Fayoum University
Faculty of Science
Chemistry Department

Synthesis of Some Interesting Heterocyclic Organic Compounds Containing Mixed and Non-mixed Systems

By

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A Thesis submitted in Partial fulfillment

Of

The requirements for the degree of

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In

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Synthesis of Some Interesting Heterocyclic Organic Compounds Containing Mixed and Non-mixed Systems

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The present thesis is submitted to the Faculty of Science, Fayoum University in the partial fulfillment of the requirements of Degree of Master of Science in Organic Chemistry.

Beside the works carried out in this thesis, the candidate ***ShaimaaRabie Mohammed*** has passed successfully the following graduate courses for one academic year:

1. Advanced Heterocyclic Chemistry.
2. Natural Products.
3. Organometallic.
4. Spectroscopy.
5. Instrumental Analysis.
6. C-Nucleoside.
7. Chemotherapy.
8. Advanced Quantum Chemistry.
9. Inorganic Reaction Mechanism.
10. Organic Reaction Mechanism.
11. Advanced Physical Organic Chemistry.
12. Advanced Organic Chemistry.
13. Photochemistry.
14. Stereochemistry.
15. Polymer Chemistry.
16. Dyes.

Dean of the College and supervisor of Chemistry Department

Prof. Dr. ArafaSabriGomaa

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List of Abbreviations

HIV: Human immunodeficiency virus.

DNA: Deoxyribonucleic acid.

RNA: Ribonucleic acid.

VEGFR-2: Vascular endothelial growth factor.

PC-3: Prostate cancer.

TRPV1: Transient Receptor Potential Vanilloid-receptor 1.

DG: Diacylglycerol.

AChE: Acetylcholinesterase.

DIEA: Diisopropylethylamine.

***p*-TSA:** *p*-toluenesulfonic acid.

MTT: Methyl thiazolyltetrazolium.

DMSO: Dimethyl sulphoxide.

DMF: N, N-dimethylformamide.

MCF-7: Michigan Cancer Foundation-7.

This thesis describes the studying of the behavior of the corresponding 6-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile **II** towards some electrophiles and nucleophiles to produce some heterocyclic compounds having expected antimicrobial activities.

The thesis consists of the following parts:

1- Summary

2- Introduction:

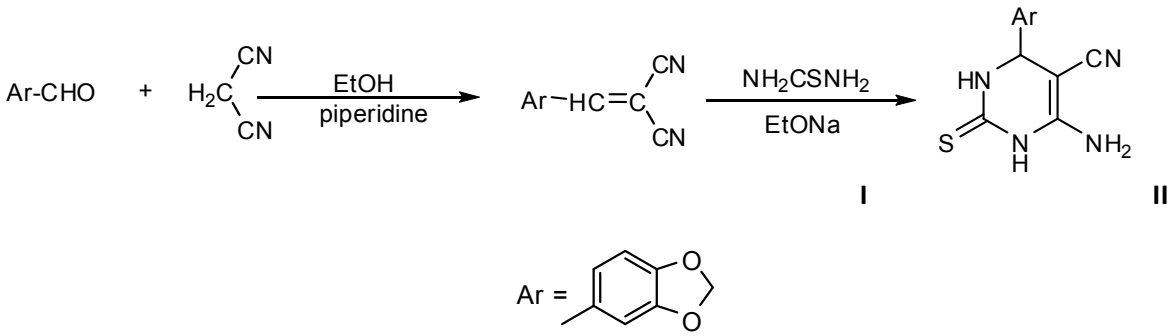
In this section brief literatures review of the different methods of preparation, reactions and applications of pyrimidinethione derivatives.

3-Discussion:

It deals with the discussion of the experimental methods adopted for the synthesis of the designed compounds as well as the result of different analytical methods applied for the characterization of the new compounds.

Scheme 1-6 illustrate the synthetic pathways followed in the preparation of the target compounds.

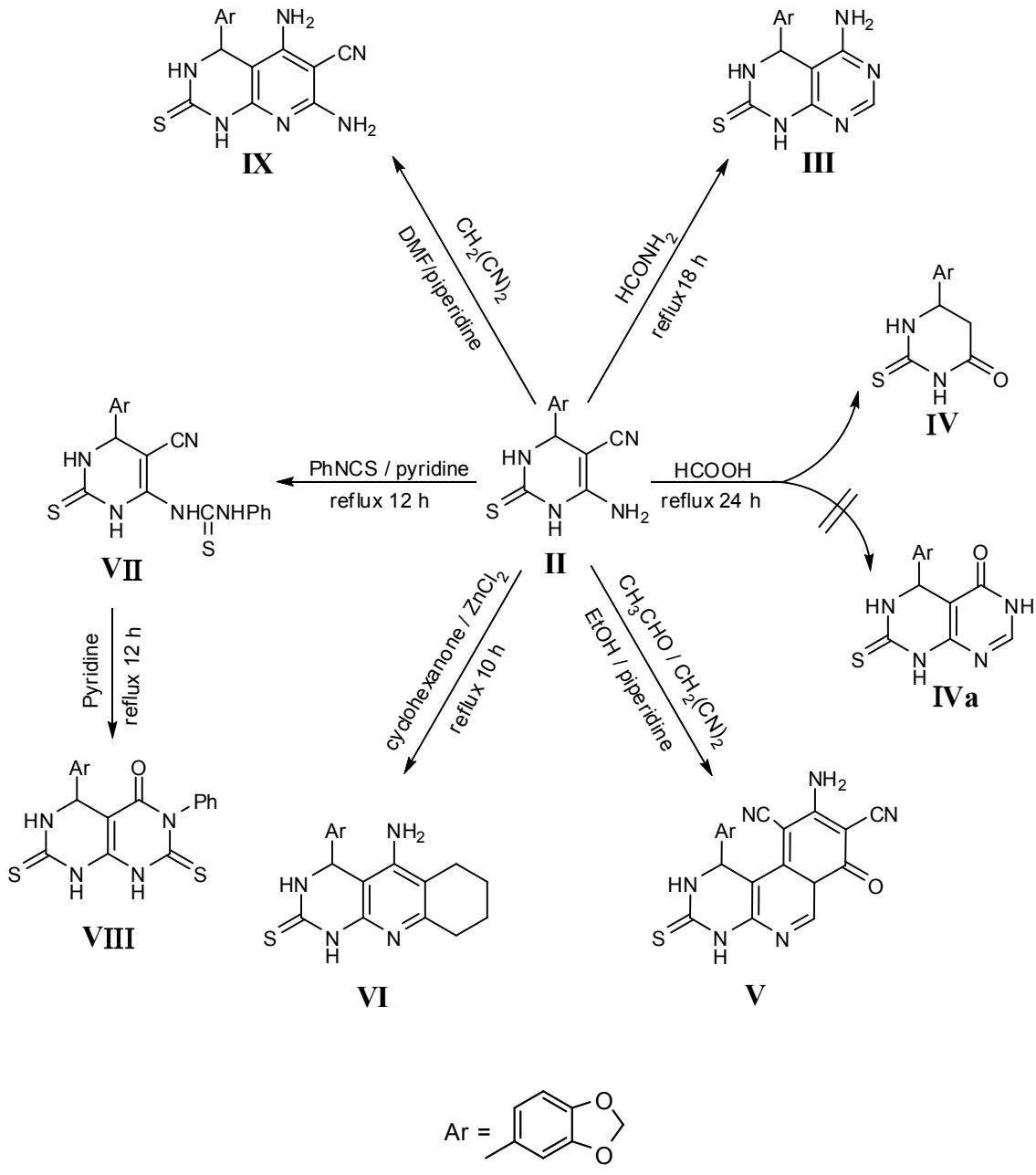
In this part the author synthesis 6-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile **II** by reaction of arylidene malononitrile **I** with thiourea in sodium ethoxide solution (Scheme 1).



(Scheme 1)

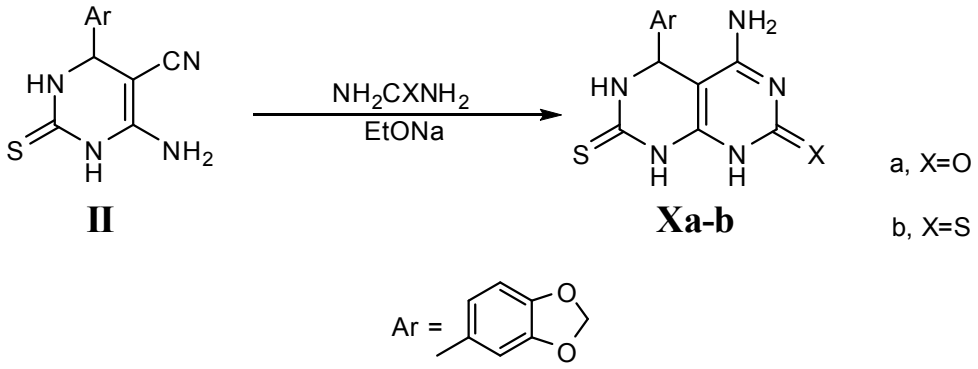
Compound **II** reacted with formamide and afforded aminopyrimido-pyrimidine derivative **III**, while the interaction between compound **II** and formic acid furnished compound **IV** rather than **IVa**, the desired product was investigated using analytical and spectral data. Also, condensation of compound **II** with acetaldehyde and malononitrile in presence of ethanol and piperidine gave pyrimido[4,5-*c*]isoquinoline derivative **V**. In addition, compound **II** refluxed with cyclohexanone in presence of anhydrous zinc chloride to yield pyrimido[4,5-*b*]quinoline derivative **VI**. Refluxing a mixture of compound **II** and

phenylisothiocyanate in pyridine produced compound **VII** which on cyclization by refluxing in pyridine for another 12 h gave pyrimido[4,5-*d*]pyrimidin-4(1*H*)-one derivative **VIII**. Treatment of compound **II** with malononitrile in presence of DMF and few drops of piperidine afforded pyrido[2,3-*d*]pyrimidine derivative **IX** (Scheme 2).



(Scheme 2)

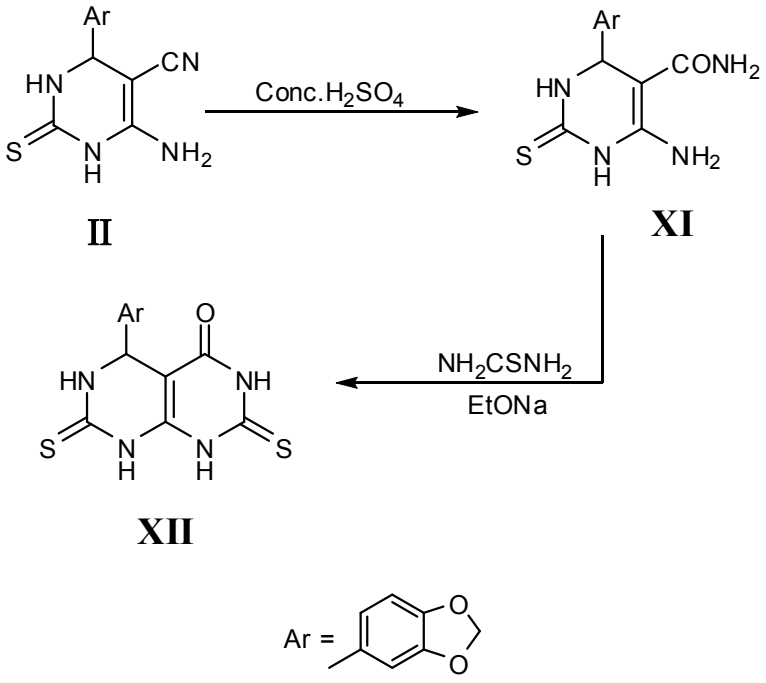
Reaction between compound **II** and urea or thiourea in sodium ethoxide solution furnished compound **Xa** or **Xb**, respectively (Scheme 3).



II **Xa-b**

(Scheme 3)

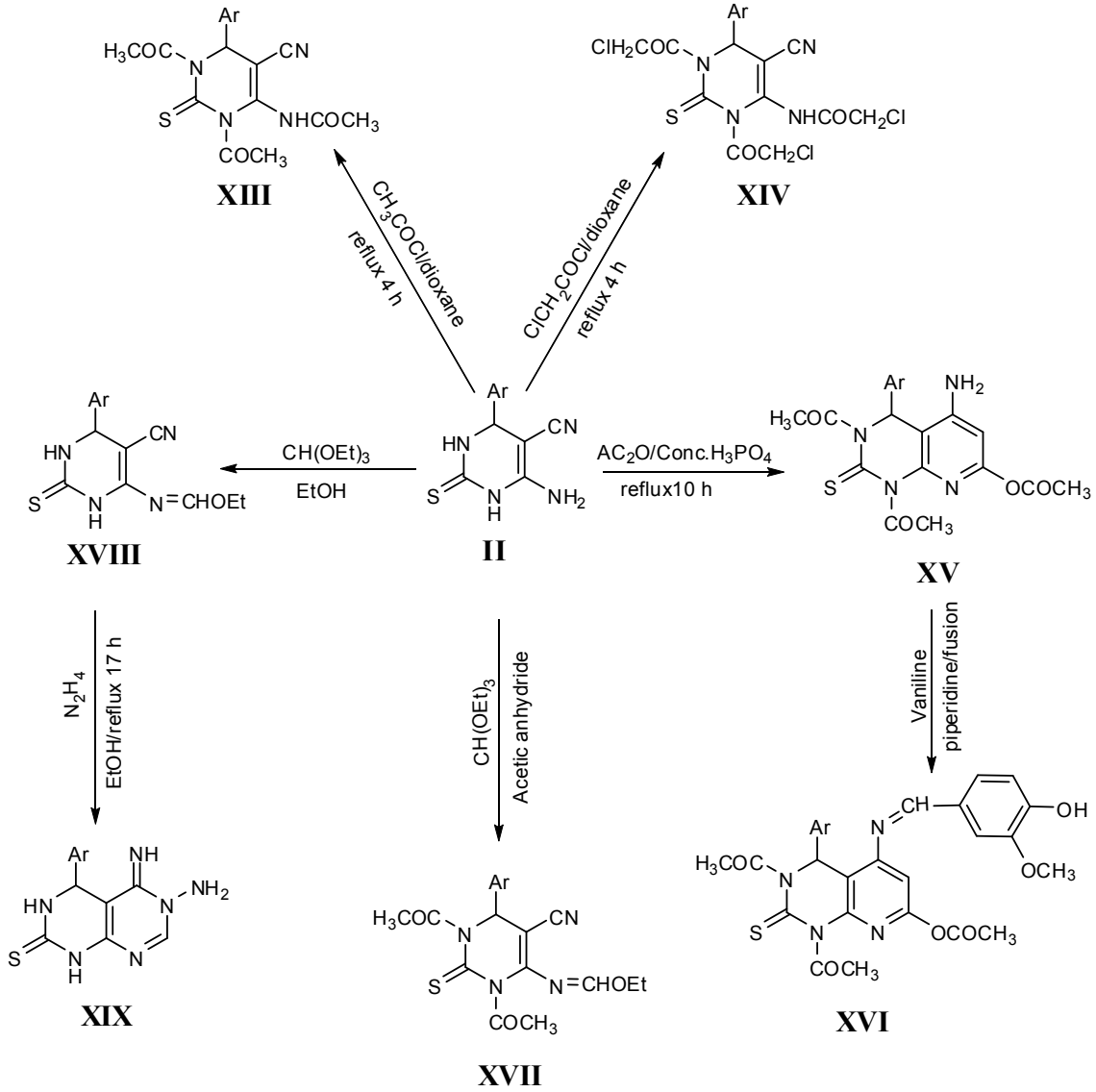
The acid hydrolysis of nitriles to amides by using sulfuric acid (96 %) afforded compound **XI** which was cyclized into compound **XII** by refluxing with thiourea in sodium ethoxide solution (Scheme 4).



II **XI** **XII**

(Scheme 4)

Acetylation of compound **II** with acetyl chloride in dry dioxane afforded compound **XIII**, while chloroacetylation using chloroacetyl chloride gave compound **XIV**. On the other hand, compound **II** reacted with acetic anhydride in presence of concentrated phosphoric acid under reflux for 10 h to afford compound **XV** which further treated with an aromatic aldehyde namely, vaniline, to produce compound **XVI**. Moreover, compound **II** reacted with triethyl orthoformate in presence of acetic anhydride to furnish compound **XVII**, while treatment of compound **II** with triethyl orthoformate in refluxing ethanol instead of acetic anhydride afforded compound **XVIII** in which no acetylation was occurred. After that, compound **XVIII** refluxed with hydrazine hydrate in boiling ethanol to give the cyclized compound **XIX** (Scheme 5).



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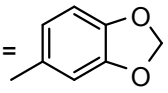
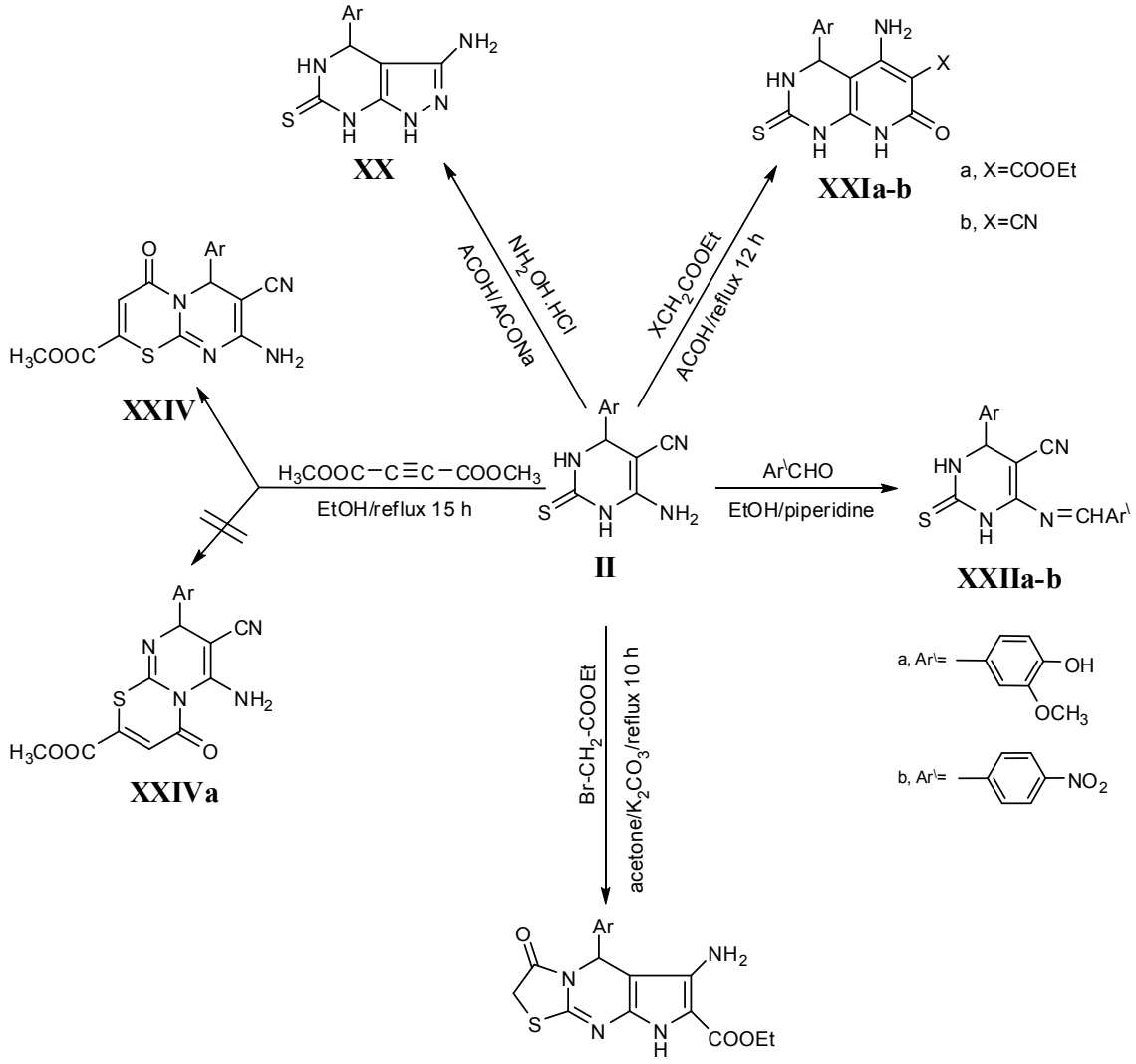


(Scheme 5)

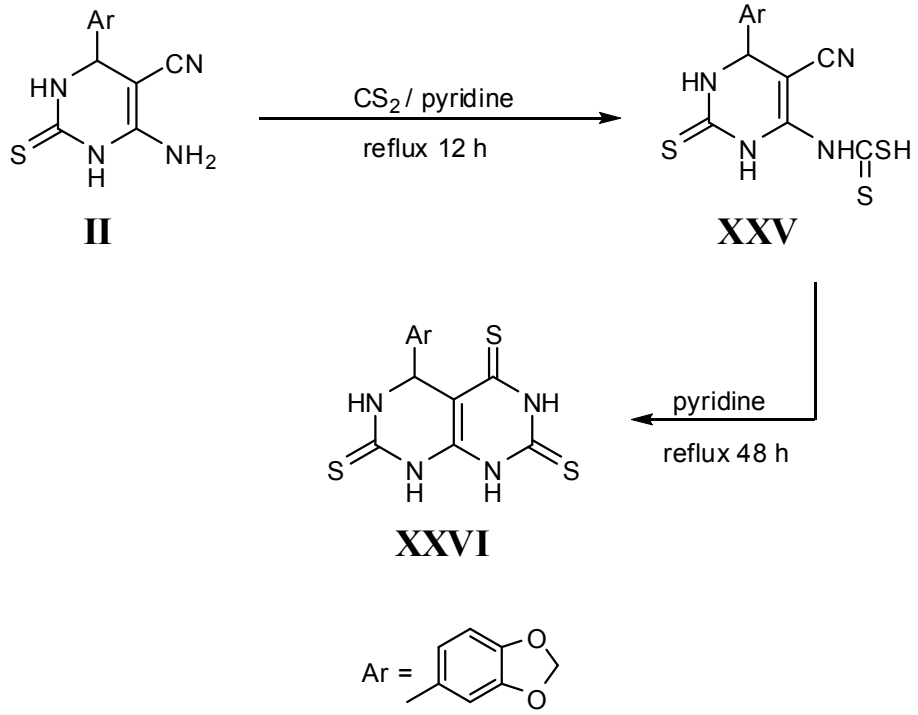
Refluxing a mixture of compound **II** and hydroxylamine hydrochloride in glacial acetic acid containing a catalytic amount of anhydrous sodium acetate furnished pyrazolo [3,4-*d*] pyrimidine-6(7*H*)-thione derivative **XX**. The reaction of compound **II** with active methylene compounds such as diethyl malonate or ethyl cyanoacetate afforded compound **XXIa** or **XXIb**, respectively. For synthesis of the Schiff's base, a mixture of compound **II** and an aromatic aldehyde (namely vaniline or *p*-nitrobenzaldehyde) was fused in oil bath in presence of few drops of piperidine to afford compound **XXIIa** or **XXIIb**, respectively. The

alkylation of compound **II** with α-halo acetic acid derivatives (namely ethyl bromoacetate) was achieved in dry acetone containing anhydrous potassium carbonate and afforded pyrrolo[2,3-*d*]thiazolo[3,2-*a*]pyrimidine-7-carboxylate derivative **XXIII**. Finally, reaction of compound **II** with dimethyl acetylenedicarboxylate in refluxing ethanol furnished 4,6-dihydropyrimido[2,1-*b*][1,3]thiazine-2-carboxylate derivative **XXIV** rather than 4,8-dihydropyrimido[2,1-*b*][1,3]thiazine-2-carboxylate derivative **XXIVa** (Scheme 6).



(Scheme 6)

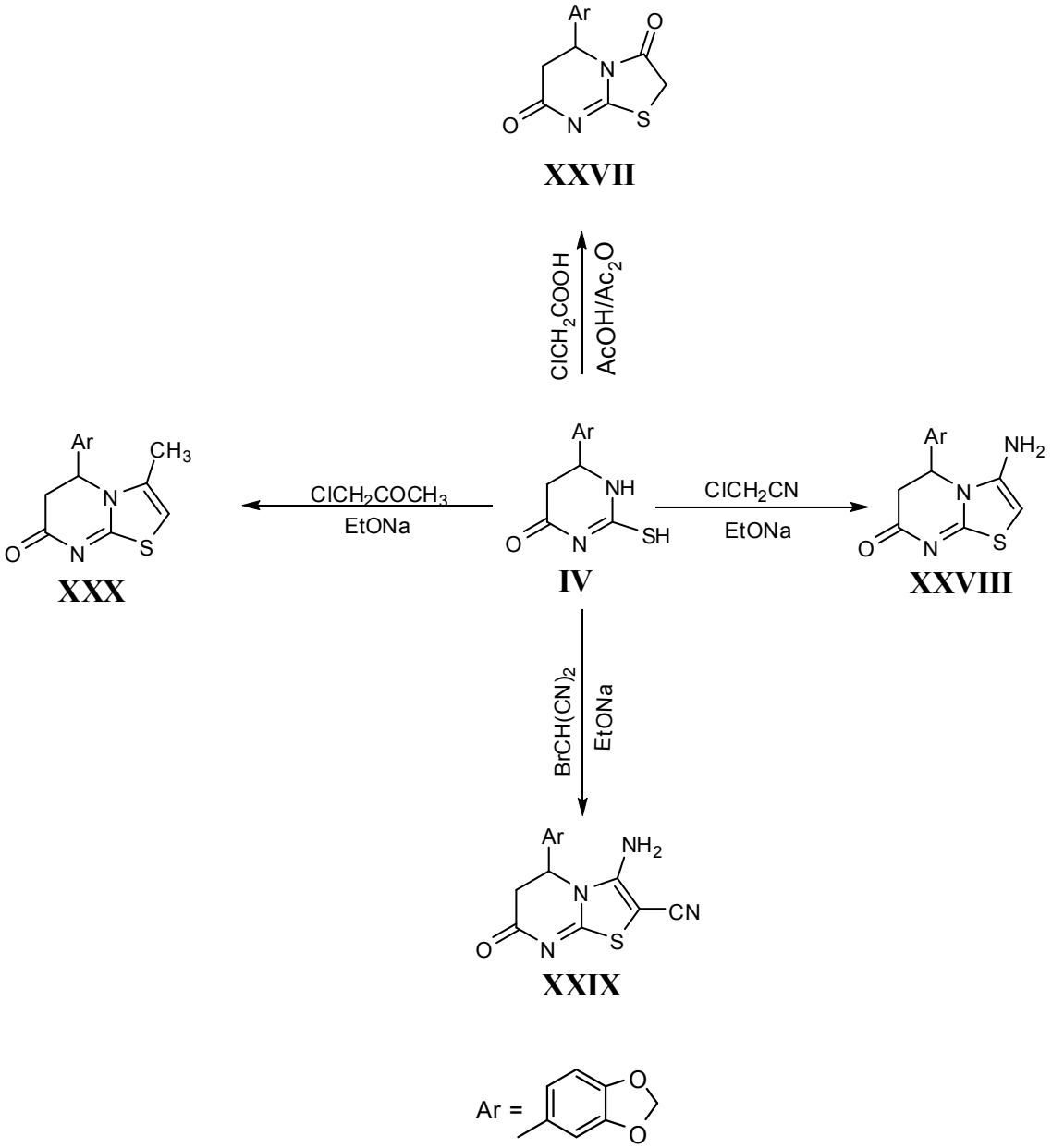
Refluxing a mixture of compound **II** and carbon disulphide in pyridine produced compound **XXV** which on cyclization by refluxing in pyridine for additional 48 h gave dihydropyrimido[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trithione derivative **XXVI** (Scheme 7).



II **XXV** **XXVI**

(Scheme 7)

For synthesis of thiazolopyrimidine derivatives, compound **IV** reacted with chloroacetic acid in presence of a mixture of glacial acetic acid and acetic anhydride (3:1) containing anhydrous sodium acetate to afford compound **XXVII**. While the reaction between compound **IV** and α-halo compounds, namely, chloroacetonitrile, mono bromomalononitrile and chloroacetone in presence of sodium ethoxide solution gave the cyclic products **XXVIII**, **XXIX** and **XXX**, respectively (Scheme 8).



(Scheme 8)

4-Exprimental:

In this part, the practical procedures used for the synthesis of the new compounds, in addition to their physical, spectral and micro-analytical data are cited.

5- Applications:

In this part, some of the newly synthesized pyrimidinethione derivatives were tested for the anti-bacterial activity.

6- References

7-Arabic summary