Review Article: An Outline to Preparation of Biological Active Benzimidazoles Using Microwave Approach

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ABSTRACT

Benzimidazole and its derivatives have a lot of diverse biological activities, including antimicrobial, antiviral, antidiabetic, anticancer activity. Different benzimidazole derivatives in good yield produced by condensation of ortho-phenyl diamine with aromatic aldehyde using various catalysts. In this work, we reviewed many microwaves assisted reactions involving the synthesis of benzimidazole derivatives.

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1. Introduction

Heterocyclic compounds are compounds that contain one or more cyclic rings, with one or more heteroatom like N, O and S. Mostly in nature and drugs, nitrogen containing heterocyclic compounds play an essential role in the forms of proteins like purine, histidine proline and pyrimidine bases in the genetic material like DNA and RNA are more critical which play a vital role in life such as metabolism of all living cells. They also play an essential role as enzymes, coenzymes, and many natural products. Most biologically active molecules such as hormones, acids, enzymes, neurotransmitters, may contain many heterocyclic rings. Out of these most common heterocyclic compounds is benzimidazole as an important nucleus.

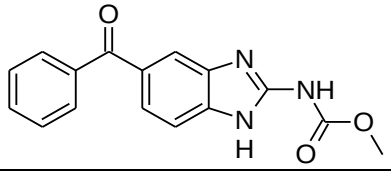
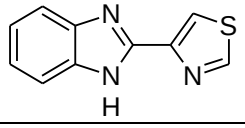
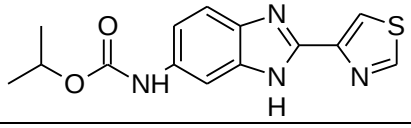
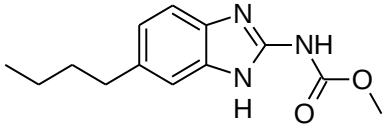
There are various pharmacologically active heterocyclic compounds, such as benzimidazole, which have clinical usage. A wide range of synthetic and naturally occurring heterocyclic compounds have applications in medicines and pharma, pesticides, agrochemicals, polymers, plastic, drugs and dyes. There is a vast scope for the research leading to new heterocyclic molecules having excellent biological activity.

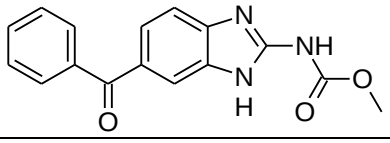
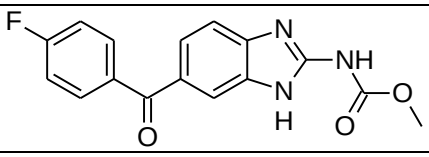
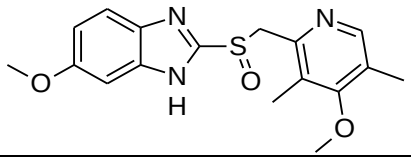
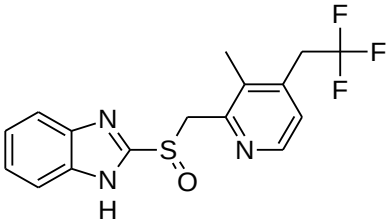
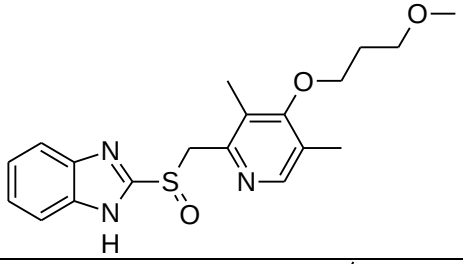
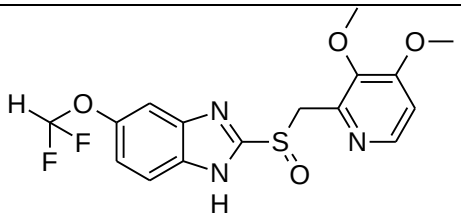
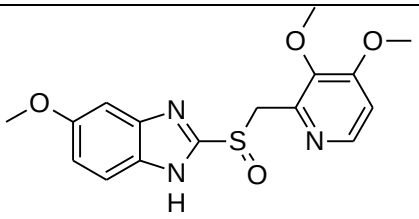
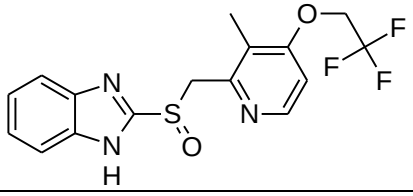
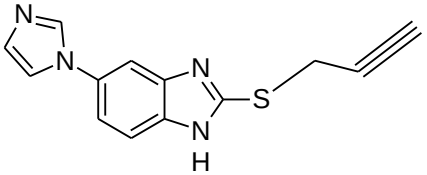
Among such vital heterocycles, benzimidazole has a prime place in Medicinal Chemistry. The benzimidazole derivatives were first realized as chemotherapeutic agents in 1950. Most common benzimidazole-containing compounds are 5,6-dimethyl-1-*D*-ribofuranosyl benzimidazole, which is a share of the structure of vitamin B-12 and other pharmaceutical drugs. Benzimidazole compounds with a broad spectrum of various biological activities such as widely human usage and anticancer assets [1]. The anthelminticactivity [2-3] is commonly known. In addition, benzimidazoles with different pharmacological properties such as, anti-ulsaral [4-6], cardiotonic [7], antihypertensive against depression [8], antibacterial and antiviral against virus and bacteria [9], antitumor [10], antimutagent[11], antiallergenic [12] are already reported. It also exhibits analgesic, anti-inflammatory and antipyretic activity [13]. Moreover, it also shows hypoglycaemic [14] anticalmodulin [15] and anti-aggregate [16] activities.

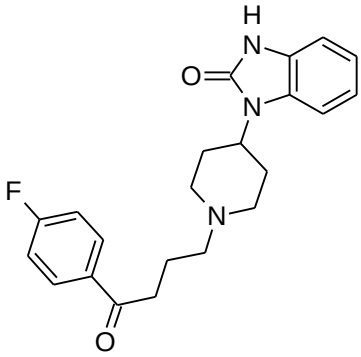
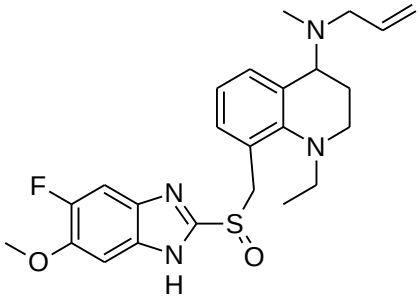
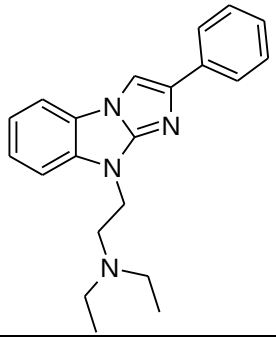
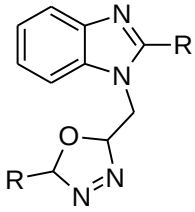
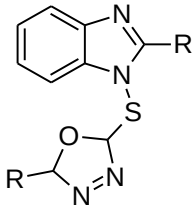
2. Importance of benzimidazole ring system

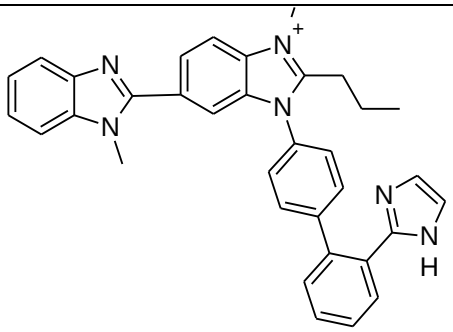
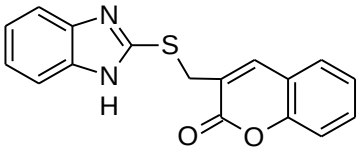
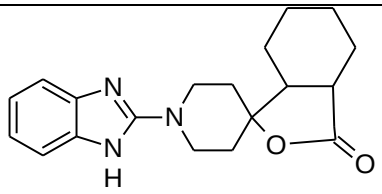
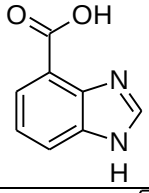
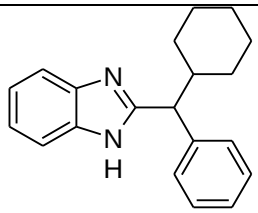
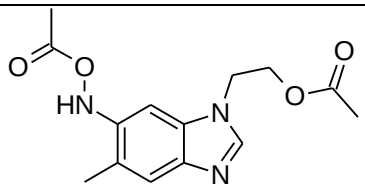
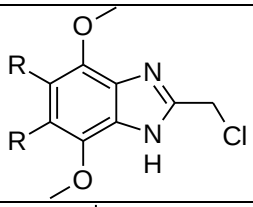
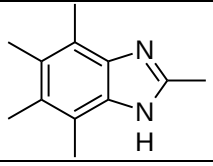
A wide range of benzimidazole and its derivatives find uses in pharmaceutical and veterinary drugs showing rapeutic activities. Some of the commercially essential benzimidazole derivatives are listed in **Table 1**.

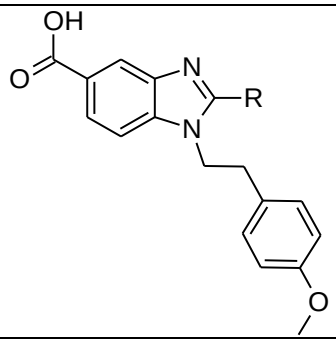
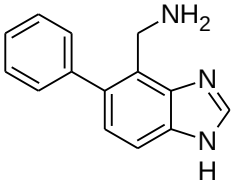
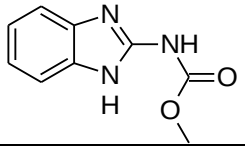
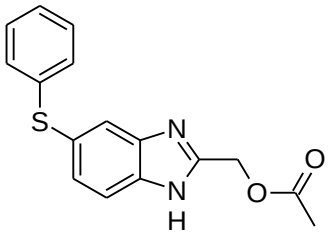
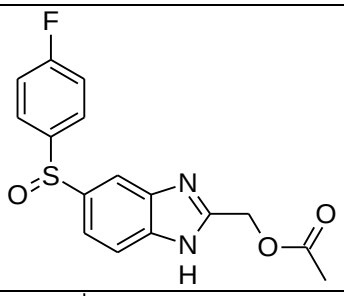
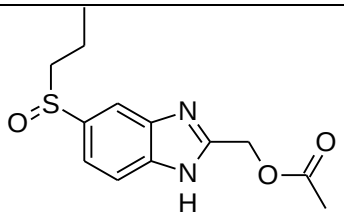
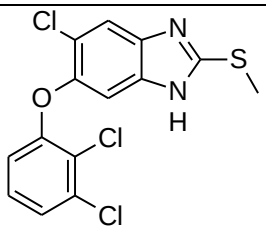
Table 1. Benzimidazole with a wide range of biological activities

No	Typical name benzimidazoles	Benzimidazoles structures	Benzimidazoles Activities
1	Mebendazole		Anthelmintic
2	Thiabendazole		Anthelmintic
3	Cambendazole		Anthelmintic
4	Parbendazole		Anthelmintic

5	Albendazole		Anthelmintic
6.	Flubenzadzole		Anthelmintic
7	Omeprazole		Anti-ulcer drugs
8	Lansaprazole		Anti-ulcer drugs
9	Rabeprazole		Anti-ulcer drugs
10	Pantoprazole		Anti-ulcer drugs
11	Esomeprazole		Anti-ulcer drugs
12	Triethoxy-pyridyl benzimidazole derivative		Anti-ulcer drugs
13	Thiophene derivatives of benzimidazole		Anti-ulcer drugs

14	Droperidol		Anti-psychotic agents
15	Quinoline benzimidazole analog		Anti-psychotic agents
16	Imidazole derivative with benzimidazole		Anti-psychotic agents
17	Oxazole derivative with benzimidazole		Antimicrobial activity
18	Oxazole derivative with benzimidazole and thio-linkage		Antimicrobial activity

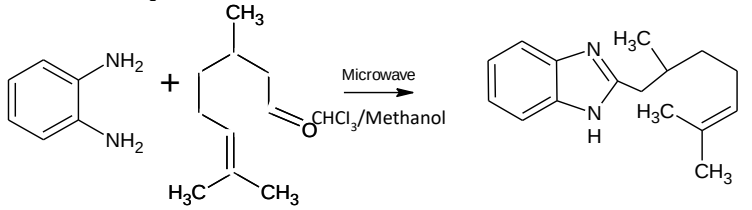
19	Bibenzoimidazole derivatives analog		Antagonist
20	Coumarine analog of benzimidazoles		Antiseptic virus c activity
21	Spiro compound of benzimidazole		NPY N5 Receptor Antagonist
22	4-Carboxylic acid benzimidazole		Selective 5 HT 4 Antagonist
23	Phenylcyl and cohexyl derivative of benzimidazole		Amp Activated protein kinase activator
24	Amide derivative of benzimidazole		Anticancer activity
25	Benzimidazole analog		Anticancer activity
26	Alkyl substituted benzimidazole		Antiamoebic activity

27	Benzyl and carboxyl substituted benzimidazole		Antilukamic activity
28	Phenyl and amine substituted benzimidazole		Antidiabetic activity
29	Amide derivative of benzimidazole		Cyticidal activity
30	Thioether derivatives of benzimidazole		Nematicide and taenicid
31	Oxfendazole		Roundworms and tapeworms
32	Ricobendazole		Anthelmintic
33	Triclabendazole		anthelmintic

Beside very high efficiency for the synthesis of benzimidazoles, many of the methods required to be improved for the very high reaction temperature, very long reaction times, highly toxic solvent and high-cost catalyst [17]. Therefore, developing simple, mild, efficient, and environmentally benign protocol for synthesizing benzimidazoles is still a hot topic for researchers. After the first reports of applications of microwaves in synthetic chemistry in 1986, now a day's microwave-assisted synthesis has become popular, particularly during the last two decades, due to generally short reaction times, the high purity and yields of the resulting products with high purity. Up to now, several microwave-assisted methodologies for the synthesis of benzimidazoles have been reported. In this review we have reported the different method for synthesizing of benzimidazole derivatives using microwave reactions.

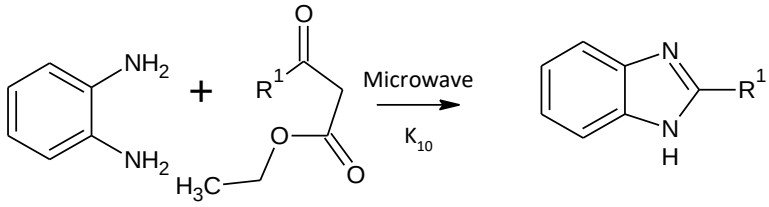
3. Miscellaneous method of benzimidazoles synthesis using microwave reactions

Microwave synthesis of benzimidazole derivatives involved citronellal extracted from *Citrus hystrix* DC leaves in water is reported along with OPDA and aromatic aldehyde [18]. The reaction of citronellal and 1,2-phenylenediamine (1:1mole ratio) was performed using methanol and dichloromethane as a solvent in various reaction times (at 30, 40, 50, 60, and 70 minutes) as depicted in **Scheme 1**.



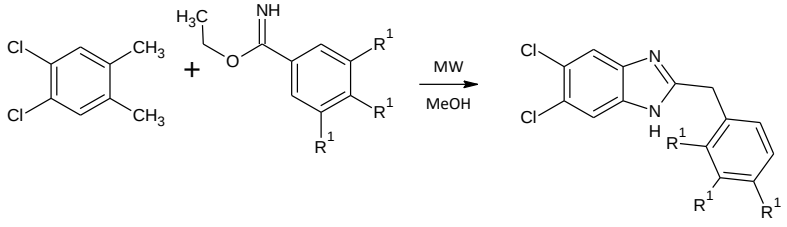
Scheme 1

The microwave-assisted benzimidazole synthesis consists of 1,2-diaminobenzene (or 4-substituted-1,2-diaminobenzene) and ethyl acetoacetate (or ethyl benzoylacetate) on solid mineral supports or other support in dry media is achieved (**Scheme 2**) [19].



Scheme 2

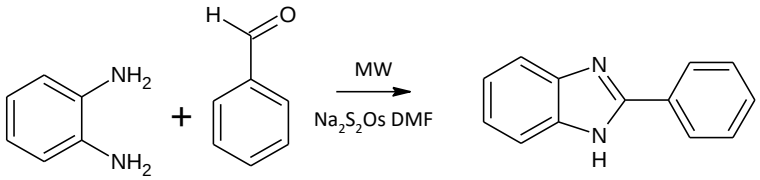
A simple protocol was developed to synthesize of benzimidazoles with good yields and in a concise reaction time (**Scheme 3**) [20]. It involves the microwave-assisted reaction of iminoester hydrochlorides of phenylacetic with 4,5-dichloro-1,2-phenylenediamine or their derivatives.



Scheme 3

1,2-Diaryl-benzimidazole and 2-aryl-1*H*-benzimidazole derivatives were synthesized using microwave irradiation and conventional heating procedures (**Scheme 4**). Usually higher yields were obtained with the former method.

The reaction requires significantly less time [21].

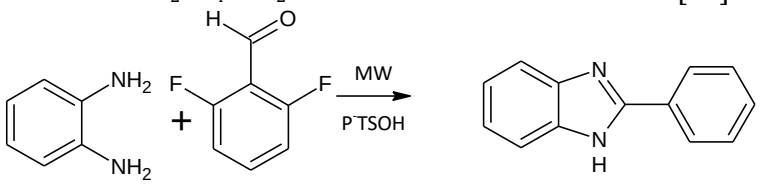


Scheme 4

Also, simple microwave-assisted one-pot synthesis of benzimidazoles from 1, 2-phenylenediamine and aromatic aldehyde catalyzed oxalic acid as a catalyst is described. Advantage technique, use the inexpensive and readily available catalyst, reaction time was decreased and the products were obtained in higher yields and having easy isolation [22].

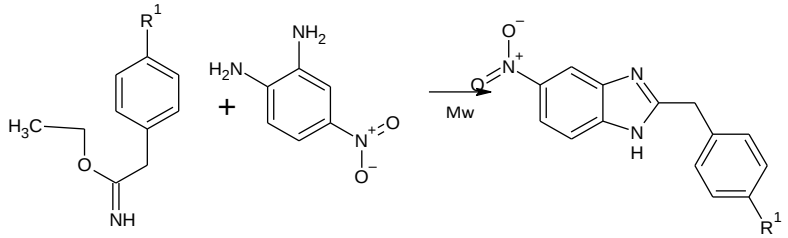
The *o*-phenylene diamine and aromatic aldehyde were placed on H_2SO_4-SiO_2 and transformed under microwave irradiation. The reaction was run at 80°C for 5 min, and after the completion of the reaction, the product was obtained by the extraction and purification by column chromatography [23].

This reaction (**Scheme 5**) was reported by Angela Rao *et. al*. This reaction is between the substituted aromatic aldehyde and ortho-phenyl diamine. The reactions give a higher yield in a concise reaction time [24].



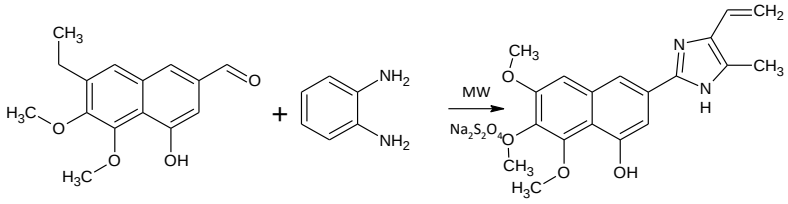
Scheme 5

Different 5-nitrosubstituted benzimidazole and 6-nitro substituted benzimidazole derivatives were synthesized using imino ester hydrochloride and 4-nitro-*o*-phenylenediamine under microwave irradiation (**Scheme 6**). It gives excellent yield in a very short reaction time [25].



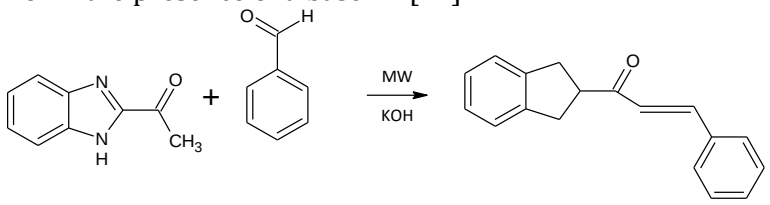
Scheme 6

2-Quinolizinyl benzimidazole and 2-naphthalyl benzimidazole derivatives (with various 5- and 6-positioned substituents) prepared in moderate to excellent yields *via* the condensation of 4-oxo-4*H*-quinolizinecarbaldehyde (or naphthalene carbaldehyde) with substituted *o*-phenylene diamine (**Scheme 7**). The reaction occurs at a lower temperature than the conventional method and at a concise reaction time [26].



Scheme 7

As illustrated in **Scheme 8**, 2-acetyl benzimidazoles reacted with substituted aldehydes in methanol in the presence of a base under microwave conditions. Herein, the reaction occurs in a short time and high yield [27].



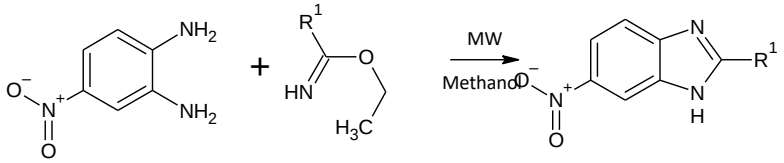
Scheme 8

The 2-alkyl and 2-aryl substituted benzimidazole derivative is synthesized by reacting *o*-phenylenediamine with several carboxylic acids in the presence of polyphosphoric acid (PPA) as a catalyst using the irradiation microwave method. The reaction required significantly less time and good yield [28].

This involves a simple procedure in which benzimidazoles are synthesized from 2-nitroaniline and benzaldehyde over Cu-Pd/-Al_2O_3 catalysts. The modification by Mg of the Cu-Pd/-Al_2O_3 catalyst improved the catalytic activity expressively. The reaction carried in a microwave at 100w gave better yield with good purity [29].

From condensation of o-phenylene diamine and different substituted aromatic carboxylic acids and aromatic aldehydes, derivatives of 2-aryl benzimidazole were synthesized using the microwave approach with good yield and purity. The reaction was catalyzed by ammonium chloride and water [30].

In this method 5(6)-nitro-2-alkyl/aryl-1*H*-benzimidazoles were easily obtained from the reaction of iminoester hydrochlorides and 4-nitro-ophenylenediamine (**Scheme 9**). All these reactions are carried out using the microwave approach [31].



Scheme 9

Synthesis of some benzimidazole derivatives with anti-inflammatory activity is reported by an eco-friendly, one pot, and the microwave-assisted reaction of phenylene diamine with aryl and/or heteryl aldehydes in solvent-free conditions in the presence of zirconium oxychloride as catalyst. This reaction gives good yield and purity [32].

2-(Substituted phenyl)-1*H*-benzimidazole derivatives synthesized via microwave irradiation using $Na_2S_2O_5$ as oxidant. This is a simple, fast, and effective preparation of benzimidazoles using readily available reagents under solvent-free conditions [33].

In addition, benzimidazoles synthesis in the presence of $Yb(OTf)_3$ as catalyst under solvent-free condition [34].

2-Aryl benzimidazole synthesis is described by the reaction of *o*-phenylenediamine and various aromatic aldehydes in the presence of cobalt (II) chloride hexahydrate as a catalyst. This is a high-yielding, selective method for synthesizing 2-aryl benzimidazole [35].

Another microwave-assisted synthesis of benzimidazoles and tri-substituted imidazoles is reported. The condensation reaction of 1,2-phenylenediamine with carboxylic acids and acetoacetic ester is performed without a catalyst to produce benzimidazoles. In addition, trisubstituted imidazoles were synthesized by condensation of benzil, aromatic aldehyde and ammonium acetate in the presence of glacial acetic acid using microwave irradiation [36].

Microwave-assisted condensation of resin-bound esters with 2-aminothiophenols gives the corresponding benzothiazoles and benzimidazole. The condensation of ester with 2-aminothiophenol in 15% of methane sulfonic 1,2-dichlorobenzene system provided the highest yield of 2-phenylbenzothiazoles. Most esters, including nicotinate ester, were converted to the corresponding benzothiazoles and benzimidazole (**Scheme 10**) [37].

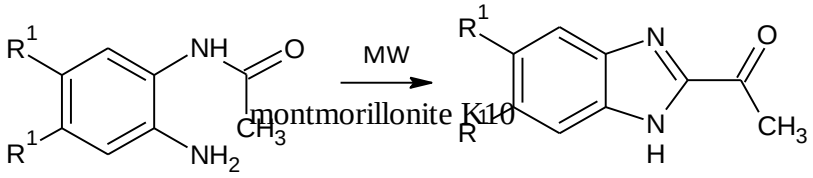
Scheme 10

o-Phenylenediamine, carboxylic acid derivatives and alumina or silica gel (or zeolite) were mixed. The reaction mixture was then irradiated in a domestic microwave oven at 160-560 W. The reaction gives good yield and purity [38].

Acetic acid and *o*-phenylenediamine were reacted under microwave irradiation three times at the 18% total output power (162 W) in the presence of the PPA. This reaction gives good yield and purity [39].

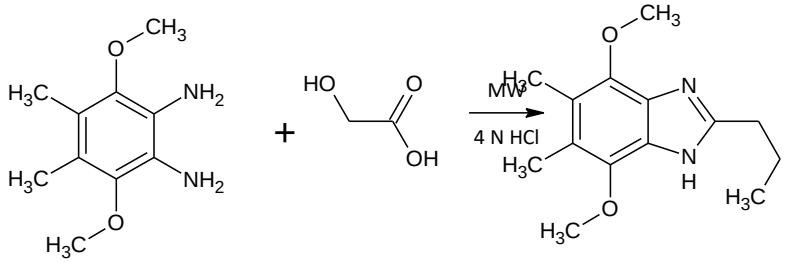
o-Phenylenediamine and aldehyde condense in a minimum amount of acetonitrile. Then, DDQ was added to the mixture and irradiated in a microwave oven. The progress of the reaction was monitored by TLC [40].

Synthesis of 2-trifluoromethyl benzimidazoles through cyclocondensation of *N*-(carbotrifluoromethyl)-*ortho*-arylenediamines on montmorillonite K10 was performed under a domestic microwave oven with good yields (**Scheme 11**) [41].



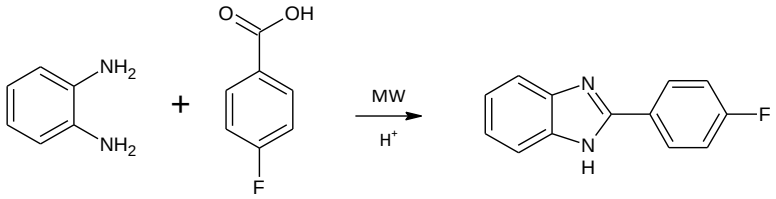
Scheme 11

Boufatah *et al*. have reported the preparation of some biologically active benzimidazole-4,7-dione derivatives in 7 steps through microwave irradiation. In the ring-closing step benzimidazole derivative is achieved (**Scheme 12**) [42, 43].



Scheme 12

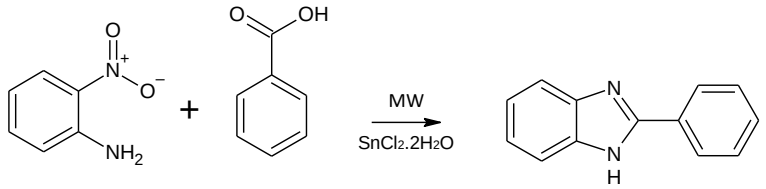
Getvoldsen *et al*. have reported 2-([4-F] fluorophenyl) benzimidazole synthesis from the cyclocondensation reaction of 1,2-diaminobenzene with radiolabelled [4-F] fluorobenzoic acid in neat methanesulfonic and polyphosphoric acids under the microwave (**Scheme 13**) [44].



Scheme 13

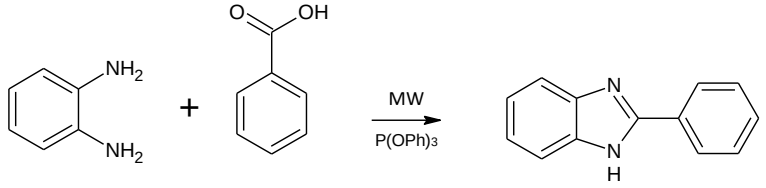
Martinez-Palou *et al*. described the synthesis of 2-long alkyl chain substituted benzimidazole with high yields by the reaction of 1,2-diaminobenzene and stearic acid via microwave irradiation in the presence of silica gel [45].

Viletet *al* described a one pot procedure for generating 2-substituted benzimidazoles with high-yield directly from 2-nitroanilines using $SnCl_2$ as areduction agent and carboxylic acid under microwave irradiation (**Scheme 14**) [46].



Scheme 14

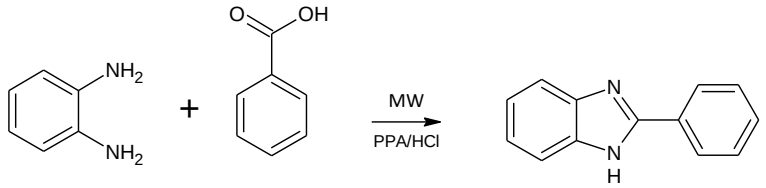
Lin *et al.* reported a microwave-assisted one-pot synthesis of several benzimidazole derivatives from readily available starting compounds such as 1,2-diaminobenzene, 4,5-diaminopyrimidine, *cis*-1,2-diaminocicylohexane and several carboxylic acids, including heteroaromatic carboxylic acids (**Scheme 15**) [47].



Scheme 15

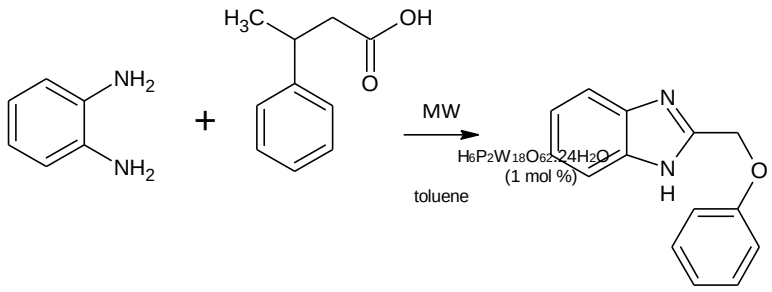
Synthesis of benzimidazoles is described from the reaction of 1,2-diamino benzenedihydrochloride and esters under microwave irradiation. In this protocol, various benzimidazole derivatives are synthesized by ethylene glycol as solvent [48].

Algul*et al*have described the synthesis of some 2-substituted benzimidazole, benzothiazole and indole derivatives using microwave irradiation and conventional heating methods (**Scheme 16**) [49].



Scheme 16

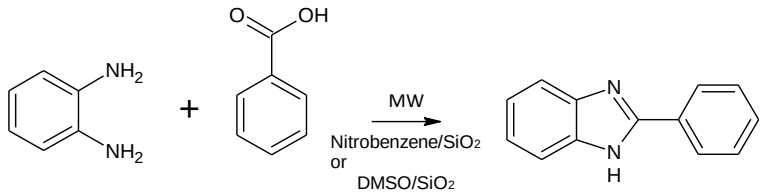
Hosamani and co-workers described a convenient protocol for preparing 5-nitro-2-arylsubstituted phenoxymethyl-1*H*-benzimidazole both under microwave irradiation and conventional heating methods using hydrochloride acid as catalyst [50]. The reaction is a simple condensation reaction between *o*-phenyl diamine and the acid functional group as depicted in **Scheme 17**.



Scheme 17

Hasaninejad *et al*. have reported the synthesis of some 2-substituted benzimidazole derivatives from benzene-1,2-diamine with mono and dicarboxylic acids under microwaveirradiation using silphox [$POCl_3$-n(SiO_2)n] catalyst in high yield and short reaction times [51]

Ben-Alloum *et al*. have described oxidative heterocyclization of aldehydes and *o*-phenylenediamine with nitrobenzene or dimethylsulfoxide impregnated on silica gel irradiated with microwave in good yields and high purity (**Scheme 18**) [52].

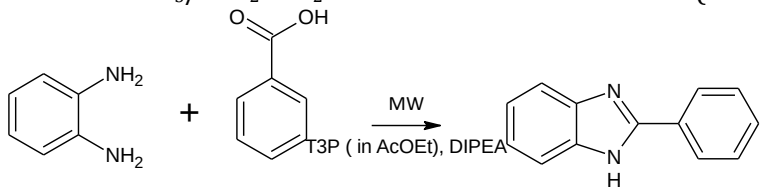


Scheme 18

Zahran and co-workers described the synthesis of heterocyclic compounds containing pyrazol-5-one coupled with benzimidazole under dry media. They also discovered the antitumor activity of synthesized heterocycles. Some of them were found to be more effective than thalidomide [53].

Aromatic aldehydes and 1,2-diaminobenzene reacted in the presence of $MoO_3/CeO_2.ZrO_2$ as catalyst under solvent-free conditions in both conventional and microwave processes [54] to produce benzimidazole derivatives.

An environmentally, one-pot, and efficient synthesis of benzimidazoles reported by Wen *et al.* under propylphosphonic anhydride(T_3P) mediate from the reaction of various carboxylic acids and 1,2- diaminobenzene under microwave irradiation (**Scheme 19**) [55].



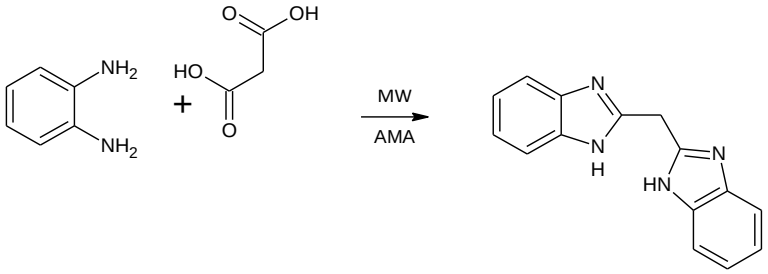
Scheme 19

Microwave technique employed for the preparation of 2-arylbenzimidazole. A mixture of various aldehyde, *o*-phenylene diamine and TBAF (5 moles %) was dissolved in water and irradiated under ultrasonic irradiation or microwave process. Further, the reaction procedure monitored by TLC [56].

Microwave irradiation process for the production of 2-substituted benzimidazoles and bis-benzimidazoles is reported by Niknam *et al.* from the reaction of phenylene diamine and dicarboxylic acid using alumina-methane sulfonic acid (AMA) as a catalyst with good to excellent yield [57].

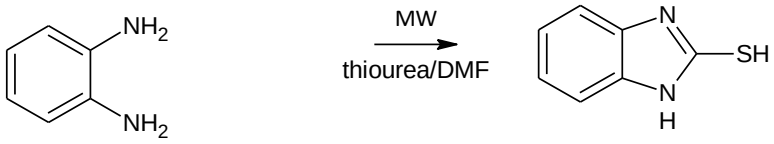
A mixture of 1, 2-phenylenediamine carboxylic acid, alumina and methanesulfonic acid reacted under microwave irradiation (900 W, with a

frequency of 2450 MHz) as depicted in **Scheme 20** [58].



Scheme 20

Singh and co-workers prepared 1, 3-dihydrobenzimidazol-2-thione derivatives by reacting *o*-phenylenediamine and thio urea in a microwave at 40% intensity until the brown color appears (**Scheme 21**). In addition, various derivatives of 1,3-dihydro-benzimidazol-2-thione are also prepared, such as cholorosulfonic derivatives [59].



Scheme 21

Zhang *et al*. reported one-pot synthesis of 2-substituted benzimidazole derivatives by reacting *o*-phenylene diamine ortho-ester and $ZrOCl_2.8H_2O$ (10 mole %) under microwave irradiation [60].

5. Conclusions

For many years, benzimidazoles structures and their properties have attracted the attention of many scientists. Benzimidazole is an essential pharmacophore in modern drug discovery component. Most the benzimidazole derivatives are synthesized by heating, sonication, or microwave energy. Now adays, chemical methods have been an increasingly popular concept in chemistry. Most of these methods are the reaction of 1,2-diaminobenzenes with types of carboxylic acids or the reaction of 1,2-diaminobenzenes with aldehydes using an oxidative reagent. This method involves using microwave reactions that require a concise life time, good yield and purity. These methods are ecologically benign processes for benzimidazole preparations which attracts scientists' attention. This article wishes to study and review the reported prepares in the field of microwave-assisted synthesis of benzimidazoles.

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