Synthesis and Reactions of Some Heterocyclic Candidates Based on 2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene Moiety as Anti-Arrhythmic Agents

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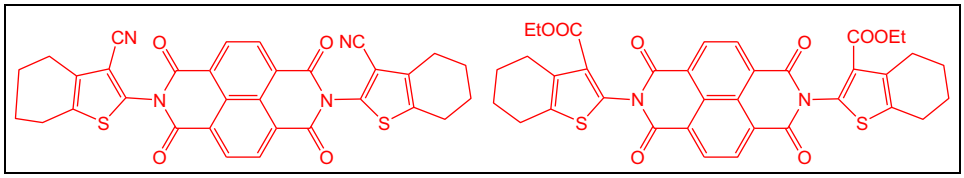

In continuation of our previous work, a series of novel thiophene derivatives **4–16** were synthesized by the reaction of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate **(1)** or 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile **(2)** with different organic reagents. Fusion of **1** with ethylcyanoacetate or maleic anhydride afforded the corresponding thienooxazinone derivative **4** and *N*-thienylmalimide derivative **5**, respectively. Acylation of **1** with chloroacetylchloride afforded the amide **6**, which was cyclized with ammonium thiocyanate to give the corresponding *N*-theinylthiazole derivative **8**. On the other hand, reaction of **1** with substituted aroylisothiocyanate derivatives gave the corresponding thiourea derivatives **9a–e**, which were cyclized by the action of sodium ethoxide to afford the corresponding *N*-substituted thiopyrimidine derivatives **10a–e**. Condensation of **2** with acid anhydrides in refluxing acetic acid afforded the corresponding imide carbonitrile derivatives **11–13**. Similarly, condensation of **1** with the previous acid anhydride yielded the corresponding imide ethyl ester derivatives **14–16**, respectively. The structures of newly synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, MS spectral data, and elemental analysis. The detailed synthesis, spectroscopic data, LD_{50}, and pharmacological activities of the synthesized compounds are reported.

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INTRODUCTION

Thiophene derivatives are very important compounds because of their high reactivity usefulness in organic chemistry as key starting materials to form various classes of biological-active compounds. Also, they play a part in animal metabolism. For example, in Figure 1, Biotin®, one of the vitamins (Vitamin H), is a tetrahydrothiophene; however, aromatic thiophenes do occur in some plants, in association with polyacetylenes with which they are biogenetically linked, and Banminth® (pyrantel), available anthelmintic used in animal husbandry, is one of the thiophene compounds in chemotherapy.

In the previous work, several of thiophene derivatives are known as analgesic [1,2], anticonvulsant, anti-inflammatory and antibacterial [3–6], antipyretic [7], antitumor [8,9], antiparasitic [10], antimicrobial [11], antihistaminic (H_1) [12], anti-anxiety [13], anti-arrhythmic [14], and serotonin antagonist [15] agents. Also, we reported the synthesis of substituted heterocyclic derivatives as antimicrobial [16], anti-inflammatory [17–19], and antitumor [20–22] agents. On the other hand, thioxopyrimidine and thiazolopyrimidine derivatives have promising biological and anticancer activities [23–25]. In addition, in our previous work, the newly substituted heterocyclic compounds exhibited anti-androgenic [26], anti-inflammatory [27], anticancer [28], anticonvulsant [29], and antiarrhythmic [30] activities. Recently, some thienopyrimidinone and *p*-methoxyphenyl pyrrolidine derivatives were synthesized, which exhibit analgesic, antiparkinsonian, anti-inflammatory, serotonin antagonist, and anti-anxiety activities [31–33]. In view of the aforementioned facts and continuation of our previous work [34] on tetrahydrobenzothiophene, it seemed most interesting to synthesize some new heterocyclic thiophene derivatives with the aim to evaluate their anti-arrhythmic activity.

RESULTS AND DISCUSSION

Chemistry. Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate **(1)** and 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile **(2)** were synthesized according to the reported procedures [35–38] as starting materials (Scheme 1).

Fusion of ethyl aminothiophene carboxylate **1** with ethylcyanoacetate afforded the corresponding thienooxazinone

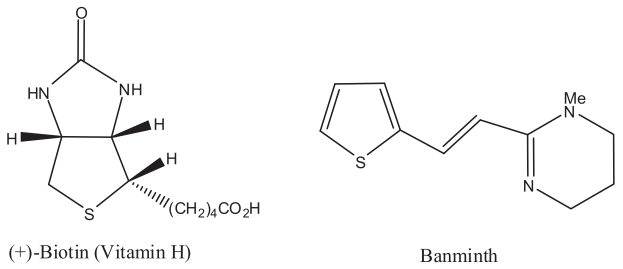
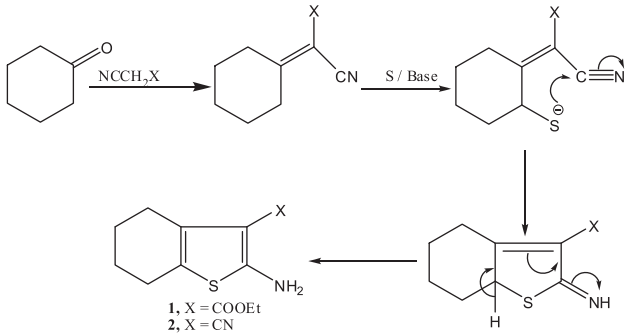


Figure 1. Chemical structure of (+)-biotin and banminth.

Scheme 1. Synthetic routes for starting materials **1** and **2**.



derivative **4** via the non-isolable cyanoacetamide **3**. Condensation of amino ester **1** with maleic anhydride in refluxing glacial acetic acid afforded the corresponding *N*-thienylmalimide **5** (Scheme 2).

Acylation of amino ester **1** with chloroacetylchloride afforded chloroacetamide derivative **6**, which was cyclized with ammonium thiocyanate to give the corresponding *N*-theinylthiazole derivative **8** via the non-isolable thiocyanate derivative **7**. On the other hand, reaction of **1** with substituted aroylisothiocyanate derivatives in refluxing dry acetone gave the corresponding thiourea derivatives **9a–e**, which were cyclized by refluxing in ethanolic sodium ethoxide to afford the corresponding *N*-substituted thiopyrimidine derivatives **10a–e** (Scheme 3).

Condensation of 2-amino-4,5,6,7-tetrahydrobenzo[b] thiophene-3-carbonitrile **(2)** with acid anhydrides, namely, 3,4,5,6-tetrachlorophthalic anhydride, 1,2,4,5-benzenetetracarboxylic dianhydride, and 1,4,5,8-naphthalene tetracarboxylic dianhydride in refluxing acetic acid afforded the corresponding imide **11** and bis-imide **12** and **13** carbonitrile derivatives, respectively (Scheme 4). The IR spectra of compounds **11–13** showed the absence of ν (NH_2) at 3455–3320 cm^{-1} for compound **2** and the presence of bands at 1696–1688 cm^{-1} corresponding to ν (C═O, imide) and at 2220–2210 cm^{-1} corresponding to ν (CN).

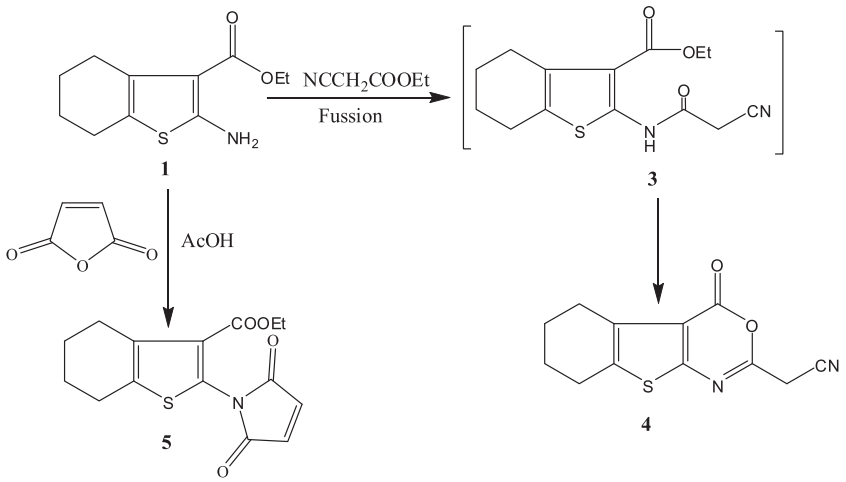
Similarly, condensation of **1** with the previous acid anhydrides in refluxing acetic acid yielded the corresponding imide **14** and bis-imide **15** and **16** ethyl ester derivatives, respectively (Scheme 5). The IR spectra of compounds **14–16** showed the absence of ν (NH_2) at 3460–3400 cm^{-1} for compound **1** and the presence of bands at 1680–1675 cm^{-1} and 1725–1715 cm^{-1} corresponding to ν (C═O, imide) and ν (C═O, ester), respectively.

Pharmacological screening. ***Anti-arrhythmic activity.*** Procaine amide 5 mg kg^{-1} i.v. and lidocaine 5 mg kg^{-1} i.v. lead to an increase in LD_{100} by 65%, which corresponds to an LD_{100} of approximately 9 μg/100 mg (Fig. 2).

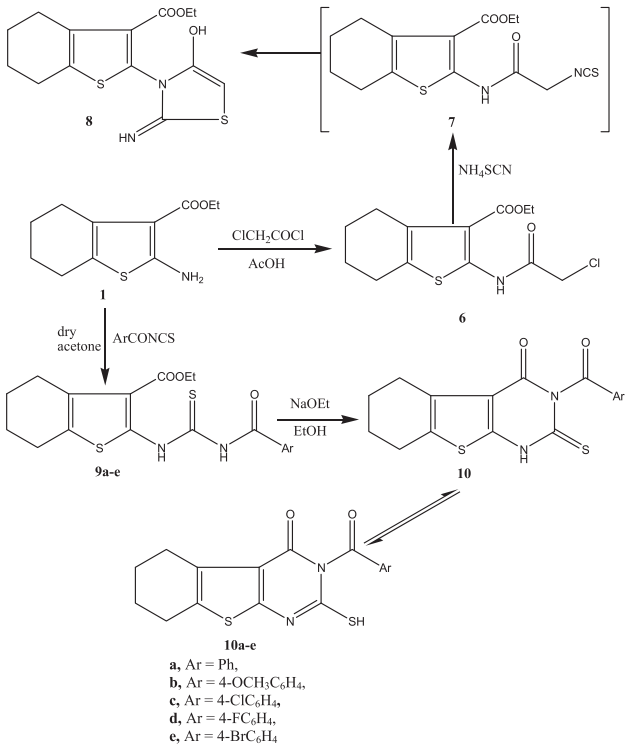
In Table 1 and Figure 2, all the tested compounds showed potent anti-arrhythmic activities, where the compounds **4**, **6**, **9c**, **10b**, **10c**, **11**, and **15** are more potent than procaine amide and lidocaine.

Determination of acute toxicity (LD_{50}). The LD_{50} was determined by using rats. They were injected with different increasing doses of the synthesized compounds.

Scheme 2. Synthetic routes for compounds **3–5**.



Scheme 3. Synthetic routes for compounds **6a–e** to **10a–e**.



The dose that killed 50% of the animal was calculated according to Austen *et al*. [39] and summarized in Table 2.

CONCLUSION

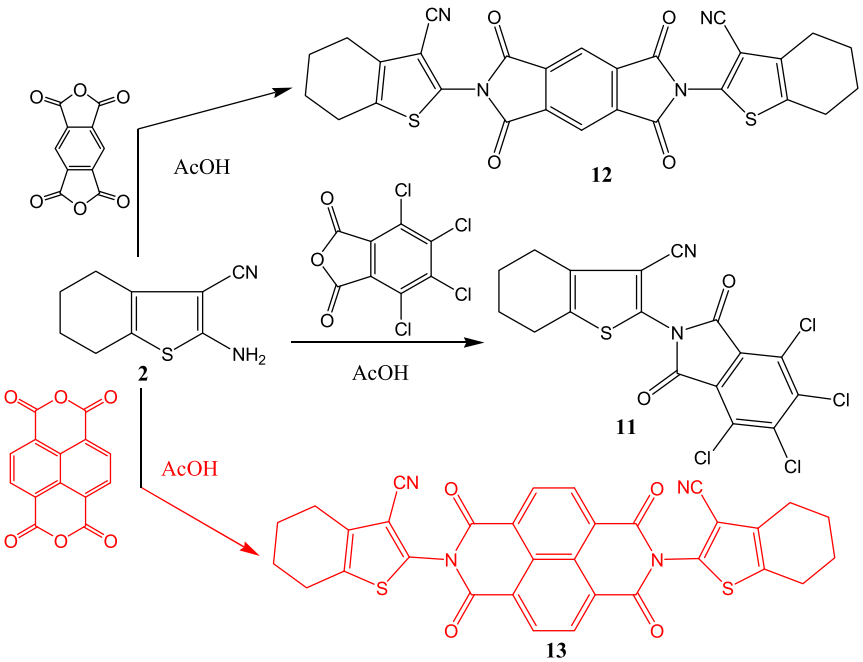
A series of new thiophene heterocyclic candidates were synthesized as anti-arrhythmic agent by using 2-amino-tetrahydrobenzo[b]thiophene derivatives as starting materials. The anti-arrhythmic screening showed that many of these obtained compounds have good activities comparable with the reference controls. The detailed synthesis, spectroscopic data, LD_{50}, and pharmacological activities of the synthesized compounds are reported herein.

EXPERIMENTAL

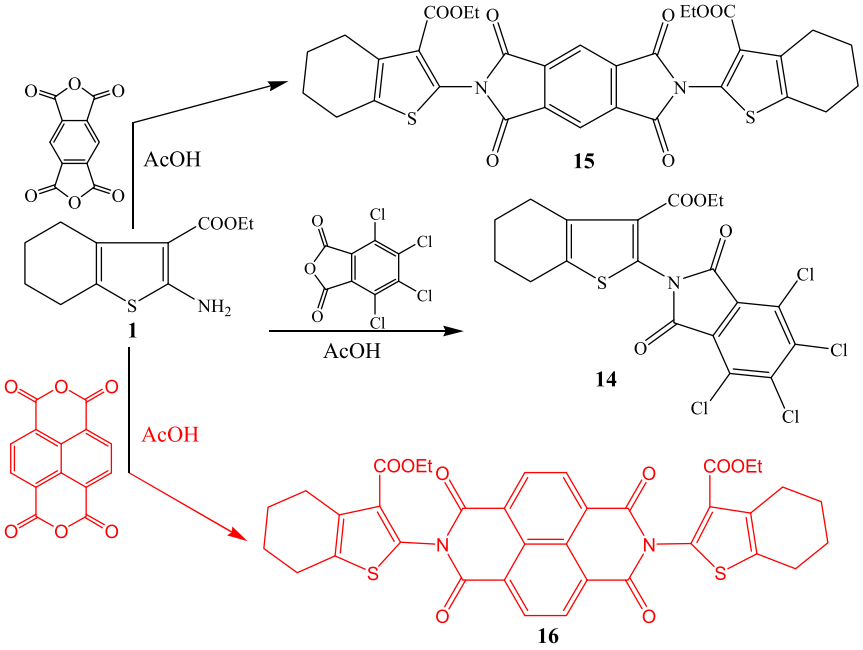
All melting points are uncorrected and measured using an Electrothermal IA 9100 apparatus (Shimadzu, Tokyo, Japan). IR spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer (Perkin-Elmer, Norwalk, CT, USA). ^{1}H NMR was determined on a Jeol-Ex-270 NMR spectrometer (JEOL, Tokyo, Japan), and chemical shifts were expressed as parts per million, ppm (δ values), against TMS as internal reference. Mass spectra were recorded on VG 2AM-3F mass spectrometer (Thermo Electron Corporation, USA). Microanalyses were operated using a Mario El Mentar apparatus, Organic Microanalysis Unit (NRC), and the results were within the accepted range (±0.2%) of the calculated values. Follow-up of the reactions and checking the purity of the compounds were made by TLC on silica gel-coated aluminum sheets (Type $60F_{254}$, Merck, Darmstadt, Germany).

Synthesis of 3-cyanomethyl-4,5,6,7,-tetrahydrobenzo[b] thiono[2,3-d]oxazine-4-(3H)-one (4). A mixture of amino ester derivative **1** (2.25 g, 0.01 mol) and ethyl cyanoacetate

Scheme 4. Synthetic routes for compounds **11–13** (color figure can be viewed in the online issue which is available at www.interscience.wiley.com).



Scheme 5. Synthetic routes for compounds **14–16** (color figure can be viewed in the online issue which is available at www.interscience.wiley.com).



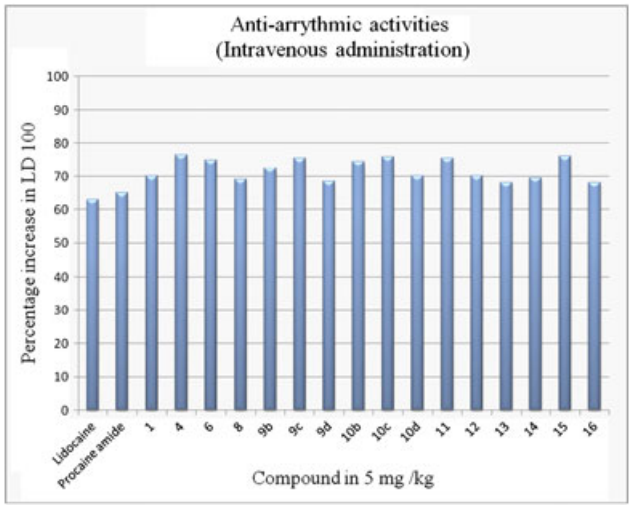


Figure 2. Antiarrhythmic activities of known and newly synthesized compounds (color figure can be viewed in the online issue which is available at www.interscience.wiley.com).

Table 1

Antiarrhythmic activities of known and newly synthesized compounds.

Compound (5 mg kg^{-1})	Percentage increase in LD_{100}
Lidocaine	63
Procaine amide	65
1	70.00
4	76.60
6	75.00
8	69.10
9b	72.50
9c	75.50
9d	68.50
10b	74.60
10c	76.00
10d	70.10
11	75.60
12	70.00
13	68.00
14	69.50
15	76.10
16	68.00

(1.13 g, 0.01 mol) was fused together for 1 h at 120°C. The solid obtained was crystallized from acetic acid to give the corresponding oxazinonone derivative **4** as brown crystals. Yield 90%; mp 260–262°C; IR (KBr): ν = 2216–2210 (CN), 1690–1682 (C=O), 1605 (C=C) cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6): δ = 1.70–2.88 (m, 8H, cyclohexane), 4.55 (s, 2H, CH_2); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 20.08 (CH_2), 22.88, 23.15, 23.62, 24.78 (4CH_2), 128.88, 139.03, 139.65, 151.45 (thiophene-C), 116.32 (CN), 154.15 (C=O), 164.96 (C=N); ms: *m/z* 246 (M^+, 8), 220 (32), 164 (100), 136 (10), 108 (12), 79 (76); *Anal*. Calcd for $C_{12}H_{10}N_2O_2S$ (246.28): C, 58.52; H, 4.09; N, 11.37; S, 13.02. Found: C, 58.45; H, 4.00; N, 11.30; S, 12.95.

Synthesis of ethyl 2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-carboxylate (5). A solution of **1** (2.25 g, 0.01 mol) and maleic anhydride (~0.1 g, 0.01 mol) in glacial acetic acid (20 mL) was refluxed for 3 h. The reaction mixture was evaporated under reduced pressure, and the obtained residue was solidified with diethyl ether. The obtained solid was collected by filtration, dried, and crystallized from ethanol to give dioxopyrrolo derivative **5** as yellow crystals. Yield 94%; mp 110–112°C; IR (KBr): ν = 1688, 1740 (2C=O) cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6): δ = 1.32 (t, 3H, *J* = 7.3 Hz, CH_3), 1.62–2.88 (m, 8H, cyclohexane), 4.18 (q, 2H, *J* = 7.3 Hz, CH_2),

Table 2

Acute toxicity (LD_{50}) of known compounds and newly synthesized compounds.

Compound no.	LD_{50} / mg kg^{-1}
Buspirone	113 ± 0.18
Diazepam	102 ± 0.10
1	184 ± 0.17
4	233 ± 0.15
6	208 ± 0.19
8	128 ± 0.18
9a	222 ± 0.18
9b	295 ± 0.15
9c	276 ± 0.18
9d	236 ± 0.17
9e	125 ± 0.10
10a	226 ± 0.19
10b	245 ± 0.11
10c	232 ± 0.15
10d	198 ± 0.19
10e	245 ± 0.17
11	248 ± 0.16
12	156 ± 0.12
13	175 ± 0.15
14	188 ± 0.18
15	276 ± 0.17
16	142 ± 0.15

6.75 (d, 2H, pyrrol-H); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 14.20 (CH_3), 22.95, 23.10, 23.65, 24.85 ($4CH_2$), 60.45 (CH_2), 97.12, 142.05, 125.96, 127.35 (thiophene-C), 147.95, 162.03 (3C=O), 135.66 (2C, pyrrol-C); ms: *m/z* 305 (M^+, 12), 279 (100); *Anal.* Calcd for $C_{15}H_{15}NO_4S$ (305.35): C, 59.00; H, 4.95; N, 4.59; S, 10.50. Found: C, 58.94; H, 4.90; N, 4.54; S, 10.44.

Synthesis of ethyl 2-(2-chloroacetamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (6). A mixture of **1** (2.25 g, 0.01 mol) and chloroacetylchloride (1.12 g, 0.01 mol) in acetic acid (20 mL) was stirred for 2 h at room temperature. The separated solid formed upon dilution with water (40 mL), filtered off, dried, and crystallized from acetic acid to give chloroacetamide **6** as brown crystals. Yield 80%; mp 80–82°C; IR (KBr): ν = 3388 (NH), 1742, 1664 (2C=O) cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6): δ = 1.25 (t, 3H, *J* = 7.5 Hz, CH_3), 1.68–2.85 (m, 8H, cyclohexane), 4.24 (q, 2H, *J* = 7.5 Hz, CH_2), 4.32 (s, 2H, CH_2), 8.84 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 14.18 (CH_3), 23.14, 23.54, 23.88, 24.86 ($4CH_2$), 42.76, 60.55 ($2CH_2$), 99.12, 1126.08, 127.15, 175.12 (thiophene-C), 148.44, 164.94 (2C=O); ms: *m/z* 303 (M^+ + 2, 12), 301 (M^+, 37), 207 (100); *Anal.* Calcd for $C_{13}H_{16}ClNO_3S$ (301.79): C, 51.74; H, 5.34; Cl, 11.75; N, 4.64; S, 10.62. Found: C, 51.68; H, 5.28; Cl, 11.70; N, 4.59; S, 10.58.

Synthesis of ethyl 4,5,6,7-tetrahydro-2-(4-hydroxy-2-iminothiazol-3(2H)-yl)benzo[b]-thiophene-3-carboxylate (8). A mixture of compound **6** (3.01 g, 0.01 mol) and ammonium thiocyante (0.76 g, 0.01 mol) in ethanol (20 mL) was refluxed for 3 h. The separated solid formed upon dilution with water (20 mL), filtered off, dried, and crystallized form acetic acid to give hydroxythiazole derivative **8** as light brown crystals. Yield 80%; mp 278–280°C; IR (KBr): ν = 3434 (NH), 1742 (C=O, ester), 1668 (C=N) cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6): δ = 1.28 (t, 3H, *J* = 7.3 Hz, CH_3), 1.60–2.92 (m, 8H, cyclohexane), 4.20 (q, 2H, *J* = 7.3 Hz, CH_2), 7.02 (s, 1H, thiazol-H), 10.90 (s, 1H, NH exchangeable with D_2O), 12.60 (s, 1H, OH exchangeable with D_2O); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 14.18 (CH_3), 23.18, 23.24, 23.82, 24.52 ($4CH_2$), 60.58 (CH_2), 112.45, 127.97, 132.45, 138.06 (thiophene-C), 148.64 (C=O), 75.10, 151.44, 198.35 (thiazol-C); ms: *m/z* 324 (M^+, 24), 164 (100); *Anal.* Calcd for $C_{14}H_{16}N_2O_3S_2$ (324.42): C, 51.83; H, 4.97; N, 8.63; S, 19.77. Found: C, 51.76; H, 4.92; N, 8.58; S, 19.70.

Synthesis of ethyl-2-(aroylisothiocyanate)amino-5,6,7,8-tetrahydrobenzo[b]thiophene-3-carboxylate (9a–e). A mixture of **1** (2.25 g, 0.01 mol) and aroylisothiocyante derivatives, namely, benzoyl, *p*-methoxybenzoyl, *p*-chlorobenzoyl, *p*-fluorobenzoyl, or 4-bromobenzoyl-isothiocyanate (0.01 mol) in dry acetone (20 mL) was refluxed for 3 h. The reaction mixture was concentrated under reduced pressure, and the obtained solid was filtered, dried, and crystallized from ethanol to give thiourea derivatives **9a–e**, respectively.

Ethyl 2-(3-benzoylthioureido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (9a). Yield 97%; mp 173–175°C; IR (KBr): ν = 3416 (NH), 1742, 1686 (2C=O) cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6): δ = 1.26 (t, 3H, *J* = 7.3 Hz, CH_3), 1.58–2.90 (m, 8H, cyclohexane), 4.24 (q, 2H, *J* = 7.3 Hz, CH_2), 7.25–7.86 (m, 5H, Ar–H), 8.45, 9.15 (2s, 2H, 2NH exchangeable with D_2O); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 14.22 (CH_3), 23.16, 23.26, 23.78, 24.46 ($4CH_2$), 60.66 (CH_2), 113.55, 128.05, 138.01, 164.10 (thiophene-C), 148.66, 165.12 (2C=O), 176.56 (C=S), 127.32, 128.05, 132.13, 133.02 (Ph–C); ms: *m/z* 388 (M^+, 6), 343 (12), 238 (8), 105 (76), 164 (100); *Anal.* Calcd for $C_{19}H_{20}N_2O_3S_2$ (388.50): C, 58.74; H, 5.19; N, 7.21; S, 16.51. Found: C, 58.70; H, 5.16; N, 7.15; S, 16.42.

Ethyl 2-(3-(4-methoxybenzoyl)thioureido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (9b). Yield 92%; mp 190–192°C; IR (KBr): ν = 3422 (NH), 1737, 1686 (2C=O) cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6): δ = 1.30 (t, 3H, *J* = 7.4 Hz, CH_3), 1.64–2.88 (m, 8H, cyclohexane), 3.65 (s, 3H, OCH_3), 4.18 (q, 2H, *J* = 7.4 Hz, CH_2), 6.95–7.78 (m, 4H, Ar–H), 8.52, 9.05 (2s, 2H, 2NH exchangeable with D_2O); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 14.18 (CH_3), 22.97, 23.10, 23.67, 24.12 ($4CH_2$), 60.64 (CH_2), 60.45 (OCH_3), 112.95, 128.05, 138.45, 164.12 (thiophene-C), 148.64, 165.18 (2C=O), 176.88 (C=S), 106.86, 127.98, 142.35, 153.08 (Ar–C); ms: *m/z* 418 (M^+, 12), 311 (46), 267 (18), 195 (100), 167 (76); *Anal.* Calcd for $C_{20}H_{22}N_2O_4S_2$ (418.10): C, 57.39; H, 5.30; N, 6.69; S, 15.32. Found: C, 57.25; H, 5.18; N, 6.58; S, 15.24.

Ethyl 2-(3-(4-chlorobenzoyl)thioureido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (9c). Yield 86%; mp 194–196°C; IR (KBr): ν = 3408 (NH), 1745, 1686 (2C=O) cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6): δ = 1.28 (t, 3H, *J* = 7.5 Hz, CH_3), 1.64–2.84 (m, 8H, cyclohexane), 4.25 (q, 2H, *J* = 7.5 Hz, CH_2), 7.75 (d, 2H, *J* = 8.6 Hz, Ar–H), 7.92 (d, 2H, *J* = 8.6 Hz, Ar–H), 8.65, 9.45 (2s, 2H, 2NH exchangeable with D_2O); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 14.15 (CH_3), 23.12, 23.32, 23.80, 24.56 ($4CH_2$), 60.49 (CH_2), 113.56, 128.15, 138.12, 164.34 (thiophene-C), 148.56, 165.32 (2C=O), 176.64 (C=S), 128.02, 130.15, 131.15, 137.32 (Ph–C); ms: *m/z* 424 (M^+ + 2, 7), 422 (M^+, 20), 139 (100); *Anal.* Calcd for $C_{19}H_{19}ClN_2O_3S_2$ (422.95): C, 53.96; H, 4.53; Cl, 8.38; N, 6.62; S, 15.16. Found: C, 53.90; H, 4.47; Cl, 8.32; N, 6.55; S, 15.12.

Ethyl 2-(3-(4-fluorobenzoyl)thioureido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (9d). Yield 82%; mp 188–190°C;

IR (KBr): ν = 3412 (NH), 1737, 1690 (2C=O) cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ = 1.25 (t, 3H, *J* = 7.3 Hz, CH_3), 1.65–2.80 (m, 8H, cyclohexane), 4.24 (q, 2H, *J* = 7.3 Hz, CH_2), 7.65 (d, 2H, *J* = 8.5 Hz, Ar–H), 8.05 (d, 2H, *J* = 8.5 Hz, Ar–H), 8.76, 9.65 (2s, 2H, 2NH exchangeable with D_2O); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 14.05 (CH_3), 22.98, 23.24, 23.75, 24.50 ($4CH_2$), 60.59 (CH_2), 113.66, 128.32, 138.24, 164.30 (thiophene-C), 148.60, 165.38 (2C=O), 176.75 (C=S), 115.46, 128.76, 129.01, 166.30 (Ph–C); ms: *m/z* 406 (M^+, 20), 311 (100); *Anal*. Calcd for $C_{19}H_{19}FN_2O_3S_2$ (406.49): C, 56.14; H, 4.71; N, 6.89; S, 15.78. Found: C, 56.10; H, 4.65; N, 6.83; S, 15.70.

Ethyl 2-(3-(4-bromobenzoyl)thioureido)-4,5,6,7-tetrahydrobenzo [b]thiophene-3-carboxylate (9e). Yield 86%; mp 216–218°C; IR (KBr): ν = 3418 (NH), 1746, 1686 (2C=O) cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ = 1.22 (t, 3H, *J* = 7.4 Hz, CH_3), 1.70–2.75 (m, 8H, cyclohexane), 4.18 (q, 2H, *J* = 7.4 Hz, CH_2), 7.68 (d, 2H, *J* = 8.6 Hz, Ar–H), 7.90 (d, 2H, *J* = 8.6 Hz, Ar–H), 8.85, 9.76 (2s, 2H, 2NH exchangeable with D_2O); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 14.05 (CH_3), 23.16, 23.28, 23.69, 24.45 ($4CH_2$), 60.62 (CH_2), 113.67, 128.29, 138.32, 164.18 (thiophene-C), 148.55, 165.26 (2C=O), 176.78 (C=S), 126.24, 129.46, 131.14, 132.34 (Ph–C); ms: *m/z* 406 (M^+, 20), 311 (100); *Anal*. Calcd for $C_{19}H_{19}BrN_2O_3S_2$ (467.40): C, 48.82; H, 4.10; N, 5.99; S, 13.72. Found: C, 48.75; H, 4.02; N, 5.94; S, 13.68.

Synthesis of 3-arylmethanone-2-thio-5,6,7,8,-tetrahydrobenzo [b]thieno[2,3-d]pyrimidin-4-(3H)-one (10a–e). A mixture of compounds **9a–e** (0.01 mol) and sodium ethoxide (0.68 g, 0.01 mol) in ethanol (20 mL) was refluxed for 3 h. The reaction mixture was acidified with HCl (10 mL, 20%) and diluted with water. The obtained solid was filtered off, dried, and crystallized from ethanol to give thiopyrimidine derivatives **10a–e**, respectively.

Ethyl (4-oxo-2-mercapto-4,5,6,7-terahydrobenzo[b]thieno[2,3-d]pyrimidin-3(4H)-yl)-(phenyl) carboxylate (10a). Yield 95%; mp 280–282°C; IR (KBr): ν = 1707, 1678 (2C=O), 1660 (C=N) cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ = 1.62–2.88 (m, 8H, cyclohexane), 7.10–7.86 (m, 5H, Ar–H), 10.10 (s, 1H, SH exchangeable with D_2O); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 23.15, 23.45, 23.85, 24.66 ($4CH_2$), 117.54, 124.25, 138..85, 155.40 (thiophene ring), 127.10, 128.08, 131.16, 131.76 (Ph-C), 168.75, 170.35 (2C=O), 164.95 (C–SH); ms: *m/z* 342 (M^+, 16), 265 (100); *Anal*. Calcd for $C_{17}H_{14}N_2O_2S_2$ (342.43): C, 59.63; H, 4.12; N, 8.18; S, 18.73. Found: C, 59.56; H, 4.06; N, 8.10; S, 18.66.

Ethyl (4-oxo-2-mercapto-4,5,6,7-terahydrobenzo[b]thieno [2,3-d]pyrimidin-3(4H)-yl)-(4-methoxyphenyl) carboxylate (10b). Yield 95%; mp 118–120°C; IR (KBr): ν = 1705, 1676 (2C=O), 1662 (C=N) cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ = 1.65–2.92 (m, 8H, cyclohexane), 3.62 (s, 3H, OCH_3), 7.36–7.82 (m, 4H, Ar–H), 10.12 (s, 1H, SH exchangeable with D_2O); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 23.08, 23.48, 23.80, 24.65 ($4CH_2$), 60.36 (OCH_3), 117.45, 124.15, 138..75, 155.32 (thiophene ring), 107.10, 128.22, 141.56, 153.06 (Ph–C), 168.64, 169.85 (2C=O), 164.55 (C–SH); ms: *m/z* 372 (M^+, 12), 195 (100); *Anal*. Calcd for $C_{18}H_{16}N_2O_3S_2$ (372.06): C, 58.04; H, 4.33; N, 7.52; S, 17.22. Found: C, 57.92; H, 4.25; N, 7.42; S, 17.08.

Ethyl (4-oxo-2-mercapto-4,5,6,7-terahydrobenzo[b]thieno[2,3-d]pyrimidin-3(4H)-yl)-(4-chlorophenyl) carboxylate (10c). Yield 76%; mp 288–290°C; IR (KBr): ν = 1704, 1682 (2C=O), 1662 (C=N) cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ = 1.60–2.84 (m, 8H, cyclohexane), 7.56 (d, 2H, *J* = 8.5 Hz, Ar–H), 7.88 (d, 2H, *J* = 8.5 Hz, Ar–H), 10.05 (s, 1H, SH exchangeable with D_2O); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 22.96, 23.33, 23.35, 24.16 ($4CH_2$), 117.48, 124.95, 139.76, 155.35 (thiophene ring), 128.12, 129.08, 130.16, 136.86 (Ph–C), 168.35, 169.45 (2C=O), 165.06 (C–SH); ms: *m/z* 376 (M^+, 64), 164 (100); *Anal*. Calcd for $C_{17}H_{13}ClN_2O_2S_2$ (376.88): C, 54.18; H, 3.48; Cl, 9.41; N, 7.43; S, 17.02. Found: C, 54.08; H, 3.40; Cl, 9.35; N, 7.36; S, 16.96.

Ethyl (4-oxo-2-mercapto-4,5,6,7-terahydrobenzo[b]thieno[2,3-d]pyrimidin-3(4H)-yl)-(4-fluorophenyl) carboxylate (10d). Yield 82%; mp 248–250°C; IR (KBr): ν = 1705, 1685 (2C=O), 1660 (C=N) cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ = 1.65–2.78 (m, 8H, cyclohexane), 7.36 (d, 2H, *J* = 8.6 Hz, Ar–H), 8.05 (d, 2H, *J* = 8.6 Hz, Ar–H), 9.98 (s, 1H, SH exchangeable with D_2O); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 22.94, 23.16, 23.45, 24.10 ($4CH_2$), 117.52, 124.98, 139.36, 155.42 (thiophene ring), 115.45, 127.08, 128.36, 165.86 (Ph–C), 167.82, 169.55 (2C=O), 165.14 (C–SH); ms: *m/z* 360 (M^+, 32), 132 (100); *Anal*. Calcd for $C_{17}H_{13}FN_2O_2S_2$ (360.43): C, 56.65; H, 3.64; N, 7.77; S, 17.79. Found: C, 56.60; H, 3.60; N, 7.70; S, 17.73.

Ethyl (4-oxo-2-mercapto-4,5,6,7-terahydrobenzo[b]thieno[2,3-d]pyrimidin-3(4H)-yl)-(4-bromophenyl) carboxylate (10e). Yield 62%; mp >300°C; IR (KBr): ν = 1708, 1686 (2C=O), 1664 (C=N) cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ = 1.72–2.72 (m, 8H, cyclohexane), 7.46 (d, 2H, *J* = 8.6 Hz, Ar–H), 7.94 (d, 2H, *J* = 8.6 Hz, Ar–H), 10.14 (s, 1H, SH exchangeable with D_2O); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 23.04, 23.18, 23.34, 24.18 ($4CH_2$), 117.48, 124.92, 139.24, 155.16 (thiophene ring), 126.15, 129.12, 130.03, 131.55 (Ph–C), 167.90, 169.65 (2C=O), 164.18 (C–SH); ms: *m/z* 421 (M^+, 24), 255 (100); *Anal*. Calcd for $C_{17}H_{13}BrN_2O_2S_2$ (421.33): C, 48.46; H, 3.11; N, 6.65; S, 15.22. Found: C, 48.40; H, 3.05; N, 6.60; S, 15.16.

Synthesis of tetrachlorodioxoisoindolyl derivatives 11 and **14**. A mixture of compound **2** or **1** (1 mmol) and 1,2,3,4-tetrachlorophthalic anhydride (0.285 g, 1 mmol) in glacial acetic acid (50 mL) was refluxed for 6 h. The solvent was evaporated under reduced pressure, the obtained residue was solidified with dry ether, and the crude product was collected by filtration and purified by recrystallization from the proper solvent to yield the corresponding compounds **11** and **14**, respectively.

2-(4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbo-nitrile (11). Yield 66%; mp 236–238°C (DMF/H_2O); IR (KBr): ν = 2218 (CN), 1690 (C=O, imide), 1640 (C=N) cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ = 1.65–2.76 (m, 8H, CH_2, cyclohexyl-H); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 22.96, 23.32, 23.88, 24.46 ($4CH_2$), 77.52, 128.12, 128.76, 146.14 (thiophene-C), 116.54 (CN), 167.32 (2C=O), 127.92, 133.12, 135.08 (Ph–C); ms: *m/z* 446 (M^+, 65), 204 (100); *Anal*. Calcd for $C_{17}H_8Cl_4N_2O_2S$ (446.13): C, 45.77; H, 1.81; Cl, 31.79; N, 6.28; S, 7.19. Found: C, 45.70; H, 1.78; Cl, 31.73; N, 6.22; S, 7.15.

Ethyl 2-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-carboxylate (14). Yield 75%; mp 218–220°C (EtOH); IR (KBr): ν = 1745 (C=O, ester), 1690 (C=O, imide), 1640 (C=N) cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ = 1.24 (t, 3H, CH_3), 1.72–2.96 (m, 8H, cyclohexane), 3.80 (q, 2H, CH_2); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 14.05 (CH_3), 23.14, 23.28, 23.76, 24.36 ($4CH_2$), 60.65 (CH_2), 97.55, 126.05, 127.01, 142.10 (thiophene-C), 148.65, 167.12 (3C=O), 127.32, 133.05, 135.13 (Ph–C); ms: *m/z* 493 (M, 8), 495 ($M^+ + 2$, 3), 251 (100); *Anal*. Calcd for $C_{19}H_{13}Cl_4NO_4S$

(493.19): C, 46.27; H, 2.66; Cl, 28.75; N, 2.84; S, 6.50. Found: C, 46.22; H, 2.60; Cl, 28.68; N, 2.80; S, 6.45.

Synthesis of bis[substituted cyclohexa[b]thien]pyrroloisoindolyl derivatives 12 and **15**. A mixture of compound **2** or **1** (2 mmol) and 1,2,4,5-benzenetetracarboxylic dianhydride (0.218 g, 1 mmol) in glacial acetic acid (50 mL) was heated under reflux for 6 h. The residue formed was filtered off and crystallized from the proper solvent to yield the corresponding compounds **12** and **15**, respectively.

2,2′-(1,3,5,7-Tetraoxopyrrolo[3,4-f]isoindole-2,6(1H,3H,5H,7H)-diyl)bis(4,5,6,7-tetrahydro-benzo[b]thiophene-3-carbonitrile) (12). Yield 72%; mp >300°C (AcOH/H_2O); IR (KBr): ν = 2218 (CN), 1692 (C═O, imide), 1656 (C═N) cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ = 1.70–2.90 (m, 16H, CH_2, cyclohexyl-H), 7.79 (s, 2H, Ar-H); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 23.26, 23.42, 23.66, 24.34 ($8CH_2$), 97.38, 126.25, 127.24, 142.25 (2 thiophene-C), 116.45 (2CN), 148.62, 167.45 (6C═O), 125.03, 135.26 (Ph–C); ms: *m/z* 538 (M^+, 16), 350 (100); *Anal*. Calcd for $C_{28}H_{18}N_4O_4S_2$ (538.60): C, 62.44; H, 3.37; N, 10.40; S, 11.91. Found: C, 62.40; H, 3.32; N, 10.33; S, 11.86.

Diethyl 2,2′-(1,3,5,7-tetraoxopyrrolo[3,4-f]isoindole-2,6-(1H,3H,5H,7H)-diyl)bis-(4,5,6,7-tetra-hydrobenzo[b]thiophene-3-carboxylate) (15). Yield 65%; mp >300°C (AcOH); IR (KBr): ν = 1748 (C═O, ester), 1688 (C═O, imide), 1654 (C═N) cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ = 1.25 (t, 6H, CH_3), 1.62–2.86 (m, 16H, CH_2, cyclohexyl-H), 3.84 (q, 4H, CH_2); 7.84 (s, 2H, Ar-H); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 13.95 ($2CH_3$), 23.22, 23.32, 23.77, 24.42 ($8CH_2$), 60.72 ($2CH_2$), 97.45, 126.15, 127.12, 142.22 (2 thiophene-C), 148.58, 167.34 (6C═O), 124.95, 135.23 (Ph–C); ms: *m/z* 632 (M^+, 8), 423 (15), 214 (45), 209 (100); *Anal*. Calcd for $C_{32}H_{28}N_2O_8S_2$ (632.70): C, 60.75; H, 4.46; N, 4.43; S, 10.14. Found: C, 60.70; H, 4.38; N, 4.36; S, 10.06.

Synthesis of 2,7-bis-[substituted cyclohexa[b]thien]benzo[l,m,n][3,8]phenanthrolines 13 and **16**. A mixture of compound **2** or **1** (2 mmol) and 1,4,5,8-naphthalenetetracarboxylic dianhydride (0.268 g, 1 mmol) in glacial acetic acid (50 mL) was heated under reflux for 6 h. The obtained solid was filtered off, washed with acetic acid, dried, and crystallized from the proper solvent to afford the corresponding derivatives **13** and **16**, respectively.

2,2′-(1,3,6,8-Tetraoxoisoindolo[5,6-f]isoindole-2,7(1H,3H,6H,8H)-diyl)bis(4,5,6,7-tetrahydro-benzo[b]thiophene-3-carbonitrile) (13). Yield 55%; mp >300°C (DMF/H_2O); IR (KBr): ν = 2219 (CN), 1688 (C═O, imide), 1656 (C═N) cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ = 1.66–2.85 (m, 16H, CH_2, cyclohexyl-H), 7.94 (d, 4H, Ar-H); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 23.23, 23.39, 23.70, 24.43 ($8CH_2$), 97.40, 126.28, 127.35, 142.55 (2 thiophene-C), 116.65 (2CN), 167.48 (4C═O), 129.66, 133.90, 135.12 (naphth-C); ms: *m/z* 588 (M^+, 6), 264 (100); *Anal*. Calcd for $C_{32}H_{20}N_4O_4S_2$ (588.66): C, 65.29; H, 3.42; N, 9.52; S, 10.89. Found: C, 65.23; H, 3.36; N, 9.46; S, 10.83.

Diethyl 2,2′-(1,3,6,8-tetraoxoisoindolo[5,6-f]isoindole-2,7(1H,3H,6H,8H)-diyl)bis-(4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate) (16). Yield 65%; mp >300°C (AcOH); IR (KBr): ν = 1742 (C═O, ester), 1689 (C═O, imide), 1657 (C═N) cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ = 1.18 (t, 6H, CH_3), 1.70–2.88 (m, 16H, CH_2, cyclohexyl-H), 3.74 (q, 4H, CH_2); 7.85 (d, 4H, Ar–H); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 14.18 ($2CH_3$), 23.26, 23.38, 23.82, 24.50 ($8CH_2$), 60.80 ($2CH_2$), 97.55, 126.24, 127.16, 142.32 (2 thiophene-C), 148.62, 167.44 (6C═O), 129.75, 133.86, 135.03 (naphth-C); ms: *m/z* 682 (M^+, 18), 264 (100); *Anal*. Calcd for $C_{36}H_{30}N_2O_8S_2$ (682.76): C, 63.33; H, 4.43; N, 4.10; S, 9.39. Found: C, 63.26; H, 4.35; N, 4.02; S, 9.33.

Pharmacological screening. Antiarrhythmic activity [40–42]. ***Purpose and rational.*** The plant alkaloid aconitine persistently activates sodium channel. Infusion of aconitine in the anesthetized rat causes ventricular arrhythmias. Drugs considered to have anti-arrhythmic properties can be tested in aconitine-intoxicated rats.

Procedure. Male Ivanovas rats weighing 300–350 g are used. The animals are anesthetized by intraperitoneal injection of 1.25 g kg^{-1} urethane: 5 mg kg^{-1} aconitine dissolved in 0.1 N HNO_3 is administered by continuous infusion into the saphenous vein of 0.1 mL min^{-1} and the electrocardiogram in leadII is recorded every 30 s. The test compound is injected IV at a screening dose of 5 mg kg^{-1} 5 min before the start of the aconitine infusion; 24 animals are used per compound.

Evaluation. The anti-arrhythmic effect of a test compound is measured by the amount of aconitine/100 g animal (duration of infusion), which was induced.

- Ventricular extra systoles
- Ventricular tachycardia
- Ventricular fibrillation

Higher doses of aconitine in the treated group compared with the untreated control group are an indication of anti-arrhythmic activity. Statistical significance between the groups is assessed by the student's *T*-test.

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