Imidazole and Benzimidazole Derivatives as Chemotherapeutic Agents

Mariana Boiani and Mercedes González*

Departamento de Química Orgánica, Facultad de Ciencias-Facultad de Química, Universidad de la República, Iguá 4225, CP 11400, Montevideo, Uruguay

Abstract: Imidazole and benzimidazole systems are presented in a large number of common therapeutics agents. They were widely used in organic and medicinal chemistry, but recently the development of *N*-oxide derivatives got an improvement from the point of view of its chemical and biological activity.

Though we will review recent developments in chemical and biological profiles (as antitumoral, antiparasitic, antiviral and antimicrobial agents) of these heterocycle systems and the corresponding *N*-oxides.

1- INTRODUCTION

Imidazole and benzimidazole nucleus (**I** and **II** respectively, Fig. (**1**)) are important pharmacophore in drug discovery [1]. Since they are commonly encountered in drugs that display diversity of pharmacological activities such as anti-inflammatory [2], histamine-H3 antagonist [3], antioxidant [4], gastroprotective [5], antitumoral and antiparasitic. The biological relevance of these kind of heteroaromatic groups is because they are good bioisosters of biomolecules. It is well-known that cysteinyl moiety share common properties with imidazole functionalities [6] as was recently reported farnesyl protein transferase inhibitors were developed taking in advantage this characteristic [7]. Also, it is described that benzimidazole are used as biomimetics of guanine residues, as is reported for analogs of *L*-valacyclovir, an orally active prodrug of the antiviral drug acyclovir [8]. Another bioisoster property was used when it is changed a butylamide moiety by an imidazole in order to enhance chemical stability [9]. Imidazole rings are widely employed as spin trapping species, a fact that transform them in an interesting feature in the design of drugs with neuroprotective activity [10]. Little attention has been taken in the *N*-oxide derivatives of imidazole and benzimidazole regarding its bio-activity, but they have been well studied from a chemical point of view.

In this review we are briefly presenting the newest and interesting synthesis description of imidazole, benzimidazole, and their *N*-oxide derivatives as well as, the biological characterization regarding only their antimicrobial, antifungal, antiviral, antiprotozoal and antitumoral activities.

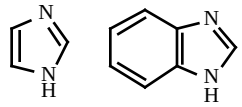
2- SYNTHESIS

2.1- Imidazole and Imidazole *N*-Oxide

Imidazole and imidazole *N*-oxide derivatives synthesis have been extensively reviewed [11,12]. There is a variety of methods to obtain imidazole derivatives but few have a general application. Herein, new strategies towards the synthesis of highly functionalized imidazole derivatives and the improvement on reaction yields are presented.

*Address correspondence to this author at the Departamento de Química Orgánica, Facultad de Ciencias-Facultad de Química, Universidad de la República, Iguá 4225, CP 11400, Montevideo, Uruguay; Tel: +598-2-5258618; Fax: +598-2-5250749; E-mail: megonzal@fq.edu.uy

Recently, a process for the preparation of multikilogram quantities of 2,4-disubstituted imidazoles has been developed [13]. These compounds were obtained in high yield from condensation of amidines and α-haloketones. From a medicinal chemistry point of view it is also important to obtain imidazoles with diverse functionalities as quickly as possible. Subsequently, techniques such as solid-phase synthesis [14, 15, 16] (Scheme 1), one-pot synthesis [17] and microwave-assisted chemistry [18] have been successfully applied to the synthesis of the imidazole system.



I **II**

Fig. (1). Imidazole and benzimidazole general structures.

Imidazole *N*-oxide derivatives cannot be obtained in practicable yields by direct *N*-oxidation and are generally prepared by cyclization of 1,2-dicarbonyl monooximes with aldimines or aldoximes. But these reactions are limited to the synthesis of poly or per-substituted derivatives. Other option is the reaction of 1,2-diimines with aldoximes, which lead to various 3-substituted derivatives [19]. Although yields are low they can be improved in solvent-free conditions [20]. Regioselective functionalization of imidazole at position 2, 4 and 5 has been possible through a directed lithiation and metal-halogen exchange methodology [21,22]. Remarkably, imidazole *N*-oxides are useful intermediates in the synthesis of structurally diverse imidazoles [23, 24] (Scheme 2).

2.2- Benzimidazole and Benzimidazole *N*-Oxide

The synthesis of the benzimidazole nucleus has been reviewed recently [11]. Here we mentioned on new developments in the areas of solid-phase, parallel, and regioselective synthesis.

An important number of solid-phase synthesis of benzimidazoles has been reported and in most cases *o*-fluoronitrobenzene derivatives attached to a polymer are used as the starting material [25-32]. This approach does not allow much substituent diversity on the benzene ring. To overcome this it has been reported that the synthesis of

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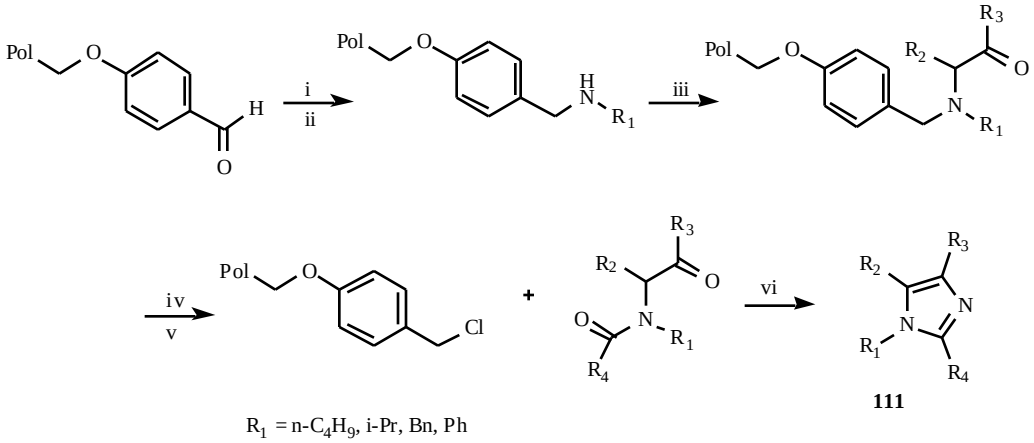


Scheme 1. Imidazole derivatives solid-phase synthesis.

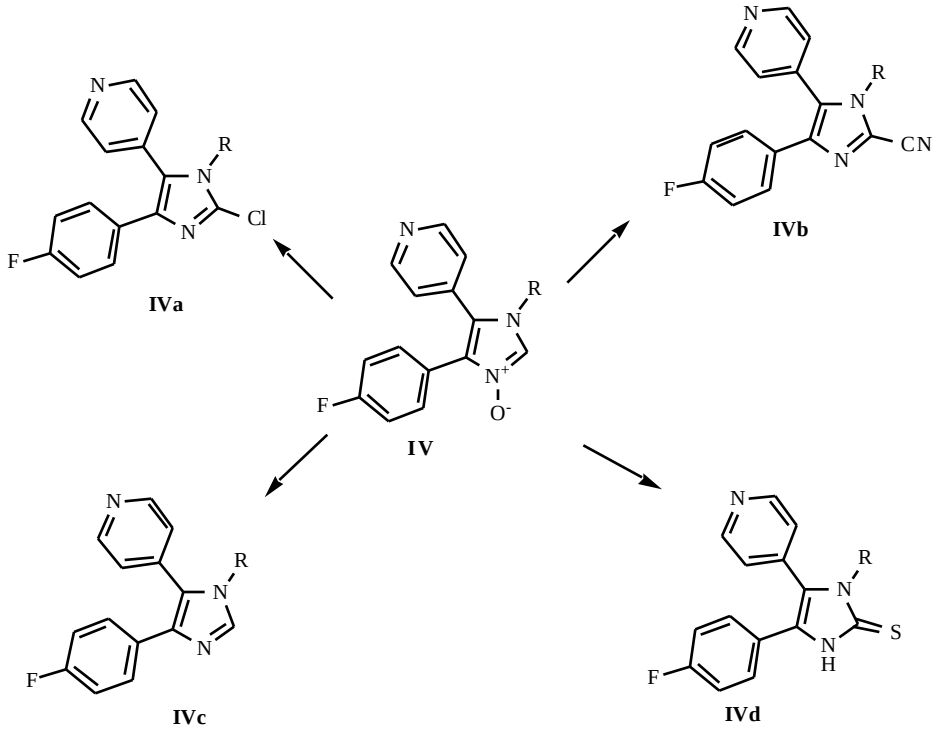
Notes Scheme 1. a. Reagents: (i) R_1NH_2, THF/TMOF; (ii) $LiBH_4$ (iii) α-haloketone, DIPEA, DMF; (iv) R_4COCl, NMM, DMF; (v) aminomethylpolystirene, DCM, (vi) NH_4OAc, AcOH, residual DMF.

benzimidazole libraries with peptoid side chain [33] (Scheme 3).

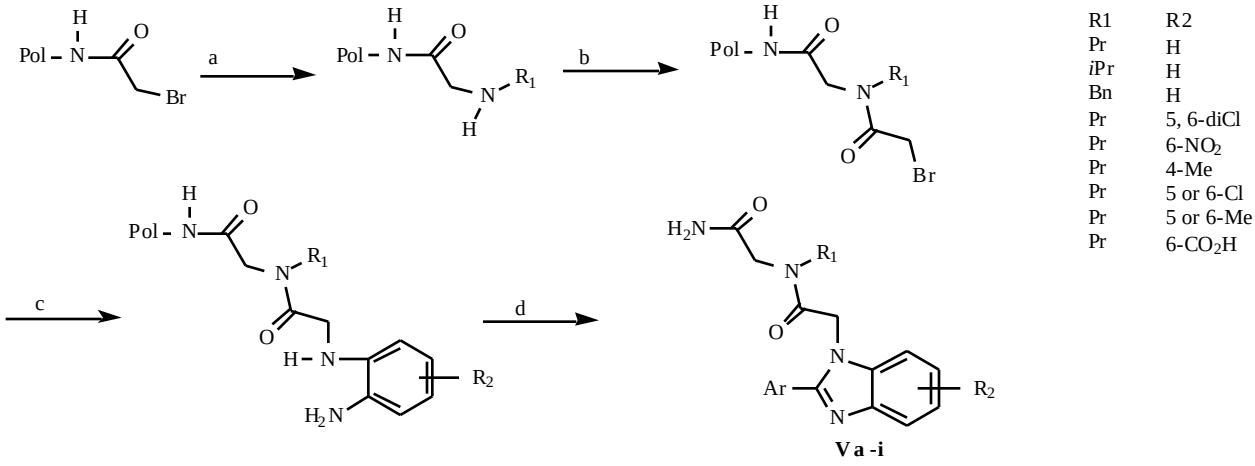
As an alternative to solid-phase combinatorial synthesis a liquid-phase analog has emerged as a powerful tool in drug discovery [34, 35] (Scheme 4). Microwave-assisted liquid-phase combinatorial synthesis of benzimidazole has also been described [36] as for example one-pot cyclization to 2-arylbenzimidazoles.

A limitation with the majority of benzimidazole synthesis is that *N*-substitution is generally non-regioselective. Recently, an intramolecular palladium-catalyzed aryl amination protocol was used to obtain regioselective *N*-substitution [37]. Also, palladium-catalyzed synthesis has been used to obtain chiral benzimidazoles (Scheme 5) [38].

Benzimidazole *N*-oxide presents a very interesting chemistry as it cannot be obtained by direct *N*-oxidation of benzimidazole, so reviews covering its synthesis and reactivity are found [11, 39, 40]. The traditional synthesis implies partial reduction of *o*-nitroanilides by catalytic



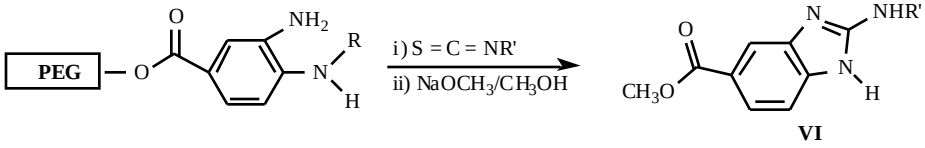
Scheme 2. Imidazole *N*-oxides as intermediates in the synthesis of imidazoles.



R1	R2
Pr	H
*i*Pr	H
Bn	H
Pr	5, 6-diCl
Pr	6-NO_2
Pr	4-Me
Pr	5 or 6-Cl
Pr	5 or 6-Me
Pr	6-CO_2H

Scheme 3. Solid-phase synthesis of benzimidazoles with peptoid side chain.

Notes Scheme 3. a. Reagents: (a) R_1NH_2, DMSO; (b) bromoacetic acid, CDI, DMF; (c) o-phenylenediamines, DMSO; (d) ArCHO, Py, TFA.



Scheme 4. Solid-phase combinatorial synthesis of benzimidazole derivatives.

hydrogenation or by reducing agents. In a recent work, enzymatic reduction with Baker's yeast was used successfully to prepare benzimidazole *N*-oxide derivatives in good yields [41] (Scheme 6).

Others modifications to old synthesis are the cyclodehydration of *N*,*N*-disubstituted 2-nitroaniline derivatives by organic acids [42] and cyclization of *N*-substituted 2-nitroaniline without an electron withdrawing substituent β to the amino group [43,44]. Also, benzimidazole *N*-oxide analogs have been prepared from benzofuroxan by a two-step reaction with aromatic aldehydes [45] (Scheme 7).

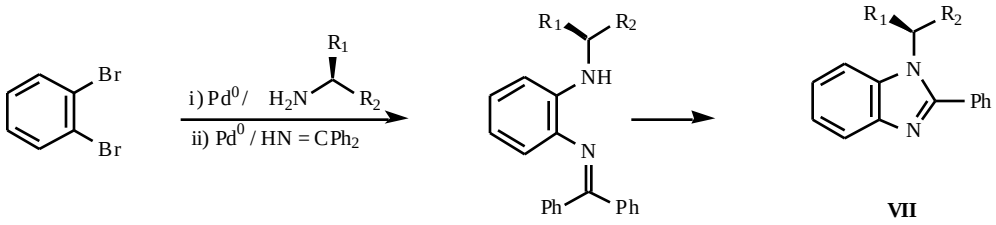
3- BIOLOGICAL ACTIVITY AND SAR

3.1- Imidazole and Imidazole *N*-Oxide Derivatives

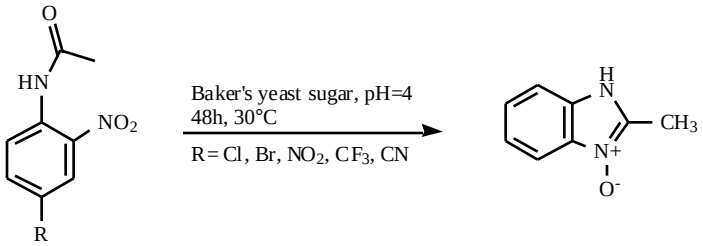
Concerning bio-activity, imidazoles are organized, according to the presence or absence of nitro functionality, in two groups: nitroimidazole and non nitroimidazole.

3.1.1- Nitroimidazole

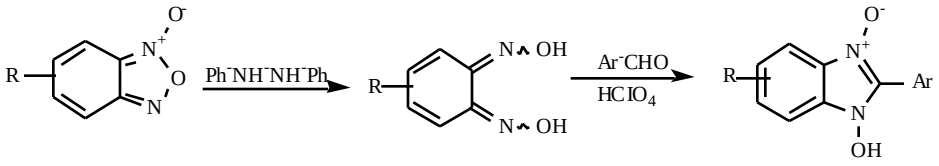
Many drugs commonly used in clinic belong to this category and their use in chemotherapy has been reviewed [46]. Compounds as Metronidazole, Benznidazole and Misonidazole (Fig. (**2**)) exhibit antibacterial, antiprotozoal



Scheme 5. Synthesis of chiral benzimidazole derivatives.



Scheme 6. Benzimidazole *N*-oxide synthesis using Baker's yeast.



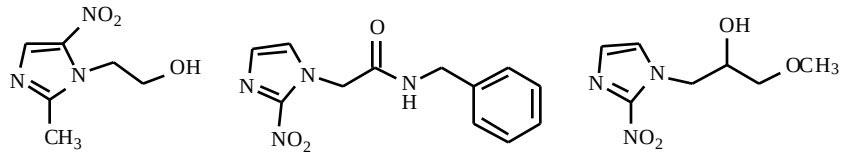
IX

Scheme 7. Benzimidazole *N*-oxide synthesis from benzofuroxan.

and radiosensitizing activities, respectively [47-51]. These properties have been related to the reduction potential of the one-electron transfer NO_2/ $NO_2^{\cdot-}$ [52].

Parasitocidal nitroimidazoles such as Metronidazole rely their activity on the generation of oxidative damage on the microorganism mediated by bioreduction of the nitro group.

Substitution at position 4 either abolished or diminished activity against *Trypanosomatidae*; it could be related to the loss of planarity of the system as previously shown [56]. What is more, an isomer of Megazol with the nitro group at position 4 was inactive something already noticed for other nitroimidazoles [57]. From these results the authors



1, metronidazole **2, benznidazole** **3, misonidazole**

Fig. (2). Nitroimidazole used in clinical.

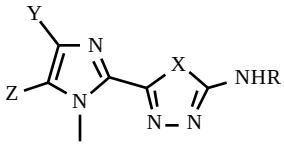
Recently, a study on enzymatic reduction of nitroheterocycles, including Metronidazole and Megazol (**4a**, Table 1), both 5-nitroimidazoles with antiprotozoal activity, has been reported [53,54]. It was observed that reduction take place even with an unfavorable equilibrium if the reaction is influenced by the reduction of molecular oxygen, an irreversible step. Besides, reduction rates were related to electron affinities and not to structure.

On the other hand, a series of Megazol analogs were synthesized to deepen on structure-activity relationships [55] (Table 1).

suggested that the enzyme implicated in the bioreduction process was sensitive to structure. Previous theoretical calculations performed in a series of isomeric nitroimidazoles showed that they have very different electron affinities depending on the position of the nitro group, being the order as follow 2-NO_2 > 5-NO_2 >> 4-NO_2 [58]. This could imply that the lack of activity of the 4 isomer is due to its low electron affinity.

The study of metronidazole-resistant strains of *Trichomona vaginalis (T. vaginalis), Entamoeba histolytica (E. histolytica) and Giardia lamblia (G. lamblia)* has lead

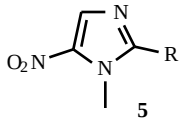
Table 1. Structural Modifications on Megazol



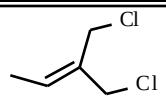
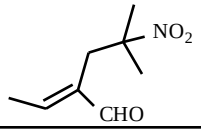
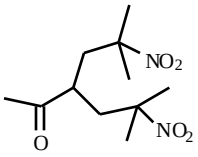
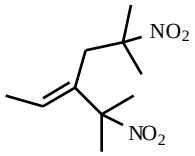
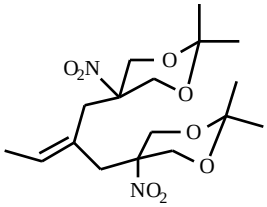
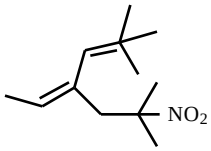
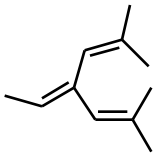
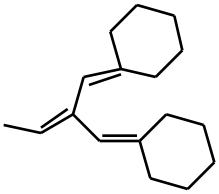
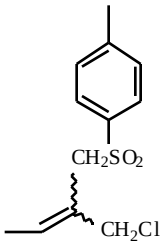
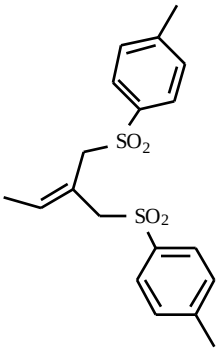
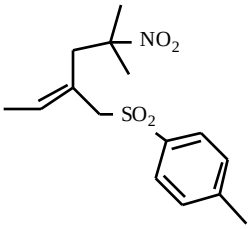
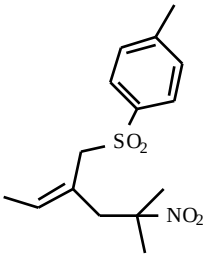
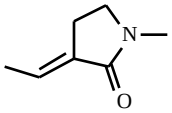
4

Comp.	X	Y	Z	R	Comp.	X	Y	Z	R
4a, Megazol	S	H	NO_2	H	**4g**	O	H	NO_2	$COCH_3$
4b	S	CH_3	NO_2	H	**4h**	S	H	NO_2	$CO(CH_2)_7CH_3$
4c	S	Br	NO_2	H	**4i**	S	H	NO_2	$CO(CH_2)_{12}CH_3$
4d	S	NC_5H_{10}	NO_2	H	**4j**	S	H	NO_2	$COCF_3$
4e	S	SC_6H_5	NO_2	H	**4k**	S	H	NO_2	H
4f	S	CF_3	NO_2	H	**4l**	S	NO_2	H	H

Table 2. Antiprotozoal Activity of 2-Substituted-5-Nitroimidazole Derivatives Against a Metronidazole-Sensitive Strain of *T. vaginalis*



5

Comp.	R	MLC[a] (μM)	Comp.	R	MLC (μM)
5a		10	**5h**		<1
5b		>50	**5i**		<1
5c		10	**5j**		<1
5d		5	**5k**		50
5e		5	**5l**		5
5f		5	**5m**		5
5g		<1	**1(metronidazole)**		50

Notes Table 2. a. MLC lowest concentration of metronidazole at which no viable organisms were observed following exposure to the drug for 3 days and growth for a further 4 days in a fresh drug-free medium.

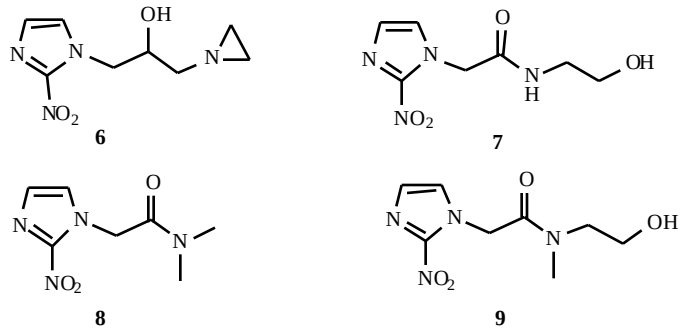


Fig. (3). 2-Nitroimidazole cytotoxins in hypoxia and radiosensitizers.

to the identification of a group of small iron-sulphur proteins, termed ferredoxins, responsible for the reduction of metronidazole [59-61]. Subsequent studies on the reactivities of ferredoxins toward nitroimidazoles have shown that the kinetics of the electron transfer reaction parallel the cytotoxic effect in the parasite [62]. Besides, the electron transfer rate was influenced by the size of the alkyl substituent at position *N*-1, with larger groups hindering approach of the electron accepting nitro group to the electron donating iron-sulphur center.

In order to overcome the problem of resistance differently 2-substituted 5-nitroimidazole derivatives have been developed (Table 2) and though some of them perform better than metronidazole against metronidazole-sensitive *T. vaginalis* none was active against metronidazole-resistant strains [63].

5-Nitroimidazoles and 5-nitrofurans are the kind of nitroheterocyclic compounds mostly used as antibacterial agents [64]. Because of their low reduction potential, 5-nitroimidazoles show selective cytotoxicity toward anaerobic organisms. As already was established, the one-electron nitro radical anion has been proposed as the active damaging species and DNA as the target biomolecule [65,66]. From QSAR studies it could be derived that inhibitory activity was related to the half-life of the reduced intermediate rather than the reduction of the initial nitro compound [67,68].

As mentioned before nitroimidazoles are also used as radiosensitizers or hypoxic cell cytotoxins in the treatment of solid tumors. In this category are found 2-nitroimidazoles derivatives such as Misonidazole (**3**, Fig. (**2**)), RSU1069, and Etanidazole (**6** and **7**, Fig. (**3**)). Their cytotoxicity is based on the reaction of the nitroso or hydroxylamine intermediates with biomolecules, DNA and proteins [69]. 2-Nitroimidazoles have also been used as hypoxia-selective drug delivery systems [70]. Recently, Hori and co-workers designed a bifunctional hypoxic cell radiosensitizers, KIN-806 (**8**, Fig. (**3**)) which suppress tumor metastasis and enhance immunoresponse [71,72]. Also, they have designed and synthesized 2-nitroimidazole acetamide, TX-1877 (**9**, Fig. (**3**)) and analogs as antimetastatic hypoxic cell radiosensitizers [73]. From molecular orbital calculation and electrochemical studies they concluded that TX-1877 analogs with high electron affinity (>0.9 eV) and LUMO coefficient localized on 2-nitroimidazole moiety showed satisfactory radiosensitizing activities. While, antimetastatic activity was related to presence of the *N*,*N*- dimethyl-carboxamide group.

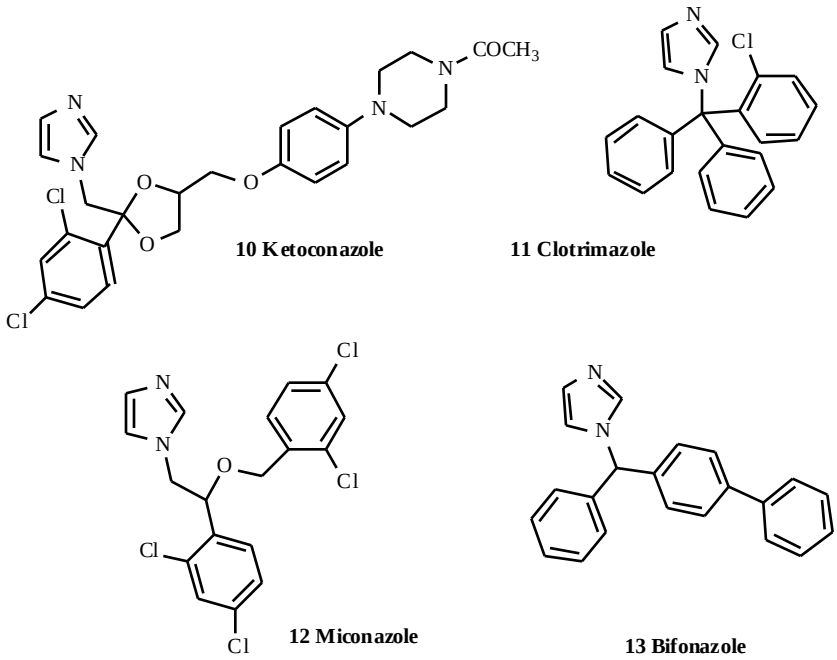


Fig. (4). Antifungal imidazole derivatives used in clinical practice.

3.1.2. Non Nitroimidazole

Under this group are found antifungal imidazoles used in clinical practice (Fig. (**4**)). An exhaustive review on azoles as antifungal agents has appeared recently [74].

Azole antifungals block ergosterol biosynthesis by inhibition of sterol 14α-demethylase (cytochrome $P450_{14DM}$, CYP51). In fact, they inhibit the binding of the natural substrate lanosterol to CYP51 by coordination of the ring nitrogen atom (*N*-3 of imidazole) to the sixth coordination position of the iron ion of the enzyme protoporphyrin system [75]. Recently, a QSAR study of 2,4-dichlorobenzylimidazole derivatives as anti-*Candida* agents has been reported [76]. Using Catalyst® module HYPO1 the authors developed a pharmacophore model with four feature: one aromatic nitrogen with a lone pair of electrons plus three aromatic rings. This finding confirmed that the key interaction with the enzyme is the coordination with the iron ion, while aromatic rings could interact with aminoacids in the proximity of the heme group. This model did not exhibit a clear preference for one enantiomer or the other in disagreement with a previous report on CYP51 inhibitors [77].

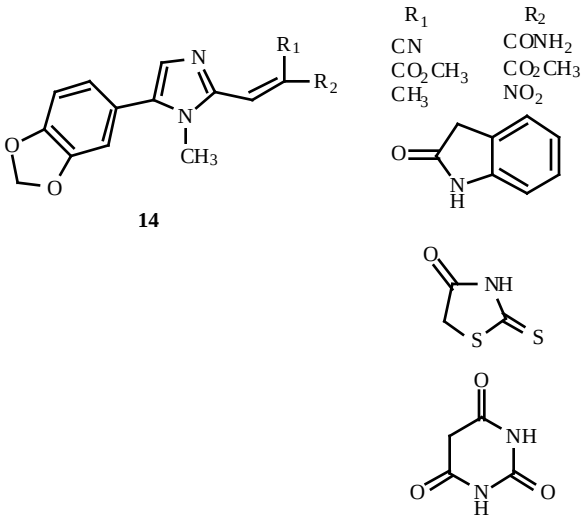


Fig. (5). Imidazole-2-carbaldehyde derivatives tested as leishmanicidal agents.

Some antifungal imidazoles have been studied as antiprotozoal agents, Ketoconazole and Clotrimazole. They block the proliferation of *Trypanosoma cruzi* (*T. cruzi*) *in vitro* by inhibiting the cytochrome P-450 dependent C-14 α-demethylation of lanosterol to ergosterol. However, they displayed poor activity *in vivo*, so others 1,2,4-triazole antifungals are currently in development with better results [48,78]. Besides, Ketoconazole have probed effectiveness as a second-line for oral treatment of visceral Leishmaniasis enhancing the effect of meglumine antimoniate [79]. In another work other *N*-substituted imidazole derivatives of general structure **14** have been studied as anti-*Leishmania* agents and some of them showed promising activity [80] (Fig. (**5**)).

4,5-Diphenylimidazoles have been identified as potential antibacterial agents that act in the bacterial cell-wall biosynthesis. In a preliminary study, certain structural requirements have been defined: the presence of two aryl rings, the imidazole *NH* and a good electron-withdrawing group at C-2 [81]. Other bactericidal imidazole derivatives are 1,4-disubstituted derivatives, they act inhibiting the enoyl acyl carrier protein reductase (FabI). This enzyme catalyzes the final step in bacterial fatty acids synthesis in *Staphylococcus aureus* and *Escherichia coli*. Evaluation of several imidazole derivatives together with X-ray co-crystallization of the enzyme/inhibitor complex has been reported [82]. In Fig. (**6**) there are shown the structure requirements for the inhibition of FabI enzyme.

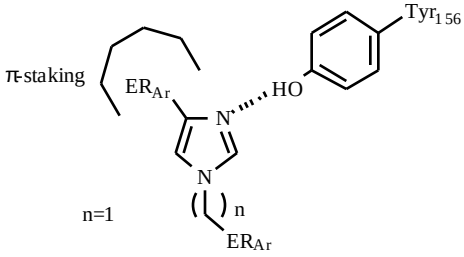
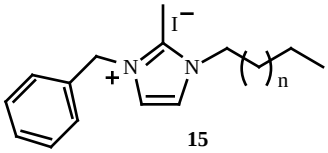


Fig. (6). Structural features of imidazole inhibitors of FabI. ^{ER}Ar stand for electron-rich aromatic.

Histidine protein kinases (HPKs), one of the major components in the two-components regulatory system, play a key role in prokaryotic signal transduction. Imidazole derivatives of general structure **15** have been described as inhibitors of YycG (HPK from *Bacillus subtilis*) and they have shown that enzyme inhibition correlates with antibacterial activity for most derivatives, see **15a-e** at Table 3 [83].

Table 3. IC_{50} and MIC of YycG Inhibitors



Comp.	n	IC_{50} (μM)	MIC(μg/mL)
15a	13	6.6	1.56
15b	11	18	6.25
15c	9	40	1.56
15d	5	>120	>12.5
15e	1	>140	>12.5

Oxime and oxime ether derivatives of anticonvulsant nafimidone **16** have been screened for antibacterial and antifungal activity due to their structural resemblance to oxiconazole **17,** a recognized antifungal agent [84] (Fig. (**7**)). Some derivatives showed growth inhibition of *Staphylococcus aureus* (*S. aureus*), which was found to be stereoselective, being *E*-isomer 16-fold more active than *Z*-isomer.

Inhibition of cytochrome P450 enzymes by azoles, which has already been exploited in antifungal agents, is also a potential strategy in the treatment of cancer. The steroidal enzyme 17α-hydroxilase-$C_{17,20}$-lyase ($P450_{17α}$), which is involved in androgen biosynthesis, has been presented as a target in the treatment of androgen-dependant diseases like

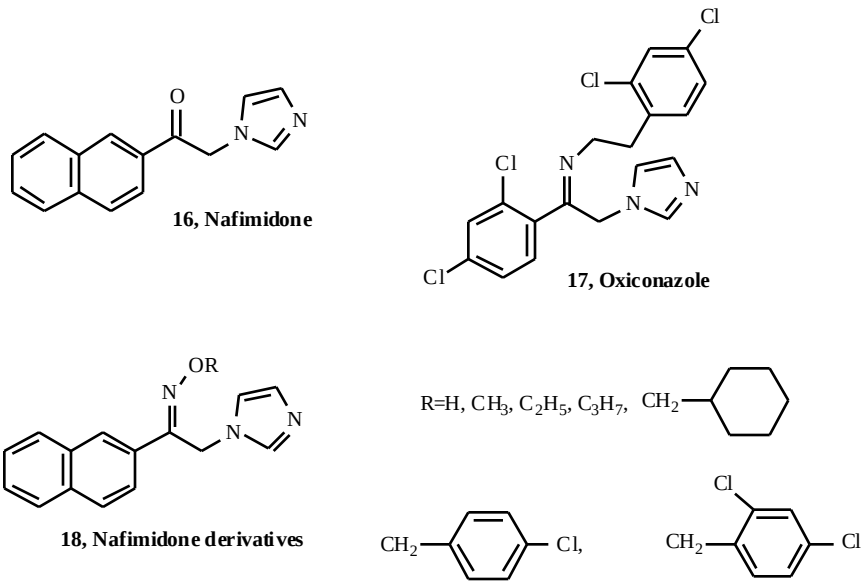
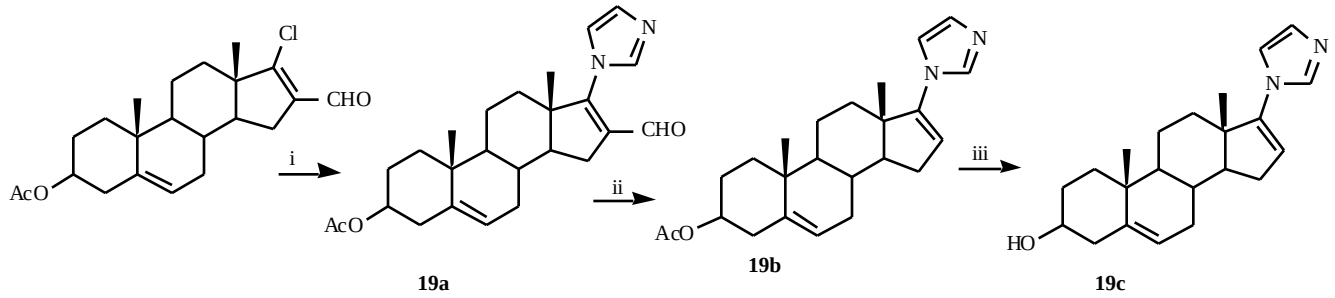


Fig. (7). Structure of nafimidone, oxiconazole and nafimidone derivatives.



Scheme 8. Synthesis of 17-azolyl-steroids.

Notes Scheme 8. a Reagents and conditions: (i) Imidazole, K_2CO_3, DMF, N_2, 80 ºC; (ii) 10% Pd on activated charcoal, PhCN, reflux; (iii) 10% methanolic KOH, N_2, rt.

prostatic cancer. Brodie and co-workers have synthesized and characterized 17-azolyl-steroids as potent inhibitors of $P450_{17\alpha}$ [85] (Scheme 8). Using UV-vis difference spectroscopy they observed the coordination of a steroidal nitrogen (*N*-3 of imidazole) to the enzyme's heme iron. Other authors have taken a different approach to obtain $P450_{17\alpha}$ inhibitors by synthesizing imidazole substituted biphenyls as A-C ring mimetic of steroids [86].

Alkylating properties of dimethyltriazeno group have been used in the development of antitumor agents. Decarbazin, 4(5)-(3,3-dimethyl-1-triazeno)imidazole-5(4)-carboxamide, has long been used in combined chemotherapy of malignant melanoma, Hodgkin's disease and osteogenic and fibrous sarcomas under clinical conditions. Recently, a few numbers of dimethyltriazenophenylimidazoles have been synthesized in order to improve stability of the compounds [87] Fig. (**8**).

Imidazole has also been used to improve pharmacokinetic properties of Combretastin A-4 (**CA-4**), a natural product that exhibit a strong antitubulin activity and is active against a broad spectrum of human cancer lines [88]. In this study, the ethylene bridge in **CA-4** was replaced by an imidazole ring and 4,5-disubstituted derivatives **(21c)** were found to be the most active ones (Fig. (**9**)).

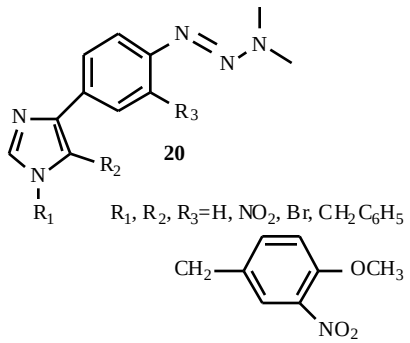
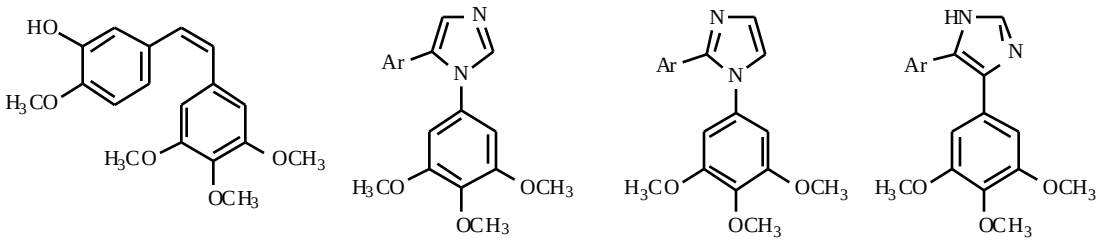


Fig. (8). Dimethyltriazenophenylimidazole derivatives.

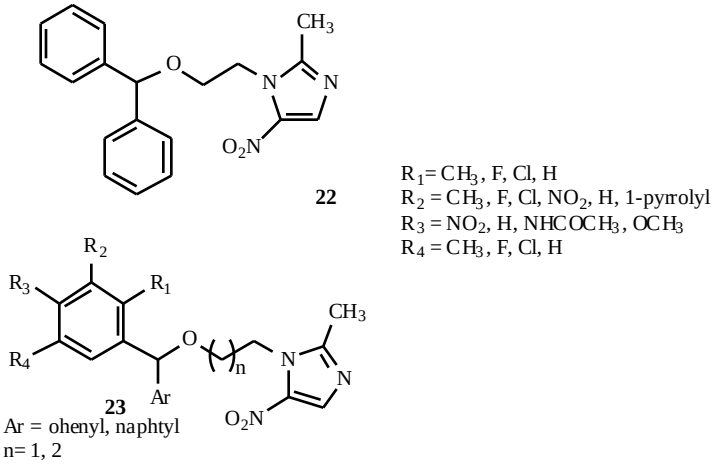
A key target in the search for anti-HIV drugs is the enzyme reverse transcriptase (RT). A number of RT inhibitors have been developed as being an important group nonnucleoside RT inhibitors (NNRTI). A general feature of NNRTI is the ability to adopt a conformation designated "butterfly-like" orientation. A novel family of NNRTIs are 1-[2-(diarylmethoxy)ethyl]-2-methyl-5-nitroimidazoles, named with the acronym DAMNIs, derivate from **22** (**23**, Fig. (**10**)) [89]. An important number of these derivatives have been synthesized and assayed for anti-HIV activity. SAR studies have shown that both methyl and nitro



CA-4 **21a** **21b** **21c**

Fig. (9). Combretastin A-4 and imidazole-based Combrestatin A-4 analogs.

substituents bound to the imidazole ring were highly important for activity. While, substitution of a phenyl ring by a 2-naphthyl ring as well as the lengthening of the alkyl chain connecting the diphenylmethoxy group resulted in a net decrease of antiviral activity. Despite being nitroimidazoles derivatives we decided to place them under this category because biological activity was not directly related to nitro group as nitroimidazoles discussed previously.



22

R_1= CH_3, F, Cl, H
R_2 = CH_3, F, Cl, NO_2, H, 1-pyrrolyl
R_3 = NO_2, H, $NHCOCH_3$, OCH_3
R_4 = CH_3, F, Cl, H

23

Ar = ohenyl, naphtyl
n= 1, 2

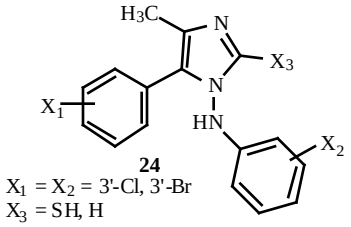
Fig. (10). A new family of NNRTIs, known as DAMNIs.

In a recent work, a novel series of imidazoles with anti-HIV activity have been presented, *N*-aminoimidazoles (NAIMs) [90]. Despite their mechanism of action have not been elucidated it has been suggested that some derivatives interfere with a postintegrational event instead of inhibiting the HIV-1 RT. The most active products of this series are shown in Fig. (**11**).

There are few studies on imidazole *N*-oxide derivatives as chemotherapeutic agents, which could be explained by the difficulty to obtain adequately functionalized derivatives. A patent on antibacterial activity was disclosed in 1980 [91]. In the last year, our group have synthesized and evaluated a series of imidazole N_1-substituted N_3-oxide derivatives of general structure **25** as antiprotozoal agents, against *T. cruzi* and *T. vaginalis* (Fig. (**12**)). They were inactive against the first parasite, displaying an inhibition growth percentage nearly 50% at 100µg/mL against *T. vaginalis*. In order to explain this low activity compare with metronidazole we determined some physicochemical properties such as lipophilicity as R_M and first reduction potential. We found that these parameters correlate with the trichomonicidal activity [92].

3.2. Benzimidazole and Benzimidazole *N*-Oxide

In order to emphasize structure-activity relationship benzimidazole derivatives are organized by structure in three main categories: 1*H*-benzimidazoles, 1-substituted benzimidazoles and bisbenzimidazoles. In doing so, we wish to remark that not only substituent characteristic but also pattern of substitution could influence on the bioactivity.



24

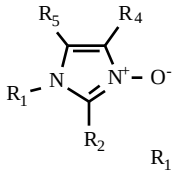
X_1 = X_2 = 3'-Cl, 3'-Br
X_3 = SH, H

Fig. (11). Structural requirements for anti-HIV activity of *N*-aminoimidazoles.

3.2.1. 1H-Benzimidazole

An important group of 1*H*-benzimidazoles are 2-carbamates-benzimidazole derivatives, which posses antihelmintic activity, such as Albendazole (**26**) and Mebendazole (**27**) employed in clinic for the 70 decades (Fig. (**13**)). This group have been extensively reviewed and we will not discuss it further [93,94]. It is well-known that they act by binding to helmintic tubulin, disrupting microtubule

structure and functions [95]. In order to do so, the presence of a carbamate moiety at C-2 and an unsubstituted NH is essential.



25

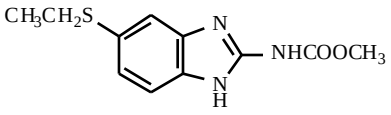
$R_1 = CH_2CH_2Ph$, CH_2 Furyl, *p*-$PhCH_3$
$R_2 = H$, CH_3
$R_4 = CH_3$, $CO_2CH_2CH_3$
$R_5 = CH_3$, H

Fig. (12). Imidazole *N*-oxide derivatives assayed for parasitocidal activity.

It has also been reported that modification of lactate dehydrogenase (LDH) activity by antihelmintic benzimidazoles in various trematode and cestode parasites is part of their mode of action [96]. Recently, a variety of benzimidazole derivatives **28**, including benzimidazole its unsubstituted at the benzene ring and bearing an aryl (benzene or pyridine) bounded to the sulphur atom showed moderate activity against *Mycobacterium* species. Introduction of electron withdrawing groups in the benzyl moiety gave compounds more active than the control drug (isoniazid) against nontuberculus mycobacterium [103].

A closely related compound, the sulfoxide omeprazole (**34**), a proton pump inhibitor, is used in combinatorial therapies against the gastric pathogen *Helicobacter pylori* (*H. pylori*). Recently, sulphide omeprazole-related compounds **35** were studied as anti *H. pylori* agents *in vitro* [104] (Fig. (**17**)). From SAR analysis it was concluded that lipophilic substituents in the pyridyl ring were necessary for activity and that substitution on the benzimidazole moiety had a small effect. However, proton-pump inhibitory activity could not be separated from antibacterial one.

A series of 2,5-disubstituted benzimidazole derivatives with general structure **36** have been assayed for antimicrobial



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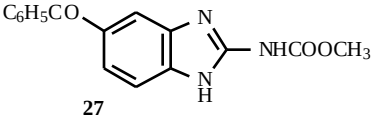


27

Fig. (13). Albendazole and Mebendazole used as antihelmintic drugs in clinical.

have been assayed as antiparasitic agents against the protozoa *G. lamblia* and *E. histolytica* and the helminth *Trichinella spiralis* (Fig. (**14**)) [97].

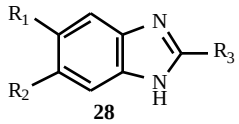
Most of them perform better than Albendazole and Metronidazole against protozoa but none was active against helminth. Only derivatives bearing a 2-carbamate function inhibit tubulin polymerization but there was no correlation with antiparasitic activity.

Use of benzimidazole derivatives together with common drugs employed in the treatment of giardiasis has already been reviewed [98].

In 1965, Merck & Co. claimed in a patent, the synthesis and antihelminthic activity of some benzimidazole 1-oxide derivates, possessing a 2-thiazolyl moiety [99]. Further, in 1969 they also patented their reduced counterpart [100] where Thiabendazole emerged, being one of the drugs actually employed in clinical (Fig. (**15**)).

In our search for antichagasic drugs with a mechanism of action by free radical production, we reported the first *N*-oxide derivatives active against *T. cruzi*. The pharmacophore bear a benzofuroxan group where **31** resulted as the most active [101] (Fig. (**16**)). Continuing our study on other *N*-oxide containing heterocycles, we selected the benzimidazole *N*-oxides for their similarity to **31**. Among the benzimidazole *N*-oxide derivatives studied, **32** possessing a 2-butilamide moiety was the most active but with an activity 10-fold lower than the most active benzofuroxan. Also, we prepared *O*-alkylated derivatives of benzimidazoles, **33,** in order to increase their lipophilicity; an enhancement of bioactivity was consequently, found (Fig. (**16**)) [102].

2-Alkylsulphonyl derivatives of benzimidazole have been described as potential antibacterial agents. Derivatives activity [105]. Despite showing moderate to poor activity it could be seen that activity spectrum (Gram positive and Gram negative bacteria and Yeast) was related to 5-substituent (Table 4).

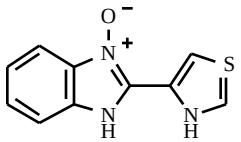


28

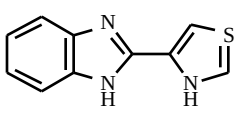
R_1, R_2 = H, Cl R_3 = H, NH_2, SH, SCH_3, CH_3, $NHCO_2CH_3$

Fig. (14). Some 1*H*-benzimidazole derivatives tested against *G. Lamblia*, *E. histolytica* and *T. spiralis.*

The importance of the functionality at the 2-position for antibacterial activity was studied for a series of 5-amidino benzimidazole derivatives [106]. Amidino benzimidazoles have been identified as inhibitors of the bacterial two-component systems (TCS) implicated in signal transduction pathways. Many of these inhibitors also displayed good *in vitro* antibacterial activity. Differently substituted phenyl groups were placed at position 2 and 2-hydroxy-3-*t*-butylphenyl was identified as the optimum substituent for inhibitory activity. Although *N*-methyl derivative displayed as well as unalkylated one as TCS inhibitor, its antibacterial activity was 2-to 4-fold lower.

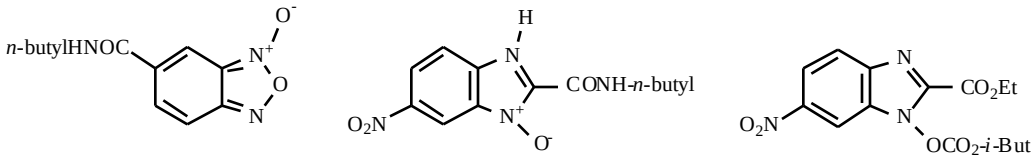


29, 2-(2-thiazolyl)benzimidazole 3-oxide



30, Thiabendazole

Fig. (15). 2-Thiazolyl benzimidazole derivatives active against helminthiasis.



31 **32** **33**

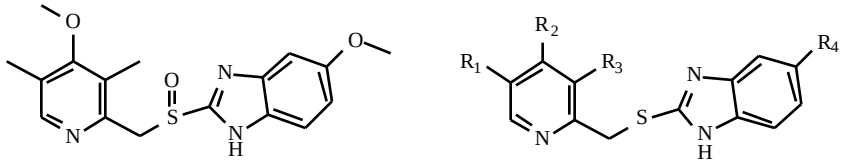
Fig. (16). *N*-Oxide derivatives as antichagasic agents.

Other disubstituted benzimidazoles, 2-arylbenzimidazole-4-carboxamides, were studied as anticancer agents [107]. These compounds inhibited the Poly(ADP-ribose) polymerase (PARP), an enzyme implicated in DNA repair. From this study, it was concluded that a primary carboxamide was essential for activity and an 1*H*-benzimidazole was optimum. Compound **37**, NU 1085, has probed to potentate the growth inhibition of Topotecan, a recognized topoisomerase inhibitor (Fig. (**18**)). Some 2-pyridinyl and 2-thiomethyl benzimidazole-4,7-diones derivatives i.e. **38** and **39** Fig. (**18**)**,** have demonstrated to possess high antiproliferative activity on leukemia and lymphoma cells, but the mechanism of action has not been elucidated [108].

3.2.2. 1-Substituted-Benzimidazole

As it was mentioned above, an important group of RT inhibitors are nonnucleoside RT inhibitors (NNRTI), with a conformation designated "butterfly-like" orientation. Recently, *N*-benzyl-2-arylbenzimidazole derivatives have been assayed as NNRTI, and some of them were more active than the control drug TZB (Fig. (**19**)) [109]. Compound **40** emerged as a leader in this drug discovery approach (Fig. (**19**)). The good performance observed against variant forms of RT was assigned to their major flexibility that allowed them to assume different butterfly-like conformations to interact with various RT mutations.

It has been demonstrated that certain 2,5,6-trichloro and 2-bromo-5,6-dichlororibofuranosylbenzimidazole have potent

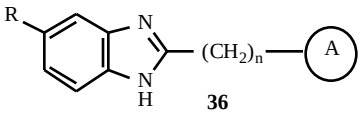


34

R_1 = H, CH_3
R_2 = $O(CH_2)_3OCH_3$, OCH_2-*i*-Propyl, OCH_3, OCH_2CH_3
R_3 = H, CH_3
R_4 = H, F **35**

Fig. (17). Omeprazole and related compounds.

Table 4. 2-Cycloakyl-5-Benzimidazole Derivatives Active Against Gram Positive and Gram Negative Bacteria and Yeast



36

n=1, 2

A = cyclopentyl, cyclohexyl

			Gram +		Gram -		Yeast
Comp.	R	Sa[a]	Sf[a]	Bs[a]	Ec[a]	Pa[a]	Ca[a]
36a	H	I [b]	I	A	I	A	I
36b	CH_3	I	I	I	I	I	A
36c	NO_2	A[c]	I	I	I	I	I
36d	Cl	A	A	A	I	I	I

Notes Table 4. All compounds bearing a cyclohexyl moiety. a) Abbreviations: Sa, *Staphylococcus aureus;* Sf, *Streptococcus faecalis*; Bs, *Bacillus subtilis;* Ec, *Escherichia coli;* Pa; *Pseudomonas aeruginosa*; Ca, *Candida albicans*. b) I- inactive(MIC>12.5 µg/mL); c) A- active(MIC≤12.5 µg/mL).

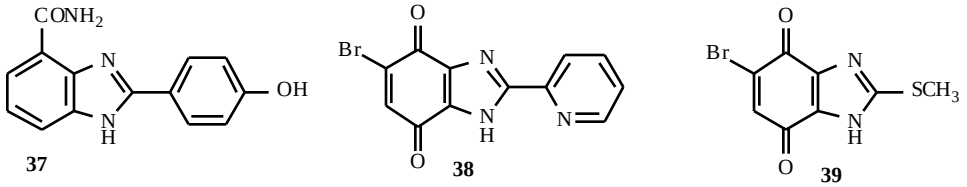


Fig. (18). 2-Substituted benzimidazole with antitumoral activity.

activity against human cytomegalovirus (HCMV) by inhibition of DNA processing and virus assembly [110,111]. Substitution of halogen at position 2 by isopropylamine resulted in the discovery of maribavir (**41**) (Fig. (**19**)) a compound that does not inhibit DNA processing but target the HCMV UL97 protein kinase [112]. Previously, the same research group described 2-benzylthio derivatives as anti-DNA virus agents but they were very cytotoxic. They also studied several acylnucleosides but only 2-thiobenzyl analogs showed any activity.

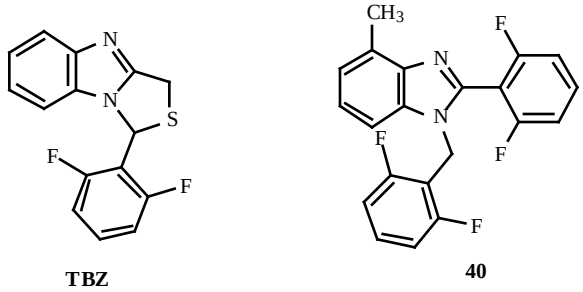


Fig. (19). NNRTI active against HIV.

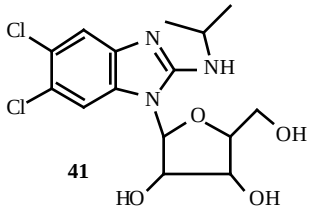


Fig. (20). Maribavir.

Compounds of general structure **42** (Fig. (**21**)) have shown good activity against RNA viruses (Coxsackie B5, Mumps) and selective inhibition of (+)-strand RNA synthesis was proposed as a probable mechanism [113]. Replacement of benzenesulphonyl group by ribofuranosyl moiety and acyclovir side-chain abolished antiviral activity [114].

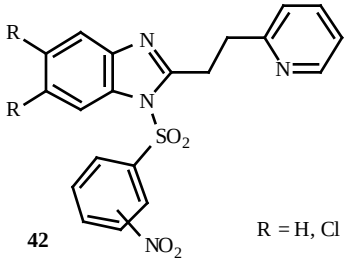
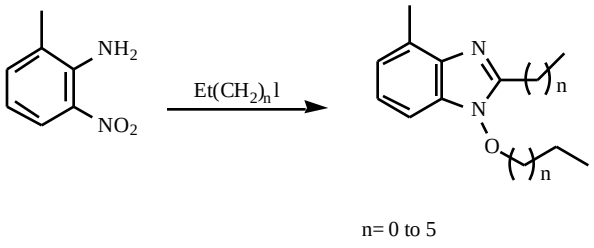


Fig. (21). General structure of *N*-benzenesulphonyl-benzimidazole of anti-RNA viruses.

A number of *N*-alkoxybenzimidazoles **43** have been described as active against HIV-1 [115] and cancer cell lines [116] (Scheme 9). As regards to antiviral activity, compounds containing alkyl groups were selective while compounds bearing aryl or vinyl functionalities showed no selectivity. Beside antiviral selectivity was strongly related to chain length being the best that of 4 or 5 carbons.



Scheme 9. *N*-Alkoxybenzimidazoles active against HIV-1 and cancer cell lines.

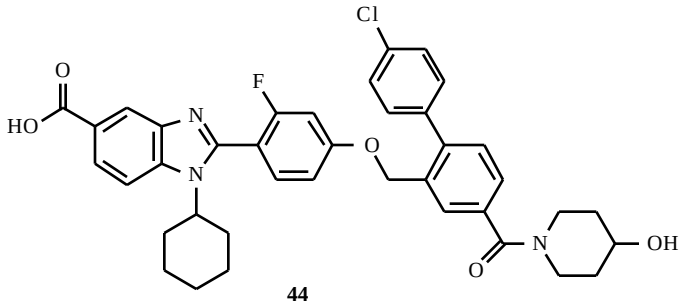
An important target for anti-hepatitis C viral investigation is the RNA polymerases, between which the non-structural protein 5B (NS5B) can be found. Two families of *N*-cyclohexylbenzimidazole derivatives (**44** and **45**, Fig. (**22**)) have been identified as potent inhibitors of NS5B [117].

Several 1,2,5-trisubstituted benzimidazoles have been studied as antibacterial agents [118-120]. Although a clear SAR was not deduced, certain rules could be drawn: *N*-substitution gave only slightly increased activity, benzyl groups performed better than alkyl ones, and 2-aryl moieties produced more active compounds as well as 5-halogen substitution. 2-Aryl-1-hidroxy-5-(2-thienoyl)benzimidazole 3-*N*-oxide (**46**, Fig. (**23**)) have also been studied as antibacterial agents, [45] displaying moderate activity against *E. coli* and *C. albicans*.

Benzimidazole-4,7-diones are the only example of benzimidazole parasitocidal drug substituted at nitrogen. These compounds have been studied as inhibitors of purine nucleoside phosphorylase (PNP) from *Toxoplasma gondii*, a unicellular protozoan [121]. A preliminary SAR showed that *N*-benzyl derivatives were more active than *N*-alkyl ones and substitution at 2-position provided selectivity over human PNP.

Aromatase inhibitors are very useful in the therapy of some estrogen-dependant cancers (i.e. breast cancer) [122]. A series of 2-furylbenzimidazole derivatives have shown aromatase inhibitory activity, which was increased by the presence of substituent at 1 and/or 5 position [123]. In this series *N*-benzoyl derivatives were more active than *N*-alkyl ones.

N-trimethylsilylpropyl substituted benzimidazoles have shown antitumoral activity *in vitro* and *in vivo*, which is probably related to their DNA-cleaving ability [124].



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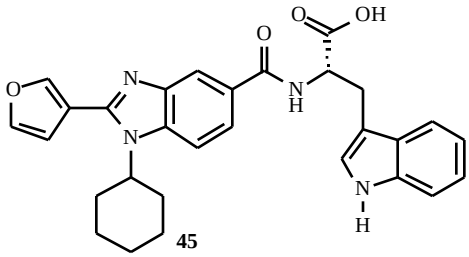


45

Fig. (22). Nonnucleoside inhibitors of Hepatitis C-viral polymerase.

3.2.3- Bisbenzimidazoles

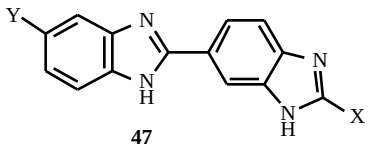
Bisbenzimidazole derivatives are among the class of DNA minor groove interacting molecules. The parent compound of this family is the cell stain Hoechst 33258, 2'-(4-hydroxyphenyl)-5-(4-methylpiperazinyl)-2,5'-bis-1*H*-benzimidazole [125], which inhibit the binding of TATA-box binding protein to DNA and also the mammalian DNA topoisomerase I.

Several Hoechst 33258 analogs (**47a-h**, Table 5) have been developed as topoisomerase I inhibitors and cytotoxins against cancer cell lines [126]. QSAR analysis on their topoisomerase I inhibitory activity has recently been reported and showed that two parameters of greatest significance were ClogP (calculated octanol/water partition coefficient) and CMR (calculated molecular refractivity) [127].

Another 3D-QSAR was recently developed between analogs of Hoechst 33258 and others DNA minor groove binders. It was shown that steric contribution was bigger than electrostatic one, confirming that an isohelical conformation was fundamental to improve the complementarity to DNA [128].

In the compounds mentioned above, benzimidazoles are bind in an asymmetric head-to-tail pattern. Another possibility that was explored was a head-to-head

Table 5. Topoisomerase I Inhibitors

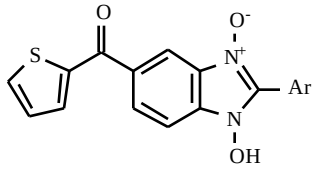


47

Compound	X	Y	Topoisomerase I-mediated cleavage[a]	Cytotoxicity IC_{50} (μM)[b]
47a	4-ethoxyphenyl	4-methylpiperazinyl	1.0	0.03
47b	2-tolyl	-CN	>> 100	1.2
47c	4-tolyl	$-CONH_2$	10	> 25
47d	2-naphtyl	$-CONH_2$	100	0.74
47e	1-naphtyl	4-methylpiperazinyl	20	0.33
47f	6-benzimidazolyl	phenyl	1.0	0.09
47g	6-quinoxalinyl	phenyl	> 100	20
47h	6-indolyl	phenyl	5	0.015

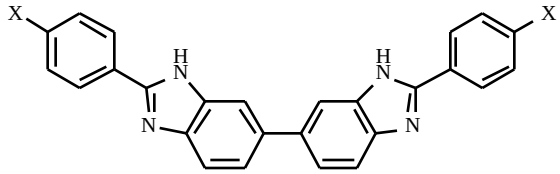
Notes Table 5. [a] Relative effective concentration, relative to 46a, able to produce the same cleavage on the plasmid DNA in the presence of topoisomerase I. [b] RPMI 8402, human lymphoblast tumor cell line.

arrangement, that lead to the synthesis of **48** Fig. (**23**) [129]. This compound displayed good antitumoral activity *in vitro* and was an effective inhibitor of transcription. Other head-to-head bisbenzimidazole analogs target human tumor helicases [130].



Ar= 2-furyl, 2-thienyl, 2-bis-thienyl, fenyl
4-FC_6H_4, 3-FC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$

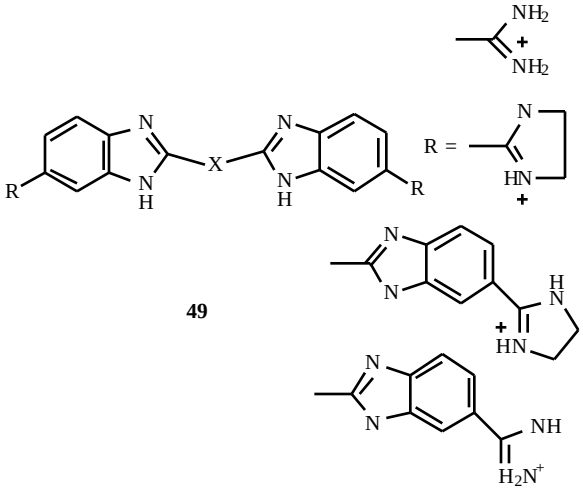
Fig. (23). Trisubstituted benzimidazole *N*-oxide derivatives as bactericidal agents.



48 X = O-$(CH_2)_3$-$N(CH_3)_2$

Fig. (24). Bisbenzimidazole bind head-to-head.

Another important group of bisbenzimidazoles are anti-PCP (*Pneumocystis carinii* pneumonia) agents. These compounds bind tightly to DNA and inhibit topoisomerase II enzyme of the microorganism [131]. DNA binding ability of various bisbenzimidazole dications was also studied using different linkers and cationic moieties (**49**, Fig. (**25**))[132].

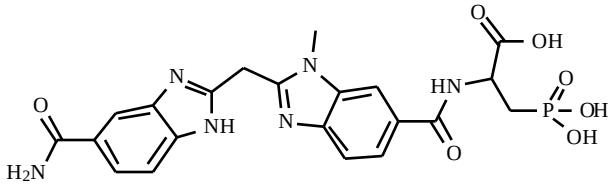


49

Fig. (25). Bisbenzimidazole dications with ethenyl and alkyl linker.

These bisbenzimidazole dications strongly bind to DNA AT rich sequences, which are characteristic of a minor groove binding mode. Derivatives with an ethenyl linker bind stronger than those with an alkyl one and binding diminish with alkyl chain length. Although enhanced binding ability gave more active compounds they were also more cytotoxic. Other dicationic bisbenzimidazole compounds were studied as antifungal agents against *C. albicans* and *C. neoformans* [133]. Compounds possessing an heteroaryl linker were as active as pentamidine while those bearing an alkyl linker were inactive.

Finally, a series of bisbenzimidazole derivatives have been reported as Zn^{2+}-dependant inhibitors of HCV (Hepatitis C Virus) NS3 serine protease [134]. The phosphonoalanine derivative APC-6336 (**50**, Fig. (**26**)) was identified as a potent inhibitor in the presence of Zn^{2+}.



50

Fig. (26). APC-6336 inhibitor of NS3 serine protease.

Recently, the same group developed a second generation of NS3 serine protease inhibitors with increased binding affinity with an additional phosphoalanine side chain at the left hand side of the bisbenzimidazole [135].

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