Recent Progress in the Pharmacology of Imidazo[1,2-*a*]pyridines

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Abstract: Imidazo[1,2-*a*]pyridine is a bicyclic system with a bridgehead nitrogen atom, of growing interest in medicinal chemistry. The paper deals with the recent progress realised in the comprehension of the pharmacological properties of this scaffold. From the many imidazo[1,2-*a*]pyridine analogues described in the literature, those discussed herein will be presented in three parts concerning first the enzyme inhibitors, then the receptor ligands and finally the anti-infectious agents.

Key Words: Imidazo[1,2-*a*]pyridine, pharmacological properties, enzyme inhibitors, receptor ligands, anti-infectious agents.

1. INTRODUCTION

The imidazo[1,2-*a*]pyridine ring system **1** was described by Chichibabin [1] in 1925 (Fig. **1**). For a long time, this skeleton was poorly studied, in part because of the lack of efficient methods of functionalization allowing the rapid preparation of structural variants, notably on the pyridine moiety. Nevertheless, in the past decades, many works were done on the synthesis, the physical properties and the reactivity of this series. In particular, the progress in metallo-catalyzed chemistry has allowed easy access to new functionalities**. From the simple preparation of this heterocycle, its good stability and the recently developed methods of functionalization, pharmacology of imidazo[1,2-*a*]pyridine is currently the object of renewed interest as demonstrated by the number of recent patents concerning this series. Indeed, out of 1470 patents containing this scaffold, 56% have been published since 2000. In this mini-review, we have chosen to illustrate the high diversity of the pharmacological properties of the imidazo[1,2-*a*]pyridine template.

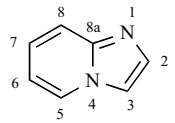

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Fig. (1). Structure of imidazo[1,2-*a*]pyridine.

Among the commercialized imidazo[1,2-*a*]pyridines, Zolpidem **2** was the first reaching the market as a hypnotic (Fig. **2**). This compound is the most widely used in treating insomnia in the world, but will not be discussed herein as it has already been frequently reviewed [2]. In 1991, Alpidem **3,** a peripheral benzodiazepine receptor ligand, was marketed as an anxiolytic. It was withdrawn from the market in 1995 because of its hepatotoxicity [3]. Zolimidin **4** was marketed notably in the United States and Italy as an anti-ulcer agent [4], but is not commercialized any more. Finally, Olprinone **5**, a phosphodiesterase 3 (PDE 3) inhibitor, is used for treating acute heart failure in Japan [5].

Finally, SCH 28080 **6** has been described as a reversible proton pump inhibitor. Unfortunately, clinical development of this compound was discontinued because of liver toxicity in animals and elevated liver enzyme activity in the serum of volunteers [6].

From the many imidazo[1,2-*a*]pyridine analogues described in the literature, those discussed herein will be presented in three different chapters concerning first the enzyme inhibitors, then the receptor ligands and finally the anti-infectious agents.

2. IMIDAZO[1,2-*a*]PYRIDINES AS ENZYME INHIBITORS

2.1. Inhibitors of Cyclin-dependent Kinases

The cyclin-dependent kinases (CDK's) form a family of serine/threonine kinases that are important in controlling entry into cell cycle and transition through each phase [7]. From high-throughput screening of an Astra-Zeneca library, the imidazo[1,2-*a*]pyridine derivative **7** was identified as a CDK4 inhibitor (IC_{50} = 8 μM) and later on as a CDK2 inhibitor (Table **1**). A series of analogues was then synthesized and evaluated. Acetylation of the amino group gave **8,** which showed a little increase in potency towards CDK2. On the contrary, trifluoroacetamido and benzamide derivatives were less potent. The aniline compound **9** presented a highly decreased IC_{50} against CDK2. Finally, *para* substitution of aniline with sulphonamide functionality **10** or with an ether group **11** further increased the activity against CDK2 or CDK4. Crystal structure of CDK2 complexed with **8** demonstrated a hydrogen bonding interaction between the pyrimidine N_1 and the Leu83 backbone NH, the amido NH and the Leu83 backbone carbonyl O and N_1 of imidazopyridine and the Lys33 amino group. Finally, a water molecule bridges between the amidocarbonyl O and the Asp86 side chain. In the case of the 2-desmethyl-**10**, crystal data showed that the para-sulfonamide group forms hydrogen bonds with the Asp86 backbone NH and with its carboxylic side chain [8]. Further pharmacomodulation was then investigated. Changing the enzyme inhibition protocol led to an IC_{50} of

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** A. Gueiffier, C. Enguehard-Gueiffier, review in preparation

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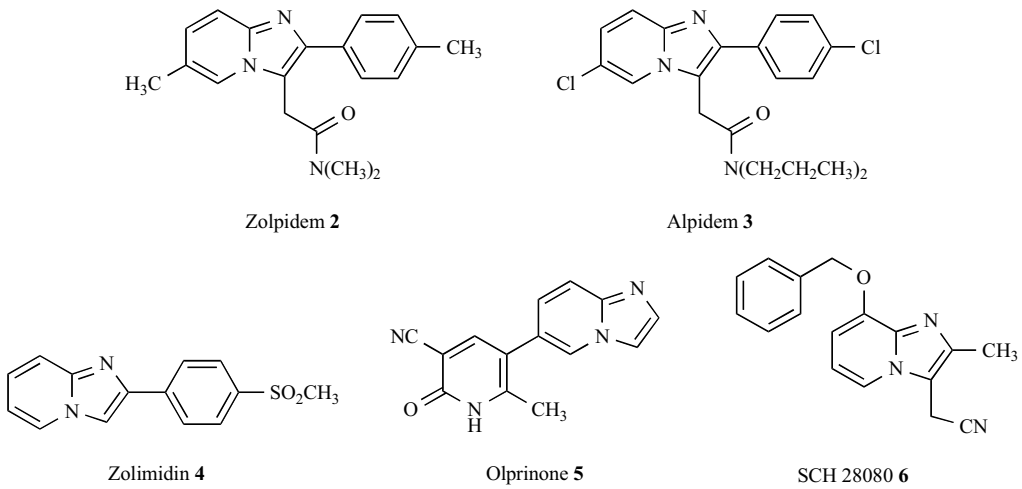


Fig. (2). Imidazo[1,2-*a*]pyridine derivatives commercialized or developed for their therapeutic potentialities.

0.21 nM for **9** and 0.038 nM for **10** against CDK2. Introducing a chlorine in position 2 of the aniline group was detrimental (IC_{50} = 8.8 nM) while introducing the chlorine in position 3 or 4 slightly influenced the activity (IC_{50} = 0.15 nM and 0.6 nM respectively). Removing the methyl in position 2 significantly increased the potency with an IC_{50} < 0.003 nM for the desmethyl-**9** compound. Introducing chlorine or bromine in position 5 of the pyrimidine ring preserved the inhibitory activity, while a phenylthio group gave inactive compound. This is consistent with this substituent approaching Phe80 at the close end of the binding pocket. Finally, bromine, cyano, ethyl or phenylthio groups in position 6 of the imidazopyridine preserved the inhibitory properties which are consistent with this group being directed towards solvent at the open end of the binding pocket [9].

From these results, AZ703 (**12**) was subjected to further studies (Fig. **3**) [10-11]. *In vitro* kinase assays showed IC_{50}s of 34 and 29 nM against cyclinE/cdk2 and cyclinB/cdk1, but also inhibition of cdk7 and cdk9 with IC_{50}s of 2.1 μM and 521 nM, respectively. In contrast, AZ703 did not inhibit cdk4. AZ703 gave growth arrest involving multiple cell cycle phases upon the concentration in U20S, NCI-H1299 and A549 cells. This cell cycle arrest is associated with reduced phosphorylation of retinoblastoma protein (Rb), a true tumour suppressor [12] and $p27^{Kip1}$, a Cdk inhibitory protein [13].

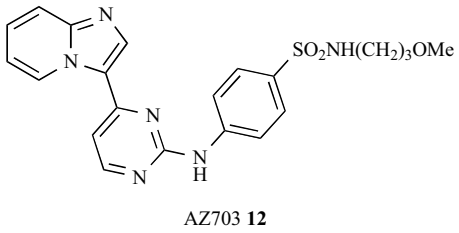
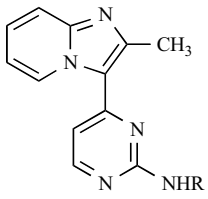


Fig. (3). Structure of CDK inhibitor AZ703.

Table 1. Inhibitors of Cyclin-Dependent Kinases



Compounds	R	IC_{50} CDK2 (μM)	IC_{50} CDK4 (μM)
7	H	4	8
8	$COCH_3$	2.9	8.9
9	C_6H_5	0.036	3.6
10	$pSO_2NH_2C_6H_4$	<0.003	2.5
11	$p[Me_2NCH_2CH(OH)CH_2O]C_6H_4$	0.032	0.15

In the same manner, from a library screening, an Eli Lilly group showed the interest of benzimidazoles as inhibitors of several kinases. From their early work, they were interested in 2-aminoimidazo[1,2-*a*]pyridine as a new scaffold for protein serine/threonine kinase inhibitors. Starting from known ATP-competitive inhibitors, docking experiments, SAR studies and X-ray data, they obtained a new lead **13** with potent inhibiting activities against CDK2 (IC_{50} = 0.028 μM), CDK4 (0.464 μM) and CDK1 (0.143 μM) (Fig. **4**). This compound presented high selectivities towards PKA-α (6.34 μM), PKC-BII (3.26 μM), CAMKII (3.89 μM) and GSK3-β (>20 μM) [14]. The compound was shown to inhibit proliferation in HCT 116 cells in tissue culture in a drug exposure time dependent manner *via* the inhibition of the CDK2-dependent phosphorylation of Rb. In HCT 116, the analogue **14** induced caspase-3 activity, and accumulation of cells in G_2-M phase. The crystal structure of the analogs **14** (K_i = 0.324 μM) and **15** (K_i = 0.122 μM) bound to the inactive form of human CDK2 was solved. This study showed that the inhibitors occupy the ATP binding site of CDK2. Hydrogen binding was shown between N_1 of the imidazopyridine and the backbone amide NH of Leu83, the hydrogen of the amine with the carbonyl oxygen of Leu83 and between the carbonyl oxygen of the benzoyl group (in position 6) and the backbone NH of Asp145. The difference observed between **14** and **15** was internal hydrogen bonding between the amino group and the carbonyl oxygen for **14**. Further studies using chemical modi-fications in positions 3 and 6 of the imidazo[1,2-*a*]pyridine were undertaken [15]. In a first step, the optimization was carried out on the benzoyl group in position 6. A substitution in position *ortho* with an electron withdrawing functionality appeared necessary to keep the affinity under 1 μM. A 2,6-disubstitution was proved to be even more interesting. The linker was demonstrated to require a sp^2 carbon and in particular a vinyl group **16** (K_i = 63 nM). With regard to the benzoyl group in position 3, an *ortho* substitution was also required and a *para* substitution was tolerated. Starting from the hypothesis that a possible interaction with lysine89 could replace the internal hydrogen bond in **14**, further structural modifications were investigated using formation of secondary aniline or pyridin-4-ylamino in position 2 without substitution in position 3 (**17**) [16]. The *N*-(*p*-methylsulfonyl) anilino compound **18** showed good affinity with a K_i of 1.21 μM while the *meta* compound was less potent (K_i = 2.86 μM). The *para*-carbamoylanilino and *para*-(*N*,*N*-dimethyl-carbamoyl)anilino derivatives were in the same range of affinity. Changing to the methylthioanilino compounds increased the K_i of 1 log magnitude. The sulfamoyl, guanidinosulfamoyl and benzamidosulfamoyl were more potent with K_i in the range of 0.25-0.67 μM as well as the corresponding carboxylic acid (K_i = 0.74 μM). Finally, the pyridin-4-ylamino compounds were inefficient probably from insufficient size preventing formation of the hydrogen bond with Lys89 as well as the 4-(phenyloxy)anilino derivative presumably being too bulky to be accommodated in the area. Crystal structure of the sulfamoyl derivative complexed with CDK2 showed the expected hydrogen bond.

In the same pharmacological area, starting from pyrazolo[3,4-*b*]pyridine and pyrazolopyrimidine, Dwyer *et al*. reported 6-aryl-3-bromo-8-benzylaminoimidazo[1,2-a]pyridines as CDK2 inhibitors. Compound **19** showed an IC_{50} of 0.076 μM (Fig. **5**) [17, 18].

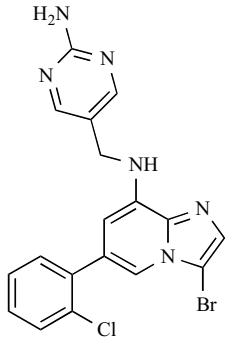


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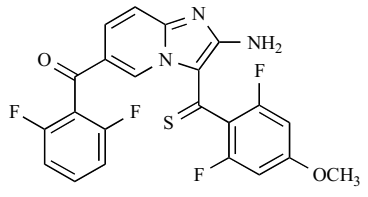
Fig. (5). CDK2 inhibitor.



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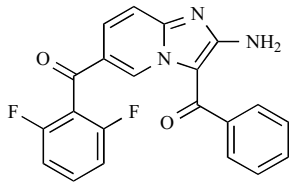

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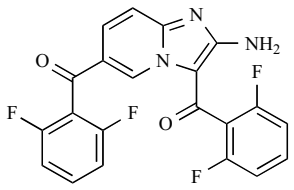

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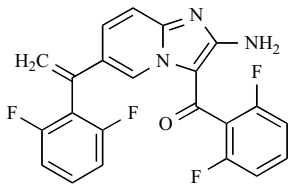

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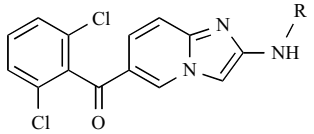

17 R = pyridin-4-yl, substituted phenyl
18 R = $pCH_3SO_2C_6H_4$

Fig. (4). Inhibitors of cyclin-dependent kinases.

2.2. Inhibition of MEK (MAPK/ERK Kinase)

The Ras-Raf-MEK/MAPK pathway is an evolutionary conserved pathway involved in the control of many fundamental cellular processes that include cell proliferation, survival, differentiation, apoptosis, motility and metabolism [19]. From these, MEK inhibitors are of interest in cancer treatment [20]. Imidazo[1,2-*a*]pyridines **20** were reported by Agouron Pharmaceutical to present MEK inhibition activity using inhibition of ERK phosphorylation in murine colon 6 carcinoma cells, with an IC_{50} of 27 nM for the acid (R = OH) and 1.9 nM for the carboxamide ($R = NH_2$) (Fig. **6**) [21].

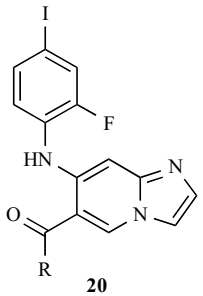

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Fig. (6). MEK inhibitor.

2.3. Inhibition of PI3K

Phosphoinositide 3-kinases (PI3K) represent a family of intracellular proteins which control important cellular functions such as proliferation, apoptosis and migration. Recent findings suggest an involvement of PI3K in the pathogenesis of numerous diseases including cancer, heart failure and auto-immune/inflammatory disorders [22]. Imidazopyridines conveniently substituted at C3 were patented as potent inhibitors of PI3K. As an example, **21** was claimed to be more than ten times more potent than the known PI3K inhibitor LY294002 **22** (Fig. **7**). Furthermore, some compounds showed good cancer cell growth inhibition in colon HCT116 cells. Compounds **21** and **23**, were also potent in the growth inhibition of melanoma A375 cell lines with an IC_{50} lower than 1 μM (8.39 μM for LY 294002) [23].

2.4. Inhibition of Hedgehog Signaling Cascade

The Hedgehog (Hh)-signaling pathway is essential for numerous developmental processes in *Drosophila* and vertebrate embryos [24]. In addition, Hh proteins and Hh signal-transduction components are expressed in post natal and adult tissues suggesting that they function in mature organisms and play a key role in different human diseases [25]. In particular, the Hedgehog signalling is crucial in tumorigenesis [26]. Recent data have shown that ligand-dependent activation of Hh pathway is frequently found in small-cell lung carcinoma [27], digestive tract tumours such as oesophageal carcinoma [28], gastric carcinoma [29], pancreatic carcinoma [30], hepatic carcinoma [31] and breast cancer [32]. Imidazopyridine **24** was shown to inhibit the activation of the Hedgehog signaling pathway with an EC_{50} of 30 nM against proliferation of Daoy cells (medulloblastoma cells) and without any toxic effect on normal human dermal fibroblast cells (Fig. **8**). Furthermore, the EC_{50} was measured at 30 nM to block Shh-mediated (Sonic hedgehog) pathway activation [33].

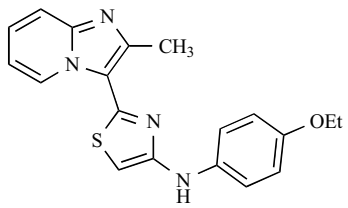

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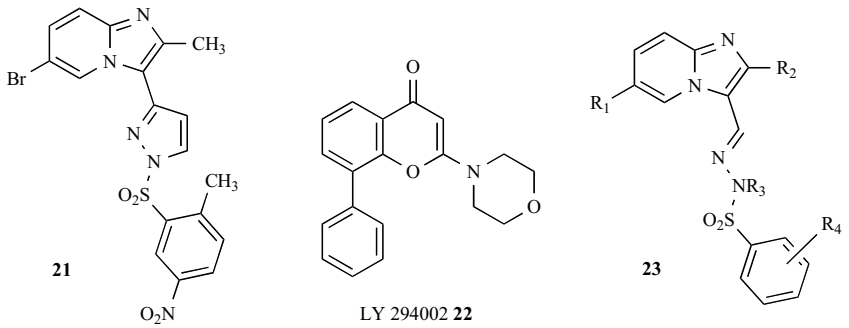
Fig. (8). Inhibitor of the Hedgehog signalling pathway.

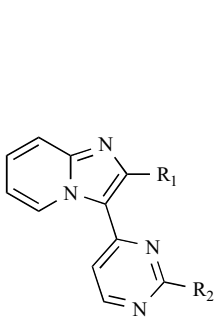
2.5. Inhibition of GSK3

Glycogen synthase kinase-3 is inhibited by insulin *via* activation of the protein kinases Akt/PKB [34], making GSK3 an attractive target for the treatment of diabetes. An abnormal increase of GSK3 level and activity is also associated with neuronal death, paired helical filament tau formation, neuron retraction as well as decline in cognitive performance and in stroke. From this, GSK3 is also a drug target for CNS therapy [35]. Astra-Zeneca reported 3-(pyrimidin-4-yl)imidazo[1,2-*a*]pyridines **25** as GSK3 inhibitors (Fig. **9**) [36]. Starting from staurosporine **26** and bis-aryl maleimide as GSK3 inhibitors, an Eli Lilly group reported new bis-aryl maleimides including imidazo[1,2-*a*]pyridine skeleton **27** [37, 38]. The synthesized compounds showed an IC_{50} in the range of 1.1-5.2 μM (56 μM for staurosporine) further confirmed in a P-Tau assay with IC_{50} = 0.7-41 μM. A methyl in position 6 of the imidazopyridine was detrimental, while the best activity was obtained with fluorine on the di-



21 LY 294002 **22** **23**

Fig. (7). PI3K inhibitors.



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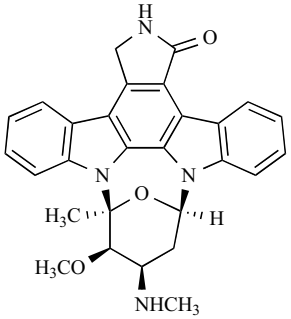
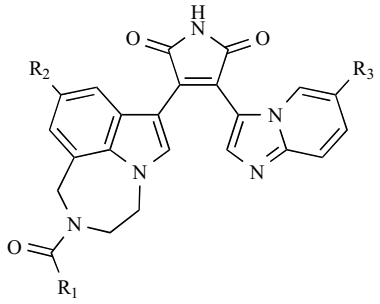
R_1 = H, substituted anilino
R_2 = H, NH_2, OH, Cl, SMe



Staurosporine **26**



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R_1 = O*i*Pr, piperidinyl, morpholinyl, dimethylamino
R_2 = H, F
R_3 = H, CH_3

Fig. (9). Inhibitors of GSK3.

azepinoindole part. All the compounds were inactive against numerous other kinases (*ie* cdk4, cdk2, p38). Concomitantly, the compounds reduced glucose levels in the range of 37-78% in rats at a dose of 10 mg/kg after oral administration. Nevertheless, some compounds showed moderate to medium oral bioavailability.

2.6. Other Selected Enzymes Inhibition Activities

Imidazo[1,2-*a*]pyridines were also described as PLK1 (Polo-Like kinase 1) inhibitors [39], tyrosine kinase signal transduction inhibitor, regulator and/or modulator [40], and nitrogen monoxide synthase inhibitors [41].

3. IMIDAZO[1,2-*a*]PYRIDINES AS RECEPTOR LIGANDS

3.1. Inhibition of Activin-like Kinase 5 (ALK-5)

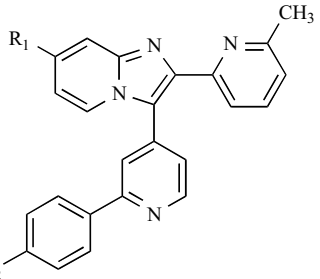
ALK-5 is a TGF-β-type I receptor that transduces the signal to the nucleus by phosphorylating a specific subset of Smad proteins, the so-called receptor regulated (R)-Smad [42]. From the several functions of TGF-β, potential therapeutic utilities of ALK-5 inhibitors are important in cancer [43] and fibrotic diseases such as renal [44], hepatic [45] and pulmonary fibrosis [46]. The discovery of imidazo[1,2-*a*] pyridine as inhibitor of ALK-5 was according to the author, made by serendipity. From the compounds synthesized, the pharmacological properties were reported only for two derivatives, **28** and **29** (Table **2**) [47]. Their IC_{50} as ALK-5 receptor modulators are 11 and 15 nM and against TGF-β cellular activity, 125 and 127 nM respectively.

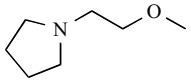
More recently, Sato *et al*. described the scaffold **30** as ALK-5 inhibitors (Fig. **10**) [48] while W.-C. Lee *et al*. patented **31** as ALK-4 and/or ALK-5 inhibitors [49].

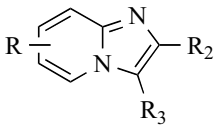
3.2. Inhibition of KDR (Kinase Insert Domain Containing Receptor)

KDR is a receptor for the Vascular Endothelium Growth Factor (VEGFRs) and function as a key regulator of angio-

Table 2. ALK-5 Receptor Modulators



Compounds	R_1	R_2	ALK-5 Receptor Modulator Activity IC_{50} (nM)	TGF-β Cellular Activity IC_{50} (nM)
28	H	SO_2CH_3	11	125
29	CH_3		15	127



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R_2 = pyridin-2-yl, 4-methylthiazol-2-yl...
R_3 = 4-alkoxyphenyl, benzothiazol-7-yl.....

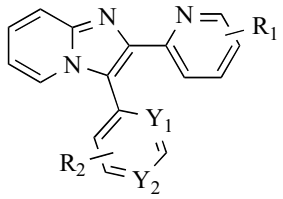

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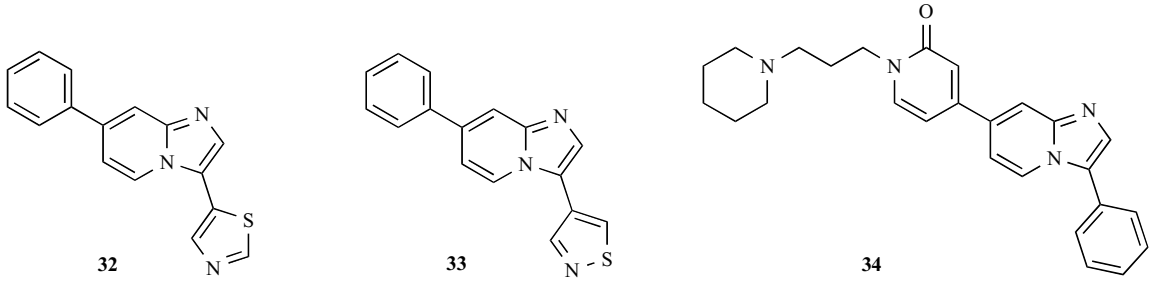
Fig. (10). ALK-4 and/or ALK-5 inhibitors.

genesis. Inhibitors of KDR were shown to induce tumour regression and reduce metastatic potential in preclinical models [50]. Starting from 3,6-diarylpyrazolo[1,5-*a*]pyrimidines and 1,5-diarylbenzimidazoles as potent inhibitors of VEGF-receptor KDR, Merck has developed 3,7-diarylimidazo[1,2-*a*]pyridine analogues [51]. From the 3,7-diphenylimidazo[1,2-*a*]pyridine [52], optimization in position 3 led to five membered rings as 1,3-thiazol-5-yl **32** and isothiazol-4-yl **33** possessed higher activities (IC_{50}s of 42 and 50 nM respectively (Fig. **11**)). Concerning the 7-substitution, a convenient substituted pyridine group was demonstrated as being more potent (**34**). Nevertheless, compounds **32** and **34** showed no selectivity towards PDGFRβ (platelet-derived growth factor receptor beta) and poor selectivity against Flt-1 (fms-related tyrosine kinase 1) and Flt-4.

oesophageal reflux disease [53]. In 2002, Mutel *et al*. surprisingly discovered that some imidazo[1,2-*a*]pyridine could act as mGluR5 antagonists. The most potent compound, 2-(3,4-dimethylphenyl)imidazo[1,2-*a*]pyridine **35** (IC_{50} = 0.037μM) was shown to lack strong affinity toward the benzodiazepine receptors (Fig. **12**) [54]. More recently, Campbell *et al*. described compounds with the scaffold **36** as mGluR5 antagonists [55]. The compounds showed activities lower than 5 μM in a calcium flux assay and under 100 μM in a phosphatidyl-inositol hydrolysis assay.



32 **33** **34**

Fig. (11). Inhibitors of KDR.

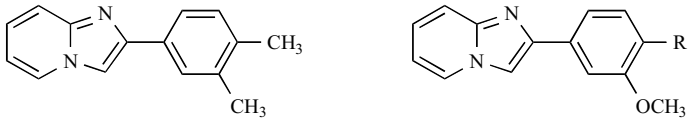
3.3. Antagonists of mGluR5 Receptors

mGluR5 receptors belong to the group I of metabotropic glutamate receptors and could be used for the treatment or prevention of acute and/or chronic neurological disorders such as psychosis, epilepsy, schizophrenia, Alzheimer's disease, cognition disorders, memory deficit, chronic and acute pain, substance abuse and withdrawal, obesity and gastro-

3.4. Agonists/Antagonists of 5-HT Receptors

In the past decades, many imidazopyridines have been patented as 5-HT receptor antagonists or agonists. In 1992, **37** was described as a 5-HT_3 antagonist with a K_i of 4.9 nM in NG108-15 cell assay (Table **3**) [56]. Two years later, compound **38** was claimed as a 5-HT_4 antagonist (no values reported) [57]. Then, **39** was described as a 5-HT_4 agonist [58]. From these results, Nagushi *et al*. reported **40** and **41** as dual 5-HT_3 antagonists and 5-HT_4 agonists [59].

Furthermore, SC-53606 **42** was shown to be a potent 5-HT_4 antagonist (Fig. **13**) [60]. Recently, the structure-activity relationship was studied from this compound. Removing the

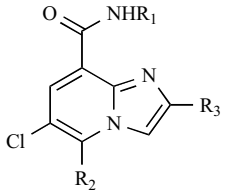


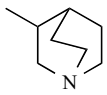
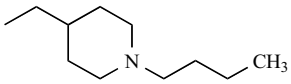
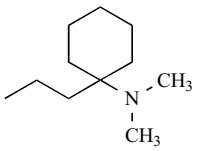
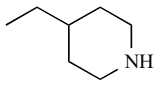
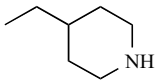
35 **36**

R = Me, pyridin-2-yl

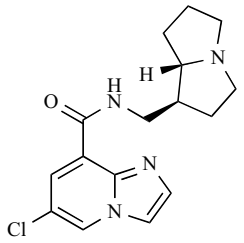
Fig. (12). Antagonists of mGluR5 receptors.

Table 3. Agonists/Antagonists of 5-HT Receptors



Compounds	R_1	R_2	R_3
37		H	H
38		H	H
39		H	H
40		NH_2	H
41		NH_2	CH_3

chlorine in position 6, introducing a methyl in position 3 or changing the amide to an ester functionality decreased the activity. Interestingly, **42** was selective towards 5-HT_1, 5-HT_2, 5-HT_3, α_1, α_2, β, D_1 and D_2 receptors, preventing extrapyramidal side effects and hyperprolactinemia observed with metoclopramide. Unfortunately, this compound was positive in the Ames assay and was not pursued as a clinical candidate [61].



SC-53606 **42**

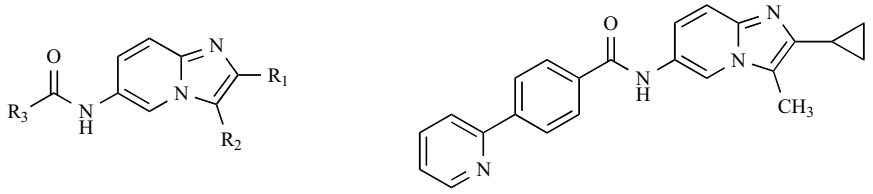
Fig. (13). Potent 5-HT_4 antagonist.

3.5. Antagonists of Melanin-Concentrating Hormone-Receptor-1 (MCH-R1)

Melanin-concentrating hormone (MCH) is a cyclic neuropeptide which centrally regulates food intake and stress. Antagonism of MCH-R1 appeared as potential target for obesity, anxiety, and depressive syndromes [62]. From data in the literature, Banyu Pharmaceutical Company patented imidazo[1,2-*a*]pyridine **43** as a MCH-R1 antagonist (Fig. **14**). The IC_{50} for selected compounds were in the range of 2.0 to 10.5 mM. From these, **44** dose-dependently inhibited the increase in food intake induced by MCH administered in the rat's third ventricle [63].

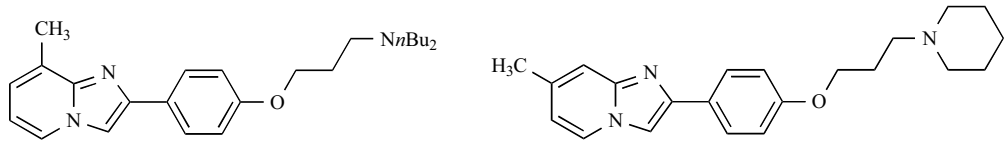
3.6. Antagonists of Histamine H_3 Receptors

The H_3 receptors is predominantly expressed in neuronal tissues and H_3 antagonists have been proposed as drugs with benefits in disorders of cognition, attention, pain, allergic rhinitis and obesity [64]. From a high throughput screening of a Johnson and Johnson library, RWJ-20085 **45** has emerged as a weak H_3 receptor ligand (K_i = 4 μM) (Fig. **15**) and pharmacomodulation of **45** was investigated [65]. Maintaining the di-*n*-butylamino functionality, the pyridine ring supported many substituents in different positions (K_i = 1000 nM for 7-CH_3 to 4800 nM for 6,8-diBr), with the exception of the 8-nitro (K_i = 11000 nM). Introducing a methoxy group in position 3 of the phenyl ring slightly increased the affinity while a methyl in position 2 or 3 or two methoxy groups in position 3 and 5 decreased the affinity. Conserving the methyl in position 8 of the imidazopyridine, the terminal amine was then optimized. In terms of chain length, the af-



43 **44**

Fig. (14). Antagonists of MCH-R1.



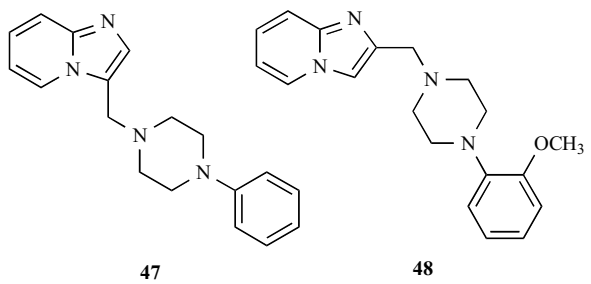
RWJ-20085 **45** **46**

Fig. (15). Antagonists of histamine H_3 receptors.

finity was enhanced from the di-*n*-pentylamino to the dimethylamino (Ki = 7900 nM to 13 nM respectively). Interestingly, tertiary alicyclic amine *e.g.* piperidin-1-yl was highly potent with a K_i of 3 nM. Finally, bioisosteric modification of the oxygen linker or introducing multiple bonds always decreased the affinity. The 7-methyl derivative **46** was then studied in more detail (Fig. **15**). First, it was demonstrated as a highly selective compound (>1000-fold) toward H_1, H_2 and H_4 receptors, as well as numerous biogenic amine and neuropeptide receptors, ion channel and neurotransmitter transporters. Functional activity versus the stably expressed human H_3 receptor was measured with $pA_2 = 8.62$. In terms of pharmacokinetic properties, this compound was also demonstrated to penetrate the blood-brain barrier, to present an oral bioavailability of 57% and a half-life of 5.2 ±1.2 hours.

3.7. Ligands for D_4 Receptors

The chemistry of D4 agonists [66] and D4 antagonists [67] has recently been reviewed. In 1999, Löber *et al*. demonstrated that 3-(phenylpiperazinylmethyl)imidazo[1,2-*a*]pyridine **47** showed high affinity and selectivity for the dopamine D_4 receptor (Fig. **16**) [68], a result further confirmed by Abadi [69]. From these works, we recently reported that 2-(phenylpiperazinylmethyl) derivatives are even more potent. Some of the compounds appeared as full antagonists while PIP3EA **48** was a partial agonist with an intrinsic activity of 57% in the GTPγS binding test with respect to quinpirole, a non-selective compound. Furthermore, we could demonstrate that PIP3EA induced penile erection in rats [70], in a dose-dependent manner independently of the administration route, concomitantly with an increase of nitric oxide in the paraventricular nucleus [71].

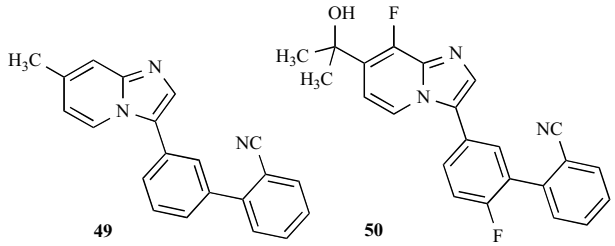


47 **48**

Fig. (16). D4 receptors ligands.

3.8. $GABA_A$ Receptor Ligands

From Zolpidem and Alpidem, CNS drugs sharing the imidazo[1,2-*a*]pyridine core were pursued. As an example, Merck Sharp and Dohme has reported 5,8-difluoroimidazo [1,2-*a*]pyridines derivatives as $GABA_A$ α2/α3 ligands for treating anxiety and/or depression [72]. Later on, **49** was claimed to present higher affinity towards α5 receptor subtypes (K_i = 1.2 nM) with K_i for α2 and α3 of 4.5 and 3.6 nM respectively (Fig. **17**). Due to its poor bioavailability (2%), this compound was abandoned [73]. In order to minimize the antagonist effect at α1 (supposedly responsible for the sedative effect) and maximize the agonist effect at α3 (supposedly responsible for the anxiolytic properties), further pharmacomodulations were carried out. Compound **50** emerged with high affinity for α1 and α3 (K_i = 0.20 and 0.32 nM respectively), but a lower efficacy at the α1 receptor subtypes with a maximal response of 34% compared to chlordiazepoxide versus 104% at the α3 subtypes [74].



49 **50**

Fig. (17). $GABA_A$ receptor ligands.

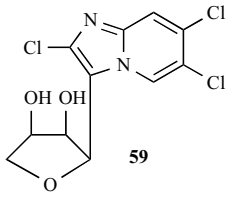
3.9. Other Selected Receptor Ligands Reported

Imidazo[1,2-*a*]pyridines were also described as β3 agonists [75, 76] and antagonists of gonadotropin releasing hormone activity [77].

4. IMIDAZO[1,2-*a*]PYRIDINES AS ANTI-INFECTIOUS AGENTS

From changing the purine moiety of acyclovir to imidazo[1,2-*a*]pyridine, we have shown that the hydroxyethylthiomethyl side chain in the 3 position *ie* **51** gives better antiviral activity than the ether isosters against human cytomegalovirus (HCMV) and varicella-zoster virus (VZV) (Table **4**) [78]. Introducing a methyl in position 7 (**52**) slightly enhanced the activity. Interestingly, on the contrary to acyclovir, the activity was maintained against a thymidine kinase-deficient strain of VZV. In a second step of the optimization, we studied the pharmacomodulation of position 3 and the pyridinic portion. From the different thioether side chains introduced, the benzylthiomethyl was shown to be the most beneficial for antiviral activity, and an 8-methyl group (**53**) was preferred to a 7-methyl (**54**). Changing the benzylthiomethyl to phenethylthiomethyl (**55**) and the 8-methyl to 6-methyl (**56**) preserved the activity. Unfortunately, these compounds were shown to be rather toxic against CEM and HeLa cells [79]. Introduction of a bromine in position 6 (**57**) was well tolerated and strongly diminished the toxicity. The methyl group in position 2 (**58**) was also well accepted [80] as well as many other substituents *ie* pyridin-2-yl, trifluoromethyl, *t*-butyl, with the exception of pyridin-4-yl and furan-2-yl groups [81]. Further optimization is in progress in the laboratory. L.B. Townsend also reported on 2,6 and 2,6,7-di(or tri)chloroimidazo[1,2-*a*]pyridines as acyclic nucleosides [82]. 3-Ethylthiomethyl and 3-allyloxymethyl compounds demonstrated moderate antiviral activities against HCMV and herpes simplex virus-1 (HSV-1).

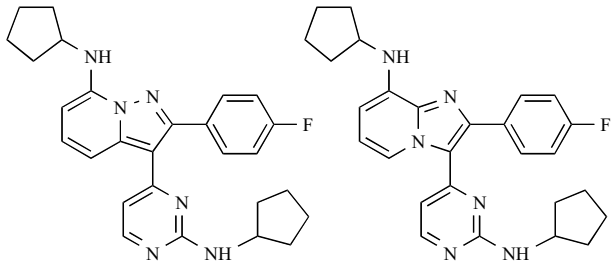
From the same series of compounds, Gudmundsson *et al*. also reported the synthesis and the antiviral properties of 3-erythrofuranosyl derivatives. The α-anomer **59**, was active against HCMV and HSV-1 with IC_{50}s of 8 and 24 μM for the racemic compound, 2.9 and 14 μM for the D-enantiomer, while the L-enantiomer was inactive (Fig. **18**) [83].



59

Fig. (18). Anti-HCMV and anti-HSV-1 agent.

Starting from a cell-based high throughput screening to find novel inhibitors of viral replication, 7-amino-3-(pyrimidin-4-yl)pyrazolo[1,5-*a*]pyridine GW3733 **60** has emerged (Fig. **19**). Changing the bicyclic heterocycle in imidazo[1,2-*a*]pyridine led to GW4637 **61** as a more potent and selective inhibitor of HSV-I than **60** with an IC_{50} = 0.4 μM [84]. Structure-activity relationship data demonstrated that many

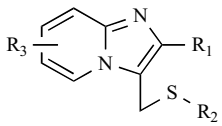


GW3733 **60** GW4637 **61**

Fig. (19). HSV-1 inhibitors.

pharmacomodulations are tolerated in this series as for example changing the phenyl group in position 2 to a naphthyl group. In position 8, the cyclopentylamino substituent could be changed to amino, secondary alkylamine, or tertiary cyclic amine groups as well as chlorine. An amino group could also be introduced in position 6. Finally, the cycloalkylamino

Table 4. EC_{50} Values for Anti-CMV and Anti-VZV Activities

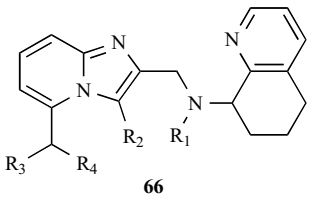


Cpds.	R_1	R_2	R_3	CMV AD169 Strain (μg/mL)	VZV YS Strain TK+ (μg/mL)	VZV YS/R Strain TK- (μg/mL)
51	H	CH_2CH_2OH	H	40	25	25
52	H	CH_2CH_2OH	7-CH_3	10	6	7
53	H	$CH_2C_6H_5$	8-CH_3	0.2	0.3	>1
54	H	$CH_2C_6H_5$	7-CH_3	3.5	17	10
55	H	$CH_2CH_2C_6H_5$	7-CH_3	0.33	0.5	0.66
56	H	$CH_2C_6H_5$	6-CH_3	0.3	6.4	1.2
57	H	$CH_2C_6H_5$	6-Br, 8-CH_3	0.12	7	0.88
58	CH_3	$CH_2C_6H_5$	H	0.12	0.23	0.28

group of the pyrimidine ring could also been changed to an aniline group [85].

From the structure of enviroxime **62**, a potent broad spectrum antiviral agent particularly active against rhinovirus and enterovirus, Hamdouchi *et al*. were interested in scaffold **63** (Fig. **20**) [86, 87]. When position 3 was unsubstituted or substituted with an iodine, no antirhinovirus (human rhinovirus-14) activity was measured. Introducing the isopropylsulfonyl group of enviroxime (R = $(CH_3)_2CHSO_2$) gave an antiviral compound with an IC_{50} of 0.64 μg/mL. Surprisingly, the sulfenyl derivative (R = $(CH_3)_2CHS$) was more potent (IC_{50} = 0.14 μg/mL) while changing to a phenyl group (R = C_6H_5) led to a compound with an IC_{50} of 0.27 μg/ml. These results showed that position 3 clearly influences activity. The 2,5-difluorophenyl and 2,3,4-trifluorophenyl groups in the 3 position slightly influenced the antiviral effect (IC_{50} = 0.18 and 0.17 μg/ml respectively), whereas the 2-trifluoromethyl-4-fluorophenyl derivative was less potent with an IC_{50} of 0.44 μg/mL. This last result suggests the importance of the electronic effect on the antiviral activity. In term of toxicity, these compounds showed a ratio TC_{50}/IC_{50} >17. In a further study [88], the same authors were interested in introducing carbonyl functionality as an isosteric replacement for the sulfonyl group of enviroxime **62** and enviradene **64** leading to scaffold **65**. The acetyl compound was weakly active (IC_{50} = 2.48 μg/mL) while in contrast, the *t*-butylcarbonyl compound displayed high activity with an IC_{50} of 0.17 μg/mL. The benzoyl and 4-fluorobenzoyl groups were also well tolerated with IC_{50}s of 0.24 and 0.37 μg/mL. In terms of toxicity, the benzoyl derivatives showed a ratio TC_{50}/IC_{50} = 12.3 and 10.7 respectively, whereas the *t*-butylcarbonyl was quite safe with a ratio >59. Finally, semi-empirical calculations using AM1 Hamiltonian were undertaken. The activity seemed correlated with the dihedral angle around the carbonyl at C-3 (C2,C3,CO,O) with a high dihedral angle (45°) for the most potent compound and a very small angle (-1.7°) for the inactive one.

Recently, Smithkline Beecham patented imidazo[1,2-*a*] pyridine derivatives **66** as antagonists of CXCR4 (Chemokine CXC motif receptor 4) and/or CCR5 (Chemokine CC motif receptor 5), associated with important anti-HIV activities (Fig. **21**) [89].



66

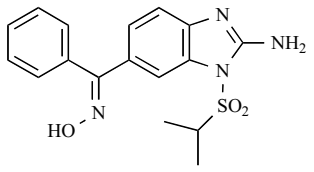
Fig. (21). CXCR4 and/or CCR5 antagonists.

Antibacterial activities were also described in this series. The *N*-(5,7-disubstituted-imidazo[1,2-*a*]pyridin-2-yl)-*N*'-ethylureas **67** and **68** were active against *Neisseria gonorrhoeae* with MICs less than 1 μg/mL (Fig. **22**) [90].

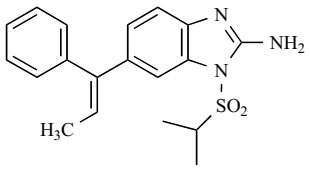
Imidazo[1,2-*a*]pyridine derivatives were also described as antiprotozoal agents against *Trypanosoma brucei rhodesiense*, *Trypanosoma cruzi*, *Plasmodium falciparum*, *Toxoplasma gondii* and coccidiosis in poultry or mammals [91-94]. Some of the molecules reported are diamidines [91-92], in which the imidazo[1,2-*a*]pyridine portion serves as spacer between the two dicationic groups, a function that is also performed by several other linkers. Recently, compounds of general structure **69** were described as inhibitors of the parasite specific cGMP-dependent protein kinase, but were positive in the Ames mutagenesis assay, precluding them for further development (Fig. **23**) [95, 96]. Further structural modifications and SAR of this series of compound was reported [97]. Some of them also block the growth of *Leishmania major* promastigotes *in vitro* through the inhibition of casein kinase 1 [98].

CONCLUSION

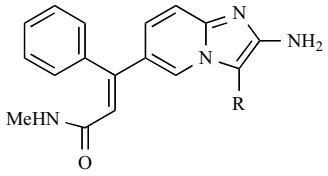
Since the discovery of Zolpidem, imidazo[1,2-*a*]pyridine appears as a very interesting scaffold in medicinal chemistry notably from its easy access and its great stability. Suitable functionalizations led to compounds that act at numerous



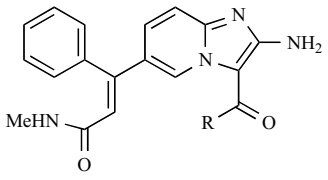
Enviroxime **62**
IC_{50} = 0.045 μg/:mL



Enviradene **64**
IC_{50} = 0.15μg/mL



63



65

Fig. (20). Antiviral agents.

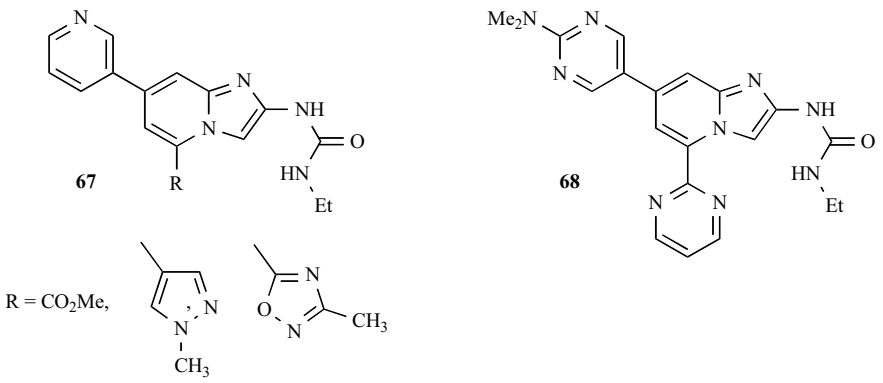


Fig. (22). Antibacterial agents.

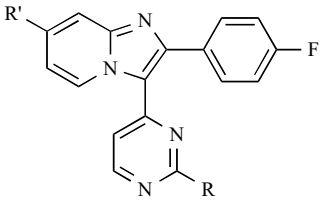


Fig. (23). Antiprotozoal agent.

targets including enzymes, receptors and infectious agents. Thus, many potential therapeutic applications are envisaged for imidazo[1,2-*a*]pyridine derivatives in various domains like cancerology, neurology, virology, endocrinology… In the future, the introduction in therapeutic of new imidazo[1,2-*a*]pyridines is highly probable.

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