Synthesis and biological evaluation of some heterocyclic compounds as antiviral

A Thesis

Submitted for the Award of Ph.D.degree in Organic Chemistry

Presented by

Alaa Eldin Ramadan Ibrahim

M. Sc. In Organic Chemistry

Department of Chemistry

Faculty of Science

Ain Shams University

Supervised by:

Prof. Dr. **Wael S. I. Abou –ElMagd**

Prof. Dr. **Salah Mohamed ElKousy**

Prof. Dr. **Samir Abdelmoez A. Nasif**

2017

Synthesis and biological evaluation of some heterocyclic compounds as antiviral

A Thesis Submitted for Ph. D. Degree in Organic Chemistry

Presented by

Alaa Eldin Ramadan Ibrahim

Thesis Advisors	**Thesis Approved**
Prof. Dr. Wael S. I. Abou El-Magd Professor of Organic Chemistry, Faculty of Science, Ain Shams University.	…….
Prof. Dr. Salah Mohamed Elkousy Professor of Organic Chemistry**,**Faculty of Science**,**Elmenofia University.	**…….....**
Prof. Dr. Samir Abdelmoaz A. Nasif Professor of viral poultry diseases, (CLEVB) Agriculture Research Center	**...**……..

Head of Chemistry Department

Faculty of Science, Ain Shams University

Prof. Dr. Ibraim H.A.Badr

Acknowledgment

*First and foremost, all thanks to **Allah** for showing me the right path and helping me to complete this work.*

*I wish to express my deepest thanks and gratitude to Prof. Dr. **Wael S. I. Abou El-Magd**; Professor of Organic Chemistry, Faculty of Science, Ain shams University, Prof. Dr. **Salah Mohamed Elkousy** Professor of Organic Chemistry, Faculty of Science, Elmenofia University Prof. Dr. **Samir Abdelmoaz A. Nasif** Professor of viral poultry diseases, (CLEVB) Agriculture Research Center, not only for suggesting the subjects investigated, but also for their continuous advice and valuable criticism during the course of this work.*

Alaa Eldin Ramadan Ibrahim

ABSTRACT

The chemistry of 2(3*H*)- furanones had received great attention in the last decades. The importance of these compounds is due to facile opening of the furanone ring to give acyclic products which can recyclize again to afford a variety of heterocyclic systems of synthetic and biological importance e.g pyrrolones, pyridazinones, isothiazolones, oxadiazoles .etc.

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

***Part* 1:** In this part, the acid hydrazide derivative **1** bearing 1,3-diphenyl-pyrazolyl moiety at position-3 was prepared, and utilized for the construction of pyridazine, pyridazinone, pyrazole, pyrazolone, phthalazinedione and schiff bases upon condensation with different carbonyl compounds.

***Part* 2**: In this part, the behavior of the previous hydrazide derivative towards carbon disulphide to form potassium dithiocarbamate salt was studied. The later salt was converted to pyridazinotriazole, triazolothiadiazole and triazolothiadiazine derivatives as examples of fused heterocyclic compounds.

The structures of the newly synthesized compounds in parts 1 &2 were established on the basis of IR, ^{1}H-NMR, mass spectral data, and elemental analyses.

***Part 3*: Biological activity part**: In this part, All the prepared compounds were evaluated against highly pathogenic avian influenza H_5N_1 after doing the toxicity test to all concentrations prepared after excluding the toxic concentrations. Some of the tested compounds showed promising activities.

SUMMARY

2(3*H*)-Furanones represent an important type of five-membered heterocyclic systems. The importance of these compounds stems from facile opening of the lactone ring with both nucleophilic and electrophilic reagents to give acyclic product. These acyclic products are the precursors of a wide variety of synthetically and biologically important heterocyclic systems e.g. pyridazinones, oxadiazoles, triazoles, isothiazolones…etc.

In this investigation, ring transformation of pyrazolyl substituted 2(3*H*)-furanone into novel fused and unfused nitrogen containing heterocycles, and the behavior of the synthesized compounds against highly pathogenic avian influenza H_5N_1 are studied.

The original work of this thesis **consists of three main parts:**

Part 1: In this part, the acid hydrazide (**1**) was obtained from hydrazinolysis of 2(*3H*)-furanone bearing pyrazolyl moiety at position-3.

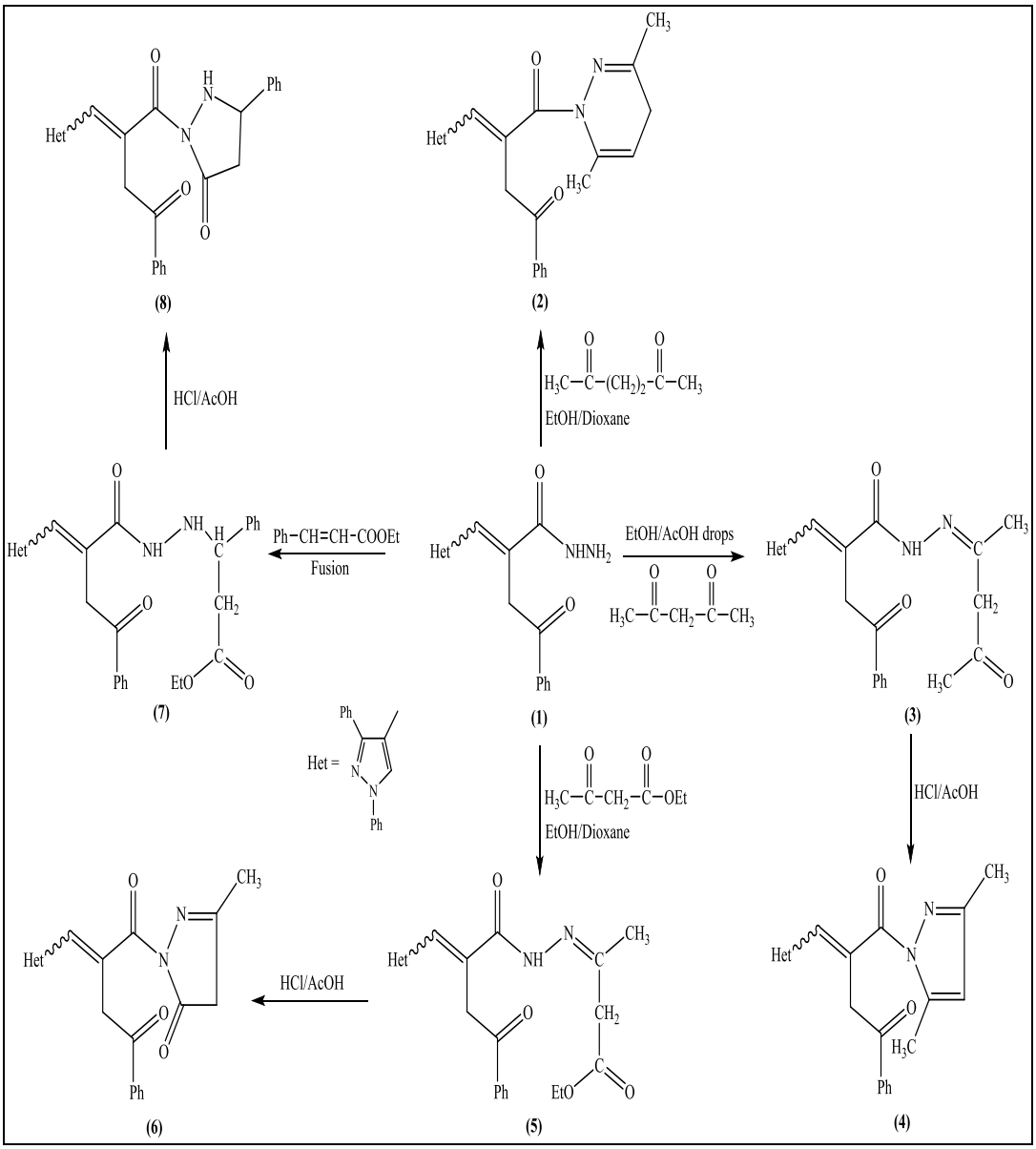
The reactions of the acid hydrazide (**1)** with different carbonyl compounds were studied. Thus, when reacted with acetylacetone, ethyl acetoacetate or ethyl cinnamate gave the pyrazole derivatives (**4), (6**) or **(8)** respectively. On the other hand, the reaction with acetonylacetone led to the formation of the pyrridazine derivative (**2**). The pyrazoldione derivative (**9**) was obtained via refluxing (**1**) with diethyl malonate in ethanol.

The phthalazinedione derivative (**10**) was obtained upon treatment the acid hydrazide with phthalic anhydride.

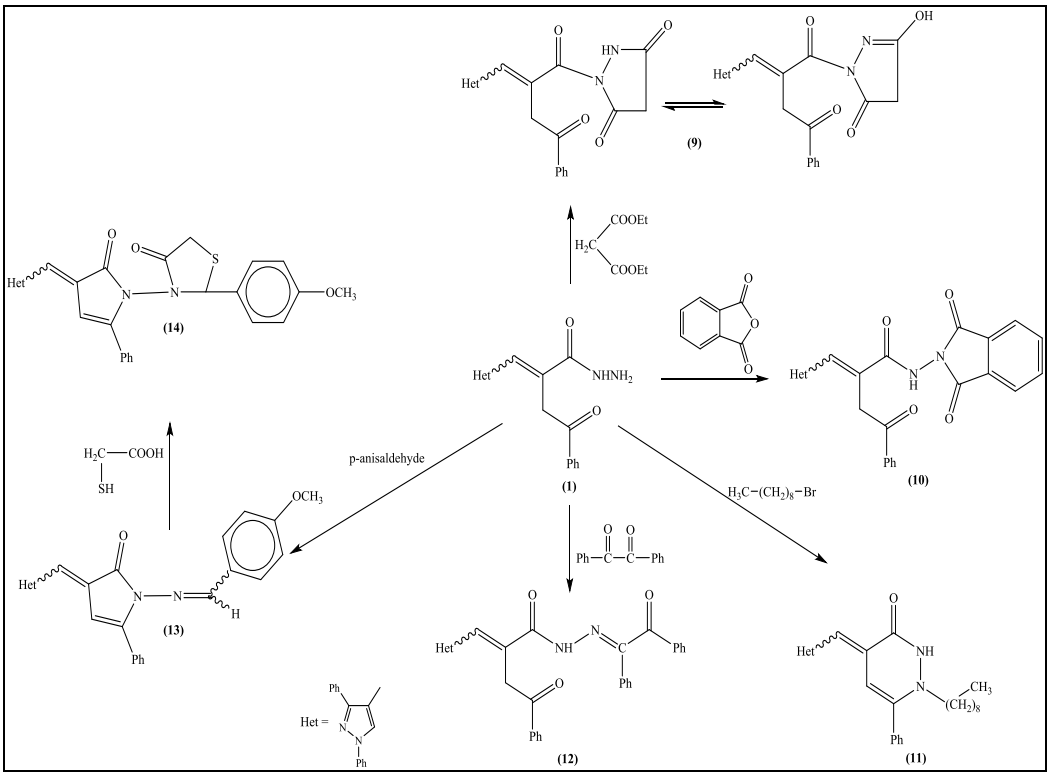
The open-chain Shciff base products (**12**) and (**14**) were obtained upon condensation of the acid hydrazide with benzil and p-anisaldehyde respectively.

Reaction of the Schiff base product (**13**) with thioglycolic acid gave the thiazolidinone product (**14**)

The chemical transformations in this part can be represented by the two Schemes (A) and (B).

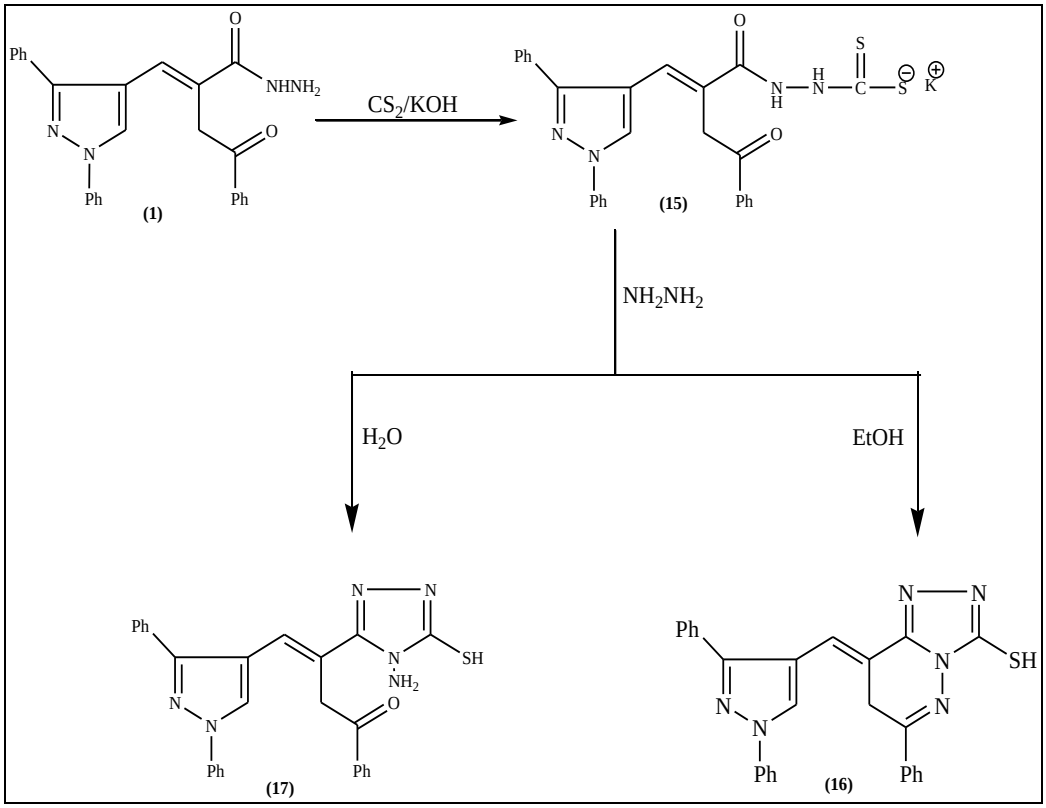


Scheme A. Ring transformations of **1** into pyridazine, pyrazole, pyrazolone and pyridazinone derivatives **2,4,6** and **8** respectively



Scheme B. Ring transformations of **1** into pyrazolone, phthalazindione, pyridazinone and thiazolidinone derivatives **9,10,11** and **14**respectively

Part 2: In this part, the potassium dithiocarbamate (**15**) was prepared by reaction of the acid hydrazide with carbon disulphide and potassium hydroxide. The behavior of the latter compound with hydrazine in different solvents was studied. The results obtained reveal that, in case of ethanol as solvent the mercapto derivative (**16**) was isolated as a sole product. But when the above reaction was repeated in water as solvent the target compound 1-amino-2-mercapto derivative (**17**) was isolated (Scheme C).



(Scheme C)

The presence of mercapto and amino groups adjacent to each other in compound **17** and mercapto group in compound **16** made them valuable key precursors for the formation of fused N-heterocycles. Thus, refluxing compound **17** with benzoyl chloride, carbon disulfide and/or urea yielded the triazolothiadiazole derivatives **18**, **19** and **20** respectively. On the other hand, the triazolothiadiazine derivatives **21** was obtained upon treatment compound **17** with benzoin. (Scheme D).