Fused thieno[2,3-b]pyridines: synthesis and characterization of new condensed pyridothienopyrimidines

Etify A. Bakhite, Ahmed Abdou O. Abeed,* and Ola E. A. Ahmed

Department of Chemistry, Faculty of Science, University of Assiut, Assiut 71516, Egypt.
E-mail: ahmed.abdelrahman1@science.au.edu.eg

Received 12-16-2016 Accepted 03-05-2017 Published on line 05-14-2017

Abstract

Reaction of cyanopyridine-2(1H)-thiones 2a,b with chloroacetonitrile gave the corresponding 3-aminothieno[2,3-b]pyridine-2-carbonitriles 4a,b. Condensation of 4a,b with triethyl orthoformate produced the methanimidate derivatives 6a,b which upon treatment with hydrazine hydrate resulted in the formation of 3-amino-4-imino[3',2':4,5]thieno[3,2-d]pyrimidines 7a,b. Aminothieno[2,3-b]pyridine-2-carboxamide 5 was prepared and reacted with triethyl orthoformate to give pyrimidine-4(3H)-one derivative 14. Chlorination of 14 with phosphorus oxychloride gave 4-chloropyrimidine 15, which in turn was reacted with hydrazine hydrate to produce 4-hydrazinopyrimido[3',2':4,5]thieno[3,2-d]pyrimidine 17. Compounds 7a,b and 17 were used as precursors for synthesizing other new pyridothienopyrimidines as well as triazolopyrido-thienopyrimidines, and pyridothienopyrimidotriazinoindoles. Structural formulas of all newly synthesized compounds were confirmed by elemental and spectral (IR, NMR, and mass) analyses.
Keywords: Thienopyridines, thienopyrimidines, pyridothienopyrimidines, triazolopyridothienopyrimidines, pyridothienopyrimidotriazinoindoles

Introduction

Many thieno[2,3-b]pyridines have been synthesized and investigated in relation to their biological and pharmacological importance.\textsuperscript{1,2} Some of them proved to possess antiviral,\textsuperscript{3,4} anti-diabetic,\textsuperscript{5} antimicrobial,\textsuperscript{6,7} anti-inflammatory,\textsuperscript{8} antitumor,\textsuperscript{9} antiparasitic\textsuperscript{10} and neurotropic activities.\textsuperscript{11} Also, thienopyrimidine derivatives have been the subject of several chemical and biological studies on account of their wide spectrum of biological activity.\textsuperscript{12,13} Furthermore, some pyrido[3',2':4,5]thieno[3,2-d]pyrimidines are reported to exhibit antimicrobial,\textsuperscript{6,7} antiallergic,\textsuperscript{14} antiprotozoal\textsuperscript{15} and anti-anaphylactic activities.\textsuperscript{16,17} In view of the above observations and as a continuation of our previous work on pyridothienopyrimidines,\textsuperscript{18-20} we describe herein the synthesis and characterization of the title compounds which are expected to be biologically active ones owing to the incorporation of different pharmacophores.

Results and Discussion

The broad synthetic utility reported for several 3-cyano-pyridine-2(1H)-thiones as starting materials of many heterocyclic systems, especially thieno[2,3-b]pyridines, prompted us to use 4-aryl-3-cyano-5-ethoxycarbonyl-6-methylpyridine-2(1H)-thiones 2a,b as starting compounds in this investigation. These compounds 2a,b were prepared by the reaction of arylidenecyanothioacetamides 1a,b with ethyl acetoacetate in the presence of piperidine as a basic catalyst, according to the reported methods.\textsuperscript{21} Reaction of 4-aryl-3-cyano-5-ethoxycarbonyl-6-methylpyridine-2(1H)-thiones 2a,b with chloroacetonitrile, by refluxing in ethanol in the presence of sodium acetate, gave the corresponding 3-aminothieno[2,3-b]pyridine-2-carbonitriles 4a,b rather than the expected 2-(cyanomethylthio) pyridines 3a,b. The latter compounds 3a,b were carefully obtained by reacting 2a,b with chloroacetonitrile at room temperature. On heating compounds 3a,b in ethanol containing sodium acetate, they underwent intramolecular Thorpe-Ziegler cyclization forming the corresponding thienopyridines 4a,b. In contrast, 3-amino-4-(4-methoxyphenyl)-5-ethoxycarbonyl-6-methylthieno[2,3-b]pyridine-2-carboxamide 5 was prepared by reacting compounds 2a with chloroacetamide in ethanol containing a slightly excess amount of sodium ethoxide according to our reported method\textsuperscript{21} (Scheme 1).

The condensation of o-aminocarbonitriles 4a,b with triethyl orthoformate by refluxing in acetic anhydride produced the methanimidate derivatives 6a,b. Treatment of compounds 6a,b with hydrazine hydrate in dioxane at room temperature resulted in the formation of ethyl 3-amino-9-aryl-3,4-dihydro-4-imino-7-methylpyrido[3',2':4,5]thieno[3,2-d]pyrimidine-8-carboxylates 7a,b in good yields. Compounds 7a,b, having the aminonime structure, were utilized as new precursors for synthesizing novel fused heterocyclic compounds containing pyrido-thienopyrimidine moiety. Thus, refluxing compounds 7a,b with an excess amount of triethyl orthoformate, under neat condition furnished ethyl 7-aryl-9-methyl[1,2,4]triazolo[2'',3''-c]-pyrido[3',2':4,5]thieno[2,3-e]pyrimidine-8-carboxylates 8a,b. On the other hand, the 2-methyl analogs 9a,b were prepared by reacting compounds 7a,b with acetic anhydride at reflux temperature. Heating compounds 7a,b with phenyl iso-thiocyanate in dry pyridine for a long time led to the formation of anilinotriazolopyridothienopyrimidines 10a,b. When compounds 7a,b were allowed to react with isatin, a cyclocondensation reaction occurred and the fused hexacyclic compounds 11a,b were obtained in good yields (Scheme 2).
On treatment of compound 7a with phenacyl bromide in boiling ethanol containing an equimolar amount of sodium acetate, the product was identified as 2H-pyrido[3″,2″:4′,5′]thieno[3′,2′:4,5]pyrimido[1,6-b][1,2,4]triazine 12 rather than the related isomer 13 (Scheme 3).

Scheme 1. Reagents and conditions: (i) Ethyl acetoacetate, piperidine, EtOH, 6 h; (ii) Chloroacetonitrile, AcONa, EtOH, stir. 3 h; (iii) Chloroacetonitrile, AcONa, EtOH, 3 h; (iv) Sodium acetate, EtOH, 3 h; (v) Chloroacetamide, EtONa, EtOH, 3 h.

This assignment based on the spectral data of this product. Thus, its IR spectrum revealed the absence of any band attributed to ν NH and its 1H NMR spectrum confirmed the presence of a characteristic signal corresponding to CH₂ group in the triazine ring. Refluxing o-aminocarboxamide 5 with triethyl orthoformate in acetic anhydride led to the formation of ethyl 9-(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate 14.
Scheme 2. Reagents and conditions: (i) Triethyl orthoformate, Ac₂O, 2 h; (ii) Hydrazine hydrate, dioxane, stir. 4 h; (iii) Triethyl orthoformate, 3 h; (iv) Acetic anhydride, 2 h; (v) Phenyl iso-thiocyanate, steam bath 8 h; (vi) Isatin, EtOH, 3 h.

Chlorination of 14, by heating with an excess amount of phosphorus oxychloride, produced ethyl 4-chloro-9-(4-methoxyphenyl)-7-methylpyrido[3',2':4,5]thieno[3,2-d]pyrimidine-8-carboxylate (15) in a good yield. The latter compound underwent a nucleophilic substitution reaction upon treatment with thiourea to give pyrimidine-2(1H)-thione 16. Also, the reaction of 15 with hydrazine hydrate gave 4-hydrazinopyrimidine derivative 17 (Scheme 4).

The compound 17 was also served as a facile point to departure to other pyridothieno-pyrimidine derivatives. Thus, its condensation with 4-chlorobenzaldehyde gave 4-(4-chlorobenzylidene) hydrazinopyrimidine derivative 18. Similarly, the hydrazone 19 was obtained by reacting compound 17 with acetophenone (Scheme 7). Heating compound 17 with acetylacetone at reflux temperature produced the dimethylpyrazole derivative 20. Treatment of compound 17 with ethyl (ethoxymethylene)cyanoacetate led to the formation of ethyl 4-(3'-amino-4'-ethoxycarbonylpyrazol-2'-yl)-7-methyl-9-(4-methoxyphenyl)pyrido[3',2':4,5]thieno[3,2-d]-pyrimidine-8-carboxylate (21) (Scheme 5).
Scheme 3. Reagent and condition: (i) Phenacyl bromide, AcONa, EtOH, 3 h.

Heating hydrazino compound 17 in formic acid for a long time resulted in the formation of triazolo derivative 8a rather than the expected isomer 23 (Scheme 6). From the thermodynamic point of view, the compound 8a seems to be more stable than the corresponding isomer 23. The pathway of the latter reaction may be involving firstly the usual formation of compound 23 via the intermediacy of acid hydrazide 22. Under the applied reaction conditions, compound 23 underwent spontaneously Dimroth in situ to give the most stable isomer 8a. The triazole intermediate 23 was successfully prepared by heating hydrazino compound 17 with triethyl orthoformate, under the neat condition, at reflux temperature (Scheme 6). Beside elemental and spectral analyses, the above structure 8a was further confirmed by comparison with authentic sample (m. p., mixed mp and TLC) previously prepared in this paper.
Scheme 4. Reagents and conditions: (i) Triethyl orthoformate, Ac₂O, 4 h; (ii) Phosphorus oxychloride, dioxane, steam bath 3 h; (iii) Thiourea, EtOH, 6 h; (iv) Hydrazine hydrate, EtOH, 2 h.

Scheme 5. Reagents and conditions: (i) 4-Chlorobenzaldehyde, AcOH, EtOH, 4 h; (ii) Acetophenone, AcOH, EtOH, 4 h; (iii) Acetyl acetone, 4 h; (iv) Ethyl (ethoxymethylene) cyanoacetate, EtOH, 4 h.
Scheme 6. Reagents and conditions: (i) Formic acid, 3 h; (ii) Triethyl orthoformate, 4 h.

Scheme 7. The mechanism of the Dimroth rearrangement for triazole derivative 23.

The mechanism of the Dimroth rearrangement \(^{23}\) under investigation is given in scheme 7. This rearrangement is promoted here by aqueous acid (Formic acid 85%). It involves initially covalent hydration of 23. The hydroxy group enters position 5, then the pyrimidine ring opens and forms the carbonyl intermediate A; the CO group then attacks the most nucleophilic N-2 of the triazole ring and cyclizes to give the rearranged triazolopyrimidine \(8a\).
Experimental Section

General. Starting materials were obtained from commercial suppliers and used without further purification. All melting points were determined on a Gallenkamp apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer (KBr; \( \nu_{\text{max}} \) in cm\(^{-1} \)). The NMR spectra were taken on a Varian EM-390, 90 MHz spectrometer or on a JEOL LA 400 MHz FT-NMR spectrometer using TMS as an internal standard. Chemical shifts are given in \( \delta \) ppm and coupling constant \( (J) \) is given in Hz. Electron impact (EI) MS spectra were carried out on a JEOL JMS-600 spectrometer. Elemental analyses (C, H, N and S) were performed on an Elemental Analyses system GmbH vario EL V2.3 1998 CHNS Mode (Assiut University). The reactions were monitored by TLC.

4-Aryl-3-cyano-5-ethoxycarbonyl-6-methylpyridine-2(1H)-thiones (2a,b). These compounds were prepared according to the reported method.\(^{21} \)

4-Aryl-3-cyano-2-cyanomethylthio-5-ethoxycarbonyl-6-methylpyridines (3a,b). To a suspension of compound 2a,b (10 mmol) and sodium acetate trihydrate (1.36 g, 10 mmol) in ethanol (40 mL), chloroacetonitrile (0.64 mL, 10 mmol) was added. The resulting mixture was stirred at room temperature for 3 h. The white precipitate that formed was collected and recrystallized from ethanol to give 4a,b.

3-Cyano-2-cyanomethylthio-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methylpyridine (3a). Prepared as white needles in 92% yield; mp 121-122 °C. IR (KBr) cm\(^{-1} \): 2250 (C=\( \equiv \)N, non conjugated), 2220 (C=\( \equiv \)N, conjugated), 1731 (C=O); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm: 7.30-7.32 (dd, \( J \) 2.3 Hz, 2H, Ar-H), 6.97-7.00 (dd, \( J \) 2.3 Hz, 2H, Ar-H), 4.05-4.11 (q, \( J \) 7.0 Hz, 2H, OCH\(_2\)), 4.07 (s, 2H, SCH\(_2\)), 3.85 (s, 3H, OCH\(_3\)), 2.67 (s, 3H, CH\(_3\)), 0.98-1.02 (t, \( J \) 7.0 Hz, 3H, CH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) ppm: 166.6, 161.0, 159.2, 158.8, 152.6, 129.7, 126.7, 126.2, 115.8, 114.3, 114.1, 105.1, 61.9, 55.4, 23.4, 15.9, 13.7. MS: \( m/z \) 367 (M\(^+\), 100%), 352 (M\(^+\)-CH\(_3\), 12%), 337 (M\(^+\)-2CH\(_3\), 25%), 322 (M\(^+\)- OC\(_2\)H\(_5\), 14%). Anal. Calcd. for C\(_{19}\)H\(_{13}\)N\(_2\)O\(_3\)S (367.1): C, 62.11; H, 4.66; N, 11.44; S, 8.73%. Found: C, 62.43; H, 4.49; N, 11.90; S, 8.92%.

(4-Chlorophenyl)-3-cyano-2-cyanomethylthio-5-ethoxycarbonyl-6-methylpyridine (3b). Prepared as white needles in 90% yield; mp 97-99 °C. IR (KBr) cm\(^{-1} \): 2248 (C=\( \equiv \)N, none conjugated), 2217 (C=\( \equiv \)N, conjugated), 1735 (C=O); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm: 7.46-7.49 (dd, \( J \) 2.3 Hz, 2H, Ar-H), 7.29-7.32 (dd, \( J \) 2.3 Hz, 2H, Ar-H), 4.05-4.10 (m, 4H, SCH\(_2\) and OCH\(_2\)), 2.70 (s, 3H, CH\(_3\)), 0.98-1.01 (t, 3H, CH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) ppm: 166.0, 159.7, 159.1, 151.6, 136.5, 132.5, 129.5, 129.1, 126.4, 115.7, 113.6, 104.9, 62.1, 23.5, 16.0, 13.6. MS: \( m/z \) 371 (M\(^+\), 100%), 373 (M\(^+\)+2, 42%), 343 (24%), 336 (10%), 326 (M\(^+\)- OC\(_2\)H\(_5\), 15%). Anal. Calcd. for C\(_{18}\)H\(_{14}\)ClN\(_2\)O\(_2\)S (371.1): C, 58.14; H, 3.79; N, 11.30; S, 8.62%. Found: C, 58.46; H, 3.72; N, 11.65; S, 8.27%.

3-Amino-4-aryl-5-ethoxycarbonyl-6-methylthieno[2,3-b]pyridine-2-carbonitriles (4a,b).

Method (A) To a mixture of compound 2a,b (10 mmol) and sodium acetate trihydrate (1.50 g, 11 mmol) in ethanol (40 mL), chloroacetonitrile (0.64 mL, 10 mmol) was added. The resulting mixture was heated under reflux for 3 h. The precipitate that formed was collected and recrystallized from ethanol to afford 4a,b.

3-Amino-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methylthieno[2,3-b]pyridine-2-carbonitrile (4a).

Prepared as yellow needles in 90% yield; mp 184-185 °C. IR (KBr) cm\(^{-1} \): 3476, 3342 (NH\(_2\)), 2976 (C-H, aliphatic); 2199 (C=\( \equiv \)N); 1729 (C=O); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm: 7.27-7.30 (dd, \( J \) 2.4 Hz, 2H, Ar-H), 7.00-7.03 (dd, \( J \) 2.4 Hz, 2H, Ar-H), 4.32 (s, 2H, NH\(_2\)), 4.01-4.06 (q, \( J \) 7.0 Hz, 2H, OCH\(_2\)), 3.88 (s, 3H, OCH\(_3\)), 2.67 (s, 3H, CH\(_3\)), 0.99-
1.03 (t, J 7.2 Hz, 3H, CH₃ of ester); ¹³C NMR and Dept 135 (100 MHz, CDCl₃) δ ppm: 167.5, 161.3, 160.6, 156.3, 149.3, 143.8, 130.0 (CH), 127.6, 125.4, 118.5, 114.7, 114.1 (CH), 61.6 (OCH₂), 55.4 (OCH₃), 23.1 (CH₃ at C-6), 13.8 (CH₃ of ester group). MS: m/z 367 (M⁺, 100%), 339 (M⁺-CO, 10%), 322 (M⁺-OEt, 15%), 321 (M⁺-EtOH, 15%). Anal. Calcd. for C₁₉H₁₇N₃O₃S (367.1): C, 62.11; H, 4.66; N, 11.44; S, 8.73%. Found: C, 62.00; H, 4.70; N, 11.83; S, 9.02%.

**3-Amino-4-(4-chlorophenyl)-5-ethoxycarbonyl-6-methylthieno[2,3-b]pyridine-2-carbonitrile (4b).** Prepared as yellow needles in 93% yield; mp 175-176 °C. IR (KBr) cm⁻¹: 3484, 3343, 3228 (NH₂), 2977 (C-H aliphatic), 2200 (C=,N), 1727 (C=O); ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.49-7.52 (dd, J 2.4 Hz, 2H, Ar-H), 7.31-7.34 ((dd, J 2.4 Hz, 2H, Ar-H), 4.23 (s, 2H, NH₂), 4.03-4.09 (q, J 7.4 Hz, 2H, OCH₂), 2.69 (s, 3H, CH₃), 1.00-1.03 (t, J 7.2 Hz, 3H, CH₃); ¹³C NMR and DEPT 135 (100 MHz, CDCl₃) δ ppm: 167.1, 161.4, 156.5, 148.7, 142.5, 136.1, 132.0, 130.1 (CH), 129.0 (CH), 127.1, 118.0, 114.5, 61.8 (OCH₂), 23.2 (CH₃ at C-6), 13.7 (CH₃ of ester group); MS: m/z 371 (M⁺, 100%), 373 (M⁺+2, 39%), 343 (M⁺-CO, 21%) and 326 (M⁺-OEt, 12%). Anal. Calcd. for C₁₉H₁₄ClN₃O₂S (371.1): C, 58.14; H, 3.79; N, 11.30; S, 8.62%. Found: C, 58.23; H, 3.70; N, 11.48; S, 8.72%.

**Method (B).** A suspension of compound 3a,b (10 mmol) and sodium acetate trihydrate (0.14 g, 1 mmol) in ethanol (30 mL) was heated at reflux for 3 h. The crystalline product that formed on cooling was collected and recrystallized from ethanol in the form of yellow needles of 4a,b. These products are identical with those reported in method A in all aspects (yield: 83-88%).

**3-Amino-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methylthieno[2,3-b]pyridine-2-carboxamide (5).** This compound was prepared according to the reported method.²¹

**Ethyl N-[4-aryl-2-cyano-5-ethoxycarbonyl-6-methylthieno[2,3-b]pyridin-3-yl]-methanimidates (6a,b).** A mixture of compound 4a,b (10 mmol), triethyl orthoformate (5 mL in acetic anhydride (15 ml) was heated under reflux for 2 h and then allowed to cool. The solid that formed was collected and recrystallized from ethanol to afford 6a,b.

**Ethyl N-[2-cyano-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methylthieno[2,3-b]pyridin-3-yl]-methanimidate (6a).** Prepared as white needles in 90% yield; mp 154-155 °C. IR (KBr) cm⁻¹: 2974, 2836 (C-H aliphatic), 2212 (C=N), 1731 (C=O), 1632 (C=N); ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.54 (s, 1H, N=CH), 7.10-7.12 (d, J 8.4 Hz, 2H, Ar-H), 6.89-6.92 (d, J 8.8 Hz, 2H, Ar-H), 4.03-4.08 (q, J 7.2 Hz, 2H, OCH₂ of ester group), 3.84 (s, 3H, OCH₃), 3.60-3.65 (q, J 6.8 Hz, 2H, OCH₂ of ethoxygroup), 2.69 (s, 3H, CH₃ at C-6), 1.12-1.16 (t, J 7.2 Hz, 3H, CH₃ of ethoxygroup), 0.98-1.01 (t, J 7.0 Hz, 3H, CH₃ of ester group); ¹³C NMR and DEPT 135 (100 MHz, CDCl₃): δ 167.7, 160.7, 159.9, 156.5 (N=CH), 156.3, 151.2, 145.0, 130.5 (CH), 128.5, 126.8, 122.5, 114.1, 114.0, 112.9 (CH), 91.9, 62.9 (OCH₂), 61.6 (OCH₂), 55.3 (OCH₃), 23.1 (CH₃ at C-6), 13.7 (CH₃ of ester group), 13.6 (CH₃ of ethoxygroup); MS: m/z 423 (M⁺, 100%), 378 (M⁺-OEt, 13%), 367 (46%) and 132 (13%). Anal. Calcd. for C₂₂H₂₁N₃O₄S (423.1): C, 62.40; H, 5.00; N, 9.92; S, 7.57%. Found: C, 62.17; H, 4.79; N, 9.57; S, 7.82%.

**Ethyl N-[4-(4'-chlorophenyl)-2-cyano-5-ethoxycarbonyl-6-methylthieno[2,3-b]pyridin-3-yl]-methanimidate (6b).** Obtained as white needles in 92% yield; mp 146-147 °C. IR (KBr) cm⁻¹: 2981 (C-H aliphatic), 2213 (C=N), 1727 (C=O), 1634 (C=N); ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.59 (s, 1H, N=CH), 7.37-7.39 (dd, J 2.0 Hz, 2H, Ar-H), 7.14-7.16 (dd, J=2.0 Hz, 2H, Ar-H), 4.03-4.09(q, J 8.0 Hz, 2H, OCH₂ of ester), 3.56-3.62 (q, J 7.0 Hz, 2H, OCH₂ of ethoxy group), 2.70 (s,3H, CH₃), 1.17-1.20 (t, J 7.0 Hz, 3H, CH₃ of ethoxygroup), 0.98-1.02 (t, J 7.2 Hz, 3H, CH₃ of ester group); ¹³C NMR and DEPT 135 (100 MHz, CDCl₃) δ ppm: 167.2, 160.7, 156.8, 156.5 (N=CH), 150.8, 143.8, 134.7, 133.2, 130.6 (CH), 128.0, 127.7 (CH), 122.1, 113.8, 92.1, 63.2 (OCH₂), 61.7 (OCH₂), 23.2 (CH₃ at C-6), 13.7 (CH₃ of ester group), 13.7 (CH₃ of ethoxy group); MS: m/z 427 (M⁺, 100%), 429 (M⁺+2, 41%), 382 (M⁺-OEt, 14%), 371 (60%), 343 (21%). Anal. Calcd. for C₂₁H₁₈ClN₃O₃S (427.1): C, 58.95; H, 4.24; N, 9.82; S, 7.49%. Found: C, 58.82; H, 4.31; N, 9.67; S, 7.72%.
Ethyl 3-amino-9-aryl-3,4-dihydro-4-imino-7-methylpyrido[3’,2’:4,5]thieno[3,2-d]pyrimidine-8-carboxylates (7a,b). To a suspension of compound 6a,b (5 mmol) in dioxane (20 mL), hydrazine hydrate 99% (2 mL) was added. The reaction mixture was stirred at room temperature for 4 h. The solid that formed was collected and recrystallized from ethanol to give 7a,b.

Ethyl 3-amino-3,4-dihydro-4-imino-9-(4-methoxyphenyl)-7-methylpyrido[3’,2’:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (7a). Obtained as white needles in 78% yield; mp 204-206 °C. IR (KBr) cm⁻¹: 3306, 3157 (NH, NH₂), 2979 (C-H aliphatic), 1707 (C=O), 1609 (C=N); ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.89 (s, 1H, CH pyrimidine), 7.27-7.29 (d, J 8.8 Hz, 2H, Ar-H), 6.93-6.95 (d, J 8.8 Hz, 2H, Ar-H), 4.77 (s, 2H, NH₂), 4.05-4.08 (q, J 7.0 Hz, 2H, OCH₂), 3.87 (s, 3H, OCH₃), 2.71 (s, 3H, CH₃), 1.00 -1.04 (t, J 7.0 Hz, 3H, CH₃ of ester); ¹³C NMR and DEPT 135 (100 MHz, CDCl₃) δ ppm: 168.3, 161.9, 159.8, 155.4, 154.4, 148.2 (CH pyrimidine), 145.9, 145.9, 130.7 (CH), 128.6, 126.9, 124.0, 121.4, 112.9 (CH), 61.5 (OCH₂), 55.2 (OCH₃), 23.1 (CH₃ at C-6), 13.8 (CH₃ of ester group); MS: m/z 409 (M⁺, 100%), 393 (M⁺- NH₂, 19%), 367 (17%) and 365 (10%). Anal. Calcd. for C₂₀H₁₉N₅O₃S (409.1): C, 58.67; H, 4.68; N, 17.10; S, 7.83%. Found: C, 58.44; H, 4.70; N, 17.36; S, 7.61%.

Ethyl 3-amino-9-(4-chlorophenyl)-3,4-dihydro-4-imino-7-methylpyrido[3’,2’:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (7b). Obtained as white needles in 85% yield; mp 208-209 °C. IR (KBr) cm⁻¹: 3309, 3161 (NH, NH₂), 2986 (C-H aliphatic), 1708 (C=O), 1613 (C=N); ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.87 (s, 1H, CH pyrimidine), 7.38-7.40 (dd, J 2.4 Hz, 2H, Ar-H), 7.27-7.29 (dd, J 2.4 Hz, 2H, Ar-H), 4.78 (s, 2H, NH₂), 4.05-4.10 (q, J 7.0 Hz, 2H, OCH₂), 2.72 (s, 3H, CH₃), 1.00 -1.03 (t, J 7.2 Hz, 3H, CH₃ ester); ¹³C NMR and DEPT 135 (100 MHz, CDCl₃) δ ppm: 167.8, 161.9, 155.7, 154.3, 148.3 (CH pyrimidine), 145.6, 144.6, 134.6, 133.1, 130.7 (CH), 128.0, 127.7 (CH), 123.7, 121.6, 61.7 (OCH₂), 23.2 (CH₃ at C-6), 13.7 (CH₃ ester); MS: m/z 413 (M⁺, 100%), 415 (M⁺+2, 41%), 397 (M⁺- NH₂, 13%), 371 (16%). Anal. Calcd. for C₁₉H₁₅ClN₃O₃S (413.1): C, 55.14; H, 3.90; N, 16.92; S, 7.75%. Found: C, 55.09; H, 4.11; N, 16.78; S, 8.00%.

General procedures for the synthesis of ethyl 7-aryl-9-methyl[1,2,4]triazolo[2”,3”-c]pyrido[3’,2’:4,5]thieno[2,3-e]pyrimidine-8-carboxylates (8a,b)

Method (A). Compound 7a,b (2 mmol) in triethyl orthoformate (10 mL) was heated at reﬂux for 3 h. The precipitate that formed while hot was collected and recrystallized from ethanol to afford 8a,b.

Ethyl 7-(4-methoxyphenyl)-9-methyl[1,2,4]triazolo[2”,3”-c]pyrido[3’,2’:4,5]thieno[2,3-e]pyrimidine-8-carboxylate (8a). Obtained as white fine needles in 76% yield; mp 205-206 °C. IR (KBr) cm⁻¹: 1726 (C=O); ¹H NMR (400 MHz, CDCl₃) δ ppm: 9.11 (s, 1H, CH pyrimidine), 8.46 (s, 1H, CH triazole), 7.34-7.36 (d, 2H, Ar-H), 6.99-7.02 (dd, 2H, Ar-H), 4.10-4.14 (q, 2H, OCH₂), 3.91 (s, 3H, OCH₃), 2.77 (s, 3H, CH₃), 1.03-1.05 (t, 3H, CH₃ ester); MS: m/z 419 (M⁺, 100%), 387 (20%); 347 (11%). Anal. Calcd. for C₂₁H₁₇N₅O₃S (419.1): C, 60.13; H, 4.09; N, 16.70; S, 7.64%. Found: C, 60.08; H, 4.11; N, 16.56; S, 7.39%.

Ethyl 7-(4-chlorophenyl)-9-methyl[1,2,4]triazolo[2”,3”-c]pyrido[3’,2’:4,5]thieno[2,3-e]pyrimidine-8-carboxylate (8b). Obtained as white fine needles in 80% yield; mp 244-245 °C. IR (KBr) cm⁻¹: 2979 (C-H, aliphatic), 1727 (C=O), 1623 cm⁻¹ (C=N); ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.98 (s, 1H, CH pyrimidine), 8.47 (s, 1H, CH triazole), 7.45-7.47 (d, 2H, Ar-H), 7.34-7.36 (d, 2H, Ar-H), 4.08-4.14 (q, 2H, OCH₂), 2.78 (s, 3H, CH₃), 1.03-1.06 (t, 3H, CH₃ ester); MS: m/z 423 (M⁺, 100%), 425 (M⁺+2, 40%). Anal. Calcd. for C₂₀H₁₄ClN₃O₂S (423.1): C, 56.67; H, 3.33; N, 16.52; S, 7.56%. Found: C, 56.80; H, 3.31; N, 16.77; S, 7.34%.

Method (B). Compound 17 (1.64 g; 4 mmol) in formic acid 85% (20 mL) was heated at reﬂux for 6 h. The precipitate that formed on cooling was collected by ﬁltration and recrystallized from ethanol in the form of white needles of compound 8a (yield: 67%). This product is identical to that reported above in all aspects.
Ethyl 7-aryl-2,9-dimethyl[1,2,4]triazolo[2''',3'''-c]pyrido[3',2':4,5]thieno[2,3-e]pyrimidine-8-carboxylates (9a,b). Compound 7a,b (2 mmol) in acetic anhydride (10 mL) was heated under reflux for 2 h. The crystalline precipitate that formed while hot collected by filtration and recrystallized from ethanol to give 9a,b.

Ethyl 2,9-dimethyl-7-(4-methoxyphenyl)[1,2,4]triazolo[2''',3'''-c]pyrido[3',2':4,5]thieno[2,3-e]pyrimidine-8-carboxylate (9a). Obtained as white crystals in 88% yield; mp 220-221°C. IR (KBrs) cm⁻¹: 2964 (C-H aliphatic), 1736 (C=O), 1612 (C=N). ¹H NMR (400 MHz, CDCl₃): δ 7.99 (s, 1H, CH pyrimidine), 7.34-7.36 (dd, J 1.8 Hz, 2H, Ar-H), 6.99-7.01 (dd, J 1.8 Hz, 2H, Ar-H), 4.08-4.14 (q, J 7.0 Hz, 2H, OCH₂), 3.91 (s, 3H, OCH₃), 2.77 (s, 3H, CH₃), 2.67 (s, 3H, CH₃ triazole), 1.03-1.06 (t, J 7.0 Hz, 3H, CH₃ of ester); ¹³C NMR and DEPT 135 (100 MHz, CDCl₃) δ ppm: 168.1, 165.9, 162.1, 160.0, 156.0, 148.8, 145.5, 144.5, 135.6 (CH pyrimidine), 130.5 (CH), 128.9, 126.9, 122.9, 119.2, 113.2 (CH), 61.6 (OCH₂), 55.3 (OCH₃), 23.2 (CH₃ pyrimidine), 14.5 (CH₃ triazole), 13.8 (CH₃ ester); MS: m/z 433 (M⁺, 100%), 404 (M⁺- Et, 25%), 388 (M⁺- EtO, 30%) and 360 (M⁺- CO₂Et, 35%). Anal. Calcd. for C₂₂H₁₉N₆O₃S (433.1): C, 60.96; H, 4.42; N, 16.16; S, 7.40%. Found: C, 61.13; H, 4.41; N, 16.00; S, 7.18%.

Ethyl 7-(4-chlorophenyl)-2,9-dimethyl[1,2,4]triazolo[2''',3'''-c]pyrido[3',2':4,5]thieno[2,3-e]pyrimidine-8-carboxylate (9b). Obtained as white crystals in 85% yield; mp 245-247 °C. IR (KBrs) cm⁻¹: 2979 (C-H aliphatic), 1727 (C=O), 1623 (C=N). ¹H NMR (400 MHz, CDCl₃): δ 8.980 (s, 1H, CH pyrimidine), 7.455-7.471 (dd, J 2.0 Hz, 2H, Ar-H), 7.340-7.361 (dd, J 2.0 Hz, 2H, Ar-H), 4.087-4.141 (q, J 7.2 Hz, 2H, OCH₂), 2.787 (s, 3H, CH₃), 2.682 (s, 3H, CH₃ attached to triazole ring), 1.030 -1.065 (t, J 7.0 Hz, 3H, CH₃ of ester); ¹³C NMR and DEPT 135 (100 MHz, CDCl₃) δ ppm: 167.69, 166.02, 162.02, 156.20, 148.30, 146.18, 148.17, 144.14, 144.24, 144.16, 136.76 (CH pyrimidine), 134.89, 133.20, 130.58 (CH), 128.45, 128.07(CH), 122.56, 119.52, 61.84 (OCH₂), 23.29 (CH₃ attached to pyridine ring), 14.57(CH₃ attached to triazole ring), 13.73 (CH₃ of ester group); MS: m/z 437 (M⁺, 100%), 439 (M⁺+2, 41), 408 (M⁺-Et, 25%), 392 (M⁺-OC₂H₅, 41), 365 (M⁺-CO₂Et, 22%) and 356 (13%). Anal. Calcd. for C₂₂H₁₆ClN₆O₃S (437.1): C, 57.60; H, 3.68; N, 15.99; S, 7.32%. Found: C, 57.23; H, 3.70; N, 15.70; S, 7.54%.

Ethyl 2-anilino-7-aryl-9-methyl[1,2,4]triazolo[2''',3'''-c]pyrido[3',2':4,5]thieno[2,3-e]pyrimidine-8-carboxylates (10a,b). To a solution of compound 7a,b (5 mmol) in pyridine (10 mL), phenyl isothiocyanate (0.65 mL, 5 mmol) was added. The reaction mixture was heated on a steam bath for 8 h and then allowed to stand at room temperature overnight. The precipitate that formed was collected and recrystallized from DMF-H₂O mixture to afford 10a,b.

Ethyl 2-anilino-7-(4-methoxyphenyl)-9-methyl[1,2,4]triazolo[2''',3'''-c]pyrido[3',2':4,5]thieno[2,3-e]pyrimidine-8-carboxylate (10a). Prepared as pale yellow crystals in 73% yield; Yield: 73%; mp 285-286 °C. IR (KBrs) cm⁻¹: 3500 (NH), 2976 (C-H aliphatic), 1720 (C=O). ¹H NMR (400 MHz, CDCl₃) δ ppm: 6.92-7.83 (m, 11H, CH pyrimidine, NH and Ar-H), 4.02 (q, 2H, OCH₂), 3.77 (s, 3H, OCH₃), 2.68 (s, 3H, CH₃), 0.97 (t, 3H, CH₃ of ester); MS: m/z 510 (M⁺, 3%), 393 (M⁺-PhNCN, 100%), 365 (42%), 349 (13%), 321 (18%). Anal. Calcd. for C₂₇H₂₂N₆O₃S (510.1): C, 63.52; H, 4.34; N, 16.46; S, 6.28%. Found: C, 63.34; H, 4.11; N, 16.43; S, 6.30%.

Ethyl 2-anilino-7-(4-chlorophenyl)-9-methyl[1,2,4]triazolo[2''',3'''-c]pyrido[3',2':4,5]thieno[2,3-e]pyrimidine-8-carboxylate (10b). Prepared as pale yellow crystals in 78% yield; mp 300-302 °C. IR (KBrs) cm⁻¹: 3500 (NH), 1725 (C=O), 1644 (C=N). ¹H NMR (90 MHz, CF₃CO₂D) δ ppm: 8.10 (s, 1H, CH pyrimidine), 7.10-7.70 (m, 9H, Ar-H), 4.00-4.40 (q, 2H, OCH₂), 2.80 (s, 3H, CH₃), 1.00-1.30 (t, 3H, CH₃ of ester); MS: m/z 514 (M⁺, 10%), 397 (M⁺-PhNCN, 100%), 369 (58%), 353 (20%), 325 (27%). Anal. Calcd. for C₂₆H₁₉ClN₆O₂S (514.1): C, 60.64; H, 3.72; N, 16.32; S, 6.23%. Found: C, 60.59; H, 3.83; N, 16.16; S, 6.11%.

Condensation of compounds 8a,b with isatin; formation of fused hexacyclic compounds 11a,b. A mixture of compound 7a,b (2 mmol) and isatin (0.30 g, 2 mmol) in ethanol (20 mL) was heated under reflux for 3 h. The precipitate that formed while hot collected and recrystallized from dioxane to give 11a,b.
3-Ethoxycarbonyl-4-(4-methoxyphenyl)-2-methylpyrido[3''',2'''',4'',5''']-thieno[3',2':4',5']pyrimido[1',6':2,3][1,2,4]triazino[5,6-b]indole (11a). Prepared as red crystals in 82% yield; mp 334-335 °C. IR (KBr) cm⁻¹: 2947 (CH aliphatic), 1727 (C=O), 1634 (C=N); MS: m/z 520 (M⁺, 100%), 519 (M⁺-H, 29%), 491 (M⁺-Et, 26%). Anal. Calcd. for C₂₈H₂₀N₆O₃S (520.1): C, 64.60; H, 3.87; N, 16.14; S, 6.16%. Found: C, 64.51; H, 3.91; N, 16.00; S, 6.18%.

4-(4-Chlorophenyl)-3-ethoxycarbonyl-2-methylpyrido[3''',2'''',4'',5''']-thieno[3',2':4',5']pyrimido[1',6':2,3][1,2,4]triazino[5,6-b]indole (11b). Prepared as red crystals in 81% yield; mp 342-343 °C. IR (KBr) cm⁻¹: 1727 (C=O), 1631 (C=N). ¹H NMR (90 MHz, CDCl₃) δ ppm: 9.70 (s, 1H, CH pyrimidine), 7.40-8.70 (m, 8H, Ar-H), 4.20-4.60 (q, 2H, OCH₂), 3.20 (s, 3H, CH₃), 1.00-1.30 (t, 3H, CH₃ of ester); MS: m/z 524 (M⁺, 100%), 526 (M⁺+2, 40%), 495 (M⁺-Et, 28%), 451 (M⁺-CO₂Et, 14%). Anal. Calcd. for C₂₇H₁₇ClN₆O₂S (524.1): C, 61.77; H, 3.26; N, 16.01; S, 6.11%. Found: C, 61.40; H, 3.23; N, 15.89; S, 6.07%.

Ethyl 8-(4-methoxyphenyl)-10-methyl-3-phenyl-2H-pyrido[3''',2'''',4'',5'',6''',7''][1,2,4]triazine-9-carboxylate (12). To a mixture of compound 7a (0.82 g, 2 mmol) and phenacyl bromide (0.40 g; 2 mmol) in ethanol (20 mL), anhydrous sodium acetate (0.33 g; 4 mmol) was added. The reaction mixture was heated under reflux for 3 h. The precipitate that formed while hot was filtered, washed with water and recrystallized from ethanol to afford 12. Obtained as pale yellow needles in 81% yield; mp 237-238 °C. IR (KBr) cm⁻¹: 2836 (C-H, aliphatic), 1716 (C=O), 1671 (C=N); ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.80 (s, 1H, CH pyrimidine), 6.88-7.73 (m, 9H, Ar-H), 4.76 (s, 2H, CH₂ triazine), 4.01-4.02 (q, 2H, OCH₂), 3.81 (s, 3H, OCH₃), 2.64 (s, 3H, CH₃), 0.97 (s, 3H, CH₂); MS: m/z 509 (M⁺, 100%), 405 (M⁺-PhCN, 23%), 377 (17%). Anal. Calcd. for C₂₈H₂₃N₅O₃S (509.1): C, 66.00; H, 4.55; N, 13.74; S, 6.29%. Found: C, 65.87; H, 4.41; N, 13.80; S, 6.40%.

Ethyl 9-(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydropyrido[3''',2'''',4'',5''][3,2-d]pyrimidine-8-carboxylate (14). A mixture of compound 5 (1.92 g, 5 mmol) and triethyl orthoformate (5 mmol) in acetic anhydride (15 mL) was heated under reflux for 4 h. The precipitate that formed while hot was collected by filtration, washed with ethanol and crystallized from DMF to give 14. Obtained as white needles in 80% yield; mp 298-299 °C. IR (KBr) cm⁻¹: 3220 (NH), 1731 (C=O, ester), 1659 (C=O, pyrimidine); ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 12.75 (s, 1H, NH), 8.03 (s, 1H, CH pyrimidine), 7.26-7.28 (s, J 8.0 Hz, 2H, Ar-H), 6.98-7.00 (d, J 8.0 Hz, 2H, Ar-H), 4.06-4.08 (q, 2H, OCH₂), 3.83 (s, 3H, OCH₃), 2.64 (s, 3H, CH₃ at C-7), 0.95-0.97 (t, 3H, CH₃ ester); MS: m/z 395 (M⁺, 100%), 366 (M⁺-Et, 28%), 350 (M⁺-OC₂H₅, 36%), 322 (M⁺-CO₂Et, 22%). Anal. Calcd. for C₂₀H₁₅N₃O₅S (395.1): C, 60.75; H, 4.33; N, 10.63; S, 8.11%. Found: C, 60.66; H, 4.41; N, 10.86; S, 7.85%.

Ethyl 4-chloro-9-(4-methoxyphenyl)-7-methylpyrido[3''',2'''',4'',5''][3,2-d]pyrimidine-8-carboxylate (15). A suspension of compound 14 (1.97 g, 5 mmol) in an excess amount of phosphorus oxychloride (25 mL) was heated under reflux on a steam bath for 3 h. The reaction mixture was cooled and then poured with vigorous stirring into ice-cooled water (150 mL). The solid that separated was filtered and crystallized from ethanol to afford 15. Obtained as white pale yellow crystals in 79% yield; mp 166-167°C. IR (KBr) cm⁻¹: 2936 (C-H aliphatic), 1732 (C=O), 1608 (C=N); ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.81 (s, 1H, CH pyrimidine), 7.31-7.34 (dd, J 2.4 Hz, 2H, Ar-H), 6.99-7.01 (dd, J 2.4 Hz, 2H, Ar-H), 4.08-4.14 (q, J 7.0 Hz, 2H, OCH₂), 3.90 (s, 3H, OCH₃), 2.77 (s, 3H, CH₃), 1.02-1.06 (t, J 7.2 Hz, 3H, CH₃ ester). Anal. Calcd. for C₂₀H₁₅ClN₃O₅S (431.1): C, 58.04; H, 3.90; N, 10.15; S, 7.75; Cl, 8.57%. Found: C, 57.87; H, 4.11; N, 10.14; S, 8.13; Cl, 8.40%.

Ethyl 9-(4-chlorophenyl)-8-ethoxycarbonyl-7-methyl-4-thioxo-3,4-dihydro-pyrido[3''',2'''',4''][3,2-d]pyrimidine-8-carboxylate (16). A mixture of 4-chloro compound 15 (2.07 g; 5 mmol) and thiourea (0.76 g; 10 mmol) in ethanol (30 mL) was heated under reflux for 6 h and then allowed to cool. The precipitated solid was collected, dissolved in sodium hydroxide solution 8% (20 mL) and filtered. The clear filtrate was acidified with acetic acid whereby a yellow product precipitated. It was collected by filtration and crystallized from
acetic acid to afford 16. Obtained as yellow crystals in 80% yield; mp 276-277 °C. IR (KBr) cm⁻¹: 3150 (NH aliphatic), 1730 (C=O, ester); ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.38 (s, 1H, CH pyrimidine), 7.34-7.36 (dd, J 2.2 Hz, 2H, Ar-H), 6.97-6.99 (dd, J 2.0 Hz, 2H, Ar-H), 6.65 (s, 1H, NH), 4.06-4.11 (q, J 7.2 Hz, 2H, OCH₂), 3.89 (s, 3H, OCH₃), 2.74 (s, 3H, CH₃), 1.01-1.05 (t, J 7.2 Hz, 3H, CH₃ ester). Anal. Calcd. for C₂₀H₁₇N₃O₃S₂ (411.1): C, 58.38; H, 4.16; N, 10.21; S, 15.58%. Found: C, 58.17; H, 4.30; N, 10.08; S, 15.29%

**Ethyl 4-hydrazino-9-(4-methoxyphenyl)-7-methylpyrido[3',2':4,5]thieno[3,2-d]pyrimidine-8-carboxylate (17).** A mixture of compound 15 (2.07 g; 5 mmol) and hydrazine hydrate 99% (1.0 mL, 20 mmol) in ethanol (20 mL) was heated at reflux for 2 h. The precipitate was collected and recrystallized from dioxane to give 17. Prepared as white crystals in 88% yield. mp 239-240 °C. IR (KBr) cm⁻¹: 3380, 3251 (NHNH₂), 2972 (C-H aliphatic), 1723 (C=O), 1659 (C=N); ¹H NMR (400 MHz, CDCl₃) δ ppm: 9.04 (s, 1H, NH), 7.38 (s, 1H, CH pyrimidine), 6.93 -7.29 (m, 6H, NH₂ and Ar-H), 4.03-4.06 (q, 2H, OCH₂), 3.85 (s, 3H, OCH₃), 2.71 (s, 3H, CH₃), 0.98 -1.00 (t, 3H, CH₃ ester). Anal. Calcd. for C₂₀H₁₉N₃O₅S (409.1): C, 58.67; H, 4.68; N, 17.10; S, 7.83%. Found: C, 58.56; H, 4.43; N, 17.41; S, 7.62%

**Condensation of hydrazino compound 17 with 4-chlorobenzaldehyde or acetophenone; Formation of hydrazones 18 and 19 respectively.** To a mixture of compound 17 (2.05 g; 5 mmol) and 4-chlorobenzaldehyde or acetophenone (5 mmol) in ethanol (20 mL), few drops of acetic acid were added. The reaction mixture was heated under reflux for 4 h. The solid that formed while hot was collected and recrystallized from DMF-H₂O mixture to give 18 and 19 respectively.

**Ethyl 4-(4-chlorobenzylidenehydrazino)-9-(4-methoxyphenyl)-7-methyl-pyrido[3',2':4,5]thieno[3,2-d]pyrimidine-8-carboxylate (18).** Prepared as yellow crystals in 90% yield; mp 250-252 °C. IR (KBr) cm⁻¹: 3200 (NH), 2981 (C-H, aliphatic), 1722 (C=O), 1598 (C=N); ¹H NMR (400 MHz, CDCl₃) δ ppm: 9.54 (br. s, 1H, NH), 8.45 (s, 1H, CH pyrimidine), 7.80 (s, 1H, N=CH), 7.74-7.76 (d, J 8.0 Hz, 2H, Ar-H), 7.43-7.45 (d, J 8.4 Hz, 2H, Ar-H), 7.36-7.38 (d, J 8.8 Hz, 2H, Ar-H), 6.98-7.00 (d, J 8.8 Hz, 2H, Ar-H), 4.08-4.13 (q, J 7.2 Hz, 2H, OCH₂), 3.89 (s, 3H, OCH₃), 2.78 (s, 3H, CH₃), 1.03-1.06 (t, J 7.0 Hz, 3H, CH₃ of ester); MS: m/z 531 (M⁺, 71%), 533 (M⁺-ClC₆H₄CH=N, 100%), 533 (M⁺+2, 27%), 365 (43%), 321 (30%). Anal. Calcd. for C₂₇H₂₂ClN₅O₅S (531.1): C, 60.96; H, 4.17; N, 13.16; S, 6.03%. Found: C, 60.78; H, 4.20; N, 13.00; S, 6.19%

**Acetophenone 8-ethoxycarbonyl-9-(4-methoxyphenyl)-7-methylpyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4-ylydrazone (19).** Prepared as yellow crystals in 88% yield; mp 225-226 °C. IR (KBr) cm⁻¹: 3186 (NH), 2974, 2926 (C-H, aliphatic), 1725 (C=O), 1610 (C=N); ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.648 (s, 1H, NH), 8.469 (s, 1H, CH pyrimidine), 7.95 (d, 2H, Ar-H), 7.25-7.51 (m, 5H, Ar-H), 6.98-700 (d, 2H, Ar-H), 4.07-4.12 (q, J 7.4 Hz, 2H, OCH₂), 3.90 (s, 3H, OCH₃), 2.78 (s, 3H, CH₃), 2.36 (s, 3H, CH₃ hydrazone), 1.02-1.06 (t, J 7.4 Hz, 3H, CH₃ ester); MS: m/z 511 (M⁺, 14%) 77 (C₆H₅⁺, 100%). Anal. Calcd. for C₂₈H₂₅N₅O₅S (511.1): C, 65.74; H, 4.93; N, 13.69; S, 6.27%. Found: C, 65.52; H, 4.70; N, 13.83; S, 6.02%

**Ethyl 4-(3,5-dimethyl-1-pyrazolylo)-9-(4-methoxyphenyl)-7-methylpyrido[3',2':4,5]thieno[3,2-d]pyrimidine-8-carboxylate (20).** A mixture of 17 (2.05 g; 5 mmol) and acetylaceton (15 mL) was gently heated at reflux for 4 h. The reaction mixture was triturated with ethanol (15 mL) and then left to cool. The precipitated product was collected and recrystallized from ethanol to give 20. Obtained as white crystals in 77% yield; mp 146-147 °C. IR (KBr) cm⁻¹: 2977, 2838 (C-H, aliphatic), 1726 (C=O), 1610 (C=N); ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.73 (s, 1H, CH pyrimidine), 7.36-7.38 (d, J 8.8 Hz, 2H, Ar-H), 6.99-7.01 (d, J 8.4 Hz, 2H, Ar-H), 6.09 (s, 1H, CH pyrazole), 4.076-4.129 (q, J 7.0 Hz, 2H, OCH₂), 3.91 (s, 3H, OCH₃), 2.78 (s, 3H, CH₃), 2.77 (s, 3H, CH₃ pyrazole), 2.38 (s, 3H, CH₃ pyrazole), 1.02-1.06 (t, J 7.2 Hz, 3H, CH₃ ester); MS: m/z 473 (M⁺, 100%), 444 (M⁺-Et, 25%), 428 (M⁺-OEt, 11%), 400 (M⁺-CO₂Et, 10%). Anal. Calcd. for C₂₉H₂₅N₅O₅S (473.1): C, 63.41; H, 4.90; N, 14.79; S, 6.77%. Found: C, 63.09; H, 4.88; N, 14.70; S, 8.10%.
Ethyl 4-(5-amino-4-ethoxycarbonyl-1-pyrazolyl)-9-(4-methoxyphenyl)-7-methylpyrido[3',2':4,5]thieno[3,2-d]pyrimidine-8-carboxylate (21). A mixture of 17 (2.05 g; 5 mmol) and Ethyl (ethoxymethylene) cyanoacetate (0.85g; 5 mmol) in ethanol was heated at reflux for 4 h and then left to cool. The precipitated product was collected and recrystallized from ethanol to give 21. Obtained as white crystals in 80% yield; mp 193-194 °C. IR (KBr) cm⁻¹: 3416, 3300 (NH₂), 2981, 2934, 2839 (C-H, aliphatic), 1720 (C=O, ester), 1689 (C=O, ester group attached to pyrazole ring), 1626 (C=N); ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.73 (s, 1H, CH pyrimidine), 7.99 (s, 1H, CH pyrazole), 7.65 (br. s, 2H, NH₂), 7.35-7.37 (dd, 1.8 Hz, 2H, Ar-H), 6.99-7.01 (dd, 1.6 Hz, 2H, Ar-H), 4.29-4.35 (q, J 7.0 Hz, 2H, OCH₂), 4.07-4.13 (q, J 7.0 Hz, 2H, OCH₂), 3.91 (s, 3H, OCH₃), 2.77 (s, 3H, CH₃), 1.36-1.39 (t, J 7.0 Hz, 3H, CH₃ ester), 1.02-1.06 (t, J 7.0 Hz, 3H, CH₃ ester); MS: m/z 532 (M⁺, 100%), 485 (21%), 457 (15%). Anal. Calcd. for C₂₆H₂₄N₆O₄S (532.1): C, 58.64; H, 4.54; N, 15.78; S, 6.02%. Found: C, 58.43; H, 4.70; N, 15.83; S, 6.00%.

Ethyl 7-(4-methoxyphenyl)-9-methyl[1,2,4]triazolo[4",3"-c]pyrido[3',2':4,5]thieno[2,3-c]pyrimidine-8-carboxylate (23). Compound 17 (2.05 g; 5 mmol) in triethyl orthoformate (15 mL) was heated at reflux for 4 h. The precipitate that formed while hot was collected and recrystallized from ethanol to afford 23. Obtained as white crystals in 76% yield; mp 228-229 °C. IR (KBr) cm⁻¹: 3103 (C-H, aromatic), 1723 (C=O, ester), 1609 (C=N); ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.94 (s, 1H, CH pyrimidine), 8.76 (s, 1H, CH triazole), 7.31-7.34 (dd, J 2.4 Hz, 2H, Ar-H), 6.98-7.00 (dd, J 2.2 Hz, 2H, Ar-H), 4.09-4.14 (q, J 7.2 Hz, 2H, OCH₂), 3.90 (s, 3H, OCH₃), 2.77 (s, 3H, CH₃), 1.03-1.06 (t, J 7.2 Hz, 3H, CH₃ ester). Anal. Calcd. for C₂₁H₁₇N₅O₄S (419.1): C, 60.13; H, 4.09; N, 16.70; S, 7.64%. Found: C, 60.24; H, 4.32; N, 16.58; S, 7.60%.

Conclusions

Ethyl 3-amino-9-aryl-3,4-dihydro-4-imino-7-methylpyrido[3',2':4,5]thieno[3,2-d]pyrimidine-8-carboxylates 7a,b and ethyl 4-chloro-9-(4-methoxy-phenyl)-7-methyl-pyrido[3',2':4,5]thieno[3,2-d]pyrimidine-8-carboxylate (17) were synthesized and used as keys intermediate for synthesizing the promising pyridothienopyrimidines as well as triazolopyridothienopyrimidines and pyridothienopyrimidotriazinoindoles.

Acknowledgements

The authors are grateful to Prof. Y. Yamada, professor of chemistry, Faculty of Education, Utsunomiya University, Mine, Utsunomiya 321-8505, Japan for his help in carrying out the NMR and mass spectra of the compounds.

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