CHAPTER-III

Dithiocarbamate and CuO promoted one-pot synthesis of 2-(N-substituted)-aminobenzimidazoles and related heterocycles

INTRODUCTION
3.0 Introduction

Organic compounds known to have wide range of applications and used in pharmaceuticals, agrochemicals and veterinary products. The organic compounds which have a particular heterocyclic ring system promotes activity against a specific organism based on its effective binding to any enzyme receptor site as a result replication of harmful microorganism is controlled. Heterocyclic chemistry is a very important branch of organic chemistry. Heterocyclic compounds are of widespread occurrence and are important constituents of several classes of natural products such as nucleic acids, plant alkaloids, anthocyanins, flavones, the haem pigment, chlorophyll etc. Heterocyclic systems are of great importance as they are associated with a wide variety of pharmacological activities.

Several thousands of new heterocyclic compounds, either synthesized in the laboratories or isolated from natural sources are added to the literature every year. Many of these compounds have drawn the attention of research scientists on account of their intrinsic chemical interest or on the basis of their therapeutic, biological and industrial potential.

Of the wide variety of heterocyclic systems known till today, the nitrogen heterocycles are of great importance as they are present in nucleic acids, vitamins, proteins and biologically molecular systems. Benzimidazole is one amongst such important nitrogen heterocycles since several of its derivatives have pharmacological properties and
have been marked as commercial products. The benzimidazoles ring system has also been found to be an integral part of vitamin-B$_{12}$\textsuperscript{1} in the form of 5, 6-dimethyl-1-(α-D-ribofuranosyl) benzimidazoles.

Benzimidazole is a heterocyclic aromatic organic compound. This bicyclic compound consists of the fusion of benzene and imidazole. The most prominent benzimidazole compound in nature is $N$-ribosyl-dimethyl benzimidazole which serves as an axial ligand for cobalt in vitamin B$_{12}$. Benzimidazole, in an extension of the well elaborated imidazole system, has been used as carbon skeletons for “$N$-heterocyclic carbenes”. NHCS are usually as ligands for transition metal complexes.

The benzimidazole ring system can be theoretically derived by fusion of an imidazole ring through its 4-5 bonds to a benzene ring.

![Benzimidazole Ring System](image)

The two nitrogens present in the imidazole ring are different from one another in their nature, and this makes the properties of the ring system diverse in character. The nitrogen bearing hydrogen atom
is sp³ in character and is often referred as pyrrole nitrogen. The other nitrogen is sp² in character and is often referred as pyridine nitrogen.

The hydrogen atom attached to the nitrogen in benzimidazole exhibits tautomerism as shown below²:

\[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{H}
\end{array}
\quad \leftrightarrow \quad
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{N}
\end{array}
\]

This tautomerism is analogous to that found in imidazoles and amidines. Due to this tautomerism, certain benzimidazole derivatives, which appear at first as isomers, are in reality tautomers. Because of this tautomerism, the 4th and 5th positions are equivalent to 7th and 6th positions.

Thus, 5-methylbenzimidazole is a tautomer of 6-methylbenzimidazole. Although two non-equivalent structures can be written, the two structures are tautomers and both structures represent the same compound.

**Importance of Benzimidazole Ring System:**

The benzimidazole scaffold is a useful structural motif for displaying chemical functionality in biologically active molecules. Benzimidazole has been an important pharmacophore and privileged structure in medicinal chemistry (figure 7)³, encompassing a diverse range of biological activities including antiarrhythmic, antiulcer,
anthelmintical, inotropic, antihistamine, antifungal, antiviral, and cytotoxicity.\textsuperscript{4}

Figure 7: Biologically relevant benzimidazoles.

Optimization of benzimidazole-based structures has resulted in marketed in medicines such as Omeprazole\textsuperscript{5} and Pimobendan\textsuperscript{6} and lead compounds in a wide range of therapeutic areas (e.g., casein kinase,\textsuperscript{7} factor Xa,\textsuperscript{8} hepatitis C virus\textsuperscript{9}).

Benzimidazoles are very useful building blocks for the development of molecules that are important in medicinal chemistry. Benzimidazoles are an important class of heterocycles with a wide range of applications.\textsuperscript{10-13} Although numerous methods for their synthesis have been disclosed,\textsuperscript{14} it remains difficult to access regioisomerically pure $N$-substituted benzimidazoles.

It acts by binding to the fungal microtubules and stopping hyphal growth. It also binds to the spindle microtubules and blocks nuclear division.

Benzimidazoles are useful pharmaceuticals\textsuperscript{15}, and 2-substituted benzimidazoles are used as anthelmintics in veterinary medicine\textsuperscript{16} and display significant anticancer, antiulcer, antiviral, antiallergic, and anticoagulant properties in human therapeutics.\textsuperscript{17}
Benzimidazole and its derivatives occupy pivotal positions in the synthesis of natural products and pharmaceutical materials. These compounds have been studied extensively because of their biological activities as bactericides,\textsuperscript{18} anticarcinogens,\textsuperscript{19} and peptic ulcer agents.\textsuperscript{20} There is particular interest in their activity against several viruses such as HIV,\textsuperscript{21} herpes (HSV-1),\textsuperscript{22} influenza,\textsuperscript{23} RNA,\textsuperscript{24} and human cytomegalovirus.\textsuperscript{25}

They are important intermediates in many organic reactions\textsuperscript{26} and act as ligands to transition metals for modeling biological systems.\textsuperscript{27} This has led to the development of several methods for the synthesis of benzimidazoles during the last few years.

Benzimidazole structures are classified under several classes of drugs,\textsuperscript{28} based on the possible substitution at different positions of the benzimidazole nucleus. Introduction of a small substituent into the 2- and 5-positions is characteristic for benzimidazole antihelmintics; alternatively, bulky 2-substituents characterize drugs used in the treatment of peptic ulcer and are sometimes referred as proton pump inhibitor; bulky 1- and 2-substituents are found in H1-anti-histaminics. All these compounds contain the benzimidazole skeleton and hence it has been assumed that this skeleton is necessary for the therapeutic effect.

In addition, benzimidazole derivatives have been used as topoisomerase inhibitors, selective neuropeptide YY1 receptor antagonists, angiotension II inhibitors, 5-HT3 antagonists in isolated
guinea pig ileum, potential antitumour agents, antimicrobial agents, smooth muscle cell proliferation inhibitors, a treatment for interstitial cystitis, as factor Xa inhibitors, and in diverse areas of chemistry. In light of the affinity they display towards a variety of enzymes and protein receptors, medicinal chemists would certainly classify them as privileged sub-structures for drug design. In addition, benzimidazole derivatives show fungicidal, antitumor, immunosuppressant, and anticonvulsant properties. Since benzimidazoles are commonly used as intermediates in synthetic routes and serve as ligands for the asymmetric catalysis, the preparation of benzimidazole has importance.

Benzimidazole scaffold (18) has high ROCK II affinity ($IC_{50} = 27\text{Nm}$) and cell based potency ($IC_{50} = 86 \text{Nm}$). This scaffold as novel ROCK inhibitor. Benzimidazole scaffold (19) (figure 8) had excellent affinity for ROCK-II, selectivity against PKA, and high potency in the cell-based ppMLC assay ($IC_{50} < 6 \text{Nm}$).

![Figure 8](image)

Benzimidazole scaffolds (20) and (21) are Raf kinase inhibitors (figure 9).
Figure 9

The Benzimidazole (22) derivative demonstrated very good binding affinity towards the CB2 receptor with decent selectivity over CB1 while showing partial agonist potency (figure 10).

Figure 10

Heterocycles containing a benzimidazole scaffold were reported as drug leads such as polymerase inhibitor$^{33}$ and commercial pharmaceutical products such as telmisartan (23) (figure 11) (used in the treatment of hypertension)$^{34}$.
2-[(N-substituted)-aminobenzimidazoles are widely used structural motifs in drug discovery and represent the core structure for a variety of biologically significant molecules.\textsuperscript{35} In connection with a drug discovery program, an efficient entry into a new class of potent inhibitors of the tyrosine kinase p56lck, exemplified by (24) and (25) (figure 12).\textsuperscript{36}

![Figure 12](image)

Therefore, an efficient practical method for synthesis of adverse collection of benzimidazoles would be of great value of drug discovery.

A large number of benzimidazole and its derivatives find use as pharmaceuticals, veterinary anthelmentics, bactericides and fungicides. Some of the important benzimidazole derivatives, which are of commercial importance, are shown in Table 1.
Table 3: Some important benzimidazole derivatives of commercial importance

<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fuberidazole</td>
<td><img src="image1" alt="Structure" /></td>
<td>Fungicide</td>
</tr>
<tr>
<td>Thiabendazole</td>
<td><img src="image2" alt="Structure" /></td>
<td>Human anthelmintic and Fungicide</td>
</tr>
<tr>
<td>Diabazole</td>
<td><img src="image3" alt="Structure" /></td>
<td>Vasodilator, spasmolytic Hypotensive</td>
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<td>Fenzaflor</td>
<td><img src="image4" alt="Structure" /></td>
<td>Acaricide</td>
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<tr>
<td>Mebendazole</td>
<td><img src="image5" alt="Structure" /></td>
<td>Anticancer, Veterinary Anthelmintic</td>
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<tr>
<td>Cambedazole</td>
<td><img src="image6" alt="Structure" /></td>
<td>Veterinary anthelmintic</td>
</tr>
<tr>
<td>Benzitramide</td>
<td><img src="image7" alt="Structure" /></td>
<td>Narcotic Analgesic</td>
</tr>
<tr>
<td>Chemical</td>
<td>Structure</td>
<td>Function</td>
</tr>
<tr>
<td>----------</td>
<td>-----------</td>
<td>----------</td>
</tr>
<tr>
<td>Imet 3393</td>
<td><img src="image1" alt="Structure" /></td>
<td>Anticancer</td>
</tr>
<tr>
<td>Droperidol</td>
<td><img src="image2" alt="Structure" /></td>
<td>Antiemetic and Antipsychotic</td>
</tr>
<tr>
<td>Omeprazole</td>
<td><img src="image3" alt="Structure" /></td>
<td>Antiulcer agent</td>
</tr>
<tr>
<td>Domperidone</td>
<td><img src="image4" alt="Structure" /></td>
<td>Antiemetic agent</td>
</tr>
<tr>
<td>Astemizole</td>
<td><img src="image5" alt="Structure" /></td>
<td>Antihistamine</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td><img src="image6" alt="Structure" /></td>
<td>Antiulcer agent</td>
</tr>
<tr>
<td>Benomyl</td>
<td><img src="image7" alt="Structure" /></td>
<td>Fungicide</td>
</tr>
<tr>
<td></td>
<td>Formula</td>
<td>Description</td>
</tr>
<tr>
<td>---------------</td>
<td>---------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Thiophanate</td>
<td><img src="image" alt="Thiophanate" /></td>
<td>Fungicide</td>
</tr>
<tr>
<td>Norastemizole</td>
<td><img src="image" alt="Norastemizole" /></td>
<td>Antiallergic, antihistamine</td>
</tr>
</tbody>
</table>
LITERATURE SURVEY
3.1 Literature Survey

Xiao-jun Wang et al., have been developed a procedure for preparation of a wide variety of 2-(N-substituted)-aminobenzimidazoles via CuCl/ iPr₂NEt mediated thiourea cyclization.

Devanand B. Shinde et al., have been reported one-pot efficient synthesis of 2-Aryl-1-arylmethyl-1H-benzimidazoles using Oxalic Acid Catalyst. 2-Aryl-1-arylmethyl-1H-benzimidazoles were efficiently synthesized from o-phenylenediamine and various substituted aldehydes using 10 mol% oxalic acid.

Kiumars Bahrami et al., have been explored the synthesis of substituted benzimidazoles through a one-pot condensation of o-phenylenediamines with aryl aldehydes in the presence of H₂O₂/HCl system in acetonitrile at room temperature.

Demosthenes Fokas et al., have been found a method for the preparation of a series of benzimidazoles as well of other imidazole
containing ring systems, in one step, by the reduction of o-nitroarylamines in the presence of aldehydes.

Yan-Guang Wang et al., have been developed a one-pot synthesis of 2-arylbenzimidazoles from phenylenediamines and aromatic aldehydes using iodobenzene diacetate as an oxidant.

Robert Aslanian et al., have been identified a series of non-imidazole histamine H3 receptor antagonists based on the (3-phenoxypropyl)amine motif, which is a common pharmacophore for H3 antagonists.
Daniel Pagé et al.,\textsuperscript{43} have been reported the preparation and evaluation of a novel class of CB2 agonists based on a benzimidazole moiety.

![Chemical structures]

Reagents and conditions: i) R$_1$CH$_2$NH$_2$, Et$_3$N, EtOH, 75 °C, over night; ii) H$_2$, 10% Pd/C, EtOAc, RT, over night; iii) a. (4-ethoxyphenyl)acetic acid, HATU, DIPEA, DMF, rt, 3h; b. DCE/HCl or glacial AcOH, 80 °C, 2h; iv) NH$_4$OH, EtOH, 65 °C, over night; v) (4-ethoxyphenyl)acetyl chloride, zinc dust, toluene, rt, overnight; vi) a. aldehyde, BH$_3$-pyridine, DCE, AcOH, rt, 1h; b. DCE/HCl or glacial AcOH, 80 °C, 2h; vii) MnO$_2$, dioxane, 65 °C, 24-48 h; viii) NaBH$_4$, EtOH, rt, 1 h.

Vassilios Bavetsias et al.,\textsuperscript{44} have been presented a hit generation and exploration approach led to the discovery of 31 (2-(4-(6-chloro-2-(4-(dimethylamino) phenyl)-3Himidazo[ 4,5-b]pyridin-7-yl)piperazin-1-yl)-N-(thiazol-2-yl) acetamide), a potent, novel inhibitor of Aurora-A, Aurora-B and Aurora- C kinases.
Tom G. Driver et al.,\textsuperscript{45} have been described the identity of the ortho-substituent of an aryl azide influences its reactivity toward transition metals. Substitution of a vinyl group with an imine disables rhodium(II)-mediated C-H amination and triggers a Lewis acid mechanism catalyzed by iron(II) bromide to facilitate benzimidazole formation.

Srinivas R. Adapa et al.,\textsuperscript{46} have been developed L-Proline (10 mol %) was found to be a organocatalyst for the selective synthesis of 2-aryl-1-arylmethyl-1Hbenzimidazoles from a wide range of substituted o-phenylenediamines and aldehydes using chloroform as a solvent at ambient temperature.
Ji-Feng Liu, et al.,\textsuperscript{47} have been developed the one-pot synthesis of benzimidazoles from diamines and carboxylic acids was developed under microwave irradiation condition.

Victor J. Cee et al.,\textsuperscript{48} have been described a one-pot method for the synthesis of 2-amino benzimidazoles and related hetero cycles. The reaction is mediated by a polymer-supported carbodiimide, which simplifies product isolation.

Manas Chakrabarty et al.,\textsuperscript{49} have been demonstrated the Keggin heteropoly acid, silicotungstic acid, to be highly efficient for an expeditious, one-pot synthesis of 1-methyl-2-(hetero)arylbenzimidazoles from $N$-methyl-1,2-phenylenediamine and (hetero)aryl aldehydes in ethyl acetate at room temperature.
Jan J. Scicinski et al.,\textsuperscript{50} have been described a one-pot procedure for the generation of 2-substituted benzimidazoles directly from 2-nitroanilines by in situ reduction and cyclization using a microwave procedure.

Natalya V. Ivanova et al.,\textsuperscript{51} have been developed a solution-phase synthesis for the preparation of substituted 2-(1,2,4-triazol-3-yl)benzimidazoles from triazole aldehydes and orthophenylenediamines.

Masaichi Hasegawa et al.,\textsuperscript{52} have been discovered novel benzimidazoles as potent inhibitors of TIE-2 and VEGFR-2 tyrosine
kinase receptors.

Reagents and conditions: a) NaH, DMF; b) 2-fluoro-5-trifluoromethyl-phenylisocyanate, THF; c) Pd-C, H₂, EtOH; d) BrCN, MeOH; E) RCO₂H, Et₃N, HBTU (O-bezotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate), HOBT (N-hydroxybenzotriazole), DMF; f) LiAlH₄, THF.

Savithri Ramurthy et al.,⁵³ have been designed and synthesised orally bioavailable benzimidazoles as Raf kinase inhibitors.
Reagents and conditions: a) KHMDS, K₂CO₃, DMF, 90 °C, 16 h; b) TFAA, (CH₃)₂SO₄, NaOH, CH₃CN, 16 h, rt; c) H₂, 10% Pd/C, MeOH; d) R₂NCS, MeOH, rt, 16 h; e) CH₃I, CH₃OH, 16 h, rt; f) EDCl, THF, 16 h, rt.

Yuhei Yamamoto et al.,⁵⁴ have been investigated the synthesis of r-Chloroaldoxime O-Methane sulfonates and their use in the synthesis of functionalized benzimidazoles.

Dmitry M. Volochnyuk et al.,⁵⁵ have been elaborated a one-pot method for the synthesis of 2,3- dihydro-1H-benzimidazoles. A set of 2,3-dihydro-1H-benzimidazoles was prepared from various orthodialkylaminoanilines and aldehydes using Me₃SiCl as a condensation agent and pyridine as a basic medium.
Stephen L. Buchwald et al.,\textsuperscript{56} have been described a copper-catalyzed method for the preparation of \( N \)-alkylbenzimidazoles in regioisomerically pure form starting from \( o \)-haloanilines. The method utilizing CuI and trans-\( N,N^\ominus \)-dimethyl-1,2-cyclohexanediamine allows the preparation of \( N \)-alkylbenzimidazoles.

Biswanath Das et al.,\textsuperscript{57} have been synthesized benzimidazoles by treatment of 1,2-phenylenediamine with aldehydes using (bromodimethyl) sulfonium bromide at room temperature.

Xiao-jun Wang et al.,\textsuperscript{58} have been developed a procedure for preparation of a wide variety of 2-(\( N \)-substituted)-aminobenzimidazoles via CuCl/ \( i \)Pr\(_2\)NEt mediated thiourea cyclization.
A. John Blacker et al., have been used ruthenium-catalyzed hydrogen-transfer reactions for the conversion of alcohols into benzimidazoles using crotononitrile as a hydride acceptor.

Massimo Curini et al., have been synthesised different substituted benzimidazoles in solvent-free conditions from o-phenylenediamine and aldehydes in the presence of Yb(OTf)$_3$ as catalyst.

Ping Lan et al., have been developed an approach to wide variety of 2-substituted benzimidazoles via a 2-methylsulfonyl benzimidazole (or 2-halobenzimidazole) as the common intermediate by using a solvent-free method.

Robert S. Meissner et al., have been developed a procedure for the synthesis of 2-alkylaminobenzimidazoles and a variety of analogues.
Xiaohu Deng et al.,\textsuperscript{63} have been demonstrated that CuI/L5 (N,N\textsuperscript{\textprime}-dimethyl ethylenediamine) is an catalyst system for the guanidinylation of aryl iodides. Using this catalyst system, a number of 1-H-2-amino-benzimidazoles were prepared from readily available 1,2-dihaloarenes and guanidines in one step.

Bhisma K. Patel et al.,\textsuperscript{64} have been discussed isothiocyanates reacted with o-phenylenediamine and o-aminophenol to form monothioureas, which, on treatment with a further equivalent of DIB in one pot, gave benzimidazoles

Yasuhiro Shiraishi et al.,\textsuperscript{65} have been described the Pt@TiO\textsubscript{2} enables efficient benzimidazole production under photoirradiation conditions. This is promoted by one-pot multiple catalytic transformations on Pt@TiO\textsubscript{2}, which involve a platinum-assisted
photocatalytic oxidation on TiO$_2$ and a catalytic dehydrogenation on the surface of the platinum particles.

![Chemical Reaction Diagram]

**Brindaban C. Ranu et al.,**$^{66}$ have been synthesized 2-substituted benzimidazoles by a one-pot reaction of o-phenylenediamine with aromatic aldehydes in the presence of an ionic liquid, 1-methyl-3-pentylimidazolium tetrafluoroborate, [pmim]BF$_4$ at room temperature in open air without any organic solvent.

![Chemical Reaction Diagram]

**Yulu Wang et al.,**$^{67}$ have been used sodium hydrogen sulfite to promote condensation of o-phenylenediamine with aromatic aldehydes in dimethylformamide to obtain the corresponding 2-aryl benzimidazoles.

![Chemical Reaction Diagram]

**Raquel G. Jacob et al.,**$^{68}$ have been presented the synthesis of 1,2-disubstituted benzimidazoles by the condensation of o-phenylenediamine and aldehydes using solid supported catalyst.
Mohammad Mehdi Khodaei et al.,\textsuperscript{69} have been employed the synthesis of 2-substituted benzimidazoles from 1,2-phenylenediamines and aryl aldehydes.

\[
\begin{array}{c}
\text{R} \quad \text{NH}_2 \\
\text{NH}_2
\end{array}
\xrightarrow{\text{H}_2\text{O}_2, \text{Fe(NO}_3\text{)}_3} \xrightarrow{\text{solvent-free}}
\begin{array}{c}
\text{R} \\
\text{N} \\
\text{Ar}
\end{array}
\]

Xing-Guo Zhang et al.,\textsuperscript{70} have been developed a method to synthesize \(N\)-substitued 2-(trifluoromethyl)benzimidazoles by CuI/TMEDA (L2) catalyzed coupling reaction of \(N\)-(2-haloaryl)trifluoroacetimidoyl chlorides with primary amines.

\[
\begin{array}{c}
\text{Ar} \quad \text{CF}_3 \\
\text{N} \\
\text{Cl}
\end{array}
\xrightarrow{\text{H}_2\text{N}–\text{R}, \text{CuI, L}_2} \xrightarrow{\text{Cs}_2\text{CO}_3}
\begin{array}{c}
\text{R} \\
\text{C} \\
\text{N}
\end{array}
\]

Charansingh H. Gill et al.,\textsuperscript{71} have been reported a method for the synthesis of 2-substituted-1\(H\)-imidazo[4,5-b]pyridine from 2,3-diaminopyridine with substituted aryl aldehydes in water under thermal conditions.

\[
\begin{array}{c}
\text{O} \\
\text{H} \quad \text{R} \\
\text{N} \\
\text{NH}_2 \\
\text{NH}_2
\end{array}
\xrightarrow{\text{water, 100\textdegree C, 10-12 h}}
\begin{array}{c}
\text{N} \\
\text{R}
\end{array}
\]

Yangbo Feng et al.,\textsuperscript{72} have been developed a potent series of benzimidazole-based ROCK inhibitors.
Yuhei Yamamoto et al.,\textsuperscript{73} have been demonstrated a method for the synthesis of 2-substituted benzimidazoles via tosylation of N-aryl amidoximes, which are readily available from anilines and imidoyl chlorides.

Malvinder P. Singh et al.\textsuperscript{74} have been examined a catalytic Fe(III)/Fe(II) redox cycling approach and applied towards synthesis of a wide range of benzimidazole, bis-benzimidazole and imidazopyridine derivatives from oxidative coupling of aromatic ortho-diamines with aromatic as well as heterocyclic aldehydes bearing different types of substituents.

Tharmalingam Punniyamurthy et al.,\textsuperscript{75} have been described the synthesis of substituted benzimidazoles, 2-amino benzimidazoles via intramolecular cyclization of o-bromoaryl derivatives using copper (II) oxide nano particles in DMSO under air.
Michele H. Potashman et al.\textsuperscript{76} have been designed to synthesis and evaluation of orally active benzimidazoles as vascular endothelial growth factor-2 receptor tyrosine kinase inhibitors.
RESULTS AND DISCUSSION
3.2 Results and Discussion

**General Synthesis of Benzimidazoles:**

We were particularly interested in the synthesis of 2-aminobenzimidazoles via a method suitable for large scale preparations as well as not requiring toxic starting materials and reagents.

Herein, we report a highly efficient copper(II) oxide mediated one-pot synthesis of 2-aminobenzimidazoles using various substituted diamines and substituted dithiocarbamates. Unlike isothiocyanates, dithiocarbamates are highly stable and easy to handle. They are easy to synthesize in large quantities using readily available substituted anilines. The initial experiments were performed with commercially available o-phenylenediamines and methyl-$N$-aryldithiocarbamate using CuO (0.2 equiv) and $K_2CO_3$ in DMF at 60 °C for 1–2 h. The desired 2-aminobenzimidazole was isolated (Scheme 3) in good yield. We also investigated this methodology with respect to different diamines and dithiocarbamates (Table 4). Several functionalized 2-aminobenzimidazoles were synthesized from structurally diverse diamines. The reaction gave good yields with both electron-withdrawing groups and electron-donating groups. The procedure could also be applied to other diamine moieties, providing quinazolines and purine-like products in good yields. In connection with a drug discovery program, we recently required an efficient synthetic protocol into the new class of trisubstituted purines known
as Aurora-A Kinase inhibitors. To synthesize this class of compound we applied this methodology (Scheme 4). Thus, condensation of 2,4,5-trisubstituted pyrimidines with dithiocarbamates in the presence of CuO (0.2 equiv) and K₂CO₃ in DMF at 60 °C for 2 h furnished the desired substituted purines (Table 5) in good yields.
**Table 4:** Synthesis of 2-(N-substituted)-aminobenzimidazoles

<table>
<thead>
<tr>
<th>S. No.</th>
<th>o-Phenylenediamine</th>
<th>Dithiocarbamate</th>
<th>Compound</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{O}_2\text{N}H_2)</td>
<td>(\text{NH}_2)</td>
<td>(\text{O}_2\text{N}H_2)</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>(\text{O}_2\text{N}H_2)</td>
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<td>(\text{Cl}S\text{CH}_3)</td>
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<tr>
<td>3</td>
<td>(\text{O}_2\text{N}H_2)</td>
<td>(\text{O}S\text{CH}_3)</td>
<td>(\text{O}S\text{CH}_3)</td>
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<td>4</td>
<td>(\text{NH}_2)</td>
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<td>1</td>
</tr>
<tr>
<td>5</td>
<td>(\text{NH}_2)</td>
<td>(\text{Cl}S\text{CH}_3)</td>
<td>(\text{Cl}S\text{CH}_3)</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>(\text{NH}_2)</td>
<td>(\text{O}S\text{CH}_3)</td>
<td>(\text{O}S\text{CH}_3)</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>(\text{O}_2\text{CO}H\text{NH}_2)</td>
<td>(\text{NH}_2)</td>
<td>(\text{O}_2\text{CO}H\text{NH}_2)</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>(\text{O}_2\text{CO}H\text{NH}_2)</td>
<td>(\text{Cl}S\text{CH}_3)</td>
<td>(\text{Cl}S\text{CH}_3)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Structure 1</td>
<td>Structure 2</td>
<td>Structure 3</td>
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<tr>
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**Table 5:** Trisubstituted Purines (Aurora-A kinase inhibitors)

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CONCLUSION
3.3 Conclusion

We have developed an efficient and practical procedure for the one-pot synthesis of a wide variety of 2-(N-substituted)-aminobenzimidazoles using a catalytic amount of CuO, various substituted diamines and substituted non toxic dithiocarbamates. The procedure could also be applied to other diamine moieties, providing quinazolines and trisubstituted purines known as Aurora-A Kinase inhibitors. The reaction gave good yields with both electron-withdrawing groups and electron-donating groups. This procedure can be scaled-up and can be applied to synthesize many potential drug candidates.
EXPERIMENTAL SECTION
3.4 Experimental Section

General: All reactions were performed using oven-dried glassware. Organic solutions were concentrated under reduced pressure using Buchi rotary evaporator. All other reagents and solvents were obtained from commercial suppliers and were used without further purification. Reactions and chromatographic fractions were monitored by thin layer chromatography. TLC Silica gel-60 F$_{254}$, Merck was used for TLC and silica gel (100-200 mesh, SRL, India) was used for column chromatography.

General experimental procedure for preparation of benzimidazoles:

To a suspension of o-phenylenediamines (1.0 eq) and aryldithiocarbamate (1.2 eq) in 2 ml of DMF were added copper oxide (0.2 eq) and potassium carbonate (2.0 eq). The resulting mixture was heated 60 ºC and kept for 30 min. The reaction mixture was then cooled to room temperature and filtered through celite bed and washed with ethyl acetate. The combined filtrate was washed with brine and water. The organic layer was dried over sodium sulphate and concentrated in vacuo and the resulting mixture chromatographed on silica gel (hexane-acetone, 90:10) to yield as a solid and it was confirmed by spectral data.
(5-Nitro-1H-benzoimidazol-2-yl)-phenyl-amine (3a)

The compound was prepared according to the general procedure, from 4-Nitro-benzene-1,2-diamine (0.1 g, 0.653 mmol), N-Phenyl-dithiocarbamic acid methyl ester (0.131 g, 0.718 mmol) and K$_2$CO$_3$ (0.180 g, 1.30 mmol) in the presence of CuO (0.010 g, 0.130 mmol) in DMF (2 ml) to give 0.125 g (75%) of the product as a solid; mp: 164-165 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.47 (br s, 1H, NH), 9.95 (br s, 1H, NH), 8.16-8.15 (m, 1H), 8.01-7.97 (m, 1H), 7.95-7.74 (m, 2H), 7.46-7.32 (m, 3H), 7.05-6.97 (m, 1H); $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta$ 154.18, 139.78, 128.93, 121.74, 117.95, 117.02; Mass (ESI): 255.2 [M+H]$^+$.

(4-Chloro-phenyl)-(5-nitro-1H-benzoimidazol-2-yl)-amine (3b)

The compound was prepared according to the general procedure, from 4-Nitro-benzene-1,2-diamine (0.1 g, 0.653 mmol), (4-Chloro-phenyl)-dithiocarbamic acid methyl ester (0.156 g, 0.718...
mmol) and K$_2$CO$_3$ (0.180 g, 1.30 mmol) in the presence of CuO (0.010 g, 0.130 mmol) in DMF (2 ml) to give 0.142 g (75%) of the product as a solid; mp: 304-307 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.53 (br s, 1H, NH), 10.12 (br s, 1H, NH), 8.17-8.16 (m, 1H), 8.02-7.96 (m, 1H), 7.84-7.80 (m, 2H), 7.48-7.38 (m, 3H); $^{13}$C NMR (50 MHz, DMSO-$d_6$): δ 153.75, 141.01, 138.81, 128.75, 125.17, 119.35, 117.09; Mass (ESI): 289.1 [M+H]$^+$.

**(3,4-Dimethoxy-phenyl)-(5-nitro-1H-benzoimidazol-2-yl)-amine (3c)**

![Chemical Structure](image)

The compound was prepared according to the general procedure, from 4-Nitro-benzene-1,2-diamine (0.1 g, 0.653 mmol), (3,4-Dimethoxy-phenyl)-dithiocarbamic acid methyl ester (0.174 g, 0.718 mmol) and K$_2$CO$_3$ (0.180 g, 1.30 mmol) in the presence of CuO (0.010 g, 0.130 mmol) in DMF (2 ml) to give 0.160 g (78%) of the product as a solid; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.45 (br s, 1H, NH), 9.77 (br s, 1H, NH), 8.10-8.09 (m, 1H), 7.99-7.93 (m, 1H), 7.40-7.24 (m, 3H), 6.98-6.93 (m, 1H), 3.79 (s, 3H), 3.74 (s, 3H); $^{13}$C NMR (50 MHz, DMSO-$d_6$): δ 154.77, 149.02, 144.29, 140.56, 133.31, 116.97, 112.6, 110.46, 104.16, 55.91, 55.47; Mass (ESI): 315.1 [M+H]$^+$. 
5-Methyl-\(N\)-phenyl-\(1H\)-benzo[d]imidazol-2-amine (3d)

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{N} \\
\text{Cl}
\end{array}
\]

The compound was prepared according to the general procedure, from 4-Methyl-benzene-1,2-diamine (0.1 g, 0.819 mmol), \(N\)-Phenyl-dithiocarbamic acid methyl ester (0.165 g, 0.901 mmol) and \(K_2CO_3\) (0.226 g, 1.63 mmol) in the presence of CuO (0.013, 0.163 mmol) in DMF (2 ml) to give 0.137 g (78%) of the product as a solid; mp: 166–167 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 10.77 (br s, 1H, NH), 9.32 (br s, 1H) 7.75–7.71 (m, 2H), 7.33–7.08 (m, 4H), 6.93–6.78 (m, 2H), 2.35 (s, 3H); \(^{13}\)C NMR (50 MHz, DMSO-\(d_6\)): \(\delta\) 150.46, 141.04, 140.43, 132.95, 130.59, 128.78, 121.23, 120.43, 116.99, 116.34, 115.54, 21.32; Mass (ESI): 224.3 [M+H]^+.

(4-Chloro-phenyl)-(5-methyl-\(1H\)-benzoimidazol-2-yl)-amine (3e)

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{Cl}
\end{array}
\]

The compound was prepared according to the general procedure, from 4-Methyl-benzene-1,2-diamine (0.1 g, 0.819 mmol), (4-Chloro-phenyl)-dithiocarbamic acid methyl ester (0.195 g, 0.901
mmol) and K₂CO₃ (0.226 g, 1.63 mmol) in the presence of CuO (0.013, 0.163 mmol) in DMF (2 ml) to give 0.127 g (70%) of the product as a solid; mp: 205-207 °C; ¹H NMR (400 MHz, DMSO-d₆): δ 10.90 (br s, 1H, NH), 9.46 (br s, 1H, NH), 7.80-7.77 (m, 2H), 7.34-7.12 (m, 4H), 6.83-6.81 (m, 1H), 2.35 (s, 3H); ¹³C NMR (50 MHz, DMSO-d₆): δ 159.67, 150.92, 149.53, 147.06, 145.46, 138.81, 138.24, 133.67, 131.05, 129.11, 128.30, 122.43, 122.21, 30.95; Mass (ESI): 258.2 [M+H]⁺.

**{(3,4-Dimethoxy-phenyl)-(5-methyl-1H-benzoimidazol-2-yl)-amine (3f)}**

The compound was prepared according to the general procedure, from 4-Methyl-benzene-1,2-diamine (0.1 g, 0.819 mmol), (3,4-Dimethoxy-phenyl)-dithiocarbamic acid methyl ester (0.219 g, 0.901 mmol) and K₂CO₃ (0.226 g, 1.63 mmol) in the presence of CuO (0.013, 0.163 mmol) in DMF (2 ml) to give 0.176 g (76%) of the product as a solid; ¹H NMR (400 MHz, DMSO-d₆): δ 10.68 (br s, 1H, NH), 9.05 (br s, 1H, NH), 7.37 (s, 1H), 7.26-7.24 (m, 1H), 7.17-7.04 (m, 2H), 6.91-6.88 (m, 1H), 6.79-6.74 (m, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 2.34 (s, 3H); ¹³C NMR (50 MHz, DMSO-d₆): δ 153.93, 149.01,
143.21, 134.91, 128.46, 121.17, 115.96, 115.25, 112.93, 109.04, 103.13, 6.03, 55.42, 21.26; Mass (ESI): 284.4 [M+H]+.

**(5-Methoxy-1H-benzoimidazol-2-yl)-phenyl-amine (3g)**

The compound was prepared according to the general procedure, from 4-Methoxy-benzene-1,2-diamine (0.1 g, 0.724 mmol), \( N \)-Phenyl-dithiocarbamic acid methyl ester (0.145 g, 0.797 mmol) and \( K_2CO_3 \) (0.300 g, 2.17 mmol) in the presence of CuO (0.011 g, 0.144 mmol) in DMF (2 ml) to give 0.139 g (80%) of the product as a solid; mp: 148-150 °C; \(^1\)H NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) 10.70 (br s, 1H, NH), 9.27 (br s, 1H, NH), 7.73-7.71 (m, 2H), 7.30-7.19 (m, 3H), 6.91-6.90 (m, 2H), 6.61-6.59 (m, 1H), 3.74 (s, 3H); Mass (ESI): 240.1 [M+H]+.
(4-Chloro-phenyl)-(5-methoxy-1H-benzoimidazol-2-yl)-amine (3h)

The compound was prepared according to the general procedure, from 4-Methoxy-benzene-1,2-diamine (0.1 g, 0.724 mmol), (4-Chloro-phenyl)-dithiocarbamic acid methyl ester (0.172 g, 0.797 mmol) and K$_2$CO$_3$ (0.300 g, 2.17 mmol) in the presence of CuO (0.011 g, 0.144 mmol) in DMF (2 ml) to give 0.148 g (75%) of the product as a solid; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.76 (br s, 1H, NH), 9.46 (br s, 1H, NH), 7.82-7.77 (m, 2H), 7.34-6.88 (m, 4H), 6.63-6.60 (m, 1H), 3.74 (s, 3H); Mass (ESI): 274.2 [M+H]$^+$. 

(3,4-Dimethoxy-phenyl)-(5-methoxy-1H-benzoimidazol-2-yl)-amine (3i)

The compound was prepared according to the general procedure, from 4-Methoxy-benzene-1,2-diamine (0.1 g, 0.724 mmol), (3,4-Dimethoxy-phenyl)-dithiocarbamic acid methyl ester (0.193 g, 0.797 mmol) and K$_2$CO$_3$ (0.300 g, 2.17 mmol) in the presence of CuO.
(0.011 g, 0.144 mmol) in DMF (2 ml) to give 0.177 g (82%) of the product as a solid; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.63 (br s, 1H, NH), 9.05 (br s, 1H, NH), 7.36-7.35 (m, 1H), 7.26-7.23 (m, 1H), 7.13 (s, 1H), 6.90-6.87 (m, 2H), 6.58-6.56 (m, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H); $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta$ 154.29, 151.00, 149.02, 143.18, 134.91, 115.23, 112.93, 112.20, 108.94, 107.32, 103.05, 100.39, 95.27, 56.03, 55.44, 55.37; Mass (ESI): 300.3 [M+H]$^+$. 

**5,6-Dichloro-1H-benzoimidazol-2-yl)-phenyl-amine (3j)**

The compound was prepared according to the general procedure, from 4,5-Dichloro-benzene-1,2-diamine (0.1 g, 0.568 mmol), N-Phenyl-dithiocarbamic acid methyl ester (0.114 g, 0.624 mmol) and $K_2CO_3$ (0.235 g, 1.70 mmol) in the presence of CuO (0.009 g, 0.113 mmol) in DMF (2 ml) to give 0.110 g (70%) of the product as a solid; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.07 (br s, 1H, NH), 9.62 (br s, 1H, NH), 7.73-7.70 (m, 2H), 7.51-7.47 (m, 2H), 7.34-7.30 (m, 2H), 6.98-6.94 (m, 1H); $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta$ 140.10, 128.84, 121.92, 121.27, 117.55, 113.66; Mass (ESI): 278.0 [M+H]$^+$. 
(4-Chloro-phenyl)-(5,6-dichloro-1H-benzoimidazol-2-yl)-amine (3k)

The compound was prepared according to the general procedure, from 4,5-Dichloro-benzene-1,2-diamine (0.1 g, 0.568 mmol), (4-Chloro-phenyl)-dithiocarbamic acid methyl ester (0.135 g, 0.624 mmol) and K₂CO₃ (0.235 g, 1.70 mmol) in the presence of CuO (0.009 g, 0.113 mmol) in DMF (2 ml) to give 0.122 g (69%) of the product as a solid; ¹H NMR (400 MHz, DMSO-d₆): δ 11.18 (br s, 1H, NH), 9.83 (br s, 1H, NH), 7.80-7.76 (m, 2H), 7.55-7.48 (m, 2H), 7.39-7.35 (m, 2H); Mass (ESI): 312.1 [M+H]^+.

(5,6-Dichloro-1H-benzoimidazol-2-yl)-(3,4-dimethoxy-phenyl)-amine (3l)

The compound was prepared according to the general procedure, from 4,5-Dichloro-benzene-1,2-diamine (0.1 g, 0.568 mmol), (3,4-Dimethoxy-phenyl-dithiocarbamic acid methyl ester
(0.138 g, 0.624 mmol) and K$_2$CO$_3$ (0.235 g, 1.70 mmol) in the presence of CuO (0.009 g, 0.113 mmol) in DMF (2 ml) to give 0.134 g (70%) of the product as a solid; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.05 (s, 1H, NH), 9.46 (s, 1H, NH), 7.48-7.22 (m, 3H), 7.10 (s, 1H), 6.95-6.90 (m, 1H), 3.77 (s, 3H), 3.72 (s, 3H); $^{13}$C NMR (50 MHz, DMSO-$d_6$): δ 153.01, 148.99, 143.89, 133.81, 132.85, 129.83, 122.36, 116.30, 112.74, 110.33, 109.88, 109.73, 103.74, 55.94, 55.46; Mass (ESI): 338.1 [M+H]$^+$.

(5-Fluoro-1H-benzoimidazol-2-yl)-phenyl-amine (3m)

![Chemical Structure](image)

The compound was prepared according to the general procedure, from 4-Fluoro-benzene-1,2-diamine (0.1 g, 0.793 mmol), N-Phenyl-dithiocarbamic acid methyl ester (0.159 g, 0.873 mmol) and K$_2$CO$_3$ (0.329 g, 2.38 mmol) in the presence of CuO (0.012 g, 0.158 mmol) in DMF (2 ml) to give 0.130 g (72%) of the product as a solid; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.97 (br s, 1H, NH), 9.44 (br s, 1H, NH), 7.73-7.71 (m, 2H), 7.33-7.23 (m, 3H), 7.12-7.09 (m, 1H), 6.95-6.93 (m, 1H), 6.82-6.77 (m, 1H); $^{13}$C NMR (50 MHz, DMSO-$d_6$): δ 160.09, 155.47, 151.72, 140.61, 133.39, 128.82, 120.84, 117.28, 112.21, 107.08, 106.58, 100.17, 99.65; Mass (ESI): 228.1 [M+H]$^+$. 
(4-Chloro-phenyl)-(5-fluoro-1H-benzoimidazol-2-yl)-amine (3n)

The compound was prepared according to the general procedure, from 4-Fluoro-benzene-1,2-diamine (0.1 g, 0.793 mmol), (4-Chloro-phenyl)-dithiocarbamic acid methyl ester (0.189 g, 0.873 mmol) and K₂CO₃ (0.329 g, 2.38 mmol) in the presence of CuO (0.012 g, 0.158 mmol) in DMF (2 ml) to give 0.145 g (70%) of the product as a solid; ¹H NMR (400 MHz, DMSO-d₆): δ 11.02 (br s, 1H, NH), 9.61 (s, 1H, NH), 7.80-7.79 (m, 2H), 7.37-7.25 (m, 3H), 7.13-7.11 (m, 1H), 6.84-6.79 (m, 1H); ¹³C NMR (50 MHz, DMSO-d₆): δ 160.06, 155.44, 151.26, 139.60, 128.56, 124.12, 119.41, 118.61, 107.24, 106.75; Mass (ESI): 262.2 [M+H]⁺.

(3,4-Dimethoxy-phenyl)-(5-fluoro-1H-benzoimidazol-2-yl)-amine (3o)
The compound was prepared according to the general procedure, from 4-Fluoro-benzene-1,2-diamine (0.1 g, 0.793 mmol), (3,4-Dimethoxy-phenyl)-dithiocarbamic acid methyl ester (0.212 g, 0.873 mmol) and K$_2$CO$_3$ (0.329 g, 2.38 mmol) in the presence of CuO (0.012 g, 0.158 mmol) in DMF (2 ml) to give 0.173 g (76%) of the product as a solid; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.89 (br s, 1H, NH), 9.28 (br s, 1H, NH), 7.31-7.05 (m, 4H), 6.93-6.75 (m, 2H), 3.77 (s, 3H), 3.72 (s, 3H); $^{13}$C NMR (50 MHz, DMSO-$d_6$): δ 160.00, 155.43, 152.34, 149.06, 143.55, 134.48, 133.52, 112.87, 110.20, 109.45, 106.66, 103.98, 103.44, 56.00, 55.47; Mass (ESI): 288.2 [M+H]$^+$.

**General Experimental procedure for trisubstituted Purines:**

To a suspension of $N^4$-Methyl-$N^2$-(3-morpholin-4-yl-phenyl)-pyrimidine-2,4,5-triamine (1.0 eq) and 4-Chloro-phenyl-diithiocarbamic acid methyl ester (1.2 eq) in 2 ml of DMF were added copper oxide (0.2 eq) and potassium carbonate (2.0 eq). The resulting mixture was heated to 60 ºC and kept for 2 h. The reaction mixture was then cooled to room temperature and filtered through celite bed and washed with ethyl acetate. The combined filtrate was washed with brine and water. The organic layer was dried over sodium sulphate and concentrated in vacuo and the resulting mixture chromatographed on silica gel (DCM/MeOH, 97:3) to yield compound.
**N²-(4-Chloro-phenyl)-9-methyl-N²-(3-morpholin-4-yl-phenyl)-9H-purine-2,8-diamine (3p)**

The compound was prepared according to the general procedure, from \(N^4\)-Methyl-\(N^2\)-(3-morpholin-4-yl-phenyl)-pyrimidine-2,4,5-triamine (0.1 g, 0.333 mmol), (4-Chloro-phenyl)-diithiocarbamic acid methyl ester (0.079 g, 0.364 mmol) and \(K_2CO_3\) (0.092 g, 0.666 mmol) in the presence of CuO (0.005 g, 0.066 mmol) in DMF (2 ml) to give 0.108 g (75%) of the product as a solid; mp: 215-217 °C; IR (KBr, \(\text{cm}^{-1}\)): 2959, 2924, 1672, 1610, 1565, 1494, 1453, 1411; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 9.67 (s, 2H), 8.42 (s, 1H), 7.93 (d, \(J = 8.8\) Hz, 2H), 7.44-7.42 (m, 2H), 7.24-7.17 (m, 3H), 3.78-3.71 (m, 4H), 3.69 (s, 3H), 3.14-3.12 (m, 4H); \(^{13}\)C NMR (50MHz, DMSO-\(d_6\)): \(\delta\) 154.77, 153.01, 151.43, 149.63, 142.23, 142.16, 139.07, 128.70, 128.42, 126.95, 125.09, 119.79, 109.45, 107.81, 104.95, 66.14, 48.74, 27.60; Mass (ESI): 436.4 [M+H]^+. 
**\(N^2\)-(4-Chloro-phenyl)-9-methyl-\(N^8\)-(4-morpholin-4-yl-phenyl)-9H-purine-2,8-diamine (3q)**

The compound was prepared according to the general procedure, from \(N^2\)-(4-Chloro-phenyl)-\(N^4\)-methyl-pyrimidine-2,4,5-triamine (0.1 g, 0.4 mmol), (4-Morpholin-4-yl-phenyl)-dithiocarbamic acid methyl ester (0.117 g, 0.44 mmol) and K\(_2\)CO\(_3\) (0.110 g, 0.8 mmol) in the presence of CuO (0.006 g, 0.08 mmol) in DMF (2 ml) to give 0.134 g (77\%) of the product as a solid; mp: 268–270 °C; IR (KBr, cm\(^{-1}\)): 3255, 2961, 2803, 1606, 1553, 1537; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 9.41 (s, 1H), 8.95 (s, 1H), 8.3 (s, 1H), 7.89 (d, \(J = 8.8\) Hz, 2H), 7.74 (d, \(J = 9.2\) Hz, 2H), 7.29 (d, \(J = 8.8\) Hz, 2H), 6.96 (d, \(J = 8.8\) Hz, 2H), 3.760-3.73 (m, 4H), 3.65 (s, 3H), 3.17-3.05 (m, 4H); \(^{13}\)C NMR (50MHz, DMSO-\(d_6\)): \(\delta\) 153.87, 153.46, 150.84, 146.39, 140.84, 140.58, 132.29, 128.11, 127.84, 123.28, 119.91, 119.01, 115.62, 66.12, 49.16, 27.57; Mass (ESI): 436.1 [M+H]+.
**N²-(4-Chloro-phenyl)-9-methyl-N⁸-[4-(4-methyl-piperazin-1-yl)-phenyl]-9H-purine-2,8-diamine (3r)**

The compound was prepared according to the general procedure, from **N²-(4-Chloro-phenyl)-N⁴-methyl-pyrimidine-2,4,5-triamine** (0.1 g, 0.4 mmol), **[4-(4-Methyl-piperazin-1-yl)-phenyl]-dithiocarbamic acid methyl ester** (0.123 g, 0.44 mmol) and **K₂CO₃** (0.110 g, 0.8 mmol) in the presence of **CuO** (0.006 g, 0.08 mmol) in DMF (2 ml) to give 0.133 g (74%) of the product as a solid; mp: 191-193 °C; IR (KBr, cm⁻¹): 3259, 3046, 2802, 1606, 1557, 1514, 1490; **¹H NMR** (400 MHz, DMSO-**d₆**): δ 9.43 (s, 1H), 8.93 (s, 1H), 8.32 (s, 1H), 7.89 (d, \( J = 8.8 \) Hz, 2H), 7.71 (d, \( J = 9.2 \) Hz, 2H), 7.29 (d, \( J = 8.8 \) Hz, 2H), 6.95 (d, \( J = 8.8 \) Hz, 2H), 3.65 (s, 3H), 3.09-3.01 (m, 4H), 2.50 (s, 3H), 2.49–2.44 (m, 4H); **¹³C NMR** (50 MHz, DMSO-**d₆**): δ 153.87, 153.48, 150.89, 146.42, 140.80, 140.60, 131.97, 128.12, 127.89, 123.30, 119.97, 119.03, 115.84, 54.65, 48.76, 45.72, 27.57; Mass (ESI): 449.1 [M+H]⁺.
**N-[4-[9-Methyl-8-(4-morpholin-4-yl-phenylamino)-9H-purin-2-ylamino]-phenyl]-benzamide (3s)**

The compound was prepared according to the general procedure, from N-[4-(5-Amino-4-methylamino-pyrimidin-2-ylamino)-phenyl]-benzamide (0.1 g, 0.299 mmol), (4-Morpholin-4-yl-phenyl)dithiocarbamic acid methyl ester (0.088 g, 0.329 mmol) and K$_2$CO$_3$ (0.082 g, 0.598 mmol) in the presence of CuO (0.004 g, 0.059 mmol) in DMF (2 ml) to give 0.117 g (75%) of the product as a solid; mp: 319-320 °C; IR (KBr, cm$^{-1}$): 3335, 2927, 2857, 1603, 1568, 1524, 1436, 1409, 1323; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.08 (s, 1H), 9.22 (s, 1H), 8.92 (s, 1H), 8.31 (s, 1H), 7.96 (d, $J = 6.8$ Hz, 2H), 7.81 (d, $J = 9.2$ Hz, 2H), 7.74 (d, $J = 9.2$ Hz, 2H), 7.65 (d, $J = 9.2$ Hz, 2H), 7.57-7.50 (m, 3H), 6.96 (d, $J = 8.8$ Hz, 2H), 3.76-3.73 (m, 4H), 3.66 (s, 3H), 3.07-3.04 (m, 4H); $^{13}$C NMR (50MHz, DMSO-$d_6$): $\delta$ 164.98, 154.38, 53.50, 150.62, 146.35, 141.09, 137.73, 135.17, 132.42, 131.89, 131.23, 128.27, 127.49, 120.97, 119.89, 117.79, 115.65, 66.14, 49.20, 27.56; Mass (ESI): 521.6 [M+H]$^+$. 
N-{4-[9-Methyl-2-(3-morpholin-4-yl-phenylamino)-9H-purin-8-ylamino]-phenyl}-benzamide (3t)

The compound was prepared according to the general procedure, from N⁴-Methyl-N²-(3-morpholin-4-yl-phenyl)-pyrimidine-2,4,5-triamine (0.1 g, 0.333 mmol), (4-Benzoylamino-phenyl)-dithiocarbamic acid methyl ester (0.110 g, 0.366 mmol) and K₂CO₃ (0.092 g, 0.666 mmol) in the presence of CuO (0.005 g, 0.066 mmol) in DMF (2 ml) to give 0.128 g (74%) of the product as a solid; ¹³C NMR (50 MHz, DMSO-δ₆): δ 165.07, 154.50, 153.15, 151.37, 150.10, 142.14, 141.53, 135.92, 134.98, 133.29, 131.29, 128.67, 128.24, 127.49, 127.13, 120.94, 118.63, 109.38, 107.73, 104.87, 66.13, 48.7, 27.58; Mass (ESI): 521.2 [M+H]⁺.

N-{4-[9-Methyl-2-[3-(2-morpholin-4-yl-ethoxy)-phenylamino]-9H-purin-8-ylamino]-phenyl}-benzamide (3u)

The compound was prepared according to the general procedure, from N⁴-Methyl-N²-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrimidine-2,4,5-triamine (0.1 g, 0.290 mmol), (4-Benzoylamino-
phenyl)-dithiocarbamic acid methyl ester (0.096 g, 0.319 mmol) and K₂CO₃ (0.080 g, 0.581 mmol) in the presence of CuO (0.004 g, 0.058 mmol) in DMF (2 ml) to give 0.119 g (73%) of the product as a solid; IR (KBr, cm⁻¹): 3248, 3120, 2951, 1647, 1597, 1533, 1112; ^1H NMR (400 MHz, DMSO-d₆): δ 10.18 (s, 1H), 9.26 (s, 1H), 9.15 (s, 1H), 8.38 (s, 1H), 7.97-7.95 (m, 2H), 7.87-7.85 (m, 2H), 7.75-7.73 (m, 2H), 7.63-7.51 (m, 4H), 7.38-7.35 (m, 1H), 7.15-7.11 (m, 1H), 6.48-6.45 (m, 1H), 4.10-4.04 (m, 3H), 3.68 (s, 3H), 3.60-3.58 (m, 4H), 3.17-3.16 (m, 2H), 2.72-2.69 (m, 2H); ^13C NMR (50 MHz, DMSO-d₆): δ 165.09, 158.67, 154.32, 153.22, 150.23, 142.67, 141.47, 135.89, 135.00, 133.32, 131.30, 128.98, 128.25, 127.50, 127.40, 120.95, 118.64, 110.41, 105.99, 104.16, 66.18, 65.02, 57.04, 53.63, 27.61; Mass (ESI): 565.3 [M+H]^+.

**Cyclopropanecarboxylic acid {4-[8-(4-fluoro-phenylamino)-9-methyl-9H-purin-2-ylamino]-phenyl}-amide (3v)**

![Chemical Structure](image)

The compound was prepared according to the general procedure, from Cyclopropanecarboxylic acid [4-(5-amino-4-methylamino-pyrimidin-2-ylamino)-phenyl]-amide (0.1 g, 0.335 mmol), (4-Fluoro-phenyl)-dithiocarbamic acid methyl ester (0.074 g, 0.368 mmol) and K₂CO₃ (0.092 g, 0.670 mmol) in the presence of CuO
(0.005 g, 0.067 mmol) in DMF (2 ml) to give 0.107 g (76%) of the product as a solid; IR (KBr, cm⁻¹): 3325, 2937, 1660, 1622, 1408, 1033; ¹H NMR (400 MHz, DMSO-d₆): δ 10.02 (m, 2H), 9.25-9.19 (m, 2H), 8.34 (s, 1H), 7.94-7.90 (m, 2H), 7.74-7.72 (m, 2H), 7.48-7.45 (m, 2H), 7.20-7.15 (m, 2H), 3.67 (s, 3H), 1.78-1.76 (m, 1H), 0.79-0.77 (m, 4H); ¹³C NMR (50 MHz, DMSO-d₆): δ 170.91, 154.64, 153.31, 150.13, 141.70, 136.87, 136.56, 132.51, 127.01, 125.07, 120.05, 119.97, 119.45, 118.03, 115.11, 114.89, 27.79, 14.30, 8.35; Mass (ESI): 418.2 [M+H]⁺.

**N-[4-[8-(4-Fluoro-phenylamino)-9-methyl-9H-purin-2-ylamino]-phenyl]-benzamide (3w)**

The compound was prepared according to the general procedure, from **N-[4-(5-Amino-4-methylamino-pyrimidin-2-ylamino)-phenyl]-benzamide** (0.1 g, 0.299 mmol), (4-Fluoro-phenyl)dithiocarbamic acid methyl ester (0.066 g, 0.329 mmol) and K₂CO₃ (0.082 g, 0.598 mmol) in the presence of CuO (0.004 g, 0.059 mmol) in DMF (2 ml) to give 0.105 g (77%) of the product as a solid; IR (KBr, cm⁻¹): 3338, 3099, 1651, 1402, 1213; ¹H NMR (400 MHz, DMSO-d₆): δ 10.10 (s, 1H), 9.28 (s, 1H), 9.19 (s, 1H), 8.37 (s, 1H), 7.97-7.81 (m, 6H), 7.67-7.50 (m, 5H), 7.21-7.17 (m, 2H), 3.72 (s, 3H); ¹³C NMR (50 MHz, DMSO-d₆): δ 165.06, 159.65, 154.70, 153.39, 150.21, 141.89,
137.72, 136.59, 136.54, 135.25, 132.08, 131.36, 128.39, 127.60, 127.18, 121.06, 120.21, 120.06, 117.97, 115.45, 115.01, 27.82; Mass [ESI]: 454.3 [M+H]+.

**4-Chloro-N-[4-(9-methyl-2-morpholin-4-yl-9H-purin-8-ylamino)-phenyl]-benzamide (3x)**

The compound was prepared according to the general procedure, from \(N^4\)-Methyl-2-morpholin-4-yl-pyrimidine-4,5-diamine (0.1 g, 0.478 mmol), \([4-(4-Chloro-benzoylamino)-phenyl]-dithiocarbamic acid methyl ester (0.176 g, 0.526 mmol) and K\(_2\)CO\(_3\) (0.132 g, .956 mmol) in the presence of CuO (0.007 g, 0.095 mmol) in DMF (2 ml) to give 0.173 g (78%) of the product as a solid; IR (KBr, cm\(^{-1}\)): 3329, 3099, 2848, 1654, 1597, 1485, 1415, 1112, 792; \(^{13}\)C NMR (50 MHz, DMSO-\(d_6\)): \(\delta\) 163.93, 157.15, 153.54, 149.93, 141.53, 136.16, 133.68, 132.96, 131.28, 129.47, 128.35, 127.50, 126.45, 121.00, 118.46, 66.06, 44.89, 27.44; Mass (ESI): 464.1 [M+H]+.
4-Chloro-N-[4-[9-methyl-2-(4-morpholin-4-yl-phenylamino)-9H-purin-8-ylamino]-phenyl]-benzamide (3y)

The compound was prepared according to the general procedure, from \( N^4 \)-Methyl-\( N^2 \)-(4-morpholin-4-yl-phenyl)-pyrimidine-2,4,5-triamine (0.1 g, 0.333 mmol), [4-(4-Chloro-benzoylamino)-phenyl]-dithiocarbamic acid methyl ester (0.123 g, 0.366 mmol) and \( K_2 \text{CO}_3 \) (0.092 g, 0.666 mmol) in the presence of CuO (0.005 g, 0.066 mmol) in DMF (2 ml) to give 0.140 g (76%) of the product as a solid; IR (KBr, cm\(^{-1}\)): 3285, 1660, 1606, 1311, 1226, 787; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) 10.24 (s, 1H), 9.11 (s, 1H), 9.01 (s, 1H), 8.32 (s, 1H), 7.99 (d, \( J = 6.8 \) Hz, 2H), 7.86 (d, \( J = 9.2 \) Hz, 2H), 7.73-7.59 (m, 6H), 6.88 (d, \( J = 8.8 \) Hz, 2H), 3.75-3.73 (m, 4H), 3.66 (s, 3H), 3.03-3.00 (m, 4H); \(^{13}\)C NMR (50 MHz, DMSO-\(d_6\)): \( \delta \) 163.90, 154.84, 153.31, 149.80, 145.23, 141.61, 136.12, 134.24, 133.65, 132.94, 129.43, 128.32, 120.99, 119.08, 118.47, 115.76, 66.17, 49.54, 27.58; Mass (ESI): 555.2 [M+H]\(^+\).
4-Chloro-N-{4-{9-methyl-2-[4-{4-methyl-piperazin-1-yl}-phenylamino]-9H-purin-8-ylamino]-phenyl}-benzamide (3z)

The compound was prepared according to the general procedure, from \( N^4\)-Methyl-\( N^2\)-[4-{4-methyl-piperazin-1-yl}-phenyl]-pyrimidine-2,4,5-triamine (0.1 g, 0.319 mmol), [4-{4-Chloro-benzoylamino}-phenyl]-dithiocarbamic acid methyl ester (0.118 g, 0.351) and \( K_2\)CO\(_3\) (0.088 g, 0.638 mmol) in the presence of CuO (0.005 g, 0.063 mmol) in DMF (2 ml) to give 0.136 g (75%) of the product as a solid; \(^{13}\)C NMR (50 MHz, DMSO-\( d_6\)): \( \delta \) 163.91, 154.87, 153.31, 149.80, 145.17, 141.65, 136.13, 133.99, 133.65, 132.93, 129.44, 128.32, 126.85, 121.00, 120.64, 119.12, 118.46, 116.04, 54.59, 48.98, 45.53, 27.59; Mass (ESI): 566.2 [M-H]\(^+\).

Cyclopropanecarboxylic acid \( \{4-{9-methyl-2-[4-{4-methyl-piperazin-1-yl}-phenylamino]-9H-purin-8-ylamino]-phenyl}\)-amide (3a1)
The compound was prepared according to the general procedure, from N4-Methyl-N2-[4-{4-methyl-piperazin-1-yl}-phenyl]-pyrimidine-2,4,5-triamine (0.1 g, 0.319 mmol), [4-(Cyclopropanecarbonyl-amino)-phenyl]-dithiocarbamic acid methyl ester (0.093 g, 0.351 mmol) and K2CO3 (0.088 g, 0.638 mmol) in the presence of CuO (0.005 g, 0.063 mmol) in DMF (2 ml) to give 0.120 g (76%) of the product as a solid; 13C NMR (50 MHz, DMSO-d6): δ 171.06, 154.84, 153.35, 149.90, 145.17, 141.53, 135.31, 134.06, 133.60, 126.90, 119.49, 119.13, 118.71, 116.04, 54.62, 49.01, 45.56, 27.57, 14.42, 6.94; Mass (ESI): 498.2 [M+H]+.

4-Chloro-N-[4-{2-(3,4-dimethoxy-phenylamino)-9-methyl-9H-purin-8-ylamino]-phenyl]-benzamide (3b1)

The compound was prepared according to the general procedure, from N2-{3,4-Dimethoxy-phenyl}-N4-methyl-pyrimidine-2,4,5-triamine (0.1 g, 0.363 mmol), [4-(4-Chloro-benzoylamino)-phenyl]-dithiocarbamic acid methyl ester (0.134 g, 0.399 mmol) and K2CO3 (0.100 g, 0.726 mmol) in the presence of CuO (0.006 g, 0.072 mmol) in DMF (2 ml) to give 0.150 g (78%) of the product as a solid; 13C NMR (50 MHz, DMSO-d6): δ 163.98, 154.60, 153.28, 150.01, 148.61, 142.98, 141.33, 136.18, 136.04, 135.30, 133.66, 133.10,
129.46, 128.34, 126.80, 121.03, 118.69, 112.66, 109.85, 103.88, 56.02, 55.37, 27.59; Mass (ESI): 530.1 [M+H]^+.

**Cyclopropanecarboxylic acid {4-[9-methyl-2-(4-morpholin-4-yl-phenylamino)-9H-purin-8-ylamino]-phenyl}-amide (3c1)**

The compound was prepared according to the general procedure, from $N^4$-Methyl-$N^2$-(4-morpholin-4-yl-phenyl)-pyrimidine-2,4,5-triamine (0.1 g, 0.333 mmol), [4-(Cyclopropanecarbonyl-amino)-phenyl]-dithiocarbamic acid methyl ester (0.097 g, 0.366 mmol) and K$_2$CO$_3$ (0.091 g, 0.666 mmol) in the presence of CuO (0.005 g, 0.066 mmol) in DMF (2 ml) to give 0.118 g (73%) of the product as a solid; mp: 300-302 °C; IR (KBr, cm$^{-1}$): 3314, 3094, 2962, 2847, 1664, 1613, 1588, 1522, 1437, 1409, 1315; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.07 (s, 1H), 9.03 (d, $J = 12.8$ Hz, 2H), 8.29 (s, 1H), 7.79 (d, $J = 9.2$ Hz, 2H), 7.69 (d, $J = 8.8$ Hz, 2H), 7.55 (d, $J = 8.8$ Hz, 2H), 6.89 (d, $J = 9.2$ Hz, 2H), 3.75 (m, 4H), 3.64 (s, 3H), 3.30 (m, 4H), 1.78 (m, 1H), 0.80 (m, 4H); $^{13}$C NMR (50 MHz, DMSO-$d_6$): δ 171.11, 154.87, 153.41, 149.98, 145.29, 141.55, 134.30, 133.65, 126.95, 119.53, 119.16, 118.75, 115.80, 66.18, 49.55, 27.53, 14.38, 6.88; Mass (ESI): 485.0 [M+H]^+.
SPECTRA
3.5 Spectra
Figure 3.6: 1H NMR spectrum of (4-Chloro-phenyl)-6-azino-1F-
benzimidazol-2yl-amine
Figure 3.7: H NMR spectrum of 2',4'-dihydroxy-4'-(5-nitro-1H-benzo[d]imidazol-2-yl)aniline.
Figure 3.9: 1H NMR spectrum of 3',4'-dimethoxy-3',4'-dihydro-1,1'-bi-naphthyl.
Figure 3.13: 1H NMR spectrum of 4-Chloro-phenyl-[5-methyl-1H-]
benzimidazol-2-yl-amine
Figure 3.15: 13C NMR spectrum of (4-Chloro-phenoxy)-4-methyl-1,4-
benzoxindole-2-ylamine
Figure 3.16: $^1$H NMR spectrum of (3,4-Dimethoxyphenyl)trimethyl-1H-oxazol-2-yl-amine
Figure 3.18: $\mu$C NMR spectrum of $O_4$-Dimethoxyphenyl-$G$-methyl-$L$-F benzimidazole-2-$y$-amine.
Figure 3.19: H-NMR spectrum of 6-Methoxy-1H-benzimidazol-2-yl-phenyl amine

Analysis: Research, Discovery Research, DrH
H-NMR (CDCl3, 400 MHz):

δ (ppm): 7.30 (1H, d, J=8.4 Hz), 7.50 (2H, m), 7.60 (1H, s), 6.50 (1H, d, J=8.4 Hz), 4.00 (3H, s), 3.00 (2H, m), 2.50 (2H, m), 1.50 (2H, m)
Figure 3.21: H-NMR spectrum of (4-Chloro-phenyl)-[S-methyl-1H]-benzimidazol-2-yl)-amine
Figure 3.22. Mass spectrum of 4-Chloro-phenyl-5-methylpyridine.
Figure 2.23: H NMR spectrum of 2-(Dinitrophenyl)-6-mercapto-1H-
benzoimidazole-2-Yl-amine.
Figure 3.25: 1H NMR spectrum of (3,4-Dimethoxyphenyl)15-anthroxy-1H-benzimidazol-2-ylamine
Figure 3.26: 1H NMR spectrum of 5,6-Dichloro-1H-benzoimidazole-2-yl-phenyl-amine
Phencyamine

Figure 3.28: 13C NMR spectrum of (6-Dichloro-1H-benzothiazolo-2,3-\textit{H})-

[Diagram of the molecule with labeled peaks]

ppm

0 20 40 60 80 100 120 140

140
Figure 3.22: Mass spectrum of 3,4-Dichloro-1,7-benzimidazol-2-yl-4,4-dimethoxy-phenylamine
Figure 2.35: Mass spectrum of (5-fluoro-1H-benzimidazol-2-yl)-phenyl-NH rigid linker.

Schematics:

Chemical structures and specifications.

Supporting information.
Figure 3.36: 13C NMR spectrum of (5-Fluoro-1H-benzimidazole-2-yl)-phenylamine
Figure 3.37: 1H NMR spectrum of 4-chloro-pently-5-hydroxy-1H-benzimidazol-2-yl-amine.
FIGURE 3.38: Mass spectrum of 4-Chloro-phenyl-5-H-pyrrole -1H-

benzimidazole-2-Y-amine

Max. 4 mg CPR

Sample 2 (Sample 1 + 2*200 mg (Rutile Sep) suspended (55.89 to 52.07 mg)

Sample 2: 50.64 ± 0.05 µM

Extraction done: 11.10.99
Prep. done: 11.10.99
Figure 3.39: 13C NMR spectrum of (4-Chloro-phenyl)-5-fluoro-1H-benzimidazole-2-ylamine
Figure 3.48: 1H-NMR spectrum of [4-Chloro-phenyl]-o-methyl-N-[4-methyl-piperazine-1-yl-piperazin-1-yl]-oH-purin-2,8-diamine.
Figure 3.49:
N-4,19-Methyl-8-(4-morpholin-4-yl-phenylamino)-9-H-purin-2-ylaminophenyl-benzamide
Figure 3.53:  
N-[4-[9-Methyl-2-(3-morpholin-4-yl)phenylamino]-9-H-purin-8-ylaminol-phenyl]-benzamid
Figure 3.56: N-(4-(9-Methyl-2-[3-(2-morpholin-4-yl-ethoxy)-phenylamino]-9H-purin-8-ylamino)-phenyl)-benzamide
Figure 3.61: (Cylopropylcarbonyl)-5-methyl-1H-pyrrole-2-carboxylic acid (4-fluoro-phenylamino)-9-methyl-1H-pyrrole-2-carboxylic acid
Figure 3.76: Cyclopentanoic acid (4-methyl)-2-[(4-methyl-piperidin-1-yl)-3-piperidinyl]piperidine

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