

Synthesis of Pyrazole, Thiazole and Benzimidazole Biological Active Heterocycles

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DOI: <https://doi.org/10.52403/ijrr.20260946>

ABSTRACT

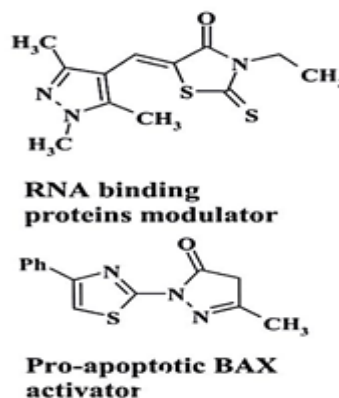
The feature of the chemistry of pyrazole, thiazole and benzimidazole as pharmacologically important scaffolds was described in number of reviews in which main approaches to the synthesis of mentioned and their biological activity were analyzed. however, the pyrazole/pyrazoline-thiazolidine, benzimidazole-based hybrid as biologically active compound is poorly discussed in the context of pharmacophore hybrid approach. therefore, the purpose of this review is to summarize the data about the synthesis and modification of heterocycles system with thiazolidine and pyrazoline/pyrazole fragments in molecules as promising object of modern bio-organic and medicinal chemistry. The description of biological activity was focused on SAR analysis and mechanistic insight of new Heterocycles.

Keywords: Heterocycles, Pyrazole, Thiazole, Benzimidazole.

INTRODUCTION

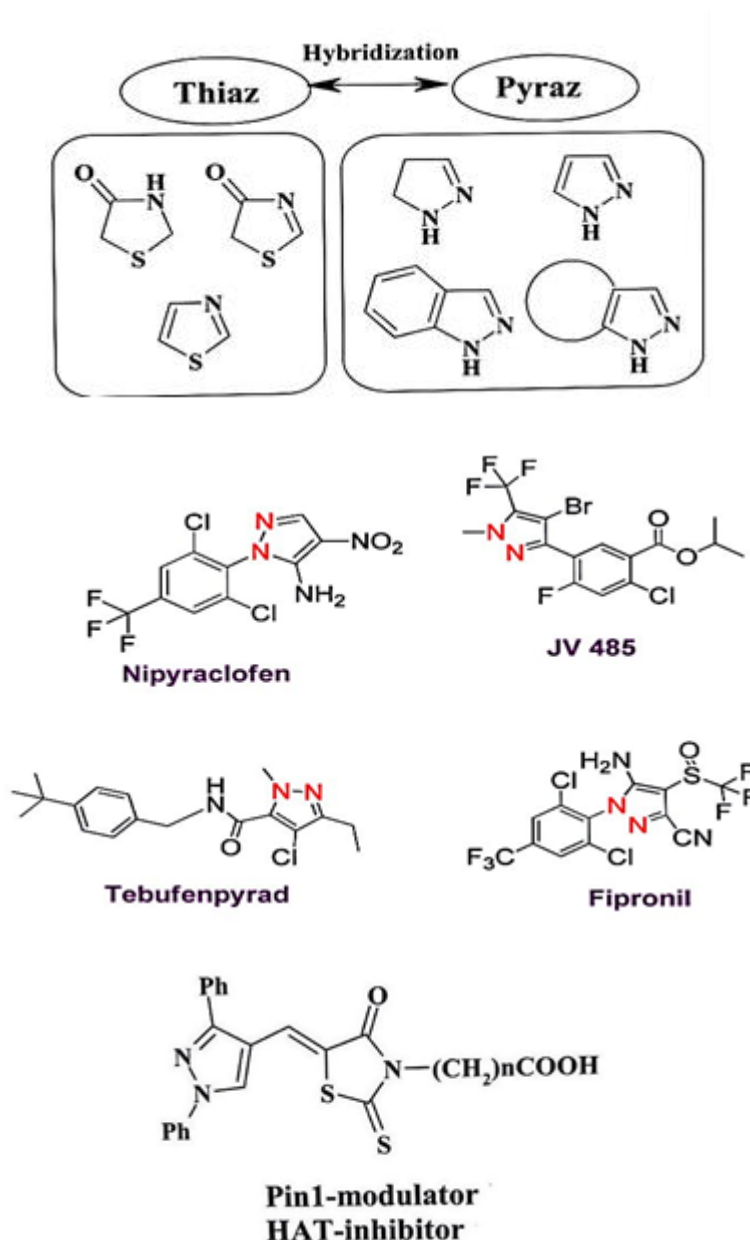
pharmacophore hybrid approach is a current in drug design and development to produce molecules with improved affinity and efficacy. some review dealing with the

concept molecular hybridization and challenge associated with these hybrid molecules along with recent advance on antimicrobial hybrids various heteroaryl base hybrids in particular isatin and coumarine, thiazolidinone have been recently review



As conjugate with remarkable inhibitory potential Design of new drug-like small molecules base on the pharmacologically attractive scaffolds of thiazolidine and pyrazoline is promising directions in modern medicinal chemistry. The chemical approaches for the synthesis of thiazolidinone and pyrazole-based derivatives and their pharmacological activity described in various reviews

However, pyrazoline and thiazolidine based conjugate as biologically active.



synthetic studies of pyrazoline-thiazolidine related hybrid and their biological investigation antitumor, antimicrobial, antiviral, antiparasitic ,anti-inflammatory activities allowed to identify the promising drug like compound thus pyrazole-thiazole have been patented as inhibitors of necroptosis ,VHR protein tyrosine phosphate inhibitors, compound for modulating RNA binding protein and activators of proapoptotic BAX ,the pyrazole-thiazolidine hybrid have been studied for their possibility to inhibit the

TNF-alpha-TNFR1 interactions as inhibitor of histone acetyl transferases and inhibitors of COX .

The purpose of this review is to summarize the data about the synthesis and biological activity of heterocyclic system with thiazolidine and pyrazole fragments in molecules. Heterocyclic compound containing nitrogen have played a major role in modern pesticides.it has been reported that more than eighty-five percentage pesticides with high activity and low toxicity contain nitrogen heterocyclic

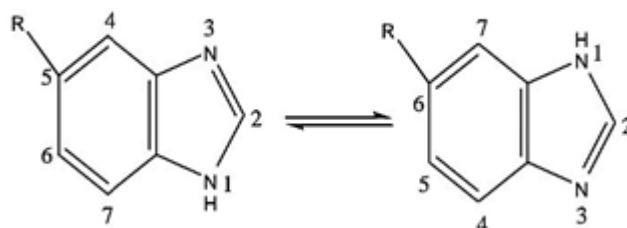
compounds. pyrazole is important Heterocyclic compound. They are also useful synthons and building blocks for many heterocyclic product and act as binucleophile with broad spectrum of remarkable biological activities. many derivatives containing pyrazole nucleus have been commercial herbicides, insecticide and fungicides and for plant protection.

The synthesis of Pyrazole, Thiazole and Benzimidazole are important in pharmaceutical and agrochemicals industries product. Pyrazole exhibit HIV-1 reverse transcriptase and IL-1 synthesis inhibition as well as antihyperglycemic antibacterial, sedative-hypnotic, anti-inflammatory, antipyretic and analgesic activity. These properties of pyrazole derivatives associated with the inhibition of prostaglandin biosynthesis in the cyclooxygenase.

Heterocyclic are among the most frequently encountered scaffolds in drugs and pharmaceutically relevant substances Heterocyclic compound are widely useful chemical substances, including those essential to human life, such as vitamins and nutrients and medicines. Natural substances are intrinsically exhibit superior properties with regard to efficacy and safety in matters related to human health. Heterocyclic compounds include many of biochemical material essential to life. The major classes of heterocyclic containing the common hetero atoms are N, O and S. Depending upon the number of hetero atoms in the ring, the heterocyclic compounds are classified as three membered Ex. Aziridine, oxirane and thiirane, four membered like azetidine, oxetane and thietane, five membered like pyrrole, furan and thiophene and six membered like pyridine, pyridinium ion, pyridone and piperidine. The paramount importance of heterocyclic compounds in natural product chemistry and pharmacology constantly drive the search

for new methods for the construction of heterocyclic compounds. Among the largest heterocyclic compounds more of them are partially aromatic and some are heterocyclic. Among them S and N containing heterocyclic compounds have maintained the interest of researchers through the decades. As evident from the literature, heterocyclic compounds containing N, O and S hetero atoms have interesting biological activities. The nitrogen, oxygen and sulphur heterocycles are an Attractive source of compounds for the identification of new biological probes. The main aim is to design and synthesize molecules involving the use of structural moiety commonly found in majority of well-established drug molecules. They have found to possess antifungal, antidepressant, anticonvulsant, anti-inflammatory, antibacterial and antitumor properties etc. The literature survey reveals that there are many methods reported in the literature for similar kind of transformations. Hence, we are demonstrating the use of different types of methods for synthesis of various types of heterocyclic compounds containing hetero atom. Several of the heterocyclic compounds are synthesized by condensation of chalcones with hydrazines and their derivatives with thiosemicarbazides under acidic or basic conditions and the cycloaddition of nitrilimines.

Benzimidazole is heterocyclic aromatic organic compound. this bicyclic compound consists of the fusion of benzene and imidazole. The most prominent benzimidazole compound in nature is N-ribosyl-dimethyl benzimidazole, which serves as an axial ligand for cobalt in vitamin B12. Benzimidazole is an extension of the well elaborated imidazole system, has been used as carbon skeletons for N-heterocyclic Carbene. They are often prepared by deprotonating an N, N-disubstituted benzimidazolium salt at the 2-position with a base.



Benzamide and its derivatives are used in organic synthesis and fungicides as they inhibit the action of certain microorganisms. The example of benzimidazole class fungicides include benomyl, carbendazim, chlorfenazole, cypendazole, debacarb, fuberidazole, furophanate, mecarbinzid, thiabendazole, thiophanate. Benzimidazole structure is the nucleus in some drug such as proton pump inhibitors and anthelmintic agent. Benzimidazole with the imide nitrogen is usually more soluble in polar solvent and less soluble in organic solvent. with the introduction of other non-polar substituents in various position of the benzimidazole ring, the solubility in

nonpolar solvent is increased, it is weakly basic, but less basic than imidazole. it is also sufficiently acidic to be general soluble in aqueous alkali and form N- metallic compound.

MATERIALS AND METHODS

A mixture of 4-acetyl -N, N-diethyl benzene sulphonamide (0.01mol) and DMF-DMA (0.012mol) in dry xylene (50 ml) was heated under reflux for 4 hrs. The separated solid was filtered off, washed with ethanol and recrystallized give (E)-4-(3-(Dimethylamino) acryloyl)-N, N-diethyl benzene sulphonamide.

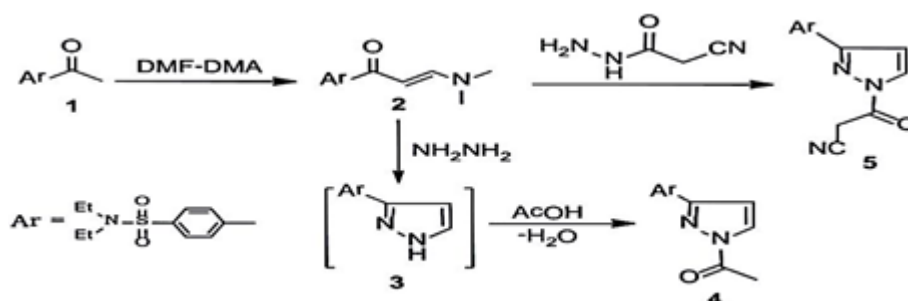


Fig- Synthesis of pyrazole derivatives.

Synthesis of 1H-pyrazolo (3,4) pyridine phosphor amides derivative cl- substituted pyrazol (3,4) pyridine (2.2 mmol) and the aminoalkylphosphoramidate (4.4mmol) dissolved in THF (10ml). The reaction mixture was heated at reflux for complete the reaction and monitored by TLC. the mixture was poured in to ice, resulting solid was filtered off. Washed with distilled water and dried with chloroform. The organic layer dried with anhydrous sodium sulphate and filtered.

Synthesis of tetrahydropyrazolopyridine.

A mixture of hydrazine hydrate (2.0mmol) and beta- dicarbonyl compound (2.1mmol) in EtoH(5mL) was magnetically stirred for 30 min.at 25⁰ c followed by addition of aldehyde (1.0 mmol) and ammonium acetate (4.0 mmol). The reaction mixture heated at reflux for 4-8 h and then cooled to 25⁰ and water (10mL) was added and the resulting mixture was stirred for 30 min. The precipitated product was filtered. washed with water and acetone then dried under vacuum.

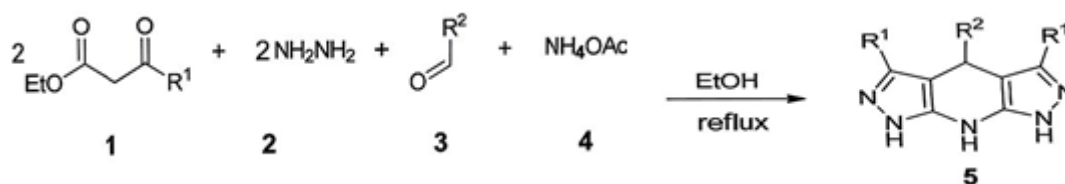


Fig-Synthesis of tetrahydropyrazolopyridine.

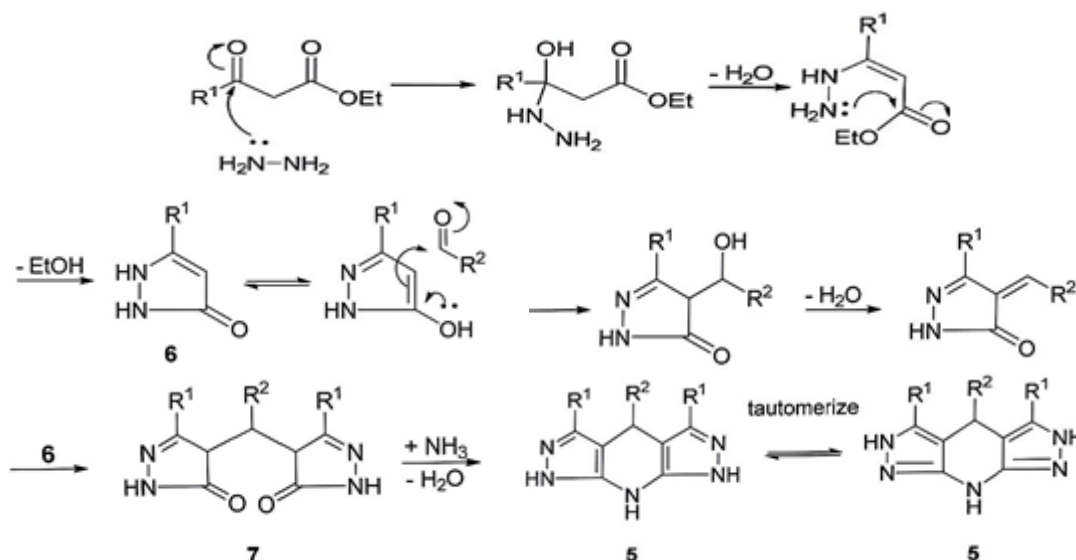


Fig- plausible mechanism of the reaction.

Synthesis of 5-Amino -1-Aryl -1H-Pyrazole-4-Carbonitrile - The solution of Aryl hydrazine (phenylhydrazine, 4-fluorophenylhydrazine hydrochloride) and 4-methoxyphenylhydrazine hydrochloride (1.2mmol) in absolute ethanol (2ml) was needed. Then (ethoxymethylene)

malononitrile was added slowly. Once complete the addition complete, the solution was carefully reflux in nitrogen atmosphere. The reaction mixture reflux for 4 hours. The reaction crude purified by column chromatography on silica gel absorption with ethyl acetate.

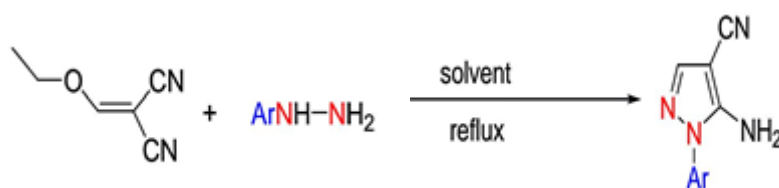


Fig-Synthesis of Synthesis of 5-Amino -1-Aryl -1H-Pyrazole-4-Carbonitrile.

Microwave Assisted synthesis of 5-methyl-2-phenyl-2,4-dihydro -3H-pyrazole-3-one - A solution of ethyl acetoacetate (0.05 mmol), phenyl hydrazine (10ml, 0.1mol) and ethanol (20mL) in the presence of piperidine (2 drop) were exposed to microwave at 200 w

(90⁰) intermittently at 5 sec intervals. The specific reactions time was kept 2-min and then the reaction was cooled in Crushed ice, progress of the reaction was monitored by TLC method. The crystalline Solid serrated was filtered, washed with ethanol, dried and purified by recrystallization from alcohol.

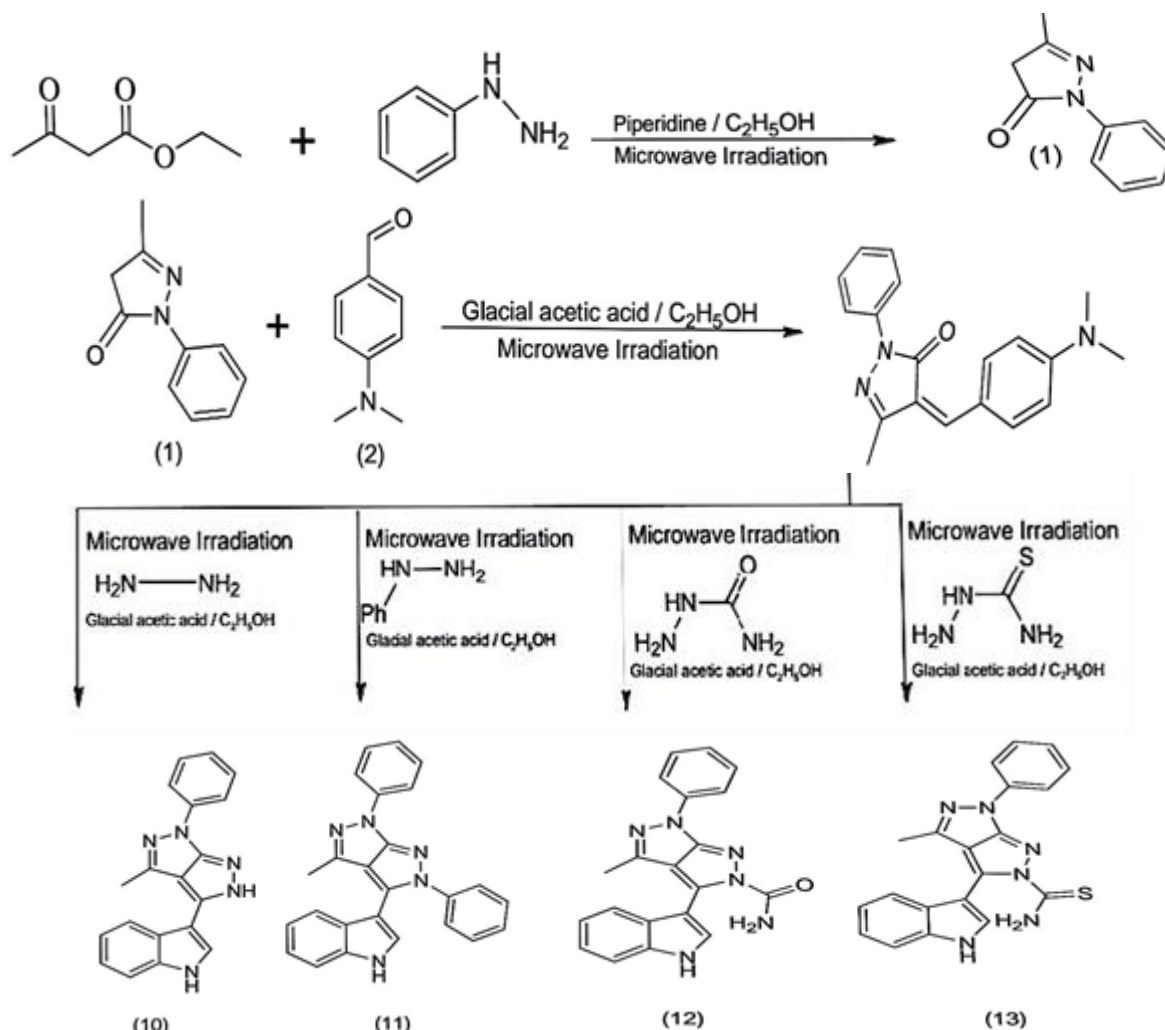


Fig- Microwave Assisted synthesis of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazole-3-one.

Microwave Assisted synthesis of pyrazole derivatives- The acetophenone (0.01mol), substituted phenylhydrazine (0.01mol) and DMF(0.5mL) exposed to microwave at 200 W intermittently at 10 s interval. specified reaction time of 3 min. observed for compound 1-substituted phenyl-2-(1-phenylethylidene) hydrazine 3. The reaction mixture was cooled with cold Water. The precipitate obtained filtered. wash with water and purified by recrystallization from ethanol. The compound 3 (0.01mol) was

added portion wise with vilsmeier-Haack reagent (POCl_3 -DMF, SiO_2 (0.03mol) after the addition was complete, the reaction flask kept at room temperature for 5 min and silica gel 3gm was added and properly mixed with the help of glass rod, till free-flowing powder was obtained. The powder irradiated in microwave oven at 400 w intermittently at 30 s interval. The specified reaction time of 5min was observed for compound 4a. The completion of reaction is monitored by TLC.

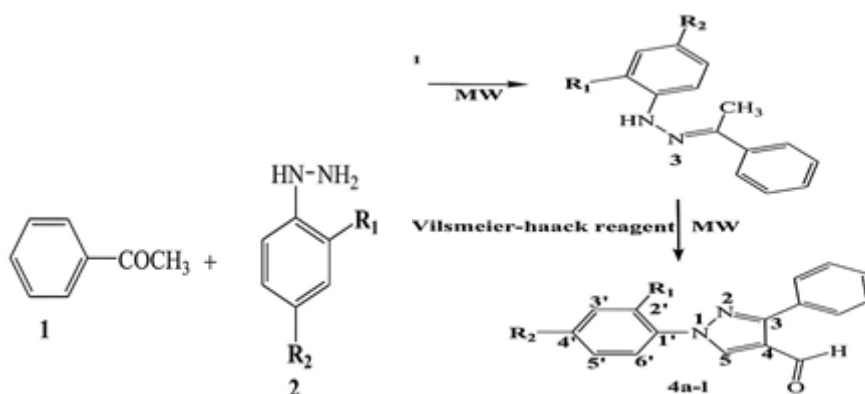


Fig-Microwave Assisted synthesis of pyrazole derivatives

Synthesis of 2,5-Di-tert-butyl-2H-pyrazole(a)- 3-ylamine- The mixture of 4,4 dimethyl -3-oxopentanenitrile (12.5g,100mmol) and tertiary butyl hydrazine (17.5 gm 198.8mmol) was reflux in ethanol (250 ml) with conc. HCl acid (8 ml) for 24 hrs. The resulted reaction mixture was made basic with sodium hydroxide and extracted with ethyl acetate. The combine organic extract were dried over anhydrous sodium sulphate. The solvent was removed on the rotary evaporator to give the desired

product as an oil and recrystallized from hexane to give desired product.

Synthesis of 2,5-Di-tert-butyl-4-nitroso-2H-pyrazole-3-ylamine(b) - 15% Ethyl nitrite/ethanol (55ml,0.58mmol) was added to 1,3-diter-butyl-1-H-pyrazole-5-amine (2.5gm,12.8mmol) in presence of Hydrochloric acid and the mixture was concentrated in vacuum recrystallized from diethyl ether.

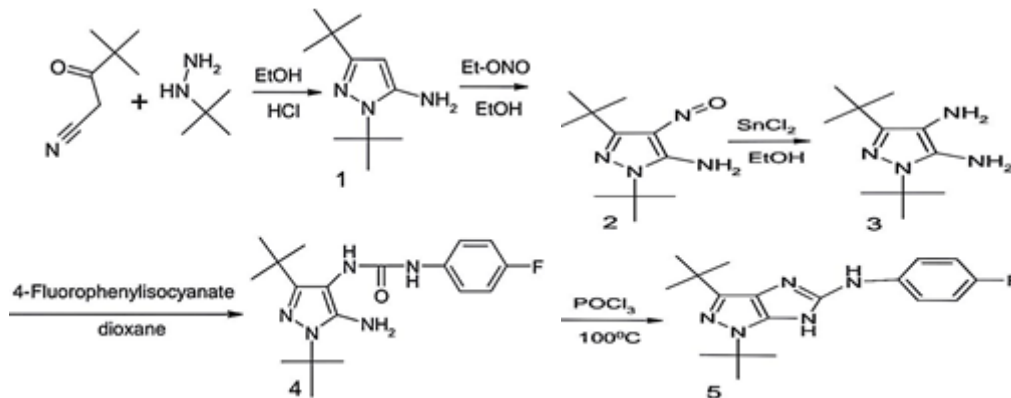


Fig- Synthesis of 2,5-Di-tert-butyl-2H-pyrazole- 3-ylamine(a).

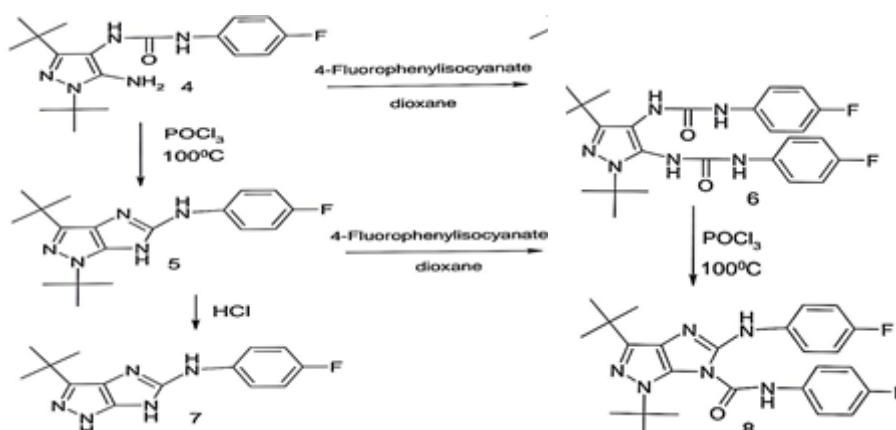


Fig-Synthesis of 2,5-Di-tert-butyl-4-nitroso-2H-pyrazole-3-ylamine (b).

Synthesis of 5-(aryl) -(3-(4-(2-phenyl-4-benzylidene-5-oxo-imidazole-1-yl)

phenyl)-4,5-Dihydropyrazole (2a) - A mixture of 4- benzylidene-1-(4-(3(aryl)prop-2-enoyl) phenyl-

Imidazole -5-one (1a) (0.01M) and 99% hydrazine hydrate (0.015M) in ethanol (50ml) as reflux gently and the progress of the reaction is monitored by TLC. after completion of the reaction, The mixture was concentrated and allowed to cool. The resulting solid was filtered, washed with ethanol and recrystallized from alcohol. Synthesis of 1-benzoyl-5-(aryl) -(3-(4-(2-

phenyl-4-benzylidene--oxo-imidazole-1-yl)phenyl-4,5-dihydropyrazole A mixture of 4- benzylidene-1-(4-(3(aryl)prop-2-enoyl) phenyl-imidazol -5-one (2a) (0.01M) and benzoyl chloride (0.01M) in dry pyridine (25ml) was stirred at room temperature and the progress of the reaction was monitored by TLC. after completion of the reaction, reaction mixture treated with cold dilute HCl (2N) The resulting solid was filtered and washed with water, cold NaOH (2%), with water, and recrystallized from glacial acetic acid.

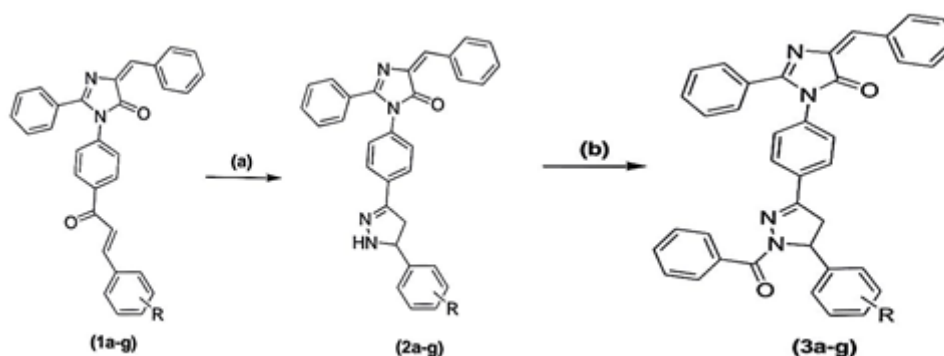


Fig- Synthesis of dihydropyrazole derivative.

Synthesis of Thiazole derivatives

2-Amino-4-phenyl thiazole- The mixture of acetophenone (0.1mol) and thiourea (0.2mol). bromine (0.2mol) was added drop wise very slowly, after complete addition reaction mixture was heated on water bath for overnight and water was added to it and again heated until most of the solid form in the solution. The reaction mixture was filtered and cooled. it was made alkaline with conc. ammonium hydroxide. Separate 2-amino-4-phenyl thiazole. The product was filtered, washed with alcohol, dried over P_2O_5 and recrystallized from ethanol.

2-chloro-N-(4-phenyl thiazol-2-yl) acetamide-

0.05 mols of 2-amino-4-phenyl thiazole dissolved in 25 ml of glacial acetic acid containing saturated solution of sodium acetate (25ml) in this mixture 0.06 moles of chloroacetyl chloride was added with stirring. then the mixture was heated on water bath for 6 hrs. then the reaction

mixture poured on crushed ice. The product is then filtered, dried and recrystallized from alcohol.

2-Hydrazinyl-N-(4-phenylthiazol-2-yl) acetamide-

0.05 moles of 2-chloro-N-(4-phenylthiazol-2-yl) acetamide was dissolved in 25 ml of alcohol. To the above mixture 0.01 moles of hydrazine hydrate was added and the resultant mixture reflux for 8 hrs. After 8 hrs the reaction mixture poured on crushed ice to separate the product.

Chalcones- 0.01 moles of substituted aromatic aldehyde and 0.01 moles of acetophenone were taken in beaker. This mixture was dissolved in minimum quantity of ethanol and 3 to 4 drops of conc. sodium hydroxide is added to the above mixture. The resultant mixture was stirred using magnetic stirrer for a period of 2 hrs. after 2 hrs. the reaction mixture poured on crushed ice form solid product.

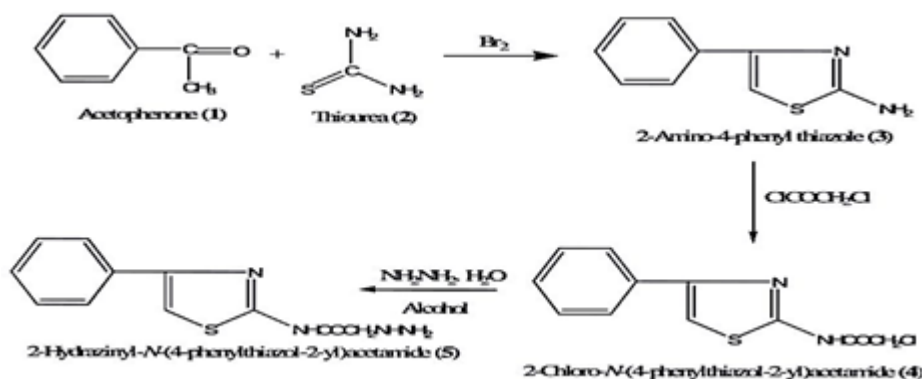


Fig. Synthesis of 2-Hydrazinyl-N-(4-phenylthiazol-2-yl) ace

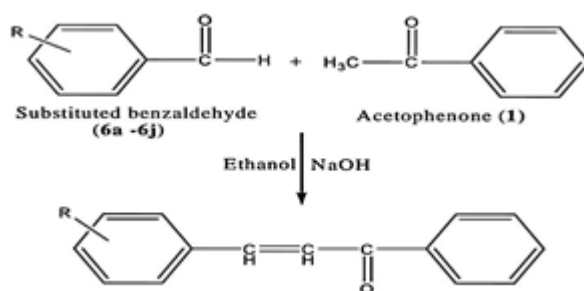


Fig. Synthesis of Chalcon

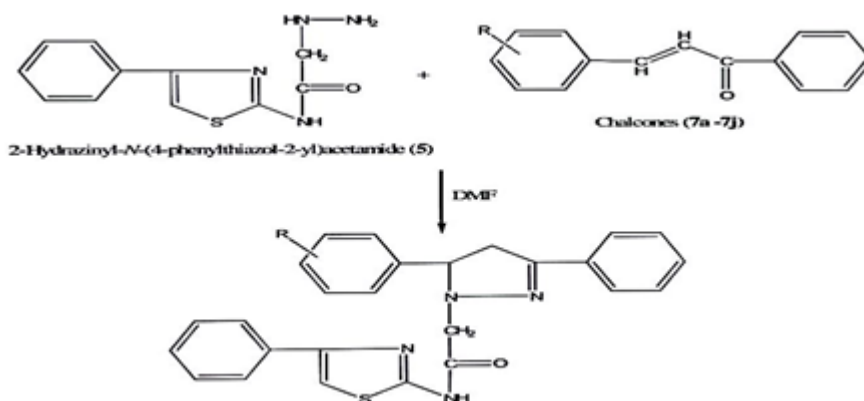


Fig. Synthesis of title compound.

Synthesis of novel 2-amino Thiazol derivatives- 3-(Tri-fluoromethyl) benzoic acid (1g.5.2mmol) was treated with SOCl₂(1.33g.11mmol) to give 3-(Tri-fluoromethyl) benzoyl chloride(148g.0.71mmol) in the presence of triethylamine (1.58g). dimethylhydroxyl amine and DCM N₂ atm. stirred at 50 °C for 30 min. give N-methoxy-N-methyl-3-Tr-fluoromethyl benzamide. process of the reaction is monitored by TLC. further react with Grignard reagent (0.80mol) in ammonium chloride at room temperature

give ketone which are further bromination with Br₂ in CHCl₃ yielded 2-bromo-1-(3-trifluoromethyl) phenylethanone (a).these compound shows cyclo-condensation with substituted thiourea to give corresponding 2-amino thiazole derivative(b).the mixture of a and b dissolved in ethanol The mixture reflux for 30 min. and then poured in to ice cold water(50 ml).it is then extracted with ethyl acetate (100ml) and washed with water, dried over mgso₄ and evaporated in vacuo. The resulting solid recrystallized from ethanol.

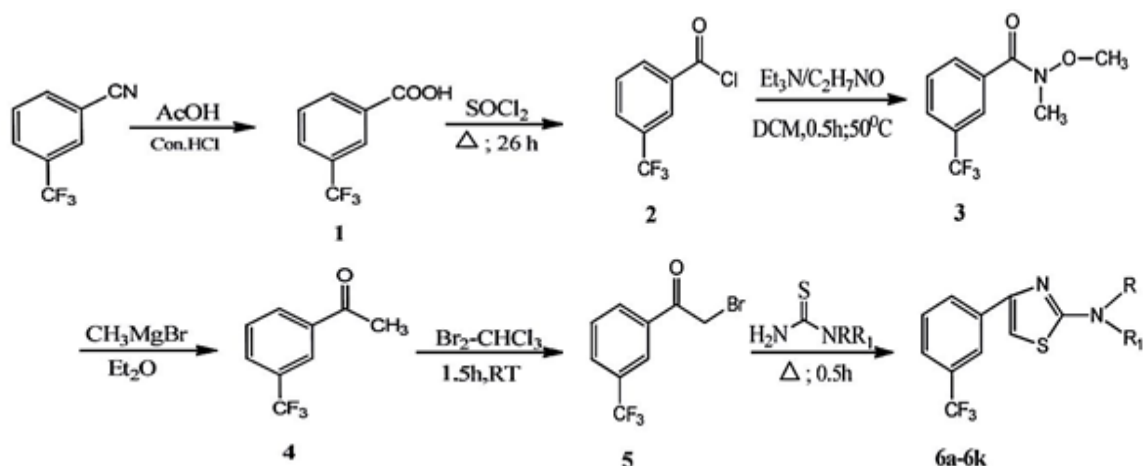


Fig- Synthesis of novel 2-amino Thiazol derivatives.

Green synthesis of Benzimidazole derivatives:

- The mixture of o-phenyleneamine (0.100g,0.92mmol) and anisaldehyde (0.125g,0.92mmol) in 4mL of ethanol was added NH_4Cl (0.15g,39mol%). The resulting mixture was stirred for 2hrs at 80°C . The completion of the reaction is

monitored by TLC. Then the reaction mixture was poured in to ice cold water and the product was precipitated as a pale-yellow solid. filtered The and the product was washed with water, recrystallized from ethanol to give pure product.

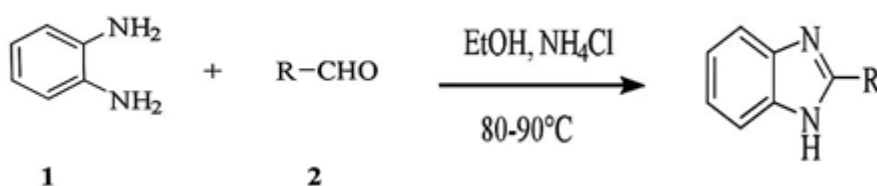


Fig. Green synthesis of Benzimidazole derivatives.

Synthesis of Anti-inflammatory and Antioxidants substituted derivatives of Benzimidazole
Synthesis of (E)-(1H-benzo(d)imidazole-1-yl)4-(2-hydroxybenzylideneamino) phenyl methanone (1a) - Benzimidazole (0.03m) and (E)-ethyl,4-(2-hydroxy2-hydroxybenzylidene amino) benzoate (0.03m) were taken in round bottom flask containing 25 ml of dry pyridine and reflux for 6-7 hrs. The reaction mixture was cooled and poured in to crushed ice to obtain the solid and recrystallized from alcohol.

Synthesis of (E)-(1H-benzo (d) imidazole-1-yl)4-(4-chlorobenzylideneamino) phenyl methanone- Benzimidazole (0.03m) and (E)ethyl,4-(4-chloro-

hydroxybenzylideneamino) benzoate (0.03m) were taken in a round bottom flask containing dry pyridine and reflux for 18 hrs. The reaction mixture was cooled and poured in to crushed ice to obtain solid.

Synthesis of 5-phenyl -1, 3, 4-oxadiazol-2-amine

Benzohydrazide (0.02m) and cyanogen bromide (0.02m) were taken in ethanol in a round bottom flask. The reaction mixture was heated on water bath at $50-60^\circ\text{C}$ for 30 min.it was cooled and neutralized with sodium bicarbonate. The reaction mixture was poured in to beaker containing crushed ice. A solid was formed which was filtered, washed with water, dried and recrystallized from alcohol.

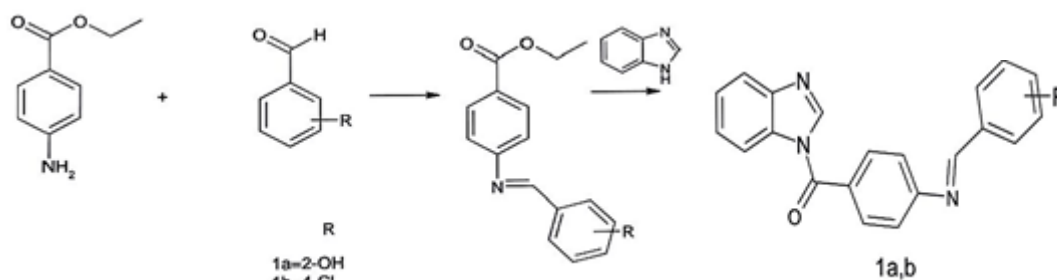


Fig. Synthesis of (E)-(1H-benzimidazole-1-yl) 4-(2-hydroxybenzylideneamino) phenyl methanone (1a)

Synthesis of benzylbenzimidazole - The mixture of o-phenylenediamine dihydrochloride (0.03mole), 20 ml of water, phenyl acetic acid (0.09 mole) under reflux for 45 min. made the cooled reaction mixture

distinctly basic by the gradual addition of concentrated ammonia solution, the precipitated product was collected and recrystallized from 40% ethanol.

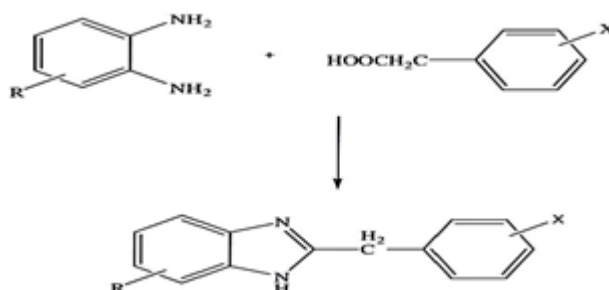


Fig- Synthesis of benzylbenzimidazole.

Synthesis of benzimidazole beta-L-2-deoxyribonucleosides: –

The identical properties of L and D-nucleosides and their precursors in a non-chiral environment. The protocol developed for chemical synthesis of their D-counterparts can be employed for the preparation of the L-enantiomer. instead of 3, 5-di-o-(4-methylbenzoyl)-2-deoxy-alpha-D-erythro-pentofuranosyl. Chloride the corresponding L-enantiomer is used as sugar. components. 3,5-Di-O-(4-methylbenzoyl)-2-deoxy-alpha-L-erythro-pentofuranosyl chloride was prepared (29). The glycosylation of 5(6)-

nitrobenzimidazole (28) with the alpha L-2-deoxyribofuranosyl halide (29) was performed in MeCN in the presence of powdered KOH using TDA-1 (tris (2-methoxyethoxy) ethyl amine) as phase transfer catalysts. The glycosylation led to a mixture of the N1 and N3 glycosylated regioisomer (30) and (31) which were separated by chromatography. The faster migration compound was isolated in 26% (30) and the slower one (31) in 32% yield. both compounds were deprotected with 1M NaOMe/MeOH and crystallized from methanol.

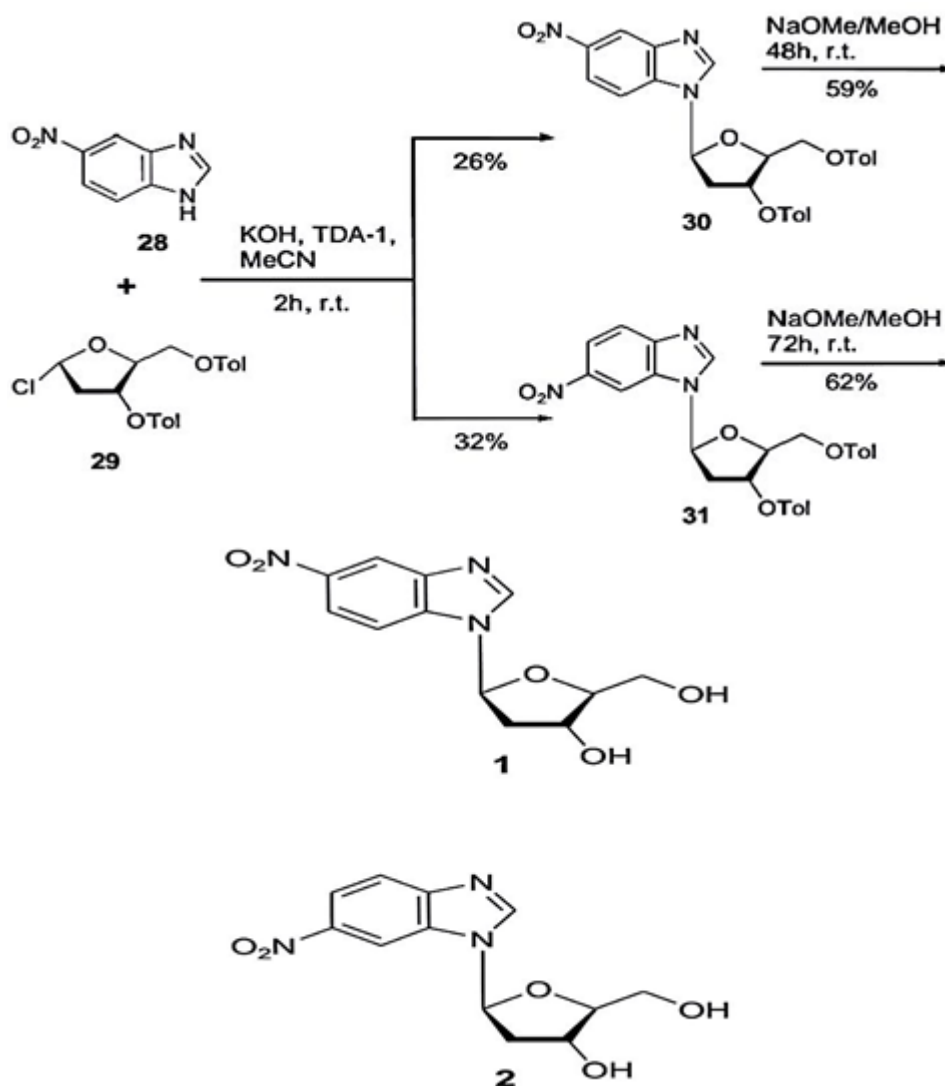


Fig. Syhthesis of benzimidazole beta-L-2-deoxyribonucleosides.

Synthesis of 2-mercapto-N-methyl imidazole substituted Benzimidazole derivatives – A mixture of 2-mercapto-N-methyl imidazole (1mmol) and sodium hydroxide (1mmol) in methanol (10ml) was stirred for about 30 min. A methanol solution (10 ml) of 5(6)-substituted 2-chloromethyl benzimidazole (1mmol) was added slowly with stirring and the mixture reflux for 8 hrs. The progress of the reaction

was monitored by TLC and after completion reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine, finally dried with anhydrous sodium sulphate. The organic layer was concentrated and the resulting crude compound was purified by column chromatography over silica gel. (5ac)

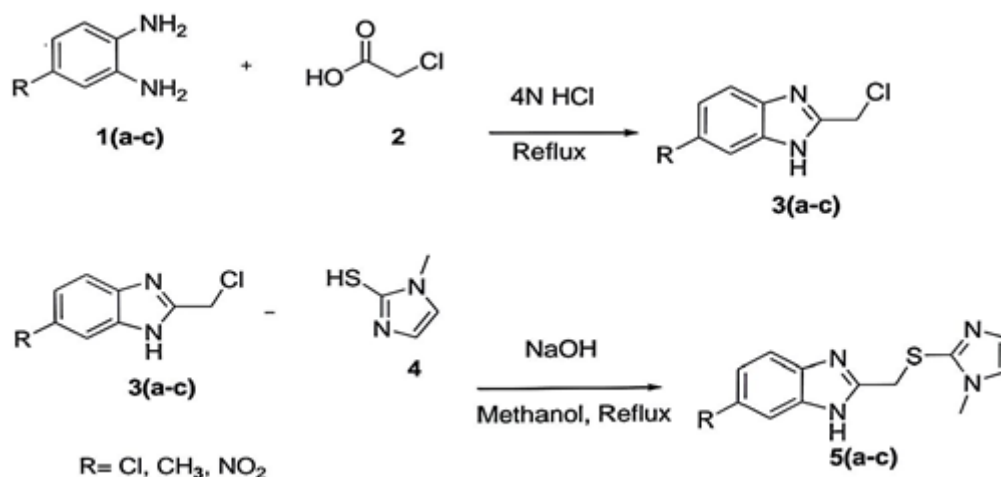


Fig. Synthesis of 2-mercapto-N- methyl imidazole substituted Benzimidazole derivative.

Novel 1,2,3-triazolo phosphonate derivatives as potential antibacterial agents

General Procedure for the Preparation of Compound.

Compound was synthesized via a copper-catalyzed azide-alkyne cycloaddition reaction. A mixture of azide 4 (0.53 mmol) and the appropriate terminal alkyne 3 (0.53 mmol) was dissolved in DMF (5 mL). To this solution, $CuSO_4 \cdot 5H_2O$ (65 mg, 0.26 mmol) and sodium ascorbate (52 mg, 0.26 mmol) were added. The resulting reaction mixture was stirred vigorously at room

temperature for 5 minutes. The progress of the reaction was monitored by thin-layer chromatography (TLC).

Upon completion, the reaction mixture was poured into crushed ice (30 g), resulting in the formation of a solid precipitate. The obtained solid was filtered, washed, and dried under appropriate conditions. Further purification was carried out by column chromatography on silica gel using a mixture of petroleum ether and ethyl acetate as the eluent to afford the desired compound.

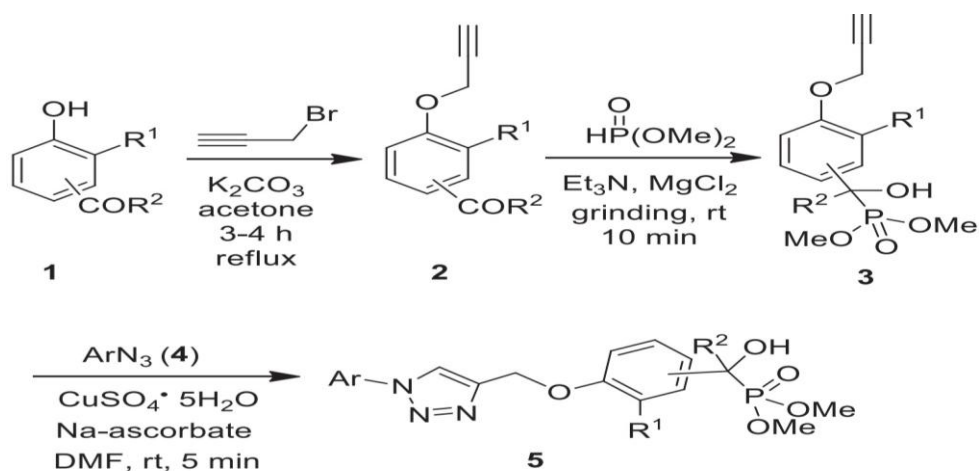


Fig. Synthesis of 1,2,3-triazolo phosphonate derivatives potential as antibacterial agents.

Synthesis of piperazine-based benzimidazole derivatives

General Procedure for the Synthesis of Compounds 5a-n

Compounds 3a-n (1 mmol) and vanillin (4, 1 mmol) were dissolved in DMF (10 mL). To this mixture, potassium carbonate (K_2CO_3 , 1.5 mmol) was added, and the reaction was stirred at room temperature for

12 h. The reaction progress was monitored by TLC. After completion, the mixture was poured into ice-cold water to precipitate the product. The resulting solid was filtered, washed with water, and dried to obtain pure compounds 5a–n.

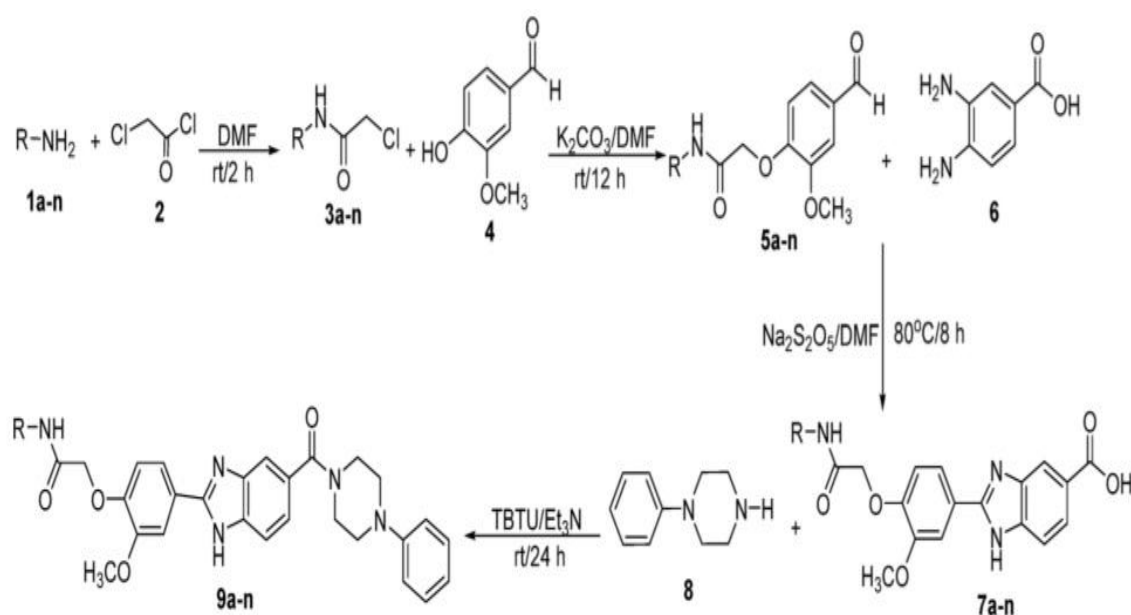
General Procedure for the Synthesis of Compounds 7a–n

Compounds 5a–n (1 mmol) was reacted with diaminobenzoic acid (6, 1 mmol) in DMF (10 mL) in the presence of sodium metabisulfite ($\text{Na}_2\text{S}_2\text{O}_5$, 1.5 mmol). The reaction mixture was refluxed for 8 h, and the progress was monitored by TLC. After completion, the mixture was poured into ice-cold water, leading to the precipitation of the product. The solid was filtered,

washed with water, and dried to yield compounds 7a–n in pure form.

General Procedure for the Synthesis of Benzimidazole Hybrids (9a–n)

Derivatives 7a–n (1 mmol) and phenylpiperazine (8, 1 mmol) were dissolved in DMF (10 mL). To this solution, TBTU (1.5 mmol) and triethylamine (Et_3N , 1.1 mmol) were added, and the reaction mixture was stirred at room temperature for 24 h. The reaction progress was monitored by TLC. Upon completion, the mixture was poured into ice-cold water to precipitate the crude product. The solid was filtered, thoroughly washed with water, and dried. The crude product was further purified by recrystallization from ethanol to afford the desired benzimidazole hybrids (9a–n) in pure form.



Scheme 1. Synthesis of benzimidazole derivatives 9a–n.

General protocol for the preparation of 2,4,5-trisubstituted imidazoles

Benzil (0.5 mmol, 105.0 mg), benzaldehyde (0.5 mmol, 51.0 μL), and ammonium acetate (1.0 mmol, 77.0 mg) were added into a test tube containing DES based on DMU: SnCl_2 : HCl (0.5 mL). The reaction mixture was stirred at 60 $^\circ\text{C}$ for 45 min, and the progress of the reaction was monitored

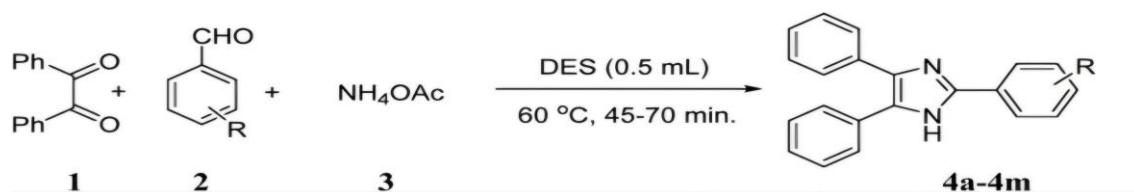
by thin layer chromatography (TLC). After completion of the reaction, water (10 mL) was added to the reaction mixture. The resulting mixture was cooled, and the precipitate formed was filtered off. The obtained precipitate was further recrystallized from ethanol. All synthesized compounds were already known

compounds, and their identity and purity were confirmed by melting point analysis.

General protocol for the preparation of 1,2,4,5-tetrasubstituted imidazoles using DMU: SnCl₂: HCl

In the experimental procedure, a mixture of benzaldehyde (0.5 mmol, 51.0 μ L), aniline (0.5 mmol, 45.0 μ L), benzil (0.5 mmol, 105.0 mg), and ammonium acetate (0.5 mmol, 39 mg) was added to DES based on DMU: SnCl₂: HCl (0.5 mL), which acted as both catalyst and solvent system. The

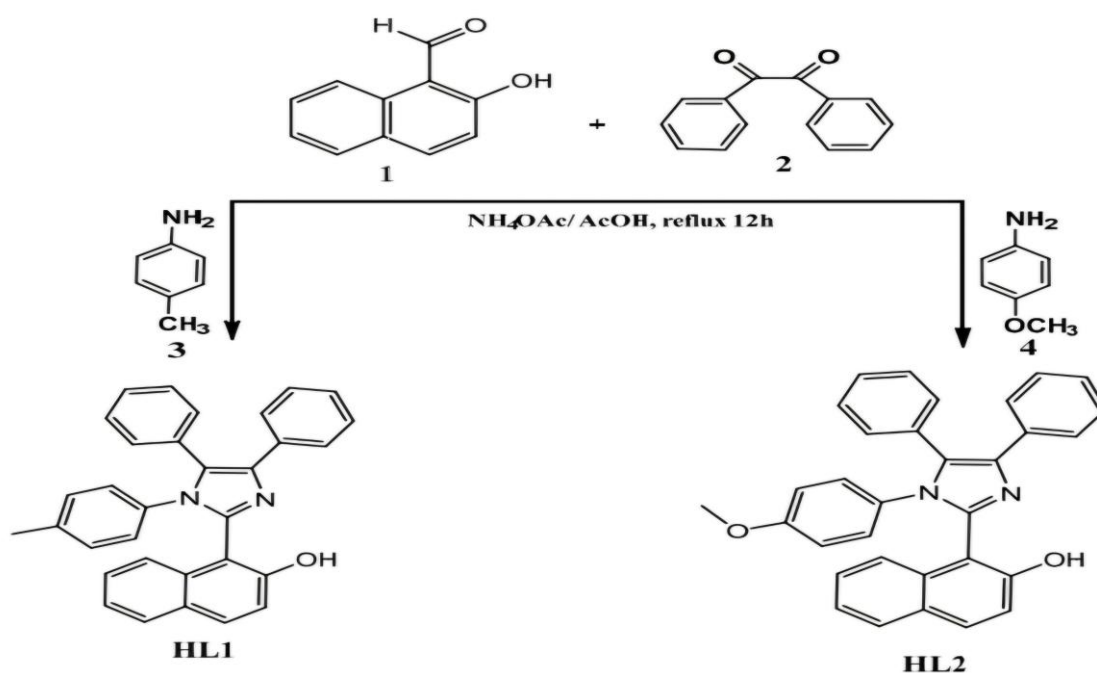
reaction mixture was heated at 90 °C for 110 min, and the progress of the reaction was monitored by TLC. After completion of the reaction, ethyl acetate (10 mL) and water (10 mL) were added to the reaction mixture. The mixture separated into aqueous and organic phases. The organic layer was collected, and ethyl acetate was removed by rotary evaporation to obtain crude 1,2,4,5-tetrasubstituted imidazole derivatives. The crude products were further recrystallized from ethanol or ethyl acetate.



Synthetic Procedures of Imidazole Derivatives (HL1 and HL2)

A solution of 2-hydroxy-1-naphthaldehyde (0.122 g, 1 mmol), benzil (0.231 g, 1.1 mmol), 4-methylaniline (0.492 g, 4 mmol) or 4-methoxyaniline (0.428 g, 4 mmol), and ammonium acetate (0.77 g, 10 mmol) in glacial acetic acid (10 mL) was refluxed under an argon atmosphere for 12 h. After

completion of the reaction, the mixture was allowed to cool to room temperature and then diluted with water (20 mL). The resulting precipitate was filtered, washed successively with 10% acetic acid (4 $\times$ 5 mL) and water, and finally dried to afford the pure imidazole derivatives HL1 and HL2.



Scheme 3. Synthesis of imidazole derivatives, HL1 and HL2.

Synthesis of Imidazole Derivatives

Najmoddin Aziizi et. al. [22] (2014) have developed a one-pot, four-component approach towards the synthesis of tetra substituted imidazoles using aldehydes, amines, ammonium acetate, and 1,2-diphenylethane-1,2-dione using iron oxide

nanoparticles as a catalyst. The advantages of these reactions are high yield of product, short reaction time and easy work up procedure. Synthesis of Substituted Imidazole Derivatives Using Different Catalysis as.

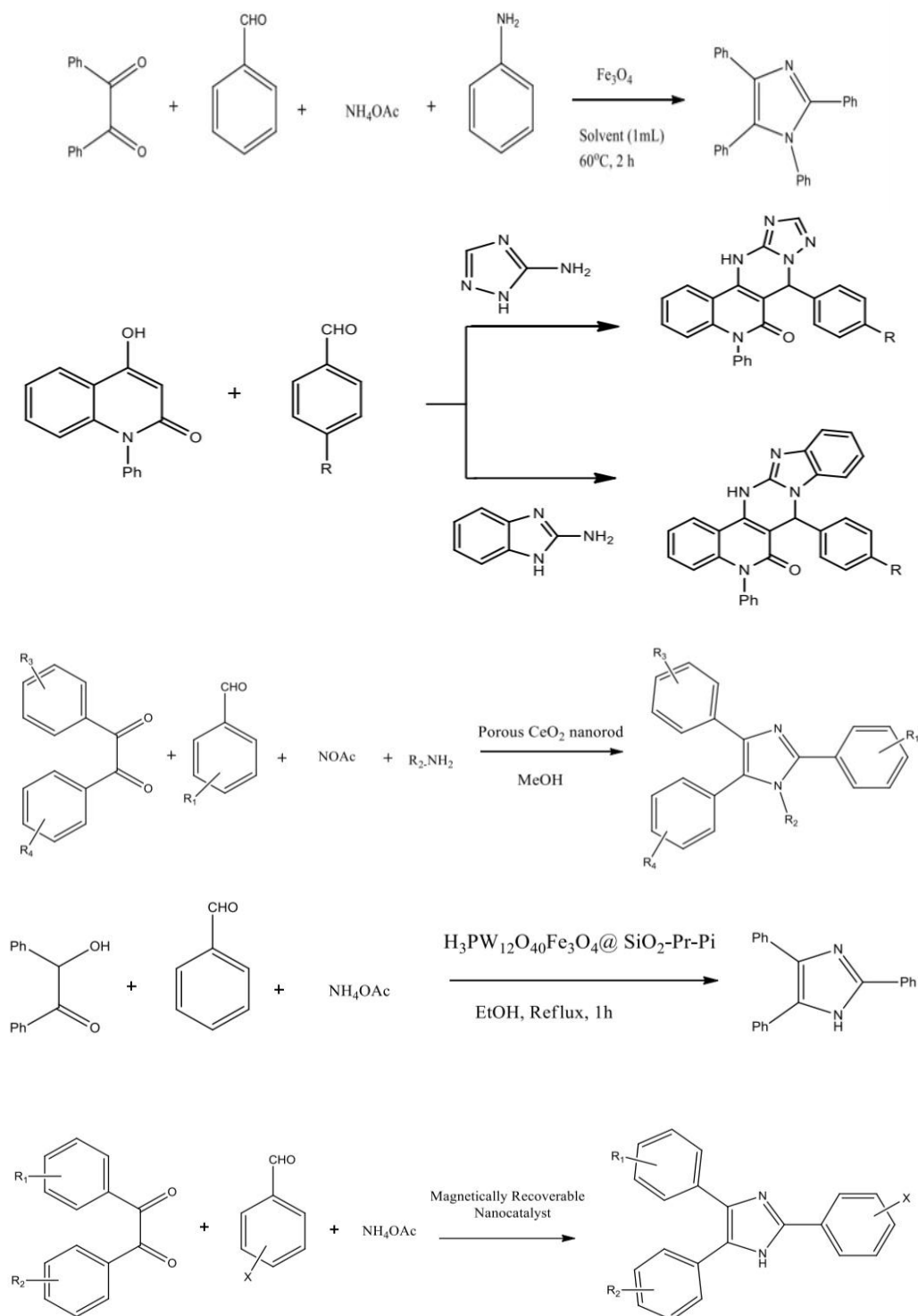


Fig. Synthesis of Substituted Imidazole Derivatives Using Diffrent Catalysis.

CONCLUSION

We have review on the synthesis of some derivatives of pyrazole, Thiazole and Benzimidazole biological important Heterocycles. The derivatives of these Heterocycle show antimicrobial, antitumor, anti-inflammatory, antifungal, antiulcer, anti-asthmatic, anti-diabetic, analgesic properties. The synthesis of these heterocycles is important for medicinal value.

Declaration by Authors

Acknowledgement: None

Source of Funding: None

Conflict of Interest: No conflicts of interest declared.

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How to cite this article: Palodkar Gajanan Hari, Santosh Shriram Katkar. Synthesis of pyrazole, thiazole and benzimidazole biological active heterocycles. *International Journal of Research and Review*. 2026; 13(9): 476-493. DOI: <https://doi.org/10.52403/ijrr.20260946>
