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RESEARCH ARTICLE

Imidazo[4,5-*b*]pyridines: from kinase inhibitors to more diversified biological properties.

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Abstract: Imidazo[4,5-*b*]pyridines are amongst the oldest known heteroaromatic derivatives. Their structural similarity with purine basis has however aroused the curiosity of biologists and resulted in the developments of innovative bioactive compounds. This review thus firstly describes the main synthetic ways currently used to produce imidazo[4,5-*b*]pyridine derivatives, and secondly gives examples of their potential, especially focusing on protein inhibition abilities, thus opening the way to applications as anti-cancer or antimicrobial agents.

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1. INTRODUCTION

Imidazopyridines, which are heterocyclic molecules composed of two five- and six-membered rings, can be found in several isomeric forms such as imidazo[1,2-*a*]pyridine **1**, imidazo[1,5-*a*]pyridine **2**, imidazo[4,5-*b*]pyridines **3**, and imidazo[4,5-*c*]pyridines **4** (Fig. 1).

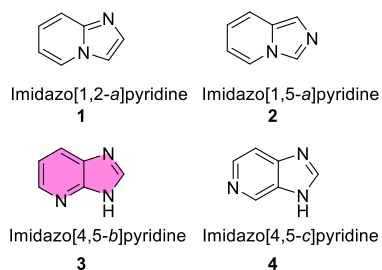


Fig. (1). The different isomers of the imidazopyridine core.

Over the years, imidazopyridines have been studied in the pharmaceutical field, due to their molecular similarity with bicyclic purine nucleic basis. That results in high biological potential. For instances, imidazopyridines could act as GABAA receptor agonists [1], anticancer agents [2,3], antiviral compounds [4-6]. They have also demonstrated anti-inflammatory [7] or anti-tuberculosis activities [8], or have been studied as modulators of the central nervous system

(CNS) [9]. A large number of potent imidazopyridine-based drugs have been introduced to the market, especially in the context of various neurodegenerative and psychic CNS disorders. The best known of these four isomers is probably the imidazo[1,2-*a*]pyridine, which is found in drugs such as Zolpidem (ambien) **5**, a hypnotic agent [10], and zolimidine **6** is used for peptic ulcer [11] (Fig. 2).

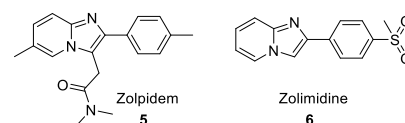


Fig. (2). Examples of drugs with imidazo[1,2-*a*]pyridine core.

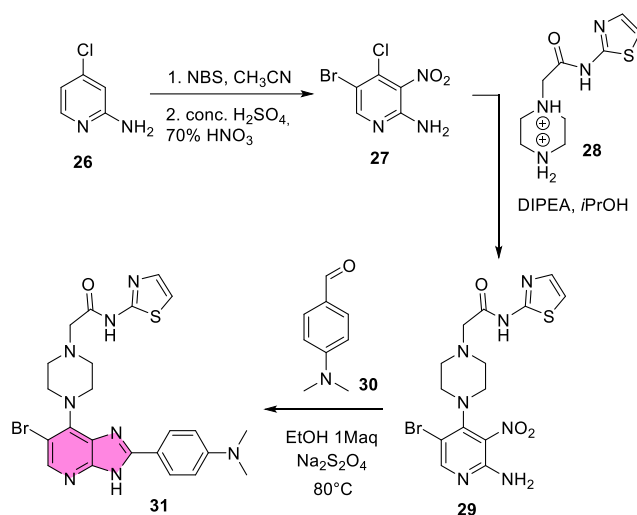
Despite the predominance of imidazo[1,2-*a*]pyridine [12], the three other subfamilies have also been widely studied and have found numerous applications in pharmacology and drug development (see a recent review for the imidazo[4,5-*c*]pyridines [13]). In this review, we will focus on imidazo[4,5-*b*]pyridines. The first part will address the synthetic strategies leading to imidazo[4,5-*b*]pyridines and the second part will be dedicated to the description of some related biological activities.

2. SYNTHETIC ROUTES TOWARDS IMIDAZO[4,5-*b*]PYRIDINES

Many efforts have been directed to develop different synthetic strategies for this privileged structure and various approaches have been adopted. These are classified into some subcategories like condensations, multicomponent reactions,

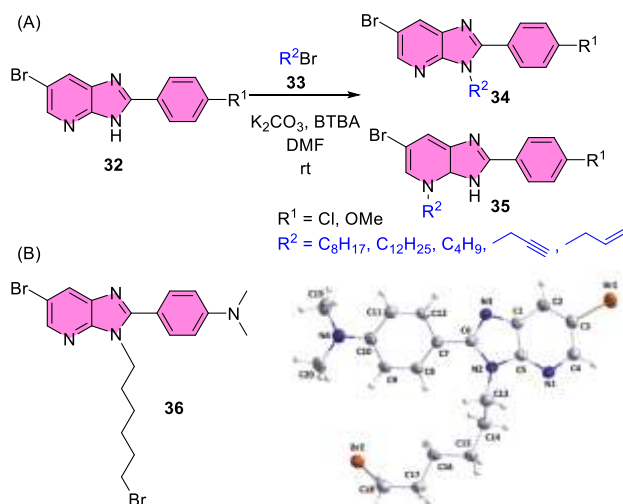
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hyposulfite to give the bioactive compound **31**. This product was synthesized to explore its ability to inhibit kinases.



Sch. (5). Synthesis of the kinase inhibitor **31**.

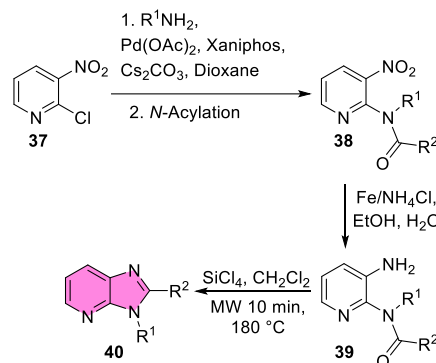
Introduction of an alkyl group allowed to modulate the physicochemical properties of the purine mimetics thanks to the nucleophilicity of the nitrogen atoms. However, selectivity between the pyridine part and the imidazole ring is crucial. Starting from preformed bicyclic building blocks **32**, Bourichi *et al.* indeed observed alkylation on both N-3 (**34**) and N-4 (**35**) atoms (Sch. 6A) [26]. The reaction was performed in DMF under phase transfer catalysis conditions alkylating reagents **33**. Jabri *et al.* confirmed that the selectivity was in favour of the imidazolyl substitution (Sch. 6B) by X-ray diffraction of **36** [27] and by DFT calculations that clearly established that the highly occupied molecular orbital (HOMO) is mainly located on the imidazole part of the molecule [28].



Sch. (6). Alkylation reaction on the imidazo[4,5-*b*]pyridine scaffold.

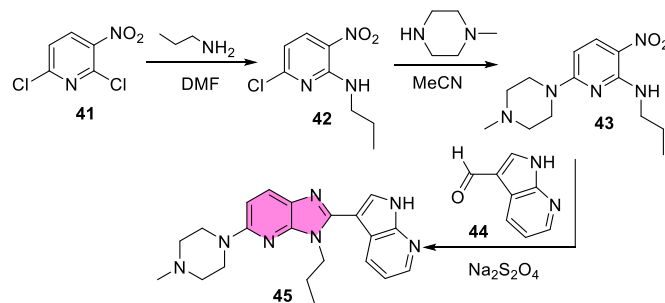
The synthesis of the imidazo-ring was alternatively performed in two steps. Thus, C. Salome *et al.* started from 2-chloro-3-nitropyridine **37** (Sch. 7), the nitro group acting as the precursor of the amino function [29]. After pallado-

catalyzed substitution of the chlorine atom by the amine R^2NH_2 , the resulting 2-aminopyridine intermediate was *N*-acylated. The nitro group in **38** was then reduced in the presence of iron under acidic conditions (\rightarrow **39**), and dehydration step assisted by microwave activation finally afforded the expected derivatives **40**.



Sch. (7). Imidazo-cyclization in two steps.

A shorter way avoiding the reduction step of the nitro function was also proposed. Cyclization that gives the imidazo ring was thus performed directly from the nitro intermediate. In this context, Chen *et al.* synthesized a library of substituted imidazopyridines. Amongst them is compound **45** interesting for its anti-inflammatory properties (Sch. 8) [30]. The synthesis started by a selective aromatic substitution on 2,6-dichloro-3-nitropyridine **41** by propylamine which gave **42**, followed by a second S_NAr with 1-methylpiperazine to afford the disubstituted pyridine **43**. Subsequent cyclization with aldehyde **44** in the presence of sodium hyposulfite provided the target **45**.



Sch. (8). Synthesis of an anti-inflammatory agent.

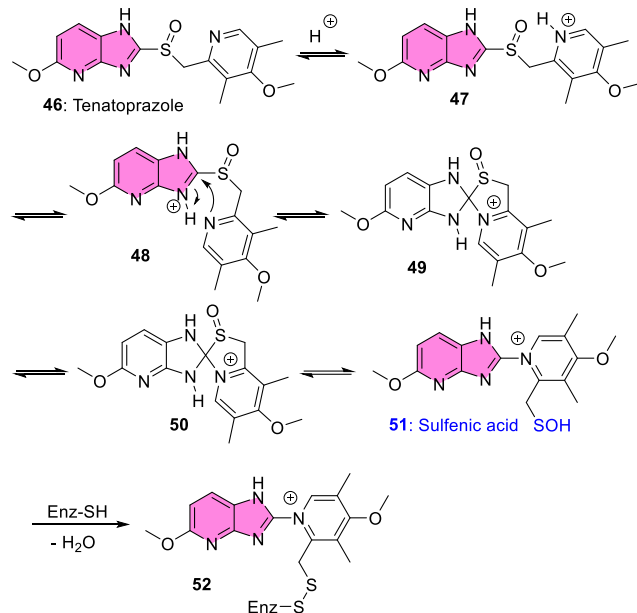
3. BIOLOGICAL PROPERTIES OF IMIDAZO[4,5-*b*]PYRIDINES

Due to the similarity of purines and the imidazo[4,5-*b*]pyridine moiety, these have been the subject of several studies for their biological properties and potential applications. This property often leads to studying the inhibition potential of molecules possessing such a bicyclic scaffold further decorated with groups capable of increasing interactions, bioactivities, and selectivity.

3.1. Proton pump inhibitor

As a first example, tenatoprazole **46** [31,32], developed by Mitsubishi Pharma at the end of the 2000's, is a pro-drug product able to be converted into a sulfenic acid **51** according

to the mechanism in Sch. 9 through derivatives **47-49**. Subsequent reaction with an accessible cysteine residue of the gastric (H^+ , K^+)-ATPase results in inhibition of this protein *via* covalent intermediate **52** [33], that explains why **46** acts as a proton pump inhibitor. It was also shown that the presence of the imidazopyridine skeleton instead of a more standard benzimidazole one increases the half-life of the drug.



3.2. AKT inhibitors

Cell proliferation or survival, as well as metabolic transformations are pivotal pathways in all living organisms [34]. Many proteins are required to ensure these biological functions. Amongst them is the serine/threonine kinase (AKT) protein, or kinase B (PKB), involved in the phosphatidylinositol-3 kinase (PI3K) intracellular pathway [35,36]. The three known isoforms (AKT1, AKT2, and AKT3) [37] are involved in tumor development and progression in breast, ovarian, pancreatic, and prostate cancers [38]. More precisely, the role of AKT1 was shown in proliferation and growth, promoting tumor initiation and suppressing apoptosis. The AKT2 isoform promotes invasiveness and metastasization whereas the role of AKT3 in cancer is still controversial [39,40].

Ashwell *et al.* [41] have performed a series of AKT inhibitors with the imidazo[4,5-*b*]pyridine core substituted at C-2, N-3, and C-5 (Fig. 3). Compound **53** (Fig. 3) showed excellent AKT selectivity with no kinase being inhibited at greater than 17%. *In vitro* absorption, distribution, metabolism and excretion (ADME) profiling results showed **53** to have good microsomal stability and a reasonable CYP450 inhibition profile. At the molecular level (Fig. 3), **54** is bound at an allosteric site localized between the kinase and the PH domains. Moreover, cocrystal structure with **54** bound to AKT1 showed that the heteroaromatic inhibitor was found in a cavity at the interface of both domains (Fig. 4).

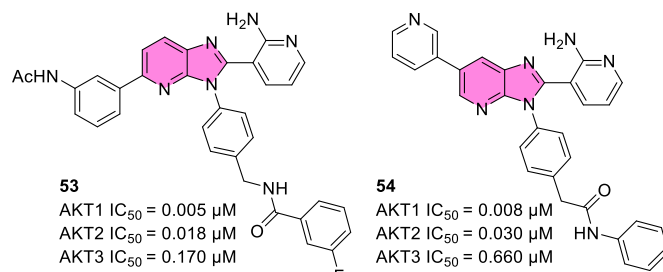


Fig. (3). AKT inhibitors with trisubstituted imidazo[4,5-*b*]pyridine scaffold.

The trisubstituted derivative **53** also demonstrated potent cellular inhibition ability of the activation of AKT (Antibody recognize all forms of the corresponding phosphor-Akt). The *in vitro* ADME studies with **53** revealed some selectivity toward AKT proteins since a lack of CYP450 inhibition was noticed.

3.3. ALK (Anaplastic Lymphoma Kinase) inhibitors

It was established that initiation and progression of lymphomas, neuroblastoma and non-small-cell lung cancer involve the anaplastic lymphoma kinase (ALK), activation of the later is achieved by translocation or mutation [42]. A series of potent ALK inhibitors based on a 7-amino-6-chloro-3*H*-imidazo[4,5-*b*]pyridine scaffold was designed and studied by Keith S. *et al.* (Fig. 4) [43], the C6-substituent indicates that chlorine is most effective in achieving the balance between ALK potency and IR selectivity, the combination of the 2-methoxy group on the 4-heterocyclic-phenyl species improved both potency and IR selectivity (**55** and **56**), the piperazinyl derivative **56** achieved sub-nanomolar ALK activity (8 nM). The attenuation of the activity of **55** and **56** without significant overall change in properties was achieved by removing the direct attachment of the heteroatom and inserting a methylene bond between the heterocycle and the aryl ring (**57** and **58**), these changes show that **57** had a higher absolute oral bioavailability and a slightly improved CYP3A4 profile.

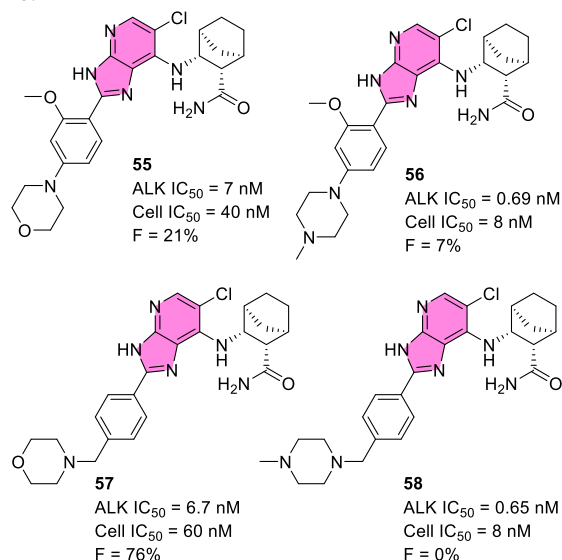


Fig. (4). Examples of ALK inhibitors.

3.4. Trk (tropomyosin receptor kinase) inhibitors

Tropomyosin receptor kinases have an important role in the phosphorylation of proteins of the MAP kinase pathway by binding to neurotrophins, proteins involved in the neuronal functions [44,45]. In order to interfere with these receptors, Tao and collaborators have synthesized two series of imidazopyridine derivatives substituted by a diazolyl heterocycle positioned either on N-3 of the imidazol ring or on C-5 of the pyridine part. The *in vivo* antitumor effects of representative examples (Fig. 5) from each series were examined [46,47]. Both compounds **59** and **60** from the two series demonstrated dose-dependent antitumor activity with doses in the range of 1 to 25 mg/kg. A significant tumor growth delay, near 4–5 days, was noticed with the 25 mg/kg dose using compound **60**. Moreover, loss of body weight, limited to 5%, was seen during the dosing period in all treatment groups.

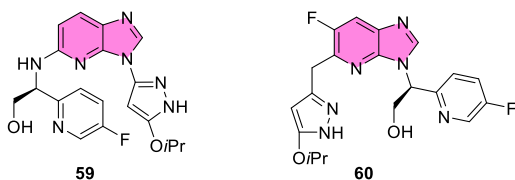


Fig. (5). Examples of TrkA inhibitors.

3.5. Aurora kinase inhibitors

Bavetsias *et al.* described the synthesis of a new class of imidazo[4,5-*b*]pyridines with activity against Aurora kinases [48]. These kinases refer to serine/threonine kinases involved in multiple facets of mitosis and cell division [49]. The related Aurora-A, B, and C are implicated in cancer initiation and progression [50,51]. IC₅₀ values of 0.042, 0.198, and 0.229 μM on Aurora A, B, and C, respectively, were obtained for the imidazopyridine derivative **61** (Fig. 6). This compound is characterized by the presence of a chlorine atom and a substituted piperazine on the pyridine ring, and of a *N,N*-dimethylaniline group on the second ring of interest. Later, the same authors have designed an orally bioavailable inhibitor, **62**, for which IC₅₀ values of 0.025 and 0.019 μM were determined on Aurora B and C, respectively [25].

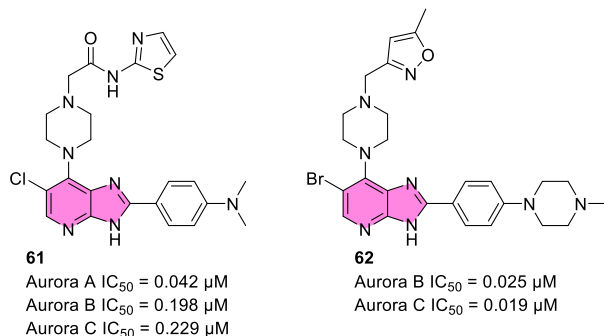


Fig. (6). Aurora kinase inhibitors.

3.6. DYRK1A Inhibitors

The Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) is a key protein involved in the development of the nervous system [52,53]. A set of

imidazopyridine-containing derivatives were synthesized by Casabar *et al.* and studied as potent DYRK1A inhibitors [54]. Product **63** (Fig. 7), bearing a diaminopyridine substituent on C-5 and two methyl groups on C-2 and N-3, showed high affinity towards DYRK1A. Similar activities were obtained from synthetic analogues for which C-2 methyl group was replaced by ethyl (**65**) or butyl (**66**) chains. Modulations of the N-3 position by butyl (**64**), trifluoroethyl motif (**67**) or with a fluorophore (**68**) did not significantly impacted with the bioactivity of such compounds.

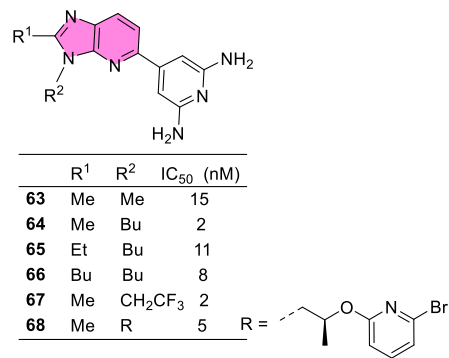


Fig. (7). DYRK1A inhibitors and their DYRK1A inhibition properties.

3.7. GSK-3 Inhibitors

The World Health Organization estimates that one third of the global population will suffer from neurological disorders [55]. Amongst these troubles of the central nervous system are for instances Parkinson's and Alzheimer's diseases, memory deficits. Finding new therapies is nowadays become an emergency. One possible biological target is the Glycogen Synthase Kinase-3 (GSK-3) which regulates glucose metabolism [56], and which is overexpressed in the central nervous system in patients with Alzheimer's disease [57]. GSK-3β is an isoform responsible for the hyperphosphorylation of the Tau protein and its further aggregation [58-60].

Imidazo[4,5-*b*]pyridines have been studied as possible modulators of the GSK-3 activities. In this context, Lee *et al.* have designed and synthesized a set of related compounds (Fig. 8) [61]. Interestingly, the substitution of the sulfonamide function on C-7 in **69** by an amide group in **70** resulted in a significant increase of the inhibition of the targeted GSK3 protein.

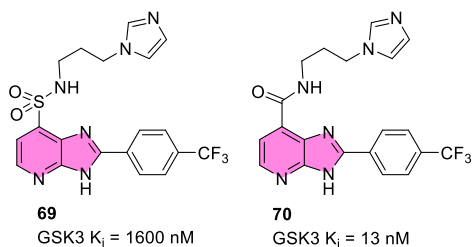


Fig. (8). GSK3 inhibitors according to Lee *et al.*

3.8. B-Raf kinase inhibitors

Mitogen-activated protein (MAP) kinases comprise a family of ubiquitous proline-directed, protein-

serine/threonine kinases, which participate in signal transduction pathways that control intracellular events [62]. This pathway consists of the Ras-Raf-MEK-ERK cascade, which is known to regulate cell growth, proliferation, differentiation, and survival [63].

Newhouse *et al.* prepared a series of imidazo[4,5-*b*]pyridine-based agents as B-Raf inhibitors [64]. Amongst these compounds, the C-6 monosubstituted derivative **71** showed an activity at the nanomolar level (Fig. 9). The introduction of a 3,4-difluorobenzene group on C-2 allowed to decrease the IC₅₀ value from 61 nM for **75** to 1.5 nM for **72**. The X-ray analysis clearly demonstrated the importance of N-3 and N-4 nitrogen atoms which are to be non-substituted to bind to the target protein. The increasing lipophilicity introduced thanks to the fluorinated aromatic group also contributed to the increase of the biological activity by inserting into pocket with tryptophan, isoleucine, glutamic acid, glycine, and serine residues.

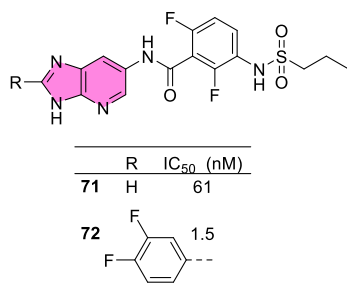


Fig. (9). B-Raf inhibitors and their IC₅₀ values.

The studied B-Raf kinase is an interesting target which participates in signaling networks inducing the Ras-Raf-MEK-ERK cascade, which has effects on cell growth, proliferation, differentiation, and survival [63].

3.9. C-Met kinase inhibitors

MET tyrosine kinase is known as a cell surface receptor for hepatocyte growth factor (HGF), a cytokine that controls pro-migratory, anti-apoptotic and mitogenic signals [65]. It also plays an important role in controlling tissue homeostasis under normal physiological conditions. C-MET kinase is responsible for the cell dispersion phenotype and is also abnormally activated in human cancers by mutation, amplification, or overexpression of the protein [66].

Several researches were conducted in order to inhibit this protein, for instance by Geng *et al.* [67]. They established that multi-heteroaromatic product **73** (Fig. 10) potently inhibits the corresponding kinase activity of C-Met with an IC₅₀ value of 10.7±0.43 nM.

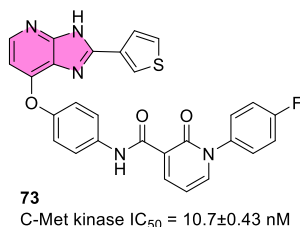


Fig. (10). Compound **73** as C-Met kinase inhibitor.

3.10. PAK4 inhibitors

Data on how imidazo[4,5-*b*]pyridines interact with kinases is also available for the PAK4 kinase and compound **74** (Fig. 11). p21-Activated kinases, or PAKs, also belong to the family of serine/threonine protein kinases [68]. As an effector protein, PAK4 is involved in the regulation and the cytoskeletal reorganization of, but also in cell motility, proliferation, survival, and filopodia formation [69]. The search for a specific inhibitor was attempted through docking studies.[68] Among the docked fragments, two compounds showed the proper binding mode and more especially the 6-bromo-2-(3-isopropyl-1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazo[4,5-*b*]pyridine **74**. For the latter, simulations showed that the small molecule interacts with the PAK4 Hinge loop through van der Waals forces involving the following residues: isoleucine 327 and alanine 402 have favour contacts with the pyrazole ring and the imidazolyl part of **74**, which also interacts with leucine 398. Alanine 348, leucine 447, and methionine 395 are close to the pyridine ring, with interesting connexion with the bromine atom and M395. In the radiometric assay, the latter inhibited PAK4 activity in a dose-dependent manner (IC₅₀ = 8.7 μM).

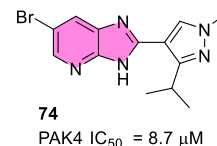


Fig. (11). Structure of **74** and its activity against PAK4.

3.11. GABA modulators

Epilepsy and cerebral ischemia are important diseases induced by an imbalance between two neurotransmitters, the glutamate and the γ-aminobutyrate known as GABA [70]. GABA also find functions in the central nervous system [71], through interactions with specific receptors. Interfering within this binding may allow to fight against such disorders and pains [72]. The heteroaromatic derivative **75** (Fig. 12) was proposed by Larsen as a GABA_A α3 receptor [73].

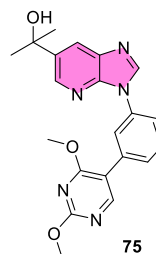


Fig. (12). An example of GABA Inhibitor.

3.12. PDE10A inhibitors

The phosphodiesterases (PDEs) are interesting targets since they are able to inactive ubiquitous intracellular second messengers cAMP and cGMP [74]. Of the 11 PDE families, PDE10A has the most restricted distribution [75,76]. A group of imidazo[4,5-*b*]pyridine compounds were studied with the aim of developing inhibitors of this protein [77]. The four

products **76-79** (Fig. 13) are characterized by a C-2 O-methoxy or propyl group, and an aminomethylpyridine or 2-aminobenzothiazole group through a small linker, either benzene or cyclobutyl. The evaluation of the biological properties yielded to 55-74% receptor occupancy (RO) at 10 mg/kg po in PDE10A *ex vivo* study. Moreover, **76** and **77** achieved 71% and 57% RO, respectively, in the *in vivo* studies. All of the compounds advanced into the RO assays also exhibited greater than 30 μM activity against other PDE isoforms.

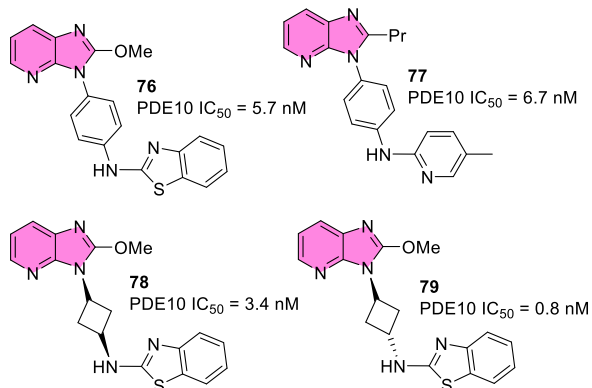


Fig. (13). Some PDE10A inhibitors.

3.13. Antimicrobial activity

The design and development of antimicrobial agents are of great interest simply in view of the resistance observed against many microbial strains leading to increasing difficulties in the control of re-emerging diseases due to parasites infecting humans, their farms as well as than its cultures. Innovative solutions have to be explored in this domain in order to kill or at least to slow the growth of parasites in other living organisms. Some studied dealing with such a challenging task were published using imidazo[4,5-*b*]pyridine as a bioactive molecular platform.

Antifungal activity. Fungicides have been used in agriculture for well over a century [78]. The corresponding market has been dominated by stobilunis, triazoles and amides [79]. However, resistance to many of the most effective fungicides has emerged. In this context, Wu and coworkers [80] reported a set of imidazo[4,5-*b*]pyridine derivatives **80** (Fig. 14) exhibiting good fungicidal activities. They introduced structural modulations through the aromatic ring at C-2, the alkyl substituent on N-3 and the linker between C-5 and the methyl group. Fungicidal activities against *Puccinia polysora*, also called American corn rust, *Erysia graminis*, another parasite of cereals, *Rhizoctania solani*, which infects buried seeds of plants, were determined and the values displayed were generally found between 30 and 85% at concentrations of 500 mg/mL. The structure-activity relationships concluded that the bests groups were 2-chlorothiazol-5-yl-methyl for the R substituent, the sulfur atom for the X residue and the 2-trifluoromethylphenyl substituent for the Ar entity. Some fungicidal activities compete with the ones obtained for the known triazolic tebuconazole **81**.

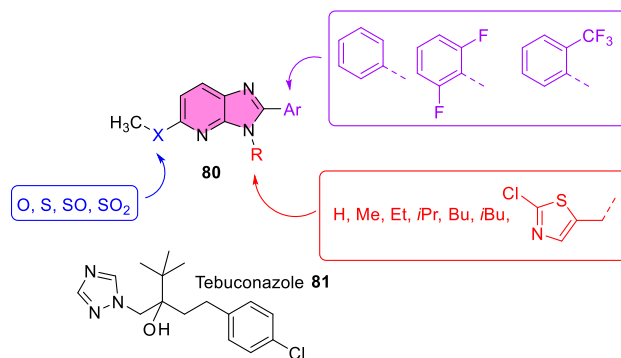


Fig. (14). Imidazo[4,5-*b*]pyridines **80** with antifungal activity.

Antibacterial activity. The search for antibiotics has again become a subject of interest. In this context, the design of such medication based on the imidazopyridine skeleton was proposed by Shelke *et al.* [81]. This team performed the synthesis of many compounds and tested them against potentially pathogenic *Escherichia coli* and the sporulating *Bacillus subtilis*. Compounds **82** and **83** (Fig. 15) were the most active molecules among the series, more potent than standard antibacterial drugs Ciprofloxacin **84** and Ampicillin **85**. **82** reached a minimum inhibition concentration (MIC) of 3.25 $\mu\text{g}/\text{mL}$ *E. coli* was a MIC of 6.0 $\mu\text{g}/\text{mL}$ against *B. subtilis* for compound **83**.

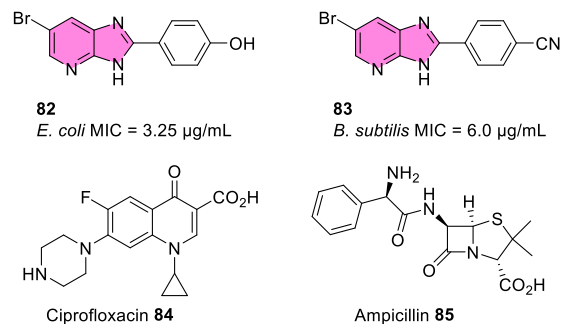


Fig. (15). Structures of antibacterial compounds and their MIC values against *E. coli* and *B. subtilis*.

Antitubercular activity. Tuberculosis, known for a long time to be a major cause of morbidity and mortality throughout the world, has for several decades been a neglected disease in both industrialized and developing countries [82]. Gawad and Bonde [83] reported the synthesis of new compounds screened for *in vitro* antitubercular activity against the pathogen *Mycobacterium tuberculosis* (H37Rv). Four compounds (Fig. 16), **86** (MIC = 0.6 $\mu\text{mol}/\text{L}$), **87** (MIC = 0.5 $\mu\text{mol}/\text{L}$), **88** (MIC = 0.8 $\mu\text{mol}/\text{L}$), and **89** (MIC = 0.7 $\mu\text{mol}/\text{L}$), were identified as potent inhibitors. These compounds are characterized by the presence of a polar or non-polar benzene group bearing either electro-donating or withdrawing functions, on C-2 and of an *o*-nitrobenzyl group grafted on C-6.

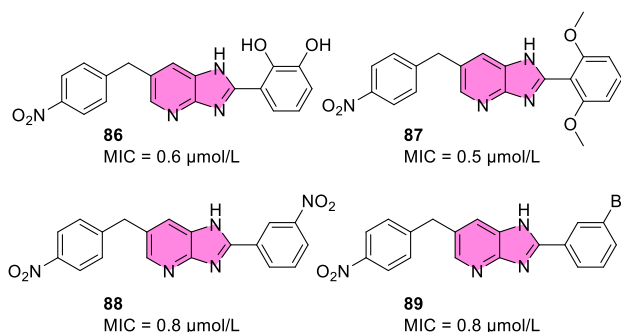


Fig. (16). Examples of imidazopyridines having anti-mycobacterial activities and their MIC values against *M. tuberculosis*.

Antiviral activity. Infection with the hepatitis B virus (HBV) results in a broad spectrum of clinical outcomes, from asymptomatic hepatitis to fulminant liver failure [84]. It is also the major causative factor of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC) [85]. HBV is one of the major global public health problems, being the 10th leading cause of death, and HBV related hepatocellular carcinoma (HCC) being the 5th most frequent cancer worldwide [86].

Gerasi *et al.* synthesized a new series of imidazo[4,5-*b*]pyridines to better understand their biological activity as potential HBV inhibitors. In order to study the optimal substitution pattern of this new core scaffold, they introduced alkyl linkers of variable length, bearing four different terminal amines at position 2 of the bicyclic ring system [87]. The presence of a flexible ethyl linker with a terminal amide group was initially indicated as essential for HBV activity. The ethylene linker and the flexible diethylamine substitution are best tolerated at position 2 of the imidazole ring. The 6-chloroimidazo[4,5-*b*]pyridine series was found to have a very interesting profile and were further studied. The most promising of these, in addition to reducing secreted HBV rcDNA, also caused a reduction in HBV cccDNA and pgRNA levels, with a concomitant accumulation of intracellular encapsidated rcDNA.

Surprisingly, the most active 2-diethylaminoethyl-substituted derivative (Fig. 17.) **90** exhibited competitive anti-HBV effect to pegylated interferon $\alpha 2b$, possibly suggesting blockage of the interferon signalling.

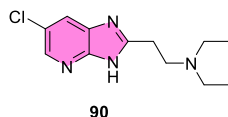


Fig. (17). Example of HBV inhibitor.

3.14. Antioxidant activities

Scavenging radical species is one important defence mode used by cells to protect themselves against radical assaults. Such a potential was studied by Bocek [88] on the basis of ferric reducing antioxidant power (FRAP) assay [89]. The electronic delocalization in the structure was increased by adding a cyanoethylene arm between the imidazopyridine part

and a dimethylaniline group (**91-94**, Fig. 18). The most pronounced FRAP activity reached 2 485.5 for compound **92**.

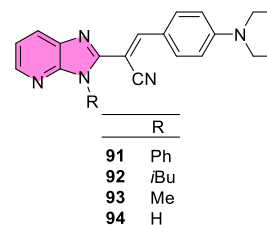


Fig. (18). Example of imidazo[4,5-*b*]pyridines with antioxidant properties.

4. CONCLUSION

This review first describes the main procedures leading to the imidazo[4,5-*b*]pyridine skeleton. Most of the time, cyclization giving the imidazole ring is performed at the end of the synthesis, so that suitably functionalized aminopyridine and aldehydes (or equivalents) need to be first prepared as key intermediates thanks to standard heteroaromatic chemistry. Numerous developments turned towards the inhibiting properties of the resulting compounds, and more especially as inhibitors of kinases, thus allowing applications in various health domains to fight cancers or nervous central system for instances. Furthermore, antimicrobial activities were also demonstrated. Through all these examples, this review underlines the high potential of applications opened by the imidazo[4,5-*b*]pyridines, even if efforts from translational medical projects have still to be more efficiently transferred to the drug market.

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CONFLICT OF INTEREST

There are no conflicts to declare.

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