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

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Abstract

The N heterocyclic scaffold has generated a lot of interest among medicinal chemists. Of those potential heterocyclic drugs, benzimidazole and imidazopyridine scaffolds are considerably prevalent. They have gained tremendous importance over the past few decades. Both are an important class of molecules due 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 their derivatives have been developed as potential anti-cancer, anti-microbial, anti-viral, and anti-inflammatory besides other chemotherapeutic agents. Benzimidazole core was found in the natural system displaying a wide range of pharmaceutical properties and it gained significant attention in medicinal chemistry reported in several full articles and communications. While imidazopyridines exhibit a vast distribution in many pharmacologically important compounds shown by its 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 are characterized as structurally potential ligands which can bind to different receptor sites for the discovery of various immerging drugs. They act as key pharmacophore motifs for the identification and optimization of lead structures to increase the medicinal chemistry toolbox. The present review outlines the synthesis and the medicinal significance of benzimidazoles and imidazopyridines for their development as lead molecules with improved therapeutic efficiencies. Here, we cover the various design used to obtain both heterocycles to establish a relationship between their combination to features the biological activities.

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

Introduction

Antimicrobial resistance (AMR) and worldwide increase in infections are recognized by the World Health Organization (WHO) as urgent risk for public health. The COVID-19 crisis, the monkeypox virus and their variants increase these risks into all domains, even worse on 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 concerns chemists also. For this purpose, some intensification of research around nitrogen-fused azoles known as lead compound in the literature, pushed our curiosity and sum up it in this review. They have a wide range of applications in medicinal chemistry. Although benzimidazole and imidazopyridine are structurally different, their pharmacological properties are quite similar. Both heterocycles and their derivatives as well as preparative methods for basic derivatives are here presented.

This review article will focus on presenting the biological activities of benzimidazoles and their synthetic methods. Also imidazopyridine compounds are presented in the same way before their combination prospects are presented.

Indeed benzimidazole derivatives are heterobicyclic aromatic compounds resulting from the adhesion between benzene and imidazole. Due to their isostructural pharmacophore, molecules possessing in their basic structures the benzimidazole scaffold, have revealed a panoply of biological activities and among them we can mention the anticancer [3], acetylcholinesterase [4], antimicrobial [5], anti-inflammatory [6] analgesic [7], antiviral [8] anti-protozoan [9], antimalarial [10] and anti-leishmanial [11] activities. Benzimidazole scaffold are present in the structure of some commercial drugs such as Thiabendazole, Mebendazole, Luxabendazole, Triclabendazole, Albendazole and Oxibendazole (Figure 1).

Naturally, the wide applications and uses in a variety of fields have led to several synthetic routes developed for the production of imidazo[1,2-a]pyridines. In recent years, this has remained progress and innovation in the synthesis of imidazos[1,2-a]pyridines using several interesting

pathways, such as multi-component reactions, tandem sequences and C-H functionalization catalyzed by transition metals. These methods provide ease of obtaining imidazos[1,2-a]pyridines from simple and readily available precursors.

This has led to many discoveries concerning their biological properties including antimicrobial, anti-inflammatory, anticancer and antiparasitic properties, [12] thus dedicating this scaffold for molecular and biological explorations. The imidazo[1,2-a]pyridine core is also present in the structure of many drugs, which have good properties on 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 an anxiolytic agent. [13] However, Alpidem was withdrawn from the market because of its toxicity. Olprinone, [15] is used in the treatment of acute heart failure. Zolimidine is active on *Escherichia Coli* (*E.Coli*) so used in the treatment of peptic ulcers. [16] An optically active drug with the imidazopyridine motif in its skeleton, GSK812397 is intended for the treatment of HIV infection. [16]

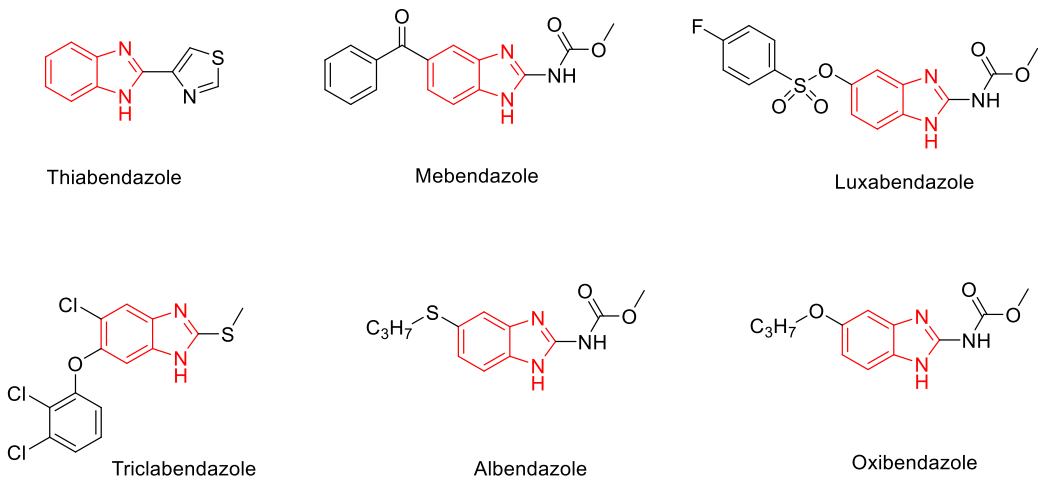

Figure 1: some drugs based on the benzimidazole scaffold

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-A) 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 of the evaluated compounds showed good antibacterial properties with Minimum Inhibitory Concentrations (MICs) between 16 and 1 µg/mL. Of these compounds, 3-[2-(5-bromo-1*H*-benzimidazol-2-yl)-vinyl]- phenol showed the best activity on all strains with MIC values between 1 µg/mL and 4 µg/mL (Figure 2-A).

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-B) 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 strains.

Amino-(2-(4-(((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)phenyl)-1*H*-benzimidazol-5yl) methaiminium (Figure 2-C) was evaluated for antibacterial activity *in vitro* on 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]

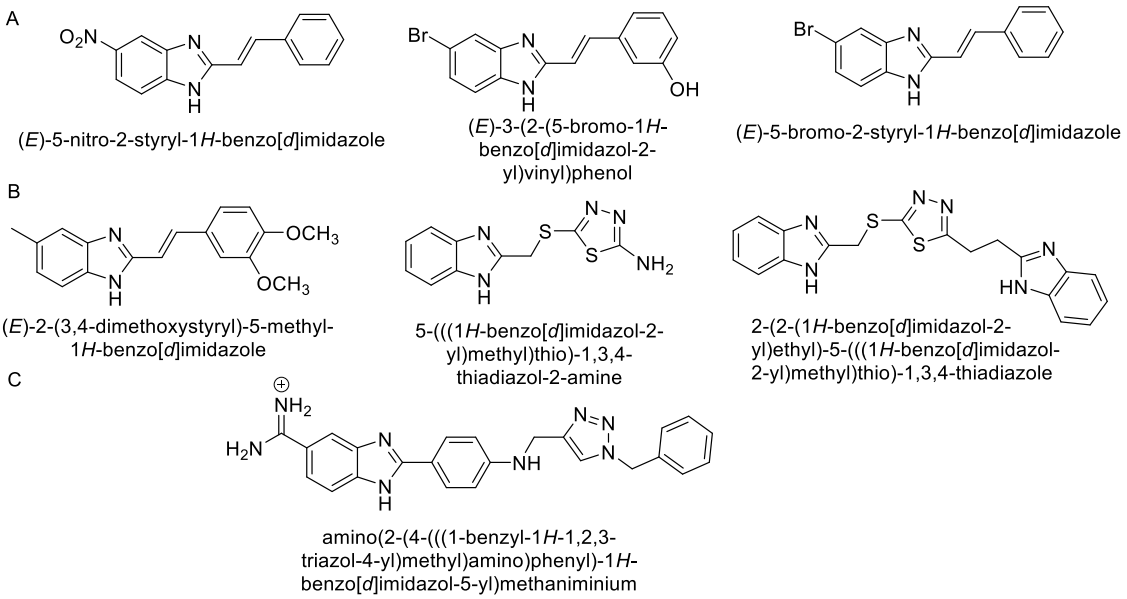

Figure 2: Compound with good antimicrobial activities-A**.** 2-styryl-1*H*-benzimidazole derivatives, B. 5-(((1*H*-benzimidazol-2-yl)methyl)thio)-1,3,4-thiadiazol-2-amine derivatives, C. Amino-(2-(4-(((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)phenyl)-1*H*-benzimidazol-5yl) methaiminium.

b. Antifungal properties of benzimidazole derivatives

The antifungal activity of the benzimidazole scaffold was first reported in 1944 by Woolley[22], [23] through chlormidazole or 1-(4-chlorobenzyl)-2-methyl-1*H*-benzimidazole. It became a fairly well-known activity of benzimidazole that has generated behind a lot of research.

Mishra et *al.* [24] showed that the 2-chloromethyl-5*H*-methylbenzimidazole derivatives substituted in the -2 position by 5-mercapto-l,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.*[25]. 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 and 2-(p-fluorophenyl)-5-nitro-1-propylbenzimidazole (Figure 3) are potent on these strains with a large antifungal activity spectrum. These benzimidazole compounds were more active on *C. albicans* with a 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 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.

Finally, Göker et *al.*[26] also evaluated the *in vitro* antifungal activity of 5-carbonitrile benzimidazole. 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.

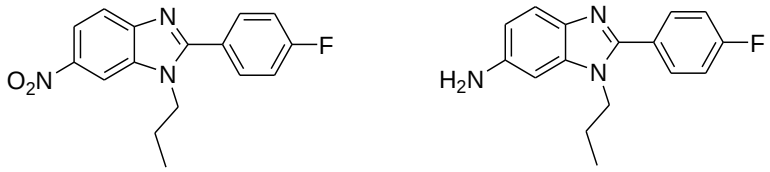

Figure 3: 2-(4-fluorophényl)-1-propyl-*1H*-benzimidazole derivatives with antifungal activities.

c. Anticancer properties of benzimidazole derivatives

The anticancer activity of benzimidazole derivatives has been described in several research studies [27], [28]. Among these works, we will mention those carried out by Hanan Refaat[29] on the determination of the anticancer activity of 2-substitued benzimidazole derivatives. The cytotoxicity of these benzimidazole compounds was evaluated on three cell lines representing three common forms of human cancer, namely a human hepatocellular carcinoma cell line (HePG2), a human breast adenocarcinoma cell line (MCF7) and a colon carcinoma cell line (HCT 116). In this work, they were able to show that the position-2 substituted benzimidazole derivatives have anticancer activity against all tumor cell lines with an IC_{50} 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, 5-chloro-2-[(3-phenyl-4-oxothiazolidin-2-ylidene)cyano-methyl]benzimidazole and 2-[3-(4-bromophenyl)-4-(2-methoxyphenylthiazol-2-ylidene)cyanomethyl]benzimidazole-5-carboxylic acid were most active against MCF7 (Figure 4-A).

Salahuddin et *al.*[30] also synthesized derivatives of 2-(naphthalen-1-ylmethyl/naphthalen-2-yloxymethyl)-1-[5-(substituephenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1*H*-benzimidazole. In this work, they showed that 2-naphthalen-1-ylmethyl-1-[5-(4-nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1*H*-benzimidazole (Figure 4-B) 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.

The2-(benzimidazol-2-yl)methylthio)-4-(substituted)-6-phenylpyrimidine-5-carbonitrile derivatives synthesized by Abdel-Mohsen et *al.*[31] were evaluated for their anticancer activities

against twelve cancer cell lines KB, SKOV-3, SF-268, NCI-H460, RKOP27, HL60, U937, K562, G361, SK-MEL-28, GOTO and NB-1. All of these benzimidazole derivatives evaluated *in vitro* showed good anticancer activity on the various cancer lines.

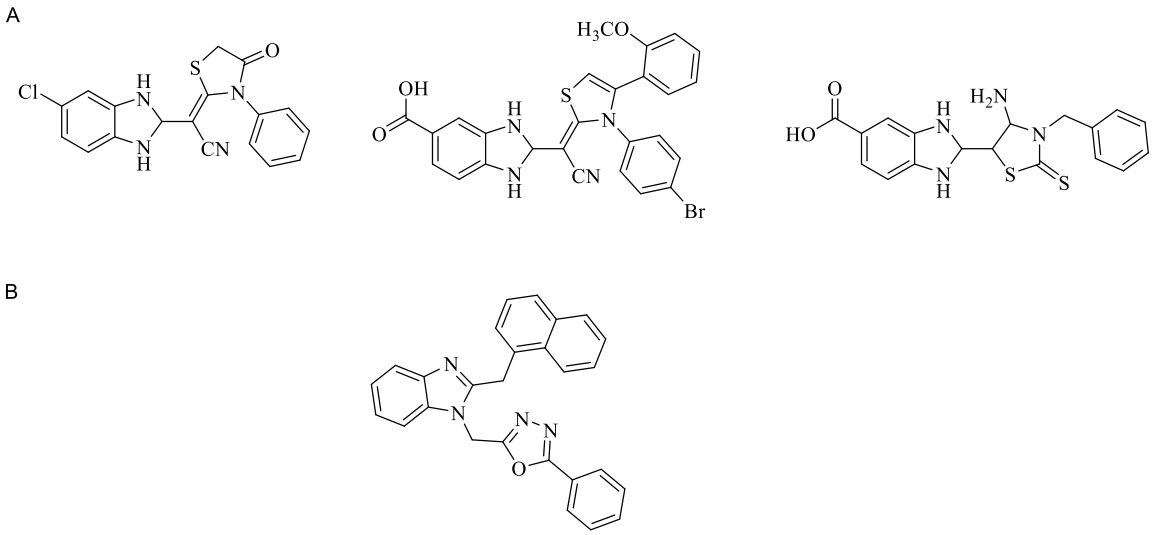

Figure 4 : Anticancer properties possessed by A. Benzimidazole derivatives against HEPG2 and MCF-7, B. 2-naphthalen-1-ylmethyl-1-[5-(4-nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1H-benzimidazole.

d. Anthelminthic properties of benzimidazole derivatives

The anthelminthic activity is one of the main properties recognized for benzimidazole derivatives. [32]–[34] Some of these compounds are used to fight parasitic diseases such as helminthiases. This is the case for Flubendazole, Mebendazole, Albendazole and Thiabendazole. Also, new derivatives of 2-((1*H*-benzimidazol-2-yl)thio)-1-(piperazin-1-yl)ethyan-1-one were synthesized (Figure 5-compound 3) by Mavrova et *al.*[35] showed strong anthelminthic activity *in vitro* against *Trichinella spiralis*. This activity was higher than that observed on the same germ when using a drug such as Albendazole.

Ramesh Sawant et *al.*[36] also showed that the new 2-phenyl benzimidazole-1-acetamide derivatives possess anthelmintic activities. Thus, anthelminthic tests have been carried out using the derivatives of 2-(((1*H*-benzimidazol-2-yl)methyl)thio)-5-phenyl-1,3,4-thiadiazole (Figure 5-compound 5) on *Pheretima Posthuma* which is an authenticated worm at the University of SSGM (Shri Sadguru Gangageer Maharaj Sciences) in India.

This work revealed that these derivatives at the -2 position have an excellent anthelmintic activity.

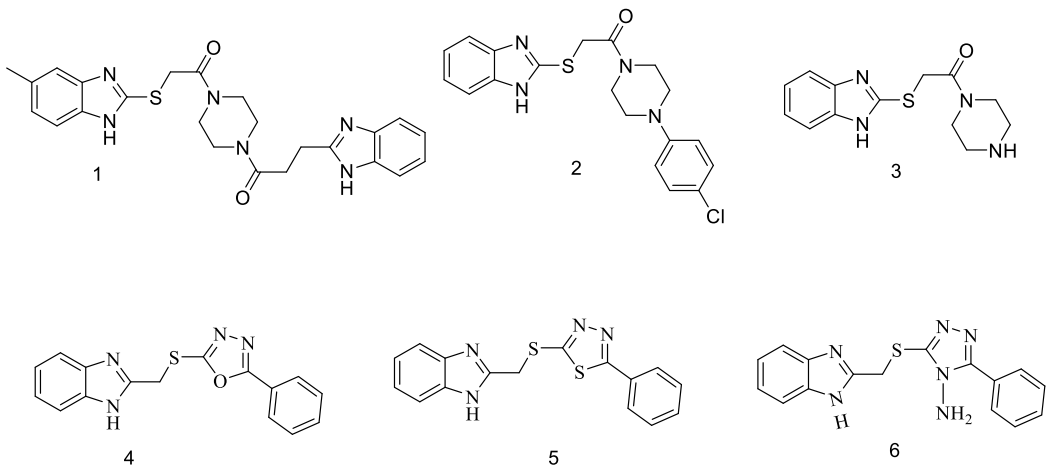

Figure 5: Benzimidazole derivatives with anthelminthic derivatives

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.[37-38] Erik De Clercq and Laura Garuti[39] synthesized benzimidazole derivatives substituted in position-1 by sulfonyl. Subsequently, the antiviral activity of these derivatives was evaluated against *Human cytomegalovirus* and *Varicella-zoster* virus. Among evaluated compounds, the 5,6-dichloro-1-(isopropylsulfonyl)-2-(2-(pyridin-2-yl)ethyl)-2,3-dihydro-*1H*-benzimidazole (Figure 6.compound 1) showed the best antiviral activity against the 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 μM and 4.1 μM.

Antiviral activity was also shown through the work of Deepika Sharma et *al.*[40] on the 4-nitrophenyl-2-phenyl-1*H*-benzoimidazol-1-ylmethanone derivatives. The demonstration of the antiviral properties of these derivatives was done. In addition, these authors showed that 4-nitrophenyl-2-(4-chlorophenyl)-1*H*-benzimidazol-1-ylmethanone and 2-bromophenyl-2-phenyl-1H-benzimidazol-1-ylmethanone (Figure 6-compounds 2 and 3) were likely good candidates for the manufacture of an antiviral vaccine.

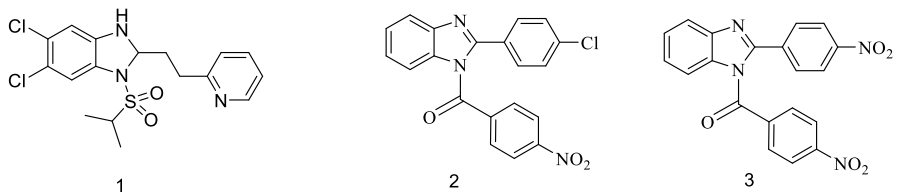

Figure 6 : Benzimidazoles derivatives with antiviral activities

f. Anti-inflammatory properties of benzimidazole derivatives

The anti-inflammatory activity of benzimidazole derivatives has been reported through several research studies.[41-42] However, the benzimidazole molecules (Figure 7-A) discussed in this section are those that have shown good anti-inflammatory properties in the work of Monika Gaba et *al.*[43]. Indeed, in this work, the anti-inflammatory activity of the molecules was compared with those of reference drugs such as Indomethacin, Nimesulide, Ibuprofen and Diclofenac. These benzimidazole derivatives showed activities above certain reference drugs.

Kavitha Achar et *al.*[44] also highlighted the anti-inflammatory activity of benzimidazole derivatives. These authors showed that some derivatives of N-((1*H*-benzimidazol-2-yl)methyl)aniline (Figure 7-B) had very good anti-inflammatory activities. This study was conducted using Nimesulide as a reference drug.

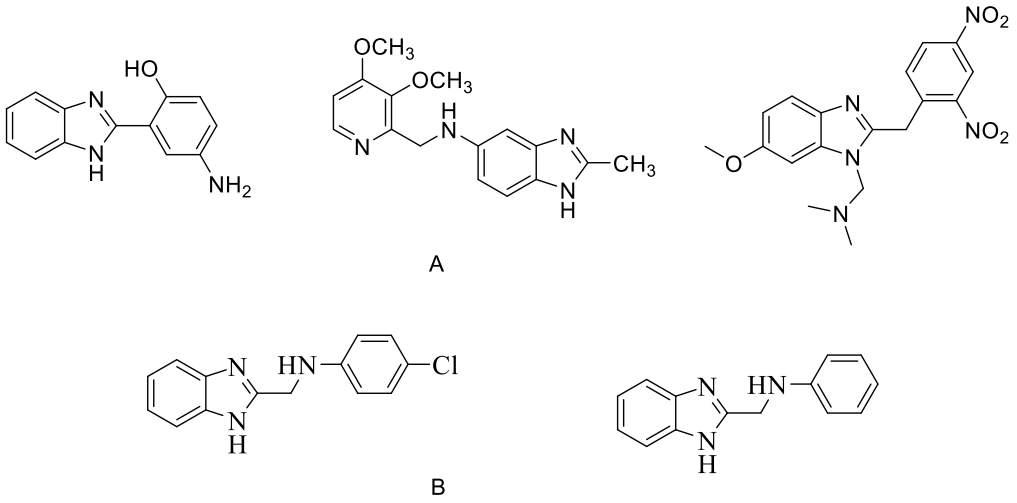

Figure 7 : A. Benzimidazole derivatives [ref.43] B. N-((1*H*-benzimidazol-2-yl)methyl)aniline derivatives with good anti-inflammatory activites [ref.44]

g. Anti-leukemia properties of benzimidazole derivatives

This biological property of benzimidazole derivatives was revealed through the work of Thimme Gowda et *al.*[45] on the synthesis and evaluation of the anti-leukemia activity of new 1-(4-methoxyphenethyl)-1*H*-benzimidazole-5-carboxylic acid derivatives. The screening of twenty-two (22) new synthesized compounds showed that methyl 2-(4-fluoro-3-nitrophenyl)-1-(4-methoxyphenyl)-1*H*-benzimidazole-5-carboxylate (Figure I-14) was a good anti-leukemic properties. This molecule inhibits human leukemia cells with an IC_{50} of 3 µM.

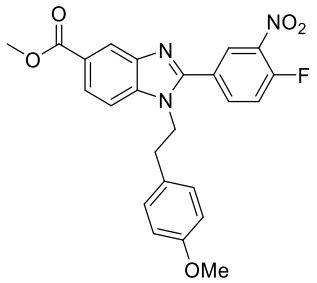

Figure 8: Structure of methyl 2-(4-fluoro-3-nitrophenyl)-1-(4-methoxyphenethyl)-1H-benzimidazole-5-carboxylate

h. Anti-plasmodial properties of benzimidazole derivatives

In our group, Ouattara Mahama et *al.*[46] demonstrated the antiplasmodial behavior of benzimidazole through the synthesis and evaluation of benzimidazolyl-chalcone derivatives (Figure 9-compounds 1, 2). In their work, anti-plasmodial screening of *Plasmodium Falciparum* (*P. falciparum*) chloroquino-sensitive and chloroquinoresistant isolates has shown that benzimidazolyl-chalcones are excellent antiplasmodial pharmacophores. Indeed, 1-(fluoro-1*H*-benzimidazol-2-yl)-3-phenylprop-2-en-1-one (compound 1) with an IC_{50} value of 5.63 µM showed the best profile on the chloroquino-sensitive *P. falciparum* isolate.

Bandyopadhyay et *al.*[47] synthesized and evaluated the antimalarial activity of benzimidazole phosphorylated derivatives against *Albopictus* and *Culex Quinquefasciatus* mosquitoes. They showed that dimethyl-(4-(1*H*-benzimidazol-2-yl)phenyl)phosphoramidate (Figure 9-compound 3) was more potent on *Albopictus* and *C. Quinquefasciatus*.

Camacho et *al.*[48] synthesized benzimidazole derivatives to test *in vitro* antimalarial activities to inhibit the formation of β-hematic (IβHS) responsible for hemoglobin hydrolysis. But also, *in vivo* study was done on a rodent like the *Plasmodium Berghei*. Among these tested molecules, 2-(5-nitrofuran-2-yl)-3*H*-benzimidazole-5-carboxylic acid (Figure 9-compound 4) showed the most inhibition of β-hematic formation, meaning the best antimalarial activity.

Divatia et *al.*[49] synthesized thiosemicarbazones supported by the 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)-2-2-[1-(5-chloro-1*H*-benzimidazol-2-yl)ethylidene]-N-(4-iodophenyl)hydrazine carbothioamine have shown excellent antimalarial activities. Indeed, the structure-activity relationship study

conducted suggests that compounds with mesomeric electron donor groups (EDG) such as halogen had excellent antimalarial activity (Figure 9-compound 5).

The work conducted by Toro et *al.*[50] on the synthesis and evaluation of the anti-plasmodial activity of benzimidazole derivatives. The anti-plasmodial tests were carried out *in vitro* against *P. falciparum* on compounds such as 2-ferrocenyl-benzimidazole and N-ferrocenylmethyl-2-ferrocenyl-benzimidazole (Figure 9-compound 6). These molecules showed good anti-plasmodial properties with IC_{50} between 10.4 to26.5 μM.

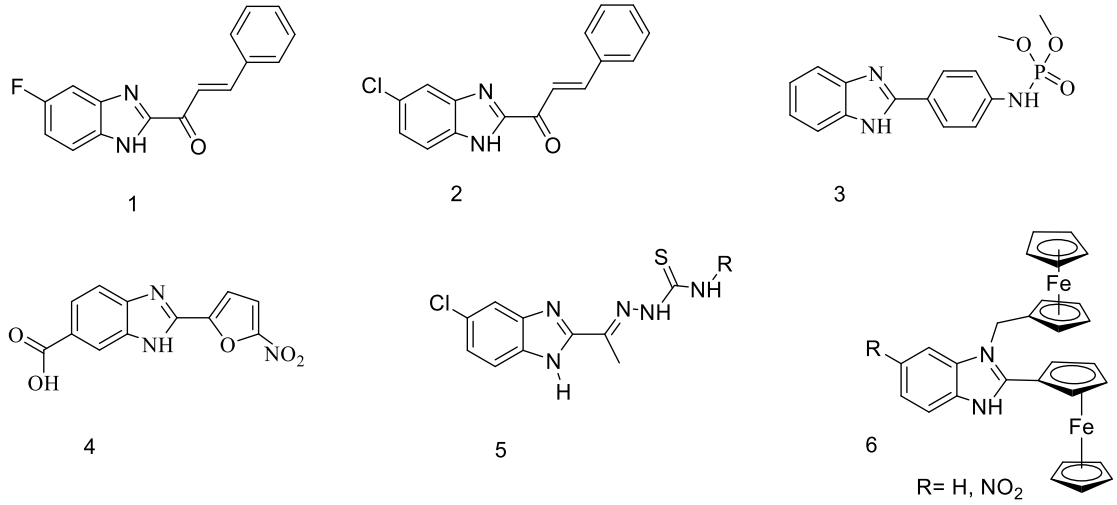

Figure 9 : Benzimidazole derivatives with antiplasmodial activity

i. Antioxidant properties of benzimidazole derivatives

Sarika Saini et *al.*[51] 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 10.A) had a higher antioxidant activity than ascorbic acid at higher concentrations.

The antioxidant activity of benzimidazole was demonstrated in the work of Dvornikova et *al.* [52]. They evaluated this activity with 2-hydroxylphenyl benzimidazole derivatives (Figure 10.B) using the *in vitro* method and compared it to a few refence 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.

R. A. Sabrina et *al.* [53] evaluated the antioxidant activity of some 5-nitrobenzimidazole derivatives (Figure 10.C) in their work. Indeed, they proved that all the 5-nitro-2-substituted benzimidazole derivatives that they synthesized had an antioxidant activity far superior to the

reference molecule with minimum inhibitory concentrations between 3.17 to 7.59 µg/mL.

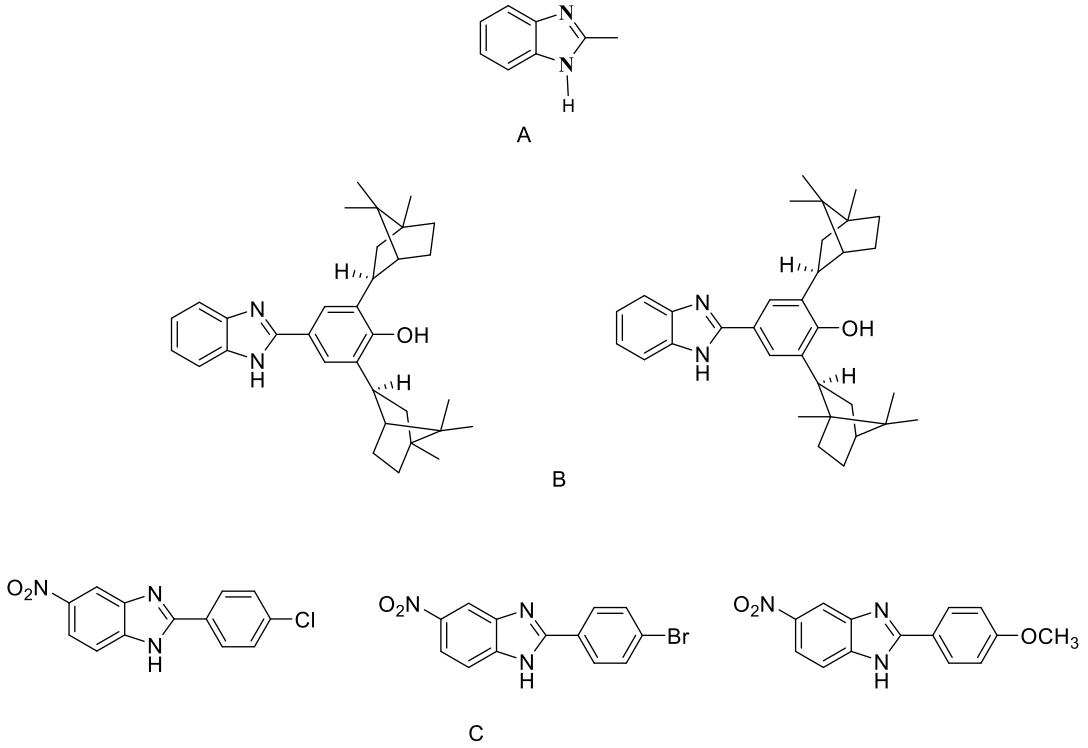

Figure 10: A. 2-methyl-1*H*-benzimidazole B. 2-hydroxylphenyl benzimidazole derivatives C. 5-nitrobenzimidazole derivatives

2. Methods for Benzimidazole and derivatives synthesis.

Benzimidazole is one of the oldest nitrogen heterocycles. It was first synthesized by Codebreaker in 1872 and then later repeated in 1878 by Ladenburg and Wundt [54]. Since then, several synthetic methods have been developed to obtain functionalized benzimidazole mainly at positions -1, -2, -3 and -5.

a. The Phillips methods

In 1928, Phillipssynthesized 2-substituted benzimidazole derivatives by reacting orthophenylenediamine (OPDA) with various organic acids in 4N hydrochloric acid under reflux for 30 to 40 minutes [55]. These 2-substituted benzimidazole derivatives were obtained with yields ranging from 50 to 70 % (Figure 11.A). This method is the most used to obtain benzimidazole derivatives. Carboxylic acid derivatives can be replaced by mercaptoacetic acid. El-Gohary et *al.*[56] were able to synthesize 2-mercaptomethyl-1*H*-benzimidazole by condensation of mercaptoacetic acid with OPDA under the same conditions as in the Phillips reaction (Figure 11.B).By condensing OPDA with benzoic acid derivatives, Odame et *al.*[57] synthesized

substituted benzimidazole derivatives at the 2-position. This reaction occurred in toluene at reflux for 6 hours in the presence of polyphosphoric acid (PPA) (Figure 11.C). Saini et *al.*[51] did the same kind of work, condensing OPDA with 90 % acetic acid at a temperature of 100°C for 2 hours. After treatment of the reaction medium, they obtained 2-methyl-1*H*-benzimidazole with a yield of 72 % (Figure 11.D).

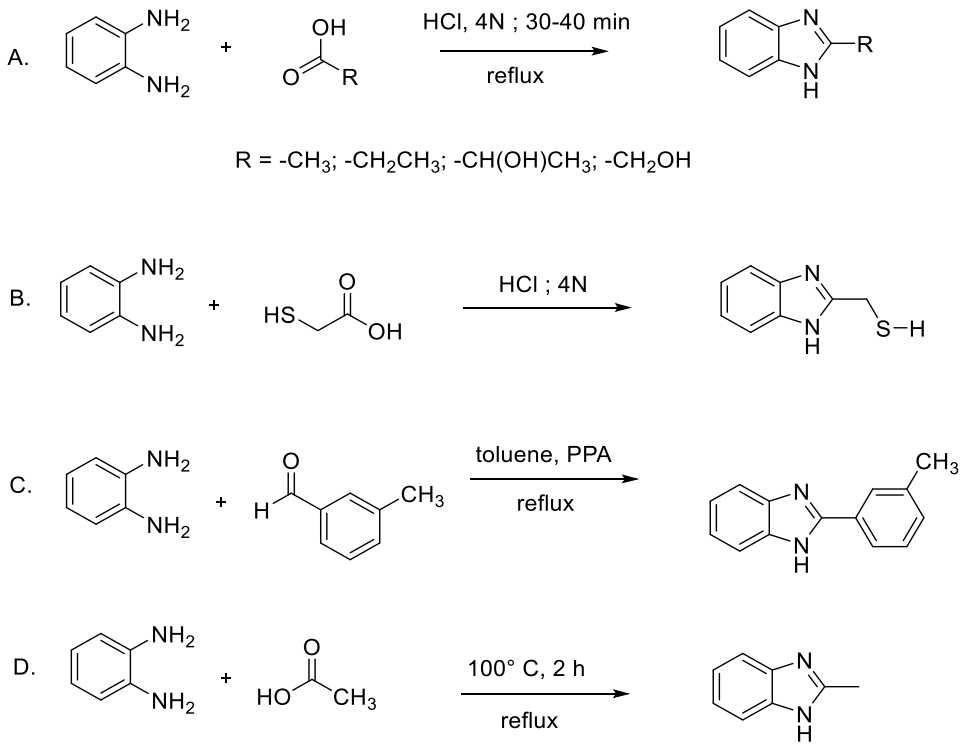

Figure 11: A. Benzimidazole synthesis by Phillips method. B. Synthesis of 2-mercaptomethylbenzimidazole. C. Synthesis of 2-m-tolyl-1H-benzimidazole according to Odame et *al*. D. Synthesis of 2-methyl-1*H*-benzimidazole according to Saini et *al.*

b. Synthesis method from orthophenylenediamine and aldehydes

The synthesis of benzimidazole from the condensation between OPDA and aldehydes are commonly the most described in the literature. The reactions of obtaining benzimidazole derivatives from OPDA and aldehydes using hydrogen peroxide (H_2O_2) and hydrochloric acid (HCl) solution at 100°C (Figure 12.A) have been described by Kiumars Bahrami et *al.*[58]. This method made possible to obtain benzimidazole derivatives substituted in position -2 by aryl groupswith yields ranging from 85 to 96 %. Shortly thereafter, same authors repeated the process at room temperature this time, replacing the water by acetonitrile[59]. This method has been used in other works. Hydrochloric acid (HCl) was replaced by cerium ammonium nitrate (CAN) and

resulted in the production of 2-aryl-1*H*-benzimidazole with yields between 92 and 97 % (Figure 12.B) [60].

In another study, Li-Hua Du et *al.*[61] 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 to 5 min to obtain substituted benzimidazole at the -2 position with yields ranging from 68 to 98 %. The best yields were obtained by using dioxane as a reaction solvent (Figure 12.C).Karthikeyan et *al.*[62] synthesized derivatives of 2-aryl-1*H*-benzimidazole substituted in position-5 by the carboxylic acid function (Figure 12.D). They put in reaction 3,4-diamimo benzoic acid or 3,4-diamino ethyl benzoate with benzaldehyde derivatives in *N*,*N*-dimethyl acetamide (DMAc) at 100°C for 6 to 12 h in the presence of sodium metabisulfite ($Na_2S_2O_5$).

The condensation of OPDA with furan carbaldehyde derivatives in ethanol at room temperature resulted in a series of benzimidazole substituted in the -2 position by furan[63] with a yield of 90 % for two hours. This reaction was catalyzed by copper II associated with a Schiff base (Figure 12.E).The synthesis of 2-alkyl-1*H*-benzimidazoles from OPDA and aldehydes was also performed by Alloum et *al.*[64]. This synthesis method involved the reaction of various aldehyde derivatives with OPDA on a solid base (silica SiO2 treated with thionyl chloride $SOCl_2$) in DCM at room temperature (Figure 12.F). This reaction occurs through the formation of imine intermediate, followed by aromatization by sulfur dioxide formed *in situ* to lead to the substituted benzimidazole derivatives in position-2.

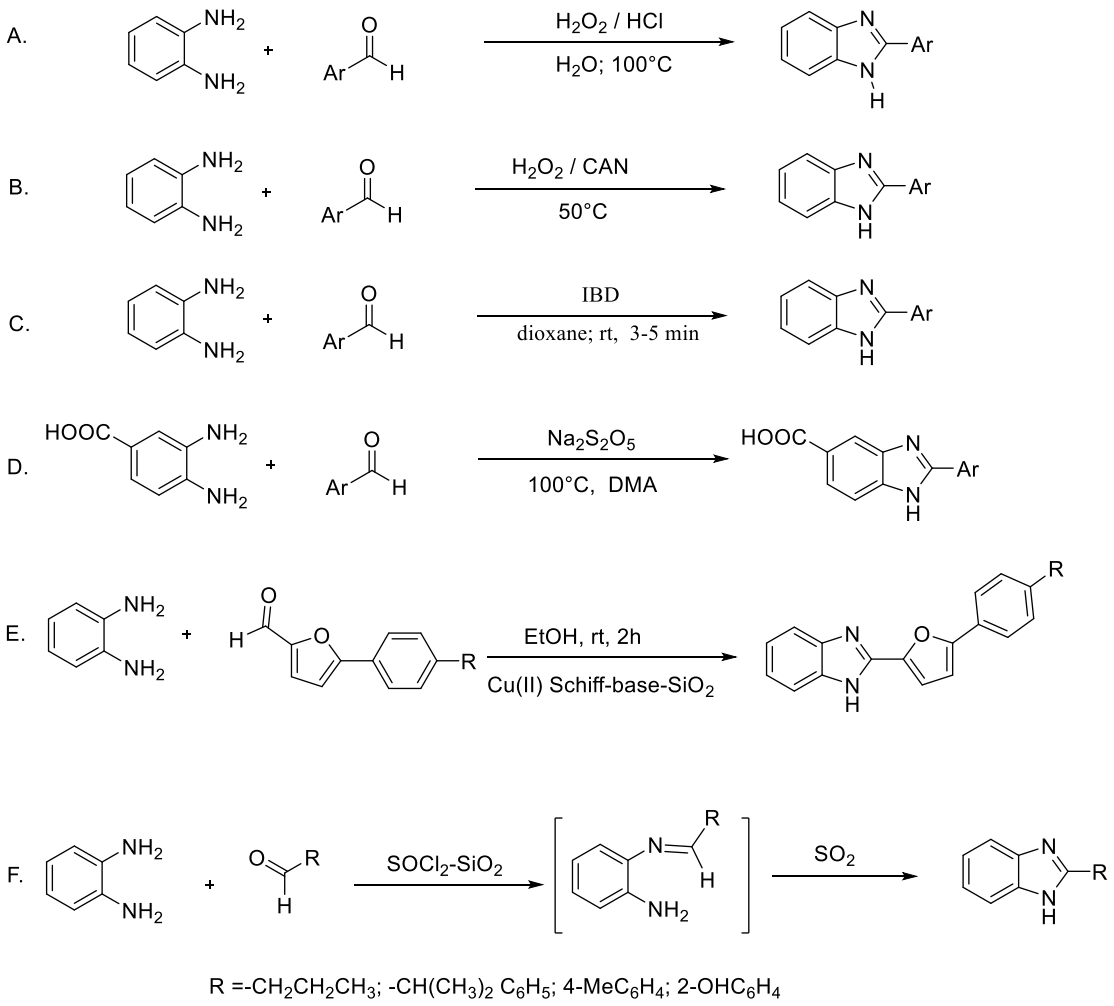

Figure 12: A.Synthesis of 2-aryl-1*H*-benzimidazole according to Kiumars Bahrami et *al*. B. synthesis of 2-aryl-1*H*-benzimidazole. C. Synthesis of the derivatives of 2-phenyl-1*H*-benzimidazole according to Li-Hua Du et *al.* D. Synthesis of derivatives of 2-aryl-1*H*-benzimidazole according to Karthikeyan 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 benzimidazole from aniline and aldehyde derivatives is most often catalyzed by transition metals. Some of these reactions are carried out in the presence of catalysts which possess oxidation or reduction properties. The work of Devuapally Mehsesh et *al.*[65] present the synthesis of benzimidazole derivatives by reacting aniline with primary amines (benzylamine) in the presence of sodium azidure (NaN_3) and copper II used as catalyst in dimethylsulfoxide (DMSO) at a moderate temperature. To improve the efficiency of this method, *ter*-butyl hydroperoxide

(THBP) and acetic acid derivatives were added to the reaction medium. This reaction worked in 10 h in the range of 52 to 79 % yield (Figure 13.A). In the same work, benzylamine derivatives were replaced by benzylic alcohol derivatives. They obtain benzimidazoles with yields ranging from 35 to 62 %, but with a longer reaction time than that of benzylamines (Figure 13.B).

Yong Kim et *al.* [66] 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 with yields ranging from 44 % to 98 %. The best yields were obtained with 2-iodoaniline in the presence of ligands such as 1,2-Dimethylethylenediamine (DMEDA) and Tetramethylethylenediamine (TMEDA) (Figure 13.C).Thanh N'guyen et *al*. [67] synthesized a 2-substituted benzimidazole variety without using an organic solvent. They condensed 2-nitroaniline with benzylamines in the presence of iron chloride for 24 h at 120°C. The 2-substituted benzimidazole derivatives were obtained with yields between 58 and 92 % (Figure 13.D).The production of benzimidazole derivatives was first described in 1872 by Hobrecker [68]. This method is one of the oldest methods to access to the benzimidazole scaffold. After a reduction of 2-nitro-5-methylacetanilide, an intramolecular cyclization followed and yielded to 2,5-dimethyl-1*H*-benzimidazole (Figure 13.E).

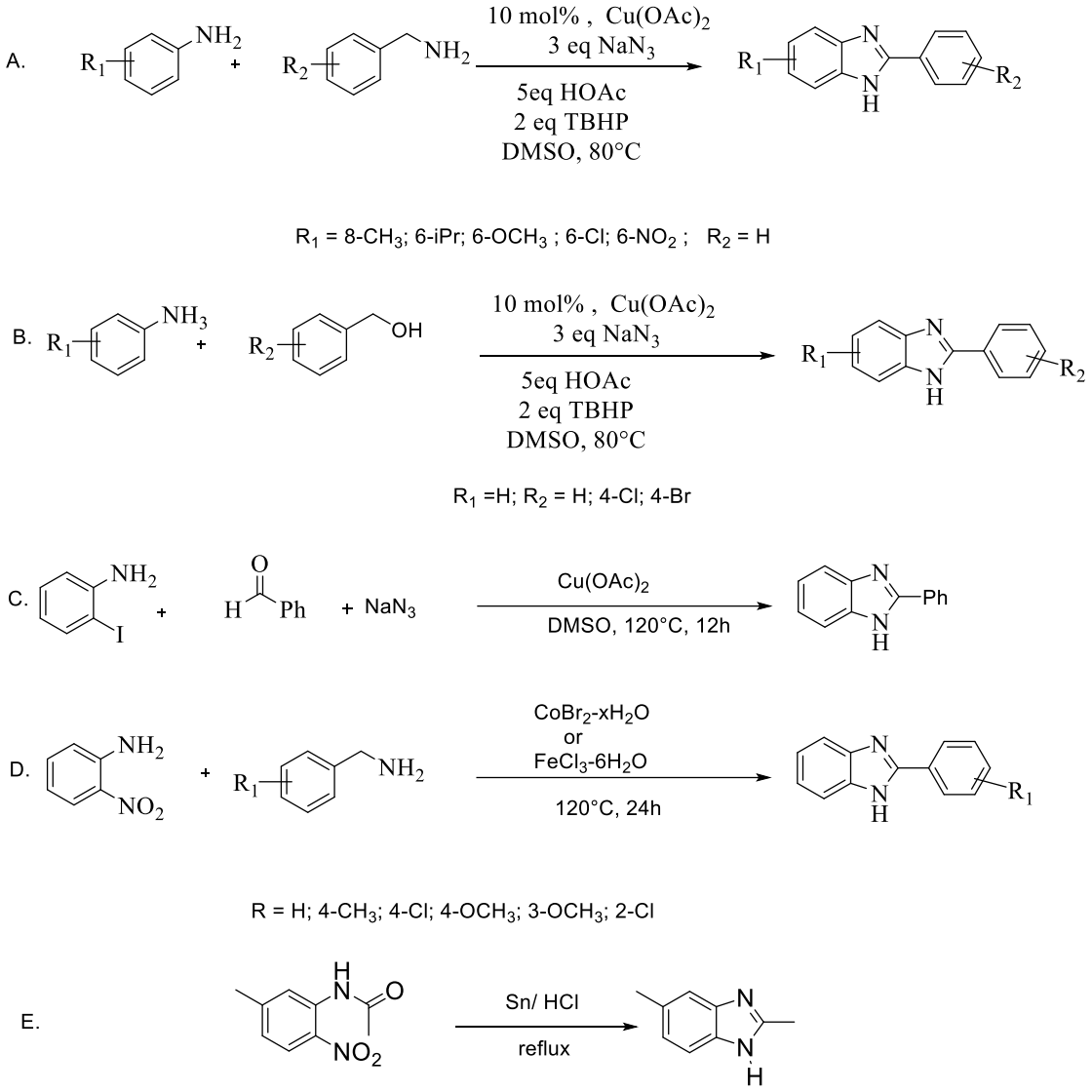

Figure 13: synthesis of the derivatives of 2-phenyl-1*H*-benzimidazole using benzylamine according to Devuapally Mehsesh et *al*. B. synthesis of the derivatives of 2-phenyl-1*H*-benzimidazole using phenylmethanol according to Devuapally Mehsesh et *al*. C. synthesis of the derivatives of 2-phenyl benzimidazole according to Yong Kim et al. D. synthesis of benzimidazole-2-substituted derivatives according to Thanh N'guyen . E. Hobrecker 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*. [69] synthesized derivatives of N-alkylbenzimidazole by reacting a variety of OPDA with formamide N-substituted with zinc diacetate ($Zn(OAc)_2$) as a catalyst in the presence of poly(methylhydrosiloxane) (PMHS) for 18 h at 120°C (Figure 14.A)**.**In our group, we worked

also on the synthesis of benzimidazole scaffold. We developed a method by Sissouma Drissa et *al.* [70], [71] in which, a thioalkyl or thioaryl group of amidinium salts was introduced to the -3 position. The condensation of these amidinium salts with OPDA in dichloromethane provided access to the 2-thioalkylbenzimidazole and 1*H*-benzimidazole derivatives (Figure 14.B).

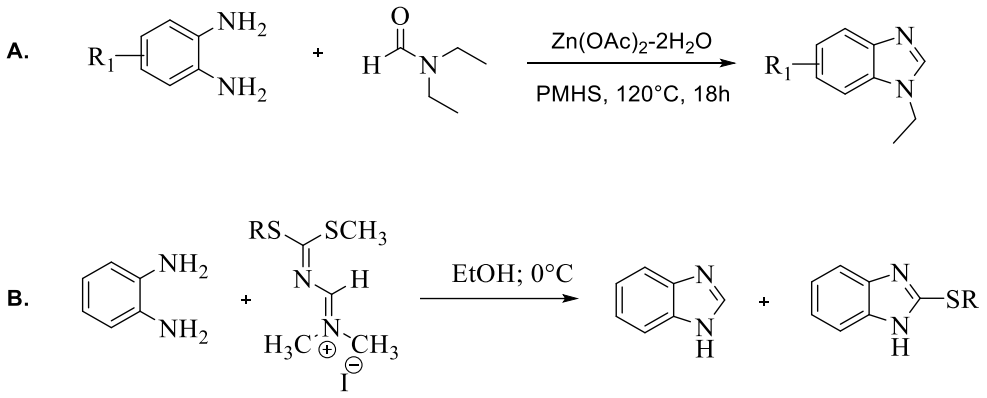

Figure 14: A. Synthesis of N-substituted benzimidazole derivatives according to Deepak Nale. B. Synthesis of benzimidazole and 2-thiobenzimidazole according to Sissouma et *al*

e. Synthesis method from benzodiazepines

We also developed another method in a work done by Timotou et *al.* [71]. We were able to synthesize benzimidazole derivatives by cyclic regression of benzodiazepines. This method consisted of treating chalcones in an alkaline medium to access benzodiazepine derivatives. Then, these benzodiazepines were treated under DMF reflux in the presence of potassium carbonate (K_2CO_3) for 24 h to obtain the benzimidazole derivatives. Camara et *al.* [72] repeated this method by treating benzodiazepine formed either in acid or basic medium under DMF reflux for 2 h. The yields have been improved in acid medium, between 60 and 80%, while in basic medium, the yields varied between 40 and 60% (Figure 15).

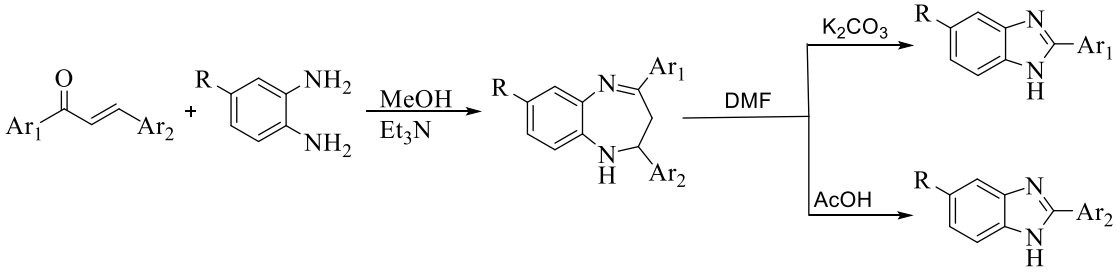

Figure 15: synthesis of derivatives of 2-aryl benzimidazole according to Camara et *al.*

f. Method of synthesis from OPDA derivatives and other reagents

By reacting OPDA with ethyl acetoacetate under reflux of xylene for 6 h, Denise Mondieig et *al.* [73] were able to synthesize benzimidazole by introducing the isopropenyl group into position-1. Thus, they obtained N-isopropenylbenzimidazolone with a yield of 70 % (Figure 16.A).

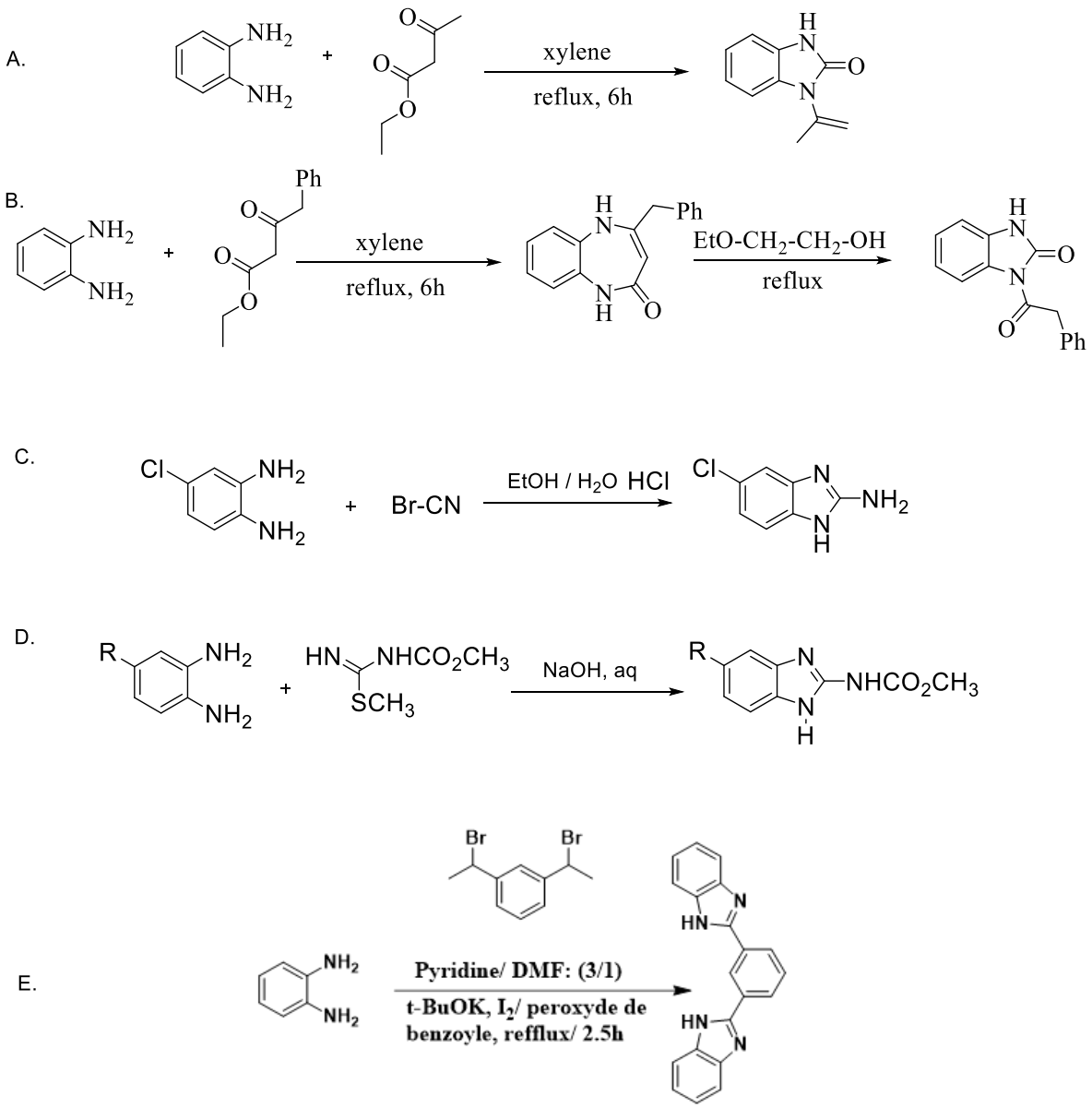

Figure 16: A.Synthesis of N-alkylbenzimidazolone derivatives according to Denise Mondieig et *al.* B. synthesis of N-alkylbenzimidazolone derivatives according to Vakhid Mamedovet et *al.* C. synthesis of derivatives of 2-aminobenzimidazole Leonard et *al.* D. Albendazole synthesis method. E. Synthesis of 1,3-bis(*1H*-benzimidazol-2-yl)benzene according to Yang et *al.*

The same method was used by Vakhid Mamedov et *al.* [74] to describe the synthesis of benzimidazolone derivatives through the formation of a reactive intermediate, benzodiazopinone. Once isolated, it was treated under reflux of methoxyethanol, allowing a rearrangement to lead to benzimidazolone derivatives with a yield of 60% (Figure 16.B). The 2-amino-5-chlorobenzimidazole was synthesized by Leonard et *al.* [75] by a reaction between p-chloro-OPDA and cyanogen bromide (BrCN). This reaction was carried out in the presence of hydrochloric acid in an EtOH/H_2O mixture at 70 °C. Thus, after cooling, the reaction medium was neutralized with a sodium hydroxide solution to give 2-amino-5 chlorobenzimidazole with a yield of 73 % (Figure 16.C). By applying the Phillips method to iminoester [76] and thiocarbamate [77] acid derivatives, benzimidazole derivatives were synthesized by reacting thiocarbamates with OPDA derivatives in an aqueous solution of sodium hydroxyde. This reaction resulted in Albendazole analogues after the removal of the thiol group and ammonia (Figure 16.D). Yang et *al.*[78] synthesized bisbenzimidazole through a condensation reaction of an excess of OPDA with 1,3-bis(dibromomethyl)benzene to produce 1,3-bis(1*H*-benzimidazol-2-yl)benzene with a yield of 87% (Figure 16.E).

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.*[79].

Thus, the action of carbon disulfide on OPDA derivatives in dimethylformamide (DMF) under magnetic agitation for 24 h leads, after addition of water into the reaction mixture to the formation of 2-mercapto-1*H*-benzimidazoles (Figure 17.A). By replacing carbon disulfide with urea, Bhanage et *al.* [78] synthesized 1,3-dihydrobenzimidazol-2-one. For this purpose, they condensed OPDA with urea in DMF at 150°C. They obtain 1,3-dihydrobenzimidazol-2-one with a 98% yield (Figure 17.B).

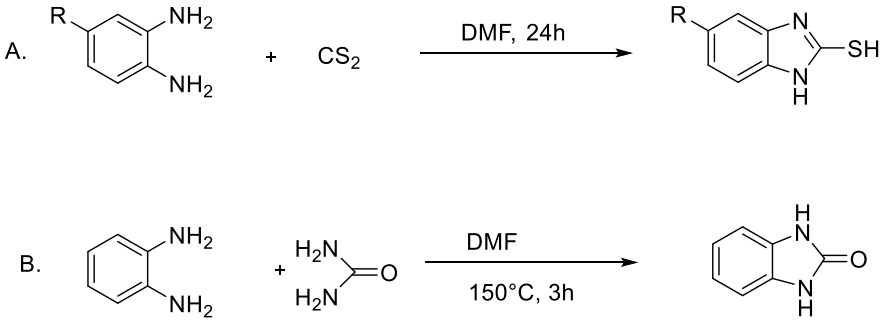

Figure 17: A. Synthesis of mercapto-1H-benzimidazole according to Van Allan et *al.* B.Synthesis of 1,3-dihydrobenzimidazol-2-one according to Bhanage et *al.*

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

Imidazo[1,2-a]pyridines are aromatic bis-heterocyclic compounds resulting from the addition of an a-type fusion of pyridine and imidazole rings with angular nitrogen connecting the two cyles. Depending on the position of the pyrrolic nitrogen and also the angular one, three isomers are obatined (**Figure 18.A)** Imidazopyridine is an important pharmacophore because it is widely used in many biologically active compounds. A multitude of research works has been donearound this bis-heterocyclic, and even some drugs came from those researchs.

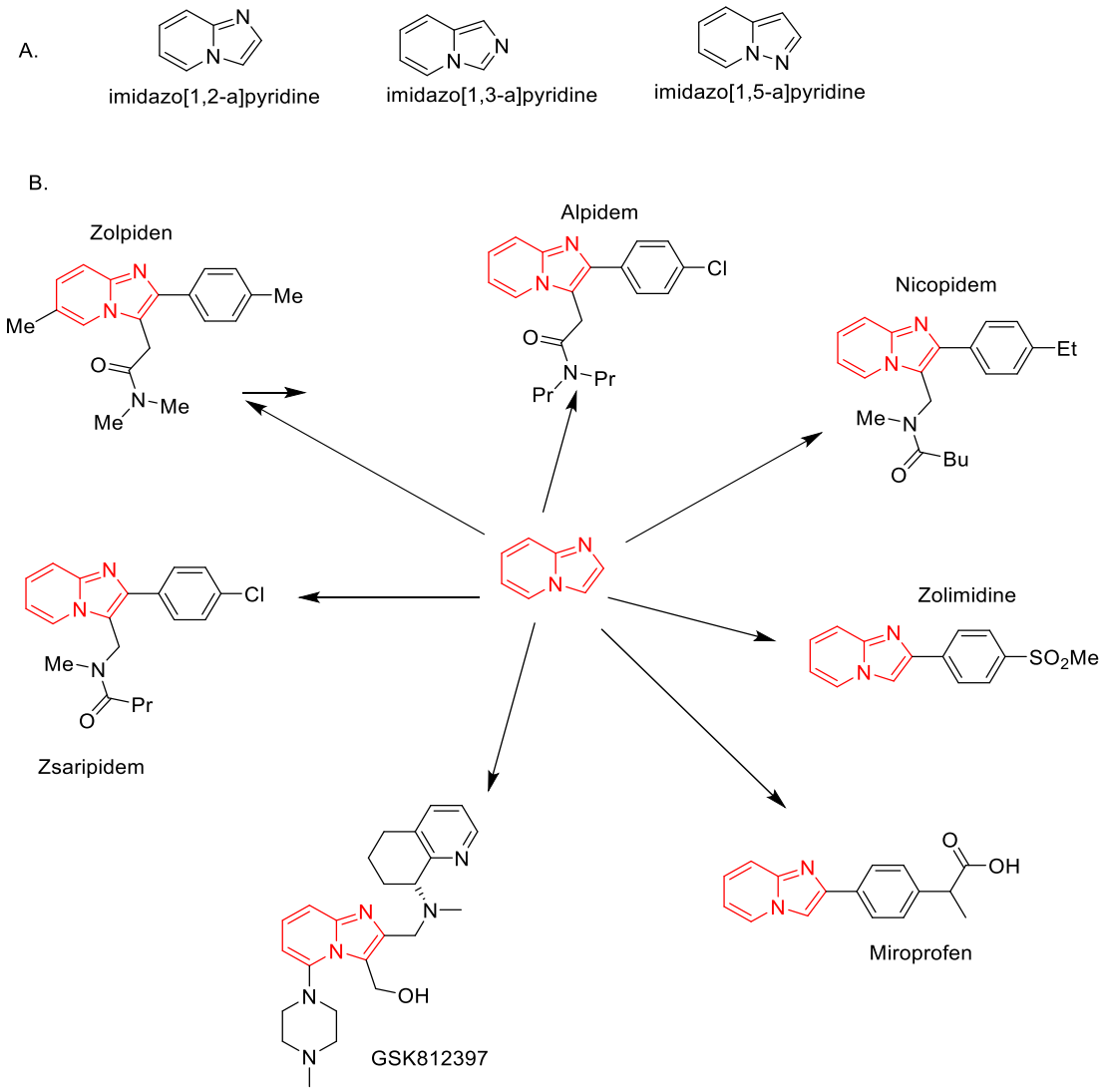

Figure 18 : A.Three imidazopyridine isomers B. Few drugs based on Imidazopyridine scaffold

II-1. Biological activities of the imidazopyridine scaffold

According to the pharmacomodulations undertaken on the different positions of the imidazo[1,2-a]pyridine moiety, in particular on the pyrrolic core, interesting biological activities are obtained. These have been described in the literature. Furthermore, the most common biological activities will be 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.*[80] 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 their synthesized compounds, at a concentration of 1000 μg/mL, showed a promising inhibition against the various microbial pathogens tested. Of the compounds synthesized (Figure 19), compounds 1a, 1c, 1e and 1g containing benzyl, 4-fluorobenzyl, 4-methylbenzyl and 4-methoxybenzyl substituents demonstrated inhibition against all pathogens. The 9c and 9e compounds with 4-fluorobenzyl and 4-methylbenzyl as their respective substituents showed moderate activity against *E. coli*. In addition, compounds 9e, 9g and 9j containing 4-methylbenzyl, 4-methoxybenzyl and 3,4,5-triflouromethybenzyl substitutes showed inhibition against *K. pneumonia*. All synthesized compounds showed less activity against *S. aureus*. Similarly, no activity was recorded by the compounds 1a, 1b, 1d, 1g, 1h, 1i and 1l at their lowest concentrations (500 μg/mL) tested against K.pneumoniae.

In addition, the work of Kai et *al*.[81] 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.

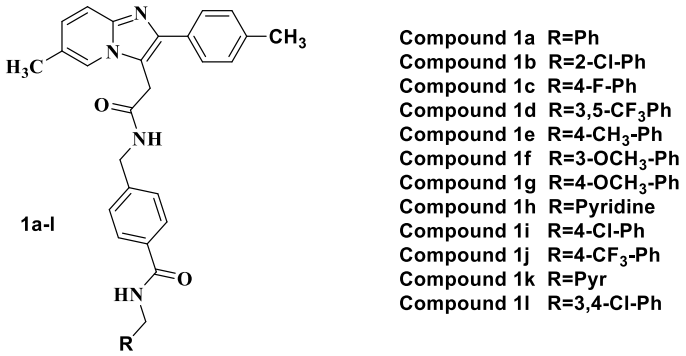

Figure 19 : Imidazo[1,2-a]pyridine derivatives by Pushpalatha Budumuru et *al.* against *E. coli* (ATCC-25922), *S.aureus* (ATCC-9144), *K. pneumoniae* (ATCC-13883) and *B. subtilis* (ATCC-6051)

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 against different cancer cell lines. These include breast, liver, colon, brain, lung and kidney cancers. [82] The anticancer effects of these compounds are primarily the result of their inhibitory effects on different molecular mechanisms. Namely, PI3K/ AKT, CENP-E, IGF-1R, CDK, inhibition of tubulin polymerization and C-encounter inhibition.

Similarly, Gui-Ting Song et *al.* [83] initiated modulations around the imidazopyridine core conferring anticancer activities. Thus the modulations at the -2 position by phenyl derivatives and at the -3 position by quinoxaline and quinoxalone derivatives led to imidazo[1,2-a]pyridine derivatives that inhibited tumour cell proliferation. This is the case with compounds 2 and 3 at the 20 µM concentration, which over 48 hours showed a very high inhibition rate on HCT-116, HeLa and MCF-7 cells.

The anticancer activity of the imidazopyridine nucleus was also demonstrated by Nurit Dahan-Farkas et *al.*[84] on colon cancer. For this purpose, the 6-substituted imidazo[1,2-a]pyridines compounds they synthesized were evaluated for their anticancer activities on the HT-29 and Caco-2 cell lines. Thus, all compounds bearing a 6-position nitro-substituent (NO_2) in the imidazopyridine nucleus and all those bearing a 2,5-dihydroxyphenyl substituent attached to imidazopyridine, showed little reduction in cell growth of colon cancer cell line. In contrast, imidazopyridine derivatives containing the protected hydroxyl group (such as OMe, compound 4) and the nitrogen-substituted phenyl group (compound 5) generally performed well by reducing the cell viability tested by more than 50% with concentration values inhibitions well above 50 µM.

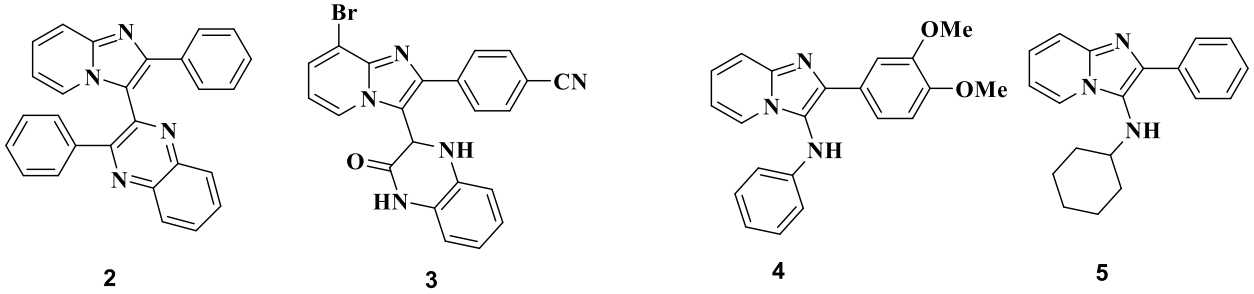

Figure 20 : Modulations around the imidazopyridine core conferring anticancer activities. Compound 2, 3 (ref 83) and 3,4 (ref 84)

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.*[85] 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 activities was translated into an inhibitory concentration of 50 (IC_{50}) and expressed in micromoles (mM). Their

results on the chloroquino-sensitive *Plasmodium falciparum* isolates reveal that the 6k and 6y compounds (IC_{50} =35.92 and 24.08 mM respectively) have moderate antiplasmodial activity, while the other three (5a, 5n and 5q) possess have very good antiplasmodial activities, between 8.65 and 6.23 mM. Five imidazopyridinyl-arylpropenone compounds (6a, 6k, 6n,6q and 6w) were found to be very active on *P. falciparum* chloroquino-resistant isolates.

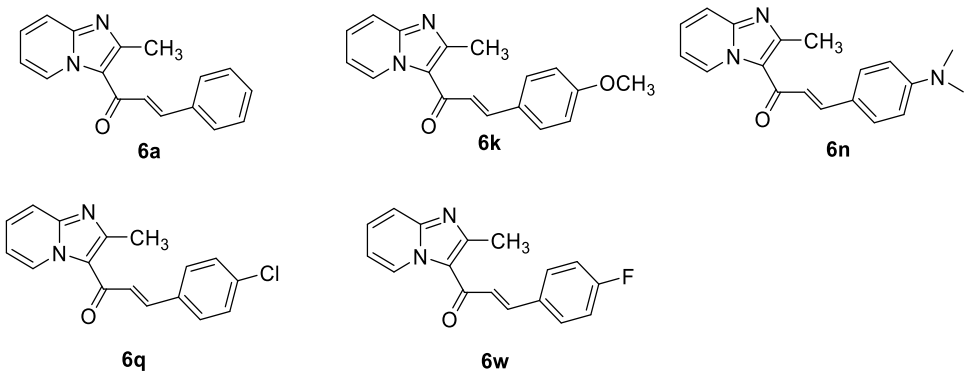

Figure 21: 3-(phenyl)-1-(2-methyl*H*-imidazo[1,2-a]pyridin-3-yl)prop-2-en-1-one derivatives against *Plasmodium Falciparum*

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

The antiviral activity of the imidazopyridine scaffold has been demonstrated by researchers since the 1990s. Thus, Chafiq Hamdouchi et *al.*[86] was able to show that some derivatives of 2-amino-3-substituted-6-[-1-phenyl-2- (N-methylcarbamoyl) vinyl] imidazo [1,2-a]pyridines (compounds 7, Figure 22) had strong anti-rhinovirus activity and no obvious cell toxicity.

Alain Gueiffier[87] et *al*. performed chemical modifications at the position-3 of the imidazo [1,2-a]pyridine ring. This improved the therapeutic index of this new class of antiviral agents. Thus, antiviral as says on the series of their molecule have shown that some of their compounds (compounds 8 and 9) appear to be as the most potent and selective inhibitors of CMV and VZV compared with three reference drugs such as ganciclovir, acyclovir and brivudin.

Several sugar-substituted imidazopyridine derivatives showed 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-Erythrofuranofuranosyl)imidazo[1,2-a] Pyridine and 2,6-dichloro-3-(α-D / L-Erythrofuranosyl)

imidazo[1,2-a]pyridine (compound 11) were both inactive against HCMV and HSV-1 and nontoxic on uninfected cells.[88] [89] In contrast, the enantiomer mixture of 2,6,7-trichloro-3- (α-D/L-Erythrofuranosyl)imidazo[1,2-a]pyridine (10) was active against HCMV and HSV-1. They noted that the α (10) anomer is more active than the β anomer.

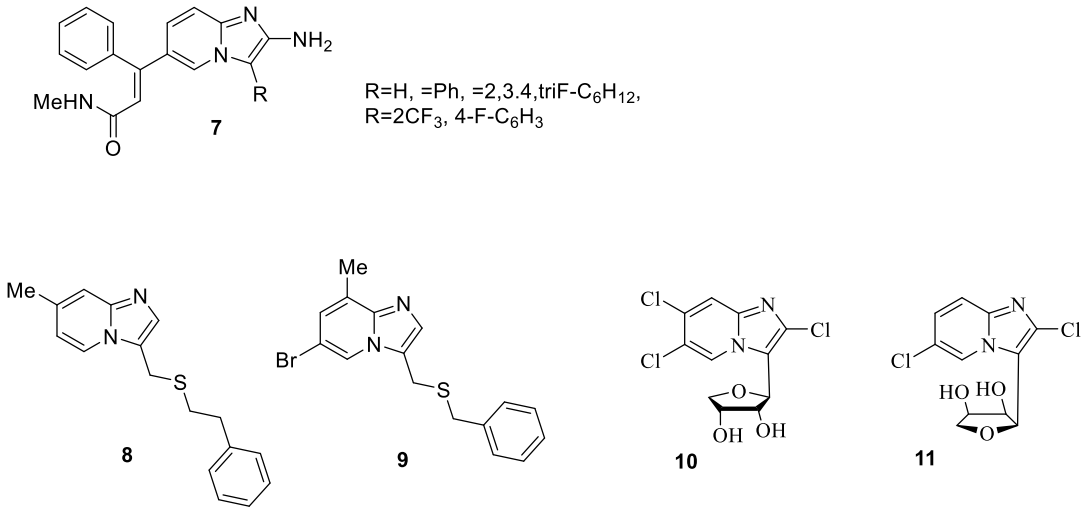

Figure 22 : Imidazopyridine derivatives with antiviral activities

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

Jean-Paul Déto et *al.* [90] described a new series of imidazo[1,2-a] pyridine-based anthelminthic, showing an action on the parasitic nematode *Strongyle Haemonchus contortus*. One (compound 12) of its compounds (Figure 23) , the most powerful inhibited the motility of worms at 31.25 μM. 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.

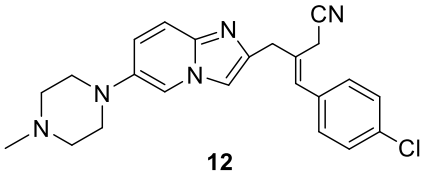

Figure 23: Structure of 4-(4-chlorophenyl)-3-((6-(4-methylpiperazin-1-yl)*H*-imidazo[1,2-a]pyridin-2-yl)methyl)but-3-enenitrile with anthelminthic activity

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

Cyril Fersing et *al.* [91] 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 (compound 13) was a successful pest control.

This single molecule exhibited low cytotoxicity to human cell-line HepG2 (CC_{50} > 100 μM) showed good antileishmanial activity (IC_{50} = 12.1 μM) against *L. donovani*, *L. infantum*, and *L. major* and good antitrypanosomian activities (IC_{50} = 1.3-2.2 μM) against *T.brucei* and *T.cruzi*, in comparison with several reference drugs such as miltefosin, fexinidazole, eflornithine and benznidazole (IC_{50} = 0.6 -13.3 μM).

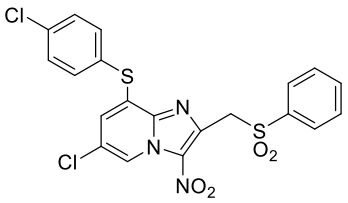

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Figure 24: Structure of 6-chloro-8-((4-chlorophenyl)thio)-3-nitro-2-((phenylsulfonyl)methyl) imidazo[1,2-a]pyridine

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

Mycobacterium tuberculosis is a major human pathogen and the cause of lung disease.[92] Through the use of high-throughput whole cell screening from a library of extended compounds, a number of imidazo[1,2-a]pyridine were obtained as highly active molecules against *M. tuberculosis* and *Mycobacterium Bovis* BCG. Some of the imidazopyridine derivatives (compounds 14,15 and 16) showed inhibitory diameters (MICs) in the 0.03 to 5 mm range against *Mycobacterium Bovis* strain. Also, work by Garrett C. Moraski et *al.* on imidazopyridines, has led to antituberculosis compounds.[93] The 2,7-dimethylimidazo[1,2-a]pyridine-3-carboxamide derivatives (17, 18) 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 (CMIs versus MDR-TB of 0.03 to 0.25 μg/mL or 0.08 to 0.7 μM, respectively) at concentrations below 1 μM.

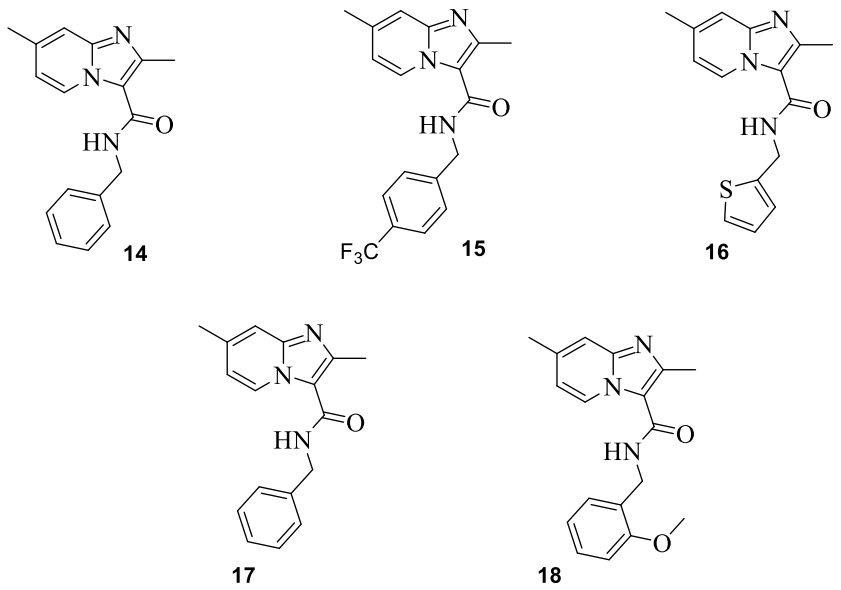
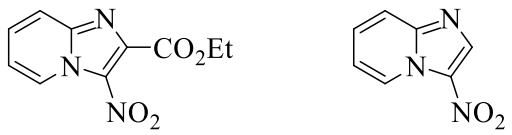


Figure25: 2,7-dimethylimidazo[1,2-a]pyridine-3-carboxamides derivatives found as antituberculosis drugs

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

The pest control potency of imidazopyridine was assessed using *Trichomonas Vaginalis*. GT3 was a highly pathogenic strain isolated in the city of Guanajuato, Mexico in 2012 [94]. Margarita Lopez-Martinez et al. showed that most of the synthezisedcompounds got antiparasitic activity after 24 h of treatment. As a result, the results, the ethyl 3-nitroimidazo[1,2-a]pyridine-2-carboxylate (19) and the 3-nitroimidazo[1,2-a]pyridine (20) had good anti-parasitic activity, requiring 2.45–3.96 uM to reach the desired effect. They also correlate partition coefficient (log P) determination and antiparasitic activity for all the tested. A mathematical descriptor correlating the exhibited pharmacological activity and log P was found (0.9 ± 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 found may be described by these two variables.

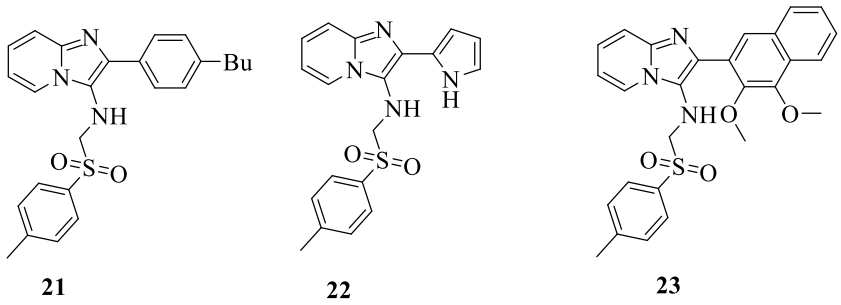


19 20

Figure26: 3-nitro-imidazopyridine derivatives possesing 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 fumigates* 3007 and *Candida albicans* 3018 [95]. The test on these strains of showed that all the prepared compounds inhibited the growth of fungi to different degrees. Among the prepared compounds, compound 23 had the highest inhibitory index of 52.12% after 96 h incubation, followed by compounds 21 and 22, which showed with inhibitory index of 49.87 and 43.51%, respectively. The authors also investigated the effect of the synthetic compounds on the unicellular fungus *C.Albicans* 3018 after 24h incubation. These compounds were tested at concentrations ranging from 0.0976 to 100 μg/mL. Compound 23 was observed to have the lowest inhibitory concentration of 0.390 μg/mL. Compounds 22 and 23 completely inhibited fungal growth at a concentration of 0.781 μg/mL.



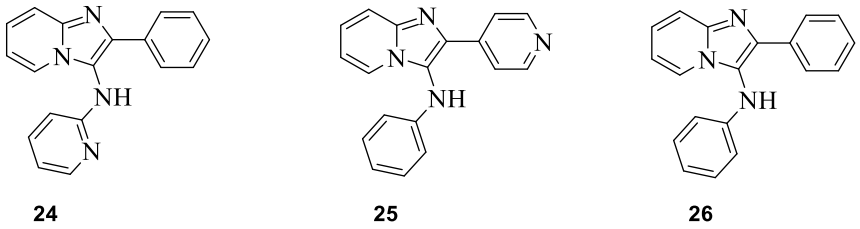
21 22 23

Figure 27: *N*-substitued- 2-aryl-imidazopyridine derivatives with antifungal acitivity

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

Renata B. [96] analyzed *in vivo* assays of Nociception, hyperalgesia, inflammation and *in vitro* of human PGHS-2 inhibitory compounds. The study suggests that some of the compounds can inhibit significant edema formation. Three (24,25,26) 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 (IC_{50} = 2.8 lumens), representing the standard anti-inflammatory drug (30% inhibition at 100 Lmol/kg).



24 25 26

Figure 28: 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 Chichibabin[97] in 1925 and for a long time, this framework was not fully studied, partly because of the lack of effective functional methods, structural variants, especially in the pyridine core. However, much work has been done on the synthesis, physical and reactivity properties of this ring for decades. In particular, advances in catalytic chemistry and metal coordination chemistry in particular have facilitate 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 famous. These include the condensation of 2-aminopyridine with α-halogenocarbonyls and the multi-component reaction between the same amino substrate itself and, a carbonyl compound and isonitrile compounds.

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

In 1961, W. L. Mosby was able to synthesize the imidazo[1,2-a]pyridine scaffold while modifying the Chichibabin method, [98] using 2-aminopyridine and bromoacetadehyde in refluxing hydrated ethanol in the presence of sodium bicarbonate (Figure 29a).

Also, Andrés A. Trabanco[99] et *al*. cycling between 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. Substituted pyridine in position-3 with a good yield in 50 min which considerably reduces the reaction time. In 2013, Castera-Ducros et al. synthesized 2-chloromethylimidazopyridine derivatives in one-step with yields ranging from 40 to 70%.[100] For their part, they performed a cyclic condensation rection between the 2-aminopyridine and 1,3-dichloroacetone derivatives by refluxing in ethanol for 4 h.

Maxwellet *al.* [101] synthesized the imidazo[1,2-a]pyridine core substituted at the position-2 by a two-stage reactive halogen. First, 2-aminopyridine reacts with 2-chloroacetic acid in water in the presence of triethylamine at 90°C for 5 hours to obtain a reactive intermediate. The latter is treated again in the presence of $POCl_3$ in toluene at 115°C for 16 h to obtain the imidazo[1,2-a]pyridine core substituted with chlorine at the -2 position .

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. [102] This compound was obtained with a 70% return.

Chezal et *al.* [103] 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.

6-bromo-2-(3,4-dichlorophenyl)-imidazo[1,2-a]pyridine was reported by Shankarrapa et *al.* [104] 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.[105]

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%. [106], [107]

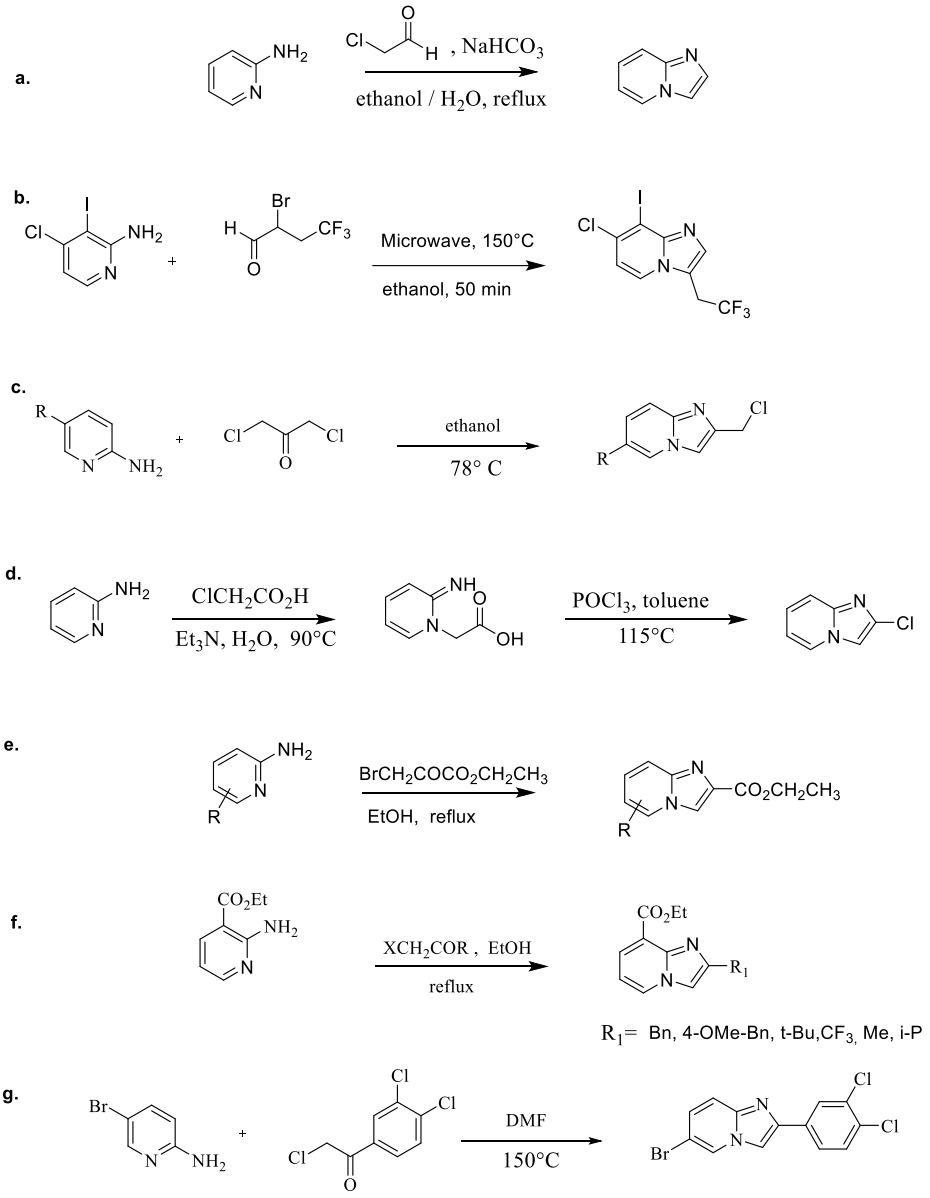


Figure 29: **a**.Chichibabin method of imidazopyridine synthesis **b**. synthesis of 3-(2,2,2-trifluoroethyl) *H*-imidazo[1,2-a]pyridine according to Andrés A. Trabanco et *al.* **c**. Synthesis method of 2-chloromethyl imidazopyridine derivatives *according* to Caroline Castera-Ducros et *al.* **d**. Synthesis methof 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-substitued imidazopyridine according to Chezal et *al.* **g**.Synthesis method of 2-(3,4-dichloro)-6-bromo imidazopyridine according to Shankarrapa 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.* [108] 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.* adopted the same reaction for their work, but made sure to replace morpholine for benzaldehyde [109] (Figure 30.a)..

Recently, in 2020, the team of Carlos et *al.*.[110] 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 30.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). [111] This reaction occurred at room temperature for 12 hours in the presence of scandium triflate ($Sc(OTf)_3$) as a catalyst (Figure 30.c).

Mehdi Adib et *al.* 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 [112] (Figure 30.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.* [113] used this method while changing reaction conditions (Figure 30.e). They react aldehyde derivatives, isocyanide and 2-amino-5-bromopyridine in the presence of magnesium chloride ($MgCl_2$) 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 [114]. After 18 h of reflux in toluene, in the presence of catalyst such as copper sulfate ($CuSO_4$) and 4-methylbenzenesulfonic acid (Figure 30.f), imidazo[1,2-a]pyridine derivatives are obtained with yields ranging from 28% to 68%.

Pushpalatha B. et *al.* [80] synthesized imidazo[1,2- a]pyridine from 4-methyl acetophenone, 2-amino-5-methyl pyridine and dibrome (Br_2) in methanol in the presence of Lewis acid ($AlCl_3$). This reaction (Figure 30.g) occurred between 0 and 5°C with a 57% yield.

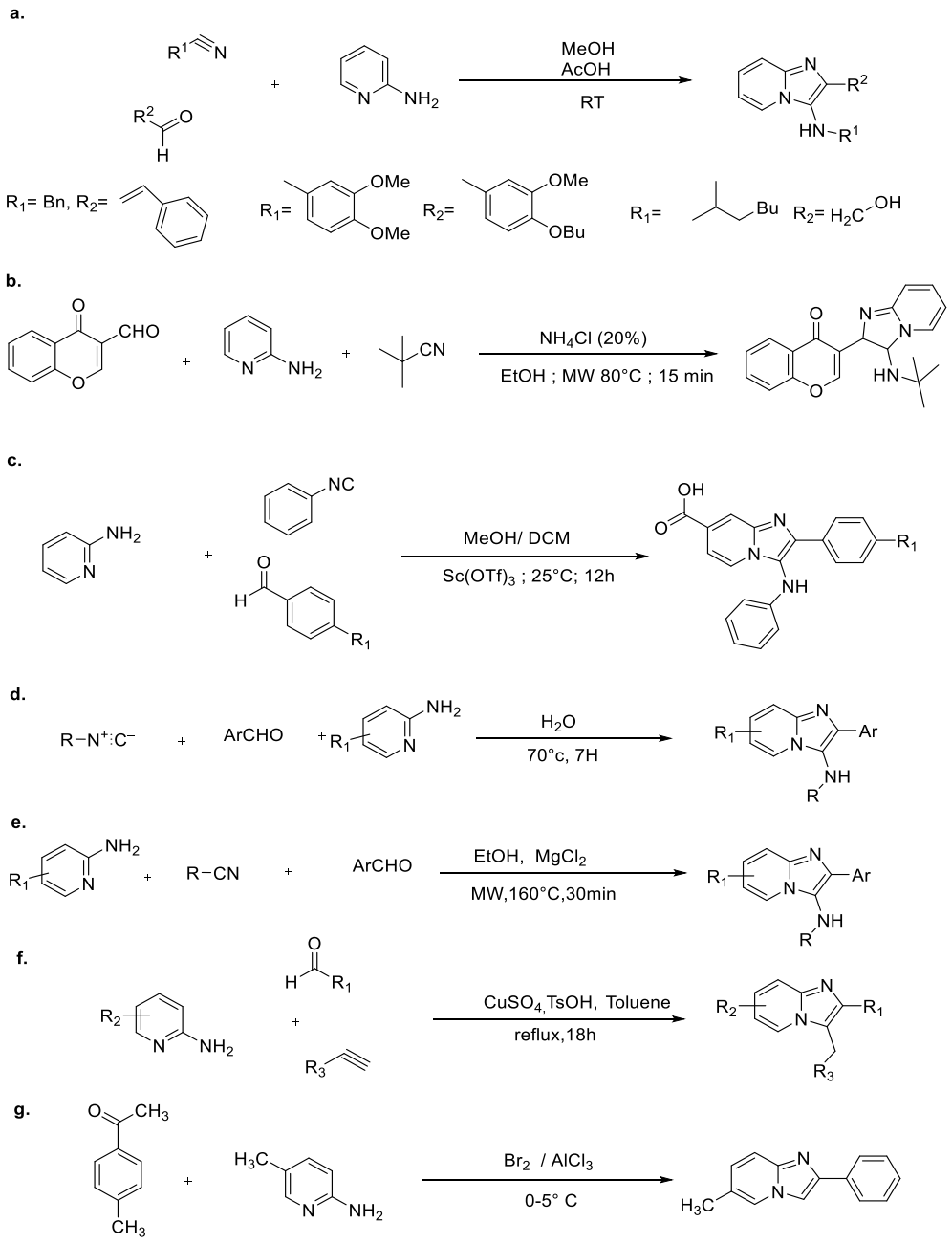


Figure 30: a. Synthesis method of imidazopyridine via muli components pathway according to Martna Hieke. **b**. Synthesis method of the 2-substituted imidazopyridine by the multicomponent pathway according to Katrin Groebke et *al.* **c.** Zarate-Hernández et *al.* synthesis method of imidazopyridine 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.** Syntheis 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.* [115] 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 ($NaICl_2$) in the DMF at 80°C for 1 hour and 30 minutes (Figure 31.a).

This reaction was carried out in several solvents such as dimethylsulfoxide (DMSO), methanol (MeOH), ethanol (EtOH) and acetonitrile (CH_3CN). 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.* [116]. Using the same reagents, they reacted in acetonitrile (CH_3CN) as a solvent with another catalyst, iodine–terbutylhydroperoxide–pyridine (TBHP-Py) to obtain the imidazopyridine core in 36 to 90% yields (Figure 31.a).. The replacement of the catalyst made it possible to increase the reaction time (12h *vs.* 1h30).

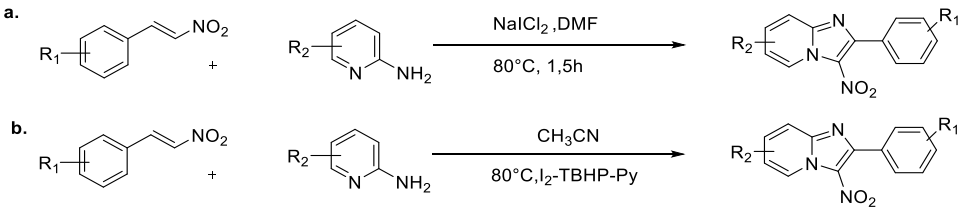


Figure 31: a.Synthesis method of 3-nitro-2-phenyl-midazopyridine derivatives according to Prashant B. Jagadhane et al. b.Synthesis method of 3-nitro-2-phenyl-midazopyridine derivatives according to Litao An et al.

d. Synthesis from α-chloro-β-diketone

In our group, Ouattara et *al.* [85] 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 32). This method resulted in a ketone function at the -3 position of the imidazo[1,2-a]pyridine core.

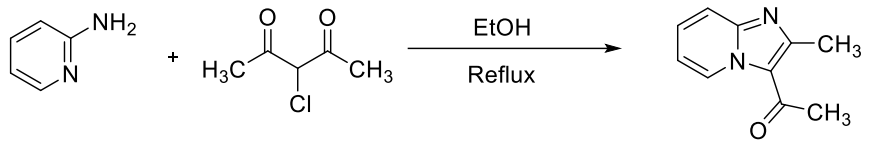


Figure 32: Synthesis method of 1-(2-methyl*H*-imidazo[1,2-a]pyridin-3-yl)ethanone via an α-chloro-β-diketone

e. Synthesis from a pyridinium salt

A synthetic route for imidazopyridine derivatives was identified by Juan A. Vega et al. [117] from pyridinium salt. In their research, two synthesic 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 33.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 33.b).

Similarly, H. Zali-Boeini et *al.* [118] 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 33.c).

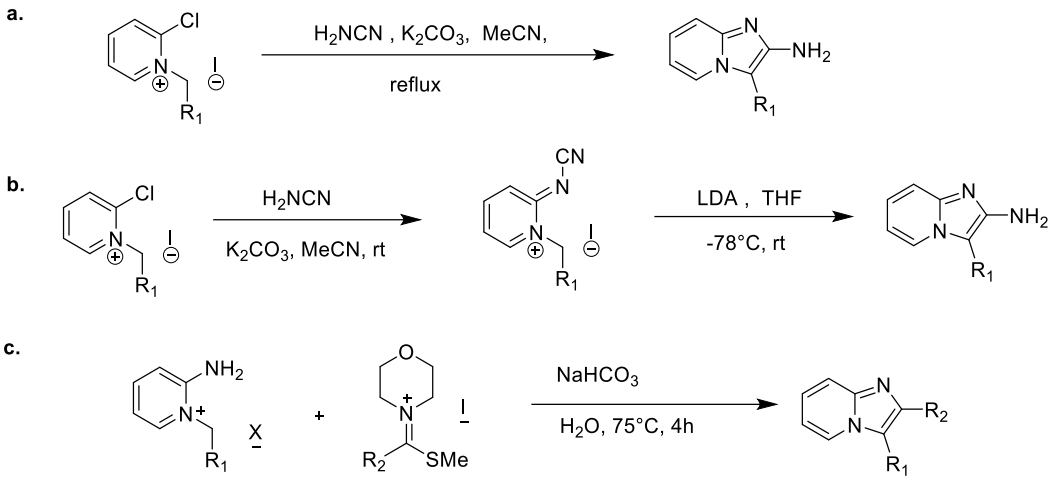


Figure 33: **a.** Synthesis method of 2-aminoimidazopyridine derivatives from pyridinium salt according to Juan A. Vega et *al.* **b**. Synthesis method of 2-aminoimidazopyridine derivatives from pyridinium salt according to Juan A. Vega in two steps. **c.** Synthesis method of 2-aminoimidazopyridine derivatives from pyridinium salt according to Zali-Beoini

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. [119] They react with trifluoroacetic acid and gold dichloro-2-pyridinecarboxylate ($PicAuCl_2$) as catalysts, alcynes 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 %.

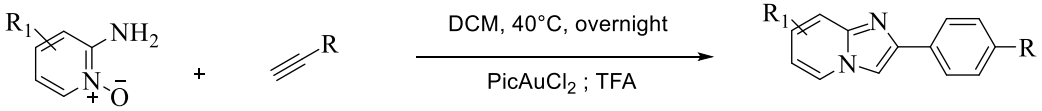


Figure 34 : Synthesis method of 2-phenyl imidazopyridine derivatives from N-oxides

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*). [120] The death toll from MRSA turned out to be even higher. The rapid emergence of *S.*

aureus strains resistant to HIV, [121] vancomycin [122], 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 certains substituents in their derivatives indicates that they can be used as pharmacologically molecules or drugs intermediates. Our point of view in perspespectives 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.

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