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A comprehensive review on 2-substituted benzimidazole derivatives and its biological importance

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Abstract

Condensation of o-phenylene-diamine with formic acid is used in the synthesis of commercially available benzimidazole. N-ribosyldimethyl benzimidazole is the most common benzimidazole compound found in nature, and it functions as an axial ligand for cobalt in vitamin B12. The benzimidazole and its derivatives are important therapeutic agents, such as antiulcer and anthelmintic drugs. Benzimidazole compounds also possess antimicrobial, antiviral, anticancer, anti-inflammatory, analgesic, and other pharmacological properties. The chemistry and pharmacological actions of substituted benzimidazoles are summarised in this article.

Keywords: Mechanism; Therapeutic Agents; Heterocyclic Compounds; Synthetic Products

1 Introduction

The accepted name for the parent compound in the series, whose numbering follows the accepted pattern for heterocyclic compounds, was imidazole. In imidazole or imidazoline, an azapyrrole, the nitrogen atom was separated by one carbon atom. This molecule was previously known as glyoxalin because it was first synthesised in 1958 from glyoxal and ammonia. Benzimidazole is the name given to the benzyl derivative of imidazole by Bansal. The common name for the series is benzimidazole; other names for benzimidazole include benzimidazole and 1,3-benzodiazole in figure 1. By using only heat, the monoacyl derivative of o-phenylenediamine can be easily converted into the corresponding benzimidazole [1].

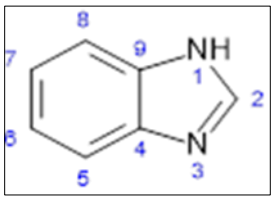

Figure 1 H-Benzimidazole

2 Chemistry of Benzimidazole

Benzimidazoles are thought to be a promising class of bioactive heterocyclic compounds with a wide range of biological activities. This nucleus in particular is a component of vitamin B12. Benzimidazole is a fused aromatic imidazole ring system in which a benzene ring is fused to positions 4 and 5 of an imidazole ring. It is also known as azindole,

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benzoglyoxaline, NCS759, N, N'-methyl-o-phenylenediamine, 1, 3- diazaindene, 1-H-benzimidazole, o-benzimidazole, BZI, 3-azaidole. They have both acidic and basic properties. The NH group present in benzimidazole is relatively strongly acidic and also weakly basic. Another characteristic of benzimidazole is that they have the capacity to form salts. Unsubstituted NH groups in benzimidazole exhibit fast prototrophic tautomerism, resulting in an equilibrium mixture of asymmetrically substituted compounds [2].

2.1 General method for the synthesis of 2-substituted benzimidazole derivatives

A mixture of o-phenylenediamine (0.1 mol) and monochloroacetic acid (0.1 mol) was refluxed for 3 h in 4 N hydrochloric acid (50 mL) on a water bath. The reaction mixture was cooled and basified with ammonium hydroxide solution. The precipitate thus obtained was dried and recrystallized from methanol with activated charcoal treatment. The pure product obtained was a slightly yellow-coloured crystals. A mixture of 2-chloromethyl benzimidazole (0.01 mol), substituted primary aromatic amine (0.01 mol) and KI (0.01 mol) in 50 mL of ethanol was heated under reflux for 6 hrs, KOH (0.01 mol in 5 mL of water) was added with continuous stirring for 2 hrs. Finally, the reaction mixture was left aside at room temperature and then poured into crushed ice. The solid product that precipitated was filtered off, recrystallized from ethanol and dried in vacuum desiccators. The synthetic route for the target compounds **3a–3j** is shown in Figure 2 and substitution for various derivatives are shown in Table 1 [3].

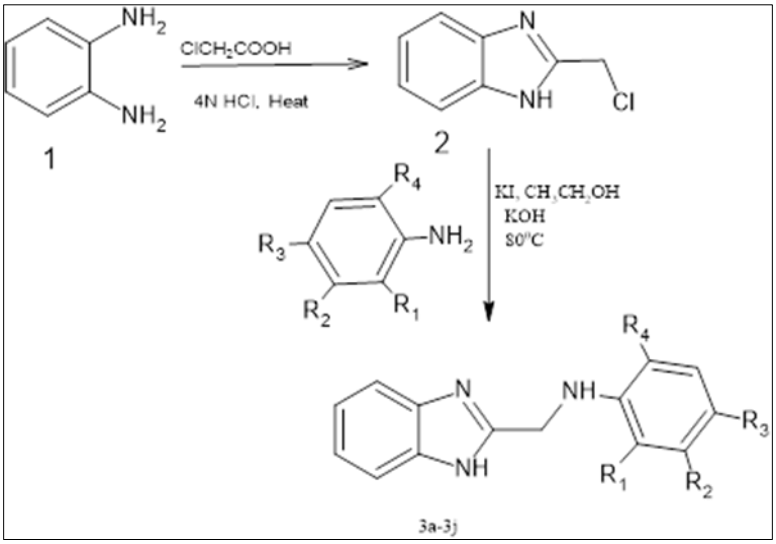


Figure 2 2-substituted benzimidazole derivatives

Table 1 Derivatives of 2-chloromethyl benzimidazole

Comp. code	R_1	R_2	R_3	R_4	Comp. code	R_1	R_2	R_3	R_4
3a	H	Cl	Cl	H	3f	H	H	F	H
3b	Cl	Cl	H	H	3g	Br	H	Br	Br
3c	NO_2	H	H	H	3h	Cl	H	NO_2	H
3d	H	H	NO_2	H	3i	H	H	SO_2NH_2	H
3e	H	NO_2	H	H	3j	H	H	I	H

In a 250 ml RBF, 2-Chloromethyl-1H-benzimidazole (0.01 mol,1.665gm) and K_2CO_3 (2.76gm,0.02mol) were stirred at room temperature in dimethylformamide (DMF, 20 ml) for half an hour and pinch of KI was added. After that various derivative of aniline (0.095 g, 0.01 mol) was added to reaction mixture which was refluxed for 16 hrs. until TLC showed completion of reaction. The reaction mixture was poured into water (20 ml) and the mixture was extracted with ethyl acetate (3X20 ml). The organic extracts were washed with water, dried over anhydrous sodium sulphate and

concentrated to obtain crude product. The residue was recrystallized from diethyl ether to give pure compound. The synthetic route for various derivatives are mentioned in below **figure 3** and various derivatives are mentioned as R [4].

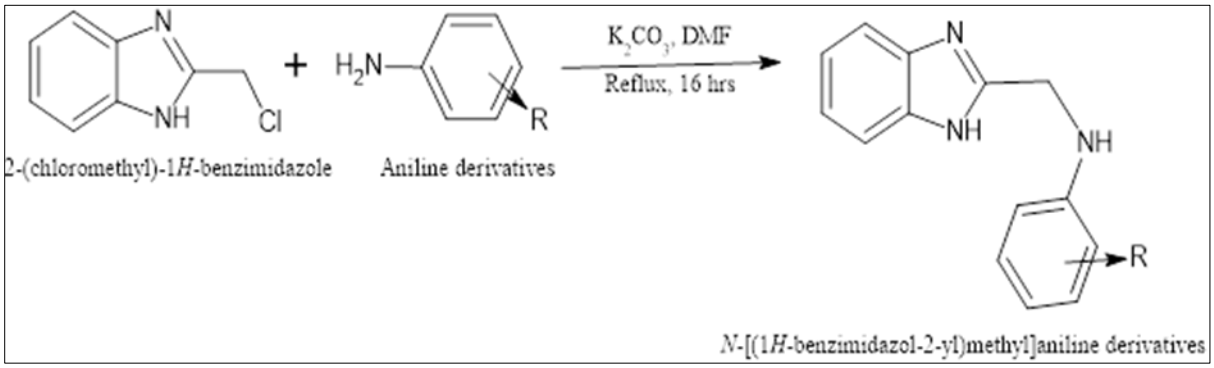


Figure 3 N- [(1H- benzimidazole-2-yl) methyl] aniline derivatives

Condensation of 2-(chloromethyl)-1H-benzimidazole derivatives with various substituted aromatic amines (10 mmol) and KI (10 mmol) in 50 mL of ethanol was heated under reflux. After 6 h, KOH (10 mmol in 5 mL of water) was added with continuous stirring for 2 h. Finally, the reaction mixture was left aside at r.t. and then poured into crushed ice water. The solid products that precipitated were filtered off and recrystallized from ethanol. The synthetic route for various derivatives are mentioned in below **figure 4** and various derivatives are mentioned as R and R^1 in table 2 [5].

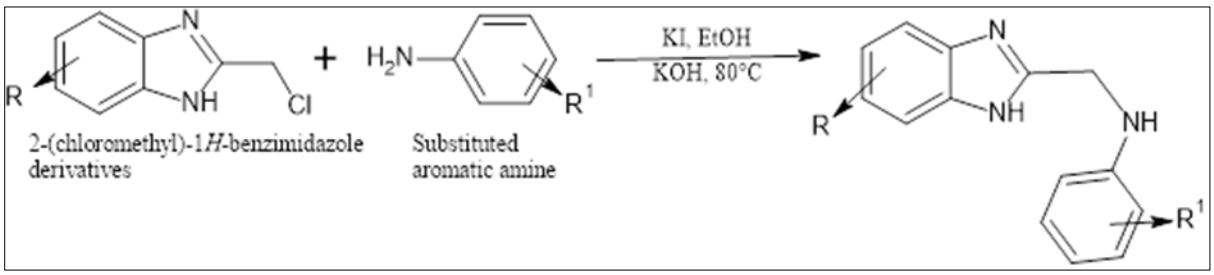


Figure 4 N- [(1H- benzimidazole-2-yl) methyl] aniline derivatives

Table 2 Various substitution for 2-(chloromethyl)-1H-benzimidazole

Compounds	**R**	**R^1**
1	H	H
2	H	Cl
3	H	Br
4	H	OCH_3
5	Br	H
6	Br	Cl
7	Br	Cl
8	Br	Br
9	Br	OCH_3
10	Br	CH_3
11	NO_2	Br

General procedure for the preparation of the 2-(4- amino phenyl) benzimidazole

O-Phenylenediamine was condensed with p-amino benzoic acid in poly phosphoric acid at 190-195 ^{0}C for 4 h. The reaction mixture was poured into crushed ice. Filtered, washed, dried and recrystalized. The product 2-(4-aminophenyl) benzimidazole was then treated with various aromatic aldehydes to obtain the Schiff bases compounds. The synthetic route for various derivatives are mentioned in below **figure 5** and various derivatives are mentioned as R [6]

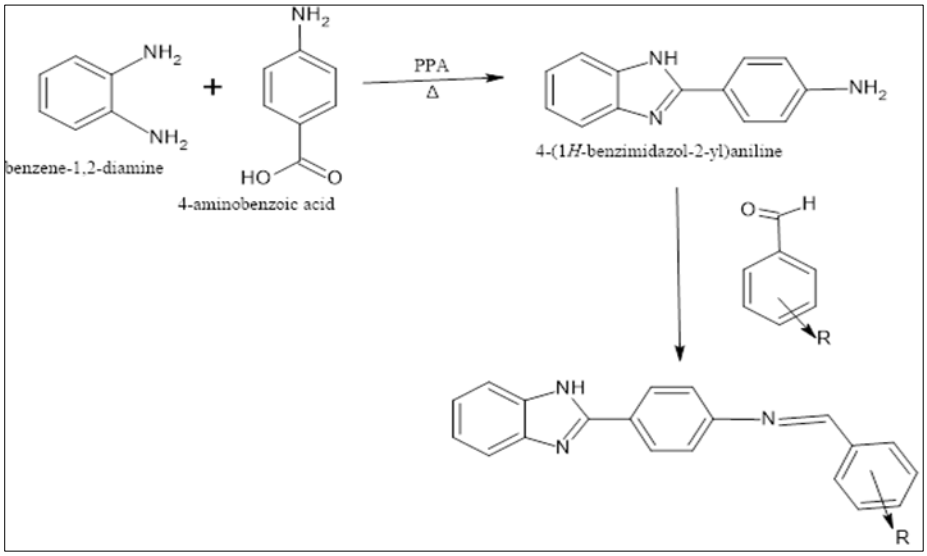


Figure 5 2-(4- amino phenyl) benzimidazole derivatives

3 Biological activities of Benzimidazole

This molecule possesses a wide diversity in terms of its biological profile. Benzimidazole and its derivatives acts as anticonvulsant agents, anti-inflammatory, antiprotozoal, diuretic, antihypertensive, antitumour, antibacterial, protein kinase inhibitor etc. Some of the activities are summarized in the figure 6.

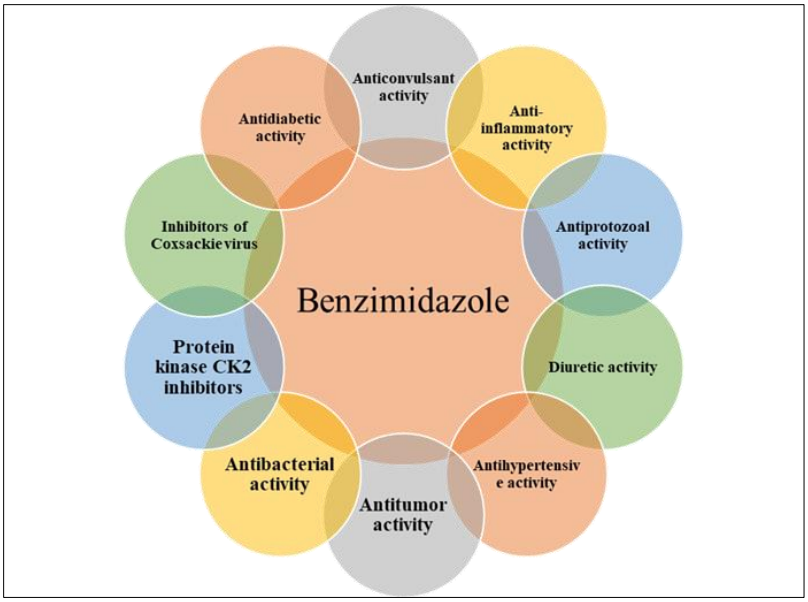


Figure 6 Biological activities of Benzimidazole

4 Study on Structural Modifications and their Pharmacological Actions

4.1 Anti-inflammatory activity

The benzimidazole moiety with carboxylic acid substitution in the second position meets the minimum and desirable structural requirements found in the majority of marketed anti-inflammatory drugs. Thakurdesai et al. synthesised benzimidazole-2-carboxylic acid and tested it for acute anti-inflammatory activity in a rat paw edema model induced by carrageenan. The test compounds were found to be safe at doses of up to 2000 mg/kg p.o. and to have good anti-inflammatory activity at doses of 100 mg/kg p.o. and higher. Their activity is largely determined by the substituents at position 5 and the length of the chain at position 2 of the benzimidazole moiety. Activity was found to increase with 1-benzyl substitution. Leonard et al. reported the synthesis and anti-inflammatory activity of various substituted phenyl benzimidazoles [7].

4.2 Antibacterial activity

Goker et al. synthesised and tested a series of 1, 2-disubstituted-1Hbenzimidazole-N alkylated-5-carboxamidine derivatives for antibacterial activity against Staphylococcus aureus and methicillin resistant Staphylococcus aureus. The study found the best activity against these species, with MIC values ranging from 0.78 to 0.39g/mL. Mohamed et al. synthesised 1-(substituted-methyl)-2(substituted-phenyl) benzimidazoles, and compounds 3a, 3b, and 3c were tested for antibacterial activity against S. aureus, B. pumillus, and P. aeurugenosa. Compound 3a had a MIC of 6.25 at 100 m/ML and demonstrated good antibacterial activity. Various chloro and dichloro substituted benzimidazoles are also antibacterial [8].

4.3 Antitumor activity

Balram Soni et al. synthesised a series of benzimidazole derivatives and tested them for cytotoxicity in vitro. The cytotoxic activity study revealed that compounds with a 2-chloro on aromatic ring and a 2-NO_2 on benzylidene amino group (4) have better cytotoxic activity against the human K-562 cell line in most cases [9].

4.4 Antihypertensive activity

Kohli et al. synthesised a series of 4'-(6-Methoxy-2-substituted-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acids. IR, 1H, NMR, MS, and elemental analysis have confirmed that 4-methoxy-1, 2-phenylenediamine, and different substituted carboxylic acids can be synthesised quickly and in good yields in the presence of BF3OEt2 as a catalyst with biphenyl carboxylic acid. The compounds in the title have been tested for antihypertensive activity using both direct and indirect methods. Some of these compounds (5a, 5b, 5c, 5d, and 5e) have been shown to have potent antihypertensive properties [10].

4.5 Diuretic activity

Diuretic activity of indolyl benzimidazoles (6) was carried out by Vittal Rao et al. Compounds 6a, 6b and 6c showed significant increase in urine volume (LV=2) and also urinary excretion of Na^+ and K^+.

Srinivasan et al. synthesised 3-(2-methyl-1, 2-dihydropyrimido (1, 2-c) benzimidazole-1-thionyl)-6, 8-dibromo-2-substituted-3H quinazolin-4-one (7) and reported that compounds 7a and 7b demonstrated moderate diuretic activity [11].

4.6 Antiprotozoal activity

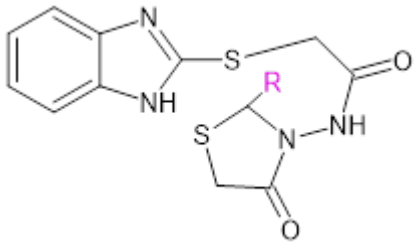
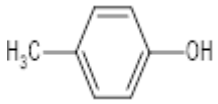
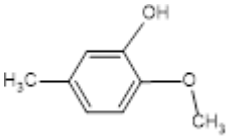
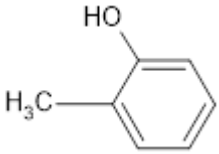
Vazquez et al. synthesised and tested 2-(trifluoromethyl)-1H-benzimidazole for anti-protozoal activity. Using a short synthetic route, a series of 2-(trifluoromethyl)-1H benzimidazole derivatives (8) with 5 and 6 position bio isosteric substituents (-Cl, -F, -CF3, -CN) were prepared. Analogues were tested in vitro against the protozoa Giardia intestinalis and Trichomonas vaginalis, with IC_{50} values of 1 M, and compound (8) was found to be more active than albendazole against T. vulgaris, as well as showing moderate antimalarial activity against Plasmodium falciparum W2 and D6 strains [12].

4.7 Antimicrobial activity

The antimicrobial activity of 1,4-dihydropyrimido[1,2-a] benzimidazoles was determined by Ranjit et al. based on the Biginelli like cyclocondensation of aromatic aldehydes and acetoacetic acid derivatives with 2-amino benzimidazole containing a guanidine fragment and synthesised compounds were evaluated for antimicrobial activity against Escherichia coli, Streptococcus pneumoniae and Staphylococcus aureus. Ansari et al. reported the efficient synthesis of

novel 3- chloro-1-5-(2-methyl-1H-bezimidazol-2-yl)-4-(substituted) phenylazetidin-2-one, and the synthesised compounds were tested for antimicrobial activity against B. substilis and E. coli, with compound 9a and 9b showing MIC at 100g/ml, 100g/ml, and 200g/ml dose [13] and compounds are mentioned in Table 3.

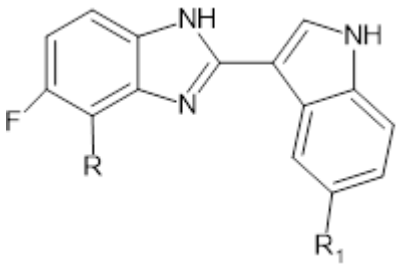
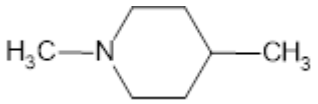
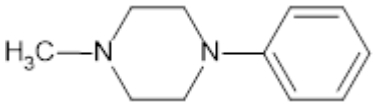
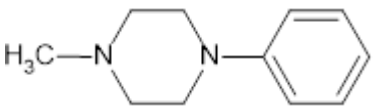
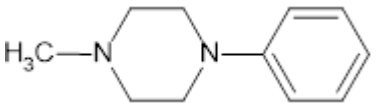
Table 3 1,4-dihydropyrimido Derivative

1,4-dihydropyrimido Derivative	R		
			

4.8 Anticonvulsant activity

Stables and colleagues created 2-substituted benzimidazole derivatives (10). The synthesised compounds 10a and 10b demonstrated anticonvulsant activity and percentage of activity (88 percent, 76 percent, and 84 percent, respectively), with compound 10a demonstrating the highest percentage of activity against maximal electroshock therapy and derivatives are mentioned in the Table 4 [14].

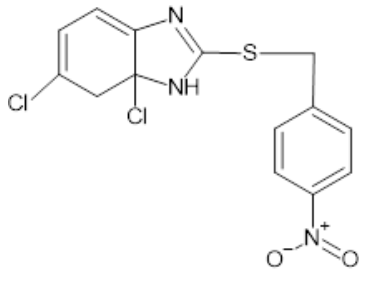
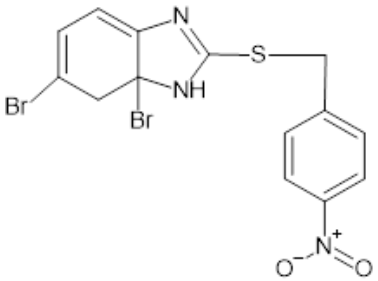
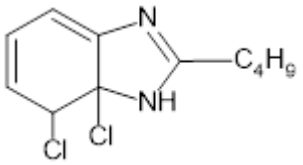
Table 4 5-fluoro-2-(1*H*-indol-3-yl)-1*H*-benzimidazole derivatives

Compound code	5-fluoro-2-(1*H*-indol-3-yl)-1*H*-benzimidazole derivatives	R	R_1
10a			H
10b			H
10c			Br
10d			OCH_3

4.9 Antimycobacterial activity

Kazimierczuk et al. reported the synthesis of substituted 2-polyfluroalkyl and 4-nitrobenzyl sufanyl benzimidazole, and the compounds were tested for antimycobacterial activity against mycobacterium strains. The compounds demonstrated significant antimycobacterial activity. Compounds 11a, 11b, and 11c had MIC values of 2mol l-1, 2mol l-1, and 4mol l-1, respectively [15] and derivatives are mentioned in the Table 5.

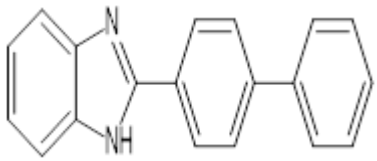
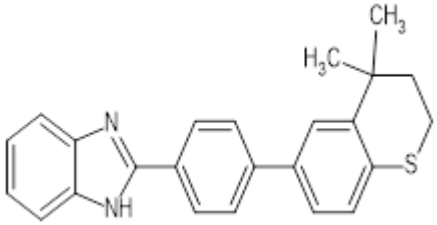
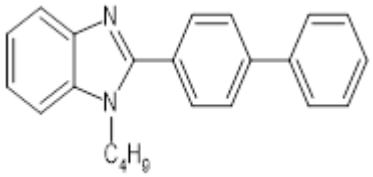
Table 5 Substituted 2-polyfluroalkyl and 4-nitrobenzyl sufanyl benzimidazole derivatives

11a	11b	11c
		

4.10 Antidiabetic activity

Kumar et al. reported the synthesis of a series of novel and functionalized benzimidazole derivatives. Antidiabetic activity against DPP-IV and PTP-IB was demonstrated by the synthesised compounds. Compounds 13a and 13b inhibited PTP-IB (1.64 percent and 2.42 percent, respectively) at 30μM doses, while compound 13c inhibited DPP-IV (3 percent) at 0.3μ M doses [16, 17] and they are shown in Table 6.

Table 6 2-([1,1'-biphenyl]-4-yl)-1H-benzimidazole derivatives

13a	13b	13c
		

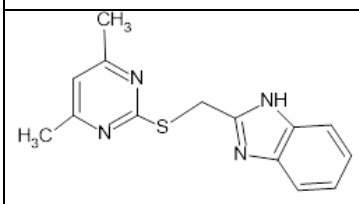
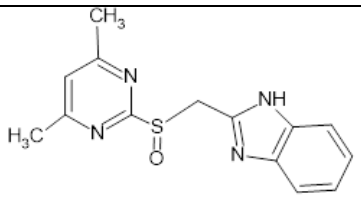
4.11 Analgesic activity

Sravanthi et al. reported the synthesis of 2-substituted benzimidazoles. Compounds 14a, 14b, and 14c showed analgesic activity when tested for analgesic activity using the tail flick method at 25 mg/kg doses orally and compared to indomethacin (86 percent , 85 percent and 74 percent)[18].

4.12 Antiulcer activity

Compounds 15a and 15b were synthesised and tested for antiulcer activity by Bariwal et al. Compounds 15a and 15b at 10 and 30 mg/kg doses reduced ulcer formation significantly, comparable to standard (Omeprazole), and compound 15a (sulfinyl derivative) was found to be more effective than compound 15b (thioderivative) [19] are mentioned in the Table 7.

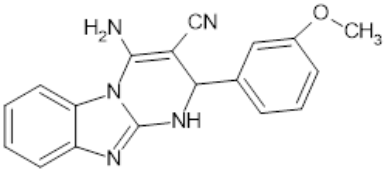
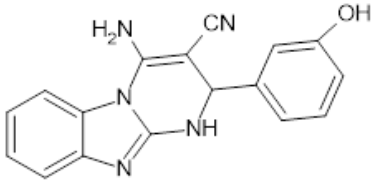
Table 7 2-{[(4,6-dimethylpyrimidin-2-yl) sulfanyl] methyl}-1*H*-benzimidazole derivatives

15a	15b
	

4.13 Antifungal activity

Deshmukh and colleagues created a 2, 3, 4, -trisubstituted 1, 2-dihydropyrimido [1, 2-a] benzimidazole derivative. Using Griseofulvin as a control, the compounds 16a and 16b were tested for fungicidal activity against Aspergillus niger-MTCC-2255 and Penicillium chrysogenum-NCIM-723 and active compounds are mentioned in the Table 8. [20].

Table 8 Trisubstituted 1, 2-dihydropyrimido [1, 2-a] benzimidazole derivatives

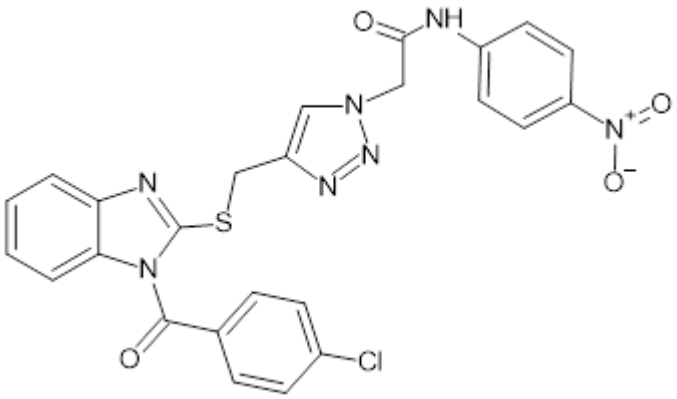
16a	**16b**
	

4.14 Antiviral activity

Heterocyclic compounds are essential as templates for a variety of antiviral drugs. In purine-based drugs such as Ganciclovir, Valganciclovir, Valacyclovir, Adefovir Dipivoxyl, and Entecavir, the imidazole ring is essential (ETV). The benzimidazole ring, on the other hand, is responsible for the anti-cytomegalovirus (CMV) activity of Maribavir (17a) and GW275175X (17b) drugs.

Luo et al. described a series of pyrrole substituted benzimidazoles, among which benzyl-2-(2-(1-methyl-1H-pyrrol-2-yl) ethyl)-1H-benzoimidazole 17g exhibited potent anti-HBV activity with an IC_{50} value of 0.41 μM. Zhao et al. described the synthesis of 1H-benzimidazole-5-ols and their evaluation as HBV inhibitors, with compound 17h proving to be an excellent antiviral agent with an IC50 value of 7.8 μM and are mentioned in the Table 9.

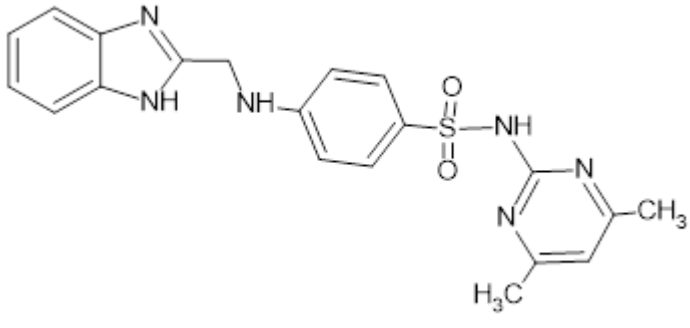
Table 9 1-[(5*S*)-5-methyloxolan-2-yl]-1*H*-benzimidazol-2-amine derivatives

17c	

4.15 Anti-HIV Agents

According to the literature, benzimidazole derivatives have excellent anti-human immunodeficiency virus (HIV) potential (18a-18c). Monforte et al. created new 2-substituted N-aryl benzimidazole derivatives as HIV-1 non-nucleoside reverse transcriptase inhibitors, with compounds 18a and 18b showing promising anti-HIV activity. Selvam et al. described the synthesis of a series of benzimidazole and pyrimidine hybrids and tested their antiviral activity in MT-4 cell lines against HIV-1 and HIV-2 viruses are described in the Table 10. [21].

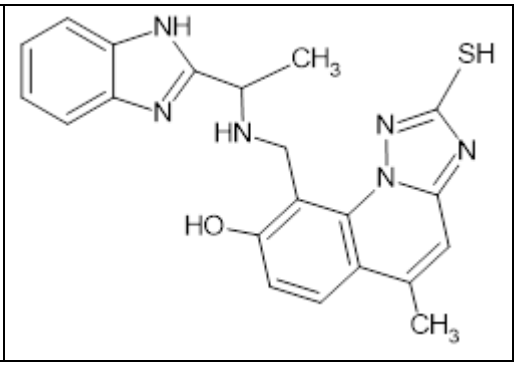
Table 10 Benzimidazole derivatives

18c	

4.16 Anti-Herpes Simplex Virus (HSV) Agents

Benzimidazole-triazole hybrids have the potential to be effective anti-HSV agents (19a-19d). These compounds were tested for their antiviral activity against flaviviruses and pestiviruses. With an EC50 value of 0.02 μM, compound 19a demonstrated excellent activity against respiratory syncytial virus (RSV). Pandey et al (Patil A, *et.al.,* 2008) developed triazolo quinolinyl-containing benzimidazole derivatives such as 7-hydroxy-4-methyl-8-(aminobenzimidazolyl)-quinolinyl-1,5c-2-mercaptotriazoles. Compound 19b in this series demonstrated antiviral activity against Japanese encephalitis virus (JEV) and herpes simplex virus-I. (HSV-1). Another set of nucleoside-based benzimidazoles was created and tested against Vero virus cell lines and these derivatives are mentioned in the Table 11 [22].

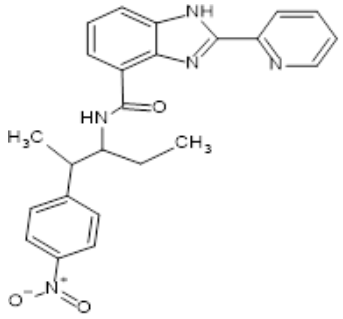
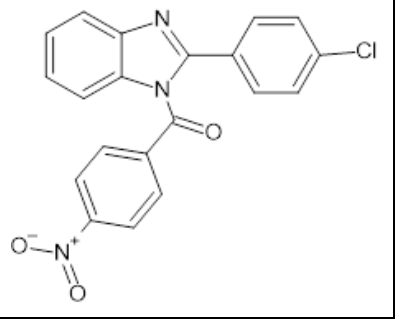
Table 11 Novel Substituted Benzimidazole-triazole hybrids

19a	

5 Inhibitors of Coxsackie virus

Wubulikasimu et al. synthesised benzimidazoles with oxadiazole and pyridine substituents as antiviral agents against Coxsackie viruses (CVB3 and CVB6). 5-(3-Methyl-1,2,4-oxadiazol-5-yl)-2-(pyridin-3-yl) -1H-benzimidazole 20a demonstrated promising activity against CVB3 with an IC50 value of 1.08 g/mL. Xue et al. created new carboxamide-based 2-substituted benzimidazoles and tested them in Vero cells against the enteroviruses Coxackie A16, B3, B6, and enterovirus 71. With an IC50 value of 1.76 g/mL, carboxamide 20b demonstrated potential activity against enterovirus. Sharma et al. described the synthesis of a novel class of substituted benzimidazole derivatives. (2-(4-Chlorophenyl)-1H-benzo[d] The most active anti-vaccinia and Coxsackie virus B4 methanones were (4-nitrophenyl) (4-nitrophenyl) methanone 20c and (4-nitrophenyl) (2-(4-nitrophenyl)-1H-benzo[d]imidazol-1-yl) methanone 20d (Maiti B, *et.al.,* 2016). Zhang et al. synthesised a new series of benzimidazole-based carboxamides and tested them against Coxackie virus B3. N-(2-Fluorophenyl)-2-(furan-2-yl) -1H-benzo[d] 20e imidazole-4-carboxamide exhibited good CVB3 inhibition activity, with IC50 values of 1.06 g/mL. Cheng, et al. also created new antiviral benzimidazole derivatives against CVB3, among which compounds 20f and 20g displayed potent antiviral activity with IC_{50} values 1.48 and 0.54 μg/mL, respectively and these derivatives are mentioned in the Table 12. [23].

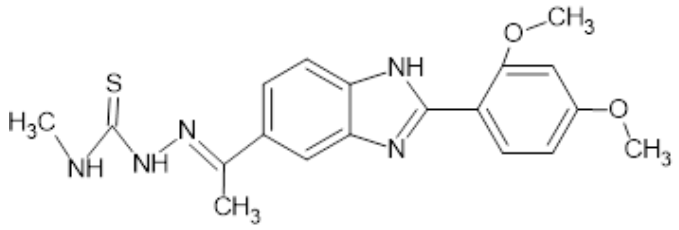
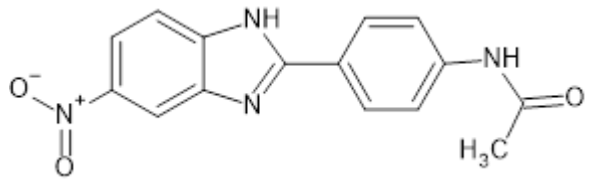
Table 12 Synthesised benzimidazoles with oxadiazole and pyridine substituents

20b	
20c	

6 RNA AND DNA of Various Viruses

Vitale et al. described the synthesis of 5-acetyl-2-aryl benzimidazole and its derivatives, some of which were tested for antiviral RNA **21a-21c** activity. **Compound 21a** was discovered to be the most effective, with an EC50 value of 0.80 μM. Tonelli et al. reported the synthesis of a new 2-substituted phenyl benzimidazole and its derivatives. These compounds were tested for their ability to inhibit the RNA and DNA of viruses such as bovine viral diarrhoea (BDVD), respiratory syncytial virus (RSV), vaccinia virus (VV), and Reo-1. With an EC50 value of 0.1 μM, **Compound 21b** demonstrated excellent activity against VV. Acetamide **21c**, on the other hand, demonstrated potent antiviral activity against BVDV with an EC50 value of 0.8 μM. Musiu et al. described the synthesis of 2, 6-bis(benzimidazole-2-yl) pyridines that inhibited BVDV and CSFV (Faheem M, ***et.al.,*** 2020) and derivatives are mentioned in the Table 13.

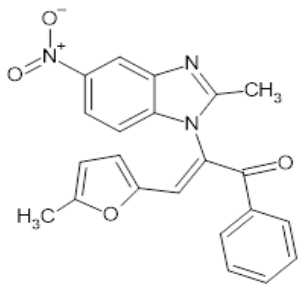
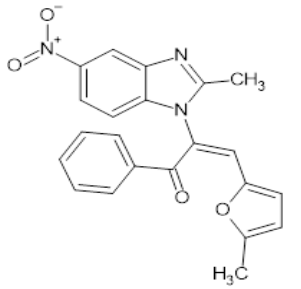
Table 13 5-acetyl-2-aryl benzimidazole derivatives

21a	
21c	

6.1 Anti-Rotavirus Agents

Shaker et al. described the synthesis of 5-nitro-1H-benzimidazole as well as a new series of analogues. These compounds were tested for their antiviral activity against rotavirus strains. 5-methylfuran-2-yl and benzimidazole hybrids (**22a** and **22b**), as well as (Z)-2-(2-methyl-5-nitro-1H-benzo[d]imidazol-1-yl)-1-phenyl-3-(thiophen-2-yl) prop-2-en-1-one **22c**, were found to have good anti-rotavirus activity [24] and active compounds are mentioned in the Table 14.

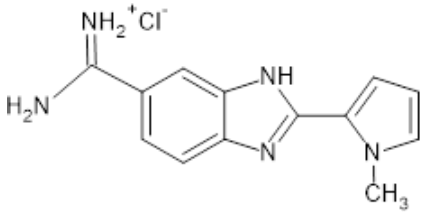
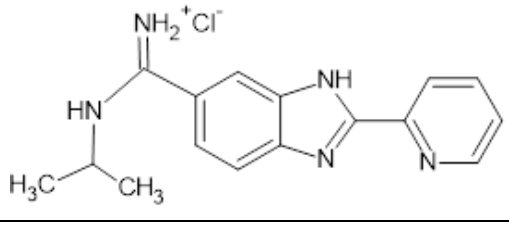
Table 14 Novel 5-nitro-1H-benzimidazole derivatives

22a	
22b	

7 Inhibitors of Adenoviruses

The preparation was described by Starcevic et al. Compounds active against adenoviruses include 2-(1-methyl-1H-pyrrol-2-yl)-1H-benzimidazole-5-carboxamidine hydrochloride and N-Isopropyl-2-pyridin-2-yl-1H-benzimidazole-5-carboxamidine hydrochloride **25a and 25b**. [25-27] and active derivatives are mentioned in the Table 15.

Table 15 2-(1-methyl-1H-pyrrol-2-yl)-1H-benzimidazole-5-carboxamidine hydrochloride derivatives

25a	
25b	

8 Inhibitors of Tobacco Mosaic and Sunn-Hemp Rosette Viruses

Tewari and Mishra described the synthesis of new N-substituted benzimidazole analogues, including 3-(1-Benzyl-1H-benzo[d]imidazol-2-yl) propanoic acid **26** with antiviral activity against tobacco mosaic and Sunn-hemp rosette (mosaic) viruses. [28].

9 Inhibitors of Spring Viraemia of CARP Virus

According to Liu et al. 7-(4-benzimidazole-butoxy)-coumarin (**Compound 27**) had a good activity against spring viraemia of carp (SVC), with a 50% decrease in viral activity for 72 hours. [29, 30].

10 Conclusion

The vast majority of procedures and evaluations for benzimidazole and its derivatives have been reported in various literatures. Based on the results of the above literature review, it is concluded that substituted benzimidazole is an important pharmacophore for a wide range of pharmacological activity in modern drug discovery. Various studies have revealed that substituted benzimidazole interacts easily with biopolymers and has pharmacological activity with lower toxicities. As a result, in the future, developing more potent benzimidazole derivatives with a wide range of biological activity and a lower toxicity profile will be an important resource for medicinal research.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that they have no conflicts of interest.

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