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Synthesis, characterization and biological evaluation of thiazolopyrimidine derivatives

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Abstract. Different substituted diesters of thiazolopyrimidine were prepared by the treatment of 3,4 dihydropyrimidine2-thione with α-haloesters using ethanol under reflux condition affording 71–85% yield. IR, ^{1}HNMR, ^{13}CNMR and elemental analyses were used for the characterization of these compounds. The crystal and molecular structure of one of the product, 5-phenyl-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidine-2,6-dicarboxylic acid diethyl ester (**3e**) was verified by single crystal X-ray diffraction method. The antimicrobial activity was evaluated against four bacterial strains and one fungal species. Few of the derivatives exhibited antibacterial and antifungal activities.

Keywords. 3,4-Dihydropyrimidine 2-thione; thiazolopyrimidine; crystal structure; antibacterial and antifungal activity.

1. Introduction

Pyrimidine derivatives are important class of compounds which display number of pharmacological properties including antiviral, antitumour, antibacterial and antihypertensive effects.[1–3] In recent years, interest has also been focused on *aza*-analogs of 1,4-dihydropyridines such as dihydropyrimidines (DHPMs), which exhibit a pharmacological profile similar to classical dihydropyridine calcium channel modulators.[4–10]

Apart from being well known for their calcium channel blocking activity, the dihydropyrimidines are also being explored for their possible therapeutic effects in treatment of AIDS.[11] This is due to the fact that their particular structure has been found in the natural marine alkaloids batzelladine A and B, which are the first low-molecular-weight natural products reported in the literature to inhibit the binding of HIV gp-120 to CD4 cells, thus opening up a new area in the development of AIDS therapy.[11] Moreover, thiazole derivatives have acquired a conspicuous significance due to their use as anti-inflammatory agents. Since the two heterocyclic moieties thiazole and pyrimidine constitute two active pharmacophores that are highly active against inflammation and pain, combining the two is expected to have a synergistic effect on their analgesic properties. This idea has been utilized to prepare thiazolopyrimidine derivatives,[12–14] and their pharmacological activity has been reported.[13–16] Thiazolopyrimidine derivatives are the biosteric analogues of purines and are potentially bioactive molecules which show anti-inflammatory activity comparable to that of some standard drugs *in vivo*, with no or minimal ulcerogenic effects.[17,18] In continuation of our search of new compounds with anticipated biological activity, we aimed to obtain new compounds of the fused thiazole system, with similar therapeutic properties and other noteworthy chemical and biological activities.

The synthesis of the compounds was followed by subsequent spectroscopic analyses using IR, ^{1}H NMR and ^{13}C NMR techniques to confirm the presence of the supposed ring systems. The structure of the derivative 5-phenyl-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidine-2,6-dicarboxylic acid diethyl ester (**3e**) was verified by single crystal X-ray diffraction so that its supramolecular structure could be investigated in terms of possible intermolecular interactions.

2. Experimental

2.1 *Materials*

All chemicals were obtained from a commercial source and used without further purification.

*For correspondence

2.2 *Analytical methods*

Melting points were determined in open capillaries using Guna melting point apparatus and are uncorrected. The IR spectra were recorded on Nicolet Impact 400D FT IR spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR were recorded on Bruker 400-MHz FT NMR spectrometer in $CDCl_3$ and DMSO-d_6 with TMS as internal standard. The reactions and purity of the products were monitored by TLC silica gel plates. Mass spectra were recorded on Finnigan MAT (Model MAT8200) spectrometer and elemental analyses were carried out using CHNS Elimentar (Vario-micro cube).

2.3 *General procedure for the synthesis of compounds* **3(a–i)**

A mixture of 3,4 dihyropyrimidine 2-thione (10 mmol) and ethyl-2-chloroacetoacetate (10 mmol) was refluxed in dry ethanol (20 ml) for 6 h. Excess of solvent was distilled off and the solid hydrochloride salt that separated was collected by filtration, dissolved in water and neutralized by aqueous sodium carbonate solution to get free base. It was filtered, washed with water, dried and recrystallized from ethyl acetate to afford yellow compound with good yield 72–85%.

2.3a *5-(4-Methoxy-phenyl)-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidine-2,6-dicarboxylic acid diethyl ester* (**3a**): IR (KBr ν_{max}, cm^{-1}): 2977 (CH), 1703 (C=O), 1600 (C=C), 1496 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 1.33 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 2.38 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.76 (s, 3H, -OCH_3), 4.15 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.25 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.10 (s, 1H, CH), 6.81–7.26 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$)δ: 12.65, 14.22, 14.35, 23.59, 55.24, 57.24, 60.04, 61.43, 102.58, 114.15, 127.91, 129.1, 134.69, 145.11, 154.67, 159.62, 161.17, 163.72, 166.51. Mass (m/z):416 M+, 401, 371, 387, 343 (base peak), 309, 253; CHNS found (calc)%: C 60.56 (60.42), H 5.81 (4.76), N 6.73 (6.83), S 7.70 (7.59).

2.3b *5-(3,4-Dimethoxy-phenyl)-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidine-2,6-dicarboxylic acid diethyl ester* (**3b**): IR (KBr ν_{max}, cm^{-1}): 2984 (CH), 1709 (C=0), 1602 (C=C), 1501 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 1.34 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 2.38 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.83 (s, 3H, -OCH_3), 3.85 (s, 3H, -OCH_3), 4.15 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.25 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.11 (s, 1H, CH), 6.74–7.26 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$) δ: 12.64, 14.22, 14.35, 55.24, 55.86, 57.22, 60.03, 61.46, 102.48, 106.89, 109.60, 111.04, 114.14, 118.81, 127.90, 134.73, 145.12, 149.16, 154.73, 159.61, 161.17, 163.81, 166.53, 166.63. CHNS found (calc)%: C 59.18 (59.04), H 5.87 (5.62), N 6.27 (6.32), S 7.18 (7.31).

2.3c *5-(4-Hydroxy-phenyl)-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidine-2,6-dicarboxylic acid diethyl ester* (**3c**): IR (KBr ν_{max}, cm^{-1}) 3342 (OH), 2992 (CH), 1707 (C=O), 1610 (C=C), 1496 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 1.31 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 2.38 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 4.16 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.24 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.10 (s, 1H, CH), 6.70–7.12 (m, 4H, ArH), 7.27 (s, 1H, -OH). CHNS found (calc)%: C 59.69 (59.55), H 5.51 (5.35), N 6.96 (7.12), S 7.97 (7.67).

2.3d *3,7-Dimethyl-5-thiophen-2-yl-5H-thiazolo[3,2-a]pyrimidine-2,6-dicarboxylic acid diethyl ester* (**3d**): IR (KBr ν_{max}, cm^{-1}): 2976 (CH), 1705, 1610 (C=O), 1506 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J = 7.2 Hz, 3H,–CH_2CH_3), 1.36 (t, J = 7.2 Hz, 3H, –CH_2CH_3), 2.44 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 4.23 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.31 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.5 (s, 1H, CH), 6.88–7.26 (m, 3H, ArH). CHNS found (calc)%: C 55.08 (55.21), H 5.14 (4.97), N 7.14 (7.22), S 16.34 (16.23).

2.3e *5-phenyl-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidine-2,6-dicarboxylic acid diethyl ester* (**3e**): IR (KBr ν_{max}, cm^{-1}): 2976 (CH), 1705 (C=O), 1610 (C=C), 1506 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 1.32 (t, J = 7.2 Hz, 3H, -CH_2CH_3), 2.38 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 4.17 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.27 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.09 (s, 1H, CH), 6.79–6.84 (m, 5H, ArH). CHNS found (calc)%: C 62.16 (62.47), H 5.74 (5.72), N 7.25 (7.32), S 8.30 (8.13).

2.3f *5-(3-Methoxy-phenyl)-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidine-2,6-dicarboxylic acid 2-ethyl ester 6-methyl ester* (**3f**): IR (KBr ν_{max}, cm^{-1}): 2992 (CH), 1709 (C=O), 1620 (C=C), 1533 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): 1.32 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 2.37 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.76 (s, 3H, -OCH_3), 3.82 (s, 3H, -OCH_3), 4.23 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.16 (s, 1H, CH), 6.78–7.26 (m, 4H, ArH). CHNS found (calc)%: C 59.69 (59.56), H 5.51 (5.33), N 6.96 (7.07), S 7.97 (8.04).

2.3g *3,7-Dimethyl-5-naphthalen-1-yl-5H-thiazolo[3,2-a] pyrimidine-2,6-dicarboxylic acid 2-ethyl ester 6-methyl ester* (**3g**): IR (KBr ν_{max}, cm^{-1}): 2996(CH), 1712(C=O), 1601(C=C), 1496(C=N). ^{1}H NMR (300 MHz, $CDCl_3$): 1.28 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 2.35 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.82 (s, 3H, -OCH_3), 4.22 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.89 (s, 1H, CH), 7.42–8.45 (m, 7H, ArH). CHNS found (calc)%: C 65.38 (65.53), H 5.25 (5.19), N 6.63 (6.72), S 7.59 (7.71).

2.3h *3,7-Dimethyl-5-thiophen-2-yl-5H-thiazolo[3,2-a] pyrimidine-2,6-dicarboxylic acid 2-ethyl ester 6-methyl ester* (**3h**): IR (KBr ν_{max}, cm^{-1}): 2992 (CH), 1710 (C=O), 1609 (C=C), 1502 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): 1.36 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 2.39 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.29 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.45(s, 1H, CH), 6.86–7.26 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$) δ: 12.46, 14.24, 14.40, 23.46, 51.23, 52.82, 60.25, 61.57, 124.67, 125.68, 126.73, 1444.28, 144.50, 161.14, 166.58. CHNS found (calc)%: C 53.95 (54.05), H 4.79 (4.63), N 7.40 (7.29), S 16.95 (16.76).

2.3i *5-(4-Hydroxy-3-methoxy-phenyl)-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidine-2,6-dicarboxylic acid 2-ethyl ester 6-methyl ester* (**3i**): IR (KBr ν_{max}, cm^{-1}): 3379 (OH), 2993 (CH), 1715 (C=O), 1611 (C=C), 1506 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): 1.31 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 2.38 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.71 (s, 3H, -OCH_3) 3.86 (s, 3H, -OCH_3), 4.27 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.09 (s, 1H, CH), 6.79–6.84 (m, 3H, ArH), 7.26 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 12.64, 14.20, 14.37, 23.49, 51.10, 55.19, 57.54, 60.10, 61.49, 102.42, 102.61, 107.14, 108.81, 110.94, 114.32, 119.50, 134.29, 145.08, 146.91, 161.11, 163.87, 166.97. CHNS found (calc)%: C 57.40 (57.31), H 5.30 (5.45), N 6.69 (6.48), S 7.66 (7.43).

2.4 *General procedure for the synthesis of compounds* **5**(**a–m**)

A mixture of 3,4 dihyropyrimidine 2-thione (10 mmol) and ethyl-4-chloroacetoacetate (10 mmol) was refluxed in dry ethanol (20 ml) for 12 h. Excess of solvent was distilled off and the solid hydrochloride salt that separated was collected by filtration, dissolved in water and neutralized by aqueous sodium carbonate solution to get free base. It was filtered, washed with water, dried and recrystallized from ethyl acetate to afford yellow compound with good yield 70–85%.

2.4a *3-Ethoxycarbonylmethyl-7-methyl-5-phenyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester* (**5a**): IR (KBr ν_{max}, cm^{-1}): 3099, 2987 (CH), 1730, 1660 (C=O), 1479 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 1.28 (t, J = 7.2 Hz, 3H, -CH_2CH_3), 2.37 (s, 3H, CH_3), 3.35 (s, 2H, CH_2), 4.11 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.17 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.21 (s, 1H, CH), 6.23 (s, 1H, S-CH), 7.24–7.32 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$) δ: 14.05, 14.35, 23.74, 33.61, 57.91, 59.75, 61.83, 100.5, 103.66, 126.39, 128.18, 128.37, 128.68, 128.82, 131.63, 142.83, 155.55, 166.29, 166.60, 167.73. CHNS found (calc)%: C 62.16 (61.98), H 5.74 (5.69), N 7.25 (7.13), S 8.30 (8.27).

2.4b *3-Ethoxycarbonylmethyl-5-(3-methoxy-phenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester* (**5b**): IR (KBr ν_{max}, cm^{-1}): 3095, 2974 (CH), 1732, 1650 (C=O), 1484 (C=N), ^{1}H NMR (400 MHz, DMSO): δ 1.24 (t, J = 7.2 Hz, 3H, -CH_2CH_3), 1.26 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 2.38 (s, 3H, CH_3), 3.32 (s, 2H, CH_2), 3.81 (s, 3H, -OCH_3) 4.12 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.19 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.16 (s, 1H, CH), 6.28 (s, 1H, S-CH), 6.98–7.26 (m, 4H, ArH). CHNS found (calc)%: C 60.56 (60.45), H 5.81 (5.99), N 6.73 (6.67), S 7.70 (7.81).

2.4c *3-Ethoxycarbonylmethyl-5-(4-methoxy-phenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester* (**5c**): IR (KBr ν_{max}, cm^{-1}): 3082, 2991 (CH), 1726, 1658 (C=O), 1481 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, J = 7.2 Hz, 3H, -CH_2CH_3), 1.33 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 2.37 (s, 3H, CH_3), 3.26 (s, 2H, CH_2) 3.79 (s, 3H, -OCH_3), 4.16 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.25 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.10 (s, 1H, CH), 6.29 (s, 1H, S-CH), 6.81–7.22 (m, 4H, ArH). CHNS found (calc)%: C 60.56 (60.43), H 5.81 (5.93), N 6.73 (6.71), S 7.70 (7.87).

2.4d *5-(3,4-Dimethoxy-phenyl)-3-ethoxycarbonylmethyl-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester* (**5d**): IR (KBr ν_{max}, cm^{-1}): 3072, 2992 (CH), 1729, 1654 (C=O), 1488 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, J = 7.2 Hz, 3H, -CH_2CH_3), 1.37 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 2.38 (s, 3H, CH_3), 3.46 (s, 2H, CH_2), 3.83 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3), 4.15 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.25 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.11 (s, 1H, CH), 6.21 (s, 1H, S-CH), 6.74–7.26 (m, 3H, ArH). CHNS found (calc)%: C 59.18(59.22), H 5.87 (5.93), N 6.27 (6.37), S 7.18 (7.14).

2.4e *3-Ethoxycarbonylmethyl-5-(4-hydroxy-phenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester* (**5e**): IR (KBr ν_{max}, cm^{-1}): 3344(OH), 3021, 2981 (CH), 1728, 1662 (C=O), 1472 (C=N). ^{1}H NMR (400 MHz, DMSO): δ 1.16 (t, J = 7.2 Hz, 3H, -CH_2CH_3), 1.21 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 2.23 (s, 3H, CH_3), 3.29 (s, 2H, CH_2), 4.00 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.10 (q, J = 7.2 Hz, 2H, CH_2CH_3), 5.96 (s, 1H, CH), 6.07 (s, 1H, S-CH), 6.66–7.05 (m, 4H, ArH), 9.50 (s, 1H, -OH). ^{13}C NMR (DMSO) δ: 13.89, 14.12, 23.18, 32.77, 56.53, 59.04, 61.07, 110.02, 104.93, 115.34, 127.32, 127.61, 131.86, 133.71, 154.16, 157.36, 165.32, 165.59, 168.05. CHNS found (calc)%: C 59.69 (59.81), H 5.51 (5.62), N 6.96 (6.87), S 7.97 (8.11).

2.4f *3-Ethoxycarbonylmethyl-7-methyl-5-naphthalen-1-yl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester* (**5f**): IR (KBr ν_{max}, cm^{-1}): 3056, 2990 (CH), 1725, 1667 (C=O), 1481 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (t, J = 7.2 Hz, 3H, -CH_2CH_3), 1.27 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 2.51 (s, 3H, CH_3), 3.28 (s, 2H, CH_2), 4.06 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.26 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.81 (S, 1H, CH), 7.05 (s, 1H, S-CH), 7.47–8.32 (m, 7H, ArH). CHNS found (calc)%: C 66.03 (66.21), H 5.54 (5.66), N 6.42 (6.29), S 7.35 (7.54).

2.4g *3-Ethoxycarbonylmethyl-7-methyl-5-thiophen-2-yl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester* (**5g**): IR (KBr ν_{max}, cm^{-1}): 3082, 2982 (CH), 1725, 1655 (C=O), 1488 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, J = 7.2 Hz, 3H, -CH_2CH_3), 1.33 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 2.58 (s, 3H, CH_3), 3.28 (s, 2H, CH_2), 4.20 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.29 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.38 (s, 1H, CH), 6.50 (s, 1H, S-CH), 6.91–7.24 (m, 3H, ArH). CHNS found (calc)%: C 55.08 (55.14), H 5.14 (5.17), N 7.14 (6.97), S 16.34 (16.47).

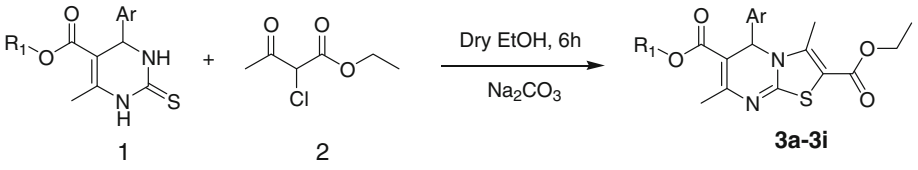
2.4h *3-Ethoxycarbonylmethyl-5-(4-hydroxy-3-methoxy-phenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester* (**5h**): IR (KBr ν_{max}, cm^{-1}): 3387(OH), 3066, 2976 (CH), 1730, 1653 (C=O), 1484 (C=N). ^{1}H NMR (400 MHz, DMSO): 1.18 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 1.23 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 2.47 (s, 3H, CH_3), 3.38 (s, 2H, CH_2), 3.83 (s, 3H, -OCH_3), 4.19 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.25 (q, J = 7.2 Hz, 2H, CH_2CH_3), 5.85 (s, 1H, CH), 6.10 (s, 1H, S-CH), 6.74–6.85 (m, 3H, ArH), 7.77 (s, 1H, OH). ^{13}C NMR (DMSO) δ: 13.87, 14.18, 23.17, 32.81, 55.46, 56.73, 59.06, 60.64, 99.87, 104.89, 110.17, 115.65, 118.60, 131.97, 134.19, 146.64, 147.28, 154.29, 165.39, 165.65, 168.1. CHNS found (calc)%: C 58.32 (58.49), H 5.59 (5.73), N 6.48 (6.37), S 7.41 (7.28).

2.4i *3-Ethoxycarbonylmethyl-5-(3-methoxy-phenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid methyl ester* (**5i**): IR (KBr ν_{max}, cm^{-1}): 3021, 2981 (CH), 1728, 1662 (C=O), 1472 (C=N). ^{1}H NMR (400 MHz, DMSO): δ 1.21 (t, J = 7.2 Hz, 3H, -CH_2CH_3), 2.38 (s, 3H, CH_3), 3.29 (s, 2H, CH_2), 3.76 (s, 3H, -OCH_3), 3.92 (s, 3H, -OCH_3), 4.18 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.16 (s, 1H, CH), 6.28 (s, 1H, SH), 6.79–7.28 (m, 4H, ArH). ^{13}C NMR (DMSO) δ: 13.96, 23.07, 32.08, 55.00, 56.71, 57.09, 61.32,102.13, 105.17, 112.35, 113.25, 118.21, 129.96, 130.25, 143.70, 154.05, 159.33, 160.46, 162.63, 165.36. CHNS found (calc)%: C 59.69 (59.88), H 5.51 (5.53), N 6.96 (7.04), S 7.97 (7.71).

2.4j *3-Ethoxycarbonylmethyl-5-(4-hydroxy-phenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid methyl ester* (**5j**): IR (KBr ν_{max}, cm^{-1}): 3348(OH), 3056, 2987 (CH), 1732, 1659 (C=O), 1486 (C=N). ^{1}H NMR (400 MHz, DMSO): δ 1.19 (t, J = 7.2 Hz, 3H, CH_2CH_3), 2.46 (s, 3H, CH_3), 3.29 (s, 2H, CH2), 3.84(s, 3H, OCH_3), 4.22 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.10 (s, 1H, CH), 6.20 (s, 1H, SCH), 6.76–7.19 (m, 4H, ArH), 8.65 (s, 1H, -OH). CHNS found (calc)%: C 58.75 (58.71), H 5.19 (5.33), N 7.21 (7.10), S 8.26 (8.42).

2.4k *3-Ethoxycarbonylmethyl-7-methyl-5-naphthalen-1-yl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid methyl ester* (**5k**): IR (KBr ν_{max}, cm^{-1}): 3031, 2998 (CH), 1727, 1653 (C=O), 1483 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (t, J = 7.2 Hz, 3H, -CH_2CH_3), 2.50 (s, 3H, CH_3), 3.31 (s, 2H, CH_2), 3.83(s, 3H, OCH_3), 4.20 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.80 (s, 1H, CH), 6.85 (s, 1H, SCH), 7.37–8.42 (m, 7H, ArH). CHNS found (calc)%: C 65.38 (65.27), H 5.25 (5.15), N 6.63 (6.71), S 7.59 (7.74).

2.4l *3-Ethoxycarbonylmethyl-7-methyl-5-thiophen-2-yl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid methyl ester* (**5l**): IR (KBr ν_{max}, cm^{-1}): 3044, 2995 (CH), 1735, 1654 (C=O), 1489 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 2.57 (s, 3H, CH_3), 3.31 (s, 2H, CH_2), 3.78 (s, 3H, -OCH_3), 4.31 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.38 (s, 1H, CH), 6.50 (s, 1H, SCH), 6.88–7.25 (m, 3H, ArH). CHNS found



Scheme 1. Synthesis of 5-(aryl substituted)-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidine- 2, 6-dicarboxylic acid diester.

(calc)%: C 53.95 (53.77), H 4.79 (4.96), N 7.40 (7.36), S 16.95 (16.66).

2.4m *3-Ethoxycarbonylmethyl-5-(4-hydroxy-3-methoxy-phenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid methyl ester* (**5m**): IR (KBr): 3392 (OH), 3033, 2987 (CH), 1725, 1666 (C=O), 1481 (C=N). ^{1}H NMR (400 MHz, DMSO): δ 1.30 (t, J = 7.2 Hz, 3H,-CH_2CH_3), 2.32 (s, 3H, CH_3), 3.37 (s, 2H, -CH_2), 3.82 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.29 (q, J = 7.2 Hz, 2H, CH_2CH_3), 5.85 (s, 1H, CH), 6.09 (s,1H, SCH), 6.82–6.97 (m, 3H, ArH), 8.19 (s, 1H, OH). CHNS found (calc)%: C 57.40 (57.22), H 5.30 (5.43), N 6.69 (6.75), S 7.66 (7.49).

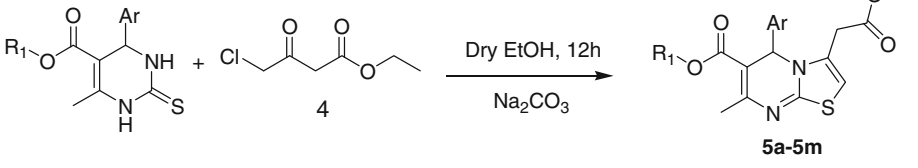
2.5 *Crystallography*

Yellow coloured single crystal of compound **3e** was obtained by slow evaporation of 1:1 mixture of ethyl acetate and methanol solvents. The X-ray diffraction data for the compound **3e** was collected on a Bruker Smart CCD Area Detector, using MoKα (λ = 0.71073Å) radiation. Intensity data were collected up to a maximum of 23° in the ω–Φ scan mode. The data were reduced using SAINT-PLUS.[19] The structure was solved by direct methods using SHELXS97[20] and refined by difference Fourier syntheses using SHELXL97.[20] The positional and anisotropic displacement parameters of all non-hydrogen atoms were included in the full-matrix least-square refinement. A total of 9700 reflections were collected, resulting in 3348 [R(int) = 0.0467] independent reflections of which the number of reflections satisfying I>2σ(I) criteria was 2514. The R factor for observed data finally converged to R = 0.0541 with wR2 = 0.1356. Molecular diagrams were generated using ORTEP.[21] The mean plane calculation was done using the program PARST.[22]

The CIF file was deposited at the Cambridge Crystallographic Data Centre, The deposition number is CCDC-**841973**

2.6 *Antimicrobial activity*

Antibacterial activities of the synthesized compounds **3(a–i)** were tested against the following standard bacterial strains: *Bacillus subtilis* (MTCC 121), *Staphylococcus aureus* (7443), *Escherichia coli* (7410) and *Pseudomonas aeruginosa* (MTCC 7903) by Paper disc diffusion method.[23,24] The standard strains were procured from the (MTCC) and the pathological strains were produced. The sterile medium (Nutrient Agar medium, 15 mL) in each Petri plates was uniformly smeared with cultures of Gram +ve and Gram -ve bacteria. Sterile discs of 10 mm diameter (Hi-Media) were made in each of the Petri plates, to which 50 µL (1 mg/mL i.e., 50 µg/disc) of the different test compounds were added. The treatments also included 50 µL of ethyl acetate and gentamicin as negative and positive control for comparison. For each treatment, three replicates were maintained. The plates were incubated at 37°C for 24 h and the size of the resulting zone of inhibition, if any, was determined. The data were subjected to analysis of variance (ANOVA). The results of the antimicrobial activity of the compounds **3(a–i)** are shown in table 4.



Scheme 2. Synthesis of 3-Ethoxycarbonylmethyl-5-(substituted aryl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ester.

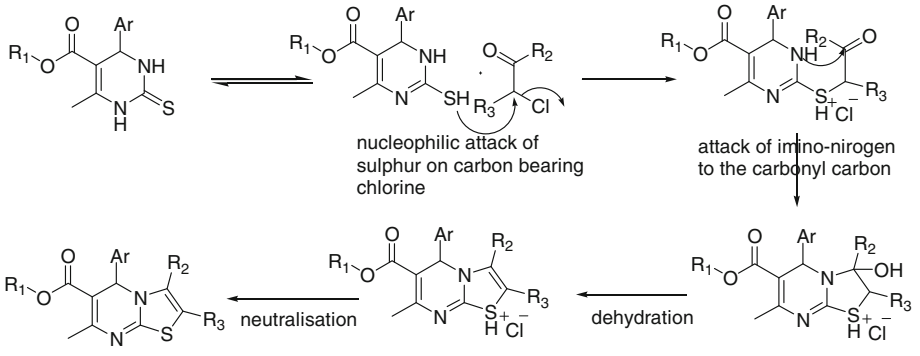
3. Result and discussion

3.1 *Synthesis*

The parent compound (dihydropyrimidine derivatives) **1** was obtained on refluxing the substituted aryl aldehydes, thiourea and ethyl/methyl acetoacetate in ethanol for 7–9h in the presence of catalytic amount of concentrated hydrochloric acid. The reaction mixture was kept overnight and the precipitate obtained was filtered and the compound was recrystallized with ethanol in good yield.[25]

The treatment of **1** with α-haloester in ethanol under reflux for about 6 h and 12 h afforded **3(a–i)** as shown in scheme 1 and **5(a–m)** as shown in scheme 2 respectively. The proposed mechanism for the above reaction is given in scheme 3. Yields of these one pot protocol reactions following recrystallization from ethanol were in the order of 71–85% as shown in table 1.

The IR spectra of compounds **3(a–i)** and **5(a–m)** showed the absence of the sharp absorption peak at 3200–3400 cm^{-1}, which is the characteristic absorption of NH group of starting material. This marks the evidence for the formation of the expected products.



Scheme 3. Mechanism for the synthesis of compounds (**3a–3i**) and (**5a–5m**).

Table 1. Physical and analytical data of the compounds **(3a–3i)** and **(5a–5m)**.

Products	Ar	R1	Yield (%)	m.p. (°C)	Mol. formula
3a	4-OCH_3C6H_4	OEt	81	117–118	$C_{21}H_{24}N_2O_5S$
3b	4-OCH_3 3-$OCH_3C_6H_3$	OEt	83	109–110	$C_{22}H_{26}N_2O_6S$
3c	4-OHC_6H_4	OEt	78	117–118	$C_{20}H_{22}N_2O_5S$
3d	C_4H_3S (Thienyl)	OEt	76	114–115	$C_{18}H_{20}N_2O_4S_2$
3e	C_6H_5	OEt	85	132–133	$C_{20}H_{22}N_2O_4S$
3f	3-$OCH_3C_6H_4$	OMe	83	112–113	$C_{20}H_{22}N_2O_5S$
3g	α-napthyl	OMe	72	119–120	$C_{23}H_{22}N_2O_4S$
3h	C_4H_3S (Thienyl)	OMe	76	117–118	$C_{17}H_{18}N_2O_4S_2$
3i	4-OH 3-$OCH_3C_6H_3$	OMe	75	115–116	$C_{20}H_{22}N_2O_6S$
5a	C_6H_5	OEt	74	134–135	$C_{20}H_{22}N_2O_4S$
5b	3-$OCH_3C_6H_4$	OEt	82	141–142	$C_{21}H_{24}N_2O_5S$
5c	4-$OCH_3C_6H_4$	OEt	70	133–134	$C_{21}H_{24}N_2O_5S$
5d	4-OCH_3 3-$OCH_3C_6H_3$	OEt	73	138–139	$C_{22}H_{26}N_2O_6S$
5e	4-OHC_6H_4	OEt	71	134–135	$C_{20}H_{22}N_2O_5S$
5f	α-napthyl	OEt	72	135–136	$C_{24}H_{24}N_2O_4S$
5g	C_4H_3S (Thienyl)	OEt	74	133–134	$C_{18}H_{20}N_2O_4S_2$
5h	4-OH 3-$OCH_3C_6H_3$	OEt	78	128–129	$C_{21}H_{24}N_2O_6S$
5i	3-$OCH_3C_6H_4$	OMe	85	104–105	$C_{20}H_{22}N_2O_5S$
5j	4-OHC_6H_4	OMe	75	112–113	$C_{19}H_{20}N_2O_5S$
5k	α-napthyl	OMe	72	106–107	$C_{23}H_{22}N_2O_4S$
5l	C_4H_3S (Thienyl)	OMe	79	111–112	$C_{17}H_{18}N_2O_4S_2$
5m	4-OH 3-$OCH_3C_6H_3$	OMe	75	108–109	$C_{20}H_{22}N_2O_6S_2$

Table 2. Crystal data and structure refinement for compound **3e**.

Empirical formula	C20 H22 N2 O4 S
Formula weight	386.46
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	
a (Å)	12.520(3)
b (Å)	12.179(3)
c (Å)	12.544(3)
α (°)	90
β (°)	93.160(4)
γ (°)	90
Volume	1909.7(7)Å^3
Z	4
Calculated density (mg/m^3)	1.344
Absorption coefficient	(0.198 mm^{-1})
F(000)	816
Crystal size	0.40 mm × 0.35 mm × 0.30 mm
Theta range for data collection	2.33 to 24.99
Limiting indices	−14<=h<=1 −13<=k<=14 −14<=l<=11
Reflections collected/unique	9700/3348 [R(int) = 0.0467]
Completeness to theta	24.99 99.8%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3348/0/248
Goodness-of-fit on F^2	1.096
Final R indices [I > 2sigma(I)]	R1 = 0.0541, wR2 = 0.1356
R indices (all data)	R1 = 0.0740, wR2 = 0.1633
Largest diff. peak and hole (e Å^{-3})	0.709 and −0.335

Further confirmation of the products **3(a–i)** was done from ^{1}H NMR spectra, where the appearance of additional triplet signal at 1.30–1.35 ppm, quartet signal at 4.2–4.3 ppm and singlet at 2.45 ppm corresponds to the formation of new CH_3, CH_2 and CH_3 groups, respectively. Downfield shift of the 5H proton to 6.1 ppm is a further confirmatory evidence for the product formation. In support of the formation of the products **5(a–m)** by ^{1}H NMR spectra, the triplet signal at 1.30–1.35 ppm, quartet signal at 4.2–4.3 ppm, singlet at 2.45 ppm corresponds to the formation of additional

Table 3. Non-bonded interactions and possible hydrogen bonds (Å, °) for compound **3e**.

D—H···A	D—H	H···A	D···A	D—H···A
C1-H1C...O3^{i}	0.960(3)	2.564(2)	3.510(3)	168.57
C11-H11...N1^{ii}	0.930(3)	2.637(2)	3.507(4)	156.1
C7-H7A$_\pi$...HI4$^{i}_{g}$	0.969(2)	3.282(2)	4.164(4)	152.1

(D-donor; A-acceptor; H-hydrogen)
Symmetry code: (i) x − 1/2, −y + 1/2 + 1, +z − 1/2
(ii) x − 1/2, −y + 1/2 + 1, +z + 1/2
(ii) $x + 1/2, 3/2 - y, z + 1/2$

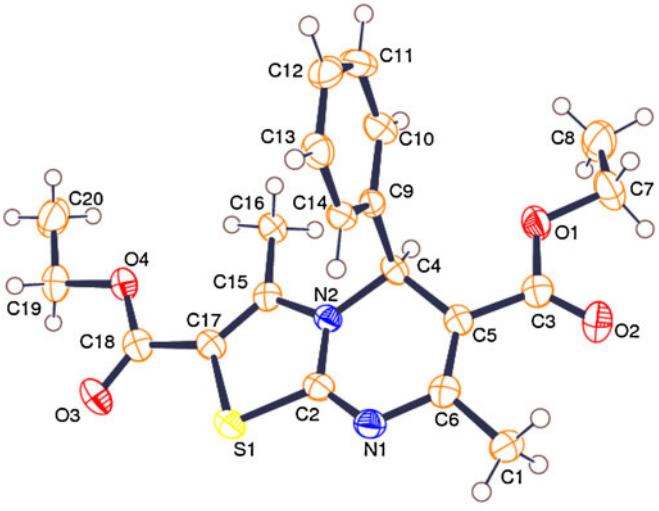


Figure 1. Ortep view of compound **3e**, showing 50% probability ellipsoids and the atom numbering scheme.

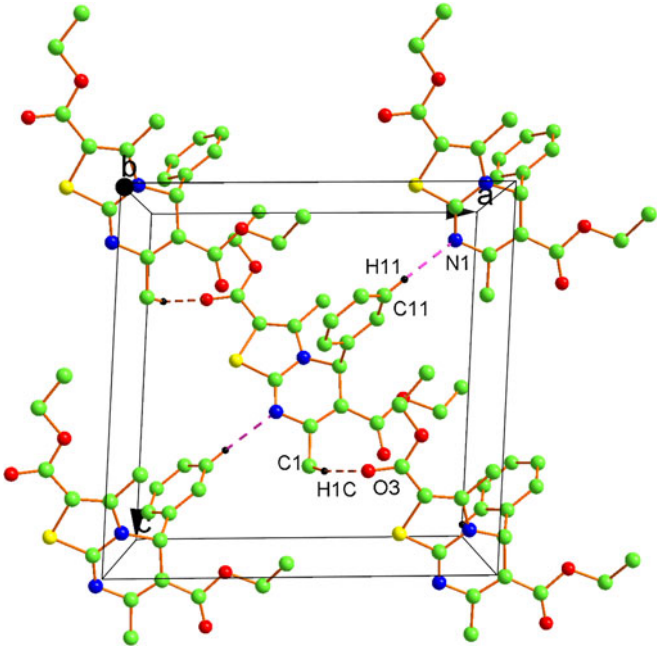


Figure 2. A unit cell packing of the title compound showing intermolecular interactions with dotted lines. H-atoms not involved in hydrogen bonding have been excluded.

CH_3, CH_2 and CH_2 groups respectively. Appearance of singlet at 6.2 ppm confirms the 1H of thiazole.

3.2 *Crystal structure analysis*

Summary of the crystallographic data and other structure refinement parameters of the compound **3e** are shown in table 2. Table 3 shows the respective hydrogen bond interactions of the compound. The ORTEP view of the molecule with atomic labelling (thermal ellipsoids drawn at 50% probability) is shown in figure 1. Figure 2 shows the packing of molecules in the crystal structure.

In the compound **3e** the thiazolopyrimidine ring is substituted with the aryl ring at C4 chiral carbon atom and is positioned axially to the dihydropyrimidine ring,[26] whereas carboxylic acid ethyl ester and the methyl, groups are on either side of the ring. The dihedral angle between the planes of the aryl and thiazolopyrimidine rings is 86.49°. The 4-aryl substituent (methoxy group) adopts a synperiplanar configuration with respect to C4–H4 bond. In **3e**, the central pyrimidine ring with a chiral C4 atom at the point of substitution of a benzene ring (C9–C14) is significantly puckered and adopts a conformation which is best described as an intermediate between a boat and a screw boat form.[27] The ring puckering parameters[28] for the pyrimidine ring are Q (2) = 0.2217(3) Å, φ (2) = −8.02(7)° and q = 117.06(6)°, respectively.

The crystal structure is primarily stabilized by some interesting features that comprise intermolecular C–H…O and C–H…N interactions. A strong intermolecular C–H…O interaction results in chain of molecule along b axis. On the other hand a strong C–H…N hydrogen bond results in forming bridge between the two chains of molecules.The molecular packing is further stabilized by π-π stacking interactions between the thiazolopyrimidine rings as the C5–C17 (-x, 1-y, -z) is disposed at a distance of 3.518(3) Å. In addition, π-ring interactions of the type C–H…C_g (C_g being the centroid of the rings) are also observed in the crystal structure, table 2.

Table 4. Inhibition zone diameter (mm) of synthesized compounds against tested bacterial strains by paper disc diffusion method.

	Gram-positive bacteria		Gram-negative bacteria		Fungi
Compounds	*Bacillus subtilis*	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albicans*
3a	–	–	15.0 ± 1.00	–	15.66 ± 0.56
3b	–	–	–	–	–
3c	–	18.00 ± 1.00	–	–	–
3d	–	–	–	–	–
3e	–	19.66 ± 0.56	–	–	16.00 ± 1.0
3f	–	–	–	–	–
3g	–	–	–	–	13.66 ± 1.52
3h	–	–	–		–
3i	–		–		–
Gentamicin (10 µg/disc)	25	26	30	20	ND
Nystatin (10 µg/disc)	ND	ND	ND	ND	20

Note: "–" Not active, "ND" – Not determined.

3.3 *Antimicrobial evaluation*

The antimicrobial activity was performed using disc diffusion method with different stains of bacteria and fungi. The results with test compounds **3(a–i)** indicate some degrees of antimicrobial activity. Gentamicin was used as a reference to evaluate the potency of tested compounds. Compounds **3a**, **3c**, **3e** and **3g** showed moderate antimicrobial activity, while compounds **3b**, **3d**, **3f**, **3h** and **3i** did not show any activity against the tested microorganisms. The results of the antimicrobial activity is given in table 4.

4. Conclusion

The present work reports the synthesis of diesters of thiazolopyimidine derivatives. The formation of the thiazolopyrimidine moiety was confirmed by analytical data. The investigation of antimicrobial screening reveals that the compounds **3a**, **3c**, **3e** and **3g** have moderate antimicrobial activities against *Staphylococcus aureus, Escherichia coli* and *Candida albicans* comparable to the standard *Gentamicin* and *Nystatin.* Additionally, X-ray analysis was carried out for one of the derivative in order to establish supramolecular assembly with the specific aim of assessing various weak interactions including CH…O, CH…N, $\pi\ldots\pi$ and CH…π that control the architecture of organic solids.

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