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Review Article

BENZIMIDAZOLES: THE LATEST INFORMATION ON BIOLOGICAL ACTIVITIES

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ABSTRACT

Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. Benzimidazole and its derivatives play an important role in medical field with large number of Pharmacological activities such as antimicrobial, antiviral, antidiabetic and anticancer activity. This review is summarized to know about the chemistry of different derivatives of benzimidazoles along with their biological actions such as antioxidant, antimicrobial, anthelmintic, analgesic, antiprotozoal, antiulcer, antiviral, anticancer, antihypertensive, antineoplastic, anti-inflammatory, antifungal and anticonvulsant activity.

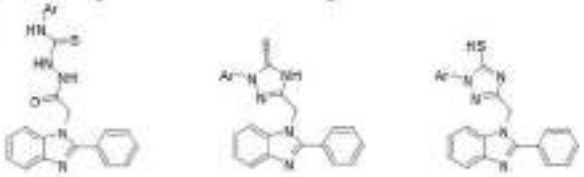
KEY WORDS: Benzimidazoles, Substituted benzimidazoles, Chemistry, Biological actions

INTRODUCTION

Benzimidazoles are an important group of heterocyclic compounds that are biologically active and of significant importance in medicinal chemistry. Benzimidazole is a bicyclic compound having imidazole ring, containing two Nitrogen atom at adjacent position fused to benzene ring. The benzimidazole ring is an important pharmacophore in modern drug discovery. A variety of benzimidazole is in use, like thiabendazole and flubendazole (anthelmintic), omeprazole and lansoprazole (antiulcerative) and astemizole (antihistaminic). In light of the affinity, they display towards a variety of enzymes and protein receptors, medicinal chemists would certainly classify them as privileged 'sub-structures' for drug dosing. The chemistry and pharmacology of benzimidazoles have been of great interest to medicinal chemistry because its derivatives possessed various biological activities such as antioxidant[1], antimicrobial[2], anthelmintic[3], anticancer[4], antihypertensive[5], antineoplastic, anti-inflammatory[6], analgesic[7], antiprotozoal[8], anti-hepatitis B virus[9], antiulcer [10], antiviral[11], antifungal[12] and anticonvulsant[13] activity. Almost all benzimidazole derivatives with their two ring systems bear different functional substituents and this leads to essential modification of the physico-chemical, metabolic and pharmacokinetic properties of these drugs. In the past few decades, benzimidazole and its derivatives have received much attention due to their chemotherapeutic values.

Antioxidant Activity

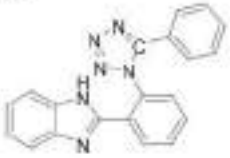
Oxygen-derived free radicals such as the superoxide (O_2•-), nitric oxide (NO•), hydroxyl (OH•) and peroxyl (RO_2 •) radicals play an important role in human diseases including atherosclerosis, rheumatoid arthritis and carcinogenesis.[14] Peroxyl radicals are formed during lipid oxidation chain reactions. Any species which is capable of abstracting a hydrogen atom from polyunsaturated fatty acid side chain in lipids present in cell membrane.[15] Antioxidant defense system is activated in the body due to the attack of free radical, Scavenging specific species which including enzymatic systems (superoxide dismutase, catalase) and both aqueous (glutathione-GSH and ascorbate) and nonaqueous scavengers (vitamin E). This is the imbalance between the antioxidant protection and free radical production that may lead to various diseases including autoimmune disease.[16] The drugs which have antioxidant and free radical scavenging properties are considered to be used for the prevention or treatment of diseases that are directly related to the lack of an antioxidant capacity of the organisms. Synthesis of some Indole and benzimidazole derivatives and check their activity to prevent myocardial damage in rats.[17] Incorporation of thiadiazoles, triazoles as well as their open-chain counterparts thiosemicarbazides in the 1st position of a benzimidazole ring yield more potent antioxidant compounds.[18]



Benzimidazole dihydrochlorides, also possess antioxidant activity, these salts also possess mild platelet and erythrocyte antiaggregant activity.[19] Presence of trimethyl group with benzimidazole also adds antioxidative property by 5-lipoxygenase inhibitory action. [20]

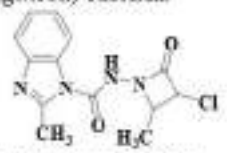
Antimicrobial and Antibacterial Activity

Benzimidazole shows their antibacterial activity by inhibiting the bacterial nucleic acid and proteins synthesis. This ability of benzimidazole is due to their structural similarities with the purine. [21-22] 2-substituted benzimidazole derivatives are found to be pharmacologically more potent and hence the design and synthesis of 2-substituted benzimidazoles are the potential area of research.[23-25] 2-{2-(5-phenyl-1*H*-tetrazol-1-yl)phenyl}-1*H*-benzo[d]imidazole were synthesized and their antimicrobial activity ware tested against Gram positive *Staphylococcus aureus* and Gram negative *Escherichia coli* The effect produced by the sample was compared with the effect produced by the positive control (Reference standard Ciprofloxacin 5 Gg/disc) . The result indicated that compound were more active against the microorganisms with reference to standard.[26]



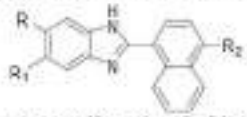
Schiff base of 2-Phenyl benzimidazole derivatives were synthesized and these compounds show some good antibacterial activity. The basic N=C group believed to

enhance antimicrobial activity. Therefore they may be used as lead compounds for further development.[27] Benzimidazole containing azetidine-2-one moiety are also synthesized and they show antimicrobial activity against gram positive (*S. aureus, S. mutans* and *B. subtilis*) and gram negative (*E. coli, S. typhi* and *P. aeruginosa*) bacteria.[28]

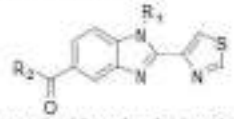


Antimicrobial and Antiviral Activity

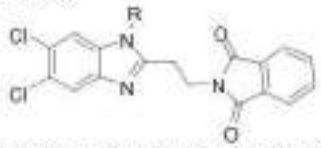
Recent study has indicated that some benzimidazole derivatives could exhibit potent anti-HBV activity with very low cytotoxicity. Benzimidazole may be considered a 1, 3-dideazapurine and may replace this base in the formation of nucleosides in viral replication and show their inhibitory activity. Therefore, A series of 2-arylbenzimidazole derivatives were synthesized which show inhibitory activity against *Flevivirus, Pestivirus, Reteroviridae, Piconiviridae, Reoviridae, Herpesveridae* and *Foxviridae*.[29]



A library of two structurally related thiazolylbenzimidazole derivatives was designed and prepared. All the synthesized compounds were evaluated for their anti-HBV activity and cytotoxity on HepG 2.2.15 cells, with the antiviral drug lamivudine as reference control. [30]



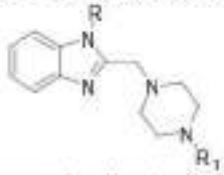
A series of novel benzimidazole derivatives was synthesized and evaluated for their anti-hepatitis B virus (HBV) activity and cytotoxicity *in vitro*. Strong activity against HBV replication and low cytotoxicity were generally observed in these benzimidazoles. The most promising compounds show high antiviral potency (IC50 = 0.9 and 0.7 μM, respectively) and remarkable selectivity indices (>1111 and 714, respectively). They were selected for further evaluation as novel HBV inhibitors.[31]



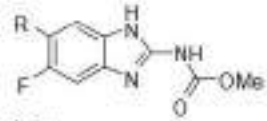
A research also indicate that *N*-substituted and 2-Substituted Benzimidazoles have activity against *Tobacco Mosaic virus*.[32]

Antimicrobial and Antifungal Activity

The antifungal activity of benzimidazoles is due to its close relationship with structure of purines. The purines is one of the essential component of biological system and it was discovered that 5,6-dimethyl-1-(α-D-ribofuranosyl) benzimidazole is an integral part of structure of Vit.B_{12} [33] A fungal selective 14α-demethylase inhibitor is expected to act as an antifungal agent. Considersble effort has been made for the design of fungal – selective 14α-demethylase inhibitors and this has resulted in useful, orally active antifungal agents which are effective against both topical and systemic fungal infections. [34] Various Benzimidazole derivatives were prepared by condensing the benzimidazole and substituted piperazinyl group. The antifungal activity of synthesized compounds was determined against *Candida albicans* using Ketoconazole as reference standard. The compound showed comparable antifungal activity to Ketoconazole.[35]

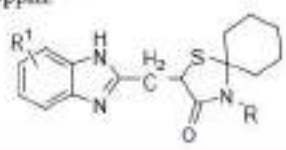


Microtubules are present in all eukaryotic cells and are very important because of their role in cell mitosis. Benzimidazole derivatives have a broad spectrum antifungal activity and show their antifungal activities by blocking the polymerization of α-and β-tubulin subunit. Antitubulin agents, especially benzimidazoles, disrupt microtubule function in eukaryotic organisms such as fungi, protozoa and helminths.[36-37] Benzimidazole carbamates are useful for the treatment of *Giardia lamblia, Cryptococcus neoformans, Trichomonas vaginalis, Pneumocystis carinii* and *Encephalitozoon intestinalis*. Therefore some new methyl benzimidazole carbamate derivatives having 5(6)-fluoro-6(5)-substituted heterocyclic rings have been synthesize and their antifungal activities were investigated against *C. albicans*.[38]



Anthelmintic Activity

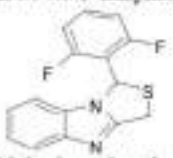
Benzimidazole nucleus possesses anthelmintic activity. A series of 2-(trifluoromethyl)-1*H*- Benzimidazole derivatives were prepared using Phillips cyclocondensation of substituted 1,2-phenylenediamine and trifluoroacetic acid. The synthesized compounds were screened *in vitro* against various protozoan parasites, *Giardia intestinalis, Entamoeba histolytica, Trichomonas vaginalis* and *Leishmania mexicana*, and they showed nanomolar activities against some of the above mentioned protozoa. The compounds were also tested *in vitro* and *in vivo* against the nematode *Trichinella spiralis*. [38] In another study two series of benzimidazole derivatives were synthesized. The first series was based on 5,6-dinitrobenzimidazole and the second series comprises 2-thicalkyl- and thioaryl-substituted benzimidazoles. Antiprotozoal activity of the newly synthesized compounds was studied. Some thioalkyl derivatives showed remarkable activity against nosocomial strains of *Stenotrophomonas malthophilia*, and an activity comparable to that of metronidazole against Gram-positive and Gram-negative bacteria. 5,6-dichloro-2-(4-nitrobenzylthio)benzimidazole showed the most distinct antiprotozoal activity.[39] Some new compounds were prepared by incorporationg two biologically active pharmacophore, thiazolidinone and benzimidazole to form a single molecule. The synthesized compounds were evaluated for nematicidal activity by aq. *In vitro* screening techniques at various concentrations on *Ditylenchus myceliophagus* and *Caenorhabditis elegans*. The results have been expressed in terms of LD_{50}. Two compounds showed promising nematicidal activity on both species with LD_{50} value of 220ppm and 260ppm. [40]



Substituted 2-trifluorobenzimidazoles also reported anthelmintic activity. [41]

HIV-Inhibitors

The development of new non nucleoside inhibitors of HIV-1 type-1 reverse transcriptase (RT) active against the drug-induced mutations in RT continues to be a very important goal of AIDS research. The lead structure 1-(2,6-difluorophenyl)-1*H*,3*H*-thiazolo[3,4-a]benzimidazole (TZB) is a known inhibitor of HIV-1 RT was used for drug design with the objective of making more potent inhibitors against both wild-type (WT) and variant RTs. A series of structurally related 1,2-substituted benzimidazoles was synthesized and evaluated for their ability to inhibit *in vitro* polymerization by HIV-1 Wild Type RT. A structure activity relationship study was carried out for the series of compounds to determine the optimum groups for substitution of the benzimidazole ring at the N1 and C2 positions. The best inhibitor, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-methylbenzimidazole (MB), has an IC_{50} = 200 nM against HIV-1 Wild Type in an *in vitro* enzyme assay. [42]



In another study which is related in the field of non nucleoside RT inhibitors (NNRTIs), structure activity relationship (SAR) study and molecular modeling of 1*H*,3*H*-thiazolo[3,4-a]benzimidazole derivatives (TBZs) leads to the design and synthesis of a series of 2,3-diaryl-1,3-thiazolidin-4-ones. Some derivatives proved to be highly effective in inhibiting human immunodeficiency virus type-1 (HIV-1) replication at nanomolar concentrations with minimal toxicity, acting as reverse transcriptase (RT) inhibitors. Computational studies were used in order to probe the binding of our ligands to HIV-1-RT. [43]

Several benzofuran derivatives containing heterocyclic ring substituents show potential anti-HIV-1 activity. Further investigation lead to the formation of several new benzofuran derivatives derived from 2-acetylbenzofuran and 2-bromoacetylbenzofuran. Various related benzimidazoles derived from 2-acetylbenzimidazole and from 2-cyanomethylbenzimidazole were also prepared as isosteres. The synthesized compounds were preliminarily evaluated for their *in vitro* anti-HIV-1and they show weak anti-HIV-1 activity.[44] Tetrahydro-imidazo[4,5,ljk][1,4]-benzodiazepin-2 (1*H*)-one (TIBO) is a noncompetitive non nucleotide antiretroviral drug with a specific allosteric binding site of HIV-1 RT. TIBO derivatives have proved to be potent, highly selective and specific inhibitors of HIV-1 replication *in vitro*.[45]

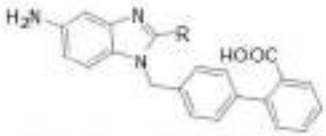
Anticancer Activity

Benzimidazole chalcones, benzimidazole mercaptoacetohydrazide and benzimidazole thiosemicarbazide derivatives were synthesized and show potency against PC12 (pheochromocytoma of the rat adrenal medulla) cells. Benzimidazole-2-isoxazole derivative also exhibited high potency against HEPG2 (human liver carcinoma cell line) and PC12 cells. [4]

A Series of new nitrobenzimidazoles were synthesized and they possess cytotoxic activity against breast cancer. In this reported research it was also found out that the compounds like thiadiazole, tetrazole, triazines and imidazoles also possess the activity. [46] 2-substituted benzimidazoles: 2-[(4-oxothiazolidin-2-ylidene) methyl and (4-amino-2-thioxothiazol-5-yl) benzimidazoles, 2-[(4-fluorobenzylidene and cycloalkylidene) cyanomethyl] benzimidazoles derivative synthesized and products were subjected to *in vitro* anticancer screening that revealed that all the tested compounds exhibited antitumor activity against human hepatocellular carcinoma (HEPG2), human breast adenocarcinoma (MCF7) and human colon carcinoma (HCT 116) cell lines, with IC50's<10 microg/ml.[47] Some bis(benzimidazoles), bis(benzoxazoles), benzothiazoles, and their derivatives were synthesized and all the compounds subjected to *in vitro* antitumor activities against A-549, BFTC-905, RD, MES-SA, and HeLa cell lines. The synthesized compound show good anticancer activity. [48]

Anti Hypertensive Agents

5-substituted (amino)-2-phenyl-1-(2'-carboxy biphenyl-4-yl) benzimidazoles differ from the previously reported antihypertensive agents and related compounds because they produce potent hypertensive effect upon oral administration. It is a type of non peptide angiotensin (A-II) receptor antagonist.[49] 2-position of biphenyl is essential for the activity. [50] Only ortho substituted acid possess both high affinity for the AII receptor and oral anti-hypertensive potency. [49]

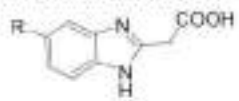


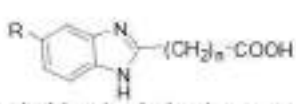
Benzimidazole derivatives (2-{6-Chloro-5-nitro-1-[2-(1*H*-tetrazol-5-yl) biphenyl-4-ylmethyl] 1H-benzoimidazol-2-yl}-phenyl)-(Substituted benzylidene) amine was synthesized and screened for their antihypertensive activity. All the synthesized compounds showed significant antihypertensive activity.[51] 5- substituted aryl or alkyl caboxamido derivatives were synthesized and they report to possess Angiotensin-II AT1 receptor antagonistic activity.[52]

Anti-Inflammatory Activity

Presence of carboxylic acid moiety at 2-position of the benzimidazole ring fulfills the minimum structural requirements that are commonly present in the marketed anti-inflammatory drugs.

Therefore benzimidazole-2-carboxylic acid derivatives were synthesized and tested for acute anti-inflammatory activity against carrageenan induced rat paw edema model. The tested compounds were found to be safe upto 2000 mg/kg, p.o. doses and exhibited good anti-inflammatory activity at 100 mg/kg p.o. and higher doses. Their activity largely depends on substituents at position 5 and chain length at position 2 of benzimidazole moiety. With 1-benzyl substitution, activity was found to increase. [53]

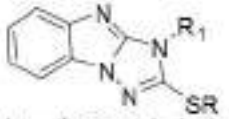




A series of 2-methylaminobenzimidazole derivatives were synthesized by the reaction of 2-(chloromethyl)-1H-benzimidazole derivatives with primary aromatic amines. The newly synthesized compounds showed potent anti-inflammatory activities compared with standard drug Nimesulide respectively. [54] 1-(N-Substituted amino) methyl-2-ethyl benzimidazole derivatives were synthesized by the reaction between 2-ethylbenzimidazole and substituted primary and secondary amines. All the synthesized compounds were screened for anti-inflammatory activity against carrageenan induced paw oedema in rats. The entire compound show good anti-inflammatory. [55]

Analgesic Activity

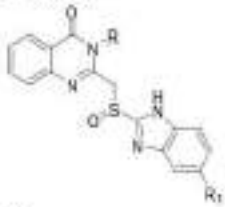
1-acyl-2-alkylthio-1,2,4-triazolo[2,3-a]-benzimidazole were synthesized, most of these compounds showed potent analgesic effect compared to indomethacin. [56]



The analgesic activity of 1,2,5-trisubstituted benzimidazole derivatives have been investigated by using the modified Koster test. Among the Synthesized compounds, (1-diethylaminomethyl)-2-(p-chlorophenyl)-5-nitro benzimidazole hydrochloride) has shown higher activity than acetylsalicylic acid (ASA) and indometacin.[57] A series of *N*-(acridin-9-yl)-4-(benzo[d]imidazol/oxazol-2-yl) benzamides has been synthesized by the condensation of 9-aminoacridine derivatives with benzimidazole or benzoxazole derivatives. Schiff's bases are prepared by the condensation of 2-hydroxy naphthaldehyde with functionalized diamines. Synthesized compounds showed good analgesic activity.[58]

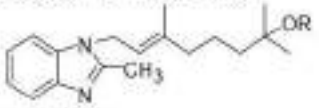
Antiulcer Activity

Benzimidazole sulfinyl methyl pyridine is a well established class of H^+/K^+ATPase inhibitors, useful in the treatment of acute and chronic ulcer conditions.[59] Insertion of pyrimidine ring instead of pyridine in the benzimidazole sulfinyl methyl pyridine moiety, resulted in an increase in antiulcer activity.[60] Substituted benzimidazoles are potent inhibitors of Parietal cell proton pump, the H+/K+ ATPase, and are capable of blocking gastric acid secretion in response to some stimuli. For the activity sulfoxide group, methylene group with hetercycles is important for activity.[61] A new series of 2-[5-substituted-1*H*-benzo(d)imidazol-2-yl sulfinyl] methyl-3-substituted quinazoline-4-(3*H*)-one derivatives were synthesized and tested for antiulcer activity against pylorus ligation-induced, aspirin induced and ethanol induced ulcer in rat model. Some compounds showed higher activity than omeprazole used as standard. [62]



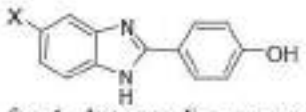
Insecticidal Activity

Most of the insect growths regulators (IGRs) with juvenile hormone (JH) activity have been reported and are derived from monoterpenes and sesquiterpenes. [63] On the other hand, several imidazole compounds have been shown to inhibit the epoxidation of methyl farnesoate to JH III in vitro.[64] These facts leads to synthesis of 1-(3,7-dimethyl-7-methoxy-2-octenyl)-2-methylbenzimidazole and the 7-ethoxy analog , having a structural resemblance to JH mimics, had high insecticidal activity against the housefly. [65]



DNA Inhibitory Activity

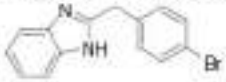
Several benzimidazole derivatives are active as inhibitors of type I DNA topoisomerases (topo I).[66] Three 1*H*-benzimidazole derivatives with different electronic characteristics at position 5-, namely 5-chloro-4-(1*H*-benzimidazole-2-yl)phenol, 5-methyl-4-(1*H*-benzimidazole-2-yl)phenol and 4-(1*H*-benzimidazole-2-yl)phenol , were synthesized and evaluated for their effects on mammalian type I DNA topoisomerase activity using quantitative *in vitro* plasmid supercoil relaxation assays. Compound 5-methyl-4-(1*H*-benzimidazole-2-yl)phenol showed potent topoisomerase I inhibition. [67]



Some novel fused heterocyclic compounds of 2,5-disubstituted-benzoxazole and benzimidazole derivatives were investigated for their inhibitory activity on both eukaryotic DNA topoisomerase I and II in a cell free system. Some of the synthesized compounds were found to be more potent as eukaryotic DNA topoisomerase I poisons than the reference drug camptothecin. [68]

Androgen Receptor Antagonist Activity

Oxobenzimidazoles, is a novel series of androgen receptor antagonists, were discovered through de novo design guided by structure-based drug design.[69] N-benzyl, N-aceto, and N-ethylene ether derivatives of 2-(2,2,2-trifluoroethyl)-5,6-dichlorobenzimidazole as novel androgen receptor antagonists were synthesized. SAR studies led to the discovery of 4-bromo-benzyl benzimidazole as a potent androgen receptor antagonist in the rat prostate. [70]



Antiallergic Activity

1-[2-{2-(4-hydroxy-2,3,5-trimethylphenoxy)ethoxy}ethyl]-2-(4-methyl-1-homo piperazino) benzimidazole were synthesized and they potently suppressed histamine release from rat peritoneal mast cells triggered by the antigen-antibody reaction.[71] In another study1-[2-{2-(4-Hydroxy-2,3,5-trimethylphenoxy) ethoxy} ethyl]-2-(4-methyl-1-homopiperazino)-1*H*-benzimidazole difumarate show antiallergic pharmacological activities when it is hybridized with trimethylhydroquinone derivatives. [72]

Antidiabetic Activity

4-thiazolidinones and 1,3,4-oxadiazoles containing 2-mercapto benzimidazole moiety were synthesized and screened for antidiabetic activity using Oral Glucose Tolerance Test (OGTT). Some of the synthesize compounds showed excellent antidiabetic activities. [73]

Anticonvulsant Activity

A series of new 2-[(1-substituted phenylethylidine) hydrazine]-*N*-phenyl-1*H*-benzo[*d*]imidazole-1-carbothioamides were designed and synthesized. All the newly synthesized compounds were screened for anticonvulsant activity using two most adopted models, maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ). Some compounds showed potent anticonvulsant activity and in the neurotoxicity screening, most of the compounds were devoid of toxicity at the dose of 60 and 100 mg/kg.[74]

Antiproliferative Activity

Benzimidazole retinoids have the property to suppress cell growth in a dose dependent manner. These novel Benzimidazole retinoids showing significant amount of antiproliferative effects on HL-60 may be used as potential anticancer agents.[75] A new series of substituted 2-diphenylbenzimidazoles were synthesized which have antiproliferative activity.[76]

Antitubercular Activity

Alkyl sulphonyl benzimidazole derivative were prepared and evaluated for antitubercular activity by Serial dilution method and Disc Diffusion Method using Middlebrook 7H9 medium (broth and agar based) and ATCC 25177 strains. Most of them reported good antitubercular activity.[17] N'-substituted-2-(5-nitrofuran or 5-nitrothiophen-2-yl)-3*H*-benzo[d]imidazole-5-carbohydrazide derivatives were synthesized and selected compounds showed better antitubercular activity compared to rifampin against multidrug-resistant MDR-MTB strains.[18]

CONCLUSION

Benzimidazole is an important heterocyclic moiety for the discovery of new drugs. This has been noticed so far, that modifications on benzimidazole moiety displayed valuable biological activities. It will be interesting to observe that these modifications can be utilized as potent therapeutic agents in future. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. Since now, researchers have been attracted toward designing more potent Benzimidazole derivatives having wide diverse of biological activity

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