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Synthesis, Characterization, and Anticonvulsant Activity of Enaminones. Part 5: Investigations on 3-Carboalkoxy-2-methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-one Derivatives

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Abstract—A new series of anticonvulsant 3-carboalkoxy-2-methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-ones is herein reported. 2-Aminothiophenols underwent cyclocondensation with 4-carboalkoxy-5-methylcyclohexane-1,3-diones in refluxing dimethylsulfoxide (DMSO) to yield 3-carboalkoxy-2-methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-ones, **4a–k**. In the case of the carbo-*tert*-butoxy derivatives (**4c** and **4k**) prolonged reaction times led to the isolation of the respective 3-unsubstituted-2-methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-ones (**4l** and **4m**) instead. Significant anticonvulsant activity was displayed by these analogues, most particularly **4k**, which was active at 30 mg/kg intraperitoneally (ip) in mice in the maximal electroshock seizure (MES) evaluation, with no toxicity noted at dosages up to 300 mg/kg. Oral (po) rat evaluation of **4k** in the MES evaluation provided an ED_{50} of 17.60 mg/kg, with no toxicity noted at dosages up to 500 mg/kg, providing a protective index ($PI = TD_{50}/ED_{50}$) > 28.40. These compounds represent the first reported series of phenothiazines which possess anticonvulsant activity.

Introduction

In an attempt to discover analogues of the prototype anticonvulsant methyl 4-[(4′-chlorophenyl)-amino]-6-methyl-2-oxocyclohex-3-en-1-oate, **1** (Fig. 1),[1–5] we have targeted alkyl 4-[(5′-chloro-2′-pyridinyl)amino]-6-methyl-2-oxocyclohex-3-en-1-oates, **2** [R = CH_3 (**2a**); R = C_2H_5 (**2b**)][1,2] (Fig. 1), and alkyl 4-[(5′-methyl)-3′-isoxazolylamino]-6-methyl-2-oxocyclohex-3-en-1-oates, **3** [R = CH_3 (**3a**); R = C_2H_5 (**3b**); R = $C(CH_3)_3$ (**3c**)] (Fig. 1).[6] Recent nuclear magnetic resonance (NMR) studies of **1** revealed a strong 2-D NOE interaction between its vinylic and 2′-hydrogens.[2,5,6] Compounds **2** and **3** displayed H-bonding interactions between its vinylic and 2′-ring nitrogen, as indicated by the downward shift in their ^1H NMR signal when compared to prototype **1**.[6] Therefore, in considering conformationally restricted analogues of **1**, we were prompted to include analogues having the two positions β- to the enaminic nitrogen linked in a tricyclic structure. This report covers the linkage through a sulfur atom. Hence, a series of 3-carboalkoxy-2-methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-ones (**4a–k**) as well as the unsubstituted analogue **4l** has been synthesized and evaluated for anticonvulsant activity.

The phenothiazine ring system has been shown to be an essential pharmacophore for tranquilizers, anticancer

Key words: anticonvulsants; NMR; X-ray crystal structures.
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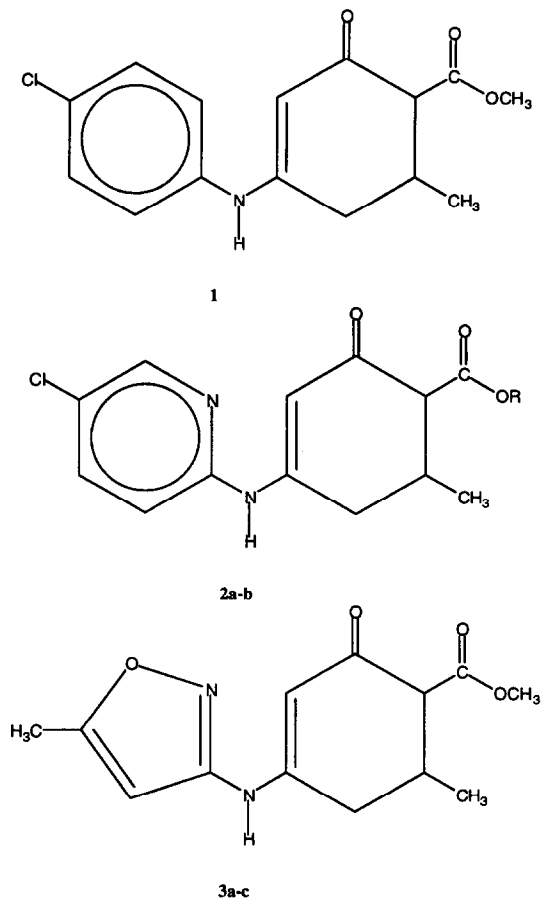


Figure 1. Previous active enaminones reported by Scott et al.: methyl 4-[-4′-(chlorophenyl)amino]-6-methyl-2-oxocyclohex-3-en-l-oate, **1**; alkyl 4-[5′-(chloro-2′-pyridinyl)amino]-6-methyl-2-oxocyclohex-3-en-l-oate, **2a** (R = methyl), **2b** (R = ethyl); alkyl 4-[5′-(methyl)isoxazolyl)amino]-6-methyl-2-oxocyclohex-3-en-oate, **3a** (R = methyl), **3b** (R = ethyl), **3c** (R = butyl).

agents, antiinflammatory agents, antihistaminics, anthelmintics, local anesthetics, antiseptics, growth inhibitors, and in the treatment of neuropsychiatric disorders.[7–9] The mechanism for the variety of therapeutic activities is believed to be due to the presence of a fold along the nitrogen–sulfur axis.[10] However, until this report, these agents have not been shown to display significant anticonvulsant activity. Anticonvulsant activity was, however, reported for a related series of 2,3-dihydro-3-oxo-5*H*-pyrido[3,4-*b*]benzothiazine-4-carbonitriles.[11]

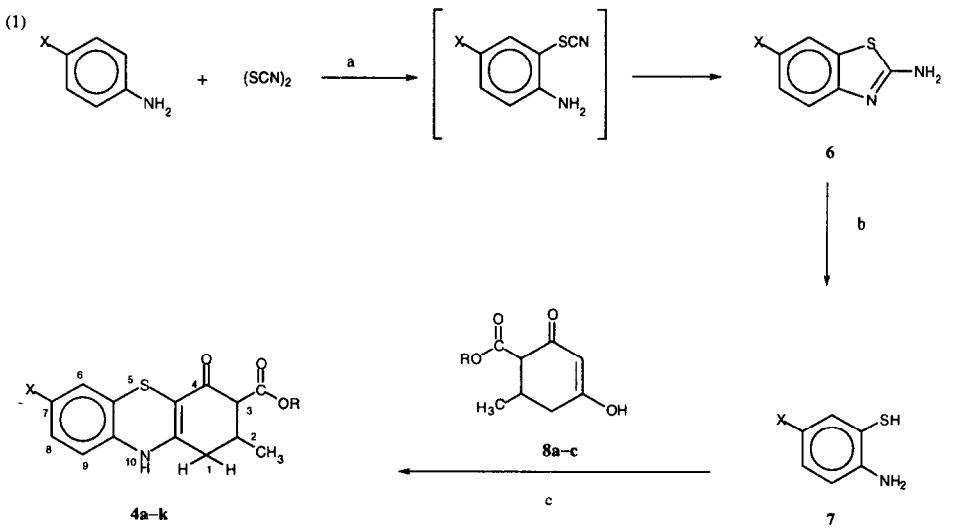
Chemistry

Thiazines have been previously synthesized in our laboratories by employing enamines (derived from acetylenic nitriles and esters).[12] For this work, the synthetic method (Scheme 1) follows the classical one-pot reaction of Miyano and co-workers[13] involving the condensation and oxidative cyclization of the appropriately substituted 2-aminobenzenethiols (**7**) with the β-dicarbonyl esters, **8** [R = CH_3 (**8a**); R = C_2H_5 (**8b**); R = $C(CH_3)_3$ (**8c**)] in refluxing dimethylsulfoxide (DMSO) to provide **4a–k** in reasonably pure form. These compounds are provided in Table 1. The precursor thiol compounds (**7**) were derived from the base-catalyzed hydrolytic fission of the 6-substituted-2-aminobenzothiazoles (**6**) prepared by the action of potassium thiocyanate and bromine (generating thiocyanogen, [$(SCN)_2$], in situ), on *p*-substituted anilines as described in the literature.[14–16] When experimental conditions for the final step were identical for each ester (i.e., 30 min reflux in DMSO) the *tert*-butyl compounds **4c** and **4k** underwent thermal decomposition to give their respective 2,3-dihydro-2-methyl-1*H*-phenothiazin-4[10*H*]-ones (**4l** and **4m**). Here, thermal decomposition of the desired phenothiazine **4c** and **4k** to butylene and the β-keto acid (**4**), is suspected, followed by decarboxylation of the latter compound. This is substantiated by the formation of **4c** by employing shorter reflux times in DMSO. Stability studies of the 3-carbo-*tert*-butoxyphenothiazine **4c** confirmed the lability of the 3-carbo-*tert*-butoxy substituent with refluxing DMSO for periods up to 20 min. Prior decarboxylation of **8c**, the starting β-dicarbonyl compound cannot, however be ruled out. Friary and co-workers have shown that **8c** is readily decarboxylated under acid-catalyzed conditions to form **10** (Scheme 2).[17] In view of the need for large quantities of **4k** (see Pharmacology), optimization of the cyclocondensation reaction conditions was necessary. Various reaction times and solvents were used in this study. The results are shown in Table 2 and the details in the experimental section.

The *trans* stereochemistry about the C_2–C_3 bond of the phenothiazines **4a–k** was confirmed by the ^1H NMR spectroscopy, which indicated the presence of a methine doublet at ca. 3.1 with $J_{H\text{-}H}$ 11 Hz. Hydrogens at $C_{1,2}$ coincided as a 3H multiplet at 2.3. Assignments to the $H_{8,9}$ aromatic hydrogens were unambiguously made by noting the weak *meta*-coupling (J = 3.0 Hz) of $H_{6\text{–}8}$. To distinguish between the isomeric forms **4** and **5**, a nuclear Overhauser enhancement (NOE) study was performed. In addition, 2-D correlation of these and other signals, allowed for ^{13}C assignments and is included in the Experimental section.

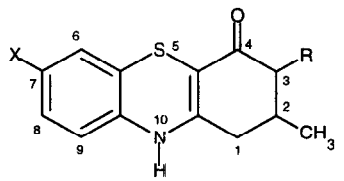
X-ray Crystallography

In view of the possible enantiomeric forms of the reported phenothiazines[7] and to reaffirm the NOE and NMR data, an X-ray diffraction study of **4b** (Fig. 2) was



Scheme 1. Conditions: (a) Br_2, KSCN, HOAc, 15 °C; (b) NaOH; (c) DMSO, Δ.

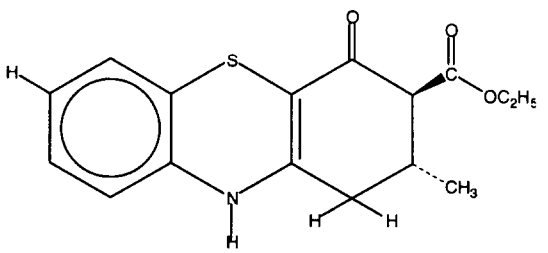
Table 1. Anticonvulsant phenothiazines



Compound	R	X	ASP classification[a]
4a	CO_2CH_3	H	1
4b	$CO_2C_2H_5$	H	1
4c	$CO_2C(CH_3)_3$	H	1
4d	CO_2CH_3	Cl	1
4e	$CO_2C_2H_5$	Cl	1
4f	$CO_2C(CH_3)_3$	Cl	1
4g	CO_2CH_3	CH_3	1
4h	$CO_2C_2H_5$	CH_3	1
4i	CO_2CH_3	Br	1
4j	$CO_2C_2H_5$	Br	1
4k	$CO_2C(CH_3)_3$	Br	1
4l	H	H	3[b]
4m	H	Br	nd

[a]Anticonvulsant Screening Project classification where 1 = anticonvulsant activity at 100 mg/kg or less; 2 = anticonvulsant activity at doses greater than 100 mg/kg; 3 = no anticonvulsant activity at doses up to and including 300 mg/kg.
[b]Submitted for TTE evaluation; on retest activity = 1.
nd = not tested.

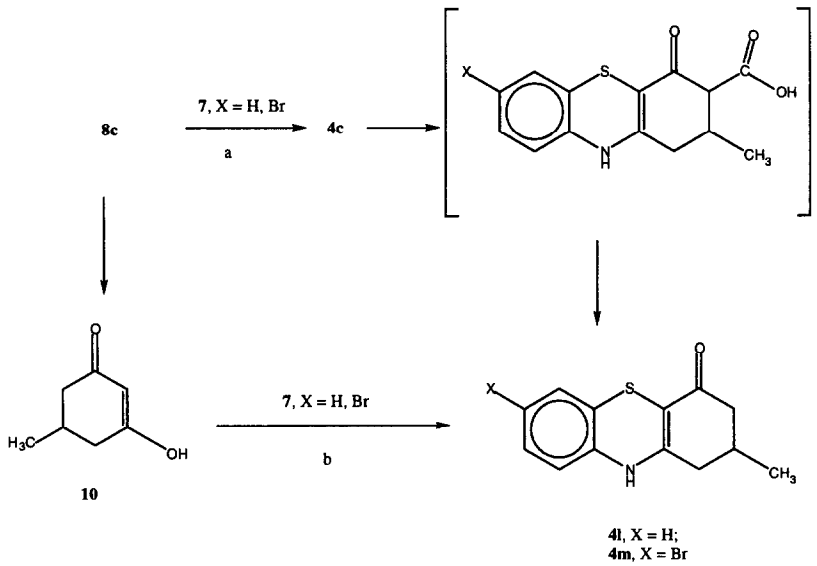
performed. A summary of the atomic coordinates of **4b** is provided in Table 3. Additionally, **4l** is a known compound[18] and was unequivocally synthesized via cyclocondensation of 5-methyl-1,3-cyclohexanedione (**10**) and **7** (X = H). We duplicated this procedure and it was compared to the product obtained from the decarboxylation of *tert*-butoxy ester. These proved to be identical. The single enantiomeric form of **4l** was concluded.



4b

Pharmacology

Pharmacological testing of the compounds listed in Table 1 has been provided by the Antiepileptic Drug Development (ADD) Program, Epilepsy Branch, Neurological Disorders Program, National Institute of Neurological Disorders and Stroke (NINDS). These testing procedures have been described.[19] Phase I evaluation of the reported phenothiazines involved three tests: maximal electroshock seizure (MES), subcutaneous pentylenetetrazol (ScMet), and neurologic toxicity (Tox) in mice. Phase I data for these phenothiazines is shown in Table 4. As previously reported,[1] to differentiate the results between different rodent species, the most active class 1 analogues, **4b** and **4k** were subsequently evaluated for oral (po) activity (Phase VIA) in the rat. Data is shown in Table 5. Phase



Scheme 2. Conditions: (a) Reflux DMSO, 5–8 min; (b) Reflux DMSO, 5–8 min.

VI data for phenytoin, carbamazepine, and valproate are provided for comparative purposes. As a result of this evaluation, **4k** was chosen for further study. Rat quantification (Phase VIB) provided an ED_{50} at 4 h of 17.60 mg/kg and a $TD_{50} > 500$ mg/kg, providing a protective index (TD_{50}/ED_{50}) >28.40, which compared favorably with phenytoin (PI = 6.9) and carbamazepine (PI = 8.1) under the same experimental conditions.[1] However, in contrast with **1** and phenytoin, **4k** was inactive in the hippocampal kindling screen at 100 mg/kg, displaying no apparent activity against either seizure score or afterdischarge duration.[20] To complete the evaluation of **4k** and to determine the mechanism of action, a Phase V protocol was instituted. Phase V evaluation furnishes quantification against bicuculline and picrotoxin. This screen provides information on the mechanism of action of the anticonvulsant activity. Bicuculline and picrotoxin correspond to GABA inhibitory and chloride channel inhibition, respectively. Compound **4k** was not active in the bicuculline or picrotoxin screens at doses up to 500 mg/kg. Additional studies on the effect on sodium channels[5] is under study and will be reported shortly. The TTE test[21] was performed on the initially inactive phenothiazine **4l**. This test is a clinically nonselective, electroconvulsive seizure model that identifies compounds that raise seizure threshold as well as those that prevent seizure spread and has been reported by us earlier.[5,22] As noted in Table 1, **4l** proved to be active at 100 mg/kg at 0.5 and at 2 h ip in mice. The MES reevaluation confirmed the 0.5 h TTE evaluation, but did not confirm the 2 h result.

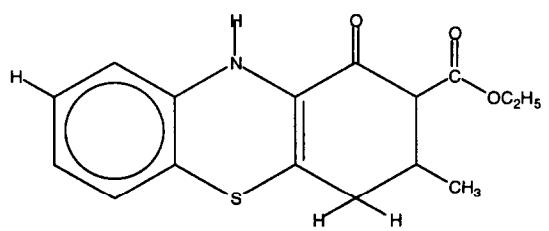
Table 2. Optimization of reaction conditions for formation of **4k**[a]

Trial	Solvent[b]	Temperature (°C)	Time (min)	% of desired compound
1	DMSO	198	30	7
2	DMSO	155	30	13
3	DMSO	155	20	35
4	DMSO	155	10	77
5	Toluene	125	30	25

[a]See Experimental.
[b]DMSO = dimethylsulfoxide.

Results and Discussion

The stereochemistry of the cyclocondensation reaction and the products was investigated by NOE and X-ray diffraction studies. It was theoretically possible that the cyclocondensation reaction could form either **4b** or **5b**, corresponding to N_{10} or N_5, respectively, however on NOE irradiation of the N–H proton produced two peaks indicating that **4b** was indeed the sole product formed. X-ray diffraction analysis confirmed that a single isomer formed with a trans C_2-C_3 orientation of the chiral centers.



5b

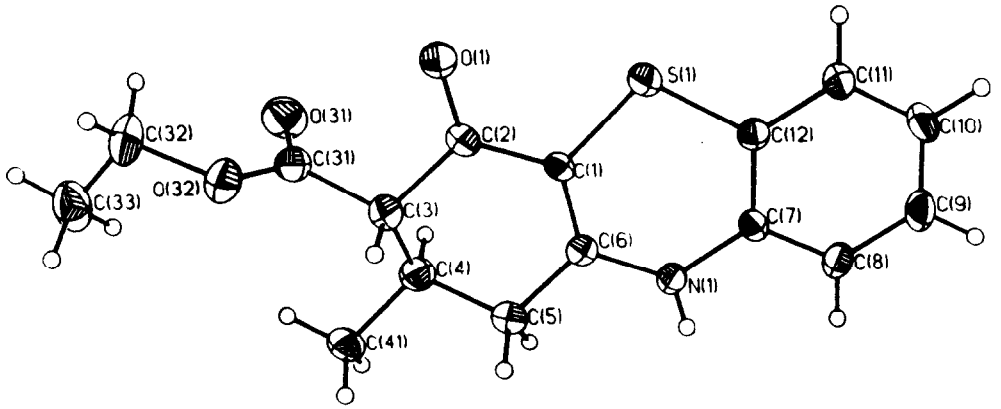


Figure 2. X-ray crystal structure of 3-carbethoxy-2-methyl-2,3-dihydro-1*H*-phenothiazin-4-[10*H*]-one (**4b**).

Data on the anticonvulsant evaluation for the phenothiazines synthesized in Table 1 disclosed significant anticonvulsant anti-MES activity for all of the 3-carboalkyl phenothiazines. In addition, the profile of anticonvulsant activity seen with these analogues parallels that of the previous studies on the open-chain analogues.[1–6] Clog P[23] measurements were determined on the protonated species, which predominates at physiological pH and indicates that the MES-active phenothiazines varied from 5.81 for the highly active carbo-*tert*-butoxy analogue **4k**, to 3.46 for the unsubstituted carbomethoxy analogue **4a**. The Clog P data for the decarboxylated analogue **4l**, the only analogue evaluated for anticonvulsant activity, was 3.79, and was greater that than of the active carbomethoxy analogue **4a**. It was concluded that while lipophilicity played a role in the activity of these analogues, as shown with **4k**, the 3-carboalkoxy group must be maintained in order for anticonvulsant activity to be enhanced. In this report, several carboalkoxy analogues possessed Clog P values >4.0; that is, carbethoxy **4e** (4.95), carbo-*tert*-butoxy **4f** (5.66); carbethoxy **4j** (5.10), and carbo-*tert*-butoxy **4k**. Of interest is the Clog P data for the prototype antipsychotic phenothiazine, chlorpromazine, **9a**, which is 7.78. This high lipophilic value is due principally to the aminoalkyl substitution on N10 which the currently reported phenothiazines lack.[24] The N_{10} unsubstituted phenothiazine ring system, **9b**, has a Clog P of 4.75 and was inactive as an antipsychotic agent. While a strict comparison of these present analogues to the antipsychotic phenothiazines may not be valid in view of the saturation of the C1-4 ring and the concomitant spatial difference imposed by this saturation, Clog P data analysis may partially explain the unique therapeutic effectiveness of these newer anticonvulsant phenothiazines. We have previously shown[5] that the ester functionality is useful in modifying activity, most probably through a combination of steric (E_s)[25] and lipophilic parameters, thus the rapid onset of anti-MES activity was noted at 30 mg/kg for the carbethoxy analogue **4b** (E_s −0.07), and at 100 mg/kg for the 7-chloro analogue **4e**, as well as the carbomethoxy analogue **4a** (E_s 0.00). In contrast, the bulky and highly lipophilic carbo-*tert*-butoxy analogue **4c** (E_s −1.54) exhibited a longer onset of activity, displaying activity at 100 mg/kg at 2 h and 4 h while the 7-chloro analogue, **4f**, was active at 4 h as well. The peak effect of **4k** at 4 h was consistent with the high lipophilicity of the compound. Of further

Table 3. Atomic coordinates [×10⁴] and equivalent isotropic displacement parameters [Å×10³] for 3-carbethoxy-2-methyl-2,3-dihydro-1*H*-phenothiazin-4[10]-one (**4b**)

	x	y	z	U (eq)[a]
S (1)	1126 (1)	605 (2)	5 (2)	56 (1)
O (1)	303 (3)	−1214 (6)	1659 (6)	80 (2)
O (31)	977 (5)	−4045 (7)	2390 (7)	98 (2)
O (32)	747 (4)	−3053 (6)	4167 (7)	81 (2)
N (1)	3451 (5)	429 (7)	430 (6)	53 (2)
C (1)	1843 (5)	−404 (7)	983 (6)	43 (2)
C (2)	1237 (5)	−1213 (8)	1723 (7)	55 (2)
C (3)	1762 (6)	−2013 (9)	2718 (10)	68 (2)
C (31)	1116 (6)	−3139 (8)	3074 (10)	64 (2)
C (32)	145 (9)	−4139 (10)	4628 (12)	101 (4)
C (33)	782 (12)	−5035 (12)	5305 (11)	116 (4)
C (4)	2811 (5)	−2358 (9)	2391 (9)	66 (3)
C (41)	3337 (6)	−3115 (10)	3399 (9)	72 (3)
C (5)	3421 (5)	−1237 (9)	1986 (7)	54 (2)
C (6)	2869 (4)	−386 (7)	1091 (7)	44 (2)
C (7)	3139 (5)	1222 (7)	−532 (6)	44 (2)
C (8)	3857 (6)	1854 (8)	−1230 (8)	61 (2)
C (9)	3574 (7)	2654 (9)	−2177 (10)	72 (2)
C (10)	2578 (8)	2792 (8)	−2479 (10)	73 (2)
C (11)	1844 (6)	2126 (8)	−1822 (7)	56 (2)
C (12)	2107 (5)	1366 (7)	−842 (7)	49 (2)

[a]U (eq) is defined as one-third of the orthogonalized U_{ij} tensor.

Table 4. Anticonvulsant screening project (ASP): Phase I test results in mice (ip)

Compound	Clog P[a]	Dose (mg/kg)[b]	MES[c] (30 min)	MES[c] (4 h)	Tox[d] (30 min)	Tox[d] (4 h)
4a	3.46	30	0/1	0/1	0/4	0/2
		100	3/3	1/3	0/8	0/4
		300	1/1	1/1	1/4	0/2
4b	3.99	30	0/1	0/1	0/4	0/2
		100	1/3	0/3	0/8	0/4
		300	1/1	0/1	0/4	0/2
4c	4.70	30	0/1	0/4	0/4	0/2
		100[e]	0/3	1/3	0/8	0/4
		300	0/1	1/1	0/4	0/2
4d	4.42	30	0/1	0/1	0/4	0/2
		100	0/3	2/3	0/8	0/4
		300	0/1	1/1	0/4	0/2
4e[f]	4.95	30	0/1	0/1	0/4	0/2
		100	2/3	1/3	0/8	0/4
		300	1/1	1/1	0/4	0/2
4f	5.66	30	0/1	0/1	0/4	0/2
		100	0/3	1/3	0/8	0/4
		300	0/1	1/1	0/4	0/2
4g	4.19	30	0/1	0/1	0/4	0/2
		100[g]	0/3	1/3	0/8	0/4
		300	1/1	1/1	0/3	0/1
4h	4.71	30	2/4	0/1	0/4	0/2
		100	1/3	0/3	0/8	0/4
		300	1/1	1/1	0/4	0/2
4i[h]	4.57	10	0/1	0/1	0/4	0/2
		30	1/3	0/3	0/8	0/4
		100	1/1	0/1	0/4	0/2
4j	5.10	30	0/3	0/3	0/8	0/4
		100	0/1	0/1	0/4	0/2
		300	3/3	2/3	0/8	0/4
4k	5.81	30	1/1	0/1	0/4	0/2
		100	3/3	2/3	0/8	0/4
		300	1/1	1/1	0/4	0/2
4l	3.79	30	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/8	0/4
		300	0/1	0/1	0/4	0/2

[a]See ref 23.

[b]Subcutaneous pentylenetetrazol test (number of animals protected/number of animals tested). This test was uniformly inactive except where indicated.

[c]Maximal electroshock test (number of animals protected/number of animals tested).

[d]Rotorod toxicity (number of animals exhibiting toxicity/number of animals tested).

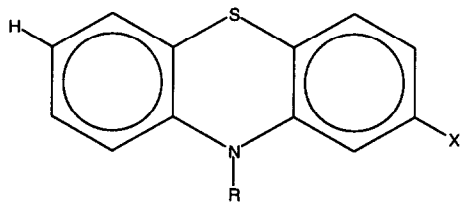
[e]At 2 h, 1/3 MES animals protected, 1/3 toxic; at 6 h, 0/3 MES animals protected, 0/3 toxic.

[f]scMet: at 4 h, 2/5 animals protected at 100 mg/kg.

[g]At 0.25 h, 2/3 MES protected.

[h]scMet: at 30 min, 0/1 animals underwent continuous seizure activity at 10 mg/kg and at 30 mg/kg; at 4 h, 0/1 animals died following continuous seizure at 300 mg/kg.

interest is the prolonged activity displayed by **4a** which was also active at 100 and 300 mg/kg at 4 h as well.



9

a R = -$(CH_2)_3N(CH_3)_2$; X = -Cl

b R = X = -H

Conclusion

This new and hitherto unreported series of anticonvulsant phenothiazines will be subsequently evaluated utilizing the Craig analysis[26] previously employed in our laboratories in the anticonvulsant evaluation of anilino enaminones.[3] The fact that addition of a lipophilic, electron-donating group (e.g. 7-methyl, **4g**, **4h**; $+\pi$, $-\sigma$) as well as lipophilic, electron-withdrawing groups (e.g. 7-chloro, **4d**, **4e**, **4f**; and 7-bromo, **4i**, **4j**, **4k**; $+\pi$, $+\sigma$) all led to potent analogues creates an interesting dilemma. Further research in this area is under way and will be reported shortly.

Experimental

Chemistry

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and were uncorrected. Observed boiling points were also uncorrected. Infrared spectra were recorded on samples in KBr, as diluted chloroform solutions in matched sodium chloride cells, or neat with a Perkin–Elmer 1660 series FTIR spectrophotometer. ^{1}H NMR and ^{13}C spectra were recorded on a General Electric QE 300-MHz spectrometer in deuterated solvents using tetramethylsilane as an internal reference. TLC analysis employed ethyl acetate-cyclohexane (3/1) elution solvent mixture and 5×10 cm and 5×20 cm fluorescent plates (Whatman silica gel 60A). Preparative TLC was performed Uniplate-T® 2000 mM Taper Plate (Analtech, Inc., Newark, DE 19714). Elemental analyses (C, H, N, S and halogen) were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY 11377. X-ray crystal analysis was performed on a Nicolet P3 diffractometer.

Table 5. Oral rat test results

Compd	Evaluation[a]	Time (h)	Dose (mg/kg)	MES[b]	Dose (mg/kg)	Tox[c]	ED_{50} (mg/kg)	TD_{50} (mg/kg)
1	VIB	0.25	10 (6)[d]	3/4		nd	5.8	> 380
		0.50		4/4 (3/4)[d]		nd		
		1.00		4/4 (2/4)[d]		nd		
		2.00		4/4 (1/4)[d]		nd		
		4.00		3/4		nd		
4a	VIA	0.25	30	0/4	30	0/4	nd	nd
		0.50		1/4		0.4		
		1.00		2/4		0/4		
		2.00		1/4		0/4		
		4.00		2/4		0/4		
4b	VIB	0.25	30	3/4		0/4		
		0.50		1/4		1/2		
		1.00		2/4		0/4		
		2.00		0/4		0/4		
		4.00		4.4		0.4		
4d	VIA	0.25	30	0/4	30	0/4	nd	nd
		0.50		0/4		0/4		
		1.00		3/4		0/4		
		2.00		3/4		0/4		
		4.00		2/4		0/4		
4e	VIA	0.25	30	0/4	30	0/4	nd	nd
		0.50		1/4		0/4		
		1.00		3/4		0/4		
		2.00		3/4		0/4		
		4.00		3/4		0/4		
4g	VIA	0.25	30	0/4	30	0/4	nd	nd
		0.50		2/4		0/4		
		1.00		3/4		0/4		
		2.00		1/4		0/4		
		4.00		0/4		0/4		
4k	VIB	0.25	15	1/4	500	0/2	17.6	> 500
		0.50		1/4		0/4		
		1.00		0/4		0/2		
		2.00		0/4		0/2		
		4.00		2/4 5/8[d]		0/2		
		6.00		1/8		0/2		
		8.00		nd		0/2		
		24.00		nd		0/2		
Phenytoin[e]							29.8	> 3000
Carbamazepine[e]							8.50	813
Valproate[e]							490	280

[a]For details see Experimental section.
[b]Maximal electroshock test (refer to Table 4 for definition).
[c]Rotorod toxicity (refer to Table 4 for definition).
[d]Results of a repeat test.
[e]Values from ref 28.
nd = not determined.

4-Carbo-*tert*-butoxy-5-methylcyclohexane-1,3-dione,[5,17] 4-carbomethoxy-5-methyl-cyclohexane-1,3-dione,[1] 4-carbethoxy-5-methylcyclohexane-1,3-dione,[1] and 5-chloro-2-aminobenzenethiol, 5-methyl-2-aminobenzenethiol and 5-bromo-2-aminobenzene-thiol[14] were prepared by literature methods. 2-Aminothiophenol was obtained from Aldrich Chemical Company and used without further purification.

Typical experiments illustrating the general procedures for the preparation of the phenothiazines are described below.

General procedure for the preparation of phenothiazines

***trans*-3-Carbomethoxy-2-methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-one (4a).** A mixture of 4-carbomethoxy-5-methylcyclohexane-1,3-dione (**8a**) (5.52 g, 30 mmol)[1] and 2-aminothiophenol (**7**) (X = H, 3.75 g, 30 mmol) were dissolved in DMSO (10 mL) and placed onto a preheated heating mantle and the reaction mixture was stirred and refluxed for 0.5 h. Upon standing, the reaction mixture formed a solid. The crystals were filtered and the remaining mother liquid was poured into cold water, whereupon further precipitation occurred. The precipitates were recrystallized twice from methanol and proved to be identical. Compound **4a** (4.8 g, 55%), mp 218–221 °C, light-orange crystals: IR ν 3259, 1736, 1587, 1200, 1153 cm^{-1}; ^1H NMR δ 0.93 (d, J = 5.2 Hz, 3 H), 2.32 (m, 3H), 3.18 (d, J = 11.2 Hz, 1H), 3.64 (s, 3H), 6.57 (d, J = 7.8 Hz, 1H), 6.76 (m, 3H), 9.17 (s, 1H); ^{13}C NMR δ 18.71 (q), 30.41 (d), 34.25 (t), 51.53 (s), 59.21 (d), 96.55 (s), 115.92 (d), 119.58 (s), 124.83 (d), 126.36 (d), 126.88 (d), 136.00 (s), 155.78 (s), 170.50 (s), 184.07 (s). Anal. calcd for $C_{15}H_{15}NO_3S$: C, 62.27; H, 5.24; N, 4.84; S, 11.06. Found C, 62.13; H, 5.35; N, 5.01; S, 11.21.

***trans*-3-Carbethoxy-2-methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-one (4b).** Prepared from 4-carbethoxy-5-methylcyclohexane-1,3-dione (**8b**) and **7** (X = H) as described above. On recrystallization twice from methanol, provided **4b** in 30.8% yield mp 201–202 °C as light-orange crystals: IR ν 3261, 1738, 1567, 1317, 1143 cm^{-1}; ^1H NMR δ 0.93 (d, J = 5.1 Hz, 3 H), 1.19 (t, 3H), 2.31 (m, 3H), 3.14 (d, J = 11.8 Hz, 1H), 4.13 (q, 2H), 6.56 (d, J = 7.8 Hz, 1H), 6.76 (m, 3H), 9.16 (s, 1H); ^{13}C NMR δ 13.97 (s), 18.59 (q), 30.39 (d), 34.24 (t), 59.53 (d), 62.12 (s) 60.12 (s), 96.60 (s), 115.85 (d), 119.57 (s), 124.75 (d), 126.31 (d), 126.82 (d), 136.02 (s), 155.63 (s), 169.92 (s), 184.12 (s). Anal. calcd for $C_{16}H_{17}NO_3S$: C, 63.35; H, 5.66; N, 4.62; S, 10.55. Found C, 62.93; H, 5.63; N, 4.56; S, 10.56.

***trans*-3-Carbo-*tert*-butoxy-2-methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-one (4c).** Prepared from 4-carbo-*tert*-butoxy-5-methylcyclohexane-1,3-dione (**8c**) and **7** (X = H) as described above, except that the reaction period was shortened to 10 min. On recrystallization twice from methanol provided **4b** in 48.6% yield mp 221–222 °C as light-orange crystals: IR ν 3275, 1726, 1566, 1288, 1157 cm^{-1}; ^1H NMR δ 0.95 (d, J = 5.3 Hz, 3 H), 1.41 (s, 9H), 2.29 (m, 3H), 2.97 (d, J = 11.1 Hz, 1H), 6.56 (d, J = 8.2 Hz, 1H), 6.75 (m, 3H), 9.08 (s, 1H); ^{13}C NMR δ 18.18 (q), 27.59 (d), 30.41 (d), 34.23 (t), 60.35 (d), 96.73 (s), 115.74 (d), 119.54 (s), 124.61 (d), 126.24 (d), 126.74 (d), 136.11 (s), 155.31 (s), 169.09 (s), 184.50 (s). Anal. calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.40; N, 4.23; S, 9.66. Found C, 65.19; H, 6.44; N, 4.37; S, 9.70.

***trans*-7-Chloro-3-carbomethoxy-2-methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-one (4d).** Prepared **8a** and 5-chloro-2-aminothiophenol (**7**) (X = Cl) as described above. On recrystallization from ethanol provided **4b** in 36.7% yield, mp 226–227 °C, as light-orange crystals: IR ν 3257, 1744, 1566, 1284, 1143 cm^{-1}; ^1H NMR δ 0.94 (d, J = 5.8 Hz, 3H), 2.30 (m, 3H), 3.19 (d, J = 11.4 Hz, 1H), 3.63 (s, 3H), 6.54 (d, J = 8.3 Hz, 1H), 6.54 (m, 2H), 9.26 (s, 1H); ^{13}C NMR δ 18.64 (q), 30.33 (d), 34.16 (t), 59.41 (d), 96.26 (s), 116.99 (s), 122.31 (d), 125.53 (d), 126.50 (d), 128.11 (s), 135.07 (s), 155.56 (s), 170.34 (s), 184.13 (s). Anal. calcd for $C_{15}H_{14}ClNO_3S$: C, 55.64; H, 4.37; Cl, 10.95; N, 4.33; S, 9.88. Found C, 55.50; H, 4.24; Cl, 10.92; N, 4.38; S, 9.86.

***trans*-7-Chloro-3-carbethoxy-2-methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-one (4e).** Prepared from **8b** and **7** (X = Cl) as described for **4c** above. On recrystallization twice from methanol provided **4b** in 50.9% yield, mp 261–262 °C, as light-orange crystals: IR ν 3278, 1723, 1588, 1285, 1156 cm^{-1}; ^1H NMR δ 0.93 (d, J = 5.8 Hz, 3 H), 1.19 (t, 3H), 2.30 (m, 3H), 3.15 (d, J = 11.1 Hz, 1H), 4.13 (q, 2H), 6.50 (d, J = 8.3 Hz, 1H), 6.88 (m, 2H), 9.25 (s, 1H); ^{13}C NMR δ 18.42 (q), 30.37 (d), 34.15 (t), 60.26 (d), 96.41 (s), 116.84 (d), 122.27 (d), 125.48 (d), 126.41 (d), 127.95 (s), 135.18 (s), 155.16 (s), 168.90 (s), 184.67 (s). Anal. calcd for $C_{16}H_{16}ClNO_3S$: C, 56.89; H, 4.78; Cl, 10.49; N, 4.15; S, 9.47. Found C, 56.63; H, 4.68; Cl, 10.53; N, 4.38; S, 9.45.

***trans*-7-Chloro-3-carbo-*tert*-butoxy-2-methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-one (4f).** Prepared from **8c** and **7** (X = Cl) as described for **4c** above. On recrystallization twice from methanol provided **4f** in 50.9% yield, mp 262 °C, as light-orange crystals: IR ν 3257, 1738, 1566, 1318, 1142 cm^{-1}; ^1H NMR δ 0.93 (d, J = 5.8 Hz, 3 H), 1.41 (t, 9H), 2.30 (m, 3H), 3.15 (d, J = 11.1 Hz, 1H), 3.64 (s, 3H), 4.13 (q, 2H), 6.50 (d, J = 8.3 Hz, 1H), 6.87 (m, 2H), 9.08 (s, 1H); ^{13}C NMR δ 18.52 (q), 30.33 (d), 34.15 (t), 59.41 (d), 96.29 (s), 116.93 (d), 122.27 (d), 125.51 (d), 126.47 (d), 128.05 (s), 135.07 (s), 155.46 (s), 169.78 (s), 184.22 (s). Anal. calcd for $C_{18}H_{20}ClNO_3S$: C, 59.09; H,

5.52; Cl, 9.69; N, 3.83; S, 8.73. Found C, 58.80; H, 5.49; Cl, 9.47; N, 3.59; S, 8.77.

***trans*-3-Carbomethoxy-2,7-dimethyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-one (4g).** Prepared from **8a** and **7** (X = CH_3) as described for **4a** above. On recrystallization twice from methanol provided **4g** in 21.7% yield, mp 225 °C, as light-orange crystals: IR ν 3254, 1740, 1562, 1318, 1147 cm^{-1}; ^1H NMR δ 0.94 (d, J = 5.3 Hz, 3 H), 2.30 (m, 3H), 3.19 (d, J = 11.2 Hz, 1H), 3.62 (s, 3H), 6.49 (d, J = 8.0 Hz, 1H), 6.70 (m, 2H), 9.07 (s, 1H); ^{13}C NMR δ 18.64 (q), 30.30 (d), 34.18 (t), 59.43 (d), 96.10 (s), 115.72 (s), 119.38 (d), 126.50 (d), 128.11 (s), 135.07 (s), 155.56 (s), 170.34 (s), 184.13 (s). Anal. calcd for $C_{16}H_{17}NO_3S$: C, 63.35; H, 5.66; N, 4.62; S, 10.55. Found C, 63.29; H, 5.69; N, 4.68; S, 10.88.

***trans*-3-Carbethoxy-2,7-dimethyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-one (4h).** Prepared from **8b** and **7** (X = CH_3) as described for **4a** above. On recrystallization twice from ethanol provided **4h** in 21.9% yield, mp 224 °C, as light-orange crystals: IR ν 3278, 1723, 1588, 1285, 1156 cm^{-1}; ^1H NMR δ 0.93 (d, J = 5.1 Hz, 3 H), 1.19 (t, 3H), 2.31 (m, 3H), 3.14 (d, J = 11.8 Hz, 1H), 4.13 (q, 2H), 6.56 (d, J = 7.8 Hz, 1H), 6.76 (m, 2H), 9.16 (s, 1H); ^{13}C NMR δ 18.61 (q), 30.39 (d), 34.24 (t), 59.51 (d), 96.16 (s), 115.79 (s), 119.43 (d), 126.67 (d), 127.07 (s), 133.26 (s), 134.07 (s), 155.38 (s), 169.99 (s), 183.88 (s). Anal. calcd for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.05; N, 4.41; S, 10.08. Found C, 64.10; H, 5.83; N, 4.61; S, 10.18.

***trans*-7-Bromo-3-carbomethoxy-7-methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-one (4i).** Prepared from **8a** and **7** (X = Br) as described for **4a** above. On recrystallization twice from methanol provided **4i** in 13.9% yield, mp 188–191 °C, as light-orange crystals: IR ν 3258, 1740, 1562, 1281, 1152 cm^{-1}; ^1H NMR δ 0.93 (d, J = 5.7 Hz, 3H), 2.31 (m, 3H), 3.22 (d, J = 11.4 Hz, 1H), 3.64 (s, 3H), 6.57 (d, J = 8.3 Hz, 1H), 6.58 (m, 2H), 9.30 (s, 1H); ^{13}C NMR δ 18.66 (q), 30.38 (d), 34.22 (t), 59.45 (d), 96.24 (s), 117.09 (s), 122.33 (d), 125.63 (d), 126.60 (d), 128.21 (s), 134.98 (s), 155.63 (s), 170.39 (s), 184.33 (s). Anal. calcd for $C_{15}H_{14}BrNO_3S$: C, 48.93; H, 3.84; Br, 21.70; N, 3.80; S, 8.69. Found C, 49.09; H, 4.04; Br, 21.99; N, 3.89; S, 8.77.

***trans*-7-Bromo-3-carbethoxy-2-methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-one (4j).** Prepared from **8b** and **7** (X = Br) as described for **4a** above. On recrystallization twice from methanol provided **4j** in 56.7% yield, mp 203–205 °C, as light-orange crystals: IR ν 3280, 1728, 1590, 1280, 1160 cm^{-1}; ^1H NMR δ 0.93 (d, J = 5.9 Hz, 3H), 1.21 (t, 3H), 2.34 (m, 3H), 3.19 (d, J = 11.3 Hz, 1H), 4.18 (q, 2H), 6.59 (d, J = 8.6 Hz, 1H), 6.90 (m, 2H), 9.33 (s, 1H); ^{13}C NMR δ 18.46 (q), 30.44 (d), 34.20 (t), 60.33 (d), 96.53 (s), 116.88 (d), 122.30 (d), 125.50 (d), 126.42 (d), 128.02 (s), 135.22 (s), 155.18(s), 168.93 (s), 184.73 (s). Anal. calcd for $C_{16}H_{16}BrNO_3S$: C, 50.27; H, 4.23; Br, 20.90; N, 3.67; S, 8.37. Found C, 50.09; H, 4.29; Br, 20.53; N, 3.38; S, 8.54.

***trans*-7-Bromo-3-carbo-*tert*-butoxy-2-methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-one (4k) General procedure for trials 1–4.** Into a 100 mL two-neck pear shape flask equipped with an air condenser and a thermometer was added **8c** (6.79 g, 0.03 mol) and **7** (X = Br; 6.11 g, 0.03 mol) and 10 mL DMSO and the system purged with nitrogen. After solution, the flask was immersed into a thermostatically controlled oil bath at the temperatures listed in Table 2. After the elapsed time, the flask was removed, immediately immersed in an ice bath and stored in a freezer. Quantitative TLC isolated the desired product, 4k (Rf 0.85) from 7-bromo-2-methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-one (**4m**) (R_f 0.47).

General procedure for trial 5. The above experiment was repeated using 10 mL toluene and a reflux condenser. Compound **4k** was obtained as brownish red crystals, mp 196–198 °C, from toluene: IR ν 3264, 1740, 1573, 1327, 1159 cm^{-1}; ^1H NMR δ 0.93 (d, J = 5.7 Hz, 3 H), 1.43 (t, 9H), 2.32 (m, 3H), 3.18 (d, J = 11.3 Hz, 1H), 3.65 (s, 3H), 4.15 (q, 2H), 6.55 (d, J = 8.3 Hz, 1H), 6.92 (m, 2H), 9.12 (s, 1H); ^{13}C NMR δ 18.59 (q), 30.43 (d), 34.22 (t), 59.43 (d), 96.32 (s), 117.03 (d), 122.33 (d), 125.52 (d), 126.50 (d), 128.09 (s), 135.09 (s), 155.53 (s), 169.81 (s), 184.27 (s). Anal. calcd for $C_{18}H_{20}BrNO_3S$: C, 52.69; H, 4.92; Br, 19.47; N, 3.41; S, 7.80. Found C, 52.77; H, 4.49; Br, 19.89; N, 3.59; S, 7.77.

2-Methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-one (4l). (a) Compound **8c** (3.09 g, 13.7 mmol), **7** (R = H, 1.71 g, 13.7 mmol), and 10 mL of DMSO were added to a 100 mL round bottom flask and placed in an oil bath, and while stirring, the mixture was refluxed for 45 min. After refrigeration a solid formed. The crystals were filtered and the remaining mother liquor was poured into cold water, where a precipitate formed. The precipitates were dried, combined, and recrystallized from methanol with decolorizing carbon to provide **4l** in 15.4% yield, mp 282 °C (lit. 266–268 °C (dec.),[18] as light-orange crystals: IR ν 3248, 1577, 1259; ^1H NMR δ 0.97 (d, J = 4.4 Hz, 3H), 2.07 (m, 3H), 2.29 (t, J = 12.5 Hz, 2H), 6.55 (d, J = 8.1 Hz 1H), 6.74 (m, 3H), 8.88 (s, 1H); ^{13}C NMR δ 20.17 (q), 27.33 (d), 35.62 (t), 44.08 (d), 97.47 (s), 115.54 (d), 119.78 (d), 124.34 (d), 126.27 (d), 126.69 (s), 136.61 (s), 155.03 (s), 186.69 (s). Anal. calcd for $C_{13}H_{13}NOS$: C, 67.51; H, 5.68; N, 6.06; S, 13.84. Found C, 67.60; H, 5.49; N, 6.39; S, 13.77. (b) Compounds **10** and **7** were reacted under previously reported conditions[18] to provide authentic **4l** which was identical to that produced in method (a).

7-Bromo-2-Methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-one (4m). Employing the procedure (a) for **4l**, **4c** and **7** (R = Br) were refluxed for 45 min. Compound **4m** in 15.4% yield, mp 225–231 °C (dec.), as light-orange crystals: IR ν 3248, 1577, 1259; ^{1}H NMR δ 0.98 (d, J = 5.1 Hz, 3H), 2.06 (m, 3H), 2.29 (t, J = 12.5 Hz, 2H), 6.55 (d, J = 8.1 Hz 1H), 6.74 (m, 3H), 8.88 (s, 1H); ^{13}C NMR δ 20.17 (q), 27.31 (d), 35.54 (t), 43.99 (d), 97.35 (s), 115.35 (d), 117.06 (d), 122.90 (d), 128.14 (d), 129.32 (s), 134.14 (s), 154.88 (s), 188.83 (s). Anal. calcd for $C_{13}H_{11}BrNOS$: C, 50.34; H, 3.91; Br, 25.76; N, 4.52; S, 10.32. Found C, 50.86; H, 3.96; Br, 25.71; N, 4.40; S, 10.47.

X-ray crystal analysis

trans-3-Carbethoxy-2-methyl-2,3-dihydro-1*H*-phenothiazin-4[10*H*]-one, **4b**, was crystallized from an ethanol/water mixture. All experimental details related to the structural analysis are provided in Figure 2, Table 3 and supplemental material. The structure was solved by direct methods of the ShelXTLPC program and refined by the ShelXTL program.[27]

Pharmacology

Initial evaluations for anticonvulsant activity were performed by the Antiepileptic Drug Development (ADD) Program, Epilepsy Branch, Neurological Disorders Program, National Institute of Neurological Disorders and Stroke and included phases I, II, VIA and VIB test procedures which have been described.[19] These tests were performed in male Carworth Farms no. 1 (CF1) mice (Phases I and II) or male Sprague–Dawley rats (Phases VIA and VIB). Phase I and phase VIA of the evaluation included three tests: maximal electroshock (MES), subcutaneous (scMet), and the rotorod test for neurological toxicity (Tox). Compounds were suspended in 0.5% aqueous methylcellulose and were administered at three dosage levels (30, 100, and 300 mg/kg) with anticonvulsant activity and motor impairment noted 30 min and 4 h (and in some cases 2 h and 6 h) after administration. Phase II and phase VIB testing quantitated the anticonvulsant activity and motor impairment observed for the most promising compounds in phase I. Phase II quantified data in CF1 mice by intraperitoneal (ip) administration, while phase VIB provided oral rat data comparable to phase II ip data in mice. Data for the respective evaluations are provided in Tables 4 and 5. Phase V of the ADD testing protocol measured the ability of **4k** to provide protection against seizures induced by subcutaneous injection of the CD_{97} of the following convulsant agents: bicuculline (2.7 mg/kg), and picrotoxin (3.15 mg/kg). Male Sprague–Dawley rats were employed in this evaluation. Compound **4k** was uniformly inactive in this phase of testing. The TTE test[21] performed on **4l** is described as follows. Twenty mice were pretreated with 100 mg/kg of the test compound. At several time intervals (15 min, 30 min, 1 h, 2 h and 4 h) post treatment with the test compound, four mice at each time point were challenged with 12.5 mA of electrical current for 0.2 s via corneal electrodes. This stimulation produced a TTE seizure in the animals. For each time interval, results were expressed as a ratio of the number of animals protected over the number of animals tested.

Supplemental material

Additional X-ray crystal data is provided for **4b** (4 tables) and a unit cell of **4b** and is available from the authors.

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