Synthesis and CLOGP Correlation of Imidooxy Anticonvulsants

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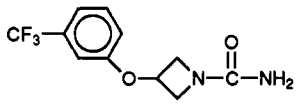
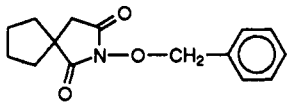
Continuing structure–activity studies on the anticonvulsant activity of analogs of *N*-(benzyloxy)-2-azaspiro[4.4]nonane-1,3-dione (**2a**), which displayed anti-electroshock seizure (MES) activity and a protective index (TD50/ED50) of >4.5 are reported. An in-depth analysis of this moiety was studied employing the Topliss structure activity and the Craig plot analytical approaches as well as a semiempirical method. CLOG P analysis was also applied to this series after experimentally determining the NOR fragment. All compounds were minimized and these physicochemical parameters correlated to anticonvulsant activity. Several interesting substituted benzyloxy compounds emerged from this study: the 2′,4′-dichloro (**2b**), 4′-(trifluoromethyl) (**2c**), 2′-bromo (**2d**), 3′-chloro (**2o**), 2′-chloro (**2r**), 2′-fluoro (**2p**), and 3′-fluoro (**2w**) analogs, all of which had comparable, or better activity than the parent unsubstituted analog (**2a**). X-ray crystal analysis of the active **2a** versus inactive *N*-benzyl-2-azaspiro[4.4]nonane-1,3-dione (**10**) is discussed.

Approximately 2.5 million Americans are afflicted with epilepsy, making this disorder the second leading neurological disease.[1] Despite the optimal use of antiepileptic drugs marketed in the United States, many patients with epilepsy fail to experience seizure control and others do so only at the expense of significant toxic side effects.[2] Increased interest in anticonvulsant drug development has resulted in the recent introduction of three new entities into the United States: gabapentin,[3] felbamate,[4] and dezinamide (AHR-11748, ADD-94057) (3-[3-(trifluoromethyl)phenoxy]-1-azetidinecarboxamide, **1**.[5]



1

Research in our laboratory led to the synthesis and evaluation of *N*-(benzyloxy)-2-azaspiro[4.4]nonane-1,3-dione (**2a**), which displayed protection against maximal electroshock seizures (MES) and a protective index (TD50/ED50) of >4.5.[6,7]



2a

Comparison of **2a** to **1** reveals a similar anticonvulsant pharmacophore, O=CNCOAr in **1** vs O=CNOCAr in **2a**. This report provides a systematic evaluation of the electronic and steric effects involved in aromatic substitution on anticonvulsant activity.

Results and Discussion

Chemistry. The spirosuccinimides reported in Table I were synthesized as shown in Scheme I using a modification of the procedure previously reported.[6] Cyclopentanone was subjected to a Knoevenagel condensation with ethyl cyanoacetate, and the resultant cyclopentylidenecyanoacetate, **4**, was treated with cyanide, and the α-(cyanocyclopentyl)acetonitrile, **5**, was isolated. We had previously employed this procedure to decrease the hazard involved in the subsequent step.[6,8] Acidification of **5** provided the tetramethylene succinic acid, **6**. Treatment of **6** with acetic anhydride provided the respective anhydride **7** quantitatively. Anhydride **7** was converted into *N*-hydroxyspirosuccinimide **8** with hydroxylamine (generated in situ).[9] Compound **8** was converted into its sodium salt, **8a**, with sodium ethoxide, and after separation and purification, **8a** was sufficiently stable to be produced in suitable quantities to be employed in the condensations with the substituted benzyl halides to provide the substituted *N*-(benzyloxy)-2-azaspiro[4.4]nonane-1,3-diones, **2** (method A). Alternatively, anhydride **7** was condensed with substituted (benzyloxy)hydroxylamines (method B). In a manner reported previously,[10] anhydride **7** was reacted with benzylamine in refluxing xylene to provide, after fractional distillation, the desired **10**. Physical properties for these compounds are detailed in Table I.

X-ray Analysis. As previously reported *N*-benzyl-2-azaspiro[4.4]nonane-1,3-dione (**10**) was ineffective as an anticonvulsant; however, in contrast to *N*-hydroxy-2-azaspiro[4.4]nonane-1,3-dione, **8**, it was nontoxic at 300 mg/kg.[6] In order to account for the difference in activity of these compounds, their molecular and crystal structures were determined. The summary of the intensity data and

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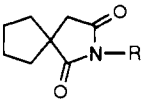
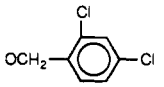
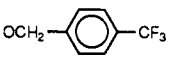
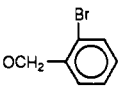
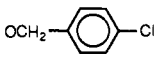
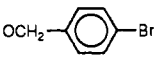
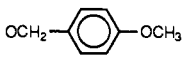
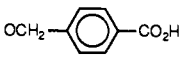
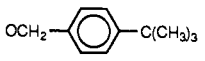
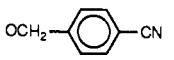
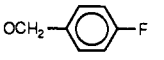
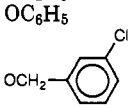
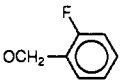
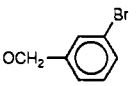
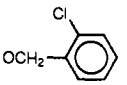
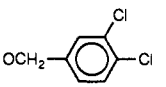
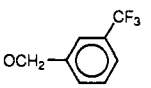
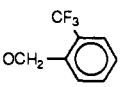
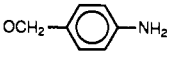
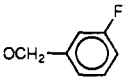
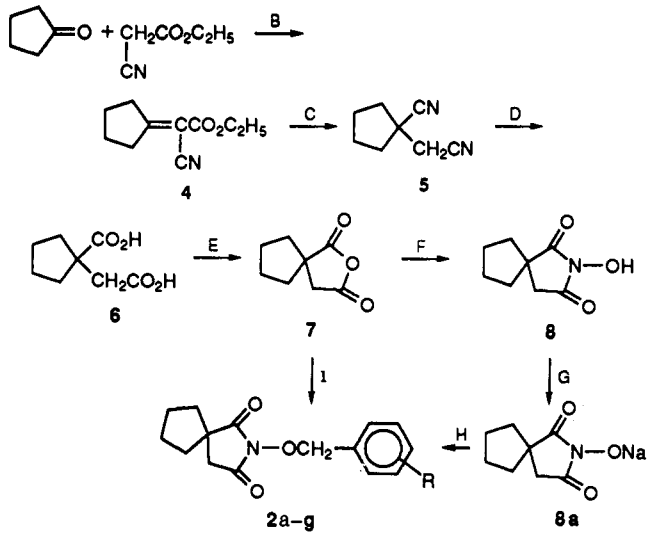
Table I. Physical Properties of Imidooxy Derivatives[a]



compd	R	% yield	method	mp, °C or bp, °C (mm)	formula	anal.[b]
2a	$OCH_2C_6H_5$	83	A	140–141[c]	$C_{15}H_{17}NO_3$	C,H,N
		76	B	139–141[d,e]		
2b		63	A	103–104[f]	$C_{15}H_{15}NO_3Cl_2$	C,H,N,Cl
2c		60	A	156–157[f]	$C_{16}H_{16}NO_3F_3$	C,H,N,F
2d		36	A	64–66[f]	$C_{15}H_{16}NO_3Br$	C,H,N,Br
2e		83	A	144–145[f]	$C_{15}H_{16}NO_3Cl$	C,H,N,Cl
2f		72	A	144–145[f]	$C_{15}H_{16}NO_3Br$	C,H,N,Br
2g		47	A	99–100[f]	$C_{16}H_{19}NO_4$	C,H,N
2h		33	A	177–180 dec[f]	$C_{16}H_{17}NO_5$	C,H,N
2i		79	A	159–160[f]	$C_{19}H_{25}NO_3$	C,H,N
2j		69	A	153–156[f]	$C_{16}H_{16}N_2O_3$	C,H,N
2k		56	A	149–151[f]	$C_{15}H_{16}NO_3F$	C,H,N,F
2l	OCH_3	11	A	59–61[g]	$C_9H_{13}NO_3$	C,H,N
2m	OC_2H_5	29	A	118 (0.25)	$C_{10}H_{15}NO_3$	C,H,N
2n	OC_6H_5	65	A	106–108[h]	$C_{14}H_{15}NO_3$	C,H,N
2o		67	A	123–125[h]	$C_{15}H_{16}NO_3Cl$	C,H,N,Cl
2p		71	A	47–49[g]	$C_{15}H_{16}NO_3F$	C,H,N,F
2q		71	A	118–119[f]	$C_{15}H_{16}NO_3Br$	C,H,N,Br
2r		55	A	65–67[g]	$C_{15}H_{16}NO_3Cl$	C,H,N,Cl
2s		74	A	149–150[f]	$C_{15}H_{15}NO_3Cl_2$	C,H,N,Cl
2t		80	A	109–111[f]	$C_{16}H_{16}NO_3F_3$	C,H,N,F
2u		43	A	56–59[g]	$C_{16}H_{16}NO_3F_3$	C,H,N,F
2v		30	A	179–180[f]	$C_{15}H_{18}N_2O_3$	C,H,N
2w		74	A	135–136[f]	$C_{15}H_{16}NO_3F$	C,H,N,F
8	OH	68		117–118[c]	$C_8H_{11}NO_3$	C,H,N
8a	ONa	90		210–213[i]	$C_8H_{10}NO_3Na$	C,H,N
10	$CH_2C_6H_5$	64		63.5[f]	$C_{15}H_{17}NO_2$	C,H,N

[a] The infrared and ^1H NMR spectra were consistent with assigned structures. Recrystallization solvents as indicated. [b] All compounds gave satisfactory C, H, N, and halogen (when required) analyses (±0.4%). [c] Toluene. [d] Ethyl acetate. [e] References 6 and 8. [f] Methanol. [g] Ethyl acetate–petroleum ether (bp 38–54 °C). [h] 2-Propanol. [i] Ethyl acetate–acetone.

Scheme I[a]



[a] B = HOAc, NH_4OAc; C = KCN; D = HCl; E = Ac_2O; F = NH_2OH·HCl, Na_2CO_3; G = NaOEt, EtOH; H = $C_6H_5CH_2X$; I = $C_6H_5CH_2ONH_2$·HCl, $NaHCO_3$.

structure refinement is given in Table II, and the atomic coordinates of the two compounds are provided in Table III. Although the degree of accuracy of the structure determination for **2a** was not as high as that noted with **10**, due to the poorer crystal specimen, the difference in the conformation of molecules **2a** and **10** is apparent as shown in Figure 1. The detailed analysis of the molecular geometry of the two compounds indicates that the corresponding bond distances were within 3σ, with the exception of the $N-C_3$ bond which was 0.034 Å shorter in **2a**, suggesting the strong electron-withdrawing effect of the O_3 atom. Another difference noted was in the length of the C_5-C_6 bond which is also shorter in **2a** due to a considerably higher temperature factor of the C_6 atom in **2a** than in **10**. The bond angles of all of the atoms are in agreement with their hybridization. In both compounds the homocyclic five-membered ring has an envelope conformation with the ring-puckering coordinates (as defined by Nardelli[11] q_2 = 0.333(4) Å, ϕ_2 = −174(1), for **2a** and q_2 = 0.396(2) Å, ϕ_2 = 0.0(5) for **10**, and with the C_4 atom deviating from the plane formed by the C_5, C_6, C_8 atoms by 0.518(3) and 0.608 Å for **2a** and **10**, respectively. Analysis of the best least-squares planes indicated that the heterocyclic five-membered ring is more planar for **2a** (with atomic deviation between 0.007(3) and −0.011(3) Å) than for **10** (with atomic deviation between 0.072(2) and −0.099(2) Å). The phenyl rings are planar in both molecules. The significant difference between the two molecules is in the mutual orientation of the phenyl ring and the five-membered heterocyclic ring. The angle between the least-squares planes of these rings is 5.9(1)° for **2a** and 102.4(1)° for **10**. As a result, the two ketonic oxygen atoms are considerably closer to the center (P) of the phenyl group in **10** than in **2a**. The distances are O_1-P 5.214(5), O_2-P 5.892(5) for **2a** and 4.472(3), 4.788(3) for **10**, respectively. However, all four values fall within the range of analogous values considered in the Camerman's model,[12] along with the specific spatial arrangement of the hydrophobic region of six antiepileptic agents as their important geometrical descriptors. Yet, **2a** is active, while **10** is inactive. This fact seems to stress the importance of the orientation of the phenyl ring with respect to the heterocyclic ring; when these rings lie in parallel planes, as in **2a**, the compound is active, whereas if they are approximately perpendicular, as **10**, the compound is inactive. Analogous observations were reported for the active spirohydantoin derived from tetrahydroisoquinoline and the inactive spirohydantoin derived from α-tetralone.[13] Hydrogen bonds, often considered as the important feature of antiepileptic drugs,[14] are not present in the structures studied here since the molecules do not possess a positively charged hydrogen.

log *P* Determinations. The dependence of biological activity in a set of congeneric agents on lipophilic character has been shown in many types of drug action.[15] In particular, the reports by Lien and co-workers indicated that anticonvulsant activity of different types of compounds was correlated with lipophilicity.[16] However, it has been observed that the maximum potency of drugs which act on the central nervous system are obtained with congeners having an optimum lipophilicity (log P_0) near 2.[15] In this study, we attempted to correlate the anticonvulsant activity of the spiro benzyloxy analogs with their calculated log *P* values, CLOGP.[17] However, in the analysis of these analogs, the CLOGP algorithm did not recognize the NOR fragment.[18] Thus, experimental log *P* (or π) values were determined using the octanol–water method[19] for *N*-methoxy- (**2l**), *N*-ethoxy- (**2m**), *N*-phenoxy- (**2n**), *N*-(benzyloxy)- (**2a**),[6] *N*-[(4′-chlorobenzyl)oxy]- (**2e**), and *N*-[(4′-methoxybenzyl)oxy]-2-azaspiro[4.4]nonane-1,3-dione (**2g**), respectively, both in our laboratories as well as independently.[20] The data is presented in Table V and in Figure 2. As observed, the experimental values (open circles) were in good agreement with the theoretical values (closed circles). The CLOGP for inactive and toxic *N*-hydroxy (**8**) (1.461), inactive *N*-phenoxy (**2n**) (1.616), and (4′-methoxybenzyl)oxy (**2g**) (1.723) are less lipophilic than *N*-(benzyloxy) (**2a**) (1.805); however, (4′-chlorobenzyl)oxy (**2e**) (2.517) is considerably more lipophilic but also inactive. As with the X-ray data, subtle changes in the parent molecule, **2a**, result in the loss of activity. This is especially true when electronic and positional effects are taken into consideration. These factors are critical to a clearer understanding of these spiro analogs.

Molecular Modeling Studies. Each spiro analog in Table I was analyzed by classical molecular mechanics.[21] The common torsional angle of the analogs is depicted in Figure 3

$$\pi_1 = C(2)-N(1)-O(3)-C(9)$$

$$\pi_2 = N(1)-O(3)-C(9)-C(10)$$

with π_1 being the slowest varying and π_2 being the fastest. Each structure was minimized, and the lowest energy conformer superimposed onto phenytoin using the common carbonyl(s) as we have previously reported.[22] These superimposed conformers were rigidly fit, and the van der Waals volume was determined by two methods: the union volume, which displays all van der Waals volumes for both structures, and the intersection volume, that area where the structures overlap. Volume map data for the spiro analogs are shown in Table VI. The average intersection volume is 71.52 Å, while the union volume for the active analogs is 374.78 Å. The values for the inactive analogs are 69.85 and 375.63 Å, respectively. These small differences are not statistically significant and as previously noted in the discussion suggest that both active and inactive spiro analogs may approach the same receptor

Table II. Crystallographic Data and Summary of Data Collection and Structures Refinement for Compounds 2a and 10

	2a	10
Crystal Data		
mol formula	$C_{15}H_{17}NO_3$	$C_{15}H_{17}NO_2$
mol wt	259.30	243.30
space group (*Z*)	*C*2/*c* (8)	$P2_1/n$ (4)
a (esd), Å	25.550 (5)	13.388 (2)
b (esd), Å	12.078 (3)	6.608 (1)
c (esd), Å	8.881 (2)	14.963 (2)
β (esd), deg	90.70 (2)	100.98 (1)
V (Å^3)	2740.4 (1.06)	1299.5 (3)
density meas, g cm^{-3}	1.25	1.24
density calc, g cm^{-3}	1.257	1.244
crystal shape and color	colorless plates	colorless rods
crystal size, mm	0.3 × 0.3 × 0.04	0.30 × 0.24 × 0.12
crystallization solvent	ethyl acetate	ethanol
Intensity Measurement		
diffractometer CAD4	Cu Kα, λ = 1.5418 Å; Mo Kα, λ = 0.710 73 Å	
ω–2θ scan at room temp	graphite-monochromated radiation	
maximum θ (deg)	50	25
no. of reflections measured	1442	2282
no. of observed unique refl with $\|F_o\| > \sigma(F)$	1257	1964
Structure Refinement		
corrections applied	Lorentz, polarization effects	
refinement method	full-matrix least squares on $\|F_o\|$	
parameters refined	173	231
non-H atoms	positional and anisotropic thermal	
H atoms	positional and isotropic thermal (for 5b fixed in the last refinement cycles)	
weighting scheme	$w = k[\sigma^2(F_o) + gF_o^2]^{-1}$	
k and *g* converged to	2.3804, 0.0007	0.8867, 0.0015
R, R_w	0.061, 0.070	0.054, 0.057
max., min, height in final difference Fourier map (e Å^{-3})	0.21, −0.34	0.15, 0.15

Table III. Fractional Coordinates (10^5) and Equivalent Isotropic Displacement Parameters ($A^2 \times 10^4$) with esd's in Parentheses for the Non-Hydrogen Atoms of Compound 2a

$$U_{eq} = (^1/_3)\sum_i\sum_j U_{ij}a_i^*a_j^*a_ia_j$$

atom	*x*/*a*	*y*/*b*	*z*/*c*	U_{eq}
O1	24350(10)	20958(20)	−20237(28)	653(8)
O2	32299(10)	−1244(25)	14047(33)	900(9)
O3	22793(8)	3838(19)	−75(24)	518(7)
N	27558(9)	8593(21)	−3087(28)	404(8)
C1	33516(13)	20948(26)	−12358(37)	468(9)
C2	27965(12)	17342(28)	−13115(35)	414(9)
C3	32000(13)	5999(29)	4607(38)	485(9)
C4	36291(11)	13577(26)	−756(34)	399(9)
C5	38745(14)	20010(31)	12358(39)	598(11)
C6	44048(18)	22665(51)	7514(60)	1201(13)
C7	45584(16)	14444(42)	−4027(62)	1000(11)
C8	40942(13)	7238(30)	−6952(42)	603(10)
C9	22155(14)	−6593(30)	−8242(43)	602(10)
C10	16461(13)	−8844(26)	−8740(35)	444(9)
C11	14249(14)	−17224(31)	−367(37)	569(10)
C12	8970(15)	−19257(34)	−1204(43)	698(10)
C13	5795(15)	−12730(38)	−10119(49)	767(11)
C14	7941(16)	−4382(35)	−18431(45)	756(11)
C15	13259(15)	−2586(30)	−17673(40)	608(10)

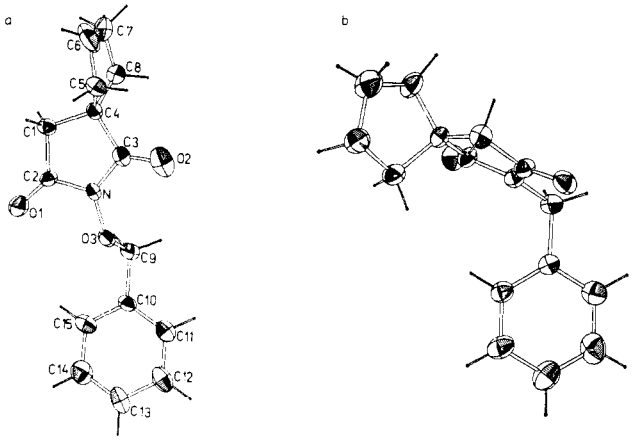


Figure 1. Molecular conformations and atomic labeling schemes for compound **2a** (panel a) and 10 (panel b). The atomic labeling scheme for 10 follows that given in panel a. Thermal ellipsoids are scaled to enclose 30% probability. The drawing was made with computer program ORTEP (ref 35).

pocket, or different receptor pockets with similar capacity. In the former case, possible changes of the allosteric site could explain the difference in activity. In the latter, the changes could be due to a different spiro–receptor complex. These differences have been reported for the cholecystokinin/gastrin antagonists,[23] dopamine D-1 receptor antagonists,[25] and most appropriately for this study, for 4-amino-*N*-phenylbenzamide anticonvulsants.[25] Addition of electronegative substituents in the ortho and para positions of the active benzyloxy moiety tend to increase *anti*-pentylenetetrazole (scMet) activity as shown with **2b**, **2c**, and **2d**. Alkyl substituents, in contrast, abolish activity. Of equal significance is the comparison of the 4′-chloro, **2e**, 3′-chloro, **2o**, and 2′-chloro, **2r**, in the MES evaluation. The 4′-chloro was inactive and the 2′ analog had comparable activity to unsubstituted **2a**, while the 3′ analog possessed enhanced activity. Since the lipophilicity is very similar with these three analogs, the increased potency of **2o** strongly suggests that a steric interaction is present. Dichloro analogs also verify this hypothesis as **2b** is more anti-MES active than **2s**, **2b** having *o*-chloro substitution, while **2s** did not.

Pharmacology. Preliminary pharmacological testing of the compounds listed in Table I has been provided by the Anti-epileptic Drug Development (ADD) Program, Epilepsy Branch, Neurological Disorders Program, National Institutes of Neurological and Communicative Disorders and Stroke (NINCDS), by testing procedures that have been described.[26] Phase I results of the active

Table IV. Fractional Coordinates (10^5) and Equivalent Isotropic Displacement Parameters ($A^2 \times 10^4$) with esd's in Parentheses for the Non-Hydrogen Atoms of Compound 10

$$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$$

atom	x/a	y/b	z/c	U_{eq}
O1	48165(12)	23339(25)	53543(10)	666(6)
O2	20249(11)	17215(24)	31197(10)	635(6)
N	35381(11)	22326(24)	41002(10)	432(5)
C1	32676(17)	4043(41)	53637(14)	561(7)
C2	39877(15)	17219(30)	49826(13)	478(7)
C3	25876(14)	13494(30)	38340(12)	457(6)
C4	24171(14)	-1260(30)	45588(12)	457(6)
C5	25010(18)	-23099(35)	42350(16)	569(8)
C6	19642(22)	-35681(43)	48475(21)	718(11)
C7	12281(28)	-21581(51)	51870(32)	940(16)
C8	13425(18)	-980(43)	47647(19)	659(9)
C9	39901(17)	36464(33)	35448(14)	502(8)
C10	47317(14)	26962(29)	30305(12)	443(6)
C11	55397(19)	38298(41)	28619(16)	639(9)
C12	62127(22)	30446(53)	23567(20)	816(12)
C13	60854(22)	11318(53)	20100(18)	803(12)
C14	52847(22)	-274(45)	21764(17)	700(10)
C15	46104(17)	7514(34)	26797(14)	533(7)

Table V. CLOGP for Spiroimidooxy Analogs[a]

compd	-NOX	experimental log P	fragment value	theoretical CLOGP value[b]
8	H	-0.26	-0.999	1.461
2l	CH_3	1.15	-2.280	0.740
2m	C_2H_5	1.26	-2.280	1.200
2n	Ph	1.77; 1.82[b]	-2.804	1.616
2g	Bz	2.23	-3.100	1.723
2a	Bz	2.30	-3.100	1.805
2e	Bz	2.53	-3.100	2.517

[a] See the Experimental Section. [b] Theoretical CLOGP calculated by subtracting the respective fragment value from CLOGP (ref 17). [c] Partition coefficient was calculated using absorbance data at two wavelengths to verify agreement.

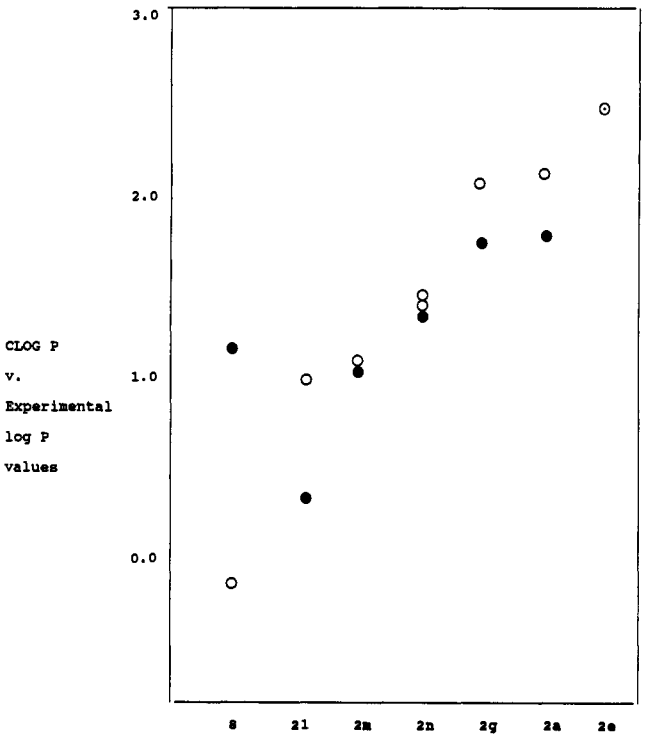


Figure 2. As drawn using the data from Table V, open circles (○) are experimental, closed circles (●) are theoretical, and circles with dots (⊙) are coincident values. Numbers on *x* axis refer to compounds found in Table I.

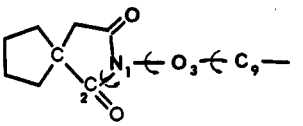


Figure 3. Common torsional angles for minimization of *N*-(benzyloxy)spiranes.

moieties in mice are shown in Tables VII and VIII. The three tests were maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (scMet), and neurologic toxicity (Tox). These data are provided on Table VII. An additional phase I evaluation for each of the active spiranes is provided at 100 mg/kg ip between 15 min and 4 h and is shown in Table VIII. As a result of these tests, compounds **2b**, **2c**, **2d**, and **2o** were advanced to phase II trials for quantification of the anticonvulsant activity and neurotoxicity in mice by determining the median effective dose (ED50) and median toxic dose (TD50). Compounds **2o** and **2r** are currently undergoing phase II trials. These data are shown in Table IX. Also included are data for several currently marketed anticonvulsants for comparison as well as the template for the study, **2a**. Due to the large quantities required, data for **2c** were incomplete. No toxicity was observed, however, at doses >500 mg/kg. It should be noted that each of the analogs of **2a** possessed significant anti-scMet activity, whereas **2a** displayed no such property. Of interest is the significant anti-MES activity of **2o** at 100 mg/kg and anti-scMet activity at 300 mg. Additional evaluations of **2a** and **2b** were performed in our laboratory for their ability to protect against MES. Compound **2a** was also evaluated for its ability to elevate the threshold for electroshock-induced maximal (tonic extension) seizures in mice. These data are shown in Table X. As noted in the phase II data provided by the ADD Program and in our laboratory, only **2o** surpassed **2a**. Compounds **2d** and **2o** were evaluated for oral activity in the rat by the ADD Program. These compounds were marginally active at 50 mg/kg in the MES evaluation (1/4 animals protected, 0/4 animals toxic at 2 h for **2d** and 1/4 animals protected at 1 h, 0/4 animals toxic for **2o**) and the scMet evaluation (1/4 animals protected at 1 h, 0/4 animals protected for **2d**).

Structure–Activity Correlation. In view of the activity of **2a**,[6] we undertook a systematic evaluation of the electronic effects involved in aromatic substitution. We had previously employed a similar technique in our earlier study of anticonvulsant spirosuccinimides[10] and more recently in our study of anticonvulsant enaminones.[22,27] In the latter references, we employed the Craig plot[28] to select substituents such that electronic (σ) effects versus lipophilicity (π) contributions to anticonvulsant activity could be evaluated. In addition, due to the poor correlation between anticonvulsant activity and the para-substituted compounds with the Craig method, the Topliss[29] approach was used to select additional mono- as well as disubstituted compounds for evaluation. Finally, a semiempirical approach was initiated to assess the effect of ortho substitution on anticonvulsant activity. Each method is discussed.

(a) Craig Method. Of the compounds in Table I, 4′-(trifluoromethyl), **2c**, 4′-chloro, **2e**, 4′-bromo, **2f**, and 4′-fluoro, **2k** represent $+\sigma$, $+\pi$ substituents; the 4′-carboxy, **2h**, and 4′-cyano, **2j**, are $+\sigma$, $-\pi$ substituents; 4′-amino, **2v**, is a $-\sigma$, $-\pi$ substitution; and 4′-methoxy, **2g**, and 4′-*tert*-butyl, **2i**, are $-\sigma$, $+\pi$ substituents. As noted in Table VII, we observed an increase in activity only with **2c**. We had previously noted that para substitution on an active anticonvulsant benzylamine enaminone had little en-

Table VI. Molecular Volumes of (Benzyloxy)spiranes

compd	molecular volume[a] intersection[b]	union[b]	activity
2a	67.8	358.0	2
2b	69.0	386.9	2
2c	72.8	388.8	2
2d	68.1	376.3	2
2e	68.1	372.4	3
2f	68.1	376.4	3
2g	68.1	384.3	3
2h	68.1	384.3	3
2i	68.1	413.0	3
2j	68.1	377.6	3
2k	68.1	364.0	3
2l	68.1	287.3	3
2m	68.1	298.7	3
2n	78.4	333.9	3
2o	68.1	371.6	1
2p	91.1	342.2	1
2q	65.3	363.8	3
2r	68.3	386.1	2
2s	78.9	378.3	3
2t	68.9	384.2	3
2u	68.7	381.4	1
2v	68.6	385.1	nd[c]
2w	69.9	381.8	2
8	66.4	275.0	3
10	78.9	341.8	3

[a] See the Experimental Section. [b] Average intersection and union volume for class 3 compounds (excluding non-benyloxy compounds 2l, 2m, 2n, 8, and 10) were 69.9 and 375.6, respectively; for class 2 compounds 69.3 and 379.6, respectively; and for class 1 compounds 76.0 and 365.1, respectively. [c] nd = not determined.

Table VII. Anticonvulsant Screening Project (ASP): Phase I Test Results in Mice

compd	dose, mg/kg	activity scMet[a] 30 min	scMet[a] 4 h	MES[b] 30 min	MES[b] 4 h	Tox[c] 30 min	Tox[c] 4 h	ASP classification[d]
2b	300	1/1 (2/4)	1/1 (0/4)	1/1	1/1	1/4[e] (0/4)	0/2 (0/4)	2
2c	300	1/1 (1/4)	0/1	1/1 (3/4)	0/1	0/4	0/2	2
2d	300	1/1 (4/4)	0/1	1/1	0/1	4/4 (4/4)[e]	0/2	2
2o	100	0/1	0/3	2/3	0/3	0/8	0/4	1
	300	1/1	0/1	1/1	0/1	4/4[e]	2/2	
2p	100	0/1	0/1	2/3	0/3	0/8	0/4	1
	300	1/1[f]	0/1	1/1	0/1	4/4[e]	0/2	
2r	100	0/1	0/1	0/3	0/3	0/8	0/4	2
	300	0/1	0/1	1/1	0/1	4/4[e]	0/2	
2u	100	2/5	0/1	1/3	0/3	0/8	0/4	1
	300	5/5	0/1	1/1	0/1	0/4	0/2	

[a] Subcutaneous pentylenetetrazole test (number of animals protected/number of animals tested). [b] Maximal electroshock test. [c] Rotorod toxicity (number of animals exhibiting toxicity/number of animals tested). [d] The classifications are as follows: 1, anticonvulsant activity at 100 mg/kg or less; 2, anticonvulsant activity at doses greater than 100 mg/kg. Results in parentheses are the results of a second trial. [e] Toxic at 30 min. [f] Anesthetized.

hancement of activity while the same substitution greatly increased the anticonvulsant activity of the aniline enaminones.[27] These similar observations both indicate a steric component in anticonvulsant activity.

(b) Topliss Method. The lack of a correlation between anticonvulsant activity and σ and π for our para-substituted compounds in the Craig method prompted an analysis by the Topliss approach which led to the synthesis of dichloro derivatives **2b** and **2s**; 3′-chloro, **2o**; 3′-bromo, **2q**; 3′-(trifluoromethyl), **2t**; and 3′-fluoro, **2w**. The results revealed that activity was increased with the 2′,4′-dichloro analog **2b**, the 3′-fluoro analog **2w**, and the 3′-chloro analog

Table VIII. Phase I Test Results: 100 mg/kg Intraperitoneal (ip) Study in Mice

compd	time, h	dose, mg/kg	scMet[a]	MES[b]	Tox[c]
2b	0.25	100	nd[d]	0/2	0/2
	1.00		nd[d]	0/2	0/2
2c	0.25	100	nd[d]	0/2	0/2
	1.00		nd[d]	0/2	0/2
2d	0.25	100	2/2	2/2	0/4
	1.00		0/2	1/2	0/4
2o	0.25	50	nd[d]	0/4	0/4
	0.50		nd[d]	0/4	0/4
	1.00		nd[d]	1/4	0/4
	2.00		nd[d]	0/4	0/4
	4.00		nd[d]	0/4	0/4
2p	0.25	50	nd[d]	0/4	0/4
	0.50		nd[d]	1/4	0/4
	1.00		nd[d]	1/4	0/4
	2.00		nd[d]	2/4	0/4
	4.00		nd[d]	0/4	0/4
2r	0.25	50	nd[d]	0/4	0/4
	0.50		nd[d]	0/4	0/4
	1.00		nd[d]	0/4	0/4
	2.00		nd[d]	1/4	0/4
	4.00		nd[d]	0/4	0/4
2u	0.25	50	nd[d]	0/4	0/4
	0.50		nd[d]	0/4	0/4
	1.00		nd[d]	0/4	0/4
	2.00		nd[d]	2/4	0/4
	4.00		nd[d]	0/4	0/4

[a] Pentylenetetrazol seizure test (refer to Table VII for definition). [b] Maximal electroshock test (refer to Table VII for definition). [c] Rotorod toxicity (refer to Table VII for definition). [d] nd = not determined.

2o. The fact that 4′-(trifluoromethyl) analog **2c** was active while the 3′-analog **2t** was inactive was surprising due to the reported anticonvulsant activity of dezinamide, **1**, and 3-(trifluoromethyl)cinnamamides.[31]

(c) Semiempirical Method. This method involved the use of the Craig and Topliss principles and our own intuitive approach. Based on the above studies it was noted that (i) anticonvulsant activity was enhanced by $+\sigma$, $+\pi$ substituents; (ii) activity of the fluoro and chloro compounds was enhanced by meta substitution compared to para substitution; and (iii) the 2′,4′-dichloro analog **2b** was more active than the 3′,4′-isomer **2s** all pointed to the fact that $+\sigma$, $+\pi$ substituents in the 2′-position may further enhance anticonvulsant activity. Thus, the following 2′-analogs were synthesized and evaluated: bromo **2d**, fluoro **2p**, chloro **2r**, and trifluoromethyl **2u**. The results did in fact verify our initial hypothesis that a steric factor is a vital component in the evaluation of these analogs. The 4′-, 3′-, and 2′-fluoro analogs **2k**, **2w**, and **2p**, respectively, illustrate this point. Anticonvulsant activity classification (ASP classification, see Table VII) for these compounds in the MES evaluation are: 3 (inactive), 2 (active at doses greater than 100 mg/kg), and 1 (active at doses 100 mg/kg or less), respectively. Topliss[29a] noted that *p*-fluoro substitution produces a minimal change in σ and π effects compared to the unsubstituted compound, thus **2k** should have been active when compared with **2a**. The increase in activity on changing the fluorine atom from the para to the meta and to the ortho position may be related to its strong electron-withdrawing and hydrogen-bonding effect which may effect its interaction with the receptor and/or to maintain the spirane in a preferred configuration for its interaction. This ortho effect enhancing anticonvulsant activity has been reported.[25] More research on this phenomena is continuing in our laboratories and will be reported shortly.

(d) Conclusion. The general inferences that can be made on the anticonvulsant activity of the spiroimidooxy

Table IX. Anticonvulsant Screening Project (ASP): Phase II Quantification Data in Mice

compd	ED50[a,b] MES	ED50[a,b] scMET	TD50[a,c]	PI[d] MES	PI[d] scMet	TPE[e] activity	TPE[e] toxicity
2b	241 (174–296)	190 (123–242)	360 (306–445)	1.5	1.9	1.00	0.50
2c	300	300	>500	>1.7	>1.7	2.00	0.25
2d	113 (98–237)	154 (107–193)	260 (211–277)	2.3	1.7	0.25	0.25
2a	111 (100–122)		>500	>4.5		0.25	4.00
phenytoin	9.5 (8.1–10.4)	*f*	65.5 (52.5–72.1)	6.9		2.00	2.00
carbamazepine	8.8 (5.5–14.1)		72 (52.5–135)	8.1		0.25	0.25
phenobarbital	21.8 (15.0–25.5)	13.2 (5.9–15.9)	69.0 (62.8–72.9)	3.2	5.2	1.0	0.50
valproate	272 (247–338)	149 (123–177)	426 (369–450)	1.6	2.9	0.25	0.25
ethosuximide	>1000	130 (111–151)	441 (383–485)		3.4	0.50	0.50

[a] ED50 and TD50 values are in milligram/kilograms of test drug delivered intraperitoneally (ip). [b] Measured at time of peak effect. [c] Measured at time of peak neurologic deficit. [d] PI = protective index (TD50/ED50). [e] Time of peak effect. TPE for activity determined in the MES test for compounds **2a**, **2b**, **2c**, and **2d** and in the scMet test for **2b**, **2c**, and **2d**. Numbers in parentheses are 95% confidence limits. [f] Not effective.

Table X. Elevation of Threshold for Electroshock-Induced Seizures in Mice

compd	MES route of adminstration; time, h	MES dose, mg/kg	MES no. of mice protected/no. tested; %	MES ED50[a], mg/kg	route of adminstration; time, h	dose, mg/kg	% elevation of threshold	TID_{20}[b], mg/kg
2a	po; 0.5	200	1/8; 13		ip; 0.5	60	14	
		300	2/8; 25	494 (273–895)		80	26	71
		400	2/5; 40			90	28	
2b	ip; 0.5	100	1/12; 8		nd[c]	nd[c]	nd[c]	nd[c]
		150	3/12; 25	216 (166–281)				
		200	5/12; 42					
		250	5/8; 63					

[a] Dose protecting 50% of mice from tonic hind limb extension. Numbers in parentheses are 95% confidence limits. [b] Dose elevating the threshold for maximal (tonic extension) electroconvulsions by 20%. [c] nd = not determined.

Table XI. Summary of ASP Classification for Substituents[a]

position	substituent (compd)	ASP classification	van der Waals radii[b]
para	F (**2k**)	3	1.35
	Br (**2f**)	3	1.95
	Cl (**2e**)	3	1.80
	CF_3 (**2c**)	2	2.15[c]
meta	F (**2w**)	2	1.35
	Br (**2q**)	3	1.95
	Cl (**2o**)	1	1.80
	CF_3 (**2t**)	3	2.15[c]
ortho	F (**2p**)	1	1.35
	Br (**2d**)	2	1.95
	Cl (**2r**)	2	1.80
	CF_3 (**2u**)	1	2.15[c]
2,4	Cl_2 (**2b**)	2	
3,4	Cl_2 (**2s**)	3	
	H (**2a**)	2	1.20

[a] Anticonvulsant Screening Project (ASP), phase I results. For an explanation of the classifications see Table VII. [b] Data from ref 38. [c] Calculated from the difference of fluorine and hydrogen (1.35–1.2 = 0.15) and adding it to methyl (2.0, ref 38).

analogs include the following: (1) although the general trend is for anticonvulsant activity to increase with CLOGP values for the spiroimidooxy analogs, steric and electronic effects must also be considered; (2) X-ray crystallographic analysis of compound **2a** indicates that anticonvulsant activity is retained when the substituted phenyl ring is oriented in a parallel plane with the heterocyclic ring of the spiroimidooxy moiety; (3) molecular modeling studies with phenytoin did not reveal any significant correlation between activity and energy minima; (4) an increase in anticonvulsant activity was observed in the monofluoro compounds (**2k**, **2w**, **2p**) with the maximum activity observed in ortho position. The increased potency of the **2p** may indicate a favorable electronic effect; (5) in the monochloro-substituted analogs (**2e**, **2o**, **2r**), the order of anticonvulsant activity was meta (**2o**) > ortho (**2r**) > para (**2e**), suggesting that a steric interaction was a prominent factor; (6) except for compound **2r**, the active analogs also displayed activity against scMet seizures. This broad spectrum of anticonvulsant activity is a potential advantage over the commercial anticonvulsants.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Observed boiling points were also uncorrected. IR spectra were recorded on samples in Nujol, or as diluted chloroform solutions in matched sodium chloride cells or neat with a Perkin-Elmer 1330 spectrophotometer. ^1H NMR spectra were recorded on a General Electric QE 300-MHz spectrometer in deuterated solvents using tetramethylsilane as an internal reference. The octanol–water partition coefficients (*P*) were determined either on a Perkin-Elmer Lambda 2 or a Varian DMS100S double beam ultraviolet spectrophotometer. These data were verified independently by Midwest Research Institute, Kansas City, MO. Elemental analyses (C, H, N, and halogen) were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY. Where analyses are indicated only by the symbols of the elements, analytical results for the elements were within 0.4% of the theoretical values. Experimental data for all of the imidooxy spiranes are provided in Table I. Ethyl α-cyclopentylidene-α-cyanoacetate (**4**),[31a,b] 1-(cyanomethyl)-1-cyanocyclopentane (**5**),[8] 1-carboxycyclopentane-1-acetic acid (**6**),[31a,c] 1-carboxycyclopentane-1-acetic acid anhydride (**7**),[31a] *N*-hydroxy-2-azaspiro[4.4]nonane-1,3-dione (**8**),[6] *N*-(benzyloxy)-2-azaspiro[4.4]nonane-1,3-dione (**2a**),[6] method B, and *N*-benzyl-2-azaspiro[4.4]nonane-1,3-dione (**10**)[6] were prepared by literature procedures; however, in the case of anhydride **7**, acetyl chloride was replaced with acetic anhydride with comparable yields.[8] Typical experiments illustrating the general procedures for the preparation of the imidooxy derivatives are described below.

A. Chemistry. *N*-(Benzyloxy)-2-azaspiro[4.4]nonane-1,3-dione (2a). The "one-pot" method of Lange[32] was employed as follows. Sodium (0.75 g, 0.033 mol) was dissolved in 35 mL of absolute ethanol in a 250-mL single-neck round-bottom flask equipped with a magnetic stirrer, a Claisen adapter sealed with a septum, a condenser, and a drying tube. After 15 min, the mixture was heated to reflux for 30 min. Five grams (0.030 mol) of **8**,[6] dissolved in 50 mL of absolute ethanol, was added as rapidly as possible. The solution changed from clear to light brown, and a fine white precipitate of the sodium salt formed. On continued

heating, the precipitate dissolved. This mixture was refluxed an addtional hour. Benzyl chloride (4.13 g, 0.033 mole) was added via a syringe over 5 min, and the mixture was refluxed an additional 4 h. The mixture was filtered to remove the sodium chloride, and the filtrate was evaporated under reduced pressure, whereupon a brown solid formed. This mass was recrystallized from toluene as white needles, mp 140–141 °C, yield 6.34 (82.5%). A mixture melting point with authentic **2a** prepared by method B[6] showed no depression.

***N*-Hydroxy-2-azaspiro[4.4]nonane-1,3-dione, Sodium Salt (8a).** *N*-Hydroxy-2-azaspiro[4.4]nonane-1,3-dione (**8**) (16.92 g, 0.10 mole) was dissolved in 60 mL of absolute ethanol. To this solution was added sodium ethoxide (prepared with 2.3 g (0.1 mol) of sodium in 60 mL of absolute ethanol) with stirring. The mixture was stirred for an additional 16 h at room temperature. The precipitate which formed was collected by filtration, washed with cold absolute ethanol, and air-dried. The amorphous powder, 18.95 g (95.2%), mp 210–213 °C, was stored in a vacuum desiccator until use.

***N*-((2′,4′-Dichlorobenzyl)oxy)-2-azaspiro[4.4]nonane-1,3-dione (2b). Method A.** The sodium salt, **8a** (2.68 g, 0.014 mol), was dissolved in a mixture of 40 mL of acetone and 14 mL of water. To this solution was added 0.021 mol of 2,4-dichlorobenzyl chloride in 30 mL of acetone while stirring at room temperature. The reaction mixture was refluxed for 15 h, with removal of approximately one-third of the solvent mixture. The resultant precipitate was collected and recrytallized from methanol to a constant mp 103–104 °C. Yield: 2.89 g (63%).

B. X-ray Crystal Analysis. All experimental details concerning the structural analysis of compounds **2a** and **10** are given in Table II. The structures were solved by direct methods with the SHELXS86[33] program and refined with SHELX76.[34] Geometric calculations were carried out with PARST,[11] and the figure was drawn with ORTEP.[35]

C. log *P*. A pH 7.4 buffer was prepared by dissolving a premixed phosphate buffer salt (Fischer Scientific) in an appropriate volume of deionized water. The aqueous buffer was saturated with octanol prior to partitioning by adding octanol, mixing, and allowing the phases to separate overnight. Portions of octanol were saturated with the buffer in the same manner. A stock solution was prepared for each compound by adding 1.5 mL of methanol to the contents of the sample vial. The resulting solution was then added dropwise to a 150-mL portion of the buffer to obtain adequate absorbance. A portion of the buffer was used as a blank for the stock solutions with an appropriate volume of methanol added. The sample solutions and blank were shaken for 1 h at ambient temperature and then gravity filtered to remove any undissolved compound. Aliquots (~10 mL) of the blank and stock solution were transferred to test tubes and centrifuged for approximately 45 min before determining the absorbance. A 100-mL portion of each stock and blank solution was volumetrically transferred to a separatory funnel, and 2 mL of octanol was added. After the separatory funnels were gently inverted approximately 100 times, the phases were allowed to separate for about 1 h. Aliquots (~10 mL) of the partitioned blank and sample solutions were transferred to test tubes and centrifuged for approximately 45 min before determining the absorbance. The absorbance of the aqueous phase was determined for each solution before and after partitioning, scanning from 400 to 200 nm. The appropriate blank was used to determine the baseline for each solution. Data is presented in Table V and Figure 1.

D. Molecular Modeling. Computations were performed on a Silicon Graphics Personal Iris 4D/35 workstation running Molecular Simulations Quanta and CHARMM molecular mechanics software[21] as previously detailed.[22] A principal structure file (PSF) was derived for the C(=O)NOC fragment. All other fragments were available in the residual topology file (RTP). Each spiro structure in Table I was initially minimized employing steepest descents (100 minimization steps) and subsequently by adopted-basis Newton Raphson (ABNR, 1000 steps). These individual minima were saved for a conformational search employing the torsional angles previously discussed. All torsions were restricted to 180° ± 20° as noted by previous studies.[22] These analogs were minimized employed ABNR (100 steps), and the lowest energy conformer was retained for molecular simularity studies with phenytoin. The minimized analog and phenytoin were matched using the carbonyl groups. The molecular volumes were calculated within grid point range of 0.500 Å. Data is shown in Table VI.

E. Pharmacology. Initial evaluation for anticonvulsant activity was done by the Epilepsy Branch, National Institute of Neurological and Communicative Disorders and Stroke.[26] These tests were performed in male Carworth Farms no. 1 (CF1) mice. Phase I of the evaluation included three tests: maximal electroshock (MES), subcutaneous pentylenetetrazole (scMet), and rotorod test for neurological toxicity (Tox). Compounds were either dissolved or suspended in 30% poly(ethylene glycol) 400 and were administered by intraperitoneal injection at three dosage levels (30, 100, and 300 mg/kg) with anticonvulsant activity and neurotoxicity noted 30 min and 4 h after administration. The compounds listed in Table VII were those which displayed significant activity in phase I evaluations. An additional phase I evaluation tested the candidate spiranes between 15 min and 4 h after administration at 100 mg/kg. These data are provided in Table VIII. Phase II testing quantitated the anticonvulsant activity and neurotoxicity observed for the most promising compounds in phase I. Thus **2b**, **2c**, and **2d** were evaluated in this scheme. These data are provided in Table IX. Phase II determined the median effective dose (ED50) and median toxic dose (TD50). The ED50 and TD50 values and their confidence limits were determined at the time of peak effect of each compound by the method of Litchfield and Wilcoxon.[36] The MES and elevation of maximal seizure threshold tests done in our laboratory (Table X) were also performed in CF1 male mice (23–34 g). All compounds were administered in a 0.5% methylcellulose suspension by either ip or oral (po) administration. The method for the MES test was the same as that employed by the ADD Program. The elevation of maximal seizure threshold test was that described by Loscher and Schmidt[37] and was previously reported.[22] Phase VIA provided oral rat data comparable to phase II ip data in mice. Male Sprague–Dawley rats were employed in this evaluation. Compound **2d** was evaluated in this procedure; however, there was no MES protection at 50 mg/kg.

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