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Review Article

Benzimidazole: A Versatile Pharmacophore For Diverse Therapeutic Applications

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ABSTRACT

Benzimidazole, a bicyclic compound formed by the fusion of benzene and imidazole rings, is recognized for its profound biological activity and significant impact on medicinal chemistry. This review provides a comprehensive analysis of benzimidazole derivatives, highlighting their key pharmacological activities, including analgesic, anti-inflammatory, diuretic, antimicrobial, antiulcer, antioxidant, anti-asthmatic, anti-diabetic, anticancer, antiviral, antiarrhythmic, anticonvulsant, antiprotozoal, hypotensive, and neuroprotective effects. The robust affinity of benzimidazoles for a diverse array of enzymes and protein receptors underscores their status as privileged sub-structures in pharmacological design.. The integration of the benzimidazole nucleus in drug development continues to play a crucial role in contemporary therapeutic research, offering versatile and effective treatments for a wide range of diseases.

INTRODUCTION

Benzimidazole stands as a bicyclic compound distinguished by an imidazole ring housing two nitrogen atoms positioned nonadjacently and fused to a benzene ring. It occupies a pivotal role within heterocyclic compounds, celebrated for its profound biological activity and significant impact on medicinal chemistry.[1] The robust affinity of benzimidazoles for a diverse array of enzymes and protein receptors has elevated them to the status of privileged 'sub-structures' in the realm of pharmacological design. The integration of the benzimidazole nucleus serves as a cornerstone in the strategic development of antimicrobial drugs, underscoring its pivotal role in contemporary therapeutic research. This heterocyclic aromatic

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organic compound, benzimidazole, epitomizes a vital pharmacophore in medicinal chemistry. Its bicyclic structure arises from the fusion of benzene and imidazole rings, rendering it a favored moiety in modern pharmacological investigations due to its multifaceted pharmacological attributes.[1,2]

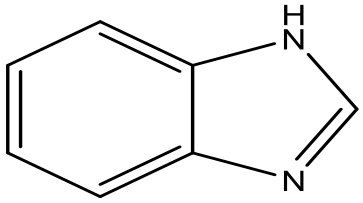


Figure 1. H Benzimidazole

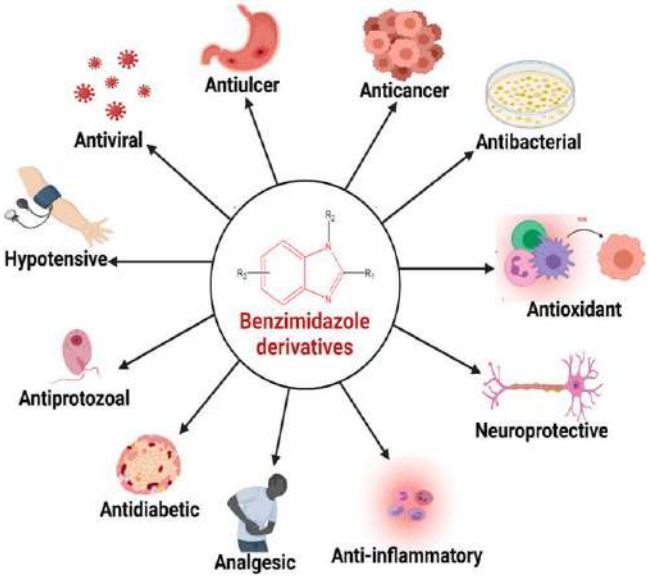


Figure 2. Pharmacological Actions of Benzimidazole[3]

The benzimidazole nucleus, entrenched as a well-established pharmacophore in medicinal chemistry, exhibits remarkable versatility as a heterocyclic entity endowed with a broad spectrum of biological activities.

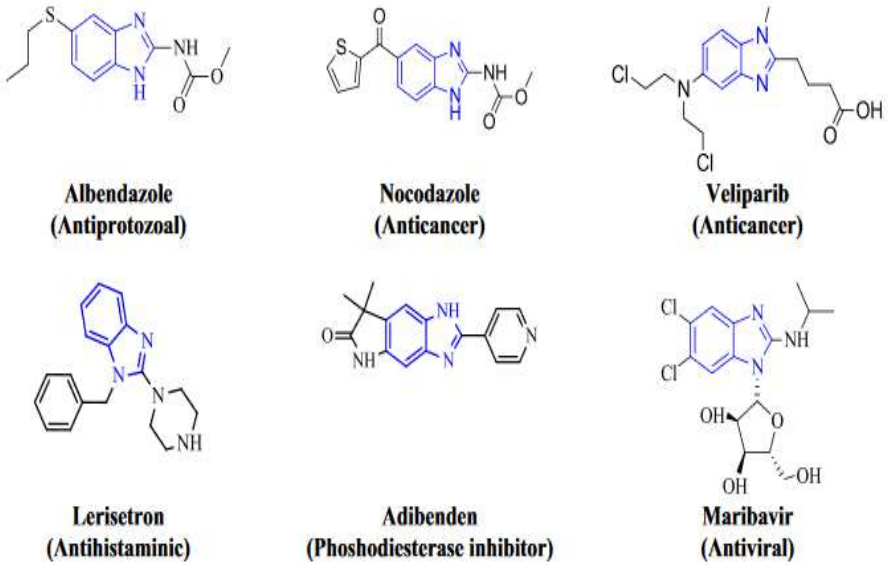


Figure 3.some benzimadazoles containing medicinal preparation[4]

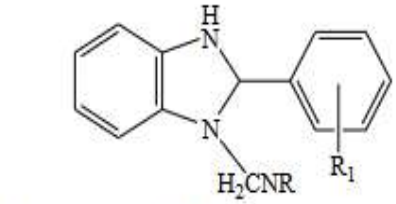
Benzimidazole derivatives function as structural isosteres of endogenous nucleotides, thereby enhancing their efficacy in interacting with a diverse array of biological targets.[2] In this study, our objective is to comprehensively collate and analyze the contemporary biological properties of

the benzimidazole nucleus, illuminating its pivotal roles and applications in cutting-edge biomedical research endeavors.

KEY PHARMACOLOGICAL ACTIVITIES

Analgesic and Anti-inflammatory Activity

Leonardo et al conducted studies on the synthesis and anti-inflammatory properties of phenyl benzimidazole (4) . Compounds 4a, 4b, 4c, and 4d were scrutinized for their efficacy in mitigating inflammation, revealing inhibition percentages of 22.1%, 52.2%, 54.6%, and 49.6%, respectively, at 50 mg/kg doses. Notably, compound 4c demonstrated the highest potency with 54.6% inhibition of edema at the tested dosage.[5] Saha et al conducted a study on the synthesis and biological assessment of various disubstituted benzimidazole derivatives(5) The compounds, labeled as 5a, 5b, 5c, and 5d, were created by condensing o-phenylenediamine with aromatic aldehydes, using an ammonium salt catalyst. In vivo study was conducted in Swiss mice, compounds 5c, 5a, and 5b at a dose of 25 mg/kg reduced the number of writhes by 88.81%, 69.40%, and 64.93%, respectively ($P<0.05$), compared to the standard aceclofenac.[6]



R= morpholine,diphenylamine,dimethylamine,imidazole

R_1= Cl

Figure 4.phenyl benzimidazole

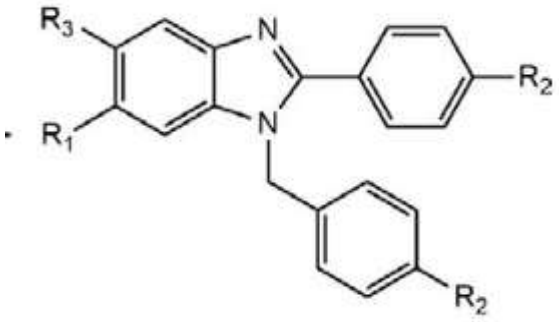
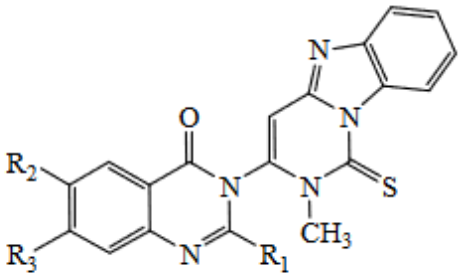


Figure 5. 1,2 disubstituted benzimidazole derivative

Diuretic Activity

Srinivasan et al reported the synthesis of 3-(2-methyl-1,2-dihydropyrimido(1,2-c)benzimidazole-1-thionyl)-6,8-dibromo-2-substituted-3H-quinazolin-4-one (6), highlighting moderate diuretic effects .[7]

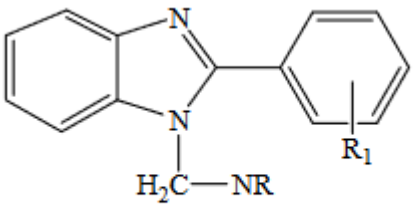


$R_1 = CH_3, Br, R_2 = C_6H_5, H, R_3 = H, Br$

Figure 6 .3-(2-methyl-1,2-dihydropyrimido(1,2-c)benzimidazole-1-thionyl)-6,8-dibromo-2-substituted-3H-quinazolin-4-one

Antimicrobial Activity

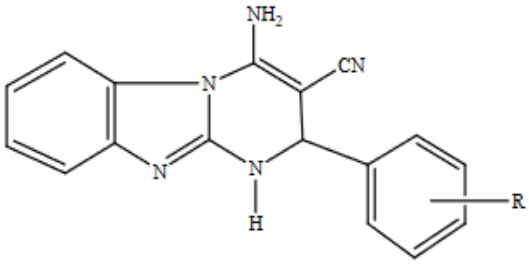
In their research, Leonardo et al also synthesized derivatives of 1-(substituted-methyl)-2-(substituted-phenyl)benzimidazole (7) and assessed their antimicrobial potential against S. aureus, B. pumilus, and P. aeruginosa. Compound 3a displayed significant antibacterial activity with a MIC of 6.25 at 100 μM/mL[5] Meanwhile, Deshmukh et al synthesized 2,3,4-trisubstituted-1,2-dihydropyrimido[1,2-a]benzimidazole derivatives (8), revealing promising fungicidal activity against Aspergillus niger and Penicillium chrysogenum.[8]



R= piperazine, dimethylamine, diethylamine

R_1= Cl

Figure 7. 1-(substituted-methyl)-2-(substituted-phenyl)benzimidazole



R = -OCH_3, -OH

Figure 8. 2,3,4-trisubstituted-1,2-dihydropyrimido[1,2-a]benzimidazole derivatives

Antiulcer Activity

Bariwal et al synthesized novel pyrimidyl-thio-methylbenzimidazole (9) evaluating their antiulcer properties. Notably, the compound is responsible in reducing ulcer formation at dose of 10 mg/kg, comparable to Omeprazole.[9]

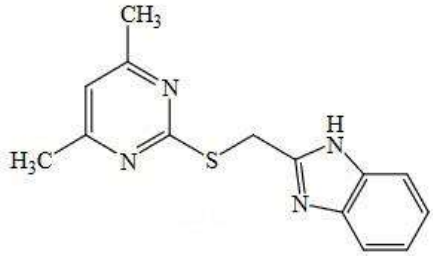
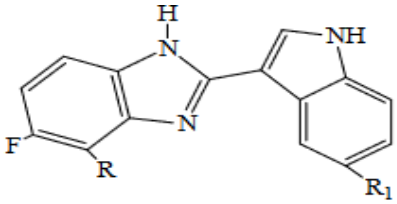


Figure 9 .pyrimidyl-thio-methylbenzimidazole

Antioxidant Activity

Alagoz et al synthesized 6-fluoro-5-substituted benzimidazole derivatives(10), incorporating indole and 1,4,4,4-tetramethyl-1,2,3,4-tetrahydro naphthalene groups at the 2-position, and evaluated them for antioxidant potential. Compound 10e exhibited potent super scavenging activity against superoxide anions at a concentration of 10-3 M.[10]

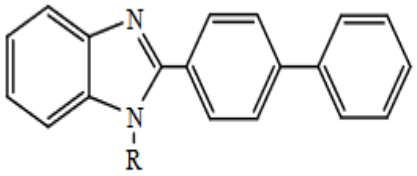


	R	R_1
a	4-$CH_3C_5H_{10}N$	–
b	4-$CH_3C_5H_{10}N$	–
c	4-$C_6H_5C_4H_9N_2$	–
d	4-$C_6H_5C_4H_9N_2$	Br
e	4-$C_6H_5C_4H_9N_2$	OCH_3

Figure 10. 6-fluoro-5-substituted benzimidazole derivatives

Anti-Asthmatic Activity

Kumar et al reported the synthesis of novel functionalized benzimidazole derivatives (11) and evaluated their potential anti-asthmatic effects against PDE-IV. Compounds 11a, 11b, and 11c demonstrated inhibitory activities of 3.40%, 13.52%, and 8.91%, respectively, at 1 μM doses, with compound 11b showing promising anti-asthmatic activity.[11]



R= H, C_2H_5, $CH_2CH_2CH_3$

Figure 11. benzimidazole derivatives 11a, 11b, and 11c

Anti-Diabetic Activity

Kumar et al also synthesized a series of novel benzimidazole derivatives (12) and tested their anti-diabetic activities against DPP-IV and PTP-IB. Compounds 12a and 12b exhibited inhibitory activities of 1.64% and 2.42%, respectively, against PTP-IB at 30 μM doses, while compound 12c demonstrated 3% inhibition against DPP-IV at 0.3 μM doses.[11]

Anti Cancer activity

Kumar et al. synthesized carbomethoxy-substituted benzimidazole derivatives of the natural product UK-1 from a Streptomyces strain. They assessed the cytotoxicity of these compounds using Alamar Blue assays on MCF-7, HL-60, HT-29, and PC-3 cell lines. The compound methyl 2-[2-(2-hydroxyphenyl)-1,3-benzoxazol-4-yl]-1H-benzimidazole-4-carboxylate (13) showed cytotoxic effects with IC50 values ranging from 7.0 to 100 µM .[12] Vedula et al .synthesized new styryl sulfones were tested for their anticancer activity against various cancer cell lines, including those causing breast, CNS, colon, lung, melanoma, ovarian, prostate, and renal cancers. The compound 6-chloro-1H-(benzo[d]imidazol-2-yl) methyl [(E)-2-(4-chloro-3-methylphenyl)-1-ethenyl] sulphone (14) demonstrated a 51% reduction in tumor activity. growth inhibition in mice implanted with HT-29 human carcinoma at 400 mg/kg orally .[13]

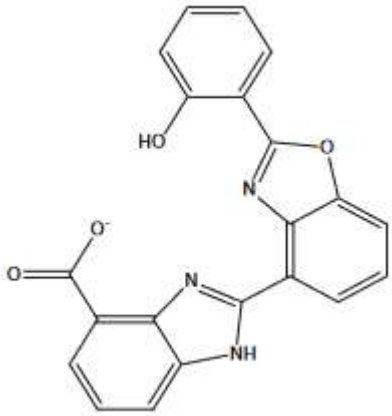


Figure 12. methyl 2-[2-(2-hydroxyphenyl)-1,3-benzoxazol-4-yl]-1H-benzimidazole-4-carboxylate

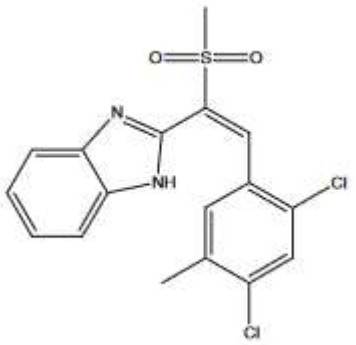


Figure 13. 6-chloro-1H-(benzo[d]imidazol-2-yl) methyl [(E)-2-(4-chloro-3-methylphenyl)-1-ethenyl] sulphone

Anti viral Activity

Starcevic et al synthesized heterocyclic benzimidazole derivatives with amidino groups at the C-5 position and various heterocyclic groups (pyridine, N-methyl pyrrole, or imidazole) at the C-2 position. They evaluated these compounds for antiviral activity against coxsackieviruses and echoviruses. Notably, compounds 15 (2-(1-methyl-1H-pyrrol-2-yl)-1H-benzimidazole-5-carboxamidine hydrochloride) and 16 (n-isopropyl-2-pyridin-2-yl-1H-benzimidazole-5-carboxamidine) showed strong activity against adenovirus, making them promising leads for adenoviral replication inhibition.[14]

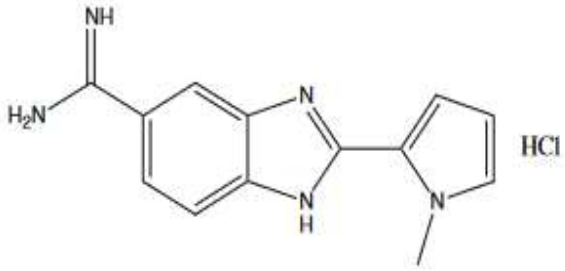


Figure 14. 2-(1-methyl-1H-pyrrol-2-yl)-1H-benzimidazole-5-carboxamidine hydrochloride

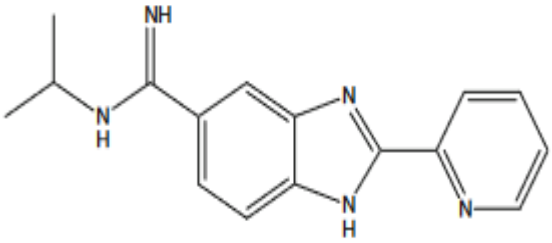


Figure 15. n-isopropyl-2-pyridin-2-yl-1H-benzimidazole-5-carboxamidine

Antiarrhythmic Activity

Anisimova et al synthesized 9-dialkylaminoethyl-2-oxy(dioxy)phenylimidazo[1,2-a]benzimidazole derivatives (17), assessing their antiarrhythmic properties. Compounds 17a, 17b, and 17c demonstrated antiarrhythmic activity, with compound 17 a showing efficacy close to the reference drug Quinidine in terms of minimum effective concentration (MIC mole/L).[15]

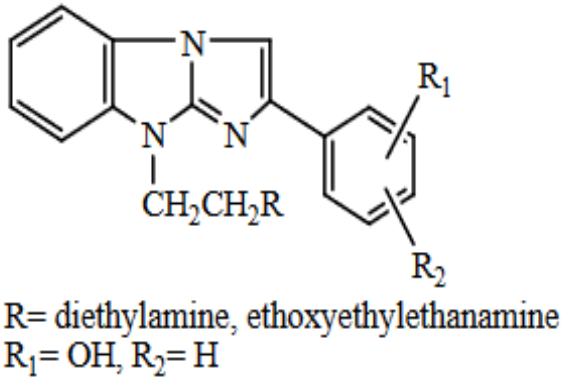


Figure 16. 9-dialkylaminoethyl-2-oxy(dioxy)phenylimidazo[1,2-a]benzimidazole derivatives

Anticonvulsant Activity

Chimrri et al reported on the synthesis of novel 1-H pyrrolo(1,2-a)benzimidazole-1-one derivatives (18), evaluating their anticonvulsant effects. Compounds 18a, 18b, and 18c exhibited significant anticonvulsant activity by the maximal electroshock method at 25 mg/kg orally, with compound 18a demonstrating the highest efficacy among them.[16]

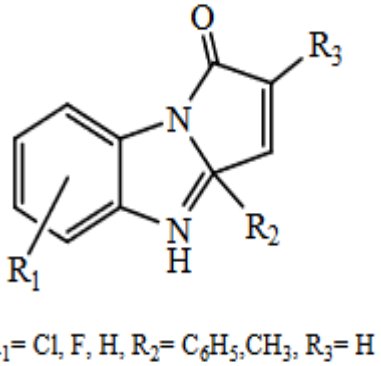


Figure 17. 1-H pyrrolo(1,2-a)benzimidazole-1-one derivatives

Antiprotozoal Activity

Andrzejewska et al synthesized two series of S-substituted 4,6-dihalogeno-2-mercapto-1H-benzimidazoles (19) and evaluated their in vitro antiprotozoal activity against G. intestinalis and T. vaginalis, using albendazole and metronidazole as reference standards.Among them compounds 19a, 19b and 19c were found to be most potent and comparable to standard drugs.[17]

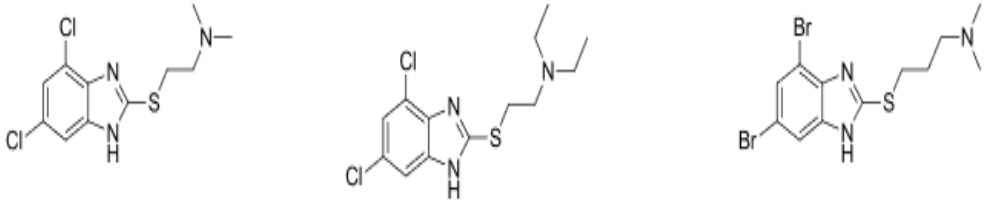


Figure 18. S-substituted 4,6-dihalogeno-2-mercapto-1H-benzimidazoles

Vazquez et al synthesized 2-(trifluoromethyl)-1H-benzimidazole (20) and evaluated the anti-protozoal activity. These analogues were tested in vitro against the protozoa Giardia intestinalis and Trichomonas vaginalis, compared to Albendazole and Metronidazole, and showed IC50 values of less than 1 μM.[18

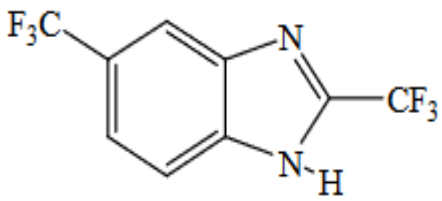
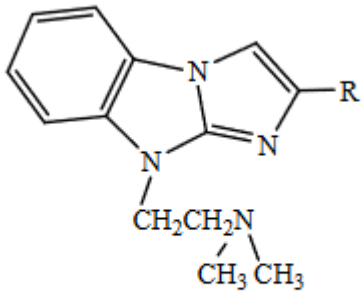


Figure 19. 2-(trifluoromethyl)-1H-benzimidazole

Hypotensive Activity

Anisimova et al reported the synthesis of 9-dialkylaminomethyl-2-oxy(dioxy)phenylimidazo[1,2-a]benzimidazole (21). Compounds 21a, 21b, and 21c exhibited hypotensive activity with ED50 values of 2.8 mg/kg, 0.8 mg/kg, and 0.13 mg/kg, respectively, and LD50 values of 121.0 mg/kg, 182 mg/kg, and 143 mg/kg, respectively. The LD50/ED50 ratios were 43.2, 227.5, and 1100. Among these, compound 21c was the most active, surpassing the reference drugs Dibazole and Apressin in terms of hypotensive effect (ED50: 22.1, 4.0) .[19]



R= 1-4 dihydroxymethylbenzene,
1-3 dihydroxymethylbenzene,

Figure 20. 9-dialkylaminomethyl-2-oxy(dioxy)phenylimidazo[1,2-a]benzimidazole

Neuroprotective Activity

Muhammad Imran et al synthesized and characterized eight novel benzimidazole acetamide derivatives (FP1, FP2, FP5−FP10) to explore their neuroprotective effects against ethanol-induced neurodegeneration in a rat model. Pretreatment with the new benzimidazole acetamide derivatives (FP1, FP7, and FP8) significantly improved ethanol-induced memory deficits, reduced oxidative stress, and lowered proinflammatory markers (TNF-α, NF-κB, IL-6, NLRP3) in the cortex.. These findings suggest that benzimidazole acetamide derivatives (FP1, FP7, and FP8) hold promise as neuroprotective agents against ethanol-induced neurodegeneration, likely by disrupting the neuroinflammatory-oxidative stress cycle.[20]

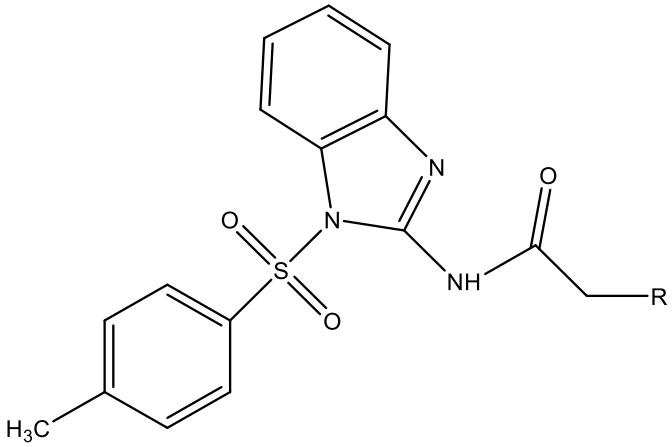
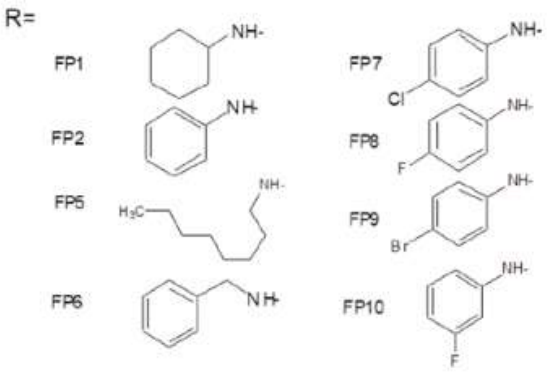


Figure 21.Benzimidazole acetamide derivatives



CONCLUSION

The benzimidazole nucleus proves to be a versatile and powerful pharmacophore with a broad spectrum of biological activities. Its integration into various derivatives underscores its importance in the design of novel therapeutic agents. This comprehensive review of benzimidazole derivatives and their pharmacological properties highlights their critical role in advancing medicinal chemistry and underscores their potential in developing effective treatments for a wide range of diseases.

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