Research Article

Thioxopyrimidine in Heterocyclic Synthesis II: Novel Synthesis of Some Triazoles and Triazepine Derivatives with a Pyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidine Skeleton

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Condensation of ethoxymethyleneamino-thieno[2,3-*d*]pyrimidines **4** with appropriate amino compounds afforded the corresponding 7-substituted-8-imino-pyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidines **6a**, **6b**, and **7** and 2-substituted-pyrimido[3',2':4,5]thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **9a**, **9b**, respectively. Also, hydrazinolysis of compound **4** in ethanol which yielded the key intermediate 7-amino-8-imino-pyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidine (**10**), which can be cyclized with appropriate isothiocyanates **14a–14g** in refluxing pyridine, afforded the corresponding 2-(substituted-amino)-pyrimido[3',2':4,5]thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **15a–15g**. Furthermore, intramolecular cyclization of compound (**10**) with appropriate 1,3-dibromopropane and Mannich bases **18a–18c** under the basic condition afforded the corresponding (tri)dihydropyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*][1,2,4]triazepines **16** and **18a–18c**, respectively. On the other hand, the 11-substituted-pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*][1,2,4]triazepines **21a–21e** were also obtained by the intramolecular cyclization of compound (**10**) with appropriate enaminone derivatives **19a–19e** under the acidic condition.

1. Introduction

Pyrimidine and its derivatives are biologically important as antimicrobial [1, 2], antitumor [3], antihypertensive [4], and anti-inflammatory activities [5]. Among the derivatives of thieno[2,3-*d*]pyrimidines, substances have been observed that have antiviral, fungicidal, and insecticidal activity [6], antibacterial and antiplastic properties [7], antihypertensive [8] and anticonvulsant activity [9], and antihistaminic [10] action. Compounds with triazepine skeletons have attracted much attention as a result of their interesting biological properties [11, 12]. On the other hand, condensed heterocyclic 1,2,4-triazepines were found to have salidiuretic and renal vasodilator, antioxidant, and analgesic and immunomodulating activities [13–15]. Further, the fusion of pyrimidine with triazepine moiety shows enhanced pharmacological effects as antiviral, antifungal [16], and antidiabetic [17] and also acts as inhibitors [18] in cancer chemotherapy.

Recently, it has been demonstrated that heterocycles attached to seven-membered rings show important biological activities [19–21]. Likewise, fused triazepine derivatives with a bridgehead nitrogen atom in the molecule exhibit interesting biological properties [22]. Various conventional methods for the synthesis of fused triazepines are exemplified in the literature [23, 24] using cycloaddition [25] and photochemical methods, but pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*][1,2,4]triazepines are the least investigated group among the fused triazepines. Moreover, no general method is ever reported for the synthesis of the title compounds starting from 7-amino-8-imino-pyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidine (**10**). In view of these, it was considered of interest to synthesize some new triazoles and triazepine derivatives of structure fused to pyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidine (PTP) ring in the hope that they may be biologically active. In preceding papers [26–29], we have described the

synthesis of some new pyrimido[2,3:4,3]pyrazolo[1,5-*a*]pyrimidines, 1,2,4-triazolo[1,5-*a*]pyrimidothieno[2,3-*d*]pyrimidine, and 1,3,4-oxadiazole-thieno[2,3-*d*]pyrimidines from 5-cyano-1,6-dihydro-4-methyl-2-phenyl-6-thioxopyrimidine **1** [26], respectively. In continuation of our studies [26–30], we report herein the synthesis of some new pyrimido[3',2':4,5]thieno[3,2-*e*][1,2,4]-triazolo[1,5-*c*]pyrimidines and pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*][1,2,4]triazepine derivatives by making use of the key intermediate 7-amino-8-imino-pyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidine (**10**), easily obtained from the thioxopyrimidine **1**. The substrate proved to be a versatile compound by virtue of its vicinal amino and imino functions, evaluating the reactivity in several cyclization reactions performed with the aim of obtaining new triazoles and triazepines with a conserved PTP core.

2. Experimental

All melting points are uncorrected and in °C. IR spectra were recorded on a JASCO FTIR-3 spectrometer (KBr); ¹H NMR spectra were obtained on a Bruker AM-300 WB FI-NMR 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 Finnigan Mat TSQ-46C spectrometer. Microanalyses for C, H, and N were performed on a Perkin-Elmer 240 elemental analyzer. Commercially available reagents were purchased from Aldrich and used directly. Reactions were routinely monitored by thin layer chromatography (TLC (ethyl acetate and hexane (3:7))) on silica gel (precoated F₂₄₅ Merck plates). Compounds **17a–17c** [30, 31] and **19a–19e** [26] were prepared according to known procedures.

2.1. 5-Amino-6-cyano-4-methyl-2-phenyl-thieno[2,3-*d*]pyrimidine (3). A mixture of compound **1** (2.27 g, 10 mmol), potassium carbonate anhydrous (2.76 g, 20 mmol), and chloroacetonitrile **2** (0.64 g, 10 mmol) 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 ethyl acetate/ethanol to give pale yellow needles. Yield 2.44 g (92%), mp 259°C; IR: ν 3511, 3359 (NH₂), 2204 (CN) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 2.60 (3H, s, CH₃), 6.23 (2H, br, NH₂), 8.55–8.53, 7.53–7.48 (5H, m, phenyl-H); MS: 266(M⁺, 100). Anal. Calcd. for C₁₄H₁₀N₄S: C, 63.15; H, 3.75; N, 21.05. Found: C, 63.23; H, 3.80; N, 21.12%.

2.2. 6-Cyano-5-ethoxymethyleneamino-4-methyl-2-phenyl-thieno[2,3-*d*]pyrimidine (4). A solution of compound **3** (2.66 g, 10 mmol) and triethyl orthoformate (8 mL) was refluxed in acetic anhydride (15 mL) for 24 h. The reaction mixture was cooled. The resulting solid product was collected by filtration and recrystallized from ethanol to furnish **4** as pale yellow crystals. Yield 2.67 g (83%), mp 150°C; IR: ν 2215 (CN), 1627 (N=C) cm⁻¹; ¹H NMR (CDCl₃): δ 1.48 (3H, t, *J* = 1.42 Hz, CH₃), 2.92 (3H, s, CH₃), 4.50 (2H, q, *J* = 2.12 Hz,

OCH₂), 8.09 (1H, s, N=CH), 8.55–8.53, 7.52–7.50 (5H, m, phenyl-H); MS: 322(M⁺, 100), 293(13), 277(32), 266(96), 250(4), 191(5), 163(33), 153(9), 104(18), 77(19). Anal. Calcd. for C₁₇H₁₄N₄OS: C, 63.35; H, 4.34; N, 17.39. Found: C, 63.33; H, 4.40; N, 17.41%.

2.3. 7-Ethyl-8-imino-4-methyl-2-phenyl-7,8-dihydropyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidine (6a). To a solution of compound **4** (0.322 g, 1 mmol) in ethanol (10 mL), ethylamine (10 mL) was added. The reaction mixture was refluxed for 4–5 h. After cooling, the precipitate was filtered and recrystallized from acetic acid/ethanol to furnish **6a** as pale yellow crystals. Yield 0.29 g (92%), mp 225°C; IR: ν 3307 (NH), 1614 (C=N) cm⁻¹; ¹H NMR (CDCl₃): δ 1.47 (3H, t, *J* = 1.47 Hz, CH₃), 3.13 (3H, s, CH₃), 4.10 (2H, q, *J* = 2.15 Hz, CH₂), 8.57–8.55, 7.52–7.50 (5H, m, phenyl-H), 7.90 (1H, s, 6-H); MS: 321 (M⁺, 100). Anal. Calcd. for C₁₇H₁₅N₅S: C, 63.55; H, 4.67; N, 21.80. Found: C, 63.65; H, 4.70; N, 21.97%.

2.4. 2,7-Diphenyl-8-imino-4-methyl-7,8-dihydropyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidine (6b). This compound was synthesized from compound **4** (0.322 g, 1 mmol) and aniline (0.092 g, 1 mmol) in a similar way to that described for the preparation of **6a**. It was recrystallized from acetic acid/DMF to furnish **6b** as pale yellow crystals. Yield 0.33 g (90%), mp 249°C; IR: ν 3310 (NH), 1609 (C=N) cm⁻¹; ¹H NMR (CF₃COOD): δ 2.68 (3H, s, CH₃), 8.87–8.85, 8.33–8.01 (10H, m, phenyl-H), 9.22 (1H, s, 6-H), 9.41 (1H, br, NH); MS: 369(M⁺, 100), 265(12), 184(11), 153(2), 136(2), 104(9), 77(21). Anal. Calcd. for C₂₁H₁₅N₅S: C, 68.29; H, 4.06; N, 18.97. Found: C, 68.49; H, 4.30; N, 19.19%.

2.5. 7-Formyl-8-imino-4-methyl-2-phenyl-7,8-dihydropyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidine (7). A mixture of compound **4** (0.322 g, 1 mmol) and formamide (10 mL) was refluxed for 1 h. After cooling, the precipitate was filtered and recrystallized from acetic acid/ethanol to furnish **7** as brown crystals. Yield 0.31 g (97%), mp 240°C; IR: ν 3305 (NH), 1678 (CO), 1616 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 3.10 (3H, s, CH₃), 8.86 (1H, s, 6-H), 8.45–8.44, 7.54–7.47 (5H, m, phenyl-H), 8.33 (1H, br, NH), 8.54 (1H, s, CHO), MS: 321(M⁺, 2), 293(100), 266(2), 190(22), 163(9), 136(2), 103(4), 77(2). Anal. Calcd. for C₁₆H₁₁N₅OS: C, 59.81; H, 3.42; N, 21.80. Found: C, 59.95; H, 3.33; N, 21.92%.

2.6. 2,9-Diphenyl-7-methyl-pyrimido[3',2':4,5]thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (9a). A mixture of compound **4** (0.322 g, 1 mmol) and benzoylhydrazine **8a** (0.136 g, 1 mmol) in 2-methoxyethanol (10 mL) was refluxed for 7 h. After cooling, the resulting solid product was collected by filtration and washed with water, and the crude product was recrystallized from ethanol/glacial acetic acid to furnish **9a** as white crystals. Yield 0.34 g (87%), mp 306°C; IR: ν 1603 (C=N) cm⁻¹; ¹H NMR (CF₃COOD): δ 3.42 (3H, s, CH₃), 8.43–8.40, 7.88–7.76 (10H, m, phenyl-H), 9.93 (1H, s, 5-H); MS: 394 (M⁺, 100), 317(2), 290(20), 262(3), 197(10), 153(3), 118(10), 105(20), 77(24). Anal. Calcd. for

$C_{22}H_{14}N_6S$: C, 67.00; H, 3.55; N, 21.31. Found: C, 67.23; H, 3.42; N, 21.45%.

2.7. 2-(4-Pyridyl)-7-methyl-9-phenyl-pyrimido[3',2':4,5]thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (9b). This compound was synthesized from compound **4** (0.322 g, 1 mmol) and isonicotinic acid hydrazide (0.137 g, 1 mmol) in a similar way to that described for the preparation of **9a**. It was recrystallized from ethanol/DMF to furnish **9b** as pale yellow crystals. Yield 0.32 g (83%), mp $>340^\circ\text{C}$; IR: ν 1607 (C=N) cm^{-1} ; ^1H NMR (CDCl_3): δ 3.73 (3H, s, CH_3), 7.87–7.82, 7.74–7.71 (5H, m, phenyl-H), 8.40 (2H, d, $J = 1.00$ Hz, 3,5-H of pyridyl), 8.85 (2H, d, $J = 1.00$ Hz, 4,6-H of pyridyl), 9.83 (1H, s, 5-H); MS: 395(M^+ , 100), 317(2), 291(20), 267(4), 236(1), 197(10), 190(2), 103(4), 77(8). Anal. Calcd. for $\text{C}_{21}\text{H}_{13}\text{N}_7\text{S}$: C, 63.79; H, 3.29; N, 24.81. Found: C, 63.98; H, 3.42; N, 24.99%.

2.8. 7-Amino-8-imino-4-methyl-2-phenyl-7,8-dihydropyrimido[3,2:4,5]thieno[2,3-d]pyrimidine (10). A mixture of compound **4** (0.322 g, 1 mmol) and hydrazine hydrate (8 mL, 80%) in ethanol (20 mL) was refluxed for 24 h. After cooling, the resulting solid product was collected by filtration and washed with water, and the crude product was recrystallized from ethanol/DMF to furnish **(10)** as pale yellow crystals. Yield 0.27 g (89%), mp 285°C ; IR: ν 3315, 3247 (NH_2 , NH), 1603 (C=N) cm^{-1} ; ^1H NMR (CF_3COOD): δ 3.21 (3H, s, CH_3), 5.13 (2H, s, NH_2), 8.11–8.07, 7.51–7.37 (5H, m, phenyl-H), 8.69 (1H, s, 6-H), 9.23 (H, s, NH); MS: 308(M^+ , 100), 292(2), 278(38), 251(18), 225(2), 188(4), 176(10), 148(6), 120(4), 104(19), 77(16). Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{N}_6\text{S}$: C, 58.44; H, 3.89; N, 27.27. Found: C, 58.66; H, 3.82; N, 27.36%.

2.9. 8-(Acetylamino)-7-diacetyl-amino-4-methyl-2-phenyl-pyrimido[3,2:4,5]thieno[2,3-d]pyrimidine (11). A mixture of compound **(10)** (0.308 g, 1 mmol) and acetic anhydride (10 mL) was refluxed for 2 h. After cooling, the precipitate was filtered and recrystallized from acetic acid/ethanol to furnish **(11)** as orange crystals. Yield 0.41 g (96%), mp 236°C ; IR: ν 1718 (CO), 1639 (C=N) cm^{-1} ; ^1H NMR (CF_3COOD): δ 2.32 (3H, s, COCH_3), 2.56 (6H, s, $(\text{COCH}_3)_2$), 2.79 (3H, s, CH_3), 8.47–8.44, 7.97–7.78 (5H, m, phenyl-H), 9.15 (1H, s, 6-H); MS: 434(M^+ , 20), 393(40), 350(93), 308(100), 280(34), 251(12), 191(2), 176(6), 148(5), 120(4), 103(3). Anal. Calcd. for $\text{C}_{21}\text{H}_{18}\text{N}_6\text{O}_3\text{S}$: C, 58.06; H, 4.14; N, 19.35. Found: C, 58.26; H, 4.04; N, 19.48%.

2.10. 2,7-Dimethyl-9-phenyl-pyrimido[3',2':4,5]thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (12). A mixture of compound **(10)** (0.308 g, 1 mmol) and glacial acetic acid (10 mL) was refluxed for 2 h. After cooling, the precipitate was filtered and recrystallized from acetic acid/ethanol to furnish **(12)** as pale brown crystals. Yield 0.31 g (93%), mp 271°C ; IR: ν 1615 (C=N) cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 2.06 (3H, s, CH_3), 3.17 (3H, s, CH_3), 8.51–8.49, 7.58–7.53 (5H, m, phenyl-H), 8.72 (1H, s, 5-H); MS: 332(M^+ , 20), 318(6), 293(100),

278(11), 267(1), 229(5), 190(24), 163(9), 103(4). Anal. Calcd. for $\text{C}_{17}\text{H}_{12}\text{N}_6\text{S}$: C, 61.44; H, 3.61; N, 25.30. Found: C, 61.69; H, 3.42; N, 25.55%.

2.11. 7-(4-Dimethylaminophenyl)azo-8-imino-4-methyl-2-phenyl-7,8-dihydropyrimido[3,2:4,5]thieno[2,3-d]pyrimidine (13). A mixture of compound **(10)** (0.308 g, 1 mmol) and N,N-dimethyl-4-nitrosoaniline (0.15 g, 1 mmol) in glacial acetic acid (10 mL) was stirred at $70\text{--}80^\circ\text{C}$ for 2 h. The reaction mixture was cooled and poured into ice-water; the precipitate was filtered and recrystallized from acetic acid/ethanol to furnish **13** as brown crystals. Yield 0.28 g (64%), mp 247°C ; IR: ν 3305 (NH), 1629 (C=N) cm^{-1} ; ^1H NMR (CF_3COOD): δ 3.51 (6H, s, $\text{N}(\text{CH}_3)_2$), 3.61 (3H, s, CH_3), 8.34–8.32, 7.86–7.67 (9H, m, phenyl-H), 8.66 (1H, s, 6-H); MS: 412(M^+ , 10), 397(3), 347(3), 332(8), 319(13), 308(10), 293(100), 278(9), 267(8), 215(5), 191(19), 163(10), 136(11), 121(8), 104(8), 77(12). Anal. Calcd. for $\text{C}_{23}\text{H}_{20}\text{N}_8\text{S}$: C, 62.72; H, 4.54; N, 25.45. Found: C, 62.86; H, 4.64; N, 25.68%.

2.12. General Procedures for the Preparation of 2-(substituted-amino)-7-methyl-9-phenyl-pyrimido[3',2':4,5]thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines (15a–15g). A mixture of compound **(10)** (0.308 g, 1 mmol) and appropriate isothiocyanates **14a–14g** (1 mmol) in pyridine (10 mL) was refluxed for 7–8 h. The reaction mixture was cooled and poured into ice-water the precipitate was filtered and recrystallized from DMF/ethanol to furnish **15a–15g**.

2.13. 2-(Methylamino)-7-methyl-9-phenyl-pyrimido[3',2':4,5]thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (15a): Yellowish Brown Crystals. Yield 0.19 g (55%), mp 286°C ; IR: ν 3309 (NH), 1612 (C=N) cm^{-1} ; ^1H NMR (CF_3COOD): δ 3.35 (3H, s, CH_3), 3.81 (3H, s, CH_3), 8.53–8.45, 7.99–7.81 (5H, m, phenyl-H), 9.48 (1H, br, NH), 9.87 (1H, s, 5-H); MS: 347(M^+ , 31), 332(10), 304(3), 293(12), 278(7), 174(1), 163(9), 79(4). Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{N}_7\text{S}$: C, 58.78; H, 3.74; N, 28.24. Found: C, 58.89; H, 3.82; N, 28.45%.

2.14. 2-(Ethylamino)-7-methyl-9-phenyl-pyrimido[3',2':4,5]thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (15b): Pale greenish yellow crystals. Yield 0.10 g (28%), mp 327°C ; IR: ν 3303 (NH), 1614 (C=N) cm^{-1} ; ^1H NMR (CF_3COOD): δ 1.92 (3H, t, $J = 1.50$ Hz, CH_3), 3.81 (3H, s, CH_3), 4.92 (2H, q, $J = 1.00$ Hz, CH_2), 8.55–8.49, 8.00–7.81 (5H, m, phenyl-H), 9.15 (1H, br, NH), 9.88 (1H, s, 5-H); MS: 361(M^+ , 41), 350(84), 347(100), 332(8), 319(22), 304(4), 293(12), 278(16), 265(8), 215(18), 174(20), 147(9), 103(38), 77(10). Anal. Calcd. for $\text{C}_{18}\text{H}_{15}\text{N}_7\text{S}$: C, 59.83; H, 4.15; N, 27.14. Found: C, 59.99; H, 4.35; N, 27.26%.

2.15. 2-(Phenylamino)-7-methyl-9-phenyl-pyrimido[3',2':4,5]thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (15c): Greenish Yellow Crystals. Yield 0.20 g (49%), mp 295°C ; IR: ν 3311 (NH), 1605 (C=N) cm^{-1} ; ^1H NMR (CF_3COOD):

δ 3.78 (3H, s, CH₃), 8.46–8.45, 7.92–7.77 (10H, m, phenyl-H), 9.79 (1H, s, 5-H); MS: 409(M⁺, 21), 350(100), 332(8), 304(15), 293(16), 278(8), 247(5), 201(10), 174(8), 147(3), 103(10), 77(4). Anal. Calcd. for C₂₂H₁₅N₇S: C, 64.54; H, 3.66; N, 23.96. Found: C, 64.69; H, 3.88; N, 24.11%.

2.16. 2-(4-Chlorophenylamino)-7-methyl-9-phenyl-pyrimido[3',2':4,5]thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**15d**): Pale Greenish Yellow Crystals. Yield 0.27 g (62%), mp 266°C; IR: ν 3314 (NH), 1612 (C=N) cm⁻¹; ¹H NMR (CF₃COOD): δ 2.45 (3H, s, CH₃), 7.68 (2H, d, J = 1.00 Hz, 3,5-H of phenyl-H), 7.78 (2H, d, J = 1.00 Hz, 2,6-H of phenyl-H), 8.65–8.64, 8.09–7.97 (5H, m, phenyl-H), 9.98 (1H, s, 5-H); MS: 443.5(M⁺, 21), 407(2), 392(14), 350(100), 332(4), 319(5), 304(12), 293(30), 278(11), 255(13), 247(5), 213(16), 174(16), 147(40), 103(20), 91(31), 71(33). Anal. Calcd. for C₂₂H₁₄ClN₇S: C, 59.52; H, 3.15; N, 22.09. Found: C, 59.69; H, 3.28; N, 22.21%.

2.17. 2-(Benzylamino)-7-methyl-9-phenyl-pyrimido[3',2':4,5]thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**15e**): Yellow Crystals. Yield 0.20 g (47%), mp 306°C; IR: ν 3314 (NH), 1601 (C=N) cm⁻¹; ¹H NMR (CF₃COOD): δ 2.60 (3H, s, CH₃), 4.15 (2H, s, CH₂), 8.80–8.79, 8.29–7.83 (10H, m, phenyl-H), 8.79 (1H, s, 5-H); MS: 422(M⁺, 10), 350(100), 332(2), 308(20), 304(8), 293(9), 278(12), 265(6), 247(2), 201(4), 174(6), 153(4), 103(28), 91(14), 77(7). Anal. Calcd. for C₂₃H₁₆N₇S: C, 65.40; H, 3.79; N, 23.22. Found: C, 65.49; H, 3.88; N, 23.36%.

2.18. 2-(2-Methylphenylamino)-7-methyl-9-phenyl-pyrimido[3',2':4,5]thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**15f**): Greenish Yellow Crystals. Yield 0.18 g (43%), mp 285°C; IR: ν 3308 (NH), 1608 (C=N) cm⁻¹; ¹H NMR (CF₃COOD): δ 2.47 (3H, s, CH₃), 2.54 (3H, s, CH₃), 8.78–8.45, 8.24–7.79 (9H, m, phenyl-H), 9.78 (1H, s, 5-H); MS: 423(M⁺, 6), 350(100), 332(12), 318(20), 304(8), 293(68), 278(7), 265(8), 247(3), 215(6), 201(5), 190(16), 174(6), 147(3), 103(6), 77(4). Anal. Calcd. for C₂₃H₁₇N₇S: C, 65.24; H, 4.01; N, 23.16. Found: C, 65.36; H, 3.95; N, 23.25%.

2.19. 2-(1-Naphthylamino)-7-methyl-9-phenyl-pyrimido[3',2':4,5]thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**15g**): Greenish Yellow Crystals. Yield 0.23 g (51%), mp 282°C; IR: ν 3309 (NH), 1613 (C=N) cm⁻¹; ¹H NMR (CF₃COOD): δ 2.41 (3H, s, CH₃), 8.58–8.55, 8.32–7.89 (12H, m, phenyl-H and naphthyl-H), 9.89 (1H, s, 5-H); MS: 459(M⁺, 7), 396(4), 350(100), 332(18), 318(18), 304(11), 293(61), 278(6), 265(7), 247(5), 201(7), 174(8), 163(10), 147(6), 103(10), 77(7). Anal. Calcd. for C₂₆H₁₇N₇S: C, 67.97; H, 3.70; N, 21.35. Found: C, 68.11; H, 3.88; N, 21.47%.

2.20. 4-Methyl-2-phenyl-8H-9,10,11-trihydropyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-b][1,2,4]triazepine (**16**). There was a mixture of compound (**10**) (0.308 g, 1 mmol), potassium carbonate anhydrous (3.036 g, 2.2 mmol), and 1,3-dibromopropane (0.201 g, 1 mmol) in DMF (30 mL). The

reaction mixture was stirred at 60°C for 9 h. After cooling, the reaction mixture was poured into ice-water (50 mL) and neutralized with 10% hydrochloric acid. The solid formed was collected by filtration, washed with water, and recrystallized from acetic acid/ethanol to give reddish brown crystals. Yield 0.29 g (83%), mp 175°C; IR: ν 3308 (NH), 1611 (C=N) cm⁻¹; ¹H NMR (CF₃COOD): δ 2.32 (2H, m, 10-CH₂), 2.92 (3H, s, CH₃), 3.42 (2H, t, J = 1.60 Hz, 11-CH₂), 4.42 (2H, t, J = 1.70 Hz, 9-CH₂), 8.45–8.33, 7.84–7.81 (5H, m, phenyl-H), 9.84 (1H, s, 6-H), 10.12 (1H, br, NH); MS: 348(M⁺, 11), 333(13), 318(89), 308(8), 293(39), 218(100), 263(3), 251(8), 215(9), 190(14), 175(38), 163(9), 121(10), 104(21), 77(22). Anal. Calcd. for C₁₈H₁₆N₆S: C, 62.06; H, 4.59; N, 24.13. Found: C, 62.19; H, 4.65; N, 24.26%.

2.21. General Procedures for the Preparation of 9-substituted-4-methyl-2-phenyl-10,11-dihydro-pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-b][1,2,4]triazepines (**18a–18c**). A mixture of compound (**10**) (0.308 g, 1 mmol), Mannish base **17a–17c** (N,N-dimethyl-2-benzoethylamine hydrochloride **17a**, N,N-dimethyl-2-furoylethylamine hydrochloride **17b**, and N,N-dimethyl-2-thenylethylamine hydrochloride **17c**) (1 mmol), and anhydrous potassium carbonate (0.304 g, 2.2 mmol) was refluxed in DMF (10 mL) for 8 h. After cooling, solid formed was collected by filtration and recrystallized from chloroform/ethanol.

2.22. 2,9-Diphenyl-4-methyl-10,11-dihydropyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-b][1,2,4]triazepine (**18a**): Pale Brown Crystals. Yield 0.35 g (83%), mp 172°C; IR: ν 1609 (C=N) cm⁻¹; ¹H NMR (CDCl₃): δ 3.11 (3H, s, CH₃), 3.26 (2H, t, J = 1.00 Hz, 10-CH₂), 4.21 (2H, t, J = 1.00 Hz, 11-CH₂), 8.54–8.51, 7.57–7.41 (10H, m, phenyl-H), 8.72 (1H, s, 6-H); MS: 422(M⁺, 38), 394(5), 345(4), 332(13), 318(96), 293(100), 278(36), 250(7), 214(10), 190(39), 163(22), 159(9), 115(10), 103(39), 77(61). Anal. Calcd. for C₂₄H₁₈N₆S: C, 68.24; H, 4.26; N, 19.90. Found: C, 68.49; H, 4.45; N, 20.15%.

2.23. 9-(2-Furyl)-4-methyl-2-phenyl-10,11-dihydropyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-b][1,2,4]triazepine (**18b**): Brown Crystals. Yield 0.32 g (79%), mp 162°C; IR: ν 1615 (C=N) cm⁻¹; ¹H NMR (CDCl₃): δ 3.16 (3H, s, CH₃), 3.22 (2H, t, J = 1.00 Hz, 10-CH₂), 4.19 (2H, t, J = 1.00 Hz, 11-CH₂), 6.84 (1H, dd, J = 1.00, 1.00 Hz, 4-H of furyl), 7.59 (1H, d, J = 1.00 Hz, 3-H of furyl), 8.49–8.44, 7.54–7.49 (5H, m, phenyl-H), 8.54 (1H, d, J = 1.0 Hz, 5-H of furyl), 8.71 (1H, s, 6-H); MS: 412(M⁺, 20), 384(5), 345(4), 332(3), 318(50), 293(100), 278(26), 250(4), 215(8), 190(39), 163(21), 153(7), 120(7), 103(28), 95(29), 77(30), 51(9). Anal. Calcd. for C₂₂H₁₆N₆OS: C, 64.07; H, 3.88; N, 20.38. Found: C, 64.19; H, 3.98; N, 20.45%.

2.24. 9-(2-Thienyl)-4-methyl-2-phenyl-10,11-dihydropyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-b][1,2,4]triazepine (**18c**): Pale Yellow Crystals. Yield 0.35 g (82%), mp 154°C; IR: ν 1621 (C=N) cm⁻¹; ¹H NMR (CDCl₃): δ 3.16 (3H, s, CH₃), 3.28 (2H, t, J = 1.00 Hz, 10-CH₂), 4.23 (2H, t, J = 1.00 Hz,

11-CH₂), 7.08 (1H, dd, $J = 1.00, 1.00$ Hz, 4-H of thienyl), 8.57–8.40, 7.54–7.42 (6H, m, 3-H of thienyl and phenyl-H), 8.62 (1H, d, $J = 1.00$ Hz, 5-H of thienyl), 8.73 (1H, s, 6-H); MS: 428(M⁺,10), 400(5), 345(2), 332(6), 318(19), 293(100), 278(22), 250(4), 215(5), 190(40), 163(23), 153(9), 110(45), 103(32), 77(30), 51(10). Anal. Calcd. for C₂₂H₁₆N₆S₂: C, 61.68; H, 3.73; N, 19.62. Found: C, 61.78; H, 3.88; N, 19.80%.

2.25. 7-[1-(4-Pyridyl)prop-2-enone-3-yl]amino-8-imino-4-methyl-2-phenyl-7,8-dihydropyrimido[3,2:4,5]thieno[2,3-d]pyrimidine (**20**). Method A: a mixture of compound (**10**) (0.308 g, 1 mmol) and 3-dimethylamino-1-(4-pyridyl)prop-2-enone **19e** (0.176 g, 1 mmol) in glacial acetic acid (10 mL) was stirred at 80°C for 7 h. The reaction mixture was cooled. The resulting solid product was collected by filtration and recrystallized from DMF/ethanol to give brownish yellow crystals. Yield 0.26 g (60%), mp 207°C; IR: ν 3215 (NH), 1668 (C=O), 1632 (C=N) cm⁻¹; ¹H NMR (CF₃COOD): δ 2.59 (3H, s, CH₃), 4.00 (1H, d, $J = 1.05$ Hz, COCH=), 8.68 (2H, d, $J = 1.00$ Hz, 3,5-H of pyridyl), 8.78–8.74, 8.26–8.07 (6H, m, -NCH= and phenyl-H), 9.27 (2H, d, $J = 1.00$ Hz, 2,6-H of pyridyl), 9.53 (1H, s, 6-H); MS: 439(M⁺,20), 421(100), 394(14), 367(29), 333(20), 319(88), 308(58), 293(29), 278(27), 215(9), 210(16), 174(15), 121(10), 104(22), 77(23), 51(14). Anal. Calcd. for C₂₃H₁₇N₇OS: C, 62.87; H, 3.87; N, 22.32. Found: C, 62.88; H, 3.98; N, 22.47%. Method B: a mixture of compound (**10**) (0.308 g, 1 mmol) and **19e** (0.176 g, 1 mmol) in glacial acetic acid (10 mL) was stirred at 50–55°C for 3 h. The reaction mixture was cooled. The resulting solid product was collected by filtration and recrystallized to obtain **20** (0.31 g, 70%).

2.26. General Procedures for the Preparation of 11-substituted-4-methyl-2-phenyl-pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-b][1,2,4]triazepines (**21a–21d**). A mixture of compound (**10**) (0.308 g, 1 mmol) and appropriate 3-dimethyl-amino-1-(substituted)prop-2-enones **19a–19d** (1 mmol) in glacial acetic acid (10 mL) was refluxed for 10 h. The reaction mixture was cooled and poured into ice-water; the precipitate was filtered and recrystallized from DMF/ethanol to obtain **21a–21d**.

2.27. 2,11-Diphenyl-4-methyl-pyrimido[3',2':4,5]thieno [3,2:4,5]pyrimido[1,6-b][1,2,4]triazepine (**21a**): Pale Reddish Brown Crystals. Yield 0.29 g (70%), mp 194°C; IR: ν 1611 (C=N) cm⁻¹; ¹H NMR (CF₃COOD): δ 2.22 (3H, s, CH₃), 7.08 (2H, d, $J = 1.00$ Hz, 10-H), 7.48 (2H, d, $J = 1.00$ Hz, 9-H), 8.03–7.68, 7.59–7.53 (10H, m, phenyl-H), 9.51 (1H, s, 6-H); MS: 420(M⁺,100), 387(12), 366(48), 318(23), 308(30), 293(45), 278(29), 263(8), 210(14), 190(19), 120(9), 105(38), 77(56). Anal. Calcd. for C₂₄H₁₆N₆S: C, 68.57; H, 3.80; N, 20.00. Found: C, 68.69; H, 3.95; N, 20.25%.

2.28. 11-(2-Furyl)-4-methyl-2-phenyl-pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido [1,6-b][1,2,4]triazepine (**21b**): Greenish Yellow Crystals. Yield 0.26 g, (64%) mp 244°C; IR: ν 1619 (C=N) cm⁻¹; ¹H NMR (CF₃COOD): δ 2.23 (3H, s, CH₃),

7.05 (2H, d, $J = 1.00$ Hz, 10-H), 6.60 (1H, dd, $J = 1.00, 1.00$ Hz, 4-H of furyl), 6.69 (1H, d, $J = 1.00$ Hz, 3-H of furyl), 7.91–7.81, 7.76–7.61 (6H, m, 9-H, and phenyl-H), 8.34 (1H, d, $J = 1.00$ Hz, 5-H of furyl), 9.53 (1H, s, 6-H); MS: 410(M⁺,100), 356(42), 319(82), 293(48), 278(42), 250(18), 229(10), 205(13), 190(23), 174(18), 163(14), 129(25), 104(44), 95(51), 77(42). Anal. Calcd. for C₂₂H₁₄N₆OS: C, 64.39; H, 3.41; N, 20.48. Found: C, 64.49; H, 3.68; N, 20.55%.

2.29. 11-(2-Thienyl)-4-methyl-2-phenyl-pyrimido [3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-b][1,2,4]triazepine (**21c**): Yellowish Brown Crystals. Yield 0.27 g (63%), mp 231°C; IR: ν 1623 (C=N) cm⁻¹; ¹H NMR (CF₃COOD): δ 2.24 (3H, s, CH₃), 7.33 (2H, d, $J = 1.00$ Hz, 10-H), 7.84 (2H, d, $J = 1.00$ Hz, 9-H), 7.20 (1H, dd, $J = 1.00, 1.00$ Hz, 4-H of thienyl), 7.13 (1H, d, $J = 1.00$ Hz, 3-H of thienyl), 7.91–7.90, 7.31–7.29 (5H, m, phenyl-H), 8.11 (1H, d, $J = 1.0$ Hz, 5-H of thienyl), 9.54 (1H, s, 6-H); MS: 426(M⁺,10), 399(5), 333(7), 319(100), 279(13), 213(2), 190(7), 121(3), 111(77), 77(8). Anal. Calcd. for C₂₂H₁₄N₆S₂: C, 61.97; H, 3.28; N, 19.71. Found: C, 62.12; H, 3.38; N, 19.87%.

2.30. 11-(2-Pyrazinyl)-4-methyl-2-phenyl-pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-b][1,2,4]triazepine (**21d**): Brown Crystals. Yield 0.22 g (53%), mp 240°C; IR: ν 1624 (C=N) cm⁻¹; ¹H NMR (CF₃COOD): δ 2.32 (3H, s, CH₃), 6.71 (2H, d, $J = 1.00$ Hz, 10-H), 7.45 (2H, d, $J = 1.00$ Hz, 9-H), 8.24 (1H, d, $J = 1.00$ Hz, 6-H of pyrazinyl), 8.41–8.36, 7.93–7.77 (5H, m, phenyl-H), 8.49 (1H, d, $J = 1.00$ Hz, 5-H of pyrazinyl), 8.98 (1H, s, 3-H of pyrazinyl), 9.19 (1H, s, 6-H); MS: 422(M⁺,24), 395(9), 319(35), 293(100), 238(4), 215(10), 190(41), 163(22), 147(8), 104(19), 77(23). Anal. Calcd. for C₂₂H₁₄N₈S: C, 62.55; H, 3.31; N, 26.54. Found: C, 62.74; H, 3.48; N, 26.78%.

2.31. 11-(4-Pyridyl)-4-methyl-2-phenyl-pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-b][1,2,4]triazepine (**21e**). Method A: this compound was synthesized from compound (**10**) (0.308 g, 1 mmol) in glacial acetic acid in a similar way to that described for the preparation of **21a–21d**. It was recrystallized from DMF/ethanol to give pale brown crystals. Yield 0.29 g, (68%) mp 237°C; IR: ν 1622 (C=N) cm⁻¹; ¹H NMR (CF₃COOD): δ 3.19 (3H, s, CH₃), 7.30 (2H, d, $J = 1.0$ Hz, 10-H), 7.97 (2H, d, $J = 1.00$ Hz, 3,5-H of pyridyl), 8.14–8.12, 7.50–7.38 (5H, m, phenyl-H), 8.16 (2H, d, $J = 1.00$ Hz, 9-H), 8.31 (1H, s, 6-H), 8.54 (2H, d, $J = 1.00$ Hz, 2,6-H of pyridyl); MS: 421(M⁺,100), 367(4), 333(8), 318(19), 308(44), 293(66), 278(42), 214(8), 198(10), 190(22), 163(12), 120(5), 104(22), 77(26). Anal. Calcd. for C₂₃H₁₅N₇S: C, 65.55; H, 3.56; N, 23.27. Found: C, 65.74; H, 3.68; N, 23.48%. Method B: the filtrate from the above reaction **20** was poured into cold water (20 mL) and stirred for 15 min. The resulting precipitate was collected by filtration and recrystallized to give **21e** (0.026 g, 6.3%). Method C: a mixture of **20** (0.439 g, 1 mmol) and glacial acetic acid (10 mL) was refluxed for 10 h. The reaction mixture was cooled and poured into ice-water; the precipitate was filtered and recrystallized to obtain **21e** (0.022 g, 48%).

SCHEME 1

SCHEME 2

14a, 15a R = CH_3 , **14b, 15b** R = C_2H_5 , **14c, 15c** R = C_6H_5 , **14d, 15d** R = $p\text{-ClC}_6\text{H}_4$,
14e, 15e R = $p\text{-CH}_2\text{C}_6\text{H}_4$, **14f, 15f** R = $o\text{-CH}_3\text{C}_6\text{H}_4$, **14g, 15g** R = naphthyl

SCHEME 3

3. Results and Discussion

Cyclization of thioxopyrimidine **1** with chloroacetonitrile **2** in DMF in the presence of excess anhydrous potassium carbonate formed the nonisolable S-alkylated intermediate, which via nucleophilic substitution and intramolecular cyclocondensation afforded the 5-amino-6-cyanothieno[2,3-*d*]pyrimidine **3**, and the latter reacted with triethyl orthoformate to give the 5-ethoxymethyleneamino-thieno[2,3-*d*]pyrimidines **4** (Scheme 1). Moreover, the reactivity of compound **4** towards amino compounds was also investigated. In treatment of **4** with phenylhydrazine in ethanol, an addition product formed, from which elimination of ethyl formate phenylhydrazone gave the compound **3** instead of the compound **3'**, while with amino compounds **5a, 5b**,

and formamide afforded the corresponding 7-substituted-8-imino-pyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidines **6a, 6b**, and **7**, respectively (Scheme 2). The structure of compounds **6a, 6b**, and **7** was established on the basis of their elemental analysis and spectra data. The IR spectra of compounds **6a, 6b**, and **7** showed the characteristic absorption band at $3310\text{--}3301\text{ cm}^{-1}$ for the NH group. In addition, the ^1H NMR spectra (CDCl_3) of compound **6a** revealed a triplet at δ 1.47 (3H, s) and a quartet at 4.10 (2H, q), which were readily assigned to the ethyl group (CH_2CH_3) and a singlet at 7.90 (1H, s) which was assigned to the hydrogen attached at C₆ of the pyrimidine ring, which was also confirmed by the mass spectrum m/z 321 (M^+). Further, the ^1H NMR spectra ($\text{DMSO-}d_6$) of compound **7** revealed three singlets at δ 8.33 (1H, s), 8.54 (1H, s), and 8.86 (1H, s), which

SCHEME 4

were readily assigned to the NH, HCO, and C₆-H protons, respectively. Nevertheless, the compound **4** was cyclized with acid hydrazides **8a**, **8b** under different conditions to form a new tetracyclic compound. Thus, compound **4** with acid hydrazides **8a**, **8b** in refluxing 2-methoxyethanol afforded the corresponding 2-substituted-pyrimido[3',2':4,5]thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines **9a**, **9b**. The ¹H NMR spectra (CF₃COOD) of the compounds **9a**, **9b**, which showed a singlet at δ 9.93 (1H, s) and 9.83 (6H, s), were readily assigned to the hydrogen attached at C₆ of the pyrimidine ring, respectively. Hydrazinolysis of compound **4** in ethanol yielded the key intermediate (**10**) for the preparation of new triazoles and triazepines (Scheme 2). Moreover, the IR spectra of compound (**10**) showed the characteristic absorption band at 3315 and 3247 cm⁻¹ for the NH₂ and NH groups, respectively. The ¹H NMR spectra (CF₃COOD) of compound (**10**) revealed three singlets at δ 5.12 (1H, s), 9.23 (1H, s), and 8.69 (1H, s), which were readily assigned to the NH₂, NH, and C₆-H protons, respectively, which was also confirmed by the mass spectrum *m/z* 308(M⁺).

Next, as described in Scheme 3, several pyrimido[3,2:4,5]thieno[2,3-d]pyrimidines (PTP) substituted at positions 7 and 8 with different heterocyclic residues were obtained via treatment of compound (**10**) with different reagents. Thus, upon heating compound (**10**) in refluxing acetic anhydride, introduced three acetyl groups afforded the 8-(acetylamino)-7-diacetylamino-4-methyl-2-phenylpyrimido[3,2:4,5]thieno[2,3-d]pyrimidine (**11**). Also, the compound (**10**) cyclized in glacial acetic acid at 70–80 °C for 2 h afforded the 2,7-dimethyl-pyrimido[3',2':4,5]thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**12**). The structure of compounds (**11**), (**12**) was established on the basis of their elemental analysis and spectral data. The IR spectra of compounds (**11**), (**12**) indicated the complete disappearance

of NH and NH₂ groups. The ¹H NMR spectra (CF₃COOD) of the compound (**11**), which showed additional two signals at δ 2.32 (3H, s) and 2.56 (6H, s), which were assigned to the protons COCH₃ attached at imino and amino groups of PTP moiety, respectively, were also confirmed by the mass spectrum *m/z* 434 (M⁺). Moreover, reaction of (**10**) with N,N-dimethyl-4-nitrosoaniline in refluxing glacial acetic acid afforded the 7-(4-dimethyl-aminophenyl)azo-8-imino-4-methyl-2-phenyl-7,8-dihydropyrimido[3,2:4,5]thieno[2,3-d]pyrimidine **13**, because the molecular ion *m/z* 440 of compound **13** is unstable and could not be recorded in the electron impact mass spectra but showed the presence of the ion peaks *m/z* 412, *m/z* 397, *m/z* 319, and *m/z* 293. The possible mass fragmentation pathway of compound **13** is shown in Scheme 6. In addition, the structure of compound **13** was supported by the ¹H NMR spectra, which showed a sharp singlet at δ 3.51 (6H, s) assigned to the N(CH₃)₂ protons.

On the other hand, the 2-(substituted-amino)-pyrimido[3',2':4,5]thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines **15a–15g** were obtained by intramolecular cyclization of compound (**10**) with appropriate isothiocyanates **14a–14g** in refluxing pyridine (Scheme 3). Obviously this reaction proceeded via the thiourea intermediate **15'** with concomitant dehydrosulfurization. The structure of compounds **15a–15g** was established on the basis of their elemental analysis and spectral data. The ¹H NMR spectra of **15a–15g** showed a singlet at δ 9.98–8.79 (1H, s) assigned to the hydrogen attached at C₅ of the pyrimidotriazole ring. In addition, the ¹H NMR spectra of compound **15b** revealed a triplet at δ 1.92 (3H, s) and a quartet at 4.92 (2H, q), which were readily assigned to the ethyl group (CH₂CH₃) and a singlet at 9.15 (1H, br) which was assigned to the NH group. Also,

SCHEME 5

it has been observed that electron impact (EI) spectral has many common features. Compounds **15a-15g** exhibited m/z 332, m/z 304, m/z 293, m/z 278, and m/z 174 piece peaks. Next, cyclocondensation of compound (**10**) with 1,3-dibromopropane in DMF in the presence of excess anhydrous potassium carbonate at 60°C form the 9,10,11-trihydropyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*][1,2,4]triazepine **16**. In particular, the ^1H NMR spectra of compound **16** revealed two additional triplets at δ 3.42 (2H, t) and 4.42 (2H, t), which were readily assigned to

the hydrogen attached at C_{11} and C_9 of the triazepine ring, respectively, a singlet at δ 10.12 (1H, br) assigned to the NH group, and a multiplet at δ 2.32 (2H, m) assigned to the hydrogen attached at C_{10} of the triazepine ring, which was also confirmed by the mass spectrum m/z 348 (M^+).

Work was further extended to study the behavior of compound (**10**) towards the different reagents with a view to synthesizing various heterocyclic ringsystems. Thus, treatment of compound (**10**) with Mannich bases [30, 31] **17a-17c** in DMF in the presence

SCHEME 6

SCHEME 7

of excess anhydrous potassium carbonate afforded the corresponding 9-substituted-10,11-dihydropyrimido thieno[3,2:4,5]pyrimido[1,6-*b*][1,2,4]triazepines **18a–18c** (Scheme 4). The mechanism involves the condensation of amino group in compound (**10**) with the carbonyl group,

followed by dehydration and subsequent nucleophilic cyclization with loss of *N,N*-dimethylamine hydrochloride [26]. The ^1H NMR spectra of compounds **18a–18c** revealed two additional triplets at δ 3.22–3.28 (2H, t) and 4.19–4.23 (2H, t), which were readily assigned to the hydrogen attached

at C₁₀ and C₁₁ of the triazepine ring, respectively. These structures get further support from mass spectroscopy. It has been observed that Electron Impact (EI) spectral has many common features. Compounds **18a–18c** exhibited *m/z* 345, *m/z* 332, *m/z* 318, *m/z* 293, *m/z* 278, *m/z* 250, *m/z* 215, *m/z* 190, and *m/z* 163 piece peaks. The possible mass fragmentation pathway of compounds **18a–18c** is shown in Scheme 7.

Furthermore, the behavior of compound (**10**) with enaminone derivatives **19a–19e** was also investigated (Scheme 5). To optimize the reaction temperature, the reaction of compound (**10**) and enaminone **19e** was studied in glacial acetic acid, at different temperatures such as 50°C–55°C, 80°C, and reflux, respectively. It has been found that the treatment of compound (**10**) and enaminone **19e** carried out at 50–55°C for 3h only afforded the open-chain product **20** in 70% yield, while at 80°C for 7h incomplete cyclocondensation was observed (as examined by TLC (ethyl acetate and hexane (3:7))); work-up of the reaction mixture yielded a mixture of two products **20** (60% yield) and **21e** (6.3% yield) which were separated. Also, it was interesting to find that prolonging the reaction time (10h) and increasing the reaction temperature (reflux), the yield for compound **21e** increased greatly from 6.3% to 68%.

The structures of **20** and **21e** were established on the basis of microanalysis and spectra data as well as comparison (IR, mixed mp, TLC (ethyl acetate and hexane (3:7))). The IR spectra of the compound **20** showed the characteristic absorption band at 3215 cm⁻¹ for the NH group and at 1668 cm⁻¹ for the C=O group. The ¹H NMR spectra of compound **20** showed a doublet at δ 4.00 (1H, d) assigned to the COCH= of 1-(4-pyridinyl)prop-2-enone moiety and a multiplet at δ 8.78–8.74, 8.26–8.07 (6H, m) assigned to the NCH= of 1-(4-pyridinyl)prop-2-enone moiety and phenyl protons. In addition, the IR spectra of compound **21e** indicated the absence of the NH₂ and NH groups. The ¹H NMR spectra of compound **21e** revealed two doublets at δ 7.52 (1H, d) and 8.16 (1H, d), which were readily assigned to the hydrogen attached at C₁₀ and C₉ of the triazepine ring, respectively. The structure of compound **21e** was further confirmed via an independent synthesis of compound **21e** by reaction of compound **20** in glacial acetic acid under reflux 10 h to afford a product identical in all respects (mp, mixed mp, TLC (ethyl acetate and hexane (3:7)) and spectra), with those of compounds **21e** in 48% yield. Moreover, treatment of compound (**10**) with enaminones **19a–19d** in glacial acetic acid under reflux afforded the corresponding 11-substituted-pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-b][1,2,4]triazepines **21a–21d**, respectively (Scheme 5). The formation of compound **21a–e** would involve an initial Michael addition of the exocyclic amino group in compound (**10**) to the activated double bond in enaminone **19** to form the intermediate **20'**, which then undergoes cyclization and aromatization via loss of both water and N,N-dimethylamine [26] affording the final product **21a–21e**. The ¹H NMR spectra of compounds **21a–21e** revealed two additional doublets at δ 7.33–6.71 (1H, d) and 8.16–7.45 (1H, d), which were readily assigned to the hydrogen attached at C₁₀ and

C₉ of the triazepine ring, respectively, and a singlet at δ 9.54–8.31 (1H, s) assigned to the hydrogen attached at C₆ of the triazepine ring. These structures get further support from mass spectroscopy.

4. Conclusion

In conclusion, 7-amino-8-imino-pyrimido[3,2:4,5]thieno pyrimidine (**10**) has been shown to be a useful building block for the synthesis of several novel 2-(substituted-amino)-pyrimido[3',2':4,5]thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **15a–15g**, (tri)dihydro-pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido [1,6-*b*][1,2,4] triazepines **16** and **18a–18c**. On the other hand, the 11-substituted-pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*][1,2,4] triazepines **21a–21e** were also obtained from compound (**10**).

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References

- [1] S. Bondock, W. Fadaly, and M. A. Metwally, "Enaminonitrile in heterocyclic synthesis: synthesis and antimicrobial evaluation of some new pyrazole, isoxazole and pyrimidine derivatives incorporating a benzothiazole moiety," *European Journal of Medicinal Chemistry*, vol. 44, no. 12, pp. 4813–4818, 2009.
- [2] A. P. Keche, G. D. Hatnapure, R. H. Tale, A. H. Rodge, S. S. Birajdar, and V. M. Kamble, "A novel pyrimidine derivatives with aryl urea, thiourea and sulfonamide moieties: synthesis, anti-inflammatory and antimicrobial evaluation," *Bioorganic & Medicinal Chemistry Letters*, vol. 22, no. 10, pp. 3445–3448, 2012.
- [3] X. J. Song, Y. Shao, and X. G. Dong, "Microwave-assisted synthesis of some novel fluorinated pyrazolo[3,4-*d*] pyrimidine derivatives containing 1,3,4-thiadiazole as potential antitumor agents," *Chinese Chemical Letters*, vol. 22, no. 9, pp. 1036–1038, 2011.
- [4] K. M. Amin, F. M. Awadalla, A. A. M. Eissa, S. M. Abou-Seri, and G. S. Hassan, "Design, synthesis and vasorelaxant evaluation of novel coumarin-pyrimidine hybrids," *Bioorganic & Medicinal Chemistry*, vol. 19, no. 20, pp. 6087–6097, 2011.
- [5] E. P. da S. Falcão, S. J. de Melo, R. M. Srivastava, M. T. J. Catanho, and S. C. D. Nascimento, "Synthesis and anti-inflammatory activity of 4-amino-2-aryl-5-cyano-6-{3- and 4-(*N*-phthalimidophenyl)} pyrimidines," *European Journal of Medicinal Chemistry*, vol. 41, no. 2, pp. 276–282, 2006.
- [6] J. M. Cox, J. H. Marsden, R. A. Burrell, and N. S. Elmure, *Chemical Abstracts*, vol. 87, Article ID 128906, 1977, German Offen Patent 2, 654, 090, 1976.
- [7] P. Schmidt and K. Eichenberger, *Chemical Abstracts*, vol. 75, Article ID 88638, 1971, German Offen Patent 2, 060, 968, 1970.
- [8] J. B. Press and R. K. Russel, *Chemical Abstracts*, vol. 107, Article ID 115604, 1987, US Patent 4, 670, 560, 1986.

- [9] B. V. Ashalatha, B. Narayana, K. K. Vijaya Raj, and N. Suchetha Kumari, "Synthesis of some new bioactive 3-amino-2-mercapto-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives," *European Journal of Medicinal Chemistry*, vol. 42, no. 5, pp. 719–728, 2007.
- [10] F. F. Janssens, L. E. J. Kennis, J. F. Hens, J. L. G. Torremans, and G. S. M. Diels, *Chemical Abstracts*, vol. 109, Article ID 37821, 1988, US Patent 4, 695, 575, 1987.
- [11] M. Gupta, S. Paul, and R. Gupta, "Efficient and novel one-pot synthesis of antifungal active 1-substituted-8-aryl-3-alkyl/aryl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines using solid support," *European Journal of Medicinal Chemistry*, vol. 46, no. 2, pp. 631–635, 2011.
- [12] M. Gupta, "Efficient synthesis of antifungal active 9-substituted-3-aryl-5*H*,13*aH*-quinolino[3,2-*f*][1,2,4]triazolo[1,2,4]triazepines in ionic liquids," *Bioorganic & Medicinal Chemistry Letters*, vol. 21, no. 16, pp. 4919–4923, 2011.
- [13] D. M. Bailey, *Chemical Abstracts*, vol. 75, Article ID 140910, 1971, US 3, 607, 866, 1971.
- [14] O. Bruno, C. Brullo, S. Schenone et al., "Progress in 5*H*[1]benzopyrano[4,3-*d*]pyrimidin-5-amine series: 2-methoxy derivatives effective as antiplatelet agents with analgesic activity," *Il Farmaco*, vol. 57, no. 9, pp. 753–758, 2002.
- [15] A. Padmaja, T. Payani, G. D. Reddy, and V. Padmavathi, "Synthesis, antimicrobial and antioxidant activities of substituted pyrazoles, isoxazoles, pyrimidine and thioxopyrimidine derivatives," *European Journal of Medicinal Chemistry*, vol. 44, no. 11, pp. 4557–4566, 2009.
- [16] Q. Chen, X. L. Zhu, L. L. Jiang, Z. M. Liu, and G. F. Yang, "Synthesis, antifungal activity and CoMFA analysis of novel 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives," *European Journal of Medicinal Chemistry*, vol. 43, no. 3, pp. 595–603, 2008.
- [17] H. W. Lee, B. Y. Kim, J. B. Ahn et al., "Molecular design, synthesis, and hypoglycemic and hypolipidemic activities of novel pyrimidine derivatives having thiazolidinedione," *European Journal of Medicinal Chemistry*, vol. 40, no. 9, pp. 862–874, 2005.
- [18] T. Mohamed and P. P. N. Rao, "Design, synthesis and evaluation of 2,4-disubstituted pyrimidines as cholinesterase inhibitors," *Bioorganic and Medicinal Chemistry Letters*, vol. 20, no. 12, pp. 3606–3609, 2010.
- [19] D. Gala, D. J. DiBenedetto, M. Kugleman, and M. S. Puar, "Pyrimidine to guanine PDE inhibitors: determination of chemical course via structure elucidation," *Tetrahedron Letters*, vol. 44, no. 13, pp. 2717–2720, 2003.
- [20] A. Mayasundari and N. Fujii, "Efficient formation of 4,6-disubstituted pyrrolo[2,3-*d*]pyrimidines: a novel route to TWS119, a glycogen synthase kinase-3 β inhibitor," *Tetrahedron Letters*, vol. 51, no. 27, pp. 3597–3598, 2010.
- [21] A. Angelucci, S. Schenone, G. L. Gravina et al., "Pyrazolo[3,4-*d*]pyrimidines c-Src inhibitors reduce epidermal growth factor-induced migration in prostate cancer cells," *European Journal of Cancer*, vol. 42, no. 16, pp. 2838–2845, 2006.
- [22] R. A. Mathes and F. D. Stewart, *Chemical Abstracts*, vol. 45, Article ID 4273c, 1951, (B. F. Goodrich Co.) US Patent 2, 535, 858, 1950.
- [23] W. Seebacher, G. Michl, and R. Weis, "Synthesis of new triazepinethiones," *Tetrahedron Letters*, vol. 43, no. 42, pp. 7481–7483, 2002.
- [24] E. A. Savel'eva, Y. A. Rozin, M. I. Kodess et al., "Synthesis of mesoionic[1,2,3]triazolo[5,1-*d*][1,2,5]triazepines," *Tetrahedron*, vol. 60, no. 25, pp. 5367–5372, 2004.
- [25] M. Gupta, S. Paul, and R. Gupta, "Efficient and novel one-pot synthesis of antifungal active 1-substituted-8-aryl-3-alkyl/aryl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepines using solid support," *European Journal of Medicinal Chemistry*, vol. 46, no. 2, pp. 631–635, 2011.
- [26] Y. W. Ho and C. T. Yao, "Synthesis of some new 6,8-disubstituted 7,8-dihydro-pyrimido[2,3:4,3] pyrazolo[1,5-*a*]pyrimidines and 6,7,8-trisubstituted pyrimido[2,3:4,3] pyrazolo[1,5-*a*]pyrimidine derivatives," *Journal of the Chinese Chemical Society*, vol. 50, no. 2, pp. 283–296, 2003.
- [27] Y. W. Ho, "5-(1-Pyrrolyl)-2-phenylthieno[2,3-*d*]pyrimidine as building block in heterocyclic synthesis: novel synthesis of some pyrazoles, pyrimidines, imidazo[1,2-*a*]pyrimidines, pyrazolo[1,5-*a*]pyrimidines, pyrido-(pyrimido) pyrazolo[1,5-*a*]pyrimidines, 1,2,4-triazolo[1,5-*a*]pyrimidine and a 1,2,3,4-tetrazolo[1,5-*a*]pyrimidine derivative," *Journal of the Chinese Chemical Society*, vol. 54, no. 4, pp. 1075–1085, 2007.
- [28] Y. W. Ho and M. C. Suen, "Synthesis and structure of novel thieno[2,3-*d*]pyrimidine derivatives containing 1,3,4-oxadiazole moiety," *Journal of the Chinese Chemical Society*, vol. 56, no. 2, pp. 408–415, 2009.
- [29] Y. W. Ho and W. H. Yao, "The synthesis and spectral characteristics of novel 6-(2-substituted-1,3,4-oxadiazol-5-yl)-2-phenylthieno[2,3-*d*]pyrimidine fluorescent compounds derived from 5-cyano-1,6-dihydro-4-methyl-2-phenyl-6-thioxopyrimidine," *Dyes and Pigments*, vol. 82, no. 1, pp. 6–12, 2009.
- [30] Y. W. Ho, "Synthesis of new 2-[(Substituted-pyrazolin-1-yl)carbonyl]-thieno[2,3-*b*]pyridine derivatives," *Journal of the Chinese Chemical Society*, vol. 46, no. 1, pp. 91–96, 1999.
- [31] M. Abid and A. Azam, "1-*N*-substituted thiocarbamoyl-3-phenyl-2-pyrazolines: synthesis and in vitro antiamebic activities," *European Journal of Medicinal Chemistry*, vol. 40, no. 9, pp. 935–942, 2005.