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VERSATILITY OF BENZIMIDAZOLE AND ITS DERIVATIVES; AN INSIGHT

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Keywords:

Benzimidazole derivatives, Fused heterocycle, Anti-cancer, Anti-fungal

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ABSTRACT: Benzimidazole, a fused heterocyclic moiety containing benzene and imidazole, has gained considerable attention in the field of medicinal chemistry due to its wide array of pharmacological activities. Be it as a antifungal, anticancer agent, proton pump inhibitors, anthelmintic, anti-microbial, analgesic, it has become an intrinsic part of the pharmaceutical world. The presence of Nitrogen in its heterocyclic ring has made it a more biologically active pharmaceutical agent. The fact that benzimidazole residue is a constituent of vitamin B12 supports its potential use in therapeutics. Benzimidazole derivatives are the structural isosters of naturally occurring nucleotides such as purine, allow them to interact effectively with the biopolymers of the living system such as proteins, enzymes, and receptors. Benzimidazoles exhibit significant activity as a potential anti-tumour agent, smooth muscle cell proliferation inhibitors, a treatment for intestinal cystitis, and in a diverse area of medicinal chemistry. The synthesis of novel benzimidazole derivatives remains as the main focus of medicinal research. This current review covers the chemistry and significance of benzimidazole and its derivatives, also helps to develop the derivatives of benzimidazole in this antimicrobial-resistant era.

INTRODUCTION: Benzimidazole resembles the structure of Purine. This was discovered by Woolley in 1944. This lead to the further development of the benzimidazole moiety [1]. Looking at the nature and importance of this moiety it was thought that it would be worthwhile to design and develop some new benzimidazole derivatives which consist of oxadiazole moiety and screen their biological activity. Over the few decades of active research, it has been proved that Benzimidazole, as an important pharmacophore can show a large range of antibiotic effects and also fight against a huge number of bacteria [2].

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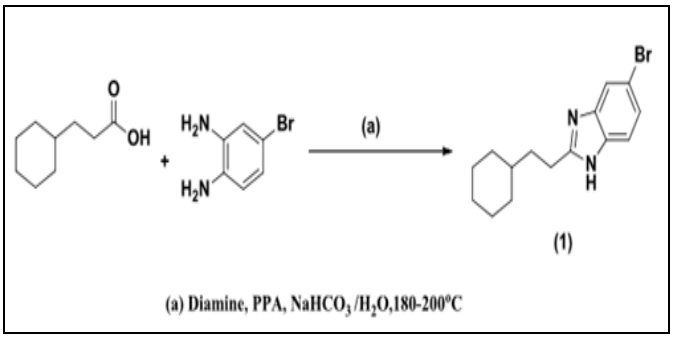
Based on the biological activity of the drug, they are classified into the following types.

Antituberculotic Activity:

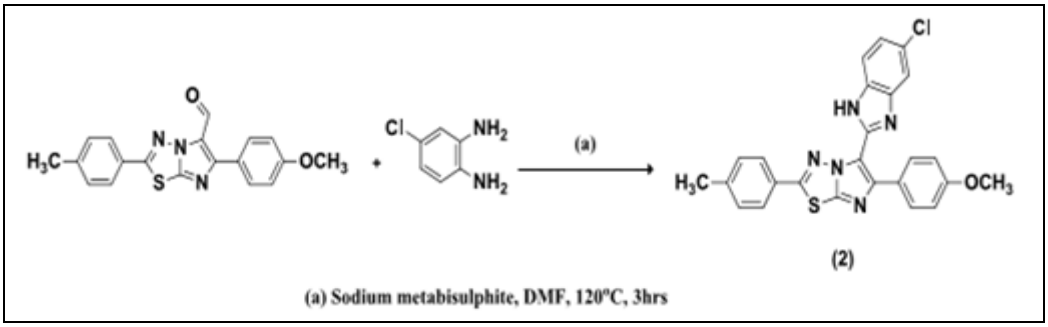
1. Gobis K *et al*., have discovered various novel benzimidazole analogues and evaluated them for tuberculostatic activity.



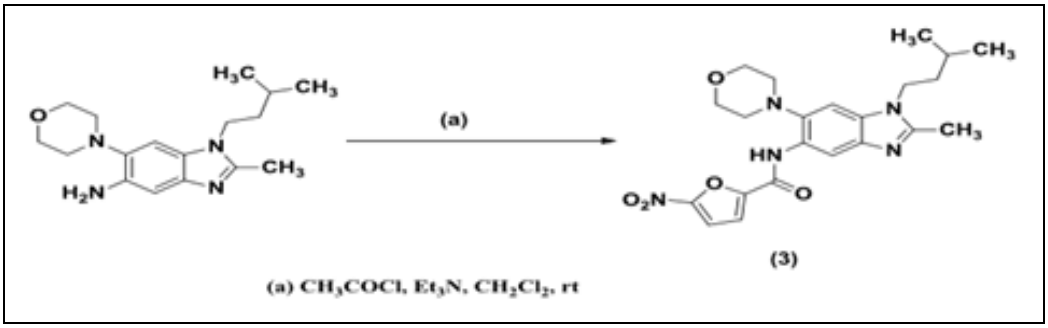
The bromo substituted analogues showed excellent activity against *Mycobacterium tuberculosis* and *Mycobacterium bovis* with MIC ranging from

0.751.5 µg/mL. Compound (5-bromo-2-(2-cyclo-hexylethyl)-1H-benzo[d]imidazole) (1) showed the highest potency.

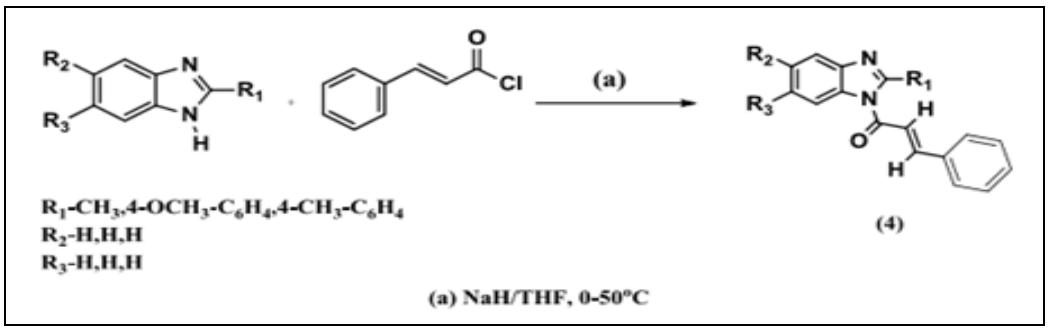
2. Ramprasad J *et al.,* have prepared a new series of imidazo (1, 3, 4) thiadiazole-benzimidazole derivatives. The synthesized compounds were screened for antitubercular activity. It had been found that most of the derivatives showed anti-tubercular activity with a MIC of 3.125mg/mL. 5-chloro- 2- (6-(4-methoxyphenyl)-2-p-tolylimidazo [2,1-b][1,3,4]thiadiazol-5-yl)-1Hbenzo[d]imidazole (2) was the most potent derivative.



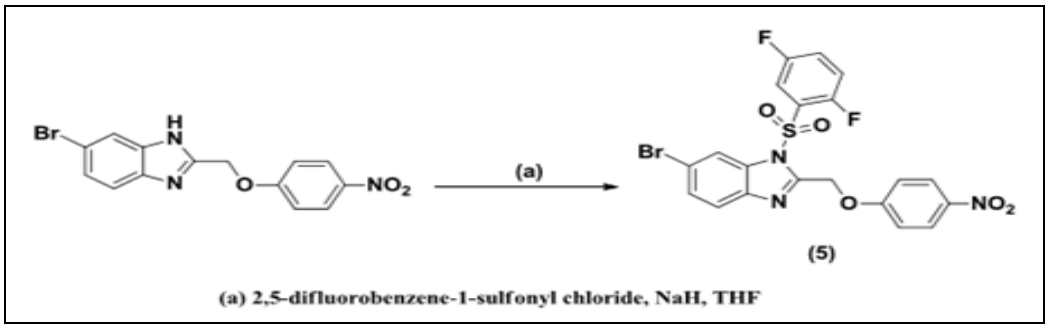
3. Gong Y *et al*., have synthesized various benzimidazole based compounds and evaluated them in replicating and non-replicating *M. tuberculosis* (Mtb). The study revealed that many compounds exhibited antitubercular activity but N-(1- cyclobutyl- 2- methyl- 6-morpholin benzo[d] imidazol-5-yl)-5-nitrofuran-2-carboxamide and N-(1- isopentyl- 2-methyl-6morpholino- 1H-benzo[d] imidazol-5-yl)- 5-nitrofuran-2- carboxamide (3) were more active.



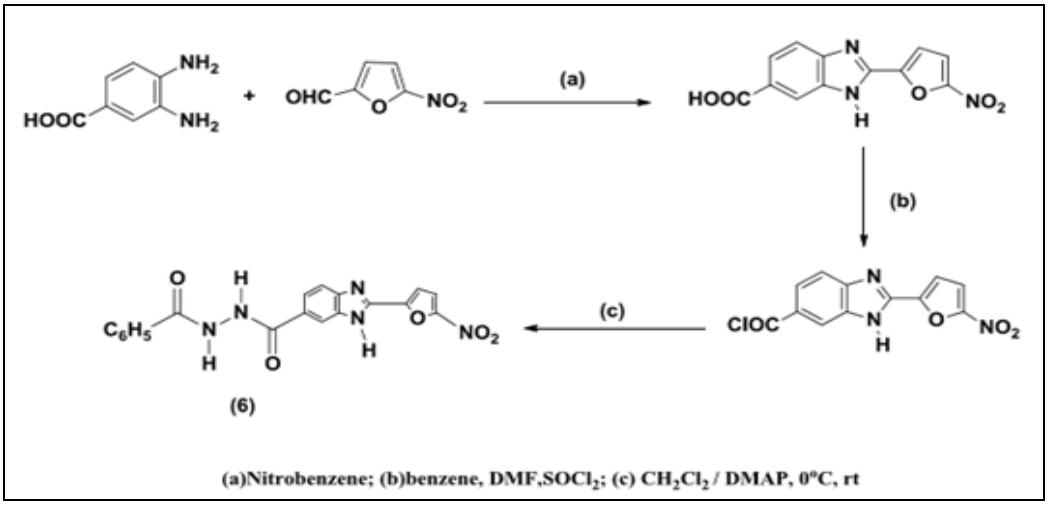
4. Kalalbandi V K A *et al.,* have synthesized a series of phenylprop-2-enoyl-benzimidazole derivatives. The synthesized compounds were screened for anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain and cytotoxic activity. Compound (E)-3-phenyl-1(2-(p-tolyl)-1H-benzo[d] imidazol-1-yl)prop-2-en-1-one (4) exhibited a promising antimycobacterial and cytotoxic activity.



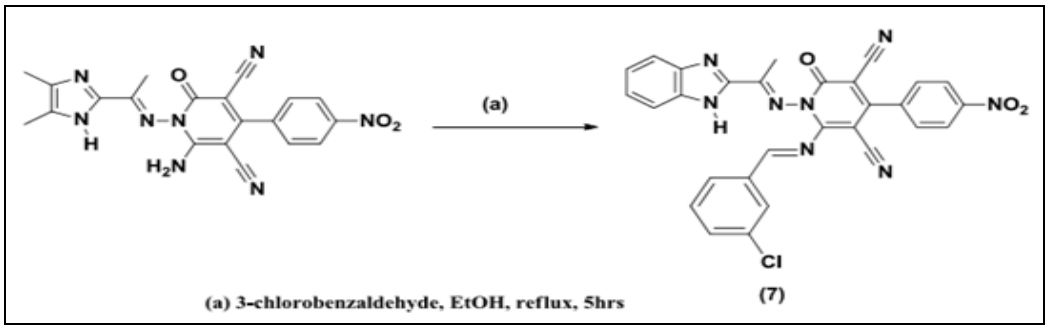
5. Ranjith P K *et al.,* reported a series of positional isomers of 5 and 6-bromo-1[(phenyl)sulfonyl]-2-[(4-nitrophenoxy)methyl]-1Hbenzimidazoles (5) derivatives. They were evaluated for antibacterial, antifungal and antitubercular activity. Several compounds showed activity against *Mycobacteruim tuberculosis* H37Rv strain.



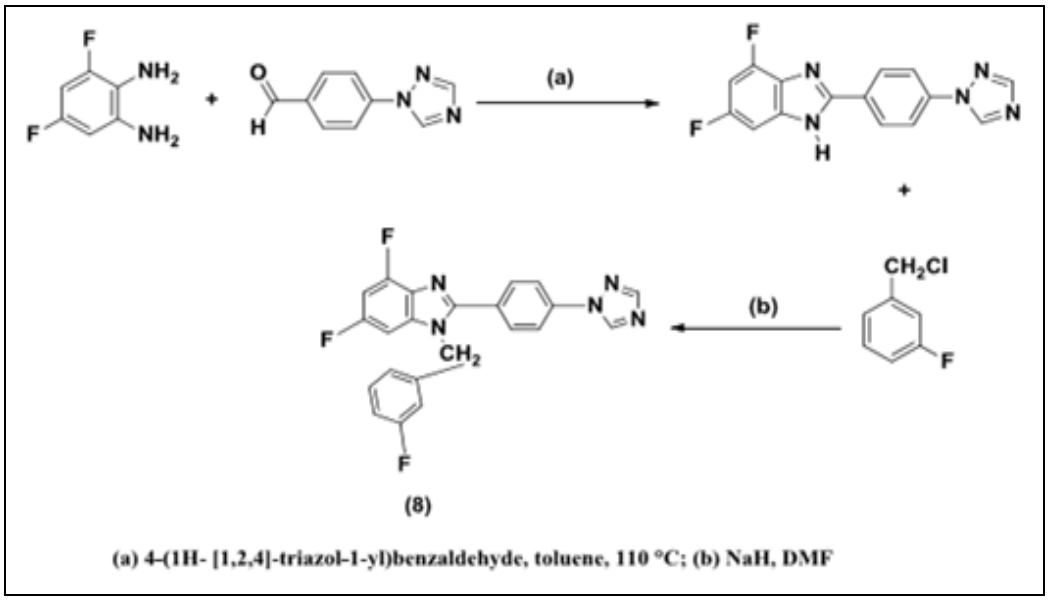
6. Camacho J *et al.,* have prepared a series of benzimidazole-5-carbohydrazide derivatives. The synthesized compounds were investigated for their abilities to inhibit β-hematin formation, hemoglobin hydrolysis, and *in-vivo* for their antimalarial efficacy. Selected analogues were evaluated for their antitubercular activity against sensitive Mtb H37Rv and multi drug-resistant MDR-Mtb strains. Compound N'-benzoyl-2-(5-nitrofuran- 2- yl)- 3H- benzo[d]imidazole- 5carbo-hydrazide (6) showed better antitubercular activity compared to rifampin against MDRMtb strains.



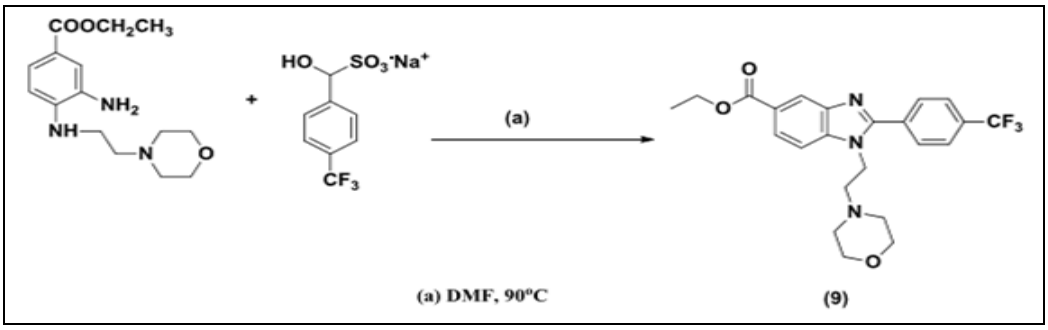
7. Desai NC *et al.,* have synthesized benzimidazole bearing 2-pyridone motifs and evaluated for their *in-vitro* antibacterial and antitubercular activity. All compounds were also examined for their cytotoxic study on VERO cell line. Compound 1-((1-(1H-benzo[d]imidazol- 2yl)ethylidene)amino)- 6- ((3-chlorobenzylidene)amino)- 4- (4-nitrophenyl)- 2-oxo-1,2dihydropyridine-3,5-dicarbonitrile (7) was proved to be the most potent antitubercular agent.



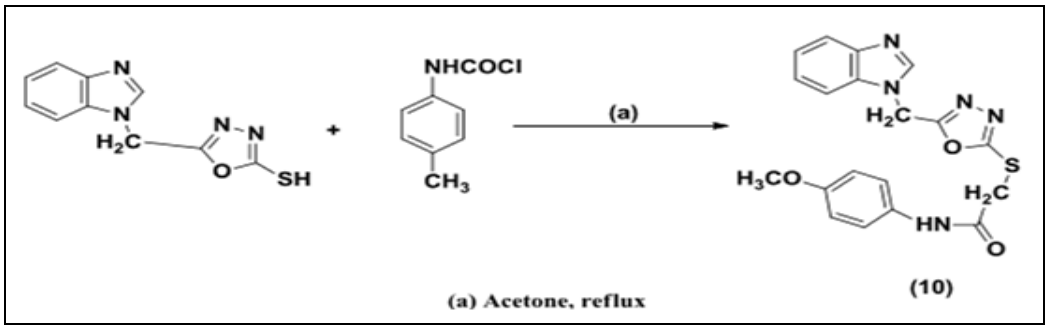
8. Jadhav GR. *et al.,* have discovered a series of novel [1,2,4]-triazol-1-yl, clubbed fluorobenzimi-dazole derivatives. The compounds were screened for their *in-vitro* antibacterial and antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain. It was observed that 2-(4-(1H-1,2,4-triazol-1-yl)phenyl)-4,6-difluoro-1-(3-fluorobenzyl)-1Hbenzo[d]imidazole compound (8) showed promising anti-tubercular activity.



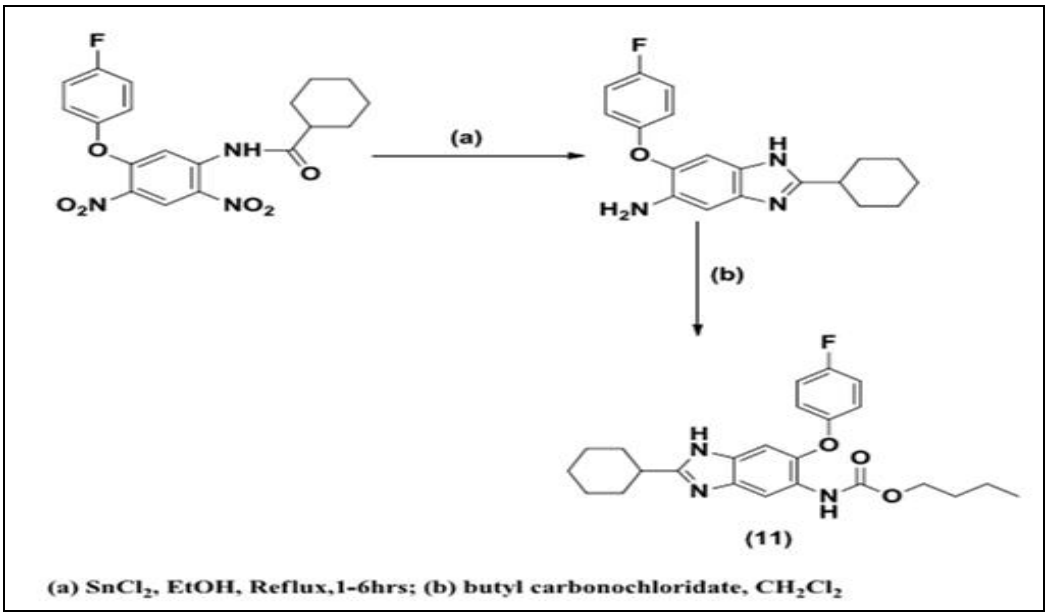
9. Yoon YK *et al.*, discovered new benzimidazole aminoesters and evaluated their antimycobacterial activity. Compound ethyl 2-(4-(trifluoromethyl) phenyl)- 1- (2morpholinoethyl)- 1H- benzo[d] imidazole-5-carboxylate (9) was found to be the most active with IC_{50} of 11.52 µM.



10. Patel RV *et al.*, [10] have synthesized a series of benzimidazole based 1,3,4-oxadiazoles derivatives and assessed them for their antimicrobial & antitubercular activity. The Nbenzothiazoyl acetamides series showed broad-spectrum antimicrobial & antitubercular potential. Amongst them 2-(5-((1H-benzo(d)imidazole-1-yl)methyl-1, 3,4-oxadiazol-2-ylthio)(4-methoxyphenyl)acetamide (10) showed most potent activity with MIC value of 6.25µg/mL.



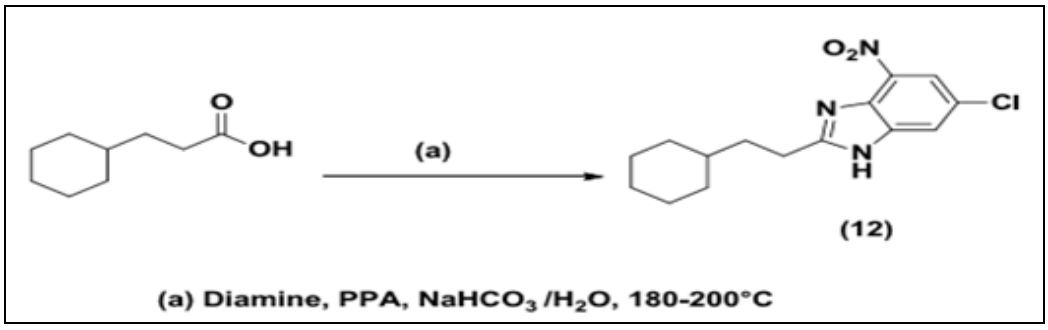
11. Park B *et al.*, [11] have discovered novel 2,5,6-trisubstituted benzimidazole derivatives bearing ether or thioether linkages. The synthesized derivatives were screened against Mtb-FtsZ protein for antitubercular activity. Amongst the tested compounds 5-Butoxycarbonylamino-2-cyclohexyl-6-(4-fluorophenoxy)-1H-benzo[d]imidazole (11) showed potent activity with MIC value of 0.63µg/mL.



(11)

(a) $SnCl_2$, EtOH, Reflux,1-6hrs; (b) butyl carbonochloridate, CH_2Cl_2

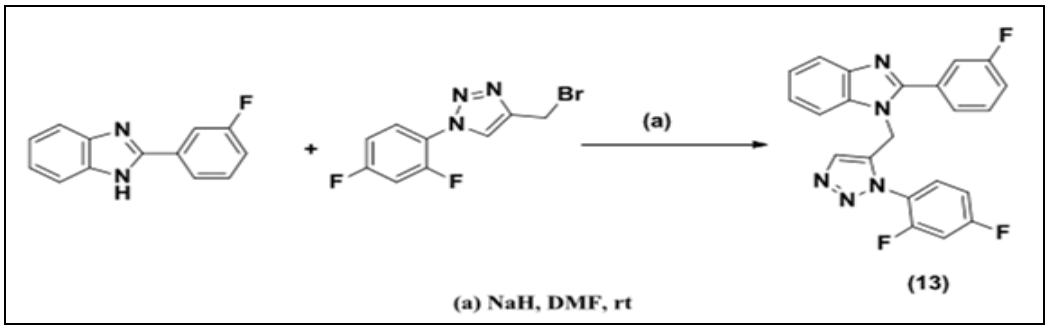
12. Gobis K *et al.*, [12] have synthesized series of novel cyclohexylpropanoic acid-derived nitrogen-based heterocyclic compounds and evaluated them for tuberculostatic activity. The derivatives (12) bearing benzimidazole like system showed most potent tuberculostatic activity with the MIC value ranging from 1.5 to12.5 µg/mL.



(12)

(a) Diamine, PPA, $NaHCO_3$ /H_2O, 180-200°C

13. Gill C *et al.*, [13] have reported novel (1,2,3) triazole clubbed with fluorine benzimidazole derivatives. These derivatives were evaluated for antitubercular activity. 1-((1-(2,4difluorophenyl)-1H-1,2,3-triazol-5-yl)methyl)-2-(3-fluorophenyl)-1H-benzo[d]imidazole (13) showed MIC value of 0.32µM, which was found to be better than the standard rifampin.

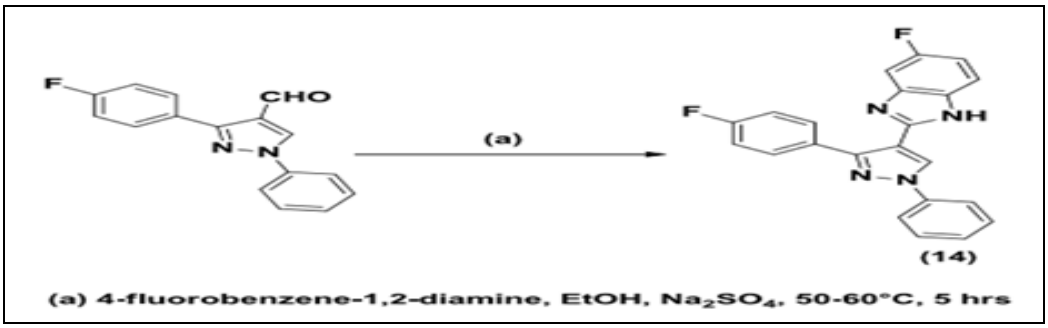


(13)

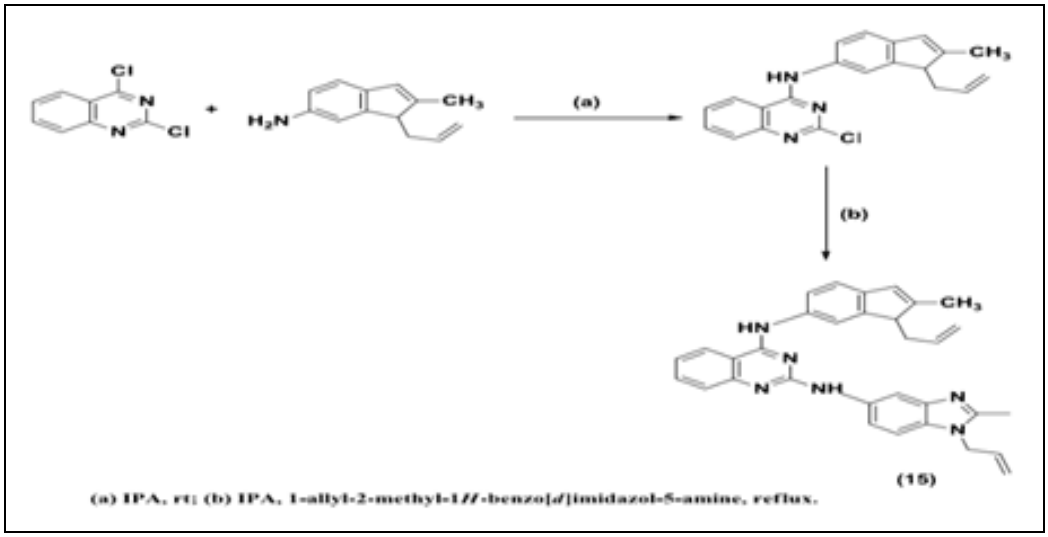
(a) NaH, DMF, rt

Anticancer Agent:

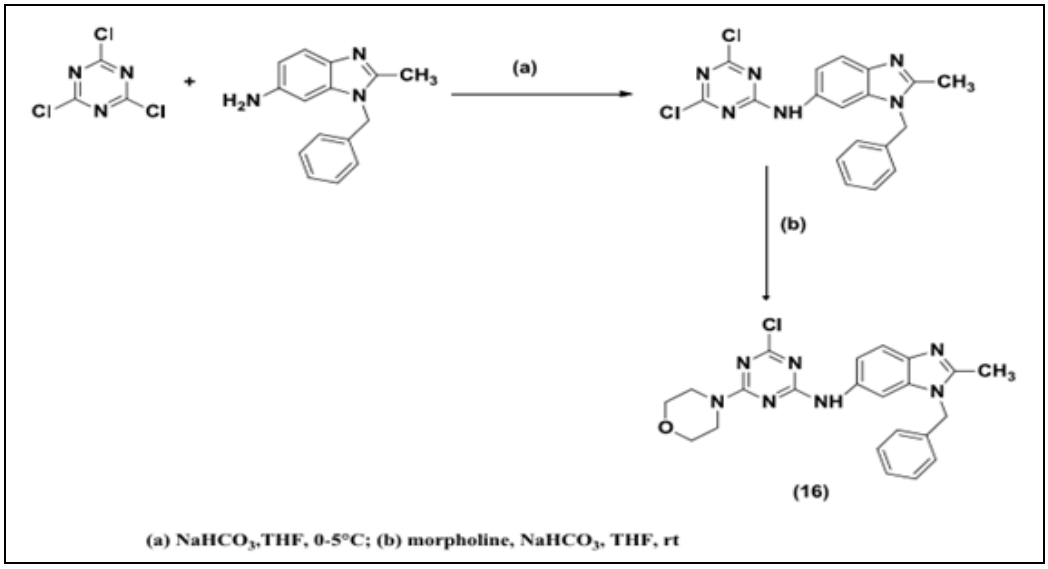
14. Reddy T S *et al.*, have synthesized a series of pyrazole containing benzimidazole hybrids. These hybrids were evaluated for their anti-proliferative activity against three human tumor cell lines- lung (A549), breast (MCF-7), and cervical (HeLa). Compound 5-fluoro-2-(3-(4fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole (14) showed potent growth inhibition with IC_{50} values of 0.83-1.81µM.



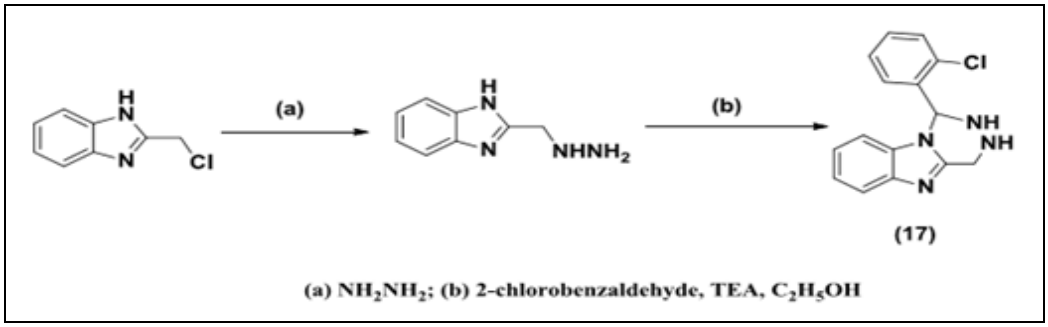
15. Paul K *et al.,* [15] have generated new hybrids by combining the structural features of quinazoline and benzimidazole. Evaluation of these molecules was carried out against various cancer cell lines. The methoxy substituted compound (15) exhibited remarkable anticancer activity towards colon and prostate cancer cell lines with GI_{50} value of 0.34 & 0.31 µM respectively.



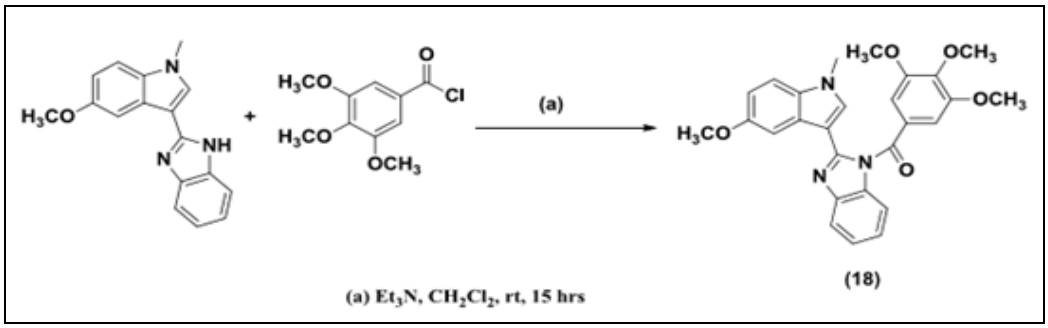
16. Singla P *et al.*, have prepared a new series of triazine-benzimidazole hybrids. These hybrids were evaluated for their inhibitory activities over various tumor cell lines & mammalian dihydrofolate reductase. (3-benzyl-2-methyl-3H-benzimidazol-5-yl)- (4-chloro-6-morpholin-4yl- [1,3,5]triazin-2-yl)-amine (16) showed broad spectrum antitumor activity with GI_{50} value of 9.79µM. It also displayed DHFR inhibition with an IC_{50} value of 1.05 µM.



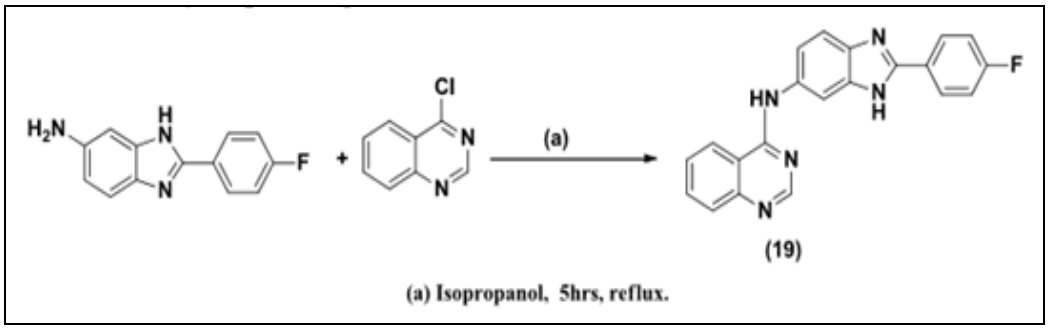
17. El-Nassan H B *et al.,* developed a series of novel 1, 2, 3, 4 tetrahydro[1,2,4]triazino[4,5a] benzimidazoles bearing a variety of aryl and heteroaryl groups at position 1. The compounds were tested *in-vitro* on human breast adenocarcinoma cell line (MCF7). Some of the test compounds showed potent antitumor activity, especially 1-(2-chlorophenyl)-1, 2, 3, 4tetrahydro [1,2,4]triazino[4,5-a] benzimidazole (17) displayed the highest activity.



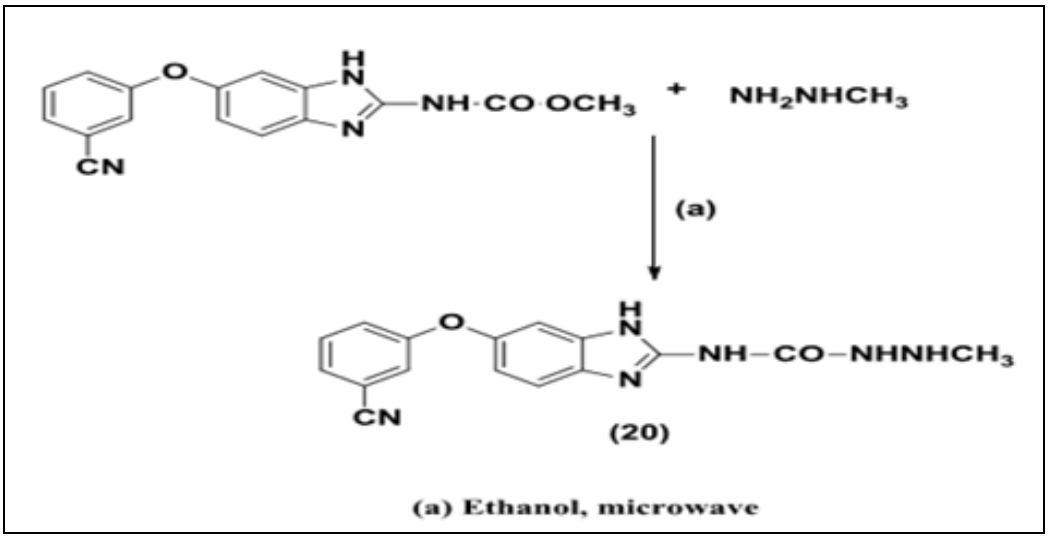
18. Wang Y *et al.,* have prepared a series of 1-benzene acyl-2-(1-methylindol-3-yl)benzimidazole derivatives and investigated them as potential tubulin polymerization inhibitors and for the cytotoxicity against anthropic cancer cell lines. 1-(3, 4, 5-trimethoxy-benzene acyl)-2-(5-methoxy-1-methylindol-3-yl)-benzimidazole (18) showed potent inhibitory and antiproliferative activity.



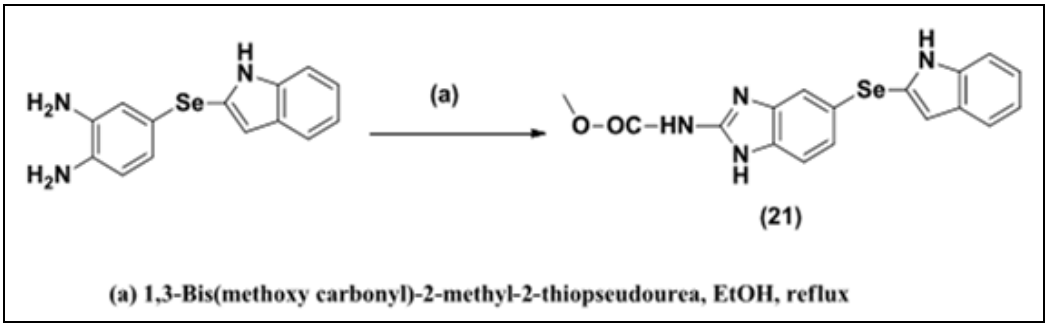
19. Shi L *et al.,* designed a series of quinazoline and benzimidazole bearing fragments and identified them as dual c-Met and VEGFR-2 inhibitors. Among them N-(2-(4-fluorophenyl)1H-benzo[d]imidazol-6-yl)quinazolin-4-amine (19) exhibited the most potent inhibitory activity against c-Met and VEGFR-2 with IC_{50} of 0.05µM and 0.02 µM respectively. It also showed the highest anticancer activity against the cancer cell lines with IC_{50} of 1.5µM against MCF-7 and 8.7µM against Hep-G2.



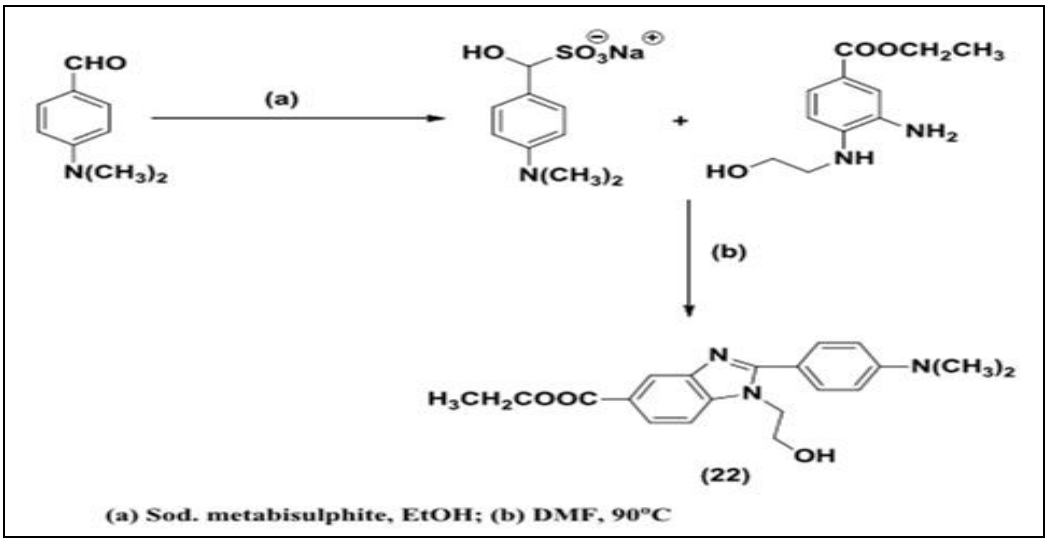
20. Wang W *et al.,* discovered a series of benzimidazole-2- urea derivatives as novel tubulin inhibitors. Among them, compound N-(6-(3-cyanophenoxy)- 1H-benzo[d]imidazol- 2- yl)- 2 methylhydrazinecarboxamide (20) suppressed the proliferation of a panel of human cancer cells with IC_{50} ranging from 0.040 to 1.774µM. It also inhibited NCI-H460 spindles formation and induced cell cycle arrest at G 2/M phase.



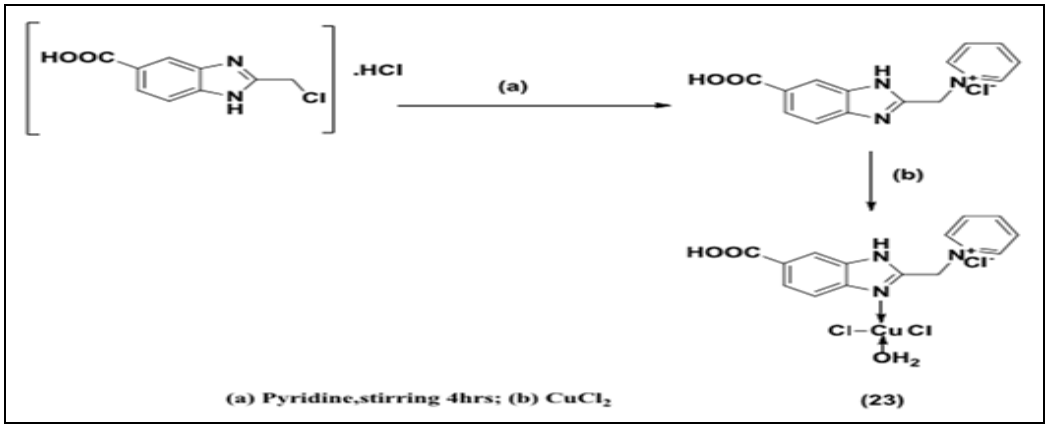
21. Guan Q *et al*., prepared a series of novel benzimidazole carbamates bearing indole moieties which were connected with sulphur or selenium atoms. The compounds were evaluated for their antiproliferative activities against three human cancer cell lines; SGC-7901, A-549 and HT-1080. Methyl 5-[(1H-indol-3-yl)selanyl]-1H-benzoimidazol-2-ylcarbamate (21) showed the most potent antitumour activity.



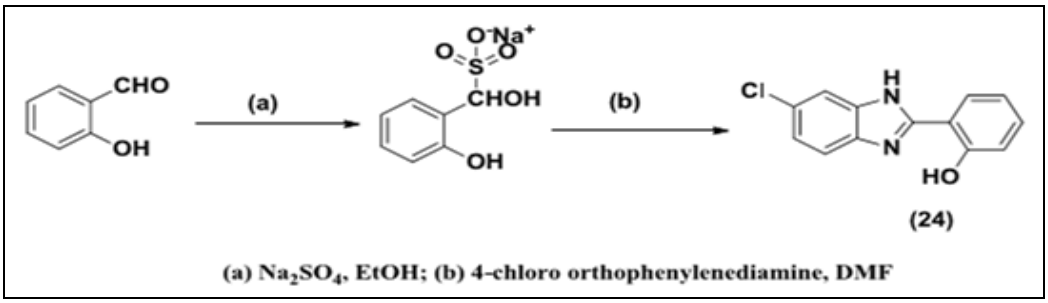
22. Yoon YK *et al.,* designed and synthesized a series of novel benzimidazole derivatives as sirtuin inhibitors. Compound ethyl 2-(4-(dimethylamino) phenyl)-1-(2-hydroxyethyl)-1Hbenzo[d] imidazole-5-carboxylate (22) showed best inhibitory activity for SIRT 1 and SIRT 2 with IC_{50} values of 58.43µM & 45.12µM respectively. It also showed good anti-tumor activity against different breast cancer cell lines.



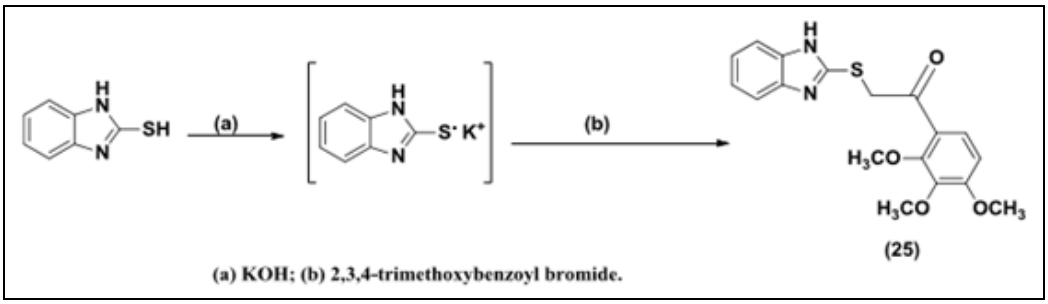
23. Galal SA *et al.,* synthesized novel benzimidazole -5- carboxylic acid derivatives and their transition metal-metal complexes with $Cu^{2+,}$ Co^{2+}, Zn^{2+}. They were evaluated for their growth inhibitory activity against 21 human cancer cell lines. Among them, 1-((5(or 6)-carboxy-1Hbenzo [d] imidazol-2-yl)methyl)pyridinium copper(II) chloride hydrate (23) inhibited topoisomerase-II activities at 10 times lower concentration than etoposide.



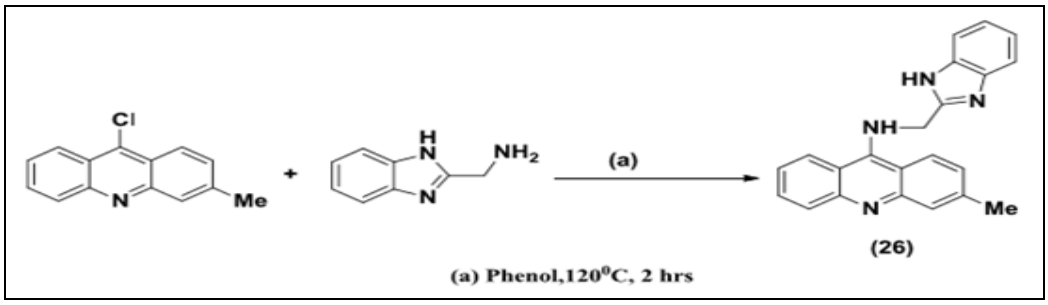
24. Coban G *et al.,* synthesized several benzimidazole derivatives with substitution at 2 & 5 positions. They were screened to identify if they interfered with mammalian type I DNA topoisomerase activity *via in-vitro* supercoil relaxation assays. Some compounds were subjected to cytostatic assays using various cancer cell lines. Results showed that 5-chloro-2(2-hydroxyphenyl)-1H-benzimidazole (24) exerted the most profound topoisomerase I inhibition and cytotoxicity.



25. Abdel-Aziz H A *et al.,* developed a series of 2-((benzimidazol-2-yl)thio)- 1-arylethan- 1- ones as potent anti-tumor agent that target both cancer stem cells and the bulk of tumor cells. They were evaluated for their antiproliferative activity towards colon HT-29 cancer cell line. 2-((1H-benzo[d]imidazol-2-yl)thio)-1-(2, 3, 4-trimethoxy-phenyl)ethan-1-one (25) was the most active anti-proliferative analog with 50.11±4.05 % inhibition effect.

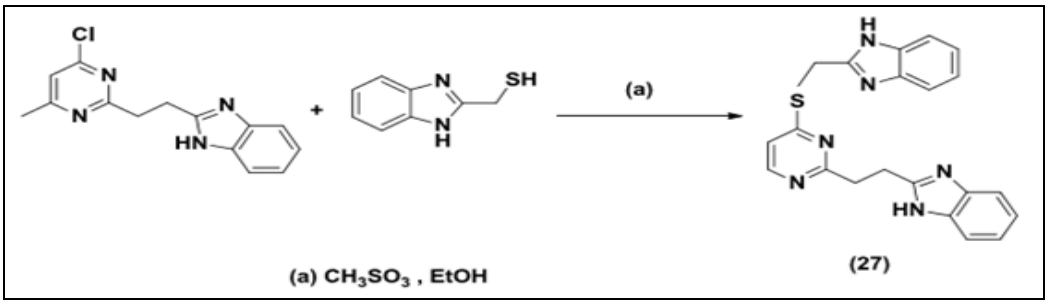


26. Gao C *et al.,* have synthesized various benzimidazole acridine derivatives. These were evaluated as potential DNA binding and apoptosis-inducing agents. Amongst them N-((1Hbenzo(d) imidazole- 2- yl)methyl- 3- methylacridin-9-amine) (26) displayed good anti proliferative activity against both K-562 & HepG-2- cells.

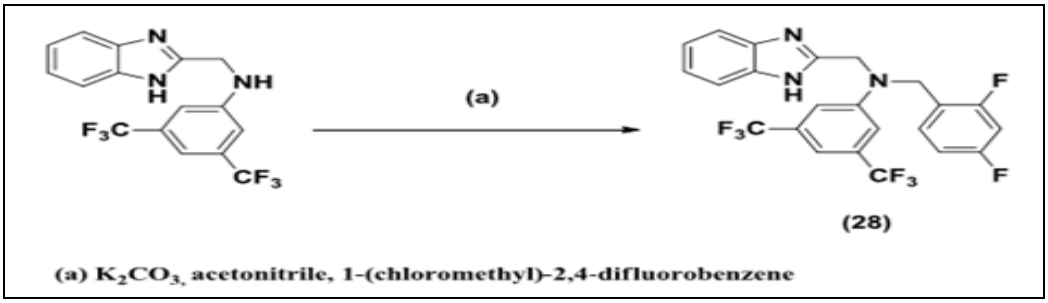


Anti-Microbial Activity:

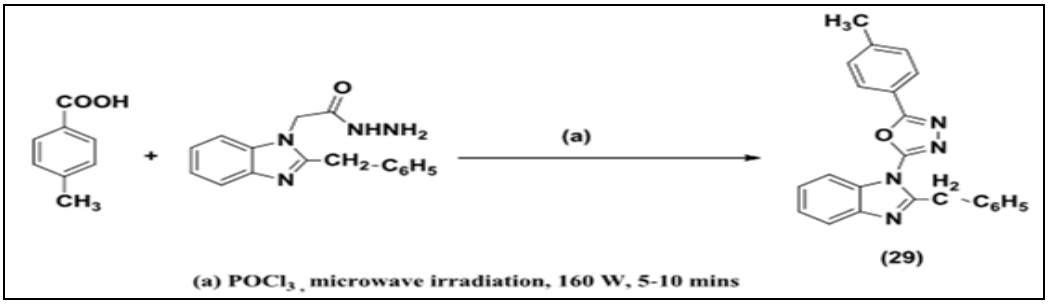
27. Seenaiah. D *et al.*, prepared a variety of pyrimidinyl benzoxazoles, benzothiazoles, and benzimidazoles linked by thio, methylthio, and amino moieties. They were evaluated for their antimicrobial activity. The compound pyrimidinyl bis methylthio benzimidazole (27) was potent against *Staphylococcus aureus* (29 mm, MIC 12.5 mg/mL) and *Penicillium chrysogenum* (38 mm, MIC 12.5 mg/mL).



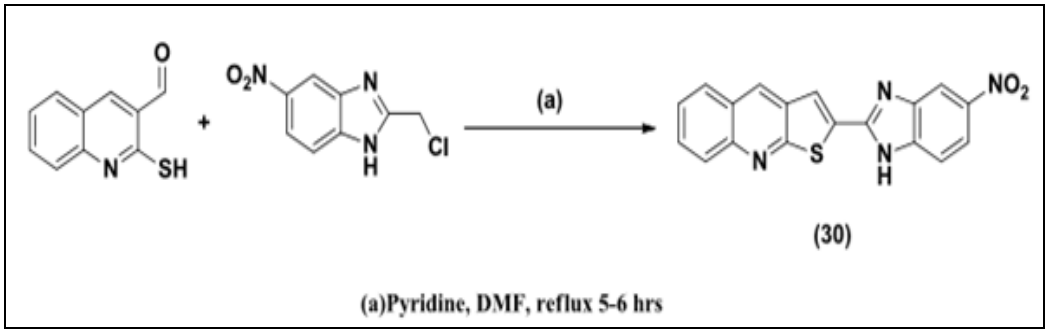
28. Zhang H *et al.*, [28] designed a series of benzimidazole type of fluconazole analogues & screened them for their anti-microbial activities. The compound 3,5-bis(trifluoromethyl)phenyl benzimidazole (28) displayed a stronger anti-bacterial and anti-fungal activity. The combination of 2,4-difluorobenzyl benzimidazole derivatives & its hydrochloride with antibacterial chloromycin showed broad spectrum activity.



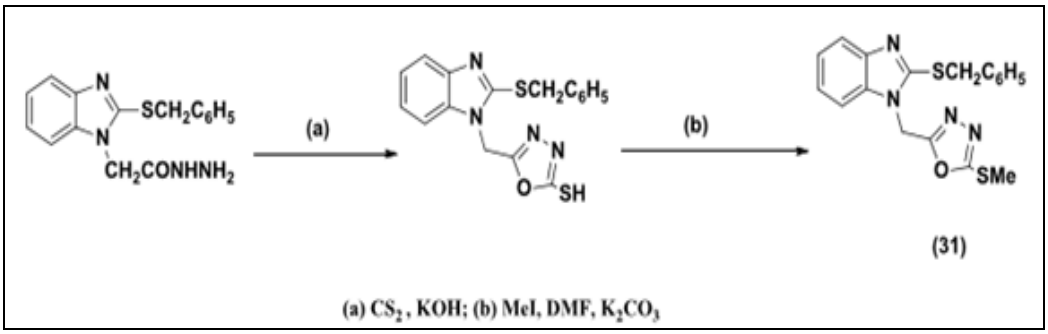
29. Gowda J *et al.*, [29] synthesized a series of 1,3,4-oxadiazoles bearing benzimidazole moiety as antimicrobial agents. Compounds carrying benzyl group at the 2-position of the benzimidazole ring and electron releasing group on the phenyl groups showed significant activity. Among them 2-benzyl-1-{[5-(p-tolyl)-1, 3, 4-oxadiazol-2-yl] methyl}-1H benzimidazole (29) displayed good activity.



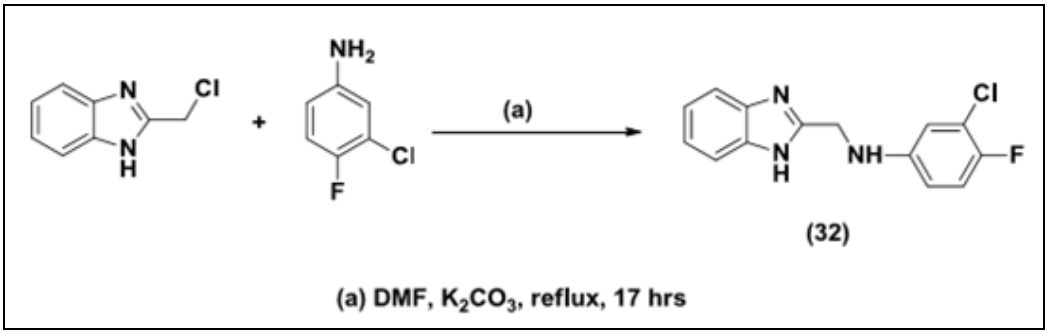
30. Gowda J *et al.,* prepared a series of benzimidazole derivatives carrying quinolone moiety by one step process, which included nucleophilic substitution and cyclization. They were evaluated for their anti-bacterial activity. The compound with nitro group at the 5-position of the benzimidazole moiety; 2-(5-nitro-1H- benzimid-azole-2-yl) thieno [2,3-b]-quinoline (30) displayed good antibacterial activity.



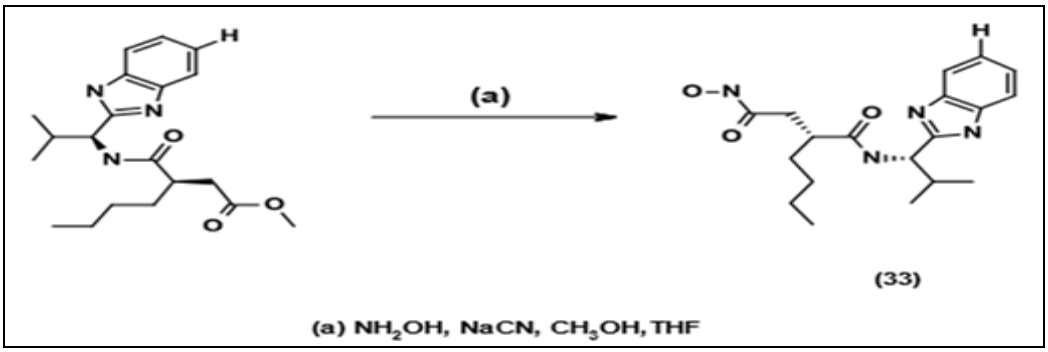
31. Eisa HM *et al.,* prepared a series of benzimidazole derivatives fused with oxadiazoles and triazoles. The synthesized compounds were screened for antimicrobial activity. Among them 1-[(5-methylthio-3,4-oxadiazol-2-yl)methyl]-2-benzyl-thio-1H-benzimidazole (31) exhibited significant activity.



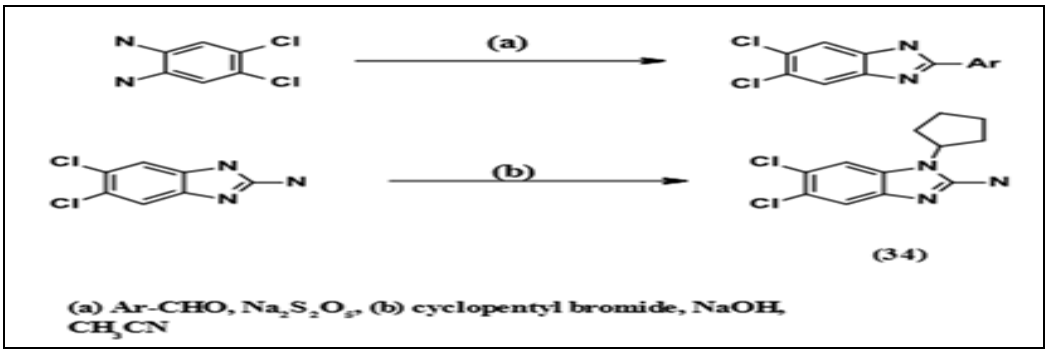
32. Petkar K *et al.,* prepared a series of 2-chloromethyl-1H-benzimidazole derivatives and screened them for their anti-fungal activity against *Candida albicans*. Among the synthesized compounds, (1H-benzimidazole -2-ylmethyl)-(3-chloro- 4- fluoro-phenyl)- amine (32) showed significant activity with MIC value of 12.5 µg/ml.



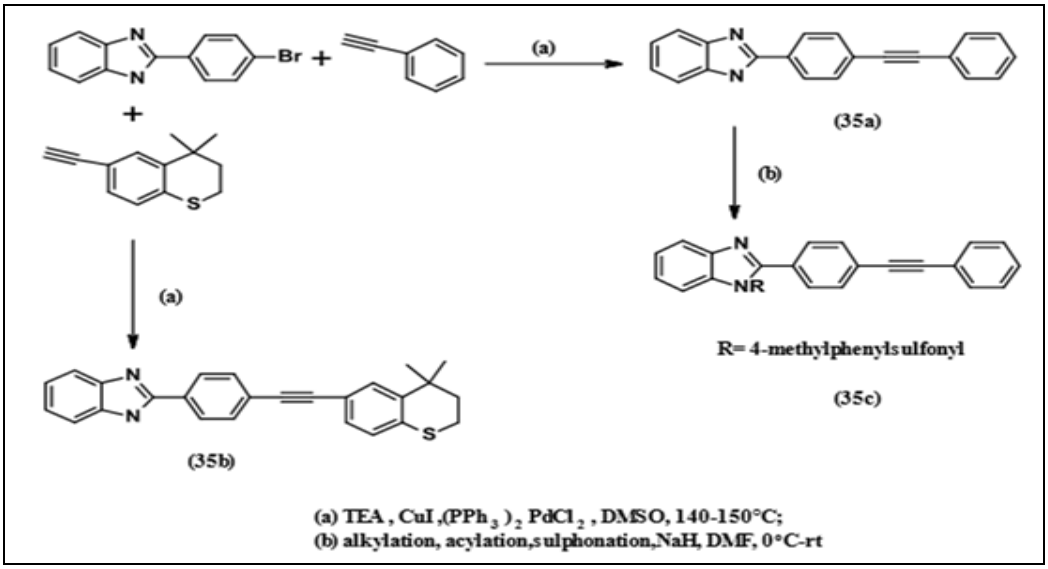
33. Zhang D *et al.,* designed and synthesized novel actinonin derivatives containing benzimidazole heterocycles and evaluated there *in-vitro* antibacterial activity. Among them, compound (R)-2-butyl-N4-hydroxy-N1- [1- (S)- (benzimidazol-2-yl)-2-methyl]propylsuccinamide (33) with an unsubstituted benzimidazole ring exhibited potent antibacterial activity with MIC 2 µg/ml, 0.5 µg/ml and 4 µg/ml against *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Sarcina lutea* respectively with comparison to the standard cefoperazone.



34. Tuncbilek M *et al.,* synthesized novel benzimidazole derivatives and evaluated for antimicrobial activity. Compounds 5,6-dichloro-2-(4-fluorophenyl)-1H-benzimi-dazole,5,6dichloro-2-(4- chlorophenyl)- 1H-benzimidazole, 2- (4-t-butyl-phenyl)-5, 6-dichloro-1- Hbenzimidazole, which have no substitution of N-1 position displayed better antibacterial activity than those of standards (ciprofloxacin, ampicillin and sultamicillin) against both the drug-resistant bacteria (MRSA, standard and clinical isolates). While derivative 2-amino-5, 6-dichloro-1-cyclopentyl-1H-benzi-midazole (34) exhibited the most potent antibacterial activity with MIC 3.12 µg/ml against *Staphylococcus aureus*.

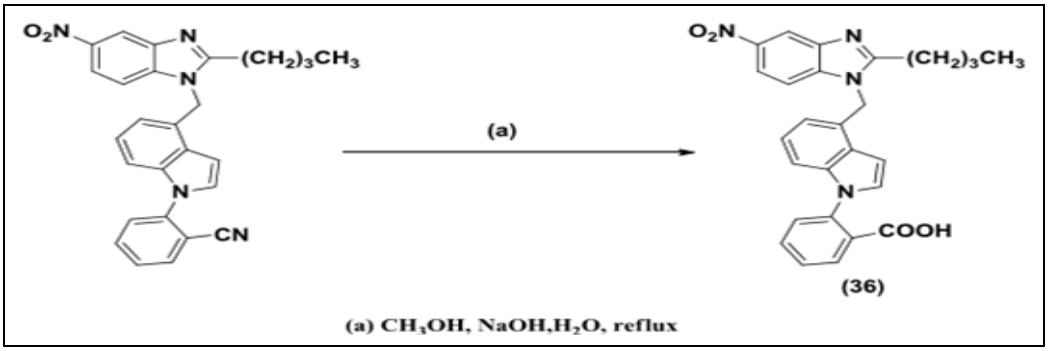


35. Vinodhkumar R *et al.,* synthesized novel N-substituted-2-(4-phenylethynylphe-nyl)-1Hbenzi-midazoles and N-substituted 2[4-(4,4-dimethyl-thiochroman-6-yl-ethynyl)-phenyl)- 1H benzimida-zoles and screened them for their potential anti-bacterial agents. Compounds 2-(4phenylethyn-yl phenyl)-1H-benzimidazole (35a) 2-[4-(4,4-dimethyl-thiochroman-6-ylethynyl)-phen-yl]-1H-benzimida-zole (35b) 2-(4- phenylethynyl-pheny)-1-(toluene-4sulfonyl)-1H-benzimidazole (35c) showed complete inhibition against both *S. aureus* and *S. typhimurium*.

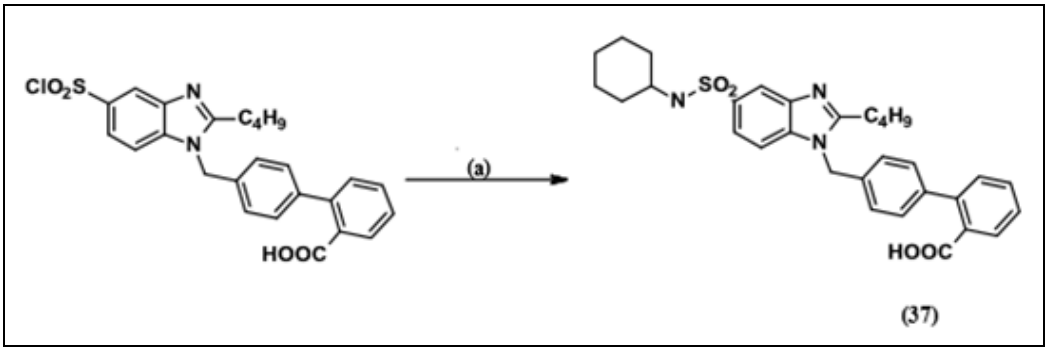


Angiotensin II Receptor Antagonist Activity:

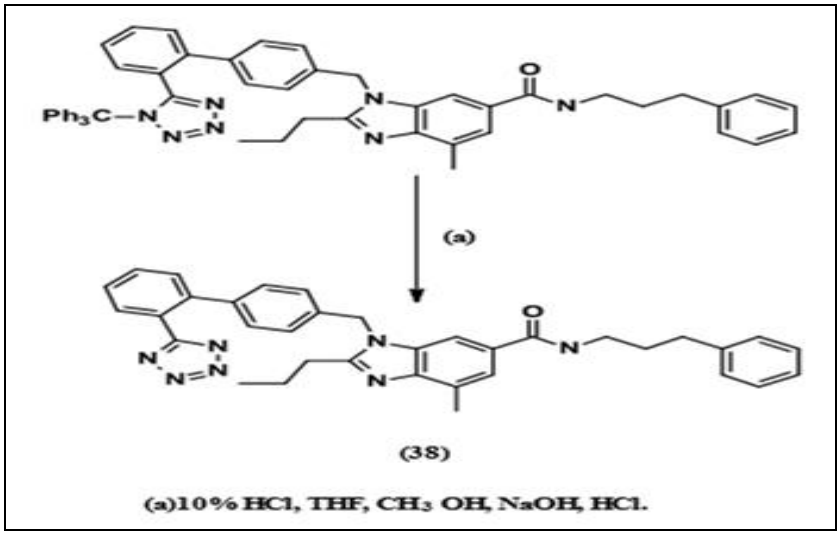
36. Zhu W *et al.,* synthesized some 5-nitro benzimidazole with 1,4-disubsituted or 1,5-disubsituted indole derivatives and screened them for their novel angiotensin II receptor antagonist activity. The results revealed that 2-(4-((2-butyl-5-nitro-1H-benzo[d]imidazol-1yl)methyl)-1H-indol-1-yl)benzoic acid (36) displayed a high affinity for the angiotensin II type 1 receptor with IC50 value of 1.03 ± 0.26 nM.



37. Kaur N *et al.,* designed and synthesized 5-alkylsulfamoyl benzimidazole derivatives as angiotensin II receptor antagonists. The *in-vitro* and *in-vivo* tests reveals 4´-[(2-butyl-5cyclohexyl-sulfamoyl-1H-benzimidazol-1-yl)methyl]biphen-yl -2-carboxylic acid (37) as the most promising compound.

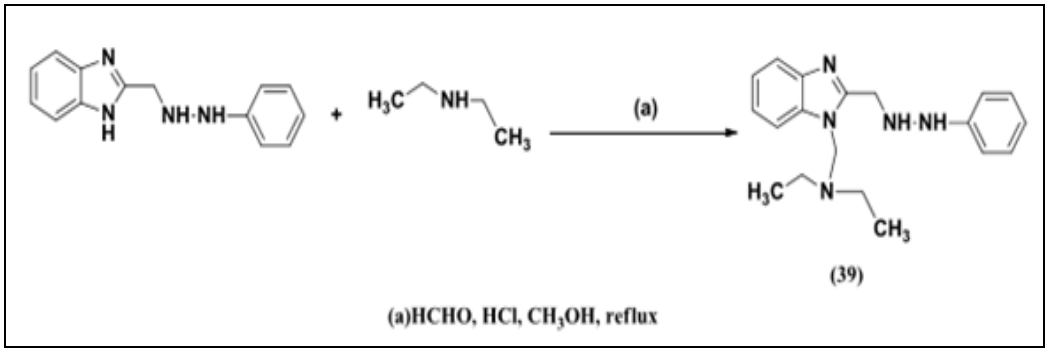


38. Zhang J *et al.,* designed and synthesized a series of 6-substituted carbamoyl benzimidazoles as new nonpeptidic angiotensin II AT1 receptor antagonists. The various pharmacological evaluation revealed compound N-(2-phenyl) propyl-1-[2´-(1 -H–tetrazol-5-yl)-1,1´-biphenyl4-yl]methyl-4-methyl-2-n-propyl-1H-benzimidazole-6-carboxamide (38) as an orally active AT1 receptor antagonist with low toxicity.

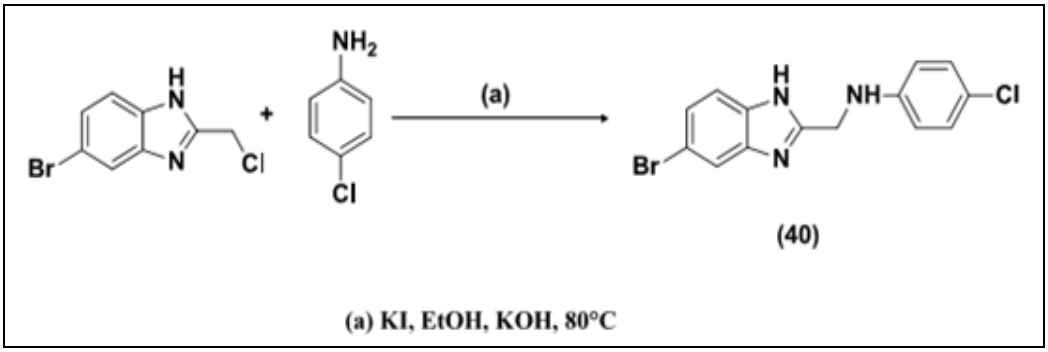


Analgesic Activity:

39. Srivastava S *et al.,* synthesized a series of novel 2-phenylhydrazinomethyl derivatives substituted at the N- 1-position of benzimidazole nucleus. The compound were screened for analgesic activity; among them N-ethyl-N-({2-[(2-phenylhydrazinyl) methyl]-1Hbenzimidazole-1 yl}methyl) ethanamine (39) exhibited a promising activity when compared to the standard drug diclofenac sodium. The fusion of a phenylhydrazinomethyl nucleus at the 2-position of benzimidazole compound gave a biologically active pharmacophore.

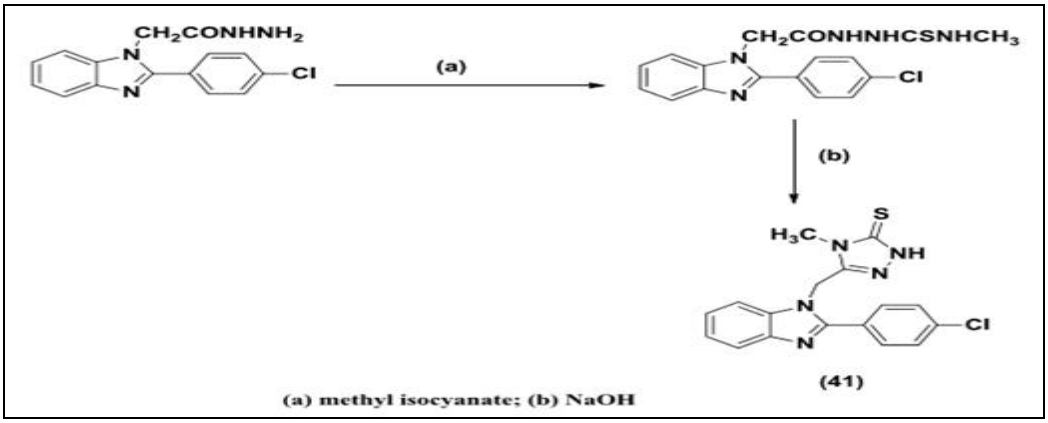


40. Achar K C S *et al.,* synthesized a series of 2-methylaminobenzimidazole derivatives by the reaction of 2-chloromethylbenzimidazole with different aromatic amines. These compounds were screened for analgesic and anti-inflammatory activities on acetic acid-induced writhing in mice and rats. Compound N-[(5-bromo-1H-benzimid-azol-2-yl) methyl]-3-chloroaniline (40) showed good result.

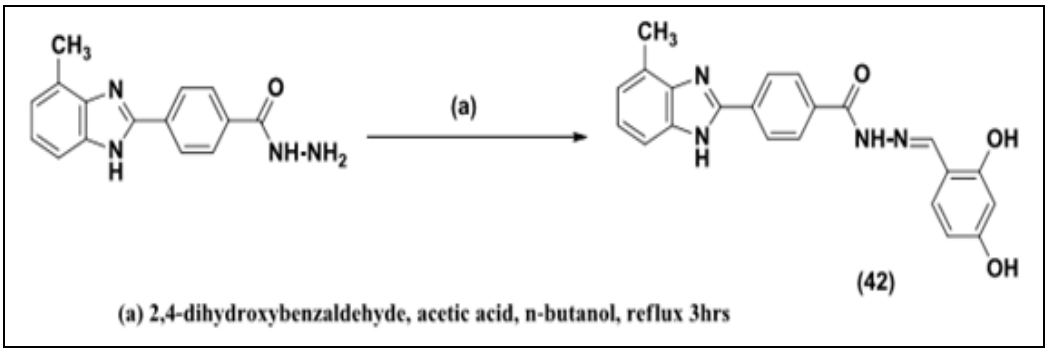


Anti-oxidant Activity:

41. Kus C *et al.,* developed a series of thiadiazol-2-amine & triazole-3(4H)- thione derivatives of benzimidazole class. These were evaluated for their antioxidant properties. Compound 5-[(2- (chloro-phenyl)- 1H- benzimidazol-1-yl) methyl]-4-methyl-2H-1,2,4-triazole-3(4H)-thiones (41) inhibited the microsomal ethoxyresorufin-O-deethylase (EROD) activity with IC_{50} of 4.5×10^{-4}M.

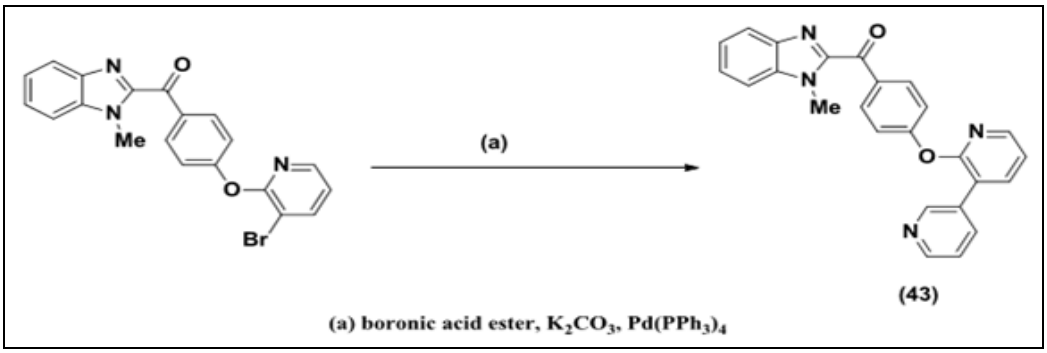


42. Taha M *et al.,* have synthesized novel 4-Methylbenzimidazole derivatives. These were evaluated for their antioxidant activity. N'-(2,4-dihydroxybenzylidene)-4-(4-methyl-1Hbenzo[d] imidazol-2-yl)benzohydrazide (42) showed excellent antioxidant activity better than the standard n-propyl gallate with IC_{50} value of 27.45 µM.

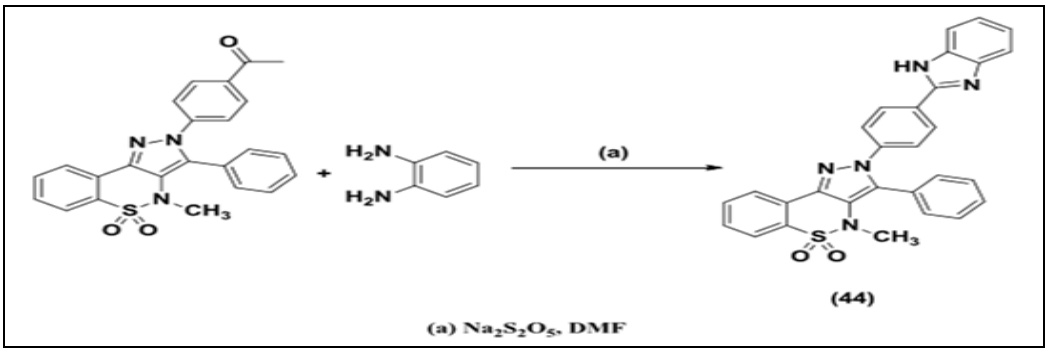


Miscellanous Activity:

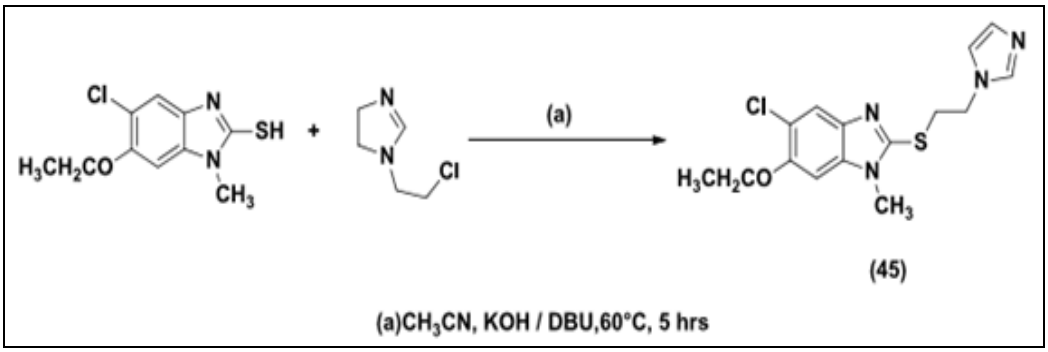
43. Yang H *et al.,* have discovered some benzimidazole analogues as phosphodiesterase 10A (PDE10A) inhibitors. (4-([3,3'-bipyridin]-2-yloxy) phenyl)(1- methyl- 1H- benzo[d]imidazol- 2yl) methanone (43) showed high potency & in vitro selectivity with IC_{50} value of 3.73 nM.



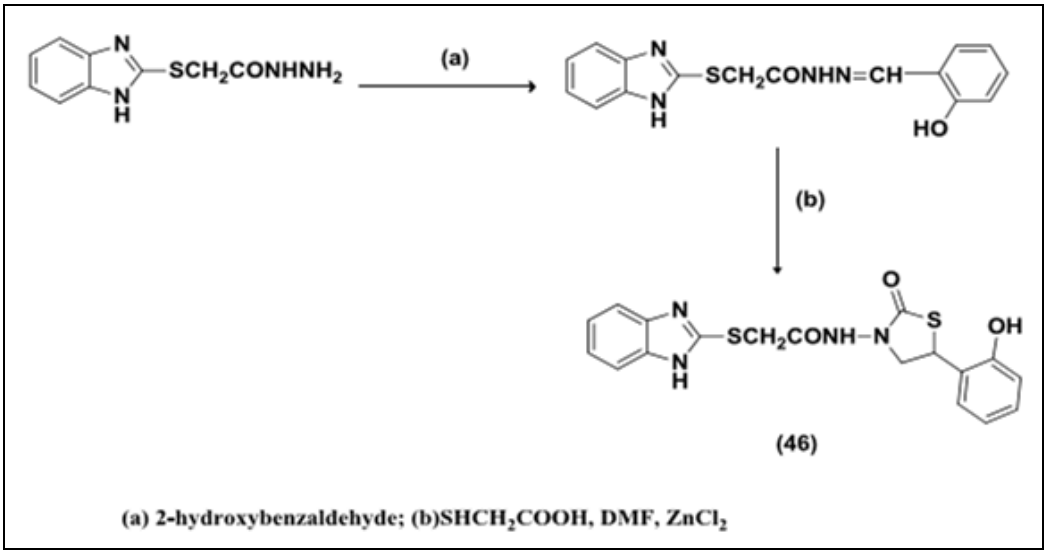
44. Aslam S *et al.,* developed novel hybrids of pyrazolobenzothiazine and benzimidazoles. The phenylene connected hybrid compounds were investigated as inhibitors of acetylcholinesterase (AChE). Compound 2-[4-(1H-benzimidazol-2-yl) phenyl]-4-methyl-3phenyl-2,4-dihydropyrazolo [4,3-c][1,2]benzothiazine 5,5-dioxide (44) was the most potent AChE inhibitor with IC_{50} value of 11 nM.



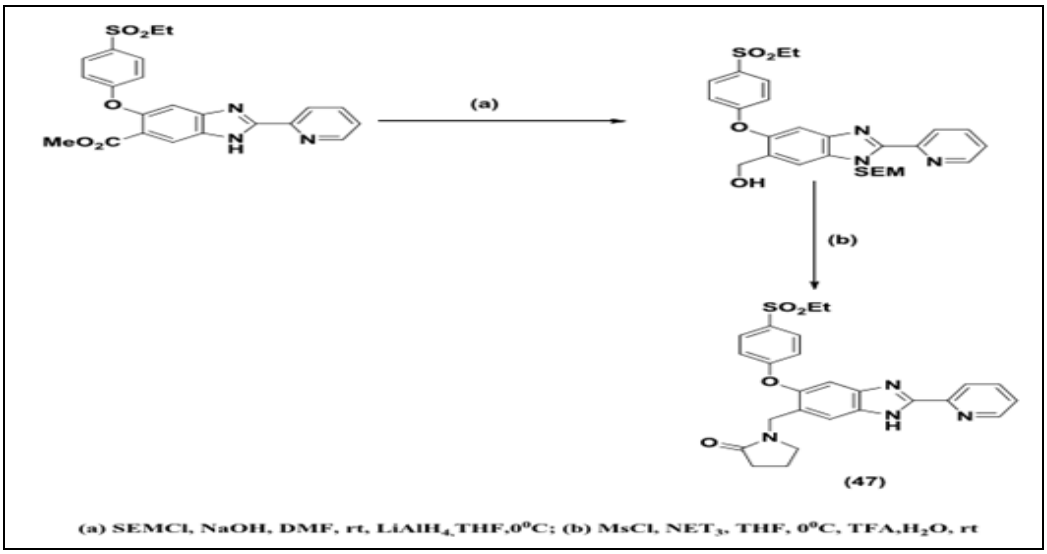
45. Pérez-Villanueva J *et al.,* synthesized a series of new 2-{[2-(1H-imidazol-1yl)ethyl]sulfanyl}-1H-benzimidazole derivatives (45). The novel compounds were tested against various species of protozoa; *Trichomonas vaginalis*, *Giardia intestinalis* and *Entamoeba histolytica*. The antiprotozoal evaluation revealed strong activity for all tested compounds, with IC_{50} values in the nanomolar range, which were even better than the standard metronidazole drug.



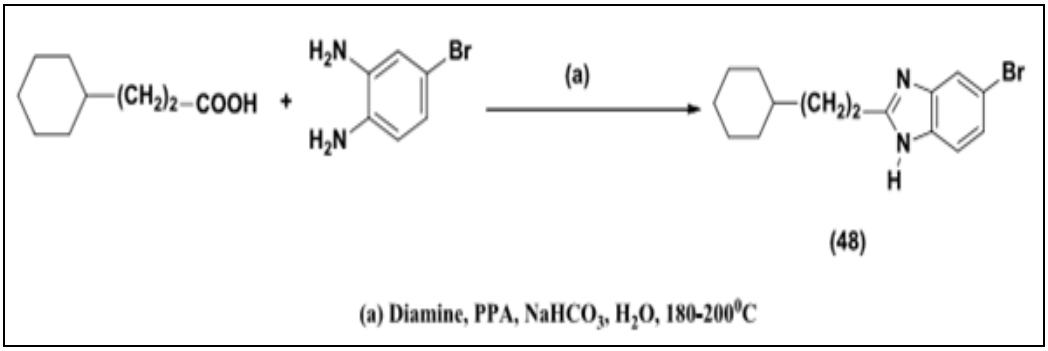
46. Shingalapur R V *et al.,* synthesized a group of 4-thiazolidinones containing 2- mercapto benzimidazole moiety and evaluated them for *in-vivo* anticonvulsant activity by maximal electroshock (MES) model. 3-(1H-benzimidazol-2-ylsulfanyl-methyl)- 2- (2-hydroxy-phenyl)- thiazolidin-4-one (46) exhibited excellent anticonvulsant activity. The pharmacophore derived from active molecules suggests the presence of –OH group in all the active compounds.



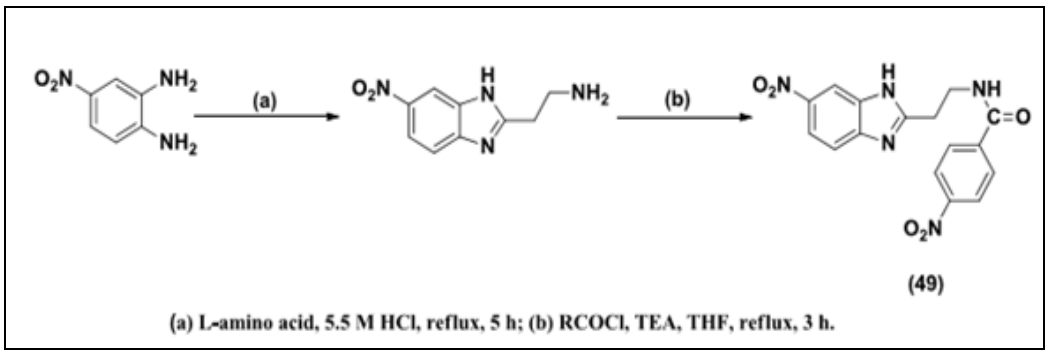
47. Takahashi K *et al.,*.have designed a series of 2-(pyridine-2-yl)-1H- benzimidazole derivatives (47) and evaluated them as glucokinase activators. Among them, the potent activator exhibited good hypoglycemic activity.



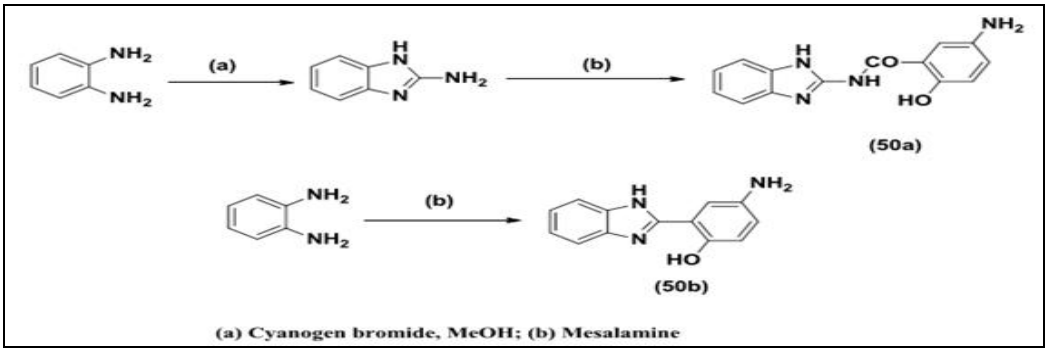
48. Xue F *et al.*, have synthesized a series of novel benzimidazole derivatives and evaluated for their antiviral activity. Strong activities against enterovirus were observed in these benzimidazoles. The most promising compound was (L)-2-(pyridin-2-yl)-N-(2-(4nitrophenyl)pentan-3-yl)-1H-benzimidazole-4-carboxamide (48) with a high antiviral potency (IC_{50} = 1.76 l μg/mL) and a remarkable selectivity index of 328.



49. Elshihawy H *et al.*, have designed and synthesized various benzimidazole and quinoxaline derivatives as methionine synthase inhibitors. Compound N-((5nitro-1H-benzimidazole-2yl)methyl) benzamide (49) showed highest inhibition activity with IC_{50} of 18μM.



50. Bansal Y *et al.*, have reported various benzimidazole-ibuprofen/mesalamine conjugates and evaluated them for immunomodulatory activities. Among them 2-[(5-amino-2hydroxy)phenyl]benzimidazole (50a) exhibited pronounced immunostimulatory and antiinflammatory effects and compound 2-[(5-amino-2-hydroxy)benzoylamino]-5–Nitrobenzimidazole (50b) showed maximum immunosuppressive response for various multifactorial disorders.



51. Loudfy H. Makaur discovered the Inhibition of Corrosion of copper in nitric acid by benzimidazole and its derivatives. The inhibitive performance of seven synthesized 2-(2-benzimidazolyl)-4 (phenylazo) phenol (BPP_1–7) derivatives was investigated experimentally on the corrosion of copper in 2.0 M HNO_3 acid using mass loss, thermometric and DC potentiodynamic polarization techniques.

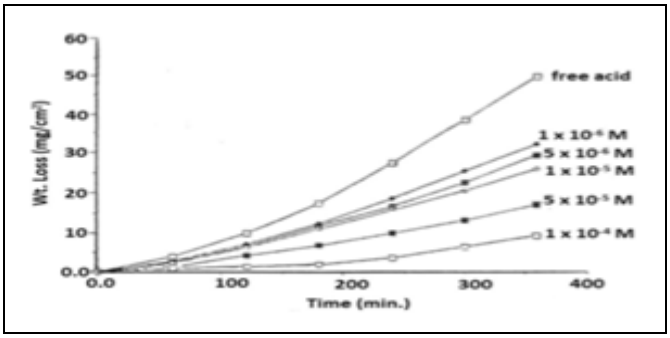
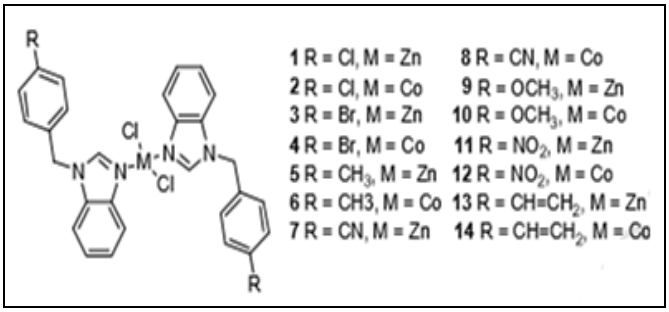
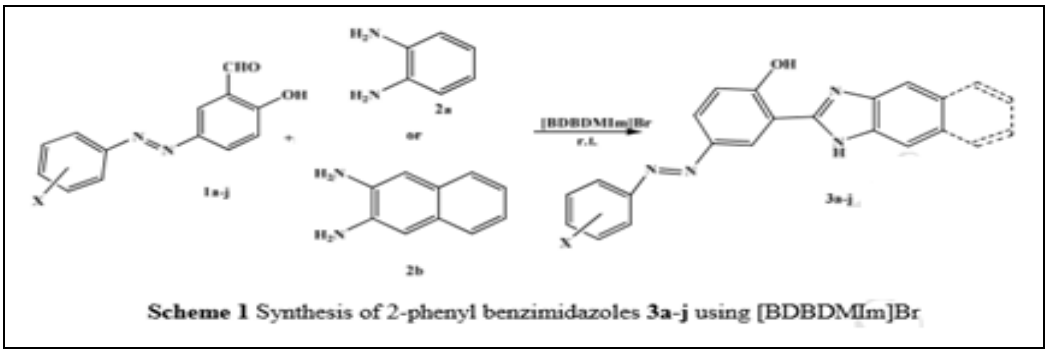


FIG. 1: VARIATION OF WEIGHT LOSS AGAINST TIME FOR COPPER CORROSION IN 2.0 M HNO_3 IN THE PRESENCE OF DIFFERENT CONCENTRATION OF BPP_1 AT 303 K

52. Elif Apohan synthesized fourteen novel cobalt (II) or zinc (II) complexes of benzimidazoles from the 1-(4-substitutedbenzyl)-1H-benzimidazoles and $CoCl_2.6H_2O$ or $ZnCl_2$. Cytotoxic activities of novel complexes were investigated against lung cancer cells (A549) and BEAS-2B.



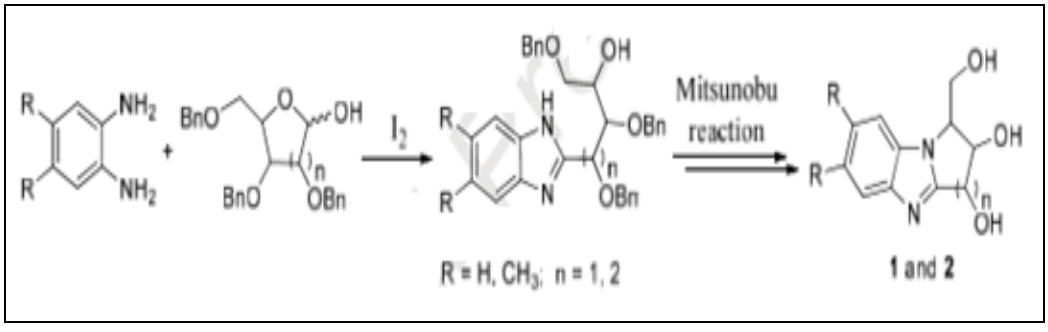
53. Mohammad Nikpassand has synthesised novel azo-linked 2-phenyl benzimidazoles using ionic liquid. In this research, novel series of benzimidazoles were synthesized using the reaction between various synthetized salicylaldehydes, and naphthalene2,3-diamine or 1,2-diaminobenzene in the presence of a catalytic amount of 3,3-(butane-1, 4diyl)bis(1, 2-dimethyl- 1H-imidazole-3-ium)Br by a one-pot procedure without additional organic solvents and oxidants.



Scheme 1 Synthesis of 2-phenyl benzimidazoles **3a-j** using [BDBDMIm]Br

In conclusion, he has developed a simple, convenient and efficient protocol for the synthesis of 2-phenyl benzimid-azoles using ionic liquid as an efficient catalyst [BDBDMIm]Br. The simplicity, easy workup, together with the use of inexpensive, environ-mentally friendly, and reusable catalyst, is the notable features of this catalytic procedure. To the best of knowledge, this is the first report for the synthesis of a new library of benzimidazole compounds bearing azo linkage moiety that enhances the biological activity.

54. Lianhai Yau has synthesized tricyclic benzimidazole-iminosugars as potential glycol-sidase inhibitors *via* a Mitsunobu reaction. A series of tricyclic benzimidazole-iminosugars 1(a-f) and 2(a-f) were constructed through the intramolecular cyclization of NH and OH by the key Mitsunubo reaction, providing an effective protocol for the preparation of the tricyclic iminosugars. Three compounds derived from D-ribose exhibited specific and good inhibitory effects on β-glucosidase.



CONCLUSION: It can be concluded from the present review study that Benzimidazole is a very promosing hetrocyclic ring structure possessing various activities and I believe that more studies such as DNA interaction studies, metal complex chelation and *in-vivo* animal studies can be carried out this versatile moiety.

ACKNOWLEDGEMENT: The author acknowledges Principal KLE College of Pharmacy, Belagavi for providing the facilities and my students Mr. Varun and Ms. Shreya, who extensively searched the data available on Benzimidazoles.

CONFLICTS OF INTEREST: The authors confirm that the contents of this review article bear no conflict of interest.

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