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Synthesis, Spectral Analysis and Pharmacological Evalutionof Pyrido Thieno Triazolo Pyrimidin

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ABSTRACT

The were two possible 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 .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 hydrazonoylhalides 5 in dioxane under reflux in presence of triethylamine has been done by first method . The alternative route proceeded via reaction of 3with the appropriate activechloromethylene compounds followed by coupling the products with benzenediazoniumchloride which afforded the azo coupling products and then was converted in situ to 8. The reaction mechanism was evaluated and the products were investigated for their pharmacology activity.

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

Introduction

Nowadays , the thienopyrimidines are getting particular interest for the synthesis of some non-steroidal anti-inflammatory drugs (NSAIDs) [1]. Also, they have been

Identified as potent inhibitors of VEGFR-2 kinase [2].Moreover, condensed heterocycles containingthienopyrimidines have acquired great popularity

in recent years because of their wide variety of spectrum Pharmacologicalactivities including analgesic, anticonvulsant andantimicrobial agents [3]. On the other hand, fused triazolesare proved to have diverse applications as antibacterial-,antidepressent-, antiviral-, antitumorial agents [4,5]. Thisreaction get inspired us to synthesize new heterocyclic systemnamely pyrido [3´,2´:4,5]thieno[3,2-d][1,2,4]triazolo[5,4-a] pyrimidin-5-ones 8, .These compounds were studied in continuation of ourprevious work on the synthesis of bridgehead nitrogenpolyheterocycles [6-10].

Experimental

Melting points were recorded on Gallenkampelectrothermal apparatus and are uncorrected. Infraredspectra (KBr) were determined on a PyeUnicam SP-3000 infraredpectrophotometer. 1H NMR was determined on a Varian Gemini 300 spectrometer (300 MHz) in DMSO-d6 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 .Hydrazonoyl halides 5 [11-16] were prepared by literature methods. The biological evaluation of the products wascarried out at the Regional Center for Mycology andBiotechnology at Cmj University, Modrina Mansion LaitumkhrahShillongMeghalaya.

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

A solution of ethoxycarbonylisothiocyanate [preparedby 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 toa 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 refluxin a water bath for 2 hours, and then evaporated undervacuum. The remaining product was triturated with ethanol, then collected by filtration, dried andrecrystallized from ethanol as yellow crystals of2 Mp 268 °C; yield 70% - IR 3406, 3384 (2NH), 1689,1672 (2CO) cm-1 - 1 H NMR d (DMSO-d6) 1.30 (t, 3H),1.32 (t, 3H), 4.12 (q, 2H), 4.29 (q, 2H), 2.54 (s, 3H, CH3),2.82 (s, 3H, CH3), 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)-C16H19N3O4S2(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 asolution 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 30minutes. The solvent was evaporated in vacuum, somewater was added to the residue, and the mixture was acidified to pH = 4 with hydrochloric acid. The productwhich separated was collected and recrystallized fromdioxane as white crystals of 3. Mp 312 °C [Lit. mp>300] [18], yield 70% - IR 3220, 3360 (2NH), 1680 (CO)cm-1 - 1H NMR □ (DMSO-d6) 2.50 (s, 3H, CH3), 2.84 (s,3H, CH3), 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) - C11H9N3OS2 (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 K2CO3 (2.07 g, 15 mmol), was added methyliodide (1.42 g, 10 mmol). The reaction mixture was stirredat room temperature for one hour then poured into icewater.The solid formed was filtered, washed with water, dried and recrystallized from DMF to give white crystalsof 4. Mp 287 °C; yield 78% - IR 3332 (NH), 1666(CO) cm-1 - 1H NMR ™ (DMSO-d6) 2.49 (s, 3H, CH3), 2.86 (s, 3H, CH3), 3.11 (s, 3H, SCH3), 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) -C12H11N3OS2 (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-v .

Method 1: 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 thepresence of triethylamine (1.4 mL, 10 mmole), was added the apropriatehydrazonoyl

halides 5 (10 mmol). Thereaction mixture was refluxed for 6-10 h until all thestarting materials have been disappeared (monitored byTLC) and hydrogen sulfide gas ceased to liberate. Thesolvent was evaporated and the residue was triturated withmethanol. The solid that formed was filtered andrecrystallized from DMF to give compounds 8.

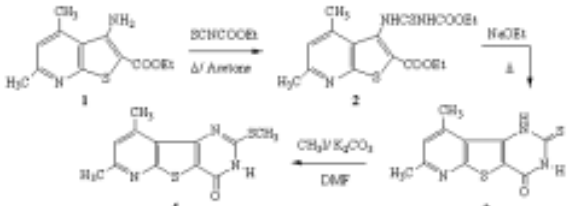
Method 2: To a solution of 7,9-dimethyl-2-methylthiopyrido[3´,2´:4,5] thieno [3,2-d] pyrimidin-4(3H)-one 4 (2.77 g, 10 mmol) in dioxane (50 mL) in thepresence of triethylamine (1.4 mL, 10 mmole), was addedthe appropriate hydrazonoyl halides 5 (10 mmol). Thereaction mixture was refluxed for 6-10 h and worked up as usual to give the products which were found to beidentical in all respects (mp. mixed mp. and IR) withproducts 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) 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 1701 (CO) cm-1 - 1H NMR (DMSO-d6) ™ = 2.55 (s, 3H, CH3), 2.93 (s, 3H, CH3),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) -C24H17N5OS (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] hieno[3,2-d][1,2,4] triazolo[5,4-a] pyrimidin-5-one (8b)Mp 238 °C; yield 72% - IR 1724, 1690 (2CO) cm-1 - 1HNMR (DMSO-d6) ™ = 2.53(s, 3H, CH3), 2.78 (s, 3H, CH3), 2.84 (s, 3H, COCH3), 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)-C20H15N5O2S (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 1701, 1666 (2CO) cm-1 - 1HNMR (DMSO-d6) ™ = 2.38 (s, 3H, CH3), 2.52 (s, 3H,CH3), 2.77 (s, 3H, CH3), 2.83 (s, 3H, COCH3), 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)-C21H17N5O2S (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 1705, 1662 (2CO) cm-1 - 1HNMR (DMSO-d6) ™ = 2.57 (s, 3H, CH3), 2.78 (s, 3H,CH3), 2.88 (s, 3H, COCH3), 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) -C20H14ClN5O2S (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 1744, 1694 (2CO) cm-1 - 1HNMR (DMSO-d6) ™ = 2.52 (s, 3H, CH3), 2.78 (s, 3H,CH3), 2.86 (s, 3H, COCH3), 3.56 (s, 3H, OCH3), 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) - C21H17N5O3S(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% Mp 207 °C; yield 74% - IR 1735, 1666 (2CO)cm-1 - 1H NMR (DMSO-d6) □ = 2.58 (s, 3H, CH3), 2.71(s, 3H, CH3), 2.82 (s, 3H, CH3), 7.24 (s, 1H, Pyr-H), 7.72 (d, 2H, CH2), 8.5 (d, 2H) - MS, m/z (%) 435 (M++1, 15),434 (M+---, 36), 263 (100), 205(61), 131 (21) -C20H14N6O4S (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]ieno[3,2] [1,2,4]triazolo[5,4-a]pyrimidin-3-carboxylate (8g) Mp 228 °C; yield 72%-IR 1751, 1705 (2CO)cm-1 - 1H NMR (DMSO-d6) ™ = 1.45 (t, 3H, CH3), 2.56 (s,3H, CH3), 2.84 (s, 3H, CH3), 4.55 (q, 2H, CH2), 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) -C21H17N5O3S (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-á]pyrimidin-3-carboxylate (8h) Mp 260 °C; yield 71% - IR 1755, 1701 (2CO)cm-1 - 1H NMR (DMSO-d6) ™ = 1.42 (t, 3H, CH3), 2.38 (s, 3H, CH3), 2.53 (s, 3H, CH3), 2.83 (s, 3H, CH3), 4.54 (q, 2H, CH2), 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)-C22H19N5O3S (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 1761, 1705 (2CO)cm-1 - 1H NMR (DMSO-d6) ™ = 1.40 (t, 3H, CH3), 2.58(s, 3H, CH3), 2.82 (s, 3H, CH3), 4.56 (q, 2H, CH2), 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) - C21H16ClN5O3S(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 1751, 1705 (2CO)cm-1 - 1H NMR (DMSO-d6) ™ = 1.41 (t, 3H, CH3), 2.59(s, 3H, CH3), 2.81 (s, 3H, CH3), 4.56 (q, 2H, CH2), 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)-C21H16ClN5O3S (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 1751, 1705 (2CO)cm-1 - 1H NMR (DMSO-d6) ™ = 1.41 (t, 3H, CH3), 2.54(s, 3H, CH3), 2.85 (s, 3H, CH3), 4.55 (q, 2H, CH2), 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)-C21H16N6O5S (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 3437 (NH), 1674, 1627(2CO) cm-1 - 1H NMR (DMSO-d6) ™ = 2.61 (s, 3H, CH3),2.86 (s, 3H, CH3), 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) -C25H18N6O2S (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 , 1 0 - D i m e t h y l - 1 - (4 - m e t h y l p h e n y l) - 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 3406 (NH), 1674, 1627(2CO) cm-1 - 1H NMR (DMSO-d6) ™ = 2.39 (s, 3H, CH3),2.56 (s, 3H, CH3), 2.91 (s, 3H, CH3), 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) - C26H20N6O2S (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 - C h l o r o p h e n y l) - 8 , 1 0 - d i m e t h y l - 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 3236 (NH), 1674, 1662(2CO) cm-1 - 1H NMR (DMSO-d6) ™ = 2.61 (s, 3H, CH3),2.92 (s, 3H, CH3), 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) -C25H17ClN6O2S (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 1742, 1674 (2CO)cm-1 - 1H NMR (DMSO-d6) ™ = 2.71 (s, 3H, CH3), 2.84(s, 3H, CH3), 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)-C25H17N5O2S (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 1740, 1681 (2CO)cm-1 - 1H NMR (DMSO-d6) □ = 2.36 (s, 3H, CH3), 2.71(s, 3H, CH3), 2.84 (s, 3H, CH3), 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) - C26H19N5O2S(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 1739, 1693 (2CO)cm-1 - 1H NMR (DMSO-d6) □ =

2.61 (s, 3H, CH3), 2.53(s, 3H, CH3), 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) - C25H16ClN5O2S (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 1742, 1690 (2CO)cm-1 - 1H NMR (DMSO-d6) ™ = 2.60 (s, 3H, CH3), 2.54(s, 3H, CH3), 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) - C25H16ClN5O2S(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 1746, 1666 (2CO)cm-1 - 1H NMR (DMSO-d6) ™ = 2.73 (s, 3H, CH3), 2.82(s, 3H, CH3), 3.62 (s, 3H, CH3), 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) - C26H19N5O3S(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 1739, 1678 (2CO)cm-1 - 1H NMR (DMSO-d6) ™ = 2.53 (s, 3H, CH3), 2.88(s, 3H, CH3), 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)-C25H16N6O4S (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 1705, 1664 (2CO)cm-1 - 1H NMR (DMSO-d6) ™ = 2.53 (s, 3H, CH3), 2.82(s, 3H, CH3), 7.14 (s, 1H, Pyr-H), 6.40-7.75 (m, 7H, Ar - H) - MS, m/z (%) 475 (M+, 23), 11 (100), 104 (28) -C23H14ClN5O3S (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. 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 1742, 1690 (2CO)cm-1 - 1H NMR (DMSO-d6) ™ = 2.60 (s, 3H, CH3), 2.54(s, 3H, CH3), 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) - C25H16ClN5O2S(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 1746, 1666 (2CO)cm-1 - 1H NMR (DMSO-d6) ™ = 2.73 (s, 3H, CH3), 2.82(s, 3H, CH3), 3.62 (s, 3H, CH3), 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) - C26H19N5O3S(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 1739, 1678 (2CO)cm-1 - 1H NMR (DMSO-d6) ™ = 2.53 (s, 3H, CH3), 2.88(s, 3H, CH3), 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)-C25H16N6O4S (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 1705, 1664 (2CO)cm-1 - 1H NMR (DMSO-d6) ™ = 2.53 (s, 3H, CH3), 2.82(s, 3H, CH3), 7.14 (s, 1H, Pyr-H), 6.40-7.75 (m, 7H, Ar - H) - MS, m/z (%) 475 (M+, 23), 11 (100), 104 (28) -C23H14ClN5O3S (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 1705, 1651 (2CO)cm-1 - 1H NMR (DMSO-d6) ™ = 2.56 (s, 3H, CH3), 2.88(s, 3H, CH3), 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)-C23H14ClN5O2S2 (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.

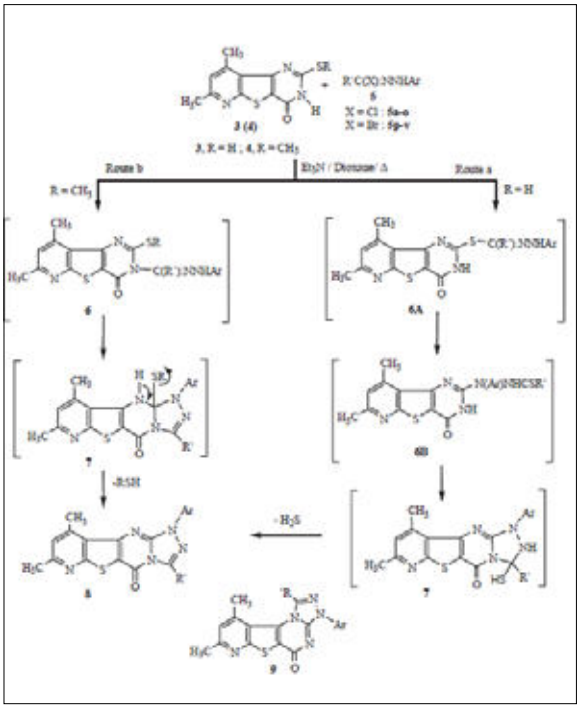
Synthesis of 11a-c General procedure:To a solution of 3 (2.63 g, 10 mmol)in ethanol (20 mL) was added an aqueous solution ofpotassium hydroxide (1 mL, 75%) and the mixture waswarmed for 10 min. in a water bath at 80 °C then addedthe appropriate chloromethylene compounds 10a-c (10mmol) dropwise while 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 fromDMF to give pure 11a-c with the following physical andspectral 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 3224 (NH), 1742 (2CO)cm-1 - 1H NMR (DMSO-d6) ™ = 2.11 (s, 6H, 2 COCH3),2.54 (s, 3H, CH3), 2.76 (s, 3H, CH3), 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) - C16H15N3O3S2 (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. Ethyl2-[(2,3-dihydro-7,9-dimethyl-4-oxopyrido[3´,2´:4,5] thieno[3,2-d]pyrmidin-2-yl) thio]-3-oxobutanoate(11b)Mp 180 °C; yield 72% - IR 3128 (NH), 1740, 1674(2CO) cm-1 - 1H NMR (DMSO-d6) ™ =1.42 (t, 3H, CH3),2.53 (s, 3H, CH3), 2.76 (s, 3H, CH3), 4.10 (q, 2H, CH2),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) - C17H17N3O4S2 (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 3425, 3294 (2NH), 1738,1654 (2CO) cm-1 - 1H NMR (DMSO-d6) ™ = 2.72 (s, 3H,CH3), 2.81 (s, 3H, CH3), 2.89 (s, 3H, CH3), 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) - C21H18N4O3S2 (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.

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 reportedrecently [19] as depicted in Scheme 1. Thus, reaction ofethyl 3-amino-4,6-dimethyl-thieno[2,3-b]pyridine-2-carboxylate 1 [17] with ethoxycarbonylisothiocyanatein acetone under reflux in water bath afforded thecompound 2. Treatment of the latter with ethanolicsolution of sodium ethoxide under reflux followed byacidification 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 withthat reported for the same compound which was preparedby another method [18]. For example, the IR spectrumrevealed the 2 NH and CO bands in the regions 3360,3220 and 1680 cm-1, respectively. The 1H NMR spectrumof 3 exhibited, in addition to the aromatic proton, twocharacteristic signals at d 2.50-2.86, 9.11-11.00 assignableto CH3 and NH protons, respectively. Methylation of thelatter 3 with methyl iodide in DMF in the presence ofanhydrous potassium carbonate afforded thecorresponding 2-methylthio derivative 4. The 1H NMRspectrum of 4 displayed the signals of Ar-CH3, S-CH3and NH at d 2.49-2.86, 3.11 and 11.08, respectively.



Reaction of 3 with hydrazonoyl halides 5 in dioxanein presence of triethylamine under reflux was found togive 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 ratherthan 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	8e	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

The direct formation of products 8 from the reactionof compound 3 withhydrazonoyl halides 5 indicates thatthe intermediate thiohydrazonate esters 6A underwentSmiles rearrangement [21] to give the correspondingthiohydrazides6B, which in situ underwent cyclizationwith concurrent elimination of hydrogen sulfide to give8 as end products (Route a, Scheme 2). All attempts toisolate the intermediates 6A and 6B were failed since theywere consumed as soon as they were formed under theemployed reaction conditions. The formation of 6A from reaction of 3 with 5 (Route a, Scheme 2) is analogous toS-alkylation reactions reported for2-thioxopyrimidines [22]. Alternatively, the formation of8 from 2-methylthio derivative 4 and hydrazonoyl halides5 can be accomplished via cyclization of the intermediateamidrazone6 with concurrent elimination of methanethiolto give 8 as end products (Route b, Scheme 2). To account for these transformations (Routes a,b, Scheme 2), analternative way of synthesis of the products 8 was thought. The synthesis that employed in the present work for thepreparation of the latter compounds is based onapplication of Japp-Klingemann reaction [23] and Smilesrearrangement [21]. Thus, treatment of 3 with each ofactive chloromethylene compounds 10a-c in KOH/DMF at room temperature yielded the S-alkylation products11a-c respectively [22]. The structure of the latterproducts was evidenced by its microanalysis and spectral data (mass, IR, 1HNMR). The 1HNMR data showedsinglet signals near d = 2.72 and 4.4 ppm assignable tothe CH3CO and S-(CH)-R protons in addition to thecharacteristic signals of COCH3, COOEt and CONHPhgroups in the compounds 11a-c, respectively (Scheme3).Treatment of 11a-c with benzenediazonium chloridein ethanol in presence of sodium acetate at lowtemperature (0-5°C) yielded the correspondingthiohydrazonate esters 12a-c via Japp-Klingemann cleavage of the acetyl group [23]. The latter 12a-cunderwent in situ Smiles rearrangement [21] to give theproducts 13a-c and then cyclization of the latter accompanied by elimination of hydrogen sulfide gaveproducts identical in all respect (mp, mixed mp, IR), withthat obtained from reactions of each of compounds 3 and4 with hydrazonoyl halides 5. Pharmacological Evalution The compounds 8d, 8f-h, 8k and 8o were tested fortheir antimicrobial activities using four fungi speciesnamely AspergillusfumigatusAF, Penicilliumitalicum PI, SyncephalastrumracemosumSR and CandidaalbicansCA. Also, four bacteria species namely,Staphylococcus aureusSA, Pseudomonas aeruginosa PA, Bacillus subtilisBS and Escherichia coli EC weretested. The organisms were tested against the activity ofsolutions of concentration of 5 mg/mL of each compoundand using inhibition zone diameter in cm (IZD) ascriterion for the antimicrobial activity. The fungicideTerbinafinand the bactericide Chloramphenicol wereused as references to evaluate the potency of the tested compounds under the same conditions. The results aredepicted in Table 1. The results disclosed that compounds 8h and 8kexhibited moderate inhibition against AF, whilecompounds 8f and 8o have high inhibition effect against EC. All the tested compounds have little inhibition effectagainst CA and PA. The biological activities of the othercompounds against the tested organisms are weak, however, the activities of the tested compounds are lessthan that of standard antifungal and antibacterial agentsused.

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

Compound No.	AF	PI	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; AspergillusfumigatusPI; Penicilliumitalicum, SR; Syncephalastrumracemosum, CA; Candida albicansSA; StaphylococcusaureusPA; Pseudomonas aeruginosa, BS; Bacillus subtilis, EC; Escherichia coli

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