

Synthesis of Bioactive Imidazoles: A Review

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Abstract

Heterocyclic compounds are acquiring more importance in recent years because of their pharmacological activities. The imidazole nucleus is an important synthetic strategy in drug discovery. Imidazole is a planar five-member ring system with N atom in 1 and 3 positions. The systemic name for the compound is 1, 3 diazole, one of the N bear an H atom and other to be regarded as a pyrrole type N. Imidazole was first named as glyoxaline. It is amphoteric in nature, susceptible to electrophilic and nucleophilic attack. It also occurs in the purine nucleus & amino acid histidine, 4-amino-imidazole-5-carboxamide occurs naturally as a riboside. This interesting group of heterocyclic compound has diverse biological activities such as antimicrobial, anticancer, analgesic, anti-inflammatory, antiviral, anthelmintic, anticonvulsant, antiulcer, anti-allergic activity etc. Numerous methods for the synthesis of imidazoles and also their various structure reactions offer enormous scope in the field of medicinal chemistry. This articles aims to review the work reported, their chemistry and pharmacological activities of imidazole during past years.

Keywords: Imidazole; Heterocyclic; Antibacterial; Anti-inflammatory; Antifungal and antitumor.

Introduction

Heterocyclic compounds are also used in pharmacy and agriculture. Analysis of scientific papers in the last two decades revealed that there is a general trend in research for new drugs involving modification of existing biologically active matrices and molecular design of the structures of compounds. The imidazoles nucleus is an important synthetic strategy in drug discovery. Imidazole derivatives exhibited antimicrobial, anti-inflammatory, analgesic, anti-tubercular and anticancer activity. One of the most important application of imidazole derivatives is their use as material for treatment of denture stomatitides. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Imidazole drugs have broadened scope in clinical medicines. Medicinal properties of imidazoles include anticancer, anticoagulants, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antidiabetic and antimalarial [1-7]. Imidazole and its derivatives are reported to be physiologically and pharmacologically active and find applications in the treatment of several diseases. Imidazole is an organic compound with the formula $(CH)_2N(NH)CH$. It is a colourless solid that dissolves in water to give mildly basic solution. In chemistry, it is an aromatic heterocycle, classified as a diazole and as an alkaloid. Imidazoles are a common component of a large number of natural products and pharmacologically active molecules (Figure 1) Imidazole was first synthesized by Heinrich Debus in 1858, but various imidazole derivatives [8-11] have been discovered as early as the 1840s, it used glyoxal [12] and formaldehyde [13, 14] in ammonia to form imidazole. This synthesis, while producing relatively low yields, is still used for creating C-substituted imidazoles [15].

Imidazoles containing free imino hydrogen and a substituent in the 4- and 5- position, or two dissimilar substituents in these positions, might be expected to occur in the isomeric forms. These isomers differ in the position of the imino hydrogen which may be attached to either of the two nitrogen atoms.

Over the years, the imidazole nucleus has attracted the attention of the scientific community due to its chemical and biological properties [16, 17]. For example, this nucleus is present in the structures of several natural products in the form of the essential amino-acid histidine

or in alkaloids exhibiting anti-tumoral, anti-cancer (dacarbazine), antihistaminic (cimetidine), anti-parasitic (metronidazole), and antihypertensive (losartan) and anti-bacterial activities [18-20]. A great numbers of medicines contain the imidazole nucleus, including ketoconazole which are used to treat fungal infections, bacterial infections, and gastric ulcers, respectively (Figure 2) [21, 22]. Due to their importance, it has become an attractive target for the synthetic and medicinal chemist. There are many synthetic methodologies that have been developed for assembling and decorating the imidazole ring with diverse functional groups.

Synthesis of imidazoles

Bunev et al. [23] have been synthesized a new series of 1,4,5-trisubstituted imidazoles 3 containing trifluoromethyl group has been developed using van Leusen reaction, which incorporates two-component condensation reaction trifluoroacetimidoyl chlorides 1 with tosylmethylisocyanide 2. This protocol provides a novel and improved method for obtaining trifluoromethyl containing 1, 4, 5-trisubstituted imidazoles in good yields (Scheme 1).

Sharma et al. [24] reported two novel series of 2-(substituted phenyl)-1H-imidazole 7 and (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-methanone 10 analogues it is achieved by the reaction of substituted aniline 5 in HCl/water mixture were diazotized using solution of sodium nitrite. Imidazoles were added in intermediate 6. Compound 10 were synthesized by the reaction of compound 7 in diethyl ether was added to a solution of corresponding benzoic acid 8 with substituted benzoyl chloride 9 (Scheme 2).

Pandya et al. [25] also reported a simple and concise route for the synthesis of highly substituted imidazole derivatives 12 have been

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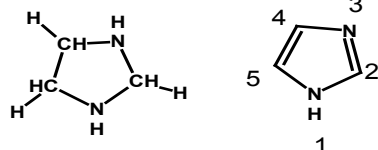


Figure 1: Imidazoles.

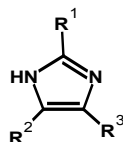


Figure 2: C-substituted imidazoles.

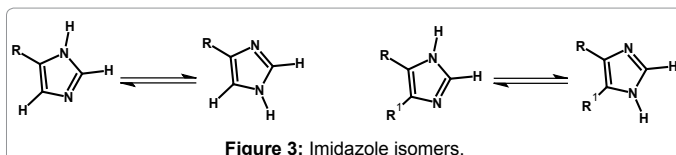
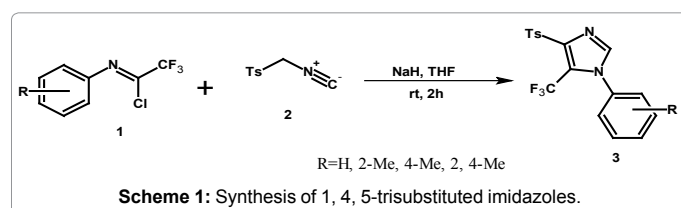


Figure 3: Imidazole isomers.



Scheme 1: Synthesis of 1, 4, 5-trisubstituted imidazoles.

developed by the reaction of 10 with aromatic aniline 11 via copper-mediated oxidative C–H functionalization in good to high yields. The advantage of the reaction lies in its mild reaction conditions and readily available starting materials (Scheme 3).

Liu et al. [26] have synthesized a series of 2-(4-(2-(substituted-1-yl) ethoxy) phenyl)-1H-phenanthro [9, 10-d] Imidazole 15 and 2-(4-(4-(substituted-1-yl) butoxy) phenyl)-1H-phenanthro [9, 10-d] imidazole 16 by multicomponent reaction method (Scheme 4).

Kathrotiya et al. [27] reported a series of some new quinoline based imidazole-5-one derivatives 19, 21 have been synthesized by the fusion of oxazol-5-ones 17, with various p-substituted anilines 18, 20 and zeolite in pyridine (Scheme 5).

Mungra et al. [28] also reported another series of some new tetrazolo[1,5-a]quinoline based tetrasubstituted imidazole derivatives 26 have been synthesized by a reaction of tetrazolo[1,5-a]quinoline-4-carbaldehyde 22, benzyl 23, aromatic amine 25 and ammonium acetate 24 in the presence of iodine through one-pot multi-component reaction (MCR) approach (Scheme 6).

Desai et al. [29] reported the synthesis of N-(4-((2-chloroquinolin-3-yl) methylene)-5-oxo-2-phenyl-4, 5-dihydro-1H-imidazol-1-yl) (aryl) amides 30 by the reaction of 2-chloroquinoline-3-carbaldehyde 27 and N-amino arylcarboxamides 28 in pyridine. They were react with 4-((2-Chloroquinolin-3-yl) methylene)-2-phenyloxazol-5(4H)-one 29 was heated with again an N-amino arylcarboxamides in pyridine (Scheme 7).

Li et al. [30] have been synthesized trisubstituted imidazoles 33 by the reaction of 1, 2-di (furan-2-yl)-2-oxoethyl carboxylates 31 in

presence of RCOCl they form an intermediate 32 then it is converted into the synthesized compound (Scheme 8).

Chen et al. [31] reported a series of 1-R¹-2-R-4, 5-di (furan-2-yl)-1H-imidazole derivatives 39 were synthesized in multisteps. Reaction start with furan-2-carbaldehyde 34 and vitamin B1 to gave 1, 2-di (furan-2-yl)-2-hydroxyethanone 35. 35 react with benzyl chloride or allyl chloride and pyridine to form an intermediate 36, it were react with sodium acetate and gave substituted difuran imidazole 37. This was followed by NaH/THF to form the final compound 38 (Scheme 9).

Ziarani et al. [32] also reported SiO₂-Pr-SO₃H catalyst based 1,2,4,5-tetrasubstituted imidazoles 43 by reaction with four-component, one-pot reaction of 1,2-diketones 39, aryl aldehydes 40, ammonium acetate 41 and substituted aromatic amines 42 in excellent yields under solvent free conditions (Scheme 10).

Jawaharlal et al. [33] reported tetrasubstituted imidazole 48 by the refluxing of 9, 10-phenanthraquinone 44 with aryl aldehyde 46, primary amines 47 and ammonium acetate 45 in the presence of glacial acetic acid (Scheme 11).

Lavanya et al. [34] also reported the synthesis of 6-bromo-2-substitutedphenyl-1H-imidazo [4, 5-b] pyridine derivatives 51 were prepared with 5-Bromopyridine-2, 3-diamine 49 underwent facile condensation with various aromatic carboxylic acid derivatives 50 in the presence of Etan's reagent (Scheme 12).

Prabhu et al. [35] reported another series of some novel aryl imidazole derivatives 57 were prepared by the condensation of compounds containing primary aromatic amine 52 and aryl aldehydes 53 to give respective Schiff's bases 54, which was further reacted with ammonium acetate 55 and isatin 56 in the presence of glacial acetic acid (Scheme 13).

Sathe et al. [36] have synthesized 4-Fluoro-3-chloroanilline 58 treated with potassium thiocyanate in presence of glacial acetic acid and bromine was converted into 2-amino-6-fluoro-7-chlorobenzothiazole 59, resulting into 2-amino benzothiazole. The synthesized compound in presence of 2-phenyl-4-benzylidene-5-oxazolinone 60 refluxed in pyridine to obtained 2-(2-Phenyl-4-benzylidene-5-oxo-imidazol-1-ylamino)-6-fluoro-7-substituted (1,3) benzothiazoles 62, 61 (Scheme 14).

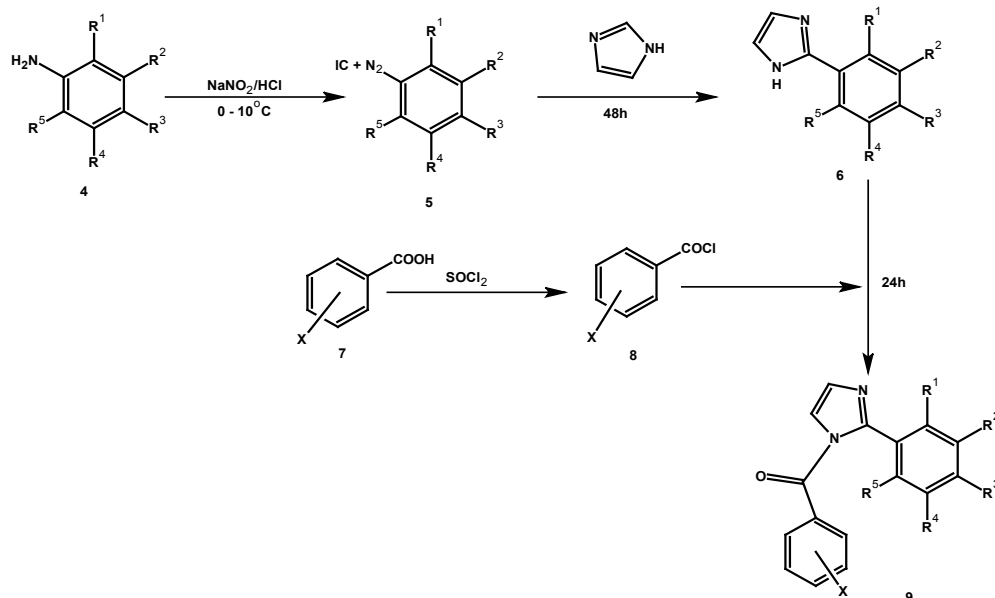
Stella et al. [37] reported an efficient and practical synthesis of imidazolyl derivatives 65 were achieved through thiocyanation of aniline derivatives 63 to gave the intermediate 64 which followed by the reaction with ethylene diamine in the presence of carbondisulphide (Scheme 15).

Lakshmanan et al. [38] also reported the synthesis of 1-(4-substitutedphenyl)-2-(2-methyl-1H-imidazol-1-yl) ethanone 67 and synthesis of 1-(4-substituted phenyl)-2-(1H-imidazol-1-yl) ethanone 68 by the reaction of para substituted phenacyl bromides 66 with imidazoles (Scheme 16).

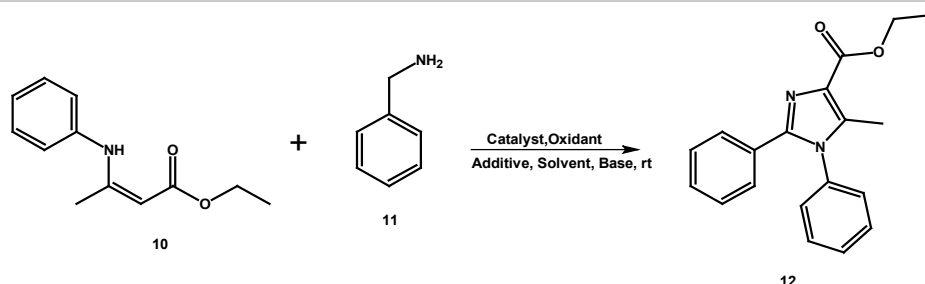
Husain et al. [39] reported a series of 1,2,4-trisubstituted-1 H-imidazoles 72 were synthesized by the 2,4-disubstituted-1 H-imidazoles 71 and the title compounds were synthesized from 4-methoxyphenyl glyoxal 70 with following multistep synthesis (Scheme 17).

Pharmacological Profile of Imidazoles

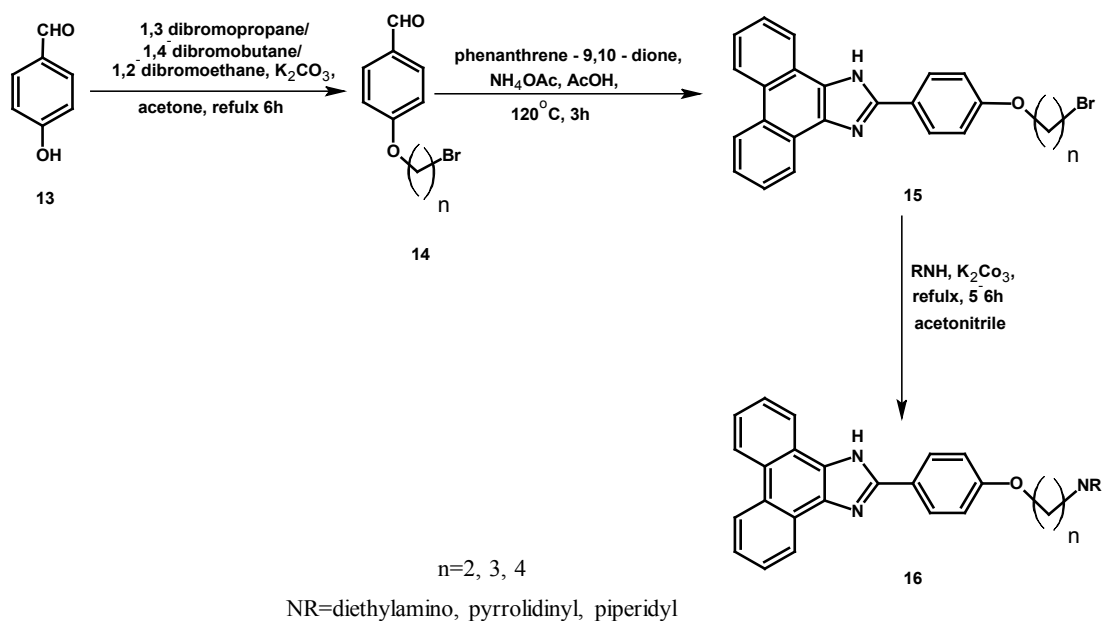
Imidazole and their derivatives are still the most widely used in the therapeutic areas and have shown a broad spectrum of activity against various pathogens. Since the discovery of various drugs



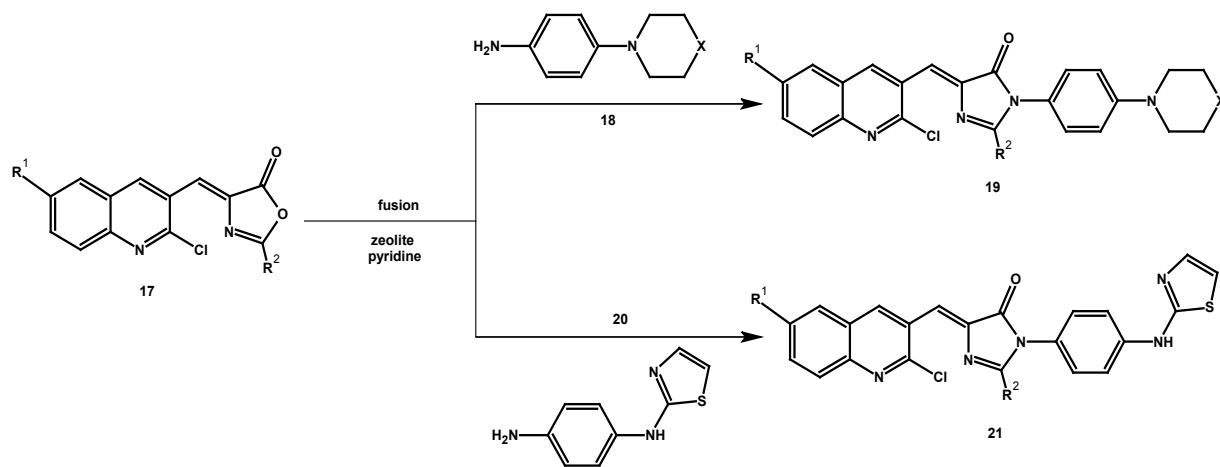
Scheme 2: Synthesis of 2-(substituted phenyl)-1H-imidazoles and (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-methanone.



Scheme 3: Synthesis of ethyl 5-methyl-1,2-diphenyl-1H-imidazole-4-carboxylate.

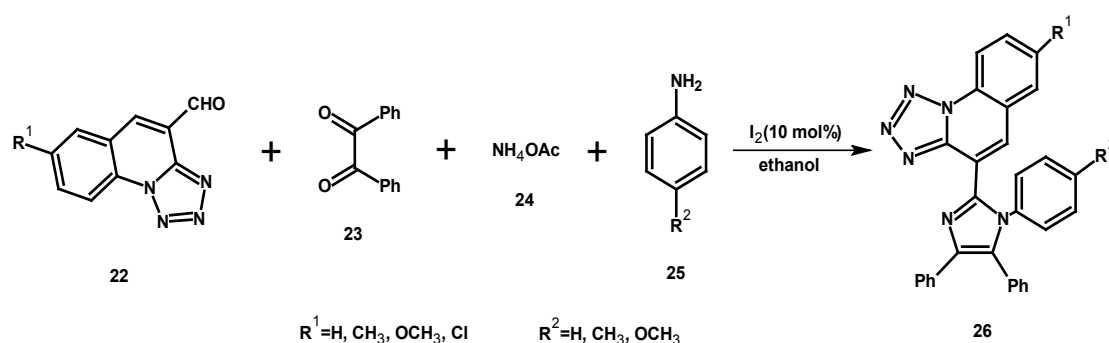


Scheme 4: The organic synthesis of 2-(4-(2-(substituted-1-yl) ethoxy) phenyl)-1H-phenanthro [9, 10-d] Imidazole and 2-(4-(4-(substituted-1-yl) butoxy) phenyl)-1H-phenanthro [9, 10-d] imidazole.



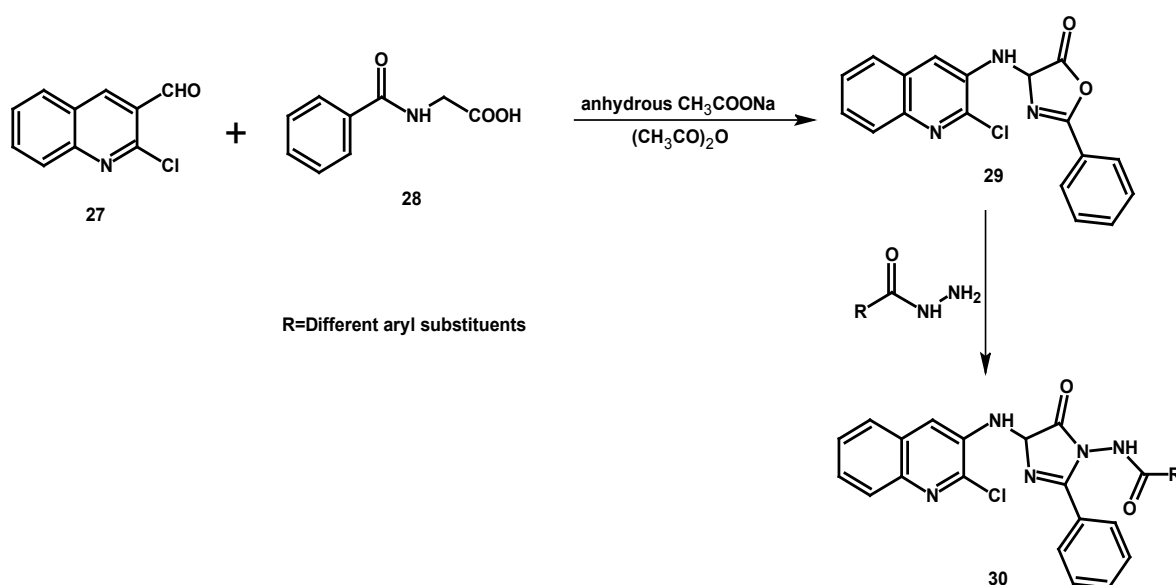
$R^1 = \text{H, CH}_3, \text{OCH}_3, R^2 = \text{CH}_3, \text{Phenyl}, X = \text{O, N-CH}_2\text{-CH}_3, \text{N-CH}_3$

Scheme 5: Synthesis of some new quinoline based imidazole-5-one derivatives.



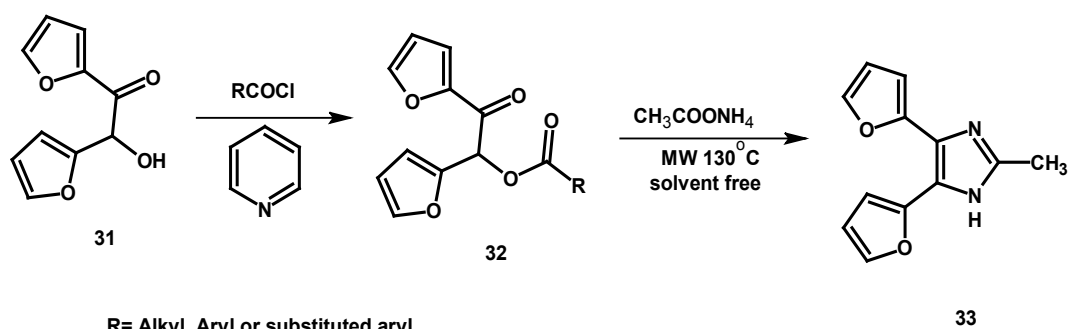
$R^1 = \text{H, CH}_3, \text{OCH}_3, \text{Cl} \quad R^2 = \text{H, CH}_3, \text{OCH}_3$

Scheme 6: Synthesis of new tetrazolo [1, 5-a] quinoline based tetrasubstituted imidazole derivatives.

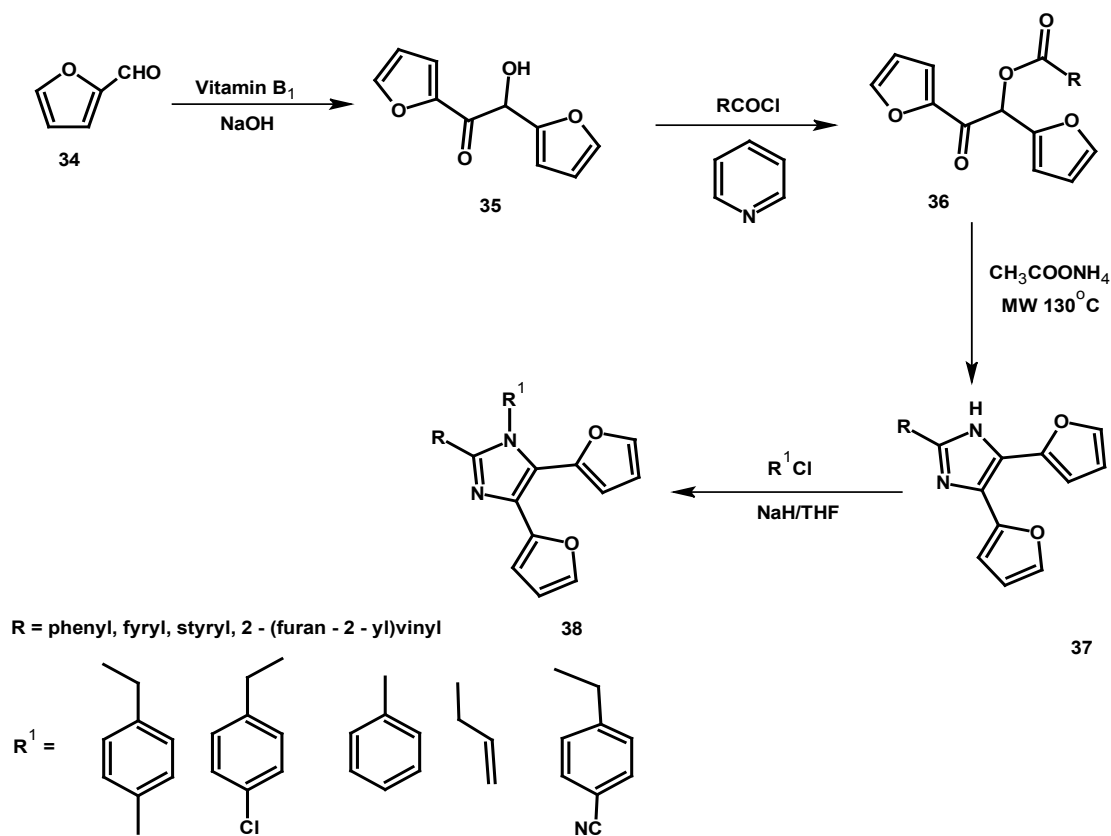


R=Different aryl substituents

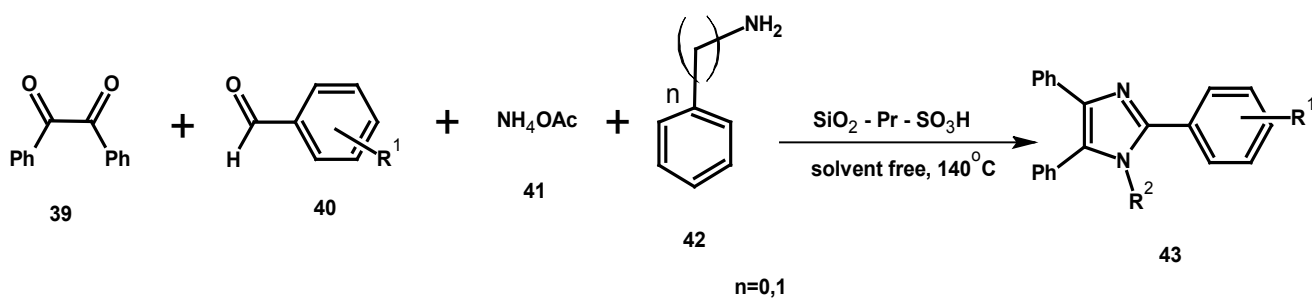
Scheme 7: Synthesis of N-(4-((2-chloroquinolin-3-yl) methylene)-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl)(aryl)amides.



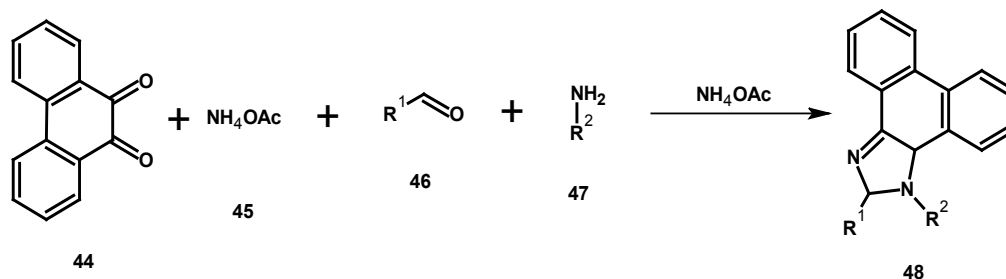
Scheme 8: Synthesis of trisubstituted imidazoles containing furan rings.



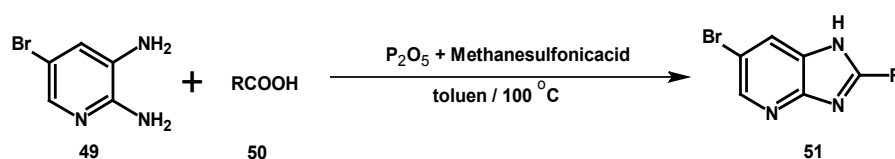
Scheme 9: Synthesis of 1-R¹-2-R-4, 5-di (furan-2-yl)-1H-imidazole derivatives.



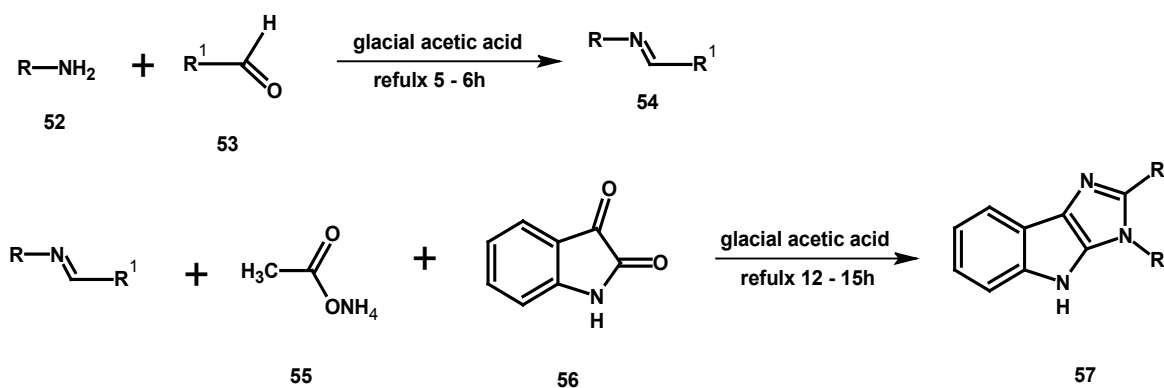
Scheme 10: Synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles in presence of SiO₂-Pr-SO₃H.



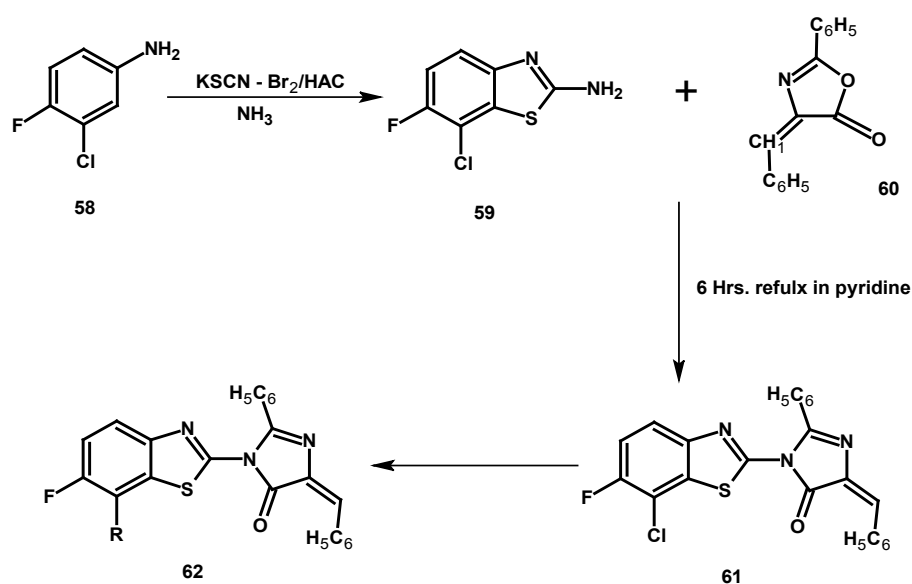
Scheme 11: Synthesis of tetrasubstituted imidazole.



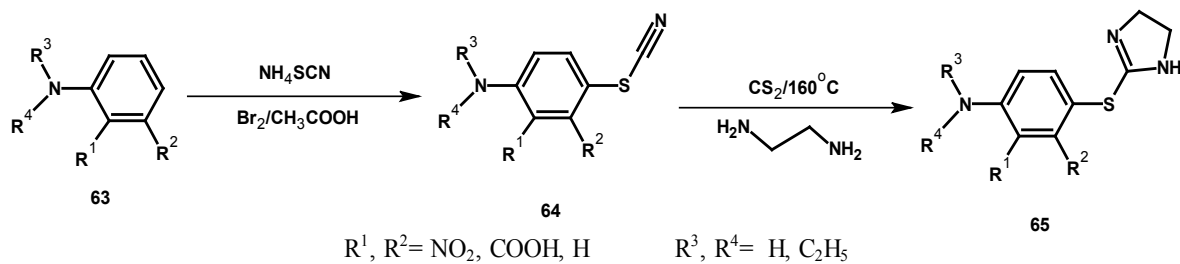
Scheme 12: Synthesis of 6-bromo-2-substitutedphenyl-1H-imidazo [4,5-b]pyridine derivatives.



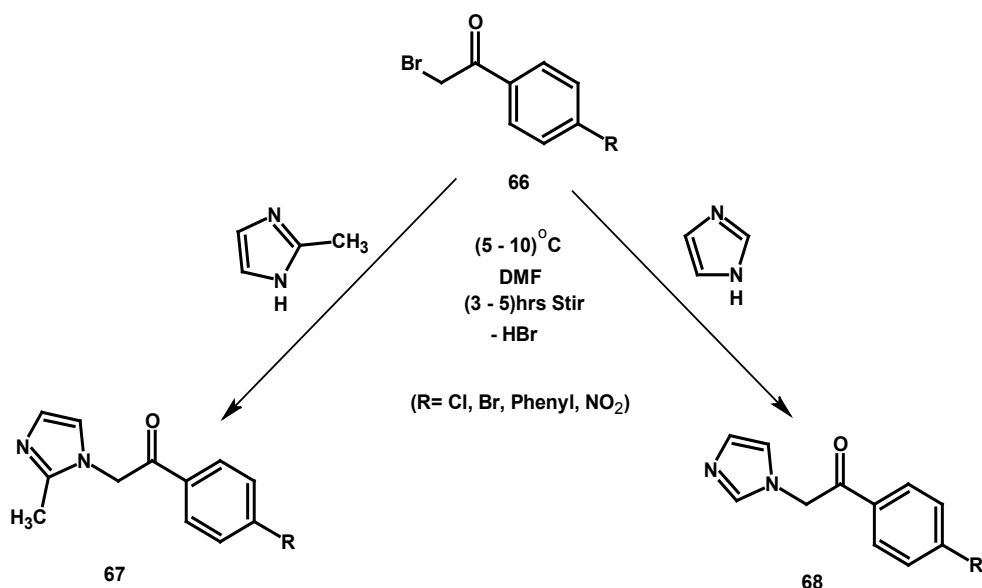
Scheme 13: Synthesis of 4-[2-(2-hydroxyphenyl) imidazo [4,5-b] indol - 3 (4H) -yl] benzenesulfonamide.



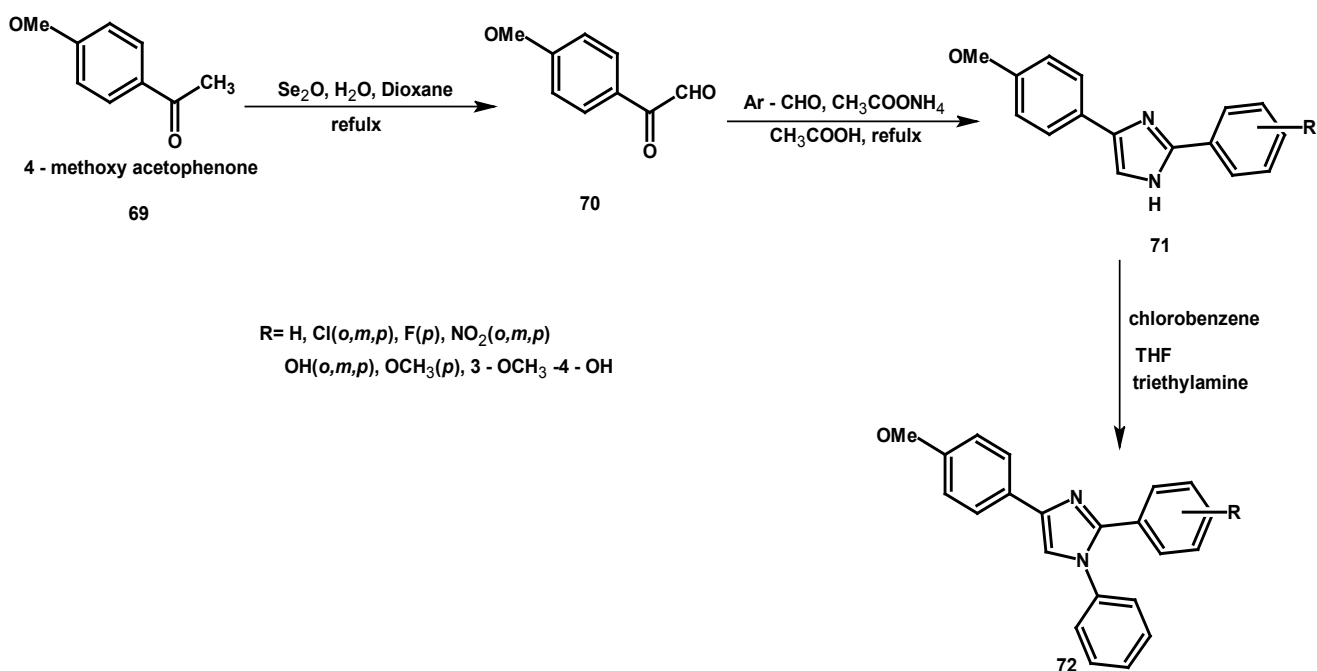
Scheme 14: Synthesis of 2-(2-Phenyl-4-benzylidene-5-oxo-imidazolin-1-ylamino)-6-fluoro-7-substituted (1,3) benzothiazoles.



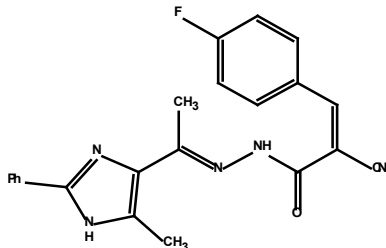
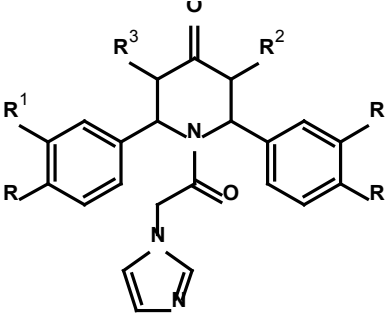
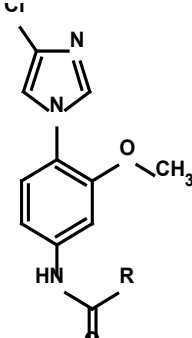
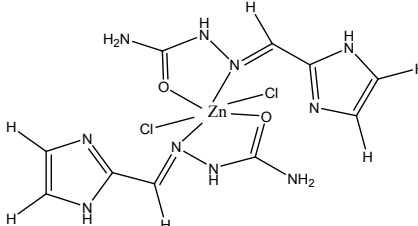
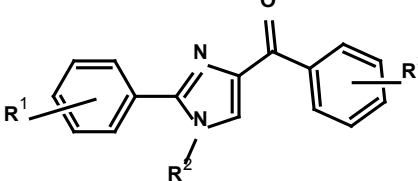
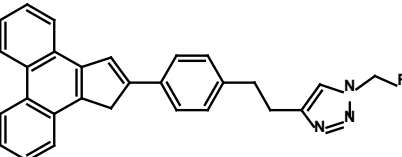
Scheme 15: Synthesis of imidazolyl derivatives.

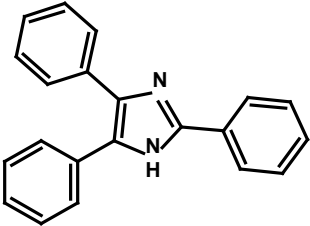
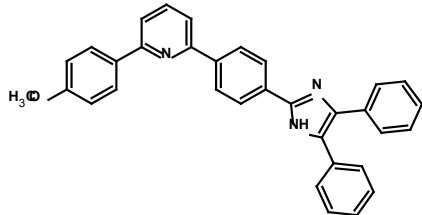
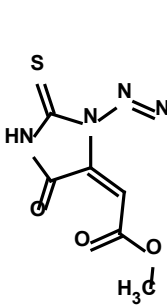
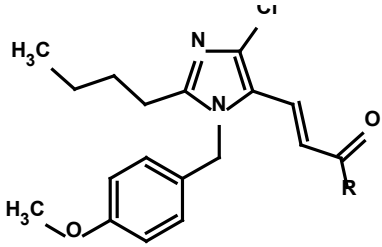
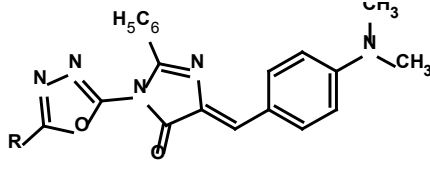
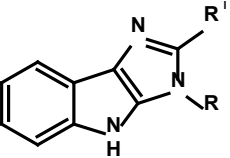
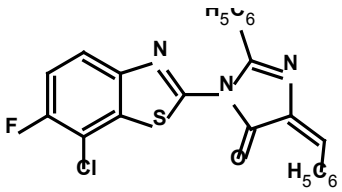


Scheme 16: Synthesis of 1-substituted imidazoles.



Scheme 17: Synthesis of 1, 2, 4 trisubstituted 1-H-imidazoles.

S.No.	Chemical Structure	Chemical Name	Activity
1		2-Cyano-3-(4-fluorophenyl)- <i>N</i> -[1-(5-methyl-2-phenyl-1 <i>H</i> -imidazol-4-yl)ethylidene]acrylohydrazide	Antimicrobial, antioxidant, anti-hemolytic and cytotoxic [40].
2		1-[2-(1 <i>H</i> -imidazol-1-yl)acetyl]-3-methyl-2,6-diphenylpiperidin-4-one	Antibacterial and antifungal [41].
3		2,4-Dichloro- <i>N</i> -(4-(4-chloro-1 <i>H</i> -imidazol-1-yl)-3-methoxyphenyl)benzamide	Antimicrobial and Antitubercular [42].
4		transition metal(II) complexes of imidazole-2-carbaldehyde semicarbazone (H ₂ L)	Antimicrobial [43].
5	 R ¹ =4-Br, R ² =H, R ³ =3,4,5-(OCH ₃) ₃	(2-aryl-1 <i>H</i> -imidazol-4-yl)methanone	Antiproliferative [44].
6		3-(4-((4-(1 <i>H</i> -phenanthro[9,10-d]imidazol-2-yl)phenoxy)methyl)-1 <i>H</i> -1,2,3-triazol-1-yl)propan-1-amine	Alzheimer's disease [21].

7		2,4,5-triphenyl-1 <i>H</i> -imidazole	Antimicrobial [45].
8		2-[4-(4,5-Diphenyl-1 <i>H</i> -imidazol-2-yl)-phenyl]-6-(40-methoxy-biphenyl-4-yl)-pyridine (MPBI)	Antibacterial, Antifungal [46].
9		methyl(2 <i>Z</i>)-[3-((<i>E</i>)-[3-aryl-1 <i>H</i> -pyrazol-4-yl]methylidene)amino]-5-oxo-2-thioxoimidazolidin-4-ylidene]ethanoate	Antibacterial [47].
10		3-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1 <i>H</i> -imidazol-5-yl-1-arylprop-2-en-1-one	antibacterial, antifungal [48].
11		(5 <i>Z</i>)-5-[4-(dimethylamino)benzylidene]-3-(5-substituted -1,3,4-oxadiazol -2-yl)-2-phenyl-3,5-dihydro-4 <i>H</i> -imidazol-4-one	Anthelmintic [49].
12		4-[2-(2-hydroxyphenyl)imidazo[4,5- <i>b</i>]indol-3(4 <i>H</i>)-yl]benzenesulfonamide	antibacterial and antihelmintic [35].
13		2[2'- Phenyl - 4'- benzidiny- 5'- oxo- imidazoline- 1yl- amino] -6 fluoro- 7- chloro (1,3) benzothiazole	anti-inflammatory [36].

14		4-(4-methoxyphenyl)-1,2-diphenyl-1 <i>H</i> -imidazole	Anti-inflammatory, antifungal [39].
15		2,3-dihydroimidazo[1,2-b][1,4,2]benzodithiazines	Anti-HIV [50].
16		<i>N</i> -(2,4-dihydroxybenzylidene)-2-(2-(phenylthiomethyl)-1 <i>H</i> -benzo[<i>d</i>]-imidazol-1-yl)acetohydrazide	Antitumor [51].
17		3-bromo-3-deazaneplanocin	Antiviral [52].

Table 1: Various imidazole derivatives show various pharmacological activities.

contain the imidazole nucleus, including ketoconazole, metronidazole and cimetidine, which are used to treat fungal infections, bacterial infections and gastric ulcers, respectively. On the basis of various literature surveys imidazole derivatives shows various pharmacological activities (Table 1).

Conclusion

Imidazole is a five membered heterocyclic compound. There were so many different conventional methods to synthesize imidazole and its derivatives. On the basis of the literature it was found that imidazole was synthesized under solvent free condition and refluxing method with the help of efficient and different catalyst and without catalyst with good yield. Imidazole is a base in nature due to nitrogen atom. It under goes electrophilic substitution but nucleophilic substitution is rare one. From the extensive literature survey it was found that it has antimicrobial, anticancer, analgesic, antiinflammatory, anticonvulsant, antiviral, anthelmintic, antiulcer, anti allergic activity etc. So from the above discussion it can be concluded that imidazole is a therapeutically

active versatile moiety, which had been exploited in the past years for synthesizing various compounds having diverse pharmacological activities, and still imidazole can be further utilized for the future prospective against various diseases or disorders.

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