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Journal of Current Pharma Research 4 (2), 2014, 1159-1167.

Journal of Current Pharma Research

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Review Article

Benzimidazole: An Important Biological Heterocyclic Scaffold

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Received 03 February 2014; received in revised form 16 March 2014; accepted 16 March 2014
Available online 23 March 2014

Abstract

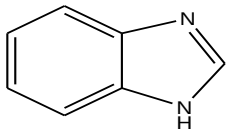
Various heterocyclic scaffolds have drawn special attention of medicinal chemists and hence, extensive efforts are being carried out in search of lead molecules related to it. Benzimidazole is an important pharmacophore owing to its inherent properties and therapeutic actions. These exhibit many biological activities like anticancer, anticonvulsant, antiHIV, antimicrobial and many more. Such biological applications of benzimidazole derivatives have attracted attention and stimulated new search for its novel derivatives with improved biological activities and these are being extensively studied. The present review includes rigorous literature survey on the search of biologically active benzimidazole ring linked and fused with other heteroaromatic systems.

Keywords: Benzimidazole, Anticancer, Antimicrobial, Anticonvulsant, Anti-HIV.

1. Introduction

Heterocyclic compounds are very widely distributed in nature and are particularly important because of the wide variety of physiological activities associated with this class of substances. Several of the important compounds like alkaloids, antibiotics, chlorophyll, other plants pigments, amino acids, dyes, drugs, enzymes and genetic material contain heterocyclic rings[1]. Amongst the important heterocyclic compounds, benzimidazole has stimulated considerable interest because of its diversified biological activities. It is a fused aromatic imidazole ring system where a benzene ring is fused to the 4 and 5 positions of an imidazole ring. Benzimidazole is also known as 1, 3-benzodiazoles. It possesses both acidic and basic characteristics. The cyclic –NH- group present in benzimidazole is relatively strongly acidic and also weakly basic. These also have the capacity to form salts. Benzimidazole with unsubstituted –NH- groups, exhibit fast prototropic tautomerism instead of isomerism.

But when the group attached to the nitrogen in the l-position is larger than hydrogen, such tautomerism is not indicated and isomeric forms exist[2].



Benzimidazole

Table 1: Physicochemical properties of benzimidazoles.

Molecular Formula	**$C_7H_6N_2$**
Molecular Weight	118.149g/mol
Refractivity	34.09
Log P Value	1.67
PKa	2.5(Strong basic)
Melting Point	170.5°c
Boiling point	>360°c
Solubility in water	1.70±01 g/l.

Benzimidazole is considered to be an important pharmacophore and a privileged structure in medicinal chemistry. Literature

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survey has revealed that 2-substituted benzimidazole derivatives have diverse therapeutic applications. Hence, synthesis of 2-substituted derivatives is potential area of research[2]. Many linked and fused benzimidazole heterocycles have been developed by structural manipulations at this substituted position to improve chemical stability, potency and biological or therapeutic effectiveness. The various biological activities that have been explored for this heterocycle include anticancer, anti-HIV, anticonvulsant, antimicrobial, and many more. A recent finding related to some of these activities has been the objective of this review article.

Biological Activities

Anticancer Activity

Styskala J *et. al* [3] have reported the synthesis of derivatives of 1,2,4-triazino[4,5-a]benzimidazol-1-ones, containing additional benzimidazole ring. Their biological activities were examined by comparing cytoxicity, using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay towards the drug-sensitive leukemia cell lines CEM (T lymphoblastic) and K562(myeloid), and some drug-resistant lines. They found that compounds with the lipophilic substituents (Figure No.-1) were highly active in leukemia cell lines at low micromolar concentrations, substitutions with 4-chlorophenyl or 4-nitrophenyl groups substantially decreased the cytotoxic potency. However, this was not the case in human carcinoma cell lines, where a higher level of substitution in position 4 demonstrated the opposite effect and generally increased the cytotoxic activity. But these compounds were found to be less active against Multidrug Resistance Protein (MRP-1) positive and topoisomerase IIα negative CEM-DNR bulk cells.

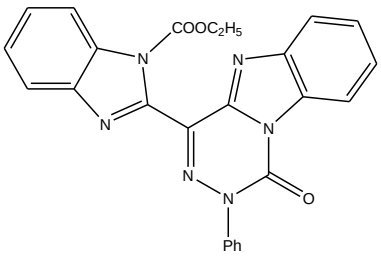


Figure No.-1

Gellis A *et. al* [4] synthesized new benzimidazole-4,7-diones substituted at 2-position as bioreductive anticancer agents. The cytotoxicity was evaluated on breast (T47D), lung (A549) and colon (HT29) cancer cell lines using MTT assay. Amongst all the tested compounds, the dimer (Figure No.-2) proved to be most effective on breast (T47D), lung (A549) and colon (HT29) cancer cell lines and efficiency was comparable to the reference prototype bioreductive anticancer drug mitomycin C.

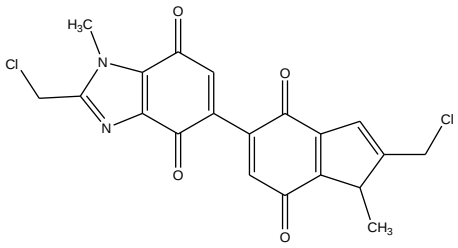
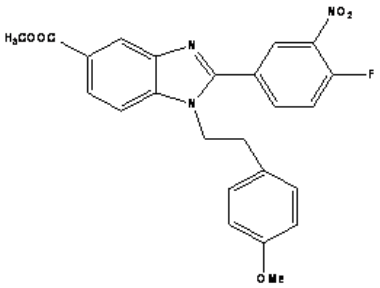


Figure No.-2

Thimme N R *et. al* [5] reported the synthesis of 1-(4-methoxyphenethyl)-1H-benzimidazole-5-ester derivatives and their precursors acids as potential chemotherapeutic agents. On comparing these two sets of compounds, they found that ester derivatives exhibited better activity than the acid derivatives. Methyl 1-(4-methoxyphenethyl)-2-(4-fluoro-3-nitrophenyl)-1H-benzimidazole-5-carboxylate (Figure No.-3) was found to induce maximum cell death in leukemic cells with an IC_{50} value of 3 µM and showed good amount of DNA strand breakage even at 10 µM. Fluorescence-activated cell sorting (FACS) analysis showed that this compound induces S/G2 cell cycle arrest, triggering activation of apoptosis.



(Figure No.-3)

Abdel-Mohsen HT, *et. al* [6] discovered a new class of benzimidazole–pyrimidine conjugates as potent antitumor agents. They performed MTT assay according to the Mossman's method, against 12 cell lines. It revealed that the presence of substituted basic group at position 4 on pyrimidine ring gives potent antitumour action. The substituents R with 4-aminopyridino, 2-aminothiazolo and 2-aminopyridino (Figure No.-4) were found to be the most active compounds against CNS cancer, leukemia and neuroblastoma.

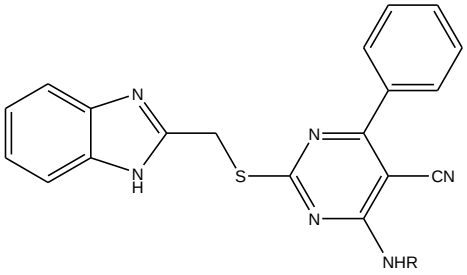


Figure No.- 4

Patel OB *et. al* [7] have studied the synthesis of 2-(aryl)-1-benzo[d]imidazol-1-yl ethanones The aryl group may be benzotriazole or benzimidazole. They have reported the cytotoxic activity of compound by 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide (XTT) assay method using human lungs cancer cell line VERO and NCI cell lines. Compound (Figure No.-5) was found to be the most potent, after 48hrs, in both series but less active than the standard drug doxorubicin. It was also observed that the cytotoxicity of the all synthesized molecules significantly increased with the incorporation of nitrogen function.

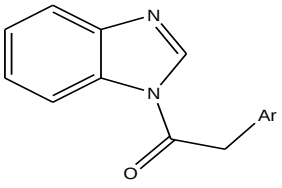


Figure No.-5

Vedula MS *et. al* [8] have reported the synthesis of a novel class of styryl sulfone compounds and their 3D QSAR studies using Molecular Similarity Indices in Comparative Analysis (CoMSIA) method. They demonstrated that these compounds have potent antiproliferative activity. The compound selection for *in vivo* studies was based on pharmacokinetic profiles. It was revealed that the compound (Figure No.-6) exhibited good efficacy against HT-29 human carcinoma inhibiting 51% tumour growth at 400 mg kg^{-1} dose.

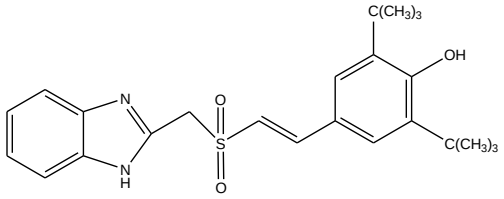


Figure No.- 6

Anti HIV Activity

Miller JF *et. al* [9] described the lead optimization of a series of N-substituted benzimidazole antagonists. It was found that side chain modifications and stereo chemical optimization led to substantial improvements in potency with low nM antiHIV activity. Amongst all, compound (Figure No.-7) emerged as a promising candidate showing antiviral activity at 2nM, a 1000-fold cytotoxicity window and reduced the protein shift down to two-fold and provided a three-fold activity increase.

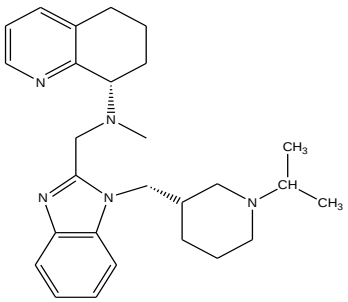


Figure No.-7

Gardiner J.M. et. al 10 reported the synthetic approaches towards acyclic analogues of the HIV-l RT inhibitor s with 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*j*,*k*][1,4] benzodiazepin-2(1H)-one (TIBO) ring system. Several of the compounds were found to inhibit HIV- 1 infectivity and all the compounds were significantly cytotoxic with highest selectivity index. The compounds bearing 7-methyl and 7-bromo substitution had reasonable EC_{50} of 4

µM and 8 µM and selectivity indices of 10and 25; respectively.

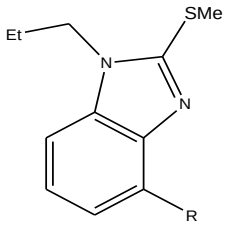


Figure No.-8

Monforte AM *et. al* [11] have synthesized 1, 3-dihydro-benzimidazol-2-ones and their analogues which later on were found to be potent non-nucleoside HIV-1 reverse transcriptase inhibitors. The derivatives were tested by enzymatic assay and also against RTs containing single amino acid mutations responsible for resistance to NNRTIs. Among all the tested compounds an excellent HIV-1 inhibitory profile was exhibited by following compound (Figure No.-9) with a potency superior to that of nevirapine and comparable to that of efavirenz but with a higher selectivity index (>61857).

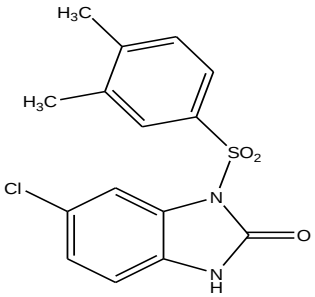


Figure No.-9

Anticonvulsant Activity

Several derivatives of 4-thiazolidinones and 1, 3, 4-oxadiazoles containing 2-mercapto benzimidazole moieties were synthesized by Shingalapur SV *et. al* [12]. The compounds were screened for anticonvulsant activity by the maxima electro shock (MES) test using phenytoin as standard drug. Compounds containing amide linkage and electron donating groups like o-phenol, p-phenol at second position of 4-thiazolidinones (Figure No.-10) exhibited potent anticonvulsant action as compared to phenytoin while compounds with 5-substituted 1, 3, 4-oxadiazoles (Figure No.-11) showed greater activity than glibenclamide. They also studied DNA cleavage by agarose gel electrophoresis method and revealed that some compounds cleaved the DNA completely, as no traces of DNA were found.

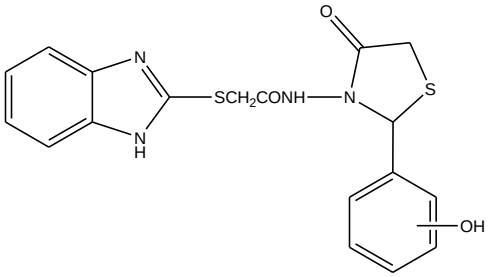


Figure No.- 10

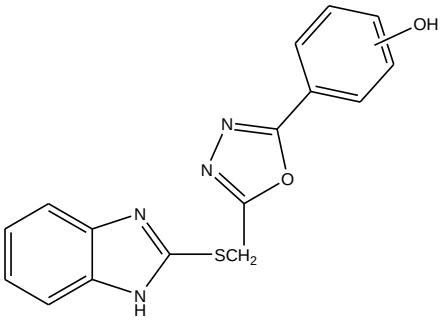


Figure No.- 11

Anandarajagopal K *et. al* [13] have synthesized 2-mercaptobenzimidazole derivatives by Mannich reaction. The anticonvulsant activity was carried out by MES induced convulsion method. All the synthesized compounds at a dose of 20 mg/kg, was found to exhibited anticonvulsant activity (26.10 – 85.98 % protection) in comparison to the standard drug phenytoin but the compounds (Figure No.-12) exhibited excellent anticonvulsant activity.

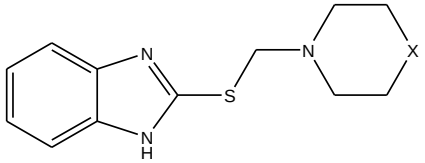


Figure No.-12

X=NH/O

Bhrigu, B. *et. al* [14] described the synthesis of various 2- substituted benzo[d]imidazole-1-carbothioamides and studied their anticonvulsant activity. The synthesis of these compounds was carried out from 2-mercaptobenzimidazole using reagent hydrazine hydrate, substituted acetophenones and phenylisothiocyanate. The resulting compounds were screened in the rats using MES and subcutaneous pentazocine (PTZ) models while neurotoxicity was measured by rotarod test. Phenytoin was used as a standard. The derivatives were substituted with electron withdrawing groups at *o* and *p*-positions and some compounds (Figure No.-13) showed neurotoxicity less than phenytoin.

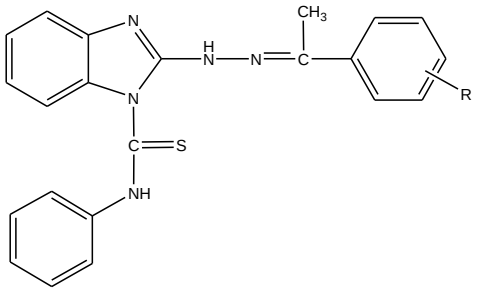


Figure No.-13

R= Br or cl or NO_2

Antitubercular Activity

Gill C *et. al* [15] developed an efficient methodology for the synthesis of 2-(3-fluoro-phenyl)-1-[1-(substituted-phenyl)-1H-[1,2, 3]-triazol-4-yl-methyl)-1H-benzo[d] imidazole derivatives (Figure No.-14) as pharmacophore for antituberculor activity and compared against rifampicin. All compounds were screened for antimycobacterial activity against *S. aureus, P. aeruginosa, E. coli and S. typhii*. These derivatives which contained mono- or di-fluoro substitution at various position on phenyl ring showed better activity against the mycobacteria with >96% inhibition at 6.25 mg concentration.

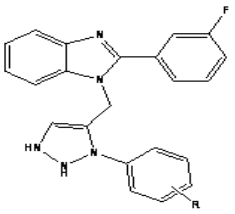


Figure No.-14

Shingalapur, *et. al* [16] synthesized novel 5-(nitro/bromo) substituted-2-styryl benzimidazole derivatives. These compounds showed good antibacterial, antifungal and antitubercular activities against various strains of microbes and fungi. Compound (Figure No.-14) showed good activity against *M. tuberculosis* strain. The moderately electron donating groups on phenyl ring were found to confer higher activity compared to electron withdrawing nitro derivatives.

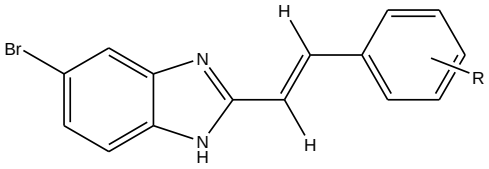


Figure No.-15

Antimicrobial Activity

Desai, N.C. *et. al* [17] synthesized benzimidazole linked with 2-pyridone derivatives as antibacterial and antifungal agents. The activity was assessed *in vitro* against *S. aureus S. pyogenes, E. coli, P. aeruginosa, C. albicans, A. niger, A. clavatus* using the conventional broth dilution method. Amongst these, compounds (Figure No.-16) showed potent antibacterial action with 2- to 4-fold higher MIC (12.5–25 mg/mL) than the standard drug chloramphenicol. When substitutent is chloro, compound showed superior antifungal activity as compared to standard drug ketoconazole.

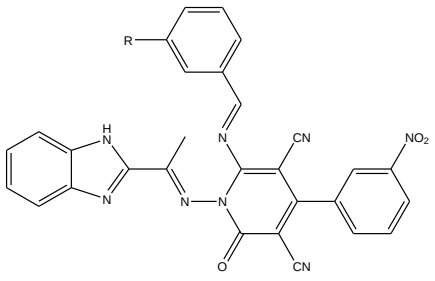


Figure No.-16

R= F/NO_2

Salahuddin, *et. al* [18] have synthesized 1,3,4-oxadiazoles bearing 1H-benzimidazole derivatives by condensation of ortho

phenylene diamine with phenoxyacetic acid, forming acid hydrazide and cyclising with phosphorus oxychloride to afford derivatives. These were screened for antibacterial activity against *S. aureus and E. coli* and antifungal activity against *A. flavus* and *C. albicans* by agar diffusion technique using ofloxacin and ketoconazole as reference drugs; respectively. Compound (Figure No.-17) was found to be most active as antibacterial and antifungal agents.

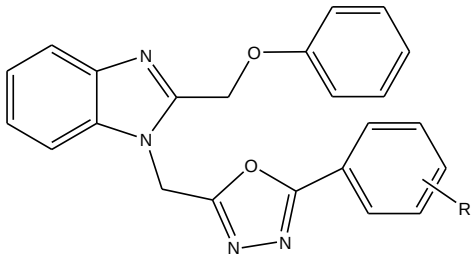


Figure No.-17

R= 4Cl/Br/CH_3/NO_2

Tuncbilek, M. *et. al* [19] synthesized various substituted derivatives of benzimidazole and screened them for antimicrobial activity against gram positive *S. aureus, methicillin resistant S. aureus* (MRSA, standard and clinical isolates), *Bacillus subtilis*, gram-negative *E. coli* and antifungal activity against *C. albicans* by tube dilution method. Compound (Figure No.-18) was found to possess better activity against both of the drug-resistant bacteria and fungi than standards ciprofloxacin, ampicillin and sultamicillin.

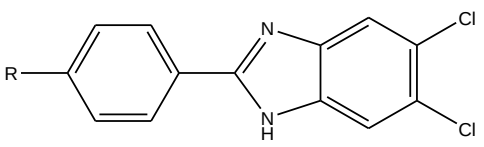


Figure No.-18

R=F/Cl/t-butyl

Antiviral Activity

2-phenylbenzimidazole derivatives were synthesized by Tonelli, M. *et. al* [20] and evaluated for cytotoxicity and antiviral activity against 10 types of RNA and DNA viruses in cell-based assay. Fifty-six of the tested compounds exhibited antiviral activity against one or more viruses, and thirty nine of them showed EC50 ≤ 10 μM against at least one virus. The 2-substituted anilinobenzimidazole derivatives were found to be more effective against more number of viruses. Compounds with nitro and chloro substitution exhibited lowest toxicity for the host cells. The very high cytotoxicity observed in some of these compounds may also warrant their evaluation as possible ant-proliferative agents.

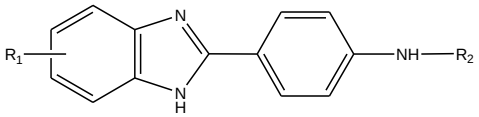


Figure No.-19

Cheng, J. *et. al* [20] have reported the synthesis of various substituted Pyridyl-1H-benzimidazole-4-carboxamide derivatives and were evaluated for their antiviral activity against Coxsackie virus B3 in VERO cells. They have tried H and hydroxyethyl group on amide nitrogen position but result in less active compound while compounds with aryl substitution on -N- (Figure No.-20) gives better antiviral activity. From SAR study they concluded that 2-pyridyl derivatives at 2-position are much better than 3- and 4-pyridyl derivatives.

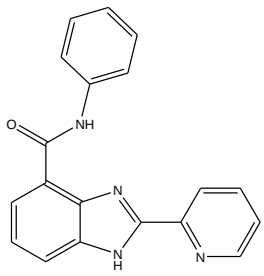


Figure No.-20

J.R. Hwu, *et. al* [21] derived synthesis of series of substituted benzimidazole–coumarin conjugates linked with methylenethio group (Figure No.-21) and evaluated against Hepatitis C virus in the Huh 5-2 replicon system. Some compounds possesses sugar moiety at N-1and 5-position inhibited HCV replication by means of a quantitative RT–PCR assay in three HCV replicon models.

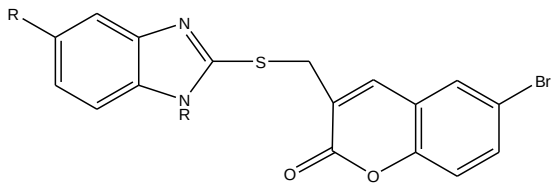


Figure No.-21

Various 2-substituted benzimidazole-N-carbamates were synthesized by L. Garuti, *et. al*[22]. All the compounds were tested in-vitro for the inhibition of Herpes Simplex Virus type 2 and Coxsackie virus B2 replication in VERO cells. Only two derivatives were found moderately active without cytotoxicity. They have concluded that presence of the carbamoyl moiety is not essential for antiviral activity and presence of the isopropyl carboxamide and methyl-thiomethyl group at position 2 of benzimidazole (Figure No.-22) are valuable.

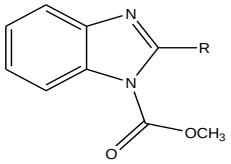
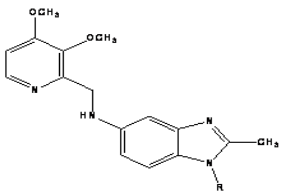


Figure No.-22

R= $CONHCH(CH_3)_3$ / CH_2SCH_3

Antiinflammatory and Analgesic Activity

El-Nezhawy A *et. al* [23] have demonstrated the synthesis of benzimidazole sugar conjugates carrying substituted pyrid-2-yl moiety from 2-methyl-N-(substituted-pyridin-2-ylmethyl)-1H-benzimidazol-5- amine and cyclic sulphate benzyl 2,3-O-isopropylidene- 5,6-O-sulfuryl-a-D-mannofuranoside and explored in vivo anti-inflammatory activity using carrageenan-induced paw oedema model in rats. Amongst all the synthesized compounds, they found that compound (Figure No.-23) containing N-sugar moiety only decreases the inflammation by 62% and 72%; respectively as compared to standard drug diclofenac (73%). Moreover these compounds act as ulcer inhibiting agents when tested in alcohol-induced gastric ulcer in mice and pylorus ligation-induced gastric ulcer in rats. They concluded in SAR that compound lacking sugar moiety exhibited mild anti-ulcer activity. Also, the compounds with moderate electron donating groups in the pyridine moiety were found to be much active as anti-inflammatory agents.



FigureNo.-23

R= sugar moiety / H

Gaba M *et. al* [24] have reported the synthesis of novel 5-substituted-1-(phenylsulfonyl)-2-methylbenzimidazole derivatives (Figure No.-24). These compounds were tested *invivo* for anti-inflammatory and analgesic activities by carrageenan-induced rat paw oedema model and acetic acid-induced writhing method in albino mice; respectively. It was found that anti-inflammatory and analgesic activity was comparable to that of standard drug indomethacin and aspirin; respectively. These compounds also have low ulcerogenic properties than indomethacin.

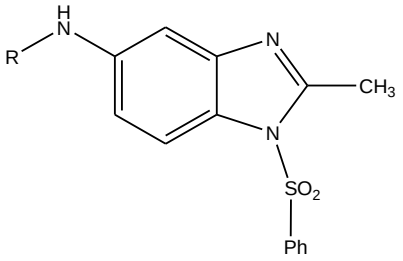


Figure No.-24

R= *o/p*-$NH_2C_6H_4$/ *p*-$NH_2C_7H_6$

Kankala S *et. al* [25] have designed the regioselective synthesis of 5-substituted 1-isoxazole mercaptobenzimidazole hybrids (Figure No.-25) as anti-inflammatory and analgesic agents. The analgesic activity of synthesized compounds was assessed by hot plate method with standard drug pentazocine while anti-inflammatory effect was tested by carrageenan-induced rat paw edema model using standard drug diclofenac. Compounds with 5-bromo substitution on benzimidazole showed potent anti-inflammatory and analgesic effect while that of nitro group exhibited moderate activity but higher than standard drugs diclofenac and pentazocine; respectively. SAR studies have demonstrated that compounds possessing electron withdrawing groups show higher activity than compounds with electron donating groups.

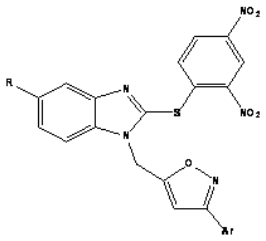


Figure No.-25

R= Br/NO_2
Ar= 4-F/CN-C_6H_4

Anandarajagopal K *et. al* [26] have reported the anti-inflammatory and antimicrobial activities of newly synthesized 2-mercaptobenzimidazole derivatives by carrageenan induced paw oedema method and cup plate method; respectively. These compounds were synthesized by reaction of various cyclic and noncyclic secondary amines and formaldehyde with 2-mercaptobenzimidazole. It has been seen that compounds containing noncyclic nitrogen in side chain (Figure No.-26) showed better anti-inflammatory effect (nearly 50% inhibition) as compared to standard drug diclofenac sodium (61.9% inhibition). All other compounds showed mild to moderate antibacterial and antifungal activities against standard drug amikacin and ketoconazole; respectively.

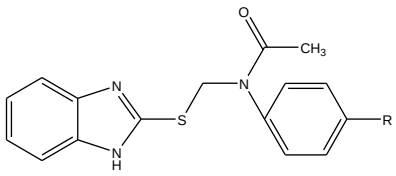


Figure No.-26

R= H/OH

Antialzeimer's Activity

Jain P *et. al* [27] have designed the synthesis of 6-O-linked series of benzimidazoles by molecular modelling on roscovitine which is a moderately selective CDK5/p25 inhibitor, used in the treatment of Alzheimer's disease. This disease is caused either by extra neuronal accumulation of β-amyloid (Aβ) or by intra neuronal deposition of neurofibrillary tangles (NFTs). The major component of these NFTs is the structural protein tau. It was found that CDK5 mediated tau hyperphosphorylation at Ser202 and/or Thr205.causes both NFT formation and the loss of cytoskeletal integrity that facilitates Aβ mediated apoptotic cell death. They replaced the amino substituted adenine core of roscovitine by 6-O-substituted (etheral) benzimidazole. Amongst all, compound (Figure No.-27) showed significant enzyme inhibition because of terminal hydroxyl group that possesses proper binding orientation for hydrogen bonding with Gln130 residue on CDK5.

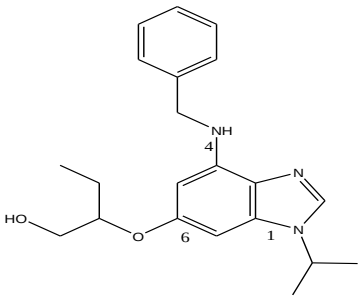


Figure No.-27

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Source of Support: Nil. Conflict of Interest: None declared

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