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ORIGINAL RESEARCH

Synthesis and anticonvulsant activity of some new series of pyrrole derivatives

A. Idhayadhulla · R. Surendra Kumar · A. Jamal Abdul Nasser · S. Kavimani · S. Indumathy

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Abstract A new series of compounds **3a–f** were synthesized from condensation method. Newly synthesized compounds were established by IR, ^{1}H NMR, ^{13}C NMR, mass spectral and elemental analysis. Synthesized compounds **3a–f** were screened for anticonvulsant activity. The compound 2,2′-({3-methyl-5-[2-phenylethenyl]-1*H*-pyrrole-2,4-diyl}dicarbonyl)dihydrazinecarbothioamide **3a** showed significant activity compared with other compounds **3b–f** against pentamethylene tetrazole-induced seizures.

Keywords Pyrrole and thiosemicarbazone derivatives · Spectral analysis · Anticonvulsion activity · Structure–activity relationships

Introduction

In recent years, anticonvulsants drug development has been one of the most prominent research areas. Although several new anticonvulsants are already in clinical use, some types of seizures are still not adequately treated with current therapy and have limitations, intolerable side effects. In response to these limitations, the development of new drugs to optimally manage seizures has been strongly advocated. Thus, the search for new anticonvulsant drugs continues to be an active area of investigation in medicinal chemistry. Pyrrole derivative has received considerable attention of synthetic importance (Toja *et al.*, 1987) and importance of anticonvulsant activity (Sorokina *et al.,* 1989; Carson *et al.,* 1997) and other pharmacological activity, such as antiviral (Almerico *et al.*, 2000), cytotoxicity (Dannhardt *et al.*, 2000) and treatment of hyperlipidemias (Justin *et al.*, 2004).

Our previous investigations have shown that the 1,4-dihydropyridine connecting with thiosemicarbazide and their anticonvulsant activity (Surendra Kumar *et al.,* 2010) and more example for other pervious finding thiosemicarbazone derivatives and their anticonvulsant activity (Chapleo *et al.*, 1988; Pandeya and Dimmock 1993; Ragab *et al.*, 2010; Aly *et al.*, 2010; Kshirsagar *et al.*, 2009; Karki *et al.*, 2009; Yogeeswari *et al.*, 2002, 2005; Mohsen *et al.*, 2010; Taroual *et al.,* 1996; Dimmock et al., 1990, 1995), and other activity of thiosemicarbazone derivatives, such as antimicrobial (Surendra Kumar *et al.*, 2010), anticoagulant (Surendra Kumar *et al.*, 2011a, b, c), anticancer activities (Surendra Kumar *et al.*, 2011a, b, c), anti-inflammatory (Bindu *et al.,* 1999), and antifertility properties (Srivastava *et al.,* 2002). Structure–activity relationships (SARs) have been very useful in the search of patterns that correlate the anticonvulsant activity of a molecule with its structural properties and reactivity features (Tripathi *et al.*, 2011). These references will serve as the main rationales for the synthesis of new pyrrole connecting thiosemicarbazione derivatives **3a–f** (Scheme 1) and evaluate them for anticonvulsion activity.

Results and discussion

Chemistry

The route used for synthesis of the new pyrrole derivatives assessed in this study is shown in Scheme 1. Ethyl-3-oxo-5-

A. Idhayadhulla · R. Surendra Kumar · A. Jamal Abdul Nasser (✉)
P.G & Research Department of Chemistry, Jamal Mohamed College, Tiruchirappalli 620020, Tamil Nadu, India
e-mail: jamal_abdulchem@ymail.com

S. Kavimani · S. Indumathy
Department of Pharmacology, Mother Theresa Post Graduate & Research Institute of Health Science, Puducherry 605006, India

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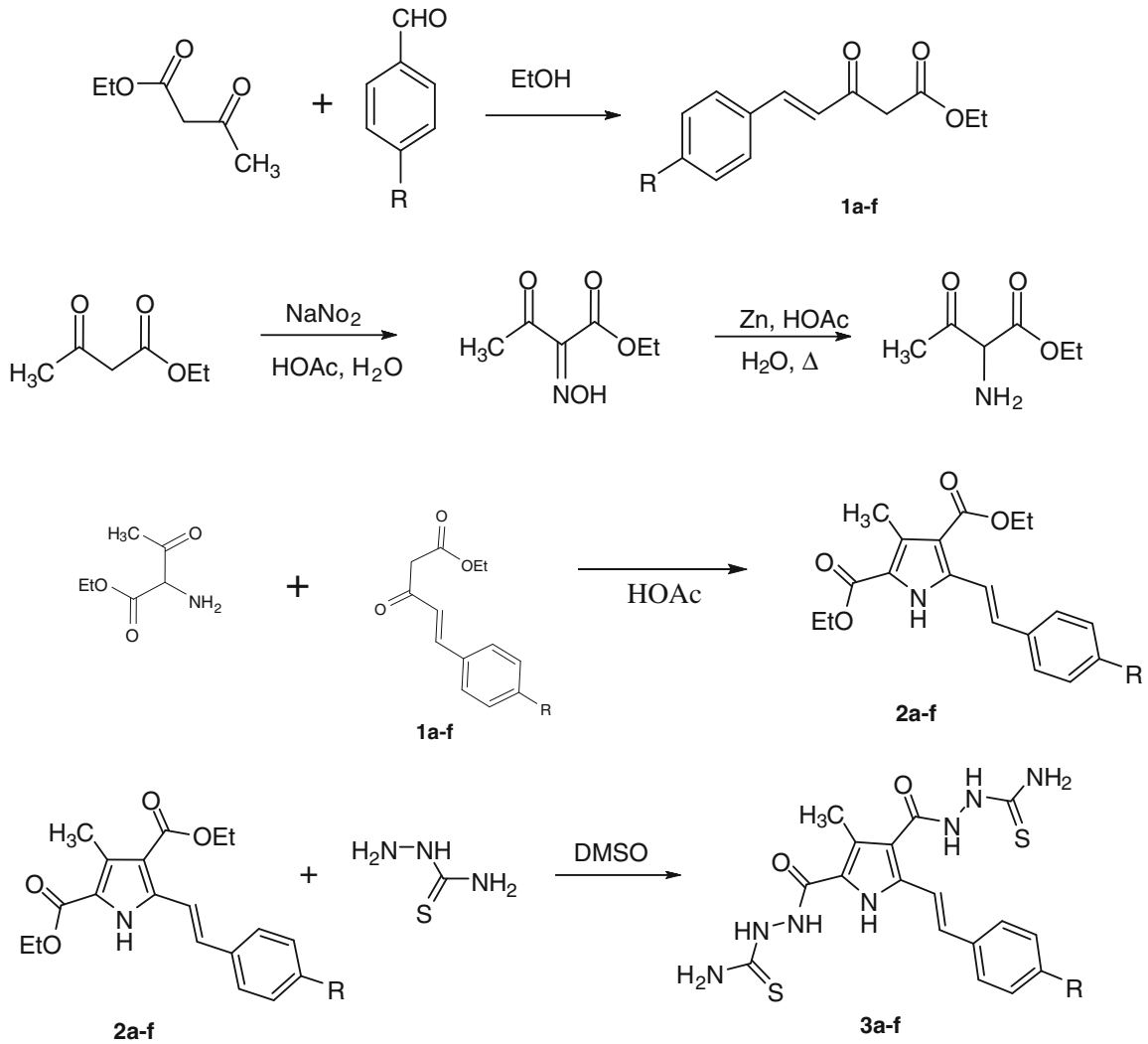


Scheme 1 Synthetic route of compounds **1a–f**, **2a–f** and **3a–f**

phenylpent-4-enoate (**1a**) was synthesized directly by refluxing ethyl acetoacetate, benzaldehyde in ethanol medium.

Diethyl 3-methyl-5-[2-phenylethenyl]-1*H*-pyrrole-2,4-dicarboxylate (**2a**) was prepared from Fischer and Noller condensation method by ethyl acetoacetate and glacial acetic acid, and was cooled to an efficient freezing mixture to 5°C. Sodium nitrite was added dropwise with vigorous stirring at such a rate that the temperature remained between 5 and 7°C and added dropwise to compound **1a**, and the mixture was stirred at room temperature. Zinc dust was added to the reaction mixture and the mixture was heated and refluxed for 1 h and poured into the water. After standing overnight, the crude product was obtained then filtered by suction, and washed with water (Fischer and Noller 1935).

2,2′-({3-Methyl-5-[2-phenylethenyl]-1*H*-pyrrole-2,4-diyl} dicarbonyl)dihydrazinecarbo thioamide (**3a**) was synthesized from compound (**2a**) reacted with thiosemicarbazide DMSO and ethanol medium by hydrazinolysis method (Refaat *et al.*, 2004; Ojha *et al.*, 2007). The physicochemical characteristics of compounds are presented in (Table 1).

The structure of the synthesized compounds is established on the basis of IR, ^{1}H NMR and ^{13}C NMR and elemental analyses. The IR spectra of the compound **1a** show an absorption band at 1,755 cm^{-1} corresponding to C=O stretching in ester group, with another absorption band at 3,050 cm^{-1} corresponding to phenyl ring CHstr. Compound **1b**, shows an absorption band at 832 cm^{-1} corresponding to Cl–C group, compound **1c** shows an absorption band at 1465 cm^{-1} corresponding to OH–C group and compound **1d** shows an absorption bands observed at 1534 cm^{-1} corresponding to NO_2–C group.

The ^{1}H NMR spectrum of compound **1a** shows a singlet at δ 7.64 attributable to *H*C=CH protons closest to the phenyl ring and δ 6.92 attributable to HC=C*H* proton closest to carbonyl group.

Table 1 Physicochemical data of synthesized compounds

Compd. no.	R	M.P.	Yield %	M.W.
1a	H	127	56	188.22
1b	4-Cl	135	61	222.66
1c	4-OH	141	67	204.22
1d	4-NO_2	158	66	233.22
1e	4-CH_3O	147	57	218.24
1f	4-$(CH_3)_2N$	156	51	231.29
2a	H	115	57	327.37
2b	4-Cl	127	65	361.81
2c	4-OH	132	54	343.37
2d	4-NO_2	141	57	372.37
2e	4-CH_3O	154	58	357.40
2f	4-$(CH_3)_2N$	160	51	370.44
3a	H	95	67	417.50
3b	4-Cl	112	57	451.95
3c	4-OH	118	59	433.50
3d	4-NO_2	121	62	462.50
3e	4-CH_3O	101	54	447.53
3f	4-$(CH_3)_2N$	91	65	460.57

The IR spectrum of compound **2a** shows an absorption band at 3,342 cm^{-1} corresponding to NHstr group, and another absorption band at 1,747 cm^{-1} corresponding to C=Ostr in the ester group. The ^{1}H NMR spectrum of compound **2a** shows a singlet at δ 7.01 attributable to *H*C=CH proton closest to the phenyl ring protons and δ 6.92 attributable to HC=C*H* protons closest to carbonyl group.

A singlet was observed at δ 6.12 corresponding to NH protons in pyrrole ring. Another important peak observed at δ 4.20, 1.30 corresponding to OCH_2CH_3 and OCH_2CH_3 protons in pyrrole ring.

The IR spectrum of the compound **3a** shows an absorption bands at 3354, 3249, 1267, 1717, 1096 and 812 cm^{-1} corresponding to NH, NH_2, C=S, C=O, N–C–N and Ar-Hstr group, respectively. The ^{1}H NMR spectrum of compound **3a** shows a singlet at δ 9.66 corresponding to NH_2 protons and NH, 2,4-CONH protons resonated as a singlet at δ 6.15, 10.71, respectively. The ^{13}C NMR spectrum of the compound **3a** shows peaks at δ 123.6, 143.5, 118.5 and 144.7 corresponding to 2C, 3C, 4C and 5C carbons present in pyrrole ring. The peaks obtained at δ 164.8 and 162.5 corresponding to the 2-position of CONH and the 4-position of CONH groups, respectively. Mass spectrum of compound **3a** shows the molecular ion peak (*m*/*z* 418.50) in Fig. 1, which is confirmed by the molecular mass of the compound **3a**. Mass spectral fragmentation is representing in Fig. 2.

Anticonvulsant activity

The compounds **3a–f** were evaluated for anticonvulsant activity. Figure 3 shows the effect of compounds **3a–f** on the duration of convulsions induced by pentamethylene tetrazole. Anticonvulsant activity values of the compounds **3a–f** are summarized in Table 2.

Compounds **2a–f** is inactive at the doses tested, while compounds **3a–f** causes a slight decrease at 10 mg/kg, which is not of a high statistical significance.

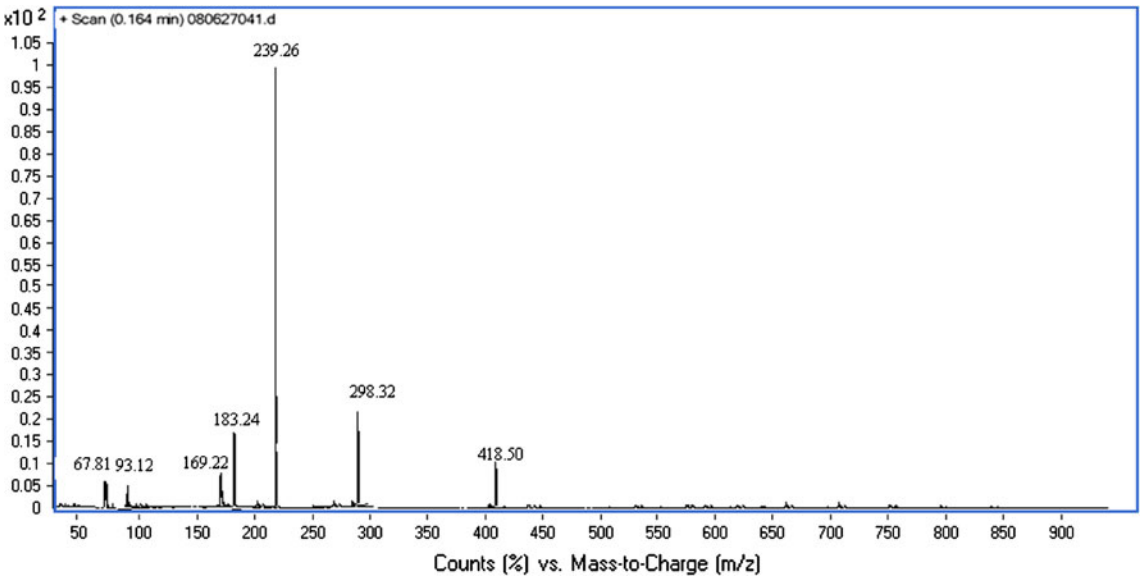


Fig. 1 Mass spectrum of compound **3a**

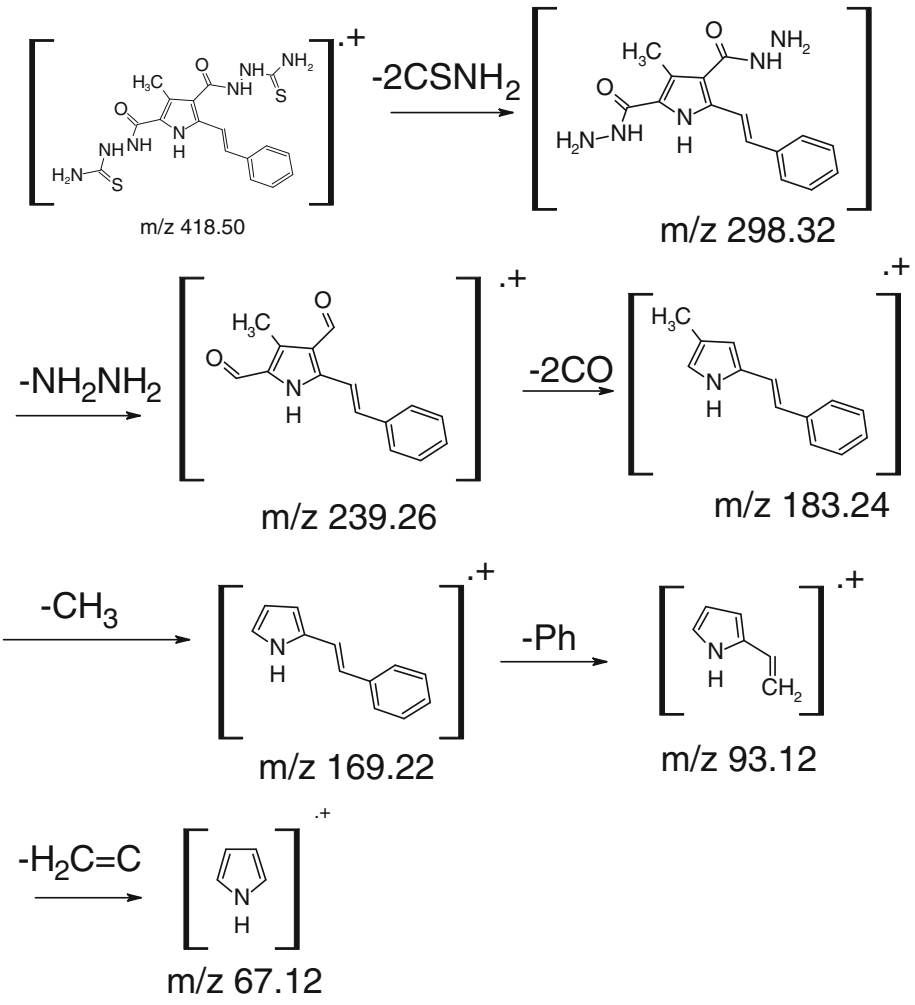


Fig. 2 Mass spectral fragmentation of compound **3a**

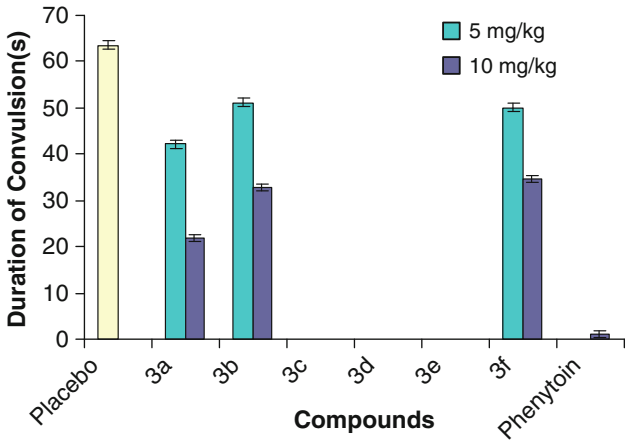


Fig. 3 Compounds **3a–f** against duration of convulsion(s), Phenytoin is used as a standard

The effect of compounds **3a–f** on neuronal excitability as measured by their influence on the percentage of animals affected by convulsion is shown in Table 3. The compound **3c–e** was inactive in this test, since this compound does not alter the threshold of neuronal excitability towards chemically induced convulsions. Instead, all compounds studied, and especially **3a**, cause a significant decrease in the number of animals affected by convulsions.

Compounds **3b** and **3f** show that low activity compared with compound **3a**, it can be conciliated that the compound **3a** displays good anticonvulsant properties, while the compounds **3c–e** are no activity at both doses tested (5 and 10 mg/kg). The doses can be concluded as being far from lethal, since doses of 10 mg/kg caused no signs of toxicity during the 24 h following its administration to a group of animals.

It can be concluded that the compound **3a** seems to act by raising the threshold of neuronal excitability without affecting the propagation of impulses, since they cause a decrease in the percentage of animals affected by convulsions but do not significantly alter the duration of the seizures. Such behaviour resembles that of barbiturates rather than that displayed by classical anticonvulsant pyrrole derivatives like phenytoin. Further pharmacological and

Table 2 Effect of compounds **3a–f** on the duration of pentamethylene tetrazole-induced convulsions, *P*, statistical significance according to Student's *t* test

Compound	Dose (mg/kg)	Duration of convulsion (s) mean ± SEM	*P*	Percentage of activity
Placebo	–	63.6 ± 0.92	–	–
3a	5	42.2 ± 1.23	>0.001	33
	10	21.8 ± 1.82	>0.001	66
3b	5	51.2 ± 1.07	>0.001	19
	10	32.8 ± 1.34	>0.001	48
3c	5	0[a]	0	0
	10	0[a]	0	0
3d	5	0[a]	0	0
	10	0[a]	0	0
3e	5	0[a]	0	0
	10	0[a]	0	0
3f	5	50.1 ± 1.56	>0.001	21
	10	34.5 ± 1.48	>0.001	46
Phenytoin	10	1.2 ± 0.61	>0.001	98

Values are mean ± SEM, and $P > 0.001$ statistically significant from control group ($n = 5$). Each compound screened for five animals per dose 5 and 10 (mg/kg)

[a] No response for screening

Table 3 Effects of compounds **3a–f** on the % of convulsed animals after administration of pentamethylene tetrazole

Treatment (dose)	Convulsed animals (%)
Placebo	100
3a (5 mg/kg)	60
3a (10 mg/kg)	30
3b (5 mg/kg)	70
3b (10 mg/kg)	60
3c (5 mg/kg)	0
3c (10 mg/kg)	0
3d (5 mg/kg)	0
3d (10 mg/kg)	0
3e (5 mg/kg)	0
3e (10 mg/kg)	0
3f (5 mg/kg)	60
3f (10 mg/kg)	50
Phenytoin	100

preclinical investigations are currently underway in compound **3a**.

Stereochemistry

The ^{1}H NMR spectra of **3a** are used as examples for stereochemistries assignment. The assignment has been made

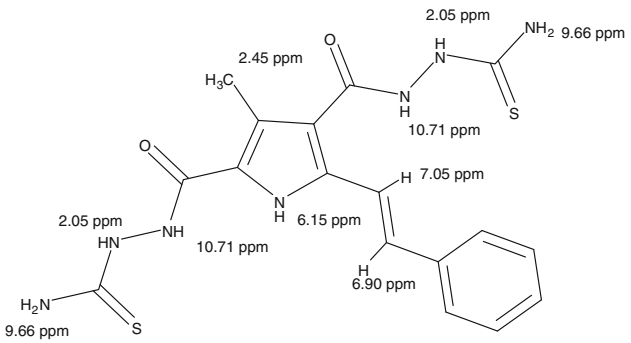


Fig. 4 ^{1}H NMR signals in compound **3a**

based on characteristic signal positions of functional groups, spin multiplicity. Aromatic proton peaks of **3a** appear in the region of 7.39–7.62 ppm as multiples. The methyl protons attached to the pyrrole ring is resonating in the region of 2.45 ppm as singlet with three proton integrals. Pyrrole ring carbon 2,4 attached CONH appears at 10.75 ppm as a doublet and NH–N*H* at 2.05 ppm as a doublet. The doublet splitting with coupling constant value of 3.00 Hz at 10.71 ppm and the doublet splitting with coupling constant value of 3.50 Hz at 2.05 ppm are due to two proton of carbon 2,4 attached –CO–N*H*–N*H*, respectively. Another interesting point here is that since the C*H*=CH in pyrrole 5 position singlet 7.05 ppm and CH=C*H* singlet appeared at 6.90 ppm of geometrical E isomer is expected as ^{1}H NMR provide set of signals (Fig. 4).

The ^{13}C NMR spectrum of compound **3a**, aromatic carbon in the region of 137.50–128.50 ppm and methyl group at 3-position in pyrrole ring, thus the peak appearing in the downfield of the two signals 12.1 ppm. The carbons 2 and 3 resonated at 123.6 and 143.5 ppm and *C*H=CH in pyrrole 5 position singlet 123.7 ppm and CH=*C*H singlet appeared at 131.2 ppm of geometrical E isomer is conformed by ^{13}C NMR signals.

Another important carbonyl group CONH and CSNH resonated at 164.1 and 182.5 ppm, respectively (Fig. 5).

Structural activity relationship

In the present study various pyrrole-containing thiosemicarzone derivatives were synthesized and investigate the pharmacophoric subsistent. The 4-substituted phenyl ring acts as a lipophilic domain, C=S presenting in thiosemicarbazone act as corresponding to electron donor and NH presenting in thiosemicarbazone act as hydrogen bonding domain. Therefore, the above group containing pyrrole ring may be stated that essential pharmacophoric requirements for anticonvulsant activity.

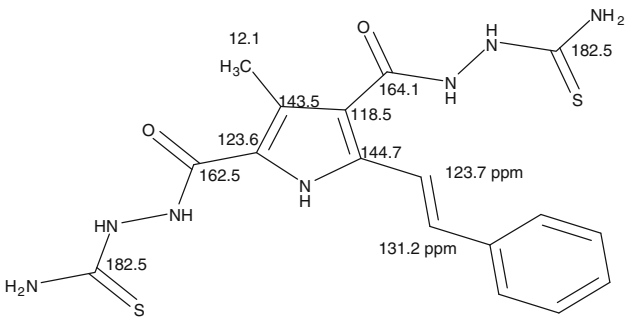
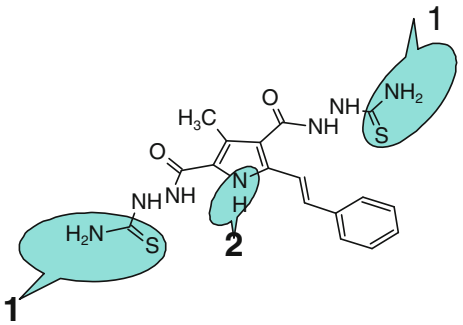


Fig. 5 ^{13}C NMR signals in compound **3a**

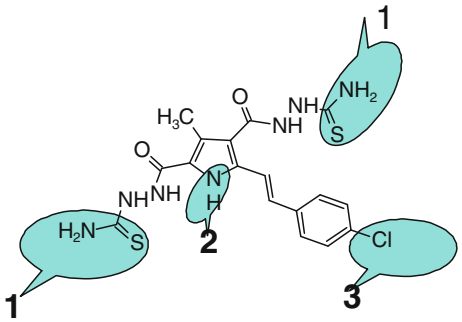
Activity variation in following compounds

(i) Compound **3a** pyrrole derivative exhibited high anticonvulsant activity compared to other compound but low activity than standard at concentration 10 mg/kg. Higher activity due to presence of CSNH (1), NH in pyrrole ring (2) groups in compound **3a**.



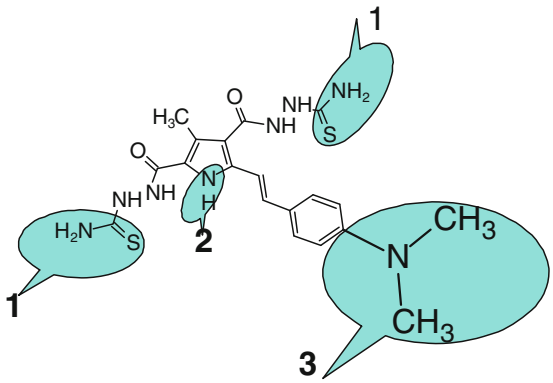
Compound **3a**

(ii) Compound **3b** shows that profound anticonvulsant activity reduced compared with compound **3a** at concentration 10 mg/kg. Lower activity due to 4-Cl substituted phenyl ring in compound **3b**.



Compound **3b**

(iii) Compound **3f** was found to be lose activity compared to other compounds **3a** and **3b** due to the presence of dimethylamine in 4-position of phenyl ring.



Compound **3f**

Experimental

General

Melting points were recorded in open capillary tubes and were uncorrected. The IR spectra (KBr) were recorded on a Shimadzu 8201pc (4,000–400 cm^{-1}). The ^{1}H NMR and ^{13}C NMR was recorded on a Bruker DRX-400 MHz. Mass spectra (EI) were recorded on a Jeol JMS D-300 spectrometer operating at 70 eV. The elemental analysis (C, H, N and S) was recorded using an Elementer analyzer model (Varian EL III). The purity of the compounds was checked by thin layer chromatography (TLC) with silica gel plates.

Chemistry

*Synthesis of ethyl-3-oxo-5-phenylpent-4-enoate (**1a**)*

A mixture of ethyl acetoacetate (0.01 mol), benzaldehyde (0.01 mol) in ethanol; the reaction mixture was refluxed for 2 h. The reaction mixture was poured into ice water. The precipitate was collected by filtration and recrystallized by absolute ethanol. The above procedure was followed by all remaining compounds **1b**–**f**.

IR (KBr, cm^{-1}): 3,050 (CHstr of phenyl ring), 1,755 (C=O in ester); 1,692 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.64 (s, 1H, *H*C=CH), 7.35–7.60 (m, 5H, Ph-ring), 6.92 (s, 1H, HC=C*H*), 4.20 (q, 2H, $J = 1.6$ Hz, $-OCH_2CH_3$), 3.92 (s, 2H, CH_2), 1.30 (t, 3H, $J = 1.8$ Hz $-OCH_2CH_3$).

*Ethyl-5-(4-chlorophenyl)-3-oxopent-4-enoate (**1b**)*

IR(KBr, cm^{-1}): 3,042 (CHstr of phenyl ring), 1,759 (C=O in ester), 1,684 (C=O), 832 (C–Cl); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.69 (s, 1H, *H*C=CH), 7.64–7.42 (dd, 4H, Ph-ring), 6.96 (s, 1H, HC=C*H*), 4.14 (q, 2H, $J = 1.5$ Hz, $-OCH_2CH_3$), 3.92 (s, 2H,CH_2), 1.33 (t, 3H, $J = 1.4$ Hz, $-OCH_2CH_3$).

*Ethyl-5-(4-hydroxyphenyl)-3-oxopent-4-enoate (**1c**)*

IR (KBr, cm^{-1}): 3,064 (CHstr of phenyl ring), 1,747 (C=O in ester), 1,689 (C=O), 1,465 (C–OH); ^{1}H NMR ($CDCl_3$, 400 MHz): 9.38 (s, 1H, OH), 7.61 (s, 1H, *H*C=CH), 7.55–6.68 (dd, 4H, Ph-ring), 6.95 (s, 1H, HC=C*H*), 4.25 (q, 2H, $J = 1.7$ Hz, –OCH_2CH$_3$), 3.98 (s, 2H, CH_2), 1.37 (t, 3H, $J = 1.8$ Hz, –OCH$_2$CH_3).

*Ethyl-5-(4-nitrophenyl)-3-oxopent-4-enoate (**1d**)*

IR (KBr, cm^{-1}): 3,052 (CHstr of phenyl ring), 1,769 (C=O, ester), 1,681 (C=O), 1,534 (C–NO_2); ^{1}H NMR ($CDCl_3$, 400 MHz): 8.11–8.01 (dd, 4H, Ph-ring), 7.59 (s, 1H, *H*C=CH), 7.24 (s, 1H, HC=C*H*), 4.19 (q, 2H, $J = 1.6$ Hz, –OCH_2CH$_3$), 3.99 (s, 2H, CH_2), 1.41 (t, 3H, $J = 1.7$ Hz, –OCH$_2$CH_3).

*Ethyl-5-(4-methoxyphenyl)-3-oxopent-4-enoate (**1e**)*

IR (KBr, cm^{-1}): 3,041 (CHstr of phenyl ring), 1,762 (C=O, ester), 1,674 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.66 (s, 1H, *H*C=CH), 7.64–6.90 (dd, 4H, Ph-ring), 6.98 (s, 1H, HC=C*H*), 4.32 (q, 2H, $J = 1.5$ Hz, –OCH_2CH$_3$), 3.96 (s, 2H, CH_2), 3.87 (s, 3H, –OCH_3), 1.44 (t, 3H, $J = 1.4$ Hz, –OCH$_2$CH_3),

*Ethyl-5-[4-(dimethylamino)phenyl]-3-oxopent-4-enoate (**1f**)*

IR (KBr, cm^{-1}): 3,047 (CHstr of phenyl ring), 1,771 (C=O, ester), 1,688 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz):7.71 (s, 1H, *H*C=CH), 6.90 (s, 1H, HC=C*H*), 6.71–7.76 (dd, 4H, Ph-ring), 4.41 (q, 2H, $J = 1.5$ Hz, Hz –OCH_2CH$_3$), 3.86 (s, 2H, CH_2), 3.08 (s, 1H, –N$(CH_3)_2$), 1.18 (t, 3H, $J = 1.6$ Hz, –OCH$_2$CH_3),

*Synthesis of diethyl 3-methyl-5-[2-phenylethenyl]-1H-pyrrole-2,4-dicarboxylate (**2a**)*

A mixture was prepared of ethyl acetoacetate and glacial acetic acid, and was cooled to an efficient freezing mixture to 5°C. Sodium nitrite was added dropwise with vigorous stirring at such a rate that the temperature remained between 5 and 7°C and added dropwise to compound **1a**, and the mixture was stirred at room temperature. Zinc dust was added to the reaction mixture and the mixture was heated and refluxed for 1 h and poured into water. After standing overnight, the crude product was obtained then filtered by suction and washed with water. The above procedure was followed for all remaining compounds **2b**–**f**.

IR (KBr, cm^{-1}): 3,342 (NHstr), 3,043 (CHstr of phenyl ring), 1,747 (C=O, ester);^{1}H NMR ($CDCl_3$, 400 MHz): 7.30–7.62 (5H, Ph-ring), 7.01 (s, 1H, *H*C=CH), 6.92 (s, 1H, HC=C*H*), 6.12 (s, 1H, NH of pyridine ring), 4.20 (q, 2H, $J = 1.7$ Hz, –2OCH_2CH$_3$ and –4OCH_2CH$_3$), 2.31(s, 3H, CH_3), 1.30 (t, 3H, $J = 1.9$ Hz, –2OCH$_2$CH_3 and –4OCH$_2$CH_3). Elemental analysis: Calculated for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28; Found: C, 69.75; H, 6.51; N, 4.22%

*Diethyl 5-[2-(4-chlorophenyl)ethenyl]-3-methyl-1H-pyrrole-2,4-dicarboxylate (**2b**)*

IR (KBr, cm^{-1}): 3,347 (NHstr), 3,045 (CHstr of phenyl ring), 1,744 (C=O in ester); 831 (C–Cl); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.42–7.61(m, 5H, Ph-ring), 7.05 (s, 1H, *H*C=CH), 6.94 (s, 1H, HC=C*H*), 6.20 (s, 1H, NH in pyridine ring), 4.26 (q, 2H, $J = 1.8$ Hz, –2OCH_2CH$_3$ and –4OCH_2CH$_3$), 2.32 (s, 3H, CH_3), 1.37 (t, 3H, $J = 1.7$ Hz, –2OCH$_2$CH_3 and –4OCH$_2$CH_3). Elemental analysis: Calculated for $C_{19}H_{20}ClNO_4$: C, 63.07; H, 5.57; N, 3.87; Found: C, 63.12; H, 5.51; N, 3.82%.

*Diethyl 5-[2-(4-hydroxyphenyl)ethenyl]-3-methyl-1H-pyrrole-2,4-dicarboxylate (**2c**)*

IR (KBr, cm^{-1}): 3,342 (NHstr), 3,043 (CH str of phenyl ring), 1,747 (C=O in ester), 1,465 (C–OH); ^{1}H NMR ($CDCl_3$, 400 MHz): 9.38 (s, 1H, OH), 7.12 (s, 1H, *H*C=CH), 6.96 (s, 1H, HC=C*H*), 6.64–7.30 (dd, 4H, Ph-ring), 6.11 (s, 1H, NH in pyridine ring), 4.33 (q, 2H, $J = 1.7$ Hz, –2OCH_2CH$_3$ and –4OCH_2CH$_3$), 2.42(s, 3H, CH_3),1.34 (t, 3H, $J = 1.8$ Hz, 2,4-OCH$_2$CH_3). Elemental analysis: Calculated for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08; Found: C, 66.41; H, 6.18; N, 4.13%.

*Diethyl 5-[2-(4-methoxyphenyl)ethenyl]-3-methyl-1H-pyrrole-2,4-dicarboxylate (**2d**)*

IR (KBr, cm^{-1}): 3,339 (NH str), 3,036 (C–H str in phenyl ring), 1,740 (C=O in ester); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.11 (s, 1H, *H*C=CH), 6.90–7.60 (dd, 4H, Ph-ring), 6.88 (s, 1H, HC=C*H*), 6.21 (s, 1H, NH in pyridine ring), 4.41 (q, 4H, $J = 1.8$ Hz, –2OCH_2CH$_3$ and –4OCH_2CH$_3$), 2.41 (s, 3H, CH_3), 3.88 (s, 3H, –OCH_3), 1.15 (t, 6H, $J = 1.9$ Hz, 2,4-OCH$_2$CH_3). Elemental analysis: Calculated for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92; Found: C, 67.25; H, 6.52; N, 3.95%.

*Diethyl 3-methyl-5-[2-(4-nitrophenyl)ethenyl]-1H-pyrrole-2,4-dicarboxylate (**2e**)*

IR (KBr, cm^{-1}): 3,332 (NH str), 3,039 (C–H str in phenyl ring), 1,755 (C=O in ester), 1,531 (C–NO_2); ^{1}H NMR ($CDCl_3$, 400 MHz): 8.22–8.04 (dd, 4H, Ph-ring), 7.12 (s,

1H, *H*C=CH), 7.01 (s, 1H, HC=C*H*), 6.24 (s, 1H, NH in pyridine ring), 4.32 (q, 2H, $J = 1.7$ Hz, –2OCH_2CH$_3$ and –4OCH_2CH$_3$), 2.26 (s, 3H, CH_3), 1.37 (t, 6H, $J = 1.8$ Hz, 2,4-OCH$_2$CH_3). Elemental analysis: Calculated for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52; Found: C, 61.31; H, 5.52; N, 7.56%.

*Diethyl 5-(4-(dimethylamino)styryl)-3-methyl-1H-pyrrole-2,4-dicarboxylate (**2f**)*

IR(KBr, cm^{-1}): 3,329 (NH str), 3,041 (C–H str in phenyl ring), 1,738 (C=O in ester); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.21 (s, 1H, *H*C=CH), 6.69–7.74 (dd, 4H, Ph-ring), 6.90 (s,1H, HC=C*H*), 6.27 (s, 1H, NH in pyridine ring), 4.22 (q, 4H, $J = 2.3$ Hz, –2OCH_2CH$_3$ and –4OCH_2CH$_3$), 2.29 (s, 3H, CH_3), 3.08 (s, 6H, –N(CH$_3$)$_2$), 1.22 (t, 3H, $J = 2.2$ Hz, 2,4-OCH$_2$CH_3). Elemental analysis: Calculated for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56; Found: C, 68.14; H, 7.10; N, 7.51%.

*Synthesis of 2,2′-({3-methyl-5-[2-phenylethenyl]-1H-pyrrole-2,4-diyl}dicarbonyl)dihydrazinecarbothioamide (**3a**)*

A mixture of compound **2a** (0.1 mol), thiosemicarbazide(0.2 mol) and few drops of DMSO in ethanol; the reaction mixture was refluxed for 7 h. The reaction mixture was poured into crushed ice. The precipitate was collected by filtration and recrystallized by absolute ethanol. The above procedure was followed by remaining compounds **3b**–**f**.

IR (KBr, cm^{-1}): *v* 3,354 (NH), 3,249 (NH$_2$), 3,021 (Ar–H), 1,717 (CONH), 1,267 (C=S), 1,096 (N–C–N); 812 (Ar–H); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.75 (d, 2H, $J = 3.00$ Hz, –2CON*H* and –4CON*H*), 9.66 (s, 2H, NH$_2$), 7.39–7.62 (m, 5H, Ph-ring), 7.05 (s, 1H, *H*C=CH), 6.90 (s, 1H, HC=C*H*), 6.15 (s, 1H, NH in pyridine ring), 2.45 (s, 3H, CH$_3$), 2.05 (d, 2H, $J = 3.50$ Hz, 2,4-NHCS); ^{13}C NMR (DMSO-d_6, 400 MHz): δ 182.5 (C=S), 164.8 (C=O), 162.5 (C=O), 144.7 (C-5 in pyrrole ring), 143.5 (C-3 in pyrrole ring), 123.6 (C-2 in pyrrole ring), 118.5 (C-4 in pyrrole ring), 123.7 (H*C*=CH), 131.2 (HC=*C*H), 137.5, 127.9, 128.6, 128.5 (Ph), 12.1(C$_3$–*C*H$_3$); MS (*m/z*, (relative abundance, %)): 418.50 (M$^+$+1, 12.01), 358.32 (M$^{+)}$, 298.32 (M$^+$−1), 239.26 (M$^+$, 100.00), 183.24 (M$^+$), 169.22(M$^+$), 93.12(M$^+$−1), 67.11(M$^+$). Elemental analysis: Calculated for $C_{17}H_{19}N_7O_2S_2$: C, 48.90; H, 4.59; N, 23.48; S, 15.36; Found: C, 48.95; H, 4.52; N, 23.41; S, 15.40%.

*2,2′-({5-[2-(4-Chlorophenyl)ethenyl]-3-methyl-1H-pyrrole-2,4-diyl}dicarbonyl)dihydrazinecarbothioamide (**3b**)*

IR (KBr, cm^{-1}):*v* 3,365 (NH), 3,222 (NH$_2$), 3,041 (Ar–H), 1,715 (C=O), 1,268 (C=S), 1,096 (N–C–N), 837 (C–Cl), 812 (Ar–H); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.43 (d, 1H, $J = 3.10$ Hz, –2CON*H* and –4CON*H*), 9.68 (s, 2H, NH$_2$), 7.44–7.62 (m, 4H, Ph-ring), 7.00 (s, 1H, *H*C=CH), 6.91 (s, 1H, HC=C*H*), 6.32 (s, 1H, NH of pyridine ring), 2.35 (s, 2H, CH$_3$), 2.13(d, 1H, $J = 3.56$ Hz, –NHCS); ^{13}C NMR (DMSO-d_6, 400 MHz): δ 181.7 (C=S), 163.8 (C=O), 160.5 (C=0), 145.0 (C-5 in pyrrole ring), 143.8 (C-3 in pyrrole ring), 122.7 (C-2 in pyrrole ring), 119.8 (C-4 in pyrrole ring), 123.5 (H*C*=CH), 131.2 (HC=*C*H), 142.1, 188.5, 128.7, 128.2 (Ph–Cl), 12.8 (C$_3$–*C*H$_3$); MS (*m/z,* (relative abundance, %)): 52.90 (M$^+$+1, 12.01), 392.86 (M$^+$, 36.21), 332.77(M$^+$−1, 27.08), 273.71 (M$^+$, 100.00), 163.21(M$^+$, 63.01), 150.16 (M$^+$−1, 38.17), 67.08(M$^+$, 20.01). Elemental analysis: Calculated for $C_{17}H_{18}ClN_7O_2S_2$: C, 45.18; H, 4.01; N, 21.69; S, 14.19; Found: C, 45.14; H, 4.06; N, 21.66; S, 14.15%.

*2,2′-({5-[2-(4-Hydroxyphenyl)ethenyl]-3-methyl-1H-pyrrole-2,4-diyl}dicarbonyl) dihydrazinecarbothioamide (**3c**)*

IR (KBr, cm^{-1}): *v* 3,361 (NH), 3,241 (NH$_2$), 3,019 (Ar–H), 1,718 (C=O), 1,460 (OH–C), 1,264 (C=S), 1,098 (N–C–N), 816 (Ar–H); ^{1}H NMR (DMSO-d_6, 400 MHz) : δ 10.32 (d, 1H, $J = 3.0$ Hz, –2CON*H* and –4CON*H*), 9.50 (s, 2H, NH$_2$), 9.37 (s, 1H, OH), 7.01–7.22 (dd, 4H, Ph-ring), 6.98 (s, 1H, *H*C=CH), 6.90 (s, 1H, HC=C*H*), 6.26 (s, 1H, NH in pyridine ring), 2.40 (s, 3H, CH$_3$), 2.16 (d, 2H, $J = 3.49$ Hz, 2,4-NHCS); ^{13}C NMR(DMSO-d_6, 400 MHz): δ 181.7 (C=S), 164.9 (C=O), 162.7 (C=0), 145.0 (C-5 in pyrrole ring), 143.8 (C-3 in pyrrole ring), 123.8 (C-2 in pyrrole ring), 118.5 (C-4 in pyrrole ring), 123.8 (H*C*=CH), 131.8 (HC=*C*H), 142.5, 135.7, 128.5,127.9 (Ph–OH), 12.6 (C$_3$–*C*H$_3$); MS (*m/z,* (relative abundance, %)): 434.22 (M$^+$+1, 55.22), 373.41 (M$^+$, 41.01), 255.26 (M$^+$, 18.21), 239.26 (M$^+$, 36.22), 163.17 (M$^+$, 28.01), 151.16 (M$^+$, 100.00), 122.19 (M$^+$−1,48.07). Elemental analysis: Calculated for $C_{17}H_{19}N_7O_3S_2$: C, 47.10; H, 4.42; N, 22.62; S, 14.76; Found: C, 47.15; H, 4.46; N, 22.66; S, 14.71%.

*2,2′-({5-[2-4-Methoxyphenyl)ethenyl]-3-methyl-1H-pyrrole-2,4-diyl}dicarbonyl)dihydrazinecarbothioamide (**3d**)*

IR (KBr, cm^{-1}): *v* 3,373 (NH), 3,244 (NH$_2$), 3,047 (Ar–H), 1,721 (C=O), 1,265 (C=S), 1,080 (N–C–N), 834 (Ar–H); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.41 (d, 1H, $J = 3.1$ Hz, –2CON*H* and –4CON*H*), 9.49 (s, 2H, NH$_2$), 7.10 (s, 1H, *H*C=CH), 6.99–7.66 (dd, 4H, Ph-ring), 6.96 (s, 1H, HC=C*H*), 6.33 (s, 1H, NH of pyridine ring), 2.40 (s, 2H, CH$_3$), 2.18(d, 1H, $J = 3.5$ Hz, –NHCS); ^{13}C NMR (DMSO-d_6, 400 MHz): δ 184.8 (C=S), 164.5 (C=O), 161.8 (C=0), 145.9 (C-5 in pyrrole ring), 144.2 (C-3 in pyrrole ring), 123.6 (C-2 in pyrrole ring), 117.5 (C-4 in pyrrole

ring), 123.8 (HC=CH), 130.5 (HC=CH), 143.3, 136.1, 129.6, 129.8 (Ph–NO_2), 12.0 (C_3–CH_3); MS (*m/z*, (relative abundance, %)): 463.45 (M^++1, 40.2), 416.41 (M^+, 20.2), 344.32 (M^+, 22.08), 313.28 (M^+−1, 30.27), 284.26 (M^+, 32.18), 238.26 (M^+−1, 41.08), 164.10 (M^++1, 35.71), 151.16 (M^+, 100.00), 123.19(M^+, 61.71), 95.14 (M^+, 41.71). Elemental analysis: Calculated for $C_{18}H_{21}N_7O_3S_2$: C, 48.31; H, 4.73; N, 21.91; S, 14.33; Found: C, 48.33; H, 4.76; N, 21.96; S, 14.37%.

*2,2′-({3-Methyl-5-[2-(4-nitrophenyl)ethenyl]-1H-pyrrole-2,4-diyl}dicarbonyl)dihydrazinecarbothioamide (**3e**)*

IR (KBr, cm^{-1}): *v* 3,378 (NH), 3,221 (NH_2), 3,043 (Ar–H), 1,723 (C=O), 1,530 (C–NO_2), 1,277 (C=S), 1,095 (N–C–N), 812 (Ar–H); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.33 (d, 1H, J = 3.2 Hz, –2CONH and –4CONH), 9.68 (s, 2H, NH_2), 8.22–8.06 (m, 4H, Ph-ring), 7.21 (s, 1H, HC=CH) 6.99 (s, 1H, HC=CH), 6.39 (s, 1H, NH of pyridine ring), 2.38 (s, 2H, CH_3), 2.14 (d, 1H, J = 3.3 Hz, –NHCS); ^{13}C NMR(DMSO-d_6, 400 MHz): δ 190.2 (–CH_3O), 183.7 (C=S), 164.7 (C=O), 161.5 (C=0), 144.0 (C-5 in pyrrole ring), 12.7 (C_3-CH_3); MS (*m/z,* (relative abundance, %)): 144.7 (C-3 in pyrrole ring), 124.1 (C-2 in pyrrole ring), 119.3 (C-4 in pyrrole ring), 123.4 (HC=CH), 133.2 (HC=CH), 141.7, 138.5, 128.7, 129.5 (Ph). Elemental analysis: Calculated for $C_{17}H_{18}N_8O_4S_2$: C, 44.15; H, 3.92; N, 24.23; S,13.87; Found: C, 44.19; H, 3.91; N, 24.25; S, 13.83%; MS (*m/z,* (relative abundance, %)): 448.50 (M^++1, 41.73), 388.44 (M^+, 38.01), 329.35 (M^+, 30.01), 299.32 (M^+, 100), 213.27(M^+−1, 100.00), 183.24 (M^+, 63.01), 107.81(M^+, 38.17), 95.83 (M^+, 20.01).

*2,2′-({3-Methyl-5-[2-(4-dimethylaminophenyl) ethenyl]-1H-pyrrole-2,4-diyl}dicarbonyl) dihydrazinecarbothioamide (**3f**)*

IR (KBr, cm^{-1}): *v* 3,369 (NH), 3,224 (NH_2), 3,034 (Ar–H), 1,701 (C=O), 1,271 (C=S), 1,089 (N–C–N), 811 (Ar–H); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.42 (d, 2H, J = 3.0 Hz, –2CONH and –4CONH), 9.71 (s, 2H, NH_2), 7.10 (s,1H, HC=CH), 6.91 (s, 1H, HC=CH), 6.75–7.76 (dd, 4H, Ph-ring), 6.34 (s, 1H, NH in pyridine ring), 3.10 (s, 6H, –$N(CH_3)_2$), 2.33 (s, 3H,CH_3), 2.10 (d, 1H, J = 3.4 Hz, –NHCS); ^{13}C NMR (DMSO-d_6, 400 MHz): δ 182.8 (C=S), 164.8 (C=O), 161.8 (C=0), 140.8 (C-5 in pyrrole ring), 145.2 (C-3 in pyrrole ring), 125.8 (C-2 in pyrrole ring), 118.7 (C-4 in pyrrole ring), 123.8 (HC=CH), 133.8 (HC=CH), 142.7, 138.7, 127.8, 128.5 (Ph), 12.5 (C_3–CH_3); MS (*m/z*, (relative abundance, %)): 461.57 (M^++1, 31.01), 401.48 (M^+, 28.27), 342.39 (M^+, 22.08), 281.33 (M^+−1, 15.07), 239.26 (M^+, 20.01), 163.17 (M^+, 2.08), 151.16 (M^+, 100.00), 122.19 (M^+−1, 12.08). Elemental analysis: Calculated for $C_{17}H_{19}N_8O_4S_2$: C, 44.15; H, 3.92; N, 24.23; S,13.87; Found: C, 44.20; H, 3.97; N, 24.27; S, 13.83%.

Pharmacology

Anticonvulsant activity

The anticonvulsant evaluation was undertaken by the Department of Pharmacology, Mother Theresa Post Graduate & Research Institute of Health Science, Puducherry, 605006, India.

Compounds **3a–f** were screened for their anticonvulsant activity by the method given in the literature (Krall *et al.*, 1978; Porter *et al.*, 1985). Swiss albino rats weighing 150 g were divided into eight groups each containing five animals and subjected to the following tests for each of the compounds studied:

Placebo group

Isotonic saline solution was intraperitoneally administered, followed 15 min later by an intravenous 48.7 mg dose of pentamethylene tetrazole dissolved in physiological saline.

Assay group

A solution of the compound being tested in physiological saline was intraperitoneally administered. After 15 min, a time that was considered sufficient for complete absorption, the same doses of pentamethylene tetrazole was administered.

Reference group

10 mg/kg of sodium diphenylhydantoin dissolved in physiological saline was intraperitoneally administered. After 15 min, the same dose of pentamethylene tetrazole was applied. In each case, the number of animals of each group which suffered convulsions was recorded. Results were statistically analyzed using the student's *t* test.

Conclusion

Compound **3a** is found to possess anticonvulsant activity hence can be used as lead to develop antiepileptic drugs. Also further substitutions on pyrrole nucleus can lead to more potent compounds.

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