Benzimidazole Derivatives as Multifunctional Agents: Exploring Their Role in Combating Viral, Microbial, and Inflammatory Diseases

Renu, Shilpa*, Sanjiv Duggal
Global College of Pharmacy, Kahnpur Khui, Anandpur Sahib, Punjab, India, 140117

Corresponding Author detail:
Shilpa
Assistant Professor
Global College of Pharmacy,
Kahnpur Khui, Anandpur Sahib, Punjab, India, 140117
Email Id: somasharma378@gmail.com

ABSTRACT

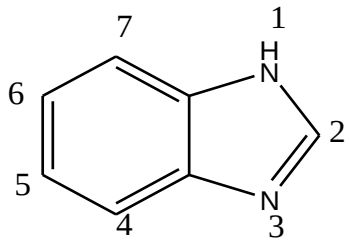
Benzimidazole is a significant heterocyclic compound derived from the fusion of benzene ring, which has six carbon atoms with an imidazole ring, which has five atoms at specific points, characterized by the presence of nitrogen, oxygen, and sulphur atoms. It is an important structure found in many medicines because it helps create compounds that have different useful effects for health. This molecular structure has emerged as a critical pharmacophore in pharmaceutical chemistry, demonstrating exceptional potential across multiple therapeutic domains. The compound's remarkable biological profile encompasses a broad spectrum of pharmacological activities, including antiviral, antimicrobial, anti-inflammatory properties. Its diverse molecular framework enables targeted interactions with biological systems, making it a valuable scaffold for drug development. Benzimidazole and its related compounds have shown promising effects in treating various diseases. Because of these structures are recognized as crucial in drug discovery process. This review provides an overview of different benzimidazole derivatives and their pharmacological activities.

Key words: Benzimidazole, Benzimidazole derivatives, Antiviral activity, Antimicrobial activity, Antiinflammatory activity.

Introduction

Benzimidazole is a bicyclic hetero-aromatic organic compound made up of two rings: a benzene ring and imidazole ring that are connected at the 4^{th} and 5^{th} positions [1]. This compound was once called glyoxalin because it was first created in 1858 by the German chemist Heinrich Debus using glyoxal, formaldehyde, and ammonia [2]. Benzimidazole is a type of organic compound that combines a six-membered benzene ring with a five-membered imidazole ring. It is considered a derivative of imidazole. Its **IUPAC** name is **1H-Benzimidazole** and it is also referred to as **1H-1,3-Benzimidazole** or 1H-Benzo[d] imidazole. It was first produced by **Hobrecker** in 1872[3].

Molecular formula;- $C_7H_6N_2$



Benzimidazole

Benzimidazole with hydrogen in the 1^{st} position (imide nitrogen) has unique solubility characteristics. They typically dissolve well in polar solvents but poorly in organic solvents. However, the solubility can be significantly altered by introducing different substitutent:
Non-polar substituents: Adding nonpolar groups to the benzimidazole ring increases its solubility in nonpolar solvents. For example, 2-methyl benzimidazole becomes more soluble in ether.

Polar substituents: Introducing polar groups to the benzimidazole nucleus enhances its solubility in polar solvents. A specific example is 2-aminobenzimidazole, which becomes water soluble [4].The various physical properties of benzimidazole show in **Fig. 1**[5].

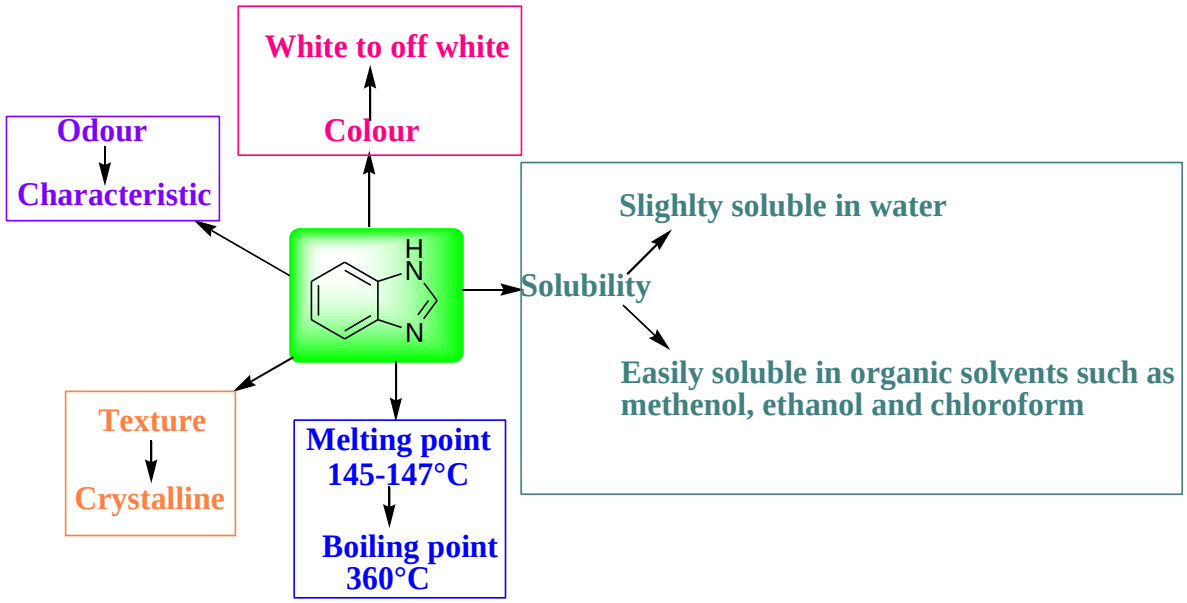


Fig. 1: Physical Properties of Benzimidazole

Benzimidazole derivatives are used in various approaches such as antiviral, antimicrobial, antiinflammatory show in **Fig. 2** [6].

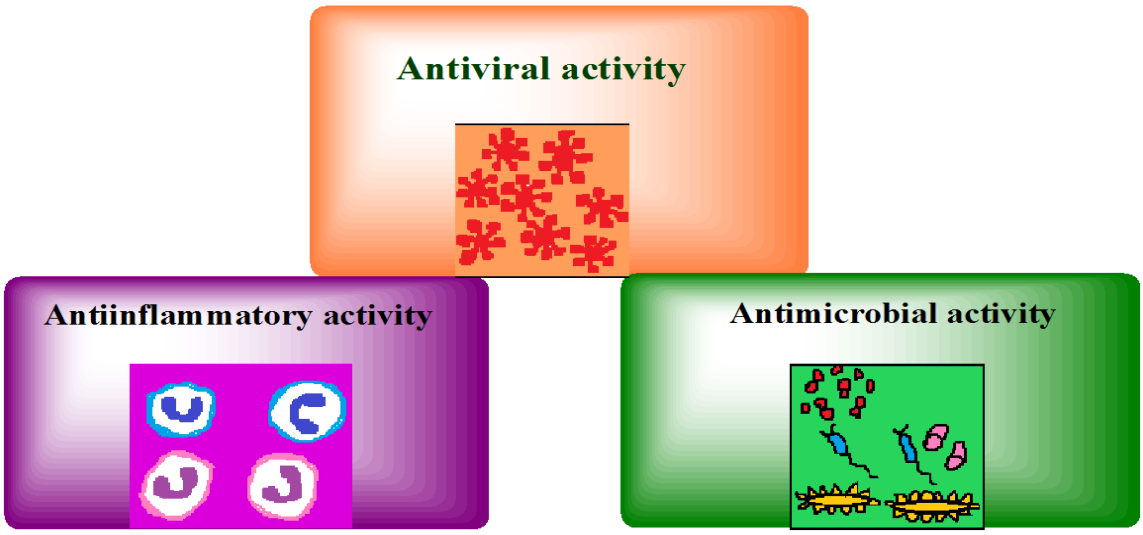


Fig. 2: Pharmacological Activities of Benzimidazole Derivatives

Mechanism of Actions of Benzimidazole Derivatives as an Antiviral:

Antiviral activity: Benzimidazole binds to viral enzymes, such as proteases and polymerases, particularly the RNA-dependent RNA polymerase of hepatitis C virus, and leading to inhibition of viral replication. It interacts with viral RNA, preventing transcription and translation. It blocks viral entry into host cells by binding to viral surface proteins. Benzimidazole prevents release of new viral particles from infected cells, enhance host

immune response, increasing production of cytokines and activating immune cells as shown as in **Fig. 3** [7].

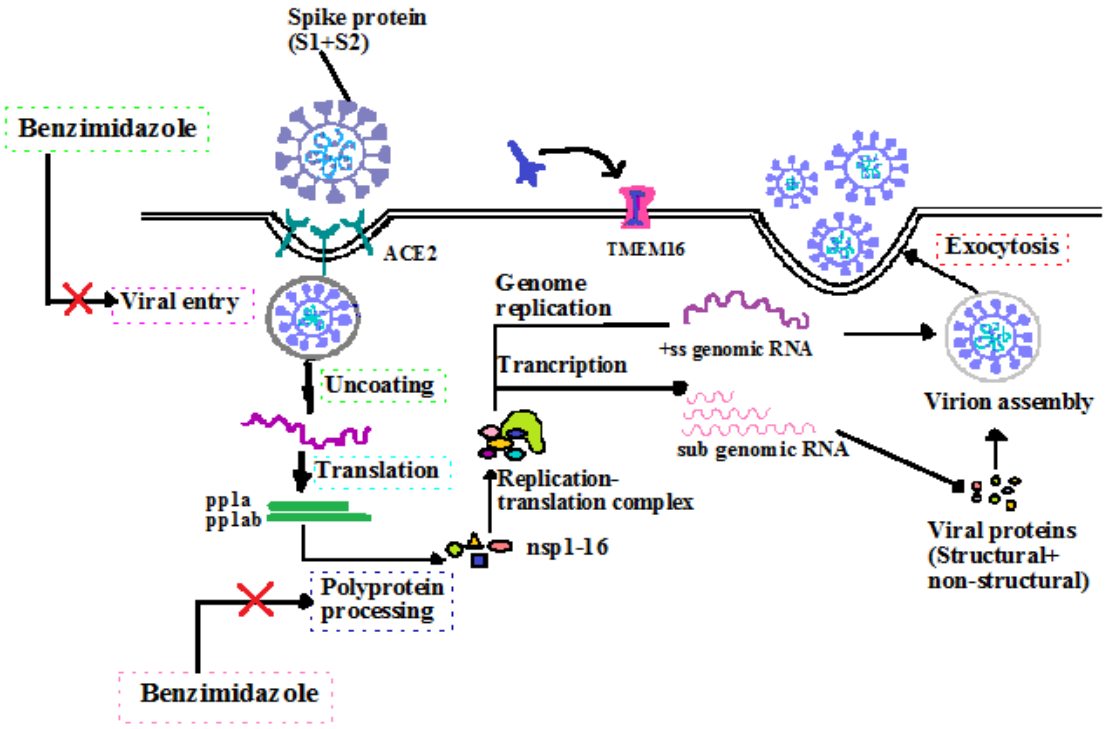
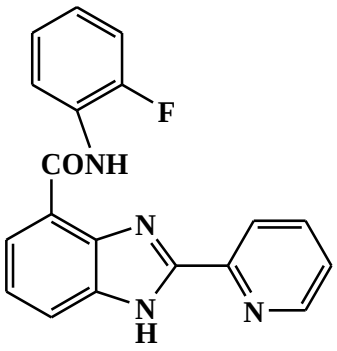


Fig. 3: Mechanism of Action of Benzimidazole as an Antiviral Activity

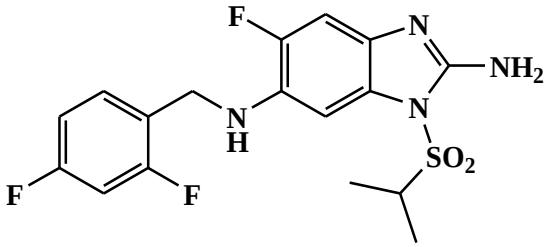
Literature review

Cheng et al. created new benzimidazole compounds and assessed their ability to fight the Coxsackie virus B3 in VERO cells. The **compound 1** which showed strong antiviral activity with IC_{50} value of 0.54 µg/mL, when compared with standard drug ribavirin, which had an IC_{50} value of 411.7 µg/mL and a selective index greater than 2.42 [8]



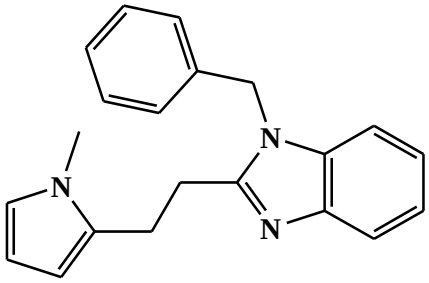
1

Li et al. developed a new group of benzimidazole compounds and investigated them for their ability to inhibit the hepatitis B virus. The **compound 2** with IC_{50} value of 0.70µM, showed excellent anti-HBV activity, similar to the effectiveness of lamivudine and adefovir [9].



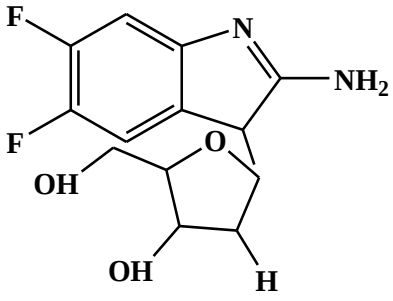
2

Luo et al. created a several new benzimidazole compounds .In their study, the **compound 3** with IC_{50} value of <0.41µM, demonstrated strong antiviral activity against hepatitis B virus and for toxicity in HepG 2.2.15 cells using lamivudine with IC_{50} value of 5µM as a reference drug [10].



3

Kharitonova Ml et al. reported that they arrange β-D-ribo- and 2′-deoxyribofuranosides of 2-amino-5,6-difluorobenzimidazole nucleosides using an enzymatic transglycosylation process. In their study, the **compounds 4 and 5** showed strong antiviral activity against a wild strain of the herpes simplex virus, as well as against virus strains resistant to cidofovir, acyclovir, and foscarnet. It is suggested that this compound could be used to treat herpes infections in cases where acyclovir is not effective [11].



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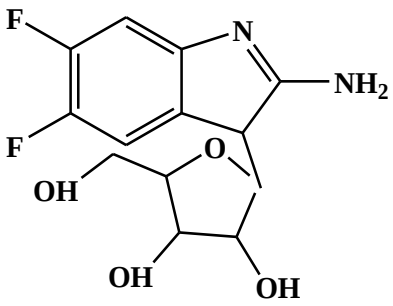
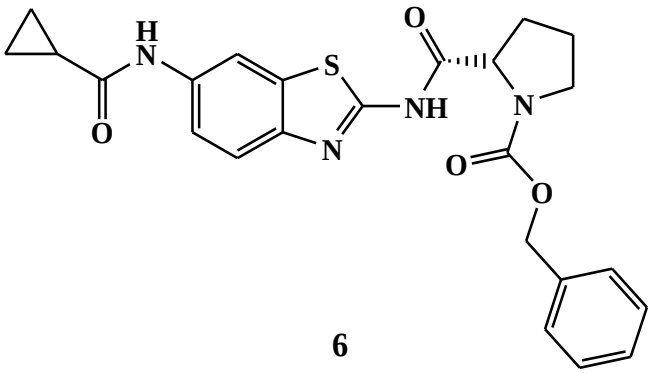


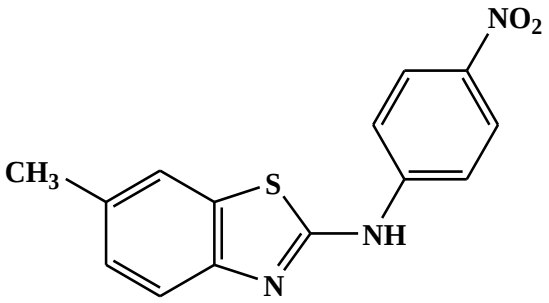
5

Liu N et al. showed that the benzimidazole derivative **compound 6** has strong activity against HCV, with an IC_{50} value of 26.81 µM. The compound was effective against other HCV stains as well, including the genotype 1b replicon, where it had an IC_{50} of 9.3 µM [12].



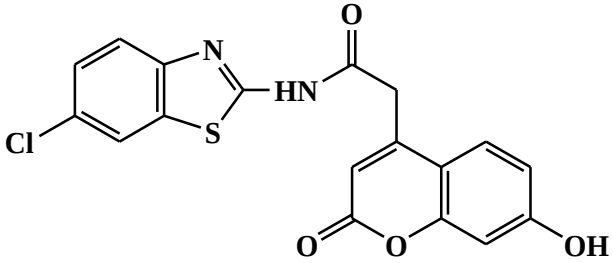
6

Peng et al. showed that the **compound 7 [**2-(4-nitroanilino)-6-methylbenzothiazole] has strong anti-HCV activity with an EC_{50} value of 8 µM. This benzothiazole compound was found to block the HCV RNA-dependent RNA polymerase and stop HCV RNA replication in a dose-dependent way. The inhibition followed a non- competitive pattern, with a kinetic constant of 7.76 µM [13].



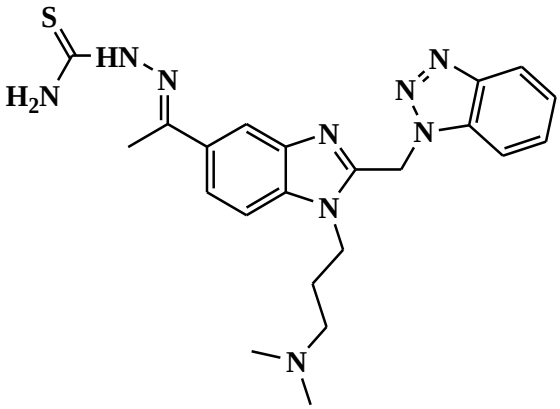
7

Bhavsar et al. reported that hybrid benzothiazolyl-coumarins could be potential anti-HIV agents. They found that the **compound 8** (6-chlorobenzothiazole derivative) displayed a promising anti-HIV effect with EC_{50} value of less than 7 µg/ml [14].



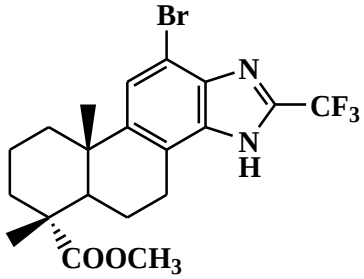
8

De Clercq et al. showed that **compound 9** was found to be most effective antiviral with CC_{50} values of >100µM, this compound had ability to stop RSV replication as ribavirin. Ribavirin is the only drug which is currently used to treat RSV infections, but it has limited effectiveness and a narrow safety margin, so it is only used for high- risk children [15].



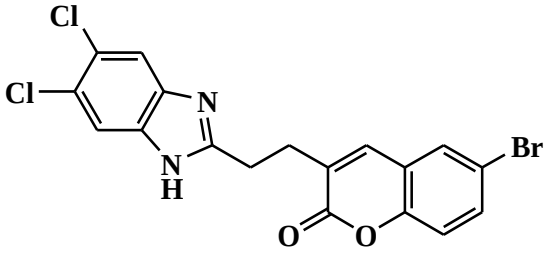
9

Fonseca et al. developed various benzimidazole compounds, incorporating them into naphthalene and hydrophenanthrene structures. **Compound 10** showed the strongest activity against cytomegalovirus with IC_{50} values 0.2 to 3.2 µg/mL and 0.2 to 2.8 µg/mL against varicella-zoster virus. The results were compared to the standard antiviral drugs Acyclovir and Ganciclovir [16].



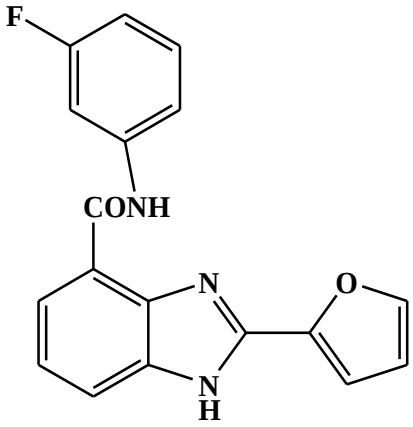
10

Hwu et al. developed a new benzimidazole compounds linked to coumarin ring structures. The **compound 11** showed the strongest antiviral activity against hepatitis C virus, with EC_{50} values of 2.3µM. [17].



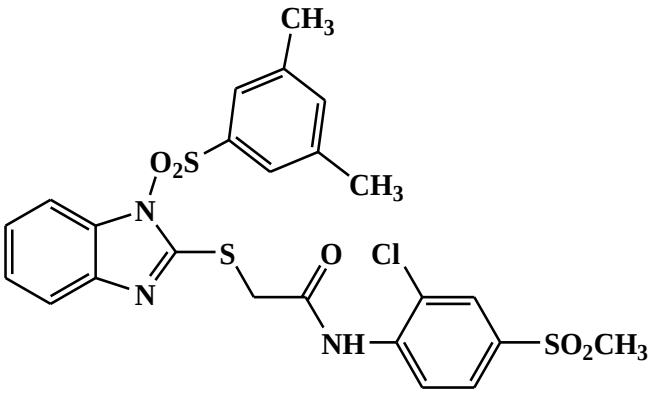
11

Zhang et al. also developed new benzimidazole compounds. They found that the **compound 12** showed strong antiviral activity, with IC_{50} value of 1.06 µg/mL against CVB3 virus. Use ribavirin as reference drug with IC_{50} value of 353.33 µg/mL [18].



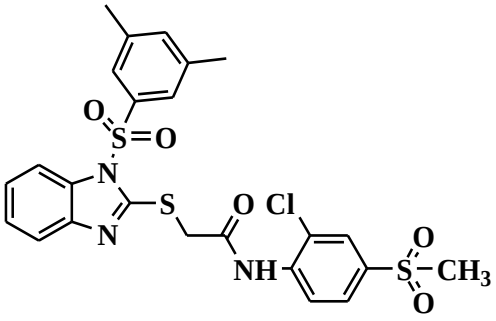
12

Monforte et al. developed new benzimidazole compounds and tested their ability to inhibit Human immunodeficiency virus type-1. The **compound 13** showed the strongest activity without causing toxicity, with IC_{50} value of 0.12 µM, when compared to the standard HIV drugs Nevirapine and Efaviranz [19].



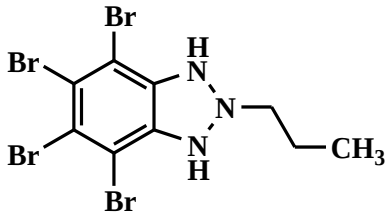
13

Tahlan et al. developed a new benzimidazole **compound 14.** This compound was found to block the growth of human immunodeficiency virus type-1 [20].



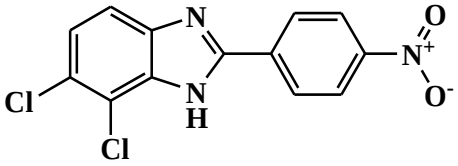
14

Maria et al. developed N-alkyl derivatives to enhance the antiviral activity. The **compound 15** which contain 4,5,6,7-tetrabromo-1H-benzimidazole, showed strong antiviral activity against several viruses, including Hepatitis C, West Nile, Dengue, and Japanese encephalitis viruses [21].



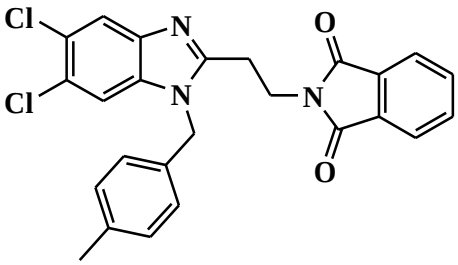
15

Michele et al. developed 2-phenylbenzimidazole analogues and tested the **compound 16** showed strong antiviral effects against viruses like poxviruses, pest viruses, and Hepatitis C, which are harmful to humans [22].



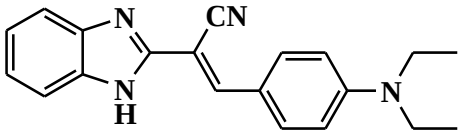
16

Li et al. showed that the derivatives of 5,6-dichlorobenzimidazole phthalimide. The **compound 17** was found to be the most promising to fight hepatitis B virus [23].



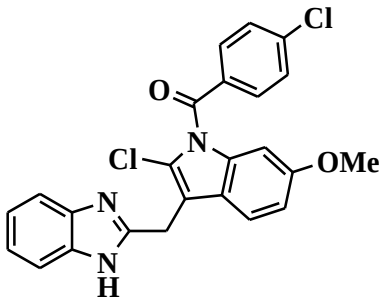
17

Pan et al. developed a series of benzimidazole derivatives and tested the **compound 18** showed strong antiviral activities with IC_{50} value of 3.45 nM against HIV [24].



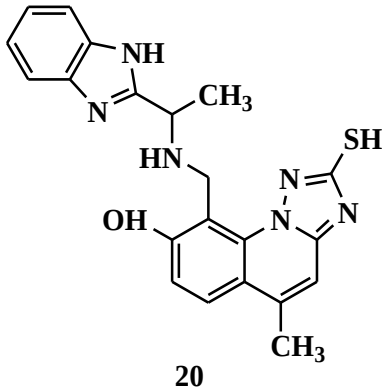
18

Masoudi et al. synthesized various benzimidazole derivatives and tested the **compound 19** demonstrated significant activity with an EC_{50} value of 1.15 mg/mL against both HIV-1 and HIV-2 [25].



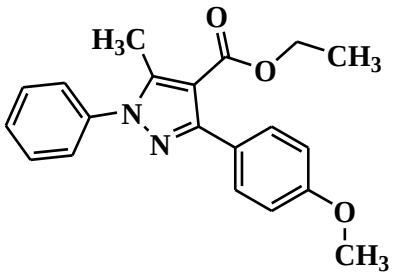
19

Davidse et al. developed a benzimidazole-triazole hybrid. The **compound 20** with an EC_{50} value of 0.02 µM, showed strong activity against respiratory syncytial virus [26].



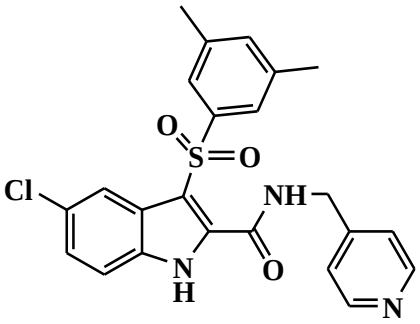
20

Meng et al. created a pyrazole-based **compound 21** with IC_{50} value of 5.4 µM, by used a one-pot synthesis method, combining 4-methoxy benzaldehyde, ethyl acetoacetate, and phenylhydrazine with PEG 400 and ceric (IV) ammonium nitrate for developing an anti-influenza drug [27].



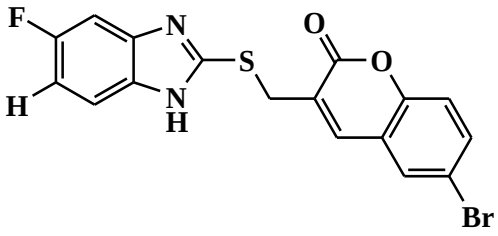
21

Regina et al. successfully created indolylarylsulfone compounds with anti-HIV activity. The **Compound 22** with an EC_{50} value of 2.0 nM was found to be a weakly toxic inhibitor of the NL43 strain in MT4N cells [28].



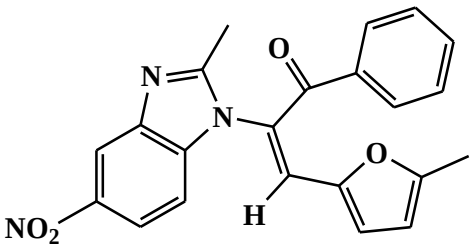
22

Hwu et al. developed several new coumarin-benzimidazole hybrid compounds and find out the **compound 23** was found to be effective with EC_{50} value of 3.4µM against the hepatitis C virus [29].



23

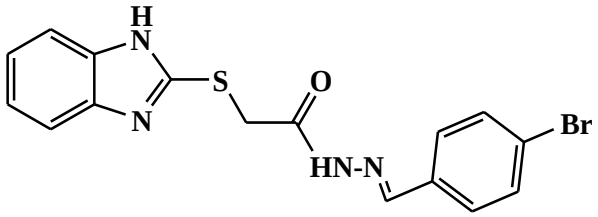
Shaker et al. created a series of 5-nitro-1H-benzimidazole analogs. They determine that the **Compound 24** was the most effective against both adenovirus type-7 and rotavirus. It reduced the number of infectious rotavirus particles by 70% and adenovirus type-7 by 56.7% [30].



24

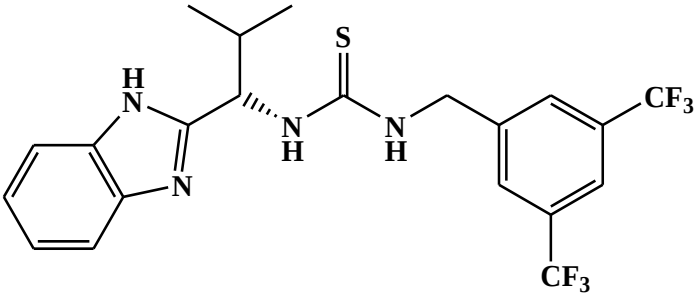
Antimicrobial activity

Yadav et al. created a series of new benzimidazole compounds and find out **compound 25** with MIC value of 0.032 mg/mL, showed the strongest antimicrobial activity against *S. aureus, B. subtilis, E. coli, C. albicans, and A. niger* [31].



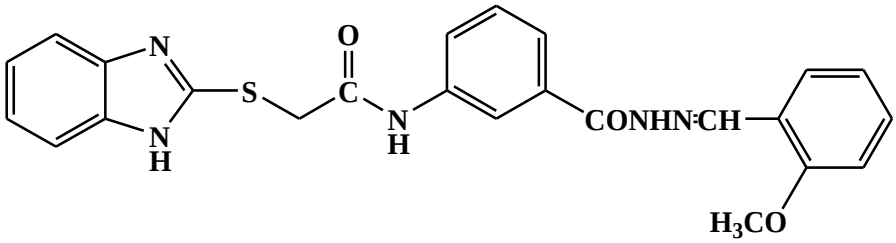
25

Madabhushi et al. developed a new group of chiral thioureas with benzimidazole groups. The **compound 26** with MIC value of 12.5 µg/mL showed the best antibacterial effects against *S. aureus, B. subtilis, S. aureus MLS16, M. luteus, K. planticola, E. coli, and P. aeruginosa* [32].



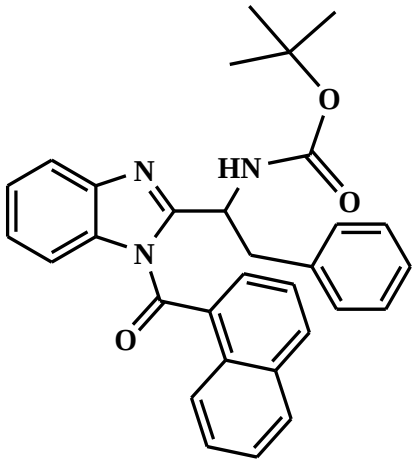
26

Tahlan et al. created a group of benzimidazole Schiff base derivatives. **Compound 27** showed strong antimicrobial effects, with MIC value of 0.68 µM/Ml for bacterial species and 2.72 µM/Ml for fungal species [33].



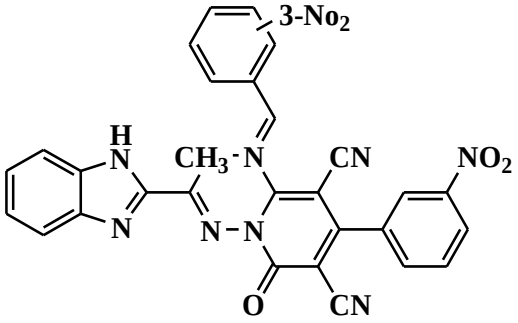
27

Erkut et al. developed a **compound 28** showed a low minimum inhibitory concentration against the eukaryotic microorganism Candida albicans, which is a normal part of the mouth´s flora but can cause infections that weaken the immune system. Since this compound could be developed as a potential alternative treatment for C. albicans infections. Additionaly, this may also help inhibit Pseudomonas aeruginosa, which could be used for treating cystic fibrosis [34].



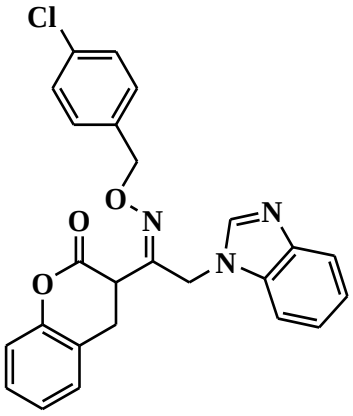
28

Desai et al. developed a series of 2-pyridone-based benzimidazole compounds. Due the presence of electron-withdrawing groups like nitro in **Compound 29** at certain positions showed the best antibacterial activity, with MIC values ranging from 12.5 µg/ml, when compared to the standard ketoconazole (MIC=50 µg/ml) [35].



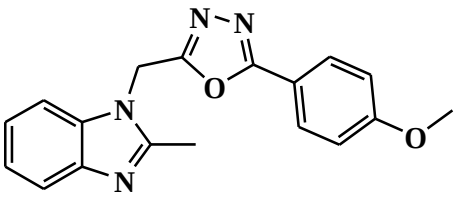
29

Singh et al. created a group of coumarin-benzimidazole hybrid compounds. The **Compound 30** stood out as a strong antibacterial agent, effective against a variety of bacteria, including *P. aeruginosa, S. aureus, B. subtilis, and P. vulgaris* [36].



30

Ansari et al. synthesized derivatives of 2-substituted 1H-benzimidazole through nucleophillic substitution reactions and assessed the **compound 31** showed strong antibacterial activities against *Bacillus subtilis, and Staphylococcus aureus*, while the **compound 32** was particularly effective against fungi against *Candida albicans* [37].



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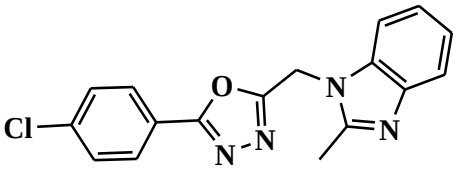
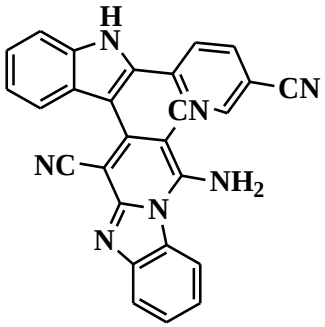
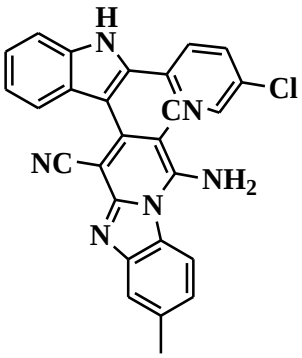


32

Kathrotiya and Patel et al. synthesized a certain indole- based pyrido[1,2-a]benzimidazole compounds, specifically the **compound 33** showed significant antibacterial effects against *Salmonella typhi*, with MIC value 12.5 mg/mL. This performance was better than that of the reference antibiotics ampicillin (MIC 100 mg/mL), chloramphenicol (MIC 50 mg/mL), and ciprofloxacin (MIC 25 mg/mL). Furthermore, **compound 34** demonstrated notable antifungal activity against *Candida albicans*, with an MIC of 250 mg/Ml, which is more effective than the standard drug griseofulvin (MIC 500 mg/mL) [38].

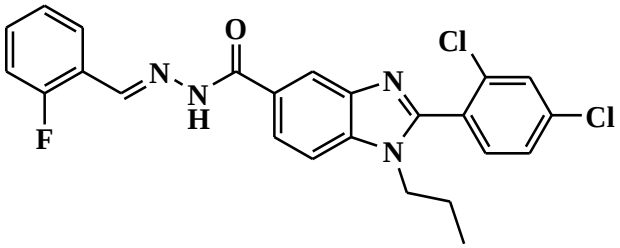


33



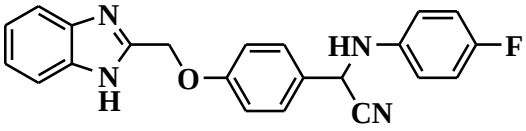
34

Vasantha et al. synthesized a series of N-arylidene-2-(2,4-dichlorophenyl)-1-propyl-1H-benzo[d] imidazole-5-carbohydrazide derivatives. The **compound 35** showed great potential as both an antibacterial and antifungal agent, with an MIC value of 3.12 mg/mL against most bacterial and fungal strains [39].



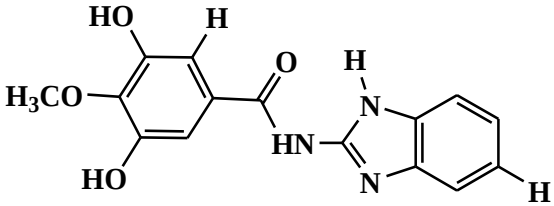
35

Wang et al. developed various purine benzimidazole hybrids. The **compound 36** showed the strongest antibacterial activity with MIC value between 3.9 mg/mL against different types of bacteria [40].



36

Cindric et al. described the most effective compound identified was **compound 37**, which contains two hydroxy groups and one methoxy group on the phenyl ring. This compound demonstrated selective antibacterial activity against the Gram-positive bacterium *Enterococcus faecalis*, with a MIC value of 8µM [41].



37

Antiinflammatory activity

Mechanism of action of benzimidazole as an antiinflammatory: Benzimidazole inhibits cyclooxygenase (COX) enzymes, reducing prostaglandin production and subsequent

inflammation. It prevents nuclear factor kappa B activation, reducing expression of pro-inflammatory genes. It also reduces production of pro-inflammatory cytokines, such as TNF-α and IL-1β. Benzimidazole modulates immune response, reducing inflammation and promoting healing **Fig. 4** [42].

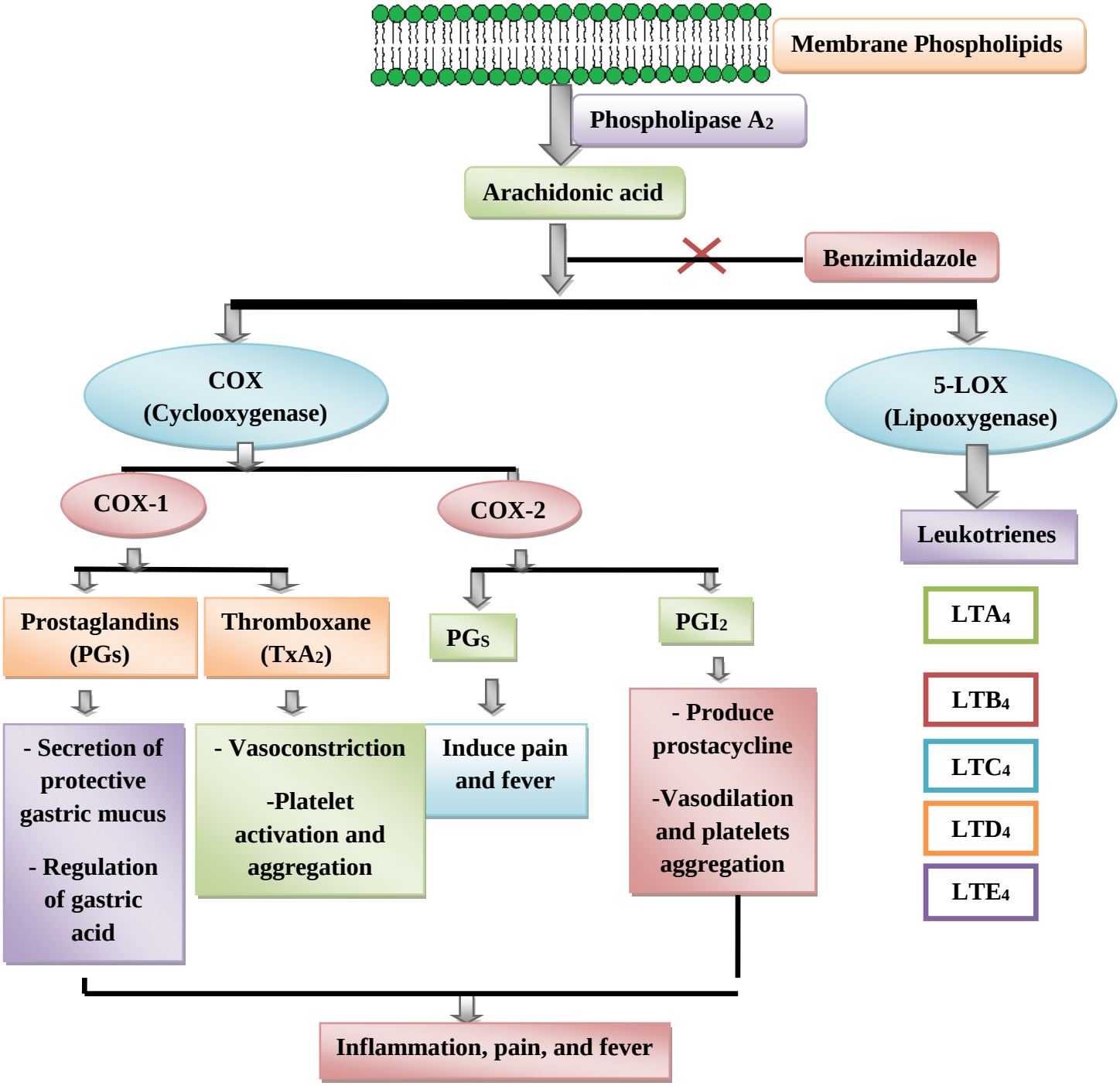
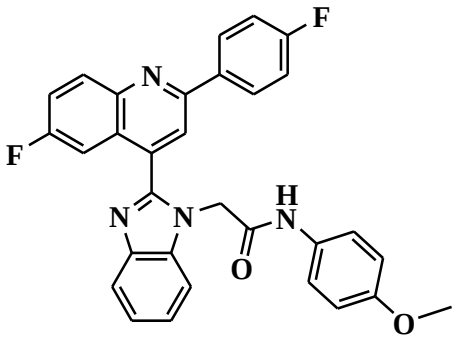


Fig. 4: Mechanism of Action of Benzimidazole as an Antiinflammatory Activity

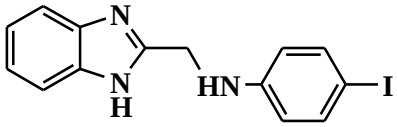
El-Feky et al. created a series of novel benzimidazole derivatives that incorporate fluorinated quinoline compounds. The **compound 38** which is 55% effective at 50 mg/kg dose stood out by showing the most potent anti-inflammatory activity and compared their effectiveness to

celecoxib. It also had the strongest binding to the COX-2 enzyme site, surpassing the performance of celecoxib which is 50% effective at 50 mg/kg dose [43].



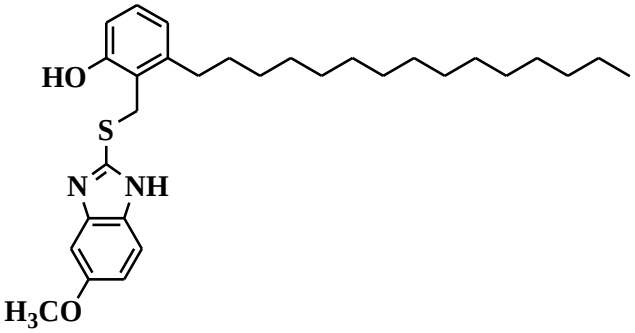
38

Mariappan et al. developed a group of 2-substituted benzimidazole compounds. They discovered that the **compound 39** with X±SE value of 0.02 at 4h demonstrated notable effectiveness in reducing inflammation and pain by compared with pentazocine as a reference drug [44].



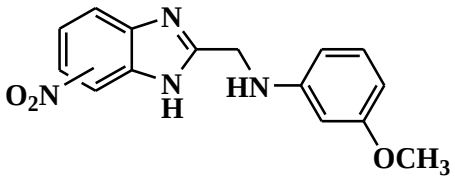
39

Paramashivappa et al. developed a series of benzimidazole derivatives. In the study, specific **compound 40** with IC_{50} value of 384 µM for COX-1 enzyme and 1 µM for COX-2 enzyme, demonstrated the most potent enzyme inhibition activity, with their performance being compared against rofecoxib [IC_{50} value of 11.4 and 0.057 µM] for COX-1 and COX-2 enzymes as a reference standard [45].



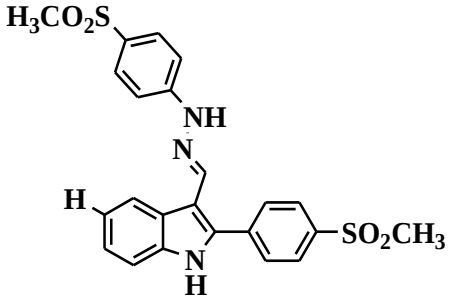
40

Hosamani KM et al. investigated series of 2-methylaminobenzimidazole derivatives. This newly created **compound 41** demonstrated exhibiting potent anti-inflammatory with 100% effectiveness at 100 mg/kg body weight, which were comparable to or even better than the standard drug Nimesulide [46].



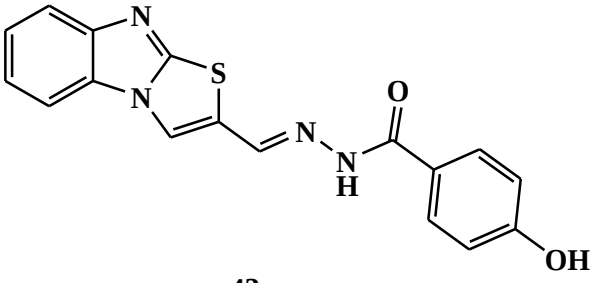
41

Ahmed et al. examined various hydrazone derivatives for their anti-inflammatory potential. They reveal that **Compound 42** showed the highest COX-2 inhibitory activity, with very low IC_{50} values of 0.1 nM and also edema inhibition of 93.5%. For comparison, standard drugs celecoxib and indomethacin achieved 94.7% and 96.6% inflammation reduction, respectively [47].



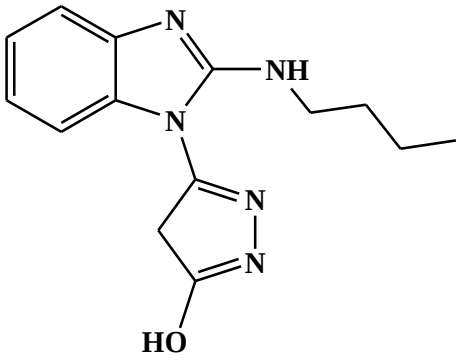
42

Vinuta et al. investigated various chemical derivatives for their anti-inflammatory potential using the bovine albumin protein denaturation method. The study revealed that specific **compound 43** demonstrated superior anti-inflammatory activities with IC_{50} value of 31.16 µg/mL, using Diclofenac sodium as the standard drug for comparison [48].



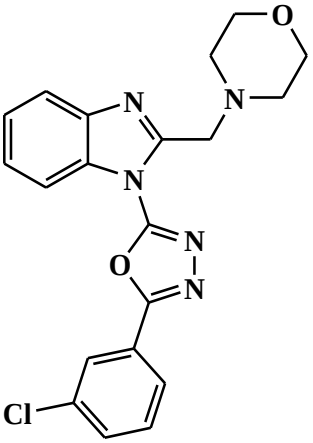
43

Moneer et al. developed a series of benzimidazole-pyrazole derivatives. **Compound 44** demonstrated exceptional cyclooxygenase inhibition. Specifically, this compound exhibited COX-1 inhibition at IC_{50} value of 0.2272 nM and COX-2 inhibition at IC_{50} value of 0.0469 nM. It is more effective than the standard drug diclofenac [49].



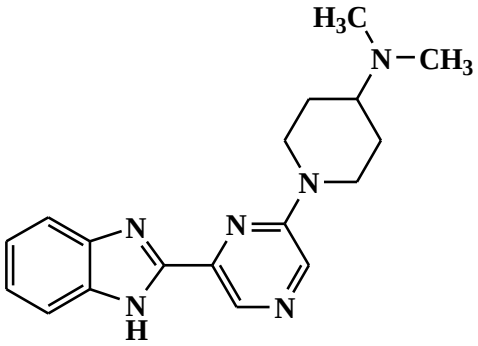
44

Rathore et al. developed a series of benzimidazole derivatives containing 1, 3, 4-oxadiazole and morpholine groups. The study finding that **compound 45**, which has a chloro substitutent at the ortho position of the phenyl ring, demonstrated significant anti-inflammatory effect 1.28% compared to the standard drug indomethacin 1.71% [50].



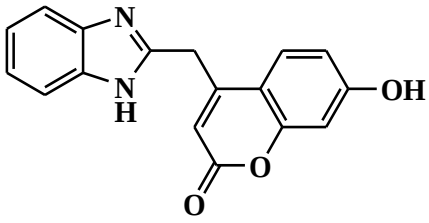
45

Shankar et al. developed a series of 2-(6-alkyl-pyrazin-2-yl)-1H-benzo[d]imidazole compounds targeting the COX-2 enzyme. **Compound 46** showed significant COX-2 enzyme inhibition with percentages of 71.45%. This study further attributed the compound superior performance to the presence of an N-phenyl piperazine group in its benzimidazole structure [51].



46

Purva Sethi et al. developed new benzimidazole derivatives by combining coumarin and benzimidazole structures. The **compound 47** demonstrated the most potent anti-inflammatory activity, comparable to the standard anti-inflammatory drug indomethacin [52].



47

Conclusion

Benzimidazole derivatives demonstrate remarkable pharmacological potential across multiple therapeutic domains. It is demonstrated potent antiviral effectiveness against HIV-1, strong inhibitory activity, and exhibit impressive broad-spectrum antimicrobial activity against various microorganisms including ***Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Candida albicans,*** **and** ***Aspergillus niger***. Furthermore, some benzimidazole-based agents show remarkable COX-2 inhibitory activity, which highlights their potential as powerful anti-inflammatory drugs. These diverse pharmacological activities underscore benzimidazole potential as a versatile scaffold for developing novel therapeutic agents across multiple medical disciplines, including antiviral, antimicrobial, and anti-inflammatory therapies.

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