

Synthesis, reactions, and antiarrhythmic activities of some novel pyrimidines and pyridines fused with thiophene moiety

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We report herein the synthesis and antiarrhythmic activities of some newly synthesized heterocyclic theino[2,3-c]pyrimidine and theino[2,3-c]pyridine derivatives fused with thiophene moiety. Initially the acute toxicity of the compounds was assayed via the determination of their LD₅₀. The antiarrhythmic activities for the compounds were determined and all the tested compounds were found more potent than Procaine amide[®] and Lidocaine[®] as positive antiarrhythmic controls.

Key Words: Pyrimidine, pyrimidinethione, thiazolopyrimidine, antiarrhythmic activity.

Introduction

Our previous work reported that thiopyrimidines possess antimicrobial,¹ anticonvulsant,^{2,3} antiarrhythmic,⁴ anti-inflammatory,^{5,6} and antitumor^{7–10} activities. In addition, we reported that certain of our newly prepared heterocyclic compounds exhibit antiparkinsonian,¹¹ antitumor,¹² antimicrobial¹³ and anti-inflammatory¹⁴ activities. On the other hand, many condensed heterocyclic systems, especially those linked to a pyrimidine ring, play an important role as potential medicinal agents and in cancer and virus research.^{15,16} Recent studies reported on the synthesis of some new thiazole candidates as antimicrobial and anticancer agents.^{17–20} In view of these reports and in continuation of our previous works in heterocyclic chemistry, we synthesized some new

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thiopyrimidine and thiazolopyrimidines fused with thiophene ring for the evaluation of their antiarrhythmic activity compared to Procaine amide[®] and Lidocaine[®] as positive antiarrhythmic controls.

Experimental

Synthesis

Melting points were determined on an Electrothermal IA 9000 SERIES digital melting point apparatus (Electrothermal, Essex, UK) and are uncorrected. Elemental analyses were performed in the Microanalytical Unit, National Research Centre, Cairo, Egypt, and were found within $\pm 0.4\%$ of the theoretical values. The IR spectra (KBr) were recorded on a FT IR-8201 PC Spectrophotometer. The ¹H-NMR (270 MHz) and ¹³C-NMR (67.5 MHz) spectra were measured with Jeol (Japan) in DMSO-d₆ or CDCl₃ as solvents. The chemical shifts were recorded (δ , ppm) relative to TMS. The mass spectra were run at 70 eV with a Finnigan SSQ 7000 spectrometer. All reactions were followed by TLC (silica gel, aluminum sheets 60 F₂₅₄, Merck). All animals were obtained from the Animal House Colony, Research Institute of Ophthalmology, Giza, Egypt.

7-Alkyl-2-thioxo-2,3,5,6,7,8-hexahydro-1H-9-thia-1,3,7-triaza-fluoren-4-ones (3a,b)

A mixture of **2a,b** (10 mmol) and thiourea (0.8 g, 10 mmol) was fused together in an oil bath at 180 °C for 3 h. The oily residue was solidified with ethanol, and the formed solid was collected by filtration, dried, and recrystallized from the appropriate solvent to give compounds **3a,b**.

7-Ethyl-2-thioxo-2,3,5,6,7,8-hexahydro-1H-9-thia-1,3,7-triazafuoren-4-one (3a): Yield 65%; mp 280-282 °C (dioxane). - IR [ν , cm⁻¹, KBr]: 3340 (NH), 1665 (C=O), 1260 (C=S). -¹H-NMR (270 MHz, δ ppm, DMSO-d₆): 1.30 (t, 3H, CH₃), 2.44 (q, 2H, CH₂N), 2.75 and 2.85 (2t, 4H, CH₂CH₂), 3.50 (s, 2H, CH₂), 9.50 and 10.0 (2s, 2H, 2NH, exchangeable with D₂O). -MS m/z (%): 267 [M⁺] (32), corresponding to the molecular formula C₁₁H₁₃N₃OS₂ and base peak at 252 [M⁺-CH₃] (100). Anal. Calcd for C₁₁H₁₃N₃OS₂ (267.36): C, 49.42; H, 4.90; N, 15.72; S, 23.98. Found: C, 49.38; H, 4.86; N, 15.68; S, 23.94.

7-Propyl-2-thioxo-2,3,5,6,7,8-hexahydro-1H-9-thia-1,3,7-triazafuoren-4-one (3b): Yield 54%; mp 270-272 °C (dioxane). - IR [ν , cm⁻¹, KBr]: 3335 (NH), 1658 (C=O), 1270 (C=S). -¹H-NMR (270 MHz, δ ppm, DMSO-d₆): 1.00 (t, 3H, CH₃), 1.20-1.22 (m, 2H, CH₂), 2.30 (t, 2H, CH₂N), 2.60 and 2.80 (2t, 4H, CH₂CH₂), 3.50 (s, 2H, CH₂), 10.50 and 11.00 (2s, 2H, 2NH, exchangeable with D₂O). -¹³C-NMR (67.5 MHz, δ ppm, DMSO-d₆): 11.2 (CH₃), 20.9, 23.0, 52.1, 55.95 and 58.05 (C₅), 160.12 (C=O), 174.10 (C=S), 115.85, 126.05, 135.80 and 169.10 (thiophene carbons). -MS m/z (%): 281 [M⁺] (12), corresponding to the molecular formula C₁₂H₁₅N₃OS₂ and base peak at 266 [M⁺-CH₃] (100). Anal. Calcd for C₁₂H₁₅N₃OS₂ (281.39): C, 51.22; H, 5.37; N, 14.93; S, 22.79. Found: C, 51.18; H, 5.32; N, 14.88; S, 22.75.

7-Alkyl-2-methyl-5,6,7,8-tetrahydro-1H-9-thia-1,3,7-triazafuoren-4-ones (4a,b)

A stream of dry hydrogen chloride gas was passed through a solution of **2a,b** (1 mmol) and acetonitrile (10 mL) in ethanol (100 mL) for 3 h with stirring at room temperature. The reaction mixture was poured onto ice water and basified with potassium bicarbonate. The solid formed was collected by filtration and recrystallized from the appropriate solvent to yield compounds **4a,b**.

7-Ethyl-2-methyl-5,6,7,8-tetrahydro-1H-9-thia-1,3,7-triazafuoren-4-one (4a): Yield 82%; mp 250-252 °C (EtOH). - IR [ν , cm^{-1} , KBr]: 3380 (NH), 1645 (C=O); $^1\text{H-NMR}$ (270 MHz, δ ppm, DMSO- d_6): 1.20 (t, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.60 (q, 2H, CH_2N), 2.85 and 2.92 (2t, 4H, CH_2CH_2), 3.70 (s, 2H, CH_2), 11.50 (bs, 1H, NH, exchangeable with D_2O). - $^{13}\text{C-NMR}$ (67.5 MHz, δ ppm, DMSO- d_6): 13.30, 25.00 (2 CH_3), 22.75, 48.55, 52.10 and 58.00 (C_4), 162.90 (C=O), 163.77 (C=N), 126.50, 135.65, 144.58 and 169.05 (thiophene carbons); -MS m/z (%): 249 [M^+] (8), corresponding to the molecular formula $\text{C}_{12}\text{H}_{15}\text{N}_3\text{OS}$ and base peak at 192 [$\text{M}^+ - \text{NH-CCH}_3 - \text{NH}$] (100). Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{OS}$ (249.33): C, 57.81; H, 6.06; N, 16.85; S, 12.86. Found: C, 57.76; H, 6.00; N, 16.80; S, 12.79.

7-Propyl-2-methyl-5,6,7,8-tetrahydro-1H-9-thia-1,3,7-triazafuoren-4-one (4b): Yield 85%; mp 249-250 °C (dioxane). - IR [ν , cm^{-1} , KBr]: 3385 (NH), 1640 (C=O); $^1\text{H-NMR}$ (270 MHz, δ ppm, CDCl_3): 0.90 (t, 3H, CH_3), 1.40-1.44 (m, 2H, CH_2), 2.40 (t, 2H, CH_2N), 2.50 (s, 3H, CH_3), 2.70 and 2.90 (2t, 4H, CH_2CH_2), 3.65 (s, 2H, CH_2), 10.50 (bs, 1H, NH, exchangeable with D_2O). -MS m/z (%): 263 [M^+] (4), corresponding to the molecular formula $\text{C}_{13}\text{H}_{17}\text{N}_3\text{OS}$ and base peak at 234 [$\text{M}^+ - \text{C}_2\text{H}_5$] (100). Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{OS}$ (263.35): C, 59.29; H, 6.51; N, 15.96; S, 12.17. Found: C, 59.24; H, 6.48; N, 15.90; S, 12.13.

Ethyl 2-acetylamino-6-alkyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylates (5a,b)

A solution of **2a,b** (10 mmol) in acetic anhydride (10 mL) was heated under reflux for 2 h. The solvent was evaporated under reduced pressure and the residue was extracted with ethyl acetate then solidified with diethyl ether. The obtained solid was filtered off and recrystallized from the appropriate solvent to give compounds **5a,b**.

Ethyl 2-acetylamino-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (5a)²¹: Yield 48%; mp 110-112 °C (EtOH). - IR [ν , cm^{-1} , KBr]: 3304 (NH), 1725 (C=O), 1675 (C=O). $^1\text{H-NMR}$ (270 MHz, δ ppm, CDCl_3): 1.10 and 1.40 (2t, 6H, 2 CH_3), 2.40 (s, 3H, COCH_3), 2.70 (m, 2H, CH_2N), 2.78-2.96 (m, 4H, CH_2CH_2), 3.52 (s, 2H, CH_2), 4.50 (q, 2H, CH_2), 11.50 (bs, 1H, NH, exchangeable with D_2O). -MS m/z (%): 296 [M^+] (12), corresponding to the molecular formula $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$ and base peak at 252 [$\text{M}^+ - \text{COCH}_3$] (100). Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$ (296.38): C, 56.74; H, 6.80; N, 9.45; S, 10.82. Found: C, 56.70; H, 6.76; N, 9.41; S, 10.77.

Ethyl 2-acetylamino-6-propyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (5b): Yield 40%; mp 100-102 °C (EtOH). - IR [ν , cm^{-1} , KBr]: 3310 (NH), 1735 (C=O), 1665 (C=O). $^1\text{H-NMR}$ (270 MHz, δ ppm, CDCl_3): 0.90 and 1.10 (2t, 6H, 2 CH_3), 1.30-1.42 (m, 2H, CH_2), 2.40 (t, 2H, CH_2N), 2.45 (s, 3H, COCH_3), 2.60, 2.80 (2t, 4H, CH_2CH_2), 3.50 (s, 2H, CH_2), 4.50 (q, 2H, CH_2), 11.05 (bs, 1H, NH, exchangeable with D_2O). - $^{13}\text{C-NMR}$ (67.5 MHz, δ ppm, CDCl_3): 11.42, 13.74, 22.52 (3 CH_3), 21.00, 23.08, 52.98, 56.00, 58.44 and 60.42 (C_6), 159.40, 168.38 (2C=O), 98.85, 123.00, 128.45 and 176.32 (thiophene carbons). -MS m/z (%): 310 [M^+] (8), corresponding to the molecular formula $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$ and base peak at 281 [$\text{M}^+ - \text{C}_2\text{H}_5$] (100). Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$ (310.41): C, 58.04; H, 7.14; N, 9.02; S, 10.33. Found: C, 57.98; H, 7.10; N, 8.98; S, 10.28.

Ethyl 6-alkyl-2-(4,5,6,7-tetrachloro-1,3-dioxo-1,3,4,5-tetrahydroisoindol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylates (6a,b)

A mixture of **2a,b** (1 mmol) and 3,4,5,6-tetrachlorophthalic anhydride (0.28 g, 1 mmol) in glacial acetic acid (10 mL) was refluxed for 3 h. The solvent was concentrated under reduced pressure and the solid formed

was collected by filtration, dried and recrystallized from the appropriate solvent to give the imide **6a,b**.

Ethyl 6-ethyl-2-(4,5,6,7-tetrachloro-1,3-dioxo-1,3,4,5-tetrahydroisoindol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (6a): Yield 65%; mp 210-212 °C (DMF). - IR [ν , cm^{-1} , KBr]: 1730 (C=O), 1720 (CO, imide); $^1\text{H-NMR}$ (270 MHz, δ ppm, CDCl_3): 1.00 and 1.30 (2t, 6H, 2CH_3), 2.60 (q, 2H, CH_2N), 2.70 and 2.80 (2t, 4H, 2CH_2), 3.50 (s, 2H, CH_2), 4.30 (q, 2H, CH_2). -MS m/z (%): 520 [M^+] (16), corresponding to the molecular formula $\text{C}_{20}\text{H}_{16}\text{Cl}_4\text{N}_2\text{O}_4\text{S}$ and base peak at 491 [$\text{M}^+ - \text{Et}$] (100). Anal. Calcd for $\text{C}_{20}\text{H}_{16}\text{Cl}_4\text{N}_2\text{O}_4\text{S}$ (522.23): C, 46.00; H, 3.09; Cl, 27.16; N, 5.36; S, 6.14. Found: C, 45.96; H, 3.00; Cl, 27.12; N, 5.32; S, 6.10.

Ethyl 6-propyl-2-(4,5,6,7-tetrachloro-1,3-dioxo-1,3,4,5-tetrahydroisoindol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (6b): Yield 76%; mp 220-222 °C (DMF). - IR [ν , cm^{-1} , KBr]: 1735 (C=O), 1715 (C=O, imide). $^1\text{H-NMR}$ (270 MHz, δ ppm, CDCl_3): 0.90 and 1.20 (2t, 6H, 2CH_3), 1.28-1.32 (m, 2H, CH_2), 2.40 (t, 2H, CH_2N), 2.60, 2.80 (2t, 4H, CH_2CH_2), 3.50 (s, 2H, CH_2), 4.50 (q, 2H, CH_2). -MS m/z (%): 534 [M^+] (24), corresponding to the molecular formula $\text{C}_{21}\text{H}_{18}\text{Cl}_4\text{N}_2\text{O}_4\text{S}$ and base peak at 507 [$\text{M}^+ - \text{C}_2\text{H}_5$] (100). Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{Cl}_4\text{N}_2\text{O}_4\text{S}$ (536.25): C, 47.04; H, 3.38; Cl, 26.44; N, 5.22; S, 5.98. Found: C, 46.99; H, 3.34; Cl, 26.40; N, 5.18; S, 5.92.

Ethyl 6-alkyl-2-[6-(6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)-1,3,5,7-tetra-oxo-3, 5,6,7-tetrahydro-1H-pyrrolo[3,4-f]isoindol-2-yl]-4,5,6,7-tetrahydrothieno[2,3-c]-pyridine-3-carboxylates (7a,b)

A mixture of **2a,b** (2 mmol) and 1,2,4,5-benzenetetracarboxylic acid dianhydride (0.22 g, 1 mmol) in glacial acetic acid (10 mL) was heated under reflux for 3 h. The formed solid was filtered off, dried, and recrystallized from the appropriate solvent to yield bis-imides **7a,b**.

Ethyl 6-ethyl-2-[6-(6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)-1,3,5,7-tetra-oxo-3, 5,6,7-tetrahydro-1H-pyrrolo[3,4-f]isoindol-2-yl]-4,5,6,7-tetrahydrothieno[2,3-c]-pyridine-3-carboxylate (7a): Yield 65%; mp 245-247 °C (AcOH). - IR [ν , cm^{-1} , KBr]: 3175 (Ar-H), 1736 (C=O), 1718 (C=O, imide). $^1\text{H-NMR}$ (270 MHz, δ ppm, CDCl_3): 1.00 and 1.30 (2t, 12H, 4CH_3), 2.60 (q, 4H, $2\text{CH}_2\text{N}$), 2.70 and 2.80 (2t, 8H, $2\text{CH}_2\text{CH}_2$), 3.50 (s, 4H, 2CH_2), 4.30 (q, 4H, 2CH_2), 8.30 (s, 2H, Ar-H). -MS m/z (%): 690 [M^+] (18), corresponding to the molecular formula $\text{C}_{34}\text{H}_{34}\text{N}_4\text{O}_8\text{S}_2$ and base peak at 632 [$\text{M}^+ - \text{CH}_2\text{NC}_2\text{H}_5$] (100). Anal. Calcd for $\text{C}_{34}\text{H}_{34}\text{N}_4\text{O}_8\text{S}_2$ (690.78): C, 59.12; H, 4.96; N, 8.11; S, 9.28. Found: C, 59.07; H, 4.91; N, 8.06; S, 9.22.

Ethyl 6-propyl-2-[6-(6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)-1,3,5,7-tetra-oxo-3, 5,6,7-tetrahydro-1H-pyrrolo[3,4-f]isoindol-2-yl]-4,5,6,7-tetrahydrothieno[2,3-c]-pyridine-3-carboxylate (7b): Yield 70%; mp 235-237 °C (AcOH). - IR [ν , cm^{-1} , KBr]: 3190 (Ar-H), 1732 (C=O), 1715 (C=O, imide). $^1\text{H-NMR}$ (270 MHz, δ ppm, CDCl_3): 0.90 and 1.10 (2t, 12H, 4CH_3), 1.30-1.50 (m, 4H, 2CH_2), 2.40 (t, 4H, $2\text{CH}_2\text{N}$), 2.60 and 2.80 (2t, 8H, $2\text{CH}_2\text{CH}_2$), 3.50 (s, 4H, 2CH_2), 4.40 (q, 4H, 2CH_2), 8.50 (s, 2H, Ar-H). -MS m/z (%): 718 [M^+] (35), corresponding to the molecular formula $\text{C}_{36}\text{H}_{38}\text{N}_4\text{O}_8\text{S}_2$ and base peak at 660 [$\text{M}^+ - \text{NC}_3\text{H}_7$] (100). Anal. Calcd for $\text{C}_{36}\text{H}_{38}\text{N}_4\text{O}_8\text{S}_2$ (718.83): C, 60.15; H, 5.33; N, 7.74; S, 8.92. Found: C, 60.09; H, 5.28; N, 7.70; S, 8.88.

Ethyl 6-alkyl-2-(3-phenylureido-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylates (8a,b)

A mixture of **2a,b** (10 mmol) and phenylisocyanate (1.3 g, 10 mmol) was heated on a steam bath at 80 °C for 1 h. The obtained residue was triturated and solidified with a small amount of ethanol, filtered off, dried, and recrystallized from the appropriate solvent to give semicarbazide derivatives **8a,b**.

Ethyl 6-ethyl-2-(3-phenylureido-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (8a): Yield 74%; mp 135-137 °C (EtOH). - IR [ν , cm⁻¹, KBr]: 3310 (NH), 3150 (Ar-H), 1710 (C=O), 1680 (C=O). - ¹H-NMR (270 MHz, δ ppm, CDCl₃): 1.10 and 1.30 (2t, 6H, 2CH₃), 2.50 (q, 2H, CH₂N), 2.60 and 2.80 (2t, 4H, CH₂CH₂), 3.50 (s, 2H, CH₂), 4.20 (q, 2H, CH₂), 7.50-7.58 (m, 5H, ArH), 11.10 and 11.30 (2s, 2H, 2NH, exchangeable with D₂O). -MS m/z (%): 373 [M⁺] (12), corresponding to the molecular formula C₁₉H₂₃N₃O₃S and base peak at 328 [M⁺-OEt] (100). Anal. Calcd for C₁₉H₂₃N₃O₃S (373.46): C, 61.11; H, 6.21; N, 11.25; S, 8.58. Found: C, 60.98; H, 6.16; N, 11.19; S, 8.52.

Ethyl 6-propyl-2-(3-phenylureido-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (8b): Yield 70%; mp 130-132 °C (EtOH). - IR [ν , cm⁻¹, KBr]: 3340 (NH), 3160 (Ar-H), 1715 (C=O), 1675 (C=O). - ¹H-NMR (270 MHz, δ ppm, CDCl₃): 0.90 and 1.30 (2t, 6H, 2CH₃), 1.40-1.50 (m, 2H, CH₂), 2.50 (t, 2H, CH₂N), 2.60 and 2.80 (2t, 4H, CH₂CH₂), 3.50 (s, 2H, CH₂), 4.20 (q, 2H, CH₂), 7.40-7.50 (m, 5H, Ar-H), 10.70 and 10.90 (2s, 2H, 2NH, exchangeable with D₂O). -MS m/z (%): 387 [M⁺] (16), corresponding to the molecular formula C₂₀H₂₅N₃O₃S and base peak at 358 [M⁺-Et] (100). Anal. Calcd for C₂₀H₂₅N₃O₃S (387.49): C, 61.99; H, 6.50; N, 10.84; S, 8.27. Found: C, 61.93; H, 6.46; N, 10.80; S, 8.24.

Ethyl 6-alkyl-2-(3-phenylthioureido-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylates (9a,b)

A mixture of **2a,b** (10 mmol) and phenylisothiocyanate (1.3 g, 10 mmol) was heated on a steam bath (90 °C) for 2 h in the presence of a few drops of triethylamine as a catalyst. The obtained residue was triturated with ethanol and the formed solid was filtered off, dried, and recrystallized from the appropriate solvent to yield thiosemicarbazide derivatives **9a, b**.

Ethyl 6-ethyl-2-(3-phenylthioureido-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (9a): Yield 70%; mp 160-162 °C (EtOH). - IR [ν , cm⁻¹, KBr]: 3320 (NH), 3165 (Ar-H), 1715 (C=O), 1270 (C=S). - ¹H-NMR (270 MHz, δ ppm, CDCl₃): 1.20 and 1.40 (2t, 6H, 2CH₃), 2.50 (q, 2H, CH₂), 2.70 and 2.90 (2t, 4H, CH₂CH₂), 3.70 (s, 2H, CH₂), 4.20 (q, 2H, CH₂), 7.45-7.50 (m, 5H, ArH), 10.45 and 11.50 (2s, 2H, 2NH, exchangeable with D₂O). - ¹³C-NMR (67.5 MHz, δ ppm, CDCl₃): 13.05, 13.86 (2 CH₃), 23.15, 48.90, 52.32, 58.18 and 60.25 (C₅), 159.16 (C=O), 180.5 (C=S), 124.24, 126.15, 128.78, 136.35 (Ph-C), 113.18, 129.55, 135.0 and 164.66 (thiophene carbons). -MS m/z (%): 389 [M⁺], corresponding to the molecular formula C₁₉H₂₃N₃O₂S₂ and base peak at 344[M⁺-OEt] (100). Anal. Calcd for C₁₉H₂₃N₃O₂S₂ (389.53): C, 58.59; H, 5.95; N, 10.79; S, 16.46. Found: C, 58.54; H, 5.92; N, 10.74; S, 16.42.

Ethyl 6-propyl-2-(3-phenylthioureido-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (9b): Yield 75%; mp 150-152 °C (EtOH). - IR [ν , cm⁻¹, KBr]: 3315 (NH), 3175 (Ar-H), 1710 (C=O), 1260 (C=S). - ¹H-NMR (270 MHz, δ ppm, CDCl₃): 0.90 and 1.20 (2t, 6H, 2CH₃), 1.40-1.50 (m, 2H, CH₂), 2.40 (t, 2H, CH₂N), 2.60 and 2.80 (2t, 4H, CH₂CH₂), 3.50 (s, 2H, CH₂), 4.10 (q, 2H, CH₂), 7.40-7.48 (m, 5H, Ar-H), 10.68 and 12.10 (2s, 2H, 2NH, exchangeable with D₂O). -MS m/z (%): 403 [M⁺] (23), corresponding to the molecular formula C₂₀H₂₅N₃O₂S₂ and base peak at 374 [M⁺-Et] (100). Anal. Calcd for C₂₀H₂₅N₃O₂S₂

(403.55): C, 59.53; H, 6.24; N, 10.41; S, 15.89. Found: C, 59.48; H, 6.20; N, 10.38; S, 15.83.

7-Alkyl-3-phenyl-2-thioxo-2,3,5,6,7,8-hexahydro-1H-9-thia-1,3,7-triazafuoren-4-ones (10a,b)

A mixture of **9a,b** (10 mmol) and polyphosphoric acid (10 mL) in the presence of glacial acetic acid (2 mL) was heated on a steam bath at 100 °C for 2 h. The reaction mixture was poured onto ice water and the solid formed was collected, dried, and recrystallized from the appropriate solvent to yield thiopyrimidine derivatives **10a,b**.

7-Ethyl-3-phenyl-2-thioxo-2,3,5,6,7,8-hexahydro-1H-9-thia-1,3,7-triazafuoren-4-one (10a): Yield 55%; mp 95-97 °C (EtOH). - IR [ν , cm^{-1} , KBr]: 3318 (NH), 3165 (Ar-H), 1648 (C=O), 1255 (C=S). - $^1\text{H-NMR}$ (270 MHz, δ ppm, CDCl_3): 1.10 (t, 3H, CH_3), 2.30 (q, 2H, CH_2), 2.60 and 2.80 (2t, 4H, CH_2CH_2), 3.50 (s, 2H, CH_2), 7.44-7.52 (m, 5H, Ar-H), 9.80 (bs, 1H, NH, exchangeable with D_2O). - $^{13}\text{C-NMR}$ (67.5 MHz, δ ppm, CDCl_3): 13.0 (CH_3), 22.88, 48.88, 52.05 and 58.10 (C_4), 160.35 (C=O), 178.86 (C=S), 121.16, 124.14, 129.05, 132.15 (Ph-C), 116.0, 126.16, 135.75 and 169.18 (thiophene carbons). -MS m/z (%): 343 [M^+] (18), corresponding to the molecular formula $\text{C}_{17}\text{H}_{17}\text{N}_3\text{OS}_2$ and base peak at 314 [$\text{M}^+ - \text{Et}$] (100). Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{OS}_2$ (343.46): C, 59.45; H, 4.99; N, 12.23; S, 18.67. Found: C, 59.40; H, 4.94; N, 12.18; S, 18.63.

7-Propyl-3-phenyl-2-thioxo-2,3,5,6,7,8-hexahydro-1H-9-thia-1,3,7-triazafuoren-4-one (10b): Yield 72%; mp 105-107 °C (EtOH). - IR [ν , cm^{-1} , KBr]: 3330 (NH), 3175 (Ar-H), 1655 (C=O), 1250 (C=S). - $^1\text{H-NMR}$ (270 MHz, δ ppm, CDCl_3): 1.10 (t, 3H, CH_3), 1.30-1.40 (m, 2H, CH_2), 2.35 (t, 2H, CH_2N), 2.50 and 2.70 (2t, 4H, CH_2CH_2), 3.35 (s, 2H, CH_2), 7.38-7.58 (m, 5H, ArH), 10.06 (bs, 1H, NH, exchangeable with D_2O). -MS m/z (%): 357 [M^+] (15), corresponding to the molecular formula $\text{C}_{18}\text{H}_{19}\text{N}_3\text{OS}_2$ and base peak at 328 [$\text{M}^+ - \text{Et}$] (100). Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{OS}_2$ (357.48): C, 60.48; H, 5.36; N, 11.75; S, 17.94. Found: C, 60.42; H, 5.33; N, 11.71; S, 17.90.

Ethyl 2-(3-allylthioureido)-6-alkyl-4,5,6,7-tetrahydrotheino[2,3-c]pyridine-3-carboxylates (11a,b)

A mixture of **2a,b** (10 mmol) and allyl isothiocyanate (10 mmol) was heated on a steam bath for 2 h at 90 °C. The solid formed was triturated and solidified with a small amount of ethanol, filtered off, dried, and recrystallized from the appropriate solvent to give isothioureas **11a,b**.

Ethyl 2-(3-allylthioureido)-6-ethyl-4,5,6,7-tetrahydrotheino[2,3-c]pyridine-3-carboxylate (11a): Yield 60%; mp 170-172 °C (EtOH). - IR [ν , cm^{-1} , KBr]: 3315 (NH), 1716 (C=O), 1265 (C=S). - $^1\text{H-NMR}$ (270 MHz, δ ppm, DMSO-d_6): 1.00 and 1.20 (2t, 6H, 2CH_3), 2.60 (q, 2H, CH_2N), 2.90-3.15 (m, 4H, CH_2CH_2), 3.70 (s, 2H, CH_2), 4.40 (q, 2H, CH_2), 5.10-5.30 (m, 4H, 2CH_2), 5.70-5.74 (m, 1H, CH), 9.80 and 10.50 (2s, 2H, 2NH, exchangeable with D_2O). -MS m/z (%): 353 [M^+] (35), corresponding to the molecular formula $\text{C}_{16}\text{H}_{23}\text{N}_3\text{O}_2\text{S}_2$ and base peak at 308 [$\text{M}^+ - \text{OEt}$] (100). Anal. Calcd for $\text{C}_{16}\text{H}_{23}\text{N}_3\text{O}_2\text{S}_2$ (353.49): C, 54.36; H, 6.56; N, 11.89; S, 18.14. Found: C, 54.30; H, 6.52; N, 11.85; S, 18.10.

Ethyl 2-(3-allylthioureido)-6-propyl-4,5,6,7-tetrahydrotheino[2,3-c]pyridine-3-carboxylate (11b): Yield 65%, mp 160-162 °C (EtOH). - IR [ν , cm^{-1} , KBr]: 3325 (NH), 1712 (C=O), 1255 (C=S). - $^1\text{H-NMR}$ (270 MHz, δ ppm, DMSO-d_6): 1.00 and 1.20 (2t, 6H, 2CH_3), 1.50-1.52 (m, 2H, CH_2), 2.45 (t, 2H, CH_2N), 2.60-2.80 (m, 4H, CH_2CH_2), 3.60 (s, 2H, CH_2), 4.50 (q, 2H, CH_2), 5.20-5.55 (m, 4H, 2CH_2), 5.80-5.85 (m, 1H, CH), 10.50 (bs, 2H, 2NH, exchangeable with D_2O). - $^{13}\text{C-NMR}$ (67.5 MHz, δ ppm, DMSO-d_6): 11.18

and 14.08 (2 CH₃), 21.04, 23.05, 48.65, 52.98, 56.0, 58.42 and 60.28 (C₇), 115.86, 134.42 (CH₂=CH), 159.80 (C=O), 181.3 (C=S), 113.08, 129.09, 135.22 and 164.08 (thiophene carbons). -MS m/z (%): 367 [M⁺] (100), corresponding to the molecular formula C₁₇H₂₅N₃O₂S₂ and also as base peak. Anal. Calcd for C₁₇H₂₅N₃O₂S₂ (367.52): C, 55.56; H, 6.86; N, 11.43; S, 7.45. Found: C, 55.50; H, 6.82; N, 11.38; S, 7.40.

7-Alkyl-2-methyl-5,6,7,8-tetrahydro-1,9-dithia-3a,7,10-triazacyclopenta[b]fluoren-4-ones (12a,b)

Dry hydrogen chloride acid gas was passed through a refluxing solution of thiourea derivatives 11a,b (10 mmol) in absolute ethanol (10 mL) for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was basified with 5% sodium bicarbonate solution. The obtained precipitate was collected, dried, and recrystallized from the appropriate solvent to yield thiazolopyrimidines 12a,b.

7-Ethyl-2-methyl-5,6,7,8-tetrahydro-1,9-dithia-3a,7,10-triazacyclopenta[b]fluoren-4-one

(12a): Yield 58%; mp 145-147 °C (EtOH). - IR [ν , cm⁻¹, KBr]: 1670 (C=O). -¹H-NMR (270 MHz, δ ppm, CDCl₃): 1.20 (t, 3H, CH₃), 2.40 (q, 2H, CH₂N), 2.50 (s, 3H, CH₃), 2.60 and 2.80 (2t, 4H, CH₂CH₂), 3.50 (s, 2H, CH₂), 4.50 (s, 1H, CH). -MS m/z (%): 305[M⁺] (72), corresponding to the molecular formula C₁₄H₁₅N₃OS₂ and base peak at 262 [M⁺-C₂H₅N] (100). Anal. Calcd for C₁₄H₁₅N₃OS₂ (305.44): C, 55.06; H, 4.95; N, 13.76; S, 20.99. Found: C, 54.98; H, 4.91; N, 13.70; S, 20.95.

7-Propyl-2-methyl-5,6,7,8-tetrahydro-1,9-dithia-3a,7,10-triazacyclopenta[b]fluoren-4-one

(12b): Yield 68%; mp 140-142 °C (EtOH). - IR [ν , cm⁻¹, KBr]: 1660 (C=O). -¹H-NMR (270 MHz, δ ppm, CDCl₃): 0.95 (t, 3H, CH₃), 1.10-1.30 (m, 2H, CH₂), 2.30 (t, 2H, CH₂N), 2.42 (s, 3H, CH₃), 2.65-2.80 (m, 4H, CH₂CH₂), 3.48 (s, 2H, CH₂), 4.36 (s, 1H, CH). -¹³C-NMR (67.5 MHz, δ ppm, CDCl₃): 11.22, 23.3 (2 CH₃), 21.14, 23.10, 56.02, 52.15 and 58.06 (C₅), 163.01 (C=N), 165.20 (C=O), 123.95, 125.35 (C=C), 126.24, 136.0, 155.33 and 177.18 (thiophene carbons). -MS m/z (%): 319 [M⁺] (100), corresponding to the molecular formula C₁₅H₁₇N₃OS₂. Anal. Calcd for C₁₅H₁₇N₃OS₂ (319.47): C, 56.40; H, 5.36; N, 13.15; S, 20.07. Found: C, 56.34; H, 5.32; N, 13.12; S, 19.96.

Pharmacological screening

Determination of acute toxicity (LD₅₀)

The LD₅₀ was determined using rats (Table 1). The synthesized final compounds were injected in different increasing doses. The dose that killed 50% of the animals was calculated according to Austen et al.²²

Antiarrhythmic activity²³⁻²⁸

Procedure

Male Ivanovas rats weighing 300-350 g were used. The animals were anesthetized by intraperitoneal injection of 1.25 g/kg urethane; 5 mg/kg aconitine dissolved in 0.1N HNO₃ was administered by continuous infusion into the saphenous vein by 0.1 mL/min and the ECG in lead II was recorded every 30 s. The tested compound was injected at a screening dose of 3 mg/kg 5 min before the start of the aconitine infusion; 24 animals were used per compound.

Evaluation

The antiarrhythmic effect of a tested compound was measured by the amount of aconitine/100 g animal (duration of infusion) that induces

- Ventricular extra systoles.
- Ventricular tachycardia.
- Ventricular fibrillation.

Higher doses of aconitine in the treated group as compared to an untreated control group are an indication of antiarrhythmic activity. Statistical significance between the groups was assessed by Student's t-test.

Results and discussion

Chemistry

2-Amino-3-carbethoxy-5-alkyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridines **2a,b** were prepared from *N*-alkylpiperidone **1a,b**, ethyl cyanoacetate, and sulfur powder in ethanol in the presence of diethyl amine as a catalyst according to a known method²⁹ (Figure 1).

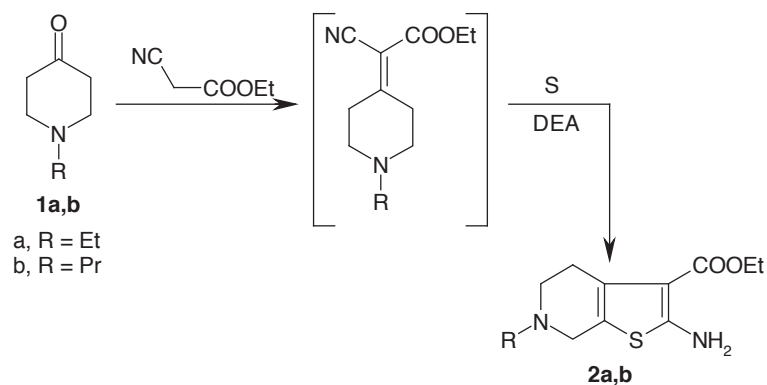


Figure 1. Synthesis of the starting compounds **2a,b**.

Compounds **2a,b** and thiourea were fused together without solvent at 180 °C to yield the corresponding thiopyrimidine derivatives **3a,b**. Moreover, compounds **2a,b** were reacted with acetonitrile in ethanol during bubbling dry hydrogen chloride gas with stirring at room temperature to afford the methyl pyrimidone derivatives **4a,b**. Acetylation of **2a,b** with acetic anhydride yielded *N*-acetyl thieno[2,3-c]pyridine derivatives **5a,b**, while **2a,b** were condensed with 3,4,5,6-tetrachlorophthalic anhydride or 1,2,4,5-benzenetetra-carboxylic acid dianhydride in refluxing glacial acetic acid to afford the corresponding imides **6a,b** and bis-imides **7a,b**, respectively (Figure 2).

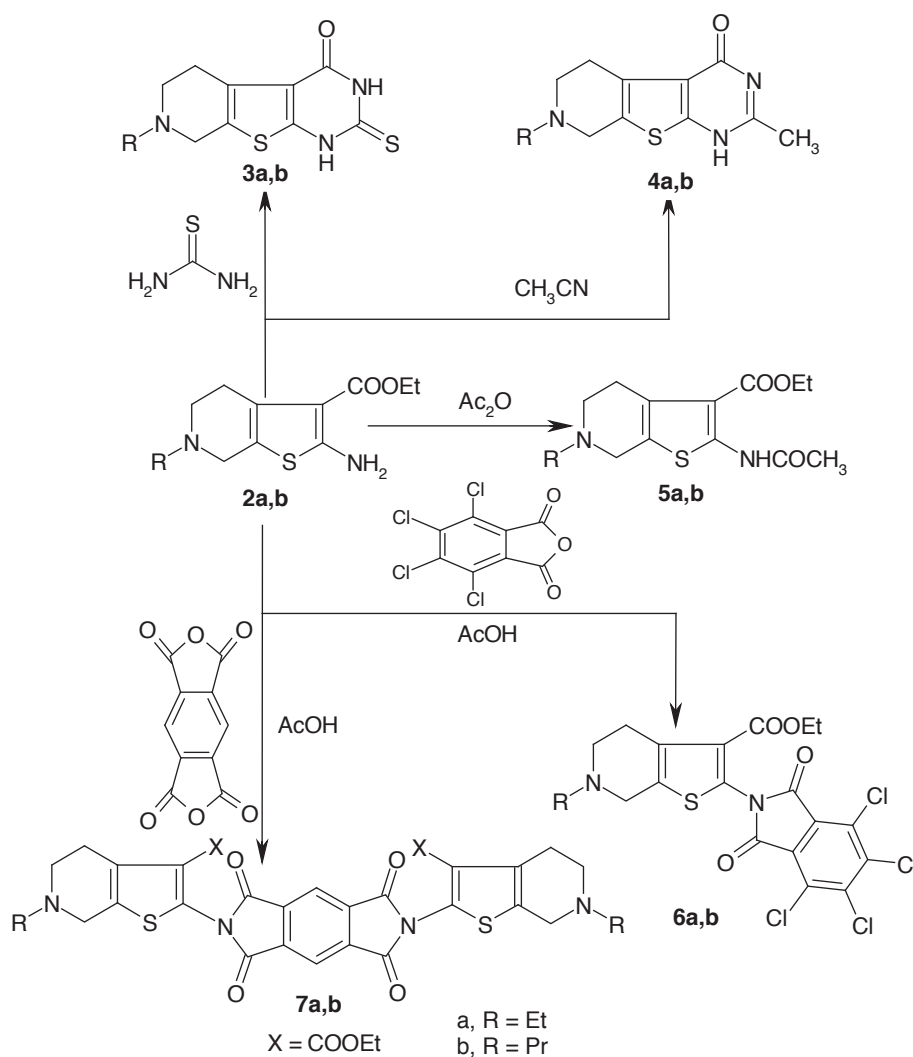


Figure 2. Synthetic route of compounds 3-7.

Heating of **2a,b** with phenyl isocyanate on the steam bath at 80 °C afforded the corresponding semi-carbazide derivatives **8a,b**. Similarly, compounds **2a,b** were reacted with phenyl isothiocyanate or allyl isothiocyanate at 90 °C in the presence of triethylamine as a catalyst to give thiosemicarbazides **9a,b** and **11a,b**, which were cyclized with refluxing polyphosphoric acid (PPA) or by passing dry hydrogen chloride gas in refluxing ethanol to yield the corresponding thiopyrimidines **10a,b** and thiazolopyrimidines **12a,b**, respectively (Figure 3).

Pharmacological screening.

Initially the acute toxicity of the compounds was assayed by determining their LD_{50} . Interestingly, all the synthesized compounds were less toxic (Table 1).

Then the newly synthesized compounds were pharmacologically screened for their antiarrhythmic activities (Table 2).

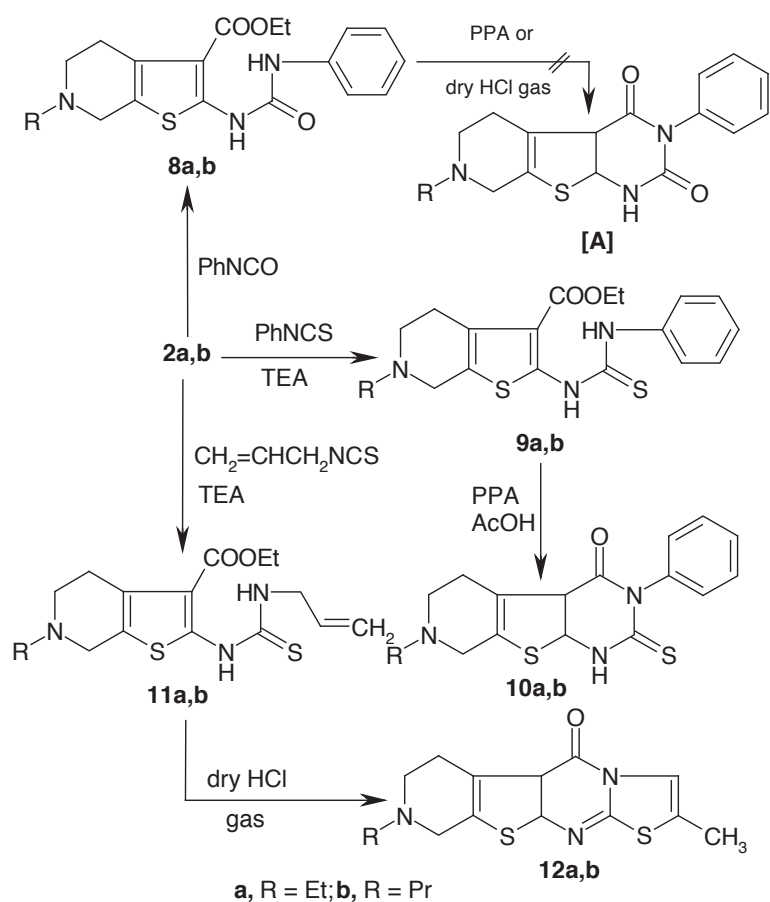


Figure 3. Synthetic route of compounds 8-12.

Antiarrhythmic activities

Purpose and rational

The plant alkaloid aconitine persistently activates the sodium channel. Infusion of aconitine in the anesthetized rat causes ventricular arrhythmias. Drugs considered to have antiarrhythmic properties can be tested in aconitine-intoxicated rats.

All the tested compounds showed antiarrhythmic activities more than that of the reference standards Lidocaine and Procain amide and the activity in descending order was **12b**, **7a**, **8b**, **10a**, **6a**, **2a**, **10b**, **3b**, **6b**, **3a**, **4b**, **8a**, **7b**, **12a**, (**4a**, **9b**), **11a**, **2b**, and **9a**. Compounds **12b**, **7a**, and **8b** are the most potent derivatives.

Structure-activity relationship (SAR) for anti-arrhythmic activities

From the results shown in Table 2, we can deduce that the antiarrhythmic activity is due to the following:

- Thieno[2,3-c]pyridine moiety is essential for potency

- Cyclic carbamates **10** and **12** are more active than acyclic ones **9** and **11**.
- Bis-theino[2,3-c]pyridine **7a** sharply increases the activities.
- N-phenyl moiety sharply increases the activity compared with allyl substituted and non-substituted ones.

Table 1. Acute toxicity (LD₅₀) of the synthesized compounds.

Compound	LD ₅₀ [mg/kg]
2a	313.33 ± 0.25
2b	409.29 ± 0.33
3a	338.87 ± 0.47
3b	211.85 ± 0.39
4a	487.49 ± 0.33
4b	240.98 ± 0.49
6a	196.56 ± 0.29
6b	201.87 ± 0.39
7a	256.52 ± 0.37
7b	234.49 ± 0.32
8a	328.67 ± 0.42
8b	278.46 ± 0.37
9a	417.37 ± 0.43
9b	337.99 ± 0.31
10a	234.76 ± 0.35
10b	229.84 ± 0.26
11a	409.31 ± 0.44
12a	447.75 ± 0.22
12b	231.41 ± 0.28

Table 2. Antiarrhythmic activities of the synthesized compounds.

Compound in (5 mg/kg)	Percentage increase in LD ₁₀₀
2a	81
2b	68
3a	75
3b	77
4a	70
4b	74
6a	82
6b	76
7a	88
7b	72
8a	73
8b	86
9a	66
9b	70
10a	84
10b	80
11a	69
12a	71
12b	91
Procaine amide	65
Lidocaine	65

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