Journal of Qassim University for Science
2025, *Vol 4* (Issue 1), pp. 25-73.
Received: 9 March 2025
Revised: 8 April 2025
Accepted: 8 April 2025
Published: 27 April 2025

JQUS

Pyrazole Derivatives: A New Synthesis, Biological Importance, and Recent Practical Applications

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Abstract: Heterocyclic compounds and their equivalents that include nitrogen have historically been valuable sources of pharmaceuticals. In a five-membered ring structure, the aromatic compound pyrazole, which contains two nitrogen atoms, offers a variety of uses and stereochemical complexity. Numerous pyrazole compounds have demonstrated a range of pharmacologic and physiological advantages over the past decade of research. This arises from apprehensions that the complete efficacy of a substance might be constrained by its pharmacological characteristics and their correlation with its structural and functional attributes. Diverse variants of the pyrazole nucleus provide extensive applications in technology, medicine, and agriculture. They are explicitly classified as antioxidants, protein glycation inhibitors, *anti*-viral agents, *anti*-bacterial agents, *anti*-fungal agents, *anti*-cancer agents, *anti*-depressants, *anti*-inflammatory agents, and *anti*-tuberculosis agents This review examines the most notable results by scientists and chemists concerning the pyrazole compound, including its general properties, various synthesis methods, prominent derivatives, reactions, and biological applications, particularly in antibacterial, antimicrobial, antifungal, antimalarial, and anticancer activities.

Keyword: Synthesis, heterocyclic compounds, pyrazole, biological properties, anticancer, antibacterial, antimicrobial, antioxidant.

1.Introduction

Pyrazole derivatives have numerous biological applications in pharmaceutical chemistry. The diverse pharmacological effects exhibited by derivatives of pyrazoles, aromatic heterocycles with five carbon atoms and two nitrogen atoms nearby, make them a popular structural issue in drug development [1]. They are members of a unique and practical class of compounds. Numerous biological, chemical, and physical properties are displayed by these substances [2]. The structural nucleus of heterocyclic compounds, which are present in a wide range of natural products, including vitamins, hormones, antibiotics, and alkaloids, is essential for metabolism [3-5]. In the azole class, pyrazoles are the most studied group of compounds. They are referred to as five-membered heterocycles, being highly helpful in producing organic molecules. In fact, a wide range of synthesized analogs and synthesis methods have been successfully reported over time [6]. The pyrazole nucleus exists in various structures, which enable a wide range of applications in fields such as technology, medicine, and agriculture. Because of their intriguing pharmacological characteristics, pyrazole derivatives are currently gaining increasing attention as biomolecules. These drugs particularly prevent protein glycation and are antiviral, antibacterial, antifungal, anticancer, antidepressant, anti-inflammatory, anti-tuberculosis, antioxidant, and antiviral [7-9].

Pyrazole **1** has the basic chemical formula $C_3H_4N_2$. It is an aromatic system with six π- electrons spread out around the ring. (Figure 1) Multiple pyrazoles covering pyrazoline **4**, **5**, and **6**, pyrazolidine **2**, and pyrazolone **3**, are associated with pyrazole. Pyrazole heterocyclic structure having a with two nitrogen atoms, one of which is a pyrrole at position 1 and the other a pyridine at position 2, is considered to be an excess of one. Two nitrogen atoms, one neutral and one basic, are present [3].

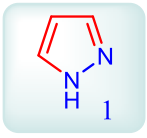


Figure 1: Chemical structure of pyrazole

Pyrazole derivatives are aromatic because they contain four π-electrons in addition to an unshared pair of electrons on the NH nitrogen. There are three pyrazole variants that are partially reduced: Four, two, five, and six are the initial pyrazolines [4] (Figure 2). In these aromatic systems, there are conjugated planar ring structures with six π-electrons that are significantly delocalized. Multiple analyses have shown that the third and fourth atomic locations have a very long bond length. When it comes to heterocyclic compounds of the pyrazoline type, 2-pyrazolines are by far the most studied. [5]

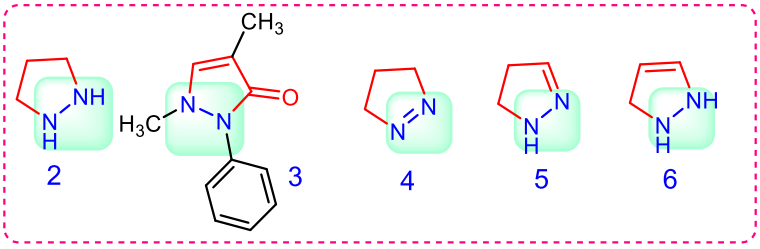


Figure 2: pyrazolidine **2**, pyrazolone **3,** 1-pyrazoline **4**, 2-pyrazoline **5**, and 3-pyrazoline **6**

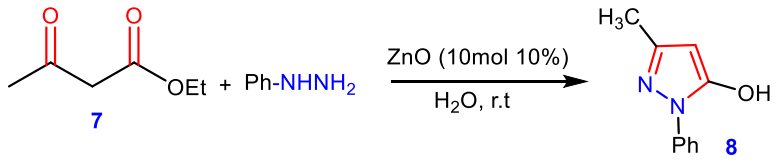
Pyrazoles are significantly weaker bases than imidazole and the conjugate acid of pyrazole possesses a pKa of 2.52. Unlike the imidazolium ion, the positive charge of the pyrazolium ion is less delocalized. Pyrazoles and imidazole's have demonstrated proton affinities, thermodynamic and kinetic basicity, and gas-phase basicity. NH-acidity is displayed by unsubstituted pyrazoles at the first position. The pKa value of pyrazole is 14.21, identical to that of imidazole. The sodium salt is formed through the combination of pyrazole with sodium.

2. CHEMISTRY: Synthetic approach to pyrazole derivatives

2.1 from non-cyclic compounds

2.1.1 From 1,3-dicarbonyl

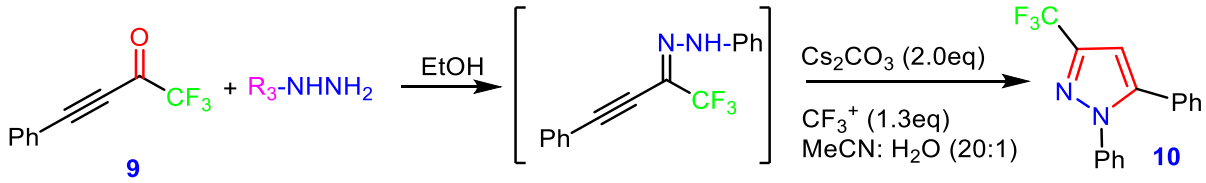
A quick and easy way to produce 1-phenyl 3-methyl 5-hydroxy pyrazoles **8** is to cyclo-condensate ethyl acetoacetate **7** and phenyl hydrazine in a water medium with zinc oxide as a catalyst **(Scheme 1)** [9]



Scheme 1: Synthesis of 1-phenyl 3-methyl 5-hydroxy pyrazoles **8**

2.1.2 Starting with acetylenic ketones

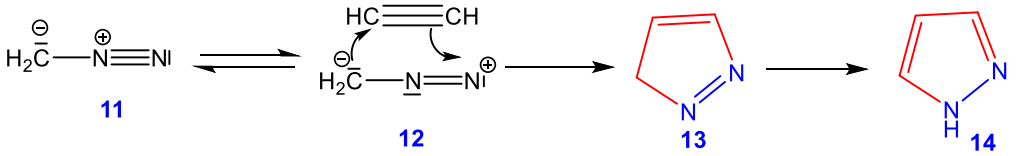
It has been known for over a century that pyrazoles **10** are formed by the cyclo-condensation reaction of hydrazine derivatives on acetylenic ketones **9**. On the other hand, two regio-isomers **10** are produced by the process once again. **(Scheme 2)** [10].



Scheme 2: 3-trifluoromrthylpyrazole synthesis by acetylenic ketone cyclization

2.1.3 From diazoalkanes and acetylenes via 1,3-dipolar cycloaddition

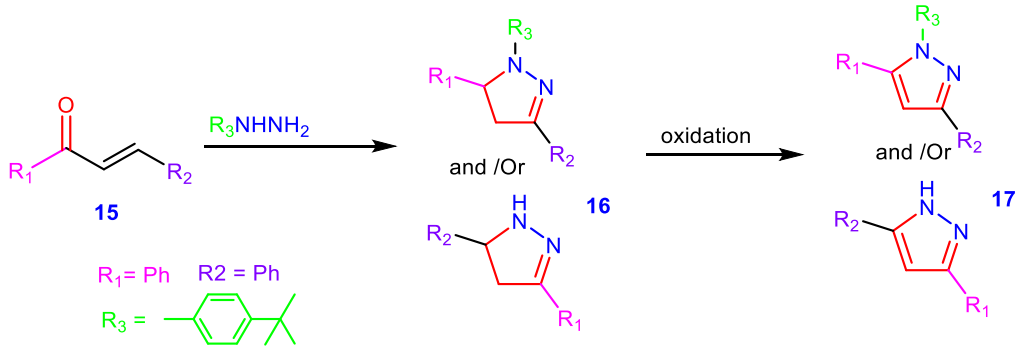
In a coordinated [3+2] cycloaddition of diazomethane **11** and acetylene, 3-pyrazole is rapidly isomerized to pyrazole **14**. Following scheme 3, dihydropyrazoles **13** are generated by means of the 1,3-dipolar cycloaddition of acetylenes to diazoalkanes **(Scheme 3)** [11].



Scheme 3: Pyrazole derivatives via 1,3-dipolar cycloaddition

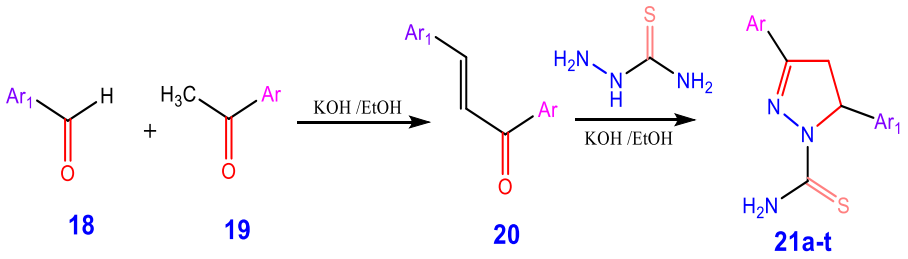
2.1.4 From α,β-unsaturated ketones:

A combination of pyrazole regio isomers **17** is produced when *α, β*-unsaturated ketones undergo a cyclo-condensation reaction with hydrazine derivatives. **(Scheme 4)** [12].



Scheme 4: Synthesis of a mixture of pyrazole regio isomers **17**

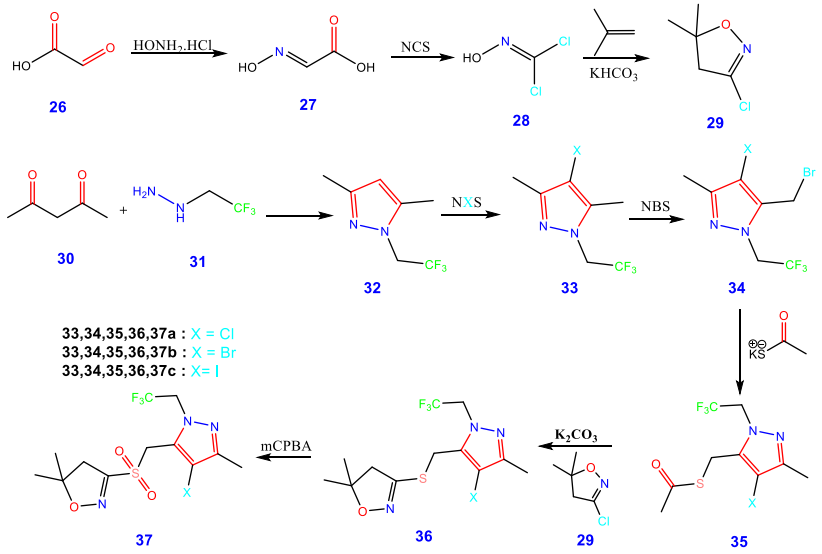
Next scheme presents the synthesis procedure proposed by Chimenti et al [13,14] **(Scheme 5)**. for a large number of monoamine oxidase inhibitory N-1-thiocarbamoyl-3,5 di(hetero) aryl-4,5-dihydro-1*H*-pyrazole derivatives. The first 1,3-di-(hetero) aryl-2-propenones **20** were produced using this method by refluxing a substituted aryl or heteroaryl aldehyde **18** with an appropriate substituted aryl or heteroaryl ketone **19**. This process is known as Claisen Schmidt condensation. The required products **21a-t** were obtained in good yields by adding thio-semicarbazide to these intermediates in KOH/EtOH without additional purification.



21a . Ar = Ph , Ar_1=Ph
21b . Ar = Ph , Ar_1=4'-CH_3-Ph
21c . Ar = Ph , Ar_1=4'-Cl-Ph
21d . Ar = Ph , Ar_1=fur-2'-yl
21e . Ar = 4'-CH_3-Ph , Ar_1=4'-F-Ph
21f . Ar = 4'-CH_3-Ph , Ar_1=thiophen-2'-yl
21g . Ar = 4'-F-Ph , Ar_1=thiophen-2'-yl
21h . Ar = 4'-Cl-Ph , Ar_1=4'-CH_3-Ph
21i . Ar = 4'-Cl-Ph , Ar_1=4'-F-Ph
21j . Ar = 4'-Cl-Ph , Ar_1=4'-Cl-Ph
21k . Ar = 4'-Cl-Ph , Ar_1=Pyrrol-2'-yl
21l . Ar = fur-2'-yl , Ar_1=4'-CH_3-Ph
21m . Ar =fur-2'-yl , Ar_1=4'-F-Ph
21n. Ar = fur-2'-yl , Ar_1=thiophen-2'-yl
21o . Ar = thiophen-2'-yl , Ar_1=Pyrrol-2'-yl
21p . Ar = Pyrrol-2'-yl , Ar_1=Ph
21q . Ar = Pyrrol-2'-yl , Ar_1=4'-F-Ph
21r . Ar = Pyrrol-2'-yl , Ar_1=4'-Cl-Ph
21s . Ar = Pyrrol-2'-yl , Ar_1=fur-2'-yl
21t . Ar = Pyrrol-2'-yl , Ar_1=thiophen-2'-yl

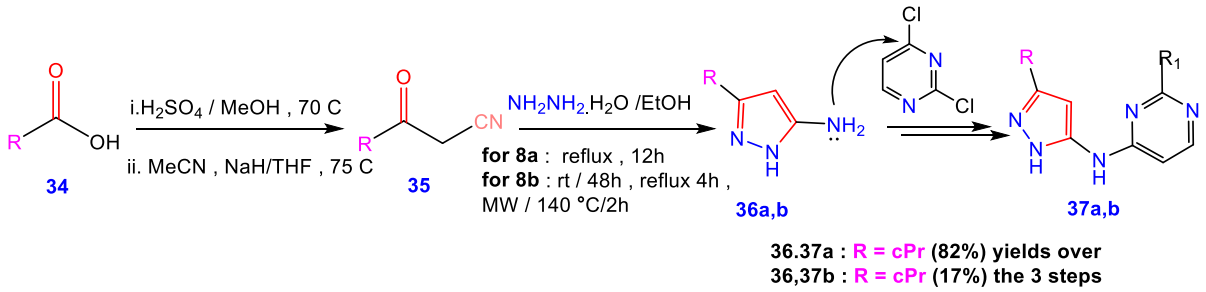
Scheme 5: Claisen Schmidt synthesis of pyrazole from chalcone using carbonyl materials

In contrast, a multi-step synthesis method is used to synthesize herbicidal derivatives of trifluoro ethyl pyrazole **33a-c** **(Scheme 6)** [15]. After reacting of hydroxylamine hydrochloride and glyoxalic acid **22** to create the intermediate **25**, it was then treated with *m*CPBA and reacted with trifluoro ethyl prazole ethanethioate **31** to produce the intended outcome.



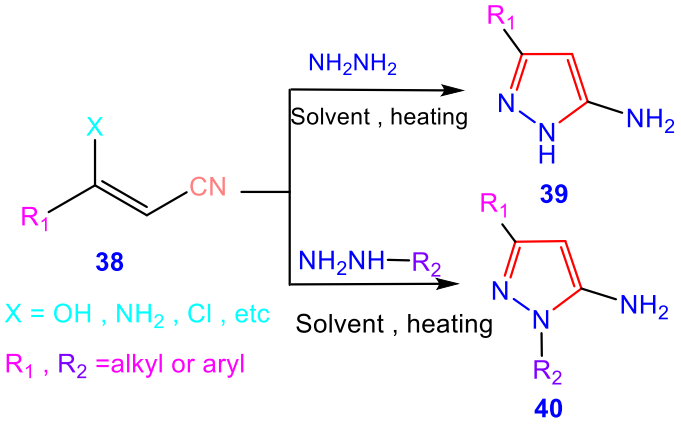
Scheme 6: Synthetic route to pyrazole derivatives bearing oxazoline

In order to prepare 5-alkyl-3-amino-1*H*-pyrazoles **36a,b**, Pilakowski et al. [19] used carboxylic acids **34a, b** as a starting material. The related ketonitrile **35** was prepared by first developing an esterification process, and then treating the corresponding ester with sodium hydride and acetonitrile. The compounds **36a** and **36b** were isolated from this intermediate by treating it with hydrazine hydrate. Then, these were evaluated for their potential as Nek1-inhibitors by forming N-substituted pyrazoles by a reaction with dichloro-pyrimidine **(Scheme 7)** [16].



Scheme 7: Synthesis of pyrazole linked with pyrimidine

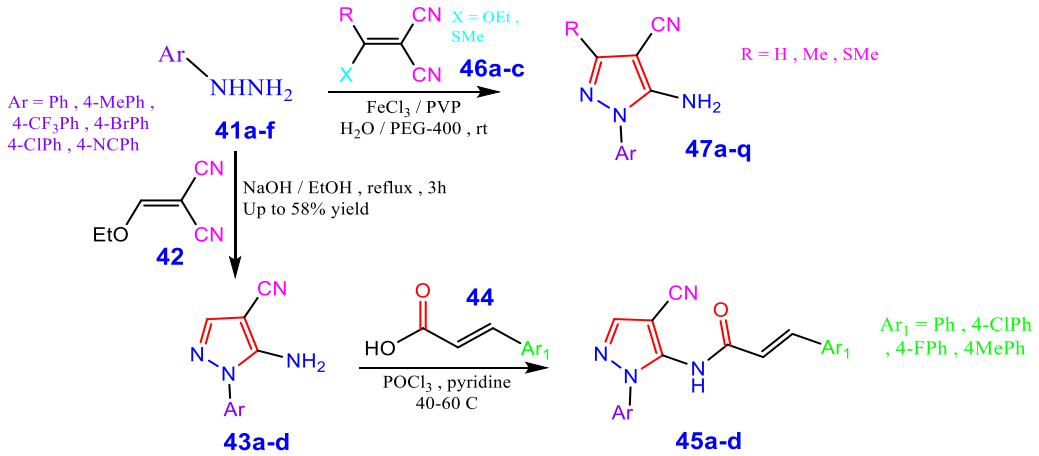
It is possible to functionalize pyrazoles by electrophilic substitution on the pyrazole ring or by adding extra groups to the original molecules. The amino group is removed immediately from the starting material in the reaction between hydrazine derivatives and unsaturated nitriles with an easily displaceable group to create 5-aminopyrazoles **39** and **40**, for instance. **(scheme 8)** [17].



Scheme 8: Synthesis of 5-aminopyrazoles **34** and **44**.

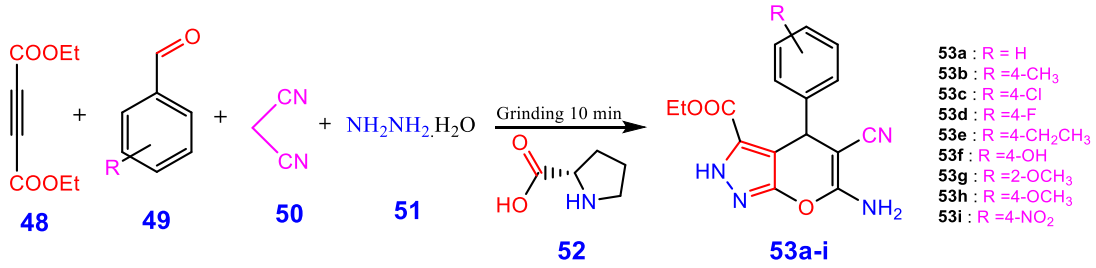
Elnagdy and Sarma [18] presented a homogeneous catalytic system a year later; it synthesises with $FeCl_3$/PVP and employs water/PEG-400 as a green solvent. By combining arylhydrazines **41a-f** with malononitrile derivatives **46a-c**, the cyclo-condensation reaction yields the 4-amino-1-aryl-1H-pyrazole-4-carbonitriles **47a-q.** Compounds **41a-f** was added to the **46a-c** double bond using polyvinyl-pyrrolidine (PVP) and ferric chloride as catalysts. After that, a yield of up to 97% was achieved in the synthesis of products **47a-q** using intramolecular cyclization. **(scheme 9)**.

Rental et al [19] developed 5-amino-aryl-pyrazole-4-carbonitriles **43a-d** by reacting a combination of arylhydrazine hydrochloride **41a-f**, 2-(ethoxy methyl) malononitrile **42**, ethanol, and sodium hydroxide using a conventional cyclo-condensation process. Carboxamide was converted utilizing 5-aminopyrazoles **43a-d** to produce derivatives **45a-d**, which were then evaluated as compounds that inhibited succinate dehydrogenase and three fungal strains **(scheme 9)**.



Scheme 9: Synthesis pathway of amino-cyano-pyrazole and 4-amino-pyrazole-carbonitriles

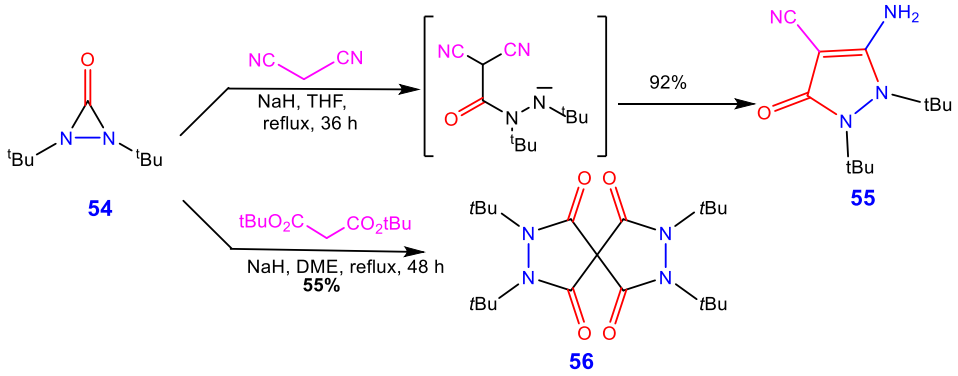
By grinding aryl aldehyde, malonitrile, hydrazine hydrate, and diethyl acetylene dicarboxylate, Ambedkar et al. [20] produced a multicomponent and eco-friendly synthetic method for producing pyrano-pyrazole derivatives as antibacterial and antioxidant agents **53a-i**. **(Scheme10).**



Scheme 10: One pot synthesis of pyrano-pyrazole

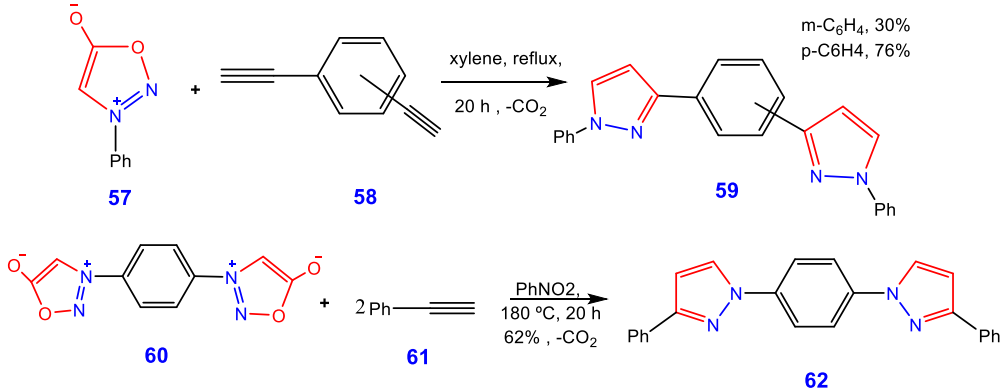
2.2 From heterocycles

The large range of heterocyclic compounds allows for the generation of pyrazoles [21]. While there are a few intriguing synthetic outliers, the original heterocycles are usually hard to come by, and the techniques used aren't quite fit for a generalized problem. These reactions can be seen in the following schemes: pyrazole-producing expansion, ring modification, and ring contraction. Enlargement of the diaziridinone **54** ring through contact with a bifunctional carbanion. the production of pyrazolinone **59** or spiro-heterocycles **56**. **(Scheme 11)** [22].



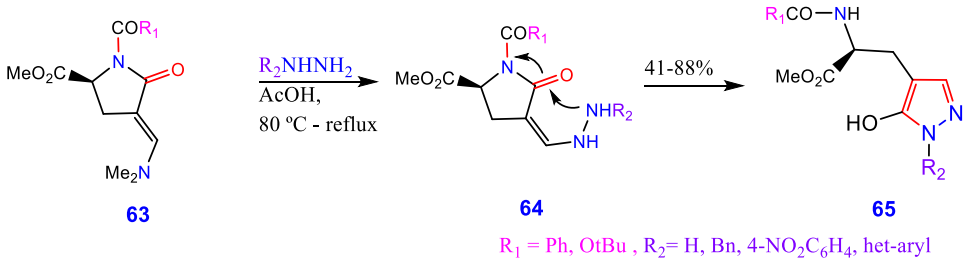
Scheme 11: Pyrazole derivatives from diaziridinone

Pyrazoles are created by 1,3-dipolar cycloadditions of sydnones with different dienophiles. *Meta*- and *para*-phenylene *di*-pyrazoles **59** are produced when 3-phenylsydnone **57** reacts with *meta*- and *para*-diethynyl benzene in refluxing xylene [23]. Similarly, 3,3'-diphenyl-1,1-*para*-phenylene enpiprazole **62** is produced when para-phenylene 3,3'-diydnone **60** reacts with phenylacetylene. By reacting 3,4-disubstituted sydnones with 1-aryl-3,3,3-trifluoromethylpropynes, a range of poly-substituted pyrazoles have been produced in high yield and with improved regioselectivity [24]. The 1,3-dipolar cycloaddition reactions of nitril-imines with different heterocyclic compounds, several of which produce pyrazoles, have been reviewed [25] **(scheme 12).**



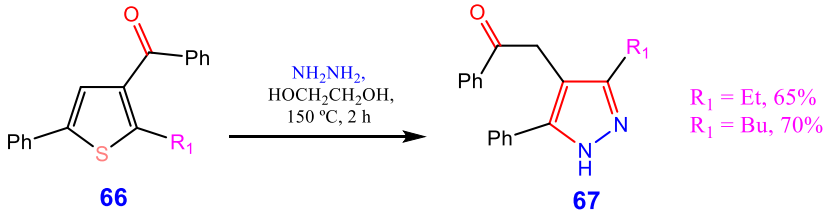
Scheme 12: Pyrazole synthesis via 1,3-dipolar cycloaddition from 3-phenylsydnone

Hydrazine derivatives reacted with (S)-1-methylpyrrolidin-2-ones **63** under reflux of acetic acid resulting the hydroxy-pyrazole ester **65 (Scheme 13)** [26].



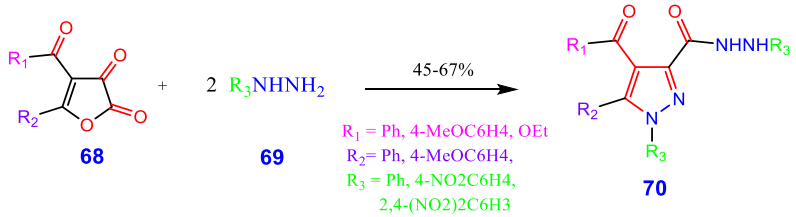
Scheme 13: Pyrazole synthesis from (S)-1-methylpyrrolidin-2-ones

The combination of hydrazine and 3-benzoyl-2-substituted-5-phenylthiophene **66** produce the corresponding 4-benzoylmethyl-3(5)-phenyl pyrazoles **67 (Scheme 14)** [27].



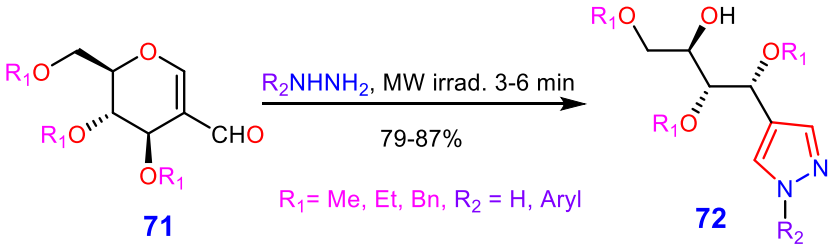
Scheme 14: Single step synthesis of 4-benzoylmethyl-3(5)-phenyl pyrazoles **67**

Furan-2,3-diones **68** lead to pyrazole-3-carboxylic acid hydrazides **70** when react with substituted hydrazine under certain conditions **(scheme 15)** [28].



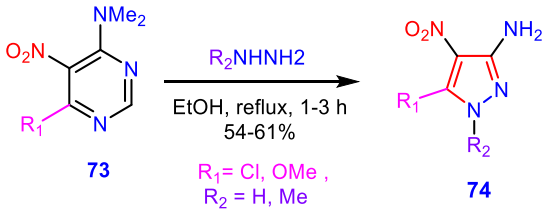
Scheme 15: Elaboration of pyrazole-3-carboxylic acid hydrazides **70** from furan-2,3-diones

By employing microwave heating to efficiently condense formyl glycals **71** with arylhydrazines in solvent-free conditions, the corresponding optically pure 4-substituted pyrazoles **72** were produced in 79-87% yields with increased selectivity (scheme 16). Hydrazine hydrate provides significant yield of the corresponding pyrazoles, exactly as aryl hydrazine produces.[29]



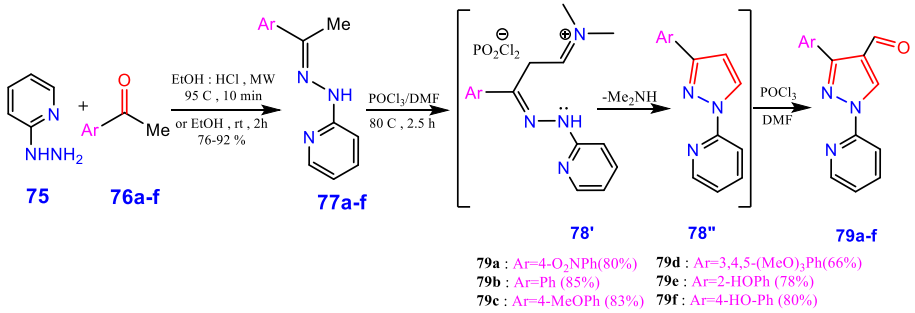
Scheme 16: Microwave-assisted synthesis of optically pure 4-substituted pyrazoles

Recent studies have demonstrated that 4-(dimethylamino)-6-chloro (or 6-methoxy)-5-nitropyrimidine **73** can be efficiently treated with hydrazine hydrate or methylhydrazine (2 equivalents) to yield 3,5-diamino-4-nitropyrazole and 3,5-diamino-1-methyl-4-nitropyrazole **74**, respectively, as shown in **(scheme 17)** [30,31].



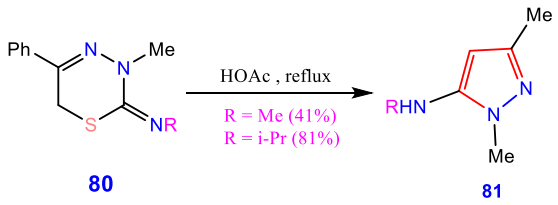
Scheme 17: Conversion of pyrimidines derivatives to corresponding pyrazoles

A research group has described the synthesis of 3-aryl-1-(pyridin-2-yl)-1*H*-pyrazole 4-carbaldehydes **79a–f** through the Vilsmeier-Haack cyclization-formulation of various hydrazones **81a–f**, which were produced from 2-hydrazinylpyridine **75** and acetophenones **80a-f**. Prior to Cursor **78a-f** under Vilsmeier-Haack conditions was changed in the 1,3-biselectrophilic intermediate **81**, which is then cyclo-condensed to pyrazole **78**, which is then formylated to produce 4-formylpyrazole **79** in 66–85% yields **(Scheme 18)**[32].



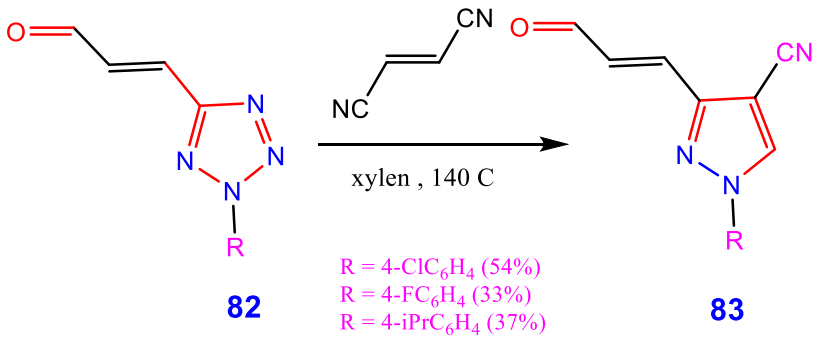
Scheme 18: Synthesis of pyrazole via the Vilsmeier-Haack cyclization-formulation

5-aminopyrazoles **81** were generated in a good yield when 3-methyl-6*H*-1,3,4-thiadiazine **80** was heated under acetic acid reflux **(Scheme 19)** [33].



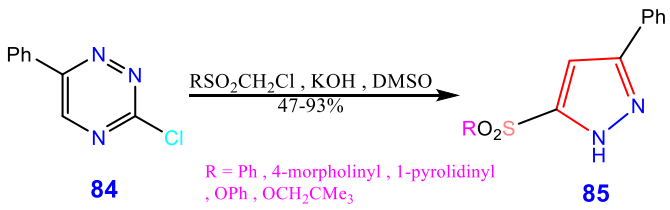
Scheme 19: Conversion of 3-methyl-6*H*-1,3,4-thiadiazine to 5-aminopyrazoles

When fumaronitrile and tetrazolyl acroleins **82** react in xylene at 140 °C, the corresponding pyrazole formation **83** is produced (Scheme 20) [34].



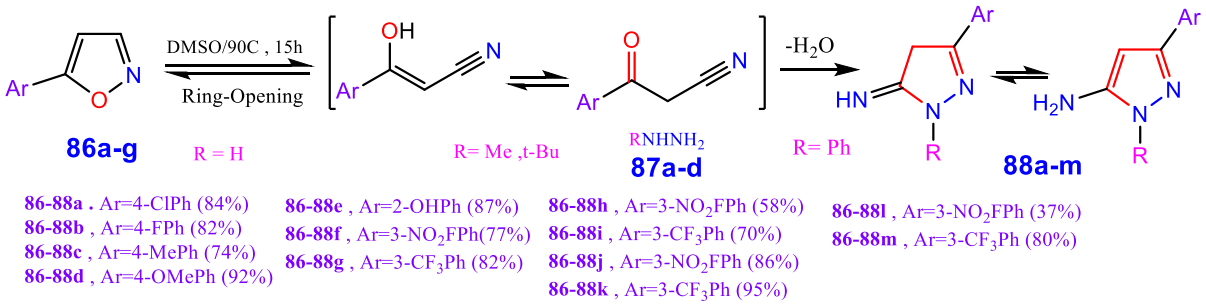
Scheme 20: Synthetic route to cyano-pyrazoles

Rykowski et al [35] produced the corresponding pyrazoles **85** by condensation of 3-chloro-6-phenyl-1,2,4-triazines **84** on α-chlorosulfonyls derivatives in the presence of potassium hydroxide **(Scheme 21).**



Scheme 21: Synthesis of sulfonyl-pyrazole

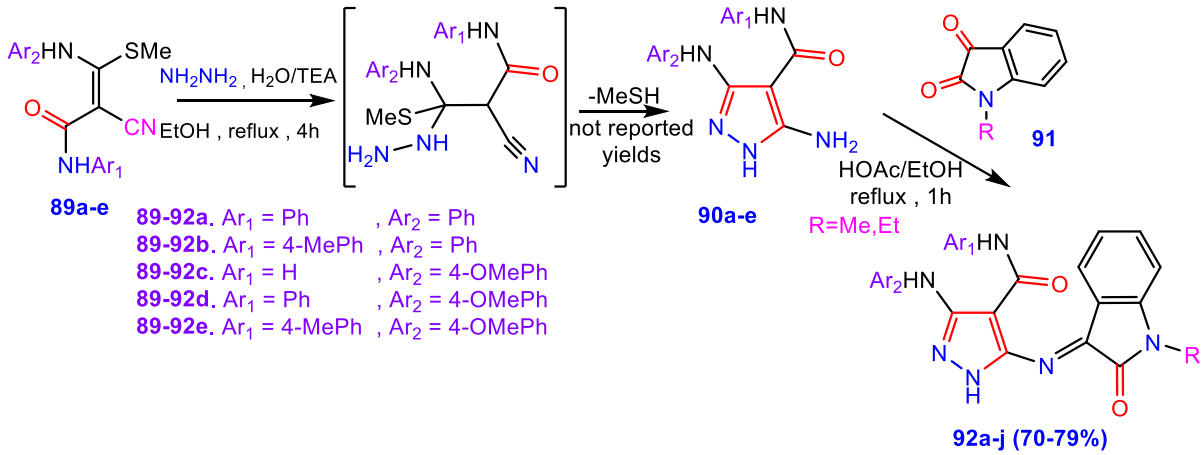
As the synthetic counterparts of ketonitriles **86**, a regioselective synthesis of amino-pyrazoles from isoxazoles **86a-g**. Through ring-opening, the reaction produces an intermediate keto-nitrile **86**, which subsequently combines with the hydrazine derivatives **87a-d** to give the corresponding product of cyclo-condensation **88a-m (Scheme 22)** [36].



86-88a . Ar=4-ClPh (84%)
86-88b , Ar=4-FPh (82%)
86-88c , Ar=4-MePh (74%)
86-88d , Ar=4-OMePh (92%)
86-88e , Ar=2-OHPh (87%)
86-88f , Ar=3-NO_2FPh(77%)
86-88g , Ar=3-CF_3Ph (82%)
86-88h , Ar=3-NO_2FPh (58%)
86-88i , Ar=3-CF_3Ph (70%)
86-88j , Ar=3-NO_2FPh (86%)
86-88k , Ar=3-CF_3Ph (95%)
86-88l , Ar=3-NO_2FPh (37%)
86-88m , Ar=3-CF_3Ph (80%)

Scheme 22: Synthesis of amino-pyrazoles from isoxazoles **86a-g**

In 2021, Hassan and associates reported that pyrazole-oxo-indole hybrid systems **92a-g** were produced via the reaction of 5-aminopyrazoles **90a-e** with N substituted isatin **(Scheme 23)** [37]**.** 2-cyano-3-methyl-thio-N-aryl-3-aryl-amino Hetero-amines **90a-e** were produced by cyclo-condensing acrylamides **89a-e** with hydrazine derivative. The substitution of arylamines and amides at positions 3 and 4 in intermediates allows for a range of post-functionalization of the core.



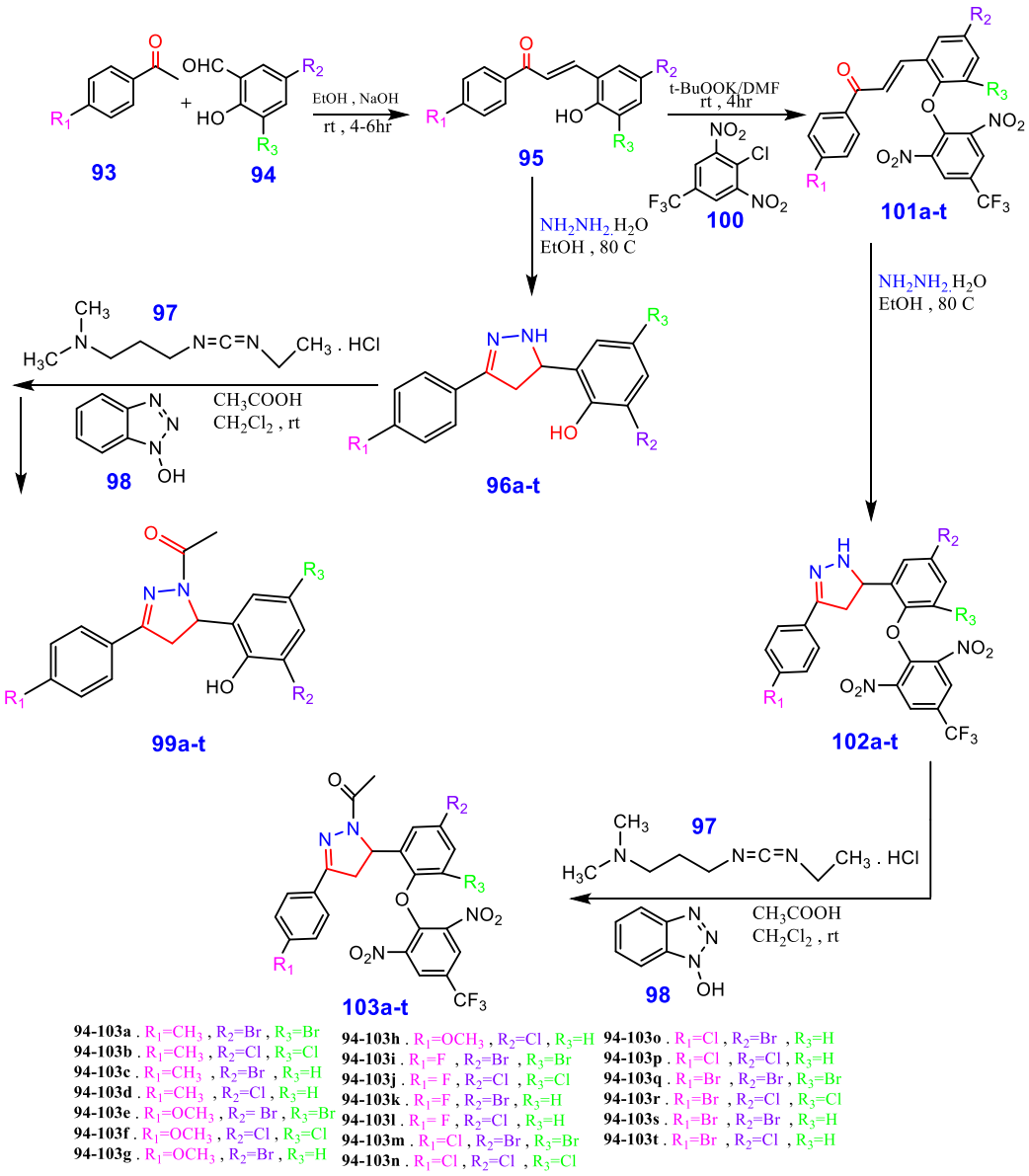
89-92a. Ar_1 = Ph , Ar_2 = Ph
89-92b. Ar_1 = 4-MePh , Ar_2 = Ph
89-92c. Ar_1 = H , Ar_2 = 4-OMePh
89-92d. Ar_1 = Ph , Ar_2 = 4-OMePh
89-92e. Ar_1 = 4-MePh , Ar_2 = 4-OMePh

Scheme 23: Synthetic process of hybrid pyrazole-oxo-indole

2.3 From aromatic derivatives

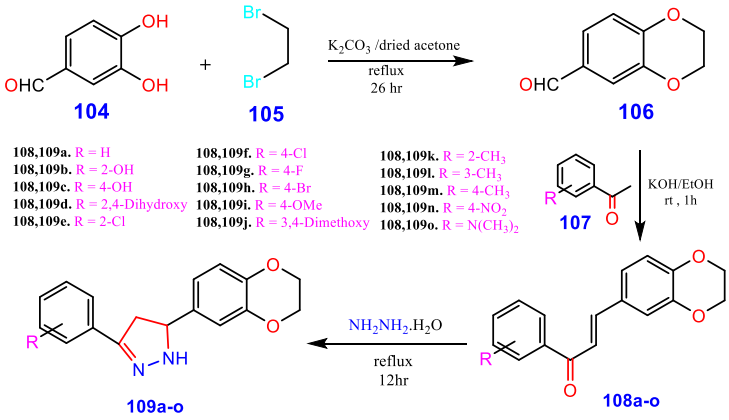
Using chalcones and hydrazine hydrate, Liu et al. synthesized 4,5-dihydro-2*H*-pyrazole 2-hydroxyphenyl derivatives as BRAF inhibitors using 40% KOH as a catalyst, the substituted acetophenones **93** and substituted salicylaldehyde **94** produced the chalcones **95a-t**. By treating the solution of compounds **96a-t** with 1-ethyl-3 dimethylaminopropyl-carbodiimide (EDC) and hydroxy benzotriazole (HOBT), the N-acetyl group was added to produce the final products **99a-t** [38]. Additionally, they described a somewhat altered synthetic pathway for the synthesis of 4,5-dihydro-1*H*-pyrazole derivatives **103a-t** as inhibitors of DNA gyrase. First, 1-chloro-2,6-dinitro-4-trifluoromethylbenzene was allowed to react with the chalcones **95** in the presence of **101a-t** is produced

by potassium *tert*-butoxide and subsequently reacted with hydrazine hydrate in refluxing ethanol for eight hours. The solution of compound **102a-t** was then treated with EDC and HOBT to provide the intended product **103a-t** [38,39] **(Scheme 24).**



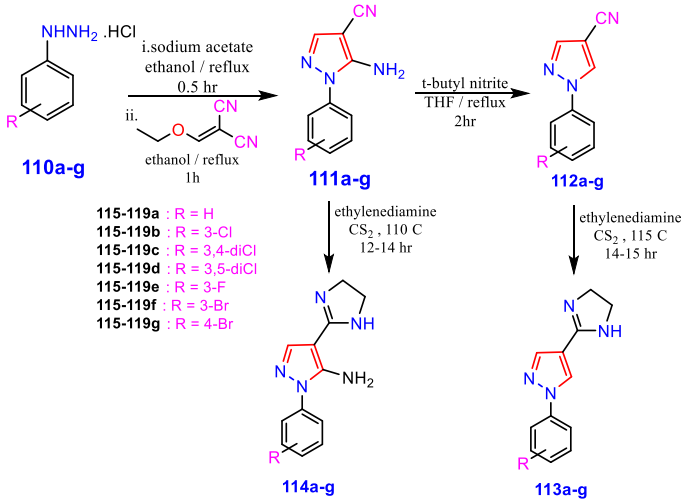
Scheme 24: Synthesis method of 4,5dihydro1Hpyrazole derivatives **108a-t**

A method was proposed by Khalilullah et al [40] to synthesis a series of pyrazole derivatives **109a-o** from chalcones and hydrazine hydrate as antihepatotoxic drugs. by reacting 3,4-dihydroxy benzaldehyde **104** and ethylene dibromide **105** with anhydride K_2CO_3, the starting material 2,3-dihydro-1,4-benzodioxane-6-carbaldehyde **106** was created. This condensation with substituted acetophenone **107** produced corresponding chalcones **108a-o**, which were then treated with hydrazine to produce pyrazole derivatives **109a-o (scheme 25)**.



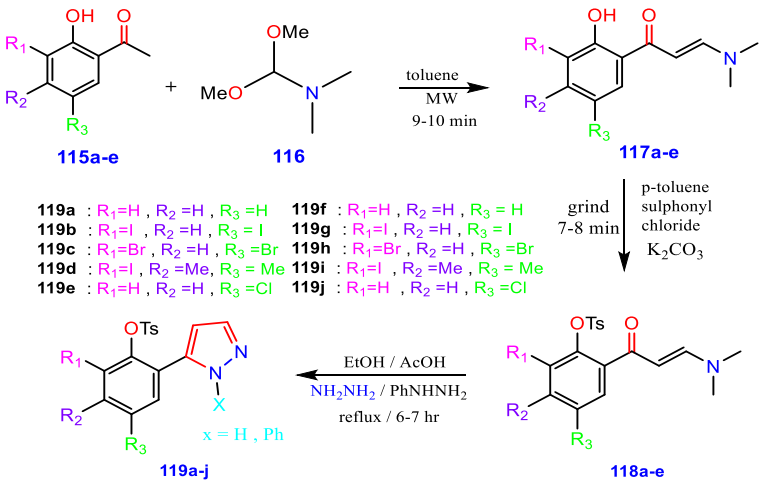
Scheme 25: Multiple steps synthesis a series of pyrazole derivatives **114a-o**

Santos et al. [41] presented a successful synthesis of 1-aryl-4-(4,5-dihydro-1H-imidazol-2-yl)-1*H*-pyrazoles **113a-g** and 5-amino-1-aryl-4,4,5-dihydro-1H-imidazol-2-yl-1*H*-pyrazoles **114a-g** are synthesized from intermediates **111a-g**, which are generated using ethoxy-methylene malonitrile and arylhydrazine hydrochlorides **110a-g**. These intermediates then undergo aprotic deamination with ter-butyl nitrite, resulting in the formation of pyrazole carbonitriles **112a-g**. In conclusion, ethylenediamine and carbon disulphide were employed to accomplish the objectives **(Scheme 26).** [41,42]



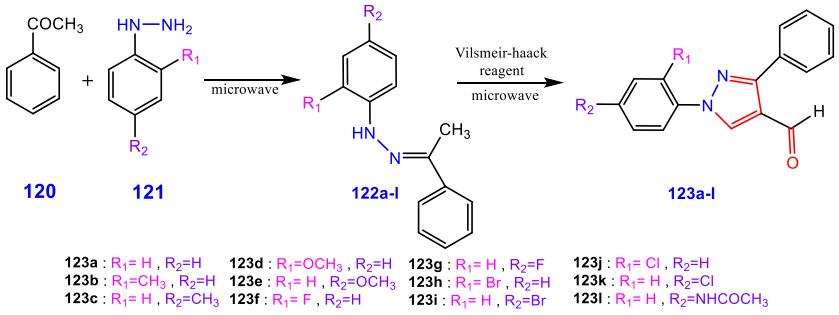
Scheme 26: Synthesis of amino-imidazole-pyrazole derivatives

Kendre et al. [43] synthesized some novel 1*H*-pyrazole compounds with an aryl sulfonate moiety that functioned as COX2 inhibitors **(Scheme 27).** By reacting 2-hydroxy acetophenone **115a-e** [44],with N,N-dimethyl formamide dimethyl acetal (DMF-DMA) **116** under microwave irradiation, the intermediate **117a-e** was produced in this synthetic route [45]. When it reacted with *p*-toluene sulfonyl chloride in the presence of anhydride K_2CO_3 as a catalyst afforded the products **118a-e** witch reacted with hydrazine hydrates to produce **119a-f**.



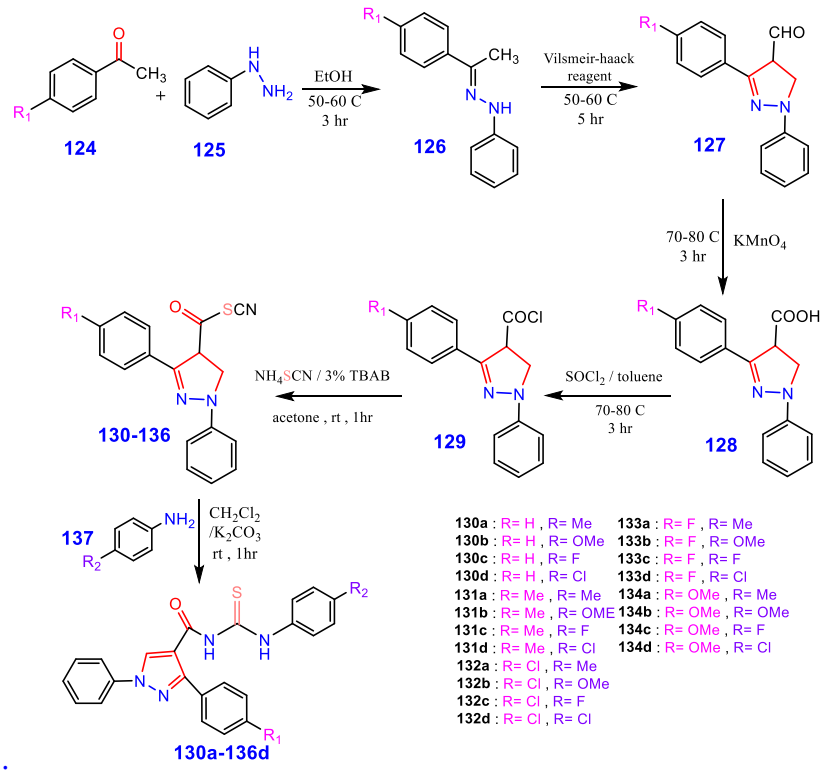
Scheme 27: Novel 1*H*-pyrazole compounds with an aryl sulfonate moiety

Selvam et al. [46] presented an alternative microwave-assisted synthesis method for the production of pyrazole-4-carbaldehyde, which exhibits anti-inflammatory and analgesic properties. Through this approach, 1-substituted phenyl-2-phenylethylidene hydrazino **122a-l** was synthesized via microwave exposure of acetophenone **120** and substituted aryl hydrazine **121**, followed by the Vilsmeir-Haack reaction to yield the target compounds **123a-l**. **(Scheme 28).**



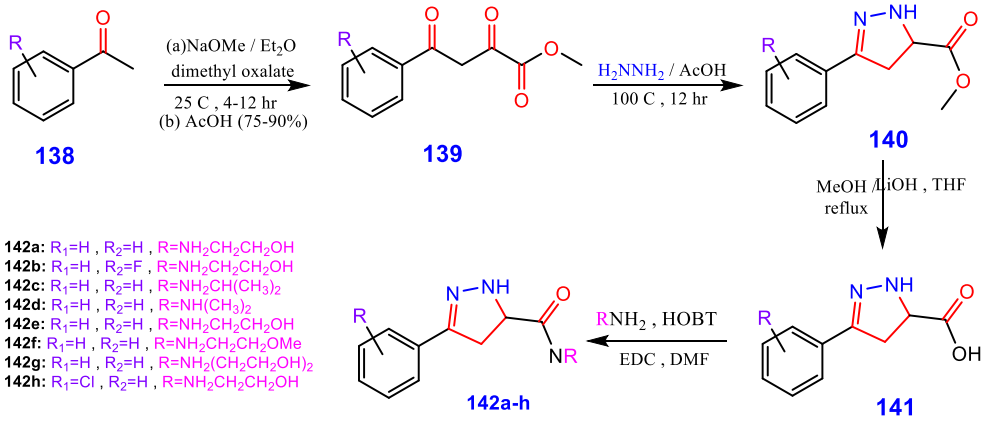
Scheme 28: Synthesis of pyrazole aldehydes via Vilsmeir-Haack reaction

Sun et al [47] reported a similar synthesis approach that involved cyclization and condensation of phenyl hydrazine with several substituted acetophenones, followed by the Vilsmeier-Haack reaction. This synthesis approach involved the interaction of substituted cyanic 1,3-diphenyl-1*H*-pyrazole-4-carboxylic thioanhydride **130-136** with substituted anilines to create a sequence of 1,3-diphenyl-N phenyl carbamothioyl-1*H*-pyrazole-4-carboxamide derivatives **130a-136d**. **(Scheme 29)**



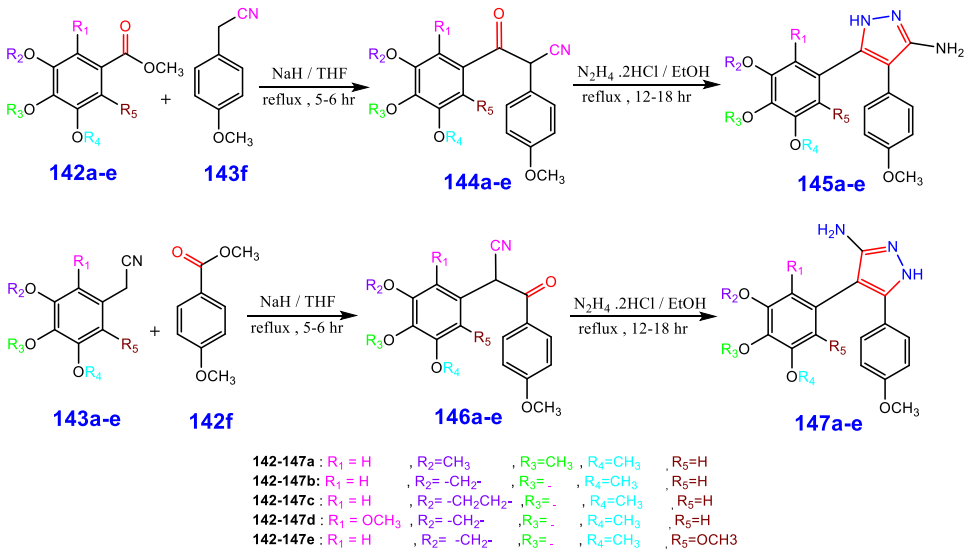
Scheme 29: Synthesis method of functionalized of pyrazole derivatives **135a-141d**.

Pyrazole amides **142**, which are selective inhibitors of tissue-nonspecific alkaline phosphatases, were synthesized from pyrazole-carboxylic acids **(Scheme 30)** [48]. These acids were produced when 1,3-dicarbonyls was produced by reacting acetophenone derivatives with sodium methoxide and dimethyl oxalate. Following the reaction of diketone derivatives **139** and hydrazine, pyrazole ester **140** was produced, which upon saponification gave rise to pyrazole-carboxylic acids **141**.



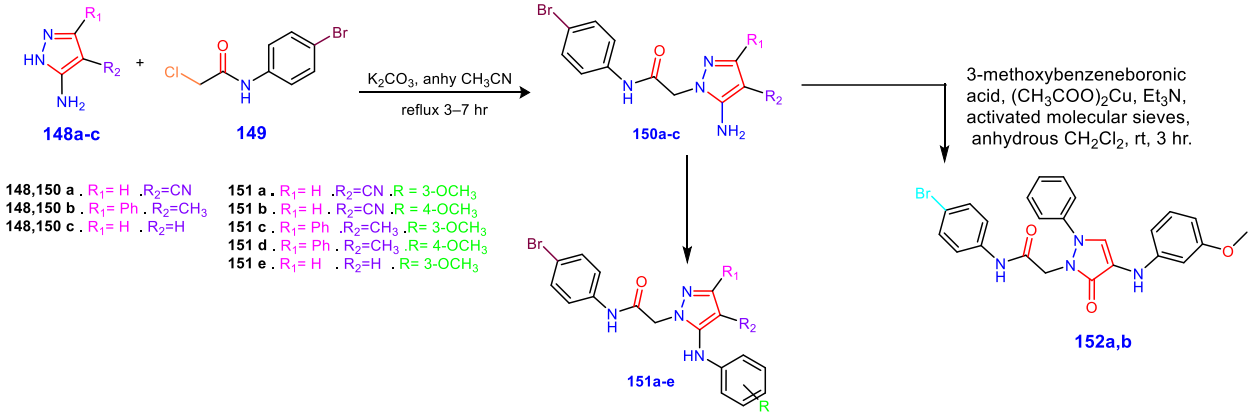
Scheme 30: Four steps synthesis of Pyrazole amides

A highly regioselective method for synthesizing cis restricted 3-amino pyrazole **(Scheme 31)** [49]. Using hydrazine hydrochloride, esters **148** and aromatic acetonitrile **149** undergo base-mediated condensation to produce α-keto-nitriles **150** and **152**, which then cyclized into pyrazoles **151a-e** and **153a-e**.



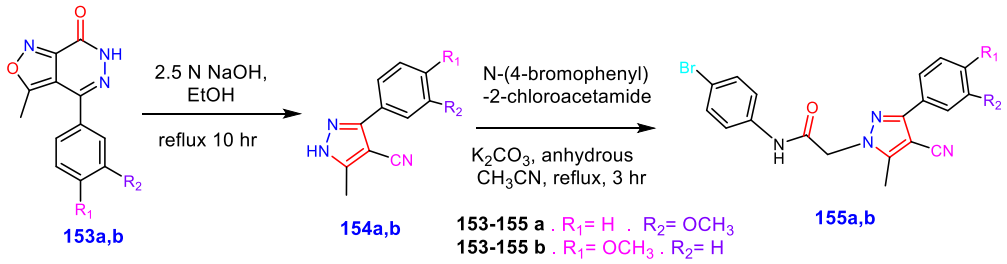
Scheme 31: Synthesis of novel amino-pyrazole derivatives from esters and acetonitrile derivatives

The synthetic routes to the pyrazole derivatives, altered at positions 3-, 4-, and 5-, are illustrated in **(schemes 32)** [50]. Compounds **151** were synthesized from the suitable commercially available precursors **148**, which were treated with N-4-bromophenyl-2-chloroacetamide in anhydrous CH_3CN to provide the intermediate 5-aminopyrazoles **150**. A coupling process between **150** and the appropriate 3- or 4-methoxybenzeneboronic acid, using copper (II) acetate and Et_3N as catalysts, yielded the final required compounds **151**. The synthesis process for the new pyrazolones **152**, which exclude the 4-Br-phenylacetamide chain at the pyrazolone N-1 position. The appropriate pyrazolones **152a** and **152b** underwent alkylation with fragment 2, resulting in the formation of **152a** and **152b**, respectively. The subsequent two compounds were coupled with 3-methoxy boronic acid to produce the desired pyrazole.



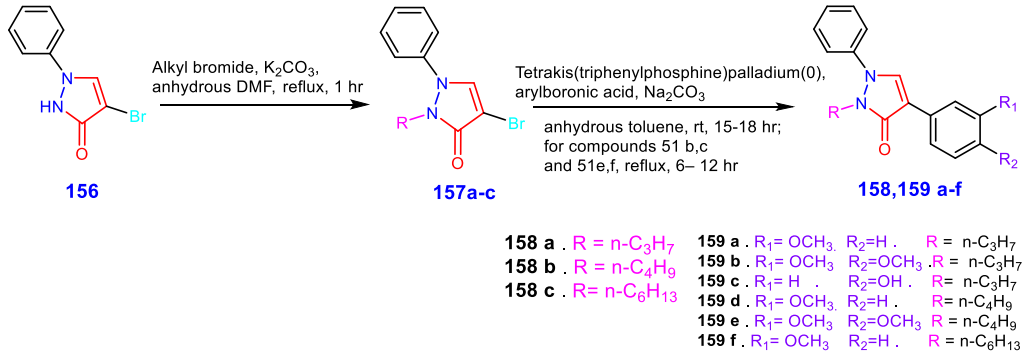
Schemes 32: Synthesis of some pyrazole derivatives

Conversion of isoxazolo-pyridazinones **154** into the appropriate 5-methylpyrazole allowed for the production of **155a,b (Scheme 33)** [51].



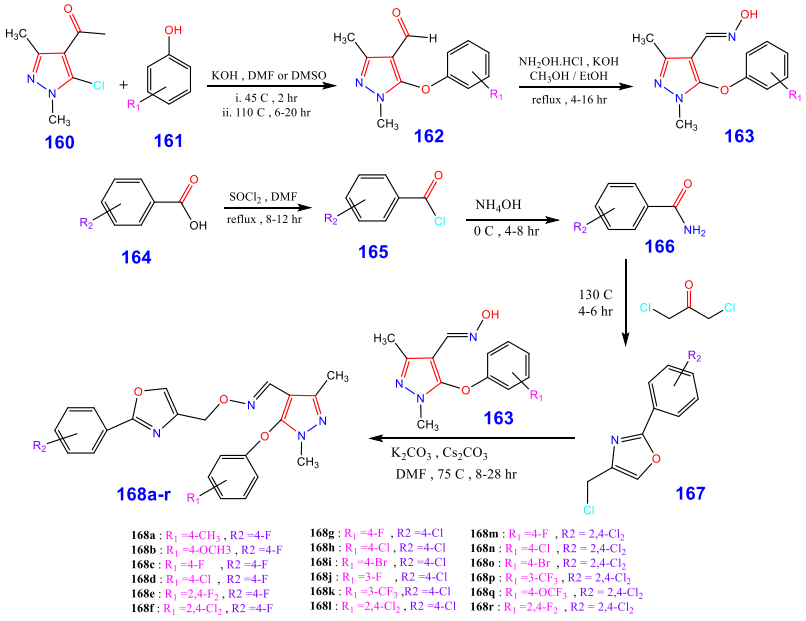
Scheme 33: Synthesis of cyano-amide-pyrazole derivatives

The starting compound **156** was reacted with the appropriate alkyl bromide under standard conditions to generate derivatives **157a-c**, which present an alkyl chain at N-1 of pyrazolone. These intermediates, **157a-c**, were then converted into compounds **158a-f** and **159 a-f** through a cross-coupling reaction with the appropriate aryl boronic acid, palladium (0) *tetra*-kis triphenylphosphine (Tetrakis), and Na_2CO_3 in anhydrous toluene, as shown in **Scheme 34** [51].



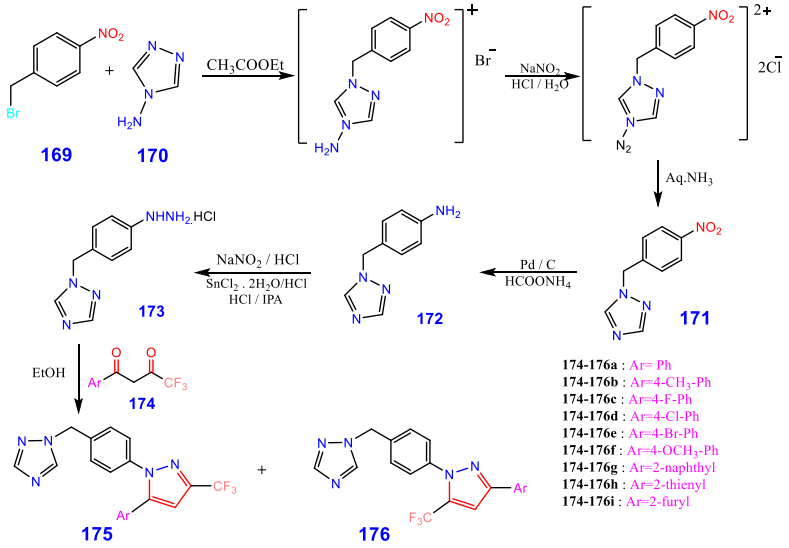
Scheme 34: Pd catalysed synthesis of pyrazalone derivatives

Starting with pyrazole aldehyde **162**, some researchers reported a synthesis pathway of pyrazole derivatives **168a-r** with an oxazole ring that exhibited fungicidal, insecticidal, and acaricidal properties. After being treated with hydroxylamine, aldehyde **162** was immediately transformed into the crucial intermediate **163**. Using substituted benzoic acid **164**, intermediate 4-chloromethyl-2- aryl-oxazole was subsequently made. The target chemical was created via a subsequent reaction between **163** and **167** under conditions that promoted Cs_2CO_3 **(Scheme 35)** [52].



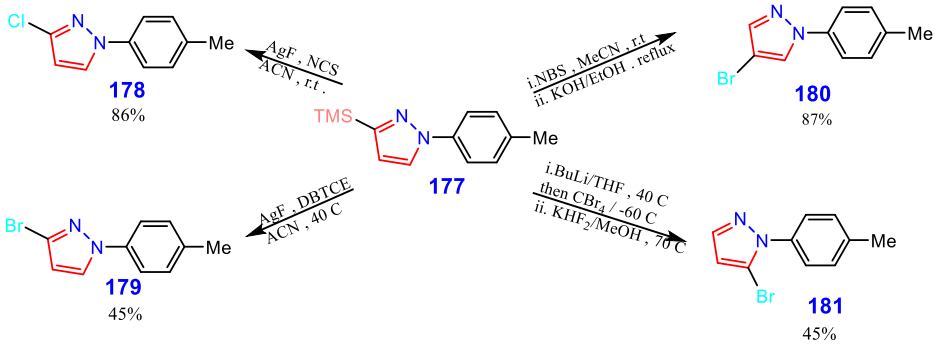
Scheme 35: Synthesis pathway of pyrazole derivatives **168a-r** with an oxazole ring

Using 4-hydrazinophenyl methyl-1*H*-1,2,4-triazole hydrochloride, Chandna et al. have devised an intriguing synthesis of pyrazolyl benzyl triazole derivatives **175, 176** as cyclooxygenase inhibitors. Condensation of 4-nitrobenzyl bromide and 4-aminotriazole in ethyl acetate, followed by diazotization and reduction, produced the triazole intermediate. Target compounds were obtained by treating the intermediate with trifluoromethyl-*β*-diketones **174**. **(Scheme 36)** [53].



Scheme 36: Synthesis of regio iso-trifluoro-methyl-pyrazole derivatives

It has been disclosed that 3-trimethylsilyl pyrazole **177** experienced a regioselective halogenation process. Due to their unique properties and orthogonal reactivity, halogen atoms were successfully introduced at positions 3, 4, and 5. Position 3 features the trimethylsilyl group TMS, which can be readily eliminated under mild conditions to generate a carbanion capable of reacting with electrophilic substrates such as N-chlorosuccinimide and 1,2-dibromo *tetra*-chloroethane, resulting in the formation of chlorinated **178** and brominated **179** pyrazoles, respectively. Position 4 exhibits the highest nucleophilicity on the ring; consequently, the TMS group undergoes deprotection following a direct reaction with N-bromosuccinimide. The compound 1-aryl-4-bromopyrazole **189** has been successfully synthesized. Given that position 5 of the pyrazole ring contains the most acidic proton, halogenation at this position can be effectively conducted to yield the corresponding 5-bromopyrazole **181**. This process involves the use of a base such as butyllithium in conjunction with tetrabromomethane, followed by the deprotection of TMS. **(Scheme 37)** [54].



Scheme 37: Synthesis of bromo pyrazole derivatives

4. Biological activities of pyrazole derivatives

Pyrazoles are well documented in the literature to display a diverse array of therapeutic activities, covering antimicrobial [55-58], antifungal [59-62], antitubercular [63-66], anti-inflammatory [67-72], anticonvulsant [73-76], anticancer [77-81], antiviral [82-87], angiotensin-converting enzyme (ACE) inhibition [88-91], neuroprotection [92-95], cholecystokinin-1 receptor antagonism [96-98], and estrogen receptor (ER) ligand activity [99-101].

Within the disciplines of medicinal chemistry and chemical synthesis, pyrazole is a heterocyclic motif that holds significant importance. Though few pyrazole-containing compounds exist in nature, recent studies have indicated that the pyrazole ring is progressively important in the synthesis of pharmaceutical pipelines. Currently sold all throughout the world are more than fifty synthetic medications including pyrazole [102].

The United States Food and Drug Administration (US FDA) has approved more than thirty medications containing pyrazole since 2011, with a peak of six drugs receiving approval in 2019 alone. The pyrazole-containing medications currently available on the market target various clinical conditions, including hereditary angioedema, non-small cell lung cancer (NSCLC), sickle cell disease, cystic fibrosis, rheumatoid arthritis, and others [102].

Numerous pyrazole derivatives have been clinically used as nonsteroidal anti-inflammatory drugs [103,104], including **Ramifenazone 182** analgesic and antipyretic [105]**, metamizole 183** spasm and fever reliever drug [106], **aminophenazone 184** classified as non-narcotic analgesic drug and prescreened for the treatment of anti-inflammatory, antipyretic, and analgesic [107] **phenylbutazone 185** is an anti-inflammatory and antipyretic, primarily for osteoarthritis, rheumatoid arthritis, spondylitis, and Reiter's disease, **sulfinpyrazone 186** is a uricosuric drug used in gout treatment. **Celecoxib 196** is frequently employed to alleviate pain and inflammation. It is utilized for the management of acute pain, arthritis, ankylosing spondylitis, dysmenorrhea, and migraines **(figure 3).**

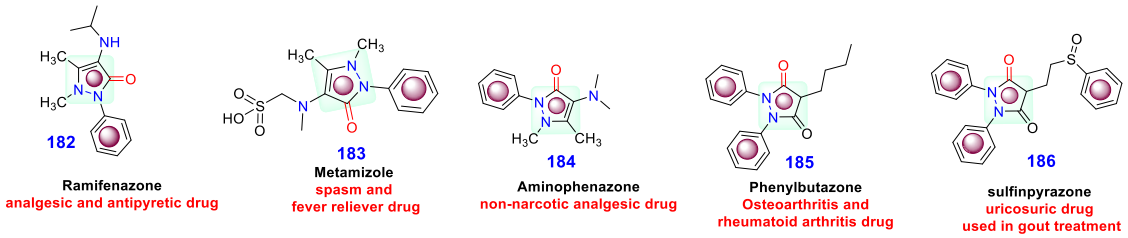


Figure 3: Nonsteroidal anti-inflammatory pyrazole drugs

In the other hand, others marketed drug was widely known for therapeutic treatment of several diseases. In this context, according to Cahill and Ussher (2011) [108], **rimonabant 188** is classified as a cannabinoid-1 receptor antagonist. The level of abstinence from smoking for a period of one year is increased by sixty percent when compared to the placebo [109]. It has been established that the chemical **Lonazolac 189** is both an anti-inflammatory and an anti-hyperglycemic medication [110]. One such small molecule inhibitor of tyrosine kinases is **Axitinib**, also known as **190**, made by Pfizer. The treatment of advanced renal cell carcinoma makes use of it [111]. **Axitinib** blocks angiogenesis, tumor proliferation, and metastasis by targeting and inhibiting vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, and VEGFR-3). **Axitinib** functions by inhibiting the activity of a dysfunctional protein that drives cancer cell proliferation, hence aiding in the cessation or deceleration of cancer cell dissemination [112].

Slightly useful in treating insomnia, **zaleplon 190** mostly addresses trouble falling asleep. By increasing sleep latency, zaleplon drastically lowers the time needed to fall asleep and may thus help with sleep induction instead of sleep maintenance [113-115]. Although zaleplon may be used to help with middle-of-the-night awakenings, its ultrashort elimination half-life makes it unlikely to be useful in lowering early awakenings. Zaleplon has not, however, been found empirically to raise overall sleep duration [116]. One of the medications used to treat pulmonary arterial hypertension and erectile dysfunction is **sildenafil 191**. It helps men achieve and maintain an erection by boosting blood flow to the penis. By reducing tension in the blood vessel walls, **sildenafil** improves blood circulation.

Reversan 192 is a strong modulator of drug resistance driven by MRP1 both in vitro and in vivo. Not only was **reversan** effective in vitro against neuroblastoma, but it also raised the sensitivity of other drug refractory tumor cells (e.g., colon and renal cell carcinoma) to conventional chemotherapeutic agents that were themselves MRP1 substrates [117]. **Reversan** was effective against both MRP1 and P-glycoprotein but not against MRP2-5 according analysis of transporter specificity. **(Figure 4)** [118]

The scientific community makes use of the anxiolytic medicine tracazolate. The non-benzodiazepines are a physically diverse class of medications that share the same receptor targets as benzodiazepines but have different chemical structures. This particular class of drugs includes this pyrazolo pyridine derivative, which is most closely related to pyrazolopyrimidine drugs like **zaleplon**.

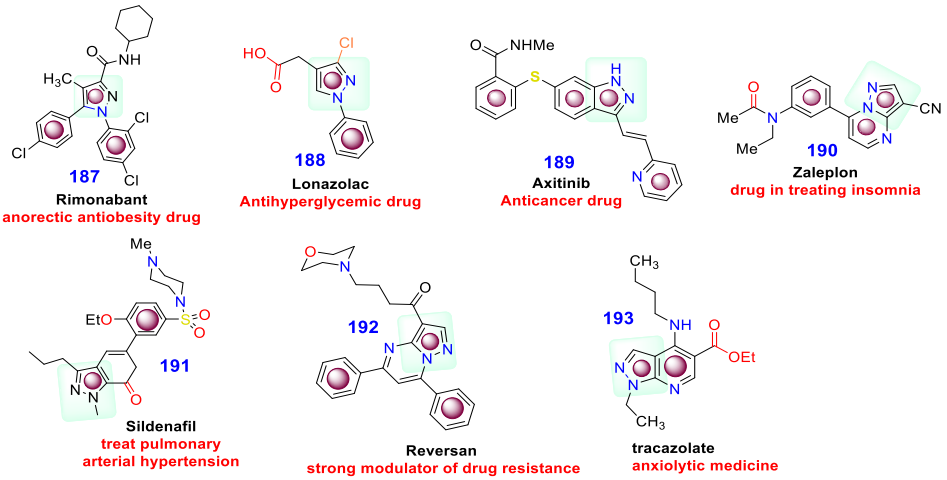
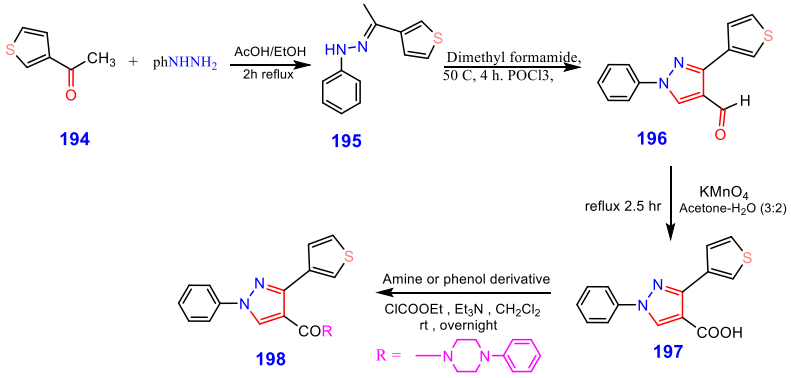


Figure 4: Marketed pyrazole drug

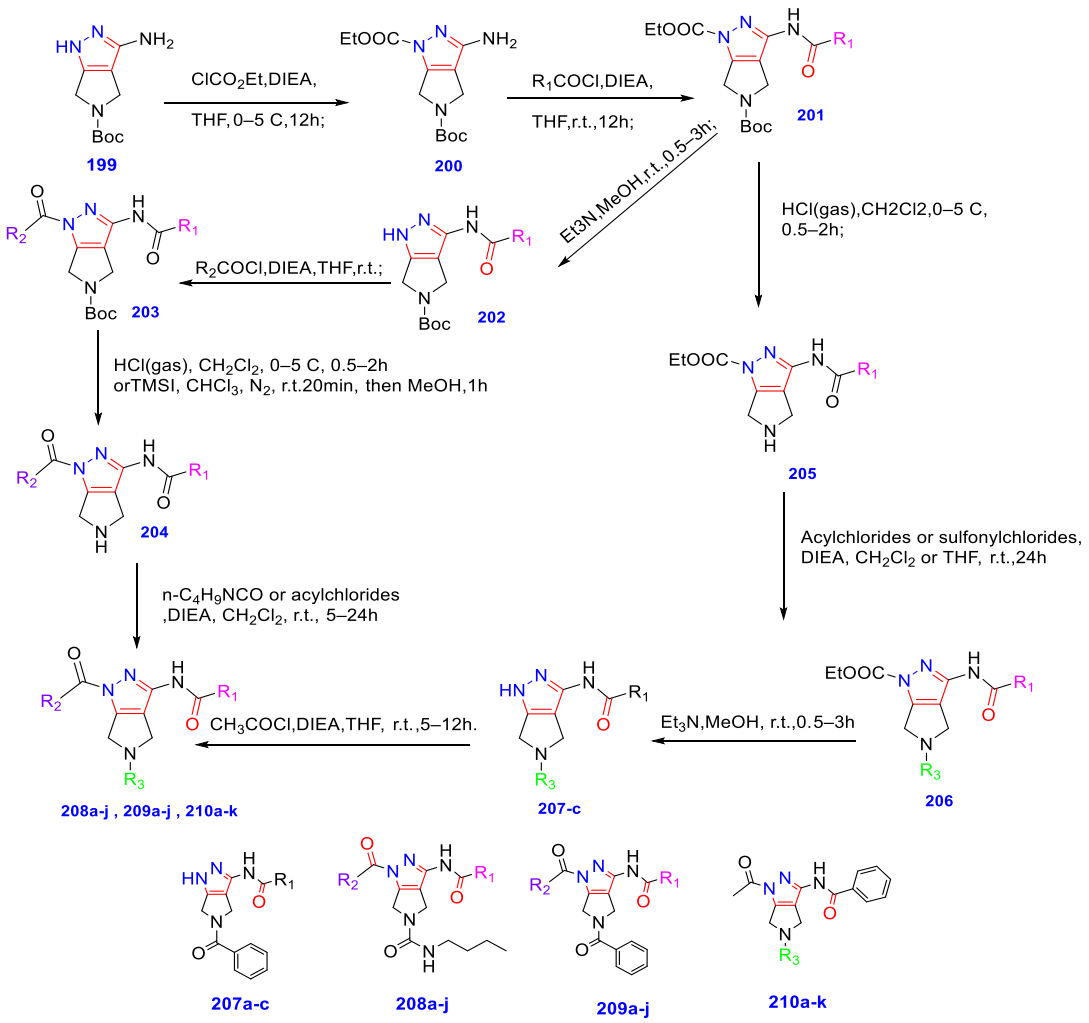
4.1 Anticancer Activity:

New and effective anticancer medications have been developed through extensive research into the pyrazole family, an essential heterocyclic group with anticancer properties. The unregulated growth of malignant cells is a defining characteristic of this disease. An effective technique to fight cancer is believed to be the blocking of proliferative pathways. Many compounds like 1-phenyl-3-thiophen-3-yl-1*H*-pyrazole-4-carboxylic acid or its ester or amide derivatives were found to have anticancer effects. The compound **198**, which contains a phenyl-piperidine group in its amide component, outperformed all of the other produced amide derivatives in terms of inhibitory effects and performance against the HL60 and Raji cell lines. **(Scheme 38)** [118].



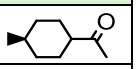
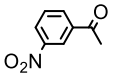
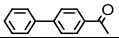
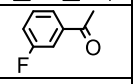
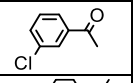
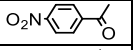
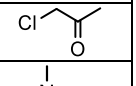
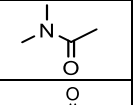
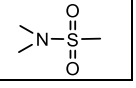
Scheme 38: Preparation of thiophene phenyl-1*H*-pyrazole carbaldehyde

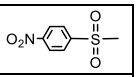
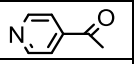
Their subsequent approach involved the development and synthesis of many novels 1-acyl-3-amino-1,4,5,6-tetrahydropyrrolo[3,4-c] pyrazole compounds. After evaluating the in vitro anticancer activity of their derivatives against the human colon carcinoma HCT-116 cell line, compounds **209a** and **209b** were chosen for further evaluation. which were tested in vitro against five additional human cancer cell lines. The bulk of the target compounds have robust anticancer characteristics in vitro, as these results indicate. The activity of synthetic compound **209a** against 12 kinases was studied, and then its contact way was determined through docking studies with glycogen synthase kinase-3b (GSK3b) and cyclin-dependent kinase 5 (CDK5). There was a significant increase in activity compared to (R)-roscovitine (IC_{50}:16.38μM) when compounds **207a-c, 208a-b,** and **210a,g**, and **210k** were included. It was found that **209a**, the most powerful compound with an IC_{50} of 0.58 μM, was 4-28 times more effective than (R)-roscovitine against six different types of human cancer cells. **(Scheme 39)** [119].



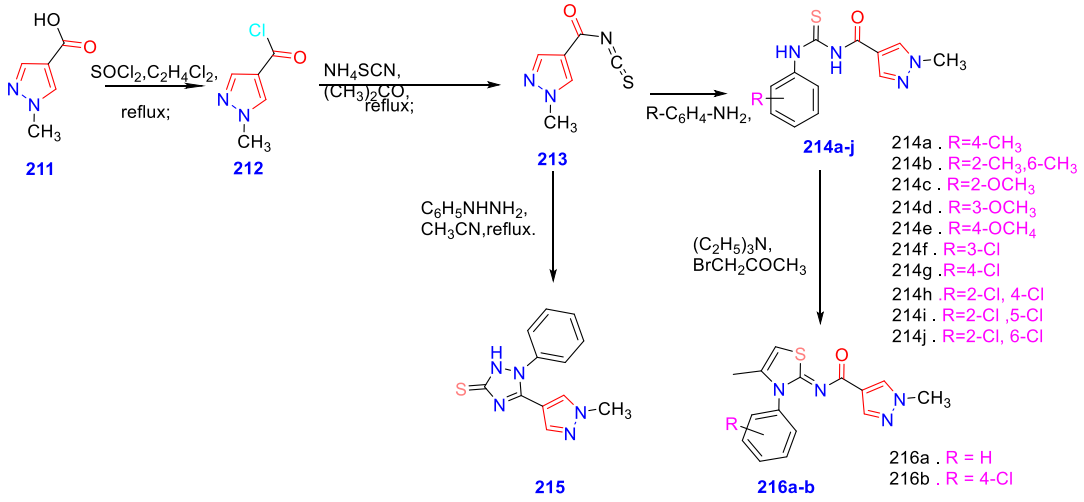
Scheme 39: New 1-acyl-3-amino-1,4,5,6-tetrahydropyrrolo[3,4-c] pyrazole derivatives as anticancer activity

Table 1: Substituted acyl-3-amino-pyrazole derivatives

compound	R1	R2	compound	R1	R2	compound	R3
208a	Ph	cyclopropyl	**209a**	Ph	-Me	**210a**	
208b	Ph	Ph	**209b**	Ph	-Et	**210b**	
208c	4-CH_3-Ph	cyclopropyl	**209c**	Ph	-Pr	**210c**	
208d	4-CH_3-Ph	Ph	**209d**	Ph	Cyclopropyl	**210d**	
208e	4-F-Ph	cyclopropyl	**209e**	Ph	Ph	**210e**	
208f	4-F-Ph	Ph	**209f**	Ph	Bn	**210f**	
208g	4-OCH_3-Ph	cyclopropyl	**209g**	4-F-Ph	cyclopropyl	**210g**	
208h	4-OCH_3-Ph	Ph	**209h**	4-F-Ph	Ph	**210h**	
208i	Bn	cyclopropyl	**209i**	4-OCH_3-Ph	cyclopropyl	**210i**	

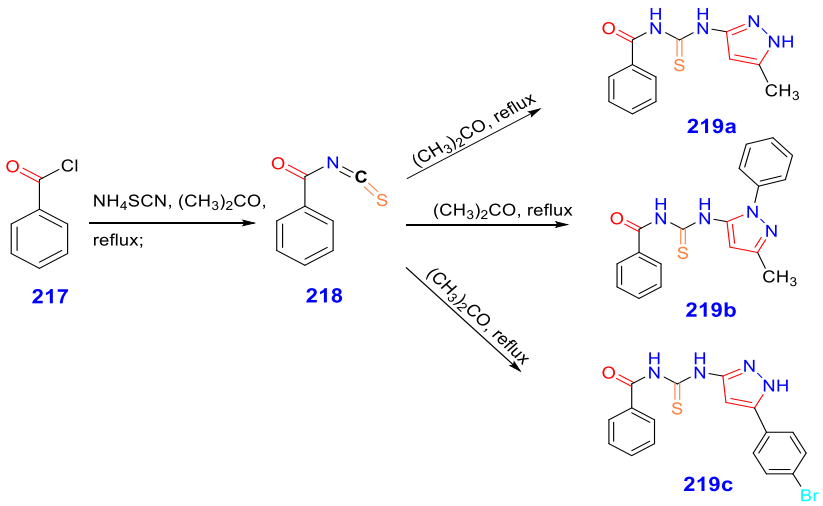
208j	Bn	Ph	**209j**	4-OCH_3-Ph	Ph	**210j**	
207a	Ph	-				**210k**	
207b	4-F-Ph	-					
207c	4-OCH_3-Ph	-					

The studied N-(1-methyl-1H-pyrazole-4-carbonyl)-N'-(aryl) thioureas **214** did not demonstrate any significant impact on cancer cells, except for a limited number of cell lines that showed a growth suppression exceeding 50%. Through the process of addition. The inhibitory activity decreases when the thiourea moiety is linked to a 1,2,4-triazole-3-thione ring, as demonstrated in compound **215**. The anticancer effects are enhanced when the thiourea group is converted into a thiazol-2 (3*H*)-ylidene ring. SCHN renal cells, DU-145 prostate cancer cells, SK MEL-2 melanocytes, and HCT-15 and HT29 colon cells exhibit the highest susceptibility to the anticancer effects of compounds **216a** and **216b**. **(scheme 40)** [120].



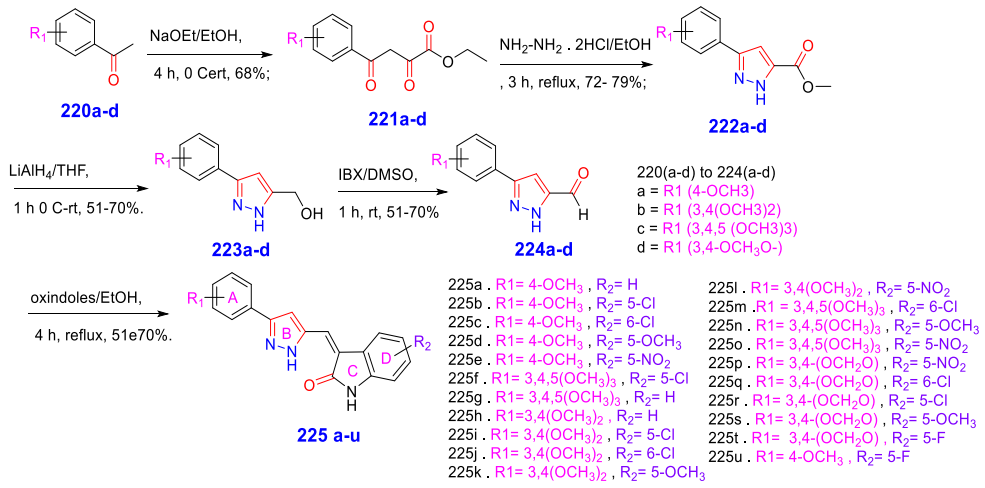
Scheme 40: Synthetic process of *N*-1-methyl-*1H*-pyrazole-4-carbonyl-N-aryl thioureas

The thiourea derivatives **219a** exhibit a minor impact on the proliferation of most of the tested cell lines. The introduction of a phenyl group at position 1 of the pyrazole ring **219b** markedly improves anticancer efficacy; however, the stimulatory effect is considerably diminished, with the most pronounced inhibitory effects observed in leukemia cells. The acyl-alkyl function of the pyrazole ring on the thiourea molecule requires inversion for Compound **219c** to exhibit an anticancer effect. The substitution of 4-bromophenyl for methyl in **219a** likely contributed the additional bulk and lipophilicity required to inhibit CDKs. This model is applicable for the synthesis of thiazolylidene derivatives from molecules **219b** and **219c**. Indicates that the **219b**, **c** molecules are expected to undergo a transformation into potentially valuable thiazolylidene derivatives. **(Scheme 41)** [120].



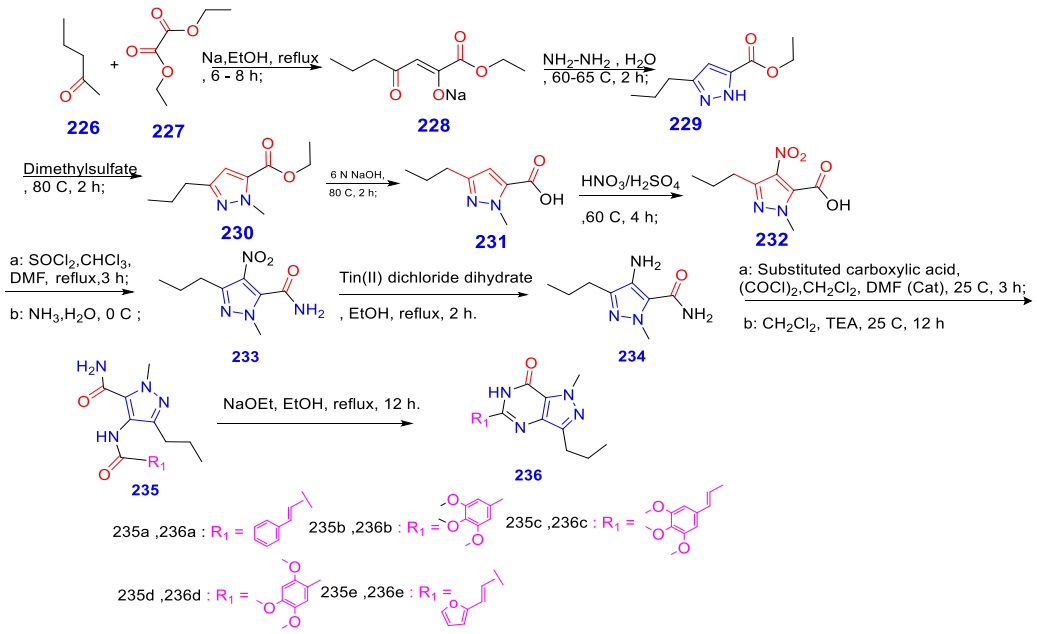
Scheme 41: Thiourea pyrazole as anti-cancer activity

The antiproliferative effects of twenty-one compounds having pyrazole and oxindole conjugates were tested on several human cancer cell lines. These compounds were synthesized by Knoevenagel condensation. Despite their promising anticancer activity against all tested cell lines, congeners **225b**, **225c**, and **225d** exhibited significant cytotoxicity and inhibited tubulin assembly. The range of its IC_{50} values was 3 μM to 7.5 μM. The results of **225b**, **225c**, and **225d** treatments were an increase in cyclin B1 protein, disruption of the microtubule network, and cell accumulation in the G2/M phase. Zebrafish screening revealed that **225b** and **225d** caused developmental problems. As shown in **scheme 42** from the docking investigations, the congeners occupy the colchicine binding pocket of tubulin [121].



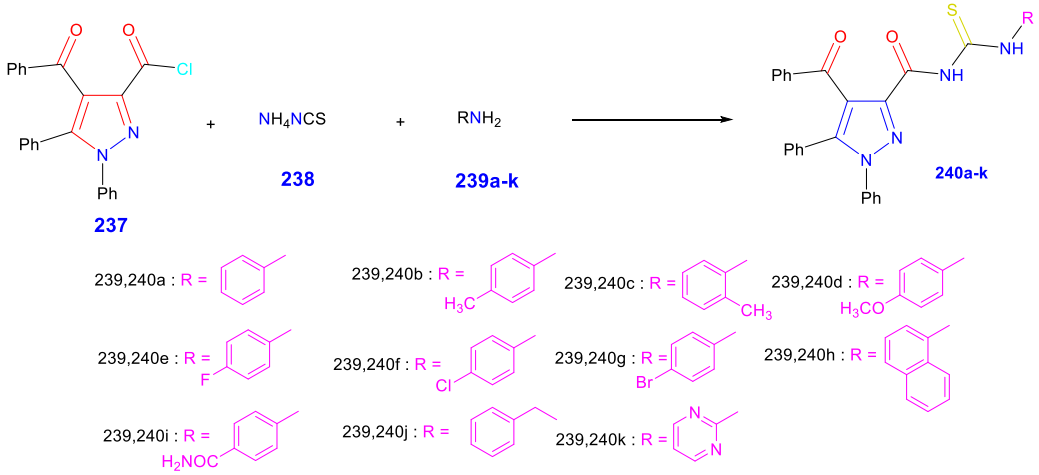
Scheme 42: Synthesis of pyrazole-oxindole conjugates **225 a-u**

The cytotoxic effects of compound **235,236 a-e** against SGC 7901 and MGC-803 cells were investigated in these screening assay tests. We used the human breast cancer cell line Bcap-37 to study its activity with different types of cancer cells. Series 5-propyl-1*H*-pyrazole 3-carboxamide **235** was found to frequently increase inhibitory action. In terms of effectiveness against MGC-803 cells, compound **235a** performed better than the positive control, 5-fluorouracil, with an IC_{50} value of 3.01±0.23 μM. For this structural moiety, precursor compounds manifest better than cyclization compounds. Despite 5-fluorouracil's superior activity against BCAP 37 cells, all the drugs were successful against gastric cancer cells **(Scheme 43)**[122].



Scheme 43: cytotoxic effects of pyrazole-based amide and pyrimidine

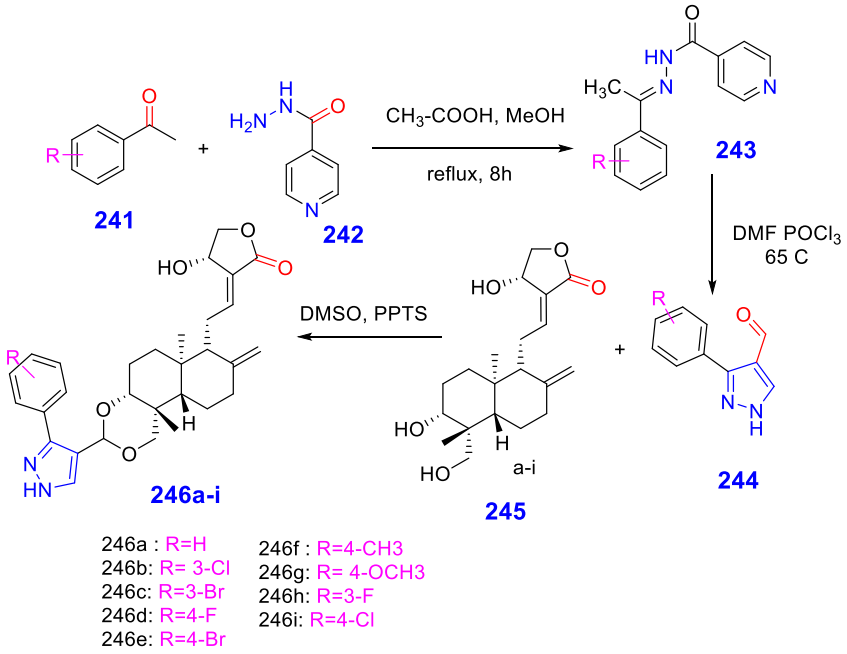
This research assesses the anticancer properties of synthesized pyrazolyl acyl thiourea derivatives on human cancer cell lines, focusing on liver, leukemia, and colon cancer types. Cells were subjected to five concentrations varying from 10^{-4} to 10^{-8} M of compounds. The compounds **240a, 240b, 240d, 240h, 240j** and **240k** exhibited notable inhibition, surpassing 50%, on Jurkat cells at both the 24-hour and 48-hour marks. Compounds **240a, 240d,** and **240f** exhibited anti-tumor activity at the 24-hour mark. All compounds, with the exception of three, exhibited notable anti-cancer activity in both DLD-1 and HepG2 cells. Compounds demonstrate a higher level of inhibition in HepG2 cells relative to DLD-1 cells, and they show a more pronounced inhibitory effect on DLD-1 cells than on Jurkat cells, as indicated by the limited anticancer activity of compounds **240c, 240e, 240g, 240i** and **240k.** Compound **240i** demonstrates the least anticancer activity compared to the other compounds assessed in this study. The **240i** compound demonstrates insufficient efficacy in inhibiting DLD-1 cancer cells, resulting in a survival rate of ninety-five percent among the cells when exposed to it. This group of compounds demonstrates notable anticancer activity in HepG2 cells **(Scheme 44)** [123].



Scheme 44: Tested pyrazolyl-acyl thiourea derivatives for anti-proliferative effect

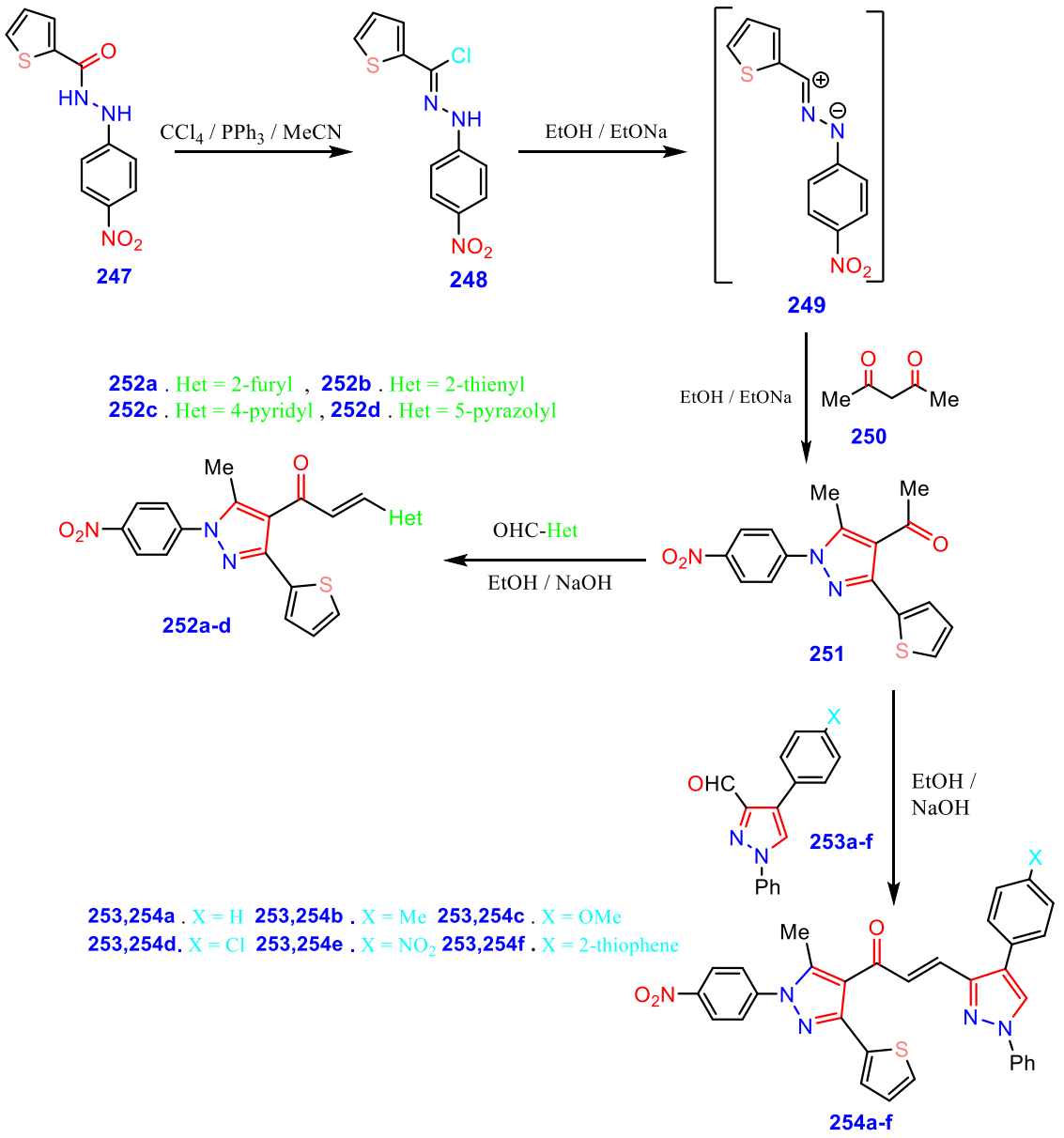
Recently synthesized nine aryl-pyrazole acetals were investigated for their anticancer properties as andrographolide derivatives. To evaluate the nine pyrazole compounds **246a-i** at a dose of 10 µM, the first 60 cell lines in total were used. Seven compounds-more especially, **246a-g** have shown minimum number of cell lines necessary for threshold inhibition. NCI thus chose these seven compounds for maximum dose screening in order to determine their 50% growth inhibitory activity (GI_{50}), total growth

inhibition (TGI), and 50% lethal concentration (LC_{50}) values over all cell lines. The screening results indicate that four compounds, specifically the *para*-bromo-substituted **246e** and *para*-methoxy derivatives **246g**, as well as the *meta*-Br-substituted **246c** and *meta*-Cl-substituted **246b** derivatives, exhibit significant activity and demonstrate favorable GI_{50} values against most of the cell lines tested. Compound **246c** demonstrated the highest efficacy, followed closely by compound **246b**, exhibiting GI_{50} values of 1.28 μM and 2.13 μM, respectively, across nearly all cell lines **(Scheme 45) [**124].



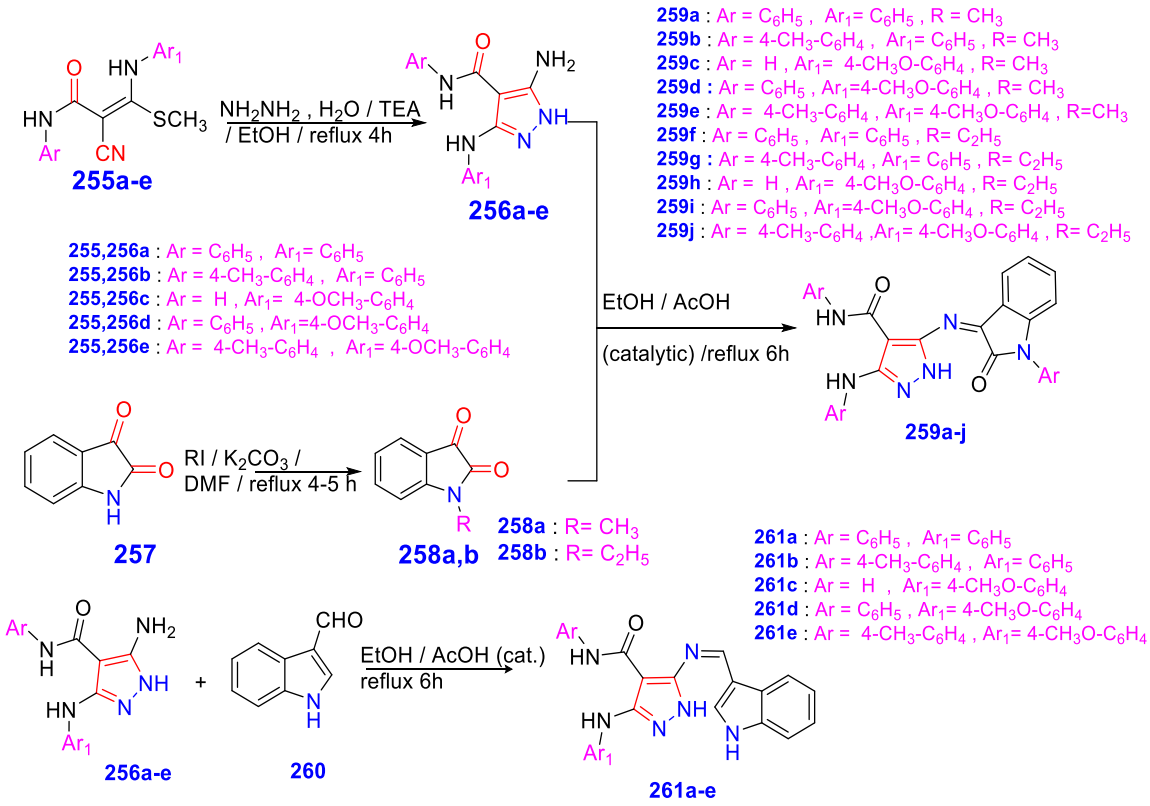
Scheme 45: Synthesis of aryl-pyrazole cyclic acetals via pyrazole aldehyde intermediates.

Special series of pyrazolyl-chalcone compounds were synthesized using the Claisen-Schmidt condensation method. The required chalcone derivatives **253a-d** and **254a-f** in good yields were obtained by reacting the 4-acetyl-5-thiophene-pyrazole with appropriate heteroaryl aldehyde derivatives. Apart from the normal cell line BJ1, in vitro evaluation of the anti-cancer potential of the recently synthesized chalcone derivatives utilizing the three human cancer cell lines MCF7, PC3, and PACA2 revealed. In comparison to the reference medication doxorubicin (IC_{50} = 52.1 μM), compound **254e** had the most promising activity against PACA2 cells (IC_{50} = 27.6 μM). On the other hand, compound 261d demonstrated anticancer efficacy (IC_{50} = 42.6 μM) against MCF7 cells (IC_{50} = 48 μM) compared to the reference drug. Using breast and pancreatic cell lines, we evaluated the gene expression, DNA damage, and DNA fragmentation percentages of compounds **252d** and **254e (Scheme 46)** [125].



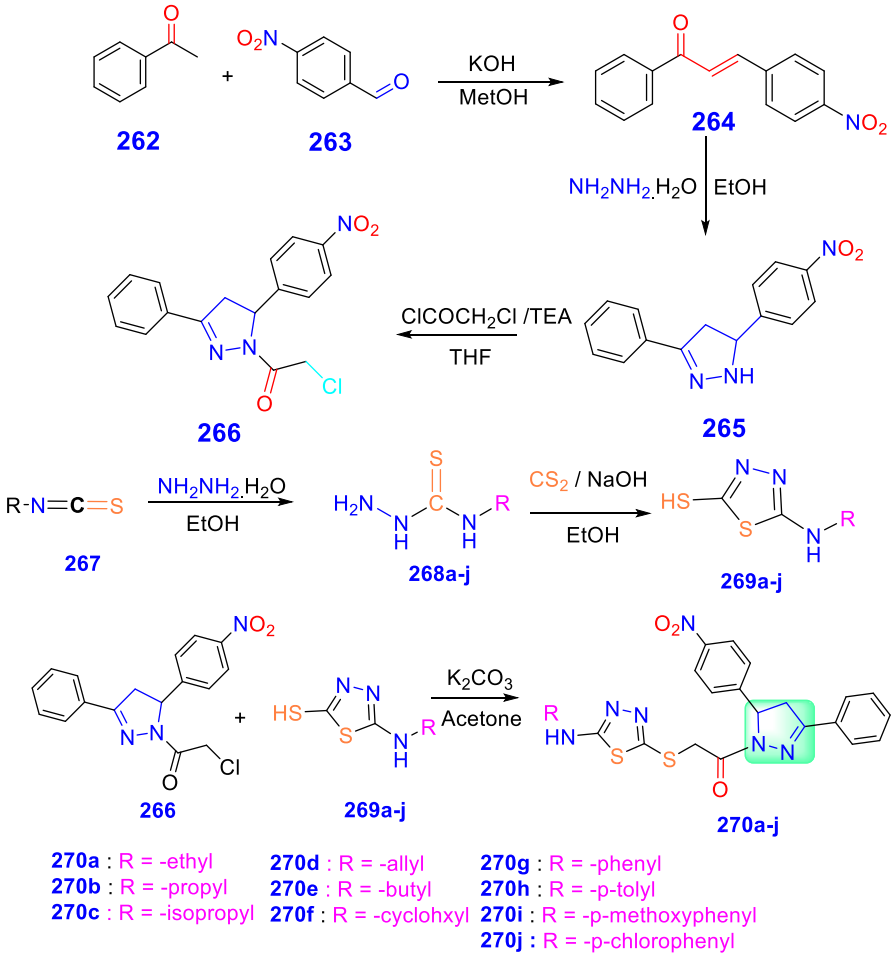
Scheme 46: Synthesis of thiophene bis-pyrazole

A novel approach to drug discovery, molecular hybridization has great promise. A number of novel anticancer medications involving indole derivatives linked to the pyrazole moiety were created and refined through molecular hybridization. To make **259a-j** and **261a-e**, respectively, we employed the 2-aminopyrazoles **255a-e** and N-substituted isatin **258a, b** and 1-*H*-indole-3-carbaldehyde **260**. To define each product, a suite of analytical and spectroscopic techniques was employed. In vitro cytotoxic activities against four human cancer types (HCT-116, MCF-7, HepG2, and A549), as well as a colorectal carcinoma, a breast adenocarcinoma, and a lung malignancy, were assessed for two compounds, **259a-j** and **261a-e**. The results showed that the newly synthesized compounds have good to excellent anticancer efficacy. For example, when tested against the HepG2 cancer cell line, compounds **261a** and **261b** demonstrated better anticancer inhibitory action than the gold standard drug, doxorubicin, with IC_{50} values of 6.1±1.9 and 7.9±1.9 μM, respectively. The next step was to analyze the two powerful anticancer medicines, **261a** and **261b**, in HepG2 cells using flow cytometry to examine cell cycle analysis and apoptosis **(Scheme 47)** [126].



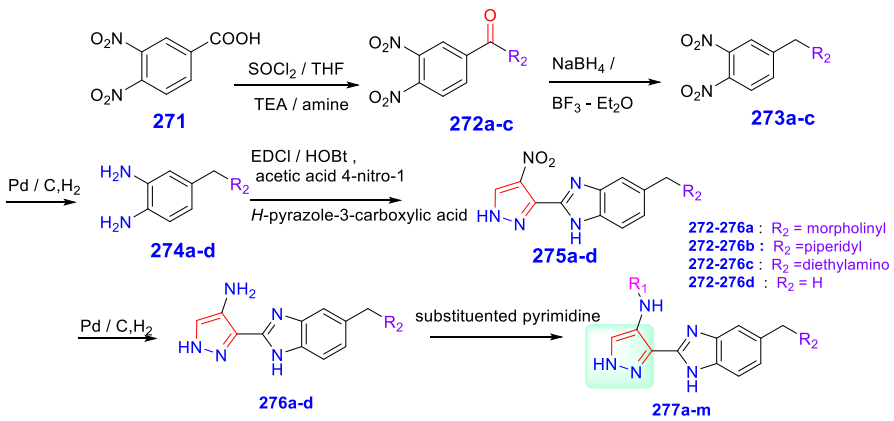
Scheme 47: Synthesis of amide indole pyrazole derivatives

Among the many cancers, lung cancer ranks high in terms of both incidence and fatality. While epidermal growth factor receptor (EGFR) levels are a strong indicator of lung cancer, there is encouraging evidence that EGFR inhibitors may be useful in the fight against the illness. This led to the development of a number of novel EGFR inhibitor candidates that have pyrazole and thiadiazol rings. The activities of the compounds were investigated using the following in vitro assays: cytotoxicity, flow cytometry monitoring of mitochondrial membrane potential (MMP), and EGFR inhibition. MTT is a chemical name for this substance. The A549 cell line was inhibited by compounds **270d**, **270g**, and **270j**, respectively, with IC_{50} values of 5.176±0.164, 1.537±0.097, and 8.493±0.667 μM. Using MMP flow cytometry, we found that compound **270g** has an 80% transmembrane potential. Based on the findings of the EGFR inhibitory experiment, compound **270g** inhibits the EGFR enzyme, as its IC_{50} value is 0.024±0.002 μM. **(Scheme 48)** [127].



Scheme 48: Cytotoxicity of pyrazole connected to thiadiazole rings

There are new pyrazole-benzimidazole compounds on the market. All substances were tested in vitro against cancer cell lines U937, K562, A549, LoVo, and HT29 to see if they inhibited the Aurora A/B kinase. Compounds **277a-l** demonstrated significant inhibitory effects on Aurora A/B kinase as well as on various cancer cell lines. Molecular modeling studies indicated that four hydrogen bonds were formed by the derivatives in the active site of Aurora A kinase. To ascertain the structural elements essential for activity, these compounds were subjected to quantum chemical investigations. Immunofluorescence was utilized to investigate **277k** cellular activity **(Scheme 49)** [128].



Scheme 49: Synthesis of Benzimidazole pyrazole derivatives

4.2 Antimicrobial activity

Their antibacterial activities were tested against *Pseudomonas putida*, Bacillus cereus, *Staphylococcus aureus*, and *Escherichia coli* after they synthesized a variety of 1*H*-pyrazole-3-carboxylic acid derivatives. Compound **278** showed antibacterial action against both Gram-positive and Gram-negative bacteria, making it the best chemical in the series according to the data. A variety of new pyrazoles were synthesized and tested for antibacterial activity; each one had a quinolinyl chalcone group. Compound **279** was the most effective strain-specific antimicrobial and antifungal agent [129,130] **(Figure 5)**.

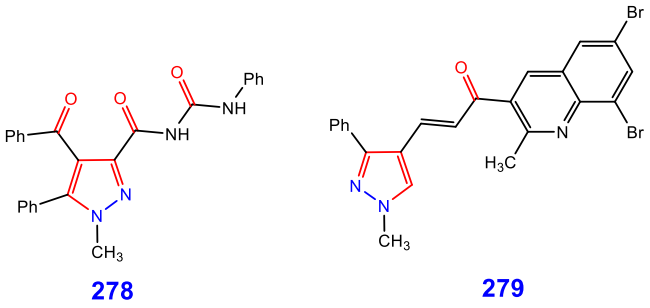
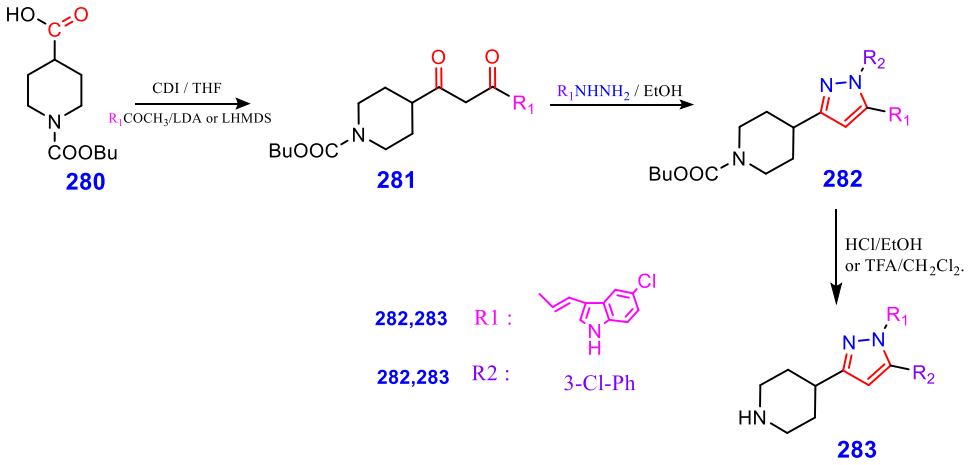


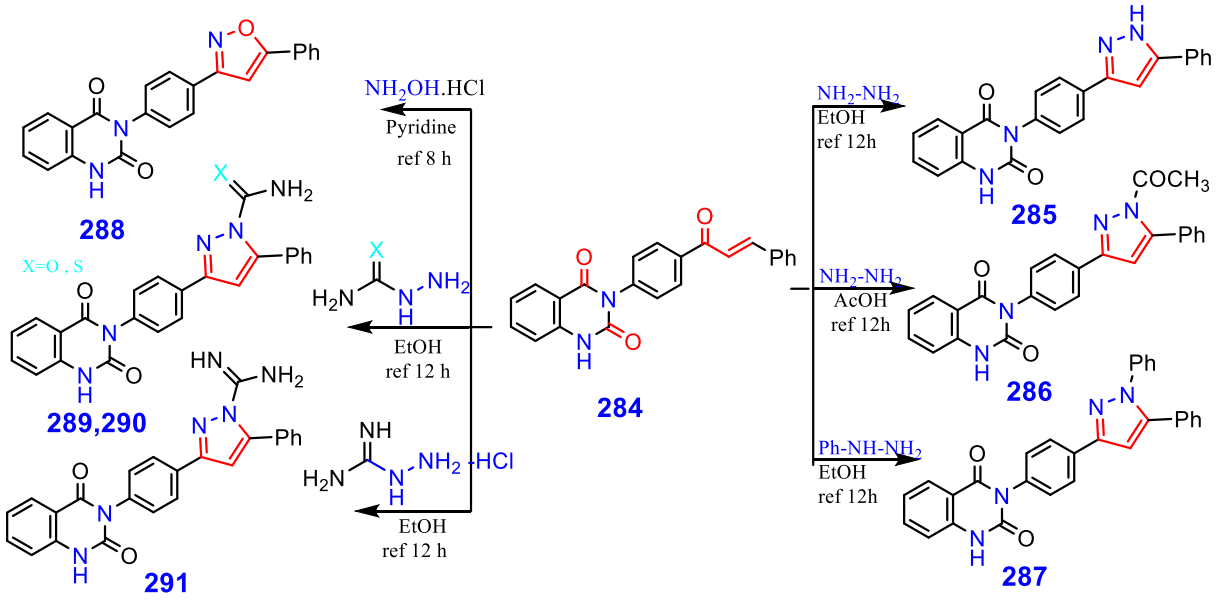
Figure 5: Pyrazole derivatives as antimicrobial compounds

Previously discovered that pyrazole derivative inhibits DNA gyrase and topoisomerase IV, in addition to antimicrobial activity. Novel pyrazole **283** compounds was developed using synthetic means and discovered that 5-[(E)-2-(5-chloroindol-3-yl) vinyl-phospho-thiazole has strong antimicrobial and selective inhibitory effects on bacterial topoisomerases. The least inhibitory concentration values (MICs) of several of the produced pyrazole derivatives were comparable to those of susceptible strains, and they were effective against clinically isolated Gram-positive bacteria that were resistant to quinolones or coumarins **(Scheme 50)** [131].



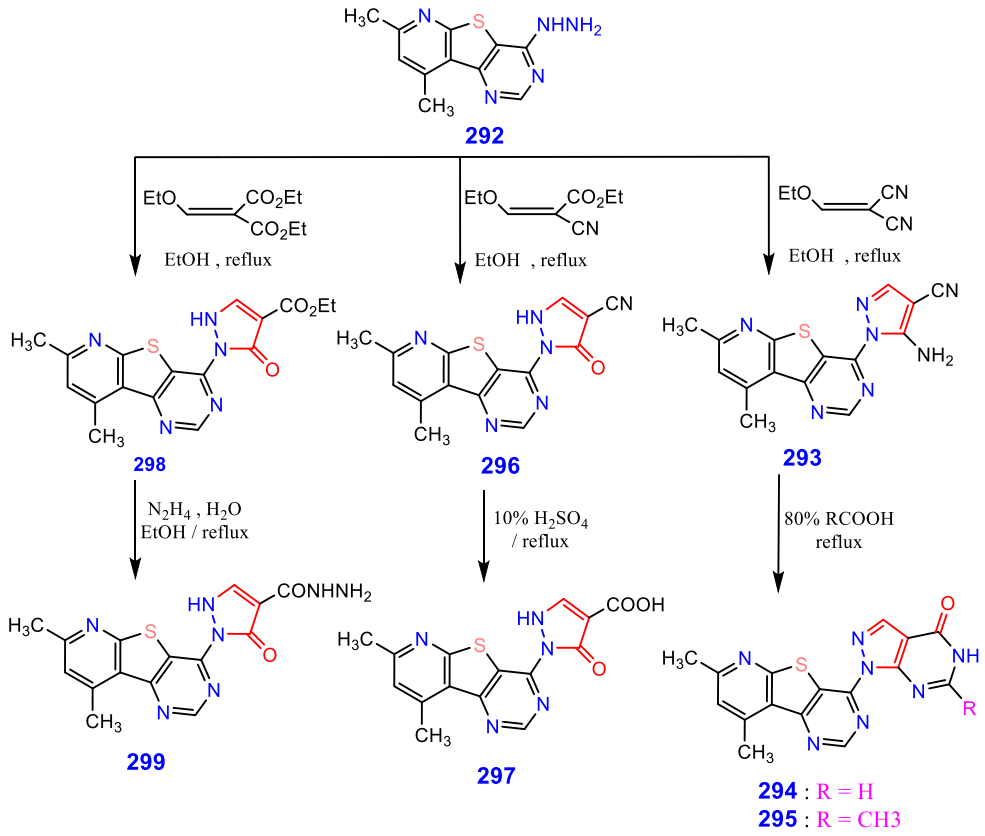
Scheme 50: Piperidine pyrazole as antimicrobial

A novel class of N-heterocyclic compounds **285-291** was studied for its antibacterial activity against a range of harmful microorganisms. MIC, or minimum inhibitory concentration, is the MIC is the average of the lowest doses that can stop the growth of pathogenic microorganisms. The tested newly manufactured compounds **285-291** were also calculated. According to the results, the majority of the ligand molecules that were examined were able to stop the growth of the chosen microorganisms at low concentrations. For example, at low doses between 10 and 20 µg/mL, compounds 1*H*-pyrazole derivative **285**, 1*H*-pyrazole-1-carboxamide derivative **289**, and 1*H*-pyrazole-1-carboximidamide **291** demonstrated a substantial inhibitory effect against the tested microorganisms. At low concentrations, compounds **287** and **288** had strong antibacterial activity against the two tested G-five bacterial strains. **(Scheme 51)** [132].



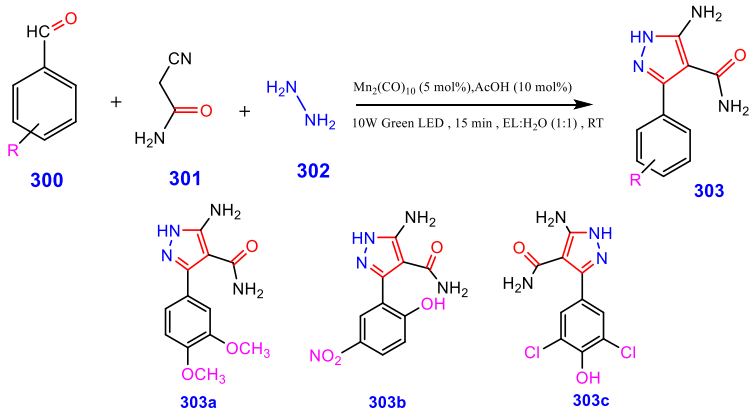
Scheme 51: Pyrazole bearing uracil derivatives as antibacterial activity

The antibacterial activities of the newly synthesized pyrido thieno-pyrimidine derivatives were tested with three microorganisms: Gram-positive *B. subtilis*, Gram-negative *Streptomyces species*, and *Gram-negative P. aeruginosa*. The antibacterial activities screening revealed that compounds **297**, **298**, and **299** had the highest activity against *B. subtilis*, with minimum inhibitory concentration (MIC) values of 75 µg/mL, followed by compounds **293, 294,** and **295.** In terms of inhibiting *P. aeruginosa*, compound **296** is the most effective. Out of all the derivatives that were examined, compounds **295**, **296**, **298**, and **299** had the highest effectiveness against Streptomyces species, with MIC values of 75 µg/mL **(Scheme 52)** [133].



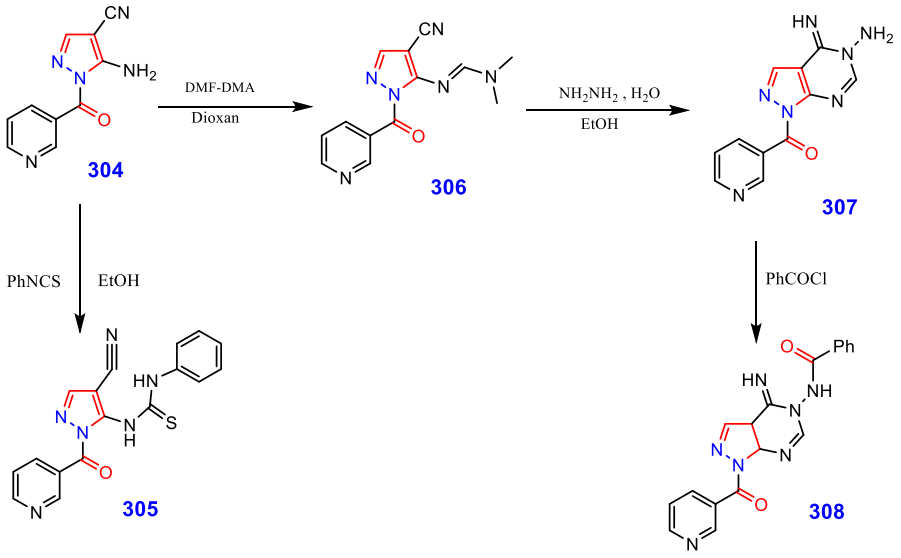
Scheme 52: Newly synthesized pyrido thieno-pyrimidine derivatives as potent antibacterial

Three different bacterial strains were tested for antibacterial activity using the conventional agar dilution method. These strains included the Gram-negative *Pseudomonas aeruginosa* and *Escherichia coli*, as well as the Gram-positive *Staphylococcus aureus*. The synthetic 1*H*-pyrazole-4-carboxamides **303a-c** showed promising results. The inhibitory action of these substances was assessed by calculating the MIC values, which are expressed in µg/mL. To create a range of *E. coli* concentrations, nutritive agar medium was supplemented with *E. coli* at various concentrations. Among the 1*H*-pyrazole-4-carboxamides tested, compounds **303a**, **303b**, and **303c** exhibited the most potent action. **(Scheme 53)** [134].



Scheme 53: Green and facile synthesis of 1H-pyrazole-4-carboxamide derivatives.

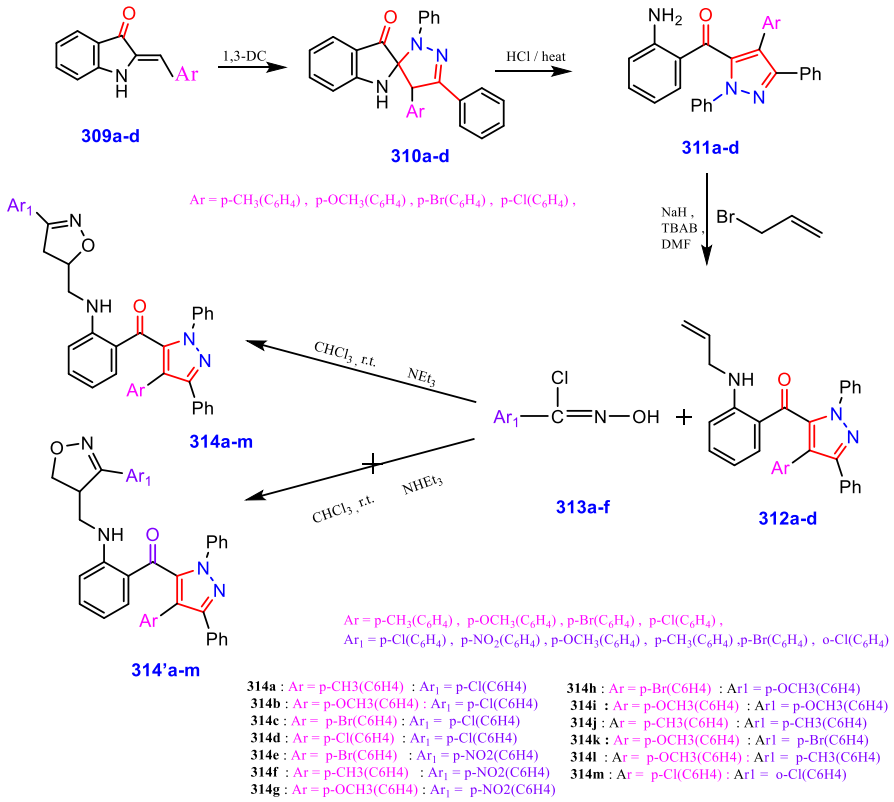
Several compounds have shown effectiveness against nine different types of bacteria. Significant antibacterial activity was demonstrated by three compounds **305, 307** and **308**. Against the gram-negative *Klebsiella pneumoniae* bacteria, it demonstrates the first screening of the compounds. Two compounds, **305** and **307**, showed an inhibitory zone. *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, and *Staphylococcus xylosus* were the three gram-positive isolates that compound **305** inhibited. But against *Staphylococcus saprophyticus*, it had no effect. In addition, it inhibited the growth of *Alcaligenes faecalis*, but it demonstrated effectiveness against three types of gram-negative bacteria: *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas*. The antibacterial activity of compound **308** was seen against all gram-positive bacteria (*S. aureus, MRSA, Xylosus*, and *saprophyticus*) as well as one gram-negative bacterium (*Alcaligenes faecalis*). Both **307** and **308** were shown to have antifungal properties. An extremely active compound was **308** **(Scheme 54)** [135].



Scheme 54: pyrido-pyrimidine and pyrido-thiourea pyrazole as antimicrobial activity

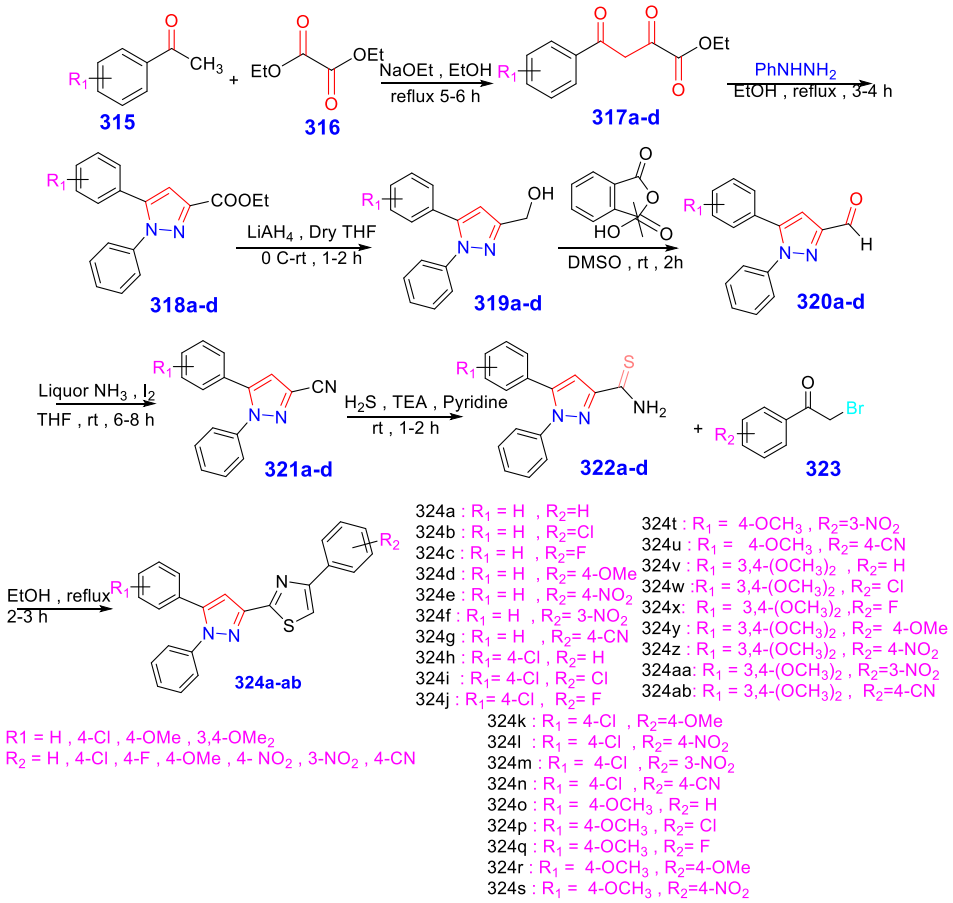
Their Effective implementation of alkylation and 1,3-dipolar cycloaddition has led to the development of a novel class of hybrid poly-heterocycles that incorporate pyrazole and isoxazole line

rings. The analyzed hybrids exhibit notable and varied antibacterial activity against the tested pathogenic strains, as evidenced by the outcomes of the antimicrobial screening. The combined effect of the pyrazole and isoxazoline pharmacophores accounts for the notable activity observed. Some compounds with specific substituents showed more activity than others, according to the results. The assessed hybrids showed sensitivity to the Gram-positive bacterium *B. subtilis* with inhibition rates of 93.7% and 90.6%, respectively, when compared to ampicillin, the standard antibiotic. The compound with the highest percentage of inhibition against *Staphylococcus aureus*, at 78.6%, is **314d**. **(Scheme 55)** [136].



Scheme 55: New hybrid poly-heterocycles isoxazole integrate pyrazole as antibacterial activity

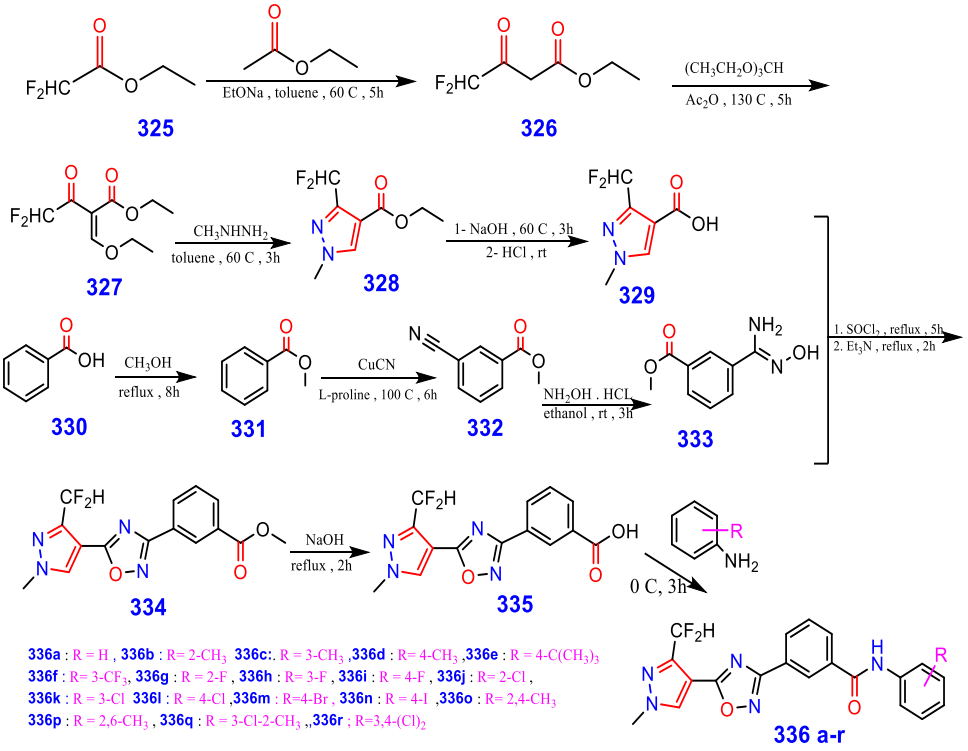
Reactions involving 1,5-diphenyl-1*H*-pyrazole-3-carbothioamide **322a-d** and substituted phenacyl bromide **323a-f** resulted in a novel series of 2-(5-aryl-1-phenyl-1*H*-pyrazol-3 yl)-4-aryl thiazoles **324a-ab**. Compounds **324a-ab** were tested for their antibacterial effect in vitro against *E. coli*, *P. mirabilis*, *B. subtilis*, and *S. aureus*, as well as their antifungal effect against *A. niger* and *Candida albicans*. Out of the twenty-eight pyrazolyl-thiazole derivatives, six compounds **324g, 324h, 324i, 324j, 324o,** and **324t** showed promising activity against *P. mirabilis*; four compounds **324q, 324u, 324y,** and **324z** showed promising activity against *S. aureus*; and twenty-four derivatives showed promising antifungal activity against *A. Niger*. Compounds **324g, 324q, 324r, 324s**, and **324ab** showed similar action compared with the reference drug ravuconazole. **(Scheme 56)** [137].



Scheme 56: Synthesis 2-(5-aryl-1-phenyl-1*H*-pyrazol 3-yl)-4-aryl thiazole **324a-ab** derivatives and tested as antibacterial activity

4.3 Antifungal Activity

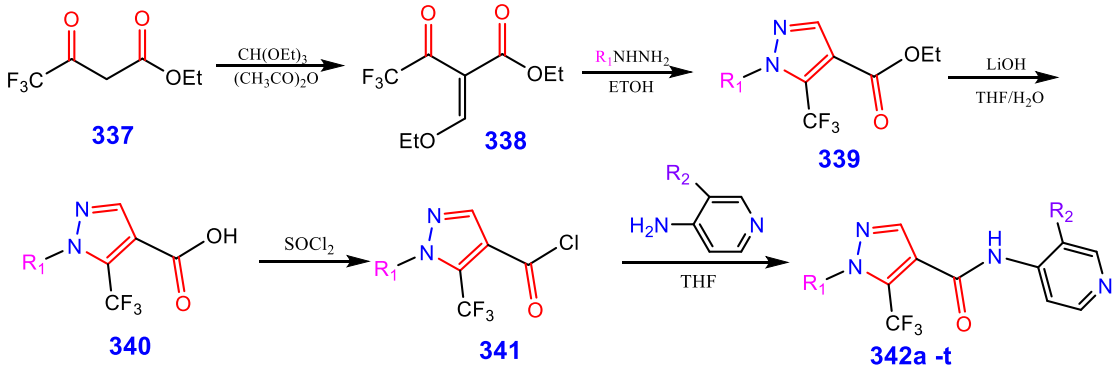
Target compounds **336a-r** fungicidal efficacy against nine tested fungi at 50 mg/L is listed. The drug used as a control was bixafen. Most of the target compounds showed antifungal properties. Superior fungicidal activity against *Sclerotinia sclerotium* and *pyricularia oryzae* was demonstrated by the target compounds. *Pyricularia oryzae* was inhibited by compounds **336f, 336h, 336k,** and **336r** at inhibition rates varying from 52.9 to 100%. Similar to bixafen, compound **336h** exhibited a 100% inhibition rate. A number of substances demonstrated strong anti-fungal action against *Sclerotinia sclerotium*, including **336f** (50.0%), **336h** (50.0%), **336k** (69.2%), and **336o** (60.6%). Compounds **336f**, **336h**, and **336k** were chosen for further EC_{50} bioassays based on initial findings on their fungicidal efficacy (>70% inhibitory), with bixafen serving as the control medication. The fungicidal activity against *pyricularia oryzae* was robust in compounds **336f** (8.28 μg/mL) and **336h** (5.49 μg/mL) **(Scheme 57)** [138].



336a : R = H , **336b** : R= 2-CH_3 **336c**:. R = 3-CH_3 ,**336d** : R= 4-CH_3 ,**336e** : R = 4-$C(CH_3)_3$
336f : R= 3-CF_3, **336g** : R = 2-F , **336h** : R= 3-F , **336i** : R = 4-F , **336j** : R= 2-Cl ,
336k : R = 3-Cl **336l** : R = 4-Cl ,**336m** : R=4-Br , **336n** : R = 4-I ,**336o** : R= 2,4-CH_3
336p : R = 2,6-CH_3 , **336q** : R = 3-Cl-2-CH_3 ,,**336r** ; R=3,4-$(Cl)_2$

Scheme 57: Synthesis of difluoro methyl-pyrazole-oxadiazole as antifungal

Included are the preliminary results of the target compounds' in vitro antifungal efficacy against seven distinct types of pathogenic fungi. At a concentration of 100 mg/L, some compounds, such as **342m**, **342n**, and **342q**, showed remarkable and widespread antifungal activity. A combination of **342m**, **342n**, and **342q** efficiently reduced the growth of several bacteria, including *G. zeae* (16.8 mg/L), *B. dothidea* (13.9 mg/L), *F. prolifeatum* (13.3 mg/L), and *Fusarium oxysporum* (21.4 mg/L). In vitro antifungal activity studies revealed that methyl, isopropyl, and cyclohexyl had reduced antifungal activity compared to **342m**, **342n** and **342q**, which were effective antifungal compounds when ortho-substituted phenyls were used as pyrazole substituents **(Scheme 58)** [139].

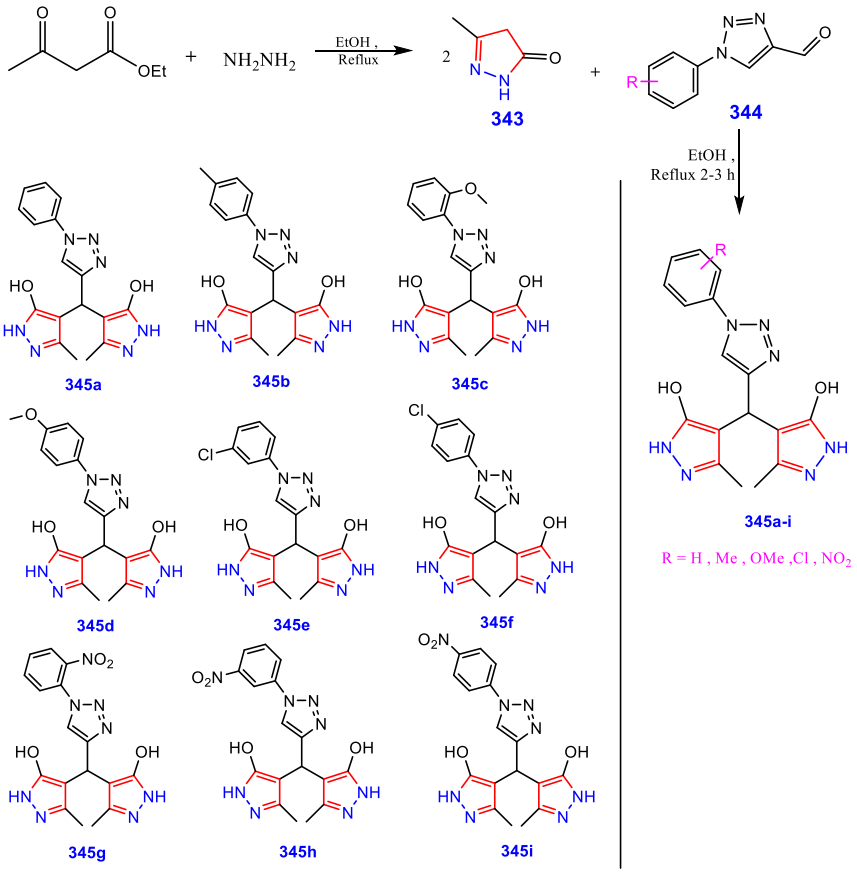


342a ;R= methyl . R_2= H , **342b** R= methyl .R_2=CH3 ,**342c** ;R = methyl. R_2= Cl , **342d**:R= methyl .R_2=F , **342e** :R= isopropyl .R_2=H
342f: R= isopropyl .R_2=CH3 , **342g** : R= isopropyl .R_2=Cl , **342h**: R= isopropyl. R_2= F , **342i**:R= cyclohexyl .R_2=H , **342j** : R= cyclohexyl .R_2=CH3
342k :R= cyclohexyl .R_2=Cl , **342l** :R= cyclohexyl .R_2=F , **342m** :R= o-methylphenyl. R_2= H
342n :R = o-methylphenyl .R_2=CH3 , **342o** :R= o-methylphenyl. R_2= Cl ,**342p**: R = o-methylphenyl .R_2= F , **342q** : R= o-trifluorophenyl .R_2=H
342 r :R= o-trifluorophenyl.R_2= CH3 , **342s** :R= o-trifluorophenyl .R_2= Cl, **342 t** : R= o-trifluorophenyl .R_2=F

Scheme 58: Synthesis of N-(pyridin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide

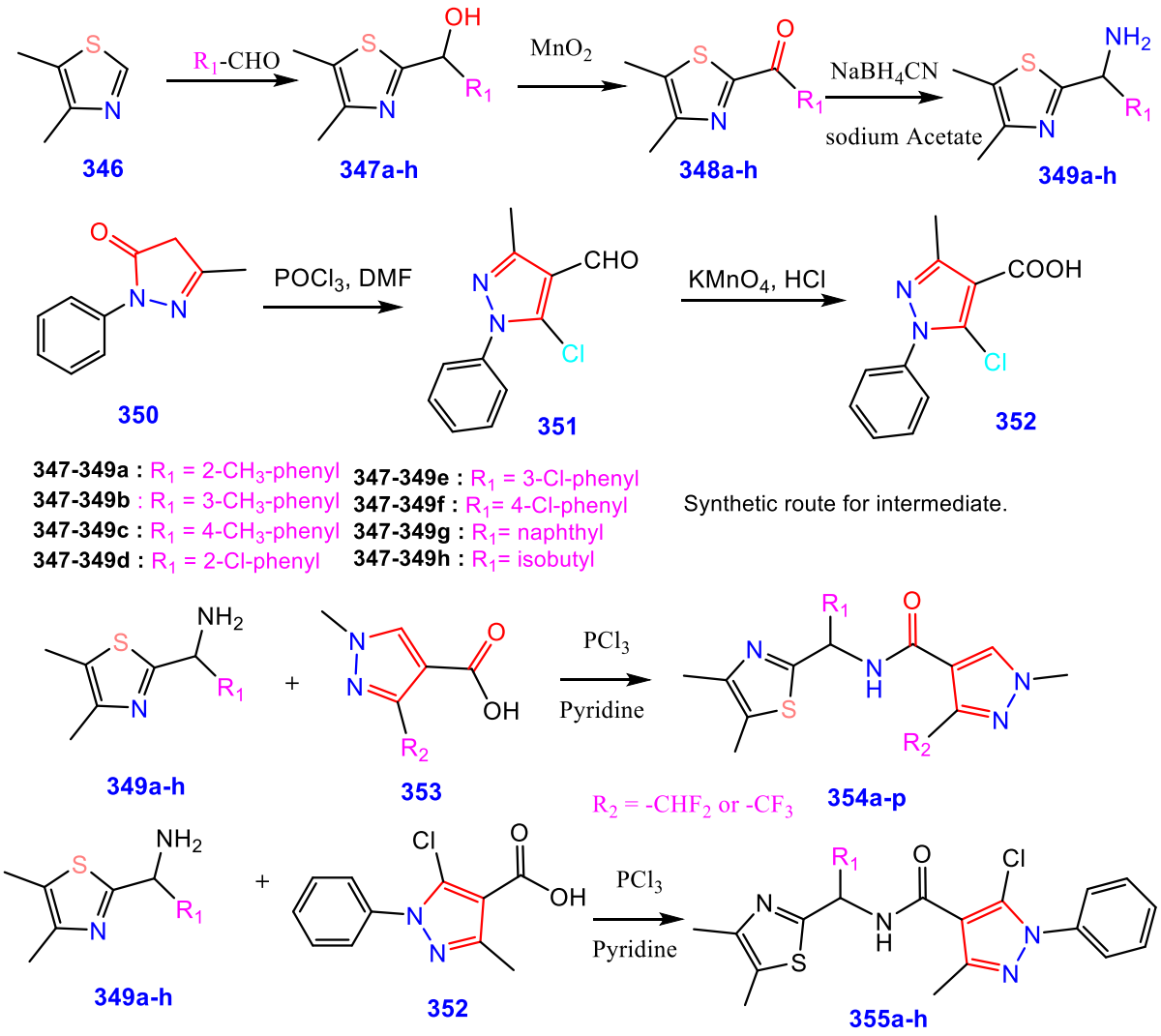
Researchers conducted an examination of the newly synthesized 1,2,3-triazole appended bis-pyrazole derivatives, specifically compounds **345a-i**, to assess their in vitro antifungal activity against seven distinct fungal strains, which include *Candida albicans 1 and 2*, *Candida neoformans*, *A. fumigatus*, *Aspergillus niger*, *Candida tropicalis*, and *Glabrata*. All of the produced compounds demonstrated exceptional antifungal activity against seven fungal strains, with their peak effectiveness

noted against strains of *Candida albicans*. Tested against *Candida albicans*, compounds **345b, 345e**, **345f** and **345i** exhibited exceptional antifungal activity, achieving a minimum inhibitory concentration (MIC) value of 4 µg/mL. In contrast, compounds **345a** and **345d** displayed good antifungal activity with a MIC value of 8 µg/mL. Compounds **345d** and **345e** exhibited significant antifungal activity against Candida albicans, achieving a MIC value of 8µg/mL. Compound **345e** demonstrated significant antifungal efficacy against *C. neoformans*, exhibiting a MIC value of 8 µg/mL. Compound **345f** demonstrated significant antifungal efficacy against *C. glabrata*, exhibiting a MIC value of 8µg/mL. Compound **345a** demonstrated the most potent antifungal activity against *C. glabrata*, exhibiting a MIC value of 2µg/mL. Furthermore, the other compounds in the series exhibited good to moderate antifungal activity against different strains, with MIC values of 16, 32, 64, and 128 µg/mL **(Scheme 59)** [140].



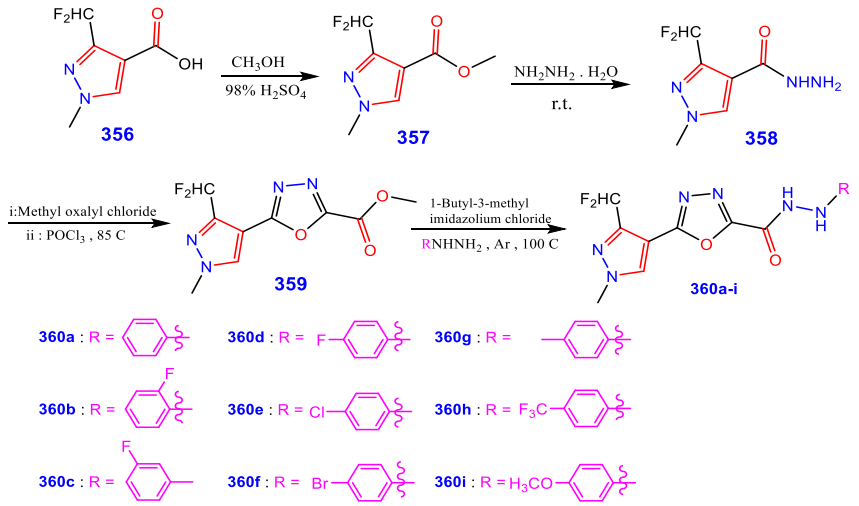
Scheme 59: bis-pyrazole triazole derivatives candidate as potent antifungal inhibitory

By preventing mycelial growth, the in vitro biological activity of target compounds **363a-p, 364a-h** against nine fungi at a concentration of 40 mg/L was ascertained. According to the screening results, the new pyrazole carboxamide thiazole derivatives shown strong antifungal properties against the chosen fungi. The majority of the target compounds have antifungal activity against nine fungi in vitro that above 50%, with compound **364i** having the most notable antifungal properties. *Sclerotinia sclerotium* and *V. mali* had respective inhibition rates of 81% and 91%. Effective concentrations (EC_{50}) were calculated against *V. mali, S. sclerotiorum, R. solani* and *T. viride*. The results of the study indicate that target compound **363f** exhibited the most significant inhibitory effect against *S. Sclerotium* and *V. mali*, with EC_{50} values recorded at 5.07 and 1.77 mg/L, respectively. Compound **364c** exhibited remarkable inhibitory activity against *V. mali*, with an EC_{50} value of 1.97 mg/L **(Scheme 60)** [141].



Scheme 60: Strong antifungal properties of new pyrazole carboxamide thiazole derivatives

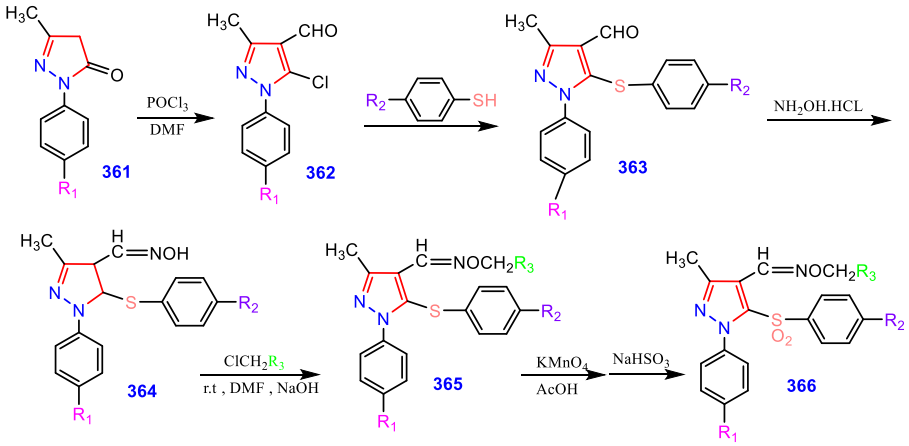
The subsequent substances underwent bioassessment through the evaluation of mycelium growth rates in relation to six distinct fungal strains and one representative oomycete. The bioassay outcomes indicated that numerous target compounds exhibited significant multifunctional bioactivities. For instance, compounds **360a-c** exhibited commendable antifungal and actinomycetes activities, achieving inhibitory rates ranging from 96.1% to 100%. These results were comparable to those of commercial medications CB and PC, and slightly superior to those of HM, BS, FP, and AZX. Compounds **360d-f** demonstrated the capacity to entirely and specifically inhibit the growth of G. z., indicating that potent bioactive components targeting G. z. were progressively identified. All compounds exhibited satisfactory inhibitory effects for the *anti-B.d.* and *anti-R. s.* activities, with relevant rates spanning from 57.4 to 80.8% (excluding compounds **360g** and **360i** against *R. s.)*, and were also associated with broad-spectrum biological activity. Molecules **360a-c** demonstrate significant antibacterial properties, warranting further refinement to explore their highly bioactive potential **(Scheme 61)** [142].



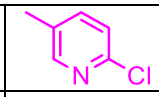
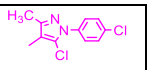
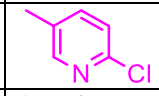
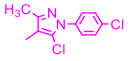
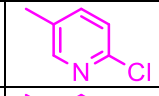
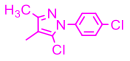
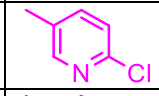
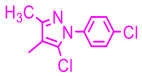
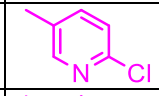
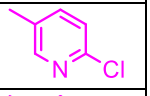
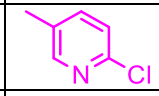
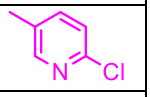
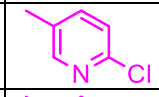
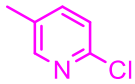
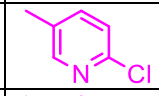
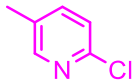
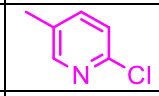
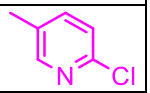
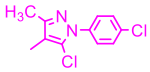
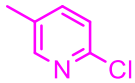
Scheme 61: Synthesis of difluoromethyl-1*H*-pyrazol-4-yl-1,3,4-oxadiazole-2-carbohydrazide as antifungal

4.5 Antiviral activity

The method outlined is employed to evaluate the antiviral bioassay against TMV, with most of the developed compounds demonstrating modest antiviral activity against TMV in vivo at a concentration of 500 mg/L. The title compounds **365a-n** and **365a-h** exhibited protection activities ranging from 15.7% to 44.8% at a concentration of 500 mg/L. Specifically, compounds **365g**, **365l**, **365m**, **365c** and **375g** demonstrated moderate protection activities of 43.5%, 44.8%, 41.0%, 40.2%, and 42.2 µg/mL, respectively, which are comparable to the standard reference of 59.9%. Moreover, the protective activities of compounds **365c-f**, **h-k** and **365a-b**, **d-f-h** were observed to be below 40% at a concentration of 500 µg/mL. The compounds designated as **365a-n** exhibit promising bioactivities related to inactivation, as demonstrated by their respective values of 90.4, 71.2, 65.9, and 61.7%. The values obtained at a concentration of 500 µg/mL were as follows: 61.2, 34.5, 80.6, 56.6, 61.0, 43.0, 55.9, 51.2, 50.9, and 36.7%. The inactivation rates of 90.4% and 80.6% against TMV at a concentration of 500 µg/mL indicate that **365a** and **365g** exhibit markedly superior activity compared to the other compounds tested. Moreover, compounds **365a, b** and **365g** demonstrated significant antiviral efficacy. The antiviral efficacy of **365a** surpassed that of the other pharmaceuticals, demonstrating a potency akin to that of Ningnanmycin (EC_{50} =52.7 µg/mL) in the context of TMV **(Scheme 62)** [143].

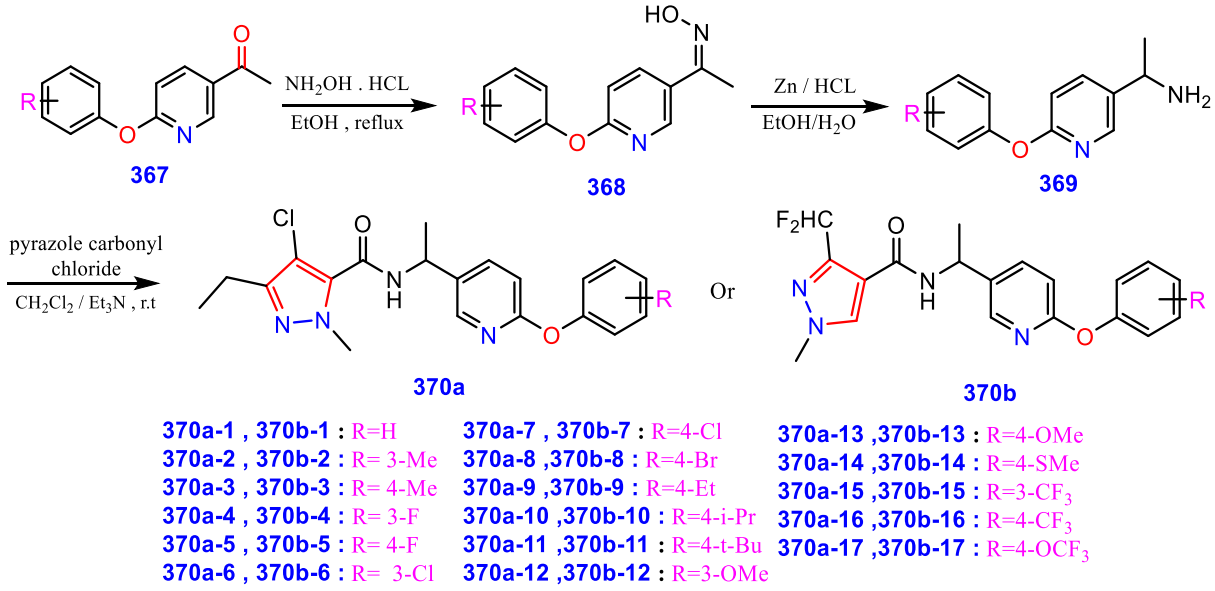


Scheme 62: Synthetic process of Sulfonyl pyrazole derivatives as antiviral

365a	R_1= H	R_2=Me	R_3=		**365k**	R_1= H	R_2=F	R_3=	
365b	R_1= H	R_2=OMe	R_3=		**365l**	R_1= 4-Me	R_2=Me	R_3=	
365c	R_1= H	R_2=F	R_3=		**365m**	R_1= 4-Me	R_2=F	R_3=	
365d	R_1= 3-Cl	R_2=F	R_3=		**365n**	R_1= 4-Cl	R_2=Me	R_3=	
365e	R_1= 4-Cl	R_2=Me	R_3=		**366a**	R_1= H	R_2=Me	R_3=	
365f	R_1= 4-Cl	R_2=OMe	R_3=		**366b**	R_1= H	R_2=OMe	R_3=	
365g	R_1= 4-Cl	R_2=F	R_3=		**366c**	R_1= H	R_2=F	R_3=	
365h	R_1= 4-Me	R_2=F	R_3=		**366d**	R_1=3-Cl	R_2=F	R_3=	
365i	R_1= 4-Me	R_2=Me	R_3=		**366e**	R_1=4-Cl	R_2=Me	R_3=	
365j	R_1= 4-Me	R_2=F	R_3=		**366f**	R_1=4-Cl	R_2=OMe	R_3=	

4.6-Insecticidal activities

The target compounds insecticidal properties against a range of pests, such as *F. occidentalis*, *N. lugens*, *P. xylostella*, and *A. craccivora Koch*. Compound **370a** showed significantly greater IA overall in contrast to **370b**, this indicates that the pyrazole-acyl group plays an important part in how these chemicals interact with various complexes of respiratory chains. Compound **370a** and **370b** showed a 100% fatal rate against *P. xylostella*. Even when focused the fatal rates of compounds **370a-7** and **370a-14** at 100 μg/mL Still, **370b-7**, **370b-8**, and **370b-16** achieved 90–100%. This suggests that P. xylostella is extremely sensitive to several substances, Much like *tolfenpyrad*. But for the majority of compounds, the IA that of *tolfenpyrad* exceeded that of *F. occidentalis*. In particular, **370a-4**, **370a-17**, **370b-1**, and **370b-17** compounds showed the highest IA, with a mortality rate at a concentration of more than 60% 100 μg/mL. This mortality rate was much higher than that *Ethylspinetoram* and *oftolfenpyrad*. These findings show that potential of these substances to create effective pesticides directed toward *F. occidentalis* emphasizing their potential as bright prospects for the creation of novel pesticides **(Scheme 63)** [144].

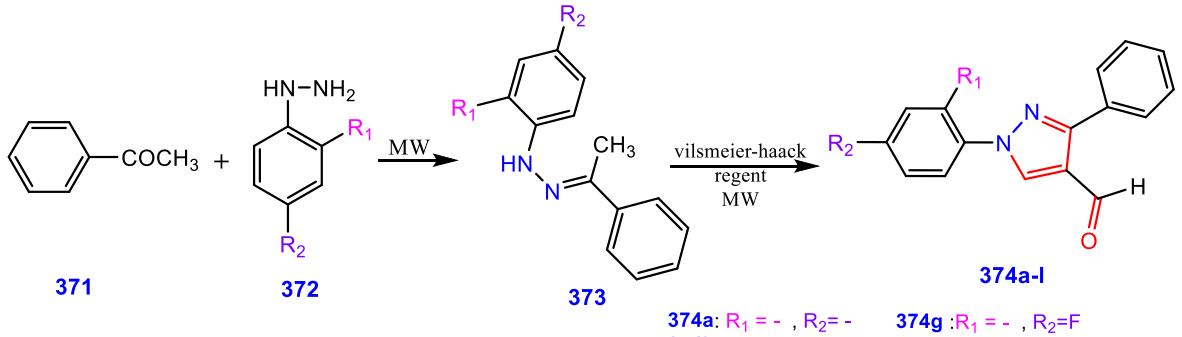


370a-1 , 370b-1 : R=H
370a-2 , 370b-2 : R= 3-Me
370a-3 , 370b-3 : R= 4-Me
370a-4 , 370b-4 : R= 3-F
370a-5 , 370b-5 : R= 4-F
370a-6 , 370b-6 : R= 3-Cl
370a-7 , 370b-7 : R=4-Cl
370a-8 ,370b-8 : R=4-Br
370a-9 ,370b-9 : R=4-Et
370a-10 ,370b-10 : R=4-i-Pr
370a-11 ,370b-11 : R=4-t-Bu
370a-12 ,370b-12 : R=3-OMe
370a-13 ,370b-13 : R=4-OMe
370a-14 ,370b-14 : R=4-SMe
370a-15 ,370b-15 : R=3-CF_3
370a-16 ,370b-16 : R=4-CF_3
370a-17 ,370b-17 : R=4-OCF_3

Scheme 63: Pyrido-amide pyrazole derivatives as insecticidal

4.7 Anti-inflammatory activity

The results indicated that every substance assessed was a derivative of pyrazole-4-carbaldehyde as illustrated in **Scheme 64** [145]. demonstrated a significant divergence in anti-inflammatory effectiveness. It is clear that among the pyrazole-4-carbaldehydes assessed, the activities of **374 c, e, g** were notably superior in comparison to those of **374i, 374k** and **374l**. In comparison to their respective para-position derivatives, exemplified by compounds 383c, e, and l, the findings further indicated that in specific cases, the presence of para-position halogen moieties **374g, 374i** and **374k** enhances the anti-inflammatory effect. The correlation between the presence of para-position halogen moieties and the enhancement of anti-inflammatory activity is evident. The data indicates that compounds **374c, 374e, 374g, 374i, 374k**, and **374l** exhibited enhanced anti-inflammatory properties, demonstrating efficacy ranging from 53% to 65% at a dosage of 20 mg/kg and from 35% to 46% at a dosage of 10 mg/kg. The compound **374g** demonstrated significant anti-inflammatory activity, achieving 65% efficacy at a dosage of 20 mg/kg and 46% at 10 mg/kg, marking it as the most potent among the tested substances. Conversely, compounds that are unsubstituted or possess ortho derivatives, including **374a, 274b, 374d, 374f** and **374j**, exhibited diminished anti-inflammatory activities, with ranges of 35% to 50% at a dosage of 20 mg/kg and 18% to 30% at a dosage of 10 mg/kg, respectively.



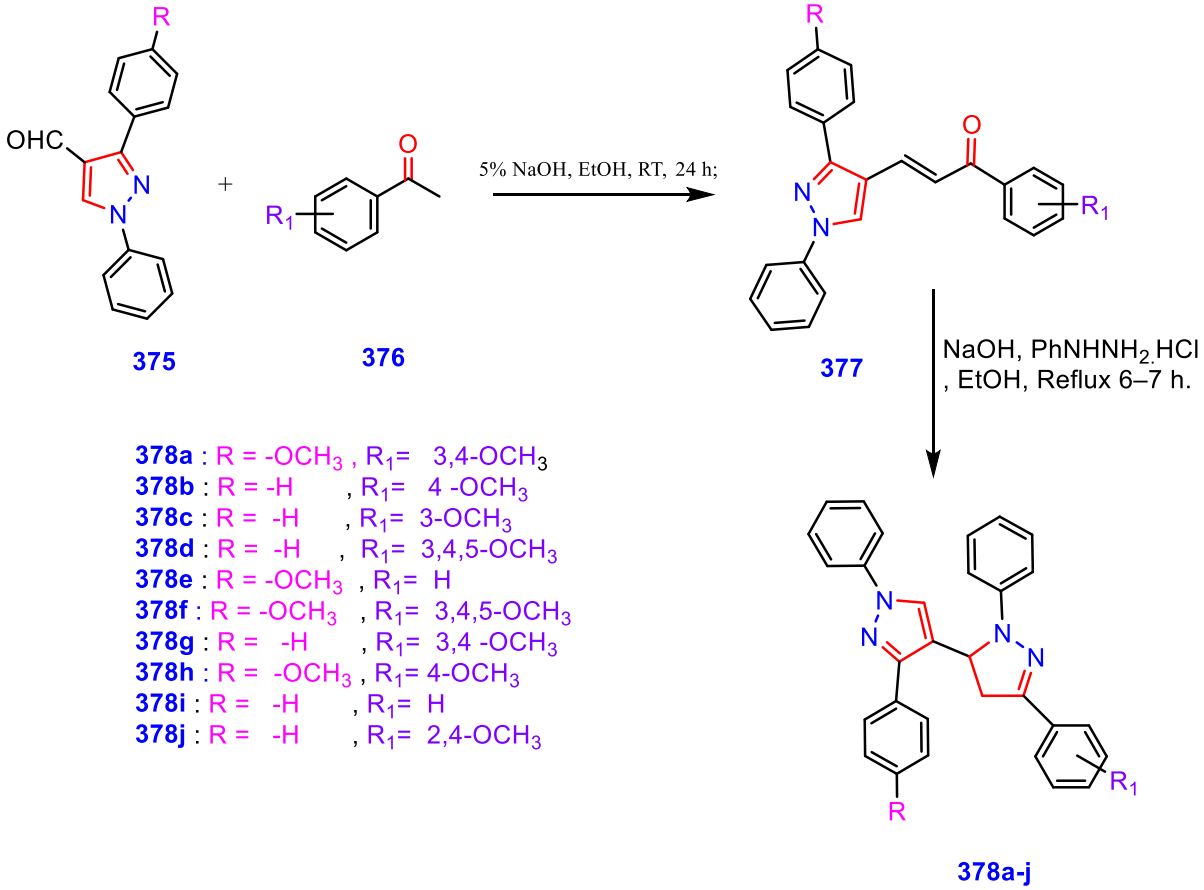
Pyrazole-4-carbaldehyde derivatives.

374a: R_1 = - , R_2= -
374b: R_1 =CH_3 , R_2= -
374c: R_1 = - , R_2=CH_3
374d: R_1 =OCH_3 , R_2= -
374e: R_1 = - , R_2=OCH_3
374f: R_1 = F , R_2= -
374g :R_1 = - , R_2=F
374h: R_1 = Br , R_2= -
374i : R_1 = - , R_2=Br
374j : R_1 = Cl , R_2= -
374k :R_1 = - , R_2=Cl
374l :R_1 = - , R_2=$NHCOCH_3$

Scheme 64: Synthesis of pyrazole-4-carbaldehyde as *anti*-inflammatory activity

Some arthritic illnesses may produce auto-antigens due to the denaturation of tissue proteins. Denaturation of tissue proteins may thus be considered an indicator of anti-inflammatory disorders.

One potential candidate for the creation of anti-inflammatory drugs is the chemical that can prevent protein denaturation. The anti-inflammatory efficacy of all the produced pyrazoline derivatives was assessed using the protein denaturation method. In comparison to conventional diclofenac sodium, compounds **378b**, **378g**, and **378h** shown substantial anti-inflammatory effects, while compounds **378f, 378j, 378a** and **378i** exhibited good activity. The remaining compounds exhibited moderate activity **(Scheme 65)** [146]**.**



Scheme 65: *di*-pyrazole derivatives as potent *anti*-inflammatory activity

4.7 Antidiabetic activity

Numerous pyrazole compounds are recognized for their anti-diabetic properties, particularly as inhibitors of α-amylase and α-glucosidase [147]. A range of pyrazole structures was examined for their capacity to inhibit α-amylase, including pyrazoles featuring thiazolidine-4-one frameworks **379** [148], pyrazole-thiazole hybrids **380** [149], derivatives of 4,4′-[ethane-1,2-diylbis(sulfandiyl methanediyl)] bis(3,5-dimethyl-1*H*-pyrazole) **381** [150], hybrid pyrazole-tetrazole derivatives **382** [151], thiazolidine-2,4-dione-pyrazole conjugates **392** [152], 1*H*-pyrazole-3-carbonyl-N-phenylhydrazine-1-carboxamide **393** [153], and rhodanine-pyrazole conjugates **385** [154]. Furthermore, it has been documented that pyrazole derivatives, such as the benzothiazine-pyrazole hybrid **386** [155], (E)-5-methyl-N′-(pyridin-2-ylmethylene)-1*H*-pyrazole-3-carbohydrazide **387**, and acyl pyrazole sulfonamide derivatives **388** [156], serve as effective α-glucosidase inhibitors **(Figure 6).**

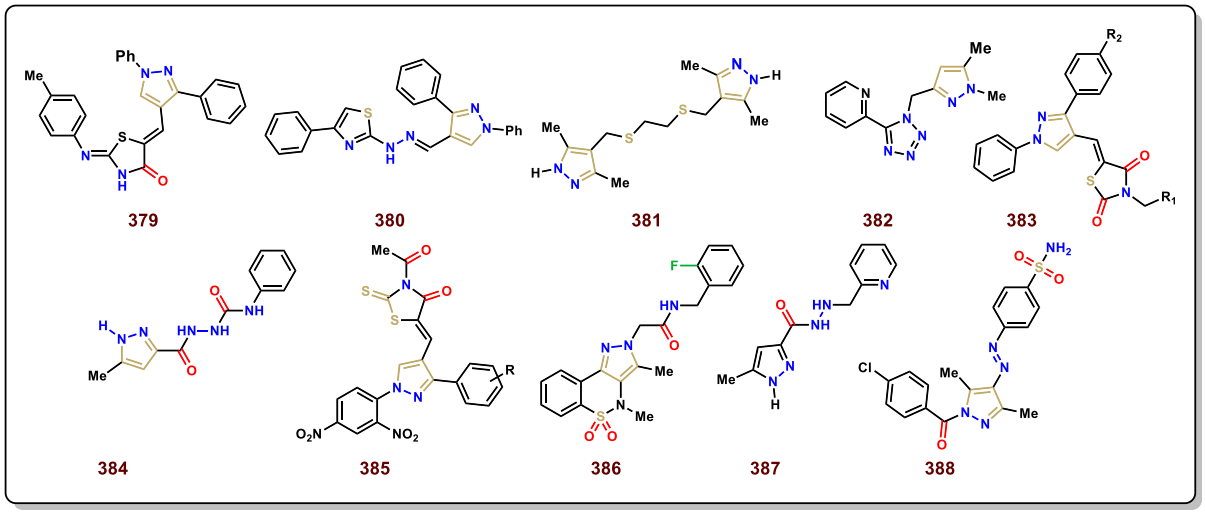
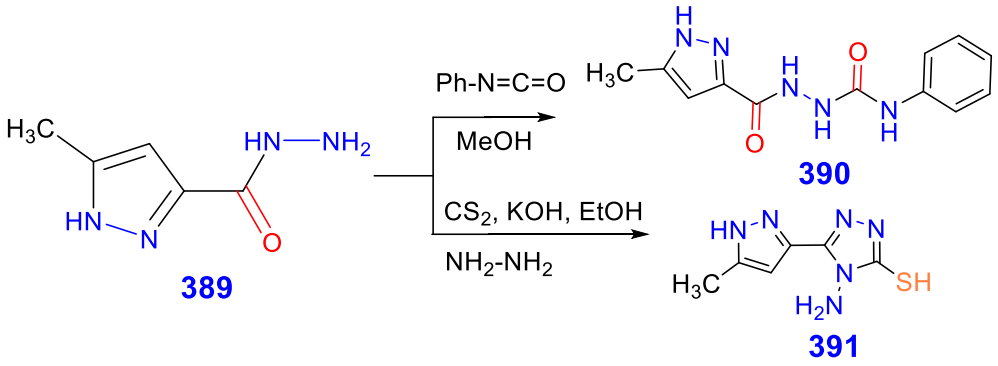


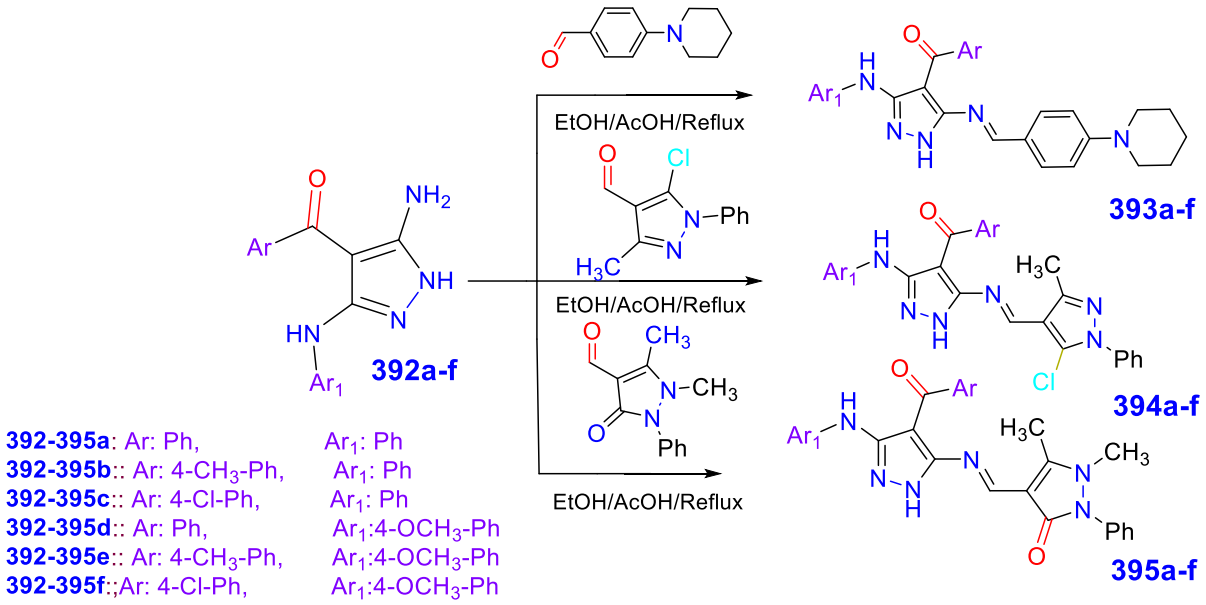
Figure 6: Drugs for diabetes include pyrazole derivatives.

The two pyrazole derivatives studied here are 2-(5-methyl-1*H*-pyrazole-3-carbonyl) N-phenylhydrazine-1-carboxamide **390** and 4-amino-5-(5-methyl-1*H*-pyrazol-3-yl) 4*H*-1,2,4-triazole-3-thiol **391**. The anti-diabetic effects of **390** and **391** were studied *in vitro*. In terms of their ability to prevent diabetes, **390** and **391** demonstrated strong inhibition of α-glucosidase and α-amylase, respectively, with IC_{50} values of 75.62 ± 0.56 and 95.85 ± 0.92 and 119.3 ± 0.75 and 120.2 ± 0.68 µM, as compared to Acarbose (IC_{50}(α-glucosidase) = 72.58 ± 0.68 µM, IC_{50} (α-amylase) = 115.6 ± 0.574 µM). With IC_{50} values of 24.32 ± 0.78 and 10.75 ± 0.54 µM, respectively, **390** and **391** demonstrated outstanding inhibitory activity in the xanthine oxidase experiment **(Scheme 66)** [157].



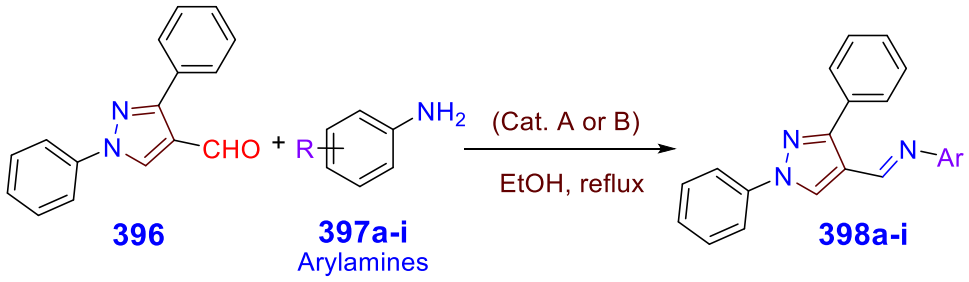
Scheme 66: Pyrazole urea and thio-amino-triazole derivatives as antidiabetic

This research seeks to identify pyrazole-based Schiff bases as novel multi-target agents. In this context, we re-synthesized three series of pyrazole-based Schiff bases, **393a-f**, **394a-f**, and **395a-f**, to assess their biological uses. The data from in vitro biological experiments, including antioxidant. The scavenging activities, anti-diabetic, anti-Alzheimer's, and anti-inflammatory properties of the pyrazole-based Schiff bases **393a-f**, **394a-f**, and **395a-f** indicated that the six compounds **393a**, **393d**, **393e**, **394f**, **395a**, and **395f** exhibit the most significant biological properties among those assessed. The cytotoxicity was assessed against human lung (A549) and colon (Caco-2) cancer cell lines, in addition to normal lung (WI-38) cell lines. The cytotoxicity findings indicated that **395a** demonstrated the maximum cytotoxicity against colon (Caco-2) cells. The analysis revealed that the three Schiff bases **393d**, **393e**, and **395a** exhibit strong activity against lung (A549) cells **(Scheme 67)** [158].



Scheme 67: Synthesis of acylated *bi*-pyrazole as antidiabetic

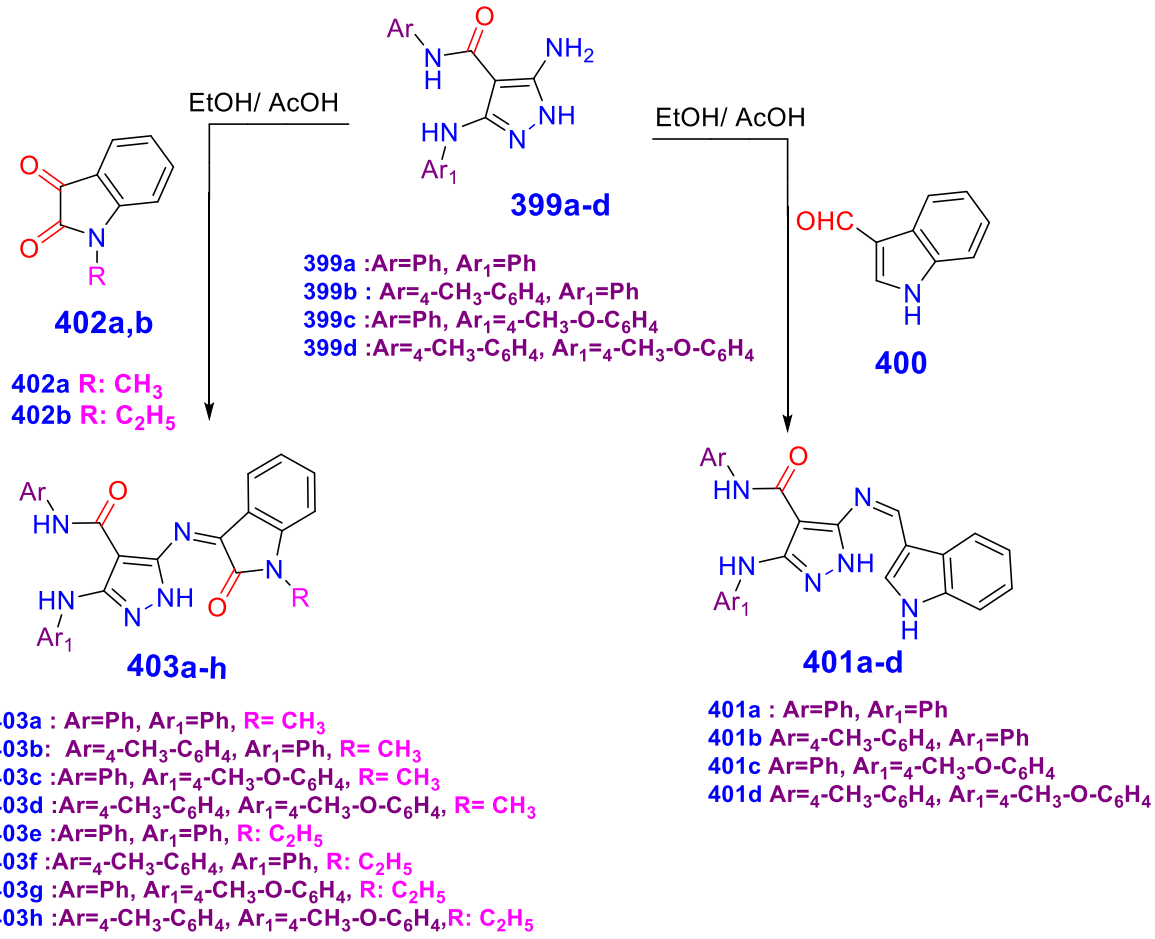
Using two catalysts, ammonium chloride (catalyst A) or acetic acid (catalyst B), a sequence of pyrazole-Schiff base derivatives, **398a-i**, was produced by reacting arylamines **397a-i** with pyrazole aldehyde **396**. Various in vitro tests were used to evaluate their antidiabetic inhibitory effects on α-glucosidase, α-amylase enzymes. Analogs **398c** (α-amylase IC_{50} = 19.57±0.07 µM, α-glucosidase IC_{50} = 17.13±0.28 µM) and **398h** (α-amylase IC_{50} = 22.50±0.06 µM, α-glucosidase IC_{50} = 20.75±0.17 µM) showed very promising in vitro antidiabetic outcomes. Both products **398c** and **398h** demonstrated activity close to the standard acarbose (IC_{50} (α-amylase) = 16.28±0.24 µM, IC_{50} (α-glucosidase) = 13.19±0.26 µM). The presence of a free phenolic hydroxy group in **398c** and a benzothiazole motif in **398h** could help to explain their greater antidiabetic and antioxidant properties than those of other compounds. These results also support the several biological purposes connected with their antidiabetic action, including their antioxidant action **(Scheme 68)** [159].



Scheme 68: Synthesis of pyrazole-containing Schiff bases as potential double inhibitors of *alpha*-amylase and *alpha*-glucosidase.

The in vitro enzymatic evaluation indicated that the pyrazole-indole conjugate **401b** has significant activity against (i) α-amylase (% = 65.74 ± 0.23, IC_{50} = 4.21 ± 0.03 µg/mL).α-glucosidase (% = 55.49 ± 0.23, IC_{50} = 2.76 ± 0.01 µg/mL); (ii) protein denaturation enzyme (% = 49.30 ± 0.17) and proteinase enzyme (% = 46.55 ± 0.17) with an IC_{50} value of 6.77 ± 0.01 µg/mL; (iii) COX-1, COX-2, and 5-LOX enzymes with IC_{50} values of 5.44 ± 0.03, 5.37 ± 0.04, and 7.52 ± 0.04, respectively, which are comparable to the IC_{50} of indomethacin and zileuton drugs. The computational assessment results

indicated that (i) compound **401b** has lipophilic surface qualities, enabling it to traverse cell membranes and demonstrating efficacy in therapy; (ii) all conjugates had a TPSA value over 140 Å², hence indicating favorable intestine absorption. **(Scheme 69)** [160]



Scheme 69: Evaluations of pyrazole-isatin and pyrazole-indole conjugates as anti-diabetic agents.

5. Conclusion

Nitrogen-containing heterocyclic compounds and their analogues were previously used as valuable sources of medical pharmaceuticals. Pyrazole, an aromatic compound containing two nitrogen atoms, offers many functionalities and stereochemical intricacies inside its five-membered ring structure. Pyrazole molecular template-guided an extensive number of distinctive structural components has been produced within numerous substitutes of chemical groups and ring systems, in conjunction with the intertwining of sub-structures utilizing a wide variety of synthons, starting materials, and intermediates. Furthermore, novel synthetic methodologies have yielded compounds and noteworthy leads that exhibit a diverse range of pharmacological activities. An extensive examination of diverse categories of biologically significant compounds has been presented, highlighting their activity profiles which encompass antimicrobials, antivirals, anti-parasitic agents, anti-cancer agents, anti-inflammatory substances, antioxidants, anti-hypertensives, and anti-diabetics. Each compound is meticulously detailed, accompanied by their respective synthetic schemes that highlight the synthetic protocols, with pyrazole recognized as the central pharmacophore accountable for the observed activity. A multitude of structures originating from the pyrazole nucleus has shown significant potential for continued investigation focused on the development of bioactive compounds, novel chemical entities, lead compounds, and pharmaceuticals to advance drug discovery initiatives. The urea molecular template acts as a cornerstone for active organo-medicinal products, presenting considerable promise for the swift and effective advancement of novel drug candidates spanning various domains of bioactivity and pharmacological action. This investigation can deepen the intricacies of drug design and the ensuing drug discovery process, as well as activity prediction, structural mapping, and toxicity evaluations, employing in vivo, in vitro, and in silico approaches. The current landscape of structural diversification

and the multitude of notable bioactivities presents a unique opportunity to understand the mechanisms of action of pyrazole-derived compounds, encompassing both those under development and those that are already established. This comprehension is essential for investigating metabolomics and toxic-kinetics to address and eradicate the inherent toxicity, adverse effects, and biological cross-reactivity of these products, which present obstacles to forthcoming drug development efforts. The impressive range of pharmacological activities, coupled with structural diversification and the enduring pyrazole pharmacophore, alongside the biological potentials of variously substituted pyrazole, offers a compelling selection of structures. These may be generated via combinatorial and parallel synthesis, with their bioactivity validated through high throughput screenings. This presents fresh avenues in uncharted domains of chemical synthesis, drug design, and development, as well as the incorporation of innovative pharmacological activities associated with the pyrazole framework to investigate.

REFERENCES

[1] Ansari A, Ali A, Asif M, and Shamsuzzaman S. Review: biologically active pyrazole derivatives. *New Journal of Chemistry*. 41,16–41, 2016.

[2] Becerra, D., Abonia, R. and Castillo, J.C., Recent applications of the multicomponent synthesis for bioactive pyrazole derivatives. *Molecules*, *27*, 4723. 2022.

[3] H. Zhai *et al.*, "Pyrazole: An important core in many marketed and clinical drugs," *Russ J Bioorg Chem*, vol. 48, no. 6, pp. 1175–1189, 2022.

[4] "Heterocyclic Compounds. in *A Comprehensive Guide to the Hazardous Properties of Chemical Substances*. Wiley. 484–495, 2007.

[5] Faisal M, Saeed A, Hussain S, Dar P, and Larik F. A. Recent developments in synthetic chemistry and biological activities of pyrazole derivatives. *Springer*. 2019.

[6] Ameziane El Hassani I. Rouzi K., Assila H, Karrouchi K, and Ansar M. Recent Advances in the Synthesis of Pyrazole Derivatives: A Review. *Reactions*. 4, 478–504, 2023.

[7] Ríos M. C. and Portilla, J. "Recent Advances in Synthesis and Properties of Pyrazoles," Sep. 01, 2022, *MDPI*.

[8] Knorr L. Einwirkung von Acetessigester auf Phenylhydrazin. *Berichte der deutschen chemischen Gesellschaft*. 16, 2597–2599, 1883.

[9] Girish Y. R, Kumar K. S. S, Manasa H. S, and Shashikanth S. ZnO: An Ecofriendly, Green Nano-catalyst for the Synthesis of Pyrazole Derivatives under Aqueous Media. *Journal of the Chinese Chemical Society*. 61, 1175–1179, 2014.

[10] Ji G, Wang X, Wang J et al. Synthesis of 3-trifluoromethylpyrazoles via trifluoromethylation/cyclization of α, β-alkynic hydrazones using a hypervalent iodine reagent. Chemical Communications. 4361-4363. 2014

[11] Eicher T, Hauptmann S, and Speicher A. Five-Membered Heterocycles: Sections 5.22–5.36. in *The Chemistry of Heterocycles*. Wiley. Pages 179–184, 2003

[12] Karrouchi K, *et al.* Synthesis and pharmacological activities of Pyrazole derivatives: A review. *MDPI AG*. 2018

[13] Chimenti F, *et al.* Synthesis and inhibitory activity against human monoamine oxidase of N1-thiocarbamoyl-3,5-di(hetero)aryl-4,5-dihydro-(1H)-pyrazole derivatives. *Eur J Med Chem*. 45, 800–804, 2010.

[14] Chimenti F *et al.* Synthesis, Molecular Modeling Studies, and Selective Inhibitory Activity against Monoamine Oxidase of 1-Thiocarbamoyl-3,5-diaryl-4,5-dihydro-(1H)- pyrazole Derivatives. *J Med Chem*. 48, 7113–7122, 2005.

[15] Ma H.-J *et al.* Synthesis and herbicidal activity of novel N-(2, 2, 2)-trifluoroethylpyrazole derivatives. *J Agric Food Chem*. 58, 4356–4360, 2010.

[16] Pilakowski J, Baumann G, Shih Y.-H, Meckel T, and Schmidt B. Design, synthesis and biological evaluation of novel aminopyrazole- and 7-azaindole-based Nek1 inhibitors and their effects on zebrafish kidney development. *Bioorg Med Chem Lett*. 53, 128418, 2021.

[17] Ortiz M.-C and Portilla J. Access to five-membered N-heteroaromatic compounds: Current approach based on microwave-assisted synthesis. *Targets Heterocycl. Syst*, 25, 436–462, 2021.

[18] Elnagdy H. M. F and Sarma D. $FeCl_3$ /PVP as Green Homogeneous Catalyst to Synthesize 5-Amino-1 *H* -Pyrazole-4-Carbonitriles from Malononitrile Derivatives. *ChemistrySelect*. 4, 783–787, 2019.

[19] Ren Z, *et al.* Design, synthesis, and antifungal activity of novel cinnamon–pyrazole carboxamide derivatives. *Drug Dev Res*. 79, 307-312, 2018

[20] Ambethkar S, Padmini V, and Bhuvanesh N. A green and efficient protocol for the synthesis of dihydropyrano [2, 3-c] pyrazole derivatives via a one-pot, four component reaction by grinding method. *J Adv Res*. 6, 975–985, 2015.

[21] Elguero J, Silva A. M. S, and Tomé A. C. Five-Membered Heterocycles: 1, 2-Azoles. Part 1. Pyrazoles. in *Modern Heterocyclic Chemistry*. Wiley-VCH.ch8. 2, 635–725, 2011.
[22] Komatsu M, Kajihara Y, Kobayashi M, Itoh S, and Ohshiro Y. Ring enlargement of diaziridinone: reactions with bifunctionalized carbanions leading to functionalized pyrazolines or novel spiroheterocycles. *J Org Chem*. 57, 26, 7359–7361, 1992.
[23] Stille J. K, Harris F. W, and Bedford M. A. Phenyl substituted dipyrazoles: 1, 3-Dipole addition reactions of sydnones and nitrilimines. *J Heterocycl Chem*. 3, 155–157, 1966.
[24] Meazza G, Zanardi G, and Piccardi P. A convenient and versatile synthesis of 4-trifluoromethyl-substituted pyrazoles. *J Heterocycl Chem*. 30, 365–371, 1993.
[25] Shawali A. S. Reactions of heterocyclic compounds with nitrilimines and their precursors. *Chem Rev*. 93, 2731–2777, 1993.
[26] Skof M, Svete J, and Stanovnik B. Transformations of (S)-1-Acyl-3-[(E)-(dimethylamino) methylidene]-5-(methoxycarbonyl) pyrrolidin-2-ones. A One-Step Synthesis of (S)-N-Benzoyl-3-(1-heteroaryl-5-hydroxy-1H-pyrazolyl-4) alanine Esters, *Heterocycles: an international journal for reviews and communications in heterocyclic chemistry*. 53, 339–346, 2000.
[27] Okuro K, Furuune M, Miura M, and Nomura M. Palladium-catalyzed cross-carbonylation of aryl iodides and 1-aryl-2-alkyn-1-ones. *J Org Chem*. 57, 4754–4756, 1992.
[28] Ilhan I. O, Saripinar E, and Akcamur Y. Synthesis of some pyrazole-3-carboxylic acid-hydrazide and pyrazolopyridazine compounds. *J Heterocycl Chem*. 42, 117–120, 2005.
[29] Yadav J. S, Reddy B. V. S, Satheesh G, Lakshmi P. N, Kumar S. K, and Kunwar A. C. Rapid and efficient synthesis of optically active pyrazoles under solvent-free conditions. *Tetrahedron Lett*. 45, 46, 8587–8590, 2004.
[30] Guillard J, Goujon F, Badol P, and Poullain D. New synthetic route to diaminonitropyrazoles as precursors of energetic materials .*Tetrahedron Lett*. 44, 31, 5943–5945, 2003.
[31] Takagi K, and Hubert-Habart M. Ring transformation of 5-acylpyrimidines and 5-acyluracils into pyrazoles with hydrazines in acidic medium. *J Heterocycl Chem*. 33, 4, 1003–1015, 1996.
[32] Orrego-Hernández, Jessica; Portilla, Jaime. Synthesis of Dicyanovinyl-Substituted 1-(2-Pyridyl)pyrazoles: Design of a Fluorescent Chemosensor for Selective Recognition of Cyanide. The Journal of Organic Chemistry, (), acs.joc.7b02460. 2017.
[33] Pfeiffer W.-D, Dilk E, Rossberg H, and Langer P. Synthesis and Reactivity of 3, 4-Dimethyl-4H-1, 3, 4-thiadiazines. *Synlett*. 2003, 15, 2392–2394, 2003.
[34] Simoni D, Rondanin R, Furnò G, Aiello E, and Invidiata F. P. Facile synthesis of pyrazoles and pyrroles via thermolysis of tetrazolo[1,5-b]pyridazines, tetrazolo[1,5-a]pyrimidines and tetrazolo[1,5-a]pyridines. *Tetrahedron Lett*. 41, 2699–2703, 2000.
[35] Rykowski A and Branowska D. SULFONYL. SULFONAMIDO AND SULFONYLOXY GROUPS.
[36] Kallman, Neil; Cole, Kevin; Koenig, Thomas; Buser, Jonas; McFarland, Adam; McNulty, LuAnne; Mitchell, David. Synthesis of Aminopyrazoles from Isoxazoles: Comparison of Preparative Methods by in situ NMR Analysis. Synthesis, s-0035-1561861. 2016.
[37] Hassan A. S, Moustafa G. O, Awad H. M, Nossier E. S, and Mady M. F. Design, Synthesis, Anticancer Evaluation, Enzymatic Assays, and a Molecular Modeling Study of Novel Pyrazole–Indole Hybrids. *ACS Omega*. 6,18, 12361–12374, 2021.
[38] Liu J.-J *et al.* Synthesis, biological evaluation of novel 4,5-dihydro-2H-pyrazole 2-hydroxyphenyl derivatives as BRAF inhibitors. *Bioorg Med Chem*. 20, 6089–6096, 2012.
[39] Liu J.-J, Sun J, Fang Y.-B, Yang Y.-A, Jiao R.-H, and Zhu H.-L. Synthesis, and antibacterial activity of novel 4,5-dihydro-1H-pyrazole derivatives as DNA gyrase inhibitors. *Org. Biomol. Chem.*12, 998–1008, 2014.
[40] Khalilullah H, Khan S, Ahsan M. J, and Ahmed B. Synthesis and antihepatotoxic activity of 5-(2,3-dihydro-1,4-benzodioxane-6-yl)-3-substituted-phenyl-4,5-dihydro-1H-pyrazole derivatives. *Bioorg Med Chem Lett*. 21,7251–7254, 2011.
[41] dos Santos M. S *et al.* Synthesis and antileishmanial evaluation of 1-aryl-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole derivatives. *Bioorg Med Chem Lett*. 21, 7451–7454, 2011.
[42] CHENG C. C and ROBINS R. K. Potential Purine Antagonists. VI. Synthesis of 1-Alkyl- and 1-Aryl-4-substituted Pyrazolo[3,4-d]pyrimidines1,2. *J Org Chem*. 21,1240–1256, 1956.
[43] Kendre B. V, Landge M. G, Jadhav W. N, and Bhusare S. R. Synthesis and bioactivities of some new 1H-pyrazole derivatives containing an aryl sulfonate moiety. *Chinese Chemical Letters*. 24, 325–328, 2013.
[44] Patil B. R, Bhusare S. R, Pawar R. P, and Vibhute Y. B. Iodine and iodic acid: an efficient reagent combination for iodination of aryl hydroxy ketones. *Tetrahedron Lett*. 46, 7179–7181, 2005.
[45] Patwari S. B, Baseer M. A, Vibhute Y. B, and Bhusare S. R. Pyridinium bromochromate: a new and efficient reagent for bromination of hydroxy aromatics. *Tetrahedron Lett*. 44, 4893–4894, 2003.

[46] Selvam T. P, Kumar P. V, Saravanan G, and Prakash C. R. Microwave-assisted synthesis, characterization and biological activity of novel pyrazole derivatives. *Journal of Saudi Chemical Society*.18, 1015–1021, 2011.
[47] Sun J, *et al.* Synthesis, biological evaluation and molecular docking studies of pyrazole derivatives coupling with a thiourea moiety as novel CDKs inhibitors. *Eur J Med Chem*. 68, 1–9, 2013.
[48] Sidique S *et al.* Design and synthesis of pyrazole derivatives as potent and selective inhibitors of tissue-nonspecific alkaline phosphatase (TNAP). *Bioorg Med Chem Lett*. 19, 222–225, 2009.
[49] Tsyganov D. V *et al.* cis-Restricted 3-aminopyrazole analogues of combretastatins: synthesis from plant polyalkoxybenzenes and biological evaluation in the cytotoxicity and phenotypic sea urchin embryo assays. *Nat Prod*. 76, 1485–1491, 2013.
[50] Vergelli C, *et al.* Synthesis, biological evaluation, molecular modeling, and structural analysis of new pyrazole and pyrazolone derivatives as N-formyl peptide receptors agonists. *Chem Biol Drug Des*. 98, 582–603, 2021.
[51] Park H.-J *et al.* Identification of antitumor activity of pyrazole oxime ethers. *Bioorg Med Chem Lett*. 15, 3307–3312, 2005.
[52] Wang S.-L, Shi Y.-J, He H.-B, Li Y, Li Y, and Dai H. Synthesis and bioactivity of novel pyrazole oxime derivatives containing oxazole ring. *Chinese Chemical Letters*. 26, 672–674, 2015.
[53] Chandna N, Kapoor J. K, Grover J, Bairwa K, Goyal V, and Jachak S. M. Pyrazolylbenzyltriazoles as cyclooxygenase inhibitors: synthesis and biological evaluation as dual anti-inflammatory and antimicrobial agents. *New Journal of Chemistry*. 38, 3662–3672, 2014.
[54] Onodera S, Kochi T, and Kakiuchi F. Synthesis of N-Arylpyrazoles by Palladium-Catalyzed Coupling of Aryl Triflates with Pyrazole Derivatives. *J Org Chem*. 84, 6508–6515, 2019.
[55] Marinescu M. Synthesis of Antimicrobial Benzimidazole–Pyrazole Compounds and Their Biological Activities. *Antibiotics*. 10, 1002, 2021.
[56] Ibrahim S. A, Fayed E. A, Rizk H. F, Desouky S. E, and Ragab A. Hydrazonoyl bromide precursors as DHFR inhibitors for the synthesis of bis-thiazolyl pyrazole derivatives; antimicrobial activities, antibiofilm, and drug combination studies against MRSA. *Bioorg Chem*,116, 105339, 2021.
[57] Othman I. M. M, Alamshany Z. M, Tashkandi N. Y, Gad-Elkareem M. A. M, Anwar M. M, and Nossier E. S. New pyrimidine and pyrazole-based compounds as potential EGFR inhibitors: Synthesis, anticancer, antimicrobial evaluation and computational studies. *Bioorg Chem*. 114, 105078, 2021.
[58] Draoui Y *et al.* Novel family of bis-pyrazole coordination complexes as potent antibacterial and antifungal agents. *RSC Adv*. 12,17755–17764, 2022.
[59] Liang Z, *et al.* Design, synthesis and antifungal activity of novel pyrazole amides derivates. *J Mol Struct*. 1277,134881, 2023.
[60] Ebenezer O, Shapi M, and Tuszynski J. A. A Review of the Recent Development in the Synthesis and Biological Evaluations of Pyrazole Derivatives. *Biomedicines*.10, 1124, 2022.
[61] Hao Y, *et al.* Synthesis and antifungal evaluation of novel triazole derivatives bearing a pyrazole-methoxyl moiety. *Eur J Med Chem*. 275, 116637, 2024.
[62] Desai N. C, Bhatt K, Monapara J, Pandit U, and Khedkar V. M. Conventional and Microwave-Assisted Synthesis, Antitubercular Activity, and Molecular Docking Studies of Pyrazole and Oxadiazole Hybrids. *ACS Omega*. 6, 42, 28270–28284, 2021.
[63] Zala M, Vora J. J, and Khedkar V. M. Synthesis, Characterization, Antitubercular Activity, and Molecular Docking Studies of Pyrazolylpyrazoline-Clubbed Triazole and Tetrazole Hybrids. *ACS Omega*. 8, 23, 20262–20271, 2023.
[64] Mohamed-Ezzat R. A, *et al.* Synthesis, biological evaluation, and docking studies of pyrazole-linked benzothiazole hybrids as promising anti-TB agents. *J Mol Struct*. 1311,138415, 2024.
[65] Alshabani L. A *et al.* Synthesis, biological evaluation and computational studies of pyrazole derivatives as *Mycobacterium tuberculosis* CYP121A1 inhibitors. *RSC Med Chem*. 13, 1350–1360, 2022.
[66] Bekhit A. A *et al.* Investigation of the anti-inflammatory and analgesic activities of promising pyrazole derivative. *European Journal of Pharmaceutical Sciences*. 168, 106080, 2022.
[67] Mantzanidou M, Pontiki E, and Hadjipavlou-Litina D. Pyrazoles and Pyrazolines as Anti-Inflammatory Agents. *Molecules*. 26, 3439, 2021.
[68] Abdellatif K. R. A, Abdelall E. K. A, Elshemy H. A. H, Lamie P. F, Elnahaas E, and Amin D. M. E. Design, synthesis of new anti-inflammatory agents with a pyrazole core: COX-1/COX-2 inhibition assays, anti-inflammatory, ulcerogenic, histopathological, molecular Modeling, and ADME studies. *Mol Struct*. 1240,130554, 2021.
[69] Abd El-Karim S. S, Mohamed H. S, Abdelhameed M. F, El-Galil E, Amr A, Almehizia A. A, and Nossier E. S. Design, synthesis and molecular docking of new pyrazole-thiazolidinones as potent anti-inflammatory and analgesic agents with TNF-α inhibitory activity. *Bioorg Chem*.111, 104827, 2021.

[70] Ahmed A. H. H *et al.* Design, synthesis, and molecular docking of novel pyrazole-chalcone analogs of lonazolac as 5-LOX, iNOS and tubulin polymerization inhibitors with potential anticancer and anti-inflammatory activities. *Bioorg Chem*. 129,106171, 2022.
[71] Sihag M *et al.* Synthesis of pyrazole and pyrazoline derivatives of β-ionone: Exploring anti-inflammatory potential, cytotoxicity, and molecular docking insights. *European Journal of Medicinal Chemistry Reports*.12, 100204, 2024.
[72] Kapri A, Gupta N, and Nain S. Therapeutic Potential of Pyrazole Containing Compounds: an Updated Review. *Pharm Chem J*. 58, 252–267, 2024.
[73] Kerzare D. R, Menghani S. S, Rarokar N. R, and Khedekar P. B. Development of novel indole-linked pyrazoles as anticonvulsant agents: A molecular hybridization approach. *Arch Pharm (Weinheim)*. 354, 2021.
[74] Nagib M. M *et al.* Inhibition of TRPC3 channels by a novel pyrazole compound confers antiseizure effects. *Epilepsia*. 63, 1003–1015, 2022.
[75] Murugan R *et al.* Neuroprotective potential of pyrazole benzenesulfonamide derivative T1 in targeted intervention against PTZ-induced epilepsy-like condition in in vivo zebrafish model. *Int Immunopharmacol*.131,111859, 2024.
[76] Zhang Y, Wu C., Zhang N, Fan R, Ye Y, and Xu J. Recent Advances in the Development of Pyrazole Derivatives as Anticancer Agents. *Int J Mol Sci*. 24,16, 12724, 2023.
[77] Ashour G. R. S *et al.* Synthesis, modeling, and biological studies of new thiazole-pyrazole analogues as anticancer agents. *Journal of Saudi Chemical Society*. 27, 101669, 2023.
[78] Halim P. A, Sharkawi S. M. Z, and Labib M. B. Novel pyrazole-based COX-2 inhibitors as potential anticancer agents: Design, synthesis, cytotoxic effect against resistant cancer cells, cell cycle arrest, apoptosis induction and dual EGFR/Topo-1 inhibition. *Bioorg Chem*.131, 106273, 2023.
[79] Huo H, Jiang W, Sun F, Li J, and Shi B. Synthesis and biological evaluation of novel steroidal pyrazole amides as highly potent anticancer agents. *Steroids*. 176, 108931, 2021.
[80] Nitulescu G. M. Quantitative and Qualitative Analysis of the Anti-Proliferative Potential of the Pyrazole Scaffold in the Design of Anticancer Agents. *Molecules*. 27, 3300, 2022.
[81] Rokkam S. K *et al.* Synthesis of novel pyrazole acetals of andrographolide and isoandrographolide as potent anticancer agents. *RSC Adv*. 14, 36, 26625–26636, 2024.
[82] El Hassani I. A *et al.* 5-methyl-N'-(thiophen-2-ylmethylene)-1H-pyrazole-3-carbohydrazide as potent anticancer agent: Synthesis, spectroscopic characterization, anticancer activity and DFT studies. *J Mol Struct*, 1324, 140919, 2025.
[83] Boshta N. M, Temirak A, El-Shahid Z. A, Shafiq Z, and Soliman A. A. F. Design, synthesis, molecular docking and biological evaluation of 1,3,5-trisubstituted-1H-pyrazole derivatives as anticancer agents with cell cycle arrest, ERK and RIPK3- kinase activities. *Bioorg Chem*. 143, 107058, 2024.
[84] Edukondalu P *et al. Design*, synthesis and biological evaluation of sulfonamide derivatives of Benzothiazol-Quinoline-Pyrazoles as anticancer agents. *Chemical Data Collections*. 101136, 2024.
[85] Nehra B, Kumar M, Chawla P. A, and Chawla V. Therapeutic Potential of Natural Metabolites Coupled Pyrazole and Its Bio-Isosteres: Medicinal Perspectives and SAR Studies. *ChemistrySelect*, 9, 13, 2024.
[86] Murugan R *et al.* Multifaceted evaluation of pyrazole derivative (T4)-chitosan (CS) nanoparticles: Morphology, drug release, and anti-tumor efficacy in a rat model. *Int J Biol Macromol*. 283, 137702, 2024.
[87] Fadaly W. A. A, Elshaier Y. A. M. M, Ali F. E. M, El-Bahrawy A. H, Abdellatif K. R. A and Nemr M. T. M. Vicinal diaryl pyrazole with tetrazole/urea scaffolds as selective angiotensin converting enzyme-1/cyclooxygenase-2 inhibitors: Design, synthesis, anti-hypertensive, anti-fibrotic, and anti-inflammatory. *Drug Dev Res*. 85, 2024.
[88] Rodríguez J. E, Andrade-Jorge E, Barquet-Nieto A, Estrada-Soto S. E, I. A. Gallardo-Ortíz, and Villalobos-Molina R. BMY 7378, a selective α1D-adrenoceptor antagonist, is a new angiotensin converting enzyme inhibitor: In silico, in vitro and in vivo approach," *Biochimica et Biophysica Acta (BBA) - General Subjects*. 1869, 130732, 2025.
[89] Lusardi M, Spallarossa A, and Brullo C. Amino-Pyrazoles in Medicinal Chemistry: A Review. *Int J Mol Sci*. 24, 7834, 2023.
[90] Gerni S, Ozturk C, Almaz Z, Bayrak C, and Tan A. Celecoxib Derivatives Containing Pyrazole Linked-Sulfonamide Moiety. Carbonic Anhydrase I–II and Acetylcholinesterase Inhibition Profiles, Molecular Docking Studies. *ChemistrySelect*. 8, 29, 2023.
[91] Das S *et al.* Recent Advancement of Pyrazole Scaffold Based Neuroprotective Agents: A Review. *CNS Neurol Disord Drug Targets*. 21, 940–951, 2022.
[92] Zhu P *et al.* Identification of 3-methyl-1-(3-methylpyridin-2-yl)-1H-pyrazol-5-ol as promising neuroprotective agent. *Bioorg Med Chem Lett*. 114, 129983, 2024.

[93] Murugan R *et al.* Neuroprotective potential of pyrazole benzenesulfonamide derivative T1 in targeted intervention against PTZ-induced epilepsy-like condition in in vivo zebrafish model. *Int Immunopharmacol*. 131, 111859, 2024.
[94] Liu X *et al.* The Neuroprotection of 1,2,4-Triazole Derivative by Inhibiting Inflammation and Protecting BBB Integrity in Acute Ischemic Stroke. *CNS Neurosci Ther*. 30, 11, 2024.
[95] Singh H, Kumar R, and Mazumder A. Pyrazoline and Analogs: Substrate-based Synthetic Strategies. *Curr Org Synth*. 21, 823–836, 2024.
[96] Fabitha K, Chandrakanth M, Pramod R. N, Arya C. G , Li Y, and Banothu J. Recent Developments in the Synthesis of Indole-Pyrazole .Hybrids*ChemistrySelect*. 7, 21, 2022.
[97] Ahmadi E, Khazaei A, and Akbarpour T. [Fe3O4@CQD@Si(OEt)(CH2)3NH@CC@Ad@SO3H]+Cl−: As a new, efficient, magnetically separable and reusable heterogeneous solid acid catalyst for the synthesis of 5-amino-1,3-diphenyl-1H-pyrazole 4-carbonitril and pyrano[2,3-c] pyrazole derivatives. *Research on Chemical Intermediates*. 49, 2099–2122, 2023.
[98] Corre P. H. C, Mainwaring J. M, Peralta K. K. Z, Lokman P. M, Porteous R, and Wibowo E. Low dose of propyl-pyrazole-triol, an agonist of estrogen receptor alpha, administration stimulates the Coolidge effect in fadrozole-treated male rats. *Horm Behav*. 161, 105520, 2024.
[99] Ananda H, Sharath Kumar K. S, Sudhanva M. S, Rangappa S, and Rangappa K. S. A trisubstituted pyrazole derivative reduces DMBA-induced mammary tumor growth in rats by inhibiting estrogen receptor-α expression. *Mol Cell Biochem*. 449, 137–144, 2018.
[100] Nishiguchi G. A, Rodriguez A. L, and Katzenellenbogen J. A. Diaryl-dialkyl-substituted pyrazoles: regioselective synthesis and binding affinity for the estrogen receptor. *Bioorg Med Chem Lett*. 12, 947–950, 2002.
[101] Li G, Cheng Y, Han C, Song C, Huang N , and Du Y. Pyrazole-containing pharmaceuticals: target, pharmacological activity, and their SAR studies. *RSC Med Chem*. 13, 1300–1321, 2022.
[102] Bekhit A. A *et al.* Investigation of the anti-inflammatory and analgesic activities of promising pyrazole derivative. *European Journal of Pharmaceutical Sciences*. 168, 106080, 2022.
[103] Mantzanidou M, Pontiki E, and Hadjipavlou-Litina D.Pyrazoles and pyrazolines as anti-inflammatory agents," *Molecules*. 26, 3439, 2021.
[104] Abou-Zied H. A, Beshr E. A. M, Hayallah A. M, and Abdel-Aziz M. Emerging insights into pyrazoline motifs: A comprehensive exploration of biological mechanisms and prospects for future advancements. *J Mol Struct*. 1296, 136807, 2024.
[105] Lampl C, and Likar R. Metamizole (dipyrone): mode of action, drug–drug interactions, and risk of agranulocytosis. *Der Schmerz*. 28, 584–590, 2014.
[106] S. L. Walker, S. G. Withington, and D. N. J. Lockwood, "Leprosy," in *Manson's Tropical Infectious Diseases*. Elsevier, 506-518, 2014.
[107] Cahill K and Ussher M. H. Cannabinoid type 1 receptor antagonists (rimonabant) for smoking cessation. *Cochrane database of systematic reviews*. 3, 2007.
[108] Sotiriou I. Chalkiadaki K, Nikolaidis C, Sidiropoulou K and Chatzaki E. Pharmacotherapy in smoking cessation: Corticotropin releasing factor receptors as emerging intervention targets. *Neuropeptides*. 63, 49–57, 2017.
[109] Kumar R, Kaur R, Dahiya L , and Kumar M. Vicinal Diaryl Pyrazole: A Therapeutically Potential Molecular Scaffold. in *Vicinal Diaryl Substituted Heterocycles*. Elsevier. 161–189, 2018.
[110] Nonomura N *et al.* Final analysis of post-marketing surveillance for avelumab+ axitinib in patients with renal cell carcinoma in Japan," *Cancer Med*. 14, e70275, 2025.
[111] Oya M, Ito T, Sato M, Morita M, Kajita M, and Nonomura N. Avelumab+ axitinib treatment in older patients with advanced renal cell carcinoma in Japan: Subgroup analyses of post-marketing surveillance data by age. *Cancer Med*. 14, e70186, 2025.
[112] Marbin A, Brooke M, Thomas B, Martinez B. M, Blum B, and Neuhut S. Zaleplon Versus Zolpidem Use in Older Adults Being Treated for Insomnia: A Review. *The American Journal of Geriatric Psychiatry*. 31, S68–S69, 2023.
[113] Huedo-Medina T. B, Kirsch I, Middlemass J, Klonizakis M , and Siriwardena A. N. Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. *Bmj*. 345, 2012.
[114] Ebbens M. M and Verster J. C. Clinical evaluation of zaleplon in the treatment of insomnia. *Nat Sci Sleep*. 115–126, 2010.
[115] Dooley M and Plosker G. L. Zaleplon: a review of its use in the treatment of insomnia. *Drugs*. 60, 413–445, 2000.
[116] Hasan U, Chauhan M, Basu S. M, and Giri J. Overcoming multidrug resistance by reversan and exterminating glioblastoma and glioblastoma stem cells by delivering drug-loaded nanostructure hybrid lipid capsules (nHLCs). *Drug Deliv Transl Res*. 14, 342–359, 2024.

[117] Hasan U, Rajakumara E , and Giri J. Reversal of multidrug resistance by the synergistic effect of reversan and hyperthermia to potentiate the chemotherapeutic response of doxorubicin in glioblastoma and glioblastoma stem cells. *ACS Appl Bio Mater*, 6, 5399–5413, 2023.
[118] Inceler N, Yılmaz A, and Baytas S. N. Synthesis of ester and amide derivatives of 1-phenyl-3-(thiophen-3-yl)-1 H-pyrazole-4-carboxylic acid and study of their anticancer activity. *Medicinal Chemistry Research*. 22, 3109–3118, 2013.
[119] Bai X. G *et al.* Design, synthesis and anticancer activity of 1-acyl-3-amino-1,4,5,6- tetrahydropyrrolo[3,4-c]pyrazole derivatives. *Bioorg Med Chem Lett*. 22, 6947–6951, 2012.
[120] Nitulescu G. M, Draghici C, and Missir A. V. Synthesis of new pyrazole derivatives and their anticancer evaluation. *Eur J Med Chem*, vol. 45, no. 11, pp. 4914–4919, Nov. 2010, doi: 10.1016/j.ejmech.2010.07.064.
[121] Kamal A *et al.* Design and synthesis of pyrazole-oxindole conjugates targeting tubulin polymerization as new anticancer agents . *Eur J Med Chem*. 92, 501–513, 2015.
[122] Shi J. B, Tang W. J, Qi X. B, Li R, and Liu X. H. Novel pyrazole-5-carboxamide and pyrazole-pyrimidine derivatives: Synthesis and anticancer activity. *Eur J Med Chem*. 90, 889–896, 2015.
[123] Koca I, Özgür A, Coşkun K. A, and Tutar Y. Synthesis and anticancer activity of acyl thioureas bearing pyrazole moiety. *Bioorg Med Chem*, 21, 3859–3865, 2013.
[124] Rokkam S. K *et al.* Synthesis of novel pyrazole acetals of andrographolide and isoandrographolide as potent anticancer agents. *RSC Adv*. 14, 26625–26636, 2024.
[125] Yasser N, Sroor F. M, El-Shorbagy H. M, Eissa S. M, Hassaneen H. M, and Abdelhamid I. A. Synthesis, anticancer evaluation of novel hybrid pyrazole-based chalcones, molecular docking, DNA fragmentation, and gene expression: in vitro studies. *RSC Adv*.14, 21859–21873, 2024.
[126] Hassan A. S, Moustafa G. O, Awad H. M, Nossier E. S, and Mady M. F. Design, synthesis, anticancer evaluation, enzymatic assays, and a molecular modeling study of novel pyrazole-indole hybrids. *ACS Omega*. 6, 12361–12374, 2021.
[127] Kurban B, Sağlık B. N, Osmaniye D, Levent S, Özkay Y, and Kaplancıklı Z. A. Synthesis and Anticancer Activities of Pyrazole-Thiadiazole-Based EGFR Inhibitors. *ACS Omega*. 8, 31500–31509, 2023.
[128] Zheng Y *et al.* Design, synthesis, quantum chemical studies and biological activity evaluation of pyrazole-benzimidazole derivatives as potent Aurora A/B kinase inhibitors," *Bioorg Med Chem Lett*, 23, 3523–3530, 2013.
[129] Akbas E, Berber I, Sener A, and Hasanov B. Synthesis and antibacterial activity of 4-benzoyl-1-methyl-5-phenyl-1H-pyrazole-3-carboxylic acid and derivatives. *Il Farmaco*. 60, 23–26, 2005.
[130] Prasath R, Bhavana P, Sarveswari S, Ng S. W, and Tiekink E. R. T. Efficient ultrasound-assisted synthesis, spectroscopic, crystallographic and biological investigations of pyrazole-appended quinolinyl chalcones. *J Mol Struct*, 1081, 201–210, 2015.
[131] Tanitame A *et al.* Synthesis and antibacterial activity of a novel series of potent DNA gyrase inhibitors. Pyrazole derivatives. *J Med Chem*. 47, 3693–3696, 2004.
[132] El-Naggar M , Rashdan H. R. M , and Abdelmonsef A. H. Cyclization of Chalcone Derivatives: Design, Synthesis, In Silico Docking Study, and Biological Evaluation of New Quinazolin-2,4-diones Incorporating Five-, Six-, and Seven-Membered Ring Moieties as Potent Antibacterial Inhibitors. *ACS Omega*. 8, 27216–27230, 2023.
[133] Zayda M. G, Abdel-Rahman A. A. H, and El-Essawy F. A. Synthesis and Antibacterial Activities of Different Five-Membered Heterocyclic Rings Incorporated with Pyridothienopyrimidine. *ACS Omega*. 5, 6163–6168, 2020.
[134] Govindaraju S *et al.* Mn2(CO)10 catalyzed visible-light-promoted synthesis of 1H-pyrazole-4-carboxamides; A sustainable multi-component statergy with antibacterial and cytotoxic evaluations. *J Organomet Chem*. 1022, 2024.
[135] Farghaly A. R, Ahmed S. A, Ismail K. S, Ibrahim D, Amri N, and Elgogary S. Synthesis, antitumor activity, antimicrobial evaluation and molecular docking studies of some hydrazone, 1,3,4-oxadiazole, 1,2,4-triazole and pyrazole derivatives bearing nicotinoyl moiety. *Results Chem*. 7, 2024.
[136] Chalkha M *et al.* Synthesis, Characterization, DFT Mechanistic Study, Antimicrobial Activity, Molecular Modeling, and ADMET Properties of Novel Pyrazole-isoxazoline Hybrids. *ACS Omega*. 7, 50, 46731–46744, 2022.
[137] Nandurkar Y, Shinde A, Bhoye M. R, Jagadale S, and Mhaske P. C. Synthesis and Biological Screening of New 2-(5-Aryl-1-phenyl-1H-pyrazol-3-yl)-4-aryl Thiazole Derivatives as Potential Antimicrobial Agents. *ACS Omega*. 8, 8743–8754, 2023.
[138] Shao Y *et al.* Synthesis, biological activity and toxicity to zebrafish of benzamides substituted with pyrazole-linked 1,2,4-oxadiazole. *RSC Adv*. 12, 23544–23551, 2022.

[139] Yang J, Xie D, Zhang C, Zhao C, Wu Z, and Xue W. Synthesis, antifungal activity and in vitro mechanism of novel 1-substituted-5-trifluoromethyl-1H-pyrazole-4-carboxamide derivatives," *Arabian Journal of Chemistry*. 15, 2022.
[140] Danne A. B, Deshpande M. V, Sangshetti J. N, Khedkar V. M, and Shingate B. B. New 1,2,3-Triazole-Appended Bis-pyrazoles: Synthesis, Bioevaluation, and Molecular Docking. *ACS Omega*. 6, 24879–24890, 2021.
[141] Li M *et al.* Design, Synthesis, and Evaluation of Antifungal Bioactivity of Novel Pyrazole Carboxamide Thiazole Derivatives as SDH Inhibitors. *J Agric Food Chem*. 71, 11365–11372, 2023.
[142] Long Z. Q. *et al.* Fabrication of Versatile Pyrazole Hydrazide Derivatives Bearing a 1,3,4-Oxadiazole Core as Multipurpose Agricultural Chemicals against Plant Fungal, Oomycete, and Bacterial Diseases. *J Agric Food Chem*. 69, 8380–8393, 2021.
[143] Ouyang G *et al.* Synthesis and antiviral activities of pyrazole derivatives containing an oxime moiety. *J Agric Food Chem*. 56 , 10160–10167, 2008.
[144] Liu Y *et al. Synthesis* and Biological Activities of Novel Pyrazole Carboxamides Containing an Aryloxypyridyl Ethylamine Module. *J Agric Food Chem*. 72, 3342–3353, 2024.
[145] Mahesh P *et al.* Antiproliferative Activity of New Pyrazole-4-sulfonamide Derivatives: Synthesis and Biological Evaluation. *ACS Omega*. 8, 25698–25709, 2023.
[146] Peerzade N. A *et al.* Pyrazole-based N-phenyl pyrazolines: Synthesis, docking, and pharmacological evaluation. *Results Chem*. 11, 2024.
[147] Khator R. , Monga V., Recent advances in the synthesis and medicinal perspective of pyrazole-based α-amylase inhibitors as antidiabetic agents, *Future Med. Chem.* 16, 173-195. 2024.
[148] Kumar P., Duhan M., Kadyan K., Sindhu J., Kumar S., Sharma H., Synthesis of novel inhibitors of α-amylase based on the thiazolidine-4-one skeleton containing a pyrazole moiety and their configurational studies, Medchemcomm. 8, 1468–1476, 2017
[149] M. Duhan, R. Singh, M. Devi, J. Sindhu, R. Bhatia, A. Kumar, P. Kumar, Synthesis, molecular docking and QSAR study of thiazole clubbed pyrazole hybrid as α-amylase inhibitor, J. Biomol. Struct. Dyn. 39 (2021) 91–107.
[150] V. Maksimov, R. Zaynullin, N. Akhmadiev, E.P. Segura-Ceniceros, J.L. Martínez Hernández, E. Bikbulatova, V. Akhmetova, R. Kunakova, R. Ramos, A. Ilyina, Inhibitory effect of 4, 4′-[ethane-1, 2-diylbis (sulfandiylmethanediyl)] bis (3, 5-dimethyl-1 H-pyrazole) and its derivatives on alpha-amylase activity, Med. Chem. Res. 25 (2016) 1384–1389.
[151] A. Oulous, N.E. Daoudi, T. Harit, M. Cherfi, M. Bnouham, F. Malek, New pyrazole-tetrazole hybrid compounds as potent α-amylase and non-enzymatic glycation inhibitors, Bioorg. Med. Chem. Lett. 69 (2022) 128785.
[152] G. Bansal, S. Singh, V. Monga, P.V. Thanikachalam, P. Chawla, Synthesis and biological evaluation of thiazolidine-2, 4-dione-pyrazole conjugates as antidiabetic, anti-inflammatory and antioxidant agents, Bioorg. Chem. 92 (2019) 103271.
[153] S. Mortada, K. Karrouchi, E.H. Hamza, A. Oulmidi, M.A. Bhat, H. Mamad, Y. Aalilou, S. Radi, M. Ansar, A. Masrar, Synthesis, structural characterizations, in vitro biological evaluation and computational investigations of pyrazole derivatives as potential antidiabetic and antioxidant agents, Sci. Rep. 14 (2024) 1312.
[154] P. Singh, S. Mothilal, N. Kerru, A. Singh-Pillay, L. Gummidi, O.L. Erukainure, M.S. Islam, Comparative α-glucosidase and α-amylase inhibition studies of rhodanine–pyrazole conjugates and their simple rhodanine analogues, Med. Chem. Res. 28 (2019) 143–159.
[155] S. Taj, M. Ahmad, A. Alshammari, A. Alghamdi, U.A. Ashfaq, Exploring the therapeutic potential of benzothiazine-pyrazole hybrid molecules against alpha-glucosidase: Pharmacological and molecular modelling based approach, Saudi J. Biol. Sci. 29 (2022) 1416–1421.
[156] A. Ahmed, S. Zaib, M.A. Bhat, A. Saeed, M.Z. Altaf, F.T. Zahra, G. Shabir, N. Rana, I. Khan, Acyl pyrazole sulfonamides as new antidiabetic agents: synthesis, glucosidase inhibition studies, and molecular docking analysis, Front. Chem. 12 (2024) 1380523.
[157] Mortada, S., Karrouchi, K., Hamza, E.H., Oulmidi, A., Bhat, M.A., Mamad, H., Aalilou, Y., Radi, S., Ansar, M.H., Masrar, A. and Faouzi, M.E.A., 2024. Synthesis, structural characterizations, in vitro biological evaluation and computational investigations of pyrazole derivatives as potential antidiabetic and antioxidant agents. *Scientific Reports*, *14*(1), p.1312.
[158] Naglah, A.M., Almehizia, A.A., Al-Wasidi, A.S., Alharbi, A.S., Alqarni, M.H., Hassan, A.S. and Aboulthana, W.M., 2024. Exploring the Potential Biological Activities of Pyrazole-Based Schiff Bases as Anti-Diabetic, Anti-Alzheimer's, Anti-Inflammatory, and Cytotoxic Agents: In Vitro Studies with Computational Predictions. *Pharmaceuticals*, *17*(5), p.655.
[159] Aroua, L.M., Alkhaibari, I.S., Alminderej, F.M., Messaoudi, S., Chigurupati, S., Al-mahmoud, S.A., Albadri, A.E., Emwas, A.H. and Mohammed, H.A., 2025. Synthesis, bioactivity, and molecular docking

of pyrazole bearing Schiff-bases as prospective dual alpha-amylase and alpha-glucosidase inhibitors with antioxidant activity. *Journal of Molecular Structure*, *1320*, p.139291.

[160] Naglah, A.M., Almehizia, A.A., Ghazwani, M., Al-Wasidi, A.S., Naglah, A.A., Aboulthana, W.M. and Hassan, A.S., 2025. In Vitro Enzymatic and Computational Assessments of Pyrazole–Isatin and Pyrazole–Indole Conjugates as Anti-Diabetic, Anti-Arthritic, and Anti-Inflammatory Agents. *Pharmaceutics*, *17*(3), p.293.