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The role of pyrazole and its derivatives in heterocyclic chemistry

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ABSTRACT

Pyrazole is associated with wide range of biological properties. These ring systems are incorporated into drugs used for AIDS, cancer, anti-viral treatment etc. Pyrazole derivatives are well established in the literature as important biologically active compounds. They have a long history of application in agrochemicals and pharmaceutical industry as herbicides and active pharmaceuticals. Pyrazole and their numerous derivatives have continued to capture the concentration of chemists since their existence in the biologically active materials have been known to produce additive effect on the bio-efficacy of the molecules.

Keywords: Anti-viral, Alkaloid, Herbicides, Pharmaceutical.

1. INTRODUCTION

1.1. Importance of pyrazole

Pyrazole is an aromatic heterocyclic diazole alkaloid characterized by 5-membered aromatic ring structure composed of three carbon and two nitrogen atoms in adjacent position in which one nitrogen is basic and another nitrogen is neutral in nature (Figure 1). A great deal of research is carried out to prepare new heterocyclic molecules having therapeutic uses and also so many heterocyclic derivatives are synthesized till now having desired pharmacological effect. Out of them pyrazole derivatives are catagorised in a higher position as the other heterocyclic compound possess in the heterocyclic chemistry. Being so composed and having pharmacological effects on human, pyrazoles have a great value in the field of medicinal chemistry. In 1959, the first natural pyrazole, 1-pyrazolyl-alanine, was isolated from seeds of watermelon [1].

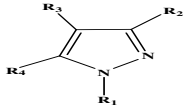


Figure-1: Structure of pyrazole.

1.2. Biological aspects

Pyrazoles are an imperative class of heterocyclic compounds for new drug development that attracted much concentration. Pyrazoles represent a key motif in heterocyclic chemistry and occupy a leading place in medicinal, pesticide and agrochemical industry [2] due to their potential to reveal a broad range of bioactivities such as anti-inflammatory [3], anti-depressent [4], analgesic [5], anti-microbial [6], anti-viral [7], anti-cancer [8], anti-platelet [9], anti-convulsant [10], anti-histaminic [11], anti-biotics [12], anti-mutagenic [13], anti-oxidant [14], anti-aggregating [15] and CNS regulants [16] *etc.* Pyrazole derivatives also act as A3 adenosine receptor antagonists [17], neuropeptide YY5 receptor antagonists [18] and thrombopiotinmimetics [19].

2. PYRAZOLE MOTIF PRESENT IN DRUGS

Pyrazoles containing compounds have aroused much interest owing to their valuable pharmacological properties and therefore, extensively explored for their application in the field of medicines. Some of the pyrazole possessing drugs like celecoxib [20], lonazolac [21], pyrazofurin [22], fezolamin [23], rimonabant [24], etc. are already in use (Figure 2).

Ruxolitinib [25] used for the treatment of HIV and Crizotinib [26] are the pyrazole containing drugs that have been synthesized for preventing the progression of cancer and Tepoxalin [27] is a non-steroidal anti-inflammatory drug used for the treatment of pain and inflammation associated with canine osteoarthritis (Figure 3).

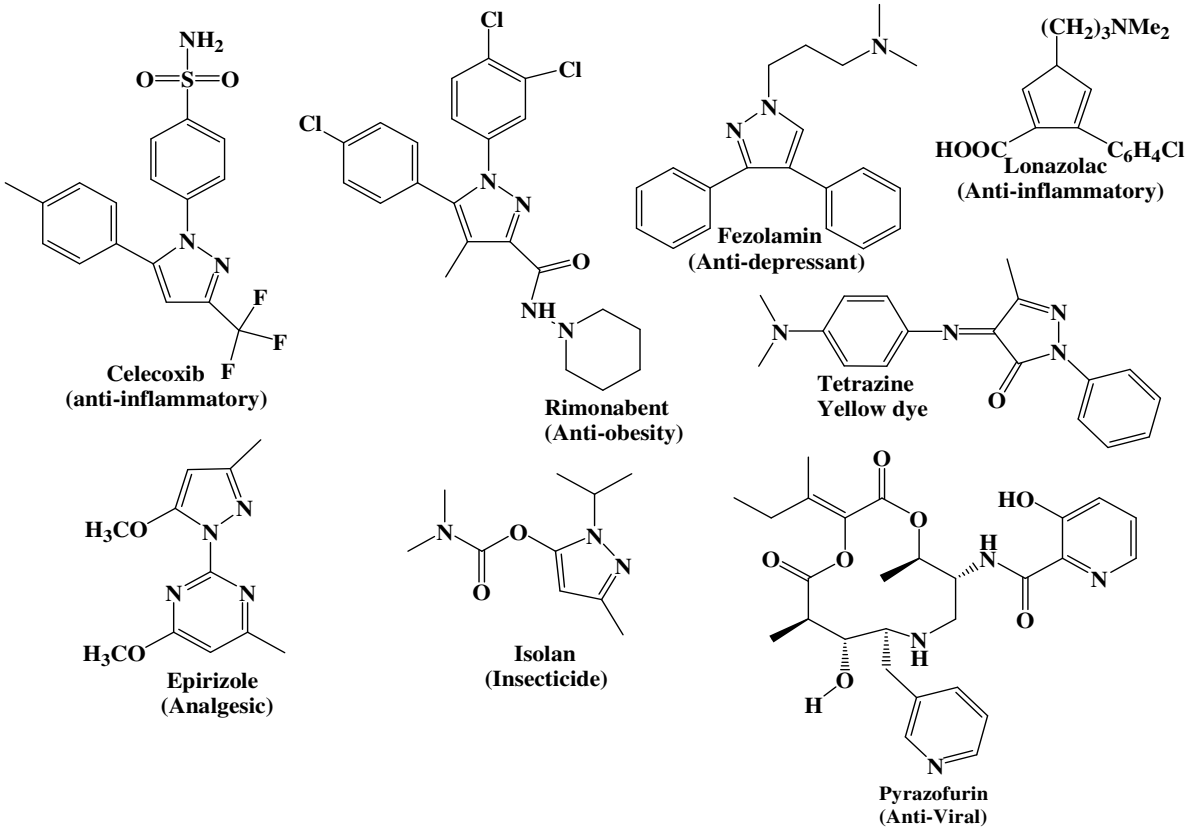


Figure - 2: Pyrazole motif present in drugs.

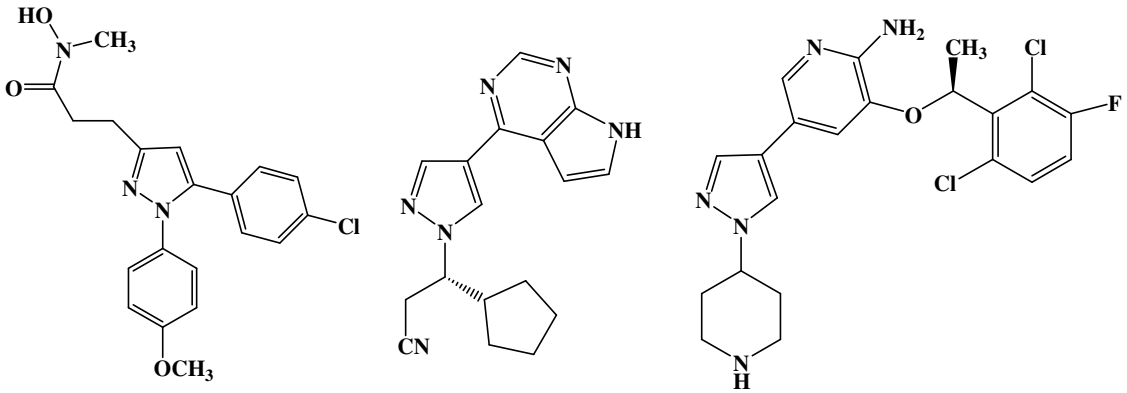


Figure - 3: Pyrazole containing drugs.

2.1. Pyrazole as anti-inflammatory agent

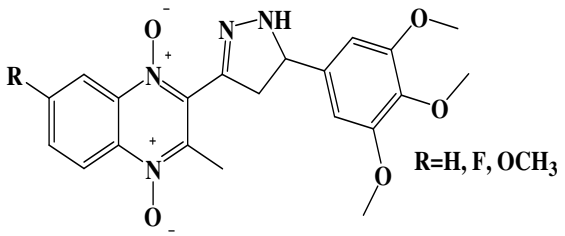


Figure - 4: Structure of 4 ,5-dihydro-(1H)-pyrazole analogues.

The Literature review shows that pyrazole derivatives have lots of pharmacological and biological activities; anti-inflammatory and analgesic activities are the most potent activities shown by pyrazole nucleus.

Burguete *et al.* have synthesize 4,5-dihydro-(1H)-pyrazole analogues (Figure 4) and reported their anti-inflammatory activity [28].

2.2. Pyrazole as CNS depressant

Sarangan *et al.* have synthesized number of derivatives of pyrazole- (3, 4-d) pyrimidine-4-6-diones (Figure 5) and reported the screening for C.N.S depression properties [29].

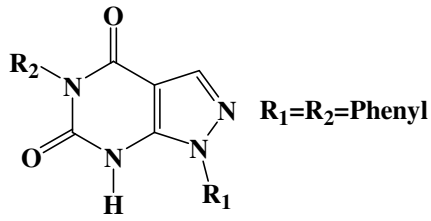


Figure - 5: Structure of pyrazole- (3, 4-d) pyrimidine-4-6-diones.

2.3. Pyrazole as anti-cancer agent

Lv *et al.* have synthesized a series of pyrazole derivatives (Figure 6) designing for potential EGFR kinase inhibitors as well as anti-proliferative activity against MCF-7 with potent inhibitory activity in tumor growth inhibition [30].

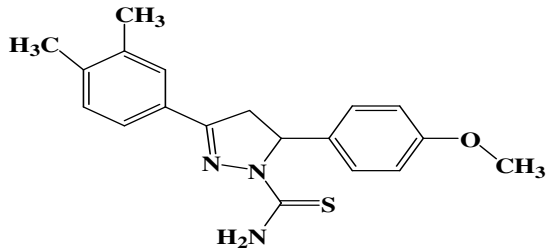


Figure - 6: Structure of 3-(3,4-Dimethyl-phenyl)-5-(4-methoxy-phenyl)-4,5-dihydro-pyrazole-1-carbothioic acid amide.

2.4. Pyrazole as hypoglycemic agent

Smith *et al.* have synthesized 3, 5-dimethyl pyrazole and 3- methyl pyrazole 5-carboxylic acid (Figure 7) and examined their hypoglycemic activity [31].

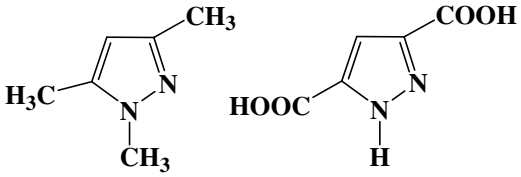


Figure - 7: Structure of 3, 5-dimethyl pyrazole and 3- methyl pyrazole 5-carboxylic acid

2.5. Pyrazole as Ca^{++} channel blocker

Ishikawa *et al.* have reported that 4-methyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-1,2,3-thiadiazole-5-carboxanilide (Figure 8) work as Ca^{++} channel blocker and have anti-hypertensive activity [32].

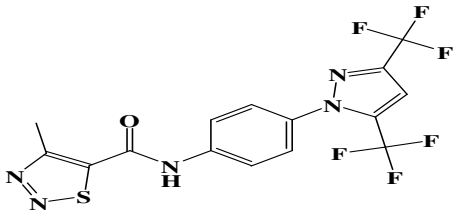
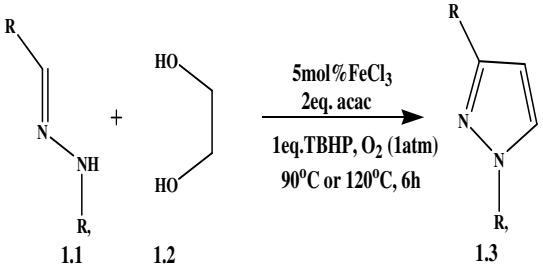


Figure - 8: Structure of -methyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-1,2,3-thiadiazole-5-carboxanilide.

3. Synthetic aspects of pyrazole

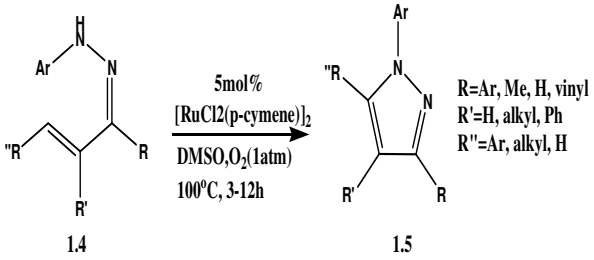
The biological significance of the pyrazole has led us to synthesise substituted pyrazole derivatives. Several synthetic strategies have been developed in the literature for the preparation of different analogues of pyrazole, of which a few examples are given below.

A regioselective iron-catalyzed reaction of diarylhydrazones **(1.1)** and vicinal diols **(1.2)** gives 1,3-and 1,3,5-substituted pyrazoles **(1.3)** (Scheme 1) [33].



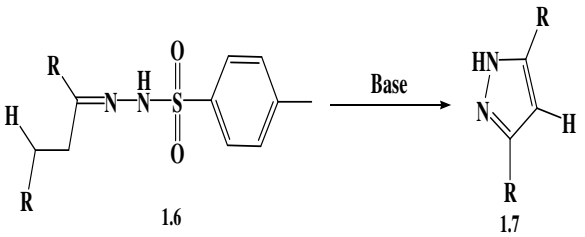
Scheme - 1: Synthesis of 1,3-substituted pyrazoles.

An ruthenium(II)-catalyzed oxidative C-N coupling intramolecular synthesis of tri- and tetrasubstituted pyrazoles **(1.5)** using oxygen as oxidant (Scheme 2) [34].



Scheme - 2: Synthesis of tetrssubstituted pyrazoles.

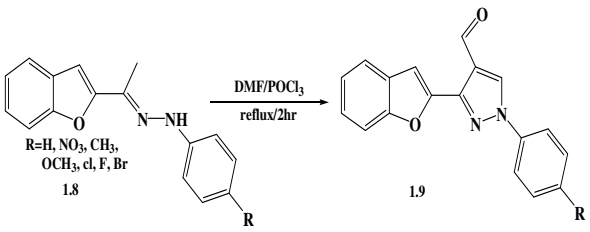
Synthesis of pyrazole derivatives **(1.7)** refers to the 1,3-cycloaddition of the corresponding tosyl hydrazones **(1.6)** of the carbonyl compounds using a base in dry media (Scheme 3) [35].



Scheme - 3: Synthesis of 3,5-substituted-1H-pyrazole.

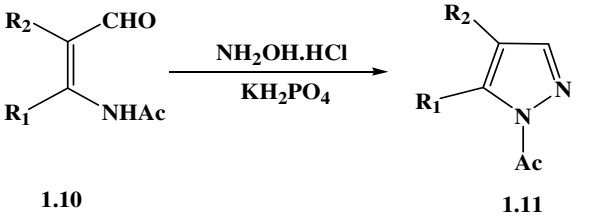
The 2-acyl benzofurohydrazones (**1.8**) subjected to Vilsmeir-Haach reaction *i.e.* reaction with DMF/$POCl_3$ at appropriate molar ratio which

underwent smooth cyclization followed by formylation afforded 3-(1-benzofuran-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehyde **(1.9)** (Scheme 4) [36].



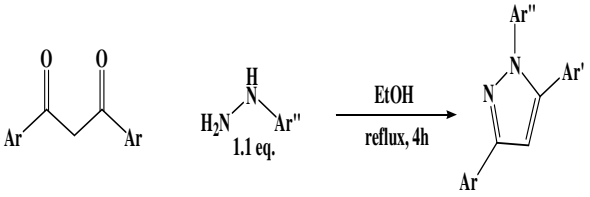
Scheme - 4: Synthesis of 3-Benzofuran-2-yl-1-p-tolyl-1H-pyrazole.

A novel one-pot synthesis of pyrazoles **(3.011)** has been accomplished by the reaction of β-formyl enamides **(1.10)** with hydroxylamine hydrochloride catalysed by potassium dihydrogen phosphate in acidic medium (Scheme 5) [37].



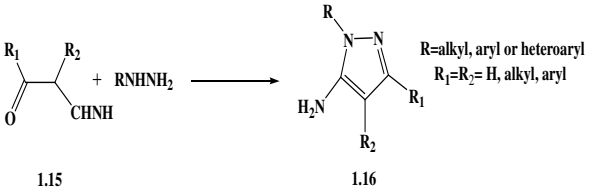
Scheme - 5: Synthesis of 1-(4,5-Disubstituted-pyrazol-1-yl)-ethanone.

The reaction of the easily accessible 1,3-bisaryl-monothio-1,3-diketone or 3-(methylthio)-1,3-bisaryl-2-propenones **(1.12)** with arylhydrazines **(1.13)** gives 1-aryl-3,5-bisarylpyrazoles **(1.14)** with complementary regioselectivity at position 3 and 5 (Scheme 6) [38].



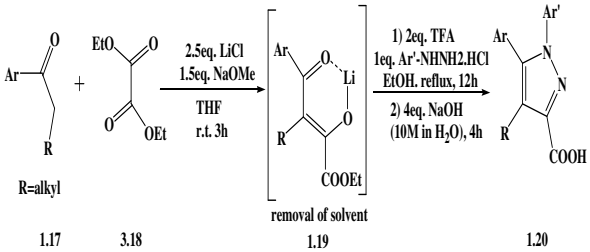
Scheme - 6: Synthesis of 1,3,5-Trisubstituted-1H-pyrazole.

An efficient Synthesis of 5-aminopyrazole **(1.16)** has been reported by the smooth reaction of β-ketonitriles **(1.15)** with hydrazines (Scheme 7) [39].



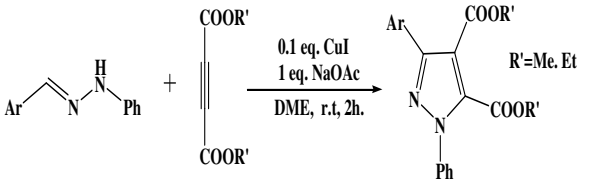
Scheme - 7: Synthesis of 2,4,5-trisubstitutedl-2H-pyrazol-3-ylamine.

One-Pot Synthesis of 4-Substituted 1,5-Diaryl-1*H*-pyrazole-3-carboxylic Acids **(1.20)** via a MeONa/LiCl-Mediated Sterically Hindered Claisen Condensation-Knorr Reaction-Hydrolysis Sequence (Scheme 8) [40].



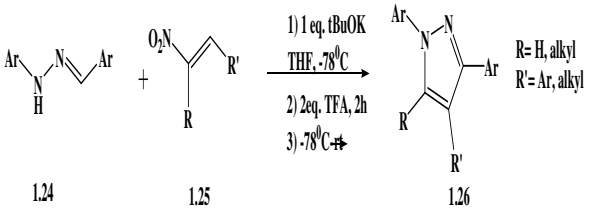
Scheme - 8: Synthesis of 4-Substituted 1,5-Diaryl-1*H*-pyrazole-3-carboxylic Acids.

An efficient copper-catalyzed synthesis of polysubstituted pyrazoles **(1.23)** has been observed from the reaction of phenylhydrazones **(1.21)** and dialkyl ethylenedicarboxylates **(1.22)** (Scheme 9) [41].



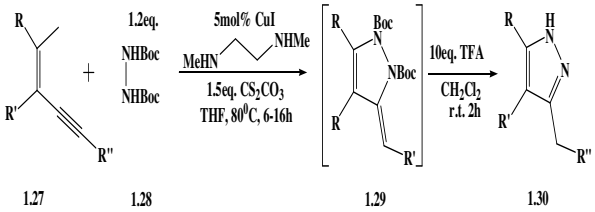
Scheme - 9: Synthesis of polysubstituted pyrazoles.

A regioselective synthesis of tri- or tetrasubstituted pyrazoles **(1.26)** by the reaction of hydrazones **(1.24)** with nitroolefins **(1.25)** mediated with strong bases such as *t*-BuOK exhibits a reversed, exclusive 1,3,4-regioselectivity. Subsequent quenching with strong acids such as TFA is essential to achieve good yields (Scheme 10) [42].



Scheme - 10: Regioselective synthesis of tri- or tetrasubstituted pyrazoles.

A highly flexible Cu-catalyzed domino C-N coupling/hydroamination reaction constitutes a straightforward alternative to existing methodology for the preparation of pyrroles and pyrazoles **(1.30)** (Scheme 11) [43].



Scheme - 11: Synthesis of 3-Ethyl-4,5-dimethyl-1H-pyrazole.

4. CONCLUSION

In this short review we prepared the different types of pyrazole derivatives through many types of reactions. And these derivatives are useful in many activities like anti-cancer, anti-inflammatory and analgesic etc.

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