Ain Shams University

Faculty of Science

Chemistry Department

A Thesis Title

Synthesis of some Heterocyclic Compounds Containing Nitrogen With expected biological activity

Researcher Name:

Eslam Mourad Abbass Mosbah

Supervisors:

Prof. Dr. Mohamed Mahmoud Mohamed Mohamed

Professor of organic chemistry

Chemistry department, Faculty of Science, Ain Shams University

Dr. Ali Khalil Ali Khalil

Assistant Professor of organic chemistry

Chemistry department, Faculty of Science, Ain Shams University

Dr. Abeer Mohamed El-Sayed El-Naggar

Assistant Professor of organic chemistry

Chemistry department, Faculty of Science, Ain Shams University

Head of Chemistry Department

Prof. Dr. Ibrahim Hosainy Ali Badr

AIN SHAMS UNIVERSITY
كلية العلوم

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Researcher name:

Eslam Mourad Abbass Mosbah
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Thesis advisor **Approved**

Prof. Dr. Mohamed Mahmoud Mohamed Mohamed ……
Professor of Organic Chemistry
Chemistry department, Faculty of Science, Ain Shams University

Dr. Ali Khalil Ali Khalil ……
Assistant Professor of Organic Chemistry
Chemistry department, Faculty of Science, Ain Shams University

Prof. Dr. Ahmed Fouad El-Farargy ……
Professor of Organic Chemistry
Chemistry department, Faculty of Science, Zagazig University

Prof. Dr. Emtisal Ahmed Bahaa Eldin El-sawy ……
Professor of Organic Chemistry
Chemistry department, Faculty of Girls, Ain Shams University

Head of Chemistry Department

Prof. Dr. Ibrahim Hosainy Ali Badr

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Design, synthesis of new pyrimidine derivatives as anticancer and antimicrobial agents

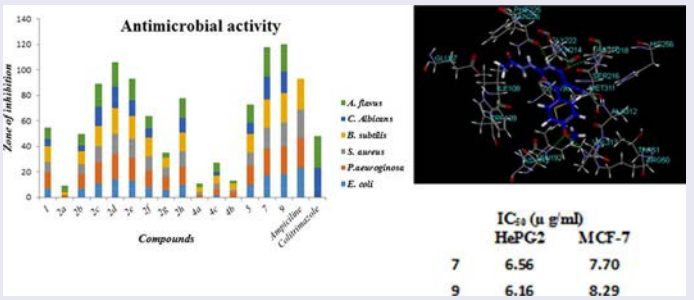
Mohamed M. Mohamed, Ali K. Khalil, Eslam M. Abbass, and Abeer M. El-Naggar

Department of Chemistry, Faculty of Science, Ain Shams University, Abbassia, Cairo, Egypt

ABSTRACT

A new series of 6-aryl-5-cyano thiouracil derivatives were synthesized. Cyanouracil **1** was condensed with monochloroacetic acid and different aldehydes to give thiazolopyrimidine **2**. On the other hand, treatment of cyanouracil **1** with 2-chloro-*N*-substituted-phenylac etamide afforded **4**. Hydrazinolysis of **6** afforded the hydrazino derivatives **7** which upon reaction with different electrophilic reagents such as acetic anhydride, benzoyl chloride, and carbon disulfide yielded pyrimidine derivatives **8**–**15**. Some of the new derivatives were explored for their antimicrobial activities. Compounds **7** and **9** have a promising activity, relatively equipotent to the reference drug. All of the new synthesized compounds were tested *in vitro* for their antiproliferative activities against HePG-2 and MCF-7 cell lines. Compounds **7**, **9**, and **2d** displayed potent growth inhibitory effect toward the two cell lines more than the standard drug 5-FU. Furthermore, a docking study of the most active compounds was performed with thymidylate synthase enzyme.

GRAPHICAL ABSTRACT



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Introduction

Dihydropyrimidines occupy a unique place in medicinal chemistry due to their wide application as drug and drug-intermediates possessing diverse pharmacological activities including antitumor, analgesic, antineoplastic, cardiovascular, and antiallergic activities.[1–5] Similarly, the related thiouracil therapeutic derivatives have been known as potential antiviral, antioxidant, anticancer, and antimicrobial agents.[6–9] Moreover,

CONTACT Abeer M. El-Naggar elsayedam@sci.asu.edu.eg Department of Chemistry, Faculty of Science, Ain Shams University, Abassia, Cairo 11566, Egypt.
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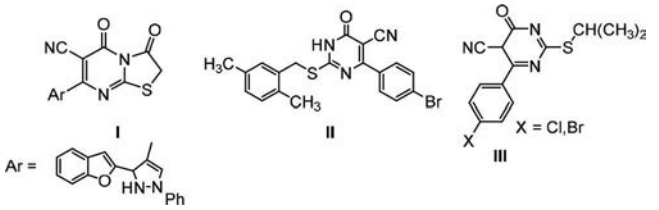


Figure 1. Structure of some potent 5-cyano-2-thiouracils.

literature survey revealed that the thiouracil carbonitrile ring system has occupied a marked position in the design and synthesis of novel chemotherapeutic agents with remarkable antitumor and antimicrobial and HCV-inhibiting activities (Fig. 1).[10–14] It is well established that uracil derivatives exert their anticancer activity through inhibition of folate metabolism, which is considered as an important target for the development of new anticancer agents due to its role in the biosynthesis of nucleic acid precursors.[15] The inhibition of folate-dependent enzymes such as thymidylate (dTMP) synthase, which catalyzes the reductive methylation of deoxyuridylate (dUMP) to dTMP has also been recognized as an interesting target for drug discovery.[16] In the light of the aforementioned facts, this work aims to design and synthesize a new series of thiouracil carbonitrile derivatives hoping that they could have some chemical and biological interest.

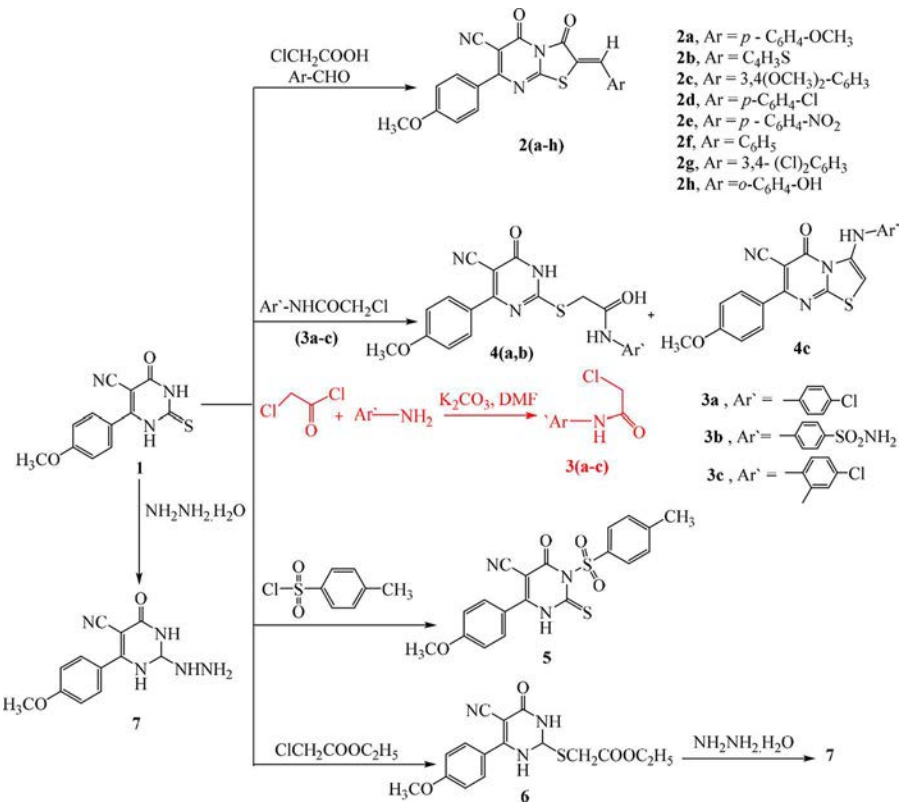
Results and discussion

Chemistry

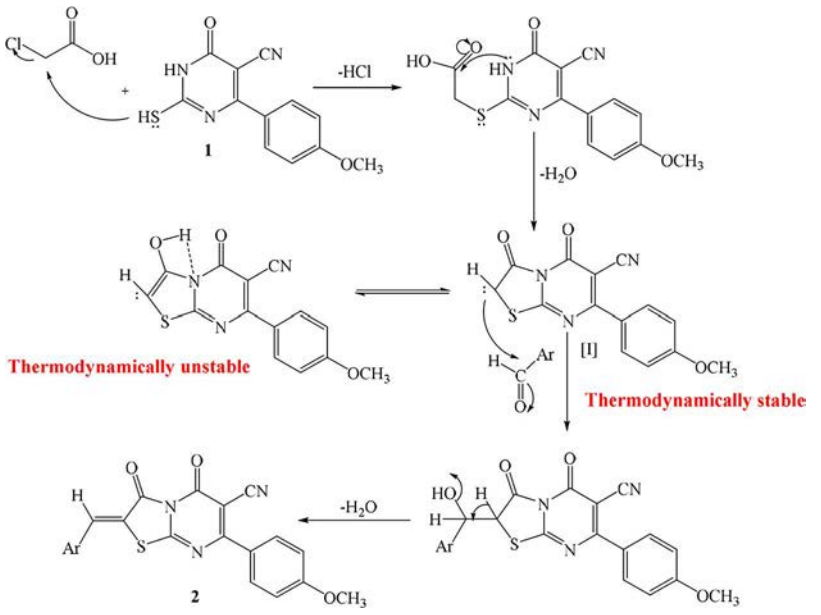
In connection with our program aiming to the synthesize and evaluate the biological activity of fused heterocycles,[17–19] we have tried to design and synthesiz a novel series of biologically active pyrimidine derivatives and evaluated their anticancer activity. Thus, thioxopyrimidine **1** was condensed with chloroacetic acid and different aromatic aldehydes in a mixture of acetic acid and acetic anhydride in the presence of fused sodium acetate to yield thiazolopyrimidine derivatives **2a–h** (Scheme 1).

The structures of compounds **2a–h** were confirmed by their analytical and spectral data. Thus the IR spectrum of **2** showed the disappearance of NH band and presence of characteristic absorption band corresponding to the vibrational coupling of carbonyl groups around 1769–1671 cm^{-1} which elucidate the rout of cyclization, this direction of cyclization may be due to the steric hindrance of anisyl group moiety.[20,21] ^{1}H NMR spectra for this group exhibited a singlet signal corresponding to the ethylinic protons at the range 7.07–8.46 ppm. Further evidence was gained from their mass spectra that showed the correct molecular ion peaks beside some of abundant peaks (cf. experimental). The mechanistic pathway for the transformation of **1** to **2** is represented in Scheme 2.

Compound **1** was allowed to react with the appropriate 2-chloro-*N*-substituted-phenylacetamide (**3a–c**) in the presence of potassium carbonate, in dimethylformamide (DMF) to yield the target compounds 2-((5-cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidin-2-yl)thio)-*N*-(4-aryl) acetamide and 3-((4-chloro-2-methylphenyl) amino)-7-(4-methoxyphenyl)-5-oxo-5*H*-thiazolo[3, 2-a]pyrimidine-6-carbonitrile (**4a-c**) in good yield. Synthesis of the intermediate and target compounds was accomplished



Scheme 1. Synthetic pathway of compounds **2–7**.



Scheme 2. Proposed mechanism for the synthesis of compound **2**.

according to the steps depicted in Scheme 1. The reaction proceeded through nucleophilic substitution reaction followed by cyclization in case of **4c**. IR spectra of **4a,b** revealed the existence of bands in the frequency of 3293–3308 and 1654–1711 cm^{-1} corresponding to NH_2, NH, and C=O groups, respectively. ^{1}H NMR spectra comfirmed the structure of compounds **4a–c**, where spectrum of **4a** showed signals at 4.16, 10.41 ppm corresponding to CH_2 and two NH group, respectively. Meanwhile, **4b** spectrum showed signals at 4.19, 10.67, and 13.78 ppm corresponding to CH_2, NH and NH_2 groups, respectively. However, ^{1}H-NMR spectrum of **4c** exhibited a singlet signal at 9.63 corresponding to NH which supported the suggested structure. On the other hand, *N*-alkylation of **1** with *p*-toluene sulfonyl chloride produced 6-(4-methoxyphenyl)-4-oxo-2-thioxo-1-tosyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**5**) which was performed by stirring in dry DMF utilizing potassium carbonate as base catalyst. The IR spectra of compound **5** showed the disappearance of NH bands and the appearance of characteristic absorption bands corresponding to SO_2 at 1167 cm^{-1}. The ^{1}H NMR spectra of compound **5** revealed two singlet signals at 2.69, 13.11 ppm assignable to CH_3 and NH groups, respectively. On the other hand, Compound **1** was alkylated with ethylchloroacetate, in the presence of anhydrous potassium carbonate to give the ethyl ester derivative **6**. Analytical and spectral data were in agreement with the proposed structure. The IR spectrum showed signals at 3301, 1735, and 1660 cm^{-1} corresponding to NH, (CO ester) and (CO) amide, respectively. The ^{1}H NMR spectrum of **6** revealed signals at 1.08, 4.05, and 13.7 ppm for CH_3, CH_2, and NH, respectively. The structure of compound **6** was established chemically by the reaction with hydrazine hydrate in boiling ethanol afforded 2-hydrazinyl-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile **7** (Scheme 1). The hydrazine derivative **7** was also isolated by treating **1** with hydrazine hydrate under the same reaction condition. The structure of compound **7** was corroborated by spectroscopic data.

The IR spectrum showed bands at 3324, 3277, and 1685 cm^{-1} attributed to NH_2, NH, and C=O groups, respectively. The ^{1}H NMR spectrum of compound **7** showed signals at 3.49 and 8.19 attributed to NH_2, NH and at 10.15 for NH (amide) groups, respectively. A plausible mechanism for the formation of the hydrazine derivative **7** is outlined in Scheme 3. Hydrazino pyrimidines can be considered as key starting precursor for synthesis of new pyrimidine derivatives which might have chemotherapeutic and biological activity. So, the hydrazino derivative **7** was reacted with some electrophilic reagents such as arylidine malononitrile, formic acid, acetic anhydride, cyclopentanone, benzoyl chloride, and cabon disulfide. Thus, when the hydrazino derivative **7** was subjected to react with arylidene in pyridine, it afforded the Schiff base product **8**. Synthetic pathway of compounds **8–11** (Scheme 4). The conversion of **7** to **8** could be visualized on the basis of the nucleophilic attack by nitrogen of the hydrazino group at the electron deficiency β- carbon of the arylidene followed by elimination of malononitrile molecule. (C.f. Scheme 5).

IR of **8** showed bands at 3223, 1658 cm^{-1} corresponding to NH, C=O groups, respectively. ^{1}H NMR of **8** revealed signals at 3.79, 3.82, 8.10, 12.19, and 12.37 corresponding to 2 OCH_3, olifinic CH, and 2NH groups. A strong evidence for the structure of **8** was gained chemically by reacting the hydrazine derivative **7** with *p*-methoxybenzaldehyde under the same condition. Refluxing of hydrazino derivative **7** with acetic anhydride afforded the mono acetyl derivative **9**. The spectral data of compound **9** was in agreement with the assigned structure. IR spectrum displayed bands at 3226, 1630–1660 cm^{-1} corresponding to NH, 2(CO) groups, respectively. ^{1}H NMR showed signals at 1.89, 10.19 ppm