Universal Journal of Green Chemistry
http://ojs.wiserpub.com/index.php/UJGC/

Review

A Recent Trends on Green Synthesis and Bioactivity of Imidazole

Irum Jamila, Faisal Nawaza*, Maryam Shafiqa, Muqdssa Rashid, Areeba Akrama, Aleeza Siddiquea, Shanza Taimura, Tehreem Zahra

Department of Chemistry, University of Wah, Quaid Avenue, Wah Cantt., Rawalpindi, Punjab 47040, Pakistan
E-mail: faisal.nawaz@uow.edu.pk

Received: 8 January 2024; **Revised:** 27 March 2024; **Accepted:** 17 April 2024

Abstract: Imidazole is a five-membered, planar heterocyclic ring made up of 3C, 2N, and N in the 1st and 3rd places. Purine, histamine, histidine, and nucleic acid are only a few significant natural compounds that contain the imidazole ring. It is utilised as a cure to optimize the solubility and bioavailability properties of proposed weakly soluble lead compounds since it is an aromatic chemical that is polar and ionizable and so improves the pharmacokinetic features of lead molecules. Derivatives of imidazole have a special place in medicinal chemistry. An essential synthesis technique in the process of discovering new drugs is the integration of the imidazole nucleus. Due to the remarkable therapeutic efficacy of medications related to imidazole, medicinal chemists have been inspired to create numerous innovative chemotherapy agents. This review summarized the work that has been done in recent years about different synthetic approaches of imidazole derivatives and their potential activity as anti-HIV, anticancer, anticovid, antifungal, antidiabetic, antidepressant, antioxidant, and antituberculosis.

***Keywords*:** green synthesis; heterocyclic compounds; imidazole; imidazole derivatives; bioactivity

1. Introduction

Nowadays, green chemistry and its methods for synthesis of metal nanoparticles have become a major point of interest[1]. Green chemistry (sustainable development) is ultimate goal that can meet our present as well as future needs. Chemistry is considered as hazardous science due to toxicity of chemicals and its harmful effects on environment. In this regard Sustainable development played a vital role. In order to minimize the threatening effects of different hazardous chemicals we need green chemistry[2]. Green synthesis is beneficial as it's economical, less contaminated and better for environment and human health[3]. Comparison of Conventional and Synthetic methods is shown in the Figure 1.

DOI: https://doi.org/10.37256/ujgc.2120244234

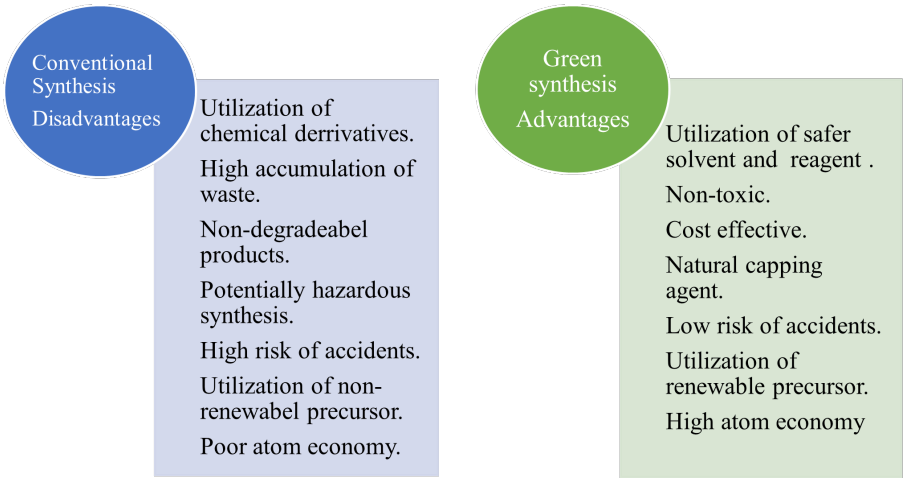


Figure 1. Advantages of green synthesis over conventional synthesis[4].

Heterocyclic compounds are the compounds which contain at least one heteroatom (oxygen, nitrogen, Sulphur, etc.) in cyclic ring[5]. Many of the heterocyclic compounds are the starting materials in the synthesis of various drugs such as antimalarial, anticancer, antiulcer, antineoplastic and antipsychotic. Heterocyclic compound shows the electrophilic as well as nucleophilic properties. They are part of one of the more diverse classes of organic molecules and seem to be more useful across many chemistries[6]. The majority of biomass, nucleic acids, synthetic colors, as well as various natural products including alkaloids, herbicides, vitamins, antibiotics, hormones, and pharmaceutics are included in this group of compounds[7]. Organic and medicinal chemists place a great deal of importance on heterocyclic compounds, and the synthesis of such molecules is constantly difficult from both an academic and industrial perspective[8]. Due to variations in their bio molecular structures, heterocyclic systems with varied architectures exhibit a variety of biologic functions. Due to their distinct physicochemical characteristics and presence of aromatic heterocycles in the side groups, all of these systems have been utilized as drugs in numerous human and veterinary medications, as well as pesticides and insecticides in agriculture. The presence of these rings demonstrated that these types of compounds possess medicinal capabilities and can simultaneously serve as a platform for other pharmacophoric groups that interact with receptors. Through the development of organic synthesis, the main focus of research has been on heterocyclic molecules that include nitrogen and Sulphur. The majority of them are the structural subunits of several biologically active chemicals, such as tetrazoles, triazoles, fused thiazoles, oxadiazoles, and thiadiazoles[9]. Due to the strong aromaticity of the ring structure, which also aids in acquiring significant in vivo stability and decreasing the toxicity of higher vertebrates, including humans, derivatives of thiadiazoles have biological activity[10]. Pyranopyrimidines and derivatives of benzimidazole are a crucial class of heterocyclic pharmaceuticals among other heterocycles. These substances have fascinating biological characteristics such anti-inflammatory, anti-fungal, anti-microbial, anti-phlogistic, anti-bacterial, anti-thrombotic, and anti-genotoxic activity[11]. Oxazole, an oxygen-containing heterocyclic molecule, is crucial in the development of many biologically active medications, including analgesics, anti-inflammatory, anti-cancer, anti-depressant, and anti-microbial agents[12]. Additionally, for a number of years, research into the anti-microbial properties of pyrrole derivatives sparked the creation and evaluation of hundreds of unique compounds, including monodeoxypyoluteorin and derivatives of 2-(2′-hydroxybenzoyl) pyrrole bromine[13]. Analysts have thus long been looking for such distinctive synthetic approaches that would enable us to approach the heterocyclic cores in more practical, effective, and focused manners. Likewise, there are numerous effective examples in the literature. One of the most effective and simple ways to access the cores of various heterocyclic compounds is through cycloaddition processes[14]. These kinds of reactions provide for exceptional atom economy in addition to manufacturing of two bonds although this method is limited[15]. Nitrogen based heterocyclic compounds can be three (Aziridine), four (Azetidine), five (Pyrrol) and six membered (Pyridine)[16] as shown in Figure 2.

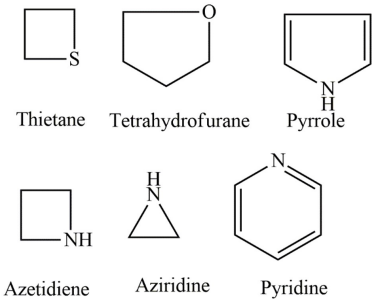


Figure 2. Nitrogen containing heterocyclic compound.

Imidazole is a five membered heterocyclic compound which contain nitrogen at least at 1 and 3 position [17] as shown in Figure 3, synthesis in 1858 by Heinrich Debus by using glyoxal and formaldehyde in ammonia with the loss of water [18]. Imidazole is a quite important heterocyclic compound and have many versatile chemical synthesis and pharmaceutical properties [18].

Figure 3. Structure of imidazole.

They act as a primary source or building block for human body [19]. Among various heterocyclic ring, imidazole are predominant natural product with various biological activities including [20].

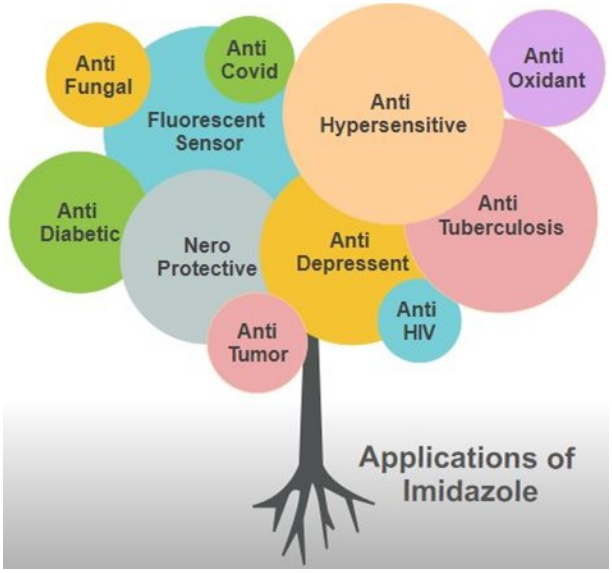


Figure 4. Applications of imidazole derivatives.

By using these structural features and electron rich properties imidazole ring is used by various researcher in order to develop imidazole based drugs. Furthermore, imidazole salts of liquidsare used as electrolyte and solvent in organic synthesis, stable ligand as metalloenzymes and liquid crystal. And also used in cyclic carbonates form epoxides, these

activities make it “ecofriendly” Imidazole derivatives have gained a lot of interest in recent years due to their photo physical and chemical properties[21]. Studies shows that imidazole derivatives due to their nitrogen atomic functional group have been used in optoelectronic, and act as fluorescent biological imaging and chemo sensor. They can also act as synthase inhibitors, hemeoxygenase inhibitors, anti-malarial carboxypeptidase, anti-aging agent, anti-coagulant, anti-inflammatory, strong anti-bacterial, and anti-fungal, anti-viral, anti-tubercular and anti-diabetic etc as shown in Figure 4.

The use of imidazole derivatives in medicinal chemistry has advanced significantly. Numerous imidazole-based therapeutic medications have proved essential in the treatment of many different diseases, and novel imidazole derivatives with medical potential are currently being actively researched and developed throughout the world. There are two equivalent tautomeric forms of it, and one of them allows the hydrogen atom to reside on either of the two nitrogen atoms. The electron-rich nitrogen heterocycles might also easily generate a variety of weak interactions in addition to being able to take or donate protons with ease[22]. Due to the imidazole ring’s unique structural properties, its derivatives are able to interact with a wide range of enzymes and receptors in biological systems by means of hydrogen bonds, coordination, ion-dipole, cations, anion, hydrophobic effects, van der Waals forces, and other mechanisms, resulting in a variety of bioactivities. In reality, a variety of bioactive compounds in human metabolism and naturally occurring chemicals contain imidazole ring in varying degrees[23]. The fact that nature chooses this particular type of imidazole ring to exert various biological functions in many biological molecules, including histamine, vitamin B12, deoxyribonucleic acid (DNA), and hemoglobin, suggests that the imidazole ring should be essential to the physiological action for significant biological activities[24]. Imidazole-based medicinal chemistry has been drawing particular interest due to these unique physiological features and particularly significant roles in essential processes[25].

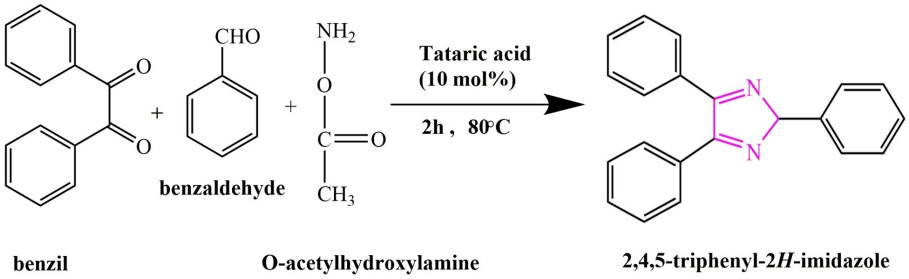
2. Imidazole Derivative and Their Biological Activity

2.1 *Tri-Substituted Imidazole Derivative*

Formation of metal complexes ligand and proteins are known as molecular dockings. It is based on structure of proteins and ligands which combine to form resultant complex. Substituted Imidazole establish many natural products, organically active compounds also act as inhibitors such as anticancer, glucagon receptor antagonist, B-raf kinase, cycloxygenase-2 inhibitors, herbicides and plant growth regulators. For the formation of tri-substituted ımidazole derivatives various catalyst like ionic liquids, cyanuric acid, di hydroquinilone and copper catalyst etc.

Although the most preferable catalyst used for ımidazole derivatives is “tartaric acid” which is cheaper, available and stable at high temperature but in case of ımidazole derivatives synthesis harsh conditions favor the reaction.

By taking 3-nitrobenzylaldehyde (1 mmol), ammonium acetate (2 mmol) and benzyl (1 mmol) in a round bottom flask. 10% of tartaric acid was added as catalyst as shown in Scheme 1. Reaction mixture was put on a water-bath with temperature as 80 °C. After completion of reaction take thin layer chromatography (TLC) of filtrate the solution is cooled at room temperature and then put in ice water-bath. Solid product is obtained which was then recrystallize using ethanol in order to get pure product. Different tri substituted ımidazole derivatives are formed with different yield. Tartaric acid activates the carbonyl of benzyl and aldehydes in order to lower the activation energy of transition state.



Scheme 1. Synthesis of trisubsituted imidazole derivative.

The antibacterial activity was check by taking four different bacterial strains as "*Escherichia coli*, *Bacillus subtilis*, *Salmonella typhi* and *Pseudomonas aeruginosa*" alongside the reference bacteria "Gentamicine". The source of these bacterial strain were soil and meat. The strains were placed on a petri dish with nutrient agar medium and four different concentrations were provided. Gentamicin was used as positive control and a disc of paper coated in DSMO was used as negative control. Results showed that ımidazole derivatives have high antibacterial activities against "*Escherichia coli*, *Bacillus subtilis*, *Salmonella typhi*" while pseudomonas aeruginosa show moderate activity because of electron with drawing groups such as –OH , $–CH_3$ of benzaldehyde of ımidazole[26].

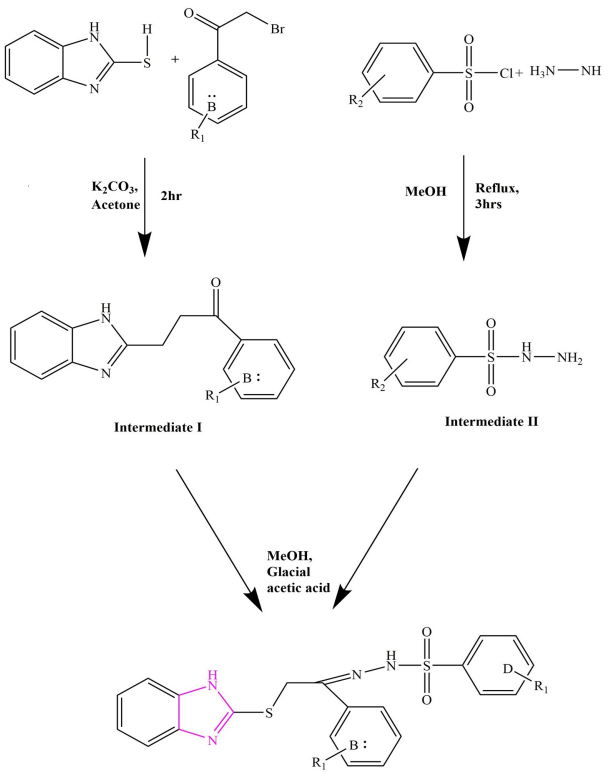
2.2 *2-Mercaptobenzimidazole Bearing Sulfonamide Group against Diabetes Type (II)*

In three stages, the sulfonamide-containing derivatives of 2-mercaptobenzimidazole and 6-metnoxy-2-mercapto-benzimidazole (1–17) were synthesised as shown in Scheme 2:

Step 1: several substituted phenacylbromides were dissolved in acetone (20 mL) to form 2-mercaptobenzimidazole/6-metnoxy-2-mercaptobenzimidazole. Next, potassium carbonate was added as a catalytic amount, and the reaction mixture was agitated for 2 h at room temperature. After the reaction was finished, the reaction mixture was cooled to a temperature of 10–15 °C and the precipitate was filtered, producing the intermediate (I), a substance with a texture like white cotton.

Step 2: equivalent amounts of hydrazine hydrate and various substituted sulfonyl chlorides were reacted in methanol, and the reaction mixture was refluxed for three hours. After the reaction was finished, the solvent was expelled under vacuum to produce the intermediate product (II).

Step 3: involved Intermediate product (I) and intermediate product (II) were combined in methanol, the reaction medium was acidified with 3–7 drops of glacial acetic acid, and the combination was then refluxed for 4 h. Precipitate generated in the reaction media after the reaction was finished. After filtering these precipitates, benzimidazole with a sulfonamide moiety was obtained (1–17).



Scheme 2. 2-Mercaptobenzimidazole bearing sulfonamide group.

According to the most recent estimates and projections, there may be 383 million to 592 million diabetic patients worldwide by the year 2035[27]. Defects in insulin secretion and action increase blood glucose levels, which specifically harm blood vessels and bring on consequences such neuropathy, retinopathy, ulceration, cardiovascular disease, and nephropathy, respectively. The intricately inventive study revealed that the practical approaches to glycemic management involve suppressing the intestinal hydrolyze enzymes -amylase and -glycosidase, which maintain postprandial hyperglycemia at a normal level. Ca^{2+} ion is found in the active pocket of the hydrolyze enzyme-amylase. Through the involvement of a water molecule, it catalyses the conversion of starch into glucose and maltose as depicted in Figure 5. Because of its potential to target 1,4-glycosidic acid, alpha-amylase is attracting a lot of research[28].

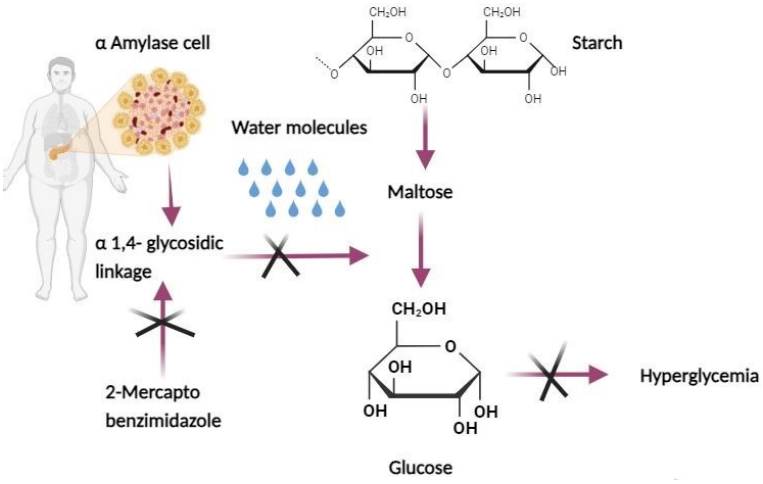
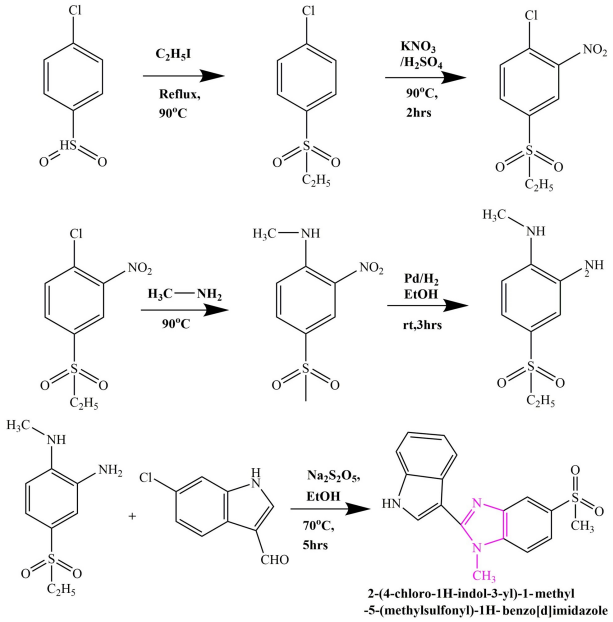


Figure 5. Role of benzimidazole in diabetes mellitus.

2.3 *2-(4-chloro-1-H-indol-3-yl)-1-methyl-5-(methyl sulfonyl)-1-H-benzo[d]imidazole Derivative*

An amine derivative (15 mmol) was added to a solution of 4-(ethyl sulfonyl)-1-chloro-2-nitrobenzene (2) in ethanol (5 mL) and heated under reflux until the starting material was used up (determined by TLC, 8–48 h) as shown in Scheme 3. Water was added after the mixture had cooled.

By utilizing a mixture of hexane and ethyl acetate in different percentages as the eluent, the resulting yellow residue of 4-(ethyl sulfonyl)-*N*-methyl-2-nitroaniline was either crystallized from ethanol or purified by column chromatography (cc). Perform hydrogenation of the compound (3.5 mmol) with ethanol (75 mL). Again filter through celite and recrystallized (ethanol) to obtain crude amine of 4-(ethyl sulfonyl)-N1-methyl benzene-1,2-diamine compound. Take a (1 mmol) mixture of 6-chloro-1-H-indole-3-carbaldehyde in ethanol (4 mL) , $Na_2S_2O_5$ (2 mL) was added and heated under reflux (70 °C) for 5 h. Upon pouring and filtering the reaction mixture the precipitate of 2-(4-Chloro-1H-indol-3-yl)-1-methyl-5-(methyl sulfonyl)-1-H-benzo[d] imidazole was obtained which is purified by column chromatography(cc)[29].



Scheme 3. 2-(4-Chloro-1-H-indol-3-yl)-1-methyl-5-(methylsulfonyl)-1-H-benzo[d]imidazole derivative.

2.4 *Bioactivity*

Almost 14.1 million cancer cases and 8.2 million cancer-related deaths have been reported, according to the Cancer Society. This means that one in seven fatalities is caused by cancer, which is more common than the combined effects of TB, AIDS, and protozoal illnesses. By 2030, it is projected that this pattern will result in 21.6 million new instances of cancer and approximately 13.0 million cancer-related deaths[30]. According to the presence of estrogen receptor (ER), progesterone receptor (PR), and/or human epidermal growth factor receptor 2 (HER2/ ERBB2) activity, breast cancer, one of the most common cancer types affecting women worldwide, can be conventionally subtyped. Regarding prognosis, incidence, therapeutic response, and tumour aggressiveness, these subtypes differ from one another[31]. Since estrogens (E2) play important roles in the growth of breast cancer, a lot of study has been done on how to either stop their manufacture or control their activity. As a result, hormone-dependent breast tumours have commonly been treated using medications that act as antiestrogens in mammary tissue. Through E2 binding, nuclear receptors ERα and ERβ participate in a variety of cellular processes, including proliferation and differentiation as shown in Figure 6. Additionally, they can be in equilibrium and regulate their downstream components differently in response to selective estrogen receptor modulators (SERMs). Their levels of expression vary between different organs, whereas the expression of ER is closely linked to breast cancer physiology and the prognosis of breast cancers. In addition, to create novel selective ER modulators, indole-benzimidazole

hybrids have been created by fusing the indole nucleus with benzimidazole. These indole-benzimidazoles could be brand-new, powerful ERα antagonists with intriguing potential for the development of novel SERMs for the treatment of breast cancer. According to recent investigations on benzimidazoles, diverse heterocycles in the 2-position provide powerful anticancer agents for various carcinoma cell lines.

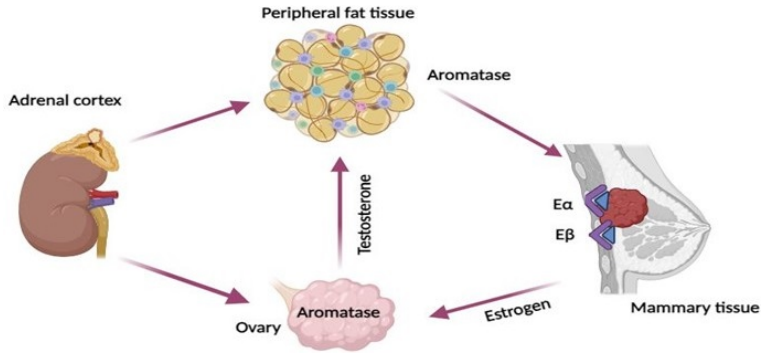
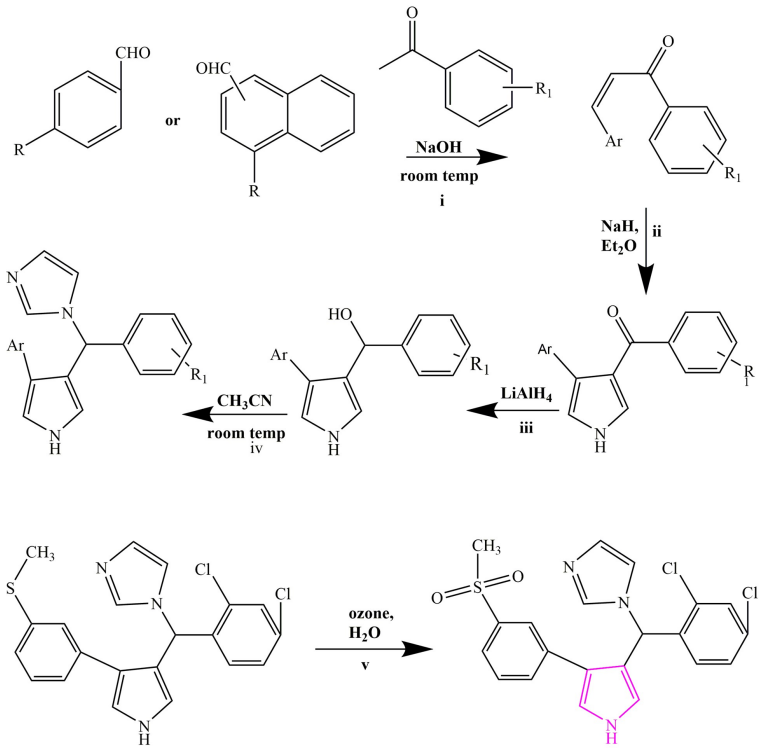


Figure 6. Schematic representation of breast cancers.

2.5 *Synthesis of 1-(phenyl) (1-phenyl-1H Pyrrole 3 yl) methyl)-1H against Malarial Action*

Imidazole derivative 1-(phenyl) (1-phenyl-1H pyrrole 3 yl) methyl)-1H has an antiprotozoal agent having structural relationship with which it shows activity at micro level against parasites. In past parasites i.e., Plasmodium, malaria, L. donovani and T.b rhodesiense and trypanosomatid has drastic effect on our health and cause wide spread death worldwide due to their vector borne infections. These derivative able to inhibit these parasites in bloodstream of Tab (in the range of 7.39–89.25 micro meter with SI range from 1 to 3. The presence of aryl group at 2 position in pyrrole ring is 28 times less potent than parent molecule. This derivative gives different by using different component and temperature as shown in Scheme 4. By mixing NaOH and EtOH at room temperature it will give us 50 to 100% yield. By using YosMIC, NaH, DMSO, Et_2O at room temperature for 15–60 min gives 18–85% yield. LiAlH, THF at) degree centigrade for 30 min gives 96–100% yield. The CDI, CH_3CN in dry form for 45 min gives 24–100% yield. Ozone, H_2O, MeOH at 0 °C gives 100% yield[32].



Scheme 4. Synthesis of 1-(phenyl) (1-phenyl-1H Pyrrole 3 yl) methyl)-1H.

2.6 *Inhibitory Action of Novel azo Imidazole Derivative against COVID-19*

For computational study on inhibitory potential of the 6 novel azo imidazole derivatives against main protease of SARS-CoV-2.

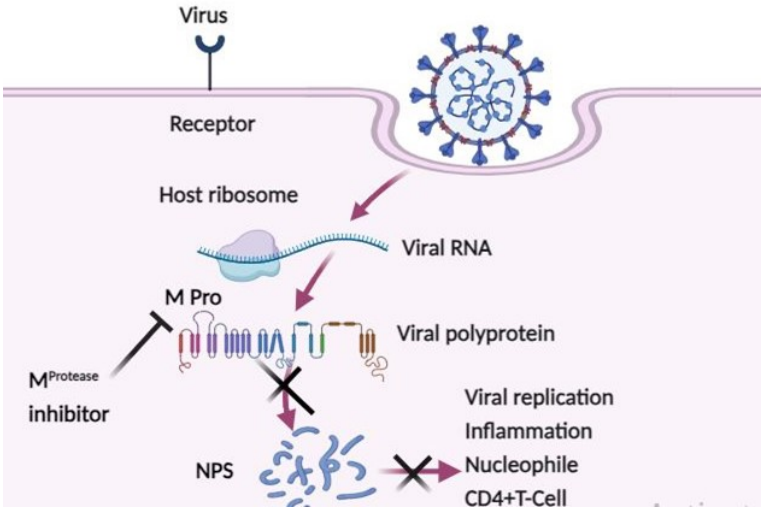
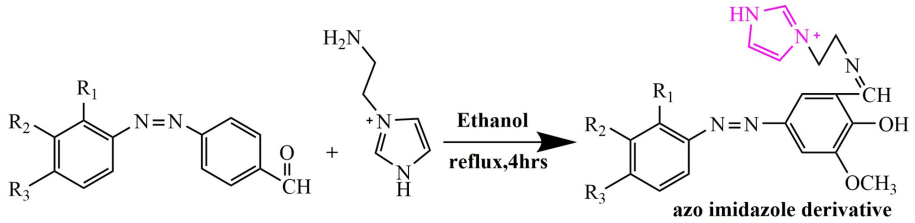


Figure 7. Action of M^{pro} Protease inhibitor in COVID virus.

Inhibitory action of novel azo imidazole derivative against COVID-19 as shown in Figure 7 was synthesizes by taking 5 mmL of 1-(-2-Aminoethyl)-3-methylimidazolium hexaflourophosphate and add in absolute ethanol according to Scheme 5, then add this solution into the 5 mmL of ethanolic solution of azo coupled o-vaniline precursor for 10 min. The reaction mixture was refluxed for 6 h in an oil bath with constant stirring at 90 °C. Perfom TLC by taking 10% Ethyl acetate in hexane as an eluent. Place the final solution overnight for cooling, filter it out, washed it with ethanol and ethyl ether. Recrystallized the solid product with hot ethanol solution and dried it under vacuum.

Natural diazo compounds are alkaloid in nature and can be obtained from microorganism, marine organisms, plant parts, fungi, ascomycetes. They possess various biological activities such as antiviral anti-tumor, antifungal, ant inflammatory and hypotensive activities. An FDA approved drug Prontosil which is antibacterial and phenazopyridine, which has local effect on urinary track both contain azo linkage. Assimilation of diazo and imidazole ring results in the formation of such compounds which have an interesting properties and biological activities [8].

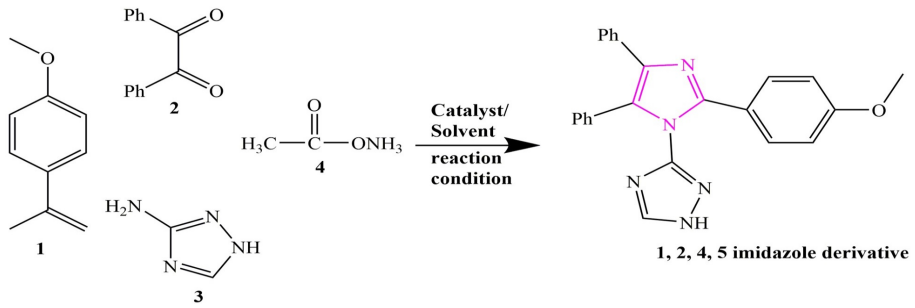


Scheme 5. Synthesis of novel azo imidazole derivative.

2.7 *1,2,4,5-imidazole Derivative Synthesis with Red Brick Clay as Heterogonous Catalyst*

Multi substituted Imidazole derivatives have a great importance in natural products as medicinal and pharmaceutical properties. 1,2,4,5-tetra substituted ımidazole derivatives have gain a lot of attention due to their biological activities. Several methodologies like nano crystalline sulfated zirconia, zeolite, and HNO_3 and chitosan SO_3H catalyst are used for synthesis of these kinds of derivatives.

In order for preparation of 1,2,4,5-tetra substituted ımidazole derivatives we use red brick clay due to its homogenous morphology and presence of O, Si, Al and Fe as its main components. 1 mmol of benzol, 1 mmol of aldehyde, 1 mmol of aldehyde, 1 mmol of ammonium acetate and 1 mmol of 1,2,4-triazole was added into crushed rick brick clay powder. Temperature was optimized at 60 °C for 40 min in an aqueous media as mentioned in Scheme 6. The material was then cooled, filtered and vacuum distilled. The solid part was then washed with diethyl ether to get the result.



Scheme 6. 1,2,4,5-imidazole derivative synthesis.

Red brick clay act as heterogeneous catalyst can be recycled without any change in its catalytic properties for five times. However, rate of reaction affected by various factors such as temperature and solvent quantity. Red brick clay gives high yield and show impressive catalytic activity due to elements like Si, Fe, Al present in its structure moreover at room

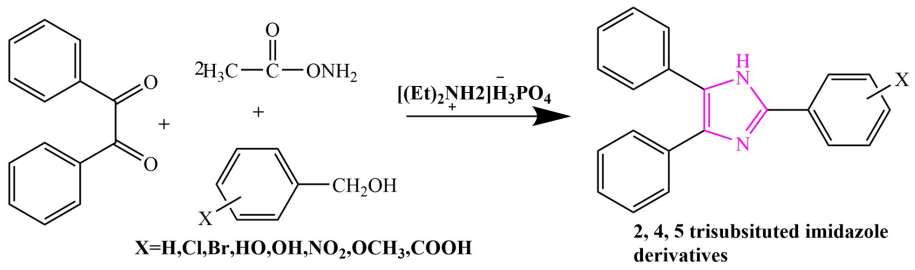
temperature high quantity of product was formed while by increasing Temperature inferior yield was obtained. It has been observed that water proved to be the best solvent used, while other organic solvents like methanol, ethanol and DMF prove to be unsatisfactory. By maintain all the reaction condition at optimum we get higher yield with environmental friendly, cheap and less hazardous catalyst. The catalyst was recovered after the completion of reaction which is an important factor of using heterogeneous catalyst[33].

2.8 *2,4,5-trisubsituted Imidazole Derivatives Synthesis*

Ionic liquids are class of inorganic salts that are liquid at low temperature (<100 °C). Ionic liquids have become environmentally friendly because of their properties such as low vapor pressure, high thermal stability and solubility of dissolving both organic and inorganic substrates. Due to their special qualities, including a structure that can be customized, a variety of forms that are readily available, and ecologically favorable characteristics, Ionic liquids (ILs) have tremendous promise in the disciplines of green chemistry, environmental science, and sustainable technology. Two distinctive characteristics of ILs are as follows, based on multiscale simulations and experimental characterizations: (1) strong coupling interactions between electrostatic forces and hydrogen bonds, specifically in the Z-bond; and (2) the distinctive semi ordered structure and properties of ultrathin films, particularly with regard to the quasi-liquid. Ionic liquids contain nitrogen, Sulphur and phosphorus as central metal atom with imidazolium, piperidine and pyridinium, etc. They have been used with various organic substances as cations with BF_4, CF_3 as anions. These ionic liquids have been used in synthesis of 2,4,5-triarylimidazole being a highly substituted ımidazole derivative[34].

Ionic liquids are used as catalyst. For its preparation, Diethylamine was taken in a three neck flask with phosphoric acid being added dropwise, it was stirred with continuous heat. After completion of reaction, the non-ionic part was distilled in order to obtain clear Diethyl ammonium hydrogen phosphate.

For synthesis of triarylimidazole we added benzol, aldehyde, and ammonium acetate and diethyl ammonium hydrogen phosphate in a round bottom flask. Placed it in an oil bath with 100 °C temperature as shown in Scheme 7. After completion TLC was performed on filtrate and solid residue was recrystallize using ethanol. After this characterization was performed.



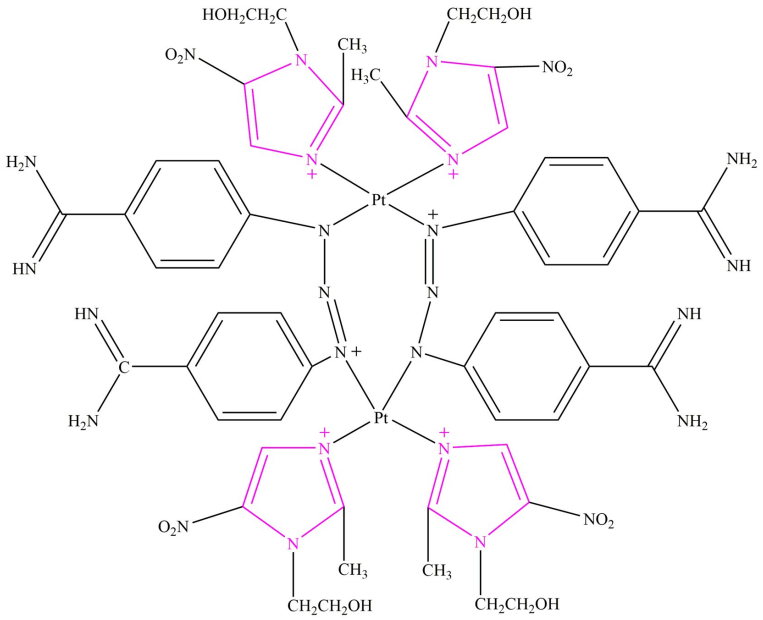
Scheme 7. 2,4,5-trisubsituted ımidazole derivatives synthesis.

The catalyst used is of homogenous nature and is Bronsted acid. The method is found to be advantageous with outrageous yield because of differing substituted and structurally diverging aldehydes. It is also observed that electron withdrawing groups give higher yield as compare to aromatic aldehydes with electron donating groups which show reaction inactive. This process prove to be cost effective, easy assembly, reusable or regeneration of catalyst with good yield and after reaction rate[35].

2.9 *Preparation of Pt_2(1-methyl-5-nitroimidazole-2-yal) ethanol) 4(Berenil)$_2$ against Breast Cancer*

Take 30 mL (deionized water) in which K_2PTCl_4 (0.72 mmol), potassium iodide (7.2 mmol) was added and stirred for 30 min. 2-(1-methyl-5-nitroimidazole-2-yl) ethanol (2 mmol) was added and continue stirring for 24 h as shown in Scheme 8, filter, recrystallize (by deionized water) and dried under vacuum to obtain the precipitate of Pt(2-(1-methyl-5-nitroimidazole-2-yl)ethanol). Then prepare a solution of silver nitrate ($AgNO_3$) 1.14 mmol in 5 mL water. After dissolving

precipitate in this mixture were settle down. Heat and stirrer (24 h) in the absence of light to obtain ppt. of silver chloride (AgI). Take the filtrate (AgI), solution of (Berenil 0.57 mmol, 10% NaCl (5 mL) was added and stirrer it for 24 h. After removal filter and recrystallized (with HCl, deionized water, and ethyl ether) the solution to obtain the ppt. of platinum complex formed. Dried it under vacuum to obtain 76.5% yield of yellow precipitate.



Scheme 8. Preparation of Pt_2(1-methyl-5-nitroimidazole-2-yal)ethanol) 4(Bernie)$_2$.

Presence of platinum(II) complex with imidazole ligand not only increase the anti-tumor activity, but also suppress the side effect (neuro and nephron) due to their intracellular penetration ability by regulating hydrophilicity and hydrophobicity ratio. It shows ant proliferation activity against breast MCf-7 cancer line topoisomerase enzyme is responsible for DNA repair. Above mention drug act as a Topoisomerase Iiα-antibody cause cell apoptosis. With the help of DNA segmentation, it block the tumor growth[36].

2.10 *Synthesis of Different Imidazole Using Ionic liquids*

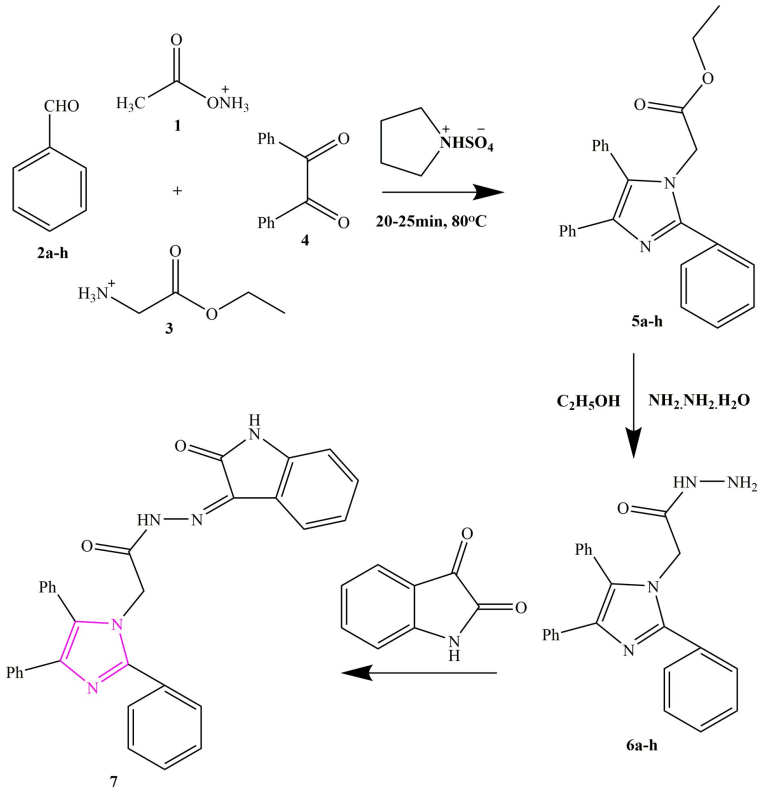
Ionic Liquids are organic salts contain ions which have melting point below 100 °C. They consist of inorganic anions and organic cations and their combination can increase the polarity and hydrophilicity/hydrophobicity of ionic liquids.

The advantages of PHS are eco-friendly catalyst, cost effectiveness, reusability, no flammability, high viscosity, thermal and oxidative stability, good solvation power, no volatility.

The advantages of this process are cost effectiveness of catalyst, reusability of catalyst, easy work-up and purification of products by non-chromatographic methods, best yields, and less time consumption reactions (20–50 min).

Their application extensively reviewed as catalytic phase in diverse organometallic reactions. Ionic liquids are alternate solvents and also termed as TSIL task specific ionic liquids.

A crucial coupling step of the intermediate of benzaldehyde mine is present in the one-pot multicomponent cyclocondensation of 1,2-diphenylethane-1,2-dione, ethyl glycinate, the handy aromatic aldehyde, and ionic liquid in the presence of 1 mol of ammonium acetate (I). Ethyl glycinate, on the other hand, attacks the activated benzil to create αamino ketone (II). The in situ produced imine then undergoes a nucleophilic attack on the carbonyl of the aryl ketoimine, resulting in the intermediate (III). Following their subsequent intermolecular interaction, intermediate (IV), which dehydrates to the 1,2,4,5-tetrasubstituted imidazole, is formed as shown in Scheme 9.



Scheme 9. Synthesis of different imidazole derivatives using Ionic liquids.

At the end NMR AND IR techniques used. By changing amount of the ionic liquid catalyst we get different yields and 4 mol% gave the highest yield about 96%.

3. Antioxidant Activity

By using limited oxidative stress biomarkers assays determined the antioxidant activities of present compound. These compounds contained malondialdehyde level (MDA), liver reduced glutathione content (GSH) and nitric oxide (NO). All of these oxidative stress biomarkers showed different results with all tested compounds.

3.1 *Ethyl 4,5-diphenyl-2-(substituted)-1H-imidazole-1-carboxylate (5a-h)*

As a catalyst, 4 mol% PHS ionic liquid was mixed with 20 mmol of aromatic aldehydes, 20 mmol of 1,2-diphenylethane-1,2-diodes, 20 mmol of ammonium acetate, and 20 mmol of ethyl glycinate. According to Scheme 9, the reaction mixture was given the proper amount of time to reflux. Thin-layer chromatography (TLC) was used to monitor the reaction, which was completed, and the mixture was then washed with water. The solid product was then purified by recrystallization from ethanol or methanol. While the ionic liquid in the filtrate can be recovered once all solvents have been evaporated and an oily mass of ionic liquid has accumulated, the ionic liquid can now be utilized again for other processes in the future.

3.2 *2-(substituted)-4,5-diphenyl-1H-imidazol1-yl) acetohydrazide (6a-h)*

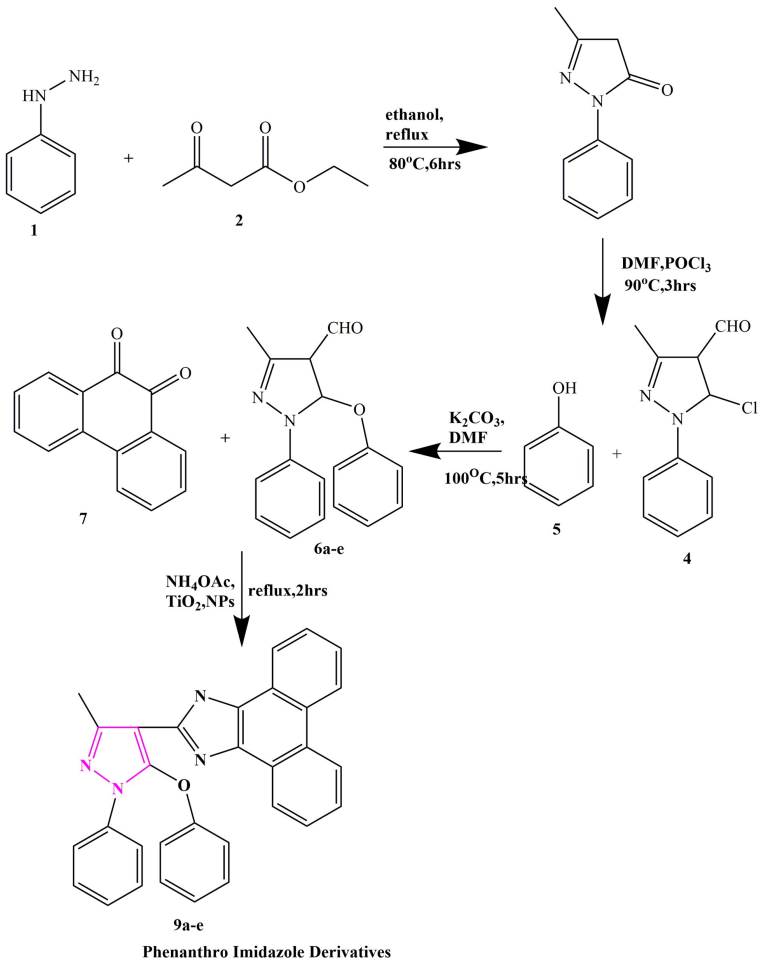
Hydrazine hydrate (5.1 mmol, 100%) was gradually added while stirring to a solution of ethyl 4,5-diphenyl-2-(substituted)-1-himidazole-1-carboxylate (5 mmol) in ethanol as depicted in Scheme 9. The reaction mixture was cooled at

25 °C after being allowed to reflux for 3 h. Filtration was used to collect the separated product, which was then dried and crystallized from methanol or ethanol[37].

3.3 *Novel Phenanthro Imidazole Derivatives against Anti-Oxidant Activity*

In this method, imidazole derivatives were prepared by using titanium dioxide nanoparticles. These nanoparticles were extracted from the leaves of sunflower. First of all, sunflower leaves were taken. They were dried for one week, then grounded. A small amount of this powder was added to distilled water. When the precipitates settled down, it was filtered. Then this leaf extract was very slowly added to metal salt solution of (TIF). This process was done under harsh conditions of continuous stirring for 180 min until brownish green precipitates formed. Then it was centrifuged, washed (with double distilled water) to eradicate impurities. Precipitates were dried in an oven at high temperature. Then white colored powdered nanoparticles were obtained.

A mixture of 3-methyl-5-phenoxy-1-phenyl-1H-pyrazole-4-carbaldehyde derivatives (1 mmol), 9,10-phenanthrene quinone (1 mmol), TiO_2NPs (70 mg), ammonium acetate (2.5 mmol) and acetic acid (5 mL) was made. It was refluxed at 120 °C (different solvents were used in reflux for different period of time) as shown in Scheme 10. Completion of reaction was confirmed by thin layer chromatography. The mixture was allowed to cool down (25 °C). After that it was added to extremely cold environment i.e., crushed ice. Solid product was obtained which remained in that environment for half an hour. After that it was filtered and purified by column chromatography. Then recrystallized with ethyl alcohol to get better yield and purity of imidazole derivatives.



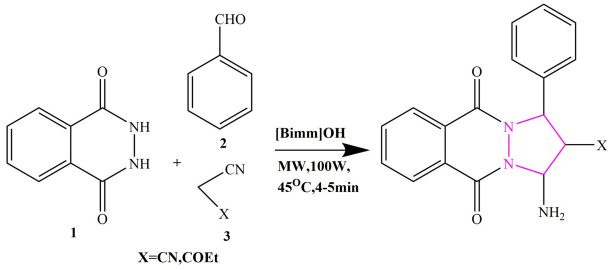
Scheme 10. Phenanthro imidazole derivatives.

Dilutions of synthesized derivatives and ascorbic acid were made and then mixed with DPPH solution. Then nurtured it for half an hour without any light source. Found absorbance and then percentage inhibition of antioxidant was calculated:
%of inhibition $= [(AB - AA)/AB] \times 100$,
where AB = blank solution absorption, AA = test sample absorption.

3.4 *Green Synthesis of 1H-pyrazolo[1,2]phthalazine 5,10 Dione Derivative and Photophysical Studies and Activity against Antibacterial, Anti-Inflammatory and Antihypoxic*

The structure of diversity oriented synthesis (DOS) is considered as the important component for natural products and drugs. However the most applied method available for their synthesis are sequential multicomponent reactions. Pyrazole is an important organic compound based on new drug and biological properties as they are prescribed as antibacterial, anti-inflammatory and antihypoxic. Despite of their vast properties there exit only two multicomponent for synthesis of 1H-pyrazolo[1,2]phthalazine-Dione i.e., by sonochemitry in presence of triethylamine and ethanol but they proved to be toxic. In order to get greener approach researchers uses phthalhydrazide, aromatic aldehyde and melanonitrile in presence of 45 °C.

Optimum conditions are checked and then a multi component reaction of benzaldehyde, phthalhydrazide and melanonitrile in 1-butyl-3-methylimidazolium hydroxide were treated in presence of ethanol as mentioned in Scheme 11.



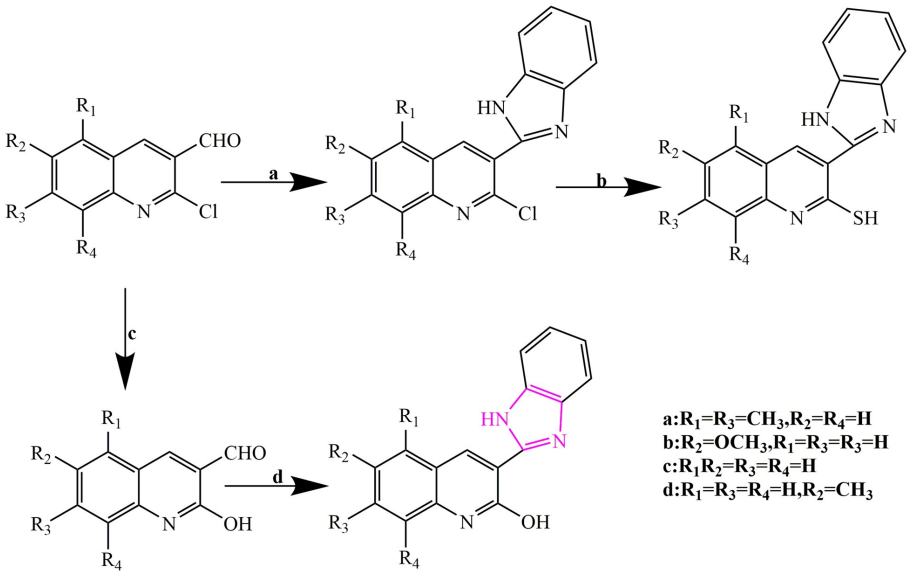
Scheme 11. 1H-pyrazolo[1,2]phthalazine-5,10-dione derivative.

The result obtain shows that [Bimm]OH gives the higher yield of 92%. However keeping molecular weight at 100 W and 45 °C major yield of product is obtained. Increase in temperature decreases the yield.

The derivatives formed during these processes show photoluminescence and electronic absorption properties due to cyano functionally and ester linkage. But during observation of UV visible spectroscopy showed the stokes shift of cyano group was lower as compare to ester[38].

3.5 *Thio-Derivative Imidazoquinoline*

The precursor 2-chloro-3-formylquinoline (1a) was made via the traditional Vilsmeier-Haack reaction on acetanilide. The 3-formyl-2-hydroxyquinoline a was then created by treating the produced chemical with 4N HCl as depicted in Scheme 12. In the presence of triethylamine (4.33 mmol), appropriate amounts of 2-hydroxyquinoline-3-carbaldehyde (2.89 mmol), *o*-phenylenediamine (3.17 mmol), and ethanol (20 mL) were combined and refluxed for ten hours. The resulting precipitate was then filtered, and compound (3) [3-(1H-benzo[d]imidazole-2-yl) quinolin-2-ol] was produced by recrystallizing it from ethanol. *O*-phenylenediamine (1.15 mmol) was combined with triethylamine (1.56 mmol), 2-chloroquinoline-3-carbaldehyde (3.04 mmol), and ethanol (20 mL) and refluxed for ten hours. To create compound 4[3-(1H-benzo[d]imidazole-2-yl)-2-chloroquinoline]. The resulting precipitate was recrystallized from chloroform. Dimethylformamide was mixed in chloro imidazoquinoline (4) (0.71 mmol) and sodium sulphide (1.07 mmol) and agitated for five hours at room temperature. To obtain the thio-imidazoquinoline 5, the reaction mixture was extracted using ethyl acetate, and the crude product was purified using silica gel column chromatography with a 1:1 ratio of EA to hexane.



Scheme 12. Thio-derivative imidazoquinoline derivative.

3.5.1 *Bioactivity against Bacterial Action and Antioxidant Activity*

Maximum antibacterial activity compared to other imidazoquinoline was demonstrated by the electron withdrawing group (–Cl) on the quinoline ring of 5f, reaching the level of the standard. In comparison to the standard butylated hydroxytoluene (10 mg/disc), 5f showed greater activity at high concentrations (100 mg/disc) against *E. coli*, *K. pneumonia*, *S. paratyphi*, *S. typhi*, and *M. butyricum*. Compounds 4f and 3f as well as other electron-withdrawing substituents displayed moderate activity. Compared to other imidazoquinoline with comparable substituents, 5e's quinoline ring had a moderate activity for electron-donating groups ($–OCH_3$) (4e and 3e). In addition, moderate activity was obtained with chloro- and thio-imidazoquinoline of 4-5(a-d) compared to hydroxyl-imidazoquinoline of 3(a-e). The order of imidazoquinoline' antibacterial activities was shown here for overall comparison, 5f > 4f > 5e.

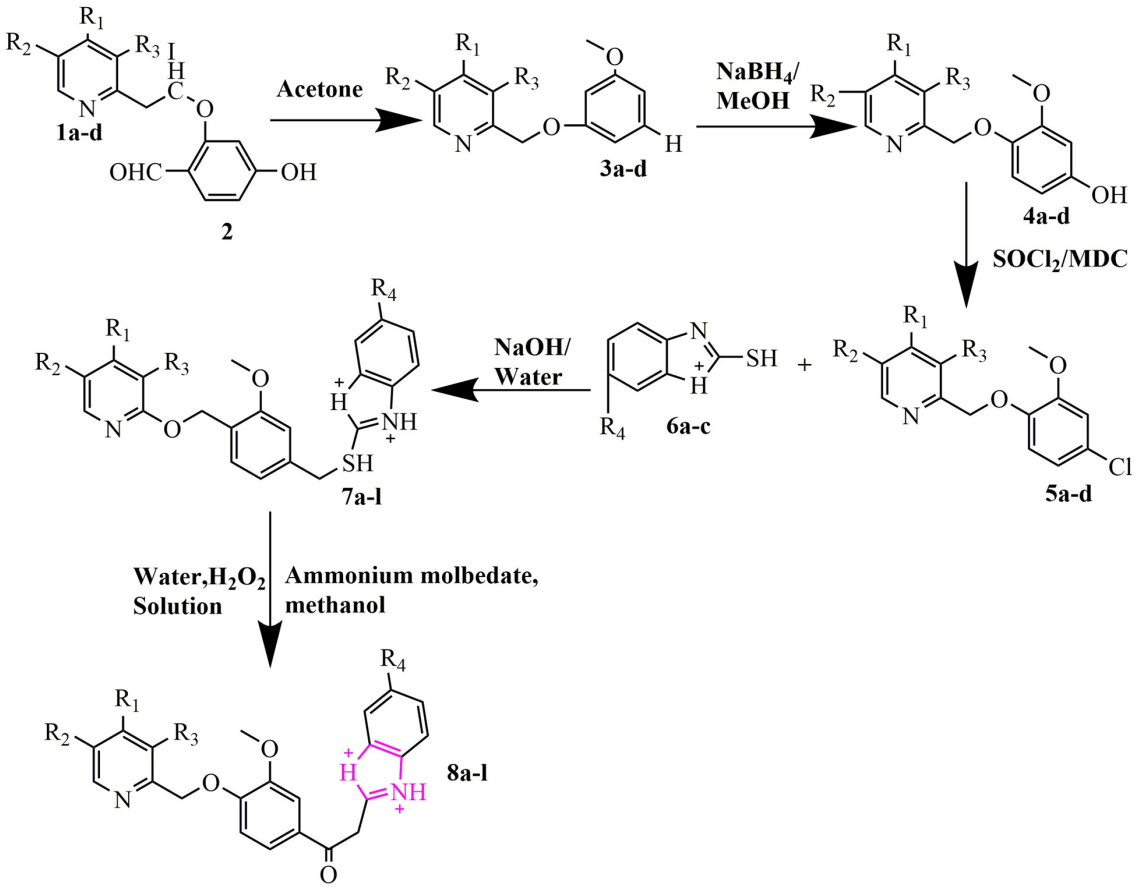
3.5.2 *Antioxidant Activity Using FRAP Assay*

The FRAP assay can be used to quantify the conversion of ferric (Fe^{3+}) to ferrous (Fe^{2+}) ions in the presence of antioxidants. Based on the reducing capacity of the produced compounds, which could serve as a significant indicator of their powerful antioxidant activity. Compound 5f demonstrated greater ferric reducing capacity than other compounds,. This value of the conventional butylated hydroxytoluene and the thio-functionalized imidazoquinoline 5f was comparable (BHT). Series 5a-remaining e's compounds also showed good to moderate activity. The thio-functionalized derivatives (5(a-f)) often have a higher reducing power than the hydroxyl- functionalized derivatives (3(a-f)). However, compared to the chloro-functionalized imidazoquinoline 4(a-f), 3(a-f) had a higher reducing power. Consequently, the sequence of imidazoquinoline lowering power[39].

3.6 *Synthesis of methoxybenzyl-sulfonyl-1H-benzo[d]imidazole*

Charged into 40 mL of methanol and 0.02 g (1.6×10^{-5} mol) of ammonium molybdate tetra hydrate was 1.0 g. of substituted 4-[2-pyridylmethoxy] phenyl methylthio-substituted-benzimidazole (7a-l). 8.8×10^{-3} moles of H_2O_2 were added gently to 0.8 mL of a 30% volume solution. At 68°, the reaction mixture was agitated for two to three hours. Following TLC compliance, the reaction mass was quenched with water, the organic layer was concentrated under vacuum at 35 °C, and the reaction mass was extracted using methylene dichloride (MDC). Following methanol isolation, the product was dried under vacuum to produce compounds 8a-l (methoxybenzyl-sulfonyl-1H- benzo[d]imidazole) as shown in Scheme 13.

The growing patient population shows that gastrointestinal disorders continue to pose a serious hazard to human society. H^+, K^+ ATPase type 2 has recently been implicated in the adaptive spread of latent renal A-type, according to reports. These facts motivated us to examine ulcer treatment options. According to histology, an ulcer is a break in the skin's, epitheliums, or mucous membrane's impermanence caused by shedding from inflammatory necrotic tissue. In accordance with this assertion, HRBC membrane stabilization was done to make sure the suggested chemicals could protect the membrane. In this study, it is suggested to synthesis a series of substituted methoxybenzyl-sulfonyl-1H-benzo[d]imidazole derivatives (8a-l), while keeping benzimidazole as the structural base, and to assess these derivatives' therapeutic effects on inhibiting H^+/K^+-ATPase and treating ulcers as shown in Figure 8. The primary method utilized to produce the desired chemicals was oxidation of sulphur compounds. Impurities like n-oxide and sulfonyl n-oxide are typically expected during oxidation reactions.



Scheme 13. Synthesis of methoxybenzyl-sulfonyl-1H-benzo[d]imidazole derivative.

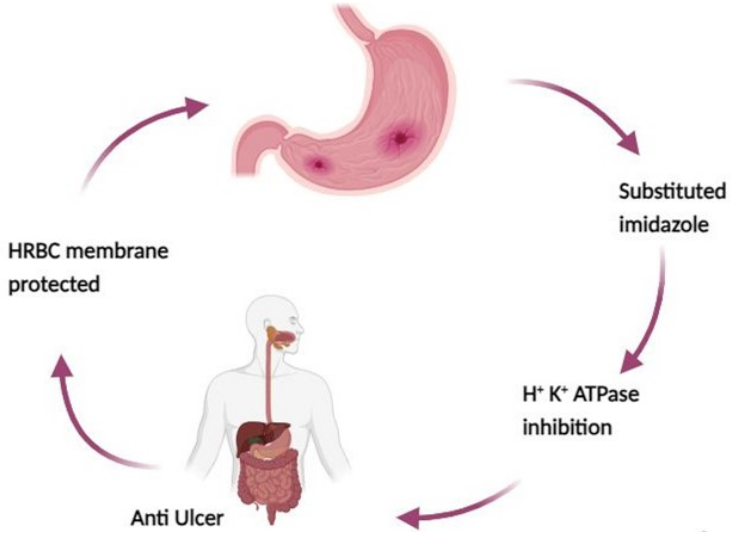


Figure 8. Mechanism action of benzimidazole for treatment of gastrointestinal disorder.

3.7 *Green Synthesis of Novel Imidazole Derivatives and Evaluation of Anticancer and Anthelmintic Activity*

Organic compounds with heterocycles are important in the fields of electronics, biology, optics, medicine, material sciences, and other fields is a well-known name. The heterocyclic nucleus is important in medicinal chemistry and acts as a vital template for the synthesis of numerous therapeutic medicines.

Nitrogen-containing heterocyclic rings are a frequent structural element of commercially accessible medications. Among these heterocycles, a wide range of bioactive compounds contain imidazole/fused imidazole rings. Such structures can interact with a variety of biomolecules due to their distinctive characteristics, such as their high polarity and capacity for hydrogen bonding and coordination chemistry, and compounds containing imidazole or fused imidazole have been reported to have a variety of biological activities. The imidazole derivatives exhibit crucial molecules for pharmacology. The DNA-interacting imidazole molecules include groove binders, DNA alkylating substances, and one of the most often used classes of chemotherapy medications in cancer treatment is intercalates. Additionally, medicinal chemists and molecular biologists are eager to comprehend both the precise mechanism of action of these medications and the DNA damage that cancer cells experience. Many anticancer medications are designed to work by poisoning DNA topoisomerases and intercalating planar aromatic chemicals into the DNA double helix.

The researcher is drawn to discover new compounds of imidazole due to their major importance and therapeutic utility substances with increased anti-cancer action.

Thus, the synthesis of new imidazole derivatives using both conventional and microwave techniques was intended. The structures of produced compounds are also determined using FTIR, 1H, 13C, and mass spectral data. Investigated were the newly created imidazole derivatives' anticancer and anthelmintic properties. The presence of phenolic groups in compounds 2b and 3b significantly affects the ability of these compounds to bind to cytoplasmic hormone receptors activity. Because they include the nitro group, which is electronegative in nature, compounds 1b and 7b are more efficient. The potential of compound 8b is further improved by the methoxy group.

N-acetylated isatin (0.01 M) was added to Schiff base (0.01 M) made using conventional methods, together with an excess of nitrous acetate (0.1 M). The reaction mixture was stirred and refluxed on a hot plate for roughly 14–17 h using a magnetic stirrer.

3.7.1 *Conventional Method*

The reaction mixture was poured into 250 mL of water, filtered, and dried in a hot air oven to get rid of the ammonium acetate and acetic acid. The crude product was washed with 2 × 20 mL of benzene, and the products were recrystallized with ethyl acetate to remove any unreacted *N*-acetylated isatin/*N*-benzoylated isatin. Table 1 showed that highest yield was obtained from microwave method than Conventional Method.

Table 1. Comparison of conventional method with microwave method with respect to reaction time and %yield.

	Conventional Method		Microwave Method	
Compound	**Reaction Time (h)**	**Yield%**	**Reaction Time (min)**	**Yield%**
1b	14.5	27.64	23.5	65.61
2b	15.5	31.82	25	77.64
3b	15.5	33.24	25	83.61
4b	15	29.42	24	74.67
5b	14.5	24.2	23.5	61.78
6b	14	23.97	23	61.37
7b	15	26.21	23.5	63.94
8b	16	27.21	24.5	69.13

3.7.2 *Microwave Method*

In a dry mortar, Schiff base, excess ammonium acetate (0.1 M), and N-acetylated isatin (0.01 M) were added. (0.01 M) collected using the prior microwave technique. It was triturated to obtain a homogeneous mixture. After that, the reaction mixture was poured into a 100 mL beaker. The microwave oven's other beakers with various reaction mixtures were assembled in a circle, and microwave irradiation was carried out at 1000 W for roughly 22–25 min. Intermittent cooling was done every 60 s of microwave irradiation. Throughout the intermittent cooling, the reaction mixtures were thoroughly agitated. The responses were recorded using TLC. When the reaction mixtures should be taken out of the microwave oven was determined using TLC data collected at regular intervals.

3.7.3 *Anticancer Activity by SRB Assay*

The SRB assay technique was used to investigate the anticancer activity in the Hep-2 cell line. The monolayer was created using medium containing 10% new-born calf serum. Trypsinization was performed on the cell culture, and 1.0×10^5 cells/mL was set as the cell density. The diluted suspension (about 10,000 cells) was added to each well of the 96-well microtitreplate in a quantity of 0.1 mL. After 24 h, when a partial monolayer had formed, the supernatant was discarded, the monolayer was washed once, and L of various drug concentrations were administered to the cells in microtitre plates. The plates were then examined and observed under a microscope every 24 h over a three-day incubation period at 37 °C and 5% CO_2. 25 L of 50% trichloroacetic acid are added after 72 h.

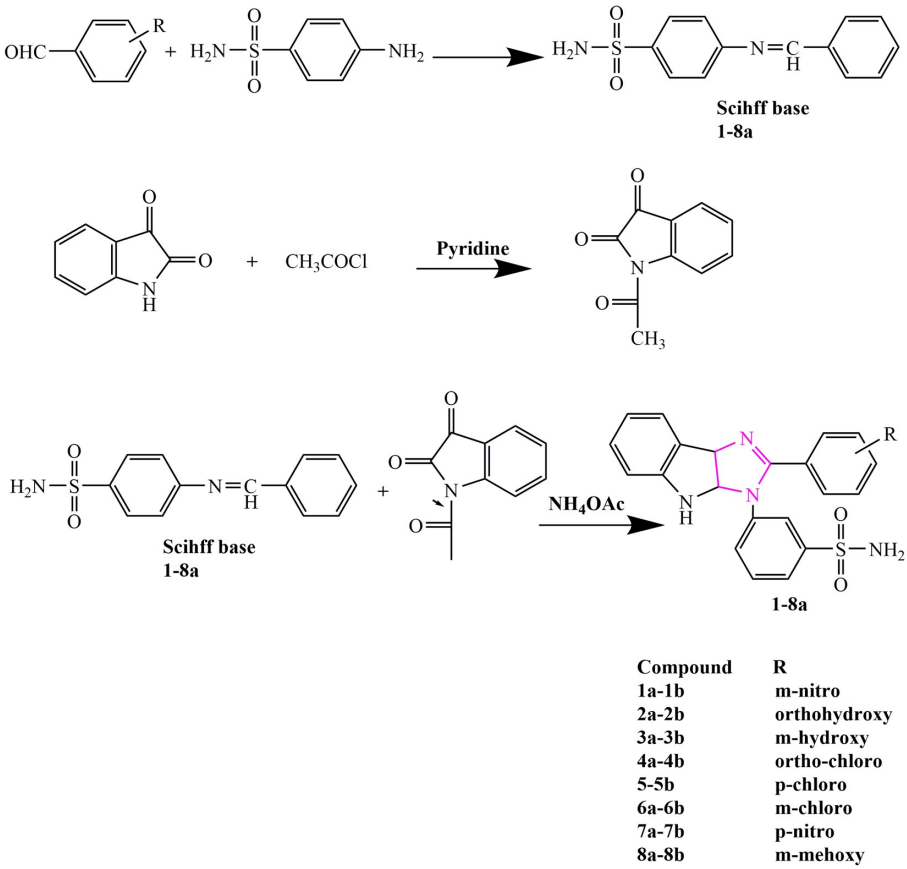
3.7.4 *Anthelmintic Activity*

Earthworms of the Eudrilus species were used to assess the anthelmintic activity at a dose of 2 mg/mL. Synthetic compounds (100 mg) were triturated with Tween 80 (0.5%) and distilled water to create sample suspensions, which were then stirred for 30 min with a mechanical stirrer. The test samples were diluted in the suspensions to 0.2 *w*/*v*%. A suspension of the reference drug, mebendazole, was created in a similar manner using the same concentration. Each of the three sets of five earthworms, measuring about 2 inches long, was put into a Petri dish with a diameter of 4 inches, along with 50 mL of a room-temperature suspension of the test sample and the reference medication. Five earthworms from the control group were kept in a 50 mL container with distilled water and Tween. The paralysis and death times were noted for sets of

three, and the mean was calculated. The earthworm would be alive if it. By submerging it in warm water (50 °C), which encouraged movement, the death period was calculated.

The condensation reaction as shown in Scheme 14 was carried out in microwave heating at the following temperatures: 1000 W intermittently for 23–25 min at 60 s intervals. While the traditional method for making (1b-8b) takes 14–16 h to complete the reaction (Table 1). Additionally, compared to conventional methods, the microwave approach produces chemicals with a higher %yield. These results suggest that microwave irradiation is superior to the conventional method.

All of the newly synthesized compounds' structures were verified using FTIR, 1H NMR, and mass spectrum analysis [40].



Compound	R
1a-1b	m-nitro
2a-2b	orthohydroxy
3a-3b	m-hydroxy
4a-4b	ortho-chloro
5-5b	p-chloro
6a-6b	m-chloro
7a-7b	p-nitro
8a-8b	m-mehoxy

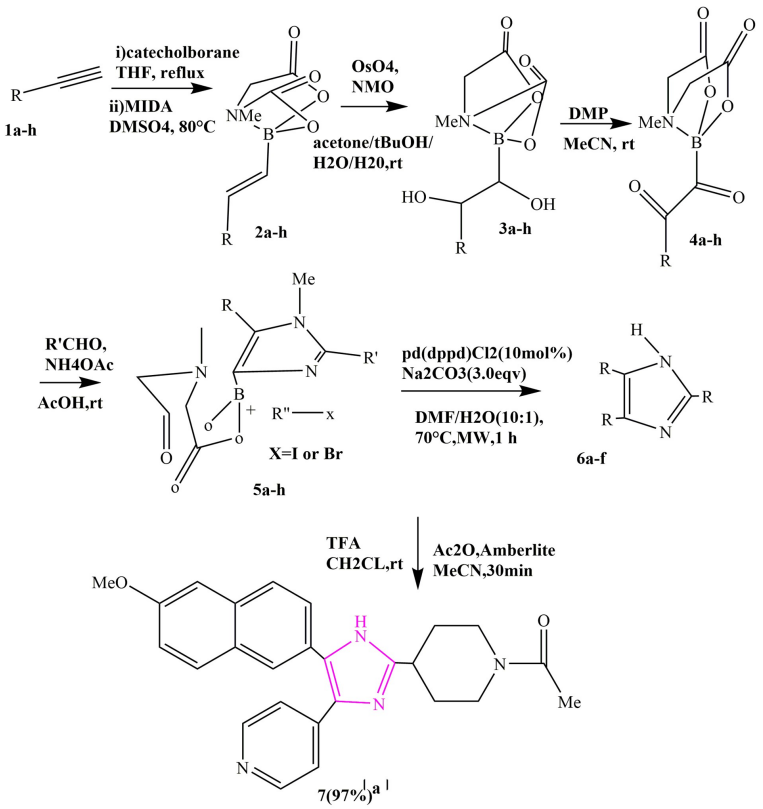
Scheme 14. Synthesis of novel imidazole derivatives.

3.8 *2,4,5-trisubstituted Borylated Imidazole*

Oxalyl boronate are used as building block to synthesize 2,4,5-trisubstituted borylated imidazole using acetic acid (AcOH) at room temperature by cross coupling reactions with aldehydes and carboxaldehydes are shown in Scheme 15. The product formed is highly colored and play vital role in various photo and physiochemical reaction.

3.8.1 *Bioactivity*

These are used to inhibit protein kinase STK10 and SLK to stop the growth of cancerous cells. They can be used in regulation of lymphocytes, cell reproduction, mitosis or if any damage to DNA occur they response to nervous system about it [41].



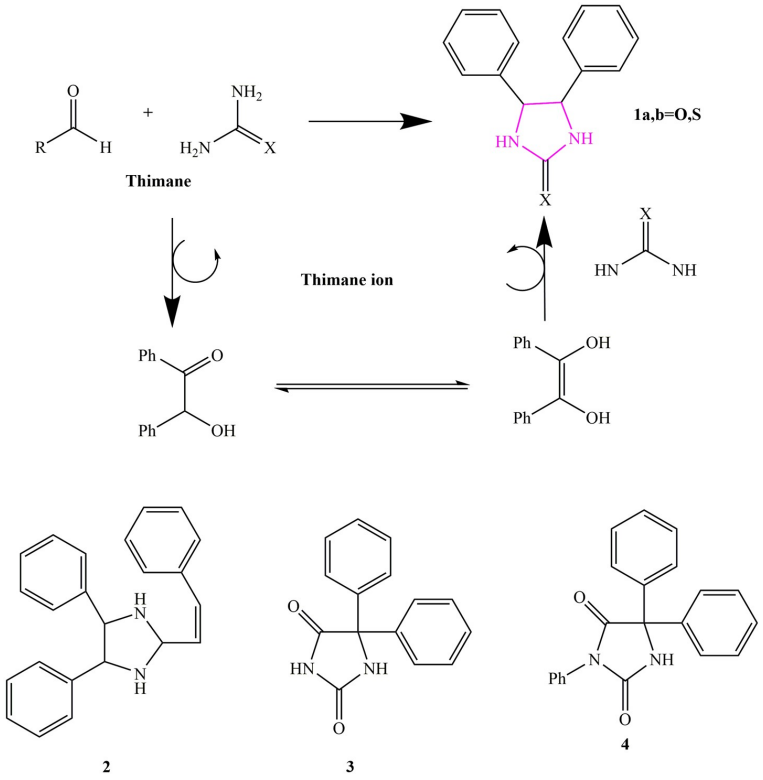
Scheme 15. 2,4,5-trisubstituted borylated imidazole.

4. Efficient Green Synthesis of Heterocyclic Derivatives as Insecticidal Agents

In this procedure, aromatic aldehydes, thiamine and urea derivatives reacted through one pot step wise mechanism to prepare 4,5-diarylimidazol-2-one. Thiamine is used as catalyst to promote reaction from benzoin or benzil and reacted in multicomponent reaction by grindstone chemistry for 3–10 min.

4.1 *Synthesis*

According to Scheme 16, aromatic aldehydes and the catalyst mixed together. Add bisnucleophile (as urea, thiourea, phenylurea, phenylthiourea, and thiosemicarbazide) with small amount of ethyl alcohol and butyl alcohol, conc. HCl in pestle and mortar and grind them. At the end, solid mass is obtained (which was monitored during grinding by TLC). Wash with cold water and perform recrystallization. Reaction is failed with Guanidine.



Scheme 16. 4,5-diarylimidazol-2-one derivative.

Some the derivatives reacted with benzaldehyde to form arylidene. DFT (density functional theory) showed, Benzaldehyde is preferred to react with amino imidazole as compared to its reaction with thiamine. Phenylurea and phenylthiourea, through isomerization and rearrangement, formed products. These derivatives showed activity against *Plutella xylostella* and *Helicoverpa armigera*[42].

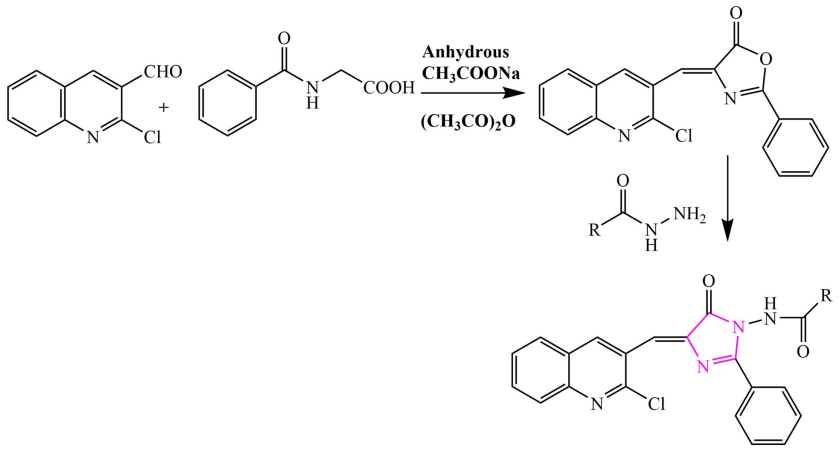
5. Quinoline Based Imidazole Derivative against Antimicrobial Activity

5.1 *Conventional Mthod*

2-Chloroquinoline-3-carbaldehyde (1) (47.75 g, 0.25 mol), hippuric acid (44.75 g, 0.25 mol), acetic anhydride (28.28 mL, 0.30 mol), and anhydrous sodium acetate (20.50 g, 0.25 mol) were combined and heated in a 250 mL round bottom flask while being stirred continuously shown in Scheme 17. When the mixture had completely liquefied, the flask was moved to a water bath and heated for an additional four hours. Then, ethanol (100 mL) was slowly added to the flask, and the mixture was left to stand overnight in the refrigerator. The resulting crystalline product was filtered, washed with ice-cold alcohol, and then the crude product was recrystallized from benzene using boiling water.

5.2 *Microwave Method*

Hippuric acid (44.75 g, 0.25 mol), acetic anhydride (28.28 mL, 0.30 mol), compound 2-chloroquinoline-3-carbaldehyde (1) (47.75 g, 0.25 mol), and anhydrous sodium acetate (20.50 g, 0.25 mol) were combined and thoroughly mixed in a reaction vessel. The mixture was microwave- irradiated for 3 min at 300 W while being continuously shaken and intermittently irradiated every 30 s. TLC kept track of the reaction's development. After the reaction was finished, the vessel was cooled, ethanol was added, and the mixture was refrigerated overnight. The resultant crystalline product was filtered, washed with ice-cold alcohol, and then crude product was recrystallized from benzene using boiling water.



Scheme 17. Quinoline based imidazole derivative.

5.3 *Bioactivity*

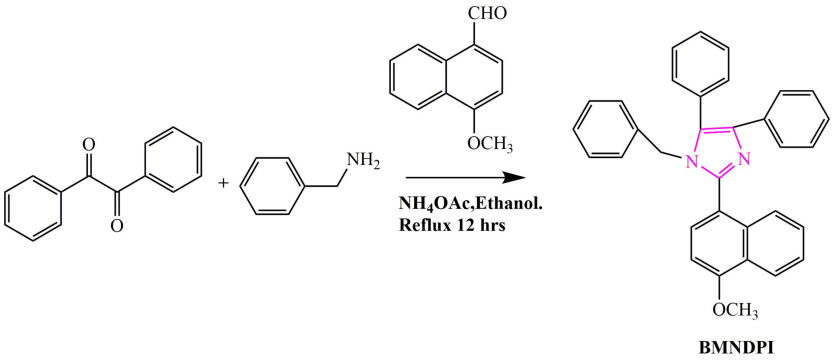
The quinoline-imidazole derivatives' substitution pattern was carefully chosen to provide the molecules a new electrical environment. Thus, the target compounds' chemical structures were chosen as substituents, and electron giving groups to aromatic rings like phenyl, hydroxyl, and pyridine and electron withdrawing groups from aromatic rings like nitro and halogen were chosen. Compounds 3d and 3h, which contain electron withdrawing groups, exhibit more potent antibacterial activity (MIC 25 g/mL) against Gram-negative bacteria *E. coli* than the reference drug ampicillin. However, it has been discovered that nitro, hydroxy, and phenyl substituted compounds are equally effective against *E. coli* as the reference drug. A higher MIC value than ampicillin was demonstrated by compounds designed to contain electron-donating groups against the majority of bacterial species.

When compared to the standard medicine griseofulvin, compounds 3c, 3e, 3f, and 3h containing electron-withdrawing groups chloro, fluoro, and nitro demonstrated greater efficacy. Electron-withdrawing substituents like chloro, fluoro, and nitro compounds have a wider antibacterial spectrum than the other compounds out of the ones that were chosen. Our goal was to investigate due to their exceptional in vitro antibacterial efficacy, we have determined that compounds 3c, 3d, 3f, 3h, and 3j are the most unique derivatives found in this investigation. As a result, the development of antibacterial candidates would be successful using such chemicals as a matrix. There are currently efforts being made to optimize the lead structure, and the outcomes of these efforts will serve as the foundation for our future research endeavor SAR patterns and identify potential areas for further optimization.

Using environmentally-friendly methods, such as selective MW heating of pristine reactants under solvent-free circumstances, we have effectively synthesized heterocyclic molecules [43].

6. Synthesis of 1-benzyl-2-(4-methoxynaphthalen-1-yl)−4,5-diphenyl-1H-imidazole (BMNDPI) against COVID-19

The four-part reaction mixture contains 4 methoxy-1-naphthaldehyde (6.0 mmol), benzyl amine (27.0 mmol), ammonium acetate (24 mmol), and benzil (6.0 mmol) in absolute ethanol (20 mL) with boron trifluoride diethyl etherate (1/2 drop) acting as a catalyst as shown in Scheme 18. When the reaction was complete, the reaction mixture was cooled and the thin layer chromatography (TLC) technique was used to monitor it using ethyl acetate: benzene (2:8 *v*) as the eluent. The reaction mixture was refluxed for roughly 24 h at the boiling point of ethanol (78 °C). Dichloromethane was used to extract the reaction mixture, and column chromatography was used to purify the end product. The end product, 1-benzyl-2-(4-methoxynaphthalen-1-yl)-4,5-diphenyl-1H-imidazole, was recrystallized from ethanol by slow evaporation.



Scheme 18. Synthesis of 1-benzyl-2-(4-methoxynaphthalen-1-yl)−4, 5-diphenyl-1H-imidazole.

6.1 *Bioactivity*

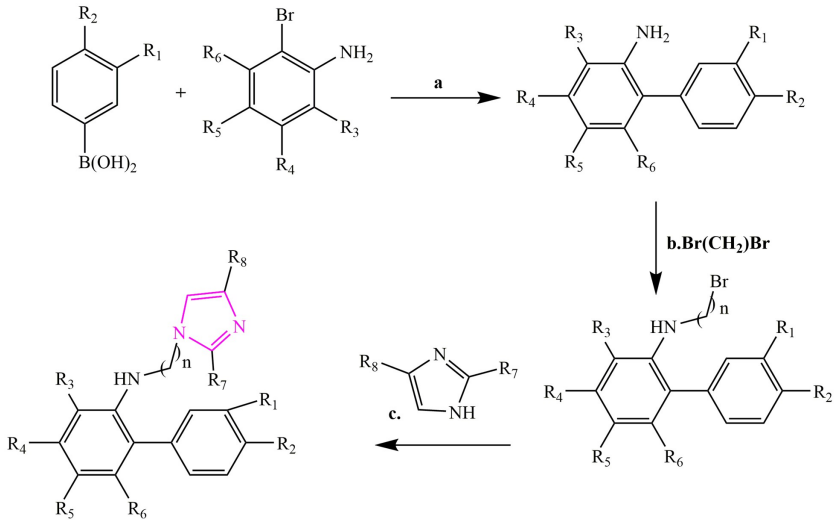
The primary protease receptor of COVID-19, has an unliganded active site. The major protease of SARS-CoV-2 is crucial for digesting poly-proteins translated from viral RNA and is thought to be essential for the survival and expansion of the virus. Via carbon hydrogen bonds, π-cations, π-anion, π-donor hydrogen bonds, π-loan pairs, mixed alkyl and π-alkyl hydrophobic interactions, the chemical was strongly attached to receptor. By means of π-lone pair interaction, the phenyl group is joined to the residue. Due to the hydrophobic interactions between the amino acids and the benzyl and naphthyl moiety, the molecule has a high binding energy to the receptor. However, the conventional hydroxy chloroquine has less binding energy as a result of fewer interactions between the ligand and receptor including mixed alkyl and π-alkyl hydrophobic contacts and carbon hydrogen bond interactions. The molecule can be thought of as a possible antiviral drug against COVID-19 receptors, according on molecular docking data [44].

7. Synthesis of Diphenyl Conjugated Imidazole Derivative against Alzheimer's Disease

$Pd(DPPF)_2Cl_2$ and K_2CO_3 solution (2 mol/L, 10 mL) were added to a solution of bromaniline or derivatives (1 equiv.) and phenylboronic acid or derivatives (1.2 equiv.) in 1,4-dioxane. The mixture was heated to 100 °C in an atmosphere of Ar. The reaction was quenched with a saturated NaCl solution after three hours (1 mL). Ethyl acetate (20 mL ×3) was used to extract the reaction mixture. The mixed organic phase was filtered, concentrated under reduced pressure, dried with anhydrous Na_2SO_4, and washed with saturated NaCl solution. To produce the intermediate I the residue was cleaned by flash column chromatography (silica gel, ethyl acetate/hexane, gradient elution).

Anhydrous K_2CO_3 (2 equiv.) and 1,3-dibromopropane or 1,2-dibromoethane (7 equiv.) were added to intermediate I (1 equiv.) in anhydrous acetonitrile (6 mL), and the mixture was warmed and refluxed overnight as shown in Scheme 19. The acetonitrile was withdrawn under decreased pressure after the mixture reached room temperature, followed by the addition of water (20 mL), ethyl acetate (20 mL × 3), and extraction of the water phase. The mixed organic phase was filtered, concentrated under reduced pressure, dried with anhydrous Na_2SO_4, and washed with saturated NaCl solution. To produce the intermediate ii, the residue was purified by flash column chromatography (silica gel, ethyl acetate/hexane, gradient elution).

The proposed inhibitors were produced by the nucleophile substitution reaction of ii (1 equiv.) and imidazole (1 equiv.) using the steps from Step 2.



Scheme 19. Diphenyl conjugated imidazole derivative.

7.1 *Bioactivity*

Alzheimer's disease (AD) is the most common type of neurodegeneration and the leading cause of dementia and other cognitive impairments in elderly adults. By 2025, it is anticipated that there will be 25 million patients worldwide.

The pathogenesis of Alzheimer's disease (AD) has received a great deal of attention, and the Aβ pathology—in which the Aβ peptides generated from the proteolytic cleavage of the amyloid precursor protein (APP) by β- and γ-secretase are thought to initiate AD pathogenesis via their aggregating forms—is well established. 4, 5 targeting a pathogenesis was thought to be a potential strategy in this sense for preventing AD and perhaps other dementias. Unfortunately, even though the behavior of AD can be improved in AD model mice by reducing Aβ peptide production or aggregation or increasing clearance, many crucial aspects of the disease's neurobiology are still debatable, and there is no effective treatment for AD that can be used before the disease progresses to significant memory loss and functional decline. Glutaminyl cyclase (QC, also known as QPCT, EC 2.5.2.3), which is broadly distributed in mammalian brain with robust expression in the hippocampus and cortex, catalyses the pyroglutamylation of N-truncated, N-terminal Glu-Aβs. The production of pE-Aβ and other Aβ's in AD brains is connected with steadily elevated QC expression. Additionally, QC mRNA levels are higher in AD brains compared to age-matched normal brains, and a direct link has been shown between QC expression and ty of AD (Figure 9).

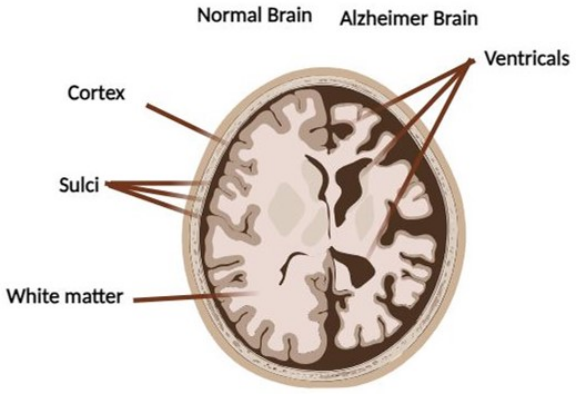


Figure 9. Normal vs. Alzheimer's Brain.

It is discovered that QC inhibition greatly alleviated the AD-like pathology, decreased the formation of Aβ plaques, and inhibited the creation of pE-Aβ in a mouse brain used as an AD model. Despite this theoretical demonstration, the blood-brain-barrier (BBB) permeability of these QC inhibitors is low. Therefore, it is critically necessary to find QC inhibitors with high activity and suitable BBB penetrability in order to introduce these innovative anti-AD medications into clinical practice. We outline the creation and discovery of several DPCIs that exhibits higher QC inhibitory potency and improved in vitro BBB penetrability. Through conformational restriction and polarity tweaking based on rational design, these DPCIs improved inflexibility and BBB penetration while maintaining the general features necessary for reported inhibitory actions (Figure 10)[45].

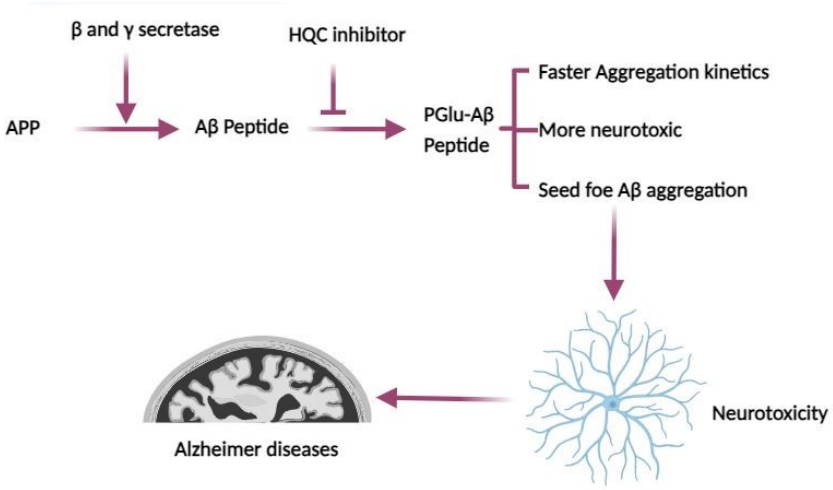


Figure 10. Role HQC inhibitor in Alzheimer’ s disease.

8. Imidazole Compound as Potential Agents against COVID

Worldwide interest in coronaviruses has grown as a result of the recent, exceptional coronavirus epidemic that drastically altered human history. The Nidovirales group includes Coronaviruses (CoVs). Order, Coronaviridae family, and Coronavirinae subfamily Contain four different types, including alpha, beta, gammacorona, and delta coronaviruses and are enormous (genome size). Positive-sense, single-stranded, enveloped, Animals and human’s ribonucleic acid (RNA) viruses. There are six different human coronaviruses, including HCoV 229E, HCoV OC43, MERS (Middle East Respiratory Syndrome), HCoV-NL63, and HCoV-HKU1. SARS (severe acute respiratory syndrome)-CoV and other zoonotic-derived CoVs. Coronaviruses (CoVs) are common in both domestic and wild mammals as well as many different bird species. They cause significant economic losses, especially in the pig and poultry farming industries. Furthermore, MERS-CoV and SARS-CoV were discovered to be caused by CoVs. They have become significant human pathogens after the advent of SARS-CoV in 2002 and MERS CoV in the Arabian Peninsula in 2012. The two deadliest coronaviruses now known to exist in humans, SARS-CoV and MERS CoV, with fatality rates of 10% and 40%, respectively. These two viruses were spread between different animals, as well. Both SARS and MERS viruses were created by modifying bat coronaviruses. Heterocyclic or diazole compounds are imidazole compounds. Many of them are chemically produced or derived from natural product chemicals like alkaloids. Imidazole and its derivatives are used to treat a variety of disorders and are said to have physiological and pharmaceutical effects. Several of them, such as antibacterial, anti-inflammatory. Anti-tubercular, anti-viral, anti-diabetic, anti-fungal, and anti-malaria medications (Figure 11).

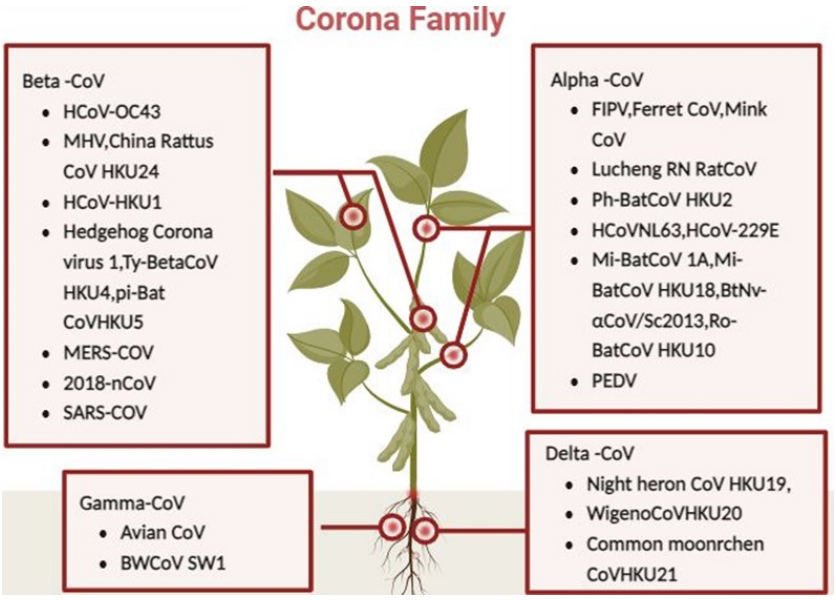


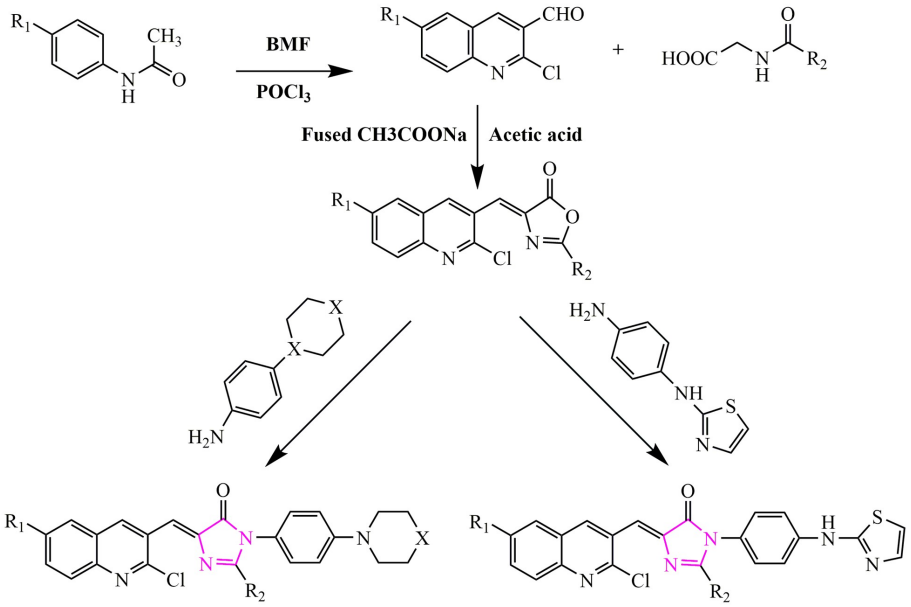
Figure 11. Ancestral details of corona virus family.

Aromatic rings having one or more branching heteroatoms, such as O, F, N, or Cl, are a characteristic shared by all imidazole compounds. Proteins (active sites) and substances interact in a variety of ways, including hydrogen bonds, π-πinteractions, electrostatic interactions, Hydrophobic and hydrophilic interactions. The more binding pressures that are applied to the protein in the active site, the more a stable compound between the inhibitor and the protein formed, and Increased capacity for inhibition. Characteristics, dimensions, and shape. The interactions between the inhibitor and active site throughout the substituted groups may depend on the amino acids. Compound below connects with the active site through two types and stops the virus interactions, OH group-OH hydrogen bonding. Furthermore, researchers concluded 18 more nucleosides of imidazole against COVID, the mode of action is hypothetical and could differ based on the chemical properties of the particular molecule. One possibility is the machinery used by Viruses to replicate directly inhibited. Additionally, the analogues may influence cellular nucleotide pathways. Metabolism, which may also be the cause of the toxicity brought on by a few substances. To learn more about the stereochemistry As well as several replacements of the decahydroisoquinoline ring the X-ray crystallography is done[46].

9. Quuinolinyl Substituted imidazole-5-onederivatives Catalyzed by Zeolite and Their Antimicrobial Activity

Multi-drug resistant bacteria have become a serious problem in several nations around the world over the past few decades. The use of most antimicrobial medicines is constrained by the inadequate state of current bacterial and fungal treatments as well as the rapidly growing antibiotic resistance Illnesses induced by such bacteria provide a significant challenge to the medical industry; therefore, it is crucial to create new antimicrobial agents. In order to achieve this, our research activities. Are concentrated on creating novel structural molecules with potential antibacterial characteristics. A comprehensive medicinal chemistry database's many-topical computer analysis discovered the one of the most common chemotypes is imidazolinone scaffold. Zeolite is a special catalyst that has a supercage framework system coupled by a three-dimensional network. Array of channels with a large diameter that makes it much easier for reactants and products to diffuse and utilize for several of these transformations as a mild alternative heterogeneous catalyst. Zeolite has garnered a lot of attention. Due to its acceptable acidity, eco-friendliness, ease of availability, and low cost, it has attracted attention and is a potential material.

In pyridine, the required amount of oxazol-5-ones (1 mmol), different *p*-substituted anilines, and 0.2 g (20%) zeolite were combined (5 mL). For 3–4 h, the reaction mixture was refluxed over an oil bath. The reaction mixture was cooled to room temperature after the reaction (confirmed by TLC) and poured over HCl that has been diluted and added to crush ice as shown in Scheme 20. Filtered, hot water was used to wash the separated precipitates until Neutral pH for title composition. With a good yield (52–72%), the imidazolin-5-ones 6a-x were synthesised utilizing zeolite as a catalyst. Without a catalyst, the yield was extremely low during optimization. Good yield was indicated by the reaction's zeolite content. By using the disc diffusion method, in vitro antibacterial activity was tested against 24-hour-old cultures of three bacteria and two fungi. The antibacterial activity of compounds against Gram-negative *E. coli*, Gram-positive *Bacillus subtilis* and *Bacillus cereus*, and antifungal activity against *Aspergillus parasiticus* and *Sclerptum rolfsii* have all been studied. The bacteria and fungus were cultured using nutrient agar and potato dextrose, respectively. In DMF solution, the compounds were evaluated at 1000 ppm. For the sake of comparing the antibacterial and antifungal activity, respectively, ampicillin and griseofulvin were utilised as benchmarks. By measuring the diameter of the inhibition zone at the end of 24 h for bacteria at 35 °C and 48 h for fungi at 28 °C, inhibition was reported.



Scheme 20. 3-quuinolinyl substituted imidazole-5-onederivatives.

10. Imidazole-Based 1,4-naphthoquinones and Their Anticancer, Antibacterial and Antifungal Activity

Naphthoquinones are very essential in various cellular and other energy production processes because of their property of forming bond with many biological compounds through π-π stacking, hydrogen bonding or other electrostatic interactions.

10.1 *Bioactivity*

Naphthoquinones base imidazole derivatives act as intercalating DNA probe for cancer treatment as shown in Scheme 21. For chemotherapy we insert these derivative into cancerous cells which kill their DNA and give protection against cancer i.e., lungs, breast and cervical cancer. In the range of 154–200 μM. The B-3 is most effective in showing antibacterial activity against gram positive possess peptiglycan and gram negative bacteria possessing lipopolysaccharide

i.e., streptomycin, amoxicillin are used but due to presence of cell wall in gram negative bacteria, as shown in Figure 12, they are somewhat resistant in bioactivity.

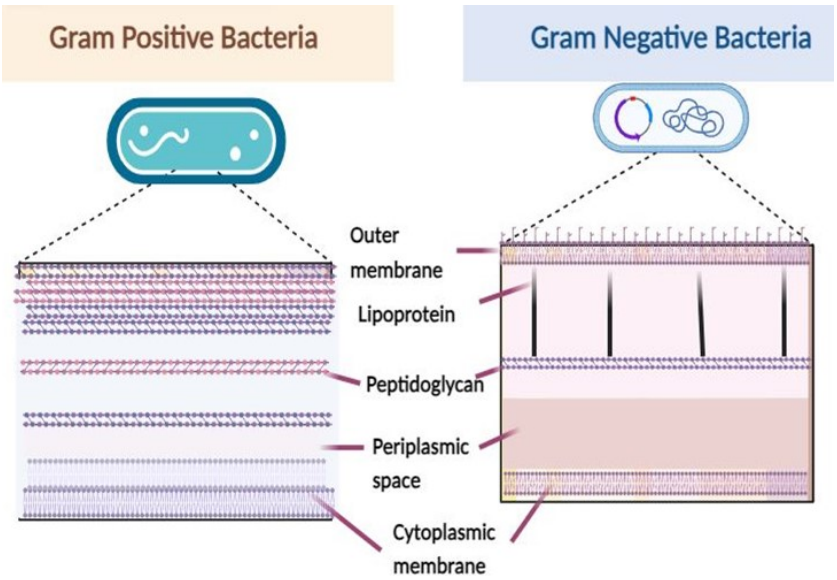
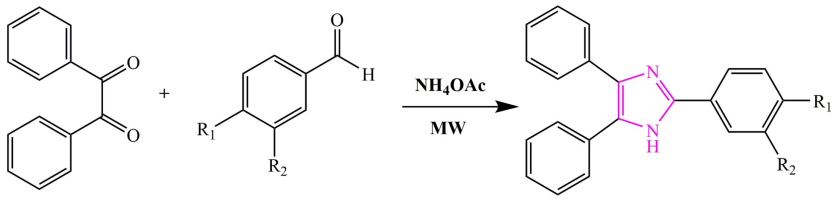


Figure 12. Comparison of Gram positive and negative bacteria.

The compound B-2 and B-3 shows antifungal activity against two strains C-albicans NCIM 3483 and B, C albicans NCIM 27[47].



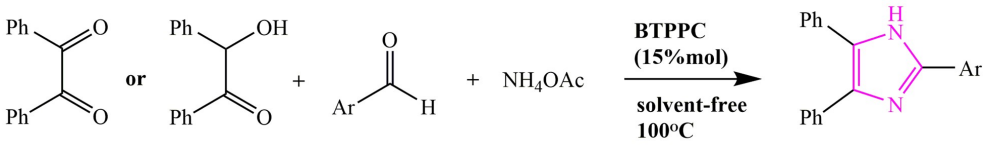
Scheme 21. Imidazole-based 1,4-naphthoquinones.

11. One-Pot Synthesis of 2,4,5-trisubstituted Imidazole Derivatives Catalyzed by BTPPC under Solvent Free Conditions

One-pot-synthesis is a procedure in which the reactant undergoes various chemical changes within the given system. There are various methods to synthesize the trisubsituted imidazole derivatives like hetero-cope rearrangement, four-component condensation etc. Many catalysts (like zirconium tetrachloride, europium triflate, sulfated zircona, iodine, ytterbium triflate, nano magnesium oxide, nano silicon dioxide supported ferric hydrogen sulfate, etc.) were used to synthesize these derivatives but they were less beneficial due to their low yield, took long time in completion, required expensive apparatus and chemicals for the completion of reactions. There was a need to shift to a less expensive, simple catalyst that can be available without any difficulty. That's why we chose BTPPC as a catalyst to synthesize these derivatives.

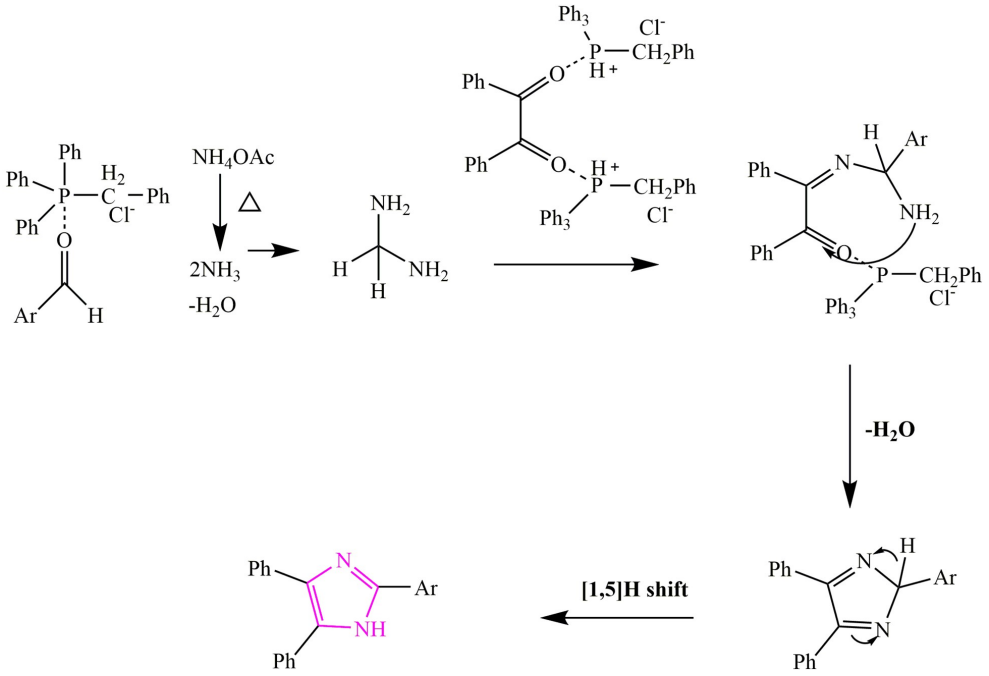
Here, we're using the process in which no solvent will be used. It provides a new method to minimize the pollution and monetary cost[48].

Synthesis of 2-aryl-4,5-diphenyl imidazole derivatives can be synthesized by forming a mixture of aldehyde, benzyl, ammonium acetate (to get ammonia from it) and the catalyst BTPPC as shown in Scheme 22. Stir this mixture at 100 °C in solvent less conditions.



Scheme 22. Synthesis of 2-aryl-4,5-diphenyl imidazole derivatives.

Thin layer chromatography was used to check out the reaction progress. Then the mixture was dissolved in ethyl alcohol and after that it was immersed in universal solvent as shown in Scheme 23. It resulted in precipitate formation which was then filtered and recrystallized by using ethanol (to get the product in pure form)[49].



Scheme 23. Mechanism of 2-aryl-4,5-diphenyl imidazole derivatives.

12. 7-Chloro-4-aminoquinoline Imidazole Derivatives

These type of imidazole derivatives are synthesized by one-pot two step protocol. An intermediate is formed in the first step, which on further reaction gets converted into the final product.

12.1 *Synthesis of N-(7-chloroquinolin-4-yl) ethane-1,2-diamine*

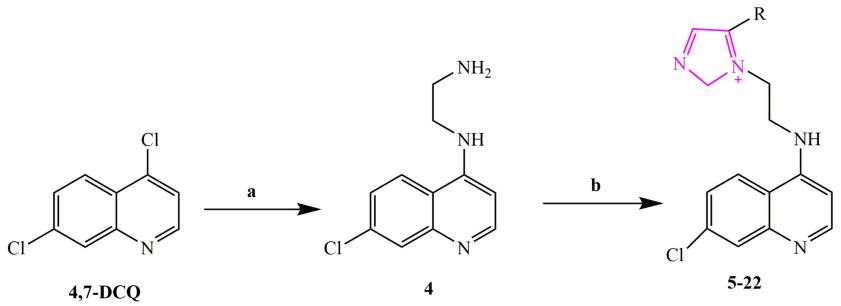
Take 1 equiv. of 4,7-dichloroquinoline, 5 equiv. of 1,2-diaminoethane and mix them. Heat the mixture slowly from 25 °C to 80 °C. Stir it for one hour. Increase the temperature from 80 °C to 120–130 °C with continuous stirring for 6–8 h. It will result in completion of the reaction. Let the mixture cool down until it reaches 25 °C. Pour it in chloromethane. Wash the organic layer with 5% aqueous sodium bicarbonate then with water and lastly with brine. Dry the organic layer using anhydrous sodium sulphate. Remove the solvent by applying reduced pressure. Precipitate out the residue by using mixture of hexane and chloroform (80:20). Product (yellow solid) is obtained with promising yield of 85%.

12.1.1 *Synthesis of 7-chloro-4-amino Quinolone Imidazole Derivatives*

A series (i.e., 5-22) of 7-chloro-4-aminoquinoline imidazole derivatives have been synthesized by this method. (0.48 mmol) of aldehyde and (0.48 mmol) of amine were taken and dissolve in 10 mL of Dimethyl Formamide. Heat the mixture at 90 °C for 6–8 h as shown in Scheme 24. Add (0.96 mmol) of potassium carbonate and (0.48 mmol) of touene sulfonyl methyl isocyanide (TOSMIC) to the reaction mixture and stirred the solution at 90 °C for half day. Completion of reaction is monitored by performing thin layer chromatography.

Perform extraction by using 20 mL of water and 60 mL of ethyl acetate. Using sodium sulphate dry the organic phase and by applying pressure, concentrate it. Perform column chromatography to purify the crude substance by using eluent i.e., 60–120 mesh in methanol or chloroform.

General reaction for the synthesis of 7-chloro-4-aminoquinoline imidazole derivatives.



Scheme 24. Synthesis of 7-chloro-4-aminoquinoline imidazole derivatives.

12.1.2 *Bioactivity*

The 4-aminoquinoline imidazole derivatives show antimalarial activity. Chloroquine, due to its mode of action, tolerance power and inexpensiveness is considered the most suitable drug against malaria. Table 2 depict the recent data of imidazole derivatives and their bioactivity. Furthermore, these derivatives inhibit the β-hematic formation. And these derivatives gather at the target to perform their action.

• Series of 4-aminoquinoline-imidazole derivatives are prepared. They are analyzed for in vitro antiplasmodial activity against CQ-sensitive (3D7) and CQ-resistant (K1) strains of the plasmodium falciparum.

• SAR studies suggest that activity is affected by type of substitution on the imidazole ring. Substitution on phenyl ring affects activity of these derivatives. Results showed that the compounds having heterocyclic structure attached to imidazole imparts mild effect in inhibiting parasitic growth against CQ-resistant strain. Compounds having phenol and naphthalene substituents on imidazole showed no activity against both the strains. Compounds having electron withdrawing group showed prominent inhibiting effect against CQ-R strain as compared to those having electron donating groups (Hematic group causes toxicity in the tissues, organelles of organisms because it produces the reactive oxygen [50]). 4-aminoquinoline derivatives help in the inhibition of Beta-hematic formation [51].

Table 2. Imidazole derivatives and their bioactivities.

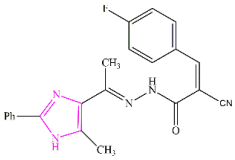
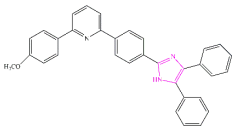
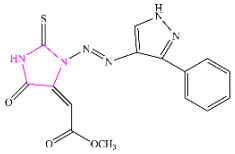
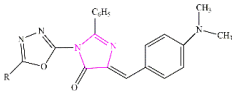
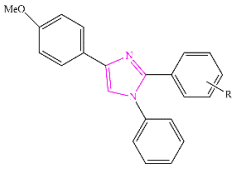
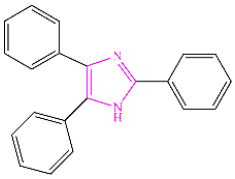
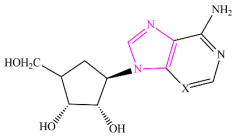
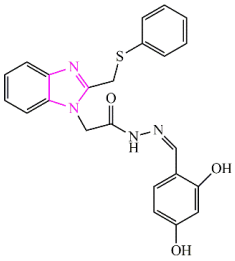
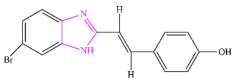
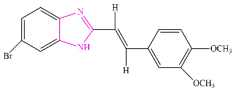
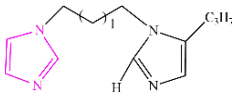
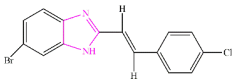
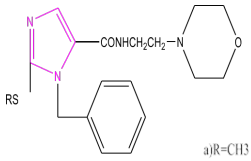
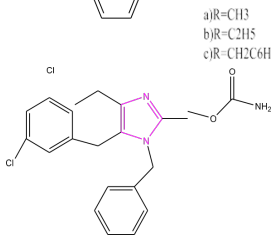
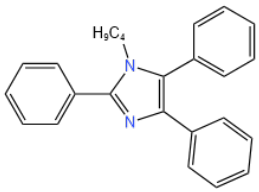
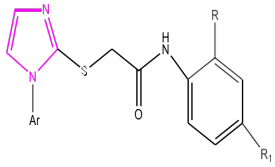
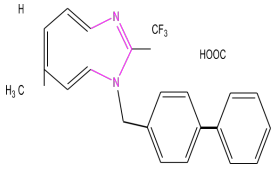
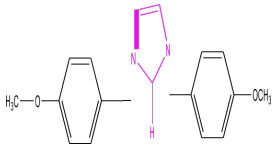
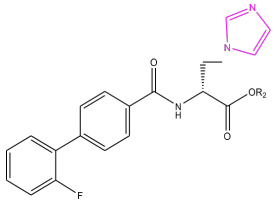
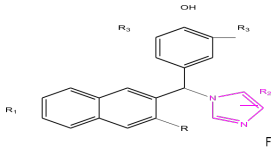
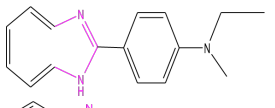
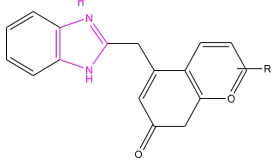
No.	Chemical Structure	Chemical Name	Activity
1		2-cyano-3-(4-fluorophenyl)-*N*-[1-(5-methyl-2-phenyl -1H-imidazol-4-yl) ethylene] acrylohydrazie	anti-microbial, anti-oxidant, anti-hemolytic, anti-ctotoxic [52]
2		2-[4-(4,5-diphenyl-1H-imidazol-2-yl)-phenyl] -6-(40-mathoxy-biphenyl-4-yl)-pyridine (MPBI)	anti-bacterial, anti-fungal [53]
3		methyl (2Z)-[3-((E)-[3-aryl-1H-Pyrazole-4-yl] methylidene amino) -5-oxo-2-thioxoimidazolidine-4-ylidene] ethanoate	anti-bacterial [54]
4		(5Z)-5-[4-(dimethyl amino) benzylidene]-3-(5-substituted -1,3,4-oxadiazol-2-yl)-2-phenyl-3,5-dihydro-4H-imidazole-4-one	anthelmintic [55]
5		(5Z)-5-[4-(dimethyl amino) benzylidene]-3-(5-substituted -1,3,4-oxadiazol-2-yl)-2-phenyl-3,5-dihydro-4H-imidazole-4-one	anti-inflammatory, anti-fungal [56]
6		2,4,5-triphenyl-1H-imidazole	anti-microbial [57]
7		3-bromo-3-deazaneplanocin	anti-viral [58]
8		*N*-(2,4-dihydroxybenzylidene)-2-(2-(phenylthiomethyl) -1H-benzo[d]-imidazole-1-yl) acetohydrazide	anti-tumor [59]
9		4-((E)-2-(6-bromo-1H-benzo[d]imidazole-2-yl)vinyl)phenol	anti-fungal, anti-bacterial [59]
10		2-(3,4-dimethoxystyryl)-6-bromo-1H-benzo[d]imidazole	anti-fungal [60]
11		1-(3-(1H-imidazol-1-yl)propyl-1H-imidazole	anti-tubercular [61]
12		*N*-((6-bromo-1H-benzo[d]imidazole-2-yl)methyl)-4-chlorobenzenamine	anti-inflammatory, analgesic [62]

Table 2. *Cont.*

No.	Chemical Structure	Chemical Name	Activity
13		moclobmide	anti-depressant [63]
14		capravarine	anti-HIV [64]
15		2-substituted-4,5-diphenyl-*N*-alkyl imidazole derivative	anti-bacterial [64]
16		5-substituted-1-(phenylsulfonyl)-2-methylbenzimidazole	analgesic [65]
17		dexamethasone	anti-hypertensive [66]
18		1,2-bis(*p*-methoxybenzyl)imidazole	anti-leishmanial activity
19		biphenylimidazole	anti-fungal [67]
20		tri-substituted imidazole derivative	anti-malarial [68]
21		4-benzimidazole-*N*-methyl-*N*-ethylflouro imidazole	anti-cancer [68]
22		1,2,5-substituted benzimidazole derivative	anti-inflammatory [67]

Imidazole derivatives of several novel medications that have recently been developed have superior effects and reduced toxicity.

Most Recent Research on Imidazole derivatives and their biological applications is listed in Table 3.

Table 3. Most recent research on imidazole derivatives and their biological applications

No.	Derivative	Application	Year of Publication	Reference
1	2-poly hydroxy alkyl 1-H-Imidazo[4,5-f] [1,10]phenanthrolines	anti-tumor	2024	[69]
2	2-aryl-1-H-benzo[d]imidazole	anti-cancer	2024	[70]
3	2-(diethoxymethyl)-1-tosyl-1-H-[d] imidazole	anti-oxidant	2024	[71]
4	1-H-benzo[d]imidazole	anti-oxidant	2023	[72]
5	diphenyl -1-H-imidazole	SARS-CoV-2	2024	[73]
6	imidazole[1,2-a]pyrimidine	SARS-CoV-2	2023	[74]
7	2,4,5-trisubstituted imidazole	anti-diabetic	2023	[75]
8	4,5-diphenylimidazole-α-aminophosphonate hybrid	anti-diabetic	2023	[76]
9	imidazole[2,1-b][1,3.4] triazole moiety	anti-bacterial	2024	[77]
10	2,4,5-trisubstituted imidazole	anti-microbial & anti-fungal	2023	[78]

13. Conclusions

In this present review article, we have summarized different therapeutic activities of Imidazole and derivatives. From this study we came to know that imidazole and their derivatives can be synthesized via various synthetic methods and these imidazole derivatives exhibit a range of antibacterial, anti-inflammatory, analgesic, anti-tubercular, and anticancer properties. Imidazole and its derivatives proved as useful template for further modifications or by making minor changes in the substituents on the basic imidazole nucleus to design more biologically active compounds.

14. Future Perspective

Imidazole compounds, extensively researched since ancient times, remain pivotal in new medication development, targeting various ailments like antifungal, antiepileptic, and ACE inhibitors. Ongoing medicinal chemistry focuses on creating molecules with imidazole moieties, aiming for increased selectivity and reduced side effects. Commercially available imidazole-based antifungals, particularly targeting the 14-demethylase enzyme, are gaining interest. Synthesizing imidazole derivatives from natural sources enhances efficiency, economy, and availability. Due to rising cancer rates and limitations in anticancer drugs, there's a pressing need for biologically active heterocyclic molecules. Medical chemists strive for novel imidazole derivatives with superior pharmacodynamics and pharmacokinetics, harnessing their diverse physiological and pharmacological properties.

Confilict of Interest

Authors declare no conflict of interests.

References

[1] Iravani, S. Green synthesis of metal nanoparticles using plants. *Green Chem.* **2011**, *13*, 2638-2650.

[2] Singh, A.; Gautam, P. K.; Verma, A.; Singh, V.; Shivapriya, P. M.; Shivalkar, S.; Sahoo, A. K.; Samanta, S. K. Green synthesis of metallic nanoparticles as effective alternatives to treat antibiotics resistant bacterial infections: A review. *Biotechnol. Rep.* **2020**, *25*, e00427. https://doi.org/10.1016/j.btre.2020.e00427.

[3] Ying, S.; Guan, Z.; Ofoegbu, P. C.; Clubb, P.; Rico, C.; He, F.; Hong, J. Green synthesis of nanoparticles: Current developments and limitations. *Environ. Technol. Innov.* **2022**, *26*, 102336. https://doi.org/10.1016/j.eti.2022.102336.

[4] Dadkhah, M.; Tulliani, J. M. Green synthesis of metal oxides semiconductors for gas sensing applications. *Sensors* **2022**, *22*, 4669. https://doi.org/10.3390/s22134669.

[5] Al-Mulla, A. A review: biological importance of heterocyclic compounds. *Der. Pharma. Chem.* **2017**, *9*, 141-147. (ISSN 0975-413X CODEN).

[6] Ghaemi, M.; Pordel, M. Isoxazolo [4, 3-e] indazole as a new heterocyclic system: Design, synthesis, spectroscopic characterization, and antibacterial activity. *Chem. Heterocycl. Compd.* **2016**, *52*, 52-57. https://doi.org/10.1007/s10593-016-1833-7.

[7] Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among US FDA approved pharmaceuticals: Miniperspective. *J. Med. Chem.* **2014**, *57*, 10257-10274. https://doi.org/10.1021/jm501100b.

[8] Ferouani, G.; Nacer, A.; Ameur, N.; Bachir, R.; Ziani Cherif, C. Facile Heterocyclic Synthesis and Antibacterial Activity of Substituted Isoxazol-5 (4H)-ones. *J. Chin. Chem. Soc.* **2018**, *65*, 459-464. https://doi.org/10.1002/jccs.201700334.

[9] Mohan, S.; Ananthan, S. A new approach for the synthesis of some novel sulphur bridged pyrazoles and their characterization. *J. Chem. Pharm. Res.* **2011**, *3*, 402-413. (ISSN No: 0975-73840).

[10] Al-jubouri, A. A.; Qasir, A. J. Synthesis and Antibacterial Activity of bis Heterocyclic Derivatives of 1, 3, 4-thiadiazole. *Iraqi J. Pharm. Sci.* **2015**, *24*, 59-67. https://doi.org/10.31351/vol24iss1pp59-67.

[11] Ameli, S.; Pordel, M.; Davoodnia, A.; Jajarmi, M. Synthesis and antibacterial activity of some new benzo [5, 6] chromeno [2, 3-d] pyrimidines. *Russ. J. Bioorg. Chem.* **2017**, *43*, 429-434. https://doi.org/10.1134/S1068162017040100.

[12] Aaglawe, M. J.; Dhule, S. S.; Bahekar, S. S. Wakte, P. S.; Shinde, D. B. Synthesis and antibacterial activity of some oxazolone derivatives. *J. Korean Chem. Soc.* **2003**, *47*, 133-136. https://doi.org/10.5012/jkcs.2003.47.2.133.

[13] Sayed Mohamed, M.; El-Domany, R.; Abd El-Hameed, R. Sinteza derivata pirola kao antimikrobnih tvari. *Acta Pharm.* **2009**, *59*, 145-158. https://doi.org/10.2478/v10007-009-0016-9.

[14] Padwa, A.; Bur, S. Recent advances of 1, 3-dipolar cycloaddition chemistry for alkaloid synthesis. *Adv. Heterocycl. Chem.* **2016**, *119*, 241-305. https://doi.org/10.1016/bs.aihch.2016.03.005.

[15] Ferlin, F.; Luciani, L.; Viteritti, O.; Brunori, F.; Piermatti, O.; Santoro, S.; Vaccaro, L. Polarclean as a sustainable reaction medium for the waste minimized synthesis of heterocyclic compounds. *Front. Chem.* **2019**, *6*, 659. https://doi.org/10.3389/fchem.2018.00659.

[16] Bhaskaruni, S. V.; Maddila, S.; Gangu, K. K.; Jonnalagadda, S. B. A review on multi-component green synthesis of N-containing heterocycles using mixed oxides as heterogeneous catalysts. *Arab. J. Chem.* **2020**, *13*, 1142-1178. https://doi.org/10.1016/j.arabjc.

[17] Anderson, E. B.; Long, T. E. Imidazole-and imidazolium-containing polymers for biology and material science applications. *Polymer* **2010**, *51*, 2447-2454. https://doi.org/10.1016/j.polymer.2010.02.006.

[18] Verma, A.; Joshi, S.; Singh, D. Imidazole: having versatile biological activities. *J. Chem.* **2013**, *2013*. https://doi.org/10.1155/2013/329412.

[19] Kerru, N.; Bhaskaruni, S. V.; Gummidi, L.; Maddila, S. N.; Maddila, S.; Jonnalagadda, S. B. Recent advances in heterogeneous catalysts for the synthesis of imidazole derivatives. *Synth. Commun.* **2019**，*49*, 2437-2459. https://doi.org/10.1080/00397911.2019.1639755.

[20] Chhetri, A.; Chettri, S.; Rai, P.; Mishra, D. K.; Sinha, B.; Brahman, D. Synthesis, characterization and computational study on potential inhibitory action of novel azo imidazole derivatives against COVID-19 main protease (Mpro: 6LU7). *J. Mol. Struct.* **2021**, *1225*, 129230. https://doi.org/10.1016/j.molstruc.2020.129230.

[21] Abd El-Lateef, H. M.; Shalabi, K.; Abdelhamid, A. A. One-pot synthesis of novel triphenyl hexyl imidazole derivatives catalyzed by ionic liquid for acid corrosion inhibition of C1018 steel: Experimental and computational perspectives. *J. Mol. Liq.* **2021**, *334*, 116081. https://doi.org/10.1016/j.molliq.2021.116081.

[22] Shingalapur, R. V.; Hosamani, K. M.; Keri, R. S. Synthesis and evaluation of in vitro anti-microbial and anti-tubercular activity of 2-styryl benzimidazoles. *Eur. J. Med. Chem.* **2009**, *44*, 4244-4248. [https://doi.org/10.1016/j.ejmech.2009.05.021.

[23] Narasimhan, B.; Sharma, D.; Kumar, P. Biological importance of imidazole nucleus in the new millennium. *Med. Chem. Res.* **2011**, *20*, 1119-1140. https://doi.org/10.1007/s00044-010-9472-5.

[24] Shalini, K.; Sharma, P. K.; Kumar, N. Imidazole and its biological activities: A review. *Der Chem. Sin.* **2010**, *1*, 36-47. [ISSN: 0976-8505].

[25] Bhatnagar, A.; Sharma, P. K.; Kumar, N. A review on "Imidazoles": Their chemistry and pharmacological potentials. *Int. J. PharmTech. Res.* **2011**, *3*, 268-282. [ISSN: 0974-4304].

[26] Desai, N. C.; Maheta, A. S.; Rajpara, K. M.; Joshi, V. V.; Vaghani, H. V.; Satodiya, H. M. Green synthesis of novel quinoline based imidazole derivatives and evaluation of their antimicrobial activity. *J. Saudi Chem. Soc.* **2014**, *18*, 963-971. https://doi.org/10.1016/j.jscs.2011.11.021.

[27] Guariguata, L.; Whiting, D. R.; Hambleton, I.; Beagley, J.; Linnenkamp, U.; Shaw, J. E. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res. Clin. Pract.* **2014**, 103, 137-149. https://doi.org/10.1016/j.diabres.2013.11.002.

[28] Hussain, S.; Taha, M.; Rahim, F.; Hayat, S.; Zaman, K.; Iqbal, N.; Selvaraj, M.; Sajid, M.; Bangesh, M. A.; Khan, F.; Khan, K. M. Synthesis of benzimidazole derivatives as potent inhibitors for α-amylase and their molecular docking study in management of type-II diabetes. *J. Mol. Struct.* **2021**, *1232*, 130029. https://doi.org/10.1016/j.molstruc.2021.130029.

[29] Karadayi, F. Z.; Yaman, M.; Kisla, M. M.; Keskus, A. G.; Konu, O.; Ates-Alagoz, Z. Design, synthesis and anticancer/antiestrogenic activities of novel indole-benzimidazoles. *Bioorg. Chem.* **2020**, *100*, 103929. https://doi.org/10.1016/j.bioorg.2020.103929.

[30] Sharma, P. C.; Goyal, R.; Sharma, A.; Sharma, D.; Saini, N.; Rajak, H.; Sharma, S.; Thakur, V. K. Insights on fluoroquinolones in cancer therapy: Chemistry and recent developments. *Mater. Today Chem.* **2020**, *17*, 100296. https://doi.org/10.1016/j.mtchem.2020.100296.

[31] Gajulapalli, V. N.; Malisetty, V. L.; Chitta, S. K.; Manavathi, B. Oestrogen receptor negativity in breast cancer: A cause or consequence? *Biosci. Rep.* **2016**, *36*, e00432. https://doi.org/10.1042/BSR20160228.

[32] Saccoliti, F.; Madia, V. N.; Tudino, V.; De Leo, A.; Pescatori, L.; Messore, A.; De Vita, D.; Scipione, L.; Brun, R.; Kaiser, M.; Maser, P. Design, synthesis, and biological evaluation of new 1-(Aryl-1 H-pyrrolyl)(phenyl) methyl-1 H-imidazole derivatives as antiprotozoal agents. *J. Med. Chem.* **2019**, *62*, 1330-1347. https://doi.org/10.1021/acs.jmedchem.8b01448.

[33] Kerru, N.; Gummidi, L.; Bhaskaruni, S. V.; Maddila, S. N.; Jonnalagadda, S. B. Green synthesis and characterization of novel 1,2,4,5-tetrasubstituted imidazole derivatives with eco-friendly red brick clay as efficacious catalyst. *Mol. Divers.* **2020**, *24*, 889-901. https://doi.org/10.1007/s11030-019-10000-5.

[34] Wang, Y.; He, H.; Wang, C.; Lu, Y.; Dong, K.; Huo, F.; Zhang, S. Insights into ionic liquids: From Z-bonds to quasi-liquids. *JACS Au.* **2022**, *2*, 543-561. https://doi.org/10.1021/jacsau.1c00538.

[35] Ahmed, N. S.; Hanoon, H. D. A green and simple method for the synthesis of 2,4,5-trisubstituted-1 H-imidazole derivatives using acidic ionic liquid as an effective and recyclable catalyst under ultrasound. *Res. Chem. Intermed.* **2021**, 47, 4083-4100. https://doi.org/10.1007/s11164-021-04517-4.

[36] Czarnomysy, R.; Radomska, D.; Muszyńska, A.; Hermanowicz, J. M.; Prokop, I.; Bielawska, A.; Bielawski, K. Evaluation of the anticancer activities of novel transition metal complexes with berenil and nitroimidazole. *Molecules* **2020**, 25, 2860. https://doi.org/10.3390/molecules25122860.

[37] Abdelhamid, A. A.; Salah, H. A.; Marzouk, A. A. Synthesis of imidazole derivatives: Ester and hydrazide compounds with antioxidant activity using ionic liquid as an efficient catalyst. *J. Heterocycl. Chem.* **2020**, *57*, 676-685. https://doi.org/10.1002/jhet.3808.

[38] Fahmy, A. F.; Rizk, S. A.; Hemdan, M. M.; El-Sayed, A. A.; Hassaballah, A. I. Efficient green synthesis and computational chemical study of some interesting heterocyclic derivatives as insecticidal agents. *J. Heterocycl. Chem.* **2018**, *55*, 2545-2555. https://doi.org/10.1002/jhet.3308.

[39] Raghuvanshi, D. S.; Singh, K. N. A highly efficient green synthesis of 1H-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives and their photophysical studies. *Tetrahedron Lett.* **2011**, *52*, 5702-5705. https://doi.org/10.1016/j.tetlet.2011.08.111.

[40] Desai, N. C.; Maheta, A. S.; Rajpara, K. M.; Joshi, V. V.; Vaghani, H. V.; Satodiya, H. M. Green synthesis of novel quinoline based imidazole derivatives and evaluation of their antimicrobial activity. *J. Saudi Chem. Soc.*. **2014**, *18*, 963-971. https://doi.org/10.1016/j.jscs.2011.11.021.

[41] Saxena, P.; Kumar, U.; Kumar, P.; Saxena, A. Green Synthesis of Novel Imidazoles Derivatives and Evaluation of Anticancer and Anthelmintic Activity. *Pharm. Biosci. J.* **2021**, *31*, 49-56. https://doi.org/10.20510/10.20510/pbj/9/i4/1644.

[42] Lee, C. F.; Holownia, A.; Bennett, J. M.; Elkins, J. M.; St, Denis, J. D.; Adachi, S.; Yudin, A. K. Oxalyl boronates enable modular synthesis of bioactive imidazoles. *Angew. Chem. Int. Ed.* **2017**, *56*, 6264-6267. https://doi.org/10.1002/anie.201611006.

[43] Fahmy, A. F.; Rizk, S. A.; Hemdan, M. M.; El-Sayed, A. A.; Hassaballah, A. I. Efficient green synthesis and computational chemical study of some interesting heterocyclic derivatives as insecticidal agents. *J. Heterocycl. Chem.* **2018**, *55*, 2545-2555. https://doi.org/10.1002/jhet.3308.

[44] Velmurugan, K.; Don, D.; Kannan, R.; Selvaraj, C.; VishnuPriya, S.; Selvaraj, G.; Singh, S. K.; Nandhakumar, R. Synthesis, antibacterial, anti-oxidant and molecular docking studies of imidazoquinolines. *Heliyon* **2021**, *7*. https://doi.org/10.1016/j.heliyon.2021.e07484.

[45] Anthony, L. A.; Nethaji, P.; Sundararajan, G.; Rajaraman, D. One-pot synthesis, Spectral, X-ray crystal structure, Hirshfeld surface and computational study on potential inhibitory action of novel 1-benzyl-2-(4-methoxynaphthalen-1-yl)-4, 5-diphenyl-1H-imidazole derivatives against COVID-19 main protease (Mpro: 6WCF/6Y84). *J. Mol. Struct.* **2022**, *1250*, 131892. https://doi.org/10.1016/j.molstruc.2021.131892.

[46] Li, M.; Dong, Y.; Yu, X.; Li, Y.; Zou, Y.; Zheng, Y.; He, Z.; Liu, Z.; Quan, J.; Bu, X.; Wu, H. Synthesis and evaluation of diphenyl conjugated imidazole derivatives as potential glutaminyl cyclase inhibitors for treatment of Alzheimer's disease. *J. Med. Chem.* **2017**, 60, 6664-6677. https://doi.org/10.1021/acs.jmedchem.7b00648.

[47] Seck, I.; Nguemo, F. Triazole, imidazole, and thiazole-based compounds as potential agents against coronavirus. *Results Chem.* **2021**, *3*, 100132. https://doi.org/10.1016/j.rechem.2021.100132.

[48] Choudhari, D.; Salunke-Gawali, S.; Chakravarty, D.; Shaikh, S. R.; Lande, D. N.; Gejji, S. P.; Rao, P. K.; Satpute, S.; Puranik, V. G.; Gonnade, R. Synthesis and biological activity of imidazole based 1, 4-naphthoquinones. *New J. Chem.* **2020**, *44*, 6889-6901. https://doi.org/10.1039/C9NJ04339J.

[49] Tanaka, K.; Toda, F. J. Solvent-free organic synthesis. *Chem. Rev.* **2000**, *100*, 1025-1074. https://doi.org/10.1021/cr940089p.

[50] Alikarami, M.; Amozad, M. One-pot synthesis of 2,4,5-trisubstituted imidazole derivatives catalyzed by btppc under solvent-free conditions. *Bull. Chem. Soc. Ethiop.* **2017**, *31*, 177-184. https://doi.org/10.4314/bcse.v31i1.16.

[51] Aich, A.; Freundlich, M.; Vekilov, P. G. The free heme concentration in healthy human erythrocytes. *Blood Cells Mol. Dis.* **2015**, *55*, 402-409. https://doi.org/10.1016/j.bcmd.2015.09.003.

[52] Kondaparla, S.; Manhas, A.; Dola, V. R.; Srivastava, K.; Puri, S. K.; Katti, S. B. Design, synthesis and antiplasmodial activity of novel imidazole derivatives based on 7-chloro-4-aminoquinoline. *Bioorg. Chem.* **2018**, *80*, 204-211. https://doi.org/10.1016/j.bioorg.2018.06.012.

[53] Abdel-Wahab, B. F.; Awad, G. E.; Badria, F. A. Synthesis, antimicrobial, antioxidant, anti-hemolytic and cytotoxic evaluation of new imidazole-based heterocycles. *Eur. J. Med. Chem.* **2011**, *46*, 1505-1511. https://doi.org/10.1016/j.ejmech.2011.01.062.

[54] Nagarajan, N.; Vanitha, G.; Ananth, D. A.; Rameshkumar, A.; Sivasudha, T.; Renganathan, R. Bioimaging, antibacterial and antifungal properties of imidazole-pyridine fluorophores: Synthesis, characterization and solvatochromism. *J. Photochem. Photobiol. B* **2013**, *127*, 212-222. https://doi.org/10.1016/j.jphotobiol.2013.08.016.

[55] Vijesh, A. M.; Isloor, A. M.; Telkar, S.; Arulmoli, T.; Fun, H. K. Molecular docking studies of some new imidazole derivatives for antimicrobial properties. *Arab. J. Chem.* **2013**, *6*, 197-204. https://doi.org/10.1016/j.arabjc.2011.10.007.

[56] Patel, K.; Ch, ran, J. E.; Shah, R.; Vijaya, J.; Sreenivasa, G. M. Synthesis, characterization and anthelmintic activity (Perituma posthuma) of new oxadiazole incorporated with imidazole and pyrazole. *Int. J. Pharm. Bio. Sci.* **2010**, *1*, 1-3. ISSN 0975-6299.

[57] Husain, A.; Drabu, S.; Kumar, N.; Alam, M. M.; Bawa, S. Synthesis and biological evaluation of di-and tri-substituted imidazoles as safer anti-inflammatory-antifungal agents. *J. Pharm. Bioallied Sci.* **2013**, *5*, 154. https://doi.org/10.4103.

[58] Jourshari, M. S.; Mamaghani, M.; Shirini, F.; Tabatabaeian, K.; Rassa, M.; Langari, H. An expedient one-pot synthesis of highly substituted imidazoles using supported ionic liquid-like phase (SILLP) as a green

and efficient catalyst and evaluation of their anti-microbial activity. *Chin. Chem. Lett.* **2013**, *24*, 993-996. https://doi.org/10.1016/j.cclet.2013.06.005.

[59] Liu, C.; Chen, Q.; Schneller, S. W. 3-Bromo-3-deazaneplanocin and 3-bromo-3-deazaaristeromycin: Synthesis and antiviral activity. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5182-5184. https://doi.org/10.1016/j.bmcl.2012.06.075.

[60] Liu, T.; Sun, C.; Xing, X.; Jing, L.; Tan, R.; Luo, Y.; Huang, W.; Song, H.; Li, Z.; Zhao, Y. Synthesis and evaluation of 2-[2-(phenylthiomethyl)-1H-benzo [d] imidazol-1-yl) acetohydrazide derivatives as antitumor agents. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3122-3125. https://doi.org/10.1016/j.bmcl.2012.03.061.

[61] Shingalapur, R. V.; Hosamani, K. M.; Keri, R. S. Synthesis and evaluation of in vitro anti-microbial and anti-tubercular activity of 2-styryl benzimidazoles. *Eur. J. Med. Chem.* **2009**, *44*, 4244-4248. https://doi.org/10.1016/j.ejmech.2009.05.021.

[62] Achar, K. C.; Hosamani, K. M.; Seetharamareddy, H. R. In-vivo analgesic and anti-inflammatory activities of newly synthesized benzimidazole derivatives. *Eur. J. Med. Chem.* **2010**, *45*, 2048-2054. https://doi.org/10.1016/j.ejmech.2010.01.029.

[63] Gujjarappa, R.; Kabi, A. K.; Sravani, S.; Garg, A.; Vodnala, N.; Tyagi, U.; Kaldhi, D.; Velayutham, R.; Singh, V.; Gupta, S.; Malakar, C. C. Overview on biological activities of imidazole derivatives. In *Nanostructured Biomaterials: Basic Structures and Applications*; Springer Singapore: Singapore, 2022; pp. 135-227. https://doi.org/10.1007/978-981-16-8399-2_6.

[64] Hadi, Z. F.; Hosseinzadeh, H.; Motamed, S. V.; Seyfi, M.; Kazemi, S. Synthesis and antidepressant activity of N-substituted imidazole-5-carboxamides in forced swimming test model. *Iran. J. Pharm. Res.* **2008**, *7*, 29-33.

[65] Verma, A.; Joshi, S.; Singh, D. Imidazole: Having versatile biological activities. *J. Chem.* **2013**, *2013*, 329412. https://doi.org/10.1155/2013/329412.

[66] Arulmurugan, S.; PKavitha, H.; Sathishkumar, S.; Arulmozhi, R. Biologically active benzimidazole derivatives. *Mini-Rev. Org. Chem.* **2015**, *12*, 178-195. https://doi.org/10.1016/j.rechem.2021.100200.

[67] Zhao, D.; Zhao, S.; Zhao, L.; Zhang, X.; Wei, P.; Liu, C.; Hao, C.; Sun, B.; Su, X.; Cheng, M. Discovery of biphenyl imidazole derivatives as potent antifungal agents: Design, synthesis, and structure-activity relationship studies. *Bioorg. Med. Chem.* **2017**, *25*, 750-758. https://doi.org/10.1016/j.bmc.2016.11.051.

[68] Zang, H.; Su, Q.; Mo, Y.; Cheng, B. W.; Jun, S. Ionic liquid [EMIM] OAc under ultrasonic irradiation towards the first synthesis of trisubstituted imidazoles. *Ultrason. Sonochem.* **2010**, *17*, 749-751. https://doi.org/10.1016/j.ultsonch.2010.01.015.

[69] Gómez-Bra, A.; Gude, L.; Arias-Pérez, M. S. Synthesis, structural study and antitumor activity of novel alditol-based imidazophenanthrolines (aldo-IPs). *Bioorg. Med. Chem.* **2024**, *99*, 117563. https://doi.org/10.1016/j.bmc.2023.117563.

[70] Park, S. J.; Song, I. H.; Yeom, G. S.; Nimse, S. B. The microtubule cytoskeleton: A validated target for the development of 2-Aryl-1H-benzo [d] imidazole derivatives as potential anticancer agents. *Biomed. Pharmacother.* **2024**, *171*, 116106. https://doi.org/10.1016/j.biopha.2023.116106.

[71] Almansour, A. I.; Arumugam, N.; Soliman, S. M.; Viswanathan, E.; Dege, N.; Karuppiah, P.; Premnath, D.; Kumari, J.; Sriram, D.; Perumal, K. Eco-friendly synthesis, structural elucidation, computational investigation and in vitro antioxidant activity of a new N-tosylated benzimidazole derivative. *J. Mol. Struct.* **2024**, *1296*, 136825. https://doi.org/10.1016/j.molstruc.2023.136825.

[72] Mohammed, S. M.; Shehab, W. S.; Emwas, A. H.; Jaremko, M.; Abdellattif, M. H.; Zordok, W. A.; Tantawy, E. S. Eco-Friendly Synthesis of 1 H-benzo [d] imidazole Derivatives by ZnO NPs Characterization, DFT Studies, Antioxidant and Insilico Studies. *Pharmaceuticals* **2023**, *16*, 969. https://doi.org/10.3390/ph16070969.

[73] Vora, A.; Kanhed, A.; Thakkar, A.; Gudepalya, R. R.; Sh, il, R.; Yogi, M.; Harisha, R.; Singh, M.; Narayanan, S. Design and synthesis of Diphenyl-1H-imidazole analogs targeting MPro/3CLpro enzyme of SARS-CoV-2. *Med. Chem. Res.* **2024**. https://doi.org/10.21203/rs.3.rs-3975613/v1.

[74] Azzouzi, M.; El Ouafi, Z.; Azougagh, O.; Daoudi, W.; Ghazal, H.; El Barkany, S.; Abderrazak, R.; Mazières, S.; El Aatiaoui, A.; Oussaid, A. Design, synthesis, and computational studies of novel imidazo [1, 2-a] pyrimidine derivatives as potential dual inhibitors of hACE2 and spike protein for blocking SARS-CoV-2 cell entry. *J. Mol. Struct.* **2023**, *1285*, 135525. https://doi.org/10.1016/j.molstruc.2023.135525.

[75] Kumar, P.; Syal, B.; Seboletswe, P.; Cele, N.; Olofinsan, K.; Singh, P.; Shahidul, Islam, M.; Singh, D.; Gupta, P. Synthesis, Biological Evaluation, Molecular Docking and Kinetic Investigation of New 2, 4, 5-Trisubstituted Imidazole Derivatives as Antidiabetic Agents. *ChemistrySelect* **2023**, *8*, e202300924. https://doi.org/10.1002/slct.202300924.

[76] Zareei, S.; Ranjbar, S.; Mohammadi, M.; Ghasemi, Y.; Golestanian, S.; Avizheh, L.; Moazzam, A.; Larijani, B.; Mohammadi-Khanaposhtani, M.; Tarahomi, M. M.; Mahdavi, M. Discovery of novel 4, 5-diphenyl-imidazol-α-aminophosphonate hybrids as promising anti-diabetic agents: Design, synthesis, in vitro, and in silico enzymatic studies. *Bioorg. Chem.* **2023**, *141*, 106846. https://doi.org/10.1016/j.bioorg.2023.106846.

[77] Xu, W. B.; Li, S.; Zheng, C. J.; Yang, Y. X.; Zhang, C.; Jin, C. H. Synthesis and Evaluation of Imidazole Derivatives Bearing Imidazo [2, 1-b][1, 3, 4] thiadiazole Moiety as Antibacterial Agents. *Med. Chem.* **2024**, *20*, 40-51. https://doi.org/10.2174/0115734064248204230919074743.

[78] Zarenezhad, E.; Behrouz, S.; Behrouz, M.; Rad, M. N. Synthesis, Anti-microbial, Antifungal and In Silico Assessment of Some 2, 4, 5-Trisubstituted Imidazole Analogues. *J. Mol. Struct.* **2023**, *11*, 136839. https://doi.org/10.1016/j.molstruc.2023.136839.