University of Basrah
College of Pharmacy

Pyrazole, Synthesis and Biological Activity

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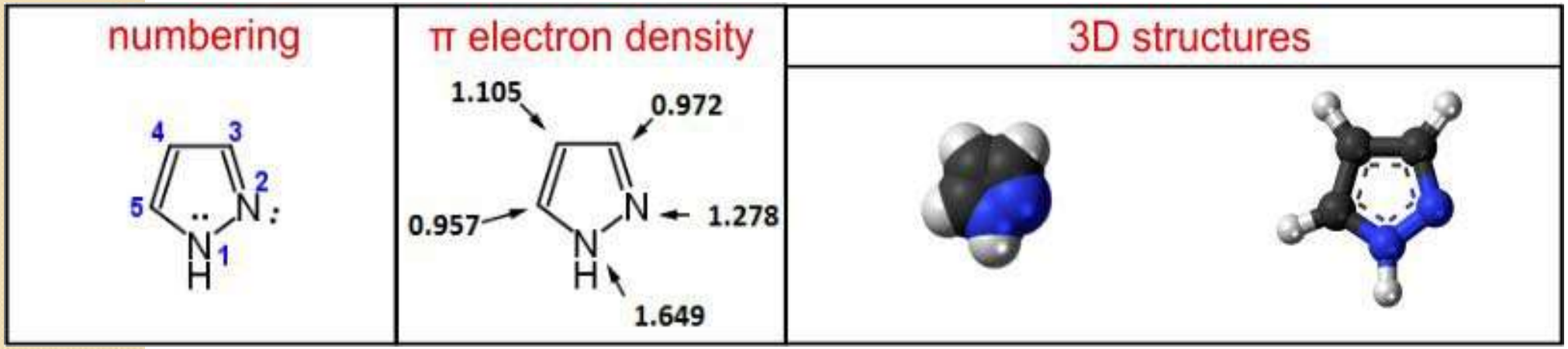
Contents

Introduction

Pyrazole is a five-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions as represented by the molecular formula $C_3H_4N_2$. It is a weak base, with pK_b 11.5 (pKa of the conjugated acid 2.49 at 25°C).

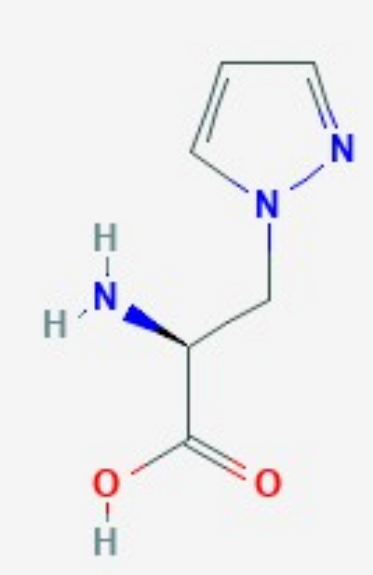


Structure of pyrazole.

pyrazole was first invent by Ludwig Knorr in 1883. Due to its composition and unique pharmacological effects on human beings, they are classified as alkaloids.

German chemist ,
Ludwig Knorr

1-pyrazolyl-alanine was the first natural pyrazole isolated from watermelon seeds in the year 1959.



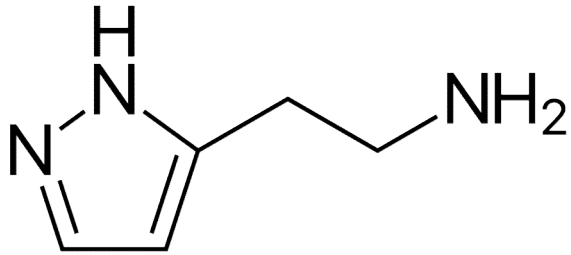
Pyrazoles are reported to possess a wide range of biological activities in literature such as

- anti-microbial,
- anti-fungal,
- anti- tubercular,
- anti-inflammatory,
- anti-convulsant,
- anticancer,
- anti-viral,
- angiotensin converting enzyme (ACE) inhibitory,
- neuroprotective,
- cholecystokinin-1 receptor antagonist, etc..

Marketed products containing pyrazole moiety

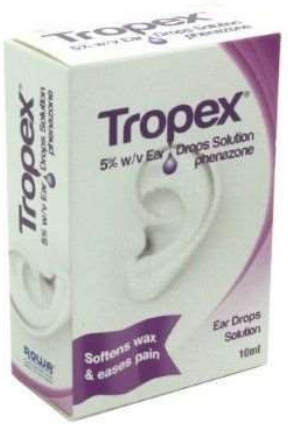
Betazole

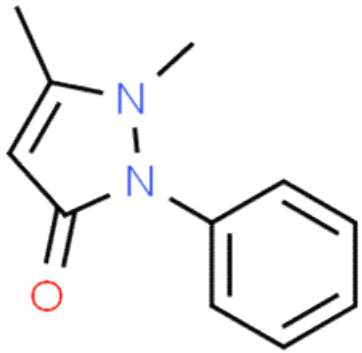
A histamine H2 agonist used clinically to test gastric secretory function



Phenazone

An analgesic and antipyretic that has been given by mouth and as ear drops. Antipyrine is often used in testing the effects of other drugs or diseases on drug-metabolizing enzymes in the liver



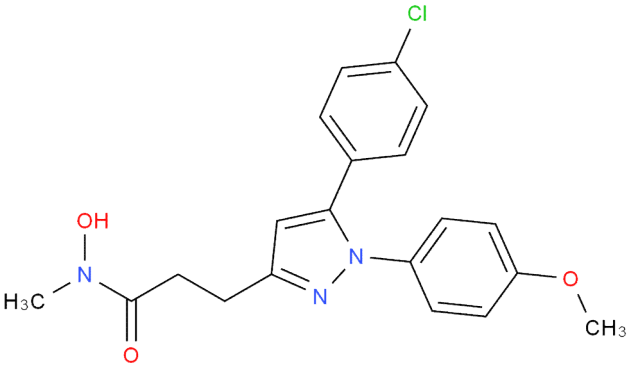


Celecoxib

Is a non-steroidal anti-inflammatory drug (NSAID), used in treatment of osteoarthritis, rheumatoid arthritis, acute pain and painful menstruation

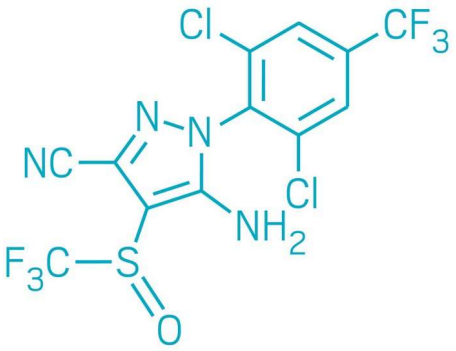
Tepoxalin

A non-steroidal anti-inflammatory drug approved for veterinary use in United States &the European Union.



Fipronil

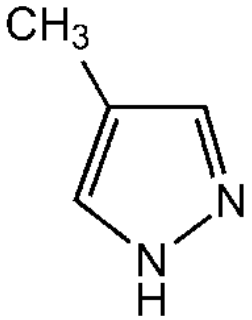
Has broad spectrum insecticide that disrupts the insect central nervous system by blocking the passage of chloride ions through the GABA receptor and glutamate-gated chloride channel , components of central nervous system.



Fipronil

Fomepizole

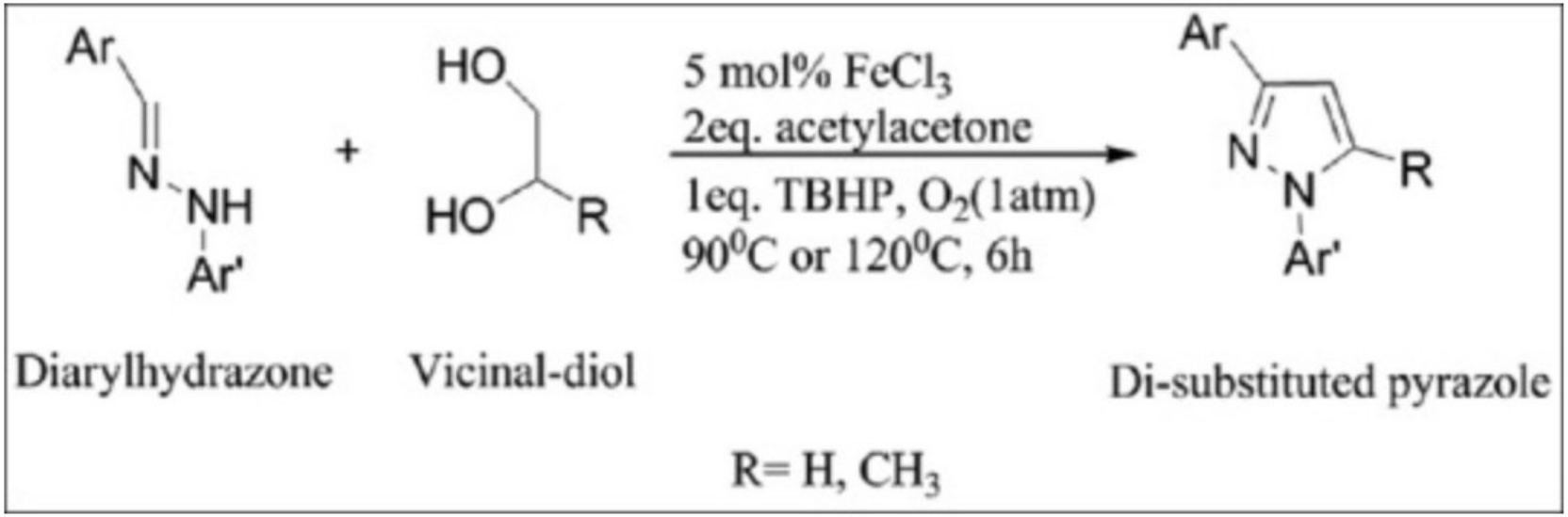
Use as an antidote in confirmed & suspected methanol or ethylene glycol poisoning.



Synthesis of pyrazole

1. Synthesis of 1, 3-substituted pyrazoles:

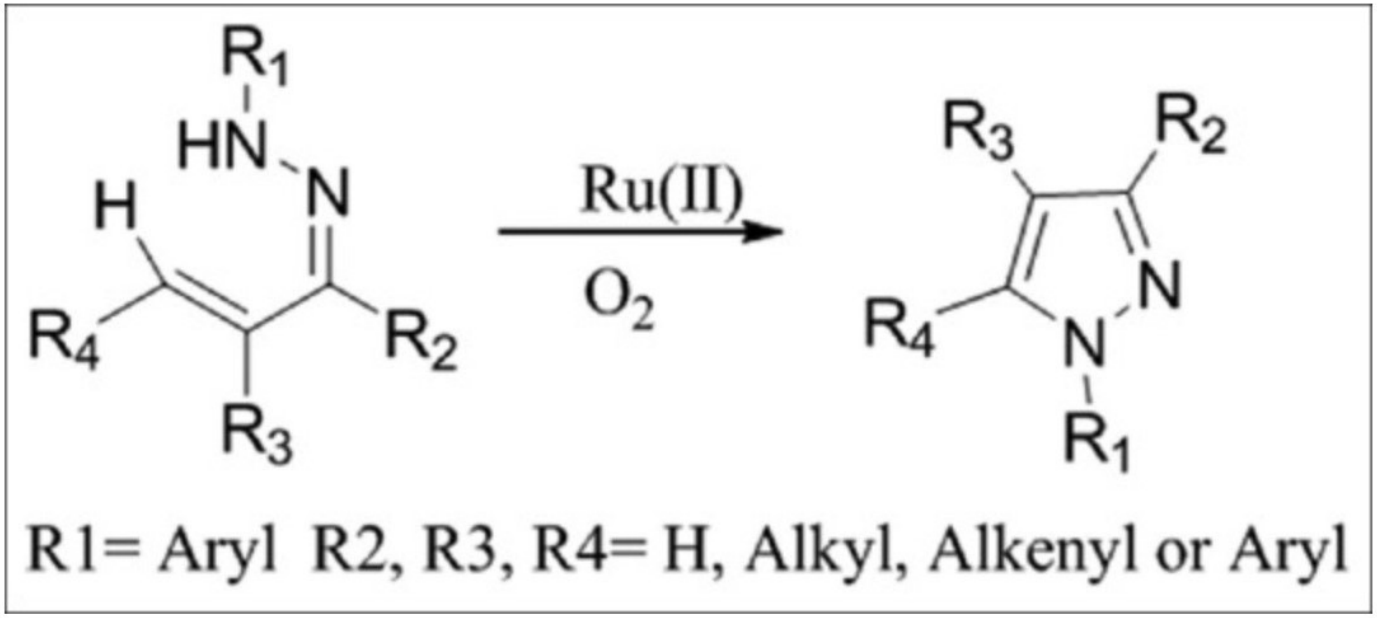
An iron-catalyzed route for the synthesis of 1,3- and 1,3,5-substituted pyrazoles from the reaction ofdiarylhydrazones and vicinal diols.



Synthesis of 1,3- and 1,3,5-substituted pyrazoles

2. Synthesis of tri- and tetra-substituted pyrazoles:

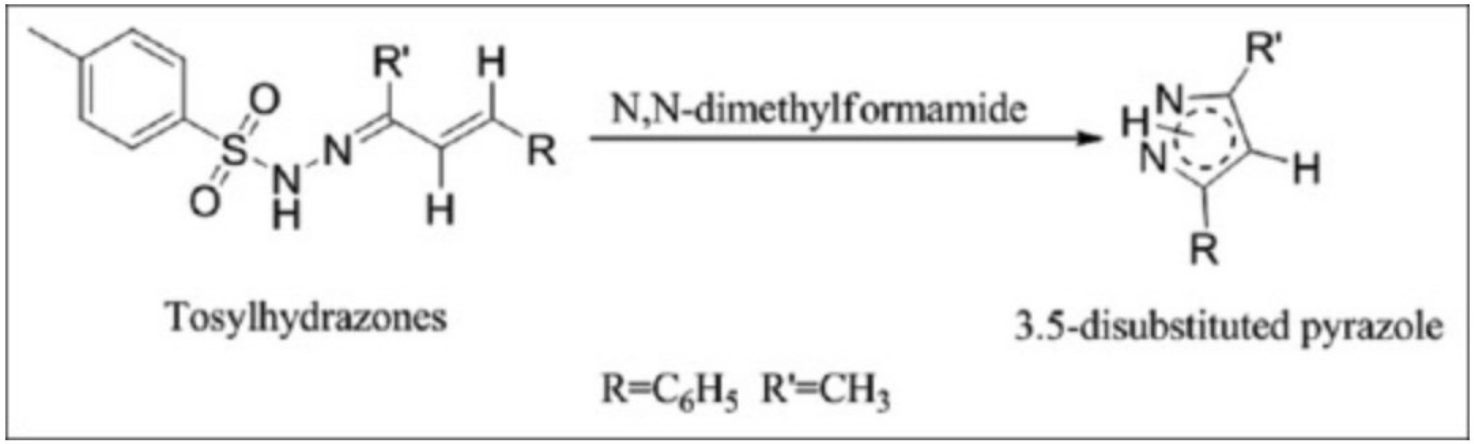
A ruthenium (II)-catalyzed intramolecular oxidative CN coupling method for the facile synthesis of a tri- and tetra- substituted pyrazoles. Dioxygen gas is employed as the oxidant in this transformation and the reaction demonstrates excellent reactivity, functional group tolerance, and high yields.



Synthesis of tri- and tetra-substituted pyrazoles

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

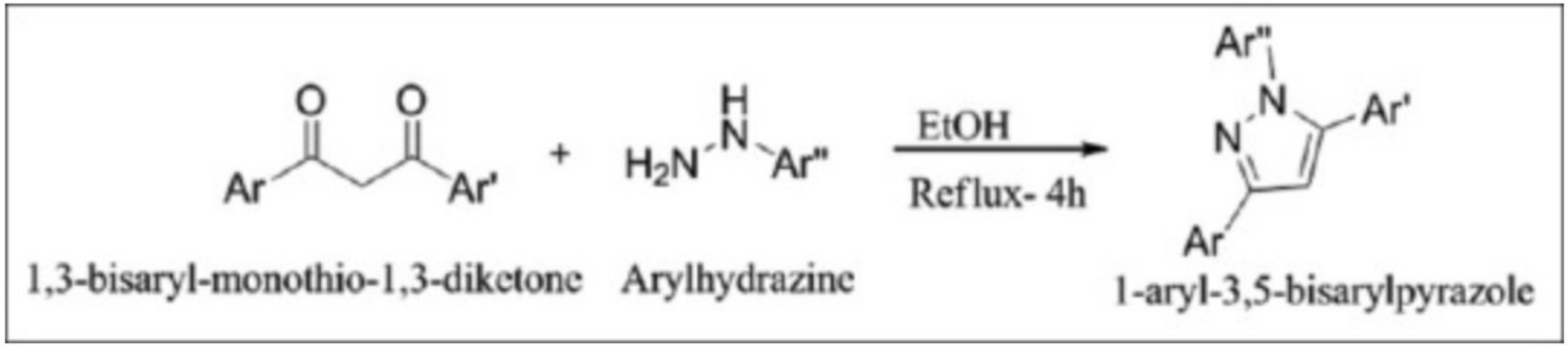
A novel approach to the synthesis of pyrazole derivatives from tosylhydrazones of α, β-unsaturated carbonyl compounds possessing a β-hydrogen is proposed, exploiting microwave activation coupled with solvent free reaction conditions.



Synthesis of 3,5-substituted-1H-pyrazole

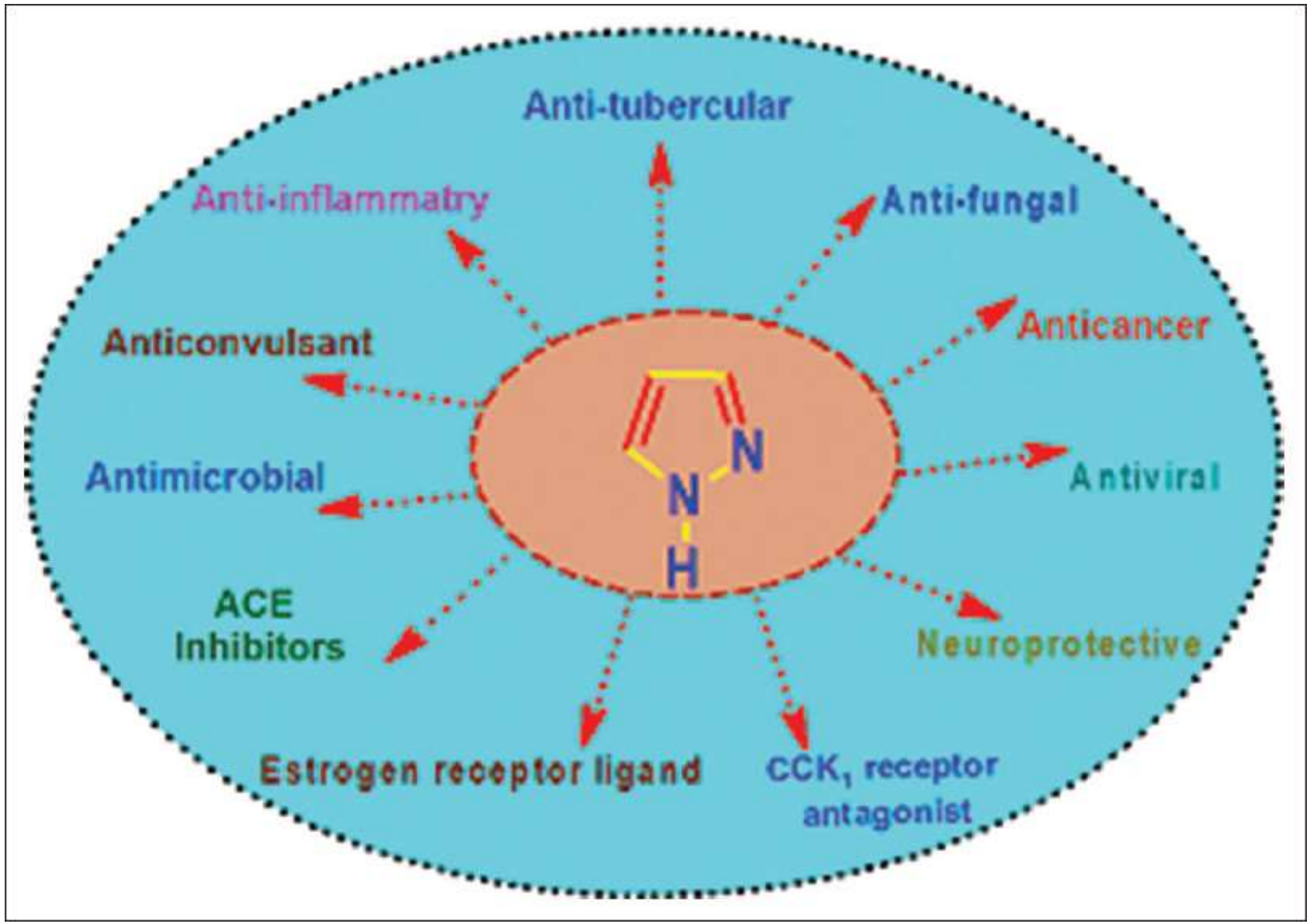
4. Synthesis of 1,3,5-trisubstituted-1H-pyrazole:

The reaction of the easily accessible 1, 3-bisaryl-monothio-1,3-diketone or 3-(methylthio)-1,3-bisaryl-2-propenones with arylhydrazines gives 1-aryl-3,5-bisarylpyrazoles.



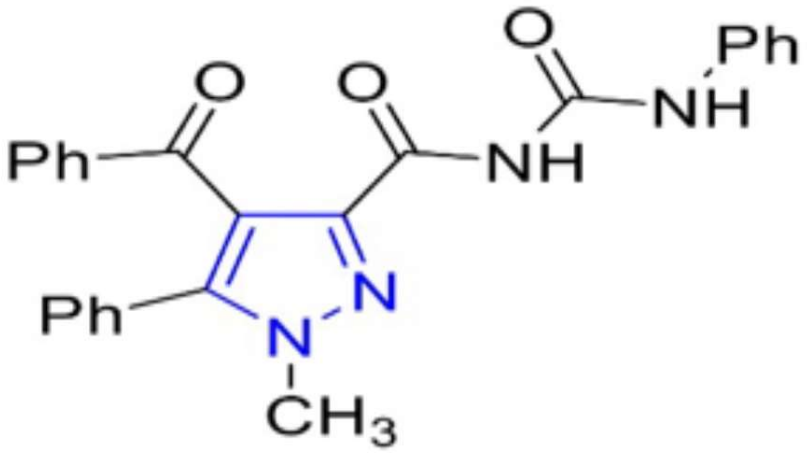
Synthesis of 1,3,5-trisubstituted-1H-pyrazole

Pharmacological activity



1) Antibacterial and Antifungal Activity

The compound 151 was the best compound in the series, exhibiting antibacterial activity against both Gram positive and Gram-negative bacteria



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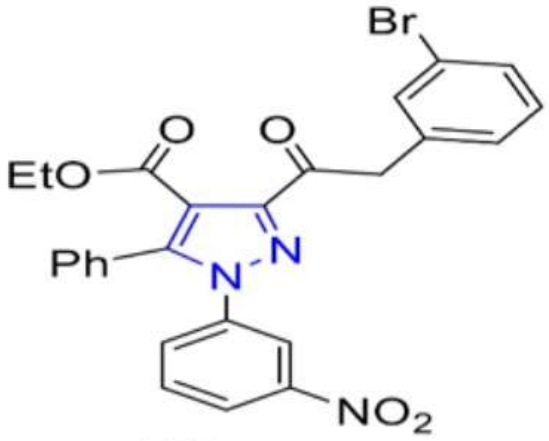
Anti fungal activity these molecules 153, 154 and 155 demonstrated some inhibitory effects on Candida parapsilosis, Candida tropicalis, and Candida glabrata strains



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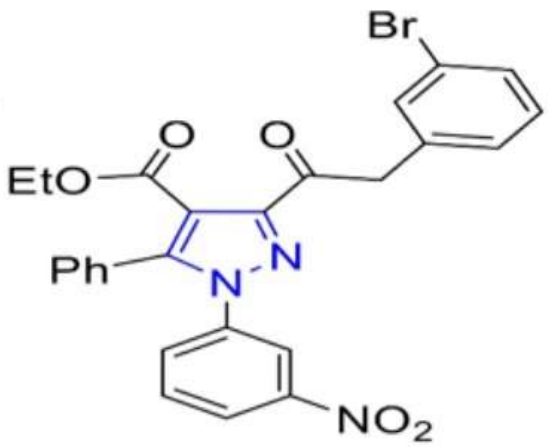

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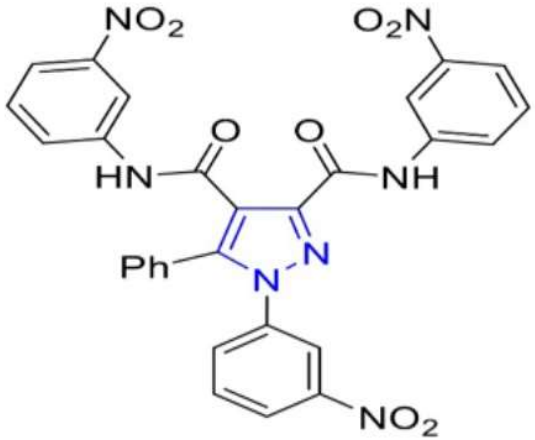

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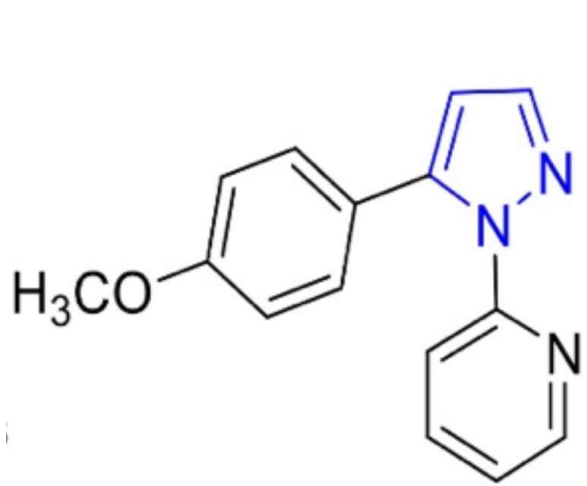
2) Anticancer activity:

* **Pyrazoles derivatives have a good anti-proliferative like in this compaund 216.**

* **The synthetized compound 217 exhibit potent cytostatic properties displaying IC_{50} values of 1.5 µM**



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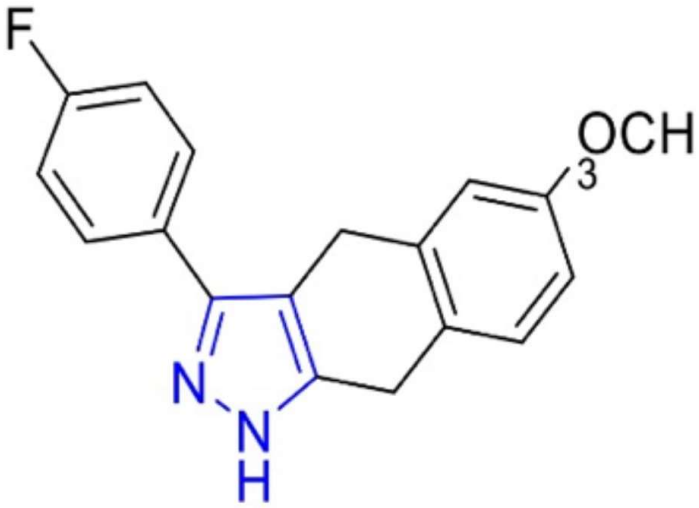

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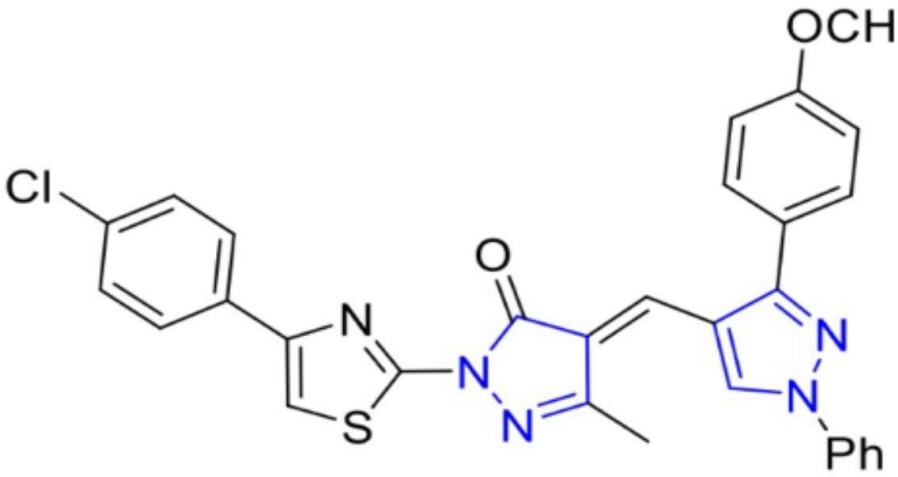
3) Anti-Inflammatory and Analgesic Activity:

*** A new group of pyrazole derivatives were designed for evaluation as selective cyclooxygenase-2 (COX-2) inhibitors. Results indicated that the compound 294 exhibited significant COX-II inhibition.**

*** Compound 295 exhibited anti-inflammatory activity comparable to that of indomethacin (LD50 > 500 mg/Kg), and showed good selective inhibitory activity against COX-2 enzyme.**



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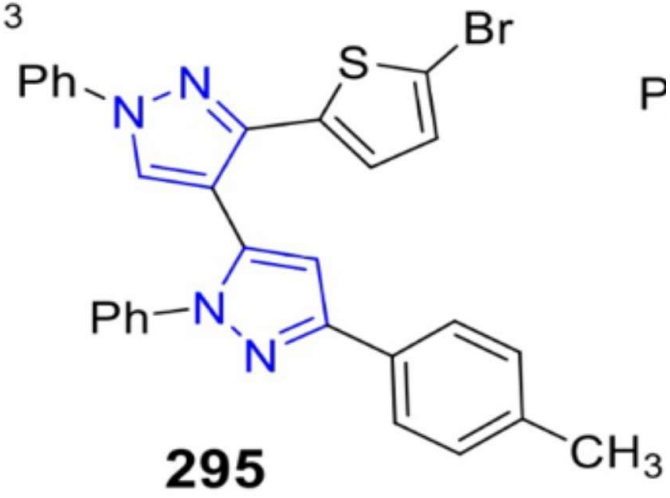
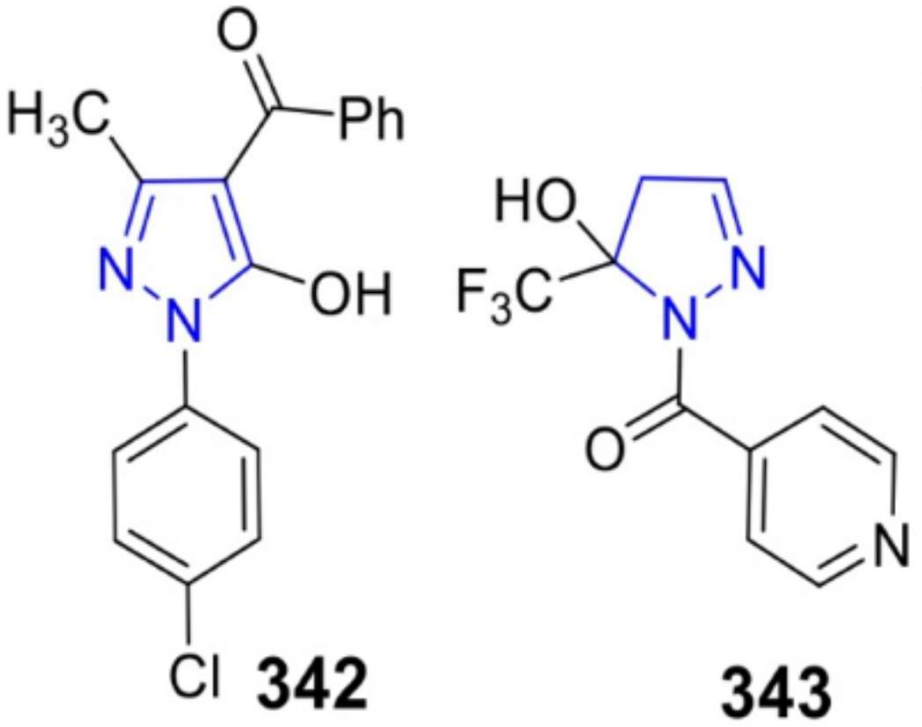


295

4) Anti-Tubercular Activity:

* **Manetti et al. identified new inhibitors of Mycobacterium tuberculosis . Compound 342 was found to be most active agent with a MIC value of 25 µg/mL.**

* **Amongst the synthesized compounds, compound 343 was found to be the most active agents against susceptible M. tuberculosis and several INH-resistant strains.**

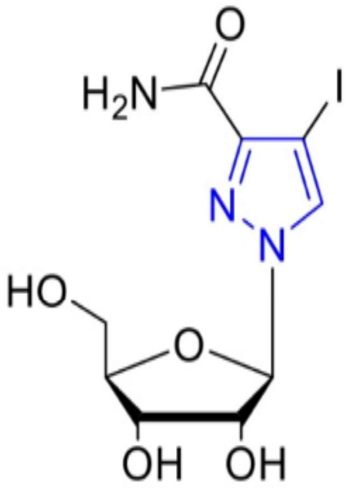


5) Anti-Viral Activity:

- **Pyrazole was prepared as antiviral activities against herpes simplex type I (HSV-1), africain swine fever (ASFV), polio, coxsackie, vescicular stomatitis virus (VSV), and HIV-1.**

- **compound 390 showed a selective and inhibited the HIV-1 multiplication in infected cells.**

- **Compound 391 proved active against respiratory syncytial virus , vaccinia virus, vesicular stomatitis virus, and influenza A virus at concentrations ranging from 4 to 20 µg/mL .**



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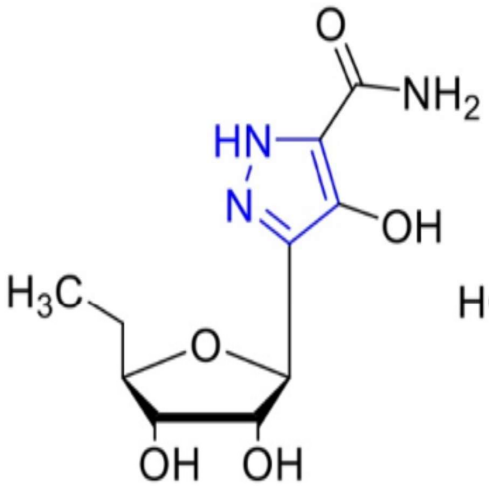


391

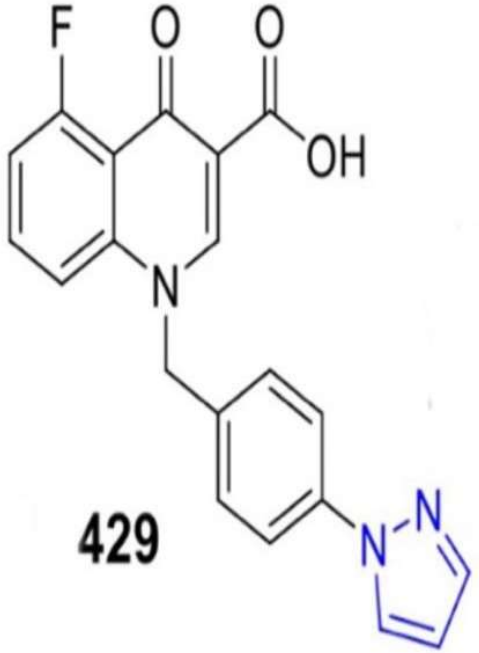
6) Anti-Azheimer's Activity:

- Pyrazoles have ability to inhibit reversibly monoamine oxidase-A (MAO-A) and monoamine oxidase B (MAO-B).

  - Compound 428 showed good inhibitory activity against MAO-A and MAO-B, but low selectivity

  - compound 429 as a potent and selective full agonist of the M1 positive allosteric modulators.

428



429

Conclusions:

- **Pyrazoles represent a major pharmacophore with various biological properties, and some pyrazole-containing derivatives have already been used for therapeutic purposes.**

- **structural modifications of the basic structure of pyrazole, have allowed the preparation of new derivatives with a broad spectrum of biological activity, with the most important structural variations concerning the substituents at the 1-position, the carbon at the 3-position and the substituent at the 5-position,so that pyrazole derivatives are pharmacologically very potent and giving it antimicrobial, anticonvulsant, analgesic, anti-inflammatory, anti-viral, anti-malarial and anti-cancer properties.**


Thank you