CHAPTER 3

REVIEW OF LITERATURE

3.1 REVIEW ON BENZIMIDAZOLE DERIVATIVES

3.1.1 Synthesis of Benzimidazole Derivatives

Weinkauf et al [74] have reported the synthesis of Substituted 5H-benzimidazo[1,2-b]isoquinolin-11-ones according to the following scheme (Figure 3.1).

![Figure 3.1 Synthesis of substituted 5H-Benzimidazo[1,2-b]isoquinolin-11-ones](image)

The synthesis of benzimidazoles by intermolecular cyclization reaction of 2-Iodoanilines with nitriles has been developed by Xiang et al [75] (Figure 3.2).

![Figure 3.2 Synthesis of benzimidazoles](image)

Ansari and Lal[76] have synthesized several substituted 2-substituted-1-[(5-substituted alkyl/aryl)-1,3,4-oxadiazol-2-yl] methyl]-1H-benzimidazoles following the scheme (Figure 3.3).
Ajani et al [77] have reported a facile synthesis of some new 2,3-Disubstituted benzimidazole derivatives. The authors have reported that a series of five 2-substituted benzimidazole precursors were synthesized via [4 + 1] condensation and imino compound by simple condensation in the presence of conc. HCl as catalyst. Synthetic modification of N-1 position was achieved in order to obtain new 5-Chloro-2,4-dinitrophenyl bearing 1,2-disubstituted benzimidazole, 3-chlorobenzyl bearing 1,2-disubstituted benzimidazole in good to excellent yields (Figure 3.4).
Ahmad et al [78] have reported the use of $H$-alpha zeolite catalyst for the synthesis of various benzimidazoles by using substituted OPDA and a series of aldehydes at room temperature (Figure 3.5). It was reported that this method is quite simple and selective and the catalyst gave high isolated yield of the derivatives of benzimidazoles in a shorter reaction time at room temperature and can be recycled several times.

![Figure 3.5 Synthesis of benzimidazoles using zeolite catalyst](image)

Khan et al [79] have reported the synthesis of novel benzimidazole molecules belonging to the fused heterocyclic system from amino acids. The reaction between benzimidazole with $N$-[4-(2-chloroacetyl)phenyl]acetamide affords $N$-[4-(2-(1H-benzimidazol-1-yl)acetyl] phenyl acetamide, which upon hydrolysis yield 1-(4-aminophenyl)-2-(1H-benzimidazole-1-yl)ethane. The Diazotization of 1-(4-aminophenyl)-2-(1H-benzimidazol-1-yl)ethanone coupled with salicylic acid gave the final compound (Figure 3.6).

![Figure 3.6 Synthesis of benzimidazole metal complexes](image)
Rao and coworkers [80] have described the microwave-assisted synthesis of $1H,3H$-thiazolo[3,4-a]benzimidazoles and 2-aryl-1-benzylbenzimidazoles (Figure 3.7 and 3.8) in shorter reaction time and higher yields.

![Figure 3.7 Microwave assisted synthesis of 1H,3H-thiazolo[3,4-a]benzimidazoles derivatives](image)

Kidwai et al [81] have reported polyethylene glycol recyclable solvent system for the synthesis of benzimidazole derivatives using ceric ammonium nitrate (CAN) as catalyst (Figure 3.9). It was reported that CAN efficiently catalyzed the synthesis of benzimidazole derivatives from o-phenylenediamine and aldehydes in PEG. This method provides a novel route for the synthesis of benzimidazoles in good yields with little catalyst loading. The recovery and the successful reutilization of the solvent system are also reported.

![Figure 3.8 Synthesis of 2-aryl-1-benzylbenzimidazole derivatives](image)
Figure 3.9 Synthesis of benzimidazole derivatives using CAN catalyst

Ravishankara and Chandrashekar [82] have reported the synthesis of some novel benzimidazole derivatives (Figure 3.10) by simple condensation reaction between benzimidazole derivatives and phenylsulphonyl chloride derivatives.

Figure 3.10 Synthesis of some new benzimidazole derivatives
Sonwane et al [83] have reported the synthesis of some novel azetidinone derivatives of methylbenzimidazole (Figure 3.11) by conventional and microwave assisted methods. A mixture of 2-methylbenzimidazole and ethyl chloroacetate was subjected to microwave irradiation. The reaction mixture was extracted with ethanol to get benzimidazoles.

![Figure 3.11. Synthesis of azetidinone derivatives of methylbenzimidazole](image)

Xiangming et al [84] have developed a simple one pot synthesis of 2-aryl substituted benzimidazole (Figure 3.12) by the condensation of o-phenylenediamine with arylaldehyde catalyzed by p-TsOH.

![Figure 3.12 TsOH catalysed synthesis of 2-aryl substituted benzimidazoles](image)
Yadav and Srivastava [85] have reported the microwave assisted, rapid and efficient synthesis of some novel benzimidazole assembled 1,5-benzodiazepine and 1,5-benzothiazepine derivatives (Figure 3.13). 2-Acetyl benzimidazoles were reacted with appropriately substituted aromatic aldehydes in the presence of base to furnish substituted chalcones. These chalcones were further reacted with \( \sigma \)-phenylenediamine and 2-amino thiophenol to give substituted benzimidazole assembled 1,5-benzodiazepine and 1,5-benzothiazepine derivatives respectively.

\[ \text{Figure 3.13 Synthesis of benzimidazole assembled benzodiazepine and benzothiazepine derivatives} \]

Synthesis of some benzimidazolone derivatives (Figures 3.14 & 3.15) containing piperidine ring were synthesized by the reaction of 1-(piperidine-4-yl)-

$1H$-benzo-$d$-imidazole-$2$-$3(H)$-one in dichloromethane, disopropylethylamine was added then resulting mixture was cooled to 0 to 5°C. The solution of benzylchloroformate in dichloromethane was added slowly under agitation [86].

Sun and Hu [87] have reported that in the presence of catalytic amount of iodine in THF-$H_2$O, the condensation of aldehydes with 1,2-phenylenediamine gave the benzimidazole derivatives (Figure 3.16) under mild conditions in good yields.

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**Figure 3.14** Synthesis of $1$-($1$-($3$-phenylpropanoyl)piperidin-$4$-yl)$-1H$-benzo[$d$]imidazol-$2$($3H$)-one

**Figure 3.15** Synthesis of $1$-($1$-phenylpiperidin-$4$-yl)$-1H$-benzo[$d$]imidazol-$2$($3H$)-one

**Figure 3.16** $I_2$ catalysed synthesis of benzimidazole derivatives
A series of substituted benzimidazoles was 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. This study was described by Eshghi et al [88] (Figure 3.17).

![Figure 3.17 Synthesis of substituted benzimidazoles](image)

Mukhopadhyay et al [89] have reported an efficient and versatile synthesis of 2, 2'--(alkanediyl)-bis-1\( H \)-benzimidazoles (Figure 3.18) employing aqueous fluoroboric acid as catalyst.

![Figure 3.18 Synthesis of 2, 2'--(alkanediyl)-bis-1\( H \)-benzimidazoles](image)

An efficient and simple process was developed for the green synthesis of various 2-aryl-1-(arylmethyl)-1\( H \)-benzimidazoles [90] in high yields by acetic acid-promoted condensation of \( o \)-phenylenediamine with aldehydes in air under microwave irradiation and transition metal catalyst-free conditions (Figure 3.19).

![Figure 3.19 Green synthesis of 2-aryl-1-(arylmethyl)-1\( H \)-benzimidazoles](image)
Rekha et al [91] have described the synthesis and characterization of novel benzimidazole derivatives (Figure 3.20). The starting material fluoro-chloroaniline was treated with acetic anhydride to obtain acetyl derivative i.e. fluoro-chloroacetanilide. Fluoro-chloro acetanilide was nitrated at second position to get flouro-chloronitroacetanilide. The compound obtained is then deacetylated with glacial acetic acid and conc. HCl to get 5-Chloro-4-fluoro-2-nitrobenzenamine, this on further reduction using Zn and HCl gave the diamine compound. The diamino compound is cyclized to obtain 2-amino benzimidazole compound, which is then converted into Schiff’s bases by treating with nickel nitrate and various aromatic aldehydes.

![Figure 3.20 Synthesis of novel benzimidazole derivatives](image)

Synthesis of novel substituted benzimidazoles (Figure 3.21) was reported by Goud et al [92]. o-Phenylenediamine was refluxed with potassium hydroxide and carbon disulphide in the presence of ethanol to give mercaptobenzimidazole derivatives. The mercaptobenzimidazole was then treated with potassium hydroxide and chloro acetic acid to yield
(1H-benzimidazole-2-ylthio)acetic acid. Mixture of pyridine and acetic anhydride was added to (1H-benzimidazole-2-ylthio)acetic acid to get 1,3 thiazolo (3,2-a) benzimidazole-3-2H-one. Final product of 2-(1H-benzimidazol-2-ylsulfonyl-N-(2-hydroxy-5-methyl phenyl)acetamide was obtained by the reaction of (1,3)thiazolo (3,2-a) benzimidazol-3(2H)-one with substituted or unsubstituted aniline.

Ziarani et al [93] have reported a simple and convenient synthesis of 2-Aryl-1-arylmethyl-1H-1,3-benzimidazole, (1,2-disubstitutedbenzimidazoles) (Figure 3.22) via condensation of 1,2-phenylenediamine and aromatic aldehydes using SBA-Pr-SO₃H as a nanoporous solid acid catalyst in green protocol.
Dowlati et al [94] have described the electrochemical synthesis of benzimidazole (Figure 3.23) derivative using carbon electrode in aqueous medium. Electrochemical oxidation of catechol in the presence of carbohydrazide in aqueous solution has been studied on a carbon electrode by cyclic voltammetry and controlled-potential coulometry techniques. A direct electron transfer (DET) mechanism occurred during the process on the surface of carbon anode.

Figure 3.22 Synthesis of 2-aryl-1-arylmethyl-1H-1,3-benzimidazole, (1,2-disubstitutedbenzimidazoles)

Figure 3.23 Electrochemical synthesis of benzimidazole derivative
Momeni and Bagheri [95] have reported the synthesis of 2-substituted benzimidazoles (Figure 3.24) using P$_2$O$_5$-SiO$_2$ as useful catalyst under solvent-less and in solvent conditions from o-phenylenediamine and aldehydes.

Various substituted benzimidazoles were synthesized by a combination of o-phenylenediamines and aldehydes in the presence of boron sulfonic acid in water and under a mild reaction conditions. This method [96] is also applicable for precursors such as aromatic and unsaturated aldehydes and o-phenylenediamines (Figure 3.25).

Patil et al [97] have reported an efficient, greener synthesis of 2-Aryl-1 arylmethyl-1H-benzimidazoles (Figure 3.26) using polystyrene sulfonic acid as a catalyst. Incorporation of polymer supported PSSA as catalyst renders excellent chemoselectivity in the synthesis of 2-Aryl-1-arylmethyl-1H-benzimidazoles from the reaction of o-phenylenediamine with several aryl aldehydes. The captivating aspects of this method are the greenness of water mediated system and efficient, selective achievement of desired product within 30 - 40 min.
3.1.2 Biological Activities of Benzimidazole Derivatives

3.1.2.1 Antimicrobial activities

Babu et al [98] have reported the antimicrobial screening of some 1-substituted benzimidazole derivatives of the type (20). All the compounds were screened for their in vitro antimicrobial activity against pathological bacterial and fungal strains. The compounds showed moderate to good effective zone of inhibitions. Sugumaran and Kamal [99] have reported the antimicrobial activity of novel 2,5-Disubstituted benzimidazole derivatives of the type (21). The compounds were evaluated for their antibacterial activity against the bacterial strains, such as *Proteus vulgaris*, *Klesibella pneumonia*, *Bacillus cereus* and *Enterococcus faecium*, and antifungal strains, such as *Aspergillus niger* and *Aspergillus fumigatus* by disc diffusion method. All the synthesized compounds showed good antibacterial and antifungal activity. Vaidehi et al [100] have reported the antibacterial activity of 2-substituted benzimidazole derivatives. The synthesized compounds were screened for their in-vitro antibacterial activity against standard strains by cup plate method (22).

![Chemical structures](image)

Walia et al [101] have reported the novel substituted benzimidazole derivatives of the type (23) as potential antimicrobial agents. The antimicrobial activity was evaluated against bacterial strains, such as *Escherichia coli* and *Staphylococcus aureus* and antifungal strains, such as *Candida albicans*. The results of the study show that the zone of inhibition is more in compounds possessing the electron withdrawing groups. A series of nine 2-Chloromethyl-benzimidazole derivatives of the type (24) were screened for their antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis* (Gram positive), *Escherichia coli*, and *Pseudomonas aeruginosa* (Gram negative). The compounds showed good to
moderate antimicrobial activity as compared to the standard drug streptomycin [102]. The antimicrobial activity of some 3-(2-(1H-benzo[d]imidazol-2-yl)phenyl)-2-aryltiazolidin-4-ones of the type (25) was reported by Desai et al [103]. The compounds were tested against antibacterial strains, such as *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Streptococcus pyogenes*, and antifungal strains, such as *Candida albicans*, *Asperigillus niger* and *Asperigillus clavatus*.

![Chemical Structures](image)

Antibacterial activity of novel *N*-substituted 2-(4-styrylphenyl)-1H-benzimidazole(26) and *N*-substituted-3-[4-(1H-benzimidazole-2-yl)-phenyl]-acrylic acid tert-butyl ester(27) was reported by Vinodkumar et al [104]. Some of the compounds were found to have good antibacterial activity against *Salmonella typhimurium*. However, they were found to have less activity against *S. aureus*.

Shet and Shelar [105] have reported the antimicrobial activity of alkyl thioaryl substituted benzimidazole derivatives. The compounds, viz., 2-[[2, 4, 5-Trichlorophenyl)thio methyl]-1H-benzimidazole (28) and 2-[[2, 5, dichloro-4-nitrophenyl]thio]methyl-1H-benzimidazole (29) have shown a considerable level of antifungal activity. Al-Mohammed et al [106] have reported antibacterial evaluation of some novel benzimidazole sulfonamides. The authors have reported that among the tested compounds, the compound, viz., *N*-4 methylbenzenesulfonyl ((N-(4-methylbenzenesulfonyl)-benzimidazol-2-yl)methylthio)benzimidazole (30) has a significant antibacterial activity against the gram positive and gram negative bacteria.
Antimicrobial activity of some novel 4-(1H-Benz[d]imidazol-2yl)-1,3-thiazol-2-amines of the type (31) was reported by Reddy and Reddy [107]. The newly synthesized compounds were evaluated for their antibacterial and antifungal activity against clinical isolates of Gram-positive and Gram-negative bacteria. Some of these hybrids in this series exhibited antibacterial activity comparable to standard Streptomycin and Benzyl penicillin, and antifungal activity against Fluconazole. Kucukbay et al [108] have reported the antimicrobial activities of some bridged bis-benzimidazole derivatives of the type (32). The compounds were screened for their in vitro antimicrobial activities against gram-positive (Staphylococcus aureus and Bacillus megaterium) and gram-negative bacteria (Klebsiella pneumoniae and Escherichia coli), and yeasts like fungi (Candida globrata 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.
3.1.2.2 Antiinflammatory activity of benzimidazole

Babu et al [109] have reported novel \(N-(1H\text{-}\text{Benzimidazole}\text{-}2\text{-}yl)\text{-}2\text{-}Isatinylidene-hydrazinecarboxamide\) derivatives as antiinflammatory agents (33). The results of antiinflammatory data revealed that the compounds possess significant activity which is comparable with the standard drug. Antiinflammatory activity of 2-Substituted benzimidazole derivatives was studied by Reddy [110]. 2-substituted benzimidazole (34) confirmed significant effect over carrageenan induced paw edema. Achar et al [111] have reported the in-vivo analgesic and antiinflammatory activity of benzimidazole derivatives of the type (35). Authors have done antiinflammatory activities on acetic acid induced writhing in mice and carrageenan induced paw oedema in rats. All the compounds possess good antiinflammatory activity compared to the standard drug Nimesulide. The antiinflammatory evaluation of benzimidazole derivatives of some schiff’s bases was reported by Sondhi et al [112]. A series of \(N\text{-}(\text{Acradin-9-yl})\text{-}4\text{-}(\text{benzo[d]imidazol/oxazol-2-yl})\) benzamides (36) were screened for antiinflammatory activity. From the results of the study, benzimidazole containing benzamides showed good antiinflammatory activity.
3.1.2.3 Anticancer activity of benzimidazole

Nofal et al [113] have reported the synthesis of novel benzimidazole derivatives of the type (37) as expected anticancer agents. The anticancer activity was evaluated against HEPG2 (human liver carcinoma cell line) and PC12 (pheochromocytoma of the rat adrenal medulla) cells. The results of the study showed that the synthesized compounds have fairly good activity against the tested cell lines. Blaszczyk-Swiatkiewicz et al [114] have reported a series of new benzimidazole derivatives of the type (38) with potential cytotoxic activity.

Cytotoxic activity on MCF-7 cell line and mutagenic activity of platinum (II) complexes with 2-substituted benzimidazole ligands (39) was reported by Gumus et al [115]. Four Pt(II) complexes with 2-H/or-methyl/or-aminomethylbenzimidazole or 1,2-dimethylbenzimidazole ligands as “non-leaving groups” were synthesized and their antiproliferative properties were tested against the human MCF-7 breast cancer cell line. The mutagenic potentials of the complexes were tested in Salmonella typhimurium strains TA 98 and TA 100 in the absence of S9 rat liver fraction. The Pt(II) complexes tested were found to be less active than cisplatin. Antitumor activity of some novel benzimidazole derivatives (Compound 40-44) was reported by Vijayakumar and Ahamed [116].
3.1.2.4 Antioxidant activity

Maheshwaran et al [117] have reported the antioxidant activity of 7-\((1H\)-benzimidazole -2-yl\)-5-substituted phenyl) pyrido(2,3-D) pyrimidin-4-amine \(45\). Antioxidant activity study was done by DPPH method. The compounds have shown mild to moderate antioxidant activity. Rajasekaran et al [118] have reported the antioxidant activity of some substituted benzimidazole derivatives. The compounds were found to show moderate antioxidant activity irrespective of the substitution. However, the compound with pyridyl substituted oxadiazole \(46\) has shown good antioxidant activity within the series of compounds synthesized.
3.1.2.5 Antihypertensive activity

Kumar et al [119] have reported the benzimidazole derivatives of the type (47) as antihypertensive agents. The 5-Substituted(amo)no)-2-phenyl-1-(2′carboxybiphenyl-4-yl)benzimidazoles produce a potent hypertensive effect upon oral administration. It has been found that 2′-position of biphenyl is essential. Only ortho substituted acid possesses both high affinity for the AII receptor and oral antihypertensive potency.

![Chemical Structure 47]

3.1.2.6 Antiviral activity

Budow et al [120] have reported the antiviral activity of substituted benzimidazoles against selected RNA and DNA viruses including HIV-1, BVDV, YFV, DENV-2, WNV, HBV, HCV and human RSV (48). Antiviral cytotoxicity studies of some novel N-substituted benzimidazole derivatives (49) was reported by Selvam et al [121]. Tonelli and coworkers [122] have studied the antiviral activity of benzimidazole derivatives and 2-Phenylbenzimidazole derivatives (30-35).

![Chemical Structures 48, 49, 50]

![Chemical Structures 51, 52]
Hwu et al [123] have synthesized a series of new benzimidazole-coumarin conjugates and evaluated them for their activities against various hepatitis C viruses. In this compound library, several new conjugates resulted in an inhibitory effect on HCV replication and the conjugate (55) displayed an EC$_{50}$ of 3.4µM. The N-glucoside (56) inhibited HCV RNA replication by 90% and 99% at concentrations of 5.0 µM and 16µM, respectively. These conjugates may be considered as potential lead anti-HCV compounds for further selectivity optimization. Antiviral activity of N-substituted-2-substituted benzimidazole derivatives (Compound 57 & 58) was reported by Tewari and Mishra [124].
3.1.2.7 Antiallergic activity

Benzimidazole derivative of the type (Compound 59) as antiallergic agents with 5-Lipoxygenase inhibiting action was reported by Nakano and coworkers [125]. In this paper, the authors have studied the suppression of histamine release from rat peritoneal mast cells, triggered by the antigen–antibody reaction, inhibition of 5-lipoxygenase in rat basophilic leukemia-1 (RBL-1) cells and prevention of NADPH-dependent lipid peroxidation induced by Fe31–ADP in rat liver microsomes. They also described the antagonistic action of representative synthetic compounds on the contraction of guinea pig ileum induced by histamine.

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3.1.2.8 Antiulcer activity

Antiulcer activity of 2-[5-Substituted-1-\(H\)-benzo(d) imidazol-2-yl sulfinyl]methyl-3-substituted quinazoline-4-(3\(H\)) ones (60) was reported by Patil et al [126]. Antiulcer activity of some new substituted 2-(Pyrimidinylsulfinyl) benzamidazole derivatives (61 and 62) was reported by Farhan and Asnani [127]. The antiulcer activities of the compounds were assessed by Acetylsalicylic acid (ASA) induced gastric ulcer.

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\text{60} & & \text{61} & & \text{62}
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3.1.2.9 Anticonvulsant activity

Siddiqui and Alam [128] have reported the anticonvulsant and toxicity evaluation of new 1-{1-(2-Substitutedbenzyl)-1H-benzo[d]imidazol-2-yl)methyl}-3-arylthio ureas of the type (63). Synthesis and anticonvulsant activity of 2-Mercaptobenzimidazole derivatives of the type (64) was reported by Anandarajagopal et al [129]. The anticonvulsant activity was evaluated by maximal electrical shock induced convulsion method. Bhrigu et al [130] have studied the anticonvulsant evaluation of some newer series of new 2-[(1-substituted phenylethylidene) hydrazine]-N-phenyl-1H-benzo[d]imidazole-1-carbothioamides of the type (65). The anticonvulsant activity was screened by two most adopted models, viz., maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ). Interestingly, these compounds exhibited potent anticonvulsant activity.

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63 \quad 64 \quad 65
\end{align*}
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3.1.2.10 Antiprotozoal activity

Valdez-Padilla and coworkers [131] have reported the antiprotozoal activity of novel 1-Methylbenzimidazole derivatives of the type (66). Kazimierczuk et al [132] have reported the antiprotozoal activity of nitro- and halogeno-substituted benzimidazole derivatives of the type (67). The authors have synthesized two series of benzimidazole derivatives. The first one was based on 5,6-dinitrobenzimidazole and the second one comprises 2-thioalkyl- and thioaryl-substituted modified benzimidazoles. Some thioalkyl derivatives showed remarkable activity against nosocomial strains of *Stenotrophomonas malthophilia*. 
5-Nitrobenzimidazole derivatives with varying substituents at 2-position have been designed, synthesized and evaluated for angiotensin II antagonistic activity [133]. A drug–receptor interaction model has been proposed by the authors. Substituted benzimidazole nucleus coupled to carboxylbiphenyl methyl group has been evaluated for Ang II antagonism. Compound with nitro group at 5-position and n-butylchain at 2-position have been found to be more potent than candesartan (68).

Guo et al [134] have reported the biological activities of novel nonpeptide angiotensin II receptor antagonists benzimidazole derivatives of the type (69) bearing a heterocyclic ring. The synthesized compounds were evaluated in vitro using an AT1 receptor binding assay.

Borza and coworkers [135] have reported benzimidazole-2-carboxamides of the type (70) as novel NR2B selective NMDA receptor antagonists. The influence of some structural elements, like H-bond donor groups placed on the benzimidazole skeleton and the substitution pattern of the piperidine ring, on the biological activity were also studied by authors. Hashimoto and coworkers[136] have reported the Benzimidazole-5-sulfonamides (71) as novel Nonpeptide Luteinizing Hormone Releasing Hormone (LHRH) Antagonists. The optimization towards derivatives free from mechanism-based CYP3A4 inhibition was also described by the authors.
3.1.2.12 Antimalarial activity

Camacho et al [137] have reported the evaluation of benzimidazole-5 carbohydrazide derivatives of the type (72) as antimalarial activity. In the study, the authors have screened the compounds for in vitro and in vivo antimalarial activity.

3.1.2.13 Fasciolicidal Activity

Hernandez-Campos et al [138] have reported the fasciolicidal activity of 5-Chloro-2-methylthio-6-(1-naphthyloxy)-1H-benzimidazole (73).
3.1.2.14 Trichomonicidal activity

Villanueva and coworkers [139] have reported the Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA) of some benzimidazole derivatives of the type (74) with trichomonicidal activity.

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\text{73}
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3.1.2.15 Anthelmintic activity

Navarro and coworkers [140] have reported the anthelmintic activity of benzimidazole derivatives of the type (75) against *Toxocara canis* second-stage larvae and *Hymenolepis nana* adults. Each compound and albendazole was tested *in vitro* against *Toxocara canis* larvae and *in vivo* against *Hymenolepis nana* adult. Results of the *in vitro* screening showed moderate to good anthelmintic activity. Sawant and Kawade [141] have reported the synthesis of a series of 2-Phenylbenzimidazole-1-acetamide derivatives of the type (76) and evaluated for anthelmintic activity using Indian adult earthworms, Pheretima posthuma.

Anthelmintic activity of benzimidazole derivatives was reported by Sreena *et al* [142]. All the benzimidazoles showed significant anthelmintic activity. Among the tested compounds, the compound, viz., 2-phenylbenzimidazole (77) showed potent anthelmintic activity.
3.1.2.16 Antitubercular activity

Evaluation of antitubercular activity of some thiobenzimidazolyl derivatives was reported by Gupta and Pancholi [143]. A series of alkyl sulphonyl benzimidazole was prepared by the oxidation of substituted sulphanyl benzimidazole. A set of benzimidazoles bearing indole-2, 3-dione substituents were also synthesized. Intermediate benzimidazolyl-2-mercaptoacetic acid hydrazide was condensed with 5 unsubstituted indole-2,3-dione to give different benzimidazolyl-5-(un)substituted-2-oxoindoline-3-ylidine acetohydrazide (78 and 79).

3.1.2.17 Molecular docking studies

Molecular docking is routinely used for understanding drug-receptor interaction in modern drug design. Sivakumar et al [144] have reported computer aided drug studies of benzimidazole containing isoxazole derivatives as targeted antibiotics. The inhibitory activities against *Escherichia coli* β-ketoacyl-acyl carrier protein synthase III (ecKAS III) were investigated by molecular docking using the HEX docking software. All the designed compounds showed good binding energy when compared with the binding energies of standard drugs, such as Ciprofloxacin (-211.04), Amoxilin (-182.23) and cefotaxime (-207.62). Among all the designed compounds, the compound (80) shows more binding energy values (-298.32).
QSAR and k-Nearest Neighbour Molecular Field Analysis (k-NN MFA) classification analysis studies of some benzimidazoles derivatives of the type (81) against *Escherichia coli* was reported by Sharma *et al* [145].

More and coworkers [146] have reported the docking studies of benzimidazole derivatives as Coenzyme-A Carboxylase (ACCase) Inhibitor. The authors used acetyl coenzyme-A carboxylase (ACCase) as the target which is essential for pathogen survival.

### 3.1.2.18 Nematicidal activity

Srinivas *et al* [147] have reported the synthesis and nematicidal activity of 2-((1H-benzo[d]imidazol-2-ylmethyl)-4-aryl-1-thia-4-azaspiro[4,5]decan-3-one of the type (82).
3.2 REVIEW ON BENZOXAZOLE DERIVATIVES

3.2.1 Synthesis of Benzoxazole Derivatives

Synthesis of 2-(3-Phenoxyphenyl)-substituted benzoxazoles from nitriles containing Diphenyl oxide fragment was reported by Popov et al [148] (Figure 3.27).

Moskvichev et al [149] have reported the synthesis of 2-Substituted benzoxazoles from arylsulfonyl(thio)propionitriles (Figure 3.28).

Maradolla et al [150] reported a one-pot regioselective synthesis of 2-aryl benzoxazoles (Figure 3.29) in excellent yield.

Hangirgekar [151] has reported the use of Phenyl-trimethyl-ammonium tribromide. Phenyl-trimethyl-ammonium tribromide, a stable, crystalline organic ammonium tribromide as an alternative electrophilic bromine source for the efficient oxidative cyclisation of substituted benzaldehydes and 2-aminophenols to the corresponding benzoxazoles (Figure 3.30) under mild conditions.
Barbero et al [152] have reported a comprehensive study of the reactions between 2-aminothiophenol with various carboxylic acid derivatives or aldehydes and ketones, in order to obtain benzoxazolines in the presence of catalytic amount of o-benzenedisulfonamide to provide benzoxazoles (Figure 3.31).

Stella et al [153] have reported the synthesis of benzoxazole derivatives (Figure 3.32). The reaction of aniline compounds with ammonium thiocyanate and bromine in glacial acetic acid yielded 4-thiocyananiline. The Benzoxazole derivatives were synthesized by treating 4-thiocyananiline with o-aminophenol and carbon-di-sulphide.

A series of 4-(1,3-benzoxazol-2-yl)-2-phenylnaphtho[1,2-d][1,3]oxazole derivatives (Figure 3.33) have been synthesized by Phatangare et al [154] in the presence of PCl₃.
Figure 3.33  Synthesis of 4-(1,3-benzoxazol-2-yl)-2-phenylnaphtho[1,2-d][1,3]oxazole

The polyester fluorescent brighteners that contain a benzoxazole group are usually prepared from appropriate \( o \)-aminophenol and carboxylic acid or one of its derivatives (Figure 3.34) was reported by Um [155].

Figure 3.34 Synthesis of fluorescent brighteners containing benzoxazoles

Kamal and coworkers [156] have reported the synthesis of benzoxazole pyrrolo[2,1c][1,4]benzodiazepine conjugates (Figure 35).
Figure 3.35 Synthesis of benzoxazole pyrrolo[2,1-c][1,4]benzodiazepine conjugates

Padalkar et al [157] have reported the synthesis of novel dipodal-benzoxazole from cyanuric chloride. The reaction of 4,4’-((6-(4-(diethylamino)phenyl)-1,3,5-triazine-2,4-diyl)bis(oxy))dibenzaldehyde with o-aminophenol in ethanol gave benzoxazole (Figure 36).

Figure 3.36. Synthesis of novel dipodal-benzoxazole
Koyama et al [158] have reported a novel synthesis of bis(benzoxazole) derivatives (Figure 3.37) via tandem Claisen rearrangement.

![Figure 3.37 Synthesis of bis(benzoxazole) derivatives](image)

Figure 3.37 Synthesis of bis(benzoxazole) derivatives

Deluca and Kerwin [159] has described the synthesis of benzoxazole derivatives derived from 3-hydroxyanthranilic acid (Figure 3.38).

![Figure 3.38 Synthesis of benzoxazole derivatives](image)

Figure 3.38 Synthesis of benzoxazole derivatives

Praveen et al [160] have reported the microwave-assisted one-pot synthesis of benzoxazole e libraries via PIFA promoted cyclocondensation of 2-aminophenols with aldehydes (Figure 3.39 & 3.40) under one-pot condition in good to excellent yields.
Mohammadpoor-Baltork et al [161] have reported a simple, rapid and efficient method for the preparation of benzoxazoles (Figure 3.41), from the reaction of orthoesters with \( o \)-aminophenols, in the presence of silica sulfuric acid under heterogeneous and solvent-free conditions.

Sapijanskaitė et al [162] have reported the synthesis of a new series of 2-substituted naphtho[2,3-d]imidazole and benzoxazole derivatives (Figure 3.42).
Onkol et al [163] have reported the microwave assisted synthesis of 5-Chloro-2-3(3\textit{H})-benzoxazolinone-3-acetyl-2-(p-substituted banzal) hydrazone and 5-chloro-2-(3\textit{H})-benzoxazolinone-3-acetyl-2-(p-substituted acetophenone)hydrazone derivatives (Figure 3.43).

![Figure 3.43 Microwave synthesis of benzoxazole derivatives](image)

An efficient soluble polymer-supported method has been developed by Chanda et al [164] for the parallel synthesis of substituted benzimidazole linked benzoxazoles using focused microwave irradiation. The key step involves the amidation of 4-hydroxy-3-nitrobenzoic acid with polymer-immobilized \textit{o}-phenylenediamine. Application of mild acidic conditions promoted the ring closure to furnish the benzimidazole ring. After hydrogenation of the nitro-group to amine, the resulted polymer conjugates underwent efficient ring closure with various alkyl, aryl and heteroaryl isothiocyanates to generate the polymer-bound benzimidazolyl benzoxazoles. The polymer-bound compounds were finally cleaved from the support to furnish benzimidazole linked benzoxazole derivatives (Figure 3.44).
Lee et al [165] have reported the synthesis and characterization of fluorine-containing polybenzoxazoles (Figure 3.45) by high-temperature direct polycondensation. The 2,5 difluoroterephthalic acid was used for the preparation of new poly(benzoxazole)s by high-temperature direct polycondensation with bis(ωaminophenol)s in PPA.
Kangani et al [166] reported the one pot synthesis of benzoxazoles (Figure 3.46) by the reaction of 2-aminophenols with carboxylic acids using the Deoxo-Fluor reagent.

2-Substituted benzoxazoles (Figure 3.47) were synthesized [167] via condensation reaction of 2-aminophenol with various aldehydes using molecular iodine in solvent-free conditions under microwave irradiation in short time with good to excellent yields.
Figure 3.47 Synthesis of 2-Substituted benzoxazoles

2-Substituted benzoxazoles (Figure 3.48) can be smoothly synthesized [168] by treatment of N-(2-hydroxyaryl) cyclopropyl amides with PPh₃/CCl₄ in acetonitrile in good yields.

Figure 3.48 Synthesis of 2-(3-Chloropropyl)benzoxazoles

Parallel synthesis of a library of benzoxazoles (Figure 3.49) can be achieved [169] by using ligand-accelerated copper-catalyzed cyclizations of ortho-halobenzenilides. This reaction involves an intramolecular C-O cross-coupling of ortho-halobenzenilides and is believed to proceed via an oxidative insertion/reductive elimination pathway through a Cu(I)/Cu(III) manifold.

Figure 3.49 Copper catalyzed synthesis of benzoxazole derivatives
A convenient one step method for the preparation of benzoxazole (Figure 3.50) is described by Perumal [170]. Ortho amino phenol reacts with formic acid in the presence of boric acid as a catalyst and ethanol as a solvent to yield benzoxazole.

Figure 3.50 One step synthesis of benzoxazole

Chikhale et al [171] have reported Poly (Ethylene Glycol)-bound sulphonylic acid as a novel catalyst for the synthesis of benzoxazoles (Figure 3.51). PEG-SO₃H is found to be economical and reusable catalyst with low catalytic loading. The authors have reported that the percentage yield was satisfactory, experimental set-up and purification of final products was facile and easy.

Figure 3.51 PEG-SO₃H catalyzed synthesis of benzoxazoles

Kumar et al [172] have reported the synthesis of 2-Arylbenzoxazoles (Figure 3.52) promoted by Silica supported sodium hydrogen sulphate. Benzoxazole derivatives have been prepared through the reaction of 2-Amino phenols and aldehydes in the presence of catalytic amount of silica supported sodium hydrogen sulphate (NaHSO₄-SiO₂) under refluxing in Dioxane solvent to obtained excellent yields.

Figure 3.52 NaHSO₄-SiO₂ catalyzed synthesis of 2 Arylbenzoxazoles
3.2.2 Biological Activities of Benzoazoles Derivatives

3.2.2.1 Antimicrobial activity

Modiya and Patel [173] have reported the antibacterial and antifungal activity of 5-chloro-1,3-benzoxazol-2(3H)-one derivatives of the type (83). Authors have screened the compounds against various Gram-positive and Gram-negative bacteria and fungi. The results of the study shows that the tested compounds have good antibacterial and antifungal activity compared with Ampicillin and Cephalexin. Chilumula et al [174] have reported novel methyl-2-(2-(arylideneamino)oxazol-4ylamino) benzoazole-5-carboxylate derivatives (84) as antimicrobial agents. The new compounds were tested in vitro against bacterial strains such as *Staphylococcus aureus*, *Bacillus subtilis*, *S.typhi* and *Escherichia coli*, and fungal strains, such as *Candida albicans* and *A.niger*. Microbiological results showed that the compounds possessed a diffuse spectrum of antibacterial activity against these microorganisms.

Balaswamy et al [175] have reported the antimicrobial activity of novel benzoazole derivatives. Antibacterial activity was observed for all the compounds screened against Gram (+ ve) bacterial strains, such as *Staphylococcus Aureus*, *Bacillus pumilis*, *Proteus mirabilis* and the Gram (-ve) bacterial strain, *Escherichia Coli*. Among the tested compounds, compounds (85 and 86) were found to be more active.
Gadegoni et al. [176] have studied novel 2-[5-(Substituted phenyl)-1,3,4]oxadiazol-2-yl]-benzoxazoles as potential antimicrobial agents. The compounds were screened against four human pathogenic bacteria, such as *Escherichia coli*, *Klebsella pneumoniae*, *Shigella dysentriae* and *Shigella flexnei*. The result of the study reveals that the compound, viz., 2-(5-(2-bromophenyl)-1,3,4-oxadiazol-2-yl)benzo[d]oxazole (87) is highly active against all the test organisms employed. The compounds were also screened for their antifungal activity against antifungal strains, such as *Aspergillus niger*, *Candida albicans*, *Aspergillus flavus* and *Rhizopus oryzae* at concentration of 500 μg/mL using cup-plate method. The antifungal activity of the compounds was compared with the standard drug Griseofulvin. It is observed that the compound, viz., 2-(5-o-tolyl-1,3,4-oxadiazol-2-yl)benzo[d]oxazole (88) is found to be highly active against *A. niger*, *C. albicans* and *A. flavus*.

Nacak et al. [177] have reported the antimicrobial activity of some new Mannich bases of 7-acyl-5-chloro-2-oxo-3H-benzoxazole derivatives of the type (89). The compounds were evaluated for their *in vitro* antibacterial and antifungal activity by broth microdilution method. Ampicillin and fluconazole were used as standards for comparison. The observation from the antimicrobial activity of the compounds showed no considerable activity against tested bacteria and fungi.
Jyothi and Merugu [178] have reported the antibacterial and antifungal activity of some newly substituted benzoxazoles. Among the tested compounds, compounds viz., 5-(2-Substituted-1,3-benzoxazol-5-yl)-4-phenyl-4,5-dihydro-3H-1,2,4-triazole-3-thiols (90), 2-Substituted-5-[5-(substituted sulfanyl)-1,3,4-oxadiazol-2-yl]-1,3-benzoxazoles (91) and 3-(Substituted amino) methyl-5-(2-substituted-1,3-benzoxazol-5-yl)-1,3,4-thiadiazole-2(3H)-thiones (92) were found to possess fairly good antibacterial activity against the tested bacteria strains.

Singh et al [179] have reported the antimicrobial activity of some 2-phenyl-benzoxazole derivatives. The compounds were screened for their in vitro growth inhibiting activity against different strains of bacteria and fungi. The compounds (93-95) exhibited potent antibacterial and antifungal activity.
Ramalingan et al [180] have studied the antibacterial and antifungal activities of novel 1-[2-(benzoxazol-2-yl)ethoxy]-2,6-diarylpiperidin-4-ones against various strains of bacteria and fungi. Among the compounds, compounds (96-98) exerted potent *in vitro* antibacterial activity against *Streptococcus faecalis* while compounds (99 and 100) exhibited potent *in vitro* antifungal activity against *Candida albicans*. 
Braun et al have [181] reported 1-Acylated benzimidazole-2-thiones and benzoxazole-2-thiones as new leads for the inhibition of Streptococcus agalactiae strain 4755 Hyal. Structure-based optimization led to N-(3-phenylpropionyl) benzoxazole-2-thione(101), one of the most potent compound known to date.

Kuroyanagi and coworkers [182] have reported the *in vitro* antifungal evaluations of 1,3-benzoxazole-4-carbonitrile4(102), which was found to be a superior scaffold structure with moderate growth inhibition against *Candida* species. Temiz et al [183] have studied the microbiological activity of some novel 5- or 6-Methyl-2-(2,4-disubstituted phenyl) benzoxazole derivatives. The compounds were tested *in vitro* against three Gram positive bacteria, three Gram-negative bacteria and the yeast *Candida albicans*, in comparison with several control drugs. Microbiological results exhibited that the compounds possess a broad spectrum of antimicrobial activity against the tested microorganisms. The compounds (103 and 104) indicated antimicrobial activity against *Staphylococcus aureus* having a minimum inhibitory concentration (MIC) of 12.5µg/ml. Moreover, the compound (105) revealed a significant antibacterial activity against the enterobacter *Pseudomonas aeruginosa* showing a MIC value of 25 µg/ml, i.e. more potent than the control drugs tetracycline and streptomycin.
5-Chloro-2-(2-cyclohexylethyl)benzimidazole (106) was found as the most active compound against the screened Gram-positive bacteria strains at a minimum inhibitory concentration (MIC) value of 12.5 mg/ml. However, it exhibited lower antibacterial potency than the control drugs [184]. Arpaci et al [185] have reported the antimicrobial activity of some novel 2-(p-substituted-phenyl)-5-substituted-carbonylaminobenzoxazoles. The compounds were tested in vitro against *Staphylococcus aureus*, *Streptococcus faecalis* and *Bacillus subtilis* as Gram-positive, *Pseudomonas aeruginosa* and *Escherichia coli* as Gram-negative bacteria and the yeast *Candida albicans*. Microbiological results showed that the compounds possessed a diffuse spectrum of antibacterial activity against these microorganisms. Among the tested compounds, compound (107) which bears a phenylacetamido moiety at position 5 and 4-fluorophenyl group at the 2-position of benzoxazole ring (108) was the most active derivatives against *S. aureus*, *S. faecalis* and *P. aeruginosa* with a MIC value of 12.5 µg/ml.
3.2.2.2 Antiinflammatory activity

Chilumuru et al [186] have reported in vivo evaluation of antiinflammatory activity of 5-(2-(2-(Arylideneamino) oxazol-5-ylamino) benzoxazol-5-yl)-3- ((dialkylamino) methyl)-1, 3, 4-oxadiazole-2(3h)-thiones (109) Carrageenan induced rat paw edema method. All the tested compounds exhibited significant antiinflammatory activity.

Ampati et al have [187] reported in vivo antiinflammatory activity of a novel series of benzoxazole derivatives of the type (110). This study reports moderate to potent anti inflammatory activity of the derivatives. It has been observed that the increased antiinflammatory activity is attributed to the presence of pharmacologically active thiazole ring on the benzoxazole moiety at 2-position.

Patil and Bhatt [188] have reported the N’[Substituted sulfonyl]-1,3-benzoxazole-5-carbohydrazides as an antiinflammatory agents. The antiinflammatory activity was determined using formalin induced oedema method and it was found that the compounds (111 to 113) possessed significant antiinflammatory activity compared with the standard drug Ibuprofen.
Janardhan et al [189] have reported the antiinflammatory activity of a novel series of substituted 5-([1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)-1,3-benzoxazole derivatives by Carrageenan induced paw edema rat model. Among the derivatives compound (114 to 117) showed potent antiinflammatory activity.
3.2.2.3 Anticancer activity

Jiang et al [190] have reported the antitumor activity of benzoxazole (118) and its transition metal complexes. McKee and Kerwin [191] have reported anticancer activity 2-(20-Hydroxyphenyl) benzoxazole analogs of UK-1(119). Huang et al [192] have reported the anticancer evaluation of bis(benzoxazoles) (120). Four classes of UK-1 analogues were screened for their cytotoxicity against human A-549, BFTC-905, RD, MES-SA, and HeLa carcinoma cell lines. Abdelgawad et al [193] have reported the antibreast cancer activity of some benzoxazole derivatives. All the tested compounds revealed potent antitumor activity, especially the N-methyl piperazinyl substituted derivative (121) displayed the most potent inhibitory activity with IC<sub>50</sub> value 17 nM.

3.2.2.4 Anti-HIV

Medebielle et al [194] have studied some new difluoromethylene benzoxazole and 1,2,4-oxadiazole derivatives as potent non-nucleoside HIV-1 reverse transcriptase inhibitors. Out of the tested compounds, compound (122) was found to be active against HIV.
3.2.2.5 Agonists activity

A series of benzoxazole derivatives were synthesized and identified as melatonin receptor agonists. Among the tested compounds, compound (123) shows highly potent human MT1 receptor selectivity. Sun and coworkers [195] have reported the structure–activity relationship of novel benzoxazole derivatives as melatonin receptor agonists. The binding affinity of these compounds for human MT1 and MT2 receptors was determined using 2-[125I]-iodomelatonin as the radioligand. From this series of benzoxazole derivatives, compounds (124 and 125) were identified as good melatonin receptor agonists.

Martin and coworkers [196] have reported the benzoxazole piperidines of the type (126) as selective and potent somatostatin receptor subtype 5 antagonists.
Li et al [197] have reported the biological estimation of 1-(Benzoazole-2-yl)piperazine and 4-(Benzoazole-2-yl)piperidine derivatives as potential α1-AR antagonists. Biological assay \textit{in vitro} indicated that the compound \(127\) shows potent activity. Gim et al [198] have reported the benzoazole containing indole analogs \(128\) and \(129\) as peroxisome proliferator-activated receptor-c/d dual agonists. Gao et al [199] have studied the new carbon-11 labeled benzoazole derivatives of the type \(130\) for PET imaging of 5-HT3 receptor. Geldern et al [200] have reported that the Benzoazole benzenesulfonamides are novel allosteric inhibitors of Fructose-1,6 bisphosphatase with a distinct binding mode. The authors have identified benzoazole benzenesulfonamide \(131\) as a novel allosteric inhibitor of fructose-1,6-bisphosphatase (FBPase-1). Paramashivappa et al [201] have reported the 2-[[2-alkoxy-6-pentadecylphenyl)methyl]thio]-1H-benzoazoles of the type \(132\) as human cyclooxygenase-2 enzyme COX-2 inhibitors. The active compounds were screened for cyclooxygenase-1 (COX-1) inhibition also.
Song and coworkers [202] have designed a series of benzoxazoles as 5-LOX inhibitors. Most of the synthesized compounds showed the inhibition of LTC4 formation with IC$_{50}$ value of 0.12–23.88 µM. Among them, the two compounds (133 and 134) showed improved airway hypersensitiveness. Yang and coworkers [203] have studied a new class of 2-substituted benzoxazole carboxamides as potent functional 5-HT3 receptor antagonists. A chemistry optimization program was conducted and identified 2-aminobenzoxazole (135) as orally active 5-HT3 receptor antagonists with good metabolic stability. The authors advocate that these novel analogues possess drug-like characteristics and have potential utility for the treatment of diseases attributable to improper 5-HT3 receptor function, especially diarrhea predominant irritable bowel syndrome (IBS-D). Lopez-Tudanca et al [204] have studied pharmacological characterization of new benzoxazole derivatives as potent 5-HT3 Receptor Agonist. Among the synthesized compounds, N-(2-Benzoxazol-2-yl-ethyl)-guanidine hydrochloride (136) showed high affinity for the 5-HT3 receptor.

Lai et al [205] have studied a series of novel benzoxazole benzenesulfonamides as inhibitors of fructose-1,6-bisphosphatase (FBPase-1). Extensive SAR studies led to potent inhibitors (137 and 138) with excellent bioavailability and good pharmacokinetic profile in rats.

Sessions and coworkers [206] have reported the benzoxazole based inhibitors of Rho kinase. Among these inhibitors, the compound (139) is found to possess good microsomal stability, low cytochrome P-450 inhibitions and good oral bioavailability.
3.2.2.6 Amino peptidase activity

Cellier et al [207] have reported 2-benzoxazole derivatives of the type (140) as fluorogenic substrates for the nitroreductase and aminopeptidase activity in clinically important bacteria. The majority of Gram negative bacteria produced strongly fluorescent colonies.
3.2.2.7 Antioxidant activity

Jayanna et al [208] have reported the antioxidant evaluation of novel 1-(5,7-Dichloro-1,3-benzoxazol-2-yl)-1H-pyrazolo[3,4-b]quinolinederivatives (141 and 142). Antioxidant activity of novel dichloro substituted benzoxazole-triazolo-thione derivatives (143-145) was reported by Satyendra et al [209].

3.2.2.8 Antituberculosis

Klimesova et al [210] have reported the in vitro evaluation of benzylsulfonyl benzoxazole derivatives of the type (146) as potential antituberculosis agents against Mycobacterium tuberculosis, non-tuberculous mycobacteria and multidrug-resistant M. tuberculosis.
3.3 REVIEW ON IMIDAZOLE DERIVATIVES

3.3.1 Synthesis of Imidazole Derivatives

One-pot synthesis of imidazoles from aromatic nitriles with nickel catalyst was reported by Horneff et al [211] (Scheme 3.53).

![Scheme 3.53 Nickel catalyzed synthesis of imidazoles](image)

Iv et al [212] have reported the use of barium managanate for the conversion of imidazolines to imidazoles in presence of sulphur. Imidazolines obtained from alkyl nitriles and 1, 2-Ethanediamine on reaction with BaMnO$_4$ yielded 2-Substituted imidazoles (Figure 3.54).

![Figure 3.54 Synthesis of 2-substituted imidazoles](image)

Marek et al [213] have reported the facile synthesis of optically active imidazole derivatives by the condensation of the corresponding α-bromoketones with formamidine acetate in liquid ammonia (Figure 3.55).

![Figure 3.55 Synthesis of optically active imidazole derivatives](image)
Qasim et al [214] have reported the synthesis and characterization of novel series of the imidazoles under solvent free conditions by using sodium dihydrogen phosphate. (Figure 3.56)

![Synthesis of novel series of imidazoles](image)

**Figure 3.56 Synthesis of novel series of imidazoles**

Parveen et al [215] have reported the efficient synthesis of 2,4,5-triaryl substituted imidazoles (Figure 3.57) under solvent free conditions at room temperature by grinding 1,2-diketones, aromatic aldehydes and ammonium acetate in the presence of molecular iodine as catalyst.

![Iodine catalyzed synthesis of 2,4,5-triaryl substituted imidazoles](image)

**Figure 3.57 Iodine catalyzed synthesis of 2,4,5-triaryl substituted imidazoles**

An efficient and green procedure for the synthesis of 2, 4, 6-triaryl-1H-imidazole in polyethylene glycol under microwave irradiation has been developed by Nalage et al [216] (Figure 3.58).

![Microwave synthesis of 2, 4, 6-triaryl-1H-imidazole](image)

**Figure 3.58 Microwave synthesis of 2, 4, 6-triaryl-1H-imidazole**
An efficient and a quick microwave-assisted synthesis of trisubstituted imidazoles (Figure 3.59) were developed by the condensation of benzil, aromatic aldehyde and ammonium acetate in the presence of glacial acetic acid [217].

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{Ph} & \quad \text{O} \\
& \quad + \quad \text{ArCHO} \quad + \quad \text{NH}_2\text{OAc} \\
& \quad \text{HOAc} \quad \text{MW} \\
& \quad \rightarrow \quad \text{Ph} \quad \text{N} \quad \text{Ar} \quad \text{Ph} \\
\end{align*}
\]

Figure 3.59 Microwave assisted synthesis of trisubstituted imidazoles

One pot synthetic method has been developed for the synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetra substituted Imidazoles (Figure 3.60) by Vikrant et al [218]. The synthetic sequence, via a multi-component condensation catalyzed by p-toluenesulfonic acid (PTSA) provide a good isolated yields under mild conditions.

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{Ph} & \quad \text{O} \\
& \quad + \quad \text{NH}_2\text{OAc} \quad + \quad R\text{-}\text{Ph} \quad \text{CHO} \\
& \quad \text{PTSA, 5 mol\%} \quad \text{Ethanol 80°C} \\
& \quad \rightarrow \quad R\text{-}\text{Ph} \quad \text{N} \quad \text{Ph} \quad \text{Ph} \\
\end{align*}
\]

Figure 3.60 p-toluenesulfonic acid synthesis of imidazoles derivatives

Dandale and Solanki [219] have reported the efficient synthesis of imidazoles under microwave irradiation. (Figure 3.61)

\[
\begin{align*}
\text{R} \quad \text{R}_1 \quad \text{R}_2 \quad \text{COCH}_2\text{Br} \\
& \quad + \quad \text{R}_3 \quad \text{H}_2\text{N} \quad \text{NH}_2 \\
& \quad \text{TEBA, Ethanol} \quad 3-5 \text{ min} \\
& \quad \rightarrow \quad \text{R} \quad \text{R}_2 \quad \text{R}_1 \quad \text{NH} \quad \text{NH} \quad \text{R}_3 \\
\end{align*}
\]

Figure 3.61 Microwave synthesis of imidazoles

Salehi et al [220] have reported a simple and efficient method for the synthesis of 2,4,5-triaryl-1H-imidazole derivatives in good to excellent yields by reaction between hexamethyldisilazane and arylaldehydes, benzyl alcohols, benzyl halides in molten tetrabutylammonium bromide (Figure 3.62).
Shelke et al [221] have reported an efficient synthesis of 2,4,5-Triaryl-1H-imidazole derivatives (Figure 3.63) catalyzed by boric acid in aqueous media under ultrasound irradiation.

Ceric ammonium nitrate (CAN) is used as an efficient catalyst for the synthesis of 2,4,5-triaryl-1H-imidazoles (Figure 3.64) via condensation of benzoin/benzil, ammonium acetate and aromatic aldehydes [222].
3.3.2 Biological Activities of Imidazole Derivatives

3.3.2.1 Antimicrobial activity

Novel imidazole derivatives of the type (147) and evaluation of their antimicrobial activity was studied by Jawaharmal et al [223]. Prabhu and Radha [224] have reported the evaluation of antibacterial activity of some novel aryl imidazole derivatives of the type (148). All the compounds showed moderate to good antibacterial activity against the tested bacteria. Antimicrobial activity of imidazole derivative of the type, viz., 2-Chloro-7-methyl-3-formylquinoline (149) was reported by Parab and Dixit [225].

3.3.2.2 Antioxidant activity

Naik et al [226] have reported 5-Substituted 1-aryl-2,3-diphenyl imidazoles of the type (150) by employing three in vitro assays like 2,2-Diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay, 2,2’-Azino-bis(3-ethylbenzthiazoline-6-sulfonic acid (ABTS) assay and iron reducing power assay. All the compounds showed predominant antioxidant activity. Suresh et al [227] have reported the antioxidant activity studies on 2-Benzylsulfonyl-1H-imidazoles (151). All the compounds showed good antioxidant activity.
3.3.2.3 Antiinflammatory activity

Puratchikody and Doble [228] have reported the synthesis of 2-substituted-4,5-diphenyl-1H-imidazoles and checked the antiinflammatory activity based on Carrageenan-induced paw edema method using indomethacin as reference drug. This compound (Compound 152) showed maximum activity.

\[
\text{HN} \quad \text{C}_6\text{H}_5 \quad \text{N} \quad \text{OCH}_2\text{C}_6\text{H}_5
\]

3.3.2.4 Antituberculosis activity

Preeti Gupta et al [229] describe the antimycobacterium tuberculosis activities of ring substituted 1H-imidazole-4-carboxylic acid derivatives of the type (153) against drug-sensitive and drug-resistant M. tuberculosis strains.

\[
\text{R}_1 \quad \text{OC}_2\text{H}_5 \quad \text{R}_2 \quad \text{HN} \quad \text{N} \quad \text{O}\]

Jyoti and coworkers [230] synthesized a series of imidazole derivatives and screened the compounds against *M. tuberculosis*. Among the tested compounds, the compound (154) showed good antitubercular activity.

\[
\text{C}_3\text{H}_7
\]
3.3.2.5 Antidepressant activity

Hadizadeh et al [231] synthesized moclobemide analogues by replacing moclobemide phenyl ring with substituted imidazole (155) and studied the antidepressant activity using forced swimming test.

\[ \text{155} \]

3.3.2.6 Antitumor activity

Congiu et al [232] synthesized a series of 1,4-diarylimidazole-2(3H)-one derivatives and their 2-thione analogues and evaluated antitumor activity. This compound (156) showed potent antitumor activity among the tested compounds.

\[ \text{156} \]

3.3.2.7 Antiviral activity

Deepika Sharma et al [233] synthesized a series of imidazole derivatives and screened the compounds for antiviral activity. Among the tested compounds, the compound viz., (substitutedphenyl)-[2-(substituted phenyl)-imidazol-1-yl]-
methanones (157) exhibited potent antiviral activity. Ribavirin was used as the standard drug.

\[ \text{157} \]

3.3.2.8 Antilishmanial activity

Bhandari et al [234] synthesized a series of substituted aryloxy alkyl and aryloxy aryl alkyl imidazole of the type (158) and evaluated \textit{in vitro} as antileishmanial activity against Leshmania donovani. All the compounds exhibited 94–100% inhibition.

\[ \text{158} \]
3.4 REVIEW ON TETRAZOLE DERIVATIVES

3.4.1 Synthesis of Tetrazole Derivatives

Gowd and Pasha [235] have reported a versatile and an efficient synthesis of 5-Substituted-1H-tetrazoles (Figure 3.65).

![Figure 3.65 Synthesis of 5-substituted-1H-tetrazoles](image)

Demko and Sharpless [236] have reported the convenient method for the transformation of α-aminonitriles to the tetrazole analogues of α-amino acids by refluxing the starting material in water/2-propanol at 80°C with sodium azide and zinc bromide catalyst (Figure 3.66).

![Figure 3.66 Synthesis of Tetrazoles](image)

Palde and Jamison [237] have reported the safe and efficient tetrazole synthesis in a continuous flow micro reactor (Figure 3.67).

![Figure 3.67 Microwave synthesis of Tetrazoles](image)
Bond et al [238] have reported the synthesis of tetra-tetrazole macrocycles, (Figure 3.68) containing two 1,3-bis(tetrazole)benzene units linked by a variety of \( n \)-alkyl chain lengths.

![Figure 3.68 Synthesis of tetra-tetrazole](image)

Crawford et al [239] have studied the high-yield syntheses of trifluoroacetonitrile, pentafluoropropionitrile and heptafluorobutyronitrile under mild reaction conditions using readily available starting materials. Furthermore, the perfluoroalkyl nitriles with sodium azide in acetonitrile form Sodium 5-trifluoromethyltetrazolate, Sodium 5-pentafluoromethyltetrazolate and Sodium-heptafluoromethyltetrazolate (Figure 3.69).

![Figure 3.69 Synthesis of Sodium 5-pentafluoromethyltetrazolate](image)
Chimirri et al [240] have synthesized novel 11\(H\)-Tetrazolo[1,5-c][2,3]benzodiazepines following the scheme (Figure 3.70)

![Figure 3.70 Synthesis of 11\(H\)-Tetrazolo[1,5-c][2,3]benzodiazepines](image)

Cristau et al [241] have reported the syntheses of tetrazole precursors (Figure 3.71) using Schmidt rearrangement using Trimethylsilyl azide with various \(\alpha\)-Dialkylated \(\beta\)-Ketoesters.

![Figure 3.71 Synthesis of tetrazole precursors](image)

Dondoni and Marra [242] have addressed the scope of the azide-nitrile cyclo addition in glycoconjugate chemistry. New glyoclusters constituted ribosylmethyl, galactomethyl, galaosylmethyl and glucosylmethyl fragments assembled on a calyx(4)arene platform by means of propoxy tetrazole spacers have
been prepared by coupling the corresponding sugar azide with $p$-Toluenesulfonyl cyanide and then reacting 1-Glycosylmethyl-5-sulfonyl-tetrazole derivatives thus formed with a calyx(4)arene tetrol (Figure 3.72)

Figure 3.72 Synthesis of Calyx(4)arene tetrol

Dabbagh et al [243] have described the synthesis of 5-(1-(2-(1H-tetrazole-5-yloxy)naphthalene-1-yl)naphthalene-2-yloxy)-1H-tetrazole (BIZOL) as the first bis-tetrazole BINOL-type ligands (Figure 3.73).
Figure 3.73 Synthesis of 5-(1-(2-(1H-tetrazole-5-yloxy)naphthalene-1-yl)naphthalene-2-yloxy)-1H-tetrazole

Guillou et al [244] have reported the synthesis of the tricyclic 7-Azidofurazano[3,4-b]tetrazolopurazine (Figure 3.74).

Figure 3.74 Synthesis of tricyclic 7-Azidofurazano[3,4-b]tetrazolopurazine

Godovikova et al [245] have synthesized a number of 5-(1,2,5-Oxadiazol-3-yl)-1H-tetrazoles (Figure 3.75) in high yields by reactions of 3-Cyano-1,2,5-oxadiazoles with sodium azide or by nitrosation of furazan-based amidrazones.

Figure 3.75 Synthesis of 5-(1,2,5-Oxadiazol-3-yl)-1H-tetrazoles

Gyoung et al [246] have synthesized a variety of 2-Allylated-5-substituted tetrazoles (Figure 3.76) in excellent yields through the reaction of alkyl and arylidenemalononitriles, allyl acetates and trimethylsilyl azide in the presence of palladium catalyst.
Gavrilyuk et al [247] have described a method for the synthesis of polypeptides modified with a tetrazole ring at the N-terminates. Reaction of the N-terminal amino group of solid-supported peptides with arylisothiocyanates generates thiourea intermediates, which upon treatment with Mukaiyama’s reagent (2-Chloro-1-methylpyridinium iodide) generate electrophilic carbodiimide functionality. Trapping by the azide anion and electrocyclization of the intermediate imidazolidine generates an Aryl-substituted 5-amino tetrazole (Figure 3.77) at the N-terminus of the peptide.

Alam and Nasrollahzadeh [248] have reported a simple and efficient method for the preparation of 5-Arylamino-1H-tetrazoles and 5-Amino-1-aryl-1H-
tetrazoles (Figure 3.78), with excellent yields and high purity from secondary arylcyanamides in glacial acetic acid at room temperature.

![Figure 3.78 Synthesis of 5-Amino-1-aryl-1H-tetrazoles](image)

Sureshbabu et al [249] have studied an efficient synthesis of tetrazole analogues of amino acids starting from 4-N-Fmoc amino acid in a three step protocol. The free amino tetrazoles (Figure 3.79) were obtained in good yields and with excellent purity after the removal of the Fmoc group.

![Figure 3.79 Synthesis of amino tetrazoles](image)

Kessenich et al [250] have synthesized 2-Triphenylphosphanimino-4-azidotetrazolo[5,1-a]-[1,3,5]triazine by reaction of 2,4,6-Triazido-1,3,5-triazine triphenylphosphane. Raman and X-ray data revealed that only one azide group formed a tetrazole ring system (Figure 3.80), whereas the second azide group did not undergo ring closure.
Athanassopoulos et al [251] have reported the efficient synthesis of 5-Aminoalkyl-1H-tetrazoles and of polyamines incorporating tetrazole ring. Linear $N^\omega$-tritylated $\omega$-amino thiobenzylamides and $N^\omega,N^\omega$-Sitritylated polyamino mono- or bis-thioamides were efficiently converted to the corresponding tetrazole derivatives (Figure 3.81) upon treatment with azidotrimethylsilane under Mitsunobu reaction conditions.

**Figure 3.80** Synthesis of 2-Triphenylphosphanimino-4-azidotetrazolo[5,1-a]-[1,3,5]triazine
Figure 3.81 Synthesis of 5-Aminoalkyl-1H-tetrazoles

A very potent HIV-1 protease inhibitor, comprising two tetrazole heterocycles as carboxyl group bioisosteres, was prepared in one pot by microwave promoted cyanation of bromo precursor and a subsequent cycloaddition reaction. Alterman and Hallberg [252] have prepared aryl and vinyl nitriles from the corresponding bromides using palladium-catalyzed reactions with microwave irradiation. Further, flash heating was done for the conversion of these nitriles into aryl and vinyl tetrazoles by cycloaddition reactions (Figure 3.82).

Figure 3.82 Synthesis of microwave irradiation of tetrazole

Polivanova et al [253] have reported a new one step reaction between 1,1-Difluoroazides and primary amines for tetrazole formation (Figure 3.83).
4-(Arylmethyl)tetrazolyl-pyroglutamic and proline derivatives were synthesized by Lenda et al [254] from Dimethyl-2,4-dibromoglutarlyle in good yield using mild reaction conditions. The tetrazole derivatives were prepared by the selective $N_2$-Alkylation of 5-Substituted tetrazole with Dimethyl-2,4-dibromoglutarlyle (Figure 3.84).

Hill et al [255] have synthesized the titanium coordination complex (Figure 3.85) by treating TiCl$_4$ with two equivalents of 5-Phenyltetrazole in dichloromethane. The complexes have been characterized spectroscopically and crystallographically.
Figure 3.85 Synthesis of titanium coordination tetrazole complex

One-pot synthesis of 1-Substituted 5-alkyl(or aryl)sulfanyl tetrazole have been demonstrated by Han et al [256]. Addition of alkyl or aryl halides into the mixture of organic isothiocyanates, NaN₃ and pyridine in water at room temperature exclusively formed 1-Substituted 5-alkyl(or aryl)sulfanyl tetrazoles (S-derivatives) in high yields (Figure 3.86).

Figure 3.86 Synthesis of 1-Substituted 5-alkyl(or aryl)sulfanyl tetrazoles

Jin et al [257] have synthesized 1-Substituted tetrazoles (Figure 3.87) via the (3+2) cycloaddition between isocyanides in the presence of an acid catalyst and MeOH. The authors have reported that the reaction proceeds through the in-situ formation of hydrazoic acid followed by a successive (3+2) cycloaddition with isocyanide activated by an acid.
Kang et al [258] have synthesized a series of tetrazole-biarylpyrazoles (Figure 3.88). In this work, generic acid was converted to acyl chloride with thionyl chloride and this intermediate was then treated with ammonium hydroxide solution in methylene chloride to afford the corresponding amide. Subsequently nitrile was prepared by condensation of amide with phosphoryl chloride in high yield. Treatment of nitrile with sodium azide efficiently gave rise to tetrazole.

The first and unprecedented examples of inverse electron demand Diels-Alder reactions of 5-(1-Nitrosovinyl)-1-phenyl-1H-tetrazole (Figure 3.89)
generated *in situ* from the corresponding bromoxime with electron rich alkenes and heterocycles was reported by Lopes *et al* [259].

**Figure 3.89 Synthesis of 5-(1-Nitrovinyl)-1-phenyl-1H-tetrazole**

May and Abell [260] have reported the synthesis of a *cis*-dipeptide mimic n-boc-phe(COCN$_4$)-Gly-Obn, containing the non-hydrolysable alpha-keto tetrazole isostere and an unusual 2,5-Disubstituted alpha-keto tetrazole-based peptidomimetic. The incorporation of the novel *cis*-amide bond isostere was achieved via direct alkylation of a precursor five substituted(1H)-tetrazole (Figure 3.90).

**Figure 3.90 Synthesis of five Substituted(1H)-tetrazole**
Ma et al [261] have synthesized organoantimony(V) complexes with 1-Phenyl-1*H*-tetrazole-5-thiol (Figure 3.91) and characterized the complexes by spectral and X-ray crystallographic studies.

![Figure 3.91 Synthesis of 1-Phenyl-1*H*-tetrazole-5-thiol](image)

Muttenthaler et al [262] have synthesized di-tetrazole ligands (Figure 3.92) and studied their spin-cross over behavior.

![Figure 3.92 Synthesis of di-tetrazole](image)

Mansoori et al [263] have synthesized a series of new Bis(5-oxy-1*H*-tetrazole) (Figure 3.93) derivatives by the reaction with cyanogen bromide in the presence of triethylamine to form the product.

![Figure 3.93 Synthesis of Bis(5-oxy-1*H*-tetrazole)](image)
Mohite et al [264] have synthesized a series of novel 5-Phenyl-1,1-acyl-1,2,3,4-tetrazoles (Figure 3.94) via condensation of 5-Phenyl-1,2,3,4-tetrazoles with various acylating reagents. 5-Phenyl-1,2,3,4-tetrazoles was synthesized by the cycloaddition of benzodinitrile with sodium azide and ammonium chloride in the presence of dimethylformamide as solvent.

![Figure 3.94 Synthesis of 5-Phenyl-1,1-acyl-1,2,3,4-tetrazoles](image)

Muraglia and coworkers [265] have synthesized a series of Aryltetrazolylacetanilides (Figure 3.95) and evaluated as HIV-1 non-nucleoside reverse transcriptase inhibitors on wild-type virus and on the clinically relevant K103N mutant strain.

![Figure 3.95 Synthesis of Aryltetrazolylacetanilides](image)

Santos et al [266] have described the new liquid crystalline heteroatomic compounds containing the five-membered tetrazole rings (Figure 3.96).
Nasrollahzadeh et al [267] have reported an efficient method for the preparation of arylaminotetrazoles (Figure 3.97) using natrolite zeolite as a natural catalyst.

Ortar et al [268] have synthesized a series of 1,5-Disubstituted carbomyl tetrazoles (Figure 3.98) as potent inhibitors of the cellular uptake of the endocannabinoid anandamide.
3.4.2 Biological Activities of Tetrazole Derivatives

3.4.2.1 Antimicrobial activity

Chao et al [269] have reported the synthesis of several new 5-[4’-(5-Phenyl-1,3,4-oxadiazol-2-ylsulfanyl)methyl]-biphenyl-2-yl]-tetrazole (159) derivatives and evaluated the antibacterial activities of the compounds. Pandey et al [270] have synthesized new fused heterocyclic systems, viz., Triazolo[4,3-a]-quinazolin-7-ones, [1,2,4,5]-Tetrazino[4,3-a]-quinazolin-8-ones and Indolo[2,3-c][1,2,4]triazino[4,3-a]-quinazolin-8-ones from the key intermediate 3-(Substituted-phenyl)-2-hydrazino-quinazolin-4-ones. All the synthesized compounds have been screened for their antibacterial activity against Gram-negative bacteria, such as *Escherichia coli*, *Pseudomonas aeruginosa*, and Gram-positive bacteria, such as *Streptococcus pneumonia* and *Bacillus subtilis*. The compounds also demonstrated significant antifungal activity against fungi, such as *Candida albicans*, *Aspergillus fumigates*, *Aspergillus flavus* and *Aspergillus niger*. Among the tested compounds, compound (160) exhibited potent activity against the tested microorganism.

Yildirir and coworkers [271] have studied the antimicrobial activity of some new Phenylselanyl-1-(toluene-4-sulfonyl)-1H-tetrazole derivatives of the type (161) using sulfamethoxazole (SMX) and sulfamerazine (SRZ) as the standard drug for comparison. Dayanithi et al [272] have reported a series of novel 1-Substituted tetrazole derivatives and evaluated their antibacterial and antifungal activity. In this
study, thiazole attached tetrazole derivatives (162) were most active than the piperazine attached tetrazole derivatives.

He et al [273] have reported a series of new 5-(1-Aryl-1H-tetrazol-5-ylsulfanyl)methyl)-N-(2,3,4-tri-o-acetyl-β-D-xylopyranosyl)-1,3,4-thiadiazol-2-amines (163) and 5-(1-Aryl-1H-tetrazol-5-ylsulfanyl)methyl)-N-(2,3,4-tri-o-acetyl-β-D-xylopyranosyl)-1,3,4-thiadiazole-2-amines (164) under mercuric acetate/alcohol system of acetic anhydride/phosphoric acid system, then deacetylated in the solution of CH$_3$ONa/CH$_3$OH. Some of the synthesized compounds displayed PTP 1B inhibition and microorganism inhibition. Antimicrobial activities of the synthesized compounds were investigated against Gram-positive Bacillus subtilis, Gram-negative Escherichia coli and fungi Candida albicans and Aspergillus niger. Some of the tested compounds showed significant antimicrobial activity by Kategaonkar et al [274].
Patel et al [275] have synthesized a series of substituted 2-Benzimidazole bearing a cyclohexyl tetrazole moiety of the type (165). All the compounds were screened in vitro for their potential antibacterial and antifungal properties. The tested compounds exhibited good to moderate activities.

![Chemical Structure](image)

**165**

Umarani and Ilango [276] have described the synthesis of new series of tetrazolo quinoxalines (166) as antimicrobial agents. Cup-plate agar diffusion method was used for the in vitro antimicrobial activity. Some of the synthesized compounds showed interesting antimicrobial activity comparable to the standard drugs, Ofloxacin and Griseofulvin. Varadaraji et al [277] have synthesized several 5-Thio-substituted tetrazole derivatives (167). All the synthesized compounds were screened for their antibacterial and antifungal activities.

![Chemical Structures](image)

**166**  **167**

Upadhayaya et al [278] have synthesized a series of novel substituted tetrazoles (168 and 169) and evaluated for antifungal activity against Candida spp., Cryptococcus neoformans and Asperillus spp., in vitro. The authors have reported
that the presence of the methyl group at the C-3 of compounds is the key structural element of antifungal potency.

3.4.2.2 Antihypertensive activity

Sharma et al [279] have synthesized a series of substituted 5-Nitrobenzimidazoles bearing a biphenyl tetrazole moiety at the 2-position (170) and evaluated for Angiotension II (AII) receptor antagonistic antihypertensive activity. Sharma et al [280] have synthesized some (2-{6-Chloro-5-nitro-1-[2-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]1H-benzimidazol-2-yl}-phenyl)-(substituted-benzylidene)-amine of the type (171) and 5,6-Substituted-1-[2’-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-2-trifluoromethyl-1H-benzimidazole (172) and screened their antihypertensive activity. All the compounds showed significant antihypertensive activity.
3.4.2.3 Anticonvulsant activity

Dun et al [281] have reported the anticonvulsant activity of 6-(4-Chlorophenoxy)-tetrazole[1,5-α] phtalazine (173) in various experimental seizure models. Bhaskar and Mohite [282] have synthesized some novel 5-Phenyl tetrazoles of the type (174). The newly synthesized compounds were screened for anticonvulsant activity and found to be potent.

3.4.2.4 Antiproliferative activity

Gundugola et al [283] have synthesized a series of 1,4-Diaryl tetrazol-5-ones of the type (175) by copper mediated N-arylation of 1-Phenyl-1H-tetrazol-5(4H)-one with aryl boronic acids. The 1,4-Diaryltetrazol-5-ones substituted with OMe, Cl, CF₃ and Br with Lawesson’s reagent yielded the corresponding
5-Thio derivatives. The 1-(2-Bromophenyl)-4-phenyl-1H-tetrazole-5(4H)-thione so obtained was subjected to lithiation/protonation and Sonogashira coupling to produce 1,4-Diphenyl-1H-tetrazole-5(4H)-thione and 1-(Ethynylphenyl)-4-phenyltetrazole-5-thione, respectively. Three of these novel compounds were found to inhibit L1210 leukemia cell proliferation and SK-BR-3 breast cancer cell growth over several days in culture *in vitro*. Shorter tetrazole derivative treatments also reduced the expression of the Ki-67 marker of cell proliferation in SK-BR-3 cells and the rate of DNA synthesis in L1210 cells.

![Chemical structure of 1-(2-Bromophenyl)-4-phenyl-1H-tetrazole-5(4H)-thione](image)

### 3.4.2.5 Cytotoxic activity

Popsavin *et al* [284] have reported the synthesis of 3(5)-Carbozamido-4-(β-D-ribofuranosyl)pyrazoles bearing 2’-benzamido and 3’-mesyloxy isosteric groups, as well as the tetrazole (176) C-nucleosides with 2-Benzamido-2-deoxy-β-D-ribofuranose and 3-Azido-3-deoxy-β-D-xylofuranose as sugar segments, starting from D-glucose, by utilizing the 2,5-Anhydro-D-glucose ethylene acetal derivatives and as divergent intermediates. The C-nucleotides were shown to be moderate inhibitors of the *in vitro* growth of both N2a and BHK 21 tumor cell lines, whereas showed a selective, although not potent cytotoxic activity against N2a cells. Voitekhovich *et al* [285] have studied the complexes CuL$_2$Cl$_2$, PdL$_2$Cl$_2$ and PtL$_2$Cl$_2$, where L is a novel ligand from the series of 2-Substituted 5-aminotetrazoles, namely 5-Amino-2-tert-butyltetrazole (177). Platinum complex demonstrates promising cytotoxicity against human cervical carcinoma cells with IC$_{50}$ value average between those of cisplatin and carboplatin.
3.4.2.6 Antihyperglycemic activity

A series of 5-[(5-Aryl-1H-pyrazol-3-yl)methyl]-1H-tetrazoles of the type (178) was synthesized by Sharon et al [286]. The compounds were evaluated for their in vivo antihyperglycemic activity. Some of the synthesized compounds have shown significant glucose lowering activity in male Sprague-Dawley rats in sucrose loaded model. The compounds were also evaluated for their peroxisome proliferator activated receptor γ agonistic property, but none of them displayed any significant activity.

3.4.2.7 Hypoglycemic Activity

Gao and coworkers [287] have designed and synthesized some novel tetrazole-bearing N-glycosides of the type (179) as SGLT2 inhibitors. The hypoglycemic activity of the compounds has been tested in vivo by mice glucose tolerance test (OGTT). Two compounds are found to be more potent than the positive control Dapagliflozin. The structure activity relationship was also investigated.
3.4.2.8 Analgesic activity

Rajasekaran and Thambi [288] have synthesized a series of novel 5[β-(Phenothiazinyl-10-yl)ethyl]-1-acyl)-1,2,3,4-tetrazoles of the type (180) and demonstrated that these compounds possessed good analgesic activity when tested by acetic acid induced writhing and hot plate methods. The most promising compounds having analgesic activity were 5[β-(Phenothiazinyl-10-yl)ethyl]-1-(benzoyl)-1,2,3,4-tetrazoles and 5[β-(Phenothiazinyl-10-yl)ethyl]-1-(p-tolyl)-1,2,3,4-tetrazoles. Khanage et al [289] have synthesized 5-Phenyl-1-[(5-substituted aryl-4H-1,2,4-triazol-3-yl)methyl]-1H-tetrazole derivatives of the type (181) and screened for analgesic activity by acetic acid induced writhing method and hot plate method. Functional groups like –Cl, –OCH₃ and –NO₂ containing derivatives are found to be promising analgesic compounds from the newly synthesized series.

Bhaskar and Mohite [290] have reported the synthesis of different derivatives of substituted 5-Phenyl-1-(5-substituted phenyl)-4,5-dihydro-1H-pyrazole-3-yl)-1H-tetrazole (182). The compounds were screened for analgesic activity by acetic acid induced writhing method and hot plate method. The results of this investigation revealed that the observed increase in analgesic activity is
attributed to the presence of 4-NO$_2$, 4-OH and 4-Cl in phenyl ring at 5-position of pyrazoline ring of synthesized compounds containing tetrazole.