2)º, T = 296(2) K, Volume = 2641.0(6) $Å^3$, μ (Mo–Kα)= 0.145 mm^{-1}, 29006 reflections measured, 2737 unique (R_{int} = 0.0570). The final $R_1(I > 2\sigma(I))$ was 0.1242, GOF = 1.045.

Crystal data of compound (15'a): CCDC reference number 894068, $C11H11BrN_2OS$, M = 299.19, Orthorhombic, space group P-1, Z = 4, a = 10.01289(3) Å, b = 11.2225(3) Å, c = 11.7532(4) Å, α = 94.059(2)º , β = 112.599(2)º, γ = 90.00(2)º, T = 296(2) K, Volume = 1151.66(7) $Å^3$, μ (Mo–Kα)= 3.729 mm^{-1}, 18708 reflections measured, 3592 unique (R_{int} = 0.0851). The final $R_1(I > 2\sigma(I))$ was 0.0866, GOF = 1.383.

III.6. References

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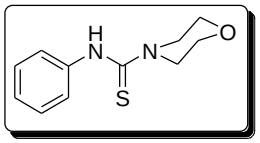
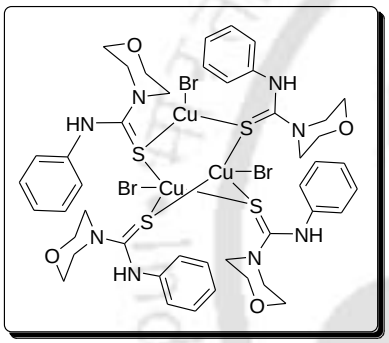
III.7. Spectral Data

_N_-Phenylmorpholine-4-carbothioamide (1):



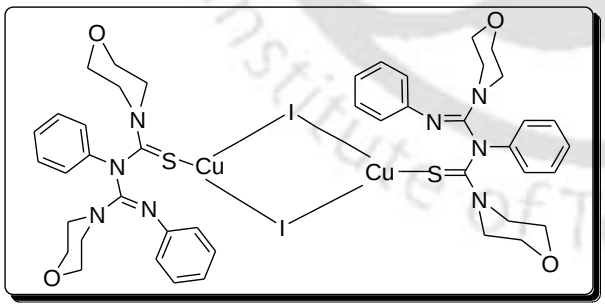
M. p. 124–126 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (t, 4H, J = 4.8 Hz), 3.73 (t, 4H, J = 4.4 Hz), 7.13 (m, 3H), 7.30 (t, 2H, J = 8.0 Hz), 7.66 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.4, 66.1, 123.7, 125.4, 129.0, 139.9, 183.2; IR (KBr): 3436, 3170, 3027, 2917, 2851, 1651, 1594, 1532, 1495, 1409, 1321, 1264, 1205, 1111, 1026, 935, 853 cm^{-1}; Anal. Calcd for $C_{11}H_{14}N_2OS$: C, 59.43; H, 6.35; N, 12.60; S, 14.42.; found: C, 59.48; H, 6.42; N, 12.53; S, 14.48; MS (ESI): 223.2543 (MH^+).

Complex $[Cu^{I}_3(\mu_2–S)_4Tu_4X_3]$ (C)



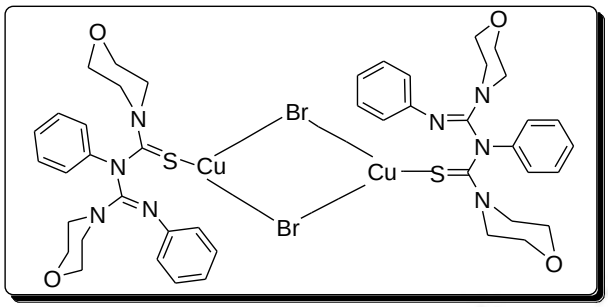
Pale yellow solid; M.p. 138–139 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.53 (s, 8H), 7.00 (t, 1H, J = 7.2 Hz), 7.19 (m, 4H), 10.22 (brs, 1H); IR (KBr): 3164, 3129, 2959, 2846, 1591, 1536, 1515, 1446, 1360, 1322, 1267, 1228, 1196, 1115, 1024, 951, 764, 689 cm^{-1}; Anal. Calcd for $C_{44}H_{56}Cu_3Br_3N_8O_4S_4$: C, 40.05; H, 4.28; N, 8.49; S, 9.72; found: C, 40.12; H, 4.34; N, 8.43; S, 9.67.

Complex $[Cu_2^{I}(\mu–I)_2Tag_2]$ (A).



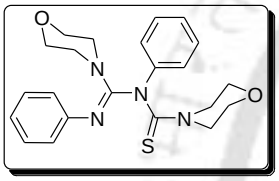
M.p. 212–213 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.45 (m, 16H), 6.97 (m, 4H), 7.11 (t, 2H, J = 7.2 Hz), 7.18 (t, 4H, J = 7.6 Hz); IR (KBr): 2964, 2920, 2853, 1640, 1587, 1486, 1422, 1356, 1299, 1276, 1239, 1108, 1063, 993, 850, 765, 753 cm^{-1}; Anal. Calcd for $C_{44}H_{52}Cu_2I_2N_8O_4S_2$: C, 43.97; H, 4.36; N, 9.32; S, 5.34; found: C, 44.01; H, 4.41; N, 9.27; S, 5.29.

Complex $[Cu_2^{I}(\mu\text{–}I)_2Tag_2]$ (B).



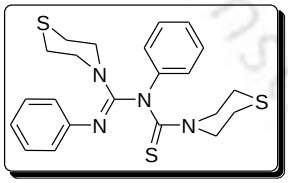
Pale yellow solid; M.p. 206–207 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.46 (m, 16H), 6.97 (d, 4H, J = 8.0 Hz), 7.11 (t, 2H, J = 7.2 Hz), 7.18 (t, 4H, J = 8.0 Hz); IR (KBr): 2961, 2921, 2855, 1637, 1586, 1485, 1421, 1302, 1239, 1157, 1109, 1062, 994, 935, 765, 753, 691 cm^{-1}; Anal. Calcd for $C_{44}H_{52}Cu_2Br_2N_8O_4S_2$: C, 47.70; H, 4.73; N, 10.11; S, 5.79; found: C, 47.76; H, 4.78; N, 10.05; S, 5.72.

***N*-((*E*)-Morpholino(phenylimino)methyl)-*N*-phenylmorpholine-4-carbothioamide (1a):**



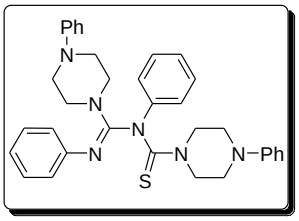
White solid; M.p. 163–165 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.90-3.52 (m, 16H), 6.95 (d, 2H, J = 8.0 Hz), 6.98 (d, 2H, J = 7.6 Hz), 7.09 (t, 2H, J = 7.6 Hz), 7.17 (t, 2H, J = 8.0 Hz), 7.30 (d, 2H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.8, 50.6, 65.4, 66.2, 121.2, 122.1, 122.8, 122.9, 124.7, 128.8, 129.7, 142.8, 149.3, 185.2; IR (KBr): 2963, 2920, 2856, 1637, 1587, 1485, 1421, 1302, 1277, 1239, 1109, 1062, 994, 765, 753, 691 cm^{-1}; MS (ESI): 411.2045 (MH^+).

***N*-((*E*)-Thiomorpholino(phenylimino)methyl)-*N*-phenylthiomorpholine-4-carbothioamide (1b):**



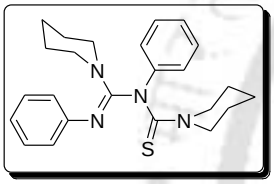
White solid; M.p. 188–190 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42–3.53 (m, 16H), 6.87–6.92 (m, 4H), 7.06 (t, 2H, J = 7.2 Hz), 7.13 (t, 4H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.5, 26.6, 48.9, 53.0, 121.0, 122.1, 122.8, 125.1, 128.8, 129.8, 143.2, 149.2, 149.5, 186.4; IR (KBr): 3446, 2919, 2855, 1630, 1586, 1474, 1416, 1358, 1295, 1274, 1223, 1019, 945, 751 cm^{-1}; MS (ESI): 443.1050 (MH^+).

_N_,4-Diphenyl-_N_-((_E_)-(phenylimino)(4-phenylpiperazin-1-yl)methyl)piperazine-1-carbothioamide (1c):



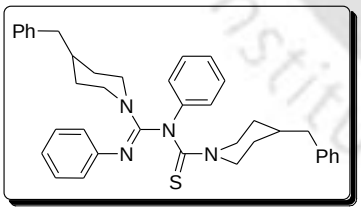
White solid; M.p. 200–201 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.61–3.66 (m, 16H), 6.62 (d, 2H, J = 8.8 Hz), 6.74 (d, 4H, J = 6.8 Hz), 6.88 (t, 2H, J = 7.2 Hz), 7.00 (t, 4H, J = 7.2 Hz), 7.08–7.26 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.3, 47.8, 48.6, 50.0, 115.5, 116.1, 116.3, 120.0, 120.3, 122.3, 122.9, 124.8, 128.9, 129.2, 129.3, 129.7, 143.1, 149.3, 149.7, 150.3, 151.2, 185.3 ; IR (KBr): 3431, 2904, 2819, 1638, 1591, 1479, 1413, 1305, 1252, 1224, 1152, 1048, 1024, 993, 918, 758, 691 cm^{-1}; MS (ESI): 561.2363 (MH^+).

_N_-Phenyl-_N_-((_E_)-(phenylimino)(piperidin-1-yl)methyl)piperidine-1-carbothioamide (1d):



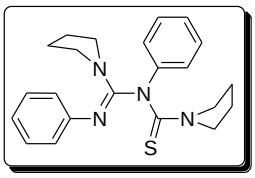
White solid; M.p. 183–184 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–1.67 (m, 12H), 2.63–3.82 (m, 8H), 6.90 (t, 2H, J = 7.6 Hz), 7.02–7.12 (m, 3H), 7.16 (t, 2H, J = 8.4 Hz), 7.26–7.40 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.6, 24.5, 24.6, 24.9, 47.4, 51.4, 122.1, 122.3, 124.1, 128.4, 129.2, 143.7, 149.7, 150.0, 184.9; IR (KBr): 2936, 2854, 1632, 1588, 1481, 1454, 1295, 1240, 1028, 989, 749 cm^{-1}; MS (ESI): 407.2261 (MH^+).

_N_-Benzyl-_N_-((_E_)-(4-benzylpiperidin-1-yl)(phenylimino)methyl)-_N_-phenylpiperidine-1-carbothioamide (1e):



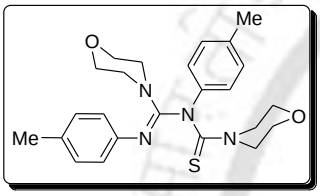
White solid; M.p. 151–152 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–4.12 (m, 22H), 7.00 (m, 5H), 7.15 (t, 2H, J = 7.2 Hz), 7.23 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.8, 37.4, 38.0, 42.5, 43.0, 46.8, 50.9, 122.4, 123.0, 124.2, 125.9, 126.1, 128.2, 128.3, 128.6, 129.1, 129.2, 129.3, 139.9, 140.3, 143.8, 149.8, 184.9; IR (KBr): 3428, 2989, 3024, 2921, 2848, 1651, 1589, 1493, 1396, 1296, 1236, 1221, 1142, 1056, 963, 746, 697 cm^{-1}; MS (ESI): 587.2807 (MH^+).

***N*-Phenyl-*N*-((*E*)-(phenylimino)(pyrrolidin-1-yl)methyl)pyrrolidine-1-carbothioamide (1f):**



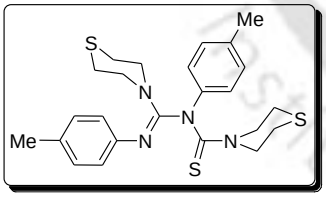
White solid; M.p. 153–155 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05–2.50 (m, 12H), 3.37–3.90 (m, 4H), 6.82 (m, 1H), 6.89 (t, 1H, *J* = 7.2 Hz), 6.96 (m, 1H), 7.04 (t, 1H, *J* = 7.6 Hz), 7.09 (d, 2H, *J* = 7.6 Hz), 7.15 (m, 2H), 7.19–7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 25.1, 25.8, 26.2, 47.2, 48.4, 51.9, 53.7, 120.9, 122.2, 123.2, 123.9, 128.4, 129.3, 129.8, 141.8, 150.0, 181.0; IR (KBr): 2962, 2863, 1587, 1488, 1438, 1415, 1330, 1288, 1260, 1175, 906, 859, 770 cm^{-1}; MS (ESI): 379.1642 (MH^+).

***N*-((*E*)-(p-Tolylimino)(morpholino)methyl)-*N*-p-tolylmorpholine-4-carbothioamide (2a):**



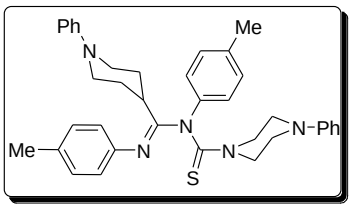
White solid; M.p. 140–141 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 3H), 2.25 (s, 3H), 2.82–3.47 (m, 16H), 6.84 (d, 4H, *J* = 8.0 Hz), 6.92 (d, 4H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7, 20.8, 46.6, 50.5, 65.2, 66.1, 121.0, 121.8, 129.1, 130.1, 131.6, 134.3, 140.1, 146.6, 149.3, 185.1; IR (KBr): 3436, 3021, 2959, 2920, 2855, 1630, 1605, 1505, 1472, 1438, 1288, 1232, 1158, 1115, 1068, 1000, 855, 828 cm^{-1}; MS (ESI): 439.1779 (MH^+).

***N*-((*E*)-(*p*-Tolylimino)(thiomorpholino)methyl)-*N*-*p*-tolylmorpholine-4-carbothioamide (2b):**



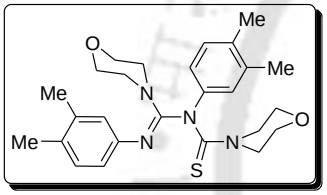
White solid; M.p. 161–162 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 2.33(s, 3H), 2.50–3.62 (m, 16H), 6.90 (d, 2H, *J* = 8.0 Hz), 7.02 (d, 2H, *J* = 8.0 Hz), 7.17 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 20.9, 26.4, 26.6, 48.8, 52.9, 121.9, 129.3, 130.3, 131.9, 134.8, 140.7, 146.6, 149.6, 186.4; IR (KBr): 2911, 2851, 1633, 1605, 1505, 1473, 1414, 1358, 1306, 1278, 1224, 1135, 1018, 946, 891, 832 cm^{-1}; Anal. Calcd for $C_{24}H_{30}N_4S_3$: C, 61.24; H, 6.42; N, 11.90; S, 20.44; found C, 61.29; H, 6.45; N, 11.86; S, 20.49.

_N_-((_E_)-(_p_-Tolylimino)(1-phenylpiperidin-4-yl)methyl)-4-phenyl-tolylpiperazine-1-carbothioamide (2c):



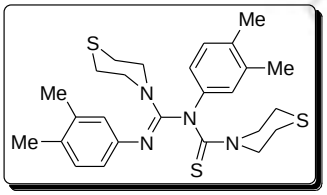
White solid; M.p. 215–216 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (s, 3H), 2.27 (s, 3H), 2.70–3.52 (m, 16H), 6.68 (d, 2H, J = 8.0 Hz), 6.83 (m, 5H), 6.94 (m, 6H), 7.20 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 20.9, 46.2, 47.8, 48.5, 50.0, 115.9, 116.2, 119.9, 120.2, 122.0, 129.3, 129.4, 130.2, 131.8, 134.4, 140.7, 146.9, 150.4, 151.3, 185.3; IR (KBr): 3430, 2919, 1633, 1598, 1505, 1486, 1412, 1305, 1230,. 1193, 1102, 998, 891, 792, 756 cm^{-1}; MS (ESI): 589.2782 (MH^+).

_N_-((_E_)-(3,4-Dimethylphenylimino)(morpholino)methyl)-_N_-(3,4-dimethylphenyl) morpholine-4-carbothioamide (3a):



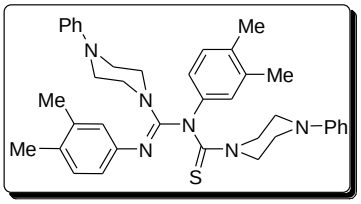
Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.11 (s, 3H), 2.18 (s, 6H), 2.85–3.76 (m, 16H), 6.69 (d, 2H, J = 7.6 Hz), 6.77 (s, 2H), 6.89 (d, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 19.2, 19.8, 20.1, 46.6, 50.6, 65.4, 66.2, 119.1, 123.3, 129.7, 130.4, 133.0, 136.4, 137.9, 140.4, 147.0, 149.3, 185.1; IR (Neat): 3444, 2962, 2919, 2856, 1633, 1448, 1423, 1303, 1236, 1114, 1065, 1020, 992, 860, 818, 734 cm^{-1}; Anal. Calcd for $C_{26}H_{34}N_4O_2S$: C, 66.92; H, 7.34; N, 12.01; S, 6.87; found C, 66.97; H, 7.37; N, 11.98; S, 6.92.

_N_-((_E_)-(3,4-Dimethylphenylimino)(thiomorpholino)methyl)-_N_-(3,4-dimethylphenyl) thiomorpholine-4-carbothioamide (3b):



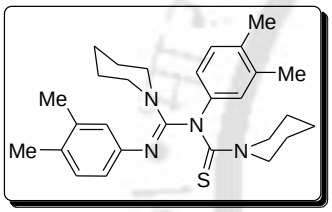
White solid; M.p. 188–189 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.12 (s, 3H), 2.14 (s, 3H), 2.17 (s, 3H), 2.19–3.72 (m, 16H), 6.34-7.01 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 19.1, 19.7, 20.0, 26.2, 26.5, 26.8, 48.7, 52.8, 119.0, 123.2, 129.6, 129.9, 130.2, 130.5, 133.2, 136.4, 137.9, 140.7, 146.9, 149.3, 186.1; IR (Neat): 3426, 3005, 2911, 2857, 1633, 1497, 1448, 1416, 1341, 1296, 1216, 1190, 1166, 1021, 952, 841 cm^{-1}; MS (ESI): 499.2154 (MH^+).

***N*-((*E*)-(3,4-Dimethylphenylimino)(4-phenylpiperazin-1-yl)methyl)-*N*-(3,4-dimethylphenyl)-4-phenylpiperazine-1-carbothioamide (3c):**



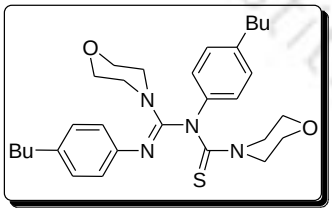
White solid; M.p. 190–191 ^{o}C ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.11 (s, 3H), 2.18 (s, 6H), 2.85–3.76 (m, 16H), 6.69 (d, 2H, J = 7.6 Hz), 6.77 (s, 2H), 6.89 (d, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 19.2, 19.9, 20.2, 46.2, 47.9, 48.6, 50.0, 116.0, 116.2, 119.3, 119.8, 120.3, 123.7, 129.2, 129.3, 129.9, 130.5, 133.0, 136.6, 138.1, 140.8, 147.0, 150.4, 151.2, 185.1; IR (Neat): 3432, 2913, 2846, 2824, 1632, 1598, 1497, 1448, 1388, 1305, 1281, 1227, 1153, 991, 924, 908, 812, 762 cm^{-1}; MS (ESI): 617.3067 (MH^+).

***N*-((*E*)-(3,4-Dimethylphenylimino)(piperidin-1-yl)methyl)-*N*-(3,4-dimethylphenyl) piperidine-1-carbothioamide (3d):**



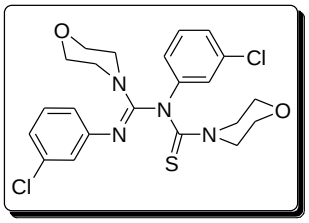
White solid; M.p. 188–189 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.69-1.80 (m, 12H), 2.09 (s, 6H), 2.17 (s, 6H), 2.87–3.73 (m, 8H), 6.14-7.03 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 19.1, 19.7, 19.9, 47.3, 51.5, 119.5, 121.5, 123.5, 125.2, 129.5, 129.7, 130.1, 132.3, 136.0, 137.3, 141.4, 147.4, 150.3, 184.9; IR (Neat): 3447, 3014, 2929, 2856, 1628, 1601, 1473, 1416, 1300, 1270, 1239, 1117, 999, 822 cm^{-1}; MS (ESI): 463.2850 (MH^+).

***N*-((*E*)-(4-Butylphenylimino)(morpholino)methyl)-*N*-(4-butylphenyl)morpholine-4-carbothioamide (4a):**



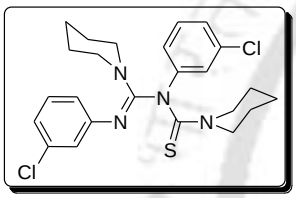
Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (m, 6H), 1.29 (m, 4H), 1.49 (m, 4H), 2.47 (m, 4H), 2.88–3.48 (m, 16H), 6.87 (d, 2H, J = 8.0 Hz), 6.96 (d, 2H, J = 8.0 Hz, 7.07 (M, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.2, 22.4, 33.4, 33.8, 34.9, 35.0, 46.7, 50.5, 65.4, 66.1, 121.8, 128.6, 129.5, 136.9, 139.5, 140.5, 146.8, 149.4, 185.3; IR (Neat): 3464, 2957, 2927, 2856, 2634, 1604, 1505, 1467, 1416, 1359, 1297, 1234, 1160, 1115, 1066, 1017, 998, 941, 838 cm^{-1}; MS (ESI): 523.2705 (MH^+).

***N*-((*E*)-(3-Chlorophenylimino)(morpholino)methyl)-*N*-(3-chlorophenyl)morpholine-4-carbothioamide (5a):**



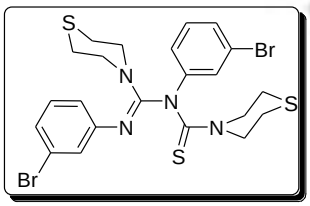
White solid; M.p. 172–173 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.25–3.78 (m, 16H), 6.83 (d, 2H, *J* = 8.0 Hz), 6.94 (d, 2H, *J* = 8.4 Hz), 6.96 (d, 2H, *J* = 4.8 Hz), 7.11 (t, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.9, 50.8, 65.5, 66.2, 119.1, 120.6, 122.2, 122.9, 125.1, 129.9, 130.8, 134.3, 135.6, 143.7, 149.2, 150.5, 184.5; IR (KBr): 3054, 2978, 2895, 2850, 1639, 1583, 1474, 1297, 1239, 1160, 1111, 1064, 938, 861, 776.cm^{-1}; MS (ESI): 479.0717 (MH^+).

***N*-((*E*)-(3-Chlorophenylimino)(piperidin-1-yl)methyl)-*N*-(3-chlorophenyl)piperidine-1-carbothioamide (5d):**



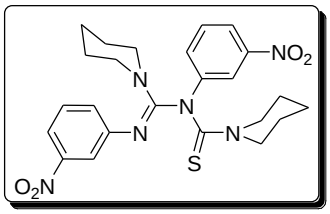
White solid; M.p. 123–125 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23–1.71 (m, 16H), 3.11–3.51 (m, 4H), 6.87 (t, 4H, *J* = 4.8 Hz), 6.98 (s, 1H), 7.05 (d, 2H, *J* = 7.2 Hz), 7.24 (d, 1H, *J* = 3.2 Hz).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.7, 24.5, 24.8, 25.1, 47.7, 51.9, 119.9, 121.0, 122.4, 124.5, 129.6, 130.4, 134.0, 135.0, 144.6, 150.1, 150.9, 184.3; IR (KBr): 3446, 2929, 2851, 1637, 1584, 1474, 1420, 1364, 1294, 1233, 1204, 1183, 1026, 989, 853, 768, 747, 694 cm^{-1}; Anal. Calcd for $C_{24}H_{28}Cl_2N_4S$: C, 60.62; H, 5.94; N, 11.78; S, 6.74; found C, 60.67; H, 5.99; N, 11.72; S, 6.78.

***N*-((*E*)-(3-Bromophenylimino)(thiomorpholino)methyl)-*N*-(3-bromophenyl) thiomorpholine-4-carbothioamide (6b):**



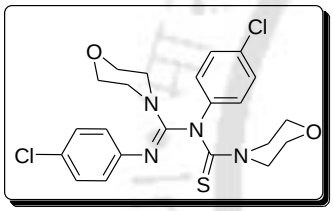
Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96-3.53 (m, 16H), 6.82 (m, 2H), 7.03 (m, 4H), 7.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.4, 48.8, 53.0, 120.9, 122.2, 123.1, 124.2, 124.7, 125.5, 128.0, 128.6, 130.0, 130.3, 130.6, 130.9, 143.8, 150.3, 185.1; IR (KBr): 3403, 3058, 2960, 2914, 2851, 1735, 1621, 1580, 1470, 1437, 1418, 1291, 1223, 1197, 1127, 1052, 1032, 951, 910, 806, 755 cm^{-1}; MS (ESI): 600.9188 (MH^+).

***N*-((*E*)-(3-Nitrophenylimino)(piperidin-1-yl)methyl)-*N*-(3-nitrophenyl)piperidine-1-carbothioamide (7d):**



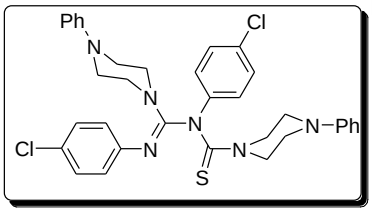
Yellow solid; M.p. 178–180 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91–1.92(m, 12H), 3.35 (m, 8H), 7.14–7.41 (m, 3H), 7.50 (t, 1H, J = 7.6 Hz), 7.63–7.86 (m, 3H), 7.93 (d, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.6, 24.3, 25.0, 47.9, 52.2, 116.8, 117.1, 119.53, 127.4, 129.3, 130.4, 144.4, 148.9, 150.5, 184.1; IR (KBr): 3080, 2942, 2925, 2851, 1637, 1606, 1522, 1479, 1444, 1352, 1299, 1280, 1244, 1206, 1182, 1027, 901, 739 cm^{-1}; MS (ESI): 497.1540 (MH^+).

***N*-((*E*)-(4-Chlorophenylimino)(morpholino)methyl)-*N*-(4-chlorophenyl)morpholine-4-carbothioamide (8a):**



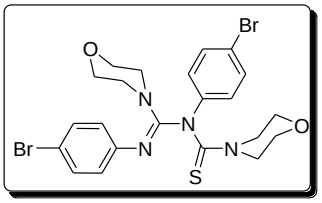
White solid; M.p. 162–164 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.81–3.92 (m, 16H), 6.74 (m, 2H), 6.93 (d, 2H, J = 8.0 Hz), 7.17 (d, 2H, J = 8.0 Hz), 7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.9, 50.9, 65.5, 66.3, 122.3, 123.5, 128.3, 128.9, 130.1, 130.5, 141.2, 147.7, 149.5, 184.9; IR (KBr): 2963, 2889, 2845, 1637, 1584, 1487, 1461, 1416, 1360, 1297, 1273, 1258, 1232, 1207, 1159, 1112, 1094, 1074, 1010, 997, 825 cm^{-1}; Anal. Calcd for $C_{22}H_{24}Cl_2N_4O_2S$: C, 55.12; H, 5.05; N, 11.69; S, 6.69; found C, 55.17; H, 5.09; N, 11.63; S, 6.73.

***N*-((*E*)-(4-Chlorophenylimino)(4-phenylpiperazin-1-yl)methyl)-*N*-(4-chlorophenyl)-4-phenylpiperazine-1-carbothioamide (8c):**



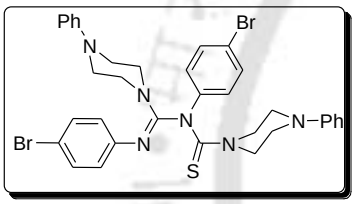
White solid; M.p. 159–160 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.80–3.67 (m, 16H), 6.77 (d, 2H, J = 8.0 Hz), 6.87 (m, 5H), 6.96 (d, 2H, J = 8.4 Hz), 7.17 (d, 2H, J = 8.4 Hz), 7.24 (m, 5H), 7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.3, 48.0, 48.6, 50.3, 116.3, 116.4, 120.1, 120.6, 123.5, 128.0, 128.8, 129.2, 129.3, 129.9, 130.2, 141.4, 147.9, 150.2, 151.0, 184 .8; IR (KBr): 3433, 2910, 2840, 1633, 1600, 1487, 1422, 1299, 1226, 1157, 1092, 998, 890, 833, 761 cm^{-1}; MS (ESI): 629.2162 (MH^+).

_N_-((_E_)-(4-Bromophenylimino)(morpholino)methyl)-_N_-(4-bromophenyl)morpholine-4-carbothioamide (9a):



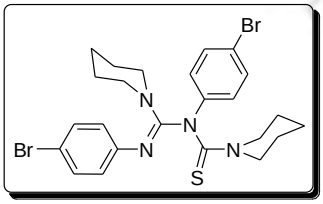
White solid; M.p. 174–175 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60–3.81 (m, 16H), 6.85 (brs, 2H), 6.87 (d, 2H, J = 8.4Hz), 7.31 (d, 2H, J = 8.4 Hz), 7.49 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.9, 50.9, 65.5, 66.3, 115.8, 118.0, 121.9, 123.9, 131.8, 132.9, 141.7, 148.3, 148.7, 149.3, 184.8; IR (KBr): 3046, 2964, 2921, 2853, 1633, 1578, 1485, 1417, 1359, 1296, 1274, 1235, 1156, 1113, 1067, 999, 854, 831, 785 cm^{-1}; Anal. Calcd for $C_{22}H_{24}Br_2N_4O_2S$: C, 46.49; H, 4.26; N, 9.86; S, 5.64; found C, 46.43; H, 4.30; N, 9.81; S, 5.68.

_N_-((_E_)-(4-Bromophenylimino)(4-phenylpiperazin-1-yl)methyl)-_N_-(4-bromophenyl)-4-phenylpiperazine-1-carbothioamide (9c):



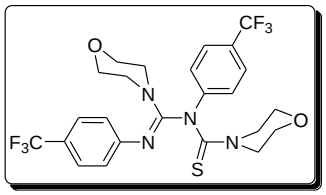
Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.79–3.63 (m, 16H), 6.76 (d, 2H, J = 8.0 Hz), 6.84 (t, 5H, J = 7.6 Hz), 6.90 (d, 2H, J = 9.2 Hz), 7.22 (t, 5H, J = 7.2 Hz), 7.30 (d, 2H, J = 8.4 Hz), 7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.2, 48.0, 48.5, 50.3, 115.6, 116.3, 117.8, 120.1, 120.5, 124.0, 129.2, 129.3, 131.7, 132.8, 141.8, 148.3, 149.2, 150.1, 151.0, 184.5; IR (KBr): 3433, 2894, 2846, 1632, 1599, 1484, 1427, 1386, 1300, 1224, 1168, 1067, 999, 891, 828, 761 cm^{-1}; MS (ESI): 719.1096 (MH^+).

_N_-((_E_)-(4-Bromophenylimino)(piperidin-1-yl)methyl)-_N_-(4-bromophenyl)piperidine-1-carbothioamide (9d):



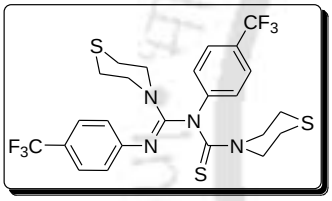
White solid; M.p. 177–179 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01–1.85 (m, 12H), 2.81–3.87 (m, 8H), 6.77 (m, 2H), 6.88 (d, 2H, J = 8.4 Hz), 7.26 (d, 2H, J = 8.4 Hz), 7.42 (d, 2H, J = 4.4Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8, 24.5, 24.9, 25.1, 47.7, 51.9, 115.2, 117.4, 123.1, 124.2, 131.5, 132.5, 142.8, 148.8, 150.1, 184.7; IR (KBr): 3006, 2936, 2917, 2851, 1630, 1578, 1483, 1423, 1362, 1297, 1270, 1240, 1205, 1185, 1066, 1051, 1026, 1005, 987, 891, 851, 822, 776 cm^{-1}; Anal. Calcd for $C_{24}H_{28}Br_2N_4S$: C, 51.08; H, 5.00; N, 9.93, S, 5.68; found C, 51.14; H, 5.03; N, 9.87; S, 5.72.

***N*-((*E*)-(4-(Trifluoromethyl)phenylimino)(morpholino)methyl)-*N*-(4-(trifluoro methyl)phenyl)morpholine-4-carbothioamide (10a):**



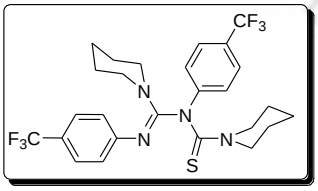
White solid; M.p. 148–149 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92–3.95 (m, 16H), 6.90 (brs, 2H), 7.07 (d, 2H, J = 8.0 Hz), 7.47 (d, 2H, J = 8.0 Hz), 7.62 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.9, 51.0, 65.4, 66.2, 120.5, 121.1, 122.3, 122.4, 124.9, 125.2, 125.3, 125.9, 126.1, 126.5, 126.8, 127.2, 145.4, 148.9, 152.5, 184.5; IR (KBr): 2965, 2920, 2857, 1640, 1602, 1514, 1475, 1424, 1324, 1292, 1261, 1235, 1159, 1113, 1064, 1035, 1013, 998, 942, 844 cm^{-1}; Anal calcd for $C_{24}H_{24}F_6N_4O_2S$: C, 52.74; H, 4.43; N, 10.25; S, 5.87; found: C, 52.77; H, 4.39; N, 10.28; S, 5.80.

***N*-((*E*)-(4-(Trifluoromethyl)phenylimino)(thiomorpholino)methyl)-*N*-(4-(trifluorometh-yl)phenyl)thiomorpholine-4-carbothioamide (10b):**



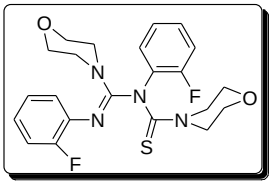
White solid; M.p. 170–1471 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 187-3.75 (m, 16H), 7.01 (d, 2H, J = 8.4 Hz), 7.43 (d, 2H, J = 8.0 Hz), 7.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.5, 46.8, 49.0, 53.3, 122.2, 123.1, 125.0, 126.0, 127.1, 145.6, 148.9, 152.3, 185.4; IR (KBr): 3060, 2917, 1634, 1601, 1469, 1416, 1321, 1200, 1176, 1125, 1064, 1012, 951, 845 cm^{-1}; MS (ESI): 579.1278 (MH^+).

***N*-((*E*)-(4-(Trifluoromethyl)phenylimino)(piperidin-1-yl)methyl)-*N*-(4-(trifluoromethyl) phenyl)piperidine-1-carbothioamide (10d):**



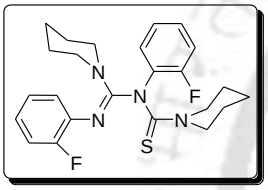
White solid; M.p. 138–140 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22–1.76 (m 16H), 3.06–3.26 (m, 4H) 6.95 (s, 2H), 7.04 (d, 2H, J = 8.0 Hz), 7.38 (d, 2H, J = 8.0 Hz), 7.53 (d, 2H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.6, 24.4, 24.9, 25.0, 47.8, 52.0, 121.5, 122.5, 123.4, 124.3, 124.6, 125.3, 125.8, 126.7, 146.4, 149.8, 153.0, 184.2.; IR (KBr): 3065, 2936, 2854, 1635, 1597, 1479, 1432, 1327, 1302, 1239, 1163, 1118, 1100, 1064, 891, 840 cm^{-1}; Anal calcd for $C_{26}H_{28}F_6N_4S$: C, 57.55; H, 5.20; N, 10.33; S, 5.91; found C, 57.59; H, 5.24; N, 10.29; S, 5.96.

***N*-((*E*)-(2-Fluorophenylimino)(morpholino)methyl)-*N*-(2-fluorophenyl)morpholine-4-carbothioamide (11a):**



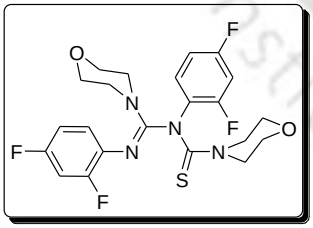
White solid; M.p. 123–125 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.68–3.74 (m, 16H), 6.87–7.33 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.2, 50.5, 66.1, 66.4, 114.6114.8, 11.1, 115.3, 116.7, 116.9, 121.9, 123.4, 123.5, 124.0, 124.5, 124.9, 125.3, 125.7, 126.2, 127.3, 130.4, 136.4, 150.6, 154.5, 186.3; IR (KBr): 3368, 2954, 2905, 2849, 1629, 1603, 1496, 1455, 1276, 1235, 1156, 1111, 1064, 1009, 938, 856, 755 cm^{-1}; MS (ESI): 447.1290 (MH^+).

***N*-((*E*)-(2-Fluorophenylimino)(piperidin-1-yl)methyl)-*N*-(2-fluorophenyl)piperidine-1-carbothioamide (11d):**



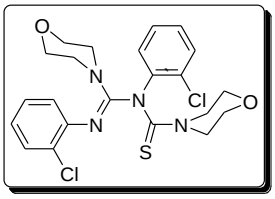
White solid; M.p. 104–106 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25–1.83 (m, 12H), 3.38-3.46 (m, 8H), 6.61–7.27 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 24.9, 25.5, 45.1, 47.5, 48.0, 114.3 114.5, 115.0, 116.3, 116.5, 121.7, 122.6, 122.7, 123.5, 124.3, 124.6, 126.0, 126.7, 127.6, 127.7, 151.5, 153.9, 154.3, 186.0; IR (KBr): 3240, 3170, 3098, 3052, 1661, 1588, 1537, 1492, 1423, 1311, 1005, 831, 755 cm^{-1}; MS (ESI): 443.2314 (MH^+).

***N*-((*E*)-(2,4-(Difluorophenylimino)(morpholino)-*N*-(2,4-(difluorophenyl)morpholine-4-carbothioamide (12a):**



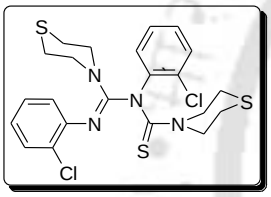
White solid; M.p. 138–140 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.36 (t, 4H, J = 4.4 Hz), 3.62-3.67 (m, 8H), 3.81 (t, 4H, J = 4.4 Hz), 6.73-6.81 (m, 4H), 7.30-7.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.2, 48.7, 66.1, 66.4, 103.3, 103.6, 103.8, 104.1, 104.3, 104.4, 104.6, 111.0, 111.1, 111.2, 111.3, 123.7, 124.0, 129.2, 129.3, 154.8, 157.7, 159.4, 161.9, 162.0, 183.1 ppm; IR (KBr): 2956, 2923, 2859, 1625, 1513, 1433, 1333, 1253, 1117, 1028, 969, 852, 800, 727 cm^{-1}; MS (ESI): 483.1043 (MH^+).

_N_-((_E_)-(2-Chlorophenylimino)(morpholino)methyl)-_N_-(2-chlorophenyl)morpholine-4-carbothioamide (13a):



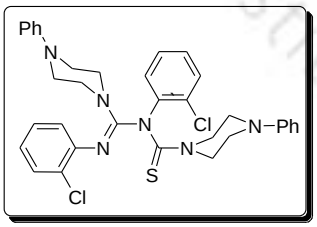
Mp 154–155 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50–4.60 (m 16H), 6.39–7.68 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.1, 47.0, 50.9, 66.0, 121.5, 122.8, 123.4, 126.2, 126.4, 127.3, 128.0, 129.1, 131.0, 139.6, 145.7, 148.5, 187.2; IR (KBr): 3057, 2950, 2894, 2849, 1632, 1580, 1470, 1427, 1401, 1363, 1303, 1272, 1237, 1219, 1206, 1159, 1150, 1119, 1109, 1051, 1031, 999, 953, 876, 757.cm^{-1}. Anal. Calcd for $C_{22}H_{24}Cl_2N_4O_2S$: C, 55.12; H, 5.05; N, 11.69; S, 6.69; found C, 55.17; H, 5.09; N, 11.63; S, 6.73.

_N_-((_E_)-(2-Chlorophenylimino)(thiomorpholino)methyl)-_N_-(2-chlorophenyl)thiomorpholine-4-carbothioamide (13b):



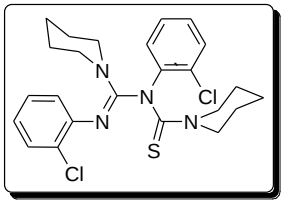
Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84–3.78 (m 16H), 6.87 (m, 2H), 7.08 (m, 4H), 7.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.5, 48.9, 53.1, 121.0, 122.3, 123.2, 124.8, 125.6, 128.1, 130.1, 131.0, 144.0, 149.2, 150.4, 185.3; IR (KBr): 3443, 2950, 2889, 2851, 1634, 1581, 1465, 1426, 1410, 1299, 1223, 1179, 1135, 1061, 947, 901, 836, 784, 772 cm^{-1}; MS (ESI): 511.0250 (MH^+).

_N_-((_E_)-(2-Chlorophenylimino)(4-phenylpiperazin-1-yl)methyl)-_N_-(2-chlorophenyl)-4-phenylpiperazine-1-carbothioamide (13c):



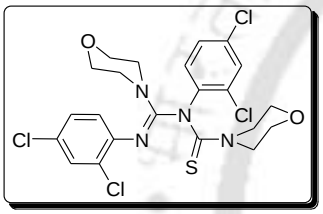
Mp 207–208 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.83–3.64 (m 16H), 6.76 (d, 2H, J = 8.8 Hz), 6.85 (m, 5H), 6.95 (m, 1H), 7.08 (m, 2H), 7.24(m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.4, 48.1, 48.7, 50.3, 116.5, 120.2, 120.7, 121.3, 122.4, 123.3, 123.7, 125.0, 125.8, 127.9, 129.3, 129.4, 130.2, 131.0, 144.1, 149.3, 150.2, 150.7, 151.1, 184.4; IR (KBr): 3431, 2901, 2826, 1635, 1599, 1580, 1470, 1424, 1385, 1307, 1223, 1152, 1001, 907, 757, 693 cm^{-1}; Anal. Calcd for $C_{34}H_{34}Cl_2N_6S$: C, 64.86; H, 5.44; N, 13.35; S, 5.09; found C, 64.91; H, 5.49; N, 13.31; S 5.13.

_N_-((_E_)-(2-Chlorophenylimino)(piperidin-1-yl)methyl)-_N_-(2-chlorophenyl)piperidine-1-carbothioamide (13d):



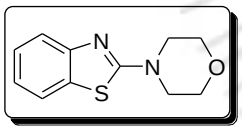
Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83-2.01 (m, 16H), 3.68 (m, 4H), 6.62-7.39 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 24.7, 25.1, 25.7, 48.3, 51.9, 121.5, 122.2, 122.9, 123.7, 126.4, 126.9, 127.7, 128.9, 130.7, 140.5, 142.0, 147.5, 187.7; IR (KBr): 3448, 2935, 2853, 1620, 1580, 1475, 1440, 1297, 1234, 1207, 1176, 1031, 755 cm^{-1}; Anal. Calcd for $C_{24}H_{28}Cl_2N_4S$: C, 60.62; H, 5.94; N, 11.78; S, 6.74; found C, 60.67; H, 5.99; N, 11.72; S, 6.78.

_N_-((_E_)-(2,4-(Dichlorophenylimino)(morpholino)-_N_-(2,4-(dichlorophenyl)morpholine-4-carbothioamide (14a):



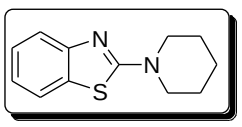
Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40-3.67 (m, 16H), 6.89 (m, 3H), 7.25 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.2, 51.0, 65.9, 66.4, 121.8, 122.8, 126.5, 127.2, 127.7, 127.9, 128.4, 128.6, 130.7, 132.6, 134.4, 144.6, 153.9, 186.7; IR (KBr): 2961, 2921, 2856, 1633, 1471, 1423, 1358, 1294, 1235, 1145, 1114, 1034, 999, 820, 737 cm^{-1}; MS (ESI): 548.9885 (MH^+).

2-Morpholinobenzo[_d_]thiazole (11'a):



White solid; M.p. 120–122 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.59 (t, 4H, J = 4.4 Hz), 3.80 (t, 4H., J = 4.4 Hz), 7.07 (t, 1H, J = 7.6 Hz), 7.28 (t, 1H, J = 8.0 Hz), 7.57 (dd, 1H, J_1 = 6.4 Hz, J_2 = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.5, 66.2, 119.4,120.8, 121.7, 126.1, 130.6, 152.5, 169.0 IR (KBr): 2918, 2854, 1591, 1537, 1441, 1377, 1289, 1229, 1113, 1067, 1032, 945, 859, 756 cm^{-1}; Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72; S, 14.56; found C, 60.07; H, 5.55; N, 12.62; S, 14.48.

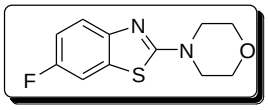
2-(Piperidin-1-yl)benzo[_d_]thiazole (11'd):



White solid; M.p. 96–97 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67 (s, 6H), 3.58 (s, 4H), 7.03 (t, 1H, J = 8.0 Hz), 7.26 (t, 1H, J = 8.0 Hz), 7.55 (dd, 2H, J_1 = 8.0 Hz, J_2 = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 25.4, 49.7, 118.9, 120.7, 121.1, 126.0, 130.8, 153.1, 169.0; IR (KBr): 2934, 2922, 2849, 1588, 1534, 1440,

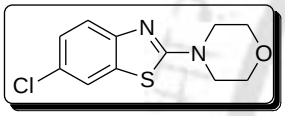
1382, 1332, 1257, 1234, 1209, 1120, 1006, 760 cm^{-1}; Anal. Calcd for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83; S, 14.69; found C, 66.08; H, 6.50; N, 12.76; S, 14.55.

6-Fluoro-2-morpholinobenzo[*d*]thiazole (12'a):



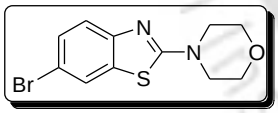
White solid; M.p. 157–158 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.51 (t, 4H, J = 4.8 Hz), 3.75 (t, 4H, J = 4.4 Hz), 6.97 (m, 1H), 7.25 (m, 1H), 7.44 (m, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 48.4, 66.1, 107.4, 107.6, 113.6, 113.9, 119.7, 119.8, 131.2, 131.4, 148.9, 157. 0, 159.4, 168.5; IR (KBr): 2982, 2901, 2863, 1673, 1597, 1538, 1459, 1376, 1343, 1287, 1234, 1181, 1111, 1073, 1029, 948, 920, 844 cm^{-1}; MS (ESI): 239.0662 (MH^+).

6-Chloro-2-morpholinobenzo[*d*]thiazole (14'a):



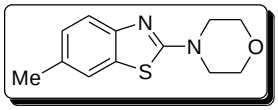
White solid; M.p. 144–145 ^oC; ^1H NMR (400 MHz, $CDCl_3$)*:* δ 3.61 (t, 4H, J = 4.8 Hz), 3.81 (t, 4H, J = 5.2 Hz), 7.19 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.0 Hz), 7.39 (d, 1H, J = 8.8 Hz), 7.49 (d, 1H, J = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.4, 66.1, 119.9, 120.4, 126.5, 126.7, 131.8, 151.2, 169.0; IR (KBr): 2943, 2919, 2859, 1594, 1537, 1447, 1330, 1279, 1233, 1110, 1027, 940, 814 cm^{-1}; MS (ESI): 255.0448 (MH^+).

6-Bromo-2-morpholinobenzo[*d*]thiazole (15'a):



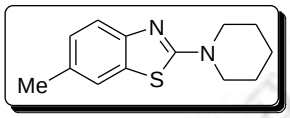
White solid; M.p. 165–167 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.57 (t, 4H, J = 4.8 Hz), 3.80 (t, 4H, J = 4.8 Hz), 7.37 (s, 2H), 7.68 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 48.5, 66.3, 114.0, 120.5, 123.3, 129.4, 132.4, 151.6, 169.1; IR (KBr): 2918, 2857, 1591, 1535, 1443, 1372, 1280, 1258, 1229, 1110, 1026, 940, 863, 813 cm^{-1}; Anal. Calcd for $C_{11}H_{11}N_2OSBr$: C, 44.16; H, 3.71; N, 9.36; S, 10.72; found C, 44.23; H, 3.76; N, 9.28; S, 10.64.

6-Methyl-2-morpholinobenzo[*d*]thiazole (18'a):



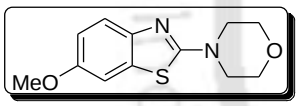
White solid; M.P. 134–136 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.56 (t, 4H, J = 4.8 Hz), 3.79 (t, 4H, J = 4.8 Hz), 7.09 (d, 1H, J = 8.0 Hz), 7.39 (s, 1H), 7.44 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 48. 6, 66.3, 119.0, 120.9, 127.4, 130.7, 131.6, 150.4, 168.6; IR (KBr): 2963, 2912, 2856, 1599, 1575, 1544, 1464, 1434, 1352, 1281, 1235, 1113, 1026, 943, 811 cm^{-1}; MS (ESI): 235.1035 (MH^+).

6-Methyl-2-(piperidin-1-yl)benzo[*d*]thiazole (18'd):



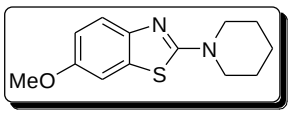
White solid; M.p. 105–107 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.66 (s, 6H), 2.35 (s, 3H), 3.55 (s, 4H), 7.06 (d, 1H, J = 8.0 Hz), 7.36 (s, 1H), 7.44 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 24.4, 25.5, 49.8, 118.6, 120.8, 127.2, 130.9, 150.9, 168.6; IR (KBr): 3434, 2924, 2852, 1569, 1537, 1459, 1440, 1382, 1336, 1264, 1240, 1121, 1006, 810, 626 cm^{-1}; MS (ESI): 233.1284 (MH^+).

6-Methoxy-2-morpholinobenzo[*d*]thiazole (19'a):



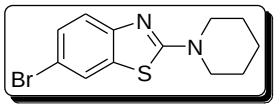
White solid; M.p. 130–132 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.53 (t, 4H, J = 4.4 Hz), 3.77 (t, 4H, J = 4.4 Hz), 3.78 (s, 3H), 6.89 (dd, 1H, J = 8.8Hz, J = 2.4 Hz), 7.12 (d, 1H, J = 2.8 Hz), 7.45 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.6, 56.0, 66.3, 105.3, 113.9, 119.9, 131.7, 146.8, 155.4, 167.8; IR (KBr): 3447, 2925, 2850, 1599, 1547, 1474, 1437, 1371, 1289, 1264, 1235, 1179, 1111, 1026, 946, 802, 652 cm^{-1}; MS (ESI): 251.1026 (MH^+).

6-Methoxy-2-(piperidin-1-yl)benzo[*d*]thiazole (19'd):



White solid; M.p. 108–110^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.66 (s, 6H), 3.53 (s, 4H), 3.79 (s 3H), 6.86 (dd, 1H, J = 8.0 Hz, J = 2.8 Hz), 7.11 (d, 1H, J = 2.4 Hz), 7.42 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 25.4, 49.8, 56.1, 105.4, 113.6, 119.3, 131.6, 147.1, 155.0, 167.8; IR (KBr): 3245, 2923, 2852, 1631, 1603, 1490, 1407, 1389, 1232, 1216, 1035, 986, 797 cm^{-1}; MS (ESI): 249.1063 (MH^+).

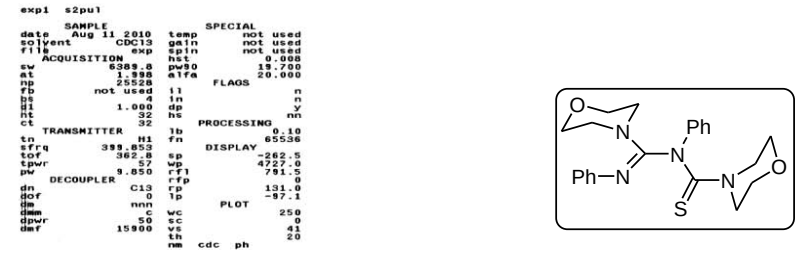
6-Bromo-2-(piperidin-1-yl)benzo[*d*]thiazole (20'd):

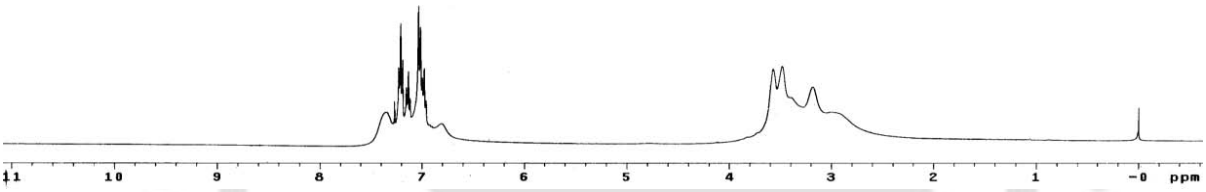


White solid; M.p. 118–120 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68 (s, 6H), 3.58 (s, 4H), 7.35 (s, 2H), 7.67 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 24.3, 25.4, 49.8, 113.3, 120.0, 123.2, 129.2, 132.5, 152.2, 169.0; IR (KBr): 3445, 2927, 2852, 1629, 1594, 1536, 1442, 1380, 1334, 1255, 1208, 1124, 1004, 812 cm^{-1}; MS (ESI): 297.0067 (MH^+).

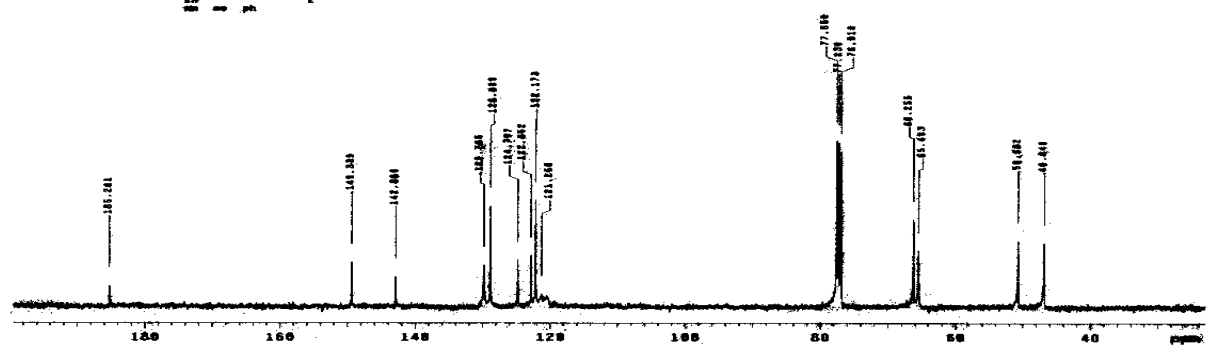
III.8. Selected Spectra

_N_-((_E_)-Morpholino(phenylimino)methyl)-_N_-phenylmorpholine-4-carbothioamide (1a). ^{1}H NMR (400 MHz, $CDCl_3$):

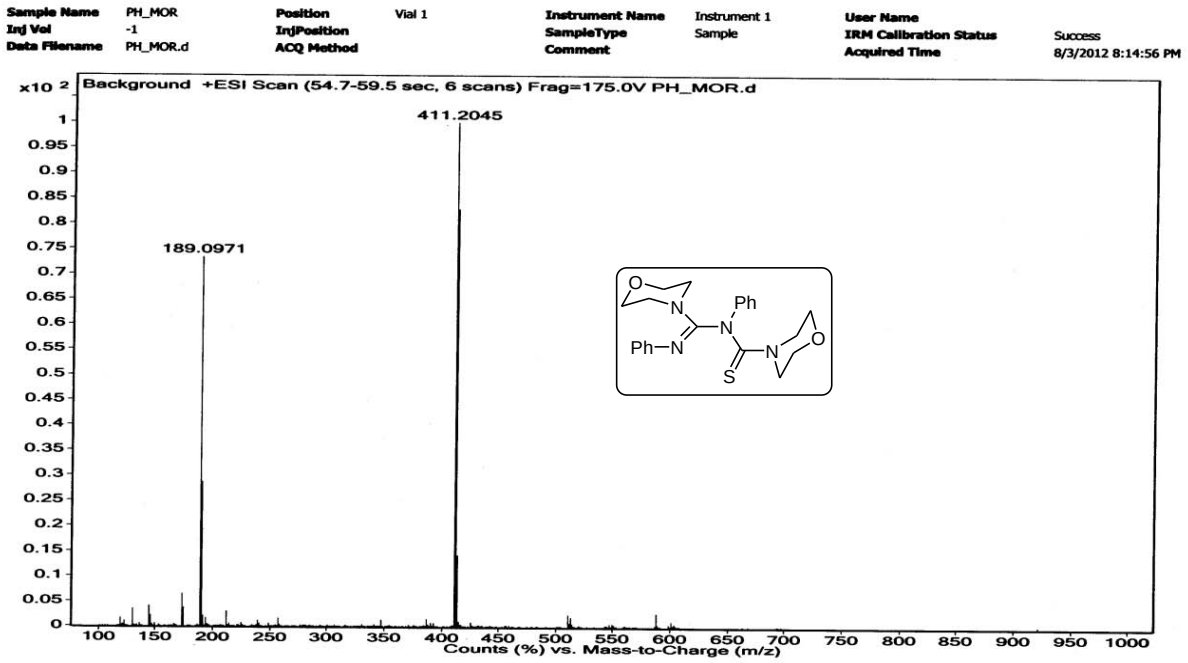




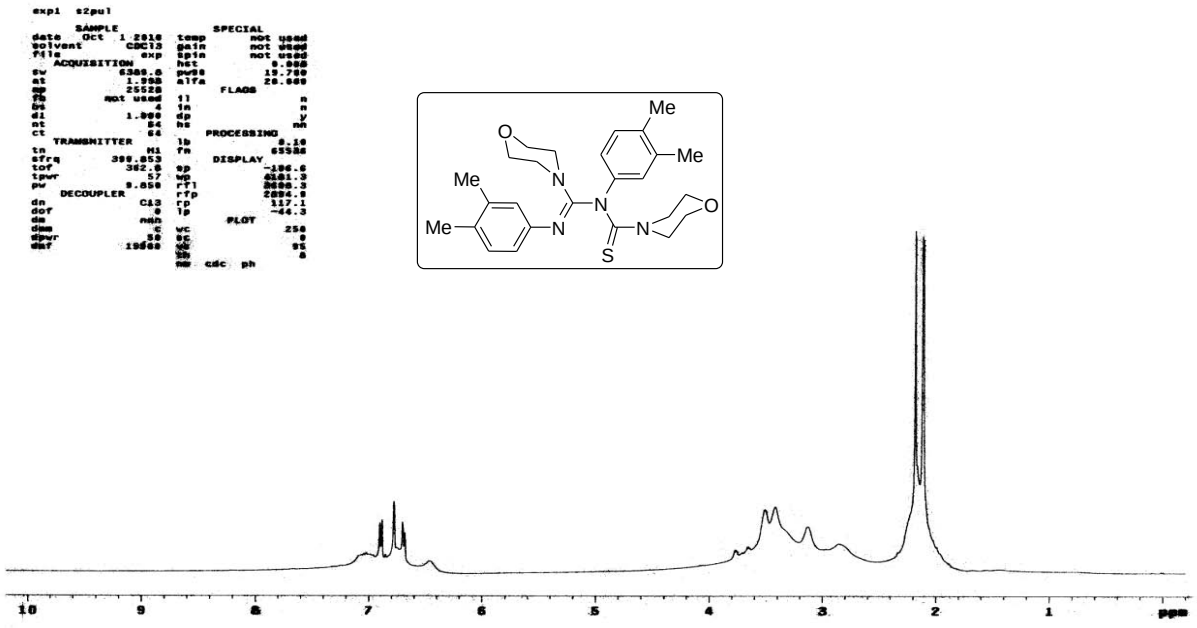
_N_-((_E_)-Morpholino(phenylimino)methyl)-_N_-phenylmorpholine-4-carbothioamide (1a). ^{13}C NMR (100 MHz, $CDCl_3$):



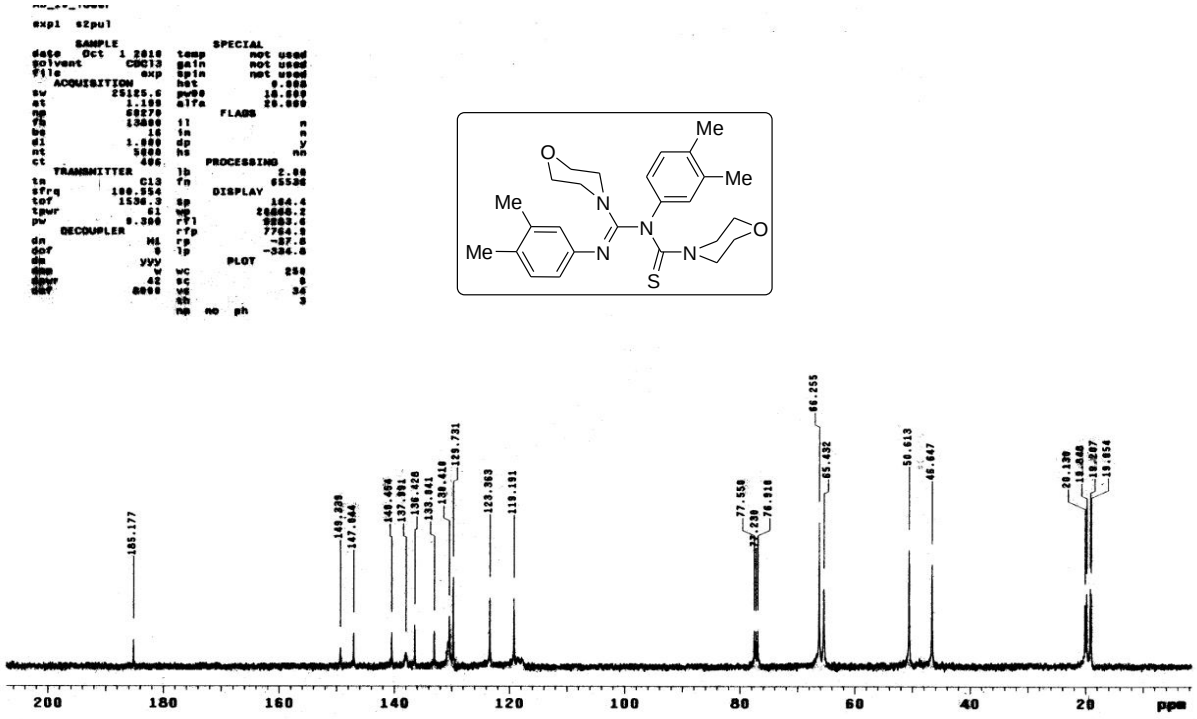
_N_-((_E_)-Morpholino(phenylimino)methyl)-_N_-phenylmorpholine-4-carbothioamide (1a). MASS SPECTRA:



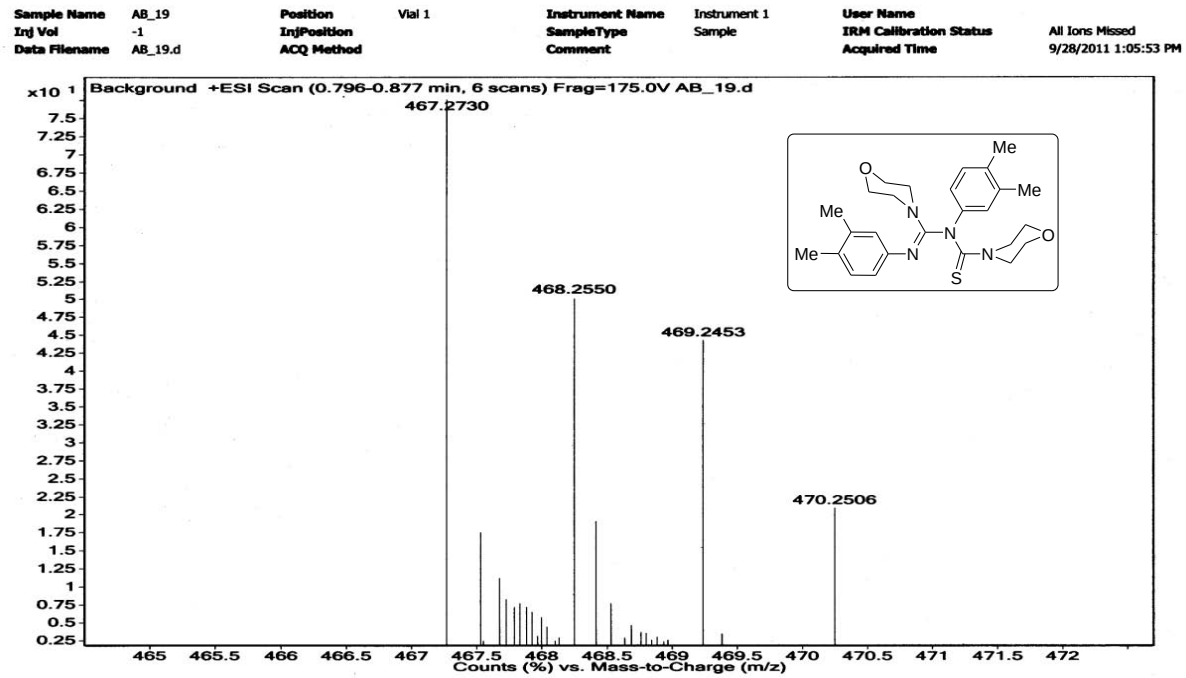
_N_-((_E_)-(3,4-Dimethylphenylimino)(morpholino)methyl)-_N_-(3,4-dimethylphenyl)morpholine-4-carbothioamide (3a). ^{1}H NMR (400 MHz, $CDCl_3$):



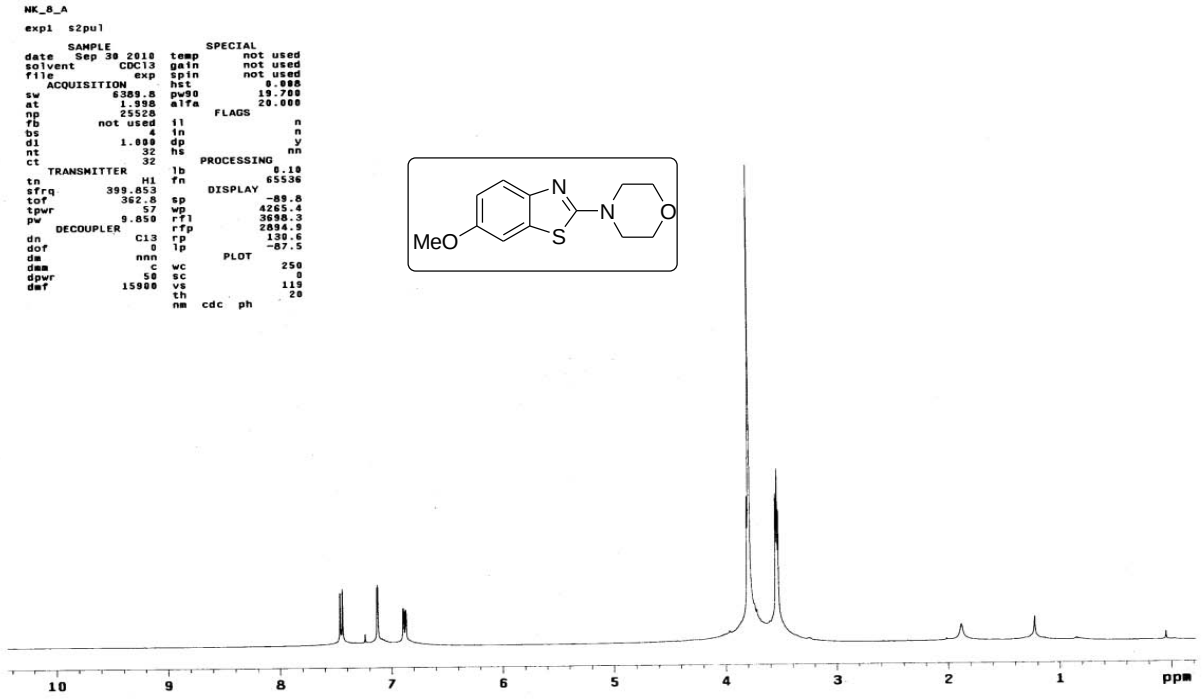
_N_-((_E_)-(3,4-Dimethylphenylimino)(morpholino)methyl)-_N_-(3,4-dimethylphenyl)morpholine-4-carbothioamide (3a). ^{13}C NMR (100 MHz, $CDCl_3$):



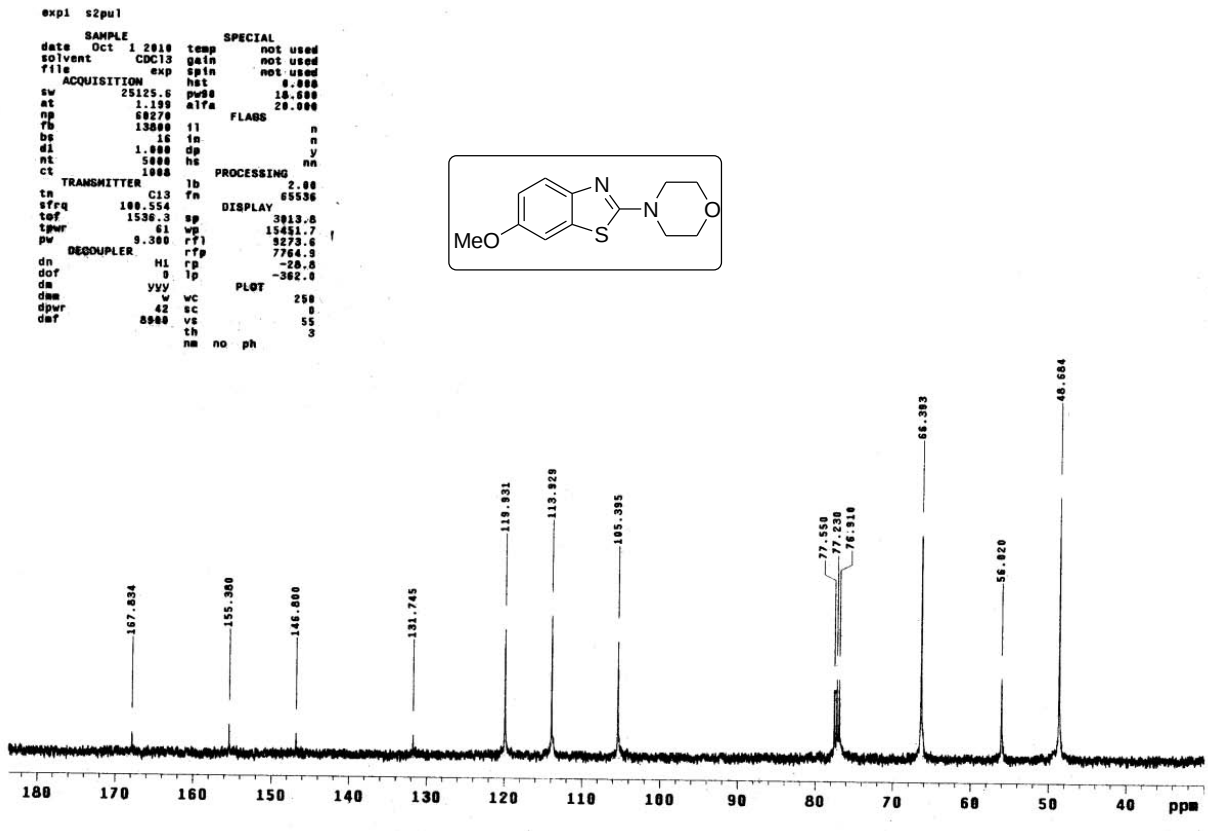
_N_-((_E_)-(3,4-Dimethylphenylimino)(morpholino)methyl)-_N_-(*3,4*-dimethylphenyl)morpholine -4-carbothioamide (3a). MASS SPECTRA:



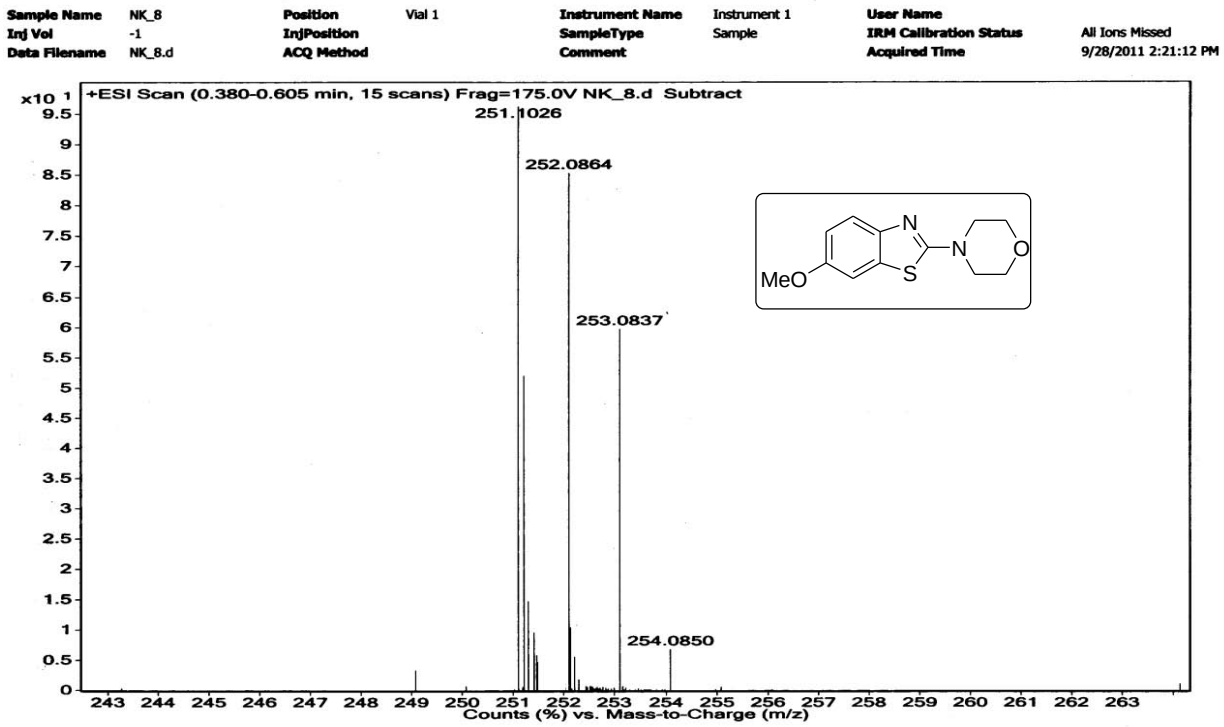
6-Methoxy-2-morpholino[*d*]thiazole (19'a). ^{1}H NMR (400 MHz, $CDCl_3$):



6-Methoxy-2-morpholino[*d*]thiazole (19'a). ^{13}C NMR (100 MHz, $CDCl_3$):



6-Methoxy-2-morpholino[*d*]thiazole (19'a). MASS SPECTRA:

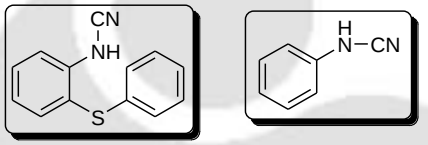


CHAPTER IV

IV. Copper(I) Catalyzed Cascade Synthesis of 2-Arylsulfanyl-arylcyanamide

IV.1. Structure and Nomenclature

Details of nomenclature of heterocycles were discussed in CHAPTER I. This chapter deals with the following two types of cyanamides namely substituted *S*-arylated arylcyanamide and arylcyanamide.



2-(phenylthio)phenyl cyanamide **phenylcyanamide**

Synthesis of arylcyanamides from *in-situ* generated aryl thioamides derived from arylisothiocyanates and ammonia using Cu(I) catalyst

IV.2. Importance and Applications

The wide spread applications of organic cyanamides in organic synthesis are now well documented which are useful intermediates for the synthesis of various biologically active compounds. Due to their unique structure and reactivity, cyanamides have attracted considerable attention in organic synthesis (*Figure IV.2.1*).[1] Cyanamides are key precursors to *N*-alkyl- or *N*-arylimides[2] and also serve as a useful protecting group in the synthesis of heterocycles containing secondary and tertiary amines.[3] They are important precursors in the synthesis of herbicides[4] and pharmaceutically active heterocycles such as tumor inhibitors,[5] and a vasodilator medication called minoxidil,[4] known for its ability to reduce hair loss and promote hair regrowth. Tetrazoles are an important class of heterocycle prepared from cyanamide and are present in

several drug molecules.[6a,b] A variety of bio-active construction of heterocycles using cyanamides are illustrated below.[6]

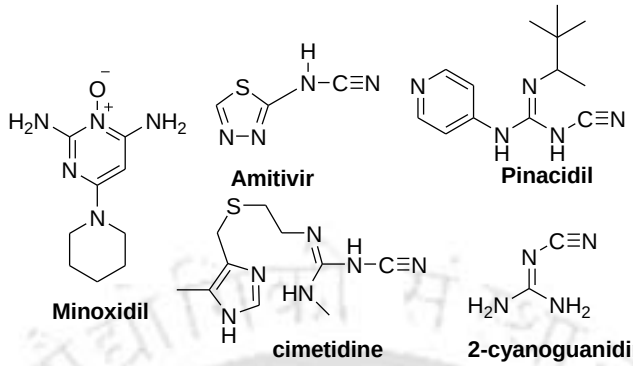
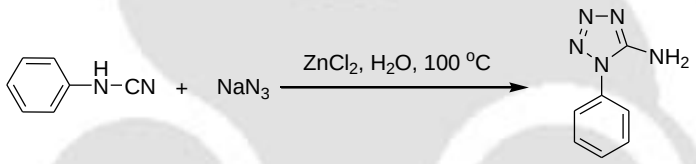


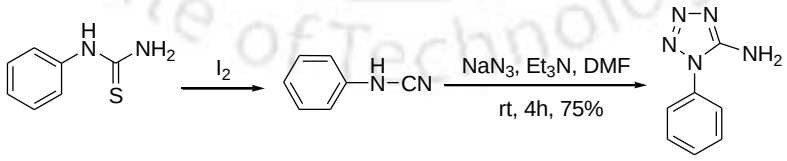
Figure IV.2.1. *Structures of some biologically active cyanamides*

Habibi *et al.* have synthesized aryl aminotetrazole derivatives efficiently by the action of arylcyanamides and sodium azide using $ZnCl_2$ as the catalyst in an aqueous medium under a refluxed condition (*Scheme IV.2.1*).[6a]



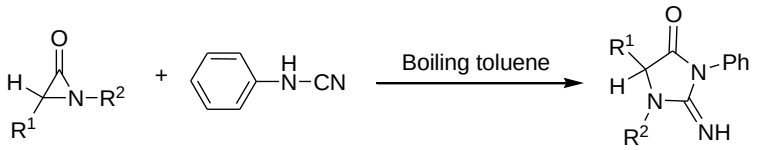
Scheme IV.2.1. *Synthesis of aryl aminotetrazole from arylcyanamides*

Recently, our group has synthesized aryl aminotetrazoles efficiently from the *in situ* generated arylcyanamides and sodium azide at room temperature. Iodine acts as a desulfurizing agent in the presence of triethylamine for the formation of cyanamide in the first step. (*Scheme IV.2.2*).[6b]



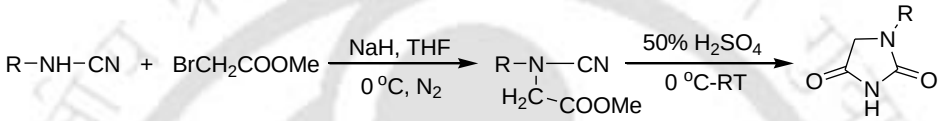
Scheme IV.2.2. *Synthesis of aryl aminotetrazole from in situ generated arylcyanamides*

The imidazolidinones, were obtained by acyl–nitrogen bond cleavage of aziridinones with phenyl cyanamide, followed by cyclization involving intramolecular nucleophilic attack on the nitrile (*Scheme IV.2.3*).[6c]



Scheme IV.2.3. *Synthesis of imidazolidinones form phenylcyanamide*

Monoalkyl / aryl cyanamides on treatment with methyl bromoacetate in the presence of sodium hydride in tetrahydrofuran affords methyl *N*-cyano-*N*-alkyl / arylaminoacetate, which undergoes hydrolysis followed by cyclization in the presence of 50% H_2SO_4 to afford *N*-1 substituted hydantoins in very good to excellent yields (*Scheme IV.2.4*).[6d]

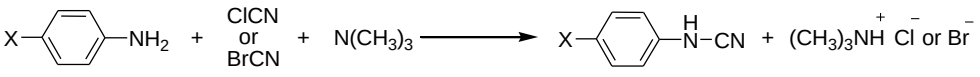


Scheme IV.2.4. *Substituted hydantoins from arylcyanamides*

Aromatic cyanamides are used as popular ligands for binding with various metals, such as, octaethylporphyrin iron(III) complexes containing cyanamide derivatives as axial ligand,[7a] Rh^{III} polypyridine complexes with phenylcyanamide derivative ligands,[7b] tetraphenylporphyrin manganese(III) complexes of phenylcyanamide ligands,[7c] *cis*-bis(bipyridine) cobalt(III) complexes of phenylcyanamide ligands[7d] and *cis*-bis(bipyridine) *etc*.

IV.3. Available Synthetic Methods

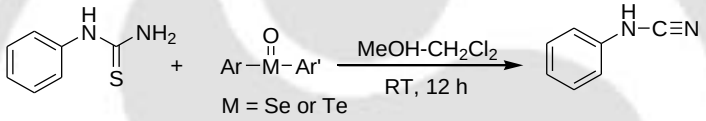
The various applications of cyanamides have resulted in the development of several methods for their synthesis over the years. The most frequently adopted method for the synthesis of cyanamides is the cyanation of amine using cyanogen halides, (*Scheme IV.3.1*) or its synthon (CN^+).[8]



Scheme IV.3.1. *Synthesis of aryl cyanamides from aryl amines*

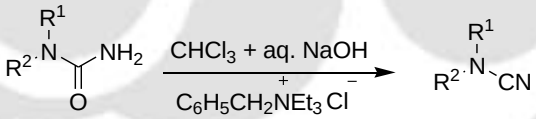
To avoid the use of toxic cyanogen halides, some electrophilic cyanating reagent that can serve as a cyano cation (CN^+) equivalent, have been prepared. The reagents capable of delivering electrophilic cyanogens (CN^+) are 2-chlorobenzyl thiocyanate,[9a] 1-cyanoimidazole,[9b] 2-cyanopyridazin-3-(2*H*)-ones,[9c] 1-cyanobenzotriazole and metal cyanide,[9d] tosylcyanide,[9e,f] thiocyanogen,[9g] and cyanogens azide etc.[9h]

Though cyanogens (CN^+) derived reagents are environmentally not benign from synthetic prospective therefore alternative methods have been explored. Cyanamides have been synthesized from 1-phenylthioureas using various methods, such as, polymer supported diaryl selenoxide or telluroxide mediated dehydrosulfurization (*Scheme IV.3.2*),[10a] treatment with superoxide (KO_2) in pyridine at 60 ^oC under N_2,[10b] and methylation followed by a basic work-up.[10c]



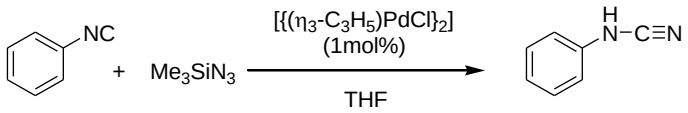
Scheme IV.3.2. *Synthesis of aryl cyanamides from 1-phenyl thioureas*

In an alternative approach, cyanamides are obtained from ureas through a dehydrative path using chloform and NaOH (*Scheme IV.3.3*)[11a] or trichloromethyl chloroformate.[11b]



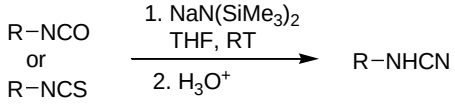
Scheme IV.3.3. *Cyanamides are synthesized from ureas*

The other less commonly adopted method is the Tiemann rearrangement of amidoximes (*Scheme IV.3.4*).[11c]



Scheme IV.3.4. *Synthesis of cyanamide using Tiemann rearrangement*

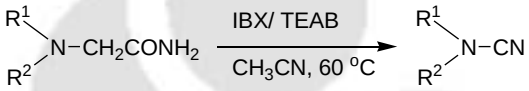
Cyanamides have been prepared in one-pot by reacting isocyanate or isothiocyanate with sodium bis(trimethylsilyl)amide as deoxygenating or desulfurizing agents in THF at room temperature (*Scheme IV.3.5*).[12a,b]



R = R = aryl, benzoyl, benzyl, t-butyl, cyclohexyl, naphthyl

Scheme IV.3.5. *Synthesis of cyanmamide from isocyanate or isothiocyanates*

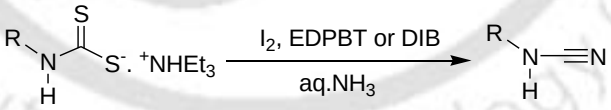
In yet another method, cyanamides have been prepared from *N,N'*-disubstituted glycylamide using a pentavalent iodine reagent in the presence of tetraethylammonium bromide at ambient temperature through one-carbon dehomologation of primary carboxamides (*Scheme IV.3.6*).[12c]



IBX = 1-hydroxy-1,2-benziodoxyl-3(1H)-one
TEAB = Et_4NBr

Scheme IV.3.6. *Synthesis of cynamide using hypervalent iodine*

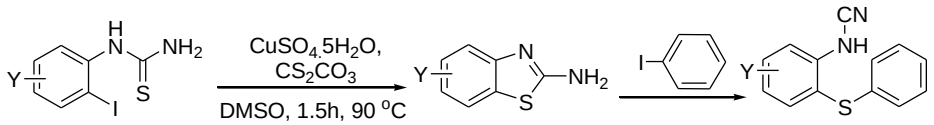
Our group has disclosed a high yielding, environmentally benign methods for the preparation of cyanamide from dithiocarbamate salt using DIB (diacetoxy iodo benzene), molecular iodine and ditribromide reagent 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) (*Scheme IV.3.7*).[12d-f]



R = Aryl, Alkyl group

Scheme IV.3.7. *Synthesis of cyanamide from dithiocarbamate salt using thiophilic reagents*

Recently, Punniyamurthy *et al.* have reported a cascade synthesis of arylsulfanyl-arylcyanamide from 2-iodo substituted aryl thioamides by using copper(II) catalyst under a ligand free condition in DMSO solvent (*Scheme IV.3.8*).[13]



Scheme IV.3.8. *Synthesis of arylsulfanyl-arylcyanamide using Cu(II) catalyst*

Thus in spite of a plethora of methods available for the synthesis of cyanamides and its derivatives due to the immense importance of these heterocumulenes there is always scope for newer and milder strategy for their synthesis. These methods suffer from a limited number of suitable substrates for diverse synthesis. Here, we felt that a catalytic approach involving newer type cynamide derivatives compounds via a cascade C–S bond formation and desulfurization strategy would be useful.

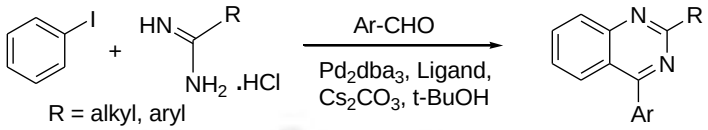
IV.4. Cascade or Domino Catalysis

The interest in metal catalyzed-multistep processes such as cascade, tandem and domino reactions in which one or more catalysts are employed for two or more transformations in one-pot has experienced an explosive development in recent years.[14]

A **cascade reaction** or **tandem reaction** or **domino reaction** is a consecutive series of intramolecular organic reactions which often proceed via highly reactive intermediates. It allows the organic synthesis of complex multinuclear molecules from a single acyclic precursor. The substrate contains several functional groups that take part during chemical transformations one at a time. Often a functional group is generated in situ from the previous chemical transformation. The definition includes the prerequisite intramolecular in order to distinguish this reaction type from a multi-component reaction. The main advantage of a cascade reaction in organic synthesis is that the reaction is often fast due to its intramolecular nature.

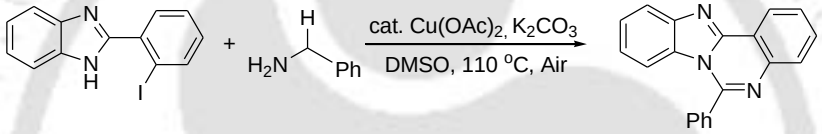
"A domino reaction is a process involving two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step" -L. F. Tietze.[15a]

They have several advantages such as (a) rapid transformations, (b) minimizing the number of reaction steps and chemical waste, and displays high atom economy and (c) the occurrence of two or more bond-forming reactions under identical reaction conditions. An example of a domino reaction is illustrated below (*Scheme IV.4.1*).[15b]



Scheme IV.4.1. *Synthesis of quinazoline derivative compounds using Pd catalyst*

An example of Cu(II)-catalyzed cascade reaction has been reported by Zhang *et al.* via a sequential Ullmann *N*-arylation and an aerobic oxidative C–H amination in DMSO at 110 °C which produces polysubstituted indoloquinazoline in good to excellent yields (*Scheme IV.4.2*).[15c]



Scheme IV.4.2. *Synthesis of substituted indoloquinazoline from benzimidazoles*

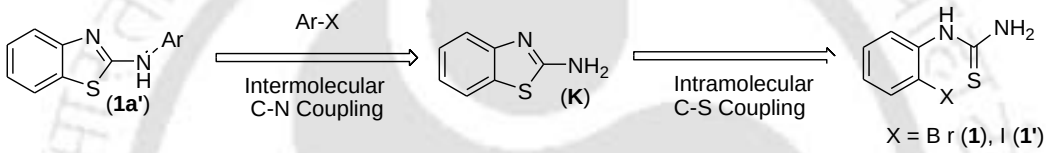
IV.5. Present Work

IV.5.1. Copper(I) Catalyzed Cascade Synthesis of 2-Arylsulfanyl-arylcyanamide

The interest in metal-catalyzed multistep processes such as cascade, tandem and domino reactions in which one or more catalysts are employed for two or more transformations in one-pot has experienced an explosive development in recent years.[16] Of all the metal catalysts, the Cu-catalyzed inter- and intramolecular domino reactions involving carbon-heteroatom bond formations for the synthesis of a wide variety of heterocycles have advantages over the others in terms of efficacy, selectivity and low cost.[17] Even though the chemistry of Cu-catalyzed C–C, C–N and C–O bond formations is well explored,[18] methods available for C–S bond formation are relatively fewer in the literature, which of course is growing in number.[19] Several reports revealed that the ligand-assisted Ullmann type coupling not only lowers the reaction temperatures but also accelerates the reaction rates.[17e,20] Furthermore, an orthogonal selectivity

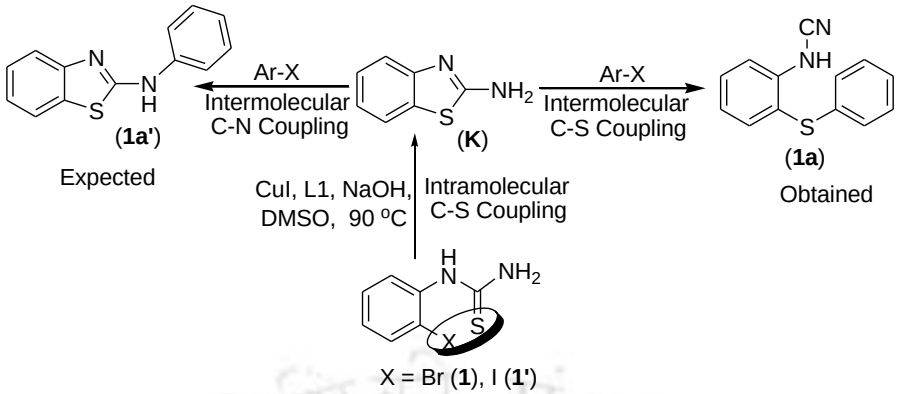
has been observed in Cu-catalyzed reactions when assisted by a ligand.[20e] Thus, a proper selection of ligand would not only prevent aggregation of the metal and improve the solubility of the catalyst/co-catalyst but also increase the reaction rate.

As a part of our ongoing research in developing alternative methods for the synthesis of heterocycles,[21,22] and taking cues from our recent double *S*-arylation strategy involving intra- and intermolecular C–S coupling,[16h] we envisaged a one-pot synthesis of *N*-aryl-2 aminobenzothiazoles. The retro synthetic strategy is shown in *Scheme IV.5.1.1.* In this strategy, an initial intramolecular *S*-arylation of 2-halo-1-arylthioamide yields the intermediate 2-aminobenzothiazole (**K**), which is then followed by an intermolecular *N*-arylation, directly giving *N*-aryl-2-aminobenzothiazole (**1a'**) using a single catalytic system (*Scheme IV.5.1.1*).



Scheme IV.5.1.1. *The design of a one-pot synthesis of N-aryl-2-aminobenzothiazoles*

Initially, the coupling of 1-(2-bromophenyl)thiourea (**1**) and iodobenzene (**a**) was chosen to optimize the reaction conditions. The reaction was performed by taking CuI (5 mol%) as the precatalyst, 1,10-phenanthroline (**L1**) (10 mol%) as the ligand and NaOH (3 equiv.) as the base at 90 ^{o}C in DMSO (*Scheme IV.5.1.2*). Complete disappearance of the starting materials, 1-(2-bromophenyl)thiourea (**1**) and iodobenzene (**a**) was observed within 45 minutes. On isolation and characterization, the product was found to be 2-(phenylthio) phenylcyanamide (**1a**) and not the expected *N*-aryl-2-aminobenzothiazole (**1a'**) (*Scheme IV.5.1.2*). The structure of the product (**1a**) has been further confirmed by X-ray crystallography (*Figure IV.5.1.1*).



Scheme IV.5.1.2. *The design of a one-pot synthesis of* ***1a/1a'***

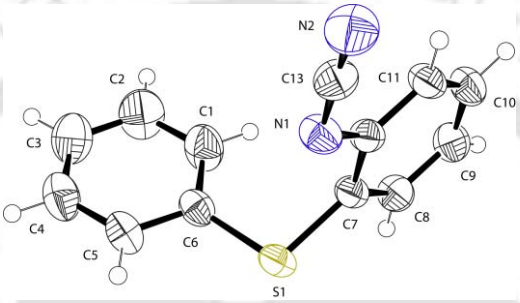
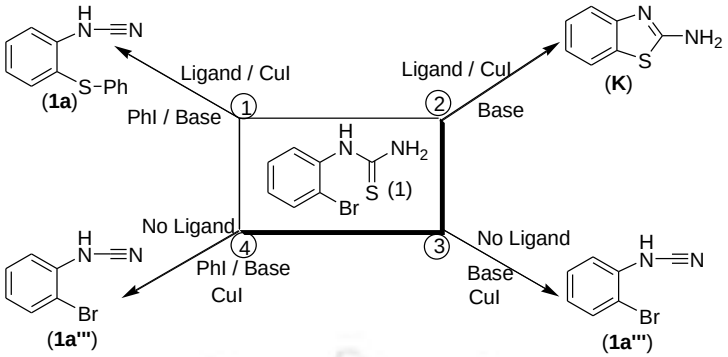


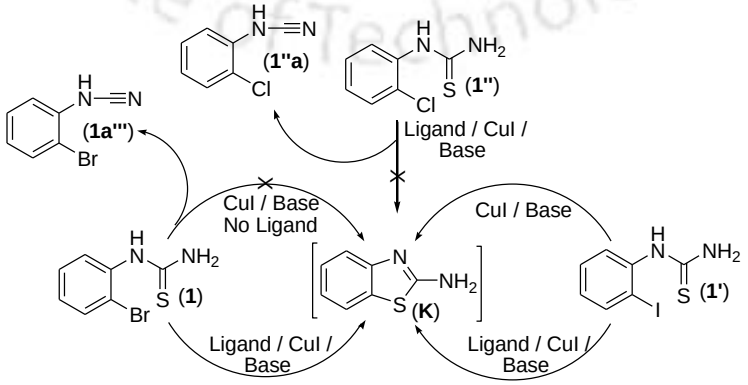
Figure IV.5.1.1. *ORTEP view of* ***1a***

The failure to achieve the target synthesis of *N*-aryl-2-aminobenzothiazole (**1a'**) was rather surprising because following a similar strategy we have recently accomplished the synthesis of several 2-arylthiobenzothiazoles[16h] where we have observed a facile intramolecular *S*-arylation. Thus, in the present reaction, 2-aminobenzothiazole (**K**) (*Scheme IV.5.1.1*) must have been an intermediate in this overall transformation. To ascertain this, when 1-(2-bromophenyl)thiourea (**1**) was treated with Cu(I), 1,10-phenanthroline (**L1**) and base (NaOH), in the absence of iodobenzene (**a**), 2-aminobenzothiazole (**K**) (*Scheme IV.5.1.3 and 4*) was obtained exclusively supporting our assumption of the facile intramolecular *S*-arylation (*Scheme IV.5.1.3, path 2*). Furthermore, when the isolated intermediate, 2-aminobenzothiazole (**K**) was treated with iodobenzene (**a**) in the presence Cu(I), 1,10-phenanthroline (**L1**) and NaOH, 2-(phenylthio)phenylcyanamide (**1a**) was obtained exclusively, further proving the intermediacy of 2-aminobenzothiazole (**K**) (*Scheme IV.5.1.3 and 4*).



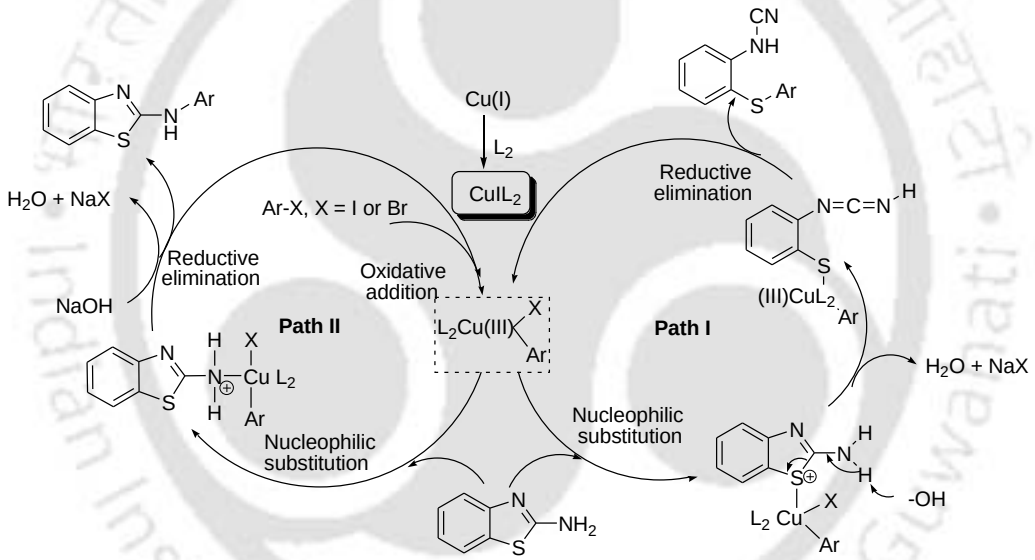
Scheme IV.5.1.3. *Ligand dependency of the coupling reaction*

When the above reaction was carried out in the absence of 1,10-phenanthroline ligand (**L1**), the exclusive product obtained was 2-bromophenylcyanamide (**1a'''**), irrespective of the presence or absence of phenyl iodide (**a**) in the reaction medium (*Scheme IV.5.1.3, path 3 and path 4*). This observation is similar to the recently reported ligand-free $CuSO_4$-catalyzed reaction where 2-bromophenylcyanamide (**1a'''**) was obtained from 1-(2-bromophenyl)thiourea (**1**) but at a much longer reaction time (3–6 h).[13] A ligand free reaction of 1-(2-halophenyl)thiourea gives as product 2-(phenylthio)phenylcyanamide (1a) only when the halogen substituent in the 2-position is an iodo group (**1'**) (*Scheme IV.5.1.4*) and not a bromo (**1**).[13] Thus, the present work is a further demonstration of the increasing reactivity and differential selectivity in the Ullmann reaction when assisted by a ligand. Thus, this ligand-assisted reaction not only accelerates the first step, i.e., intramolecular C–S bond formation giving the intermediate 2-aminobenzothiazole (**K**) but also accelerates the C–S bond cleavage leading to *S*-arylated cyanamide (**1a**). However, when the 2-halo group in 1-(2-halophenyl)thiourea (**1''**) is –Cl, the intramolecular *S*-arylation could not take place (*Scheme IV.5.1.4*) even when the reaction was assisted by a ligand and the product obtained was 2-chloro phenylcyanamide (**1a''**, *Table IV.5.1.3*).



Scheme IV.5.1.4. *Ligand dependency of the reaction*

One can envisage the formation of *S*-arylated cyanamide (**1a**) by the *in-situ* formation of 2-phenylthiocyanamide (**Y**) followed by an intermolecular *S*-arylation. When the isolated 2-aminobenzothiazole (**K**) was treated with Cu(I), ligand (**L1**) and base, it did not undergo any change but the same reaction when carried out in the presence of iodobenzene (**a**) gave 2-(phenylthio)phenylcyanamide (**1a**) in quantitative yield. We have also observed that once the intermediate 2-aminobenzothiazole (**K**) is formed, C–S bond cleavage giving 2-(phenylthio)phenylcyanamide (**1a**) is quite facile indicating that the intramolecular *S*-arylation is the rate-determining step in this reaction. This led us to postulate the following mechanism as shown in *Scheme IV.5.1.5* (path I).



Scheme IV.5.1.5. *Proposed mechanism for the formation of* ***1a*** *(path I) and* ***1a'*** *(path II)*

This transformation was found to be effective giving complete conversion to product with 5 mol% of the precatalyst Cu(I) in less than 0.75 h when assisted by 1,10-phenanthroline as ligand (**L1**), thus there was no necessity for further optimization. When the coupling of the substrate (**1**) was carried out with phenyl iodide (**a**) with less than 5 mol% of the catalyst and 10 mol% of the ligand, the outcome was completely different, i.e., similar to the ligand-free conditions.[13] For example, with 1 mol% of the catalyst and 2 mol% of the ligand, the only product observed after 4 h was 2-bromophenylcyanamide (**1a'''**, 85%). The observation was the same even when 2.5 mol% of the catalyst was used giving product (**1a'''**, 92%) in 2 h. Thus, the catalyst quantity was

maintained at 5 mol% for all the substrates having a 2-bromo substituent. The reactivity changes with changes in the ligand (*Figure IV.5.1.2*) but the selectivity remains the same. Consistent with our previous report on intramolecular C–N bond formation,[22a] 1,10-phenanthroline (**L1**) was found to be an efficient ligand giving 93% isolated yield of the product. Interestingly, the less expensive dimethylethylenediamine (DMEDA) (**L7**) was found to be even better giving quantitative conversion (by GC) and 97% isolated yield.

Various solvents were tested during the optimization reaction such as DMF, 1,4-dioxane, DMSO, DMA, toluene, acetonitrile, amongst which DMSO was found to be the best giving quantitative conversion in a shorter reaction time (0.75 h). In all other solvent systems, reactions either took a longer time or gave a mixture of products. Organic bases such as Et_3N, DBU, DABCO, DBN only gave the intramolecular product 2-aminobenzothiazole (**K**) which neither underwent *N*-arylation to give our targeted *N*-aryl-2-aminobenzothiazole (**1a'**) nor cleavage of the C–N bond to afford 2-(phenylthio)phenylcyanamide (**1a**).

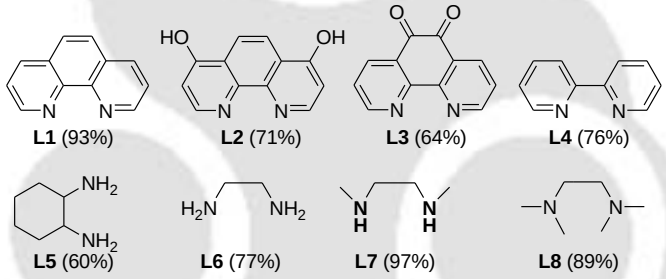


Figure IV.5.1.2. *Effect of ligands on the Cu(I)-catalyzed reaction*

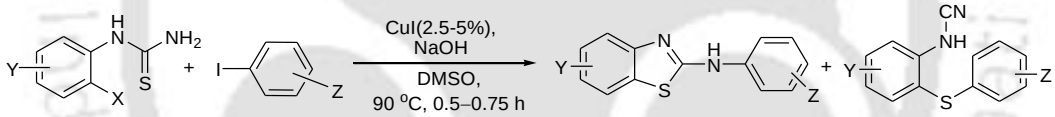
Inorganic bases such as Na_2CO_3, K_2CO_3, Cs_2CO_3 were found to be better than organic bases but took longer reaction times (3–6 h). Alkali hydroxides NaOH, KOH were superior to carbonates and were equally good when used in DMSO. Thus NaOH was used for the coupling reactions but, if desired, particularly for substrates possessing sensitive functional groups, carbonates (Na_2CO_3, K_2CO_3, Cs_2CO_3) can be used. The precatalyst CuI was found to be the best among the series of Cu salts tested such as CuBr, Cu_2O, $CuBr_2$, $CuCl_2{\cdot}2H_2O$, $Cu(OAc)_2{\cdot}2H_2O$ and $CuSO_4{\cdot}5H_2O$. With other Cu salts, the reaction time was longer even when assisted by ligand (**L7**), for example $CuSO_4{\cdot}5H_2O$ took 1.5 h even when carried out in the presence of DMEDA ligand (**L7**) as opposed to 0.5 h when Cu(I) was used. Bromobenzene and chlorobenzene were found to be ineffective giving a number of side products, thus coupling was

done mostly with the iodoarenes, a trend (I> Br>> Cl) followed for most coupling reactions.[17e–f,18e,23] Thus, from a series of experiments, the optimum ratio of the 1-(2-bromophenyl)thiourea (**1**), iodobenzene (**a**), CuI, ligand (**L7**), base (NaOH) was found to be 1:1:0.05:0.10:3.

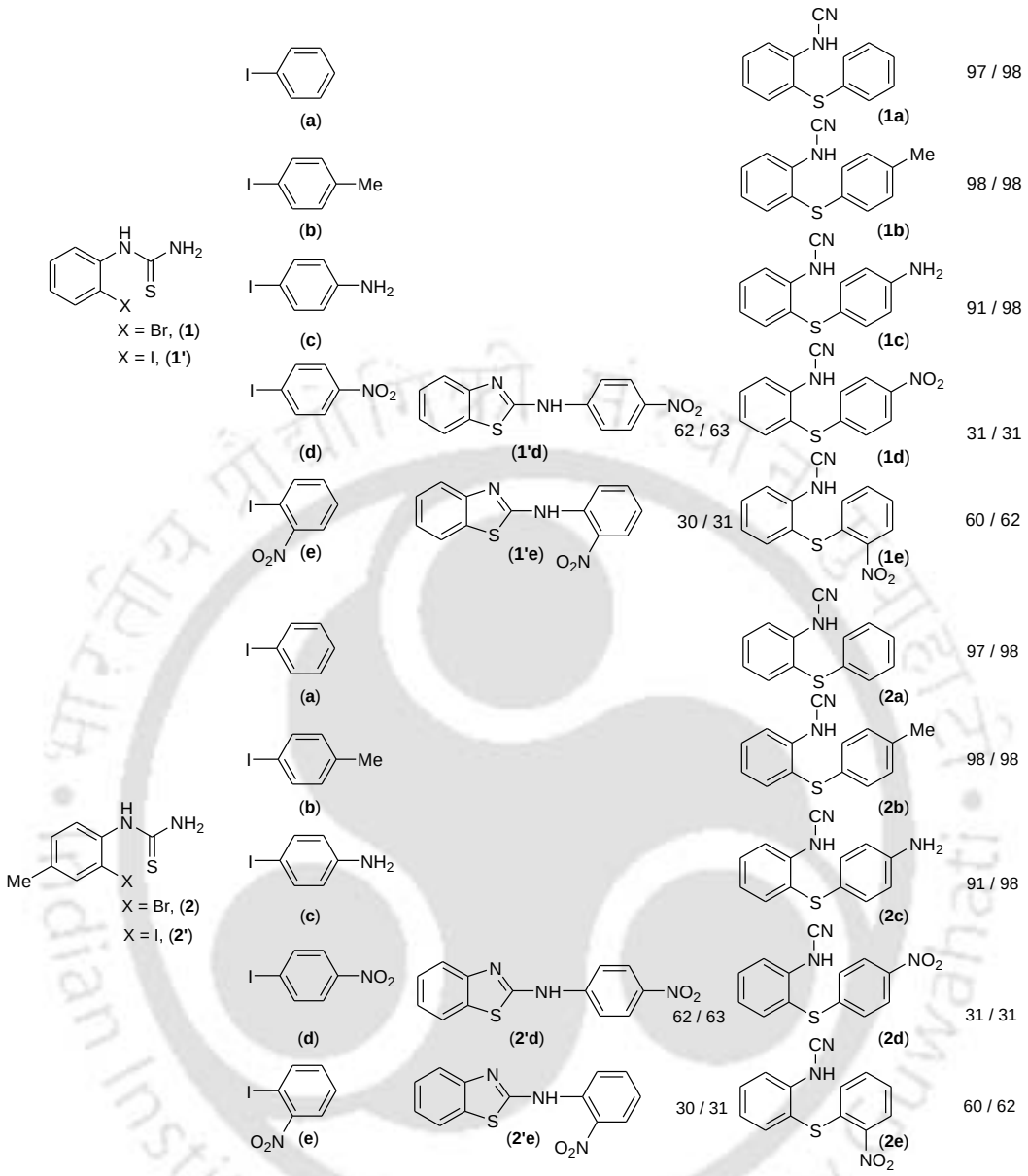
We next investigated the influence of various aryl iodides on the coupling reactions. As can be seen from *Table IV.5.1.1*, the present catalytic system has substantial substrate scope. Electron-donating aryl iodides such as *p*-methyl iodobenzene (**b**) and *p*-amino iodobenzene (**c**) gave exclusively *S*-arylated cyanamides (**1b**) and (**1c**) respectively, in excellent yields by a cascade coupling process. However, an interesting change in the reactivity profile was observed when an electron-withdrawing group ($-NO_2$) is present in the aryl iodide either in a para (**d**) or in ortho (**e**) position. For the first time the formation of *N*-aryl-2-aminobenzothiazole (**1d'**, 62%) or (**1e'**, 30%) was observed in addition to the *S*-arylated cyanamides (**1d**, 31%) or (**1e**, 60%) as the case may be. The formation of *N*-aryl-2-aminobenzothiazole (**1d'**) and (**1e'**) can be explained by the initial intramolecular *S*-arylation of 1-(2-bromophenyl)thiourea (**1**) to 2-aminobenzothiazole (**K**). This is then followed by an intermolecular *N*-arylation with nitroaryl iodides (**d** or **e**) leading to the direct synthesis of *N*-aryl-2-aminobenzothiazole (**1d'**) and (**1e'**) as we anticipated at the beginning. It may be mentioned here that a non-ligand-assisted reaction of analogous substrates is reported to give exclusively *S*-arylated cyanamides and no traces of *N*-aryl-2 aminobenzothiazole.[13] Thus, this is yet another manifestation of the differential reactivity/selectivity of a non-ligand-assisted over a ligand-assisted reaction. It is known that for heteroarylations, iodoarenes having a strong electron-donating group react more slowly as compared to substrates possessing an electron-withdrawing group.[24] Perhaps a highly active species is formed by the oxidative addition of iodo nitroarenes (**d**) and (**e**) (*Scheme IV.5.1.5*). This active species could undergo nucleophilic substitution either with the soft sulfur nucleophile (path I) or with the hard amine nucleophile (path II) giving *S*-arylated cyanamides and *N*-aryl-2-aminobenzothiazole, respectively. When the nitro group is present in the ortho position (**e**), only 30% of the 2-arylaminobenzothiazoles (**1e'**) was obtained as compared to the 62% of the product (**1d'**) when the nitro group is in the para position (**d**). This can be accounted due to the higher steric hindrance for a substrate having an *o*–NO_2 group (**e**) in path II compared to its para (**d**) analogue.

Various 1-(2-bromophenyl)thioureas having substituents such as *p*-Me (**2**), *p*-OMe (**3**), *p*-Br (**4**) and *p*-(1,3-dithiolane) (**5**) underwent the cascade reaction with a range of aryl iodides bearing *p*-Me (b), *p*-NH_2 (c) when coupled in the presence of Cu(I) and assisted by the ligand (**L7**) giving the corresponding *S*-arylated cyanamides (*Table IV.5.1.1*). While aryl iodides bearing an electron-withdrawing group (–NO_2) (**d**) and (**e**) gave a mixture of products consisting of *N*-aryl-2-aminobenzothiazole (**1d'**), (**1e'**), (**2d'**), (**2e'**), (**3e'**) and *S*-arylated cyanamides (**1d**), (**1e**), (**2d**), (**2e**), (**3e**) as the case may be as shown in *Table IV.5.1.1*. As was observed for (**d**) when an electron-withdrawing (–NO_2) group is present in the para position in an aryl iodide, a higher percentage of 2-*N*-aryl-2-aminobenzothiazoles **1d'** (62%), **2d'** (54%) was obtained compared to *S*-arylated cyanamides **1d** (31%), **2d** (38%). However, the trend was nearly reversed when the –NO_2 group is present in the ortho position, (*Table IV.5.1.1*) i.e., a higher percentage of *S*-arylated cyanamides **1e** (60%), **2e** (53%), **3e** (46%) was obtained compared to 2-arylaminobenzothiazoles **1e'** (30%), **2e'** (42%), **3e'** (36%).

Table IV.5.1.1. *Synthesis of arylsulfanyl-arylcyanamide and N-aryl-2-aminobenzothiazole*[a]



Substrate	Aryl Iodide	Products[a]	Yields% (Br / I)[b]

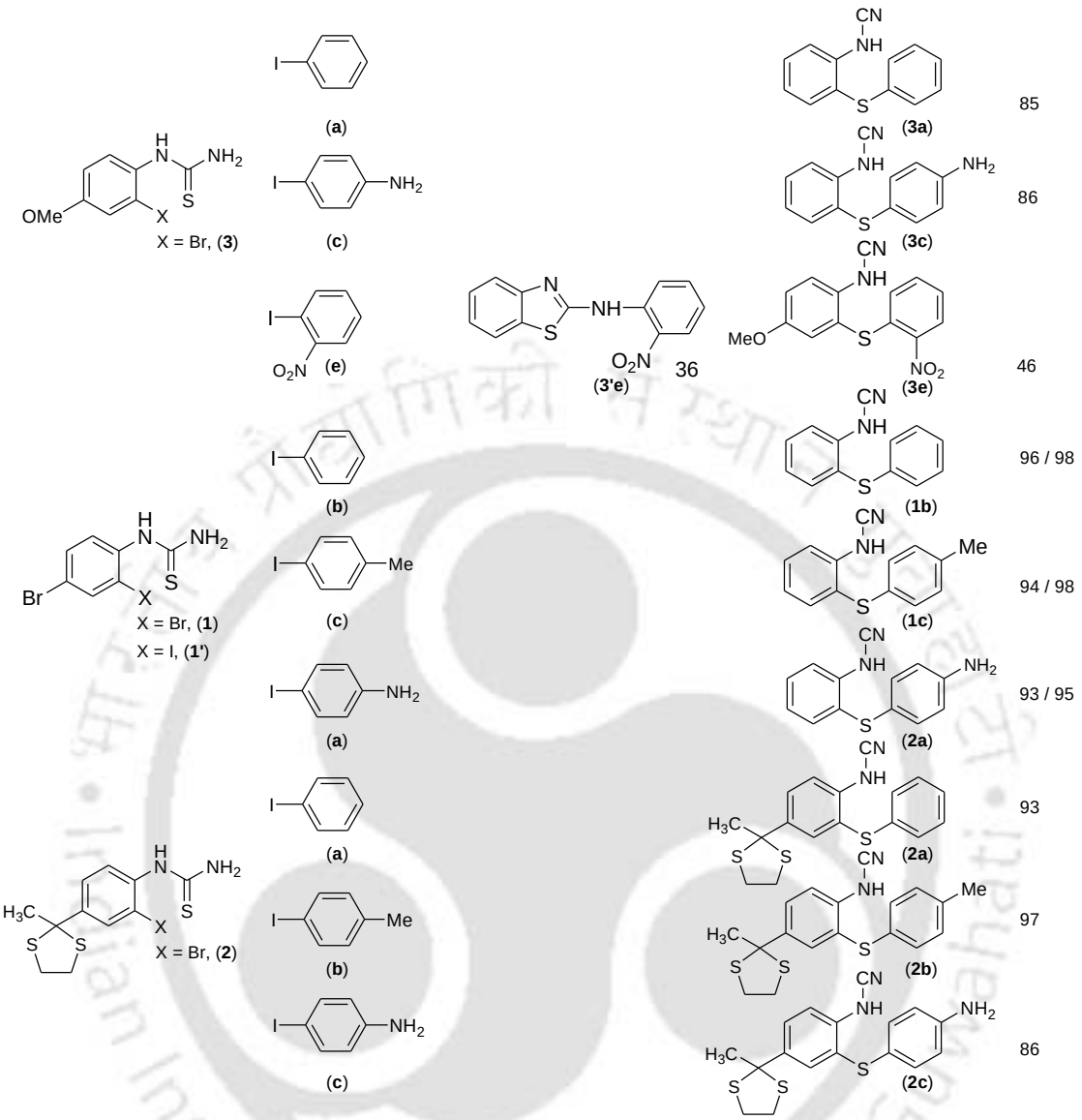


[a]Confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. [b]Isolated yields.

Continued…

Table IV.5.1.1. *Continued…*

Substrate	Aryl Iodide	Products[a]	Yields% (Br / I)[b]



[a]Confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. [b]Isolated yields.

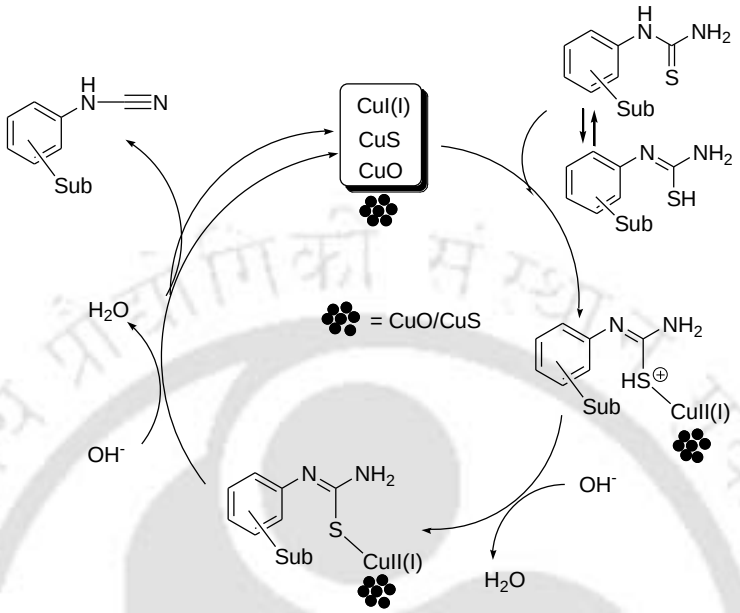
The scope of this strategy was then extended to other thioureas containing a 2-iodo substituent instead of a 2-bromo substituent. As discussed above, and as was observed by others, the intramolecular *S*-arylation is very facile when the halo substituent is an iodo group and proceeds without a ligand with 2.5 mol% of the catalyst ($CuSO_4.5H_2O$).[13] However, when assisted by the ligand (**L7**), the same reaction can be carried out with just 1 mol% of the catalyst, when the catalyst used is CuI instead of $CuSO_4.5H_2O$. Further, the superiority of Cu(I) catalyst over $CuSO_4.5H_2O$ can be judged by the fact that with 2.5 mol%, each of these in the absence of any ligand and Cs_2CO_3 as the base in DMSO the former gave product 2-

(phenylthio)phenylcyanamide (**1a**, 95%) within 3 h, whereas the latter gave 40% of intermediate 2-aminobenzothiazole (**K**) and only 60% of (**1a**) at a similar reaction time. It is therefore not surprising that substrates 1-(2-iodophenyl)thiourea (**1'**) and 2-iodophenylthioureas having substituents such as *p*-Me (**2'**), and *p*-Br (**4'**) underwent similar cross-coupling reactions with various aryl iodides bearing *p*-Me (**b**), *p*-NH_2 (**c**), when coupled in the presence of Cu(I) and assisted by the ligand (**L7**), to give *S*-arylated cyanamides (*Table V.5.1.1*). Here again, aryl iodides bearing an electron-withdrawing group (–NO_2) in its ortho (**d**) or para (**e**) position gave a mixture of products consisting of *N*-aryl-2-aminobenzothiazole (**1d'** and **2d'**) and *S*-arylated cyanamides (**1d** and **2d**), as the case may be, as shown in *Table V.5.1.1*. Perhaps the most interesting aspect is that the ratio of the product *N*-aryl-2-aminobenzothiazole (**1d'**) and *S*-arylated cyanamide (**1d**) formed was nearly identical irrespective of the starting materials 1-(2-bromophenyl)thiourea (**1**) or 1-(2-iodophenyl)thiourea (**1'**) used. This regioselectivity in the product formation in these reactions further confirms the intermediacy of 2-aminobenzothiazole (**K**) via an intramolecular *S*-arylation. Irrespective of its origin either from (**1**) or (**1'**), once the intermediate 2-aminobenzothiazole (**K**) is formed in the media, it undergoes a cascade reaction with 1-iodo-4-nitrobenzene (**d**), either via path I or by path II (*Scheme IV.5.1.5*) to yield product (**1d**) and (**1d'**) in the same ratio of 2:1.

As can be seen from *Scheme IV.5.1.3*, during the cross coupling of 1-(2-bromophenyl)thiourea (**1**) with phenyl iodide in the absence of any ligand, only 2-bromophenylcyanamide (**1a'''**) was obtained. Further, we have noticed that 1-(2-chlorophenyl)thiourea in the presence of Cu(I) and ligand did not undergo intramolecular *S*-arylation to give 2-aminobenzothiazole (**K**), rather, 2-chlorophenylcyanamide (**1a''**) was obtained exclusively. This prompted us to develop a catalytic strategy for the synthesis of aryl and alkylcyanamides from their corresponding thioureas.

The optimized reaction conditions were basically the same as were employed for the above reactions except the reactions were performed in the absence of any ligand. Thus, in a typical reaction, 2-bromophenylthiourea (**1**) (1 equiv.), Cu(I) (2.5 mol%), NaOH (3 equiv.) in DMF (1 mL) was heated at 90 ^{o}C. Complete conversion to 2-bromophenylcyanamide was observed

within 2 h and the product was isolated in 92% after usual work-up and purification. The proposed mechanism for the formation of cyanamide is shown in *Scheme IV.5.1.6*.



Scheme IV.5.1.6. *Proposed mechanism for the formation of cyanamide*

The catalyst CuI, after the first cycle, presumably gets converted to CuS or forms an array of polynuclear anions containing sulfur rings or a chain which is well known in the text books.[25] Alternatively, at this temperature, some of the CuS would decompose to form CuO which can serve the same purpose in the second cycle. The existence of CuO and CuS can be judged from the EDX analysis of the sample obtained from the reaction. Some of the regions in the SEM picture (*Figure IV.5.1.3*, **A**) are rich in CuO, known to be an efficient catalyst,[18d,26] while the other regions are composed of fine fibrous CuS particles (*Figure IV.5.1.3*, **B**).

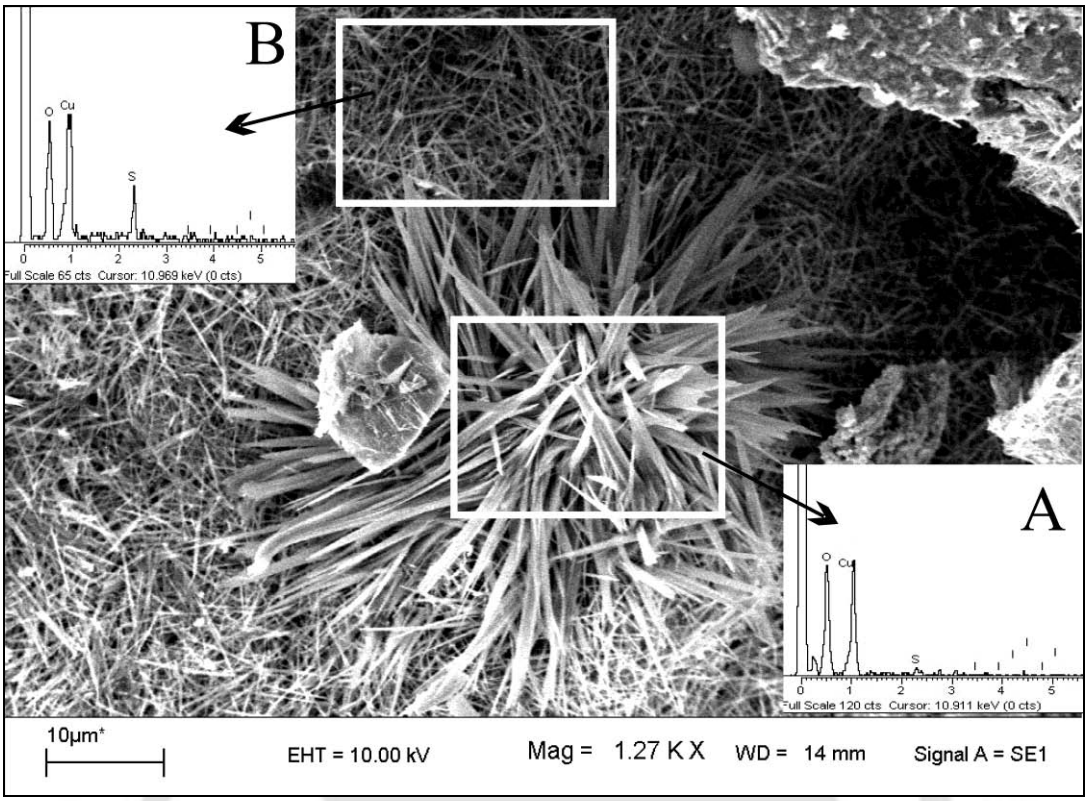
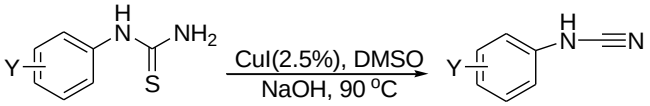
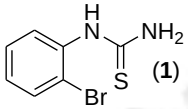
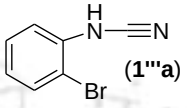
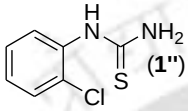
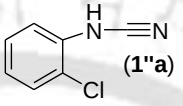
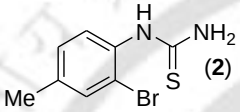
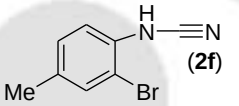
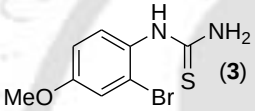
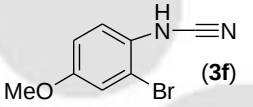
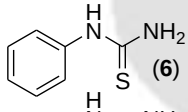
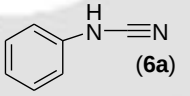
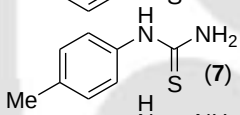
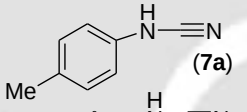
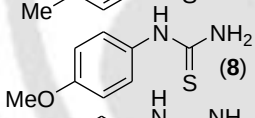
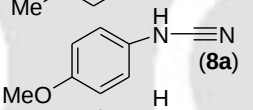
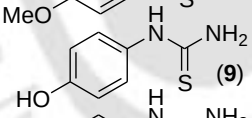
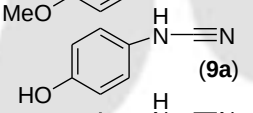
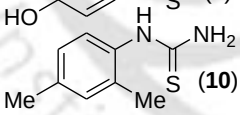
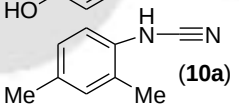
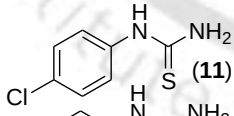
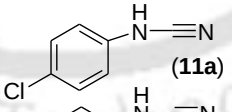
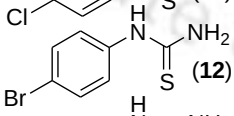
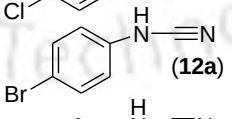
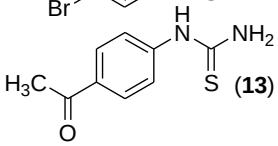
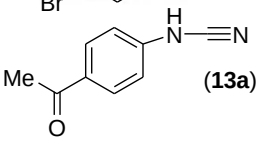


Figure IV.5.1.3. *SEM and EDX analysis of the Cu-salt*

Irrespective of the mechanism of the reaction, this is one of the most efficient methods for the synthesis of cyanamides from thioureas. Gratifyingly, various mono- (**1**, **1''**, **7**, **8**, **9**, **11**, **12**, **13**, **14**, **15**) and di- (**2**, **3**, **10**) substituted thioureas having electron-donating and electron withdrawing substituents all gave their corresponding cyanamides in good to excellent yields. Electron-withdrawing substituents took a slightly longer time giving lower yields compared to substrates having electron-donating substituents (*Table IV.5.1.2*). Aliphatic thioamide (**16**) gave a poor yield of corresponding cyanamide (**16a**), an observation consistent with our previous report,[12d-f] which is due to the higher pKa of its parent amine thereby explaining the difficulty in deprotonation during the cyanmide formation. Both benzylic (**17**) as well as benzoylic (**18**) thioamides gave their cyanamides (**17a**) and (**18a**) in excellent yields (*Table IV.5.1.2*).

Table IV.5.1.2. *Synthesis of cyanamides from thioureas*[a]

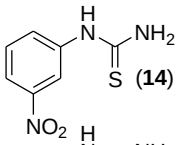
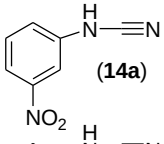
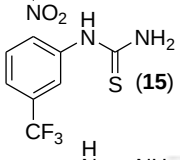
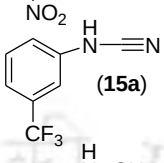
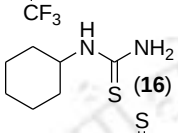
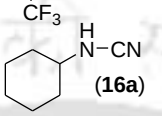
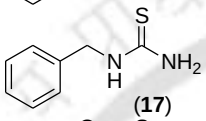
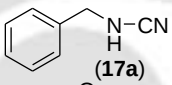
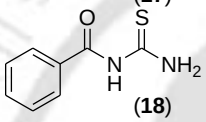
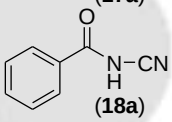


Substrate	Product	Time	Yield %
 (**1**)	 (**1'''a**)	2	92
 (**1''**)	 (**1''a**)	2	94
 (**2**)	 (**2f**)	1.5	95
 (**3**)	 (**3f**)	1.5	91
 (**6**)	 (**6a**)	2	98
 (**7**)	 (**7a**)	2	97
 (**8**)	 (**8a**)	2	88
 (**9**)	 (**9a**)	2	87
 (**10**)	 (**10a**)	2	93
 (**11**)	 (**11a**)	2.5	87
 (**12**)	 (**12a**)	3	89
 (**13**)	 (**13a**)	2.5	85

[a]Confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. [b]Isolated yields.

Continued…

Table IV.5.1.2. *Continued…*

Substrate	Product	Time	Yield %
 (**14**)	 (**14a**)	3.5	88
 (**15**)	 (**15a**)	3.5	85
 (**16**)	 (**16a**)	2.5	52[c]
 (**17**)	 (**17a**)	2.5	80
 (**18**)	 (**18a**)	2.5	91

[a]Confirmed by IR, [1]H NMR, and [13]C NMR spectroscopy. [b]Isolated yields. [c]Reaction was performed at room temperature.

In conclusion, an efficient ligand-assisted, Cu(I)-catalyzed cascade reaction has been developed. Two different reaction paths are followed depending on the nature of the aryl halide. In one path, 2-bromo-/iodothioamide undergoes an intramolecular *S*-arylation followed by an *N*-arylation, particularly for aryl halides having a nitro group, directly giving *N*-aryl-2-aminobenzothiazole. Aryl bromides are resistant to intramolecular *S*-arylation when performed in the absence of a ligand but are very facile when assisted by ligands. Further, selectivity is completely different particularly for aryl iodides having a nitro group. The reactivity changes with the change in the ligand but the overall selectivity remains the same. The ligand-assisted reactions are much faster compared to the non-ligand-assisted reactions and proceeds with less catalyst loading. Finally, an efficient catalytic method for the synthesis of cyanamide from mono substituted thiourea has been developed under ligand-free condition. The low catalyst loading, inexpensive metal catalyst and ligands, lower reaction temperature, and shorter reaction time make these methods a better alternative to some of the existing methods of their preparation.

IV.6. Experimental Section

IV.6.1. Instrumentation and Characterization

As described in Chapter II, Section II.6.1.

IV.6.2. General Procedure for the Synthesis of 2-(Phenylthio)phenylcyanamides (1a) From 1-(2-Bromophenyl)thiourea (1)

1-(2-Bromophenyl)thiourea (**1**) (5 mmol, 1.155 g), iodobenzene (5 mmol, 1.02 g), NaOH (600 mg, 15 mmol), CuI (0.25 mmol, 0.048 g) and DMEDA (L7) (0.5 mmol, 0.045g) in DMSO (7 mL) were stirred in a preheated oil bath at 90 ^{o}C. Progress of the reaction was monitored by TLC using ethylacetate and hexane (2:8) as the eluent. After 45 minutes, the reaction mixture was cooled to room temperature and diluted with ethylacetate (20 mL). Then the reaction mixture was filtered over celite and washed with ethylacetate (3 x 10 mL). The filtrate was washed successively with 1N HCl (2 x 5 mL) and with water (2 x 10 mL). The ethylacetate layer was dried over anhydrous Na_2SO_4 and the solvent was removed under a reduced pressure. The crude product so obtained was purified over a column of silica gel using EtOAc : hexane (1:9) as the eluents to give the product **1a** (1.16 g) 97% isolated yield.

IV.6.3. General Procedure for Preparation of 2-Bromophenylcyanamide (1a'")

1-(2-Bromophenyl)thiourea (**1**) (5 mmol, 1.155g), NaOH (600 mg, 15 mmol), CuI (0.125 mmol, 0.024 g) in DMSO (7 mL) were stirred in a preheated oil bath at 90 ^{o}C. The progress of the reaction was monitored by TLC using ethylacetate and hexane (2:8). After 2h, the reaction mixture was cooled to room temperature and diluted with ethylacetate (20 mL). Then reaction mixture was filtered over celite and washed with ethylacetate (3 x 10 mL). The filtrate was washed successively with 1N HCl (2 x 5 mL) and with water (2 x 10 mL). The ethylacetate layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The

crude product was purified over a column of silica gel with EtOAc : hexane (2:8) as the eluents to give the product **1a'''** in (0.906 g) 92% isolated yield.

IV.6.4. Crystallographic Description

Crystal data of compound (1a): CCDC reference number 772182, $C_{13}H_{10}N_2S$, M = 226.06, Monoclinic, space group P 21/c, Z = 2, a = 6.1325(2) Å, b = 7.7677(2) Å, c = 12.5135(3) Å , α = 90.00º, β = 102.482(2)º, γ = 90.00º, T = 296(2) K, Volume = 582.00(3) $Å^3$, μ (Mo–Kα)= 1.278 mm^{-1}, (R_{int} = 0.0520). The final $R_1(I > 2\sigma(I))$ was 0.1295, GOF = 0.869.

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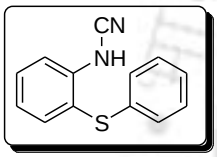
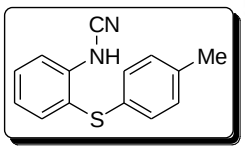
IV.8 Spectral Data

2-(Phenylthio)phenylcyanamide (1a):



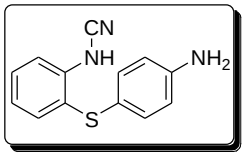
White solid, mp 92-94 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.02 (d, 2H, J = 8.8 Hz), 7.11 (t, 1H, J = 7.6 Hz), 7.17 (d, 1H, J = 7.2 Hz), 7.24 (t, 2H, J = 7.6 Hz), 7.41 (d, 1H, J = 8 Hz), 7.48 (t, 1H, J = 8 Hz), 7.58 (d, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 110.3, 115.4, 117.5, 124.2, 126.6, 127.1, 129.5, 131.9, 135.1, 137.7, 139.9; IR (KBr): 3135, 2923, 2238, 1590, 1578, 1438, 1410, 1288, 1024, 760, 739, 686, 596 cm^{-1}; Anal. Calcd. for $C_{13}H_{10}N_2S$: C, 68.99; H, 4.45; N, 12.37; S, 14.16; found: C, 69.10; H, 4.39; N, 12.32; S, 14.08.

2-(*p*-Tolylthio)phenylcanamide (1b):



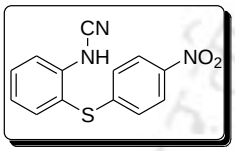
White solid, mp 117-119 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.28 (s, 3H), 6.98 (d, 2H, J = 8 Hz), 7.07 (m, 3H), 7.31 (d, 1H, J = 8 Hz), 7.44 (t, 1H, J = 7.6 Hz), 7.55 (d, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.2, 110.5, 115.5, 118.7, 124.3, 128.0, 130.5, 131.4, 131.6, 137.0, 137.3, 139.7; IR (KBr): 3158, 2961, 2791, 2239, 1588, 1578, 1489, 1449, 1407, 1288, 1165, 1019, 805, 757, 503 cm^{-1}; Anal. Calcd. for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.65; S, 13.34; found: C, 69.89; H, 4.96; N, 11.61; S, 13.25.

2-(4-Aminophenylthio)phenylcyanamide (1c):



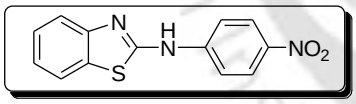
White solid, mp 131-133 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.75 (brs, 2H), 6.59 (d, 2H, J = 8 Hz), 7.03 (m, 3H), 7.26 (d, 1H, J = 8 Hz), 7.36 (t, 1H, J = 7.6 Hz), 7.47 (d, 1H, J = 8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 110.6, 115.3, 116.3, 121.2, 121.5, 124.2, 130.7, 131.8, 135.9, 138.6, 146.6; IR (KBr): 3394, 3310, 3100, 2802, 2227, 1590, 1579, 1490, 1449, 1412, 1287, 1258, 1138, 817, 764, 609 cm^{-1}; Anal. Calcd. for $C_{13}H_{11}N_3S$: C, 64.70; H, 4.59; N, 17.41; S, 13.28; found: C, 64.63; H, 4.61; N, 17.32; S, 13.21.

2-(4-Nitrophenylthio)phenylcyanamide (1d):



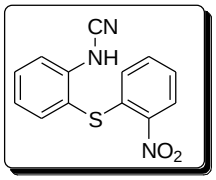
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.06 (d, 2H, J = 9.2 Hz), 7.23 (d, 1H, J = 9.2 Hz), 7.36 (d, 1H, J = 9.2), 7.46 (m, 2H), 7.61 (d, 1H, J = 9.2 Hz), 8.07 (d, 1H, J = 9.2 Hz), 8.11 (d, 1H, J = 9.2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 116.0, 121.7, 124.5, 124.7, 125.7, 126.0, 129.8, 131.8, 131.3, 135.9, 146.7, 151.1; IR (KBr): 3292, 3099, 2925, 2853, 2235, 1580, 1509, 1493, 1338, 1305, 1283, 1183, 1110, 912, 815, 741 cm^{-1}; Anal. Calcd. for $C_{13}H_9N_3O_2S$: C, 57.55; H, 3.34; N, 15.48; S, 11.82; found: C, 57.49; H, 3.29; N, 15.38; S, 11.69.

***N*-(4-Nitrophenyl)benzo[*d*]thiazole-2-amine(1d'):**



Yellow solid, mp 211-213 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.62 (d, 1H, J = 9.28 Hz), 7.10 (m, 2H), 7.32 (d, 1H, J = 8.8 Hz), 7.67 (d, 2H, J = 9.2 Hz), 7.42 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 110.5, 122.2, 123.1, 123.3, 125.6, 126.6, 129.8, 140.5, 142.1, 147.5, 162.3; IR (KBr): 3327, 3076, 2929, 2856, 1610, 1580, 1520, 1495, 1470, 1346, 1215, 1108, 1077, 910, 852, 805, 745 cm^{-1}; Anal. Calcd. for $C_{13}H_9N_3O_2S$: C, 57.55; H, 3.34; N, 15.49; S, 11.81; found: C, 57.43; H, 3.29; N, 15.43; S, 11.74.

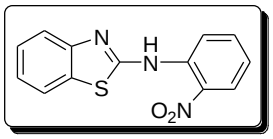
2-(2-Nitrophenylthio)phenylcyanamide (1e):



Yellow solid, mp 155-157 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.64 (d, 1H, J = 8 Hz),7.09 (brs, 1H), 7.23 (t, 1H, J = 8.8 Hz),7.31 (t, 1H, J = 8.4 Hz), 7.42 (m, 2H), 7.61 (m, 2H), 8.28 (d, 1H, J = 8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 110.1, 116.0, 121.7, 124.5, 124.7, 125.7, 126.0, 129.8, 131.3, 135.9,

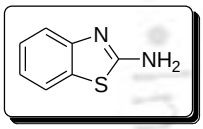
138.5,142.6,146.7; IR (KBr): 3197, 2901, 2829, 2236, 1592, 1567, 1517, 1490, 1449, 1441, 1337, 1305, 1290, 1163, 1107, 1041, 910, 854, 757 cm^{-1}; Anal. Calcd. for $C_{13}H_9N_3O_2S$: C, 57.55; H, 3.34; N, 15.49; S, 11.81; found: C, 57.39; H, 3.25; N, 15.38; S, 11.77.

_N_-(2-Nitrophenyl)benzo[*d*]thiazole-2-amine (1e'):



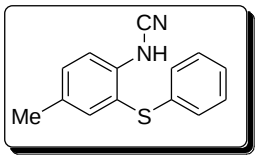
Yellow solid, mp 155-157 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.64 (d, 1H, J = 8 Hz),7.09 (brs, 1H), 7.23 (t, 1H, J = 8.8 Hz),7.31 (t, 1H, J = 8.4 Hz), 7.42 (m, 2H), 7.61 (m, 2H), 8.28 (d, 1H, J = 8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 110.1, 116.0, 121.7, 124.5, 124.7, 125.7, 126.0, 129.8, 131.3, 135.9, 138.5,142.6,146.7; IR (KBr): 3197, 2901, 2829, 2236, 1592, 1567, 1517, 1490, 1449, 1441, 1337, 1305, 1290, 1163, 1107, 1041, 910, 854, 757 cm^{-1}; Anal. Calcd. for $C_{13}H_9N_3O_2S$: C, 57.55; H, 3.34; N, 15.49; S, 11.81; found: C, 57.39; H, 3.25; N, 15.38; S, 11.77.

Benzo[*d*]thiazol-2-amine (K):



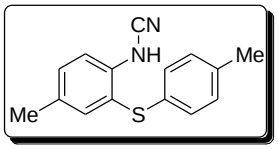
White solid, mp 120-122 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.2 (brs, 2H), 7.13 (t, 1H, J = 8 Hz), 7.31 (t, 1H, J = 8 Hz), 7.53 (d, 1H, J = 8 Hz), 7.58 (d, 1H, J = 8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 119.3, 121.4, 122.7, 126.5, 131.6, 152.1, 167.1; IR (KBr): 3388, 3175, 2925, 2851, 1644, 1528, 1446, 1374, 1284, 1236, 1106, 887, 741 cm^{-1}; Anal. Calcd. for $C_7H_6N_2S$: C, 55.97; H, 4.02; N, 18.65; S, 21.34; found: C, 55.84; H, 4.07; N, 18.57; S 21.29.

4-Methyl-2-(phenylthio)phenylcyanamide (2a):



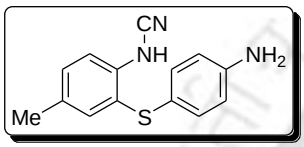
Yellow solid, mp 131-133 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): δ2.32 (s, 2H), 6.08 (brs, 1H), 7.02 (d, 2H, J = 7.2 Hz), 7.18 (d, 2H, J = 7.2 Hz), 7.25 (m, 3H), 7.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.7, 110.7, 115.4, 117.2, 129.6, 132.7, 134.1, 135.4, 137.5, 138.0; IR (KBr): 3212, 2920, 2840, 2224, 1606, 1580, 1495, 1439, 1387, 1286, 1154, 1072, 1024, 806, 746 cm^{-1}; Anal. Calcd. for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.65; S, 13.34; found: C, 69.83; H, 5.07; N, 11.52; S, 13.21.

2-(*p*-Tolylthio)-4-methylphenylcyanamide (2b):



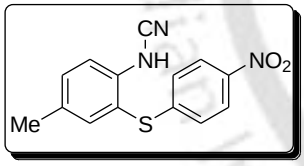
White solid, mp 105-107 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.29 (s, 3H), 2.31 (s, 3H), 6.96 (d, 2H, J = 8 Hz), 7.06 (d, 2H, J = 8 Hz), 7.22 (m, 2H), 7.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.7, 21.1, 110.6, 115.3, 118.0, 127.7, 130.4, 131.5, 132.3, 134.1, 136.9, 137.1, 137.6; IR (KBr): 3153, 2922, 2846, 2231, 1607, 1498, 1410, 1389, 1288, 1155, 1080, 1015, 809, 591 cm^{-1}; Anal. Calcd. for $C_{15}H_{14}N_2S$: C, 70.83; H, 5.54; N, 11.01; S, 12.60; found: C, 70.71; H, 5.47; N, 11.08; S, 12.47.

2-(4-Aminophenylthio)-4-methylphenylcyanamide (2c):



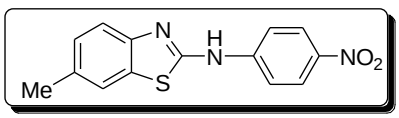
White solid**,** mp 110-112 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.27 (s, 3H), 6.58 (d, 2H, J = 8 Hz), 6.90 (d, 2H, J = 8 Hz), 7.01 (d, 1H, J = 7.6 Hz), 7.15 (s, 1H), 7.28 (d, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.7,115.3, 116.2, 116.3, 120.9, 121.8, 130.8, 131.3, 131.6, 133.9, 136.2, 146.5; IR (KBr): 3381, 2923, 2222, 1627, 1495, 1459, 1388, 1288, 1177, 816, 731 cm^{-1}; Anal. Calcd. for $C_{14}H_{13}N_3S$: C, 65.85; H, 5.13; N, 16.45; S, 12.55; found: C, 65.71; H, 5.16; N, 16.51; S, 12.42.

2-(4-Nitrophenylthio)-4-methylphenylcyanamide (2d):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.36 (s, 3H), 7.05 (d, 2H, J = 9.2 Hz),7.31(d, 1H, J = 8.4 Hz),7.39 (d, 2H, J = 8 Hz), 8.09 (d, 2H, J = 9.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.7, 112.2, 116.2, 124.6, 125.7, 126.0, 133.9, 134.5, 138.2, 138.7, 145.5; IR (KBr): 3326, 2927, 2851, 2243, 1604, 1505, 1339, 1237, 1110, 1014, 985, 849, 808, 742 cm^{-1}; Anal. Calcd. for $C_{14}H_{11}N_3O_2S$: C, 58.93; H, 3.88; N, 14.72; S, 11.23; found: C, 58.99; H, 3.76; N, 14.64; S, 11.17.

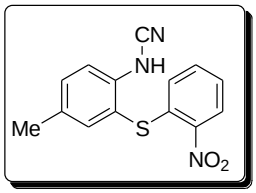
6-Methyl-*N*-(4-nitrophenyl)benzo[*d*]thiazol-2-amine (2d'):



Gummy, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.3 (s, 3H), 6.52 (d, 1H, J = 8 Hz), 6.93 (d, 1H, J = 8.4 Hz), 7.14 (s, 1H), 7.66 (d, 2H, J = 8.8 Hz), 8.41 (d, 2H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1, 110.3, 122.5, 123.0, 125.3, 125.6, 127.3, 129.7, 133.3, 128.3, 142.2, 162.6; IR (KBr): 3336, 3053, 2919, 2850, 1610, 1523, 1497, 1345, 1245, 1109, 848, 805, 738 cm^{-1};

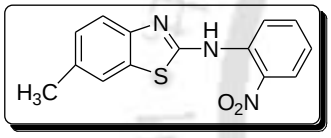
Anal. Calcd. for $C_{14}H_{11}N_3O_2S$: C, 58.93; H, 3.88; N, 14.72; S, 11.23; found: C, 58.85; H, 3.79; N, 14.76; S, 11.11.

2-(2-Nitrophenylthio)-4-methylphenylcyanamide(2e):



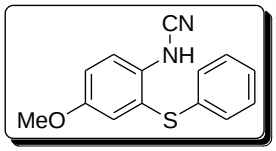
Gummy; NMR ($CDCl_3$, 400 MHz): δ 2.36 (s, 3H), 6.66 (d, 1H, J = 9.2 Hz), 7.28 (m, 2H), 7.40 (m, 3H), 8.25 (d, 1H, J = 9.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ20.7, 110.5, 115.4, 116.0, 126.1, 126.5, 127.3, 133.9, 134.5, 134.8, 136.1, 138.3, 138.6, 145.4; IR (KBr): 3216, 2927, 2853, 2243, 1717, 1511, 1155, 1106, 1041, 955, 911, 853, 816, 783 cm^{-1}; Anal. Calcd. for $C_{14}H_{11}N_3O_2S$: C, 58.93; H, 3.88; N, 14.72; S, 11.23; found: C, 58.85; H, 3.92; N, 14.75; S, 11.12.

6-Methyl-*N*-(2-nitrophenyl)benzo[*d*]thiazol-2-amine (2e'):



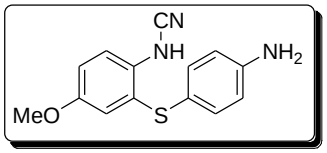
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ2.32 (s, 3H), 6.00 (brs, 2H), 637 (d, 1H, J = 8.4 Hz), 6.91 (d, 1H, J = 8.0 Hz), 7.14 (d, 1H, J = 3.2 Hz), 7.56 (d, 1H, J = 8.0 Hz), 7.65 (t, 1H, J = 8.0), 7.82 (t, 1H, J = 8.0 Hz), 8.19 (d, 1H, J = 9.6 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 21.2, 110.1, 122.6, 123.1, 126.6, 127.4, 129.6, 130.7, 132.0, 133.3, 135.2, 138.2, 147.0, 163.4; IR (KBr): 3332, 3094, 2925, 1717, 1613, 1531, 1493, 1361, 1236, 1096, 984, 849, 783 cm^{-1}; Anal. Calcd. for $C_{14}H_{11}N_3O_2S$ (285.32): C, 58.93; H, 3.88; N, 14.72; S, 11.23; found: C, 58.86; H, 3.93; N, 14.69; S, 11.09.

4-Methoxy-2-(phenylthio)phenylcyanamide (3a):



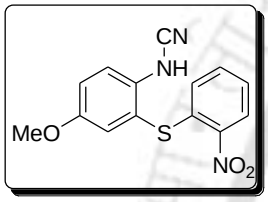
White solid, mp 119-121 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.78 (s, 3H), 7.01 (d, 1H, J = 2.8 Hz), 7.05 (d, 2H, J = 7.2 Hz), 7.10 (d, 1H, J = 2.8 Hz), 7.18 (t, 1H, J = 7.6 Hz), 7.25 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 56.0, 111.0, 116.6, 117.8, 118.6, 122.0, 126.9, 127.3, 129.7, 133.0, 134.9, 156.1; IR (KBr): 3189, 2999, 2962, 2926, 2851, 2228, 1605, 1578, 1497, 1438, 1393, 1257, 1215, 1176, 1043, 1031, 884, 831, 751 cm^{-1}; Anal. Calcd. for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.71; N, 10.92; S, 12.50; found: C, 65.53; H, 4.67; N, 10.98; S, 12.49.

2-(4-Aminophenylthio)-4-methoxyphenylcyanamide (3c):



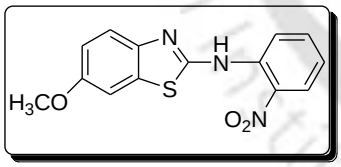
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.77 (s, 3H), 6.46 (d, 2H, *J* = 8.8 Hz), 6.90 (dd, 1H, *J* = 6.0 Hz, *J* = 2.8 Hz), 7.06 (d, 1H, *J* = 6.8 Hz), 7.20 (d, 1H, *J* = 7.2 Hz) 7.39 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 56.1, 110.5, 111.0, 115.1, 117.2, 117.6, 118.4, 128.7, 138.1, 146.3, 156.4; IR (KBr): 3381, 2926, 2852, 2236, 1621, 1487, 1375, 1265, 1218, 1179, 1034, 816, 737 cm^{-1}; Anal. Calcd. for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.82; N, 15.48; S, 11.81; found: C, 61.86; H, 4.75; N, 15.56; S, 11.72.

2-(2-Nitrophenylthio)-4-methoxyphenylcyanamide (3e):



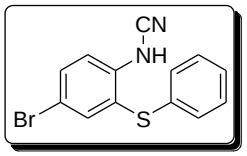
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.8 (s, 3H), 6.8 (d, 1H, *J* = 8 Hz), 7.14 (d, 1H, *J* = 8.8 Hz), 7.30 (m, 3H), 7.42 (t, 1H, *J* = 8.8 Hz), 8.28 (d, 1H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 56.1, 116.5, 117.2, 119.3, 122.5, 125.7, 126.3, 126.6, 127.2, 128.8, 134.0, 134.6, 145.4, 156.5; IR (KBr): 3217, 2925, 2853, 2241, 1591, 1567, 1505, 1395, 1337, 1293, 1216, 1148, 1041, 853, 783, 734 cm^{-1}; Anal. Calcd. for $C_{14}H_{11}N_3O_3S$: C, 55.80; H, 3.67; N, 13.94; S, 10.64; found: C, 55.69; H, 3.73; N, 13.88; S, 10.58.

6-Methoxy-*N*-(2-nitrophenyl)benzo[*d*]thiazol-2-amine (3e'):



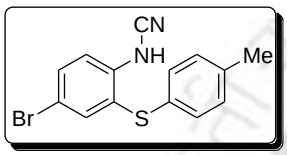
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.78 (s, 3H), 6.40 (d, 1H, *J* = 8.8 Hz), 6.66 (dd, 1H, *J* = 6.0 Hz, *J* = 2.8 Hz), 6.9 (d, 1H, *J* = 2.8 Hz), 7.57 (d, 1H, *J* = 8 Hz), 7.66 (t, 1H, *J* = 8.8 Hz), 7.82 (t, 1H, *J* = 7.6 Hz), 8.19 (d, 1H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 56.1, 108.1, 110.6, 112.7, 124.2, 126.6, 129.9, 130.4, 131.9, 134.4, 135.1, 147.1, 156.2, 162.6; IR (KBr): 3333, 2936, 2835, 1614, 1584, 1531, 1488, 1351, 1269, 1210, 1059, 1031, 849, 784 cm^{-1}; anal. calcd. for $C_{14}H_{11}N_3O_3S$: C, 55.80; H, 3.67; N, 13.94; S, 10.64; found: C, 55.71; H, 3.63; N, 13.89; S, 10.57.

4-Bromo-2-(phenylthio)phenylcyanamide (4a):



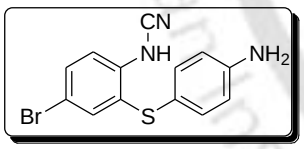
White solid, mp 104-106 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.07 (d, 2H, *J* = 8 Hz), 7.26 (m, 4H), 7.57 (dd, 1H, *J* = 6 Hz, *J* = 2.4 Hz), 7.70 (d, 1H, *J* = 2.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 109.7, 116.2, 116.9, 127.4, 127.8, 129.9, 134.0, 134.7, 138.9, 139.5; IR (KBr): 3201, 3049, 2925, 2846, 2224, 1569, 1479, 1440, 1375, 1280, 1153, 1086, 1023, 888, 805, 741, 691 cm^{-1}; Anal. Calcd. for $C_{13}H_9BrN_2S$: C, 51.16; H, 2.97; N, 9.17; S, 10.50; found: C, 51.08; H, 2.92; N, 9.23; S, 10.43.

2-(*p*-Tolylthio)-4-bromophenylcyanamide (4b):



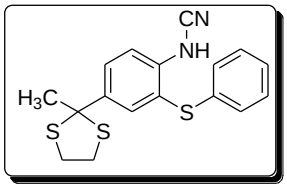
White solid, mp 114-116 ^{o}C; IR (KBr): ν = 3148, 2920, 2234, 1670, 1569, 1481, 1447, 1406, 1378, 1283, 1155, 1084, 816, 804 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.2 (s, 3H), 6.93 (d, 2H, *J* = 8.4 Hz), 7.00 (d, 2H, *J* = 8 Hz), 7.08 (d, 2H, *J* = 8.8 Hz), 7.42 (dd, 1H, *J* = 6.4 Hz, *J* = 2.4 Hz), 7.55 (d, 1H, *J* = 2.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.3, 110.1, 116.1, 117.0, 128.8, 130.2, 130.7, 131.0, 134.2, 137.8, 138.6, 138.8; Anal. Calcd. for $C_{14}H_{11}BrN_2S$: C, 52.67; H, 3.47; N, 8.77; S, 10.04; found: C, 52.55; H, 3.41; N, 8.69; S, 9.91.

2-(4-Aminophenylthio)-4-bromophenylcyanamide (4c):



White solid, mp 128-130 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.82 (brs, 2H), 6.6 (d, 2H, *J* = 8.4 Hz), 7.08 (d, 2H, *J* = 8.4 Hz), 7.30 (d, 1H, *J* = 8.4 Hz), 7.43 (dd, 1H, *J* = 6.4, *J* = 2.4), 7.51 (d, 1H, *J* = 2.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 110.1, 116.2, 116.4, 116.8, 119.9, 124.2, 132.9, 133.0, 137.1, 137.3, 147.2; IR (KBr): 3400, 3332, 3078, 2917, 2239, 1592, 1570, 1480, 1411, 1376, 1262, 1227, 1178, 1086, 848, 769 cm^{-1}; Anal. Calcd. for $C_{13}H_{10}BrN_3S$: C, 48.76; H, 3.14; N, 13.12; S, 10.01; found: C, 48.68; H, 3.18; N, 13.16; S, 9.92.

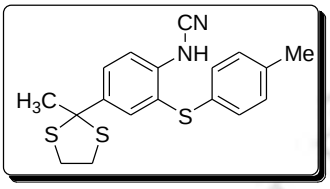
4-(2-Methyl-1,3-dithiolane-2-yl)-2-(phenylthio)phenylcyanamide (5a):



Oily liquid ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.12 (s, 3H), 3.36 (m, 2H), 4.45 (m, 2H), 7.02 (d, 2H, *J* = 8 Hz), 7.16 (t, 1H, *J* = 7.6 Hz), 7.25 (m, 2H), 7.85 (dd, 1H, *J* = 6.4 Hz, *J* = 2.4 Hz), 7.97 (d, 1H, *J* = 2.0 Hz); ^{13}C

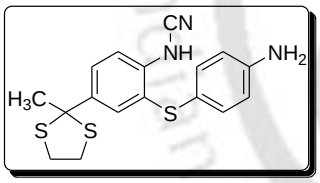
NMR ($CDCl_3$, 100 MHz): δ 33.7, 40.9, 67.7, 115.1, 116.9, 126.8, 127.1, 129.7, 130.8, 135.1, 136.2, 138.8, 142.5; IR (neat): 3211, 2923, 2851, 2244, 1681, 1596, 1494, 1440, 1385, 1291, 1159, 1078, 824, 739 cm^{-1}; Anal. Calcd. for $C_{17}H_{16}N_2S_3$: C, 59.26; H, 4.68; N, 8.13; S, 27.92; found: C, 59.18; H, 4.61; N, 8.09; S, 27.81.

2-(*p*-Tolylthio)-4-(2-methyl-1,3-dithiolan-2-yl)-phenylcyanamide (5b):



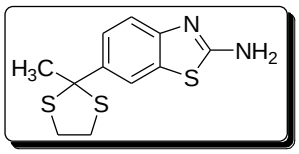
Oily liquid; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.12 (s, 3H), 2.28 (s, 3H), 3.36 (m, 2H), 3.46 (m, 2H), 6.96 (d, 2H, *J* = 8.4 Hz), 7.06 (d, 2H, *J* = 8 Hz), 7. 24 (d, 1H, *J* = 8.8 Hz), 7.83 (dd, 1H, *J* = 6.0 Hz, *J* = 2.4 Hz), 7.96 (d, 1H, *J* = 2.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.2, 33.7, 40.8, 67.7, 110.4, 115.0, 117.8, 127.7, 130.5, 131.2, 135.8, 137.0, 138.5, 142.4; IR (neat): 3217, 2976, 2863, 2245, 1597, 1574, 1494, 1385, 1292, 1275, 1084, 1016, 908, 804 cm^{-1}; Anal. Calcd. for $C_{18}H_{18}N_2S_3$: C, 60.29; H, 5.05; N, 7.81; S, 26.82; found C, 60.21; H, 5.09; N, 7.88; S, 26.76.

2-(4-Aminophenylthio)-4-(2-methyl-1,3-dithiolan-2-yl)-phenylcyanamide (5c):



Oily liquid; ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.09 (s, 3H), 3.33 (m, 2H), 3.45 (m, 2H), 3.75 (brs, 2H), 6.59 (d, 2H, *J* = 8.8 Hz), 7.01 (d, 2H, *J* = 8.4 Hz), 7.18 (d, 1H, *J* = 8.4 Hz), 7.75 (dd, 1H, *J* = 6.4 Hz, *J* = 2.4 Hz), 7.88 (d, 1H, *J* = 2.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 33.6, 40.8, 68.7, 110.6, 114.9, 116.3, 120.3, 121.4, 129.6, 131.5, 134.5, 137.6, 142.1, 146.5; IR (neat): 3367, 2975, 2923, 2225, 1620, 1596, 1495, 1384, 1290, 1178, 1077, 908, 823, 733 cm^{-1}; Anal. Calcd. for $C_{17}H_{17}N_3S_3$: C, 56.79; H, 4.76; N, 11.68; S, 26.75; found: C, 56.71; H, 4.72; N, 11.76; S, 26.63.

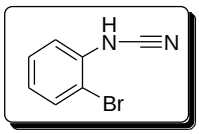
6-(2-Methyl-1,3-dithiolan-2-yl)-benzo[*d*]thiazol-2-amine (5f):



Oily liquid; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 3.76 (m, 2H), 3.46 (m, 2H), 5.79 (brs, 2H), 7.41 (d, 1H, *J* = 8.4 Hz), 7.67 (dd, 1H, *J* = 6.4 Hz, *J* = 2.4 Hz), 8.0 (d, 1H, *J* = 2.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 34.2, 40.6, 68.9, 118.3, 119.5, 125.6, 131.1, 140.3, 150.9, 167.4; IR (neat): 3310, 3131, 2964, 2922, 1621, 1531, 1461, 1307, 1278, 1190, 1109, 904, 822, 732 cm^{-1}; Anal. Calcd.

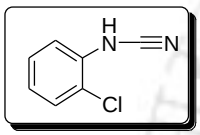
for $C_{11}H_{12}N_2S_3$: C, 49.22; H, 4.50; N, 10.43; S, 35.83; found: C, 49.29; H, 4.46; N, 10.39; S, 35.72.

2-Bromo-phenyl cyanamide (1a''):



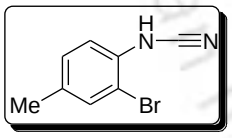
White solid**,** mp 95 ^{o}C (Lit. 94.5 ^{o}C[23]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.36 (brs, 1H), 6.96-7.01 (m, 1H), 7.25-7.39 (m, 2H) 7.52-7.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 109.9, 110.0, 116.1, 124.9, 129.2, 133.0, 135.3; IR (KBr): 3150, 2237, 1602, 1504, 1425, 1286, 1026, 738 cm^{-1}; Anal. Calcd. for $C_7H_5BrN_2$: C, 42.67; H, 2.55; N, 14.21; found: C, 42.61; H, 2.62; N, 14.11.

2-Chloro-phenyl cyanamide (1'''a):



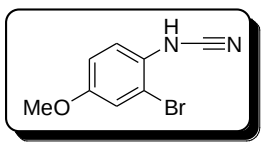
White solid, mp 101-103 ^{o}C (Lit. 101-103 ^{o}C[22]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.56 (brs, 1H), 7.05 (m, 1H), 7.31 (m, 2H), 7.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 110.0, 116.2, 120.4, 124.5, 128.6, 129.9, 134.3; IR (KBr): 3163, 2921, 2243, 1598, 1500, 1426, 1295, 1049, 746 cm^{-1}; Anal. Calcd. for $C_7H_5ClN_2$: C, 55.10; H, 3.30; N, 18.36; found: C, 55.11; H, 3.32; N, 18.29.

2-Bromo-4-methyl-phenyl cyanamide (2f):



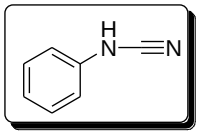
Brown solid, mp 91-92 ^{o}C (Lit. 91-93 ^{o}C[23]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.31 (s, 3H), 6.23 (s, 1H), 7.14-7.19 (m, 2H) 7.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.5, 109.6, 110.4, 115.9, 129.8, 132.7, 133.2, 135.0; IR (KBr): 3211, 2923, 2226, 1608, 1509, 1424, 1287, 1038, 863, 804, 743 cm^{-1}; Anal. Calcd. for $C_8H_7BrN_2$: C, 45.52; H, 3.34; N, 13.27; found: C, 45.61; H, 3.29; N, 13.20.

2-Bromo, 4-Methoxy phenyl cyanamide (3f):



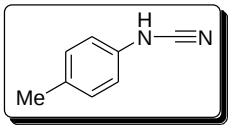
White solid, mp 107-111 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.9 (s, 3H), 5.28 (brs, 1H), 6.92 (dd, J_1 = 6.0 Hz, J_2 = 2.8 Hz, 1H), 7.08 (d, J = 2.8 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 56.01, 104.1, 115.2, 122.8, 130.06, 130.3, 135.1, 157.4; IR (KBr): 3287, 2925, 2251, 2220, 1611, 1507, 1399, 1286, 1218, 1036, 870, 794cm^{-1}; Anal. Calcd. for $C_8H_7BrN_2O$: C, 42.31; H, 3.10; N, 12.34; found: C, 42.28; H, 3.15; N, 12.31.

Phenyl cyanamide (6a):



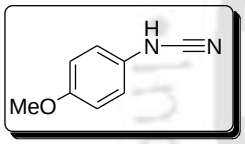
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.02-7.07 (m, 3H), 7.28-7.33 (m, 2H), 7.64 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 112.2, 115.5, 123.6, 129.8, 137.4; IR (KBr): 3175, 2919, 2227, 1600, 1501, 1249, 891, 748 cm^{-1}; Anal. Calcd. for $C_7H_6N_2$: C, 71.16; H, 5.12; N, 23.71; found: C, 71.27; H, 5.09; N, 23.67.

***p*-Tolyl cyanamide (7a):**



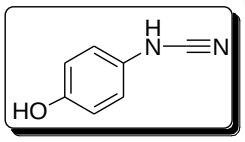
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.28 (s, 3H), 6.91 (d, 2H, J = 8.4 Hz), 7.10 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.7, 112.4, 115.5, 130.3, 133.2, 134.9; IR (KBr): 3165, 2950, 2228, 1620, 1515, 1249, 809 cm^{-1}; Anal. Calcd. for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.19; found: C, 72.27; H, 5.99; N 21.15.

4-Methoxy-phenyl cyanamide (8a):



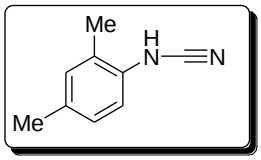
White solid, mp 86-89 ^{o}C (Lit. 86-89 ^{o}C[23]); IR (KBr): ν = 3180, 2926, 2218, 1509, 1295, 1238, 1105, 1037, 826, 795 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.78 (s, 3H), 6.87 (d, 2H, J = 8.8 Hz), 6.95 (d, 2H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 55.8, 112.8, 115.2, 117.0, 130.6, 156.1; Anal. Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91; found: C, 64.91; H; 5.40; N, 18.93.

4-Hydroxy-phenyl cyanamide (9a):



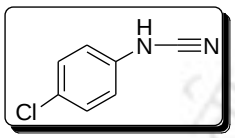
White solid, mp 259-260 ^{o}C (Lit. 259-261 ^{o}C[22]); IR (KBr): ν = 3213, 2992, 2230, 1613, 1519, 1444, 1258, 1224, 815 cm^{-1}; ^{1}H NMR ($CDCl_3$ / DMSO-d_6, 400 MHz,): δ = 5.67 (brs, 1H), 6.77 (d, 2H, J = 8.8 Hz), 6.83 (d , 2H, J = 8.8 Hz), 8.98 (brs, 1H); ^{13}C NMR ($CDCl_3$ / DMSO-d_6, 100 MHz,): δ = 112.8, 115.6, 115.8, 129.5, 152.2; Anal. Calcd for $C_7H_6N_2O$: C, 62.67; H, 4.50; N, 20.89; found: C, 62.72; H, 4.55; N, 20.83.

2, 4-Dimethyl-phenyl cyanamide (10a):



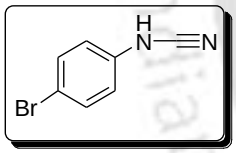
White solid**,** mp 117-119 ^{o}C (Lit. 115-119 ^{o}C[22]); IR (KBr): ν = 3186, 2915, 2233, 1599, 1512, 1433, 1271, 1031, 812 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.18 (s, 3H), 2.26 (s, 3H), 6.74 (brs, 1H), 6.93 (s, 1H), 6.99 (d, 1H, *J* = 8.0 Hz), 7.05 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.3, 20.7, 112.8, 115.7, 124.7, 127.9, 131.8, 133.2, 133.3; Anal. Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16; found: C, 73.87; H, 6.86; N, 19.14.

4-Chloro-phenyl cyanamide (11a):



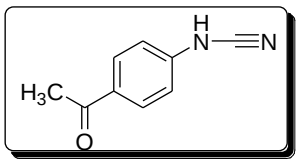
White solid, mp 96 ^{o}C (Lit. 95 ^{o}C[22]); IR (KBr): ν = 3166, 2954, 2234, 1600, 1494, 1399, 1251, 1091, 1011, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.91 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 111.4, 116.9, 128.9, 129.9, 136.2; Anal. Calcd. for $C_7H_5ClN_2$: C, 55.10; H, 3.30; N, 18.36; found: C, 55.09; H, 3.33; N, 18.32.

4-Bromo-phenyl cyanamide (12a):



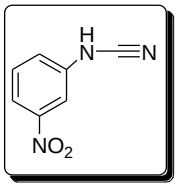
White solid, mp 110-111 ^{o}C (Lit. 112 ^{o}C); IR (KBr): ν = 3153, 3078, 2958, 2884, 2228, 1594, 1503, 1493, 1394, 1281, 1251, 1073, 813 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.90 (d, 2H, *J* = 8.4 Hz), 7.11 (brs, 1H), 7.43 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 111.2, 116.4, 117.2, 132.8, 136.5; Anal. Calcd. for $C_7H_5BrN_2$: C, 42.67; H, 2.55; N, 14.21; found: C, 42.61; H, 2.62; N, 14.11. (Lit **12a** C.-Y. Chen, F. F. Wong, , J.-J. Hwang, S.-K. Lin, M.-Y. Yeh, *Tetrahedron Lett.* **2008**, *49*, 6505

4-Acetyl-phenylcyanamide (13a):



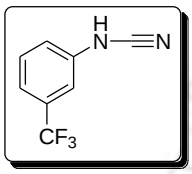
White solid, mp 153-157 ^{o}C (Lit. 153-157 ^{o}C [22]); IR (KBr): ν = 3188, 2966, 2228, 1666, 1599, 1585, 1411, 1362, 1278, 1176, 962, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$ / DMSO-d_6, 400 MHz,): δ = 2.56 (s, 3H), 7.08 (d, 2H, *J* = 8.8 Hz), 7.91 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$ / DMSO-d_6, 100 MHz,): δ = 25.9, 110.9, 114.5, 129.8, 131.2, 142.9, 196.2; Anal. Calcd. for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.48; found: C, 67.53; H, 5.08; N, 17.44.

3-Nitro-phenyl cyanamide (14a):



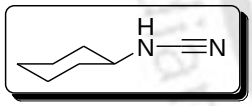
Yellow solid, mp 134-136 ^{o}C (Lit. 133-135 ^{o}C[23]); IR (KBr): ν = 3147, 2919, 2241, 1621, 1531, 1354, 1260, 1071, 937, 871, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$ / DMSO-d_6, 400 MHz): δ = 7.38 (d, 1H, J = 8.4 Hz), 7.52 (t, 1H, J = 8.4 Hz), 7.85 (m, 2H); ^{13}C NMR ($CDCl_3$ / DMSO-d_6, 100 MHz,): δ = 109.6, 110.7, 116.8, 120.8, 130.1, 139.9, 148.4; Anal. Calcd. for $C_7H_5N_3O_2$: C, 51.54; H, 3.09; N, 25.76; found: C, 51.58; H, 3.12; N, 25.70.

3-Trifluoromethyl phenyl cyanamide (15a):



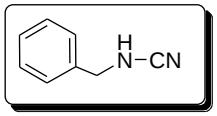
White solid, mp 82-85 ^{o}C; IR (KBr): ν = 3116, 2998, 2928, 2240, 1620, 1490, 1332, 1165, 1130, 877, 794, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.97 (brs, 1H), 7.21-7.26 (m, 2H), 7.36 (d, 1H, J = 8.0 Hz), 7.48 (t, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 111.1, 112.5, 118.7, 120.5, 122.3, 125.0, 130.6, 132.2, 132.5, 132.9, 138.1; Anal. Calcd. for $C_8H_5F_3N_2$: C, 51.62; H, 2.71; N, 15.05; found: C, 51.54; H, 2.69; N, 15.01.

Cyclohexyl-cyanamide (16a):



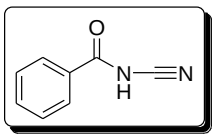
Gummy; IR (KBr): ν = 3196, 2933, 2857, 2217, 1453, 1367, 1167, 892 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.31 (m, 5H), 1.61 (m, 1H), 1.78 (m, 2H), 1.95 (m, 2H), 3.09 (m, 1H), 3.91 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.3, 25.1, 32.6, 54.3, 115.9; Anal. Calcd. for $C_7H_{12}N_2$: C, 67.70; H, 9.74; N, 22.56; found: C, 67.67; H, 9.70; N, 22.50.

Benzyl cyanamide (17a):



Gummy; IR (KBr): ν = 3207, 2925, 2220, 1455, 1359, 1155, 1014,735,698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.11 (d, J = 5.2 Hz, 2H, CH_2), 4.66 (brs, 1H), 7.27-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 49.9, 116.7, 127.9, 128.4, 128.9, 136.4; Anal. Calcd. for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.19; found: C, 72.66; H, 6.13; N, 21.11.

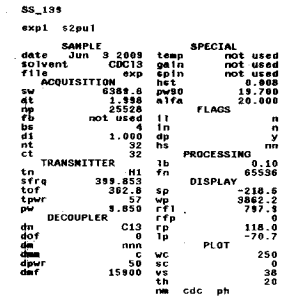
Benzoyl cyanamide (18a):

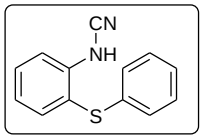


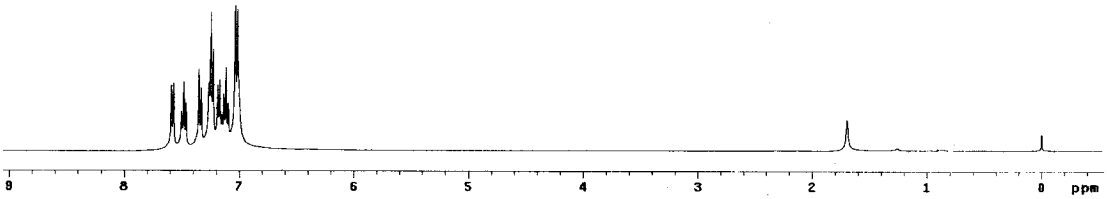
White solid, mp 135-137 ^{o}C (Lit. 132-136 ^{o}C); IR (KBr): ν = 3242, 2254, 1678, 1602, 1504, 1463, 1268, 1001, 890, 706 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.48 (t, 2H, *J* = 7.6 Hz), 7.61 (t, 1H, *J* = 7.6 Hz), 7.95 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 108.6, 128.5, 128.8, 130.2, 133.8, 166.9; Anal. Calcd. for $C_8H_6N_2O$: C, 65.74; H, 4.13; N, 19.17; found: C, 65.63; H, 4.18; N, 19.09. (Lit. **18a** R. Ketcham, E. Schaumann, *J. Org. Chem.* **1980**, *45*, 3748.)

IV.9. Selected Spectra

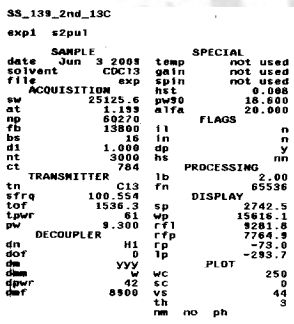
2-(Phenylthio)phenylcyanamide (1a): ^{13}C NMR (100 MHz, $CDCl_3$):

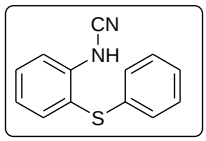


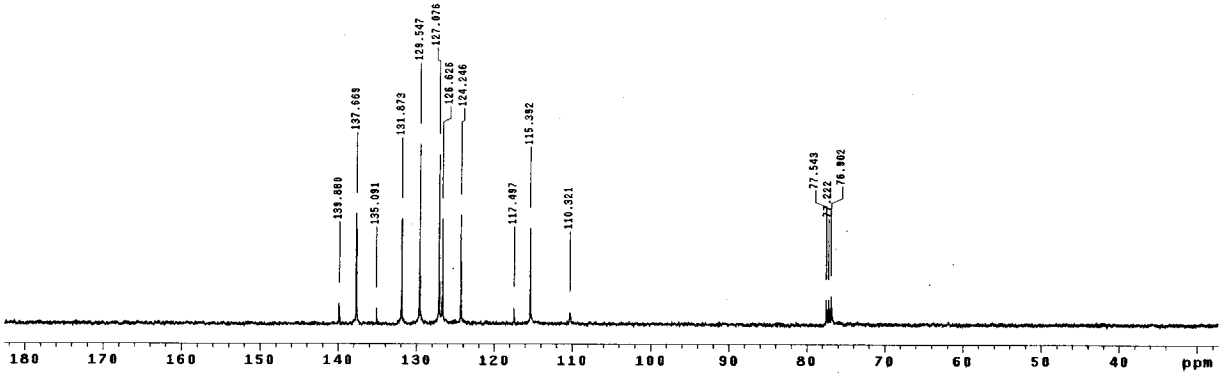




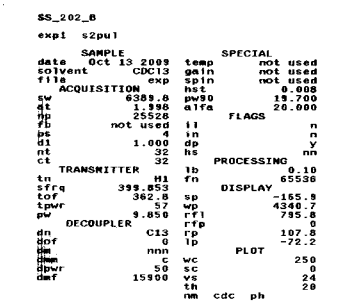
2-(Phenylthio)phenylcyanamide (1a): ^{13}C NMR (100 MHz, $CDCl_3$):

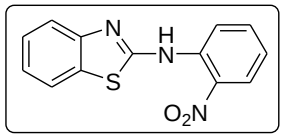


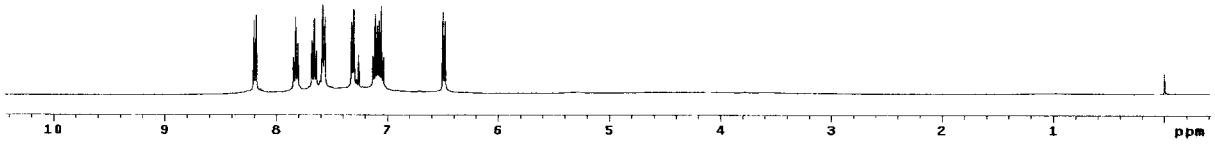




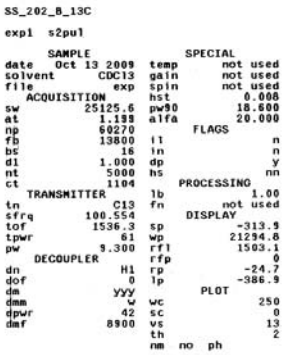
_N_-(2-Nitrophenyl)benzo[_d_]thiazole-2-amine(1e'): ^{1}H NMR (400 MHz, $CDCl_3$):

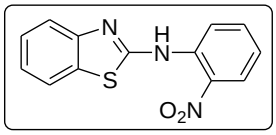


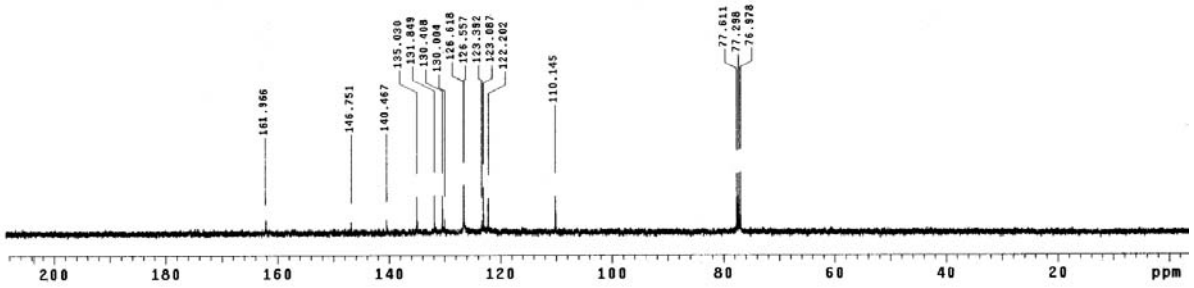




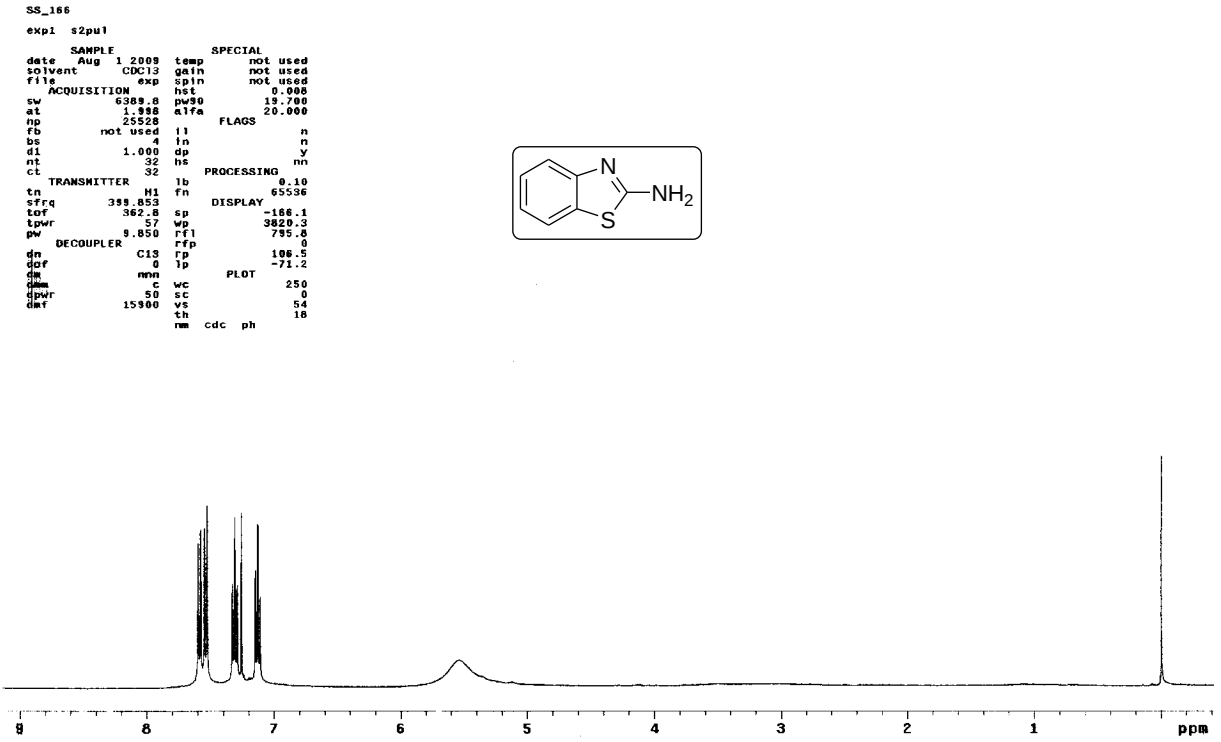
_N_-(2-Nitrophenyl)benzo[_d_]thiazole-2-amine(1e'): ^{13}C NMR (100 MHz, $CDCl_3$):



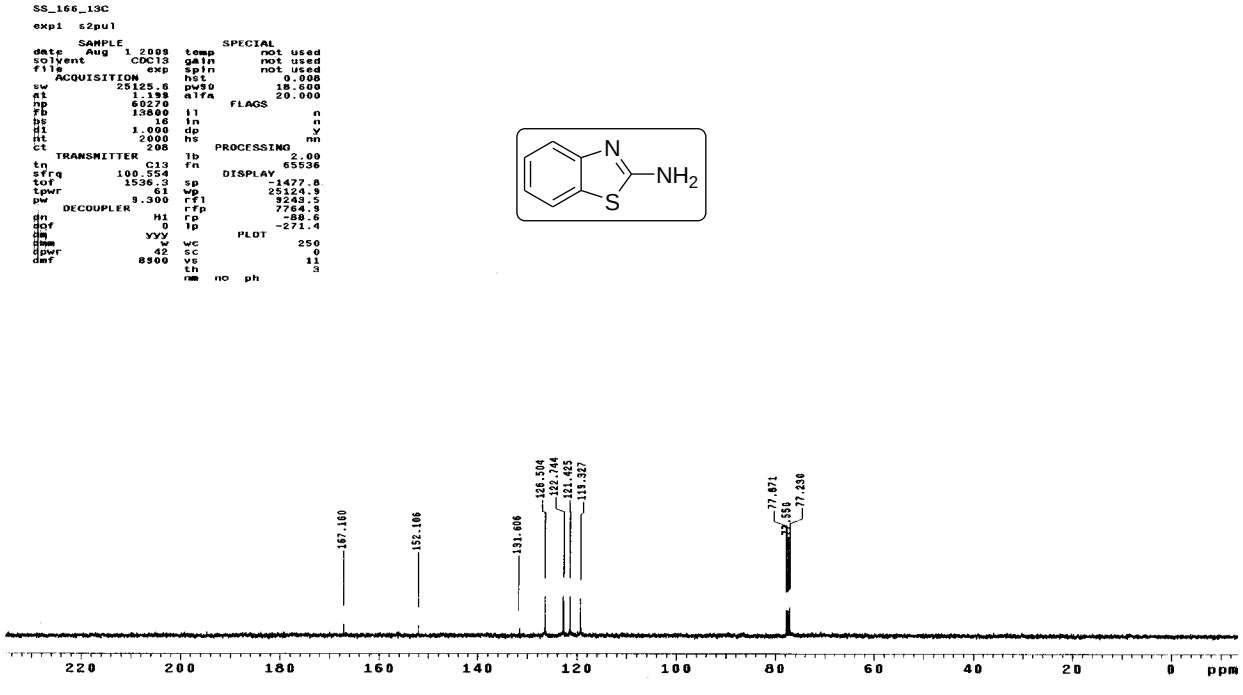




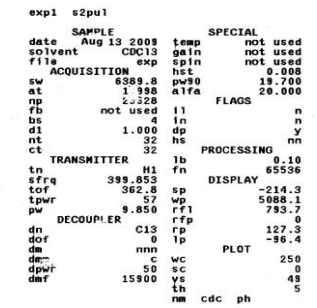
Benzo[*d*]thiazol-2-amine (K): ^{1}H NMR (400 MHz, $CDCl_3$):

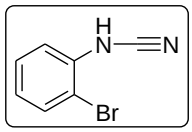


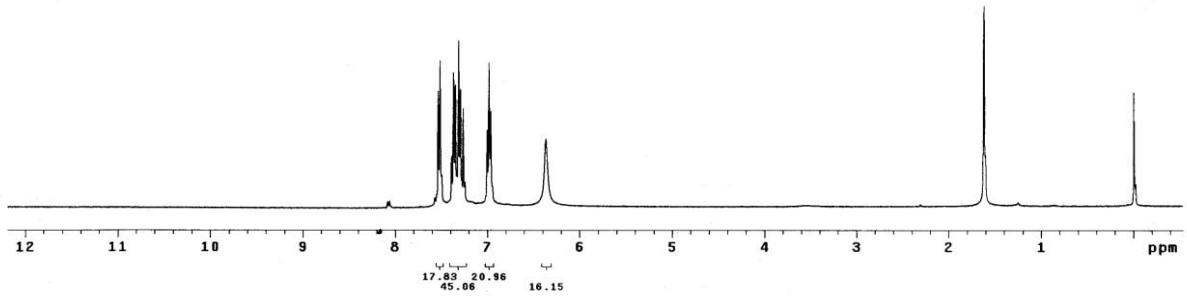
Benzo[*d*]thiazol-2-amine (K): ^{13}C NMR (100 MHz, $CDCl_3$):



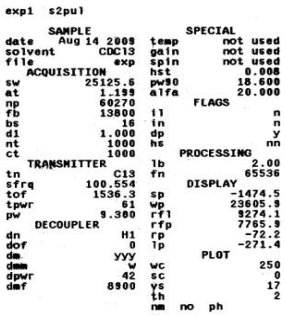
2-Bromo phenyl cyanamide (1a'''): ^{1}H NMR (400 MHz, $CDCl_3$):

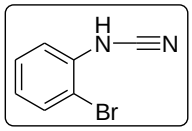


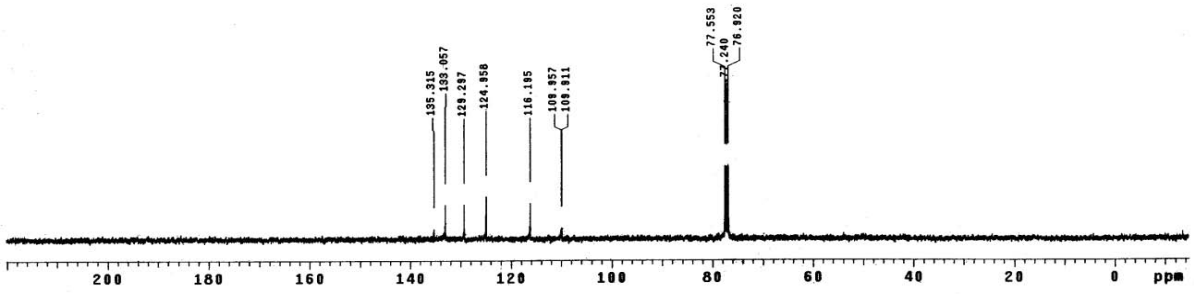




2-Bromo phenyl cyanamide (1a'''): ^{13}C NMR (100 MHz, $CDCl_3$):





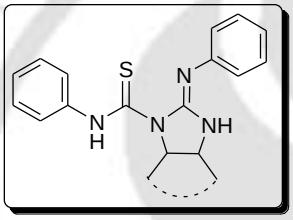


CHAPTER V

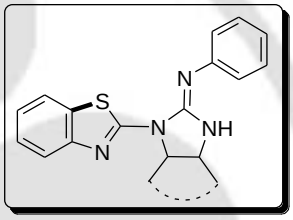
V. Copper Catalyzed Cascade Synthesis of Imidazolidine-benzothiazole Hybrid Heterocycles from *bis*-Thioureas

V.1. Structure and Nomenclature

Details of nomenclature of heterocycles were discussed in CHAPTER I. This chapter deals with the oxidative synthesis of guanidine derivatives namely imidazolidine-carbothioamide (ImCAT) and imidazolidine-benzothiazole (ImBT).



Imidazolidinecarbothioamide (ImCAT)



Imidazolidinebenzothiazole (ImBT)

Synthesis of (ImCAT) and (ImBT) from *in-situ* generated *bis*-thiourea derived from arylisothiocyanates and 1,2-diamines using Cu(II) catalyst

V.2. Importance and Applications

Recently hybrid heterocyles possessing benzothiazole and/or guanidino derivates have gained remarkable importance in drugs discovery and other biological applications. For example positron emission tomography labeled ligands, *N*-(4-(6-(isopropylamino)pyrimidine-4-yl)-1,3-thiazole-2-yl)-4-methoxy-*N*-methylbenzamide (**I**) are used for imaging metabotropic glutamate receptor type **1** (mgluR1) in rhodant brain.[1a] 2-Methyl-*N*-(3-(nitro)phenyl)-4,5-dihydrothiazole[4.5-h]quinazoline-8-amine (**II**) analogues are second generation CDK inhibitors.[1b] 4-(4-Benzylpiperazine-1-carbonyl)-*N*-(4-oxo-4H-3,1benzothiazin-2-yl)benzamide derivatives (**III**) were identified as structurally novel antagonist at adenosine receptors (AR's).[1c] Small molecule inhibitors (**IV**) linked by an oxalamide to a *p*-halide-substituted phenyl group are potential next generation therapeutics and microbicides against HIV-1[1d] Molecule (**V**) and (**VI**)

exhibit single digit micromolar activity against APE-1 enzyme and comparable activity in HeLa whole cell extract.[1e] Alkaloid variolin-B (**VII**) and its derivatives shows considerable cytotoxicity to human tumor cell line and also exhibit antimitotic activity.[1f] Thus combining the important pharmacophoric units *viz.* imidazolidine and benzothiazole for the construction of imidazolidine-benzothiazole (ImBT) hybrid heterocycle would be useful from the point of view of pharmaceutical properties.

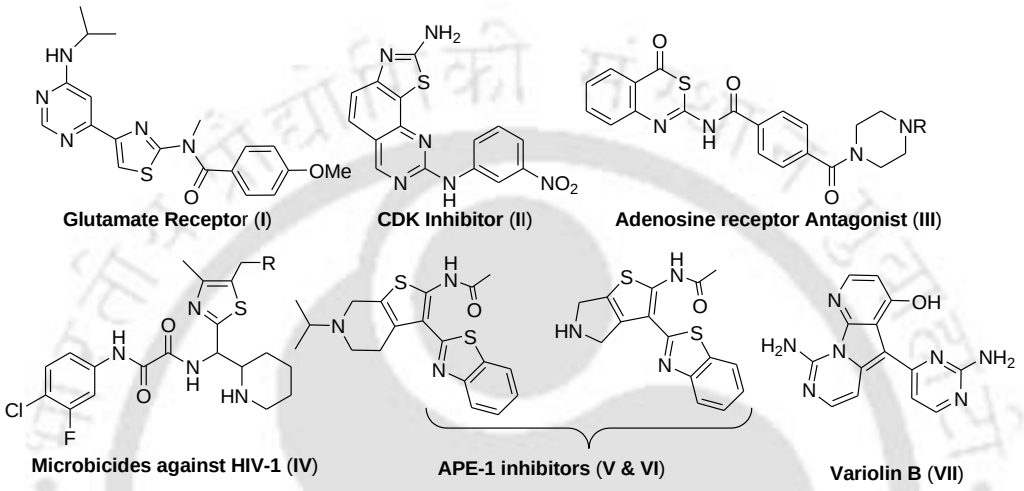
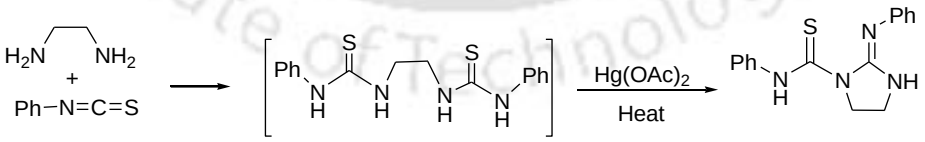


Figure V.2.1. *Structures of some bioactive hybrid heterocycles*

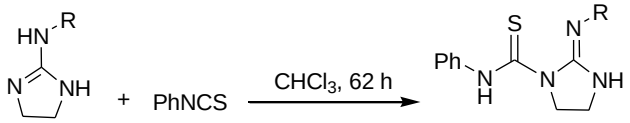
V.3. Available Synthetic Procedure for the Synthesis of Imidazolidinecarbothio-amides

The classical method for the synthesis of imidazolidinecarbothioamide (ImCAT) involves the desulfurization of bis-thiourea using toxic mercuric salt.[2a]



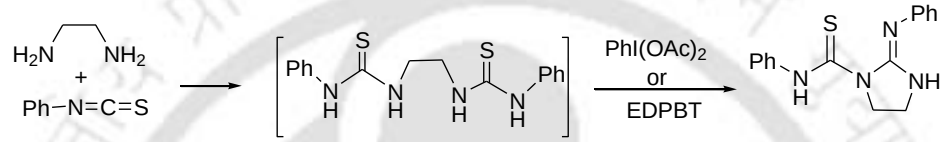
Scheme V.3.1. *Imidazolidinecarbothioamide synthesis via the desulfurization of bis-thiourea*

The other method involves the treatment of 2-methylamino-2-imidazoline with aryl isothiocyanates to generate the imidazolidinecarbothioamide (ImCAT).[2b]



Scheme V.3.2. *Imidazolidinecarbothioamide synthesis using phenylisothiocyanate and imidazole-amines*

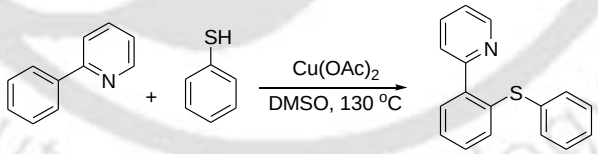
Recently our group have developed two greener approaches one using slightly expensive reagent diacetoxy-iodobenzene (DIB)[3a] and the other using unconventional ditribromide reagent EDPBT (1,1′-(ethane-1,2-diyl)dipyridinium bistribromide).[3b]



Scheme V.3.3. *Imidazolidinecarbothioamide synthesis using DIB and EDPBT*

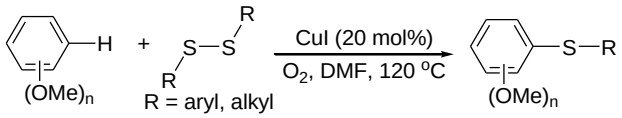
V.4. Reported Synthetic Methods of Copper Catalyzed Intermolecular *S*-Arylations via C-H activation Strategy

In 2006 Yu *et al*. have demonstrated intermolecular ortho-selective C–H functionalized thioetherification reactions by a combination of 2–arylpyridines and thiophenols using stoichiometic amount $Cu(OAc)_2$ salt in presence of DMSO solvent at 130 ^oC.[4a]



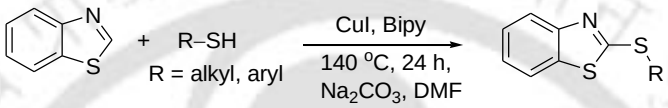
Scheme V.4.1. *Thioetherification of 2–arylpyridines using Cu(II) salt*

Cheng group have achieved a nonchelation-assisted Cu(I)-catalyzed thiolation of arene C–H bonds in di- or trimethoxybenzene using ArS–SAr in the presence of oxone as oxidant in DMF at 120 ^oC.[4b]



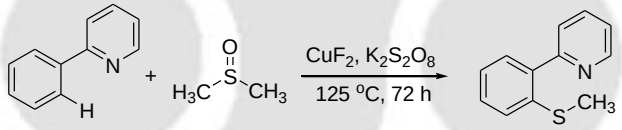
Scheme V.4.2. *Thioetherification of methoxybenzene via C–H bond cleavage*

Liu and coworkers have reported the synthesis of a series of aryl- or alkylsubstituted 2-mercaptobenzothiazoles by direct thiolation of benzothiazoles with aryl or alkyl thiols via copper-mediated aerobic C−H bond activation in the presence of stoichiometric CuI, 2,2′-bipyridine and Na_2CO_3.[4c]



Scheme II.4.3. *CuI/Bipy-mediated direct sulfurization of benzothiazole with thiols*

An unprecedented Cu(II)-mediated methylthiolation of aryl C-H bonds has been achieved under an oxidative conditions that employs DMSO as the methylating reagent. However, in this procedure an excess amount (4 equivalent) of Cu(II) salt is required to fuctionalized the ortho-C–H bond.[4d]



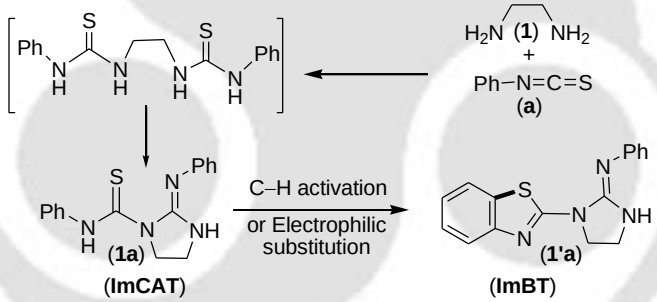
Scheme V.4.4. *CuI/Bipy-mediated direct thiolation of 2-phenyl pyridine*

V.5. Present Work

V.5.1. Copper Catalyzed Cascade Synthesis of Imidazolidine-Benzothiazole Hybrid Heterocycles from *bis*-Thioureas

Recently, we have demonstrated that a catalytic quantity of Cu salt in the presence of base can efficiently desulfurize arylthioureas to aryl cyanamides.[5a] The ability of Cu salts as an efficient desulfuring agents has been further demonstrated by us during the synthesis of amino substituted tetrazoles, triazoles, oxadiazoles and thiadiazoles by an oxidative desulfurization of

their respective thiourea precursors.[5b] Furthermore, copper catalyzed intermolecular thiolations *via* C−H activations are well documented in the literature,[4] but selective formation of C−S bonds are still fewer in numbers. This is because of the catalyst poisoning caused by sulfur compounds and the tendency of thioamidic substrates toward oxidative dimerization and oxidation to amides.[6] Taking cues from the desulfurizing[5] and C−H activating ability[4] of Cu, the construction of a hybrid molecule possessing an imidazolidine (guanidine) and a benzothiazole pharmacophores can be envisaged from the *bis*-thioureas derived from arylisothiocyanates and aliphatic 1,2-diamines. If copper behave as a thiophilic/desulfurizing agent similar to other thiophilic reagents such as DIB or iodine the *bis*-thiourea would yield imidazolidine-carbothioamide (**1a**) (*Scheme V.5.1.1*). Since copper has an intramolecular as well as an intermolecular C−H activation potential thus formation of a benzothiazole *via* a C−H activation path giving imidazolidinebenzothiazole (ImBT) cannot be ruled out. Alternatively, if the thiophilic power of Cu prevails, it may activate the sulfur towards an intramolecular electrophilic substitution reaction forming a benzothiazole skeleton thus giving a hybrid molecule imidazolidine-benzothiazole (ImBT) (**1'a**) (*Scheme V.5.1.1*).



Scheme V.5.1.1. *Possible reaction path for the formation of ImCAT and ImBT*

To test the feasibility of our proposed strategy the in situ generated thiourea obtained by reacting phenylisothiocyanate (**a**) and ethylenediamine (**1**) was treated with CuI (20 mol%) and Na_2CO_3 (1 equiv.) in an ethanolic medium and the reaction mixture was stirred at room temperature. Thiophilic salt CuI was chosen because of our recent success during the catalytic synthesis of cyanamides from arylthioamides.[5a] The reaction mixture however was not so clean while monitoring by TLC. Several *N* and *S* donor atoms are likely to be present in the expected product which may form a complex with the copper salt. In order to characterize the product (ligand), the metal bound ligand was removed from the complex by treating the reaction mixture

with an aqueous ammonia solution. The organic products were extracted out with EtOAc and the major product phenyl(phenylimino)imidazolidine-carbothioamide (**1a**) was obtained in 58% yield along with a traces (~5%) of imidazolidinebenzothiazole (ImBT) (**1'a**) (*Scheme V.5.1.1*). Structure of the product (**1'a**) have been confirmed by X-ray crystallographic analysis (*Figure V.5.1.1*)

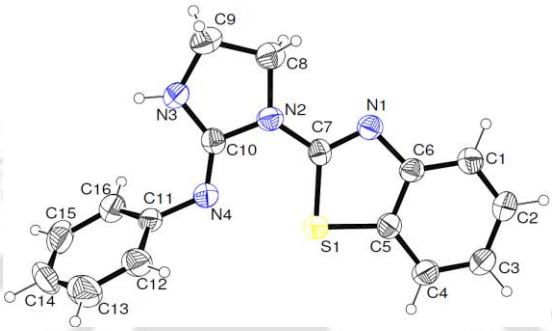
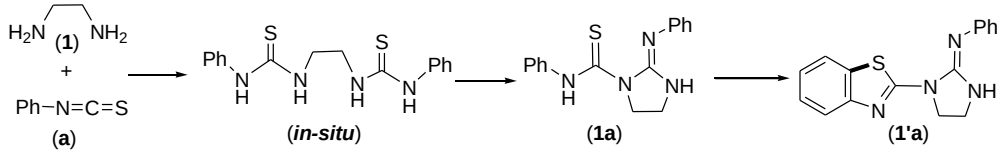


Figure V.5.1.1. *ORTEP view (30% probability ellipsoids) of **1'a***

Formation of both these products (**1a** and **1'a**) revealed that our anticipated strategy is indeed working well. Decent conversion using sub-stoichiometric amount of CuI suggest the catalytic nature of the reagent. Further, the reaction condition was optimized with various copper(I) and copper(II) salts such as $CuBr_2$, $CuCl_2.2H_2O$, $Cu(OAc)_2.2H_2O$, $Cu(NO_3)_2.3H_2O$, $CuSO_4.5H_2O$, $Cu(OH)_2$, CuO and $CuCl_2.2H_2O$ (20 mol%) was found to be much more effective for the transformation of intermediate imidazolidinecarbothioamide (ImCAT) (**1a**). Ethanol was preferred over other solvents such as MeOH, THF, DMSO, CH_3CN tested because of better yield and environmental acceptability. The use of Na_2CO_3 as the base gave better results compared to other bases such as K_2CO_3, $NaHCO_3$ and Et_3N tested (*Table V.5.1.1*). Thus EtOH as the solvent $CuCl_2.2H_2O$ as the catalyst and Na_2CO_3 as the base gave an isolated yield of 85 % for (**1a**) along with 3% of (**1'a**) at room temperature after 12 h.

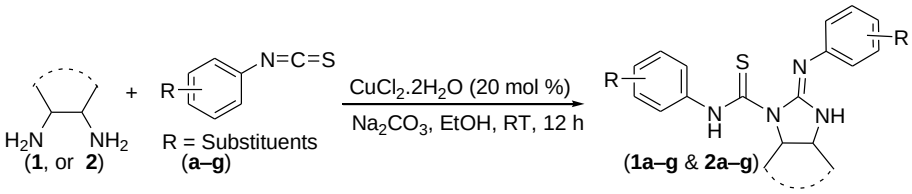
Table 5.V.1.1. *Screening of reaction conditions*[a-b]

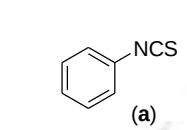
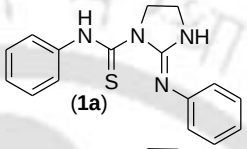
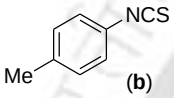
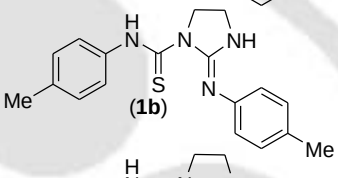
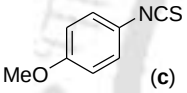
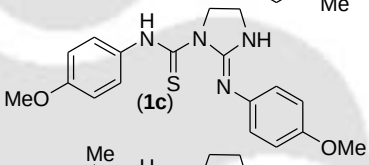
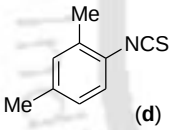
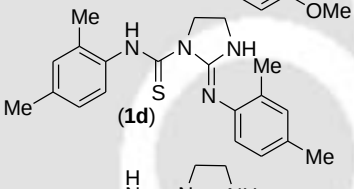
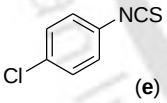
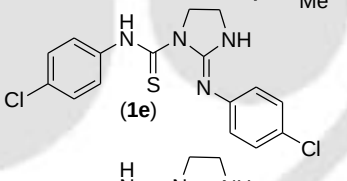
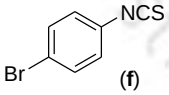
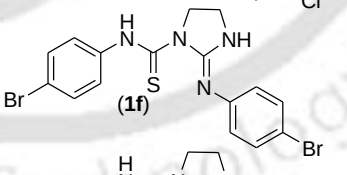
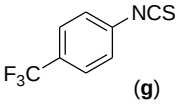
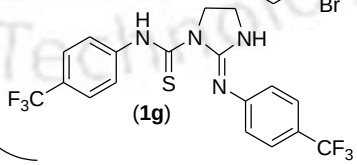
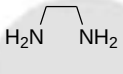


Entry	Catalyst (Mol%)	Base	Solvent	Time (h)	Temp (^{o}C)	Yield (%)[1a]	Yield (%)[1'a]
1	CuI (20)	Na_2CO_3	EtOH	12	25	58	05
2	CuBr (20)	Na_2CO_3	EtOH	12	25	75	02
3	CuCl (20)	Na_2CO_3	EtOH	12	25	61	03
4	CuO (20)	Na_2CO_3	EtOH	12	25	38	nd[c]
5	$Cu(OH)_2$ (20)	Na_2CO_3	EtOH	12	25	46	nd[c]
6	$CuSO_4.5H_2O$ (20)	Na_2CO_3	EtOH	12	25	68	05
7	$Cu(OAc)_2.2H_2O$ (20)	Na_2CO_3	EtOH	12	25	69	05
8	$Cu(NO_3)_2.3H_2O$ (20)	Na_2CO_3	EtOH	12	25	48	nd[c]
9	$CuCl_2.2H_2O$ (10)	Na_2CO_3	EtOH	12	25	63	nd[c]
10	$CuCl_2.2H_2O$ (10)	Na_2CO_3	EtOH	12	50	52	05
11	$CuCl_2.2H_2O$ (10)	Na_2CO_3	EtOH	12	60	48	05
12	$CuCl_2.2H_2O$ (10)	Na_2CO_3	EtOH	12	70	43	05
11	**$CuCl_2.2H_2O$ (20)**	**Na_2CO_3**	**EtOH**	**12**	**25**	**88**	**03**
12	$CuCl_2.2H_2O$ (20)	K_2CO_3	EtOH	12	25	76	05
13	$CuCl_2.2H_2O$ (20)	Et_3N	EtOH	12	25	69	03
14	$CuCl_2.2H_2O$ (20)	Na_2CO_3	THF	12	25	56	nd[c]
15	$CuCl_2.2H_2O$ (20)	Na_2CO_3	DMSO	12	25	58	08
16	$CuCl_2.2H_2O$ (20)	Na_2CO_3	MeOH	12	25	68	05
17	$CuCl_2.2H_2O$ (20)	Na_2CO_3	CH_3CN	12	25	86	03
18	**$CuCl_2.2H_2O$ (40)**	**Na_2CO_3**	**EtOH**	**28**	**25**	**08**	**65**
19	$CuCl_2.2H_2O$ (30)	Na_2CO_3	EtOH	28	50	12	36
20	$CuCl_2.2H_2O$ (30)	Na_2CO_3	EtOH	28	60	08	28
21	$CuCl_2.2H_2O$ (20)	Na_2CO_3	EtOH	28	70	23	12
22	$CuCl_2.2H_2O$ (40)	Na_2CO_3	CH_3CN	28	25	05	63

[a]Isolated yield. [b]Reaction monitored by TLC and GC. [c]nd = not detected

Table V.5.1.2. *Synthesis of imidazolidinecarbothioamides from arylisothiocyanates and 1,2-diamines*[a]

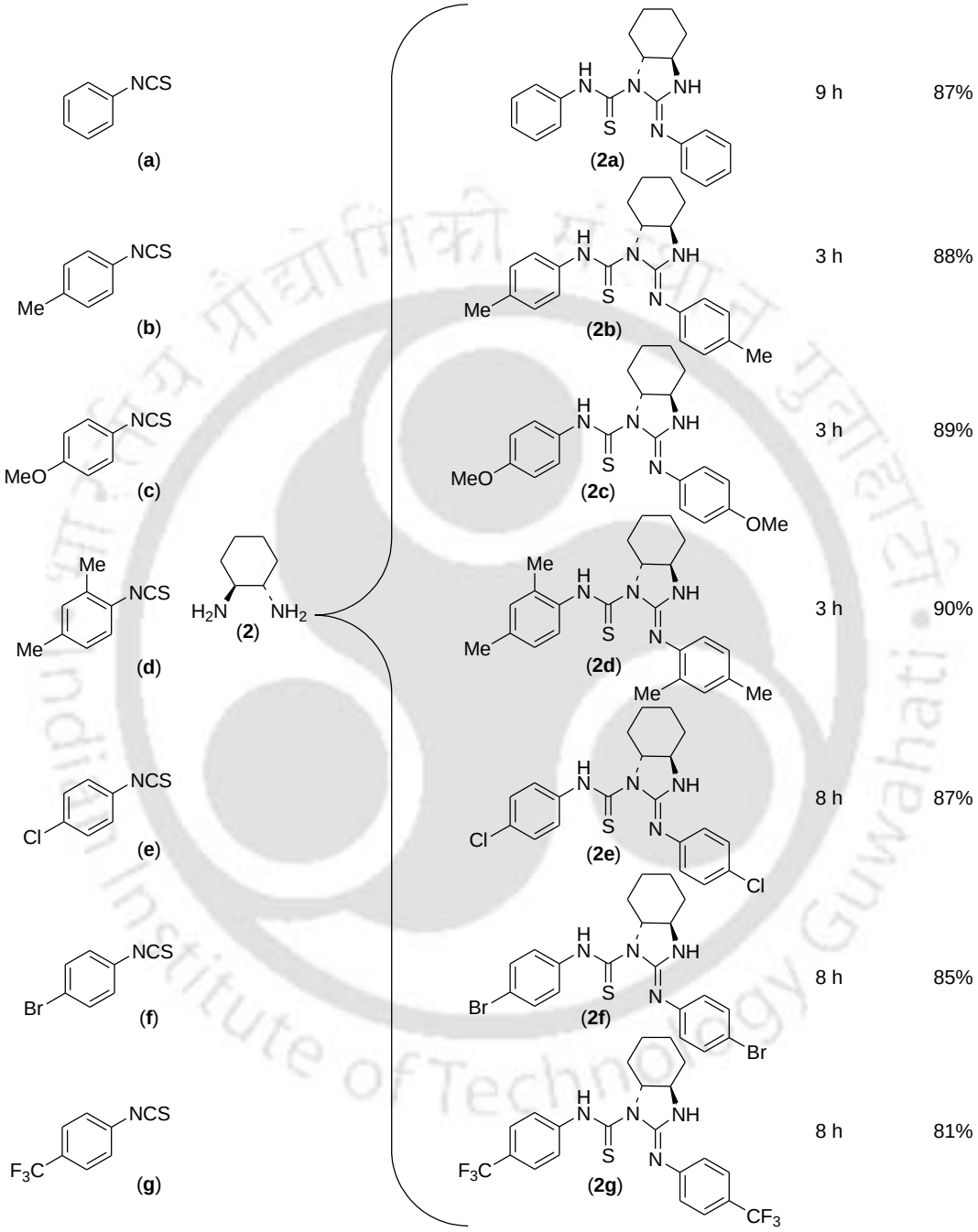


Substrate	Product	Time	Yield[b]
 (**a**)	 (**1a**)	12 h	85%
 (**b**)	 (**1b**)	11 h	86%
 (**c**)	 (**1c**)	9 h	87%
 (**d**)	 (**1d**)	10 h	89%
 (**e**)	 (**1e**)	10 h	80%
 (**f**)	 (**1f**)	10 h	82%
 (**g**)	 (**1g**)	12 h	76%
 (**1**)			

[a] Reaction monitored by TLC. [b] Confirmed by IR, ^{1}H, ^{13}C NMR spectra.

Continues….

Table V.5.1.2. *Continues….*

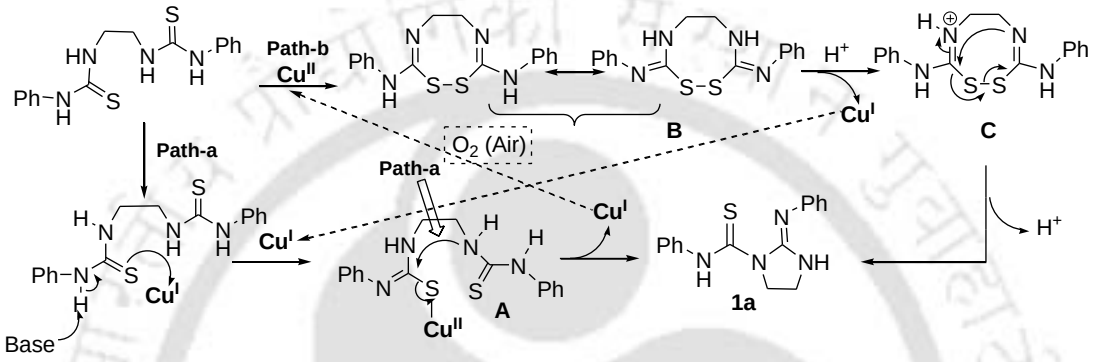
Substrate	Product	Time	Yield[b]
 (**a**)	(**2a**)	9 h	87%
(**b**)	(**2b**)	3 h	88%
(**c**)	(**2c**)	3 h	89%
(**d**)	(**2d**)	3 h	90%
(**e**)	(**2e**)	8 h	87%
(**f**)	(**2f**)	8 h	85%
(**g**)	(**2g**)	8 h	81%

(**2**)

[a]Reaction monitored by TLC. [b]Confirmed by IR, ^{1}H, ^{13}C NMR spectra.

Thus the mechanism as proposed in *Scheme V.5.1.2* might be operating for the imidazolidinecarbothioamide (ImCAT) conversion. One of the sulfur atom of *bis*-thiourea is

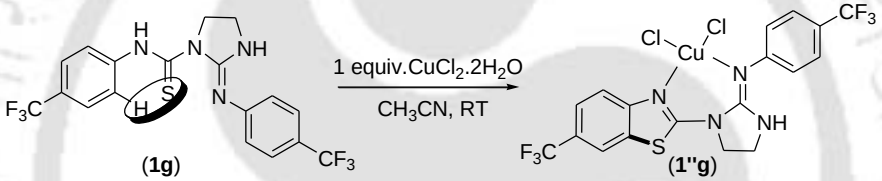
activated by the thiophilic metal salt Cu(I), followed by an intramolecular attack of an adjacent nitrogen atom path-a would give the product phenyl(phenylimino)imidazolidinecarbothioamide (**1a**) with the expulsion of Cu(II). Replacement of a Cu(II) salt instead of a Cu(I) for the formation of product (**1a**) from *bis*-thiourea may goes via an eight member disulfide intermediate facilitated by the redox active Cu(II) salt[7] followed by an imine-disulfide rearrangement (path-b) as has been proposed using oxidizing agent EDPBT.[3b] The reduced copper species is then reoxidized in the presence of atmospheric oxygen to complete the catalytic cycle.



Scheme V.5.1.2. *Proposed mechanism for the formation of* ***1a***

Having the optimized conditions in hand this strategy was then applied to other *in-situ* generated *bis*-diarylthioureas derived from 1,2-ethylendiamine (**1**) and various arylisothiocyanates (**a**–**f**) possessing electron-donating *p*–Me (**b**), *p*–OMe (**c**), 2,4-*di*–Me (**d**), moderately electron withdrawing *p*–Cl (**e**), *p*–Br (**f**), as well as strong electron-withdrawing *p*–CF_3 (**g**) groups in the aryl rings gave exclusively imidazolidine-carbothioamide (ImCAT) products (**1a**–**1f**) (*Table V.5.1.2*). Cyclic aliphatic 1,2-diamine such as *trans*-1,2-diaminocyclohexane (**2**) and arylisothiocyanates derived thioureas having electron donating *p*–Me (**b**), *p*–OMe (**c**), 2,4-*di*–Me (**d**), moderately electron withdrawing *p*–Cl (**e**), *p*–Br (**f**), as well as strongly electron withdrawing *p*–CF_3 (**g**) groups in the aryl rings of isothiocyanate all gave superior yields of their respective products (**2a**–**2f**) compared to thioureas derived from aliphatic acyclic diamine (**1**). It may be mention here that in general *bis*-thioureas derived from the rigid aliphatic cyclic 1,2-diamine (**2**) gave superior yields in shorter reaction time compared to *bis*-thioureas derived from conformational flexible ethylenediamine (**1**) (*Table V.5.1.2*). Substrates possessing electron-donating substituents gave marginally better yields compared to the substrates having electron withdrawing groups (*Table V.5.1.2*).

In the above cases as the imidazolidine-carbothioamides (ImCAT) were obtained as the major products (*Table V.5.1.2*) along with the traces of imidazolidine-benzothiazoles (ImBT). When the reaction was prolonged the percentage of imidazolidine-benzothiazoles (ImBT) increased which probably was formed *via* a C–H activation path (*Scheme V.5.1.1*) or by an aromatic electrophilic reaction promoted by the copper. It may be noted here that there is not a single report on the synthesis of hybrid heterocycle imidazolidine-benzothiazoles (ImBT) thus the reaction parameters were further optimized. The highly nitrogenous compound imidazolidine-carbothioamides (ImCAT) having several hetero atoms might be complexing with the copper there by reducing its catalytic efficiency. In order to ascertain this, one of the isolated ImCAT compound (**1g**) was treated with $CuCl_2.2H_2O$ (1 equiv.) in acetonitrile. A Cu(II) complex (**1''g**) was isolated from the reaction mixture (*Scheme V.5.1.3*) and structure of the product was determined by X-ray crystallography (*Figure V.5.1.3*).



Scheme V.5.1.3. *C–H Bond activation associated with ImBT-Cu complex from ImCAT*

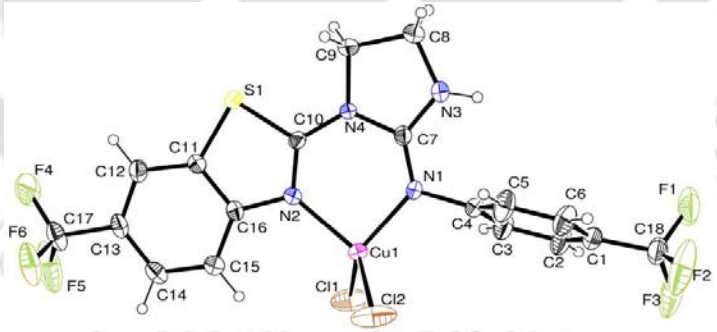


Figure V.5.1.3. *ORTEP view (30% probability ellipsoids) of complex **1''g***

A closer look at the structure (**1''g**) (*Figure V.5.1.3*) revealed that the complex formed is not with the starting ligand ImCAT (**1g**) but it is with the transformed ImBT ligand (**1'g**). Which means the complexation to Cu occur only after the C–S bond formation (C–H activation). The hybrid molecule ImBT (**1'g**) is coordinated to Cu(II) with benzothiazole–*N* and imine–*N*. Before complexing the benzothiazole-*N* and imine-*N* are *trans* oriented and benzothiazole–*S* and imine–

N are *cis* oriented for an analogous ligand **1'a** (*Figure V.5.1.1*). Where as in the imidazolidine-benzothiazole (ImBT) copper (**1''g**) the benzothiazole–*N* and imine–*N* are *cis* and benzothiazole–*S* and imine–*N* are *trans* to each other. The distorted tetrahedral geometry around the Cu(II) centre is satisfied by *N*, *N* donor set of ligand and two chloride ions. The distortion of the copper centre form the regular tetrahedron geometry is evident from the bond angles. The bond parameters around copper centre are Cu1–N1 = 1.959(4) Å, Cu1–N2 = 1.992(4) Å, Cu1–Cl1 = 2.223(2) Å, Cu1–Cl2 = 2.203(2) Å, N1–Cu1–N2 = 92.1(2), N1–Cu1–Cl1 = 127.6(1)°, N1–Cu1–Cl2 = 102.9(1)°, N2–Cu1–Cl1 = 105.4(1)°, N2–Cu1–Cl2 = 123.4(1)° and Cl1–Cu1–Cl2 = 107.7(1)° respectively. The copper complexes are assembled into infinite chains through N–H···F hydrogen bonding interaction (N3–H3···F6 = 3.006(5) Å) between the imidazolidine proton and the fluorine atom. The neighboring chains are subsequently organized into a 2D sheet *via* a C–H···Cl (C9–H9···Cl1 = 3.746(6), C9–H9···Cl2 = 3.282(5), C8–H8···Cl2 = 3.352(5) and Cl···π (3.347(4)Å) interactions from the adjacent strand as shown in *Figure V.5.1.4*.

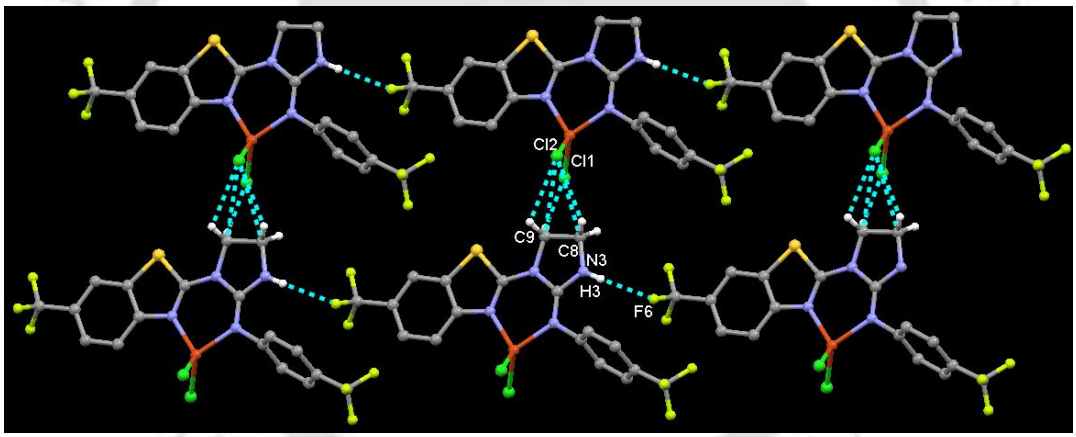
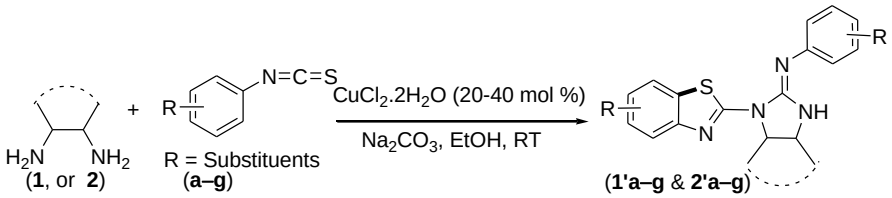
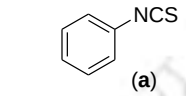
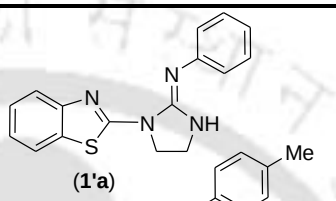
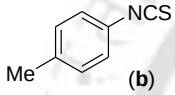
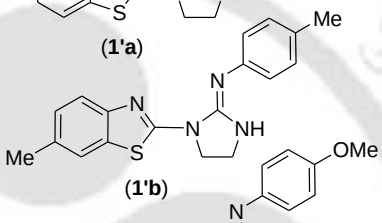
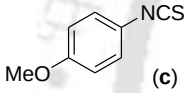
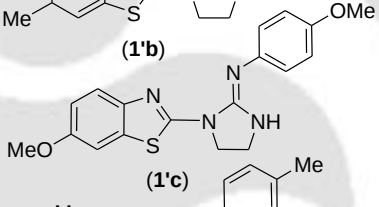
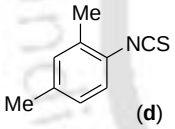
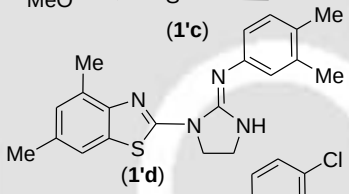
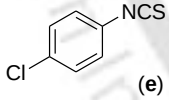
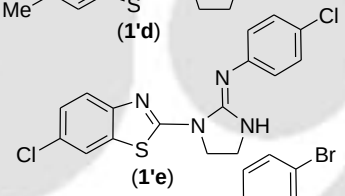
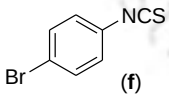
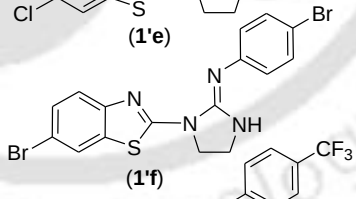
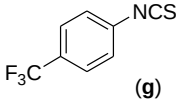
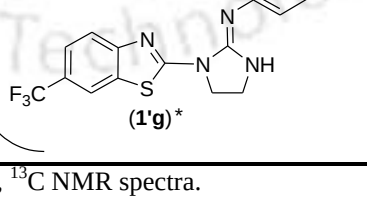
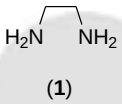


Figure V.5.1.4. *Self-organization of 1D copper complex **1''g** via week interactions*

Table V.5.1.3. *Synthesis of imidazolidinebenzothiazoles from arylisothiocyanates and 1,2-diamines*[a]



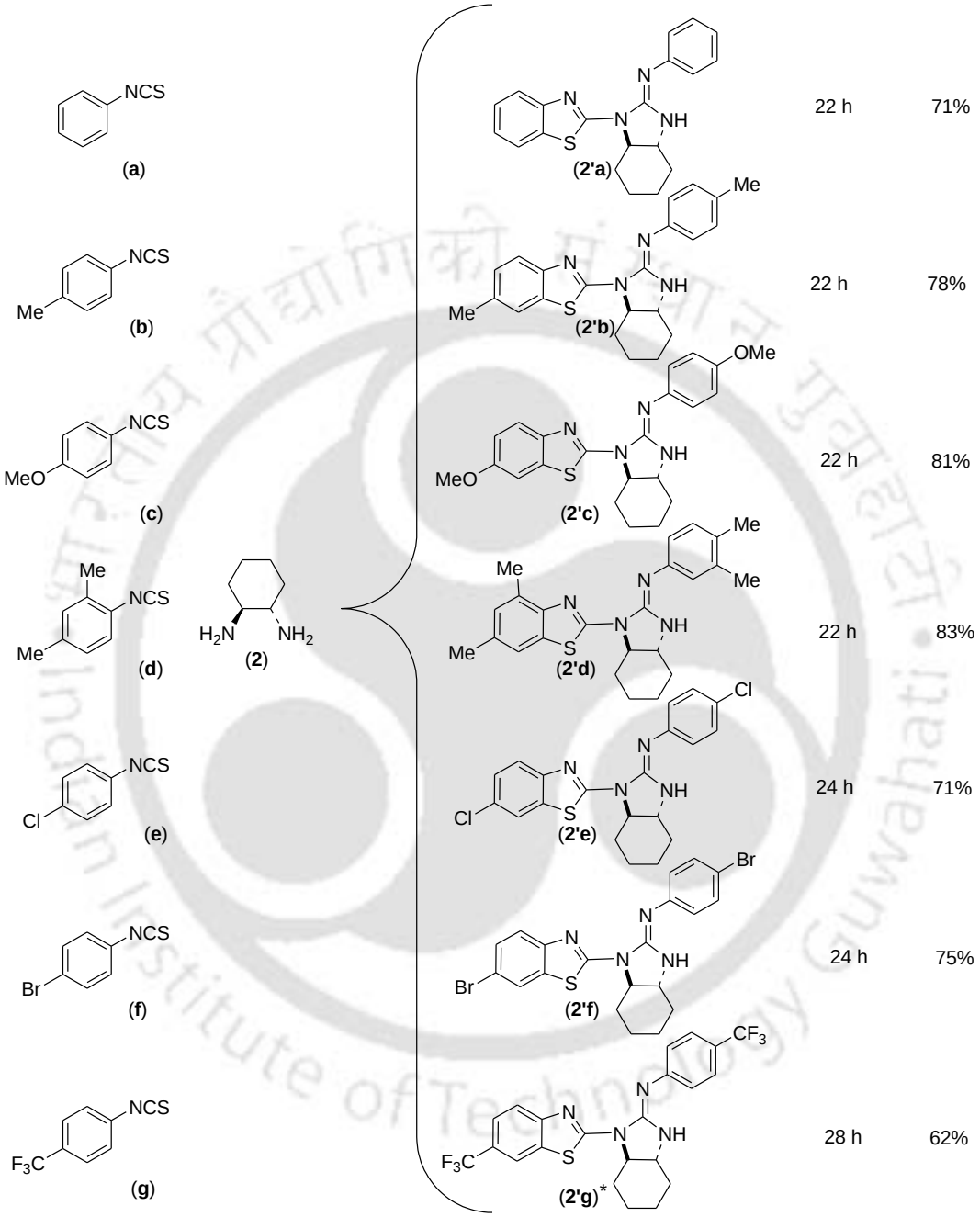
Substrate	Product	Time	Yield[b]
 (**a**)	 (**1'a**)	28 h	65%
 (**b**)	 (**1'b**)	32 h	75%
 (**c**)	 (**1'c**)	30 h	78%
 (**d**)	 (**1'd**)	30 h	80%
 (**e**)	 (**1'e**)	30 h	62%
 (**f**)	 (**1'f**)	30h	58%
 (**g**)	 (**1'g**)*	30 h	55%



[a]Reaction monitored by TLC. [b]Confirmed by IR, ^{1}H, ^{13}C NMR spectra.

Continues….

Table V.5.1.3. *Continues….*

Substrate	Product	Time	Yield[b]
 (**a**)	(**2'a**)	22 h	71%
(**b**)	(**2'b**)	22 h	78%
(**c**)	(**2'c**)	22 h	81%
(**d**)	(**2'd**)	22 h	83%
(**e**)	(**2'e**)	24 h	71%
(**f**)	(**2'f**)	24 h	75%
(**g**)	(**2'g**)*	28 h	62%

(**2**)

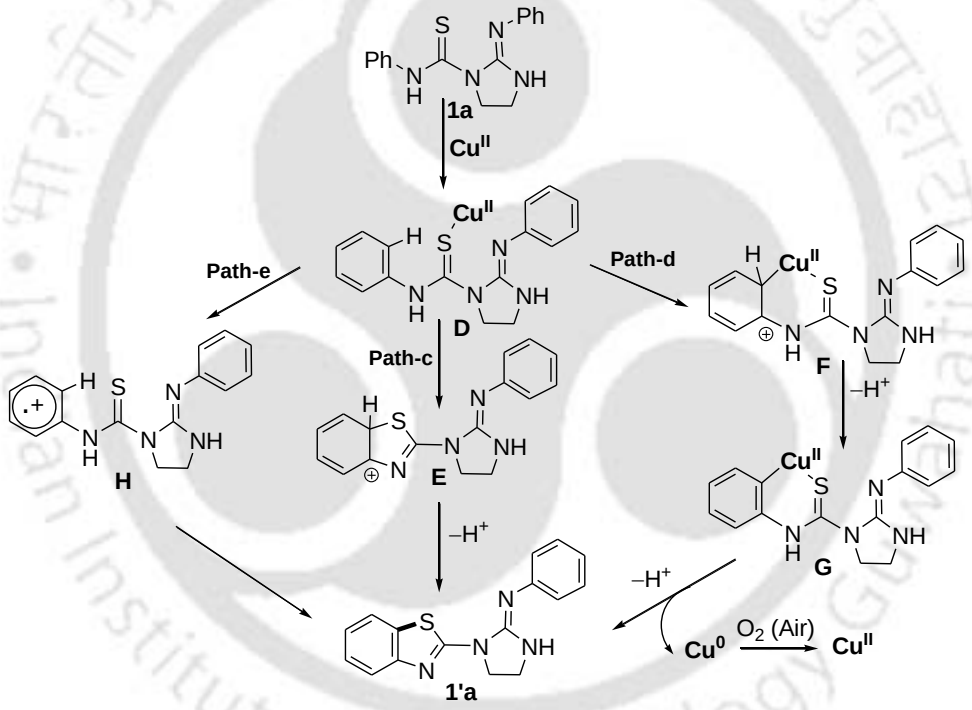
[a]Reaction monitored by TLC. [b]Confirmed by IR, ^{1}H, ^{13}C NMR spectra.*1 equiv. of $CuCl_2.2H_2O$ and CH_3CN solvent was used.

Thus the inefficiency of the Cu as the catalyst after the formation of imidazolidine-benzothiazole (ImBT) (**1'g**) could be due to its propensity to form complex (**1''g**) with it. Taking

cues from the above results, the reaction conditions were further optimized for the exclusive formation of imidazolidine-benzothiazole products (ImBT). The *in-situ* generated thiourea obtained by reacting phenylsiothiocyanate (**a**) and ethylenediamine (**1**) with 20 mol% of $CuCl_2.2H_2O$ gave only imidazolidine-carbothioamide (ImCAT) (**1a**) as the major product along with a traces of (ImBT) (**1'a**) after 12 h. No substantial improvement in the yield of the later product (**1'a**) could be observed even after prolonging the reaction time to 48 h or heating the reaction mixture. This is because the catalyst remained bound to (ImBT) forming a Cu(ImBT)-complex. However upon increasing the catalyst quantity to 40 mol% and keeping the reaction for 28 h the product obtained upon an aqueous ammoniacal workup was found to be the imidazolidine-benzothiazole products (ImBT) (**1'a**). The details of further optimizations are shown in *Table V.5.1.1*. It may be mention here that requirement of 40 mol% of the catalyst become essential for the arylisothiocyanates possessing electron withdrawing groups such as *p*–Cl (**e**), *p*–Br (**f**) but for the substrates possessing electron donating groups *p*–Me (**b**), *p*–OMe (**c**), 2,4-di–Me (**d**) the reaction goes efficiently with 20 mol% of the catalyst. Having the optimized conditions in hand this strategy was then applied to other *in-situ* generated *bis*-diarylthioureas derived from acyclic diamine (**1**) and cyclic 1,2-diamine (**2**) and various arylisothiocyanates possessing electron donating *p*–Me (**b**), *p*–OMe (**c**), 2,4-di–Me (**d**) and electron withdrawing groups *p*–Cl (**e**), *p*–Br (**f**). All the *in-situ* generated *bis*-diarylthioureas gave exclusively their imidazolidinebenzothiazoles (ImBT) products (**1'a**–**1'f**) and (**2'a**–**2'f**) (*Table V.5.1.3*). For substrate possessing strong electron-withdrawing group such as *p*–CF_3 (**g**) a stoichiometric amount of $CuCl_2.2H_2O$ was essential to achieve the conversion (**1'g**) and (**2'g**) in a modest yield. For electron poor substrates a polar aprotic solvent such as acetonitrile was found to be better compared to polar protic solvent ethanol. It is noteworthy to observe that electron rich substrates showed higher reactivity compare to substrates having electron withdrawing groups in the aryl ring towards intramolecular C–H activation (*Table V.5.1.3*). These results are consistent with the observation made by Buchwald and Nagasawa's for similar C–N and C–O bond formations.[8]

Although we have not thoroughly investigated the reaction mechanism for the formation of hybrid molecule (**1'a**) from (**1a**) a plausible mechanism could be analogous to the one that has been proposed for the similar C–N coupling by Buchwald[8a] or C–O coupling by Nagasawa.[8b,c]

After the formation of (**1a**) it is co-ordinate to Cu(II) through the sulfur atom giving the intermediate **D** (*Scheme V.5.1.4*). Attack of the arene π-system (intramolecular electrophilic substitution) to the co-ordinated thioamidic sulfur followed by an aromatization (path-c) would give the ImBT (**1'a**). Alternatively, the reaction may proceed in path-d. The formation of a six-member metallacycle *via* an oxidative addition is followed by a reductive elimination to afforded the product (**1'a**). The reduced copper species is then reoxidized in the presence of atmospheric oxygen to complete the catalytic cycle. This reaction also proceed efficiently with arylsubstrates possessing electron withdrawing substituents such as *p*-Cl (**e**), *p*-Br (**f**), *p*-CF_3 (**g**), there by ruling out the possibility of an electrophilic mechanism (path-c) and might proceed either *via* path-d or by a SET mechanism *via* path-e (*Scheme V.5.1.4*).



Scheme V.5.1.4. *Proposed mechanism for the formation of **1'a***

In conclusion, starting from the *in situ* generated *bis*-diarylthioureas derived from aliphatic 1,2-diamines and arylisothiocyanates an efficient copper catalyzed cascade synthesis of an imidazolidine-benzothiazole (ImBT) have been developed. This reaction goes via an imidazolidine-carbothioamide (ImCAT) intermediate, followed by an intramolecular C–H activation forming a C–S bond at room temperature giving hybrid heterocycle ImBT. This is a unique demonstration of copper salts serving both as a desulfurizing as well as a C–H activating

agent at an ambient temperature. This is also the first and only cascade synthesis of an imidazolidine-benzothiazole derivative. Besides synthesis of new class of molecules the use of cheap and environmentally benign catalyst and room temperature C–H activation are attractive features of this methodology. Further, biological activities of these molecules would be of interests to medicinal chemist.

V.6. Experimental Section

V.6.1. Instrumentation and Characterization

As described in Chapter II, Section II.6.1.

V.6.2. General Procedure for Preparation of *E*-*N*-(Phenyl-2-(phenylimino) imidazolidine-1-carbothioamide (1a) Using $CuCl_2.2H_2O$.

To a solution of phenylisothiocyanate (**a**) (270 mg, 2 mmol) in EtOH (10 mL) was added ethylene diamine (**1**) (60 mg, 1 mmol) and the reaction mixture was stirred at room temperature. Complete formation of *bis*-thiourea was observed within 20 minutes (monitored by TLC) which is associated with the formation of a white precipitate. To this heterogeneous reaction mixture was added Na_2CO_3 (1 mmol), $CuCl_2.2H_2O$ (0.2 mmol) and the reaction was stirrer at room temperature. Progress of the reaction was monitored by TLC by taking small amount of aliquots, diluted with ethyl acetate and the mixture was treated with a few drops of 30 % aqueous ammonia. After shaking for a minute the aqueous layer turn to blue color and the product present in the ethyl acetate layer was spotted in TLC. After complete disappearance of starting thiourea ethanol was removed under a reduced pressure and the reaction mixture was admixed with ethyl acetate 25 mL) to which was added aqueous ammonia 30 % (5 mL) and the biphasic layer was stirred for 5 minutes. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under a reduced pressure. The crude product so obtained was purified over a short column of silica gel using EtOAc : hexane (2:8) as the eluents to give the product (**1a**) (255 mg, yield 85%). The identity and purity of the product was confirmed by spectroscopic analysis.

V.6.3. General Procedure for Preparation of *(E)-N*-(1-(Benzo[d]thiazol-2-yl)-imidazolin-2-ylidine)benzenamine (1'a) Using $CuCl_2.2H_2O$.

Procedure similar to (**1a**) was adopted except the $CuCl_2.2H_2O$ (0.4 mmol) was used instead of 0.2 mmol.

V.6.4. General Procedures for Preparation of Complex (1''g)

To a solution of 4-trifluoromethyl)phenylimino)-*N*-(4-(trifluoromethyl)phenyl)octahydro-benzo[*d*]imidazole-1-carbothiamide (**1g**) (1 mmol, 432 mg) in acetonitrile (15 mL), was added drop wise over a period of 5 minutes an acetonitrile solution of $CuCl_2.2H_2O$ (1 mmol, 170 mg). Then resultant solution turned to dark brown colored which was left for crystallization. A dark red crystalline solid was obtained upon standing. Yield of first crops of (**1''g**) 76% (428 mg).

V.6.5. Crystallographic Description

Crystal data of compound (1'a): CCDC 890889 and 890935. Crystal dimension (mm): 0.34 x 0.28 x 0.32. $C_{16}H_{14}N_4S$, Mr = 294.38. Triclinic, space group P-1; a = 10.6434(4) Å, b = 11.5113(5) Å, c = 12.6753(5) Å; α = 91.860(2)^o, β = 96.6473(3)^o, γ = 104. 623(3)^o, V = 1450.43(10) Å^3; Z = 4; ρ_{cal} = 1.348 g/cm^3; μ (mm^{-1}) = 0.221; *F (000)* = 616.0; Reflection collected / unique = 5029 / 3702; Refinement method = Full-matrix least-squares on F^2; Final R indices [I>2σ_I] R1 = 0.0400, wR2 = 0.1349, R indices (all data) R1 = 0.0434, wR2 = 0.1408; GOF = 1.129.

Crystal data of compound (1''g): Crystal dimension (mm): 0.36 x 0.26 x 0.28., $C_{18}H_{12}N_4SCuCl_2F_6$, Mr = 564.84. Triclinic, space group P-1; a = 9.0339(14) Å, b = 10.9100(15) Å, c = 12.7810(3) Å; α = 109.442(10)^o, β = 103.210(11)^o, γ = 104. 266(7)^o, V = 1082.7(4) Å^3; Z = 2; ρ_{cal} = 1.733 g/cm^3; μ(mm^{-1}) = 1.417; *F (000)* = 562.0; Reflection collected / unique = 4940 / 39376; Refinement method = Full-matrix least-squares on F^2; Final R indices [I>2σ_I] R1 = 0.0633, wR2 = 0.1347, R indices (all data) R1 = 0.0634, wR2 = 0.1347; GOF = 1.097.

V.7. References

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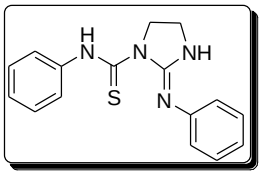
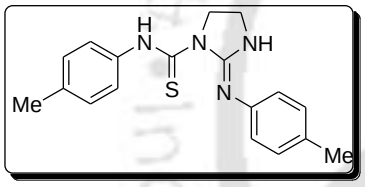
V.8. Spectral Data

***E*-*N*-(Phenyl-2-(phenylimino)imidazolidine-1-carbothioamide (1a).**



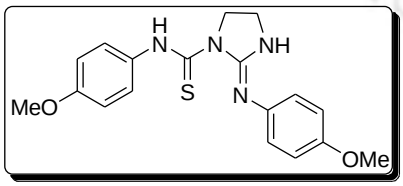
White solid; R_f = 0.60 (EtOAc/hexane; 2:8); M.p. 190–191 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.44 (t, 2H, *J* = 7.6 Hz), 4.46 (t, 2H, *J* = 8.0 Hz), 4.77 (brs, 1H), 6.99 (d, 2H, *J* = 7.2 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 7.18 (t, 2H, *J* = 7.6 Hz), 7.33 (m, 4H), 7.60 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.6, 48.7, 122.8, 124.7, 126.1, 128.8, 129.8, 132.8, 139.3, 146.6, 152.0, 179.0; IR (KBr): 3361, 3288, 3230, 2900, 1663, 1588, 1572, 1480, 1404, 1377, 1322, 1289, 1212, 1127, 1068, 1020, 822, 783, 731, 695 cm^{-1}; MS (ESI): 297.1326 (MH^+). Anal. Calcd for $C_{16}H_{16}N_4S$: C, 64.83; H, 5.44; N, 18.90; S, 10.81; found: C, 64.87; H, 5.49; N, 18.85; S, 10.76.

***(E)*-2-(*p*-Tolylimino)-*N*-(*p*-tolylimidazolidine-1-carbothioamide (1b).**



White solid; R_f = 0.62 (EtOAc/hexane; 2:8); M.p. 128–129 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.32 (s, 3H), 3.38 (t, 2H, *J* = 7.6 Hz), 4.40 (t, 2H, *J* = 8.0 Hz), 4.82 (brs, 1H), 6.89 (d, 2H, *J* = 7.2 Hz), 7.14 (t, 4H, *J* = 8.0 Hz), 7.44 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 21.1, 38.5, 48.5, 122.4, 124.7, 129.3, 130.2, 133.4, 135.7, 136.6, 143.9, 152.0, 179.0; IR (KBr): 3398, 2921, 2851, 1670, 1625, 1563, 1506, 1470, 1408, 1364, 1314, 1283, 1127, 1076, 821 cm^{-1}; MS (ESI): 325.1190 (MH^+). Anal. Calcd for $C_{18}H_{20}N_4S$: C, 66.63; H, 6.21; N, 17.26; S, 9.88; found: C, 63.67; H, 6.19; N, 17.21; S, 9.84.

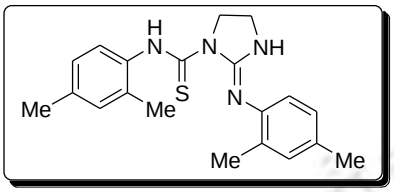
***(E)*-2-(4-Methoxyphenylimino)-*N*-(4-methoxyphenylimidazolidine-1-carbothioamide (1c).**



White solid; R_f = 0.55 (EtOAc/hexane; 2:8); M.p. 108–109 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.36 (t, 2H, *J* = 8.0 Hz), 3.75 (s, 3H), 3.76 (s, 3H), 4.36 (t, 2H, *J* = 8.0 Hz), 4.91 (brs, 1H), 6.86 (d, 4H, *J* = 8.0 Hz), 6.92 (d, 2H, *J* = 8.8 Hz), 7.44 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.4, 48.5, 55.4, 55.5, 113.8, 114.8, 123.3, 126.2, 132.1, 139.5, 152.2, 156.0, 157.5, 179.2; IR (KBr): 3351, 2956, 2925, 2851, 2835, 1659, 1626, 1504, 1428, 1399, 1324, 1237, 1174, 1127, 1029, 827, 765 cm^{-1}; MS (ESI): 357.1313 (MH^+).

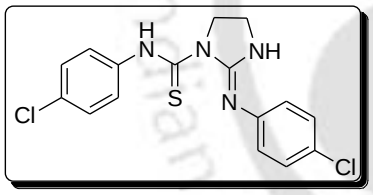
Anal. Calcd for $C_{18}H_{20}N_4SO_2$: C, 60.65; H, 5.65; N, 15.71; S, 8.99; found: 60.68; H, 5.67; N, 15.671; S, 8.93.

***(E)*-2-(2,4-Dimethylphenylimino)-*N*-(2,4-dimethylphenyl)imidazolidine-1-carbothioamide (1d).**



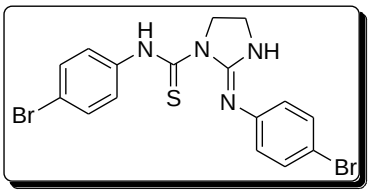
White solid; R_f = 0.65 (EtOAc/hexane; 2:8); M.p. 163–164 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 2.15 (s, 3H), 2.26 (s, 3H), 2.28 (s, 3H), 2.30 (s, 3H), 3.42 (t, 2H, *J* = 8.0 Hz), 4.45 (t, 2H, *J* = 8.0 Hz), 4.58 (brs, 1H), 6.81 (d, 1H, *J* = 8.0 Hz), 7.00 (m, 4H), 7.51 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 18.3, 20.9, 21.1, 38.6, 48.7, 121.6, 127.0, 127.1, 127.5, 130.6, 131.3, 131.7, 133.5, 136.6, 142.6, 151.4, 180.1; IR (KBr): 3326, 2916, 2851, 1650, 1598, 1495, 1394, 1303, 1266, 1226, 1109, 1070, 1031, 976, 877, 838, 760 cm^{-1}; Anal. Calcd for $C_{20}H_{24}N_4S$: C, 68.15; H, 6.86; N, 15.89; S, 9.10; found: C, 68.19; H, 6.89; N, 15.84; S, 9.07.

***(E)*-2-(4-Chlorophenylimino)-*N*-(4-chlorophenyl)imidazolidine-1-carbothioamide (1e).**



White solid; M.p. 179–180 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.46 (t, 2H, *J* = 8.0 Hz), 4.45 (t, 2H, *J* = 8.0 Hz), 4.72 (brs, 1H), 6.92 (d, 2H, *J* = 8.8 Hz), 7.29 (m, 4H), 7.55 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.5, 48.6, 124.1, 125.7, 128.8, 129.4, 129.8, 131.1, 137.7, 145.0, 152.1, 178.9; IR (KBr): 3435, 2917, 2851, 2720, 1649, 1565, 1488, 1414, 1368, 1316, 1279, 1203, 1113, 1083, 1006, 827, 762 cm^{-1}; MS (ESI): 365.1304 (MH^+). Anal. Calcd for $C_{16}H_{14}N_4Cl_2S$: C, 52.61; H, 3.86; N, 15.33; S, 8.77; found: C, 52.65; H, 3.83; N, 15.28; S, 8.72.

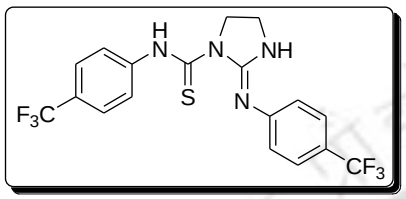
***(E)*-2-(4-Bromophenylimino)-*N*-(4-bromophenyl)imidazolidine-1-carbothioamide (1f).**



White solid; R_f = 0.53 (EtOAc/hexane; 2:8); M.p. 182–183 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.46 (t, 2H, *J* = 8.0 Hz), 4.44 (t, 2H, *J* = 8.0 Hz), 4.74 (brs,1H), 6.87 (d, 2H, *J* = 8.4 Hz), 7.44 (m, 4H), 7.50 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.5, 48.6, 117.0, 118.9, 124.5, 126.0, 131.8, 132.8, 145.5, 152.0, 178.8; IR (KBr): 3423, 2922, 2851,

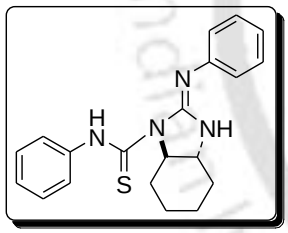
1648, 1485, 1413, 1387, 1316, 1278, 1200, 1110, 1068, 1001, 824, 760 cm^{-1}; MS (ESI): 455.0766 (MH^+). Anal. Calcd for $C_{16}H_{14}N_4Br_2S$: C, 42.31; H, 3.10; N, 12.33; S, 7.06; found: C, 42.35; H, 3.13; N, 12.30; S, 6.97.

***(E)*-2-(4-Trifluoromethyl)phenylimino)-*N*-(4-trifluoromethyl)phenyl)imidazolidine-1-carbothioamide (1g).**



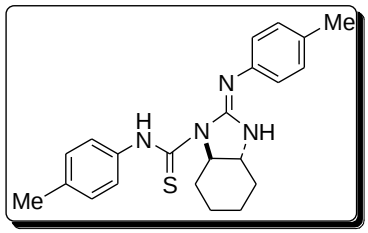
White solid; R_f = 0.50 (EtOAc/hexane; 2:8); M.p. 186–187 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.45 (t, 2H, *J* = 8.0 Hz), 4.42 (t, 2H, *J* = 8.0 Hz), 4.87 (brs, 1H), 7.11 (d, 2H, *J* = 8.4 Hz), 7.58 (t, 4H, *J* = 8.0 Hz), 7.80 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.4, 48.5, 123.1, 123.8, 125.9, 126.4, 127.0, 127.5, 142.3, 149.7, 151.9, 178.7; IR (KBr): 3466, 2918, 1659, 1608, 1577, 1418, 1371, 1329, 1171, 1101, 1061, 1015, 838 cm^{-1}; MS (ESI): 433.1838 (MH^+). Anal. Calcd for $C_{18}H_{14}N_4F_6S$: C, 49.99; H, 3.26; N, 12.95; S, 7.41; found: C, 50.05; H, 3.29; N, 12.89; S, 7.37.

***(E,3aR,7aR)*-Octahydro-N-phenyl-2-(phenylimino)benzo[d]imidazole-1-carbothiamide (2a).**



White solid; R_f = 0.65 (EtOAc/hexane; 1:9); M.p. 140–141 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (m, 7H), 3.11 (m, 1H), 4.78 (m, 2H), 4.78 (brs, 1H), 7.00 (d, 2H, *J* = 7.6 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 7.17 (t, 1H, *J* = 8.0 Hz), 7.33 (t, 4H, *J* = 7.2 Hz), 7.54 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 29.8, 30.0, 31.8, 59.5, 66.2, 122.7, 124.1, 124.9, 126.0, 128.7, 129.7, 139.2, 146.3, 154.9, 181.4; IR (KBr): 3380, 2927, 2860, 1650, 1559, 1490, 1448, 1394, 1372, 1337, 1248, 1179, 1079, 1079, 899, 744 cm^{-1}; MS (ESI): 351.1196 (MH^+). Anal. Calcd for $C_{20}H_{22}N_4S$: C, 68.53; H, 6.32; N, 15.98; S, 9.14; found: C, 68.57; H, 6.36; N, 15.93; S, 9.09.

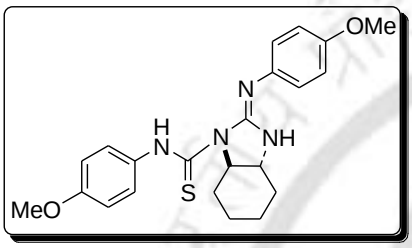
***(E,3aR,7aR)*-2-(*p*-Tolylimino)octahydro-*N*-*p*-tolylbenzo[d]imidazole-1-carbothiamide (2b).**



White solid; R_f = 0.63 (EtOAc/hexane; 1:9); M.p. 160–161 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (m, 4H), 1.93 (m, 3H), 2.35 (s, 6H), 3.07 (m, 1H), 3.75 (m, 2H), 4.88 (brs, 1H), 6.94 (d, 2H, *J* = 7.2 Hz), 7.17 (d, 4H, *J* = 7.6 Hz), 7.43 (d, 2H, *J* = 7.6 Hz); ^{13}C

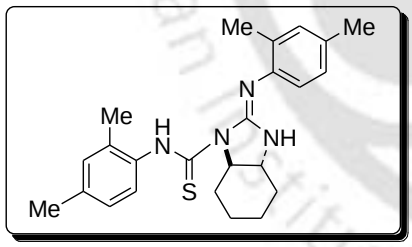
NMR (100 MHz, $CDCl_3$): δ 20.9, 21.1, 24.1, 24.2, 29.8, 31.7, 59.3, 66.0, 122.4, 124.8, 129.2, 130.1, 133.4, 135.5, 136.5, 143.5, 154.8, 181.3; IR (KBr): 3373, 2932, 2864, 1647, 1607, 1548, 1506, 1366, 1326, 1233, 1181, 1098, 1072, 824, 752, 721 cm^{-1}; MS (ESI): 379.1575 (MH^+). Anal. Calcd for $C_{22}H_{26}N_4S$: C, 69.80; H, 6.92; N, 14.80; S, 8.47; found: C, 69.85; H, 6.96; N, 14.75; S, 8.43.

***(E,3aR,7aR)*-2-(4-Methoxyphenylimino)octahydro-*N*-(4-methoxyphenylbenzo[d]imidazole-1-carbothiamide (2c).**



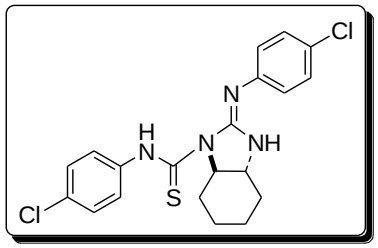
Gummy; R_f = 0.60 (EtOAc/hexane; 1:9); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (m, 10H), 3.78 (s, 6H), 6.88 (m, 4H), 6.94 (m, 2H), 7.41 (d, 2H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 24.3, 30.0, 31.9, 55.6, 59.5, 66.2, 113.9, 114.9, 123.5, 126.6, 132.2, 155.2, 156.3, 157.6, 181.8; IR (KBr): 3445, 2926, 2851, 1644, 1509, 1462, 1366, 1325, 1248, 1104, 1064, 1028, 825 cm^{-1}; Anal. Calcd for $C_{22}H_{26}N_4O_2S$: C, 64.36; H, 6.38; N, 13.65; S, 7.81; found: C, 64.39; H, 6.41; N, 13.61; S, 7.83.

***(E,3aR,7aR)*-2-(2,4-Dimethylphenylimino)octahydro-*N*-(2,4-dimethylphenylbenzo[d]imidazole -1-carbothiamide (2d).**



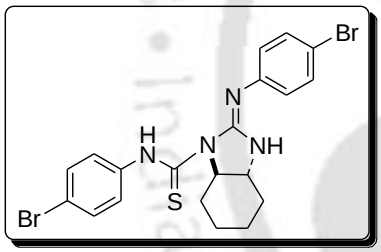
Gummy; R_f = 0.66 (EtOAc/hexane; 1:9); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (m, 8H), 2.13 (s, 3H), 2.25 (s, 3H), 2.29 (s, 3H), 2.31 (s, 3H), 3.11 (m, 1H), 3.79 (m, 1H), 4.60 (brs, 1H), 6.81 (d, 1H, J = 8.0 Hz), 6.98 (m, 4H), 7.33 (d, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 18.4, 20.9, 21.2, 24.3, 24.4, 30.0, 32.0, 59.6, 66.4, 121.6, 127.0, 127.3, 127.6, 130.6, 131.4, 131.6, 131.7, 133.5, 133.9, 135.4, 136.6, 142.4, 154.4, 182.5; IR (KBr): 3441, 2924, 2851, 1652, 1544, 1492, 1456, 1369, 1327, 1248, 1220, 1110, 1070, 1042 cm^{-1}; MS (ESI): 407.2998 (MH^+). Anal. Calcd for $C_{24}H_{30}N_4S$: C, 70.89; H, 7.43; N, 13.77; S, 7.88; found: C, 70.93; H, 7.40; N, 13.72; S, 7.83.

***(E,3aR,7aR)*-2-(4-Chlorophenylimino)-N-(4-chlorophenyl)-octahydrobenzo-[*d*]imidazole-1-carbothiamide (2e).**



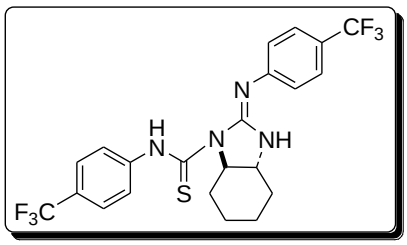
White solid; R_f = 0.61 (EtOAc/hexane; 1:9); M.p. 165–166 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (m, 1H), 1.60 (m, 6H), 3.08 (t, 1H, *J* = 11.2 Hz), 3.70 (m, 2H), 4.84 (brs, 1H), 6.93 (d, 2H, *J* = 7.2 Hz), 7.28 (d, 4H, *J* = 8.0 Hz), 7.48 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 24.3, 29.9, 31.7, 59.5, 66.3, 124.1, 126.0, 128.8, 129.4, 129.8, 131.1, 137.6, 144.6, 155.1, 181.2; IR (KBr): 3394, 2942, 2851, 1645, 1595, 1547, 1485, 1390, 1370, 1237, 1187, 1087, 1009, 837, 751 cm^{-1}; MS (ESI): 419.0916 (MH^+). Anal. Calcd for $C_{20}H_{20}N_4SCl_2$: C, 57.27; H, 4.80; N, 13.35; S, 7.64; found: C, 57.31; H, 4.84; N, 13.31; S, 7.60.

***(E,3aR,7aR)*-2-(4-Bromophenylimino)-N-(4-bromophenyl)-octahydrobenzo[d]imidazole-1-carbothiamide (2f).**



White solid; R_f = 0.60 (EtOAc/hexane; 1:9); M.p. 160–161 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (m, 8H), 3.66 (m, 2H), 4.84 (brs, 1H), 6.88 (d, 2H, *J* = 8.8 Hz), 7.43 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 24.3, 29.9, 31.7, 59.5, 66.3, 117.1, 118.9, 124.5, 126.3, 131.7, 132.7, 138.1, 145.1, 155.0, 181.1; IR (KBr): 3386, 2942, 2858, 1642, 1589, 1542, 1482, 1368, 1338, 1236, 1182, 1068, 1008, 835, 749, 677 cm^{-1}; Anal. Calcd for $C_{20}H_{20}N_4SBr_2$: C, 47.26; H, 3.97; N, 11.02; S, 6.31; found: C, 47.30; H, 4.01; N, 10.98; S, 6.27.

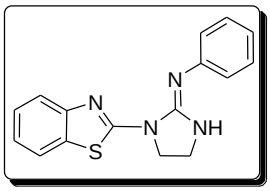
***(E,3aR,7aR)*-2-(4-(Trifluoromethyl)phenylimino)-N-(4-(trifluoromethyl)phenyl)-octahydrobenzo[d]imidazole-1-carbothiamide (2g).**



Solid; R_f = 0.57 (EtOAc/hexane; 1:9); M.p. 155–156 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (m, 8H), 3.64 (m, 2H), 4.94 (brs, 1H), 7.13 (d, 2H, *J* = 8.4 Hz), 7.58 (m, 4H), 7.74 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 24.3, 29.8, 31.6, 59.5, 66.3, 119.1, 121.2, 123.1, 124.1, 125.9, 126.5, 127.0, 142.2, 149.3, 155.0, 181.0; IR (KBr): 3414, 2946, 2862, 1650, 1602, 1568, 1512, 1368,

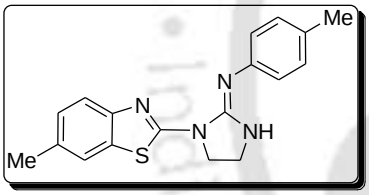
1320, 1218, 1159, 1107, 1064, 1011, 843 cm^{-1}; MS (ESI): 487.2304 (MH^+). Anal. Calcd for $C_{22}H_{20}N_4SF_6$: C, 54.31; H, 4.14; N, 11.51; S, 6.59; found: C, 54.35; H, 4.17; N, 11.47; S, 6.55.

***(E)*-*N*-(1-(Benzo[d]thiazol-2-yl)imidazolin-2-ylidene)benzenamine (1'a).**



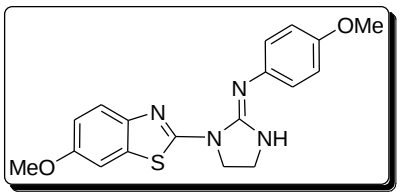
White solid; R_f = 0.33 (EtOAc/hexane; 2:8); M.p. 166–167 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.63 (t, 2H, *J* = 7.6 Hz), 4.37 (t, 2H, *J* = 7.6 Hz), 4.66 (brs, 1H), 7.04 (d, 2H, *J* = 6.4 Hz), 7.19 (t, 1H, *J* = 7.2 Hz), 7.31 (t, 4H, *J* = 7.2 Hz), 7.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.4, 46.5, 119.8, 120.4, 121.2, 122.8, 123.1, 125.9, 129.0, 129.6, 132.5, 149.5; IR (KBr): 3291, 2961, 2897, 2851, 1690, 1591, 1517, 1477, 1424, 1333, 1266, 1113, 1068, 786, 756, 724, 693 cm^{-1}; MS (ESI): 295.0627 (MH^+). Anal. Calcd for $C_{16}H_{14}N_4S$: C, 65.28; H, 4.79; N, 19.03; S, 10.89; found: C, 65.32; H, 4.82; N, 18.99; S, 10.85.

***(E)*-4-Methyl-*N*-(1-(6-methylbenzo[d]thiazol-2-yl)imidazolin-2-ylidene)benzenamine (1'b).**



White solid; R_f = 0.35 (EtOAc/hexane; 2:8); M.p. 171–172 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.42 (s, 3H), 3.66 (t, 2H, *J* = 8.0 Hz), 4.27 (t, 2H, *J* = 8.0 Hz), 7.01 (d, 2H, *J* = 8.0 Hz), 7.11 (d, 2H, *J* = 7.6 Hz), 7.17 (d, 1H, *J* = 8.4 Hz), 7.50 (s, 1H), 7.62 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 21.5, 41.6, 46.8, 119.9, 121.0, 122.3, 122.6, 127.3, 129.5, 130.1, 132.7, 147.6, 149.7, 158.5; IR (KBr): 3344, 2921, 2851, 1685, 1607, 1519, 1503, 1419, 1323, 1267, 1115, 1059, 809 cm^{-1}; MS (ESI): 323.0591 (MH^+). Anal. Calcd for $C_{18}H_{18}N_4S$: C, 67.05; H, 5.62; N, 17.37; S, 9.94; found: C, 67.09; H, 5.60; N, 17.33; S, 9.91.

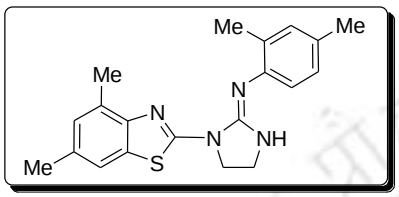
***(E)*-4-Methoxy-*N*-(1-(6-methoxybenzo[d]thiazol-2-yl)imidazolin-2-ylidene)benzenamine (1'c).**



White solid; R_f = 0.30 (EtOAc/hexane; 2:8); M.p. 179–180 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.58 (t, 2H, *J* = 7.6 Hz), 3.75 (s, 3H), 3.80 (s, 3H), 4.29 (t, 2H, *J* = 7.6 Hz), 4.61 (brs, 1H), 6.84 (d, 2H, *J* = 8.8 Hz), 6.94 (d, 2H, *J* = 8.4 Hz), 7.19 (d, 1H, *J* = 2.4 Hz), 7.61 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 40.4, 46.4, 55.7, 56.0, 104.7, 114.1, 114.9, 120.8, 123.4, 134.4, 141.4, 143.8, 149.4, 155.6, 156.0, 157.2; IR (KBr): 3364,

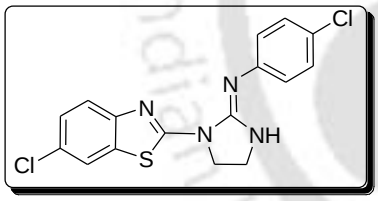
3010, 2906, 2829, 1668, 1602, 1501, 1470, 1423, 1336, 1223, 1122, 1061, 1030, 841, 821 cm^{-1}; MS (ESI): 355.0413 (MH^+). Anal. Calcd for $C_{18}H_{18}N_4SO_2$: C, 60.99; H, 5.12; N, 15.81; S, 9.05; found: C, 60.97; H, 5.15; N, 15.77; S, 9.00.

***(E)*-4-Dimethyl-*N*-(1-(4,6-dimethylbenzo[d]thiazol-2-yl)imidazolin-2-ylidene)benzenamine (1'd).**



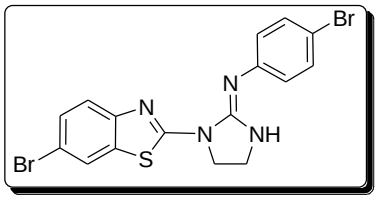
Gummy; R_f = 0.41 (EtOAc/hexane; 2:8); ^1H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 6H), 2.40 (s, 6H), 3.52 (brs, 2H), 4.33 (brs, 2H), 4.50 (brs, 1H), 7.01 (m, 4H), 7.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 18.4, 20.9, 21.4, 40.2, 46.5, 118.3, 121.2, 127.2, 127.8, 129.5, 131.5, 132.2, 133.2, 134.3, 144.4, 146.7, 148.5, 157.1; IR (KBr): 3438, 2918, 2851, 1676, 1514, 1478, 1411, 1328, 1253, 1097, 1064, 1037, 832 cm^{-1}; MS (ESI): 351.1953 (MH^+). Anal. Calcd for $C_{20}H_{22}N_4S$: C, 68.54; H, 6.33; N, 15.98; S, 9.15; found: C, 68.59; H, 6.37; N, 15.95; S, 9.11.

***(E)*-4-Chloro-*N*-(1-(6-chlorobenzo[d]thiazol-2-yl)imidazolin-2-ylidene) benzenamine (1'e).**



White solid; R_f = 0.32 (EtOAc/hexane; 2:8); M.p. 186–187 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.66 (brs, 2H), 4.31 (brs, 2H), 4.67 (brs, 1H), 6.99 (s, 1H), 7.30 (m, 4H), 7.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.6, 46.5, 120.7, 121.2, 123.8, 126.5, 128.2, 129.2, 134.5, 148.1, 149.2, 158.9; IR (KBr): 3446, 2912, 2846, 1728, 1660, 1523, 1481, 1423, 1338, 1269, 1119, 1089, 995, 834, 812, 700 cm^{-1}; MS (ESI): 363.0960 (MH^+). Anal. Calcd for $C_{16}H_{12}N_4SCl_2$: C, 52.90; H, 3.33; N, 15.42; S, 8.83; found: C, 52.93; H, 3.32; N, 15.39; S, 8.79.

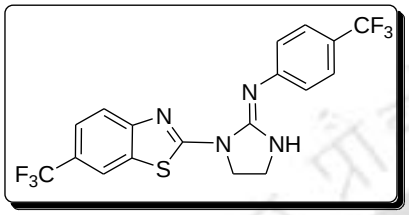
***(E)*-4-Bromo-*N*-(1-(6-bromobenzo[d]thiazol-2-yl)imidazolin-2-ylidene)benzenamine (1'f).**



White solid; R_f = 0.31 (EtOAc/hexane; 2:8); M.p. 199–200 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.61 (t, 2H, J = 8.0 Hz), 4.30 (t, 2H, J = 8.0 Hz), 4.80 (brs, 1H), 6.88 (d, 2H, J = 8.4 Hz), 7.40 (m, 3H), 7.56 (d, 1H, J = 8.8 Hz), 7.78 (d, 1H, J = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.4, 46.3, 115.6, 115.8, 121.6, 123.6, 124.5, 129.1, 132.5, 135.1, 147.1,

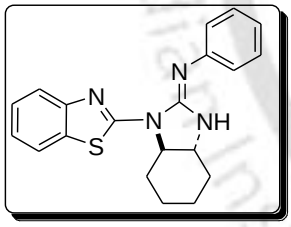
148.3, 149.1, 158.8; IR (KBr): 3419, 2972, 2925, 2851, 1659, 1542, 1485, 1408, 1321, 1303, 1278, 1256, 1124, 1070, 1034, 1007, 826 cm^{-1}; MS (ESI): 452.8834 (MH^+). Anal. Calcd for $C_{16}H_{12}N_4SBr_2$: C, 42.50; H, 2.67; N, 12.39; S, 7.09; found: C, 42.53; H, 2.65; N, 12.36; S, 7.04.

***(E)*-4-Trifluromethyl-*N*-(1-(6-trifluromethyl)benzo[d]thiazol-2-yl)imidazolin-2-ylidene)benzenamine (1'g).**



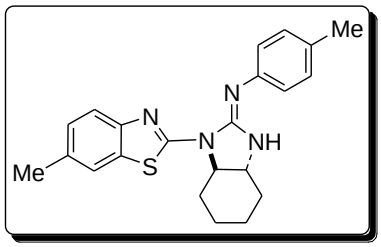
White solid; R_f = 0.27 (EtOAc/hexane; 2:8); M.p. 165–166 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 3.67 (t, 2H, *J* = 7.6 Hz), 4.37 (t, 2H, *J* = 7.6 Hz), 4.87 (brs, 1H), 7.11 (d, 2H, *J* = 8.0 Hz), 7.56 (m, 3H), 7.78 (d, 1H, *J* = 8.4 Hz), 7.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.4, 46.4, 118.7, 120.5, 122.9, 125.3, 126.8, 133.5, 149.1, 151.3, 151.8, 160.6; IR (KBr): 3399, 2924, 2851, 1679, 1608, 1508, 1485, 1428, 1317, 1269, 1168, 1098, 1059, 839 cm^{-1}. MS (ESI): 431.1509 (MH^+). Anal. Calcd for $C_{18}H_{12}N_4SF_6$: C, 50.23; H, 2.81; N, 13.02; S, 7.45; found: C, 50.27; H, 2.84; N, 12.99; S, 7.40.

***(E)*-*N*-(3aR,7aR)-3-(Benzo[d]thiazol-2-yl)hexahydro-1*H*-benzo[d]imidazol-2(3H)-ylidene)benzenamine (2'a).**



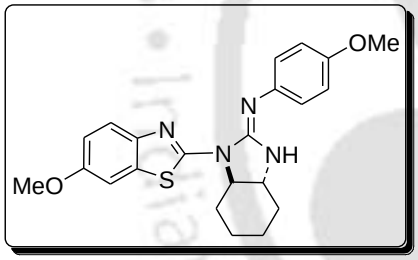
White solid; R_f = 0.64 (EtOAc/hexane; 1:9); M.p. 208–209 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 1.60 (m, 8H), 3.52 (m, 2H), 4.76 (brs, 1H), 7.04 (m, 3H), 7.19 (t, 1H, *J* = 7.6 Hz), 7.32 (m, 3H), 7.73 (t, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 24.5, 29.9, 30.1, 60.7, 66.2, 120.2, 120.7, 120.9, 122.6, 122.8, 123.1, 125.5, 128.9, 129.1, 129.5, 149.5, 151.3; IR (KBr): 3446, 3285, 2929, 2852, 1687, 1592, 1504, 1444, 1360, 1281, 1228, 1113, 1066, 836, 755, 694 cm^{-1}; MS (ESI): 349.0748 (MH^+). Anal. Calcd for $C_{20}H_{20}N_4S$: C, 68.93; H, 5.78; N, 16.10; S, 9.20; found: C, 68.98; H, 5.81; N, 16.06; S, 9.17.

(*E*)-*N*-(3aR,7aR)-Hexahydro-3-(6-methylbenzo[*d*]thiazol-2-yl)-1*H*-benzo[*d*]imidazol-2(3H)-ylidene)-4-methylbenzenamine (2'b).



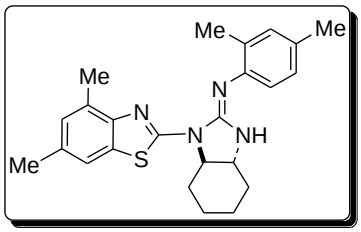
White solid; R_f = 0.62 (EtOAc/hexane; 1:9); M.p. 160–161 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71 (m, 7H), 2.34 (s, 3H), 2.44 (s, 3H), 3.45 (m, 3H), 4.78 (brs, 1H), 6.93 (d, 2H, *J* = 8.0 Hz), 7.12 (m, 3H), 7.49 (s, 1H), 7.60 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 21.5, 24.1, 24.4, 29.8. 30.0, 60.6, 66.0, 120.2, 120.7, 122.4, 126.9, 130.1, 132.4, 132.5, 133.3, 145.3, 147.4, 151.3, 159.4; IR (KBr): 3244, 2931, 2853, 1678, 1606, 1504, 1463, 1369, 1355, 1277, 1245, 1114, 1064, 831, 807 cm^{-1}. MS (ESI): 377.0966 (MH^+). Anal. Calcd for $C_{22}H_{24}N_4S$: C, 70.17; H, 6.42; N, 14.88; S, 8.52; found: C, 70.21; H, 6.45; N, 14.85; S, 8.48.

(*E*)-*N*-(3aR,7aR)-Hexahydro-3-(6-methoxybenzo[*d*]thiazol-2-yl)-1*H*-benzo[*d*]imidazol-2(3H)-ylidene)-4-methoxybenzenamine (2'c).



White solid; R_f = 0.59 (EtOAc/hexane; 1:9); M.p. 145–146 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25-3.47 (m, 10H), 3.79 (s, 3H), 3.83 (s, 3H), 6.88 (d, 2H, *J* = 8.8 Hz), 6.97 (m, 3H), 7.22 (t, 1H, *J* = 13.2 Hz), 7.63 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 24.4, 29.8, 30.0, 55.6, 55.9, 60.0, 66.0, 104.2, 113.9, 114.8, 121.1, 123.4, 134.3, 141.1, 143.8, 151.5, 155.6, 156.0, 158.5; IR (KBr): 3233, 2930, 2851, 1682, 1601, 1505, 1469, 1355, 1240, 1218, 1179, 1102, 1032, 839, 718 cm^{-1}; MS (ESI): 409.0947 (MH^+). Anal. Calcd for $C_{22}H_{24}N_4SO_2$: C, 64.68; H, 5.92; N, 13.71; S, 7.85; found: C, 64.71; H, 5.90; N, 13.67; S, 7.81.

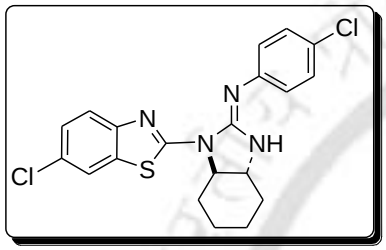
(*E*)-*N*-(3aR,7aR)-Hexahydro-3-(4,6-dimethylbenzo[*d*]thiazol-2-yl)-1*H*-benzo[*d*]imidazol-2(3H)-ylidene)-2,4-dimethylbenzenamine (2'd).



White solid; R_f = 0.65 (EtOAc/hexane; 1:9); M.p. 163–164 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69 (m, 8H), 2.27 (s, 3H), 2.32 (s, 3H), 2.41 (s, 3H), 2.63 (s, 3H), 3.70 (m, 2H), 4.60 (brs, 1H), 6.87 (d, 1H, *J* = 8.0 Hz), 6.97 (d, 1H, *J* = 7.6 Hz), 7.00 (s, 1H), 7.06 (s,

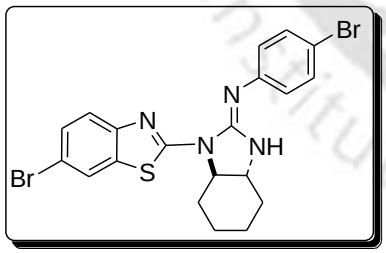
1H), 7.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0, 18.4, 20.9, 21.5, 24.2, 24.6, 29.9, 30.0, 60.4, 66.3, 118.1, 121.3, 127.2, 127.5, 129.7, 131.1, 131.6, 132.3, 133.0, 144.2, 146.6, 150.5; IR (KBr): 3446, 3351, 2922, 2851, 1665, 1521, 1494, 1451, 1392, 1327, 1261, 1098, 1064, 1039, 805 cm^{-1}; MS (ESI): 405.2620 (MH^+). Anal. Calcd for $C_{24}H_{28}N_4S$: C, 71.25; H, 6.98; N, 13.85; S, 7.93; found: C, 71.22; H, 6.96; N, 13.81; S, 7.89.

***(E)*-4-Chloro-*N*-(3aR,7aR)-3-(6-chlorobenzo[*d*]thiazol-2-yl)-hexahydro-1*H*-benzo[*d*]imidazol-2(3H)-ylidene)benzenamine (2'e).**



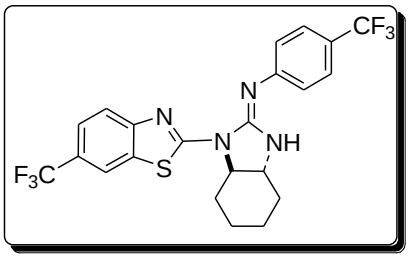
White solid; R_f = 0.60 (EtOAc/hexane; 1:9); M.p. 174–176 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69 (m, 8H), 3.47 (m, 2H), 6.94 (d, 2H, *J* = 8.4 Hz), 7.25 (m, 3H), 7.61 (d, 1H, *J* = 8.4 Hz), 7.64 (d, 1H, *J* = 1.6Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 24.4, 29.9, 60.7, 66.2, 120.4, 121.5, 123.9, 126.1, 128.1, 128.3, 129.5, 134.5, 146.2, 148.0, 151.2, 160.1; IR (KBr): 3412, 3378, 2941, 2857, 1671, 1586, 1509, 1487, 1445, 1389, 1366, 1277, 1248, 1139, 1098, 838, 725 cm^{-1}; MS (ESI): 417.00 (MH^+). Anal. Calcd for $C_{20}H_{18}N_4SCl_2$: C, 57.56; H, 4.35; N, 13.42; S, 7.68; found: C, 57.58; H, 4.37; N, 13.38; S, 7.63.

***(E)*-4-Bromo-*N*-(3aR,7aR)-3-(6-bromobenzo[*d*]thiazol-2-yl)-hexahydro-1*H*-benzo[*d*]imidazol-2(3H)-ylidene)benzenamine (2'f).**



White solid; R_f = 0.59 (EtOAc/hexane; 1:9); M.p. 192–193 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (m, 8H), 3.46 (m, 2H), 4.80 (s, 1H), 6.88 (s, 2H), 7.14 (m, 3H), 7.56 (m, 1H), 7.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 24.4, 29.8, 30.0, 60.8, 66.3, 115.7, 116.0, 122.0, 123.3, 124.4, 128.9, 132.5, 135.1, 146.7, 148.4, 151.2, 160.1; IR (KBr): 3394, 3362, 2941, 2857, 1687, 1671, 1588, 1505, 1482, 1441, 1388, 1366, 1275, 1244, 1108, 1067, 1003, 802, 718 cm^{-1}; MS (ESI): 507.0880 (MH^+). Anal. Calcd for $C_{20}H_{18}N_4SBr_2$: C, 47.45; H, 3.58; N, 11.07; S, 6.33; found: C, 47.48; H, 3.55; N, 11.02; S, 6.29.

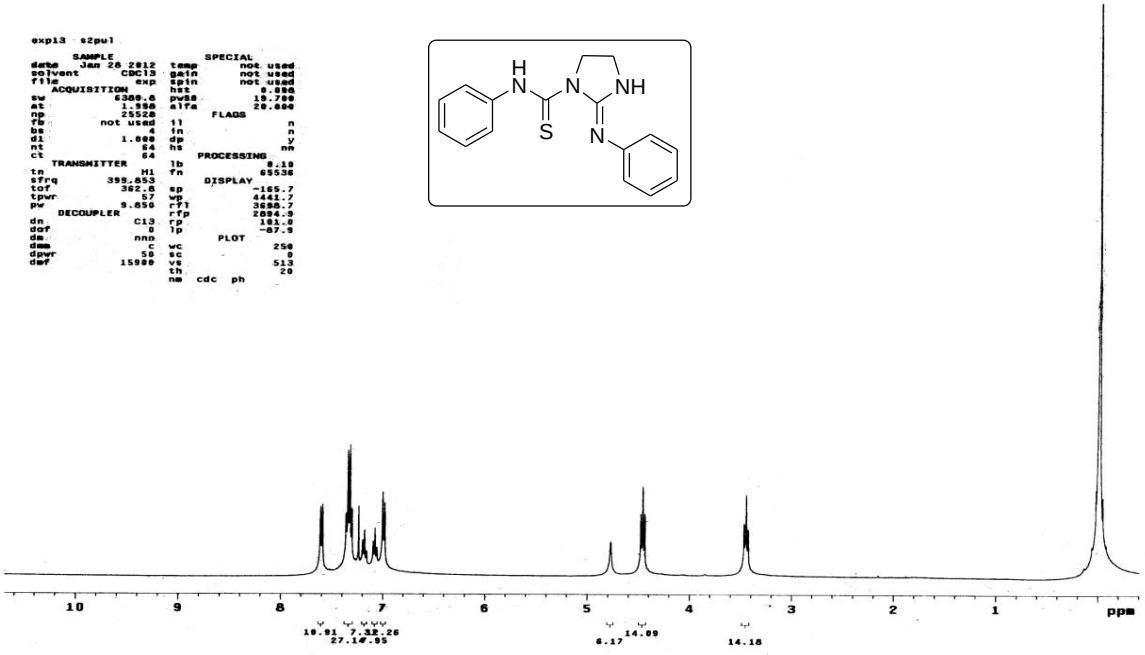
***(E)-4*-(Trifluoromethyl)-*N*-((3aR,7aR)-3-(6-trifluoromethylbenzo[*d*]thiazol-2-yl)-hexahydro-1*H*-benzo[*d*]imidazol-2(3H)-ylidene)benzenamine (2'g).**



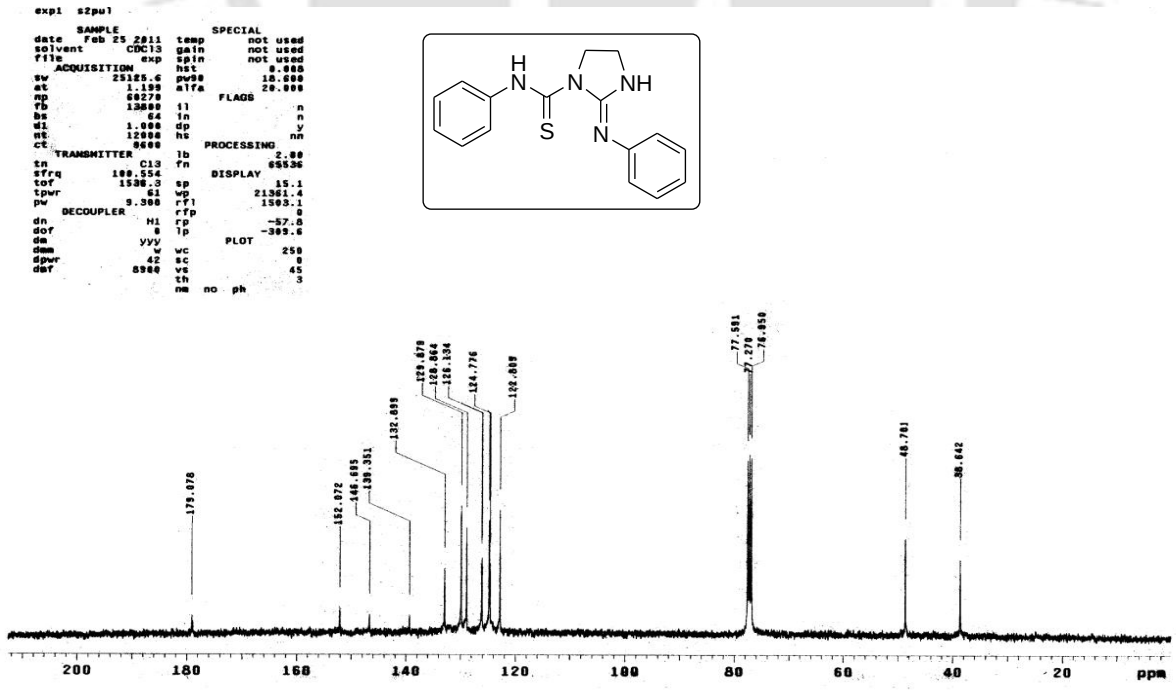
White solid; R_f = 0.55 (EtOAc/hexane; 1:9); M.p. 139–140 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 (m, 8H), 3.51 (m, 2H), 4.96 (brs, 1H), 7.11 (d, 2H, J = 8.0 Hz), 7.57 (t, 3H, J = 6.4 Hz), 7.78 (d, 1H, J = 8.8 Hz), 7.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 24.4, 29.7, 30.0, 60.9, 66.4, 118.4, 120.8, 122.7, 122.8, 123.3, 123.4, 124.7, 125.1, 125.3, 126.0, 126.1, 126.7, 133.4, 151.0, 151.2, 151.8, 162.0; IR (KBr): 3438, 2945, 2862, 1670, 1607, 1510, 1393, 1320, 1284, 1169, 1116, 1066, 10009, 826 cm^{-1}; MS (ESI): 485.2362 (MH^+). Anal. Calcd for $C_{22}H_{18}N_4SF_6$: C, 54.54; H, 3.74; N, 11.56; S, 6.62; found: C, 54.59; H, 3.77; N, 11.52; S, 6.59.

V.9. Selected Spectra

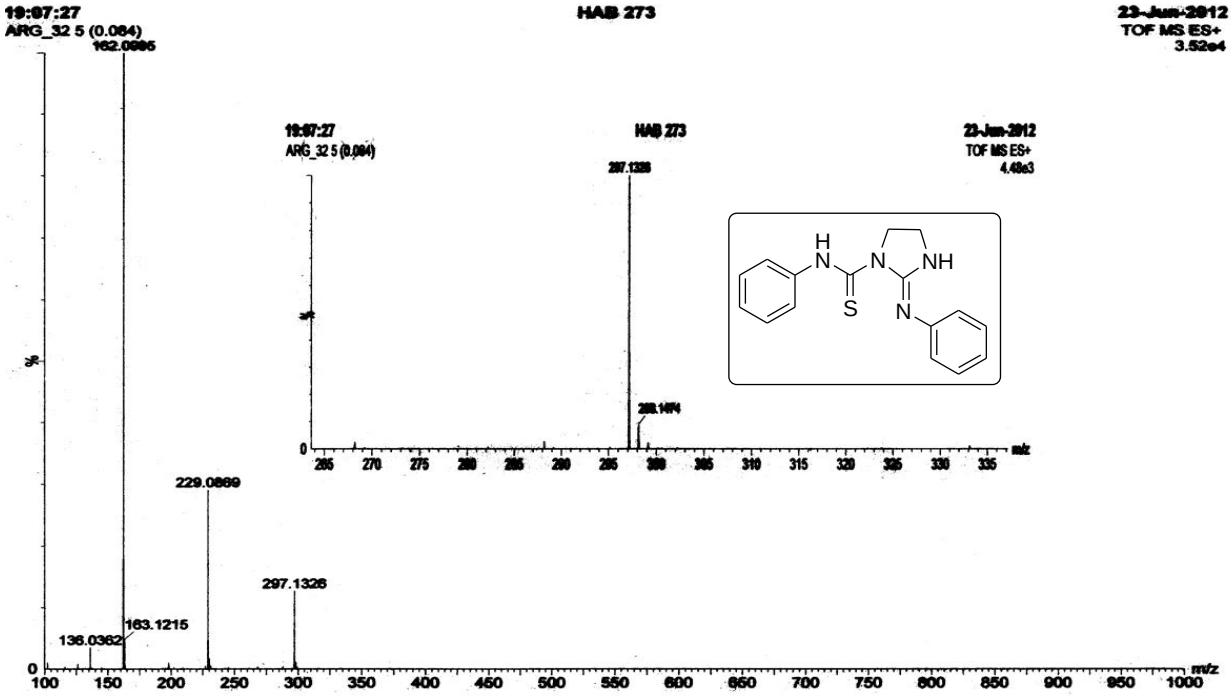
***E*-*N*-(Phenyl-2-(phenylimino)imidazolidine-1-carbothioamide (1a). ^{1}H NMR (400 MHz, $CDCl_3$):**



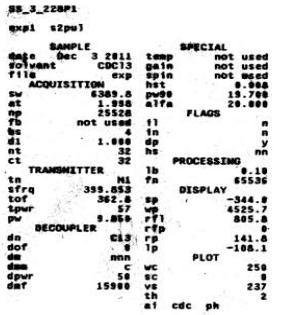
***E*-*N*-(Phenyl-2-(phenylimino)imidazolidine-1-carbothioamide (1a). ^{13}C NMR (100 MHz, $CDCl_3$):**

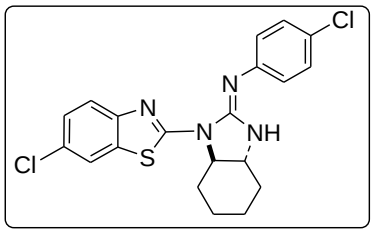


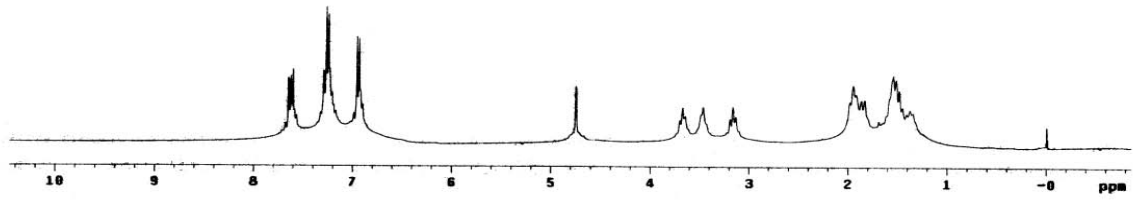
_E_-_N_-(Phenyl-2-(phenylimino)imidazolidine-1-carbothioamide (1a). MASS SPECTRA:



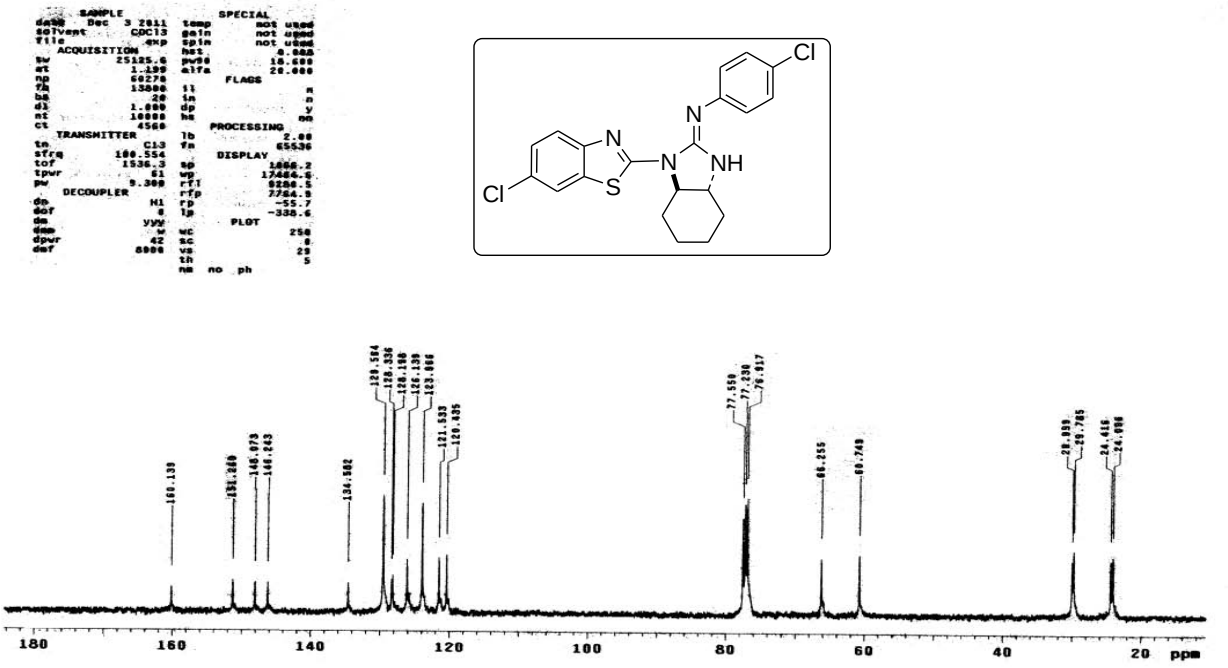
***(E)*-4-Chloro-*N*-(3aR,7aR)-3-(6-chlorobenzo[d]thiazol-2-yl)-Hexahydro-1*H*-benzo[*d*] imidazol-2(3H)-ylidene)benzenamine (12'a) ^{1}H NMR (400 MHz, $CDCl_3$):**







(*E*)-4-Chloro-*N*-(3aR,7aR)-3-(6-chlorobenzo[d]thiazol-2-yl)-Hexahydro-1*H*-benzo[*d*] imidazol-2(3H)-ylidene)benzenamine (12'a) ^{13}C NMR (100 MHz, $CDCl_3$):



(*E*)-4-Chloro-*N*-(3aR,7aR)-3-(6-chlorobenzo[d]thiazol-2-yl)-Hexahydro-1*H*-benzo[*d*] imidazol-2(3H)-ylidene)benzenamine (12'a) MASS SPECTRA: