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Research Article

Thioxopyrimidine in Heterocyclic Synthesis I: Synthesis of Some Novel 6-(Heteroatom-substituted)-(thio)pyrimidine Derivatives

Yuh-Wen Ho and Maw Cherng Suen

Department of Creative Fashion Design, Taoyuan Innovation Institute of Technology, Jhongli 32091, Taiwan

Correspondence should be addressed to Yuh-Wen Ho; wen@tiit.edu.tw

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A series of novel N-cycloalkanes, morpholine, piperazines, pyrazole, pyrimidine, benzimidazolo[1,2-a]pyrimidine, 1,2,3,4-tetrazolo[1,5-a]pyrimidine, azopyrazolo[1,5- a]pyrimidine, pyrimido[4', 5' :3,4]pyrazolo[1,5-a]pyrimidines and pyridine derivatives incorporating a 5-cyano-4-methyl-2-phenyl-(thio)pyrimidine moiety were obtained by the intramolecular cyclization of 6-methylthio-pyrimidine, 6-(benzoylmethyl)thio- pyrimidine and 2-[(5-cyano-4-methyl-2-phenylpyrimidin-6-yl)thio]-3-dimethylamino-1-phenyl-prop-2-en-1-one with appropriate amines and enaminone compounds, respectively. The structure of all new synthesized compounds was established from their spectral data, elemental analysis and the X-ray crystal analysis.

1. Introduction

Pyrimidine derivatives attracted organic chemists very much due to their biological and chemotherapeutic importance. Pyrimidine derivatives and related fused heterocycles are important classes of heterocyclic compounds that exhibit a broad spectrum of biological activities such as anticancer [1–5], antiviral [6], antibacterial [7, 8], antioxidant [9, 10], anxiolytic [11], and antidepressant activities [12]. Furthermore, they possess anti-inflammatory [13–19] and analgesic activities that are well documented in the literature [20–22]. The incorporation of two moieties increases biological activity of both and thus it was of value to synthesize some new heterocyclic derivatives having two moieties in the same molecules. The course of our researches was devoted to the development of new classes of pyrimidines substituted at position-6 with different fused heterocycles moiety in the hope that they may be biologically active. In preceding papers [23–25] we have described the synthesis of a series of novel 5-(1-pyrrolyl)-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine derivatives containing chalcones, pyridines, pyridin-2(1*H*)-ones, 2*H*-pyran-2-one, pyrazoles, pyrimidines imidazolpyrimidines, pyrazolopyrimidines, and 1,3,4-oxadiazoles moiety. In continuation of our studies, we report herein the use of thioxopyrimidine **1** for the synthesis of various N-cycloalkanes, morpholine, piperazines, pyridines, pyrazole, pyrimidine, benzimidazolo[1,5-*a*]pyrimidine, 1,2,3,4-tetrazolo [1,5-*a*]pyrimidine, azopyrazolo[1,5-*a*]pyrimidine, and pyrimido[4′,5′:3,4]pyrazolo[1,5-*a*]pyrimidine incorporating a (thio)pyrimidine moiety. The structure of the new compounds was verified by spectroscopic methods and the X-ray crystal structure of compound **13** is also discussed.

2. Experimental

All melting points are uncorrected and in °C. IR spectra were recorded on a JASCO FTIR-3 spectrometer (KBr); ^{1}H-NMR spectra were obtained on a Bruker AM-300 WB FINLR spectrometer, and chemical shifts are expressed in δ ppm using TMS as an internal standard. Electron impact mass spectra were obtained at 70 eV using a Finingan Mat TSQ-46C spectrometer. Microanalyses for C, H, and N were performed on a Perkin-Elmer 240 elemental Analyzer. Enaminone derivatives **14a–f**, 5-amino-4-phenylazo-3-methyl-1*H*-pyrazole **26**, and 3-amino-4-methyl-6-phenyl-pyrazolo-[3,4-*d*]pyrimidine **28** were prepared following the methods in the literature [24, 26, 27].

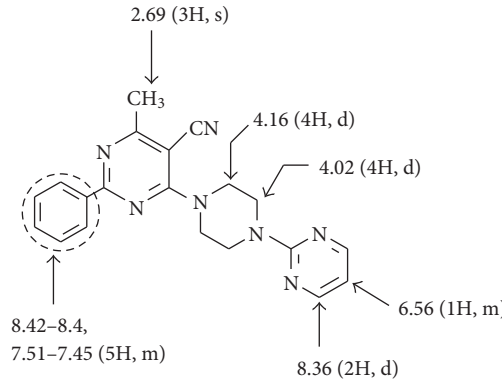


Figure 1: Structural assignment of typical protons in **5f** by ^{1}H NMR.

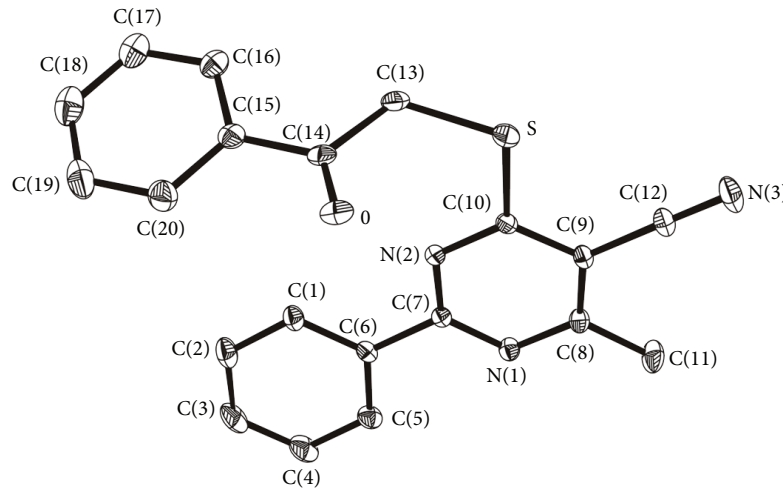
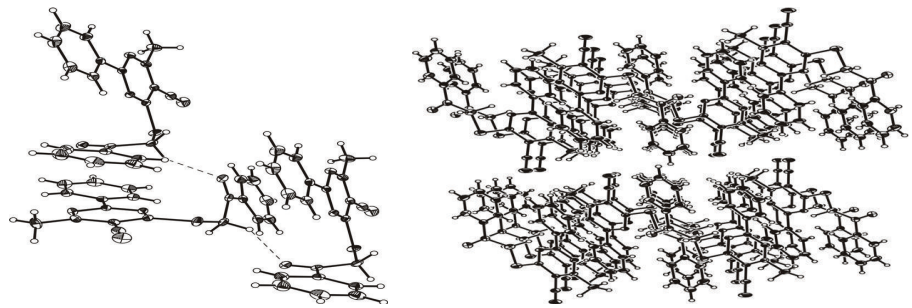


Figure 2: Perspective view of compound **13** with atomic numbering.

2.1. 5-Cyano-1,6-dihydro-4-methyl-2-phenyl-6-thioxopyrimidine (**1**). To a suspension of ammonium thiocyanate (7.60 g, 0.1 mol) in dry dioxane (100 mL), benzoyl chloride (14 g, 0.1 mol) was added. The reaction mixture was refluxed for 5 min., then treated with 3-aminocrotononitrile (8.20 g, 0.1 mol). The reaction mixture was refluxed for 2 h and poured into ice water. The solid product was collected by filtration, washed with water, and recrystallized from ethanol to give 17 g of yellow needle crystals (74% yield), mp 212°C; IR: ν 2225 (CN), 1200 (C=S) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.50 (3H, s, CH_3), 2.90 (1H, s, NH), 7.66–7.51, 8.11–8.08 (5H, m, phenyl-H); m/z: 227 (M^+). Anal. Calcd. for $C_{12}H_9N_3S$: C, 63.43; H, 3.96; N, 18.50. Found: C, 63.40; H, 4.00; N, 18.60%.

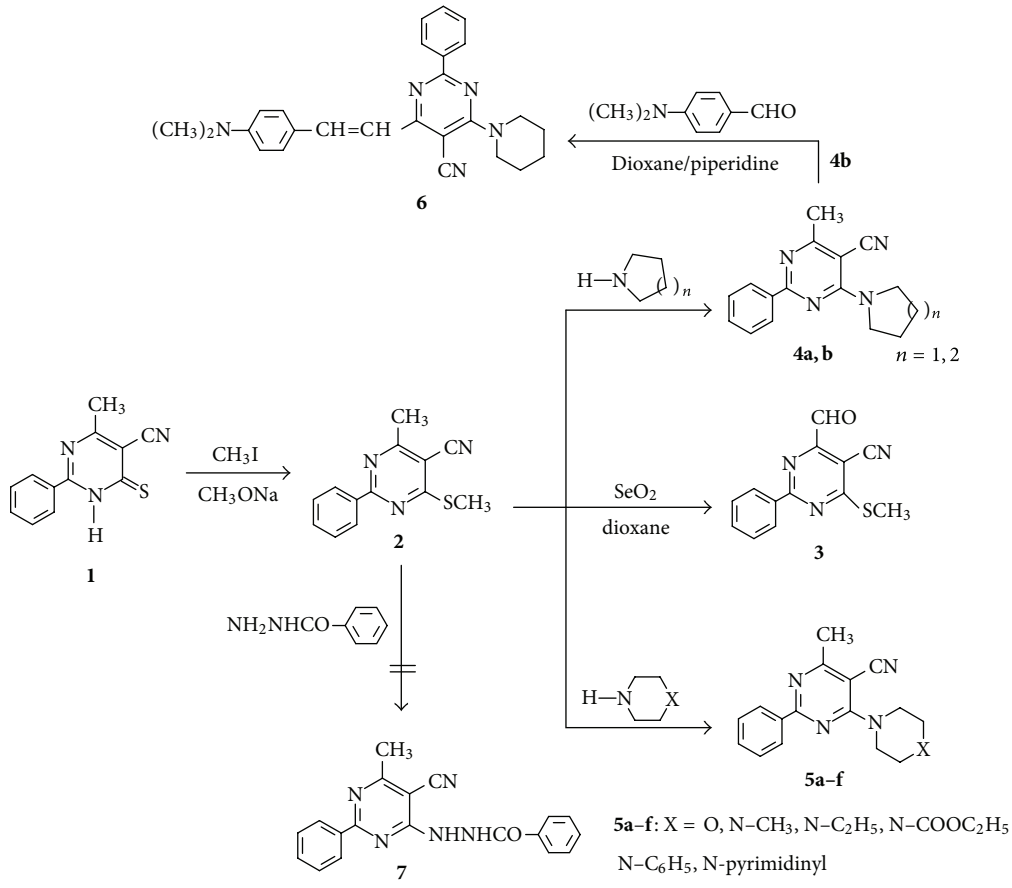
2.2. 5-Cyano-4-methyl-2-phenyl-6-methylthio-pyrimidine (**2**). A mixture of compound **1** (0.23 g, 1 mmol) in methanol (10 mL) and sodium methoxide (0.08 g, 1.5 mmol) and methyl iodide (0.17 g, 1.2 mmol) were added. After stirring at room temperature for 4 h, the resulting solid product was collected by filtration, washed with water, and recrystallized from THF to give 0.21 g of pale yellow crystals (87% yield), mp 144°C; IR: ν 2207 (C≡N) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.70 (3H, s, CH_3), 2.75 (3H, s, SCH_3), 8.49–8.47, 7.55–7.49 (5H, m, phenyl-H); MS (m/z, %): 241(M^+,100), 227(4), 195(4), 153(14), 138(9), 111(3), 104(17), 244(2), 77(10), 51(6). Anal. Calcd. for $C_{13}H_{11}N_3S$: C, 64.73; H, 4.56; N, 17.42. Found: C, 64.88 H, 4.54; N, 17.55%.

2.3. 5-Cyano-4-formyl-2-phenyl-6-methylthio-pyrimidine (**3**). A mixture of 5-cyano-4-methyl-2-phenyl-6-methylthio-pyrimidine **2** (0.24 g, 1 mmol) and selenium oxide (0.11 g, 1 mmol) in dioxane (10 mL) was refluxed for 1 h. After cooling, the mixture was filtered. The filtrate was evaporated under reduced pressure, and the resulting residue was purified by column chromatography (light petroleum ether/ethyl acetate 7 : 3 v/v as eluent) to give 0.2 g of reddish brown needles (78% yield), mp 164°C; IR: ν 2218 (C≡N), 1689 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.74 (3H, s, SCH_3), 8.40, 7.61–7.52 (5H, m, phenyl-H), 9.85 (1H, s, CHO); MS (m/z, %): 255(M^+, 18), 241(100), 277(61), 200(22), 138(10),



(a) (b)

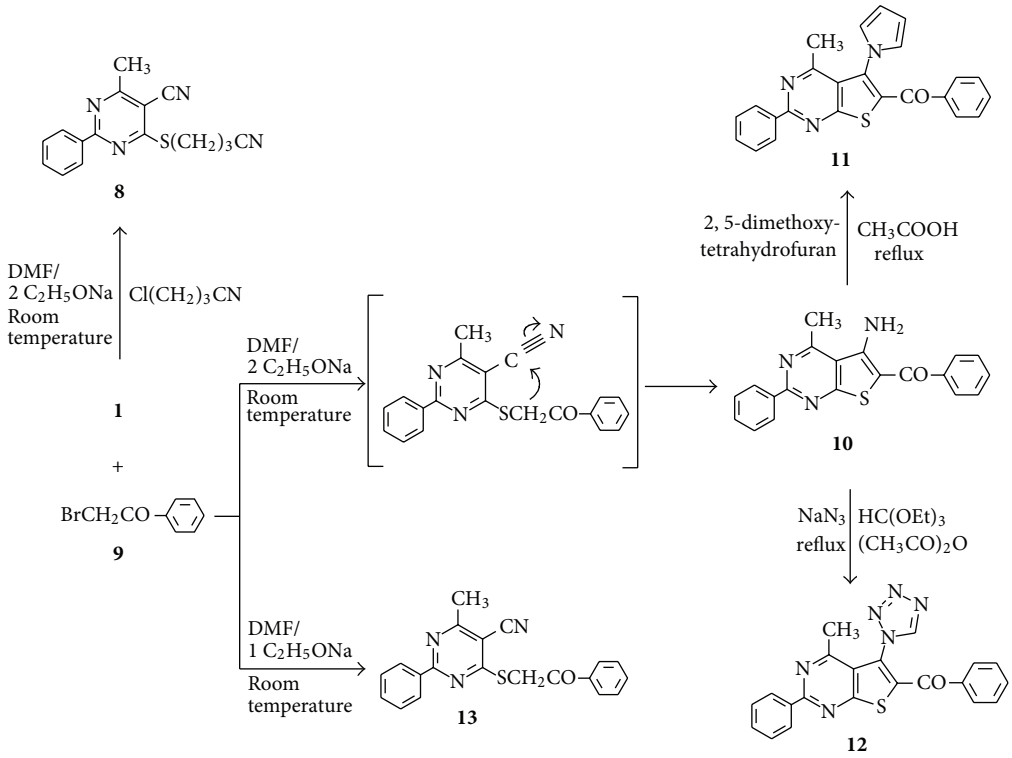
Figure 3: (a) Packing diagram for **13** showing the C–H—O hydrogen bonds (C–H—O = 2.261 Å, ∠C–H—O = 145.5°). (b) Packing diagram for **13** showing the interactions between the layers.



Scheme 1

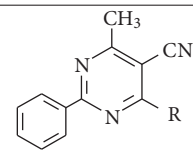
104(12), 97(5). Anal. Calcd. for $C_{13}H_9N_3OS$: C, 61.17; H, 3.52; N, 16.47. Found: C, 61.13; H, 3.72; N, 16.45%.

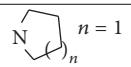
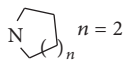
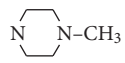
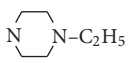
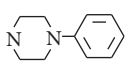
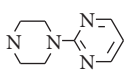
2.4. 6-Substituted-5-cyano-4-methyl-2-phenyl-pyrimidine Derivatives (**4a**,**b** and **5a**-**f**) *General Procedure.* A mixture of compound **2** (0.24 g, 1 mmol) and excess secondary amines (pyrrolidine, piperidine, morpholine, N-methylpiperazine, N-ethylpiperazine, ethyl 1-piperazinecarboxylate, 1-phenylpiperazine, and 1-(2-pyrimidyl)piperazine) (5 mmol) was refluxed for 10 h and poured into ice-water, and the precipitated product was collected by filtration, washed with water, and the crude product recrystallized from chloroform/THF. The physical constants and spectral data of compounds **4a**,**b** and **5a–f** are recorded in Tables 1 and 2.



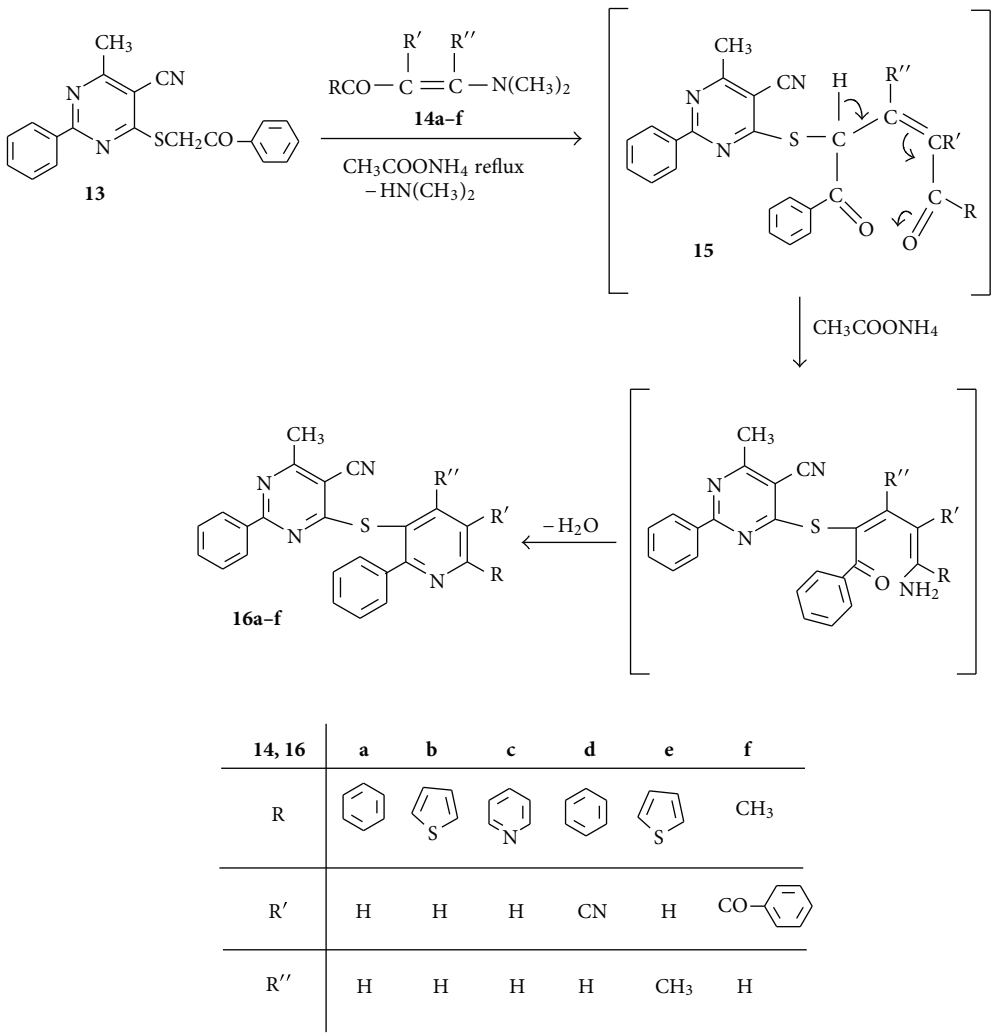
Scheme 2

Table 1: Physical and analytical data of 6-substituted-pyrimidine derivatives (**4a**, **b** and **5a**–**f**).



Compd.	R	M.P. (°C)[a]	Yield (%)	Molecular formula	Elemental Analysis (%) Calcd/Found.		
					C	H	N
4a		154	89	$C_{16}H_{16}N_4$	72.72 72.79	6.06 6.01	21.21 21.24
4b		111	88	$C_{17}H_{18}N_4$	73.38 73.41	6.47 6.51	20.14 20.11
5a		178	79	$C_{16}H_{16}N_4O$	68.57 68.59	5.71 5.72	20.00 19.98
5b		130	28	$C_{17}H_{19}N_5$	69.62 69.58	6.48 6.58	23.89 23.88
5c		118	87	$C_{18}H_{21}N_5$	70.35 70.39	6.84 5.78	22.80 22.75
5d		174	71	$C_{19}H_{21}N_5O_2$	64.95 65.04	5.98 6.02	19.94 20.01
5e		164	67	$C_{22}H_{21}N_5$	74.36 74.28	5.91 6.09	19.71 19.88
5f		185	64	$C_{20}H_{19}N_7$	67.22 67.39	5.32 5.14	27.45 27.61

[a]Recrystallization from $CHCl_3$/THF.

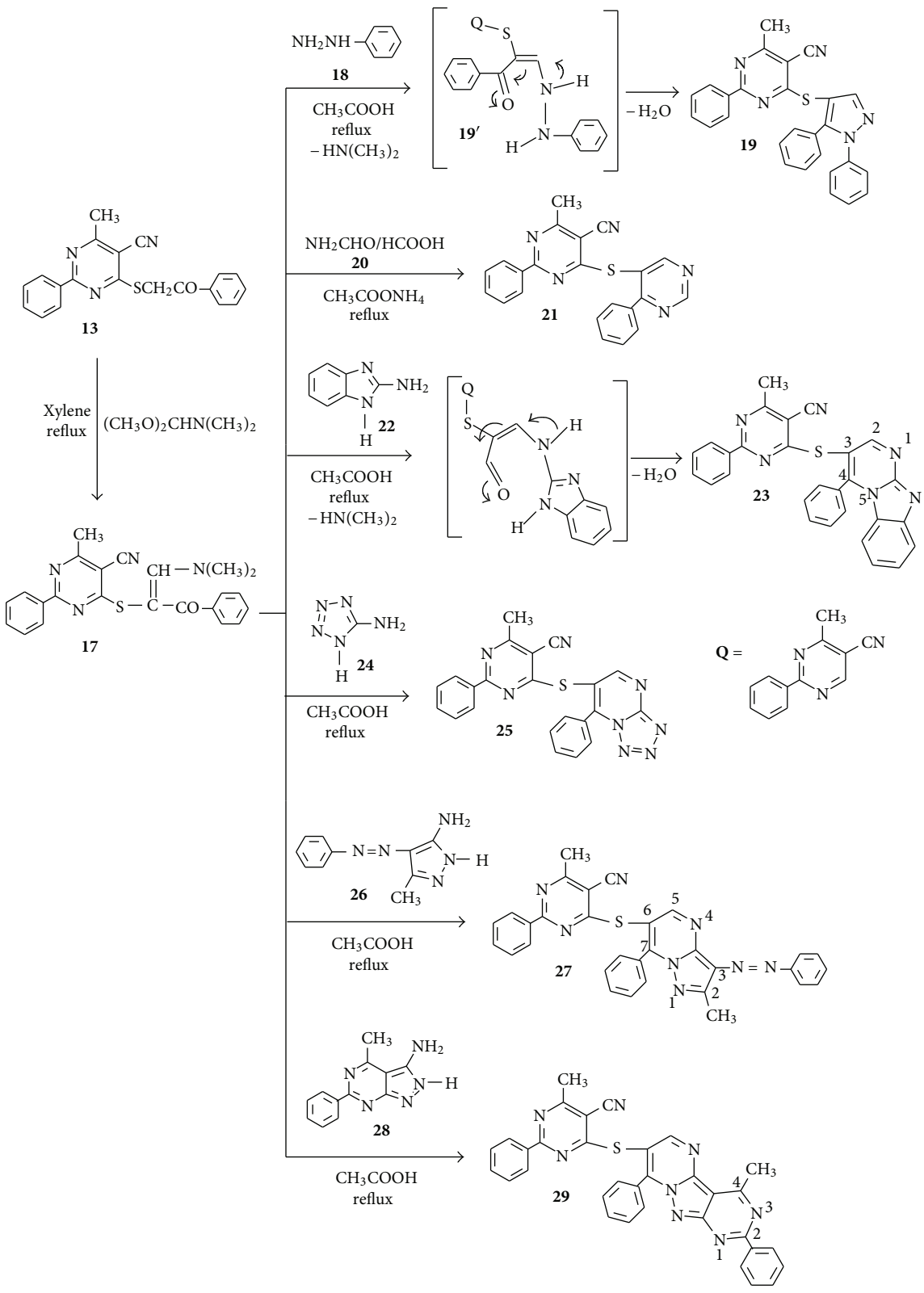


14, 16	a	b	c	d	e	f
R						CH_3
R′	H	H	H	CN	H	
R″	H	H	H	H	CH_3	H

Scheme 3

2.5. 4-[(4-N,N-Dimethylamino)-2-phenylvinyl)]-6-piperidinyl-5-cyano-2-phenyl-pyrimidine (**6**). A mixture of 6-piperidinyl-4-methyl-pyrimidine **4b** (0.28 g, 1 mmol) and N,N-dimethylaminobenzaldehyde (0.15 g, 1 mmol) in dioxane (10 mL) in the presence of catalytic amount of piperidine was refluxed for 8 h. After cooling, the resulting solid product was collected by filtration and washed with water, and the crude product recrystallized from ethanol/glacial acetic acid to give 0.15 g of pale yellow needles (37% yield), mp 103°C; IR: ν 2212 (C≡N) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.07–2.96, 1.75–1.62 (10H, m, piperidinyl-H), 3.09 (6H, s, CH_3), 6.70 (1H, d, J = 2.0 Hz, –CH=), 7.74 (1H, d, J = 2.0 Hz, =CH–), 8.57–8.55, 7.52–7.44 (9H, m, phenyl-H); MS (m/z, %): 409(M^+, 100), 381(9), 366(3), 326(5), 289(7), 222(4), 205(6), 195(8), 190(5), 104(7), 85(5). Anal. Calcd. for $C_{26}H_{27}N_5$: C, 76.28; H, 6.60; N, 17.11. Found: C, 76.01; H, 6.42; N, 17.31%.

2.6. 6-Cyanopropylthio-5-cyano-4-methyl-2-phenyl-pyrimidin (**8**). A mixture of 5-cyano-1,6-dihydro-4-methyl-2-phenyl-6-thioxopyrimidine **1** (2.27 g, 0.01 mol), sodium ethoxide (1.36 g, 0.02 mol), and 4-chlorobutyronitrile (1.03 g, 0.01 mol) in DMF (50 mL). The reaction mixture was stirred at room temperature for 4 h and then diluted with cold water (50 mL) was collected by filtration, washed with water, and recrystallized from DMF/ethanol to give 2.88 g of yellow needles (98% yield), mp 144°C; IR: ν 2220 (C≡N) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.21 (2H, t, J = 2.54 Hz, CH_2), 2.58–2.56 (2H, m, CH_2), 2.71 (3H, s, CH_3), 3.54 (2H, t, J = 2.27 Hz, CH_2), 8.47-8.46, 7.55–7.49 (5H, m, phenyl-H); MS (m/z, %): 294(M^+,22), 254(60), 241(100), 227(28), 194(9), 153(31), 104(15), 77(16). Anal. Calcd. for $C_{16}H_{14}N_4S$: C, 65.30; H, 4.76; N, 19.04. Found: C, 65.23; H, 4.70; N, 19.13%.


NH2NH
18
CH3COOH
reflux
– HN(CH3)2
19′
– H2O
19
13
NH2CHO/HCOOH
20
CH3COONH4
reflux
21
Xylene
reflux
(CH3O)2CHN(CH3)2
22
CH3COOH
reflux
– HN(CH3)2
– H2O
23
17
24
CH3COOH
reflux
25
Q =
26
CH3COOH
reflux
27
28
CH3COOH
reflux
29

Scheme 4

Table 2: Spectral data of 6-substituted-pyrimidine derivatives (**4a**, **b** and **5a**–**f**).

Compd.	MS (m/e M^+)	IR (KBr) ν (cm^{-1})	^{1}H-NMR[a] ($CDCl_3$) δ (ppm)
4a	264(98), 235(100), 209(30), 70(8).	2204 (C≡N)	2.30–2.11 (4H, m, 3,4-H of pyrrolidinyl), 2.82 (3H, s, CH_3), 4.09 (2H, t, J = 1.40 Hz, 5-H of pyrrolidinyl), 4.21 (2H, t, J = 1.40 Hz, 2-H of pyrrolidinyl), 8.08–8.07, 7.76–7.57 (5H, m, phenyl-H).
4b	278(100), 263(7), 249(92), 236(26), 223(24), 210(8), 196(12), 154(30), 104(42), 77(17), 55(3).	2208 (C≡N)	1.76, 4.02 (10H, m, piperidinyl-H), 2.69 (3H, s, CH_3), 8.41–8.39, 7.50–7.45 (5H, m, phenyl-H).
5a	280(100), 249(32), 236(17), 223(91), 194(16), 153(46), 125(4), 104 (37), 77(24), 56(7).	2210 (C≡N)	2.69 (3H, s, CH_3), 3.85 (4H, d, J = 1.0 Hz, 2,6-H of morpholinyl), 4.07 (4H, d, J = 1.0 Hz, 3,5-H of morpholinyl), 8.40–8.38, 7.52–7.45 (5H, m, phenyl-H).
5b	293(9), 249(4), 236(19), 223(100), 194(4), 153(11), 104(14), 83(46), 70(43), 55(7).	2205 (C≡N)	2.43 (3H, s, CH_3), 2.68 (3H, s, N-CH_3), 2.66 (4H, d, J = 1.0 Hz, 2,6-H of piperazinyl), 4.14 (4H, d, J = 1.0 Hz, 3,5-H of piperazinyl), 8.40–8.38, 7.50–7.45 (5H, m, phenyl-H).
5c	307(12), 263(4), 249(5), 236(29), 223(65), 194(4), 153(11), 104(12), 97(60), 84(100), 72(14), 55(7).	2206 (C≡N)	1.14 (3H, t, J = 1.44 Hz, N-$CH_2\underline{CH_3}$), 2.67 (3H, s, CH_3), 2.51 (2H, q, J = 2.16 Hz, N-$\underline{CH_2}$CH3), 2.62 (4H, d, J = 1.0 Hz, 2,6-H of piperazinyl), 4.11 (4H, d, J = 1.0 Hz, 3,5-H of piperazinyl), 8.40–8.38, 7.50–7.44 (5H, m, phenyl-H).
5d	351(95), 336(1), 322(8), 306(2), 283(17), 278(2), 249(9), 236(382), 223(100), 194(6), 153(1), 141(10), 58(4).	1705 (C=O) 2207 (C≡N)	1.30 (3H, t, J = 1.43 Hz, $OCH_2\underline{CH_3}$), 2.69 (3H, s, CH_3), 3.67 (4H, t, J = 1.06 Hz, 2,6-H of piperazinyl), 4.05 (4H, d, J = 1.00 Hz, 3,5-H of piperazinyl), 4.20 (2H, q, J = 2.13 Hz, $COOCH_2$), 8.40–8.38, 7.53–7.45 (5H, m, phenyl-H).
5e	355(42), 249(5), 236(28), 223(100), 194(3), 177(4), 153(10), 132(94), 120(31), 104(44), 77(20), 55(5).	2200 (C≡N)	2.70 (3H, s, CH_3), 3.37 (4H, d, J = 1.09 Hz, 2,6-H of piperazinyl), 4.25 (4H, d, J = 1.00 Hz, 3,5-H of piperazinyl), 8.43–8.42, 7.52–6.91 (10H, m, phenyl-H).
5f	357(57), 262(9), 249(15), 236(34), 223(100), 194(5), 179(6), 153(11), 147(44), 134(67), 123(24), 108(39), 103(16), 80(22), 55(5).	2204 (C≡N)	2.69 (3H, s, CH_3), 4.02 (4H, d, J = 1.06 Hz, 2,6-H of piperazinyl), 4.16 (4H, d, J = 1.06 Hz, 3,5-H of piperazinyl), 6.56 (1H, m, 5-H of pyrimidinyl), 8.36 (2H, d, J = 1.0 Hz, 4,6-H of pyrimidinyl), 8.42–8.40, 7.51–7.45 (5H, m, phenyl-H).

[a]Abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

2.7. 5-Amino-6-benzoyl-4-methyl-2-phenylthieno[2,3-d]pyrimidine (**10**). A mixture of 5-cyano-1,6-dihydro-4-methyl-2-phenyl-6-thioxopyrimidine **1** (2.27 g, 0.01 mol), 2-bromoacetophenone **9** (1.99 g, 0.01 mol), and sodium ethoxide (1.36 g, 0.02 mol) in DMF (50 mL) was stirred at room temperature for 4 h and then diluted with cold water (50 mL). The resulting solid product was collected by filtration, washed with water, and recrystallized from DMF/ethanol to give 3.17 g of yellow needles (92% yield), mp 236°C; IR: ν 3421, 3288 (NH_2), 1663 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.56 (3H, s, CH_3), 3.71 (2H, br, NH_2), 8.39–8.37, 7.95–7.72 (10H, m, phenyl-H); MS (m/z, %): 345(M^+,100). Anal. Calcd. for $C_{20}H_{15}N_3OS$: C, 69.56; H, 4.34; N, 12.17. Found: C, 69.71; H, 4.50; N, 12.43%.

2.8. 6-Benzoyl-4-methyl-5-(1-pyrrolyl)-2-phenylthieno [2,3-d]pyrimidine (**11**). A mixture of 5-amino-6-benzoyl-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine **10** (0.34 g, 1 mmol) and 2,5-dimethoxytetrahydrofuran (0.13 g, 1 mmol), in glacial acetic acid (20 mL) was refluxed for 12 h. After cooling, the resulting solid product was collected by filtration and washed with water, and the crude product recrystallized from ethanol/glacial acetic acid to give 0.18 g of brown needles (46% yield), mp 130°C; IR: ν 1663 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.31 (3H, s, CH_3), 6.10 (2H, m, 3,4-H of pyrrolyl), 6.71 (2H, m, 2,5-H of pyrrolyl), 8.59–8.57, 7.69–7.31 (10H, m, phenyl-H); MS (m/z, %): 395(M^+,100). Anal. Calcd. for $C_{24}H_{17}N_3OS$: C, 72.91; H, 4.30; N, 10.63. Found: C, 73.01; H, 4.42; N, 10.67%.

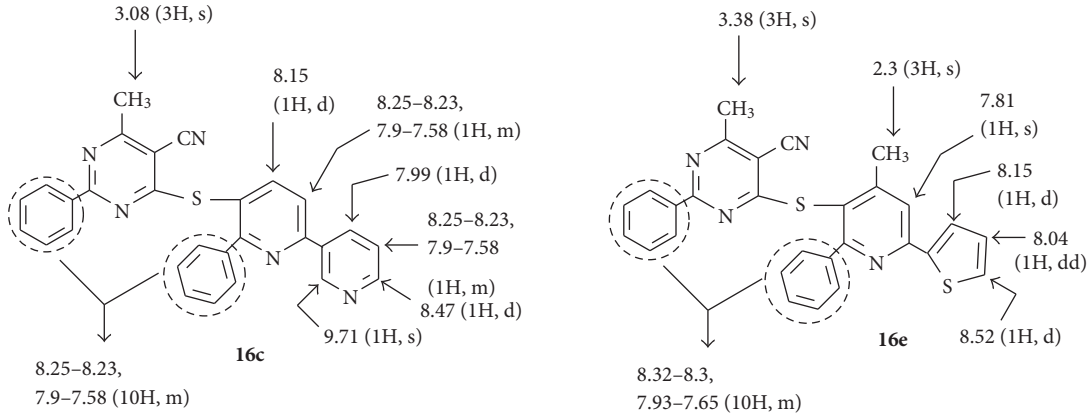


Figure 4: Structural assignment of typical protons in **16c** and **16e** by ^{1}H NMR.

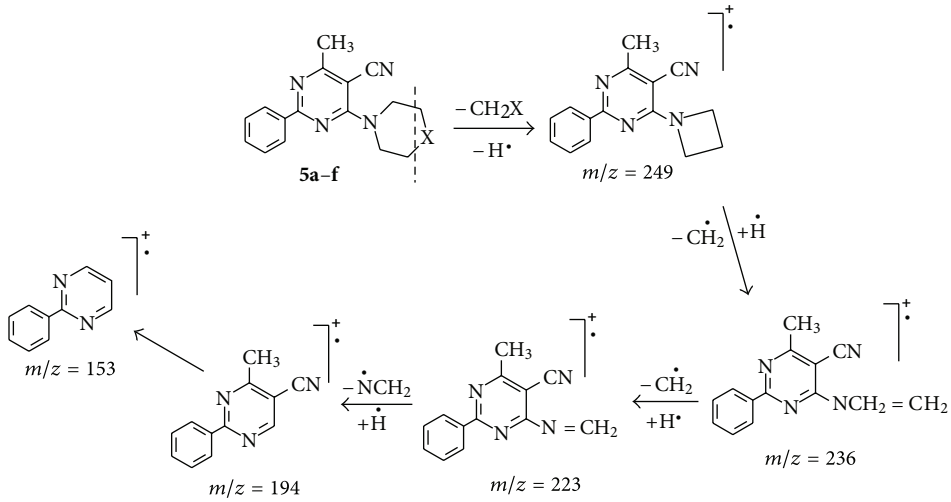


Figure 5

2.9. 5-(1,2,3,4-Tetrazol-1-yl)-6-benzoly-4-methyl-2-phenyl-thieno[2,3-d]pyrimidine (**12**). A mixture of 5-amino-6-benzoyl-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine **10** (0.34 g, 1 mmol), sodium azide (0.065 g, 1 mmol), and triethyl orthoformate (8 mL) was refluxed in acetic anhydride (15 mL) for 4 h. The reaction mixture was cooled. The resulting solid product was collected by filtration and washed with water, and the crude product recrystallized from DMF/glacial acetic acid to give 0.31 g of orange yellow needles (78% yield), mp 196°C; IR: ν 1662 (C=O) cm^{-1}; ^{1}H-NMR (CF_3COOD): δ 2.61 (3H, s, CH_3), 8.83 (1H, s, 5-H of tetrazoly), 8.64–8.62, 8.21–7.96 (10H, m, phenyl-H); MS (*m*/*z*, %): 398(M^+,10), 367(13), 344(100), 268(3), 240(10), 211(2), 105(5). Anal. Calcd. for $C_{21}H_{14}N_6OS$: C, 63.31; H, 3.51; N, 21.10. Found: C, 63.45; H, 3.66; N, 21.31%.

2.10. 6-[(Benzoylmethyl)thio]-5-cyano-4-methyl-2-phenyl-pyrimidine (**13**). A mixture of 5-cyano-1,6-dihydro-4-methyl-2-phenyl-6-thioxopyrimidine **1** (2.27 g, 0.01 mol), sodium ethoxide (0.68 g, 0.01 mol), and 2-bromoacetophenone **9** (1.99 g, 0.01 mol) in DMF (50 ml). The reaction mixture was stirred at room temperature for 4 h and then diluted with cold water (50 mL) was collected by filtration, washed with water, and recrystallized from chlorofrom/ethanol to give 3.1 g of pale yellow needles (90% yield), mp 169°C; IR: ν 2220(C≡N), 1679 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.67 (3H, s, CH_3), 4.77 (2H, s, SCH_2), 8.11–8.06, 7.70–7.22 (10H, m, phenyl-H); MS (*m*/*z*, %): 345(M^+,85), 319(15), 312(30), 242(3), 240(30), 134(10), 105(100), 77(4). Anal. Calcd. for $C_{20}H_{15}N_3OS$: C, 69.56; H, 4.34; N, 12.17. Found: C, 69.68; H, 4.40; N, 12.33%.

2.11. 6-[(4,5,6-Trisubstituted-2-phenyl-pyridin-3-yl)thio]-5-cyano-4-methyl-2-phenyl-pyrimidine (**16a–f**) General Procedure. A mixture of compound **13** (0.35 g, 1 mmol) and enaminone derivatives **14a–f** (1 mmol) and ammonium acetate (2 mmol) was refluxed in glacial acetic acid (10 mL) for 11 h. After cooling, the resulting solid product was collected by filtration, washed with water, and recrystallized from ethanol/glacial acetic acid. The physical constants and

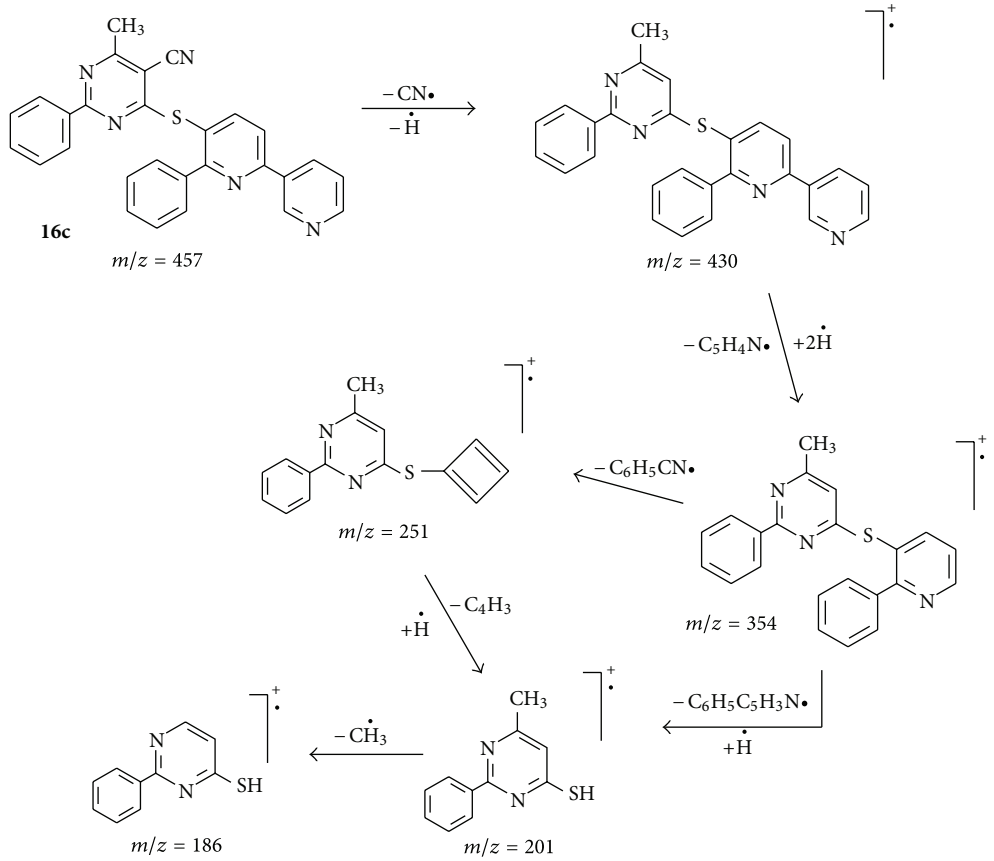


Figure 6

spectral data of compounds **16a–f** are recorded in Tables 6 and 7.

2.12. 2-[(5-Cyano-4-methyl-2-phenylpyrimidin-6-yl)thio]-3-dimethylamino-1-phenyl-prop-2-en-1-one (**17**). A mixture of compound **13** (0.35 g, 1 mmol) and N,N-dimethylformamide dimethylacetal (1 mmol) was refluxed in xylene (5 mL) for 5 h. After cooling, the resulting solid product was collected by filtration, washed with water, and recrystallized from ethanol/glacial acetic acid afforded 0.26 g of yellow crystals (66% yield), mp 185°C; IR: ν 2214 (C≡N), 1654 (C=O) cm^{-1}; ^{1}H-NMR (CF_3COOD): δ 2.94 (6H, s, $N(CH_3)$), 3.43 (3H, s, CH_3), 7.47 (1H, s, =CH–N), 8.27–8.23, 7.81–7.57 (10H, m, phenyl-H); MS (*m*/*z*, %): 400(M^+,10), 344(100). Anal. Calcd. for $C_{23}H_{20}N_4OS$: C,69.00; H, 5.00; N, 14.00. Found: C, 59.93; H, 5.23.; N, 14.33%.

2.13. 6-[(4-Phenyl-pyrimidin-5-yl)thio]-5-cyano-4-methyl-2-phenyl-pyrimidine (**21**). A mixture of compound **17** (0.40 g, 1 mmol) and formamide/formic acid (1 : 1, 1 mmol) **20**and ammonium acetate (2 mmol) was refluxed for 7 h. After cooling, the resulting solid product was collected by filtration, washed with water, and recrystallized from ethanol/glacial acetic acid to give 0.21 g of yellow needles (56% yield), mp 258°C; IR: ν 2209 (C≡N) cm^{-1}; ^{1}H-NMR (CF_3COOD): δ 3.84 (3H, s, CH_3), 8.21 (1H, s, 6-H of pyrimidinyl), 8.26 (1H, s, 2-H of pyrimidinyl), 8.70–8.69, 8.24–8.02 (10H, m, phenyl-H); MS (*m*/*z*, %): 381(54), 345(100), 280(16), 256(8), 210(1), 121(2), 105(22), 98(6), 57(4). Anal. Calcd. for $C_{22}H_{15}N_5S$: C, 69.29; H, 3.93; N, 18.37. Found: C, 69.38; H, 4.01; N, 18.44%.

2.14. 6-[(Substituted)thio]-5-cyano-4-methyl-2-phenyl-pyri-midine Derivatives (*19, 23, 25, 27 and 29) General Procedure.* A mixture of compound **17** (0.40 g, 1 mmol) and phenylhydrazine **18**, 2-amino-benzimidazole **22**, 5-amino-1*H*-tetrazole **24,** and 5-amino-pyrazoles **26**, **28** (1 mmol) in the presence of glacial acetic acid (5 mL) was refluxed for 7 h. After cooling, the resulting solid product was collected by filtration, washed with water, and the crude product recrystallized from DMF/glacial acetic acid.

2.15. 6-[(1,5-Diphenyl-1h-Pyrazol-4-yl)thio]-5-cyano-4-methyl-2-phenyl-pyrimidine (**19**). Yield 38%, mp 240°C; IR: ν 2201 (C≡N) cm^{-1}; ^{1}H-NMR (CF_3COOD): δ 3.34 (3H, s, CH_3), 7.76 (1H, s, 3-H of pyrazole), 8.25–8.23, 7.81–7.79, 7.70–7.57 (15H, m, phenyl-H); MS (*m*/*z*, %): 445(M^+,7), 422(6), 355 (4), 344(100), 268(3), 93(2). Anal. Calcd. for $C_{27}H_{19}N_5S$: C, 72.80; H, 4.26; N, 15.73. Found: C, 72.91; H, 4.47; N, 15.89%.

Table 3: Crystal data and structure refinement for compound **13**.

Empirical formula	$C_{20}H_{15}N_3OS$
Formula weight	345.41
Temperature	297(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/n
Unit cell dimensions	$a = 13.5314(9)$ Å $\alpha = 90^{\circ}$. $b = 9.5316(6)$ Å $\beta = 110.7820(10)^{\circ}$. $c = 14.7941(10)$ Å $\gamma = 90^{\circ}$
Volume	1783.9(2) Å^3
Z	4
Density (calculated)	1.286 Mg/m^3
Absorption coefficient	0.193 mm^{-1}
F(000)	720
Crystal size	0.67 × 0.63 × 0.46 mm^3
Theta range for data collection	2.60 to 26.01°.
Index ranges	$-16 \le h \le 16$, $-11 \le k \le 11$, $-11 \le l \le 18$
Reflections collected	9753
Independent reflections	3499 [R(int) = 0.0305]
Completeness to theta = 26.01°	99.7%
Absorption correction	Empirical
Max. and min. transmission	0.9163 and 0.8813
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3499/0/226
Goodness-of-fit on F^2	1.016
Final R indices [I > 2 sigma(I)]	$R_1 = 0.0478$, $\omega R_2 = 0.1350$
R indices (all data)	$R_1 = 0.0587$, $\omega R_2 = 0.1474$
Largest diff. peak and hole	0.322 and −0.391 e·Å^{-3}

2.16. 6-[(4-Phenyl-benzimidazolo[1,2-a]pyrimidinyl-3-yl) thio]-5-cyano-4-methyl-2- phenyl-pyrimidine (**23**). Yield 54%, mp 232°C; IR: ν 2204 (C≡N) (C=N) cm^{-1}; ^{1}H-NMR (CF_3COOD): δ 2.51 (3H, s, CH_3), 8.53 (1H, s, 2-H of benzimidazolo- pyrimidinyl), 8.09-8.08, 7.98-7.86 (14H, m, benzimidazolyl-H and phenyl-H); MS (m/z, %): 470(11), 430(2), 367(2), 355(30), 345(100), 276(2), 227(8), 105(4). Anal. Calcd. for $C_{28}H_{18}N_6S$: C, 71.48; H, 3.82; N, 17.87. Found: C, 71.39; H, 3.99; N, 17.98%.

2.17. 6-[(4-Phenyl-1,2,3,4-tetrazolo[1,5-a]pyrimidinyl-3-yl)thio]-5-cyano-4-methyl-2-phenyl-pyrimidine (**25**). Yield 50%, mp 233°C; IR: ν 2206 (C≡N) cm^{-1}; ^{1}H-NMR (CF_3COOD): δ 2.63 (3H, s, CH_3), 8.65 (1H, s, 2-H of tetrazolopyrimidinyl), 8.22–8.17, 8.11–7.99 (10H, m, phenyl-H); MS (m/z, %): 422(6), 344(100), 292(2), 212(5), 105(3). Anal. Calcd. for $C_{22}H_{14}N_8S$: C, 62.55; H, 3.32; N, 26.54. Found: C, 62.74; H, 3.45; N, 26.66%.

2.18. 6-[(5-Cyano-6-methyl-2-phenylpyrimidin-4-yl)thio]-2-methyl-3-phenylazo-7-phenyl-pyrazolo[1,5-a]pyrimidine (**27**). Yield 67%, mp 230°C; IR: ν 2200 (C≡N) cm^{-1}; ^{1}H-NMR (CF_3COOD): δ 2.62 (3H, s, CH_3), 2.91 (3H, s, CH_3), 8.00 (1H, s, 5-H of pyrazolopyrimidinyl), 8.28-8.27, 7.84–7.61 (15H, m, phenyl-H); MS (m/z, %): 538(15), 461(8), 344(100), 316(10), 240(4), 182(1), 124(1), 93(2). Anal. Calcd. for $C_{31}H_{22}N_8S$: C, 69.14; H, 4.08; N, 20.81. Found: C, 69.26; H, 4.22; N, 20.66%.

2.19. 7-[(5-Cyano-6-methyl-2-phenylpyrimidin-4-yl)thio]-4-methyl-2,8-diphenyl-pyrimido[4′,5′:3,4]pyrazolo[1,5-a]pyrimidine (**29**). Yield 65%, mp 289°C; IR: ν 2201 (C≡N) cm^{-1}; ^{1}H-NMR (CF_3COOD): δ 2.37 (3H, s, CH_3), 3.52 (3H, s, CH_3), 7.67 (1H, s, 6-H of pyrimidopyrazolopyrimidinyl), 8.41–8.39, 7.95–7.72 (15H, m, phenyl-H); MS (m/z, %): 562(15), 460(1), 418(2), 316(10), 368(100), 344(20), 249(4), 225(16), 197(10), 153(12), 104(13), 77(17), 51(4). Anal. Calcd. for $C_{33}H_{22}N_8S$: C, 70.46; H, 3.91; N, 19.92. Found: C, 70.66; H, 4.12; N, 20.16%.

2.20. X-Ray Structure Study of Compound **13**. The diffraction data of compound **13** was collected on a Siemens CCD diffractometer, which was equipped with graphite-monochromated Mo-K_α (K_α = 0.71073 Å) radiation. Data reduction was carried by standard methods with use of well-established computational procedures [28, 29]. A pale yellow crystal of compound **13** was mounted on the top of a glass fiber with epoxy cement. The hemisphere data collection method was used to scan the data points at $3.34 < 2\theta < 52.02^{\circ}$. The structure factors were obtained after Lorentz and polarization correction. The final residuals of the final refinement were $R_1 = 0.0478$, $\omega R_2 = 0.1350$. The crystallographic data of compound **13** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 752301. Copy of this information may be obtained free of charge via http://www.ccdc.cam.ac.uk or from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +441223/336–033; email: deposit@ccdc.cam.ac.uk).

3. Results and Discussion

All relevant reactions are depicted in Schemes 1, 2, 3, and 4. The required compound 5-cyano-1,6-dihydro-4-methyl-2-phenyl-6-thioxopyrimidine **1** was prepared by treating benzoylisothiocyanate with 3-aminocrotononitrile in refluxing dioxane [26]. Several pyrimidines substituted at position-6 with different heterocyclic residues were obtained via treatment of thioxopyrimidine **1** with different reagents. Thus, reaction of thioxopyrimidine **1** with methyl iodide in the presence of sodium methoxide to yield the 6-methylthio-4-methyl-2-phenyl-pyrimidine **2**, which reacted with selenium oxide in dioxane afforded the 4-formyl-6-methylthio-2-phenyl-pyrimidine **3** (Scheme 1). The IR spectra of compound **3** showed the characteristic absorption bands at 1689 cm^{-1} for the HC=O group and 2218 cm^{-1} for

Table 4: Selected bond lengths [Å] and angles [°] for compound **13**[a].

S–C(10)	1.743(17)
O–C(14)	1.209(2)
N(1)–C(7)	1.341(2)
N(2)–C(7)	1.339(2)
C(1)–C(6)	1.383(3)
C(6)–C(7)	1.481(2)
C(9)–C(10)	1.401(2)
N(6)–C(12)	1.423(3)
C(14)–C(15)	1.482(3)
C(10)–S–C(13)	100.0(9)
C(10)–N(2)–C(7)	117.0(13)
N(1)–C(7)–C(6)	117.3(15)
C(8)–C(9)–C(10)	118.0(14)
N(2)–C(10)–S	119.6(12)
O–C(14)–C(15)	122.1(19)
C(15)–C(14)–C(13)	116.3(17)
C(16)–C(15)–C(14)	122.8(2)
S–C(13)	1.784(2)
N(1)–C(8)	1.335(2)
N(2)–C(10)	1.334(19)
N(3)–C(12)	1.135(3)
C(5)–C(6)	1.389(3)
C(8)–C(9)	1.387(3)
C(13)–C(14)	1.523(3)
C(13)–C(14)	1.349(5)
C(15)–C(16)	1.393(3)
C(8)–N(1)–C(7)	117.4(15)
N(1)–C(7)–N(2)	125.7(14)
N(2)–C(7)–C(6)	116.8(14)
N(2)–C(10)–C(9)	120.9(15)
C(9)–C(10)–S	119.3(12)
O–C(14)–C(13)	121.4(19)
C(16)–C(15)–C(20)	118.6(2)
C(20)–C(15)–C(14)	118.6(2)

[a]Standard deviations in parentheses.

the C≡N group. In addition, the ^{1}H NMR spectra (DMSO-d_6) of compound **3** revealed two singlets at δ 2.74 (3H, s) and 9.85 (1H, s), which were readily assigned to the SCH_3 and HC=O groups, respectively. On the other hand, a series of novel 6-substituted-pyrimidine derivatives **4a,b** and **5a–f** were also obtained by the condensation reaction of compound **2** with appropriate secondary amines such as pyrrolidine, piperidine, morpholine, N-methylpiperazine, N-ethylpiperazine, ethyl 1-piperazinecarboxylate, 1-phenyl-piperazine and 1-(2-pyrimidyl)piperazine, (Scheme 1). Compounds **4a,b** and **5a–f** were obtained generally in 28–89% yields. The structures of **4a,b** and **5a–f** were verified by elemental analysis and by spectroscopic methods. Physical and spectral data of compounds **4a,b** and **5a–f** are recorded in Tables 1 and 2, respectively. Typical assignments for **5f** by ^{1}H-NMR are shown in Figure 1. These structures get further support from mass spectroscopy. The mass fragmentation pattern of compound **5d** showed the presence of the ion peaks $[M–CH_3]^+$ at m/z 336, $[M–CH_2CH_3]^+$at m/z 322, $[M–OCH_2CH_3]^+$ at m/z 306 and $[M–COOCH_2CH_3]^+$ at m/z 278. Also, it has been observed that electron impact (EI) spectral has many common features. Compounds **5a–f** exhibited m/z 249, m/z 236, m/z 223, m/z 194 and m/z 153 piece peaks. The possible mass fragmentation pathways of compounds **5a–f** are shown in Figure 5.

Next, treatment of 6-piperidinyl-4-methyl-pyrimidine **4b** with N,N-dimethyl-aminobenzaldehyde in refluxing dioxane in the presence of catalytic amount of piperidine yielded the 4-[(4-N,N-dimethylamino)-2-phenylvinyl)]-6-piperidinyl-5-cyano-2-phenyl-pyrimidine **6**. The ^{1}H-NMR spectra ($CDCl_3$) of compound **6** revealed a sharp singlet at δ 3.09 (6H, s) assigned to the $–N(CH_3)_2$ protons and at δ 6.70 (1H, d) and 7.74 (1H, d) assigned to the –CH=CH– of 4-dimethylaminophenylethylene moiety, two multiplets at δ 3.07–2.96, 1.75–1.62 (10H, m) assigned to the piperidinyl protons and a multiplet at δ 8.57–7.44 (9H, m) assigned to the phenyl protons, were also confirmed by the mass spectrum m/z 409(M^+). However, reaction of compound **2** with benzhydrazide did not produce the desired compound **7**, but led only to the recovery of starting material. On the other hand, the 6-cyanopropylthio-pyrimidine **8** was also obtained by treatment of compound **1** with 4-chlorobutyronitrile in DMF at room temperature in the presence of sodium ethoxide in a molar ratio of 1 : 2 (Scheme 2). Nevertheless, under same reaction conditions, treatment of compound **1** with 2-bromoacetophenone **9** formed the nonisolable S-alkylated intermediate, which *via* nucleophilic substitution and intramolecular cyclocondensation afforded the corresponding 5-amino-6-benzoly-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine **10**, which when reacted with 2,5-dimethoxy-tetrahydrofuran in glacial acetic acid produced the 5-(1-pyrrolyl)-6-benzoly-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine **11**. Also, reaction of compound **10** with sodium azide and triethyl orthoformate in acetic anhydride afforded the corresponding 5-(1,2,3,4-tetrazol-1-yl)-6-benzoly-2-phenyl-thieno[2,3-*d*]pyrimidine **12** (Scheme 2). The structure of compounds **10–12** was established on the basis of their elemental analysis and spectral data. The IR spectra of compounds **11** and **12** indicated the complete disappearance of NH_2 and showed the characteristic absorption band at 1663-1662 cm^{-1} for the C=O group. The ^{1}H-NMR spectra ($CDCl_3$) of compound **11** revealed two multiplets at δ 6.10 (2H, m) and 6.71 (2H, m), which were readily assigned to the hydrogen of the pyrrolyl ring. Moreover, compound **12** showed a singlet at δ 8.83 (1H, s) assigned to the hydrogen attached at C_5 of the tetrazolyl ring.

On the other hand, treatment of compound **1** with 2-bromoacetophenone **9** in the presence of sodium ethoxide in a molar ratio of 1:1 afforded the open-chain product 6-(benzoylmethyl)thio-2-phenyl-pyrimidine **13** in 90% yield (Scheme 2). The IR spectra of compound **13** indicated the characteristic absorption bands at 1679 cm^{-1} for the C=O

Table 5: Selected torsion angles for compound **13**.

C(13)–S–C(10)–N(2)	−16.1°
C(13)–S–C(10)–C(9)	165.5°
C(1)–C(6)–C(7)–N(2)	−175.1°
C(1)–C(6)–C(7)–N(1)	−175.1°
C(16)–C(15)–C(14)–O	165.7°
C(20)–C(15)–C(14)–O	−14.1°
C(13)–C(14)–C(15)–C(16)	−13.2°
C(13)–C(14)–C(15)–C(20)	167.0°
S–C(13)–C(14)–O	11.3°
S–C(13)–C(14)–C(15)	−169.7°

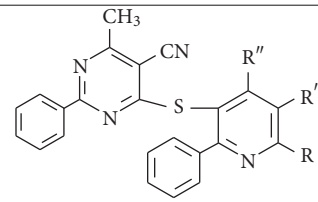
group and 2220 cm^{-1} for the C≡N group. In particular, the ^{1}H-NMR spectrum ($CDCl_3$) of compound **13** revealed a singlet at δ 4.77 (2H, s) assigned to the SCH_2CO protons. The structure of **13** was unambiguously confirmed by X-ray crystallography. The suitable single crystals of compound **13** were obtained by slow crystallization from chloroform/DMF at room temperature. Perspective view and the numbering of the atoms are depicted in Figure 2. This drawing clearly establishes the structural formula and also shows the conformation of the molecule. The packing diagram (Figure 3) in the solid state by intermolecular hydrogen bonding between C–H of the –S–CH_2 group and C=O atom (C–H—O = 2.261 Å, ∠C–H—O = 145.5°). The relevant crystallographic date and structure refinement are recorded in Table 3. The selected bond lengths and bond angles are listed in Table 4. The hydrogen atoms were refined isotropically in idealized positions riding on the atom to which they are attached. The crystal system of compound **13** is monoclinic, the space group is P 21/n and data was collected in the range 2.60 to 26.01°. Details of the intensity collection are recorded in Table 3.

The basal plane is formed by phenyl(C(15))-carbonylmethylthio(C(14)), carbonylmethylthio-pyrimidine(C(10)), and pyrimidine(C(7))-phenyl(C(6)) atoms, with bond lengths of 1.482(3), 1.7436(17), and 1.481(2) Å, respectively. The phenyl ring is in the *cis* (Z) configuration with respect to the S atom and the fused pyrimidine system (Figure 2). Moreover, the fused pyrimidine system is almost planar and due to the effect of carbonylmethyl-S moiety the phenyl group exhibit noticeable quinoid character that is demonstrated by the shortening of the C(17)–C(18) [1.353(5) Å], C(18)–C(19) [1.383(5) Å], C(19)–C(20) [1.385(4) Å], and C(16)–C(17) [1.374(3) Å] bond lengths compared to the standard C_{ar}–C_{ar} distance of 1.397(1) Å [30]. In addition, the C(16)–C(17) phenyl and carbonyl group are in a staggered conformation with respect to the O atom giving rise to angular distortion at C(15) and C(14) [C(16)–C(15)–C(14)C(20)–C(15)–C(14)] (Table 4). The S–C(10) [1.7436(17) Å] bond is longer than the C(6)–C(7)[1.481(2) Å], which is probably due to electron withdrawing effect of the S atom. Also, the interesting torsion angles which entirely define the molecule conformation are selected and listed in Table 5. Moreover, the C(9)–C(10) [1.401(2) Å] and N(1)–C(7) [1.341(2) Å] bonds are longer than the N(2)–C(10) [1.334(19) Å]. The C(1)–C(2) phenyl ring has a dihedral angle with N(2)–C(10) pyrimidine ring of 171.1°, while the carbonylmethylthio's dihedral angle with this pyrimidine is 101.0°. Furthermore, the C(16)–C(17) phenyl ring attached to the carbonylmethyl group and makes a dihedral angle of 112.2° with pyrimidine ring plane and the C(16)–C(17) phenyl ring has a dihedral angle with carbonylmethylthio group of 15.7°.

On the other hand, the reaction of compound **13** with enaminone derivatives **14a–f** was also investigated. Thus, it has been found that compound **13** with 3-dimethylamino-1-(phenyl)prop-2-enone **14a** in refluxing glacial acetic acid in the presence of excess ammonium acetate gave a yellow product of molecular formula $C_{29}H_{20}N_4S$ (55% yield, mp 218°C). Spectroscopic analyses revealed that 6-[(2,6-diphenyl-pyridin-3-yl)thio]-5-cyano-4-methyl-2-phenylpyrimidine **16a** was obtained (Scheme 3). The IR spectra of the reaction product indicated the absence of the C=O group and showed the characteristic absorption band at 2203 cm^{-1} for the C≡N group. The ^{1}H-NMR spectra (CF_3COOD) of the reaction product showed additional two doublets at δ 8.44 (1H, d) and 8.76 (1H, d) assigned to the hydrogen attached at C_5 and C_4 of pyridine moiety, respectively, and at δ 8.54–8.52, 8.19–7.87 (15H, m) assigned to the phenyl protons. The structure of compound **16a** was further confirmed by mass spectrum (m/z 456 (M^+)). The formation of compound **16a** would involve an initial nucleophilic substitution of the exocyclic methylene group in compound **13** to the activated double bond in enaminone **14a** to form the intermediate **15**, which then undergoes amination and intramolecular cyclization via loss of water affording the final product **16a**. Similarly, treatment of compound **13** with enaminone derivatives **14b–f**, under similar reaction conditions, afforded the corresponding 6-[(4,5,6-trisubstituted-2-phenyl-pyridin-3-yl)thio]-5-cyano-4-methyl-2-phenyl-pyri-midines **16b–f** (Scheme 3). Typical assignments for **16c** and **16e** by ^{1}H-NMR are shown in Figure 4. The physical constants and spectral data of compounds **16a–f** are recorded in Tables 6 and 7. These structures get further support from mass spectroscopy. The possible mass fragmentation pathway of compounds **16c** is shown in Figure 6.

Furthermore, treatment of 6-(benzoylmethyl)thio-pyrimidine **13** with N,N-dimethylformamide dimethylacetal (DMFDMA) gave the enaminone derivative 2-[(5-cyano-4-methyl-2-phenylpyrimidin-6-yl)thio]-3-dimethylamino-1-phenylprop-2-en-1-one **17**(Scheme 4). The ^{1}H NMR spectra (CF_3COOD) of compound **17** revealed a sharp singlet at δ 2.94 (6H, s) assigned to the –$N(CH_3)_2$ protons and at δ 7.47 (1H, s) assigned to the –C=CH–N, was also confirmed by the mass spectrum m/z 400 (M^+). On the other hand, the study was extended to investigate the behavior of enaminone derivative **17** with different nucleophiles like amino compounds with a view to synthesizing various heterocyclic ring systems. Intramolecular cyclization of enaminone derivative **17** gave different products depending on reaction reagents. Thus, treatment of enaminone derivative **17** with phenylhydrazine **18** in the presence

Table 6: Physical and analytical data of 6-[(4,5,6-trisubstituted-2-phenyl-pyridin-3-yl)thio]-5-cyano-4-methyl-2-phenyl-pyrimidine derivatives (**16a–f**).



Compd.	R	R′	R″	M.P. (°C)[a]	Yield (%)	Molecular formula	Elemental analysis (%) Calcd/Found.		
							C	H	N
16a		H	H	218	55	$C_{29}H_{20}N_4S$	76.31	4.38	12.28
							76.44	4.49	12.24
16b		H	H	203	41	$C_{27}H_{18}N_4S_2$	70.12	3.89	12.12
							70.31	3.94	12.16
16c		H	H	217	50	$C_{28}H_{19}N_5S$	73.52	4.15	15.31
							73.59	4.29	15.55
16d		CN	H	200	47	$C_{30}H_{19}N_5S$	74.84	3.95	14.55
							74.65	4.02	14.68
16e		H	CH_3	205	48	$C_{28}H_{20}N_4S_2$	70.58	4.20	11.76
							70.66	4.48	11.84
16f	CH_3		H	230	46	$C_{31}H_{22}N_4OS$	74.69	4.41	11.24
							74.88	4.52	11.36

[a]Recrystallization from CH_3COOH/DMF.

Table 7: Spectral data of 6-[(4,5,6-trisubstituted-2-phenyl-pyridin-3-yl)thio]-5-cyano-4-methyl-2-phenyl-pyrimidine derivatives (**16a–f**).

Compd.	MS (m/e M^+)	IR (KBr) ν (cm^{-1})	^{1}H-NMR[a] (CF_3COOD) δ (ppm)
16a	456(6), 354(48), 344(100), 328(1), 268(3), 251(15), 236(1), 186(2), 105(3).	2203 (C≡N)	3.67 (3H, s, CH_3), 8.44 (1H, d, J = 1.01 Hz, 5-H of pyridyl), 8.76 (1H, d, J = 1.01 Hz, 4-H of pyridyl), 8.54–8.52, 8.19–7.87 (15H, m, phenyl-H).
16b	462(5), 435(10), 430(6), 354(18), 344(100), 268(2), 251(6), 185(3), 171(4), 143(7), 129(3).	2206 (C≡N)	3.63 (3H, s, CH_3), 8.36 (1H, d, J = 1.00 Hz, 5-H of pyridyl), 8.68 (1H, d, J = 1.00 Hz, 4-H of pyridyl), 8.20 (1H, d, J = 1.00 Hz, 3-H of thienyl-H),, 8.45 (1H, d, J = 1.00 Hz, 5-H of thienyl-H), 8.47–8.45, 8.13–7.80 (11H, m, 4-H of thienyl-H and phenyl-H).
16c	457(4), 430(9), 368(3), 354(100), 344(90), 303(8), 268(20), 251(45), 201(3), 186(7), 105(10).	2208 (C≡N)	3.08 (3H, s, CH_3), 7.99 (1H, d, J = 1.00 Hz, 4-H of pyridyl), 8.15 (1H, d, J = 1.00 Hz, 4-H of S-pyridyl), 8.25–8.23, 7.90–7.58 (12H, m, 5-H of S-pyridyl, 5-H of pyridyl and phenyl-H), 8.47 (1H, d, J = 1.00 Hz, 6-H of pyridyl), 9.79 (1H, s, 2-H of pyridyl).
16d	481(4), 454(28), 430(55), 378(4), 354(100), 347(86), 303(20), 267(46), 201(4), 137(14) 105(21), 77(4).	2210 (C≡N)	3.02 (3H, s, CH_3), 8.55 (1H, s, 4-H of pyridyl), 8.32–8.30, 7.79–7.65 (15H, m, phenyl-H).
16e	476(5), 430(10), 368(55), 344(100), 327(4), 268(8), 265(18), 201(2), 105(2).	2206 (C≡N)	2.30 (3H, s, CH_3), 3.38 (3H, s, CH_3), 7.81 (1H, s, 5-H of pyridyl), 8.04 (1H, dd, J = 1.53, 1.51 Hz, 4-H of thienyl-H), 8.15 (1H, d, J = 1.00, Hz, 3-H of thienyl-H), 8.52 (1H, d, J = 1.00, Hz, 5-H of thienyl-H), 8.32–8.30, 7.93–7.65 (10H, m, phenyl-H).
16f	498(5), 430(3), 368(7), 344(100), 268(5), 201(2), 105(2), 77(2).	1688 (C=O) 2207 (C≡N)	2.32 (3H, s, CH_3), 2.82 (3H, s, CH_3), 8.84 (1H, s, 4-H of pyridyl), 8.41–8.36, 8.30–8.17 (15H, m, phenyl-H).

[a]Abbreviations: s: singlet; d: doublet; m: multiplet.

of glacial acetic acid afforded the 6-[(1,5-diphenyl-1*H*-pyrazol-4-yl)thio]-pyrimidine **19** (Scheme 4). The structure of pyrazole derivative **19** was established on the basis of their elemental analysis and spectral data. The IR spectra of compound **19** indicated the absence of the C=O group and showed the characteristic absorption bands at 2201 cm^{-1} for the C≡N group. The ^{1}H-NMR spectra (CF_3COOD) of compound **19** revealed a sharp singlet at δ 7.76 (1H, s) assigned to the hydrogen attached at C_3 of pyrazole ring and at δ 8.25–8.23, 7.81–7.79, 7.70–7.57 (15H, m) assigned to the phenyl protons, which was also confirmed by the mass spectrum *m/z* 445 (M^+). The formation of compound **19** would involve an initial nucleophilic substitution of the amino group in phenylhydrazine **18** to the activated double bond in enaminone derivative **17,** followed by deamination, to form the intermediate **19′**, which then undergoes intramolecule cyclization via loss of water [31] affording the final product **19**. Next, the bis-pyrimidine derivative 6-[(4-phenyl-pyrimidin-5-yl)thio]-5-cyano-4-methyl-2-phenyl-pyrimidine **21** was also obtained by the intramolecular cyclization of compound **17** with formamide/formic acid in the presence of excess ammonium acetate. The ^{1}H-NMR spectra (CF_3COOD) of compound **21** revealed additional two sharp singlets at δ 8.21 (1H, s) and 8.26 (1H, s) assigned to the hydrogen attached at C_6 and C_2 of pyrimidine ring and at δ 8.70-8.69, 8.24–8.02 (10H, m) assigned to the phenyl protons, which was also confirmed by the mass spectrum *m/z* 381 (M^+).

Finally, intramolecular cyclization of the enaminone derivative **17** with 2-amino-bezimidazole **22,** 5-amino-1*H*-tetrazole **24**, 3-amino-4-phenylazo-pyrazole **26** and 3-amino-4-methyl-6-phenyl-pyrazolo[3,4-*d*]pyrimidine **28** under acid conditions afforded the corresponding benzimidazolo[1,2-*a*]pyrimidine **23**, 1,2,3,4-tetrazolo[1,5-*a*] pyrimidine **25**, azopyrazolo[1,5-*a*]pyrimidine **27,** and pyrimido-[4′,5′ : 3,4]pyrazolo[1,5-*a*]pyrimidine **29**, respectively (Scheme 4). The mechanisms of compounds **23**, **25, 27,** and **29** are similar to compound **19**. The structures of compounds **23**, **25, 27,** and **29** were established on the basis of their elemental analysis and spectral data. For instance, the ^{1}H NMR spectra of compounds **23** and **27** revealed a sharp singlet at δ 8.53 (1H, s) and at δ 8.00 (1H, s), which assigned to the hydrogen attached at C_2 of benzimidazolopyrimidine and at C_5 of pyrazolopyrimidine ring, respectively.

4. Conclusion

In conclusion, 6-methylthio-pyrimidine **2**, 6-(benzoyl-methyl) thio-pyrimidine **13** and 2-[(5-cyano-4-methyl-2-phenylpyrimidin-6-yl)thio]-3-dimethylamino-1-phenyl-lprop-2-en-1-one **17** have been shown to be a useful building block for the synthesis of some new N-cycloalkanes, morpholine, piperazines, pyridines, pyrazole, pyrimidine, benzimidazolo[1,2-*a*]pyrimidine, 1,2,3,4-tetrazolo[1,5-*a*] pyrimidine, azopyrazolo[1,5-a]pyrimidine, and pyrimido [4′,5′ : 3,4]pyrazolo[1,5-*a*]pyrimidine, respectively. The structure of all newly synthesized compounds was established from their spectral data, elemental analysis, and the X-ray crystal analysis.

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