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A Facile one–pot Synthesis of Pyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5,4-a] pyrimidin-5-one

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ABSTRACT: Two convenient methods for synthesis of novel pyrido[3,2:4,5]thieno[3,2-d] [1,2,4]triazolo [5,4-a]pyrimidin-5-ones **8** were developed. The first route involved the reaction between 2,3-dihydro-7,9-dimethyl-2-thioxo-pyrido [3´,2´:4,5] thieno [3,2-d] pyrimidin-4(1H)-one **3** or its 2-methylthio derivative **4** with hydrazonoyl halides **5** in dioxane under reflux in presence of triethylamine. The alternative route proceeded *via* reaction of **3** with the appropriate active chloromethylene compounds followed by coupling the products with benzenediazonium chloride which afforded the azo coupling products and then was converted *in situ* to **8**. The reaction mechanism was elucidated and the products were investigated for their biological activity.

Key Words: pyrido [3´,2´:4,5] thieno [3,2-d][1,2,4] triazolo [5, 4-a] pyrimidin-5-one.

Introduction

The thienopyrimidines are known to have particular interest for the composition of some non-steroidal anti-inflammatory drugs (NSAIDs) [1]. Also, they have been established as potent inhibitors of VEGFR-2 kinase [2]. Moreover, condensed heterocycles containing thienopyrimidines have acquired conspicuous popularity in recent years due to their wide spectrum of biological activities including analgesic, anticonvulsant and antimicrobial agents [3]. On the other hand, fused triazoles are proved to have diverse applications as antibacterial-, antidepressent-, antiviral-, antitumorial agents [4,5]. This prompted us to synthesize new heterocyclic system namely pyrido [3´,2´:4,5]thieno[3,2-d][1,2,4]triazolo[5,4-a]pyrimidin-5-ones **8**, which have not been reported. These compounds were studied in continuation of our previous work on the synthesis of bridgehead nitrogen polyheterocycles [6-10].

Experimental

Melting points were recorded on Gallenkamp electrothermal apparatus and are uncorrected. Infrared spectra (KBr) were determined on a Pye Unicam SP-3000 infrared spectrophotometer. ^{1}H NMR was determined on a Varian Gemini 300 spectrometer (300 MHz) in DMSO-d_6 with TMS as internal standard. Mass spectra were recorded on a GCMS-QP 1000 EX Shimadzu spectrometer. Elemental analyses were carried out at the Microanalytical center, University of Cairo, Giza, Egypt. Hydrazonoyl halides **5** [11-16] were prepared by literature methods. The biological evaluation of the products was carried out at the Regional Center for Mycology and Biotechnology at Al-Azhar University, Cairo, Egypt.

Synthesis of 3-(ethoxycarbonylamino carbothioyl amino)-4,6-dimethylthieno[2,3-b] pyridine-2-carboxylate (2)

A solution of ethoxycarbonyl isothiocyanate [prepared by mixing ethyl chloroformate (1.08 g, 10 mmole) in dry acetone with ammonium thiocyanate (0.76g, 10 mmole) and heating in a water bath for 20 minutes] was added to a stirred solution of ethyl 3-amino-4,6-dimethyl-thieno [2,3-b] pyridine-2-carboxylate **1** [17] (2.50 g, 10 mmole) in acetone (30 mL). The mixture was heated under reflux in a water bath for 2 hours, and then evaporated under vacuum. The remaining product was triturated with ethanol, then collected by filtration, dried and recrystallized from ethanol as yellow crystals of **2** Mp 268 °C; yield 70% - IR ν 3406, 3384 (2NH), 1689, 1672 (2CO) cm^{-1} - ^{1}H NMR *d* (DMSO-d_6) 1.30 (t, 3H),

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1.32 (t, 3H), 4.12 (q, 2H), 4.29 (q, 2H), 2.54 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 7.17 (s, 1H, Pyr-H), 11.34 (s, 1H, NH), 14.23 (s, 1H, NH) - MS, *m/z* (%) 382 (M^++1, 26)**,** 381 (M^+, 60), 205 (100), 131 (12), 65 (13)-$C_{16}H_{19}N_3O_4S_2$ (381): calcd. C, 50.38; H, 5.02; N, 11.02; S, 16.81; Found: C, 50.21; H, 5.11; N, 10.91; S, 16.73.

Synthesis of 2,3-dihydro-7,9-dimethyl-2-thioxopyrido [3´,2´:4,5] thieno [3,2-d] pyrimidin-4(1H)-one (3)

Compound **2** (0.381 g, 1 mmol) was dissolved in a solution of sodium ethoxide [prepared by dissolving (0.23 g, 10 mg-atom) of sodium metal in absolute ethanol (20 mL)] and the solution was heated under reflux for 30 minutes. The solvent was evaporated in vacuum, some water was added to the residue, and the mixture was acidified to pH = 4 with hydrochloric acid. The product which separated was collected and recrystallized from dioxane as white crystals of **3**. Mp 312 °C [Lit. mp > 300] [18], yield 70% - IR ν 3220, 3360 (2NH), 1680 (CO) cm^{-1} - ^{1}H NMR δ (DMSO-d_6) 2.50 (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 7.05 (s, 1H, Pyr-HH), 9.11 (s, 1H, NH), 11.00 (s, 1H) - MS, *m/z* (%) 264 (M^++1, 12), 263 (M^+, 100), 205 (40), 131 (12), 65 (10) - $C_{11}H_9N_3OS_2$ (263): calcd. C, 50.17; H, 3.44; N, 15.96; S, 24.35; Found: C, 50.02; H, 3.31; N, 15.64; S, 24.28.

Synthesis of 7,9-dimethyl-2-methylthiopyrido [3´,2´:4,5] thieno [3,2-d] pyrimidin-4(3H)-one (4)

To a suspension of 2,3-dihydro-7,9-dimethyl-2-thioxopyrido [3´,2´:4,5] thieno [3,2-d]pyrimidin-4(1H)-one **3** (2.63 g, 10 mmol) in DMF (20 mL) in the presence of anhydrous K_2CO_3 (2.07 g, 15 mmol), was added methyl iodide (1.42 g, 10 mmol). The reaction mixture was stirred at room temperature for one hour then poured into ice-water. The solid formed was filtered, washed with water, dried and recrystallized from DMF to give white crystals of **4**. Mp 287 °C; yield 78% - IR ν 3332 (NH), 1666 (CO) cm^{-1} - ^{1}H NMR δ (DMSO-d_6) 2.49 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 3.11 (s, 3H, SCH_3), 7.11 (s, 1H, Pyr-H), 11.08 (s, 1H) - MS, *m/z* (%) 278 (M^++1, 0.23), 277 (M^+, 0.65), 250 (85), 204 (100), 132 (19) - $C_{12}H_{11}N_3OS_2$ (277): calcd. C, 51.96; H, 4.00; N, 15.15; S, 23.12; Found: C, 51.68; H, 4.03; N, 15.01; S, 23.08.

Synthesis of 8,10-dimethyl-1,3-disubstitutedpyrido [3´,2´:4,5] thieno [3,2-d][1,2,4] triazolo [5, 4-a]pyrimidin-5-ones 8a-ν

Method A: To a solution of 2,3-dihydro-7,9-dimethyl-2-thioxopyrido [3´,2´:4,5]thieno [3,2-d]pyrimidin-4(1H)-one **3** (2.63 g, 10 mmol) in dioxane (50 mL) in the presence of triethylamine (1.4 mL, 10 mmole), was added the appropriate hydrazonoyl halides **5** (10 mmol). The reaction mixture was refluxed for 6-10 h until all the starting materials have been disappeared (monitored by TLC) and hydrogen sulfide gas ceased to liberate. The solvent was evaporated and the residue was triturated with methanol. The solid that formed was filtered and recrystallized from DMF to give compounds **8**.

Method B: To a solution of 7,9-dimethyl-2-methylthiopyrido[3´,2´:4,5] thieno [3,2-d] pyrimidin-4(3H)-one **4** (2.77 g, 10 mmol) in dioxane (50 mL) in the presence of triethylamine (1.4 mL, 10 mmole), was added the appropriate hydrazonoyl halides **5** (10 mmol). The reaction mixture was refluxed for 6-10 h and worked up as usual to give the products which were found to be identical in all respects (mp. mixed mp. and IR) with products **8.**

8,10-Dimethyl-1,3-diphenylpyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo[5,4-a] pyrimidin-5-one (8a)

Mp 278 °C; yield 78% - IR ν 1701 (CO) cm^{-1} - ^{1}H NMR (DMSO-d_6) δ = 2.55 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 7.12 (s, 1H, Pyr-H), 7.43 - 8.28 (m, 10H, Ar-H) - MS, *m/z* (%) 424 (M^++1, 34), 423 (M^+, 100), 91 (15), 77(21) - $C_{24}H_{17}N_5OS$ (423): calcd. C, 68.07; H, 4.05; N, 16.54, S, 7.57; Found: C, 67.96; H, 4.01; N, 16.32; S, 7.41.

3-Acetyl-8,10-dimethyl-1-phenylpyrido [3´,2´:4,5] thieno [3,2-d][1,2,4] triazolo[5,4-a] pyrimidin-5-one (8b)

Mp 238 °C; yield 72% - IR ν 1724, 1690 (2CO) cm^{-1} - ^{1}H NMR (DMSO-d_6) δ = 2.53(s, 3H, CH_3), 2.78 (s, 3H, CH_3), 2.84 (s, 3H, $COCH_3$), 7.18 (s, 1H, Pyr-H) 7.43-8.2 (m, 5H, Ar-H) - MS, *m/z* (%) 391 (M^++1, 28), 390 (M^+, 100), 347 (27), 306(11), 77 (17)-$C_{20}H_{15}N_5O_2S$ (389): calcd. C, 61.68; H, 3.88; N, 17.98; S, 8.23; Found: C, 61.43; H, 3.62; N, 17.66; S, 8.03.

3-Acetyl-8,10-dimethyl-1-(4-methylphenyl) pyrido[3´,2´:4,5]thieno[3,2-d][1,2,4] triazolo[5,4-a]pyrimidin-5-one (8c)

Mp 242 °C; yield 76% - IR ν 1701, 1666 (2CO) cm^{-1} - ^{1}H NMR (DMSO-d_6) δ = 2.38 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 2.83 (s, 3H, $COCH_3$), 7.16 (s, 1H, Pyr-H), 7.41 (d, 2H), 8.01 (d, 2H)-MS, *m/z* (%) 404 (M^++1, 23), 403 (M^+, 100), 361 (18), 77 (4.4)-$C_{21}H_{17}N_5O_2S$ (403): calcd. C, 62.52; H, 4.25; N, 17.36; S, 7.93; Found: C, 62.45; H, 4.11; N, 17.19; S, 7.84.

3-Acetyl-1-(4-chlorophenyl)-8,10-dimethyl pyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5,4-a]pyrimidin-5-one (8d)

Mp 236 °C; yield 75% - IR ν 1705, 1662 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 2.57 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 2.88 (s, 3H, $COCH_3$), 7.26 (s, 1H, Pyr-H), 7.72 (d, 2H), 8.23 (d, 2H) - MS, *m/z* (%) 425 (M^++2, 40), 424 (M^++1, 27), 423 (M^+, 100), 381 (34), 340 (12) - $C_{20}H_{14}ClN_5O_2S$ (423): calcd. C, 56.67; H, 3.33; N, 16.52; S, 7.56; Found: C, 56.48; H, 3.30; N, 16.36; S, 7.43.

3-Acetyl-8,10-dimethyl-1-(4-methoxyphenyl) pyrido [3´,2´:4,5] thieno [3,2-d][1,2,4] triazolo[5,4-a]pyrimidin-5-one (8e)

Mp 250 °C; yield 65% - IR ν 1744, 1694 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 2.52 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 2.86 (s, 3H, $COCH_3$), 3.56 (s, 3H, OCH_3), 7.20 (s, 1H, Pyr-H), 7.44 (d, 2H), 8.16 (d, 2H) - MS, *m/z* (%) 420 (M^+, 6), 101 (14), 86 (100), 58 (37) - $C_{21}H_{17}N_5O_3S$ (419): calcd. C, 60.13; H, 4.09; N, 16.70; S, 7.64; Found: C, 60.01; H, 4.02; N, 16.51; S, 7.44.

3-Acetyl-8,10-dimethyl-1-(4-nitrophenyl) pyrido [3´,2´:4,5] thieno [3,2-d][1,2,4] triazolo [5,4-a]pyrimidin-5-one (8f)

Mp 207 °C; yield 74% - IR ν 1735, 1666 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 2.58 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 7.24 (s, 1H, Pyr-H), 7.72 (d, 2H, CH_2), 8.5 (d, 2H) - MS, *m/z* (%) 435 (M^++1, 15), 434 (M^+---, 36), 263 (100), 205(61), 131 (21) - $C_{20}H_{14}N_6O_4S$ (434): calcd. C, 55.29; H, 3.25; N, 19.35; S, 7.38; Found: C, 55.13; H, 3.12; N, 19.10; S, 7.31.

Ethyl 8,10-dimethyl-5-oxo-1-phenylpyrido [3´,2´:4,5] thieno[3,2-d][1,2,4]triazolo[5,4-a]pyrimidin-3-carboxylate (8g)

Mp 228 °C; yield 72%-IR ν 1751, 1705 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 1.45 (t, 3H, CH_3), 2.56 (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 4.55 (q, 2H, CH_2), 7.18 (s, 1H, Pyr-H), 7.42-8.14 (m, 5H, Ar-H) - MS, *m/z* (%) 420 (M^++1, 26), 419 (M^+, 100), 347 (42), 306 (19), 77 (21) - $C_{21}H_{17}N_5O_3S$ (419): calcd. C, 60.13; H, 4.09; N, 16.70; S, 7.64; Found: C, 60.11; H, 4.02; N, 16.50; S, 7.58.

Ethyl 8,10-dimethyl-5-oxo-1-(4-methylphenyl) pyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5,4-α] pyrimidin-3-carboxylate (8h)

Mp 260 °C; yield 71% - IR ν 1755, 1701 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 1.42 (t, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 4.54 (q, 2H, CH_2), 7.19 (s, 1H, Pyr-H), 7.37 (d, 2H), 7.98 (d, 2H) - MS, *m/z* (%) 434 (M^++1, 28), 433 (M^+, 100), 361 (14), 320 (14), 77 (18)-$C_{22}H_{19}N_5O_3S$ (433): calcd. C, 60.69; H, 4.42; N, 16.16; S, 7.40; Found: C, 60.46; H, 4.31; N, 16.01; S, 7.34.

Ethyl 1-(3-chlorophenyl)- 8,10-dimethyl-5-oxopyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5,4-a]pyrimidin-3-carboxylate (8i)

Mp 257 °C; yield 70% - IR ν 1761, 1705 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 1.40 (t, 3H, CH_3), 2.58 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 4.56 (q, 2H, CH_2), 7.22 (s, 1H, Pyr-H), 7.63-7.72 (m, 4H) - MS, *m/z* (%) 455 (M^++2, 5), 454 (M^++, 17), 453 (M^+, 8), 263 (10), 175 (14), 111(36), 86 (58), 77 (24), 55 (100) - $C_{21}H_{16}ClN_5O_3S$ (453): calcd. C, 55.57; H, 3.55; N, 15.43; S, 7.06; Found: C, 55.42; H, 3.33; N, 15.26; S, 7.02.

Ethyl 1-(4-chlorophenyl)-8,10-dimethyl-5-oxopyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5,4-a] pyrimidin-3-carboxylate (8j)

Mp 266 °C; yield 73% - IR ν 1751, 1705 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 1.41 (t, 3H, CH_3), 2.59 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 4.56 (q, 2H, CH_2), 7.2 (s, 1H, Pyr-H), 7.61 (d, 2H), 7.73 (d, 2H) - MS, *m/z* (%) 455 (M^++2, 7), 454 (M^++1, 5), 453 (M^+, 12), 381 (100), 230 (74), 131 (17)-$C_{21}H_{16}ClN_5O_3S$ (453): calcd. C, 55.57; H, 3.55; N, 15.43; S, 7.06; Found: C, 55.47; H, 3.51; N, 15.21; S, 7.01.

Ethyl 8,10-dimethyl-5-oxo-1-(4-nitro phenyl) pyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5,4-a]pyrimidin-3-carboxylate (8k)

Mp 246 °C; yield 70% - IR ν 1751, 1705 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 1.41 (t, 3H, CH_3), 2.54 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 4.55 (q, 2H, CH_2), 7.24 (s, 1H, Pyr-H), 8.41 (d, 2H), 8.64 (d, 2H) - MS, *m/z* (%) 465 (M^++1, 28), 464 (M^+, 100), 392 (92), 346 (18), 230 (10), 77 (10)-$C_{21}H_{16}N_6O_5S$ (464): calcd. C, 54.31, H, 3.47; N, 18.09; S, 6.90; Found: C, 54.22; H, 3.24; N, 17.98; S, 6.80.

8,10-Dimethyl-1-phenyl-3-(N-phenyl carbamoyl) pyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5,4-a] pyrimidin-5-one (8l)

Mp 278 °C; yield 73% - IR ν 3437 (NH), 1674, 1627 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 2.61 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 7.1 (s, 1H, Pyr-H), 7.2-8.28 (m, 10H,

Ar-H), 11.64 (s, 1H, NH) - MS, *m/z* (%) 467 (M^++1, 38), 466 (M^+, 100), 421 (64), 346 (19), 306 (18), 77 (22) - $C_{25}H_{18}N_6O_2S$ (466): calcd. C, 64.36; H, 3.89; N, 18.01; S, 6.87; Found: C, 64.29; H, 3.74; N, 17.85; S, 6.68.

8,10-Dimethyl-1-(4-methylphenyl)-3-(N-phenylcarbamoyl) pyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5,4-a] pyrimidin-5-one (8m)

Mp 274 °C; yield 70% - IR ν 3406 (NH), 1674, 1627 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 2.39 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 7.12 (s, 1H, Pyr-H), 7.22-7.4 (m, 5H, Ar-H), 7.71 (d, 2H), 8.11(d, 2H), 11.62 (s, 1H, NH) - MS, *m/z* (%) 482 (M^+, 11), 480 (100), 435 (67), 320 (17), 91(18) - $C_{26}H_{20}N_6O_2S$ (480): calcd. C, 64.98; H, 4.20; N, 17.49; S, 6.67; Found: C, 64.82; H, 4.11; N, 17.25; S, 6.43.

1-(4-Chlorophenyl)-8,10-dimethyl-3-(N-phenylcarbamoyl) pyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5,4-a] pyrimidin-5-one (8n)

Mp 286 °C; yield 78% - IR ν 3236 (NH), 1674, 1662 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 2.61 (s, 3H, CH_3), 2.92 (s, 3H, CH_3), 7.19 (s, 1H, Pyr-H), 7.23-7.51 (m, 5H, Ar-H), 7.81 (d, 2H), 8.12 (d, 2H) 11.64 (s, 1H, NH) - MS, *m/z* (%) 502 (M^++2, 18), 501 (M^++1, 28), 500 (M^+, 35), 340 (30), 263 (55), 119 (57), 77 (90), 65 (100) - $C_{25}H_{17}ClN_6O_2S$ (500): calcd. C, 59.94; H, 3.42; N, 16.78; S, 6.40; Found: C, 59.77; H, 3.31; N, 16.46; S, 6.23.

3-Benzoyl-8,10-dimethyl-1-phenylpyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5,4-a] pyrimidin-5-one (8o)

Mp 294 °C; yield 70% - IR ν 1742, 1674 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 2.71 (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 7.25 (s, 1H, Pyr-H), 7.5-8.41 (m, 10H, Ar-H) - MS, *m/z* (%) 452 (M^++1, 12), 451 (M^+, 31) 263 (100), 205 (43), 105 (29)-$C_{25}H_{17}N_5O_2S$ (451): calcd. C, 66.50; H, 3.80; N, 15.51; S, 7.10; Found: C, 66.37; H, 3.69; N, 15.36; S, 7.04.

3-Benzoyl-8,10-dimethyl-1-(4-methylphenyl) pyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5,4-a]pyrimidin-5-one (8p)

Mp 276 °C; yield 72% - IR ν 1740, 1681 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 2.36 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 7.21 (s, 1H, Pyr-H), 7.44-8.41 (m, 9H, Ar-H)-MS, *m/z* (%) 466 (M^++1, 10), 465 (M^+, 38), 263 (100), 205 (50), 59 (62) - $C_{26}H_{19}N_5O_2S$ (465): calcd. C, 67.08; H, 4.11; N, 15.04; S, 6.89; Found: C, 67.01; H, 4.05; N, 14.89; S, 6.75.

3-Benzoyl-1-(3-chlorophenyl)-8,10-dimethyl pyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5,4-a] pyrimidin-5-one (8q)

Mp 258 °C; yield 75% - IR ν 1739, 1693 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 2.61 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 7.3 (s, 1H, Pyr-H), 7.5-8.5 (m, 9H, Ar-H) - MS, *m/z* (%) 488 (M^++2, 10), 487 (M^++1, 32), 486 (M^+, 27), 105 (100), 77 (56) - $C_{25}H_{16}ClN_5O_2S$ (486): calcd. C, 61.79; H, 3.32; N, 14.41; S, 6.60; Found: C, 61.59; H, 3.17; N, 14.28; S, 6.51.

3-Benzoyl-1-(4-chlorophenyl)-8,10-dimethylpyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5, 4-a]pyrimidin-5-one (8r)

Mp 283 °C; yield 78% - IR ν 1742, 1690 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 2.60 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 7.31 (s, 1H, Pyr-H), 7.48-8.50 (m, 9H) - MS, *m/z* (%) 487 (M^++2, 37), 486 (M^++1, 30), 485 (M^+, 28), 263 (100), 205 (60), 77 (51) - $C_{25}H_{16}ClN_5O_2S$ (486): calcd. C, 61.79; H, 3.32; N, 14.41; S, 6.60; Found: C, 61.61; H, 3.27; N, 14.30; S, 6.53.

3-Benzoyl-8,10-dimethyl-1-(4-methoxy phenyl) pyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5,4-a] pyrimidin-5-one (8s)

Mp 290 °C; yield 70% - IR ν 1746, 1666 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 2.73 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 3.62 (s, 3H, CH_3), 7.20 (s, 1H, Pyr-H), 7.43-8.42 (m, 9H, Ar-H) - MS, *m/z* (%) 482 (M^++1, 35), 481 (M^+, 32), 263 (100), 205 (56), 77 (54) - $C_{26}H_{19}N_5O_3S$ (481): calcd. C, 64.85, H, 3.98; N, 14.54; S, 6.66; Found: C, 64.73; H, 3.80; N, 14.29; S, 6.54.

3-Benzoyl-8,10-dimethyl-1-(4-nitrophenyl) pyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5,4-a] pyrimidin-5-one (8t)

Mp 238 °C; yield 80% - IR ν 1739, 1678 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 2.53 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 6.61 (s, 1H, Pyr-H), 7.12-7.93 (m, 9H, Ar-H) - MS, *m/z* (%) 498 (M^+, 6) 263 (100), 205 (51), 132 (23), 59 (64)-$C_{25}H_{16}N_6O_4S$ (497): calcd. C, 60.48; H, 3.25; N, 16.93; S, 6.46; Found: C, 60.28; H, 3.09; N, 16.72; S, 6.29.

1-(4-Chlorophenyl)-8,10-dimethyl-3-(2-furoyl) pyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5,4-a] pyrimidin-5-one (8u)

Mp 253 °C; yield 68% - IR ν 1705, 1664 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 2.53 (s, 3H, CH_3), 2.82

(s, 3H, CH_3), 7.14 (s, 1H, Pyr-H), 6.40-7.75 (m, 7H, Ar - H) - MS, *m/z* (%) 475 (M^+, 23), 11 (100), 104 (28) - $C_{23}H_{14}ClN_5O_3S$ (475): calcd. C, 58.05; H, 2.97; N, 14.72; S, 6.74; Found: C, 57.89; H, 2.79; N, 14.46; S, 6.51.

1-(4-Chlorophenyl)-8,10-dimethyl-3-(2-thenoyl) pyrido [3´,2´:4,5] thieno [3,2-d] [1,2,4] triazolo [5,4-a] pyrimidin-5-one (8v)

Mp 244 °C; yield 70% - IR ν 1705, 1651 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 2.56 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 7.23 (s, 1H, Pyr-H), 6.40-7.75 (m, 7H, Ar-H) - MS, *m/z* (%) 491 (M^+, 17), 354 (33), 111 (100), 104 (14)-$C_{23}H_{14}ClN_5O_2S_2$ (491): calcd. C, 56.15; H, 2.87; N, 14.24; S, 13.04; Found: C, 55.97; H, 2.78; N, 14.02; S, 12.97.

Synthesis of 11a-c

General procedure: To a solution of **3** (2.63 g, 10 mmol) in ethanol (20 mL) was added an aqueous solution of potassium hydroxide (1 mL, 75%) and the mixture was warmed for 10 min. in a water bath at 80 °C then added the appropriate chloromethylene compounds **10a-c** (10 mmol) dropwise while stirring. After complete addition, the reaction mixture was stirred for further 18 h at room temperature. The solid that precipitated was filtered off, washed with water, dried and finally recrystallized from DMF to give pure **11a-c** with the following physical and spectral data.

3-[(2,3-Dihydro-7,9-dimethyl-4-oxopyrido [3´,2´:4,5] thieno[3,2-d]pyrmidin-2-yl) thio]-2,4-pentandione (11a)

Mp 240 °C; yield 65% - IR ν 3224 (NH), 1742 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 2.11 (s, 6H, 2 $COCH_3$), 2.54 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 4.48 (s, 1H, CH), 7.23 (s, 1H, Pyr-H), 10.47 (s, 1H, NH) - MS, *m/z* (%) 361 (M^+, 8.2), 351 (38), 301 (16), 247 (11), 185 (14), 129 (34), 95 (62), 57 (100) - $C_{16}H_{15}N_3O_3S_2$ (361): calcd. C, 53.17; H, 4.18; N, 11.63; S, 17.74; Found: C, 53.10; H, 4.11; N, 11.23; S, 17.58.

Ethyl 2-[(2,3-dihydro-7,9-dimethyl-4-oxopyrido [3´,2´:4,5] thieno[3,2-d]pyrmidin-2-yl) thio]-3-oxo-butanoate (11b)

Mp 180 °C; yield 72% - IR ν 3128 (NH), 1740, 1674 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ =1.42 (t, 3H, CH_3), 2.53 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 4.10 (q, 2H, CH_2), 4.34 (s, 1H, CH), 7.17 (s, 1H, Pyr-H), 10.41 (s, 1H, NH) - MS, *m/z* (%) 392 (M^+, 64), 345 (87), 276 (100), 263 (13), 230 (40), 131 (26) - $C_{17}H_{17}N_3O_4S_2$ (391): calcd. C, 52.16; H, 4.38; N, 10.73; S, 16.38; Found: C, 52.03; H, 4.30; N, 10.47; S, 16.19.

N-phenyl-2-[(2,3-dihydro-7,9-dimethyl-4-oxopyrido [3´,2´:4,5] thieno [3,2-d] pyrmidin-2-yl) thio]-3-oxobutamide (11c)

Mp 174 °C; yield 70% - IR ν 3425, 3294 (2NH), 1738, 1654 (2CO) cm^{-1} - ^1H NMR (DMSO-d_6) δ = 2.72 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 2.89 (s, 3H, CH_3), 4.58 (s, 1H, CH), 6.79 (s, 1H, Pyr-H), 7.1-8.13 (m, 5H), 10.31 (s, 1H, NH), 10.6 (s, 1H, NH) - MS, *m/z* (%) 438 (M^+, 1.4), 404 (2.3), 345 (15), 263 (17), 93 (100) - $C_{21}H_{18}N_4O_3S_2$ (438): calcd. C, 57.52; H, 4.14; N, 12.78; S, 14.62; Found: C, 57.41; H, 4.03; N, 12.47; S, 14.49.

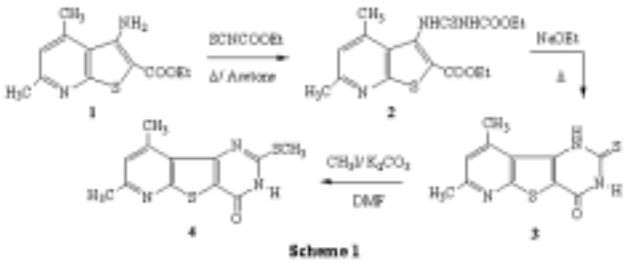
Alternate synthesis of 8b, 8g, and 8l

To a solution of the appropriate **11a-c** (10 mmol) in ethanol (40 mL) was added sodium acetate trihydrate (1.36 g, 10 mmol) and the mixture was cooled to 0-5 °C in an ice bath. To the resulting cold solution was added portionwise a cold solution of benzenediazonium chloride [prepared by treatment of aniline (0.93 g, 10 mmol) dissolved in hydrochloric acid (6 M, 6 mL) with a solution of sodium nitrite (0.7 g, 10 mmol) in water (10 mL)]. After complete addition of the diazonium salt, the reaction mixture was stirred for further 30 min in an ice bath. The solid precipitated was filtered off, washed with water, dried and recrystallized from DMF to give the corresponding products, **8b, 8g** and **8l** which were identical in all respects (mp, mixed mp and IR spectra) with those obtained from reaction of **3** with **5b, 5g** and **5l,** respectively.

Results and Discussion

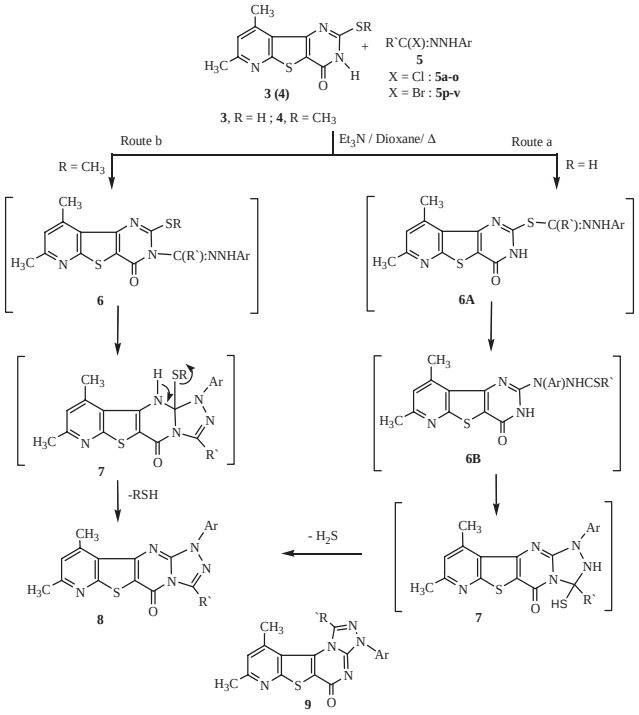
The starting compound namely 2,3-dihydro-7,9-dimethyl-2-thioxo-pyrido [3‘,2‘:4,5] thieno[3,2-d]pyrimidin-4(1H)-one **3** was prepared by adopting a procedure reported recently [19] as depicted in Scheme 1. Thus, reaction of ethyl 3-amino-4,6-dimethyl-thieno[2,3-b]pyridine-2-carboxylate **1** [17] with ethoxycarbonyl isothiocyanate in acetone under reflux in water bath afforded the compound **2**. Treatment of the latter with ethanolic solution of sodium ethoxide under reflux followed by acidification led to formation of the starting material **3**. The physical constants and the spectral data (mass, IR, ^1H NMR) of compound **3** were found to be identical with that reported for the same compound which was prepared by another method [18]. For example, the IR spectrum revealed the 2 NH and CO bands in the regions 3360,

3220 and 1680 cm^{-1}, respectively. The ^1H NMR spectrum of **3** exhibited, in addition to the aromatic proton, two characteristic signals at *d* 2.50-2.86, 9.11-11.00 assignable to CH_3 and NH protons, respectively. Methylation of the latter **3** with methyl iodide in DMF in the presence of anhydrous potassium carbonate afforded the corresponding 2-methylthio derivative **4**. The ^1H NMR spectrum of **4** displayed the signals of Ar-CH_3, S-CH_3 and NH at *d* 2.49-2.86, 3.11 and 11.08, respectively.



Scheme 1

Reaction of **3** with hydrazonoyl halides **5** in dioxane in presence of triethylamine under reflux was found to give one isolable product that was identified as tetraheterocyclic system, namely, pyrido [3‘,2‘:4,5] thieno [3,2-d] [1,2,4] triazolo [4,5-a] pyrimidin-5-one **8** rather than its isomeric structure pyrido [3‘,2‘:4,5] thieno [3,2-d] [1,2,4]triazolo[5,4-b]pyrimidin-5-one **9** (Scheme 2) [20].

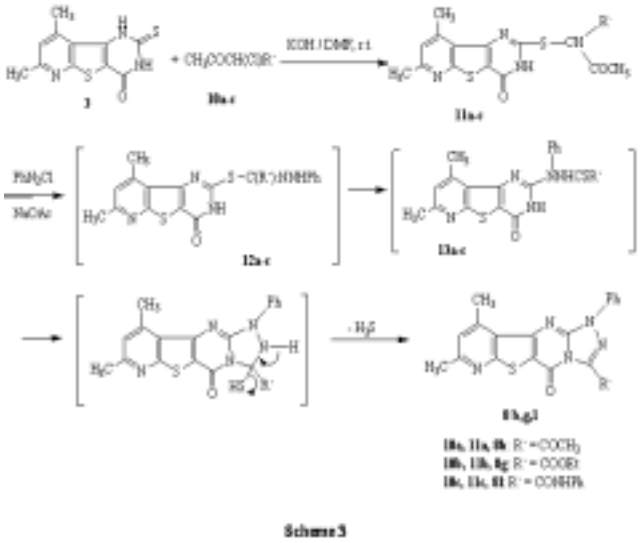


Ar = ZC_6H_4					
R’/Z	*Compd No.*	*R’/Z*	*Compd No.*	*R’/Z*	*Compd*
Ph/H	8a	COOEt/4-CH_3	8h	COPh/H	8o
$COCH_3$/H	8b	COOEt/3-Cl	8i	COPh/4-CH_3	8p
$COCH_3$/4-CH_3	8c	COOEt/4-Cl	8j	COPh/3-Cl	8q
$COCH_3$/4-Cl	8d	COOEt/4-NO_2	8k	COPh/4-Cl	8r
$COCH_3$/4-OCH_3	8c	CONHPh/H	8l	COPh/4-OCH_3	8s
$COCH_3$/4-NO_2	8f	CONHPh/4-CH_3	8m	COPh/4-NO_2	8t
COOEt/H	8g	CONHPh/4-Cl	8n	2-Furoy1/4-Cl	8u
				2-Theory1/4-Cl	8v

Scheme 2

The direct formation of products **8** from the reaction of compound **3** with hydrazonoyl halides **5** indicates that the intermediate thiohydrazonate esters **6A** underwent Smiles rearrangement [21] to give the corresponding thiohydrazides **6B**, which *in situ* underwent cyclization with concurrent elimination of hydrogen sulfide to give **8** as end products (Route a, Scheme 2). All attempts to isolate the intermediates **6A** and **6B** were failed since they were consumed as soon as they were formed under the employed reaction conditions. The formation of **6A** from reaction of **3** with **5** (Route a, Scheme 2) is analogous to S-alkylation reactions reported for 2-thioxopyrimidines [22]. Alternatively, the formation of **8** from 2-methylthio derivative **4** and hydrazonoyl halides **5** can be accomplished *via* cyclization of the intermediate amidrazone **6** with concurrent elimination of methanethiol to give **8** as end products (Route b, Scheme 2). To account for these transformations (Routes a,b, Scheme 2), an alternative way of synthesis of the products **8** was thought. The synthesis that employed in the present work for the preparation of the latter compounds is based on application of Japp-Klingemann reaction [23] and Smiles rearrangement [21]. Thus, treatment of **3** with each of active chloromethylene compounds **10a-c** in KOH/DMF at room temperature yielded the S-alkylation products **11a-c** respectively [22]. The structure of the latter products was evidenced by its microanalysis and spectral data (mass, IR, ^{1}HNMR). The ^{1}HNMR data showed singlet signals near d = 2.72 and 4.4 ppm assignable to the CH_3CO and S-(CH)-R protons in addition to the characteristic signals of $COCH_3$, COOEt and CONHPh groups in the compounds **11a-c**, respectively (Scheme 3).

Treatment of **11a-c** with benzenediazonium chloride in ethanol in presence of sodium acetate at low temperature (0-5°C) yielded the corresponding thiohydrazonate esters **12a-c** via Japp-Klingemann cleavage of the acetyl group [23]. The latter **12a-c**



Scheme 3

underwent *in situ* Smiles rearrangement [21] to give the products **13a-c** and then cyclization of the latter accompanied by elimination of hydrogen sulfide gave products identical in all respect (mp, mixed mp, IR), with that obtained from reactions of each of compounds **3** and **4** with hydrazonoyl halides **5**.

Antimicrobial Activity

The compounds **8d, 8f-h, 8k** and **8o** were tested for their antimicrobial activities using four fungi species namely *Aspergillus fumigatus* **AF**, *Penicillium italicum* **PI**, *Syncephalastrum racemosum* **SR** and *Candida albicans* **CA**. Also, four bacteria species namely, *Staphylococcus aureus* **SA**, *Pseudomonas aeruginosa* **PA**, *Bacillus subtilis* **BS** and *Escherichia coli* **EC** were tested. The organisms were tested against the activity of solutions of concentration of 5 mg/mL of each compound and using inhibition zone diameter in cm (IZD) as criterion for the antimicrobial activity. The fungicide *Terbinafin* and the bactericide *Chloramphenicol* were used as references to evaluate the potency of the tested compounds under the same conditions. The results are depicted in Table 1.

The results disclosed that compounds **8h** and **8k** exhibited moderate inhibition against **AF**, while compounds **8f** and **8o** have high inhibition effect against **EC**. All the tested compounds have little inhibition effect against **CA** and **PA**. The biological activities of the other compounds against the tested organisms are weak, however, the activities of the tested compounds are less than that of standard antifungal and antibacterial agents used.

Table 1
Antimicrobial Activity of Products[a] 8d, 8f-h, 8k and 8o, Micro-Organism/IZD (cm)*

Compound No.	*AF*	*Pl*	*SR*	*CA*	*SA*	*PA*	*BS*	*EC*
8d	++	+	+	+	0	+	0	+
8f	0	0	0	+	+	+	0	++
8g	0	+	0	+	+	+	0	0
8h	++	+	+	+	+	+	+	+
8k	++	0	+	+	0	+	+	0
8o	+	+	+	+	0	+	+	++
CA[b]					1.0	2.8	2.6	1.0
TE[c]	3.0	3.6	3.6	3.0				

a; The concentration of solution 5.0 mg/ml was tested.
[b],Cholramphenicol; [c],Terbinafin.
*IZD beyond control/(sign): 1.1-1.5 cm/(+++); 0.6-1.0 cm/(++); 0.1-0.5 cm/(+); 0 cm/(-)
AF; Aspergillus fumigatus **PI;** Penicillium italicum, **SR;** Syncephalastrum racemosum, **CA;** Candida albicans **SA;** Staphylococcus aureus **PA**; Pseudomonas aeruginosa, **BS;** Bacillus subtilis, **EC;** Escherichia coli

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