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Synthesis and biological evaluation of thiophene [3,2-*b*] pyrrole derivatives as potential anti-inflammatory agents☆

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Abstract—A series of thiophene [3,2-*b*] pyrrole derivatives were synthesized and evaluated their abilities to inhibit anti-inflammatory activity. In this series, substituent effects at the N-1, 2 and 5 positions of thiophene [3,2-*b*] pyrrole were examined. The results obtained are compared to those previously reported anti-inflammatory drugs like Tenidap sodium, Diclofenac sodium and Piroxicam. The results indicated the critical role of the group linked in the N-1 position and 2, 5 positions of thiophene [3,2-*b*] pyrrole with different functional groups.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDS) are the most commonly prescribed medications in the world. The major limiting side effects of chronic use of NSAIDs are gastrointestinal (GI) symptoms and bleeding complications. Majority of NSAIDs that are available in market are known to inhibit both isoforms, a constitutive form, COX-1 and an inducible form, COX-2 to offer therapeutic effect.

In our continuing efforts towards the synthesis and pharmacological activity of new nonsteroidal anti-inflammatory agents, we are interested in the bioisosteres of indole class of compound, particularly tenidap **1**[1,2] (Fig. 1). Tenidap is an inhibitor of prostaglandin[3] interleukin-1[4] production in the body used for the treatment of rheumatoid arthritis and osteoarthritis. It inhibits both the enzymes cycloxygenase and 5-lypoxygenase,[5] which convert arachidonic acid into prostaglandin and leukotrienes[3] and exhibit superior activity compared to naproxen[6] piroxicam,[7] diclofenac sodium,[8] indomethacin[9] and so on. The associated toxic effects and its subsequent withdrawl from the advanced clinical trials prompted us to search for a bioisostere of tenidap **1** with better pharmacological activity.

The effect of various ring substitutuents of indole moiety on the pharmacological activities is well documented in the literature.[10] There are some reports in literature related to benzo-[*b*]-thiophenes as bioisosteres of indole molecules, for example, the benzthiophene analogues of *N*-*N*-dimethyltryptamines.[11] However, there are limited literature reports on thiophene replacement of the annulated benzene ring in derivatives of piroxicam, amphetamine, phenyltetrahydroisoquinolines.

The biological activity of Tenoxicam **2** and Lornoxicam **3**[12] (Fig. 1), bioisosteres of anti-inflammatory category were particularly interesting.[12] Herein, we describe our studies directed towards synthesis and pharmacological activity of various bioisosteric analogues of tenidap compounds **4**–**6** (Fig. 2) prepared by replacing the annulated benzene ring of indole moiety with thiophene.

2. Chemistry

The title compound **5** is prepared starting from thiophene (Scheme 1). Thiophene **7** is converted into 2-for-

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mylthiophene **8** by formylation using standard procedure with DMF/$POCl_3$. The 2-formyl thiophene, thus obtained, is reduced to 2-methyl thiophene 9 with hydrazine hydrate. Frieder–Crafts alkylation reaction of **9** followed by oxidation with sodium perchlorate furnished 2-methylthiophenecarboxylicacid **10**, in good yields. The carboxylic acid **10**, on treatment with nitrating mixture gave nitro derivative **11**, which on esterification with ethanol furnished the corresponding ethylester **12**. The ester is treated with diethyloxalate to give the enol ester **13**. The enolester is converted into thiene-[*b*]-pyrrol moiety **14**[13,14] using stannous chloride dihydrate in moderate yield. This on further reaction with 2-thiophenecarbonyl chloride using stannic chloride furnished the desired bioisostere **5** in good yield.

The title compound **4** was prepared from 2-methyl thiophene **9** (Scheme 2), which was subjected to formylation under established conditions to give corresponding aldehyde **15**. The aldehyde on condensation with ethyl azidoacetate furnished the corresponding adduct **16**. The adduct on intramolecular cyclization under reflux conditions in xylene furnished the ester **17**[15] and further treatment with 2-thiophenecarbonyl chloride using stannic chloride to give the desired target **4** in good yields.

The title compound **6** was prepared from thiophene with built in chloro functionality (Scheme 3). Formylation of 2-chlorothiophene **18** gave 2-chloro-5-formylthiophene **19**. The aldehyde **19** on condensation with

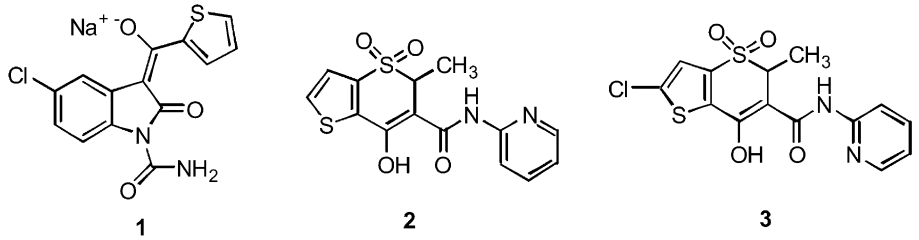


Figure 1.

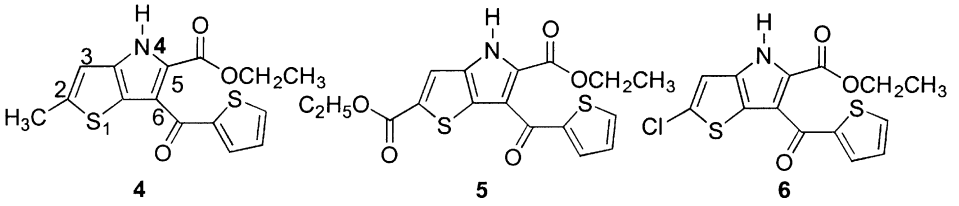
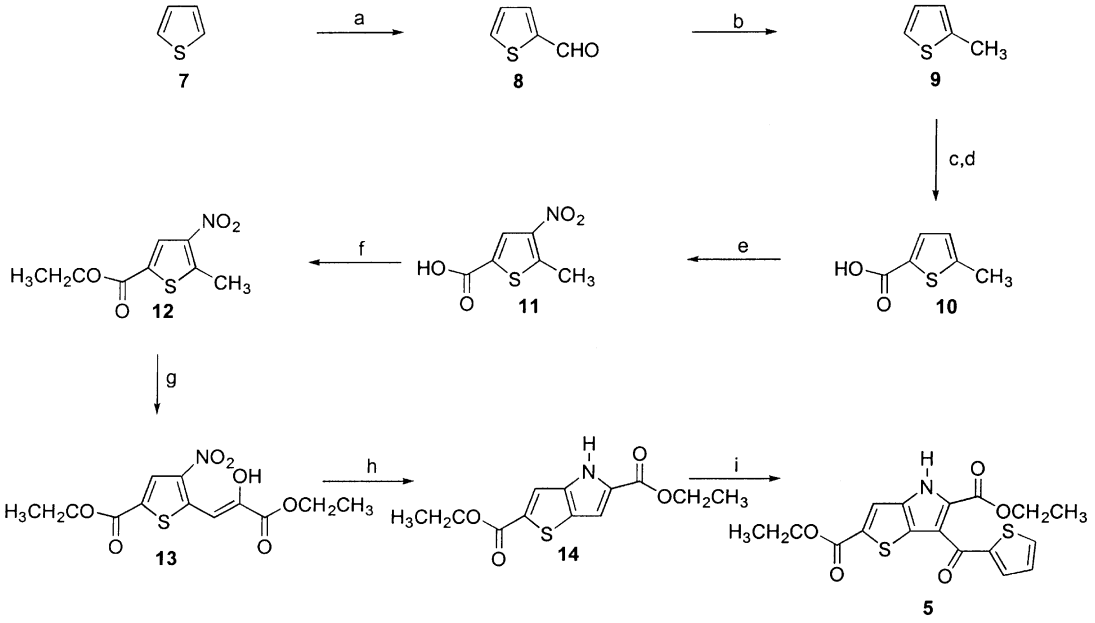
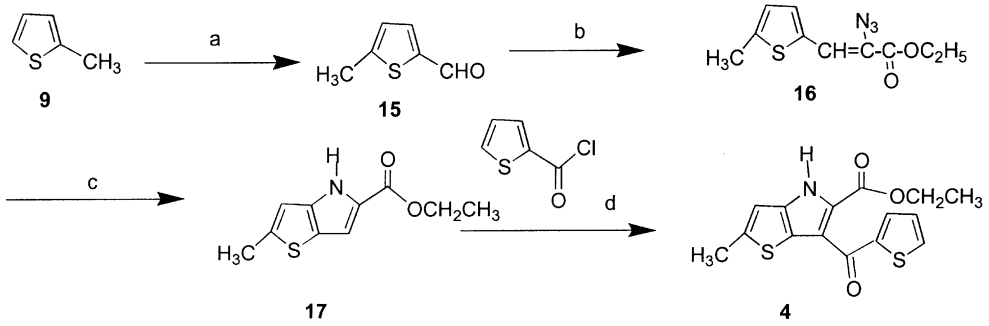


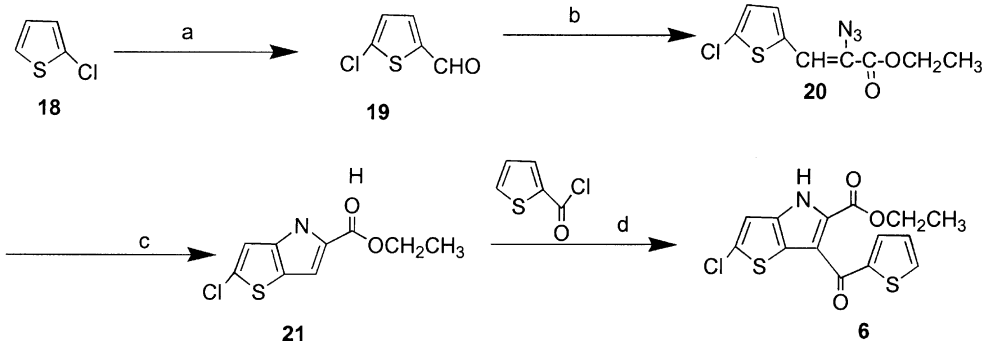
Figure 2.



Scheme 1. Reagents and conditions: (a) DMF, $POCl_3$, 80 °C); (b) ethanediol, NH_2–NH_2·H_2O/KOH, 180 °C. (c) $AC_2O/AlCl_3$, DCE, 45–50 °C; (d) NaOCl, 70–80 °C; (e) HNO_3/H_2SO_4, 0–5 °C; (f) EtOH/H+, reflux; (g) $(CO_2C_2H_5)_2$, NaOEt, ethanol, 50–60 °C; (h) $SnCl_2$ $2H_2O$/H+, ethanol, reflux; (i) $SnCl_4$/DCM, 2-thiophenecarbonyl chloride, reflux.



Scheme 2. Reagents and conditions: (a) DMF, $POCl_3$, reflux; (b) Na/EtOH, $N_3CH_2COOC_2H_5$, 5–10 °C; (c) xylene/reflux; (d) 2-thiophenecarbonyl chloride, $SnCl_4$/DCM, reflux.



Scheme 3. Reagents and conditions; (a) DMF, $POCl_3$, reflux; (b) Na/EtOH, $N_3CH_2COOC_2H_5$, 5–10 °C; (c) xylene/reflux; (d) 2-thiophenecarbonyl chloride, $SnCl_4$/DCM, reflux.

ethyl azidoacetate gave the corresponding adduct **20**. The adduct on intramolecular cyclization under reflux conditions in xylene furnished the ester **21**.[16] The ester **21** is further treated with 2-thiophenecarbonyl chloride to give the desired structural moiety **6** in good yields.

2.1. Derivatives

The substrates **4**, **5** and **6** obtained from the above Schemes 1–3 were *N*-alkylated using sodiumhydride in presence of dimethylformamide with different alkyl halo esters to give corresponding alkylated products. Some of these derivatives (**4a**, **4c**, **4g**, **5a**, **5j**, **5h**, **6d**, **6e**) were treated with alcoholic sodium hydroxide to give the corresponding acids (**4e**, **4f**, **4d**, **5g**, **5d**, **5i**, **6b**, **6c**). Acids (**5i**, **5g**) on treatment with sodium ethoxide gave the corresponding sodium salts (**5c**, **5f**). All these derivatives (see Table 1) were screened for anti-inflammatory activity (See Table 2).

2.2. Biology

2.2.1. Anti-inflammatory activities. Male/female Wister rats (120–140 g) were fasted for 16 h before the experiment. Compounds were suspended in 0.25% carboxy methyl cellulose and administered orally in a volume of 10 mL kg^{-1} 2 h before carageenan injection. Edema was induced in rats by intradermal injection of 50 μL of 1% λ-carrageenan in saline into the plantar surface of the right hind paw. The paw volume was monitored before and 3 h after carageenan injection using plethysmometer (Ugo-Basile, Italy). The paw edema was compared with the vehicle treated group and the percent inhibition was calculated (Table 2).

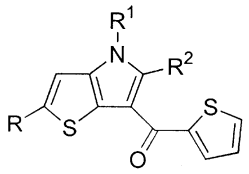
3. Results and discussion

The compounds synthesized in this study were evaluated for their abilities to inhibit anti-inflammatory activities in vivo. Since these compounds did not show any significant activity at 10 mg/kg, all the compounds were tested at higher dose 100 mg/kg. The values observed in Table 2 indicates that the anti-inflammatory activity exhibited by the derivatives of bioisosteres is significantly lower than that shown by the parent compounds Temdap Sodium. Diclofenac Sodium and Piroxicam (10 mg/kg).

4. Experimental

Solvents and reagents are obtained from commercial sources and are not purified unless specified. ^1H NMR data was obtained on a Varian Gemini 200 MHz FT NMR spectrometer. Infrared spectra (IR) were recorded on a Perkin-Elmer 1650 FT-IR spectrometer. Mass spectra were recorded on an HP-5989A quadrapole mass spectrometer. Melting points were taken in open capillaries and are uncorrected. The HPLC Purity of all these compounds were tested by using Hypercil BDS C^{18} column, mobile phase 0.01 M KH_2PO_4 and acetonitrile (40:60) with folwrate 1.0 mL/min at UV 285 nm.

Table 1.



Compd	R	R^1	R^2
4a	$-CH_3$	$-CH_2COO\ CH_2CH_3$	$-COOCH_2CH_3$
4b	$-CH_3$	$-COOCH_2CH_3$	$-COOCH_2CH_3$
4c	$-CH_3$	$-CH_2CH=CH_2$	$-COOCH_2CH_3$
4d	$-CH_3$	$-CH(CH_3)COOH$	–COOH
4e	$-CH_3$	$-CH_2COOH$	–COOH
4f	$-CH_3$	$-CH_2CH=CH_2$	–COOH
4g	$-CH_3$	$-CH(CH_3)COO\ C_2H_5$	$-COOCH_2CH_3$
5a	$-COOCH_2CH_3$	$-CH_2COOC_2H_5$	$-COOCH_2CH_3$
5b	$-COOCH_2CH_3$	$-COOCH_2CH_3$	$-COOCH_2CH_3$
5c (tri sodium salt)	$-COO^-\ Na^+$	$-CH(CH_3)-COO^-\ Na^+$	$-COO^-\ Na^+$
5d	COOH	$-CH_2CH=CH_2$	–COOH
5e	$-CONH_2$	$-CH_2CH=CH_2$	$-CONH_2$
5f (di sodium salt)	$-COO^-\ Na^+$	$-CH_2COOH$	$-COO^-\ Na^+$
5g	–COOH	$-CH_2COOH$	–COOH
5h	$-COOCH_2CH_3$	$-CH(CH_3)COOCH_2CH_3$	$-COOCH_2CH_3$
5i	–COOH	$-CH(CH_3)COOH$	–COOH
5j	$-COOCH_2CH_3$	$-CH_2CH=CH_2$	$-COOCH_2CH_3$
6a	–Cl	$-COOCH_2CH_3$	$-COOCH_2CH_3$
6b	–Cl	$-CH_2CH=CH_2$	–COOH
6c	–Cl	$-CH_2COOH$	–COOH
6d	–Cl	$-CH_2CH=CH_2$	$-COOCH_2CH_3$
6e	–Cl	$-CH_2COOCH_2CH_3$	$-COOCH_2CH_3$

Table 2. Evaluation of anti-inflammatory activities of compounds[a]

Compd	Anti-inflammatory activity (% inhibition at 100 mg/kg) rat-paw edema
4a	26
4b	24
4c	12
4d	10
4e	7
4f	3
5a	17
5b	9
5d	22
5g	36
5e	8
6a	15
6b	11
6c	4
Tenidap Sodium	60[b]
5f	11
Diclofinac Sodium	68[b]
5c	6
Peroxican	59[b]

[a] LD-50: >1000.
[b] (10 mg/kg).

4.1. Preparation of 2-methyl-5-carbethoxy-6-(2-thenoyl)-thieno-[3,2-*b*] pyrrole (4)

2-Methyl-5-carbethoxy-thieno-[3,2-*b*]-pyrrole (**18**) (10.0 g, 47.7 mmol) was dissolved in dichloromethane (100 mL) and stannic chloride (2.05 g, 14 mmol) was added, followed by 2-thiophenecarbonyl chloride (1.5 mL, 14.07 mmol) at room temperature. The contents were refluxed for 20 h. Reaction mixture was cooled to room temperature, poured into ice water with stirring. The organic layer was separated, solvent removed under reduced pressure to obtain product as viscous oil. This crude compound was dissolved in dichloromethane and triturated with petroleum ether to furnish **4** (8.5 g, 55%) as pure white color solid; mp 101–105 °C.

IR (KBr) cm^{-1}: 3274, 1672, 1626, 1405, 1290, 1215, 1194,753,502; ^1H NMR (200 MHz, $CDCl_3$): δ 8 9.3 (s 1H D_2O exchangeable), 7.7 (d, 1H), 7.6 (d, 1H), 7.1 (t, 1H), 6.5 (s, 1H), 4.2 (q, 2H), 2.5 (s, 3H), 1.1 (t, 3H); M^+ (*m*/*e*): 319 (93%), 273 (87%), 246 (10%), 236 (12%), 218 (10%), 190 (10%), 163 (10%), 134 (10%), 111 (97%). Anal. calcd for $C_{15}H_{13}NO_3S_2$: C, 56.420; H, 4.106; N, 4.389. Found: C, 56.51; H, 4.17; N, 4.43.

4.2. Preparation of 2,5-dicarbethoxy-6 (2-thenoyl) thieno [3,2-*b*] pyrrole (5)

2,5-Dicarbethoxy-thieno-[3,2-*b*]-pyrrole (**14**) (10.0 g, 37.5 mmol) was dissolved in dichloromethane (100 mL) and stannic chloride (2.05 g, 14 mmol) was added, followed by 2-thiophenecarbonyl chloride (1.5 mL, 14.07 mmol) at room temperature. The contents were refluxed for 20 h. Reaction mixture was cooled to room temperature, poured into ice water with stirring. The organic layer was separated, solvent removed under reduced pressure to obtain product as viscous oil. This crude compound was dissolved in dichloromethane and triturated with petroleum ether to furnish **5** (7.75 g, 55%) as pure white color solid; mp 97–100 °C.

IR (KBr) cm^{-1}: 3258, 1714, 1676, 1620, 1492, 1427, 1230, 1049,780,725; ^1H NMR (200 MHz, $CDCl_3$): δ 9.5 (D_2O exchangeable), 7.8 (s, 1H), 7.7 (s, 1H), 7.6 (d, 1H), 7.1 (t, 1H), 4.4 (q, 2H), 4.2 (q, 2H), 1.4 (t, 3H), 1.2 (t, 3H); M^+ (*m*/*e*): 377 (97%), 331 (60%), 303 (20%), 286 (20%), 259 (15%), 248 (10%), 202 (5%), 194 (20%), 111 (75%). Anal. calcd for $C_{17}H_{15}NO_5S_2$: C, 54.105; H, 4.009; N, 3.713. Found: C, 54.25; H, 3.98; N, 3.68.

4.3. Preparation of 2-chloro-5-carbethoxy-6 (2-thenoyl) thieno [3,2-*b*] pyrrole (6)

2-Chloro-5-carbethoxy-thieno-[3,2-*b*]-pyrrole (**22**) (10.0 g, 42.5 mmol) was dissolved in dichloromethane (100 mL) and stannic chloride (2.05 g, 14 mmol) was added, followed by 2-thiophenecarbonyl chloride (2.05 g, 14.07 mmol) at room temperature. The contents were refluxed for 20 h. Reaction mixture was cooled to room temperature, poured into ice water with stirring. The organic layer was separated, solvent removed under reduced pressure to obtain product as viscous oil. This crude compound was dissolved in dichloromethane and triturated with petroleum ether furnished **6** (8.5 g, 55%) as pure dark greenish color low melting solid.

IR (KBr) cm^{-1}: 3258, 1684, 1611, 1488, 1413, 1270, 1195, 974, 774, 721; ^1H NMR (200 MHz, $CDCl_3$): δ 9.8 (D_2O exchangeable), 7.7 (d, 1H), 7.6 (d, 1H), 7.1 (t, 1H). 6.9 (s, 1H), 4.2 (q, 2H), 1.2 (t, 3H); M^+ (*m*/*e*) 339 (96%), 293 (85%), 256 (25%), 238 (8%), 210 (10%). 202 (4%), 184 (8%), 111 (30%). Anal. calcd for $C_{14}H_{10}NO_3S_2Cl$: C, 49.560; H, 2.973; N, 4.130. Found: C, 49.76; H, 2.91; N, 4.15.

4.4. Preparation of 2-methyl-5-carbethoxy-4-carbethoxy methyl-6-(2-thenoyl)-thieno-[3,2-*b*] pyrrole (4a)

To the mixture of sodiumhydride (0.2 g, 8.33 mmol) and dry dimethylformamide (30 mL), a solution of 2-methyl-5-carbethoxy-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (**4**) (0.5 g, 1.56 mmol) in dimethylformamide (10 mL) was added at 0–5 °C. After 5 min, eyhylchloroacetate (0.4 mL, 3.7 mmol) was added slowly with stirring. Reaction temperature increased to 25–30 °C, further contents were stirred for 3–4 h. Upon completion of reaction ice water was added and adjusted the pH to 2 by addition of HCl. Reaction mass was extracted into diethylether, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain crude compound as a syrupy liquid. Purification by column chromatography furnished **4a** (0.44 g, 70%) as pale yellow solid; mp 93–95 °C.

IR (KBr) cm^{-1}: 1754, 1692, 1603, 1411, 1284, 1246, 1204, 1164, 1098, 1022, 955, 781, 501; ^1H NMR (200 MHz, $CDCl_3$): δ 7.7 (d, 1H), 7.6 (d, 1H), 7.1 (t, 1H).6.6 (s, 1H), 5.2 (s, 2H), 4.3 (q, 2H), 4.0 (q, 3H) 2.5 (s, 3H), 1.3 (t, 3H), 0.9 (t, 3H); M^+ (*m*/*e*); 405 (97%), 360 (10%), 333 (15%), 286 (20%), 258 (10%), 220 (10%). 190 (30%), 111 (70%). Anal. calcd for $C_{19}H_{19}NO_5S_2$: C, 56.28; H, 4.72: N, 3.45, Found: C, 55.98; H, 4.66; N, 3.56.

4.5. Preparation of 2-methyl-4, 5-dicarbethoxy-6-(2-thenoyl) thieno-[3,2-*b*] pyrrole (4b)

To the mixture of sodiumhydride (0.3 g, 12.5 mmol) and dry dimethylformamide (30 mL), a solution of 2-methyl-5-carbethoxy-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (**4**) (0.5 g, 1.56 mmol) in dimethylformamide (10 mL) was added at 0–5 °C. After 5 min, eyhylchloro formate (0.5 mL, 5.22 mmol) was added slowly with stirring. Reaction temperature increased to 25–30 °C, further contents were stirred for 3–4 h. Upon completion of reaction, ice water was added and adjusted the pH to 2 by addition of HC1. Reaction mass was extracted into diethylether, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain crude compound as a syrupy liquid. Purification by column chromatography furnished **4b** (0.55 g, 90%) as pale yellow solid; mp 95–98 °C.

IR (KBr) cm^{-1}: 3440, 1748, 1622, 1522, 1398, 1341, 1282, 1201, 1143, 1006, 834, 711; ^1H NMR (200 MHz, $CDCl_3$): δ 7.8 (d, 1H), 7.7 (d, 1H), 7.2 (t, 1H), 7.1 (s, 1H), 4.5 (q, 2H), 4.3 (q, 2H), 2.6 (s, 3H). 1.5 (t, 3H). 1.3 (t, 3H); M^+ (*m*/*e*): 391 (97%), 346 (85%), 319 (20%), 273 (90%), 246 (10%), 218 (10%), 190 (8%), 111 (40%). Anal. calcd for $C_{18}H_{17}N\ O_5S_2$: C, 55.23: H, 4.38; N, 3.58. Found: C, 55.58; H, 4.66; N, 3.56.

4.6. Preparation of 2-methyl-5-carbethoxy-4-allyl-6-(2-thenoyl) thieno-[3,2-*b*] pyrrole (4c)

To the mixture of sodiumhydride (1.2 g, 50 mmol) and dry dimethylformamide (20 mL), a solution of 2-methyl-5-carbethoxy-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (**4**) (2.0 g, 6.24 , mmol) in dimethylformamide (20 mL) was added at 0–5 °C. After 5 min, allylbromide (1.5 mL, 17.3 mmol) was added slowly with stirring. Reaction temperature increased to 25–30 °C. further contents were stirred for 3–4 h. Upon completion of reaction ice water was added and adjusted the pH to 2 by addition of HCl. Reaction mass was extracted into diethylether, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain crude compound as a syrupy liquid. Purification by column chromatography furnished **4c** (1.4 g, 63%) as pale yellow solid; mp 64–66 °C.

IR (KBr) cm^{-1}: 3104, 2981, 1712, 1638, 1519, 1493, 1282, 1238, 1155, 1022, 919, 795, 763, 727, 656, 556; ^1H NMR (200 MHz, $CDCl_3$): δ 7.7 (d, 1H), 7.6 (d, 1H), 7.1 (t, 1H), 6.7 (s, 1H), 6.0 (m, 1H), 5.1–5.2 (m, 2H), 4.0 (q, 2H), 2.6 (s, 3H), 1.0 (t, 3H). M^+ (*m*/*e*): 361 (96%), 372 (45%), 344 (96%), 260 (20%), 204 (15%), 160 (10%), 111 (65%). Anal. calc for $C_{18}H_{17}NO_3S_2$: C, 60.156; H, 4.771; N, 3.899. Found: C, 60.212; H, 4.66; N, 3.95.

4.7. Preparation of 2-methyl-5-carboxy-4-(2-propionic acid)-6-(2-thenoyl) thieno-[3,2-*b*] pyrrole (4d)

2-Methyl-5-carbethoxy-4-(1-ethoxy carbonyl ethyl)-6-(2-thenoyl) thieno-[3,2-*b*]-pyrrole (**4g**) (2.0 g, 4.94 mmol)

dissolved in 5% ethanolic sodiumhydroxide solution (25 mL) was heated under reflux for 1 h. Reaction mass was poured into ice water and extracted into diethyl ether and discarded. The aqueous layer was neutralized by addition of HCl. The precipitated product was filtered and dried to obtain **4d** (0.6 g, 35%; HPLC purity: 99.207%) as light yellow solid; mp 185–187 °C.

IR (KBr) cm^{-1}: 3429, 1748, 1661, 1518, 1413, 1242, 1053, 743; ^1H NMR (200 MHz. $CDCl_3$): δ 8.1 (d, 1H), 7.8 (d, 1H), 7.2 (t, 1H), 6.7 (s, 1H), 6.3 (d, 1H), 4.8 (1H D_2O exchangeable), 2.5 (s, 3H), 1.8 (d, 3H); M^+ (*m*/*e*): 363 (15%). 345 (40%), 319 (60%), 274 (27%), 258 (25%), 190 (50%), 169 (12%), 149 (30%), 111 (97%), 107 (30%), 83 (30%). Anal. calcd for $C_{16}H_{13}NO_5S_2$: C, 52.889; H, 3.609; N, 3.857. Found: C, 52.91; H, 3.62; N, 3.88.

4.8. Preparation of 2-methyl-5-carboxy-4-carboxy methyl-6-(2-thenoyl) thieno-[3,2-*b*] pyrrole (4e)

2-Methyl-5-carbethoxy-4-carbethoxymethyl-6-(2-thenoyl)thieno-[3,2-*b*] pyrrole (**4a**) (1.0 g, 2.46 mmol) dissolved in 5% ethanolic sodiumhydroxide solution (10 mL) was heated under reflux for 1 h. Reaction mass was poured into ice water and extracted into diethyl ether and discarded. The aqueous layer was neutralized by addition of HCl. The precipitated product was filtered and dried to obtain **4e** (0.7 g, 81%; HPLC purity: 94.878%) as light yellow solid; mp 210–212 °C.

IR (KBr) cm^{-1}: 2920, 1708, 1554, 1441, 1237, 1168, 1052, 949, 855, 743; ^1H NMR (200 MHz, DMSO): δ 8.1 (d, 1H), 7.6 (d, 1H), 7.2 (t, 1H), 7.1 (s, 1H), 5.2 (s, 2H), 2.2 (s, 3H); M^+ (*m*/*e*): 349 (45%), 305 (97%), 260 (25%), 247 (20%), 222 (23%), 190 (18%), 148 (30%), 127 (30%), 111 (95%). Anal. calcd for $C_{15}H_{11}NO_5S_2$: C, 51.575; H, 3.176; N, 4.012. Found: C, 51.60; H, 3.19; N, 4.12.

4.9. Preparation of 2-methyl-5-carboxy-4-allyl-6-(2-thenoyl)-thieno-[3,2-*b*] pyrrole (4f)

2-Methyl-5-carbethoxy-4-allyl-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (**4c**) (2.0 g, 5.5 mmol) dissolved in 5% ethanolic sodiumhydroxide solution (25 mL) was heated under reflux for 1 h. Reaction mass was poured into ice water and extracted into diethyl ether and discarded. The aqueous layer was neutralized by addition of HCl. The precipitated product was filtered and dried to obtain **4f** (1.7 g, 92%, HPLC purity: 95.360%) as pale yellow solid; mp 153–155 °C.

IR (KBr) cm^{-1}: 1705, 1540, 1484, 1439, 1343, 1233, 943, 849, 740; ^1H NMR (200 MHz, $CDCl_3$): δ 8.1 (d, 1H), 7.9 (d, 1H), 7.2 (t, 1H), 6.7 (s, 1H), 6.1 (m, 1H), 5.3 (d, 2H), 5.1–5.2 (m, 2H), 2.5 (s, 3H); M^+ (*m*/*e*): 331 (60%), 314 (20%), 287 (98%), 270 (25%), 218 (60%), 204 (15%), 176 (30%), 111 (65%), 83 (10%). Anal. calcd for $C_{16}H_{13}NO_3S_2$: C, 58.000; H, 3.958; N, 4.230. Found: C, 58.09; H, 3.98; N, 4.28.

4.10. Preparation of 2-methyl-5-carbethoxy-4-(1-ethoxy carbonyl ethyls)-6-(2-thenoyl) thieno-[3,2-*b*] pyrrole (4g)

To the mixture of sodiumhydride (0.2 g, 8.33 mmol) and dry dimethylformamide (30 mL), a solution of 2-methyl-5-carbethoxy-6-(2-thenoyl)-thieno-[3,2*b*]-pyrrole (**4**) (0.5 g, 1.56 mmol) in dimethylformamide (10 mL) was added at 0–5 °C. After 5 min, ethyl-2-chloropropionate (0.47 mL, 3.7 mmol) was added slowly with stirring. Reaction temperature increased to 25–30 °C, further contents were stirred for 3–4 h. Upon completion of reaction, ice water was added and adjusted the pH to 2 by addition of HCl. Reaction mass was extracted into diethylether, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain crude compound as a syrupy liquid. Purification by column chromatography furnished **4g** (0.44 g, 70%) as light yellow solid; mp 105–110 °C.

^1H NMR (200 MHz, $CDCl_3$): δ 7.7 (d, 1H), 7.5 (d, 1H), 7.1 (t, 1H), 6.7 (s, 1H), 6.1 (q, 1H),4.3 (q, 2H), 4.2 (q, 2H), 4.0 (q, 2H), 2.5 (s, 3H), 1.9 (d, 3H), 1.5 (t, 3H), 0.9 (t, 3H); M^+ (*m*/*e*): 491 (25%), 419 (97%), 374 (15%), 345 (30%), 300 (85%), 274 (20%), 234 (20%), 190 (60%), 162 (15%), 111 (80%). Anal. calcd for $C_{20}H_{21}NO_5S_2$: C, 57.267; H, 5.050; N, 3.341. Found: C, 57.28; H, 5.14; N, 3.46.

4.11. Preparation of 2,5-dicarbethoxy-4-carbethoxy methyl-6-(2-thenoyl)thieno-[3,2-*b*]-pyrrole (5a)

To the mixture of sodiumhydride (1.0 g, 41.6 mmol) and dry dimethylformamide (12.0 mL), a solution of 2,5-dicarbethoxy-6-(2-thenoyl)-thieno-[3,2*b*]-pyrrole (**5**) (2.0 g, 5.29 mmol) in dimethylformamide (5.0 mL) was added at 0–5 °C. After 5 min, eyhylchloroacetate (2.0 mL, 19 mmol) was added slowly with stirring. Reaction temperature increased to 25–30 °C, further contents were stirred for 3–4 h. Upon completion of reaction, ice water was added and adjusted the pH to 2 by addition of HC1. Reaction mass was extracted into diethylether, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain crude compound as a syrupy liquid. Purification by column chromatography furnished **5a** (1.95 g, 80%) as almost white solid; mp 80–82 °C.

IR (KBr) cm^{-1}: 3450, 3103. 2953. 1752, 1702, 1643, 1408, 1280, 1241, 1151, 1024, 729; ^1H NMR (200 MHz, $CDCl_3$): δ 8.1 (s, 1H).7.7 (d, 1H), 7.6 (d, 1H), 7.0 (t, 1H), 5.2 (s, 2H),4.4 (q, 2H),4.2 (q, 2H), 4.0 (q, 2H). 1.2–1.6 (m, 6H), 1.0 (t, 3H); M^+ (*m*/*e*): 463 (42%), 418 (8%), 377 (97%). 331 (60%). 303 (20%), 286 (20%), 259 (15%), 248 (10%), 202 (5%), 194 (20%), 111 (75%). Anal. calcd for $C_{21}H_{21}NO_7S_2$: C, 54.418; H, 4.570; N, 3.023. Found: C, 54.318; H, 4.66: N, 3.10.

4.12. Preparation of 2,4,5-tricarbethoxy-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (5b)

To the mixture of sodiumhydride (1.0 g, 41.6 mmol) and dry dimethylformamide (12.0 mL), a solution of 2.5-dicarbethoxy-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (**5**)

(2.0 g, 5.29 mmol) in dimethylformamide (5.0 mL) was added at 0–5 °C. After 5 min, ethylchloroformate (2.27 g, 20.9 mmol) was added slowly with stirring. Reaction temperature increased to 25–30 °C, further contents were stirred for 3–4 h. Upon completion of reaction, ice water was added and adjusted the pH to 2 by addition of HC1. Reaction mass was extracted into diethylether, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain crude compound as a syrupy liquid. Purification by column chromatography furnished **5b** (2.0 g, 89%) as almost white solid; mp 86–88 °C.

IR (KBr) cm^{-1}: 1822. 1763, 1730, 1638, 1391, 1258, 1127, 1013, 748; ^1H NMR (200 MHz, $CDCCl_3$): δ 8.1 (s, 1H), 7.9 (d, 1H), 7.8 (d, 1H), 7.2 (t, 1H), 4.6 (q, 2H), 4.2–4.5 (m, 4H). 1.4–1.7 (m, 6H), 1.2–1.3 (t, 3H); M^+ (*m*/*e*): 449 (60%), 40 (20%), 377 (40%), 331 (70%), 303 (15%), 248 (10%), 210 (7%), 111 (96%). Anal. calcd for C_{20} H_{19} N O_7 S_2: C, 53.44; H, 4.26; N, 3.12. Found: C, 53.58; H, 4.66; N, 3.36.

4.13. Preparation of trisodium salt of 2,5-dicarboxy-4-(1-carboxyethyl)-6-(2-thenoyl) thieno-[3,2-*b*] pyrrole) (5c)

To a freshly prepared sodium ethoxide solution [sodium metal (0.187 g, 8.13 mmol) in ethanol (50 mL) 2,5-dicarboxy-4-1-carboxy ethyl-6-(2-thenoyl)-thieno-[3,2-*b*] pyrrole (**5i**) (1.0 g, 2.54 mmol)] was added and refluxed for 1 h. The product obtained was filtered, dried under vacuum to give **5c** (1.1 g, 93.5%, HPLC purity: 99.846%) as light yellow solid; mp 200–220 °C (decomp).

IR (KBr) cm^{-1}: 2982, 2589, 1701, 1515, 1409, 1237, 1167, 739; ^1H NMR (200 MHz, DMSO): δ 8.0 (d, 2H), 7.8 (d, 1H), 7.2 (s, 1H), 7.1 (t, 1H), 5.0 (q, 1H), 1.4 (d, 3H); M^+ (*m*/*e*): 393 (10%), 335 (12%), 313 (10%), 306 (15%), 285 (20%), 217 (30%), 199 (85%), 171 (50%), 153 (50%). 125 (90%), 111 (97%). Anal. calcd for C_{16} H_8 N O_7 S_2 Na_3: C, 41.835; H, 1.757; N, 3.051, Found: C, 41.90; H, 1.71; N, 3.10.

4.14. Preparation of 2,5-dicarboxy-4-allyl-6-(2-thenoyl)-thieno-[3,2-*b*] pyrrole (5d)

2,5-Dicarbethoxy-4-allyl-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (**5j**) (4.0 g, 9.58 mmol) dissolved in 3% ethanolic sodiumhydroxide solution (60 mL) was heated under reflux for 1 h. Reaction mass was poured into ice water and extracted into diethyl ether, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain **5d** (1.6 g, 46%, HPLC purity: 99.648%) as light yellow solid; mp 210–220 °C (decomp).

IR (KBr) cm^{-1}: 3440, 3093, 2933, 2570, 1707, 1673, 1514, 1452, 1287, 1208, 1159, 1050, 1938, 726; ^1H NMR (200 MHz, $CDCl_3$): δ 7.9 (d, 1H), 7.8 (d, 1H), 7.7 (s, 1H), 7.2 (t, 1H), 6.1 (m, 1H), 5.1–5.3 (m, 4H); M^+ (*m*/*e*): 361 (10%), 342 (20%), 331 (30%), 317 (55%), 300 (50%), 273 (30%), 233 (15%), 221 (40%), 204 (32%), 191 (30%), 162 (25%), 149 (50%). 128 (27%), 111 (97%), 89 (50%). Anal. calcd for $C_{16}H_{11}NO_5S_2$: C, 53.184: H, 3.071; N, 3.879. Found: C, 53.195; H, 3.11; N, 3.90.

4.15. Preparation of 2,5-dicarbamide-4-allyl-6-(2-thenoyl)thieno-[3,2-*b*] pyrrole) (5e)

2,5-Dicarboxy-4-allyl-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (**5d**) (2.2 g, 6.08 mmol) suspended in thionyl chloride (25 mL, 342 mmol) was stirred for 12 h at 25–30 °C. The excess of thionyl chloride was distilled off and the residue was dissolved in 1,4-dioxane and passed ammonia gas over a period of 2–4 h. The Reaction mass was poured into water and extracted with ethylacetate. The organic layer was separated dried over (Na_2SO_4). The organic layer was removed under reduced pressure to get crude residue as a syrupy liquid. Purification by column chromatography using hexane/ethyl acetate mixture to afford **5e** (1.6 g, 73%) as light yellow solid; mp 220–230 °C (decomp).

IR (KBr) cm^{-1}: 3165, 1675, 1600, 1471, 1407, 1249, 1117, 940, 868, 739; H NMR (200 MHz, DMSO): δ 7.9 (d, 1H), 7.8 (d, 1H), 7.7 (s, 1H), 7.2 (t, 1H), 6.1 (m, 1H), 5.1–5.3 (m, 2H); M^+ (*m*/*e*): 359 (20%), 342 (30%), 315 (97%), 298 (15%), 285 (10%), 259 (10%), 242 (10%), 231 (20%), 219 (15%), 203 (20%), 176 (10%), 111 (50%). Anal. calcd for $C_{16}H_{13}$ $N_3O_3S_2$: C, 53.475; H, 3.649; N, 11.700. Found: C, 53.375; H, 3.65; N, 11.68.

4.16. Preparation of disodium salt of 2,5-dicarboxy-4-carboxy methyl-6-(2-thenoyl) thieno-[3,2-*b*] pyrrole (5f)

To a freshly prepared sodium ethoxide solution [sodium (0.128 g, 5.56 mmol) dissolved in ethanol (50 mL), 2,5-dicarboxy-4-carboxy methyl-6-(2-thenoyl)-thieno-[3,2-*b*] pyrrole (**5g**) (1.3 g, 3.5 mmol)] was added and refluxed for 1 h. The product obtained was filtered, dried under vacuum to give **5f** (1.37 g, 94%, HPLC purity: 99.867%) as the pale yellow solid; mp 220–230 °C (decomp).

IR (KBr) cm^{-1}: 3212, 3090, 1710, 1512, 1408, 1236, 1155, 748; ^1H NMR (200 MHz, DMSO): δ 8.2 (s, 1H), 8.0 (d, 1H), 7.7 (d, 1H), 7.2 (t, 1H), 5.2 (s, 2H); M^+ (*m*/*e*); 379 (0.2%), 358 (1%), 347 (0.2%), 242 (7%), 220 (3%), 192 (7%), 156 (15%), 136 (7%), 117 (8%), 98 (99%). Anal. calcd for C_{15} $H_7NO_7S_2Na_2$: C, 42.559; H, 1.668; N, 3.311. Found: C, 42.58; H, 1.76; N, 3.39.

4.17. Preparation of 2,5-dicarboxy-4-carboxy methyl-6-(2-thenoyl) thieno-[3,2-*b*] pyrrole (5g)

2,5-Dicarbethoxy-4-carbethoxymethyl-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (**5a**) (4.0 g, 8.8 mmol) dissolved in 3% ethanolic sodiumhydroxide solution (50 mL) was heated under reflux for 1 h. Reaction mass was poured into ice water and extracted into diethyl ether, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain **5g** (2.0 g, 60%, HPLC purity: 99.682%) as pale yellow solid; mp 225–235 °C (decomp).

IR (KBr) cm^{-1}: 3212, 3090, 1710, 1512, 1408, 1236, 1155, 748; ^1H NMR (200 MHz, DMSO): δ 8.2 (s, 1H), 8.0 (d, 1H), 7.7 (d, 1H), 7.2 (t, 1H), 5.2 (s, 2H); M^+ (*m*/*e*): 379 (0.2%), 358 (1%), 347 (0.2%), 242 (7%), 220 (3%), 192 (7%), 156 (15%), 136 (7%), 117 (8%), 98 (99%). Anal.calcd for $C_{15}H_9NO_7S_2$: C, 47.496; H, 2.393; N, 3.695. Found: C, 47.51; H, 2.42; N,3.78.

4.18. Preparation of 2,5-dicarbethoxy-4-1-carbetoxy ethyl-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (5h)

To the mixture of sodiumhydride (1.0 g, 41.6 mmol) and dry dimethylformamide (12.0 mL), a solution of 2,5-dicarbethoxy-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (**5**) (2.0 g, 5.29 mmol) in dimethylformamide (5.0 mL) was added at 0–5 °C. After 5 min, ethyl-2-chloropropionate (2.5 mL, 19.5 mmol) was added slowly with stirring. Reaction temperature increased to 25–30 °C, further contents were stirred for 3–4 h. Upon completion of reaction, ice water was added and adjusted the pH to 2 by addition of HC1. Reaction mass was extracted into diethylether, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain crude compound as a syrupy liquid. Purification by column chromatography furnished **5h** (1.95 g, 77%) as viscous oil.

IR (KBr) cm^{-1}: 1743, 1700, 1628, 1483, 1415, 1285, 1237, 1170, 1010, 745; H NMR (200 MHz, $CDCl_3$): δ 7.8 (d, 1H), 7.7 (s, 1H), 7.6 (d, 1H), 7.1 (t, 1H), 6.0 (q, 1H), 4.4 (q, 2H), 4.2 (q, 2H), 4.0 (q, 2H), 1.9 (d, 3H), 1.4 (t, 3H), 1.2 (t, 3H), 1.0 (t, 3H); M^+ (*m*/*e*): 477 (97%), 432 (55%), 403 (30%), 358 (65%), 330 (15%). 292 (20%). 248 (45%), 220 (10%), 111 (60%). Anal. calcd for $C_{22}H_{23}NO_7S_2$: C, 55.33; H, 4.85; N, 2.93. Found: C, 55.98; H, 4.66; N,3.06.

4.19. Preparation of 2,5-dicarboxy-4-1-carboxy ethyl-6-(2-thenoyl) thieno-[3,2-*b*] pyrrole (5i)

2,5-Dicarbethoxy-4-1-carbetoxy ethyl-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (**5h**) (4.0 g, 8.38 mmol) dissolved in 3% ethanolic sodiumhydroxide solution (60 mL) was heated under reflux for 1 h. Reaction mass was poured into ice water and extracted into diethyl ether, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain **5i** (1.6 g, 48.5%) as pale yellow solid; mp 220–230 °C (decomp).

IR (KBr) cm^{-1}: 2982, 1701, 1515, 1409, 1237, 1167, 739; ^1H NMR (200 MHz, $CDCl_3$): δ 8.0 (d, 2H), 7.8 (d, 1H),7.1 (t, 1H), 5.0 (q, 1H); M^+ (*m*/*e*): 394 (10%), 335 (12%), 313 (10%), 306 (15%), 285 (20%), 217 (30%), 199 (85%), 171 (50%), 153 (50%) 125 (90%), 111 (97%). Anal. calcd for C_{16} H_{11} N O_7, S_2; C, 48.855; H, 2.821; N, 3.563. Found: C, 48.90; H, 2.91; N, 3.61.

4.20. Preparation of 2,5-dicarbethoxy-4-/allyl-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (5j)

To the mixture of sodiumhydride (1.0 g, 41.6 mmol) and dry dimethylformamide (12.0 mL), a solution of 2,5-dicarbethoxy-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (**5**) (2.0 g, 5.29 mmol) in dimethylformamide (5.0 mL) was added at 0–5 °C. After 5 min, allyl bromide (1.5 mL, 17.5 mmol) was added slowly with stirring. Reaction temperature increased to 25–30 °C, further contents were stirred for 3–4 h. Upon completion of reaction, ice water was added and adjusted the pH to 2 by addition of HCl. Reaction mass was extracted into diethylether, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain crude compound as a syrupy liquid. Purification by column chromatography furnished **5j** (1.95 g, 88%) as viscous oil.

IR (KBr) cm^{-1}: 1706, 1619, 1488, 1403, 1235, 1156, 750; H NMR (200 MHz, $CDCl_3$): δ 7.8 (s, 1H), 7.7 (d, 1H), 7.6 (d, 1H), 7.1 (t, 1H), 6.0 (m, 2H), 5.1–5.2 (m, 2H), 4.4 (q, 2H), 4.1 (q. 2H). 1.4 (t, 3H), 1.0 (t, 3H); M^+ (*m*/*e*): 417 (96%), 372 (45%), 344 (96%), 260 (20%). 204 (15%), 160 (10%), 111 (65%). Anal. calcd for C_{20} H_{19} N O_5 S_2: C, 57.544; H, 4.591; N, 3.357. Found: C, 57.56; H, 4.61; N, 3.29.

4.21. Preparation of 2-chloro-4,5-dicarbethoxy-6-(2-thenoyl) thieno-[3,2-*b*] pyrrole (6a)

To the mixture of sodiumhydride (0.3 g, 12.5 mmol) and dry dimethylformamide (30.0 mL), a solution of 2-Chloro-5-carbethoxy-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (**6**) (0.5 g, 1.47 mmol) in dimethylformamide (10.0 mL) was added at 0–5 °C. After 5 min, eyhylchloroformate (0.5 mL, 5.2 mmol) was added slowly with stirring. Reaction temperature increased to 25–30 °C, further contents were stirred for 3–4 h. Upon completion of reaction, ice water was added and adjusted the pH to 2 by addition of HCl. Reaction mass was extracted into diethylether, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain crude compound as a syrupy liquid. Purification by column chromatography furnished **6a** (0.55 g, 90%) as the pale yellow solid; mp 102–105 °C.

IR (KBr) cm^{-1}: 1776, 1743, 1620, 1399, 1343, 1262, 1205, 1013, 828, 735. ^1H NMR (200 MHz, $CDCl_3$): δ 7.8 (d, 1H), 7.7 (d, 1H), 7.3 (s, 1H), 7.1 (t, 1H), 4.5 (q, 2H), 4.2 (q, 2H), 1.5 (t, 3H), 1.2 (t. 3H): M^+ (*m*/*e*): 411 (60%), 366 (20%), 339 (20%), 293 (97%), 267 (10%), 238 (8%), 210 (12%), 111 (50%). Anal. calcd for $C_{17}H_{14}ClNO_5S_2$: C, 49.58; H, 3.43; N, 3.40. Found: C, 49.68: H, 3.33; N, 3.56.

4.22. Preparation of 2-chloro-5-carboxy-4-allyl-6-(2-thenoyl)thieno-[3,2-*b*] pyrrole (6b)

2-Chloro-5-carbethoxy-4-allyl-6-(2-thenoyl) thieno-[3,2-*b*] pyrrole (**6d**) (2.0 g, 5.2 mmol) dissolved in 5% ethanolic sodiumhydroxide solution (25 mL) was heated under reflux for 1 h. Reaction mass was poured into ice water and extracted into diethyl ether and discarded. The aqueous layer was neutralized by addition ofHCl. The precipitated product was filtered and dried to obtain **6b** as solid (1.7 g. 91.7%, HPLC purity: 99.76%.

IR (KBr) cm^{-1}: 1698, 1520, 1473, 1440, 1412, 1229, 914, 733; ^1H NMR (200 MHz, $CDCl_3$): δ 8.1 (d, 1H), 7.9 (d,

1H), 7.2 (t, 1H), 7.0 (s, 1H), 6.1 (m, 1H), 5.1–5.3 (m, 2H); M^+ (*m*/*e*): 351 (50%), 307 (70%), 238 (35%), 221 (10%), 203 (10%), 160 (10%), 150 (20%), 111 (97%). 107 (40%). Anal. calcd for $C_{15}H_{10}NO_3S_2$ Cl: C, 51.285; H, 2.871; N, 3.990. Found: C, 51.31; H, 2.91; N, 4.09.

4.23. Preparation of 2-chloro-5-carboxy-4-carboxy methyl-6-(2-thenoyl) thieno-[3,2-*b*] pyrrole (6c)

2-Chloro-5-carbethoxy-4-carbethoxy methyl-6-(2-thenoyl) thieno-[3,2-*b*] pyrrole (**6e**) (1.0 g, 2.3 mmol) dissolved in 5% ethanolic sodiumhydroxide solution (10 mL) was heated under reflux for 1 h. Reaction mass was poured into ice water and neutralized by addition of HCl. Filtered the crude compound and purification by column chromatography furnished **6c** (0.70 g, 75%) as the pale yellow solid; mp 218–220 °C.

IR (KBr) cm^{-1}: 3451, 3091, 1708, 1570, 1517, 1472, 1413, 1350, 1305, 1243, 934, 725; ^1H NMR (200 MHz, $CDCl_3$): δ 8.1 (D_2O exchangeable), 7.9 (d, 1H), 7.6 (d, 1H), 7.4 (s, 1H), 7.2 (t, 1H), 5.3 (s, 2H); M^+ (*m*/*e*): 369 (15%), 351 (15%), 325 (20%), 291 (30%), 261 (22%), 221 (70%), 205 (80%), 191 (40%), 165 (35%), 150 (90%), 120 (70%), 107 (94%), 89 (20%). Anal. calcd for $C_{14}H_8ClNO_5S_2$: C, 45.47; H, 2.18; N, 3.79. Found: C, 45.98; H, 2.25; N, 3.66.

4.24. Preparation of 2-chloro-5-carbethoxy-4-allyl-6-(2-thenoyl) thieno-[3,2-*b*] pyrrole (6d)

To the mixture of sodiumhydride (0.3 g, 12.5 mmol) and dry dimethylformamide (30.0 mL), a solution of 2-chloro-5-carbethoxy-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (**6**) (0.5 g, 1.47 mmol) in dimemylformamide (10.0 mL) was added at 0–5 °C. After 5 min, allylbromide (0.5 mL, 5.82 mmol) was added slowly with stirring. Reaction temperature increased to 25–30 °C, further contents were stirred for 3–4 h. Upon completion of reaction, ice water was added and adjusted the pH to 2 by addition of HCl. Reaction mass was extracted into diethylether, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain crude compound as a syrupy liquid. Purification by column chromatography furnished **6d** (0.51 g, 91%) as viscous oil.

IR (KBr) cm^{-1}: 1700, 1525, 1460, 1445, 1420, 1230, 920, 742; ^1H NMR (200 MHz, $CDCl_3$): δ 8.0 (d, 1H), 7.9 (d, 1H), 7.2 (t, 1H), 7.1 (s, 1H), 6.1 (m, 1H), 5.1–5.3 (m, 2H), 4.1 (q, 2H), 1.1 (t, 3H); M^+ (*m*/*e*): 379 (96%), 351 (45%), 334 (96%), 307 (20%), 261 (15%), 238 (10%), 221 (65%), 191 (12%), 150 (8%), 111 (45%). Anal. calcd for $C_{17}H_{14}NO_3S_2$ Cl: C, 53.824; H, 3.722; N, 3.694. Found: C, 53.79; H, 3.73; N, 3.63.

4.25. Preparation of 2-chloro-5-carbethoxy-4-carbethoxy methyl-6-(2-thenoyl) thieno-[3,2-*b*] pyrrole (6e)

To the mixture of sodiumhydride (0.3 g, 12.5 mmol) and dry dimethylformamide (30.0 mL), a solution of 2-chloro-5-carbethoxy-6-(2-thenoyl)-thieno-[3,2-*b*]-pyrrole (**6**) (0.5 g, 1.47 mmol) in dimethylformamide (10.0 mL) was added at 0–5 °C. After 5 min, eyhylchloroacetate (0.55 mL, 5.2 mmol) was added slowly with stirring. Reaction temperature increased to 25–30 °C, further contents were stirred for 3–4 h. Upon completion of reaction, ice water was added and adjusted the pH to 2 by addition of HCl. Reaction mass was extracted into diethylether, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain crude compound as a syrupy liquid. Purification by column chromatography furnished **6e** (0.55 g, 88%) as viscous oil.

IR (KBr) cm^{-1}: 2928, 1747, 1704, 1411, 1279, 1210, 1025, 911, 856, 733 ^1H NMR (200 MHz, $CDCl_3$): δ 7.7 (d, 1H), 7.6 (d, 1H), 7.1 (t, 1H), 5.2 (m, 2H), 4.3 (q, 2H), 4.0 (q, 2H), 1.4 (t, 3H), 0.9 (t, 3H); M^+ (*m*/*e*): 425 (96%), 380 (20%), 353 (18%), 342 (10%), 306 (15%), 240 (22%), 210 (17%), 111 (25%). Anal. calcd for $C_{18}H_{16}NO_5S_2Cl$: C, 50.821; H, 3.794; N, 3.294. Found: C, 51.05; H, 3.82; N, 3.35.

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