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A systematic review on diverse synthetic route and pharmacological activities of benzimidazole as optimized lead

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Abstract

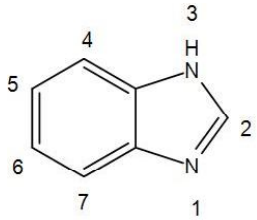
The aim of this review is to provide the systematic information of synthetic scheme and biological activity of synthesized benzimidazole derivatives. Benzimidazole is widely used lead molecule for the synthesis of various types of pharmacologically active moiety. It is heterocyclic aromatic fused colorless solid having molecular mass of 118.053 g/mol. It is basic in nature and can be served as ligand in coordination chemistry. It is bioactive compound showed various pharmacological activity till now viz. anthelmintics (albendazole, mebendazole), proton pump inhibitors (omeprazole, pantoprazole), antibiotics, antiprotozoal, antifungal, anti-cancer, anti-viral, anti-oxidant, anti-inflammatory *etc*. Various synthetic route by various methods is also already reported. Some of them are traditional convenient method, microwave reactor method, solvent free synthesis method, green synthesis method. Due to its wide variety of biological action and the similarity with biomolecule, it is frequently taken as lead for new drug discovery.

Key words : benzimidazole derivatives, bioactive, anti-cancer, anti-viral, antibiotic.

1. Introduction

Benzimidazole has been used, in various drug discovery process to enhance the value of pharmacological activity, as pharmacophore[1]. It is the basic and most used top five hetero-aromatic five-membered nitrogen containing pharmacophore[2]. Benzimidazole is highly stable molecule which is

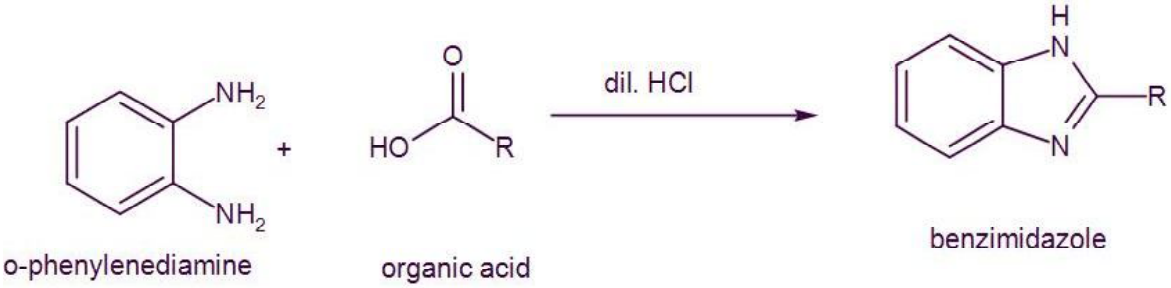
not affected by the treatment of conc. acid as well as high temperature. The ring is stable enough for the oxidative cleavage[3]. This scaffold is frequently taken as lead moiety in the field of drug design because of structural similarity to the various biological molecule present inside the body and also act as secondary bio isosteres of nucleobase[4]. Benzimidazole substructures are the privileged bioactive compound as they possess anti-bacterial, anti-viral, anti-cancer, cytotoxic, anti-oxidant, anti-helminthic, ant-inflammatory, analgesic, anti-protozoal, anti-fungal, anti-hypertensive, immunosuppressant and many more other therapeutical activities[5–7]. It shows potential inhibitory function on SARS-CoV-2 protease and glycoprotein[8]. Molecular interaction of the lead molecule gives an idea about the possibility of new target and binding pocket for the optimized benzimidazole moietv[9,10].



Benzimidazole

1.1. Phillips Method of Synthesis

Usually, it is difficult to synthesis the benzimidazole by simple heating the component together. This problem was solved by the improved Phillips method for synthesizing the benzimidazole by using dilute mineral acid at lower temperature with o-phenylenediamine and organic acid as starting materials (scheme 1). The yield of this method can be increase by the use of aromatic acid also[11,12].



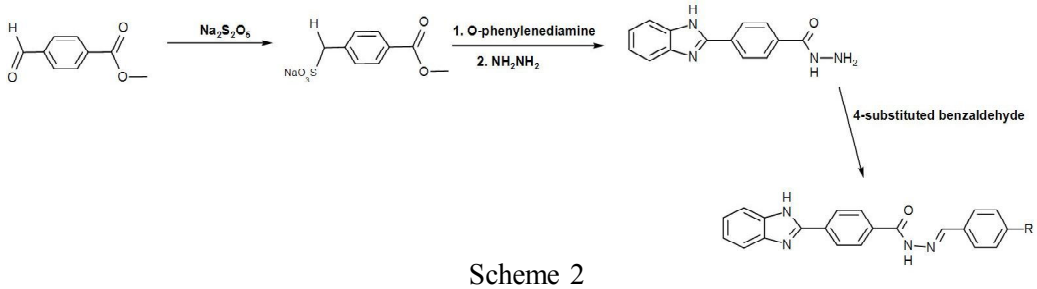
o-phenylenediamine organic acid benzimidazole

Scheme 1

2. Verified Synthetic Scheme

2.1. Monosubstituted Derivatives :

Yusuf Ozkay *et al* synthesized 12 new derivative of benzimidazole- hydrazone as potential antibacterial and antifungal compounds. They followed the four steps pathway to synthesized the derivatives of yield in the range of 68 to 81% (scheme 2).



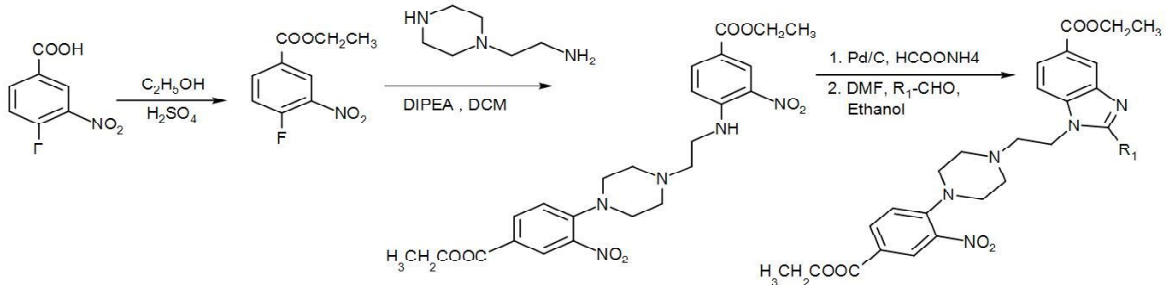
Scheme 2

Compound 4b, 4d, 4e and 4g showed the maximum response as antibacterial activity against human pathogen. Meanwhile same compounds showed the reasonable response towards fungal species. It was concluded that the halogen bearing derivatives showed the higher level of antibacterial activity (e.g., 4d, 4e, 4f)[13].

Yeong Keng Yoon *et al.* prepared seven novel benzimidazole derivatives by using 4-chloro-3-nitrobenzoic acid as starting material (scheme 3). They screened all the derivatives for the antimycobacterial activity against *Mycobacterium tuberculosis*. They kept constant substitution at N-1 position making C-2 position variable for different possible substitution. So, the synthesized compounds were considered as monosubstituted derivatives.

Table 1. Substitution and for scheme 2 and their yield

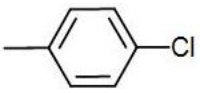
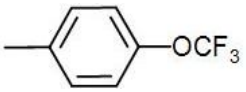
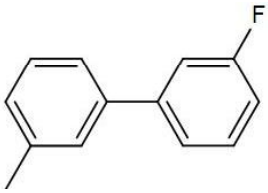
Compound	R	Yield
4b	H	81%
4c	OH	74%
4d	Cl	69%
4e	Br	-
4f	F	-
4g	COOH	80%
4k	$N(CH_3)_2$	77%



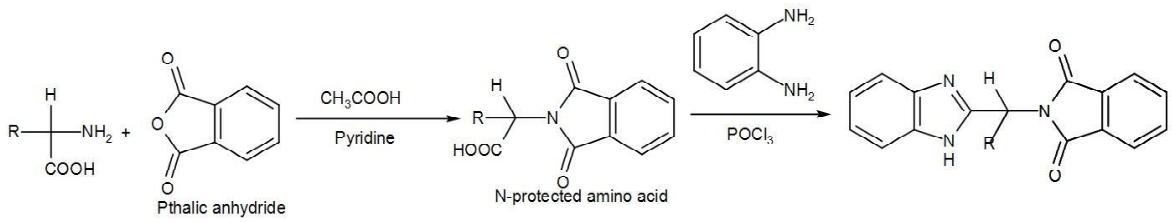
Scheme 3

From the screened data it was concluded that compound ST02, ST03, ST04 showed maximum antimycobacterial activity against *Mycobacterium tuberculosis*[14].

Table 2. Substitution for scheme 3 and their yield

Compound	R	Yield
ST02		85%
ST03		90%
ST04		66%

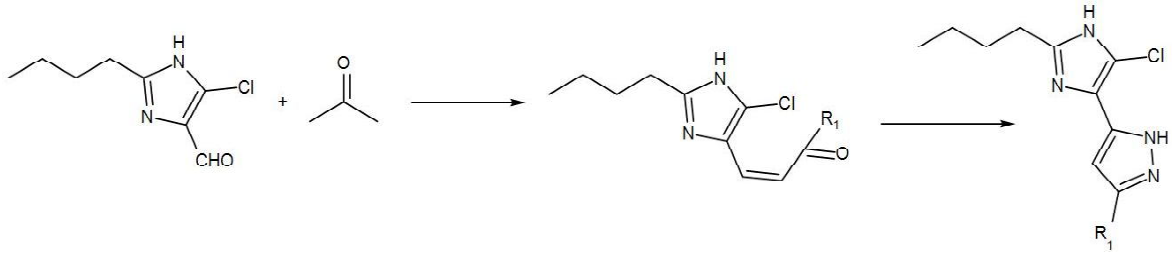
Akabar Mobinikhaledi *et al.* developed the procedure for the synthesis of benzimidazole derivatives as α-glycosidase inhibitors. Pthalic anhydride was used as protecting agent to synthesis the starting material, N-protected amino acids. Then, substituted benzimidazole was synthesized by 0-phenylenediamine and N-protected amino acid (scheme 4).



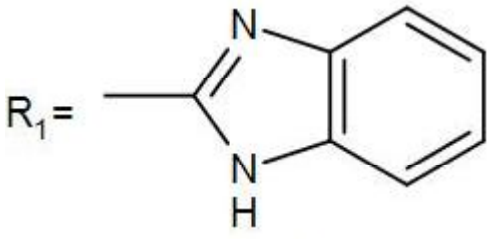
Scheme 4

Yeast and rat intestinal α- glycosidase enzyme is used to test the inhibitory effect of the synthesized compounds. Among all the screened compound only 2-(1-(1H-benzo(d)imidazol-2-yl)-2-phenylethyl) isoindoline-1, 3-dione and 2-(1-(1H-benzo(d)imidazol-2-yl)-2-(4-hydroxyphenyl) ethyl) isoindoline-1,3-dione displayed significant result for inhibition of enzyme[15].

Srinivas Rao Dasari *et al.* synthesized antibacterial benzimidazole based pyrazole derivatives. 2-butyl-4-chloro-1H-imidazole-5-carboaldehyde and acetophenone is used for the synthesis and the compounds are confirmed by IR, Mass spectroscopy, and NMR data studies (scheme 5).

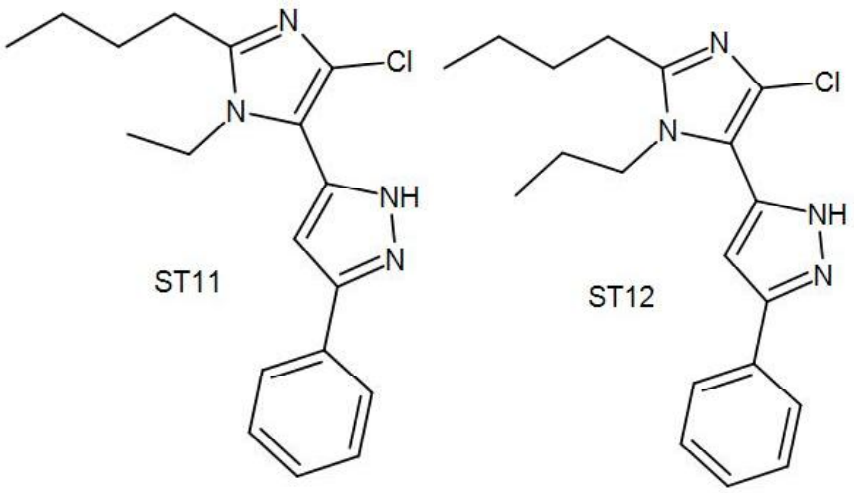


Scheme 5

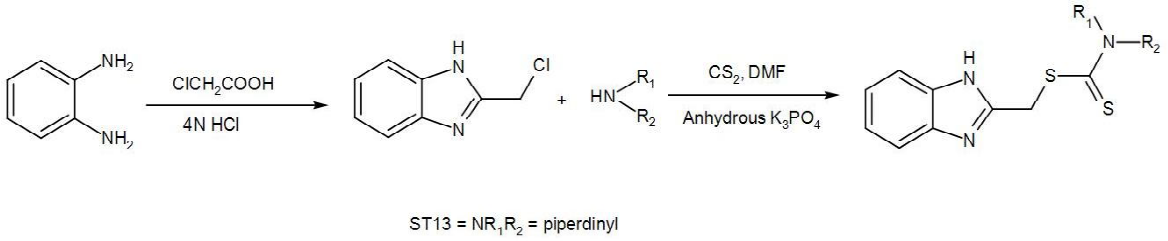


ST10

They evaluated the anti-bacterial activity against gram +ve and gram -ve strain by using streptomycin (100µg/ml) as reference. Compound ST10 was found to express high antibacterial activity. Compare to reference ST11 and ST12 also showed excellent activity. These compound also were screened for molecular docking studies[16].



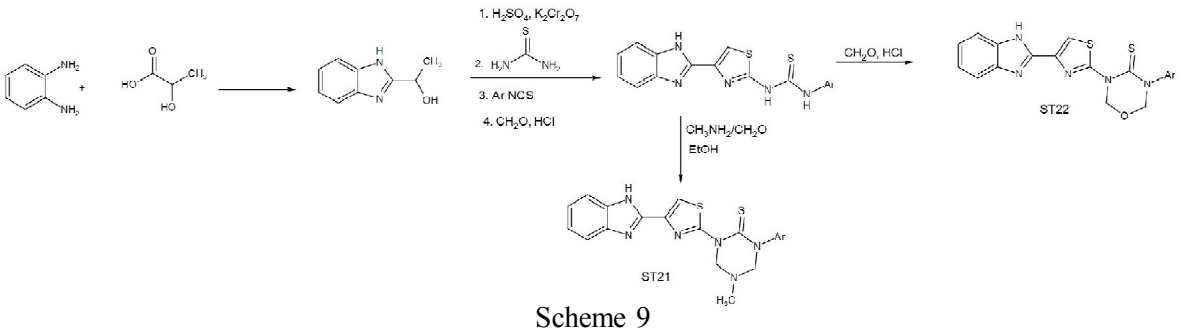
Keerthana Bacharaju *et al* synthesized key benzimidazole derivatives substituted with dithiocarbonate and evaluated as anticancer agent. Chloro acetic acid and 0-phemylenediamine are used for the synthesis. And later various amine and carbon disulphide were used for derivatives synthesis (scheme 6).



Scheme 6

Chick pea seed (Cicer arietinum) was used for evaluation of antimitotic activity and compound ST13 only showed the highest potency for antimitotic activity. All the synthesized compounds were tested for molecular docking[17].

Kamatchi Chandrasekar *et al.* performed the docking studies against topoisomerase II/ DNA gyrase enzyme and also synthesized the docked benzimidazole ligand in lab. They synthesized novel benzimidazole derivatives from the mixture of o-phenylenediamine and formic acid by reflux (scheme 7).

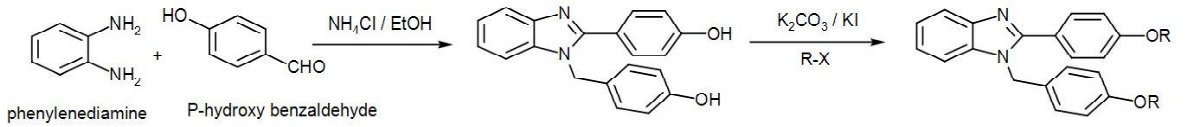


Scheme 9

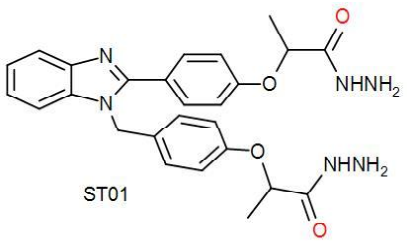
Compound substituted with electron withdrawing group and electron donating group on benzine ring exhibit different antibacterial activity. The compound ST21 and ST22 displayed better activity than reference compound Gentamycin. The docking score also recorded against the topoisomerase-II enzyme[20].

1.1. Disubstituted Derivatives:

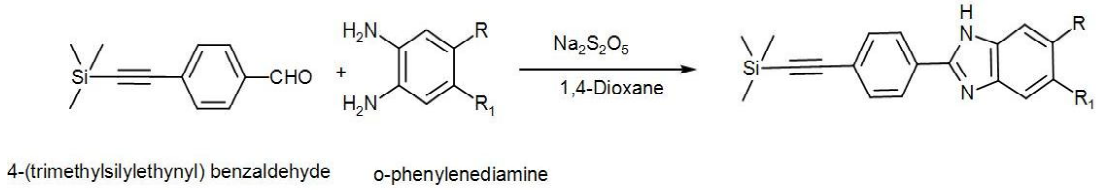
Rezk R. Ayyad *et al.* synthesized ten novel disubstituted benzimidazole derivatives and tested for the anti-inflammatory & analgesic activity. They used phenylenediamine and p-hydroxy benzaldehyde as reactant to synthesized the derivatives (scheme 10).



Scheme 10



From the synthesized ten compounds, they found compound ST01 exhibits maximum anti-inflammatory and analgesic activity(21). Abdelaaziz Ouahrouch *et al*, developed new disubstituted derivatives keeping benzimidazole as lead optimized and evaluated for pharmacological activity. They synthesized hybrid molecule by the condensation reaction of 4-(trimethylsilylethynyl) benzaldehyde and o-phenylenediamine in presence of $Na_2S_2O_5$ (scheme 11). All the compound found above 90% yield.



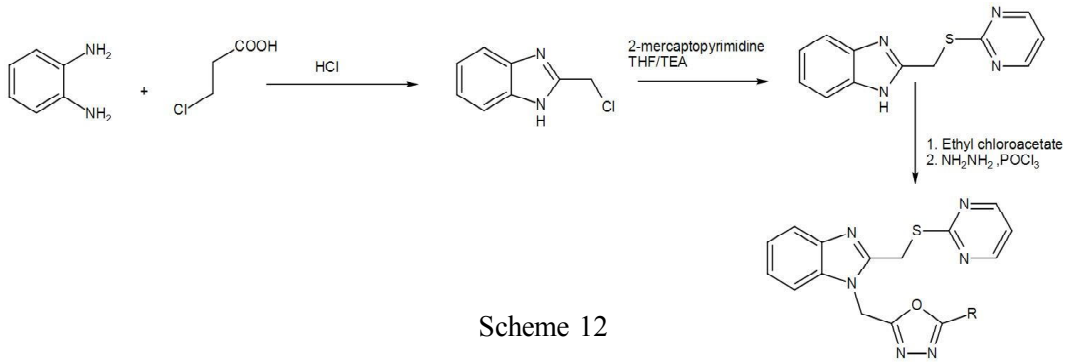
Scheme 11

Out of all compounds a modest inhibition was found with compound ST05 which is CF3 substituted derivative. Compound ST06 and ST07 also perform good pharmacological action[22].

Table 3. Substitution for scheme 11 and their yield

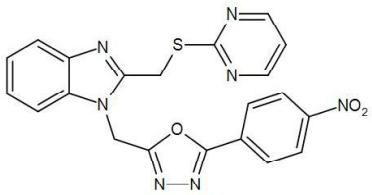
Compound	R	R^1	Yield
ST05	CF_3	H	95%
ST06	F	H	98%
ST07	Cl	Cl	95%

Ankita Rathore *et al*, discovered new analogue of extended benzimidazole derivatives and evaluated in-vitro selective cyclooxygenase (COX1 & COX2) inhibitory activity. They used o-phenylenediamine and 2-chloro ethanoic acid as starting material (scheme 12).



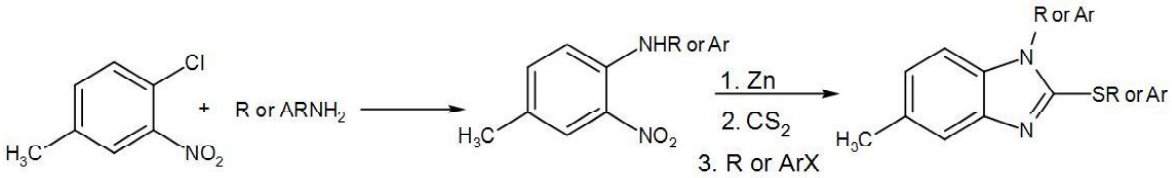
Scheme 12

Compound 5l was emerged the lead compound as it is the most potent and selective COX-2 inhibitor. This compound also has less gastric toxicity and could be developed further as new lead optimized compound for the same[23].



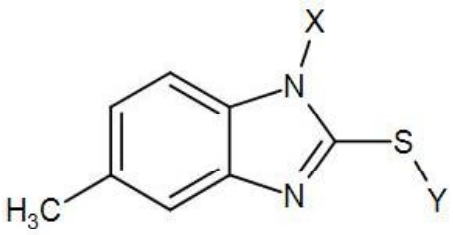
5l

Monika *et al* synthesized di-substituted methylated benzimidazole derivatives from 2-chloro-5-methyl nitrobenzene and aryl/alkylamine (scheme 13).



Scheme 13

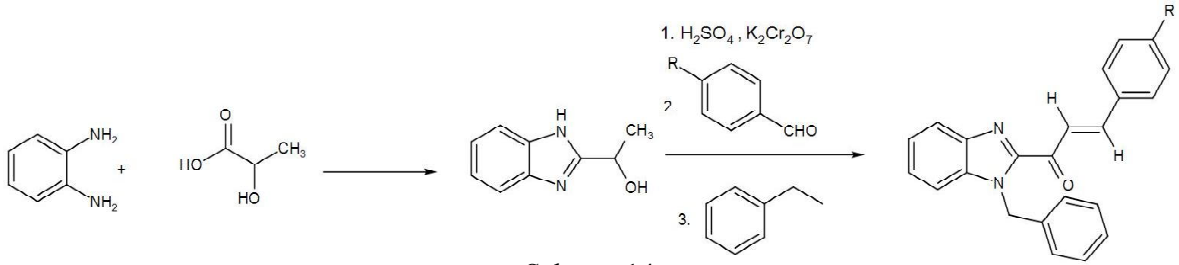
Scheme 13The benzimidazole having cyclohexyl substitution showed excellent antibacterial activity. Between the synthesized compound, ST17 and ST18 showed good antibacterial activity against both the gram +ve and gram -ve bacteria[24].



ST16 $X= C_4H_9$ $Y= C_4H_9$

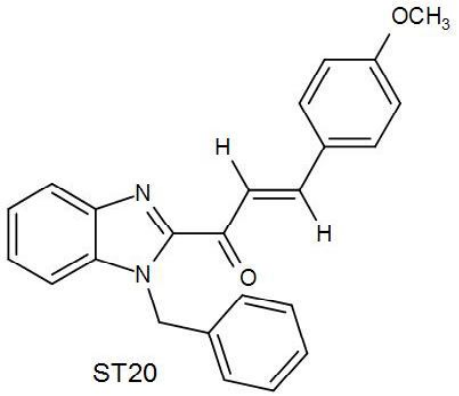
ST17 C_6H_{11} C_4H_9

Gopal K. Padhy *et al* developed the new disubstituted benzimidazole derivatives for antimicrobial activity. They used multi-step reaction method of 1,2-phenylenediamine with 2-hydroxy propanoic acid to synthesize the derivatives (scheme 14).



Scheme 14

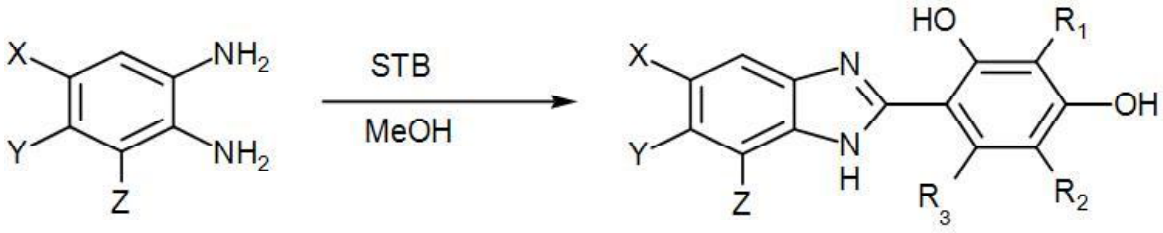
The compound ST20 showed very good antibacterial activity against *S. aureus* and *B. subtilis*. The remaining other synthesized compound indicate poor activity[25].



ST20

1.1. Trisubstituted Derivatives

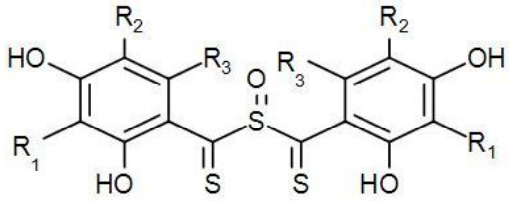
Joanna Matysiak *et al.*, synthesized novel benzimidazole derivatives modifying both the ring and their efficacy had been determined as AchE and BuchE inhibitor. The result of the compounds was supported by docking simulation studies simultaneously. 1,2-diamine and sulfinylbis [(2,4-dihydroxy phenyl) methanethione]-{STB} were used for the one step synthesis reaction (scheme 15). The percentage yield was found in between 60% to 87%.



Scheme 15

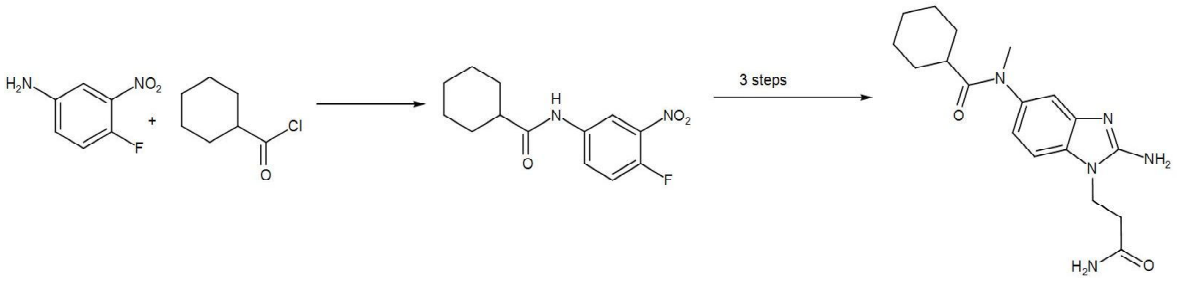
X, Y, Z = H for ST08 & X, Z = H and Y = OMe for ST09

Compound substituted with electron withdrawing groups showed the highest inhibitory action. Therefore, compound ST08 and ST09 are strongest inhibitor at the same time analogue ST09 is more active against BuchE[26].



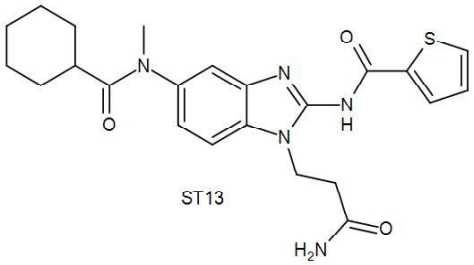
Compound	R^1	R^2	R^3
ST08	H	Cl	H
ST09	Me	H	H

Kevin J. Moriarty *et al* studied the interleukin-2T-cell kinase (Itk) inhibitory action of trisubstituted benzimidazole derivatives. They used the synthetic scheme of 4-fluoro-3-nitro phenylamine with cyclohexane carbonyl chloride for the preparation of derivatives (scheme 16).

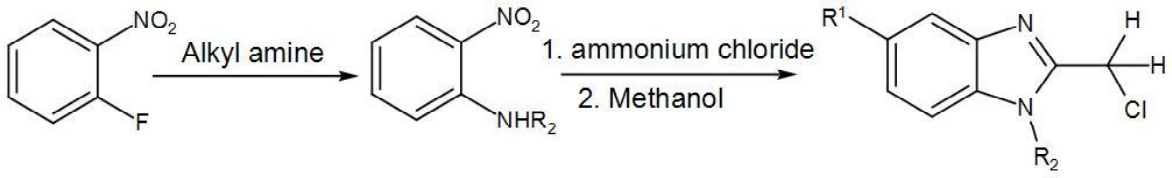


Scheme 16

From the docking studies they found compound ST13 has potential feature to become hit and they also studied the SAR of the derivatives[27].

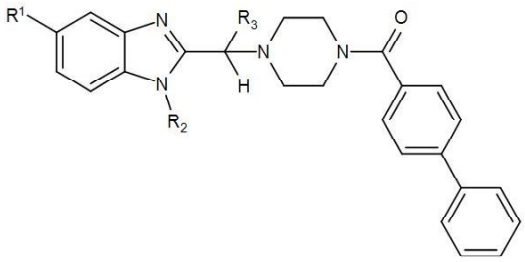


Rani S. Kankate *et al* synthesized tri-substituted benzimidazole derivatives by using microwave assisted reaction method. In microwave reactor, they used 0.24mol of 2-flurointrobenzene and 6mol of methyl/ethylamine as starting material. They used other respective reactant for derivatives synthesis (scheme 17).



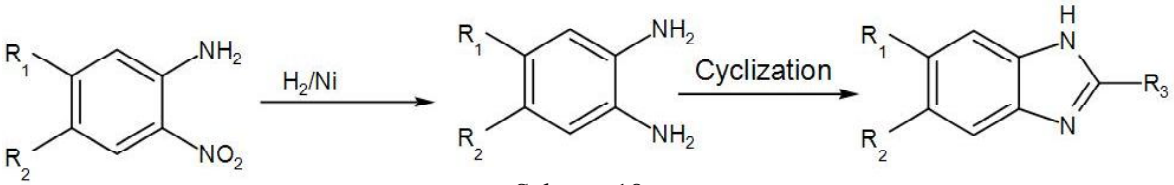
Scheme 17

Compound ST15 and ST16 showed good antifungal activity discovered after screening against fungus. They activity was found close to the reference compound ketoconazole. Docking score of the compound 10f and 10l had been justifiable for the interaction(28).



Compound	R^1	R^2	R^3
ST15	H	CH_3	Phenyl
ST16	Cl	H	Phenyl

Juan Valdez *et al* prepared halogenated and non-halogenated tri-substituted benzimidazole derivatives and screed for antiparasitic activity. The Phillips method was used for the synthesis of most of the 1H-benzimidazole. 1,2-phenylenediamine is refluxed with acetic acid for 3-4 hr. (scheme 18).



Scheme 18

Metronidazole and albendazole were used as reference for testing antiparasitic activity. Among all screened compound, it was found that compound with no substitution in the benzoic ring i.e. ST19 and compound having methylthio group at 2-position and chlorine at 5-position *i.e.* ST19 were most significant activity[29].

ST18: No Substitution
ST19: R_1= Cl R_2= H R_3= SH

1. Conclusion

This article collected various original article published from past and reviewed the synthetic route and pharmacological activity with molecular docking score of benzimidazole derivatives as optimized lead in the field of research and synthetic chemistry. It can be report that different heterocyclic, aromatic, alkyl and branched chain substitution can be attached to the lead benzimidazole to obtained the novel derivatives with improve therapeutic properties. The weak molecular interaction with protein can be enhanced by electron-rich nitrogen heterocycles and can be justify the proton receiving and donating property of the compound. The position C-2 in the ring is very much prone to substitution and show significance antibacterial and anti-tumours activity. Position C-5 and C-6 is good for the small side chain or Cl and F can incorporate to optimize the physiochemical parameters. Thus, benzimidazole behave as important optimized lead compound for wide range pharmacological activity.

2. Scope of future research

Benzimidazole is versatile lead moiety having a great scope in almost all the pharmacological activity. The activity of benzimidazole can be more expand in the field of enzyme inhibition and disease pathway breaking. More environmentally friendly synthetic route can be evaluated to enhance the scope of it in green chemistry. The present review was more focus on the traditional synthetic route but its evaluation on molecular docking and molecular dynamic level can be future scope. Detail study on docking properties of benzimidazole and nano particle catalysed synthesis of it will be interesting to see in future.

3. Acknowledgment

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4. Funding

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5. Conflict of Interest

All authors declare that there is no conflict of interest.

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