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Review

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Aminouracil and aminothiouracil as versatile precursors for a variety of heterocyclic systems

Hadeer M. Diab, Mostafa E. Salem, Ismail A. Abdelhamid* and Ahmed H. M. Elwahy*

Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt
E-mail: aelwahy@hotmail.com

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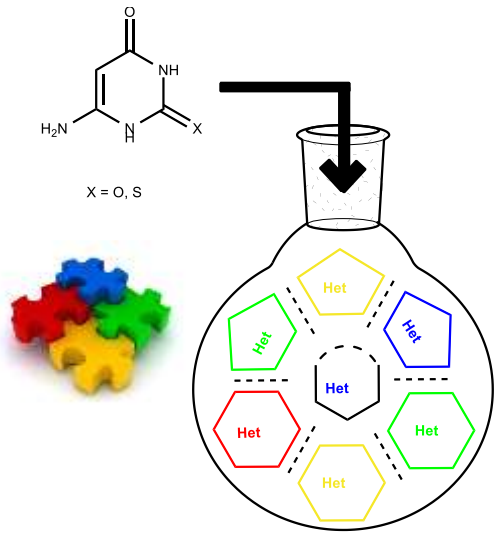
Abstract

Heterocycles, particularly pyrimidine derivatives, which are present in many natural products and many interesting synthetic compounds, are the most diverse class of organic compounds and have significant chemical, biomedical and industrial applications. Uracil, a pyrimidine derivative, constitutes a promising structure in widespread natural products and many of its derivatives exhibited significant pharmacological properties. They have been widely used as starting materials for the synthesis of a huge number of biologically important nitrogen-containing heterocycles. This review casts light on various methods for the construction of different heterocyclic systems utilizing aminouracil and aminothiouracil as versatile precursors. The heterocyclic systems mentioned in this review are categorized according to the type of the heterocyclic systems.



Keywords: Aminouracil, aminothiouracil, synthesis, heterocyclic systems

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1. Introduction

Heterocyclic compounds are being used in several areas, including agrochemistry, medicine, polymer science, and various industries. They have gained significant interest in the design of biologically active molecules and are of great importance for the chemistry of life since their structural subunits occur in many natural products such as vitamins, hormones, and antibiotics. They play an active role in numerous medical applications as anti-viral, anti-bacterial, anti-inflammatory, anti-fungal, and anti-tumor medications. Heterocyclic compounds are also used as sanitizers, developers, antioxidants, corrosion inhibitors, copolymers, and dyestuffs. In particular, nitrogen-containing heterocycles represent a highly important class of compounds that are widely used in materials science and medicinal chemistry.[1–8] They generally show superior pharmaceutical effects compared to non-nitrogen analogues. N-Heterocyclic compounds are constituents of many biologically important molecules, including many vitamins, nucleic acids, pharmaceuticals, antibiotics, dyes, and agrochemicals. [9–12] In addition, nitrogen-containing heterocycles play a significant role in coordination chemistry.[13]

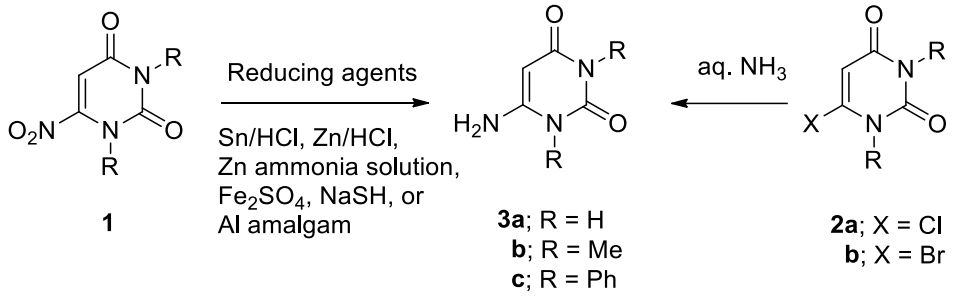
Among various nitrogen-containing heterocycles, pyrimidine derivatives constitute an interesting subclass. They are present in many natural products, such as vitamin B_1 (thiamine), and many interesting synthetic compounds, such as barbituric acid and veronal, which are used as hypnotic agents.[14,15] They demonstrated a wide variety of biological properties, including antibacterial[15–17], antifungal[15,18], antileishmanial[19], anti-inflammatory[20], analgesic[21], antihypertensive[22,23], antipyretic[24], antiviral[25], antidiabetic[26], antiallergic[27], antioxidant[28,29], antihistaminic[30], herbicidal [31], and anticancer activities [32,33].

Uracil is a very important representative of the pyrimidines. It is one of the five nucleobases and constitutes a promising structure in widespread natural products[34]. Uracil derivatives are interesting molecules in the area of drug discovery[35] since they exhibit significant pharmacological applications as antiviral[36], anticancer, cytotoxic[37], antimycobacterial[38], anti-inflammatory[39], antitumor[34,40], and antibacterial[41]. Moreover, some uracil derivatives showed antithrombotic[42], antidotal[43] and potent inhibitors of interleukin-8-induced neutrophil chemotaxis [44]. Some uracils, particularly 6-aminouracils and their corresponding thiouracil derivatives, have been widely used as starting materials for the synthesis of a huge number of biologically important nitrogen-containing heterocycles [45–48].

In continuation of our interest in reviewing various synthetic approaches to heterocyclic systems, this review highlights various synthetic methods used for the preparation of different heterocyclic systems utilizing aminouracil and aminothiouracil as versatile precursors. Depending on the size of the heterocyclic ring as well as the location and number of heteroatoms, heterocyclic compounds mentioned are arranged in this review. The review will cover the literature in this field from 2015-2020. A few of the recent reviews [49–56] on this subject appear not to have paid sufficient attention to fused uracil systems in an ordered manner with respect to the ring system.

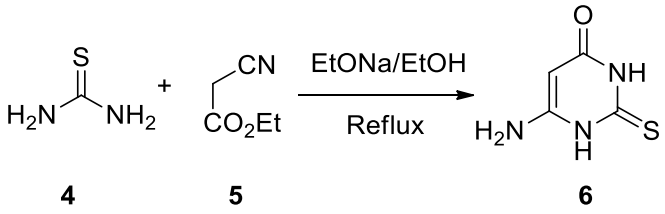
2. Synthesis of Aminouracil and Aminothiouracil

Two strategies have been described for the synthesis of 6-aminouracil **3**. The first one includes the amination of 6-chlorouracil **2a** or 6-bromouracil **2b** upon treatment with aqueous ammonia. The second strategy depends mainly on the reduction of the corresponding 6-nitrouracil **1** with different reducing agents (Scheme 1). [57–62]



Scheme 1. Synthesis of 6-aminouracils **3a-c**.

The most common method described for the synthesis of 6-aminothiouracil was the reaction of thiourea (**4**) with ethyl cyanoacetate (**5**) in the presence of sodium ethoxide in ethanol at reflux.[63,64]



Scheme 2. Synthesis of 6-aminothiouracil **6**.

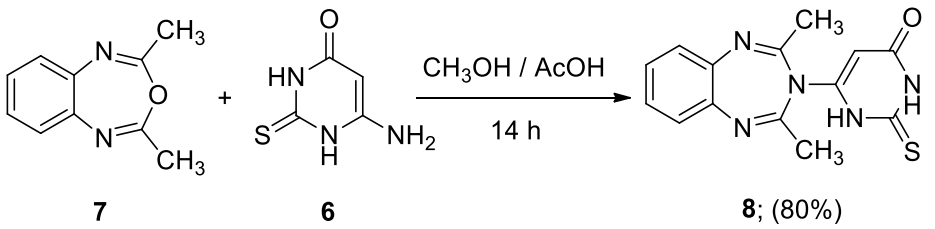
3. Synthesis of Heterocyclic Compounds using aminouracil and Aminothiouracil

3.1. Synthesis of substituted aminouracil (thiouracil) derivatives

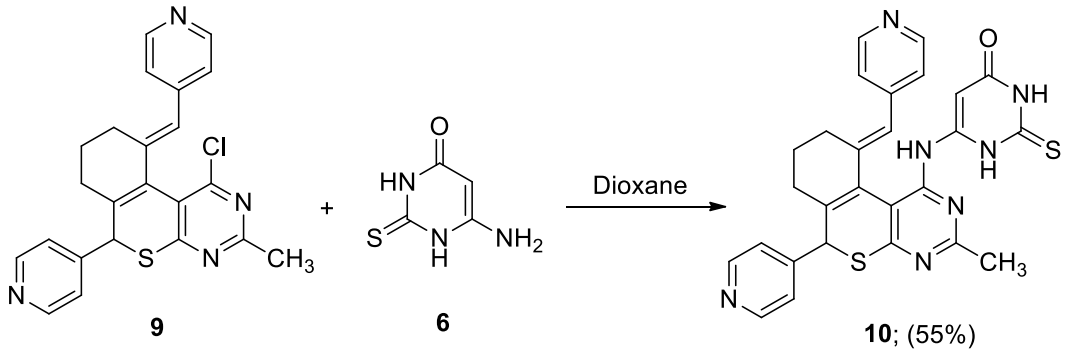
These uracil derivatives have been prepared by direct alkylation reactions.

3.1.1 *N*-Alkylation reaction. 2,4-Dimethylbenzo[*d*][1,3,6]oxadiazepine (**7**) was reacted with 6-aminothiouracil (**6**) under acidic conditions through nucleophilic substitution reaction to give compound **8** in 80% yield. The biological cytotoxic activity of compound **8** was studied using an in *vitro* Ehrlich ascites assay[65] which showed a moderate cytotoxic effect (Scheme 3).[66]

A nucleophilic amination of isothiochromeno[3,4-*d*]pyrimidin-1-one **9** with aminothiouracil (**6**) in dioxane at reflux afforded isothiochromeno[3,4-*d*]pyrimidin-1-yl)amino)-2-thioxo-2,3-dihydro pyrimidin-4(1*H*)-one **10** in 55% yield (Scheme 4).[67]

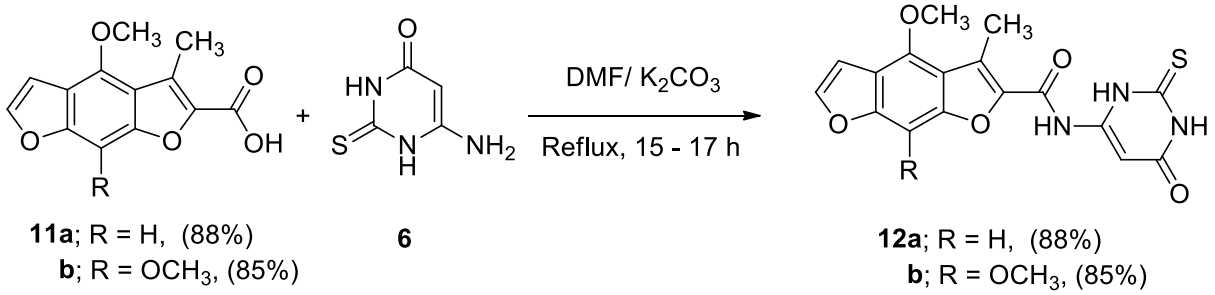


Scheme 3. Synthesis of 6-(2,4-dimethyl-3*H*-benzo[*f*][1,3,5]triazepin-3-yl)-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**8**).



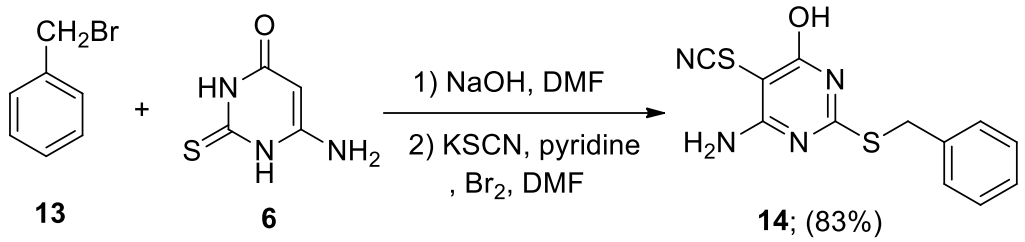
Scheme 4. Synthesis of isothiochromeno[3,4-*d*]pyrimidin-1-yl)amino)-2-thioxo-2,3-dihydro pyrimidin-4(1*H*)-one **10**.

2-Thioxo(1,2,3,6-tetrahydropyrimidin-4-yl)benzo[1,2-*b*:5,4-*b*`]difuran-2-carboxamide **12a** and **12b** were prepared in 88% and 85% yield, respectively, through reaction of 6-amino-2-thiouracil (**6**) with benzo[1,2-*b*:5,4-*b*`]difuran-2-carboxylic acid **11a** and **11b** in DMF at reflux and in the presence of anhydrous potassium carbonate (Scheme 5).[68]



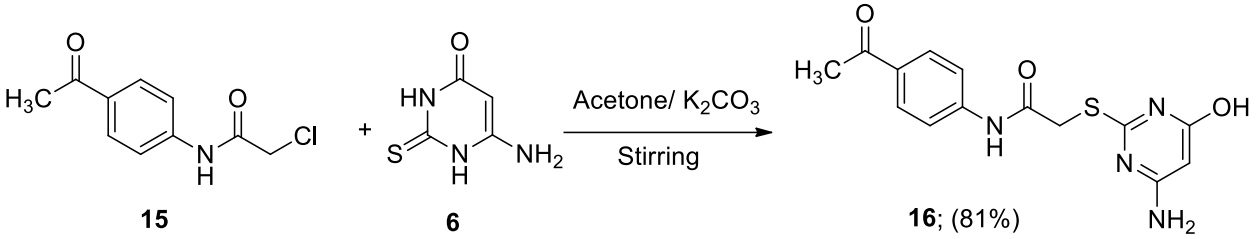
Scheme 5. Synthesis of 2-thioxo(1,2,3,6-tetrahydropyrimidin-4-yl)benzo[1,2-*b*:5,4-*b*`]difuran-2-carboxamides **12a** and **12b.**

3.1.2 *S*-Alkylation reaction. Gao *et al*. [69] reported the synthesis of 6-amino-2-(benzylthio)-5-thiocyanatopyrimidin-4-ol **14** in 83% yield upon the reaction of 6-aminothiouracil (**6**) with benzyl bromide (**13**) in the presence of sodium hydroxide followed by treatment with potassium thiocyanate in a mixture of pyridine and bromine in DMF (Scheme 6).



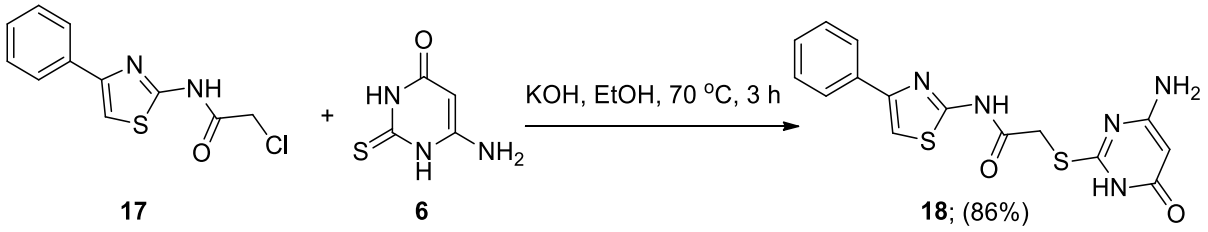
Scheme 6. Synthesis of 6-amino-2-(benzylthio)-5-thiocyanatopyrimidin-4-ol (**14**).

N-(4-Acetylphenyl)-2-((4-amino-6-hydroxypyrimidin-2-yl)thio)acetamide (**16**) was synthesized in 81% yield by the reaction of 6-aminothiouracil (**6**) with *N*-(4-acetylphenyl)-2-chloroacetamide (**15**) in acetone in the presence of potassium carbonate as a catalyst (Scheme 7). [70]



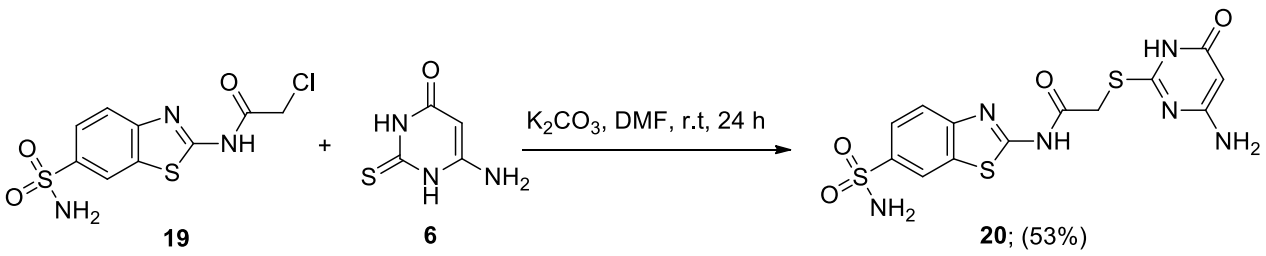
Scheme 7. Synthesis of *N*-(4-acetylphenyl)-2-((4-amino-6-hydroxypyrimidin-2-yl)thio) acetamide (**16**).

Yan *et al*.[71] reported the synthesis of 2-((4-amino-6-oxo-1,6-dihydropyrimidin-2-yl)thio)-*N*-(4-phenylthiazol-2-yl)acetamide (**18**) in 86% yield through the direct alkylation reaction of *N*-(4-acetyl phenyl)-2-chloroacetamide (**17**) with 6-aminothiouracil (**16**) under basic condition (Scheme 8).



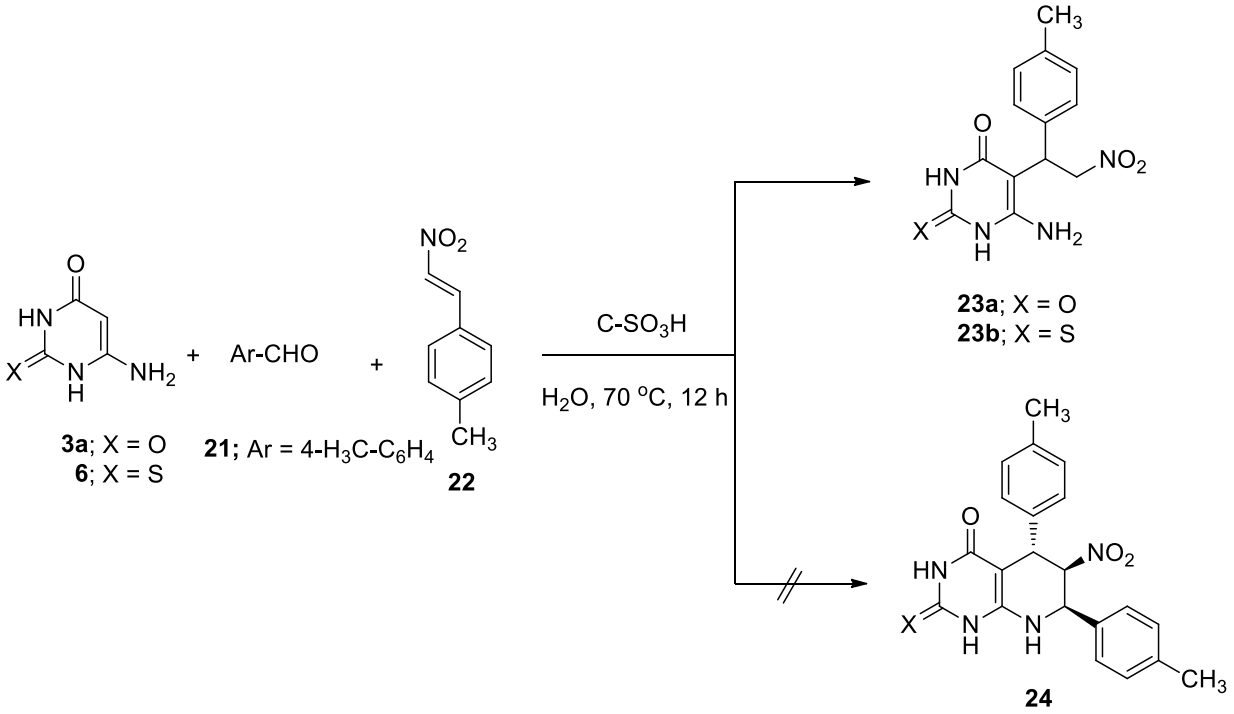
Scheme 8. Synthesis of 2-((4-amino-6-oxo-1,6-dihydropyrimidin-2-yl)thio)-*N*-(4-phenylthiazol-2-yl)acetamide (**18**) .

Ibrahim *et al*.[72] reported the synthesis of 2-[(4-amino-6-oxo-1,6-dihydropyrimidin-2-yl)thio]-*N*-[6-(aminosulfonyl)-1,3-benzothiazol-2-yl]acetamide (**20**) in 53% yield through *S*-alkylation of 2-chloro-*N*-(6-sulfamoylbenzo[*d*]thiazol-2-yl)acetamide (**19**) with 6-aminothiouracil (**6**) in DMF and in the presence of K_2CO_3. The biological activity of compound **20** was investigated as an inhibitor of different metalloenzymes of carbonic anhydrase CA I and II, IX, and XII. Compound **20** was found to exhibit a moderate inhibition effect towards CAII and CA XII compared to the other isoforms (Scheme 9).



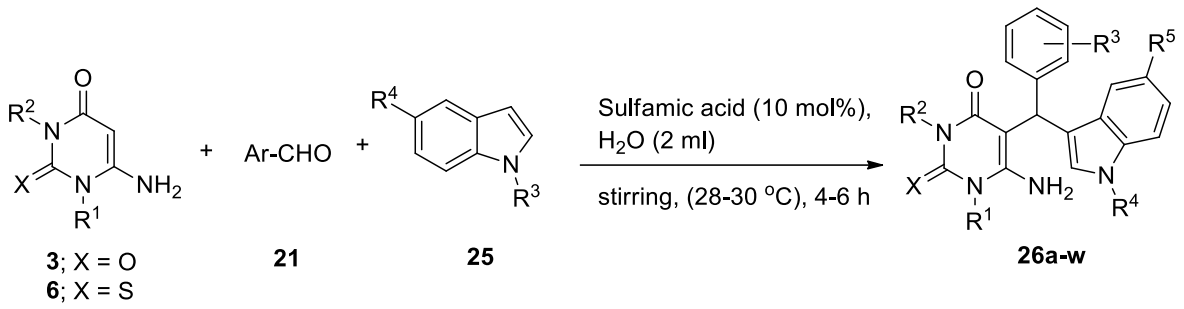
Scheme 9. Synthesis of 2-[(4-amino-6-oxo-1,6-dihydropyrimidin-2-yl)thio]-*N*-[6-(aminosulfonyl)-1,3-benzothiazol-2-yl]acetamide (**20**) .

3.1.3 *C*-Alkylation reaction. Zhang *et al*.[73] reported that the reaction of aminouracil derivatives **3a** and **6** with 4-methylbenzaldehyde (**21**) and 1-methyl-4-(2-nitrovinyl)benzene (**22**) using a recoverable carbonaceous acid (C-SO_3H) as a green catalyst afforded the substituted aminopyrimidin-2,4 diones **23a** and **23b** rather than the expected pyrido[2,3-*d*]pyrimidine **24** (Scheme 10).



Scheme 10. Synthesis of 6-amino-5-(2-nitro-1-(*p*-tolyl)ethyl)-2,3-dihydropyrimidin-4(1*H*)-one derivatives **23a** and **23b**.

Brahmachari *et al*. [74] developed a convenient green method for the preparation of 5-((indol-3-yl) (aryl)methyl)-6-aminopyrimidinediones **24a-w** through a multi-component reaction of aryl aldehydes **21** with 6-aminouracil derivatives **3** and **6** and indoles **25** under acidic condition (Scheme 11, Table 1).

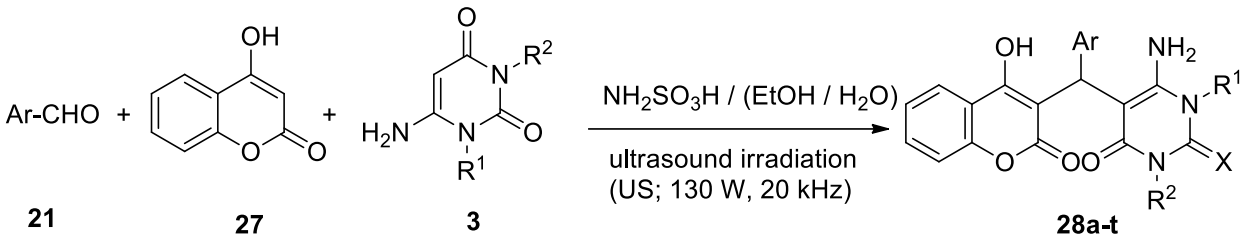


Scheme 11. Synthesis of 5-((1*H*-indol-3-yl)(aryl)methyl)-6-aminopyrimidinediones and 6-amino-2-mercapto-5-((1-methyl-1*H*-indol-3-yl)(aryl)methyl)pyrimidinediones **26a-w**.

Table 1. % Yields of compounds **26a-w**

Products	R^1	R^2	R^3	R^4	Ar	X	Yield%
a	H	H	H	H	C_6H_5	O	89
b	H	H	H	NO_2	C_6H_5	O	97
c	CH_3	H	H	NO_2	C_6H_5	O	80
d	CH_3	H	H	OCH_3	C_6H_5	O	89
e	H	H	H	OCH_3	4-H_3C-C_6H_4	O	97
f	CH_3	H	H	OCH_3	4-H_3C-C_6H_4	O	95
g	H	H	H	H	4-H_3CO-C_6H_4	O	82
h	H	H	H	OCH_3	4-H_3CO-C_6H_4	O	96
i	H	H	H	NO_2	4-H_3CO-C_6H_4	O	92
j	H	H	H	H	4-O_2N-C_6H_4	O	91
k	CH_3	H	H	H	4-O_2N-C_6H_4	O	97
l	CH_3	CH_3	H	H	4-O_2N-C_6H_4	O	96
m	H	H	H	NO_2	4-O_2N-C_6H_4	O	94
n	H	H	H	NO_2	4-F-C_6H_4	O	60
o	CH_3	H	H	F	2-F-C_6H_4	O	95
p	H	H	CH_3	H	3-Cl-C_6H_4	O	91
q	H	H	H	H	3-Br-C_6H_4	O	90
r	H	H	H	OCH_3	3-Br-C_6H_4	O	96
s	H	H	H	H	4-NC-C_6H_4	O	95
t	H	H	H	H	4-$(CH_3)_2N$-C_6H_4	O	96
u	H	H	H	Br	2-HOOC-C_6H_4	O	51
v	H	H	H	H	C_6H_5	S	96
w	H	H	H	H	4-F_3C-C_6H_4	S	95

A series of substituted 6-amino-5-((4-hydroxy-2-oxo-2*H*-chromen-3-yl)(aryl)methyl)pyrimidine-2,4-(1*H*,3*H*)-diones **28a-t** was synthesized *via* a one-pot reaction of aryl aldehydes **21**, 4-hydroxycoumarin (**27**), and 6-aminouracil derivatives **3** using sulfamic acid as an eco-friendly solid acid-catalyst in aqueous ethanol and under ultrasound irradiation as a green synthetic protocol (Scheme 12, Table 2). [75]

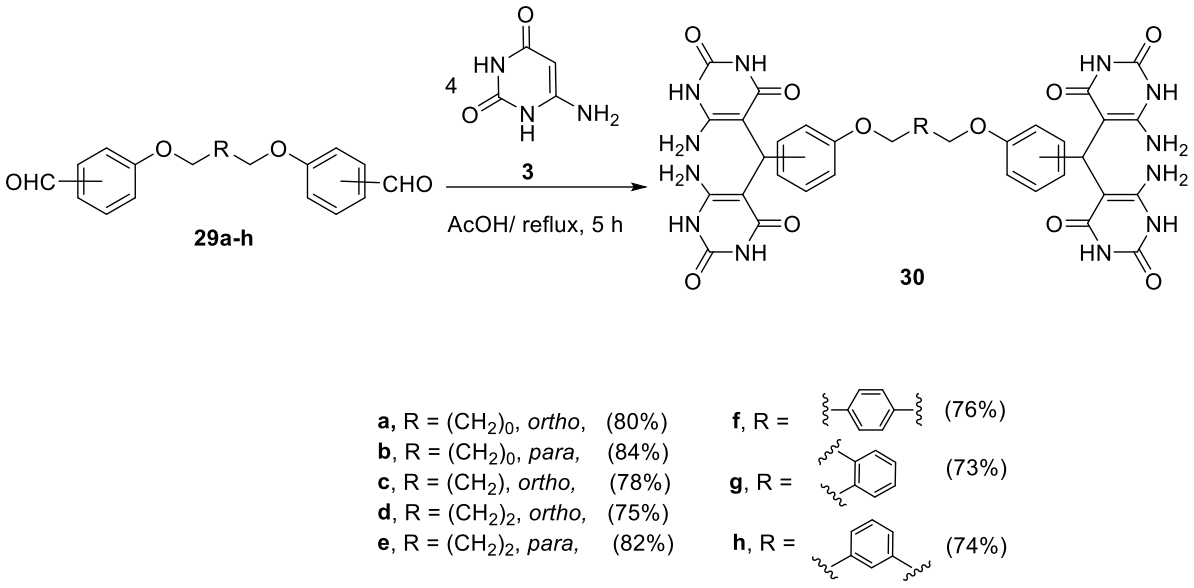


Scheme 12. Synthesis of 6-amino-5-((4- hydroxy-2-oxo-2*H*-chromen-3- yl)(aryl)methyl) pyrimidine-2,4-(1*H*,3*H*)-diones **28a-t**.

Table 2. % Yields of compounds **28a-t**

Products	R^1	R^2	Ar	Yield%
a	H	H	C_6H_5	83
b	H	H	3-Br-C_6H_4	86
c	H	H	4-F-C_6H_4	95
d	H	H	4-NC-C_6H_4	93
e	H	H	4-F_3C-C_6H_4	91
f	H	H	4-OHC-C_6H_4	92
g	H	H	4-H_3C-C_6H_4	98
h	H	H	4-H_3CO-C_6H_4	98
i	H	H	3-CH_3O-4-HO-C_6H_3	87
j	H	H	3,4-(O–CH_2–O)-C_6H_3	93
k	CH_3	H	C_6H_5	98
l	CH_3	H	3-H_3C-C_6H_4	96
m	CH_3	H	4-H_3CO-C_6H_4	98
n	CH_3	H	3,4-$(H_3CO)_2$-C_6H_3	81
o	CH_3	H	3,4,5-$(H_3CO)_3$-C_6H_3	95
p	CH_3	CH_3	C_6H_5	94
q	CH_3	CH_3	4-H_3C-C_6H_4	97
r	CH_3	CH_3	4-H_3CO-3-HO-C_6H_3	91
s	CH_3	CH_3	3-H_3CO-4-HO-C_6H_3	97
t	CH_3	CH_3	3,4-$(H_3CO)_2$-C_6H_3	80

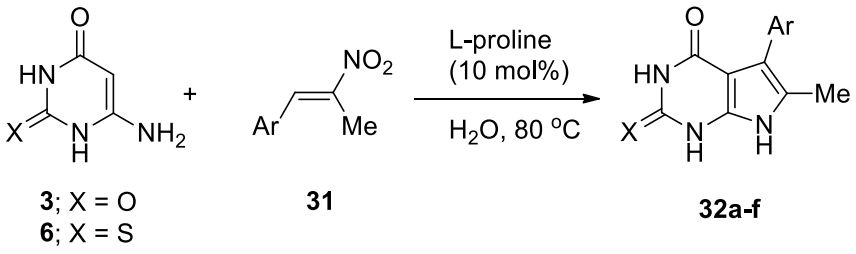
Abdelmoniem *et al*.[76] reported that the reaction of the appropriate *bis*(aldehydes) **29a-h** with 4 equivalents of 6-aminouracil (**3**) in acetic acid at reflux gave the tetrakis(6-aminopyrimidine-2,4(1*H*,3*H*)-dione) derivatives **30a-h** in a good yields (Scheme 13).



Scheme 13. Synthesis of tetrakis(6-aminopyrimidine-2,4(1*H*,3*H*)-dione) derivatives **30a-h**.

3.2. Synthesis of uracil-fused heterocycles

3.2.1 Synthesis of fused bicyclic systems. 3.2.1.1 Fused [5-6]systems: Three heteroatoms. 3.2.1.1.1 Synthesis of pyrrolo[2,3-*d*]pyrimidines. Li *et al*.[77] revealed the synthesis of pyrrolo[2,3-*d*]pyrimidin-4-ones **32a–f** *via* reaction of nitroolefins **31** with 6-aminopyrimidinedione derivatives **3** or **6** using *L*-proline as an acid catalyst (Scheme 14, Table 3).



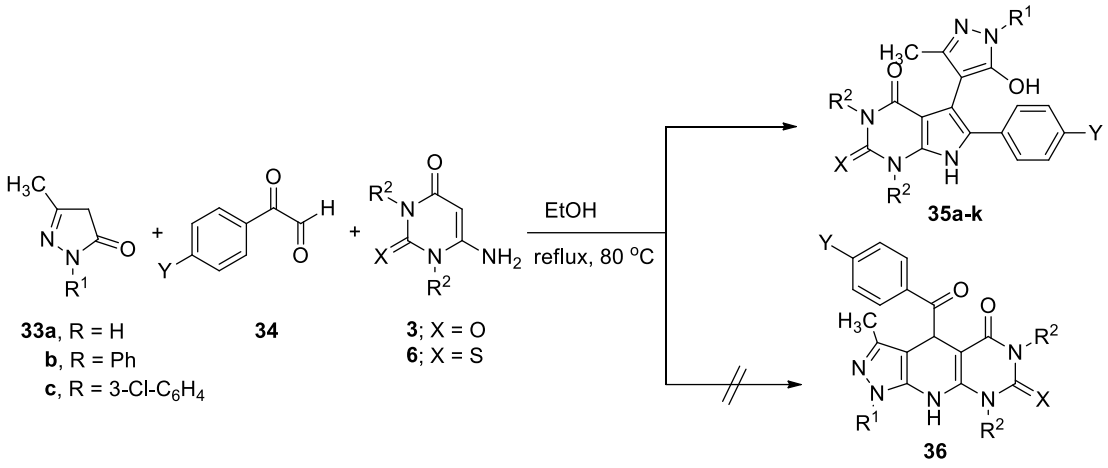
Scheme 14. Synthesis of pyrrolo[2,3-*d*]pyrimidin-4-ones **32a-f**.

Table 3. % Yields of compounds **32a-f**

Products	Ar	X	Yield%
a	4-F-C_6H_4	O	71%
b	4-Cl-C_6H_4	O	65%
c	4-Br-C_6H_4	O	61%
d	C_6H_5	S	71%
e	4-F-C_6H_4	S	73%
f	4-H_3C-C_6H_4	S	54%

Bayat *et al*.[78] reported a free catalytic approach for regioselective synthesis of pyrrolo[2,3-*d*]pyrimidine derivatives **35a-k** instead of the expected pentaaza-cyclopenta[*b*]naphthalen-5-ones **36** through a three

component reaction of 3-methyl-2-pyrazoline-5-one derivatives **33a-c**, arylglyoxal **34,** and 6-aminouracil derivatives **3** or **6** in ethanol at reflux (Scheme 15, Table 4).

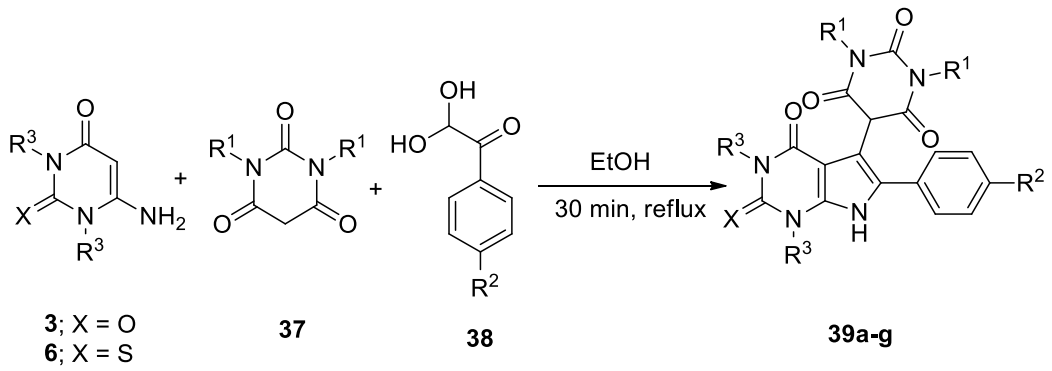


Scheme 15. Synthesis of pyrrolo[2,3-*d*]pyrimidine derivatives **35a-k**.

Table 4. % Yields of compounds **35a-k**

Products	R^1	R^2	Y	X	Yield%
a	C_6H_5	H	H	S	95
b	C_6H_5	H	F	S	80
c	3-Cl-C_6H_4	H	H	S	98
d	3-Cl-C_6H_4	H	F	S	83
e	2-Cl-C_6H_4	H	F	S	85
f	H	H	H	S	82
g	C_6H_5	CH_3	H	O	92
h	C_6H_5	CH_3	F	O	85
i	3-Cl-C_6H_4	CH_3	H	O	98
j	3-Cl-C_6H_4	CH_3	F	O	89
k	H	CH_3	H	O	80

A series of pyrrolo[2,3-*d*]pyrimidine derivatives **39a-g** were prepared in good yields through a one-pot reaction of arylglyoxal hydrate **38** with aminouracil derivatives **3** or **6** and barbituric acid **37**. However, the reaction was carried out using different conditions, the best result was achieved using used ethanol as solvent at reflux (Scheme 16, Table 5).[79]

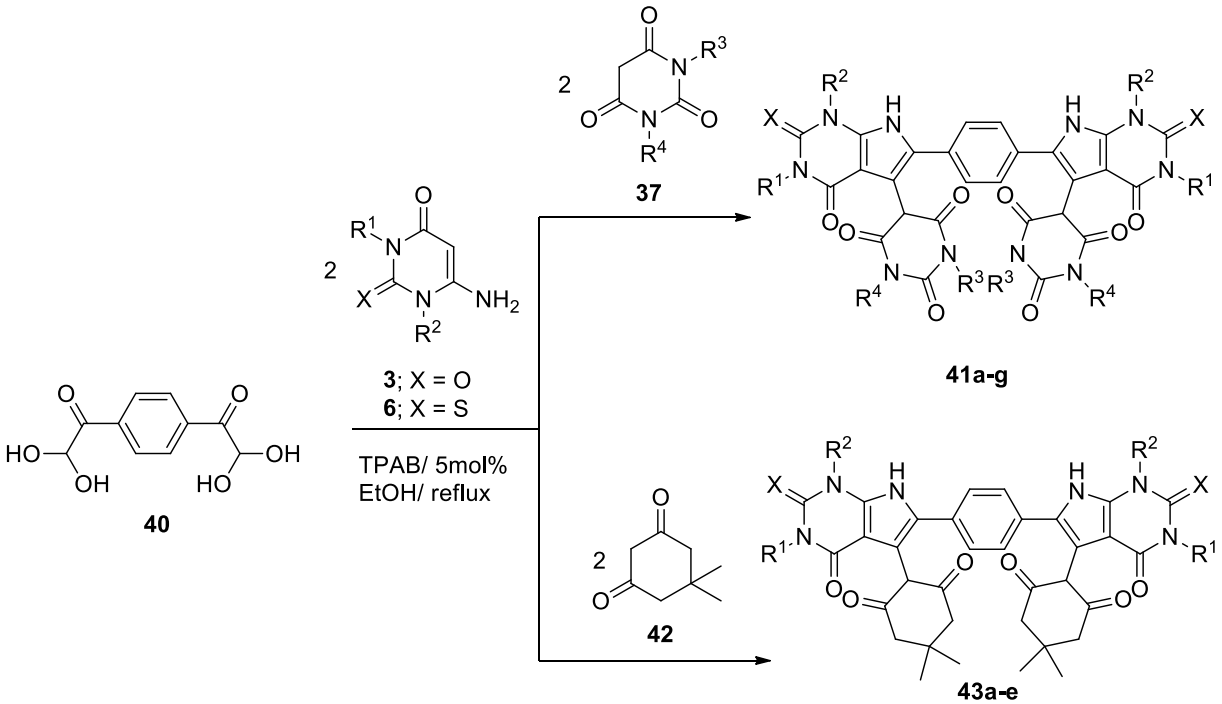


Scheme 16. Synthesis of pyrrolo[2,3-*d*]pyrimidine derivatives **39a-g**.

Table 5. % Yields of compounds **39a-g**

Products	R^1	R^2	R^3	X	Yield%
a	CH_3	H	CH_3	O	88
b	H	H	CH_3	O	86
c	CH_3	OCH_3	H	O	79
d	H	OCH_3	CH_3	O	84
e	CH_3	H	H	S	76
f	CH_3	Br	H	S	82
g	H	Br	H	S	74

Sabegh *et al*.[80] reported the synthesis of *bis*-pyrrolo[2,3-*d*]pyrimidine derivatives **41a–g** and **43a-e** through a multicomponent reaction of 1,4-phenylene-bis-glyoxal (**40**) with 6-aminouracil derivatives **3** or **6** and either barbituric acid **37** or dimedone (**42**) (Scheme 17, Table 6).

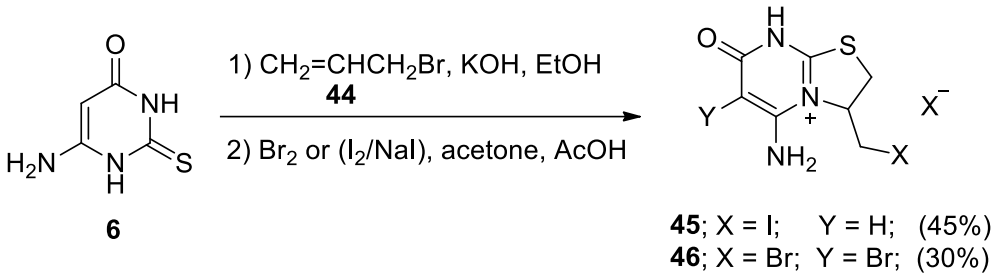


Scheme 17. Synthesis of *bis*-pyrrolo[2,3-*d*]pyrimidine derivatives **41a–g** and **43a–e**.

Table 6. % Yields of compounds **41a–g** and **43a–e**

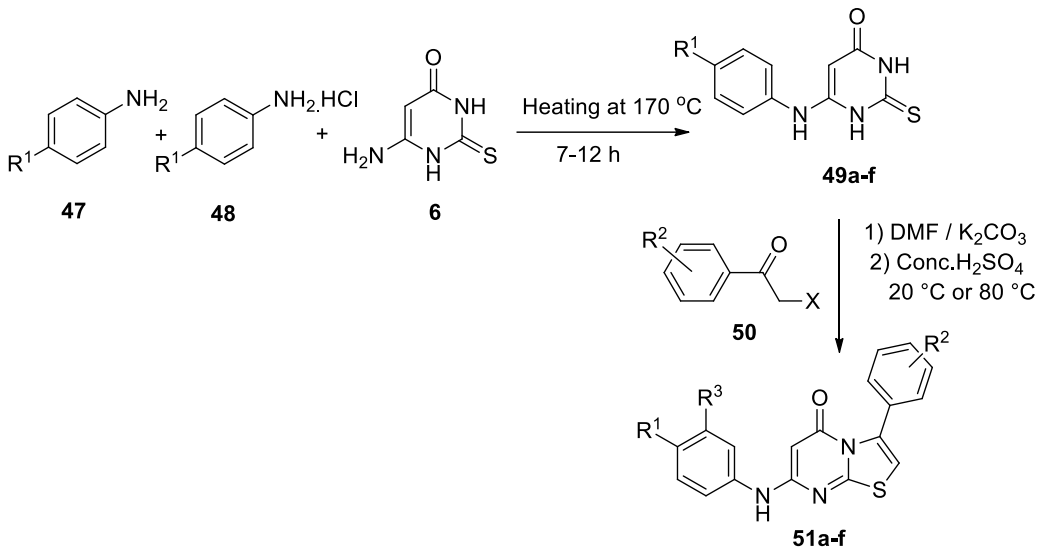
Products	R^1	R^2	R^3	R^4	X	Yield%
41a	H	H	H	H	O	95
41b	H	H	CH_3	CH_3	O	96
41c	H	CH_3	H	H	O	96
41d	H	CH_3	CH_3	CH_3	O	94
41e	CH_3	CH_3	CH_3	CH_3	O	95
41f	CH_2CH_3	CH_2CH_3	CH_3	CH_3	O	92
41g	H	H	CH_3	CH_3	S	93
43a	H	H	-	-	O	93
43b	H	CH_3	-	-	O	95
43c	CH_3	CH_3	-	-	O	92
43d	CH_2CH_3	CH_2CH_3	-	-	O	90
43e	H	H	-	-	S	94

3.2.1.1.2 Synthesis of thiazolo[3,2-*a*]pyrimidine. The reaction of 6-amino-2-thiouracil (**6**) with 3-bromoprop-1-ene (**44**) in the presence of KOH in aqueous ethanol gave firstly, the corresponding *S*-alkyl derivatives. Subsequent treatment of the latter compound with either iodine or bromine in acetic acid afforded thiazolo[3,2-*a*]pyrimidin-4-ium halides **45** and **46** in 45% and 30% yield, respectively (Scheme 18).[81]



Scheme 18. Synthesis of thiazolo[3,2-*a*]pyrimidin-4-ium halides **45** and **46**.

Thiazolo[3,2-*a*]pyrimidin-5-ones **51a-f** were obtained in good yields *via* reaction of the appropriately substituted phenacyl halides **50** with 6-substituted anilino-2-thiouracil **49** (prepared from the reaction of 6-amino-2-thiouracil (**6**) with substituted anilines **47** in the presence of aniline hydrochloride **48** at high temperature) in the presence of anhydrous potassium carbonate followed by cyclization upon heating with conc. H_2SO_4. Compounds **51a-f** were reported to display significant antibacterial inhibitory activities against *Mycobacterium smegmatis* (Scheme 19, Table 7).[82]

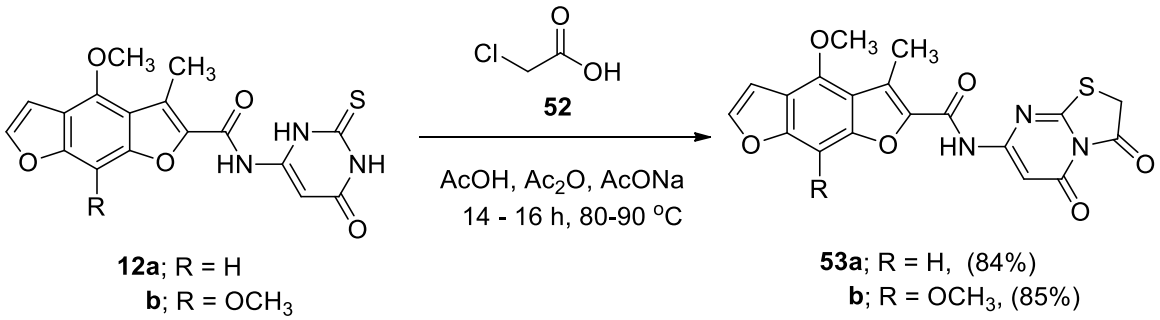


Scheme 19. Synthesis of thiazolo[3,2-*a*]pyrimidin-5-ones **51a-f**.

Table 7. % Yields of compounds **51a–f**

Products	R^1	R^2	R^3	Yield%
a	SO_3H	3-NO_2	H	92
b	SO_3H	4-NO_2	H	92
c	CH_3	3-NO_2	SO_3H	91
d	CH_3	4-NO_2	SO_3H	89
e	OCH_3	3-NO_2	SO_3H	79
f	OCH_3	4-NO_2	SO_3H	80

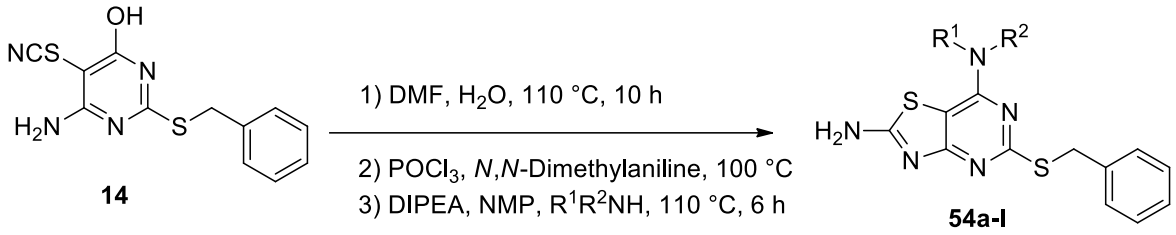
Thiazolo[3,2-*a*]pyrimidin-7-ylbenzo[1,2-*b*:5,4-*b*`]difuran-2-carboxamides **53a** and **53b** were synthesized in 84% and 85% yields, respectively, upon reaction of 2-thioxo-1,2,3,6-tetrahydro pyrimidin-4-yl)benzo[1,2-*b*:5,4-*b*`]difuran-2-carboxamide **12a** and **12b**, respectively, with chloroacetic acid **52** in a mixture of glacial acetic acid/acetic anhydride and anhydrous sodium acetate. Thiazolopyrimidines **53a** and **53b** were found to display a high inhibition effect on cyclooxygenase enzyme (COX). Besides, the same compounds were reported to possess high anti-inflammatory activities expressed in a significant reduction in interleukin-1 beta (IL-1 β) concentration (Scheme 20).[68]



Scheme 20. Synthesis of thiazolo[3,2-*a*]pyrimidin-7-ylbenzo[1,2-*b*:5,4-*b*`]difuran-2-carboxamides **53a** and **53b**.

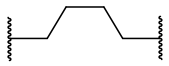
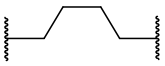
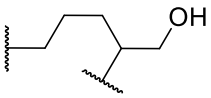
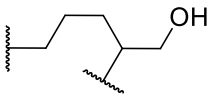
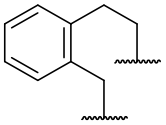
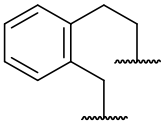
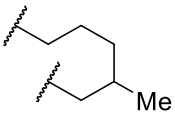
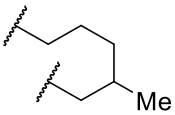
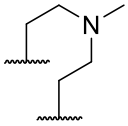
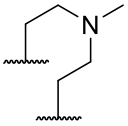
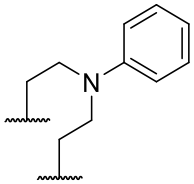
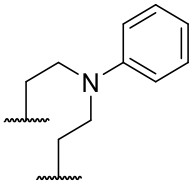
3.2.1.2. Fused [5-6]systems: Four heteroatoms. 3.2.1.2.1. Synthesis of thiazolo[4,5-*d*]pyrimidine. A series of thiazolo[4,5-*d*]pyrimidine derivatives **54a-l** were synthesized in 38-51% yield, *via* a cyclocondensation of 6-amino-2-(benzylthio)-5-thiocyanatopyrimidin-4-ol (**14**) in DMF at reflux followed by treatment with $POCl_3$ in *N*,*N*-dimethylaniline, and subsequent reaction with the appropriate secondary amine (Scheme 21, Table 8).

The anti-cancer activity of thiazolo[4,5-*d*]pyrimidine derivatives **54a-l** was studied against colorectal cancer by testing its inhibitory effect on PAK4 (p21-activated kinase 4). It was found that all compounds have a potential PAK4 (p21-activated kinase 4) inhibitory effect. In particular, compound **54j** revealed the highest inhibitory effect among the tested compounds.[83]

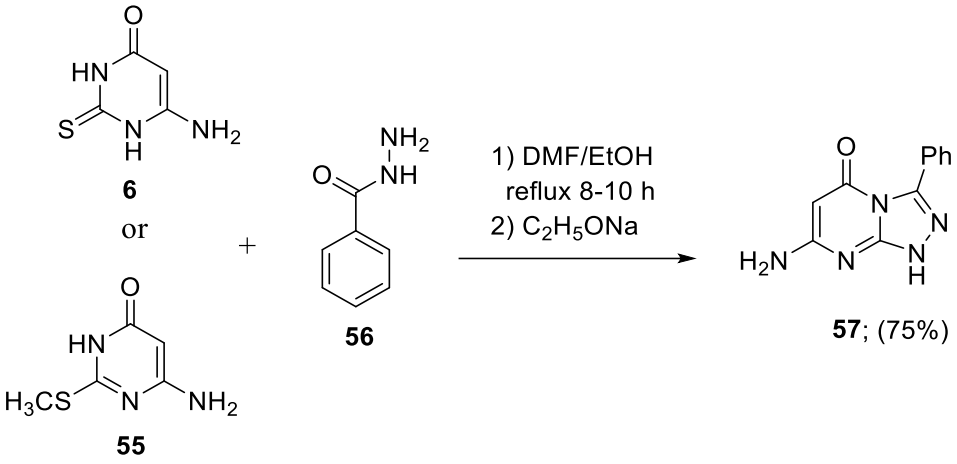


Scheme 21. Synthesis of 2-amino-5-(benzylthio)thiazolo[4,5-*d*]pyrimidin-7-ols.

Table 8. Synthesis of compounds **54a-l**

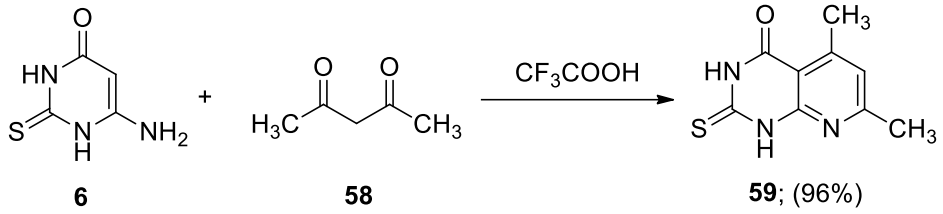
Products	R^1	R^2
a	H	$-(CH_2)_2OH$
b	H	$-(CH_2)_3OH$
c	H	$-CH(CH_2OH)_2$
d	H	$-(CH_2)_2N(CH_3)_2$
e	H	2-Morpholinoethyl
f	$-CH_3$	$-CH_3$
g		
h		
i		
j		
k		
l		

3.2.1.2.2. Synthesis of triazolo[4,3-*a*]pyrimidine. 7-Amino-3-phenyl[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one (**57**) was prepared through two distinct paths, using either 6-aminothiouracil (**6**) or 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (**55**) (prepared by the action of methyl iodide on **6** in ethanolic potassium hydroxide solution). Upon reacting one of the latter compounds with benzohydrazide (**56**) in DMF/ EtOH mixture followed by stirring at reflux in sodium ethoxide, compound **57** was obtained in 75% yield (Scheme 22).[84]



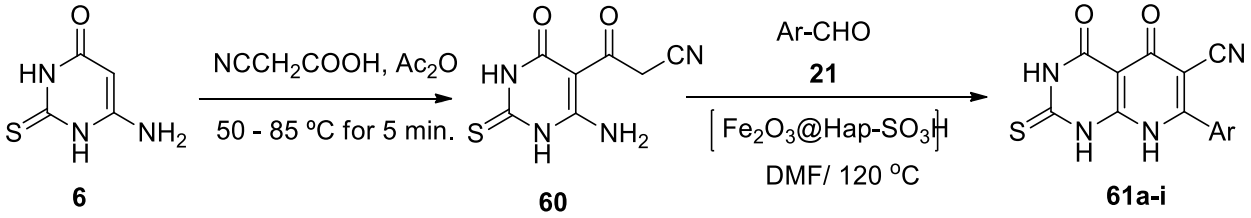
Scheme 22. Synthesis of 7-Amino-3-phenyl[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one (**57**).

3.2.1.3. Fused [6-6]systems: Three heteroatoms. 3.2.1.3.1. Synthesis of pyrido[2,3-*d*]pyrimidine. Reaction of 6-aminothiouracil (**6**) with acetylacetone (**58**) in triflouroacetic acid gave 5,7-dimethyl-2-thioxo-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (**59**) in 96% yield (Scheme 23).[85]



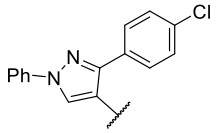
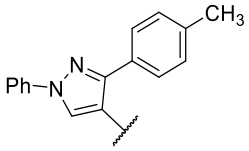
Scheme 23. Synthesis of 5,7-dimethyl-2-thioxo-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (**59**).

Mamaghani *et al*.[86] reported the synthesis of hexahydropyrido[2,3-*d*]pyrimidine derivatives **61a-i** through the reaction of 3-(6-amino-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3-oxopropanenitrile (**60**) with aromatic aldehydes **21** at reflux in DMF using heterogeneous nanocatalyst. Compound **60** was obtained upon the reaction of 6-aminouracil (**6**) with cyanoacetic acid in acetic anhydride (Scheme 24, Table 9).



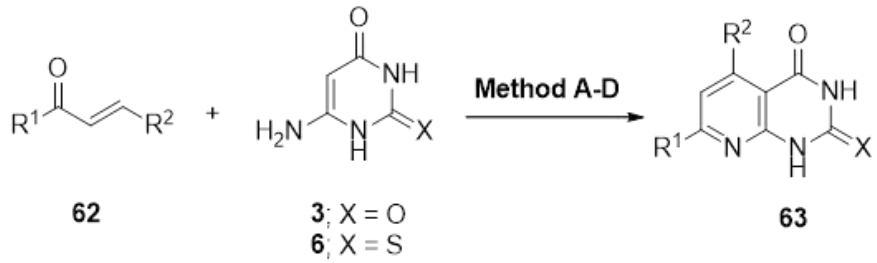
Scheme 24. Synthesis of hexahydropyrido[2,3-*d*]pyrimidine derivatives **61a-i**.

Table 9. % Yields of compounds **61a–i**

Products	Ar =	Yield%
a	4-Cl-C_6H_4	96
b	4-F-C_6H_4	96
c	2-Thienyl	87
d	3-Pyridyl	84
e	2-HO-C_6H_4	84
f	2-Naphthyl	85
g	-$(CH_2)_2$-C_6H_5	87
h		84
i		86

Some aminouracil derivatives **3** and **6** reacted with a variety of chalcones **62** under different conditions to give pyrido[2,3-*d*]pyrimidines **63** successfully in good yields. It is worth mentioning that some of the reported compounds in (Table 10) have shown various bioactivities.

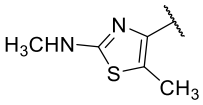
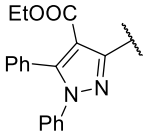
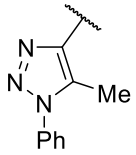
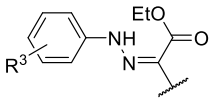
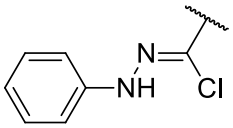
Fares *et al*.[87] reported that some of the synthesized pyrido[2,3-*d*]pyrimidine derivatives displayed anti-microbial and anti-fungal activities. Among the tested derivatives, compound **63** (R^1 = 4-Cl-C_6H_4, R^2 = C_6H_5) was found to exhibit the most potent effect against *Streptococcus pneumoniae* and *Escherichia coli*. On the other hand, compounds **63** (R^1 = 4-Cl-C_6H_4, R^2 = 4-H_3CO-C_6H_4), (R^1 = 2-Thienyl, R^2 = 4-F-C_6H_4) and (R^1 = 2-Thienyl, R^2 = 4-H_3CO-C_6H_4) were reported to have the most active anti-fungal agents against *Aspergillus fumigatus*. Otherwise, Nassar *et al*.[88] reported that pyrido[2,3-*d*]pyrimidine **63** (R^1 = 2-Thienyl, R^2 = 4-H_3CO-C_6H_4) showed the most anti-microbial effect against Gram-negative *Pseudomonas aeruginosa* (Scheme 25, Table 10).



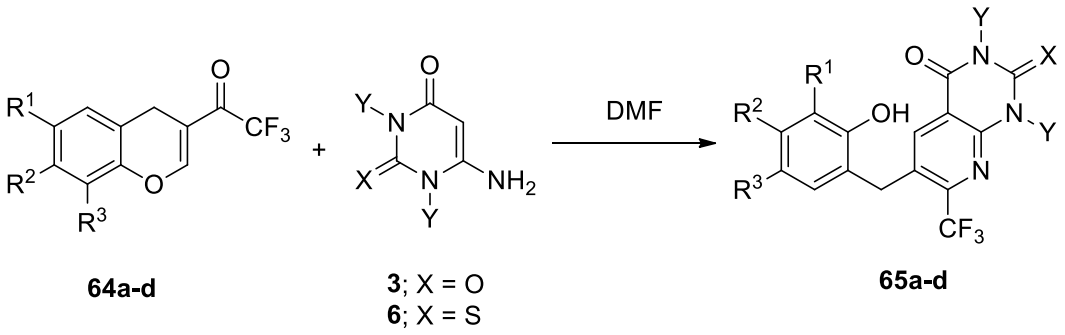
Method A: Dry DMF, reflux
Method B: AcOH / grinding, r.t
Method C: AcOH / reflux
Method D: EtOH / reflux

Scheme 25. Synthesis of pyrido[2,3-*d*]pyrimidine derivatives **63**.

Table 10. % Yields of compounds

Method	R^1	R^2	X	Yield%	Ref.
A	4-Cl-C_6H_4, 2-Thienyl	(C_6H_5, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-H_3CO-C_6H_4, 4-O_2N-C_6H_4)	S	40-65	87
A	2-Benzofuranyl	4-(Piperidin-1-yl)phenyl	O, S	72-75	88
C	2-Thienyl	2-Thienyl	S	76	89
C		4-F-C_6H_5 2,4-Cl_2-C_6H_5	S	75-78	90
B		C_6H_5	S	79	91
C		C_6H_5	S	79	92
C	 (R^3 = C_6H_5, 3,5-$(Me)_2$ C_6H_3)	C_6H_5	S	75-80	93
D		C_6H_5	S	70	94
A	3-Pyridyl	(C_6H_5, 3-H_3CO- C_6H_4, 2-Br-C_6H_4)	S	61-67	95–97
C	2-Benzofuranyl	3-Indolyl	S	80	98
C	3-Indolyl	(4- H_3C-C_6H_5, 4-Cl-C_6H_4)	S	72-76	99

Popova *et al*.[100] reported that the reaction of benzopyran derivatives **64a-d** with an equimolar ratio of 6-amino thiouracil derivatives **3** or **6** in DMF at reflux gave the corresponding 1,3-dimethyl-7-(trifluoromethyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **65a-d** in moderate yields (Scheme 26, Table 11).

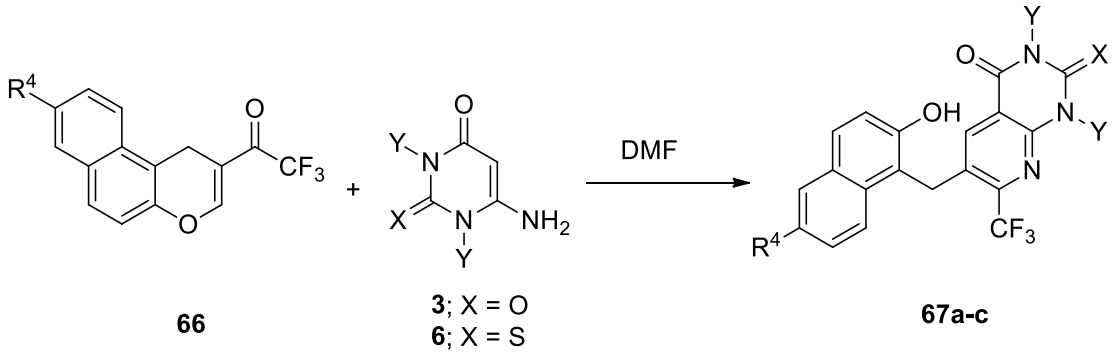


Scheme 26. Synthesis of pyrido[2,3-*d*]pyrimidine derivatives **65a-d**.

Table 11. % Yields of compounds **65a-d**

Products	R^1	R^2	R^3	X	Y	Yield%
a	1-Adamantyl	H	CH_3	O	CH_3	64
b	H	CH_3	CH_3	O	CH_3	61
c	H	H	NO_2	O	CH_3	73
d	H	CH_3	CH_3	S	H	62

In a similar manner, 2-(hydroxynaphthalen-1-yl)7-(trifluoromethyl)-2,3-dihydropyrido[2,3-*d*] pyrimidine-4(1*H*)-one derivatives **67a-c** were synthesized in 68, 72 and 59% yields, respectively, by the reaction of aminouracil derivatives **3** or **6** with 2-trifluoroacetyl-1*H*-benzo[*f*]chromenes **66** (Scheme 27, Table 12).[100]



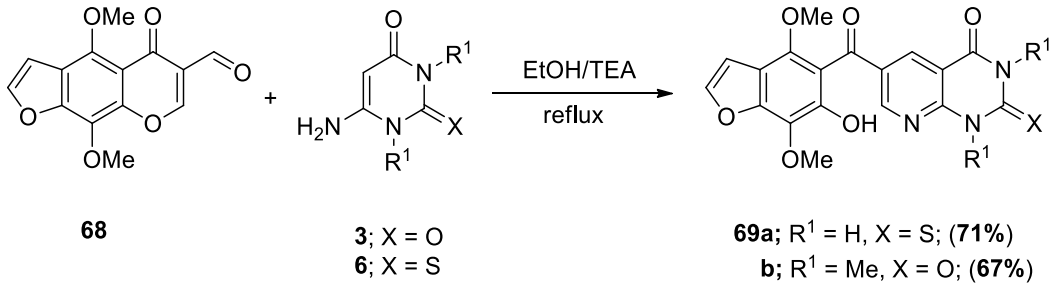
Scheme 27. Synthesis of pyrido[2,3-*d*]pyrimidine derivatives **67a-c**.

Table 12. % Yields of compounds **67a-c**

Products	R^4	X	Y	Yield%
a	H	O	CH_3	68
b	1-Adamantyl	O	CH_3	72
c	H	S	H	59

Treatment of furo[3,2-*g*]chromene-6-carbaldehyde **68** with 6-aminouracil derivatives **3** or **6** led to the formation of pyrido[2,3-*d*]pyrimidine derivatives **69a** and **69b**, respectively, *via* ring-opening / ring closure

reaction in good yield. The synthesized compounds showed high antimicrobial activities against two types of Gram-positive bacteria (Scheme 28).[101]

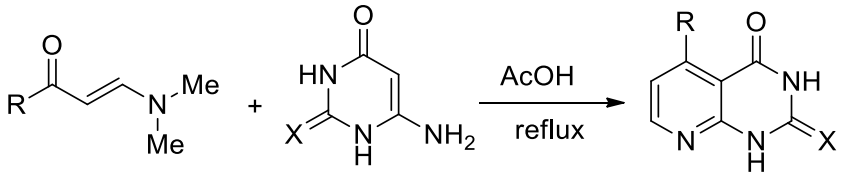


68 **3**; X = O, **6**; X = S

69a; R^1 = H, X = S; (**71%**)
b; R^1 = Me, X = O; (**67%**)

Scheme 28. Synthesis of pyrido[2,3-*d*]pyrimidine derivatives **69a** and **69b**.

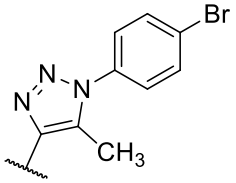
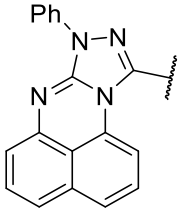
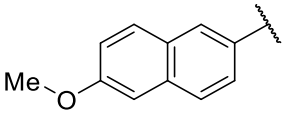
Enamine **70** reacted with aminouracils **3** and **6** mostly under acidic conditions to give different derivatives of pyrido[2,3-*d*]pyrimidines **71a-c**. Compound **71c** showed a potent tyrosine kinase inhibition effect when studied as an anti-cancer agent (Scheme 29, Table 13).



70 **3**; X = O, **6**; X = S **71a-c**

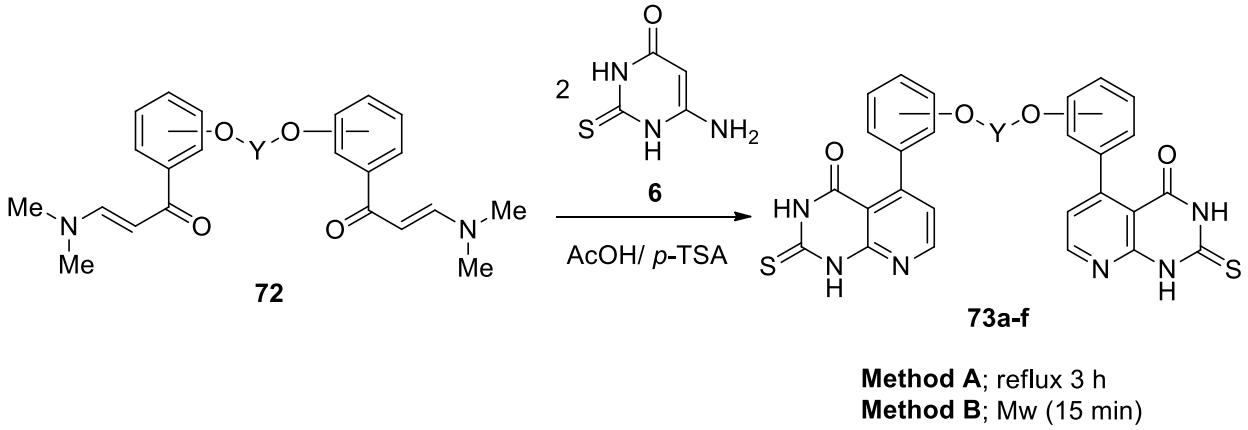
Scheme 29. Synthesis of pyrido[2,3-*d*]pyrimidine **71a-c**.

Table 13. % Yields of compounds **71a-c**

Products	R	X	Yield%	Ref.
a		S	90	[102]
b		S	83	[103]
c		a; X = O b; X = S	57-61	[104]

The synthesis of *bis*(2-thioxo-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one) derivatives **73a-f** was performed *via* a direct reaction of 6-aminothiouracil (**6**) with *bis*(enaminones) **72**. The reactions were carried

out in acetic acid at reflux in the presence of *p*-TSA using conventional heating or microwave irradiation (Scheme 30, Table 14).[105]

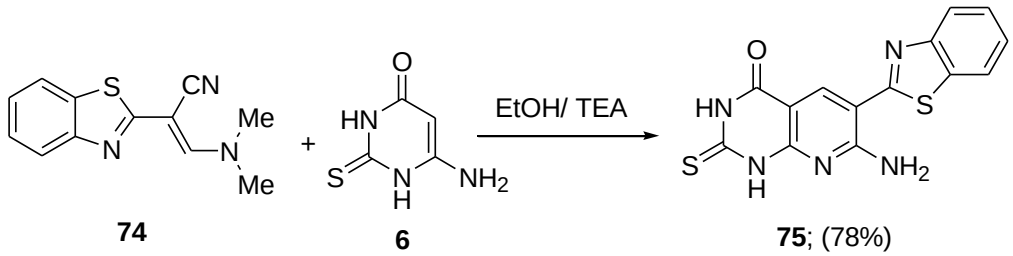


Scheme 30. Synthesis of *bis* pyrido[2,3-*d*]pyrimidines **73a-f**.

Table 14. % Yields of compounds **73a-f**

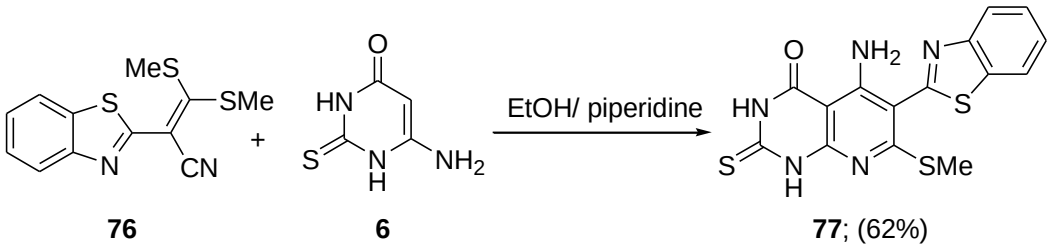
Products	Y	Isomer	Yield%	
			A	**B**
a	$-(CH_2)_2-$	*o*-isomer	78	81
b	$-(CH_2)_2-$	*p*-isomer	82	85
d	$-(CH_2)_3-$	*p*-isomer	92	94
e	$-(CH_2)_4-$	*o*-isomer	73	77
f	$-(CH_2)_4-$	*p*-isomer	75	80

Fadda *et al*.[106] reported the regioselective synthesis of 7-amino-5-(benzo[*d*]thiazol-2-yl)-2-thioxo-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (**75**) in 78% yield by the reaction of 2-(benzo[*d*]thiazol-2-yl)-3-(dimethylamino)acrylonitrile (**74**) with 6-aminothiouracil (**6**) in ethanol at reflux in the presence of TEA as a catalyst. The reaction proceeds by the Michael type addition of the most nucleophilic ring carbon, C-5 of uracil, to the activated double bond of the vinyl ketone forming a Michael adduct as an intermediate which underwent a cycloaddition reaction. The authors have not commented on the regioselective formation of compound **75** (Scheme 31).



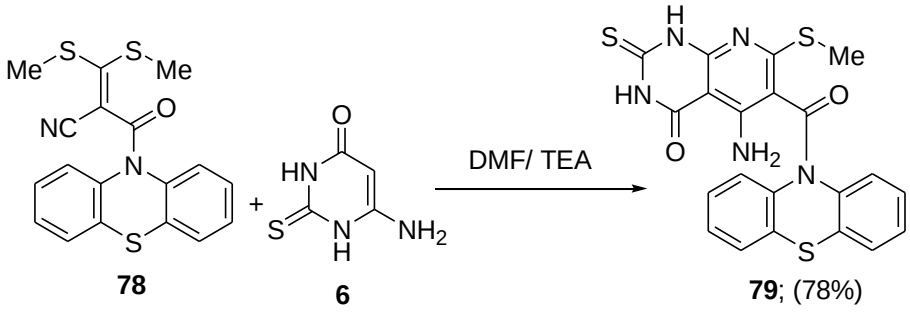
Scheme 31. Synthesis of 7-amino-5-(benzo[*d*]thiazol-2-yl)-2-thioxo-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (**75**).

On the other hand, the same authors reported the synthesis of pyrido[2,3-*d*]pyrimidinone **77** in 62% yield through the reaction of 6-aminothiouracil (**6**) with 2-(benzo[*d*]thiazol-2-yl)-3,3-*bis*-(methylthio)acrylonitrile (**76**) in ethanol at reflux and in the presence of piperidine as a basic catalyst. Compound **77** exhibited potent anti-microbial activity against the Gram-positive Bacillus subtilis (Scheme 32). [106]



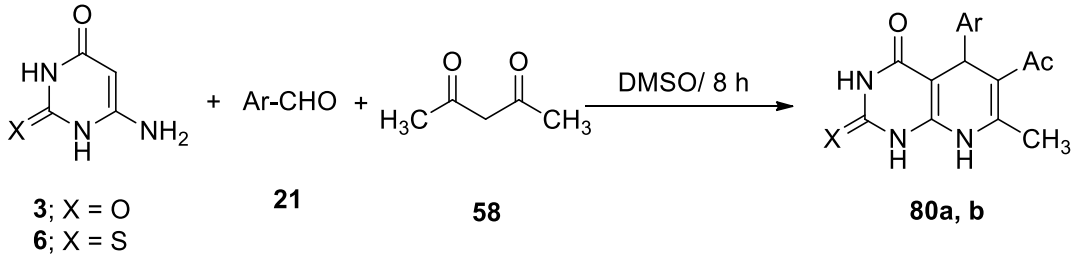
Scheme 32. Synthesis of pyrido[2,3-*d*]pyrimidine-4-one **77**.

The reaction of 3,3-*bis*(methylthio)-2-(10*H*-phenothiazine-10-carbonyl)acrylonitrile (**78**) with 6-aminothiouracil (**6**) in DMF at reflux and in the presence of TEA as a catalyst afforded pyrido[2,3-*d*] pyrimidin-4(1*H*)-one **79** in 78% yield (Scheme 33).[107]



Scheme 33. Synthesis of pyrido[2,3-*d*] pyrimidin-4(1*H*)-one **79**.

Ohanjanyan *et al*.[108] reported the synthesis of dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **80a** and **80b** in 52% and 58% yields, respectively, *via* a multi-component reaction of 6-aminothiouracil **3** or **6** with aryl aldehydes **21** and pentane-2,4-dione **58** (Scheme 34, Table 15).

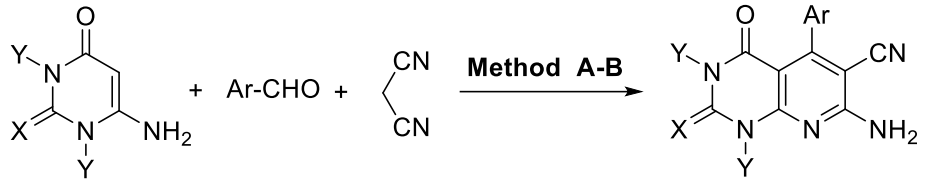


Scheme 34. Synthesis of dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **80a** and **80b**.

Table 15. % Yields of compounds **80a** and **80b**

Products	Ar	X	Yeild%
a	1,3- Benzodioxol-5-yl	O	52
b	3-Pyridinyl	S	58

The reaction of 6-aminouracil derivatives **3** or **6** with different aldehydes **21** and malononitrile (**81**) under different reaction conditions was reported to give a series of pyrido[2,3-*d*]pyrimidines **82** as shown in (Scheme 35). Abdelgawad *et al*.[109] reported that pyrido[2,3-*d*]pyrimidine derivatives (prepared by method A) revealed anti-inflammatory activity by inhibiting cyclooxygenase-2 (COX-2) enzymes (Scheme 35, Table 16).



Method A: EtOH/Et_3N, reflux, 4 h
Method B: Nano MgO/ H_2O/ 80^oC
Method C: Fe_3O_4@TiO_2@NH_2@$PMo_{12}O_{40}$/ MNPs H_2O/ 80 ^oC
Method D: Electrolysis 50 mA, ROH or MeCN, NaBr = Et, Me, *n*-Pr

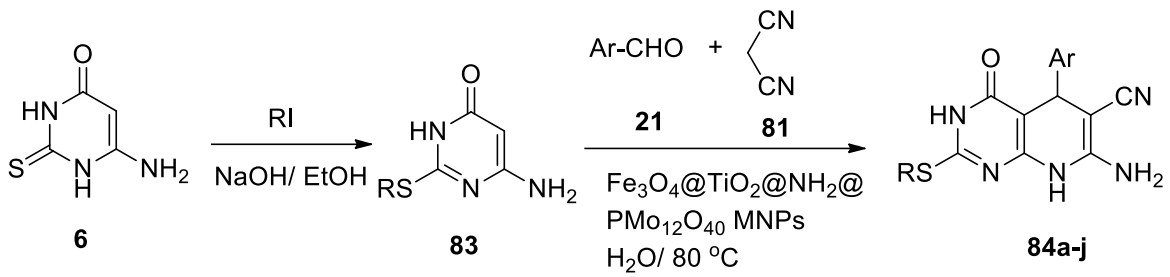
Scheme 35. Synthesis of pyrido[2,3-*d*]pyrimidines **82**.

Table 16. % Yields of compounds **82**

Method	Ar	X	Y	Yield%	Ref.
A	(3-H_3CO-C_6H_4, 2,3-H_3CO-C_6H_4, 3,4,5-H_3CO-C_6H_4)	S	H	79-87	109
B	(C_6H_5, 2-Cl-C_6H_4, 4-Cl-C_6H_4, 4-H_3CO-C_6H_4, 4-H_3C-C_6H_4, 3-O_2N-C_6H_4, 4-O_2N-C_6H_4, 4-Cl-C_6H_4; 3-Cl-C_6H_4, 2-Cl-C_6H_4, 3-Br-C_6H_4, 4-F-C_6H_4, C_6H_5, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4)	O, S	H, Me	84-96	110
C	(4-Cl-C_6H_4, 3-O_2N-C_6H_4, 4-$(H_3C)_2N$-C_6H_3, 3-Cl-C_6H_4, 4-F-C_6H_4, 2,4-Cl_2-C_6H_4, 4-Br-C_6H_4, 2-Cl-C_6H_4, 2,6-Cl_2-C_6H_3, 4-O_2N-C_6H_4, 3-H_3CO-C_6H_4, 2-O_2N-C_6H_4)	S	H	92-98	111
D	(C_6H_5, 4-H_3CO-C_6H_4, 4-O_2N-C_6H_4, 3-O_2N-C_6H_4, 2,4-Cl_2-C_6H_3, 3-HO-C_6H_4, 4-Cl-C_6H_4, 4-O_2N-C_6H_4)	O	H, Me	90-93	112

A series of tetrahydropyrido[2,3-*d*]pyrimidines **84** were prepared in excellent yields *via* a three component reaction of compound **83** with the appropriate aryl aldehydes **21** and malononitrile **81** using magnetic

nanoparticles $Fe_3O_4@TiO_2@NH_2@PMo_{12}O_{40}$ as a recoverable catalyst. Compounds **83** were synthesized upon alkylation of 6-aminothiouracil (**6**) with the appropriate alkyl halides under basic condition (Scheme 36, Table 17).[111]

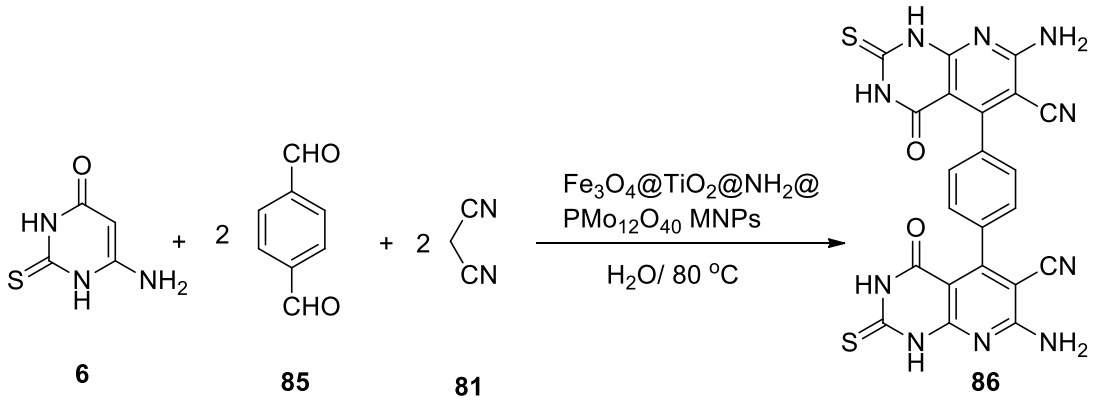


Scheme 36. Synthesis of tetrahydropyrido[2,3-*d*]pyrimidines **84a-j**.

Table 17. % Yields of compounds **84a-j**

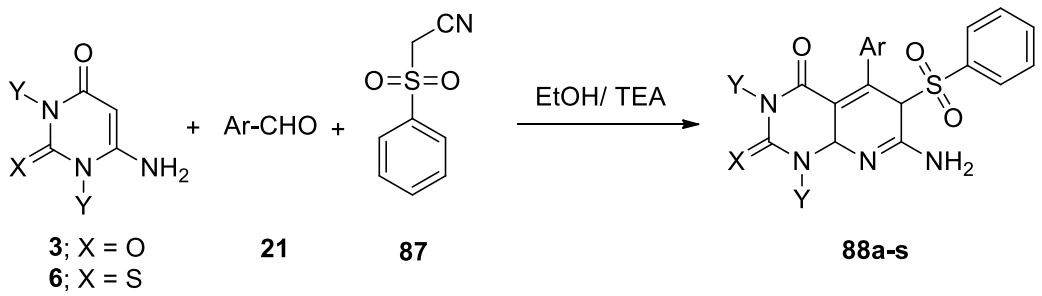
Ar	R	Yeild%	Ref.
(3-O_2N-C_6H_4, 2,6-Cl_2-C_6H_4, 4-Cl-C_6H_4, 2,4-Cl_2-C_6H_4, 3- O_2N -C_6H_4, 4-Cl-C_6H_4, 3-O_2N -C_6H_4, 4-F-C_6H_4; 2,4-Cl_2-C_6H_4, 3-O_2N -C_6H_4)	C_2H_5, C_3H_7, C_4H_9	94-98	111

A *bis*(pyrido[2,3-*d*]pyrimidine-6-carbonitrile) **86** was prepared through a one pot reaction of terephthalaldehyde (**85**) with two equivalents of both of 6-aminothiouracil (**6**) and malononitrile (**81**) (Scheme 37).[111]



Scheme 37. Synthesis of *bis* pyrido[2,3-*d*]pyrimidine-6-carbonitrile **86**.

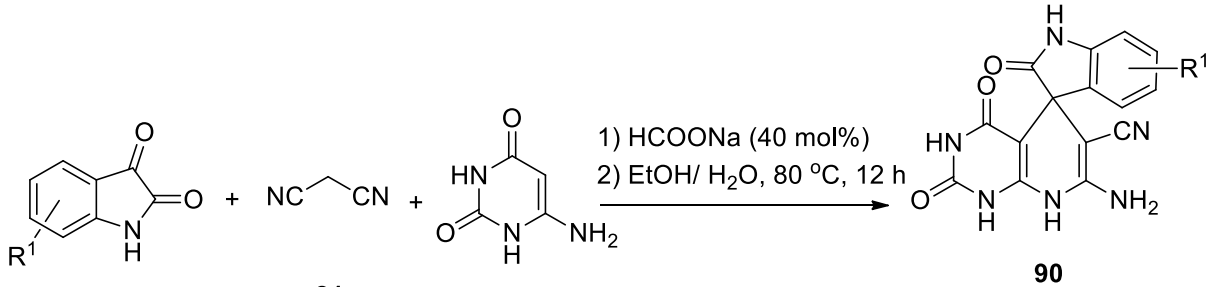
Dihydropyrido[2,3-*d*]pyrimidine derivatives **88a-s** were prepared *via* a three component reaction of aminothiouracil derivatives **3** or **6** with each of aromatic aldehydes **21** and 2-(phenylsulfonyl) acetonitrile (**87**) in ethanol at reflux and in the presence of trimethylamine as a catalyst (Scheme 38, Table 18).[113]



Scheme 38. Synthesis of dihydropyrido[2,3-*d*]pyrimidine derivatives **88a-s**.

Table 18. % Yields of compounds **88a-s**

Products	Ar	Y	X	Yield%
a	4-H_3C-C_6H_5	Me	O	67
b	3-H_3C-C_6H_4	Me	O	63
c	C_6H_5	Me	O	79
d	4-Br-C_6H_4	Me	O	85
e	3-Br-C_6H_4	Me	O	89
f	4-Cl-C_6H_4	Me	O	77
g	2-Cl-C_6H_4	Me	O	81
h	4-F-C_6H_4	Me	O	74
i	4-O_2N-C_6H_4	Me	O	69
j	3-O_2N-C_6H_4	Me	O	72
k	4-H_3C-C_6H_4	H	S	68
l	3-H_3C-C_6H_4	H	S	60
m	4-H_3CO-C_6H_4	H	S	62
n	C_6H_5	H	S	87
o	4-Br-C_6H_4	H	S	91
p	3-Br-C_6H_4	H	S	92
q	4-Cl-C_6H_4	H	S	81
r	2-Cl-C_6H_4	H	S	91
s	4-O_2N-C_6H_4	H	S	75

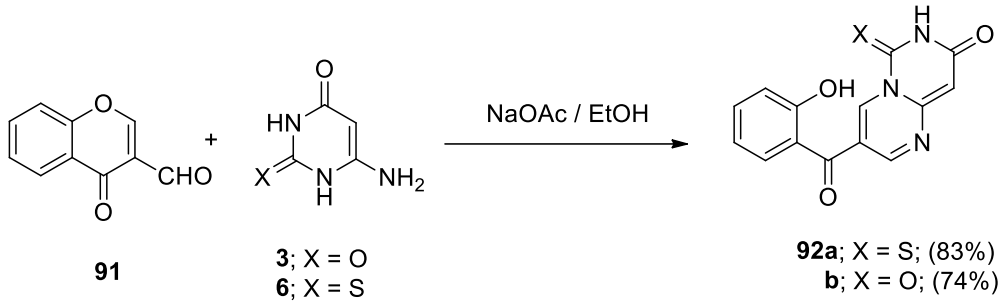


a; R = 5-H, (86%) **e**; R = 5-**I**, (78%)
b; R = 5-Br, (88%) **f**; R = OCF_3, (80%)
c; R = 5-Cl, (90%) **g**; R = 3,6-Cl, (82%)
d; R = 5-F, (84%)

Scheme 39. Synthesis of spiro[indoline-3,5`-pyrido[2,3-*d*]pyrimidine] derivatives **90a-g**.

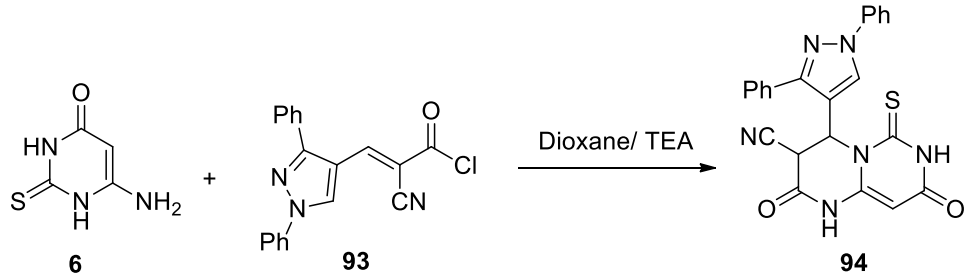
A series of some spiro[indoline-3,5`-pyrido[2,3-*d*]pyrimidine] derivatives **90a-g** were synthesized *via* a multicomponent reaction of isatins **89**, aminouracil (**3**), and malononitrile (**81**) in aqueous ethanol at reflux using sodium format as an organocatalyst (scheme 39).[114]

3.2.1.3.2. Synthesis of pyrimido[1,6-*a*]pyrimidine. Cyclocondensation of aminouracil derivatives **3** or **6** with 4-oxo-4*H*-chromene-3-carbaldehyde **91** in the presence of anhydrous sodium acetate afforded pyrimido[1,6-*a*]pyrimidinones **92a** and **92b** in 83% and 74% yields, respectively (Scheme 40).[115]



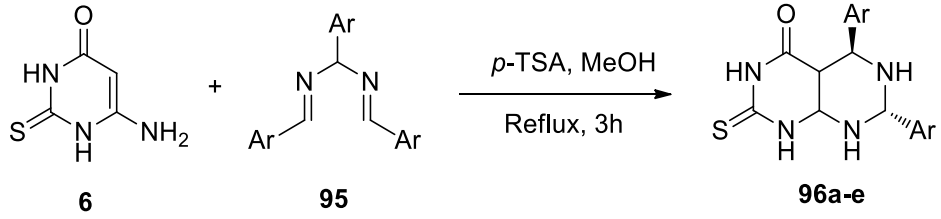
Scheme 40. Synthesis of pyrimido[1,6-*a*]pyrimidinones **92a** and **92b**.

Pyrimido[1,6-*a*]pyrimidine-3-carbonitrile **94** was prepared by the reaction of 6-aminothiouracil (**6**) with 2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acryloyl chloride (**93**) at reflux in dioxane in the presence of TEA (scheme 41).[116]



Scheme 41. Synthesis of pyrimido[1,6-*a*]pyrimidine-3-carbonitrile **94**.

3.2.1.4. Fused [6-6]systems: Four heteroatoms. 3.2.1.4.1. Synthesis of pyrimido[4,5-*d*]pyrimidine. Khodabakhshi *et al*.[117] reported the synthesis of tetrahydropyrimido[4,5-*d*]pyrimidine-2,4-dione derivatives **96a-e** through cyclization of 6-aminothiouracil (**6**) with *N*,*N*'-*bis*(arylmethylidene) arylmethanes(diimines) **95** using *p*-TSA as a catalyst. The ^{1}H-NMR spectroscopy indicated the presence of the *anti*-configured diastereomer in all products. (Scheme 42, Table 19).

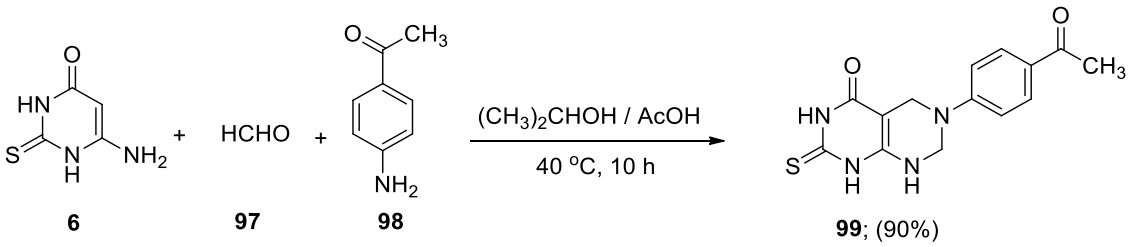


Scheme 42. Synthesis of tetrahydropyrimido[4,5-*d*]pyrimidine-2,4-diones **96a-e**.

Table 19. % Yields of compounds **96a-e**

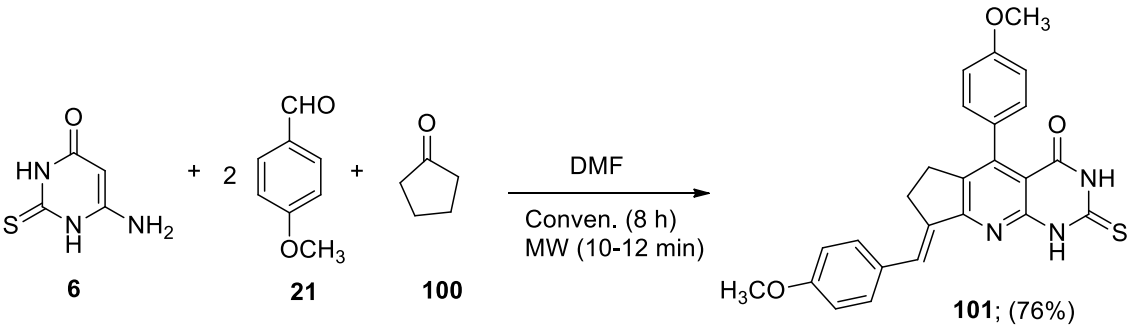
Products	Ar	Yield%
a	C_6H_5	80
b	4-H_3C-C_6H_4	75
c	4-H_3CO-C_6H_4	78
d	2-H_3C-C_6H_4	72
e	2-Thienyl	93

6-(4-Acetylphenyl)-2-thioxo-hexahydro-1*H*-pyrimido[4,5-*d*]pyrimidin-4-one (**99**) was synthesized in 92% yield through the reaction of 6-aminothiouracil (**6**) with each of 4-aminoacetophenone (**98**) and formaldehyde (**97**) in a mixture of acetic acid and isopropyl alcohol (Scheme 43).[109]



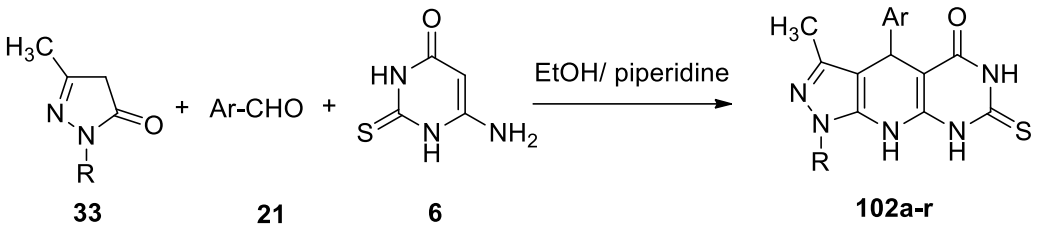
Scheme 43. Synthesis of 6-(4-acetylphenyl)-2-thioxo-hexahydro-1*H*-pyrimido[4,5-*d*]pyrimidin-4-one **99**.

3.2.2. Synthesis of fused tricyclic systems. 3.2.2.1. Fused [5-6-6]systems: Three heteroatoms. 3.2.2.1.1. Synthesis of cyclopenta[5,6]pyrido[2,3-*d*]pyrimidine. Hexahydro-4*H*-cyclopenta[5,6]pyrido[2,3-*d*]pyrimidin-4-one **101** was prepared through a cyclocondensation reaction of one equivalent of each of cyclopentanone (**100**) and aminothiouracil (**6**) with two equivalent of *p*-anisaldehyde (**21**) in DMF. The reaction was carried out under conventional heating or microwave irradiation (Scheme 44). Compound **101** showed a good corrosion inhibitory effect for API 5L X52 carbon steel in 5% sulfamic acid solutions (Scheme 44). [118]



Scheme 44. Synthesis of hexahydro-4*H*-cyclopenta[5,6]pyrido[2,3-*d*]pyrimidin-4-one **101**.

3.2.2.2. Fused [5-6-6]systems: five heteroatoms. 3.2.2.2.1 Synthesis of pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidin-5-one. The synthesis of a variety of pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidin-5-one derivatives **102a-r** was established in good yields *via* a one pot reaction of 6-aminothiouracil (**6**) with aldehydes **21** and 3-methyl-1-aryl-2-pyrazoline-5-one **33** in ethanol at reflux in the presence of piperidine as a basic catalyst (Scheme 45, Table 20).[119]

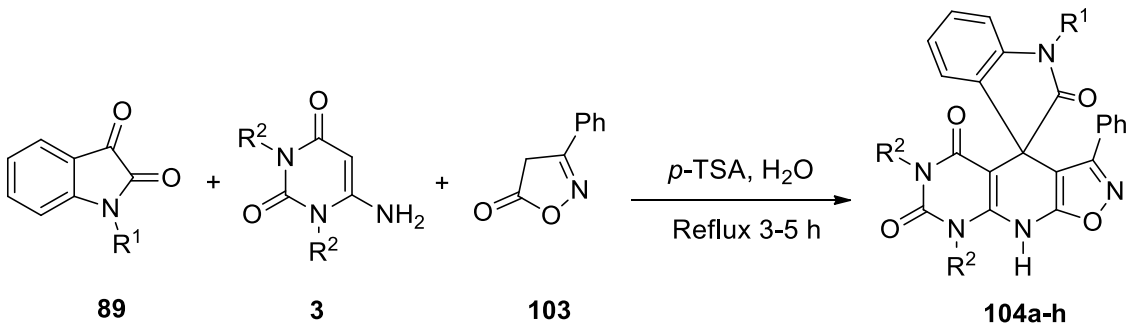


Scheme 45. Synthesis of pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidin-5-one derivatives **102a-r**.

Table 20. % Yields of compounds **102a-r**

Products	R	Ar	Yeild%
a	C_6H_5	4-Cl-C_6H_4	96
b	C_6H_5	4-F_3C-C_6H_4	69
c	C_6H_5	4-H_3CO-C_6H_4	74
d	C_6H_5	4-Br-C_6H_4	95
e	C_6H_5	4-F-C_6H_4	72
f	C_6H_5	4-O_2N-C_6H_4	94
g	C_6H_5	2-Cl-C_6H_4	70
h	C_6H_5	3-Cl-C_6H_4	89
i	C_6H_5	3-F-C_6H_4	98
j	3-Cl-C_6H_4	4-Cl-C_6H_4	98
k	3-Cl-C_6H_4	4-Br-C_6H_4	92
l	3-Cl-C_6H_4	4-F-C_6H_4	69
m	3-Cl-C_6H_4	4-F_3C-C_6H_4	75
n	3-Cl-C_6H_4	3-F-C_6H_4	98
o	3-Cl-C_6H_4	4-O_2N-C_6H_4	95
p	3-Cl-C_6H_4	4-Cl-C_6H_4	78
q	3-Cl-C_6H_4	4-F-C_6H_4	91
r	3-Cl-C_6H_4	4-O_2N-C_6H_4	85

3.2.2.2.2. Synthesis of isoxazolo[4',5':5,6]pyrido[2,3-*d*]pyrimidine. Poomathi *et al.*[120] reported the synthesis of spiroindoline-3,4'isoxazolo[4',5':5,6]pyrido[2,3-*d*]pyrimidine derivatives **104a-h** in good yields *via* a one pot reaction of isatin **89** with each of 6-aminouracil **3** and 3-phenylisoxazol-5(4*H*)-one (**103**) in the presence of *p*-toluenesulfonic acid as a catalyst in water as a green solvent (Scheme 46, Table 21).

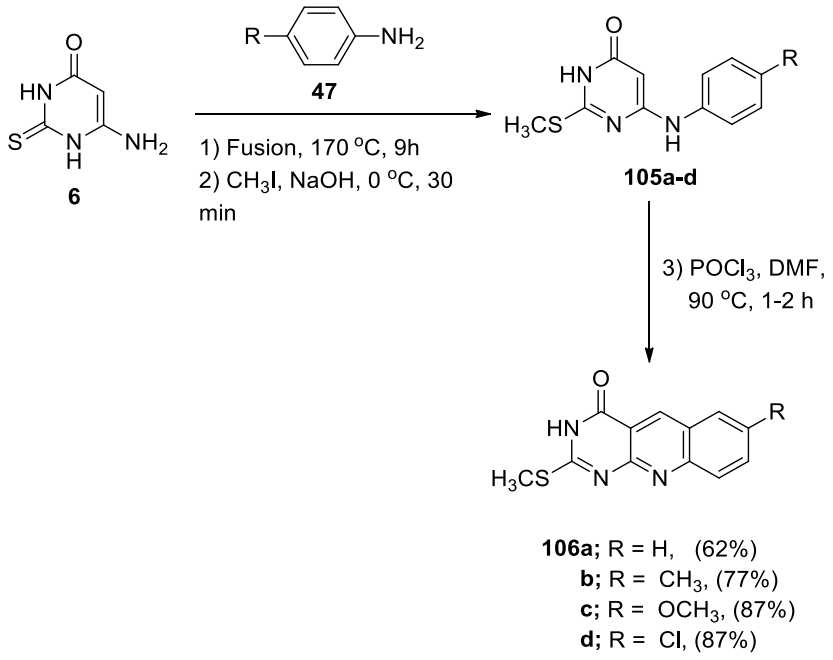


Scheme 46. Synthesis of spiroindoline-3,4'isoxazolo[4',5':5,6]pyrido[2,3-*d*]pyrimidines **104a-h**.

Table 21. % Yields of compounds **104a-h**

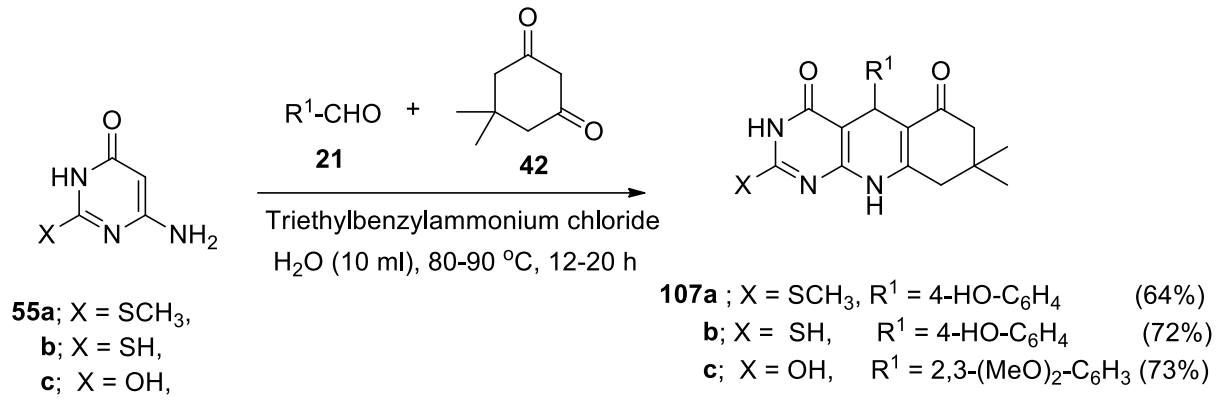
Products	R^1	R^2	Yield%
a	CH_3	CH_3	87
b	CH_2CH_3	CH_3	89
c	$CH_2CH{=}CH_2$	CH_3	86
d	CH_2-C_6H_5	CH_3	79
e	CH_3	H	88
f	CH_2CH_3	H	87
g	$CH_2CH{=}CH_2$	H	87
h	CH_2-C_6H_5	H	81

3.2.2.3. Fused [6-6-6]systems: three heteroatoms. 3.2.2.3.1. Synthesis of pyrimido[4,5-*b*]quinolone. Malki *et al*.[121] reported the synthesis of 2-(methylthio)pyrimido[4,5-*b*]quinolin-4(3*H*)-one derivatives **106a-d** by firstly, the reaction of 6-aminothiouracil (**6**) with the appropriate aniline **47** to give the corresponding 6-anilino derivatives **105a-d**. The latter compounds were then cyclized through Vilsmeier-Haack reaction to give compounds **106a-d** in good yields (Scheme 47).



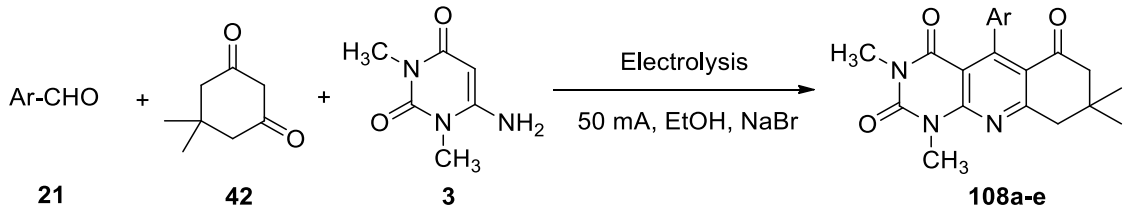
Scheme 47. Synthesis of 2-(methylthio)pyrimido[4,5-*b*]quinolin-4(3*H*)-one derivatives **106a-d**.

Hovsepyan *et al*.[122] reported the synthesis of pyrimido[4,5-*b*]quinolone derivatives **107a-c** in acceptable yields through a three-component cyclization of 6-amino-2-substituted pyrimidines **55a-c** with each of aryl aldehydes **21** and dimedone (**42**) in H_2O at reflux and in the presence of triethylbenzylammonium chloride as a catalyst (Scheme 48).



Scheme 48. Synthesis of pyrimido[4,5-*b*]quinolone derivatives **107a-c**.

Pyrimido[4,5-*b*]quinoline derivatives **108a-e** were synthesized *via* electrochemically induced condensation of aryl aldehydes **21** with 6-amino-1,3-dimethyluracil (**3**) and dimedone (**42**) in EtOH and in the presence of NaBr (Scheme 49, Table 22).[112]

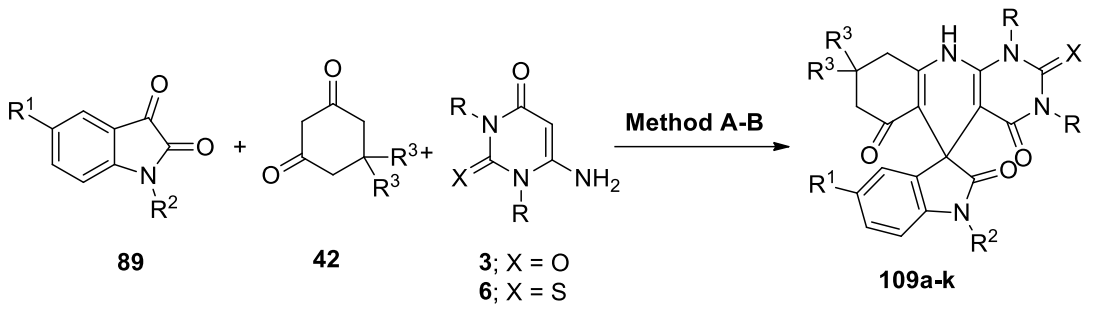


Scheme 49. Synthesis of pyrimido[4,5-*b*]quinoline derivatives **108a-e**.

Table 22. % Yields of compounds **108a-e**

Products	Ar	Yeild%
a	4-HO-C_6H_4	88
b	4-H_3CO-C_6H_4	92
c	4-O_2N-C_6H_4	92
d	4-Cl-C_6H_4	93
e	4-Br-C_6H_4	90

A variety of spirocyclic oxindole derivatives **109a-k** were synthesized in good yields *via* a multi-component reaction of isatin **89**, aminouracils **3** or **6** and dimedone (**42**) using different catalytic systems. Baharfar *et al*.[123] reported that most spirocyclic oxindoles **109a-k** possessed antioxidant effect by examined its radical scavenging activity (Scheme 50, Table 23). [123,124]



Method A: SBA-15-$PhSO_3H$, H_2O: EtOH (4:1), 80 ^oC
Method B: H_2O, 20 mol% *p*-TSA, 80 ^oC

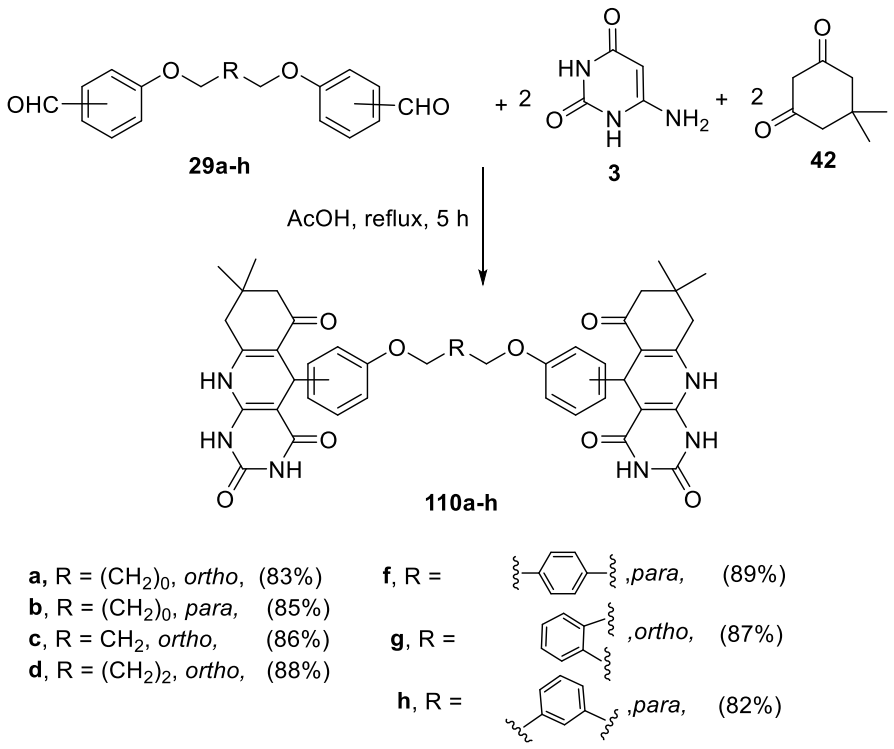
Scheme 50. Synthesis of pyrimido[4,5-*b*]quinoline derivatives **109a-k**.

Table 23. % Yields of compounds **109a-k**

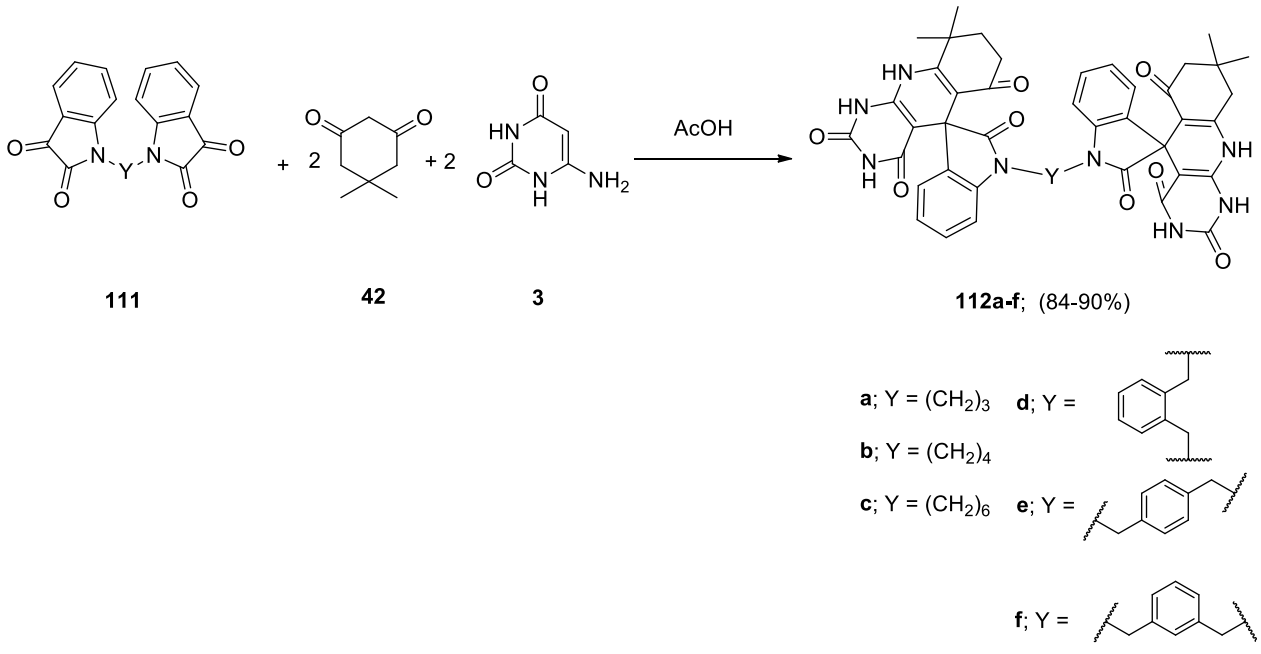
Products	Method	R^1	R^2	R^3	R	X	Yield%
a	A, B	H	H	CH_3	CH_3	O	94-92
b	A	H	H	H	CH_3	O	92
c	A	Cl	H	CH_3	CH_3	O	91
d	A	Cl	H	H	CH_3	O	90
e	A	Br	H	H	CH_3	O	93
f	A	NO_2	H	CH_3	CH_3	O	90
g	A	H	Et	CH_3	CH_3	O	92
h	A	H	CH_2COOEt	CH_3	CH_3	O	91
i	A	H	Bn	CH_3	CH_3	O	89
j	B	H	H	CH_3	H	O	88
k	A, B	H	H	CH_3	H	S	90-87

A three component reaction of *bis*(aldehydes) **29a-h** with two equivalents of both of 6-aminouracil (**3**) and dimedone (**42**) under acidic catalytic condition afforded a series of *bis*(pyrimido[4,5-*b*]quinolones) **110a-h** in good yields (Scheme 51). [76]

Mohamed *et al.*[125] reported the synthesis of *bis*(spiro-cyclic 2-oxindole) linked to pyrimido[4,5-*b*] quinolonetetraone derivatives **112a-f** by the reaction of *bis*-isatin **111**, dimedone (**42**) and 6-aminouracil (**3**) in acetic acid at reflux. The latter compounds exhibited a potent cytotoxic effect more than the standard drug fluorouracil (5-FU). Among the tested derivatives, compound **112a** was found to be the most active and promising one in this series against MCF7, HCT116, and A549 cell lines (Scheme 52).



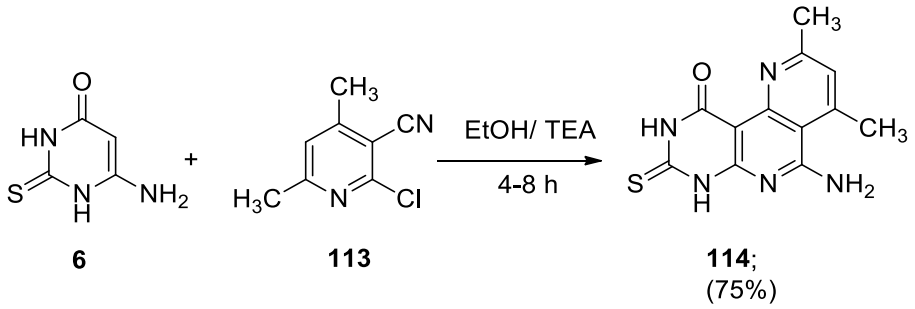
Scheme 51. Synthesis of *bis*(pyrimido[4,5-*b*]quinolones) **110a-h**.



Scheme 52. Synthesis of *bis*(spiro-cyclic 2-oxindole) linked to pyrimido[4,5-*b*]quinolonetetraone derivatives **112a-f**.

3.2.2.4. Fused [6-6-6]systems: Four heteroatoms. 3.2.2.4.1. Synthesis of pyrimido[4,5-*h*][1,6]naphthyridin-10(7*H*)-one. 5-Amino-2,4-dimethyl-8-thioxo-8,9-dihydropyrimido[4,5-*h*][1,6]naphthyridin-10(7*H*)-on (**114**) was

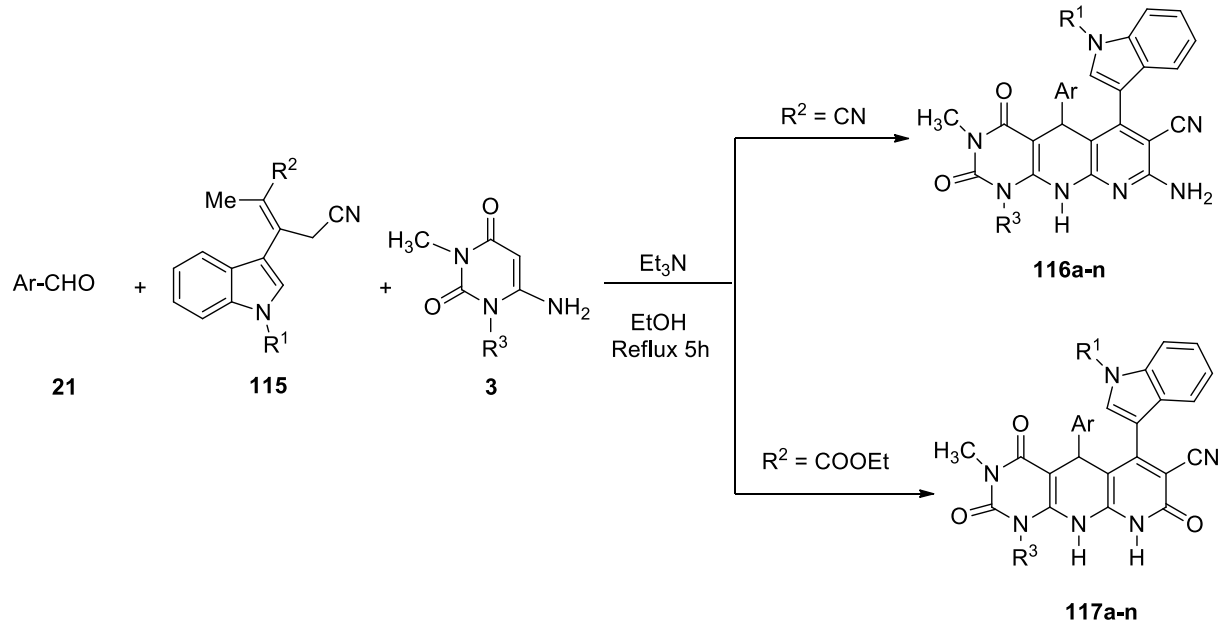
prepared in 75% yield by the reaction of 6-aminothiouracil (**6**) with 2-chloro-4,6-pyridine-3-carbonitrile (**113**) in ethanol at reflux in the presence of TEA as a catalyst (Scheme 53).[106]



6 **113** **114**; (75%)

Scheme 53. Synthesis of 5-amino-2,4-dimethyl-8-thioxo-8,9-dihydropyrimido[4,5-*h*][1,6] naphthyridin-10(7*H*)-one (**114**).

3.2.2.4.2. Synthesis of pyrimido[4,5-*b*]-1,8-naphthyridine. Naidu *et al.*[126] reported the synthesis of pyrimido[4,5-*b*]-1,8-naphthyridine derivatives **116a-n** and **117a-n** by the reaction of 2-cyano-3-(1*H*-indol-3-yl)-pent-2-enedinitrile or ethyl-2,4-dicyano-3-(1*H*-indol-3-yl)but-2-enoate derivatives **115** with aryl aldehydes **21** and 6-aminouracil derivatives **3** in the presence of Et_3N in ethanol at reflux (Scheme 54, Table 24).



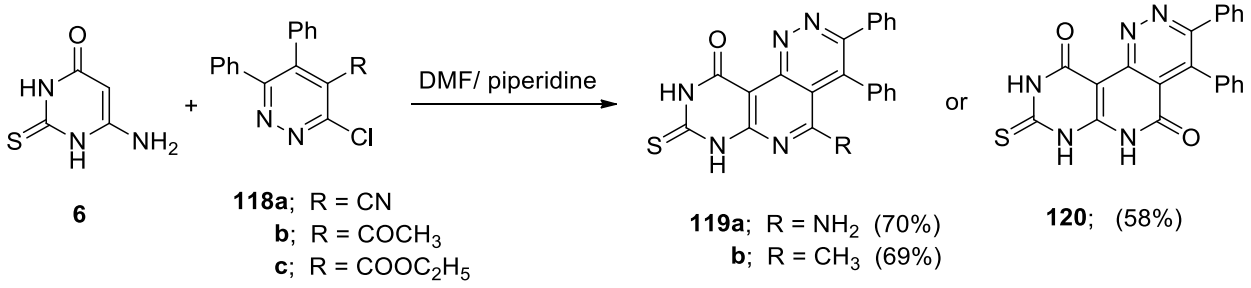
21 **115** **3** **116a-n** **117a-n**

Scheme 54. Synthesis of pyrimido[4,5-*b*]-1,8-naphthyridine derivatives **116a-n** and **117a-n**.

Table 24. % Yields of compounds **116a-n** and **117a-n**

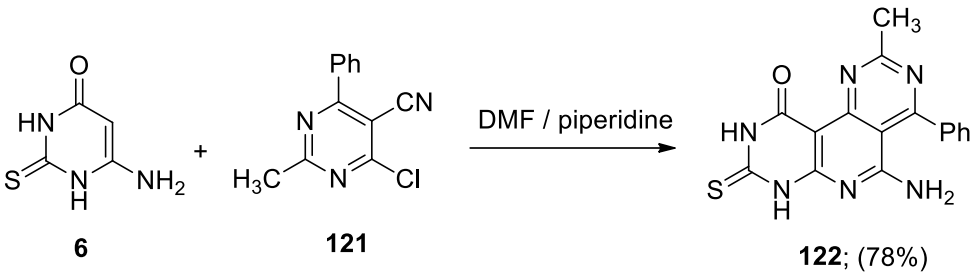
Products		Ar	R^1	R^3	Yield%
116a-l	**117a-l**				
a	**a**	-C_6H_5	H	CH_3	80-79
b	**b**	4-H_3C-C_6H_4	H	CH_3	83-84
c	**c**	4-H_3CO-C_6H_4	H	CH_3	85-86
d	**d**	4-Cl-C_6H_4	H	CH_3	76-74
e	**e**	4-Br-C_6H_4	H	CH_3	78-75
f	**f**	4-O_2N-C_6H_4	H	CH_3	66-65
g	**g**	-C_6H_5	CH_3	CH_3	80-80
h	**h**	4-H_3CO-C_6H_4	CH_3	CH_3	81-83
i	**i**	4-Cl-C_6H_4	CH_3	CH_3	75-77
j	**j**	4-O_2N-C_6H_4	CH_3	CH_3	64-62
k	**k**	-C_6H_5	H	H	76-75
l	**l**	2-Pyrrolyl	H	CH_3	74-73
m	**m**	2-Thienyl	H	CH_3	72-72
n	**n**	*i*-Pr	H	CH_3	70-70

3.2.2.5 Fused [6-6-6]systems: Five heteroatoms. 3.2.2.5.1. Synthesis of pyrimido[5′,4′:5,6]pyrido[4,3-*c*]pyridazine. Pyrimido[5′,4′:5,6]pyrido[4,3-*c*]pyridazines **119a**, **119b** and **120** were synthesized *via* reaction of aminothiouracil (**6**) with chloropyridazines **118a**, **118b** and **118c** in DMF in the presence of piperdine as a catalyst (Scheme 55).[106]



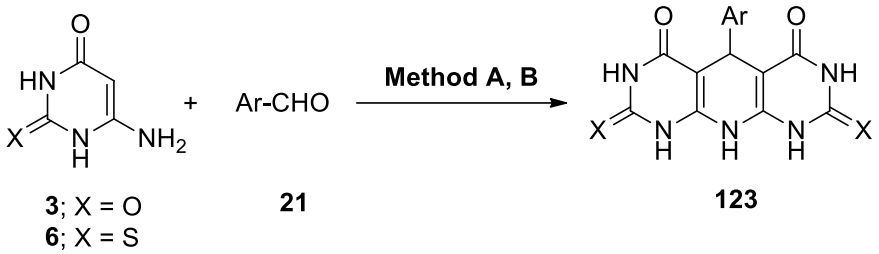
Scheme 55. Synthesis of pyrimido[5′,4′:5,6]pyrido[4,3-*c*]pyridazines **119a**, **119b** and **120**.

3.2.2.5.2. Synthesis of pyrido[2,3-*d*:4,5-*d′*]dipyrimidine. The reaction of 6-aminothiouracil (**6**) with 4-chloro-2-methyl-6-phenyl pyrimidine-5-carbonitrile (**121**) in DMF in the presence of piperdine as catalyst afforded dihydropyrido[2,3-*d*:4,5-*d′*]dipyrimidin-10(7*H*)-one **122** in 78% yield (Scheme 56).[106]



Scheme 56. Synthesis of dihydropyrido[2,3-*d*:4,5-*d'*]dipyrimidin-10(7*H*)-one **122**.

3.2.2.5.3. Synthesis of pyrido[2,3-*d*:6,5*d'*]dipyrimidine. Cyclization of 6-amino-2,3-dihydro-1*H*-pyrimidin-4-one derivatives **3** or **6** with different aryl aldehydes **21** under different reaction conditions afforded pyrido[2,3-*d*:6,5-*d'*]dipyrimidine derivatives **123** in good yields (Scheme 57, Table 25).[109,127]



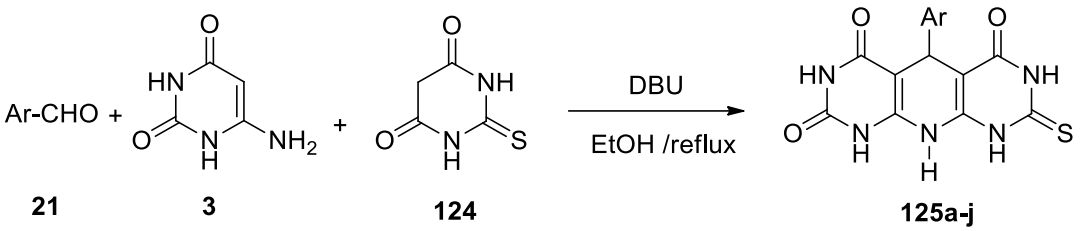
Method A: CH_3OH, HCl, stirring, r.t., 3 h
Method B: SBA-15-SO_3H., solvent free, 120 ^oC

Scheme 57. Synthesis of pyrido[2,3-*d*:6,5-*d'*]dipyrimidine derivatives **123**.

Table 25. % Yields of compounds **123**

Method	Ar	X	Yield%	Ref.
A	(2-HO-C_6H_4, 4-HO-C_6H_4, 4-H_3CO-C_6H_4, 2-HO-3-H_3CO-C_6H_3, 2-HO-5-Br-C_6H_3, 2-HO-3-H_3CO-5-Br-C_6H_2)	S	66-82	109
B	(C_6H_5, 4-O_2N-C_6H_4, 4-Cl-C_6H_4, 2,4-Cl_2-C_6H_4, 2-Br-C_6H_4, 3-O_2N-C_6H_4, 4-H_3C-C_6H_4, 4-H_3CCONH-C_6H_4; 4-HO-C_6H_4, 2-HO-6-Br-C_6H_3, 3-Cl-C_6H_4, 4-H_3CO-C_6H_4)	O	73-98	127

Pyrido[2,3-*d*:6,5-*d'*]dipyrimidine derivatives **125a-j** could also be synthesized in good yields through one-pot reaction of aryl aldehydes **21** with aminouracil **3** and thiobarbituric acid (**124**) using DBU as a nitrogen-based organocatalyst in ethanol at reflux (Scheme 58, Table 26).[128]

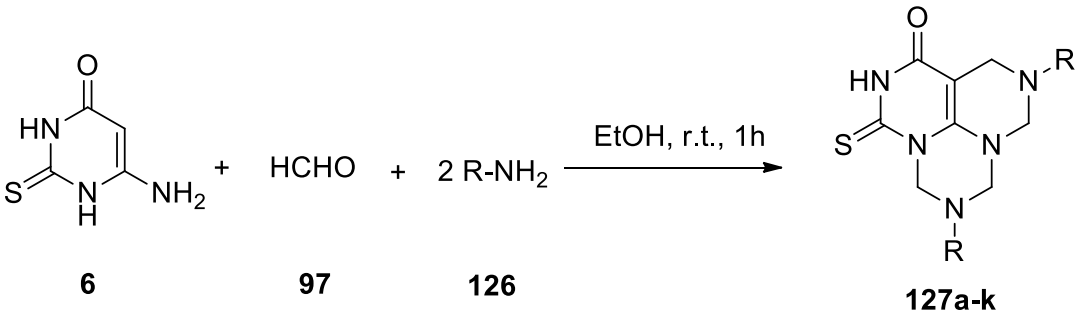


Scheme 58. Synthesis of pyrido[2,3-*d*:6,5-*d'*]dipyrimidine derivatives **125a-j**.

Table 26. % Yields of compounds **125a-j**

Products	Ar	Yield%
a	C_6H_5	83
b	4-H_3C-C_6H_4	72
c	4-Cl-C_6H_4	78
d	4-H_3CO-C_6H_4	81
e	3,4-H_3CO-C_6H_4	79
f	4-HO-C_6H_4	89
g	3-O_2N-C_6H_4	82
h	2-Furanyl	81
i	2-Thienyl	78
j	2-Pyrrolyl	83

3.2.2.5.4. Synthesis of 2,5,7,9,11-pentaazaphenalenes. Mannich reaction of 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**6**) with each of primary amines **126** and excess of formaldehyde solution **97** in ethanol afforded thioxo-5,6,9,10-tetrahydro-4*H*,8*H*-2,5,7,9,11-pentaazaphenalene-3-ones **127a-k** in good yields. The synthesized compounds were screened for antimicrobial activity and showed significant activities against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans*, *Geotrichum candidum,* and *Trichophyton rubrum*. It was reported that the introduction of aromatic amine (as in compounds **127d–k**) improved the activity 1–3 times more than the introduction of aliphatic amines (as in compounds **127a–c**) (Scheme 59, Table 27).[129]

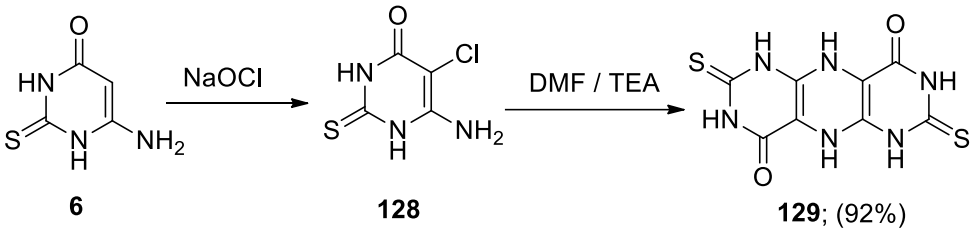


Scheme 59. Synthesis of thioxo-5,6,9,10-tetrahydro-4*H*,8*H*-2,5,7,9,11-pentaazaphenalene-3-ones.

Table 27. % Yields of compounds **127a-k**

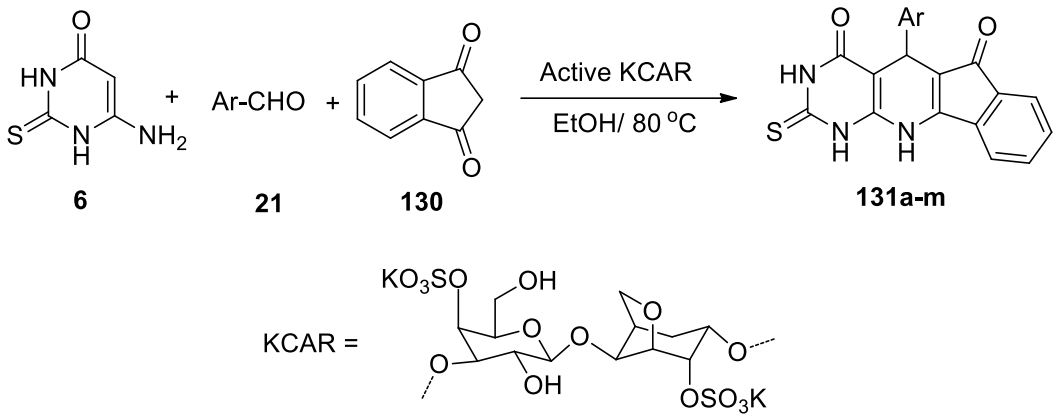
Products	R	Yeild%
a	$-CH_2CH_3$	93
b	$-CH_2CH(CH_3)$	95
c	$-CH_2CH_2CH_2CH_3$	92
d	$-H_2CC_6H_5$	85
e	$-C_6H_5$	82
f	$3-H_3CO-C_6H_4$	94
g	$3-H_3C-C_6H_4$	85
h	$4-H_3C-C_6H_4$	87
i	$4-Cl-C_6H_4$	90
j	$4-Br-C_6H_4$	89
k	2-Naphthyl	83

3.2.2.6. Fused [6-6-6]systems: (six heteroatoms). 3.2.2.6.1. Synthesis of pyrimido[4,5-*g*]pteridine. Treatment of 6-aminothiouracil (**6**) with sodium hypochlorite furnished 6-amino-5-chloro-1,3-dihydrouracil (**128**) in 87% yield. Heating of the latter compound in DMF and in the presence of trimethylamine, provided hexahydropyrimido[4,5-*g*]pteridine **129** in 92% yield. The latter compound showed moderate anti-microbial activity against the Gram-positive *Bacillus subtilis* (Scheme 60).[106]



Scheme 60. Synthesis of hexahydropyrimido[4,5-*g*]pteridine **129**.

3.2.3. Synthesis of fused tetracyclic systems. 3.2.3.1. Fused [6-5-6-6]systems: Three heteroatoms. 3.2.3.1.1. Synthesis of indeno[2`,1`:5,6]pyrido[2,3-*d*]pyrimidine. Three component reaction of 6-aminothiouracil (**6**) with aryl aldehydes **21** and 1,3-indandione (**130**) in ethanol at reflux using kappa-carrageenan (KCAR) as a catalyst afforded indeno[2`,1`:5,6]pyrido[2,3-*d*]pyrimidine derivatives **131a-m** in good yields (Scheme 61, Table 28).[130]

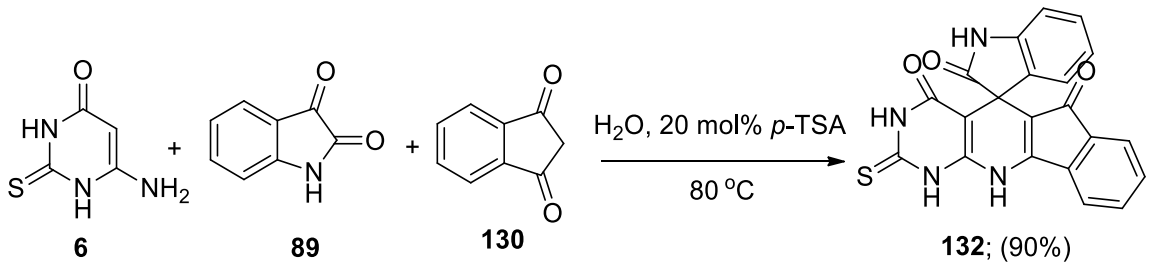


Scheme 61. Synthesis of indeno[2`,1`:5,6]pyrido [2,3-*d*]pyrimidine derivatives **131a-m**.

Table 28. % Yields of compounds **131a-m**

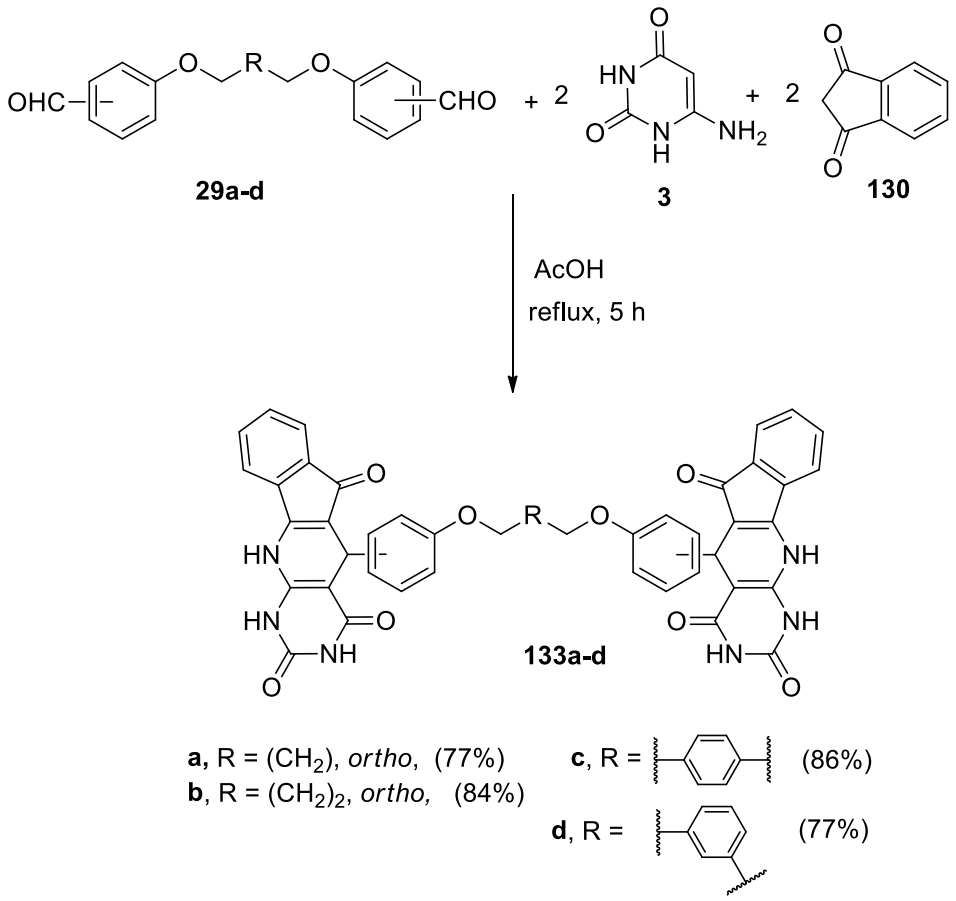
Products	Ar =	Yield%
a	4-Cl-C_6H_4	94
b	4-Br-C_6H_4	82
c	4-F-C_6H_4	86
d	4-F_3C-C_6H_4	65
e	4-H_3CO-C_6H_4	72
f	4-HO-C_6H_4	61
g	3-Cl-C_6H_4	82
h	3-F-C_6H_4	88
i	2-HO-3-H_3CO-C_6H_3	93
j	2,6-Cl_2-C_6H_3	82
k	2-Cl-C_6H_4	88
l	3-H_3CO-C_6H_4	65
m	3-H_3COOC-C_6H_4	95

Abdelmoniem *et al*.[124] reported the synthesis of spiro[indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-5,3′-indoline]trione **132** in 90% yield through a one pot reaction of isatin (**89**) with 6-aminothiouracil (**6**) and indanedione (**130**). The reaction was carried out in distilled water using *p*-TSA as an acidic catalyst (Scheme 62).



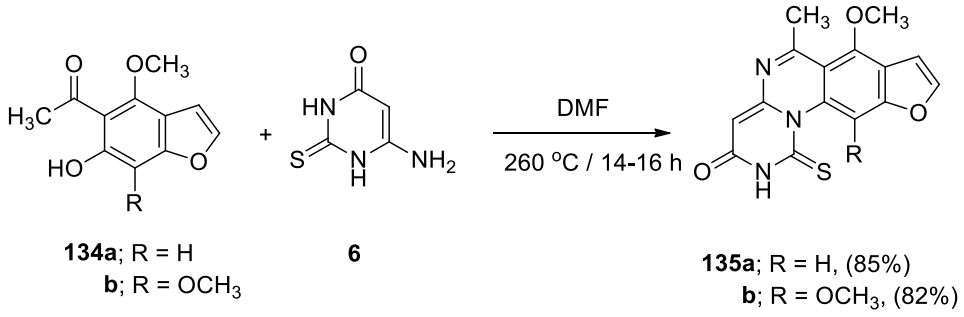
Scheme 62. Synthesis of spiro[indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-5,3′-indoline]trione **132**.

Condensation of *bis*(aldehydes) **29a-d** with two moles of both 6-aminouracil (**3**) and indanedione (**130**) in acetic acid at reflux gave a series of *bis*(indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidines) **133a-d** in good yields (Scheme 63). [76]



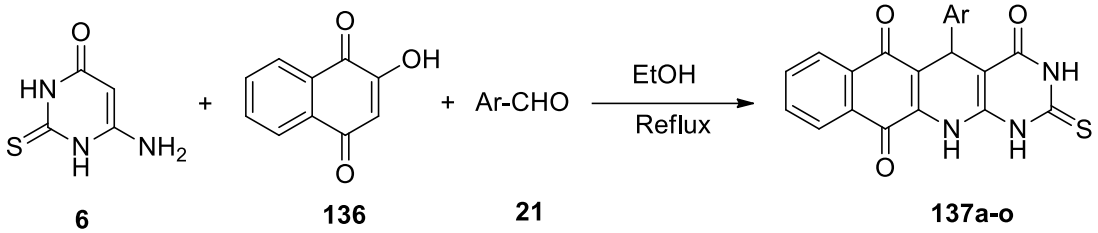
Scheme 63. Synthesis of *bis*(indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidines) **133a-d**.

3.2.3.2. Fused [5-6-6-6]systems: Three heteroatoms. 3.2.3.2.1. Synthesis of furo[3,2-*g*]pyrimido[1,6-*a*]quinazolin-3-one. Furo[3,2-*g*]pyrimido[1,6-*a*]quinazolin-3-one derivatives **135a** and **135b** were synthesized in 85% and 82% yield, respectively, upon heating acetyl benzofuran derivatives **134a** and **134b** with 6-aminothiouracil (**6**) in DMF at reflux (Scheme 64).[131]



Scheme 64. Synthesis of furo[3,2-*g*]pyrimido[1,6-*a*]quinazolin-3-one derivatives **135a** and **135b**.

3.2.3.3. Fused [6-6-6-6]systems: Three heteroatoms. 3.2.3.3.1. Synthesis of benzo[*g*]pyrimido[4,5-*b*]quinolintrione. Three component reaction of 6-aminothiouracil (**6**) with aryl aldehydes **21** and 2-hydroxy-1,4-naphthoquinone (**136**) in ethanol at reflux afforded benzo[*g*]pyrimido[4,5-*b*]quinoline-4,6,11(1*H*)-trione derivatives **137a-o** in good yields (Scheme 65, Table 29).[132]

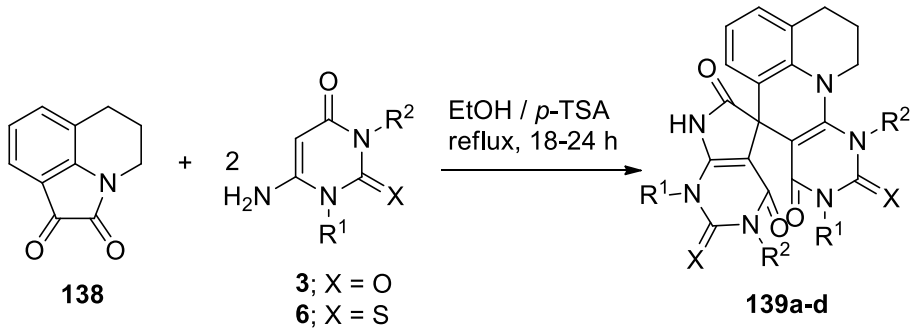


Scheme 65. Synthesis of benzo[*g*]pyrimido[4,5-*b*]quinoline-4,6,11(1*H*)-trione derivatives **137a-o**.

Table 29. %Yields of compounds **137a-o**

Products	Ar	Yield%
a	C_6H_5	70
b	4-Cl-C_6H_4	75
c	3-Cl-C_6H_4	73
d	2-Cl-C_6H_4	55
e	4-Br-C_6H_4	78
f	4-F-C_6H_4	68
g	3-F-C_6H_4	61
h	4-O_2N-C_6H_4	67
i	2-O_2N-C_6H_4	58
j	4-HO-C_6H_4	65
k	4-H_3CO-C_6H_4	77
l	3-H_3CO-C_6H_4	79
m	3,4-$(H_3CO)_2$-C_6H_4	75
n	4-H_3COOC-C_6H_4	58
o	4-H_3C-C_6H_4	70

3.2.3.3.2. Synthesis of pyrido[3,2,1-*ij*]pyrimido[4,5-*b*]quinoline-7,5'-pyrrolo[2,3-*d*]pyrimidine. Reaction of 6-aminouracil **3** or **6** with pyrrolo[3,2,1-*ij*]quinoline-1,2-dione (**138**) in ethanol at reflux in the presence of *p*-TSA as a catalyst, afforded spirocycle derivatives **139a-d** in good yields (Scheme 66, Table 30).[133]

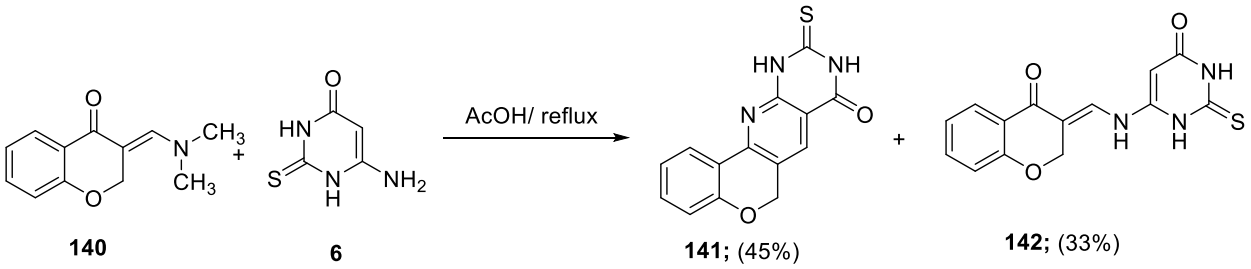


Scheme 66. Synthesis of spiro-pyrido[3,2,1-*ij*]pyrimido[4,5-*b*]quinoline-7,5'-pyrrolo[2,3-*d*]pyrimidines **139a-d**.

Table 30. %Yields of compounds **139a-d**

Products	R^1	R^2	X	Yield%
a	H	H	O	77
b	CH_3	H	O	85
c	CH_3	CH_3	O	78
d	H	H	S	83

3.2.3.4. Fused [6-6-6-6]systems: Four heteroatoms. 3.2.3.4.1. Synthesis of chromeno[4',3':4,5]pyrido[2,3-*d*]pyrimidine. Reaction of 2-dimethylaminomethylenechromanone (**140**) with 6-amino-2 thioxopyrimidin-4-one (**6**) in acetic acid at reflux gave a mixture of 10-thioxo-6,9,10,11-tetrahydro-8*H*-chromeno[3',4':5,6] pyrido[2,3-*d*]pyrimidin-8-one (**141**) and 6-(((4-oxochroman-3-ylidene)methyl)amino)-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**142**) in 45% and 33% yields, respectively (Scheme 67). [134]



Scheme 67. Synthesis of chromeno[4',3':4,5]pyrido[2,3-*d*]pyrimidine-1-one **141**.

4. Conclusions

Heterocycles, in particular nitrogen-containing heterocycles, have been found to show a range of important applications in various fields. Among the different nitrogen-containing heterocycles, pyrimidine derivatives are the most active class of six-membered heterocycles due to their wide variety of applications. This review highlighted the synthetic utilities of aminouracil and aminothiouracil as versatile precursors for various heterocyclic systems. The heterocyclic compounds described in this review are arranged on the basis of the size of the heterocyclic ring as well as the location and number of heteroatoms. It is hoped that this review of the recent literature will be useful not only for synthetic organic chemists, but also for researchers interested in medicinal and biological chemistry.

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Authors' Biographies

Hadeer M. Diab was born in 1992 in Giza, Egypt. She graduated from the Faculty of Science, Cairo University, Egypt in 2013. She got her M.Sc degree in 2018.

Mostafa E. Salem was born in Egypt in July 1983. He graduated from the Faculty of Science, Cairo University, Egypt in 2003. He got M.Sc. and Ph.D. degrees in 2011 and 2016, respectively, in the field of organic synthesis. In the same year he was appointed as lecturer of Organic chemistry at Cairo University.

Ismail A. Abdelhamid was born in Egypt in December 1978. He graduated from Cairo University, Egypt in 2001 then he got his M.Sc. and Ph.D. degrees in 2005 and 2007, respectively, at Cairo University in the field of organic synthesis. In 2017 he was appointed as a full Professor of Organic chemistry at Cairo University. He was awarded the Alexander von Humboldt research fellowship in 2008–2011 and in 2014, 2017, and 2019 with Prof. Holger Butenschön, at Hannover University, Germany. He received several research prizes; Cairo University Incentive Award (2012), Cairo University Scientific Excellence Award (2016) and State Incentive Award (2019).

Ahmed H. M. Elwahy was born in 1963 in Giza, Egypt. He graduated from Cairo University, Egypt in 1984 then he got his M.Sc. and Ph.D. degrees in 1988 and 1991, respectively, at Cairo University in the field of organic

synthesis. He was awarded the Alexander von Humboldt research fellowship in 1998–2000 and in 2003, 2005, 2009, 2010 and 2012 with Prof. Klaus Hafner, at TU Darmstadt, Germany. In 2002 he was appointed as a full Professor of Organic chemistry at Cairo University. In 2001 he received the State-Award in Chemistry and in 2016 received Cairo University Appreciation-Award in Basic Science. He has published around 140 scientific papers in distinguished international journals.