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Recent Bioactive Benzimidazole Derivatives: A Review

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ABSTRACT

Benzimidazoles (BZ) are medicinally significant scaffolds due its pharmaceutical potential as an antitumor, antagonist, antidiabetic, anti-Neuroprotective, antiulcer etc. Now Days, Heterocyclic moiety incorporated with benzimidazole is highly focused by researchers for potent Drug Design. In this review we have tried cover efforts made on BZ in last two years which will be useful to design novel Molecules.

KEYWORDS: *Benzimidazole, Biological activities, Synthetic routes*

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INTRODUCTION

Benzimidazole (BZ) moiety is a important pharmacophore among Heterocycles, which possess a versatile wide spectrum of biological activities.[1] BZ based derivatives shows excellent action as a antitumor[2], antagonist[3], antidiabetic[4], Nueroprotective[5], analgesic [6], antibacterial[7], antifungal[8],antiulcer[9]. Nocodazole (anticancer), rabeprazole (proton pump inhibitor), thiabendazole (anthelmintic), Candesartan (antihypertensive) drugs are available in the market.[10] Recently No of routes were developed to obtained BZ derivatives from its main precursor o phenelene diamine.[11]

In this review, we have discussed potent pharmaceutical molecules and their activities from literature of last two years.

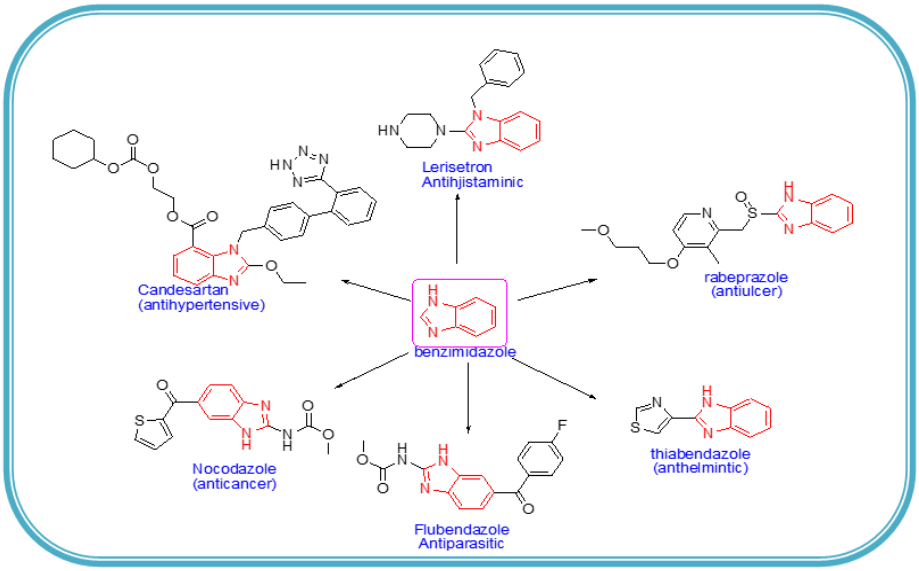


Figure 1: Marketed Drugs of BZ

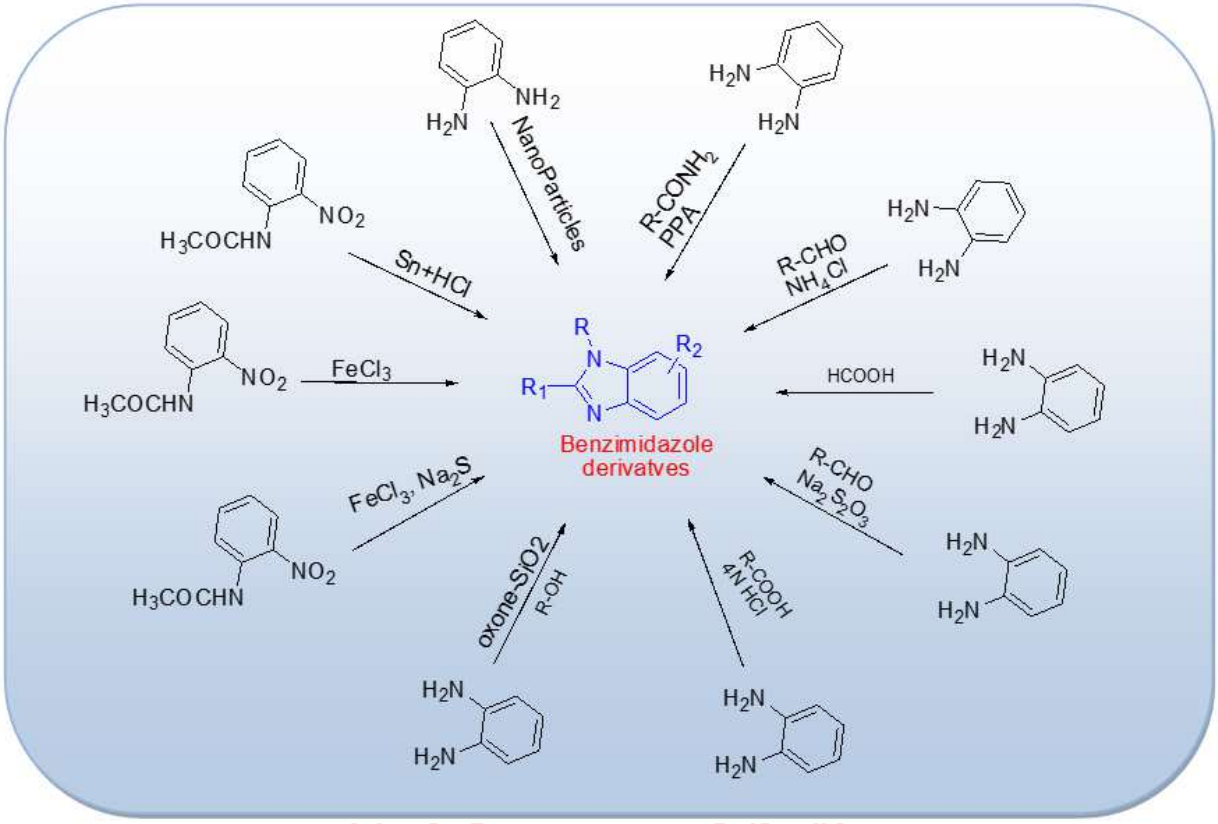
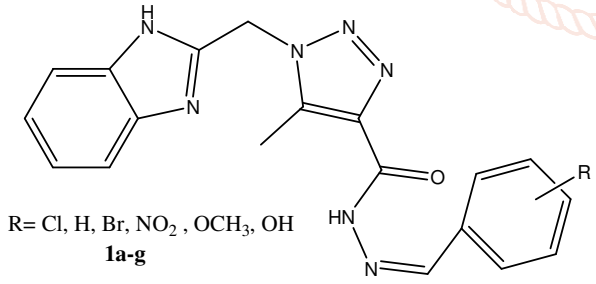


Figure 2: Synthesis Approaches for benzimidazole[11]

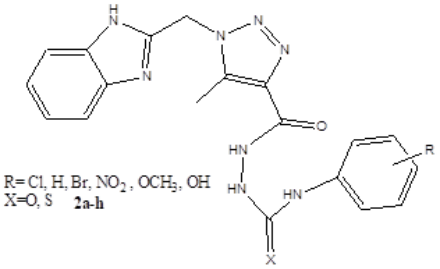
ANTICANCER:

D. I. A. Othman et al. synthesized novel series of triazole clubbed benzimidazole Schiff bases **1a-g** and carbothioamide, carboxamide **2a-h**. Anticancer screening was carried out and Cloro substituted hydrazine carbothiamide have shown most potential with IC_{50} value 7.68, 8.34,6.81,3.87 with against HepG-2, HCT-116, MCF-7, eLa human cell lines respective. [12]



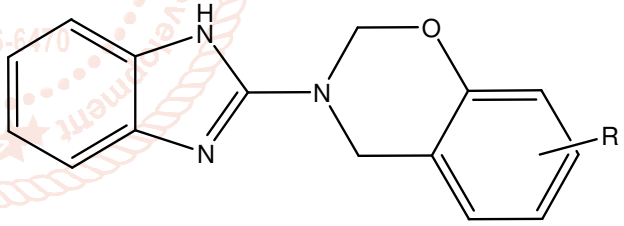
R= Cl, H, Br, NO_2 , OCH_3, OH

1a-g



R= Cl, H, Br, NO_2 , OCH_3, OH
X=O, S **2a-h**

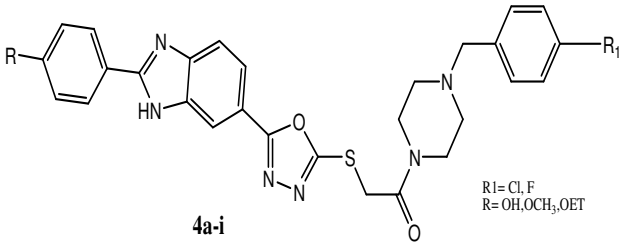
Gali Srinivas et al. reported novel series of 3a-k benzo[e][1,3] oxazine clubbed benzimidazoles. 7-methoxy substituted com had shown highest cytotoxic effect with IC_{50} value 8.60 and 6.3 against MCF-7 and MDAMB-231 cell line respectively. -8 .0 to -9.4 docking score of12a-k was achieved against Epidermal Growth Factor Receptor [13]



R=butyl,Cl,Br,NO_2,OCH_3,H , F , Ph

3a-k

Çevik et al reported novel series of bezimidazole clubbed oxadiazole and piperizine 4a-I and evaluated against MCF7 A549, HepG2, HeLa. 4-Cl and 4-F displayed huge potential against the MCF-7 (IC50= 5.132 ± 0.211, 6.554 ± 0.287 µM).[14]

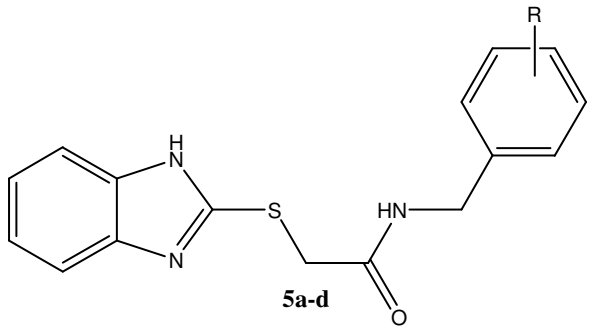


R1= Cl, F
R= OH,OCH_3,OET

4a-i

El Hameed et al reported novel derivatives of 2-(1H-benzoimidazol-2-ylthio)-N-benzyl-acetamide 5a-d a.

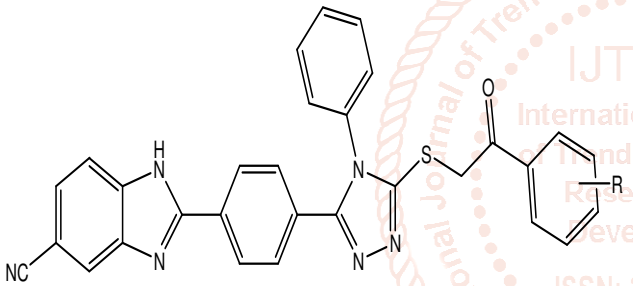
R=H and Cl derivatives showed growth inhibition - 54.92 and 4.87 against HCT-116 and TK-10 cell lines respectively[15]



5a-d

ANTIFUNGAL:

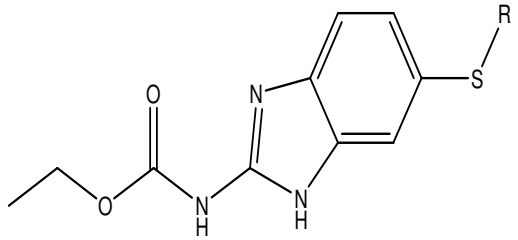
Guzel et al. reported novel triazole incorporated benzimidazole derivatives **6a-l. 6a-l** were displayed excellent MIC value (0.97 to 125 µg/mL) against C. parapsilosis, C. glabrata, C. krusei, C. albicans. 4-methoxy and 4-chloro derivatives are demonstrated as a most active antifungal agent. Cytotoxic activity shown under 50% viability against L929 cell lines[16]



R=Cl,Br,NO_2,OCH_3,H , F , Ph

6a-l

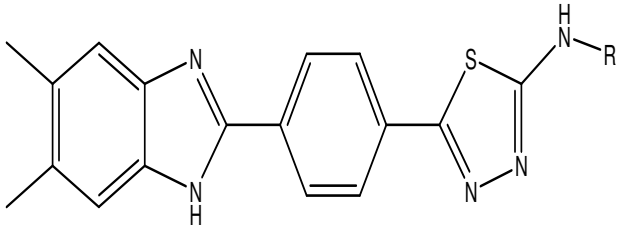
Lei Yang et al reported 7a-o thioether and carbamate derivatives. Trifluorobut-3-en-1-yl substituted com. shown 69%, 40% inhibition against V. daliaeand and C. mandshurica respectively Methoxy substituted com. shown 70%, 75% inhibition against V. daliaeand and P. infestans[17]



R= benzyl, Cl-benzyl, F-benzyl,NO_2-benzyl,pyridine , Cl-pyridine , methoxy, ethoxy

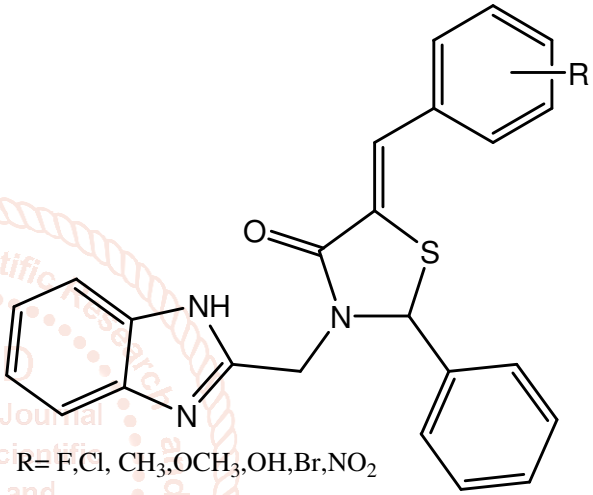
7a-o

Celik et al reorted N-sub-5-(4-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)phenyl)-1,3,4-thiadiazol-2-amine series 8a-h. Methyl, propyl, methoxy phenyl derivatives showed MIC value 7.81,7.81 and 1.95 µg/mL against C. albicans[18]



8a-h

N C Deasai et al reported banzimidazole based thiazolidone arylidine 9a-o and evaluated against C. albicans A. niger A. clavatus stains. 4-CL,4-OCH_3, CH_3 substituted molecules have showed parallel to standard Griseofulvin with MIC value 500 µg/mL[19]

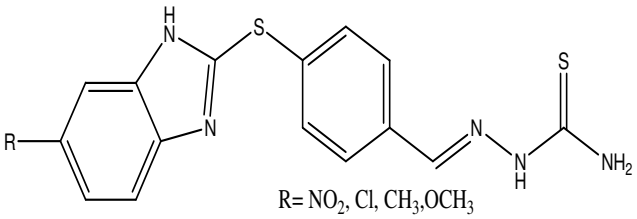


R= F,Cl, CH_3,OCH_3,OH,Br,NO_2

9a-o

ANTIBACTERIAL:

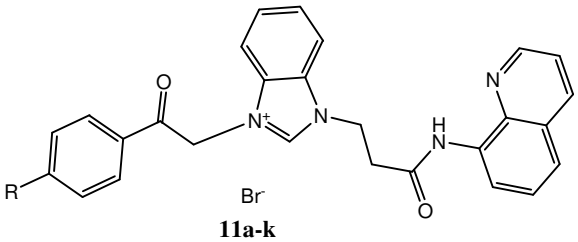
R. Champa et al reported novel Schiff bases of benzimidazole 10a-e and demonstrated antibacterial, anticancer and antioxidant activities. Chloro derivative displayed huge inhibition against *S.aureus*, *B. cereus*,*E. coli* and *Acetobacter* sp. Nitro derivative shows highest cytotoxic action with IC_{50} 25.79 ± 2.62 (µg/mL). Cl and NO_2 derivative having antioxidant action with IC50 value of 55.74 ± 3.19 and 45.32 ± 3.78. [20]



R= NO_2, Cl, CH_3,OCH_3

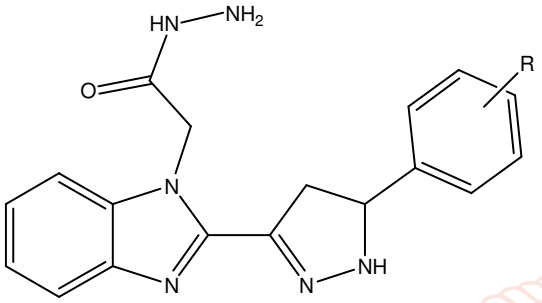
10a-e

Diaconu et al reported quinoline based benzimidazole derivatives 11a-k and demonstrated against E.coli and S.auresus. Floro and cloro derivatrives have shown good (24 and 20 mm) inhibition against e.coli. Floro derivative have also excellent inhibition against HL-60, RPMI-8226, SR, MCF7, T-47D, MDA-MB-468 cancer cell line.[21]



11a-k

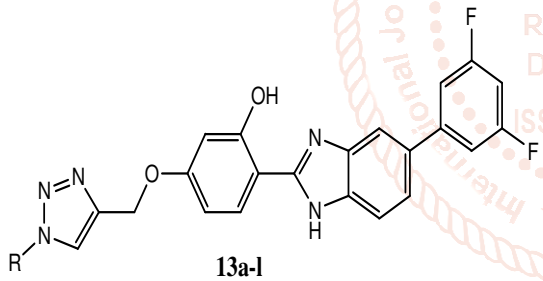
Gopal Krishna et al reported new pyrazoline clubbed benzimidazole series 12a-d. MIC value of 62.5–500 µg/mL obtained during demonstration against S. aureus, B. subtilis, E. coli and P. aeruginosa[22]



R= H, Cl, F, Br ,CH3

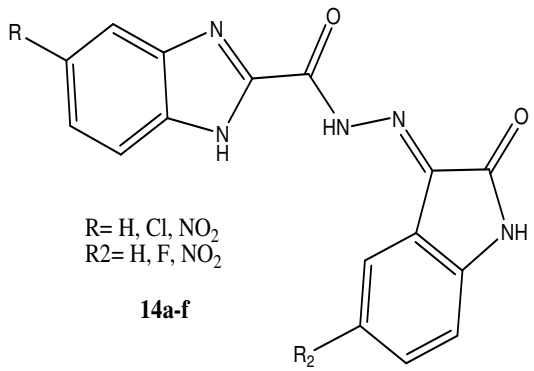
12a-d

Mallikanti Veerabhadraiah et al synthesized new triazole clubbed benzimidazole derivatives 13a-l and shown excellent inhibition against S. aureus, B. subtilis, E. coli and P. aeruginosa[23]



13a-l

Suvaiv singh et al reported schff base of isatin incorporated benzimidazole derivatives 14a-f. Antibacterial study shown strong inhibition of 4-Cl benzimidazole and 4-F isatin com with value of 27,27,17,19 mm against S. aureus, B. subtilis, E. coli and P. aeruginosa respectively. 4-Cl BZ and 5-NO2 isatin displays -8.4 kcal/mol docking score against amino acid site.[24]

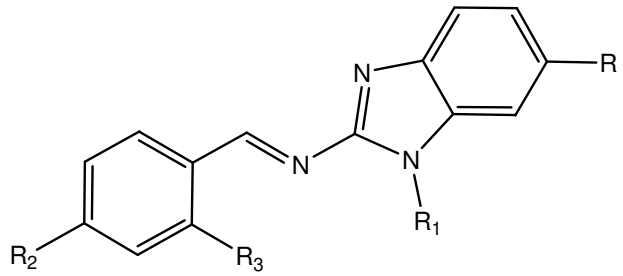


R= H, Cl, NO_2

R2= H, F, NO_2

14a-f

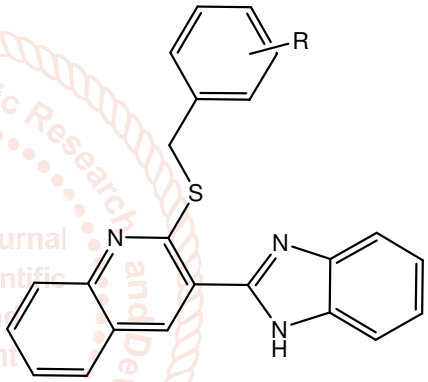
Anja bec et al reported novel Schiff base of benzimidazole 15a-r and N-hexyl-benzimidazole deri displayed antibacterial as well as antiproliferative activities.[25]



15a-r

ANTIDIABETIC

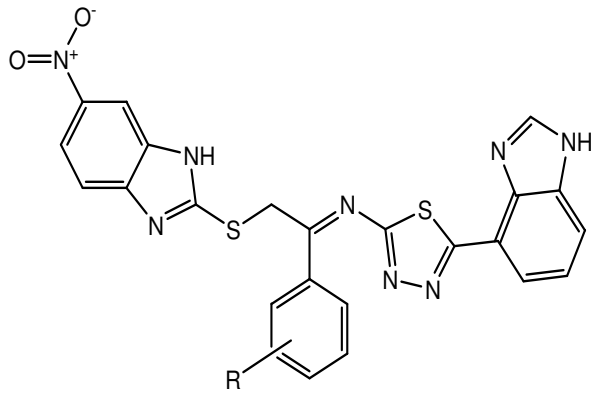
Moghadam Farid et al. reported novel series of **16a-r**. all novel derivatives were screened for glycosidase inhibitors and shown good inhibition with IC50 value 28.0–663.7 µM.[26]



R= F,Cl,Br,CH_3, NO_2, OCH_3, di Cl, di CH_3

16a-r

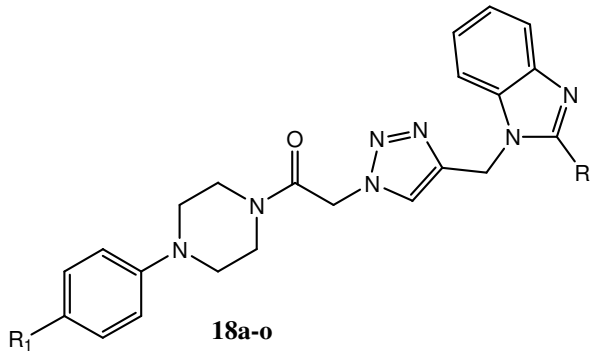
Khan S et al Reported Bis benzimidazole clubbed thiadiazole **7a-r** and evaluated against glucosidase and amylase enymes. 1**7a-r** displays inhibition ranging 0.10 ± 0.50 to 23.20 ± 0.50. triflоromethane and nitro substituted compound displayed highest inhibition 0.10 ± 0.50, 0.20 ± 0.50 towards respective enzymes.[27]



R= CF_3,OH, NO_2, CH_3,Cl,OCH_3, CN,Br, $N(CH_3)_2$,

17a-r

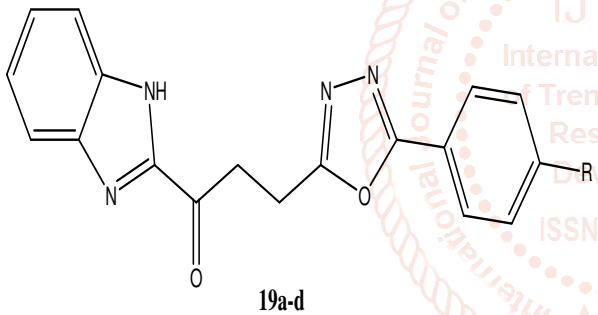
L. Deswal et al. prepared novel derivaties of trizole piperazine dopped benzimidazoles 18a-o. pyridine substitutions displays an IC_{50} value of 0.0327, 0.0144 mol/mL towards α-amylase and α-glucosidase respectively, pyridine and floro substituted derivative showed IC50 values of 0.0156 and mol/mL towards α-glucosidase[28]



18a-o

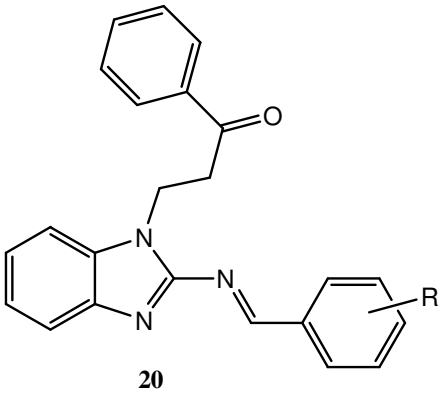
ANTIOXIDANT

Bhandari, S. V. et al. successively synthesized benzimidazole linked oxadiazole derivatives. 19a-d were evaluated against antioxidant activities using DPPH method and 3-nitro phenyl derivative displays highest IC_{50} value of 53.00±1.31 µg/ml.[29]



19a-d

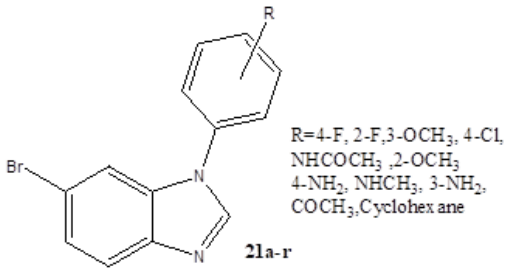
Swikriti et al demonstrated excellent antioxidant and anti inflammation potential of 3-(2-((benzylidene)amino-1H-benzo[d]imidazol-1-yl)-1-phenylpropan-1-one derivatives 20 using DPPH and paw edema method[30]



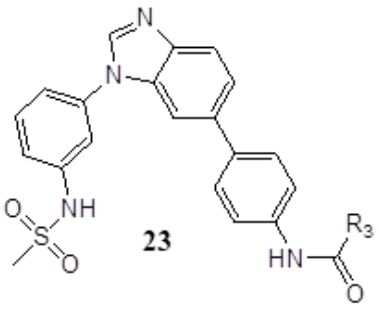
20

OTHER ACTIVITIES

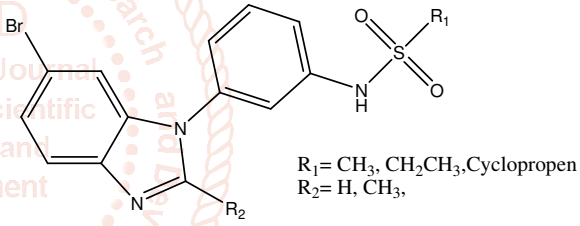
Dimitrov et al reported no of series of 6-bromo-1-substituetd phenyl-1H-benzo[d]imidazole, N-(3-(6-bromo-1H-benzo[d]imidazol-1-yl) phenyl) sulfonamide derivatives, 2-((2-(dimethylamino) ethyl)(methyl)amino)-N-(4-(1-(3-(sulfonamido)phenyl)-1Hbenzo[d]imidazol-6-yl)phenyl)acetamide derivatives and displays excellent results durind evalution as an ATP inhibitor.[31]



21a-r

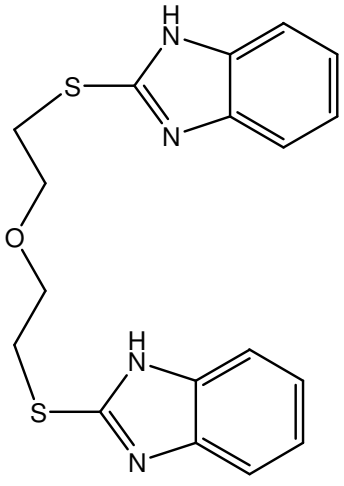


23



22a-j

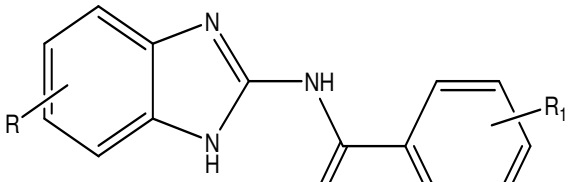
Jaafar et al reported 2-(2-(2-(1H-benzo[d]imidazol-2-ylthio)ethoxy)ethylthio)-1H-benzo[d]imidazole 24 and demonstrated as a efficient corrosion inhibitor[32]



24

Escala et al. reported a series of N-(5,6-Dichloro-1H-benzimidazol-2-yl) picolinamide derivatives 25 a-aj. 5- Methyl and 5,6 dimethyl derivatives displayed

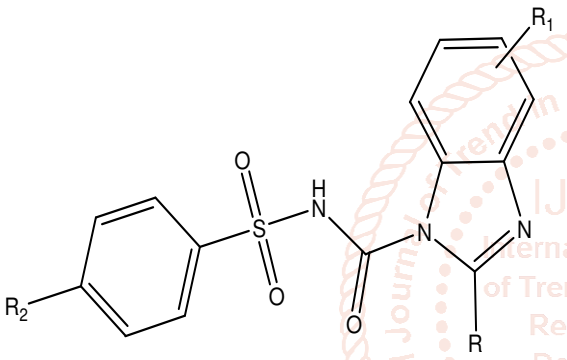
excellent groth inhibition with IC_{50} 0.98 and 0.85 respectively against the HB3 strain of falciparum parasites[33]



R_1= CH_3, OCH_3, Ph,
R= Cl, CH_3, butyl,

25a-r

Sehrish bano et al reported novel sulfonyl doped benzimidazole derivatives 26a-y and antagonists screening was performed adainst P2Y1 receptors. Di chloro derivative displayed highest 0.19 MicroM IC_{50}. Cytotoxic effect also showed good inhibition against HEK-293**,** 1321N1 cells, and HeLa cell line. [34]



26a-y

CONCLUSION

Benzimidazole derivatives can be achieved with various one pot syntheses. Pharmaceutical actions of Modified derivatives prove that they are efficient chemical entities for the Drug Development and also towards drug resistance.

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