Heterocyclic Letters
Vol. 15| No.3|621-638|May-July|2025
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

RESEARCH ADVANCES IN THE AQUEOUS PHASE SYNTHESIS OF IMIDAZOLES/BENZIMIDAZOLES

Yadavalli Venkata Durga Nageswar [a,*], Katla Ramesh[b], Katla Rakhi[c]

[a,]Indian Institute of Chemical Technology (IICT), Tarnaka, Hyderabad, Telangana, India,*
[b]Research Scientist, School of Medicine, University of Virginia, Charlottesville, VA, USA.
[c]Organic Catalysis and Biocatalysis Laboratory-OCBL/FACET, Federal University of Grande Dourados-UFGD, Dourados/Itahúm rod. km 12 s/n, 79804-970, Dourados, MS, Brazil.
**E-mail: dryvdnageswar@gmail.com*

ABSTRACT: Among the heterocyclic systems imidazole and benzimidazole skeletons are widely distributed amid natural and medicinally relevant molecules such as alkaloids, purines, vitamins and drugs. Imidazole/benzimidazole derivatives played pivotal role in the development of organic chemistry in general, medicinal chemistry and heterocyclic chemistry in particular, over few decades. These scaffolds are used extensively in the design and development of pharmaceutically valuable molecules, and for the applications in biology as well as in material sciences. Even though many protocols have been reported for the synthesis of imidazoles/benzimidazoles, currently much importance is attached to the implementation of eco-friendly strategies. This review describes recent research reports on imidazole/benzimidazole derivatives synthesized in an environmentally benign way.

KEYWORDS: Benzimidazoles, imidazoles, water, green conditions, aldehydes, amines

INTRODUCTION:

Imidazole nucleus occurs widely in nature in the form of various structures of potential significance and has attracted immense attention due to a wide range of versatile properties.[i] It belongs to a class of five-membered nitrogen containing aromatic heterocyclic compounds and represents a range of building blocks with biological and medicinal importance such as purines, biotin, histamine and histidine etc.[ii] Benzimidazole is a fused 6-membered bicyclic aromatic heterocyclic structure containing imidazole ring as a part of it. Imidazole and benzimidazole moieties are extensively used in drug design and discovery in the pharmaceutical industry.[iii]
Their analogues also exhibited potential biological properties due to their structural motifs in drug therapeutics.[iv] Various drug molecules containing imidazole and benzimidazole moieties are comprehensively used in the treatment of several types of diseases with high therapeutic potential.[v] Last few decades witnessed extensive research on imidazole chemistry.[vi]
Furthermore, many imidazole and benzimidazole molecules are featured in clinically utilized bioactive molecules in anti-cancer, anti-fungal, anti-bacterial, anti-hypertensive, anti-viral,

antiulcer, anti-histaminic, antiemetic, and anti-parasitic areas.[vii-viii] In view of this, many research groups globally pursue research to develop imidazole and benzimidazole containing drug molecules while addressing their structure activity relationship features and also their mechanism of action.[ix] Some of the potential molecules containing imidazole/benzimidazole skeleton are represented in Figure 1.

In addition to this, both imidazole and benzimidazole can act as important ligands in transition metal chemistry.[x] Especially, benzimidazole is more stable at higher temperatures and in the presence of oxidizing agents.

Heinrich Debus first reported imidazole synthesis in 1858 from glyoxal and formaldehyde in ammonia.[xi] Hoebrecker initially developed the synthesis of 2,5- and 2,6-dimethylbenzimidazoles in 1872, using benzene-1,2-diamine by the ring closure reaction.[xii] In addition to this, in 1882, highly substituted imidazoles were first synthesized by Radziszewski using condensation between 1,2-diketone and several aldehydes employing ammonia. Several methods are reported in literature for the synthesis of imidazole/benzimidazole derivatives.[xiii]

Generally organic synthetic processes involve the use inflammable hazardous organic solvents in various stages such as preparation, extraction, and recrystallization as well as for purification purposes. However, the design and development of alternate, eco-friendly green approaches are being increasingly practiced by researchers across the globe. Among alternate solvents non-flammable, non-toxic, natural and widely available water was found to be a better choice for conducting reaction processes. Greater surge in the number of research publications employing water as a solvent highlights the importance of it as a natural selection in view of the economic viability, operational simplicity and environmentally benign nature.

The present write-up focuses on recent research advances in the water medium reactions affording imidazoles/benzimidazole derivatives.

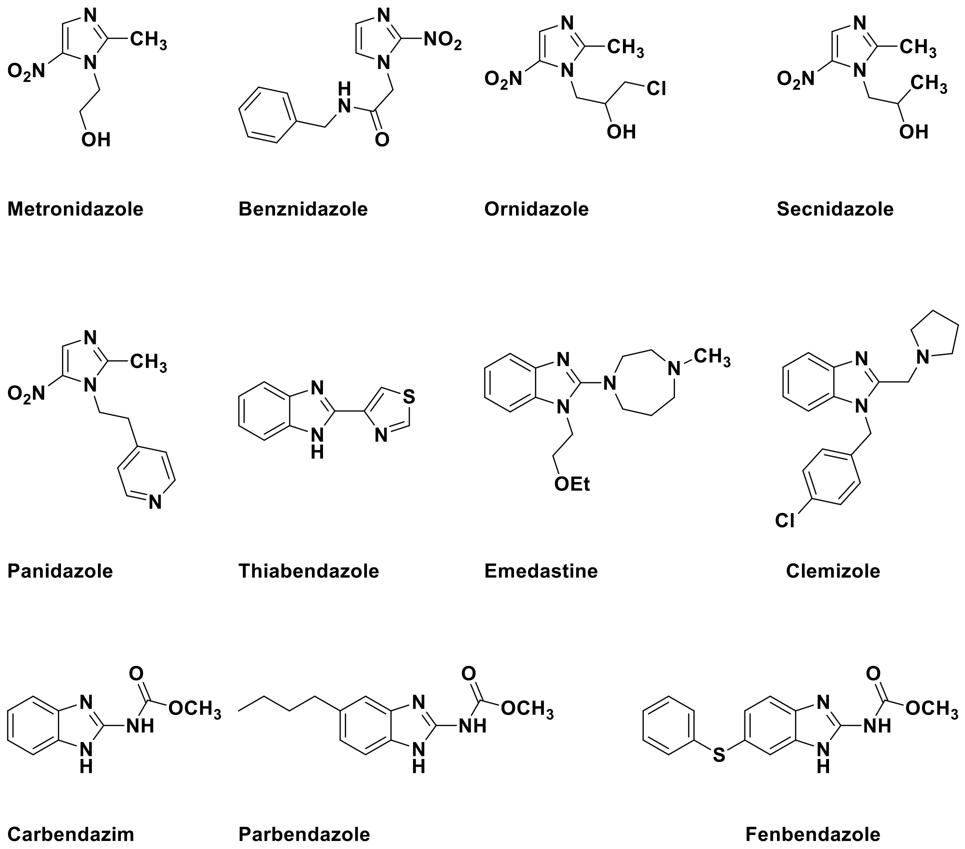
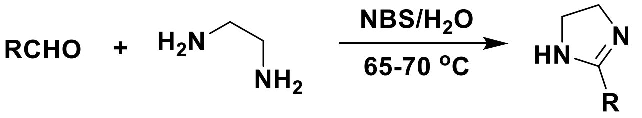


Figure 1. Bioactive compounds with imidazole and benzimidazole structures.

RECENT LITERATURE ON BENZIMIDAZOLES/IMIDAZOLES UNDER AQUEOUS MEDIUM:

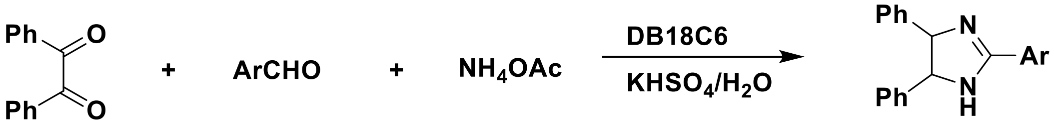
Gabriela da S. Sant' Anna and co-authors[xiv] successfully employed ultrasound irradiation in the synthesis of a series of sixteen 2-substituted-2-imidazolines in water medium by the reaction of ethylene diamine with substituted aldehydes in the presence of N-bromo succinimide. The authors reported faster reaction rates and higher yields in this methodology (Scheme 1).



R = Ph; 4-CH_3-Ph; 4-OCH_3-Ph; 3,4-$(OMe)_2$-Ph; 3,4,5-$(OMe)_3$-Ph; 4-Cl-Ph; 2-Cl-Ph; 2,4-Cl_2-Ph; 4-NO_2-Ph; 3-NO_2-Ph; 2-Naphthyl; 2-Furyl; 2-Benzofuryl; 2-Pyridinyl; 2-Quinolinyl;

Scheme 1. Preparation of 2-substituted-2-imidazolines

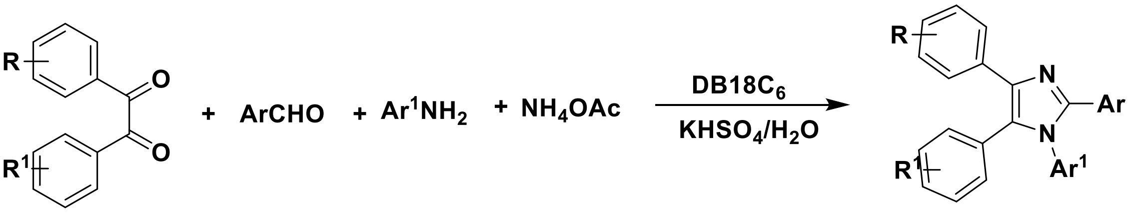
Potassium hydrogen sulfate along with dibenzo-18-crown-(DB18C6) was efficiently employed by Chhanda Mukhopadhyay and Pradipkumar Tapaswi,[xv] in an eco-friendly synthesis of a broad range of tri and tetra substituted imidazoles in water medium by the condensation of benzil, aromatic aldehydes and ammonium acetate (Scheme 2).



Ar = C_6H_5; 4-Br-C_6H_4; 3-NO_2-C_6H_4; 2-furyl; 4-OMe-C_6H_4; 4-Me-C_6H_4; CH_3; 3,4-diOMe-C_6H_3;

Scheme 2. Preparation of 2, 4, 5-trisubstituted imidazoles in the presence of DB18C6.

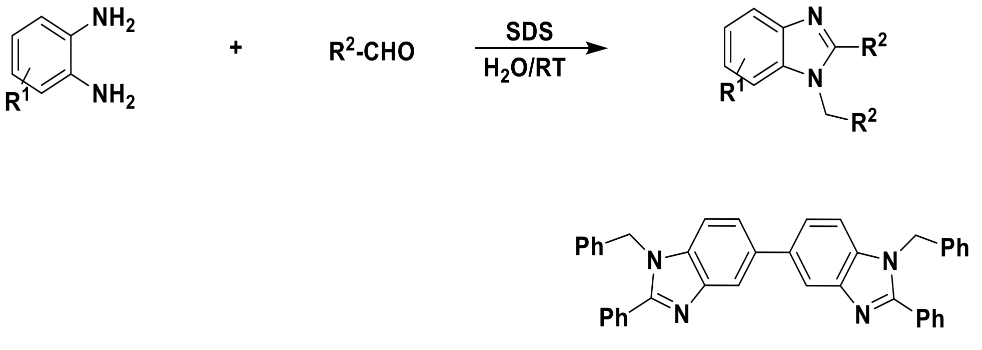
Following the same methodology 1,2,4,5-tetra substituted imidazoles were also prepared via a one-pot four component strategy by the condensation of benzil, aldehyde, aromatic amines (as well as benzyl amines) and ammonium acetate (Scheme 3). The methodology was supported by employing a wide range of aldehydes and primary amines. The aqueous part containing DB18C6/$KHSO_4$ can also be reused at least six times indicating the recyclability potential of the catalyst.



Scheme 3. Preparation of 1,2,4,5-tetra substituted imidazoles.

Mechanism of the protocols was discussed by the authors in their paper.

Pranab Ghosh and Amitava Mandal[xvi] discussed an efficient and eco-friendly selective synthesis of diversified 1, 2-disubstituted benzimidazole derivatives in water medium at room temperature conditions catalyzed by reusable and commercially available sodium dodecyl sulfate (SDS) from the reaction of o-phenylene diamines with a wide range of aromatic/hetero aromatic aldehydes (Scheme 4).



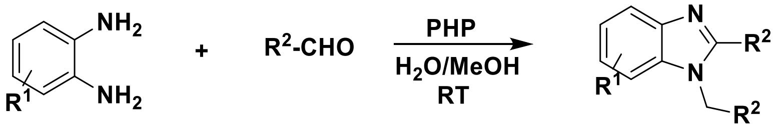
R^1 = H; 3-Me; 3-benzoyl;

R^2 = H; Ph; 4-Me-C_6H_4; 4-F-C_6H_4; 4-Cl-C_6H_4; 4-NO_2-C_6H_4; 4-NMe_2-C_6H_4;; Isopropyl-C_6H_4; 3-NO_2-C_6H_4; 3-OH-C_6H_4; 3-OPh-C_6H_4; 2-Cl-C_6H_4; 2-OH-C_6H_4; Furan-2-yl; 5-Bromo-thiophene-2-yl; Ph-CH=CH_2; 1-Naphthyl; 4-Cl-; Pyridine-4-carboxaldehyde; Valeraldehyde; Cyclohexayl

Scheme 4. Preparation of 1,2-disubstituted benzimidazoles.

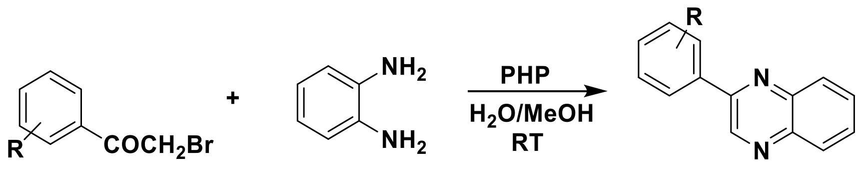
A plausible mechanism was proposed by the authors in their research paper. They reported that unsubstituted aldehydes gave the products in better yields than the substituted compounds. The aliphatic aldehydes did not give encouraging yields.

Pranab Ghosh and Amitava Mandal[xvii] developed a simple, operationally straight forward, versatile and environmentally benign protocol for the selective preparation of 1, 2-disubstitituted benzimidazoles and quinoxalines in aqueous methanol medium catalyzed by Amberlite resin bound hexaflourophosphate ion (PHP). The authors investigated the generality of the method employing a wide variety of 1, 2-diamines and aldehydes and extended this selective greener method to design certain large benzimidazole derivatives which can be useful as lead compounds in pharmaceutical research. Diversified 1, 2-disubstituted benzimidazoles were prepared from o-phenylene diamines and aryl/hetero aryl aldehydes (Scheme 5).



R^1 = H; 3-CH_3; 3-Benzoyl;

R^2 = H; Ph; 4-OMeC_6H_4; 4-F-C_6H_4; 4-Cl-C_6H_4; 4-NO_2-C_6H_4; 4-NMe_2-C_6H_4; 4-Isopropyl-C_6H_4; 3-NO_2-C_6H_4; 3-OH-C_6H_4; 3-OPh-C_6H_4; 2-Cl-C_6H_4; 2-OH-C_6H_4; Furan-2-yl; 5-Bromo-thiophene-2-yl; Ph-CH=CH_2; 1-Naphthyl; Cyclohexyl;

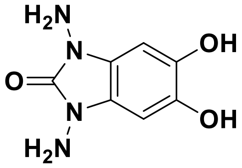


R = 4-H; 4-Me; 4-OMe; 4-Br; 4-Cl; 4-I; 4-NO_2; 3-Br; 3-NO_2; 2-OH; 2,4-Cl_2; 3,4-$(OMe)_2$;

Scheme 5. Preparation of benzimidazoles and quinoxaline derivatives.

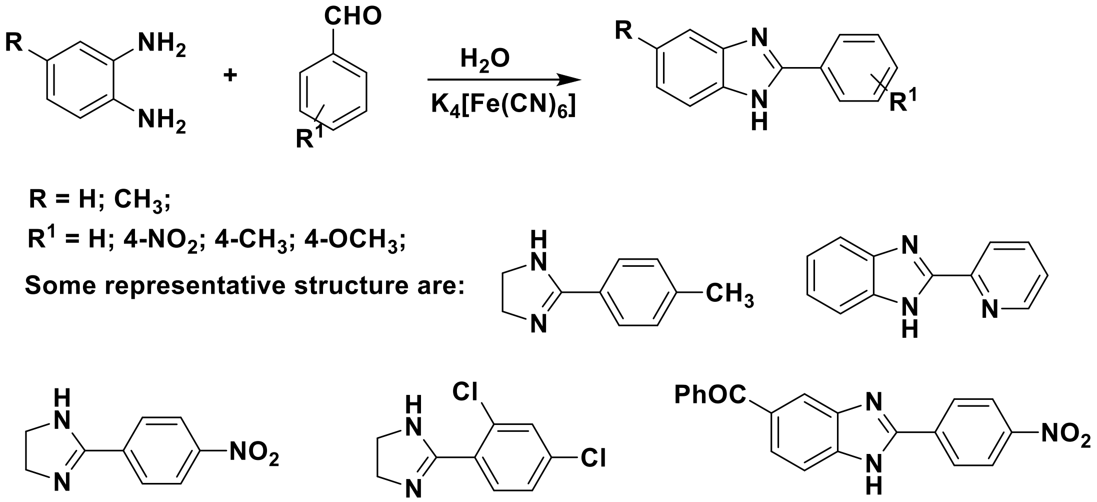
Quinoxaline derivatives were obtained by the reaction of α-bromo ketones with o-phenylene diamines. The study proved that hexafluorophosphate ion played key role in these transformations. It was confirmed that hexafluorophosphate ion binds to Amberlite 900 resin and catalyzes the reactions. Different functional groups were compatible for these condensation reactions, under the reported conditions. Plausible mechanism was also discussed by the authors.

Bahram Dowlati et al.[xviii] reported the formation of benzimidazole derivatives from different catechols during an electrochemical oxidation process in an aqueous solution in presence of carbohydrazide employing carbon electrode using cyclic voltammetry and controlled potential coulometry techniques (Scheme 6).



Scheme 6. 1,3-Diamino-5,6-dihydroxy-1H-benzo[d]imidazole-2(3H)one.

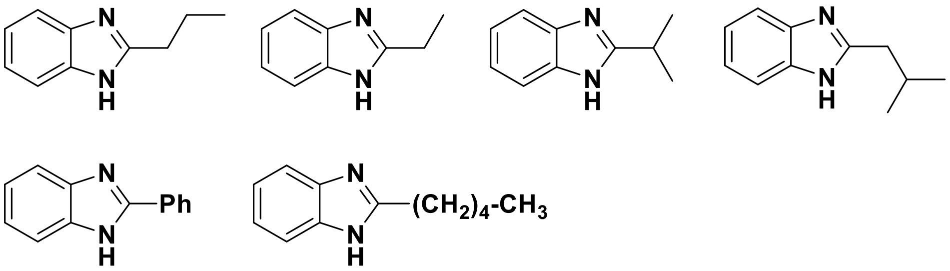
Shaikh Kabeer, A. et al.[xix] disclosed the formation of imidazolines and benzimidazoles by the reaction of aldehydes with 1, 2-diamines in water médium employing metal coordination complex $K_4[Fe(CN)_6]$ (Scheme 7).



Scheme 7. $K_4[Fe(CN)_6]$ mediated synthesis.

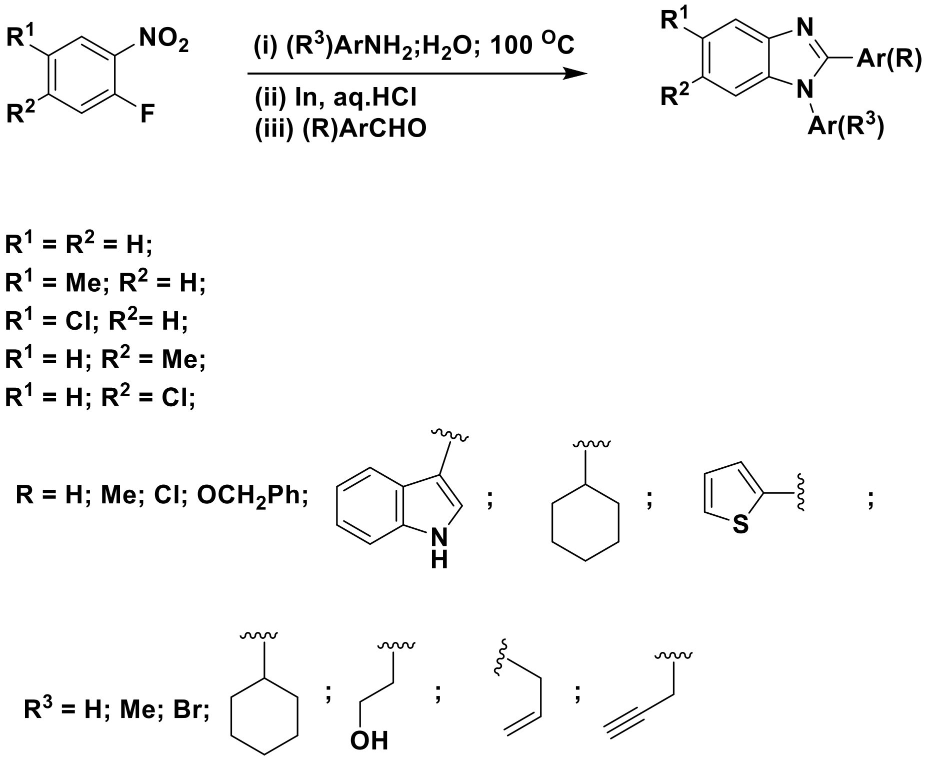
Proper mechanism was also proposed for the protocol.

Ngoc Thang Tran and Chan Sik Cho[xx] described the preparation of benzimidazoles in aqueous medium by the reaction of various trialkyl amines and o-phenylene diamines in the presence of 5% Pd/C via amine exchange reaction. Some of the compounds synthesized are given in scheme 8.



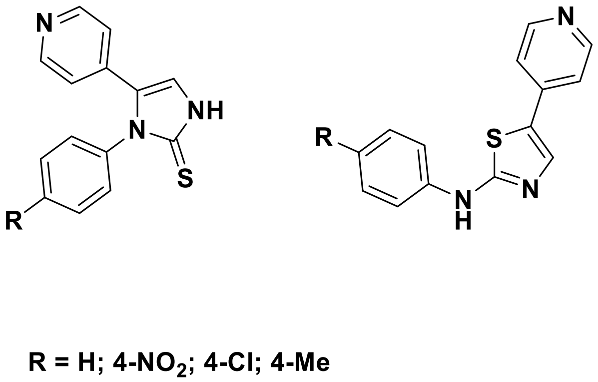
Scheme 8. Some benzimidazole derivatives

Damodara N. Kommi et al.[xxi] in an interesting paper disclosed “all water” one-pot diversity oriented preparation of regio-defined 1,2-disubstituted benzimidazoles. The authors utilized better hydrogen bond donor as well as accepter capabilities of water in this water assisted tandem aryl amino-arylation/aryl amino-alkylation-reduction-cyclization strategy under base and metal free conditions in the preparation of N-aryl/aryl alkyl/alyl-2-aryl/hetero aryl/ cycloalkyl benzimidazoles (Scheme 9). The role of water and the mechanistic aspects of the strategy employed were elaborately explained by the authors.



Scheme 9. Preparation of diversely substituted benzimidazoles.

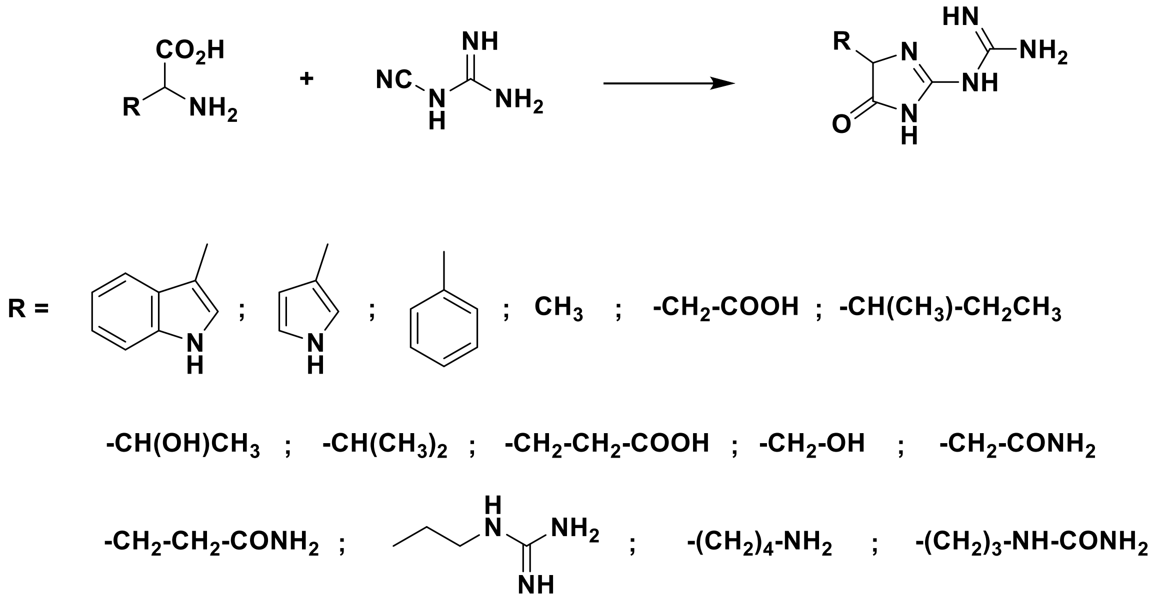
Mehdi Kalhor et al.[xxii] reported the synthesis of some novel antibacterial N.N^1-disubstituted thioureas, imidazole-2-thione and 2-amino thiazole derivatives in aqueous medium. N-substituted thiourea derivatives were obtained by reacting α-amino pyridyl ketone hydrochloride with certain aryl isothiocyanates (Scheme 10). The intramolecular cyclization of N,N^1-disubstituted thioureas and further their intermediate ketals provided the end products.



Scheme 10. Different heterocyclic derivatives.

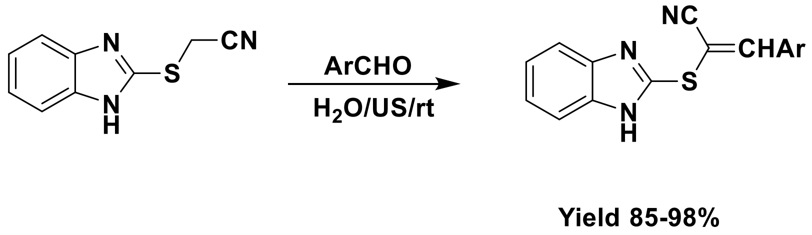
The compounds are activated employing dilute aqueous acidic acid and strong acidic conditions.

Ahmed M. Soliman[xxiii]reported the synthesis of a series of structurally modified guanidine derivatives starting from dicyandiamide. The synthetic approach involved the reaction of dicyandiamide with various amino acids in an aqueous acidic medium, as illustrated in Scheme 11. This method enabled the incorporation of different side chains from the amino acids into the guanidine framework, potentially modulating the physicochemical and biological properties of the resulting compounds.



Scheme 11. Modified guanidines.

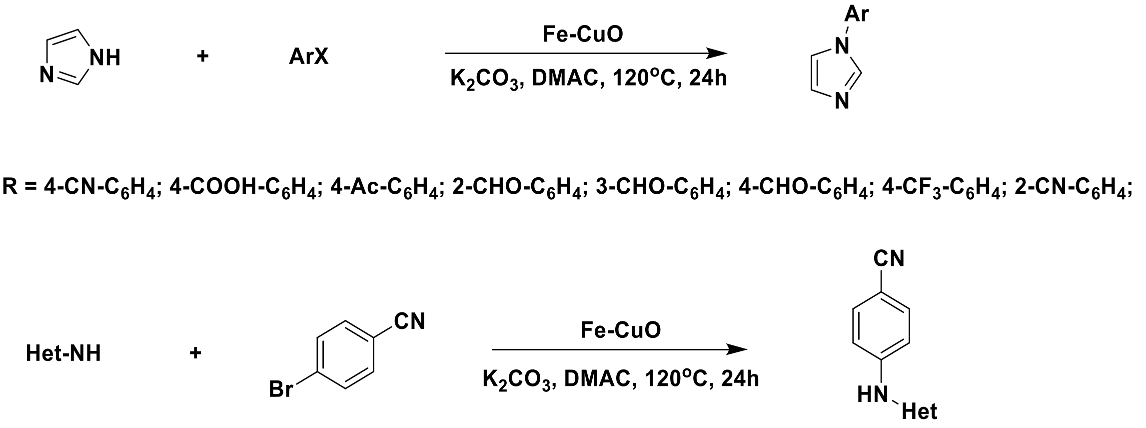
Sadhu Srinivasa Rao and co-authors[xxiv] reported an aqueous medium eco-friendly synthesis of benzimidazol-2-yl thio-unsaturated nitriles under ultra-sonic irradiation by the condensation reaction of 2-cyanothiomethyl benzimidazole with various aromatic aldehydes (Scheme 12).



Ar = C_6H_5; 4-NO_2-C_6H_4; 3-NO_2-C_6H_4; 4-Me-C_6H_4; 4-OH-C_6H_4; 2-OH-C_6H_4; 4-OMe-C_6H_4; 3-OMe-C_6H_4;

Scheme 12. Preparation of benzimidazol-2-yl derivatives.

R. Siva Kami and co-authors[xxv] explained in their interesting research paper the role played by magnetically retrievable lepidocrocite supported and copper oxide nano catalyst (Fe-CuO) in the N-arylation of imidazoles (Scheme 13). Authors prepared the eco-friendly reusable heterogeneous nano catalyst in the presence of water from readily available cost-effective starting materials. The crystal structure, morphology, surface area and magnetic properties of the catalyst were examined by employing standard procedures. After successful preparation and characterization, the authors examined the applicability of the catalyst in the present reaction.

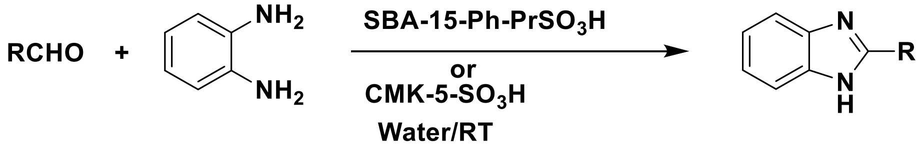


R = 4-CN-C_6H_4; 4-COOH-C_6H_4; 4-Ac-C_6H_4; 2-CHO-C_6H_4; 3-CHO-C_6H_4; 4-CHO-C_6H_4; 4-CF_3-C_6H_4; 2-CN-C_6H_4;

Scheme 13. Preparation of N-aryl imidazoles.

The authors also examined the effectiveness of the catalyst in the N-arylation studies of various other heterocycles with 4-bromo benzonitrile. Optimization studies also were conducted to assess the efficacy of various solvents, as well as bases and temperature conditions for the above reactions. A plausible three-step mechanism was proposed for the Fe-CuO-catalyzed N-arylation reactions.

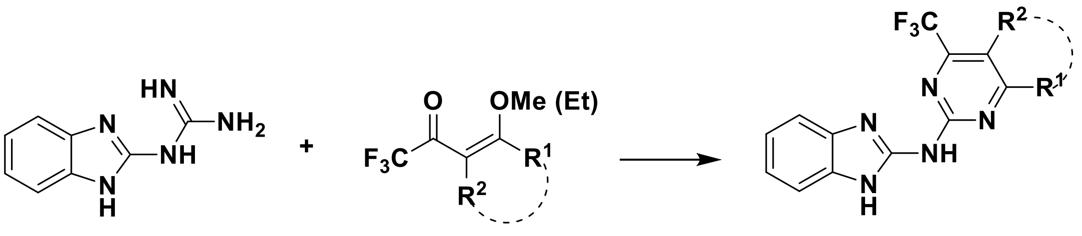
Daryoush Zareyee et al.[xxvi] discussed a simple, rapid and eco-friendly synthesis of 2-substituted benzimidazoles in water medium and disclosed the use of environmentally benign and hydrophobic heterogeneous sulfonic acid based non-porus carbon (CMK-5-SO_3H). The authors assessed the hydrophobicity of these reusable catalysts and established the relationship between hydrophobicity and the efficacy of the catalysis. Non-hydrophobic and more water resistant carbonaceous solid sulfonic acid CMK-5-SO_3H exhibited superior catalytic activity with high yields by providing facile mass transfer of hydrophobic reaction partners. These catalysts possessed appreciable hydrolytic stability in presence of water and retained their acidity even after multiple reaction cycles (Scheme 14).



R = Ph; 4-tolyl; 4-OMe-C_6H_4; 2-Cl-C_6H_4; 3-Br-C_6H_4; 4-Br-C_6H_4; 2-OH-C_6H_4; 3-OH-C_6H_4;
4-OH-C_6H_4; 2-NO_2-C_6H_4; 4-NO_2-C_6H_4; 1-naphthyl; 2-thienyl; Pr; Et;

Scheme 14. Synthesis of 2-substituted benzimidazoles.

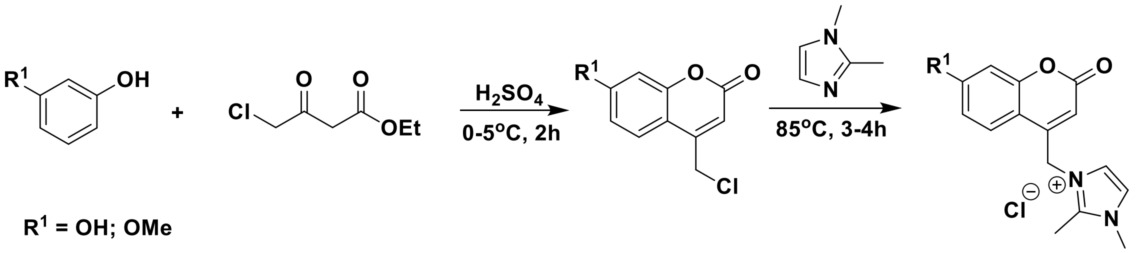
Helio G. Bonacorso et al.[xxvii] reported an efficient eco-friendly process for the synthesis of a novel series of N-(pyrimidinyl)-N-(1H-benzo[d] imidazolyl) amines obtained by the cyclo-condensation of 4-alkoxy-4-alkyl (aryl/hetero aryl)-1,1,1-trifluoro alk-3-ene-2-ones or 2,2,2-trifluoro-1-(2-methoxy cyclo hexen-1-ene-1-yl) ethanone with (beno [d]imidazolyl) guanidine in water medium (Scheme 15).



R^1 = H; CH_3; -$(CH_2)_4$-; Ph; 4-OCH_3-C_6H_4; 4-CH_3-C_6H_4; 4-Br-C_6H_4; 4-F-C_6H_4; 2-thienyl;
R^2 = H; CH_3;

Scheme 15. Synthesis of N-(pyrimidinyl)-N-(1H-benzo[d] imidazolyl) amines.

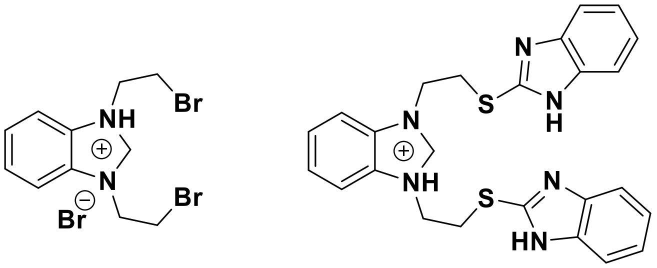
Santosh Kumari et al.[xxviii] reported the design and preparation of novel fluorescent coumarinyl linked imidazolinium salts, useful and practically applicable in the detection of commonly used explosive picric acid in water medium, even in presence of others interfering aromatic/non-aromatic compounds or metal ions. Their efficiency was established towards selective sensing of picric acid in real environmental samples (Scheme 16).



R^1 = OH; OMe

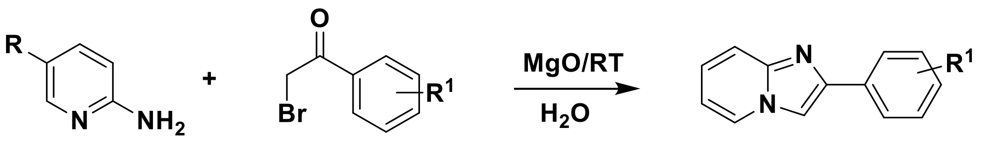
Scheme 16. Preparation of coumarinyl linked imidazolinium salts.

Aman Preet Singh and co-authors[xxix] have designed and synthesized certain novel benzimidazolium based fluorescent cations and their fluorescent aggregates fabricated employing anionic surfactants (SDS and SDBS) in water medium (Scheme 17).



Scheme 17. Novel benzimidazolium derivatives.

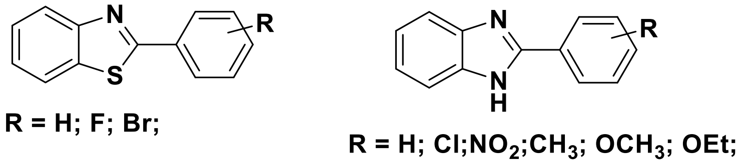
S. V. Patil and co-workers[xxx] described the synthesis of several imidazolo [1,2-a] pyridines obtained by the reaction of aromatic phenacyl bromides with amino pyridines in a single step in water medium in the presence of MgO, under mild conditions with high yields (Scheme 18).



R = H; Cl;
R^1 = 4-Cl; 4-Br; 4-NO_2; 3-NO_2; 4-OMe;

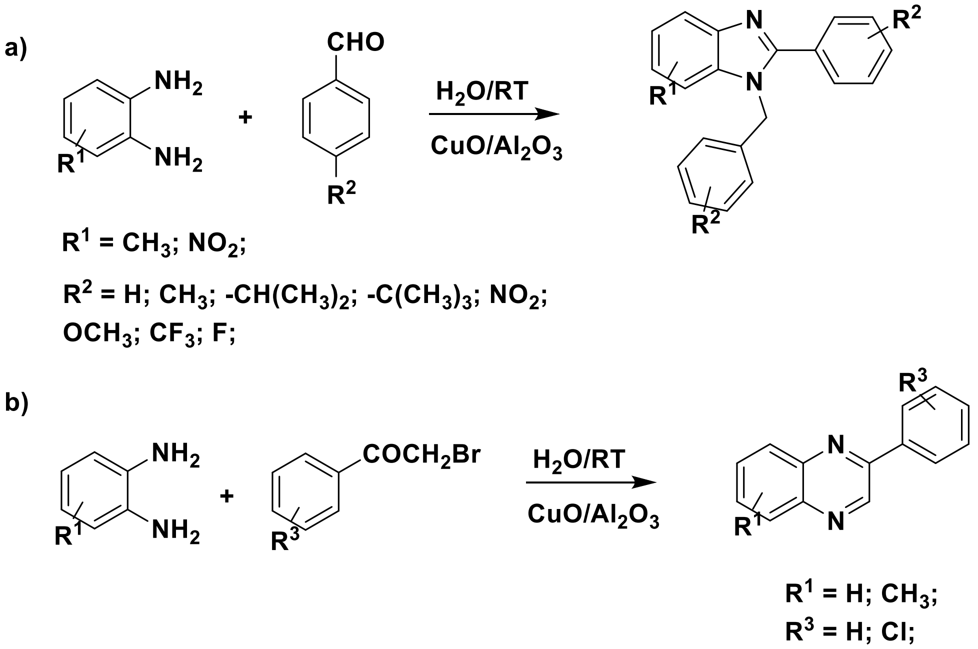
Scheme 18. Imidazolo [1,2-a] pyridines.

Dileep Kommula and Sri Rama Murthy Madugula[xxxi] reported an efficient, environmentally benign preparation of benzimidazole/benzothiazole derivatives by the reaction of 1,2-diamino benzenes, 2-amino thiophenol with substituted aromatic aldehydes catalyzed by economically viable, readily available and reusable nano-Fe_2O_3 in aqueous medium resulting in high yields of the products (Scheme 19).



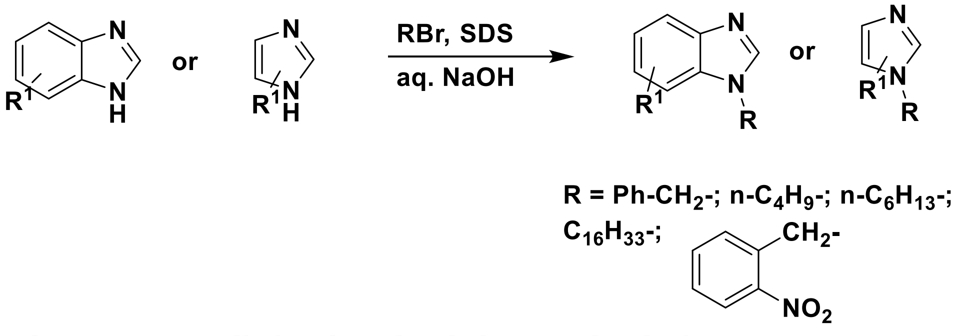
Scheme 19. Representative structures.

Jaya Pogula et al.[xxxii] discussed in their research paper about an efficient and green chemoselective synthesis of 1,2-disubstituted benzimidazoles and quinoxaline derivatives in presence of water as medium catalyzed by recyclable nano copper stabilized on alumina (Scheme 20). Plausible reaction mechanism for these condensation reactions was explained while reporting the preparation of broad range of functional heterocyclic derivatives.



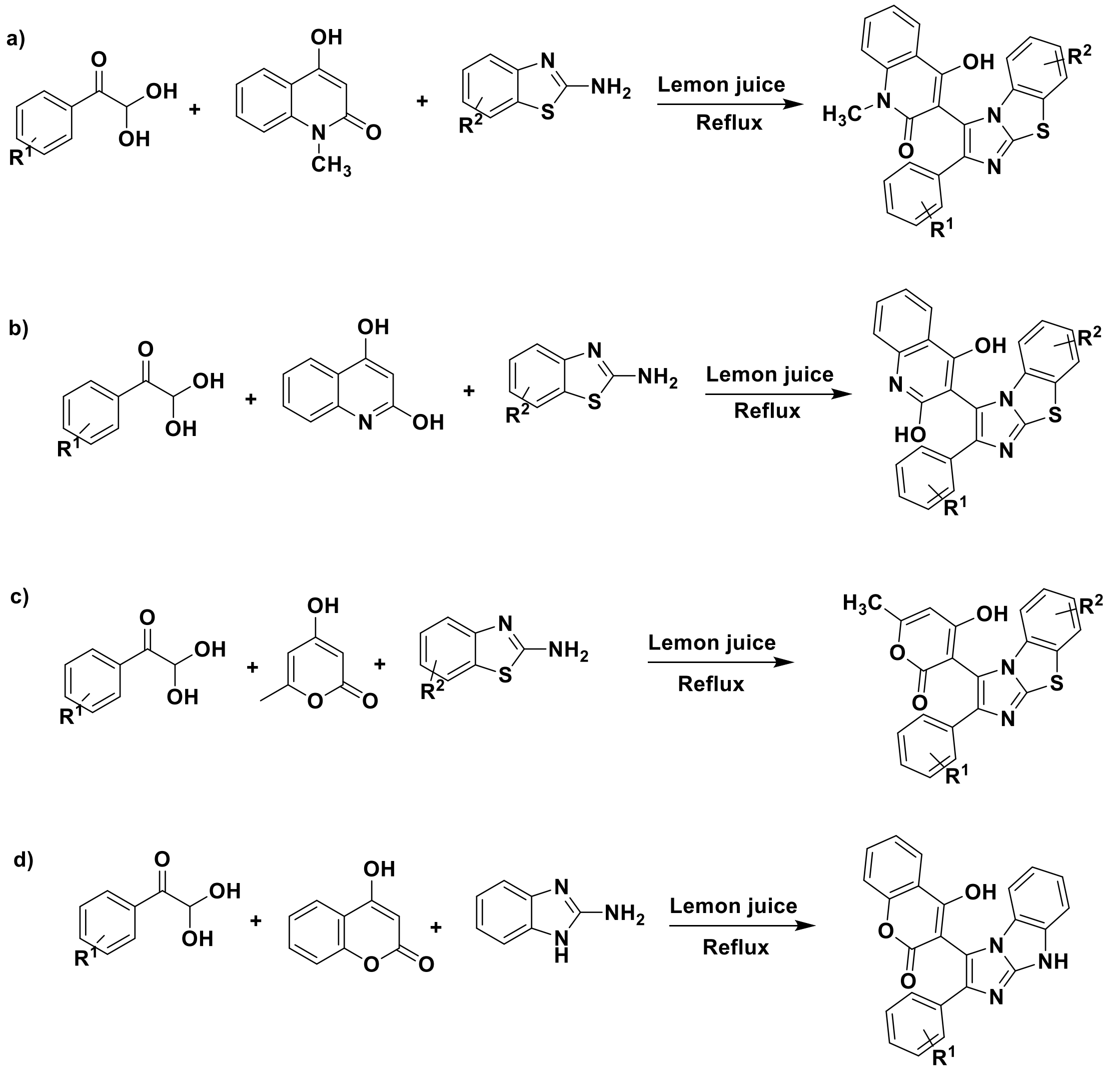
Scheme 20. Synthesis of 1,2-disubstituted benzimidazoles and quinoxaline derivatives.

Ankitha Chakraborti et al.[xxxiii] developed an efficient and environmentally benign strategy for the preparation of a series of N-1-alkyl imidazole/benzimidazole derivatives using alkaline water, SDS system providing high yields in shorter reaction times (Scheme 21).



Scheme 21. N-1-alkylated imidazole/benzimidazole derivatives.

In an interesting research paper, Argha Saha and co-authors[xxxiv] explained a newly developed one-pot three-component eco-friendly strategy for the synthesis of diversely designed pharmaceutically important tricyclic fused imidazoles tethered with aryl and different cyclic 1,3-dicarbonyls employing lemon juice in an aqueous medium. The authors executed the reaction of aryl glyoxals with cyclic 1,3-dicarbonyls such as 2,4-dihydroxyquinoline, 4-OH-coumarin, N-methyl-4-OH-quinolone and different 1,3-N,N'-bi nucleophiles such as 2-amino benzimidazoles or 2-amino benzo thiazoles under metal free conditions (Scheme 22).

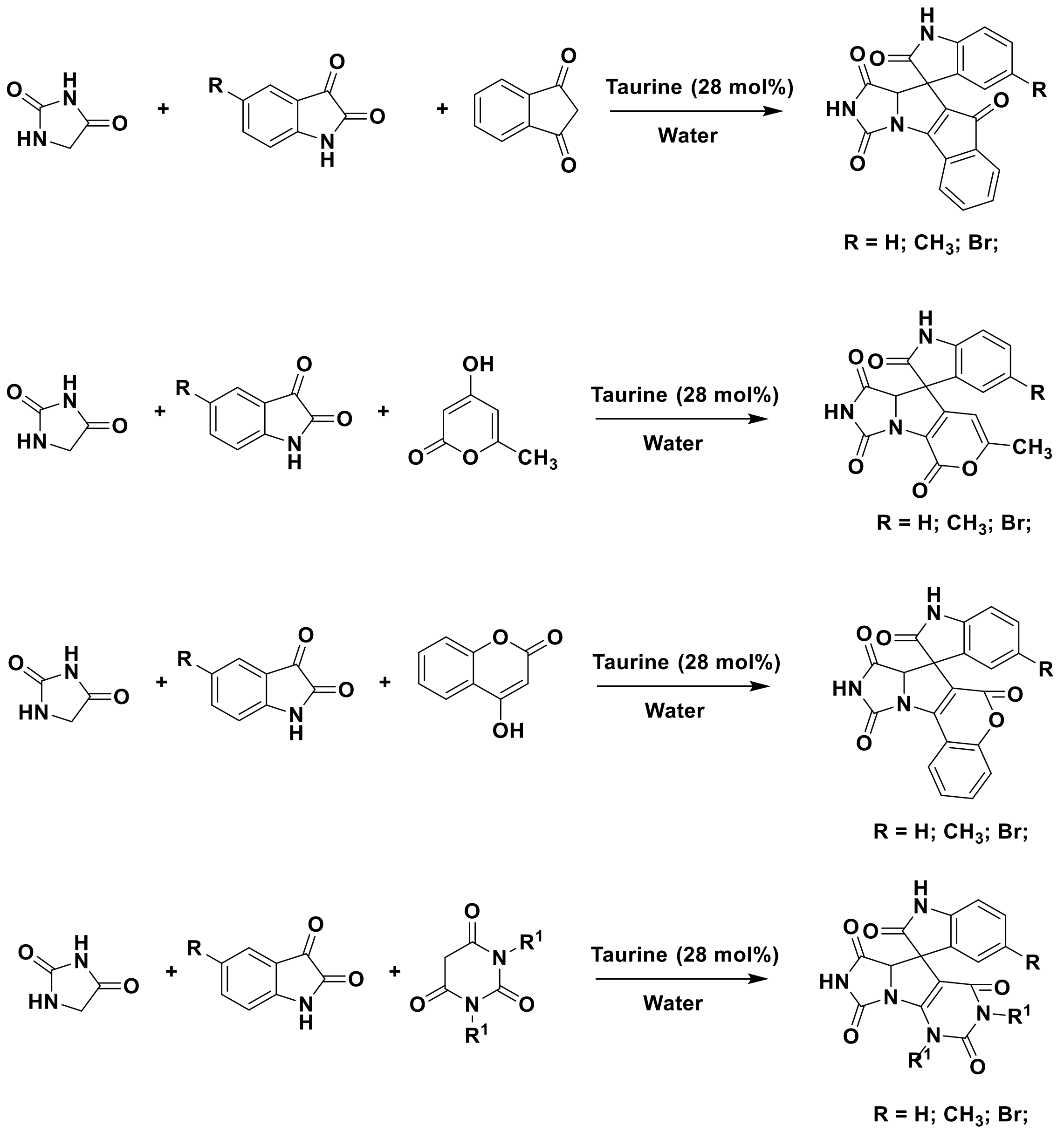


R^1 = H; 4-OMe; 3,4-diOMe; 4-F; 4-NO_2
R^2 = H; 4-Me; 4-OMe; 4-OC_2H_5; 4-Cl;

Scheme 22. Synthesis of some important tricyclic fused imidazoles.

The lemon juice can be recycled and reused for three times.

Kanchan Verma et al.[xxxv] reported the synthesis of diversified spiro heterocycles with privileged heterocyclic substructures by an efficient and environmentally benign domino protocol employing taurine- α, β-amino acid (2-amino ethane sulfonic acid) in water medium. This operationally simple and cost-effective protocol was useful in the synthesis of several structurally diverse spiro oxindoles, spiro annulated with indeno pyrrolo imidazoles, pyrano pyrrolo imidazoles, chromeno pyrrolo imidazoles and imidazo pyrrolo pyrimidines by a three-component reaction between β-diketones, isatins and hydantoin. Several representative skeletal frame works are presented in scheme 23.

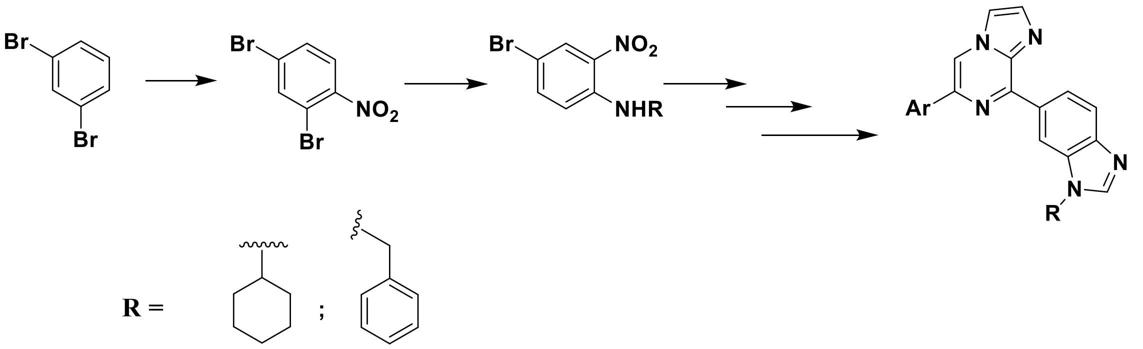


Scheme 23. Several representative heterocyclic skeletal frame works.

Iqbal Singh et al. [xxxvi] reported an efficient synthesis of a novel series of 6-substituted-8-(1-cyclohexyl-1H-benzo[d] imidazole-6-yl) imidazo [1, 2-a] pyrazines and 6-substituted-8-(1-benzyl-1H-benzo[d] imidazole-6-yl) imidazo [1, 2-a] pyrazines, which were also examined for their anticancer activity. These imidazo [1, 2-a] pyrazine and benzimidazole frame works are effective pharmacophores for anti-tumor activity (Scheme 24).

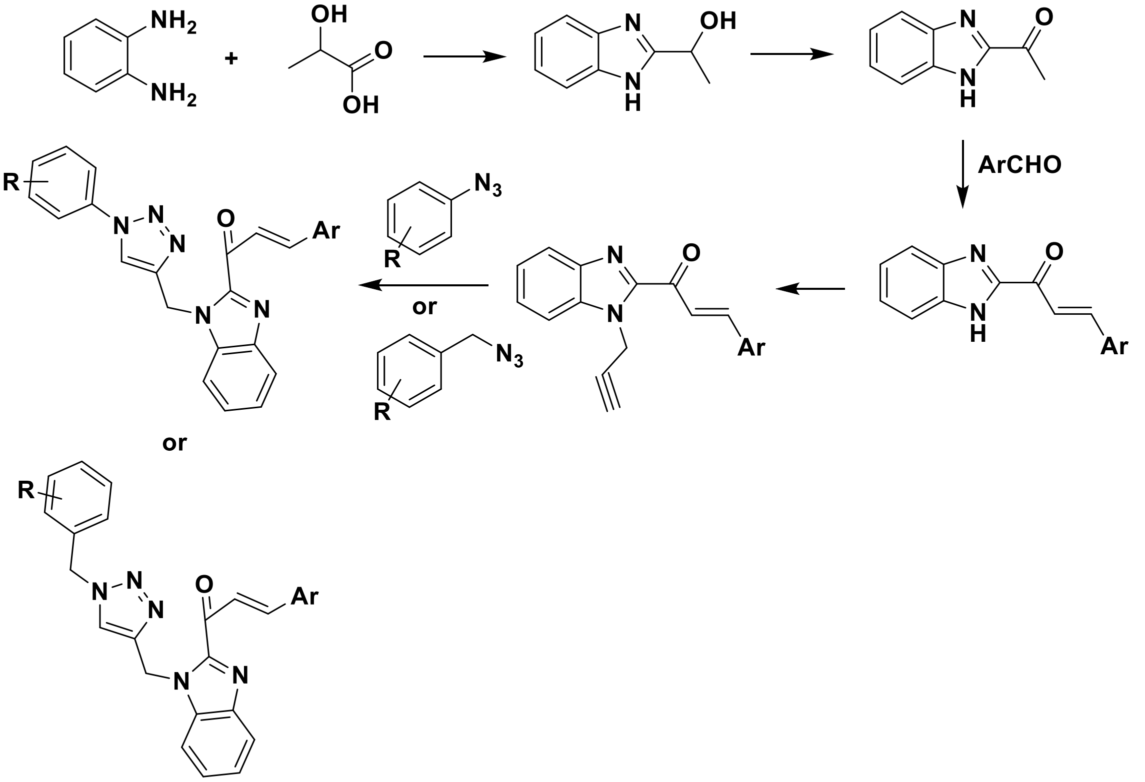
Ar = Ph; 4-OMe-C_6H_4; 4-CHO-C_6H_4; 1-naphthyl; 4-F-C_6H_4; 3-thienyl; 3-Me-C_6H_4; 4-C_2H_5-C_6H_4; 4-MeCO-C_6H_4; 4-Cl-C_6H_4; 4-Br-C_6H_4; 2-OMe-C_6H_4; 2-F-C_6H_4; 2-thienyl; 3-CF_3-C_6H_4; 6-(1-cyclohexyl-1*H*-benzo[d]imidazole); 5-(1-cyclohexyl-1*H*-benzo[d]imidazole)

Scheme 24. a) Representative compound skeletons with diversified aryl groups.



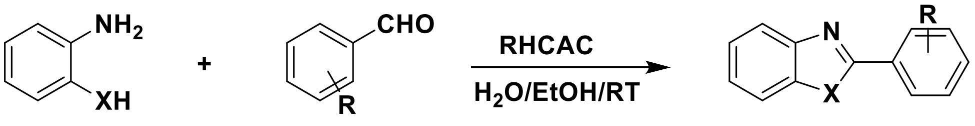
Scheme 24. b) 6-Substituted-8-(1-cyclohexyl-1H-benzo[d] imidazole-6-yl) imidazo [1,2-a] pyrazines.

Certain diversely substituted new series of 1,2,3-triazole-benzimidazole-chalcone hybrid compounds were designed and developed by Amar Djemoui et al.[xxxvii] *via* click chemistry by the reaction of substituted benzimidazole terminal alkynes with various azide compounds (Scheme 25). The authors prepared the key intermediates, N-propargyl benzimidazole chalcones starting from o-phenylene diamines and lactic acid in a four-step reaction sequence. The target compounds were synthesized by the reaction of the key intermediates with pre-synthesized azide derivatives employing click chemistry catalyzed by sodium ascorbate $CuSO_4.5H_2O$ at room temperature in good to excellent yields. The compounds having a chloro group and 1-N-benzyl-1,2,3-triazole moiety exhibited best cytotoxic effect on all the selected cell lines.



Scheme 25. 1,2,3-triazole-benzimidazole-chalcone hybrid compounds.

Archana Asatkar et al.[xxxviii] demonstrated the synthesis of N-benzimidazole, benzoxazole, benzothiazole derivatives in water/EtOH catalyzed by renewable and eco-friendly rice husk derived chemically activated carbon, from the condensation reaction of aromatic aldehydes with O-phenylenediamine, 2-aminophenol and 2-aminothiophenol (Scheme 26).

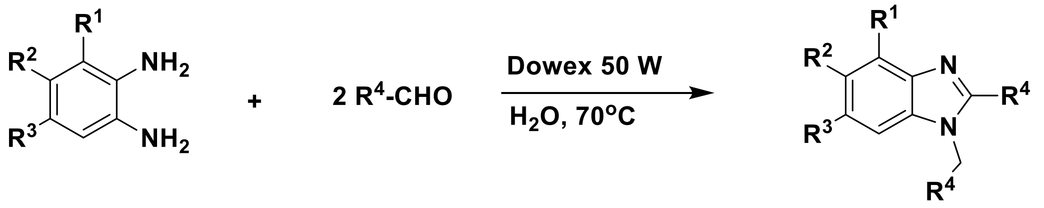


X = O; S; NH **R = H; 4-OMe; 4-Cl; 4-NO_2; 4-Br;**

Scheme 26. Synthesis of N-benzimidazole, benzoxazole, benzothiazole derivatives in water/EtOH.

The authors reported this protocol as a simple reaction with ease of isolation and purification of the products by recrystallization technique. The reaction mechanism involving RHCAC was also explained.

Chhanda Muhopadhyay and co-authors[xxxix] in an interesting research paper explained the exploration of Dowex 50W as an efficient and recyclable catalyst for an eco-friendly selective one-pot synthesis of a wide range of 2-aryl-1-aryl methyl-1H-benzimidazole derivatives obtained in very good yields. These title products were prepared by the condensation of O-phenylene diamines and aromantic/heteroaromatic/aliphatic aldehydes in water medium (Scheme 27).



R^1 = H; Me; R^2 = H; Me; Cl; R^3 = H; Me; Cl;

R^4 = Ph; 4-OMe-C_6H_4; 3-Br-C_6H_4; 4-OH-C_6H_4; 2-OMe-C_6H_4; 3-OMe-4-OH-C_6H_3; 3-OH-C_6H_4;; 2-Cl-C_6H_4; 4-NMe$_2$-C_6H_4; 4-Br-C_6H_4; 4-Cl-C_6H_4; 2-NO$_2$-C_6H_4; 4-NO$_2$-C_6H_4; 2-Furyl; 4-CN-C_6H_4; 3,4-(OMe)$_2$-C_6H_3; 2,5-(OMe)$_2$-C_6H_3; 4-Br-C_6H_4; ethyl; n-propyl;

Scheme 27. Preparation of 2-aryl-1-aryl methyl-1H-benzimidazoles catalyzed by Dowex 50W.

During the investigation, the authors compared the efficiencies of different catalysts like Amberlyst-15, Silica-H_2SO_4, Dowex-50, *L*-Proline, PSSA and Silica-$HClO_4$ for the above reaction under their experimental conditions. The advantage of the developed methodology did not envisage the need of column purification of the compounds. Probable mechanism was discussed. Other advantages of the protocol are formation of single regioisomeric product in case of unsymmetrical O-phenylene diamines, use of heterogeneous reusable, economically viable, Dowex-50w as a catalyst, wider applicability for various substrates and purification by recrystallization.

Anshu Dandia et al.[xl] prepared, characterized CdS, and Mn doped CdS nanoparticles and applied them as heterogeneous and recyclable catalysts for the chemo selective synthesis of benzothiazoles and benzimidazoles in water medium from the reaction of aromatic/hetero aromatic aldehydes with O-amino thiophenols and O-phenylene diamines (Scheme 28). Plausible mechanism was suggested by the authors.

R = H; 4-Br; 2-OMe; 4-OMe; 4-NO$_2$; 2-OH; 4-Me; 4-Cl;

R = H; 3-NO$_2$; 3-Cl; 2-Cl; 4-NO$_2$; 4-Me; 4-Cl; 4-OMe;

Scheme 28. Some representative structures of the products.

During the investigation, the catalytic efficiencies of $MeSO_3H$, PTSA, CAN, powder ZnS; Powder CdS; CdS Nps and Mn:CdS Nps were compared for the present reaction under the present experimental conditions. The authors attributed the efficient catalytic activity as well as improved product yield to the increased surface acidity of the catalyst.

CONCLUSION:

Last few decades have witnessed remarkable growth in the research frontiers of organic chemistry in general and heterocyclic chemistry in particular in the development of numerous scaffolds synthesized following eco-friendly methodologies. Wider scope can be visualized for the design and development of greener strategies towards building imidazole/benzimidazole derivatives ensuring rapid expansion of this active and key domain. This academic exercise is an attempt to bring together at one place the recent advances in imidazole chemistry involving aqueous medium synthesis. Scholars are advised to go through original research papers for thorough understanding of the topics represented here. All the structures are drawn briefly to give an idea about the chemical aspects of these contributions. We acknowledge and appreciate all the original contributors of the research papers and also their publishers cited herein.

ACKONWLEDGEMENTS: None
Research funding: None declared.

CONFLICT OF INTEREST: The authors declare no conflicts of interest regarding this chapter

REFERENCES:

i DeSimone R. W.; Currie K. S.; Mitchell S. A.; Darrow J. W.; Pippin D. A.; Privileged structures: applications in drug discovery; Comb Chem High Throughput Screen; 2004, **7**(5), 473–494.

ii Fei F.; Zhou Z.; Privileged scaffolds for the design of anti-cancer agents; Expert Opin Ther. Pat.; 2013, **23** (11), 1157–1179.

iii Gaba M.; Singh S.; Mohan C.; Heterocyclic compounds as potential anti-inflammatory agents A review; Eur. J. Med. Chem.; **2014**, *76*, 494–505.

iv Ingle R. G.; Magar D. D.; Synthesis and biological activity of some novel oxadiazoles; Int. J. Drug Res. Tech.; 2011, **1**, 26–32.

v Bhatnagar A.; Sharma P. K.; Kumar N.; Synthesis and medicinal properties of oxadiazole derivatives: A review; Int. J. PharmTech Res.; 2011, **3** (1), 268–282.

vi Narasimhan B.; Sharma D.; Kumar P.; Synthesis and antimicrobial activity of 1,3,4-oxadiazole derivatives. Med. Chem. Res.; 2011, **20** (7), 1119–1140.

vii Monika G.; Chander M.; 1,3,4-Oxadiazole: A biologically important scaffold in medicinal chemistry. Med. Chem. Res.; 2016, **25**, 173–210.

viii Gaba M.; Gaba P.; Uppal D.; Dhingra N.; Bahia M. S.; Silakari O.; Mohan C.; Design and synthesis of oxadiazole derivatives as anticonvulsant agents. Acta Pharm. Sin. B; 2015, **5**, 337–342.

ix Yadav G.; Ganguly, S.; Structure activity relationship (SAR) of 1,3,4-oxadiazole: A potent scaffold for drug development. Eur. J. Med. Chem.; 2015, **97**, 419–443.

x Sundberg R. J.; Martin, R. B.; Intermolecular forces in biological systems: Base stacking interactions in DNA; Chem. Rev.; 1974, **74**, 471–517.

xi Heinrich D.; Ueber eine neue Klasse von Basen. Justus Liebigs; Ann. Chem.; 1858, **107**, 199.

xii Wright J. B.; The chemistry of 1,2,4-triazoles; Chem. Rev.; 1951, **48** (3), 397–541.

xiii Radziszewski B.; Ueber die Bildung von Imidazolen; Chem. Ber.; 1882, **15**, 1493–1496.

xiv Gabriela S. S. A.; Corina D. D.; Loredana A. M.; Ion, G. Z.; Synthesis and cytotoxic activity of imidazole derivatives; Bioorg. Med. Chem. Lett.; 2009, **19**, 546–549.

xv Chhanda M.; Pradip, K. T.; Microwave-assisted green synthesis of benzimidazoles*;* Green Chem. Lett. Rev.; 2012, **5**, 109–120.

xvi Pranab G.; Amitava M.; $ZnCl_2$-catalyzed efficient synthesis of benzimidazole derivatives. Catal. Commun.; 2011, **12**, 744–747.

xvii Pranab G.; Amitava, M.; TFA-mediated synthesis of benzimidazoles under solvent-free conditions.; Tetrahedron Lett.; 2012, **53**, 6483–6488.

xviii Bahram D.; Davood N.; Mohamed, R. B. O.; An efficient synthesis of benzimidazoles using silica-supported reagents; Int. J. Electrochem. Sci.; 2012, **7**, 5990–5996.

xix Kabeer A. S.; Vishal A. P.; Parveen A. S.; Efficient synthesis of benzimidazole derivatives under solvent-free conditions; Chin. J. Chem.; 2012, **30**, 924–928.

xx Ngoc T. T.; Chan S. C.; Green synthesis of 2-substituted benzimidazoles using reusable catalyst; Bull. Korean Chem. Soc.; 2012, **33**, 4123–4126.

xxi Damodara N. K.; Basavoju S.; Ubaidulla U.; Ramesh, S.; Kumar A. R.; Microwave-assisted synthesis of benzimidazoles using ionic liquids; Green Chem.; 2013, **15** (3), 798–810.

xxii Mehdi K.; Mina S.; Iraj N.; Design, synthesis and biological evaluation of novel benzimidazoles; Med. Chem. Res.; 2014, **23**, 2947–2954.

xxiii Mahmoud A. E. A. A. E.-R.; Abdel-Ghany H.; Synthesis and antitumor activity of novel benzimidazole derivatives; J. Heterocycl. Chem.; 2014, **51**, 1322–1326.

xxiv Srinivas R. S.; Reddy G. B.; Babu T. R.; Swamy N. K.; Reddy K. S.; One-pot synthesis of 2-substituted benzimidazoles using green approach; Org. Chem. Int.; 2014, Article ID 403803.

xxv Sivakami R.; Sudhandiran G.; Sivakumar K.; Muthusamy S.; Magnetically recoverable Fe_3O_4@SiO_2-Py-IL catalyst for benzimidazole synthesis; RSC Adv.; 2015, **5**, 8571–8578.

xxvi Daryoush Z.; Mohsen A.; Sahar M.; Alireza R.; Shahram M.; Efficient synthesis of benzimidazole derivatives using reusable Cu catalyst; Synlett; 2016, **27**, 1251–1254.

xxvii Helio G. B.; Hugo M. C.; Luciana R. S.; Cristiane L. P.; Caio S. B.; Edson B. S.; Synthesis of new benzimidazole-based amino acid conjugates; Monatsh. Chem.; 2015, **146**, 1851–1857.

xxviii Santosh K.; Ashok P.; Nitin R.; Pankaj B.; Jitendra J.; Prashant S.; Benzimidazole-based fluorescent sensors for selective detection of metal ions; Sens. Actuators B; 2016**, 229**, 599–608.

xix Amanpreet S.; Pushap R.; Narinder S.; Benzimidazole-based fluorescent probe for selective detection of Zn^{2+}; ACS Appl. Mater. Interfaces; 2016, **8**, 28641–28651.

xxx Patil S. V.; Gaikwad N. D.; Bobade V. D.; Green synthesis of benzimidazoles using ferric sulfate catalyst; Arab. J. Chem.; 2016, **9**, 1649–1653.

xxxi Dileep K.; Sri Rama Murty M.; Efficient synthesis of benzimidazoles using silica-supported catalysts; J. Iran. Chem. Soc.; 2017, **14**, 1665–1671.

xxxii Jaya P.; Ramesh K.; Sreedhar B.; Muralikrishna R.; One-pot synthesis of benzimidazoles using copper catalyst; Catal. Lett.; 2017, **147**, 2724–2735.

xxxiii Ankita C.; Bharti P.; Vivek G.; Nitin R.; Synthesis and antimicrobial studies of novel benzimidazole derivatives; Tetrahedron; 2018, **74**, 5932–5941.

xxxiv Argha S.; Asim J.; Lokman H. C.; New fluorescent benzimidazole derivatives as chemosensors; New J. Chem.; 2018, **42**, 17909–17922.

xxxv Kanchan V.; Yogesh K. T.; Sarita K.; Esha R.; Monu A.; Mahendra K.; Efficient and environmentally sustainable domino protocol for the synthesis of diversified spiroheterocycles with privileged heterocyclic substructures using bio-organic catalyst in aqueous medium; Mol. Divers.; 2020, **24**, 1355-1365.

xxxvi Qubal S.; Dinesh K.; Chitra P.; Lalit M.; Rajeev K. S.; Bina G.; Design and synthesis of benzimidazole analogs as anticancer agents; Eur. J. Med. Chem.; 2019, **180**, 546–561.

xxxvii Djemoui A.; Amziane M.; Aissani N.; Allam W.; Belkacem N.; Chafi A.; Merazig H.; Berredjem M.; Synthesis and biological evaluation of new benzimidazole-based compounds; J. Mol. Struct.; 2020, **1204**, 127487.
xxxviii Asatkar A. K.; Mahajan M. R.; Mankar A. A.; Nandeshwar S. S.; Aswar A. S.; Development of novel benzimidazole hybrids for anticancer evaluation; Mater. Today Proc.; **2020**, 29, 738-742.
xxxix Chhanda M.; Soumita S.; Gouri, D.; Amitava M.; Solvent-free synthesis of benzimidazole derivatives and their biological evaluation; ARKIVOC; 2009, *(xiii)*, 1–22.
xl Anshu D.; Vijay P.; Kuldeep S. R.; $ZrOCl_2 \cdot 8H_2O$ catalyzed synthesis of benzimidazoles under microwave conditions; Catal. Commun.; 2012, **28**, 90–94.

Received on May 26, 2025.