



Green and Rapid Synthesis of 3-Methyl-1-Phenyl-5-Pyrazolone and Its Derivatives via an Efficient Approach

Neha Ajay Pandey

PG student, Department of Chemistry, Thakur College of Science and Commerce, Mumbai

ABSTRACT:

The synthesis of 3-methyl-1-phenyl-5-pyrazolone [PMP] had been performed in very simplest way by heating the mixture of phenyl hydrazine and ethyl acetoacetate, on cooling addition of ether, then recrystallize by aqueous ethanol. These experiments taken place in small and large amount to get the required amount of products. Treatment of a mixture of 3-methyl-1-phenyl-5-pyrazolone [PMP] with benzaldehyde derivatives in absolute ethanol results in fast (5 min) formation of 4,4'-(arylmethylene) bis-(1H-pyrazol-5-ol) and their derivatives in excellent yield. The reaction conditions such as solvent, temperature, and reaction time have been optimized to obtain high yields of the desired products. synthesized compounds have been further characterised using various spectroscopic techniques such as IR, NMR, and Mass spectroscopy. All synthesized compounds were evaluated for antioxidant activity by the N, N-diphenyl-N'-picrylhydrazyl (DPPH). These are catalyst-free tandem Knoevenagel-Michael reactions, pure products were isolated by simple filtration. 4,4'-(Arylmethylene) bis -(1H-pyrazol-5-ol) and it's derivatives are important compounds with biological and industrial applications.

Keywords: 3-methyl-1-phenyl-5-pyrazolone [PMP] , 4,4'-(arylmethylene) bis-(1H-pyrazol-5-ol), DPPH

Introduction:

Pyrazolone are five membered nitrogen containing heterocyclic compounds, where these ring system represents an important class of compounds not only for theoretical interest but also for bio-activity. The 3-pyrazolone and 5-pyrazolone are most dominant classes having importance in pharmaceutical industry. Pyrazole and its derivatives constitute an important class of five member heterocyclic compounds.(1-3) The presence of their nucleus in different structures leads to diversified applications in different areas such as technology, medicine and agriculture. In particular, they are described as inhibitors of protein glycerine , antibacterial ,antifungal, anticancer, antidepressant ,anti-inflammatory, anti-tuberculosis, antioxidant as well as antiviral agents . Pyrazolone is a key structure in numerous compounds of therapeutic importance. Day to day growing application on their synthesis and bioactive, chemists, and biologists in recent years has directed considerable attention on the research of their derivatives.(4) Based on various literature surveys it found that methyl and phenyl substituted pyrazolone derivatives exert significant pharmacological properties as per as synthesis is concerned pyrazolone are synthesized by various ways, one common method is to synthesize from chalcones .(5-7) In our current research studies, the 3-methyl-1-phenyl - pyrazol-5-one [PMP] derivatives have been the subject of many research studies due to varieties of potential biological activities (8) In the present work 3-methyl-1-phenyl derivatives of pyrazolones / pyrazole were synthesized by simplest scheme and we performed the characterization of those compound and found their biological activities. (9) Pyrazoles have attracted particular attention due to the diverse biological properties associated with this heterocyclic systems ,and have been shown to be cytotoxic to several human cell lines. Several drug currently on the market have this heterocycle as the key structural motif , and some have been approved for the treatment of different types of cancer. (10). Pyrazolones are an increasingly popular functionality with wide-range applications. They are used as cytotoxic, analgesic ,SARS -corona virus 3C-like protease inhibitors agents. Michael addition of an aromatic aldehyde with an arylpyrazolone, obtained by Knoevenagel reaction allows an easy synthesis of 4,4' -(arylmethylene)bis (1H-pyrazol-5-ols). Pyrazolone derivatives are an important class of bioactive drug targets in the pharmaceutical industry as they constitute the core structure of numerous biologically active compounds. Moreover, they are capable of exhibiting prototropic tautomerism. The compounds which contain two pyrazolone rings can be used as extractant for some metal ions (11) and ligands, 4,4'-(arylmethylene)bis (1H-pyrazol-5-ols) are usually synthesized by condensing [PMP] with various aldehydes (3) Some of these methods require long term use, use of expensive catalyst, organic solvents, and tedious workup. The current trend toward development of catalyst-free and solvent-free (12) reaction conditions encouraged us to study the same reaction without using any catalyst or highly active solvents. Condensation of ethyl acetate with phenyl hydrazine produces phenylhydrazone derivative which cyclised to pyrazolone derivatives. The pyrazole containing compounds show prominent biological actions. They are also used to prepare several pyrazolone-based drugs. (13) Heterocycles are common structural units in marketed drugs and target in the drug discovery process. Nitrogen containing rings play an especially important role in drug development because of their wide variety of therapeutic and pharmacological properties. Also, it is well known that many natural and synthesized antioxidants activities by virtue of their abilities to react with free radicals, and studies carried out on compound have shown that there is a relationship between antioxidant and anticancer activity with compounds. The presence of C=O group is of great importance, considering the fact that it can be transformed into various chloride compounds and imine compounds. The availability of the present and significant biological properties of the members known so far prompted to extend moieties like ether linkages and imine to amine derivatives. In this context, the synthesis of pyrazolones

and other derivatives was carried out. (14) Taking into consideration the basic principles of "green chemistry", catalyst-free procedures are particularly welcome. Continuously growing interest in convenient and green techniques motivates chemists to increase the tools of their arsenal. In the recent years, tandem reactions have emerged as a very attractive method giving access to complex molecules in a facile and efficient manner. Tandem Knoevenagel-Michael reaction is well known in classic organic chemistry. Moreover, the analogous 4,4'-(arylmethylene)bis(1H-pyrazol-5-ol) are used as fungicides, pesticides, insecticides, dyestuffs, and chelating and extracting reagents for different metal ions. However, most of these synthetic methods suffer from several drawbacks such as moderate yields, long reaction times, complex formations, etc (15)

Here the synthesis and characterisation of some derivatives from [PMP] have been reported.

Applications

- 3-methyl-1-phenyl-5-pyrazolone [PMP] is biochemical reagent used for carbohydrate analysis. It is radical scavenger and antioxidant. [PMP] is also known as the drug edaravone, which is used to treat amyotrophic lateral sclerosis (ALS) and acute stroke injuries. Edaravone is also used as a treatment for cardiovascular diseases and as a neuroprotectant.
- 4,4'-(arylmethylene)bis (1-phenyl-3-methyl-1H-pyrazol-5-ol) derivatives have good radical scavenging activity, and half of them are more active than ascorbic acid.
- Pyrazoles are reported to have wide range of biological activities including :

Anti-microbial, Antifungal, Anti-convulsant, Anti-viral, Anticancer, Antipyretic, Anti-tubercular, Non steroidal anti-inflammatory drugs, Estrogen receptor (ER), Angiotensin converting enzyme (ACE) inhibitory, Neuroprotective, Cholecystokinin-1-receptor antagonist.

Pyrazole-containing molecule display a broad range of biological activities :

Anti-inflammatory, Anti-convulsant, Antiviral, Antidepressant, Analgesic, Antifungal, Selective enzyme inhibition.

This has been followed by an in-depth analysis of the pyrazole with respect to their medicinal significance.

This follow-up may help the medicinal chemists to generate new leads possessing pyrazole nucleus with high efficacy.

Advantages

We have found several methods for synthesizing our compounds but to establish the most common method for carrying out synthesis of 4,4'-(arylmethylene)bis (1H-pyrazol-5-ol) at room temperature have been reported.

With the optimized conditions, the scope of the reaction was studied using various substituted benzaldehydes bearing either electron-withdrawing or electron-donating groups to give the corresponding derivatives in good to excellent yield as pure products by simple filtration.

1. Some advantages of [PMP] :

- Biochemistry : Used as a reagent to study the structure and composition of polysaccharides and to measure carbohydrates in complex media.
- Hair dye : It can be used as a hair dye.
- Derivatization : PMP can derivatize under mild conditions, which means it can simultaneously analyze acidic, neutral, and basic monomer sugar without causing isomerization during sample preparation.
- Automation : PMP can be used for automated carbohydrate analysis through in-capillary derivatization and miniaturization to microchip electrophoresis. This allows for the rapid analysis of small amount of PMP derivatives of carbohydrates.

2. Some advantages of 4,4'-(arylmethylene)bis(1H-pyrazol-5-ol) :

- High yields
- Short reaction time
- Inexpensive catalyst
- Simple experimental and isolation procedures
- Easy work-up
- Eco-friendly reaction conditions
- Reusable and cost-effective ionic liquid
- Applied as fungicides, pesticides and dyestuffs
- No requirement of special apparatus to carry out synthesis
- Solvent-free conditions make synthesis simpler, save energy, prevent solvent waste, hazards and toxicity
- Compliance with green chemistry protocols
- Efficient protocol
- Avoids the use of environmental hazardous and toxic solvents

Steps involved in synthesis :

STEP 1 :

3-methyl-1-phenyl-5-pyrazolone [PMP] is synthesized from the reaction of phenyl hydrazine and ethyl acetoacetate which is recrystallized by ethanol. The method is used because it gives [PMP] with good yield and the purity of the compound is also high. The structure of the compound is confirmed from its melting point and TLC.

STEP 2 :

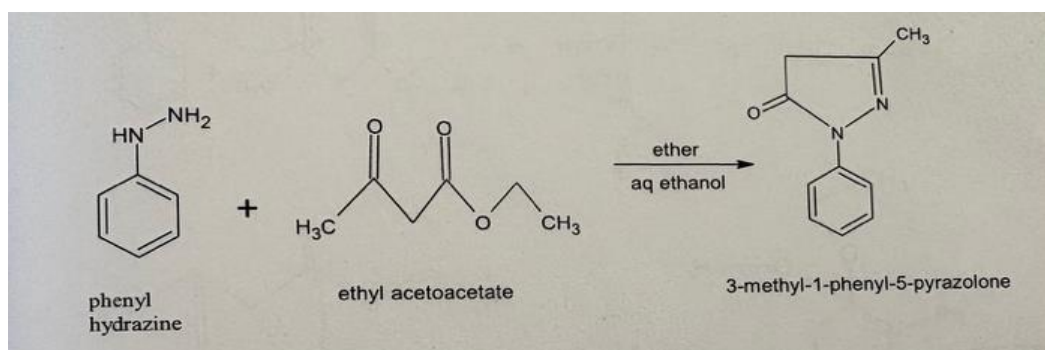
We did the reaction using [PMP] with benzaldehyde in ethanol under reflux which gave the 4,4'-(arylmethylene)bis 1H-pyrazol-5-ol in required amount of yields.

STEP 3 :

To derivatize them, we performed the reaction using [PMP] and benzaldehyde derivatives under same conditions which gave 4,4'-(arylmethylene)bis-1H-pyrazol-5-ol derivatives. The derivatives was confirmed by their melting point and TLC respectively.

STEP 4 :

These work initiated by characterisation of [PMP] , on the basis of antioxidant or antiradical activity.

Experimental Section :**Step 1 : Synthesis of PMP**

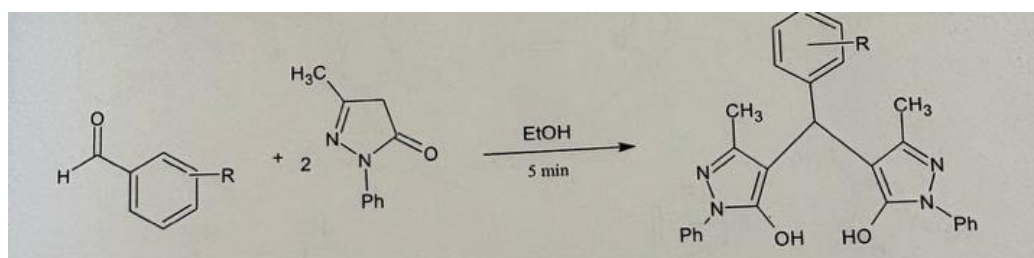
Place in 100 mL round bottom flask, freshly distilled phenyl hydrazine (5.4g /6.35 mL) in ethyl acetoacetate (6.4g / 4.9mL). Heat the mixture under reflux at 120 Degree Celsius for one hour. Cooling the red oil solution and add the ether 50 ML which starting to solidification the product. Filter the precipitate. Recrystallize the product from aqueous ethanol.

Reaction followed by the mechanism.

Yield : 90%

Melting Point : 128

Rf value : 0.3

Step 2 : Synthesis of 4,4' (aryl methylene) bis (1 H pyrazol-5 ol)

A mixture of PMP (10 mmol) and benzaldehyde (5 mmol) in ethanol (3 ml) was stirred under reflux for 5 minutes, then cooled to room temperature. The resultant precipitate was filtered off, rinsed with ice-cold ethanol (2mL) and dried under reduced pressure. The product formed is 4,4'-(arylmethylene)bis (1H-5-pyrazol-ol)s .

Preparation of derivatives:**1. Reaction of PMP with salicylaldehyde**

Yield : 87%

Melting point : 230

Rf value : 0.8

2. Reaction of PMP with benzaldehyde

Yield : 98%

Melting point : 170

Rf value : 0.78

3. *Reaction of PMP with p-hydroxybenzaldehyde*

Yield : 88.8%

Melting point : 157

Rf value : 0.52

4. *Reaction of PMP with 3- nitro benzaldehyde*

Yield : 89.34%

Melting point : 152

Rf value : 0.36

5. *Reaction of PMP with 4- methoxybenzaldehyde*

Yield : 86.6%

Melting point : 175

Rf value : 0.46

6. *Reaction of PMP with Isovanillin*

Yield : 82.6%

Melting point : 140

Rf value : 0.66

7. *Reaction of PMP with Vanillin*

Yield : 86.5%

Melting point : 125

Rf value : 0.56

Characterization of 4,4'- arylmethylene bis (1H-5- pyrazol-ol)s

Procedure :

1. Weigh 0.001g of sample
2. Extract in 1ml of ethanol
3. Prepare the solutions in different concentrations.
4. DPPH was measured versus a blank assay about 30 minutes.
5. Add 3mL of N,N- diphenyl-N'-picrylhydrazyl (DPPH)
6. For optical density measurements (O.D) , we have used spectrophotometer.
(Only if color remains purple)

Concentrations	Amount of sample	Solution
1:10	0.1	0.9
1:100	0.01	0.99
1:1000	0.001	0.999

Biological activity:

The present study was initiated in the evaluation of antioxidant activity of compound.

Calculations :

O.D = 0.27

% radical scavenging activity = Absorbance of blank- Absorbance of sample / Absorbance of blank

0.52- 0.27 / 0.52

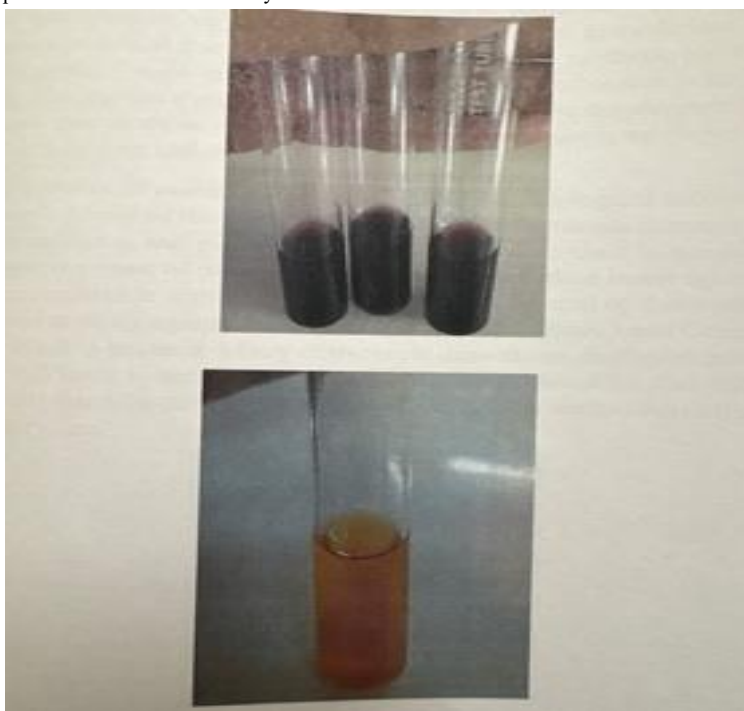
= 48.07 %

Conclusion:

The color change from purple of DPPH radical to pale yellow of reduced form of the DPPH, allow the spectrophotometric determination of the antioxidant activity. The radical scavenging activity percentage were calculated about 48.07%.

Results

Results reveal that a compound pronounced antioxidant activity.



Objective:

1. 3-methyl-1-phenyl-5-pyrazolone is a biochemical reagent, and radical scavenging drug used to treat ALS and acute stroke injuries. PMP can derivatize under mild conditions, which prevents inadvertent isomerisation during sample preparation.
2. To develop efficient green method for synthesis of 4,4'-(arylmethylene) bis (1H-pyrazol-5-ols) without use of any catalyst or solvent by simple heating or microwave irradiation (300 W) of intimate mixtures of [PMP] and benzaldehydes.
3. A range of structurally diverse aldehydes belonging to the categories aromatic and heterocyclic aldehydes were taken. [PMP] is also used as starting material in separation science because of its low price and the broad applicability of C-acylated compounds as extractants.

Results

In addition, a number of studies have shown that some pyrazolone derivatives are potent antioxidants. All synthesized compounds were evaluated for antioxidant activity by the N,N-diphenyl-N'-picrylhydrazyl (DPPH) assay as shown in table [A]. All compounds have good scavenging activity and half of them are more active than ascorbic acid used as standard. Antioxidants delay or inhibit cellular damage by inhibiting or quenching free radical reactions. Among the mechanism of action of antioxidant, are the sequential electron transfer proton transfer (SETPT) and hydrogen atom transfer (HAT) mechanisms. The studies on small molecules with antioxidant efficacy to prevent the deleterious effects is important field of research. The drug molecules that contains a pyrazole core remain as choice in medicinal chemistry towards more practical antioxidant. Several natural and synthetic pyrazole derivatives possess wide spectrum of pharmacological potentials with druggable properties. The pyrazole motif is an important core in the development of antioxidants, that alone or combined with other pharmacophore shows high degree of antioxidant activity.

Although, a plenty of research on pyrazoles and their biological activities has been reported. Many of the methods adopted for the synthesis requires drastic reactions conditions, and produces less yields, and more toxic bi-products, etc. Furthermore, the most of the pyrazole derivatives exhibited lesser antioxidant properties comparable with the standard employed. Several of these compounds showed good activity against both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria. Many of pyrazole derivatives displayed antioxidant activities, still there is need of developing efficient protocol for their synthesis, involving eco-friendly conditions, molecules of greater antioxidant efficacy and lesser toxicity, etc.

Sr no.	Compound used	Theoretical Yield	Practical Yield	Practical percentage yield	Melting point	Rf value
1.	Salicylaldehyde	0.360g	0.316g	87%	230	0.8
2.	Benzaldehyde	0.415g	0.41g	98%	170	0.78
3.	Para hydroxy benzaldehyde	0.360g	0.32g	88.8%	157	0.52

4.	3-nitro benzaldehyde	0.291g	0.26g	89.34%	152	0.36
5.	4methoxybenzaldehyde	0.323g	0.28g	86.6%	175	0.46
6.	Isovanillin	0.289g	0.239g	82.6%	140	0.66
7.	Vanillin	0.289g	0.250g	86.5%	125	0.56

Conclusion

In summary, we have developed a very simple, efficient, and environmentally benign methods for synthesis of 4,4'-(arylmethylene) bis(1H-pyrazol-5-ols) without use of any catalyst, solvent, surfactant, or solid support. We feel that this protocol is a good addition to the currently reported methods. A novel, fast and efficient catalyst-free Knoevenagel-Michael reaction of aryl aldehydes and 3-methyl-1-phenyl-5-pyrazolone leading to 4,4'-(arylmethylene)bis (3-methyl-1-phenyl-1H-pyrazol-5-ol) in excellent yields were developed. High product yields were obtained with aromatic aldehydes containing electron-donating and electron-withdrawing substituents. When changing phenylhydrazine into hydrazine hydrate, a similar result was obtained, the reaction gave the corresponding compounds in good yields. Non-catalytic conditions of this cascade procedure correspond to present day demand of green chemistry. This tandem procedure uses simple equipment and readily available starting materials. The final compounds are isolated by simple filtration of the reaction mixture and do not need further purification. The technique described offers an efficient and convenient way to these compounds, the prominent compounds with approved practical utilities and different biomedical applications. In the future studies, we can prepare and characterise more derivatives of pyrazolone by fast and convenient approach, with less time interval. We can prepare more derivatives by using chalcones. And perform the characterisation practices of all the derivatives to know about their biological activities. We examine their reactivity, presence of groups, elements by the elemental analysis by using various instruments. Considering the importance of green chemistry, the solvent-free reaction conditions are the advantageous aspect of the present method, since it avoids the use of environmental hazardous and toxic solvents.

REFERENCES:

List all the material used from various sources for making this project proposal

Research Papers:

1. Michail N. Elinson*, Olga O. Sokolova and Ruslan F. Nasybullin, "Catalyst-free tandem Knoevenagel-Michael reaction of aldehydes and pyrazoline-5-one : fast and convenient approach to medicinally relevant 4,4'-(arylmethylene) bis(1H-pyrazol-5-ols), Heterocycl. Commun . 2015 ; 21(2) : 97-101
2. Jose Eduardo Cadena-Cruz ,Luis M.Guaman -Ortiz, Juan Carlos Romero-Benavides, Natalia Bailon-Moscoso, Kelvin E. Murillo-Sotomayor , Nadia V. Ortiz-Guaman , and Jorge Heredia-Moya, " Synthesis of 4,4'-(arylmethylene) bis(3-methyl-1-phenyl-1H-pyrazol-5-ols)and evaluation of their antioxidant and anticancer activities, Cadena-Cruz et al. BMC Chemistry (2021) 15:38
3. Arpita Das Gupta, Rammohan Pal and Asok K. Mallik, " Two efficient and green methods for synthesis of 4,4'-(arylmethylene)bis (1H-pyrazol-5-ol)s without use of any catalyst or solvent, (2014) 1751-8253
4. Talaat I. El-Emary, "Synthesis of newly substituted pyrazolo[3,4-b] pyridines based on 5-amino-3-methyl-1-phenylpyrazole ,Journal of the Chinese Chemical society, (2007) ,507-518
5. Elham Ezz El-Arab, "Synthesis and Cytotoxicity of Novel Pyrazole derivatives, Egypt. J. Chem, 58, No.6 (2015),58
6. J. Belmar*, J.Alderete, C. Zuniga, C. Jimenez, V. Jimenez, H.Nunez, R. Grandy, AND A. YORI, "Synthesis of 1-Alkyl-3-methyl- AND 1-n-ALKYL-3-Phenyl-5-Pyrazolones and Formyl derivatives, (2001)
7. Zhongqiang Zhou, Yuliang Zhang, 'An eco-friendly one-pot synthesis of 4,4'-(arylmethylene) bis(1H-pyrazol-5-ol)s using [Et3NH] [HSO4] as a recyclable catalyst, Journal of the Chilean Chemical society,(2015), 2992-2996
8. Mohammed S. Mostafa*, Nasser M. Abd El Salam, and Othman Y. Alothman , "Synthesis and microbial activity of Novel 3-Methyl-2-pyrazolin-5-one Derivatives, (2013)
9. Ahlam Shaglof, Hend Elzlatene and Mohamad F. Ali, 'Synthesis and Evaluation of Biological Activity of Pyrazolone Compounds, Journal of Pharmaceutical and Applied Chemistry An International Journal, (2021)
10. C. G. Naik and G . M. Malik , "Synthesis of pyrazolone derivatives and their Biological Activities, VOL-26, Number 01 (2010),26
11. Soufiane Akhramez , Asmaa Oumessaoud , Achraf Hibot, Soumaya Talbi, Salha Hamri , El Mostafa Ketatni , Hajiba Ouchetto , Abderrafia Hafid , Houada Ayad , Noureddine El Abbadi , Chorouk Zanane , Hassan Latrache , Mostafa Khouili , Maria Dolors Pujol , "Synthesis of pyrazolo-enaminones, bipyrazoles and pyrazolopyrimidines and evaluation of antioxidant and antimicrobial properties, (2021)
12. G. Mariappan*, B.P. Saha, N. R. Bhuyan, P.R. Bharti, and Deepak Kumar, " Evaluation of Antioxidant potential of pyrazolone derivatives, J Adv Pharma Technol Res, 2010, 260-267
13. Karthik Kumara , Malledevapuram Gurumurthy Prabhudeva, Channa Basappa Vagish, Hamse Kamsewar Vivek, Kuriya Madavu Lokanatha Rai, Neratur Krishnappagowda Loknath , and Kariyappa Ajay kumar, " Design, synthesis, characterisation, and antioxidant activity studies of novel thienyl-pyrazoles , (2021)
14. Doaa Hashim Al-Abhoodi*, Naemah Jabber Al-Lami, "Antioxidant activity of newly synthesized pyrazole and 2-Oxo-3H-pyrimidine derivatives containing Imidazo (1,2 a) Pyridine, 2022 , 07-27