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REVIEW ARTICLE

An overview on novel synthetic approaches and medicinal applications of benzimidazole compounds

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KEYWORDS

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Benzimidazoles;
Synthesis;
Biological activities

Abstract Benzimidazole, a benzene-fused heterocyclic compound, has acquired significant attention in the field of contemporary medicinal chemistry because of its wide array of pharmacological activities**.** Nitrogen containing heterocyclic compounds are part of several therapeutically important agents with several recent patents shedding light on their worth. For these reasons, this review is concerned with different methods for synthesis of benzimidazole derivatives and their biological importance.

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1. Introduction:

The benzimidazole nucleus consists of a benzene ring fused to an imidazole ring. The chemistry of benzimidazole has been an interesting field of study for a considerable time. It is one of the most promising moieties that is present in many clinically useful drugs and possesses various biological activities (Chen et al., 2015; Kamal et al., 2016).

The benzimidazole fragment fulfills the minimum structural requirements that are common for anti-inflammatory compounds (El-feky et al., 2014; Gaba et al., 2015). The natural and synthetic source of different benzimidazole derivatives play a vital role in medicinal chemistry. The structure similarity of 2-aminobenzimidazole with purine shed the light on the development of such nucleus for different biological activities (Alpan et al., 2009; Sweeney et al., 2021). It has been reported that several drugs containing the benzimidazole nucleus possess powerful analgesic properties as anti-inflammatory agents (Abdel-Alim, 2013). Moreover, there are many reports of the activity of benzimidazole-substituted molecules as anti-fungal (Küçükbay et al., 2003; KÜÇÜKBAY et al., 2011), antibacterial(Kankate et al., 2015), anti-hypertensive(Sharma, 2013), antiproliferative, anthelmintic(Karminski-zamola, 2012; Ts et al., 2013), antiviral(Evans et al., 2015), anti-infective (Zhang et al., 2012), male contraceptive(Chen et al., 2013), human glucagon receptor antagonistic(Guigón-lópez et al., 2015) and H3 antagonistic(Rizzati et al., 2016) agents. These molecules are also good inhibitors for lymphocyte tyrosine kinase (Lck)(Ella, 2016), and chemokine receptor (CXCR3) (Murayama et al., 2012) and 1*H*-benzimidazole derivatives are effective at blocking stomach damage caused by inflammation inhibitors(Arora et al., 2014) (Fig. 1). This review gives a recent overview of the synthesis of different benzimidazole derivatives and covers the most recent medicinal application of benzimidazole compounds.

2. General synthesis of benzimidazoles

Generally, benzimidazole compounds can be synthesized from the reaction of *ortho*-diaminobenzene derivatives with various reagents Fig. 2.

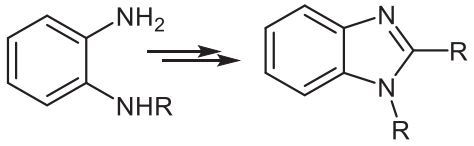


Fig. 2 General synthetic route for benzimidazole.

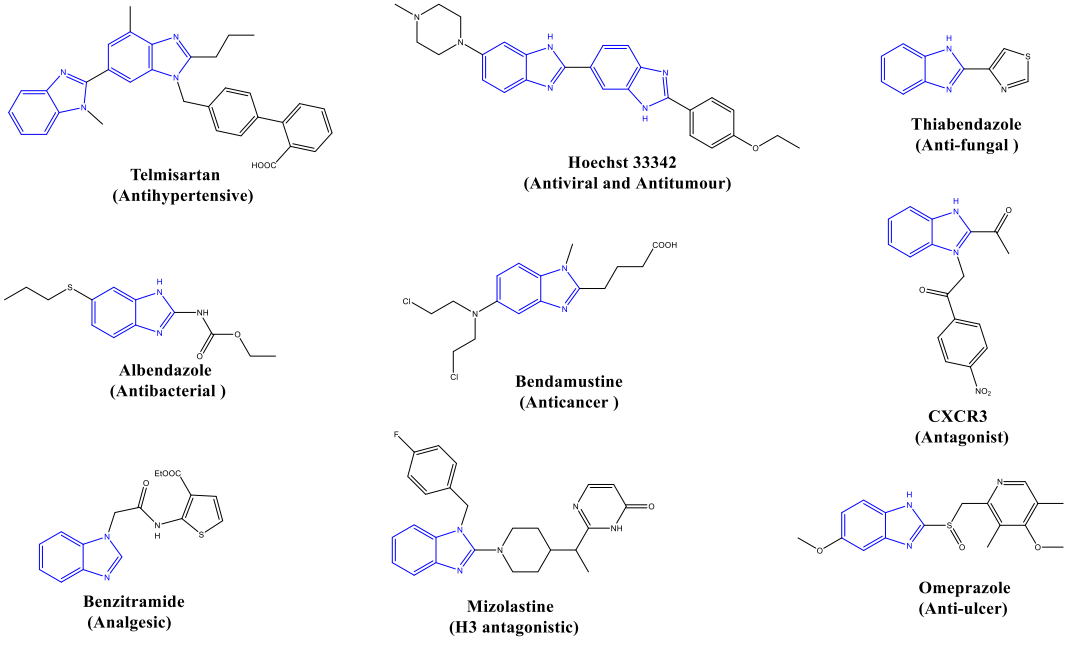
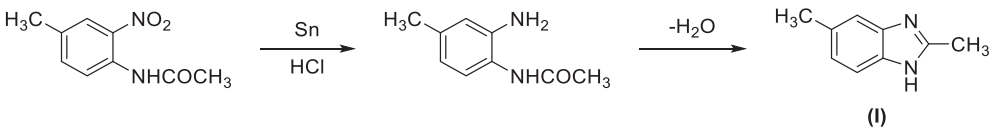
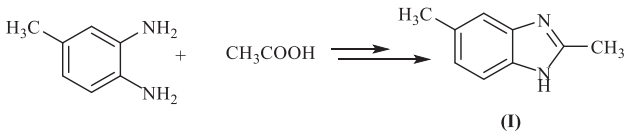


Fig. 1 Marketed drugs having benzimidazole moiety.



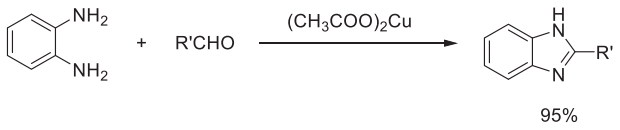
(I)

Scheme 1 First preparation of a benzimidazole derivative.



(I)

Scheme 2 General synthesis of benzimidazole from *o*-phenylenediamine.



95%

Scheme 4 Copper acetate catalyzed synthesis of benzimidazole derivatives.

Benzimidazole chemistry is of great interest since it was discovered that the 5,6-dimethylbenzimidazole moiety is a portion of the chemical structure of vitamin B12 (Brink and Folkers, 1949).

Historically the first benzimidazole was synthesized by Hoebrecker (Wright, 1951), through the reduction and dehydration of 2-nitro-4-methylacetanilide (Scheme 1).

Concurrently, Ladenburg (A. Ladenburg, 1875) obtained the same compound **I,** 2,5-dimethylbenzimidazole, by heating 3,4-diaminotoluene under reflux with acetic acid (Scheme 2).

Today, benzimidazoles play a considerable role in the pharmaceutical field and there are several reports of their synthesis through different reaction media and from different active starting compounds. The presented review summarizes different methods for the preparation of benzimidazole derivatives under different conditions.

2.1. From o-phenylenediamines:

2.1.1. Through condensation with aldehydes:

Under several conditions, 2-substituted benzimidazoles can be synthesized from the reaction of substituted aldehydes and *o*-phenylenediamines (Scheme 3).

Since the reaction undergoes through an oxidation process this can be caused by the air or more smoothly by using other oxidizing agents.

It was reported that, palladium (Saha et al., 2009; Shashi and Krishna, 2016) and copper-based catalysts can be used for preparation of benzimidazole derivatives through cross-coupling reactions of *o*-phenylenediamine with alkyl, aryl, and heterocyclic aldehydes in good yields Scheme 4.

Benzimidazole derivative **II** is prepared *via* the reaction of the corresponding *o*-phenylenediamine derivative with 2,4-dichlorobenzaldehyde in the presence of sodium metabisulphite (Suheyla Ozbey, F. Betul Kaynak, Canan Kus, 2002) Scheme 5.

Venkateswarlu *et al*. described the preparation of benzimidazole derivatives by lanthanum chloride catalysis in a one-pot synthesis from different aldehydes and *o*-phenylenediamine (Venkateswarlu et al., 2013) (Scheme 6).

K.S. Jithendra Kumara *et al*. achieved the synthesis of benzimidazole derivatives **III** and **IV** in high yield using cobalt ferrite nanoparticles ($Co@Fe_2O_4$) and silica-coated cobalt ferrite nanoparticles ($SiO_2/Co@Fe_2O_4$) as efficient catalysts for the cross-coupling reaction of *o*-phenylenediamine and different aldehydes (Kumara et al., 2017) Scheme 7.

Rushi *et al*. have reported that 2-substituted benzimidazoles have been prepared in a good yields in a single pot reaction under solvent-free conditions through condensation of aldehydes and *o*-phenylenediamine in the presence of a catalytic amount of [$In(OTf)_3$] at room temperature (Trivedi et al., 2006) (Scheme 8).

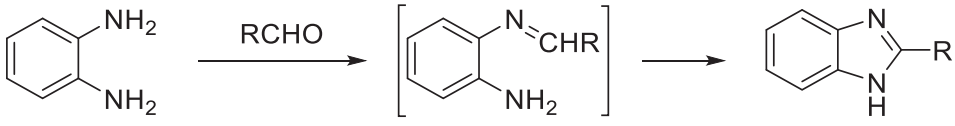
Deep eutectic solvents (DES) are green solvents used in several areas of industrial chemistry. A recent study investigated the selective synthesis of benzimidazole derivatives with the DES chlorine chloride/urea as an eco-friendly solvent.

The reaction proceeded by dissolving *o*-phenylenediamine in ChCl:urea DES followed by addition of benzaldehyde in different ratios producing different benzimidazole derivatives (Scheme 9) (Gioia et al., 2019).

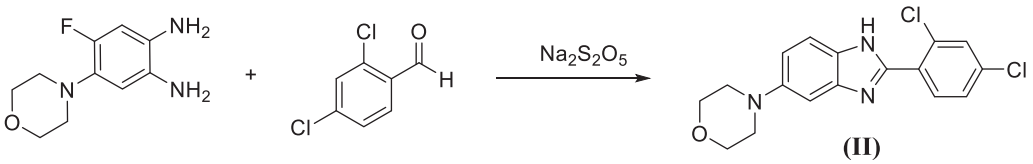
V. Kadu, *et al*., presented an ecofriendly and low-cost protocol for the synthesis of 1,2-disubstituded benzimidazoles using an aqueous extract of pods of *Acacia Concinna*, which reduce the hazardous effect of halogenated organic solvents (Scheme 10) (Kadu et al., 2019).

L. Hao *et al*., reported an effective procedure for synthesis of benzimidazoles in high yield using gold nanoparticle catalysts such as Au/TiO_2, Au/Al_2O_3, Au/ZnO (Scheme 11) (Leiduan Hao, Yanfei Zhao, Bo Yu, Hongye Zhang, 2014).

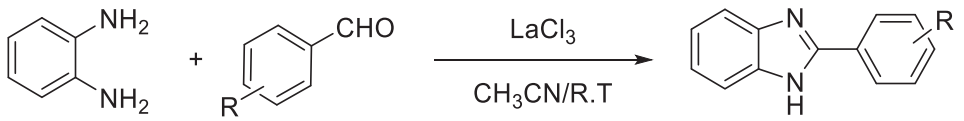
On the other hand, recent research is focused on developing these conditions with green conditions through transition metal catalysts. A different research achieved synthesis of benzimidazole derivatives from condensation of o-



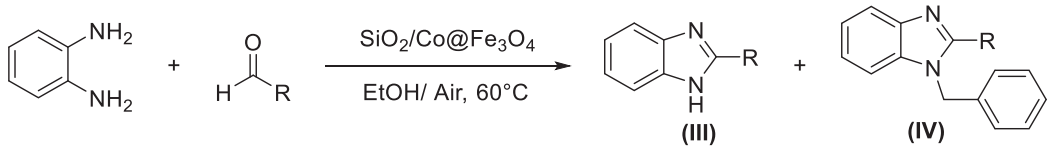
Scheme 3 General synthesis of benzimidazole from *o*-phenylenediamine and aldehyde.



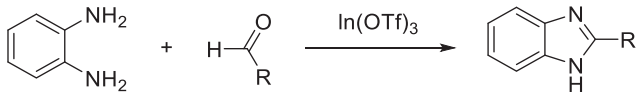
Scheme 5 Sodium metabisulphite catalyzed synthesis of a benzimidazole.



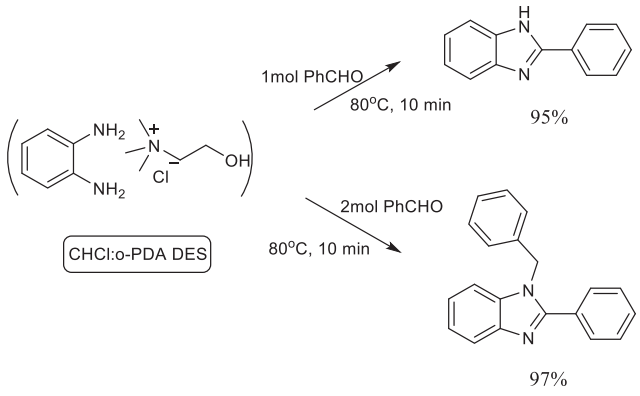
Scheme 6 One-pot synthesis of benzimidazole derivatives by lanthanum chloride catalysis.



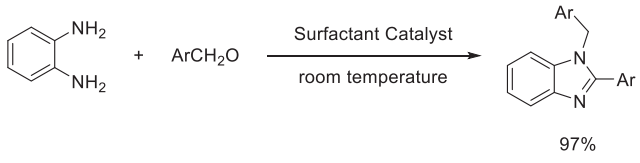
Scheme 7 Using cobalt ferrite nanoparticles for the synthesis of benzimidazole compounds.



Scheme 8 Synthesis of benzimidazole under solvent-free conditions.

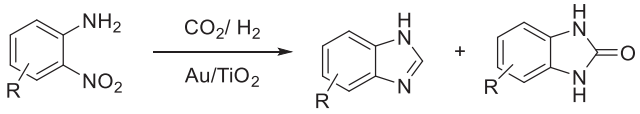


Scheme 9 Synthesis of different benzimidazoles in DES green solvent.



Scheme 10 Synthesis of benzimidazole derivatives with a surfactant catalyst.

phenylenediamine with different aldehydes in the presence of different transition metal nanoparticle catalysts. *Inamdar et al.,* synthesized new benzimidazole derivatives in good yield



Scheme 11 Synthesis of benzimidazole derivatives using gold nano particle catalysts.

(76–93%) in the presence of Si-CuO nanoparticle catalyst (CuOnp-SiO_2 10%) (Scheme 12). While *Esfahani et al.*, achieved the synthesis of benzimidazole derivatives in 88–97% yield using the nano catalyst CuII 0.34 mol % (Cu (II)-TD@nSiO2, nanosilica triazine dendrimers) (Mahboobeh Nasr-Esfahani, Iraj Mohammadpoor-Baltork, Ahmad Reza Khosropour, Majid Moghadam, Valliolah Mirkhani, 2013; Singhal et al., 2019)

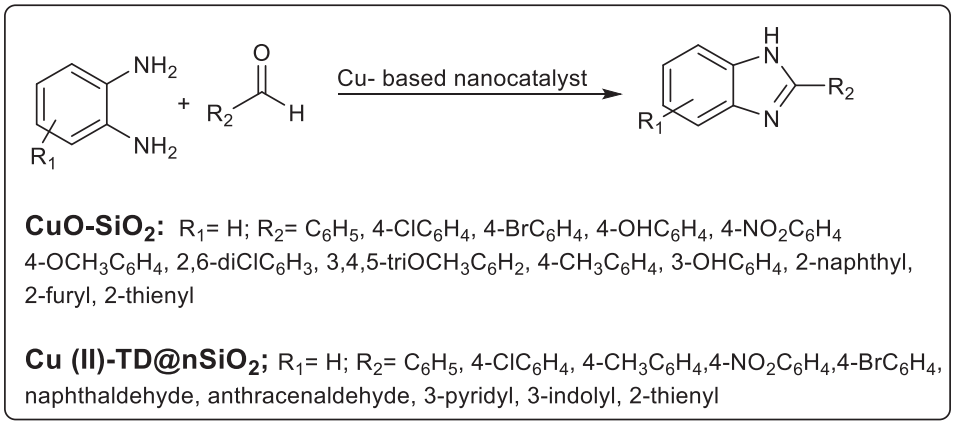
Similarly, *Kommula et al*. achieved synthesis of 2 arylbenzimidazoles using nano-Fe_2O_3 catalyzed with 70–85% yield, and *Bardajee et al*. performed the same reaction by using Fe (III)-Schiff base/SBA-15 as an effective catalyst in water in excellent yield (79–92%) (Ghasem Rezanejade Bardajee , Marzieh Mohammadi, Hasan Yari, 2015; Kommula et al., 2017).

2.1.2. Through condensation with Ketones:

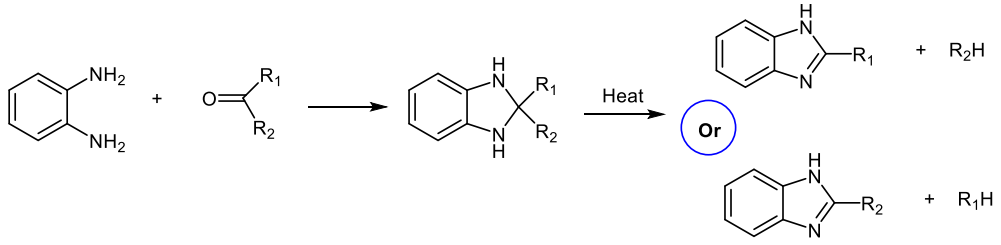
A large number of benzimidazole derivatives have been synthesized through the condensation reaction of *o*-phenylenediamine with different ketones under the general proposed pathway (Scheme 13) (Alaqeel, 2017).

The reaction of *o*-phenylenediamine with a ketone afforded the unstable 2-disubstituted benzimidazolines, which undergo decomposition to a mixture of benzimidazole derivatives depending on which of alkyl group, is eliminated (Scheme 13).

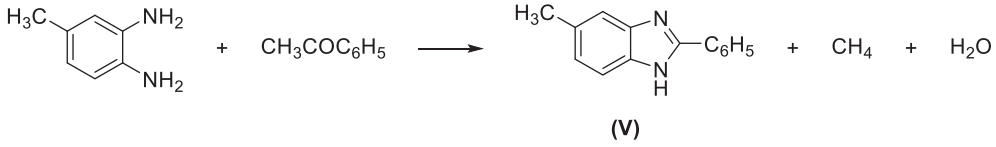
Similarly, Ladenbrug and Rugheimer reported the synthesis of 2-phenyl-5(or 6)-methylbenzimidazole by heating 3,4-diaminotoluene with acetophenone at 180 °C. In this case,



Scheme 12 Synthesis of different benzimidazole derivatives using Cu-based nanocatalyst.



Scheme 13 General procedure for synthesis of benzimidazole from ketones.



Scheme 14 Synthesis of benzimidazole using acetophenone.

the methyl group is the one, which is eliminated affording benzimidazole **V** (Scheme 14).

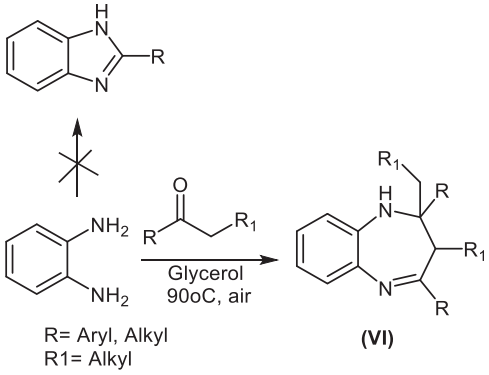
Because of several limitations of this type of reaction, such as long reaction time, difficult work up procedures, and formation of by products, better reaction conditions, such as solvent free, ionic liquid, and different catalysts have been studied.

Unfortunately, these reactions did not proceed as predicted and afforded other heterocyclic compounds rather than the desired benzimidazoles.

For instant, Catia S.Radatz *et al*., reported that the reaction of *o*-phenylenediamine and acetophenone or other ketones using glycerol as an eco-friendly and recyclable solvent at low temperature afforded benzodiazepine **VI** in low yield with the same product formed in high yield at higher temperatures, but no reaction occurred in absence of glycerol (Scheme 15) (Radatz et al., 2011).

C. S. Digwal *et al*., found that the reaction of *o*-phenylenediamine derivatives with benzil in the presence of $VOSO_4$ as a catalyst produced the 2,3-diphenyl quinoxaline derivatives **VII** instead of benzimidazole derivatives (Scheme 16) (Digwal et al., 2016).

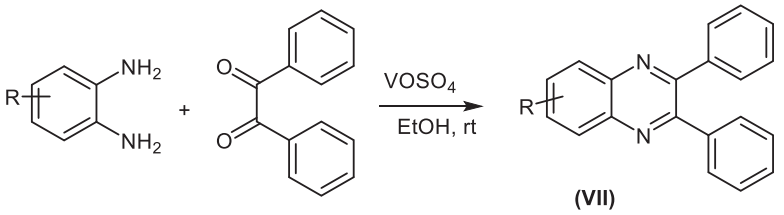
However, P. Dhanalakshmi *et al*., achieved the preparation of benzimidazole derivatives from α,β-unsaturated ketones



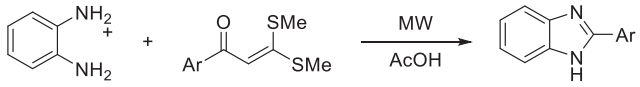
Scheme 15 Reaction of *o*-phenylenediamine with ketones in glycerol as a solvent.

with *o*-phenylenediamine both thermally or with microwave irradiation in good yields (Scheme 17) [28].

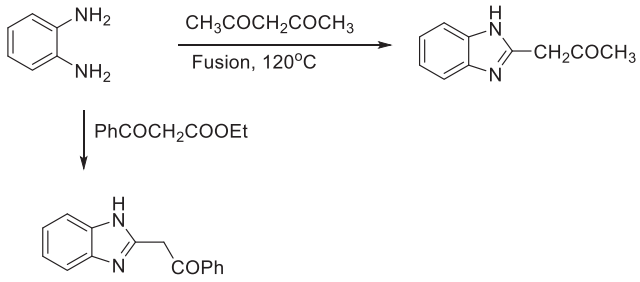
On the other hand, *o*-phenylenediamine undergoes cyclization when reacted with 1,3-dicarbonyl compounds under moderate heating in alcohol afforded the corresponding



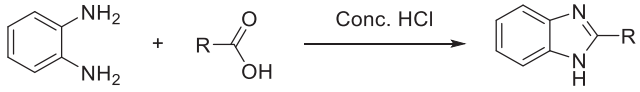
Scheme 16 Reaction of *o*-phenylenediamine with ketone using $VOSO_4$ as a catalyst.



Scheme 17 Synthesis of benzimidazoles from α,β-unsaturated ketones.



Scheme 18 Synthesis of benzimidazole from reaction of 1,3-dicarbonyl compounds.



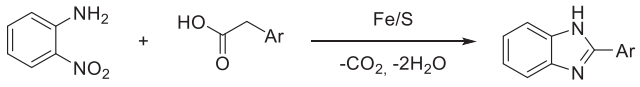
Scheme 19 General synthesis of benzimidazoles from carboxylic acids.

benzimidazole derivatives (Scheme 18) (Abdallah et al., 2015; Rafat M. Mohareb, 2020)

2.1.3. Through condensation with carboxylic acids

Several reports show that numerous benzimidazole derivatives have been synthesized from the reaction of *o*-phenylenediamine with carboxylic acids. The most common procedure involves condensation of these two reagents in the presence of concentrated hydrochloric acid (Scheme 19) (Alaqeel, 2017).

T. Ahmed *et al.*, reported the synthesis of new 2-substituted benzimidazole derivatives in good yield by refluxing an equimolar ratio of *o*-phenylenediamine and *p*-aminobenzoic acid in xylene and polyphosphoric acid for only 6 h (Ahmad et al., 2017) (Scheme 20).



Scheme 21 Fe/S catalytic redox condensation reaction for synthesis of benzimidazoles.

T. Nguyen *et al.*, reported an efficient Fe/S catalytic redox condensation reaction for the synthesis of benzimidazole derivatives from phenylacetic acid and *o*-nitroaniline in high yields and with no organic by-product (Scheme 21) (Nguyen et al., 2014).

The synthesis of benzimidazole-2-thiol derivatives was achieved by the condensation of *o*-phenylenediamine with mercaptoacetic acid under reflux. This can be followed by cyclization with chloroacetic acid or a different aromatic aldehyde to afford biologically active polynuclear fused benzimidazole derivatives (Ranza A. Elrayess, Nagat Ghareb, Marwa M. Azab, 2013) (Scheme 22).

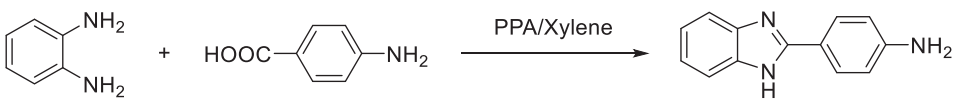
Recently, T. Huynh *et al.*, reported an efficient green synthesis of benzimidazole derivatives through condensation of *o*-phenylenediamine and mono-carboxylic acids under catalyst-free microwave irradiation (Huynh et al., 2020) (Scheme 23).

2.2. Via rearrangement

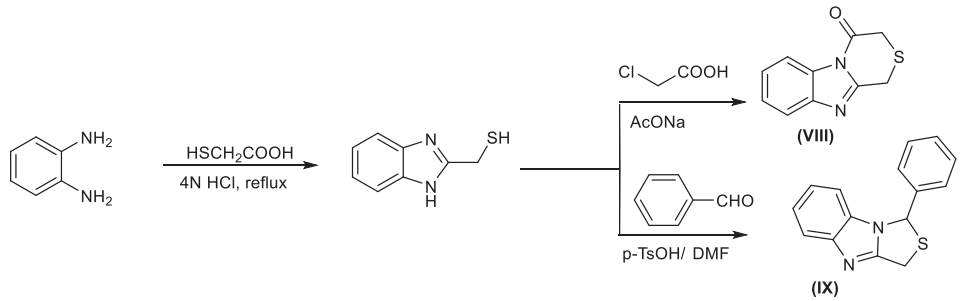
In addition to the condensation reactions described in the preceding section, some more efficient and convenient routes to benzimidazoles and benzimidazole-2-ones have been achieved through the rearrangement of different heterocyclic compounds as described below.

2.2.1. Rearrangement of Benzodiazepinones

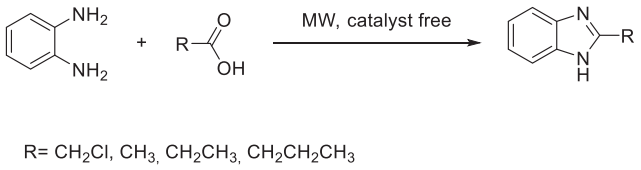
Refluxing a mixture of *ortho*-diaminobenzene with ethyl acetoacetate in boiling xylene afforded 4,7-dihydro-5-methyl-1*H*- 2,3-benzo-1,4-diazepin-7-one **X** but when the same reaction was carried out in the presence of potassium hydroxide the product was 1-isopropenylbenzimidazol-2-one (**XI**). It was proposed that the reaction takes place through elimination of molecule of ethanol followed by C-2-C-3 bond breakage



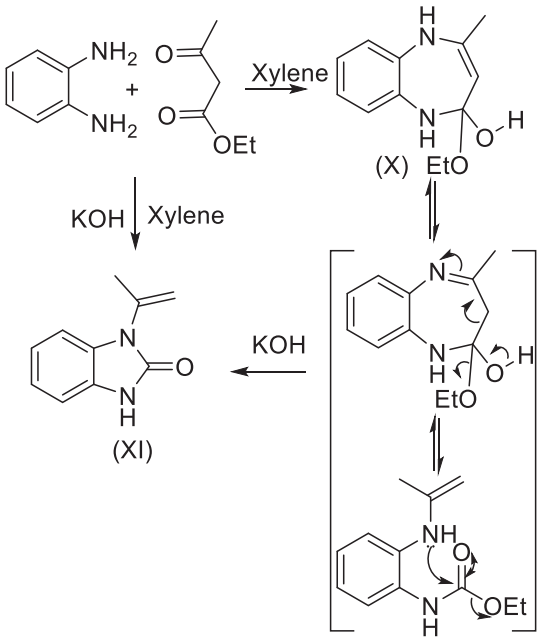
Scheme 20 Synthesis of benzimidazole from aromatic carboxylic acid.



Scheme 22 Synthesis of polynuclear fused benzimidazole derivatives.



Scheme 23 Synthesis of benzimidazole derivative under microwave irradiation.

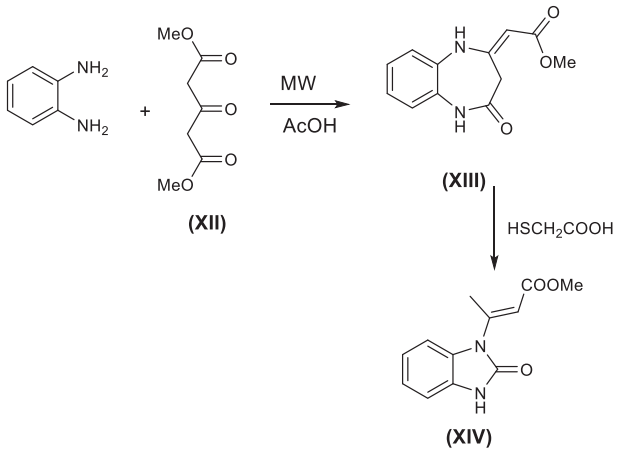


Scheme 24 General procedure for synthesis of benzimidazolone *via* rearrangement of benzodiazepinones.

with a subsequent intramolecular nucleophilic reaction (cf. Scheme 24) (Mamedov and Zhukova, 2017).

It was mentioned that this type of reaction could also occur with other dicarbonyl compounds.

El eftheriadis *et.al.*, reported that benzimidazolone derivative **XIV** was prepared from the reaction of *o*-phenylenediamine with dimethylacetone dicarboxylate (**XII**) through the formation of diazepine derivative **XIII**, which undergoes rearrangement *via* action of mercaptoacetic acid to afford the benzimidazolone **XIV** (cf. Scheme 25) (Eleftheriadis et al., 2013).



Scheme 25 Synthesis of benzimidazolone *via* rearrangement of benzodiazepinones.

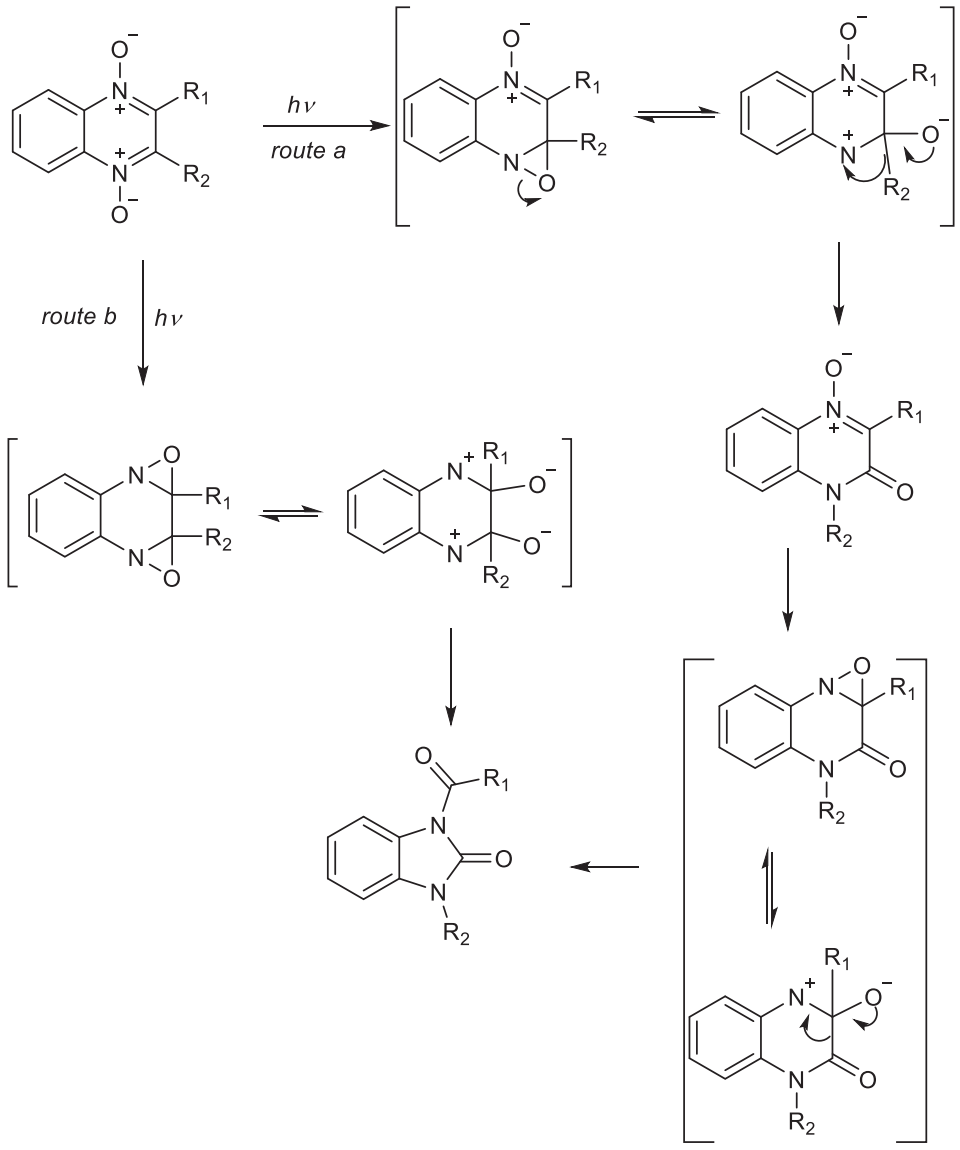
2.2.2. Rearrangement of quinoxaline derivatives

It was reported some time ago that different benzimidazole derivatives can be synthesized through rearrangement of quinoxaline-1,4-dioxides. Recent studies revealed that the rearrangement process occurs through the formation of quinoxaline-2-one as an intermediate (Scheme 26). This study prompted a search for more effective methods for the preparation of benzimidazole derivatives from quinoxalinone compounds in good yield with high efficiency and broad functional group tolerance (Mamedov and Zhukova, 2017).

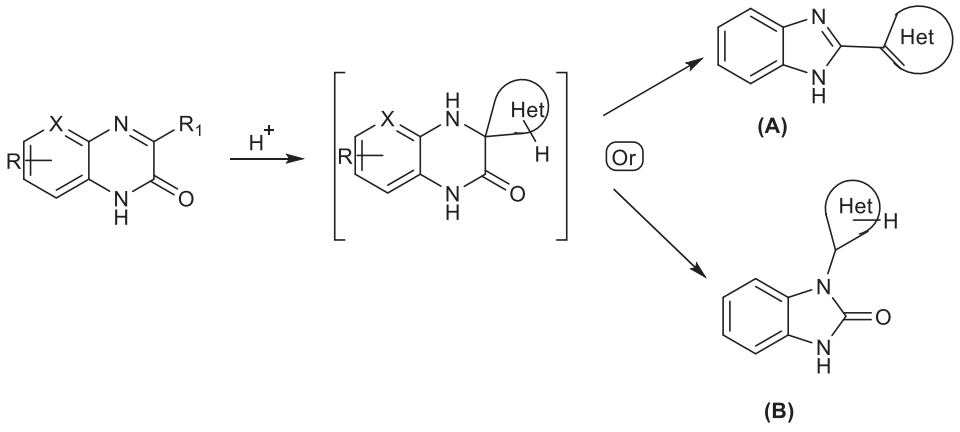
On the basis of the previous studies, recent work uses quinoxalin-2(1*H*)-ones for synthesis of different benzimidazole derivatives through an acid-catalyzed rearrangement pathway as shown in Scheme 27. (Mamedov and Zhukova, 2017; Zhukova and Mamedov, 2017) It was shown that benzimidazole derivative **A** was formed only in the presence of at least one hydrogen atom in the spiro-forming intermediate. Without presence of a hydrogen atom, benzimidazolone **B** will form with migration of the spiro-forming moiety to the 1-position.

This method possesses great advantages; for instance, it proceeds at a high rate and in high yield even under mild conditions. Moreover, it can be used with a broad range of substrates.

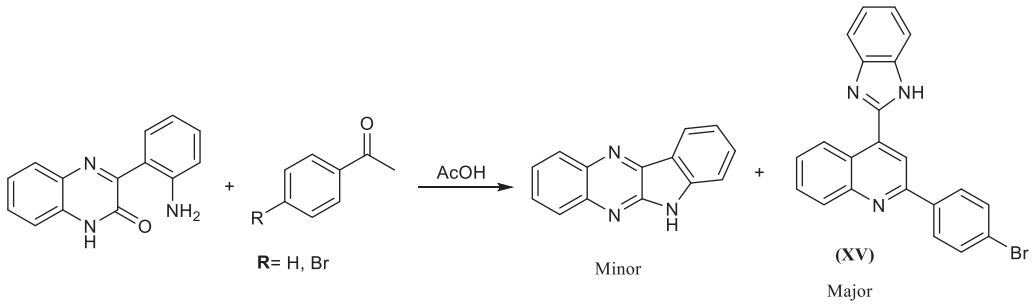
V. A. Mamedov *et al.*, developed an efficient procedure for synthesis 4-(benzimidazol-2-yl)quinolines (**XV**) from the reaction of 3-(2-aminophenyl)-quinoxalin-2(1*H*)-one with acetophenone (cf. Scheme 28) (Mamedov et al., 2014).



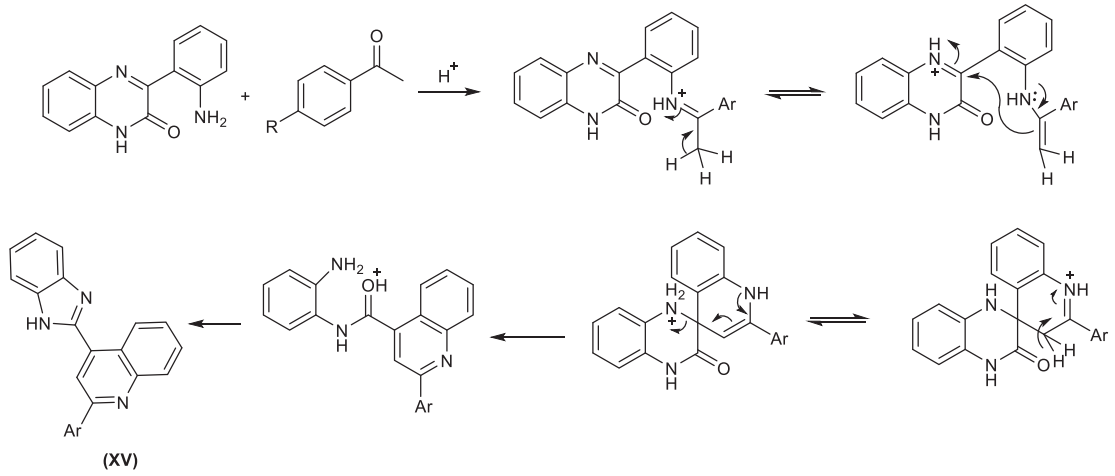
Scheme 26 Mechanistic pathway of imidazolone preparation from quinoxaline-1,4-dioxides.



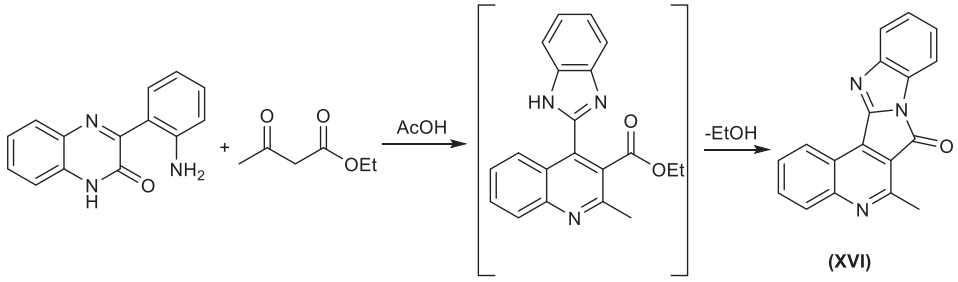
Scheme 27 Rearrangement of quinoxalin-2(1*H*)-ones to the related benzimidazole and benzimidazolone derivatives.



Scheme 28 Synthesis of benzimidazole derivative from quinoxalinone and acetophenone.



Scheme 29 Suggested mechanism for the synthesis of a benzimidazole derivative from quinoxalinone and acetophenone.



Scheme 30 Synthesis of polynuclear fused imidazole derivatives *via* rearrangement of quinoxalinone compounds.

It was suggested that compound **XV** formed through intramolecular nucleophilic addition of the imine formed as shown in Scheme 29.

The structure of imidazolone **XV** has been determined by X-ray crystallography (Fig. 3).

This approach was later extended to the reaction of 3-(2-aminophenyl)-quinoxalin-2(1*H*)-one with ethyl acetoacetate in the presence of acetic acid to construct the polynuclear fused benzimidazol derivative **XVI**, which is difficult to prepare by any other process(Mamedov et al., 2014) Scheme 30.

In the context of work toward the quinoxaline–benzimida zole rearrangement, Vakhid A. Mamedov *et al.*, developed a new method based on the acid-catalyzed rearrangement of 3′-aryl-1,2,3,4,4′,5′-hexahydrospiro[quinoxalin-2,50- pyrazol]-3-ones **XVIIIa-f**, which are obtained from the reaction of 3-ary lacylidene-3,4-dihydroquinoxalin-2(1*H*)-ones with hydrazine hydrate (Scheme 31) (Mamedov et al., 2009).

The molecular structures of the spiro-compound **XVIIIe** and imidazole **XIXa** were determined by x-ray crystallography (Fig. 4).

In a related transformation, the 3-aroylquinoxalin-2(1*H*)-ones **XXa,b** behave in a similar way when condensed with *o*-phenylenediamine under refluxing acetic acid (Mamedov et al., 2010). Scheme 32.

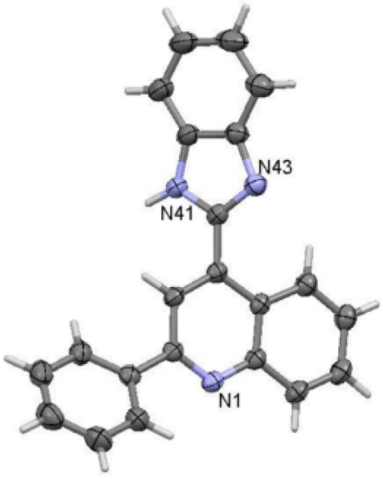
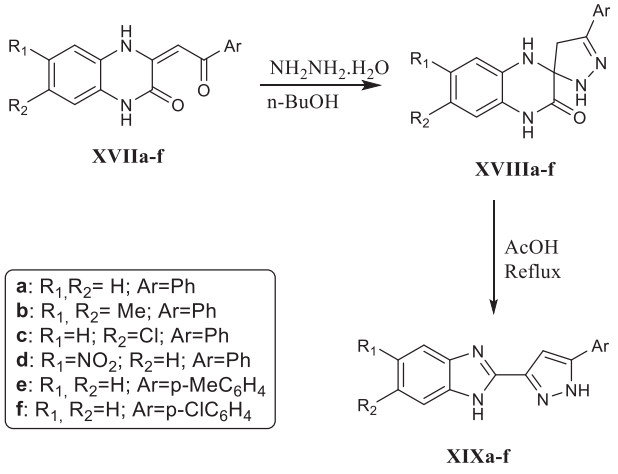


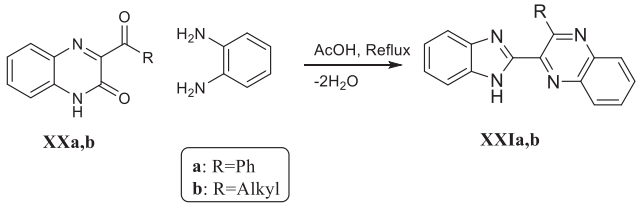
Fig. 3 Crystal structure of imidazole **XV**.



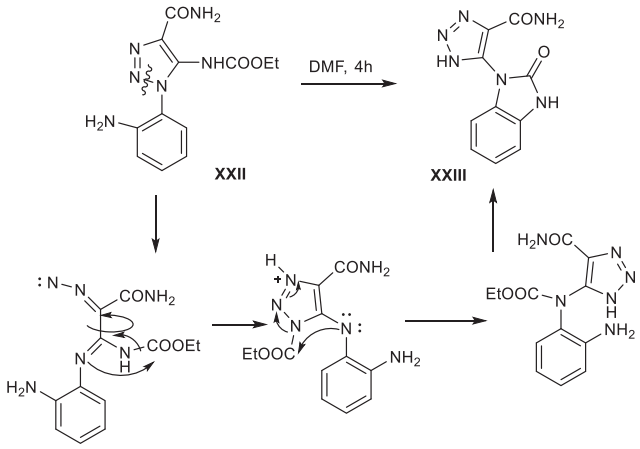
Scheme 31 Acid catalyzed quinoxaline–benzimidazole rearrangements.

2.2.3. Rearrangement of 1,2,3-triazole

A further approach for an efficient synthesis of benzimidazolone derivatives *via* a rearrangement process was demonstrated for active 1,2,3-triazole derivatives.



Scheme 32 Synthesis of benzimidazole derivatives through acid-catalyzed rearrangement in the quinoxalinone-*o*-phenylenediamine system.



Scheme 33 Synthesis of benzimidazole **XXIII** from the triazole derivative **XXII**.

It was reported that benzimidazolone derivative **XXIII** was formed upon refluxing a solution of 5-amino-4-carbamoyl-1-(2-nitrophenyl)-1*H*-1,2,3-triazol (**XXII**) for 4 h (Scheme 33) (Mamedov and Zhukova, 2017).

3. Benzimidazole based bioactive compounds

The biological importance of benzimidazole derivatives began in earnest in 1994 when it was noted that the benzimidazole moiety resembled the purine structure. Then it was discovered by Brink that 5,6-dimethylbenzimidazole is produced from Vitamin B12 degradation. According to these initial studies, it was reported that compounds containing the benzimidazole moiety possess important pharmacological applications

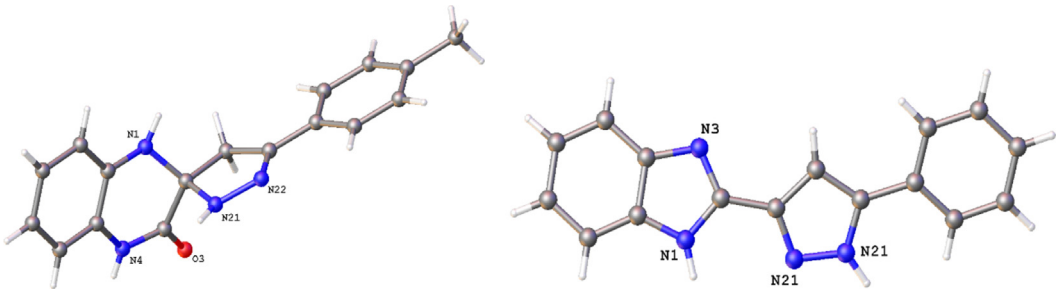
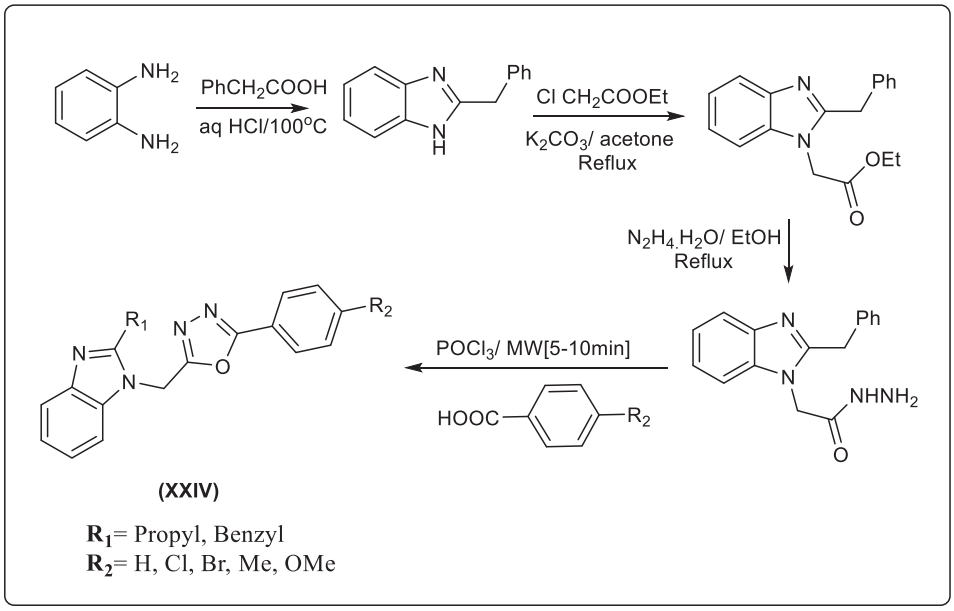


Fig. 4 ORTEP drawing of **XVIIIe** and **XIXa**. Displacement ellipsoids are drawn at the 30% probability level. H atoms are represented by circles of arbitrary size.



Scheme 34 Benzimidazoles bearing oxazole moieties as antibacterial compounds.

including as anticancer, antimicrobial, analgesic, antiviral, and antifungal agents(Bansal and Silakari, 2012; Durmaz et al., 1997; Küçükbay and Durmaz, 1997; Narasimhan et al., 2012; Yadav and Ganguly, 2015). On the other hand, there are recent studies which revealed that different benzimidazole carbamates (BZC) such as Albendazole, Mebendazole, Flubendazole and Fenbendazole have an inhibition effect on *in vitro* growth of Trichomonas vaginalis and G. lamblia. Furthermore, the clinical reports have shown their treatment of giardiasis (Valdez et al., 2002). Literature indicates that the benzimidazole derivatives are active agents against many micro-organisms and useful for the development of new drugs in the pharmaceutical field (Fig. 5) (Hiroyuki Nakano, Tsutomu Inoue, Nobuhide Kawasaki, Hideki Miyataka, Hitoshi Matsumoto, Takeo Taguchi, Naoki Inagaki, Hiroichi Nagai, 1999; Valdez et al., 2002).

3.1. Antimicrobial activities of benzimidazole derivatives

A large series of benzimidazole derivatives have shown broad effects against different types of microbes including bacteria and fungi. Several studies of the effective benzimidazole derivatives revealed that the presence of bulky groups at position 1 and 2 and small alkyl groups at other positions give the optimum antimicrobial effect (Bansal and Silakari, 2012; Güngördü et al., 2013) (Fig. 6).

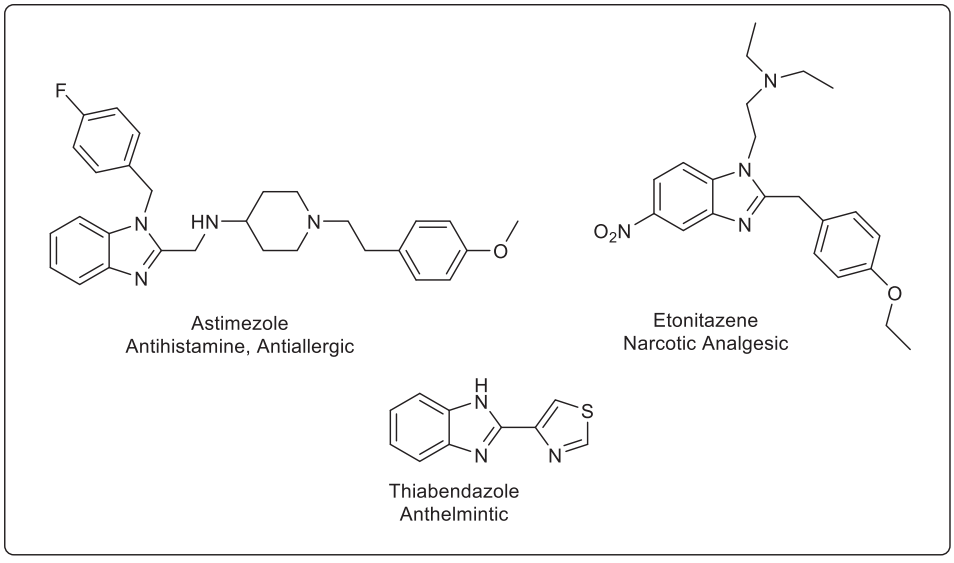


Fig. 5 Different benzimidazole derivatives as drugs for different therapeutic field.

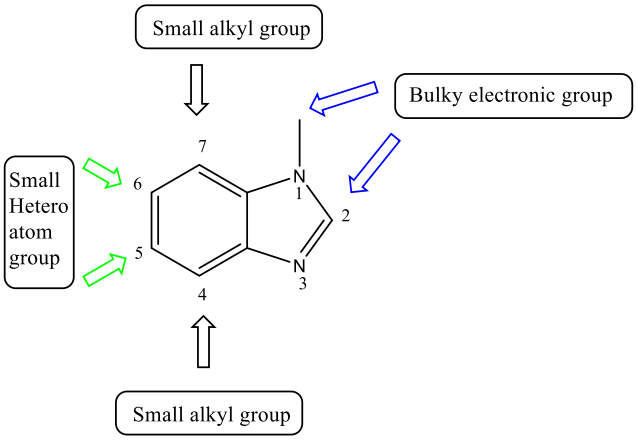


Fig. 6 Benzimidazole structure for optimum antimicrobial activity.

Gowda *et al*., developed a new series of 2-substituted-1-[(5-substituted-phenyl-1,3,4-oxadiazole-2-yl)methyl-1*H*-benzimidazoles (**XXIV**) with high antibacterial activity with 50- and 250 μg/mL MBC (minimum bactericidal concentration) against Gram negative bacteria E. coli and Gram positive bacteria S. aureus and Pseudomonas aeruginosa compared with the standard Ampicillin which showed 50- and 100 μg/mL MBC (Gowda et al., 2010). Scheme 34.

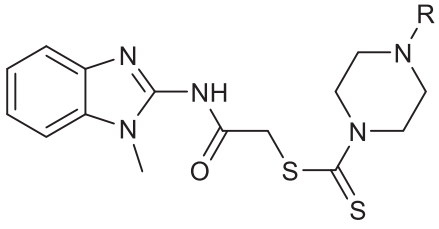


Fig. 7 1,2-disubstituted benzimidazole derivatives as antimicrobial compounds.

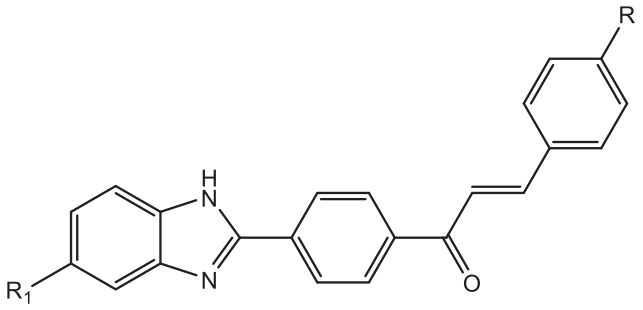


Fig. 9 Benzimidazole clubbed chalcone derivatives as antibacterial compounds.

Mehlika Dilek *et al*., reported a new class of benzimidazole compounds and screened them against the bacterial species Pseudomonas Aeruginosa, Staphylococcus aureus and Escherichia coli, and for antifungal activity against *Aspergillus flavus*, *Aspergillus Niger* and *Fusarium Solani* (Altintop et al., 2015) (Fig. 7). These showed good activity as compared with the standard ketoconazole as an antifungal and streptomycin as an antibacterial.

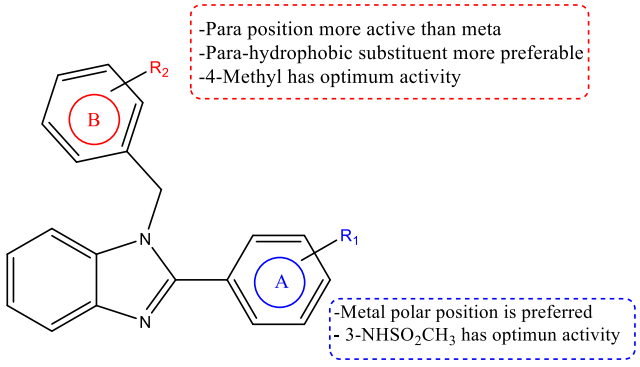


Fig. 10 The structure–activity relationship of antibacterial 1,2-disubstituted benzimidazole derivatives.

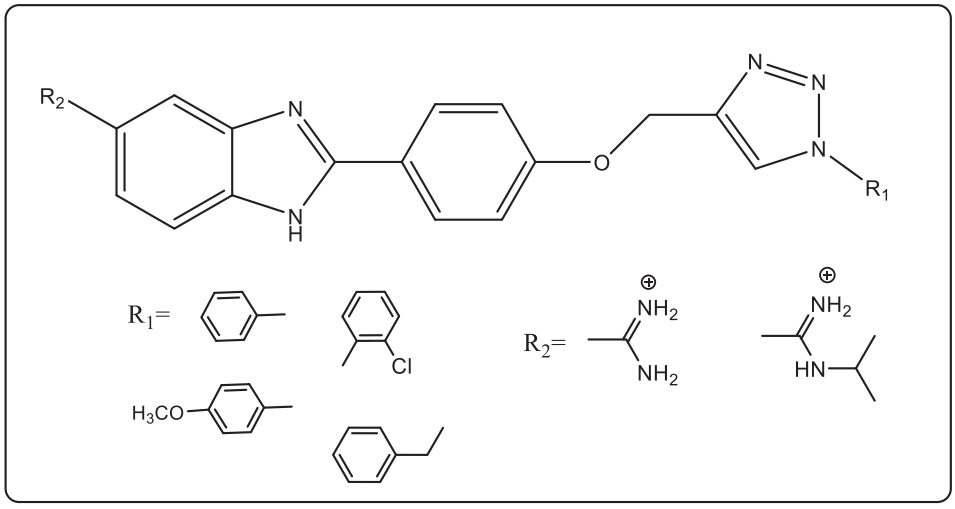


Fig. 8 Biologically active benzimidazoles linked to a triazole ring.

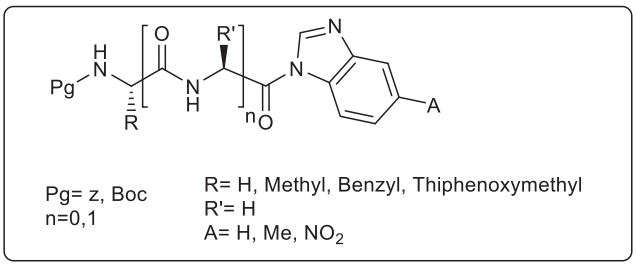
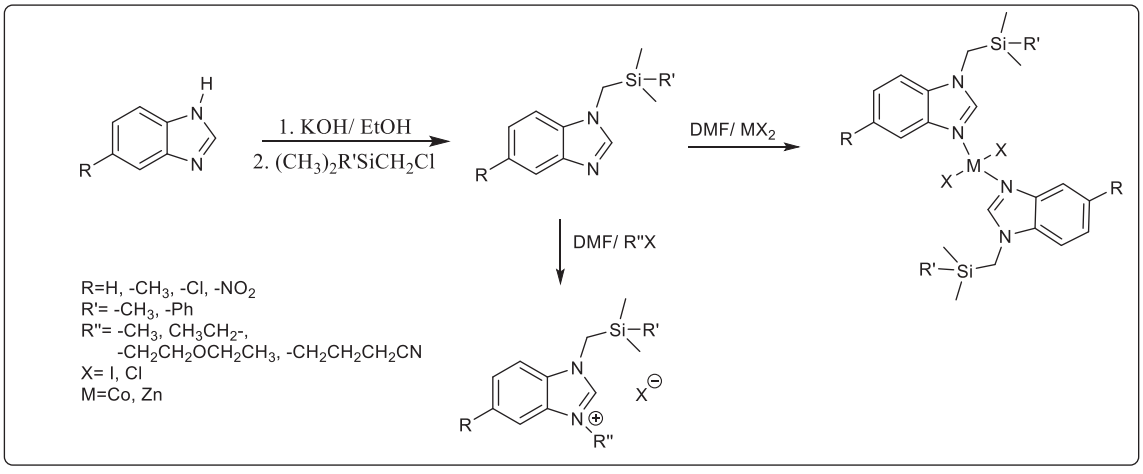


Fig. 11 Amino acid/peptide-benzimidazole conjugates as potent antifungal compounds.

Andrea Bistrović *et al*., designed new biologically active benzimidazoles linked with a triazole ring and evaluated the for their *in vitro* anti-bacterial activity against Gram-positive bacteria: S. aureus (ATCC 25923), MRSA, methicillin-sensitive S. aureus (MSSA), E. faecalis, vanco- mycin-resistant E. faecium (VREF), and Gram-negative bacteria: E. coli (ATCC 25925), P. aeruginosa (ATCC 27853), A. baumannii (ATCC 19606) and ESBL-producing K. pneumoniae. Structure-activity relationship studies showed that the non-substituted amidino benzimidazoles have the highest overall activities (Bistrović et al., 2018) (Fig. 8).

Sravanthi A. *et al*., synthesized new benzimidazole clubbed chalcone derivatives and evaluated them against Bacillus subtilis, Staphylococcus aureus, Escherichia Coli, Streptococcus pyogenes and Pseudomonas aeruginosa organisms for possible antibacterial effects. The SAR studies revealed that compounds possessing electron withdrawing groups exhibited significantly higher activity than the rest (AVUNOORI, 2020) (Fig. 9).

Eman M. E. Dokla *et al*., developed new 1,2-disubstituted benzimidazole derivatives as antimicrobial agents and studied their synergistic effect with colistin against Gram-negative bacteria. Out of thirty-three derivatives studied, seventeen exhibited moderate to potent activity against E. coli strain by varying the substituents at ring A and B or replacing ring B



Scheme 35 Synthesis of 1,3-benzimidazole salts and 1,3-benzimidazole metal complexes.

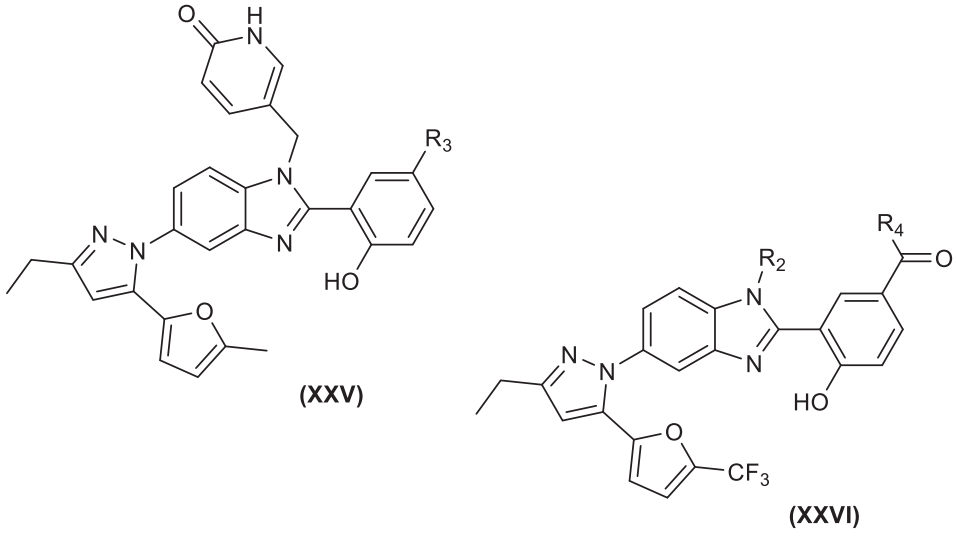


Fig. 12 Modified 5-(5-furan-2-yl-pyrazol-1-yl)-1*H*-benzimidazole at N1, C2 and C16 for HIV-1 inhibition.

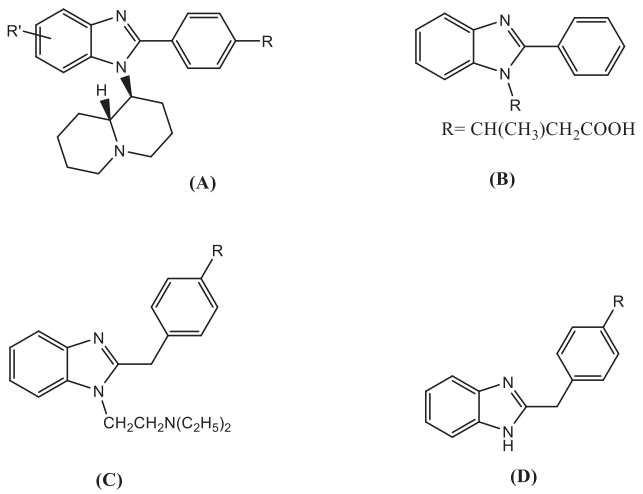


Fig. 13 Benzimidazole derivatives investigated as antiviral compounds; (A) 2-phenylbenzimidazole with basic sidechain; (B) 2-phenylbenzimidazole without basic sidechain; (C) 2-benzylbenzimidazole with basic sidechain; (D) 2-benzylbenzimidazole without basic sidechain.

with a naphthyl or cyclohexyl moiety. The structure–activity relationship for these derivatives is shown in Fig. 10 (Dokla et al., 2020)

On the other hand, Nesrin Buğday et al., synthesized new benzimidazole incorporating amino acid and dipeptide moieties with anticipated antimicrobial activities. The resulted study revealed that the new amino acid/ dipeptide conjugates possess from moderate to good effect as antifungal against C. albicans and C. tropicalis with a range of MICs between

100 and 400 μg/mL compared to the standard Fluconazole, while the antibacterial activities of these compounds on bacteria were low (Fig. 11) (Bugday et al., 2017)

Recently, Hasan Küçükbay et al., achieved new 1,3-benzimidazole salts and 1,3- benzimidazole metal complexes

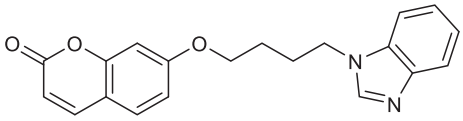


Fig. 14 Antiviral benzimidazole bearing a coumarin moiety.

as potent antibacterial and antifungal compounds, and some of them exhibit great cytotoxicity against the lung cancer cell line (A549) and healthy lung epithelial cell line (BEAS-2B). The structure activity relationship study of the tested compounds revealed that compounds with 5-position electron withdrawing or electron releasing groups possess a higher antimicrobial effect compared with those without any substituent. While the benzimidazole derivative with metal and without any substituent enhance the antimicrobial and cytotoxic properties (scheme 35) (Küçükbay et al., 2021).

3.2. Antiviral activity of benzimidazole derivatives

Several studies have shown that some benzimidazole derivatives possess important antiviral activity.

Martin Tremblay *et al.*, synthesized numerous 5-(5-furan-2-yl-pyrazol-1-yl)-1*H*-benzimidazole derivatives as HIV capsid assembly inhibitors. They showed that introduction of a pyridine side chain at N1 in **XXV**, a 2-hydroxyphenyl appendage at C2 and a C16 trifluoromethyl group (**XXVI**) were crucial for improving the antiviral potency (Fig. 12) (Tremblay et al., 2012)

Michele Tonelli *et al.*, developed novel benzimidazole derivatives as anti-coxsackie virus B5, anti-respiratory syncytial viru, and anti-staphylococcal bacteriophage-1 agents. The study showed that 2-[(benzotriazol-1/2-yl) methyl] benzimidazoles, bearing at position 1 a di-alkylaminoalkyl or quinolizidin-1-ylalkyl moiety exhibited potent activity against respiratory syncytial virus (Fig. 13).

It was observed that compounds bearing a basic sidechain were more frequently active than those devoid of it, and 1/2-phenyl and 2-benzylbenzimidazole derivatives (with and without the sidechain) were more active than benzimidazole derivatives devoid of any aromatic moiety in position 1 or 2 (Tonelli et al., 2014).

Lei Liu *et al.*, designed a new 7-(4-benzimidazole-butoxy)-coumarin (*BBC*) having an antiviral effect against SVCV infection in zebrafish.

The study found that BBC has an intense response on SVCV replication through the activation of PKCα/β-Nrf2 signaling which enhances HO-1 expression to suppress viral infection (Fig. 14) (Tonelli et al., 2014).

Recently, Mei Chen *et al.*, constructed new benzimidazole-containing flavonoids having remarkable antiviral effects against tobacco mosaic virus (TMV).

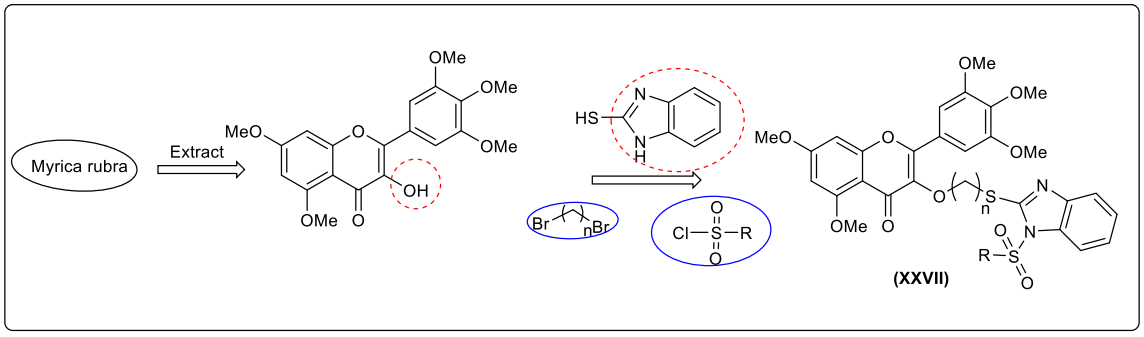


Fig. 15 Synthesis of an antiviral benzimidazole-containing 4-*H*–chromen-4-one derivative.

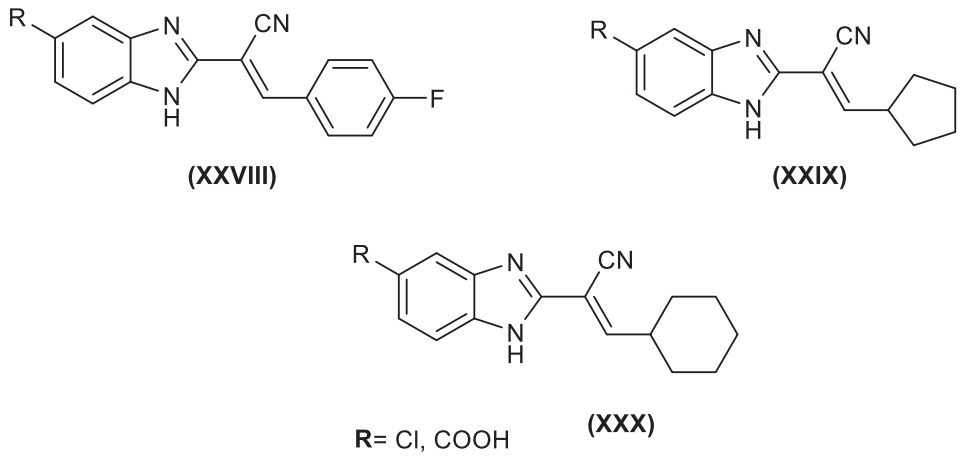


Fig. 16 Novel 2-substituted benzimidazole derivatives as active anticancer compounds.

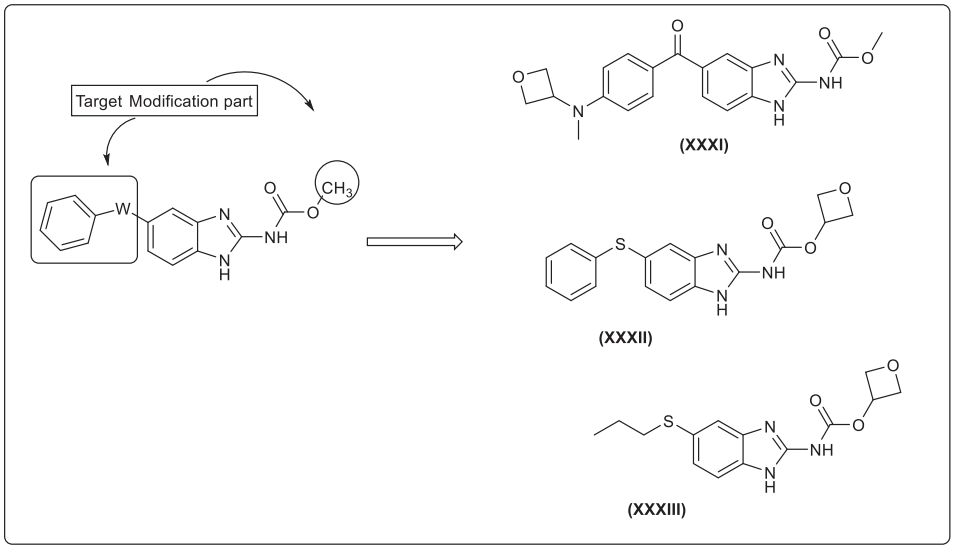


Fig. 17 New water soluble benzimidazole carbamates as anticancer drugs.

Myricetin, is a polyphenolic flavonoid compound (3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)-4*H*-chromen-4-one) which possesses different biological activities although most of them are limited to applied research in medicine. The recent study provides an active antiviral benzimidazole-containing a 4-*H*–chromen-4-one derivative (**XXVII**) (Fig. 15) (Chen et al., 2021).

3.3. Anticancer activities of benzimidazole derivatives

Several studies reported an effective anticancer effect of various benzimidazole derivatives with 2-substituted benzimidazoles known to act as potential anticancer agents. For instant, bis-benzimidazole derivatives showed an active effect in interfering with DNA topoisomerase I and possess cytotoxic effects against breast adenocarcinoma (MCF7) and skin epidermoid carcinoma (A431).

Based on this study, Hanan M Refaat achieved synthesis of certain novel 2-substituted benzimidazole derivatives that contain the 5-chloro or 5-underivatized carboxylic acid group in their framework which are potent antitumor compounds (Fig. 16) (Refaat, 2010).

The anti-helmitics Benzimidazole methyl carbamate drugs have been suggested to possess anticancer activity but have poor water solubility and poor suitability for systemic delivery to disseminated cancers. Jae Eun Cheong *et al*., developed new benzimidzoles containing an oxetane or an amine group to enhance solubility and showed them to exhibit significant inhibition of the growth of prostate and lung tumors without noticeable toxicity (Fig. 17) (Cheong et al., 2018). The solubility of anticancer compounds containing the benzimidazole carbamate moiety was achieved by incorporation of the polar functional group amine and 4-membered cyclic oxetane.

Indole and benzimidazole rings are bio-valuable molecules found in current drugs which are effective agents against different cancer cells. Phenylindole derivatives have been shown to inhibit breast cancer and recent studies show the different 2-benzimidazole derivatives have potent anticancer effects against various cancer cell lines. Fikriye Zengin Karadayi *et al*., demonstrated that new indole benzimidazoles with *p*-

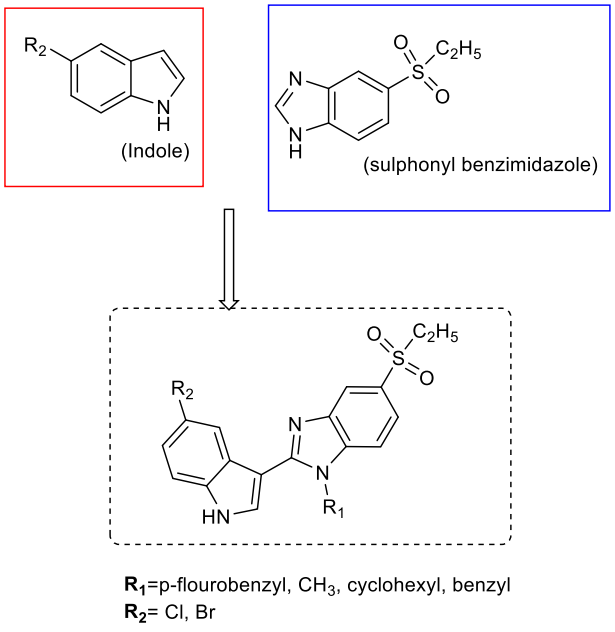


Fig. 18 Novel anticancer indole-benzimidazole derivatives.

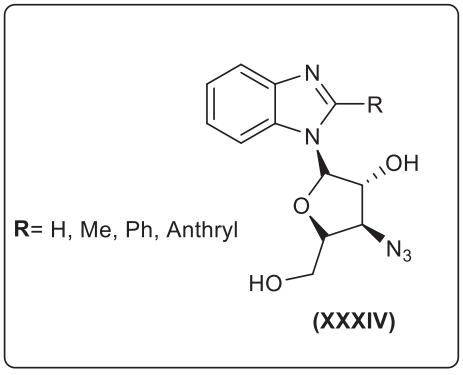


Fig. 19 Anti-cancer benzimidazole nucleosides.

fluorobenzyl or small alkyl groups at the R1-position and electron withdrawing groups at the R2-position have highly effective anticancer activities (Fig. 18) (Karadayi et al., 2020).

Modified nucleosides have valuable applications in bioorganic and medicinal chemistry. There are different nucleoside analogs that have been synthesized and evaluated for their biological activities as well as non-natural nucleosides which are of importance in medicinal chemistry and synthetic biology. Currently, efforts are underway to modify analogs of purine and pyrimidine nucleosides and to evaluate their biological activities. Benzimidazole, a structural mimic of the purine base, possesses a great spectrum of biological activities by interacting with DNA and RNA. In this direction, V. Shinde *et al.*, synthesized new sugar-modified benzimidazole nucleosides **XXXIV** with different substituents at the 2- position which displayed promising anti-cancer activities (Fig. 19) (Shinde et al., 2020).

Recently, new benzimidazole metal complexes have been synthesized and achieved great antitumor activity against A-2780 cell lines compared to the standard drug docetaxel with a LogIC50 value of − 0.81 μM ($p < 0.05$). and it was revealed that metalation of benzimidazole derivatives enhance their anticancer activity against different cell line including A-2780 (human ovarian) and DU-145 (human prostate) (scheme 36) (Yılmaz et al., 2019)

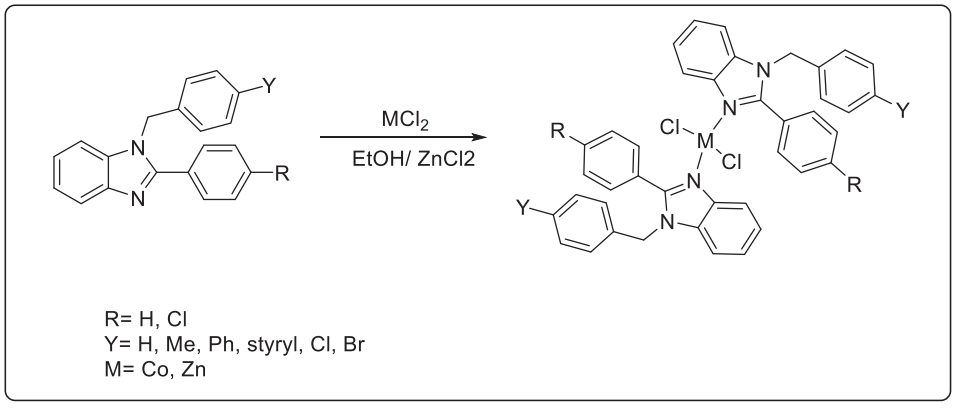
3.4. Analgesic properties of benzimidazole derivatives

There are several recent researches which revealed that different benzimidazole derivatives have remarkable pharmacological activities including analgesic and anti-inflammatory activities (Achar et al., 2010; Asma Eswayah, Souad Khaliel, Shaban Saad et al., 2017; Datar and Limaye, 2015; Kamil et al., 2016; Srivastava et al., 2013).

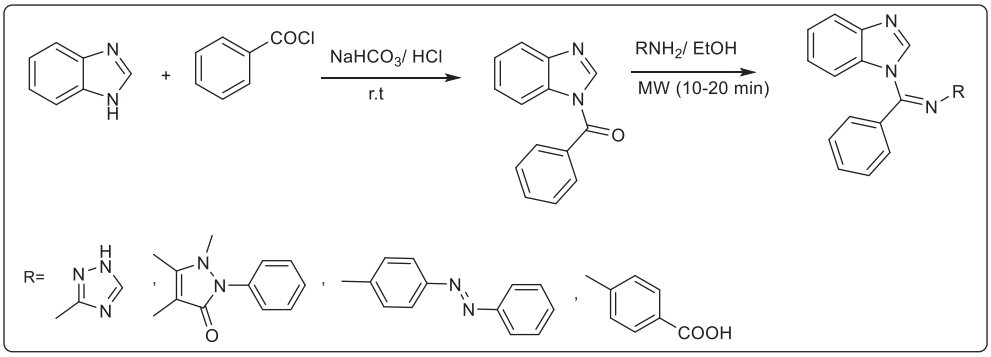
Asma Eswayah et al., achieved a series of N-substituted benzimidazole derivatives as analgesic active potent compounds, through the reaction of benzimidazole and benzoyl chloride followed by addition of different amines producing the desired active compounds (Scheme 37) (Asma Eswayah, Souad Khaliel, Shaban Saad et al., 2017).

The tested compounds gave good inhibiting activity compared to the standard aspirin (non steroidal anti-inflammatory drug (NSAID)) at the same dose.

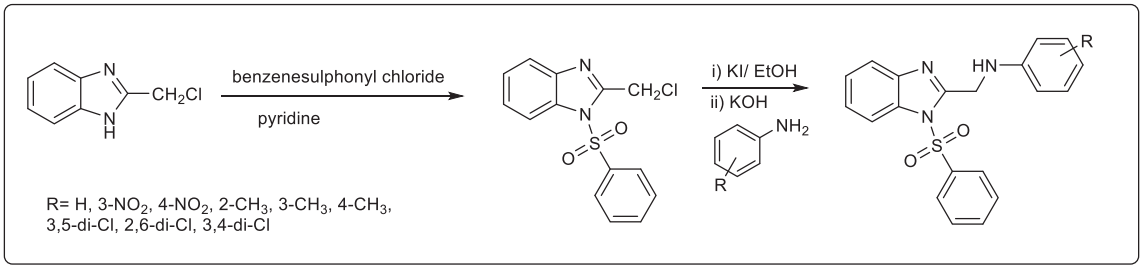
Monika Gaba et al., reported a series of new benzimidazole derivatives as GI (gastrointestinal)-friendly anti-inflammatory analgesic treatment (scheme 38). The *in vitro* and in vivo studies of these compounds showed



Scheme 36 Synthesis of new benzimidazole metal complexes as anticancer compounds.



Scheme 37 Synthetic pathway for the preparation of active analgesic N-substituted benzimidazole derivatives.



Scheme 38 synthesis of new GI-friendly anti-inflammatory analgesic benzimidazole derivatives.

encouraging anti-inflammatory activity ranging from 52.84% to 57.58% compared to the standard drug acetyl salicylic acid. It was revealed that the presence of electron donating group in the tested compounds enhanced the analgesic activity (Asma Eswayah, Souad Khaliel, Shaban Saad et al., 2017).

The previous literature SAR studies revealed that the presence of different heterocycle substituents at N1 position

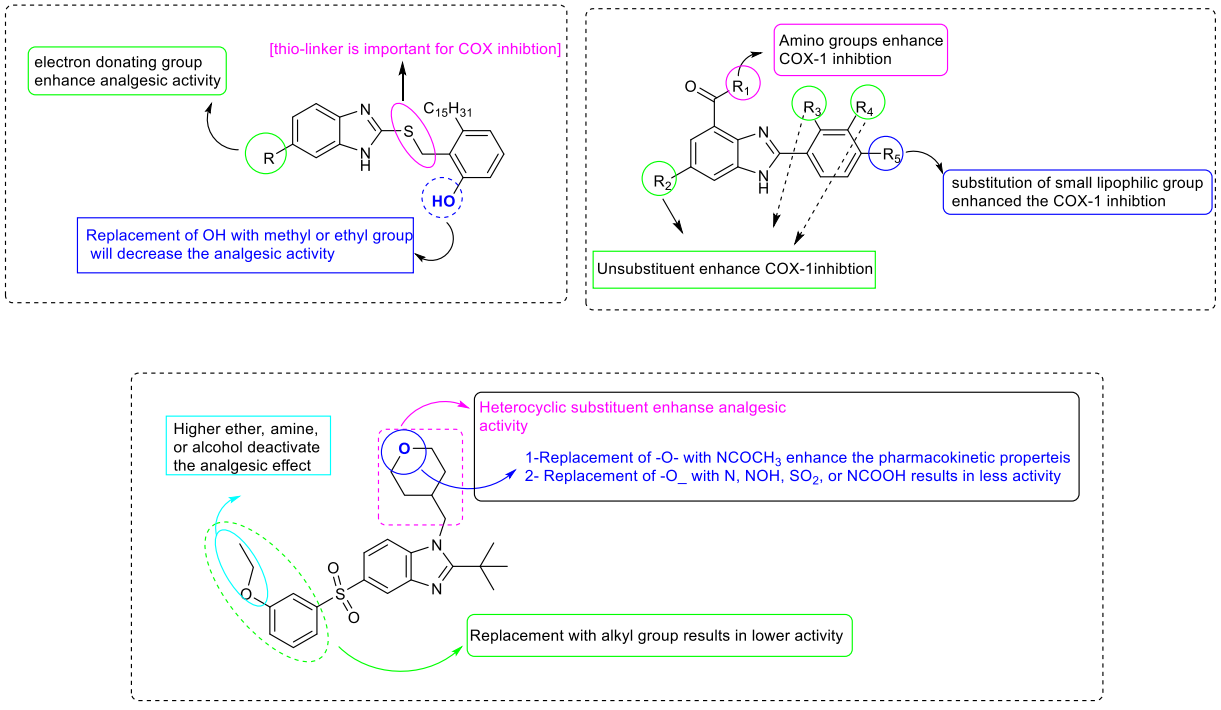


Fig. 20 Structure activity relationship studies of benzimidazole as an active analgesic compound.

enhance the anti-inflammatory analgesic activity, as well as that the presence of different substituents at C2, C5, and C6 of benzimidazole influence the anti-inflammatory activity. Structure activity relationship study of various literature synthesized benzimidazole as analgesic drug as illustrated in Fig. 20 (Gaba et al., 2015; Gijsen et al., 2012; Paramashivappa et al., 2003; Veerasamy et al., 2021).

4. Conclusion

Benzimidazole is the most important heterocycle made up imidazole and phenyl ring, which is widely used by the drug discovery and pharmaceutical industry. Based on the literature survey done, a lot of evidence has been provided that benzimidazole have a vast range of applications in the field of medicine and chemistry. They can be prepared via various routes of synthesis by using different starting materials. They can be synthesized by using a variety of different catalysts in solvent free conditions and by employing numerous solvents. All the synthesized benzimidazoles derivatives display a wide range of biological activities. The aim of this review was to demonstrate the wide synthetic strategies to benzimidazoles derivatives and their biological activities.

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