



Faculty of Science
Ain Shams University
Chemistry Department

Synthesis of some heterocyclic compounds containing nitrogen nucleus with expected biological activity

A Thesis submitted for the degree of Master of Science as a
Partial fulfillment for requirement of the Master of Science

Eman Ahmed Ghareeb Ibrahim
B.Sc. Chemistry 2015

Thesis Advisors

Prof. Dr. EL-Sayed Ahmed Soliman Abdel-Aziz
Professor of Organic Chemistry, Chemistry Department, Faculty of
Science, Ain Shams University

Prof. Dr. Eman Abdel-Fattah Abdel-Hafez El-Bordany
Professor of Organic Chemistry, Chemistry Department, Faculty of
Science, Ain Shams University

Dr. Naglaa Fawzy Hassan Mahmoud
Associate Professor of Organic Chemistry, Chemistry Department,
Faculty of Science, Ain Shams University

**Chemistry Department
Faculty of Science
Ain Shams University
Cairo -Egypt
2018**



Faculty of Science
Ain Shams University
Chemistry Department

Thesis Title
**Synthesis of some heterocyclic compounds
containing nitrogen nucleus with expected
biological activity**

By
Eman Ahmed Ghareeb Ibrahim
(B.Sc. 2015)

Submitted for M.Sc. Degree of Science in Chemistry to
Chemistry department, Faculty of Science, Ain Shams
University

Thesis Advisors

Approved

Prof. Dr. EL-Sayed Ahmed Soliman Abdel-Aziz

Professor of Organic Chemistry, Chemistry Department,
Faculty of Science, Ain Shams University.

Prof. Dr. Eman Abdel-Fattah Abdel-Hafez El-Bordany

Professor of Organic Chemistry, Chemistry Department,
Faculty of Science, Ain Shams University.

Dr. Naglaa Fawzy Hassan Mahmoud

Associate Professor of Organic Chemistry, Chemistry Department,
Faculty of Science, Ain Shams University.

Head of Chemistry Department
Prof. Dr. Ibrahim H. Badr

List of Contents

Subject	Page
Aim of the work	
Abstract	
Summary	I
Introduction	1-41
Results and discussion	42-79
Part 1: Synthesis and reactions of pyrimidinethione	43
Part 2: Biological and pharmaceutical activity	74
Figures	80-173
Experimental:	174-184
Part 1: Chemistry	174
Part 2: Biological and pharmaceutical activity	183
References	185-192
Arabic summery	

ACKNOWLEDGEMENT

*First of all, thanks to **ALLAH** for giving me the ability and strength to achieve this work.*

*I am sincerely grateful to my supervisor **Prof.Dr. El-Sayed Ahmed Soliman Abdel-Aziz**, Professor of Organic Chemistry, Faculty of Science, Ain Shams University for his kind supervision, continuous interest, suggesting the topic of the research, making the chemicals available and his encouragement in this work.*

*I would like to express my deep thanks to **Prof.Dr. Eman Abdel-Fattah Abdel-Hafez El-Bordany**, Professor of Organic Chemistry, Faculty of Science, Ain Shams University and **Dr. Naglaa Fawzy Hassan Mahmoud**, Associate Professor of Organic Chemistry, Faculty of Science, Ain Shams University for suggesting this work, generous supervision, interpretation of data, keen interest, revision of the work, continuous support, their valuable advices during the practical work and facilities provided for producing this work.*

Finally, deep thanks to my family, my friends and for all people who helped me to finish this work.

Eman Ghareeb

Abstract

Synthesis of some heterocyclic compounds containing nitrogen nucleus with expected biological activity

By

Eman Ahmed Ghareeb Ibrahim

ABSTRACT

The original work of this thesis can be classified into two parts:

Part I: Aims to the synthesis of 6-(4-methoxyphenyl)-4-oxo-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carbonitrile **1** through the reaction of ethyl 2-cyano-3-(4-methoxyphenyl) acrylate with thiourea in presence of sodium ethoxide or by the one-pot cyclic condensation reaction of *p*-methoxy benzaldehyde, ethyl cyanoacetate and thiourea in ethanol containing anhydrous potassium carbonate. Study the behavior of **1** towards different electrophilic and nucleophilic reagents to synthesize new poly functionalized series of substituted pyrimidine-2-thione derivatives.

The chloropyrimidine derivative **10** was utilized as starting material for preparation of new fused heterocyclic such as pyrimidoquinazoline derivative, 4-((4-acetylphenyl) amino)-6-(4-methoxyphenyl)-2-thioxo-1, 2-dihydropyrimidine-5-carbonitrile, dithioxopyrimidine derivative, tetrazolopyrimidine derivative and 4-hydrazinyl pyrimidine derivative by reaction with anthranilic acid, *p*-aminoacetophenone, thiourea, sodium azide and hydrazine hydrate.

The hydrazinyl pyrimidine derivative **6** was treated with electrophilic reagents such as ethyl chloroacetate, chloroacetyl chloride, ethyl chloroformate and acetylacetone gave the corresponding pyramidotriazine derivative **18**, ethyl formate derivative **19** and diazolopyrimidine derivative **20** respectively. Also, a series of 4-(4-methoxyphenyl)-6-oxo-2-

(2-(substituted benzylidene) hydrazinyl)-1, 6-dihydropyrimidine-5-carbonitrile derivatives **21a-d** were prepared by the reaction of **4** with different aromatic aldehydes in glacial acetic acid. The reaction of Schiff's base **21a** with thioglycolic acid and chloroacetyl chloride afforded Oxothiazolidin derivative **22a** and oxoazetidine derivative **23a** respectively.

Part II: This part aims to study the biological activities of the synthesized compounds as antioxidant, antimicrobial against *Staphylococcus aureus* (G+ve), *Pseudomonas aeruginosa* (G-ve), *Candida albicans* (yeast), *Aspergillus niger* (fungus) and anticancer against HePG2, HCT-116, MCF-7 cell lines.

Keywords: quinazoline, tetrazolopyrimidine, pyrimidotriazine, oxothiazolidin, oxoazetidine, pharmacological and antimicrobial activities

Aim of the work

The current work aimed at:

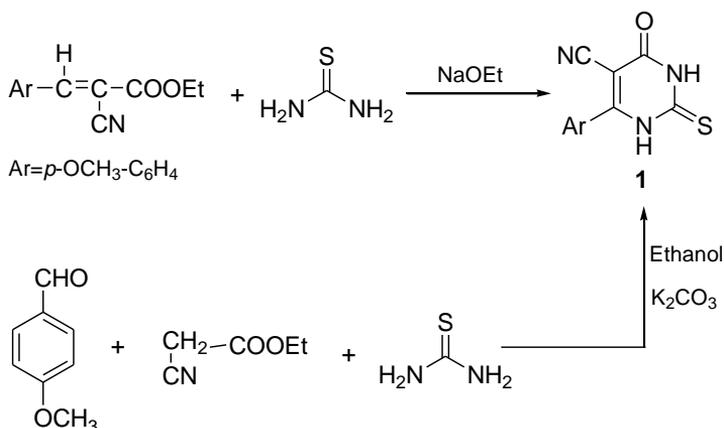
- 1- Synthesis and study the reactivity of 6-(4-methoxyphenyl)-4-oxo-2-thioxo- 1, 2, 3, 4-tetrahydropyrimidine-5-carbonitrile towards different electrophilic and nucleophilic reagents to synthesize new poly functionalized series of substituted pyrimidine-2-thione derivatives.
- 2- Elucidation of the newly synthesized compounds by spectroscopic data and elemental analysis.
- 3- Study the biological and the pharmacological activities of the synthesized products as an antioxidant, antimicrobial and anticancer.

Keywords: Quinazoline, tetrazolopyrimidine, pyrimidotriazine, oxothiazolidine, oxoazetidine, antioxidant, antimicrobial and anticancer activity.

Summary

Summary

The original work of this thesis can be classified into two parts: The first part deals with synthesis of 6-(4-methoxyphenyl)-4-oxo-2-thioxo-1, 2, 3,4-tetrahydropyrimidine-5-carbonitrile through the reaction of ethyl 2-cyano-3-(4-methoxyphenyl) acrylate with thiourea in presence of sodium ethoxide or by one-pot cyclic condensation reaction of *p*-methoxy benzaldehyde, ethyl cyanoacetate and thiourea in ethanol containing anhydrous potassium carbonate (**Scheme 1**). The behavior of **1** towards different electrophilic and nucleophilic reagents was investigated to synthesize new poly functionalized series of substituted pyrimidine-2-thione derivatives.

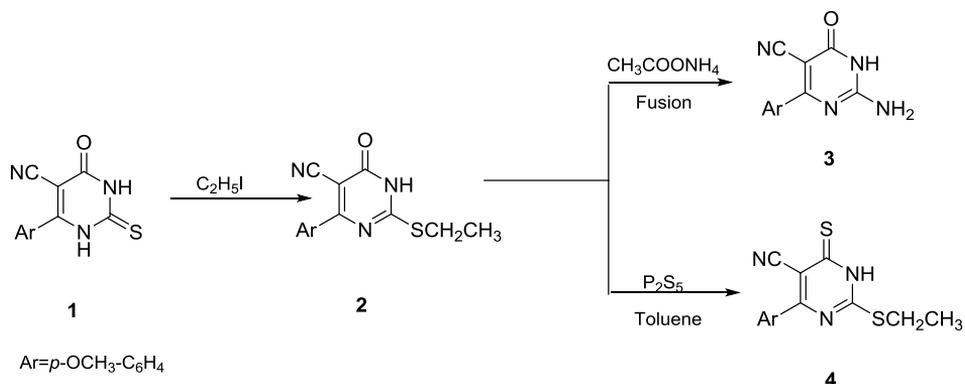


Scheme 1

Tetrahydropyrimidine derivative **1** upon alkylation with alkylating reagents such as ethyl iodide in presence of sodium acetate using (1:1) molar ratio gave the *S*-alkylated product named 2-(ethylthio)-4-(4-methoxyphenyl)-6-oxo-1, 6-dihydropyrimidine-5-carbonitrile **2**.

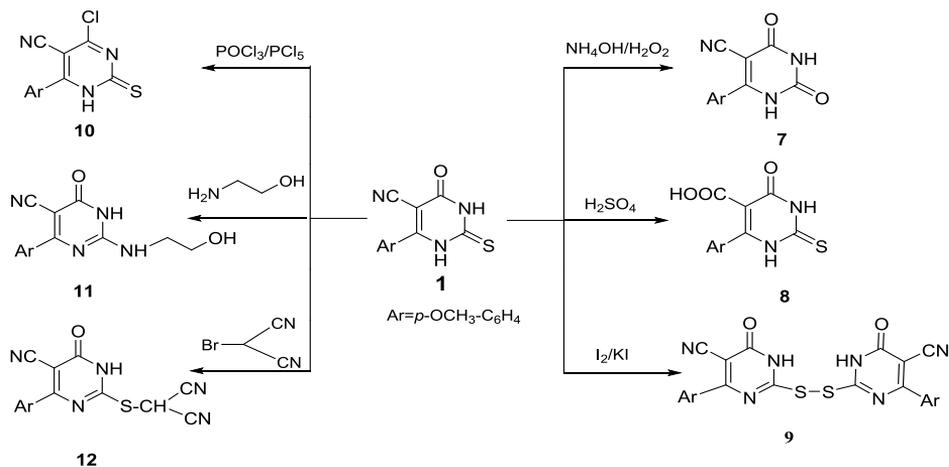
Furthermore, the fusion of 2-ethyl thio pyrimidine derivative **2** with ammonium acetate afforded 2-amino-6-(4-methoxy)-4-oxo-1, 2, 3,

4-tetrahydropyrimidine-5-carbonitrile **3**. While, the reaction of 2-ethyl thiopyrimidine derivative **2** with Phosphorus pentasulfide was afforded 2-(ethylthio)-4-(4-methoxyphenyl)-6-thioxo-1, 6-dihydropyrimidine-5-carbonitrile **4** (**Scheme 2**).



Scheme 2

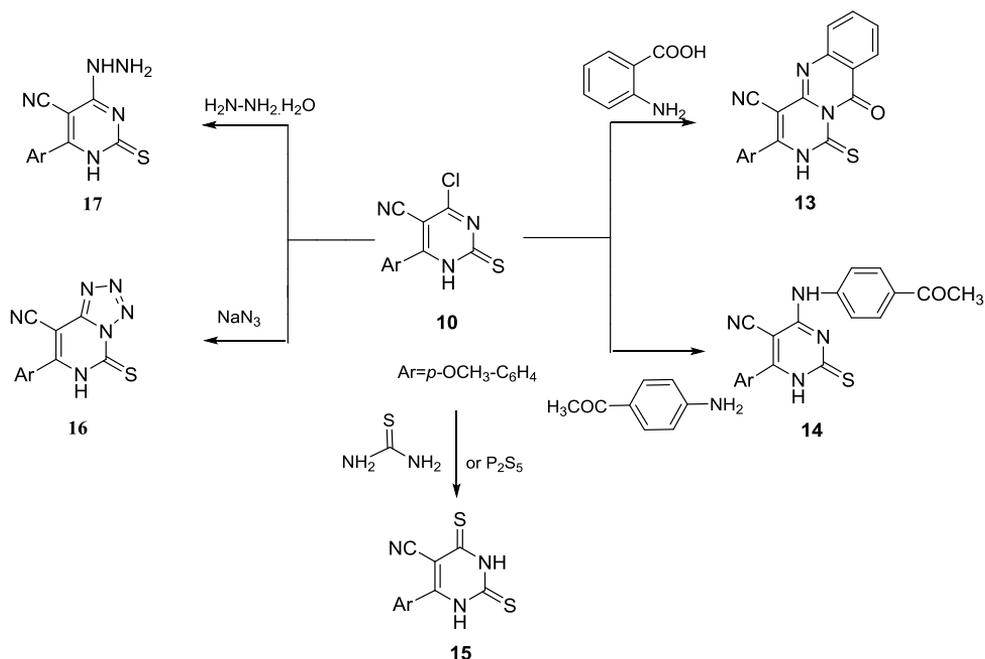
On the other hand, the reaction of tetrahydropyrimidine derivative **1** with ethyl chloroacetate in presence of anhydrous potassium carbonate afforded the ethyl ester derivative **5**. Synthesis of 6-aryl-2-hydrazinyl-4-oxo-1, 4-dihydropyrimidine-5-carbonitrile derivative **6** was achieved by the reaction of tetrahydropyrimidine **1** or treatment of S-alkylated **2** or reaction of ethyl ester derivative **5** with hydrazine hydrate in boiling ethanol (**Scheme 3**).



Scheme 4

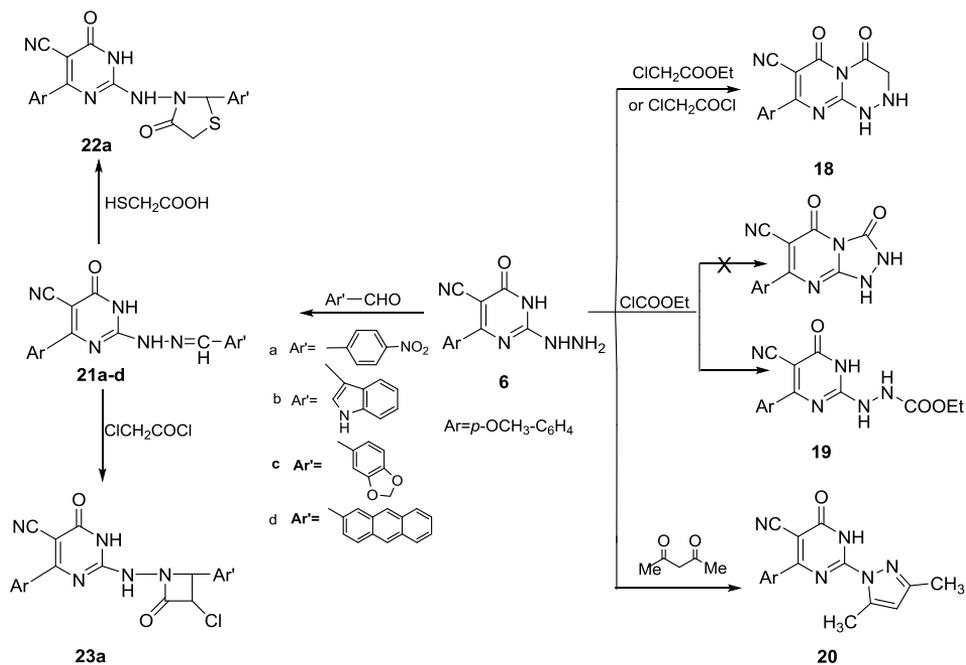
Additionally, the chloropyrimidine derivative **10** was reacted with anthranilic acid to give pyrimidoquinazoline derivative **13**. Heating of chloropyrimidine derivative **10** with *p*-aminoacetophenone in presence of drops of HCl gave 4-((4-acetylphenyl) amino)-6-(4-methoxyphenyl)-2-thioxo-1, 2-dihydropyrimidine-5-carbonitrile **14**. The chloropyrimidine derivative **10** underwent thiation under the effect of thiourea or phosphorus pentasulfide to give dithioxodihydropyrimidine derivative **15**. The reaction of chloropyrimidine derivative **10** with sodium azide in glacial acetic acid afforded tetrazolopyrimidine derivative **16**.

However, 4-hydrazinyl pyrimidine derivative **17** was achieved by reaction of chloropyrimidine derivative **10** with hydrazine hydrate in boiling ethanol (**Scheme 5**).



Scheme 5

On the other hand, treatment of hydrazinyl pyrimidine derivative **6** with electrophilic reagents such as ethyl chloroacetate, chloroacetyl chloride, ethyl chloroformate and acetylacetone gave the corresponding pyrimidotriazine derivative **18**, ethyl formate derivative **19** and diazolopyrimidine derivative **20** respectively. Also, a series of 4-(4-methoxyphenyl)-6-oxo-2-(2-(substituted benzylidene) hydrazinyl)-1, 6-dihydropyrimidine-5-carbonitrile derivatives **21a-d** were prepared by the reaction of **4** with different aromatic aldehydes in glacial acetic acid. The reaction of Schiff's base **21a** with thioglycolic acid and chloroacetyl chloride afforded oxothiazolidin derivative **22a** and oxoazetidine derivative **23a** respectively (**Scheme 6**).



Scheme 6

On the other hand, the synthesis of the novel compound thiazolo pyrimidine derivative **24** was achieved by reacting compound **1** with chloroacetic acid in dimethylformamide (DMF). Moreover, 3-amino thiazolo pyrimidine derivative **25** and 4-imino-pyrimido thiazine derivative **26** were prepared by refluxing **1** with chloroacetonitrile and acrylonitrile in ethanol in presence of few drops of triethylamine. Treatment of compound **1** with oxalyl chloride in tetrahydrofuran afforded trioxo thiazolo pyrimidine derivative **27** via nucleophilic attacks upon the carbonyl carbon atom of oxalyl chloride (**Scheme 7**).