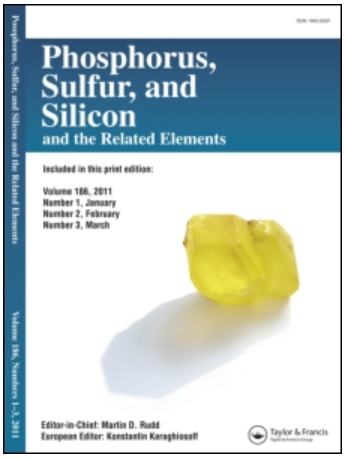

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Synthesis and Antimicrobial Activities of Some Novel Pyrido[2,3-d]pyrimidine Derivatives

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Synthesis and Antimicrobial Activities of Some Novel Pyrido[2,3-*d*]pyrimidine Derivatives

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2-Amino-(6-phenoxathiin-2-yl)-4-phenyl-nicotinonitrile has been synthesized and used as a starting material to construct a novel series of annulated and substituted pyrido[2,3-d]pyrimidine systems. Antibacterial and antifungal activities of some synthesized compounds were evaluated and reported.

Keywords Antimicrobial activity; phenoxathiin; pyrido[2,3-*d*]pyrimidines

INTRODUCTION

In recent years considerable attention has been devoted to the synthesis of pyridopyrimidine derivatives, as they possess such diverse pharmacological properties as antitumor,[1–5] antibacterial,[6,7] antifolate,[8,9] analgesic,[10,11] and antifungal.[12] Aminopyrido[2,3-*d*]pyrimidine derivatives are also used as adenosine receptor antagonists.[15–17] In addition, phenoxathiin derivatives were found to be useful for the treatment of microbial infections,[18] asthmatic, and inflammatory conditions.[19] Also, phenoxathiins were found to be active as potential antihypertensive[20] and antitumor agents.[21] Several phenoxathiin pyridinium derivatives acted as effective antifungal agents against *Aspergillus* and *Candida*.[22]

Considering the above reports in conjunction with our previous work on the synthesis of phenoxathiin derivatives as antimicrobial agents,[23] we thought it would be of interest to combine the above mentioned heterocycles in a molecular framework to investigate a possible additive effect of these rings regarding biological activity.

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RESULTS AND DISCUSSION

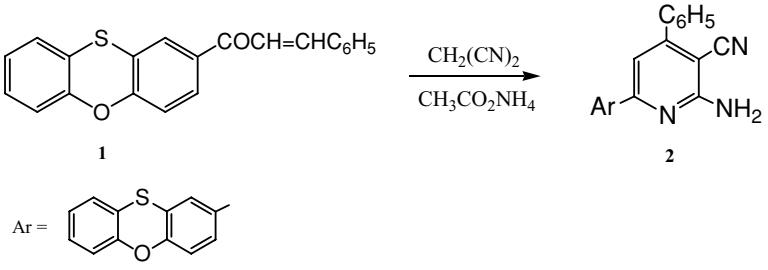
Chalcone **1** reacted with malononitrile in the presence of ammonium acetate to afford 2-amino-6 (Phenoxathiin-2-yl)-4-phenylnicotinonitrile **2** as a key precursor for the synthesis of condensed heterocyclic compounds of expected biological activity (Scheme 1). The structure assigned for compound **2** was based on the microanalytical and spectroscopic data. The IR spectrum displays absorption bands of C≡N and NH_2. Also, the ^1H NMR spectrum revealed a signal at 5.2 ppm for the NH_2 group.

Heating of **2** with formic acid under reflux afforded pyrido[2,3-*d*]pyimidine **3** (Scheme 2). The IR spectrum displays a lack of an absorption of C≡N and NH_2 and presence of CO and NH absorption.

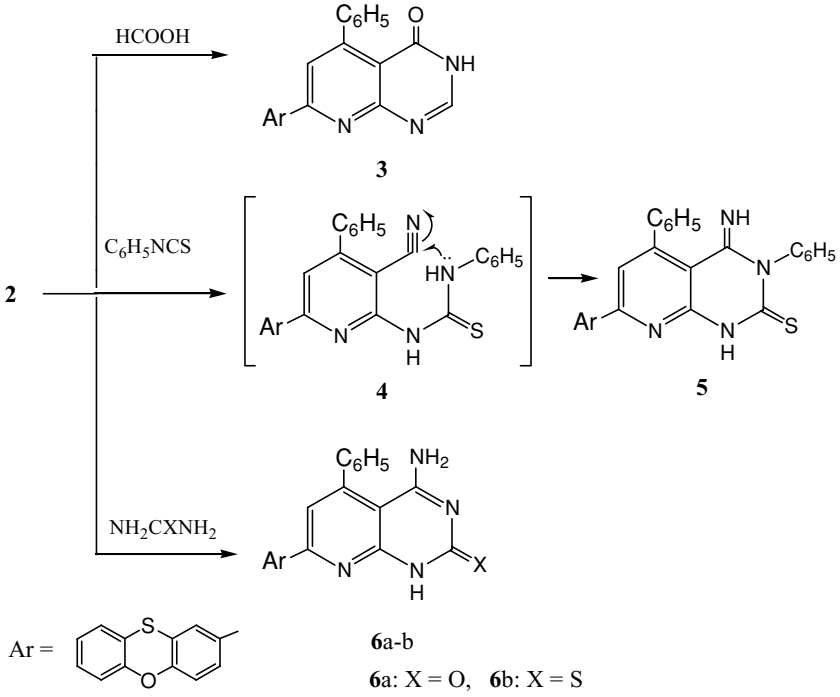
On the other hand, treatment of **2** with phenyl isothiocaynate under reflux in pyridine furnished the corresponding pyridopyrimidinethione derivative **5**. The reaction is assumed to take place via formation of thiourea intermediate **4** followed by cyclization at the adjacent C≡N group.[24]

This investigation was extended to use **2** as a reactive intermediate for the synthesis of a wide range of biologically active heterocycles. Thus, fusion of compound **2** with urea or thiourea results in the formation of **6a** and **6b**, respectively (Scheme 2).

Furthermore, treatment of **2** with carbon disulfide afforded a reaction product that could be formulated as 7-(phenoxathiin-2-yl)-5-phenyl-1*H*-pyrido[2,3-*d*]pyrimidine-2,4-dithione **7**. The aminopyridopyrimidine derivative **8** was synthesized by reaction of the nicotinonitrile **2** with formamide. Moreover, **2** reacted with triethyl orthoformate in acetic anhydride and resulted in the formation of formimidate **9**. Cyclization of the latter with methyl amine afforded pyrido[2, 3-*d*]pyrimidine **10** (Scheme 3). Hydrazinolysis of **9** with hydrazine hydrate or phenylhydrazine furnished **11a** and **11b**, respectively.



SCHEME 1

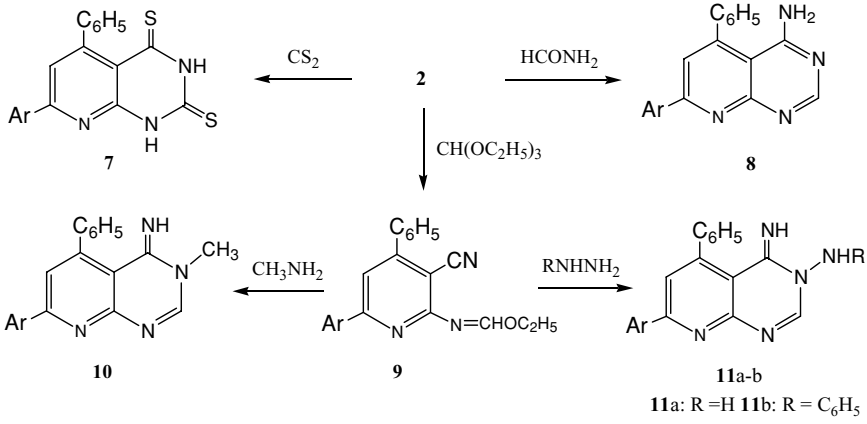


SCHEME 2

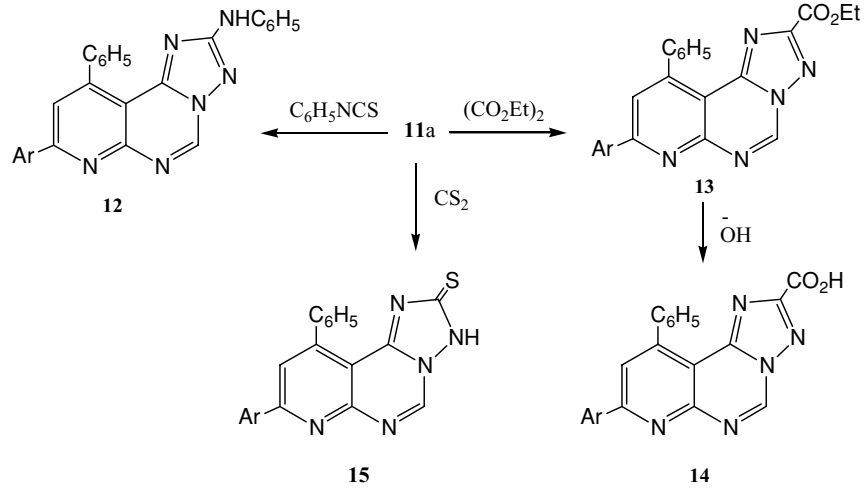
The synthesized derivative **11a** seemed to be an excellent target for the synthesis of other desired heterocyclic derivatives through its participation in a number of chemical reactions with various reagents.

Thus, pyrido[2,3-*d*]pyrimidine **11a** was employed in the synthesis of a triazole moiety fused to a pyrimidine ring as shown in Scheme 4. Treatment of **11a** with phenyl isothiocyanate afforded compound **12**. The structure of **12** was confirmed by the disappearance of the NH_2 signal in the ^1H NMR spectrum, which appeared at 6.3 ppm in **11a**. Reaction of **11a** with diethyl oxalate gave 7-(phenoxathiin-2-yl)-9-phenyl-1,3.3a,5,6-pentaazacyclopenta[a]-2-naphthoate **(13)**. Its structure was elucidated by the presence of a C=O ester absorption band and the ^1H NMR spectrum (*cf*. Experimental). Hydrolysis of the ester **13** with sodium hydroxide furnished the corresponding acid **14**.

The pyrido[2,3-*d*]pyrimidine **11a** reacted with carbon disulfide to afford the triazolethione derivative **15**. Refluxing of **11a** with ethyl cyanoacetate in ethanol resulted in the formation of the nitrile **16**. Both elemental and spectroscopic data of **16** are consistent with the assigned structure (*cf*. Experimental). Furthermore, refluxing of **11a**



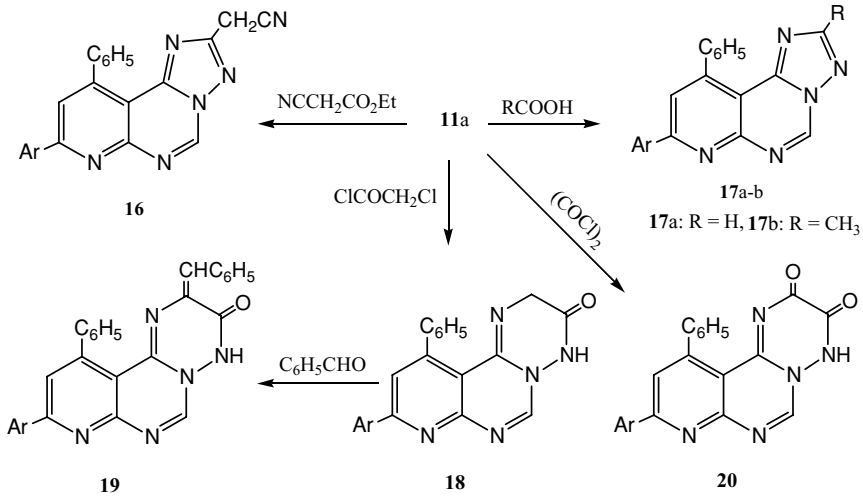
SCHEME 3



SCHEME 4

with formic and acetic acid gave the corresponding triazoles **17a** and **17b**, respectively (Scheme 5).

On the other hand, the pyrido[2,3-*d*]pyrimidine **11a** was employed in the synthesis of a triazine moiety fused to a pyrimidine ring with the aim of enhancement of the biological activity. Thus, the reaction of equimolar amounts of **11**a and chloroacetyl chloride gave the triazine **18**, which in turn reacted with benzaldehyde in the presence of sodium



SCHEME 5

acetate to give product **19**. Finally, **11**a reacted with oxalyl chloride to give the triazinedione derivative **20** (Scheme 5).

Biological Activity

Some of the synthesized compounds were tested for their antimicrobial activity. Chloramphenicol as an antibacterial agent and Terbinafan as an antifungal agent were used as references to evaluate the potency of the tested compounds under the same conditions. The tests were carried out using the filter paper and hole plate method.[25] Tested microorganisms were Gram positive (*Bacillus subtilis* and *Rhadococcus equii*) and Gram negative bacteria (Salmonella *typhimurium* and *Escherichia coli*). In addition, the antifungal activity against *Fusarium moniliforme* and *Fusarium solami* was tested.

The sensitivity of the selected microorganisms to some synthesized compounds was determined at different concentrations (125, 250, 500 μg/ml in 10% acetone) using the inhibition zone diameter as the criterion for antimicrobial activity. The results (Table I) revealed that compounds **3** and **13** possess the highest activity against *Escherichia coli* among all the considered compounds, whereas compounds **6b** and **7** showed the highest degree of inhibition of *Bacillus subtilis*. Compound **12** exhibited the maximum inhibition against *Fusarium moniliforme* and *Fusarium solami*.

TABLE I Responses of Various Micro-Organisms to Some Synthesized Compounds[a]

Compound	*B. subtilis*	*R. equii*	*S. typhimurium*	*E. coli*	*F. moniliforme*	*F. solami*
3	+	−	−	++	+	−
5	++	−	+	+	+	+
6a	−	+	−	−	+	++
6b	+++	+	−	+	−	−
7	+++	+	−	+	−	+
12	−	+	−	−	+++	+++
13	+	−	+	+++	−	+
15	++	+	−	+	+	+
20	+	−	+	−	−	+
Chloramphenicol	+++	+++	+++	+++		
Terbinafan					+++	+++

[a]Inhibition zone diameter *d* of either fungal growth or bacterial cells for each compound: +++ > 12 mm, highly active; ++ > 9 mm, moderately active; + > 7 mm, slightly active; − no inhibition observed.

It was observed that the activity of these compounds is similar to that of the standard drugs (Chloramphenicol and Terbinafan). All other compounds either do not exhibit any activity or are less active against the tested species.

EXPERIMENTAL

Melting points of the prepared products are uncorrected. All reactions were monitored by thin layer chromatography (TLC) carried out on 0.2 mm silica gel 60 F_{254} (Merck) plates. IR spectra in KBr were recorded using a Perkin-Elmer 298 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained using a Varian Gemini 200 MHz and 50 MHz instrument. The solvent used for NMR analysis was DMSO-d_6, unless stated otherwise. Mass spectra were obtained using a Shimadzu GCMS-QP 1000 EX mass spectrometer.

1-(Phenoxathiin-2-yl)-3-phenyl-propenone (1)

A mixture of 2-acetylphenoxathiin (0.01 mol), benzaldehyde (0.01 mol) and NaOH (1g in 10 mL water) in EtOH (30 mL) was stirred at rt. for about 3 h. The solid was washed, dried, and crystallized from ethanol to give chalcone **1**. Yield, 80%; m.p. 196–198°C. IR: 1690 (C=O), 1610 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.41 (d, 1H, α-CH olefinic), 7.46 (d, 1H,

β-CH olefinic), 7.13–7.90 (m, 12H, ArH). MS: *m/z* 330 (M^+). Anal. calcd. for $C_{21}H_{14}O_2S$ (330.40): C, 76.34; H, 4.27. Found: C, 76.26; H, 4.13.

2-Amino-6-(phenoxathiin-2-yl)-4-phenylnicotinonitrile (2)

A mixture of equimolar amounts of chalcone **1** and malononitrile (0.01 mol) in EtOH (30 mL) containing ammonium acetate (0.02 mol) was heated under reflux for 6 h. The reaction mixture was concentrated, cooled, and filtered, and the residue was crystallized from EtOH to give **2**. Yield, 75%; m.p. 228–230°C. IR: ν 2225 (C≡N), 3345, 3320 cm^{-1} (NH_2). ^1H NMR (DMSO-d_6): δ 5.24 (s, 2H, NH_2, exchangeable), 6.94–7.88 (m, 13H, ArH). ^{13}C NMR: δ 105.6 (C-3), 115 (CN), 117.2 (C-5), 152 (C-4), 160.8 (C-6), 164.2 (C-2), 116.7, 118.2, 120.2, 121.3, 122, 122.8, 124.8, 126,127.6, 129, 130.4, 132.2, 136.2, 157.3, 158.2 (C-phenyl and phenoxathiin moieties). MS: *m/z* 393 (M^+). Anal. calcd. for $C_{24}H_{15}N_3OS$ (393.46): C, 73.26; H, 3.84; N, 10.68. Found: C, 73.12; H, 3.65; N, 10.76.

7-(Phenoxathiin-2-yl)-5-phenyl-3*H*-pyrido[2,3-*d*]pyrimidin-4-one (3)

Nicotinonitrile **2** (0.01 mol) was heated with an excess of formic acid under reflux for 4 h. After cooling, the precipitated solid was filtered, dried, and crystallized from EtOH. Yield, 60%; m.p. 232–234°C. IR: ν 1610 (C=N), 1680 (C=O), 3300 (NH ⇆ OH) cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.83–8.21 (m, 14H, ArH + pyrimidine-H), 8.57 (s, 1H, NH, exchangeable). MS: *m/z* 421 (M^+). Anal. calcd. for $C_{25}H_{15}N_3O_2S$ (421.47): C, 71.24; H, 3.59; N, 9.97. Found: C, 71.33; H, 3.71; N, 10.12.

4-Imino-7-(phenoxathiin-2-yl)-3,5-diphenyl-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidine-2-thione (5)

A mixture of **2** (0.01 mol) and phenyl isothiocyanate (0.01 mol) in pyridine (15 mL) was refluxed for 5 h. After cooling, the reaction mixture was poured into cold aqu. HCl. The solid product was filtered, dried, and crystallized. IR: ν 1305 (C=S), 3260 (NH) cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.97-8.15 (m, 18H, ArH), 8.61, 8.94 (s, 2H, 2NH, exchangeable). MS: *m/z* 528 (M^+). Anal. calcd. for $C_{31}H_{20}N_4OS_2$ (528.65): C, 70.43; H, 3.81; N, 10.60. Found: C, 70.33; H, 3.66; N, 10.56.

Synthesis of 6a–b: General Procedure

Equimolar amounts of **2** and urea or thiourea (0.01 mol) were fused in an oil bath for 2 h. After cooling, the product was treated with water, filtered, dried, and crystallized to give **6a–b** respectively.

4-Amino-7-(phenoxathiin-2-yl)-5-phenyl-1H-pyrido[2,3-d]pyrimidine-2-one (6a)

Yield, 60% (EtOH); m.p. 260–262°C. IR: ν 1685 (C=O), 3450–3200 (NH_2 and NH) cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.22 (s, 2H, NH_2, exchangeable), 7.09–8.12 (m, 13H, Ar H), 8.87 (s, 1H, NH, exchangeable). ^{13}C NMR: δ 114.2 (C-4a), 116.3 (C-6), 150.7(C-5), 156 (C-7), 158.2 (C-8a), 161 (CO), 165.1 (C-4), (C-phenyl and phenoxathiin moieties as shown for **2**). Anal. calcd. for $C_{25}H_{16}N_4O_2S$ (436.49): C, 68.79; H, 3.69; N, 12.84. Found: C, 68.95; H, 3.78; N, 12.90.

4-Amino-7-(phenoxathiin-2-yl)-5-phenyl-1H-pyrido[2,3-d]pyrimidine-2-thione (6b)

Yield, 62% (EtOHl); m.p. 266–268°C. IR: ν 1260 (C=S), 1610 (C=N), 3370–3190 (NH_2 and NH) cm^{-1}. MS: m/z 452 (M^+). Anal. calcd. for $C_{25}H_{16}N_4OS_2$ (452.55): C, 66.35; H, 3.56; N, 12.38. Found: C, 66.41; H, 3.64; N, 12.42.

7-(Phenoxathiin-2-yl)-5-phenyl-1*H*-pyrido[2,3-*d*]pyrimidine-2,4-dithione (7)

CS_2 (0.015 mol) was added to a solution of **2** (0.01 mol) in DMF (20 mL). Then MeONa [prepared from Na (0.5 g) and MeOH (10 mL)] was added. The mixture was heated under reflux for 10 h, cooled, and poured into cold water followed by addition of NaOH (10 mL) and left overnight. The clear solution obtained by filtration was acidified with AcOH to give a solid product, which was collected by filtration, dried, and crystallized from benzene to give **7**. Yield, 58%; m.p. 222–224°C. IR: ν 3340–3260 (NH), 1290–1270 (2 C=S) cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.89–8.13 (m, 13H, ArH), 8.66, 9.11 (2s, 2H, 2NH, exchangeable). ^{13}C NMR: δ 116 (C-4a), 112.4 (C-6), 153.2 (C-5), 158.4 (C-7), 162 (C-8a), 180.3, 198.6 (2 CS), (C-phenyl and phenoxathiin moieties as shown for **2**). Anal. calcd. for $C_{25}H_{15}N_3OS_3$ (469.60): C, 63.94; H, 3.22; N, 8.95. Found: C, 64.19; H, 3.41; N, 8.70.

4-Amino-7-(phenoxathiin-2-yl)-5-phenylpyrido[2,3-*d*]pyrimidine (8)

Compound **2** (0.01 mol) in formamide (15 mL) was heated under reflux for 8 h and left to be cooled. The solid product was filtered and crystallized from EtOH to give **8**. Yield, 70%; m.p. 280–282°C. IR: ν 3390, 3340 (NH_2), 1620 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.41 (s, 2H, NH_2, exchangeable), 7.03-8.11 (m, 14H, ArH + pyrimidine H). ^{13}C NMR: δ

109.6 (C-4a), 118.2 (C-6), 150(C-5), 158.5 (C-7), 157 (C-2), 159 (C-8a), 167 (C-4), (C-phenyl and phenoxathiin moieties as shown for **2**). MS: *m/z* 420 (M^+). Anal. calcd. for $C_{25}H_{16}N_4OS$ (420.49): C, 71.41; H, 3.84; N, 13.32. Found: C, 71.31; H, 3.52; N, 13.11.

Ethyl *N*-[3-Cyano-6-(phenoxathiin-2-yl)-4-phenylpyridin-2-yl]formimidiate (9)

A mixture of **2** (0.01 mol) and triethyl orthoformate (0.01 mol) in Ac_2O (5 mL) was refluxed for 6 h, then cooled and poured into cold water. The precipitated solid was filtered, washed, dried, and crystallized from EtOH to give **9**. Yield, 80%; m.p. 195–197°C. IR: ν 2215 (C≡N), 1620 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.22–1.43 (t, 3H, OCH_2CH_3), 4.21-4.33 (q, 2H, OCH_2CH_3), 7.11-8.15 (m, 13H, ArH), 8.37 (s, 1H, CH=N). ^{13}C NMR: δ 17 (CH_3), 61(CH_2),102.2 (C-3), 117.3 (CN), 118 (C-5), 151.4 (C-4), 159 (N=CH), 161.2 (C-6), 168.3 (C-2), (C-phenyl and phenoxathiin moieties as shown for **2**). Anal. calcd. for $C_{27}H_{19}N_3O_2S$ (449.52): C, 72.14; H, 4.26; N, 9.35. Found: C, 71.91; H, 4.11; N, 9.41.

4-Imino-3-methyl-7-(phenoxathiin-2-yl)-5-phenyl-3*H*-pyrido[2,3-*d*]pyrimidine (10)

A mixture of **9** (0.01 mol) and methyl amine (0.01 mol) in EtOH (30 mL) was heated under reflux for 8 h. After cooling, the reaction mixture was poured into water and neutralized with dil. HCl. The collected solid was crystallized from *n*-butanol. Yield, 65%; m.p. 210–212°C. IR: ν 3240–3200 (NH), 1615 (CN) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.82 (s, 3H, CH_3), 7.03–7.84 (m, 14H, ArH + pyrimidine H) and 9.16 (s, 1H, NH, exchangeable). Anal. calcd. for $C_{26}H_{18}N_4OS$ (434.51): C, 71.87; H, 4.18; N, 12.89. Found: C, 71.99; H, 4.12; N, 12.73.

Synthesis of 11a–b: General Procedure

A mixture of **9** (0.01 mol) and hydrazine hydrate (0.01 mol) or phenylhydrazine (0.01 mol) in EtOH (30 mL) was heated under reflux for 6 h. The reaction mixture was allowed to cool, poured into cold water, and neutralized with AcOH. The solid product was filtered, washed with water, dried, and crystallized from proper solvent to give **11a–b** respectively.

3-Amino-4-imino-7-(phenoxathiin-2-yl)-5-phenyl-4H-pyrido[2,3-d]pyrimidine (11a)

Yield, 78% (EtOH); m.p. 216–218°C. IR: ν 3420–3350 (NH_2), 3190 (NH), 1620 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.15 (s, 2H, NH_2exchangeable), 6.89–7.90 (m, 14H, ArH + pyrimidine H), 8.93 (s, 1H, NH exchangeable); ^{13}C NMR, $\delta = 112.8$ (C-4a), 116.2 (C-6), 151 (C-5), 160 (C-7), 162 (C-2), 163 (C-4), 165 (C-8a), (C-phenyl and phenoxathiin moieties as shown for **2**). MS: *m/z* 435 (M^+). Anal. calcd. for $C_{25}H_{17}N_5OS$ (435.50): C, 68.95; H, 3.93; N, 16.08. Found: C, 68.71; H, 3.88; N, 15.81.

4-Imino-7-(phenoxathiin-2-yl)-5-phenyl-3-phenylamino-4H-pyrido[2,3-d]pyrimidine (11b)

Yield, 67% (EtOH); m.p. 196–198°C. IR: ν 3250–3200 (NH), 1600 (C=N) cm^{-1}. MS: *m/z* 511 (M^+). Anal. calcd. for $C_{31}H_{21}N_5OS$ (511.60): C, 72.78; H, 4.14; N, 13.69. Found: C, 72.92; H, 4.32; N, 13.37.

7-(Phenoxathiin-2-yl)-9-phenyl-2-phenylamino-1,3.3a,5,6-pentaazacyclopenta[a]naphthalene (12)

A mixture of **11a** (0.01 mol) and phenyl isothiocyanate (0.01 mol) in EtOH (30 mL) was refluxed for 8 h. The reaction mixture was cooled and filtered, and the resulting solid was crystallized from EtOH to give **12**. Yield, 62%; m.p. 225–226°C. IR: ν 3260 (NH), 1620 C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.94–8.33 (m, 14H, ArH + pyrimidine H), 10.17 (s, 1H, NH, exchangeable). Anal. calcd. for $C_{32}H_{20}N_6OS$ (536.61): C, 71.62; H, 3.76; N, 15.66. Found: C, 71.86; H, 3.88; N, 15.91.

Ethyl 7-(Phenoxathiin-2-yl)-9-phenyl-1,3,3a,5,6-pentaazacyclopenta[a]-2-naphthoate (13)

Equimolar amounts of **11a** and diethyl oxalate (0.01 mol) in EtOH (30 mL) were heated under reflux for 6 h. After cooling, the precipitated solid was filtered and crystallized from EtOH to give **13**. Yield, 72%; m.p. 231–233°C. IR: ν 1730 (CO), 1615 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.23–1.31 (t, 3H, OCH_2CH_3), 4.21–4.29 (q, 2H, OCH_2CH_3), 7.19–8.41 (m, 14H, ArH + pyrimidine H). Anal. calcd. for $C_{29}H_{19}N_5O_3S$ (517.56): C, 67.30; H, 3.70; N, 13.53. Found: C, 67.41; H, 3.77; N, 13.50.

7-(Phenoxathiin-2-yl)-9-phenyl-1,3,3a,5,6-pentaazacyclopenta[a]naphthalene-2-carboxylic Acid (14)

A mixture of **13** (0.01 mol) and NaOH (10%. 15 mL) was heated under reflux for 6 h. The reaction mixture was cooled and poured into cold water, then neutralized with HCl. The precipitated solid was collected by filtration, dried, and crystallized from EtOH. Yield, 65%; m.p. 240–242°C. IR: ν 3450 (OH), 1710 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.84-8.35 (m, 14H, ArH + pyrimidine H), 10.22 (s, 1H, OH, exchangeable). Anal. calcd. for $C_{27}H_{15}N_5O_3S$ (489.51): C, 66.25; H, 3.09; N, 14.31. Found: C, 66.34; H, 3.17; N, 14.43.

7-(Phenoxathiin-2-yl)-9-phenyl-1,3,3a,5,6-pentaazacyclopenta[a]naphthalene-2-thione (15)

A mixture of **11a** (0.01 mol) and CS_2 (3 mL) in EtOH (30 mL) was heated under reflux for 6 h. Once cooled, the precipitated solid was filtered and crystallized from EtOH to give **15**. Yield, 63%; m.p. 212–214°C. IR: ν 3300–3280 (NH), 1280 (C=S), 1600 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.01–8.13 (m, 14H, ArH + pyrimidine H), 8.70 (s, 1H, NH, exchangeable). MS: m/z 477 (M^+). Anal. calcd. for $C_{26}H_{15}N_5OS_2$ (477.56): C, 65.39; H, 3.17; N, 14.66. Found: C, 65.46; H, 3.26; N, 14.51.

[7-(Phenoxathiin-2-yl)-9-phenyl-1,3,3a,5,6-pentaazacyclopenta[a]naphthalene-2-yl]acetonitrile (16)

A mixture of **11a** (0.01 mol) and ethyl cyanoacetate (0.01 mol) in EtOH (30 mL) was heated under reflux for 6 h. Once cooled, the obtained solid product was filtered and crystallized from EtOH to give **16**. Yield, 67%; m.p. 223-225 °C. IR: ν 2220 (C≡N), 1610 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.93 (s, 2H, CH_2), 7.07-8.31 (m, 14H, ArH + pyrimidine H). ^{13}C NMR: δ 20.3 (CH_2), 114.8 (CN), 119 (C-8), 121.8 (C-9a), 147.2(C-9b), 149.3 (C-9), 155.6 (C-5a), 156 (C-7), 157.2 (C-4), 161.1 (C-2), (C-phenyl and phenoxathiin moieties as shown for **2**). Anal. calcd. for $C_{28}H_{16}N_6OS$ (484.53): C, 69.41; H, 3.33; N, 17.34. Found: C, 69.37; H, 3.27; N, 17.25.

Synthesis of 17a–b: General Method

A mixture of **11a** (0.01 mol) and formic acid or AcOH (10 mL) was heated under reflux for 8 h. The reaction mixture was cooled and poured into cold water. The precipitated solid was filtered, washed, dried, and crystallized from a proper solvent to give **17a–b** respectively.

7-(Phenoxathiin-2-yl)-9-phenyl-1,3,3a,5,6-pentaazacyclopenta[a]naphthalene (17a)

Yield, 65% (EtOH); m.p. 218–220°C. IR: ν 1615 (C=N) cm^{-1}. MS: *m/z* 445 (M^+). Anal. calcd. for $C_{26}H_{15}N_5OS$ (445.50): C, 70.10; H, 3.39; N, 15.72. Found: C, 70.19; H, 3.49; N, 15.77.

2-Methyl-7-(phenoxathiin-2-yl)-9-phenyl-1,3,3a,5,6-pentaazacyclopenta[a]naphthalene (17b)

Yield, 64% (EtOH); m.p. 229–230°C. IR: ν 1615 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.31 (s, 3H, CH_3), 6.82-7.84(m, 14H, ArH + pyrimidine H). Anal. calcd. for $C_{27}H_{17}N_5OS$ (459.52): C, 70.57; H, 3.73; N, 15.24. Found: C, 70.42; H, 3.81; N, 15.13.

7-(Phenoxathiin-2-yl)-5-phenyl-3*H*-1,4,8,9,10a-pentaazaphenanthren-2-one (18)

Compound **11a** (0.01 mol) and chloroacetyl chloride (0.01 mol) were dissolved in dioxane (30 mL) and left at room temperature overnight. The precipitated solid was collected by filtration and crystallized from EtOH to give **18**. Yield, 73%; m.p. 253–255°C. IR: ν 3320–3260 (NH⇆ OH), 1685 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.33 (s, 2H, CH_2), 8.37 (s, 1H, NH, exchangeable), 7.08–7.92 (m, 14H, ArH + pyrimidine H). MS: *m/z* 475 (M^+). Anal. calcd. for $C_{27}H_{17}N_5O_2S$ (475.52): C, 68.20; H, 3.60; N, 14.73. Found: C, 67.95; H, 3.81; N, 14.58.

3-Benzylidene-7-(phenoxathiin-2-yl)-5-phenyl-3H-1,4,8,9,10a-pentaazaphenanthrene-2-one (19)

Benzaldehyde (0.01 mol) and NaOAc (0.5 g) were added to a solution of **18** (0.01 mol) in AcOH (30 mL). The reaction mixture was heated under reflux for 6 h and cooled. The solid product was filtered and crystallized from EtOH to give **19**. Yield, 65%; m.p. 240-242 °C. IR: ν 3350-3240 (NH⇆ OH), 1680 (C=O) cm^{-1}. MS: *m/z* 563 (M^+). Anal. calcd. for $C_{34}H_{21}N_5O_2S$ (563.63): C, 72.45; H, 3.76; N, 12.43. Found: C, 72.58; H, 3.81; N, 12.54.

7-(Phenoxathiin-2-yl)-5-phenyl-1,4,8,9,10a-pentaazaphenanthrene-2,3-dione (20)

A mixture of **11a** (0.01 mol) and oxalyl chloride (0.01 mol) in dry benzene (30 mL) was heated under reflux for 10 h. The reaction mixture was cooled, filtered and crystallized from dioxane to give **20**. Yield, 70%; m.p.

216–218°C. IR: ν 3360–3230 (NH⇆ OH), 1710–1680 (2 C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.91-8.12 (m, 14H, ArH + pyrimidine H), 9.58 (s, 1H, NH, exchangeable). Anal. calcd. for $C_{27}H_{15}N_5O_3S$ (489.51): C, 66.25; H, 3.09; N, 14.31. Found: C, 65.88; H, 3.22; N, 14.30.

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