



Ain Shams University
Faculty of Science
Chemistry Department

A Thesis Title

Synthesis of some Heterocyclic Compounds Containing Nitrogen With expected biological activity

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Synthesis of some Heterocyclic Compounds Containing Nitrogen
With expected biological activity

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To Chemistry Department, Faculty of Science, Ain Shams University.

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List of Contents

Contents	page no.
Acknowledgment	
Publication	
Summary	a
Introduction	
I) Synthesis of Pyrimidinone and Pyrimidinethione	
1) Biginelli's Reaction	1
2) Microwave Irradiation	3
3) From Arylidene	4
II) Reaction of pyrimidinethiones	
1) Reaction with oxalyl chloride	5
2) Reaction with ammonium acetate	5
3) Reaction with chloroacetic acid and aromatic aldehyde	6
4) Reaction with diazonium salts	6
5) Mannich reaction	7
6) Reaction with 2- chloro- N- substituted phenylacetamide	8
7) Reaction with phosphorus pentachloride and phosphorus oxychloride	8

8) Alkylation reaction	9
9) Reaction with bromomalononitrile	14
10) Reaction with NaOH (10%)	14
11) Reaction with chlorobenzenesulfonyl chloride	14
12) Reaction with ethanolamine	15
13) Reaction with chloroacetylchlorid	15
14) Hydrazinolysis	16
III) Reaction of Hydrazinopyrimidine	
1) Benzoylation reaction	17
2) Reaction with phenyl isothiocyanate	17
3) Acylation reaction	18
4) Schiff base reaction	19
5) Reaction with chloroacetyl chloride	19
6) Reaction with acetyl acetone	20
7) Reaction with ethyl acetoacetate	21
8) Reaction with phthalic anhydride	21
9) Reaction with $\text{NaNO}_2/\text{AcOH}$	22
10) Reaction with arylidine	22
11) Reaction with carbon disulfide	22

12) Reaction with ethyl chloroformate	23
13) Reaction with benzil	24
IV) Biological Activities	24
Result and Discussion	30
• Part 1: preparation of thiopyrimidinon derivative as key starting material for synthesis of some new pyrimidine and thiopyrimidine derivatives	31
• Part 2: Synthesis of hydrazinopyrimidine as key starting material for synthesis of some new pyrimidine derivatives	42
• Biological activities	60
Figures	74
Experiment	148
References	172
Arabic Summary	

List of Figures

Figure	Page
• Fig.(1a) IR Spectrum of Compound (5a)	74
• Fig.(1b) ^1H -NMR Spectrum of Compound (5a)	75
• Fig.(1c) ^{13}C -NMR Spectrum of Compound (5a)	76
• Fig.(2a) IR Spectrum of Compound (5b)	77
• Fig.(2b) ^1H -NMR Spectrum of Compound (5b)	78
• Fig.(2c) ^{13}C -NMR Spectrum of Compound (5b)	79
• Fig.(3a) IR Spectrum of Compound (7a)	80
• Fig.(3b) ^1H -NMR Spectrum of Compound (7a)	81
• Fig.(3c) ^{13}C -NMR Spectrum of Compound (7a)	82
• Fig.(4a) IR Spectrum of Compound (7b)	83
• Fig.(4b) ^1H -NMR Spectrum of Compound (7b)	84
• Fig.(4c) ^{13}C -NMR Spectrum of Compound (7b)	85
• Fig.(5a) IR Spectrum of Compound (7c)	86
• Fig.(5b) ^1H -NMR Spectrum of Compound (7c)	87
• Fig.(5c) ^{13}C -NMR Spectrum of Compound (7c)	88
• Fig.(6a) IR Spectrum of Compound (8)	89
• Fig.(6b) ^1H -NMR Spectrum of Compound (8)	90
• Fig.(7a) IR Spectrum of Compound (9)	91
• Fig.(7b) ^1H -NMR Spectrum of Compound (9)	92
• Fig. (8a) IR Spectrum of Compound (10)	93
• Fig.(8b) ^1H -NMR Spectrum of Compound (10)	94
• Fig.(9a) IR Spectrum of Compound (11)	95
• Fig. (9b) ^1H -NMR Spectrum of Compound (11)	96

• Fig.(10a) IR Spectrum of Compound (12)	97
• Fig. (10b) ^1H -NMR Spectrum of Compound (12)	98
• Fig.(11a) IR Spectrum of Compound (13)	99
• Fig. (11b) ^1H -NMR Spectrum of Compound (13)	100
• Fig.(12a) IR Spectrum of Compound (14)	101
• Fig. (12b) ^1H -NMR Spectrum of Compound (14)	102
• Fig. (12c) ^{13}C -NMR Spectrum of Compound (14)	103
• Fig. (13a) IR Spectrum of Compound (15)	104
• Fig. (13b) ^1H -NMR Spectrum of Compound (15)	105
• Fig. (13c) ^{13}C -NMR Spectrum of Compound (15)	106
• Fig. (14a) IR Spectrum of Compound (16)	107
• Fig. (14b) ^1H -NMR Spectrum of Compound (16)	108
• Fig. (14c) ^{13}C -NMR Spectrum of Compound (16)	109
• Fig. (15a) IR Spectrum of Compound (17)	110
• Fig. (15b) ^1H -NMR Spectrum of Compound (17)	111
• Fig. (15c) ^{13}C -NMR Spectrum of Compound (17)	112
• Fig. (16a) IR Spectrum of Compound (18)	113
• Fig. (16b) ^1H -NMR Spectrum of Compound (18)	114
• Fig. (16c) ^{13}C -NMR Spectrum of Compound (18)	115
• Fig. (17a) IR Spectrum of Compound (19)	116
• Fig. (17b) ^1H -NMR Spectrum of Compound (19)	117
• Fig. (17c) ^{13}C -NMR Spectrum of Compound (19)	118
• Fig. (18a) IR Spectrum of Compound (20)	119
• Fig. (18b) ^1H -NMR Spectrum of Compound (20)	120
• Fig. (18c) ^{13}C -NMR Spectrum of Compound (20)	121
• Fig. (19a) IR Spectrum of Compound (21)	122

• Fig. (19b) ^1H -NMR Spectrum of Compound (21)	123
• Fig. (19c) ^{13}C -NMR Spectrum of Compound (21)	124
• Fig. (20a) IR Spectrum of Compound (22)	125
• Fig. (20b) ^1H -NMR Spectrum of Compound (22)	126
• Fig. (20c) ^{13}C -NMR Spectrum of Compound (22)	127
• Fig. (21a) IR Spectrum of Compound (23a)	128
• Fig. (21b) ^1H -NMR Spectrum of Compound (23a)	129
• Fig. (22a) IR Spectrum of Compound (24)	130
• Fig. (22b) ^1H -NMR Spectrum of Compound (24)	131
• Fig. (23a) IR Spectrum of Compound (25)	132
• Fig. (23b) ^1H -NMR Spectrum of Compound (25)	133
• Fig. (24a) IR Spectrum of Compound (26)	134
• Fig. (24b) ^1H -NMR Spectrum of Compound (26)	135
• Fig. (25a) IR Spectrum of Compound (27)	136
• Fig. (25b) ^1H -NMR Spectrum of Compound (27)	137
• Fig. (26a) IR Spectrum of Compound (28)	138
• Fig. (26b) ^1H -NMR Spectrum of Compound (28)	139
• Fig. (27a) IR Spectrum of Compound (29)	140
• Fig. (27b) ^1H -NMR Spectrum of Compound (29)	141
• Fig. (28a) IR Spectrum of Compound (30)	142
• Fig. (28b) ^1H -NMR Spectrum of Compound (30)	143
• Fig. (29a) IR Spectrum of Compound (31a)	144
• Fig. (29b) ^1H -NMR Spectrum of Compound (31a)	145
• Fig. (30a) IR Spectrum of Compound (32a)	146
• Fig. (30b) ^1H -NMR Spectrum of Compound (32a)	147

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

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

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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-phenylacetamide 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.

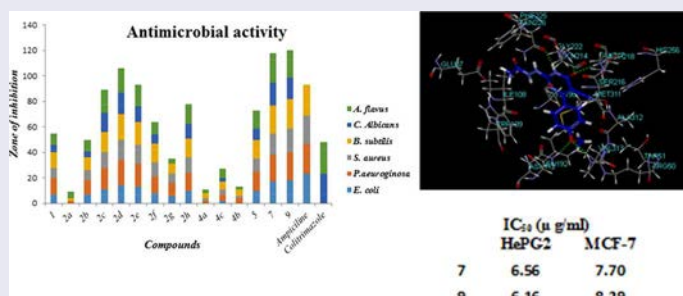
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GRAPHICAL ABSTRACT



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,

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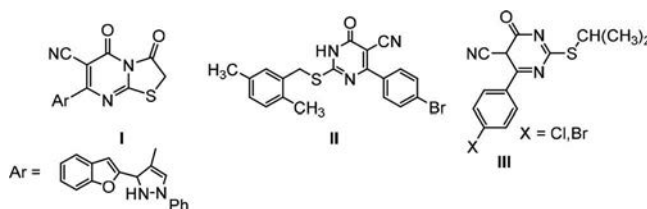


Figure 1. Structure of some potent 5-cyano-2-thiouracils.

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 deoxyuridylylate (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.

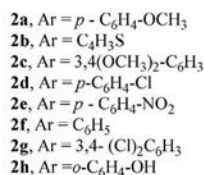
Results and discussion

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 $1769\text{--}1671\text{ cm}^{-1}$ which elucidate the rout of cyclization, this direction of cyclization may be due to the steric hindrance of anisyl group moiety.^[20,21] ¹H 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. ^1H NMR spectra confirmed 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, ^1H -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 ^1H 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 ^1H 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 ^1H 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 arylidene malononitrile, formic acid, acetic anhydride, cyclopentanone, benzoyl chloride, and carbon 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. ^1H NMR of **8** revealed signals at 3.79, 3.82, 8.10, 12.19, and 12.37 corresponding to 2 OCH_3 , olefinic 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. ^1H NMR showed signals at 1.89, 10.19 ppm