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Review

Synthetic Approaches of Pyrazole Derivatives on Various Pharmacological Activity: A Review

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Abstract:
Pyrazoles are an interesting heterocyclic class of compounds that have attracted extensive attention in medicinal chemistry as a consequence of their wide range of pharmacological activities. The compounds possess a wide variety of biological properties such as antibacterial, antifungal, anticancer, antidepressant, anti-inflammatory, and antiviral activity. Pyrazoles can be synthesized through several different routes, for example, cyclocondensation reactions between hydrazine derivatives and carbonyl systems, dipolar cycloadditions between alkynes or olefins and 1,3-dipolar compounds, and multicomponent reactions that allow the synthesis of pyrazoles in one step. Pyrazole derivatives have exhibited promise in a number of therapeutic applications, such as antimicrobial, anti-inflammatory, and anticancer activities, and thus are promising compounds for further research and development in the treatment of diseases. In general, the versatility and pharmacological relevance of pyrazoles highlight their significance in the advancement of medicinal chemistry research.

Keywords: Pyrazole, Receptor, Synthetic Scheme, Reaction, Pharmacological Activity.

INTRODUCTION

Synthetic organic chemistry is playing a vital role in the discovery and development of new drugs. Imidazole [1]a five-member nitrogenous heterocycle compound [2]. Imidazole is an organic compound with the formula C3N2H4. It is a white or colorless solid that soluble in water and forms a slightly alkaline solution. In chemistry, it is an aromatic heterocycle compound, classified as a diazole [3], and has two non-adjacent nitrogen atoms in its 5-membered ring structure [4]. Imidazole was first synthesized by Heinrich Debus in 1858, but various imidazole derivatives have been discovered as early as the 1840s, it is used glyoxal and formaldehyde in ammonia to form imidazole [5]. Imidazole ring with an electron-rich character that is a key structure feature in various clinically used anticancer drugs [6] and the development of new anticancer agents [7]. Derivatives of imidazole are sometimes used as a green solvent in the ionic liquid forms and in organometallic chemistry it involves N heterocyclic carbenes [8]. It has been found that in many natural products contain imidazole and applied in functional materials [9]. Imidazole is a weak acid (pKa=14.9) and strong base (pKb = 7.0). Imidazole derivatives substituted with electron-withdrawing moieties are strong acids than imidazole itself. Imidazole is a stable at 400°C, possesses a considerable aromatic character [10]. Imidazole nucleus has been employed extensively to develop a diverse array of antimicrobial agents [11], including antibacterial [12], antifungal [13] and antiprotozoal agents [14] [15]. The “Azole” [16] is class of antifungal agents whose molecules are based on a pharmacophore that inhibit the activity of fungal cytochrome. Imidazole, the first group to be developed in azole

antifungals also block the accumulation of methylated sterols, and disrupt the ergosterol biosynthesis [17], which is an essential, component of the fungal cell wall [18]. Cancer [19]is the first or second leading cause of premature death in people of ages 25-70 in most of the countries worldwide . It is characterized by uncontrolled cell [20] growth which may spread to other part of the body and also other tissues [21][22]. Imidazole classifies as a diazole, which is the constituent of several natural products such as histamine [23], nucleic acids [24], some alkaloids [25], etc[26]. The search of new potent drug molecules which are derived from Imidazole continues to be an intense area of development in pharmaceutic [27]. Zeolite imidazolate frameworks (ZIF-8) NPs are a series of Metal-organic frameworks (MOFs) that are composed of tetrahedrally coordinated metal ions bound to anionic ligands [28]. The imidazole ring often appears as an auxiliary donor proved that the additional imidazole unit attached to the fluorene moiety significantly affects the absorption spectrum profile, and finally, the fabricated Dye-sensitized cells (DSSCs) exhibited a power conversion efficiency (PCE) of 3.54% [29]. Reported that the synthesis of some cyclophanes, including imidazole-2-thione units from corresponding imidazolium-linked cyclophanes and we studied their interesting conformational behaviour using X-ray diffraction and NMR studies. Many imidazole-2-selones are known [30]. Many functionalized blocks and units, such as anthracene, fluorene, pyrene, triarylamine, carbazole (Cz), benzimidazole (BI), triphenylphosphine oxide (PO), and phenanthroimidazole (PI), have been developed to prepare different kinds of functional organic materials. Among these classes of blocks, imidazole is an important moiety and is widely used in the synthesis of electron transport or bipolar hosts and fluorescent or phosphorescent host materials [31].

Imidazole dicarboxylate-based complexes as anion or cation sensors have been reported in the literature, to date, no related MOFs sensing of benzaldehyde has been described. Now, investigation imidazole dicarboxylate-based Ln-MOFs with the goal of exploring their applications for molecular recognition [32]. The nucleobases, adenine and guanine, contain a fused imidazole moiety, as part of the DNA [33]. Histidine-based Schiff base metal complexes are examples of such complexes and were widely studied for their biological activity because the imidazole side chain of histidine can serve as a coordinating ligand in metalloproteins and in many case, is a catalytically important component in the active sites of enzymes [34]. The coordination of imidazole moieties from histidine to copper ions plays a key role in many enzymatic active sites. Examples are particulate methane monooxygenases (pMMO), lytic poly saccharide monooxygenases (LPMO) and tyrosinases (Ty) [35]. The imidazole are the first developed ones, the usages of which were limited for superficial mycoses, the fungal infections invading the most superficial layer of the epidermis, because of gastrointestinal intolerability and neurologic adverse effects at high doses besides their low solubility in physiological solutions [36]. the first covalent introduction of an imidazole-modified nucleobase surrogate into tetramolecular G-quadruplexes. [37]. 1-(3-aminopropyl)-imidazole is a commercial compound containing two meta-nitrogen atoms in the structure of aromatic heterocycles, which is widely used in many fields, such as antifungal drug, antimycotic agent, and insecticide [38]. The ultrafast NLO studies of an imidazole substituted ZnPc through an ethynyl bridge using 70 fs, 1 kHz pulses. Imidazole substituted phthalocyanines have been widely studied due to their possible applications in photonics, opto-electronics.[39]. Antimicrobial Photodynamic Therapy (aPDT) is reported in the literature as a promising alternative to antibiotic treatment; in this therapeutic approach the combined action of a photosensitizer (PS), light and molecular oxygen induces the production of reactive oxygen species (ROS), such as singlet oxygen (1 O 2), triggering microbial in ac tivation [40]. Imidazole ionic liquid has been investigated as a corrosion inhibitor, but the study focused on the chain length and the influence of different types of anions on the corrosion-inhibition performance. Optimizing the structure of the anion, which guides the design of efficient imidazole corrosion inhibitors, is therefore a worthwhile task [41]. the adsorption of imidazole, triazole, and tetrazole—used as archetypal models of azole inhibitors—has been characterized on Cu(111) by means of DFT calculations5,6 to

provide an atomic-scale insight into the chemistry of azole–copper bonding [42]. The vast therapeutic properties of the imidazole derivatives drugs have encouraged the chemists in the medicinal field to synthesize a huge number of novel chemotherapeutic agents. The complexity of developing the synthesis of many imidazole derivatives lies in the various facts, depending on reaction condition; it can normally enter the reaction in different forms such as the neutral, the conjugate acid and base, carbine and finally ylide (zwitterionic) [43]. The good antibacterial potential of imidazole groups has been confirmed in previous reports. Imidazole groups can destroy the cell wall components of bacterial by the release of autolytic enzymes, which result in the leakage of cell components and the death of bacteria. 1-(3-aminopropyl)-imidazole is a commercial compound containing two meta-nitrogen atoms in the structure of aromatic heterocycles, which is widely used in many fields, such as antifungal drug, antimycotic agent, and insecticide [44].

A poly (aryl ether ketone) polymer with polymethyl-sites and double bonds to synthesize and characterize the imidazole side chain type crosslinked and uncross linked AEMs base on poly (aryl ether ketone). In the AEMs, 1-vinylimidazole, 1-allyl-3- methylimidazolium chloride and polymer skeleton formed distinct hydrophilic/hydrophobic microphase separation structures, which provides a mass of wide transport channels for ion transport [45]. the ultrafast NLO studies of an imidazole substituted ZnPc through an ethynyl bridge using 70 fs, 1 kHz pulses. There are very few reports on the near-infrared NLO studies of organic molecules, in general, and phthalocyanines, in particular. Imidazole substituted phthalocyanines have been widely studied due to their possible applications in photonics, opto-electronics [46]. imidazole derivatives offer excellent thermodynamic stability, outstanding efficiency, high solubility and low toxicity. In acidic media, imidazole derivatives adsorb to the surface of carbon steel with large surface coverage, thereby inhibiting dissolution of the steel. Imidazole ionic liquid has been investigated as a corrosion inhibitor, but this study focused on the chain length and the influence of different types of anions on the corrosion-inhibition performance [47]. The hybrid phenanthrol[9,10-d] imidazole as a blocking building core inherits favourable characteristics of imidazole and phenanthrene. a five-membered heterocycle imidazole possesses two diverse nitrogen atoms with pyridine-like electron-deficient and pyrrole-like electron-rich characteristics [48]. The absorption of imidazole, triazole, and tetrazole- used as archetypal models of azole inhibitors-has been characterized on Cu (111) by mean of DFT calculations as to provide an atomic-scale insight into chemistry of azole-copper bonding [49]. Imidazole derivatives such as phenanthroimidazole and diphenyl imidazole have been used to generate deep-blue light-emitting devices16. Imidazole when combined with the triarylamines (TPA), serves as effective bipolar materials. Imidazole derivatives are being widely used because of wide absorption, bright luminescent property, and good bipolar transport characteristics. e there is notable interest in the design and synthesis of imidazole with enriched functional chromophores to improve their optical and charge transport properties [50]. Copper (II) complexes have attracted considerable attention as antitumor drugs owing to their capability of interacting directly with DNA/nuclear proteins. Copper possesses high affinity for nucleobases and has demonstrated broad anticancer activity due to the selective permeability of cancer cell membranes to copper complexes [51]. NH_4SCN demonstrated strong binding ability with NH_3. Imidazole (Imi) was a five-membered nitrogen containing compound with the ability to bind NH_3. Hence, this work chooses NH4SCN as HBD and Imi as HBA to construct DES with dual active sites. Interestingly, NH_4SCN and Imi can form DES with low viscosity [52]. IMI is hypothesized to function as auxiliary binding sites for metal ions, which would enhance the adsorption capacity of the bio-sorbent better than other types of amine groups. We have conducted extensive metal ion uptake studies which include the effects of pH and contact time on adsorption of Cu^{2+}, Pb^{2+} and Zn^{2+}[53]. Imidazole, benzimidazole and their derivatives are useful fluorophores to develop fluorescent probes. Sensors based on imidazole and benzimidazole could display excellent fluorescence properties when combined with ions. The novel fluorescence sensors were efficiently designed on the basis of imidazole and benzimidazole, which were easy to synthesize and displayed high selectivity and sensitivity for Cu2+

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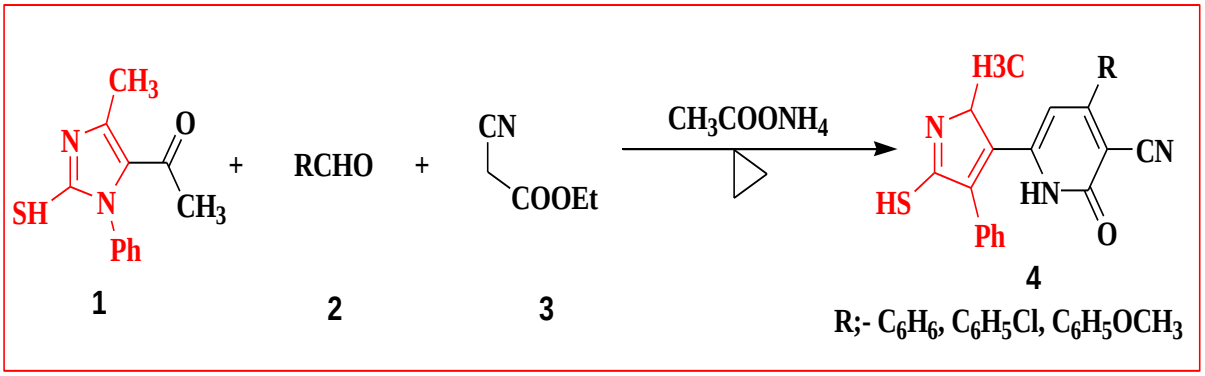
compared with other metal ions [54]. the bonding of imidazole, triazole, and tetrazole onCu2O and Cu2O-w/o-Cu^{CUS} surfaces; the latter surface is considered, because it is thermo dynamically more stable than the former in ambient oxygen atmosphere [55]. Parkinson's disease (PD) is one of most common neurodegenerative diseases with progressive neurodegeneration of the nigrostriatal pathway. The dopamine analog 6-hydroxydopamine (6-OHDA) has been reported to induce PD in animal experiments [56]. Researchers develop an alternative route that direct pyrolysis of copper salts or nanostructures, carbon and nitrogen precursors to fabricate Cu–N/C nanostructures in an inert gas atmosphere, resulting in hybrid nano catalysts that show enhanced stability, conductivity, and activity [57]. Azole heterocycles have a broad spectrum of therapeutical and pharmacological activities and represent building blocks in the structures of various natural products. Pyrazole molecules contain five-membered rings, which belong to the azole family. Various strategies used to synthesize pyrazole derivatives have been described in the literature in order. Therapeutic applications of pyrazole derivatives have been tested against cancer, contagious (i.e., AIDS), non-communicable (i.e., malaria), and neurodegenerative (i.e., Parkinson's and Alzheimer) diseases [58]. Nitrogen-rich heterocyclic compounds figure extensively in the study of energetic materials, and are likely the next generation green candidates. the various nitrogen-rich heterocyclic compounds, molecules with a symmetric, conjugated, and planar structure play a prominent role [59]. Imidazoles are a class of heterocyclic compounds that contain nitrogen and are currently under intensive focus due to their wide range of applications, because they have many pharmacological properties and play important roles in biochemical processes. the synthesis of polysubstituted imidazoles such as condensation of diones, aldehydes, primary amines, and ammonia in the presence of various acid catalysts,23-25 N-alkylation of trisubstituted imidazoles,26 and condensation of benzil or benzoin acetate with aldehydes, primary amines, and ammonia in the presence of copper acetate [60].

SYNTHESIS OF PYRAZOLE AND PYRAZOLINE DERIVATIVES.

Abbas . *e t.al.* publicized that imidazole derivative was synthesized from 1-(2-Mercapto-5-methyl-3-phenyl-3H-imidazole-4-yl)-ethanone; compound with methane (**1**) reacted with substituted aldehyde(2) and ethyl cyanoacetate (3) in the presence of ammonium acetate as a starting material (**Scheme 1**). All the synthesized compounds estimated for their anticancer activity against human breast cell line (MCF-7) and liver carcinoma cell line (HEPG2). Potential compound 4-(2-Hydroxyphenyl)-6-(2-mercapto-4-methyl-1-phenyl-1H -imidazol-5-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile(4) showed significance activity against human breast cell line (MCF-7) and liver carcinoma cell line (HEPG2).[61]



Scheme 1: Synthesis of imidazole derivatives

Siwach and Verma reported that imidazole derivate by 4,7-Dimethyl-deca-1,3,7,9-tetraene-5,6-dione (1) react with Ammonium acetate (2) and substituted benzaldehyde (3) in the presence of glacial acetic acid that give 2-(4-subsitutedphenyl)-4,5-dephenyl-1*H* -imidazol react with Potassium Butyl Carbonate that gives 2-(4-substitutedphenyl)-1-1substituted-4,5-diphenyl-1*H*-imidazole

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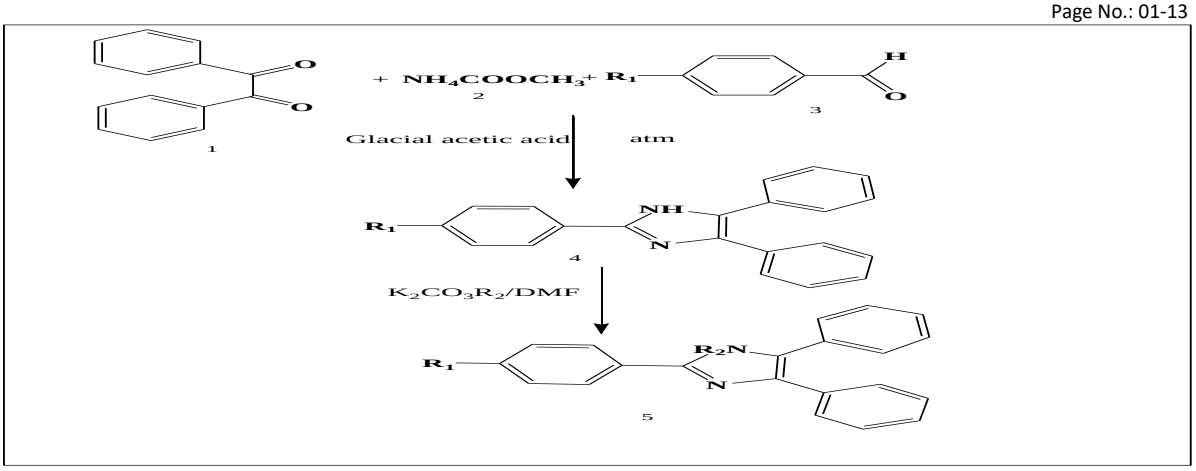
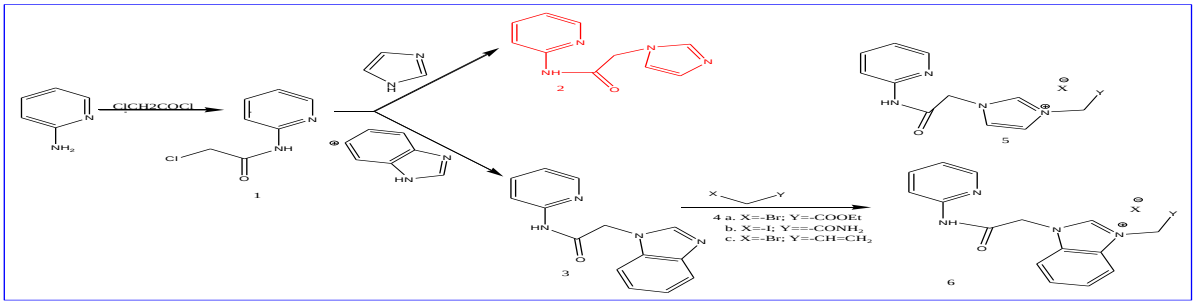


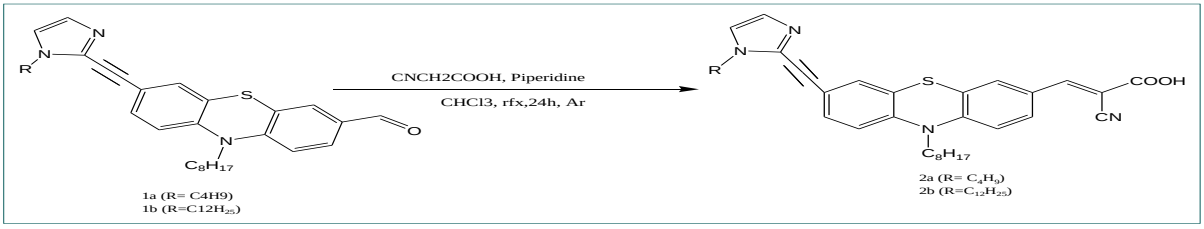
Scheme 2: Synthesis of imidazole derivatives

Mantu . e t.al.. described that imidazole derivative was synthesis involving three step procedure: N-acylation, N-alkylation, and quaternization of N-heterocycle. Thus, the N-acylation of 2-AP with 2-chloroacetyl chloride is leading to the corresponding pyridine acyl amine 1 (Scheme 1). Treatment of acyl amine 1 with Imz or bimz is leading to first class of hybrid Imz (Bimz)/pyridine derivatives 2 and 3, via an N-alkylation reaction of NH-imidazole moiety. A reaction of N-imidazole atom with activated halogenated derivatives 4 (2-bromo/iodo-alkyl esters/amide 4a,b or allyl bromide 4c) lead to hybrid N-(1-alkylcarbxy)- and N-ally-imidazole/pyridine derivatives 5a-c and benzimidazole/pyridine derivative 6a-c (Scheme 1).[63]



Scheme 3: synthesis of hybrid imidazole (benzimidazole)/pyridine derivative

Zimosz, e t,al, issue that imidazole derivative 2 new phenothiazine-based dyes 2-cyano-3-(7-(2-(1-butyl-1H-imidazole)ethynyl)-10-octyl-10-H-phenothiazine-3-yl)acrylic acid (2a) and 2-cyano-3-(7-(2-(1-dodecyl-1H-imidazole)-ethynyl)-10-octyl-10H-phenothiazine-3-yl)acrylic acid (2b) with D–π–D–π–A architecture were prepared via well-known Knoevenagel condensation of 7-[2-(1-butyl-1H imidazole)ethynyl]-10-octyl-10H-phenothiazine-3-carbaldehyde (1a) and 7-[2-(1-dodecyl-1H-imidazole)ethynyl]-10 octyl-10H-phenothiazine-3-carbaldehyde (1b), respectively, with cyanoacetic acid. The thermal properties of 2a and 2b were investigated by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). Compounds 2a and 2b exhibited the beginning of thermal decomposition with the temperature of 5% weight loss at 208 °C for derivatives with an N-butyl imidazole unit (2a) and at 226 °C for compound 2b with a longer, dodecyl alkyl chain. The DSC thermogram showed that 2a was obtained as an amorphous compound because only glass transition at 132 °C was observed contrary to 2b, which melted at 135 °C with decomposition. [64]



Scheme : Synthetic route of 2a and 2b.

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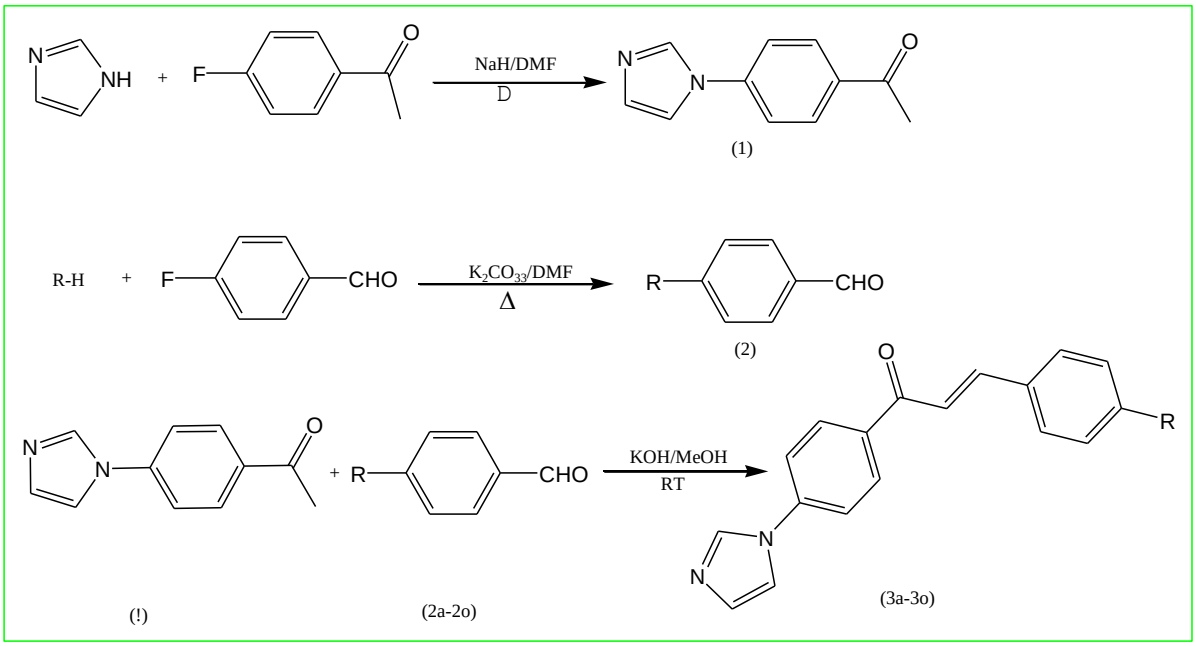
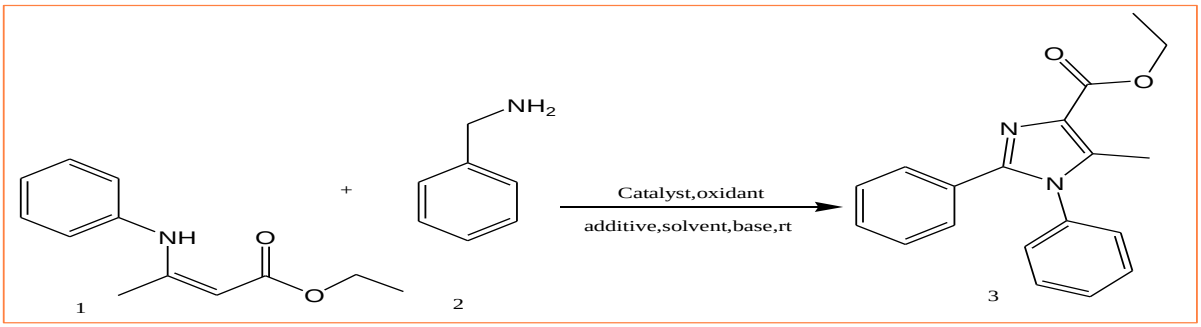
Atli. e t. al. disseminated that imizadole derivate was synthesized compounds (3a-3o) were evaluated for anticandidal activity. Initially 4'-(imidazol-1-yl) axetophenone (1) was obtained under reflux by a reaction of 1-(4-fluorophenyl)ethane-1.-one and 1H-imidazole. Secondly, 4-fluorobenzaldehyde and approprite protondonoring group were reacted in order to obtained 4-substitutedbenzaldehydes (2a-2o). In last step, target compounds (3a-3o) were synthesized by using 4'-(imidazol-1-yl)acetophenone (1) and appropriate 4-substituted benzaldehydes (2a-2o).

General procedure for the synthesis of target compounds (3a-3o): 1-(4-(1H-imidazol-1-yl)phenyl)ethane-1-one (!) and 4-substitutedbenzaldehydes (2a-2o) dervatives in methanol were stirred for 10h in the presence of potassium hydroxide. The precipitated product was washed with wated,dried,and recystallized from ethanol.[65]



Scheme . Synthesis way of the target compounds (3a-3o)

Gupta.e. t.al. disclosed that was synthesis of highly substituted imidazole derivative 5-methyl-1,2-diphenyl-1H-imidazole-4-carboxylic acid ethyl easter (3) have been developed by the reaction of 3-phenylamino-but-2-enoic acid ethyl ester; compound with ethene (1) with aromatic aniline Benzylamine (2) via copper-mediated oxidative C-H functionalization in good high yield[66]



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

Hatakeyama brings out that application not only for imidazole, but also for thiazoles and oxazole. The reaction of 4,5-dimethylthaizole (1) with naphthyl carbamate Acetic acid naphthalen-2-yl-ester (2) under the previous condition furnished no coupling product. Thus ,we applied our new protocol unreactive azole 4,5-dimethylthiazole (1). Gratifyingly,(1) and(2) cross-coupled very smoothly under the present condition to furnish 4,5-Dimethyl-2-naphthale n-2-yl—thiazole in yield [67]

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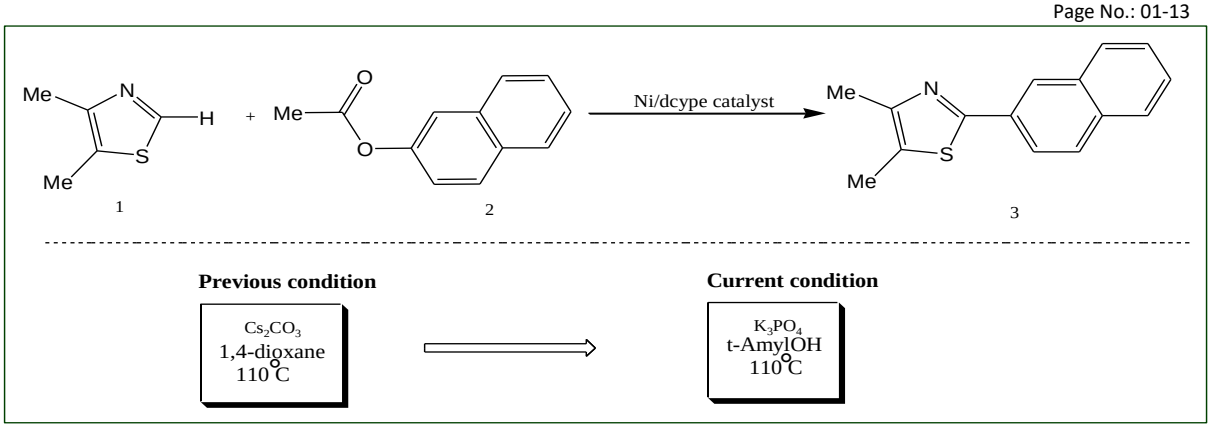
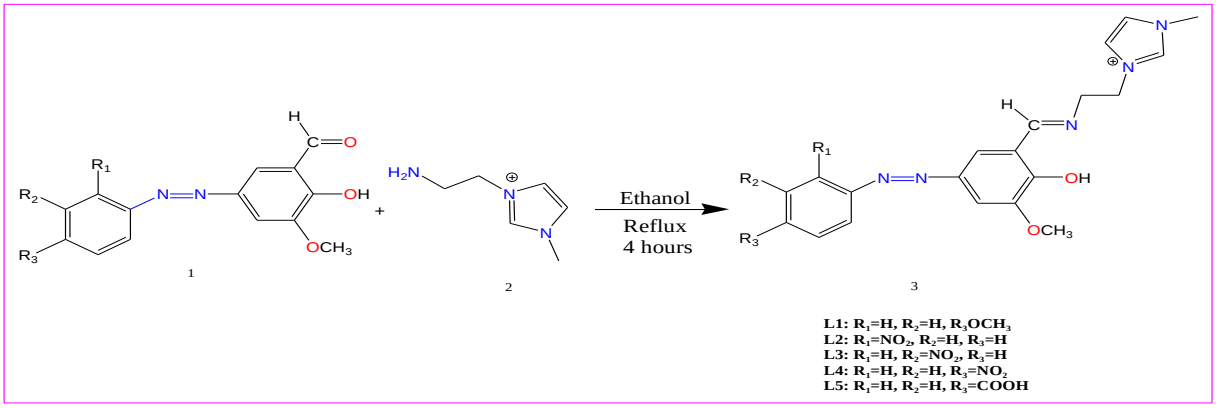


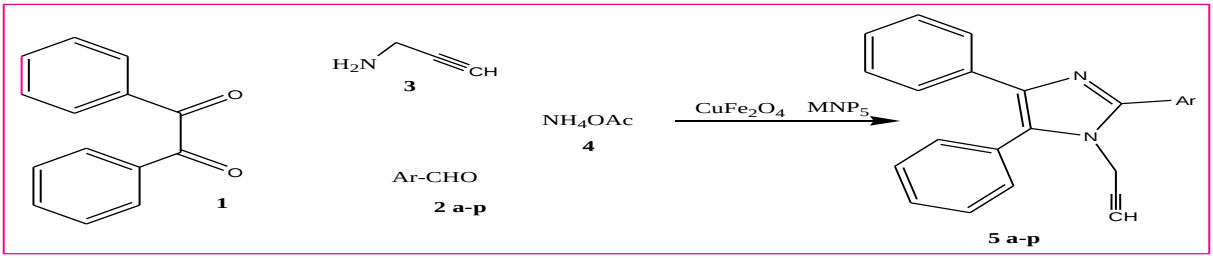
Scheme : Comparison of previous and current condition for the reaction of thiazole .

Chhetri. e t. al. publicized that synthesis of imidazole derivative has been achieved. 5 millimoles (mmol) of 1-(-2- Aminoethyl)-3-methylimidazolium hexafluoro-phosphate in absolute ethanol was added to an ethanolic solution of azo-couple o-vaniline precursors (5 mmol) during a period of 10 min. The reaction mixture was then refluxed in an oil bath for 6h at 90˚C with constant stirring and the progress of the reaction was monitored by TLC taking 10% ethyl acetate in hexane as eluent. The final solution was kept overnight for cooling and the product obtained was filtered, washed with little ethanol and diethyl ether in a portion (2ml x 2) respectively. The solid product was recrystallized from hot ethanol solution and dried over silica under vacuum. Condensation of 1-(2-Aminoethyl)-3-methylimidazolium hexafluoro-phosphate, (2aemim) with substituted azo-couple o-vaniline precursors in resulted in the formation of desired compound L1-L6. The isolated azo-imidazole compounds (L1-L6) were analyzed using Infrared spectroscopy, NMR spectroscopy and elemental analysis techniques.[68]



Scheme: Synthesis of Pyrazole Derivatives.

Mahmoud. e t. al. publicized that the non-toxic magnetic $CuFe_2O_4$ nanoparticle have been synthesized, characterized and used as an efficient catalyst for synthesis of derivatives for 1,2,4,5-tetrasubstituted imidazole. When reacted benzil (1) with aldehyde(2), propargylamine (3) and ammonium acetate (4) using magnetic $CuFe_2O_4$ nanoparticles as a novel and eco friendly heterogeneous catalyst gave new derivatives for 1,2,4,5-tetrasubtituted imidazole $5a_{a-p}$ [69].



Scheme: Synthesis of Pyrazole Derivatives.

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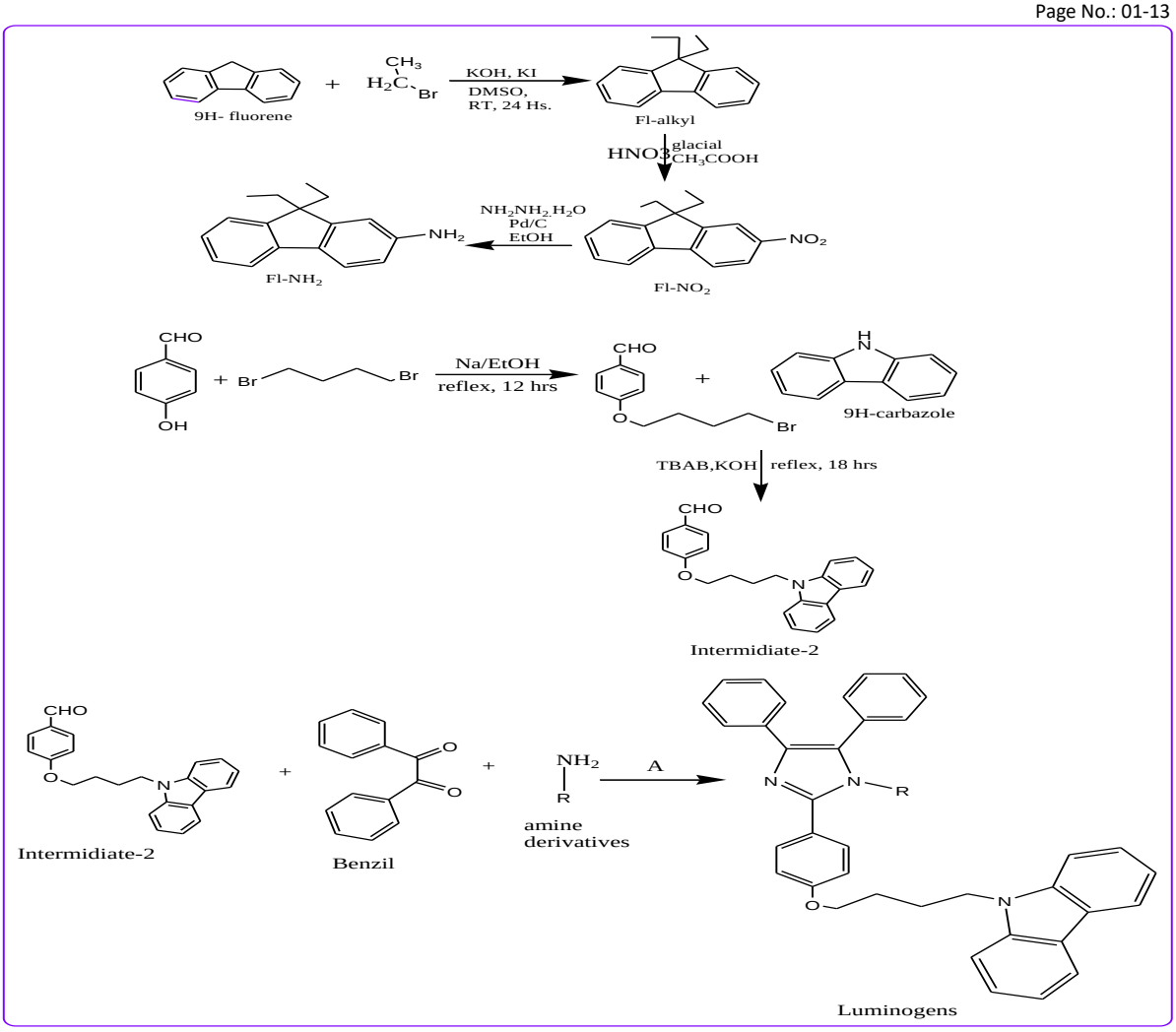

Tagare. e t.al. publicized the synthetic route of the target imidazole derivative. The 4-(4-bromobutoxy) benzaldehyde (Intermediate-1), 4-(4-(9H-carbazol-9-yl) butoxyl) benzaldehyde (Intermediate-2) and Fl-NH_2 were prepared by the research synthesis method. The target compounds were synthesized by a condensation reaction between Intermediate-2, amine derivatives, and benzil, in the presence of ammonium acetate and acetic acid.

General procedure for the synthesis of imidazole derivatives: - the mixture of benzil, amine (aniline derivatives) and intermediaye-2 the acetic acid was added, followed by added ammonium acetate and then the reaction mixture was refluxed for 12 hrs., under nitrogen atmosphere in an oil bath. The completion of reaction was monitored with thin-layer chromatography (TLC). After completion, the mixture was cooled and poured minimum amount of water. The corresponding reaction mixture was neutralized with dilute ammonium hydroxide solution. The resultant mixture was extracted with dichloromethane (DCM) followed by purification by column chromatography on silica gel with ethyl acetate/petroleum ether as the eluent. (70)

Negi. e t.al. publicized the derivative as an intermediate for synthesis of the target compounds that was prepared by using synthetic procedures. Briefly 2,3-diaminomaleonitrile was treated with $CH(OEt)_3$ in 1,4-dioxane to afford ethyl (Z)-N-(2-amino-1,2-dicyanovinyl) formimidate (**1**) which on reaction with o-chlorobenzyl amine under the catalytic influence of aniline hydrochloride in ethanol furnished N'-((z)-2-amino-1,2-di-cyanovinyl)-N-(2-aminophenyl) formimidamide (**2**). Cyclization of ethyl (Z)-N-(2-amino-1,2-dicyanovinyl) formimidate (**1**) under the influence of base resulted in the formation of 1-(2-chlorobenzyl)-5-amino-1H-imidazole-4-carbonitrile (3), which acted as the precursor for the formation of target compounds. [71]

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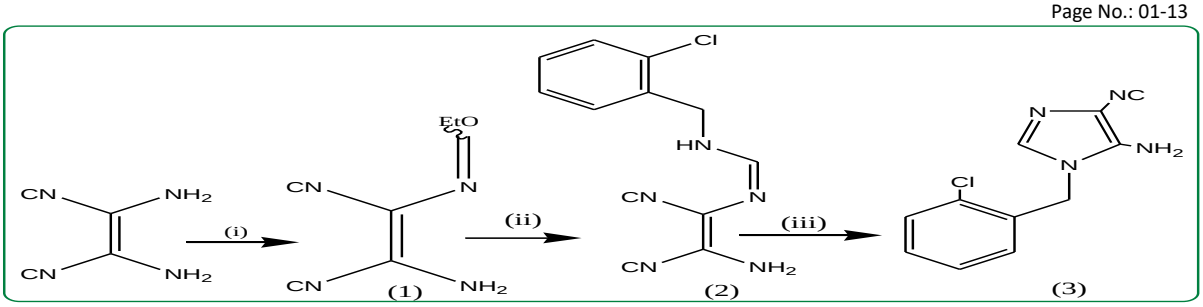
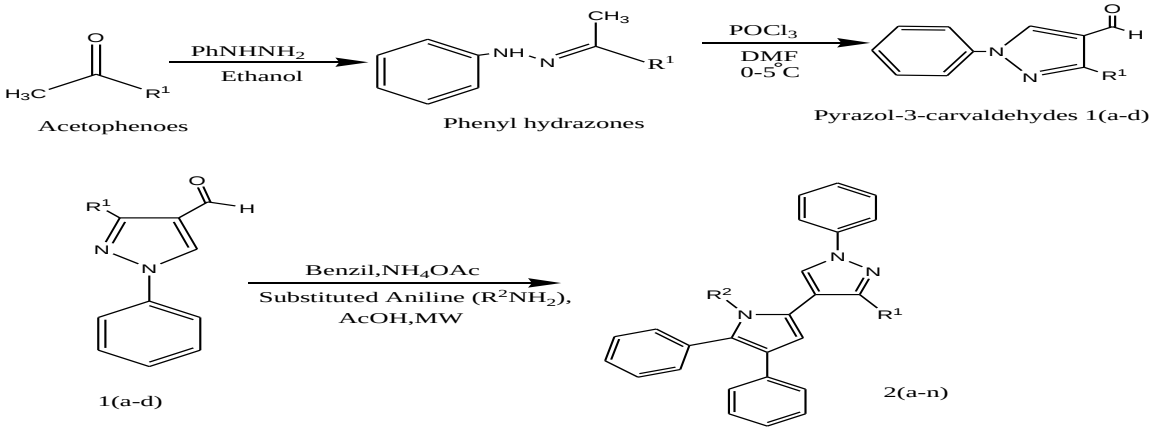


Scheme: - Reagents and conditions: (i)$CH(OEt)_3$,dry 1,4-dioxane, reflux, 8-10 h;(ii) o-Cl-$PhCH_2NH_2$, EtOH, aniline hydrochloride (1 mol%),rt, 5-6h;(iii) 1M KOH, rt,7-8h.

Chaudhry.e t, al. publicized to synthesize designed imidazolyl pyrazole scaffolds synthetic route of Scheme was employed. Different substituted pyrazole-4-carbaldehydes were prepared. The reaction has involve microwave irradiation of a mixture of four component: a pyrazole-4-carbaldehyde, substituted aniline, benzil and ammonium acetate. The reaction is fairly compatible with various aldehyde having different electron donating/withdrawing groups (1a-1d). In this way, some functionally diversified compounds (2a-2n) were prepared. The elemental composition and structural identification of novel derivatives (2a-2n) were carried out by different spectroscopic means. The elemental composition and structural identification of novel derivatives (2a-2n) were carried out by different spectroscopic means. There were visible influences of R1 and R2 substitutions on inhibition potencies of prepared compounds. The p-OCH3C6H4 group containing derivatives 2a (IC50 (µM): 178.82±0.28), 2b (IC50 (µM): 162.93±0.32) and 2c (IC50 (µM): 182.17±0.37) have weak to moderate binding capabilities but the replacement of this methoxy group with other functionalities helped in recovering the inhibition potentials. The p-ClC6H4 substituted compounds 2d (IC50 (µM): 168.92±0.27), 2e (IC50 (µM): 85.71±0.09) and 2g (IC50 (µM): 132.81±0.29) have improved inhibitory effects. However, the product 2f was proved to be the most significant agent (Inhibition (%): 96.21±0.11, IC50 (µM): 25.19±0.004). Probably, the synergistic effects of chloro and bromo substituents in one molecule augment the active nature of compound which can also be observed in case of compound 2i (IC50 (µM): 84.61±0.01). The compounds 2h and 2j, where only p-BrC6H4 functionality was present as R1, have executed moderate inhibitory effects. The electron withdrawing group containing molecules have shown excellent results and served as potent scaffolds. Therefore, switching to the m-NO2C6H4 group (as R1 in compounds 2k-2n) has contributed in regaining the enhanced binding affinities of molecules with enzyme's active sites. Out of these examples, compound 2m has displayed even better activity than that of positive control acarbose with inhibition (%): 97.52±0.26, IC50 (µM): 33.62±0.03 [72]



1a. R1 = p-OCH3C6H4
1b. R1 = p-ClC6H4
1c. R1 = p-BrC6H4
1d. R1 = m-NO2C6H

2a. R1 = p-OCH3C6H4, R2 = p-OCH3C6H4
2b. R1 = p-OCH3C6H4, R2 = p-BrC6H4
2c. R1 = p-OCH3C6H4, R2 = 3,5-(CH3)2C6H3
2d. R1 = p-ClC6H4, R2 = p-OCH3C6H4
2e. R1 = p-ClC6H4, R2 = p-ClC6H4
2f. R1 = p-ClC6H4, R2 = p-BrC6H4
2g. R1 = p-ClC6H4, R2 = 3,5-(CH3)2C6H3

2h. R1 = p-BrC6H4, R2 = p-OCH3C6H4
2i. R1 = p-BrC6H4, R2 = p-ClC6H4
2j. R1 = p-BrC6H4, R2 = 3,5-(CH3)2C6H3
2k. R1 = m-NO2C6H4, R2 = p-ClC6H4
2l. R1 = m-NO2C6H4, R2 = p-OCH3C6H4
2m. R1 =m-NO2C6H4, R2 = p-BrC6H4
2n. R1 = m-NO2C6H4, R2 = 3,5-(CH3)2C6H3

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