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IMIDAZOLE DERIVATIVES HAVING APPROPRIATE EFFECT ON VARIOUS DISEASES

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ABSTRACT: Imidazole is a compound that has been synthesized in a variety of its derivative forms over the past few years; the compound is a key source of interest to investigate its many pharmacological potentials. The chemistry of imidazole and its pharmacological effects as an antiviral, antimalarial, anticonvulsant, anticancer, antifungal, and anti-inflammatory medication are reviewed in this article by examining its different synthetic derivatives. Based to the available information, imidazole is a hetero-atomic planar five-member ring structure with a variety of chemical properties that can be utilized by generating derivatives with different pharmacological effects. In this article, the effects of various substitutions and combinations of various moieties with imidazole are discussed.

Key words: Imidazole, Antiviral, Antimalarial, Anticancer, Antifungal, Anti-inflammatory.

INTRODUCTION

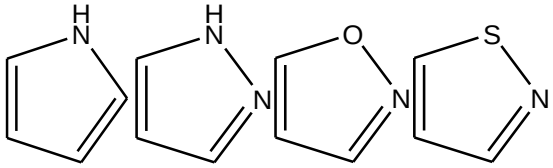
The most prevalent heteroatoms are nitrogen, oxygen, and sulfur, but heterocyclic rings including additional hetero atoms are also well known. Heterocyclic compounds are cyclic organic molecules that contain at least one hetero atom.[1,2]In recent years, especially in medical chemistry, the synthesis of molecules based on heterocyclic scaffolds containing nitrogen, oxygen, and sulphur has become more and more significant. Due to their wide range of biological action, indole derivatives among nitrogen-heterocyclic compounds need special consideration.[3,4,5,6]

The possible chemical and physical characteristics of the heterocyclic rings are of interest to biology. Since many naturally occurring products, including hormones and antibiotics, contain structural subunits, heterocyclic compounds are of great importance to the life.[7]In the field of medicine, heterocyclic molecules with nitrogen atoms rich in electrons are extremely important. Azole-based derivatives with a heterocyclic ring system, electron-rich structures, hydrogen bonds, ion-dipole interactions, hydrophobic effects, and weak connections like Vander Waals interactions with enzymes and receptors allow for a variety of biological activities.[8,9,10]

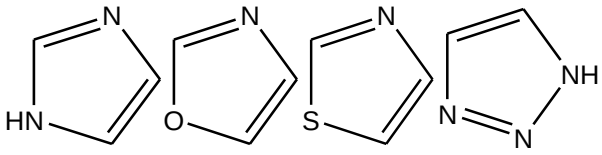
AZOLES

Azoles are five-membered heterocyclic compounds with at least one nitrogen heteroatom and one or more other heteroatoms. One nitrogen atom is present in the simplest azole, pyrrole (1). Pyrazole (2), isoxazole (3), and isothiazole (4) are the names given to the rings that include two nitrogen atoms, one oxygen and one nitrogen atom, and one sulphur and one nitrogen atom in the 1, 2 position.Both heteroatoms are referred to as imidazole (5), oxazole (6), and thiazole (7), respectively, when they are represented in a 1,3-relationship. Triazole is a name for a five-membered ring with three nitrogen atoms, such as 1, 2, 3-triazole (8) and 1, 2, 4-triazole (9). Tetrazole, on the other hand, is a five-membered ring made up of four nitrogen atoms (10). Azoles are widely present in natural sources. Numerous drugs are available that contain an azole ring in their molecular structure.

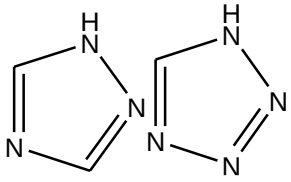
In the last two decades, there has been a lot of interest in the synthesis of different substituted imidazoles, benzimidazoles, benzoxazoles, tetrazole, and quinazolinones from aryl thiocyanates since they contain compounds with a variety of biological activities and have a variety of medicinal qualities.[11,12,13]



1) Pyrrole 2) Pyrazole 3) Isoxazole 4) Isothiazole



5) Imidazole6) Oxazole 7) Thiazole 8) 1,2,3-triazole



9) 1,2,4-triazole 10) Tetrazole

Following is a description of nitrogen-containing heterocyclic ring sizes:[14,15]

A. Five-membered heterocyclic compounds

i. Triazole (1,2,3-triazole and 1,2,4-triazole)

ii. Tetrazole

iii. Imiazole/Benimidazole

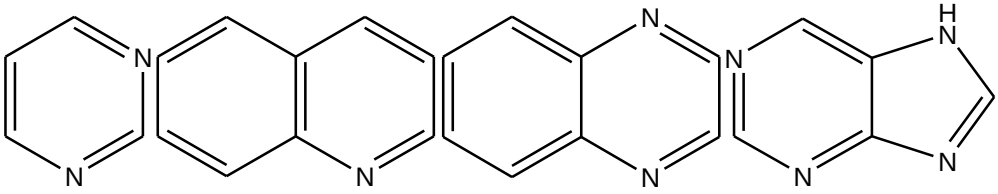
B. Six-membered heterocyclic compounds

i. Pyrimidine

ii. Quinoline

iii. Quinoxaline

iv. Purine



1) Pyrimidine2) Quinoline 3) Quinoxaline4) Purine

HISTORY OF AZOLES

The earliest description of the antifungal properties of an azole compound, benzimidazole, was made in 1944 by Woolley, but it wasn't until 1958, with the development of topical chlormidazole, that researchers began to take an interest in the antifungal properties of azole compounds. Clotrimazole, created by Bayer Ag (Germany), and miconazole and econazole, both developed by Janssen

Pharmaceutica (Belgium), were three new topical medications that were released in the late 1960s.[16,17,18]

IMIDAZOLE

Imidazoles are a significant group of heterocyclic compounds because of their wide range of medicinal and physiological effects, including their anti-inflammatory, antibacterial, anticonvulsant, and anticancer properties. Numerous drugs have imidazole nucleus in their structure like cimetidine as antihistaminics ,dacarbazine as anticancer, metronidazole as antifungal, and flumazenil as benzodiazepine antagonist.**[19,20,21,22]**

The imidazole is a planar, five-memberedheteroaromatic molecule having 3C and 2N atoms in the 1 and 3 positions. Its systemic name is 1,3-diaza-2,4-cyclopentadiene.The molecular formula of imidazole is $C_3H_4N_2$, which consists two hetero atoms (nitrogen) and two double bonds.[23,24]

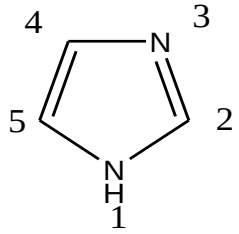


Figure 1: Imidazole

Gloxaline was its original name because it was created using glyoxal and ammonia by Heinrich Debus in 1858. Attacks of an electrophilic and nucleophilic nature might affect amphoteric nature. Highly resistant to thermal, acid, base, oxidation, and reduction conditions.[25]

Significant intramolecular hydrogen bonding is present. Because the hydrogen atom can be found on either of the two nitrogen atoms, it can exist in two identical tautomeric forms. The compound is classified as aromatic due to the existence of a sextet of π-electrons, made up of pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms in the ring.[26,27,28]

The amino acid histidine, vitamin B12, a component of DNA base structure, and purines, histamine, and biotin are among the well-known components of human creatures that have an imidazole nucleus as their primary structural component. Cimetidine, azomycin, and metronidazole are a few examples of natural or synthesised medicine compounds that contain it in their structures.[29,30]

AROMATICITY & RESONANCE

The imidazole ring is aromatic and resembles other compounds with 5-membered rings that are aromatic. The cyclic pi system receives a p-orbital from each ring atom. The aromatic sextet is made up of the nitrogen that resembles a pyrrole at position 1 and four ring atoms, including the nitrogen that resembles a pyridine. A positive charge is present on the nitrogen that resembles a pyrrole in four of the five major resonance structures, while a negative charge is present on one of the other four ring atoms. As a result, the nitrogen that resembles pyrrole is partially positive and the rest of the ring is partially negative, similar to the situation in pyrrole itself.[31]

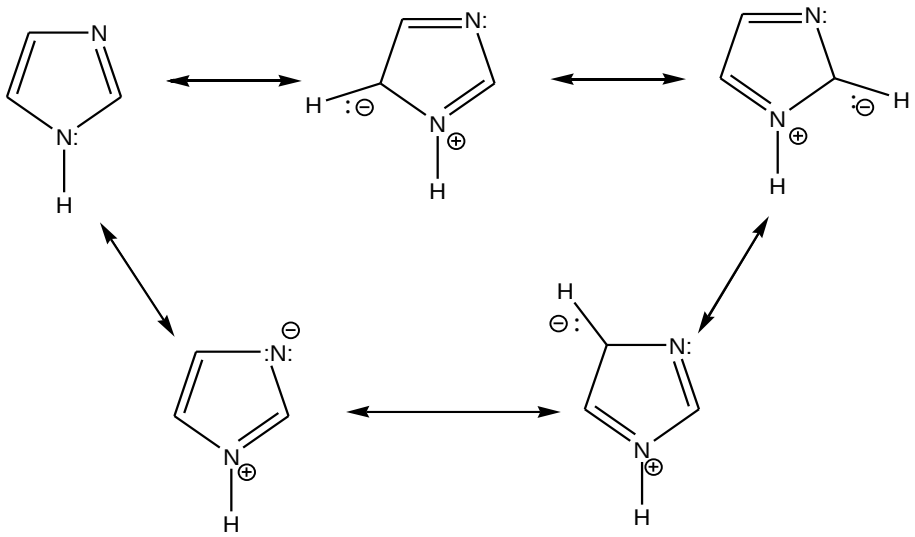


Figure 3: Resonance of imidazole

Imidazole has two tautomeric forms of the ring because each nitrogen atom in the imidazole ring has a possibility to contain a hydrogen atom. This tautomerism develops as a result of the quick proton transfer that takes place between the imidazole ring's 1- and 3-positions.[32,33]

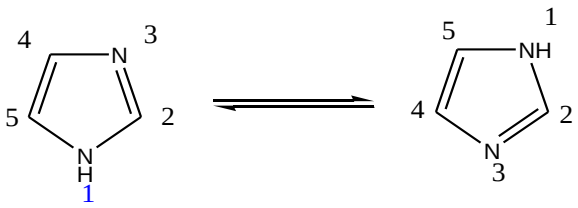
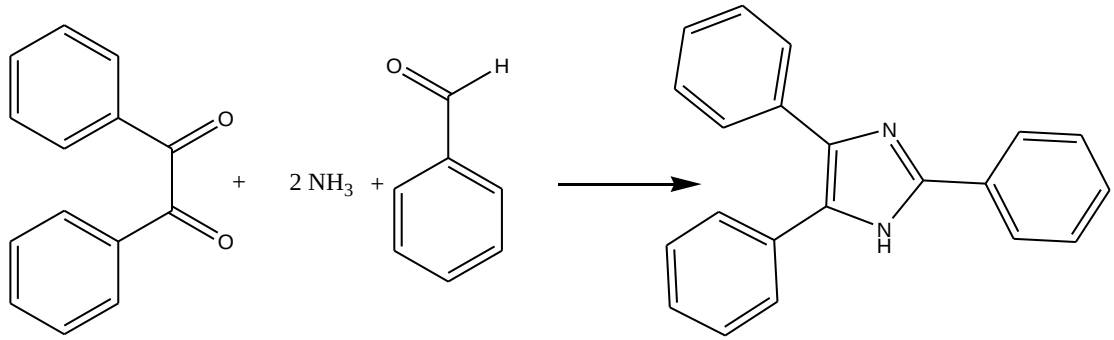


Figure 4: Tautomeric forms of imidazole

SYNTHESIS OF IMIDAZOLE:

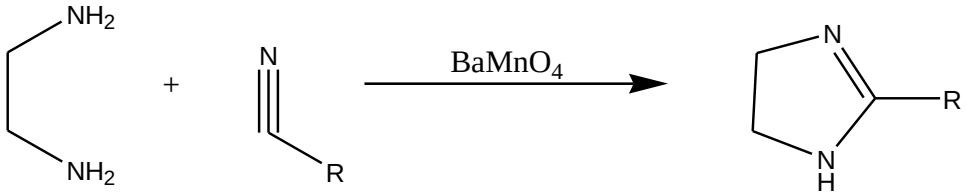
1) RADISZEWSKI SYNTHESIS –[34]

It involves combining a dicarbonyl chemical, such as glyoxal, a-ketoaldehyde, or a-diketone, with an aldehyde in the presence of ammonia. For example, when benzyl is combined with benzaldehyde, two molecules of ammonia react to produce 2,4,5-triphenylimidazole. A convenient alternative to ammonia is frequently found to be formamide.



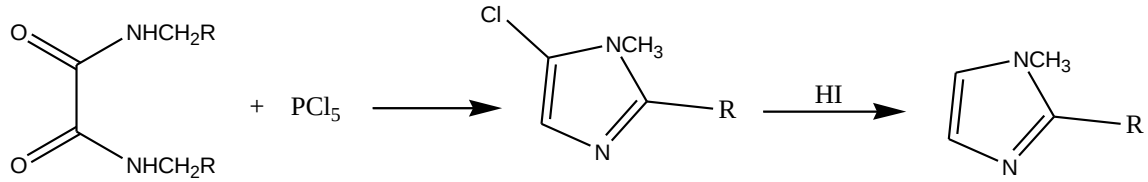
2) DEHYDROGENATION OF IMIDAZOLINE [35]

For the conversion of imidazolines to imidazoles in the presence of sulfur, Knapp and colleagues have reported the use of the gentler reagent barium managanate. When alkyl nitriles and 1, 2 ethanediamine are combined, the resulting imidazolines produce 2-substituted imidazoles.



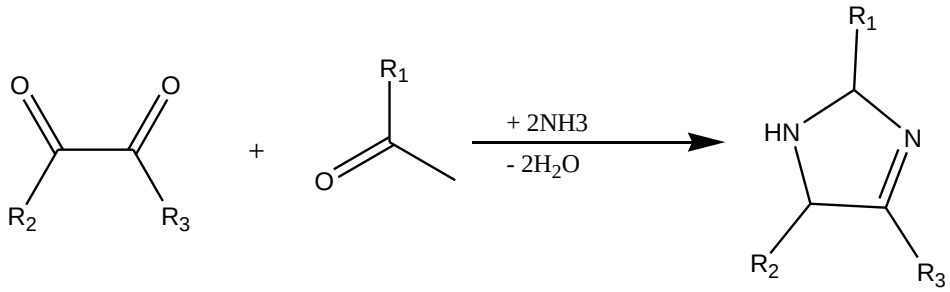
3) WALLACH SYNTHESIS[36]

According to Wallach, phosphorus pentachloride can be used to treat N, N- dimethyloxamide to produce a chlorine-containing molecule that, when reduced with hydroiodic acid, yields N- methyl imidazole . When N,N-diethyloxamide is subjected to the same condition, it transforms into a chlorine compound, which, upon reduction, yields 1-ethyl-2-methyl imidazole.



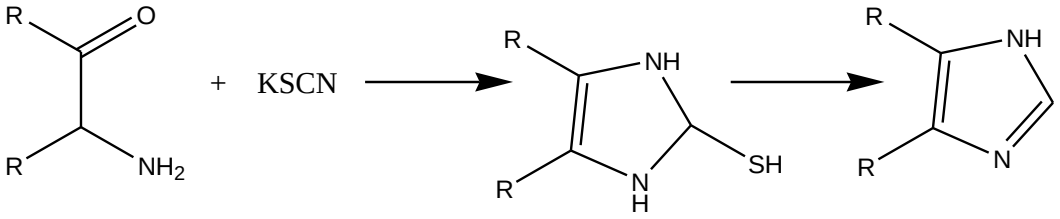
4) DEBUS SYNTHESIS[37]

Debus used formaldehyde and glyoxal in ammonia to synthesize imidazole. Despite having relatively low yields, this procedure is nevertheless employed to make C-substituted imidazoles.



5) MARKWALD SYNTHESIS [35]

For the production of 2-thiol substituted imidazoles, 2-mercaptoimidazoles are made from -amino ketones or aldehydes and potassium thiocyanate. To obtain the necessary imidazoles, the sulfur can easily be removed using a variety of oxidative methods.



PHARMACOLOGICAL EFFECTS:[38]

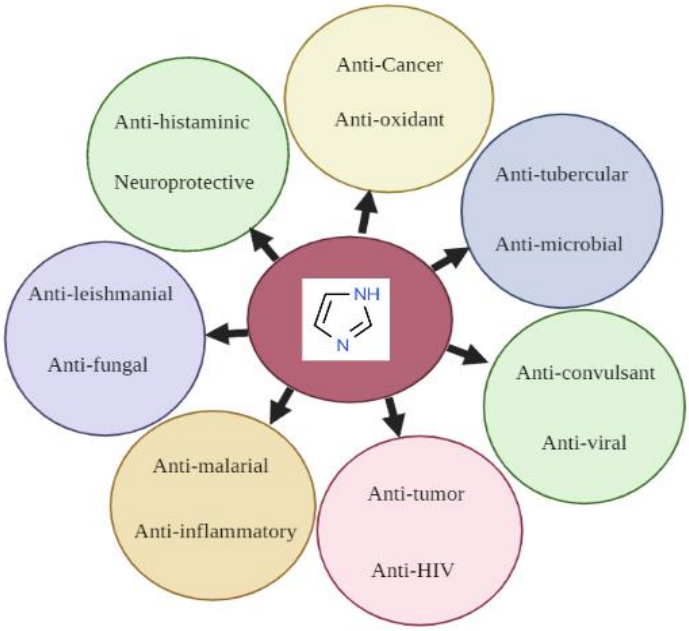
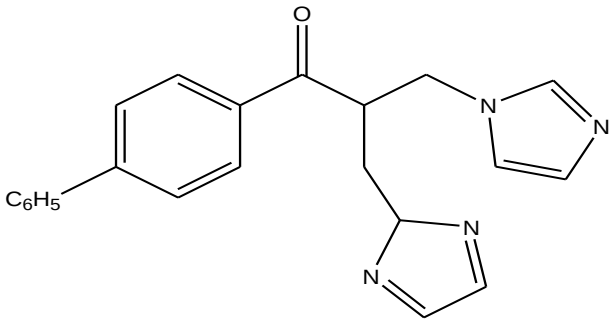


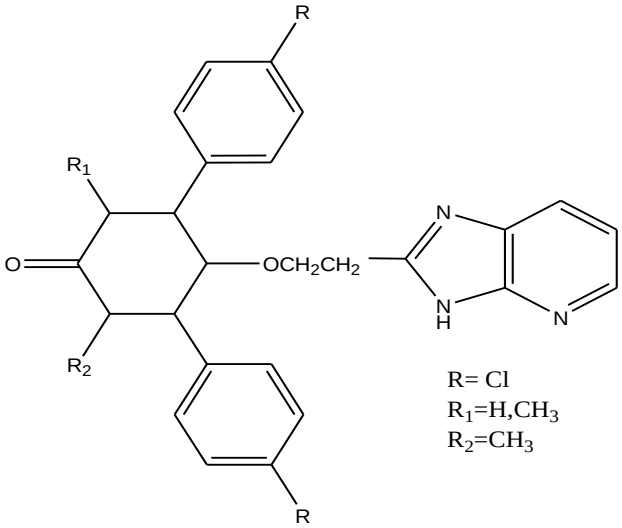
Figure 5:Pharmacological effects of Imidazole

ANTIFUNGAL AND ANTI-BACTERIAL ACTIVITY

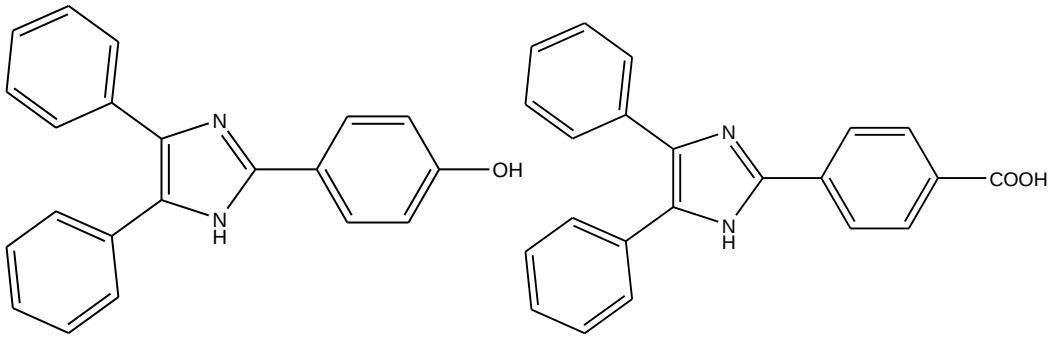
Daniele Zampieri et al., (2007) synthesized bis-imidazole derivatives and screened for antifungal and antimycobacterial activity. All compounds showed moderate to good activity against Candida albicans and Candida glabrata. Miconazole was used as reference drug.[39]



The potential antibacterial activity of a series of imidazo(4,5-b) pyridinylethoxypiperidones against Bacillus subtilis, Klebsiellapneumoniae, Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa, as well as the antifungal activity against Candida albicans-6, Candida albicans, Aspergillusniger, Candida albicans-51, and Aspergillusflavus were assessed by **G. Aridoss*et al.*(2006)** . Strong in-vitro antibacterial activity against Bacillus subtilis and Staphylococcus aureus, as well as promising antifungal activity against Aspergillusflavus, were revealed by the structure-activity relationship of the compounds.[40]

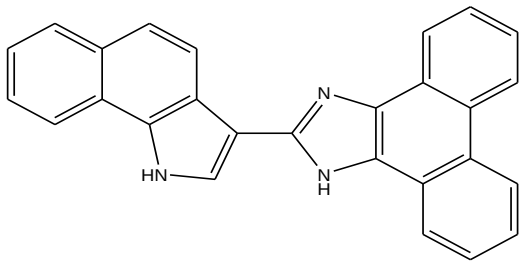


A simple highly versatile and efficient synthesis of 2,4,5-trisubstituted imidazole is achieved by three component cyclocondensation of 1,2-dicarbonyl compounds, aldehydes and ammonium acetate as ammonia source in thermal solvent free condition using Bronsted acidic methane sulphuric acid as catalyst by **Lahari MS *et al.* (2022)**. The newly obtained derivatives were confirmed by advanced spectroscopic data such as FTIR, 1HNMR, 13CNMR and LCMS and the structural determination of the desired compounds were determined by elemental analysis and the result revels that newly synthesized compounds showed satisfactorily antibacterial activity.[41]

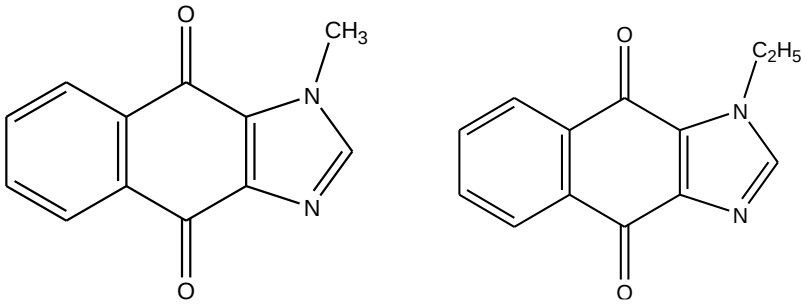


Ramos NL*et al.* (2020) report the synthesis of 2,4,5-tri (hetero) arylimidazole derivatives and their characterization by 1H and 13C nuclear magnetic resonance (NMR) and UV-Vis absorption

spectroscopies. A screening for antibacterial activity showed the inhibition of *Staphylococcus aureus* proliferation, suggesting antibacterial activity.[42]

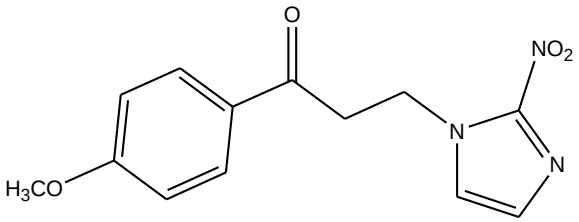


SunitaSalunke-Gawali*et al.* (2020) report syntheses of imidazole-based 1,4-naphthoquinones and their precursor compounds from 2,3- dihydronaphathalene-1,4-dione. All the compounds were tested for their antibacterial and antifungal activity showed a broad spectrum of activity against Gram-positive as well as Gram-negative bacteria.[43]



ANTIPARASITIC

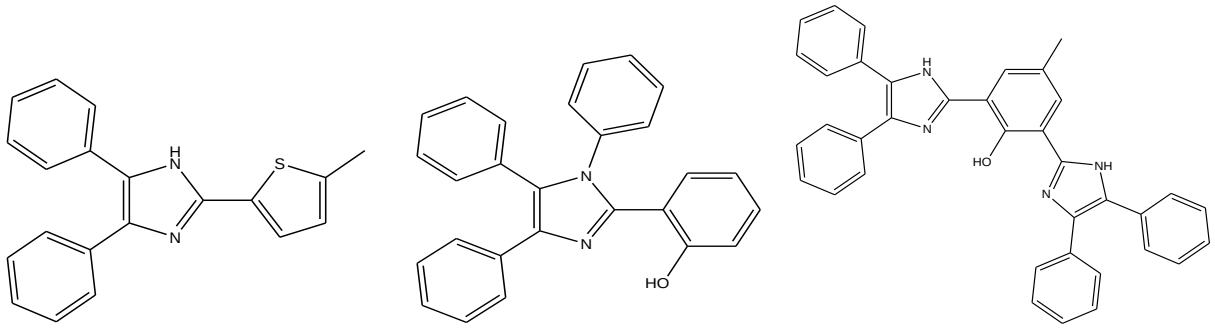
Beltran-Hortelano I *et al.* (2021)synthesised and characterised a total of 69 Mannich base-type derivatives bearing imidazole and benzimidazole-functionalized cores. The in-vitro cell-based studies were performed & it revales that these compound 1-(4-Methoxy-phenyl)-3-(2-nitro-imidazole-1-yl)-propane-1-one had the most promising trypanocidal activity across the distinct life stages of the parasite.[44]



ANTIVIRAL

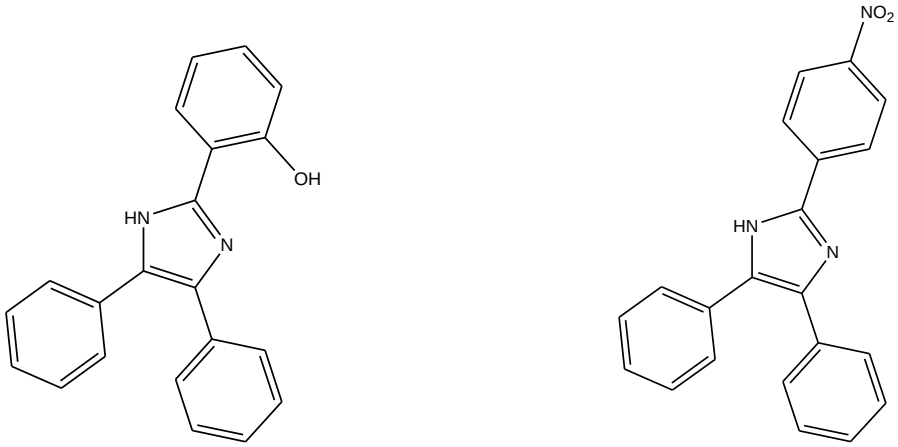
Three classes of recently synthesized imidazole derivatives were assessed for their ability to inhibit SARS-CoV-2 using an in silico method by *Johnson TO et al. (2021).* Molecular docking analysis was used to explore the therapeutic potential of the newly synthesized compounds against RNA-dependent RNA polymerase (RdRp), spike protein (Spro), and main protease (Mpro) of SARS-CoV-2. The

pharmacophore models were created, the binding free energy of the protein-ligand complexes was estimated, and the compounds absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties were ascertained. The compounds bind to the target proteins with intriguing affinities and stability.[45]

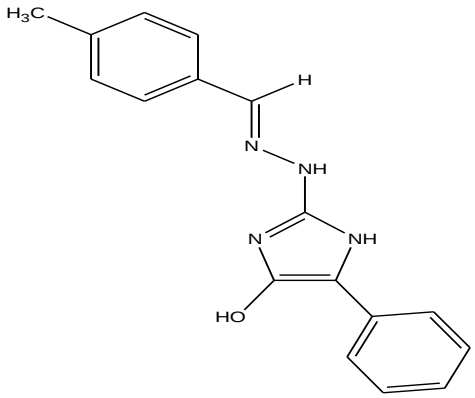


ANTIPROLIFERATIVE

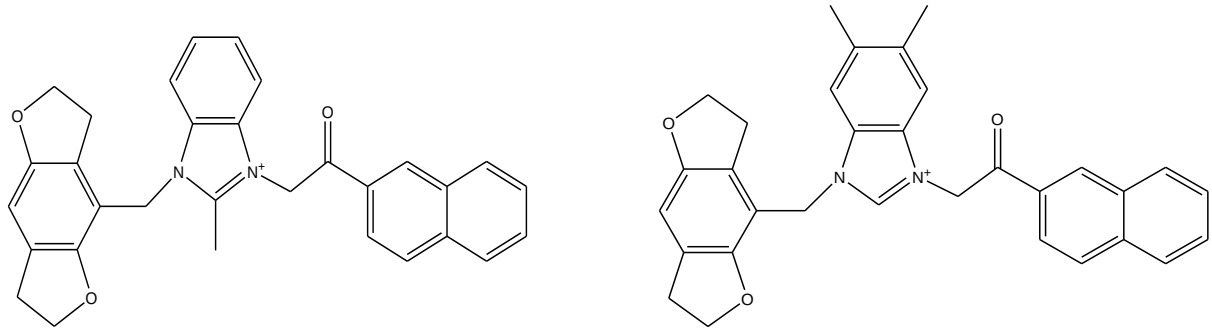
Noriega-Iribe E*et al.* (2020) synthesized a series of 13 derivatives of 2,4,5-trisubstituted imidazole and their structures were characterized and confirmed through a series of spectroscopic and spectrometric techniques. The compounds were investigated *in-vitro* as antioxidant molecules using 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2-20 -azino-bis-(3-ethylbenzothiazoline-6-sulfonate) (ABTS) assays, acetylcholinesterase (AChE) and xanthineoxidase (XO) inhibitors. The antiproliferative activity was evaluated against six cell lines from different anatomic origins, and the synthesized compounds showed from moderate to very good activities.[46]



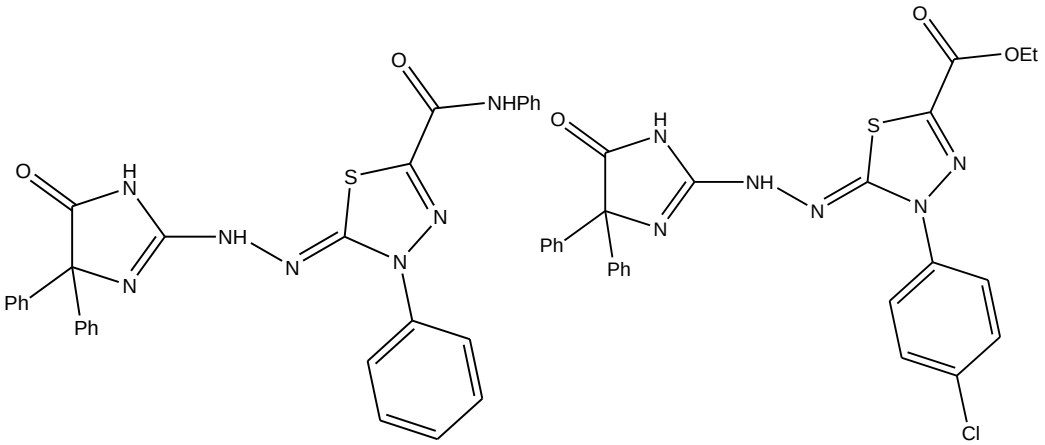
S. C. YAVUZ *et al.* (2019) synthesized imidazole derivatives from two-component condensation reaction of phenylgloxal monohydrate with guanylhydrazone and compounds were evaluated for *in-vitro* anticancer activity on human breast cancer (MCF-7) and human liver cancer (HepG2) cell lines using the MTT assay method. Most of the newly synthesized compounds displayed more cytotoxic activity against these cancerous cells than the positive control drugs, fluro-5, and irinocam.[47]



The synthesis of a series of novel 4-substituted 2,3,6,7-tetrahydrobenzo [1,2-b;4,5-b0]difuran–1H-imidazolium salts was presented by **Zhang CB *et al.* (2017)**. The biological properties of the compounds were evaluated *in-vitro* against a panel of human tumor cell lines. Results suggest that the 5,6-dimethyl-benzimidazole or 2-methyl-benzimidazole ring, and substitution of the imidazolyl-3-position with a 2-naphthylmethyl substituent or 2-naphthylacyl substituent, were important to the cytotoxic activity.[48]

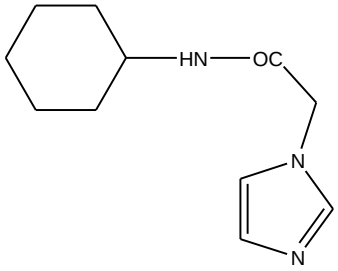


Gomha SM*et al.* (2016) synthesized a series of novel thiadiazoles bearing imidazole moiety by using 2-(5-oxo-4,4-diphenyl4,5-dihydro-1H-imidazol-2-yl)-N-phenylhydrazinecarbothioamide as the starting compound. The structure of all the newly prepared products was established based on both elemental analysis and spectroscopic data and by alternative method wherever possible. Some of the newly synthesized compounds were evaluated for their anticancer activity against the liver carcinoma cell line HEPG2-1. Also, their SAR was studied. The results indicated that many of the tested compounds showed moderate to high anticancer activity with respective to doxorubicin as a reference drug.[49]



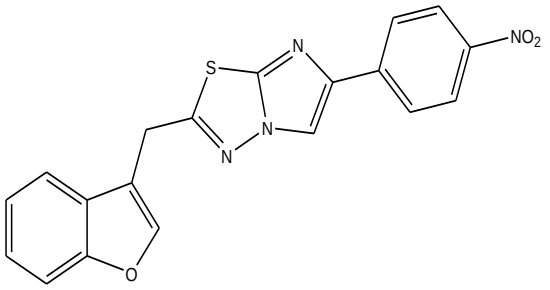
ANTIMICROBIAL

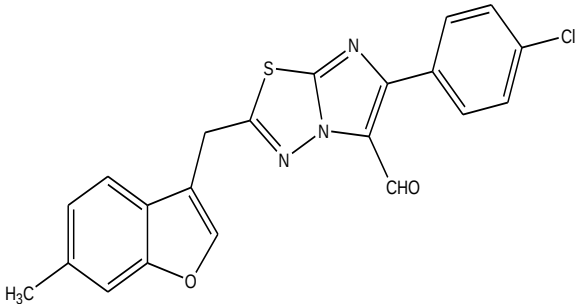
Gupta &Pathak (2011) designed & synthesized N-substituted imidazole derivatives. The compounds were characterized by FT-IR, ^{1}H-NMR and mass spectra. The synthesized compounds possessed the highest antimicrobial activity against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Candida albicans* and *Aspergillusniger* by determination of MIC (minimum inhibitory concentration) using tube dilution method.**[50]**



ANTI-INFLAMMATORY AND ANALGESIC

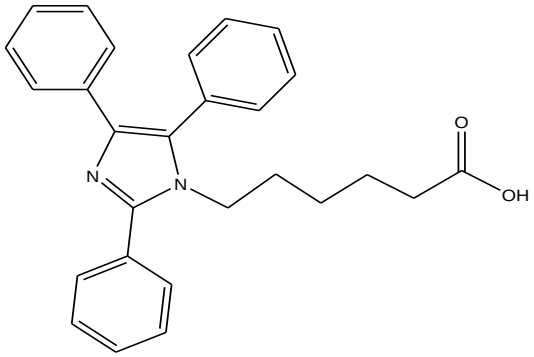
V.B. Jadhav*et al.* (2008) worked on synthesis of methylene bridged benzofuranylimidazo[2,1-b][1,3,4]thiadiazoles and a series of 6-substituted and 5,6-disubstituted 2-(6-methyl-benzofuran-3-ylmethyl)-imidazo[2,1-b][1,3,4]thiadiazoles and the newly synthesized compounds have been evaluated for their in vivo analgesic & anti-inflammatory activities. The Qualitative SAR studies was also performed and result indicated that the chloro substitution in the imidazole ring and introduction of formyl group at C-5 position of the imidazole ring increased the anti-inflammatory and analgesic activity.**[51]**

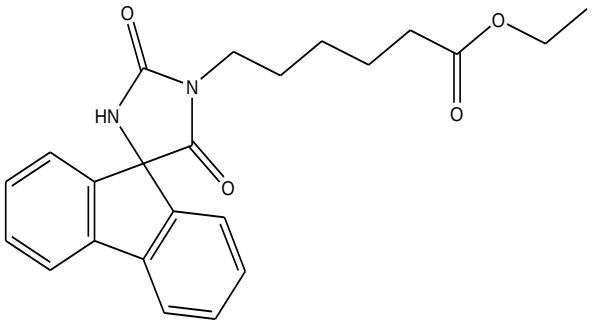




ANTICONVULSANT

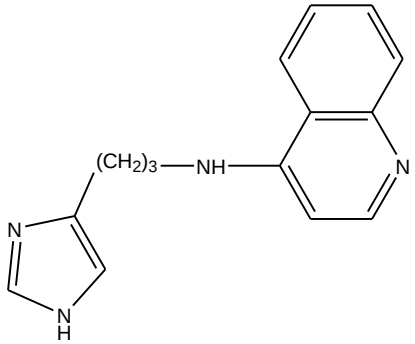
New imidazolidindiones and tetra-substituted imidazole derivatives were designed & synthesized by **Marzouk AA *et al.* (2020)**. Synthesized compounds were evaluated for the anticonvulsant activity through pentylenetetrazole (PTZ)-induced seizures and maximal electroshock (MES) tests using valproate sodium and phenytoin sodium as reference drugs, respectively. Most of the target compounds showed excellent activity against pentylenetetrazole (PTZ)-induced seizures with fair to no-activity against MES.**[52]**

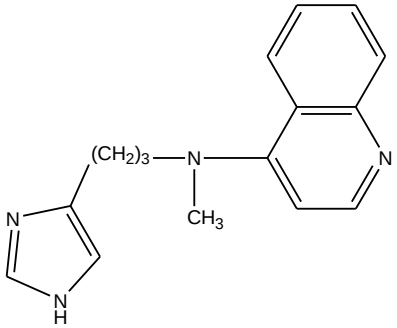




ANTIHISTAMINIC DRUGS

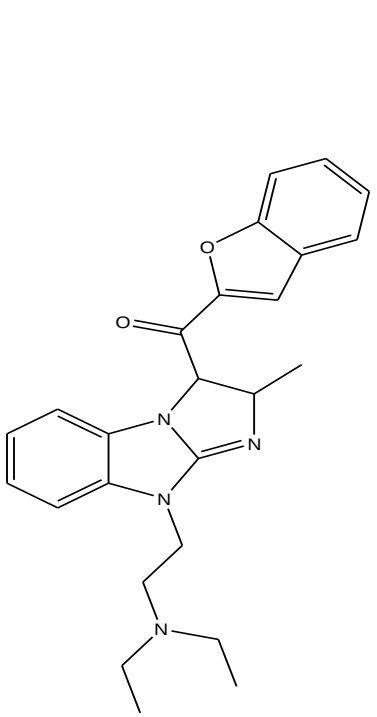
A novel class of imidazole-containing compounds with dual properties—namely, inhibitory potency at the enzyme histamine N-methyltransferase (HMT) and antagonist potency at histamine H3 receptors—have been developed and synthesised by ***S. Grabmann et al.*** Pharmacologically, these new hybrid medicines were tested in functional assays for their antagonistic effects on the synaptosomes of the rat cerebral cortex and their inhibitory potencies at rat kidney HMT. The findings demonstrated that many of the investigated compounds had antagonist efficacy at histamine H3 receptors and moderate to high inhibitory impact at the enzyme histamine N-methyltransferase (HMT), making these derivatives an important pharmacological tool for further development.[53]

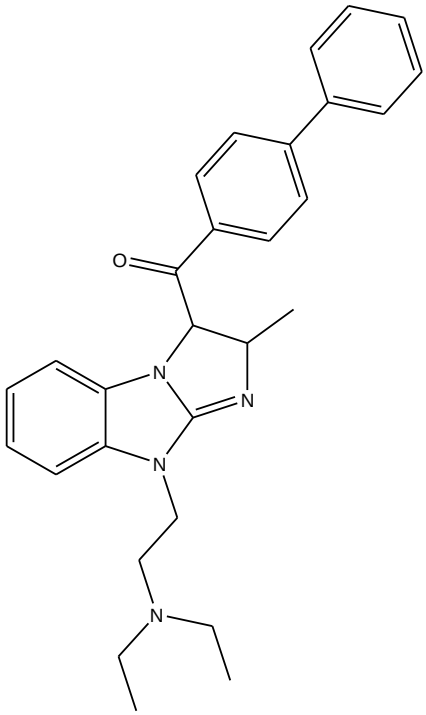




NEUROPROTECTIVE

S. Zhao, H. Zhang, H. Jin, et al. used a 3-D similarity-based screening strategy with the energy-minimized conformation of the non-selective TRPM2 inhibitor 2-APB as the query structure, leading to the discovery of a novel tricyclic TRPM2 inhibitor with a benzo[d]imidazo[1,2-a]imidazole skeleton. Following this, a number of derivatives were created and assessed using electrophysiology and calcium imaging techniques. The neuroprotection experiment revealed that several synthetic drugs may successfully lower the mortality of SH-SY5Y cells brought on by H_2O_2. These results may offer a novel method for the investigation of TRPM2 activity in disorders linked to reactive oxygen species (ROS) and enrich the structural kinds of existing TRPM2 inhibitors.[54]





ANTI HIV ACTIVITY

Imidazoles have been known as antiviral agents, one of the examples being capravirine. ***Silvestri et al.*** and ***De Martino et al.*** synthesized a number of 1-2-(diarylmethoxy)ethyl]-2-methyl-5-nitroimidazole

(DAMNI) analogs as novel HIV-1 HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) active at submicromolar concentration, with the racemic 1-2-[(thiophen-2-yl)phenylmethoxy]ethyl]-2-methyl-5- nitroimidazolebeing the most potent among all the analogs, exhibiting higher activity than efavirenz against the viral RT carrying the K103N mutation.[55]

CONCLUSION: The chemistry of several ways to synthesize imidazoleare addressed. Here, various imidazole substituted and fused compounds are examined for their various pharmacological properties as part of this chemical study. According to all study findings, imidazole is a flexible nucleus with a wide range of pharmacological actions.

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