Synthesis and Anticonvulsant Activity of 2(3*H*)-Benzoxazolone and 2(3*H*)-Benzothiazolone Derivatives

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A series of 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone derivatives were synthesized and evaluated for anticonvulsant activity. The compounds were assayed, intraperitoneally in mice and per os in rats, against seizures induced by maximal electroshock (MES) and pentylenetetrazole (scMet). Neurologic deficit was evaluated by the rotarod test. The compounds were prepared to determine the relationship between the 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone derivatives' structures and anticonvulsant activity. Several of these compounds showed significant anticonvulsant activity. Compounds **43** and **45** were the most active of the series against MES-induced seizures with ED_{50} values of 8.7 and 7.6 mg/kg, respectively. Compound **45** displayed good protection against MES-induced seizures and low toxicity in rats with an oral ED_{50} of 18.6 mg/kg and a protective index (PI = TD_{50}/ED_{50}) of <26.9. In vitro receptor binding studies revealed that compounds **43** and **45** bind to σ_1 receptors with nanomolar affinities.

Introduction

Epilepsy is the most frequent neurologic affection characterized by excessive temporary neuronal discharge.[1] The overall prevalence of the disease is 0.5−0.8% of the general population.[2] Many patients with epilepsy do not respond well to currently available antiepileptic drugs such as phenobarbital, phenytoin, carbamazepine, valproate, vigabatrin, lamotrigine, and felbamate, which are effective toward only 60−80% of patients and present some undesirable side effects such as headache, nausea, anorexia, ataxia, hepatotoxicity, drowsiness, gastrointestinal disturbance, gingival hyperplasia, and hirsutism.[3−7]

Consequently, a real need exists to develop new anticonvulsant compounds to cover seizures which are so far resistant to presently available drugs. A strategy along this line is to search for compounds with new modes of action.[8] This heurystic approach, initially not mechanism-based, has been facilitated by the existence of a screening program performed by the Anticonvulsant Drug Development (ADD) Program, Epilepsy Branch, National Institutes of Health, Bethesda, MD.[31]
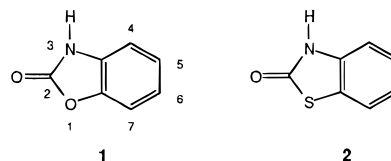
6-Methoxybenzoxazolone derivative is present in plants,[9,10] and the "naked" heterocycle was first synthesized by Groenwick[11] in 1876. Since the pioneering discovery of the hypnotic properties of 2(3*H*)-benzoxazolone (**1**) over these last 20 years, the 2(3*H*)-benzoxazolone ring became an important building block in medicinal chemistry and led to the discovery of a

Scheme 1. Synthesis of Compounds **3**−**12** (X = O, S; R = alkyl, benzyl)[a]
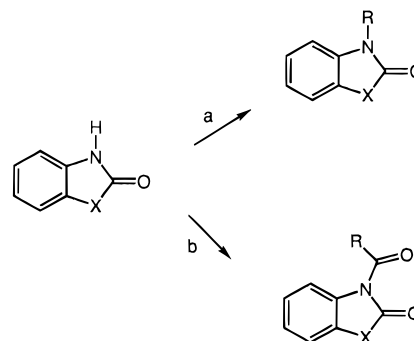
[a] Conditions: (a) K_2CO_3−DMF, RCl, 125 °C; (b) THF−TEA, RCOCl or (RCO)$_2$O, reflux, 2 h.

number of derivatives endowed with antiepileptic, analgesic, antiinflammatory, antispasmodic, antitubercular, antibacterial, antimicrobial, antifungal, and normolipemic effects.[12−20] The 2(3*H*)-benzoxazolone ring can be considered as a cyclic bioisosteric analogue of pyrocatechol.[21] 2(3*H*)-Benzothiazolone (**2**), the sulfur bioisoster of 2(3*H*)-benzoxazolone, led to the synthesis of various serotonine receptor ligands.[22,23]

Previously, Dalkara et al. (1988) described the anticonvulsant activity of a series of 3-(2-hydroxyethyl)-benzoxazolone and 3-(2-oxoethyl)benzoxazolone deriva-

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Scheme 2. Synthesis of Compounds **13**−**45** (X = O, S; R = H, alkyl, aryl; R^1 = alkylamino; n = 2 or 3)[a]
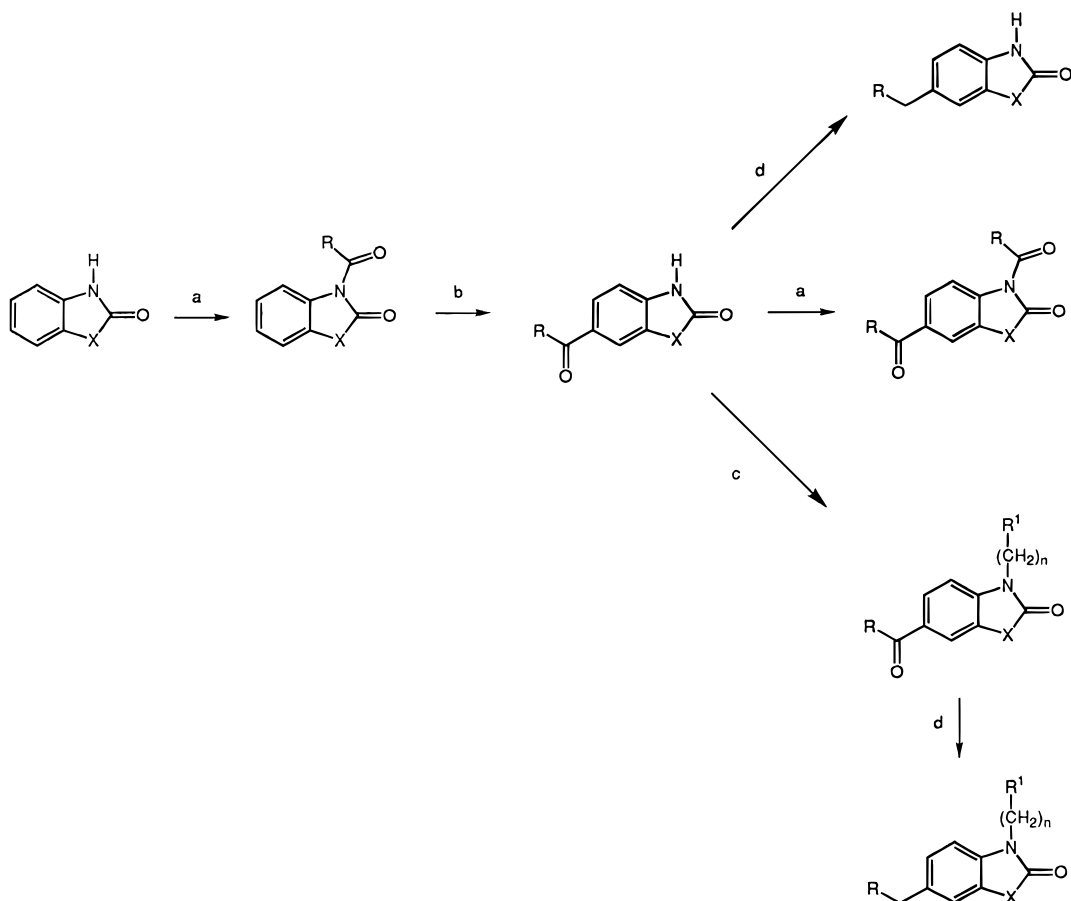
[a] Conditions: (a) RCOCl or (RCO)$_2$O, TEA, THF, reflux, 2 h; (b) AlCl$_3$, 165 °C, 3 h; (c) K$_2$CO$_3$−DMF; (d) triethylsilane−trifluoroacetic acid.

tives.[24] This activity was evidenced at high doses (300 mg/kg) against maximal electroshock (MES)- or pentylenetetrazole (scMet)-induced seizures in mice.

In this study, we report the synthesis, the pharmacological evaluation, and the structure−activity relationships of new series of 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone derivatives.

Selection of Compounds

In the MES test, 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone showed low anticonvulsant activity in mice (Table 2). In addition, the anticonvulsant activity of some benzoxazolone derivatives substituted on the 3-position was previously reported.[24]

We previously developed a very efficient synthesis of 6-acylated derivatives[26,27] of **1** and **2**. It was thus an interest to explore the impact of various combinations of 3- and 6-substitutions on the antiepileptic activity in this series. Therefore, we conducted systematic structural variations at either the 3- or 6-position. Fourty-five derivatives were obtained.

The substituent on the 3-position has been systematically modified from hydrogen to methyl, to benzyl, and to acyl groups, compounds **3**−**12**. The 6-position was substituted with acyl groups, compounds **13**, **15**, **17**, and **18**, or alkyl groups, compounds **20**−**25**. Compounds **26** and **27** are 3,6-diacyl derivatives. The other compounds (**14**, **16**, **19**, **28**−**45**) bear various substituents on both the 3- and 6-positions.

Chemistry

All the compounds were synthesized by classical procedures (Schemes 1 and 2) and were characterized by IR, ¹H NMR, ¹³C NMR, and elemental analysis. The 3-alkyl derivatives **3**−**6**, **14**, **16**, **19**, **28**−**30**, and **32**−**44** were prepared by reaction of an ω-halogenoalkyl derivative with 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone in a mixture of K$_2$CO$_3$/DMF heated[25] at 125 °C. The 3-acylbenzoxazolones and 3-acylbenzothiazolones **7**−**12**, **26**, and **27** were synthesized by heating under reflux 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone derivatives with acid anhydrides or acyl halides in THF in the presence of triethylamine.[26,27] The 3-acyl derivatives were subsequently rearranged in a "Fries-like"[27,36] type of process to give 6-acyl derivatives **13**, **15**, **17**, and **18** by heating a melt of 3-acyl derivatives and AlCl$_3$ at 165 °C for 3 h. 6-Alkyl derivatives **20**−**25**, **31**, and **45** were obtained directly from the reduction of 6-acyl derivatives. This reaction required a reducing medium, with 2 M triethylsilane in trifluoroacetic acid and a long reaction time[29] (30 h).

The physicochemical properties of 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone derivatives are reported in Table 1.

Results and Discussion

The compounds were tested for anticonvulsant activity by using the procedures described previously.[30−32] The initial evaluation (phase I) of anticonvulsant activity of synthesized compounds is presented in Table 2.

Table 1. Physical and Chemical Data[a]
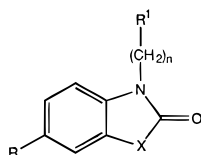
compd	X	n	R	R^1	yield (%)	mp (°C)	cryst solvent	anal.[b]
1	O	0	H	H	65	137−139	toluene	C, H, N
2	S	0	H	H	70	139	toluene	C, H, N, S
3[c]	O	0	H	CH_3	90	86	EtOH	C, H, N
4[e]	O	0	H	$CH_2C_6H_5$	88	123−124	EtOH	C, H, N
5[d]	S	0	H	CH_3	90	72−74	2-propanol	C, H, N, S
6[e]	S	0	H	$CH_2C_6H_5$	90	88−89	EtOH	C, H, N, S
7[f]	O	0	H	C_2H_5CO	99	93−95	EtOH	C, H, N
8[f]	O	0	H	C_6H_5CO	95	172−173	EtOH	C, H, N
9[f]	S	0	H	C_2H_5CO	97	86−88	EtOH	C, H, N, S
10[h]	S	0	H	C_6H_5CO	98	87−88	EtOH	C, H, N, S
11[f]	O	0	H	CH_3CO	94	95−96	EtOH	C, H, N
12[f]	S	0	H	CH_3CO	96	61−63	EtOH	C, H, N, S
13[f]	O	0	C_2H_5CO	H	88	205	EtOH	C, H, N
14[g]	O	0	C_2H_5CO	CH_3	75	157−158	EtOH	C, H, N
15[f]	O	0	C_6H_5CO	H	80	169−170	EtOH	C, H, N
16[g]	O	0	C_6H_5CO	CH_3	76	147−149	EtOH	C, H, N
17[f]	S	0	C_2H_5CO	H	83	204−205	EtOH	C, H, N, S
18[h]	S	0	C_6H_5CO	H	85	216−217	EtOH	C, H, N, S
19	O	0	C_4H_9CO	CH_3	72	139−140	EtOH	C, H, N
20	O	0	C_3H_7	H	90	105−106	cyclohexane	C, H, N
21	O	0	C_5H_{11}	H	90	88−89	cyclohexane	C, H, N
22	O	0	$CH_2C_6H_5$	H	92	144−145	cyclohexane	C, H, N
23	O	0	$CH_2C_6H_4(p\text{-}F)$	H	89	160−161	cyclohexane	C, H, N
24	S	0	C_3H_7	H	90	124−125	cyclohexane	C, H, N, S
25	S	0	C_5H_{11}	H	92	80−82	cyclohexane	C, H, N, S
26	S	0	C_2H_5CO	C_2H_5CO	90	118−119	EtOH	C, H, N, S
27	S	0	C_4H_9CO	CH_3CO	88	81−83	EtOH	C, H, N, S
28	O	2	C_6H_5CO	$(CH_3)_2N$	70	104−106	EtOH	C, H, N
29	O	2	C_6H_5CO	C_4H_8NO	72	127−129	EtOH	C, H, N
30	O	2	C_6H_5CO	$C_5H_{10}N$	75	154−156	EtOH	C, H, N
31	O	2	$CH_2C_6H_5$	C_4H_8NO	88	92−94	abs EtOH	C, H, N
32	S	2	C_6H_5CO	C_4H_8NO	80	116−118	EtOH	C, H, N, S
33	S	2	C_6H_5CO	C_4H_8N	75	96−98	EtOH	C, H, N, S
34	O	2	C_4H_9CO	$C_5H_{10}N$	80	82−83	EtOH	C, H, N
35	O	3	C_4H_9CO	$C_5H_{10}N$	82	109−111	EtOH	C, H, N
36	S	2	C_4H_9CO	$(CH_3)_2N$	78	66−68	EtOH	C, H, N, S
37	S	2	C_4H_9CO	C_4H_8NO	80	63−65	EtOH	C, H, N, S
38	O	2	C_2H_5CO	$C_5H_{10}N$	78	123−125	EtOH	C, H, N
39	O	3	C_2H_5CO	$C_5H_{10}N$	86	91−93	EtOH	C, H, N
40	S	2	C_2H_5CO	$(CH_3)_2N$	70	111−113	EtOH	C, H, N, S
41	S	2	C_2H_5CO	C_4H_8NO	75	133−135	EtOH	C, H, N, S
42	S	2	C_2H_5CO	C_4H_8N	78	79−80	EtOH	C, H, N, S
43	S	2	C_2H_5CO	$C_5H_{10}N$	80	97−98	EtOH	C, H, N, S
44	S	3	C_2H_5CO	$C_5H_{10}N$	84	92−94	EtOH	C, H, N, S
45	S	2	C_3H_7	$C_5H_{10}N$	90	147−149	abs EtOH	C, H, N, S

[a] The ^1H and ^{13}C NMR spectra were consistent with assigned structures. [b] All compounds gave satisfactory C, H, N (and S, when required) analyses (±0.4%). [c] Data from ref 20. [d] Data from ref 22. [e] Data from ref 25. [f] Data from ref 27. [g] Data from ref 28. [h] Data from ref 26.

The compounds were administered intraperitoneally at three doses (30, 100, and 300 mg/kg). Three tests were performed for each compound: maximal electroshock (MES)-induced convulsions, subcutaneous Metrazol (sc-Met)-induced convulsions, and rotarod neurotoxicity test (Tox).

As a result of preliminary screening, compounds **3**, **5**, **21**−**23**, **25**, **26**, **28**, **31**, **33**, **36**, **38**, **40**−**43**, and **45** were considered for phase II trials for quantification of their anticonvulsant activity and neurotoxicity in mice. This phase provides an evaluation of the median effective dose (ED_{50}) and the median neurotoxic dose[33] (TD_{50}). The 95% confidence interval, the slope of the regression line, and the SE of the slope were then calculated.[34] These data are shown in Table 3 in which are also included for comparison data for marketed antiepileptic drugs such as phenytoin, carbamazepine, phenobarbital, and valproate. Some of these derivatives showed a high degree of protection against MES-induced seizures. They were found less effective against scMet-induced seizures. Compound **45** was the best protection against MES with an ED_{50} of 7.6 mg/kg and a PI of 3.9. In the MES test, the ED_{50} of compounds **43** (8.7 mg/kg, PI = 5.3) and **45** (7.6 mg/kg) compared favorably with that of phenytoin (9.5 mg/kg) and carbamazepine (8.8 mg/kg). Compound **26** (ED_{50} = 19.4 mg/kg) had a pharmacological profile similar to that of phenobarbital; its PI (7.5) however was significantly higher (3.2).

The activity per os of these compounds in rats was also evaluated. They were found to be effective against MES but were ineffective against scMet-induced seizures. On the basis of the significant anticonvulsant

Table 2. Anticonvulsant and Toxicity Screening Data in Mice (ip)

compd	MES[a,b]		sc Met[a,c]		rotarod toxicity[a,d]	
	30 min	4 h	30 min	4 h	30 min	4 h
1	++	−	−	−	+	−
2	++	+	++	+	++	+
3	++	+	++	−	++	+
5	+++	++	++	+	+++	+++
13	+	−	−	−	−	−
14	++	−	++	−	++	−
15	++	−	−	−	−	−
16	++	−	+	−	-	−
17	+	−	−	−	−	−
20	++	+	++	−	++	+
21	++	+	++	−	++	−
22	++	++	++	+	++	+
23	++	++	++	+	++	+
24	++	++	+	+	++	+
25	++	++	+	+	++	+
26[e]	+++	−	−	−	+	−
27	++	+	+	+	++	−
28	++	+	−	−	−	+
31	++	++	−	−	+	−
33	++	+	−	−	+	++
34	++	−	−	−	++	−
35	++	+	−	−	++	−
36	+++	−	−	−	++	−
37	++	+	−	−	++	+
38	++	−	−	−	++	−
39	++	−	−	−	+++	+++
40	+++	+	−	−	+	+
41	++	−	+	−	++	−
42	+++	−	−	−	++	−
43[e]	+++	+	−	−	+	−
44	+++	−	−	−	+++	−
45[e]	+++	−	−	−	+	−

[a] Key: +++ = activity at 30 mg/kg, ++ = activity at 100 mg/kg, + = activity at 300 mg/kg, − = no activity or no toxicity at 300 mg/kg. [b] Maximal electroshock seizure test. [c] Subcutaneous pentylenetetrazole seizure test. [d] Neurologic toxicity (rotarod) test. [e] Data from ref 35.

activity and the favorable protective index evidenced in the preliminary screening, compounds **3**, **5**, **22**, **23**, **25**, **26**, **43**, and **45** were selected for the quantification of their anticonvulsant activity and of their neurotoxicity in rats. These data and those of the prototype anticonvulsants are shown in Table 4. As observed in mice, compounds **43** and **45** displayed high protection against MES-induced seizures (ED$_{50}$ = 27.2 and 18.6 mg/kg, respectively).

The following structure−activity relationships were observed. In the series of 3-alkyl and 3-acyl derivatives (**3**−**12**), only compounds **3** and **5**, bearing a methyl group on the 3-position, showed a high degree of protection against MES-induced seizures. For this reason, compounds **3** and **5** were subjected to phase II (quantification, Table 3) which provided MES ED$_{50}$ values of 50.2 mg/kg (PI = 2.3) and 24.3 mg/kg (PI = 2.3), respectively. Benzothiazolone derivatives are generally more effective than benzoxazolone derivatives against MES-induced seizures. The 3-acylation of the parent heterocycles was found unfavorable (**7**−**12** were inactive compounds). The acylation on the 6-position of 3-H or 3-CH$_3$ compounds gave inactive derivatives (**13**−**19**). The reduction of the carbonyl group situated on the 6-position of the 6-acyl derivatives (**13**−**19**) to a methylene group, giving compounds **20**−**25**, induced a significant increase of anti-MES activity. Of these compounds, **25** was the most potent against MES-induced seizures (ED$_{50}$ = 58.9 mg/kg).

The amino substituents on the 3-position of 6-acyl derivatives (**28**−**30**, **32**−**44**) enhanced significantly the anticonvulsant activity of these compounds. The maximal anti-MES protection was reached with 6-propanoylbenzothiazolone alkylated on the 3-position with a piperidinoethyl moiety (compound **43**, ED$_{50}$ = 8.7 mg/kg, PI = 5.3). The pyrrolidinoethyl (compound **42**, ED$_{50}$ = 13.9 mg/kg) and (dimethylamino)ethyl (compound **40**, ED$_{50}$ = 21.8 mg/kg) derivatives were less active against MES-induced seizures, while the morpholinoethyl derivative (compound **41**, ED$_{50}$ = 62.1 mg/kg) was far less active in the MES test. Compound **26**, where the alkyl chain situated on the 3-position including the piperidine ring was replaced by a propanoyl moiety, exhibited high protection and an excellent protective index (MES ED$_{50}$ = 19.4 mg/kg, PI = 7.5). This observation suggests therefore that the piperidine moiety is not an essential feature for attaining high protection against MES-induced seizures.

The lengthening of the alkyl chain, situated between the nitrogen of the heterocycle and the amino moiety, from two (compound **43**, MES ED$_{50}$ = 8.7 mg/kg) to three (compounds **35**, **39**, and **44**) methylene groups increased significantly the neurotoxicity, and no separation was observed between anti-MES activity and neurotoxicity for these compounds.

The side chain situated on the 6-position of 3-alkylbenzothiazolones had a great influence on the anti-MES activity. The maximal anti-MES activity was observed in 3-alkyl derivatives having a propanoyl group on the 6-position (compound **42**, MES ED$_{50}$ = 13.9 mg/kg), while the 6-benzoyl derivative (compound **33**, MES ED$_{50}$ = 42.5 mg/kg) displayed less activity against MES-induced seizures. The reduction of the acyl group of 3-alkylamino compounds (compound **43**, MES ED$_{50}$ = 8.7 mg/kg, PI = 5.3) situated on the 6-position to the corresponding alkyl group (compound **45**, MES ED$_{50}$ = 7.6 mg/kg, PI = 3.9) induced no change of anti-MES activity but increased slightly the neurotoxicity.

In vitro receptor binding studies were performed for the most potent anti-MES compounds: **26**, **28**, **31**, **33**, **36**, **38**, **42**, **43**, and **45**. These compounds were evaluated for their σ_1 and σ_2 affinity in competition binding experiments using [^{3}H]-(+)-pentazocine and [^{3}H]-1,3-di-(2-tolyl)guanidine ([^{3}H]DTG) in the presence of an excess of N-allylnormetazocine, respectively, as previously described.[35] These in vitro studies revealed that these compounds had high affinity and selectivity for σ_1 binding sites[35] (Table 5). Indeed, compounds **43** and **45**, which were the most active against MES-induced seizures with ED$_{50}$ values of 8.7 and 7.6 mg/kg, respectively, were found to have nanomolar affinities for σ_1 subtype receptors (K_i = 47 ± 5 and 0.6 ± 0.3 nM, respectively). In addition, compounds **39**, **44**, and **45** had no affinity to muscarinic M$_2$, dopamine D$_2$, serotonin 5-HT$_2$, and μ, δ, and κ opioid receptors.[35]

From the in vivo data and the in vitro binding data, it seems that the anticonvulsant activity of new compounds described here, at least in the case of 6-acyl and 6-alkyl derivatives alkylated on the 3-position with a secondary amine moiety (compounds **28**−**45**) or acylated on the 3-position with an acyl group (compounds **26** and **27**), might perhaps be mediated, at least in part, by their interaction with σ_1 receptors. This conclusion remains

Table 3. Phase II Quantitative Anticonvulsant Data in Mice (test drug administered ip)

compd	ED_{50}[a] MES	ED_{50}[a] scMet	TD_{50}[b]	PI[c] MES	PI[c] scMet	TPE[d] activity	TPE[d] toxicity
3	50.2 (41.8−52.8)[e]	132 (117−152)	113 (97−126)	2.3	0.85	0.25	0.25
5	24.2 (18.4−28.9)	>100	55.2 (38.3−68.4)	2.3	<0.55	0.25	0.25
21	70.8 (67.3−76.6)	80.7 (67.8−100)	168 (145−190)	2.4	2.1	0.5	1.0
22	68.3 (48.9−79.7)	77.2 (61.0−91.5)	164 (121−205)	2.4	2.1	0.5	1.0
23	125 (116−132)	218 (131−308)	356 (293−435)	2.8	1.6	1.0	1.0
25	58.9 (41.2−77.0)	90.5 (79.5−102)	137 (114−161)	2.3	1.5	0.25	0.5
26	19.4 (18.4−20.4)	>300	145 (109−185)	7.5	<0.48	0.25	0.25
28	84.6 (76.6−99.9)	>120	99 (91−111)	1.2	<0.82	0.25	0.25
31	87 (72.4−105)	>225	194 (106−218)	2.2	<0.86	1.0	1.0
33	42.5 (35.1−50.6)	>210	170 (145−195)	4.0	<0.81	0.25	0.25
36	27.3 (23.1−31.8)	>70	61.5 (52.2−69.2)	2.8	<0.87	0.25	0.25
38	61 (53−70.4)	>100	72.9 (58.6−83.2)	1.2	<0.72	0.25	0.25
40	21.8 (17.9−27.4)	>130	84.5 (38.5−57.5)	3.1	<0.65	0.25	0.25
41	62.1 (44.7−81.7)	>300	239 (186−284)	3.9	<0.80	0.25	0.25
42	13.9 (13.1−14.7)	>80	48.4 (38.5−57.5)	3.5	<0.60	0.25	0.25
43	8.7 (7−10)	>55	46.3 (43.1−49.3)	5.3	<0.84	0.25	0.25
45	7.6 (6.2−9.3)	>75	29.4 (25.5−35.1)	3.9	<0.39	0.25	0.25
phenytoin	9.5 (8.1−10.4)	>300	65.5 (52.5−72.9)	6.9	<0.22		
carbamazepine	8.8 (5.5−14.1)	>100	71.6 (45.9−135)	8.1	<0.72		
phenobarbital	21.8 (15−25.5)	13.2 (5.8−15.9)	69 (62.8−72.9)	3.2	5.2		
valproate	272 (247−338)	149 (123−177)	426 (369−450)	1.6	2.9		

[a] Doses measured in mg/kg at the time of peak effect. [b] Dose (mg/kg) determined by rotarod test at the time of peak neurotoxic effect. [c] Protective index: PI = TD_{50}/ED_{50}. [d] Time of peak effect (TPE) in h. [e] 95% confidence limits.

very speculative in view of the bias introduced by the metabolic and pharmacokinetic behavior of the compounds tested. In fact, it has been reported that several σ_1 ligands such as dextrometorphan, caramiphen, and carbetapentane[37,38] protected rats against MES-induced seizures, an effect which was potentiated in the presence of the anticonvulsant drug phenytoin and not associated with any cholinergic activity,[39] and ifenprodil and dextrometorphan block the NMDA-induced seizures.[40] It has been suggested that the anticonvulsant activity exerted by some σ ligands may be also mediated by their interaction with NMDA receptor−ion channel complex[41] or by blocking Ca^{2+} channels.[42] Calcium influx via voltage-activated Ca^{2+} channels also plays a role in epileptogenesis and neurodegenerative events,[43] raising the possibility that the blockade of Ca^{2+} channels may represent an additional mechanism of action of the σ site ligands. Indeed, several lines of evidence have pointed to a possible interaction of σ ligands with voltage-activated Ca^{2+} channels.[42] σ Binding sites may be associated with neuronal Ca^{2+} channels, and different Ca^{2+} channels blockers are competitive for σ binding sites.[42] Accordingly, different mechanisms could be

taken into consideration to explain the anticonvulsant activity of the novel compounds here described.

Experimental Section

Uncorrected melting points were determined using an Electrothermal melting point apparatus. The IR spectra (KBr pellets) were recorded on a Perkin-Elmer 457 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AC 300 spectrometer with TMS as internal standard, and the chemical shifts are reported in parts per million (δ, ppm). All compounds were found homogeneous in TLC (Merck silica gel 60F$_{254}$, ethyl acetate/acetone, 3/2, v/v). Elemental analyses (C, H, N, and S) were performed by the Medicinal Chemistry Laboratory of the University of Liège, and the analytical results for the elements were within 0.4% of the theoretical values. THF was redistilled over a bed of LiAlH$_4$. DMF (Gold label grade), AlCl$_3$, and PPA were purchased from Aldrich.

General Procedure for the Synthesis of 3-Acyl-2(3H)-benzoxazolone and 3-Acyl-2(3H)-benzothiazolone Derivatives (Compounds 7−12, 26, and 27). The acyl chloride (12 mmol) was added dropwise over 15 min to a solution of 2(3H)-benzoxazolone [or 6-acyl-2(3H)-benzoxazolone] or 2(3H)-benzothiazolone [or 6-acyl-2(3H)-benzothiazolone] (10 mmol) and dry TEA (30 mmol) in 10 mL of dry THF cooled at ~4 °C. The stirred reaction mixture was refluxed for 2 h, added to 200 mL of ice, and stirred for 1 h. The resulting precipitate

Table 4. Phase IV Quantitative Anticonvulsant Data in Rats (compounds given per os)

compound	dose (mg/kg)	time (h)	MES[a]	Tox[b]	ED$_{50}$[c]	TD$_{50}$[c]	PI
3	30	0.25	4/4	0/4	30.6	>500	16.4
		0.50	2/4	0/4	(19.9−40.7)	(nd)	
		1.00	1/4	0/4			
		2.00	0/4	0/4			
		4.00	0/4	0/4			
5	25	0.25	2/4	0/4	16.2	140	8.6
		0.50	2/4	0/4	(10.4−22.2)	(119−165)	
		1.00	4/4	0/4			
		2.00	3/4	0/4			
		4.00	2/4	0/4			
22	25	0.25	0/4	0/4	23.1	>500	21.7
		0.50	3/4	0/4	(14.3−36.6)	(nd)	
		1.00	3/4	0/4			
		2.00	2/4	0/4			
		4.00	2/4	0/4			
23	20	0.50	0/4	0/4	11.9	>220	18.5
		1.00	1/8	0/4	(7.4−17.6)	(nd)	
		2.00	1/8	0/4			
		4.00	1/8	0/4			
		6.00	6/8	0/4			
		8.00	1/4	0/4			
25	50	0.25	4/8	0/4	50.5	>120	2.4
		0.50	3/8	0/4	(34.4−73.1)	(nd)	
		1.00	4/8	0/4			
		2.00	5/8	0/4			
		4.00	4/8	0/4			
		6.00	0/4	0/4			
26	30	0.25	3/4	0/4	32.4	nd	
		0.50	2/4	0/4	(21.9−46.1)		
		1.00	1/4	0/4			
		2.00	0/4	0/4			
		4.00	0/4	0/4			
43	40	0.25	3/4	0/4	27.2	>110	4.0
		0.50	3/4	0/4	(16.7−41.3)	(nd)	
		1.00	1/4	0/4			
		2.00	1/4	0/4			
		4.00	0/4	0/4			
45	30	0.25	3/4	0/4	18.6	<500	26.9
		0.50	3/4	0/4	(12.3−26.1)	(nd)	
		1.00	1/4	0/4			
		2.00	0/4	0/4			
		4.00	1/4	0/4			
phenytoin[d]					29.8	>3000[e]	>100
					(22−39)		
carbamazepine[d]					8.50	813[e]	95.7
					(3−11)	(489−1234)	
valproate[d]					490	280[e]	0.6
					(351−728)	(191−353)	

[a] Maximal electroshock test (number of animals protected/number of animals tested). [b] Rotarod toxicity (number of animals exhibiting toxicity/number of animals tested). [c] ED$_{50}$ and TD$_{50}$ values are in mg/kg of test drug delivered orally. [d] Values from ref 33. [e] Tox data based on ataxia. nd, not determined.

was filtered by suction through a Buchner funnel, washed with cold water, dried, and recrystallized from ethanol.[27]

General Procedure for the Synthesis of 3-Alkyl-2(3H)-benzoxazolone and 3-Alkyl-2(3H)-benzothiazolone Derivatives (Compounds 3−6, 14, 16, 19, 28−30, and 32−44). Anhydrous K$_2$CO$_3$ (5.52 g, 40 mmol) and the halogenoalkylamine (15 mmol) were added, under mechanical stirring, to a solution of 6-acyl-2(3H)-benzoxazolone **7−12** (10 mmol) or 6-acyl-2(3H)-benzothiazolone (10 mmol) in anhydrous DMF (10 mL, 133 mmol). The reaction mixture was heated at 125 °C for 2 h. After cooling, the reaction mixture was poured onto ice (200 mL), and the resulting precipitate was filtered (Buchner funnel), washed with cold water, dried, and recrystallized from ethanol.[25]

General Procedure for the Synthesis of 6-Acyl-2(3H)-benzoxazolone and 6-Acyl-2(3H)-benzothiazolone Derivatives by "Fries-like" Reaction (Compounds 13, 15, 17, and 18). An intimate mixture of 3-acylbenzoxazolone or 3-acylbenzothiazolone (10 mmol) and AlCl$_3$ (3.33 g, 25 mmol) was slowly (30 min) brought to 165 °C using an oil bath. This temperature was maintained for 3 h, and after cooling, the resulting dark residue was decomposed by addition of 100 mL

of 0.1 N HCl. The resulting precipitate was stirred for 30 min, filtered (Buchner funnel), washed with cold water, dried, and recrystallized from ethanol.[27]

General Procedure for the Synthesis of 6-Alkyl-2(3H)-benzoxazolone and 6-Alkyl-2(3H)-benzothiazolone Derivatives (Compounds 20−25, 31, and 45). Triethylsilane (7.2 mL, 45 mmol) was added dropwise to a stirred solution of 6-acylbenzoxazolone or 6-acylbenzothiazolone derivatives (20 mmol) at room temperature in trifluoroacetic acid[29] (15 mL). The mixture was stirred at room temperature for 30 h and then poured onto ice. The resulting precipitate was stirred for 1 h, filtered (Buchner funnel), washed with cold water, dried, and recrystallized from an appropriate solvent (see Table 1).

Pharmacological Methods. Maximal electroshock seizure test, pentylenetetrazole test, and rotarod test were carried out by the ADD Program, Epilepsy Branch, National Institutes of Health, Bethesda, MD (Porter 1984).[31]

All compounds were tested for anticonvulsant activity with male Carworth Farms #1 mice in the 18−25-g weight range. Each compound was administered intraperitoneally at three

Table 5. Affinities of 2(3*H*)-Benzoxazolone and 2(3*H*)-Benzothiazolone Derivatives for σ Receptor Subtypes[a]

compd	K_i (nM)		σ_2/σ_1
	σ_1	σ_2	
26	63 ± 4	670 ± 40	11
28	365 ± 15	>10000	>27
31	72 ± 6	515 ± 25	7
33	54 ± 3	225 ± 16	4
36	628 ± 40	4612 ± 525	7
38	72 ± 6	900 ± 42	13
42	571 ± 42	919 ± 87	1.6
43	47 ± 5	481 ± 21	10
45	0.6 ± 0.3	18.1 ± 6.2	29

[a] Data from ref 35. Affinity constant (K_i) values are the mean $\pm$ SEM of three separate experiments, each carried out in duplicate. A one-site model was the best fit to all curves. All Hill's coefficients were not significantly different from unity ($P > 0.05$). σ_1 Binding assays were performed in guinea pig brain using [^{3}H]-(+)-pentazocine. σ_1 Binding assays were determined in guinea pig brain using [^{3}H]DTG in the presence of an excess of (+)-NANM to mask σ_1 binding sites.

dose levels (30, 100, and 300 mg/kg). The compounds were suspended in 0.5% methylcellulose.

Maximal electroshock seizures (MES) were induced 30 min after drug treatment by application of a 60-Hz current of 50 mA for 0.2 s via corneal electrodes into the eyes. The protection was defined as the abolition of hind-leg tonic maximal extension component of the seizure. The subcutaneous pentylenetetrazole (Metrazol) seizure threshold test (sc-Met) was carried out by an intraperitoneally administration of pentylenetetrazole (85 mg/kg in mice and 70 mg/kg in rats). Animals were observed over 30 min. Failure to observe the generalized clonic seizure is defined as protection.

Minimal neurotoxicity (TD$_{50}$) was measured by the rotarod test (Tox) previously reported.[32] Mice were placed on a 1-in. diameter knurled plastic rod rotating at 6 rpm after the administration of the drug, and their ability to maintain their balance was tested. Neurological deficit was indicated by the inability of the animal to maintain its equilibrium for 1 min on the rotating rod in each of three trials.

Supporting Information Available: Spectral (IR, ^{1}H NMR, and ^{13}C NMR) data for compounds **19**−**45** (11 pages). Ordering information is given on any current masthead page.

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