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THE INTRIGUING BENZIMIDAZOLE: A REVIEW

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Keywords:

Benzimidazole, Heterocyclic, *o*-phenylenediamine, 2-substituted benzimidazole

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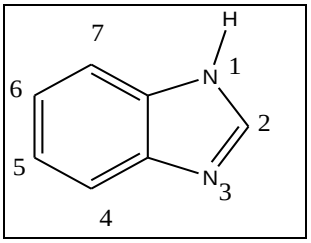
ABSTRACT: Benzimidazole is a heterocyclic aromatic organic compound containing nitrogen. This bicyclic compound is formed by the fusion of benzene with imidazole ring. It is a vital Pharmacophore and privileged structure in medicinal chemistry which exhibits various therapeutic activities like antiulcer, antihypertensive, analgesic, antiviral, antifungal, anticancer and antihistaminic. The disease conditions targeted by these activities are discussed. The present article extensively covers various procedures of synthesis of 2-substituted benzimidazole and its analogs by utilizing different catalysts, solvent conditions, reactants and microwave irradiation with the aim to obtain an inexpensive, eco-friendly, less time-consuming procedure which ensures good yield and quick isolation of the pure product. Ongoing clinical trials of different benzimidazole derivatives exploring additional pharmacological activities are also covered.

INTRODUCTION: Benzimidazole is a heterocyclic aromatic organic compound which enjoys the attention as a versatile Pharmacophore in medicinal chemistry. The benzimidazole ring is one of the privileged scaffolds for the development and synthesis of novel molecules of therapeutic value [1]. This nitrogen-containing heterocyclic moiety exhibits a diverse range of biological activities like antimicrobial, anticancer, anthelmintic, anti-convulsant, antioxidant, anti-inflammatory, anti-fungal, antipsychotic, antihistaminic, antiviral [2].

Chemistry: Benzimidazole is a six-membered bicyclic heteroaromatic compound in which benzene ring is fused to the 4- and 5-positions of the imidazole ring.

Benzimidazole ring contains two nitrogen atoms placed at position 1 and 3 which exhibit amphoteric nature, that is, possessing both acidic and basic characteristics [3].



BENZIMIDAZOLE

Benzimidazole ring exists in two equivalent tautomeric forms, in which the hydrogen atom can be located on either of the two nitrogen atoms [5].

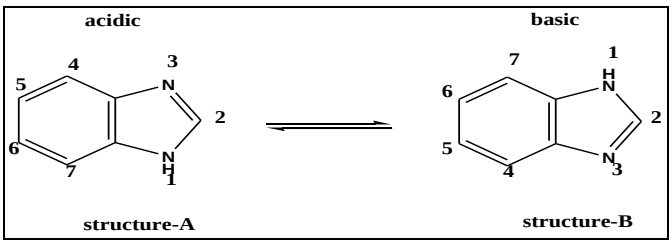


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TABLE 1: PHYSICAL CHARACTERISTICS OF BENZIMIDAZOLE [4]

S. no.	Benzimidazole	
1	Physical state	Tabular crystals
2	Molecular Formula	$C_7H_6N_2$
3	Molecular Weight	118.053 g/mol
4	Colour	Whitish
5	Odor	Characteristics
6	Melting point	170.5-171.5 ºC
7	Boiling point	360 ºC
8	Solubility	Freely soluble in alcohol, sparingly soluble in ether. Practically insoluble in benzene, petroleum ether. Soluble in aqueous solutions of acids and strong alkalis
9	Isomerism	Tautomerism

History:

TABLE 2: BIOLOGICAL HISTORY OF BENZIMIDAZOLE

Year	Biological activity reported
1943	Goodman and Nancy Hart published the first paper on antibacterial properties of benzimidazole [6]
1944	Woolley published their work on benzimidazoles He also reported the antibacterial activity of synthesized benzimidazoles against *E. coli* and Streptococcus lactic [7]
1950	CIBA pharmaceutical (now Novartis) were discovered benzimidazole derivative opioid agonist etonitazene [8]
1960	Fort et al. reported the discovery of benzimidazole derivatives as proton pump inhibitors
1965	Burton et al. Reported 2-trifluoro benzimidazoles are potent decouplers of oxidative phosphorylation in mitochondria. They are also inhibitors of photosynthesis, and some exhibit appreciable herbicidal activity [10]
1971	Mebendazole was discovered by Janssen pharmaceutical in Belgium [11]
1975	Albendazole was invented by Robert J. Gyurik and Vassilios J. Theodorides and assigned to SmithKline Corporation [12]
1977	Astemizole was discovered by Janssen pharmaceutical [13]
1989	Lackner *et al*. reported the anti-inflammatory activity of benzimidazole. Omeprazole was developed by Astra AB (now AstraZeneca) [14, 15]
1991	Telmisartan was discovered and developed by Boehringer ingelheim *et al*., [16]
1992	Candesartan is a benzimidazole which was developed at Takeda pharmaceutical [17]
1994	Devivar *et al*., reported that 6-dichlorobenzimidazole-1-βD-ribofuranoside (DRB) and its 2-substituted derivatives Show activity against human cytomegalovirus [18]
2001	Most recently, the antiprotozoal activity of substituted 2-trifluoro benzimidazoles has been reported by Navarette-Vazquez *et al*., [19]

Synthesis of Benzimidazole Derivative: Several synthetic methods are available for the synthesis of benzimidazole [20].

Benzimidazole can be synthesized from:

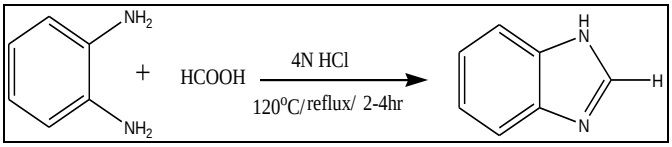
1. *o*-phenylenediamine
2. *o*-Nitroarylamines and o-dinitroarenes
3. *o*-substituted-N-benzylidene aniline
4. Amidine
5. using of green chemistry
6. miscellaneous

1. From O-phenylenediamine: *O*-phenylene-diamine reacts with -

- **A.** Carboxylic acids and their derivatives,
- **B.** Amino-ethers
- **C.** Substituted aldehydes
- **D.** Ketone
- **E.** Urea
- **F.** lactones

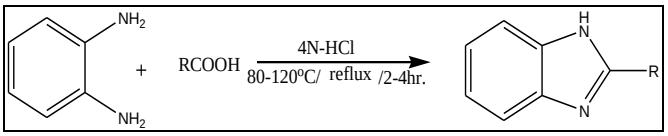
Scheme 1:

Reaction with Carboxylic Acids and their Derivatives: E. Wundt *et al*., refluxed o-phenylenediamine (A) with formic acid (B) under the acidic conditions (4N HCl) at 120 ºC for 2 to 4 h to give 75% yield of benzimidazole (C). This is a prevalent laboratory method for synthesis of benzimidazole **Scheme 1a** [21].



SCHEME 1A

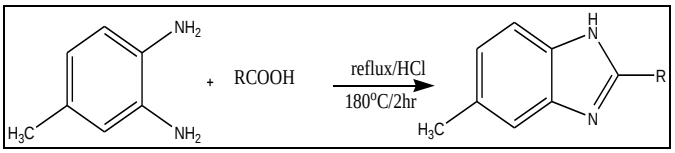
Dr. Phillips *et al*., refluxed o-phenylenediamine (A) with aliphatic acid in the presence of 4N-HCl at 80-120 ºC temperature for 2 to 4 h. This method yields 80 to 90% of 2-substituted benzimidazole **Scheme 1b** [22].



SCHEME 1B

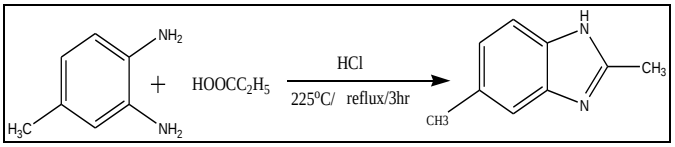
Landenberg *et al*. refluxed substituted carboxylic acid with 4-methyl-1,2-diaminobenzene(F) in the acidic medium at 180 ºC for 2 h, they found about

71% yield 5-methyl-2-substituted benzimidazole **Scheme 1c** [23].



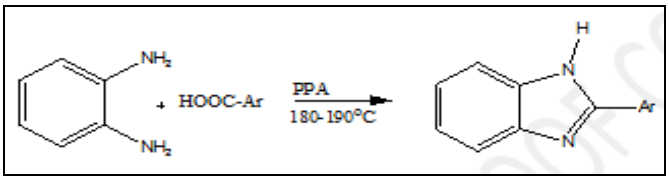
SCHEME 1C

Von Niemantowski *et al*., refluxed 4-methyl-1,2-diaminophenyl (F) with an equal amount of ethyl-carboxylic acid (G) in the presence of 4N-HCl at 225 ºC for 3 h gives 76% yield of 2,5-dimethyl-benzimidazole(H) **Scheme 1d** 24.



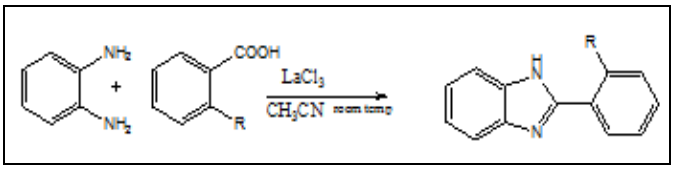
SCHEME 1D

Maleki *et al*., Condensed *o*-phenylenediamine (A) with aromatic carboxylic acid (G) in the presence of catalyst polyphosphate ester (PPA) at 180-190ºC to get 77% yield of 2-arybenzimidazole **Scheme 1e** [25].



SCHEME 1E

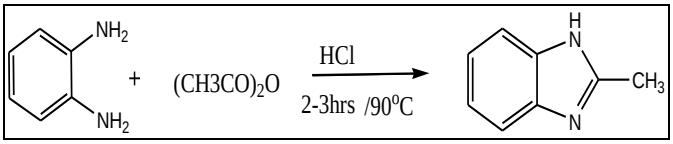
Venkateswarlu *et al*., Synthesised 2-substituted benzimidazole derivatives, from the reaction of o-phenylenediamine and substituted benzoic acid in the presence of lanthanum chloride in acetonitrile at room temperature, this method gives about 83% yield **Scheme 1f** [26].



SCHEME 1F

Scheme 2:

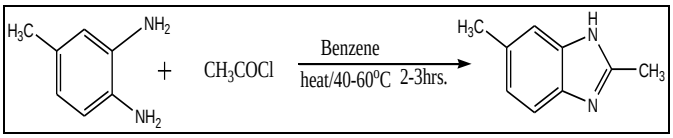
Reaction with Acidic Anhydride: Wagner *et al*., condensed *o*-phenylenediamine with acetic anhydride at the 90 ºC temperature in the presence of dil. HCl for 2 to 3 h. They found a 68% yield of 2-methyl benzimidazole **Scheme 2** [27].



SCHEME 2

Scheme 3:

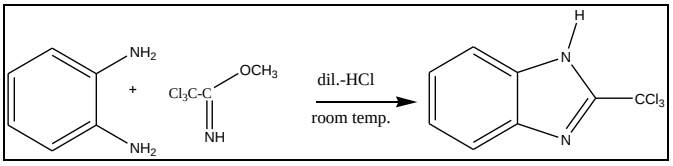
Reaction with Acetic Chloride: Benguer *et al*., condensed acetyl chloride with 5-methyl-1, 2-diaminophenyl in benzene medium at 40 to 60 ºC for 2 to 3 h it gives 71% yield of 2,6-dimethyl benzimidazole **Scheme 3** [28].



SCHEME 3

Scheme 4:

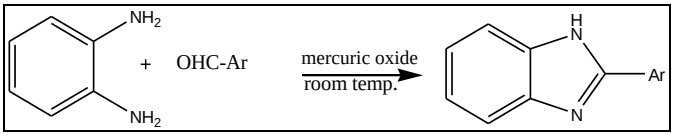
Reaction with Imino-Ethers Imidates: Acheson and King *et al*., condensed o-phenylenediamine with trichloro-acetimidate in the presence of dil. hydrochloric acid at room temperature to give about 81% yield of 2-trichloromethyl benzimidazole **Scheme 4** [29].



SCHEME 4

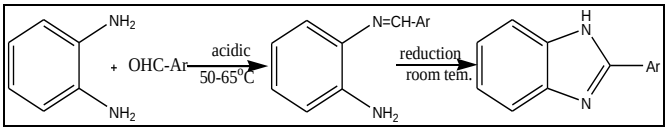
Scheme 5:

Reaction with Substituted Aldehydes: Direct condensation of *o*-phenylenediamine with aldehydes is not a good synthetic route for benzimidazole molecule as it yields a complex mixture of 1, 2-disubstituted benzimidazole and bisdihydrobenzimidazole as side products. But the use of metal catalysts namely copper (II) acetate and lead-tetra-acetate in these reactions gives better results. Ruthenium, palladium, and rhodium catalysts have also been used [30]. Smith, Rao and Ratnam *et al*., synthesized 2-aryl benzimidazole by the reaction between o-phenylenediamine and aryl aldehydes in the presence of the oxidising agents like- cupric acetate, mercuric oxide, chlorine, lead tetraacetate, manganese dioxide, Nickel peroxide at room temperature. This synthetic method is eco-friendly and gives good yield of about 85% **Scheme 5a** [31].



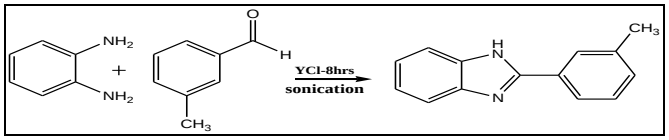
SCHEME 5A

When *o*-phenylenediamine is reacted with aromatic aldehydes in the presence of acidic medium at 50 ºC to 65 ºC, it yields an intermediate 2-(benzylideneamino) aniline which is converted into 2-substituted benzimidazole by treating with reducing agents which gives 78% yield **Scheme 5b** [32].



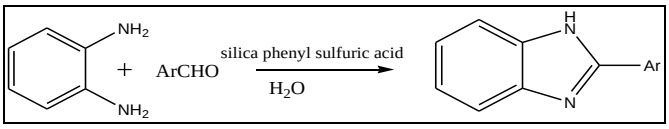
SCHEME 5B

Zhang *et al*., Developed efficient methods for the synthesis of 1, 2-disubstituted benzimidazoles under solvent-free and ultrasonic irradiation conditions, by employing rare-earth metal chlorides as catalysts to obtain 77% yield of 2-(3-methyl phenyl)-1H-benzimidazole **Scheme 5c** [33].



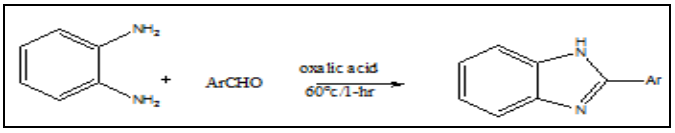
SCHEME 5C

Veisi *et al*., synthesized 2-aryl -benzimidazole by reacting o-phenylenediamine and aromatic aldehyde in the presence of silica phenyl sulfonic acid as a solid, heterogeneous catalyst in water. The yield of 2-aryl –benzimidazole was 67% **Scheme 5d** [34].



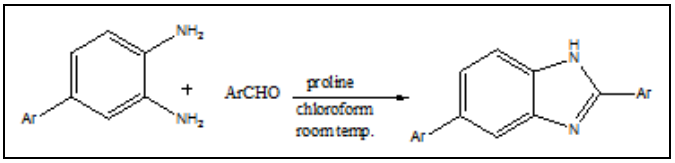
SCHEME 5D

Kokare *et al*., synthesized 2-aryl benzimidazoles by heating o-phenylenediamine and variously substituted aldehydes for one hour at 60 ºC, in the presence of catalyst oxalic acid, with a yield of about 76% **Scheme 5e** [35].



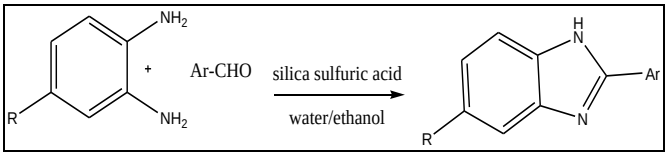
SCHEME 5E

Varala *et al*., Synthesised 2-aryl-5-alkyl-benzimidazoles by the condensation of o-phenylenediamine with aromatic aldehydes using L-proline and chloroform as a solvent to get a yield of 72-95% at ambient temperature **Scheme 5f** [36].



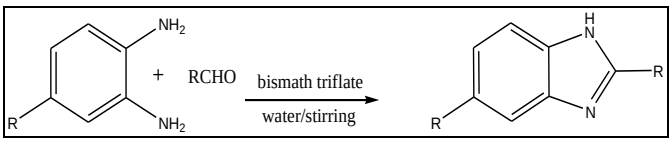
SCHEME 5F

Salehi *et al*., synthesized 2-aryl-5-alkyl-benzimidazoles by the reaction of 4-alkyl-o-phenylenediamines and aromatic aldehydes in the presence of silica sulphuric acid and ethanol or water with 76% yield. The catalyst can be reused **Scheme 5g** [37].



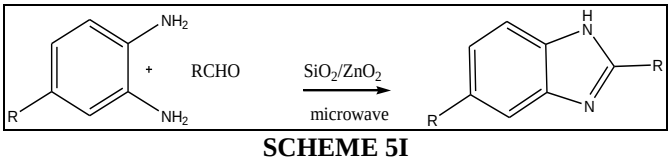
SCHEME 5G

Yadav *et al*., condensed o-phenylenediamine with alkyl aldehydes at room temperature in the presence of bismuth triflate in water with stirring to get about 73% yield of 2, 5-disubstituted benzimidazole **Scheme 5h** [38].



SCHEME 5H

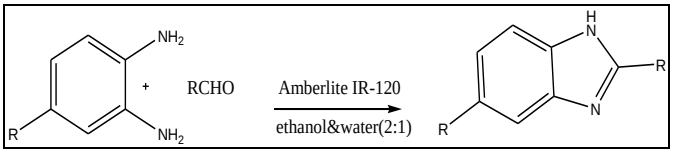
Jacob *et al*., synthesized 2, 5-disubstituted benzimidazoles using microwave reaction between 4-substituted-o-phenylenediamine and substituted aldehydes using $SiO_2/ZnCl_2$. This reaction does not use any solvents. This method is economical, eco-friendly with 81% yield **Scheme 5i** [39].



SCHEME 5I

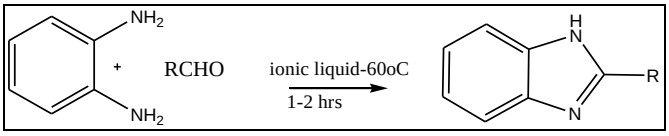
Sharma *et al*., synthesized 2, 5-substituted-benzimidazoles by the reacting 4-substituted-o-phenylenediamine with the substituted aldehydes in the presence of the heterogeneous catalyst

Amberlite IR-120 (strongly acidic cation exchange resin) in aqueous media, this media is ethanol and water solution (2:1). This method gives a 72% yield. The catalyst is recyclable without loss of activity **Scheme 5j** [40].



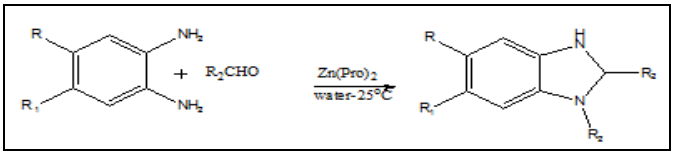
SCHEME 5J

Huiqiang *et al.,* Condensed o-phenylenediamine with aldehydes in the presence of ionic liquid ($NaCl+H_2O$) at 60 ºC for 1 to 2 h to obtain 2-substituted -benzimidazoles in 77% yield. This is an environmentally friendly methodology for the selective synthesis of 2-aryl-benzimidazoles **Scheme 5k** [41].



SCHEME 5K

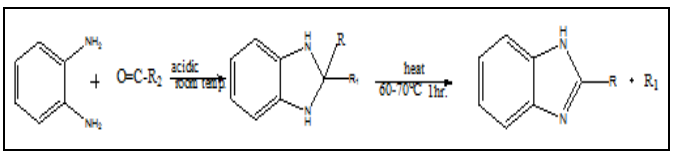
Ravi *et al.,* synthesized 1,2,4,5-tetrasubstituted benzimidazoles by reacting 4,5- substituted o-phenylenediamine with substituted aldehydes at room temperature in presence of Zn-proline, which is a water-soluble and recyclable Lewis acid catalyst for the selective synthesis of 1,2,4,5-tetrasubstituted benzimidazoles with a good yield of 81% **Scheme 5l** [42].



SCHEME 5L

Scheme 6:

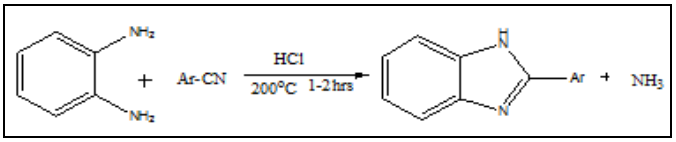
Reaction with Ketones: o-phenylenediamine reacted with the substituted ketones in the presence of acidic medium at room temperature gives a 2, 2-disubstituted-benzimidazoles, which on heating 60 to 70 ºC for 1 h, breaks down into 2-substituted-benzimidazole and a hydrocarbon **Scheme 6a** [43].



SCHEME 6

Scheme 7:

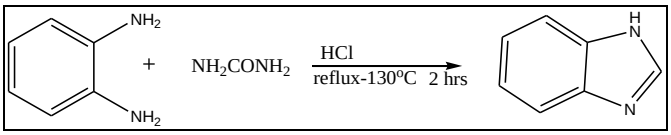
Reaction with Nitrile: Hollies and Wagner synthesized 2-substituted benzimidazole by the reaction of o-phenylenediamine with the substituted nitrile at 200 ºC for 1 to 2 h gives a 77% yield **Scheme-7** [44].



SCHEME 7

Scheme 8:

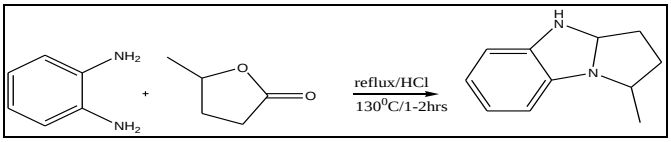
Reaction with Urea: Refluxed o-phenylene-diamine with urea in the presence of hydrochloric acid at 130 ºC for 2 h gives a 78% yield of benzimidazole **Scheme 8** [45].



SCHEME 8

Scheme 9:

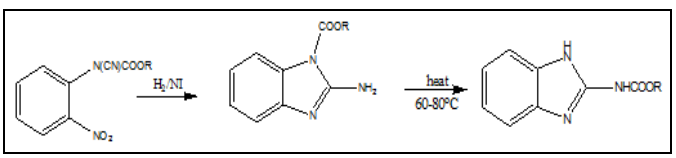
Reaction with Lactones: Refluxed Valerolactone (5-methyldihydrofuran-2(3H)-one) with o-phenyl-lenediamine at 130 ºC for 1 to 2 h in the presence hydrochloric acid gives 76% yield of 1,2-(1-methyltrimethylene) benzimidazole **Scheme 9** [46].



SCHEME 9

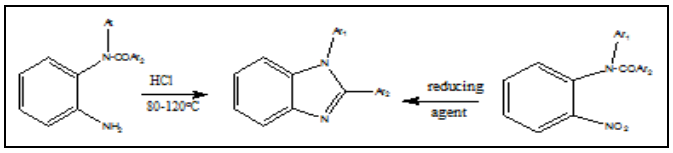
Scheme 10:

From *o*-Nitroarylamines and *o*-dinitroarenes: Benzimidazoles are synthesized from o-Nitro-arylamines, by using of the reducing agent like-nickel. Upon reduction o-Nitroarylamines converted into the 1-alkyl-2-amino-benzimidazole, which was further heated at 60 to 80 ºC gives an excellent yield of 2-substituted benzimidazole. This procedure is used in the industries for the production of large quantity of the benzimidazole because in this method yield is so high **Scheme 10a** [47].



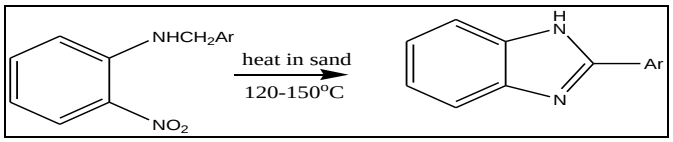
SCHEME 10A

Benzimidazoles synthesized from the o-Nitroarylamines by using a variety of reducing agents such as Sn/AcOH, $Na_2S_2O_4$, H_2/PD, Ni, $SnCl_2$/HCl, Fe/AcOH Zn dust/AcOH. And o-aminoarylamine also gives a 1, 2-sustituted benzimidazole by heating at 80 to 120 ºC in HCl **Scheme 10b** [48].



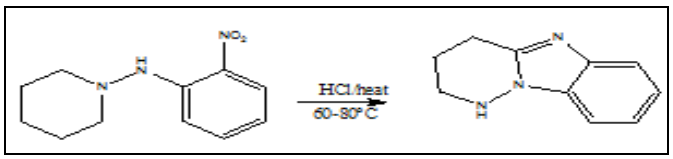
SCHEME 10B

N-substituted-*o*-nitro aniline gives 2-aryl-substituted benzimidazole, when heated on sand bath at 120 to 150 ºC temperature for 2 h this given 79% yield **Scheme 10c** [49].



SCHEME 10C

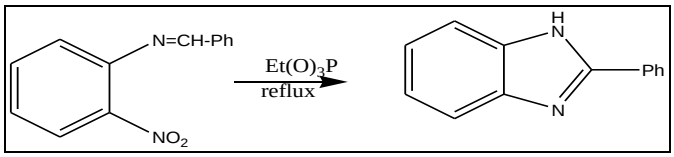
The cyclisation of the compound under the influence of hydrochloric acid with 60 to 80 ºC temperature gives 81% yield of N-amino-benzimidazole **Scheme 10d** [50].



SCHEME 10D

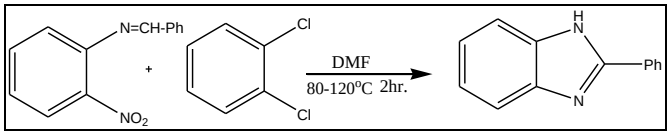
Scheme 11:

From o-substituted N-benzimidene-anilines: Refluxed N-benzyl-2-nitroaniline in the presence of reducing agent triethyl phosphate at 80 to 100 ºC for 2 h gives 89% yield of 2-phenyl benzimidazoles **Scheme 11a** [51].



SCHEME 11A

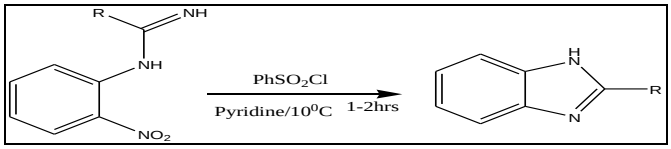
When aromatic nitro compound N-benzyl-2-nitroaniline is heated with 1, 2-dichlorobenzene in the presence of solvent dimethylformamide (DMF) at 80 to 120 ºC temperature for 2 h gives a 77% yield of 2-phenylbenzimidazole **Scheme 11b** [52].



SCHEME 11B

Scheme 12:

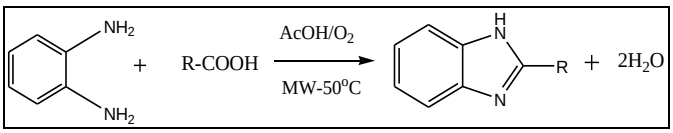
From Amidine: The derivative of Amidine reacts with the phenylsulfonyl-chloride in pyridine at 10 ºC for 1 to 2 h gives 81% yield of 2-substituted benzimidazole **Scheme 12** [53].



SCHEME 12

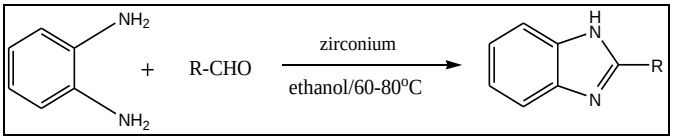
Scheme-13:

Green Synthesis of Benzimidazole: Davood Azarifar *et al.*, synthesized 2-substituted-benzimidazole by the reaction of 0-phenylenediamine with a carboxylic acid by using microwaves. They find a shorter time of reaction and get a 77% yield of 2-substituted benzimidazole. This method is promoted to green chemistry and avoided using of hazardous solvents **Scheme 13a** [54].



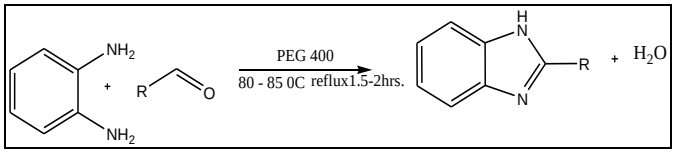
SCHEME 13A

M. Rekha *et al.*, refluxed *o*-phenylenediamine with substituted aldehydes or Ketone in the presence of the green catalysts zirconium and ethanol as a solvent at 60 ºC - 80 ºC for 3 to 4 h. These procedures are very economical and eco-friendly and also give about 82% of product yield **Scheme 13b** [55].



SCHEME 13B

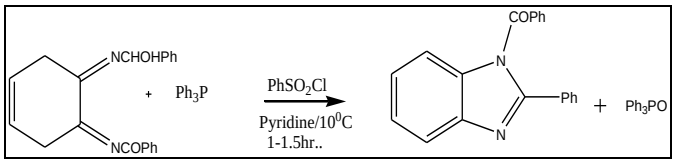
Mita D. Khunt *et al.*, refluxed o-phenylenediamine with substituted aldehydes in the presence of polyethyleneglycol-400 (PEG-400) at 80-85 ºC for 1.5 to 2 h gives 76% yield of 2-substituted-benzimidazole. PEG is a green and eco-friendly solvent **Scheme 13c** [56].



SCHEME 13C

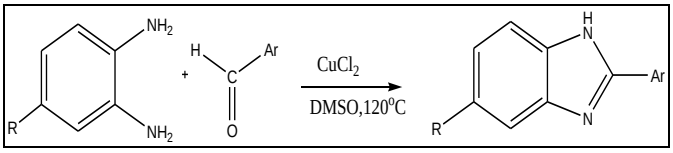
Scheme 14:

Miscellaneous: By the reductive cyclisation of N-[(1Z)-6-{[hydroxy(phenyl)methyl]imino}cyclohex-3-en-1-ylidene]benzamide with the triphenyl phosphate in the presence of pyridine and phenylsulfonyl-chloride at 10 ºC for 1 to 1.5 h gives a 76% yield of 1, 2-sustituted benzimidazole **Scheme 14a** [57].



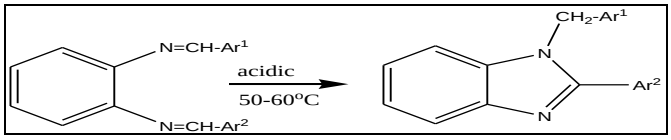
SCHEME 14A

Sunwoo Lee *et al*., condensed 4-substituted-o-phenylenediamine with substituted aldehydes in the presence of DMSO and copper as a catalyst at the 120 ºC and gives 73% yield of 5, 2-substituted benzimidazole **Scheme 14b** [58].



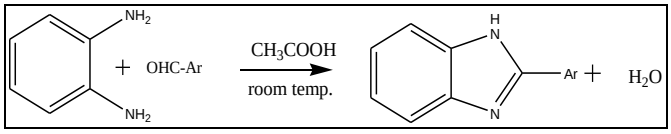
SCHEME 14B

Dianils *et al*., cyclised N, N-disubstituted-phenylenediamine under the acidic condition at 50 to 60 ºC gives 69% yield of 1, 2-disubstituted benzimidazoles **Scheme 14c** [59].



SCHEME 14C

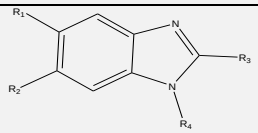
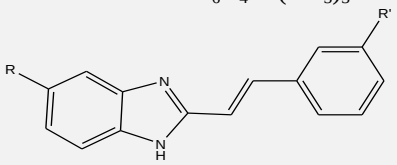
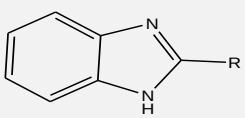
Rao *et al*., Synthesised 2-aryl benzimidazole by the reaction of o-phenylenediamine and aryl aldehyde in the presence of acetic acid at room temperature for 2 h which gives 65% yield of 2-aryl benzimidazole **Scheme 14d** [60].

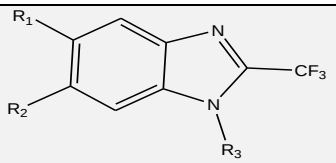
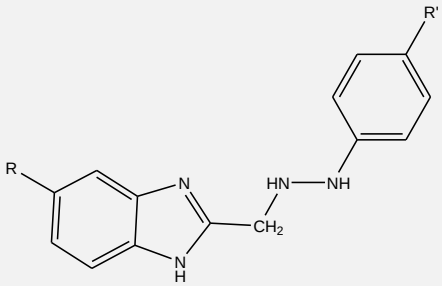
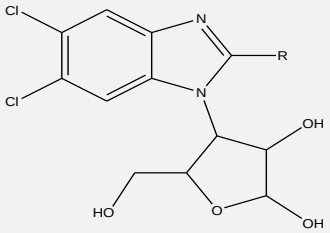
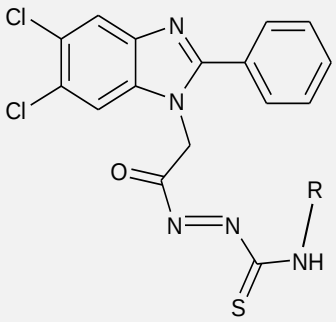
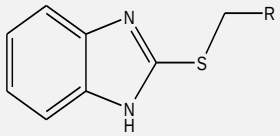


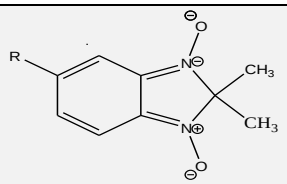
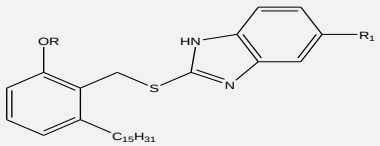
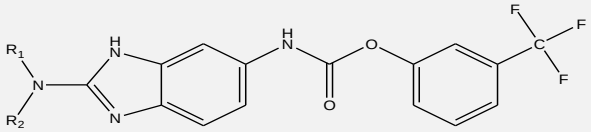
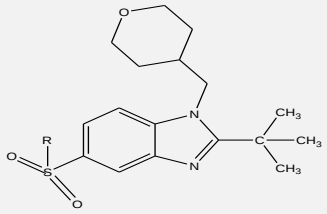
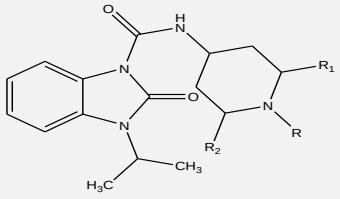
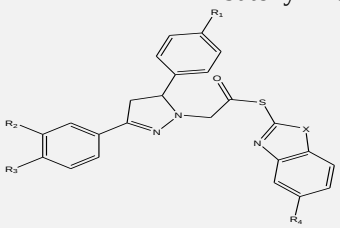
SCHEME 14D

Pharmacological Activity of Benzimidazole Derivatives: [61, 62, 63, 64]

TABLE 3: PHARMACOLOGICAL ACTIVITY OF BENZIMIDAZOLE DERIVATIVES

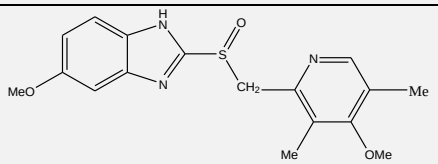
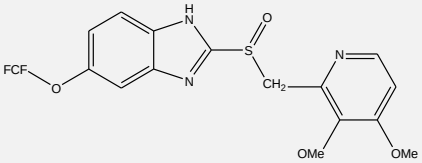
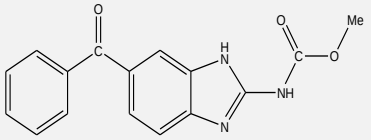
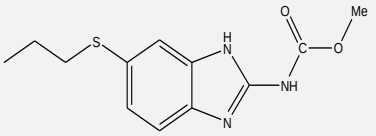
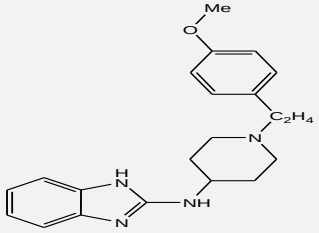
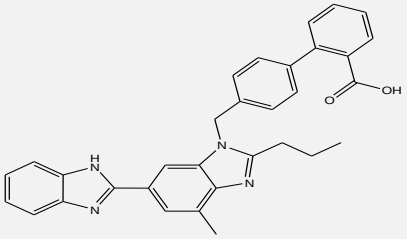
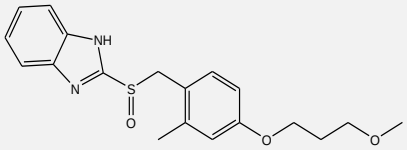
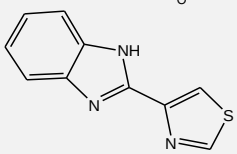
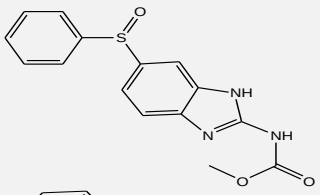
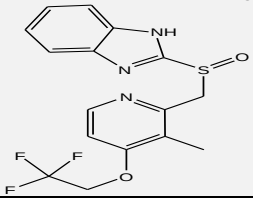
S. no.	Derivative	Structure	Activity
1	1,2,5,6-substituted-benzimidazole		Anti-mycobacterium-tuberculosis, Against-methicillin-resistance- *S. aureus*., *E. coli*
		R1 = Cl, R2 = Cl, R3 = C_6H_4F, R4 = H R1 = Cl, R2 = Cl, R3 = C_6H_4Cl, R4 = H R1 = Cl, R2 = Cl, R3 = C_6H_4-c-$(CH_3)_3$, R4 = H	
2	2-[(*E*)-2-phenylethenyl]-1*H*- substituted benzimidazole		Potent-anti-tuberculosis, *S. albus, C. abllicans*.
		R = NO_2, R' = 3,4-OCH_3 R = NO_2, R' = 4-CH_3 R = NO_2, R' = 3-OH`	
3	2-substituted benzimidazole		Anthelmintic, tapeworm, hookworm.
		R = CH_3 R = C_6H_5 R = 4-NH_2.C_6H_4	

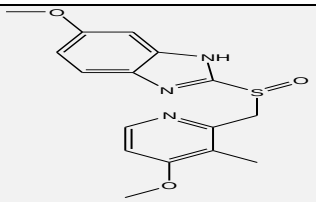
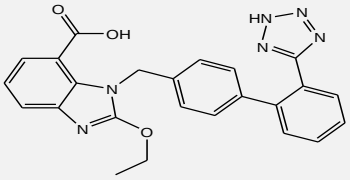
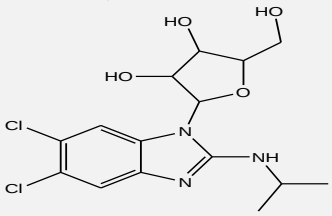
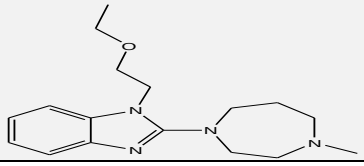
4	2-(trifluoromethyl)-5,6-1*H*-sustituted benzimidazole	 R1 / R2 / R3 2,3-$Cl_2C_6H_3O$ / H / H 2,3-$Cl_2C_6H_3O$ / H / CH_3 Cl / $C_{10}H_7O$ / CH_3	Antiprotozoal, G. *intestinalis, E. histolytica, T. vaginalis*
5	2-(1-methyl-2-phenylhydrazine)-5-substituted benzimidazole	 R / R’ H / H H / -4-NO_2 -6-NO_2 / -4-Cl	Antifungal, *Aspergillus Niger, Aspergillus flavus*
6	1-(3-(hydroxymethyl) tetrahydrofuran-2,4-diol)-5,6-dichloro-2-substituted benzimidazole.	 R SH SCH_3 SO_2CH_3	Antiviral (human influenza A3 and respiratory syncytial virus (RSV))
7	(*E*)-2-[(5,6-dichloro-2-phenyl-1*H*-benzimidazol-1-yl)acetyl]diazenecarbothioamide-5,6-dichloro-2-phenyl-benzimidazole	 R 2-chlorophenyl 4-fluorophenyl 2-bromophenyl	Antioxidant
8	2-thio-(methyl-R)-1h-substituted benzimidazole	 R Piperazine Morpholine N-phenyl benzamide	Anticonvulsant

9	2,2-dimethyl-6-sustituted benzimidazole	 R H CH_3 CH=NOH	Anti trypanosomatid
10	6-alkyl-2-thio-benzoalkyl-substituted benzimidazole	 R: H, CH_3 R1: OCH_3, H	Cox-2 inhibitor
11.	2-(dialkylamino)-6-(amino-oxo-fluorophenyl)-substituted benzimidazole	 R: H, CH_3, CH_3 R_1: pyrrolidine, pyrrolidine, $CH_3NCH_2NCH_2NCH_3$ R2: Pyrrolidine, Pyrrolidine, $CH_3NCH_2NCH_2NCH_3$	Antiasthamatic
12.	2-(trimethyl)-1-(hexo-methyl)-5-(thioalkyl)-substituted benzimidazole	 R 3-CH_3-4-pyridine 3-C_2H_5OH-4-pyridine 3-F-4-pyridine	Anticonvulsant
13.	1-(aminotrialkylpyridine)-2-oxo-3-trimethyl substituted benzimidazole	 R: CH_2, H, H R1: CH_2, H, H R2: 1-butoxy-4-luoro benzene, CH_3, 1-butoxy-4-luoro benzene	$GABA_A$-receptor agonist
14.	2-sulfo-(1-one-2-diphenylpyrazol)-5-substituted-benzimidazole	 R1: H, H, OCH_3 R2: H, CH_3, H R3: H, CH_3, H R4: Cl, Cl, Cl	Hypolipidmic

Marketed Preparation having Benzimidazole Nucleus: [65, 66, 67, 68]

TABLE 4: MARKETED PREPARATION OF BENZIMIDAZOLE

S. no.	Drug	Company	Structure	Use
1	Omeprazole	Dr.Reddy's laboratories		Antiulcer agent
2	Pantoprazole	Sun Pharma		Antiulcer agent
3	Mebendazole	Cipla limited		Antiparasitic
4	Albendazole	GlaxoSmithKline		Antiparasitic
5	Astemizole	Cadila healthcare limited.		Antihistaminic
6	Telmisartan	Zydus, Intas pharma.		Antihypertensive
7	Rabeprazole	GSK-PHARMACEUTICAL,		Proton-pump-inhibitor
8	Thiabendazole	GSK-Pharmaceutical,		Antiparasitic and fungicidal
9	Oxfendazole	Boehringer Ingelheim		Anthelmintic (for cattle's)
10	Lansoprazole	Actavis pharmaceutical		Proton-pump-inhibitor

11	Esomeprazole	Actavis pharmaceutical		Proton-pump-inhibitor
12	Candesartan	Zydus and Cadila		Antihypertensive
13	Maribavir (oral)	Viro Pharma, GSK.		Antiviral
14	Emedastine	Alcon pharmaceutical		Antihistaminic

Benzimidazole in Clinical Trials:

TABLE 5: ONGOING CLINICAL TRIALS

Drug	Condition	Study starting date	Phase	References
Benzimidazole	Chagas disease and Trypanosoma Cruzi Infection	2017	Phase-2	69
Nifurtix	Chagas Disease	2015	Phase-3	70
Benzimidazole			Phase-2	
Oxfendazole	Helminthic infection	2017	Phase-1	71
Albendazole-400mg	Soil-transmitted Helminthic Infection	2018	Phase-2	72
Triclabendazole	Parasitic Disease	2013	Phase-2	73
Albendazole	Helminthiasis Filariasis	4 Oct 2017	Phase-4	74
Albendazole	Trichuriasis	2018	Phase-2	75
Albendazole and Ivermectin			Phase-4	
Albendazole and praziquantel	Neurocysticercosis	2016	Phase-3	76
Ivermectin + Albendazole	Lymphatic Filariasis, Helminth Infection	May 19, 2017	Phase-4	77

CONCLUSION: This review contains 39 type of reaction for synthesis of benzimidazole which covers the different kind of methods for synthesis of substituted benzimidazoles like 2-substituted, 2,5-substituted, 2,1-substituted, 2,2-disubstituted.

Benzimidazole has a wide range of pharmacological activities like- antimicrobial, antifungal, antioxidant, antiviral activity, anticancer activity, anti-inflammatory activity, *etc*. Thus, we can say that benzimidazole is a moiety which has exhibited versatility in pharmacological action and has further potential for exploring its unexplored pharmacological activities.

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CONFLICT OF INTEREST: None

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