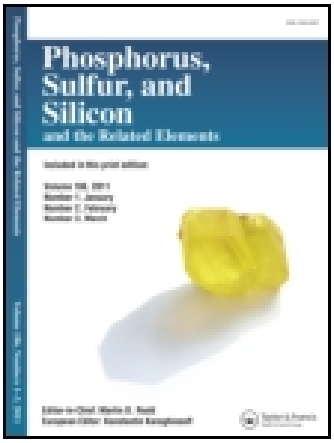

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New Hydrazides and Thiosemicarbazides Derived from Ethylenedioxythiophene as Potential Anticonvulsants

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NEW HYDRAZIDES AND THIOSEMICARBAZIDES DERIVED FROM ETHYLENEDIOXYTHIOPHENE AS POTENTIAL ANTICONVULSANTS

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A series of ethyl 7-({2-[(substituted)carbonyl]hydrazino}carbonyl)-2,3-dihydrothieno [3,4-b][1,4]dioxine-5-carboxylates (5–13) and ethyl 7-{[({2-[(substituted)carbonyl]hydrazino}carbonothioyl)amino]carbonyl}-2,3-dihydrothieno[3,4-b][1,4]dioxine-5-carboxy-lates (15–20) were synthesized in good yield by condensing ethyl-7-(chlorocarbonyl)-2,3-dihydrothieno[3,4-b][1,4]dioxine-5-carboxylate (4) with suitable hydrazides. The newly synthesized compounds were characterized using FTIR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy, and elemental analyses. The anticonvulsant activity of all the title compounds was investigated against maximal electroshock-induced seizures (MES) and pentylenetetrazole (PTZ)-induced convulsion models. None of the compounds showed toxicity at the maximum dose of 2000 mg/kg. Almost all the compounds showed protection in flexion and extension stage against induced convulsion. Among them, naphthyloxy-substituted derivatives exhibited very good response against induced seizures.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Anticonvulsant; hydrazide; MES; PTZ; thiophene; thiosemicarbazide

INTRODUCTION

Epilepsy is one of the most common neurological disorders of the brain, due to a sudden burst of abnormal electrical discharges. It has been reported that the number of people suffering from epilepsy is increasing day by day in the world.[1] Until recently, physicians have had relatively limited antiepileptic drugs (AEDs) to treat patients with seizure disorders. Among the various active drugs available in the commercial scene, phenobarbitone, phenytoin, ethosuximide, tiagabin, etizolam, phethenylate sodium, clonazepam, stiripentol, and topiramate are noteworthy. Close observation of their structures reveals that their enhanced activity is due to the presence of active functional groups like dicarboxamide,

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imide, and dioxole attached to potent base moieties such as thiophene, phenyl, and benzodiazepine. Some of the conventional drugs[2] were found to be toxic due to the presence of a cyclic dicarboxamide ring in their structure. Moreover, they have wide diversity of their effects, which has disrupted the attempt to correlate their activity with structures. Consequently, a search for new antiepileptic compounds with more selectivity and minimal toxicity has gained much importance in recent years.

Various thiophene derivatives have been reported to possess different types of CNS activities such as analgesic,[3] anti-inflammatory,[4] antipsychotic,[5] antidepressant,[6] and anticonvulsant[7–9] properties. It has been well documented that the thiophene moiety is an important pharmacophore in active anticonvulsants such as tiagabine,[7] etizolam,[8] and sodium phethenylate,[9] which belong to different classes of antiepileptic agents (Figure 1). In these molecules, the biological activity is mainly attributed to the presence of a hydrophobic

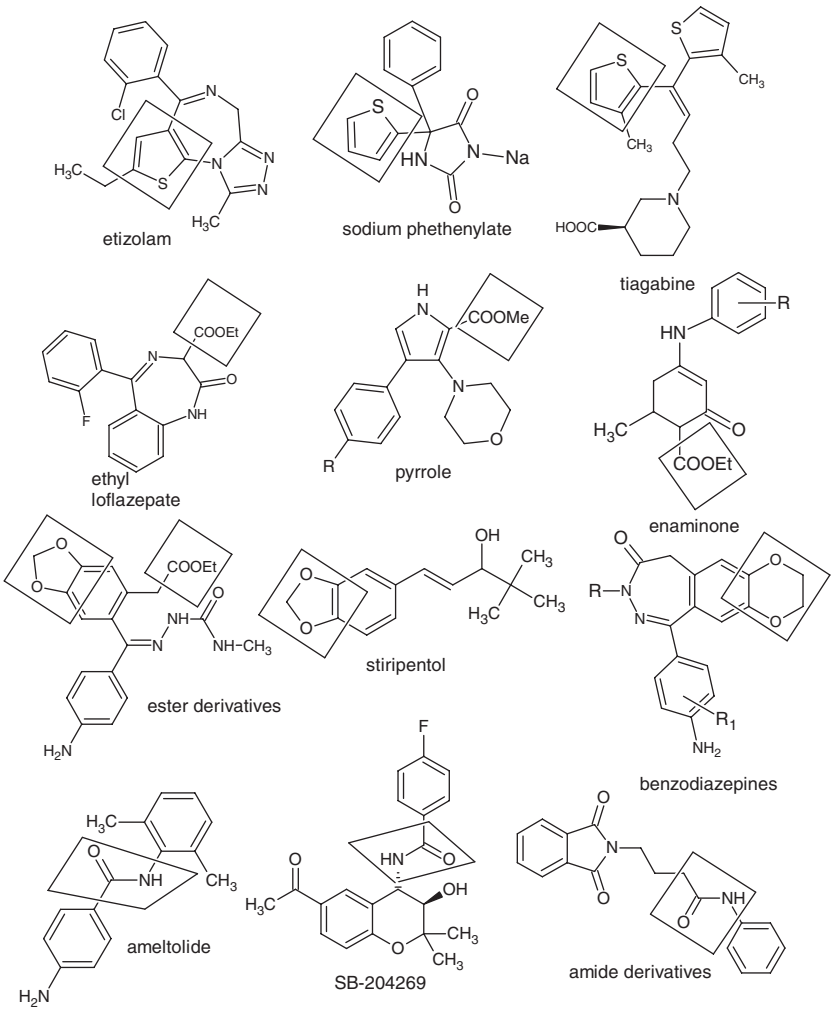


Figure 1 Structures of well-known active antiepileptic agents.

aryl-binding site, hydrogen bonding domain, and electron donor group, which are the essential requirements[10] for the molecules to show potential activity. Further, it has been noticed that the CNS active drug ethyl loflazepate[11] showed anticonvulsant activity. Here, the drug molecule contains an ester group as an important pharmacophore. This has been confirmed by the observation that 1-substituted-2-aryl derivatives[12] containing an ester in their structures displayed better activity than the other substituted derivatives. Also, Eddington et al.[13] reported that enaminones (Figure 1) containing an ester group showed superior activity compared to the unsubstituted molecules, while Unverferth et al. showed that with the introduction of an ester group in the pyrrole,[14] derivatives enhanced their activity considerably.

According to the literature, the dioxole group acts as an important bioactive moiety in the active drugs, stiripentol[15] and topiramate[16] (Figur 1). It is interesting to note that compounds containing a cyclic ether in their structure[17–19] exhibited moderate activity. On the other hand, there are a number of reports on antiepileptic studies of substituted aromatic amides[20,21] (Figure 1). It has been observed that they are capable of forming hydrogen bonding with the receptor sites during their action, which may be the main reason for their increased activity. On similar lines, hydrazides and thiosemicarbazides are expected to show good activity, as they are structurally similar to amides and are capable of forming H-bonding. Keeping this in view, it was thought to be of interest to design new thiophene derivatives (**4–13** and **15–20**) containing a hydrazide or thiosemicarbazide group at position 2, a bioactive ester group at position 5, and an electron-releasing cyclic ether group at positions 3 and 4 of the active thiophene ring. Figure 2 shows the newly designed molecule, which contains all the required pharmacophoric elements. It is hoped that combination of these active pharmacophores in the synthetic design would lead to better anticonvulsants with least neurotoxicity. In the present article, we report the synthesis, characterization, and anticonvulsant activities by MES and PTZ models of hitherto unknown ethyl 7-({2-[(substituted)carbonyl]hydrazino}carbonyl)-2,3-dihydrothieno[3,4-*b*][1,4]dioxine-5-carboxylate (**5–13**) and ethyl 7-{[({2-[(substituted)carbonyl]hydrazino}carbonothioyl)amino]carbonyl}-2,3-dihydrothieno[3,4-b][1,4]dioxine-5-carboxylate (**15–20**) derivatives.

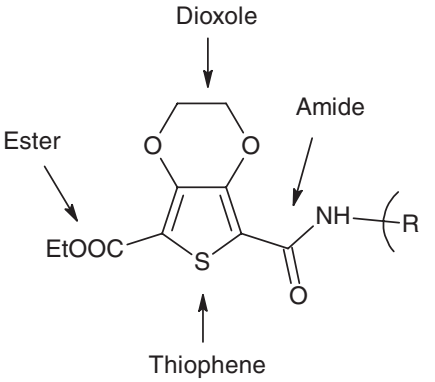
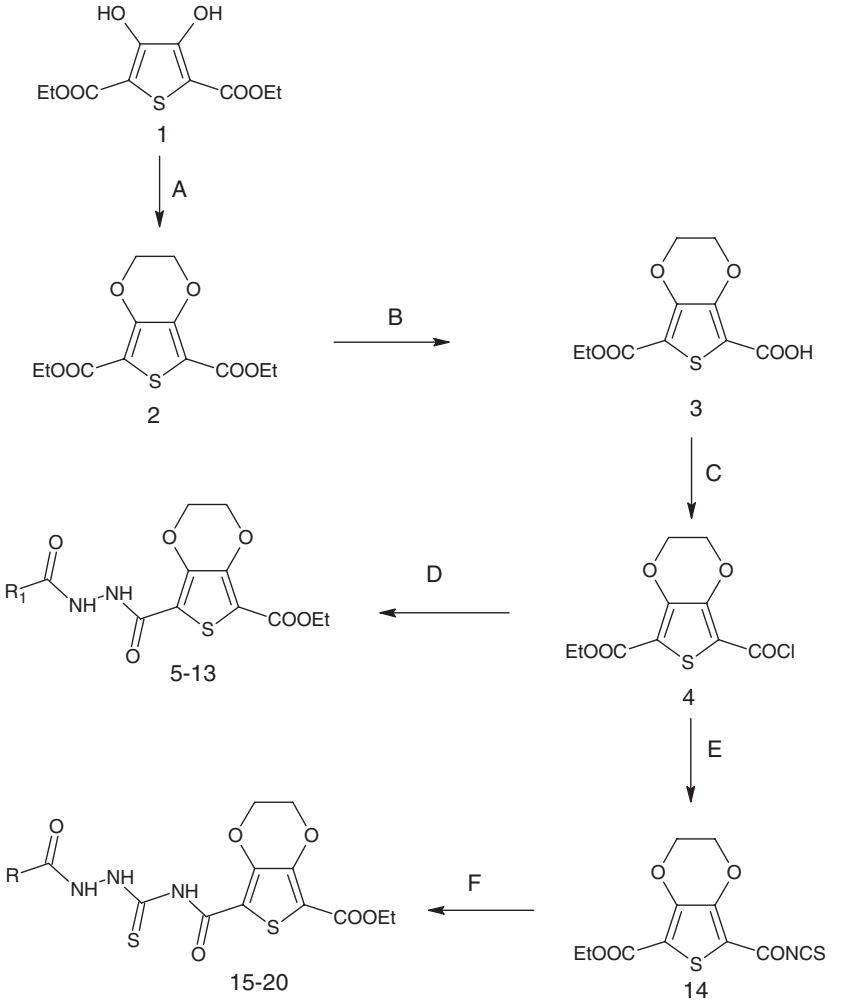


Figure 2 Structure of the newly designed target molecule.

RESULTS AND DISCUSSION

The reaction sequences employed for the synthesis of the title compounds, viz. ethyl 7-({2-[(substituted)carbonyl]hydrazino}carbonyl)-2,3-dihydrothieno[3,4-*b*][1,4]dioxine-5-carboxylates (**5–13**) and ethyl 7-{[({2-[(substituted)carbonyl]hydrazino}carbonothioyl)amino]carbonyl}-2,3-dihydrothieno[3,4-*b*][1,4]dioxine-5-carboxylates (**15–20**) are shown in Scheme 1.



Scheme 1 Synthesis of new hydrazides and thiosemicarbazides. A: Dibromoethane, K_2CO_3, DMF B: 1M ethanolic NaOH/H^+ C: $SOCl_2$, 5 h reflux, D: methylene dichloride, pyridine, hydrazide, E: NH_4SCN, methylene dichloride, PEG 600, and F: hydrazide.

The key intermediate carboxylic acid, **3** was synthesized by controlled hydrolysis of ethylenedioxythiophene diester (**2**). In this reaction, temperature and solvent ratio played an important role in obtaining a satisfactory yield. The acid **3** was converted to its acid chloride (**4**) by refluxing with thionyl chloride for 5 h. The final compounds **5–13** were

synthesized by treating the acid chloride with corresponding hydrazide in the presence of pyridine.

In another route, acid chloride (**3**) was treated with ammonium thiocyanate in the presence of phase transfer catalyst, polyethylene glycol (PEG)-600, in order to obtain the intermediate **14**. This product **14** was directly used for the next step without purification, as it is unstable. They were conveniently converted to final compounds **15–20** by condensing different hydrazides with the intermediate **14**.

The structural assignments to new compounds were based on their elemental analysis and spectral (FTIR, ^{1}H and ^{13}C NMR, and mass) data. The physical and characterization data of all the newly synthesized compounds are summarized in Tables I and II.

The IR spectrum of hydrazide (**5**) showed the absorption band at 3287 cm^{-1}, due to −NH− stretching of amide group. Further, the carbonyl stretching of the amide and ester groups appeared at 1660 and 1713 cm^{-1}, respectively. Here, the carbonyl frequency of amide was observed in the lower region than the ester carbonyl group, which is due to resonance.

In the ^{1}H NMR spectrum of **5**, the appearance of sharp peaks at δ 1.35 (triplet) and 4.28 (quartet) showed the presence of a CH_3CH_2O- group. The protons of the ethylenedioxy group resonated as a singlet at δ 4.46 ppm. The two singlets observed at δ 9.55 and 10.77 were due to a −NHNH− proton of hydrazide. The ^{13}C NMR spectrum of compound **5** showed signals at δ 14 and 60.7 due to an $-OCH_2CH_3$ group and peaks at 64.5 ppm belonging to $-OCH_2CH_2O-$ of ethylenedioxy thiophene. The peaks at 110.0, 114.6, 117.7, 129.9, 131.7, 138.8, 141.6, and 144.8 represent the thiophene and ethylenedioxy thiophene carbon. Ester and amide carbonyl carbons were observed at 159.3 and 160.1, respectively. Formation of the compound **5** from its precursor was further confirmed by its mass spectrum. In its mass spectrum, the compound displayed a molecular ion peak at *m/z* 461 (M^+ 20%), which is in agreement with the molecular formula $C_{15}H_{13}BrN_2O_6S_2$. The peaks at *m/z* 383, 327, 281, 221, and 155 were due to the fragmentation of the molecular ion with the elimination of simple molecules. The scheme of the mass fragmentation pattern is shown in the Figure S1 (available online in the Supplemental Materials). The other compounds in the series also followed the same type of fragmentation pattern in their mass spectra.

Formation of thiosemicarbazides **15–20** from the respective acid chloride (**4**) was evidenced by their FTIR, ^{1}H NMR, and mass spectral data. The IR spectrum of compound **15** showed sharp bands at 3332, 1672, 1146, and 1699 cm^{-1} due to >NH, >C=O (amide), >C=S, and >C=O (ester), respectively. Furthermore, the ^{1}H NMR spectrum displayed a sharp triplet at δ 1.25 and quartet at 4.28 due to $-CH_3$ and $-CH_2-$ protons of ester linkage, respectively. The appearance of three broad singlets at δ 10.00, 11.27, and 11.67 was attributed to the presence of three different −NH− protons. Finally, in its mass spectrum, its molecular ion peak appeared at *m/z* 520 (M^+ 100%), which is in agreement with the molecular formula $C_{16}H_{14}BrN_3O_6S_3$. The peaks at *m/z* 488, 443, 358, 307, 241, and 190 were due to the fragmentation of its molecular ion. The mass fragmentation pattern of compound **15** is shown in the Figure S2 (Supplemental Materials). Similar fragmentation patterns were observed for the other thiosemicarbazides (**16–20**).

ANTICONVULSANT ACTIVITIES

The results of the anticonvulsant activity of the newly synthesized final compounds against MES and PTZ models have been summarized, along with the data for standard drugs phenytoin and diazepam, in Tables S1 and S2 (Supplemental Materials).

Table I Physicochemical data of compounds **5–13**

Compound	R_1	M. formula/M. mass	Mp (°C)/Yield (%)	Recrystallization solvent	Elemental analysis (%): Found (cal.)			
					C	H	N	S
5	2-Bromothiophene-5-yl	$C_{15}H_{13}BrN_2O_6S_2$/461	299–300/70	DMF	39.05 (39.15)	2.82 (2.84)	6.01 (6.07)	13.98 (13.90)
6	Thiophene-2-yl	$C_{15}H_{14}N_2O_6S_2$/382	259–260/68	DMF	47.18 (47.11)	3.75 (3.69)	7.39 (7.33)	16.67 (16.77)
7	3-Methylthiophene-2-yl	$C_{16}H_{16}N_2O_6S_2$/396	120–121/74	DMF	48.41 (48.47)	4.10 (4.07)	7.12 (7.07)	16.08 (16.18)
8	Phenyl	$C_{17}H_{16}N_2O_6S$/376	245–246/78	DMF	54.30 (54.25)	4.21 (4.28)	7.49 (7.44)	8.49 (8.52)
9	Phenoxymethyl	$C_{18}H_{18}N_2O_7S$/406	246–247/80	DMF	53.16 (53.20)	4.49 (4.46)	6.97 (6.89)	7.85 (7.89)
10	4-thiomethyl Phenoxymethyl	$C_{19}H_{20}N_2O_7S_2$/452	226–227/75	DMF	50.46 (50.43)	4.55 (4.45)	24.79 (24.75)	14.19 (14.17)
11	2-Naphthoxymethyl	$C_{22}H_{20}N_2O_7S$/456	200–201/82	DMF	57.81 (57.89)	4.49 (4.42)	6.17 (6.14)	7.02 (7.02)
12	8-Quinoxymethyl	$C_{21}H_{19}N_3O_7S$/457	202–203/65	DMF	55.10 (55.14)	4.12 (4.19)	9.14 (9.19)	7.05 (7.01)
13	Benzotriazol-1-ylmethyl	$C_{18}H_{17}N_5O_6S$/431	257(char)/67	DMF	50.05 (50.11)	3.97 (3.88)	16.25 (16.23)	7.49 (7.43)

Table II Physicochemical data of compounds **15–20**

Compound	R	M. formula/M. mass	Mp (°C)/Yield (%)	Recrystallization solvent	Elemental analysis (%): Found (cal.)			
					C	H	N	S
15	2-Bromothiophene-5-yl	$C_{16}H_{14}BrN_3O_6S_3$/520	234–235/75	THF	36.86 (36.93)	2.77 (2.71)	8.12 (8.07)	18.55 (18.48)
16	Phenyl	$C_{18}H_{17}N_3O_6S_2$/435	210–211/72	DMF	49.57 (49.65)	3.98 (3.93)	9.71 (9.65)	14.79 (14.73)
17	8-Quinolinoxymethyl	$C_{22}H_{20}N_4O_7S_2$/516	224–225/81	MeOH	51.04 (51.15)	3.94 (3.90)	10.80 (10.85)	12.47 (12.42)
18	Phenoxymethyl	$C_{19}H_{19}N_3O_7S_2$/465	227–228/72	DMF	48.95 (49.02)	4.16 (4.11)	9.09 (9.03)	13.81 (13.78)
19	Benzotriazol-1-ylmethyl	$C_{19}H_{18}N_6O_6S_2$/490	242–243/75	DMF	46.59 (46.52)	3.78 (3.70)	17.17 (17.13)	12.59 (13.07)
20	2-Naphthoxymethyl	$C_{23}H_{21}N_3O_7S_2$/515	252–253/78	DMF	53.51 (53.58)	4.19 (4.11)	8.22 (8.15)	12.48 (12.44)

CONCLUSION

The present study highlights the design, synthesis, and characterization of various hydrazides and thiosemicarbazides derived from ethylenedioxythiophene and their anticonvulsant profile in the traditional animal models. The results show that thiophene hydrazides substituted with heteroaromatic systems exhibit better activity than the other compounds. Methyl substitution at the distal ring resulted in very good activity in flexion and recovery phases while the bromo derivative displayed good activity in extension, clonus, and stupor stages. Of the two series of pharmacophoric hybrids, the hydrazides were found to be more active than the thiosemicarbazide derivatives. Among them, naphthyloxy-substituted compounds possess significant activity in both convulsion-induced models. From the results, it can be concluded that ethylenedioxythiophene moiety acts as an active pharmacophore in combating induced convulsions, as it is hydrophobic in nature and less toxic.

EXPERIMENTAL

All the chemicals and the solvents, purchased from Aldrich and Merck, were used without further purification. The purity of the compounds was confirmed by thin layer chromatography, performed on a silica gel 60 F_{254}–coated aluminum sheet. Melting points were determined on open capillaries using a Stuart SMP3 (Bibby Sterlin Ltd., UK) apparatus and are uncorrected. FTIR spectra were recorded on a Nicolet Avatar 330 FTIR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on Varian 400 MHz NMR spectrophotometers using TMS as an internal standard. Chemical shifts were reported in ppm (δ), and signals were described as singlet (s), doublet (d), triplet (t), quartet (q), broad (br), and multiplet (m). The coupling constant (J) values are expressed in Hz. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 spectrophotometer/data system using argon/xenon (6 kV, 10 mA) FAB gas, at 70 eV. Elemental analysis was carried out using Flash EA 1112 series, CHNSO Analyser (Thermo).

Compound **2** was synthesized from diethyl-3,4-dihydroxythiophene-2,5-dicarboxy late following the reported procedure.[22]

7-(Ethoxycarbonyl)-2,3-dihydrothieno[3,4-b][1,4]dioxine-5-carboxylic Acid (3)

A mixture of diethyl-2,3-dihydrothieno[3,4-*b*][1,4]dioxine-5,7-dicarboxylate (**2**) (1 g, 3.5 mmol) dissolved in absolute ethanol (20 mL) and alcoholic sodium hydroxide (20 mL, 3.5 mmol) was refluxed for 5 h. It was then concentrated to one-third of its total volume under vacuum. The concentrate was diluted with water (50 mL) and stirred for 2 h at 60°C. The reaction mixture was cooled to 5–10°C. The unreacted starting material that separated was removed by filtration. The filtrate was then acidified with conc. HCl. The separated product was filtered and recrystallized using methanol to give **3** with yield 78%. Mp: 239–240°C. IR: (br) 2500–3000 cm^{-1} (-OH), 1687 cm^{-1} (>C=O). ^{1}H NMR (DMSO−d_6 300 MHz) δ (ppm): 1.26 (t, 3H, −CH_3 ester, J = 7.2), 4.23 (q, 2H, −CH_2-ester, J = 7.2), 4.34 (s, 4H, −OCH_2CH_2O−), 13.27 [br, 1H, -OH (D_2O exangeable)]. ^{13}C NMR (DMSO−d_6 300 MHz) δ (ppm): 14.0 (−CH_3), 60.8 (−OCH_2−), 65.9 (−OCH_2−), 110.0 (C_3-thiophene), 112.1 (C_4-thiophene), 144.6 (C_2-thiophene), 145.1 (C_5-thiophene), 160.1 (−CO-ester), 161.9 (−CO-acid). MS (m/z,%): 258 (M^+, 70), 230 (50), 213 (100), 169 (40) and 142 (10).

Ethyl-7-(chlorocarbonyl)-2,3-dihydrothieno[3,4-b][1,4]dioxine-5-carboxylate (4)

A mixture of 7-(ethoxycarbonyl)-2,3-dihydrothieno[3,4-*b*] [1,4]dioxine-5-carboxylic acid (**3**) (0.5 g, 1.9 mmol) and thionyl chloride (15 mL) was refluxed for 5 h. Excess thionyl chloride was removed from the reaction mixture. The residual off-white solid was extracted with methylene dichloride (50 mL), and the organic layer was washed with saturated sodium bicarbonate solution (25 mL). After drying the organic layer with anhydrous sodium sulfate, the solvent was removed under vacuum to give 0.4 g (yield 75%) of the product **4**. This was used for the next step without further purification.

General Procedure for the Synthesis of Hydrazides 5–13

To a clear solution of acid chloride **4** (0.5 g, 1.8 mmol) in N-methyl pyrrolidinone (10 mL) containing pyridine (0.1 mL) as a catalyst, an equimolar quantity of the respective hydrazide was added while stirring. The stirring was continued at 50°C for 12 h. The reaction mixture was then quenched with ice-cold water (100 mL). The product was separated by filtration and recrystallized from the appropriate solvent. The physical and characterization data of compounds **5–13** are given in Table I. The spectral data of some of the synthesized compounds are as follows:

Ethyl-7-({2-[(5-bromo-2-thienyl)carbonyl]hydrazino}carbonyl)-2,3-dihydrothieno[3,4-b] [1,4]dioxine-5-carboxylate (5). IR: 3287 cm^{-1} (>NH), 1660 cm^{-1} (>C=O amide) and 1713 cm^{-1} (>C=O ester). ^1H NMR (DMSO−d_6 400 MHz) δ (ppm): 1.35 (t, 3H, $-CH_3$ ester, J = 7.0), 4.28 (q, 2H, $-CH_2-$ ester, J = 6.9), 4.46 (s, 4H, $-OCH_2CH_2O-$), 7.32 (d, 1H, C_4-thiophene, J = 3.8), 7.68 (d, 1H, C_3-thiophene, J = 3.8), 9.55 (s, 1H, >CONH), 10.77 (s, 1H, >CONH-). ^{13}C NMR ($CDCl_3$, 400MHz) δ (ppm): 14.0 ($-CH_3$), 60.7 ($-OCH_2-$ ester), 64.5 ($-OCH_2CH_2O-$), 110.0 (C_3-EDOTthiophene), 114.6 (C_4-EDOTthiophene), 117.7 (C_2-thiophene), 129.9 (C_3-thiophene), 131.7 (C_4-thiophene), 138.8 (C_5-thiophene), 141.6 (C_2-EDOTthiophene), 144.8 (C_5-EDOTthiophene), 159.3 (−CONH−), 160.1 (ester). MS (m/z,%): 461 (M^+, 20), 383 (10), 355 (20), 327 (50), 281 (80), 221 (70).

Ethyl-7-{[2-(phenoxyacetyl)hydrazino]carbonyl}-2,3-dihydrothieno[3,4-b][1,4]dioxine-5-carboxylate (9). IR: 3184 cm^{-1} (>NH), 1625 cm^{-1} (>C=O amide) and 1702 cm^{-1} (>C=O ester). ^1H NMR (DMSO−d_6 400 MHz) δ (ppm): 1.25 (t, 3H, $-CH_3$ ester, J = 7.0), 4.23 (q, 2H, $-CH_2$-ester, J = 7.0), 4.41 (s, 4H, $-OCH_2CH_2O-$), 4.61 (s, 2H, $-OCH_2-$), 6.99–7.30 (m, 5H, aromatic), 9.38 (s, 1H, −CONH−) and 10.40 (s, 1H, −CONH−). MS (m/z,%): 407 (M^+, 70), 391 (20), 241 (60), 165 (10).

Ethyl-7-({2-[(quinolin-8-yloxy)acetyl]hydrazino}carbonyl)-2,3-dihydrothieno[3,4-b][1,4] dioxine-5-carboxylate (12). IR: 3205 cm^{-1} (>NH), 1652 cm^{-1} (>C=O amide) and 1707 cm^{-1} (>C=O ester). ^1H NMR (DMSO−d_6 400 MHz) δ (ppm): 1.25 (t, 3H, $-CH_3$ ester, J = 7.0), 4.25 (q, 2H, $-CH_2-$ ester, J = 7.0), 4.42 (s, 4H, $-OCH_2CH_2O-$), 4.89 (s, 2H, $-OCH_2-$), 7.30 (d, 1H, C_2-aromatic, J = 7.4), 7.50 (m, 3H, C_3, C_4, C_6-aromatic), 8.36 (d, 1H, C_5-aromatic, J = 7.3), 8.88 (d, 1H, C_7-aromatic, J = 2.6), 9.48 (s, 1H, >CONH-) and 10.68 (s, 1H, >CONH-). MS (m/z,%): 458 (M+1, 100), 241 (10), 214 (10), 203 (5).

General Procedure for the Preparation of Semicarbazides 15–20

To a clear solution acid chloride **4** (0.5 g, 1.8 mmol) in methylene dichloride (25 mL), ammonium thiocyanate powder (0.0027 mol) and PEG-600 (0.1 g) as PTC were added.

After stirring the reaction mixture for 2 h at room temperature, the corresponding acid hydrazide (1.8 mmol) was added, and the reaction mixture was further stirred for 4 h at room temperature. Then, water (25 mL) was added to the well-stirred mixture and the resulting slurry was filtered, washed with water, dried, and finally recrystallized from the appropriate solvent to obtain the title compounds (**15–20**). The physical and characterization data of compounds **15–20** are tabulated in Table II. The spectral data of some of the synthesized compounds are as follows:

Ethyl-7-{[({2-[(5-bromo-2-thienyl)carbonyl]hydrazino}carbonothioyl)-amino]carbonyl}-2,3-dihydrothieno[3,4-b][1,4]dioxine-5-carboxylate (15). IR: 3332 cm^{-1} (>NH), 1672 cm^{-1} (>C=O amide), 1146 cm^{-1} (>C=S) and 1699 cm^{-1} (>C=O ester). ^{1}H NMR (DMSO−d_6 400 MHz) δ (ppm): 1.25 (t, 3H, $-CH_3$ ester, J = 7.0), 4.28 (q, 2H, $-CH_2-$ ester, J = 7.0), 4.47 (s, 2H, $-CH_2-$), 4.59 (s, 2H, $-CH_2-$), 7.34 (d, 1H, C_4-thiophene, J = 3.8), 7.72 (d, 1H, C_3-thiophene, J = 3.9), 10.00 (s, 1H, -NHNHCS), 11.27 (s, 1H, −CONH−), 11.67 (s, 1H, -CSNHCO-). MS (m/z,%): 522 (M+2, 100), 520 (M^+, 100), 488 (10), 443 (20), 359 (5), 307 (50), 300 (10), 241 (5), 212 (5).

Ethyl-7-({[(2-benzoylhydrazino)carbonothioyl]amino}carbonyl)-2,3-dihydrothieno[3,4-b][1,4]dioxine-5-carboxylate (16). IR: 3355 cm^{-1} (>NH), 1661 cm^{-1} (>C=O amide), 1153 cm^{-1} (>C=S) and 1710 cm^{-1} (>C=O ester). ^{1}H NMR (DMSO−d_6 400 MHz) δ (ppm): 1.27 (t, 3H, $-CH_3$ ester, J = 7.0), 4.29 (q, 2H, $-CH_2-$ ester, J = 7.0), 4.47 (s, 2H, $-CH_2-$, J = 1.84), 4.60 (s, 2H, $-CH_2-$, J = 2.1), 7.49—7.94 (m, 5H, aromatic), 10.00 (s, 1H, −NHNHCS−), 11.18 (s, 1H, −CONH−), 11.79 (s, 1H, -CSNHCO-). MS (m/z,%): 436 (M^+, 90), 391 (5), 258 (5), 241 (50), 214 (5), 136 (80).

Ethyl-7-{[({2-[(quinolin-8-yloxy)acetyl]hydrazino}carbonothioyl)amino]-carbonyl}-2,3-dihydrothieno[3,4-b][1,4]dioxine-5-carboxylate (17). IR: 3424 cm^{-1} (>NH), 1666 cm^{-1} (>C=O amide), 1152 cm^{-1} (>C=S) and 1709 cm^{-1} (>C=O ester). ^{1}H NMR (DMSO−d_6 400 MHz) δ (ppm): 1.25 (t, 3H, $-CH_3$ ester, J = 7), 4.27 (q, 2H, $-CH_2-$ ester, J = 7.1), 4.46 (s, 2H, $-CH_2-$), 4.65 (s, 2H, $-CH_2-$), 4.95 (s, 2H, $-OCH_2-$), 7.34 (d, 1H, C_2-aromatic, J = 7.5), 7.50—7.62 (m, 3H, C_3, C_4, C_6-aromatic), 8.38 (d, 1H, C_5-aromatic, J = 7.6), 8.90 (d, 1H, C_7-aromatic, J = 2.6), 9.99 (s, 1H, −NHNHCS−), 11.53 (s, 1H, −CONH−), 12.05 (s, 1H, −CSNHCO). MS (m/z,%): 517 (M^+, 80), 460 (10), 371 (10), 241 (40), 202 (5), 186 (60).

PHARMACOLOGY

The evaluation of anticonvulsant activity of the title compounds was carried out using MES and PTZ models. Their toxicity studies were performed based on Organization for Economic Co-Operation and Development (OECD) guidelines 423. The details of evaluation procedures[23–24] are as placed in the Supplemental Materials (available online).

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