

## Synthesis and biological activity of benzimidazoles: Review

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### ABSTRACT

Benzimidazoles and their derivatives play very important role in the medical field with useful therapeutic activities like antiviral, anti-histaminic, anticancer, antiulcer, antihypertensive, antidiabetic, antifungal, and antimicrobial activity. The most prominent benzimidazole compound in nature is *N*-riboyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B12. The potency of these useful derivatives in treatment of microbial infections encouraged the development of some more potent and pharmacologically efficient compounds. This review summarizes the synthesis of different derivatives of benzimidazole and their biological activities.

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### Introduction

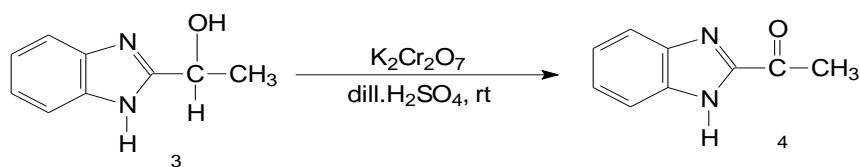
Benzimidazole is a heterocyclic aromatic organic compound it is bicyclic in nature which is formed by the fusion of benzene and imidazole [1]. Nowadays it is the moiety of choice which possesses many pharmacological properties and has been incorporated into pharmaceutical agents to form enzyme inhibitors, and DNA intercalators. Benzimidazoles are very useful intermediates/subunits for the development of molecules of pharmaceutical and biological interest. Substituted benzimidazole derivatives have found applications in diverse therapeutic areas including antiulcer, antihypertensive, antifungal, anticancer, and antihistaminic [1]. Some benzimidazole derivatives show diverse biological activities with significant clinical potential, including the treatment of leukemia and cancer. Benzimidazoles display a broad spectrum of pharmacological activities and are present in a number of pharmacologically active molecules such as Albendazole/ Mebendazole/ Thiabendazole (antihelminthic), Omeprazole (anti-ulcer). These compounds carrying different substituents in the benzimidazole structure are associated with a wide range of biological activities. Changes in their structure have offered a high degree of diversity that has proven useful for the development of new therapeutic agents having improved potency and lesser toxicity [2]. The most prominent benzimidazole compound in nature is *N*-riboyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B<sub>12</sub> [1, 3, 4]. Benzimidazole derivatives were synthesized by derivatization at *N*-H moiety of benzimidazole by electron donating groups and substitution with long chains of propyl, acetamido, thio, thiazole-amino, tetramethyl piperidine on pyridine resulting in good antiulcer activity [5].

### Synthesis of benzimidazoles

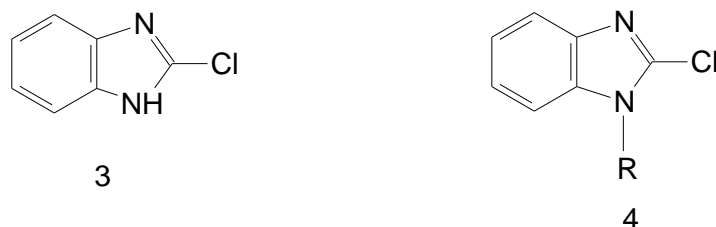
Different synthetic approaches for the building of benzimidazole ring are reported in the literature [6-14]. Anhydrous ZnCl<sub>2</sub> was used to be a catalyst for the synthesis of 2-arylsubstituted benzimidazoles efficiently. In this method a very simple procedure, easy purification and shorter reaction time. So many of benzimidazole derivatives were prepared via this method [15]. A highly efficient, simple and rapid method for the preparation of various 2-aminobenzoxazoles and other benzoxazole derivatives using a catalytic amount of poly (ethyleneglycol)-bound sulfonic acid (PEG-SO<sub>3</sub>H) is described. PEG-SO<sub>3</sub>H is found to be an economical and reusable catalyst with low catalytic loading. The percent yield was found to be satisfactory, experimental set up and purification of final products are facile and easy [16]. Benzimidazoles derivatives have been synthesized using a catalytic amount of Zinc acetate at room temperature by using mortar and pestle with excellent yields. The remarkable selectivity under mild, neutral and solvent free conditions, commercially available inexpensive catalyst is an attractive feature of this method [17]. Silica boron sulfonic acid (SBSA) was easily prepared and used as a new and efficient solid acid catalyst for the synthesis of benzimidazole derivatives with high isolated yields. Various substituted benzimidazoles were synthesized by condensation of *o*-phenylenediamines and aldehydes in the presence of boron sulfonic acid in good yields in water and under a mild reaction conditions. This method is also applicable for the condensation of aromatic and unsaturated aldehydes and *o*-phenylenediamines [18]. A series of 2-substituted benzimidazole derivatives have been synthesized via microwavemediated process [19].

A series of substituted benzimidazoles and benzothiazoles were prepared through the one-pot reaction of *o*-phenylenediamine and *o*-aminothiophenol with various aldehydes in the presence of ferric hydrogensulfate both in EtOH and water as solvent. The reactions proceed smoothly in excellent yield, high chemoselectivity and with an easy work-up [20].

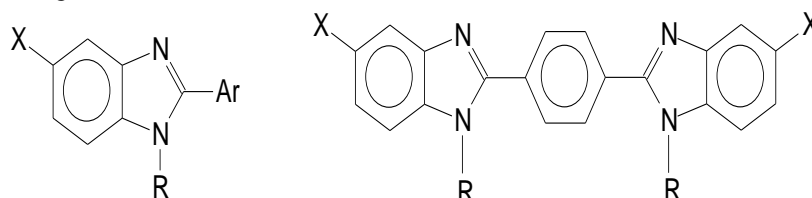
*o*-Phenylenediamine was condensed with lactic acid under Philips conditions to obtain the previously known 2-( $\alpha$ -hydroxyethyl)benzimidazole (3). Oxidation of 3 with K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> in dil. H<sub>2</sub>SO<sub>4</sub> using the literature method gave the previously reported 2-acetylbenzimidazole (4). [21-23].



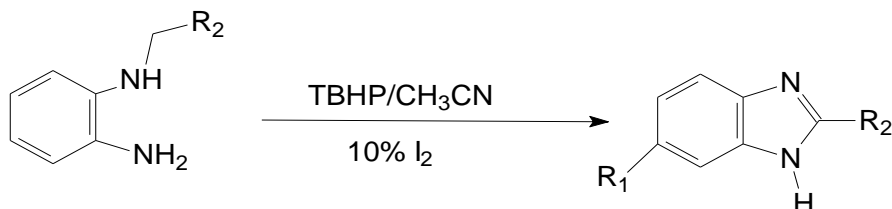
Synthesis of various benzimidazole derivatives under micro-wave irradiation from simple and substituted ortho phenylenediamines (OPDA) and isonicotinic acid using  $\text{SiO}_2/\text{H}_2\text{SO}_4$  as catalyst is described [24]. 2,2'-(Alkanediyl)-bis-1H-benzimidazoles (simple and mixed) with variable methylene spacers were synthesized in excellent yields with aqueous fluoroboric acid (45%) (0.1 ml) as catalyst under solvent-free conditions. [25]. A green procedure by using benzaldehyde and o-phenylenediamine as the model substrate, heteropolysaccharide pectin as a catalyst and water as a solvent. The generality and scope of this protocol was determined by synthesizing various derivatives of benzimidazole in good to excellent yield through this environmental friendly, time and energy saving, green method [26]. A facile and green synthesis of N-substituted-2-chlorobenzimidazoles (4) under different conditions has been developed [27]. In this method, 2-chlorobenzimidazole (3) was treated with an alkylating agent such as DMS/DES/ $\text{PhCH}_2\text{Cl}$  under green conditions i.e., by physical grinding in the presence of  $\text{K}_2\text{CO}_3$  at RT or by heating in PEG-600 as green solvent at 100°C or by irradiation with micro-wave at RT to obtain N-alkyl-2-chlorobenzimidazoles (4).



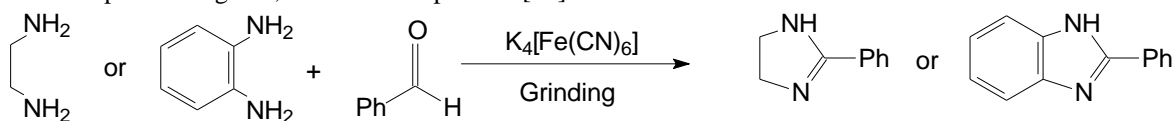
N-arylation of N-heteroaryls is described with aryl/ heteroaryl halides in the presence of CuI in ionic liquid  $[\text{Bmim}]\text{BF}_4$  as a reaction media. The reaction is very efficient and yields are very high. Moreover, the method is applicable for a variety of N-heteroaryls and Ionic liquid was recycled and reused [28]. A new convenient method for preparation of 2-substituted benzimidazoles and bis-benzimidazoles is presented. In this method, o-phenylenediamines were condensed with bisulfite adducts of various aldehydes and di-aldehydes under neat conditions by microwave heating. The results were also compared with results of synthesis by conventional methods. Short reaction times, good yields, easy purification of products, and mild reaction conditions are the main advantages of this method [29].



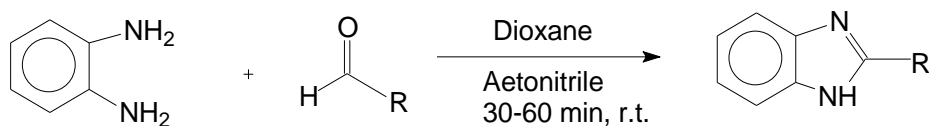
A facile and novel approach to the synthesis of 2-substituted benzimidazole was developed via a tandem reaction following  $\text{sp}^3$  C-H functionalization. A simple, efficient and tandem oxidative dehydrative coupling reaction of N-benzylbenzene-1,2-diamine in the presence of oxidant tert-butyl hydroperoxide (TBHP) in solvent acetonitrile to give substituted benzimidazole was reported [30].



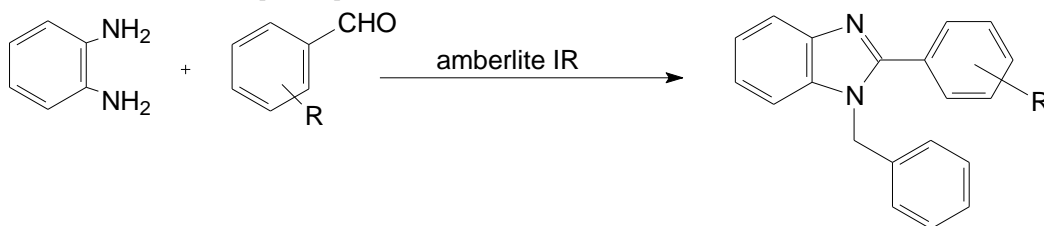
Different synthetic approaches for the building of benzimidazole ring are reported in the literature. Imidazolines and Benzimidazoles have been efficiently synthesized in high yields by treatment of 1,2-diamine with aldehydes using the metal coordinate complex  $\text{K}_4[\text{Fe}(\text{CN})_6]$  as a catalysis. The method was carried out under solvent free condition via oxidation of carbon-nitrogen bond. The process is green, mild and inexpensive [31].



One more approach wherein carboxylic acids and/or acid anhydrides were condensed with o-phenylenediamine in the presence of acid catalysts [32-33]. A new convenient and facile method for the synthesis of benzimidazole through the oxidative cyclization of o-phenylenediamine and different aldehydes using dioxane dibromide was reported [34].

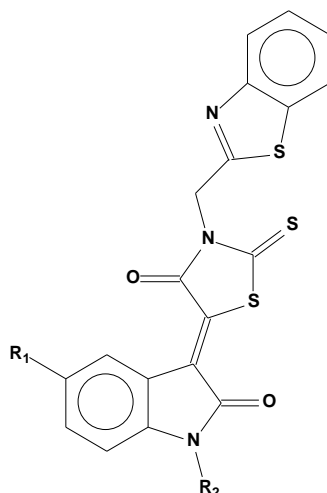


A highly selective synthesis of 2-aryl-1-arylmethyl-1H-1,3-benzimidazoles from the reaction of *o*-phenylenediamines and aromatic aldehydes in the presence of silica sulfuric acid is reported. The reactions were performed in ethanol or water and the catalyst could be reused for several runs[35, 36].

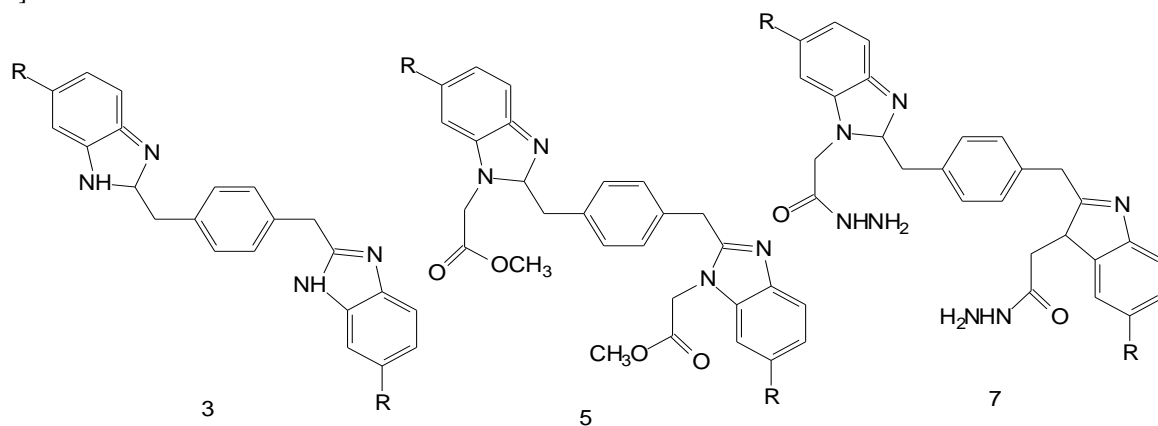


One-pot synthesis of benzimidazoles has been carried out using ortho-phenylenediamine and aldehydes. The condensation reaction smoothly took place in the presence of a mild Lewis acid cadmium chloride. All the reactions were carried out in acetonitrile at 80°C to 85°C[37].

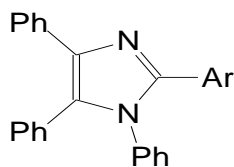
A facile one-pot synthesis of novel oxindole derivatives bearing benzothiazolymethyl-2-thioxothiazolidin-4-one was accomplished via one-pot reaction of 5-oxindolinylidene rhodanine-3-acetic acid derivatives, 2-aminothiophenol, and triphenyl phosphite in the presence of tetrabutylammonium bromide (TBAB) and nano silica-bonded 5-*n*-propyloctahydro-pyrimido[1,2-*a*]azepinium chloride (NSB-DBU) as heterogeneous reusable nanocatalyst. The target compounds were obtained in excellent yields (85 - 92%) and short reaction times under fairly mild reaction conditions [38].



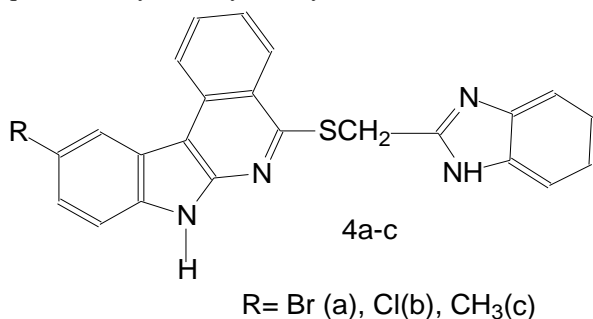
2,2'-[1,4 (1,3)-Phenylenedi(methylene)]bis-1H-benzimidazole derivatives were obtained from the reaction of 1,4- or (1,3)-bisiminoester hydrochloride and *o*-phenylenediamine derivatives under microwave irradiation. Ester and hydrazide derivatives were prepared from a free NH group. This practical method revealed good results for yield, reaction time, and quick isolation of products[39].



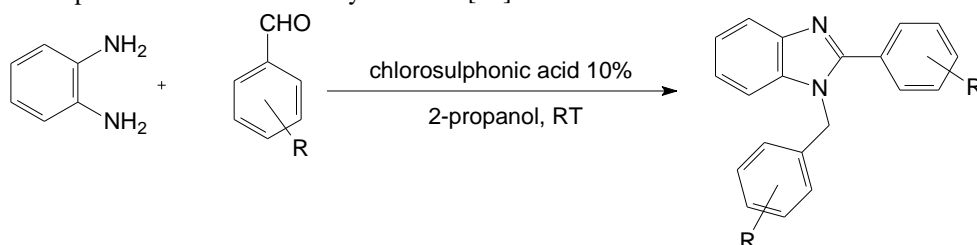
An efficient four-component synthesis of 1,2,4,5-tetrasubstituted imidazoles is described by one-step condensation of an aldehyde, benzil, ammonium acetate and primary aromatic amine with nanocrystalline magnesium aluminate in ethanol under ultrasonic irradiation. High yields, short reaction times, mild conditions, simplicity of operation and easy work-up are some advantages of this protocol[40].



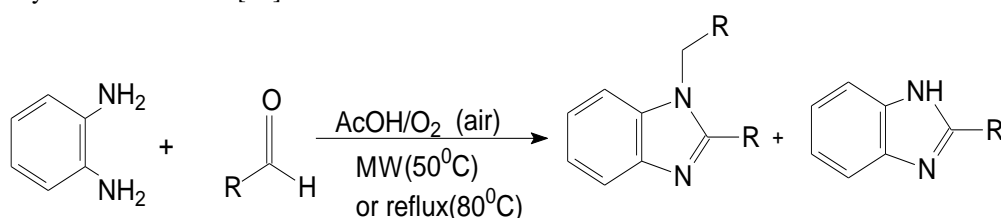
Indole-2-carboxylates are refluxed with hydrazine hydrate to form 5-substituted-3-phenylindole-2-carboxyhydrazides. These are again converted to corresponding indole-2-carboxyazides. Azides are further converted into carbamates and finally these carbamates are cyclized to form the respective substituted 6H, 11H-indolo [3,2-C] isoquinolin-2-ones (1a–c). These (1a–c) were reacted with phosphorus pentasulfide in refluxing pyridine to yield the respective thiones (2a–c). These thiones (2a–c) on reaction with chloroacetic acid and sodium acetate in acetic acid under refluxing temperature for 5 h yielded isoquinoline-thioacetic acids (3a–c). Compounds (3a–c) on reaction with orthophenylene diamine dihydrochloride in ethylene glycol at refluxing temperature yielded substituted indolo [3,2-C] isoquinolin-20-yl sulfanyl methylene benzimidazoles (4a–c)[41].



Chlorosulfonic acid (ClSO<sub>3</sub>H) used to be a catalyst for the synthesis of 2-aryl-1-arylmethyl-1H-benzimidazoles which was efficiently simple and convenient. This method afforded short reaction time, easy workup, moderate to excellent isolated yields which make this protocol practical and economically attractive[42].



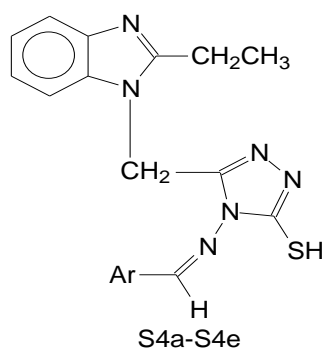
An efficient and simple procedure was developed for the green synthesis of various 2-aryl-1-(arylmethyl)-1H-benzimidazoles in high yields by acetic acid-promoted condensation of *o*-phenylenediamine with aldehydes in air under microwave irradiation and transition metal catalyst-free conditions [43].



### Biological activity of benzimidazoles

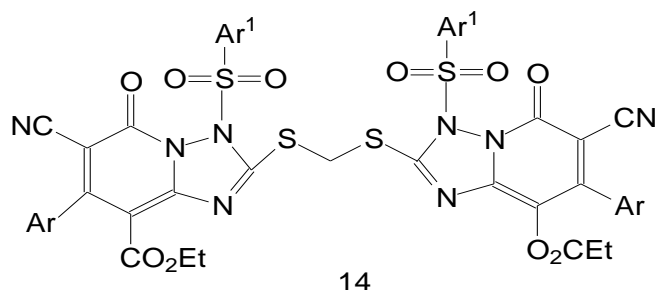
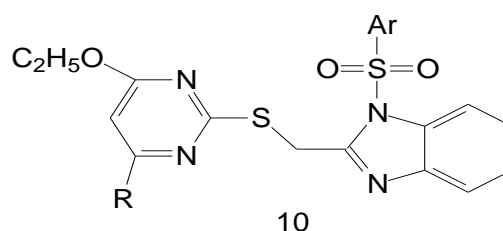
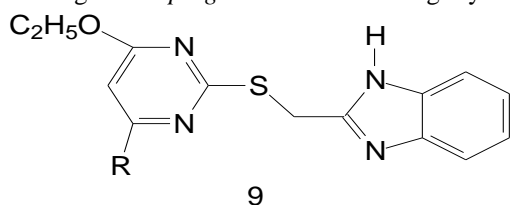
Benzimidazole derivatives play important role in medical field with many pharmacological activities such as antimicrobial, antiviral, antidiabetic and anticancer activity. The potency of these clinically useful drugs in the treatment of microbial infections and other activities encouraged the development of some more potent and significant compounds. Benzimidazoles are remarkably effective compounds against various strains of microorganisms.

A variety of 2-ethyl-5-nitro benzimidazole derivatives were synthesized from carbohydrazide [2-(2-ethyl-5-nitro benzimidazole)-1-acetohydrazide] by using ethanol, carbon disulphide, potassium hydroxide, hydrazine hydrate and different aromatic aldehydes. The synthesized compounds were screened for *in-vitro* anti-microbial activity against a variety of bacterial strains such as *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa* including fungal strains such as *Candida albicans* and *Aspergillus niger*. The compound S2, S3, S4b, S4c and S4d shows good anti-bacterial activity and the compound S2, S3, S4b and S4c shows good anti-fungal activity[44].

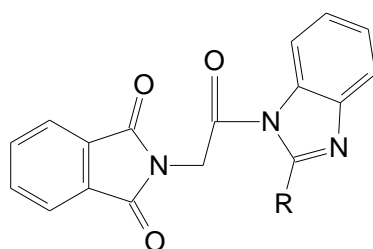


| Compound | Ar                              |
|----------|---------------------------------|
| S4a      | 2-nitrobenzaldehyde             |
| S4b      | 3-nitrobenzaldehyde             |
| S4c      | 4-chlorobenzaldehyde            |
| S4d      | 4-hydroxybenzaldehyde           |
| S4e      | 4-hydroxy-3-methoxybenzaldehyde |

Several new substituted sulfonamides and sulfinyl compound derivatives were obtained by the reaction of 2-thioxo-1,2,4-triazolo[1,5-a] pyridine and pyrimidine thiol derivatives with (2-chloromethyl) benzimidazole and/or (2-chloromethyl)benzoxazole. The synthesized compounds were screened for their antimicrobial activity. A little amount (1 mg) of compounds 9, 10 and 14 was enough to inhibit the growth of all tested bacterial strains. The tested compounds almost inhibited all the studied fungi but *Aspergillus terreus* was slightly resistance [45].



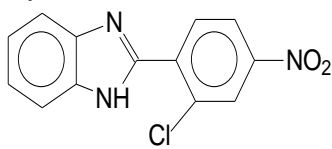
Benzimidazole derivatives of *N*-phthaloylglycine (6a-d) were synthesized and were evaluated for their *in vitro* antimicrobial activity using disc diffusion method. 6b (MIC, 1.5 mg/L), displayed good activity against methicillin-resistant *Staphylococcus aureus* (MRSA). All the synthesized compounds exhibited a wide range of antibacterial activity against all of the *Staphylococcus aureus* resistant strains tested [46].



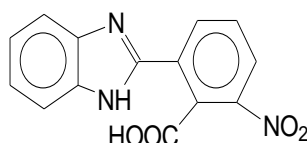
6a-d

R=H (6a), R=CH<sub>3</sub> (6b), R=C<sub>2</sub>H<sub>5</sub> (6c), R=1-ethyl alcohol (6d)

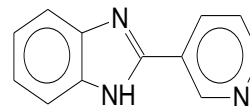
Some new 2-substituted benzimidazole derivatives were synthesized via microwave irradiation method. All compounds were screened for their *in vitro* antimicrobial activities against the standard strains: *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Bacillus pumilus*, *Candida albicans*, *Aspergillus niger*. Compound 2-Pyridin-3-yl-1H-benzimidazole (1f) was found to be the most active antimicrobial compound amongst the series. Compounds 2-(2-Chloro-4-nitro-phenyl)-1H-benzimidazole (1a), 2-(1H-Benzimidazol-2-yl)-6-nitro-benzoic acid (1e) also showed good antimicrobial activity [47].



1a

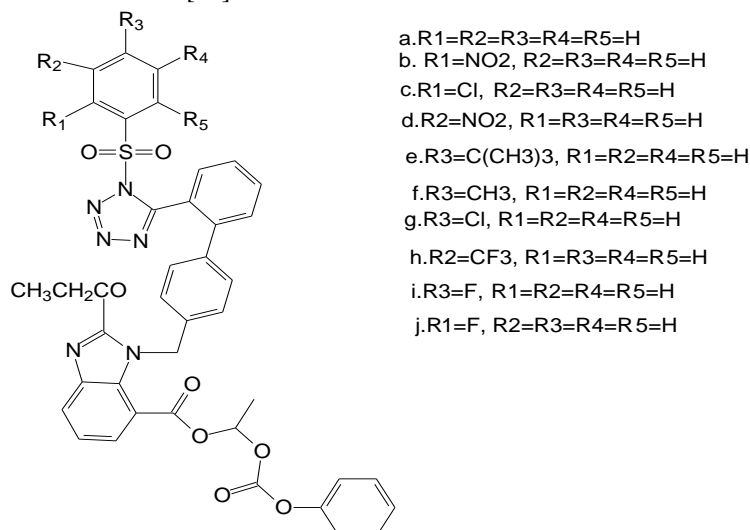


1e

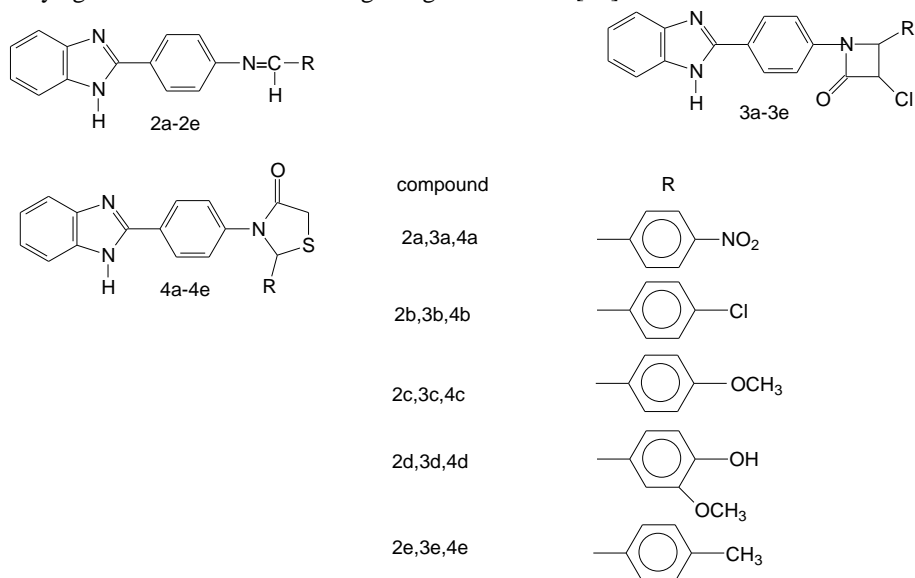


1f

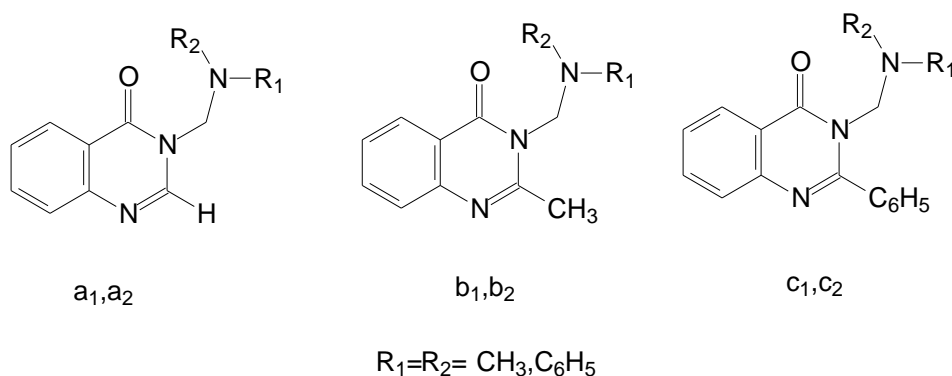
A series of new benzimidazole derivatives have been synthesized by simple condensation reaction between benzimidazole derivatives and phenyl sulphonyl chloride derivatives. These compounds were screened for antibacterial and antioxidant activities respectively. The antibacterial activities were compared with the standard drug such as chloramphenicol and the antioxidant activities were compared with the ascorbic acid [48].



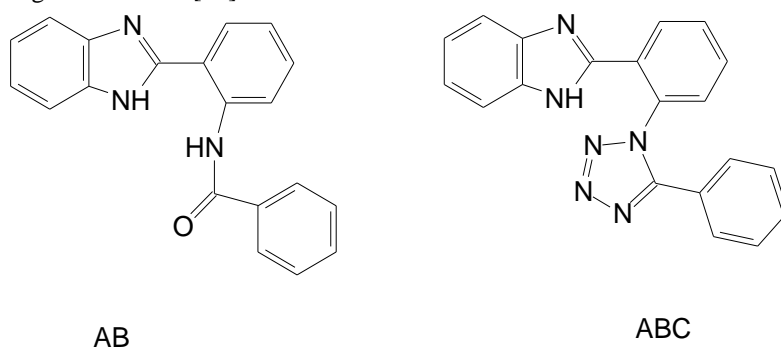
A novel series of 2-substituted benzimidazole derivatives were synthesized and screened for antibacterial (*Staphylococcus aureus* ATCC9144, *Staphylococcus epidermidis* ATCC 155, *klebsiella pneumoniae* ATCC 29665 and *Esherichia coli* ATCC 25922) and antifungal (*Candida albicans* ATCC 2091 and *Aspergillusniger* ATCC 9029) activities. The Minimum Inhibitory Concentrations was determined by agar streak dilution method. 1-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-3-chloro-4-(4-nitrophenyl)azetidin-2-one (3a) was found to exhibit the most potent *in vitro* antimicrobial activity with MIC of 15, 17, 19, 9, 11 and 15 µg/mL against *E.coli*, *K.pneumoniae*, *S.aureus*, *S.epidermidis*, *C.albicans* and *A.niger* respectively. All the other compounds exhibited moderate activity against the bacterial and fungal organism tested [49].



The novel reaction of 3-(2-methylbenzimidazol-1-yl) propanoic acid hydrazide with CS<sub>2</sub>/KOH gave Oxadiazol,methyl-derivative which via Mannich reaction give 3-[(dialkylamino) methyl]-2phenyl-4(3H)-quinazolinone. All the synthesized compounds were confirmed by spectral data and then screened for antibacterial activity against *B. subtilis*, *S. aureus* and *E. coli* and for antifungal activity against *C. albicans* and *A.niger*. Synthesized compounds a1, b1, c1 shown the highest antibacterial activity when compared with standard drug Norfloxacin. Compounds a1, b1, and c1 have shown high activity against both fungi and remaining compounds exhibited either moderate or weak activity against *C. albicans* and *A. niger*. Some N-Mannich derivatives of 4(3H)-quinazolinones can be used as a template for the future development through modification or derivatization to design a more potent antimicrobial agents [50].



The reaction of o-phenylenediamine with anthranilic acid yield compound 2-(1H-benzo[d]imidazol-2-yl)aniline (AOP). The compound AOP was condensed with aromatic acid chlorides in the presence of pyridine to get compound N-(2-(1Hbenzo[d]imidazol-2-yl)phenyl)benzamide (AB). Further it to then treated with  $\text{PCl}_5$  to get an intermediate compound then reacted with  $\text{NaN}_3$  to yield compound 2-(2-(5-phenyl-1H-tetrazol-1-yl)phenyl)-1H-benzo[d]imidazole (ABC). The compounds were synthesized in good yields and their structures were confirmed by IR,  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$  spectral data and elemental analysis. Antimicrobial activity against bacteria and fungi was studied. The results of preliminary biological tests showed that these compounds possess good biological activities [51].



A series of 2-substituted phenoxyethyl benzimidazoles and 1-alkyl-2-substituted phenoxyethyl benzimidazoles ( $\text{R}_1\text{X}_1\text{-4-R}_8\text{X}_1\text{-4}$ ) were prepared. The structures of the benzimidazole derivatives were confirmed on the basis of spectral data. The compounds were screened for their in vitro antibacterial, antifungal, antitubercular activity using bacterial strains (*E. Coli*, *Pseudomonas aeruginosa* and Coagulase positive *Staphylococcus aureus* {COPS}), fungal strains (*Candida albicans* and *Aspergillus niger*) and *Mycobacterium tuberculosis* H37RV strain. The results of preliminary screening showed that all synthesized 2-(substituted phenoxyethyl) 1-H benzimidazoles and 1-alkyl-2-(substituted phenoxyethyl) benzimidazoles has potential antifungal activity against *Candida Albicans*, but only few compounds showing activity against *Aspergillus niger*. Similarly all molecules showed good antibacterial activity against *E.coli* and *Pseudomonas aeruginosa*, but very few were resistance to *Staphylococcus aureus*. And all the synthesized compounds showed good activity against *Mycobacterium tuberculosis* even at 1mcg/ml concentration [52].

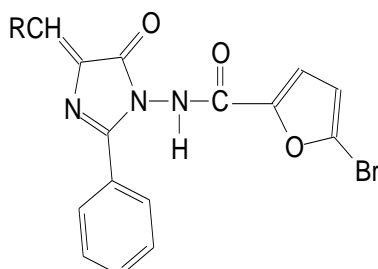


$\text{X}_1=\text{H}$ ,  $\text{X}_2= \text{CH}_3$ ,  $\text{X}_3= \text{C}_2\text{H}_5$ ,  $\text{X}_4=\text{C}_3\text{H}_7$

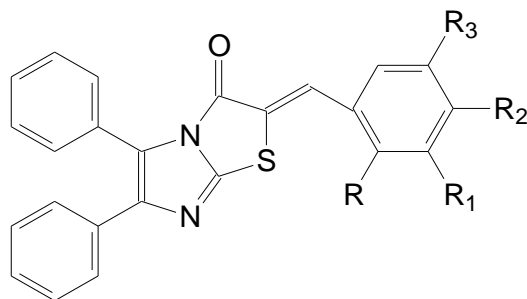
$\text{R}_1= \text{H}$ ,  $\text{R}_2= 4\text{-NO}_2$ ,  $\text{R}_3= 3\text{-NO}_2$ ,  $\text{R}_4= 4\text{Cl}$ ,  $\text{R}_5=4\text{-Br}$ ,  $\text{R}_6= 4\text{-CH}_3$ ,  $\text{R}_7= 3\text{-CH}_3$ ,  $\text{R}_8=4\text{-Cl},3\text{-CH}_3$

A series of 1-(5'-bromofuran-2'-carboxamido)-2-phenyl-4-(benzylidene / substituted benzylidene)-5-imidazolones (Ia-j) have been synthesized and evaluated for antibacterial activity. All the synthesized compounds were screened for their antibacterial activity against *S. aureus* (MTCC-96), *B. subtilis* (MTCC-441) [Gram-positive bacteria] and *E. coli* (MTCC-443), *S. paratyphi-B* (MTCC-733) [Gram-negative bacteria]. Known antibiotic Ciprofloxacin was used as standard drug. The screening results indicate that compounds Ia, Ib and Ih were found to moderately active against *S. aureus* (MTCC-96). Compounds Id, Ie, If, Ig and Ij were found to be less active against *S. aureus* (MTCC-96), whereas compounds Ic and Ii were found to be inactive be active against *S. aureus* (MTCC-96). Compounds Ia, Ib, Id, Ig and Ii were found to be active against *B. subtilis* (MTCC-441). Compounds Ic and Ie were found to be moderately active against *B. subtilis* (MTCC-441), whereas compound If, Ih and Ij was found to be less active against *B. subtilis* (MTCC-441). Compounds Ib, Ic, Ie, Ii and Ij were found to be moderately active against *E. coli* (MTCC-443), where as Ia, Id, If, Ig and Ih were found to be less active against *E. coli* (MTCC-443). Compounds Ia, Id, Ie, Ig, Ih, Ii and Ij were found to be moderately active against *S. paratyphi-B* (MTCC-733). Compounds Ib, Ic and If were found to be less active against *S. paratyphi-B* (MTCC-733) [53].

| Compound No. | R               |
|--------------|-----------------|
| <b>Ia</b>    | Phenyl          |
| <b>Ib</b>    | 2-Chlorophenyl  |
| <b>Ic</b>    | 3-Chlorophenyl  |
| <b>Id</b>    | 4-Chlorophenyl  |
| <b>Ie</b>    | 3-Bromophenyl   |
| <b>If</b>    | 4-Bromophenyl   |
| <b>Ig</b>    | 2-Nitrophenyl   |
| <b>Ih</b>    | 3-Nitrophenyl   |
| <b>Ii</b>    | 4-Nitrophenyl   |
| <b>Ij</b>    | 4-Methoxyphenyl |



Certain (2E)-substituted-2-ethylidene-5,6-diphenylimidazo[2,1-b][1,3]thiazol-3-(2H)-ones (4a-f) have been synthesized by the condensation of 4,5-diphenylimidazoin-2-thiones (3) with different aromatic aldehydes and chloroacetic acid in presence of acetic anhydride, anhydrous sodium acetate and glacial acetic acid. The title compounds were found to be efficient antibacterial agents [54].



R R1 R2R3

4a = H OCH3 OCH3 OCH3

4b = H OCH3 OH H

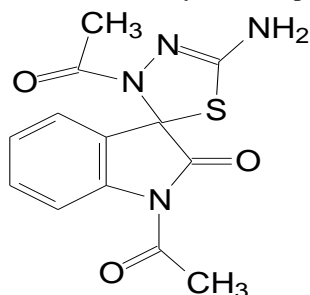
4c = OHH H H

4d = H HH H

4e = H NO2 HH

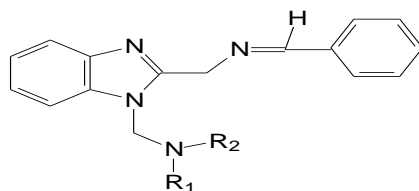
4f = H HNO2 H

The synthesis and antibacterial activity of two spiro [indole] thiadiazole derivatives [55] were reported. The compounds were tested for their antibacterial activity against gram positive and gram negative bacterial strains. Compounds showed activity against 4- gram positive and 3-gram negative bacterial strains (better activity than streptomycin, the reference standard).



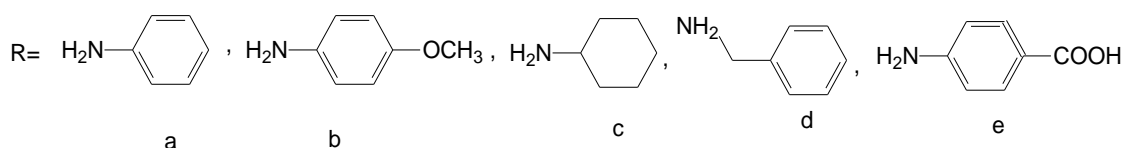
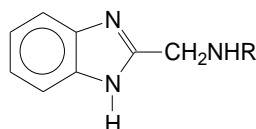
Novel Mannich base derivatives of Benzimidazole were prepared through the condensation reaction of benzimidazole derivative with formaldehyde and primary and/ secondary amine. Zinc(II), copper(II), nickel(II) and cobalt(II) complexes of Mannich bases have also been synthesized. All the compounds were screened for in-vitro antibacterial and antifungal activity against various bacterial and fungal strains. Almost all the compounds showed good potent activity against microorganisms. It was also seen that compounds with complexed form were more active as compared to un-complexed form. The prepared compounds were also screened for their cytotoxicity and results showed that only Ni(II) complexes exhibit some cytotoxicity while all other compounds were almost inactive[56].



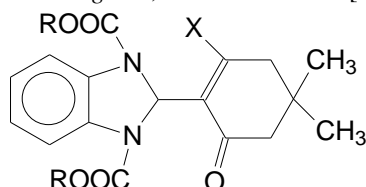


| compound       | R1                               | R2   |
|----------------|----------------------------------|--|
| L <sub>1</sub> | —CH <sub>2</sub> CH <sub>3</sub> | —CH <sub>2</sub> CH <sub>3</sub>                 |
| L <sub>2</sub> | H                                | —CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub> |
| L <sub>3</sub> | H                                |  |
| L <sub>4</sub> | H                                |  |
| L <sub>5</sub> | H                                |  |
| L <sub>6</sub> |                                  |  |

Some 2-aminomethyl benzimidazoles derivatives were synthesized by reacting 2-chloromethyl benzimidazole with several amines and the compounds synthesized were identified by IR and NMR spectroscopy. Anti bacterial activity were screened against *Staphylococcus aureus*, *Bacillus subtilis*, and *Salmonella typhi* by zone inhibition method. Most of the compound shows potential anti bacterial activity [57].



N-Acyliminium reagents derived from benzimidazole have been successfully used in reactions with active methylene nucleophiles. A series of cyclic enaminoketones or dimedone were selectively amidoalkylated at the  $\alpha$ -carbon atom of the enaminone. The new 2-substituted derivatives of 2,3-dihydrobenzimidazole are interesting both from synthetic point of view and as potential bioactive compounds. All the synthesized benzimidazole derivatives were assayed for antimicrobial activity using standardized tests (DM and DDM) against seven strains microorganisms. Eight compounds displayed antimicrobial activity against *Staphylococcus aureus*, *Enterobacter aerogenes*, *Candidaalbicans*[58].

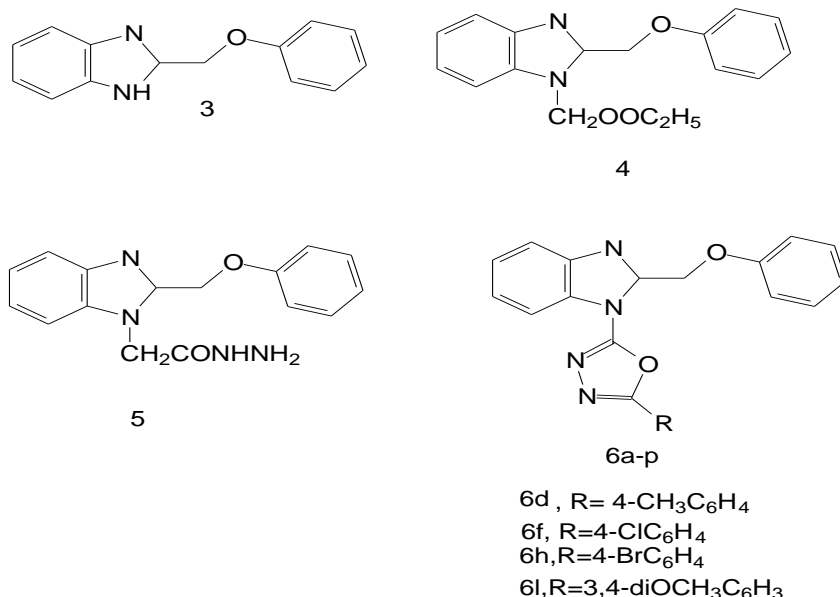


R= Me, Et., X= OH, NHR<sub>1</sub>

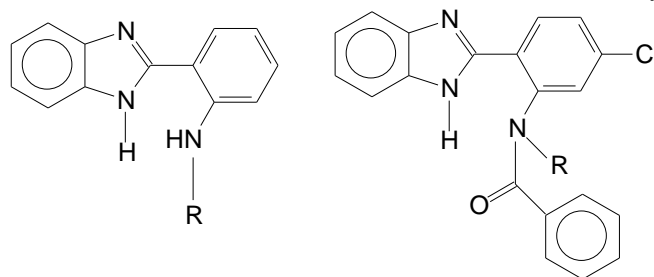
R<sub>1</sub> = Me, Et, Pr, Ph, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>CH<sub>2</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 3,4-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>

2-(Phenoxymethyl)-1H-benzimidazole (3) obtained by acidic condensation of o-phenylene diamine with phenoxyacetic acid, was reacted with ethyl chloroacetate under anhydrous condition to get ethyl [2-(phenoxymethyl)-1H-benzimidazol-1-yl]acetate (4). The ethyl [2-(phenoxymethyl)-1H-benzimidazol-1-yl]acetate (4) on treatment hydrazine hydrate gave 2-[2-(phenoxymethyl)-1H-benzimidazol-1-yl]acetohydrazide (5). The acid hydrazide group of 5 was cyclocondensed with various aromatic acids in presence of phosphorous oxychloride to get the titled compounds (6a-p). The structures of all the compounds were established on the basis of elemental and spectral analysis. The synthesized compounds were evaluated for their antimicrobial activity. The

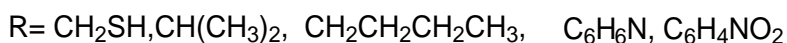
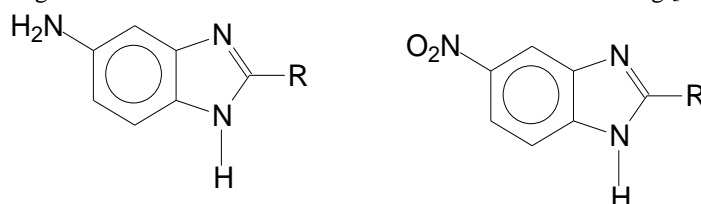
compound 6d, 6f, 6h and 6d, 6h and 6I a is most active compounds against *Escherichia coli* and *Staphylococcus aureus* respectively. The compound 6d, 6f and 6I is most active against *Candida albicans* and *Aspergillus flavus*[59].



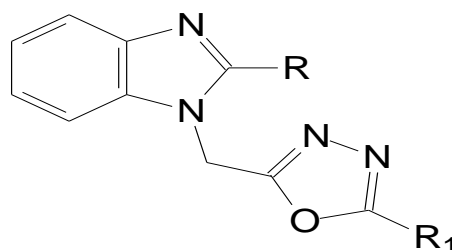
The new N-(2-(1H-benzimidazol-2-yl)phenyl)-N-phenylbenzamide derivatives were synthesized. The reaction was carried out between o-phenylenediamine with substituted anthranilic acids. Their antimicrobial activity was evaluated [60].



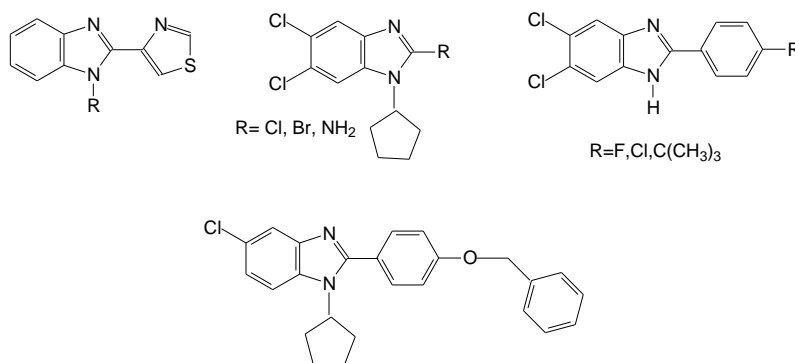
A new series of 2, 5 di-substituted benzimidazole derivatives have been synthesized and evaluated for their antibacterial; *Proteus vulgaris* (NCTC 4635), *Klebsiella pneumonia* (ATCC 29655), *Bacillus cereus* (NL98), and *Enterococcus faecium* (ATCC 29212) and antifungal (*Aspergillus niger* and *Aspergillus fumigatus*) activities by disc diffusion method. All of the synthesized compounds showed good antibacterial and antifungal activity. However the antibacterial and antifungal activity of the synthesized compounds against the tested organisms was found to be less than that of the standard drug [61].



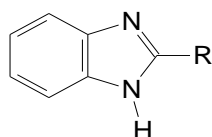
Literature survey shows that among the benzimidazole derivatives, 2-substituted ones are found to be pharmacologically more potent and hence the design and synthesis of 2-substituted benzimidazoles are the potential area of research.[62-63].



Some oxadiazol-1H-benzimidazole has been reported to possess antimicrobial activities. The compounds also showed moderate activity against tested fungi. Extensive biochemical and pharmacological studies have confirmed that its derivatives are effective against various strains of microorganisms[64-71]. The study revealed the best activity, with MIC values of 0.78 - 0.39 µg/mL against these species.

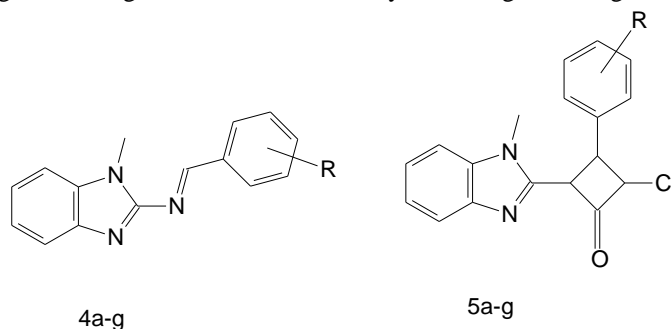


Some 2- substituted benzimidazole derivatives were synthesized by condensation of o-phenylenediamine with carboxylic acid in presence of ring closing agents (Polyphosphoric acid/ HCl). The Chemical structures of synthesized compounds were identified by spectral analysis. The synthesized compounds were screened for their in-vitro antibacterial activity against Standard strains by cup plate method [72].



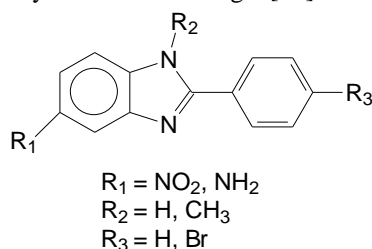
R = H, -CH<sub>3</sub>, 4-NH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, -CH<sub>2</sub>Cl

A series of 1-methyl-N-[(substituted-phenylmethylidene)-1H-benzimidazol-2-amines (4a–4g) were prepared via the formation of 1-methyl-1H-benzimidazol-2-amine (3), which was prepared by the cycloaddition of o-phenylenediamine (1) with cyanogen bromide in the presence of aqueous base followed by N-methylation with methyl iodide in the presence of anhydrous potassium carbonate in dry acetonitrile. Moreover, the four-membered b-lactam ring was introduced by the cycloaddition of 4a–4g and chloroacetyl chloride in the presence of triethylamine catalyst to give 3-chloro-1-(1-methyl-1H-benzimidazol-2-yl)-(40-substituted)-phenylazetidin-2-one 5a–5g. A total of 14 compounds were synthesized and characterized by IR, 1H NMR, 13C NMR and Mass spectral technique, in addition they were evaluated for anti-bacterial and cytotoxic properties. Among the chemicals tested 4a, 4b, 5a, 5b, 5g exhibited good antibacterial activity and 5f, 5g showed good cytotoxic activity in vitro [73].



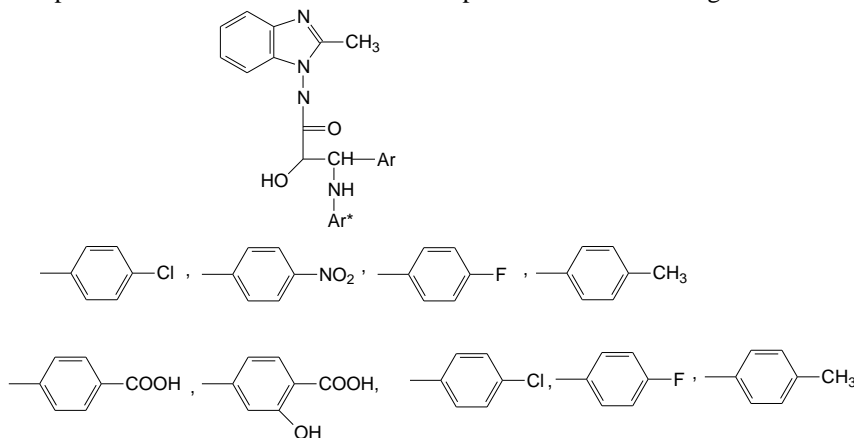
R = 4-Cl, 4-NO<sub>2</sub>, 2-NO<sub>2</sub>, 3-NO<sub>2</sub>, N,N-dimethylamino, 2,5-dimethoxy, 2-Cl

A series of the derivatives of benzimidazole were synthesized and the structures of all the synthesized compounds have been evaluated for *Candida glabrata*, and *Candida krusei*. Some of these compounds have been found to exhibit moderate to good antifungal activity when compared to commercially available antifungal [74].

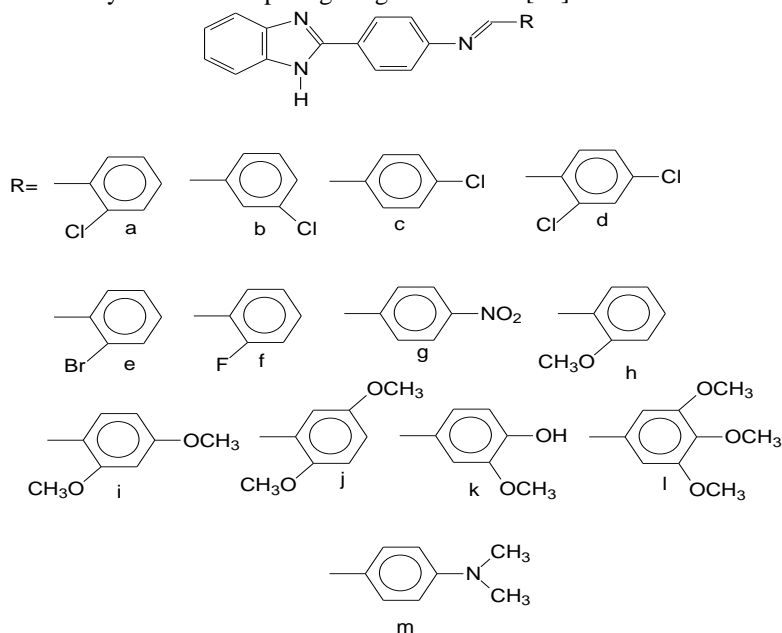


Life-threatening infections caused by pathogenic fungi are increasing day by day. There are only a few antifungal compounds available for infections like *Candidiasis*, *Cryptococcosis* which are highly attacking the immuno suppressed individuals. So there is a strong need to develop new classes of antifungal agents. The wide range of therapeutic value of benzimidazole nucleus inspiring for the synthesis of compounds with substitution at 2nd position and also substituting with different electron withdrawing and electron donating groups which would prove its potential antifungal nature. A series of 4-[1-(4-substituted phenyl)-2-hydroxy- 3-(2-methyl-benzimidazole-1-yl) - 3-oxo- propyl amino] substituted aromatic amino derivatives were synthesized by acetylating 2-methyl benzimidazole and chalcones were prepared in alkaline medium using aromatic aldehydes.

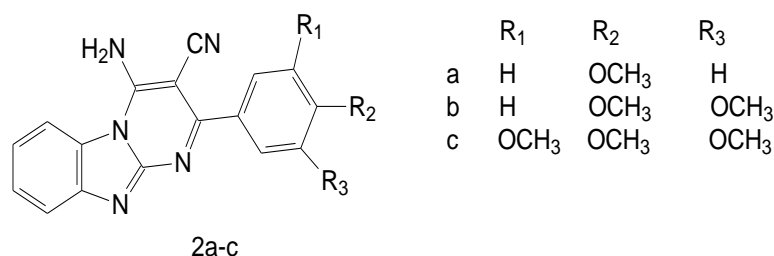
The chalconic compound was dissolved in glacial acetic acid and hydrogen peroxide for preparing the epoxide derivatives of chalcones. Then it was treated with different substituted amines which brought forth the newer compounds. The structures attributed to the newly synthesized compounds were elucidated using IR, NMR, MASS techniques besides elemental analysis. The compounds were evaluated for their antifungal potentials by two fold serial dilution in liquid media. Many of the target compounds proved to possess good antifungal activity. The compounds (AA9) - 3-(4-chlorophenyl)-3-(4-fluoro-phenyl amino) -2-hydroxy -1- (2- methyl -benzimidazole -1-yl)-propan-1-one and (AA19) - 2-hydroxy-4-[2-hydroxy-3-(2-methyl-benzimidazol-1-yl)-3-oxo-1-p-tolyl-propylamino]-benzoic acid have a minimum inhibitory concentration of 32  $\mu\text{g/ml}$ . A most distinctive derivative, 3-(4-chlorophenyl)-3-(4-chloro-phenyl amino) -2- hydroxy -1- (2-methyl-benzimidazole -1-yl)-propan-1-one - (AA10), was identified in the present study, due to its remarkable antifungal potentials and was found to be equipotent with that of the standard marketed drug, Fluconazole. The acute toxicity study of the compounds indicated that they are well tolerated. Therefore such compounds would represent a fruitful matrix for the development of better antifungal candidates [75].



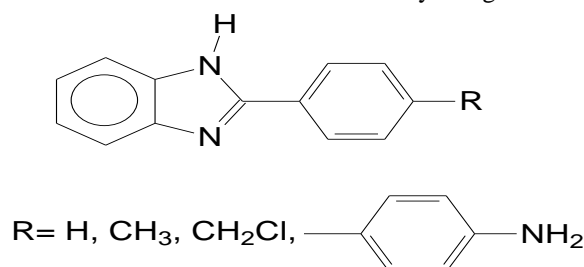
An efficient green chemistry for synthesizing a series of Schiff bases (3a-m) incorporating 4-1*H*-benzo[*d*] imidazole moiety, by microwave technique and heating conventional procedures which are used for their preparation. The newly synthesized Schiff bases are obtained by the reaction of 4-(1*H*-benzo[*d*]imidazol-2-yl) aniline with a series of different aromatic aldehydes. The evaluation of anticancer activities of synthesized Schiff bases are investigated against human cancer cell lines; Co rectal cancer cell line HCT116, human liver cancer cell line HepG2 and human ovarian cancer cell line A2780, the results show that compounds 3c,3f,3g have more activity than the comparing drug CK0106023[76].



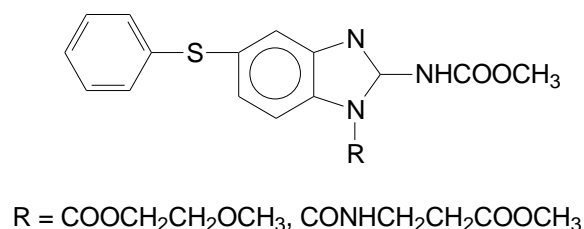
New benzimidazole derivatives, namely, (*N*-(4-methoxyphenyl)methylene)-1*H*-benzimidazol-2-amine (2a), (*N*-(3,4-dimethoxyphenyl)methylene)-1*H*-benzimidazol-2-amine (2b), and (*N*-(3,4,5-trimethoxyphenyl)methylene)-1*H*-benzimidazol-2-amine (2c) were synthesized by reaction of a Schiff base with malononitrile in absolute ethanol. Compounds 2a-c were screened for their *in vitro* anticancer potential using HeLa and PC3 cells. All compounds showed limited cytotoxicity except compound 2a that showed a moderate cytotoxic effect towards HeLa cells[77].



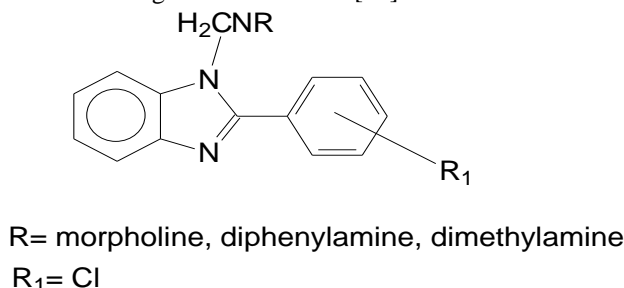
Several new nitrobenzimidazoles have been reported to possess cytotoxic activity against breast cancer. In the reported research it was also found out that the compounds like thiadiazole, tetrazole, triazines and imidazoles also possess the activity [78]. A series of 2-methylaminobenzimidazole derivatives were synthesized and reported [79]. The new synthesized compounds were screened for analgesic and anti-inflammatory activities by the author on acetic acid induced writhing in mice and carrageenan induced paw oedema in rats. Some compounds showed a potent analgesic (89% at 100 mg/kg) and anti-inflammatory (100% at 100 mg/kg) activities compared with standard drug Nimesulide (100% at 50 mg/kg) respectively. Another research was carried out indicating that benzimidazole on combination with indole skeleton give potent anti-inflammatory action similar to indomethacin [80, 81]. A number of N-alkylbenzimidazoles were synthesized by reactions of benzimidazole with alkyl halides (i-PrBr, PrBr, EthBr, Pent-2-ylBr, BuBr, BenzCl, HeptBr). The subsequent treatment of the resulting N-alkylbenzimidazoles with 1,3-(bromomethylene)benzene afforded corresponding bis-benzimidazolium salts. All the compounds were assessed for their anti-proliferation test on human colorectal cancer cell line (HCT 116). Results showed that the compounds exhibited dose dependent cytotoxicity towards the colon cancer cells with IC<sub>50</sub> ranges between 0.1 to 17.6 μM. The anti-proliferation activity of all compounds was more pronounced than that of standard reference drug 5-fluorouracil (IC<sub>50</sub> = 19.2 μM). All the synthesized bis-benzimidazolium salts showed potential anticancer activity. Out of them, some of these salts showed IC<sub>50</sub> value as low as 0.1–0.2 μM. Based on the results it can be concluded that, the bis-benzimidazolium salts could probably be the potential source of chemotherapeutic drugs [82]. A set of 2-substituted benzimidazoles were successfully synthesized. Benzimidazoles were prepared by condensation of ortho-phenylenediamine with substituted acids in presence of ring closing agents like Polyphosphoric acid/HCl. All the synthesized compounds were screened for anthelmintic activity using Albendazole as standard [83].



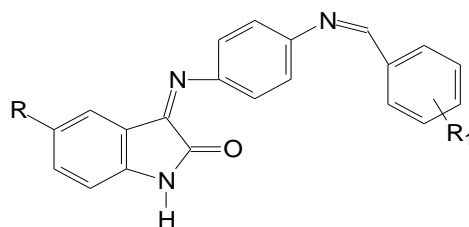
Synthesis of 2-benzimidazole carbamic acid methyl ester derivatives were reported. The compounds show anthelmintic activity against *Nippostrongylus*, *Ankilostoma* and *Haemonhus* larvae that exceeded 65% oral administration in animals (rats, sheep, dogs) at a dose of 2.5–50 mg/kg. In another group of animal inhibition action is below 40% oral administration in a dose of 50–100 mg/kg [84].



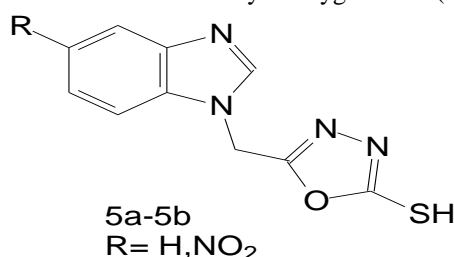
The synthesis and anti-inflammatory activity of phenyl benzimidazole was reported. The compounds were screened for anti-inflammatory activity and they showed various degrees of inhibition [85].



Synthesis of a novel Schiff bases derived from 5-substituted isatin was reported. The synthesized compounds were investigated for analgesic and anti-inflammatory. The synthesized compounds exhibited remarkable analgesic and anti-inflammatory activity when compared with standard drug (Pentazocin, 10 mg/kg, i.p. and Indomethacin 20 mg/kg) [86].

R= H, F, Cl, OCH<sub>3</sub>R<sub>1</sub>= Cl, OCH<sub>3</sub>, NO<sub>2</sub>, OH

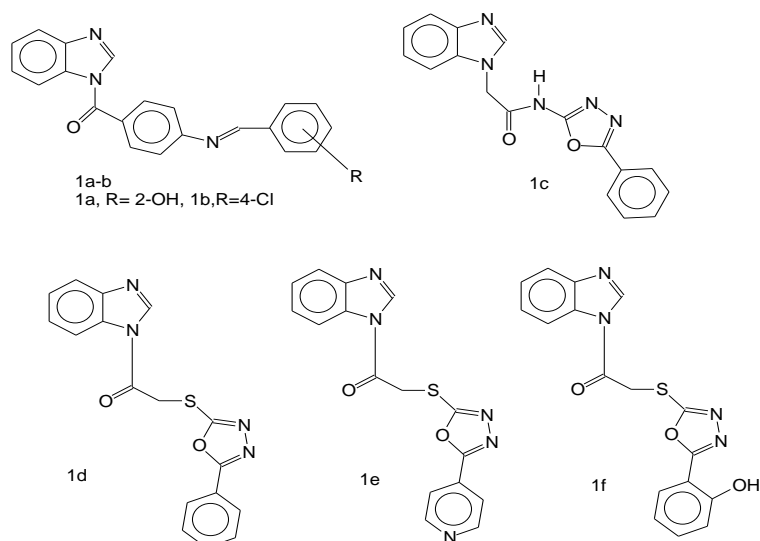
Molecular property is a complex balance of various structural features which determine whether a particular molecule is similar to the known drugs. These properties mainly hydrophobicity, molecular size, flexibility and presence of various pharmacophoric features influence the behavior of molecules in a living organism, including oral bioavailability. This investigation deals with the design and calculation of molecular properties, drug likeness, lipophilicity and solubility parameters of 5-Benzimidazole-1-yl-methyl-[1, 3, 4] oxadiazole-2-thiol and their derivatives using Osiris, Mol inspiration, Mol soft software's, and ALOPGPS 2.1 program. The compounds followed the Lipinski 'Rule of five' for better bioavailability, were synthesized and characterized by IR, NMR, and mass spectral analysis. Furthermore, the binding conformations of these compounds for anti-inflammatory activities were determined in silico docking. This is an energy optimization process concerned with the search of the lowest free energy binding mode of a ligand within a protein binding site and estimates the forces involved in the protein-ligand recognition, carried out in Mastro V 2011 in the active site of the cyclooxygenase-2 (COX-2) enzyme [87].



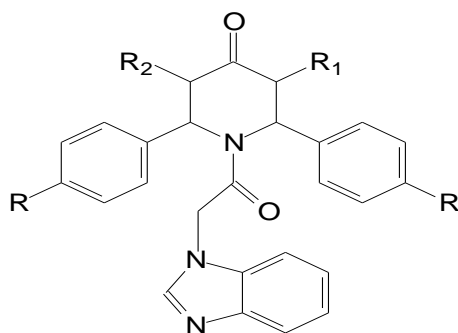
5a-5b

R= H, NO<sub>2</sub>

Benzimidazoles are an important class of compounds with a wide spectrum of biological activity ranging from anti-hypertensive, anti-viral, anti-fungal, antitumor and anthelmintic activity. In addition, few N-substituted benzimidazole derivatives have shown to exhibit significant activity against several viruses, including HIV, herpes simplex (HSV-1), influenza, picorna, human cytomegalovirus (HCMV) and hepatitis C virus. The five membered heterocyclic moiety 1,3,4-oxadiazole also confers for various biological activity. Hence a series of benzimidazole derivatives fused with oxadiazole ring system have been synthesized, characterized by UV, IR and <sup>1</sup>H NMR spectral data and evaluated for their in vitro and in vivo anti-inflammatory and antioxidant activity [88].

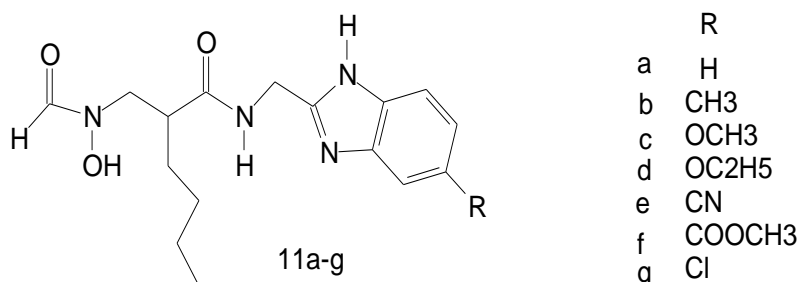


A series of 1-[2-(1H-benzimidazol-1-yl)acetyl]-2,6-diarylpiperidin-4-ones has been synthesized under mild conditions in good yield. Measurement of antimicrobial activity showed that compounds 23, 24 and 25 exhibited a better activity profile towards the tested microbial strains [89].



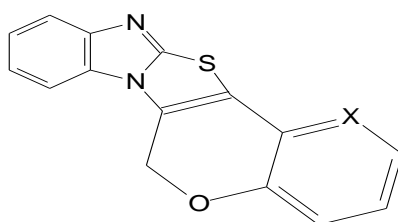
23-25

New series of N-formylhydroxylamine compounds were designed, optimized with the AutoDock 4.0.1 to investigate the interactions between the target compounds and the amino acid residues of the *Escherichia coli* PDF•Ni enzyme, and then synthesized through multi-step sequence starting from diethyl malonate. All the synthesized compounds have been screened for their antimicrobial activities. It was found that the compounds 11c, 11d, 11f and 11g exhibited potent inhibitory activity against *S. aureus in vitro* [90].



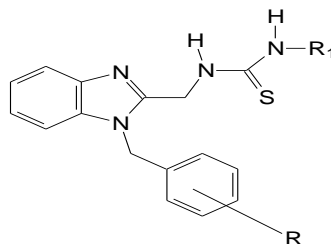
11a-g

Syntheses of novel tetra- and penta-cyclic benzopyran and pyridopyran derivatives, via direct intramolecular arylation of 2-iodophenoxymethylhetarenes and 3-(2-bromo-pyridin-3-yloxymethyl)-benzo[4,5]imidazo[2,1-*b*]thiazole in the catalytic system Pd(OAc)<sub>2</sub> / Xantphos / Cs<sub>2</sub>CO<sub>3</sub> / Ag<sub>2</sub>CO<sub>3</sub> in toluene, and a one-pot bicatalytic method for 12*H* [1]benzopyrano[3',4':4,5]thiazolo[3,2-*a*]benzimidazole directly from 3-chloromethylbenzo[4,5]imidazo[2,1-*b*]thiazole and 2-iodophenol, are described. This latter compound **4a** exhibits high cytotoxicity (MG-22A, 6 µg/mL) on the mouse hepatoma cancer cell line and low toxicity (LD<sub>50</sub>, 1058 mg/kg) on the mouse Swiss albino embryo fibroblasts 3T3. On the human fibrosarcoma cell line this compound is essentially inactive[91].



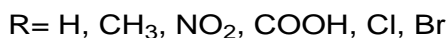
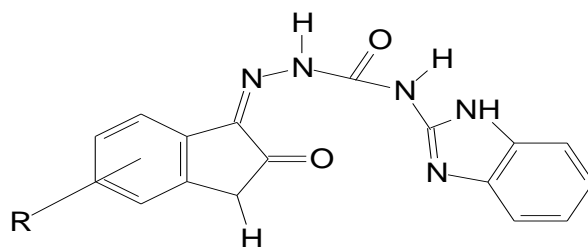
4a,b

A number of new 1-((1-(2-substituted benzyl)-1*H*-benzo[*d*]imidazol-2-yl) methyl)-3-arylthioureas compounds (3a-p) were synthesized and evaluated for their anticonvulsant and neurotoxic properties. All the newly synthesized compounds were screened for their anticonvulsant activity in ip MES and sc PTZ model and were compared with the standard drug phenytoin. Majority of the compounds exhibited significant activity against both the animal models however compounds 3g, 3l and 3o displayed promising activity and could be considered as leads for further investigations[92].

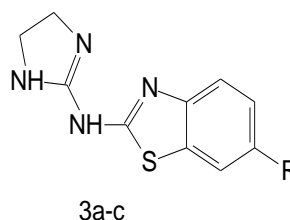
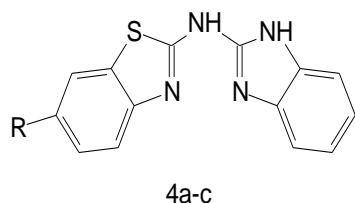


R=H, Cl  
R1= C<sub>6</sub>H<sub>5</sub>, 2-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 3-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 2-OCH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>

A series of isatin derivatives were synthesized by condensation of N-(1*H*-benzimidazol-2-yl)-hydrazine carboxamide with various isatin derivatives and evaluated for *in vivo* (rat paw edema) for their anti-inflammatory activity using carrageenan induced rat paw edema model. All the novel isatin derivatives exhibited mild to moderate activity. Compound 6b, 5-methyl isatin derivative exhibited better anti-inflammatory activity compared with control and other test compounds with percentage inhibition of 63.15[93].

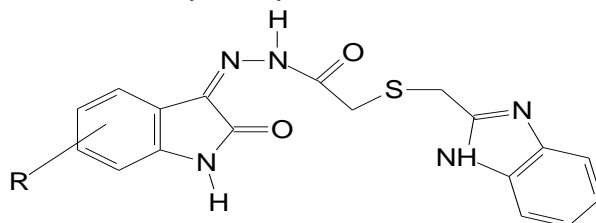


*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-6-substituted-1,3-benzothiazol-2-amines and *N*-(1*H*benzimidazol-2-yl)-6-substituted-1,3-benzothiazol-2-amines were synthesized by the reaction of 6-substituted-2-aminobenzothiazoles with carbon disulphide and methyl iodide. It was followed by the reaction with *o*-phenylene diamine/ ethylene diamine. They were screened for their anti-inflammatory, antiulcer, antitumor, entomological (antifeedant, acaricidal, contact toxicity and stomach toxicity) and antibacterial activities [94].

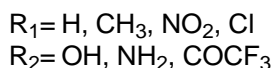
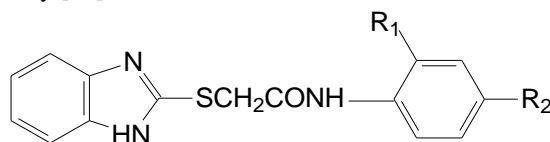


In view of the biological prominence of isatin derivatives and benzimidazole derivatives, it is planned to synthesize new isatin derivatives containing 1-*H*-benzimidazol-2-yl methane-thiol moiety in one side chain at 3rd position. Some new 2-[1-*H*-benzimidazol-2-ylmethyl)sulfanyl]-*N'*-[(3*Z*)-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene]aceto hydrazides (VIII) have been synthesized.

Investigation of anti-inflammatory activity was done by carrageenan induced rat hind paw edema method. Among the compounds tested, compounds with methyl group at 5th and 7th positions of the indole ring exhibited maximum activity with percentage inhibition of 68.56 and 61.41. Compounds with substituent (R=5-COOH, 5-Cl, 7-Cl, 5-Br, 7-NO<sub>2</sub>, -NO<sub>2</sub> and R=H) were found to be next in the order of anti-inflammatory activity [95].

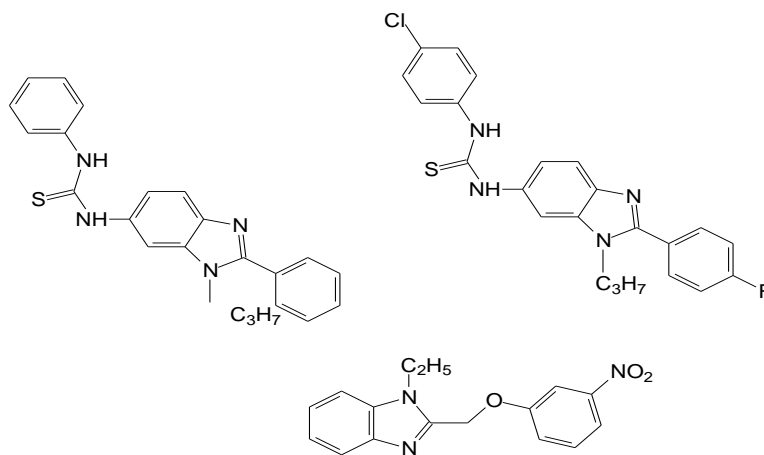


A new series of benzimidazole derivatives were synthesized. The title compounds were screened for analgesic and anti-inflammatory activities by biological evaluation method and also for other possible pharmacological activities including antibacterial activity. Among the synthesized compounds, some have shown promisingly significant analgesic, anti-inflammatory activities and moderate antibacterial activity [96].

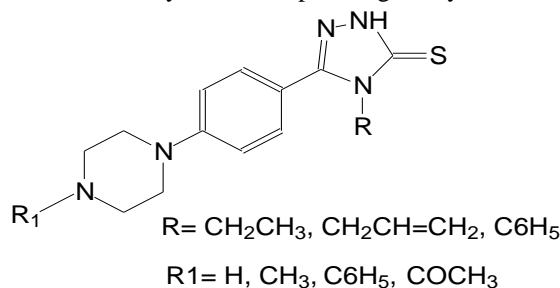


Kilcigil et al. synthesized a series of benzimidazole derivatives were tested for antifungal activity against a variety of test organisms *Candida albicans* and *Aspergillus niger* by the punch well Disc diffusion methods on the Sabouraud Dextrose Agar Broth using Fluconazole (100 µg/ml) as the standard drug. The antifungal screening was carried out with three different concentrations of the synthesized novel molecules i.e. 1 µg/ml, 10 µg/ml, 100 µg/ml using 50% Dimethyl formamide as solvent. The screening results indicate that all compounds show promising activity against *Candida albicans*, of which only 1-alkyl-2-substituted phenoxymethylbenzimidazoles and its derivatives showed comparable activity with the standard Fluconazole. Fewer compounds exhibited activity against *Aspergillus niger*, substituted phenoxymethylbenzimidazoles showed higher activity than the standard Fluconazole. Some of the compounds exhibited a non-linearity between the concentration used and the zone of inhibition. [97]

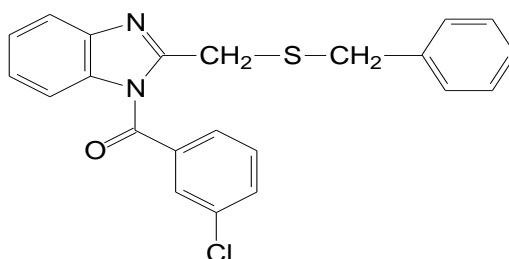




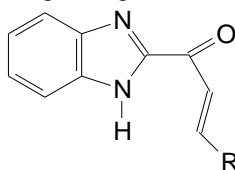
A novel series of triazole analogues possessing substituted piperazine were synthesized and their structures were elucidated using elemental analysis, IR, <sup>1</sup>H-NMR and mass spectral data. The synthesized compounds were tested for their in-vitro antimicrobial activity against the microbial strains i.e., *Staphylococcus aureus*, *Bacillus subtilis*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Aspergillus niger* and *Candida albicans* using disk diffusion method. Some of compounds displayed noticeable biological activity against all the pathogenic microorganisms tested including *Pseudomonas aeruginosa* and *Candida albicans* responsible for nosocomial infection. Structure activity relationship among the synthesized compounds was also studied[98].



New benzimidazole derivatives containing 4-chloropyridine-2-carbonyl and N-methyl picolinamide moieties in one side chain at 1H position of benzimidazoles (2-((benzylthio)methyl)-1H benzo[d]imidazol-1-yl)(4-chloropyridin-2-yl)methanones(3) have been synthesized as depicted in scheme-1. The intermediates and final compounds were purified and their chemical structures have been confirmed by IR, <sup>1</sup>H NMR, and Mass spectral data. All the derivatives were examined for their anthelmintic activity against Indian adult earthworms (*pheretima posthuma*) at various concentrations (0.2% and 0.5%), antibacterial activity against *B.subtilis*, *B.cereus*, *S.epidermidis*, *S.typhi*, *P.aeruginosa* and *K.pneumoniae* and antifungal activity against *A.flavus*, *F.oxysporium* and *P.notatum* at a concentration of 2mg/ml. Most of the compounds tested have shown promising activities when compared with the standard drugs [99].



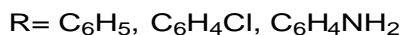
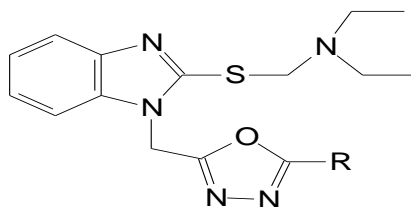
The synthesis of some benzimidazole chalcone moieties via an efficient method of microwave assisted and correlated their antimicrobial activity with CLogP value determined by ChemDraw Ultra 11.0 software. The structures of the final candidates were confirmed by spectral studies. All the synthetic derivatives were evaluated for their antimicrobial studies. Most of the derivatives were good activity towards Gram-positive bacteria and less activity towards Gram-negative bacteria. Some of the derivatives showed a moderate activity against tested fungi. SAR of the final candidates revealed a correlation between ClogP and antimicrobial studies. It has been concluded that higher logP value favours the activity ratio[100].



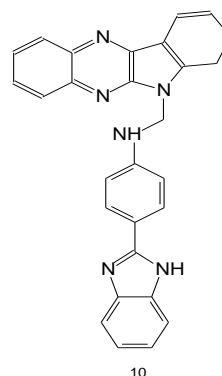
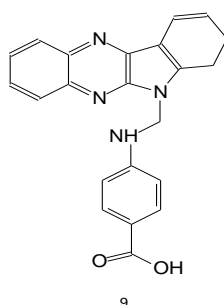
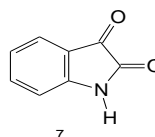
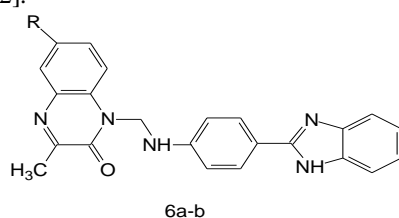
R = Phenyl, 4-chlorophenyl, 4-methoxyphenyl, 3-nitrophenyl, 2-hydroxyphenyl, cinnamyl

The earliest report of Benzimidazole derivatives antibacterial activity appeared in 1964, and more recently it was found that, two groups of substituted benzimidazoles, namely the 5,6-dinitro and 2-trifluoromethyl derivatives, to be promising candidates for

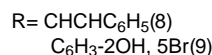
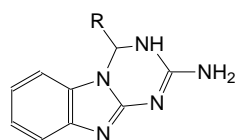
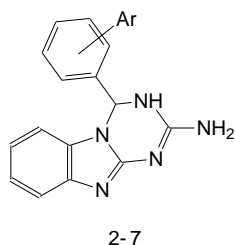
antimicrobial drugs. In this paper we present new data on the antimicrobial and antiprotozoal activities of 5,6-dinitro and 2-dialkylaminosubstituted benzimidazoles[101].



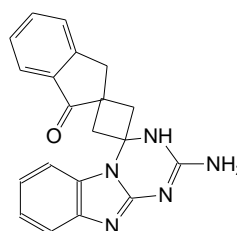
The synthesis and antimicrobial activity of the synthesized compounds as 0.1% solution in DMF was reported, against Gram negative bacteria (*Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonasaeruginosa* and *Proteus vulgarism*). Compounds (6), (7), (9) and (10) are active towards the tested Gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*) Yeast (*Candida albicans*, *Candida tropicalis*)[102].



Two novel series of 2-amino-3,4-dihydro[1,3,5]triazino[1,2-a]benzimidazoles, and 2-amino-4,4-disubstituted/spiro[1,3,5]triazino[1,2-a]benzimidazoles were synthesized and evaluated for their in vitro antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*. Molecular modeling and docking of the synthesized compounds into enoyl acyl carrier protein reductase (FabI) complexed with its bound inhibitor using Molsoft ICM 3.4-8C program was performed. Among the tested compounds, 2 and 16 were the most potent antibacterial (MIC = 25 ug/ml). Detailed synthesis, spectroscopic and biological data are reported[103].

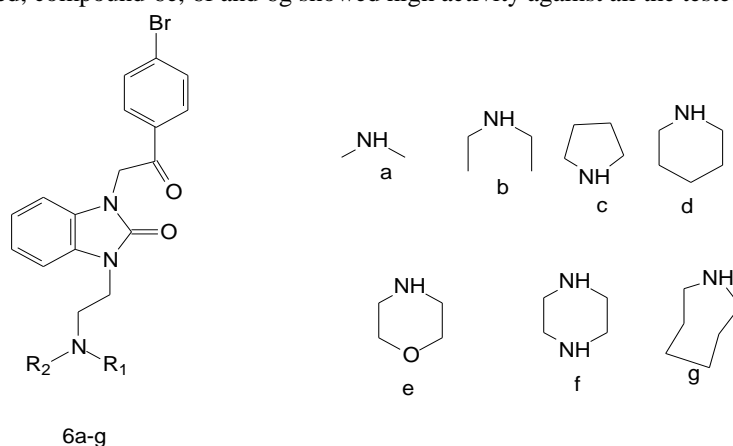


| Compound | Ar   |
|----------|--|
| 2        | 2-(OSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -CH <sub>3</sub> -4) |
| 3        | 2-(OSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -Br-4)               |
| 4        | 2-(OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> )                    |
| 5        | 4-(OSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -CH <sub>3</sub> -4) |
| 6        | 4-(OSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -Br-4)               |
| 7        | 4-OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>                       |

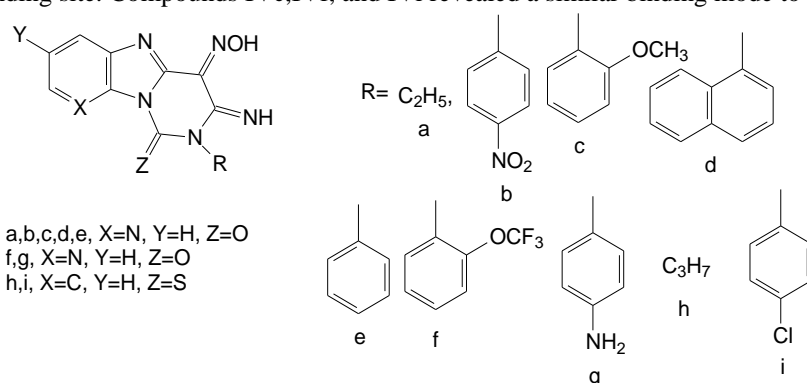


1,3-dihydro-2H-benzimidazole-2-one ring system represents the core skeleton of a large number of biologically active, structurally intriguing compounds found in a multitude of pharmaceutically important compounds. The development of efficient and practical methods for construction of this important heterocyclic remains as an active area of synthetic research. The present paper describes the synthesis and antibacterial activity of some novel 1,3-dihydro-2H-benzimidazol-2-one analogs 6a -6g from

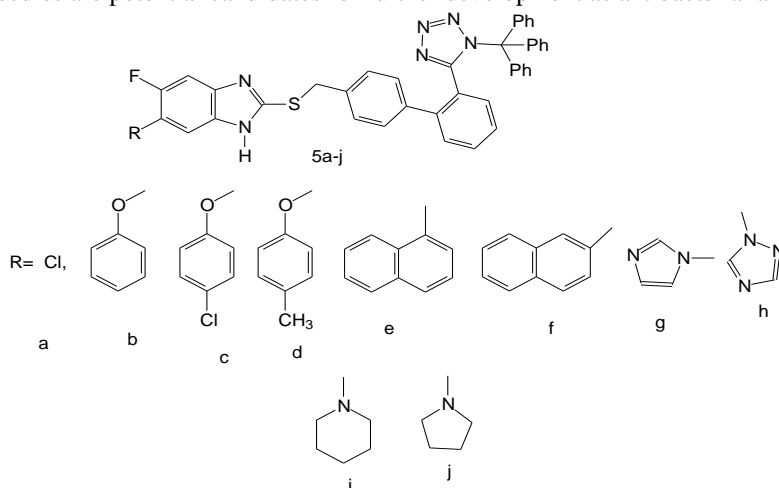
commercially available 1,2 phenylenediamine as starting material. The newly synthesized compounds, 6a-6g were screened in-vitro at a concentration of 100  $\mu\text{g}/\text{mL}$  for antibacterial activity against two Gram-positive (*Staphylococcus aureus* and *Staphylococcus pyogenes*) and two Gram-negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*). It was observed that among all the compounds tested, compound 6e, 6f and 6g showed high activity against all the tested bacterial strains [104].



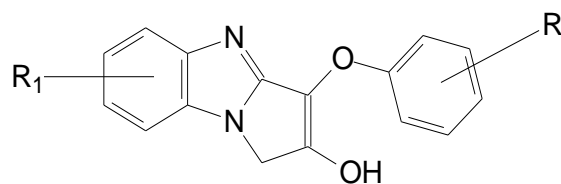
New benzimidazole and imidzopyridine derivatives were synthesized and investigated in vivo for their anti-inflammatory and analgesic activities. Some of the new compounds (IVc, IVf, and IVi) showed reasonable anti-inflammatory and analgesic activity in experimental rats in comparing to indomethacin and Diclofenac Na, as reference drugs. Moreover, some of the newly synthesized compounds tested as antimicrobial agents, IVh exhibited potent antimicrobial activities with low MIC in comparing with Cefoperazone and Fluconazole as reference drugs. Docking studies were carried out for derivatives of highest anti-inflammatory activity into the COX-2 binding site. Compounds IVc, IVf, and IVi revealed a similar binding mode to COX-2 inhibitor [105].



A series of novel 5-fluoro-2-[(2'-(1-trityl tetrazol-5-yl) biphenyl-4-yl) methyl] thio]-6-substituted-1H-benzimidazoles were prepared by alkylation of 6-substituted-2-mercapto-5-fluoro benzimidazoles with 5-[4'-(bromo methyl) biphenyl-2-yl]-1-trityl-1H-tetrazole. The synthesized compounds were screened against different strains of bacteria and fungi. The most active derivatives of the present series were the azole (imidazole and 1,2,4-triazole) substituted fluoro benzimidazoles and the para chloro phenyl ether analog indicating the importance of a halogenated diphenyl ether nucleus and the azole moiety at the 6th position. The results suggest that these three molecules are potential candidates for further development as antibacterial and antifungal agents [106].



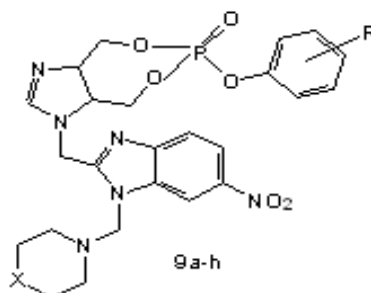
The novel Benzimidazole[a]pyrrol-(3-phenoxy)-3-yl-4-ol have been prepared by intramolecular cyclization intermediate 1-(1-H-benzo[d]imidazol-2-yl)-1-phenoxypropan-2-one and characterized by IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and GC-MS. Thus, the prepared compounds Benzimidazole[a]pyrrol-(3-phenoxy)-3-yl-4-ol has been screened antimicrobial activity, therefore all the compound shows very less active against standard [107].



R = p-CH<sub>3</sub>, m-CH<sub>3</sub>, p-Cl, p-Br, p-OCH<sub>3</sub>

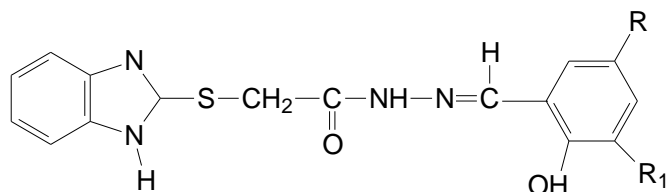
R<sub>1</sub> = H, NO<sub>2</sub>

New novelderivatives of 1-( ( 1 (piperidine-1-yl-methyl) / (morpholinomethyl) / (4-methylpiperazin-1-yl-methyl) )-6- nitro-1H-benzo [d] imidazol-2-yl ) methyl -6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-6-oxide (9a-h) The antibacterial activity of 1-((1(piperidine-1-yl-methyl)/(morpholinomethyl)/(4-methylpiperazin-1-yl-methyl) )-6-nitro- 1H-benzo [d] imidazol-2-yl ) methyl -6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-6-oxide (9a-h) were screened against the *Staphylococcus aureus* (gram positive) and *Escherichia coli* (gram negative) organisms. Most of the compounds exhibited good antibacterial activity against both bacterial strains. The presence of chloro and nitro in the structure has shown increased effect on their antibacterial activity [48]. Antifungal activity of 1-((1(piperidine-1-yl-methyl)/(morpholinomethyl)/(4-methylpiperazine-1-yl-methyl)-6-nitro- 1H-benzo [d] imidazol-2-yl) methyl-6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6- d]imidazole-6-oxide (9a-h) were screened against *Aspergillus niger*, *Candida albicans*[108,109].



|     | a               | b | c               | d                | e  | f  | g               | h                |
|-----|-----------------|---|-----------------|------------------|----|----|-----------------|------------------|
| R = | H               | H | CH <sub>3</sub> | OCH <sub>3</sub> | Cl | Br | NO <sub>2</sub> | H                |
| X = | CH <sub>2</sub> | O | O               | O                | O  | O  | O               | NCH <sub>3</sub> |

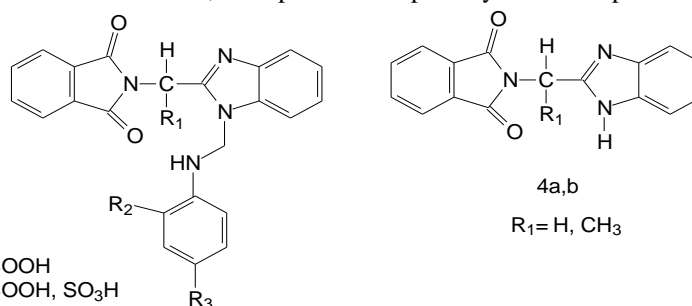
The oxovanadium (IV) complexes of the hydrazones derived from 2-benzimidazolyl mercaptoaceto hydrazide and o-hydroxy aromatic aldehydes have been described. The ligands and their oxovanadium (IV) complexes were screened for their antimicrobial activities[110].



R = H, Cl, Br, CH<sub>3</sub>

R<sub>1</sub> = H, OCH<sub>3</sub>

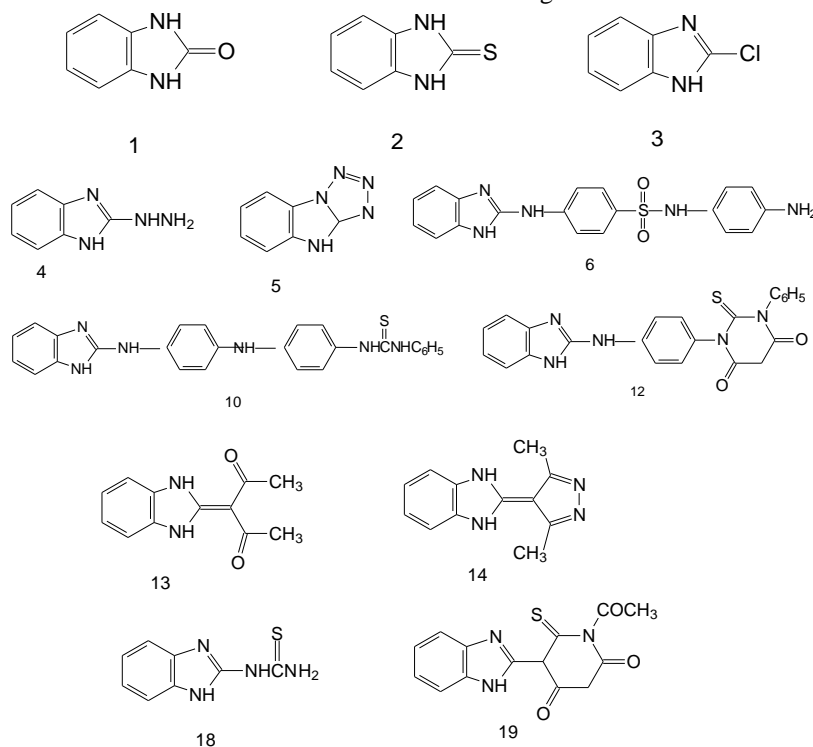
Two series of isoindoline carrying benzimidazoles (6a-n) were synthesized by mannich reaction of 2-alkyl benzimidazolyl isoindoline-1,3-dione with different aromatic primary amines using formaldehyde as condensing agent. The In-vitro anthelmintic screening of all benzimidazolyl isoindolines indicates that, have pronounced potency when compared to albendazole[111].



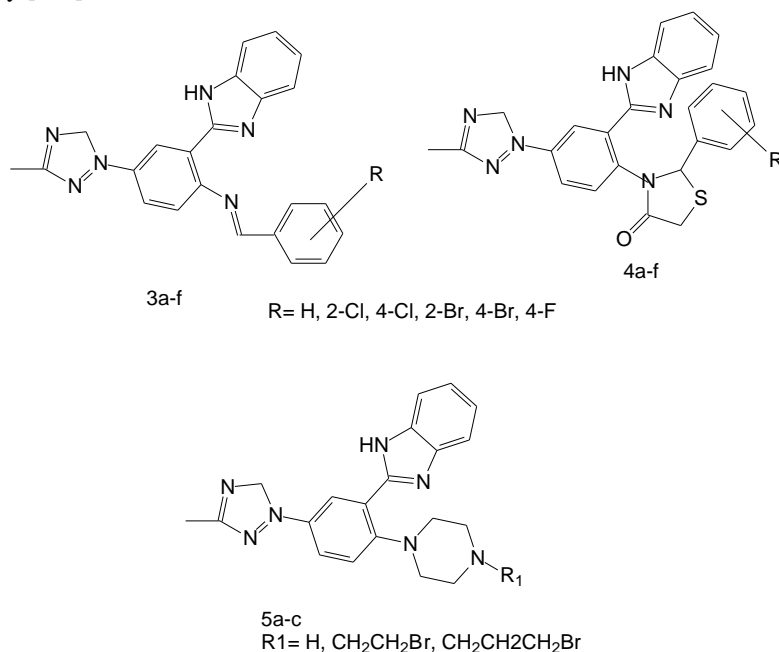
R<sub>1</sub> = H, CH<sub>3</sub>  
R<sub>2</sub> = H, OH, COOH  
R<sub>3</sub> = H, OH, COOH, SO<sub>3</sub>H

6a-n

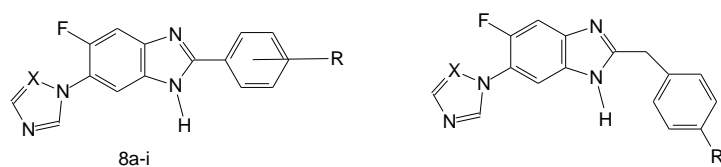
A new series of benzimidazole derivatives **1,2,3** are reported herein. Some of the newly synthesized derivatives (**4-6**, **10**, **12-14**, **18,19**) were screened for their antitumor activities and their molecular docking and the results were encouraging [112].



Several 2-[5-(3-Methyl-1H-1,2,4-triazolyl) substituted benzylideneanilin-2-yl] benzimidazole (**3a-f**), 2-[4-((3-Methyl-1H-1,2,4-triazolyl)-2-(2-substitutedphenylthiazolidinon-3-yl))phenyl] benzimidazole (**4a-f**) and 2-[[4-(3-Methyl-1H-1,2,4-triazolyl) substituted piperazinyl phenyl]]benzimidazole (**5a-c**) have been synthesized by conventional synthesis and microwave methodology. Furthermore the synthesized benzimidazoles (**3a-f**), (**4a-f**) and (**5a-c**) were screened for antimicrobial, insecticidal and anthelmintic activities. The compound **4e** displayed significant biological activities among the all synthesized derivatives and screened for the acute toxicity [113].



A series of thirteen imidazole and 1,2,4-triazole substituted fluoro benzimidazoles (**8a-i**), (**9a-b**) and (**11a-b**) with phenyl and benzyl group at 2nd position were synthesized and screened for antitubercular activity against H37RV strain and antifungal activity against *Candida* species. Both imidazole and 1,2,4-triazole substituted fluoro benzimidazoles with 2-benzyl and 4-N(CH<sub>3</sub>)<sub>2</sub> substituted 2-phenyl/2-phenyl-1-benzyl counterpart were found to be the most active of all the compounds. To examine the influence ofazole moiety on the activity chlorine substituted fluoro benzimidazole (**5**) was synthesized. In vitro antitubercular and antifungal activity data revealed that the benzimidazole scaffold with imidazole or triazole moiety were important for antitubercular and antifungal activity [114].

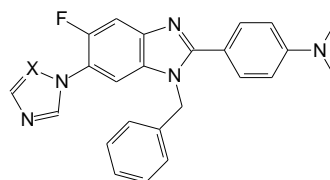
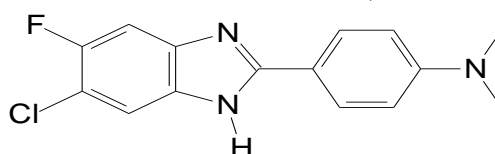


a,b,c,d

X= N, R= H, 4-Cl, 4-N(CH<sub>3</sub>)<sub>2</sub>, 3,4,5-(OCH<sub>3</sub>)<sub>3</sub>

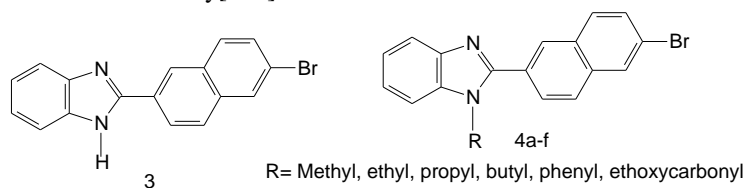
X=CH, R=H, 4-Cl

e,f,g,h,i

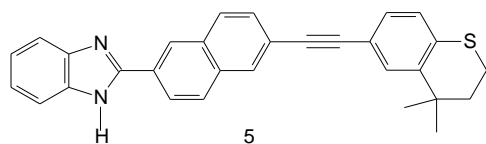
X=CH, R= H, 4-Cl, 4-OCH<sub>3</sub>, 4-N(CH<sub>3</sub>)<sub>2</sub>, 3,4,5-(OCH<sub>3</sub>)<sub>3</sub>11a-b  
X= CH, N

5

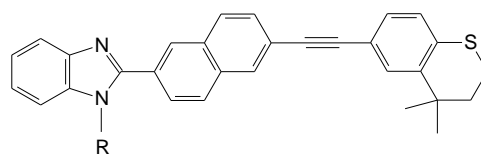
Series of new benzimidazole derivatives have been prepared starting with synthesis of 2-(6-bromo-2-naphthyl)-1H-benzimidazole by using ortho-phenyl diamine and 6-bromo-2-naphthoic acid. The compounds were further alkylated and acylated. The acetylene linkage was incorporated by reacting 6-ethynyl-4,4-dimethylthiochroman with 2-(6-bromo-2-naphthyl)-1H-benzimidazole via Sonogashira coupling resulting 2-(6-((4,4-dimethylthiochroman-6-yl)ethynyl)naphthalen-2-yl)-1H-benzimidazole. The newer benzimidazole derivatives were alkylated and acylated to obtain library of newer compounds. All the compounds were characterized by IR, <sup>1</sup>H NMR, <sup>13</sup>CMR and Mass spectroscopies. All newly synthesized benzimidazole derivatives were subjected for anthelmintic activity. To study the Anthelmintic activity Indian earthworm (*Pheretima postuma*) was used at the concentration 10 mg/ml and 20 mg/ml. Albendazole is used as reference standard. Overall study exhibited that all the compounds have moderate to excellent activity [115].



R= Methyl, ethyl, propyl, butyl, phenyl, ethoxycarbonyl



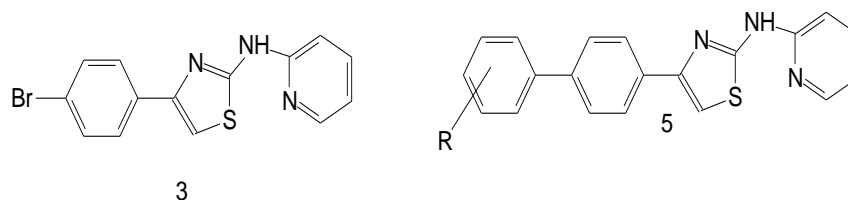
5



6a-g

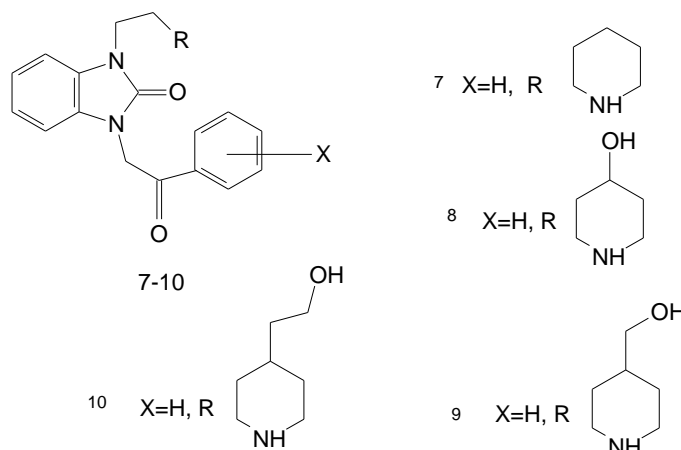
R= Methyl, ethyl, propyl, butyl, phenyl, ethoxycarbonyl, phenoxy carbonyl

4-Biphenyl substituted thiazolyl-Pyridin-2-amine derivatives were prepared by Suzuki coupling reaction, between N-[4-(4-Bromophenyl)-1,3-thiazol-2-yl]-pyridin-2-amine and substituted phenyl boronic acids. The new compounds were subjected to antibacterial, antiproliferative, anti-inflammatory and molecular docking studies. Among the compounds tested, N-[4-(4'-fluorobiphenyl-4-yl)-1,3-thiazol-2-yl]pyridine-2-amine and N-[4-(4'-(trifluoromethyl)biphenyl-4-yl)-1,3-thiazol-2-yl]pyridine-2-amine showed promising properties [116].

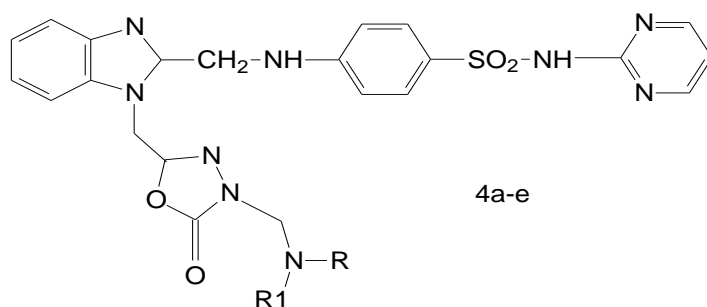


R= 3-OCH<sub>3</sub>, 4-F, 4-Cl, 4-CF<sub>3</sub>, 3-Cl, 4-NHCOCH<sub>3</sub>, 4-CN

Synthesis of some novel N1,N3-substituted 1-piperidin-4-yl-1,3-dihydro-2H-benzimidazol-2-one derivatives (7-10) were prepared from commercially available 1,2-phenylenediamine. Compounds (7-10) were tested for Gram positive: *Streptococcus pyogenes* and *Staphylococcus aureus*. Gram negative: *Escherichia coli*, *Pseudomonas arzenous*, *Proteus vulgaris*, *Salmonella typhi* bacterial cultures. Compounds 7-10 were found to be highly active against *Streptococcus pyogenes* and *Escherichia coli*[117].

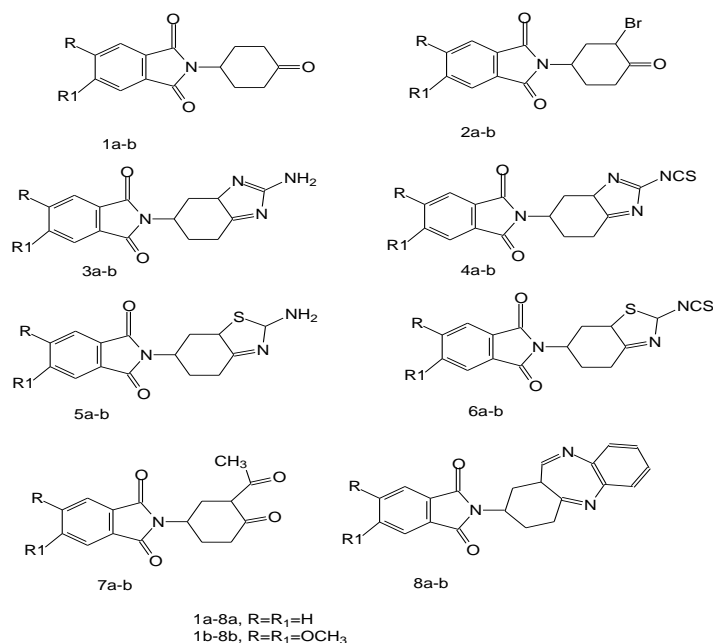


Novel heterocyclic compound namely, 4-((1-((4-((dialkylamino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)methylamino)-N-(pyrimidin-2-yl)benzenesulfonamide(4a-e) have been prepared by mannich reaction, a N-(pyrimidin-2-yl)-4-((1-((5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)methylamino)benzenesulfonamide(3) react with formaldehyde and different secondary amines. The compound (3) prepared from 4-((1-(2-hydrazinyl-2-oxoethyl)-1H-benzo[d]imidazol-2-yl)methylamino)-N-(pyrimidin-2-yl)benzenesulfonamide(2) with CS<sub>2</sub>/KOH. 4-((1H-benzo[d]imidazol-2-yl)methylamino)-N-(pyrimidin-2-yl)benzene sulfonamide(1) react with chloro acetic acid and hydrazine hydrate gives compound (2).The newly synthesized compounds were studied for their antibacterial and antifungal activities[118].

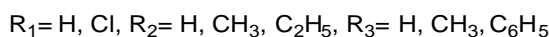
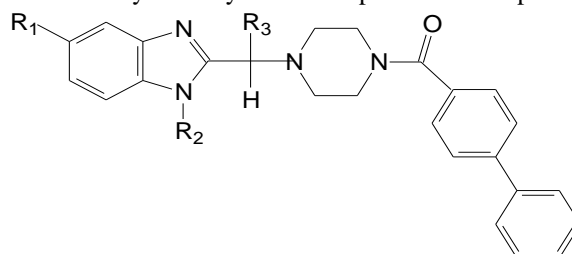


|                |    |    |    |    |    |
|----------------|----|----|----|----|----|
|                | 4a | 4b | 4c | 4d | 4e |
| R              | Me | Me | Et | Et | Ph |
| R <sub>1</sub> | Me | Et | Et | Ph | Ph |

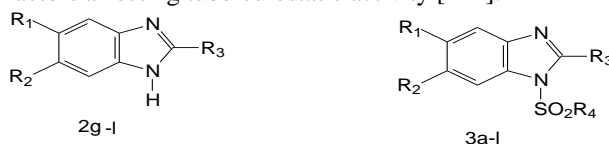
The synthesis of new phthalamide heterocycles and elucidates their biological activity. For the synthesis, phthalamide molecule was treated with various reagents as per the requirement of reaction and every time it results in the formation of novel derivatives of phthalamide. Derivatives obtained were bromo, benzimidazol, isothiocyanate, acetyl, benzothiazol, isothiocyanate and diazepin. Obtained derivatives further studied for their characterization using spectral techniques like IR, NMR and elemental analysis which established the structure of derivative. Derivatives tested for their antibacterial activity against gram positive and gram negative bacterial strains like *E. coli* and *S. aureus*[119].



A novel series of biphenyl carbonyl piperazine moiety carrying benzimidazole derivatives, based on an initial design by molecular docking study of this scaffold at the active site of the fungal enzyme of cytochrome P450 family, lanosterol 14  $\alpha$  - demethylase (CYP51) was synthesized by microwave irradiation. The synthesized compounds were characterized by elemental and spectral analysis (IR, <sup>1</sup>H NMR and mass spectrometry). The screening of the synthesized compounds for invitro antifungal activity against *Candida albicans* revealed activity in many of the compounds as comparable to that of ketoconazole [120].



A series of novel 2-(2-phenalkyl)-1H-benzo[d]imidazole derivatives and analogues (2a–3l) have been synthesized and evaluated for tuberculostatic activity. Benzimidazoles substituted at the C-2 position with phenethyl, styryl and 3,5-dichlorophenethyl moiety were obtained. Compounds 2g, 2h and 2i bearing methyl groups at the benzimidazole system and phenalkyl substituent at the C-2 positions showed high tuberculostatic activity against *Mycobacterium tuberculosis* strains with MIC values ranging from 0.8 to 6.2 lg/mL (2.5–25  $\mu$ M). More importantly, derivatives 2g (5,6-dimethyl-2-phenethyl-1H-benzo[d]imidazole) and 2i (2-(3,5-dichlorophenethyl)-5,6-dimethyl-1H-benzo[d]imidazole) appeared selective for *M. tuberculosis* as compared with eukaryotic cells: non-malignant (neonatal human dermal Fibro blasts) and malignant (mouse melanoma B16-F10 cell line). These compounds may thus represent a novel, selective class of anti-tubercular agents. SAR studies resulted in interesting conclusions on structural factors affecting tuberculostatic activity [121].

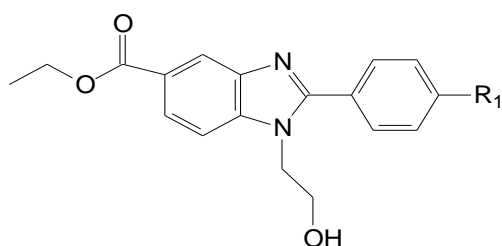


|    | R <sub>1</sub> | R <sub>2</sub> | R <sub>3</sub>                                 | R <sub>4</sub> |
|----|----------------|----------------|--|----------------|
| 3a | Me             | Me             | -CH <sub>2</sub> CH <sub>2</sub> Ph            | Me             |
| 3b | Me             | Me             | -CH=CH-Ph                                      | Me             |
| 3c | Me             | Me             | -CH <sub>2</sub> CH <sub>2</sub> -3,5-di-Cl-Ph | Me             |
| 3d | F              | H              | -CH <sub>2</sub> CH <sub>2</sub> Ph            | Me             |
| 3e | F              | H              | -CH=CH-Ph                                      | Me             |
| 3f | F              | H              | -CH <sub>2</sub> CH <sub>2</sub> -3,5-di-Cl-Ph | Me             |
| 3g | Me             | Me             | -CH <sub>2</sub> CH <sub>2</sub> Ph            | Ph             |
| 3h | Me             | Me             | -CH=CH-Ph                                      | Ph             |
| 3i | Me             | Me             | -CH <sub>2</sub> CH <sub>2</sub> -3,5-di-Cl-Ph | Ph             |
| 3j | F              | H              | -CH <sub>2</sub> CH <sub>2</sub> -Ph           | Ph             |
| 3k | F              | H              | -CH=CH-Ph                                      | Ph             |
| 3l | F              | H              | -CH <sub>2</sub> CH <sub>2</sub> -3,5-di-Cl-Ph | Ph             |

A total of 15 novel benzimidazole derivatives were designed, synthesized and evaluated for their SIRT1 and SIRT2 inhibitory activity. All compounds showed better inhibition on SIRT2 as compared to SIRT1. Among these, compound 5j displayed the best inhibitory activity for SIRT1 (IC<sub>50</sub> = 58.43  $\mu$ M) as well as for SIRT2 (IC<sub>50</sub> = 45.12  $\mu$ M). Cell cytotoxicity assays also showed that

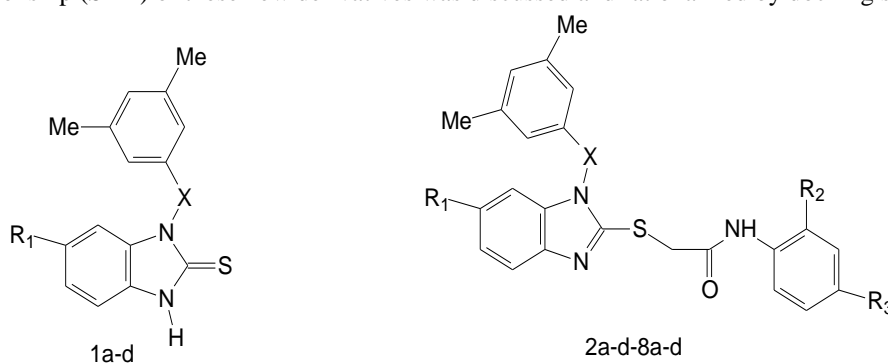


compound 5j possesses good antitumor activity against two different cancer cell lines derived from breast cancer (MCF-7 and MDA-MB-468). A simple structure–activity-relationship (SAR) study of the newly synthesized benzimidazole derivatives was also discussed[122].



R1= H (a), Br(b), Cl(c), OCF<sub>3</sub>(d), CF<sub>3</sub>(e), NO<sub>2</sub>(f),  
CH<sub>3</sub>(g), OH(h), OCH<sub>3</sub>(i), dimethylamine(j), piperidine(k), 1,3-dioxole(l)

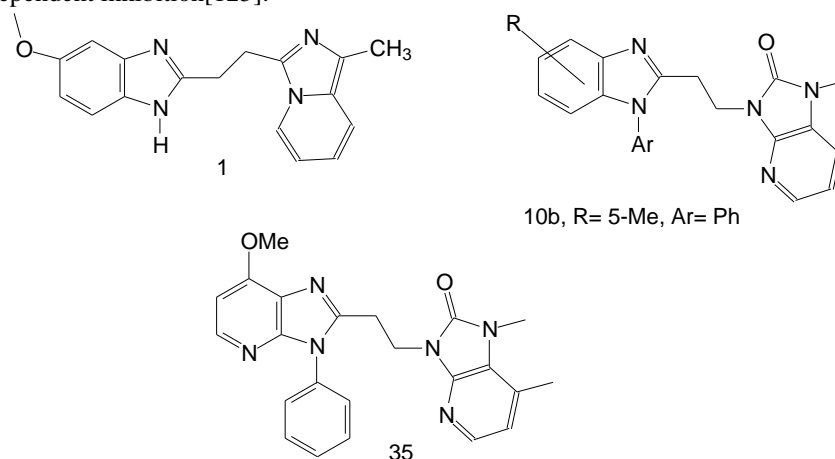
A series of novel N<sub>1</sub>-aryl-2-arylthioacetamido-benzimidazoles were synthesized and evaluated as inhibitors of human immunodeficiency virus type-1 (HIV-1). Some of them proved to be effective in inhibiting HIV-1 replication at submicromolar and nanomolar concentration acting as HIV-1 non-nucleoside RT inhibitors (NNRTIs), with low cytotoxicity. The preliminary structure–activity relationship (SAR) of these new derivatives was discussed and rationalized by docking studies [123].



R1= H,Cl, X= CH<sub>2</sub>, SO<sub>2</sub>, R<sub>2</sub>= Cl, R<sub>3</sub>= CH<sub>3</sub>, COOCH<sub>3</sub>, SO<sub>2</sub>CH<sub>3</sub>, SO<sub>2</sub>NH<sub>2</sub>

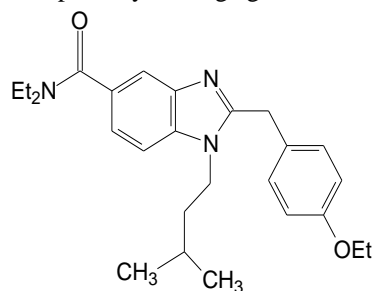
A series of 4,5,6,7-tetrahydro-1H-benzimidazole-5-carboxylic acid and 5,6,7,8-tetrahydroimidazo [1,2-a]pyridine-7-carboxylic acid derivatives designed as inhibitors of TAFIa has been prepared via a common hydrogenation–alkylation sequence starting from the appropriate benzimidazole and imidazopyridine system. A successful design strategy was presented using a conformational restriction approach resulting in potent and selective inhibitors of TAFIa. The X-ray structure of compound 5 in complex with a H333Y/H335Q double mutant TAFI indicate that the conformational restriction is responsible for the observed potency increase [124].

The identification of potent benzimidazoles as PDE10A inhibitors was report. The first identified imidazopyridine 1 as a high-throughput screening hit compound from an in-house library followed by optimization of the imidazopyridine moiety to improve inhibitory activity gave imidazopyridinone 10b. Following further structure–activity relationship development by reducing lipophilicity and introducing substituents, 35 was obtained , which exhibited both improved metabolic stability and reduced CYP3A4 time-dependent inhibition[125].

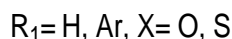
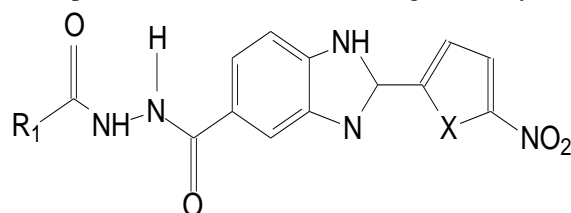


The design of bivalent ligands targeting G protein-coupled receptors (GPCRs) often leads to the development of new, highly selective and potent compounds. To date, no bivalent ligands for the human cannabinoid receptor type 2 (hCB2R) of the endocannabinoid system (ECS) are described. Therefore, two sets of homobivalent ligands containing as parent structure the hCB2R selective agonist 13a and coupled at different attachment positions were synthesized. Changes of the parent structure at these positions have a crucial effect on the potency and efficacy of the ligands. However, we discovered that bivalency has an

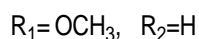
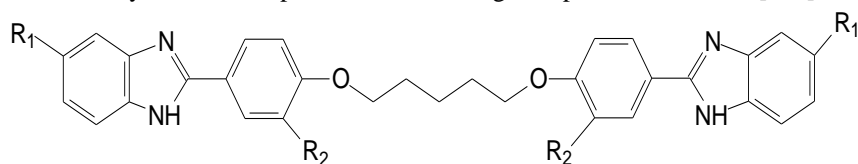
influence on the effect at both cannabinoid receptors. Moreover, we found out that the spacer length and the attachment position altered the efficacy of the bivalent ligands at the receptors by turning agonists into antagonists and inverse agonists[126].



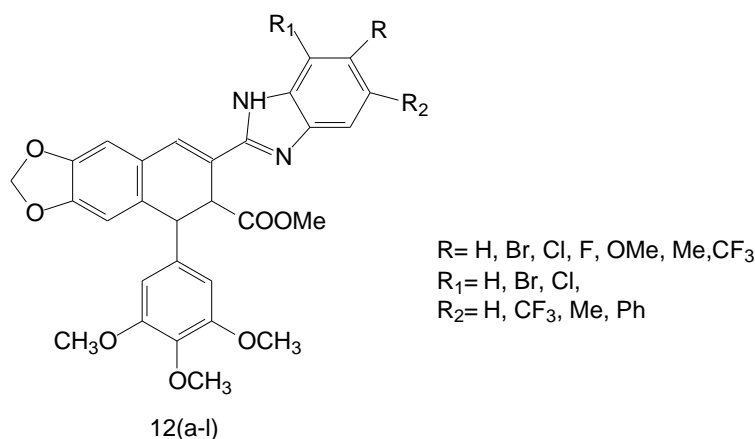
A series of N'-substituted-2-(5-nitrofuran or 5-nitrothiophen-2-yl)-3H-benzo[d]imidazole-5-carbohydrazone derivatives were synthesized and investigated for their abilities to inhibit  $\beta$ -hematin formation, hemoglobin hydrolysis and in vivo for their antimalarial efficacy in rodent *Plasmodium berghei*. Selected analogues were screened for their antitubercular activity against sensitive MTB H<sub>37</sub>Rv and multidrug-resistant MDR-MTB strains, and cytotoxic activity against a panel of human tumor cell lines and two nontumorigenic cell lines. Compounds 3a, 5a, f, 6g were the most promising as inhibitors of  $\beta$ -hematin formation, however, their effect as inhibitors of hemoglobin hydrolysis were marginal. The most active compounds to emerge from the in vitro and in vivo murine studies were 3a and 6i, suggesting an antimalarial activity via inhibition of  $\beta$ -hematin formation and are as efficient as chloroquine. The cytotoxic and antitubercular activities of the present compounds were not comparable with those of the standard drugs employed. But, however, compound 5b showed better antitubercular activity compared to rifampin against multidrug-resistant MDR-MTB strains. Compounds 3a, 6i and 5b showed a good safety index[127].



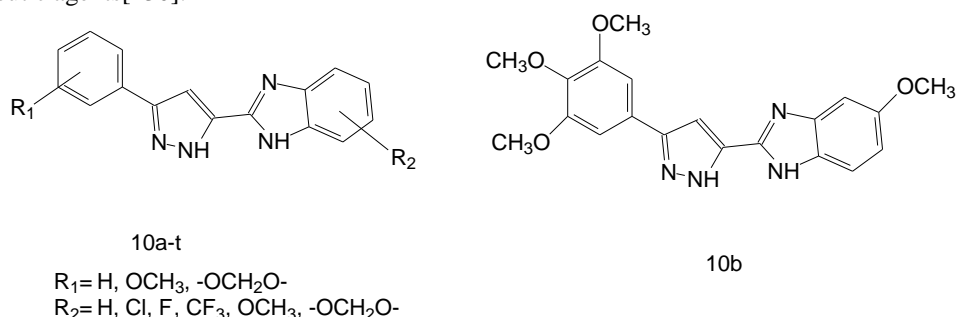
A series of ten novel hybrids from benzimidazole and pentamidine were prepared using a short synthetic route. Each compound was tested in vitro against the protozoa *Trichomonas vaginalis*, *Giardia lamblia*, *Entamoeba histolytica*, *Leishmania mexicana*, and *Plasmodium berghei*, in comparison with pentamidine and metronidazole. Some analogues showed high bioactivity in the low micromolar range ( $IC_{50} < 1 \mu\text{M}$ ) against the first four protozoa, which make them significantly more potent than either standard. 1,5-bis[4-(5-methoxy-1H-benzimidazole-2-yl)phenoxy]pentane (2) was 3- and 9-fold more potent against *G. lamblia* than metronidazole and pentamidine, respectively. This compound was 23-, 108-, and 13-fold more active than pentamidine against *T. vaginalis*, *E. histolytica* and *L. mexicana*, respectively. Studying further structure-activity relationships through the use of bioisosteric substitution in these hybrids should provide new leads against protozoal diseases[128].



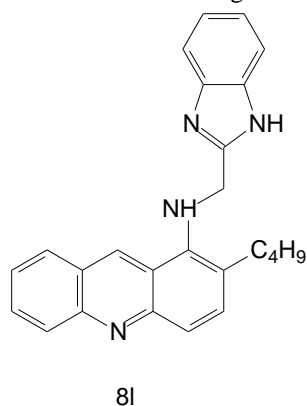
A series of new podophyllotoxin derivatives containing structural modifications at C-7, C-8, and C-9 were synthesized and evaluated for their cytotoxic activity against three human cancer cell lines. All the synthesized compounds showed significant growth inhibition with GI50 values in micromolar levels while some of the compounds were several times more potent against MCF-7 and HeLa cell lines than MIAPACA cell line. Three compounds (12a, 12d and 12e) emerged as potent compounds with broad spectrum of cytotoxic activity against all the tested cell lines with GI50 values in the range of 0.01–2.1  $\mu\text{M}$ . These compounds induce microtubule depolymerization and arrests cells at the G2/M phase of the cell cycle. Moreover, compounds 12d and 12e disrupted microtubule network and accumulated tubulin in the soluble fraction in a similar manner to their parent podophyllotoxin scaffold. In addition, structure activity relationship studies within the series were also discussed. Molecular docking studies of these compounds into the colchicine-binding site of tubulin, revealed possible mode of inhibition by these compounds[129].



In an attempt to develop potent and selective anticancer agents, a series of twenty arylpyrazole linked benzimidazole conjugates (10a–t) were designed and synthesized as microtubule destabilizing agents. The joining of arylpyrazole to the benzimidazole moiety resulted in a four ring (A, B, C and D) molecular scaffold that comprises of polar heterocyclic rings in the middle associated with rotatable single bonds and substituted aryl rings placed in the opposite directions. These conjugates were evaluated for their ability to inhibit the growth of sixty cancer cell line panel of the NCI. Among these some conjugates like 10a, 10b, 10d, 10e, 10p and 10r exhibited significant growth inhibitory activity against most of the cell lines ranging from 0.3 to 13  $\mu$ M. Interestingly, the conjugate 10b with methoxy group on D-ring expressed appreciable cytotoxic potential. A549 cells treated with some of the potent conjugates like 10a, 10b and 10d arrested cells at G2/M phase apart from activating cyclin-B1 protein levels and disrupting microtubule network. Moreover, these conjugates effectively inhibited tubulin polymerization with IC<sub>50</sub> values of 1.3–3.8  $\mu$ M. Whereas, the caspase assay revealed that they activate the caspase-3 leading to apoptosis. Particularly 10b having methoxy substituent induced activity almost 3 folds higher than CA-4. Furthermore, a competitive colchicine binding assay and molecular modeling analysis suggests that these conjugates bind to the tubulin successfully at the colchicine binding site. These investigations reveal that such conjugates having pyrazole and benzimidazole moieties have the potential in the development of newer chemotherapeutic agents [130].

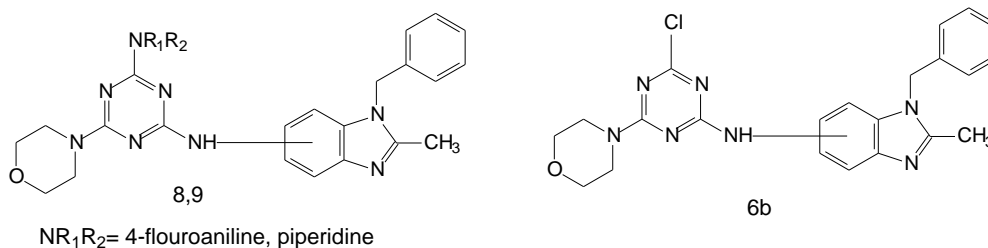


The discovery of new effective DNA-targeted antitumor agent is needed because of their clinical significance. As acridines can intercalate into DNA and benzimidazoles have the ability to bind in the DNA minor groove, a series of novel benzimidazole acridine derivatives were designed and synthesized to be new DNA-targeted compounds. MTT assay indicated that most of the synthesized compounds displayed good antiproliferative activity, among which compound 81 demonstrated the highest activity against both K562 and HepG-2 cells. Further experiments showed that 81 displayed good DNA-binding capability and inhibited topoisomerase I activity. Moreover, compound 81 could induce apoptosis in K562 cell lines through mitochondrial pathway. These data suggested that compound 81 might be potential as new DNA-binding and apoptosis-inducing antitumor agents [131].

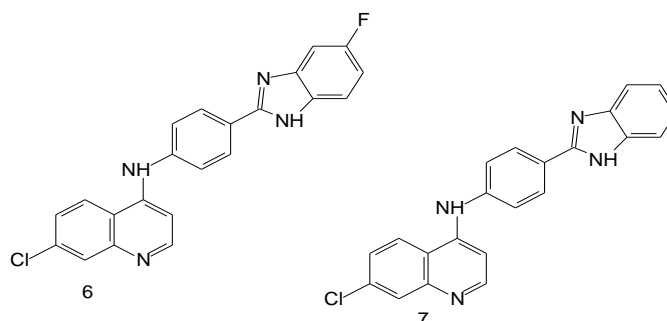
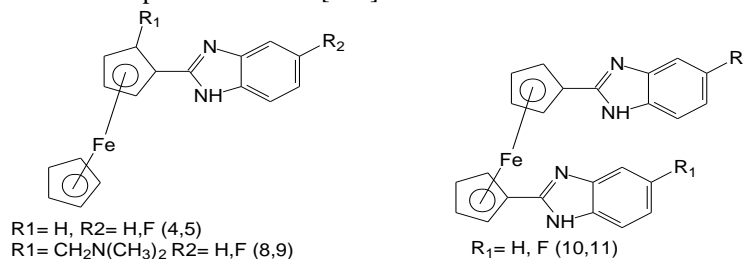


A new series of triazine–benzimidazole hybrids has been synthesized with different substitution of primary and secondary amines at one of the position of triazine in moderate to good yields. These compounds were evaluated for their inhibitory activities over 60 human tumor cell lines at one dose and five dose concentrations. Compounds 6b, 8 and 9 showed broad spectrum of antitumor activities with GI<sub>50</sub> values of 9.79, 2.58 and 3.81  $\mu$ M, respectively. DNA binding studies also indicated strong interaction properties of these compounds. These synthesized compounds also showed inhibition of mammalian

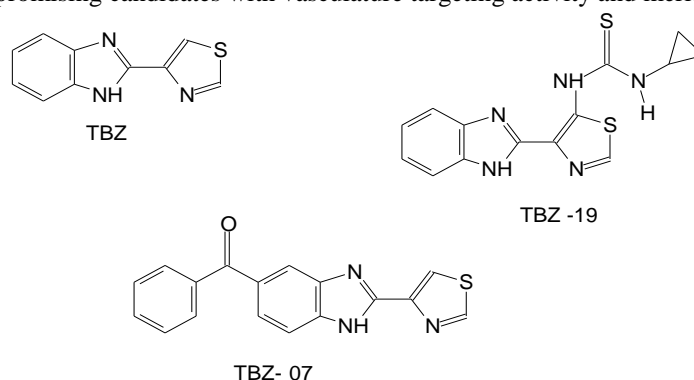
dihydrofolate reductase (DHFR). Compound 6b was depicted as the most active member of DHFR inhibitor with IC<sub>50</sub> value of 1.05 μM. Molecular modelling studies were used to identify the stabilized interactions of Compound 6b within the active site of enzyme for DHFR[132].



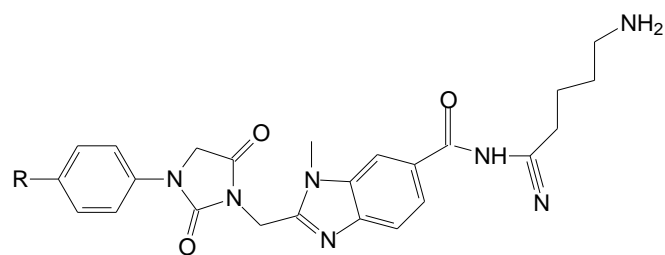
Three new series of benzimidazole derivatives were synthesized and evaluated *in vitro* against *Trypanosoma brucei gambiense*. All heterocyclic compounds were active *in vitro* with IC<sub>50</sub> values varying from 0.8 to 34 μM. Further pharmacomodulations are worth to be developed in this series[133].



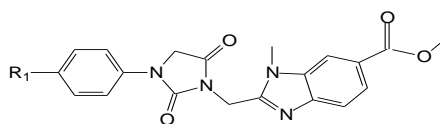
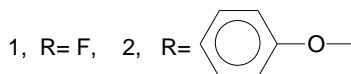
Thiabendazole, already approved by FDA for oral use as an anti-fungal and anti-helminthic drug since 1967, has recently been repurposed as a vascular disrupting agent. By optimization of the structure of the lead compound, we successfully identified compound TBZ-19 and the new derivative is over 100-fold more potent than the lead compound against the growth of four different cell lines (A549, HCT-116, HepG2 and HUVECs). The most potent two candidates TBZ-07 and TBZ-19, exhibiting moderate inhibitory cell proliferation activity, were also verified as anti-angiogenesis and vascular disrupting agents. Therefore, TBZ-07 and TBZ-19 would be promising candidates with vasculature targeting activity and merit further development[134].



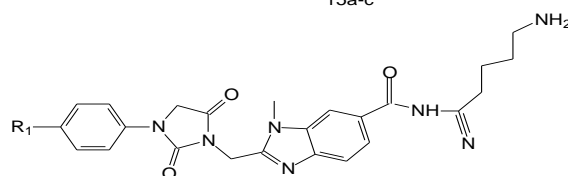
A series of plasmin inhibitors which were originally derived from the parent structure of **1** and **2**. Our efforts focused on the optimization of the P4 moiety of **2** and on the quest of alternative scaffold to pyrrolopyrimidine in the parent compounds. The results of the former gave us pivotal information on the further optimization of the P4 moiety in plasmin inhibitors and those of the latter revealed that appropriate moieties extending from the benzimidazole scaffold engaged with S4 pocket in the active site of plasmin [135].



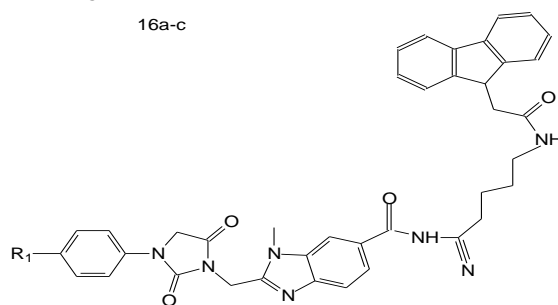
1 and 2



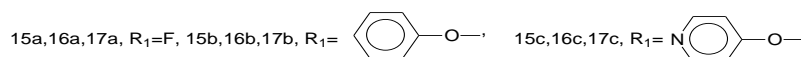
15a-c



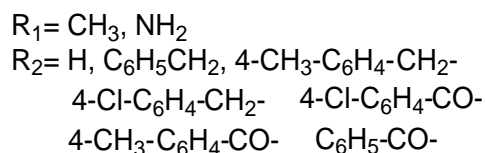
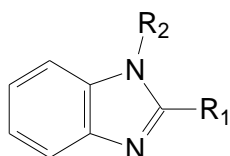
16a-c



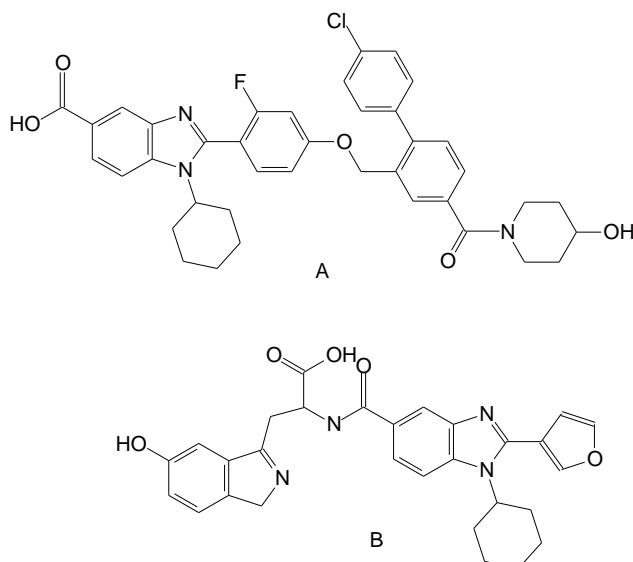
17a-c



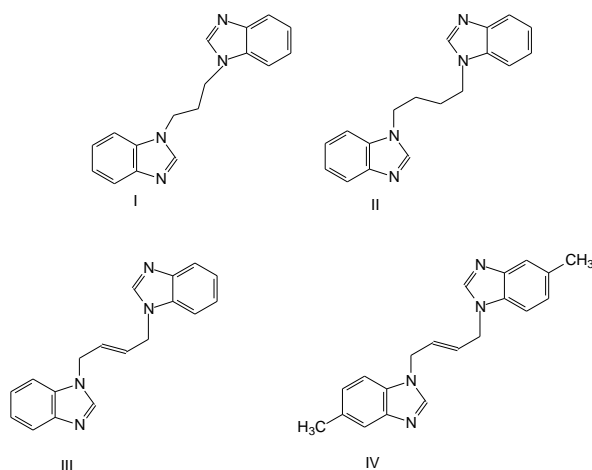
The antifungal activity of some 2-methyl and 2-aminobenzimidazole derivatives was evaluated against yeast *Saccharomyces cerevisiae*. The tested compounds displayed *in vitro* antifungal activity and minimum inhibitory concentration (MIC) was determined for all compounds. The partition coefficients of the studied compounds were measured by the shake flask method (log P) and by theoretical calculation (Clog P). The log P values were compared and the relationships between the logP values and antifungal activities were investigated. The mathematical models have been developed as calibration models for predicting the antifungal activity of this class of compounds. The quality of models was validated by the leave-one-out (LOO) technique as well as by the calculation of statistical parameters for the established models. The results may be useful for the designing of new more potent benzimidazole derivatives against yeast *Saccharomyces cerevisiae* [136].



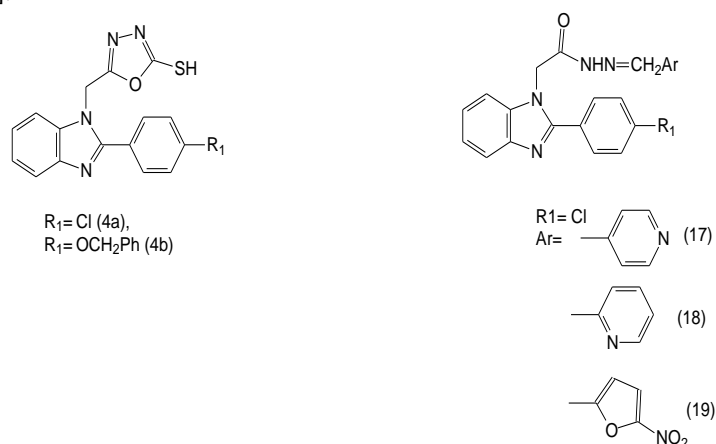
The RNA-dependent RNA polymerase of hepatitis C virus (HCV) is the catalytic subunit of the viral RNA amplification machinery and is an appealing target for the development of new therapeutic agents against HCV infection. Nonnucleoside inhibitors based on a benzimidazole scaffold have been recently reported. Compounds of this class are efficient inhibitors of HCV RNA replication in cell culture, thus providing attractive candidates for further development. Here the detailed analysis of the mechanism of action of selected benzimidazole inhibitors was reported [137].



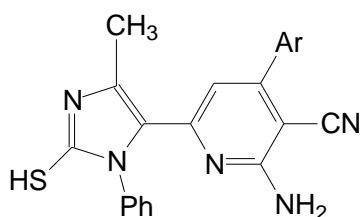
Some bis-benzimidazoles derivatives bearing allyl, crotyl, cinammyl, furfuryl, and thenyl groups were synthesized and their in vitro antimicrobial activity determined against gram-positive and gram-negative bacteria, and fungi by disk-diffusion method. All the synthesized compounds were examined for their in vitro antimicrobial activities against gram-positive (*Staphylococcus aureus* and *Bacillus megaterium*) and gram-negative bacteria (*Klebsiella pneumoniae* and *Escherichia coli*), and the yeasts like fungi (*Candida glabrata* and *Candida tropicalis*). Compared to the reference substances, Cefozine and nystatin, most of the compounds showed high antibacterial and antifungal activities against studied strains with inhibition zones between 8 and 28 mm[138].



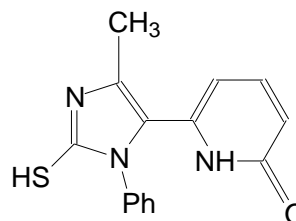
Some novel 2-(substitutedbenzylthio)-5-((2-(4-substitutedphenyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazoles (**5-12**) and 2-(2-(4-chlorophenyl)-1H-benzo[d]imidazol-1-yl)-N'-(arylmethylene)acetohydrazide derivatives (**13-22**) were prepared and their in vitro antioxidant properties were investigated by determination of rat liver microsomal NADPH-dependent inhibition of lipid peroxidation (LP) levels and microsomal ethoxyresoru\_n O-deethylase (EROD) activity. Compound **18** was found to be the most active compound with 100% inhibition on LP level and 92% inhibition on EROD. Compounds **4b**, **17**, and **19** showed the strongest inhibitory effect (97%) on EROD. The free radical scavenging capacities of the compounds were also tested in vitro determining the interaction of the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH), and compounds **4a** and **4b** exhibited good antioxidant activities[139].



The synthesis of a novel series of pyridine and bipyridine derivatives is described via one-pot multicomponent reaction of 5-acetylimidazole, malonitrile (or ethylcyanoacetate or diethylmalonate), substituted benzaldehyde (or terephthalaldehyde), and ammonium acetate in good yields. The structures of all the new compounds were elucidated on the basis of elemental analysis and spectral data. The antimicrobial activities of the synthesized compounds were screened and the results showed that most of such compounds exhibit considerable activities. Furthermore, some of the newly synthesized compounds were screened for their anticancer activity against human breast cell line (MCF-7) and liver carcinoma cell line (HEPG2) in comparison to doxorubicin. Most of the tested compounds exhibited promising activity [140].

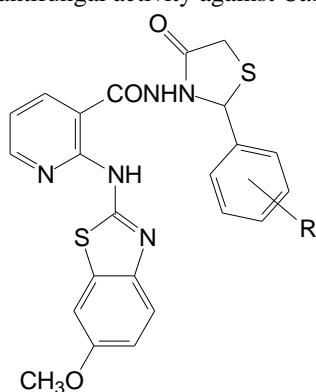
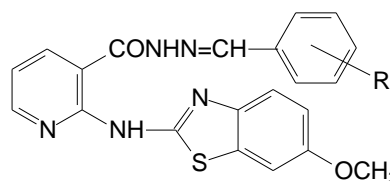


4a-e



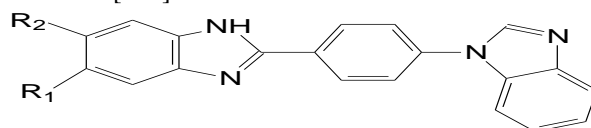
6a-e

A novel series of Schiff bases 5a-j and 4-thiazolidinones 6a-j have been prepared from the building blocks 2-chloro pyridine-3-carboxylic acid [1] and 2-amino-6-methoxy-benzothiazole [2]. These newly synthesized compounds were screened for their antimicrobial activity. Variable and modest activity was observed against the investigated strains of bacteria and fungi, however, compound 6h revealed significant antibacterial activity against *Escherichia coli*. Compounds 1, 2, 3, 5c, 5g and 5h, on the other hand, revealed potent antifungal activity against *Candida albicans* compared to the reference drug greseofulvin[141].

6h, R= 3-OCH<sub>3</sub>, 4-OH

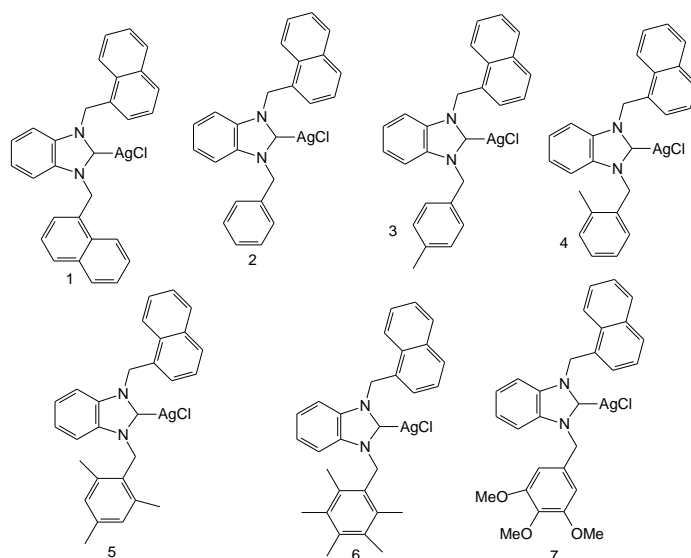
5c, R= 4-Cl  
 5g, R= 4-OCH<sub>3</sub>  
 5h, R= 3-OCH<sub>3</sub>, 4-OH

A new class of 2-[4-(1H-benzimidazol-1-yl)phenyl]-1H-benzimidazoles (13-22) were synthesized via cyclo condensation reaction of the substituted 1,2-phenylenediamines (1, 4-12) and 1-(4-formylphenyl)-1H-benzimidazole (3). The synthesized compounds were evaluated for antibacterial and antifungal activities against *S. aureus*, methicillin resistant *Staphylococcus aureus* (MRSA), and *Candida albicans* by the tube dilution method. Compounds 13, 15, 18, 20, and 21 have moderate antifungal activity against *C. albicans*[142].

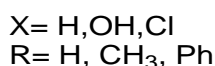
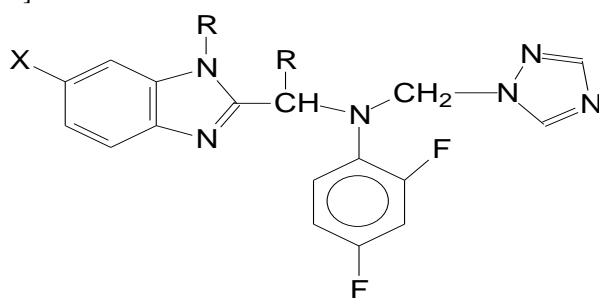


|    | R <sub>1</sub>  | R <sub>2</sub>  |
|----|-----------------|-----------------|
| 13 | H               | H               |
| 15 | CN              | H               |
| 18 | Cl              | H               |
| 20 | CH <sub>3</sub> | CH <sub>3</sub> |
| 21 | Cl              | CH <sub>3</sub> |

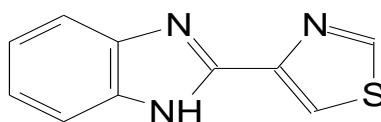
Seven novel naphthalen-1-ylmethyl substituted silver N-heterocyclic carbene (Ag-NHC) complexes (1-7) were synthesized by the interaction of benzimidazolium salts with silver carbonate in dry dichloromethane at room temperature and characterized by means of spectroscopic methods and elemental analysis techniques. The Ag-NHC compounds were tested for their in vitro antibacterial and antifungal activity against *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Candida albicans* and *Candida tropicalis* and showed high antimicrobial activities. The synthesized complexes, in particular, demonstrated better results against both fungi and gram-positive bacteria[143].



A novel series of compounds containing tertiary amine moiety, substituted benzimidazole and triazole ring, initial design by molecular docking study of this scaffold at the active site of the fungal enzymes lanosterol 14a-demethylase (homology modeled of *C. albicans*) was synthesized by microwave irradiation and characterized by Proton Nuclear Magnetic Resonance ( $^1\text{H NMR}$ ), Infra Red (IR), and Mass Spectroscopy (MS), and by elemental analysis. The screening of compound for in vitro (turbidimetric method) and in vivo (kidney burden test) antifungal activity against *C. albicans* revealed activity in many of the compounds as comparable to that of Fluconazole[144].



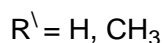
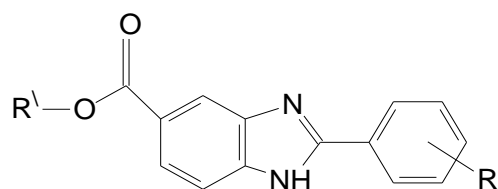
The interaction between thiabendazole (TBZ) and calf-thymus DNA (ct-DNA) was studied by experimental and molecular modeling methods. The intrinsic fluorescence of TBZ was quenched in the presence of ct-DNA. In competition experiments, TBZ could displace Hoechst 33258 (a minor groove binder to DNA), whereas it was unable to replace ethidium bromide (an intercalator). Potassium iodide could quench the fluorescence of TBZ, which indicated the nonintercalative mode of binding of TBZ to ct-DNA. UV absorbance of TBZ shows hyperchromic effect on the addition of DNA to the solution with negligible shift in wavelength. Salt effect studies showed the non-electrostatic nature of binding of TBZ to DNA. The viscosity of ct-DNA solution was almost unchanged on addition of TBZ. Circular dichroism (CD) spectra of DNA showed small changes in the presence of TBZ which is in agreement with groove binding mode of interaction. Moreover, from molecular modeling methods, a docked structure with minimum energy was obtained in which TBZ was located in minor grooves of ct-DNA[145].



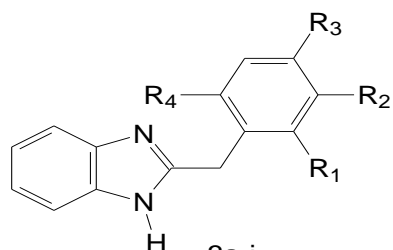
TBZ

A series of novel substituted 2-(phenyl)-3H-benzo[d]imidazole-5-carboxylic acids (1a–1j) and its methyl esters (2a–2f) were synthesized and examined for their antiproliferative effects against three breast cancer cell lines (MDA-MB231, MDA-MB468 and MCF7) in vitro. Most of the compounds exhibited comparable or greater antiproliferative effects than the reference compound cisplatin. Compound 2e bearing 5-fluoro-2-hydroxyphenyl substituent was found to be the most active derivative of the series with GI50 values of 6.23, 4.09 and 0.18  $\mu\text{M}$  against MDAMB468, MDA-MB231 and MCF7 breast cancer cell lines, respectively. Our findings described here exemplify the usefulness of the title compounds as a lead for the development of more effective cancer therapeutics for the treatment of breast cancer [146].

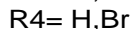
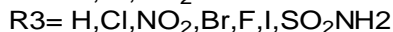
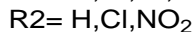
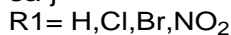




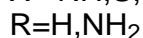
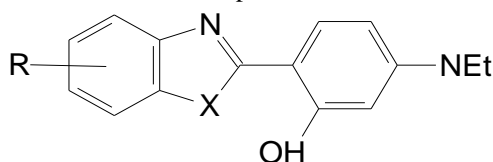
A novel series of 2-substituted benzimidazole derivatives (3a–3j) were synthesized by the reaction of 2-chloro methyl benzimidazole with substituted primary aromatic amines. The synthesized derivatives were screened for analgesic and anti-inflammatory activities. All the compounds showed significant effect [147].



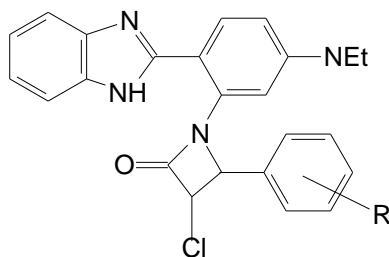
3a-j



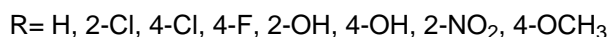
In an endeavor to find a new class of antimicrobial agents, a series of 2-(1H-benzimidazol-2-yl)-5-(diethylamino)phenol, 2-(1,3-benzoxazol-2-yl)-5-(diethylamino)phenol, 2-(1,3-benzothiazol-2-yl)-5-(diethylamino)phenol and their derivatives were synthesized starting from p-N,N-diethyl amino salicylaldehyde with different substituted o-phenylenediamine or o-aminophenol or o-aminothiophenol. All compounds were evaluated for in vitro antibacterial activities against *Escherichia coli* and *Staphylococcus aureus* strains and in vitro antifungal activity against *Candida albicans* and *Aspergillus niger* strains by using serial dilution method [148]. The antibacterial activities were expressed as the minimum inhibitory concentration (MIC) in lg/mL.



In the present investigation synthesis of some novel 1-(2-(1H-benzimidazol-2-yl)phenyl)-3-chloro-4-(Un/substitutedphenyl)azetidin-2-one (3a–3h) was reported. The newly synthesized compounds were screened for analgesic and anti-inflammatory activities on acetic acid induced writhing in mice and carrageenan induced paw edema in rats. Compound 3 g was found to have potent analgesic (46% at 20 mg/kg b.w) and anti-inflammatory (66.5% at 20 mg/kg b.w) activities as compared to standard drug nimesulide (20 mg/kg b.w). To check binding modes and binding affinity of the synthesized compounds, they docked into the active sites of enzyme COX-II. Compounds 3a, 3e and 3 h were found to have good affinity for COX-II. A good correlation was found between in silico docking analysis and in biological screening [149].

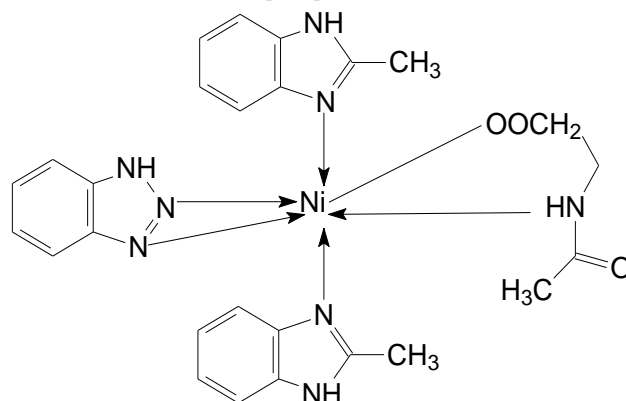


3a-h

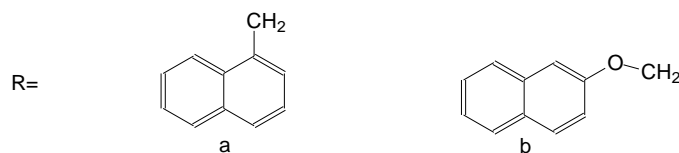
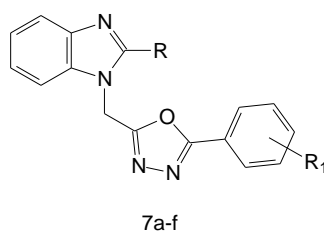
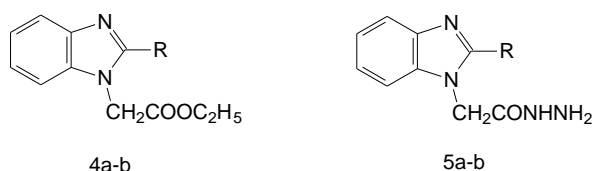


Synthesis and characterization of Mn(II), Ni(II), Cd(II) and Pb(II) mixed ligand complexes of 2-methylbenzimidazole with other ligands have been reported. The structure of the ligands and their complexes was investigated using elemental analysis, IR, UV-Vis, (1H, 13C) NMR spectroscopy, molar conductivity and magnetic susceptibility measurements. In all the studies of complexes, the 2-methylbenzimidazole behaves as a neutral monodentate ligand which is coordinated with the metal ions through

the N atom. While benzotriazole behaves as a neutral bidentate ligand which is coordinated with the Ni(II) ion through the two N atoms. Moreover, the N-acetylglycine behaves as a bidentate ligand which is coordinated with the Mn(II), Ni(II) and Pb(II) ions through the N atom and the terminal carboxyl oxygen atom. The magnetic and spectral data indicate the tetrahedral geometry for Mn(II) complex, irregular tetrahedral geometry for Pb(II) complex and octahedral geometry for Ni(II) complex. The X-ray single crystal diffraction method was used to confirm a centrosymmetric dinuclear Cd(II) complex as each two metal ions are linked by a pair of thiocyanate N= S bridge. Two 2-methylbenzimidazole N-atom donors and one terminal thiocyanate N atom complete a highly distorted square pyramid geometry around the Cd atom. Besides, different cell types were used to determine the inhibitory effect of Mn(II), Ni(II), Cd(II) and Pb(II) complexes on cell growth using MTT assay. Cd(II) complex showed cytotoxic effect on various types of cancer cell lines with different EC50 values[150].

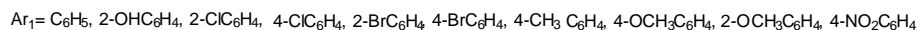
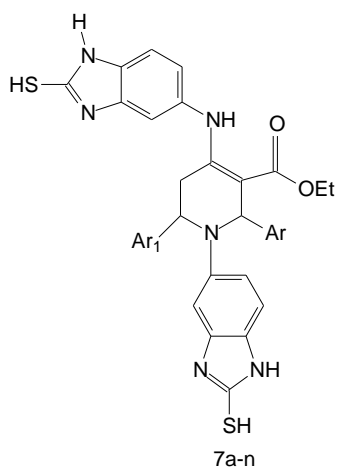


O-phenylenediamine and naphthene-1-acetic acid/2-naphthoxyacetic acid were used as a starting material through a series of steps and 2-(naphthalen-1-ylmethyl/Naphthalen- 2-yloxymethyl)-1H-benzimidazol-1-yl]acetohydrazide 5a, 5b were obtained. In the first series 1,3,4-oxadiazole derivatives have been synthesized from Schiff base of the corresponding hydrazide i.e. 2-[2-(naphthalen-1-ylmethyl)-1H-benzimidazol-1-yl]acetohydrazide 5a by using Chloramin-T. In the second series 1,3,4-oxadiazole has been synthesized from 2-{2-[(naphthalen-2-yloxy)- methyl]-1Hbenzimidazol-1-yl}acetohydrazide 5b by using phosphorous oxychloride and aromatic acid. These compounds were evaluated by IR, NMR, Mass spectrometry, elemental analysis and finally in vitro anticancer evaluation was carried out by NCI 60 Cell screen at a single high dose (10<sup>-5</sup> M) on various panel/cell lines. One compound 7c was found to be the most active on breast cancer cell line and compounds 4b and 7d were moderately active[151].

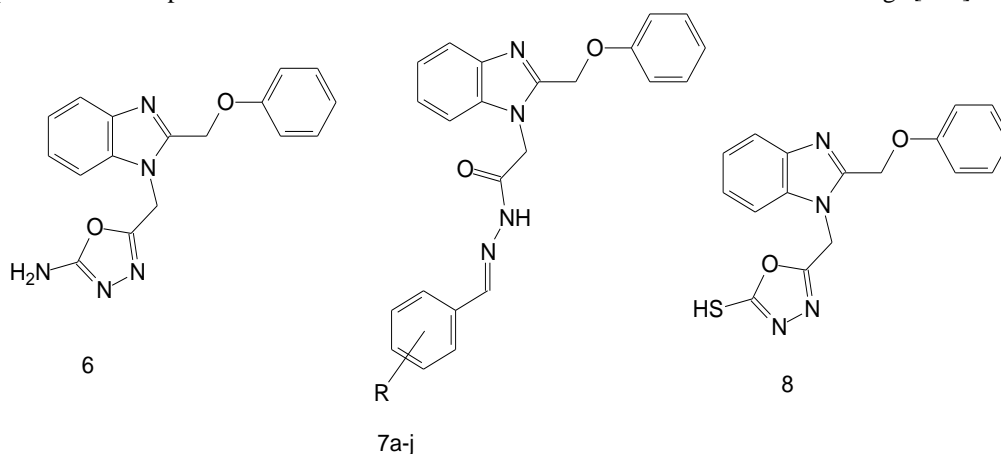


R<sub>1</sub>= H, 4-Cl, 4-NO<sub>2</sub>, 4-OCH<sub>3</sub>, 4-dimethylamino, 2-OH

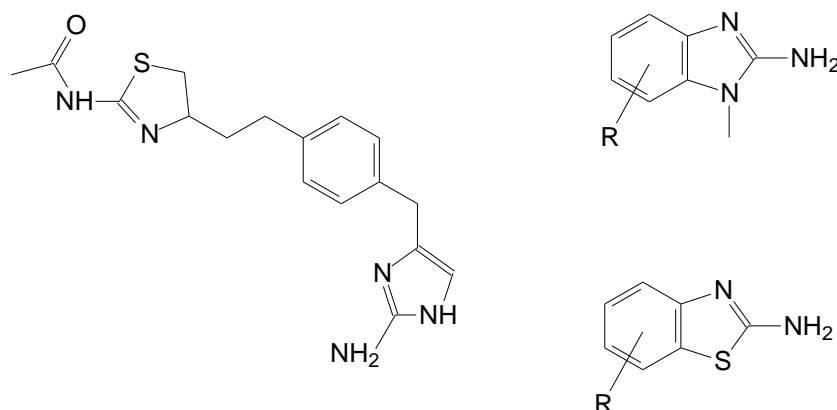
A series of novel benzo[d]imidazolyl tetrahydropyridine carboxylates 7a–n have been synthesized by one-pot multi-component reaction of (E)-5-(benzylidene amino)-1H-benzo[d]imidazole- 2-thiol 3, 5-amino-2-mercapto-benzimidazole 4, aromatic aldehyde 5, and ethyl acetoacetate 6 in acetonitrile using ceric ammonium nitrate (CAN) as Lewis acid catalyst, and evaluated for their anti-inflammatory, antioxidant, antibacterial and antifungal activities. All tested compounds showed appreciable activity against the standard drugs [152].



O-phenylenediamine and phenoxyacetic acid were used as starting material through series of steps 2-[2-(phenoxy-methyl)-1H-benzimidazol-1-yl]acetohydrazide 5 was obtained. Various derivatives of 2-[2-(phenoxy-methyl)-1H-benzimidazol-1-yl]-N0-[(Z)-phenylmethylidene]acetohydrazide and some compounds containing oxadiazole bearing benzimidazole were synthesized by using various aromatic aldehydes, cyanogens bromide and carbon disulfide/potassiumhydroxide. These were elucidated by IR, NMR and elemental analysis and their *in vivo* anticonvulsantscreening was performed using MES and scPTZ. Two compounds 7g and j were found to be potent and their protective index was found to be better than that of the standard drugs [153].

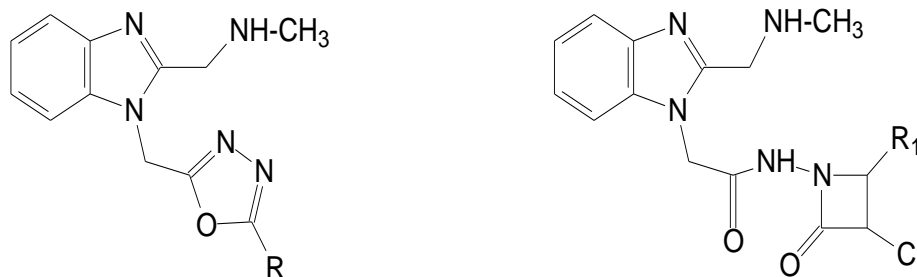


Novel thiazole derivatives were synthesized and evaluated as vascular adhesion protein-1 (VAP-1) inhibitors. Although we previously identified compound (2) with potent VAP-1 inhibitory activity in rats, the human activity was relatively weak. Here, to improve the human VAP-1 inhibitory activity of compound 2, we first evaluated the structure-activity relationships of guanidine bioisosteres as simple small molecules and identified a 1H-benzimidazol-2-amine (5) with potent activity compared to phenylguanidine (1). Based on the structure of compound 5, we synthesized a highly potent VAP-1 inhibitor (37b; human IC<sub>50</sub> = 0.019 μM, rat IC<sub>50</sub> = 0.0051 μM). Orally administered compound 37b also markedly inhibited ocular permeability in streptozotocin-induced diabetic rats after oral administration, suggesting it is a promising compound for the treatment of diabetic macular edema [154].

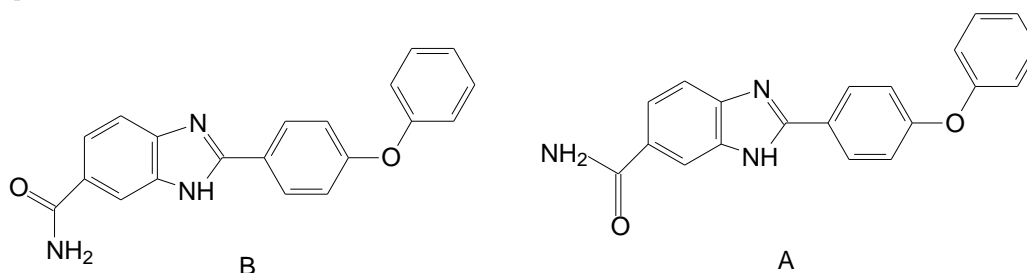


In a wide search program for new and efficient antimicrobial agents, a series of oxadiazole/azetidinone-incorporated benzimidazoles have been synthesized and evaluated against different Gram-positive and Gram-negative bacteria. Derivatives

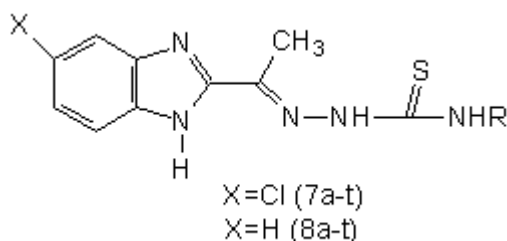
having long alkyl chain on the oxadiazole/azetidinone moiety with three or more carbon atoms have shown less antibacterial activity[155].



Two closely related binding modes have previously been proposed for the ATP-competitive benzimidazole class of checkpoint kinase 2 (CHK2) inhibitors; however, neither binding mode is entirely consistent with the reported SAR. Unconstrained rigid docking of benzimidazole ligands into representative CHK2 protein crystal structures reveals an alternative binding mode involving a water-mediated interaction with the hinge region; docking which incorporates protein side chain flexibility for selected residues in the ATP binding site resulted in a refinement of the water-mediated hinge binding mode that is consistent with observed SAR. The flexible docking results are in good agreement with the crystal structures of four exemplar benzimidazole ligands bound to CHK2 which unambiguously confirmed the binding mode of these inhibitors, including the water-mediated interaction with the hinge region, and which is significantly different from binding modes previously postulated in the literature[156].

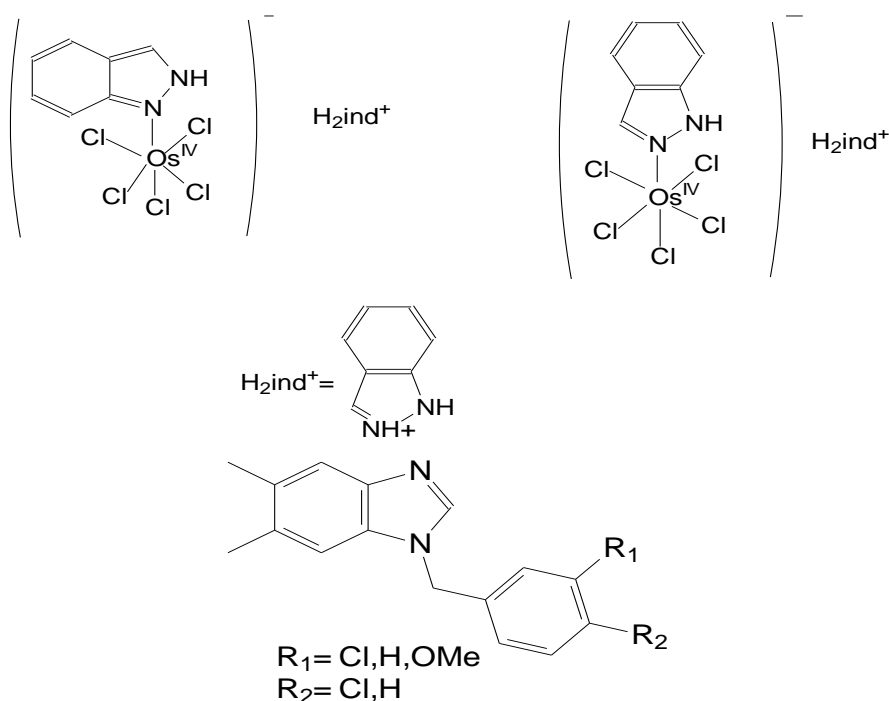


A series of (E)-2-[5-chloro-1-(1H-benzo[d]imidazol-2-yl)ethylidene] N-(substituted)hydrazine carbothioamide (7a–7t) and (E)-2-[1-(1H-benzo[d]imidazol-2-yl)ethylidene] N-(substituted)hydrazine carbothioamide (8a–8t) were prepared via the synthesis of 1-(substituted-1H-benzimidazol-2-yl) ethanol (3a–3b) which was synthesized by the condensation of substituted-phenylenediamine (2a–2b) with DL-lactic acid (1) followed by oxidation with sodium hypochlorite in mild acidic condition to form the corresponding ketones 4a–4b. Final compounds were formed by condensation of 4a–4b with different thiosemicarbazides 6a–6t. A total of 40 compounds were synthesized and characterized by FT-IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, Mass spectral technique and elemental analysis, in addition they were evaluated for anti-malarial properties. Among the compounds tested 7o, 7p, 7q, 7r, 7s, 8e and 8h exhibited good antimalarial activity in vitro[157].

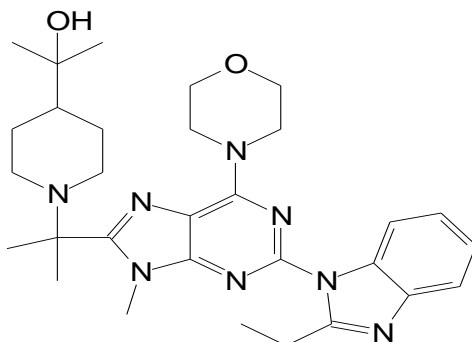


A one-pot synthesis of osmium(IV) complexes with two different tautomers of indazole, 1H-indazole and 2H-indazole, namely (H2ind)[Os<sup>IV</sup>Cl<sub>5</sub>(2H-ind)] (1) and (H2ind)[Os<sup>IV</sup>Cl<sub>5</sub>(1H-ind)] (2) is reported. The synthesized compounds were tested for their antiproliferative activity in vitro in three human cancer cell lines, CH1 (ovarian carcinoma), A549 (non-small cell lung cancer) and SW480 (colon carcinoma), as well as in vivo in a Hep3B SCID mouse xenotransplantation model. 2H-Indazole tautomer stabilization in 1 has been confirmed by X-ray diffraction[158].

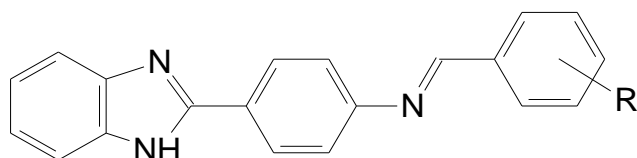
The enoyl acyl-carrier protein reductase (ENR) enzyme of the apicomplexan parasite family has been intensely studied for antiparasitic drug design for over a decade, with the most potent inhibitors targeting the NAD<sup>+</sup> bound form of the enzyme. However, the higher affinity for the NADH co-factor over NAD<sup>+</sup> and its availability in the natural environment makes the NADH complex form of ENR an attractive target. Herein, we have examined a benzimidazole family of inhibitors which target the NADH form of Francisella ENR, but despite good efficacy against *Toxoplasma gondii*, the IC<sub>50</sub> for *T. gondii* ENR is poor, with no inhibitory activity at 1 μM. Moreover similar benzimidazole scaffolds are potent against fungi which lack the ENR enzyme and as such we believe that there may be significant off target effects for this family of inhibitors [159].



In an effort to identify potent and isoform selective inhibitors of PI3K $\delta$ , GNE-293 (34) was identified. Inhibitor 2 was found to induce micronuclei formation in both the MNT and HCA in vitro assays. Compounds testing negative for genotoxicity were successfully identified through modifications of the 2-benzimidazole substituent and the methylene moiety to disrupt planarity. A variety of heteroatom linkers were explored to examine their effect on potency and isoform selectivity by restricting torsional angles to favor ligand interactions with PI3K $\delta$ 's Trp760. These modifications also resulted in an improved in vivo pharmacokinetic profile [160].

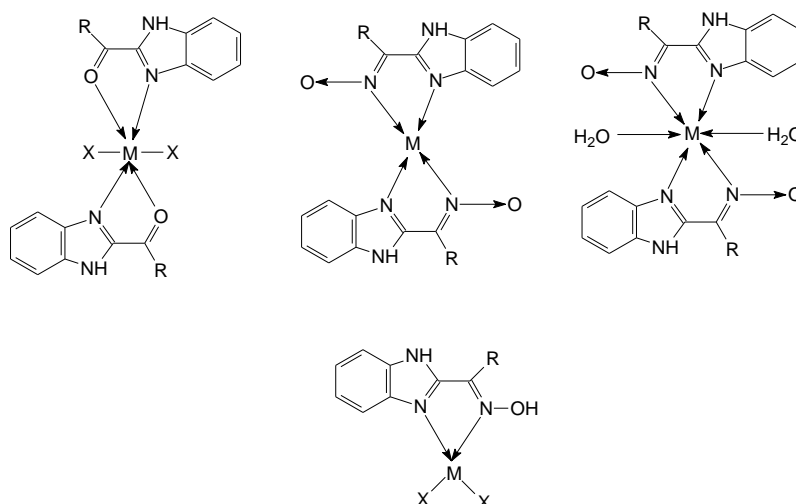


A novel series of 2-phenyl benzimidazole derivatives were synthesised by cyclocondensation with appropriate reagents. All of the synthesized compounds were evaluated for antibacterial activity against gram-positive bacterial strains like *Bacillus subtilis* and *Streptococcus aureus*, and gram-negative bacterial strains like *Escherichia coli* and *Pseudomonas aeruginosa*. Some of the compounds inhibited the growth of gram-positive bacteria (*B. subtilis* and *S. aureus*) at MIC values between 10 and 100 mg/mL. Some of the compounds exhibit antimicrobial activity against gram negative bacteria (*E. coli* and *P. Aeruginosa*) MIC values between 10 and 100 mg/mL [161].



$R = H, 2-OH, 3-NO_2, 3-OCH_3, 4-OCH_3$

The complexes of Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) with 1E-1-(1H-Benzimidazol-2-yl)-N-hydroxy-ethanimine (Hbhe) and 1E-1-(1H-Benzimidazol-2-yl)-N-hydroxy-1 phenylmethanimine (Hbhpm) of compositions  $[M(HL)_2Cl_2]$ , ( $M = CoII$ , or NiII and  $HL = Hbhe$  or Hbhpm),  $[M(HL)X_2]$ , ( $M = CuII$ , ZnII or CdII,  $HL = Hbhe$  or Hbhpm and  $X = Cl$  or Br) and  $ML_2 \cdot nH_2O$ , ( $M = CoII$ , NiII, CuII, ZnII or CdII,  $HL = Hbhe$  or Hbhpm and  $n = 0$  or 2) have been prepared and characterized. The anti-fungal activity of ligands and neutral bis-chelates  $ML_2 \cdot nH_2O$  was investigated by growth inhibition method. The complexes exhibited enhanced activity than free ligands [162].



M= Cu(II), Co(II), Ni(II), Zn(II), Cd(II)

## Conclusion

The benzimidazole ring is an important pharmacophore in modern drug discovery. Attention has been increasingly given to the synthesis of benzimidazole derivatives as a source of new antimicrobial agents. Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities like anti-microbial, anti-viral, anti-diabetic, and anti-cancer activity. The knowledge gained by various researches has suggested that substituted benzimidazoles possess pharmacological activity with low toxicities. This review summarizes the synthesis of different derivative of substituted benzimidazole along with their biological applications.

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