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A Review on Synthesis and Pharmacological Importance of Imidazole Derivatives

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ABSTRACT: Imidazole is a 5-membered planar ring, which is soluble in water and other polar solvents. In the field of five membered heterocyclic structures imidazole nucleus shows various properties. Structural frameworks have been described as privileged structures and in particular, nitrogen containing heterocylic structures have been reported to be associated with a wide range of biological activity.

Key words: Heterocylic; Nitrogen compounds; Imidazole; Biological activity.

1. Introduction

Heterocycle is one of the most complex and intriguing branch of chemistry that constitute high degree of structural diversity and economically useful as therapeutic agents [1, 2]. For more than a century, heterocycles have great advantage to drug for development of society from a biological and industrial point of view as well as to the understanding of life processes and to the efforts to improve the quality of life. Among the different heterocycles nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis [3].

Imidazole ring has five membered ring systems with 3C and 2N atom and in ring the N is present in 1st and 3rd positions and contain hydrogen binding domain, and electron donor nitrogen system [4-6].The first imidazole was described by Fischer (1882), but the nature of the ring system was demonstrated by Freud and Kuhn (1890) [7-9].The imidazole ring is a constituent of several important natural products, including purine, histamine, histidine and nucleic acid. It is also present in the structure of many synthetic market drug molecules, that is, azomycin **1** cimetidine **2** and metronidazole **3**. Imidazole containing drugs have a broaden scope in remedying various dispositions in clinical medicine [10]. Imidazole was first synthesized by Heinrich Debus in 1858, but various imidazole derivatives had been discovered as early as the 1840s. His synthesis used glyoxal and formaldehyde in ammonia to form imidazole [11]. Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines. Medicinal properties of imidazole include anticancer, b-lactamase inhibitors, 20- HETE (20-Hydroxy-5,8,11,14-eicosatetraenoic acid) synthase inhibitors, carboxypeptidase inhibitors, hemeoxygenase inhibitors, antiaging agents, anticoagulants, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antidiabetic and antimalarial etc. [12].

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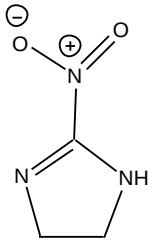

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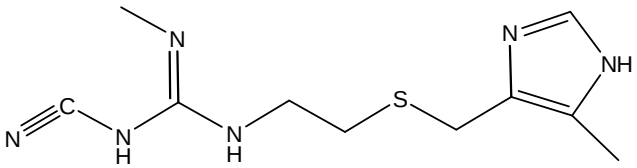

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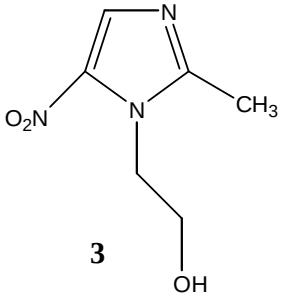


3

2. History of Heterocyclic Chemistry

Some remarkable developments

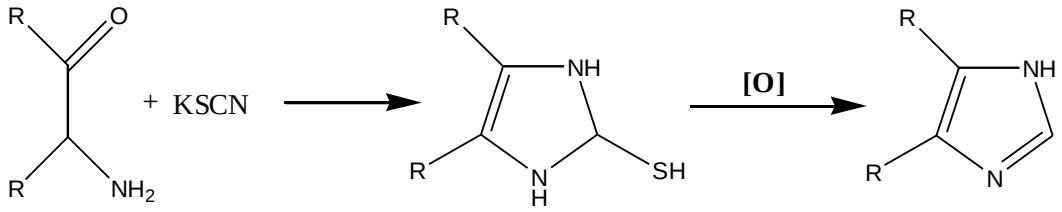
1. 1818: From uric acid, Brugnatelli isolates alloxan.
2. 1832: Dobereiner produces furfural (a furan) by mixing starch with sulfuric acid.
3. 1834: Runge isolates pyrrole ("fiery oil") by bones dry distillation.
4. 1906: Friedlander discovered indigo dye, allowing synthetic chemistry methodologies to displace a large number of agricultural industry.
5. 1936: Treibs syntheses chlorophyl derivatives from crude oil, explaining the biological source of petroleum.
6. 1951: Chargaff's rules are explained, importance the role of heterocyclic compounds (pyrimidines and purines base) in the genetic code [13].

3. Result and discussion

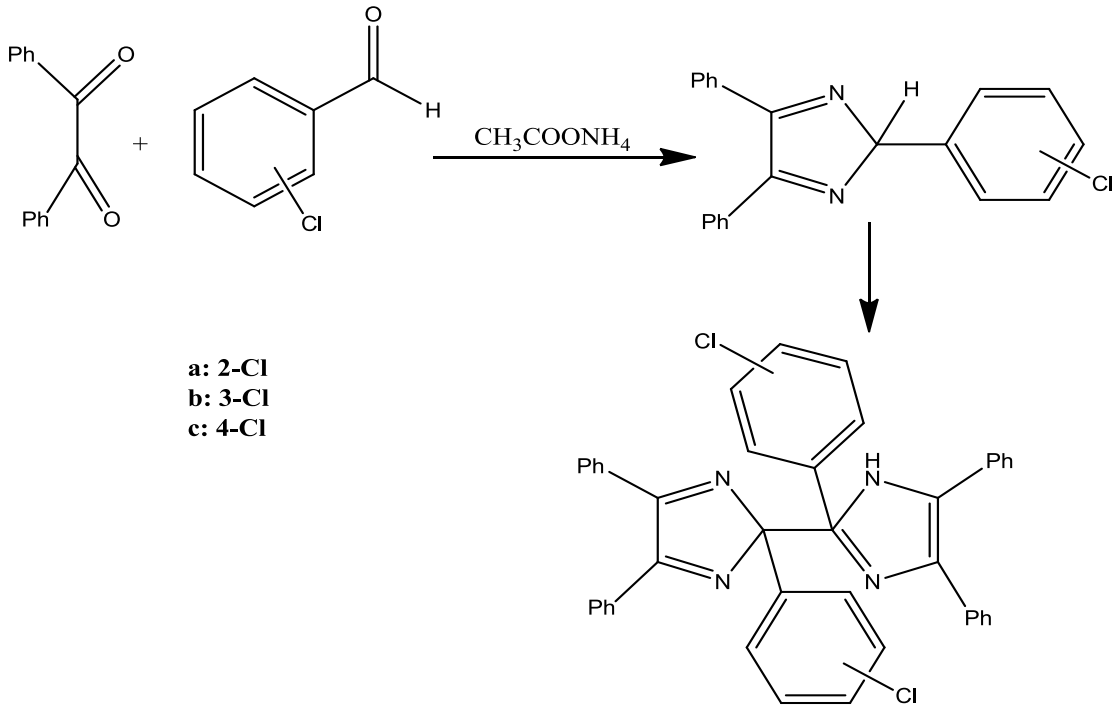
A planer five-member heterocyclic ring imidazole with 3 carbon (C) and 2 nitrogen (N) atom in the ring, where N is present in 1st and 3rd positions. The imidazole ring is a constituent of several important natural products, including hemoglobin, purine, chlorophyll, histamine, biotin, histidine, alkaloids, deoxy nucleic acid and ribo nuclic acid. Imidazole is a polar and ionisable aromatic, it improves pharmacokinetic properties of lead molecules by optimizing the solubility and bioavailability parameters of poorly soluble lead molecules. The integration of the imidazole ring is an important synthetic approach in drug discovery. Imidazole and its analogous have engaged a unique place in the meadow of medicinal chemistry. This because of unique structural feature of imidazole ring with attractive electron-rich property is beneficial to readily bind with a variety of enzymes and receptors in biological systems through diverse weak interactions, thereby showing broad range bioactivities. The related research and developments of imidazole-based medicinal chemistry have become a rapidly developing and increasingly active topic. Large number of imidazole analogous have been are being developed for different therapeutic actions to treat various types of diseases which showed huge development value.

4. Synthesis of imidazole derivatives

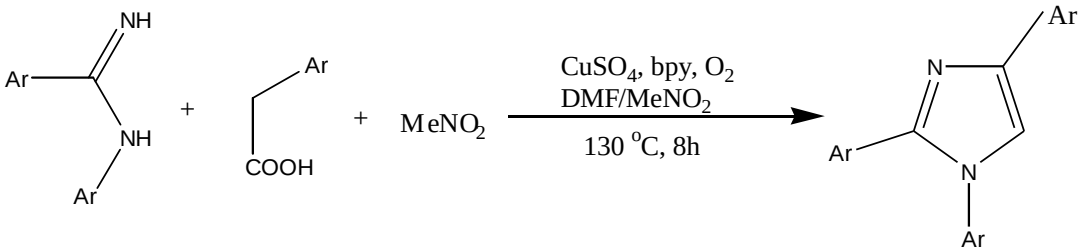
α-Amino ketones and potassium thiocyanate are used for the synthesis of 2-thiol substituted imidazoles. The sulfur in intermidiate can readily removed by a variety of oxidative method to give the desired imidazole derivatives (**Scheme 1)** [14].



On the otherhand, bis-imidazole derivatives have been synthesized by Asiri *et al*. The synthesis was achieved from benzyl, ammonium acetate and one of the three isomers of chloro benzaldehyde via an intermediate treating with potassium ferricyanide in ice bath as shown in **scheme 2** [15, 16].



A copper-catalyzed one-pot synthesis of poly substituted imidazoles was developed by Pardeshi *et al.,* by refluxing fromaryl acetic acids, *N*-arylbenzamidines, and nitroalkanes at 130 °C for 8 h using DMF as solvent. This synthesis involves the activation of C-H and N-H bonds as illustrated in **Scheme 3** [17].



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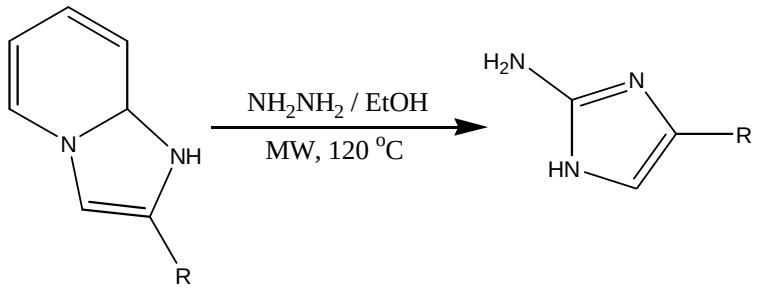
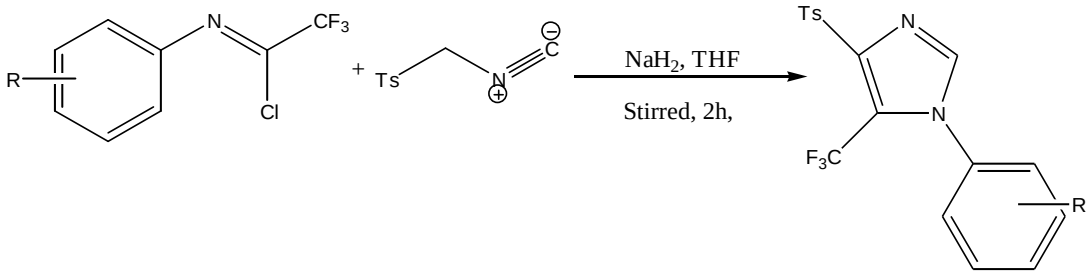
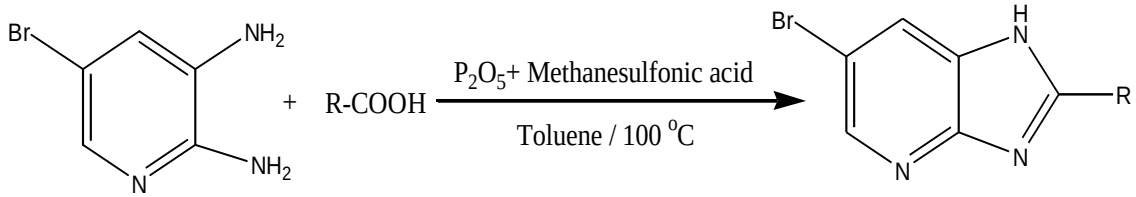
Fascinatingly, Ermolat *et al.*, described the synthesized mono and disubstituted-2-amino-1H imidazoles via microwave assisted hydrozynolysis of substituted imidazole[1,2,a] pyramidines is reported (**Scheme 4**). This method avoids strong acidic condition and is superior to the conventional cyclo condensation of a haloketones with N-acetyl guanidine [18].\



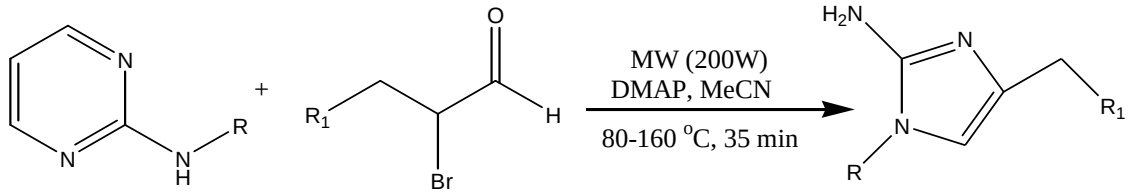
A mild and efficient method for the synthesis of 1,4,5-trisubstituted imidazoles containing trifluoromethyl group has been developed by Bunev *et al.*, using van Leusen reaction, which couples two-component condensation reaction trifluoroacetimidoyl chlorides with tosylmethylisocyanide (**Scheme 5**). This is a method for obtaining trifluoromethyl containing 1, 4, 5-trisubstituted imidazoles in good yields [19].



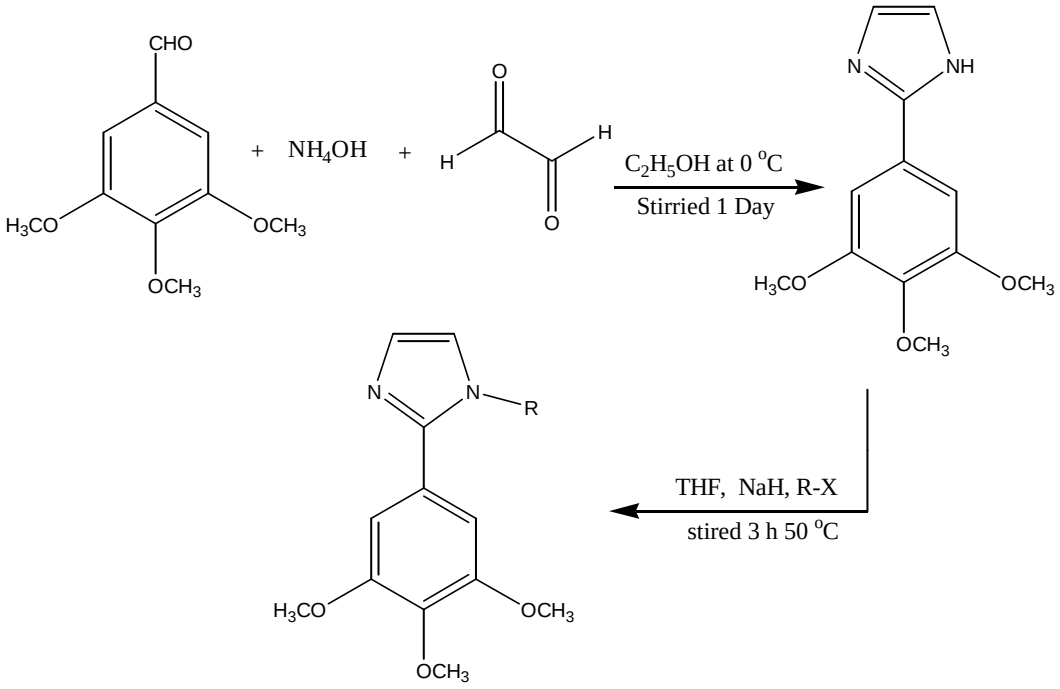
Lavanya *et al.*, prepared 6-bromo-2-substituted phenyl-1H-imidazo [4, 5-b] pyridine compounds from 5-bromopyridine-2,3-diamine condensation with aromatic carboxylic acids in the presence of Etan's reagent as described in **scheme 6** [20].



Correspondingly, Ermolatev *et al.*, developed a efficient method 2-amino-1H-imidazoles from the reaction of 2-aminopyrimidine with α-bromoketone under microwave irradiation conditions at 200W and 80-160°C for 35 min as its illustrated in **scheme 7** [21].



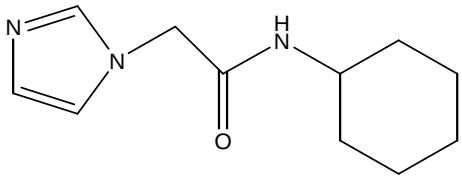
Recently, a group of researcher synthesized microtubule depolymerizing imidazole agents by reacting, 3,4,5-trimethoxy benzaldehyde with ammonium hydroxide and glyoxal to construct the imidazole ring via intermediate subject to a nucleophilic substitution or C-N coupling reaction [22].



5. Pharmacological activity of Imidazoles

Antimicrobial properties

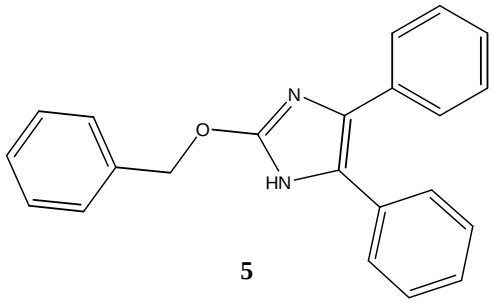
N. Gupta *etal.,* synthesized a series of N-substituted imidazole pharmacores and evaluated for the antimicrobial activity. Among the synthesized derivatives, Compound **4**, was found to be the most active antimicrobial compound [23].



4

Anti-inflammatory activity

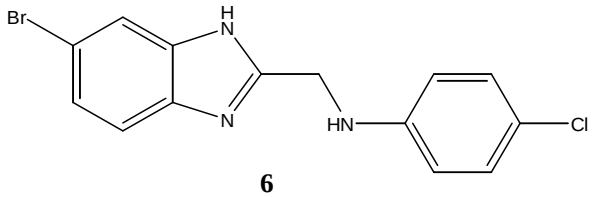
A group of researcher experimented on 2-substituted-4,5-diphenyl-1H-imidazoles and found that compound **5** showed maximum anti-inflammatory activity based on Carrageenan-induced paw edema method [24].



5

Analgesic property

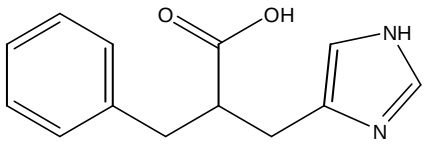
A series of 2-methylaminibenzimidazoles were synthesized by Achar*et al.,* and screened for anti-inflammatory and analgesic activities. Among the series, compound **6** shows good analgesic activity as compared to standard market drug nimesulide [25, 26].



6

Imidazoles as carboxypeptidase A inhibitors

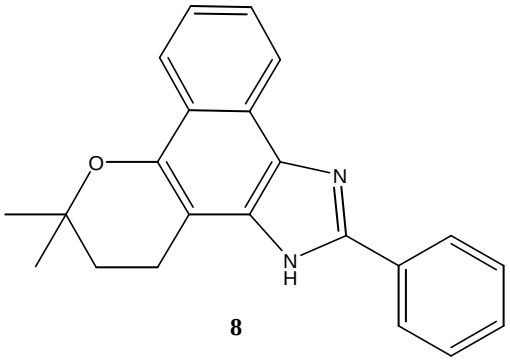
Carboxypeptidase A (CPA) is one of the most studied zinc containing proteolytic enzymes and serves as a prototypical enzyme for metalloproteases that play important roles in biological system. In view of above, Han and Kim synthesized competitive inhibitors of CPA, 2-(4-imidazolyl) hydrocinnamic acidand its congeners that bear an imidazole ring as zinc-ligating functionality been evaluated for their CPA inhibitory activity. From the study, it was reported that compound 2-benzyl-3-(1H-imidazol-4yl)propionic acid **7** may potentially be explored as therapeutic agent that can selectively control rapidly proliferating breast cancerous cells [27].



7

Imidazoles as trypanocidal agents

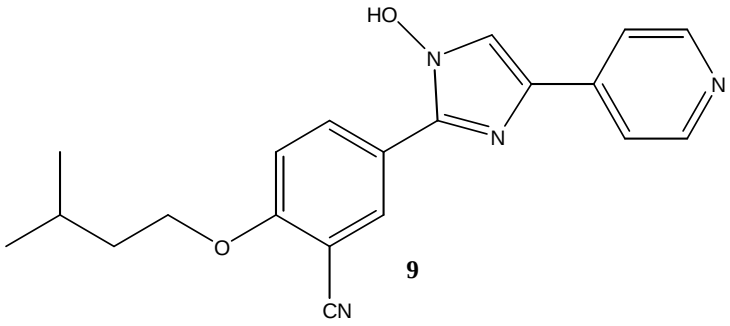
Moura *et al.,* synthesized new naphthoimidazolesform b-lapachone with an aromatic moiety linked to theimidazole ring using phenylic and heterocyclic aldehydes. 4,5-dihydro-6,6-dimethyl-6H-2-(40-methyl phenyl)-pyran[b-4,3]naphtha[1,2-d]imidazole **8** was found to be most active compound against Trypanosoma cruzi with an EC50 value of 15.5 ± 2.9 lM [28].



8

Imidazoles as xanthine oxidase (XO) inhibitors

A series of 1-hydroxy-2-phenyl-4-pyridyl-1H-imidazole derivatives as novel XO inhibitors has been developed by Zhang *et al.,* Among the synthesized series, compound **9** was found to be the most promising derivative with an IC50 value of 0.64 μM. Also, the Lineweaver-Burk plot revealed that compound **9** acted as a mixed-type XO inhibitor [29].

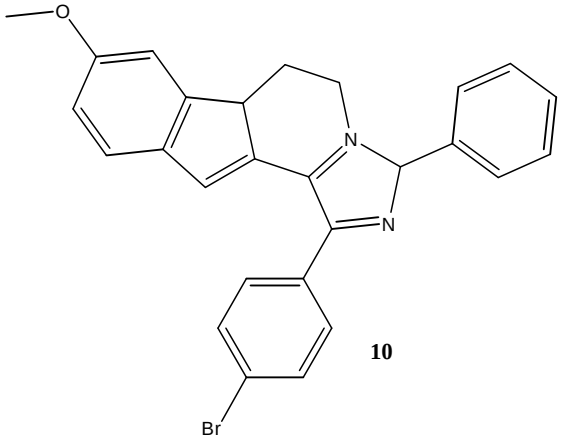


9

Role of imidazoles in diabetes mellitus

Diabetes mellitus, commonly known as diabetes, is a metabolic disease that occurs when your blood glucose is too high and causes high blood sugar. It is probably one of the oldest diseases known to man which was first reported in Egyptian manuscript about 3000 years ago [30]

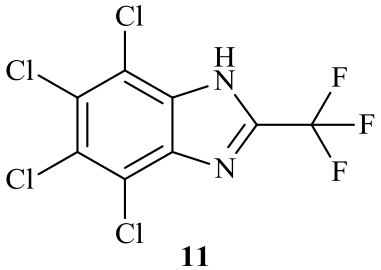
Mehdi Adib *et al.,* has reported designed and synthesized a series of fused carbazole–imidazole derivatives 6a–w and evaluated these agents for their α-glucosidase inhibitory activities. Based on inhibition assay, all of the synthesized compounds revealed more potent than the standard drug acarbose. Among the series, compound **10** (IC50 = 74.0 ± 0.7 μM) was found to be the most active inhibitor with inhibitory activity 10 fold better than standard drug [31]



10

Imidazoles as anthelmintics

It was found that imidazole is less sensitive in intestinal parasites. Types of class (2-alkyl benzimidazole) take away different species of nematodes and trematodes from different hosts. Compound **11** show high activity against the nematodes with proven potentials to kill various species of intestinal nematodes. It was also have been found to posses activity against cestodiasis of man and animal. Mebendazole a benzimadiazole drug **12** at the dose of 100 mg/kg cure patient suffering with T. Solium and T. Saginata [32].



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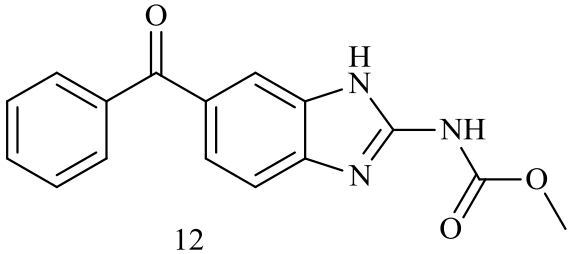
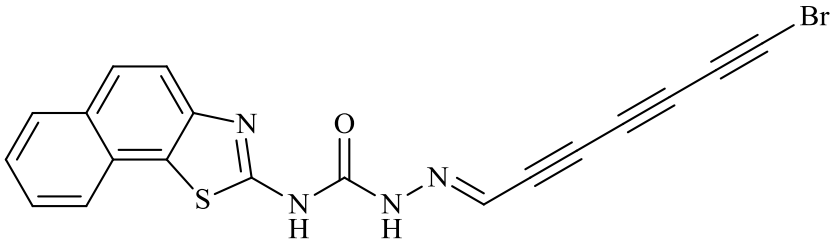


12

Anticonvulsant activity

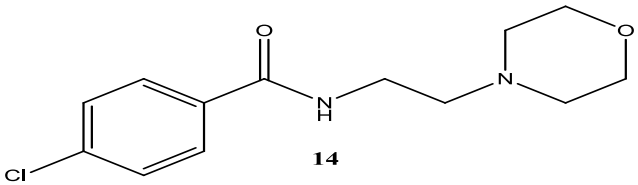
Azam et al., designed and synthesized a series of imidazozole derivatives and evaluated for their anticonvulsant and neurotoxicity studies. Among the series, compound **13** shows good anticonvulsant activity [33].



13

Anti depressant activity

Moclobemide **14** is a selective and reversible monoamine oxidase-A inhibitor and is used as an antidepressant. Hadizadeh *et al.,* synthezied moclobemide derivatives by replacing paro chloro phenyl group of moclobemide **14** and studied for the antidepressant activity using forced swimming test in mice. Among the synthetic series they found that compounds **15a-c** are more potent than moclobemide [34].



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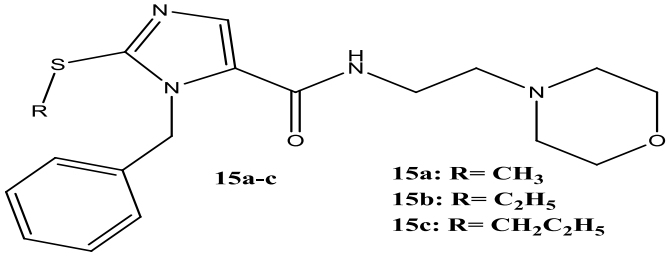

15a-c

15a: R= CH_3
15b: R= C_2H_5
15c: R= $CH_2C_2H_5$

6. Conclusion

Imidazoles have occupied a unique place in the field of medicinal chemistry. Imidazoles have large scope in various clinical medicinal field. The numerous methods for the synthesis of imidazoles have been developed and also their various structure activity relationship offer enormous scope in the field of medicinal chemistry. Therefore, this article aims to review the work reported on the introduction, brief history, synthesis and biological efficacy of Imidazole derivatives to get better understand and explore its various properties and pharmacological potentials.

Acknowledgements

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