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A Review On Substituted Benzimidazoles: Biologically Active Compounds

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ABSTRACT

Benzimidazole is the heterocyclic compound which contains a phenyl ring fused to an imidazole ring, Benzimidazole analogs are of crucial importance because of their different clinical applications and biological activity. Benzimidazoles are known as an optimistic class of bioactive heterocyclic compounds possessing a wide variety of biological activities. Benzimidazole derivatives play an important role in medical field with so many pharmacological activities such as antimicrobial, antiviral, anticancer activity, antioxidant, antiparasitic, antiproliferative, antitumor, anti-HIV, anticonvulsant, antiprotozoal, analgesic and anti-inflammatory, antihypertensive, anticancer, androgen receptor antagonist, vasorelaxant etc. This review is summarized to understand the chemistry of various derivatives of substituted benzimidazoles with their pharmacological activities.

Keywords: Substituted Benzimidazoles, Chemistry, Pharmacological activities.

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INTRODUCTION

Benzimidazole is a heterocyclic aromatic organic compound. It is a very important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic and consists of the fusion of benzene and imidazole [1]. Benzimidazole is a benzo derivative of imidazole. Although benzimidazole is the common name of the parent compound of the series, other names such as benzimidazole and 1,3-benzodiazole (Figure 1) are often used.

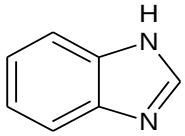


Figure 1: 1*H*-Benzimidazole

The properties of benzimidazole and its analogs have been studied for over hundred years. However a particular interest of researchers in benzimidazole derivatives was that 5, 6-dimethyl-1-(α-Dribofuranosyl)benzimidazole is a fundamental component of the structure of vitamine B_{12} [2]. Monoacyl derivative of o-phenylenediamine is converted by heat alone into the corresponding benzimidazole (Figure 2). These conversions are generally carried out at a temperature slightly above the melting point of the starting compounds. This is a convenient method for the synthesis of benzimidazoles when the monoacyl derivatives are readily obtained. The process can be improved by heating the monoacyl derivative of diamine in a nitrogen atmosphere to prevent oxidation. The diacyl derivatives of o-phenylenediamines are again converted into benzimidazoles, however higher temperatures are needed.

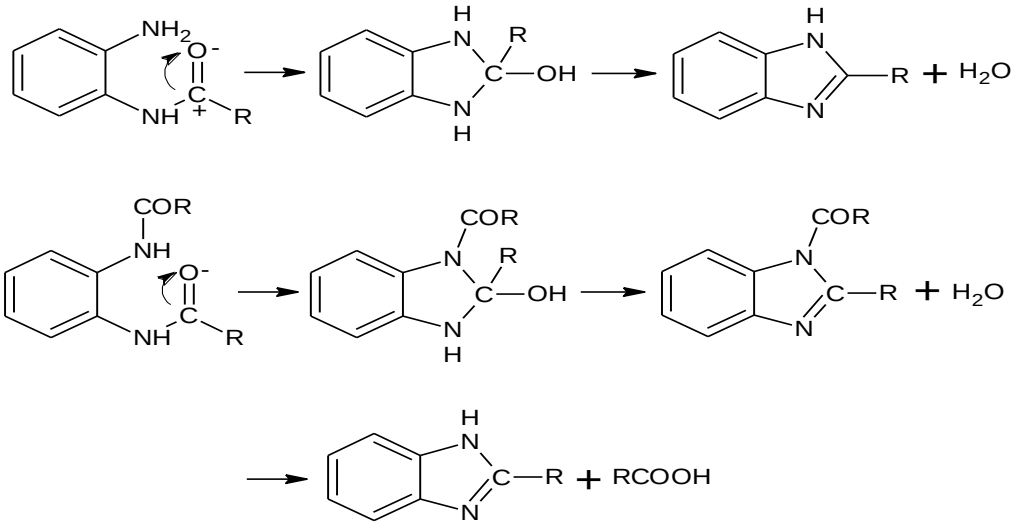


Figure 2: Synthesis of benzimidazole

Benzimidazole is also obtained from o-phenylenediamine and mono or di-basic acid. In this process, the diamine is simply heated with excess acid. This method has been recommended as a

means of identifying fatty acid α-hydroxy acid. Phenylacetic acid and diphenylacetic acid are converted to the corresponding benzimidazoles when heated with o-phenylenediamine. The Phillips modification of the above procedure consists in refluxing with the o-phenylenediamine and mono basic acid in 4N hydrochloric acid. The benzimidazole is then precipitated by neutralizing the solution with ammoniumhydroxide. Benzoic acid gives only traces of 2-phenylbenzimidazole (Figure 3). Apparently this method is not applicable to the aromatic monobasic acid.

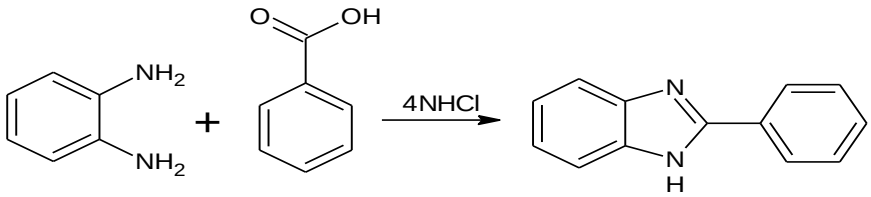


Figure 3: Phillips modification for the synthesis of benzimidazole

Benzimidazole and its derivatives are associated with various types of pharmacokinetic and pharmacodynamic properties.The benzimidazole nucleus is one of the bioactive heterocyclic compounds that have a number of biological activities. In particular, this core is part of vitamin B_{12}. The pharmacological activities of the benzimidazole containing moiety are well documented. Albendazole, Mebendazole and Thiabendazole are often used as anthelmintic drugs [3].

A literature review shows that the many derivatives of benzimidazole were synthesized because of their pharmacological activities. Some of the already synthesized compounds have found a very strong application in medical practice.

Antimicrobial activity:

Naaz F et al [4], reported that a new set of heterocyclic sulfonamide-bound molecules (Figure 4) was synthesized and tested for antibacterial activity. During antibacterial screening with the broath dilution method, it has been found that molecules are found to be highly active against different human pathogens, namely *B. cerus, S. aureus, E. coli* and *P. aeruginosa*, and most effective against *E. coli*. The results indicated a positive development of antibacterial lead using the combination approach.

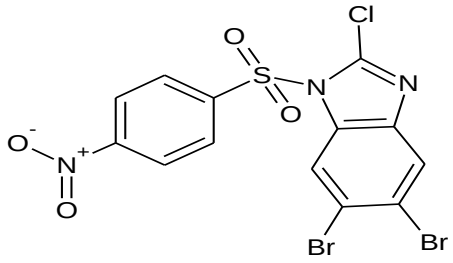
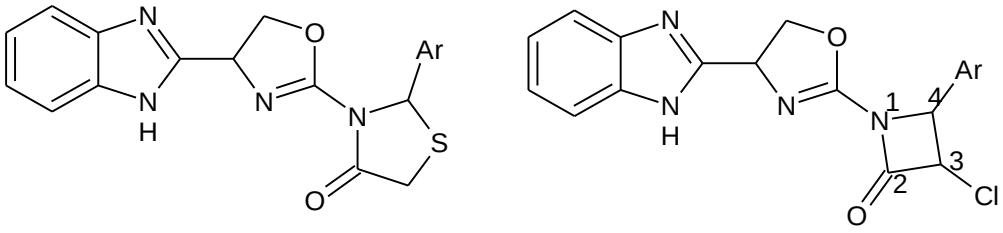


Figure 4: Sulphonamide derivative of benzimidazole

Kishore B et al [5], reported a new series of 3-[4-(1*H*-benzo[*d*] imidazol-2-yl) oxazol-2-yl]-2-thiazolidin-4-ones and 1-[4-(1*H*-benzo[*d*] imidazol-2-yl) oxazol-2-yl)-3-azetidin-2-ones (Figure 5) were prepared from 2-acetyl benzimidazole. The title compounds were tested for their antimicrobial activity. Some of the compounds show promising antimicrobial activity.



Ar= -C_6H_5, -2-ClC_6H_4, -2-BrC_6H_4, -4-$CH_3C_6H_4$, -4-$OCH_3C_6H_4$, -4-$N(CH_3)_2C_6H_4$, -2,4-$Cl_2C_6H_3$, -2,4-$Br_2C_6H_4$

Figure 5: 3-[4-(1*H*-benzo[*d*] imidazol-2-yl) oxazol-2-yl]-2-thiazolidin-4-ones and 1-[4-(1*H*-benzo[*d*] imidazol-2-yl) oxazol-2-yl)-3-azetidin-2-one derivatives

Antiparasitic effect:

Keurulainen L et al [6], designed, synthesized and tested a set of 2-arylbenzimidazoles against *Leishmania donovani*amastigotes. The left- and right- side rings of the molecule, as well as the amide linker were modified. 2-Arylbenzimidazole derivative (Figure 6) was active against *L. donovani*-infected THP-1 cells showing 46% parasite inhibition at 5 μM.

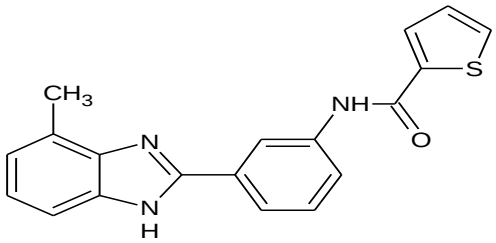


Figure 6: 2-Arylbenzimidazole derivative

Karale BK et al [7], synthesized a series of new thiadiazoles and triazoles (Figure 7, Table 1) anchored with benzimidazole and investigated their biological activities.

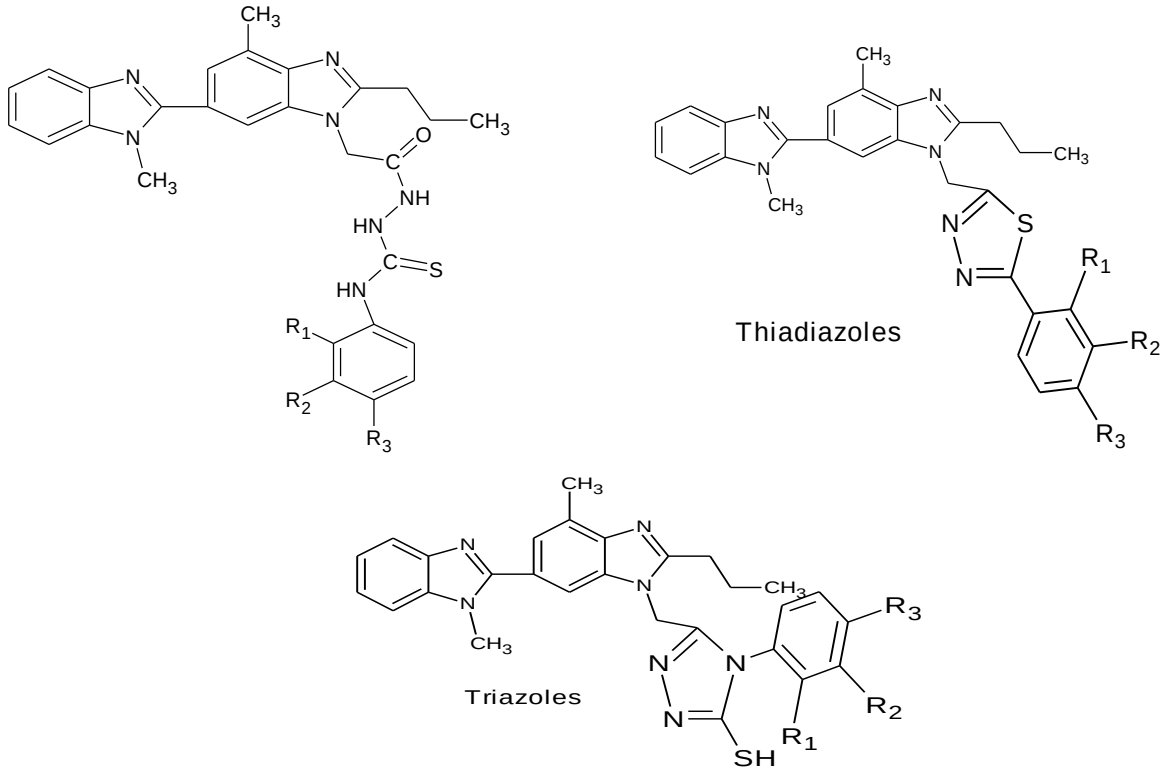


Figure 7: Benzimidazolyl anchored azoles

Table 1: Substituents for benzimidazolyl anchored azole derivatives

R_1	-H	-H	$-CH_3$	-H	$-OCH_3$
R_2	-H	-H	-H	$-CH_3$	-H
R_3	-H	$-CH_3$	-H	-H	-H

Antiulcer activity:

Nadeem H et al [8], reported that a series of six new benzimidazole-pyrazole hybrid molecule (Figure 8, Table 2) were synthesized and characterized. In vivo anti ulcerogenic activity was evaluated for all compounds synthesized. All six compounds synthesized showed higher anti-ulcer activity as compared against standard omeprazole. The results clearly show that these new benzimidazole-pyrazole hybrids may constitute a new category of potential anti ulcer compounds and may be considered as new anti-ulcer drugs upon further investigation.

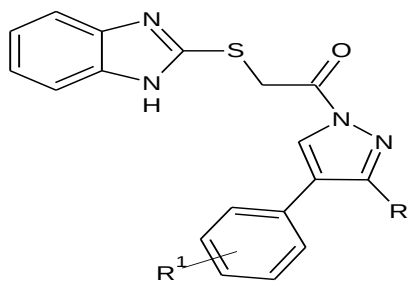


Figure 8: Benzimidazole–pyrazole hybrid molecule

Table 2: Substituents for benzimidazole-pyrazole derivatives

	a	b	C	d	e	f
R	$-C_6H_5$	$-2-OHC_6H_5$	$-2-OHC_6H_5$	$-4-OHC_6H_5NH$	$-C_6H_5$	$-3-OH,-4-OCH_3$
R^1	-2-OH	-2-OH	$-3-OH,-4-OCH_3$	-2-OH	-H	-H

Madala SR et al [9], reported that 1-methyl-2{[(3,4- di methoxy pyridine2-yl) methyl] sulfanyl}-5-nitro-1*H*-benzimidazole (Figure 9) was synthesized by coupling 1-methyl-2-mercapto-5-nitro-1H-benzimidazole with pyridine derivative in presence of a base at room temperature. The synthesized compound was tested for antiulcer activity by using the technique of cold and restraint ulcer. The results showed that the compound showed significant activity.

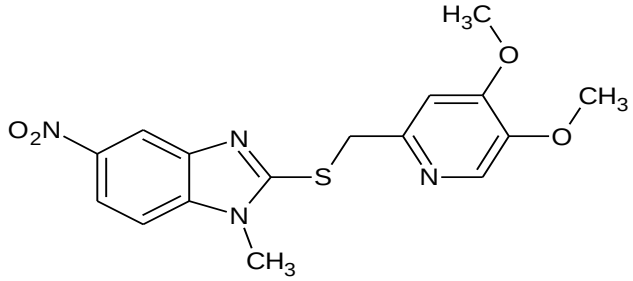


Figure 9: 1-methyl-2{[(3,4- di methoxy pyridine2-yl) methyl] sulfanyl}-5-nitro-1*H*-benzimidazole

Antiviral activity:

Kharitonova MI et al [10], reported that β-D-ribo- and 2′-deoxyribofuranosides of 2-amino-5,6-difluorobenzimidazole nucleosides (Figure 10) were synthesized using the enzymatic transglycosylation reaction. 2-Amino-5,6-difluoro-benzimidazole riboside exhibited selective antiviral activity against a wild strain of the herpes simplex virus, and against cidofovir, acyclovir and foscarnet resistant virus strains. It has been hypothesized that this compound can be used to treat herpes infections in such cases, when acyclovir is ineffective.

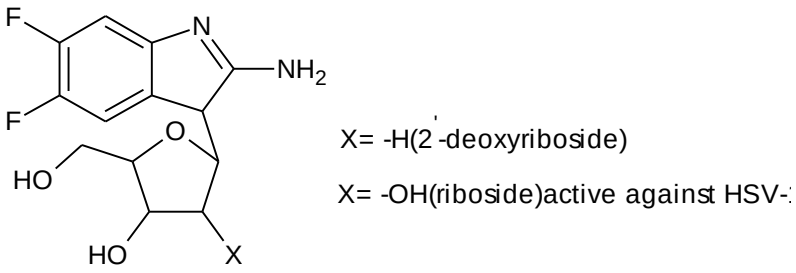


Figure 10: 2-amino-5,6-difluorobenzimidazole nucleosides

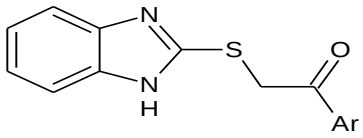
Zarubaev VV et al [11], synthesized a series of 1,3-disubstituted-2-iminobenzimidazolines (Figure 11) and a number of their tautomeric analogs. Synthesized compounds were tested for toxicity to MDCK cells and for inhibiting activity against influenza virus A/California/07/09 (H1N1) pdm09.

It has been found that some of synthesized benzimidazole derivatives have a potent virus-inhibiting activity against pandemic influenza virus with fairly modest cytotoxicity.

Figure 11: 1,3-disubstituted 2-iminobenzimidazolines

Antiproliferative activity:

Abdel-Aziz HA et al [12], reported that a series of 2-((benzimidazol-2-yl)thio)-1-arylethan-1-ones (Figure 12) were synthesized. All compounds were evaluated against anti-proliferative activity against the neoplastic colon HT-29 cell line. In addition, their inhibitory activity against cell surface expression of CD133, a potent marker for cancer stem cells (CSCs) in the same cells, was assessed by flow cytometry at 10 μM.



Ar = -2,3,4-$(OCH_3)_3$-C_5H_2

Figure 12: 2-((Benzimidazol-2-yl)thio)-1-arylethan-1-one derivatives

Kamal A et al [13], synthesized a new series of 2-aryl-1,2,4-oxadiazolo-benzimidazole conjugates (Figure 13) and investigated their antiproliferative activity in the group of sixty cancer cell lines. The compounds (**NSC**: 761109/1) and (**NSC**: 761814/1) showed remarkable cytotoxic activity against most of the cancer cell lines in the one dose assay and were administered at five dose levels (0.01, 0.1, 1, 10 and 100 μM) with GI_{50} values in the range of 0.79–28.2 μM. The flow cytometric results of these compounds showed increased cells in the G2/M phase, indicating a G2/M cell cycle arrest. Furthermore, these compounds showed inhibition of tubulin polymerization and disruption of microtubule formation.

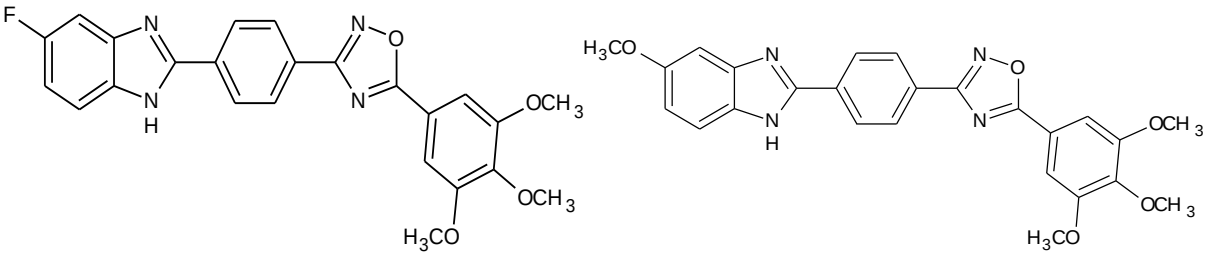


Figure 13: 2-aryl-1,2,4-oxadiazolo-benzimidazole conjugates

Antihypertensive activity:

Han XF et al [14], reported that novel angiotensin II receptor type 1 (AT_1) blockers bearing 6-substituted carbamoyl benzimidazoles with a chiral center were developed and synthesized as the first step in the development of new antihypertensive agents. The newly synthesized compounds were tested for their potential ability to displace [^{125}I] Sar^1 Ile^8-Ang II, which was specifically bound to human AT_1 receptor. The candidate (Figure 14) was identified on the basis of plasma analyses, toxicology studies, and chronic oral tests for its excellent efficacy in antihypertension and relatively low toxicity.

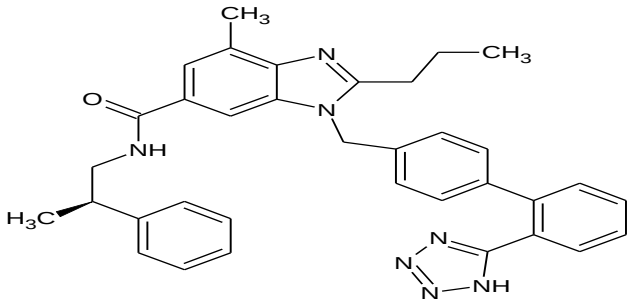


Figure 14: 6-substituted aminocarbonyl benzimidazole derivative

Wang JL et al [15], reported that a series of 6-substituted aminocarbonyl benzimidazole derivatives (Figure 15, Table 3) were designed and synthesized as nonpeptidic angiotensin II AT_1 receptor antagonists. The preliminary pharmacological evaluation revealed nanomolar AT_1 receptor binding affinity and good AT_1 receptor selectivity over AT_2 receptor for all compounds of the series.

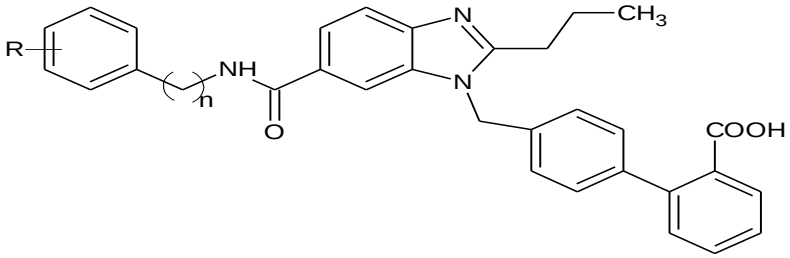


Figure 15: 6-substituted aminocarbonyl benzimidazole derivatives

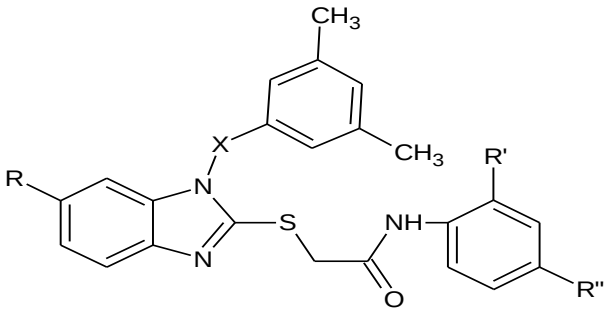
Table 3: Substituents for 6-substituted aminocarbonyl benzimidazole derivatives

N	1	1	1	1	1	2	2	2	2	2	2
R	-H	-2-OMe	-3-OMe	-4-OMe	-3,4-di-OMe	-3-OMe	-4-OMe	-3,4-di-OMe	-3,4-di-OMe	-2-F	-4-F

HIV Inhibitors:

MariaMonforte A et al [16], reported some N_1-aryl-2-arylthioacetamido-benzimidazoles (Figure 16) as a novel class of Non-nucleoside reverse transcriptase inhibitors (NNRTIs). Most of the new

compounds well tried to be very much effective in inhibiting every RT enzyme protein at nanomolar concentrations and HIV-1 replication in MT4 cells with low toxicity.



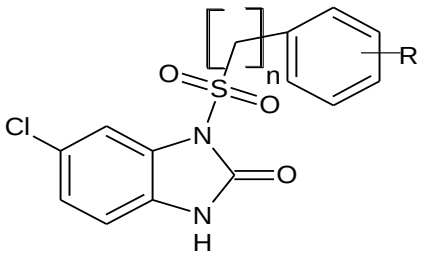
X = -CH_2, -SO_2

R = -H, -Cl

R' = -Br, -Cl, -NO_2; R"= -H, -CH_3, -$COOCH_3$, -SO_2CH_3, -SO_2NH_2

Figure 16: N_1-aryl-2-arylthioacetamido-benzimidazole derivatives

Ferro SF et al [17], reported that non-nucleoside reverse transcriptase inhibitors (NNRTIs) are an integral part of the currently available combination antiretroviral therapy (cART) which helps to reduce the AIDS-mortality and turned the disease from fatal to chronic. In this context, they recently reported a series of 6-chloro-1-(3-methylphenylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-ones (Figure 17) as potent non-nucleoside HIV-1 reverse transcriptase inhibitors. All the newly obtained compounds were evaluated as RT inhibitors and were co tested against RTs containing single amino acid mutations. Finally, molecular docking studies were conducted to rationalize the identified activity of the most promising compound.



R = -H, -2-Cl, -3-Cl, -4-Cl, -2-CH_3, -3-CH_3, -4-CH_3

n = 1 or 2

Figure 17: 6-chloro-1-(substituted-phenylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one derivatives

Antiprotozoal activity:

Farahat AA et al [18], prepared a series of novel benzimidazole diamidines (Figure 18) from the corresponding dicyano analogues either by using Pinner method or by preparing amidoximes intermediates which were reduced to the corresponding amidines. The new amidines were

evaluated against the protozoan parasite *Trypanosoma brucei rhodesiense* by *in vitro* method. The thiophene analogue and the *N*-methyl compound showed superior antitrypanosomal activity compared to that of the parent I.

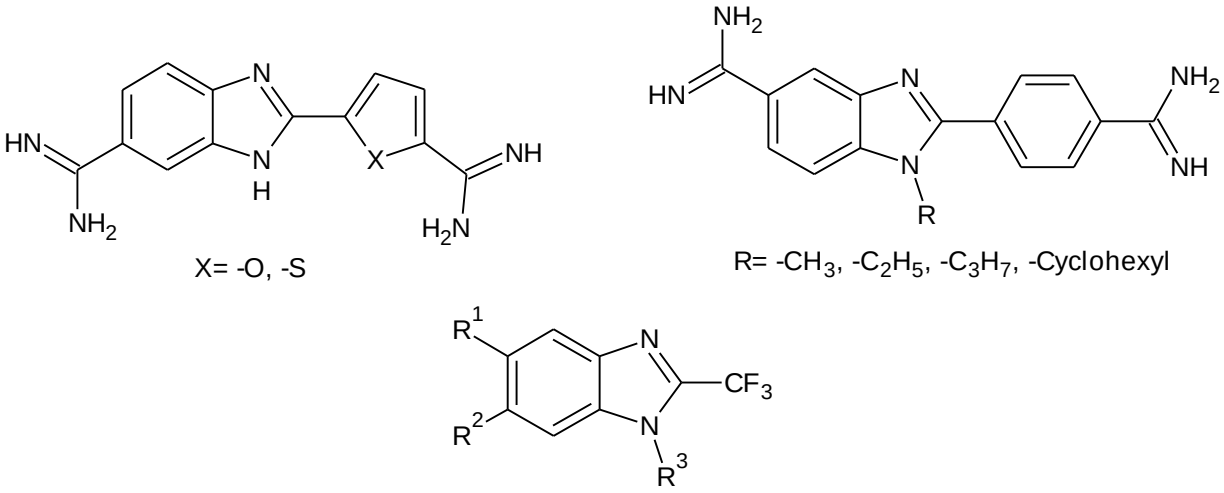


Figure 18: Benzimidazole diamidine analogues

Karaaslan C et al [19], synthesized a number of mono and dicationic new 2-anilinobenzimidazole carboxamidines (Figure 19) starting from 4-amino-3-nitrobenzonitrile and corresponding o-phenylenediamines. Their antiparasitic activity against *Plasmodium falciparum* and *Trypanosoma brucei rhodesiense* was investigated *in vitro*. Some of the dicationic compounds showed equal or very close activity against *T.b. rhodesiense* with melarsoprol and co-exhibited a promising activity against *P. falciparum* compared to chloroquine.

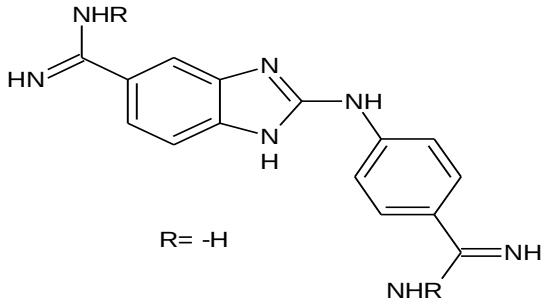


Figure 19: mono and dicationic-2-anilinobenzimidazole carboxamidines

Antitumor activity:

Gu W et al [20], designed and synthesized a series of new 1*H*-benzo[*d*]imidazole derivatives of dehydroabietic acid (Figure 20) as potent antitumor agents. In the *in vitro* method, most of the compounds showed significant cytotoxic activity against two carcinoma cells (SMMC-7721 and HepG2) and reduced toxicity to noncancerous human hepatocyte (LO2).

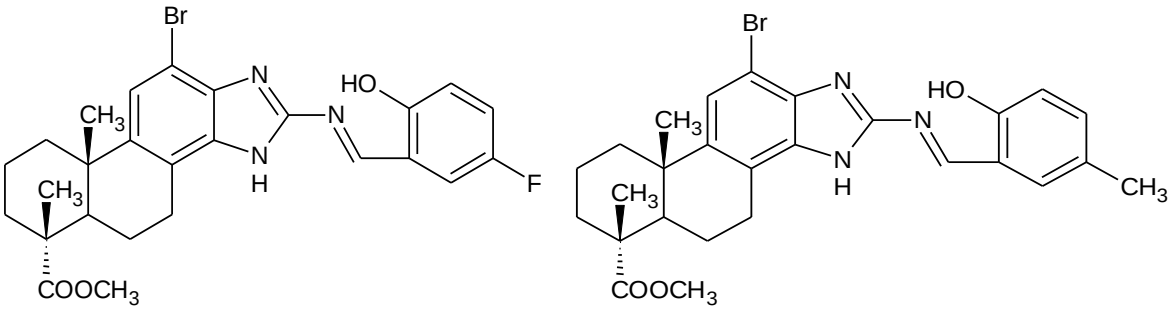
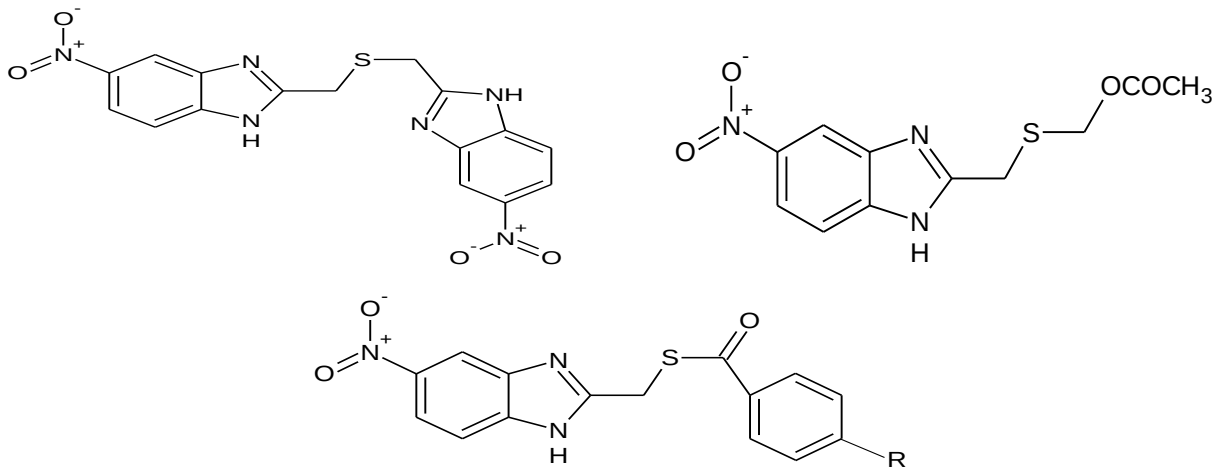


Figure 20: 1*H*-benzo[*d*]imidazole derivatives of dehydroabietic acid

El-Gohary NS et al [21], prepared and tested new benzimidazole analogs (Figure 21) for anti-tumour activity. *In vitro* antitumor screening of the new benzimidazoles toward HepG2, HCT-116 and MCF-7 cancer cell lines showed that these compounds are the most potent analogs to all cell lines tested. The three potent *in vitro* antitumor analogs were further examined for the *in vivo* method of antitumor activity on EAC in mice, and *in vitro* cytotoxicity against the normal W138 cell line. The results showed that compound 1 has the highest *in vivo* activity and that the three analogs tested are less cytotoxic to the normal W138 cell line than 5-FU.



R= a) -Cl; b) –Br

Figure 21: Some new benzimidazole analogs

Analgesic and Anti-inflammatory activity:

Gote SA et al [22], reported that a series of 7-chloro-2-[3-(1*H*-benzimidazol-2-yl)-5-aryl-4,5-dihydro-1*H*-pyrazol-1-yl]-6-fluoro-1,3-benzothiazole (Figure 22) was synthesized by the action of 7-chloro-6-fluoro-2-hydrazino-1,3-benzothiazole on chalcones in the presence of catalytic amount of glacial acetic acid and ethanol. The synthesized compounds were tested for their anti-inflammatory and analgesic activity.

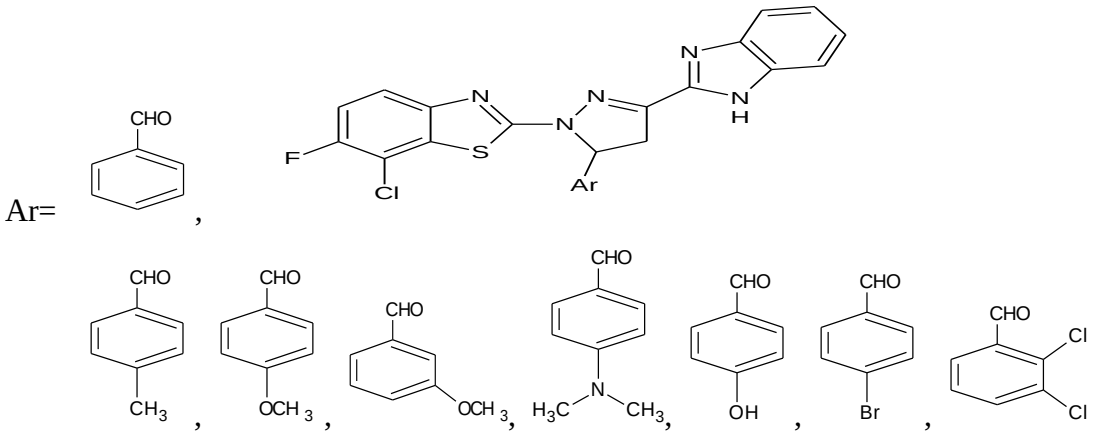
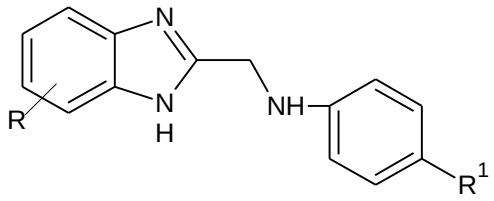


Figure 22: 7-chloro-2-[3-(1*H*-benzimidazol-2-yl)-5-aryl-4,5-dihydro-1*H*-pyrazol-1-yl]-6-fluoro-1,3-benzothiazole derivatives

Hosamani KM et al [23], reported that a series of 2-methylaminobenzimidazole derivatives (Figure 23) were synthesized by the reaction of 2-(chloromethyl)-1*H*-benzimidazole derivatives with primary aromatic amines. Some of the compounds showed strong analgesic (89% at 100 mg/kg b.w) and anti-inflammatory (100% at 100 mg/kg b.w) activities compared to standard drug Nimesulide (100% at 50 mg/kg b.w).



R= -H, -Br, -NO_2

R^1= -H, -Cl, -Br, -CH_3, -OCH_3

Figure 23: 2-Arylaminomethylbenzimidazole derivative

Antioxidant activity:

Karaali N et al [24], reported that a number of new 2-(4-nitrobenzyl)-1*H*-benzimidazole derivatives with thiosemicarbazide, triazole, oxadiazole and thiadiazole units (Figure 24, Table 4) are present in the 1st position of benzimidazole ring has been synthesized and tested for its antioxidant activity. The inhibitor activities of the synthesized compounds were determined with CUPric Reducing Antioxidant Capacity (CUPRAC), ABTS (2,2-azinobis(3-ethylbenzothiazoline-6-sulfonicacid)/persulfate and DPPH (1,1-diphenyl-2-picrylhydrazyl) assays. Most of the compounds show significant antioxidant activity.

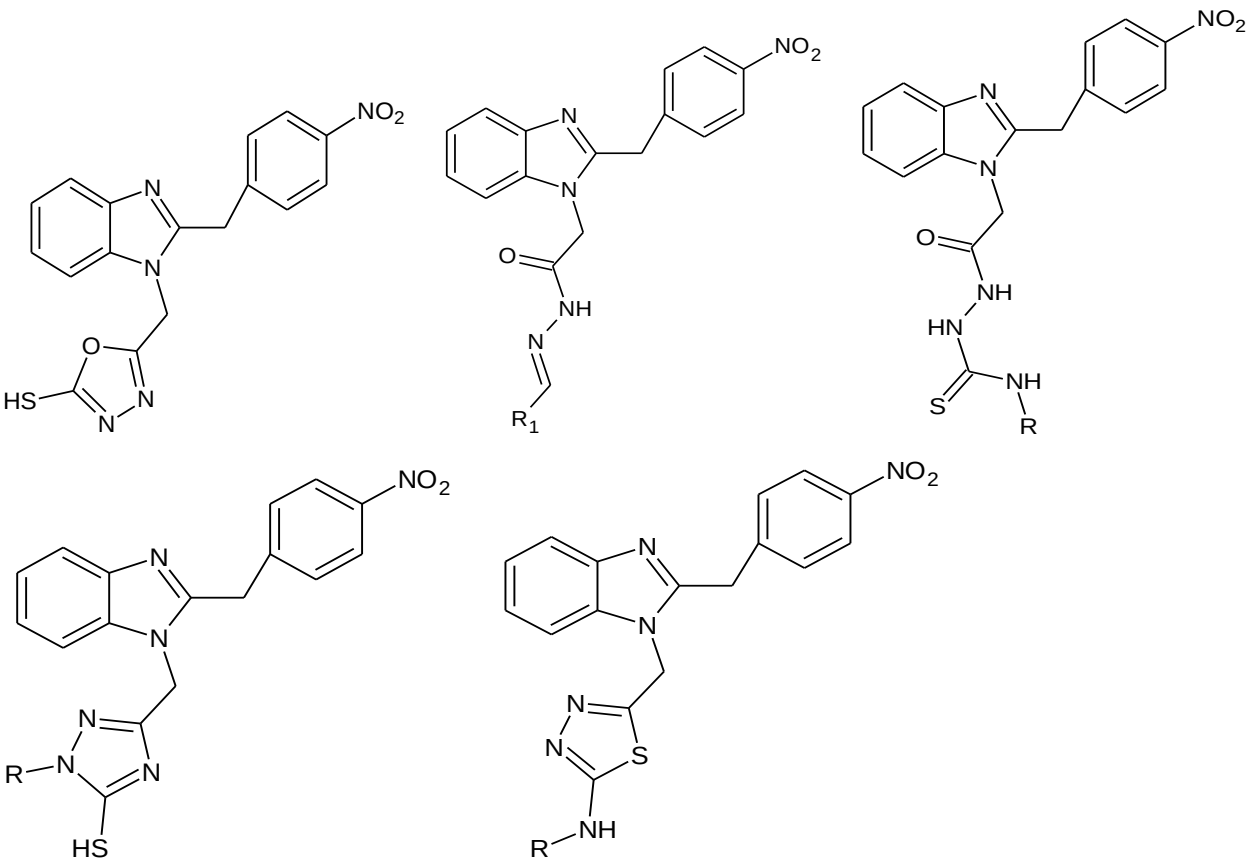
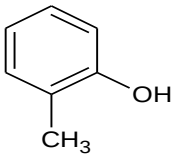
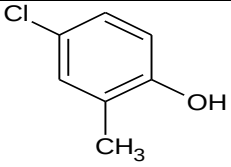
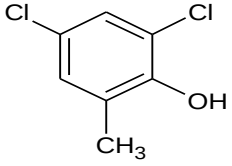


Figure 24: 2-(4-nitrobenzyl)-1*H*-benzimidazole derivatives bearing thiosemicarbazide, triazole, oxadiazole and thiadiazole moieties

Table 4: Substituents for 2-(4-nitrobenzyl)-1*H*-benzimidazole derivatives bearing thiosemicarbazide, triazole, oxadiazole and thiadiazole moieties

	a	b	c
R	-CH_3	-C_2H_5	-C_6H5
R_1			

Taha M et al [25], reported that novel 4-Methylbenzimidazole derivatives (Figure 25) were synthesized and evaluated for their antioxidant activity. All synthesized compounds were evaluated for DPPH activity. Some of the compounds showed excellent activities, ranging 12-29 μM, better than the standard drug n-Propylgallate (IC_{50} ¼ 30.30 ± 0.40 μM). For superoxide anion scavenging activity, many of the compounds showed better activity than standard n-Propylgallate (IC_{50} ¼ 106.34 ± 1.6 μM) and ranged from 82-104 μM.

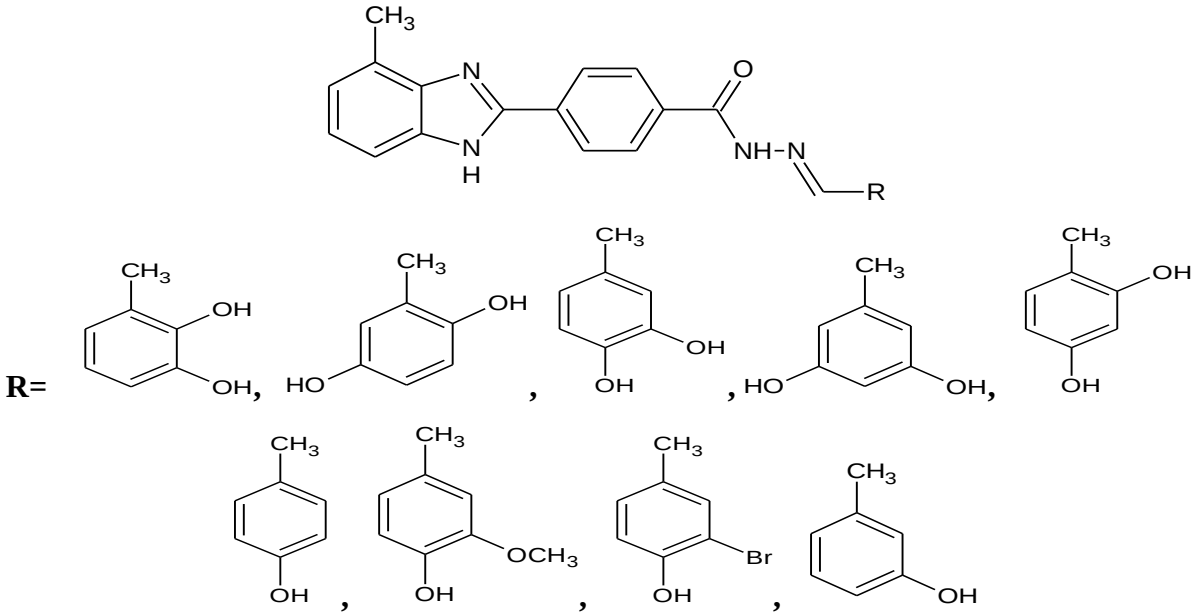


Figure 25: 4-Methylbenzimidazole derivatives

Anticancer activity:

Mook Jr RA et al [26], developed a new class of benzimidazole inhibitors of Wnt/β-catenin signaling based on SAR studies of the Niclosamide salicylanilide chemotype. These studies identified 4-chloro-2-(5-(trifluoromethyl)-1*H*-benzo[d]imidazol-2-yl) phenol (Figure 26) and concerned derivatives with higher Wnt/β-catenin signaling inhibition vs. differential effects on cellular ATP homeostasis. These compounds may be useful in elucidating the mechanism of Niclosamide's inhibition of Wnt signaling, and may aid in the discovery of inhibitors having improved pharmacologic properties in the treatment of cancer and diseases in which Niclosamide has vital biological activity.

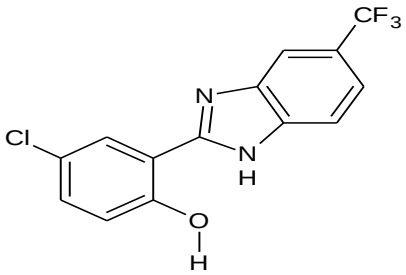
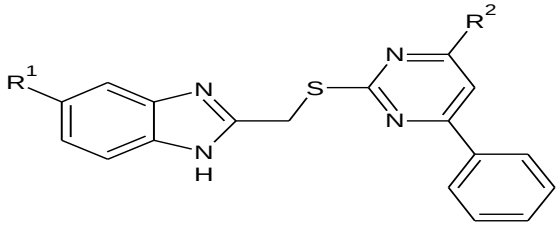


Figure 26: 4-chloro-2-(5-(trifluoromethyl)-1*H*-benzo[d]imidazol-2-yl) phenol derivative

Shao KP et al [27], synthesized a series of pyrimidine–benzimidazol hybrids (Figure 27) and investigated anticancer activity in four human cancer cell lines including MCF-7, MGC-803, EC-9706 and SMMC-7721. Some of the synthesized compounds showed moderate to strong activity against MGC-803 and MCF-7.



R^1= -H, R^2= -4-CH_3O-C_6H_5-NH-

R^1= -Cl, R^2= -4-CH_3O-C_6H_5-NH-

Figure 27: Pyrimidine–benzimidazole derivatives

Androgen receptor antagonist:

Ng RA et al [28], described the synthesis and *in vivo* SAR of 5,6-dichloro-benzimidazole derivatives (Figure 28) as new selective androgen receptor antagonists. During the screening of 2-alkyl benzimidazoles, it has been found that a trifluoromethyl group greatly improves antagonist activity in the prostate. This Benzimidazole derivative is a potent AR antagonist in the rat prostate (ID_{50} = 0.15 mg/day).

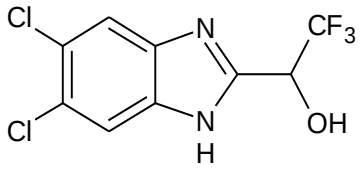
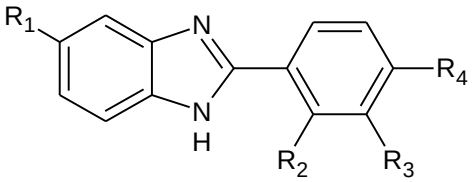


Figure 28: 5,6-dichloro-benzimidazole derivative

Vasorelaxant activity:

Navarrete-Vazquez G et al [29], reported that a series of 1*H*-benzo[d]imidazole analogues (Figure 29) of Pimobendan, substituted at position 5 with either $–CF_3$ or $–NO_2$, were synthesized using a short synthetic route. All the nitro derivatives were potent, and showed a partial endothelium-dependent vasorelaxant effects, with EC_{50}s <5 μM. 2-Methoxy-4-[5-nitro-1H-benzo[d]imidazol-2-yl]phenol was the most potent derivative in the series, showed an EC_{50} value of 1.81 μM and Emax of 91.7% for ex vivo relaxant response in intact aortic rings, resulting in a 2.5-fold higher activity compared to Pimobendan. The closely related 5-CF_3 analogue was 19 times less potent than $–NO_2$ substituted compound.



R^1= -CF_3, -NO_2

R^2= -H, -OMe, -OEt, -NO_2, -OiPr,

R^3= -H, -OMe, -O-CH_2-O,

R^4= -H, -OH, -OPr, -$N(Me)_2$, -OMe

Figure 29: Pimobendan analogues of 1*H*-benzo[d]imidazole

CONCLUSION

The present literature reveals that the benzimidazole nucleus, which can potentially be used in the field of drug discovery area and medicines, has versatile biological activities. In future, therefore, there is a great scope for developing a new class of substituted benzimidazoles to show better efficacy.

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