

Benzimidazoles and Imidazo[1,2-a]pyridines : Biological Activities, Method of Synthesis and Perspectives on Combination of Deuce Pharmacophore

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Abstract

N-Heterocyclic scaffolds have generated significant interest among medicinal chemists. Among these potential heterocyclic drugs, benzimidazole and imidazopyridine scaffolds are the most prevalent. Over the past few decades, it has gained immense attention. Both are important classes of molecules owing to their wide spectrum of biological activities and clinical applications. Both are used in fashion design and the development of novel synthetic analogs for various therapeutic disorders. A wide variety of derivatives have been developed as potential anticancer, antimicrobial, antiviral, and anti-inflammatory agents in addition to other chemotherapeutic agents. The benzimidazole core is found in a natural system, displaying a wide range of pharmaceutical properties, and has gained significant attention in medicinal chemistry, as reported in several full articles and communications. Imidazopyridines are widely distributed in many pharmacologically important compounds, as shown by their frequent occurrence in a large number of marketed drug formulations and drug candidates, as well as in other fields such as material and organometallic chemistry. These scaffolds have been structurally characterized as ligands that can bind to different receptor sites for the discovery of various emerging drugs. They act as key pharmacophore motifs for the identification and optimization of lead structures to increase the medicinal chemistry toolbox. This review outlines the synthesis and medicinal significance of benzimidazoles and imidazopyridines for their development as lead molecules with improved therapeutic efficiency. Here, we cover the various designs used to obtain both heterocycles to establish a relationship between their combination and biological activities.

Keywords: Benzimidazole, Imidazopyridine, Heterocyclic scaffold, Biological activity, Pharmacophore synthesis

Introduction

Antimicrobial resistance (AMR) and the worldwide increase in infections are recognized by the World Health Organization (WHO) as urgent public health risks. During the COVID-19 crisis, the monkeypox virus and its variants increased these risks in all domains, even worse in the world economy. AMR infections cause approximately 700 000 deaths annually, and they are expected to become the leading cause of death by the year 2050, especially in low- and middle-income countries.¹ To challenge this inauspicious outcome, the WHO launched strategic objectives and one of them set out incentivization of investments in the research of new pharmaceutical tools and medicines.² This latter strategic objective also concerns chemists. For this purpose, some intensification of research on nitrogen-fused azoles, known as lead compounds in the literature, has pushed our curiosity and summed it up in this review. These compounds have a wide range of medicinal chemistry applications. Although benzimidazoles and imidazopyridines are structurally different, their pharmacological properties are similar. Both heterocycles and their derivatives, as well as preparative methods for their basic derivatives, are presented here.

This review focuses on the biological activities of benzimidazoles and their synthesis methods. In addition, imidazopyridine compounds were presented in the same manner as before their combination prospects were presented.

Benzimidazole derivatives are heterobicyclic aromatic compounds that result from adhesion between benzene and imidazole. Because of their isostructural pharmacophores, molecules possessing a benzimidazole scaffold in their basic structures have revealed a variety of biological activities, including anticancer,³ acetylcholinesterase,⁴ antimicrobial,⁵ anti-inflammatory,⁶ analgesic,⁷ antiviral,⁸ anti-protozoan,⁹ antimalarial,¹⁰ and anti-leishmanial¹¹ activities. Benzimidazole scaffolds are present in the structures of some commercial drugs such as Thiabendazole, Mebendazole, Luxabendazole, Triclabendazole, Albendazole and Oxibendazole (Figure 1).

Naturally, have a wide range of applications in a variety of fields has led to several synthetic routes for the production of imidazo[1,2-a]pyridines. In recent years, progress has been made in the synthesis of imidazo[1,2-a]pyridines using several interesting pathways such as multicomponent reactions, tandem sequences, and C-H functionalization catalyzed by transition metals. It is easy to obtain imidazo[1,2-a]pyridines from simple and readily available precursors using these methods.

This has led to many discoveries concerning their biological properties, including antimicrobial, anti-inflammatory, anticancer, and antiparasitic properties,¹² thus dedicating this scaffold to molecular and biological explorations. The imidazo[1,2-a]pyridine core is also present in the structure of many drugs, with good properties in the central nervous system.¹³ Such is the case with Zolpidem,¹⁴ a drug used to treat insomnia. Alpidem, Nécopidem, and Saripidem are three active ingredients used as anxiolytic agents.¹³ However, Alpidem was withdrawn from the market because of its toxicity. Olprinone¹⁵ has been used to treat acute heart failure. Zolimidine is active against *Escherichia Coli* (*E.Coli*) is used in the treatment of peptic ulcers.¹⁶ An optically active drug with an imidazopyridine motif in its skeleton, GSK812397, is intended for the treatment of HIV infection.¹⁶

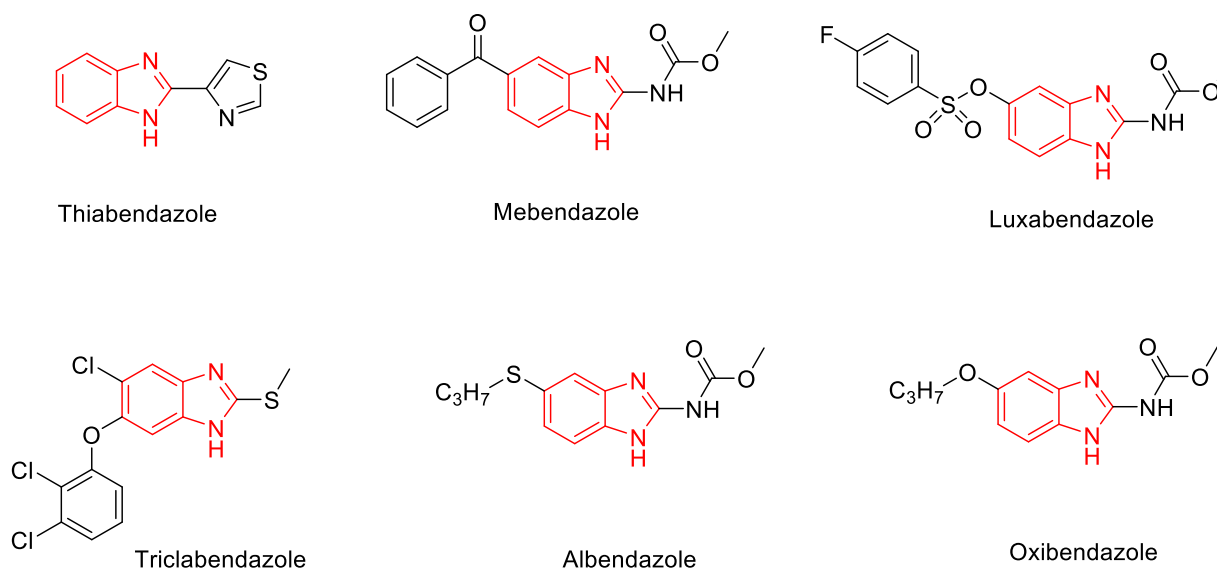


Figure 1: some drugs based on the benzimidazole scaffold

I. Benzimidazoles and Derivatives : Biological Activities and Synthesis Methods

1. Biological Activities of benzimidazole derivatives

a. Antimicrobial properties

Several benzimidazole derivatives are described in the literature and, have shown excellent antimicrobial activity.^{17,18} The work of Ramya V. Shingalapur et al.¹⁹ provided access to benzimidazole molecules with interesting antimicrobial activities. In this work, the derivatives of 2-styryl-1*H*-benzimidazole (Figure 2; **1-3**) showed good antimicrobial activity *in vitro* on two

Gram-positive strains (*Staphylococcus aureus* ATCC25923 and *Enterococcus faecalis* ATCC29212) and four Gram-negative strains (*Klebsiella pneumoniae* ATCC13883, *Escherichia coli* ATCC-25922, *Albicans candida* ATCC10145 and *Asperigillus fumigatus*). All the evaluated compounds showed good antibacterial properties, with Minimum Inhibitory Concentrations (MICs) between 16 and 1 µg/mL. Among these compounds, 3-[2-(5-bromo-1*H*-benzimidazol-2-yl)-vinyl]-phenol showed the best activity against all strains, with MIC values between 1 and 4 µg/mL (Figure 2, **1-3**).

Muayed Redayan et al.²⁰ have shown that 5-(((1*H*-benzimidazol-2-yl)methyl)thio)-1,3,4-thiadiazol-2-amine derivatives (Figure 2, **4-6**) present interesting antibacterial activities comparable to existing standard antibiotics such as Ampicillin and Ciprofloxacin. During this work, the synthesized compounds were screened for their antibacterial activities against Gram-negative (*E. coli*, *P. aeruginosa*) and Gram-positive (*B. subtilis*, *S. aureus*) bacteria. Most of these derivatives showed good antibacterial activity against all tested strains.

Amino-(2-(4-(((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)amino)phenyl)-1*H*-benzimidazol-5yl) methaiminium (Figure 2, **7**) was evaluated for in vitro antibacterial activity against two gram-positive strains (*S. Aureus* ATCC 25923 and *Enterococcus Fasalis* (ATCC 29212) and five Gram-negative strains (*E. coli* ATCC 25925, *K. pneumoniae* ATCC 700803, *P. Aeruginosa* ATCC 27853 and *Acinetobacter Baumannii* ATCC 19606). The results of the antibacterial activity of this benzimidazole-derived compound showed very good properties on Gram-positive strains compared to antibiotics such as Ceftazidime, ciprofloxacin, ampicillin and gentamicin.²¹

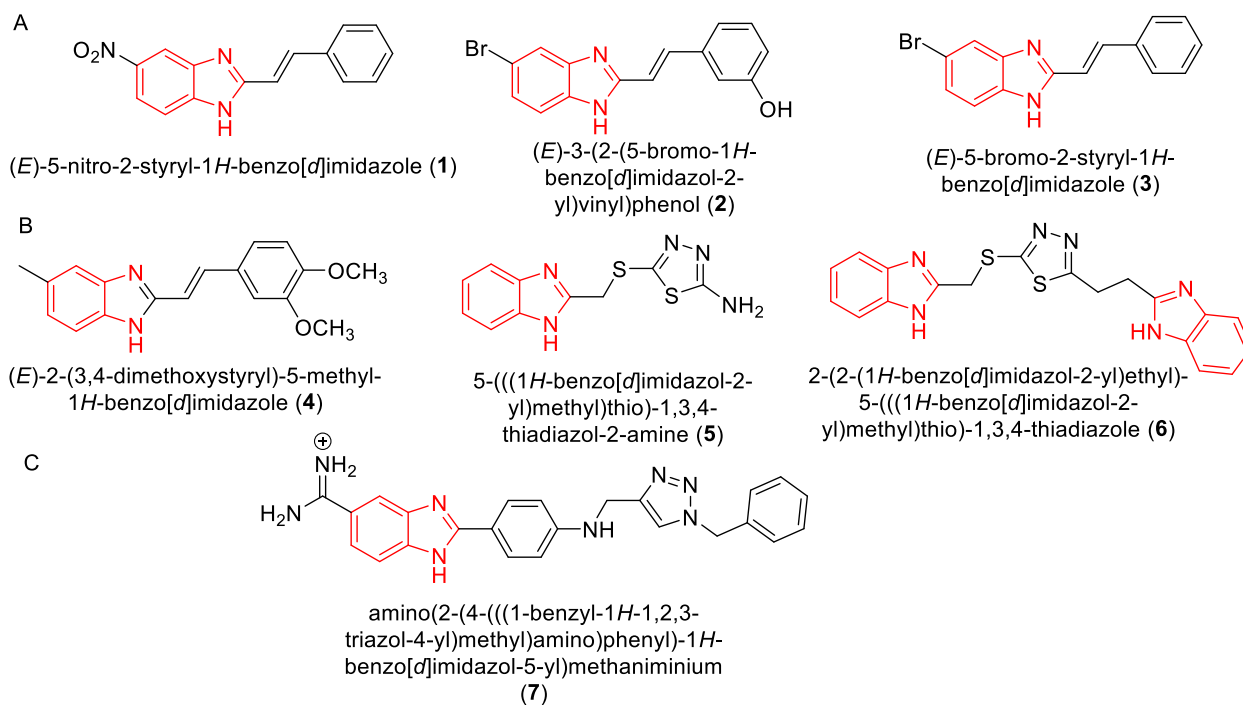
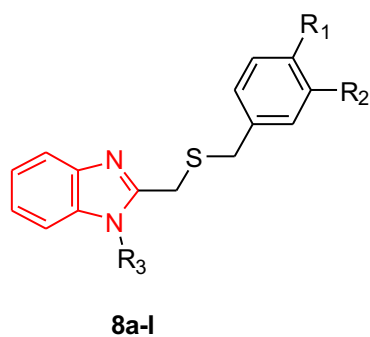


Figure 2: Compounds with good antimicrobial activity: 2-styryl-1H-benzimidazole derivatives, B. 5-(((1H-benzimidazol-2-yl)methyl)thio)-1,3,4-thiadiazol-2-amine derivatives, C. Amino-(2-(4-(((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)phenyl)-1H-benzimidazol-5-yl) methaniminium.

In our team, we also participate to find potent antibacterial agent against a set of two (2) strains *Escherichia coli* (Gram negative), *Staphylococcus aureus* (Gram positive).²² and *Pseudomonas aeruginosa* ATCC 27853.²³

Twelve (12) *N*-alkyl 2-benzylthiomethyl-1H-benzimidazole derivatives were evaluated and their antibacterial profile was determined with minimal inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs). The results showed that compounds **8a**, **8b**, **8c**, **8d**, **8e**, **8f**, **8h**, **8k**, and **8l** were potent against *Escherichia coli* and *Staphylococcus aureus*, with significant MICs values from 140 to 290 µg/mL. On *E. coli*, five (5) compounds **8b**, **8f**, **8i**, **8k** and **8l** showed bactericidal effects within common an N-alkylation by R₃= phenyl, methyl, and CH₂OH on the benzimidazole scaffold and the benzylthiol substituted by R₂= Cl or CF₃. Only *E. coli* ATTC 25922 was susceptible to the synthesized derivatives **8g**, **8f** and **8h** with a significant antibacterial activity (CMI is between 250 and 500 µg/mL).



8a : R ₃ = 4-Cl-C ₆ H ₄	R ₁ = H	R ₂ = H
8b : R ₃ = C ₆ H ₅	R ₁ = Cl	R ₂ = H
8c : R ₃ = Cl-C ₆ H ₅	R ₁ = CO ₂ Me	R ₂ = H
8d : R ₃ = C ₆ H ₅	R ₁ = H	R ₂ = NO ₂
8e : R ₃ = C ₆ H ₅	R ₁ = CH ₃	R ₂ = H
8f : R ₃ = C ₆ H ₅	R ₁ = CF ₃	R ₂ = H
8g : R ₃ = CH ₃	R ₁ = H	R ₂ = H
8h : R ₃ = CH ₃	R ₁ = Cl	R ₂ = H
8i : R ₃ = CH ₃	R ₁ = CO ₂ Me	R ₂ = H
8j : R ₃ = CH ₃	R ₁ = H	R ₂ = NO ₂
8k : R ₃ = CH ₃	R ₁ = CF ₃	R ₂ = H
8l : R ₃ = CH ₂ OH	R ₁ = Cl	R ₂ = H

Figure 3: N-alkyl-2-benzylthiomethyl-1H-benzimidazole derivatives with antibacterial properties (**8a-l**)

b. Antifungal properties of benzimidazole derivatives

The antifungal activity of the benzimidazole scaffold was first reported in 1944 by Woolley^{24,25} using chlormidazole or 1-(4-chlorobenzyl)-2-methyl-1H-benzimidazole. It is a well-known activity of benzimidazole, which has generated much research interest.

Mishra et al.²⁶ showed that the 2-chloromethyl-5H-methylbenzimidazole derivatives substituted in the -2 position by 5-mercapto-1,3,4-oxadiazole or 4-amino-5-mercapto-1,2,4-triazole showed good antifungal activity on *Rhizoctonia solani* and *Helminthosporium oryzae* fungi.

In the same vein, antifungal activities of the benzimidazole core were also highlighted by Gulgun Ayhan et al.²⁷ For example, *in vitro* testing of *Candida albicans* (*C. albicans*), *Candida glabrata* (*C. glabrata*) and *Candida krusei* (*C. krusei*) strains showed that 5-amino-2-(p-fluorophenyl)-1-propylbenzimidazole (**10**) and 2-(p-fluorophenyl)-5-nitro-1-propylbenzimidazole (Figure 4) are potent against these strains with a large antifungal activity spectrum. These benzimidazole compounds were more active against *C. albicans*, with an MIC of 12.5 g/mL compared to the reference antibiotic fluconazole. For the *C. Krusei* strain, compounds such as 5-amino-2-(p-fluorophenyl)-1-propylbenzimidazole, 2-(p-fluorophenyl)-5-nitro-1-propylbenzimidazole (**9**) and N-[2-(p-fluorophenyl)-1-propyl-benzimidazol-5yl]-N-(p-chlorophenyl)-thiourea were more effective with MICs of 5 to 6.25 g/mL.

Göker et al.²⁸ evaluated the *in vitro* antifungal activity of 5-carbonitrile benzimidazoles. This compound was very active on strains such as *C. albicans*, *C. grabrata*, *C. krusei* and *C. parapsilosis* with an activity similar to that of Fluconazole.

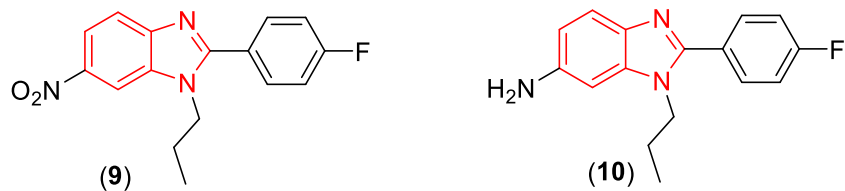


Figure 4: 2-(4-fluorophenyl)-1-propyl-*1H*-benzimidazole derivatives with antifungal activities.

c. Anticancer properties of benzimidazole derivatives

The anticancer activity of benzimidazole derivatives has been described in several studies.^{29,30} Among these studies, we will mention those carried out by Refaat et *al.*³¹ for the determination of the anticancer activity of 2-substituted benzimidazole derivatives. The cytotoxicity of these benzimidazole compounds was evaluated in three cell lines representing three common forms of human cancer: a human hepatocellular carcinoma cell line (HePG2), a human breast adenocarcinoma cell line (MCF7), and a colon carcinoma cell line (HCT 116). In this study, we showed that position-2 substituted benzimidazole derivatives have anticancer activity against all tumor cell lines, with an IC₅₀ of less than 10 mg/mL. Generally, all compounds tested tended to be more active against HePG2 and other tumor cell lines. 5-chloro-2-[(4-fluorobenzylidene)cyanomethyl]benzimidazole and 2-(4-amino-3-benzyl-2-thioxo-2,3-dihydrothiazol-5-yl)benzimidazole-5-carboxylic acid showed the most increased activity against HePG2 while 2-[(cyclohexylidene)cyanomethyl]benzimidazole-5-carboxylic (**11**), 5-chloro-2-[(3-phenyl-4-oxothiazolidin-2-ylidene)cyano-methyl]benzimidazole (**12**) and 2-[3-(4-bromophenyl)-4-(2-methoxyphenylthiazol-2-ylidene)cyanomethyl]benzimidazole-5-carboxylic acid (**13**) were most active against MCF7 (Figure 5).

Salahuddin et *al.*³² also synthesized derivatives of 2-(naphthalen-1-ylmethyl/naphthalen-2-ylloxymethyl)-1-[5-(substituephenyl)-[1,3,4]oxadiazol-2-ylmethyl]-*1H*-benzimidazole. In this work, they showed that 2-naphthalen-1-ylmethyl-1-[5-(4-nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-*1H*-benzimidazole (Figure 5, **14**) had good anticancer activity on certain lines such as leukemia, melanoma, lung cancers, colon, central nervous system, ovary, kidney, prostate and breast at a single high dose around 10⁻⁵ M.

The anticancer activities of 2-(benzimidazol-2-yl) methylthio)-4-(substitued)-6-phenylpyrimidine-5-carbonitrile derivatives synthesized by Abdel-Mohsen et *al.*³³ were evaluated against 12 cancer cell lines, KB, SKOV-3, SF-268, NCI-H460, RKOP27, HL60, U937, K562,

G361, SK-MEL-28, GOTO, and NB-1. All benzimidazole derivatives evaluated *in vitro* showed good anticancer activity against various cancer cell lines.

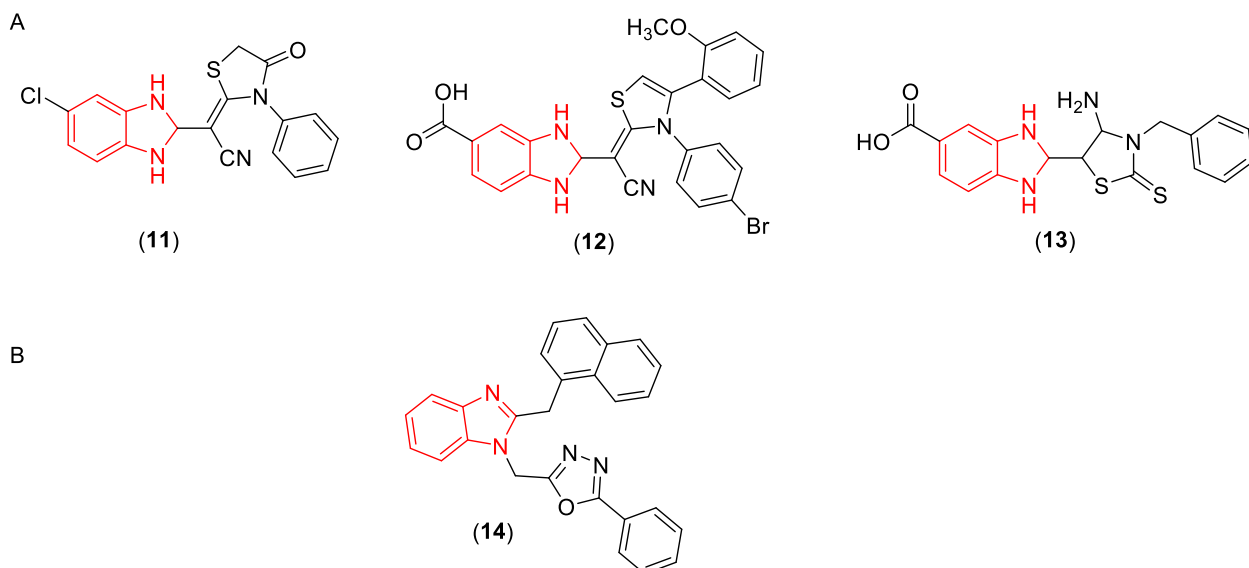


Figure 5 : Anticancer properties of A. Benzimidazole derivatives against HEPG2 and MCF-7, B. 2-naphthalen-1-ylmethyl-1-[5-(4-nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1*H*-benzimidazole.

d. Anthelmintic properties of benzimidazole derivatives

The anthelmintic activity is one of the main properties of benzimidazole derivatives.^{34–36} Some of these compounds are used to fight parasitic diseases such as helminthiases. This was also the case for Flubendazole, Mebendazole, Albendazole and Thiabendazole. In addition, new derivatives of 2-((1*H*-benzimidazol-2-yl)thio)-1-(piperazin-1-yl)ethan-1-one were synthesized (Figure 6, **17**) by Mavrova et al.,³⁷ which showed strong anthelmintic activity *in vitro* against *Trichinella spiralis*. This activity was higher than that observed in the same germ when using a drug such as albendazole.

Ramesh Sawant et al.³⁸ also showed that the new 2-phenyl benzimidazole-1-acetamide derivatives possess anthelmintic activities. Anthelmintic tests were carried out using derivatives of 2-(((1*H*-benzimidazol-2-yl)methyl)thio)-5-phenyl-1,3,4-thiadiazole (Figure 6, **19**) on *Pheretima Posthuma*, an authenticated worm at the University of SSGM (Shri Sadguru Gangageer Maharaj Sciences) in India. This study revealed that derivatives at the 2-position exhibit excellent anthelmintic activity.

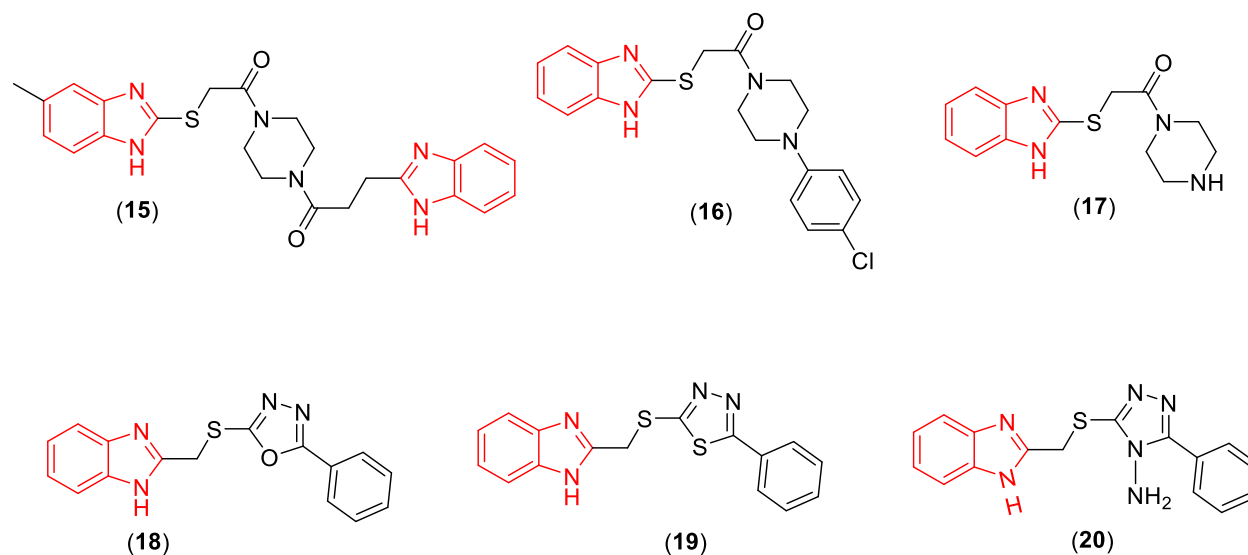


Figure 6: Benzimidazole derivatives with anthelmintic derivatives

e. Antiviral properties of benzimidazole derivatives

Several research studies have shown that benzimidazole derivatives substituted in position-1 or -2 have good antiviral properties too.^{39,40} Laura Garuti et al.⁴¹ synthesized benzimidazole derivatives substituted in position-1 by sulfonyl. Subsequently, the antiviral activities of these derivatives were evaluated against *human cytomegalovirus* and *varicella-zoster* viruses. Among the evaluated compounds, 5,6-dichloro-1-(isopropylsulfonyl)-2-(2-(pyridin-2-yl)ethyl)-2,3-dihydro-1*H*-benzimidazole (Figure 7, **21**) showed the best antiviral activity against different strains, with an IC_{50} of 1.6 to 1.1 mg/mL. In the same study, some benzimidazole-coumarin derivatives have shown excellent activities against the *hepatitis C* virus with IC_{50} between 3.4 μ M and 4.1 μ M.

Antiviral activity was also shown through the work of Deepika Sharma et al.⁴² on the 4-nitrophenyl-2-phenyl-1*H*-benzimidazol-1-ylmethanone derivatives. The antiviral properties of these derivatives have also been demonstrated previously. In addition, the authors showed that 4-nitrophenyl-2-(4-chlorophenyl)-1*H*-benzimidazol-1-ylmethanone and 2-bromophenyl-2-phenyl-1*H*-benzimidazol-1-ylmethanone (Figure 7, **22** and **23**) are good candidates for manufacturing antiviral vaccines.

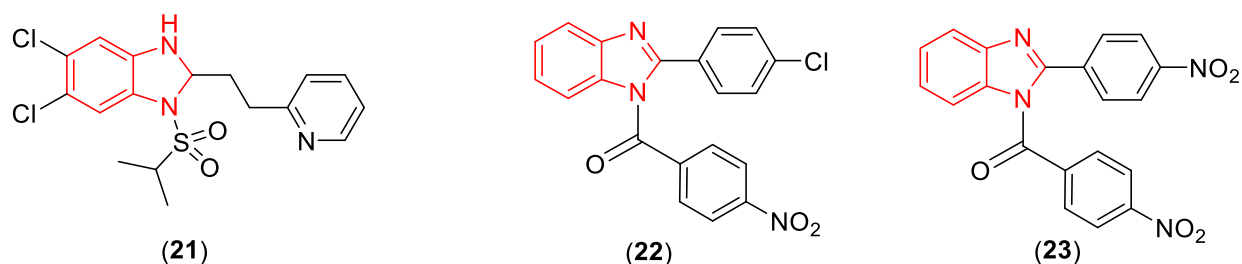


Figure 7: Benzimidazoles derivatives with antiviral activities

f. Anti-inflammatory properties of benzimidazole derivatives

The anti-inflammatory activity of benzimidazole derivatives has been reported through several research studies.^{43,44} However, the benzimidazole molecules (Figure 8, **24-26**) discussed in this section are those that have shown good anti-inflammatory properties in the work of Monika Gaba *et al.*⁴⁵ In this study, the anti-inflammatory activities of the molecules were compared with those of reference drugs such as Indomethacin, Nimesulide, Ibuprofen and Diclofenac. These benzimidazole derivatives showed activity above that of the reference drugs.

Kavitha Achar *et al.*⁴⁶ also highlighted the anti-inflammatory activity of benzimidazole derivatives. The authors showed that some derivatives of N-((1*H*-benzimidazol-2-yl)methyl)aniline (Figure 8, **27-28**) had very good anti-inflammatory activities. This study was conducted using nimesulide as the reference drug.

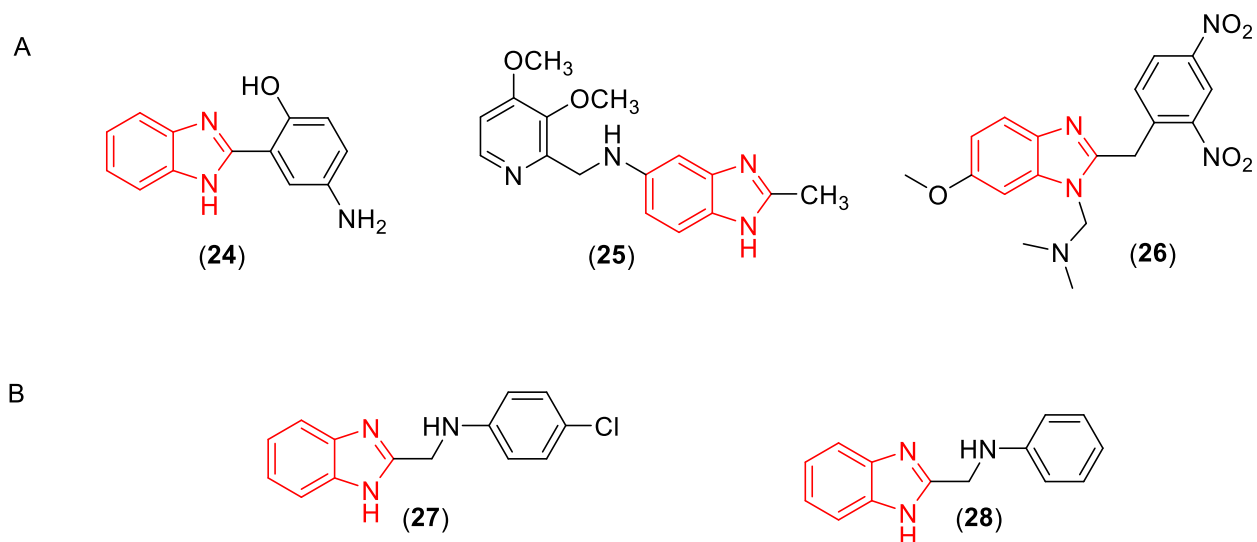


Figure 8 : A. Benzimidazole derivatives (24-26). B. N-((1H-benzimidazol-2-yl)methyl)aniline derivatives with good anti-inflammatory activities (27-28).

g. Anti-leukemia properties of benzimidazole derivatives

The biological properties of benzimidazole derivatives were revealed by Gowda *et al.*⁴⁷ for the synthesis and evaluation of the anti-leukemic activity of the new 1-(4-methoxyphenethyl)-1H-benzimidazole-5-carboxylic acid derivatives. Screening of twenty-two (22) new synthesized compounds showed that methyl 2-(4-fluoro-3-nitrophenyl)-1-(4-methoxyphenethyl)-1H-benzimidazole-5-carboxylate (Figure 9) had good anti-leukemic properties. This molecule inhibits human leukemia cells with an IC_{50} of 3 μ M.

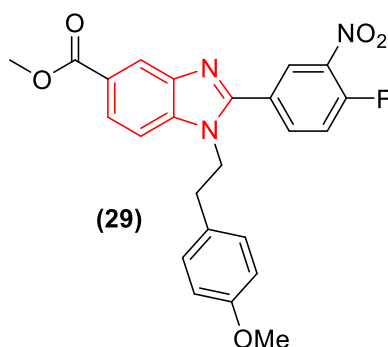


Figure 9: Structure of methyl 2-(4-fluoro-3-nitrophenyl)-1-(4-methoxyphenethyl)-1H-benzimidazole-5-carboxylate.

h. Anti-plasmodial properties of benzimidazole derivatives

In our group, Ouattara Mahama et al.⁴⁸ demonstrated the antiplasmodial behavior of benzimidazole through the synthesis and evaluation of benzimidazolyl-chalcone derivatives (Figure 10, **30-31**). In their study, anti-plasmodial screening of *Plasmodium falciparum* (*P. Falciparum*) chloroquino-sensitive and chloroquinoresistant isolates demonstrated that benzimidazolyl-chalcones are excellent antiplasmodial pharmacophores. 1-(fluoro-1*H*-benzimidazol-2-yl)-3-phenylprop-2-en-1-one (**30**) with an IC₅₀ value of 5.63 μM showed the best profile for the chloroquino-sensitive *P. falciparum* isolate.

Bandyopadhyay et al.⁴⁹ synthesized and evaluated the antimalarial activities of benzimidazole-phosphorylated derivatives in *Albopictus* and *Culex Quinquefasciatus* mosquitoes. They showed that dimethyl-(4-(1*H*-benzimidazol-2-yl)phenyl)phosphoramidate (Figure 10, **32**) was more potent against *Albopictus* and *C. Quinquefasciatus*.

Camacho et al.⁵⁰ synthesized benzimidazole derivatives to test their *in vitro* antimalarial activities to inhibit the formation of β-hemetic (IβHS) responsible for hemoglobin hydrolysis. In addition, an *in vivo* study was performed on the rodent *Plasmodium Berghei*. Among the tested molecules, 2-(5-nitrofuranyl)-3*H*-benzimidazole-5-carboxylic acid (Figure 10, **33**) showed the greatest inhibition of β-hemolytic formation, indicating the highest antimalarial activity.

Divatia et al.⁵¹ synthesized thiosemicarbazones supported by a benzimidazole scaffold and evaluated their antimalarial activity *in vitro* against *P. falciparum* in comparison to chloroquine and quinine as reference molecules. Some of the compounds synthesized include (E)-2-[1-(5-chloro-1*H*-benzimidazol-2-yl)ethylidene]-N-(benzoyl)hydrazine carbothioamine, (E)-2-[1-(5-chloro-1*H*-benzimidazol-2-yl)ethylidene]-N-(4-fluorophenyl)hydrazine carbothioamine and (E)-2-[1-(5-chloro-1*H*-benzimidazol-2-yl)ethylidene]-N-(4-iodophenyl)hydrazine carbothioamine have shown excellent antimalarial activities. Indeed, a structure-activity relationship study suggested that compounds with mesomeric electron donor groups (EDG), such as halogens, had excellent antimalarial activity (Figure 10, **34**).

The work conducted by Toro et al.⁵² reported the synthesis and evaluation of anti-plasmodial activity of benzimidazole derivatives. Anti-plasmodial tests were carried out *in vitro* against *P. falciparum* using compounds such as 2-ferrocenyl-benzimidazole and N-ferrocenylmethyl-2-ferrocenyl-benzimidazole (Figure 10, **35**). These molecules showed good anti-plasmodial properties, with IC₅₀ between 10.4 to 26.5 μM.

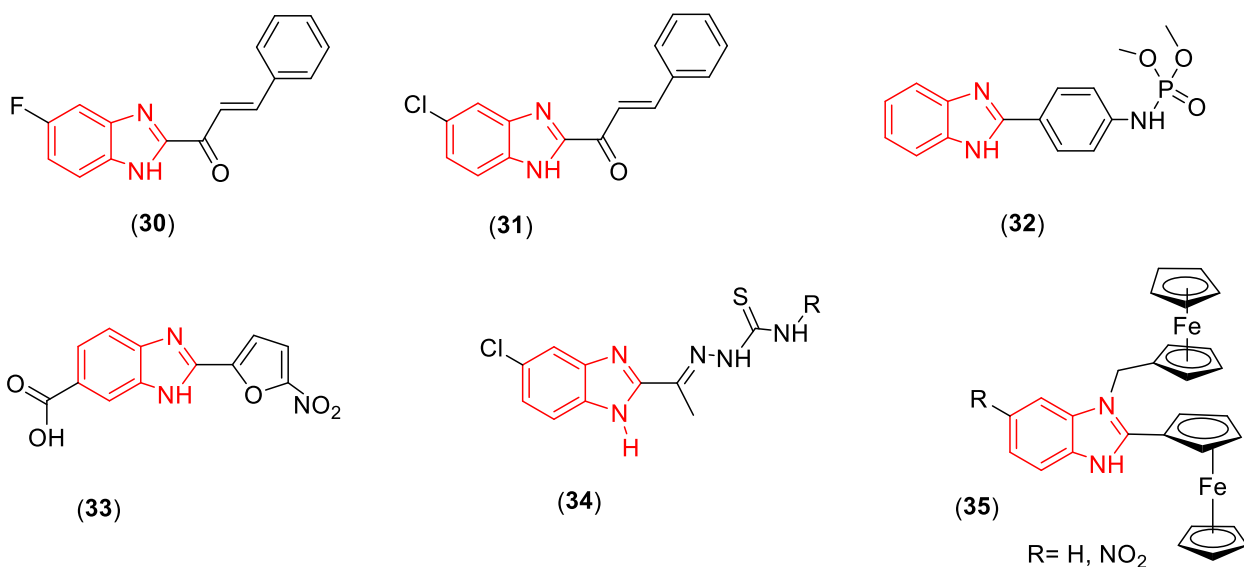


Figure 10: Benzimidazole derivatives with antiplasmodial activity.

i. Antioxidant properties of benzimidazole derivatives

Sarika Saini et al.⁵³ showed that the 2-methyl-1*H*-benzimidazole has an interesting antioxidant activity. Using 2,2-diphenyl 1-picrylhydrazyl (DDPH), they were able to show that 2-methyl-1*H*-benzimidazole (Figure 11, **36**) had a higher antioxidant activity than ascorbic acid at higher concentrations.

The antioxidant activity of benzimidazole has been demonstrated by Dvornikova et al.⁵⁴ They evaluated this activity using 2-hydroxyphenyl benzimidazole derivatives (Figure 11, **37-38**) using an *in vitro* method, and compared them to a few reference molecules. It was shown that the compounds possessing the phenol group with substituents such as isobornyl and tert-butyl showed a much higher antioxidant activity than the references.

Sabrina et al.⁵⁵ evaluated the antioxidant activity of some 5-nitrobenzimidazole derivatives (Figure 11, **39-41**) in their work. Indeed, they proved that all the 5-nitro-2-substituted benzimidazole derivatives that they synthesized had antioxidant activity far superior to that of the reference molecule, with minimum inhibitory concentrations between 3.17 to 7.59 µg/mL.

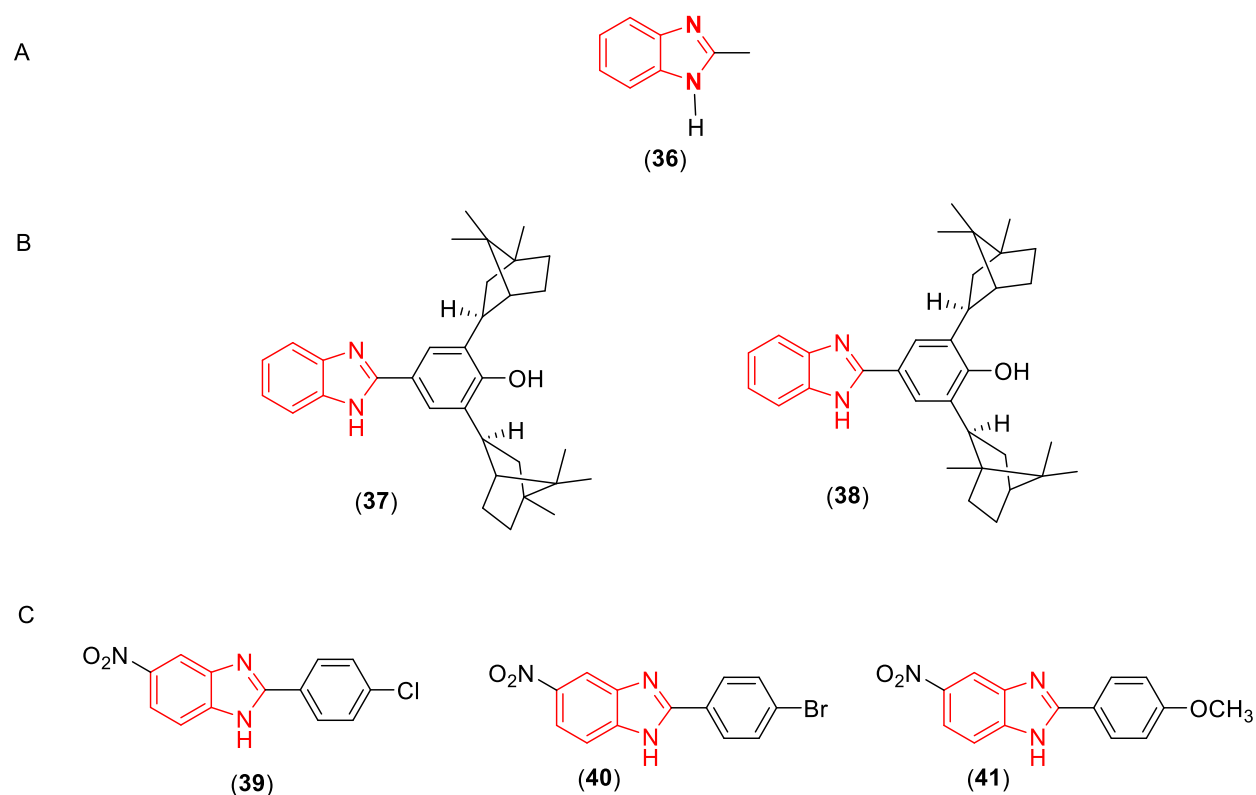


Figure 11: A. 2-methyl-1*H*-benzimidazole B. 2-hydroxylphenyl benzimidazole derivatives C. 5-nitrobenzimidazole derivatives.

2. Methods for Benzimidazole and derivative synthesis.

Benzimidazole is one of the oldest known nitrogen heterocyclic compounds. It was first synthesized by Hobercker in 1872 and later repeated in 1878 by Ladenburg and Wundt.⁵⁶ Since then, several synthetic methods have been developed to obtain functionalized benzimidazoles, mainly at positions -1, -2, -3 and -5 and they are resumed in some excellent reviews.⁵⁷

a. The Phillips methods

In 1928, Phillips synthesized 2-substituted benzimidazole derivatives by reacting orthophenylenediamine (OPDA) with various organic acids in 4N hydrochloric acid under reflux for 30–40 min.⁵⁸ These 2-substituted benzimidazole derivatives (**44**) were obtained in yields ranging from 50 to 70 % (Figure 12.A). This is the most commonly used method to obtain benzimidazole derivatives. Carboxylic acid derivatives can be replaced by mercaptoacetic acid. El-Gohary et al.⁵⁹ synthesized 2-mercaptomethyl-1*H*-benzimidazole (**46**) by condensation of mercaptoacetic acid with OPDA under the same conditions as in the Phillips reaction (Figure

12.B). Odame *et al.*⁶⁰ synthesized substituted benzimidazole derivatives at the 2-position (47) by condensing OPDA with benzoic acid derivatives. This reaction occurred in toluene under reflux for 6 h in the presence of polyphosphoric acid (PPA) (Figure 12.C). Sarika Saini *et al.*⁵³ performed the same type of work by condensing OPDA with 90 % acetic acid at a temperature of 100°C for 2 h. After treatment with the reaction medium, 2-methyl-1*H*-benzimidazole (49) was obtained in a 72 % yield (Figure 12.D).

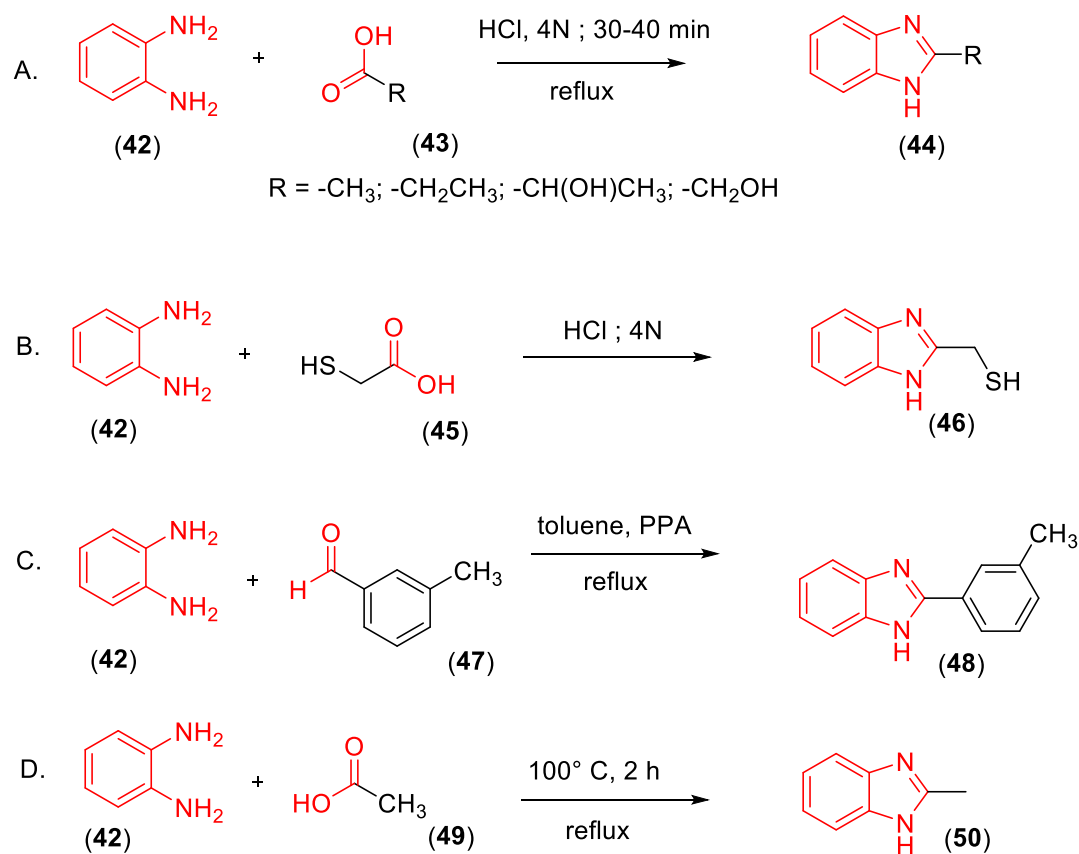


Figure 12: A. Benzimidazole synthesis by the Phillips method. B. Synthesis of 2-mercaptomethylbenzimidazole. C. Synthesis of 2-*m*-tolyl-1*H*-benzimidazole was performed according to Odame *et al.* D. Synthesis of 2-methyl-1*H*-benzimidazole according to Saini *et al.*

b. Synthesis method from orthophenylenediamine and aldehydes

The synthesis of benzimidazole via condensation between OPDA and aldehydes is commonly described in the literature. Benzimidazole derivatives were obtained from OPDA and aldehydes by using hydrogen peroxide (H₂O₂) and hydrochloric acid (HCl) solutions at 100°C (Figure 13.A) have been described by Kiumars Bahrami *et al.*⁶¹ This method made it possible to obtain

benzimidazole derivatives substituted at position -2 by aryl groups in yields ranging from 85 to 96 %. Shortly thereafter, the same authors repeated the process at room temperature by replacing water with acetonitrile.⁶² This method has been used in other study,⁶³ in which hydrochloric acid (HCl) was replaced by cerium ammonium nitrate (CAN), resulting in the production of 2-aryl-1*H*-benzimidazole in yields of 92–97 % (Figure 13.B).

In another study, Li-Hua Du et al.⁶⁴ also synthesized 2-substituted benzimidazole derivatives. They condensed OPDA derivatives with benzaldehyde derivatives in various organic solvents in the presence of iodobenzenediacetate (IBD) as an oxidizing agent. This reaction took place at room temperature for 3–5 min to obtain substituted benzimidazoles at the 2-position with yields ranging from 68 to 98 %. The highest yields were obtained when dioxane was used as the reaction solvent (Figure 13.C). Karthikeyan et al.⁶⁵ synthesized derivatives of 2-aryl-1*H*-benzimidazole substituted in position-5 by the carboxylic acid function (Figure 13.D). They reacted 3,4-diamino benzoic acid or 3,4-diamino ethyl benzoate was reacted with benzaldehyde derivatives in *N,N*-dimethyl acetamide (DMAc) at 100°C for 6–12 h in the presence of sodium metabisulfite (Na₂S₂O₅).

The condensation of OPDA with furan carbaldehyde derivatives in ethanol at room temperature resulted in a series of benzimidazole substituents at the 2-position by furan⁶⁶ with a yield of 90 % after two hours. This reaction was catalyzed by copper II, which is associated with a Schiff base (Figure 13.E). The synthesis of 2-alkyl-1*H*-benzimidazoles from OPDA and aldehydes was also performed by Alloum et al.⁶⁷ This synthetic method involves the reaction of various aldehyde derivatives with OPDA on a solid base (silica SiO₂ treated with thionyl chloride SOCl₂) in DCM at room temperature (Figure 13.F). This reaction occurs through the formation of an imine intermediate, followed by aromatization by sulfur dioxide *in situ*, leading to substituted benzimidazole derivatives at position-2.

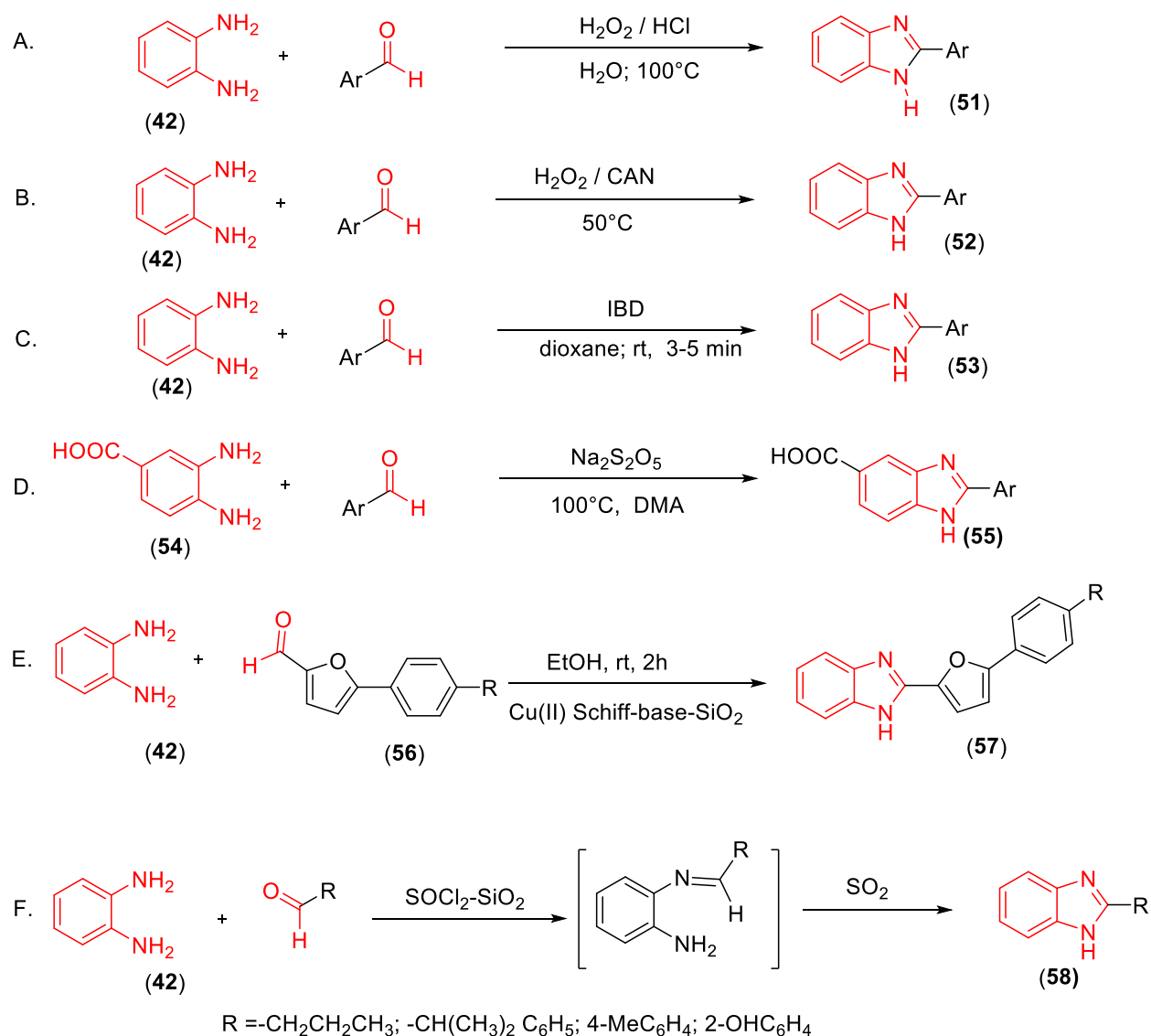


Figure 13: A. Synthesis of 2-aryl-1H-benzimidazole according to Kiumars Bahrami *et al.* B. synthesis of 2-aryl-1H-benzimidazole. C. Synthesis of the derivatives of 2-phenyl-1H-benzimidazole according to Du *et al.* D. Synthesis of derivatives of 2-aryl-1H-benzimidazole according to Karthikeyan *et al.* E. Synthesis of 2-substituted benzimidazole catalyzed by a Schiff base. F. 2-substituted benzimidazole synthesis according to Alloum *et al.*

c. Synthesis method of benzimidazole derivatives from aniline derivatives

The synthesis of benzimidazoles from aniline and aldehyde derivatives is most often catalyzed by transition metals. Some of these reactions are performed in the presence of catalysts with oxidation or reduction properties. Mehsesh *et al.*⁶⁸ reported the synthesis of benzimidazole derivatives by reacting aniline with primary amines (benzylamine) in the presence of sodium azide (NaN₃) and

copper II as a catalyst in dimethylsulfoxide (DMSO) at a moderate temperature. To improve the efficiency of this method, *tert-butyl* hydroperoxide (THBP) and acetic acid derivatives were added to the reaction medium. The reaction proceeded for 10 h in the yield range of 52–79% (Figure 14.A). In the same study, the benzylamine derivatives were replaced with benzylic alcohol derivatives. They obtained benzimidazoles in yields ranging from 35 to 62 %, but with a longer reaction time than that of benzylamines (Figure 14.B).

Yong Kim *et al.*⁶⁹ obtained benzimidazole derivatives by reacting the 2-halogeno anilines with the aromatic aldehydes for 12 h under reflux of dimethyl sulfoxide (DMSO). They were synthesized in yields ranging from 44 to 98 %. The highest yields were obtained using 2-iodoaniline in the presence of ligands such as 1,2-dimethylethylenediamine (DMEDA) and tetramethylethylenediamine (TMEDA) (Figure 14.C). Thanh N'guyen *et al.*⁷⁰ synthesized a 2-substituted benzimidazole variety without using an organic solvent. The authors condensed 2-nitroaniline with benzylamine in the presence of iron chloride for 24 h at 120°C. The 2-substituted benzimidazole derivatives were obtained in yields of 58–92 % (Figure 14.D). The production of benzimidazole derivatives was first described in 1872 by Hobrecker.⁷¹ This is one of the oldest methods to access benzimidazole scaffolds. After the reduction of 2-nitro-5-methylacetanilide, intramolecular cyclization occurred, yielding 2,5-dimethyl-1*H*-benzimidazole (Figure 14.E).

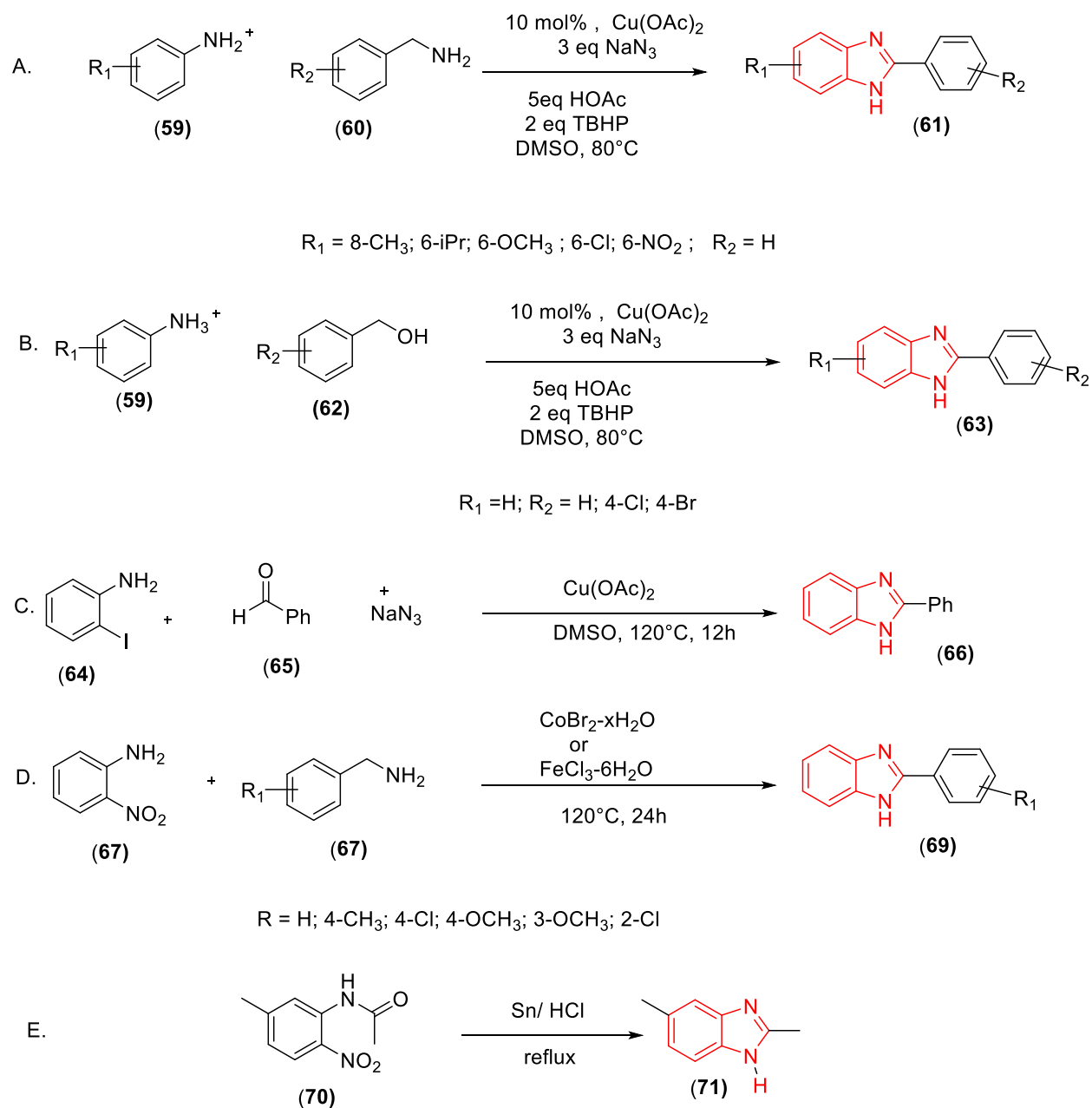


Figure 14: Synthesis of derivatives of 2-phenyl-1*H*-benzimidazole using benzylamine according to the method described by Mehshesh *et al.* B. synthesis of the derivatives of 2-phenyl-1*H*-benzimidazole using phenylmethanol, according to the method described by Mehshesh *et al.* C. synthesis of the derivatives of 2-phenyl benzimidazole according to Yong Kim *et al.* D. Synthesis of benzimidazole-2-substituted derivatives according to Thanh N' Guyen *et al.* E. Hobercker synthesis of 2-methyl-1*H*-benzimidazole.

d. Method of synthesis from orthophenylenediamine (OPDA) derivatives and N-substituted formamide and amidinium salts

Deepak Nale et al.⁷² synthesized derivatives of N-alkylbenzimidazole (**74**) by reacting a variety of OPDA with formamide N-substituted with zinc diacetate ($\text{Zn}(\text{OAc})_2$) as a catalyst in the presence of poly(methylhydrosiloxane) (PMHS) for 18 h at 120°C (Figure 15.A). In our group, we have also worked on the synthesis of benzimidazole scaffolds. We developed a method by Sissouma et al.⁷³ in which a thioalkyl or thioaryl group of an amidinium salt was introduced at the 3-position. The condensation of these amidinium salts with OPDA in dichloromethane provided access to 2-thioalkylbenzimidazole (**77**) and 1H-benzimidazole derivatives (Figure 15.B).

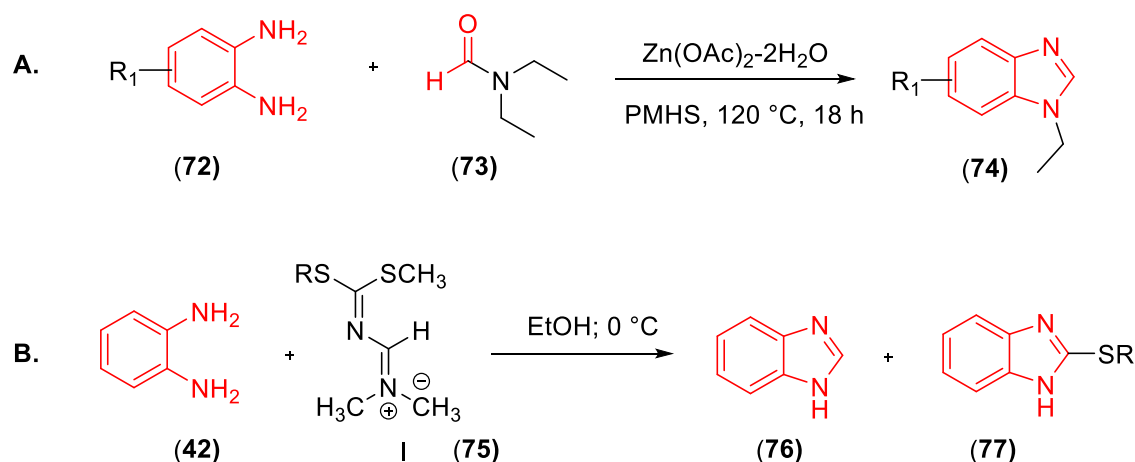


Figure 15: A. Synthesis of N-substituted benzimidazole derivatives according to Deepak Nale. B. Synthesis of benzimidazole and 2-thiobenzimidazole according to Sissouma et al.

e. Synthesis method from benzodiazepines

We also developed another method in a study conducted by Timotou et al.⁷⁴ We synthesized benzimidazole derivatives by the cyclic regression of benzodiazepines (**80**). This method involves treating chalcones (**78**) in an alkaline medium to obtain benzodiazepine derivatives (**80**). The benzodiazepines were then treated under DMF reflux in the presence of potassium carbonate (K_2CO_3) for 24 h to obtain benzimidazole derivatives. Camara et al.⁷⁵ repeated this method by treating benzodiazepine formed either in acid or basic medium under DMF reflux for 2 h. The yields were improved in acidic medium, between 60 and 80%, whereas in basic medium, the yields varied between 40 and 60% (Figure 16).

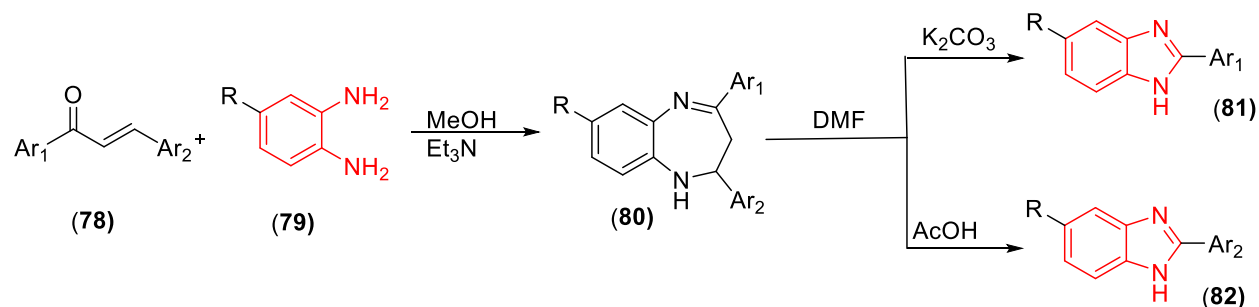


Figure 16: Synthesis of 2-aryl benzimidazole derivatives according to Camara *et al.*

f. Method of synthesis from OPDA derivatives and other reagents

By reacting OPDA with ethyl acetoacetate under reflux with xylene for 6 h, Mondieig *et al.*⁷⁶ synthesized benzimidazoles by introducing an isopropenyl group at position-1. Thus, N-isopropenylbenzimidazolone was obtained in a 70% yield (Figure 17.A). The same method was used by Mamedov *et al.*⁷⁷ to describe the synthesis of benzimidazolone derivatives *via* the formation of a reactive intermediate, benzodiazopinone. Once isolated, it was refluxed with methoxyethanol, allowing a rearrangement to lead to benzimidazolone derivatives with a yield of 60% (Figure 17.B). The 2-amino-5-chlorobenzimidazole was synthesized by Leonard *et al.*⁷⁸ *via* the reaction between p-chloro-OPDA and cyanogen bromide (BrCN). The reaction was performed in the presence of hydrochloric acid in an $\text{EtOH}/\text{H}_2\text{O}$ mixture at 70 °C. After cooling, the reaction medium was neutralized with sodium hydroxide solution to give 2-amino-5 chlorobenzimidazole in 73% yield (Figure 17.C). Benzimidazole derivatives were synthesized by reacting thiocarbamates with OPDA derivatives in an aqueous solution of sodium hydroxide and applying the Phillips method to iminoester⁷⁹ and thiocarbamate⁸⁰ acid derivatives. This reaction resulted in albendazole analogs after the removal of the thiol group and ammonia (Figure 17.D).

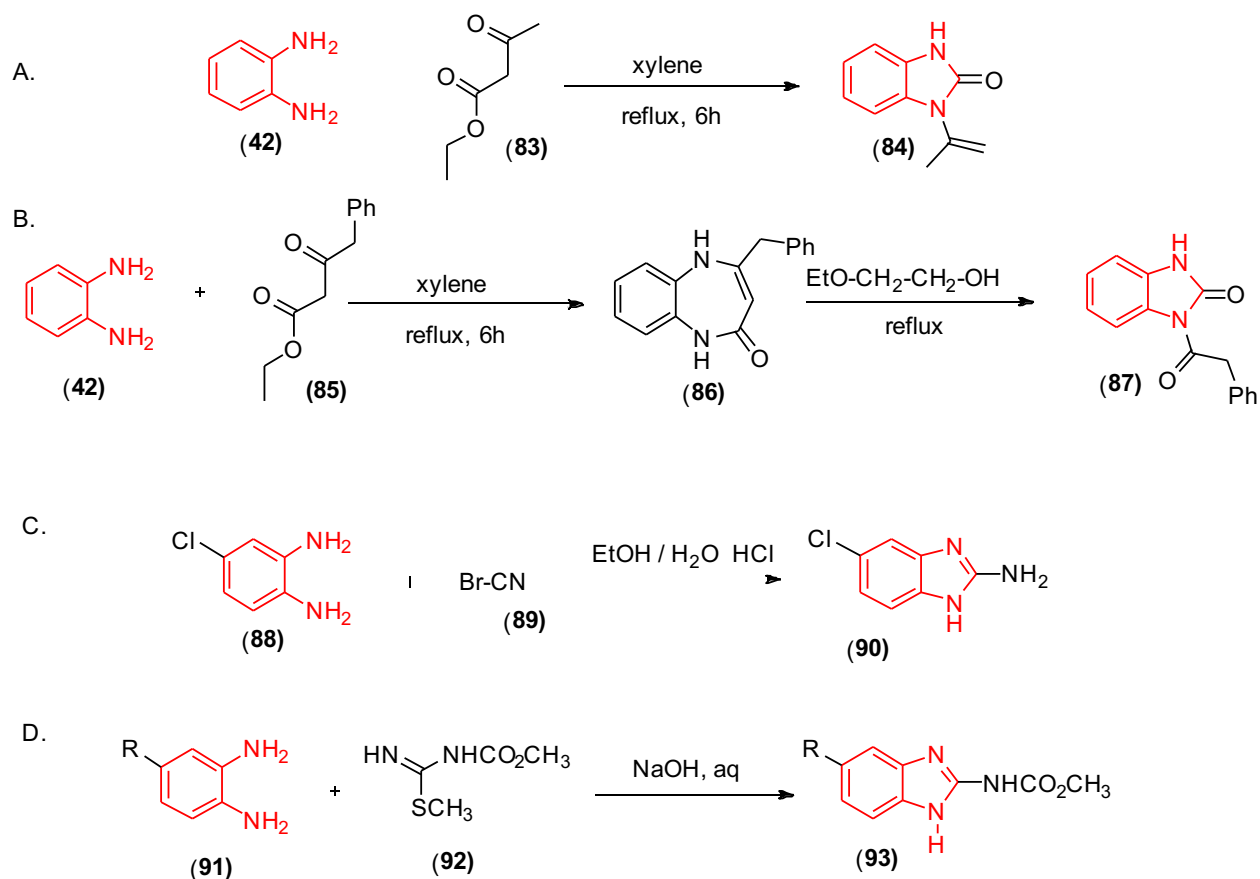


Figure 17: A. Synthesis of N-alkylbenzimidazolone derivatives according to Denise Mondieig *et al.* B. Synthesis of N-alkylbenzimidazolone derivatives according to the method of Mamedovet *et al.* C. synthesis of derivatives of 2-aminobenzimidazole Leonard *et al.* D. Albendazole synthesis method.

g. Method of synthesis from derivatives of orthophenylenediamine and carbon disulfide

The synthesis of the derivatives of 2-mercapto-1*H*-benzimidazole was carried out according to the method described by Van Allan *et al.*⁸¹

Thus, the action of carbon disulfide on OPDA derivatives in dimethylformamide (DMF) under magnetic agitation for 24 h leads, after the addition of water to the reaction mixture to the formation of 2-mercapto-1*H*-benzimidazoles (Figure 18.A). Bhanage *et al.*⁸² synthesized 1,3-dihydrobenzimidazol-2-one by replacing the carbon disulfide with urea. OPDA was condensed with urea in DMF at 150°C. They obtained 1,3-dihydrobenzimidazol-2-one in a 98% yield (Figure 18.B).

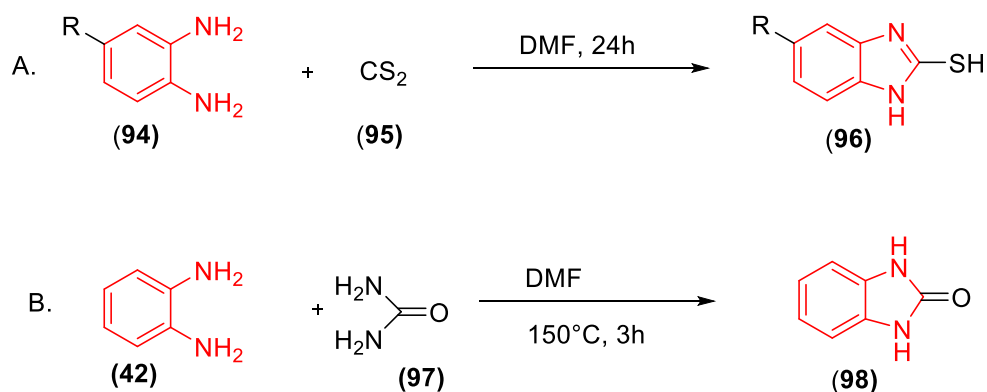


Figure 18: A. Synthesis of mercapto-1*H*-benzimidazole according to Van Allan *et al.* B. Synthesis of 1,3-dihydrobenzimidazol-2-one according to the method described by Bhanage *et al.*

II. Imidazo[1,2-*a*]pyridines : Biological Activities and Synthesis Methods

Imidazo[1,2-*a*]pyridines are aromatic bis-heterocyclic compounds that result from the addition of an *a*-type fusion of pyridine and imidazole rings with an angular nitrogen connecting the two cycles. Depending on the positions of the pyrrolic nitrogen and angular nitrogen, three isomers were obtained (Figure 19.A). Imidazopyridine is an important pharmacophore widely used in many biologically active compounds. Many studies have been conducted on this bis-heterocyclic compound, and some drugs have been obtained from these studies.

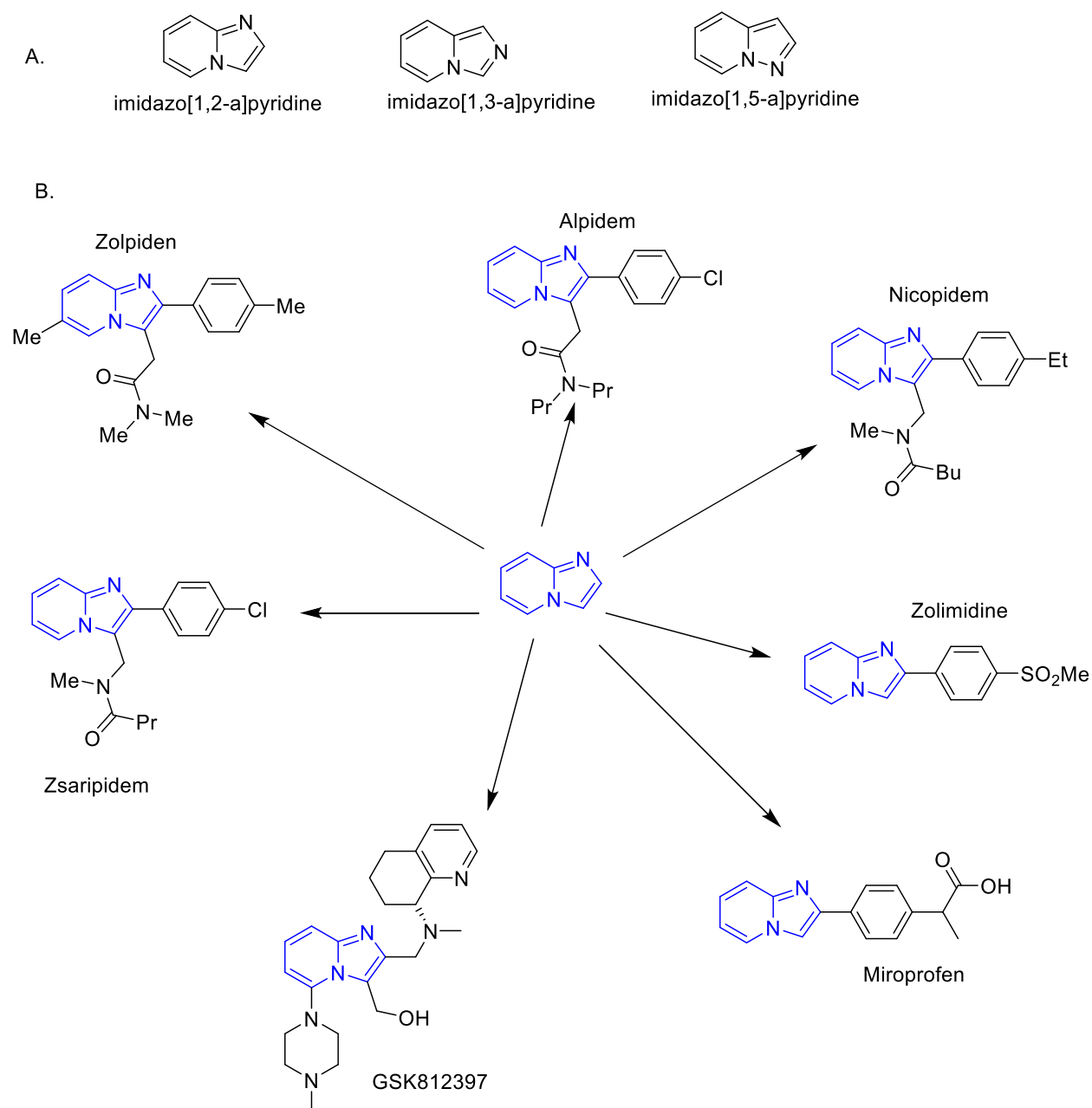


Figure 19 : A. Three imidazopyridine isomers B. Few drugs based on Imidazopyridine scaffold.

II-1. Biological activities of the imidazopyridine scaffold

According to the pharmacomodulations performed at different positions of the imidazo[1,2-a]pyridine moiety, particularly on the pyrrolic core, interesting biological activities were observed. This phenomenon has been previously described. Furthermore, the most common biological activities were mentioned.

a. Imidazo[1,2-a]pyridine as antimicrobial agent

The antibacterial activity of imidazo[1,2-a]pyridine derivatives has been proven by Pushpalatha Budumuru et al.⁸² on various strains, including in vitro antimicrobial activities against *E. coli* (ATCC-25922), *S. aureus* (ATCC-9144), *K. pneumoniae* (ATCC-13883) and *B. subtilis* (ATCC-6051). The study was performed against the reference drug streptomycin, and the inhibition zones were calculated. Thus, all the synthesized compounds, at a concentration of 1000 µg/mL, showed promising inhibition of various microbial pathogens tested. Of the compounds synthesized (Figure 20), compounds **99a**, **99c**, **99e**, and **99g** containing benzyl, 4-fluorobenzyl, 4-methylbenzyl, and 4-methoxybenzyl substituents, respectively, demonstrated inhibition against all pathogens. Compounds **99c** and **99e**, with 4-fluorobenzyl and 4-methylbenzyl as their substituents, respectively, showed moderate activity against *E. coli*. In addition, compounds **99e**, **99g**, and **99j**, containing 4-methylbenzyl, 4-methoxybenzyl, and 3,4,5-trifluoromethylbenzyl substituents, respectively, showed inhibition against *K. pneumoniae*. All the synthesized compounds showed low activity against *S. aureus*. Similarly, no activity was recorded for compounds **99a**, **99b**, **99d**, **99g**, **99h**, **99i**, and **99l** at the lowest concentrations (500 µg/mL) tested against *K. pneumoniae*. In addition, the work of Kai et al.⁸³ has led to the antimycobacterium (*Tuberculosis* bacteria) activity of new imidazo[1,2-a]pyridine-3-carboxamide derivatives. Thus, they proved that compounds with donor groups on the phenyl nucleus, had excellent antimycobacterial activity against two MTB H37RV drugs and drug-resistant clinical isolates with inhibition concentrations between 0.0041 to 2.64 µM.

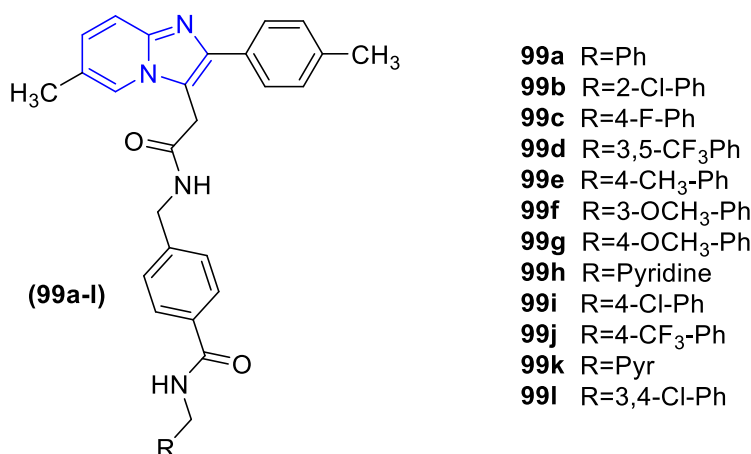
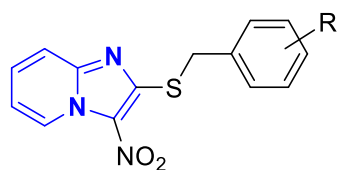


Figure 20 : Imidazo[1,2-a]pyridine derivatives by Pushpalatha Budumuru et al. against *E. coli* (ATCC-25922), *S. aureus* (ATCC-9144), *K. pneumoniae* (ATCC-13883) and *B. subtilis* (ATCC-6051).

In our own work, Ablo et al.⁸⁴ we also explore the antibacterial activity with a set of 2-thiobenzyl-3-nitro-imidazo[1,2-a]pyridine derivatives. Eight (Figure 21, **100a–h**) of them were evaluated *in vitro* on the positive gram bacterium (*S. aureus* ATCC 29213) and two others negative gram bacteria (*P. aeruginosa* ATCC 27853 and *P. aeruginosa* 933 C/21) by methods diffusion in solid medium and liquid macrodilution. Five among the eight compounds (**100a**, **1020**, **100h**, **100f** and **100g**) showed significant antibacterial activity on *P. aeruginosa* ATCC 27853 and *P. aeruginosa* 933 C/21 with MIC between 7.81 and 250 mg/mL. All compounds were inactive on *S. aureus*. The compounds **100a** and **100g** were more potent on the two strains of *P. aeruginosa* ATCC 27853.



- 100a** R=H
- 100b** R=4-Cl
- 100c** R=4-CO₂Me
- 100d** R=4-F
- 100e** R=2-NO₂
- 100f** R=3,5-dichloro
- 100g** R=4-CH₃
- 100h** R=4-CF₃

Figure 21 : Set of 2-thiobenzyl-3-nitro-imidazo[1,2-a]pyridine derivatives against *S. aureus* (ATCC-29213), *P. aeruginosa* (ATCC 27853) and *P. aeruginosa* (933 C/21).

b. Imidazo[1,2-a]pyridine as an anticancer agent

Various *in vitro* studies have shown that several imidazopyridine-based compounds have potential therapeutic effects on different cancer cell lines. These include breast, liver, colon, brain, lung, and kidney cancer.⁸⁵ The anticancer effects of these compounds are primarily due to their inhibitory effects on various molecular mechanisms. Namely, PI3K/ AKT, CENP-E, IGF-1R, CDK, inhibition of tubulin polymerization, and C-encounter inhibition.

Similarly, Song et al.⁸⁶ initiated modulations around the imidazopyridine core, which conferred anticancer activity. Thus, modulations at the -2 position by phenyl derivatives and at the -3 position by quinoxaline (**101**) and quinoxalone (**102**) derivatives resulted in imidazo[1,2-a]pyridine derivatives that inhibited tumor cell proliferation. This was the case with compounds (**101**) and (**102**) at a concentration of 20 μM, which over 48 hours showed a very high inhibition rate in HCT-116, HeLa, and MCF-7 cells.

Dahan-Farkas et al.⁸⁷ also demonstrated anticancer activity of the imidazopyridine nucleus in colon cancer. The anticancer activities of the synthesized 6-substituted imidazo[1,2-a]pyridines were

evaluated in HT-29 and Caco-2 cell lines. Thus, all compounds bearing a 6-position nitro-substituent (NO₂) in the imidazopyridine nucleus and all compounds bearing a 2,5-dihydroxyphenyl substituent attached to imidazopyridine showed little reduction in cell growth in colon cancer cell lines. In contrast, imidazopyridine derivatives containing a protected hydroxyl group (such as OMe, compound **101**) and a nitrogen-substituted phenyl group (compound **104**) generally performed well by reducing the cell viability by more than 50% with concentration values well above 50 μ M.

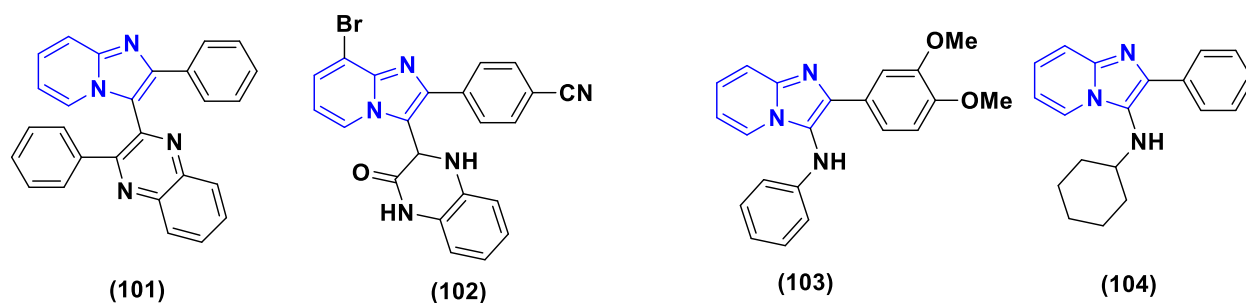


Figure 22 : Modulations around the imidazopyridine core conferring anticancer activity.

c. Imidazo[1,2-a]pyridine as an antiplasmodial

The antiplasmodial activity of the imidazo[1,2-a]pyridine motif was demonstrated in our group and published by Mahama Ouattara *et al.*⁸⁸ We designed by juxtaposition of anti-infectious moieties, a series of hybrid imidazopyridinyl-arylpropenone compounds and performed the anti-plasmodial screening of five imidazopyridinyl-arylpropenone derivatives using the Rieckmann method, followed by the determination of HRP2 antigen production by ELISA on chloroquino-sensitive and chloroquino-resistant *P. falciparum* isolates. The analysis of antiplasmodial activity was translated into an inhibitory concentration of 50 (IC₅₀) and expressed in micromoles (mM). Their results on the chloroquino-sensitive *Plasmodium falciparum* isolates reveal that the **106** and **6y** compounds (IC₅₀ = 35.92 and 24.08 mM respectively) have moderate antiplasmodial activity, while the other three (**105**, **107** and **108**) possess have very good antiplasmodial activities, between 8.65 and 6.23 mM. Five imidazopyridinyl-arylpropenone compounds (**105**, **106**, **107**, **108** and **109**) were highly active against *P. falciparum* chloroquino-resistant isolates.

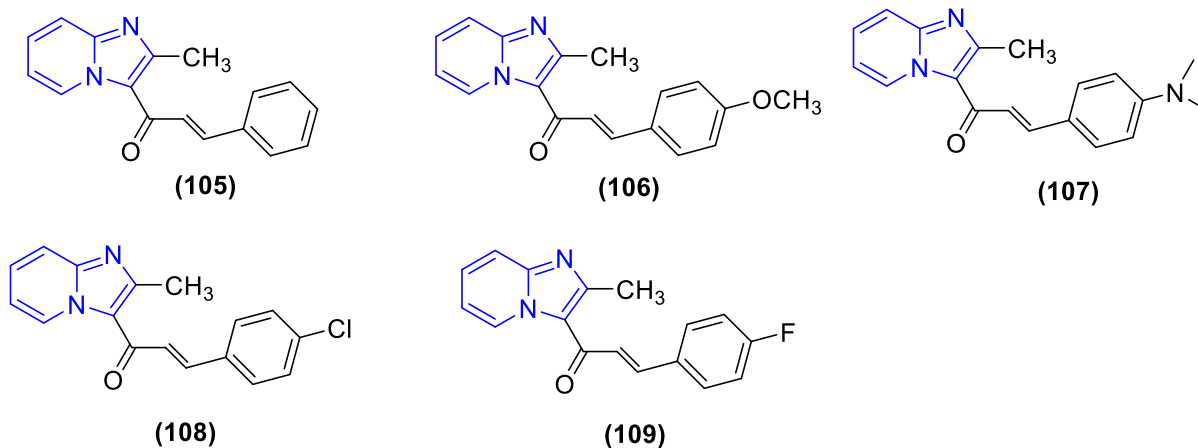


Figure 23: 3-(phenyl)-1-(2-methyl*H*-imidazo[1,2-*a*]pyridin-3-yl)prop-2-en-1-one derivatives against *Plasmodium Falciparum*

d. Imidazo[1,2-*a*]pyridine as an antiviral agent

The antiviral activity of imidazopyridine scaffolds has been demonstrated by researchers since the 1990s. Hamdouchi et al.⁸⁹ showed that some derivatives of 2-amino-3-substituted-6-[1-phenyl-2-(*N*-methylcarbamoyl) vinyl] imidazo [1,2-*a*]pyridines (Figure 24, **110**) exhibited strong anti-rhinovirus activity and no obvious cell toxicity.

Alain Gueiffier et al.⁹⁰ performed chemical modifications at the position-3 of the imidazo[1,2-*a*]pyridine the ring. This has improved the therapeutic index of this new class of antiviral agents. Thus, antiviral compounds, as indicated by the series of their molecules, have shown that some of their compounds (**111**,**112**) appear to be the most potent and selective inhibitors of CMV and VZV compared with three reference drugs, ganciclovir, acyclovir, and brivudin.

Several sugar-substituted imidazopyridine derivatives have shown significant activity against human cytomegalovirus. Indeed, the evaluation of their activities against two selected herpes and cytotoxicity studies demonstrated that racemic 2,6-dichloro-3- (β -D / L-Erythrofuranosyl)imidazo[1,2-*a*] Pyridine and 2,6-dichloro-3-(α -D / L-Erythrofuranosyl) imidazo[1,2-*a*]pyridine (**114**) were both inactive against HCMV and HSV-1 and nontoxic on uninfected cells.^{91,92} In contrast, an enantiomeric mixture of 2,6,7-trichloro-3- (α -D/L-erythrofuranosyl)imidazo[1,2-*a*]pyridine (**113**) was active against HCMV and HSV-1. They noted that the α (10) anomer was more active than the β anomer was.

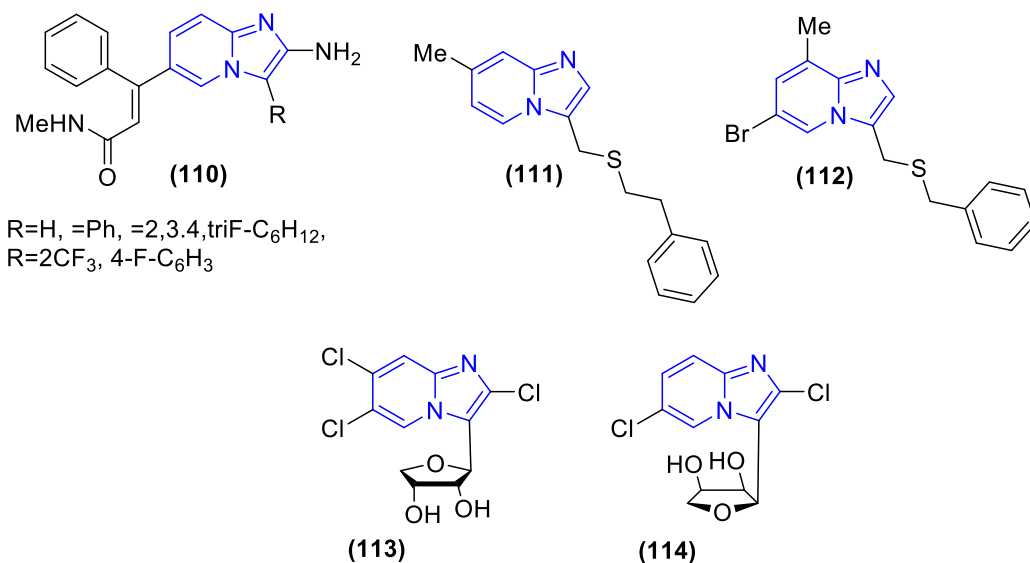


Figure 24 : Imidazopyridine derivatives with antiviral activities.

e. Imidazo[1,2-a]pyridine as an anthelmintic

Jean-Paul Déto et *al.*⁹³ described a new series of imidazo[1,2-a]pyridine-based anthelmintic, showing an action on the parasitic nematode *Strongyle Haemonchus contortus*. One of its compounds (Figure 25, **115**), the most powerful, inhibited the motility of worms at 31.25 μ M. In addition, an original mode of action was unveiled for this compound, since the observed paralysis was correlated with an antagonistic effect on the two levaamisole – nAChR1 and two other subtypes.

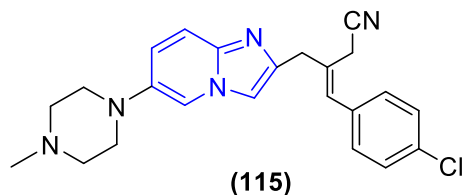


Figure 25: Structure of 4-(4-chlorophenyl)-3-((6-(4-methylpiperazin-1-yl)H-imidazo[1,2-a]pyridin-2-yl)methyl)but-3-enitrile with anthelmintic activity.

f. Imidazo[1,2-a]pyridine as an antileishmanial agent

Cyril Fersing et *al.*⁹⁴ showed that the 3-nitroimidazo[1,2-a]pyridine derivatives substituted in the 2-position by thiobenzyl have good antileishmanial activities. Indeed, the *in vitro* evaluation of these compounds showed that one of them (**116**) was successful pest control.

This single molecule exhibited low cytotoxicity to human cell-line HepG2 ($CC_{50} > 100 \mu$ M) showed good antileishmanial activity ($IC_{50} = 12.1 \mu$ M) against *L. donovani*, *L. infantum*, and *L. major* and

good antitrypanosomian activities ($IC_{50} = 1.3\text{-}2.2 \mu\text{M}$) against *T. brucei* and *T. cruzi*, in comparison with several reference drugs such as miltefosin, fexinidazole, eflornithine and benznidazole ($IC_{50} = 0.6\text{-}13.3 \mu\text{M}$).

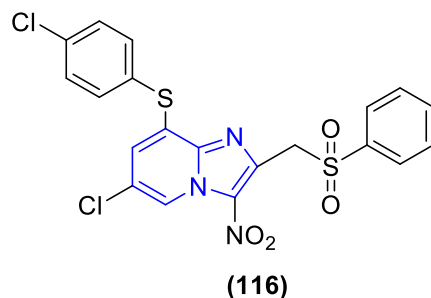


Figure 26: Structure of 6-chloro-8-((4-chlorophenyl)thio)-3-nitro-2-((phenylsulfonyl)methyl)imidazo[1,2-a]pyridine.

g. Imidazo[1,2-a]pyridine as anti-tuberculosis drug

Mycobacterium tuberculosis is a major human pathogen and the cause of lung disease.⁹⁵ Through the use of high-throughput whole-cell screening from a library of extended compounds, a number of imidazo[1,2-a] pyridines were obtained as highly active molecules against *M. tuberculosis* and *Mycobacterium Bovis* BCG. Some imidazopyridine derivatives (**117-119**) showed inhibitory diameters (MICs) in the 0.03 to 5 mm range against *Mycobacterium Bovis* strain.

In addition, Garrett C. Moraski et al. on imidazopyridines, has led to antituberculosis compounds.⁹⁶ The 2,7-dimethylimidazo[1,2-a]pyridine-3-carboxamide derivatives (**120, 121**) synthesized, were evaluated for their *in vitro* antituberculosis activities in comparison to the replication of resistant MTB strains. The synthesized imidazopyridine derivatives showed better anti-tuberculosis activities comparable to Nitroimidazole clinical candidate PA-82419 (CMI_s versus MDR-TB of 0.03 to 0.25 $\mu\text{g}/\text{mL}$ or 0.08 to 0.7 μM , respectively) at concentrations below 1 μM .

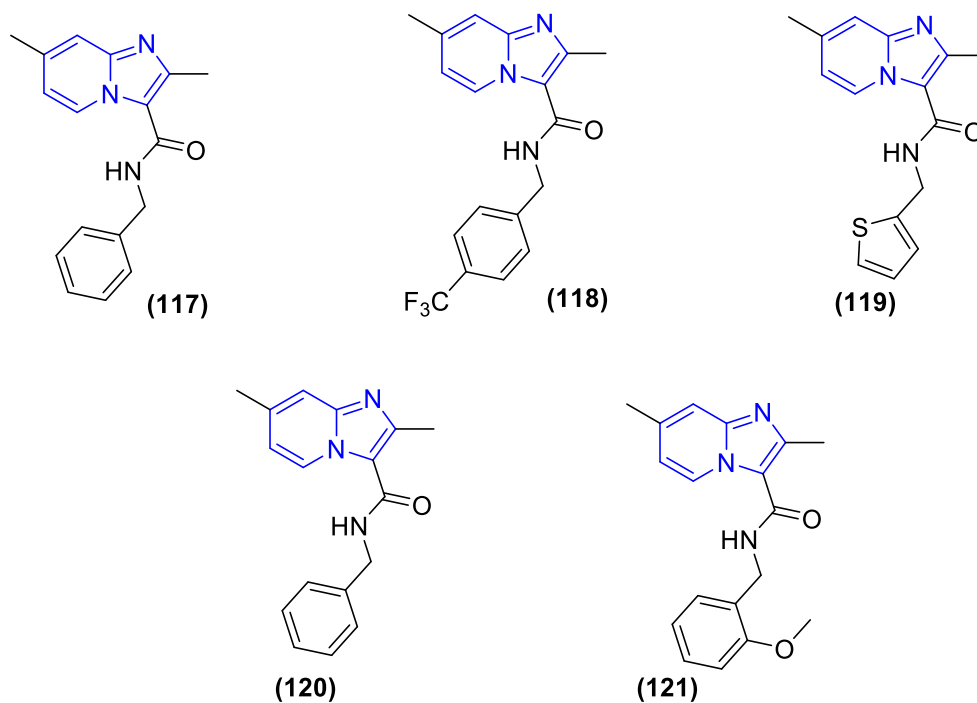


Figure 27: 2,7-dimethylimidazo[1,2-a]pyridine-3-carboxamides derivatives found as antituberculosis drugs.

h. Imidazo[1,2-a]pyridine as a pest control

Pest control potency of imidazopyridine was assessed using *Trichomonas vaginalis*. GT3 is a highly pathogenic strain isolated in the city of Guanajuato, Mexico in 2012. Margarita Lopez-Martinez *et al.*⁹⁷ showed that most of the synthesized compounds got antiparasitic activity after 24 h of treatment. As a result, the results, the ethyl 3-nitroimidazo[1,2-a]pyridine-2-carboxylate (**122**) and the 3-nitroimidazo[1,2-a]pyridine (**123**) had good anti-parasitic activity, requiring 2.45–3.96 μM to reach the desired effect. They also correlated the partition coefficient ($\log P$) and antiparasitic activity for all tested samples. A mathematical descriptor correlating the exhibited pharmacological activity and $\log P$ was found ($0.9 \pm 0.3 \log P$), which suggests that an optimum balance between hydrophilic and lipophilic properties is most convenient. Calculations based on this equation show that 84% of the total activity variation may be described by these two variables.

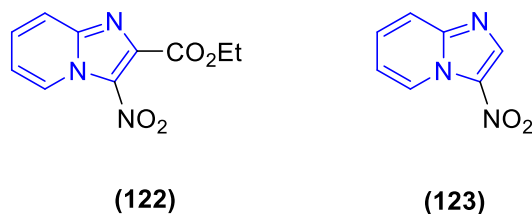


Figure 28: 3-nitro-imidazopyridine derivatives possessing antiparasitic activity.

i. Imidazo[1,2-a]pyridine as an antifungal agent

Several synthetic imidazopyridine derivatives were evaluated for their *in vitro* antifungal activities against *Aspergillus fumigatus* 3007 and *Candida albicans* 3018.⁹⁸ The test on these strains showed that all the prepared compounds inhibited the growth of the fungi to different degrees. Among the prepared compounds, compound **126** had the highest inhibitory index of 52.12% after 96 h of incubation, followed by compounds **124** and **125**, which showed inhibitory indices of 49.87 and 43.51%, respectively. The authors also investigated the effects of the synthetic compounds on the unicellular fungus *C. albicans* 3018 after 24h of incubation. These compounds were tested at concentrations ranging from 0.0976 to 100 µg/mL. Compound **126** showed the lowest inhibitory concentration (0.390 µg/mL). Compounds **125** and **126** completely inhibited fungal growth at a concentration of 0.781 µg/mL.

In one of our work, Adingra et al.⁹⁹ investigate after synthesis of fifteen (15) derivatives of 3-imidazo[1,2-a]pyridinyl-1-arylpropanone (**127a-o**), the antifungal activity on a resistant strain of *Candida albicans* by the microdilution method. The results showed that four (4) of them (**127a**, **127b**, **127c**, and **127i**) were active with minimum inhibitory concentrations (MICs) below 300 µmol/L. Of these four compounds, **127i** was more potent than the others with a MIC of 41.98 µmol/L.

In a continued work, Adingra et al.¹⁰⁰ investigated the antifungal activity of hydrazide-hydrazones derivatives (**128a-r**) containing the imidazo[1,2-a]pyridine backbone on *Candida albicans* n°396 from the CeDReS collection. The results demonstrate that antifungal activity varies according to the substituent present on the phenyl ring of each derivative. The weakly electron-donating or electron-withdrawing compounds seem to be the most active. Thus, methylated (**128d**) and brominated (**128i**) derivatives were the most efficient with respectively minimum inhibition concentrations (MICs) of 4.06 and 8.61 µmol/L.

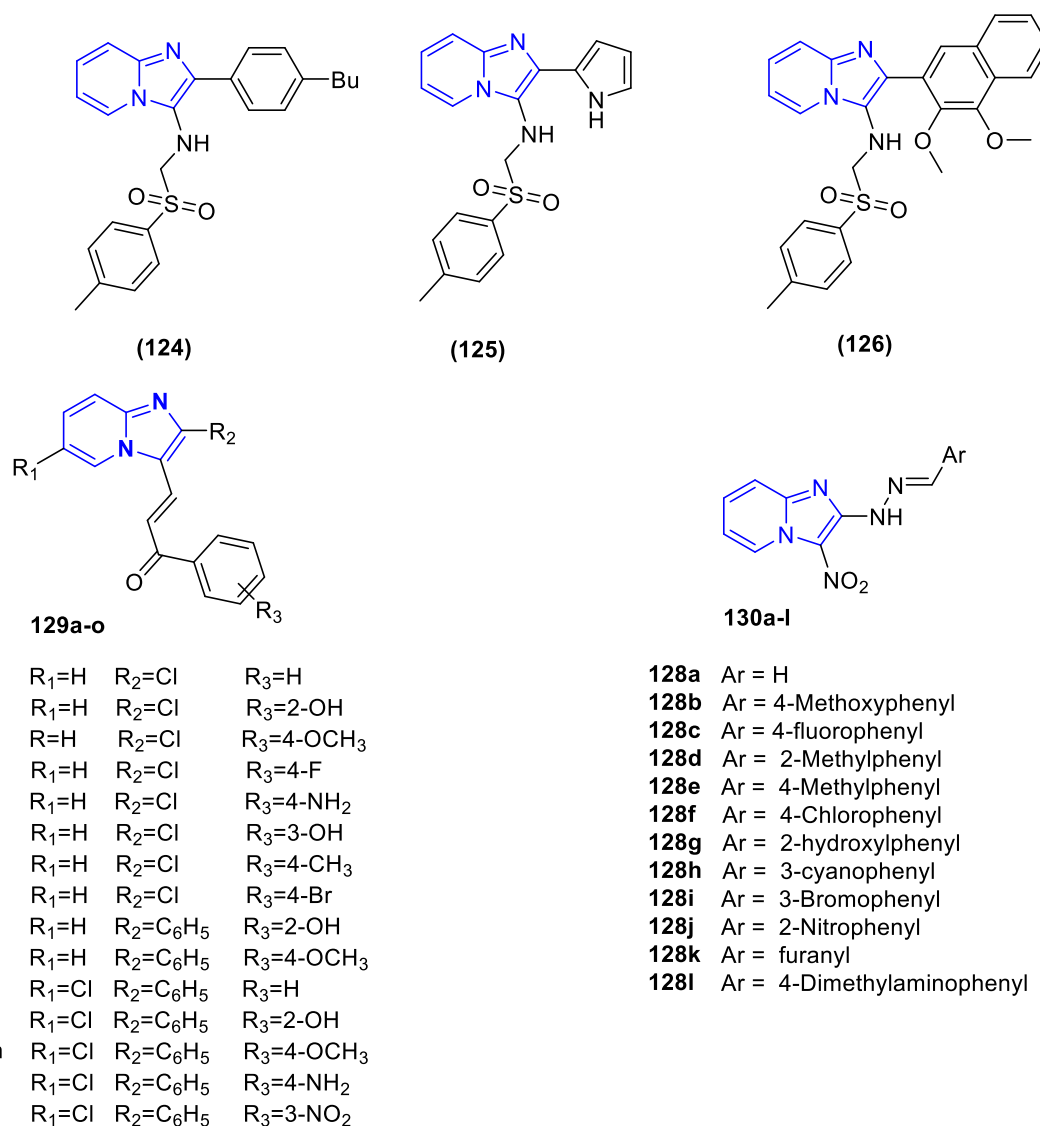


Figure 29: N-substituted-2-aryl-imidazopyridine derivatives with antifungal activity.

j. Imidazo[1,2-a]pyridine as an anti-inflammatory agent

Renata B. et al.¹⁰¹ analyzed *in vivo* assays of Nociception, hyperalgesia, inflammation and *in vitro* of human PGHS-2 inhibitory compounds. This study suggests that some compounds can significantly inhibit edema formation. Three (129,130,131) of the prepared imidazopyridine derivatives exhibited excellent anti-inflammatory activity with an inhibition concentration of 8.7 Lmol/kg (3.4 mg/kg) compared to celecoxib, a selective PGHS-2 inhibitor (IC₅₀ = 2.8 lumens), representing the standard anti-inflammatory drug (30% inhibition at 100 Lmol/kg).

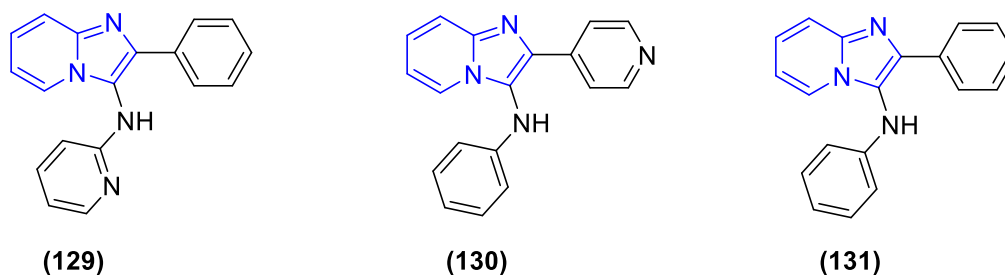


Figure 30: Imidazo[1,2-a]pyridin-3-amine derivatives with anti-inflammatory activities.

II-2. Methods of synthesis of the imidazopyridine scaffold

The imidazo[1,2-a]pyridine ring was first described by Tschitschibabin¹⁰² in 1925, and for a long time, this framework has not been fully studied, partly because of the lack of effective functional methods and structural variants, especially in the pyridine core. However, much work has been done on the synthesis, physical properties, and reactivity of this ring for decades. In particular, advances in catalytic chemistry and metal-coordination chemistry have facilitated access to new functions. It should be noted that to carry out the synthesis of imidazo[1,2-a]pyridines, several methods are described in the literature. Of all the methods, two are the most popular. These include the condensation of 2-aminopyridine with α -halogenocarbonyls and the multicomponent reaction between the same amino substrate itself and a carbonyl compound and isonitrile compounds.

a. Synthesis from 2-aminopyridine with α -halogenocarbonyl compounds

In 1961, W. L. Mosby *et al.*¹⁰³ were able to synthesize the imidazo[1,2-a]pyridine scaffold while modifying the Tschitschibabin method, using 2-aminopyridine and bromoacetaldehyde in refluxing hydrated ethanol in the presence of sodium bicarbonate (Figure 31a).

Trabanco *et al.*¹⁰⁴ cyclized 2-bromo-4,4,4-trifluorobutanal and 2-amino-4-chloro-3-iodopyridine in ethanol in the absence of a base, but in a microwave oven at 150°C. The substituted pyridine at position-3 had a good yield in 50 min, which considerably reduced the reaction time. In 2013, Castera-Ducros *et al.*¹⁰⁵ synthesized 2-chloromethylimidazopyridine derivatives in one-step with yields ranging from 40 to 70 %. They performed a cyclic condensation reaction between 2-aminopyridine and 1,3-dichloroacetone derivatives by refluxing in ethanol for 4 h.

Maxwell *et al.*¹⁰⁶ synthesized an imidazo[1,2-a]pyridine core substituted at position-2 using a two-stage reactive halogen. First, 2-aminopyridine was reacted with 2-chloroacetic acid in water in the presence of triethylamine at 90°C for 5 h to obtain a reactive intermediate. The latter was treated

again in the presence of POCl₃ in toluene at 115°C for 16 h to obtain an imidazo[1,2-a]pyridine core substituted with chlorine at the -2 position. The replacement of the imidazo[1,2-a]pyridine scaffold at the 2-position with an ester group was achieved after condensation between 2-aminopyridine and refluxing ethyl bromopyruvate in ethanol.¹⁰⁷ This compound was obtained at a 70% return.

Chezal *et al.*¹⁰⁸ were able to synthesize imidazo[1,2-a]pyridine substituted in position 2 by aryl (benzyl and p-methoxybenzyl) and alkyl groups (terbutyl, isopropyl, methyl, trifluoromethyl) by condensing various α -halogenocarbonyls with derivatives of 2-aminopyridine.

The 6-bromo-2-(3,4-dichlorophenyl)-imidazo[1,2-a]pyridine was reported by Shankarrapa *et al.*¹⁰⁹ by microwave irradiation with a yield of 60%. This was achieved by addition of 5-bromo-2-aminopyridine and 2-bromo-1-(3,4-dichlorophenyl)ethanone in DMF, while microwave irradiation achieved 150°C for 10 minutes at a power of 200 Watts. The solvent of this reaction can be replaced by cyclohexanone, but the reaction time increases at 18 hours and at a temperature of 130°C.¹¹⁰

This reaction was echoed by Dongjian Zhu *et al.* The work here consists of reacting derivatives of 2-aminopyridine with those of bromophenacyl at room temperature and without solvent. The method is the crushing of the two compounds in a mortar. They obtained derivatives of the imidazo[1,2-a]pyridine nucleus substituted in position -2 by aryl derivatives and in position -6 by methyl in a very short time with yields ranging from 90 to 95%.^{111,112}

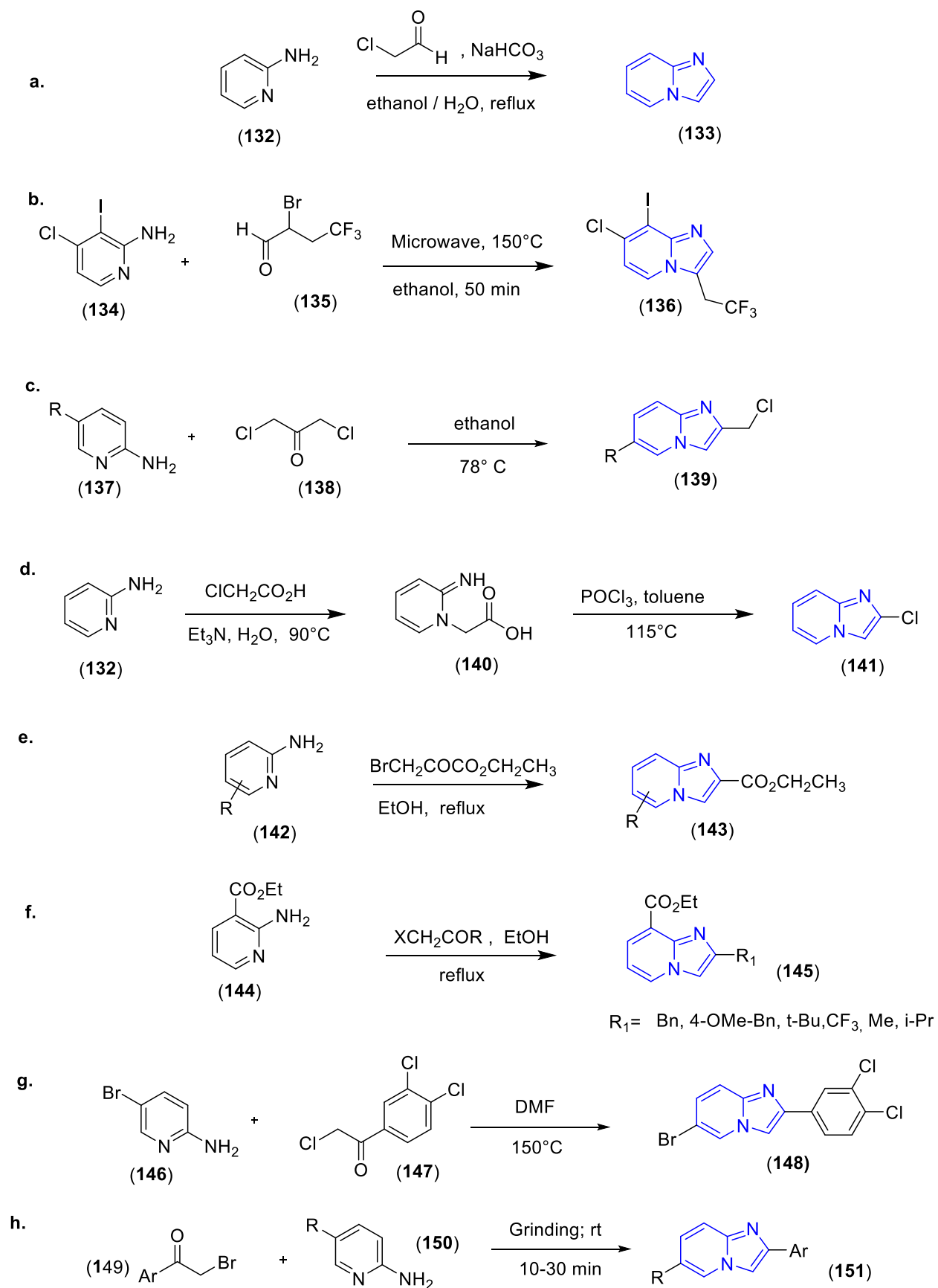


Figure 31: **a.** Tschitschibabin method of imidazopyridine synthesis **b.** synthesis of 3-(2,2,2-trifluoroethyl) *H*-imidazo[1,2-*a*]pyridine according to Andrés A. Trabanco *et al.* **c.** Synthesis method of 2-chloromethyl imidazopyridine derivatives *according* to Caroline Castera-Ducros *et al.* **d.** Synthesis method of 2-chloroimidazopyridine according to Brad D. Maxwell *et al.* **e.** Synthesis method of ethyl *H*-imidazo[1,2-*a*]pyridine-2-carboxylate derivatives **f.** Synthesis method of 2-substituted imidazopyridine according to Chezal *et al.* **g.** Synthesis method of 2-(3,4-dichloro)-6-bromo imidazopyridine according to Shankarappa *et al.* **h.** Synthesis method of 2-substituted imidazopyridine according to Dongjian Zhu.

b. Multicomponent synthesis

Multicomponent reactions are reactions that occur in one reaction step with at least three reagents. This procedure made it possible the synthesis of several rings with very interesting pharmacological properties.

Katrin Groebke *et al.*¹¹³ obtained the substituted imidazopyridine core at the 2- and 3-positions, while reacting the 2-aminopyridine with aldehydes derivatives and isonitrile. This reaction was carried out in methanol at room temperature overnight. Adding a few drops of acetic acid speeds up the condensation reaction. Derivatives of imidazo[1,2-*a*]pyridine are obtained with yields ranging from 38% to 90%. In this same dynamic, Martina Hieke *et al.*¹¹⁴ adopted the same reaction for their work, but made sure to replace morpholine for benzaldehyde (Figure 32.a).

Recently, in 2020, the team of Carlos *et al.*,¹¹⁵ this time synthesized imidazo[1,2-*a*]pyridine from the condensation of 2-aminopyridine, tert-butylisonitrile and 3-formyl-chromone in ethanol in the presence of a few drops of ammonium chloride (Figure 32.b). This reaction takes place in a microwave at 80°C for 15 min. The yields obtained (23% to 36%) are lower than previously. Long before them, the work of Taleb *et al.* followed the same path to the synthesis of imidazopyridines. For their work, they reacted a derivative of 2-aminopyridine with aldehyde derivatives and isonitrile in a methanol-dichloromethane mixture in volume ratio (2:3).¹¹⁶ This reaction occurred at room temperature for 12 hours in the presence of scandium triflate (Sc(OTf)₃) as a catalyst (Figure 32.c).

Mehdi Adib *et al.*¹¹⁷ synthesized imidazo[1,2-*a*]pyridine derivatives substituted in position-2 by aryl compounds and in position-3 by amine function, while condensing a mixture of isocyanide, various aldehydes and derivatives of 2-aminopyridine (Figure 32.d). The reaction is carried out in water at 70°C for 7 hours to obtain various imidazo[1,2-*a*]pyridine with yields ranging from 85% to 96%.

In 2012, Anneli Nordqvist et al.¹¹⁸ used this method while changing reaction conditions (Figure 32.e). They react aldehyde derivatives, isocyanide and 2-amino-5-bromopyridine in the presence of magnesium chloride (MgCl₂) in ethanol for 20 to 30 min in a microwave oven at 160°C. They obtained imidazo[1,2-a]pyridine derivatives substituted in position-2 by aryl compounds and in position -3 by amine function with a yield of 56%.

Ping Liu et al. developed a novel tri-component reaction synthesizing of imidazo[1,2-a]pyridine derivatives using 2-aminopyridine derivatives, aldehyde, and alkyne.¹¹⁹ After 18 h of reflux in toluene, in the presence of catalyst such as copper sulfate (CuSO₄) and 4-methylbenzenesulfonic acid (Figure 32.f), imidazo[1,2-a]pyridine derivatives are obtained with yields ranging from 28% to 68%.

Pushpalatha B. et al.⁸² synthesized imidazo[1,2- a]pyridine from 4-methyl acetophenone, 2-amino-5-methyl pyridine and dibrome (Br₂) in methanol in the presence of Lewis acid (AlCl₃). This reaction (Figure 32.g) occurred between 0 and 5°C with a 57% yield.

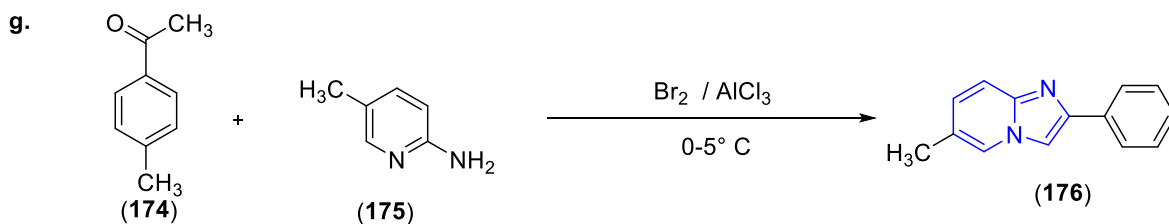
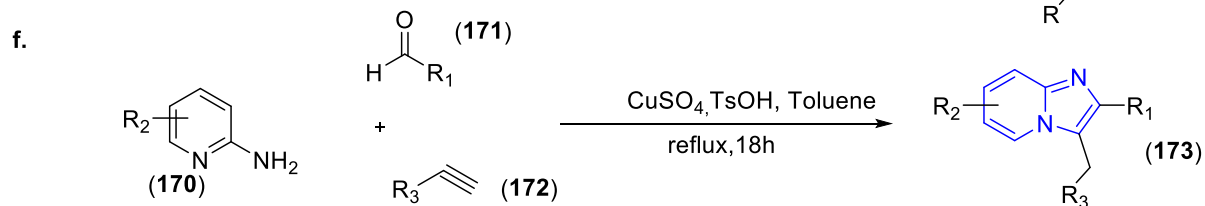
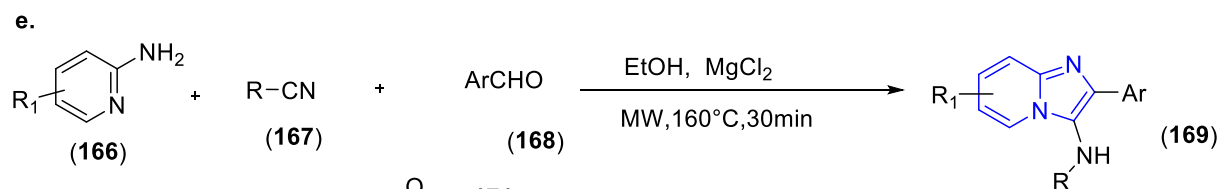
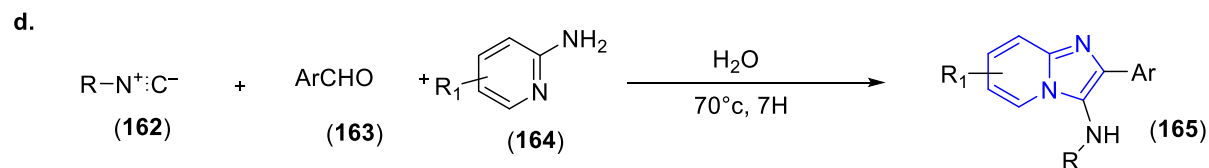
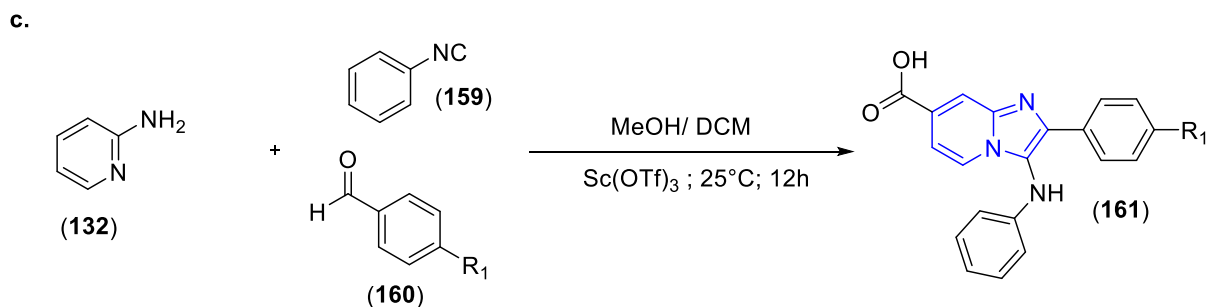
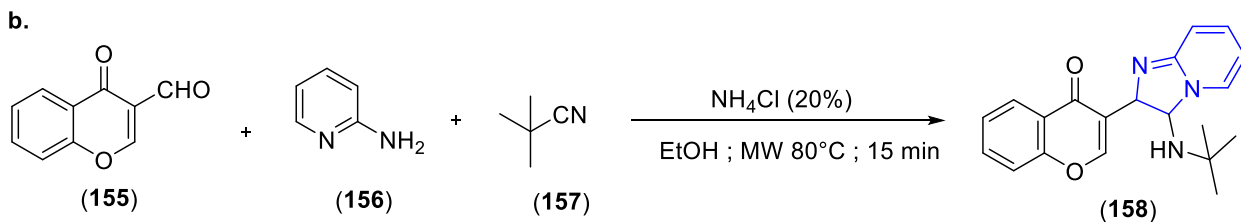
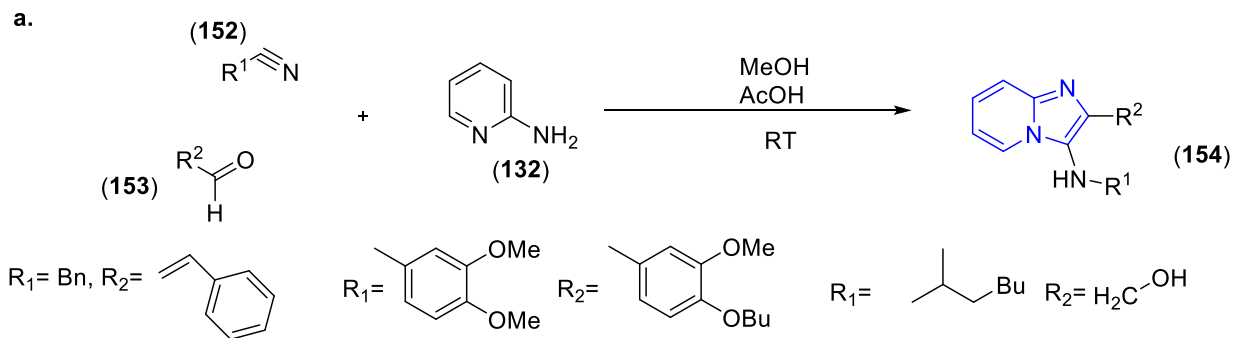


Figure 32: **a.** Synthesis method of imidazopyridine via multi components pathway according to Martna Hieke. **b.** Synthesis method of the 2-substituted imidazopyridine by the multicomponent pathway according to Katrin Groebke et al. **c.** Zarate-Hernández et al. synthesis method of imidazopyridine substituted N-derivatives **d.** synthesis of imidazopyridine substituted N-substitutes multicomponent according to Mehdi Adib et al. **e.** method of synthesis of imidazopyridine substituted N-substitutes multicomponent according to Anneli Nordqvist et al. **f.** Synthesis method of 2,3-disubstituted imidazopyridine via multi-component pathway according to Ping Liu et al. **g.** Pushpalatha Budumuru multi-component synthesis method of the derivatives of 2-phenyl imidazopyridine.

c. Synthesis from nitroolefins

The synthesis of the imidazo[1,2-a]pyridine core from the nitroolefins allowed to activate it in position 3 with the nitro group. Most of these reactions occur in the presence of a catalyst.

Prashant B. Jagadhane et al.¹²⁰ were able to synthesize the imidazo[1,2-a]pyridine core by reacting 1-(2-nitrovinyl)benzene with 2-aminopyridine in the presence of sodium dichloroiodide (NaI₂) in the DMF at 80°C for 1 hour and 30 minutes (Figure 33.a).

This reaction was carried out in several solvents such as dimethylsulfoxide (DMSO), methanol (MeOH), ethanol (EtOH) and acetonitrile (CH₃CN). However, using only dimethylformamide (DMF) as a solvent resulted in better yields of 65 to 85%.

This method was developed by Litao An et al.¹²¹ Using the same reagents, they reacted in acetonitrile (CH₃CN) as a solvent with another catalyst, iodine-terbutylhydroperoxide-pyridine (TBHP-Py) to obtain the imidazopyridine core in 36 to 90% yields (Figure 33.a). The replacement of the catalyst made it possible to increase the reaction time (12h vs. 1h30).

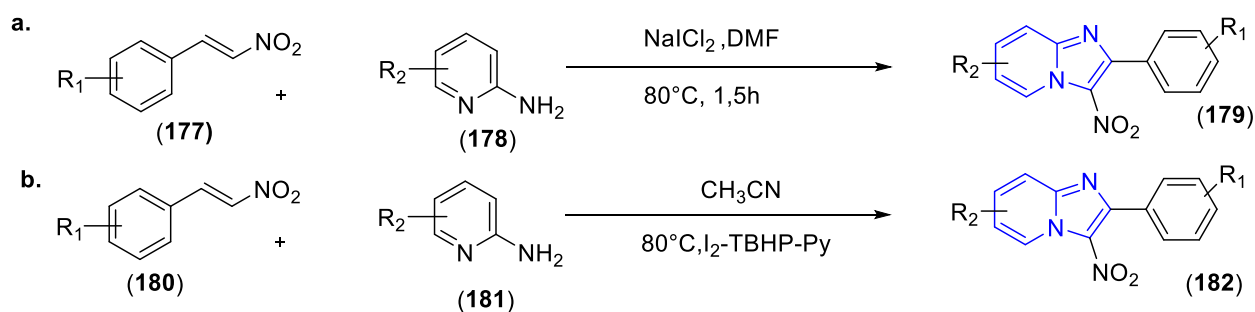


Figure 33: a.Synthesis method of 3-nitro-2-phenyl-midazopyridine derivatives according to Prashant B. Jagadhane et al. b.Synthesis method of 3-nitro-2-phenyl-midazopyridine derivatives according to Litao

An et al.

d. Synthesis from α -chloro- β -diketone

In our group, Ouattara *et al.*⁸⁸ were able to synthesize 3-acetyl-2-methylimidazo[1,2-a]pyridine by the reaction of 2-aminopyridine and 3-chloro-penta-2,4-dione after a reflux heterocyclic reaction in ethanol (Figure 34). This method resulted in a ketone function at the -3 position of the imidazo[1,2-a]pyridine core.

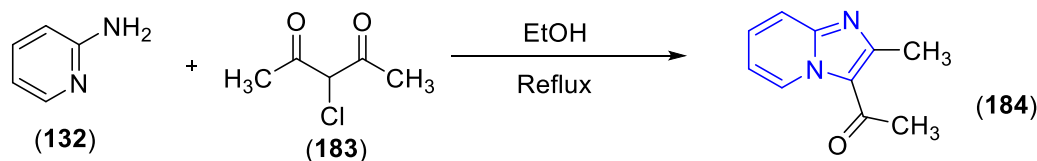


Figure 34: Synthesis method of 1-(2-methylH-imidazo[1,2-a]pyridin-3-yl)ethanone via an α -chloro- β -diketone.

e. Synthesis from pyridinium salt or pyridine.

A synthetic route for imidazopyridine derivatives was identified by Juan A. Vega *et al.*¹²² from pyridinium salt. In their research, two synthetic lines were identified. The first route is the synthesis of 2-amino imidazo[1,2-a]pyridine derivatives by reaction of 1-alkyl-2-chloropyridinium salt derivatives with reflux cyanamide (H_2NCN) in acetonitrile in the presence of potassium carbonate (K_2CO_3) for 13-20 hours with a return of 65-70% (Figure 35.a).

For the second synthetic pathway, they obtained the 2-amino imidazo[1,2-a]pyridine derivatives in two steps. First, by converting 1-alkyl-2-chloropyridinium salt into 2-ylidencyanamidopyridine. Secondly, after this transformation, the latter was treated, in the presence of LDA in tetrahydrofuran (THF) for 6 to 24 h at room temperature to finally obtain the 2-amino imidazo[1,2-a]pyridine derivatives. We noted that the best yields were obtained from this last synthesis route (Figure 35.b).

Similarly, H. Zali-Boeini *et al.*¹²³ synthesized 2,3-disubstitued imidazo[1,2-a]pyridine derivatives, by reaction of N-alkyl pyridinium with S-alkyl thiouronium salt derivatives in water at 75°C for 4 h in the presence of sodium hydrogen carbonate (NaHCO_3) (Figure 35.c).

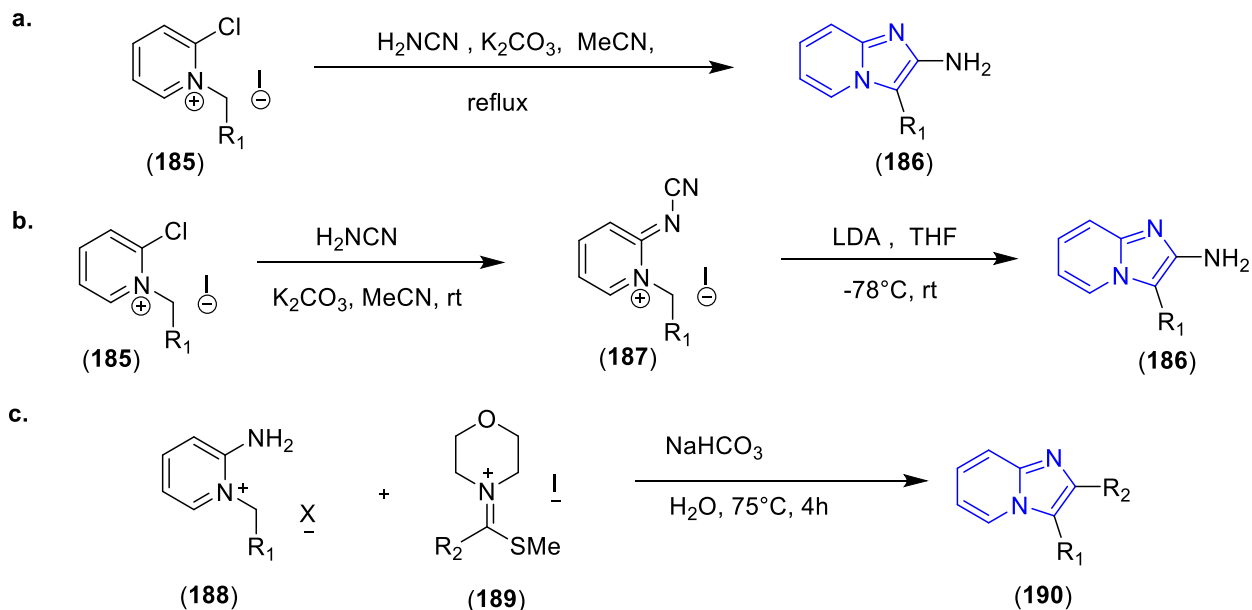


Figure 35: **a.** Synthesis method of 2-aminoimidazopyridine derivatives from pyridinium salt according to Juan A. Vega *et al.* **b.** Synthesis method of 2-aminoimidazopyridine derivatives from pyridinium salt according to Juan A. Vega in two steps. **c.** Synthesis method of 2-aminoimidazopyridine derivatives from pyridinium salt according to Zali-Beoini.

Instead of 2-aminopyridine or their derivatives, Sangjune Park *et al.*¹²⁴ demonstrate an efficient synthetic method for imidazopyridines *via* a Copper-catalyzed, formal aza-[3 + 2] cycloaddition reaction of pyridine derivatives with α -diazo oxime ethers in trifluoroethanol as solvent. The reaction occurs with a release of molecular nitrogen (N_2) and elimination of alcohol. This method also enabled a modular synthesis of a wide range of N-heterobicyclic compounds such as imidazopyridazines, imidazopyrimidines, and imidazopyrazines.

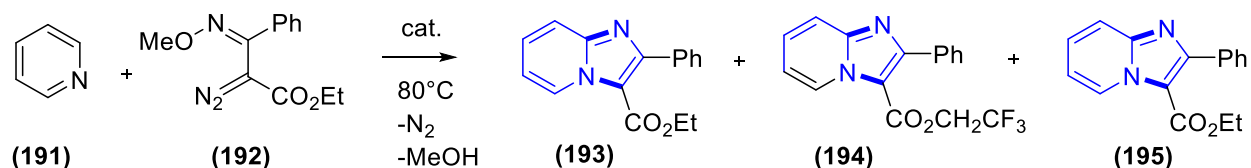


Figure 36: Synthesis method of 2-aminoimidazopyridine derivatives from cycloaddition reaction

f. Synthesis from N-oxides

The 2-substituted imidazo[1,2-a]pyridine nucleus was developed by Eric Talbot *et al.* from 2-aminopyridine N-oxide.¹²⁵ They react with trifluoroacetic acid and gold dichloro-2-pyridinecarboxylate ($PicAuCl_2$) as catalysts, alkynes and 2-aminopyridine N-oxide at 40°C

overnight in dichloromethane (DCM) as a solvent. After treatment of the reaction medium, the derivatives of the 2-substituted imidazo[1,2-a]pyridine are obtained with yields of 16 to 78 %.

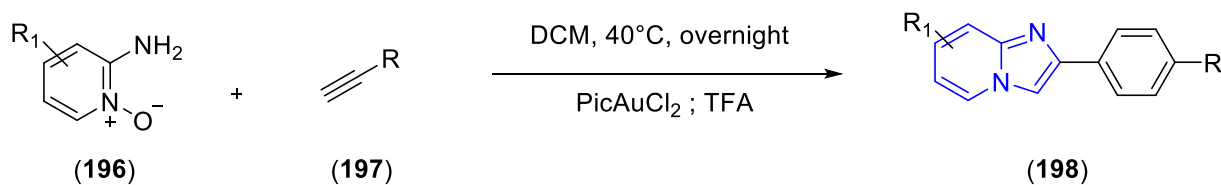


Figure 37 : Synthesis method of 2-phenyl imidazopyridine derivatives from N-oxides.

Perspectives

Antimicrobial resistance is one of the world's greatest public health threats today. Most antibiotics lose their effectiveness over time due to the virulence of toxins secreted by bacteria in defense, which leads to flare-ups of hospital-acquired disease. Another urgency is the widespread emergence of drug-resistant strains Methicillin (MRSA)-resistant *Staphylococcus aureus* (*S. aureus*).¹²⁶ The death toll from MRSA turned out to be even higher. The rapid emergence of *S. aureus* strains resistant to HIV,¹²⁷ vancomycin,¹²⁸ often considered the treatment of last resort, adds to the urgency of being able to access other active ingredients. As a result, there is an urgent need to develop new antibacterial agents that can overcome bacterial resistance, but much more emphasis on bacterial translocation proteins. Structural modification strategies of antibiotics with evolved resistance as an effective means of extending antimicrobial longevity are beginning to show their limitations. Multiple compound therapy has many potential benefits, including increased potency, reduced dosage or toxicity, and protection against development of drug resistance. This area is of increasing interest to scientists due to the enormous (un- or mis-)explored prospects for novel therapeutics. The development is partly guided by a biological systems perspective recognizing that many cellular processes are difficult to control using a single drug compound, and in part by screening multiple compounds. It is guided by high-performance computing instruments that make it quick and inexpensive. For example, when studying combinations of compounds in cancer chemotherapy, clinical evaluation of the benefits of combinations is relatively straightforward. Combinations are preferred if they have acceptable side effects and prolong long-term survival compared to alternative therapies. Therefore, the importance of developing new types of antibacterial agents, especially those with new mechanisms of action. Refocusing antimicrobial drug research on bacterial secretion pathways could be a big win.

Therefore, SecA, a key protein in the bacterial secretory pathway, has been investigated as a target for the development of antibacterial agents. Synthesis and biological activity of various compounds derived from the combination of antimicrobial pharmacophores (aminopyrimidines and benzimidazoles) discussed in this review to form a potential SecA-inhibiting benzimidazolylaminopyrimidine motif. Our suggest research on both scaffold aminopyrimidine derivatives have many bioactivities, including bactericidal action and SecA inhibitors. In addition, these compounds also contain a benzimidazole core, whose antibacterial activity is shown and demonstrated here. An analysis of this literature concluded that pyrimidines substituted with electron-withdrawing groups such as nitro on phenyl have stronger antibacterial activity *in vitro* than chlorine atoms or methoxy groups. Nitro-substituted benzimidazolylaminopyrimidines can be excellent active ingredients. Humans have no homologues of the SecA, so these new compounds probably do not pose inherent toxicity problems. Selectively targeting SecA, which has no human counterpart, seems appropriate. Furthermore, SecA is present in all bacteria, making these new antibacterial agents effective against a broad spectrum of bacteria. After extensive review of the medicinal chemistry literature for both pharmacophores, we could find a potential drug against bacteria. This study addresses the following questions: how can we effectively overcome drug resistance in bacteria? Is addition of pharmacophore will enhance the potency? Is the the best target is translocation of protein.

Conclusion

In this review article, we attempt to summarize several biological activities and synthetic routes for the synthesis of both heterocyclic benzimidazole and imidazo[1,2-a]pyridine compounds. The presence of certain substituents in their derivatives indicates that they can be used as pharmacologically molecules or drugs intermediates. Our point of view in perspectives showed how we would like to currently investigate the combination of both pharmacophore in this research.

Conflict of interest

The authors confirm that this article has no conflict of interest.

References

- [1]Blair J. M. A., Webber M. A., Baylay A. J., Ogbolu D. O., Piddock L. J. V., *Nat. Rev. Microbiol.*, **2015**, *13*, 42-51.
- [2]Organisation mondiale de la Santé, « Rapport sur la tuberculose dans le monde 2020 : résumé d'orientation », **2020**.
- [3]Sumit T., Kalavathy R., Siong M. L., Syeed A. A. S., Vasudevan M, Balasubramanian N., *BMC Chem.*, **2019**, *13*, 12.
- [4]Ulviye A. C., Begum N. S., Serkan L., Derya O., Betul K. C., Yusuf O., Zafer A. K., *Molecules*, **2019**, *24*, 861.
- [5]Sumit T., Sanjiv K. Balasubramanian. N., *BMC Chem*, **2019**, *13*, 18.
- [6]Ratika S., Alka B., and Bahadur B C., *Bio. Med. Chem. Lett.*, **2017**, *27*, 3007-3013.
- [7]Terence N. O., Latyfa E. O., Mostafa E. G., Redouane A., Hind C., Meryem E. J., Yahia C., Katim A., Amina Z., *Biochem. Res. Int.*, **2019**, *2019*, 1-9.
- [8]Tonelli M., Paglietti G., Boido V., Sparatore F., Marongiu E., La Colla P.,Loddo R., *Chem. Biodiver.*, **2008**, *5*, 2386-2401.
- [9]Paulina F. C., José M. V. L., Rodrigo A. O., Alicia H. C., Pedro J. T. S., Lilian Y. M., Raphael C., *Eur. J. Med. Chem.*, **2017**, *137*, 211-220.
- [10]John O., Christel B., Kawaljit S., Godwin A.D., Linley B., Mathew N., Sergio W.,Kelly C., *ACS Infect. Dis.*, **2019**; *5*, 372-384.
- [11]Michele T., Elene G., Francesca P., Nicoletta B., Silvia P., Bruno T., Roberta L., Fabio S.,Anna S., *J. Enzym. Inh. Med. Chem.*, **2018**, *33*, 210-226.
- [12]Amanda L. R., Pulane M.,Christopher J. P., *Tetrahedron Lett.*, **2007**, *48*, 4079-4082.
- [13]Bagdi A. K., Santra S., Monir K.,Hajra A., *Chem. Commun.*, **2015**, *51*, 1555-1575.
- [14]Assessment report, « For Zolpidem-containing medicinal products », *European Medicines Agency*, **2014**, 1-18,
- [15]Cécile E. G., Alain G., *Mini-Rev. Med. Chem.*, **2007**, *7*, 888-899.
- [16]Vidyacharan S., Shinde A. H., Satpathi B., Sharada D. S., *Green Chem.*, **2014**, *16*,1168.
- [17]Liu H.B., Gao W.W., Tangadanchu V.K.R., Zhou C.H., Geng R.X., *Eur. J. Med. Chem.*, **2018**, *143*, 63-84.
- [18]Zhou M., Eun Y.J., Guzei I.A.,Weibel D.B, *Med. Chem. Lett.*, **2013**, *4*, 880-885.
- [19]Ramya V. S., Kallappa M. H.,Rangappa S. K., *Eur. J. Med. Chem.*, **2009**, *44*, 4244-4248.

- [20]Muayed A. R., Baqir W. A., Mudhafar A. M., *Orient. J. Chem.*, **2017**, *33*, 3138-3143.
- [21]Andrea B., Luka K., Ivana S., Domagoji D., Jasminka T., Martin C. T., John M. K., Miroslav B., Silvana R. M., *J. Enzym. Inh. Med. Chem.*, **2018**, *33*, 1323-1334.
- [22]S. Coulibaly, S. Coulibali, F. Bamba, P. A. Achi , F. K. Kouadio, E. Ablo, A. Adjou; *GSC Biol. Pharm. Sci.*, **2022**, *20*, 272–279
- [23]Evrard, A., Siomenan,C., Etienne, C.T., Daouda, T., Souleymane, C., Drissa, S., Ané, A. *Adv. Biol. Chem.*, **2021**, *11*, 165-177.
- [24]Woolley D. W., *J. Biol. Chem.*, **1944**, *152*, 225-232,
- [25]Maertens J. A., *Clin. Microbiol. Infect.*, **2004**, *10*, 1-10
- [26]Mishra L., V. Singh K., Dubey N. K., Mishra A. K., *Biosci., Biotechnol Biochem.*, **1993**, *57*, 989-991.
- [27]Gulgun A. K.,Nurten A., *Turk. J. Chem.*, **2006**, *30*, 223-228
- [28]Hakan G., Canan K., David W. B., Sulhiye Y.,Nurten A., *Bioorg. Med. Chem*, **2002**, *10*, 2589-2596.
- [29]Cheong J.E., Zaffagni M., Chung I., Xu Y., Wang Y., Jernigan F.E., Zetter B.R.,Sun L., *Eur. J. Med. Chem.*, **2018**, *144*, 372-385.
- [30]Ibrahim H.A., Awadallah F.M., Refaat H.M., Amin K.M., *Bioorg. Chem.*, **2018**, *77*, 457-470.
- [31]Refaat H. M., *Eur. J. Med. Chem.*, **2010**, *45*, 2949-2956.
- [32]Salahuddin M. S., Mazumder A., Ahsan M. J., *Arab. J. Chem.*, **2014**, *7*, 418-424.
- [33]Abdel-Mohsen H. T., Ragab F. A. F., Ramla M. M.,El Diwani H. I., *Eur. J. Med. Chem.*, **2010**, *45*, 2336-2344.
- [34]Márquez-Navarro A., Nogueta-torres B., Hernandez-campos A., Soria-arteche O., Castillo R, Rodriguez-Morales S., Yépez-Mulia L., Hernandez-luis F., *Acta Trop.*, **2009**, *109*, 232-235.
- [35]Prasada R. C. M. M., Lakshmi A. J., Mani Y. G., Sudha B. S., Rekha P. B., Satyaprakash K., Dhachinamoorthi D., *World Journal Of Pharmaceutical And Medical Research*, **2018**, *4*, 245-248.
- [36]Faruk A., Biplab K. D., Kamal S., Arpita C., Pallab K., *Int. J. Drug Deliv. Technol.*, **2014**, *4*, 31-38.
- [37]Mavrova A. T., Kamelya K. A., Dimitar I. V., Jordan A. T., Pavletta S. D., Magdalena S. K. ,Mitka K. M., *Eur. J. Med. Chem.*, **2006**, *41*, 1412-1420.
- [38]Sawant R., Kawade D. *Acta Pharm.*, **2011**, *61* 353–361.

- [39] Vitale G., Corona P., Loriga M., Carta A., Paglietti G., Ibba C., Giliberti, G., Loddo R., Marongiu E., La Colla P., *Med Chem.*, **2010**, *6*, 70-78.
- [40] Barreca M. L., Rao A., Luca De L., Iraci N., Monforte A. M., Maga G., Clercq De E., Pannecouque C., Balzarini J., Chimirri A., *Bioorg. Med. Chem.*, **2007**, *17*, 956-1960.
- [41] Laura G., Erik De C., Marinella R., *Bioorg. Med. Chem.*, **2002**, *12*, 2707-2710.
- [42] Deepika S., Balasubramanian N., Pradeep K., Vikramjeet J., Rakesh N., Erik De C., Jan B., *J. Enzyme Inhib. Med. Chem.*, **2009**, *24*, 1161-1168.
- [43] Achar K.C.S., Hosamani, K.M., Seetharamareddy H.R., *Eur. J. Med. Chem.*, **2010**, *45*, 2048-2054.
- [44] Iemura R., Kawashima T., Fukuda T., Ito K., Tsukamoto G., *J. Med. Chem.*, **1986**, *29*, 1178-1183.
- [45] Monika G., Sarbjot S., Chander M., *Eur. J. Med. Chem.*, **2014**, *76*, 494-505.
- [46] Kavitha C.S. A., Kallappa M. H., Harisha R. S., *Eur. J. Med. Chem.*, **2010**, *45*, 2048-2054.
- [47] Thimme G. N. R., Kavitha C. V., Kishore K. C., Omana J., Kanchugarakoppal S. R., Sathees C. R., *Bioorg. Med. Chem.*, **2009**, *19*, 4594-4600.
- [48] Mahama O., Drissa S., William Y., Mamidou W. K., *Int. J. Biol. Chem. Sci.*, **2015**, *9*, 1697-1710.
- [49] Bandyopadhyay P., Manisha S., Sachin N. T., Ruchi Y., Pratibha S., Ashok K., Kaushik M. P., *Bioorg. Med. Chem. Lett.*, **2014**, *24*, 2934-2939.
- [50] José C., Arthur B., Neira G., Juan R., Rosario R., Abraham V., Robert G., Jaime C., *Bioorg. Med. Chem.*, **2011**, *19*, 2023-2029.
- [51] Divatia S. M., Rajani D. P., Rajani S. D., Patel H. D., *Arab. J. Chem.*, **2014**, *12*, 1641-1651
- [52] Toro P., Hugo A. K., Bruno P., Lahoz F., Pascual A., Biot C., Arancibia R., *Inorg Chem Commun.*, **2013**, *35*, 126-129.
- [53] Sarika S., Dhiman N., Aman M. et Gaurav K., *J. Drug Delivery Ther.*, **2016**, *6*, 100-102.
- [54] Dvornikova I. A., Buravlev E. V., Fedorova I. V., Shevchenko O. G., Chukicheva I. Yu., and Kutchin A. V. *Russ. Chem. Bull., International Edition*, **2019**, *68*, 1000-1005.
- [55] Sabrina R. A., Biplab K. D., MD Shahadat H., Uttom K., Abu S. S. R., *Int. J. Pharm. Pharm. Sci.*, **2017**, *9*, 308-310.
- [56] a)-Hobrecker F., *Deut. Chem. Ges. Ber*, **1872**, *5*, 920-924.; b) Ladenberg A., *Deut Chem Ges Ber*; **1875**, *8*, 677-678; c) Wundt E., *Deut Chem Ges Ber*; **1878**, *11*, 826-830.

- [57]a)-G. Yadav, S. Ganguly, *Mini Rev Med Chem*; **2015**, *97*; 419-443 ; b)- Keri, R. S., Hiremathad, A., Budagumpi, S., & Nagaraja, B. M.; *Chem. Biol. Drug Des.*, **2014**, *86*, 19–65.
- [58]Montague L. I., *J. Chem. Soc.*,**1928**, 2393-2399.
- [59]El-Gohary N. S.,Shaaban M. I., *Eur. J. Med. Chem.*, **2017**, *137*, 439-449.
- [60]Odame F., Hosten E., Betz R., Lobb K.,Tshentu Z. R., *Acta Chim. Slov.*, **2015**, 986-994.
- [61]Kiumars B., Mohammad M. K.,Iman K., *J. Chem. Res.*, **2006**, 783-784.
- [62]K. Bahrami, M. Khodaei, I. Kavianiinia, *Synthesis*, **2007**, *2007*, 547-550.
- [63]K. Bahrami, M. Khodaei, F.Naali , *J. Org. Chem.*, **2008**, *72*, 6835-6837.
- [64]Du L.-H., Wang Y.-G., *Synthesis*, **2007**, *2007*, 675-678.
- [65]Karthikeyan C., Solomon V. R., Lee H.,Trivedi P., *Arab. J. Chem.*, **2017**, *10*, 1788-1794.
- [66]Sharghi H., Mashhadi E., Aberi M., Aboonajmi J., *Appl. Organomet. Chem.*, **2021**, *35*, e6330.
- [67]Alloum B. A., Bougrin K., Soufiaoui M., *Tetrahedron Lett.*, **2003**, *44*, 5935-5937.
- [68]Duvuapally M., Sadhu P., Punniyamurthy T., *J. Org. Chem* , **2016**, *81*, 3227-3234.
- [69]Y. Kim, M. R. Kumar, N. Park, Y. Heo,S. Lee, *J. Org. Chem.*, **2011**, *76*, 9577-9583.
- [70]Thanh. B. N., Bescont J. L., Ermolenko L.,Al-Mourabit A., *Org. Lett.*, **2013**, *15*,6218-6221.
- [71]Hobrecker F., *Berichte Dtsch. Chem. Ges*, **1872**, *5*, 920-924.
- [72]Deepak B. N., Bhalchandra M. B., *Synlett*, **2015**, *26*, 2835-2842.
- [73]Sissouma D., Adjou A., Touré S. A., Zoakouma S., Gnon B., Téa G. C., *Phosphorus, Sulfur Silicon Relat. Elem.*, **2005**, *180*, 1375-1378.
- [74]Timotou A., Adjou A., Say M. V., Sissouma D., Toure S., Tea G. C., N'Guessan Y.T., *Int. J. Biol. Chem. Sci.*, **2014**, *7*, 2568.
- [75]Camara T. E., Coulibali S., Kone S., Adeyole T.,Adjou A., *World J. Pharm. Res.*, **2017**, *7*, 61-84.
- [76]Denise M., Philippe N., Jean-Michel L. Loubna L., Abdeslam E. A., Brahim L., El Mokhtar E., Bouziane B., Abdelkhalek B., *Russ. J. Phys. Chem.*, **2015**, *89*, 807-811.
- [77]Vakhid A. M., Nataliya A. Z., Oleg G. S., *Mendeleev Commun.*, **2017**, *27*, 1-11.
- [78]Leonard N. J., David Y.C., Karl M. B., *J. Am. Chem. Soc*, **1947**, *69*, 2459-2461.
- [79]Hunger A., Kebrle J., Rossi A.,Hoffmann K., *Helv. Chim. Acta*, **1960**, *43*, 1032-106.
- [80]Bhattacharaya S. C., *Chem. Sci. Trans.*, **2016**, *5*, 79-86.
- [81]Van Allan J. A., Deacon B. D., *Org. Synth.*, **1950**, *30*, 56.

- [82]Pushpalatha B., Srinivasarao G., Venkata S. S. K., *Asian J. Pharm. Clin. Res.*, **2018**, *11*, 252-258.
- [83]Kai. L., Linhu L., Wang B., Mingliang L., Wang B., Weiyi S., Huiyuan G., Yu L., *Eur. J. Med. Chem.*, **2017**, *137*, 117-125.
- [84]Ablo, E., Coulibali,S., Touré, D ., Coulibaly, S., Kablan, A. L., Kouadio, C., F. K., Sissouma, D., Kouadio, N. G., Ané, A.; *Synth. Commun.*, **2022**, *52*, 467-469.
- [85]Akram M.H. A., Mohammed A. A., Saeb H. A., *Syst. Rev. Pharm.*, **2021**, *12*, 79-85.
- [86]Gui-Ting S., Nicholas McC., Zhong-Zhu C., Xiao-Fang Y., Jiu-Hong H., Jie L., Hui-kuan L., Brendan F., Hong-yu L., Zhi-Gang X., *Adv. Synth. Catal.*, **2018**, *360*, 3655-3661.
- [87]Nurit D. F., Candice L., Amanda L. R., Dharmendra B. Yadav,Hajierah Davids, Charles B. de Koning , *Eur. J. Med. Chem.*, **2011**, *46*, 4573-4583.
- [88]Mahama O., Drissa S., Mamidou. W. K., William Y., *C. R. Chim.*, **2016**, *19*, 850-856.
- [89]Hamdouchi C, Jesus de B., Mirian del P., Joseph G., Beverly A. H.,Lori V., *J. Med. Chem.*, **1999**, *42*, 50-59.
- [90]Alain G., Sylvie M., Mohammed L., Ahmed E., Robert S., Graciela A., Olivier C., Jean-Claude T., Myriam W., Jan B., Erik De C.,Jean-Pierre C., *J. Med. Chem.*, **1998**, *41*, 5108-5112.
- [91]Kristjan S. G., John C. D., Leroy B. T., *Tetrahedron Lett.*, **1996**, *37*, 2365-2368.
- [92] Kristjan S. G., John D. W., John C. D., Leroy B. T., *J. Med. Chem.*, **2003**, *46*, 1449-1455.
- [93]Jean-Paul D. U. G., Pierre-Olivier D., Mélanie P., Claude L. C., Cédric N., Mahama O., Cécile E. G., Alain G., Hassan A., *Bioorg. Med. Chem.*, **2017**, *25*, 6695-6706.
- [94]Cyril F., Louise B., Clotilde B., Julien P., Sébastien H., Anita C., Caroline C. D., Nicolas P., Michèle L., Magali C., Sandra B. D., Mélanie P., Alix S. S., Valère B. M., Bertrand C., Elisa B. R., Marc S., Rachel M., Susan W. A. H. F., Alexis V., Pascal R., Pierre V., Patrice V.,Nadine A.; *ACS Med. Chem. Lett.*, **2019**, *10*, 34-39.
- [95]Katerine. A. A., Jonathan A.G. C., Vickey L. S., Nicholas J. L., Mark J. P., Chrystala C., Raquel F., Carlos A., Modesto J. R., David B., Lluis B.,Gurdyal S.B, *PLoS One*, **2012**, *7*,e52951
- [96]Moraski G. C., Lowell D. M., Philip A. H., Helena B., Sanghyun C., Scott G. F., Marvin J. M., *ACS Med. Chem. Lett.*, **2011**, *2*, (6), 466-470.
- [97]López-Martínez M., Salgado-Zamora H., Campos-Aldrete M. E., Trujillo-Ferrara J. G., Correa-Basurto J., Mexica-Ochoa C., *Med. Chem. Res.*, **2012**, *21*, 415-420.

- [98]Pratibha S., Deepa D., Mansi P., Latha N., Divyank M., Tapasya S., Anudeep K. N., *Research Square*, **2021**, 1-23.
- [99]Adingra, K.F., Coulibaly,S., Alain, K., Ouattara, M., Sissouma,D., *Adv. Biol. Chem.*; **2022**, *12*, 81-91.
- [100]Adingra, KF, Alain K, Coulibali S, Etienne CT, Coulibaly S, Ouattara S, Sissouma D., *ChemXpress*, *14*, 158.
- [101]Renata B. L., Cleverton K. F. d. L., Leandro L. d. S., Nelilma C. R., Ana L. P. M., Eliezer J. Barreiro, Carlos A. M. Fraga, *Bioorg. Med. Chem.*, **2009**, *17*, 74-84.
- [102]Tschitschibabin A.E., *Ber Dtsch Chem Ges*, **1925**, *58*, 1704-1706.
- [103]Mosby W. L., Heterocyclic Systems with Bridgehead Nitrogen Atoms, Part 1, *Interscience Publishers, Inc., New York*, **1961**, *15*, 461.
- [104]Andrés A. T., Gary T., Gregor J. M., Juan A. V., Ana I. d. L., Encarnación M., Aránzazu G., María L. L., Sergio A. A. d. D., José M. A., Daniel O., Abdelah A.,Wilhelmus D., Claire M., José I. A., Hilde L., JoséMaría C., *J. Med. Chem.*, **2012**, *55*, 2688-2701.
- [105]Caroline C. D., Lucie P., Pierre V., Magali C., Christophe C., Sébastien H., Floriane T., Michèle L., Vincent R., Anita C., Maxime D. C., Pascal R., Nadine A.,Patrice V., *Bioorg. Med. Chem.*, **2013**, *21*, 7155-7164.
- [106]Brad D. M., Olivier G. B., Kazunari O., *J. Labelled Compd. Radiopharm.*, **2005**, *48*, 397-406.
- [107]Alain G., Mohammed L., Ahmed E., Robert S., Graciela A., Olivier C., Jean-Claude T., Abdelali K., El Mokhtar E., Jean-Claude D., Myriam W., Yves B., Jan B., Erik D. C.,Jean-Pierre C., *J. Med. Chem.*, **1996**, *39*, 2856-2859.
- [108]Jean-Michel C., Jan P., Vincent G., Damien C., Aure L. M. C. L., Alain G., Emmanuel M., Jean-Claude T., Olivier C., Johan N., *Eur. J. Med. Chem.*, **2010**, *45*, 2044-2047.
- [109]Shankarappa A B., Venkatesh K. B., Yadav D. B., Rajesh B., *Molbank*, **2009**, *2009*, M587.2.
- [110]Rajaa B., Angela R. A., Raphael B., Nicolas R., Mathilde C., Amelie B., Romain D., Said Y., Patricia Melnyk, Laurence Agouridas, *Bioorg. Med. Chem.*, **2018**, *26*, 3296-3307.
- [111]Dongjian Z., Jiuxi C., Dengze W., Miaochang L., Jinchang D., Huayue W., *J. Chem. Res.*, **2009**, *2*, 84-86.
- [112]Dong-Jian Z., Jiu-Xi C., Miao-Chang L., Jin-Chang D., Hua-Yue W., *J. Braz. Chem. Soc.*, **2009**, *20*, 482-487.
- [113]Katrin G., Lutz W., Fridolin M., *Synlett*, **1998**, 661-663.

- [114]Martina H., Carmen B. R., Joanna M. W., Estel la B., Holger S., Manfred S. Z., Dieter S., Bettina H.,Ewgenij P., *Bioorg. Med. Chem.*, **2012**, *22*, 1969-1975.
- [115]Carlos Z. H., Unnamatla. M. V. B., Gámez-Montaña R., *Proceedings*, **2019**, *41*, 68.
- [116]Taleb H. Al-T., Raed A. Al-Q., *Eur. J. Med. Chem.*, **2010**, *45*, 5848-5855.
- [117]Mehdi A., Mohammad M., Mahsa A. N., Peiman M., *Tetrahedron Lett*, **2007**,*48*, 7263-7265.
- [118]Anneli N., Mikeal T. N., Olof L., Daniel M., Johan G., Samir Y., Luke R. O., Bachally R. S., Mats L., Sherry L. M., Anders K., *Med.Chem.Comm*, **2012**, *3*, 620.
- [119]Ping L., Li-song F., Xinsheng L., Guo-qiang L.,*Tetrahedron Lett*, **2010**, *51*, 4605-4608.
- [120]Prashant B. J., Viskas N. T., *Synlett*, **2014**, *25*, 2636-2638.
- [121]Litao A., Xiaojun S., Meng L., Jianfeng Z., Fengxia Z., Hui Z., *Z. Naturforsch.*, **2016**, *71*, 141-147.
- [122]Juan A. V., Juan J. V, Julio A. B., Jesfis E., Hamdouchi C., *Tetrahedron Lett.*, **1999**, *55*, 2317-2326.
- [123]Zali-Boeini H., Norastehfara N.,Amiri Rudbaria H., *RSC Adv.*, **2016**, *6*, 81943-81949.
- [124]Park, S., Kim, H., Son, J.-Y., Um, K., Lee, S., Baek, Y., Lee, P. H., *J. Org. Chem.*, **2017**, *82* 10209–10218.
- [125]Eric P. A. T., Melodie R., Jeffrey M. M., Dean F. T., *Adv. Synth. Catal.*, **2014**, *356*, 687-691.
- [126]D. P. Calfee, *Curr. Opin. Infect. Dis.* **2012**, *25*, 385.
- [127]Payne, D.J. *Science*, **2008**, *321*, 1644-1645.
- [128]Theresa, L. S. *N Engl J Med*, **1999**, *340*, 493-501.