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Synthesis and Biological Evaluation of Some Pyrazole Derivatives

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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.*

Keywords: Pyrazole, Heterocyclic Compound, Biological properties, Physical properties

I. INTRODUCTION

Medicinal chemistry is a multidisciplinary subject involving Organic chemistry, Pharmacology, Biochemistry, Physiology, Microbiology, Toxicology, Genetics and Computer modeling. Its explain the design and production of compounds that can be used for prevention, treatment or cure of human or animal diseases. More recently the IUPAC have recommended the following Description for the Medicinal chemistry term; Medicinal chemistry is a chemistry based discipline, also involving aspects of biological, medical and Pharmaceutical science. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and construction of structure activity relationship.

Medicinal chemistry covers the following stages:

- In the first stage new active substance or drugs are identified and prepared from natural sources Organic chemical reactions or biotechnological processes. They are known as lead molecules.
- The second stage is optimization of lead molecule to improve potency, selectivity and to reduce toxicity.
- The next stage involves optimization of synthetic route for bulk production and modification of pharmacokinetic and pharmaceutical properties of active substance to render it clinically useful.

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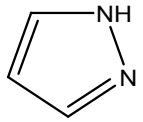
1. NUCLEUS INTRODUCTION

PYRAZOLE

Pyrazoles are important class of heterocyclic compounds possessing interesting biological, and Pharmacological properties as anti-inflammatory, anti-cancer, anti-bacterial, anti-viral, antipyretic, antiarrhythmic, tranquilizing, muscle relaxing, anticonvulsant, anti-diabetic,and anti-fungal agents. Pyrazolines obtained by cyclization of chalcones with arylhydrazines, can be easily oxidized to pyrazoles.

The compounds containing a pyrazole scaffold have been shown to exhibit HIV-1 reverse trancriptase inhibition, as well as anti hyperglycemic,antibacterial,sedative-hypnotics, anti-inflammatory, antipyretic and analgesic activity.



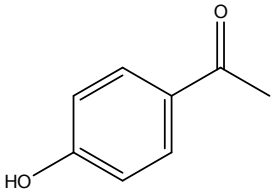
PYRAZOLE

PRODUCT IDENTIFICATION:

Other Name	:	1,2-diazole.
Molecular Formula	:	$C_3H_4N_2$
Molar Mass	:	68.07 gm/mol.
Melting Point	:	66-70 °C.
Boiling Point	:	168-188 °C.

2. INTRODUCTION OF STARTING MATERIALS

P-OH ACETOPHENONE



IUPAC name: 1-(4-hydroxyphenyl)ethanone

Other names: 4-hydroxy acetophenone, 4'-hydroxy acetophenone, (4-hydroxyphenyl) ethan-1-one, p-hydroxyacetophenone.

Molecular Formula	:	$C_8H_8O_2$
Molecular Weight	:	136.15 g/mol
Melting Point	:	107 - 111˚C
Boiling Point	:	147 - 148˚C
Solubility	:	Organic solvents

Diprenylated derivatives of p-hydroxyacetophenone can be isolated from *Ophryosporus macrodon*.

4-Hydroxyacetophenone monooxygenase is an enzyme that transforms piceol, NADPH, H+ and O_2 into 4-hydroxyphenyl acetate, NADP+ and H_2O. This enzyme is found in *Pseudomonas fluorescens.*

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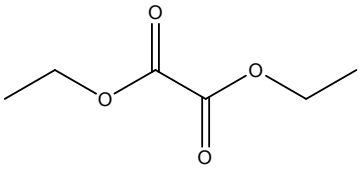
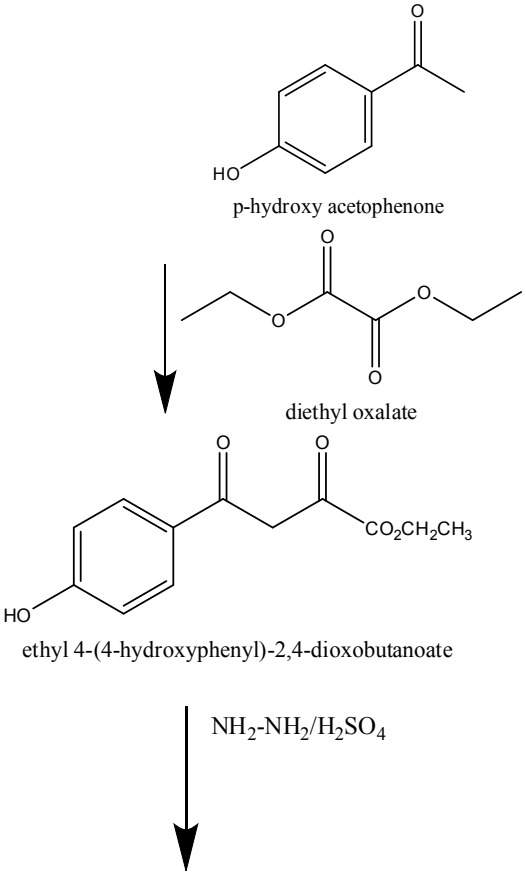
DIETHYL OXALATE



IUPAC name	**:**	Diethyl oxalate
Other name	**:**	Diethyl ester of oxalic acid
Molecular Formula	:	$C_6H_{10}O_4$
Molecular Weight	:	146.14 g/mol
Melting Point	:	-39˚C
Boiling Point	:	186˚C
Solubility	:	Organic solvents

Diethyl Oxalate is used as a solvent for paint stripping and resins, cleaner for polymeric residues, pigment dispersant. It is used as an intermediate to produce barbiturates (a group of ureides that act as nonselective central nervous system depressant) and dyes.

3. SCHEME OF WORK



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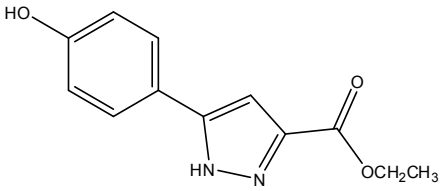
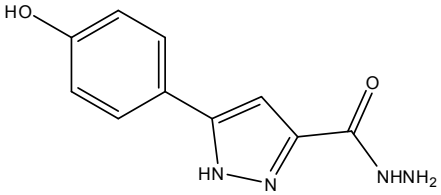


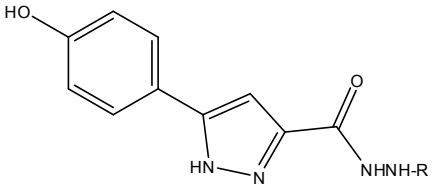
ethyl 5-(4-hydroxyphenyl)-1*H*-pyrazole-3-carboxylate

NH_2NH_2/H_2O/Ethanol



5-(4-hydroxyphenyl)-1*H*-pyrazole-3-carbohydrazide

Various aryl aldehyde/Ethanol



5-(4-hydroxyphenyl)-1*H*-pyrazole-3-carbo aryl hydrazide

R= Aryl aldehyde

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4. EXPERIMENTAL WORK

4.1 LIST OF COMPOUNDS SYNTHESIZED

S.No	Compound Code	Structure and IUPAC Name
1.	S_1	
2.	S_2	

5. PROCEDURE

STEP: 1

SYNTHESIS OF P- OH-ETHYL-2, 4-DIOXO-4-PHENYL BUTANOATE.

Treatment of equimolar amounts of para hydroxy acetophenone with diethyl oxalate in sodium ethoxide and ethanol at room temperature.

STEP: 2

SYNTHESIS OF P-OH-ETHYL-5-PHENYL-1H-PYRAZOLE-3-CARBOXYLATE.

To a solution of compound1 (0.2mole) in ethanol, hydrazine hydrate (0.2mole) is added.

The mixture is refluxed for 8 hours.

The solvent is evaporated and the solid obtained is recrystalized from petroleum ether.

STEP: 3

SYNTHESIS OF P- OH-5-PHENYL-1H-PYRAZOLE-3-CARBOHYDRAZIDE.

Compound 2 (0.1mole) in ethanol (10ml) 2ml of hydrazine hydrate is added.

The mixture is maintained under reflux for 8 hours.

After cooling, the mixture is poured on ice and the solid formed is collected

by filtration, washed with cold water and recrystalized from ethanol.

STEP: 4

SYNTHESIS OF P-OH-5-PHENYL-1H-PYRAZOLE-3CARBO ARYL ALDEHYDE HYDRAZINE.

Compound 3 (0.1mole) in 20ml of ethanol.

It is added an equimolar amount of the aryl aldehydes in the presence of acetic acid.

The mixture is maintained under reflux for 3 hours.

Then the reaction mixture is poured in cold water and the precipitate formed was filter, and wash with ethanol and recrystalized from methanol/DMF.

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6. PHYSICAL CHARACTERIZATION

All the synthesized compounds are to be characterized by following methods:

- ✓ **Melting point**
  Melting point will be measured in open-end capillary tube method by electrically heating melting point apparatus.
- ✓ **Solubility**
  At room temperature solubility of newly synthesized compound will be determined.
- ✓ **Thin Layer Chromatography**

The purity of new compound will be analyzed and reaction completion will be checked by thin layer Chromatography by measuring R_f value of product.

- ✓ **Analytical Characterization**
  - IR Spectroscopy
  - NMR Spectroscopy
  - Mass Spectroscopy

6.1 Solubility

At the room temperature, solubility of all synthesized compound was determined and shown in Table No.1

Table No.1

S.No	Compound Code	Solubility
1.	Compound 1	MeOH, EtOH, DMSO, DMF
2.	Compound 2	MeOH, EtOH, DMSO, DMF
3.	Compound 3	MeOH, EtOH, DMSO, DMF
3.	S_1	MeOH, EtOH, DMSO, DMF
4.	S_2	MeOH, EtOH, DMSO, DMF

6.2 Thin Layer Chromatography

The purity of all synthesized compounds was monitored on TLC.

Absorbent used : Precoated Silica gel- G plate
Mobile Phase : Chloroform : Methanol (3:7)
Detecting technique : Iodine chamber

$$R_f = \frac{\text{Distance travelled by solute}}{\text{Distance travelled by solvent}}$$

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Table No.

S.No	Compound Code	R_f value
1.	Compound 1	0.81
2.	Compound 2	0.71
3.	Compound 3	0.86
4.	S_1	0.80
5.	S_2	0.73

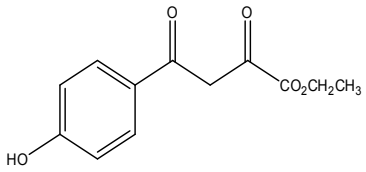
7. STRUCTURAL CONFIRMATION

SPECTRAL ANALYSIS

The objective of the spectral analysis is to confirm the chemical structures of the synthesized compounds and the various functional groups in the final compounds. The IR spectra of starting compound and intermediates were taken to confirm the changes at the reactive functional groups and then the final compounds were confirmed by IR, NMR and Mass spectroscopy.

- The Infra Red spectroscopy was performed with KBr on Perkin Elmer Spectrum Version 10.03.07 instrument.
- ^{1}HNMR spectra of the synthesized compounds in deuteriated DMSO were recorded on BRUKER AVANCE 400 MHZ instrument using TMS as the internal standard.
- Mass spectroscopy was performed on JEOL GCmate using Dimethyl sulfoxide as solvent.

Compound-I



IUPAC Name:

Ethyl 4-(4-hydroxyphenyl)-2, 4-dioxobutanoate

IR interpretation

I.R Spectral data (KBr discs) (in Cm^{-1})	
C=O str.	1697.45
C=C str.	1541.36
C-H str.	3107.26

8. BIOLOGICAL SCREENING

8.1 *IN-VITRO* ANTI-INFLAMMATORY ACTIVITY

Inflammation is normal protective response to tissue injury caused by physical trauma, noxious chemicals or microbiological agents and local response of living mammalian tissue to injurious agents, which may be due to physical agents like heat, cold, radiation, trauma; Chemical agents like organic and inorganic; Infective agents like bacteria, virus, parasites; Immunological agents like antigen-antibody reactions, cell mediated reaction. In the present study invitro anti-inflammatory activity was checked for the synthesized compounds.

HRBC Membrane Stabilisation method

The method involves the stabilization of human red blood cell membrane by hypotonicity induced membrane lysis.

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Principle

The lysosomal enzymes released during inflammatory condition produce a variety of disorders. The extra cellular activity of these enzymes is said to be related to acute or chronic inflammation. The anti-inflammatory agents act by either inhibiting the lysosomal enzymes or by stabilizing the lysosomal membrane since the human red blood cell membrane are similar to lysosomal membrane components. The prevention of hypotonicity induced HRBC membrane lysis is taken as a measure of anti-inflammatory activity of the drug.

Reagents:

- HRBC suspension : 10 %
- Alsiever solution
- Isotonic saline : 0.85%
- Phosphate buffer : 0.15M,pH-7.2
- Hypotonic saline : 0.36 %

Preparation of Alsievier's solution: 2g dextrose + 0.8g sodium citrate + 0.05g citric acid + 0.42g sodium chloride was made up with distilled water to 100ml.

Preparation of 0.5 ml of 10 % HRBC Suspension

To 3 ml of blood, add 3 ml of Alsievier's solution and centrifuge at 3000 rpm for 20 minutes then packed cells were washed with isotonic saline and later10% v/v suspension of the packed cells was made with isotonic saline.

Preparation of Hypotonic Saline

0.36g of sodium chloride in 100 ml of distilled water.

Preparation of Isotonic Saline

0.85g of sodium chloride in 100 ml of distilled water.

Procedure:

The synthesized compounds are to be used for this study. They are to be made into doses of 1000 µg/ml with DMSO (5.0 %) solution. Diclofenac sodium is taken as standard. The reaction mixture (4.5 ml) consist of 2 ml of hypotonic saline (0.36 % sodium chloride), 1 ml of 0.15 M phosphate buffer (Ph 7.4) ,1 ml of the test solution (1000 µg/ml) in normal saline and 0.5 ml of HRBC suspension in normal saline. For control test, 1 ml isotonic saline is to be used instead of test solution while product control lacked RBC. The mixture is then incubated at 56˚C for 30 minutes, then to be cooled under running tap water and centrifuged at 3000 rpm for 20 minutes. The absorbances of the supernatants are read at 560 nm.Percent membrane stabilization activity is calculated as follows:

$$\% \text{ stabilization} = \frac{\text{100-OD of test control-OD of test sample}}{\text{OD of test control}} \times 100$$

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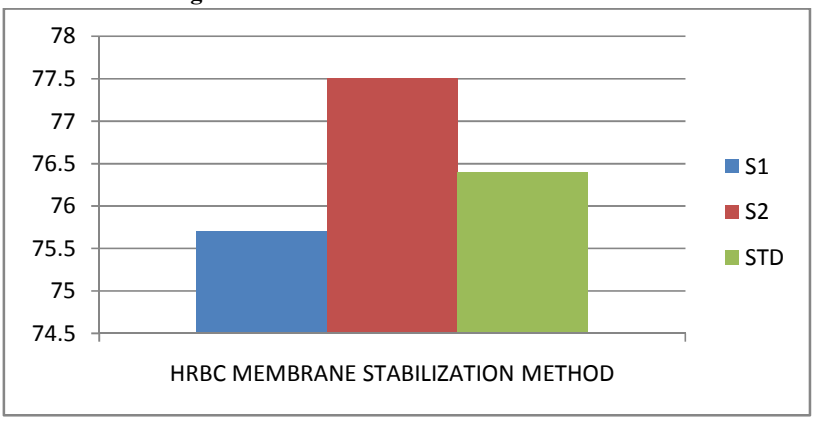
Anti-Inflammatory Activity of Compounds S_1- S_2 in µg/ml

HRBC Membrane Stabilization Method

Table.No.

S.No	Compound code	Percentage Stabilization
1	S_1	75.7
2	S_2	77.5
3	STD	76.4

Figure No.1 HRBC Membrane Stabilisation method



9. RESULTS AND DISCUSSION

Synthesis

The present study report the synthesis of pyrazole derivatives nucleophillic substitution of p-hydroxy acetophenone in diethyl oxalate was carried out stepwise at different temperature by various aldehydes. The first step involves substitution of p-hydroxy acetophenone and the next by ethyl 4-(4-hydroxy phenyl)-2, 4-dioxo butanoate. The final pyrazole derivative in the synthesized compound 3 was replaced by various aldehyde groups. Since the report regarding this compound suggest a pyrazole posses a good bioactive moiety.

Physical characterization

Melting points of the synthesized compound was taken in open capillary tubes and was uncorrected and were found to be in the range 105-120˚C.

TLC was performed using precoated silica gel plates of 0.25mm thickness. Eluents used were chloroform, methanol (3:7) spots were visualized in U.V. light.

At room temperature solubility of newly synthesized compounds were determined by various organic solvents and it was found that all compounds were freely soluble in Methanol, Ethanol, DMSO and DMF.

Structural confirmation

The Infra red spectroscopy was performed with KBr on Perkin Elmer Spectrum Version 10.03.07 instrument. Presence of stretching in the range 1500 cm^{-1} to 1700 cm^{-1} indicating the presence of C=N functional group. C=O stretching between at 1300 cm^{-1} to 1600 cm^{-1}.

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^{1}H NMR spectroscopy was recorded on Bruker 400 MZs Avance. ^{1}H NMR the chemical shifts were reported as parts per million downfield from tetra methyl silane and solvent used as DMSO. Presence of chemical shift in the range 7.02-7.49 (m, 6H, CH), 6.76-6.86 (d, 6H, CH).

Mass spectroscopy was performed on the instrument JEOL GCmate using DMSO as solvent. All the compounds showed characteristic molecular ion peak and base peak which further confirmed the structure of synthesized compounds.

In-vitro *Anti-oxidant activity*

All the compounds were subjected to *in-vitro* anti-oxidant activity using ascorbic acid as a standard by two methods i.e. by Hydrogen peroxide scavenging method and nitric oxide radical scavenging method. Antioxidant activity revealed that all the synthesized compounds have shown significant anti-oxidant activity when compared with that of standard drug. The compounds S1 showed more activity as compared to the other derivative (S2).

***In-vitro* Anti-inflammatory activity**

The synthesized compounds were subjected to *in-vitro* anti-inflammatory activity using HRBC membrane stabilizing method. The method involves the stabilization of human red blood cell membrane by hypotonicity induced membrane lysis. The prevention of hypotonicity induced HRBC membrane lysis is taken as a measure of anti-inflammatory activity of the drug. The compound S2 showed better activity as compared to the standard diclofenac. Rest of the compound (S1) showed poor activity.

***In-vivo* Anti-inflammatory activity**

The present study of membrane stabilization activity shows test compounds at concentration range of 50-250 µg/ml protect significantly the erythrocyte membrane against lysis induced by hypotonic solution. The Diclofenac (100µg/ml) offered a significant protection of the RBC's against the damaging effect of hypotonic solution. At a concentration of 250 µg/ml, test I and test II showed 68.31 % & 78.12 % respectively, where as diclofenac at 100 µg/ml showed 86.37 % inhibition of RBC haemolysis when compared with control.

II. CONCLUSION

In the present study certain pyrazole derivatives were synthesized and characterized by IR, ^{1}HNMR, and MASS spectroscopy. All the synthesized compounds show characteristic absorption peaks -in IR, ^{1}HNMR spectra. Expected molecules in (m+) fragments were observed for the entire compounds in mass spectra.

The synthesized compounds were subjected to various biological evaluations. The compounds were evaluated for anti-oxidant and anti-inflammatory studies revealed that the substitution of different aromatic aldehydes to parent pyrazole nucleus show the moderate activity.

Antioxidant activity revealed that all the synthesized compounds have showed significant antioxidant activity when compared with that of standard by Hydrogen peroxide and Nitric oxide scavenging methods.

Anti-inflammatory activity revealed that all the synthesized compounds have showed significant activity when compared with that of standard by HRBC membrane stabilization method.

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