Anticonvulsant Activities of Phenyl-Substituted Bicyclic 2,4-Oxazolidinediones and Monocyclic Models. Comparison with Binding to the Neuronal Voltage-Dependent Sodium Channel

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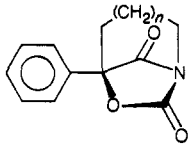
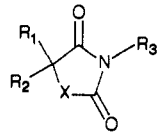
8,9-Dioxo-6-phenyl-1-aza-7-oxabicyclo[4.2.1]nonane (1) and 9,10-dioxo-7-phenyl-1-aza-8-oxabicyclo[5.2.1]decane (2), examples of anti-Bredt bicyclic 2,4-oxazolidinediones, were investigated as anticonvulsants in mice. Compound 2 was the more potent (anti-MES ED_{50} = 66 mg/kg), and its in vivo anti-MES effect was consistent with its in vitro potency of binding to the voltage-sensitive sodium channel (IC_{50} = 160 μM for the inhibition of binding of [^{3}H]BTX-B), suggesting that 2 may be a new class I anticonvulsant. Several partial structures of 2, either monocyclic lactams or monocyclic 2,4-oxazolidinediones, were also evaluated in these assays, but no correlation was observed between sodium channel binding and anti-MES effects. A significant finding was that monocyclic 5-alkyl-5-phenyl-2,4-oxazolidinediones provided relatively potent, nontoxic, broad-spectrum anticonvulsants.

Anti-Bredt bicyclic imides related to the cyclic imide anticonvulsants were originally proposed by Edward E. Smissman.[1] Our interest in these structures,[2] which we have named "smissmanones", led us to develop the first reported syntheses[3] of examples from this class, smissmanones 1 and 2, which are bicyclic 2,4-oxazolidinediones.



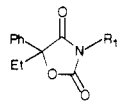
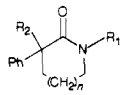


	n		X	R_1	R_2	R_3
1	2	trimethadione	O	CH_3	CH_3	CH_3
2	3	phenytoin	NH	Ph	Ph	H

Recently, the identification of molecular mechanisms of action for the anticonvulsants has received considerable attention. Numerous studies suggest that different structures act at different receptor sites, and in fact a division of anticonvulsants into three classes according to effects on seizures and interactions at receptor sites has been proposed.[4] The class I anticonvulsants act at the neuronal voltage-dependent sodium channel, the class II anticonvulsants act at GABA receptors, and class III anticonvulsants do not currently reveal a satisfactory mechanism of action. In addition to these, it now appears that a fourth class exerts its primary effect by interacting with excitatory amino acid receptors, particularly those for *N*-methyl-D-aspartate (NMDA).[5] Other mechanisms are under investigation.

3,5,5-Trimethyl-2,4-oxazolidinedione (trimethadione) is a class III anticonvulsant. It has no effect on the voltage-dependent sodium channel at concentrations up to 1 mM.[4] However, diphenylhydantoin (phenytoin), a structurally related cyclic imide, is a class I anticonvulsant with relatively potent sodium channel binding activity.[4,6] Surprisingly, we find that 2,4-oxazolidinediones 1 and 2 are, relative to values typically observed for anticonvulsants, both effective binders to the voltage-dependent sodium channel. Here we report the results of a study which utilizes partial structures of 1 and 2 in an attempt to delineate those feature which impart activity at the voltage-dependent sodium channel. Furthermore, we compare sodium channel binding affinities with whole animal anticonvulsant effects.

Table I. Partial Structures of 1 and 2

parent structure	compd	n	R_1	R_2	synthetic ref
	3		H		9
	4		CH_3		a
	5	1	H	OH	7
	6	1	CH_3	OH	7
	7	1	H	OCH_3	7
	8	1	CO_2Et	OCH_3	7
	9	2	H	OH	3
	10	2	CO_2Et	OH	3
	11	3	H	OH	3

[a] See the Experimental Section.

Chemistry. In addition to 1 and 2, the structures that were evaluated in this study are shown in Table I. As indicated, we previously reported[3,7] the syntheses that were employed for preparing all compounds except 3 and 4. Compound 3 was prepared from 2-hydroxy-2-phenylbutyramide[8] according to a literature procedure.[9] While pharmacological studies for 3 and 4 have been reported,[10] we were unable to locate a procedure for the synthesis of 4 from 3. We previously described the preparation of 4 by a different method.[2] Alternatively, here we alkylated 3 under basic conditions with dimethyl sulfate to give 4 in high yield.

Biology. Compounds 1–11 were all evaluated in synaptoneurosomal preparations (which are resealed postsynaptic elements with attached resealed presynaptic elements) from rat cerebral cortex. This assay was similar

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Table II. Biological Results

compd	Na^+ channel: IC_{50}, μM	anticonvulsant[a] phase I[b] MES	scMet	rotorod	phase II[c] time[d]	MES ED_{50}	scMet ED_{50}	rotorod TD_{50}
1[e]	380	–	+	–				
2[e]	160	++	++	++	0.25	66 [51–84]	45 [40–48]	147 [93–226]
3	>800	+	+++	+++	0.5	86 [80–94]	39 [15–45]	164 [154–173]
4	500	+	+++	+++	0.5	124 [104–139]	45 [36–55]	504 [437–558]
5[h]	>800	–	–	–				
6[h]	>800	++	+	–	0.5	84 [76–94]	128 [94–162]	~350[f]
7[h]	>800	++	+	+	0.5	120 [97–145]	50 [33–73]	239 [211–272]
8[h]	590	+	+	–	0.5	225 [196–260]	124 [96–156]	>300[g]
9[e]	>800	++	+	+	0.25	63 [52–72]	74 [49–105]	210 [162–234]
10[e]	640	++	++	+	0.25	84 [63–106]	*i*	216 [182–234]
11[e]	>800	++	+	+	0.25	80 [58–98]	108 [69–148]	199 [160–241]
trimethadione[j]	>1000[k]				1.0 (0.5)[l]	627 [538–705]	300 [265–325]	819 [652–1096]
phenytoin[j]	40[k]				2.0	10 [8–10]	inactive	66 [52–72]
carbamazepine[j]	131[k]				0.25	9 [5–14]	inactive	72 [46–135]

[a] Unless otherwise noted, all compounds were administered intraperitoneally to mice as suspensions in 30% polyethylene glycol 400. [b] All tests were performed 30 min after compound administration. Symbol meanings are as follows: – (inactive up to 300 mg/kg), + (active at 300 mg/kg), ++ (active at 100 mg/kg), +++ (active at 30 mg/kg). [c] All activities are expressed in mg/kg and are rounded off to the nearest whole number. Numbers in brackets refer to 95% confidence intervals. [d] Time of test (hour) after compound administration. [e] The solvent for anticonvulsant evaluation was 0.5% methylcellulose. [f] Estimated from an incomplete phase II study. [g] Taken from phase I data. [h] Anticonvulsant data taken from ref 7. [i] Insufficient compound to complete testing. [j] Anticonvulsant data taken from ref 12. [k] Values taken from ref 4. [l] Time of rotorod test only.

to literature procedures[11] and measured the ability of the test compound to inhibit the specific binding of [^{3}H]batrachotoxinin A 20-α-benzoate ([^{3}H]BTX-B) to neurotoxin site 2 of the voltage-dependent sodium channel. As shown in Table II, sodium channel binding activities are expressed as IC_{50} values, the concentration (μM) of anticonvulsant necessary to inhibit 50% of the specific binding of [^{3}H]-BTX-B.

Compounds 1–11 were also evaluated as anticonvulsants in mice by the Anticonvulsant Drug Development Program, which is conducted by the Epilepsy Branch of the National Institute of Neurological and Communicative Disorders and Stroke. In this screening procedure, which has been described in detail by Krall et al.,[12] candidate compounds are first subjected to a qualitative screen (phase I) in a small number of mice (1–4) at dose levels of 30, 100, and 300 mg/kg. Two anticonvulsant models are employed, one using subcutaneous Metrazol-induced convulsions (scMet) and the other using maximal electroshock-induced convulsions (MES). Toxicity is evaluated by a rotorod toxicity test. Compounds exhibiting anticonvulsant activity at 100 mg/kg or less are typically carried on to phase II evaluation for quantification of activities (ED_{50} and TD_{50}). The results are given in Table II.

Results and Discussion

[^{3}H]BTX-B binds strongly to neurotoxin site 2 of the neuronal voltage-dependent sodium channel. During normal neuronal activity this channel cycles through resting, open (active), and inactive states, but the binding of [^{3}H]BTX-B causes persistent channel activation and prevents channel inactivation. Local anesthetics, class I antiarrhythmics, and class I anticonvulsants (and possibly others) bind at pharmacologically relevant concentrations to a site (or sites) on the sodium channel that is allosterically linked to neurotoxin site 2, resulting in the inhibition of binding of [^{3}H]BTX-B. Electrophysiological studies for many of these drugs also reveal a frequency and voltage-dependent block of sodium channel conductance, allowing for an explanation of the selective effects of class I anticonvulsants on hyperactive versus normal neurons. (For reviews of these topics, see ref 13.)

Among the commonly used anticonvulsants, only two (which are designated class I anticonvulsants)[4] appear to cause their anticonvulsant effects by binding to the voltage-dependent sodium channel. These are diphenylhydantoin (IC_{50} = 40 μM for in vitro inhibition of binding of [^{3}H]BTX-B to sodium channels in rat brain synaptoneurosomes) and carbamazepine (IC_{50} = 131 μM),[4] which are both relatively narrow spectrum anticonvulsants that exhibit activities against partial and grand mal seizures.

In order to further evaluate sodium channel binding and anticonvulsant effects, we conducted the study that is summarized in Table II. The stimulus for this study was the surprising finding that 2,4-oxazolidinediones 1 and 2 were relatively effective inhibitors of [^{3}H]BTX-B binding to sodium channels, with 2 possessing sodium channel binding activity comparable to that of the class I anticonvulsant carbamazepine. As mentioned earlier 3,5,5-

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trimethyl-2,4-oxazolidinedione was not an inhibitor in this system at concentrations up to 1 mM.[4] An additional contrast with trimethadione is that compound **2** possessed significant anti-MES activity in mice, suggesting that sodium channel interactions may be the reason for the observed activity of **2**.

We then attempted to qualitatively determine the structural features of **1** and **2** that resulted in enhanced sodium channel binding (and possibly anti-MES activity) as compared to trimethadione. The approach involved comparing the above results with those for several partial structures of **1** and **2**. The structures that were of particular interest were **3**, **4**, **9**, and **11**. Compounds **3** and **4** model the oxazolidinedione ring portion of **1** and **2** (with appropriate substitutions), and compounds **9** and **11** model the lactam ring portion (with appropriate substitutions).

As shown in Table II, compounds **9** and **11** were essentially inactive in the sodium channel binding assay, yet they exhibited relatively potent anti-MES effects. This suggests that the lactam ring of **1** or **2** does not contribute significantly to the observed sodium channel effects and that the anticonvulsant effects of **9** and **11** must result from interactions at other sites. Similarly, upon comparing trimethadione to **3**, little change in sodium channel activity was noted, although the anti-MES activity of **3** increased by 5-fold. This illustrates that 5-alkyl-5-phenyl substitution on the oxazolidinedione ring leads to significant anti-MES effects that are not the result of interactions at the sodium channel. Compound **4** was approximately equipotent with **3** in the MES screen, although the former was 3 times less toxic and exhibited enhanced but moderate effects at the sodium channel. (It should be noted that anti-MES data in the cat were previously described for **3** and **4**, but reported potencies were much lower than observed in the present study.[10]) Finally, the greatest enhancement in sodium channel binding activity was noted in comparing **4** to **1** and **2**, and the anti-MES effects of **2** (based upon studies with carbamazepine and phenytoin) appeared to be consistent with its potency in the sodium channel assay.

In summary, this study suggests that, contrary to popular beliefs, appropriately substituted 2,4-oxazolidinediones provide relatively potent, broad-spectrum anticonvulsants. In some cases, such as **4**, the protective index (PI = TD_{50}/ED_{50}) is also quite large (PI = 11.2 for **4** in the scMet screen). 5-Alkyl-5-phenyl substitution appears essential for this effect and when coupled with a 3-alkyl substituent provides for moderate interactions with the voltage-dependent sodium channel. However, the greatest effect on sodium channel binding activity results from incorporating the 3,5-dialkyl substituents into a ring, indicating that the conformation of these substituents may be important. Also, these studies imply that compound **4** (and possibly the others) causes its anti-MES anticonvulsant effects through interactions with more than one receptor site, since the moderate sodium channel activity should contribute to, but not be sufficient to account for, the anti-MES potency. Finally, smissmanone **2** may represent a new class I anticonvulsant.

Additionally, the in vivo anticonvulsant activities of compounds **5–8** were known from a previous study,[7] and that for the close analogue **10** was evaluated in the present study. It was of interest to determine if any correlation existed between sodium channel binding and anti-MES effects for this closely related series of compounds. However, as shown in Table II, most interacted only weakly with the sodium channel, although some were relatively potent anti-MES anticonvulsants.

At least one other study[14] has shown significant discrepancies between in vitro [^{3}H]BTX-B binding to the voltage-dependent sodium channel and whole animal anti-MES activity for a series of experimental compounds. Such discrepancies are not particularly surprising since at least three well-characterized binding sites may result in anti-MES effects (namely, voltage-dependent sodium channels, GABA receptors, and NMDA receptors). Also, pharmacological agents other than anticonvulsants have been shown to inhibit [^{3}H]BTX-B binding to voltage-dependent sodium channels.[13] Furthermore, it has recently become apparent that neuronal voltage-dependent sodium channels are heterogeneous,[15] suggesting that selective effects may be possible at different subtypes. Although the possibility remains that robust effects on [^{3}H]BTX-B binding inhibition could be predictive of anti-MES activity, it is clear that more information concerning sodium channel structure and function must be obtained before this pharmacologically rich site can be easily targeted for the design of specific agents.

Experimental Section

Compounds **1** and **2** were prepared as previously described.[3] The synthetic procedures for obtaining compounds **3** and **5–11** are referenced in Table I. [^{3}H]Batrachotoxinin A 20-α-benzoate with a specific activity of 50 Ci/mmol was prepared as described.[16] This compound is currently available from New England Nuclear.

5-Ethyl-3-methyl-5-phenyl-2,4-oxazolidinedione (4). Sodium (0.58 g, 25 mmol) was dissolved in anhydrous methanol (15 mL). A solution of **3** (5.0 g, 24 mmol) in anhydrous methanol (15 mL) was added followed by dimethyl sulfate (3.6 g, 25 mmol). The solution was heated at reflux for 3 h, the methanol removed on a rotary evaporator, and water (80 mL) added to the residue. This was extracted with chloroform (3 × 30 mL), the extracts were dried ($MgSO_4$), and the solvent was removed on a rotary evaporator to provide a clear oil (5.2 g, 97%): bp 90 °C. (0.2 mm) (lit.[2] bp 90 °C (0.2 mm)).

Sodium Channel Binding Assay. The procedure was similar to reported methods.[11] Synaptoneurosomes were prepared from rat cerebral cortex as follows: cerebral cortex (approximately 1-g weight) was homogenized in 2 mL of buffer containing 130 mM choline chloride, 50 mM HEPES [adjusted to pH 4 with tris(hydroxymethyl)aminomethane, approximately 23 mM Tris base], 5.5 mM glucose, 0.8 mM $MgSO_4$, and 5.4 mM KCl. The tissue was homogenized with 10–12 strokes of a glass-glass homogenizer. The final volume was adjusted to 6 mL and the preparation centrifuged at 1000*g* for 15 min at 4 °C. The pellet was resuspended in a total volume of 20 mL of HEPES buffer for binding studies. Incubations were carried out for 40 min at 25 °C in a total volume of 320 μL containing 10 nM [^{3}H]BTX-B, 50 μg/mL of scorpion venom, approximately 980 μg of the particulate vesicular protein, and varying concentrations of added test compound (from 50 mM stock solutions in 50% $MeOH/H_2O$). The MeOH concentration was in all cases less than 1%. Incubations were terminated by dilution of the reaction mixture with 3 mL of ice-cold wash buffer and filtration through a Whatman GF/C filter paper. Filters were washed with wash buffer (3 × 3 mL). The wash buffer contained the following: 163 mM choline chloride, 5 mM HEPES (adjusted to pH 7.4 with Tris base), 1.8 mM $CaCl_2$, and 0.8 mM $MgSO_4$. Filters were counted in a Beckman scintillation counter using 10 mL of 3270B counting cocktail (Research Products International). Specific binding was determined by subtracting the nonspecific binding, measured in the presence of 250 μM veratridine, from the total binding of [^{3}H]BTX-B. Specific binding was about 80% of total binding. All experiments were performed in triplicate. IC_{50} values (con-

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centration of compound required to inhibit 50% of specific neurotoxin binding) were determined from a dose–response curve generated by plotting the log of anticonvulsant concentration (over a range of 10–800 μM) versus percent of specifically bound [^{3}H]BTX-B.

Anticonvulsant Assays. All anticonvulsant and neurotoxicity assays were conducted by the Anticonvulsant Drug Development Program of the Epilepsy Branch, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health. Compounds were injected intraperitoneally into mice as suspensions in either methylcellulose or 30% polyethylene glycol 400. After the time indicated in Table II, the animal was subjected to either a subcutaneous Metrazol (scMet) challenge (85 mg/kg), a maximal electroshock (MES) challenge (produced with 60 cycle AC at 50 mA for 0.2 s via corneal electrodes), or a rotorod toxicity test. The details of these procedures have been published.[12]

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Registry No. 1, 93350-08-4; 2, 93350-09-5; 3, 92288-54-5; 4, 68475-20-7; 5, 65379-06-8; 6, 87532-76-1; 7, 87532-77-2; 8, 87532-78-3; 9, 51129-01-2; 10, 93350-14-2; 11, 93350-13-1.

Synthesis of (Aryloxy)alkylamines. 2. Novel Imidazo-fused Heterocycles with Calcium Channel Blocking and Local Anesthetic Activity[1]

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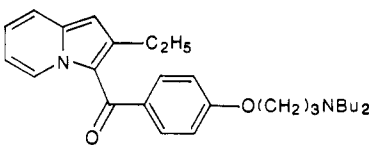
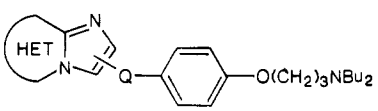
A series of imidazo-fused heterocycles substituted with an (aryloxy)alkylamine side chain were prepared as modifications to butoprozine (I) and found to possess calcium channel blocking activity similar in potency to that of bepridil in trachea smooth muscle and similar to that of verapamil in nitrendipine binding affinity in rabbit cardiac muscle. Of the various imidazo-fused heterocycles prepared, the imidazo[1,2-*a*]pyridines were also found to be potent local anesthetic agents. While most compounds in this series were equipotent to lidocaine in our initial screen, compounds **2** and **35** showed local anesthetic activity approximately 100 times more potent than lidocaine in our preliminary assays. These compounds represent a novel structural class of local anesthetic agents, and compound **2** is under further investigation.

Calcium channel blockers are utilized as antianginal agents[2] due to their peripheral vasodilating[3] and smooth muscle relaxating properties.[4] We became interested in preparing analogues of butoprozine[5] (I), an antianginal agent with antiadrenergic and calcium antagonist activities,[6] and developed a program to synthesize various heterocyclic (aryloxy)alkylamines of general structure II.



I



II

In particular, the 4-[3-(dibutylamino)propoxy]phenyl group specific to butoprozine (I) was utilized as a pharmacophore to explore the effects of altering the heterocyclic ring (HET) and the spacer Q (i.e. carbonyl, direct bond) on biological activity as well as substituent effects on these various heterocyclic moieties. For expediency, the initial plan was confined to readily synthesized derivatives of available 2-amino heterocycles.

In addition to examining the compounds for potential calcium channel blocking activity, these imidazo-fused heterocyclic (aryloxy)alkylamines were evaluated in a wide variety of pharmacological and biochemical assays in order to determine any other potential pharmacological utility. We have previously reported[1] on compounds related to target II wherein a substituted thiazole, benzoxazole, or benzothiazole moiety (instead of the imidazo-fused heterocycle) was found to be a potent inhibitor of the H^+K^+-sensitive ATPase enzyme. As a result of broad screening, a series of imidazo[1,2-*a*]pyridines, a subset of II, were discovered to possess very interesting local anesthetic activity.

Chemistry

Condensation of a variety of 2-amino heterocycles (III) with 4-hydroxy-α-bromoacetophenone[7] (IV) and subsequent alkylation of the phenol with (dibutylamino)propyl chloride produced the desired imidazo-fused heterocycles (II) but in unacceptably low yields (Scheme I). As noted previously,[1] protection of the phenol as a chloropropoxy ether as in VIa greatly improved the yields of the 2-amino heterocycle condensations. Subsequent displacement of the alkyl chloride with dibutylamine produced the desired product IIa as outlined in Scheme II. The various 2-aryl imidazo-fused heterocycles thus prepared are summarized in Table I.

(1) For the previous paper in this series, see: Sanfilippo, P. J.; Urbanski, M.; Press, J. B.; Hajos, Z. G.; Shriver, D. A.; Scott, C. K. *J. Med. Chem.*, in press.
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