

Bioactive *N*-Phenylimidazole Derivatives

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Abstract: This review article deals with different aspects of imidazole derivatives with one nitrogen atom bearing a substituted or unsubstituted phenyl moiety, such as their presence in bioactive compounds, their activity, as well as the main strategies for their preparation.

Keywords: imidazole derivatives, pharmacological activity, biological activity, imidazole synthesis.

1. INTRODUCTION

About the half of the chemical registered compounds contain heterocyclic systems. Thus, heterocyclic compounds constitute an important group in modern organic chemistry, not only because of their abundance, but primarily because of their chemical, biological and technical significance.

Imidazoles, and azoles in general, are an important family of heterocyclic compounds with a broad interest due to their bioactive properties. Indeed, various imidazole derivatives have shown a broad range of bioactivities, such as anti-neoplastic, immunosuppressive, and anti-inflammatory activities [1]. Among them, imidazoles bearing a (substituted or unsubstituted) phenyl moiety on the nitrogen have shown different attractive activities. Simple derivatives (with only *N*-substitution) interact with cytochrome P450 enzymes, and have been revealed as an interesting tool for studying the active site of them. Increasing the substitution on the imidazole ring, the corresponding compounds have shown a wide variety of potential pharmacological applications. For that reason, this review article has been structured according to the substitution pattern of the imidazoles.

To finish, the principal synthetic advances for preparing this kind of imidazoles have been taken into account. Thus, ring-closure reactions of acyclic precursors (e.g. four-component synthesis) and substituent modifications of heterocyclic compounds (e.g. *N*-arylation of imidazolyl derivatives) are the two main routes for the general preparation of these imidazole derivatives.

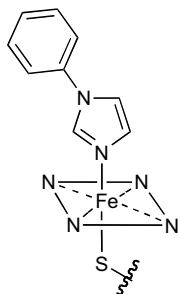
2. IMIDAZOLES WITHOUT ANY SUBSTITUENT AT THE CARBON ATOMS

Cytochrome P450 is a superfamily of monooxygenase enzymes with diverse catalytic activities. They have been found in all three phylogenetic domains of life, including many animal tissues. The primary chemical reaction catalyzed by these monooxygenases is the two-electron activation of molecular dioxygen, whereby one oxygen atom is inserted into the substrate with concomitant reduction of the second atom to water. NAD(P)H provides the required electron

equivalents via a number of different redox partners [1]. Some of the most potent reversible inhibitors of P450 enzymes are the nitrogen heterocycles, including imidazoles and quinolines. P450 inhibition by these compounds results from direct interaction between the aromatic nitrogen of the heterocycle and the heme moiety of the enzyme (Scheme 1) [2]. Imidazole and its derivatives are classical inhibitors of cytochrome P450 enzymes [3]. They exert their inhibitory effect via the direct ligation to heme iron (type II complex) at the dioxygen binding site [4-6]. Thus, phenylimidazoles are potent reversible inhibitors of the cytochrome P450 enzymes that metabolize compounds such as drugs and steroids [7], and promised to be valuable probes for studying the molecular basis of differential P450 inhibition. Among them, 1-phenylimidazole (1-PI, **1**) is a standard substance to consider as an inhibitor. The 1-PI inhibitor binds as a Type II complex with the imidazole nitrogen as a ligand of the heme iron. Analysis of the inhibitor-enzyme interactions during the molecular dynamics (MD) simulations reveals that electrostatic interactions of the imidazole with the heme and van der Waals interactions of the phenyl ring with nearby hydrophobic residues are dominant [8]. X-ray crystallographic studies of bacterial P450 complexed with 1-, 2- or 4-phenylimidazole have demonstrated that a sterically accessible lone pair provided by the heterocyclic nitrogen atom for heme iron coordination is required [9]. The small sample size and rapid measurement time make easier the route of characterization of P450 systems by resonance Raman spectroscopy, thus Raman spectra of these complexes suggest that the active site is sensitive to the steric nature of the inhibitor [10]. Considerable efforts have been devoted for modeling the behavior of these molecules in the sterically restricted active site [8,11], and for studying the interplanar torsion barriers [12] and thermodynamics [13,14] for these inhibitors.

Cytochrome P450*cam* is a member of a ubiquitous family of metabolizing heme enzymes with functions varying from steroid biosynthesis to oxidative metabolism of xenobiotics. P450*cam*, a water-soluble P450 camphor hydroxylase from the bacteria *Pseudomonas putida*, was the first member of this family to have its crystal structure solved [15]. Moreover, X-ray crystal structures of P450*cam* complexes with three phenylimidazole isomers inhibitors have been reported by the same laboratory [9]. The binding constants for these inhibitors had previously been characterized by

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Scheme 1.

by Lipscomb employing electron paramagnetic resonance (EPR) spectroscopy [4]. More recently, free energies of solvations of these phenylimidazole inhibitors have been determined by different methods and correlated them with the observed differences in the enzyme binding free energies [16]. In addition, 1-PI has been used as a competitive inhibitor for an imidazole-tethered benzophenone probe during photoaffinity labeling experiments of P450*cam*, in order to assess the specificity of the photoadducts characterized [17].

Due to the cytochrome P450 enzymes inhibition ability of the 1-PI, it has been used in a study to determinate if cytochrome P450 also contributes to the hydroperoxide cytotoxicity in isolated hepatocytes [18]. The results suggest that organic hydroperoxides are metabolically activated by some P450 enzymes (e.g. P450 2E1) in hepatocytes to form reactive radical metabolites or oxidants that cause lipid peroxidation and cytotoxicity. 1-PI has also been used in the investigation of some well-known fluorescent P450 substrates as an alternative for P450*eryF* using wild-type and mutants A245S and A245T [19]. Flitsch and co-workers used 1-PI in the characterization of recombinant P450 RhF from *Rhodococcus* sp. NCIMB 9784, which is the first example of a new class of cytochrome P450 with a novel reductase partner (FMN- and Fe/S-containing) as electron supplier [20].

Subfamily CYP4A of cytochrome P450 plays important roles in physiological catabolism of medium- and long-chain fatty acids (including prostaglandins, leukotrienes, and arachidonic acid). However, the structural basis for the ω -hydroxylation specificity of CYP4A enzymes is not known. Structure-activity studies have been carried out in order to elucidate the enzyme-substrate interactions responsible for the striking substrate specificity of CYP4A, different imidazole derivatives being suitable compounds for that study. Imidazoles containing phenyl (1-PI), benzyl, or phenylethyl substituents at N-1 interact less strongly than related *N*-alkylimidazoles of similar carbon number and hydrophobicity, suggesting that the steric bulk and/or rigidity of the phenyl ring is not well accommodated in the corresponding active site [21]. The mutation of two residues (Glu-320 and Asp-323) in CYP4A1 has been done being helpful to define the active site dimensions and the susceptibility to inactivation by mechanism-based inhibitors. In this approach, different imidazole derivatives have been used to examine the nature of the active site changes and a strong increase in binding of the 1-PI has been observed showing that lipophilicity is more important than steric constraints [22].

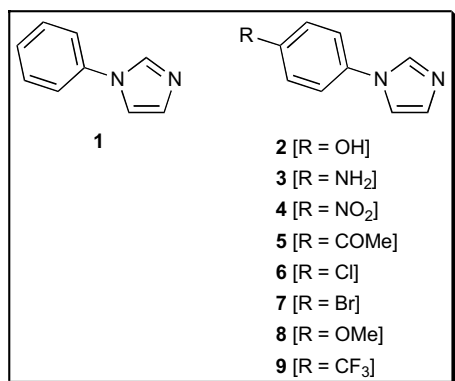
The molecular basis for reversible inhibition of rabbit CYP2B4 and CYP2B5 and rat CYP2B1 by phenylimidazo-

les has been assessed with active-site mutants and new three-dimensional models based on the crystal structure of CYP2C5. Among the inhibitors used, 1-PI was tested giving an IC₅₀ value of 0.9 μ M for CYP2B4 what was consistent with another previous report [23]. A chlorine substitution at 4 position of the phenyl moiety (compound 6) resulted in IC₅₀ values 130-fold lower for CYP2B4 than for CYP2B5, suggesting an inhibition selectivity for CYP2B4. Thus, this new generation of CYP2B models could provide valuable information for the design of selective inhibitors of human CYP2B6 and for the development of drugs that avoid drug interactions due to P450 inhibition [24]. Complete thermodynamic and spectroscopic studies have been done in order to elucidate the conformational flexibility of CYP2B4 in binding imidazole inhibitors with different ring chemistry and side chains [including 1-PI and 1-(4-chlorophenyl)imidazole] [25]. *Mycobacterium tuberculosis* (Mtb), the causative agent of tuberculosis [26], encodes a P450 derivative of the sterol demethylase family (CYP51) chromosomally located adjacent to a ferredoxin. The biophysical properties of Mtb CYP51 and interactions between the P450 and its ferredoxin partner have been examined taking into consideration the analysis of heme iron-coordinating inhibitors interactions (such as 1-PI) [27].

There are at least three nitric oxide synthase (NOS) hemoproteins responsible for the formation of nitric oxide, an important mediator in neural transmission, cytoprotection, and cardiovascular functions [28,29]. These three isoforms of NOS share an overall 65-71% primary protein sequence homology [30,31]. To develop selective reagents targeted to an individual isozyme, it is critical to understand the similarities and differences in the structure of the active site for each substrate. One approach to this goal is to use a series of homologous heme ligands to probe the environment of the heme axial coordination pocket. Many anionic ligands, which have been showed to bind tightly with other ferric hemoproteins, are not strong ligands for NOS heme, a cytochrome P450 type [32], due to the highly electronegative proximal thiolate ligand. Even the cyanide binding affinity for NOS is in the range of millimolar [33]. In contrast, neutral imidazole derivatives have been demonstrated to be among the few strong ligands for NOS isozymes. Thus, Wolff and co-workers have evaluated the effect of a series of imidazole derivatives on the enzyme activity of NOS isozymes [34,35], while Masters and her colleagues first examined the direct interactions of imidazole with NOS heme by spectral perturbation [36,37]. This direct approach has been later extended by Tsai group to kinetic and EPR analysis [38]. The direct spectral perturbation approach appears to agree that imidazole derivatives compete directly with binding of L-arginine, while data from steady-state of L-citrulline formation showed different modes of inhibition with L-arginine. The reported optical spectral perturbation of NOS heme by imidazole and its derivatives is a type II change (i.e., a red shift) due to formation of low-spin heme complexes [36-38]. This might lead to the conclusion that all imidazole derivatives interact with NOS heme through direct ligation to the heme iron in formation of the low-spin complex. Albeit both low-spin (type II) and high-spin (type I) complexes were formed with different imidazole analogues and at least four different types of high-spin heme structures present in eNOS and cNOS complexes were suggested, 1-

substituted imidazoles always yield low-spin heme complexes [39]. Regarding 1-PI, it gave poor affinity for eNOS ($K_D \gg 100$ mM), although the substituted 1-(4-hydroxyphenyl)imidazole showed a K_D of less than 1 mM.

The recombinant human inducible nitric oxide synthase (rH-iNOS) has been shown to possess a cytochrome P450-like heme in the active site. From different studies it has been established that imidazole is a competitive inhibitor of L-arginine in rH-iNOS ($IC_{50} = 59 \pm 7$ μ M). The almost 2-fold more potent inhibitor, 1-phenylimidazole (1-PI, **1**) gave a $IC_{50} = 33 \pm 3$ μ M) has also been a competitive inhibitor versus L-arginine based on the same type of analysis [40]. Substituent effects of 1-PI were also examined, so hydroxy and amino groups at the *para* position of the phenyl moiety (compounds **2** and **3** respectively) have shown no significant change in the inhibition, the 4-aminophenyl moiety exhibiting slightly better inhibition ($IC_{50} = 29 \pm 4$ μ M). However, an electron-withdrawing group [4-nitrophenyl (**4**) or 4-methylcarbonyl (**5**)] had a dramatic negative effect on the inhibition, increasing the IC_{50} value by 10-fold (up to 501 ± 67 μ M for the nitro derivative).



Comparing the studies of Tsai and Wong groups, it has been observed about a 20-fold difference in the potency of 1-PI in inhibiting human iNOS and eNOS, what gives an idea about a structural difference of the heme distal pocket between these isoforms. Further studies on the active-site structure and activity in eNOS have been done by individual mutation of eight polar amino acid residues in the putative substrate-binding region (from Thr-360 to Val-379) in human endothelial nitric-oxide synthase. Only mutations at residues Asp-369 and Arg-372 abolished eNOS activity. These positions were replaced with a variety of other amino acids and characterized the spectral properties of the resulting mutant proteins in complexes with various heme ligands (using 1-PI), in order to elucidate the roles of these residues in maintaining the heme environment. The results indicate that Asp-369 and Arg-372 residues are critically important in stabilizing eNOS oligomeric structure and heme environment [41]. The inhibitory potency of different classes of nitric oxide synthase (NOS) inhibitors (being 1-PI among them) versus peripheral neuronal NOS (nNOS) in the pig gastric fundus has been investigated by studying their influence on electrically induced relaxations in non-adrenergic non-cholinergic conditions. 1-PI, which has been shown to inhibit bovine brain nNOS [34], nearly abolished 5-hydroxytryptamine-induced tone so that the relaxant responses to electrical field stimulation (EFS: 40 V, 0.1 ms, 4 Hz) became minimal, and

the inhibitory effect could not be assessed [42]. The ability of imidazole and *N*-substituted imidazoles to promote or inhibit dimerization of heme containing iNOSox monomers, or to affect iNOS dimerization in cells, has been examined [43]. Imidazole and 1-PI promoted iNOSox dimerization, whereas other larger *N*-substituted imidazoles did not, inhibiting instead dimerization.

The affinity of 1-PI for cytochrome has been used in the investigation of the mechanisms of toxicity of different organic substances. Furan is a potent cytotoxic, non-DNA reactive rodent carcinogen, the mechanism of furan-induced carcinogenesis being related to cell death followed by compensatory cell proliferation and tumor formation. Furan-mediated mitochondrial changes observed both *in vivo* and *in vitro* have been prevented by pretreating rats with 1-phenylimidazole in the incubations, so indicating that cytochrome P450-dependent bioactivation of furan is required to cause mitochondrial changes [44]. These results indicate that uncoupling of oxidative phosphorylation is caused by cytochrome P450-dependent metabolism of furan to *cis*-2-butene-1,4-dial [45,46].

The mechanism of tumor induction in rodents by chloroform has been also studied employing phenylimidazole inhibitors. Chloroform is carcinogenic but is not mutagenic or DNA reactive, but clearly produced hepatic cytolethality and cell proliferation in B6C3F₁ mice and F-344 rats at carcinogenic doses used in the cancer bioassay [47]. Cotreatment with the cytochrome P450 inhibitor 1-PI has prevented both the cytolethality and glutathione depletion, indicating that metabolism is necessary for chloroform-induced toxicity [48].

The biogenic monoamine octopamine (OA: α -aminomethyl-*p*-hydroxybenzyl alcohol), which has been found to be present in high concentrations in various insect tissues, is the monohydroxylated analogue of the vertebrate hormone noradrenaline. OA receptors are perhaps the only non-peptide receptors whose occurrence is restricted to invertebrates. Three different receptor classes (OAR1, OAR2A, and OAR2B) had been distinguished from non-neuronal tissues, and in the nervous system of locust, a new particular receptor class OAR3 has been established by pharmacological investigations of the binding site using various agonists and antagonists. Three-dimensional pharmacophore hypotheses were built from a set of 43 agonists, 1-PI being among them, against octopamine receptor class 3 in locust nervous tissue [49]. The same research group has analyzed by molecular field analysis (MFA) the quantitative structure-activity relationship of a set of 70 octopaminergic agonists (among them 1-PI) and 20 antagonists against octopamine receptor class 3 (OAR3) in locust nervous tissue. The obtained results provide useful information in the characterization of the octopaminergic receptor [50].

Human glutaminy cyclase (QC) has been identified as a metalloenzyme as suggested by the time-dependent inhibition by the heterocyclic chelators. An initial structure activity-based inhibitor screening of imidazole-derived compounds revealed potent inhibition of QC by 1-substituted imidazole, although 1-PI showed no inhibition activity for QC [51]. The observed impact of structure modifications in the imidazole derivatives on their QC-inhibitory potency can

serve as a starting point for further and rationally driven inhibitor designs.

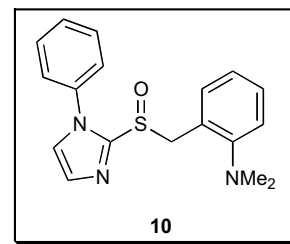
The glucuronidation of tertiary aliphatic or aromatic amines leading to the formation of a polar quaternary ammonium-linked glucuronide metabolite (N^+ -glucuronide) [52] plays a significant role in the metabolism of various xenobiotics. Incubation of 1-PI with activated human liver microsomes led to the formation of its N^+ -glucuronide metabolite, which has been isolated from the microsomal mixture. This study demonstrated that 1-substituted imidazoles are appropriate substrates to undertake investigation on substrate specificities involving the N^+ -glucuronidation of tertiary aromatic amines. With the availability of a synthetic sample, the N^+ -glucuronide has been definitively identified as a metabolite of 1-PI in human liver microsomes. A series of 1-substituted imidazoles has been investigated as model substrates for glucuronidation at an aromatic tertiary amine of polyaza heterocyclic ring systems, phenylimidazoles **1**, **4**, and **6-9** being used among the studied compounds. The human UDP-glucuronosyltransferases (UGTs) involved and substrate specificities have been investigated: nine expressed enzymes (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A9, UGT1A10, UGT2B7, and UGT2B15) were examined, but only UGT1A4 catalyzed the formation of a quaternary ammonium-linked glucuronide metabolite for six of the substrates. UGT1A3 also catalyzed the glucuronidation of the previously investigated 1-PI [53] but none of the newly investigated compounds. No glucuronidation was observed with 1-(4-nitrophenyl)imidazole (**4**) [54]. The same substituted imidazoles have been also tested for glucuronidation in liver microsomes from five species (human, guinea pig, rabbit, rat and dog). The major objectives in this investigation were to elucidate substrate specificities of the series in human microsomes and interspecies variation for the prototype molecule, 1-PI [55].

The design of reliable scoring functions for the prediction of protein-ligand binding affinities is a longstanding issue in computer-aided drug design. A new knowledge-based scoring function [potential of mean force score (PMF-score)] combines the accuracy of empirical scoring functions with the advantage of higher generality, and therefore wider applicability [56]. A data base of 3247 small molecules for binding to the FK506 binding protein (FKBP), 1-PI and other imidazole derivatives being among them, have been screened using this computer-aided research [57].

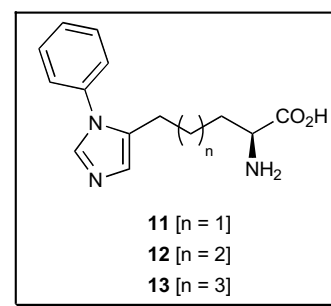
3. ONE CARBON SUBSTITUTED IMIDAZOLES

The inhibition of gastric acid secretion has been proven to be a powerful therapeutic principle in the treatment of gastric and duodenal ulcer disease. Different drugs have been discovered as H^+/K^+ -ATPase inhibitors. The so-called proton pump inhibitors (e.g. omeprazole) represent a new class of effective gastric acid secretion inhibitors [58]. Substituted 2-sulfinylimidazoles have been synthesized and investigated as potential gastric ATPase inhibitors, among them compound **10**, showing weakly inhibitory activity ($IC_{50} = 68 \mu M$) compare to omeprazole ($IC_{50} = 3.8 \mu M$). Other substituents on the imidazole nitrogen gave better inhibitory activities [59].

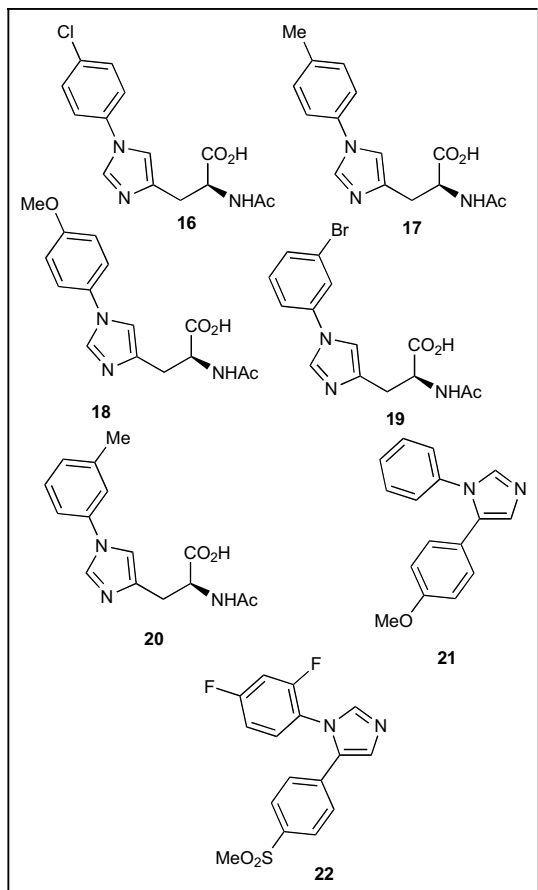
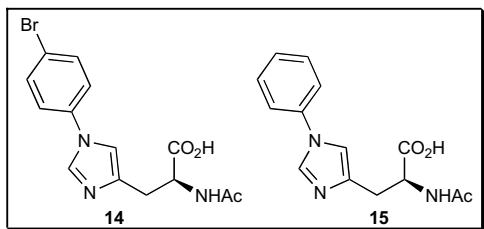
The series of L-histidine 1-phenylimidazole-containing amino acid analogues (**11-13**) has been prepared and studied their inhibition activity against the three isozymes of NOS



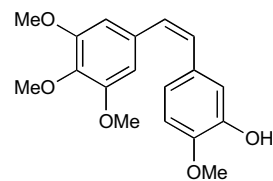
(i.e. nNOS, iNOS and eNOS). The structure-activity relationships of this class of inhibitors can be correlated with the distance between the heme and the amino acid binding sites of the enzyme. Thus, in this study the influence of the distance between the amino acid moiety and the imidazole moiety on the inhibitory potency was taking into consideration. Better inhibitor properties were registered when three or five methylene groups were located between the imidazole and the amino acid functionalities. Amino acids **11** and **12** were more selective for eNOS than the other isoforms of NOS, although the selectivity was poor [60]. Histidine derivatives have also been of interest for characterizing the chemical steps that underlie the metabolic activation, protein covalent binding, and subsequent hepatotoxicity of bromobenzene as a model for small, pharmacologically innocuous, but nevertheless hepatotoxic, aromatic compounds [61,62]. For these purpose, histidine derivatives **14-20** have been synthesized by coupling aryl halides and *N*-acetylhistidine methyl ester [63], and a KLH conjugate of compound **14** generated a high-titer immune response in rabbits. In addition, the polyclonal antiserum proved to be highly selective for hapten **15** versus the other related structures (**14**, **16-20**), or its cysteine or lysine analogues.



Chronic inflammation diseases, such as rheumatoid arthritis, are problematic therapeutic areas to overcome because their long-term curative periods limit the use of therapeutic agents with side effects. Cyclooxygenase-2 (COX-2) is an enzyme related to inflammatory lesions. Greatly efforts have been reported toward the development of selective COX-2 inhibitors, and diverse heterocycle derivatives have been explored [64]. Eighteen different 1,5-diarylimidazoles have been synthesized and evaluated for their inhibitory activities against COX-2 catalyzed PGE_2 production from LPS-induced RAW 264.7 cells. Although most of these compounds exhibited little to low inhibitory activities (even being inactive against COX-2), compounds **21** and **22** showed high inhibition (76% and 89% respectively) [65]. In contrast, 1,2-disubstituted imidazoles, with a substituted phenyl moiety at position 1 and an alicyclic tertiary alcohol in position 2, showed COX-1 selective inhibition [66].



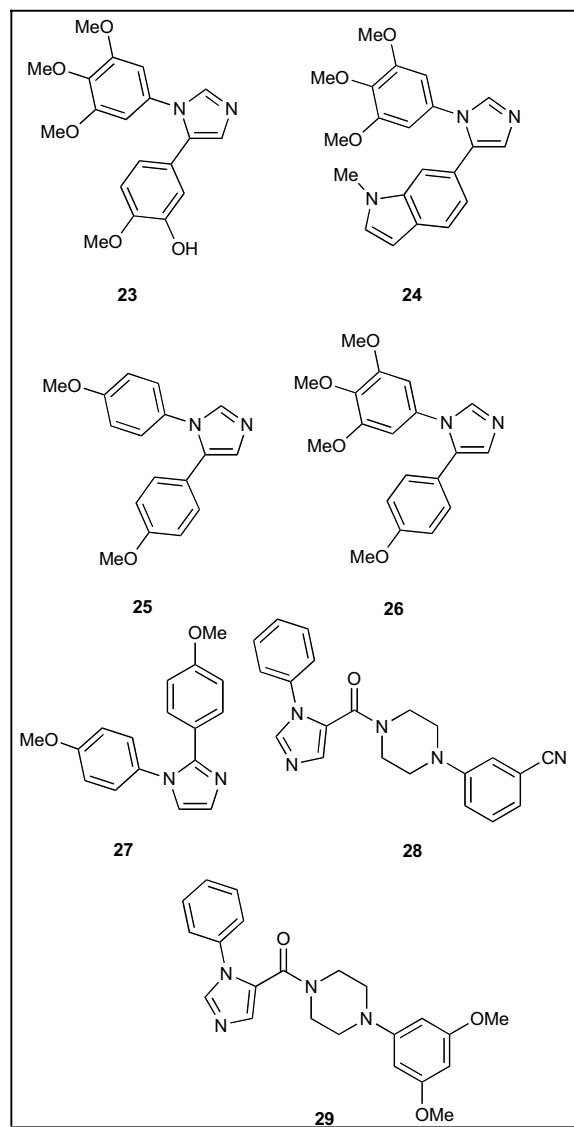
Combretastatin A-4 (CA-4, Scheme 2) is a natural product isolated from the South African tree *Combretum caffrum* and it exhibits strong antitubulin activity by binding to the colchicines binding site of tubulin. Thus, it shows evidence of potent cytotoxicity against a broad spectrum of human cancer lines including those that are MDR positive. The *cis* configuration of the double bond is essential for its anticarcinogenic activity, but it is prone to isomerize to the more thermally stable *trans* isomer, resulting in complete loss of cytotoxicity. Thus, the preparation of disubstituted five-membered aromatic heterocycles, such as imidazoles, to mimic the *Z*-double bond in CA-4 has been studied for Wang and co-workers [67]. Among the assayed compounds, 1,5-disubstituted imidazole **23** showed an interesting result regarding antitubulin activity ($IC_{50} = 7.6 \mu M$, compare to the $1.2 \mu M$ of the CA-4), but the antiproliferative potencies against NCI-H460 ($IC_{50} = 89 \text{ nM}$) and HCT-15 ($IC_{50} = 61 \text{ nM}$) were lower (CA-4 gave 1.7 nM and 3.0 nM respectively). Better results were obtained for compound **24**, both in the antitubulin activity ($IC_{50} = 1.8 \mu M$) and the cytotoxicities ($IC_{50} = 14 \text{ nM}$ for NCI-H460 and $IC_{50} = 19 \text{ nM}$ for HCT-15).



Combretastatin A-4

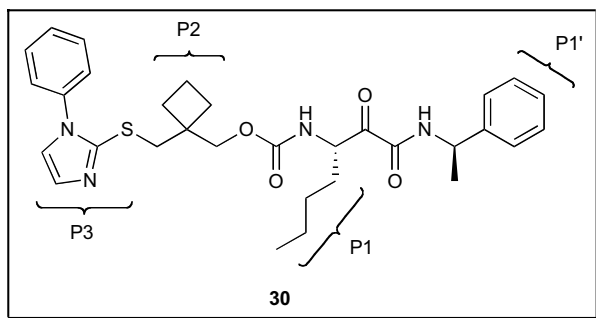
Scheme 2.

Bellina and Rossi research group has also reported the regio-selective synthesis of 1,5-diarylimidazoles and the study of their cytotoxicity against the NCI three-cell line panel consisting of MCF7, SF-268, and NCI-H460 [68]. In addition, compounds which reduced the growth of any one of these cell lines to 32% or less could be considered active and passed on for evaluation over a 5-log dose range in the NCI's *in vitro* human disease-oriented tumor cell line screening panel that consisted of 60 human tumor cell lines. Imidazole derivatives **21** and **24-26** were found to be significantly cyto-



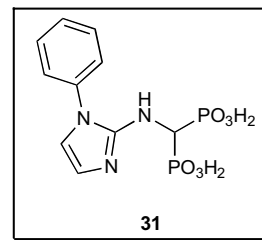
toxic, the 5-indolylimidazole derivative **24** being the most potent of the series (MG-MID log GI₅₀ = -7.09). 1,2-Diarylimidazole **27**, which has been obtained as a side product during the preparation of **25**, showed also considerable cytotoxicity. Furthermore, heteroaryl piperazinyl methanones have been pointed out as useful compounds for treating cancer due to their inhibition activity of the tubulin polymerization and, showed inhibition of tumor cell proliferation *in vitro*. Some imidazole methanone derivatives, such as compounds **28** and **29**, were among the products tested [69].

Cathepsin K, a lysosomal cysteine protease, has been involved in the osteoclast mediated bone resorption, and inhibitors of this protease could potentially treat the osteoporosis. Different cycloalkyl α -ketoamide derivatives have been described to be used as cathepsin K inhibitors in the treatment of disorders, including osteoporosis, associated with enhanced bone turnover which ultimately lead to fracture [70-72]. Modifications at the region P3 of the ketoamide-based inhibitors have been studied employing different five- and six-membered heterocyclic moieties. Thus, compound **30**, bearing a 1-phenylimidazolyl moiety linked with a sulphur atom, showed an IC₅₀ value of 87 nM versus human cathepsin K [73]. In addition, compound **30** has been employed during the study of the spatial requirements of the S3 subsite of the mentioned protease [74].

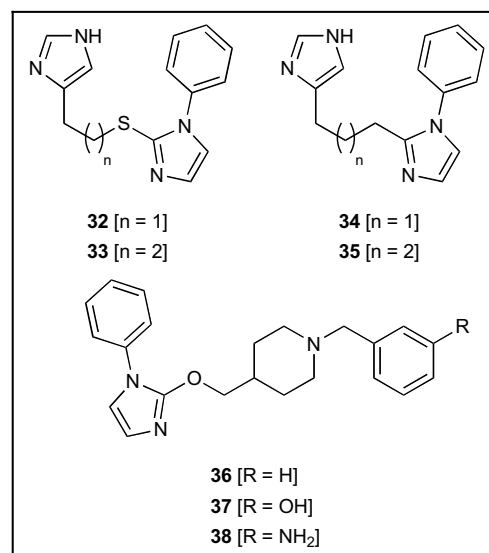


Geminal bisphosphonates (BPs) are metabolically stable analogues of the naturally occurring inorganic pyrophosphate, which have been shown by Fleisch and co-workers to impair the formation and dissolution of calcium phosphate crystals *in vitro* [75]. Like pyrophosphate, BPs have high affinity for bone mineral and at high doses can modulate calcification both *in vitro* and *in vivo*. In contrast to pyrophosphate, BPs are also orally active, although their low bioavailability often limits the usefulness of oral administration. Widler and co-workers have undertaken studies in order to improve the potency and therapeutic window of this kind of compounds for the treatment of tumor-induced hypercalcaemia, Paget's disease of bone, osteolytic metastases, and postmenopausal osteoporosis [76]. Compounds bearing different imidazole moieties were considered in the study, compound **31** being among them. Most of the aminomethylenebisphosphonates with an imidazolyl group were lesser active than expected. Taking into account these studies, Kotsikorou and Oldfield have been used quantitative structure-activity relationship techniques, together with pharmacophore modeling, to investigate the relationships between the structures of a wide variety of geminal BPs and their activity in inhibiting osteoclastic bone resorption [77]. As a result, they concluded that for heterocyclic BPs, the results

provided the first insights into structure-activity relationships at the level of protonation state or pK_a values, and particularly in the case of aminoimidazole BPs activity was low, what could be correlated with an extremely high pK_a value (~11), which could result in diminished transport.

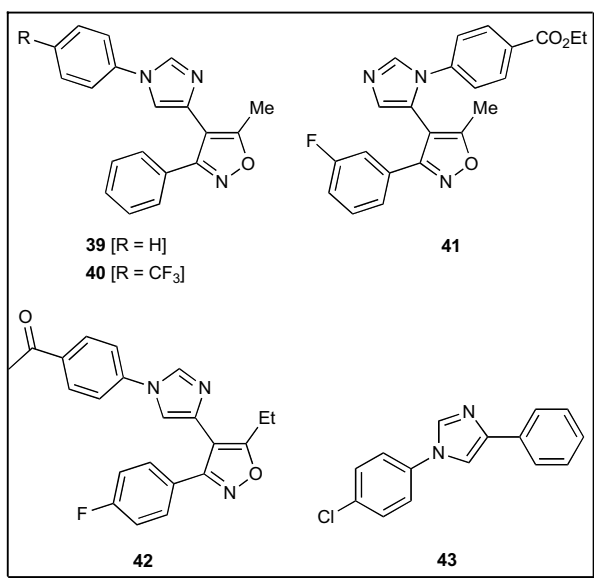


Histamine H₃ receptors are expressed in the central nervous system and, to a lesser extent, in the peripheral nervous system, where they act as autoreceptors in presynaptic histaminergic neurons, as well as to control histamine turnover by feedback inhibition of histamine synthesis and release. The H₃ receptor has also been shown to presynaptically inhibit the release of a number of other neurotransmitters (i.e. as an inhibitory heteroreceptor) including dopamine, GABA, acetylcholine, noradrenaline, and serotonin among others. Because of their ability to modulate other neurotransmitters, H₃ receptor ligands are being of interest for the treatment of numerous neurological conditions, including obesity, movement disorders, schizophrenia and ADHD (Attention-Deficit Hyperactivity Disorder) [78]. A series of heterocyclic derivatives, among them bisimidazoles **32-35**, were used to study *in vitro* their potency, affinity and selectivity towards H₃ histamine receptors. Almost all compounds presented H₃ blocking activity with a potency decreasing from imidazole to imidazoline derivatives [79]. Another class of disubstituted imidazoles, such as 2-alkoxy imidazoles **36-38**, has been described as muscarinic M₃ and serotonergic 5-HT₄ antagonists [80].

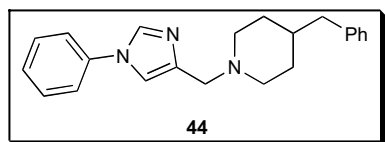


Compounds being used to modulate ligand binding to GABA_A receptor *in vivo* or *in vitro* are particularly useful in the treatment of a variety of central nervous system disorders, such as cognitive disorder and Alzheimer's disease, in mammals. Pharmaceutical compositions containing aryl-

soxazolyl imidazole derivatives, for instance compounds **39-42**, have been studied for the treatment of diseases related to the GABA_A. Unsubstituted or substituted phenyl moiety at the imidazole nitrogen gave good interaction with the receptor, so compound **42** has a K_i value of 4.7 nM for displacement of [³H]flumazenil from GABA_A α_5 subunits [81]. Grunwald and co-workers have been prepared and tested different heterocyclic compounds (mainly imidazolones and pyrrolones) concerning their anxiolytic properties due to modulation of the GABA_A receptor response, looking for interesting pharmacological activity while lacking the typical side effects of benzodiazepine receptor (BzR) agonists. The imidazole **43** has been used, among other heterocyclic compounds, giving excellent affinity to the BzR, but not good pharmacological activity. Qualitative structure-activity relationships and CoMFA models have been resulted on the basis of these studies [82].

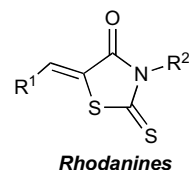


1-Substituted aminomethylimidazole and aminomethylpyrrole derivatives have been studied for the treatment of disorders of the central nervous system such as schizophrenia and depression as well as certain movement disorders such as Parkinsonism. Among those compounds, 1,4-disubstituted imidazole **44** showed IC₅₀ of 0.142 μ M against dopamine D₂ and D₃ receptor binding and K_i of 0.003 μ M for the displacement of [³H]YM-09151-2 from the human dopamine D₄ receptor [83]. The corresponding studies for the preparation of this kind of 3-piperidinomethyl imidazole derivatives have been reported [84].

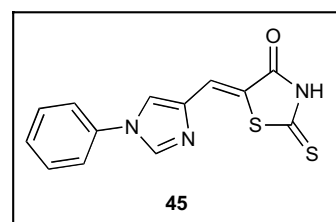


β -Lactam antibiotics such as cephalosporins and penicillins have diminished clinical effectiveness due to the hydrolytic activity of diverse β -lactamases, especially those belonging to molecular classes A and C. A structure-activity relationship study of a high-throughput screening lead resulted in the discovery of a potent and selective non- β -lactam in-

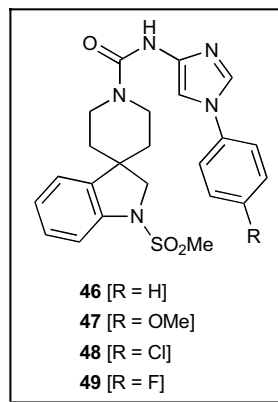
hibitor. Rhodanines represent a novel class of β -lactamase inhibitors that can be modified to show selectivity for class C β -lactamases (Scheme 3). Rhodanines differ chemically from traditional β -lactamase inhibitors such as clavulanic acid and tozobactam, but they exhibit inhibitory activity against both class A and C β -lactamases. Grant and co-workers have been reported the study of a variety of these compounds, among them compound **45** bearing a phenylimidazole moiety showed very low activity [85].



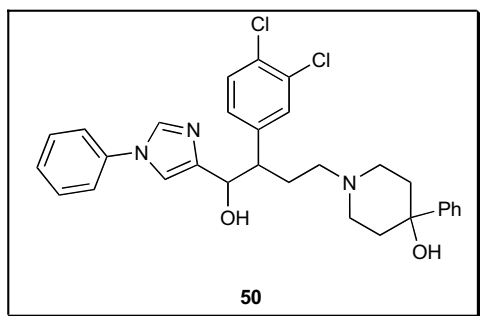
Scheme 3.



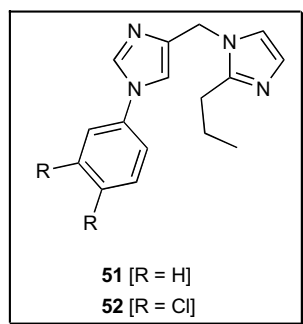
Neurons use many different chemical signals to communicate information, including neurotransmitters, peptides, cannabinoids, and even some gases like nitric oxide. A neuropeptide is any of the variety of peptides found in neural tissue (e.g. endorphins, enkephalins). About 100 different peptides are known to be released by different populations of neurons in the mammalian brain. The neuropeptide Y (NPY) is a 36 amino acid peptide neurotransmitter found not only in the brain, but also in the autonomic nervous system. NPY has been associated with a number of physiologic processes in the brain, including the regulation of energy balance, memory and learning and epilepsy. The main effects are increasing food intake and decreasing physical activity. There are six known mammalian neuropeptide Y receptors, and Y5 receptor may represent one of the postulated hypothalamic "feeding" receptors. Consequently, antagonists for this receptor could be used as treatment of obesity and the complications associated therewith, spiroindolines **46-49** having been reported for this purpose [86]. Neurokinins belonging to another family of neuropeptides, which play an important



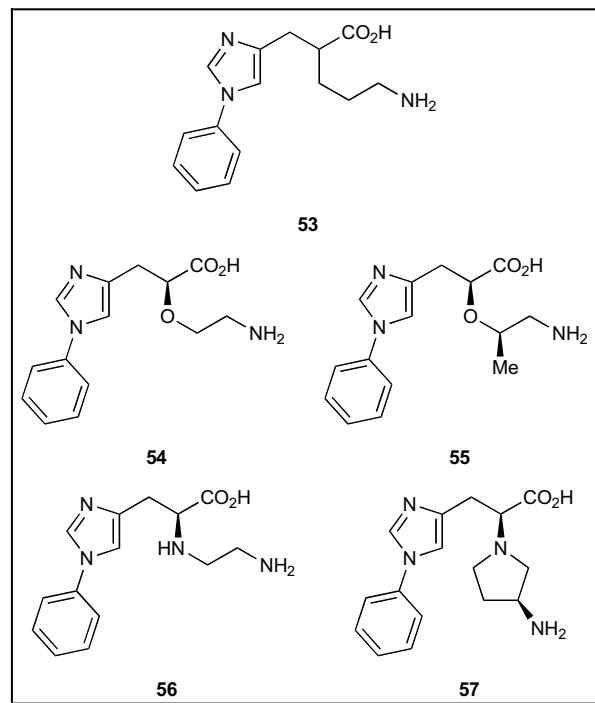
role in pain transmission, smooth muscle contraction, bronchoconstriction, activation of the immune system, and neurogenic inflammation, thus a neurokinin antagonist would be expected to have clinical potential for a variety of diseases. The 1-phenylimidazole derivative **50** has been tested as non-peptide antagonists of neurokinin A and for the treatment of asthma, showing a K_i of 34 nM in guinea pig neurokinin A receptors [87].



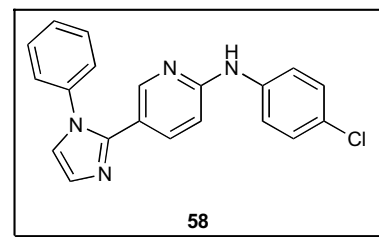
The *N*-methyl-D-aspartate (NMDA) receptor is an ionotropic one which activation of results in the opening of an ion channel that is nonselective to cations. This allows flow of Na^+ and small amounts of Ca^{2+} ions into the cell and K^+ out of the cell. Calcium flux through NMDA receptors is thought to play a critical role modulating neuronal activity and plasticity, which makes them key players in mediating processes underlying development of central nervous system as well as learning and memory formation. Different imidazole derivatives have been prepared and tested as agonist for the NMDA receptor: bisimidazoles, such as **51** and **52**, gave interesting results, the best inhibition being for compound **52** with IC_{50} of 0.007 μM in 3H-Ro-25-6981 binding test [88].



Thrombin-activatable fibrinolysis inhibitor (TAFI) is a recently described fibrinolysis inhibitor that circulates in plasma as a procarboxypeptidase and it is converted into an active form during coagulation. The physiological relevance of TAFI is not known, but it might be involved in pathways regulating fibrin deposition. Different imidazole derivatives, such as compound **53**, have been prepared and tested as TAFIa inhibitor [89]. 3-(Imidazolyl)-2-alkoxypropanoic acid derivatives, such as compounds **54** and **55**, have been demonstrated to be useful in the treatment of thrombotic conditions and other related pathologies. These compounds are potent and selective inhibitors of TAFIa with K_i values lower than 20 μM [90]. Besides, the corresponding 3-(imidazolyl)-2-aminopropanoic acids, for instance compounds **56** and **57**, have been also prepared and tested for this purpose [91].

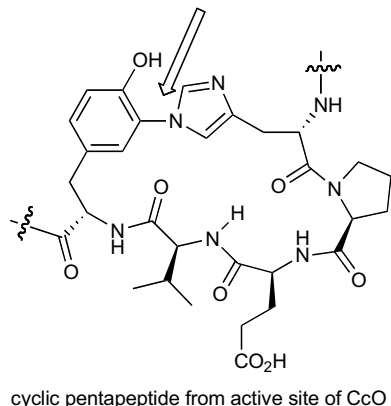


Metabotropic glutamate receptors (mGluR) are 7 transmembrane G-protein coupled receptors. There are currently 8 known mGluR subtypes divided into three groups based on their homology, pharmacology and second messenger coupling. Clinical studies suggest that mGluR5 allele frequency is associated with schizophrenia [92], and that a modest yet significant increase in mGluR5 message is found in cortical pyramidal cell layer of schizophrenic brains relative to controls [93]. Different biaryl amines have been tested as mGluR5 modulators, in order to employ them for treating disorders of the nervous system, most of those compounds having an imidazole moiety (e.g. imidazole **58**) [94].

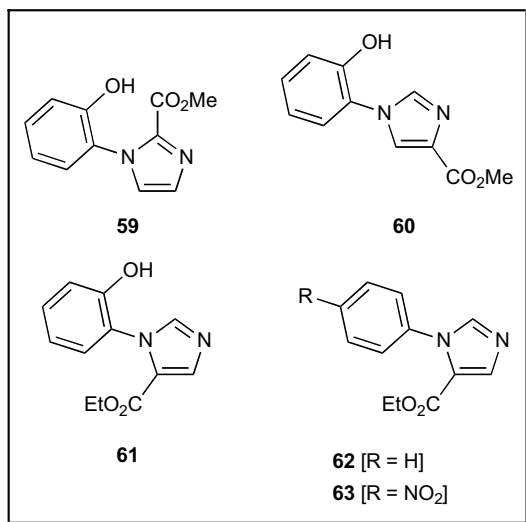


Recently, a tyrosine-histidine crosslink forming a hydroxyphenyl-imidazole covalent bond has been characterized at the active sites of both bacterial [95] and mammalian [96,97] forms of cytochrome *c* oxidase (*CcO*) by protein X-ray analyses (Scheme 4). This post-translational modification was found to be critical for maintaining the tertiary structure of *CcO*, and the phenol-functionalized imidazole that forms part of the CuB binding site is speculated to participate in the proton and electron transfer steps during the catalytic O_2 reduction. In order to decipher the key role of the crosslinked Tyr in the function of *CcO*, 1-(*o*-hydroxyphenyl)imidazole carboxylic esters **59-61** have been prepared as building blocks for the synthesis of a new generation of model compounds that incorporate a Tyr-His like structure [98]. Elliot and Konopelski have been studying the

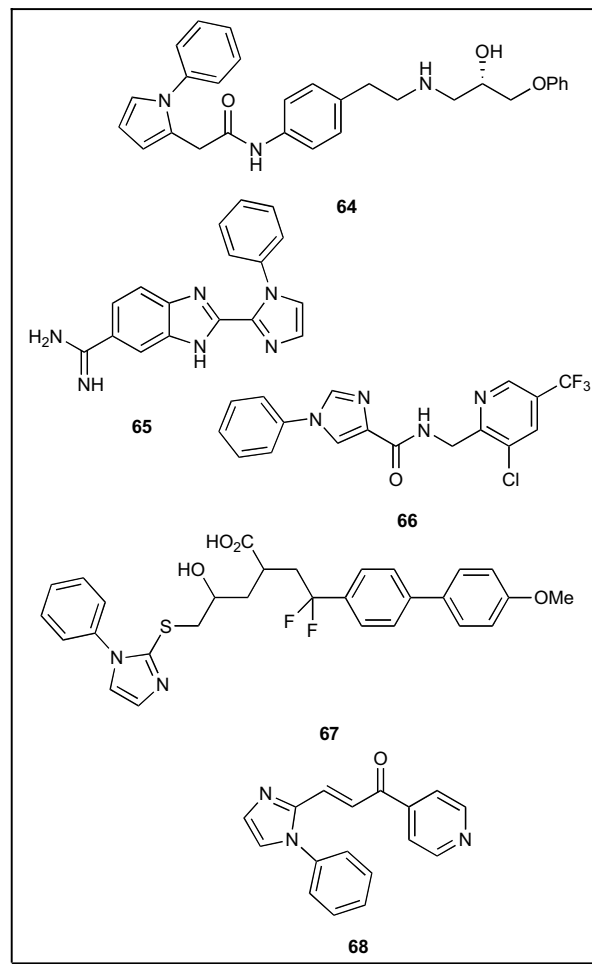
preparation of the tyrosine-histidine side chain coupled dipeptide found in the active site of CcO [99]. The reaction of anilines with ethyl glyoxylate in methanol to give α -anilino- α -methoxyacetates followed by cyclization with TosMIC has been also reported in order to prepare phenylimidazole 5-carboxylate derivatives (e.g. compounds **62** and **63**) [100].



Scheme 4.



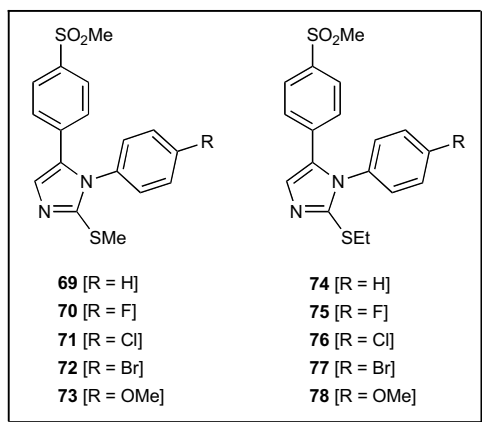
Other substituted 1-phenylimidazoles have been reported for different pharmacologic applications. Thus, compounds with an insulin secretion-promoting effect, a blood sugar-depressing effect, and a low toxicity are very interesting as useful in agents for diabetes treatment. Studies on the preparation and testing of a family of amide-containing heterocyclic compounds have been reported, the imidazole derivative **64** being one of them [101]. Amidinobenzimidazolyl heterocyclic compounds, such as compound **65**, have been prepared and tested as anticoagulants. This family of compounds showed inhibition of the Factor Xa (an enzyme of the coagulation cascade) with K_i ranging from 0.002 to 0.03 μM [102]. 1-Phenyl-4-imidazolecarboxamide **66** has been prepared and tested as fungicidal [103], and compound **67** has been reported as metalloprotease inhibitor [104]. 1-(1-Phenylimidazol-2-yl)-3-(4-pyridyl)propanone (**68**) showed an IC_{50} of 1.05 μM against synoviocyte adhesion to type II collagen [105].



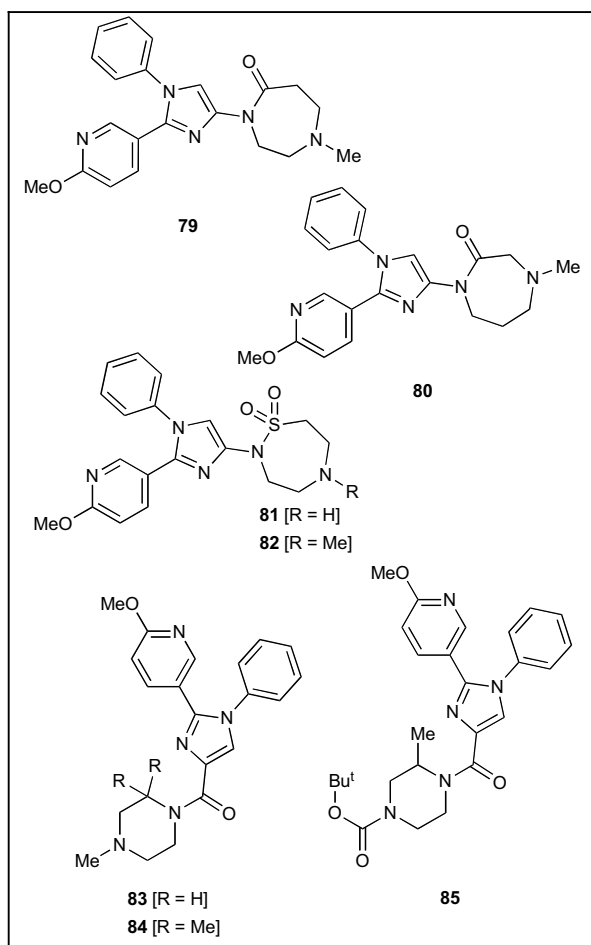
4. TWO CARBON SUBSTITUTED IMIDAZOLES

The differential tissue distribution of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) offers the possibility of the development of selective COX-2 inhibitors as anti-inflammatory and analgesic agents, reducing the gastrointestinal side effects exhibited by traditional nonsteroidal anti-inflammatory drugs which have been associated to COX-1 inhibition by long-term exposure or higher doses [106]. The series of 1,5-diarylimidazole derivatives **69-78**, bearing an alkylthio (SMe or SEt) moiety at C-2, have been prepared and evaluated as selective COX-2 inhibitors with *in vivo* anti-inflammatory activity. *In vivo* pharmacological evaluation of **69-78** was carried out to assess their potential anti-inflammatory activity. Qualitative structure-activity relationship data, acquired using the anti-inflammatory rat paw edema assay, showed that the alkylthio group at imidazole C-2 position exhibited moderate to good anti-inflammatory activity (40–91% inhibition). All the compounds showed selective inhibition for COX-2 (IC_{50} ranging from 2.61 to 0.43 μM) with no inhibition of COX-1 up to 25 μM [107]. Different trisubstituted imidazole derivatives with a halogen atom at C-2 [e.g. 2-chloro-5-(4-(methylthio)phenyl)-1-phenylimidazole] or C-4 [4-chloro-5-(4-fluorophenyl)-1-(4-(methylsulfonyl)phenyl)imidazole] have been also synthesized as selective inhibitors of COX-2, and particularly as anti-

inflammatories [108]. Additionally, De Borggraeve and co-workers have reported the preparation of different 1,5-disubstituted-4-haloimidazoles (e.g. 4-chloro-1,5-diphenylimidazole) as possible COX-2 inhibitors [109].

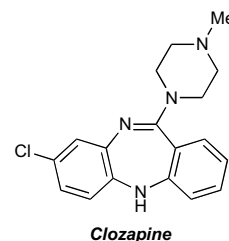


The preparation of bis-heterocyclic derivatives with a five member ring (i.e. thiazole, oxazole, pyrazole, imidazole and triazole) and a seven member ring (i.e. 1,4-oxazepan-5-one, 1,4-diazepan-1-one, and 1,4,5-oxathiazepane) have been described, 1-phenylimidazole derivatives **79-82** being among them. These compounds exhibited potent platelet aggrega-

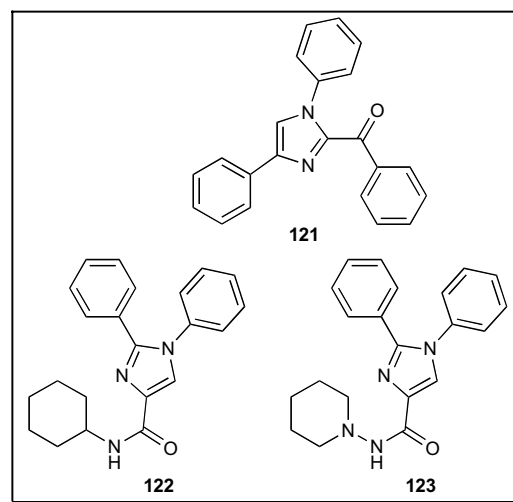
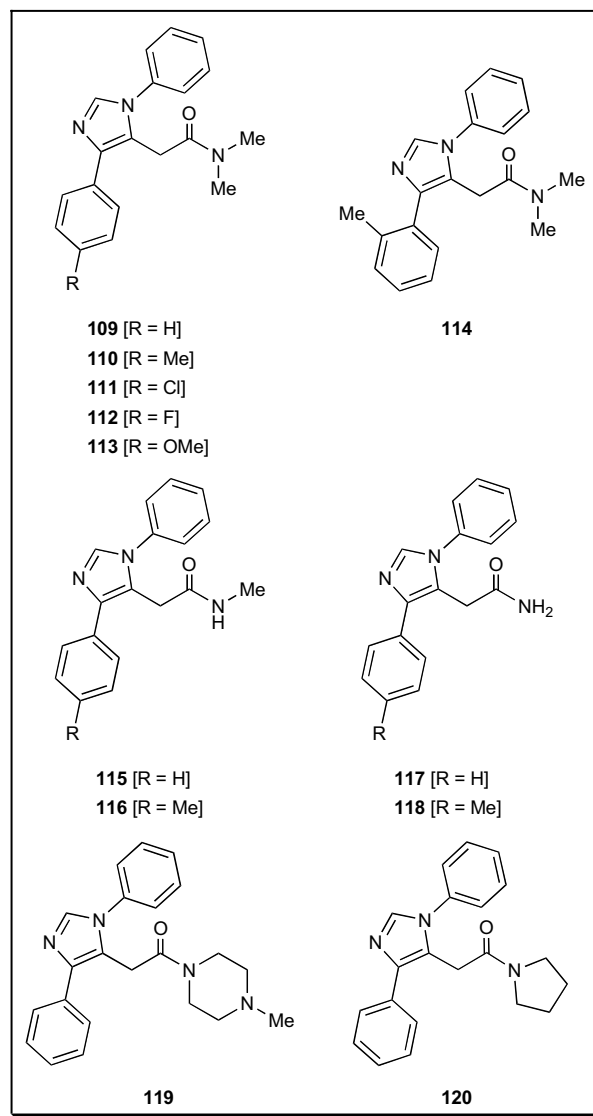
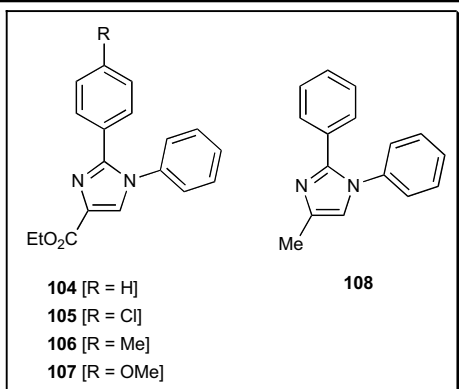
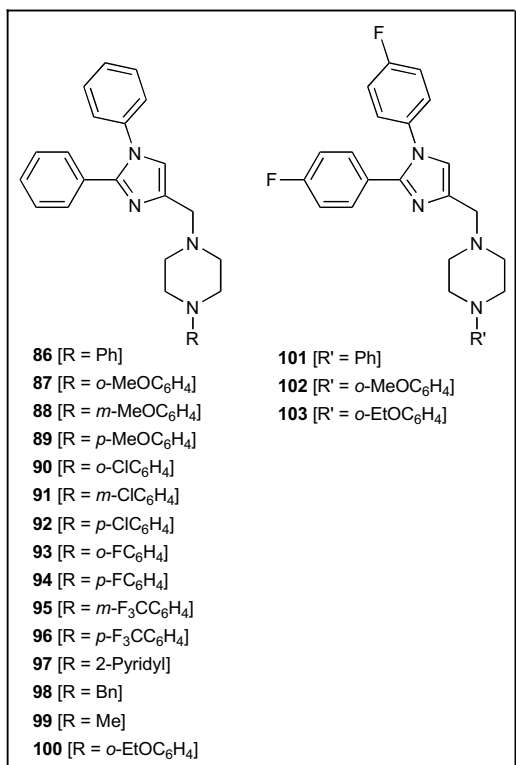


tion inhibitory-activity without inhibiting COX-1 and COX-2 and proved to be useful as preventives and/or therapeutic agents for ischemic diseases or platelet aggregation inhibitor [110]. Besides, otherazole derivatives, among them trisubstituted imidazoles **83-85**, have been described as useful for treatment of ischemia, and also as platelet aggregation inhibitors, devoid of either COX-1 or COX-2 inhibition [111].

Schizophrenia is the most common psychotic disorder, with an average worldwide incidence slightly less than 1%. Typical antipsychotic agents block the D₂ subtype of dopamine receptors in a direct relation to their clinical potency. Because the blockade of D₂ receptors by typical antipsychotics results not only in therapeutic effects but also in extrapyramidal symptoms, tardive dyskinesia, and hyperprolactinemia, which strongly limit patient compliance, the development of drugs lacking such side effects should greatly improve the clinical efficacy and tolerability of the pharmacological treatment of schizophrenia. Clozapine is the prototype of a group of "atypical" antipsychotic drugs exhibiting clinical efficacy similar to that of the classical antipsychotics but lacking (or inducing to lesser extent) most of their motor side effects (Scheme 5). These "atypical" drugs bind with moderate affinity D₂ receptors but interact also with other dopaminergic, serotonergic, adrenergic, histaminergic, GABAergic, and muscarinic receptors. This mixed action at dopamine and serotonin receptors has been suggested to contribute to their anticataleptic properties [112]. A series of 1-[(1,2-diphenyl-4-imidazolyl)methyl]-4-piperazines (**86-103**) have been synthesized as a new class of compounds with mixed dopamine (D₂) and serotonin (5-HT_{1A} and 5-HT_{2A}) affinity, looking for novel active substances with similar neurochemical and pharmacological properties than clozapine. Piperazine **87** exhibited high affinity for both type of receptors. The results of *in vitro* and *in vivo* studies demonstrated that imidazole derivative **87** behaved pharmacologically as the prototype of "atypical" antipsychotic drugs (i.e. clozapine). Furthermore, trisubstituted imidazole **87** was found to inhibit GABA-evoked Cl⁻ currents in *Xenopus laevis* oocytes expressing recombinant human GABA_A receptors composed of α 1, β 2, and γ 2L subunits in a concentration-dependent manner (0.1–300 μ M) [113]. Another series of 1,2-diphenyl-5-substituted imidazole derivatives, such as compounds **104-108**, have been synthesized and evaluated for their ability to enhance GABA-evoked currents in those GABA_A receptors. Many of these compounds improved GABA action with potencies (EC₅₀ = 0.19–19 μ M) and efficacies (maximal efficacies of up to 640%) similar to or greater than those of anesthetics such as etomidate, propofol, or alphaxalone [114]. Imidazoleacetamides **109-120** have been also prepared to be used as GABA_A agonists in treatment of disorders in GABAergic transmission associated with α 1, α 2, and α 3 subtypes [115].



Scheme 5.

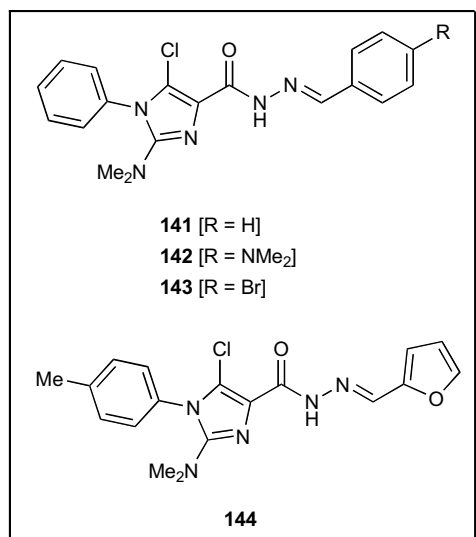


Nitrogen containing 5-membered heterocycle derivatives with an acyl moiety [e.g. (1,4-diphenyl-2-imidazolyl)phenylmethanone (**121**)] have been synthesized as possible kainic acid neurocytotoxicity inhibitors. These compounds also proved to be noncompetitive antagonists against AMPA [2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid] receptor and to be useful as nerve cell protectants or therapeutics for epilepsy [116].

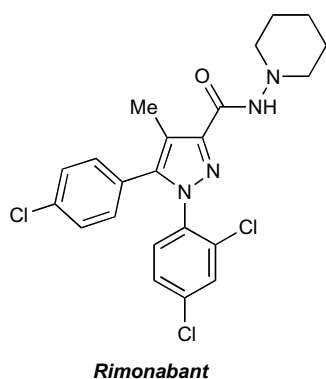
Imidazole derivatives with a carboxamide moiety at C-4 have shown a variety of pharmaceutical applications. Thus, different 1,2-diarylimidazole-4-carboxamide derivatives (e.g. imidazole **122**) have been described of use in promoting smoking cessation and maintaining abstinence. The preparation of pharmaceutical compounds comprising these imidazole derivatives in combination with one or more nicotine replacement therapies, or one nicotinic receptor modulators, have been reported [117]. The methodology for the synthesis of similar imidazole-4-carboxamides (e.g. imidazole **123**), and the corresponding studies for using them to induce

weight loss, and treating obesity and/or disorders related to obesity have been also reported [118]. Furthermore, another

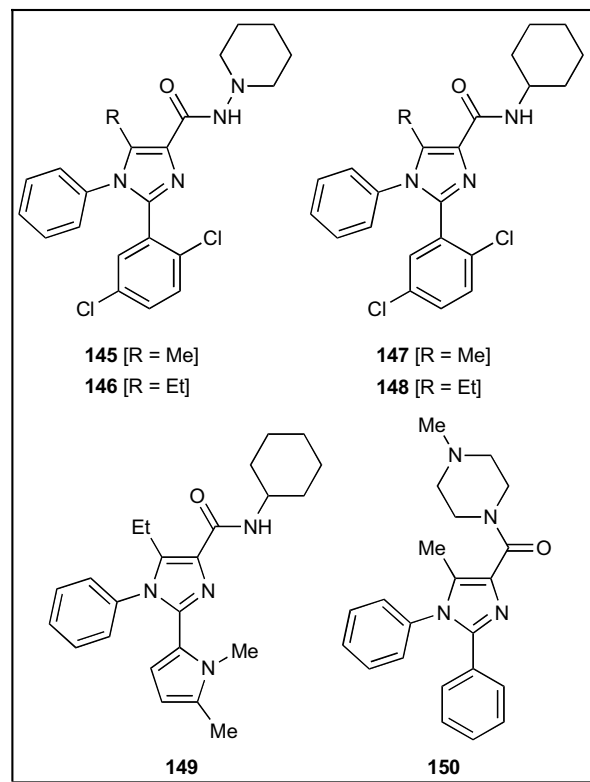
tion [125]. The 2-furyl derivative **144** was identified as the most attractive one, with the best antinociceptive profile, and presented an attracting anti-inflammatory behavior [126].



Different series of azole derivatives (i.e. thiazoles, triazoles, and imidazoles) have been designed as bioisosteres, based on the 1,5-diarylpyrazole motif that is present in the potent CB₁ receptor antagonist rimonabant (SR141716A) (Scheme 6). These classes of heterocycles exhibited, in general, high CB₁ versus CB₂ receptor subtype selectivities. A structure activity relationship study showed a close correlation between the biological results in both the imidazole and pyrazole series [127]. Thus, the imidazole-4-carboxamide derivatives **145-149** have been synthesized as possible cannabinoid CB₁ ligands, and their use for diseases involving cannabinoid neurotransmission has been studied [128]. This series of compounds have been tested as psychotropic drugs in the treatment of psychosis, memory deficits, cognitive disorders, migraine, neuropathy, neuroinflammatory disorders (such as, multiple sclerosis and Guillain-Barre syndrome), and the inflammatory sequelae of viral encephalitis, cerebral vascular accidents, and head trauma [129]. Moreover, similar azole derivatives, such as compound **150**, have been reported as useful for the treatment of ischemia, and also as platelet aggregation inhibitors, devoid of either COX-1 or COX-2 inhibition [111].

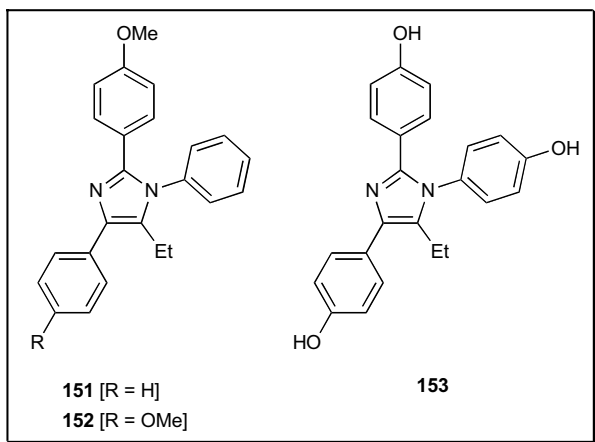


Scheme 6.

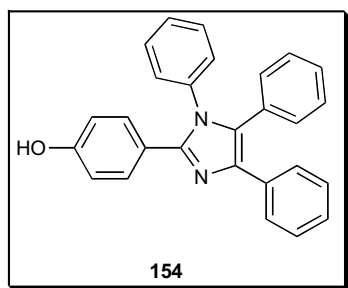


Neurodegenerative diseases such as stroke, Parkinson's and Alzheimer's diseases result from the loss of neurons and are prevalent throughout the world. An attractive approach for the generation of neurons is the use of small molecules that induce the neuronal differentiation of easily available cells or tissues. In this line of research, an imidazole based library of compounds (about 300 imidazole derivatives) with diverse substituents at the different positions has been prepared using solid support techniques. These molecules were tested for inducing neurogenesis of non-pluripotent myoblasts and the cells derived from mature, human skeletal muscle, but only few of them were active [130].

The estrogen receptor is an important transcription factor that regulates physiological processes, which are involved, for example, in the development and function of the reproductive and cardiovascular systems or in the bone density changes [131]. Non-steroidal estrogenic and antiestrogenic ligands have been developed in order to regulate these processes or their pathological dysfunction, including breast cancer, osteoporosis, and infertility. It has been demonstrated in various structure-activity relationship studies that aromatic and non-aromatic heterocycles can act as potent selective estrogen receptor modulators [132-135]. A series of C-5-substituted 1,2,4-triarylimidazoles has been synthesized (such as, compounds **151-153**) and their gene-activating properties have been determined on estrogen receptor alpha positive MCF-7 breast cancer cells, alkyl or aryl substituent at C-5 increasing the transactivation. 5-Ethyl-1,2,4-tris(4-hydroxyphenyl)imidazole (**153**) was revealed as the most active compound, its excellent transcriptional activity being not only depending on the C-5 ethyl substituent, but also on the three hydroxyl groups at the phenyl rings [136].

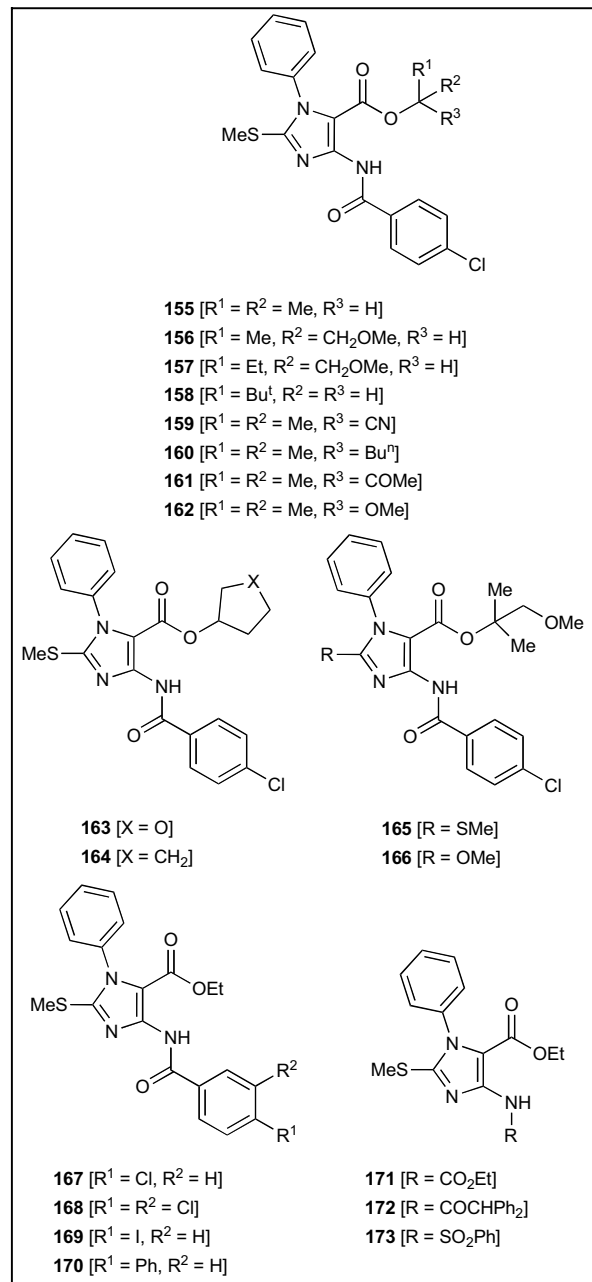


Protein tyrosine phosphatases (PTPs) represent a large family of enzymes that play a very important role in cellular signaling within and between cells. Actually, protein tyrosine phosphatase-1B (PTP1B) is a highly validated molecular target, which mediates insulin resistance in mammals. PTP1B dephosphorylates the insulin receptor, and consequently slows its ability to transduce signal upon insulin binding. Thus, inhibitors of PTP1B are expected to restore activity to the insulin receptor, being of therapeutic benefit in the treatment of diabetes. Different tetrasubstituted 1-phenylimidazole derivatives have been prepared with this therapeutic aim, and showed IC_{50} values ranging from 0.072 μ M to 31 μ M against PTP1B [137]. Those imidazole derivatives have been also proved as useful compounds for the treatment of cancer through sensitization of multi-drug resistant cancer cells to chemotherapeutic agents [138], for example, tetraarylimidazole **154** showed EC_{50} of 20 μ M in accumulation of 3H-vinblastine in CEM/VLM 1000 cells [139].



Gastroesophageal reflux disease (GERD) is the most prevalent upper gastrointestinal tract disease, and current pharmacotherapy aims to reduce gastric acid secretion, or to neutralize acid in the esophagus. Although, the major mechanism behind reflux has been considered to depend on a hypotonic lower esophageal sphincter, recent research has shown that most reflux episodes occur during transient lower esophageal sphincter relaxations (TLESR), i.e. relaxations not triggered by swallows [140]. Consequently, there is a need for a therapy that reduces the incidence of TLESR and thereby prevents reflux, and GABA_B-receptor agonists have been proved to inhibit TLESR. The preparation of a variety of imidazole derivatives, with a 2-methylthio or 2-methoxy substituent like compounds **155-173** [141] or with a 2-dimethylamino moiety like compounds **174-185** [142], have

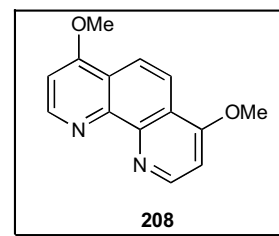
been reported, as well as their possible allosteric GABA_B receptor modulator effect. These compounds, in combination with a GABA_B agonists or not, showed to be useful for the inhibition of TLESR, for the treatment of GERD, as well as for the treatment of functional gastrointestinal disorders and irritable bowel syndrome [143].



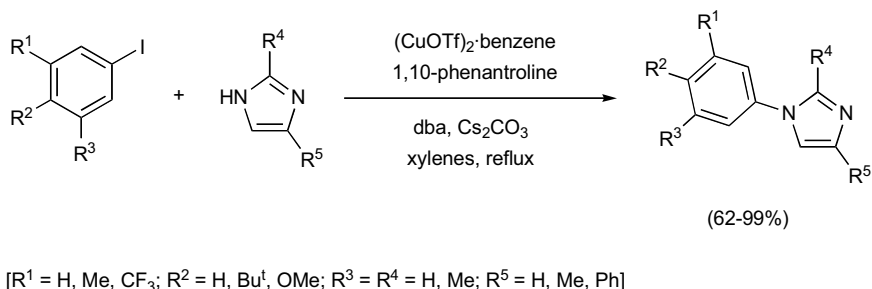
Octimibate (**186**), which is a non-prostanoid prostacyclin mimetic, has a potent inhibitory activity of human platelet aggregation (IC_{50} = 10 nM) and appears to act, at least in part, through activation of the prostacyclin (PGI₂) receptor [144]. The effects of three non-prostanoid prostacyclin mimetics (i.e. octimibate, BMY 42393 and BMY 45778) on rat peritoneal neutrophil activity have been studied, showing low efficacy as activators of adenylyl cyclase [145]. Non-prostanoid prostacyclin mimetics have proved to inhibit both

N-Arylation of imidazoles, and in general of any nitrogen containing compound, is an important and interesting route for preparation of a variety of biological, and pharmaceutical products. In recent years, copper catalyzed *N*-arylation of imidazole derivatives, and other nitrogen-containing heterocycles, with aryl halides promoted by different ligands has attracted much attention due to its economy and efficiency. Buchwald and co-workers have reported the copper catalyzed arylation of different imidazoles, employing mainly aryl iodides and using the complex (CuOTf)₂-benzene as a copper source and Cs₂CO₃ as a base. The corresponding *N*-aryl imidazoles were isolated in good yields ranging from 62 to 99% (Scheme 7) [154]. The use of a catalytic amount of copper iodide in the presence of a diamine (i.e. *trans*-cyclohexane-1,2-diamine, *trans*-*N,N'*-dimethylcyclohexane-1,2-diamine, 1,10-phenanthroline, *N,N'*-dimethylethylenediamine) [155], or an amino acid (i.e. proline, pipecolic acid [156], histidine [157]) as ligand, and a base (i.e. Cs₂CO₃, K₂CO₃) gave also good results in the arylation of different azoles. Hosseinzadeh and co-workers have reported the use of KF/Al₂O₃ as a base following the CuI/1,10-phenanthroline protocol for coupling imidazole with aryl iodides [158] and aryl bromides [159]. More recently, Buchwald's research group has developed a new improvement in the arylation of imidazoles employing a new ligand [i.e. electron-rich 4,7-dimethoxy-1,10-phenanthroline (**208**)] which permitted to use air stable Cu₂O as copper source [160]. This new catalytic system has made the reaction more general due to the use of very mild conditions, thus both aryl iodides and bromides with a variety of functional groups have been employed (Scheme 8) [161]. Copper chloride in combination with β-diketones, as ligands, has been reported for the amination of aryl bromides. The concentration of the substrates (5 M in NMP) proved to be crucial for the rate and selectivity of the coupling reaction, and K₂CO₃ could be used as base instead of Cs₂CO₃. Under these conditions, imidazole and bromobenzene gave 1-PI quantitatively [162,163]. Additionally, β-keto esters, such as

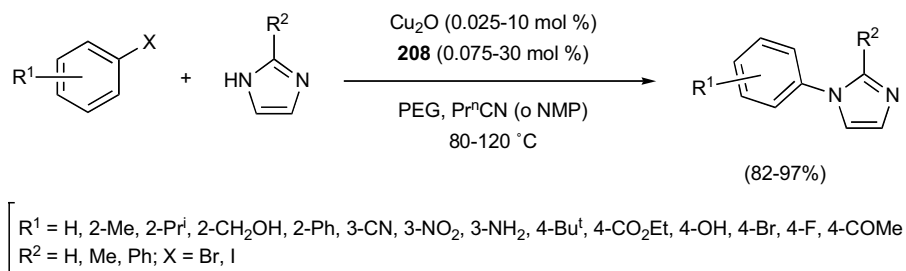
ethyl 2-oxocyclohexanecarboxylate, have been described as efficient ligands for the copper-catalyzed *N*-arylation reactions [164]. Benzotriazole has been also described as capable ligand for the copper-catalyzed *N*-arylation of imidazoles [165].



Catalysts generated from catalytic copper(I) oxide or iodide and a catalytic amount of a multidentate donor ligand, which combined oxygen- and/or nitrogen-binding sites, such as potentially bidentate oxime ligand Salox (**209**), hydrazone ligand **210**, potentially tetradentate Schiff base ligand **211** [166], or oxime-phosphine oxide **212** [167] allowed the high-yielding coupling of a variety of aryl iodides and bromides with a number of azoles in the presence of the mild base cesium carbonate. Furthermore, aminoarenethiolate-copper(I) complexes **213-218** have been also described as efficient catalysts for carbon-nitrogen bond formation reactions. Catalyst **214** gave the best results both employing NMP as solvent or under neat conditions for the coupling of bromobenzene and imidazole (Scheme 9) [168]. (*S*)-Pyrrolinylmethylimidazole **219** has been prepared and showed a highly efficiency as ligand for the copper-catalyzed *N*-arylation of imidazoles with aryl halides. This system was successful for aryl bromides, and to a less extent, for aryl chlorides [169]. The employ of iron [Fe(acac)₃] as co-catalyst for copper (CuO) has been described for *N*-arylation of various nitrogen-containing heterocycles with different substituted aryl halides. This novel bimetallic system allowed performing the coupling reaction under mild

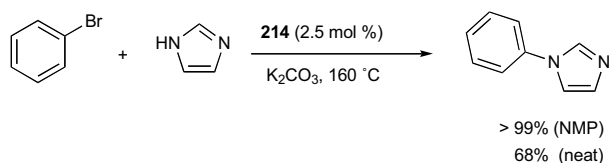
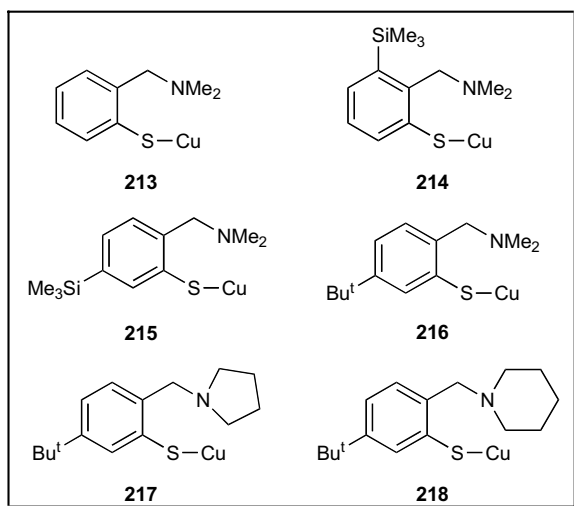
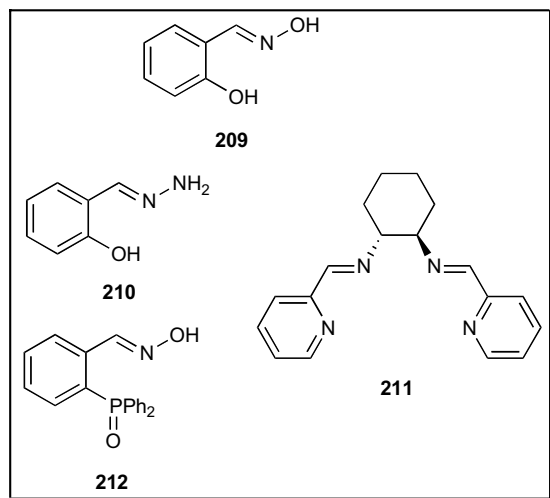


Scheme 7.

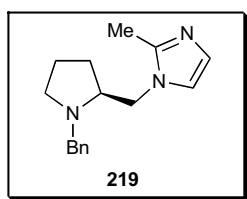


Scheme 8.

conditions (DMF, 100 °C, Cs₂CO₃). Hence, phenyl iodide and imidazole coupled with 90% yield [170].



Scheme 9.



The *N*-arylation of imidazole derivatives has been also achieved by using heterogeneous catalysts, such as copper-exchanged fluorapatite and copper-exchanged *tert*-butoxyapatite. Good yields were obtained of the corresponding coupling product performing the reaction with aryl

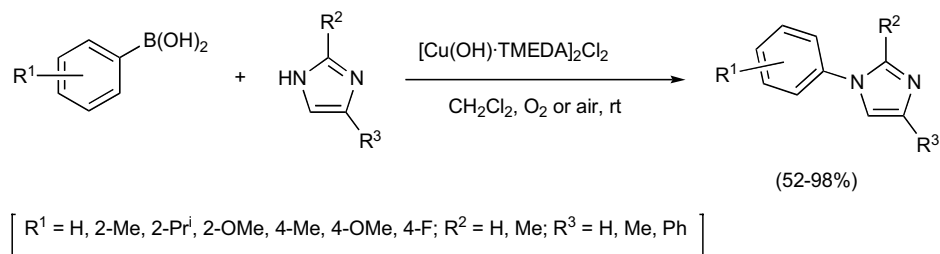
bromides and iodides (i.e. phenyl, 4-methylphenyl, 4-acetylphenyl, 4-nitrophenyl derivatives gave a range of 85-95% yield) [171], and for the corresponding aryl chlorides and fluorides with electron withdrawing (EW) groups (82-95%), whereas moderate yields (52-60%) were achieved with chloroarenes bearing electron donating (ED) groups [172]. Furthermore, Cu(II)-modified alkali exchanged zeolites Y have been used as catalyst for the coupling reaction between imidazole and an assortment of *para*-substituted phenyl chlorides, bromides, and iodides. This methodology was appropriate with chloroarenes containing EW groups (i.e. NO₂, CN, CF₃, COMe), and bromo- and iodoarenes containing EW and ED groups (i.e. COMe, Me, OMe, Cl), affording the corresponding imidazole derivative with yields from 85 to 99% [173]. Cellulose supported copper(0) catalyst has been prepared and employed for the K₂CO₃-mediated arylation reaction of imidazole with iodo-, bromo- and chlorobenzenes [174]. Besides, air stable CuO nanoparticles has been described as useful catalyst for the *N*-arylation with iodobenzene [175].

Arylboronic acids have been used for the coupling reaction with imidazole derivatives. Collman and co-workers have been reported the use of 10 mol% of the complex [Cu(OH)·TMEDA]₂Cl₂ as catalyst in the absence of base in dichloromethane (Scheme 10) [176], in water [177], or in a mixture of NMP/water [178]. Although, other diamines have been tested as chelating bidentate ligands for copper, no one gave better results than TMEDA [179]. *N*-Arylimidazole derivatives have been also prepared from the corresponding arylboronic acids in a methanol/water mixture with excellent yields (92-98%), by a catalyzed reaction using a simple copper salt [i.e. CuCl, CuBr, CuI, CuClO₄, CuCl₂·2H₂O, Cu(OAc)₂·2H₂O, Cu(NO₃)₂·3H₂O], and neither a ligand nor a base were needed [180]. Ionic liquids, such as [bmim][BF₄], together with Cu(OAc)₂·2H₂O (10 mol%) catalyzed the coupling reaction between imidazoles and boronic acids [181]. In addition, heterogeneous basic copper fluorapatite [182] and cellulose supported copper(0) [174] have been used for the arylation reaction with boronic acids.

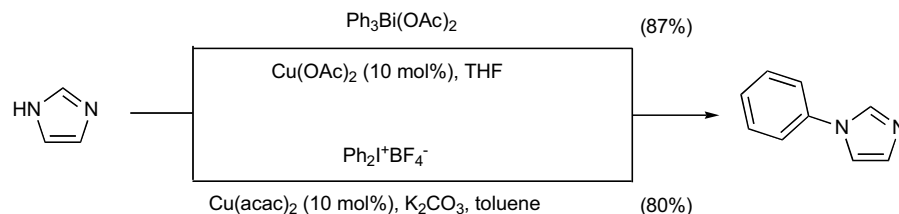
Concerning other arylating agents, triphenylbismuth diacetate [183], hypervalent iodonium compounds (Scheme 11) [184], and *o*-silylaryl triflates in the presence of CsF [185] have been considered in the copper catalyzed arylation reaction of imidazole.

The preparation of 2-functionalized 1-phenylimidazole derivatives has been achieved by selective formation of 2-lithio-1-phenylimidazole. The lithiation process was performed with an excess of lithium powder and the presence of isoprene in THF at room temperature, and the lithiated intermediate was reacted with different electrophiles affording the corresponding functionalized imidazoles with good isolated yields (Scheme 12) [186]. Hlasta and Deng have reported the preparation of 2-substituted imidazoles by reaction of imidazolium ylide with reactive carbonyl compounds in solution (Scheme 13) [187], and solid-phase [188].

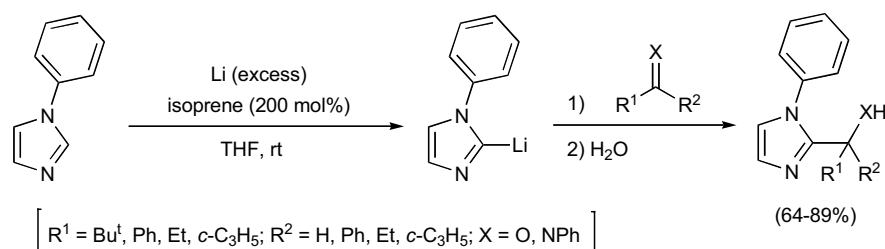
Regarding the imidazole ring formation from acyclic precursors, there are few synthesis starting from isocyanide derivatives. Thus, ethyl 1-phenyl-4-imidazolecarboxylate has been obtained starting from readily available ethyl 3-(*N,N*-dimethylamino)-2-isocyanoacrylate in combination with aniline (Scheme 14) [189]. The base induced cycloaddition



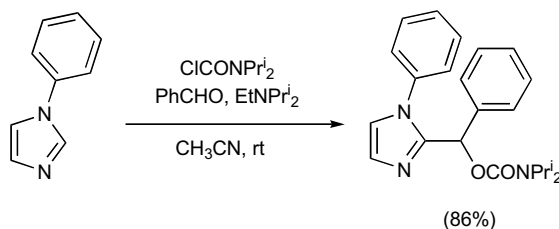
Scheme 10.



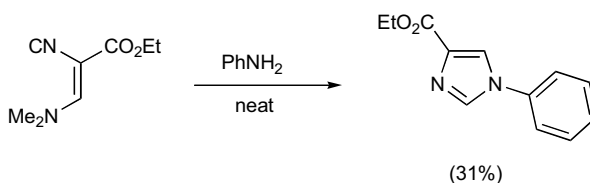
Scheme 11.



Scheme 12.



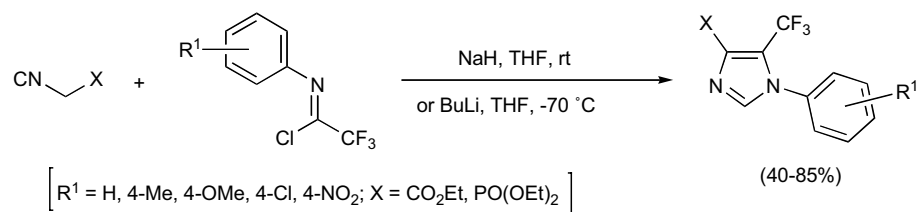
Scheme 13.



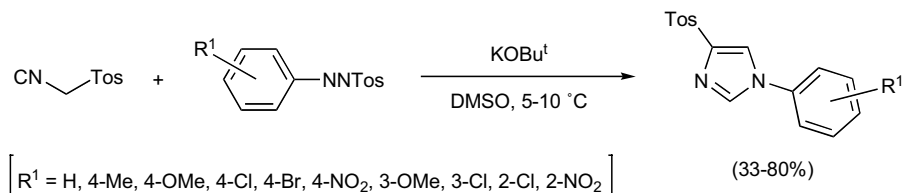
Scheme 14.

of ethyl isocyanoacetate [190], or diethyl isocyanomethylphosphonate [191] to trifluoroacetimidoyl chlorides has been described, producing the corresponding 1-substituted imidazoles (Scheme 15). Additionally in the presence of a base, arylazosulfones have been reacted with tosylmethylisocyanide (TosMIC) to prepare the corresponding 1-arylimidazoles (Scheme 16) [192]. The reaction between arylamines, chloramine T, and 2,2-diethoxy-1-isocyanoethane has been reported to give *N*-tosylguanidine derivatives which underwent

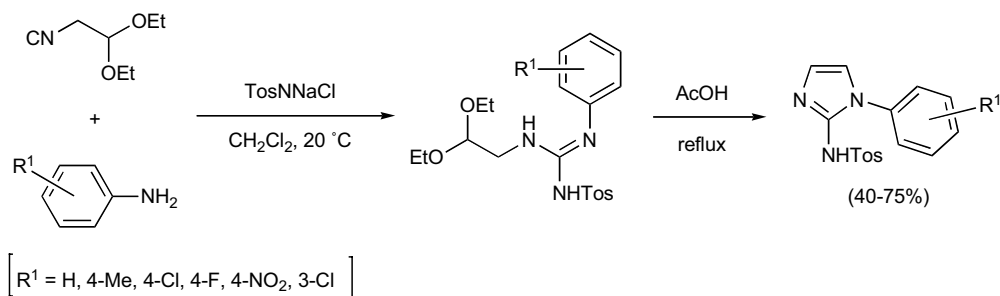
cyclization to the corresponding 1-aryl-2-(tosylamino) imidazoles (Scheme 17) [193]. Yamamoto and co-workers have prepared 1-aryl-4-substituted imidazoles via a cross-cycloaddition between two different isocyanides, performing the reaction in the presence of copper oxide and 1,10-phenanthroline (Scheme 18) [194]. Tetrasubstituted imidazoles have been prepared from isocyanides, arylglyoxals, primary amines and carboxylic acids on Wang resin [195].



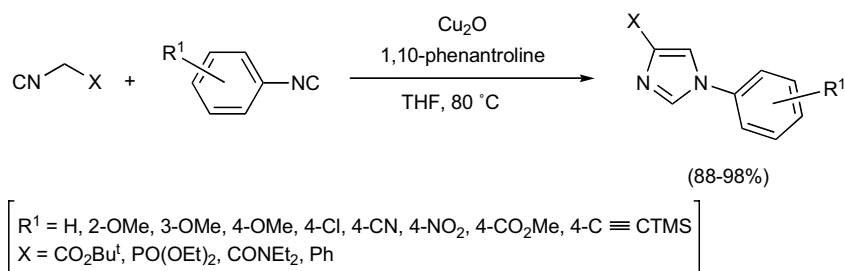
Scheme 15.



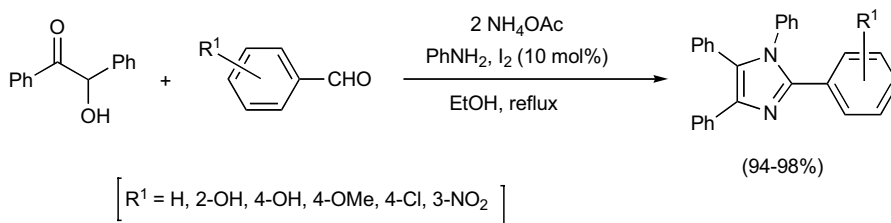
Scheme 16.



Scheme 17.



Scheme 18.



Scheme 19.

The four-component (i.e. benzoin, aniline, ammonium acetate and an aromatic aldehyde) synthesis of tetrasubstituted imidazoles have been described in the presence of catalytic iodine (Scheme 19) [196]. Different anilines have been reacted with glyoxal, formaldehyde and ammonium chloride in order to obtain the corresponding 1-aryl substituted imida-

zoles [197]. The Wang resin has been used for the preparation, on solid phase under acidic conditions, of *N*-aryl imidazole derivatives starting also from four components [198].

Finally, other heterocycles can be transformed into the corresponding imidazoles. Thus, 1-substituted imidazole-2-thiones (classically prepared by acylation of an α -amino ke-

tone or an 2-amino acetal with a thiocyanate followed by cyclization of the intermediate) undergo oxidative desulfurization with acidic hydrogen peroxide [199], MCPBA [200], dimethyldioxirane [201], and benzoyl peroxide [202] providing the corresponding imidazole derivatives. In addition, reductive desulfurization of imidazole-2-thiones to imidazoles is normally achieved using Raney nickel [203].

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