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Synthesis of Some New Pyrimidine and Pyrimido[4,5-d]pyrimidine Derivatives

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Abstract: A convenient synthesis of a series of pyrimidine carbonitrile, thiopyrimidine, and pyrimidopyrimidine derivatives, via the reactions of the versatile, readily accessible 6-aryl-4-oxo-2-thioxo-hexahydro-pyrimidine-5-carbonitrile with the appropriate reagents, is described.

Keywords: Benzaldehyde, chloroacetic acid, phenyl isothiocyanate, phosphorus oxychloride, thiourea

INTRODUCTION

The pyrimidine ring system undoubtedly belongs to the most important heterocycles in nature, as it represent the main structure of many biologically significant compounds, including nucleosides and nucleotides. For this reason many analogs and derivatives of pyrimidines have been synthesized and developed as pharmacologically active compounds or drugs. Pharmacologically active purine analogs include tricyclic structures such as imidazo[2,1-*i*]purinones (e.g., PSB-11, a potent A_3 adenosine receptor antagonist), pyrimido[4,5-*b*]indoles (e.g., APEPI, a potent A_1 adenosine receptor antagonist), and imidazo[2,1-*a*]purines (e.g., tricyclic ganciclovir analogs, which are potent antiviral agents).[1]

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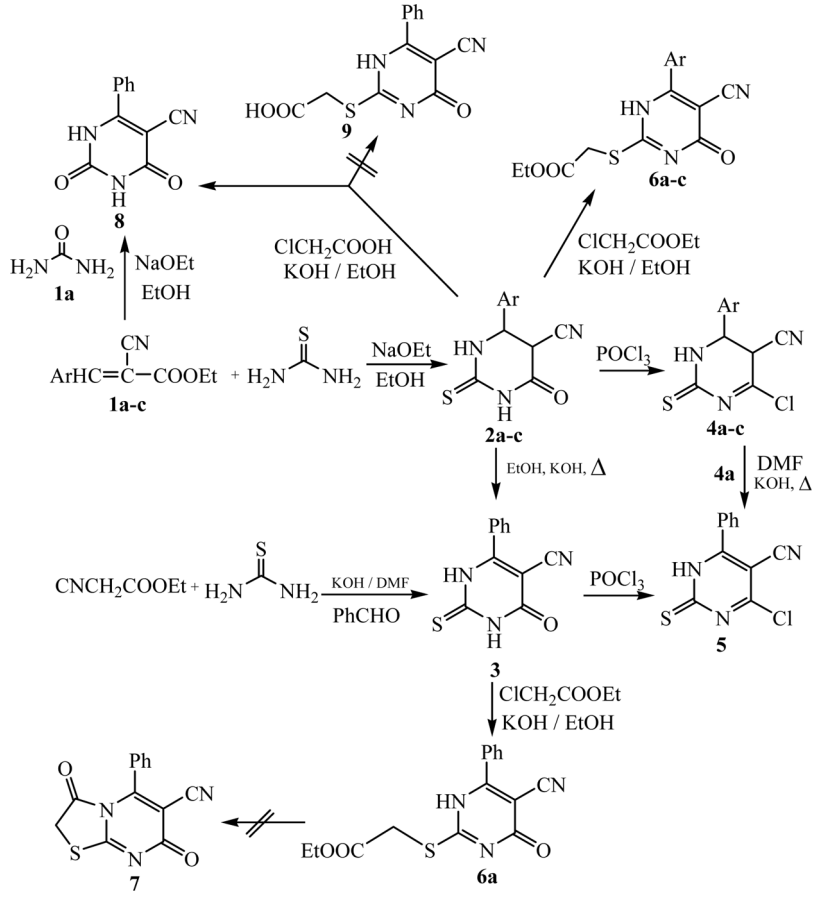
RESULTS AND DISCUSSION

Since the isolation of pyrimidine derivatives, considerable attention has been devoted to their chemistry and biological activity.[2] In recent years, there has been increasing interest in the synthesis of pyrimidine derivatives, and there are some methods used to synthesize the pyrimidine ring, allowing access to a large number of multifunctionalized pyrimidine derivatives.[3] Treatment of different ethyl arylidenecyanoacetates **(1a–c)** with thiourea in ethanol–sodium ethoxide at room temperature affords the corresponding 6-aryl-4-oxo-2-thioxo-hexahydro-pyrimidine-5-carbonitrile **(2a–c)**. Heating compound **2a** in ethanol and in the presence of potassium hydroxide led to dehydrogenation and afforded 4-oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile **(3)**.[4] Compound **3** can be prepared via the one-pot reaction of benzaldehyde with ethyl cyanoacetate and thiourea in dimethyl formamide at room temperature, in the presence of potassium hydroxide (Scheme 1).[5] Boiling pyrimidine derivatives **2a–c** in phosphorus oxychloride afforded the corresponding 6-aryl-4-chloro-2-thioxo-1,2,5,6-tetrahydro-pyrimidine-5-carbonitrile **(4a–c)**. The IR spectra of these compounds indicate the disappearance of (CO) group. For example, the IR spectrum of compound **(4a)** showed characteristic absorption bands at 3152 cm^{-1} (NH), 2221 cm^{-1} (CN), 1625 cm^{-1} (C=N), and 700 cm^{-1} (C−Cl). The mass spectrum of compound **4a** showed the molecular ion peak at m/z 249 (M^+) (Scheme 1).

In a similar manner, boiling of pyrimidine derivative **3** in phosphorus oxychloride afforded the corresponding 4-chloro-6-phenyl-2-thioxo-1,2-dihydro-pyrimidine-5-carbonitrile **(5)**. The IR spectrum of compound **5** indicates the disappearance of (CO) group and showed characteristic absorption bands at 3420 cm^{-1} (NH), 2205 cm^{-1} (CN), 1621 cm^{-1} (C=N), and 700 cm^{-1} (C–Cl). The mass spectrum of compound **(5)** showed the molecular ion peak at m/z 247 (M^+).

An alternative method for the synthesis of compound **5** was achieved by heating of pyrimidine derivative **4a** in dimethyl formamide in the presence of potassium hydroxide Scheme 1. Pyrimidine derivatives **2a–c** reacted with ethyl chloroacetate in alcoholic potassium hydroxide to afford (6-aryl-5-cyano-4-oxo-1,4-dihydro-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester **(6a–c)** (Scheme 1). The IR spectrum of compound 6a showed characteristic absorption bands at 3207 cm^{-1} (NH), 2223 cm^{-1} (CN), 1735 cm^{-1} (COOEt), and 1662 cm^{-1} (NCO). The mass spectrum of compound **6b** showed the molecular ion peak at m/z 345 (M^+). The ^1H NMR spectrum of compound **6a** revealed signals at δ 1.23 as triplet for CH_3, δ 4.04 as singlet for SCH_2, δ 4.22 as quartet for CH_2, and 7.1–7.8 as multiplets for aromatic protons.



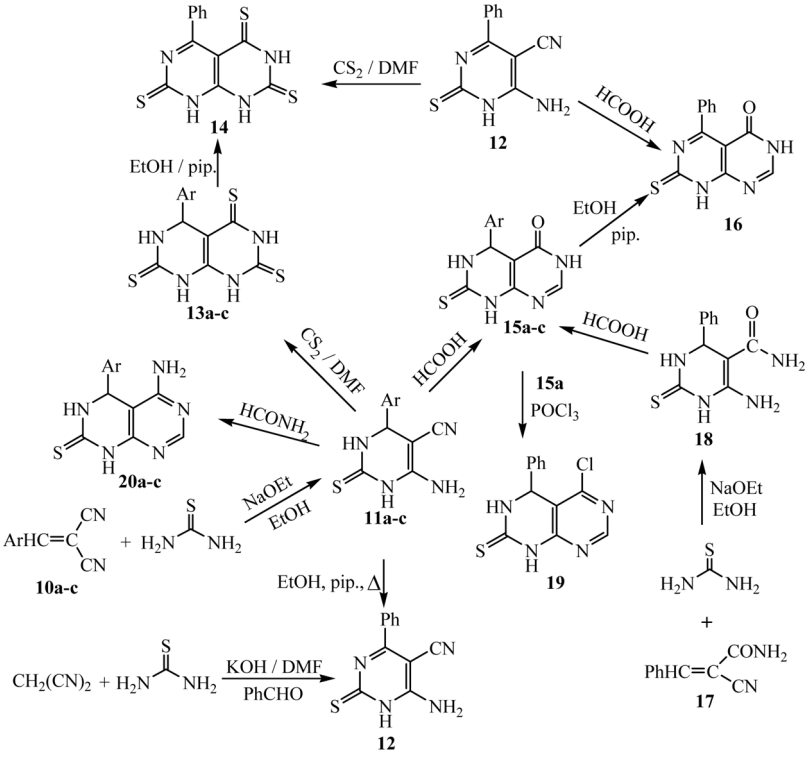
Scheme 1. (a) Ar = C_6H_5, (b) Ar = *p*-$OCH_3C_6H_4$, and (c) Ar = *p*-$N(CH_3)_2$ C_6H_4.

On the other hand, refluxing of thioxopyrimidine derivative **3** with ethyl chloroacetate in alcoholic potassium hydroxide afforded compound **6a** (Scheme 1). All attempts to synthesize thiazolo[3,2-*a*]pyrimidine derivative **7** from **6a** under different reaction conditions (refluxing in ethanol–sodium ethoxide, refluxing in acetic anhydride,[6] refluxing in $AcOH/H_2SO_4$[7]) failed. The reaction of thiopyrimidine derivative **2a** with chloroacetic acid in ethanol in the presence of potassium hydroxide gave 2,4-dioxo-6-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile **8**, not the expected *S*-alkyl derivative **9**. Compound **8** was confirmed by alternative synthesis. Thus, ethyl benzylidenecyanoacetate **1a** was reacted with urea in ethanol–sodium ethoxide at room temperature to afford a compound identical in all respects (mp, mixed mp, IR, ^{1}H NMR) to **8**

(Scheme 1). The IR spectrum of compound **8** showed characteristic absorption bands at 3425 cm^{-1} (NH), 2230 cm^{-1} (CN), 1724, and 1683 cm^{-1} (2CO). The mass spectrum showed the molecular ion peak at m/z 213 (M^+).

The reaction of different arylidenemalononitrile derivatives **(10a–c)** with thiourea in ethanol–sodium ethoxide at room temperature afforded the corresponding 6-amino-4-aryl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile (**11a–c)**. Tetrahydropyrimidine **11a**, when heated in ethanol in the presence of piperidine, underwent auto-oxidation to produce 6-amino-4-phenyl-2-thioxo-1,2-dihydro-pyrimidine-5-carbonitrile **(12)**. Dihydro-pyrimidine (**12**) can easily obtained via a one-pot reaction of malononitrile, benzaldehyde, and thiourea in dimethyl formamide in the presence of potassium hydroxide at room temperature[4] (Scheme 2).

Compounds **11a–c** and **12** were used as precursors for the synthesis of new pyrimido[4,5-*d*]pyrimidine derivatives. Thus, reaction of pyrimidines **(11a–c)** with carbon disulphide in refluxing dimethylformamide



Scheme 2. (a) Ar = C_6H_5, (b) Ar = *p*-$OCH_3C_6H_4$, and (c) Ar = *p*-$CH_3C_6H_4$.

for 2 h afforded 5-aryl-5,8-dihydro-1*H*,6*H*-pyrimido[4,5-*d*]pyrimidine-2,4,7-trithione **(13a–c)**, which was converted to 5-phenyl-1*H*,8*H*-pyrimido [4,5-*d*]pyrimidine-2,4,7-trithione (**14**) by heating **13a** in ethanol in the presence of a catalytic amount of piperidine. Pyrimido[4,5-*d*]pyrimidine-trithione **(14)** could be also synthesized by refluxing dihydro-pyrimidine **(12)** with carbon disulphide in dimethylformamide (Scheme 2). The IR spectrum of compound **13a** showed the absence of the CN absorption band and revealed the presence of characteristic absorption bands of (NH) at 3183 cm^{-1} and (C=S) at 1238 cm^{-1}. The mass spectrum of compound **13a** showed the molecular ion peak at m/z 306 (M^+). The IR spectrum of compound **14** showed the disappearance of the (CN) group and showed characteristic absorption bands at 3363 cm^{-1} (NH), 1247 cm^{-1} (C=S), and 1617 cm^{-1} (C=N). The mass spectrum of compound **14** showed the molecular ion peak at m/z 304 (M^+).

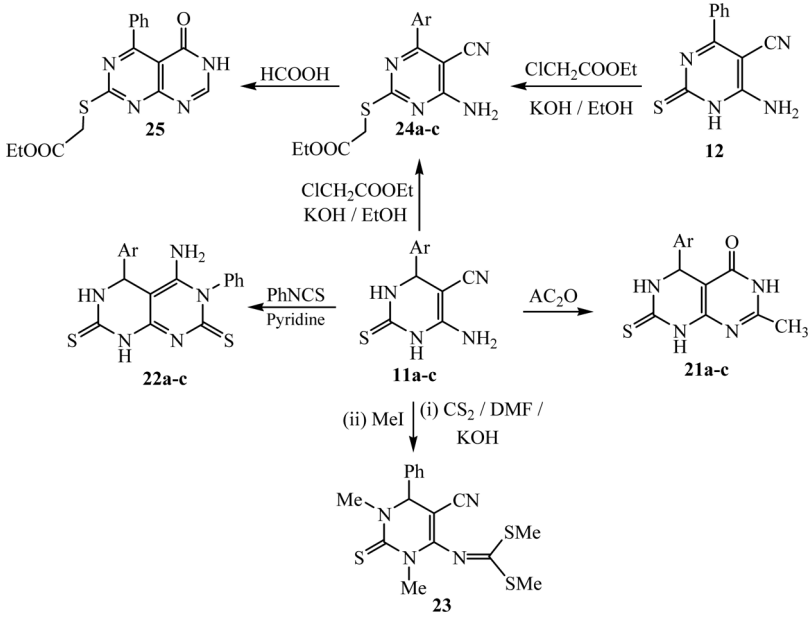
Prolonged heating of **11a–c** with an excess of formic acid afforded the corresponding 5-aryl-7-thioxo-5,6,7,8-tetrahydro-3*H*-pyrimido[4,5-*d*] pyrimidin-4-one **(15a–c)**, which converted to 5-phenyl-7-thioxo-7,8-dihydro-3*H*-pyrimido[4,5-*d*]pyrimidin-4-one **(16)** by heating in ethanol in the presence of a catalytic amount of piperidine. Refluxing dihydro-pyrimidine derivative **(12)** with an excess of formic acid afforded the corresponding dihydro-pyrimido[4,5-*d*]pyrimidine derivative **16** (Scheme 2). The IR spectrum of compound **15a** showed no absorption band at 2220 cm^{-1} corresponding to the (CN) group and showed characteristic absorption bands at 3149 cm^{-1} (NH), appearance of (C=O) at 1714 cm^{-1}, and (C=S) at 1241 cm^{-1}. The mass spectrum of compounds **15a** and **15b** showed the molecular ion peak at m/z 258 (M^+) and m/z 288 (M^+), respectively. The ^1H NMR spectrum of compound **15c** revealed signals at δ 2.32 as singlet for CH_3, at δ 5.15 as singlet for NCH, at δ 7.11 as singlet for NCHN, and at δ 10.17, 10.46, and 11.76 as singlets for 3NH. The IR spectrum of compound **16** indicates the disappearance of the (CN) group. The mass spectrum of compound **16** showed the molecular ion peak at m/z 256 (M^+).

An alternative method for the synthesis of compound **15a** was achieved by the reaction of benzylidenecyanoacetamide **(17)** with thiourea in ethanol–sodium ethoxide to afford 6-amino-4-phenyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid amide **(18)**. Refluxing compound **18** in an excess of formic acid afforded tetrahydro-pyrimido[4,5-*d*]pyrimidine **(15a)** (Scheme 2). Refluxing pyrimido[4,5-*d*]pyrimidin-4-one derivative **(15a)** with phosphorousoxychloride at 100 °C afforded the corresponding 5-chloro-4-phenyl-3,4-dihydro-1*H*-pyrimido[4,5-*d*]pyrimidine-2-thione **(19)** (Scheme 2). The IR spectrum of compound **19** showed no absorption band at 1714 cm^{-1} corresponding to the (C=O) group and showed characteristic absorption bands at 3200 cm^{-1} (NH) and

1614 cm^{-1} (C=N). The mass spectrum of compound **19** showed the molecular ion peak at m/z 276 (M^+). Boiling compounds **11a–c** under reflux with an excess of formamide afforded the corresponding 5-amino-4-aryl-3,4-dihydro-1*H*-pyrimido[4,5-*d*]pyrimidine-2-thione **(20a–c)** (Scheme 2). The IR spectrum showed the absence of the CN absorption band and revealed the presence of characteristic absorption bands at 3259 cm^{-1} (NH). The mass spectrum of compounds **20a** and **20b** showed the molecular ion peaks at m/z 257 (M^+) and m/z 287 (M^+), respectively.

On the other hand, when pyrimidine derivatives **10a–c** refluxed with acetic anhydride, they afforded directly 5-aryl-2-methyl-7-thioxo-5,6,7,8-tetrahydro-3*H*-pyrimido[4,5-*d*]pyrimidin-4-one **(21a–c)** (Scheme 3). The IR spectrum of compound **21a** showed the absence of the CN absorption band and revealed the presence of characteristic absorption bands at 3196 cm^{-1} (NH), 1726 cm^{-1} (C=O), 1599 cm^{-1} (C=N), and 1229 cm^{-1} (C=S). The ^{1}H NMR spectrum of compound **21b** revealed signals at δ 2.51 as singlet for CH_3, δ 3.76 as singlet for OCH_3, δ 5.16 as singlet for NCH, and δ 10.14, 10.46, and 11.74 as singlets for 3NH. The mass spectrum of compound **21b** showed the molecular ion peak at m/z 302 (M^+).

Tetrahydro-thioxopyrimidines **(11a–c)** were found to afford the 5-amino-4-aryl-3,4-dihydro-6-phenylpyrimido[4,5-*d*]pyrimidine-2,7(*1H,6H*)-dithione **(22a–c)**, when refluxed with phenyl isothiocyanate in pyridine



Scheme 3. (a) Ar = C_6H_5, (b) Ar = *p*-$OCH_3C_6H_4$, and (c) Ar = *p*-$CH_3C_6H_4$.

(Scheme 3). The IR spectrum of compound **22a** showed the absence of the CN absorption band and revealed the presence of characteristic absorption bands at 3206 cm^{-1} (NH_2), 3034 cm^{-1} (NH), 1624 cm^{-1} (C=N), and 1241 cm^{-1} (C=S). The mass spectrum of compound **22a** showed the molecular ion peak at m/z 366 ($M^+ - 1$).

Treatment of **11a** with carbon disulphide and methyl iodide at room temperature in dimethylformamide (DMF) in the presence of potassium hydroxide gives (dimethyl-5-cyano-6-phenyl-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yldithioimidocarbonate)pyrimidine **(23)** (Scheme 3). The IR spectrum of compound **23** showed the absence of the NH_2 and NH absorption bands and revealed the presence of characteristic absorption bands at 2224 cm^{-1} (CN), 1579 cm^{-1} (C=N), and 1230 cm^{-1} (C=S). The ^{1}H NMR spectrum of compound **22** revealed signals at δ 2.38 as singlet for $2SCH_3$, δ 3.69 as singlet for $2NCH_3$, and δ 4.76 as singlet for CH. The mass spectrum of compound **23** showed the molecular ion peak at m/z 362 (M^+).

Refluxing thioxopyrimidine derivatives **11a–c** with ethyl chloroacetate in alcoholic potassium hydroxide afforded (4-amino-6-aryl-5-cyano-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester **(24a–c)**. On the other hand, when dihydro-pyrimidine derivative **12** reacted with ethyl chloroacetate in alcoholic potassium hydroxide, it afforded (4-amino-5-cyano-6-phenyl-pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester **(24a)** (Scheme 3). The IR spectrum of compound **24a** showed characteristic absorption bands at 3336 cm^{-1} (NH), 3454 cm^{-1} (NH) 2187 cm^{-1} (CN), 1740 cm^{-1} carbonyl ester, 1659 cm^{-1} (C=N). The ^{1}H NMR spectrum of compound **24a** revealed signals at δ 1.39 as triplet for CH_3, δ 4.01 as singlet for SCH_2, δ 4.35 as quartet for OCH_2, and δ 10.19 as singlet for NH_2. Compound **24a** underewent esting for reactivity of *β*-enaminonitrile moiety by prolonged heating with an excess of formic acid to afford the corresponding (5-oxo-4-phenyl-5,6-dihydro-pyrimido[4,5-*d*]pyrimidin-2-ylsulfanyl)-acetic acid ethyl ester **(25)** (Scheme 3). The IR spectrum of compound **25** showed no absorption band at 2220 cm^{-1} corresponding to the (CN) group and revealed the presence of characteristic absorption bands at 3086 cm^{-1} (NH), appearance of (C=O) at 1712 cm^{-1}, (COOEt) at 1735 cm^{-1}, and (C=N) at 1616 cm^{-1}. The mass spectrum of compound **25** showed the molecular ion peak at m/z 342 (M^+).

EXPERIMENTAL

All melting points are recorded on a Gallenkamp electric melting-point apparatus and are uncorrected. The IR spectra ν cm^{-1} (KBr) were recorded on Perkin-Elmer infrared spectrophotometer model 157,

Table 1. Characterization data of newly prepared compounds

Compound	Formula	Mol. weight	Analytical data calc., % (Found, %)			Yield (%)	Mp (°C)
			C	H	N		
2a[4]	$C_{11}H_9N_3OS$	231.27	57.13 (57.21)	3.92 (3.98)	18.17 (18.23)		Lit.[4] mp)
2b[4]	$C_{12}H_{11}N_3O_2S$	261.30	55.16 (55.11)	4.24 (4.20)	16.08 (16.01)		Lit.[4] mp)
2c[4]	$C_{13}H_{14}N_4OS$	274.34	56.91 (56.82)	5.14 (5.09)	20.42 (20.38)		Lit.[4] mp)
3[5]	$C_{11}H_7N_3OS$	229.26	57.63 (57.51)	3.08 (3.01)	18.33 (18.27)		Lit.[4] mp)
4a	$C_{11}H_8ClN_3S$	249.72	52.91 (52.83)	3.23 (3.29)	16.83 (16.75)	70	257
4b	$C_{12}H_{10}ClN_3OS$	279.75	51.52 (51.27)	3.60 (3.48)	15.02 (15.22)	65	280
4c	$C_{13}H_{13}ClN_4S$	292.79	53.33 (53.18)	4.48 (4.51)	19.14 (19.06)	75	285
5	$C_{11}H_6ClN_3S$	247.7	53.34 (53.37)	2.44 2.49)	16.96 (16.90)	**A**, 60; **B**, 70	> 280
6a	$C_{15}H_{13}N_3O_3S$	315.35	57.13 (57.11)	4.16 (4.13)	13.33 (13.21)	85	240
6b	$C_{16}H_{15}N_3O_4S$	345.37	55.64 (55.73)	4.38 (4.44)	12.17 (12.23)	80	200
6c	$C_{17}H_{18}N_4O_3S$	358.4	56.97 (57.01)	5.06 (5.15)	15.63 (15.62)	85	215
8	$C_{11}H_7N_3O_2$	213.19	61.97 (62.16)	3.31 (3.29)	19.71 (19.69)	40	285
11a[4]	$C_{11}H_{10}N_4S$	230.29	57.37 (57.34)	4.38 (4.32)	24.33 (24.28)		Lit.[4] mp)
11b[4]	C12H12N4OS	260.31	55.37 (55.32)	4.65 (4.58)	21.52 (21.46)		Lit.[4] mp)
11c[4]	$C_{12}H_{12}N_4S$	244.32	58.99 (58.92)	4.95 (4.89)	22.93 (22.88)		Lit.[4] mp)
12[4]	$C_{11}H_8N_4S$	228.27	57.88 (57.92)	3.53 (3.58)	24.54 (24.61)		Lit.[4] mp)
13a	$C_{12}H_{10}N_4S_3$	306.43	47.03 (47.05)	3.29 (3. 39)	18.28 (18.30)	82	250
13b	$C_{13}H_{12}N_4OS_3$	336.46	46.41 (46.34)	3.59 (3.66)	16.65 (16.64)	75	260
13c	$C_{13}H_{12}N_4S_3$	320.46	48.27 (48.54)	3.77 (3.67)	17.48 (17.10)	73	> 280
14	$C_{12}H_8N_4S_3$	304.41	47.35 (47.65)	2.65 (2.88)	18.40 (18.73)	68	> 280
15a	$C_{12}H_{10}N_4OS$	258.3	55.80 (56.02)	3.90 (4.18)	21.69 (21.75)	90	251

(*Continued*)

Table 1. Continued

Compound	Formula	Mol. weight	Analytical data calc., % (Found, %)			Yield (%)	Mp (°C)
			C	H	N		
15b	$C_{13}H_{12}N_4O_2S$	288.32	54.15 (54.54)	4.20 (4.37)	19.43 (19.71)	92	220
15c	$C_{13}H_{12}N_4OS$	272.33	57.34 (57.23)	4.44 (4.12)	20.57 (20.35)	87	150
16	$C_{12}H_8N_4OS$	256.28	56.24 (56.43)	3.15 (3.47)	21.86 (22.10)	71	249
18	$C_{11}H_{12}N_4OS$	248.3	53.21 (53.68)	4.87 (4.45)	22.56 (22.13)	65	196
19	$C_{12}H_9ClN_4S$	276.74	52.08 (51.87)	3.28 (3.48)	20.24 (20.42)	62	240
20a	$C_{12}H_{11}N_5S$	257.31	56.01 (56.34)	4.31 (4.68)	27.22 (27.75)	69	> 280
20b	$C_{13}H_{13}N_5OS$	287.34	54.34 (54.69)	4.56 (4.27)	24.37 (24.11)	65	220
20c	$C_{13}H_{13}N_5S$	271.34	57.54 (57.93)	4.83 (5.03)	25.81 (25.98)	60	215
21a	$C_{13}H_{12}N_4OS$	272.33	57.34 (57.85)	4.44 (4.97)	20.57 (20.92)	72	> 280
21b	$C_{14}H_{14}N_4O_2S$	302.35	55.61 (55.25)	4.67 (4.99)	18.53 (18.83)	79	220
21c	$C_{14}H_{14}N_4OS$	286.35	58.72 (59.12)	4.93 (5.41)	19.57 (19.95)	82	150
22a	$C_{18}H_{15}N_5S_2$	379.5	59.15 (59.78)	4.14 (4.66)	19.16 (19.52)	57	250
22b	$C_{19}H_{17}N_5OS_2$	395.5	57.70 (58.03)	4.33 (4.78)	17.71 (18.09)	62	200
22c	$C_{19}H_{17}N_5S_2$	379.5	60.13 (60.56)	4.52 (4.74)	18.45 (18.61)	58	190
23	$C_{16}H_{18}N_4S_3$	362.54	53.01 (52.66)	5.00 (5.14)	15.45 (15.52)	30	185
24a	$C_{15}H_{14}N_4O_2S$	314.36	57.31 (57.89)	4.49 (4.21)	17.82 (17.65)	87	280
24b	$C_{16}H_{16}N_4O_3S$	344.39	55.80 (55.48)	4.68 (4.23)	16.27 (15.84)	77	248
24c	$C_{16}H_{16}N_4O_2S$	328.39	58.52 (58.88)	4.91 (5.24)	17.06 (17.32)	81	210
25	$C_{16}H_{14}N_4O_3S$	342.37	56.13 (56.76)	4.12 (4.59)	16.36 (16.73)	67	230

grating. The ^{1}H NMR spectra were run on a Varian spectrophotometer at 200 MHz. using TMS as an internal reference and DMSO-d_6 as solvent. The mass spectra (EI) were recorded at 70 eV with Kratos MS equipment and/or a Varian MAT 311 A spectrometer. Elemental analyses (C, H, and N) were carried out at the microanalytical center of Cairo University Giza, Egypt. The results were found to be in good agreement (±0.3%) with the calculated values. Compounds **(2)**,[4] **(3)**,[5] **(11)**,[4] and **(12)**,[4] were prepared according to literature procedures. The barbituric and dimethylbarbituric acids were purchased by Fluoka Company.

General Procedure for Synthesis of 6-Aryl-4-chloro-2-thioxo-1,2,5,6-tetrahydro-pyrimidine-5-carbonitrile (4a–c)

Compounds **2a** (1.16 g, 5 mmol), **2b** (1.30 g, 5 mmol), or **2c** (1.37 g, 5 mmol) were added to phosphorus oxychloride 30 cm^3 and refluxed on a water bath at 95 °C for 4 h. The mixture was poured onto ice-cold water. The precipitate formed and was filtered off, dried, and crystallized from ethanol to afford **4a–c**, respectively (cf. Tables 1 and 2).

Synthesis of 4-Chloro-6-phenyl-2-thioxo-2,5-dihydropyrimidine-5-carbonitrile (5)

Method A

Compound **3** (1.15 g, 5 mmol) was added to phosphorus oxychloride 30 cm^3 and refluxed on a water bath at 95 °C for 5 h. The reaction mixture was left to cool and then poured onto ice-cold water. The precipitate formed and was filtered off, dried, and crystallized from a mixture of ethanol/chloroform.

Method B

A mixture of compound **4a** (1.24 g, 5 mmol), potassium hydroxide (0.28 g, 5 mmol), and 25 cm^3 dimethylformamide was refluxed for 2 h. The reaction mixture was left to cool and then poured onto ice-cold water. The precipitate formed and was filtered off, dried, and crystallized from a mixture of ethanol/chloroform to give compound **5**. (cf. Tables 1 and 2).

Table 2. Spectral data of newly prepared compounds

Compound	Spectral data
4a	IR, ν/cm^{-1}: 3152 (NH), 2221 (C≡N), 1625 (C=N), 1150 (C–Cl) MS, m/z (%): 249 (21) (M^+)
4b	IR, ν/cm^{-1}: 3160 (NH), 2222 (C≡N), 1620 (C=N), 1153 (C–Cl)
4c	IR, ν/cm^{-1}: 3149 (NH), 2220 (C≡N), 1630 (C=N), 1152 (C–Cl)
5	IR, ν/cm^{-1}: 3420 (NH), 2205 (C≡N), 1621 (C=N), 1178 (C–Cl) MS, m/z (%): 247 (100) (M^+)
6a	IR, ν/cm^{-1}: 3207 (NH), 2223 (C≡N), 1735 (COOEt), 1662 (CON) ^{1}H NMR ($CDCl_3$), δ: 1.23 (t, 3H, CH_3), 4.04 (s, 2H, SCH_2), 4.22 (q, 2H, OCH_2), 7.26–8.07 (m, 5H, Ar–H)
6b	IR, ν/cm^{-1}: 3200 (NH), 2225 (C≡N), 1738 (COOEt), 1660 (CON) MS, m/z (%): 245 (28) (M^+)
6c	IR, ν/cm^{-1}: 3209 (NH), 2224 (C≡N), 1740 (COOEt), 1665 (CON)
8	IR, ν/cm^{-1}: 3425 (NH), 2230 (C≡N), 1724, 1683 (2CON) MS, m/z (%): 213 (44) (M^+)
13a	IR, ν/cm^{-1}: 3183 (NH), 1238 (C=S) MS, m/z (%): 306 (100) (M^+)
13b	IR, ν/cm^{-1}: 3180 (NH), 1245 (C=S)
13c	IR, ν/cm^{-1}: 3185 (NH), 1240 (C=S)
14	IR, ν/cm^{-1}: 3363 (NH), 1617 (C=N) MS, m/z (%): 304 (30) (M^+)
15a	IR, ν/cm^{-1}: 3149 (NH), 1714 (C=O), 1614 (C=N), 1241 (C=S) MS, m/z (%): 258 (47) (M^+)
15b	IR, ν/cm^{-1} : 3150 (NH), 1712 (C=O), 1610 (C=N), 1240 (C=S) MS, m/z (%): 288 (27) (M^+)
15c	IR, ν/cm^{-1} : 3156 (NH), 1716 (C=O), 1618 (C=N), 1248 (C=S) ^{1} H NMR (DMSO-d_6), δ: 2.32 (s, 3H, CH_3), 5.15 (s, 1H, NCH), 7.15–7.35 (m, 4H, Ar-H), 7.11 (s, 1H, NCHN), 10.17, 10.46, 11.7 (s, 3H, 3NH)
16	IR, ν/cm^{-1} : 3164 (NH), 1712 (C=O), 1617 (C=N), 1241 (C=S) MS, m/z (%): 256 (100) (M^+)

18	IR, ν/cm^{-1} : 3340 (NH), 3325 (NH_2), 1662 ($CONH_2$), 1238 (C = S) MS, m/z (%): 248 (18) (M^+)
19	IR, ν/cm^{-1} : 3200 (NH), 1614 (C = N), 1050 (C–Cl) MS, m/z (%): 276 (42) (M^+)
20a	IR, ν/cm^{-1} : 3316 (NH_2), 3259 (NH), 1626 (C = N), 1240 (C = S) MS, m/z (%): 257 (86) (M^+)
20b	IR, ν/cm^{-1} : 3318 (NH_2), 3263 (NH), 1630 (C = N), 1242 (C = S) MS, m/z (%): 287 (11) (M^+)
20c	IR, ν/cm^{-1} : 3320 (NH_2), 3298 (NH), 1629 (C = N), 1240 (C = S)
21a	IR, ν/cm^{-1} : 3196 (NH), 1726 (C = O), 1599 (C = N), 1229 (C = S) MS, m/z (%): 287 (11) (M^+)
21b	IR, ν/cm^{-1} : 3200 (NH), 1730 (C = O), 1601 (C = N), 1230 (C = S) ^{1}H NMR (DMSO-d_6), δ: 2.51 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 5.16 (s, 1H, NCH), 6.98–7.39 (m, 4H, Ar–H), 10.14, 10.46, 11.74 (s, 3H, 3NH) MS, m/z (%): 302 (27) (M^+)
21c	IR, ν/cm^{-1} : 3195 (NH), 1725 (C = O), 1603 (C = N), 1227 (C = S)
22a	IR, ν/cm^{-1} : 3206 (NH_2), 3034 (NH), 1624 (C = N), 1241 (C = S) MS, m/z (%): 366 (32) ($M^+ - 1$)
22b	IR, ν/cm^{-1} : 3200 (NH_2), 3025 (NH), 1620 (C = N), 1240 (C = S)
22c	IR, ν/cm^{-1} : 3205 (NH_2), 3035 (NH), 1628 (C = N), 1242 (C = S)
23	IR, ν/cm^{-1} : 2224 (C ≡ N), 1579 (C = N), 1230 (C = S) ^{1}H NMR (DMSO-d_6), δ: 2.38 (s, 6H, $2SCH_3$), 2.69 (s, 6H, $2NCH_3$), 4.76 (s, 1H, NCH), 7.29–7.6 (m, 5H, Ar–H) MS, m/z (%): 362 (100) (M^+)
24a	IR, ν/cm^{-1} : 3454 (NH_2), 3336 (NH), 2187 (C ≡ N), 1740 (COOEt), 1659 (C = N) ^{1} H NMR (DMSO-d_6), δ: 1.39 (t, 3H, CH_3), 4.01 (s, 2H, SCH_2), 4.35 (q, 2H, OCH_2), 7.16–7.41 (m, 5H, Ar–H), 10.19 (s, 2H, NH_2)
24b	IR, ν/cm^{-1} : 3328 (NH_2), 3461 (NH), 2190 (C ≡ N), 1742 (COOEt), 1655 (C = N)
24c	IR, ν/cm^{-1} : 3330 (NH_2), 3458 (NH), 2184 (C ≡ N), 1746 (COOEt), 1654 (C = N)
25	IR, ν/cm^{-1} : 3086 (NH), 1712 (C = O), 1735 (COOEt), 1616 (C = N) MS, m/z (%): 342 (45) (M^+)

General Procedure for Synthesis of (6-Aryl-5-cyano-4-oxo-1,4-dihydro-pyrimidin-2-ylsulfanyl)-acetic Acid Ethyl Ester (6a–c)

An equimolar amount of **2a** (1.16 g, 5 mmol), **2b** (1.30 g, 5 mmol), or **2c** (1.37 g, 5 mmol) and **3** (1.15 g, 5 mmol), potassium hydroxide (0.28 g, 5 mmol), ethyl chloroacetate (0.53 ml, 5 mmol), and 25 cm^3 absolute ethanol was refluxed for 3 h. The reaction mixture was left to cool and then poured onto ice-cold water. The precipitate formed and was filtered off, dried, and crystallized from ethanol to give 6a–c, respectively (cf. Tables 1 and 2).

Synthesis of 2,4-Dioxo-6-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile (8)

Method A

A mixture of **2a** (1.16 g, 5 mmol), potassium hydroxide (0.28 g, 5 mmol), chloroacetic acid (0.3 ml, 5 mmol), and 25 cm^3 absolute ethanol was refluxed for 3 h. The reaction mixture was left to cool and then poured onto ice-cold water. The precipitate formed and was filtered off, dried, and crystallized from ethanol.

Method B

To a solution of sodium ethoxide [sodium metal 0.11 g in absolute ethanol 20 cm^3], **1a** (1.01 gm, 5 mmol) and urea (0.3 g, 5 mmol) were added. The mixture was stirred at room temperature for 24 h. Then the mixture was poured onto ice-cold water and neutralized by adding dilute HCl. The precipitate formed and was filtered off, dried, and crystallized from ethanol to give compound **8** (cf. Tables 1 and 2).

General Procedure for Synthesis of 5-Aryl-5,8-dihydro-1*H*,6*H*-pyrimido[4,5-*d*]pyrimidine-2,4,7-trithione (13a–c)

A mixture of compound **11a** (1.15 g, 5 mmol), **11b** (1.30 g, 5 mmol), and/or **11c** (1.2 g, 5 mmol), carbon disulfide (0.42 ml, 7 mmol), and dimethylformamide 25 cm^3 was refluxed for 3 h. The reaction mixture was left to cool and then poured onto ice-cold water. The precipitate formed and was filtered off, dried, and crystallized from ethanol to afford **13a–c**, respectively (cf. Tables 1 and 2).

Synthesis of 5-Phenyl-1*H*,8*H*-pyrimido[4,5-*d*]pyrimidine-2,4,7-trithione (14)

Method A

A mixture of compound **13a** (1.53 g, 5 mmol) and a catalytic amount of piperidine (3 drops) in ethanol 30 cm^3 was refluxed for 3 h. The reaction mixture was left to cool, then poured onto ice water; the solid product that had formed was collected by filtration and crystallized from ethanol.

Method B

A mixture of compound **12** (1.14 g, 5 mmol), carbon disulfide (0.42 ml, 7 mmol), and dimethylformamide 25 cm^3 was refluxed for 3 h. The reaction mixture was left to cool and then poured onto ice-cold water. The precipitate formed and was filtered off, dried, and crystallized from ethanol to give compound **14** (cf. Tables 1 and 2).

General Procedure for Synthesis of 5-Aryl-7-thioxo-5,6,7,8-tetrahydro-3*H*-pyrimido[4,5-*d*]pyrimidin-4-one (15a–c)

Compound **11a** (1.15 g, 5 mmol), **11b** (1.30 g, 5 mmol), or **11c** (1.20 g, 5 mmol) and **18** (1.24 g, 5 mmol) were added to formic acid (85%, 5 mmol), and the mixture was refluxed for 2 h. The reaction mixture was left to cool, and then the formed precipitate was filtered off and washed with cold ethanol 10 cm^3 to afford **15a–c**, respectively (cf. Tables 1 and 2).

Synthesis of 5-Phenyl-7-thioxo-7,8-dihydro-3*H*-pyrimido[4,5-*d*] pyrimidin-4-one (16)

Method A

A mixture of compound **15a** (1.29 g, 5 mmol) and a catalytic amount of piperidine (3 drops) in ethanol 30 cm^3 was refluxed for 3 h. The reaction mixture was left to cool and then poured onto ice water. The solid product that had formed was collected by filtration and crystallized from ethanol.

Method B

Compound **12** (1.14 g, 5 mmol) was added to formic acid (85%), and the mixture was refluxed for 3 h. The reaction mixture was left to cool, and

then the precipitate was formed, filtered, and washed with cold ethanol to give compound **16** (cf. Tables 1 and 2).

Synthesis of 6-Amino-4-phenyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic Acid Amide (18)

A mixture of **17** (0.86 g, 5 mmol), sodium ethoxide (sodium metal 0.11 gm in absolute ethanol 20 cm^3), and thiourea (0.38 g, 5 mmol) was added. The mixture was stirred at room temperature for 24 h. The mixture was poured onto ice-cold water and neutralized by adding dilute HCl. The precipitate formed and was filtered off, dried, and crystallized from ethanol to give compound **18** (cf. Tables 1 and 2).

Synthesis of 5-Chloro-4-phenyl-3,4-dihydro-1*H*-pyrimido[4,5-*d*] pyrimidine-2-thione (19)

Compound **15a** (1.29 g, 5 mmol) was added to phosphorus oxychloride 30 cm^3 and refluxed on a water bath at 95 °C for 4 h. The mixture was poured onto ice-cold water. The precipitate formed and was filtered off, dried, and crystallized from ethanol to give compound **19** (cf. Tables 1 and 2).

General Procedure for Synthesis of 5-Amino-4-aryl-3,4-dihydro-1*H*-pyrimido[4,5-*d*]pyrimidine-2-thione (20a–c)

A solution of **11a** (1.15 g, 5 mmol), **11b** (1.30 g, 5 mmol), or **11c** (1.20 g, 5 mmol) in 20 cm^3 of formamide was heated under reflux for 2 h, at which time the color darkened after cooling at room temperature. The mixture was poured onto ice-cold water. The precipitate formed and was filtered off, dried, and crystallized from ethanol to give **20a–c**, respectively (cf. Tables 1 and 2).

General Procedure for Synthesis of 5-Aryl-2-methyl-7-thioxo-5,6,7,8-tetrahydro-3*H*-pyrimido[4,5-*d*]pyrimidin-4-one (21a–c)

Compound **11a** (1.15 g, 5 mmol), **11b** (1.30 g, 5 mmol), or **11c** (1.20 g, 5 mmol) was added to 20 cm^3 of acetic anhydride. The reaction mixture was heated under reflux for 3 h after cooling to room temperature. The mixture was poured onto ice-cold water and let stand for 24 h. The

precipitate formed and was filtered off, dried, and crystallized from ethanol to afford **21a–c**, respectively (cf. Tables 1 and 2).

General Procedure for Synthesis of 5-Amino-4-aryl-3,4-dihydro-6-phenylpyrimido[4,5-*d*]pyrimidine-2,7(1*H*,6*H*)-dithione (22a–c)

A mixture of **11a** (1.15 g, 5 mmol), **11b** (1.30 g, 5 mmol), or **11c** (1.20 g, 5 mmol) and phenylisothiocyanate (0.60 ml, 5 mmol) in pyridine 20 cm^3 was refluxed for 6 h. The reaction mixture was cooled, poured onto ice/water, and neutralized with diluted HCl. The solid product that formed was collected by filtration and crystallized from ethanol to afford **22a–c**, respectively (cf. Tables 1 and 2).

Synthesis of (Dimethyl-5-cyano-6-phenyl-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yldithioimidocarbonate)-pyrimidine (23)

A mixture of compound **11a** (1.15 g, 5 mmol), potassium hydroxide (0.56 g, 10 mmol), carbon disulfide (0.42 g, 7 mmol), and dimethylformamide 25 cm^3 was stirred for 24 h. Then methyl iodide was added (0.62 g, 10 mmol), and the mixture was stirred for another 24 h. The reaction mixture was poured onto ice/water and neutralized with diluted HCl. The precipitate formed and was filtered off and crystallized from a mixture of ethanol/chloroform to give compound **23** (cf. Tables 1 and 2).

General Procedure for Synthesis of (4-Amino-6-aryl-5-cyano-pyrimidin-2-ylsulfanyl)-acetic Acid Ethyl Ester (24a–c)

A mixture of compound **11a** (1.15 g, 5 mmol), **11b** (1.30 g, 5 mmol), **11c** (1.20 g, 5 mmol), or **12** (1.14 g, 5 mmol), potassium hydroxide (0.82 g, 5 mmol), ethyl chloroacetate (0.53 ml, 5 mol), and 25 cm^3 absolute ethanol was refluxed for 3 h. The reaction mixture was left to cool and then poured onto ice-cold water. The precipitate solid was filtered off and crystallized from ethanol to afford **24a–c**, respectively (cf. Tables 1 and 2).

Synthesis of (5-Oxo-4-phenyl-5,6-dihydro-pyrimido[4,5-*d*]pyrimidin-2-ylsulfanyl)-acetic Acid Ethyl Ester (25)

Compound **24a** (1.57 g, 5 mmol) was added to formic acid (85%, 5 mmol), and the mixture was refluxed for 3 h. The reaction mixture was left to

cool and then poured onto ice-cold water. The precipitate formed and was filtered off, dried, and crystallized from ethanol to give compound **25** (cf. Tables 1 and 2).

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