Ain Shams University
Faculty of Science
Chemistry Department

# Synthesis and Biological activity evaluation of heterocyclic compounds containing non-mixed and mixed systems and some of their metallic complexes

**A Thesis**

Submitted by

**Wafaa Hassan Abd Elhady El-Sayed**

For

Ph.D. in organic Chemistry

**Under Supervision of**

**Prof. Dr. Maher Abdel–Aziz El-Hashash (D.Sc.)**
Professor of Organic Chemistry ,Chemistry Department ,Faculty of Science, Ain Shams University

**Prof. Dr. Souad Abd El-Meged Osman**
Professor of Organic Chemistry ,Organometallic andOrganometalloidDepartment,NationalResearchCentre

**Prof. Assist. Dr. Amira Said Abd-El-All**
Prof. assist. Of Pharmaceutical and Drug Industries, Chemistry Department , Natural and Microbial products, National Research Centre.

**Dr. saad Ramadan Atta-Allah**
Lecturer of Organic Chemistry ,Chemistry Department ,Faculty of Science, Ain Shams University

**Dr. Khaled Hashem Hegab**
Researcher of Inorganic Chemical Industries and Mineral Resources, Department of Inorganic Chemistry, National Research Centre.

**2013**

# APPROVAL SHEET

## Synthesis and Biological activity evaluation of heterocyclic compounds containing non-mixed and mixed systems and some of their metallic complexes

## BY

**Wafaa Hassan abd El-hady**

Thesis Advisors Approval

Prof. Dr. Maher Abdel-Aziz El-Hashash (D.Sc.)

Prof. Dr. Souad Abd El-Meged Osman

prof. Assist. Dr. Amira Said Abd El-all

Dr. saad Ramdan Atta-Allah

Dr. khaled Hashem Hegab

**Head of the chemistry Department**

**Prof. Dr. Hesham Ahmed Madian**

**بسم الله الرحمن الرحيم**

# (قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيم)

**صدق الله العظيم**

البقرة (٣٢)

## Acknowledgement

I am deeply thankful to almighty god for showing me the right path and helping me to complete this work.

I wish to express my deep thanks and gratitude to **Prof. Dr. Souad Abd El-Meged Osman,** Professor of Organic Chemistry, National Research Centre, **Prof. Dr. Maher Abdel–Aziz El-Hashash,** Professor of Organic Chemistry, Faculty of Science, Ain Shams University, **Dr. Amira Said Abd El-All** Prof. Assist.of Pharmaceutical and Drug Industries, National Research Centre, **Dr. Saad Ramadan Atta-Allah** Lecturer of Organic Chemistry, Faculty of Science, Ain Shams University**,** and **Dr. Khaled Hashem Hegab** Researcher of Inorganic Chemical Industries and Mineral Resources, National Research Centre for suggestion the scientific problem, valuable help, discussion, criticism and unlimited effort to complete this work.

I wish to express my thanks to all the members of Chemistry Department, Faculty of Science, Ain Shams University for their kind cooperation .

# CONTENTS

# Introduction

## Part (I)

1,2,4-Triazines are important class of heterocycles since they are widely applied in different fields. So many compounds bearing 1,2,4-triazine moiety are found to exhibit tremendous activities including pharmaceutical, herbicides, pesticides and dyes [**Neunhoeffer *et al.* (1984)**, **El-Ashry *et al.* (1994)],** antimicrobial activity [**Elsilk *et al.* (2010), Hegde *et al.* (2008)]**, antifungal **[Kidwai (1998)**, **Holla *et al.* (2001)]**, anti-HIV **[El-barbary *et al.* (2005)],** anticancer **[ El-Gendy *et al.* (2001)**, **Abdel-Rahman *et al.* (1999)]**, anti-anxiety and anti-inflammatory activities **[Pooja *et al.*(2009), Abd EI. Samii (1992)]**, antiamoebic activity **[Singh *et al.* (2005)]**, antihypertensive **[Heilman *et al.* (1979)],** analgesic **[MaKhlouf *et al.* (2004)]**, antiasthma agents [**Paul *et al.* (1985)]** and also biologically active compounds containing 1,2,4-triazine ring are found in nature **[Neunhoeffer (1984), Singh *et al.* (2007)].**

It is worthy to mention that triazine phosphate derivatives can be used as enzyme inhibitor [**Hag *et al.* (2003)]** for highly active anti-tobacco mosaic virus (TMV) activity [**Dal and Chen (1997)]**, herbicides **[He *et al.* (1997)]**, insecticide [**Tiwari *et al.* (2003), Shukla *et al.* (2005)]** and antitumor agents [**Caruso *et al.* (2003)]**.

Also various derivatives of 1,2,4-triazines having many functional groups can be utilized as starting materials in different interesting heterocyclic reactions **[Osman *et al.* (2007), Kozhevnikov *et al.* (2005), Abd El-All *et al.* (2011)].**

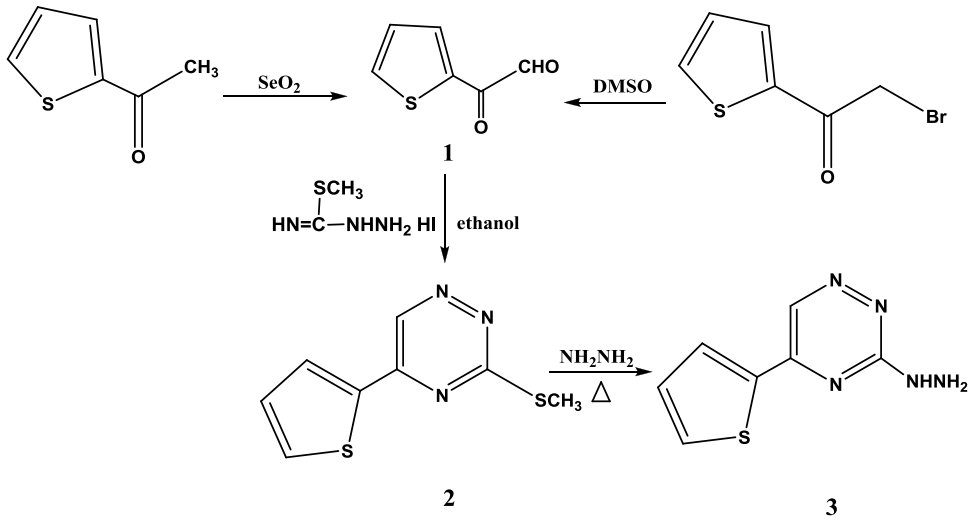
Moreover 1,2,4-triazines attracted much attention due to ability for coordinating with different transition metals. Silver (I) complex of a triazine-3-thione derivative **[Marandi *et al.* (2011)]** can quench the intrinsic

fluorescence of bovine serum albumin (BSA) through static quenching procedure (albumin serves as a carrier for multiple drugs). Furthermore, for example silver (I) complexes incorporating 1,2,4-triazine moiety have been identified as potential anticancer agents **[Ghassemzadeh *et al.* (2012)].** Copper (II) complexes of phenanthrolin-2-yl-triazine derivatives **[Galal *et al.* (2009)]** exhibited DNA cleavage activity upon acerbate or glutathione activation. Some metal complexes showed significantly enhanced antibacterial and antifungal activity against microbial strains in comparison to the free ligands **[Singh *et al.* (2012)].** Mannich bases had been reported as potential biological agents. These compounds play a vital role in pharmaceutical research and exhibit various pharmacological activities like anti tubercular **[Kumar *et al.* (2010)],** antimalarial **[Tamilvendan *et al.* (2012)],** Vasorelaxing **[Ferlin *et al.* (2002)],** anticancer **[Shawa *et al.* (2010)],** antimicrobial **[Asok *et al.* (2007)],** analgesic drug **[Malinka *et al.* (2005)]** and in the polymer industry as a paint and surface active agents **[Salem *et al.* (2004)].** Thiazole and its derivatives have been much studied in the field of organic, medicinal chemistry and agriculture. Thiazole bearing heterocyclic systems have found broad applications in drug development for the treatment of inflammation **[Haviv *et al.* (1988)],** hypertension [**Patt *et al.* (1992)**], bacterial **[Tsuji *et al.* (1994)]** and HIV infections **[Bell *et al.* (1995)].** Some analogues are used as fungicides, as an ingredient of herbicides, as schistosomicidal and anthelmintic drugs **[Metzgar *et al.* (1984)].**

## Synthesis of 1,2,4–triazine Derivatives:

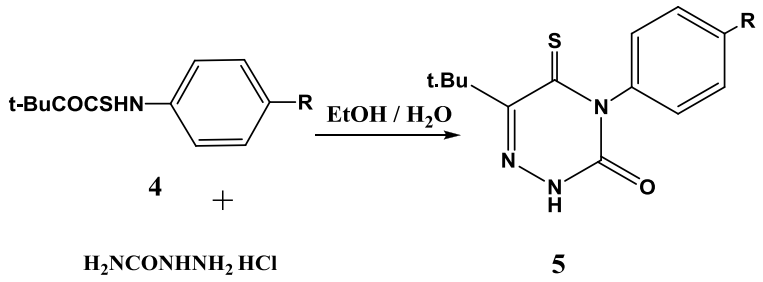
1,2,4-Triazine incorporating a thiophene moiety at position 5 could be synthesized for possible application as antimicrobial agent by oxidation of

2-acetyl thiophene with selenium dioxide to afford the corresponding thienyl glyoxal (**1**) which can be also obtained by treating 2-bromo-acetylthiophene **[Kipnis *et al.* (1949)]** with dimethyl-sulfoxide at room temperature according to the method reported by Kornblum **[Kornblum *et al*. (1957)]**. Glyoxal **(1)** was cyclized with methyl-thiosemicarbazide hydrogen iodide to afford the desired 3-(methythio)-5-(2-thienyl)-1,2,4-triazine **(2).** Compound **(2)** was refluxed with 95% hydrazine hydrate to afford the corresponding 3-hydrazino-5-(2-thienyl)-1,2,4-triazine **(3) [Michael *et al.* (1986)]. (Scheme1).**

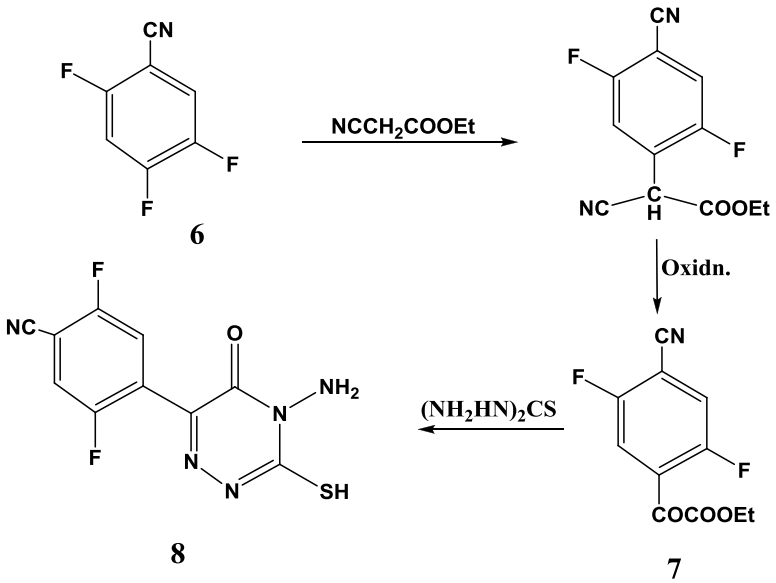



**Scheme 1**

Refluxing 4-$RC_6H_4$-*t*-BuCOCSNH **(4)** with semicarbazide hydrochloride in ethanol and water in presence of sodium acetate and acetic acid gave compound **(5) [Dong (1999)].**

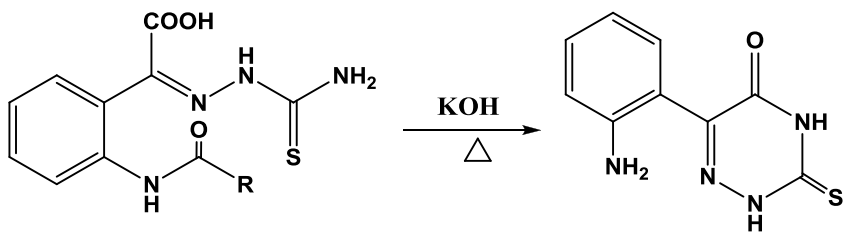



1,2,4-Triazines could be synthesized by arylation of ethylcyanoacetate with 2,4,5-triflorobenzonitrile (**6**) and the product oxidized to give (**7**) which was cyclocondensed with $(H_2NNH)_2CS$ to 1,2,4-triazine derivative **(8) [Linker *et al.* (2000)] (Scheme 2).**



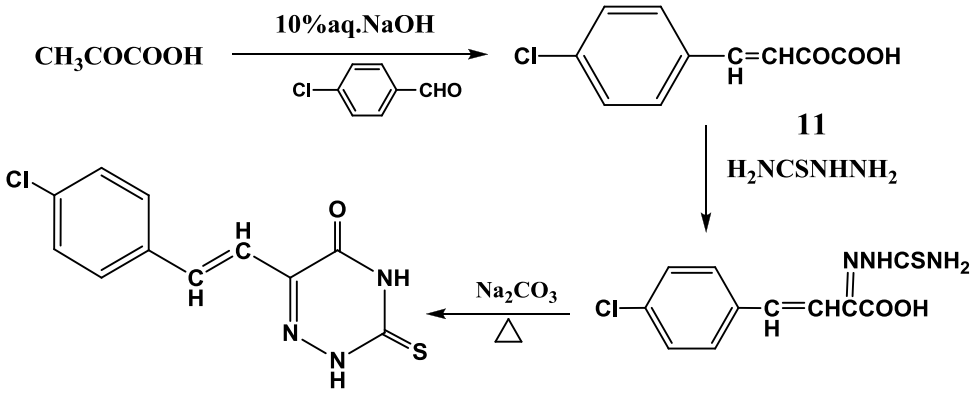

**Scheme 2**

Treatment of compound **(9)** with aqueous potassium hydroxide gave triazinone **(10) [Tomchin and Krylova (1986)].**




**9** **10**

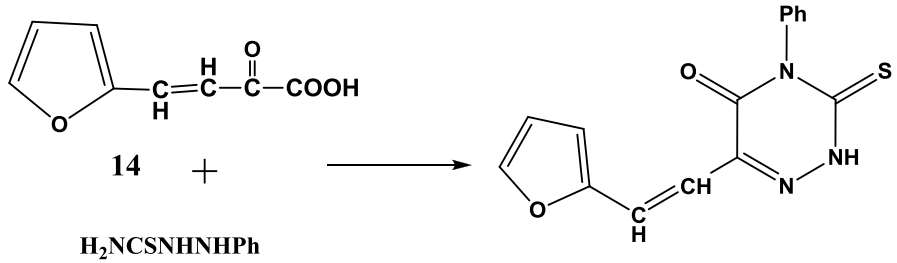
Equimolar amounts of pyruvic acid and *p*-chloro benzaldehyde stirred for one hour at 0 $^{0}$C in 10% aqueous sodium hydroxide yielded the corresponding keto acid (**11**). The reaction of **(11)** with thiosemicarbazide gave the corresponding thiosemicarbazone **(12)**, which when refluxed with aqueous sodium carbonate for 3 hours on a steam bath gave 2-thio-5-(4-chlorostyryl)-6-azauracil **(13) [Slouka and Nalepa (1969)] (Scheme 3).**




**13** **12**

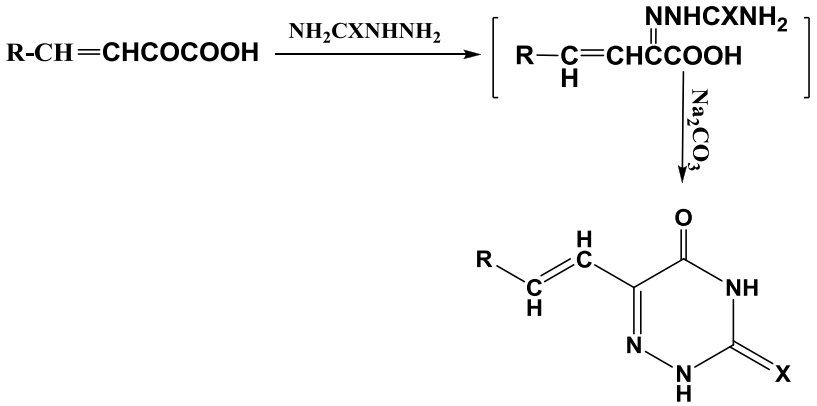
**Scheme 3**

Furfurylidene pyruvic acid **(14)** [**Stecher and Ryder (1952), Stecher *et al.* (1973), Stenz *et al.* (1980)]** condensed with 4-phenyl thiosemicarbazide to give 6-furfurylidene-4-phenyl-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-5-one **(15) [Mansour *et al.* (1976)].**




**15**

When, arylidines pyruvic acid were treated with semicarbazide and thiosemicarbazide gave the intermediate (carbazones) which cyclized to give the products **(16) [Ibrahim, El-sebai *et al.* (1979)] (Scheme 4).**



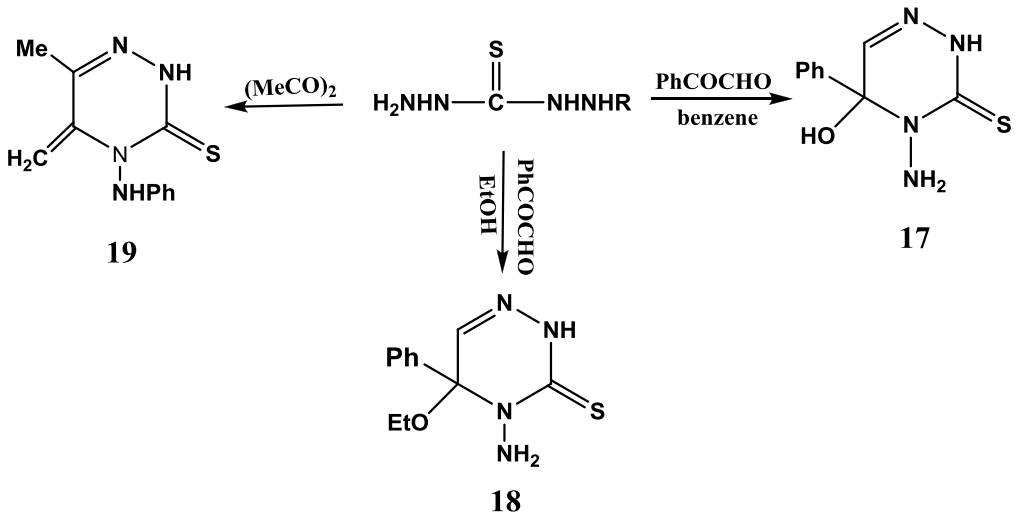

**16**

**R= 3-IC$_6$H$_4$ ,2- PhCH$_2$OC$_6$H$_4$,substituted 1-phenyl-4-pyrazolyl, PhCH=CH**
**X =O,S**

**Scheme 4**

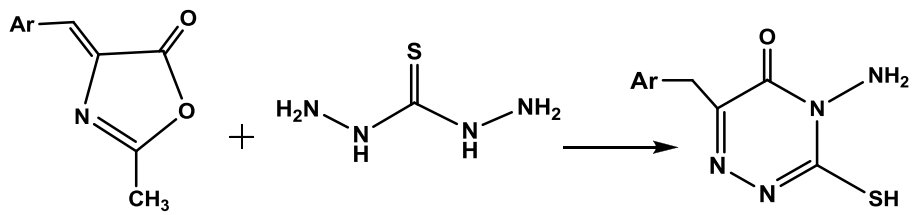
1,2,4-Triazines may be obtained via the reaction of dicarbonyl compounds with thiocarbazide. Thus, with phenylglyoxal thiocarbazide gave in the presence of benzene compound **(17),** and in ethanol the presence of the derivative (**18**). From 1-phenylthiocarbazide and diacetyl a derivative of 5-

methylene-1,2,4-triazine-3-thione was obtained **(19)[ Zelenin and Ale Kseev (1993)] (Scheme 5)**.




**Scheme 5**

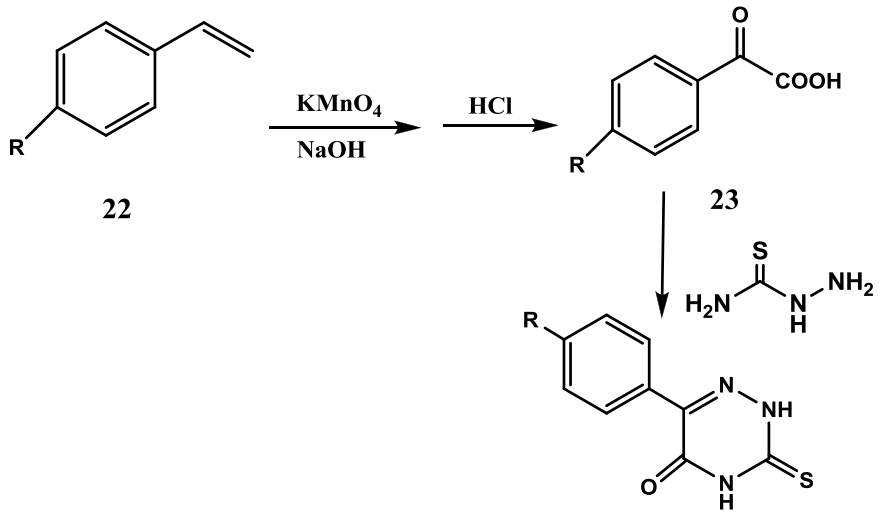
6-Substituted benzyl-4-amino-3-mercapto-1,2,4-triazin-5-ones **(21 a-c)** were obtained by reaction of 4-arylidine-2-methyl-1,3-oxazol-5-ones**(20a-c)** with thiocarbohydrazide **[Jyothi *et al.* (2008)]**.




**20a-c** **21a-c**

**a: Ar= -ph**
**b: Ar = *p*-Br-Ph**
**c: Ar = *p*-Cl-ph**

2-Aryl-2-oxoacetic acids **(23)** were prepared by reaction of **(22)** with NaOH and $KMnO_4$ then acidified using conc. HCl. Treating **(23)** with thiosemicarbazide gave 6-aryl-3-thioxo-3,4-dihydro-[1,2,4]-triazin-5(2H)-ones (**24**) **[Zhe *et al.* (2010)] Scheme 6.**




**22** **23** **24**

**R = H , Br, Cl**

**Scheme 6**

## Reactions of 1,2,4-triazine derivatives

The condensation of 5-bromothiophene-2-carboxaldehyde **(25)** with 4-amino-3-mercapto-6-methyl-5-oxo-[1,2,4]triazine **(26)** gave Schiff base **(27) [Singh *et al.* (2012)].**