INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN CHEMISTRY AND PHARMACEUTICAL SCIENCES

(p-ISSN: 2348-5213: e-ISSN: 2348-5221)
www.ijcrcps.com

Review Article

BIOLOGICAL EFFECTS OF PYRAZOLES

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Abstract

Since the beginning of this century, pyrazoles are an important class of heterocyclic compounds which have increasingly taken attention in literature because of their wide-spread of study field such as biological activity. Although pyrazoles are very rare in natural products, they have very common synthetic applications. These compounds are used in the development of agricultural products and in drug researches because they have biological activities diversity. In addition, synthesized of substitute pyrazoles may be apply the other fields because of their diverse and potent biological properties. For this reason, the methods developed for the synthesis of these compounds are becoming more importance. In this review, the synthesized substituted pyrazoles was described whether they were used or not the effect in the biological areas.

Keywords: pyrazoles, biological activity, drug researches.

Introduction

In recent years interest in the pyrazole chemistry excessively increase due to many a wide range of properties of interest by pyrazole derivatives increased. Although there are rare pyrazoles in nature, the multiple pyrazole derivatives have been implicated in a wide spectrum of pharmacological activity and agricultural chemicals. Pyrazoles were also applied successfully in other fields. For these reasons, heterocyclic chemistry is quite an interesting area of research v for the synthesis of pyrazole derivatives and investigates new methods. Pyrazole is a simple aromatic ring an organic compound of the heterocyclic series by is characterized five-membered ring structure which comprises located adjacent two nitrogen atoms and three carbon atoms (figure.1).

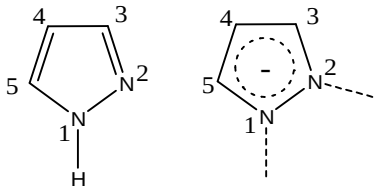


Figure1. Pyrazole

Pyrazoles have π-electrons in the heterocycle. N atom attracts ring electrons due to electro negativity so that the C(3) and C (5) become partially electropositive and these become suitable to participate in nucleophilic. All of the 1,2-azoles, pyridine nitrogen and C (4) atoms have been focused on the π-electron and moves positive charge as well as other hetero atoms. C (3) and C (5) atom of the π-electron charge can be positive or negative depending on the heterocycle. The highest degree of bond C (3)-N and C (4) -C (5) was found between atoms. Bond order is the lowest of the hetero atoms. N atom of nucleophilic and the steric accessibility can be varied by appropriate ring substitution. Although attractive features and powerful advances in the chemistry of pyrazole, the pyrazole derivatives compounds have been limited up to70s. Although pyrazole is very rare in natural products, it is encountered very common synthetic applications[1, 2]. Compounds having these groups act in a coordinated way forming ligands with a series compounds biologically active[3] have wide application in analytical agricultural and pharmaceutical chemistry. Some of these were used important as pharmaceutical agents[4] (antipyrine and congener).These compounds are used in

the development of agricultural products and in drug research because of they have diversities biological activities[5, 6]. Pharmaceutical, agricultural, biological activity of these compounds who containing pyrazole ring system in the structure some activities can be listed as known; Highcandyinhibitor[7], analgesic[8], inflammatory[9], antipyretic[10,11], anti-bacterial[12],antidepressant[13] in which they are used for activities such as pharmacology. They provide protection against plant pests[14] from the effects insecticides[15] and antifungal activity[16]forwhich they have an increasingly important role in the agricultural industry[17]. they were alsohypotensive[18] andactinganticancer[19, 20]. In addition to these, pyrazoles were reported using as ligands in the coordination chemistry[21, 22].Tosyntheticpyrazole include examples like; *Celecoxib* having feature antirheumatic used in the treatment of inflammation and pain[23-25],*Rimonabant*developedfor the treatmentobesity[26], *difenzoquat* having the lethal effects of plant pests[27], *Tartazine*[29] lemon yellow dye to widely used coloring in food in the Britain and United States (Figure 2).

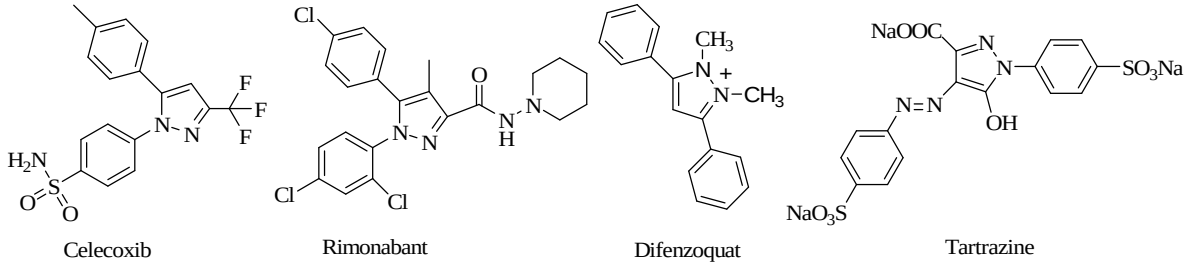


Figure 2.The important structures of the some synthetic pyrazoles

Heterocyclic compounds containing pyrazole ring are important goal molecules in the field of synthetic and medicinal chemistry. Because *Celecoxib, Pyrazofurinei. e* many more numerous biologically active compounds have a significant share in such pronounced drug molecules[29-31].The antimicrobial activity[32] of the resulting product was examined by synthesizing dipirazolino-4.4 '-dithiocarbamate derivatives in 1993 (Figure 3).

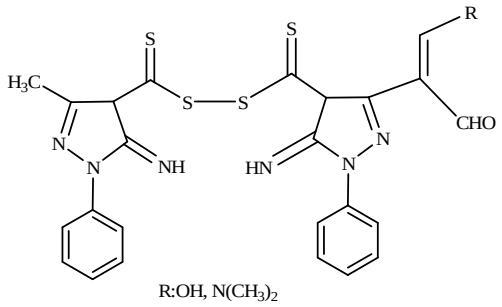


Figure3.The dipirazolino-4.4 '-dithiocarbamate

Compounds of the structure 4-[(*N*,*N*-disubstituted thiocarbamoylthio) acyl] antipyrine[33]were synthesized by reaction *N*, *N*-dithiocarbamic acid potassium salt with 4-(α-chloroacetyl) and 4-(α- chloropropionyl).The biological activities of these compounds were investigated by Cesur et al., in 2009(Figure4).

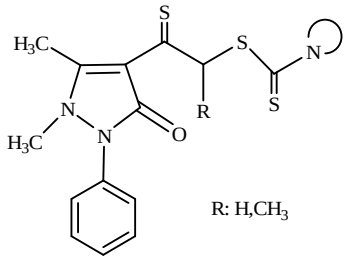


Figure4.4-[(*N*,*N*-disubstituted thiocarbamoylthio) acyl] antipyrine

Substituted pyrazoles have been made different attempts on the effects ofcarcinogens[34]. Various hypotheses have been produced that some of these bay-region, di-region and one-electron oxidation of activation theories[35, 36]. In recent years, the presence of the nitrogen atoms of some aromatic compounds have been reported activity in the literature high blood pressure, allergy, asthma, histamine inhibitors, bronchodilators, diuretic and antimicrobial against tuberculosis which results in diminished or enhances the biological activity depending on the position of substitution. These compounds were also reported activity to inhibit spasm. They were demonstrated activity muscle relaxation, blood clots, inhibit cell clusters and in the treatment of diabetic disorders[37].The best known of these was dipyrone. Analgesic was a medicament which could be used orally or parentally. Nevertheless introduced into clinical practice other pyrazole derivatives compounds have been continuing work on (Figure 5).

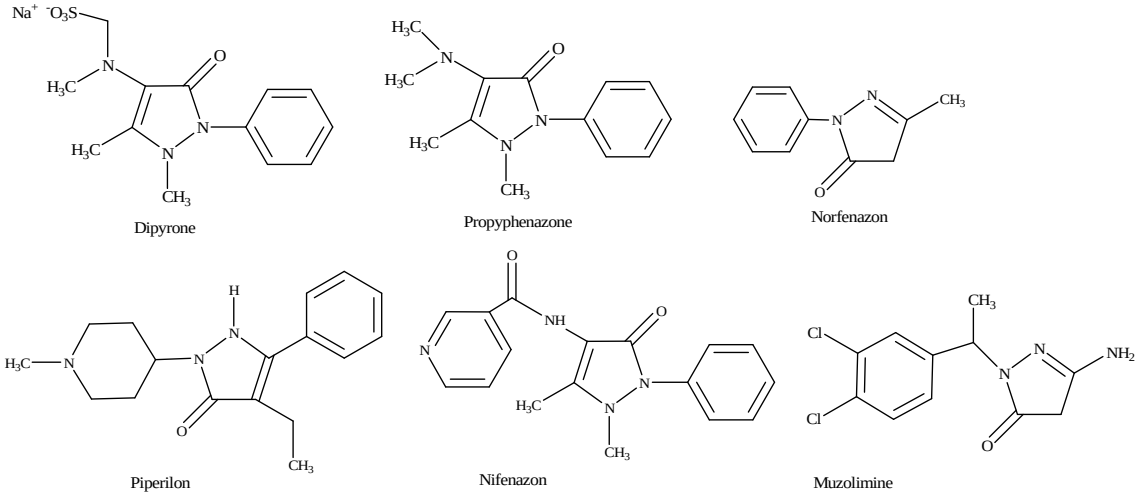


Figure 5.Substitute dpyrazoline structures

The pyrazoles are known as parts not only stronger insecticides ,herbicides ,monomers, as heat-resistant materials for the preparation of the electron beams but also antimicrobial, antitumor, anti-inflammatory, analgesic and antipsychotic. Although the wide range of products available pharmacological and technological applications, the pyrazoles have been the focus of most synthetic work in recent years[38, 39].For example, since the discovery of *Cisplatin* who was an anti-cancer of the causative agent. Many platinum complexes were designed to developclinical disorders such as nephrotoxicity and drug resistance. Cytotoxic effect of cisplatin generally accepted to cause by interaction with DNA[40]. But the applicability of cisplatin was still limited. Qu and co-workers showed successful approaches synthesized someplatinumcomplexes[41, 42]. Azo bridged to dual core of the platinum (II) complex $[(cis\text{-}Pt(NH_3)_2)_2(\mu\text{-}OH)(\mu\text{-}pz)](NO_3)_2$ cytotoxicity values were greater than the cytotoxicity ofcisplatin[43,44](Figure 6).

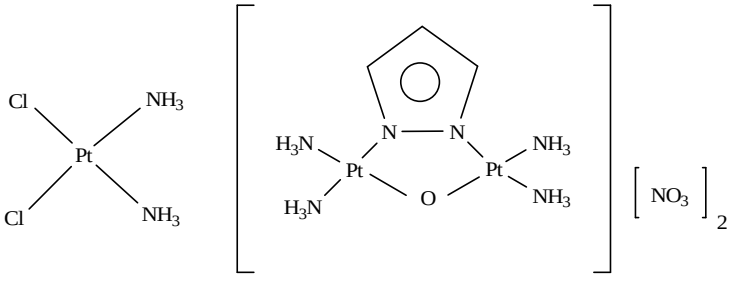
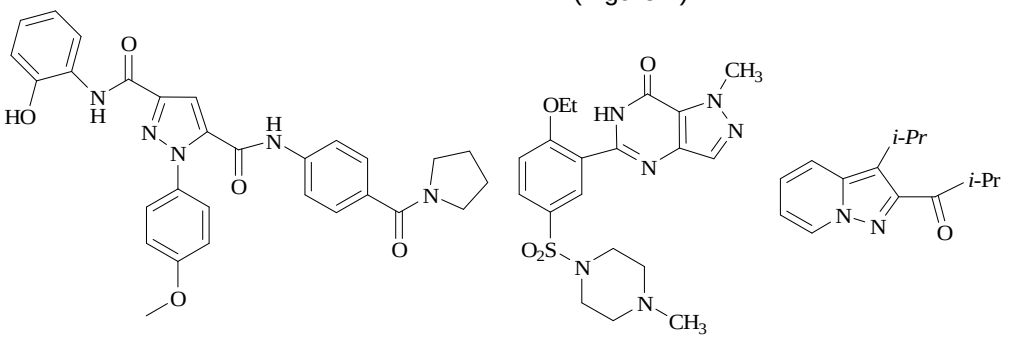


Figure 6.Azo bridged to dual core of the platinum (II) complex

Helicobacter pylori dehidrorotatedehidrojenaz (DHODase) was apyrazole-based inhibitor sample. *Helicobacter pylori* was a gram-negative microaerophilic bacterium in gastric acidic medium transmitted through 50%of the world population. Gastritis and gastric cancer elated to these gastric ulcers that have played a role in gastrointestinal disorders[45].

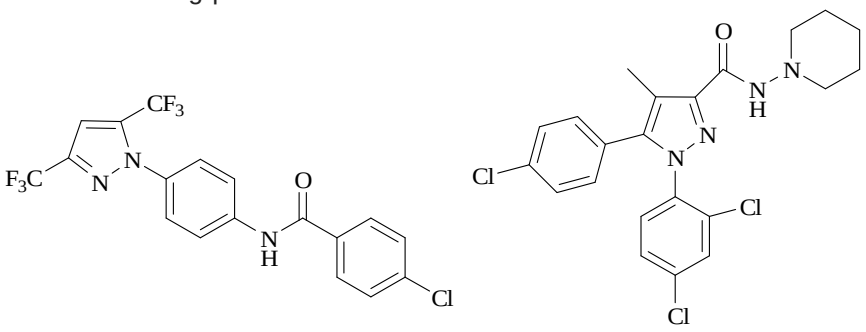
Sildenafil''selectiveinhibitorfosfodiesteraz5(PDE5)''was acausativeagent in the dysfunction treatment of male erectile and a disease known as male impotence[46].As another example, pyrazolo[1,5] pyridines were related with blood cells for treating cardiovascular diseases antiagregan drug selection and phosphor diesterase inhibitor. The above-mentioned heterocyclic pyrazoles were used for dementia of herpes virus infections Alzheimer's therapy and Parkinson's disease[47, 48](Figure 7).



DHODase PDE5 Pirazolo (1,5) pyridine

Figure 7. Structures of **dihydroorotate** dehydrogenase, fosfodiesteraz 5 and pyrazolo[1,5] pyridine

A series of bis (trifluoromethyl) pyrazoles (BTPs) were found inhibitors of production cytokine[49]. Cannabinoid receptor antagonists(CB1) were also known as other pyrazole-derived compounds. Cannabinoid was the major component psycho active of marijuana which have a potent selective cannabinoid receptor in the brain and orally active as antagonist. It was reported by Sanofi Recherche[50] in 1994. Cannabinoids have been focused on several of works long periods due to its effects on the central nervous system. Cannabinoids had effects antiemetic, psychotropicanti-inflammatory and analgesic properties in the first pharmacological tests that it used in the treatment of diseases such asasthma and glaucoma. However, widespread uses of cannabinoids as therapeutic agents were limited by the capabilities of their psychotropic[51] (Figure 8).

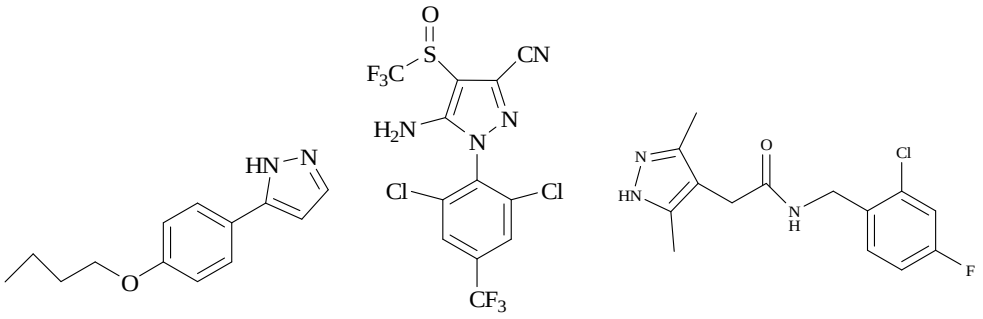


BTPs CB1

Figure8.Bis(trifluoromethyl) pyrazole and Cannabinoid receptor antagonist

20-hydroxy-5,8,11,14-eicosatetraenoic acid (20-HETE)was pyrazole derivatives effective, new and selective for synthase inhibitors. 20-HETE played an important role in the regulation of renal vessels which was an important metabolites arachidonic acid that it was produced in the kidney and contributes control arterial blood pressure with tubular function. It was also contributed to the regulation of flow cerebral blood[52].Fipronilwas another example for the biologically active pyrazole derivatives. It was the most important examples of phenylpyrazoles orfipronil

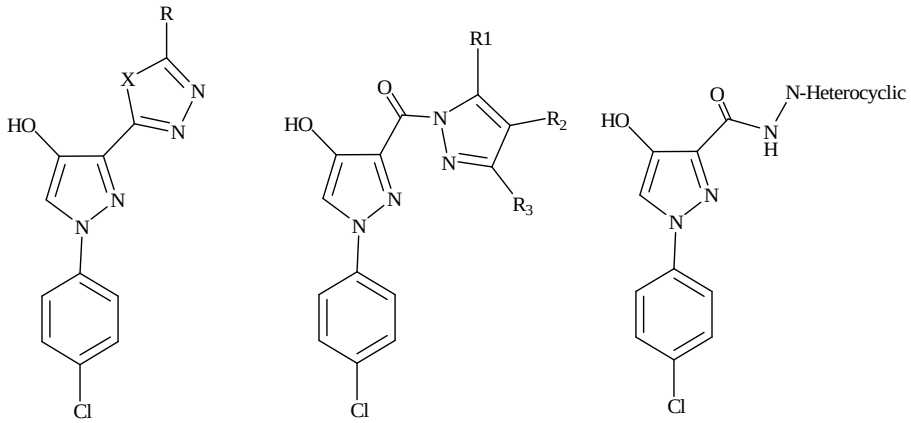
insecticide[53] (Figure 9).Acetamides(1*H*-pyrazol-4-yl)a series of structure-activity relationships were determined positive physicochemical and pharmacokinetic properties as a strong antagonist ofP2X7[54](Figure 9).



20-HETE Fipronil P2X7 antagonisti

Figure9. Structures of the 20-HETE, Fipronil and 1*H*-pyrazol-4-yl

Last twenty years ,the pyrazole-containing compounds have attracted great attention due to various chemotherapeutic potential including versatile antineoplastic activities. Some pyrazoles were determined using as agents antileukemic, antitumor and anti-proliferative. In addition to this, its capacity has been shown to produce remarkable anti-cancer effects which played an important role in cell division by inhibiting different enzymes[55-61]. Rostom and co-workers appeared in their works that they observed 1-(4-chlorophenyl)-4-hydroxy-1H-pyrazole-3-carboxylic acid hydrazide derivatives having several new general formula[62,63]as significantly anticancer activity(Figure10).



X: O, N-R_2

Figure10.Structures of 1-(4-chlorophenyl)-4-hydroxy-1H-pyrazole-3-carboxylic acid hydrazide

Pyrazoles were among the important building blocks having diverse biological activities. Functionalize dN-arylpyrazole bioactivities were examined extensively. Besides C-5 substituted pyrazoles were used in the design ofpharmaceuticalandagrochemical[64-66](Figure10).Kaung and co-workers were synthesized with a method effective by $POCl_3$ and amide solvents compounds available on the market for attaching anamidinyl group C-5position of the N-arylpyrazole. The structure-activity relationship was established. These compounds were researched effects cancer cells anti proliferative active derivatives of methyl amide[67] (Figure11).

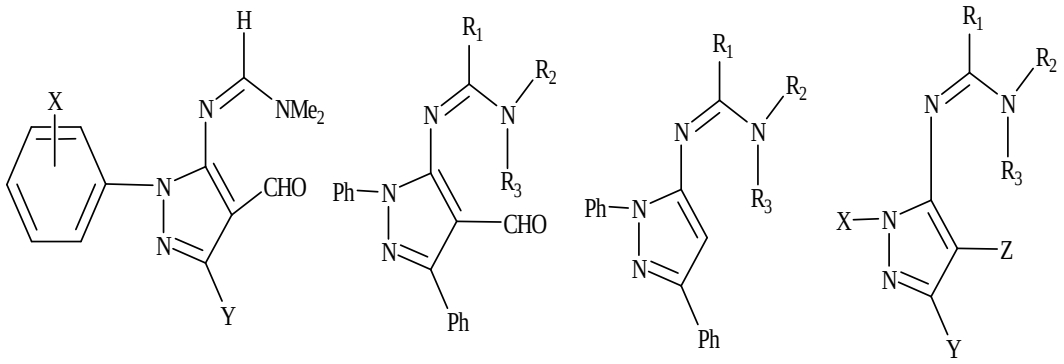


Figure11.Structures of N-arylpyrazole

A series of pyrazole sulfonamide derivatives were synthesized. These synthesized compounds were investigated the inhibition effects on human carbonic anhydrases in vitro[68] (Figure12).

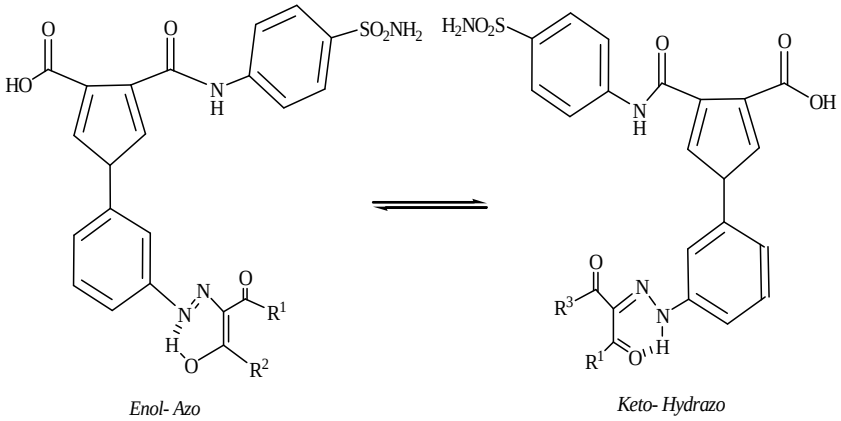


Figure12.Synthesis of target inhibitors

Jun-Ying and co-workers were synthesized a series of novel compounds. The synthesized of the compounds showed biological evaluation that could suppress A542 and H322 lung cancer cell growth[69](Figure13).

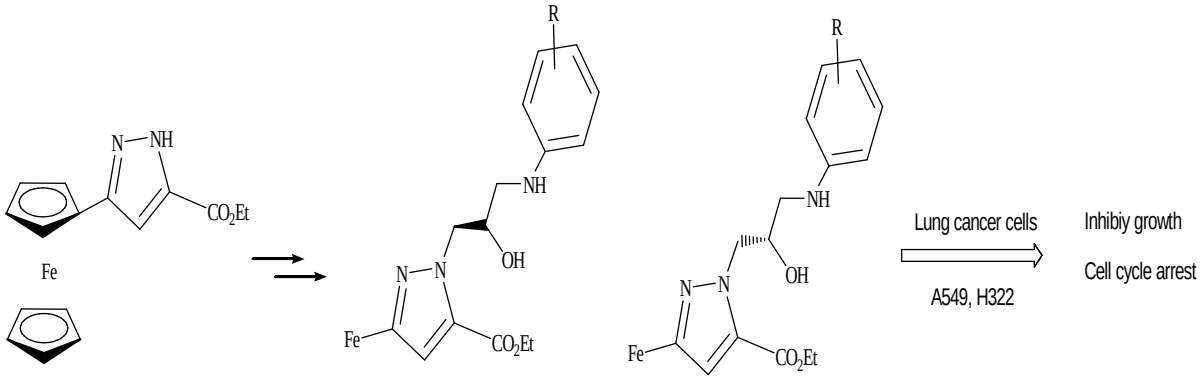


Figure13.Synthesis of 1H-pyrazole-5-carboxylate

Hasan and Esmail were prepared MWCNT pyrazole on the surface of nanotubes. These compounds were evaluated for biologic activity[70](Figure 14). Finally the authors said that the synthesized compounds could be used for conjugating to drugs and biochemical materials.

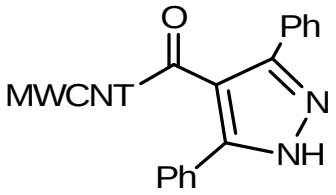


Figure14.Synthesis route of modified MWCNT-COOH

Some new pyrazole-based 1,3-thiazoles and 1,3,4-thiadiazoles compounds were tested for anticancer activity humanhepatocellular carcinoma HepG2 cell line in Figure15 by Kamal et. al.[71]

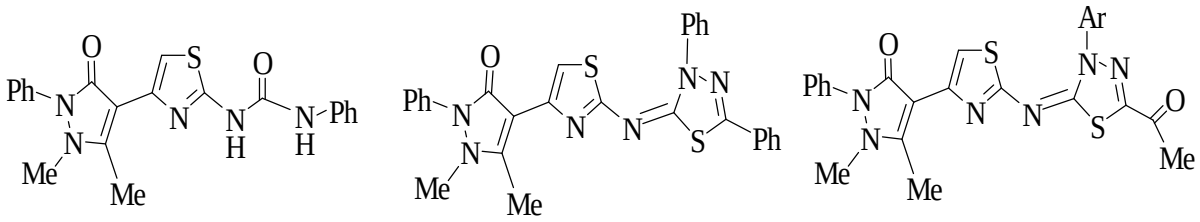


Figure15.Synthesis route of modified MWCNT-COOH

A novel series of substitute pyrazoles were synthesized.These synthesized compounds were evaluated for their antimicrobial activity[72]in Figure16.

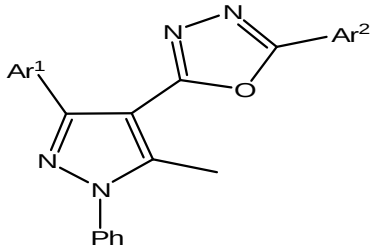


Figure16.Synthesis of substitute pyrazoles

Novel class of pyrazole-oxindole conjugates were synthesized by Knoevenagel condensation. The synthesized of compounds were investigated for their antiproliferative activity on different human cancer cell lines[73] (Figure17).

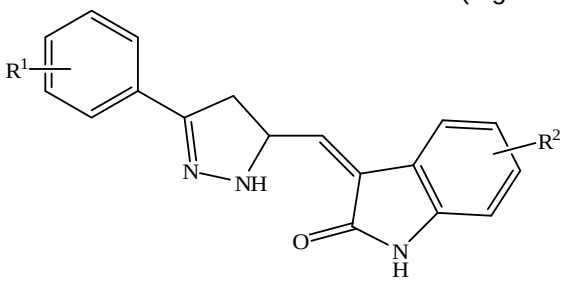


Figure17.Synthesis of pyrazole-oxindole

Zhu and co-workers were synthesized a new series of pyrazole-quinoline-pyridine hybrids which based on molecular hybridization technique by a base-catalyzed cyclocondensation reaction through one-pot multicomponent reaction.[74] These synthesized of compounds were evaluated for antibacterial and anticancer activities in Figure18.

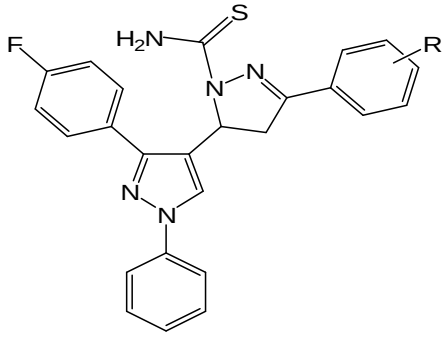


Figure18.Synthesis of substitutepyrazole-quinoline-pyridine

A series of compounds substitute pyrazoles were synthesized by Desai et. al.[75]These synthesized of compounds that fluorine-containing compounds were tested for *in vitro* antibacterial activity in Figure19. Finally, they said that particular derivatives possessing electron withdrawing groups such as halogen and nitro were identified as exhibiting potent antimicrobial activity against microbial strains.

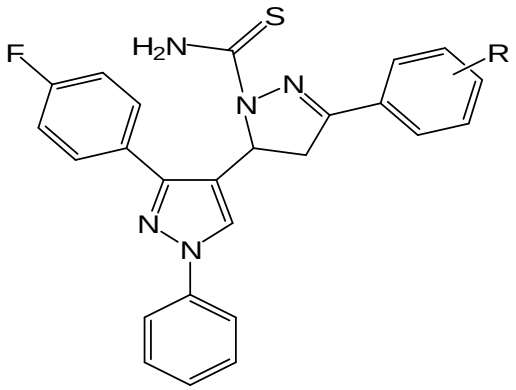


Figure 19.Synthesis of substitutepyrazole-quinoline-pyridine

Bhusare and co-workers were synthesized a new series substitute pyrazoles which have bearing an aryl sulfonate moiety[76] in Figure20. These synthesized of compounds were evaluated for their anti-inflammatory activity. Besides, these synthesized of compounds were screened against bacterial and fungal strains.

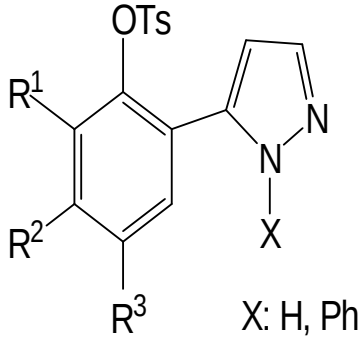


Figure20.Synthesis of substitute pyrazole

Abdel-Aziz and co-workers were synthesized new pyrazole and pyrazoline derivatives[77] in Figure21. These synthesized of compounds were tested for COX-1/COX-2 inhibition and anti-inflammatory activity. However, they were investigated molecular modeling study of pyrazole and pyrazoline derivatives as selective COX-2 inhibitors ad anti-inflammatory.

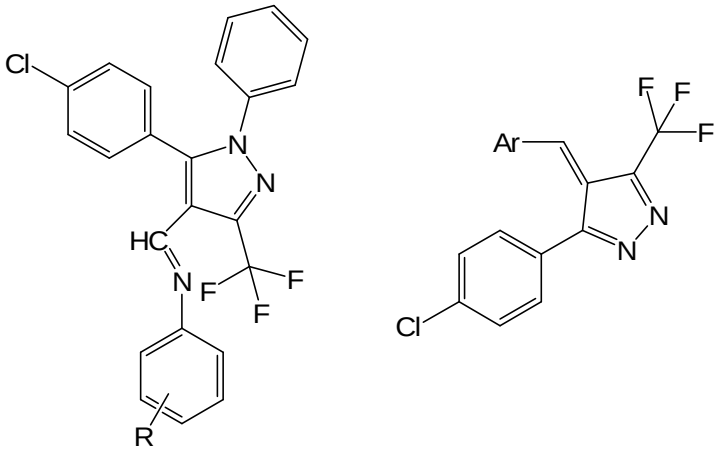


Figure21.Synthesis of substitute pyrazole and pyrazoline derivatives

Thore and co-workers were synthesized a series of novel 1H-pyrazole-4-carboxylates[78] in Figure22. These synthesized of compounds were evaluated for analgesic and anti-inflammatory activities. All of the synthesized compounds showed moderate bioactivities.

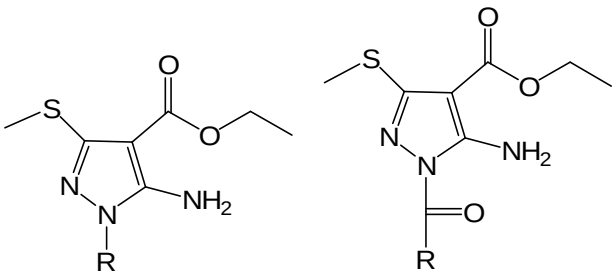


Figure22.Synthesis of substitute pyrazole and pyrazoline derivatives

Conclusion

Synthetic organic and pharmaceutical chemistry are grown very rapidly the synthesis of heterocyclic compounds, development of synthetic methods and investigation of the bioactive properties. The pyrazole compounds forming an important class of heterocyclic compounds and its derivatives bring out significant pharmacological and biological activities. In recent years a relatively contained large number of these compounds in the structure are an important group. Also the substituted pyrazoles are showed a wide variety of biological and pharmacological activities. They have wide application both pharmaceuticals and in the agricultural industry. For this reason, the methods developed for the synthesis of these compounds are becoming more importance.

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