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Synthesis and Application of Piperazine Derivatives using different Metal based ionic liquid as a catalyst.

Rohan Tembare^{1*}, Dr Ritu M Gilhotra¹

¹Gyan Vihar School of Pharmacy, Suresh Gyan Vihar University, Jaipur, Rajasthan, India.

*Corresponding Author: Rohan Tembare

E-mail: rohantembare18@gmail.com

ABSTRACT

This study explores the synthesis and characterization of piperazine derivatives using various metal-based ionic liquids (ILs) as catalysts. Metal-based ILs were employed to enhance reaction efficiency, offering a green alternative to conventional methods. The catalytic performance of different ILs was evaluated in terms of reaction time, yield, and recyclability. Among the ILs tested, [Pd, Cu, Ru, Mg, Ir, etc metal IL] demonstrated superior catalytic activity, attributed to its strong Lewis acidity and efficient coordination with the piperazine precursors. The synthesized compounds were characterized using spectroscopic techniques, including TLC, Melting Point, (NMR), (FTIR), and (MS), which confirmed their successful formation. The reaction mechanism was proposed, highlighting the role of the metal center in promoting cyclization by enhancing the

nucleophilicity of the amine group. The results suggest that these piperazine derivatives possess potential applications in pharmaceuticals due to their bioactive properties. The study demonstrates that metal-based ionic liquids are promising catalysts for piperazine synthesis, offering advantages in terms of sustainability, efficiency, and reusability. Future work will focus on optimizing reaction conditions for industrial-scale applications and further exploring the bioactivity of the synthesized derivatives.

Keyword:

Ionic liquid, catalyst, Synthesis, applications, piperazine derivatives, etc.

INTRODUCTION

Piperazines are commonly used in pharmaceuticals. In order to develop the fascinating building blocks that will be used in the formulation of the new medicine, these chemicals require further development. There is a significant contribution that the existence of the piperazine core makes to the process of creating of ailments. In the 1950s, it was discovered that piperazine was effective. In medicinal chemistry, piperazine and its derivatives have developed considerably, from their original usage as a successful therapy for threadworm infections in infants to a wider range of pharmacological uses. Originally noted for their anthelmintic qualities, piperazine-based compounds have now attracted notice for their many medicinal possibilities.

Many piperazine analogues have been created and studied in recent years for a broad range of biological functions. These include encouraging outcomes in fields including anticancer, antioxidant, and cognitive-enhancing benefits. They have also shown notable promise as antiviral, antibacterial, and antimicrobial drugs. Studies done after piperazine compounds show antifungal, anti-inflammatory, anti-HIV-1, and anti-diabetic qualities. Their uses as antidepressants,

anxiolytics, and anticonvulsants have also spread to treating illnesses including malaria and central nervous system problems. The wide pharmacological spectrum emphasizes the adaptability of the piperazine scaffold, therefore underlining its usefulness as a structural core in drug discovery and development. [1-27] In addition, piperazines synthons are of great assistance in the chemical modification of a wide variety of pharmaceuticals and natural goods.

The agricultural and pharmaceutical industries both make use of piperazine as a starting ingredient in their commercial processing operations. The modification of the piperazine moiety through chemical means has resulted in the synthesis and fabrication of monodisperse microsphere materials, neuroprotective iron chelators. Piperazine ring is present in a number of key pharmaceuticals that are now on the market. Some examples of these drugs. The research (Table 1) provides a notable benchmark for these drugs. [28-30]

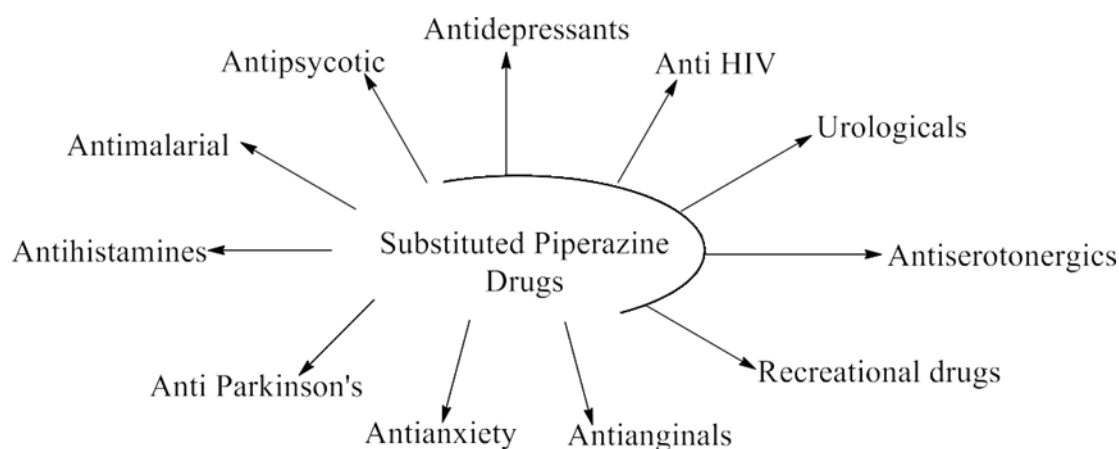


Figure 1: Therapeutic activity differences in medicines with replaced piperazine.

Versatile ligands for metal complex formation include piperazine and its derivatives including nitrogen and other possible donor atoms. Changing both secondary nitrogen atoms in the piperazine ring may result in either symmetrical or asymmetrical mono- and disubstituted derivatives. These ligands are very flexible and let simple structural changes fit certain

coordination requirements. In the piperazine ring, the nitrogen atoms may align with either a single metal center or with two separate metal ions. The piperazine ring changes shape as it binds to one metal ion, usually becoming a less stable boat shape because of ring strain. The nitrogen atoms are often replaced with functional groups to improve the coordinating capacity (tacticity) of such ligands, hence providing a great variety of coordination modes. Ostermeier et al. stand out especially as they created. This ligand may be either bidentate or tetradentate toward iron(II). In its bidentate configuration, it connects two iron centers to create a bimetallic complex (Figure 2).

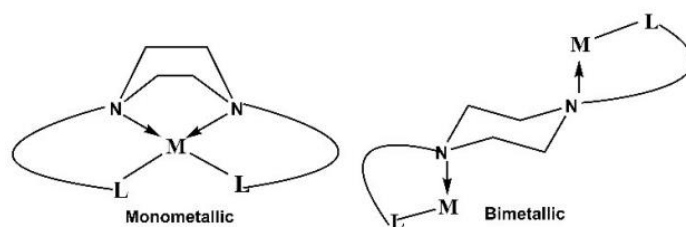


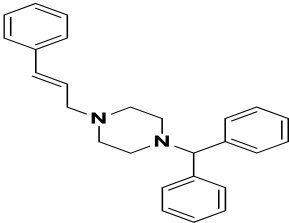
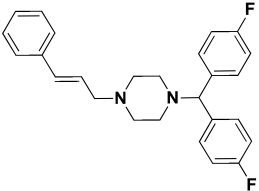
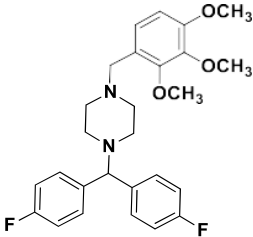
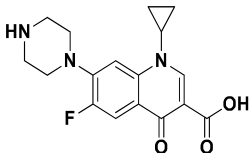
Figure 2: Two binding patterns of piperazine-based ligands

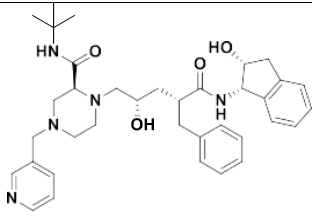
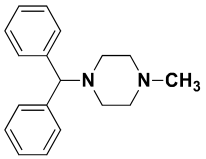
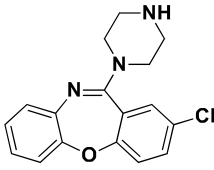
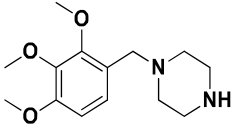
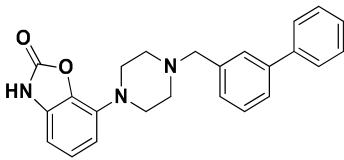
Piperazine's chemical characteristics:

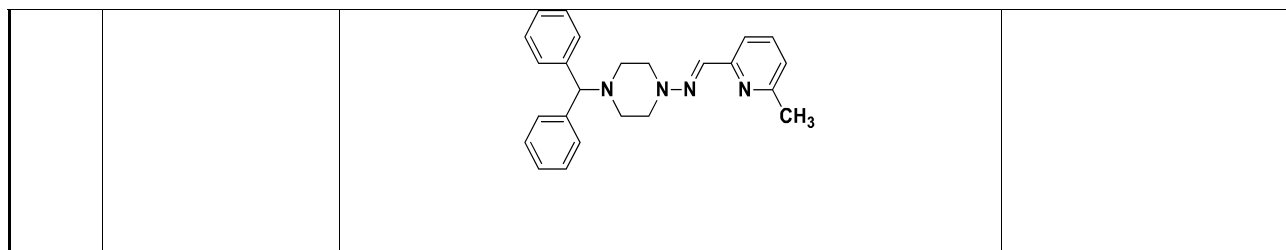
A colorless, volatile chemical, piperazine crystallizes as hexahydrate crystals. It is highly soluble in both organic and aqueous media. Piperazine exhibits mild basicity at 25 °C, as indicated by its two pKb values of 5.35 and 9.73 [31].

Table 1. Marketed piperazine pharmaceutical molecules available with several therapeutic uses [52-67].

Sr. No	Name of the Drug	Structure of the Drug	Therapeutic Uses

1.	Cinnarizine [32]		Nor-adrenaline antagonist
2.	Flunarizine [33]		Calcium channel blocker
3.	Lomerizine [34]		Calcium channel blocker
4.	Ciprofloxacin [35]		Antibiotic
5.	Indinavir [36]		(HIV-1) protease inhibitor

			
6.	Cyclizine [37]		Antihistamine
7.	Amoxapine [38]		Antidepressant
8.	Trimetazidine [39]		Antisclerotic
9.	Bifeprunox [40]		Antipsychotic
10.	Ropizine [41]		Anticonvulsant



Synthesis of Piperazine:

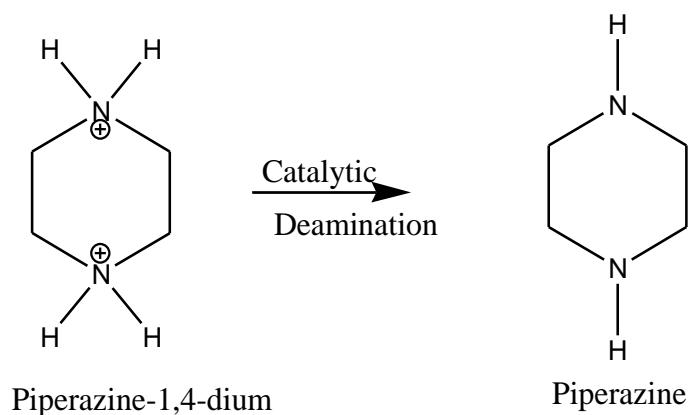


Figure.3 Synthesis of piperazine [42].

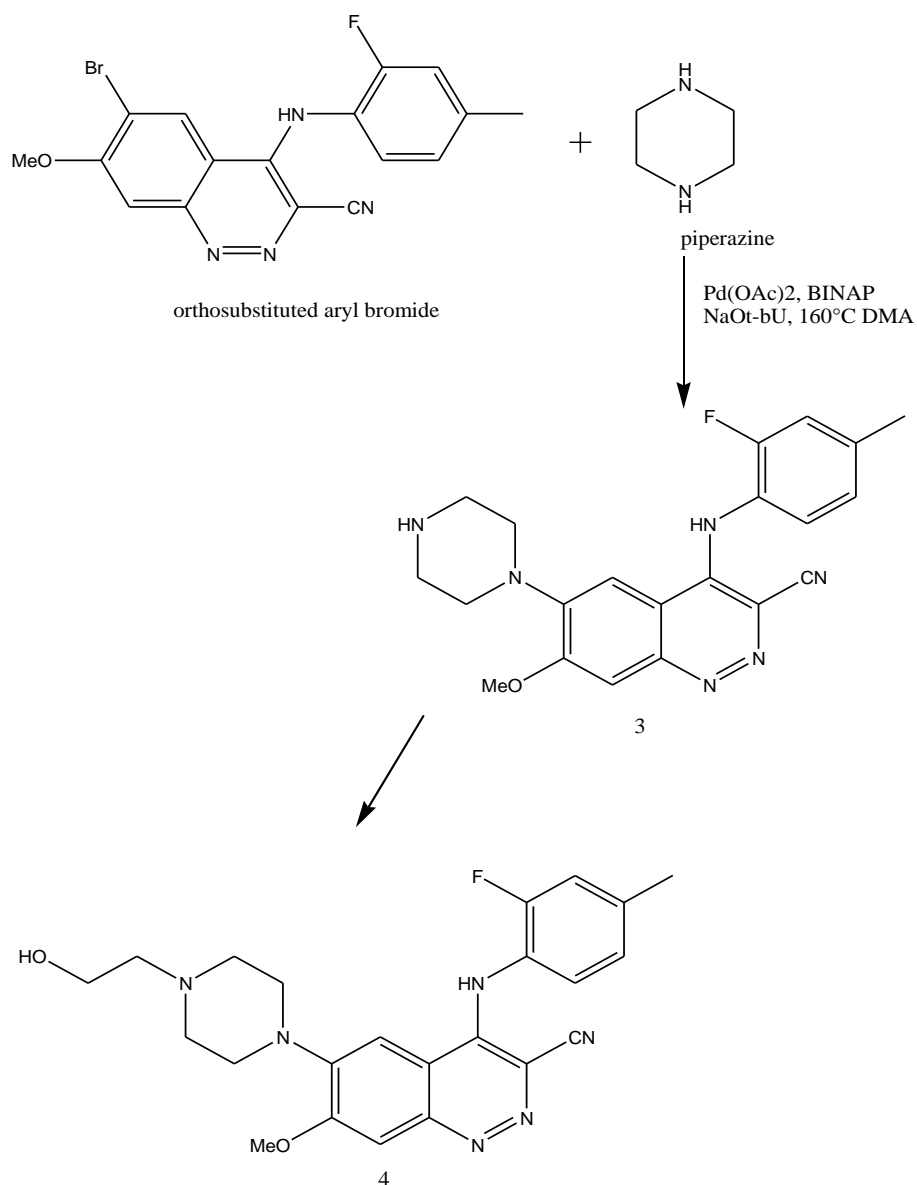
Synthesis of Piperazine derivatives using different metal based ionic liquid as a catalyst:

Buchwald hartwig coupling in synthesis of piperazine containing drugs

Many papers have shown how well palladium-catalyzed other amino derivatives work. Studies by academics [43–47] have underlined the major part palladium catalysts play in enabling these changes by demonstrating their adaptability in generating carbon-nitrogen (C–N) bonds. Further studies [48–51] have confirmed these results by showing that under palladium catalysis a broad spectrum of amino compounds including primary and secondary amines as well as heterocyclic amines can effectively couple with aryl halides. Due to their great efficiency, selectivity, and

compatibility with various functional groups, these reactions are highly useful in the manufacture of complicated compounds, particularly in pharmaceutical and material chemistry. The production of this Buchwald Hartwig amination is a unique and quite straightforward approach medicinal compounds that contain substituted piperazine. These molecules are typically difficult to manufacture in other ways. In comparison to the traditional this direct N-arylation of piperazines presents a notable avenue of synthesis at the same time as nucleophilic. When compared to C-C coupling processes, the cross-coupling reactions that are catalyzed by palladium for the production of C-N bonds have a greater number of constraints.

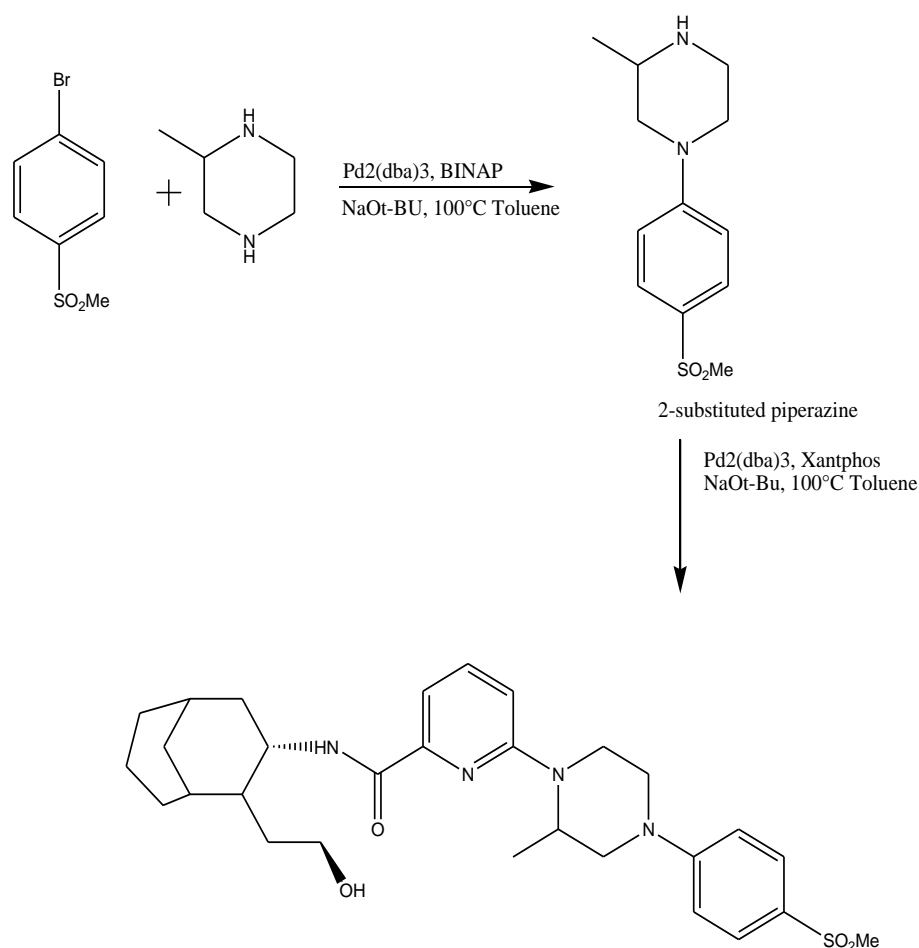
Unprotected piperazine N-arylation in the presence of BINAP ligand at high temperatures in dimethyl acetamide produces intermediate (4) [52]. The catalyst used in this reaction is Pd(OAc)₂, and the base used is sodium tertiary butoxide.



Scheme 3.1

Usually, 2-substituted piperazine's arylation happens preferentially at the less sterically hindered nitrogen atom of the unprotected piperazine core. While the next arylation at the second nitrogen has varying yields from 19% to 73%, studies have indicated that the first arylation runs with moderate efficiency, producing between 55% and 59%. The steric and electronic environment

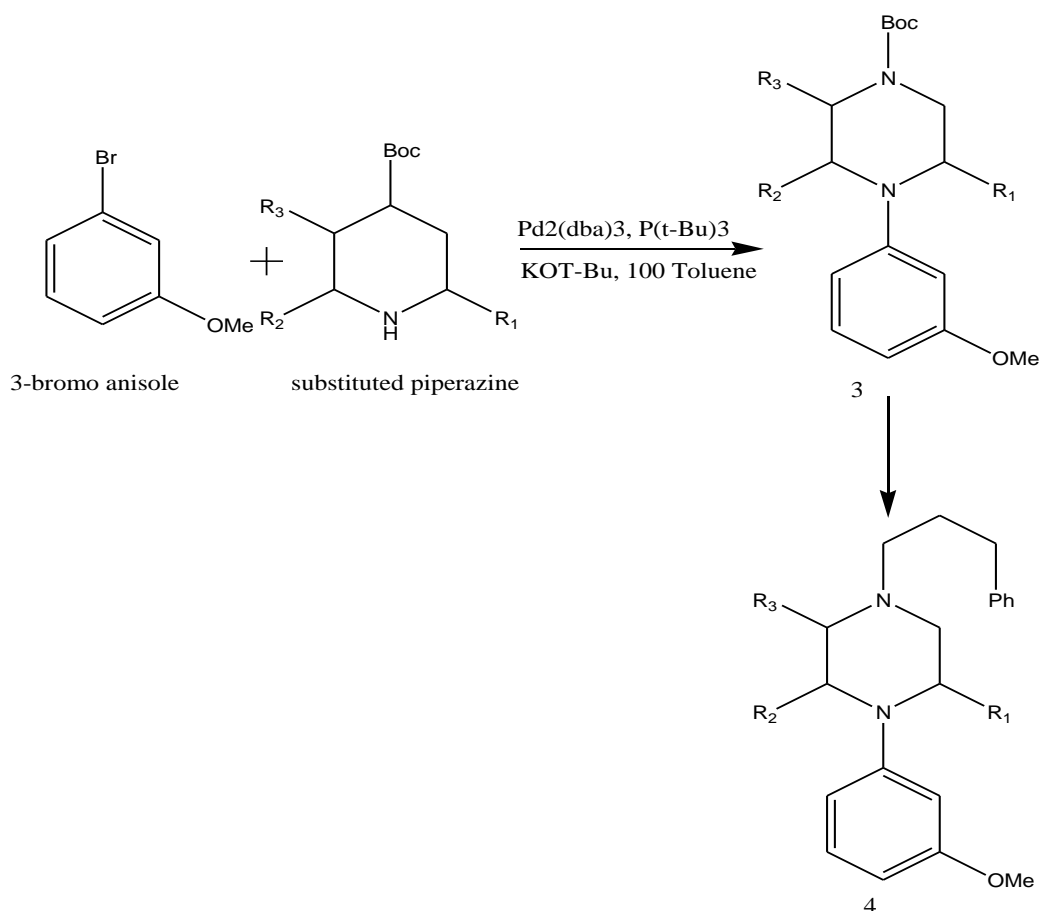
surrounding the nitrogen atoms explains this selectivity; the less hindered site is more accessible to electrophilic arylating agents. Such varied reactivity is especially beneficial in synthetic organic chemistry since it enables progressive functionalization of piperazine derivatives, which are often utilized scaffolds in drug development. Designing complicated compounds with possible therapeutic uses benefits from the ability to manage mono- versus di-arylation (Scheme .3.2) [53].



Scheme 3.2

Often, the less hindered nitrogen is temporarily shielded to guarantee selective arylation. Carroll et al. guided the coupling of 3-bromoanisole to the preferred nitrogen location using an N-Boc-protected 2-substituted piperazine. By means of intermediate compound 3, this approach allowed

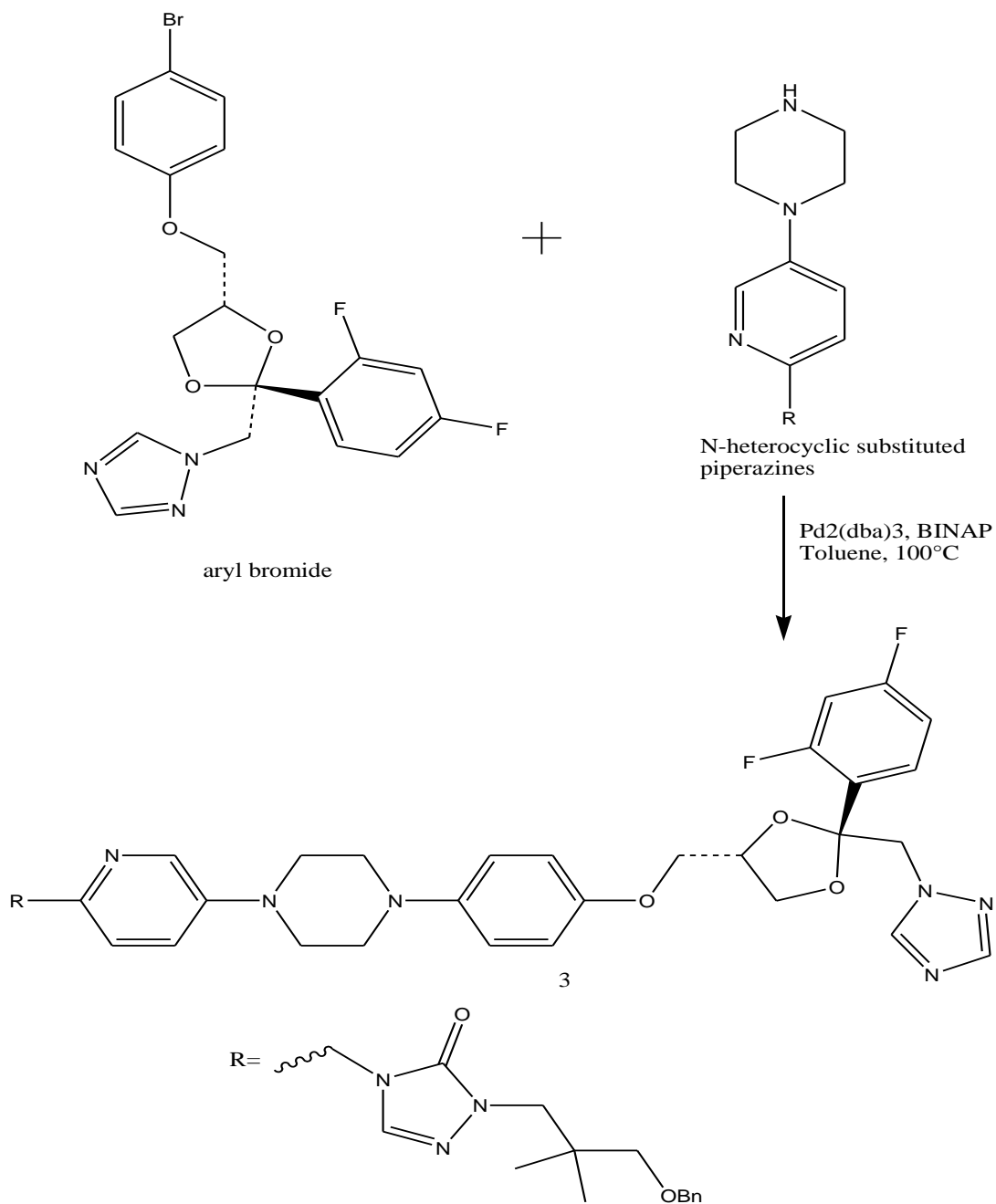
the production of opioid receptor antagonist 4, with yields varying from 46% to 98%. The synthesis at 100°C (yield 46-98%) in aprotic solvent toluene using potassium tertiary butoxide as base comprises. A palladium-based catalyst specifically Pd₂(dba)₃ along with a large ligand such as P(t-Bu)₃ can be used to couple an aryl halide with a substituted piperazine. This synergy enables the reaction to proceed smoothly and lets the two molecules combine properly. To reach the goal in following processes (Scheme 3.3), Boc deprotection and next N-alkylation were done [54].



Scheme 3.3

Yang and his team created a novel antifungal medication named compound 3 that has improved solubility and bioavailability over current triazole-based medications. Using a BINAP ligand and a palladium catalyst (Pd₂(dba)₃), they coupled an aryl bromide (compound 1) with several N-

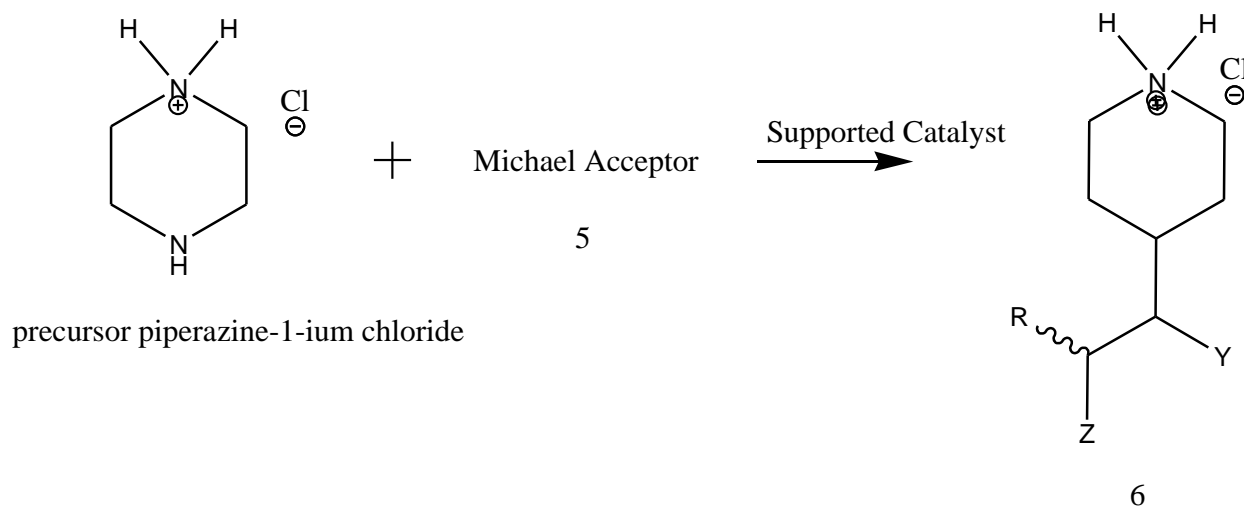
heterocyclic substituted piperazines (compound 2). As seen in Scheme 3.4, the reaction produced 67% of the end product. [55].



Scheme 3.4

Aza-Michael addition reaction:

[56] A straightforward method was reported for making N-monosubstituted piperazine compounds through a mono-aza-Michael addition reaction. In this process, different amounts of piperazine and its salt form, piperazine-1,4-dium dichloride, were mixed in methanol to form an intermediate called piperazine-1-ium chloride (compound 4) directly in the reaction mixture. Using a cation-exchange resin in an acidic environment, this intermediate then reacted with various Michael acceptors (compound 5), which have reactive to help drive the aza-Michael addition forward, leading to the final substituted products. The synthesis of the desired products (6) produced good yields. Michael Acceptor: Dimethyl Fumarate, Dimethyl maleate, etc. (Scheme 3.5)



Scheme 3.5. Formation of aza-Michael adduct

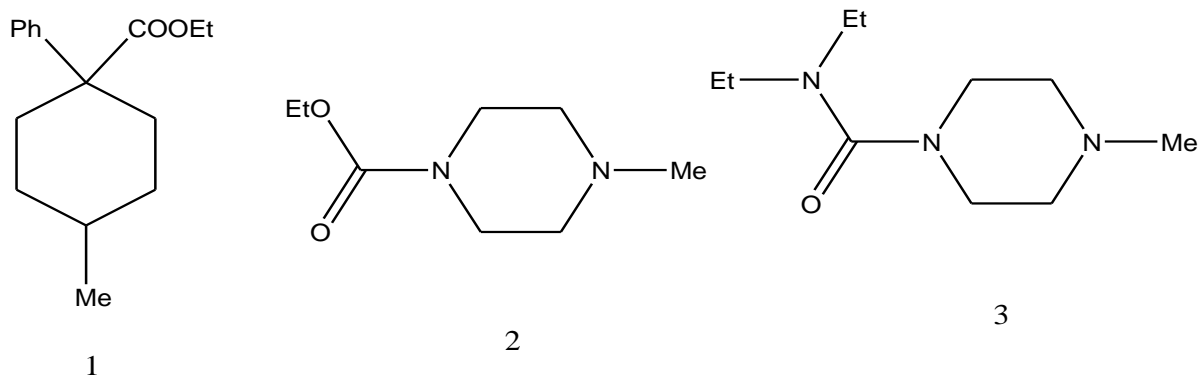
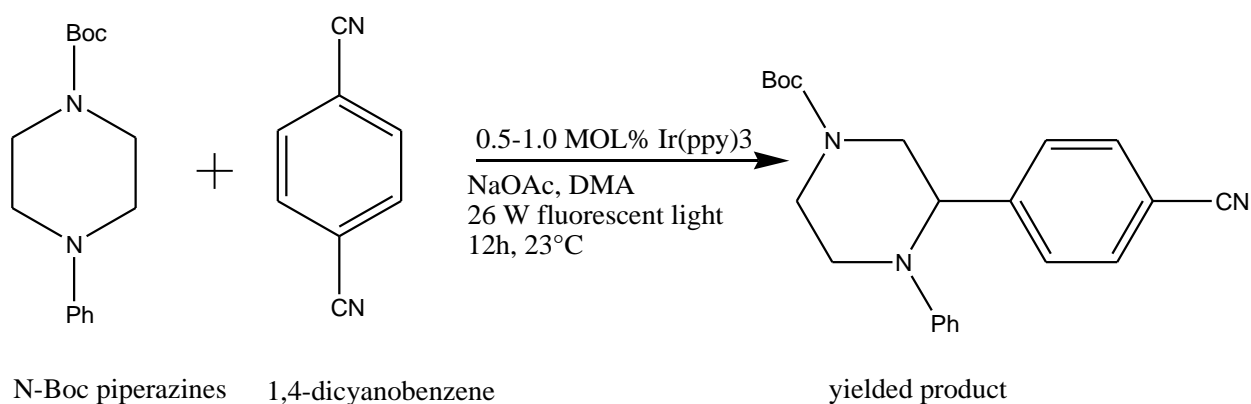


Figure.2 Mepridine's chemical structure and first derivative of 1,4-disubstituted piperazine

Photoredox α -C–H arylation:

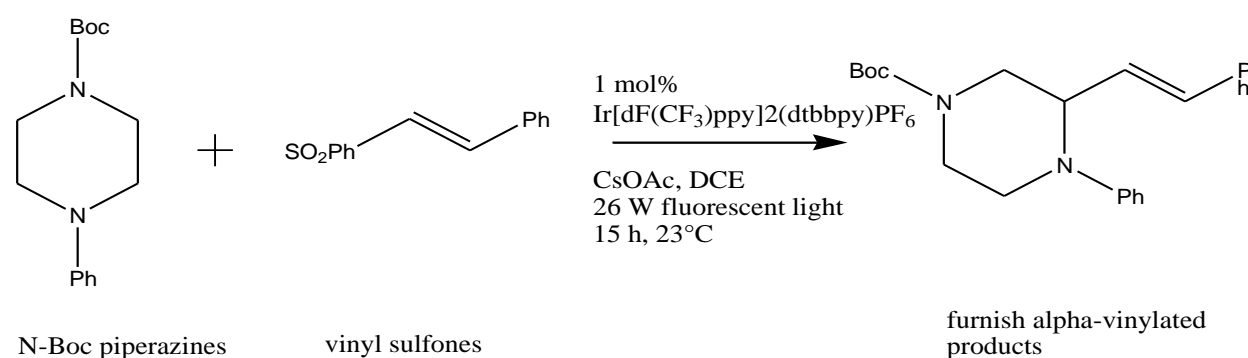
Using single-electron transfer technique, McNally et al. [57] In this reaction, Ir(ppy)₃ was used as a photocatalyst to carry out α -C–H arylation. Successfully attached to the alpha position of the piperazine ring. The reaction was done in dimethylacetamide (DMA) as the solvent, desired product, as shown in Scheme 3.6.



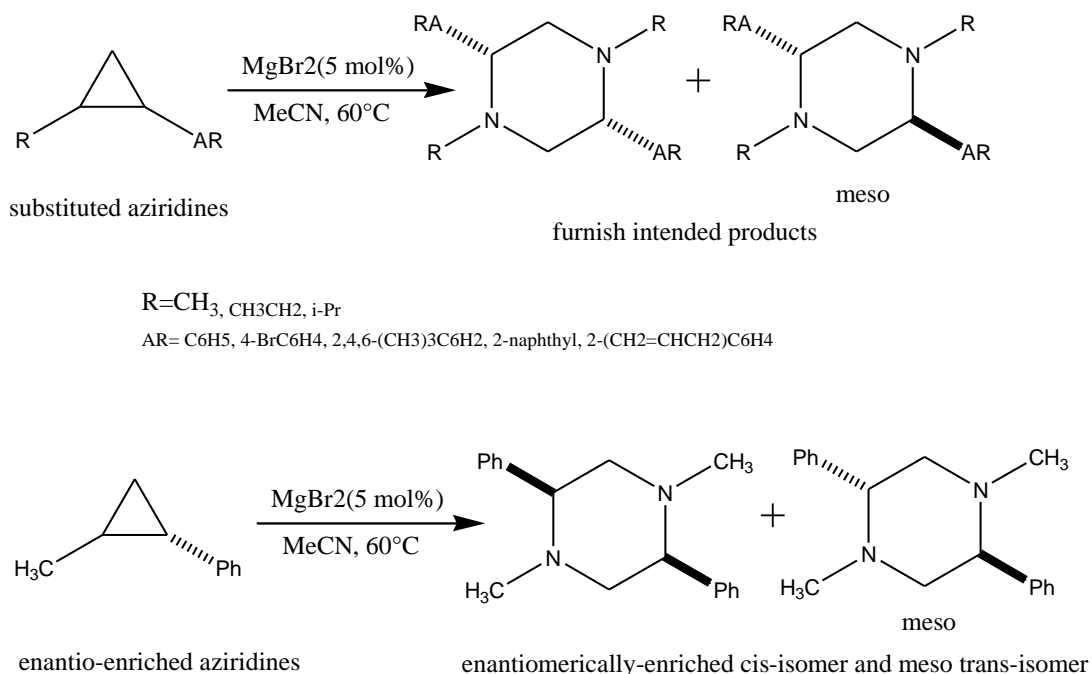
Scheme 3.6 Formation of α -C–H arylated piperazine

Photoredox α -C-H vinylation:

Carry out α -C-H vinylation on substituted piperazines, resulting in alpha-vinylated products with a high selectivity. For the best results, the reaction was done under fluorescent light using the photocatalyst IrIII[dF(CF₃)ppy]₂(dtbbpy)PF₆, with cesium acetate as the base. The process was carried out in DCE at 23 °C for 15 hours, giving the highest product yield, as shown in Scheme 3.7.

**Scheme 3.7 Photoredox α -C-H vinylation****Dimerization:**

Aziridine dimerization produced piperazine analogues, as [59] showed. Aziridines were reacted together in the presence of 5 mol% magnesium bromide as a catalyst. First, one aziridine opened its ring and then formed a new ring with another aziridine in acetonitrile at 80 °C. This reaction produced the desired product as a 1:1 mix of two diastereomers due to limited control over the stereochemistry. However, when enantiomerically enriched aziridines were used as starting materials, the reaction gave specific isomers namely, a cis-isomer and a meso trans-isomer under the same conditions, as shown in Scheme 3.8.

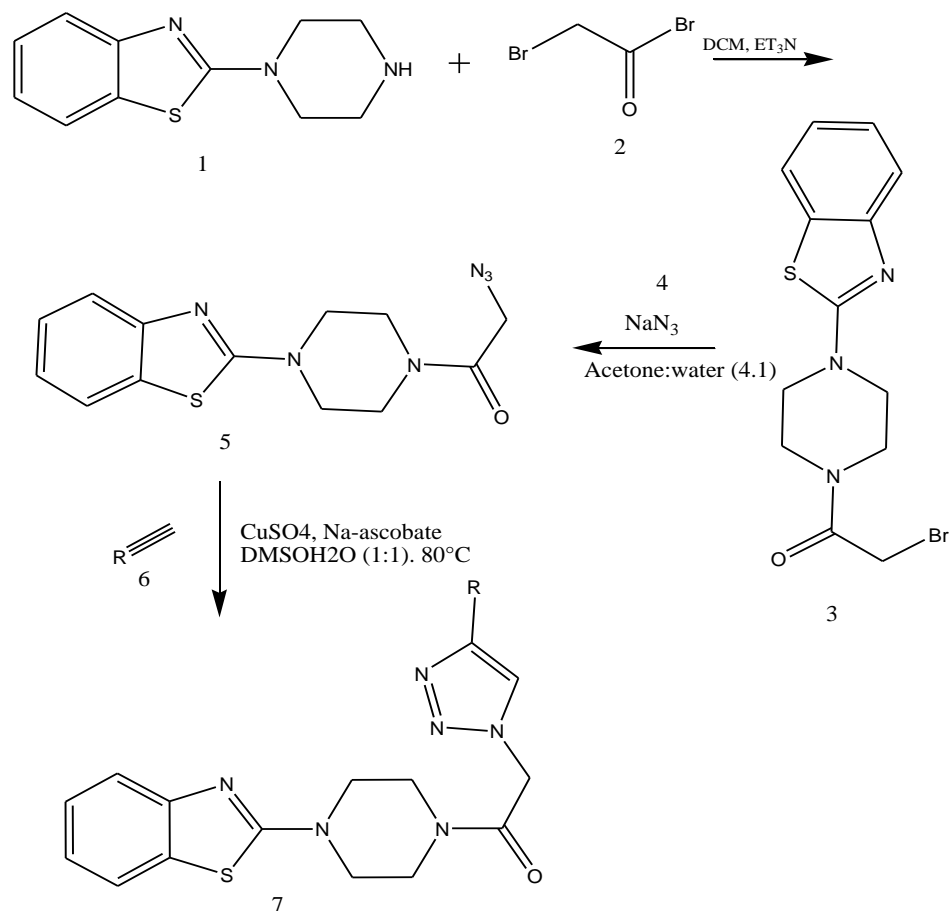


Scheme 3.8 Dimerization produces piperazine analogues

Click reaction:

A click chemistry method was used to create piperazine derivatives. Using dichloromethane as the solvent, the reaction of bromoacetyl bromide with a suitable starting material in the presence of a base started the process and produced an intermediate product. Nucleophilic replacement with sodium azide in a 4:1 combination of acetone and water on this intermediate produced an azide-functionalized molecule.

A fundamental step in (CuAAC), was done next. In a DMSO-water (1:1) solvent solution, the procedure used therefore producing the desired piperazine derivatives with both benzothiazole and triazole groups. Scheme 3.9 depicts the whole synthetic pathway and shows a quick and easy way to build multifunctional piperazine-based scaffolds.



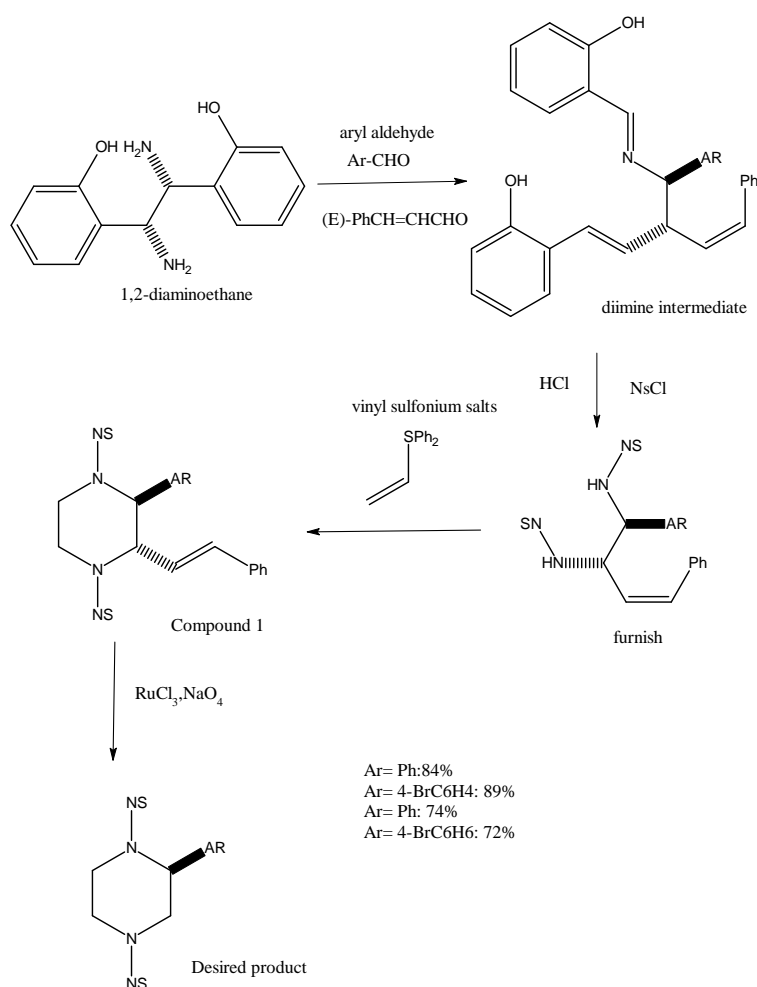
R=CH₂OH, CH₂CH₂CH₂OH, CH₂PHOH, C(Ph)₂OH, CO₂Et

Scheme 3.9 Generation of piperazines via click reaction

Annulation reaction:

Starting with the condensation of aryl aldehyde and trans-cinnamaldehyde with a substituted 1,2-diaminoethane, the synthesis produced a diimine intermediate. When treated with NsCl (p-nitrobenzenesulfonyl chloride) with hydrochloric acid, this intermediate subsequently underwent a diaza-Cope rearrangement—a [3,3]-sigmatropic shift. Establishing the proper molecular framework needed for further functionalization depended on this rearrangement phase.

Following the rearrangement was present to react the intermediate product with vinyl sulfonium ions. This process produced compound 1 with a fused heterocyclic ring structure by means of an annulation reaction. Ruthenium chloride served as the catalyst under oxidative circumstances in the last transition; sodium iodate was the oxidizing agent. This reaction neatly transformed the intermediate into the intended final product. Scheme 3.10 shows the whole synthetic route, including all important stages and chemicals, hence stressing the efficiency and selectivity of the multistep process.



Scheme 3.10. Annulation reaction for generation of piperazine hybrids

Amino-alkyl and diacetamide piperazines synthesis and their metal complexes:

Varying in chain length, amino-alkyl substituted piperazines have shown interesting promise as tetradentate ligands in the coordination chemistry of metal complexes. Their binding strength and geometric orientation around metal centers may be changed by structural tailoring of these ligands.

To allow regulated addition of linear alkyl chains of varying length, hence achieving selective substitution. This strategy change made it possible to synthesize compounds with different asymmetry and spatial characteristics progressively (shown in Figure 5). Moreover, Schiff base-type macrocyclic ligands were created using these altered piperazine derivatives (L1–L3) as main intermediates. Later complicated with many metal ions, a sequence of metal–ligand complexes was produced, hence broadening the range for uses in coordination chemistry, catalysis, and bioinorganic modeling.

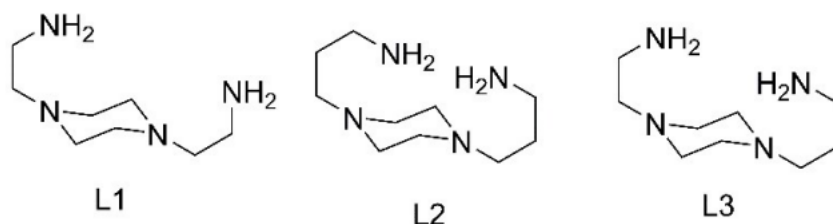


Figure 4: Different chain length bis(amino-alkyl)piperazine structures

A multicomponent reaction including benzaldehyde, piperazine, and acetamide produced. Two bis(phenylmethylene)acetamide moieties linked a symmetrical molecule from this condensation process. The donor atoms and stiff framework of L4 provide many coordination sites, thus appropriate for complexation with transition metal ions.

Following its creation, the ligand underwent complexation reactions with many divalent metal ions. Stable metal-ligand complexes formed by these reactions were structurally verified as seen

in Figure 5. The electron-donating groups and the spatial orientation given by the piperazine core affected the coordination behavior of L4. Preliminary studies on the biological characteristics of both the free ligand and its metal complexes also showed encouraging activity, which points to possible uses in bioinorganic or pharmaceutical chemistry.

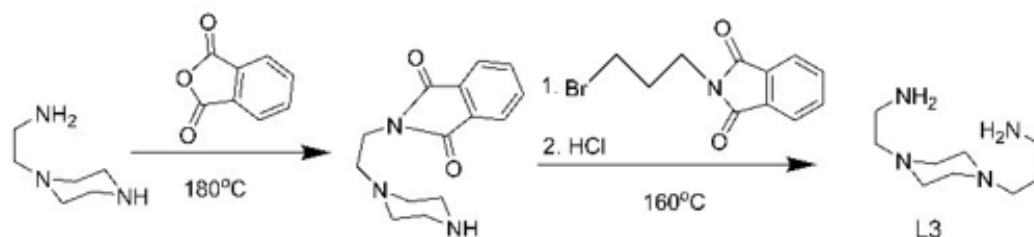


Figure 5: Synthetic method for N,N'-(2-aminoethyl)(3-aminopropyl)piperazine (L3)

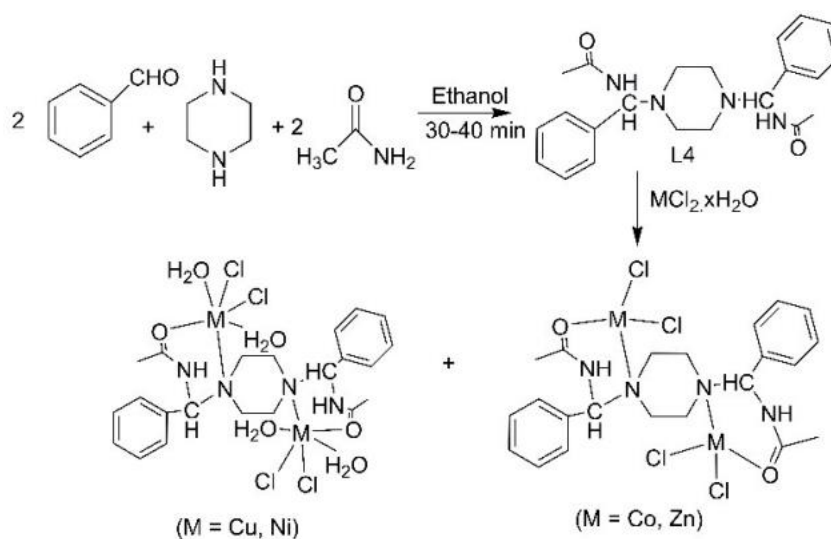


Figure 6: Synthesis of ligand (L4) and its metal complexes depending on benzaldehyde and acetamide

Synthesis of metal complexes of diformylpiperazine-bis(carbohydrazone):

Chandra et al. carried out a thorough of dinuclear copper(II) complexes produced from the ligand 1,4-diformylpiperazine-bis(carbohydrazone) (H_2L_{24}). Beginning with the acid-catalyzed reaction of alcoholic carbohydrazone using acetic acid, the ligand was created by two steps: condensation with 1,4-diformylpiperazine. Well-suited for chelating metal ions, this synthetic route produced a Schiff base-type ligand with many donor atoms.

Copper salt solutions were refluxed in an ethanol-water mix with the ligand dissolved in ethanol to create the metal complexes. As shown in Figure 6, this method produced many dinuclear copper(II) complexes including $[Cu_2(L_{24})SO_4(H_2O)_2]$, $[Cu_2(L_{24})X_2(H_2O)_2]$ where $X = Cl^-$ or NO_3^- , and $[Cu_2(L_{24})(CH_3COO)_2]$. A variety of spectroscopic methods—including electronic absorption spectroscopy, infrared (IR) spectroscopy, mass spectrometry, and electron paramagnetic resonance (EPR)—were used to then describe these complexes. The spectrum results confirmed the creation of stable dinuclear complexes by supporting the coordination of copper ions via the nitrogen and oxygen donor atoms of the ligand. These results not only showed the ligand's great chelating capacity but also provided ideas on the possible use of such complexes in biological systems, sensing, or catalysis.

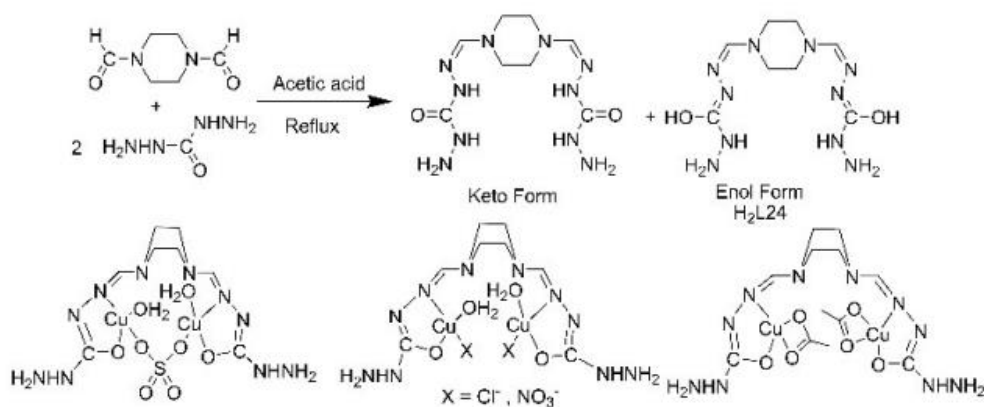


Figure 7: Synthesis of 1,4-diformylpiperazine-bis(carbohydrazone) (H₂L₂₄) and their copper complexes as [Cu₂(L₂₄)SO₄(H₂O)₂], [Cu₂(L₂₄)X₂(H₂O)₂] and [Cu₂(L₂₄)(CH₃COO)₂]

Industrial applications:

In addition to the aforementioned applications in the pharmaceutical, agricultural, chemical, and environmental sectors, the synthesis of piperazine derivatives using metal-based ionic liquids has a wide range of other industrial applications. These include roles in specialty chemicals, materials science, energy storage, and water treatment, among others. Below, we explore these industrial applications in more detail

Pharmaceutical Industry applications:

Piperazine derivatives are highly valued in the pharmaceutical industry due to their diverse pharmacological activities. Many piperazine-based compounds possess potent bioactivities, including antipsychotic, antidepressant, and anti-anxiety properties, which make them essential components of several medications used to treat mental health disorders. The synthesis of these compounds using metal-based ionic liquids improves efficiency and scalability, which is vital for large-scale production.

Anticancer Properties: Some piperazine derivatives have shown promise as anticancer agents. Their ability to interfere with DNA replication and cell division is valuable in cancer treatment, particularly for targeting rapidly dividing cancer cells.

Anti-parasitic Drugs: Piperazine derivatives are used to treat parasitic infections like those caused by helminths (roundworms and flatworms). This makes them essential in the treatment of

diseases like ascariasis, hookworm, and pinworm infections, primarily in developing regions. Metal-based ionic liquids aid in optimizing the synthetic routes for these compounds, reducing the environmental impact of the manufacturing process. [62-63]

Agricultural Applications:

Piperazine derivatives are used extensively in the agricultural sector due to their bioactivity as pesticides, herbicides, and fungicides. Many of these derivatives function by inhibiting key enzymes involved in the growth or reproduction of pests, weeds, or fungi, thereby controlling their populations and preventing crop damage.

Herbicides and Pesticides: Piperazine derivatives can be used to selectively inhibit the growth of weeds and pests without affecting the crops. Their effectiveness can be improved by synthesizing them in the presence of metal-based ionic liquids, which serve as efficient catalysts that facilitate the reactions while maintaining eco-friendly conditions. This reduces the need for toxic solvents and minimizes harmful environmental impact.

Insecticides: Certain piperazine derivatives exhibit insecticidal activity by targeting the nervous systems of pests, preventing their survival or reproduction. By utilizing metal-based ionic liquids as catalysts, these compounds can be synthesized more efficiently, leading to cost-effective production and reducing chemical waste. [64-65]

Chemical Industry Applications:

Piperazine derivatives are important intermediates in the chemical industry for producing a variety of specialty chemicals, including surfactants, resins, and plastics. The ability to synthesize these derivatives efficiently is crucial for meeting the demands of the industry.

Polymer Synthesis: Piperazine derivatives are key building blocks for the synthesis of polymers such as polyurethanes, which are used in applications ranging from foams and coatings to adhesives. Their use as catalysts in polymerization reactions can improve reaction yields, polymer structure, and properties such as flexibility, durability, and resistance to chemicals.

Surfactants: Some piperazine derivatives are used as surfactants in detergents, emulsifiers, and dispersants. These surfactants help reduce surface tension between water and oil, enabling the formation of stable emulsions. Metal-based ionic liquids can provide a more efficient synthesis route for these surfactants, contributing to more sustainable and cost-effective production. [66-67]

Environmental Applications:

Piperazine derivatives, when synthesized using metal-based ionic liquids, can contribute to various environmental applications. Metal-based ionic liquids are particularly effective in applications that aim to reduce pollution and conserve resources.

CO₂ Capture and Sequestration: One of the most promising applications of piperazine derivatives is in CO₂ capture, a critical step in combating climate change. Due to the amine groups in piperazine derivatives, they are excellent candidates for absorbing CO₂ from flue gases and other industrial emissions. Metal-based ionic liquids enhance the efficiency of this process by offering better stability, reusability, and selectivity in CO₂ capture systems.

Water Treatment: Metal-based ionic liquids are also used in water treatment processes for removing contaminants, including heavy metals, organic pollutants, and microbial agents. When combined with piperazine derivatives, these ionic liquids can help in the removal of specific pollutants from industrial wastewater, contributing to cleaner water systems and improved environmental health. [68-69]

Catalysis:

The synthesis of piperazine derivatives using metal-based ionic liquids extends beyond just the production of chemical products; they can also be used as catalysts or catalyst precursors in various industrial processes. These catalytic applications are vital in enhancing the efficiency, selectivity, and sustainability of industrial processes.

Hydrogenation Reactions: In the chemical industry, hydrogenation reactions are commonly used to convert unsaturated compounds into saturated ones, which are important for the production of many chemicals and fuels. Metal-based ionic liquids have been shown to improve the efficiency of hydrogenation reactions by stabilizing the metal catalyst, preventing its leaching, and enabling more sustainable reactions.

Polymerization: Metal-based ionic liquids can also serve as catalysts in polymerization processes, including the synthesis of polyolefins, which are widely used in the production of plastics. Their role in controlling reaction rates and selectivity helps create polymers with desired properties and ensures that the process is more environmentally friendly by minimizing waste.

Fine Chemical Synthesis: Piperazine derivatives synthesized using metal-based ionic liquids can also act as catalysts in the synthesis of fine chemicals. These are high-value chemicals used in pharmaceuticals, fragrances, and food additives. The use of metal-based ionic liquids enables more efficient, selective, and sustainable production of these specialty chemicals, meeting market demand while reducing environmental impact. [70]

Energy Storage and Conversion:

The unique properties of metal-based ionic liquids make them ideal for use in energy storage and conversion applications.

Batteries: Metal-based ionic liquids have been explored as electrolytes in rechargeable batteries, such as lithium-ion and lithium-sulfur batteries. These ionic liquids provide excellent ionic conductivity and thermal stability, which can enhance the overall performance and lifespan of energy storage devices.

Fuel Cells: In fuel cell technology, metal-based ionic liquids can be used as proton conductors or electrolytes, improving the efficiency of fuel cells used in clean energy generation. Their ability to operate at a wide range of temperatures and their low volatility make them highly suitable for use in harsh conditions.

Cosmetic Industry Applications:

Piperazine derivatives have applications in the cosmetic industry, where they are used in the formulation of products such as hair care, skin care, and anti-aging treatments.

Hair Care: Piperazine derivatives are used in the synthesis of surfactants and conditioning agents, which help improve the texture and manageability of hair. The catalytic process using metal-based ionic liquids allows for more efficient and environmentally friendly production of these chemicals.

Skin Care: These derivatives can also be used in the synthesis of moisturizing agents, anti-aging compounds, and other skin care products. The use of metal-based high-purity products that are safe for use in cosmetics.

Piperazine derivatives offers numerous industrial advantages across multiple sectors, including pharmaceuticals, agriculture, chemicals, and environmental applications. The ability to catalyze reactions with high selectivity, efficiency, and sustainability provides a significant boost to various processes, improving their economic and environmental performance. These advances are not only critical for enhancing existing technologies but also open up new opportunities for the

development of more sustainable industrial practices. By utilizing metal-based ionic liquids, industries can achieve cleaner, more efficient, and cost-effective production methods, ultimately benefiting both the economy and the environment. [71]

CONCLUSION

In this review, various metal-based ionic liquids were successfully employed as catalysts for the synthesis of piperazine derivatives. The study demonstrated that the use of these ionic liquids provided significant catalytic efficiency, leading to reduced reaction times and increased product yields compared to conventional methods. Among the tested ILs, [Pd, Cu, Ru, Mg, Ir, etc metal] exhibited the highest catalytic activity, attributed to its strong Lewis acidity and effective coordination with the piperazine precursors. The use of ionic liquids also contributed to a greener synthesis process, with minimal generation of harmful by-products. Their recyclability was particularly notable, so they might be employed several times without notable loss of catalytic activity. Spectroscopic methods including TLC, NMR, FTIR, and Mass Spectrometry verified the effective synthesis of piperazine derivatives. The results also implied, therefore, that by coordinating with nitrogen atoms the metal center in the ionic liquid was quite important for the piperazine ring formation which enhanced the nucleophilicity of the amine group and promoted cyclization. The synthesized piperazine derivatives show promise for pharmaceutical applications due to their bioactive properties, and further studies are recommended to explore their biological activities and potential in drug development. Overall, metal-based ionic liquids are a promising class of catalysts for piperazine derivative synthesis, offering a sustainable, efficient, and reusable approach. Future work should focus on scaling up the reactions and exploring the industrial applicability of these catalysts.

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