# "Synthesis and Reactions of Some Heterocycles of Expected Biological Activity"

*A Thesis Submitted*

*By*

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B. Sc. Margeb University-Libya

*(٢٠٠٤)*

*As Partial Fulfillment of the Requirements for*

*M.Sc. Degree in Organic Chemistry*

**Department of Chemistry**

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**(٢٠١٠)**

# Approval Sheet for Submission

## Thesis Title

# "Synthesis and Reactions of Some Heterocycles of Expected Biological Activity"

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## ABSTRACT

**Student Name: Selima Ali Amhamed Al-Mabrook**

**Thesis Title: "Synthesis and Reactions of Some Heterocycles of Expected Biological Activity"**

**Degree:** M.Sc. of Science in Organic Chemistry ٢٠١٠

The original work of this thesis includes:

The reaction of thioanilide derivative ٤ with α-haloketones, and α-haloesters to afford the poly heterocyclic compounds based pyrazolo[١,٥-*a*] pyrimidine derivatives. Also, the enamine derivative of compound ٣ reacts with each of hydrazine hydrate and hydroxylamine to give the pyrazolo[٣,٤-*b*]-pyrimidino[١`,`٢:٥,١]pyrazolo[٣,٤-*d*]pyridine derivative ٢٩ and isoxazolo-[٤``,٥``:٢`,٣`]pyridino[٤`,٥`:٣,٤]pyrazolo[١,٥-*a*]pyrimidine derivative ٣٢, respectively. Compound ٣ couples with aryldiazonium salts to afford the hydrazono derivatives ٣٩. The latter compounds react with malononitrile to afford fused heterocyclic compounds. The structure of the newly synthesized compounds was elucidated by elemental analysis, spectral data and X-ray crystallography for compound ٢١ and plausible mechanism has been postulated to account for their formation. The antimicrobial activity of some new selected products was investigated.



**Key words**: Pyrazolo[١,٥-*a*]pyrimidine derivative, thioanilide derivative, enamine, X-ray crystallography, antimicrobial activity.



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# *Acknowledgement*

I am really grateful to **ALLAH** by the grace of whom this work has been achieved.

I would like to thank all the professors who supervised the thesis and took from their busy schedules to help me to accomplish it in a refined profile.

I wish to thank the supervisors:

***Professor Dr. Nazmi A. Kassab**, Professor of Organic Chemistry, Faculty of Science, Cairo University.

***Professor Dr. Magda A. Abdallah**, Professor of Organic Chemistry, Faculty of Science, Cairo University.

***Professor Dr. Nadia H. Metwally**, Professor of Organic Chemistry, Faculty of Science, Cairo University.

For suggesting the subjects investigated, directing the research and interpretation of the results. Also, for continual guidance and many valuable contributions which strengthened and added many developments to this work.

I am really indebted to **my parents**, and especially to **my husband** who gave me steadfast support and continuous pushing to expand my scientific and intellectual studies.

**Selima Ali Amhamed Al-Mabrook**

Beside the work carried out in this thesis, the candidate Selima Ali Amhamed Al-Mabrook has studied the following graduate courses during the academic year and passed their examinations successfully.

١. Applied organic spectroscopy.
٢. Advanced physical organic chemistry.
٣. Polymer chemistry.
٤. Organic photochemistry.
٥. Quantum chemistry.
٦. Biochemistry.
٧. Petro chemistry.
٨. Green chemistry.
٩. Dyes chemistry.
١٠. Organometalic chemistry.
١١. Catalysis organic chemistry.
١٢. Contemporary organic chemistry.
١٣. Macro molecular chemistry.
١٤. Pericyclic chemistry.
١٥. German language.

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# *OBJECTIVES OF THE STUDY*

# OBJECTIVES OF THE STUDY

This work was aiming at the study of the reaction of ٢-cyanomethyl-٥,٧-dimethyl-٨-hydropyrazolo[١,٥-*a*]pyrimidine-٣-carbonitrile (**٣**) with phenyl isothiocyanate afforded the corresponding thioanilide derivative **٤**. The reaction of compound **٤** with α-haloketones, α-haloesters and chloroacetonitrile in dimethylformamide (DMF) afforded the polyheterocyclic compounds based- pyrazolo[١,٥-*a*]pyrimidine derivative. Also, the enamine derivative **٢٦** reacts with each of hydrazine hydrate and hydroxylamine to give the amiopyrazolo[٣,٤-*b*]pyrimidino[١`,٢`:٥,١]pyrazolo[٣,٤-*d*]pyridine derivative **٢٩** and isoxazolo[٤``,٥``:٢`,٣`]pyridino[٤`,٥`:٣,٤]pyrazolo[١,٥-*a*]pyrimidin-٥-imine derivative **٣٢**, respectively. Next, we study the condensation of compound **٣** with various aromatic aldehydes to give the corresponding arylidene derivatives **٣٣a-j**, and fused heterocyclic compounds **٣٧a-c**. Also, compound **٣** couples with aryldiazonium salts to afford the hydrazono derivatives **٣٩a-e**. Treatment of compounds **٣٩a-e** with malononitrile afforded fused heterocyclic compounds **٤٣a-e**. The structure of all the newly synthesized compounds was elucidated by elemental analysis, spectral data and X-ray crystallography for compound **٢١** and plausible mechanism has been postulated to account for their formation. The antimicrobial activity of some new selected products was investigated.

# CHAPTER I

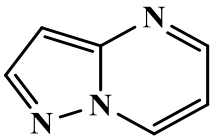
## *Literature Survey*

## *Recent Trends in Chemistry of Pyrazolo-*

## *[١,٥-a]pyrimidine Derivatives*

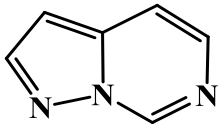
## I. ١. Introduction

Pyrazolopyrimidines are class of heterocyclic derivatives of major importance. Their importance may be attributed to the relative ease of their synthesis along with their diverse biological activities. From the structural point of view, they are fused ٥+٦ ring systems with either one ring junction nitrogen atom and the other two nitrogen atoms are extra with respect to the junction and distributed ١:١ in the two rings (two isomeric structures **I** and **II**) or four nitrogen atoms distributed ٢:٢ in the two rings (two isomeric structures **III** and **IV**).



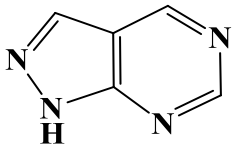
**(I)**

**Pyrazolo[1,5-*a*]pyrimidine**



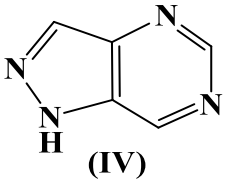
**(II)**

**Pyrazolo[1,5-*c*]pyrimidine**



**(III)**

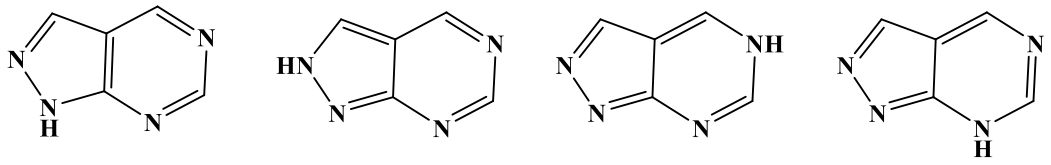
**Pyrazolo[3,4-*d*]pyrimidine**



**(IV)**

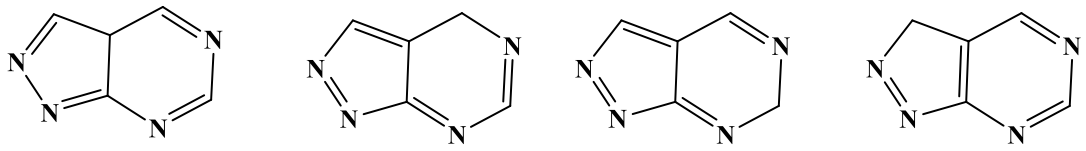
**Pyrazolo[4,3-*d*]pyrimidine**

Structures **I** and **II**, pyrazolo[١,٥-*a*]pyrimidine and pyrazolo[١,٥-*c*]pyrimidine, do not display tautomerism. Structure **III**, pyrazolo[٣,٤-*d*]pyrimidine, exists as four NH-tautomers (**i-iv)**:



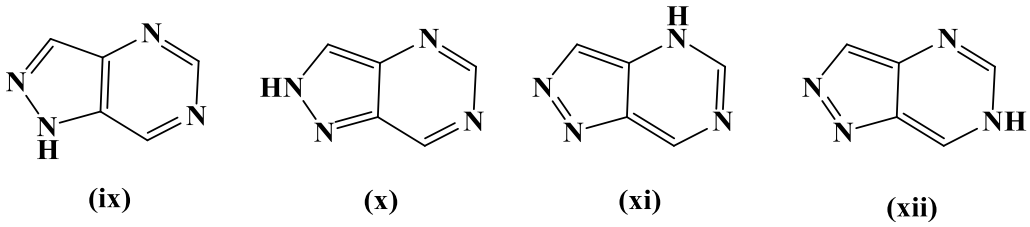
(i) (ii) (iii) (iv)

Also, CH-tautomers could represent the [٣،٤-*d*] systems, e.g. structures **v-viii**.

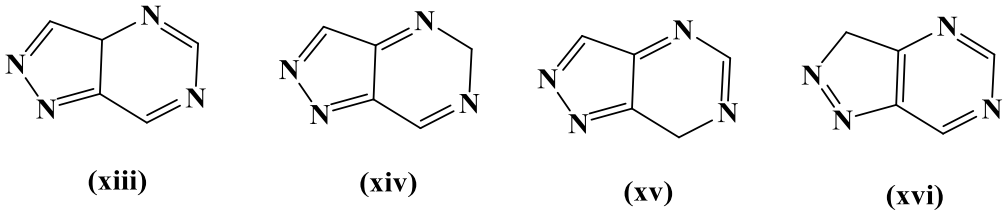


(v) (vi) (vii) (viii)

In a similar manner, structure **IV**, pyrazolo[٤،٣-*d*]pyrimidine, exists as four NH-tautomers **ix-xii** from which only **ix** and **x** are preferred (higher stability due to longer conjugation) in addition to four CH-tautomers **xiii-xvi**.



(ix) (x) (xi) (xii)



(xiii) (xiv) (xv) (xvi)

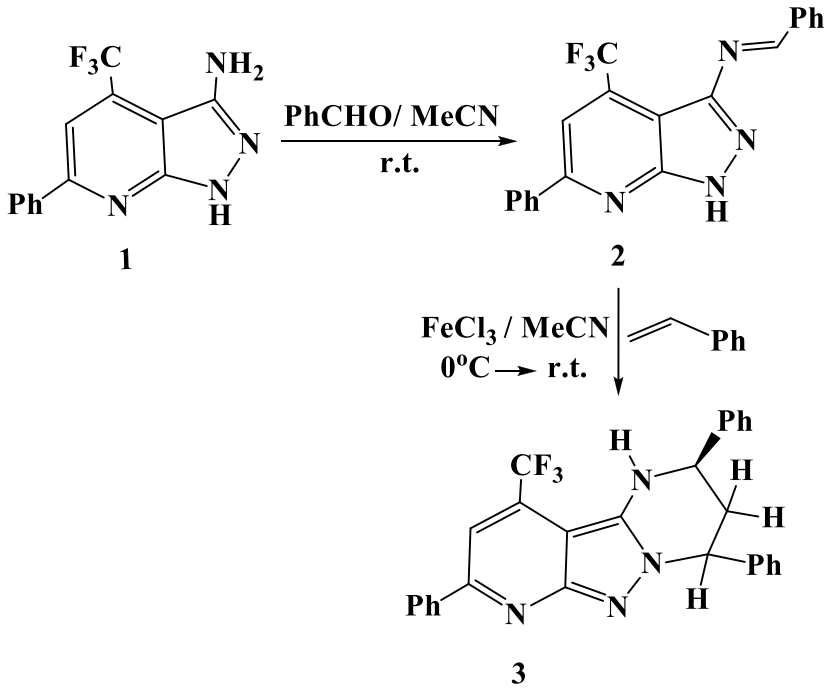
Here, we will focus this literature survey on synthesis, reactions and biological activity of pyrazolo[١،٥-*a*]pyrimidine derivatives which are related to the subject matter of this thesis. The literature has been covered up to ٢٠١٠.

## I. ٢. Synthesis of pyrazolo[١,٥-*a*]pyrimidine derivatives

The pyrazolo[١,٥-*a*]pyrimidine derivatives are reported to be synthesized from the reactions of aminopyrazoles with various compounds like, α,β-unsaturated ketones, β-ketoesters, α,β-unsaturated nitriles and enamines. Herein we review the various synthetic strategies of this ring system.

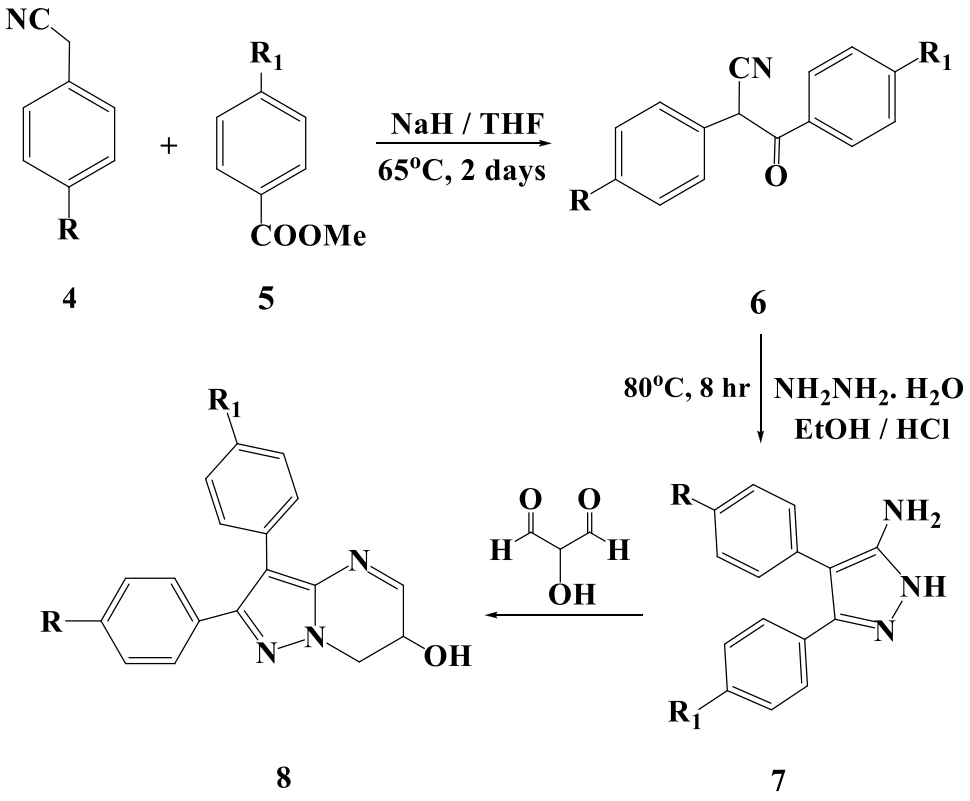
## I. ٢. ١. Synthesis from carbonyl compounds

٣-Amino-٦-phenyl-٤-(trifluoromethyl)-١*H*-indazole (١) was reacted with benzaldehyde followed by electron rich alkene in acetonitrile in presence of one equivalent of ferric chloride ($FeCl_3$) under nitrogen atmosphere at room temperature for ٣٠-٦٠ minutes to afford (٢*R*)-٢,٤,٨-triphenyl-١٠-(trifluoromethyl)-١,٢,٣,٤-tetrahydropyrido[٢`,٣`:٣,٤]-pyrazolo[١,٥-*a*]pyrimidine (٣)[١] (Scheme ١).



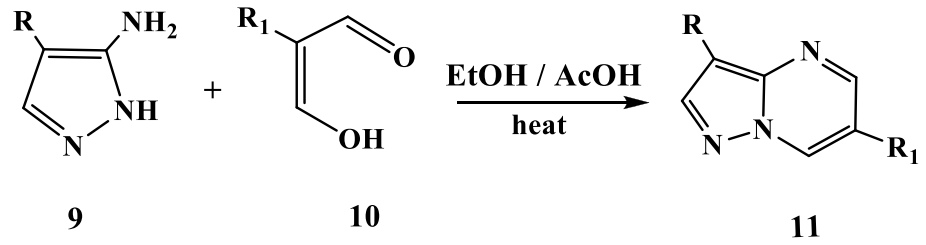

Scheme ١

A Claisen condensation between arylacetonitrile derivatives ٤ and methyl benzoate derivatives ٥ produces ٣-ketopropionitriles ٦. Condensation of compounds ٦ with hydrazine hydrate in ethanol in the presence of hydrochloric acid produces ٥-amino-١*H*-pyrazoles ٧. Condensation of ٢-hydroxy-١,٣-propanedial and aminopyrazoles ٧ afforded the corresponding pyrazolo[١,٥-*a*]pyrimidine derivatives ٨ [٢] (Scheme ٢).




Scheme ٢

Heating solutions of ٥-amino-٤-unsubstituted or arylpyrazoles ٩ and ٢-arylmalondialdehydes ١٠ in ethanol in the presence of acetic acid followed by cooling furnished ٣,٦-diarylpyrazolo[١,٥-*a*]pyrimidines ١١ [٣,٤] (Scheme ٣).

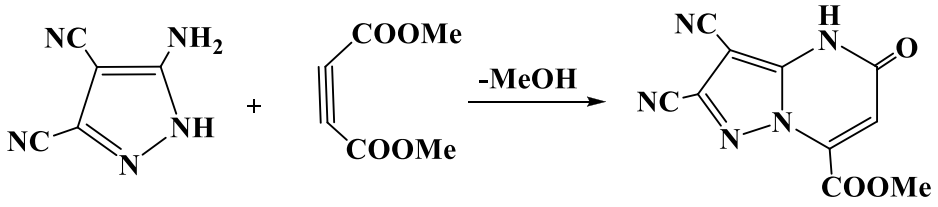



**9** **10** **11**

**R / $R_1$ : H / 4-$OMeC_6H_4$, H / 4-$ClC_6H_4$, Ph / 4-$OMeC_6H_4$**
**Ph / 4-$ClC_6H_4$, Het / Het**

Scheme ٣

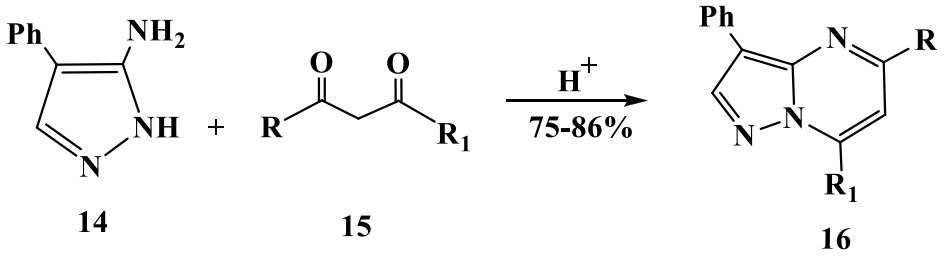
It has been reported that methyl ٢,٣-dicyano-٥-oxo-٤,٥-dihydropyrazolo[١,٥-*a*]pyrimidine-٧-carboxylate (**١٣**) is synthesized by the reaction of ٥-amino-١*H*-pyrazole-٣,٤-dicarbonitrile (**١٢**) with dimethyl acetylenedicarboxylate through methanol elimination [٥] (Scheme ٤**)** .




**12** **13**

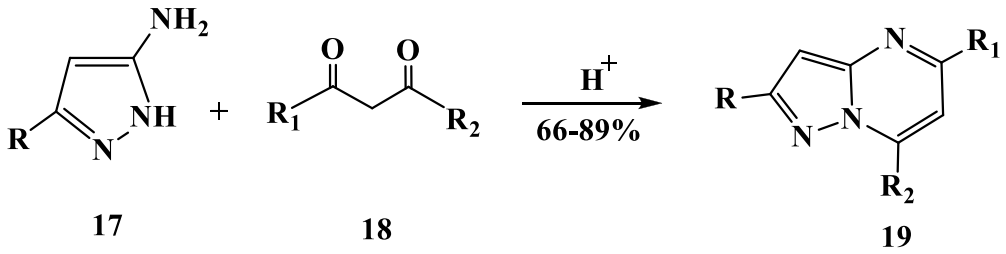
Scheme ٤

The pyrazolo[١,٥-*a*[pyrimidines **١٦** and **١٩** are prepared by condensation of ٥-aminopyrazoles **١٤** or **١٧** with ١,٣-diketones **١٥** and **١٨**, using hydrochloric acid [٦] or acetic acid [٧] as a catalyst (Scheme ٥).




14 15 16

**R / $R_1$: Me /Me, Me / Ph Ph /Ph**

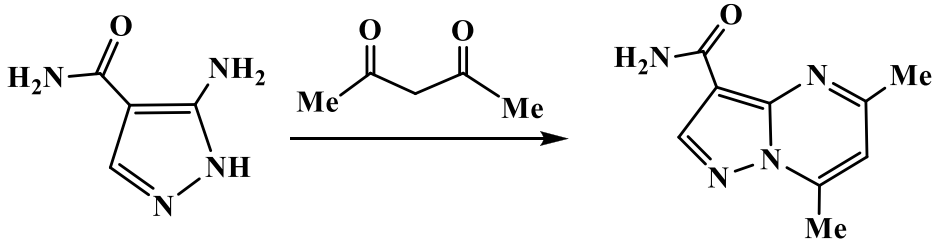



17 18 19

**R= a, H; b, Me; c, Ph; d, 4-$ClC_6H_4$**
**$R_1$ = $R_2$ = Me, Ph, 4-$ClC_6H_4$**

Scheme 5

Treatment of ٥-amino-١*H*-pyrazole-٤-carboxamide (٢٠) with acetylacetone furnished ٥,٧-dimethyl pyrazolo[١,٥-*a*]pyrimidine-٣-carboxamide (٢١)[٨] (Scheme ٦).




20 21

Scheme ٦

Pyrazolo[١,٥-*a*]pyrimidine substituted in position-٢ by a long linear perfluoroalkyl chain ($C_7F_{10}$) ٢٣ was obtained by action of ٣-fluoroalkyl-٥-amino-١*H*-pyrazoles ٢٢[١٩٩] with acetylacetone under reflux in acetic acid [٩] (Scheme ٧).