



## Green Chemistry as a Versatile Technique for the Synthesis of Benzimidazole Derivatives: Review

Anshul Chawla, Gurpreet Kaur, Anil Kumar Sharma

*CT Institute of Pharmaceutical Sciences, Shahpur, Jalandhar-144020 (Punjab), India.*

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### ABSTRACT

“Green chemistry” is the new and rapid emerging field of chemistry. It involves the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products. Microwave induced organic reaction enhancement (MORE) is a simple, clean, fast, efficient and economical method for the synthesis of organic molecules and has emerged as a tool towards green chemistry. This technique can reduce the time of chemical reaction from hours to minutes. Conventional methods of synthetic reactions need longer heating time, elaborate and tedious apparatus set up which result in higher cost and environmental pollution. The reaction rate of microwave induced organic reaction increases ten to thousand times and the yield of the product increases by 10-30 % compared to that by the conventional methods. As we know benzimidazole derivatives have been reported to have a wide range of pharmacological and biochemical activities; viz antifungal, antibacterial, antiviral anthelmintic, analgesic, anti-inflammatory, anti-neoplastic, depressive, hypnotic, anti-pyretic and anti-spasmodic. Thus, we became interested in the study of synthesis of substituted benzimidazoles by green synthesis techniques and furthermore to study their biological activities.

**Key Words:** Benzimidazole, Green chemistry, Microwave technique, Catalyst, Solvent-free.

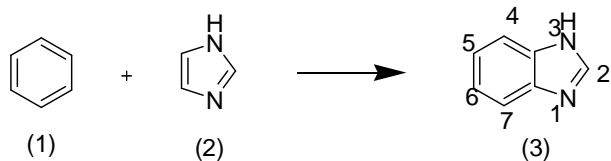
### INTRODUCTION

In 1990, at the EPS, UMB's Paul Anastas and John Warner defined Green Chemistry: “The design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances”. Human society is constantly facing such environmental issues and problems as ozone depletion, air pollution, global climate change, soil and water pollution, acid rain, the depletion of natural resources, and the accumulation of hazardous waste. There are twelve principles of Green Chemistry. Paul T. Anastas and John C. Warner<sup>1</sup> first published their 12 principles of Green Chemistry in their 1998 book, Green Chemistry: Theory and Practice. Both serve as members of the California Green Chemistry Science Advisory Panel. In summary, the 12 principles are: **1.** Prevent waste rather than treating it or cleaning it up. **2.** Incorporate all materials used in the manufacturing process in the final product. **3.** Use synthetic methods that generate substances with little or no toxicity to people or the environment. **4.** Design chemical products to be effective, but reduce toxicity. **5.** Phase-out solvents and auxiliary substances when possible. **6.** Use energy efficient processes, at ambient temperature and pressure, to reduce costs and environmental impacts. **7.** Use renewable raw materials for feedstocks. **8.** Reuse chemical intermediates and blocking agents to reduce or eliminate waste. **9.** Select catalysts that carry out a single reaction many times instead of less efficient reagents. **10.** Use

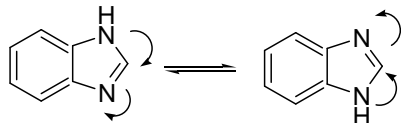
chemicals that readily break down into innocuous substances in the environment. **11.** Develop better analytical techniques for real-time monitoring to reduce hazardous substances. **12.** Use chemicals with low risk for accidents, explosions, and fires.

Continuous and batch microwave reactors were constructed for efficient, “green” synthesis with low-boiling solvents at high temperature in closed vessels. Capabilities for rapid heating-cooling, concurrent heating-cooling and differential heating facilitated novel chemical reactions and processes. Commercial microwave systems based on these developments are available. Times required for conventional reactions typically are decreased by 2-3 orders of magnitude. Green processes also have resulted through use of less or no catalyst, readily recyclable solvents, or media and yields that are often higher than normal. This technology opens up new opportunities to the synthetic chemist in the form of new reactions that are not possible using conventional heating.

Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consists of the fusion of benzene (1) and imidazole (2). The numbering system for the benzimidazole (3) is as follows:



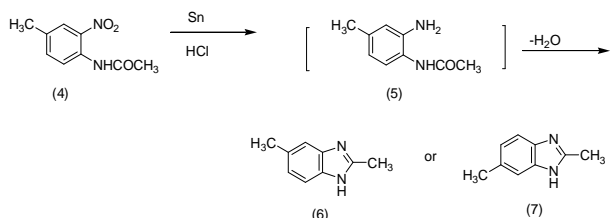
Benzimidazoles which contain a hydrogen atom attached to nitrogen in the 1-position readily tautomerize.



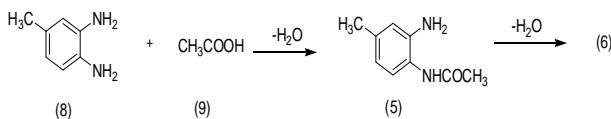
The use of benzimidazole dates many years back<sup>2</sup>. In 1990 various benzimidazole derivatives were synthesized with substitution of fluorine, propylene, tetrahydroquinoline and cyclised compound which resulted in compounds with increased stability, bioavailability and significant biological activity<sup>3,4</sup>. In 1991, benzimidazole derivatives were synthesized by dramatization at *N-H* of benzimidazole by electron donating group and substitution with long chain of propyl, acetamido, thio, thiazole-amino, tetramethyl piperidine on pyridine resulting in good antiulcer activity<sup>5,6</sup>.

### PREPARATION OF BENZIMIDAZOLE

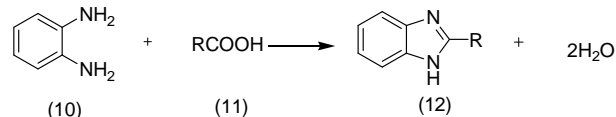
The first benzimidazole was prepared in 1872 by Hoebrecker<sup>7</sup>, who obtained 2, 5 (or 2, 6) dimethylbenzimidazole (6 or 7) by the reduction of 2-nitro-4-methylacetanilide (4).



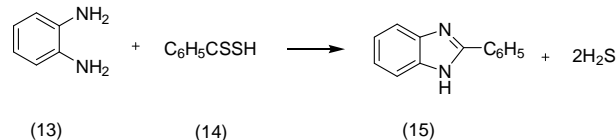
Also, Ladenburg<sup>8</sup> obtained the same compound by refluxing 3, 4-diaminotoluene (8) with acetic acid (9).



The benzimidazoles are known also as benziminazoles or benzoglyoxalines. Benzimidazole according to this nomenclature would be called methenyl-*o*-phenylenediamine and 2-methylbenzimidazole would be called ethenyl-*o*-phenylenediamine. Also, they have been named as derivatives of the grouping composing the imidazole portion of the ring. Preparation of benzimidazoles practically start with benzene derivatives possessing nitrogen-containing functions ortho to each other *i.e.* the starting material. *o*-Phenylenediamines (10) react readily with most carboxylic acids (11) to give 2-substituted benzimidazoles (12), usually in very good yield. The reaction is carried out usually by heating the reactants together on a steam bath, by heating together under reflux or at an elevated temperature, or by heating in a sealed tube.

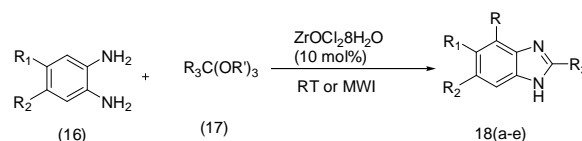


Dithiobenzoic acid (14) with *o*-phenylenediamine (13) gives about a 55 per cent yield of 2-phenylbenzimidazole (15)



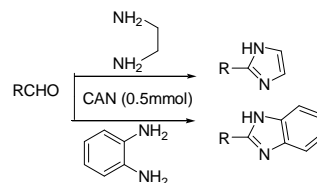
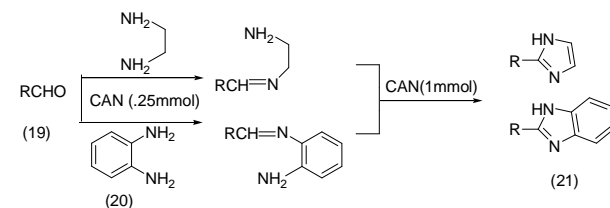
### GREEN SYNTHESIS OF BENZIMIDAZOLE DERIVATIVES

1. Reddy *et al*, 2008 reported a mild, efficient and one pot synthesis of 2-substituted benzimidazoles (18) from an appropriate *o*-phenylenediamine (16) and orthoesters (17) such as orthoformate, orthoacetate and orthovalerate using ZrOCl<sub>2</sub>·8H<sub>2</sub>O, at room temperature and under microwave irradiation<sup>9</sup>.

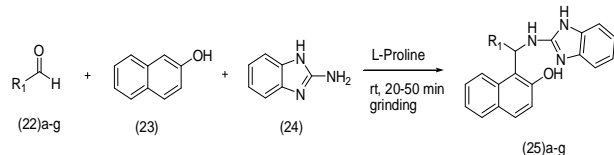


a=HC(OC<sub>2</sub>H<sub>5</sub>)<sub>3</sub>  
 b=CH<sub>3</sub>C(OC<sub>2</sub>H<sub>5</sub>)<sub>3</sub>  
 c= CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C(OCH<sub>3</sub>)<sub>3</sub>  
 d=HC(OC<sub>2</sub>H<sub>5</sub>)<sub>3</sub>  
 e=HC(OC<sub>2</sub>H<sub>5</sub>)<sub>3</sub>

2. Kumar *et al*, 2007 have synthesized some imidazolines and benzimidazoles (21) from various aldehydes (19) and 1, 2-diamines (20) in the presence of ceric (IV) ammonium nitrate (CAN). The simplicity of the reaction conditions with shorter reaction time and without use of column chromatography to get the pure products in high yields makes this method more attractive for organic chemists<sup>10</sup>.

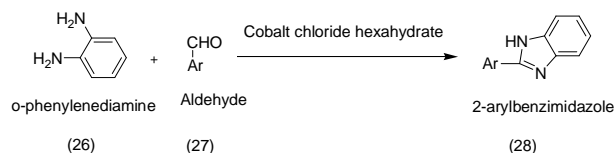


3. Javanshir *et al*, 2010 reported the reaction of 2-aminobenzimidazole (24), 2- naphthol (23) and aromatic aldehydes (22) in the presence of *L*-proline under grinding and solvent free condition at room temperature, synthesis of novel 2'-aminobenzimidazolomethylnaphthols (25) derivatives were developed<sup>11</sup>.

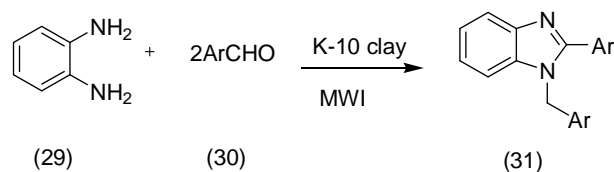


a-g = C<sub>6</sub>H<sub>5</sub>  
 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>  
 4-CN C<sub>6</sub>H<sub>4</sub>  
 4-Cl C<sub>6</sub>H<sub>4</sub>  
 4-Br C<sub>6</sub>H<sub>4</sub>  
 4-OMe C<sub>6</sub>H<sub>4</sub>  
 4-OHC<sub>6</sub>H<sub>4</sub>

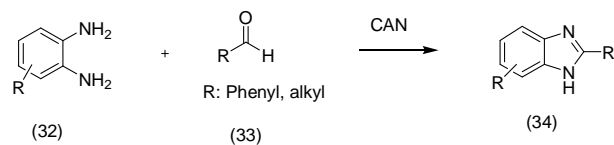
4. **Khan et al, 2009** explained simple and efficient method for the convenient synthesis of 2-arylbenzimidazole (28) on reaction with *o*-phenylenediamine (26) and various aromatic aldehydes (27) using cobalt (II) chloride hexahydrate as a catalyst<sup>12</sup>.



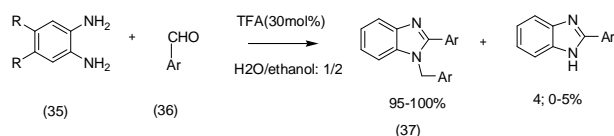
5. **Perumal et al, 2004** give series of reactions for the synthesis of 2-aryl-1-arylmethyl-1*H*-1, 3-benzimidazoles (31) expeditiously in good yields from *ortho*-phenylenediamine (29) and aromatic aldehydes (30) in the presence of montmorillonite K-10 under microwave irradiation in the absence of solvent<sup>13</sup>.



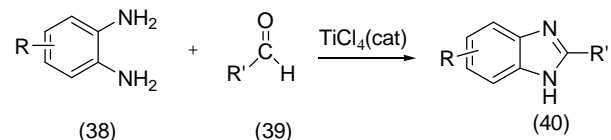
6. **Kidwai et al, 2010** described the efficiently catalyzed synthesis of benzimidazole derivatives (34) under Ceric ammonium nitrate (CAN) from *o*-phenylenediamine (32) and aldehydes (33) in PEG. This method provides a novel route for the synthesis of benzimidazoles in good yields with little catalyst loading. The recovery and the successful reutilization of the solvent system are also presented<sup>14</sup>.



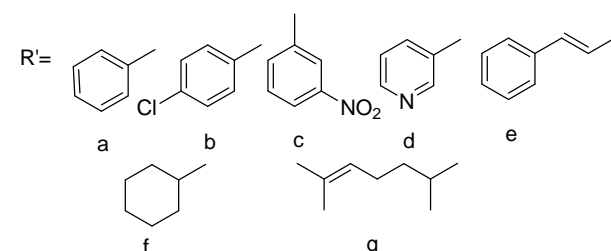
7. **Mohammadzadeh et al, 2011** reported that trifluoroacetic acid (TFA) is introduced as effective catalyst for the selective synthesis of 2-aryl-1-arylmethyl-1*H*-1, 3-benzimidazoles (37) via condensation reaction of *o*-phenylenediamine (35) derivatives and aromatic aldehydes (36) in ethanol/water at room temperature<sup>15</sup>.



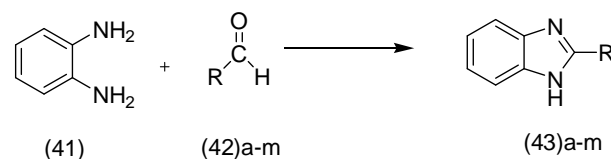
8. **Nagawade et al, 2006** synthesised differently substituted benzimidazoles (40) in solvent free conditions from *o*-phenylenediamine (38) and aldehydes (39) in the presence of TiCl<sub>4</sub> as a catalyst. The method is applicable to aromatic, unsaturated and aliphatic aldehydes<sup>16</sup>.



R=H, OMe

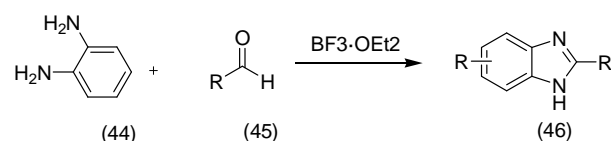


9. **Joshi et al, 2010** reported one-pot multistep reactions involving a new catalytic procedure for the synthesis of benzimidazole (43). The reaction of the substituted aldehyde (42) with *o*-phenylenediamine (41) in water under ultrasonic irradiation at ambient temperature by using 5 mol% of TBAF furnish the desired product in excellent yield. The process is highly chemoselective, and excellent yields are the main advantages of this procedure<sup>17</sup>.



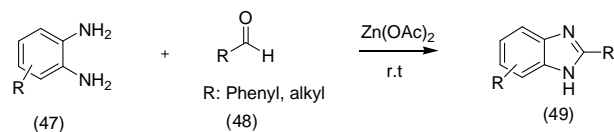
(a Benzaldehyde, b Anisaldehyde, c 4-methyl benzaldehyde, d 4-chlorobenzaldehyde, e 4-fluorobenzaldehyde, f 3-bromobenzaldehyde, g Furan-2-carbaldehyde, h Piconaldehyde, i Nicotinaldehyde, j 4-(1*H*-1,2,4-triazol-1-yl)benzaldehyde, k Napthaldehyde, l Cinnamaldehyde, m 3-nitrobenzaldehyde)

10. **Nagawade et al, 2006** synthesised differently substituted benzimidazoles (46) in very good yields in solvent-free conditions from *o*-phenylenediamine (44) and aldehydes (45) in the presence of BF<sub>3</sub>·OEt<sub>2</sub> as a catalyst. The method is applicable to aromatic, unsaturated and aliphatic aldehydes and to substituted *o*-phenylenediamines without significant differences<sup>18</sup>.

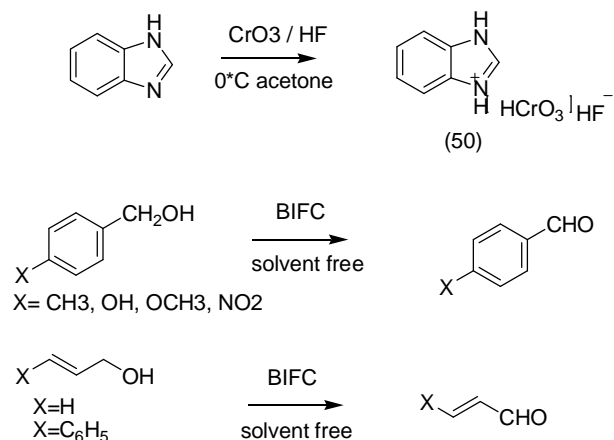


11. **Patil et al, 2010** synthesised some Benzimidazoles derivatives (49) using a catalytic amount of Zinc acetate at

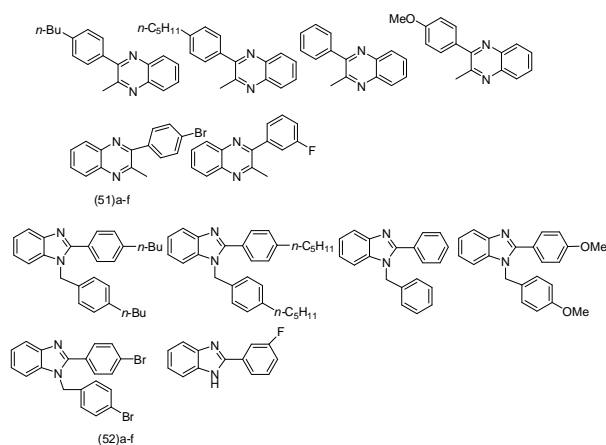
room temperature with phenylenediamine (47) and aldehydes (48). Reaction gives the excellent yield. The reaction is carried out under mild, neutral and solvent free conditions<sup>19</sup>.



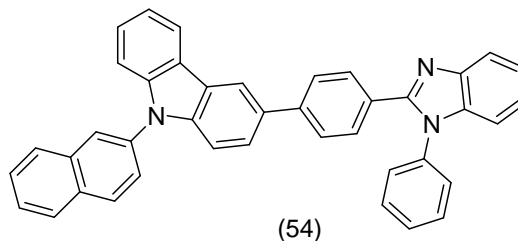
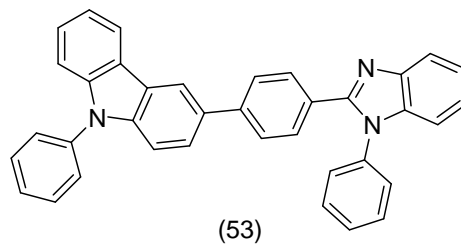
**12. Sivamurugan et al, 2005** synthesized benzimidazolium fluorochromate (BIFC) (50) under solvent free conditions. It selectively oxidizes primary alcohols in the presence of secondary alcohols. This is a new ecofriendly, economical, and effective oxidant<sup>20</sup>.



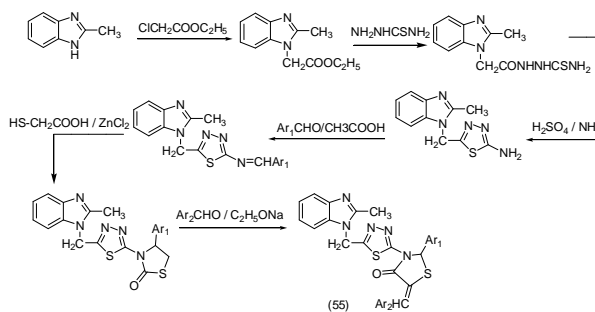
**13. Cui et al,** reported the gold-catalyzed Synthesis of Quinoxalines (51) and benzimidazoles (52)<sup>21</sup>.



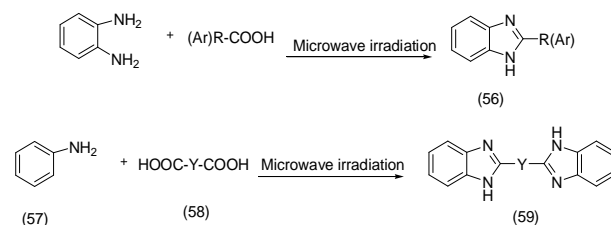
**14. Park et al, 2011** designed new green host materials, 9-phenyl-3-(4-(1-phenyl-1H-benzo[d]imidazol-2-yl)phenyl)-9H-carbazole (53) and 9-(naphthyl-2-yl)-3-(4-(1-phenyl-1H-benzo[d]imidazol-2-yl)phenyl)-9H-carbazole (54), and synthesized by attaching the electron transporting benzimidazole moiety to the hole transporting carbazole unit<sup>22</sup>.



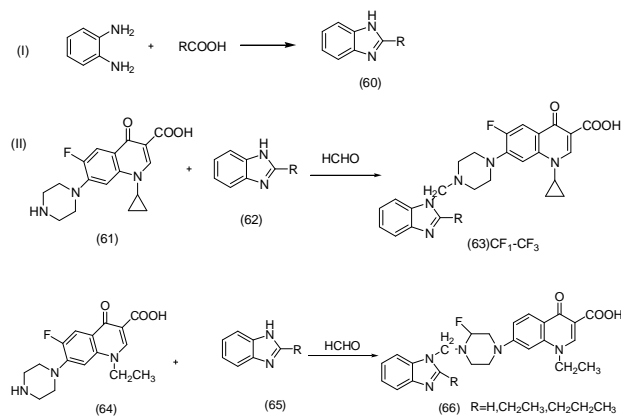
**15. Dua et al, 2010** investigated the efficiency of N1-(2-Benzylidene-imino-5'-methylene)-1',3',4'-thiadiazole]-2-methyl-benzimidazoles, N1-[2'-{2-Substituted-Phenyl-1,3-thiazolidin-4-one}-5'-methylene-1',3',4'-thiadiazole]-2-methyl-benzimidazoles, and N1-[2'-{2-substituted-phenyl-5-substituted-benzylidene-1,3-thiazolidine-4-one}-5'-methylene-1',3',4'-thiadiazole]-2-methyl-benzimidazoles (55) for the synthesis by conventional and greener approach methods in terms of yield and reaction time along with antimicrobial activity against *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumonia* and *Streptococcus aureus* bacteria and *Aspergillus niger*, *Aspergillus flavus*, *Fusarium oxysporium* and *Trichoderma viride* fungi *in vitro* at 50 and 100 ppm concentration<sup>23</sup>.



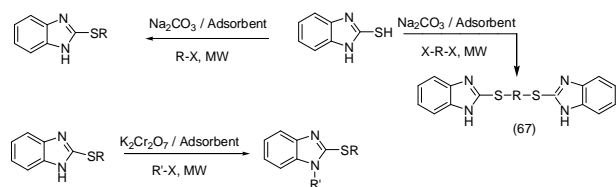
**16. Niknam et al, 2007** employed microwave-assisted synthesis of 2-substituted benzimidazoles (56) in the presence of alumina-methanesulfonic acid (AMA). In addition, by this method some new *bis*-benzimidazoles (59) from the direct reaction of phenylenediamine (57) and dicarboxylic acid (58) under microwave irradiation in good to excellent yields are described<sup>24</sup>.



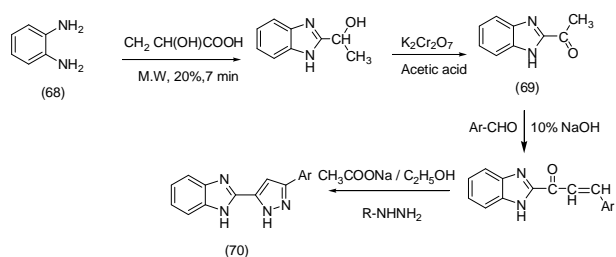
**17. Jubie et al, 2010** have synthesized a series of Mannich bases (63 and 66) of ciprofloxacin (61) and norfloxacin (64) with various benzimidazoles (60). The compounds were screened for their antibacterial and antifungal activity by cup-plate method. All the benzimidazole substituted norfloxacin derivatives (NF1, NF2 and NF3) and ciprofloxacin derivatives (CF1, CF2 and CF3) showed significant activities compared to the standards norfloxacin and ciprofloxacin and significant activity against *Candida albicans* at 50, 100 mcg/ml. The benzimidazoles showed mild antibacterial activities and significant antifungal activities<sup>25</sup>.



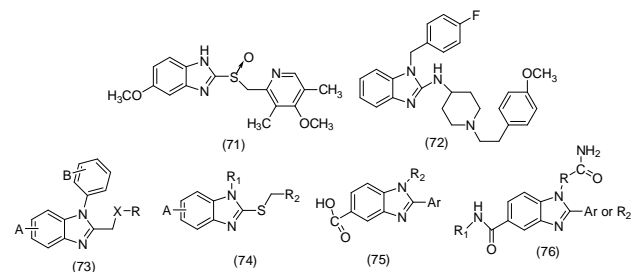
**18. Narkhede et al, 2008** explained the biological activity of 2-Mercaptobenzimidazole (MBI) derivatives (67) having substituent at either nitrogen or sulphur of a thiomide ring. MBI derivatives were synthesized in moderate to high yields in a short time to give pure required products by using solid support such as silica gel/ neutral alumina/fly ash under microwave assisted solvent less conditions<sup>26</sup>.



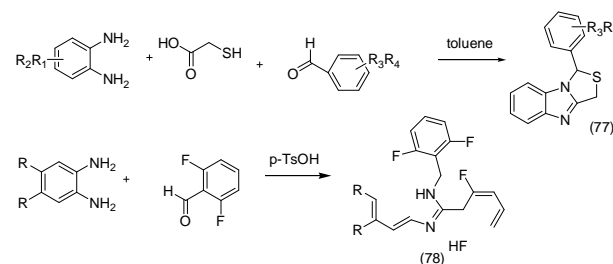
**19. Kalirajan et al, 2010** synthesized a series of pyrazole derivatives of benzimidazole (70). Condensation of substituted *o*-phenylene diamine (68) with lactic acid under microwave irradiation and further oxidation of the product with potassium dichromate gave intermediate 2-acetyl benzimidazole (69) which was then reacted with aromatic aldehydes and finally the product was cyclized with hydrazine to form final product. Compounds have shown significant anti bacterial and anti cancer activity<sup>27</sup>.



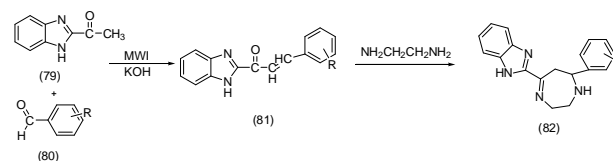
**20. Vourloumis et al, 2003** reported an efficient and highly versatile synthesis of two libraries (71-76) based on the privileged benzimidazole scaffold was described and design was aimed at obtaining molecules, biased for binding to RNA targets, by incorporating functionalities, which were found in natural RNA-ligand. The library construction was realized with the use of SPOS in high average yields and purity. Monitoring and quantification of intermediates and final products were performed by the use of NMR spectroscopy using DMF as an internal standard<sup>28</sup>.



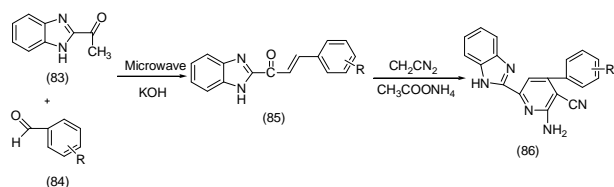
**21. Rao et al, 2004** described the microwave-assisted synthesis of 1*H*,3*H*-thiazolo[3,4-*a*] benzimidazoles (77), 2-aryl-1-benzylbenzimidazoles (78), which achieved reductions in reaction times, higher yields, cleaner reactions than for the other synthetic processes<sup>29</sup>.



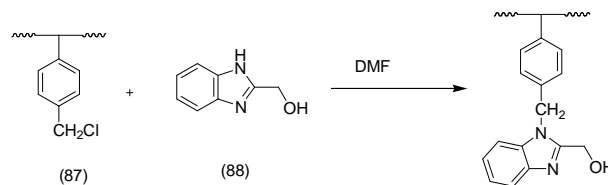
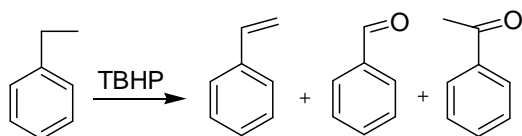
**22. Yadav et al, 2010** reported the reaction of 2-acetyl benzimidazoles (79) with substituted aldehydes (80) in methanol in presence of base afforded corresponding benzimidazolyl chalcones (81) which on treatment with ethylenediamine afforded the 1, 4- Diazepine derivative (82) under MWI condition. Compounds were screened for the antibacterial and antifungal activity *in vitro*<sup>30</sup>.



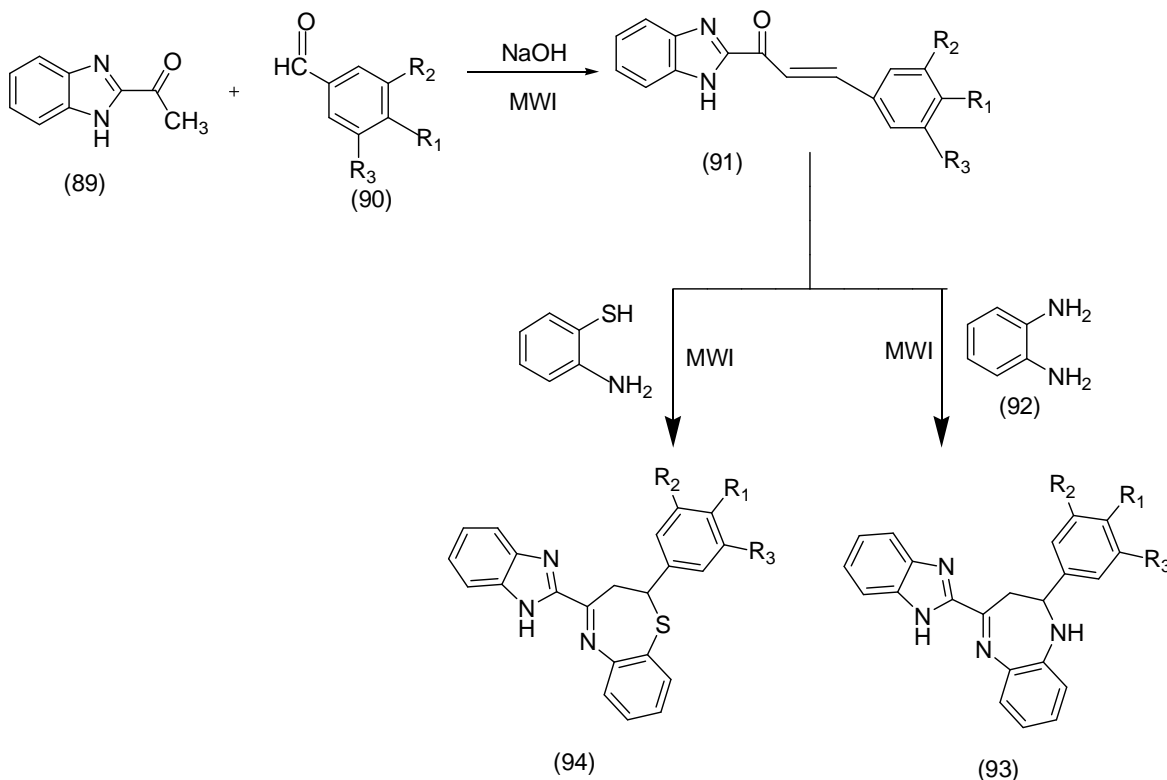
**23. Yadav et al, 2011** synthesized some new 2-amino-6-(1*H*-benzimidazol-2-yl)-4-phenyl pyridine-3- carbonitriles (86). 2-Acetyl Benzimidazoles (83) were reacted with appropriately substituted benzaldehydes (84) in presence of ethanol to furnish substituted chalcones (85). These chalcones were further treated with Malononitrile and Ammonium Acetate to afford substituted 2-amino-6-(1*H*-benzimidazol-2-yl)-4-phenyl pyridine-3- carbonitriles (86). The compounds exhibited good antibacterial and moderate antifungal activities<sup>31</sup>.



24. **Maurya et al, 2005** 2-( $\alpha$ -Hydroxymethyl) benzimidazole (88) has been covalently anchored to chloromethylated polystyrene (87) cross-linked with 5% divinylbenzene. These complexes were characterized by elemental analysis, FT-IR, EPR and electronic spectra, SEM and TGA-DTA methods. Ethyl benzene oxidation gives styrene, benzaldehyde and acetophenone as the major products. Oxidative bromination of salicylaldehyde using  $H_2O_2/KBr$  gives 5-bromosalicylaldehyde selectively in quantitative yield. EPR spectra of both freshly prepared and recovered catalysts are identical, which indicate that the metal-Schiff base moiety is intact and the co-ordination environments are not altered during the reaction<sup>32</sup>.

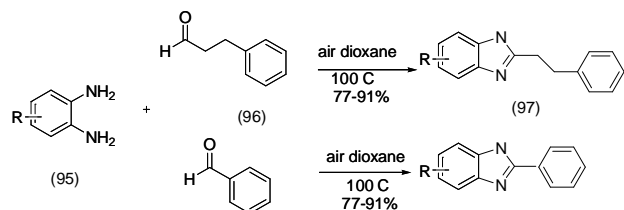


25. **Yadav et al, 2011** synthesized some 1,5 benzodiazepines (93) and 1,5 benzothiazepines (94) via microwave irradiation techniques. 2-Acetyl benzimidazoles (89) were reacted with appropriately substituted aromatic aldehydes (90) in the presence of base to furnish substituted chalcones (91). These chalcones were further reacted with ortho phenylenediamine (92) to offer 4-(1H-benzimidazol-2-yl)-2-phenyl-2,3-dihydro-1H-1,5-benzodiazepines (93). Reaction of the chalcones with 2-amino thiophenol yielded substituted 4-(1H-benzimidazol-2-yl)-2-phenyl-2,3-dihydro-1,5-benzothiazepines (94). All the synthesized compounds were characterized by elemental analysis and IR,  $^1H$  NMR and Mass spectral data. All the compounds were screened for their antimicrobial activities against gram positive bacteria *Staphylococcus aureus*, *Bacillus subtilis* and gram negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa* and fungal species like *Candida albicans* and *Aspergillus niger* organisms<sup>33</sup>.

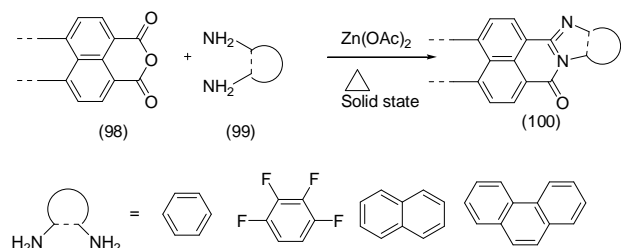


26. **Lin et al, 2005** reported direct one-step synthesis of various benzimidazoles (97) from phenylenediamines (95) and aldehydes (96) using air as the oxidant. The salient features of this method include a simple procedure, mild conditions, no coupling agents or commercial

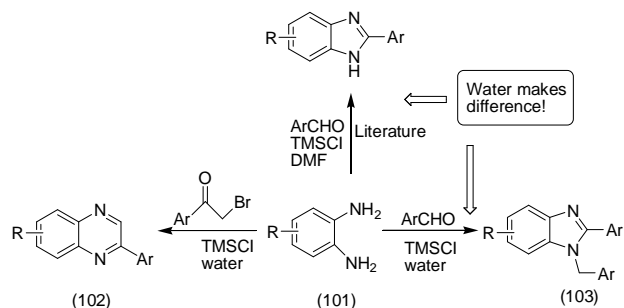
oxidants/additives used, no waste produced (only by-product being water), easy purification, and high generality<sup>34</sup>.



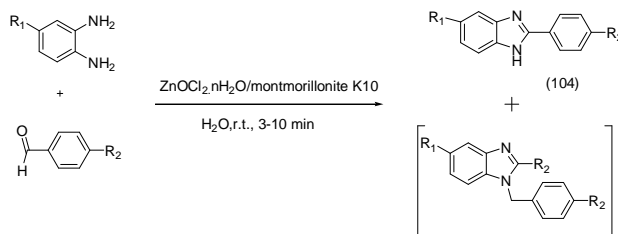
**27. Mamada *et al.*, 2011** prepared Polycyclic benzimidazole derivatives (100) using a solvent-free “green” process based on heating carboxylic acid anhydrides (98) and arylene diamines (99) in the presence of zinc acetate in the solid state. Products were isolated and purified directly by train sublimation of the crude reaction mixtures<sup>35</sup>.



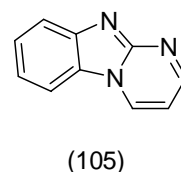
**28. Wan *et al.*, 2009** reported one-pot synthesis of 1, 2-disubstituted benzimidazoles (103) in excellent efficiency and selectivity at room temperature *via* trimethylsilyl chloride promoted reaction of *o*-phenylenediamine (101) with aldehyde by applying water as the reaction medium. This green catalyst system has also been successfully extended to the synthesis of quinoxalines (102) *via* the reaction of *o*-phenylenediamine with  $\alpha$ -bromoketone. Water displayed a specific functionality and show remarkable advantages over organic solvents in terms of yields as well as in the work up procedure of the reactions<sup>36</sup>.



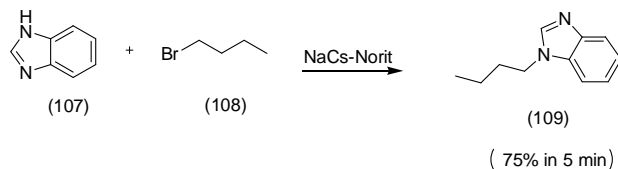
**29. Rostamizadeh *et al.*, 2009** synthesized some novel substituted 2-arylbenzimidazoles (104). These compounds were prepared in water as the solvent using  $\text{ZrOCl}_2 \cdot n\text{H}_2\text{O}$  supported on montmorillonite K10 as an efficient water tolerating Lewis acid. The reaction was performed under mild conditions with good to excellent yields and remarkable chemoselectivity in the absence of any byproduct<sup>37</sup>.



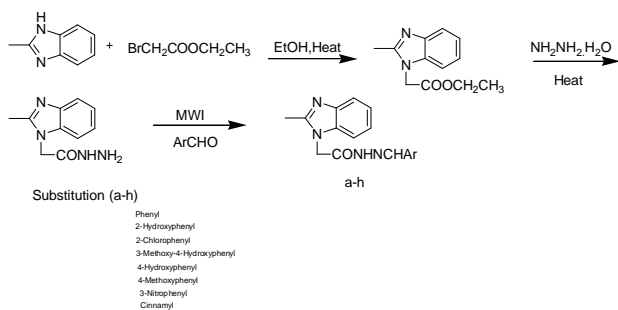
**30. Arya *et al.*, 2007** developed an efficient and greener method for one pot regioselective synthesis of pyrimido[1,2-a]benzimidazole (105). Starting from the 2-aminobenzimidazole, malononitrile and carbonyl compound, the methodology involves a ring closure by different ways based on the reaction medium was confirmed by NOE and X-ray studies<sup>38</sup>.



**31. Aranda *et al.*, 2010** reported the one-pot microwave-assisted synthesis of N-butylbenzimidazole derivatives (109) via alkylation of benzimidazole (107) with 1-bromobutane (108) over alkali-metal doped carbons in absence of any solvent. N-alkylbenzimidazole derivatives are produced in high yields and in very short reaction times when NaCs-Norit is used as catalyst (ca. 75% in 5 min<sup>39</sup>).

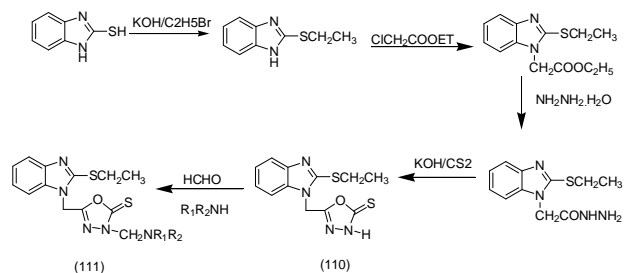


**32. Somani *et al.*, 2010** synthesized some Schiff's bases using microwaves. They were purified and characterized by means of spectral data and subsequently subjected to the *in vitro* antibacterial activity against few pathogenic strains of microbes. It was observed that *p*-substituted compounds exhibited good activity against almost all the organisms<sup>40</sup>.

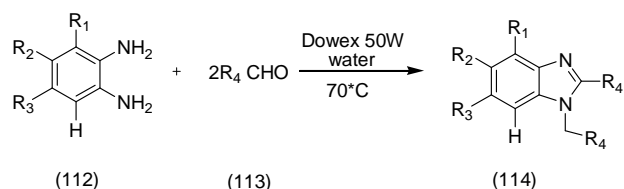


**33. Kadam *et al.*, 2009** synthesized a series of Mannich bases (111) by the reaction of 5-{2-(ethylthio)-1H-benzimidazol-1-yl}-methyl-1, 3, 4-oxadiazole-2-thione (110) with formaldehyde and appropriate amines by conventional and microwave techniques. The reaction rate

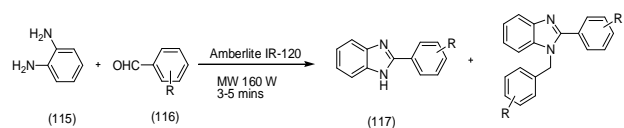
and yields were enhanced under microwave irradiation technique rather than conventional technique<sup>41</sup>.



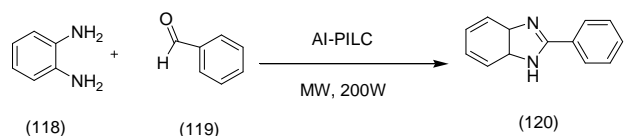
**34. Mukhopadhyay et al, 2010** synthesized 2-aryl-1-arylmethyl-1*H*-benzimidazoles (114) in excellent yields using Dowex 50W (as a catalyst in aqueous medium) from a wide variety of substituted *o*-phenylenediamines (112) and aromatic aldehydes (113)<sup>42</sup>.



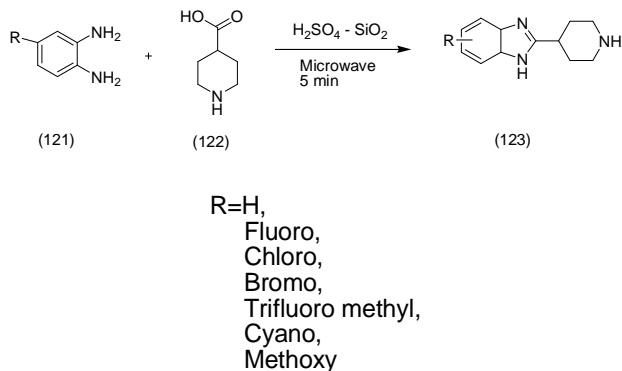
**35. Nizam et al, 2012** reported highly selective and expeditious synthesis of 2-aryl-benzimidazoles (117) by the condensation of *o*-phenylenediamine (115) with various aromatic aldehydes (116). This greener protocol is catalyzed by Amberlite IR-120 and proceeds efficiently in the absence of any organic solvent under microwave irradiation within 3–5 min<sup>43</sup>.



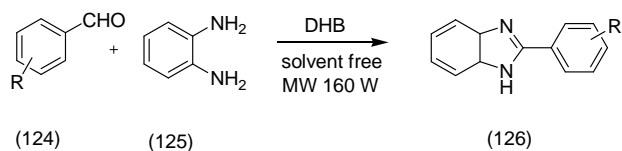
**36. Mamouni et al, 2011** reported an efficient and easy method for preparing 2-arylbenzimidazoles (120) from *o*-phenylenediamines (118) and aldehydes (119) under microwave irradiation and using a small amount of a new surfactant modified Moroccan clay catalyst. The heterogeneous reaction conditions provided a very simple, environmentally-friendly, clean, economical and selective protocol for the preparation of benzimidazole derivatives<sup>44</sup>.



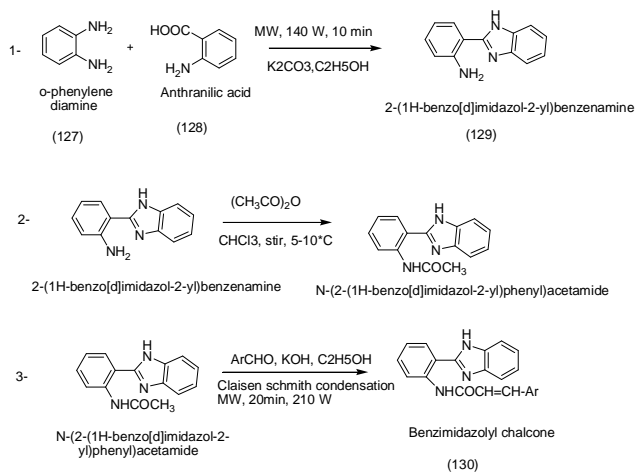
**37. Arul et al, 2011** described the synthesis of various benzimidazole derivatives (123) under micro-wave irradiation from simple and substituted ortho phenylenediamines (121) and isonicotinic acid (122) using SiO<sub>2</sub>/H<sub>2</sub>SO<sub>4</sub> as catalyst<sup>45</sup>.



**38. Forouzani et al, 2012** synthesized 2-aryl-benzimidazoles (126) by the condensation of *o*-phenylenediamine (125) with various arylaldehydes (124). The greener protocols is catalyzed by 1,3-Dibromo 5,5-dimethylhydantoin (DBH), and proceeds efficiently in the absence of any Organic solvent under thermal condition and microwave irradiation in high yields<sup>46</sup>.

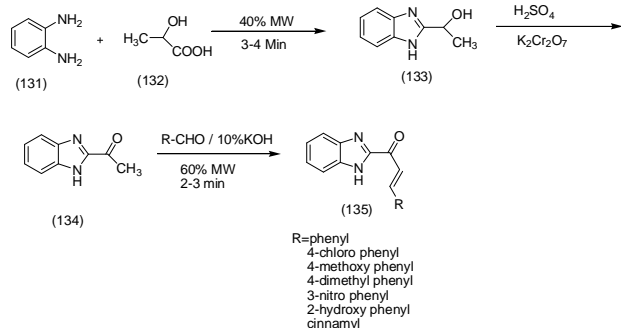


**39. Mohan et al, 2010** synthesized benzimidazole (129) by reaction between anthranilic acid (128) and *o*-phenylenediamine (127). Further the acetylated product of benzimidazole undergoes Claisen-Schmidt condensation with aryl aldehyde to produce corresponding chalcones (130)<sup>47</sup>.

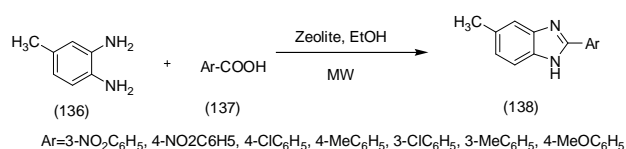


**40. Mathew et al, 2011** reported the synthesis of (2*E*)-1-(1*H*-benzimidazol-2-yl)-3-phenylprop-2-en-1-ones (135). *o*-phenylenediamine (131) reacts with lactic acid (132) gave 2-( $\alpha$ -hydroxyethyl)benzimidazole (133) which on oxidation in presence of potassium dichromate produced 2-acetyl benzimidazole (134). The chalcones were prepared by reacting 2-acetyl benzimidazole with appropriate aldehydes in the presence of a base by Claisen-Schmidt condensation<sup>48</sup>.

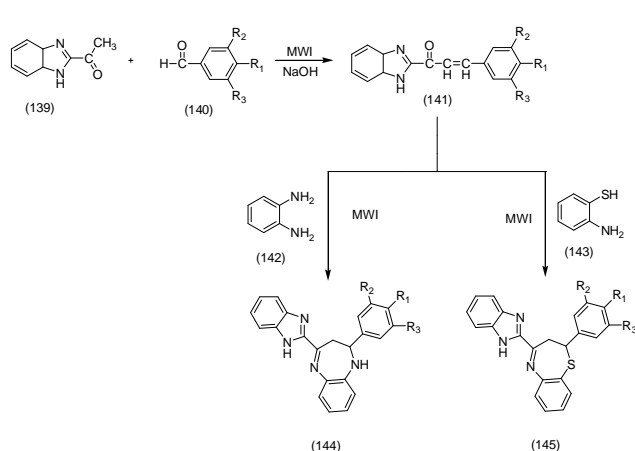




**41. Gangal et al, 2008** explained an efficient and simple synthesis of several 2-arylbenzimidazoles (138) from reaction of 4-methyl-1,2-phenylenediamine (136) and aromatic carboxylic acids (137) in the presence of zeolite catalyst. The reactions were performed under microwave irradiation, and the catalyst could be recycled and used for several times<sup>49</sup>.

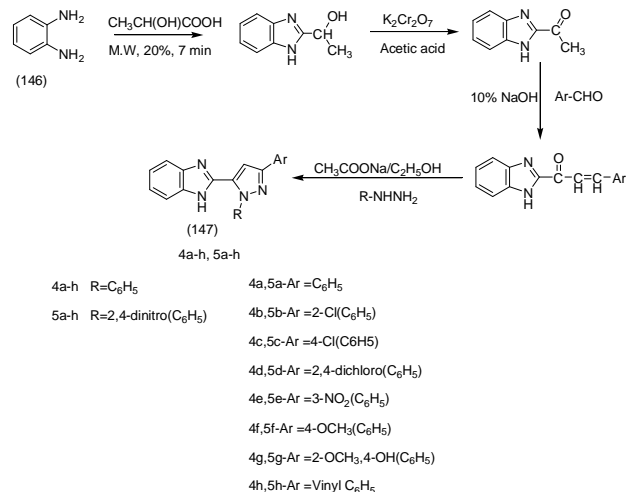


**42. Yadav et al, 2011** synthesized some 1,5 benzodiazepines (144) and 1,5 benzothiazepines (145) by employing microwave irradiation techniques and evaluated for their antimicrobial activities. 2-Acetyl benzimidazoles (139) were reacted with appropriately substituted aromatic aldehydes (140) in the presence of base to furnish substituted chalcones (141). These chalcones were further reacted with *o*-phenylenediamine (142) to offer 4-(1H-benzimidazol-2-yl)-2-phenyl-2,3-dihydro-1H-1,5-benzodiazepines (144). Reaction of the chalcones (141) with 2-amino thiophenol (143) yielded substituted 4-(1H-benzimidazol-2-yl)-2-phenyl-2,3-dihydro-1,5-benzothiazepines (145)<sup>50</sup>.

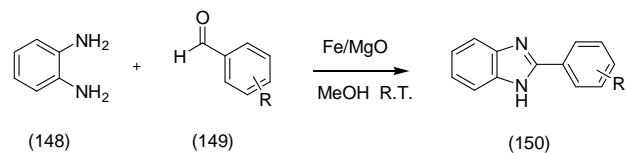


**43. Rathore et al, 2011** synthesized a series of novel and significant pyrazole substituted benzimidazoles (147) from *o*-phenylenediamine (146) under microwave radiations. All the

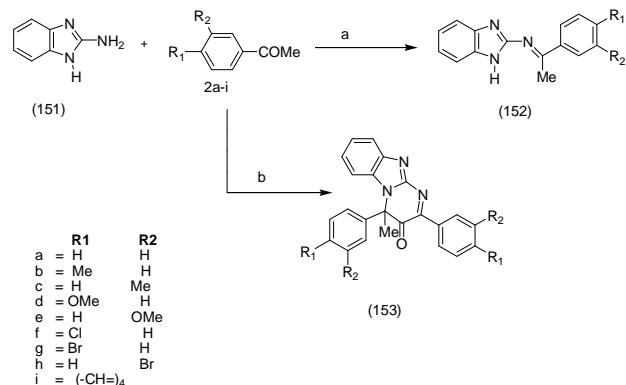
compounds are shown to possess good antimicrobial activity<sup>51</sup>.



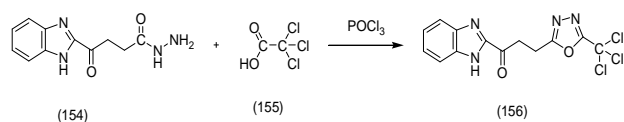
**44. Patil et al, 2012** developed a convenient and straightforward method for the synthesis of benzimidazole (150) using aryl aldehydes (149) and *o*-phenylene diamine (148) in the presence of Fe containing Magnesium oxide (Fe/MgO), at room temperature. The salient feature of this method includes mild condition, short reaction time, recyclable catalyst and large scale synthesis. The catalyst can be reused for several cycles without decrease in activity<sup>52</sup>.



**45. Neochoritis et al, 2011** synthesized number of benzimidazole Schiff bases (152) and 3-oxo-pyrimido[1,2-a]benzimidazoles (153) in excellent yields by a one-step sequence from the reaction of 2-aminobenzimidazole (151) under green chemistry conditions<sup>53</sup>.



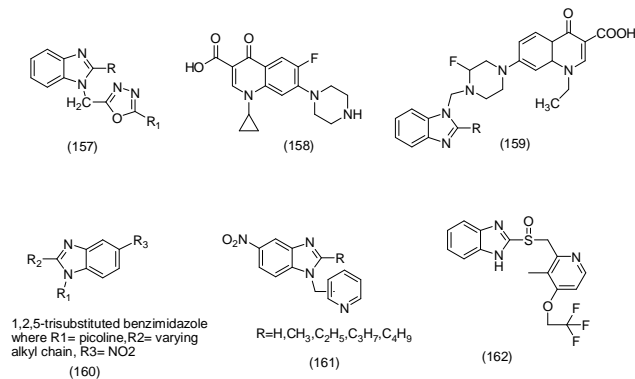
**46. Rashid et al, 2012** reported the synthesis of 1-(1H-benzimidazol-2-yl)-3-[5-(trichloromethyl)-1,3,4-oxadiazol-2-yl]propan-1-one (156) from 4-(1H-benzimidazol-2-yl)-4-oxobutanhydrazide (154) under microwave irradiation in good yield by reacting with trichloroacetic acid (155)<sup>54</sup>.



## PHARMACOLOGICAL ACTIVITY OF BENZIMIDAZOLE

Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. Nowadays it is a moiety of choice which possesses many pharmacological properties. The most prominent benzimidazole compound in nature is N-ribosyl dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B<sub>12</sub><sup>55</sup>. This compound has shown significant biological activity<sup>56,57</sup>.

2-Substituted benzimidazole (157) ones are found to be pharmacologically more potent and have shown Antimicrobial and Antibacterial effects<sup>58-60</sup>. Some widely used Antibacterial drugs such as Furacilin, Furazolidone and Ftivazide are known to contain this group<sup>61</sup>. Several compounds other than TIBO have recently been reported to specifically inhibit HIV-1 replication<sup>62</sup>. Benzimidazoles have reported to have anti viral properties against Picornavirus<sup>63</sup>, Poliovirus<sup>64</sup>, Enterovirus. The synthesized compounds are reported to be the derivatives of Ciprofloxacin (158) and Norfloxacin (159)<sup>65</sup>. Several new nitrobenzimidazoles have been reported to possess cytotoxic activity against breast cancer<sup>66</sup>. Some potential anticonvulsant compounds have been synthesized, a series of 1, 2, 5-trisubstituted benzimidazoles (160) (161) derivatives has been reported<sup>67</sup>. Other benzimidazole derivative used as antiulcer drug include lansoprazole (162)<sup>68</sup>.



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**\*Corresponding Author:**

Ms. Anshul Chawla

Asst. Professor (Pharmaceutical Chemistry)

CT Institute of Pharmaceutical Sciences,

Shahpur, Jalandhar (Punjab)-144020, India

Email: [anshul\\_chawla123@yahoo.com](mailto:anshul_chawla123@yahoo.com)