A MINI-REVIEW ON BENZIMIDAZOLE DERIVATIVES: A PHARMACOPHORE AGENT

Abstract

Nowadays, benzimidazole is an essential class of N-heterocyclic compounds. Benzimidazole that consists of six-member benzene ring system combined with five-member imidazole ring compound systems. Benzimidazole central part molecules go on with the essential center of attention among the accessible heterocyclic compounds for the reason that of more than a few pharmacological and medicinally vital properties. The biologically significant benzimidazoles accomplish the center of attention owing to their stability, stupendous bioavailability, and broad range of biological capability. The current examination on benzimidazole derivatives reveals and talks about the biological activities of benzimidazole derivatives extensively experienced as pharmacological agents.

Keywords: Benzimidazoles, Biological activity, Pharmacological agent, Medicinal chemistry, Anti-cancer, Anti-bacteria.

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I. INTRODUCTION

Heterocyclic molecules experienced for the majority of exceptional and assorted range of organic molecules. A remarkable extent of heterocyclic molecules has been synthesized up to paramount position. Heterocyclic molecules are quickly growing in quantity owing to extensive synthetic research and moreover their superior biological activity. Such heterocyclic compounds have a widespread choice of exercises in the field of medicinal chemistry. Biologically, dyestuff, sanitizers, electronics, corrosion inhibitors, optics, antioxidants, pharmacology, material sciences and copolymer synthesis are supplementary well-known applications.[1] Heterocyclic center nucleus imparts a important function in medicinal chemistry and provides as a very important central part for the move forward of a diversity of recently bare heterocyclic compounds and their analogues.

Benzimidazole is a bicyclic compound molecule in which aromatic benzene ring system combined with 4- and 5- position of the imidazole ring system and it furthermore known as benzoglyoxaline. Imidazole ring molecule seizes two nitrogen atoms at non-adjacent site in five member ring system. During 1950, when 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole was established as a central part of the molecule of vitamin B12 as shown Figure-1,[2] curiosity have been engendered to enlarge prospective pharmacological agent with benzimidazole as a crucial core nucleus.[3]

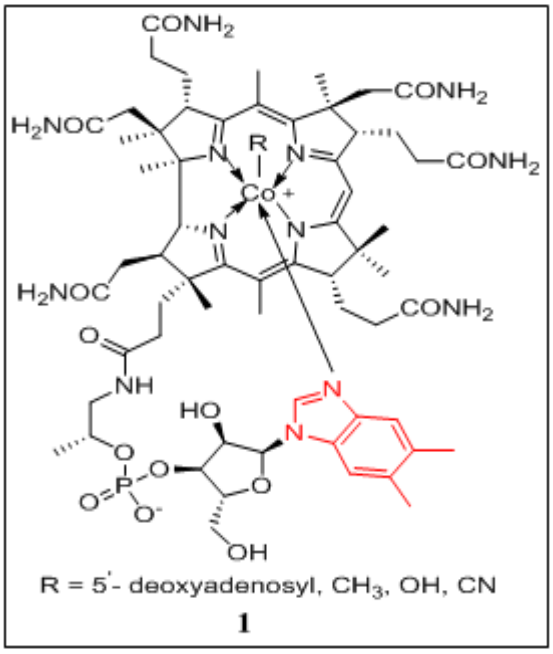


Figure 1: Vitamin B12 Enclosing Benzimidazole as a Central Part.

Benzimidazole molecule is an enormously principal and vital unit in drug development and its analogues are used because a considerable class of medicinally important compounds in the field of pioneering drug improvement. Some of benzimidazole derivatives disclose momentous biological consideration against several viruses, and have effective anti parasitic agents, antimicrobial agents, anti tumor agents, and inhibitors of the hepatitis C virus RNA polymerase. Benzimidazole derivativs as a veterinary drug are as well mostly experienced for anticipation and dealing of parasitic infections in aquaculture and

agriculture. Furthermore, a small number of them also used as pre- or post-harvest fungicides for the control of a widespread variety of fungi, which influence field crops, gathered fruit and vegetables. [4] Extension of benzimidazole central part in diverse group of pharmacological agents such as antiviral, antimicrobial, antihypertensive, anticancer, antiparasitic, and CNS stimulant in addition to antidepressants has ended it useful for the progression of various therapeutic agents. [5]

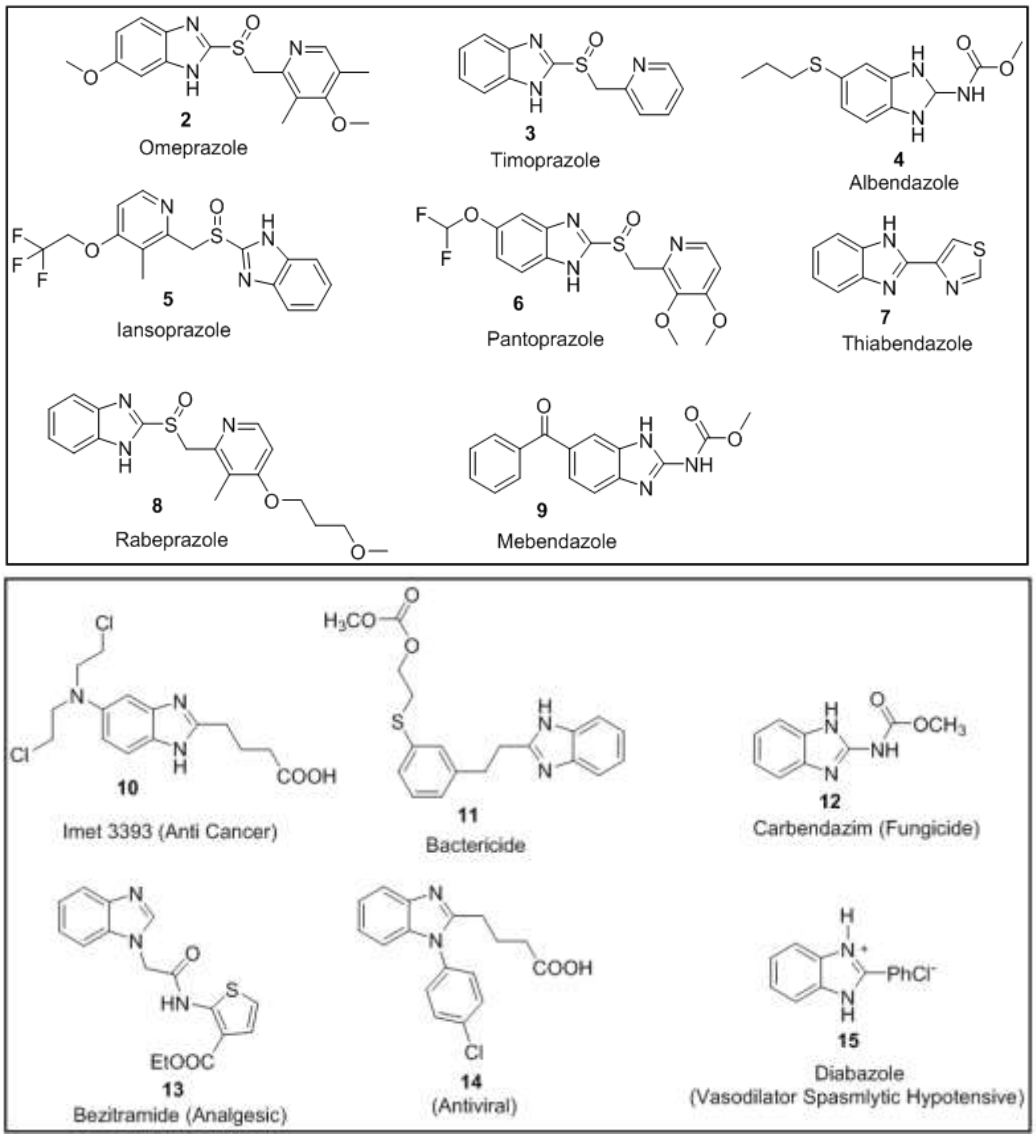
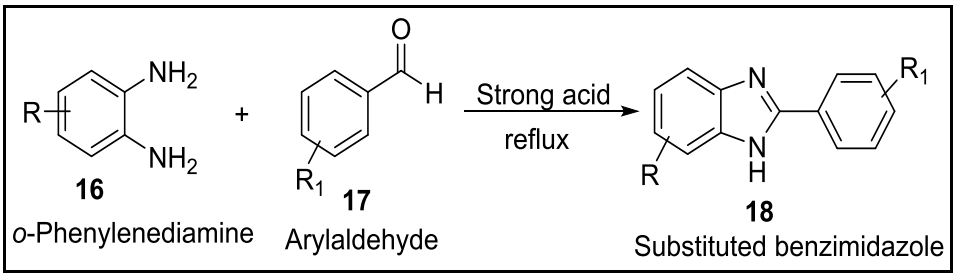


Figure 2: Bioactive Molecules Containing Benzimidazole Molecule as a Core Unit.

Chemistry and estimation of a variety of benzimidazole with substituttion analogues experienced the development of albendazole, omeprazole, rabeprazole, lansoprazole, timoprazole, pantoprazole, thiabendazole, mebendazole are broadly used anthelmintic FDA standard drugs which are commercially accessible in present market existing benzimidazole central unit in their moiety as described in Figure-2.[6] Such a considerable benzimidazole central unit was synthesized by reacting *o*-Phenylenediamine (OPDA) with carbonyl compounds, beneath strong acidic conditions (Scheme-1) which was frequently used synthetic protocol to synthesize benzimidazole analogue.[7]



Scheme 1: Traditional Synthesis of Benzimidazole Analogues.

II. TAUTOMERISM IN BENZIMIDAZOLE

Organic isomer derivatives that rapidly interconverted by a chemical reaction known as tautomerization. The outcomes of this reaction in the formal transformation of a hydrogen atom or proton, accompanied by a exchange of a single bond and adjacent double bond.[8] The perception of tautomerizations is called tautomerism.[8] The numbering of the benzimidazole ring system is described in Figure-3 even though benzimidazole as possessing the proton at N1 there essentially exhibit a rapid exchange flanked by the –NH- and =N- nitrogen atoms, and form two tautomers, **19** and **20**, might be strained for the benzimidazole molecule.[3]

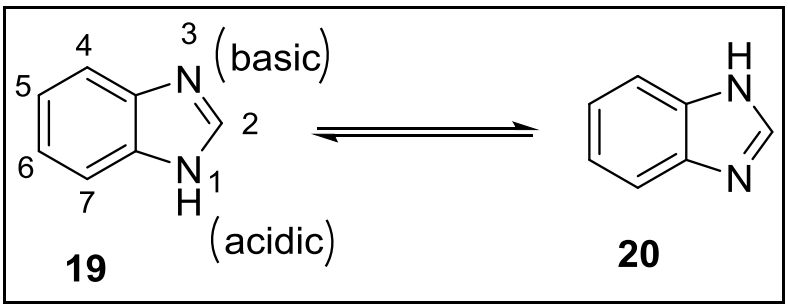


Figure 3: Existence of Tautomerism in Benzimidazole Molecule.

III. PHARMACOLOGICAL ACTIVITIES OF BENZIMIDAZOLE DERIVATIVES

Based on the resource of extensive rang literature assessment analysis benzimidazole derivatives demonstrates a wide range of pharmacological activities [9] as shown in Figure-4. Based on the pharmacologically bio-active compounds which include benzimidazole as central part, the synthetic and industrial chemist paying additional attentiveness on the synthesis of benzimidazole analogues to boost up its pharmacological activity. In the chapter we were paying attention on the pharmacological activity of benzimidazole derivatives.

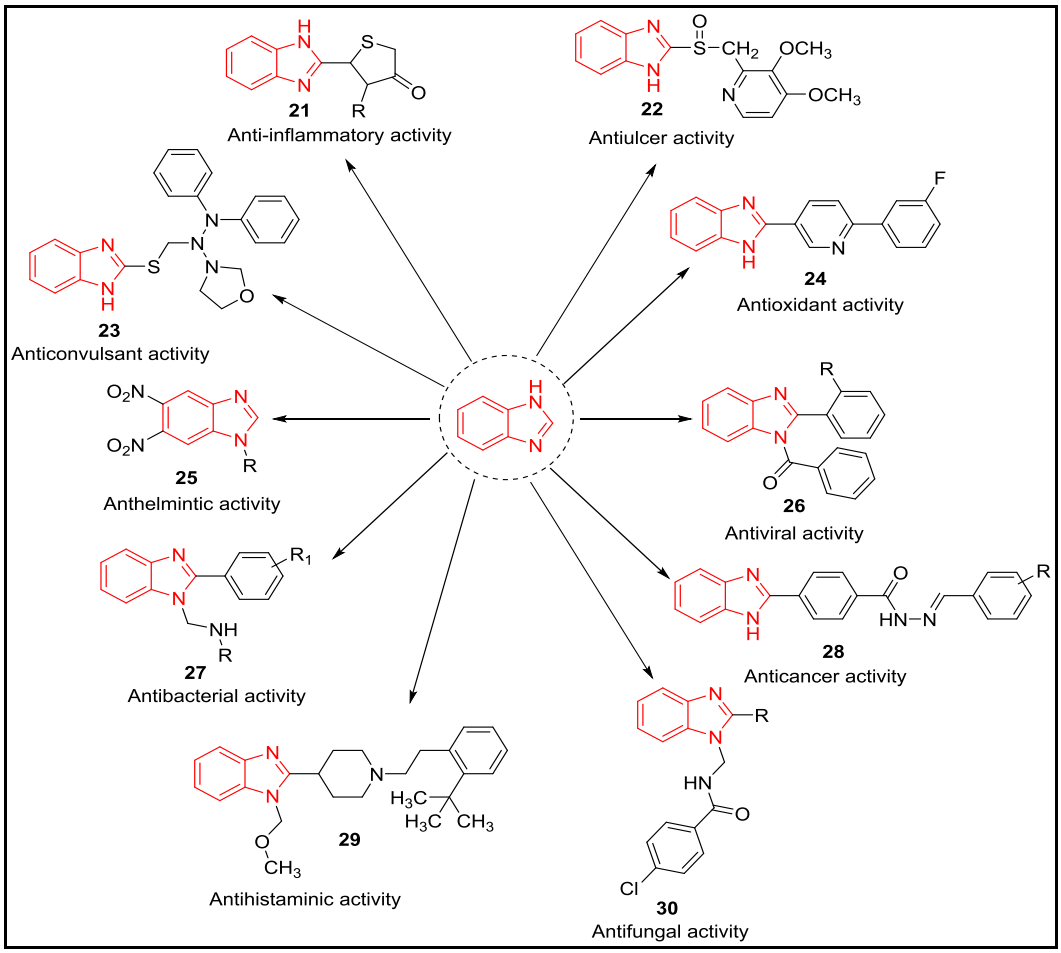
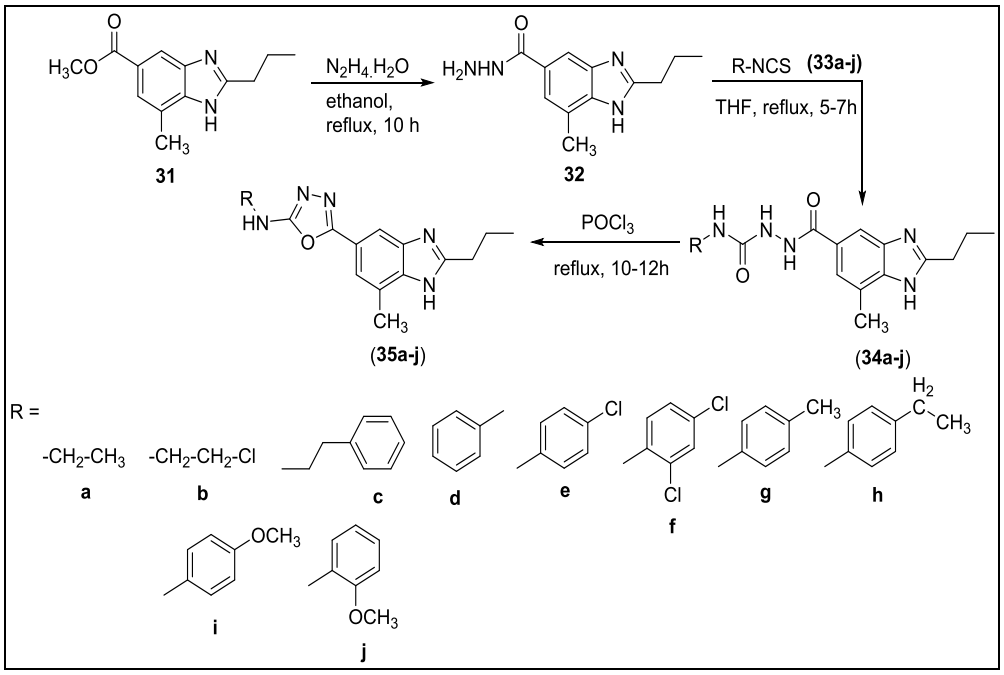


Figure 4: Significant Pharmacological Active Compounds which Enclose Benzimidazole Central Part.

R. Katikireddy *et. al* described the synthesis of benzimidazole hybrid with oxadiazol-2-*N*-alkyl/aryl amines[10] as prescribed in Scheme-2. Initially, methylester (**31**) react with hydrazine hydrate under reflux condition to form acid hydrazide (**32**). The acid hydrazide further react with different alkyl/aryl isocyanates (**33**) in THF to obtained the semicarbazide derivatives (**34**) followed by the cyclodehydration with $POCl_3$ to attained the title compound benzimidazole hybrid with oxadiazol-2-*N*-alkyl/aryl amines (**35**). All the synthesized compounds are examined for in-vitro anticancer activity by employing MTT colorimetric assay averse to the human cancer cell lines in comparison of Doxorubicin as authenticate standard drug. Among all the synthesized compounds **35f** was set up to be the most successful anticancer agent with IC_{50} values of 4.68 ± 0.04, 4.16 ± 0.02, 5.40 ± 0.08 mM against the HeLa, MCF-7, and A549 cell lines correspondingly and **35a**, **35d**, **35g**, **35i** and **35j** exhibit the less effective to human cancer cell lines than Doxorubicin.



Scheme 2: Synthesis of Benzimidazole Hybrid with Oxadiazol-2-*N*-Alkyl/Aryl Amines Derivatives.

S. E-S. Saeed *et. al* reported the synthesis and characterization of benzimidazole derivatives based on lanthanum mixed ligand complexes [12]. At first, 2-aminomethylbenzimidazole dihydrochloride was reacted with salicylaldehyde to attain the 2-(1H-benzimidazol-2-ylmethyliminomethyl) phenol as a ligand. The metal complex was synthesized in two steps. In first step Lanthanum (III) chloride was react with 2-(1H-benzimidazol-2-ylmethyliminomethyl) phenol ligand (**36**) to form the main (benzimidazole Schiff Base) complex (**37**) [La (L) Cl_2 (H_2O_2)]. The main complex was further treated with ammonia, furfural (Fur) and salicylaldehyde (Sal) as a secondary ligand to furnish the [La(L)Cl_2(NH_3)] (**38**), [La(L)Cl(Fur)] (**39**), or [La(L)Cl(Sal)] (**40**) complexes respectively as shown in Figure-5.

All the synthesized complex compounds are tested against the HCT116 cell line cytotoxicity and it was found that Compound (**36**) (HL) showed IC_{50} at 27 µg/ml, complex (**38**) [La (L) Cl_2(NH_3)] showed IC_{50} at 34.6 µg/ml, Complex (**39**) [La(L)Cl(Fur)] showed IC_{50} at 63 µg/ml, complex (**37**) [La (L) Cl_2(H_2O_2)]showed IC_{50} at 75 µg/ml, and complex (**40**) [La (L) Cl(Sal)] showed the lowest HCT116 cell line cytotoxicity at 92 µg/ml when compared with sulphorhodamine-B (SRB) as standard drug.

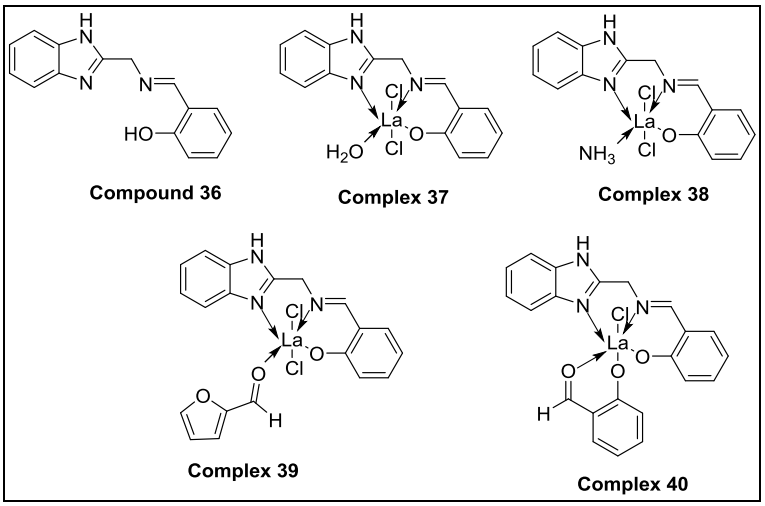
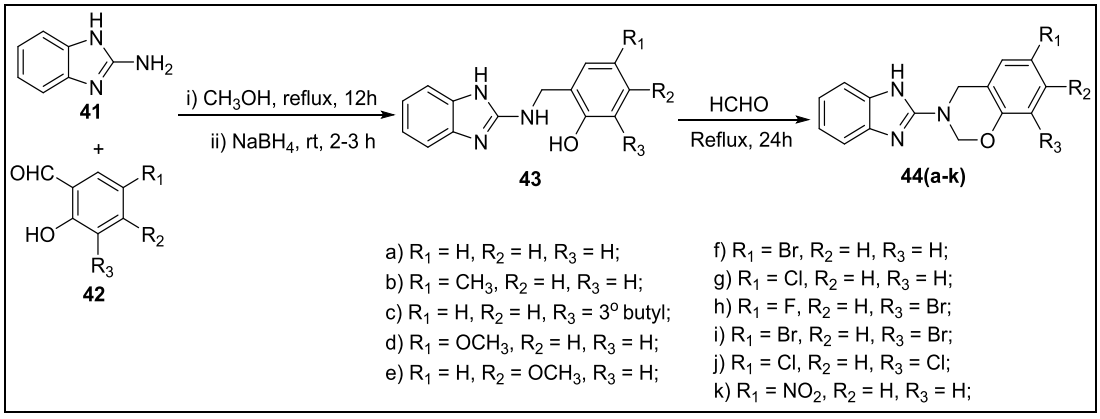


Figure 5: Compound (**36**) (HL), Complex (**37**) [La (L) $Cl_2(H_2O_2)$], Complex (**38**) [La (L) $Cl_2(NH_3)$, Complex (**39**) [La(L)Cl(Fur), and Complex (**40**) [La (L) Cl(Sal)].

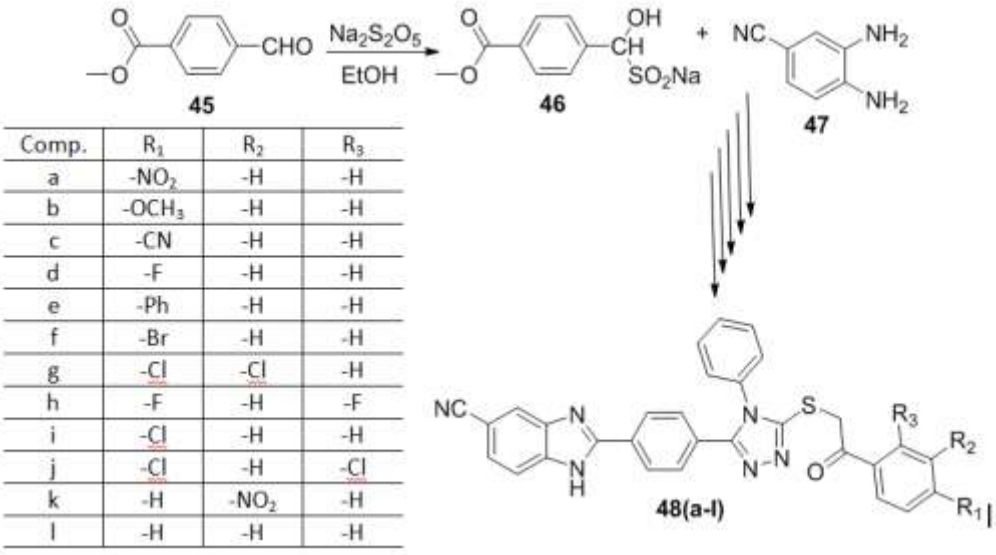
G. Srinivas *et.al* [13] described the synthesis of 3,4-dihydro-2H-benzo[e] [1, 3] oxazines tethered benzimidazole derivatives using benzimidazol-2-amine (**41**) reacted with different 2-hydroxybenzaldehydes (**42**) by the addition of $NaBH_4$ to attained the intermediate (**43**) followed by the addition of formaldehyde to furnish the target compound 3,4-dihydro-2H-benzo[e] [1, 3] oxazines tethered benzimidazole (**44a-k**) as shown in Scheme-3. The entire synthesized target derivatives were studies for the anticancer activity in view of breast cancer cell lines (MCF-7) with reference of Doxorubicin drug. Compound **44e** exhibit exceptional activity against cell lines MCF-7 with IC_{50} values of 8.60 ± 0.75, compare to the authenticate drug Doxorubicin IC_{50} value of 9.11±0.54 against MCF-7 cell line. Compounds **44i** also signified superior activity with an IC_{50} value of 9.85±0.69 μM on par with Doxorubicin against MCF-7 cells. Left over synthesized derivatives **44a**, **44b**, **44c**, **44d**, **44f**, **44g**, **44h**, **44j** and **44k** existing the excellent to reasonable activity in view of MCF-7 cell lines.



Scheme 3: Synthesis of 3,4-dihydro-2H-benzo[e] [1, 3] Oxazines Tethered Benzimidazole Derivatives.

E. Guzel *et.al* [14] reported the synthesis of benzimidazole-1,2,4-triazole derivatives in six steps as shown in Scheme-4. Initially, methyl 4-formylbenzoate (**45**) was react with

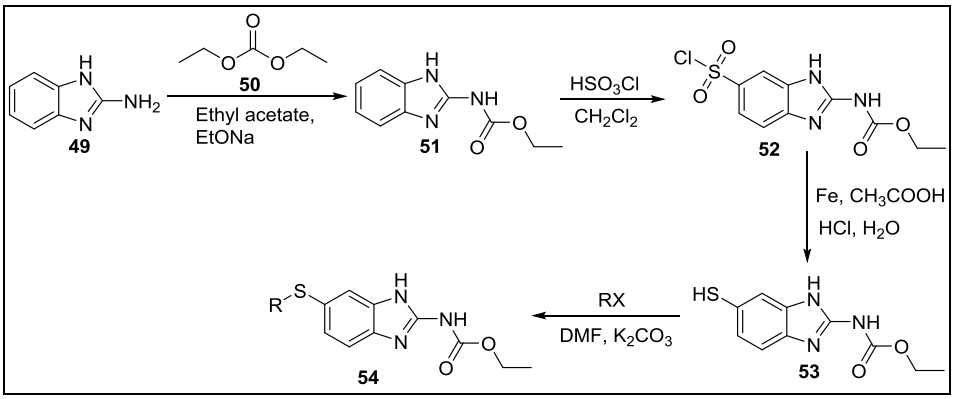
sodium metabisulfite to furnish the sodium metabisulfite (**46**) followed by the condensation reaction of 5-cyano-1,2-phenylenedi amine (**47**) to obtained the methyl 4-(5-cyano-1H-benz[d]imidazole-2- yl)benzoate intermediate. The intermediate further react with hydrazine hydrate to attain the 4-(5-cyano-1H-benz[d]imidazol-2-yl)benzohydrazide intermediate followed by the reaction phenyl isothiocyanate, NaOH in ethanol and 2-bromoacetophenone to achieve the final title compound benzimidazole-1,2,4-triazole derivatives (**48a-l**). All the synthesized derivatives were screened for their in vitro antifungal activity counter to *C. albicans, C. glabrata, C. krusei, and C. parapsilopsis. The compounds* **48b**, **48i**, and **48j** exhibited the excellent antifungal activity with their MIC values of 0.97 μg/mL compared with voriconazole and fluconazole.



Comp.	R_1	R_2	R_3
a	$-NO_2$	-H	-H
b	$-OCH_3$	-H	-H
c	-CN	-H	-H
d	-F	-H	-H
e	-Ph	-H	-H
f	-Br	-H	-H
g	-Cl	-Cl	-H
h	-F	-H	-F
i	-Cl	-H	-H
j	-Cl	-H	-Cl
k	-H	$-NO_2$	-H
l	-H	-H	-H

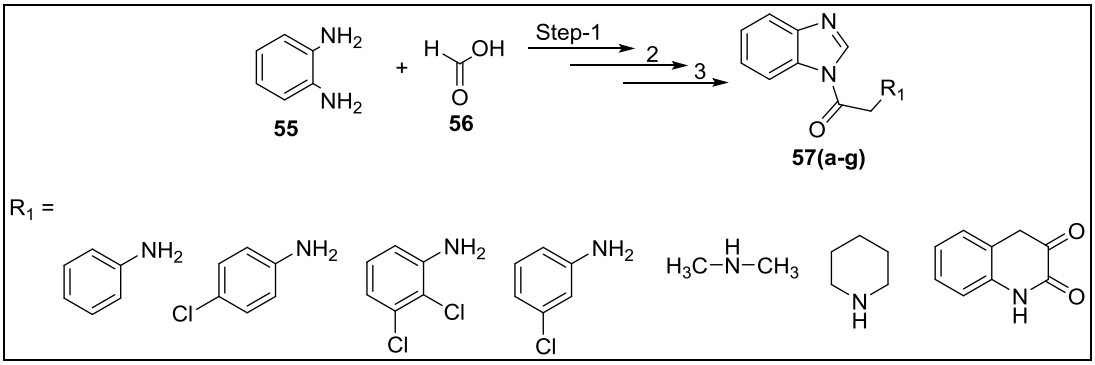
Scheme 4: Synthesis of Benzimidazole-1,2,4-triazole Derivatives.

Lei Yang reported the design and synthesis of new-fangled benzimidazole compounds including thioether and carbamate moieties.[15] Initially, benzimidazole (**49**) react with diethyl carbonate (**50**) to form a intermediate (**51**) and it is further react with sulfonic acid to obtained the intermediate (**52**) and again intermediate **52** stirred in mixture of HCl and CH_3COOH with Fe to obtained the intermediate **53**. Finally the title compound (**54**) was obtained by the reaction of intermediate **53** with K_2CO_3 and RX in DMF as described in Scheme-5. The whole synthesized analogues were tested for antifungal activity *aganist C. mandshurica, T. cucumeris, B. cinerea, V. daliae, P. infestans,* and *G. zeae* at 50μg/mL. Among all the compounds E11 and E15 exhibit the superior vitro antifungal activity against *V. daliae*, than albendazole and E11 perform immense in vitro antifungal activity against *P. infestans* (75%) to albendazole (61%).



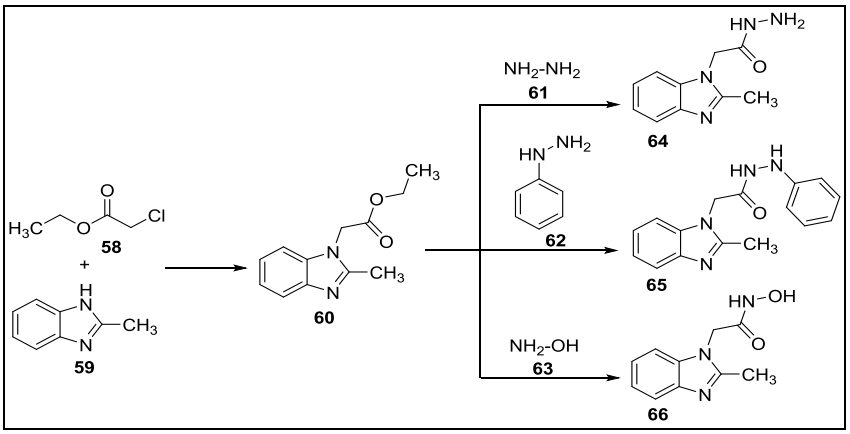
Scheme 5: Synthesis of Benzimidazole Analogues including thioether and Carbamate Moieties

Ali *et.al* addressed [16] the three step synthesis of 1-(1H-benzimidazol-1- yl)-2-(substituted) ethanone derivatives as shown in Scheme-6. In step-1 *O*-phenylene diamine (**55**) react with formic acid (**56**) to get benzimidazole and is react with chloro-acetyl chloride to obtain 1-(1H-benzimidazol-1-yl)-2-chloroetanone in step-2. Finally, in step-3 the 1-(1H-benzimidazol-1- yl)-2-chloroetanone compound is treated with chloroform to attained the title product 1-(1H-benzimidazol-1-yl)-2-(substituted) ethanone derivatives (**57**). Among all the synthesized compounds **57b, 57e** and **57g** exhibit the potential In-vitro anti-inflammatory activity using tetracycline as reference drug.



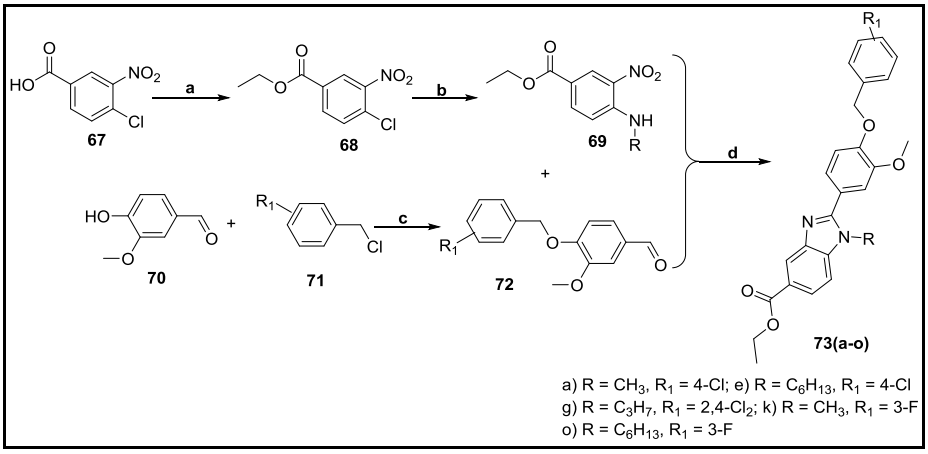
Scheme 6: Synthesis of 1-(1H-benzimidazol-1- yl)-2-(substituted) Ethanone Derivatives.

A.K. Maharana *et.al* reported the synthesis of new benzimidazole derivatives as mentioned in Scheme-7.[17] Ethylchloroacetate (**58**) in acetone is reacted with 2-methylbenzomidazole (**59**) in acetone to obtained the 2-methyl-benzimidazol with acetate group (**60**). The title compounds are synthesized by the addition of hydrazine hydrate (**61**), phenyl hydrazine (**62**) and hydroxylamine (**63**) to the (2-methyl-1H-benzimidazol-1-yl) acetate (**60**) to achieved the following desired compounds 2-(2-methyl-1H-benzimidazol-1-yl) acetohydrazide (**64**), 2-methyl-benzimidazole along with N-phenylacetohydrazide (**65**) and 2-methyl-benzimidazole along with N-hydroxy-acetamide (**66**) respectively. The synthesized benzimidazole derivatives were examined for anti-inflammatory activity make use of Carrageenan-Induced hind paw edema assay with ibuprofen as standard in rats and found that MBNHYD exhibited the good anti-inflammatory activity in contrast to standard drug.



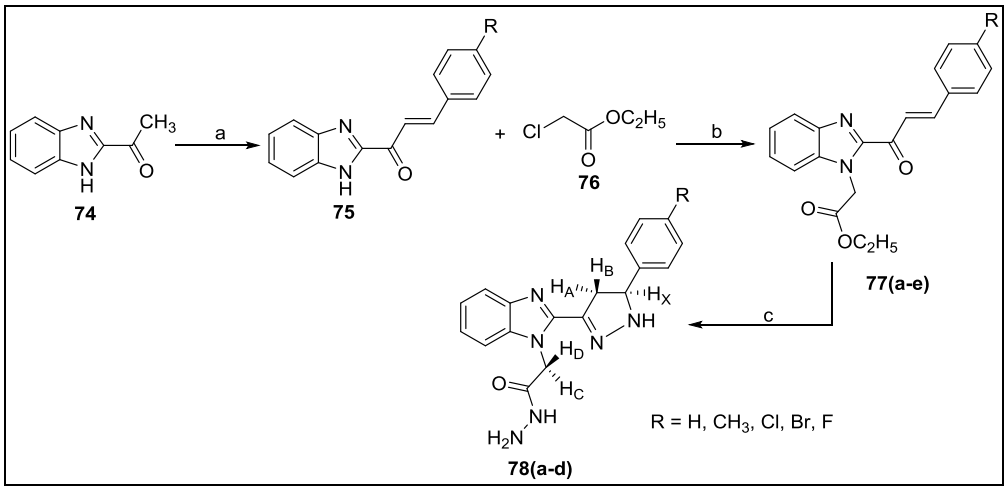
Scheme 7: Synthesis of Target Benzimidazole Derivatives.

R. Sathyanarayana *et al.*[18] synthesized the novel benzimidazole derivatives (**73a–o**) as shown in Scheme-8. The esterification of 4-chloro-3-nitrobenzoic acid (**67**) was carried out by a catalytic amount of conc. H_2SO_4 under reflux condition to produce the intermediate (**68**), subsequently reaction with 1°-amines bearing diverse alkyl group in existence of base like triethylamine to produce the intermediate (**69**). On the other hand, the derivatives of 4-(benzyloxy)-3-methoxybenzaldehyde (**72**) was synthesized by the reaction of benzyl chlorides analogues (**71**) with vanillin (**70**) by means of catalytic amount of K_2CO_3 as a base in DMF under refluxing condition for 3 h and the yield of the target products are 80-95%.
The desired products are synthesized by the reaction of intermediate **69** and **72** which are present in DMSO using reducing agent like $Na_2S_2O_4$ (sodium dithionite) formed the substituted benzimidazole analogues (**73a–o**). The synthesized compounds were studied for anti-infammatory activity by protein denaturation of bovine serum albumin. Based on in vitro anti-infammatory activity, synthesized benzimidazole derivatives **73a**, **73e**, **73g**, **73k** and **73o** were assessed for their in vivo antiinfammatory activity at 50 mg/kg dose level by examining the carrageenan–induced paw edema assay exhibited excellent anti-infammatory activity 77.50%, 75.25%, 43.35%, 72.11%, 70.10% respectively while examined to standard drug indomethacin which exhibit 74.02% inhibition.



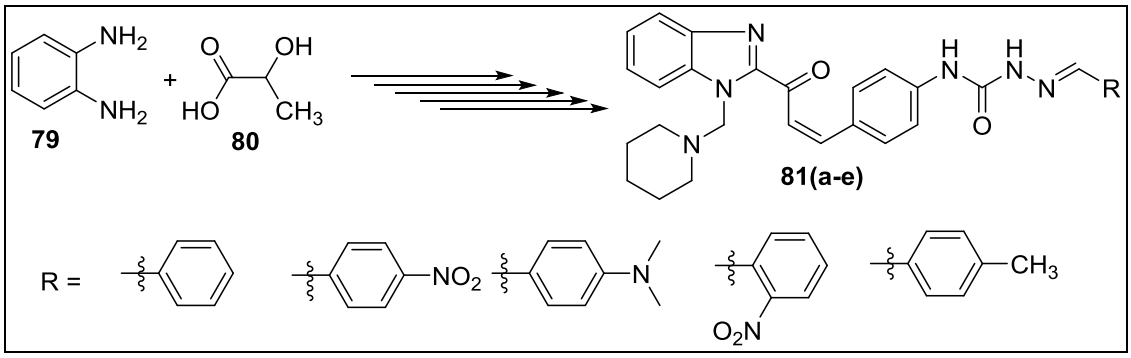
Scheme 8: Synthesis of Substituted Benzimidazole Derivatives (**73a–o**). Reagents and conditions: a) H_2SO_4, dry ethanol, 16 h; b) n-alkylamine, triethylamine, room temperature; c) K_2CO_3, DMF, 3 h; d) substituted benzyloxybenzaldehydes, sodium dithionite, 90°C, 3 h.

G. K. Padhy *et. al* [19] discussed the synthesis of novel benzimidazole-pyrazoline hybrid compounds as shown in the Scheme-9. Initially, the 2-acetylbenzimidazole (**74**) was synthesized by the reaction of lactic acid with *o*-phenylenediamine and it is reacted with arylaldehyde to attain the chalcone (**75**) synthon intermediate. The intermediate was further treated with ethyl chloroacetate (**76**) to obtain the substituted benzimidazole chalocone esters (**77a-e**). Finally, benzimidazole chalcone ester react with hydrazine hydrate to furnish the target acid hydrazides of benzimidazole linked pyrazolines (**78a-d**) compounds. The whole derivatives of synthesized compounds are examined for their antibacterial activity in comparison with ciprofloxacin as authenticate standard drug. Among all synthesized compounds **5a** exhibit the potential antibacterial activity of 62.5 µg mL^{-1} against S.aureus.



Scheme 9: Synthesis of Benzimidazole-pyrazoline hybrid Compounds. Reagents and Conditions: a) Ar-CHO, 10% NaOH, EtOH, stir; b) dry acetone, K_2CO_3, reflux; c) $NH_2.NH_2.H_2O$, alcohol, reflux.

M. Selvakumaran *et.al* addressed the synthesis of new-fangled benzimidazole linked piperidine analogues as shown in Scheme-10. *O-Phenylenediamine* (**79**) react with lactic acid (**80**) to form 1-(1H-benzimidazol-2-yl) ethanol followed by the treatment of $K_2Cr_2O_7$ and H_2SO_4 to produce 1-(1H-benzimidazol-2-yl)ethanone intermediate. In the consequent step, using Mannich base reaction the intermediate was treated with piperidine and formaldehyde to attain 1-(1-(piperidin-1-ylmethyl)-1H-benzimidazol-2-yl)ethanone. The target molecules 1-(4-sub stitutedbenzylidene)-4-(4-(3-oxo-3-(1-(piperidin-1-ylmethyl)-1H-benzimidazol-2-yl)prop-1-enyl)phenyl)semicarbazide (**81a-e)** were synthesized by the reaction of 1-(1-(piperidin-1-ylmethyl)-1H-benzimidazol-2-yl)ethanone with 4-amino benzaldehyde, sodium cyanate, hydrazine hydrate, and various aromatic aldehydes in different reaction conditions.[20] The all synthesized compounds were evaluated for their antibacterial activity. Among all the synthesized compounds, **81b, 81d** and **81e** exhibit the excellent antibacterial activity against *Bacillus subtilis*, *Klebsiella pneumonia* and *Pseudomonas aeruginosa* bacteria in comparsion with standard drug Ciprofloxacin.



Scheme 10: Synthesis of Benzimidazole Linked Piperidine Derivatives.

IV. CONCLUSION

In summary, benzimidazole analogues have paying a remarkable reflection for the reason that of their adaptable experience in the medicinal chemistry. In this chapter, we have converse a diversity of benzimidazole analogues comprehensively used in the field of medicinal chemistry and used as guide molecules in drug modernization studies. This chapter can authenticate to be unbelievably obliging for chemists or research scholars in the advancement of novel methodologies for the vast synthesis of biologically and medicinally active novel benzimidazoles derivatives and large-scale production of biologically active novel benzimidazole derivatives.

V. CONFLICT OF INTEREST

The authors state no conflict of interest, financial or else.

VI. ACKNOWLEDGEMENT

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