Synthesis and Medicinal Applications of Imidazopyridine and Imidazothiazole Derivatives: A Review

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Abstract. Imidazopyridine and its derivatives are essential heterocycles widely utilized in medicinal chemistry, natural products, and synthetic chemicals. The unique structural characteristics of the imidazopyridine ring facilitate their interaction with various enzymes and receptors through weak interactions, leading to a wide range of biological and pharmacological effects. Many imidazole derivatives are extensively used in clinical practice to treat various diseases, highlighting their significant potential for further research. This review provides a comprehensive synthesis of current research on imidazopyridine or imidazopyridine derivatives in medicinal chemistry, focusing on their roles as anti-inflammatory, anticancer, antiviral, antibacterial, and other therapeutic agents. ***Keywords:*** Imidazothiazole derivatives, Medicinal chemistry, biological effects, medicinal applications.

1 Introduction

The structural diversity and biological significance of nitrogen-containing heterocycles have made them highly attractive over the years. These heterocycles are prevalent in natural products and are renowned for their chemical and biological importance. They serve as fundamental frameworks for a wide range of applications, including drugs, food dyes, flavorings, rubber chemicals, and adhesives [1]. The synthesis of nitrogen-containing heterocycles and their derivatives holds a pivotal position in both natural and synthetic medicinal chemistry. Among heterocycles featuring a bridgehead nitrogen atom, imidazopyridine derivatives and imidazothiazole have garnered particular interest [2]. This mini-review aims to explore traditional strategies, alternative synthetic procedures, and diverse biological properties associated with these two families of heterocycles

2 Synthetic study of imidazopyridines

Numerous studies have investigated structural modifications to imidazopyridine frameworks with the aim of enhancing their efficacy. The effectiveness of these agents relies on the specific functional groups attached to the central segment of the imidazopyridine. Various synthesis techniques, including condensation tandem reactions, multicomponent reactions, oxidative coupling, hydroamination, amine oxygenation, among others, are employed for the synthesis of imidazopyridines.

Hand and Paudler [3] conducted a study in 1982 where they synthesized 2-Phenyl-imidazopyridine using 2-aminopyridine and an α-halogenated carbonyl compound in ethanol without catalysts at 60°C for 5 hours (Figure 1).

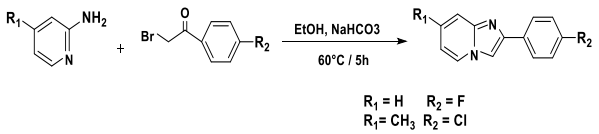

Fig. 1. Synthesis of 2-Phenyl-imidazopyridine.

- *Cyclisation mechanism:*

The mechanism of generating imidazopyridine involves two sequential steps. The initial step entails the creation of the pyridinium salt intermediate, followed by the subsequent in situ cyclization to yield the imidazopyridine derivatives (Figure 2).

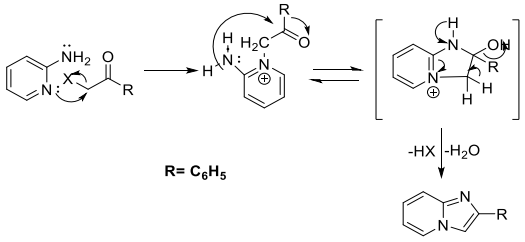

Fig. 2. Mechanism of imidazopyridine synthesis.

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2.1 Imidazopyridine synthesis from 2-aminopyridine

The synthesis of imidazopyridine compounds has often utilized 2-aminopyridine derivatives as crucial starting materials. In 1925, Tschitschibabin (also known as Chichibabin) [4] introduced a pioneering method for producing imidazopyridines. This approach involves the 2-aminopyridine reaction with bromoacetaldehyde at temperatures ranging from 150 to 200°C within a sealed tube, causing imidazopyridines to be formed, albeit with relatively low yields. Later, the Tschitschibabin method was refined by employing a base, such as $NaHCO_3$ (sodium hydrogen carbonate), under milder reaction conditions, leading to enhanced efficiency (Figure 3).

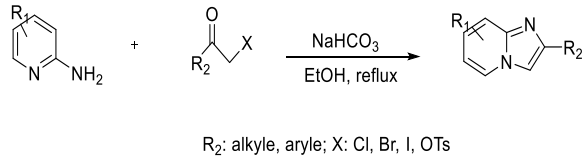

Fig. 3. Synthesis of imidazo [1, 2-a] pyridines.

2.2 Imidazopyridine synthesis from pyridine

Bijanzadeh et al. [5] have presented a single pot synthesis of imidazopyridine utilizing microwave assistance. This method involves a condensation reaction among pyridine, substituted bromoacetophenones, and ammonium acetate. The process initiates with the in-*situ* generation of N-phenacylpyridinium bromide through the addition of pyridine to substituted bromoacetophenones. Subsequent treatment with CH_3COONH_4 at 180ºC induces cyclization, resulting in the formation of imidazopyridines with good yields (Figure 4).

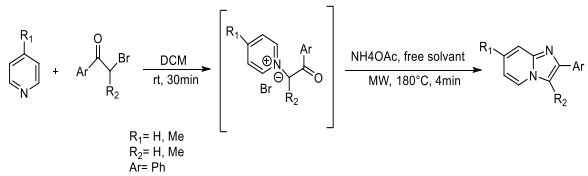

Fig. 4. Production of imidazopyridines.

Mantellini et al. [6] introduced a novel approach to produce imidazopyridines through a sequential reaction involving pyridines and 1,2-diaza-1,3-dienes. This method initiates with the addition of pyridines to the terminal carbon atom of 1,2-diaza-1,3-dienes, followed by a selective intramolecular cyclization, resulting in the formation of the desired imidazopyridine derivative (Figure 5).

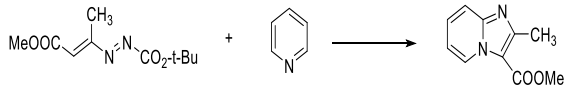

Fig. 5. Imidazopyridine synthesis pathway.

2.3 Synthesis of imidazopyridines from 2-cyanopyridine

Cheng et al. [7] successfully carried out a streamlined synthesis of 2-carbonyl-aminoimidazopyrimidines with high yields in a single step. During the synthesis, one equivalent of spiro[β-lactame-oxadiazolines] and two equivalents of 2-pyridyl isonitrile were used. Conducted under reflux conditions with 1,4-dioxane as the solvent (Figure 6).

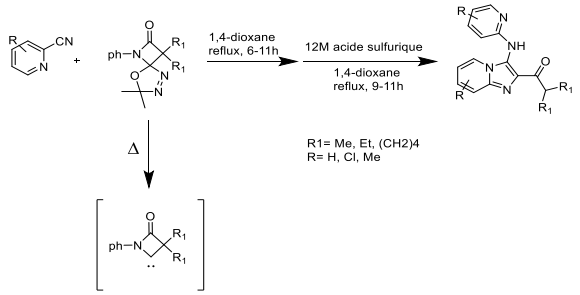

Fig. 6. Imidazopyridine synthesis

The same team presented the synthesis of imidazopyridines by a thermal dimerization reaction of 2-pyridylisonitriles (Figure 7) [8].

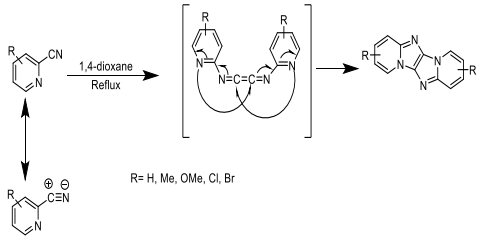

Fig. 7. New product by the Synthesis of imidazopyridine motif.

2.4 Synthesis of imidazopyridines from imidazole

Wang et al. [9] outlined an exceptionally effective approach for the one-step synthesis of imidazopyridines utilizing imidazole's and α,β-unsaturated esters in the presence of potassium carbonate as a base (Figure 8).

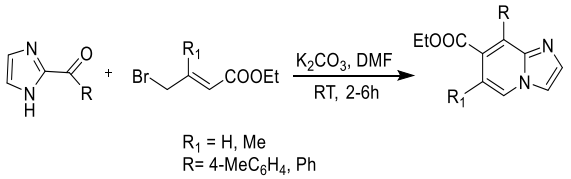

Fig. 8. Imidazopyridine synthesis.

3 Synthetic study of imidazothiazole

The conventional approach to obtaining imidazothiazoles entails the reaction between α-substituted ketones and sulfur heterocycles [10].

Hand et Paudler et al. [11] developed a method in 1982 involving the condensation reaction of α-halogenated

ketones with2-aminothiazole derivatives heated to 60°C for three hours in ethanol (Figure 9).

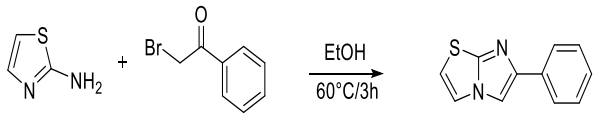

Fig. 9. Production of imidazothiazole by the Paudler synthesis.

- *Mechanism of cyclization:*

The cyclization process unfolds in two stages: initially, the generation of an intermediate thiazolium salt, succeeded by the spontaneous cyclization of the compounds to produce the targeted imidazothiazole derivatives (Figure 10).

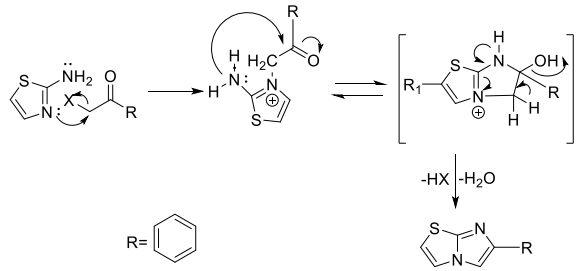

Fig. 10. Mechanism of imidazothiazole synthesis.

Yangmei Li et al. [12] successfully synthesized substituted imidazothiazole through a multi-step procedure.

They achieved this by reacting α-substituted ketones with various sulfur heterocycles, resulting in a product with a good yield (Figure 11).

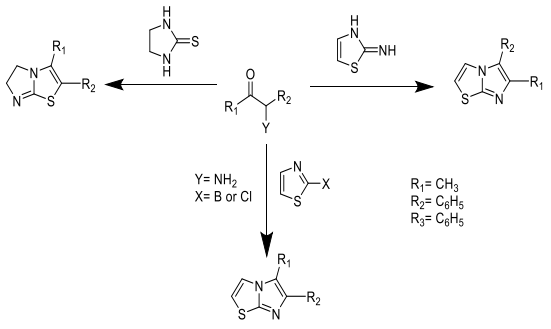

Fig. 11. General routes of imidazothiazole.

3.1 Carboxylation

Shakoor et al. [13] synthesized decarbonylate imidazoheterocycles at the C-3 position. This method offers a simple, high-yielding approach.
Moreover, this work presents the first-ever approach for coupling aryl acetaldehydes with the imidazothiazole system via a double-oxidative cross-dehydrogenative process (Figure 12).

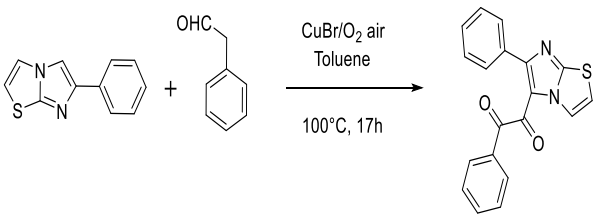

Fig. 12. Carbonylation reactions of imidazothiazole at C-5 position.

3.2 Formylation

Vilsmeier-Haack et al. [14] involves generating a formaldehyde equivalent from DMF and $POCl_3$. Its application to compounds substituted in the 2-imidazole position leads to 3-formyl-2-substituant imidazothiazole derivatives. (Figure 13).

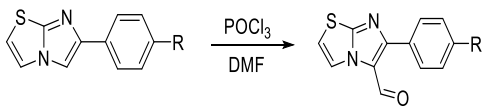

Fig. 13. Synthesis of imidazothiazole carbaldehyde

3.3 Nitrosation

Kamarul Monir et al. [15] documented the regioselective nitrosation of imidazoheterocycles and the functionalization of C(sp2)-H bonds employing tert-butyl nitrite. Initially optimized with imidazopyridines, this methodology was subsequently extended to a range of imidazothiazoles (Figure 14).

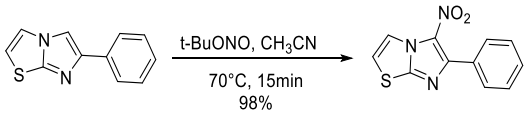

Fig. 14. Nitrosation at the C-5 position of imidazothiazole.

4 Medicinal and pharmacological applications of imidazopyridines

The production of extensively functionalized poly-heterocyclic compounds holds significant importance, as these compounds serve as crucial structural components commonly found in numerous natural and biomolecular products [16]. Among the azoles, imidazopyridine derivatives are heterocycles widely used in research in medicinal, organometallic chemistry and materials science [17,18]. Compounds based on imidazopyridine exhibit a broad spectrum of biological properties, including antibacterial [19], anticancer [20], antiviral [21], antifungal [22], antitumor [23], antiulcer [24], etc. activities. However, in addition to these biological activities, these scaffolds also demonstrate numerous photophysical properties [25].The foundational imidazopyridine structure is also present in the molecular structures of various drugs, including zolpidem, alpidem, and zolimidine [26] (Figure 15).

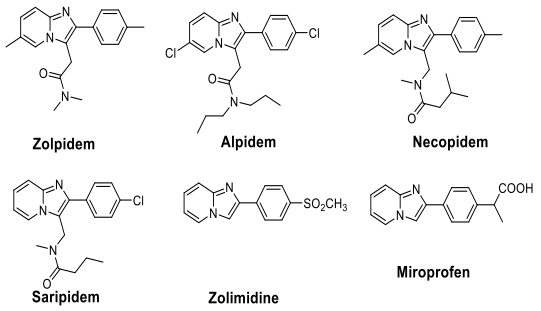

Fig. 15. Imidazopyridine motif drugs

This core is also present in GSK812397 (W) (HIV infection) [27], PI3Kα inhibitors (X) [28], mGlu2 receptors (Y) [29] and TNF-α inhibitors (Z) [30] (Figure 16).

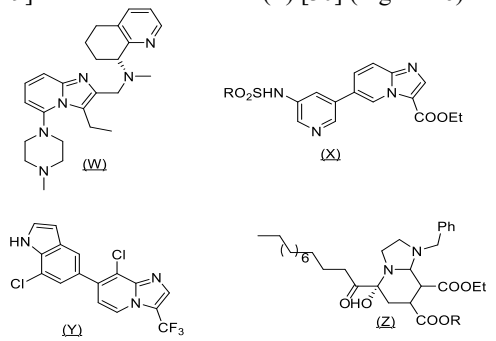

Fig. 16. Derivatives of imidazopyridines with biological activity.

Moraski et al. [31] conducted the synthesis of a series of imidazopyridine-3-carboxamides. Compounds A and B have been recognized as a highly effective class of drug-like antimycobacterial agents (Figure 17).

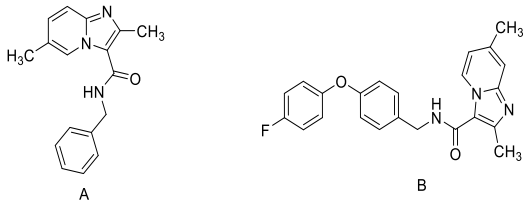

Fig. 17. Imidazopyridine-3-carboxamide derivatives as effective antimycobacterial agents.

Raju et al. [32] synthesized a novel set of imidazopyridine derivatives linked to secondary amines, which exhibited notable antibacterial and antifungal properties. These compounds demonstrated heightened efficacy against various bacterial strains such as Streptococcus pyogenes, Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli. Moreover, the two compounds displayed increased potency against fungal strains, including Candida albicans and Aspergillus niger (Figure 18).

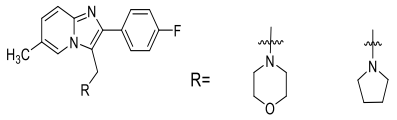

Fig. 18. Derivatives of imidazopyridines as antibacterial agents.

5 Medicinal and pharmacological applications of imidazothiazole

The interest in the imidazothiazole nucleus began in 1966 with the discovery of levamisole, or 6-phenyl-tetrahydroimidazothiazole, marketed under the name Solaskil. This compound is well-known for its anthelminthic properties used in veterinary medicine for the treatment of ascaridiasis and ancylostomiasis [33] (Figure 19).

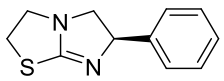

Fig 19. Structure of Levamasole or L-tetramisole

The presence of substituents in positions 5 and 6 conferred activities in fields as diverse as virology, parasitology and even oncology. Shareef et al. [34] illustrated that the imidazo[2,1-b]thiazole compound, when substituted at a concentration of 1.9 µg/ml, displayed significant antimicrobial activity against both Gram-positive and Gram-negative bacteria, specifically S. aureus MLS-16 MTCC 2940, S. aureus MTCC 96, and E. coli MTCC 739 (Figure 20).

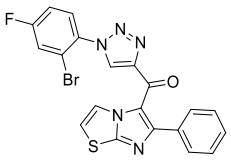

Fig. 20. Imidazothiazole substituted with antimicrobial activity.

Baig et al. [35] synthesized derivatives of imidazothiazole with potential anticancer properties. Specifically, the compound featuring imidazo [2,1-b] thiazole substitution (as depicted in Figure 21) exhibited significant cytotoxic activity against the A549 lung cancer cell line, with an IC50 value of 1.086 µM.

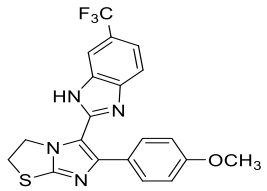

Fig. 21. Imidazothiazole substituted with anticancer activity.

Powers et al. [36] demonstrated the anti-inflammatory activity of dihydroimidazothiazoles in the 1980s by introducing substitutions at positions 2, 3, and 6 (Figure 22). They observed a loss of anti-inflammatory properties when position 6 was sterically hindered.

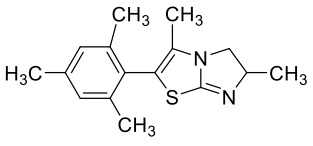

Fig. 22. Imidazothiazole substituted with anti-inflammatory activity.

6 Conclusion

Our review reveals a diversity of synthesis methodologies for creating innovative molecules based on imidazopyridine and imidazothiazole. This underscores the pharmacological significance of these compound families. Looking forward, it is prudent to explore the synthesis of novel product families incorporating imidazopyridine and imidazothiazole motifs, utilizing synthesis approaches that are cost-effective, ecofriendly, and efficient, such as (i) the initial focus will centre on synthesizing and characterizing these novel products and (ii) the subsequent aspect will involve assessing the antibacterial, antifungal, and antioxidant activities of the synthesized molecules.

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