Life Science Informatics Publications

Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences

Journal Home page http://www.rjlbpcs.com/

RJLBPCS

ISSN 2454-6348

Original Review Article **DOI: 10.26479/2025.1103.02**

SYNTHETIC STRATEGIES AND BIOLOGICAL APPLICATIONS OF PYRAZOLE: A REVIEW

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ABSTRACT: A significant group of biologically relevant heterocycles that have attracted greater interest in the field of medicinal chemistry is made up of an extensive variety of structurally varied natural compounds consisting of pyrazole nuclei. Among azoles, pyrazoles are unusual in nature, presumably due to the fact that living things have a hard time forming NeN bonds. Nonetheless, they have a wide range of biological attributes, among which are anti-inflammatory, antiviral, anticancer, antifungal, and antidiabetic properties. The current review aims to comprehend the chemistry and therapeutic significance of natural products containing pyrazoles that have been documented to date. This will undoubtedly aid the scientific community in expanding the methods for isolating and synthesizing newly discovered bioactive substances based on pyrazoles. Owing to their superior biological activity, condensed pyrazole derivates are significant heterocyclic compounds that have found widespread application in the agromedical and pharmaceutical sectors. Several condensed pyrazole compounds with an array of biological properties have been created recently and advanced to clinical trials. In order to provide assistance for the creation and manufacture of condensed pyrazole derivatives with favorable biological activities, an in-depth discussion of biological properties and applications in pharmaceutical sectors is provided.

Keywords: Pyrazole nucleus, Biological activity, Anti-cancer, Anti-inflammatory, Anti-leishmanial, Analgesic.

Article History: Received: June 10, 2025; Revised: June 22, 2025; Accepted: June 30, 2025.

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1. INTRODUCTION

Pyrazoles and their derivatives represent an important framework in pharmaceutical and agrochemical sciences. Nearly seventy percent of the heterocyclic anticancer drugs that were granted FDA approval between 2010 and 2015 comprised nitrogen-based heterocycles, making them especially noteworthy in the design of drugs to combat cancer. Research has revealed that indoles are among the most precious nitrogen heterocyclic scaffold since they may trigger cell death in a range of cancer cell types [1]. It has been demonstrated in the past few decades that indole and its derivates alter several processes in cells linked to the onset of cancer. These consist of the capability to trigger oxidative stress and cellular death, in addition to the inhibition of cell signaling, conventional progression of the cell cycle, vascularization of the tumor and the reconstruction of DNA. Vincristine and vinblastine, two of the most essential initial indole-based anticancer drugs, have been widely known from the very early to mid-1960s for hindering tubulin polymerization and continue to be employed in medical procedures presently. Although vinblastine is typically administered for the management of progressive Hodgkin's disease and carcinoma of the testes, vincristine (**Figure 1**) can be employed as a combinatorial treatment for patients with acute lymphoblastic leukemia and both Hodgkin's as well as non-Hodgkin's lymphoma. Vinblastine functions by disrupting tubulin polymerization, which suppresses cancer cell division by triggering an arrest in the cell cycle [2]. Indolocarbazoles are a closely associated indoles derivatives that have garnered a lot of curiosity currently for their potential to treat cancer since, comparable to the broader spectrum of heterocycles itself, they exhibit a wide range of actions.

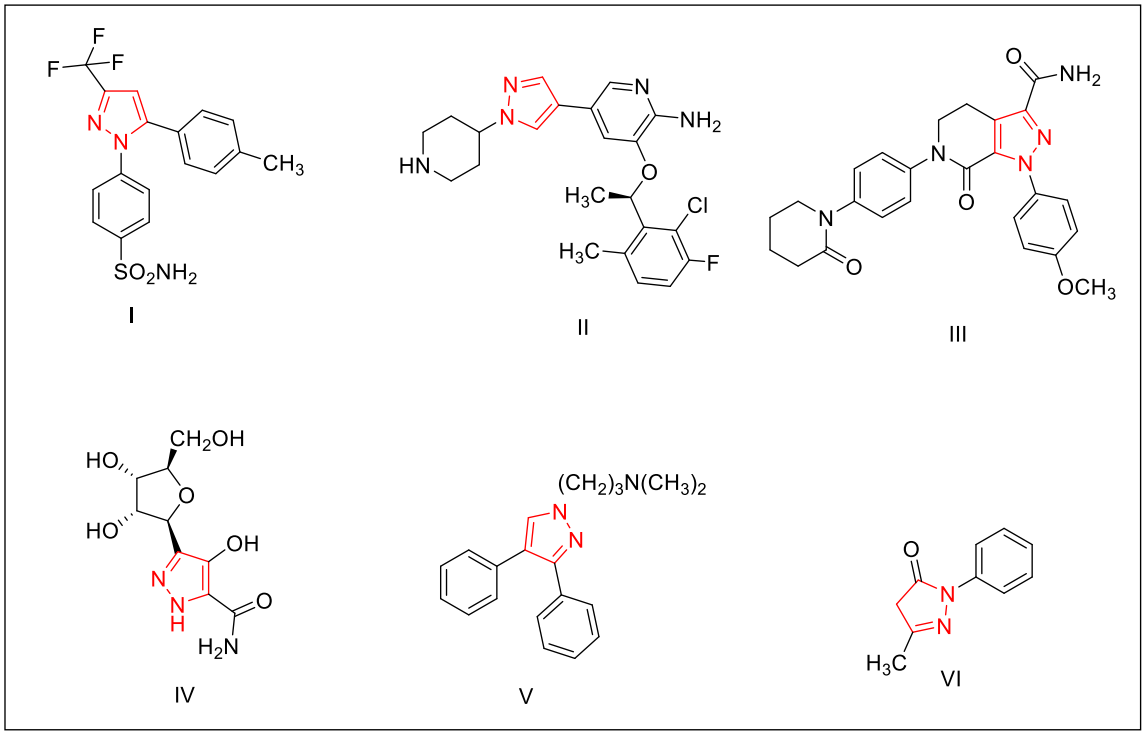

Figure 1. Biologically active compounds having pyrazole ring

Peer review under the responsibility of Life Science Informatics Publications
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A crucial framework in pharmaceutical chemistry is the pyrazole ring.Pyrazole is a heterocyclic ring with five constituent parts, composed of two adjoining nitrogen atoms and three carbons. An extensive variety of medicinal and pharmacological properties, including anticancer [3], antiviral [4], antitubercular [5], antimicrobial [6], antimalarial [7], anti-inflammatory [8], antihypertensive [9], anti-Alzheimer's [10], antipsychotic [11], and antiparkinsonian [12], have attracted a lot of attention to pyrazole derivatives. Numerous medications having pyrazole rings have entered the market, among which are celecoxib I, that possesses anti-inflammatory [13] benefits, Crizotinib II [14], which has anticancer [15] properties, Apixaban III [16], which has anticoagulant attributes, Pyrazofurin IV, which has anticancer properties, antibiotics, and fezolamine V, which has antidepressant [17] features.By boosting antioxidant enzymes like GPx and slowing down the lipid peroxidation process, the pyrazole (1,2-diazole) exhibits antioxidant activity and can stop oxidative stress. Examples of 1,2-diazole's or its related medications' pharmacological effects.

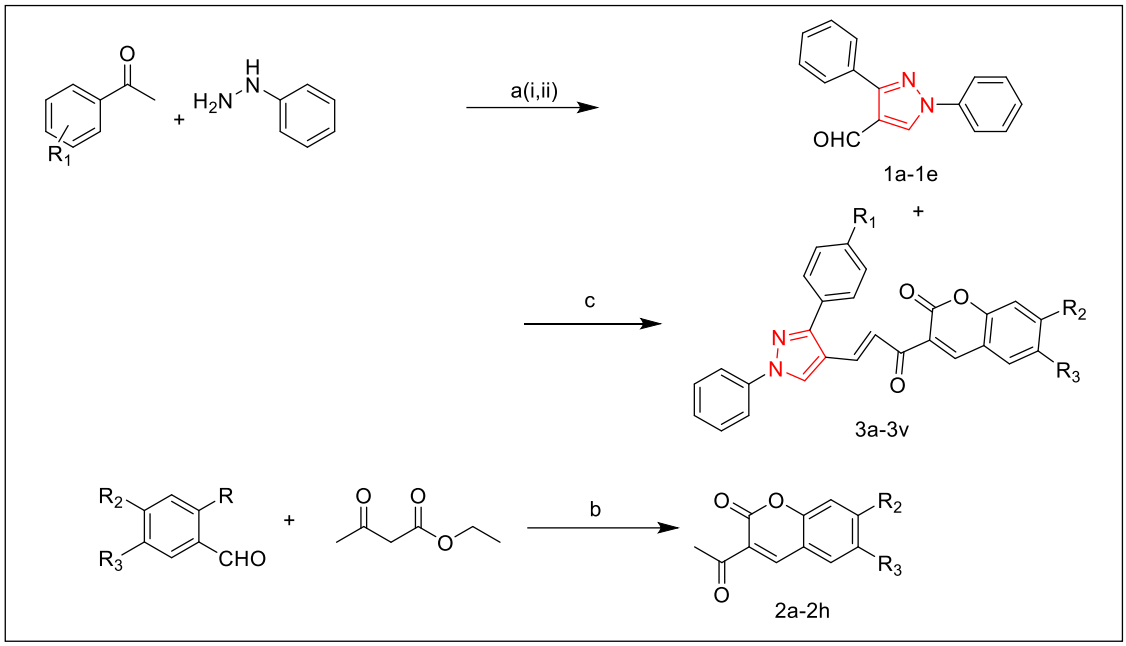
It was discovered that 1,2-Diazole successfully averted nephrotoxicity induced by the anti-neoplastic medication cisplatin [18]. A recently developed antioxidant called Edaravone VI has been utilized for the treatment of stroke patients who have recently had a cerebrovascular infarction and to augment ischemia/reperfusion-induced hepatic metabolism of energy [19-21].

Synthesis of pyrazole derivatives:

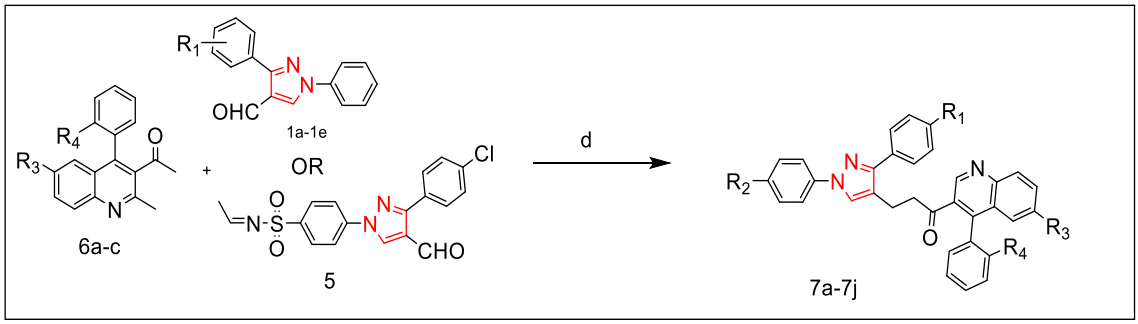
1. Synthesis of acrylic pyrazole coumarin and acrylic pyrazole-quinoline:

As depicted in Schemes 1 and 2, the corresponding compounds were synthesized. A substituted hydrazone was produced by reacting the modified acetophenones with aromatic hydrazines in methanol and glacial acetic acid. The Vilsmeier–Haack reaction was utilized to cyclize and formylate the consequent hydrazones. In order to generate modified pyrazole carbaldehydes (1a–e), the newly produced hydrazones were dissolved in dimethylformamide (DMF), introduced to the Vilsmeier–Haack reagent that was produced in situ (with $POCl_3$ and DMF), and magnetically agitated at 75°C. Three-acetyl coumarin derivatives were created via the Knoevenagel condensation method. In the presence of piperidine, the substituted salicylaldehyde and ethyl acetoacetate interacted to produce substituted 3-acetyl coumarin derivatives (2a–h). Chalcones were created using the Claisen–Schmidt condensation reaction. Acrylic pyrazole–coumarin equivalents (3a–v) have been generated by the interaction of altered pyrazole carbaldehydes with transformed 3-acetyl coumarin in a piperidine atmosphere. Sulfonamide was employed in the production of 4-hydrazinylbenzenesulfonamide hydrochloride. For the manufacture of a diazonium-based sulfonamide salt, the sulfonamide was dispersed in HCl and subsequently diazotized at 0–5°C with accessible sodium nitrite. The diazonium salt of sulfonamide is the precursor of hydrazine. Utilizing stannous chloride (dissolved in HCl at 0–5°C) to minimize the diazonium salt solution in situ, 4-hydrazinylbenzenesulfonamide hydrochloride (4) was prepared and stored in the refrigerator as long as it was required. Hydrazone was produced by the reaction of p-chloroacetophenone with 4

hydroxyzinyl benzene sulfonamide hydrochloride. The consequent hydrazones were cyclized and formylated incorporating the Vilsmeier-Haack reaction, yielding N′-((4-(3-(4-chlorophenyl)-4-formyl-1H-pyrazol-1-yl)phenyl)sulfonyl)-N,N- dimethyl formimidmide (5). Friedländer annulation was employed to yield modified 3-acetyl quinoline compounds. By refluxing altered 2-aminobenzophenone and acetylacetone with 10 mol% sodium trifluoro methane sulfonate, substituted 3-acetyl quinoline derivatives (6a–c) were prepared [22–24]. The mechanistic interaction of modified 3-acetyl quinoline with altered pyrazole carbaldehyde afforded aromatic pyrazole–quinoline compounds (7a–j).



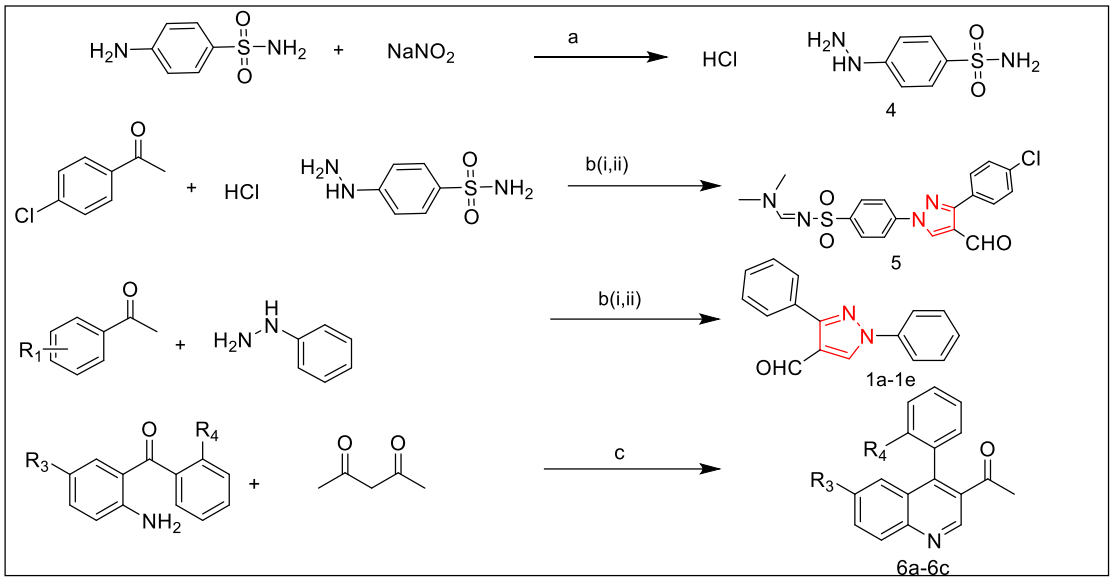
Scheme 1: Synthesis of acrylic pyrazole-coumarins



Scheme 2: Synthesis of aromatic pyrazole-quinoline compounds

The target compounds were synthesized using the procedures outlined in **Scheme 3**. The important intermediates have been produced by condensing N, N-dimethylamino methylene-4-(4-formyl-3-phenyl-1H-pyrazol-1-yl) benzene sulfonamide with N4-substituted thiosemicarbazides. Benzene sulfonamides 2a-c, N, N dimethyl aminomethylene-4- [3-phenyl-4-(substituted thiosemicarbamoyl hydrazonomethyl)-1H-pyrazol-1-yl]. By treating the essential intermediates as precursors 2a-c with ethyl bromoacetate, the corresponding thiazolidinonyl derivatives 3a-c were produced. Similarly,

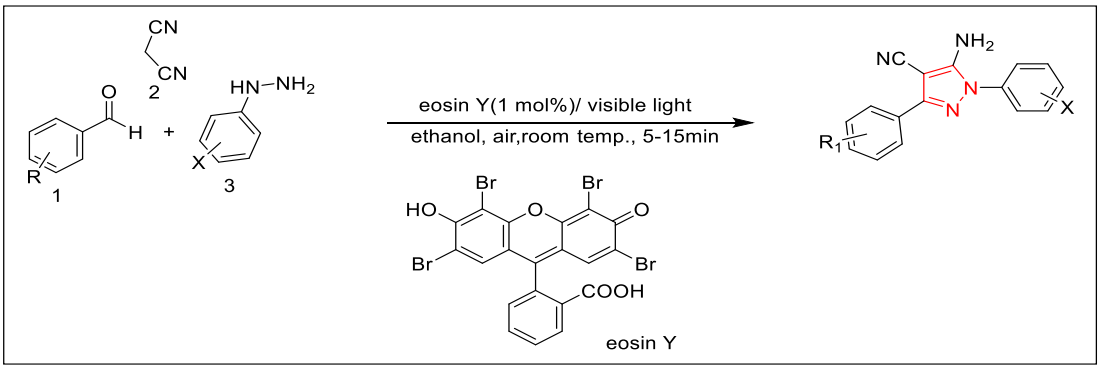
when 2a-c interacted with 4-bromophenacyl bromide, equivalent thiazolinyl counterparts 4a-c were generated. By heating the important intermediates 2a-c with a 2 M $FeCl_3$ solution, the corresponding 1,3,4-thiadiazole versions 5a-c were produced. Furthermore, intermediates 2a-c were transformed into 1,3,4-thiadiazolines 6a-c through refluxing with acetic anhydride [25].



Scheme 3: Synthesis of acrylic pyrazole-quinoline

2. Synthesis of pyrazole derivative in the presence of visible light

Aldehyde (1a) 1 mmol, malononitrile (2a) 1 mmol, and phenyl hydrazine (3a) 1 mmol were all reacted in ethanol with 1 mol% eosin Y and air in our preliminary effort. At ambient temperature, the reaction mixture was exposed to a basic, portable fluorescent lamp (CFL, 22W). Adequate purity and a high yield of the aimed product were attained. This motivated us to execute numerous assays to validate that a range of reaction factors, including catalyst, solvent, light, time, and air, are required so as to maximize the product's yield.It was inferred that ethanol is the suitably apt solvent for the reaction since its utilization led to remarkable yield and simple and feasible workup [26-28].

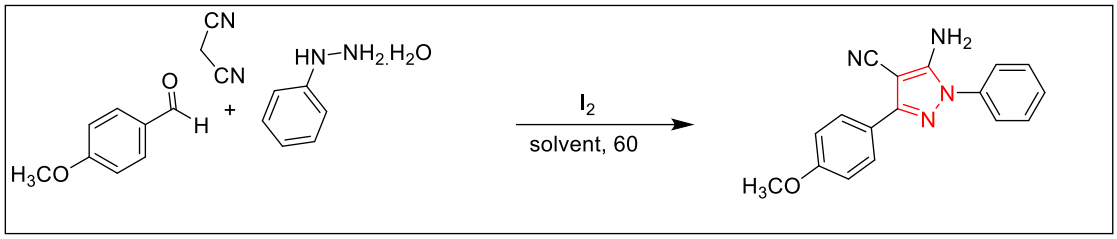


Scheme 4: Synthesis of pyrazole derivative.

3. Synthesis of pyrazole derivative

A round-bottom flask containing 50 milliliters of water was filled with 20 mol% of iodine, one mmol of aldehyde, and one mmol of malanonitrile. The following step was addition 1 mmol of phenyl hydrazine. On reaction's timely completion, water was then transferred to the reaction

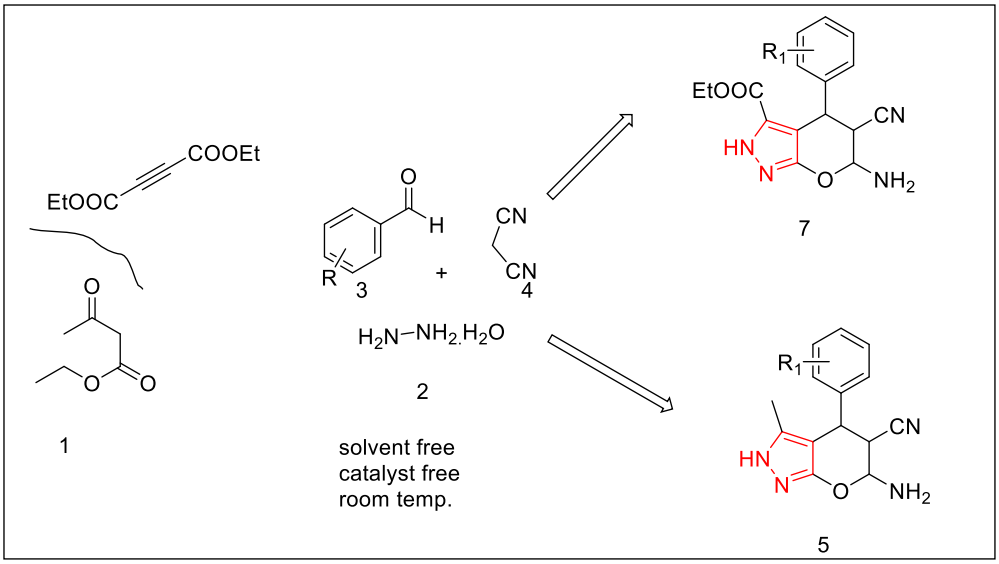
mixture (along with a tiny bit of $Na_2S_2O_3$). After being filtered, the solid crude products were cleaned with water and allowed to dry. A single spot appeared on the TLC plate (silica gel coated aluminum plates, Merk) after the isolated product was obtained and evaluated with the use of TLC. Ethyl acetate was utilized three times to extract products 5c (a semi-solid) and 5i (a liquid). To generate the final pure product, the mixed organic phases have been air-dried over anhydrous Na2SO4 and then filtered and evaporated once the reaction was terminated (as indicated by TLC).All resulting solid products (except 5i and 5c) were recrystallised from hotethanol [29-30].



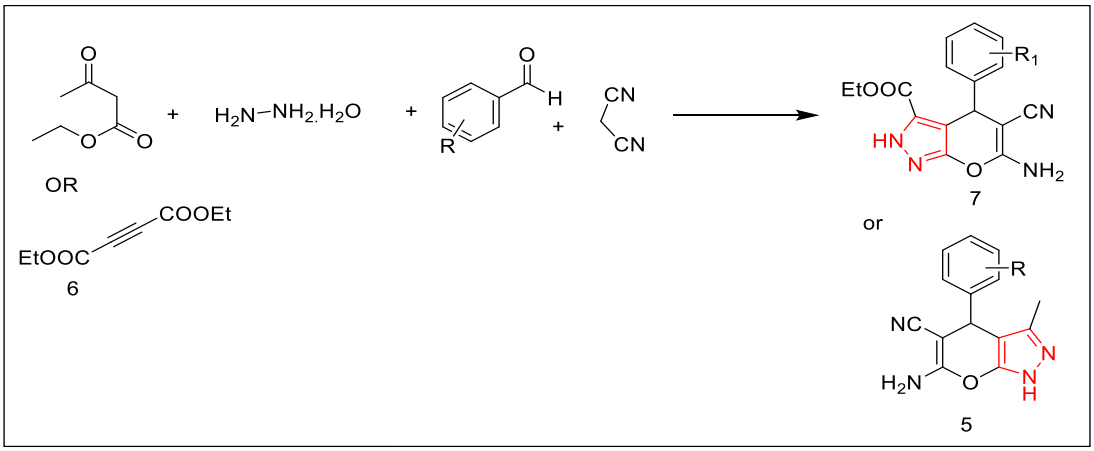
Scheme 5: Synthesis of substituted pyrazole.

4. Synthesis of dihydropyrano[2,3-c] pyrazole

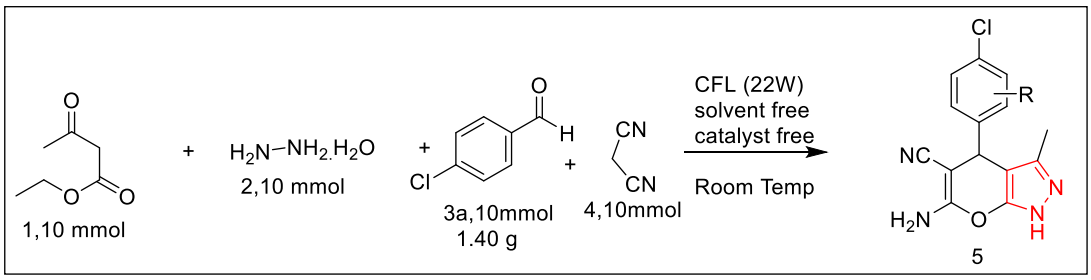
Ethylacetoacetate (**1**, 10 mmol), hydrazine hydrate (**2**, 10 mmol), 4-chlorobenzaldehyde (**3,** 10 mmol, 1.40 g) and malononitrile (**4,** 10 mmol), was reacted to attain the dihydropyrano[2,3-c]-pyrazole (**5**) with yield of about 88% in a time span of 15 minutes by utilizing CFL and usualexperimental apparatuswithout incorporating catalyst and solvent at ambient temperature (**Scheme 6,7,8**) [31-39].



Scheme 6: Synthesis of dihydropyrano[2,3-c] pyrazole



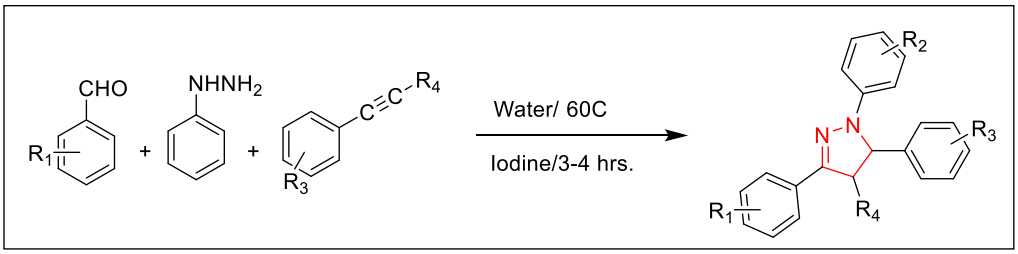
Scheme 7: Synthesis of dihydropyrano[2,3-c] pyrazole



Scheme 8: Synthesis of dihydropyrano[2,3-c] pyrazole

5. Synthesis of 1,3,5-trisubstituted pyrazole :

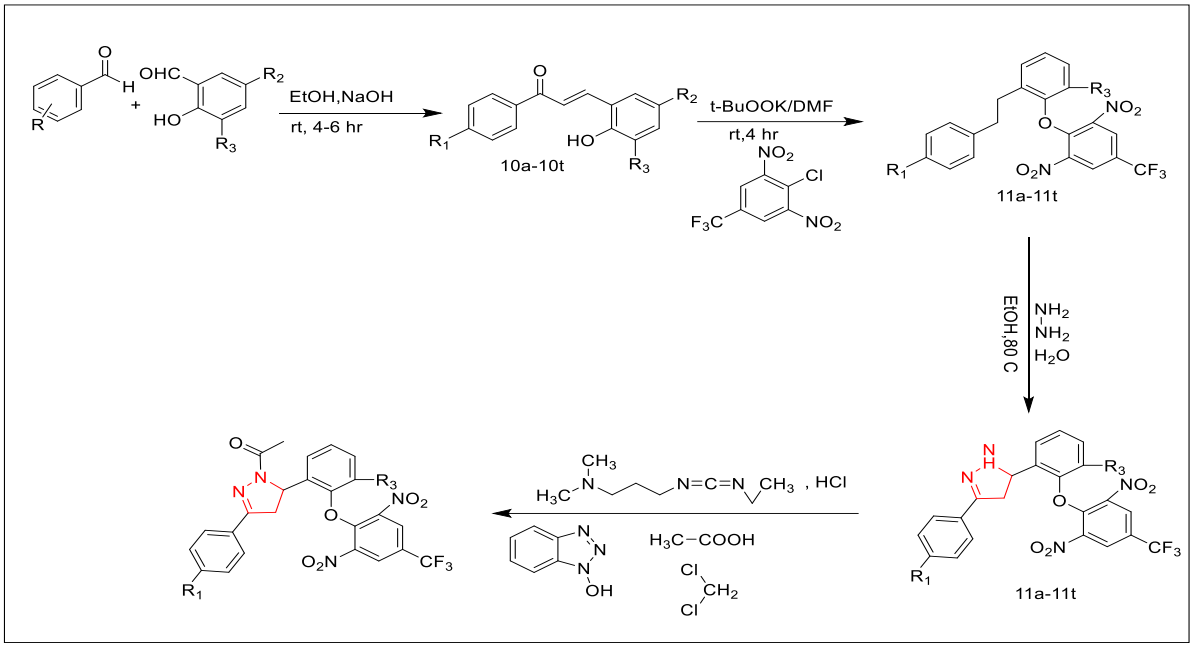
To a 20ml r.b. flask, aldehyde 1a (1mmol), hydrazine 2a (1mmol), phenylacetylene 3a (1mmol), water (5ml) and iodine (20mol %) were added subsequently. The reaction mixture was stirred at 60℃ and analyzed using TLC. Upon completion (usually 3-4 hours) water was decanted under pressure and consequently the precipitate was purified bycolumn chromatography (hexane/ethyl acetate) in silica gel to accomplish the target moeity 1,3,5 trisubstitutedpyrazoles [40-42].



Scheme 9: Synthesis of 1,3,5-trisubstituted pyrazole

6.Synthesis of 4,5-dihydro-1H-pyrazole derivatives (13a–13t) as DNA gyrase inhibitors.

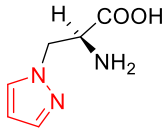
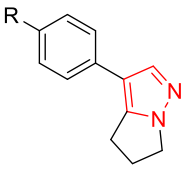
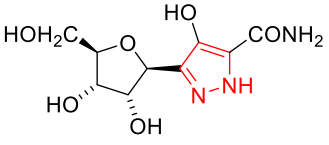
An alternate synthetic pathway to 4,5-dihydro-1H-pyrazole derivatives [43-45] as DNA gyrase inhibitors was reported [46] (**Scheme 10**). Prior to reacting with hydrazine hydrate in refluxing ethanol for eight hours, the chalcones were first enabled to react with 1-chloro-2,6-dinitro-4-tri-Fluoro methylbenzene in the presence of potassium tert-butoxide to produce 11a–11t. After that, solutions of compounds were treated with EDC (I) and HOBT (II) to get the required products .

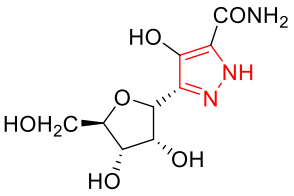
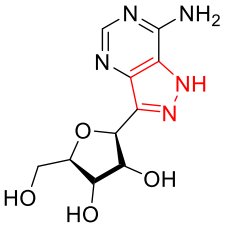
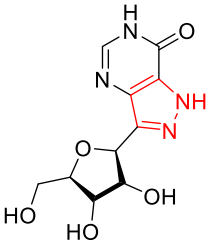
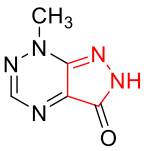
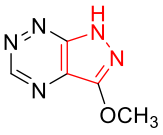
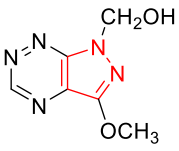


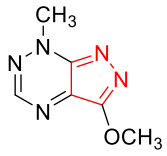
Scheme 10: Synthesis of 4,5-dihydro-1H-pyrazole derivatives .

Applications of substituted pyrazoles

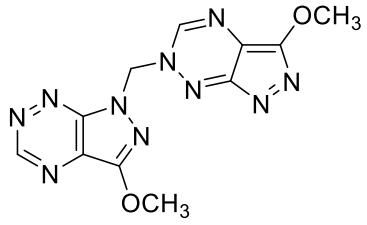
Table 1 Natural products containing pyrazole moieties and its medical applications

Name	Isolated from	Structure	Applications
L-α-Amino-β (pyrazolyl-N)-propanoic acid-First natural product containing pyrazole	*Citrullus vulgaris*		-Antidiabetic
Withasomnine 4'-Hydroxywithasomnine 4'-Methoxywithasomnine	*Withania somnifera Dun*	 R= H,OH,OMe	-Analgesic -Anti-inflammatory Depressant to -CNS(Central Nervous System) -Circulatory System
Pyrazofurin Pyrazofurin B	*Streptomyces candidus*	 Pyrazofurin	

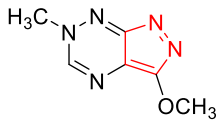
		 Pyrazofurin B	-Antitumor -Antiviral
Formycin	*Streptomyces candidus,Streptomycin lavendulae and Norcadia interforma*	 Formycin	-Antiviral -Antitumor
Formycin B	*Streptomyces lavendulae* and *Nocardia interforma*	 Formycin B	-Antiviral -Antitumor
Oxoformycin B – A metabolite of Formycin and Formycin B	*Streptomyces lavendulae* and *Nocardia interforma*		-Antiviral -Antitumor
Nostacine A	*Nostoc Spongiaeforme*	 Nostacine A	-Cytotoxic
Fluviols (A-E)	*Pseudomonas fluorescences*	 Fluviol A  Fluviol B	-Antimicrobial



Fluviol C



Fluviol D



Fluviol E

1.As anti-cancer agent

Heterocycles have been identified as crucial in the development of anti-cancer drugs especially because they are so ubiquitous in nature. It should come as no surprise that heterocycle-based compounds have frequently acted as the foundation for medicinal therapy as they represent an extraordinarily wide array of molecules with an unprecedented degree of flexibility in terms of the interactions they can engage with. When creating compounds that will interact with targets and impair the biological pathways associated with the spread of cancer, heterocyclic moieties are an excellent pick because numerous enzyme binding pockets are inclined to engage with them. These anti-cancer treatments frequently target pathways involved in cell growth and development.

The use of pyrazole scaffolds in a number of FDA-approved tyrosine kinase inhibitors (TKIs) highlights the importance of this scaffold in the creation of potent cancer treatments. Examples include Avapritinib, which is recommended for the treatment of multidrug-resistant gastrointestinal tumors, [47,48] Crizotinib and Pralsetinib, which are both used to treat non-small cell lung cancer (NSCLC), [49] and Asciminib and Rebastinib, which are used to treat chronic myeloid leukemia (Fig. 1) [50,51]. Furthermore, by interacting with several targets as tubulin [52], epidermal growth factor receptor (EGFR) [53], cyclin-dependent kinase (CDK) [54], DNA [55], topoisomerase [56] and human carbonic anhydrase (hCA) IX. [57], pyrazole derivatives have shown multiple modes of anticancer action.

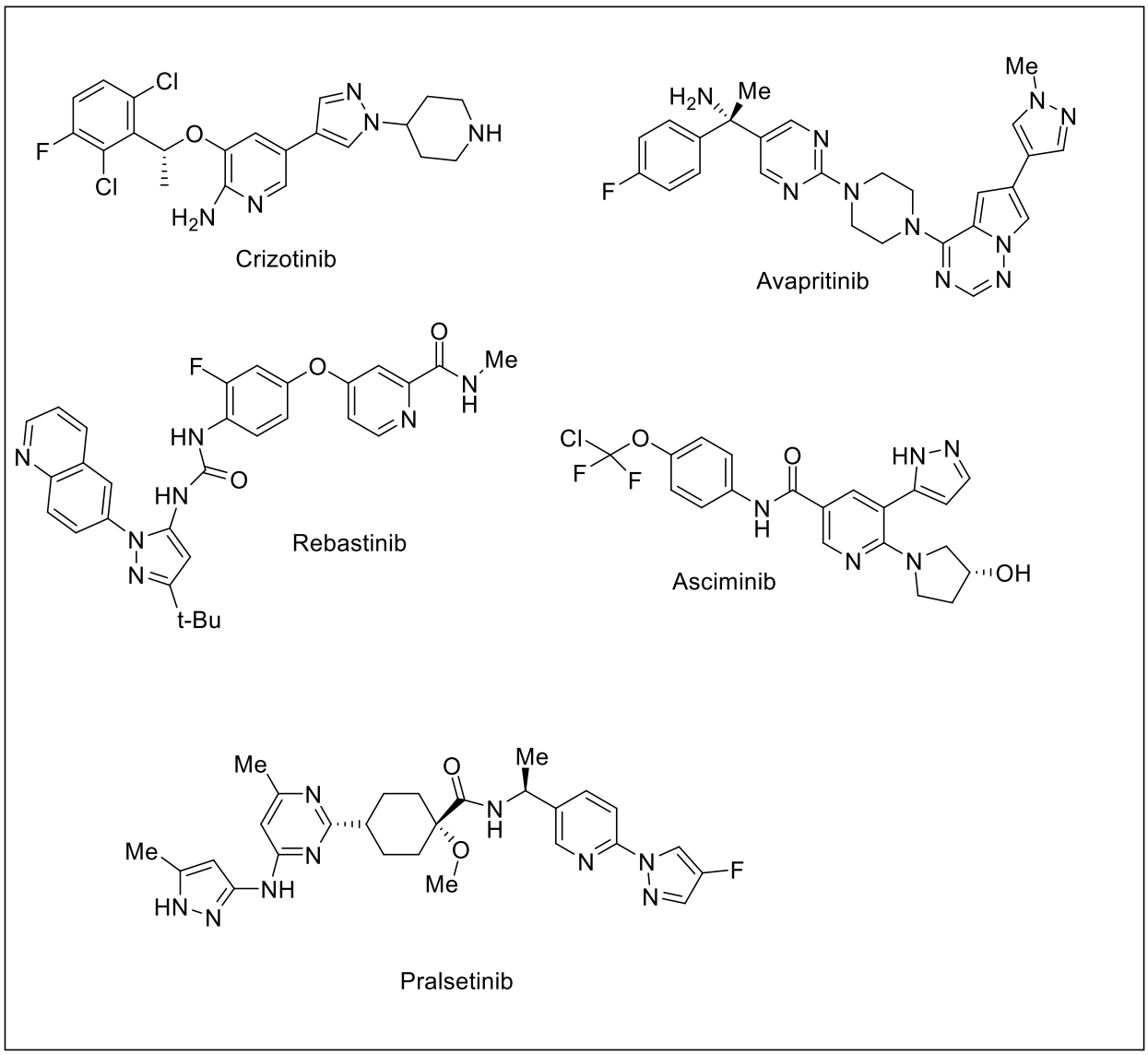


Figure 2. Fda Approved Pyrazole-Based Drugs For Cancer Treatment

By enhancing antioxidant enzymes viz. GPx and inhibiting the lipid peroxidation procedure, the pyrazole [58,59] (1,2-diazole) exhibits antioxidant activity and can avert oxidative stress. Several instances of 1,2-diazole's or its related medications' pharmacological consequences It was discovered that 1,2-Diazole effectively prevented nephrotoxicity brought on by the anti-neoplastic medication cisplatin [60]. A new antioxidant called edaravone VI (Figure 3) has been utilized to treat stroke patients who have had cerebral infarction and enhance ischemia/reperfusion-induced hepatic energy metabolism [61,62]. The pharmaceutical and agrochemical industries have long used pyrazole derivatives as active ingredients and herbicides.

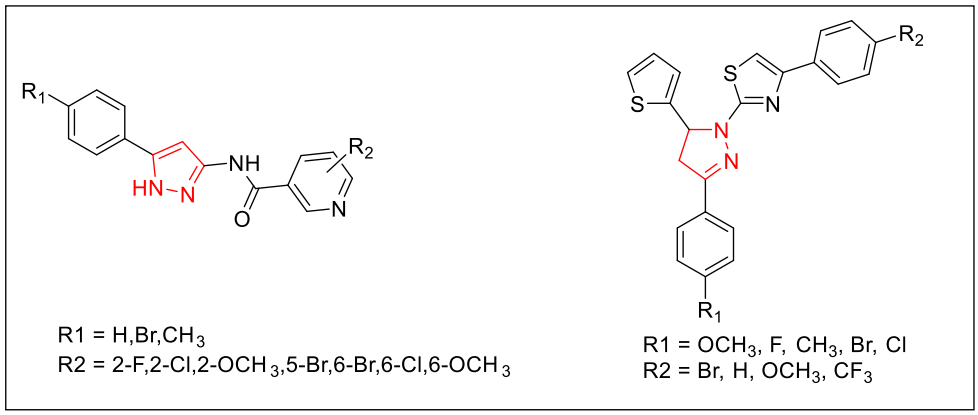


Figure 3: Pyrazole derivatives as monoamine oxidase inhibitors.

The significance of these heterocyclic rings in therapeutic Chemistry has been further emphasized by the current efficacy of the pyrazole COX-2 antagonist. A comprehensive analysis of this family of heterocyclic lead depicted that pharmacoactive compounds constituting pyrazoles are vital for pharmaceutical chemistry. The necessity for sophisticated and efficient procedures for generating these heterocyclic leads has enhanced owing to the predominance of pyrazole cores in physiologically active compounds [63]. In order to highlight the structures of the heterocycles in the discussed compounds, we colored the benzimidazole nucleus with blue, the pyrazole with green, the linker with red, and the compounds with good biological activity are marked with a rectangle.

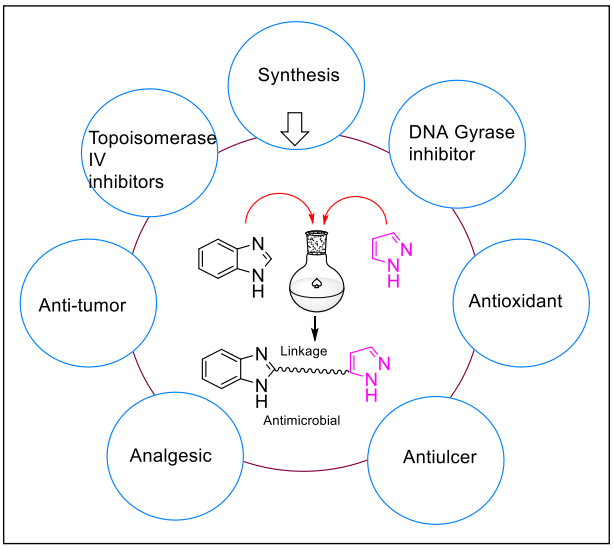


Figure 4: Schematic representation of the synthesis and biological properties of benzoimidazole–pyrazole compounds.

In addition to DNA-Gyrase inhibitors, topoisomerase IV inhibiting agents, and other biological attributes including antitumor, antioxidant, anti-inflammatory, analgesic, as well as antiulcer [64-97], the objective is to analyze the various synthesis techniques for benzimidazole–pyrazole hybrid compounds with antibacterial and antifungal features. (**Figure 5**).

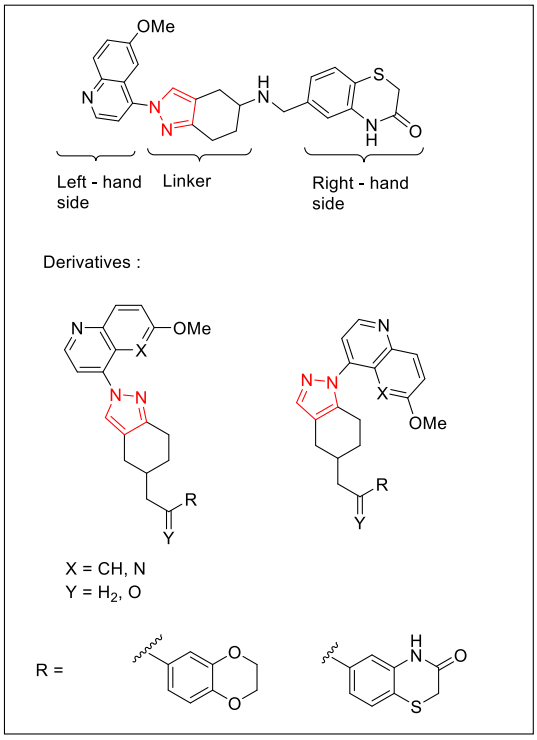
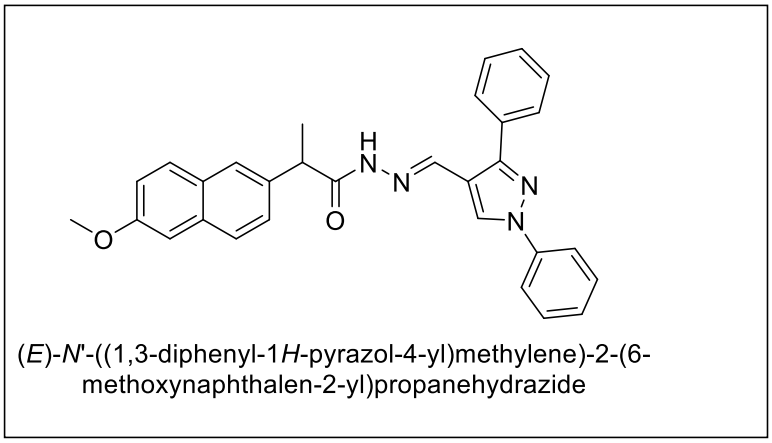


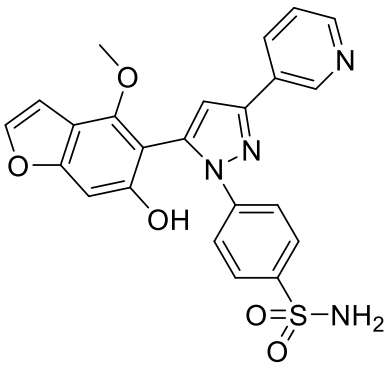
Figure 5 : Pyrazole derivatives as DNA gyrase inhibitors

Anti- inflammatory

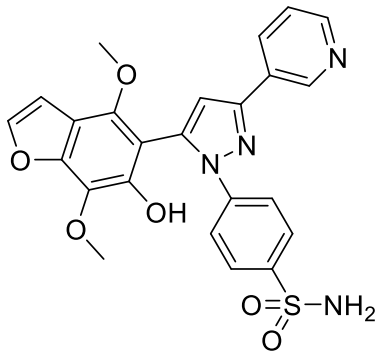
Recently, the anti-inflammatory properties of a number of pyrazolecarboxamides containing naproxen have been assessed. Of the chemicals that were produced, N-[(1E)-(1,3-diphenyl-1H-pyrazol-4-yl)methylene] the anti-inflammatory properties of -2-(6-methoxy-2-naphthyl)propionyl hydrazide were the most promising [98].



Hassan et al. created a number of celecoxib analogs by adding a benzofuran moiety, and they assessed the compounds' ability to inhibit COX-1 and COX-2 in vitro. Compounds (27) and (28) demonstrated the most anti-inflammatory properties among them. The findings showed that compounds containing C-3 pyridine-3-yl had a significant impact and effectively reduce inflammation in animal models [99].



4-(5-(6-hydroxy-4-methoxybenzofuran-5-yl)-3-(pyridin-3-yl)-1*H*-pyrazol-1-yl)benzenesulfonamide



4-(5-(6-hydroxy-4,7-dimethoxybenzofuran-5-yl)-3-(pyridin-3-yl)-1*H*-pyrazol-1-yl)benzenesulfonamide

Antileishmanial

Given the broad range of biological activity exhibited by pyrazole derivatives, including antibacterial, antiviral, anticancer, antitubercular, antifungal, antidiabetic, antidepressant, and anticonvulsant properties, the pyrazole ring is regarded as a crucial motif in medicinal chemistry [100–109]. Their properties include analgesia, antipyretic, anti-inflammatory, antiarthritic, immunosuppressive, and cerebroprotective [110–117]. Antileishmanial activity was demonstrated by a number of substances, including hydrazone A, imide B, and α, β-unsaturated carbonyl C derivatives (Figure 1) [118]. When the pyrazole ring was hybridized with other heterocyclic moieties either directly or via a specific spacer, the antileishmanial activity increased significantly in comparison to when the pyrazole ring alone was used [119,120]. The 1,3,4-oxadiazole ring D (Figure 6) is regarded as a good bioisostere of amides and esters [121,122] among these heterocyclic rings. In medicinal chemistry, pyrazolone/pyrazolinone moieties also garnered a lot of attention because they were the fundamental building blocks of several antileishmanial drugs.

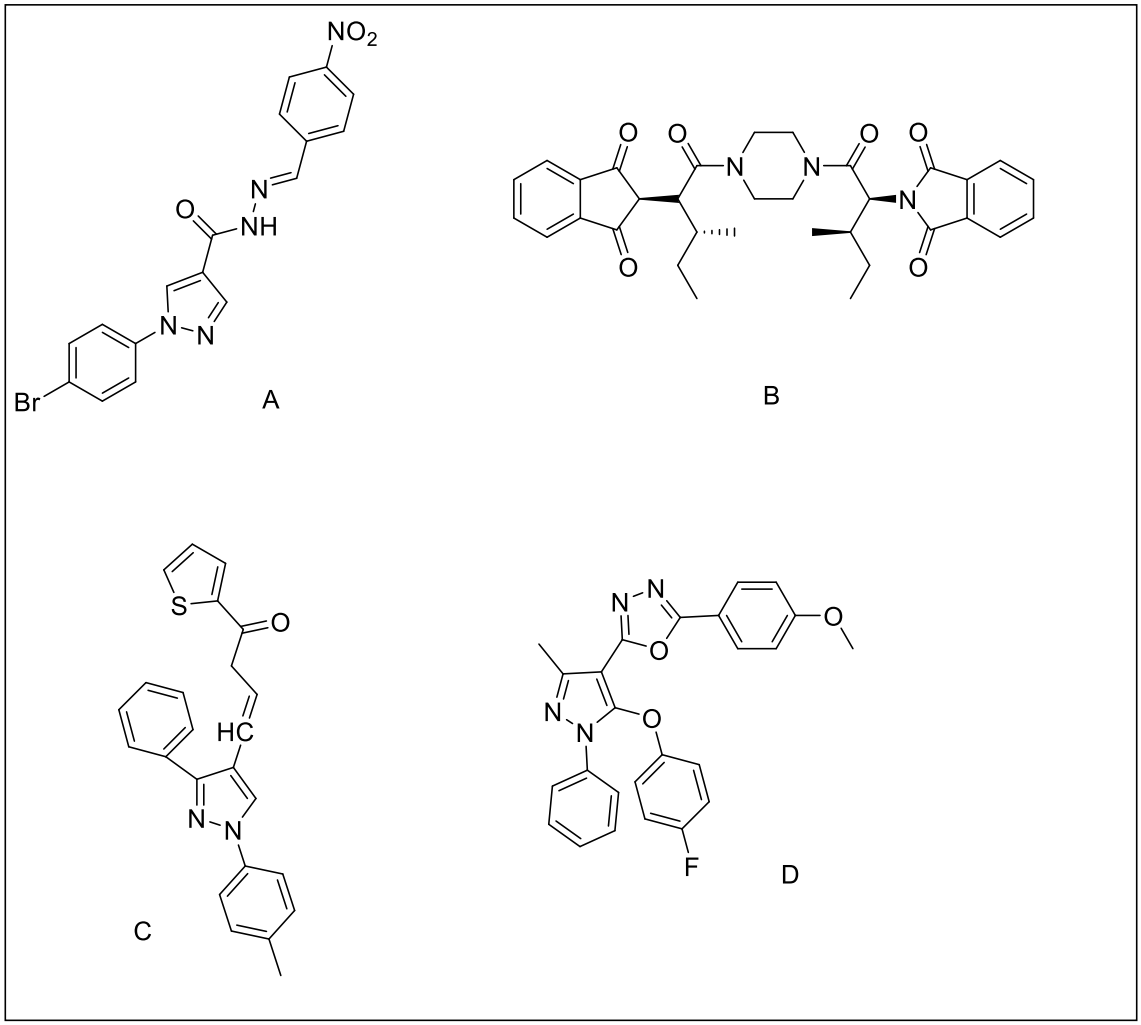


Figure 6. Structures of lead antileishmanial pyrazoles.

Analgesic

One of the most significant factors influencing quality of life is generally acknowledged to be pain, an unpleasant experience. The prevalence of anxiety and sadness is four times higher in those with chronic pain than in healthy people. In biomedical research, one of the main objectives is to find substances that can treat both acute and chronic pain with few adverse effects. Abd-El Gawad et al. [123] created pyrazole derivatives with analgesic properties (94 and 95) and proposed that activity requires at least one aryl moiety to be substituted for the pyrazole ring. With the exception of 95d, every drug reported had analgesic efficacy (Fig. 7).

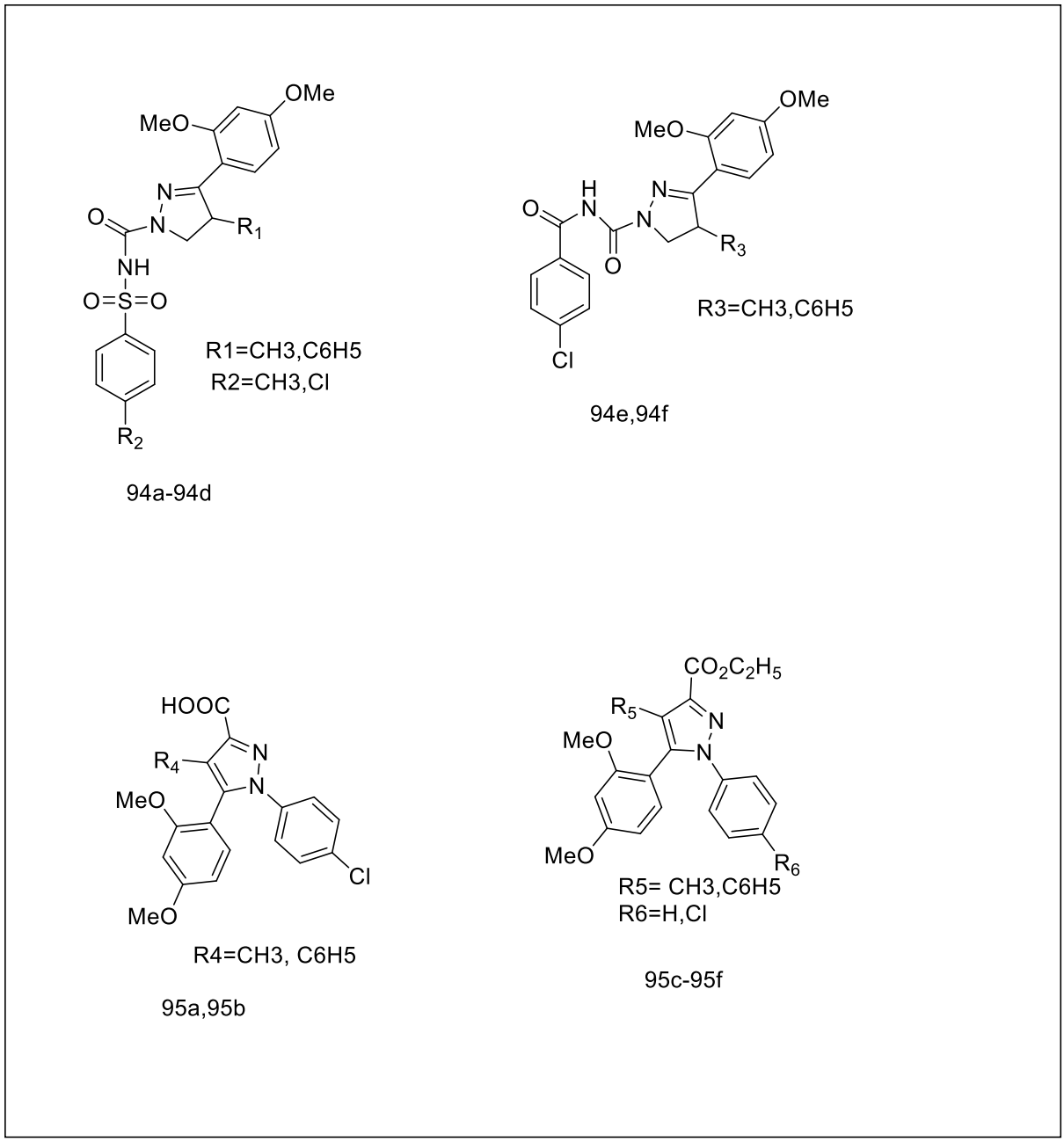


Figure 7. Pyrazole derivative as analgesics.

Antiproliferative

One of the key mechanisms in an individual's overall development is cell proliferation, which is the process that leads to an increase in the number of cells. Numerous health issues can result from abnormal cell growth and proliferation. Tumors and cancers are among the most-deadly and rapidly spreading illnesses. This group of disorders is difficult to treat and is typified by a loss of control over cellular proliferation. Huang et al. [124] described a number of pyrazolo[3,4-d]-pyrimidine derivatives with antiproliferative properties.

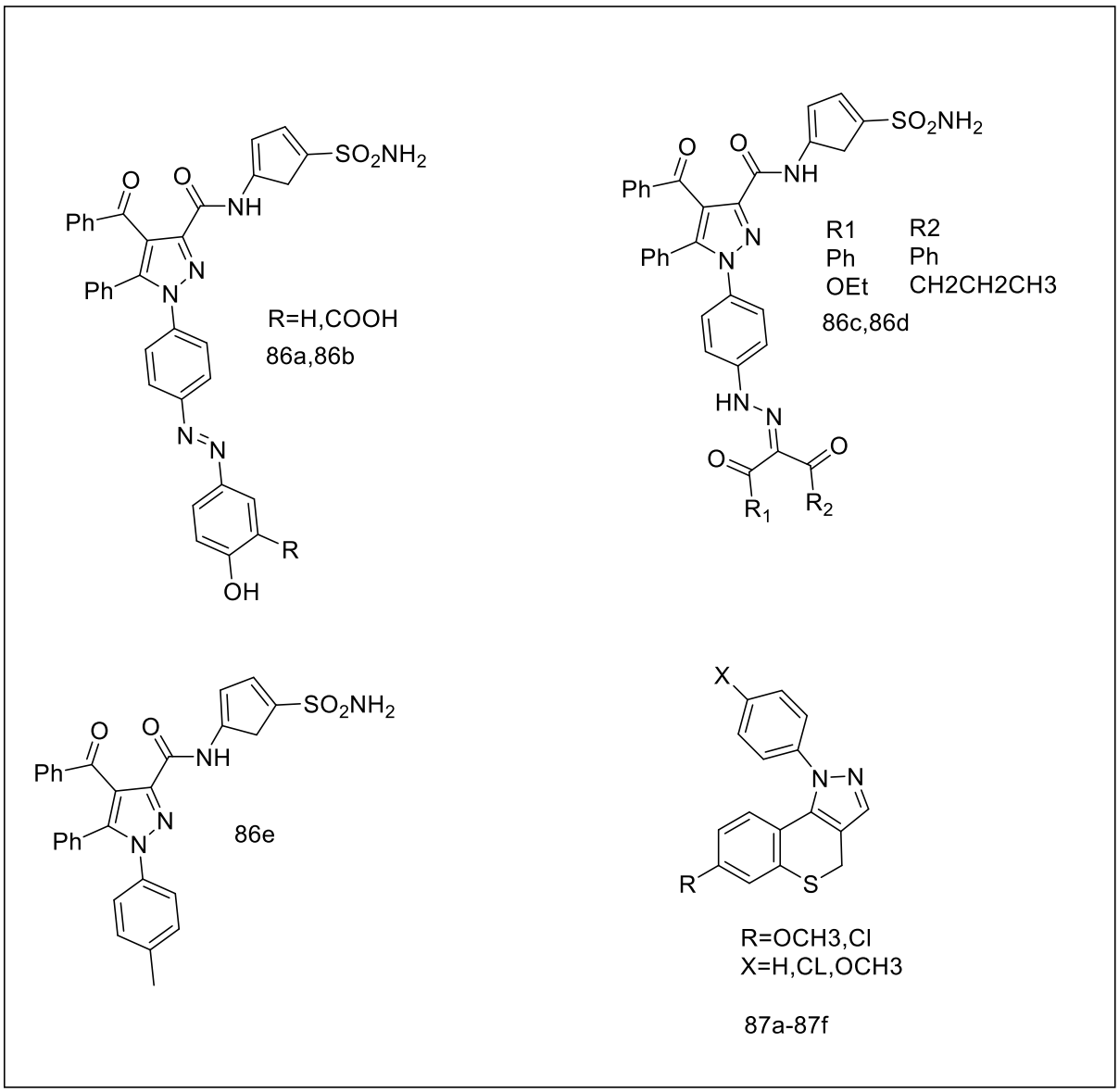


Figure 8 - Pyrazole derivatives as antiproliferative

2. CONCLUSION

Compounds with anti-inflammatory and antibacterial attributes, among others, have been investigated for both financial and societal benefits. Pyrazoles are a significant class of chemicals that have garnered a lot of interest for the creation of novel medications. As target structures, a number of pyrazole derivatives have been created and their biological activity assessed.

Although the cytotoxicity of the compounds presented in the review suggests that many pyrazole derivatives are harmless, a standardized approach for evaluating cytotoxicity is necessary to further understand the safety of the compounds and the links between safety and structure.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals or humans were used for the studies that are based on this research.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

ACKNOWLEDGEMENT

I would like to thank Department of Chemistry, Ewing Christian College, Prayagraj for their assistance and my supervisor, Prof. Vivek Bhadauria for his constant support and guidance.

CONFLICT OF INTEREST

There are no conflicts of interest for any author to disclose.

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