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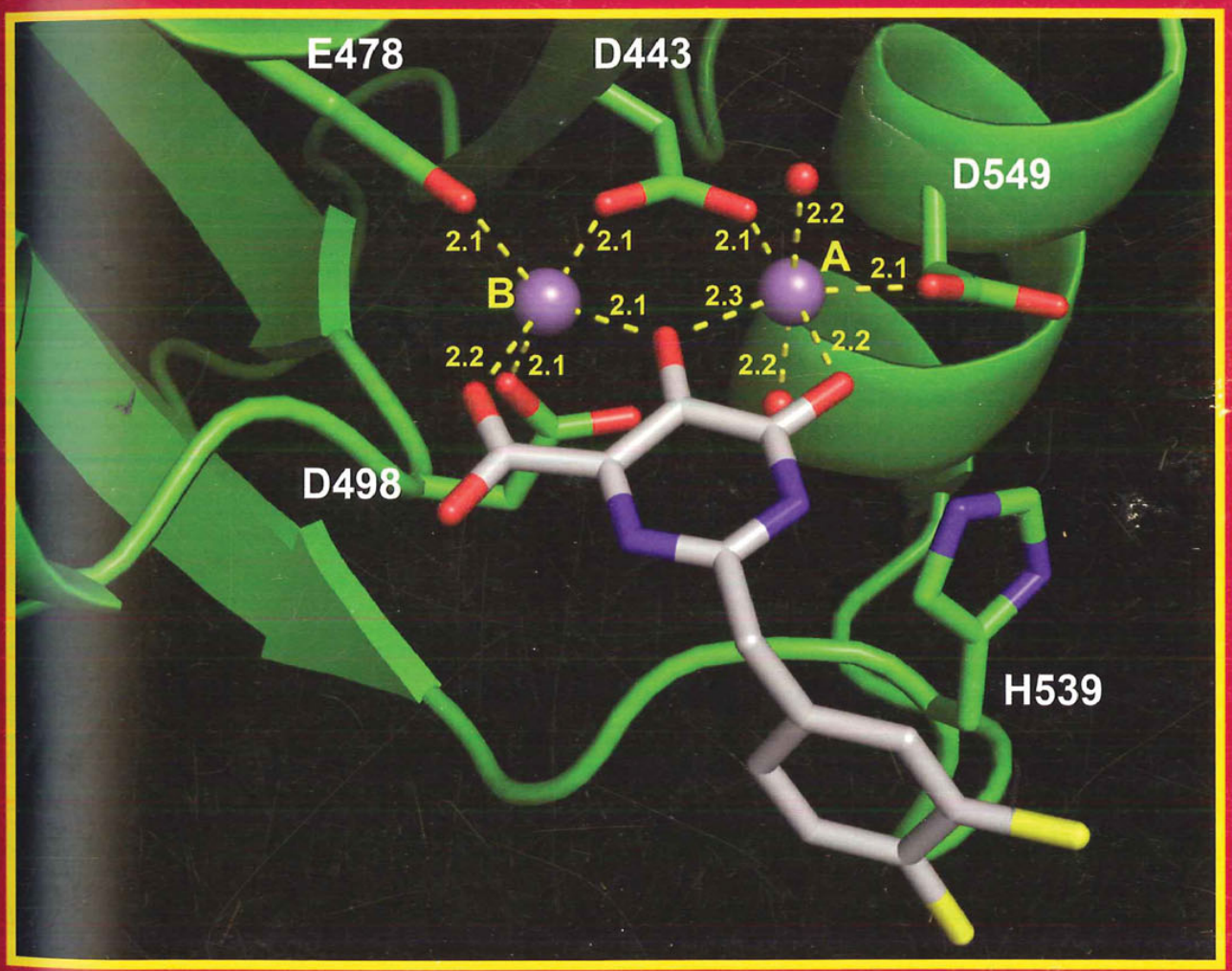

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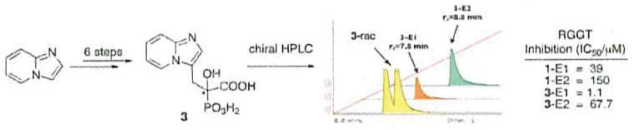
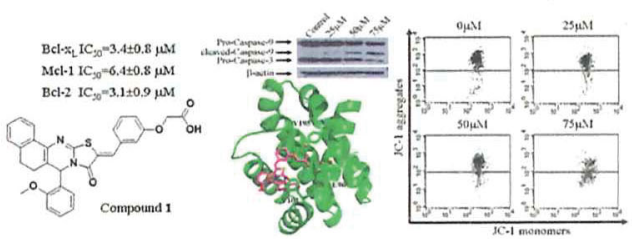
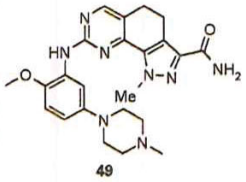
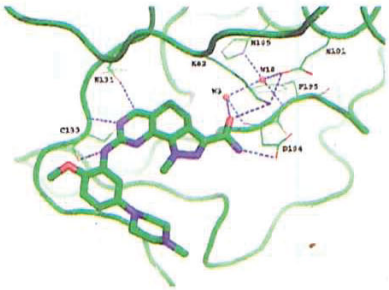
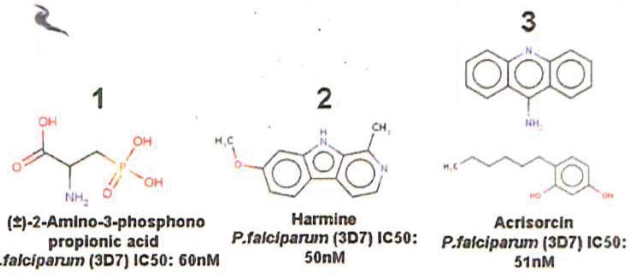
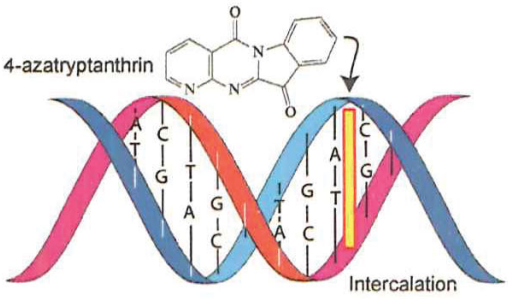


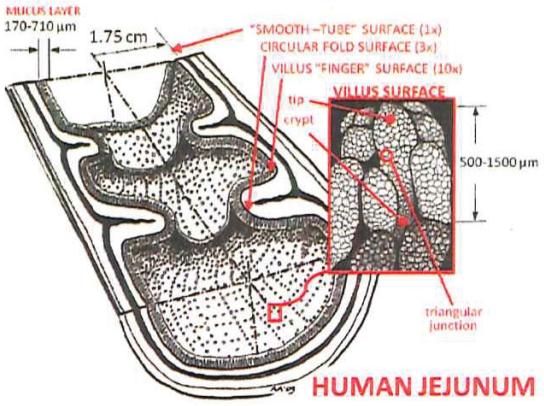


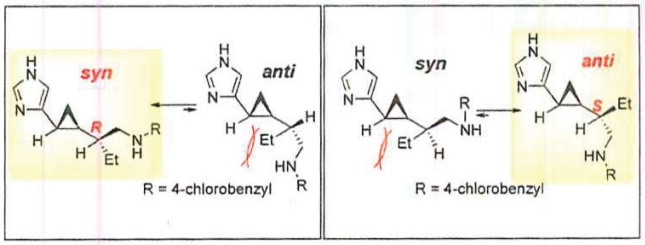


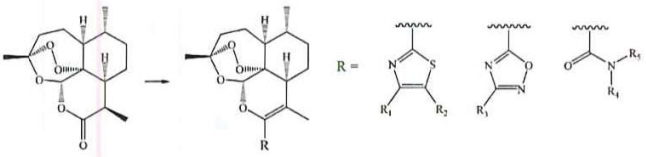


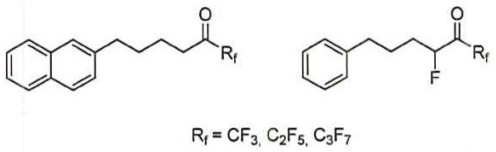


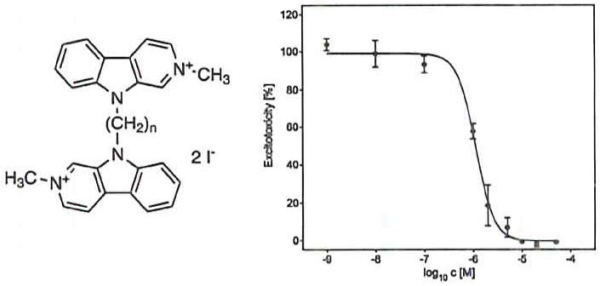


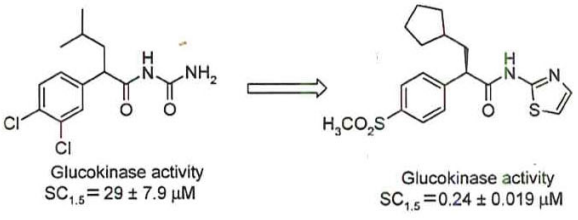




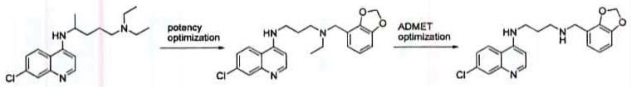








3685 **Development of a New Generation of 4-Aminoquinoline Antimalarial Compounds Using Predictive Pharmacokinetic and Toxicology Models**



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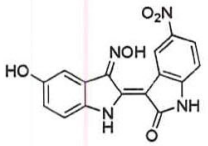
3696 ■ **5,5′-Substituted Indirubin-3′-oxime Derivatives as Potent Cyclin-Dependent Kinase Inhibitors with Anticancer Activity**



3a

5-Nitro-5'-hydroxy-indirubin-3'-oxime

CDK2 IC_{50} = 1.91 nM

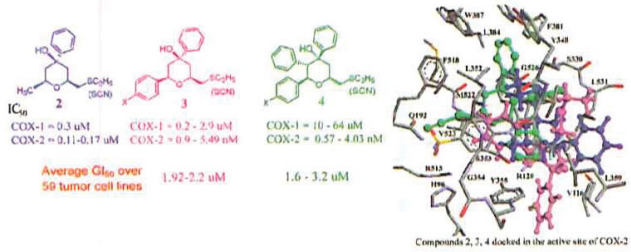
5a

5-Nitro-5'-fluoro-indirubin-3'-oxime

CDK2 IC_{50} = 1.71 nM

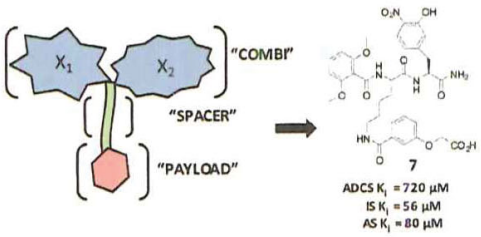
Soo-Jeong Choi, Jung-Eun Lee, Soon-Young Jeong, Isak Im, So-Deok Lee, Eun-Jin Lee, Sang Kook Lee, Seong-Min Kwon, Sang-Gun Ahn, Jung-Hoon Yoon, Sun-Young Han, Jae-Il Kim, and Yong-Chul Kim*

3707 ■ **Mono-, Di-, and Triaryl Substituted Tetrahydropyrans as Cyclooxygenase-2 and Tumor Growth Inhibitors. Synthesis and Biological Evaluation**



Palwinder Singh* and Atul Bhardwaj

3718 ■ **Targeting Multiple Chorismate-Utilizing Enzymes with a Single Inhibitor: Validation of a Three-Stage Design**



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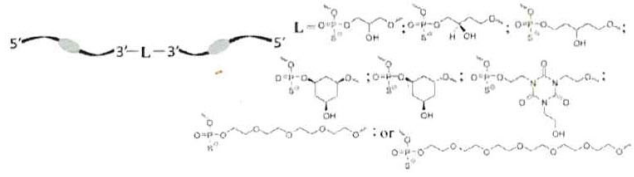
3730 ■ **Impact of Nature and Length of Linker Incorporated in Agonists on Toll-Like Receptor 9-Mediated Immune Responses**



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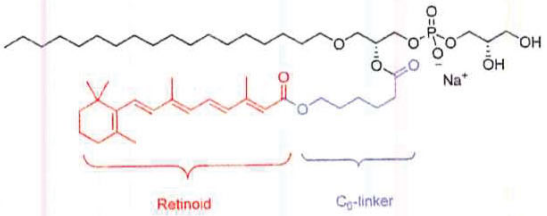

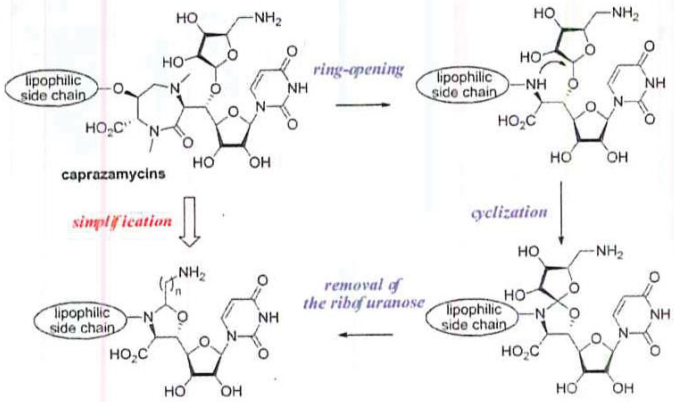

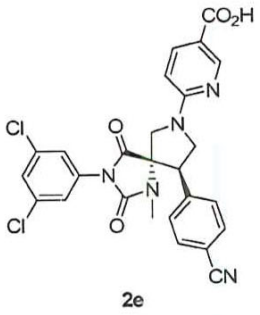

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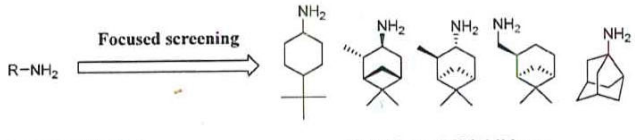

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About the cover. X-ray structure of a pyrimidinol carboxylic acid bound in the active site of the truncated RNase H domain of HIV-1 reverse transcriptase via the chelation of two manganese(II) ions. Interatomic distances are indicated in Å, and key amino acids are labeled (HIV-1 reverse transcriptase numbering) (Kirschberg, T. A.; et al. *J. Med. Chem.* **2009**, *52*, 5781–5784).

researchers noted, through immunostaining, that POP and amyloid β-peptide were colocalized in the brain of age-accelerated mice,[42] although POP activity seems to be associated with neuronal damage rather than with β-amyloid accumulation.[43] In this latter report, only POP-like activity

several peptide hormones and neuropeptides in vitro (Table 1).[1,8,12,27,51–53]

Neurons in the brain express POP, but the level of expression is different in various areas of the brain and is age-dependent.[37] POP is a synaptosomal membrane peptidase[27]

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Journal of Medicinal Chemistry Article

Merging the Structural Motifs of Functionalized Amino Acids and α-Aminoamides: Compounds with Significant Anticonvulsant Activities

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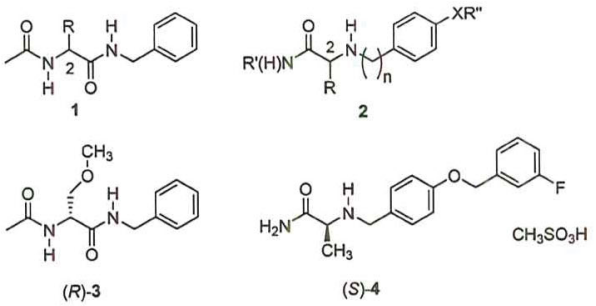
[†]*Division of Medicinal Chemistry and Natural Products, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599-7568,* [‡]*Epilepsy Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 6001 Executive Boulevard, Suite 2106, Rockville, Maryland 20892, and* [§]*Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27599-3290*

Received February 11, 2010

Functional amino acids (FAAs) and α-aminoamides (AAAs) are two classes of antiepileptic drugs (AEDs) that exhibit pronounced anticonvulsant activities. We combined key structural pharmacophores present in FAAs and AAAs to generate a new series of compounds and document that select compounds exhibit activity superior to either the prototypical FAA (lacosamide) or the prototypical AAA (safinamide) in the maximal electroshock (MES) seizure model in rats. A representative compound, (*R*)-*N*-4′-((3″-fluoro)benzyloxy)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**10**), was tested in the MES (mice, ip), MES (rat, po), psychomotor 6 Hz (32 mA) (mice, ip), and hippocampal kindled (rat, ip) seizure tests providing excellent protection with ED_{50} values of 13, 14, ~10 mg/kg, and 12 mg/kg, respectively. In the rat sciatic nerve ligation model (ip), (*R*)-**10** (12 mg/kg) provided an 11.2-fold attenuation of mechanical allodynia. In the mouse biphasic formalin pain model (ip), (*R*)-**10** (15 mg/kg) reduced pain responses in the acute and the chronic inflammatory phases.

Epilepsy is a chronic disorder, characterized by recurrent, unprovoked seizures.[1] A seizure is defined as a discrete clinical event arising from transient, hypersynchronous, abnormal neuronal behavior. Epilepsy, then, is not a disease but rather a syndrome arising from a group of nonspecific, dysfunctional events in the brain. The treatment mainstay for patients with epileptic disorders has been the long-term and consistent administration of anticonvulsant drugs.[2,3] There are more than 40 pharmacologic therapies used for the treatment of epilepsy.[4] Unfortunately, even when used optimally, these therapeutic interventions are ineffective for some 30% of patients.[5] Moreover, their use is associated, in more than 40% of patients, with untoward effects (e.g., drowsiness, dizziness, nausea, liver damage).[6] The shortcomings of current regimens highlight the need for new, more effective agents.

We have previously reported that functionalized amino acids (FAAs,[a] **1**)[7−18] exhibit excellent anticonvulsant activities in various animal seizure models. Whole-animal pharmacological studies for **1** showed a unique profile, which indicated a novel mechanism of action.[7−19] Similarly, studies have demonstrated that α-aminoamides (AAAs, **2**) provide superb seizure protection.[20,21] Representative examples for each class of compounds have advanced through clinical trials. Lacosamide ((*R*)-**3**),[16] the **1** prototype, is a first-in-class antiepileptic drug (AED) that was recently introduced in the United States and Europe for adjuvant treatment of partial-onset seizures in adults.[22] Safinamide ((*S*)-**4**) is a leading representative for **2**. (*S*)-**4** exhibited excellent protection in seizure models, and positive responses have been reported in recent phase III human clinical trials for the treatment of Parkinson disorders.[21,23,24]



Recent electrophysiology studies using cultured rat cortical neurons demonstrated that (*R*)-**3** selectively enhanced sodium channel *slow* inactivation in a time- and voltage-dependent manner, without affecting fast inactivation.[25] Similarly, examination of (*R*)-**3** with recombinant Na_V 1.3 and 1.7 voltage-gated sodium channels expressed in HEK293 cells and of Na_V1.8-type TTX-R currents from DRG neurons showed that (*R*)-**3** selectively modulated the slow inactivation state in each of these sodium channel subtypes.[26] (*R*)-**3** is the only reported antiepileptic agent that selectively enhances slow

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[a] Abbreviations: FAA, functionalized amino acids; AAA, α-aminoamides; AED, antiepileptic drug; TTX-S, tetrodotoxin-sensitive; MES, maximal electroshock seizure; SAR, structure−activity relationship; IBCF, isobutylchloroformate; NMM, *N*-methyl morpholine; TBTU, *O*-(benzotriazol-1-yl), *N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; DMTMM, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methoxymorpholinium chloride; ASP, Anticonvulsant Screening Program; NINDS, National Institute of Neurological Disorders and Stroke; scMet, subcutaneous metrazol.

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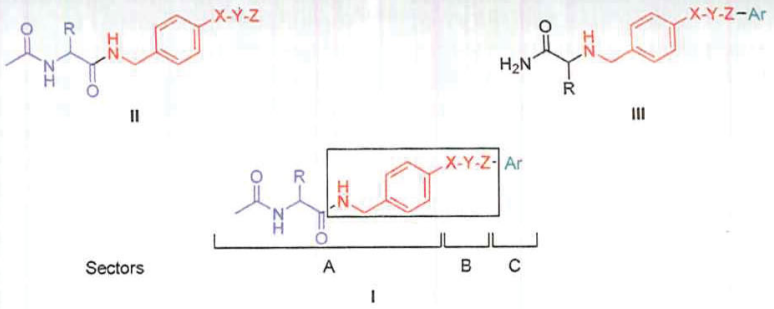


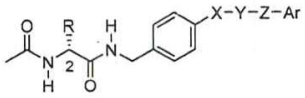
Figure 1. Overlay of Pharmacophores in **I**.

inactivation without apparent interaction with fast inactivation gating.

Patch-clamp, whole-cell electrophysiological studies using hippocampal neurons demonstrated that (*S*)-**4** inhibited tetrodotoxin-sensitive (TTX-S) *fast* Na^+ currents in a concentration-dependent manner.[21] The inhibition was voltage dependent, showing an IC_{50} of ~100 μM when currents were stimulated from a resting condition, while stronger inhibition (IC_{50} = 33 μM) was observed when sodium currents were stimulated from a −60 mV depolarized membrane potential. Together, these findings indicated that (*S*)-**4** exhibited a higher affinity for the sodium channel's inactivated state.[24] Thus, the mechanisms associated with sodium channel inhibition for (*R*)-**3** and (*S*)-**4** are different.

At first glance, (*R*)-**3** and (*S*)-**4** appear structurally similar. Both have low molecular weights ((*R*)-**3**: MW = 250; (*S*)-**4**: MW = 302 [free base]), each has a vicinal diamine backbone that contains a carbonyl (C═O) moiety, and each has one chiral center. In addition, both compounds contain an *N*-benzyl ($PhCH_2$)-type substituent. Pharmacologically, both (*R*)-**3** and (*S*)-**4** exhibited excellent seizure protection[16,19,27,28] in the maximal electroshock seizure (MES) animal model,[29] and electrophysiology studies demonstrated that both modulate sodium currents.[21,25,26] Further inspection of (*R*)-**3** and (*S*)-**4** revealed stark differences in structure and function. First, (*R*)-**3** is neutral and (*S*)-**4** is basic. Second, the (*R*)-**3** sequence of atoms attaches the *N*-benzyl moiety to an amide while in (*S*)-**4** the substituted *N*-benzyl moiety attaches to an amine. Third, there is a different structure−activity relationship (SAR) in the MES test between the two classes of antiepileptic agents **1** and **2**. For the **1** compounds, we observed a steady improvement in activity as the C(2) position was changed from H and CH_2OH to CH_3 to C_6H_5 to CH_2OCH_3.[8,16] Correspondingly, for **2**, activity in the MES test increased as the C(2) position was changed from C_6H_5 to CH_2OH to H to CH_3.[20] Fourth, (*R*)-**3** showed chiral specificity for function in the mouse (ip) (i.e., MES activity of (*R*)-**3** vs (*S*)-**3** is >22:1),[16] but (*S*)-**4** did not (i.e., MES activity of (*S*)-**4** ≈ (*R*)-**4**).[20,30] Fifth, (*S*)-**4** administration provided protection against several chemoconvulsants[27] while (*R*)-**3** did not.[19] Finally, (*R*)-**3** enhanced the slow inactivation state of the voltage-gated sodium channel thereby selectively blocking the activity of chronically depolarized neurons[25,26] while (*S*)-**4** inhibited TTX-S fast sodium currents.[21]

The structural differences between (*R*)-**3** and (*S*)-**4** likely account for their different modes of action and underscore that each compound has distinctive pharmacophores that contribute to drug function. In this study, we asked whether key structural units in **1** and **2** could be incorporated within a single compound to provide more effective anticonvulsant agents.[31] Herein, we report the design, synthesis, and pharmacological evaluation of a series of compounds that conform to the general structure of **I**, and we document that they display excellent anticonvulsant activities.



I

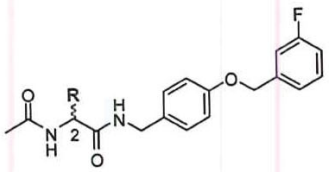
Results

Compound Design. In generating **I**, we used the generalized structure **II** for **1** and **III** for **2** (Figure 1). Both **II** and **III** include an "X-Y-Z" substituent at the *N*-benzyl 4′ site. "X-Y-Z" is a molecular unit 1−3 atoms long, or in the case **I** and **III**, it could also be a single bond. Our recent SAR study for the *N*-benzyl 4′ site in (*R*)-**3** showed that the introduction of select substituents at this position provided compounds with excellent anticonvulsant properties.[18] Similarly, the reported SAR for **2** demonstrated that significant anticonvulsant activity was observed with various linkers ("X-Y-Z") at the *N*-benzyl position that bridged the two aromatic moieties in this agent.[20] The area of pharmacophore overlap in **I** is portrayed in the box, and this overlap permitted the incorporation of key pharmacophores found in **II** (**1**) and **III** (**2**) within a unified structure (Figure 1). For convenience, we divided **I** into three sectors: A, B, and C. Sector A is the structural motif seen in **II** (**1**), sector B is the linker unit "X-Y-Z" reported in both **II** (**1**) and **III** (**2**), and sector C is the terminal aromatic ring (Ar) found in **III** (**2**).

Choice of Compounds. Tables 1−3 lists the **I** compounds evaluated in this study. We prepared 20 compounds (**5**−**22**) in which we varied the structural units in sectors A−C and the chirality of the C(2) center in sector A. Because the number of structural permutations was large, we maintained the structural pattern constancy for two sectors as we changed the other.

For compounds listed in Table 1, sector A was varied while we restricted sectors B and C to an OCH_2 and 3-(fluoro)phenyl moiety, respectively, to match (*S*)-**4**. Specifically, in this set of compounds, we evaluated key structural features important to the **1** SAR. We showed that **1** compounds containing a small *R* substituent provided excellent seizure protection in the MES test and that anticonvulsant activity typically improved when a substituted heteroatom was introduced one atom removed from the C(2) center. Moreover, anticonvulsant activity for the **1** compounds principally resided in the D-configuration.[9−11,16,18] Thus, we progressively increased the R substituent in **5**−**8** from hydrogen to methyl to

Table 1. Novel Neurological Agents: Structure–Activity Relationship of Sector A[a]

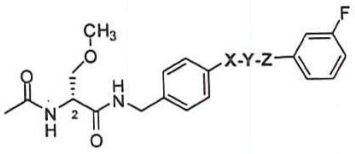


			Mice (ip)[b]				Rat (po)[f]		
Cpd No	R	Stereo	MES,[c] ED_{50}	6Hz, ED_{50}	Tox,[d] TD_{50}	PI[e]	MES,[c] ED_{50}	Tox,[g] TD_{50}	PI[e]
5	H	-	>100, <300 [4.0] >30, <100 [2]		>300 [0.5 and 4.0]		31 [1.0] (18 - 53)	>500 [1.0]	>16
(*R*)-6	(*R*)-Me	*R*	>30, <100 [0.5 and 4]		>300 [0.5]		31 [4.0] (21–44)	>500 [4.0]	>16
(*S*)-6	(*S*)-Me	*S*	>100,< 300 [0.5] > 300 [4.0]		>300 [0.5]		> 30 [0.25 to 4.0]	> 30 [0.25 to 4.0]	
(*R*)-7	(*R*)-*i*-Pr	*R*	>300 [0.5 and 4]		>300 [0.5 and 4]		>30	>30	
(*R*)-8	(*R*)-*t*-Bu	*R*	>300 [0.5 and 4]		>300 [0.5 and 4]				
(*R,S*)-9		*R, S*	28 [0.5] (20 – 36)		210 [2.0] (160 – 290)	7.6	>30 [4]	>30 [4]	
(*R*)-10	(*R*)-CH_2OMe	*R*	13 [0.25] (11 – 16)	~10 [0.25]	26 [0.5] (21 – 34)	2	14 [0.5] (6.1 - 27)	>500 [0.5]	>36
(*S*)-10	(*S*)-CH_2OMe	*S*	>300		>300				
	(*S*)-4[h]		8.0 (7.0 – 9.1)		630 (560 – 700)				
	(*R*)-4[h]		7.2 (5.9 – 8.9)		580 (410 – 830)				
	(*R*)-3[i]		4.5 [0.5] (3.7 – 5.5)		27 [0.25] (26 – 28)		3.9 [2.0] (2.9-6.2)	>500	
	phenytoin[j]		9.5 [2.0] (8.1 – 10)		66 [2.0] (53 – 72)	6.9	30 [4.0] (22 – 39)		> 100
	phenobarbital[j]		22 [1.0] (15 – 23)		69 [0.5] (63 – 73)	3.2	9.1 [5.0] (7.6 – 12)	61 [0.5] (44 – 96)	6.7
	valproate[j]		270 [0.25] (250 – 340)		430 [0.25] (370 – 450)	1.6	490 [0.5] (350 – 730)	280 [0.5] (190 – 350)	0.6

[a] The compounds were tested through the auspices of the NINDS ASP. [b] The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in milligrams per kilogram. [c] MES = maximal electroshock seizure test. [d] TD_{50} value determined from the rotorod test. [e] PI = protective index (TD_{50}/ED_{50}). [f] The compounds were administered orally. ED_{50} and TD_{50} values are in milligrams per kilogram. [g] Tox = behavioral toxicity. [h] Reference 30. [i] Reference 16. [j] Reference 32.

isopropyl to *tert*-butyl and then included in our selection list **9** and **10**, compounds that contained a substituted hetero-atom positioned one atom removed from C(2). For compounds **6** and **10**, we prepared the *R*- (D-configuration) and

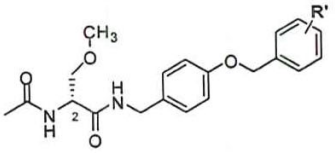
Table 2. Novel Neurological Agents: Structure–Activity Relationship of Sector B[a]



		mice (ip)[b]				rat (po)[f]		
compd no.	−X-Y-Z−	MES,[c] ED_{50}	6 Hz, ED_{50}	Tox,[d] TD_{50}	PI[e]	MES,[c] ED_{50}	Tox,[g] TD_{50}	PI[e]
(*R*)-**11**		> 10, < 30 [0.5]	< 30 [0.5]	> 100, < 300 [0.5]		2.4 [1.0] (1–3.9)	> 500	> 250
(*R*)-**12**	−O−	5.5 [0.25] (3.2–6.3)	~10 [0.5]	23 [0.25] (18–28)	4.2	< 10 [0.25–2.0]	> 10 [0.25–4.0]	
(*R*)-**13**	$-(CH_2)_2-$	> 10, < 30 [0.5]		> 30, < 100 [0.5]		< 30 [1]	> 30 [1]	
(*R*)-**14**	−CH=CH−	> 30, < 100 [0.5]	< 30 [0.25]	> 100, < 300 [0.5]		~30 [1.0, 4.0]	> 30 [0.25, 4.0]	
(*R*)-**15**	−≡−	> 30, < 100 [1.0, 4.0]		> 100, < 300 [4.0]		1.4 [4.0] (0.7 – 2.2)	> 63, < 125 [4]	
(*R*)-**16**	$-CH_2O-$	5.9 [0.25] (4.3–7.3)		10 [0.25] (9.1–13)	1.8	19 [2] (13–25)	> 400 [0.5]	> 21
(*R*)-**17**	$-N(H)CH_2-$	> 10, < 30 [0.5]		> 30, < 100 [0.5]				
(*R*)-**10**	$-OCH_2-$	13 [0.25] (11–16)	~10 [0.25]	26 [0.5] (21–34)	2	14 [0.5] (6.1–27)	> 500 [0.5]	> 36
(*R*)-**18**	$-CH_2OCH_2-$	> 30, < 100 [0.5]		> 30, < 100 [0.5]				
(*R*)-**19**	$-OCH_2\,CH_2-$	> 30, < 100 [0.5, 4.0]		> 30, < 100 [0.5]				

[a] The compounds were tested through the auspices of the NINDS ASP. [b] The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in milligrams per kilogram. [c] MES = maximal electroshock seizure test. [d] TD_{50} value determined from the rotorod test. [e] PI = protective index (TD_{50}/ED_{50}). [f] The compounds were administered orally. ED_{50} and TD_{50} values are in milligrams per kilogram. [g] Tox = behavioral toxicity.

Table 3. Novel Neurological Agents: Structure–Activity Relationship of Sector C[a]



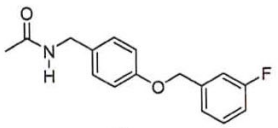
		mice (ip)[b]				rat (po)[f]		
compd no.	R′	MES,[c] ED_{50}	6 Hz, ED_{50}	Tox,[d] TD_{50}	PI[e]	MES,[c] ED_{50}	Tox,[g] TD_{50}	PI[e]
(*R*)-**20**		5.8 [0.25] (4.4–7.2)		22 [0.25] (19–25)	3.8	5.6 [0.25] (4.2–6.4)	> 250 [1.0]	> 45
(*R*)-**21**	**2-F**	6.7 [0.25] (4.8–9.1)		37 [0.5] (29–48)	5.5	11 [0.5] (7.9–13)	> 500	> 45
(*R*)-**10**	**3-F**	13 [0.25] (11–16)	~10 [0.25]	26 [0.5] (21–34)	2	14 [0.5] (6.1–27)	> 500 [0.5]	> 36
(*R*)-**22**	**4-F**	> 10, < 30 [0.5]		> 30, < 100 [0.5]		5.8 [0.5] (4.3–7.3)	> 500	> 86

[a] The compounds were tested through the auspices of the NINDS ASP. [b] The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in milligrams per kilogram. [c] MES = maximal electroshock seizure test. [d] TD_{50} value determined from the rotorod test. [e] PI = protective index (TD_{50}/ED_{50}). [f] The compounds were administered orally. ED_{50} and TD_{50} values are in milligrams per kilogram. [g] Tox = behavioral toxicity.

the *S*- (L-configuration) stereoisomers to determine whether the anticonvulsant activities for **I** mirrored those found for **1**, in which a clear stereochemical preference was observed,[9–11,16,18] or that for **2**, in which both stereoisomers displayed comparable anticonvulsant activities.[20,30] For all compounds listed in Table 1, except **5** and **9**, we prepared **I** as a single stereoisomer. Compound **5** had no chiral center, and the synthetic route for **9** provided the racemic mixture.

For compounds **10**–**19** listed in Table 2, we varied sector B's "X-Y-Z" linker region and employed the (*R*)-**3** structural motif for sector A and the (*S*)-**4** 3-(fluoro)phenyl unit for sector C. Following the SAR reported for (*S*)-**4**,[20] we incorporated one, two, and three atom linkers and varied the heteroatom content and degree of unsaturation of the linker. The choice of the "X-Y-Z" unit was also consistent with the SAR reported for (*R*)-**3**,[18] in which we showed that incorporating select substituents (e.g., alkyl, substituted alkyl, vinyl, acetylenic, aryl) at the 4′ position of the *N*-benzyl ring gave compounds with superb seizure protection in the MES test[29] in rodents with some analogues having activities comparable with (*R*)-**3** and established AEDs.[32]

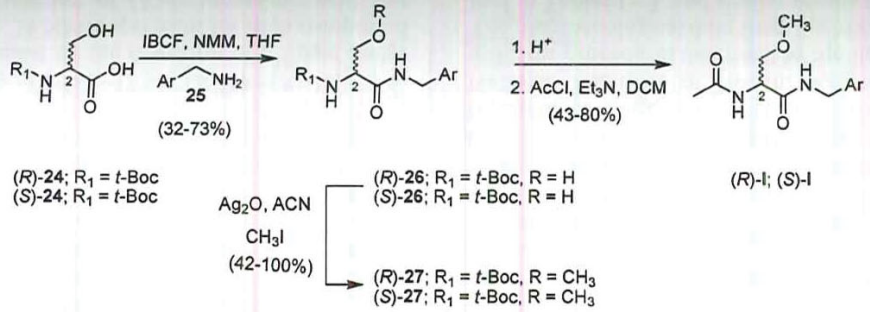
Finally, we evaluated the effect of the terminal aromatic ring by preparing compounds (*R*)-**10**, and (*R*)-**20**–(*R*)-**22** (Table 3). Here, we varied sector C to include the unsubstituted aromatic compound (*R*)-**20** and the three monofluorine–substituted regioisomers (*R*)-**10**, (*R*)-**21**, and (*R*)-**22** and set sector A to match (*R*)-**3** and sector B to match (*S*)-**4**. We also prepared compound **23**, which contains the sector C structural motif found in many of our compounds.



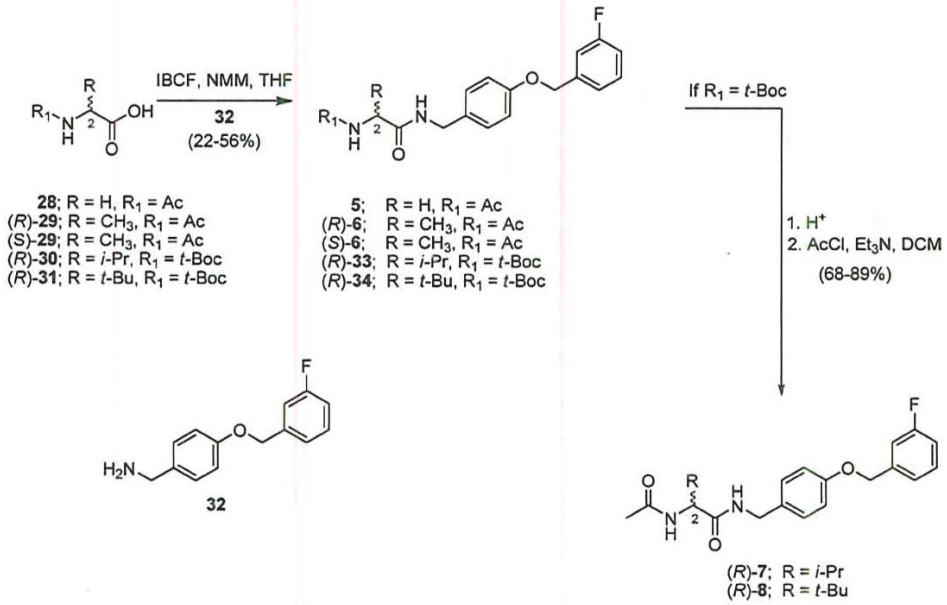
23

Chemistry. Two similar routes were employed to prepare most **I** compounds in this study and depended only on the C(2)-*R* substituent. For most **I** derivatives that incorporated the (*R*)-**3** framework in sector A, we used a recently reported procedure to prepare 4′-substituted *N*-benzylamide (*R*)-**3** analogues[18] beginning with either *tert*-Boc-protected (*R*)- or

Scheme 1. General Procedure for the Preparation of (*R*)- and (*S*)-*N*-(4′-Substituted)benzyl 2-Acetamido-3-methoxypropionamide Derivatives **I**



Scheme 2. General Procedure for the Preparation of (*R*)- and (*S*)-*N*-(4′-(3-Fluorobenzyloxy)benzyl)benzyl 2-Acetamido-2-(substituted)-acetamide Derivatives **5**−**8**



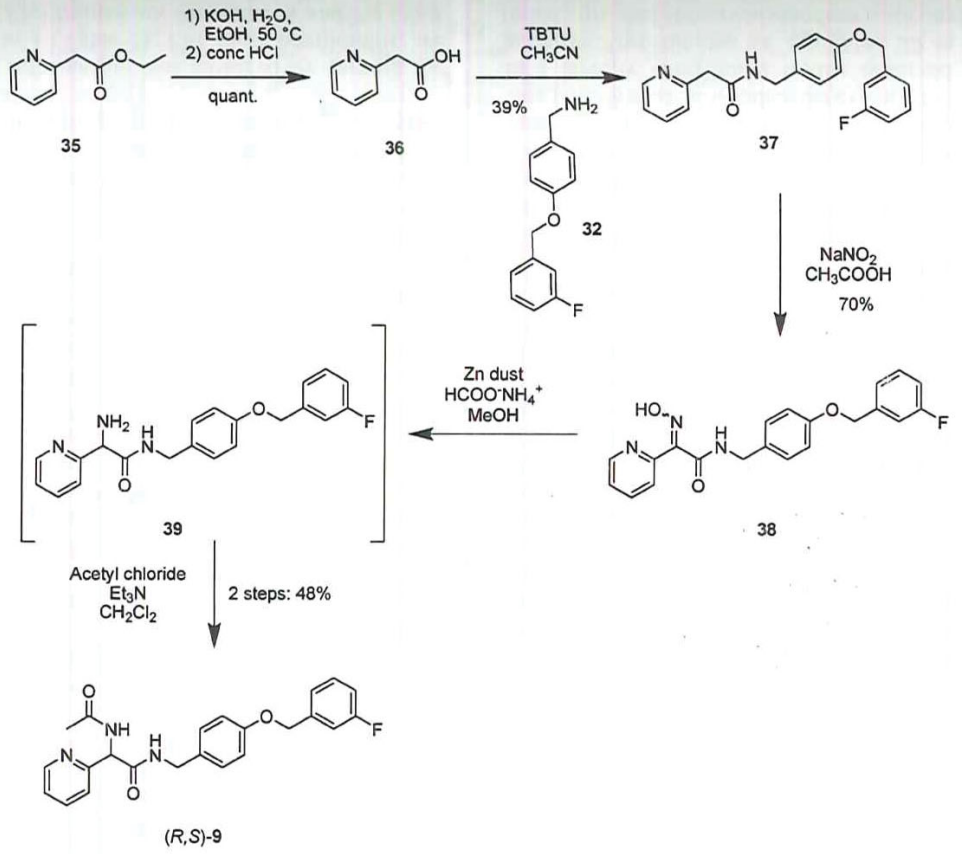
(*S*)-serine **24**. The acid was coupled with the desired benzylamine **25** using the mixed anhydride method (isobutylchloroformate (IBCF), *N*-methyl morpholine (NMM)),[33] unless otherwise indicated, to give the *N*-benzyl amide **26** without racemization of the C(2) chiral center (Scheme 1). Subsequent methylation of the serine hydroxy group (CH_3I, Ag_2O) gave ether **27**. Deprotection of the *tert*-butoxycarbonyl group with acid followed by acetylation of the amine with acetyl chloride and triethylamine gave the desired product, **I**, in 43−80% yield. Using this method, we prepared (*R*)-**10**, (*S*)-**10**, and (*R*)-**11**−(*R*)-**22**.

A similar procedure was used to prepare compounds **5**, (*R*)-**6**−(*R*)-**8**, and (*S*)-**6** (Scheme 2). We began with a commercially available amino acid. Converting the amino acid to either the *N*-acetyl (**28**, (*R*)-**29**, (*S*)-**29**) or the *N*-*tert*-butoxycarbonyl ((*R*)-**30**, (*R*)-**31**) derivative permitted mixed anhydride coupling with benzylamine **32** to give the amides (**5**, (*R*)-**6**, (*S*)-**6**, (*R*)-**33**, (*R*)-**34**). For (*R*)-**33** and (*R*)-**34** that were protected as the *tert*-Boc derivatives, acid deprotection gave the amine, which was directly reacted with acetyl chloride and base to give (*R*)-**7** and (*R*)-**8**, respectively.

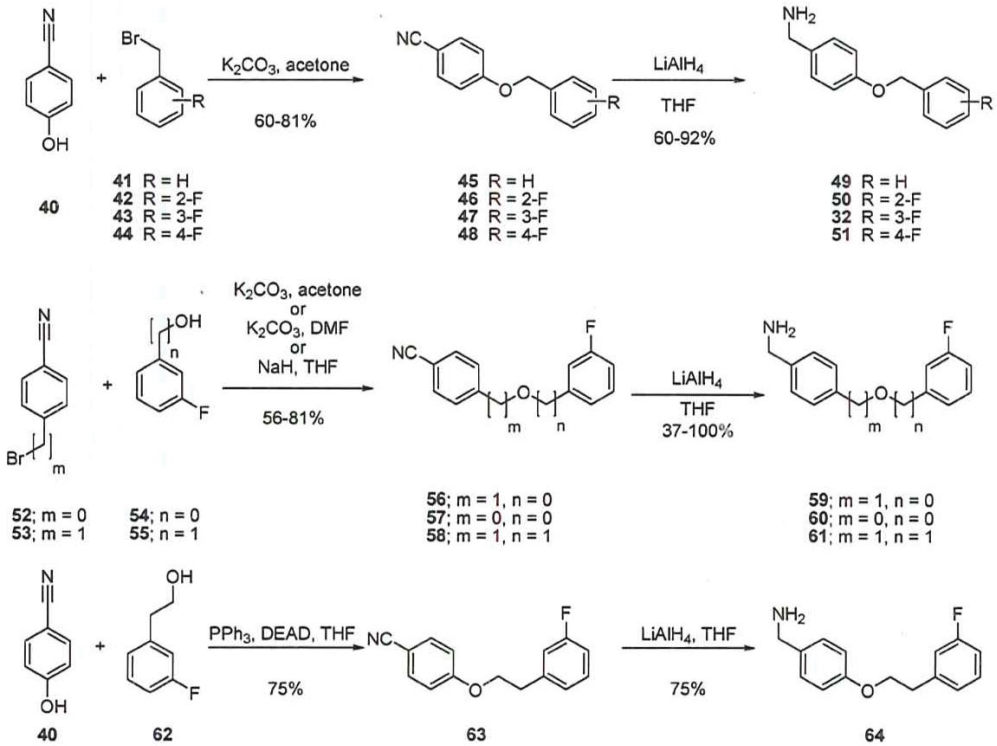
We developed a different route for the C(2) pyridyl derivative (*R*,*S*)-**9** (Scheme 3). Beginning with commercially available ethyl 2-(pyridin-2yl)acetate (**35**), basic hydrolysis provided acid **36**, which was coupled with 4-(((3′-fluoro)benzyloxy)-phenyl)methanamine (**32**) using *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) to give **37**. Treatment of **37** with $NaNO_2$ in acetic acid yielded the oximes **38** as an ∼1:1 mixture of *syn*- and *anti*-isomers. While oximes **38** could be separated by silica gel chromatography, the mixture was reduced to amine **39** with Zn dust in the presence of ammonium formate and then converted to racemic **9** with acetyl chloride and triethylamine.

The extended *N*-benzyl amide moiety within the **I** compounds was a key unit in our compounds. Thus, we used a series of methods to construct this moiety (Schemes 4−6). For many of the compounds, we reacted either 4-cyanophenol (**40**) with a substituted benzyl bromide (**41**−**44**) or a (cyano)-aryl bromide (**52**, **53**) with the substituted phenol (**54**) or aryl-substituted alcohol (**55**) under base conditions to give the ether (**45**−**48**, **56**−**58**) (Scheme 4). Subsequent reduction ($LiAlH_4$) of the nitrile in **45**−**48** and **56**−**58** gave the requisite benzylamine (**32**, **49**−**51**, **59**−**61**) for the mixed anhydride coupling reaction. We prepared nitrile **64** from 4-(hydroxy)-benzonitrile (**40**) and 3-(fluoro)phenethanol (**62**) using Mitsunobu coupling conditions[34] and then reduced nitrile **63** to benzylamine **64** with $LiAlH_4$. Correspondingly, we reacted 4-(bromo)benzonitrile (**52**) with 3-(fluoro)benzylamine (**65**)

Scheme 3. Preparation of *N*-(4-(3-Fluorobenzyloxy)benzyl) 2-Acetamido-2-(pyridin-2-yl)acetamide ((*R*,*S*)-**9**)

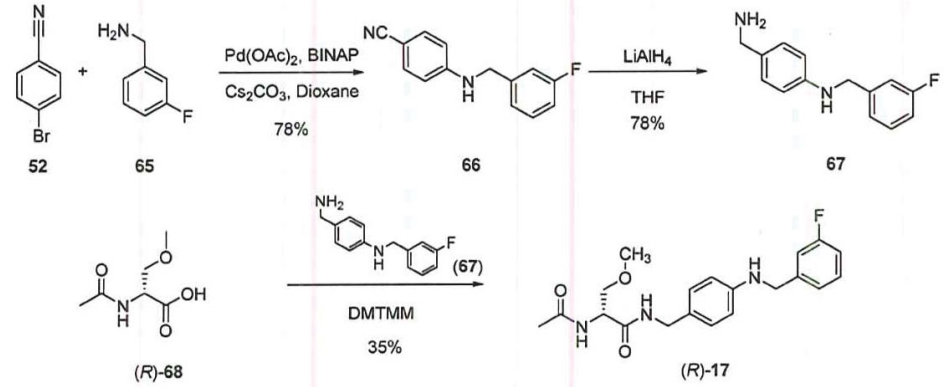


Scheme 4. Benzylamine **32**, **49**−**51**, **59**−**61**, and **64** Synthesis

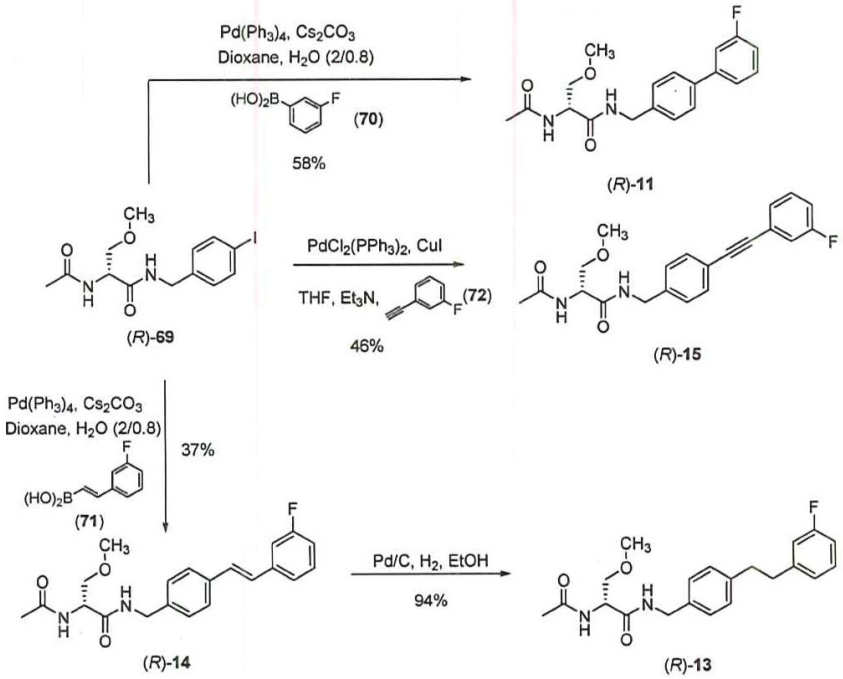


under Buchwald−Hartwig coupling conditions[35] to generate **66**, which was reduced to amine **67** (Scheme 5). Finally, (*R*)-4-(iodo)benzyl 2-acetamido-3-methoxypropionamide[18] ((*R*)-**69**) served as the starting material for **I** compounds

Scheme 5. Benzylamine **67** and Compound (*R*)-**17** Synthesis



Scheme 6. Preparation of Compounds (*R*)-**11**, (*R*)-**13**, (*R*)-**14**, and (*R*)-**15**



(*R*)-**11** and (*R*)-**13**−(*R*)-**15** (Scheme 6). Coupling (*R*)-**69** with 3-(fluoro)phenylboronic acid (**70**) under Suzuki coupling conditions[36] gave (*R*)-**11**. When *trans*-2-((3′-fluoro)phenyl)-vinylboronic acid (**71**) was substituted for 3-(fluoro)phenylboronic acid (**70**), we obtained (*R*)-**14** with an embedded trans-double bond. Reduction of (*R*)-**14** (10% Pd/C, H_2) gave (*R*)-**13**. Sonogashira coupling[37] of (*R*)-**69** with 3-(fluoro)-phenylacetylene (**72**) afforded (*R*)-**15**. For (*R*)-**17** synthesis, we coupled amine **67** with (*R*)-2-acetamido-3-methoxypropanoic acid[17] ((*R*)-**68**) using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methoxymorpholinium chloride (DMTMM)[38] (Scheme 5).

The enantiopurity of (*R*)-**6**−(*R*)-**8**, (*R*)-**10**−(*R*)-**22**, (*S*)-**6**, and (*S*)-**10** was assessed by the detection of a single acetyl methyl signal in the ^{1}H NMR spectrum for each compound when a saturated solution of (*R*)-(−)-mandelic acid was added.[39] In the cases of (*R*)-**10**−(*R*)-**22**, we also observed a single *O*-methyl peak upon addition of (*R*)-(−)-mandelic acid.

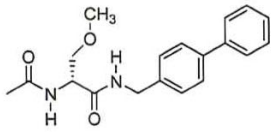
We report, in the Experimental Section, the details (synthetic procedure, characterization) of the final step for all the compounds evaluated in the seizure models. In Supporting Information, we provide a synthetic scheme for each compound tested and the experimental procedures used and physical and full spectroscopic properties for all the synthetic compounds prepared in this study.

Pharmacological Activity. Compounds **5**, (*R*)-**6**−(*R*)-**8**, (*R,S*)-**9**, (*R*)-**10**−(*R*)-**22**, (*S*)-**6**, and (*S*)-**10** were tested for anticonvulsant activity at the Anticonvulsant Screening Program (ASP), which is part of the National Institute of Neurological Disorders and Stroke (NINDS) at the U.S. National Institutes of Health. Screening was performed using the procedures described by Stables and Kupferberg.[40] The pharmacological data from the MES test[29] are summarized in Tables 1−3, and similar results obtained for (*R*)-**3**,[16] (*R*)-**4**,[30] (*S*)-**4**,[30] and the clinical antiepileptic drugs (AEDs) phenytoin,[32] valproate,[32] and phenobarbital[32] are given in Table 1. All compounds were administered intraperitoneally

(ip) to mice and orally (po) to rats. Tables 1−3 lists the values that were determined to be protective in blocking hind limb extension induced in the electrically induced MES seizure model from the rodent identification studies. For compounds that showed significant activity, we report the 50% effective dose (ED_{50}) values obtained in quantitative screening evaluations. Also provided are the median doses for 50% neurological impairment (TD_{50}) in mice, using the rotorod test[41] and the behavioral toxicity effects observed in rats.[42] TD_{50} values were determined for those compounds that exhibited significant activity in the MES test. The protective index (PI = TD_{50}/ED_{50}) for each of these analogues is also listed. Select compounds were also evaluated in the psychomotor 6 Hz (32 mA) seizure models (mice, ip).[43] When the **I** derivatives were evaluated in the subcutaneous Metrazol (scMet) seizure model,[44] none provided protection at doses up to 300 mg/kg at two time points (0.5 and 4 h) (data not shown). The absence of seizure protection in this assay is a hallmark of FAA activity[7−17] and contrasted with the data reported for (*S*)-**4**.[27]

The SAR data for **I** provided distinctive trends. In Table 1, we varied the C(2) *R* group in sector A while maintaining the (*S*)-**4** structural components found in sectors B and C. Using the mice (ip) data, we observed that as the size of the C(2) alkyl group increased from methyl ((*R*)-**6**, MES ED_{50} = >30, <100 mg/kg) to isopropyl ((*R*)-**7**, MES ED_{50} = >300 mg/kg) to *tert*-butyl ((*R*)-**8**, MES ED_{50} = >300 mg/kg), the anticonvulsant activity decreased. We also found that MES seizure protection significantly increased upon the inclusion of a C(2)-substituted heteroatom group one atom removed from the C(2) center ((*R*,*S*)-**9**, MES ED_{50} = 28 mg/kg; (*R*)-**10**, MES ED_{50} = 13 mg/kg versus (*R*)-**6**, MES ED_{50} = >30, <100 mg/kg; (*R*)-**7**, MES ED_{50} = >300 mg/kg; (*R*)-**8**, MES ED_{50} = >300 mg/kg). Similar SAR patterns were observed for **1** compounds.[7,11−14] Furthermore, for both **6** and **10**, we tested the (*R*)- and (*S*)-enantiomers and found that the principal activity resided in the (*R*)-stereoisomer (D-configuration) (MES ED_{50} (mice, ip): (*R*)-**6**, >30, <100 mg/kg vs (*S*)-**6**, >100, <300 mg/kg, and (*R*)-**10**, 13 mg/kg vs (*S*)-**10**, >300 mg/kg). Both the C(2) SAR pattern and the stereochemical preference for the (*R*)-enantiomer for seizure protection strongly indicated that anticonvulsant activity in the MES test for **I** compounds resembled the activity in **1** compounds. (*R*)-**10** was the most active among the sector A compounds, exhibiting an MES ED_{50} = 13 mg/kg. This placed (*R*)-**10** midway between phenytoin and phenobarbital in activity[32] and approximately three times less active than (*R*)-**3**.[16] The protective index (PI = TD_{50}/ED_{50}) in mice (ip) for (*R*)-**10** was 2, which was lower than (*R*)-**3** (PI = 5.2).[16] When sector A **I** compounds were evaluated in the rat (po), the effect of C(2) *R* substitution on MES seizure protection was less noticeable. In this model, we found that (*R*)-**10** (MES ED_{50} = 14 mg/kg) was more active than either **5** (MES ED_{50} = 31 mg/kg) or (*R*)-**6** (MES ED_{50} = 31 mg/kg) but that the glycine derivative **5** and the alanine analogue (*R*)-**6** showed equal seizure protection. Interestingly, none of the three compounds displayed behavioral toxicity, even at doses up to 500 mg/kg. The activity observed for (*R*)-**10** in the rat (po) exceeded that of phenytoin and phenobarbital.[32]

Further SAR information was gathered by varying the sector B linker in **I** (Table 2). For these compounds, we maintained the (*R*)-**3** framework for sector A and the (*S*)-**4** (3-fluoro)phenyl substituent for sector C. We observed differences between the mice (ip) and rat (po) data sets. In the mice, anticonvulsant activity in the MES test decreased as the linker changed from O ((*R*)-**12**) [MES ED_{50} = 5.5 mg/kg] and CH_2O ((*R*)-**16**) [MES ED_{50} = 5.9 mg/kg] to OCH_2 ((*R*)-**10**) [MES ED_{50} = 13 mg/kg] to no linker ((*R*)-**11**), CH_2CH_2 ((*R*)-**13**), $N(H)CH_2$ ((*R*)-**17**) [MES ED_{50} = >10, <30 mg/kg] to C(H)=C(H) ((*R*)-**14**), C≡C ((*R*)-**15**), CH_2-OCH_2 ((*R*)-**18**), OCH_2CH_2 ((*R*)-**19**) [MES ED_{50} = >30, <100 mg/kg]. Correspondingly, in the rat (po), we observed that the anticonvulsant activity decreased by going from C≡C ((*R*)-**15**) [MES ED_{50} = 1.4 mg/kg], no linker ((*R*)-**11**) [MES ED_{50} = 2.4 mg/kg], to O ((*R*)-**12**) [MES ED_{50} = <10 mg/kg], OCH_2 ((*R*)-**10**) [MES ED_{50} = 14 mg/kg], CH_2O ((*R*)-**16**) [MES ED_{50} = 19 mg/kg], CH_2CH_2 ((*R*)-**13**) [MES ED_{50} = <30 mg/kg] to C(H)=C(H) ((*R*)-**14**) [MES ED_{50} = ~30 mg/kg]. We were interested to find that (*R*)-**15** and (*R*)-**11** exhibited superb seizure protection in the MES test (rat, po) with ED_{50} values of 1.4 mg/kg and 2.4 mg/kg, respectively. Moreover, (*R*)-**11** displayed no evidence of behavioral toxicity at 500 mg/kg. Earlier, we reported the anticonvulsant activity of (*R*)-*N*-(biphenyl-4-yl)methyl 2-acetamido-3-methoxypropionamide ((*R*)-**73**).[18] (*R*)-**73**, like (*R*)-**11**, exhibited outstanding seizure protection in the MES test (rat, po: MES ED_{50} = 2.0 mg/kg; TD_{50} = 49 mg/kg) but, unlike (*R*)-**11**, was found to have noticeable neurotoxicity. The precise role of the 3′-fluoro group in (*R*)-**11** in modulating behavioral neurotoxicity is unclear but is under investigation. Finally, for (*R*)-**15**, we not only observed excellent anticonvulsant protection but also the duration of seizure protection extended for the entire 4 h testing period. The activities of (*R*)-**11** and (*R*)-**15** exceeded (*R*)-**3** (ED_{50} = 3.8 mg/kg)[16] and other AEDs.[32]

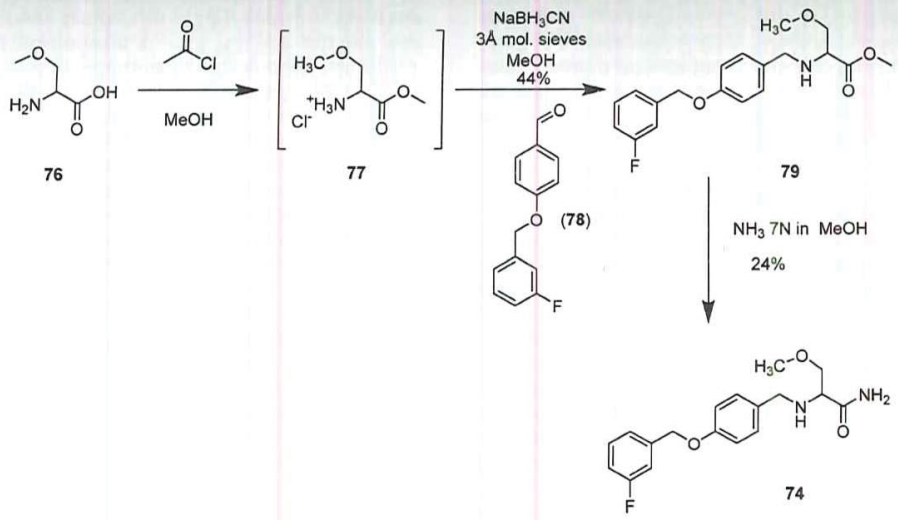


(*R*)-**73**

Sector C's terminal aryl group was the last structural unit evaluated (Table 3). For this series of compounds, we maintained the (*R*)-**3** framework for sector A and the (*S*)-**4** OCH_2 unit for sector B because both moieties provided **I** compounds with excellent activity (Tables 1, 2). We chose to evaluate the unsubstituted aryl compound, (*R*)-**20**, and the three monofluorophenyl derivatives, (*R*)-**10**, (*R*)-**21**, and (*R*)-**22**. For the three fluorinated compounds, we observed in mice (ip) that the 2″-fluoro derivative (*R*)-**21** was the most active (MES ED_{50} = 6.7 mg/kg). Correspondingly, in the rat (po) model, the 4″-fluoro isomer (*R*)-**22** was the most potent (MES ED_{50} = 5.8 mg/kg), followed by the 2″-fluoro ((*R*)-**21**, MES ED_{50} = 11 mg/kg) and the 3″-fluoro ((*R*)-**10**, MES ED_{50} = 14 mg/kg) analogues. Removing the fluoro substituent to give unsubstituted (*R*)-**20** retained seizure protection (MES ED_{50} = 5.8 mg/kg) in mice (ip), making this agent among the most potent **I** compounds tested under these conditions. Collectively, these findings demonstrated that the terminal aryl ring in **I** can influence anticonvulsant activities, thus warranting our further SAR exploration of this unit. We asked whether the extended *N*-aryl substituent in **I** directly contributed to the observed anticonvulsant activity. Accordingly, we evaluated **23** in the MES test (mice, ip) and observed modest anticonvulsant activity (MES ED_{50} = >30, <100 mg/kg).

The excellent activity for (*R*)-**10** warranted its further pharmacological evaluation in other models. In the psychomotor

Scheme 7. Preparation of **74**

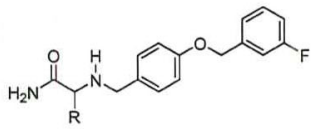


6 Hz (32 mA) seizure test,[43] (*R*)-**10** exhibited an ED_{50} = ~10 mg/kg in mice (ip) (Table 1), a value comparable with that observed for (*R*)-**3** (ED_{50} = 10 mg/kg).[19] In the sensitive rat (ip) hippocampal kindled seizure test,[44,45] its ED_{50} value was 12 mg/kg. This closely matched the value for (*R*)-**3** (ED_{50} = 14 mg/kg) in similar screening.[12] The hippocampal kindled seizure assay is a model of partial complex seizures or temporal lobe seizures, which are the most common and drug-resistant type of adult focal epilepsy.[45a,46]

Further evaluations of (*R*)-**10** were undertaken using the sciatic nerve ligation model,[47] which is used to predict potential efficacy against chronic neuropathic pain in humans. Recent pharmacological and clinical studies have documented that certain anticonvulsant compounds are effective in several different models of inflammatory and neuropathic pain.[48] Thus, it is not surprising that these antiepileptic agents are also used to manage neuropathic pain.[48,49] Neuropathic pain results from excessive neuronal activity and damage resulting in dysfunction of neuronal pathways within both the peripheral and the central nervous systems.[48,49] The sciatic ligation model was used to assess the efficacy of (*R*)-**10** in rats. Using this test, we showed that administration of (*R*)-**10** (12 mg/kg; rats, ip) provided a 11.2-fold attenuation of mechanical allodynia at 1 h.

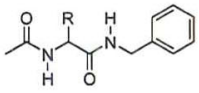
The formalin test, a chemically induced biphasic pain model, was also employed.[50] There are two phases of response measured in the test, early (acute) and late (chronic inflammatory). The acute phase results in a behavioral licking response, which is believed to be mediated by chemical activation of local C-fibres.[50] The late phase is likely due to the development of peripheral inflammation and central sensitization of dorsal horn neurons. Thus, this model is believed to provide preliminary information about the utility of the test candidate for the treatment of acute and chronic inflammatory pain. When evaluated in the formalin model, (*R*)-**10** (15 mg/kg, mice, ip) significantly reduced the pain response in both the acute (35% of control; $p < 0.01$) and the late (44% of control; $p < 0.01$) phases. These results compared favorably with (*R*)-**3**, where comparable reduction in pain was observed only in the late phase when 16 mg/kg was administered.[51]

In **5**−**22**, we constructed compounds with the principal structural motif seen in **1** and then extended the *N*-benzyl amide moiety to resemble **2**. We briefly explored the reverse, where we began with the **2** core structure and then incorporated at C(2) **1** units shown to have excellent anticonvulsant activities. Accordingly, we prepared racemic **74** and **75** using the synthetic procedures shown in Schemes 7 and 8, respectively. Compound **74** contained the (*R*)-**3** (C)2-methoxymethylene unit, and compound **75** had a 2-furanyl moiety. In the **1** series, racemic **3** and **88** displayed MES ED_{50} values (mice, ip) of 8.3 and 10 mg/kg, respectively (Table 4). When tested, (*R*,*S*)-**74** and (*R*,*S*)-**75** displayed good-to-moderate anticonvulsant activity in mice (ip) ((*R*,*S*)-**74**, MES ED_{50} = 30−100 mg/kg; (*R*,*S*)-**75**, MES ED_{50} = 10−30 mg/kg), values that were higher (lower activity) than those observed for (*R*,*S*)-**3** and (*R*,*S*)-**88** in this test (MES ED_{50} = 8.3−10 mg/kg).[11,16] Interestingly, we observed little or no activity in the scMet seizure model for (*R*,*S*)-**74** (scMet ED_{50} = > 300 mg/kg) and (*R*,*S*)-**75** (scMet ED_{50} = 100−300 mg/kg). This finding contrasted with the excellent activity reported for (*S*)-**4** in this model (scMet ED_{50} = 27 mg/kg).[27] We concluded that the SAR guidelines for **1**[7−16] did not help improve the pharmacological activity of **2**.



74 R = CH_2OCH_3

75 R = 



3 R = CH_2OCH_3

88 R = 

Discussion

In this study, we combined key pharmacophores found in **1** and **2** to provide **I**, anticipating that **I** might exhibit potent anticonvulsant activity. The structural design for **I** permitted the near seamless overlap of the pharmacophores. Moreover, the structural economy gained from this overlap permitted the design of a compact agent that conforms to Lipinski's pharmacokinetic rules for low molecular weight, oral therapeutic

Scheme 8. Preparation of **75**

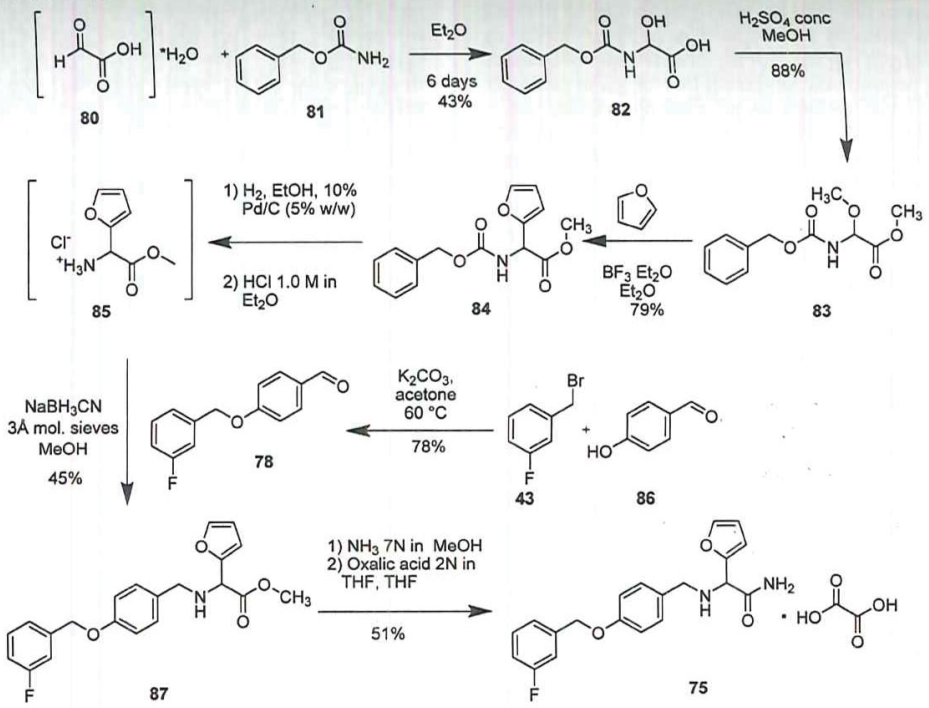
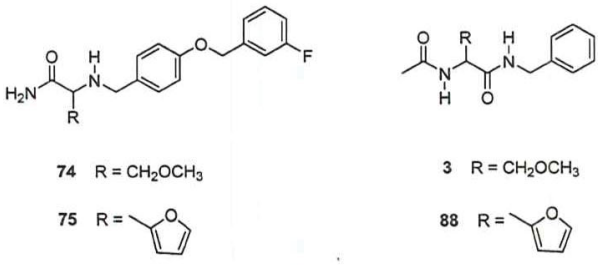


Table 4. Pharmacological Data for α-Aminoamide Derivatives **74** and **75** and Their Functionalized Amino Acid Counterparts **3** and **88**[a]



	mice (ip)[b]		
compd no.	MES,[c] ED_{50}	Tox,[d] TD_{50}	PI[e]
(*R*,*S*)-**74**	> 30, < 100 [0.5]	> 100, < 300 [0.5]	
(*R*,*S*)-**75**	> 10, < 30 [0.5]	> 100, < 300 [0.5]	
(*R*,*S*)-**3**[f]	8.3 [0.5] (7.9−9.8)	43 [0.25] (38−47)	5.2
(*R*,*S*)-**88**[g]	10 (9.1−12)	~40	~4.0
(*S*)-**4**[h]	8.0 (7.0−9.1)	630 (560−700)	78
(*R*)-**4**[h]	7.2 (5.9−8.9)	580 (410−830)	88
phenytoin[i]	9.5 [2] (8.1−10)	66 [2] (53−72)	6.9
phenobarbital[i]	22 [1] (15−23)	69 [0.5] (63−73)	3.2
valproate[i]	270 [0.25] (250−340)	430 [0.25] (370−450)	1.6

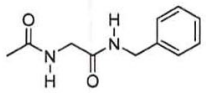
[a] The compounds were tested through the auspices of the NINDS ASP. [b] The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in milligrams per kilogram. [c] MES = maximal electroshock seizure test. [d] TD_{50} value determined from the rotorod test. [e] PI = protective index (TD_{50}/ED_{50}). [f] Reference 16. [g] Reference 11. [h] Reference 30. [i] Reference 32.

agents.[52] We expected several additional benefits from this design. First, the overlap eliminated the need for extraneous bridging units, which could confound receptor binding and provide unwanted sites for metabolism and toxicity. Second, we anticipated that **I**, like **1** and **2**,[22,24] would exhibit favorable CNS biodistribution.

We found that **I** did not prevent scMet-induced seizures in mice and that it showed a stereochemical preference for function, which corresponds to the D-amino acid, in the MES-induced seizure test in rodents. Moreover, anticonvulsant activity increased with placement of a heteroatom one atom removed from the C(2) atom in **I** (Table 1) These whole animal pharmacological responses are similar to those observed for **1** ((*R*)-**3**)[7−18] but not **2** ((*S*)-**4**).[20,30] Table 2 shows that the most potent **I** derivatives in the MES test were those in which "X-Y-Z" was a single bond ((*R*)-**11**), a rigid, linear unit ((*R*)-**15**), or a short moiety (i.e., O ((*R*)-**12**); "X-Y" [where X and Y are C(H), N(H), O, and CH_2] ((*R*)-**10**, (*R*)-**13**, (*R*)-**14**, (*R*)-**16**, (*R*)-**17**). Of these, (*R*)-**11** and (*R*)-**15** were the most potent anticonvulsants when tested in the rat (po) (MES ED_{50} = 1.4−2.4 mg/kg).

The excellent anticonvulsant activity for several **I** compounds demonstrated that seizure protection could be improved over their **1** counterpart by incorporating an extended *N*-aryl substituent similar to that found in **2** ((*S*)-**4**). For example, in the MES test (mice, ip), the glycine FAA **89** exhibited weak anticonvulsant activity (MES ED_{50} = > 100, < 300 mg/kg),[8] but glycine **5** exhibited a MES ED_{50} = > 30, < 100 mg/kg, mice (ip). When **5** was tested in the rat (po), the MES ED_{50} = 31 mg/kg, and we observed no apparent neurological toxicity at doses of 500 mg/kg. Similarly, we found superb anticonvulsant activity for (*R*)-**11** (MES ED_{50} = 2.4 mg/kg) and (*R*)-**15** (MES ED_{50} = 1.4 mg/kg) in the rat (po), which surpassed that of (*R*)-**3** (MES ED_{50} = 3.9 mg/kg). We evaluated **23** that contained the same extended *N*-benzyl substituent that was incorporated in **5** and (*R*)-**6**−(*R*)-**10** and observed only modest anticonvulsant activity in mice (ip) (MES ED_{50} = > 30, < 100 mg/kg), indicating that this group alone was not responsible for the observed seizure protection.

Finally, we found that several **I** compounds ((*R*)-**6**, (*R*)-**15**) exhibited extended duration of action in the MES model in mice (ip) and rat (po).



89

We tested (*R*)-*N*-4′-((3″-fluoro)benzyloxy)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**10**) in other neurological models. We first evaluated (*R*)-**10** in two additional seizure models. In the psychomotor 6 Hz (32 mA) test in mice (ip)[43] and the rat (ip) hippocampal kindled seizure test,[45] (*R*)-**10** provided excellent protection, giving an ED_{50} of ~10 and 12 mg/kg, respectively. Because several clinically available AEDs are used to treat pain disorders,[48,49] we evaluated (*R*)-**10** in two animal pain models. When (*R*)-**10** was tested at 12 mg/kg in the sciatic nerve ligation model[47] in rats (ip), we observed an 11.2-fold attenuation of mechanical allodynia at 1 h. In the biphasic, chemically induced formalin pain model in mice,[50] ip administration of (*R*)-**10** (15 mg/kg) reduced pain response in both the acute (35% of control) and the late (44% of control) phases. These findings document the potential value of **I** to treat a range of neurological conditions.

Conclusions

Our findings demonstrate that the incorporation of key pharmacophores in **1** and **2** to provide **I** gave compounds of significant neurological interest. Using animal tests, we observed excellent seizure protection and pronounced pain reduction. The pharmacological basis for **I** anticonvulsant activity and pain protection has not been determined. Anticonvulsants, like many neurological agents,[53] typically exert their activity through multiple pathways.[54] Current studies are directed at optimizing sectors A-C in **I** and evaluating these compounds in electrophysiology, radioligand displacement, and functional assays to provide information about the mode(s) of action of these novel agents.

Experimental Section

General Methods. The general methods used in this study were identical to those previously reported[18] and are summarized in the Supporting Information. All compounds were checked by TLC, ^1H and ^{13}C NMR, MS, and elemental analyses. The analytical results are within ±0.40% of the theoretical value. The TLC, NMR, and the analytical data confirmed the purity of the products was ≥95%.

Preparation of *N*-4′-((3″-Fluoro)benzyloxy)benzyl 2-Acetamidoacetamide (5). A THF solution (120 mL) of **28** (1.50 g, 12.8 mmol) was stirred and cooled at −78 °C under Ar, and then 4-methylmorpholine (NMM) (1.7 mL, 15.4 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (2.0 mL, 15.4 mmol) was added dropwise, leading to the precipitation of a white solid. The reaction was allowed to proceed for additional 2 min, and **32** (3.26 g, 14.1 mmol) was added portionwise at −78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The solid was purified by flash column chromatography on silica gel with methanol/EtOAc (0/10 → 5/5) as the eluant to obtain **5** as white solid (1.30 g, 31%): R_f = 0.11 (EtOAc); mp 155−156 °C. ^1H NMR ($CDCl_3$) δ 2.03 (s, 3H), 3.92 (d, *J* = 5.1 Hz, 3H), 4.38 (d, *J* = 5.7 Hz, 2H), 5.05 (s, 1H), 6.24−6.35 (br m, 2H), 6.92 (m, 2H), 6.97−7.04 (m, 1H), 7.11−7.21 (m, 4H), 7.30−7.38 (m, 1H). MS (M + H^+) (ESI^+) 331.1 [M + H^+] (calcd for $C_{18}H_{19}FN_2O_3H^+$ 331.1). Anal. ($C_{18}H_{19}FN_2O_3 \cdot 0.35H_2O$): C, H, F, N.

Preparation of (*R*)-*N*-4′-((3″-Fluoro)benzyloxy)benzyl 2-Acetamido-propionamide ((*R*)-6). Employing the procedure to prepare **5** and using THF (100 mL), (*R*)-**29** (1.50 g, 11.4 mmol), NMM (1.5 mL, 13.7 mmol), IBCF (1.8 mL, 13.7 mmol), and **32** (2.90 g, 12.6 mmol) gave (*R*)-**6** that was purified by recrystallization (EtOAc) as a white solid (905 mg, 22%): R_f = 0.16 (EtOAc); mp 158 °C; $[\alpha]^{26.2}_D$ +27.3° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.37 (d, *J* = 6.9 Hz, 3H), 1.94 (s, 3H), 4.32 (d, *J* = 5.7 Hz, 2H), 4.46−4.56 (m, 1H), 5.02 (s, 2H), 6.41 (d, *J* = 7.5 Hz, 1H), 6.79−6.85 (br m, 1H), 6.87−6.92 (m, 2H), 7.00 (td, *J* = 2.4, 8.4 Hz, 1H), 7.10−7.20 (m, 4H), 7.30−7.37 (m, 1H). MS (M + H^+) (ESI^+) 345.2 [M + H^+] (calcd for $C_{19}H_{21}FN_2O_3H^+$ 344.2). Anal. ($C_{19}H_{21}FN_2O_3$): C, H, F, N.

Preparation of (*S*)-*N*-4′-((3″-Fluoro)benzyloxy)benzyl 2-Acetamidopropionamide ((*S*)-6). Employing the procedure of (*R*)-**6** and using (*S*)-**29** (1.50 g, 11.4 mmol), NMM (1.5 mL, 13.7 mmol), IBCF, and **32** (2.90 g, 12.6 mmol) gave after workup and recrystallization (EtOAc) a white solid (1.50 g, 38%): R_f = 0.16 (EtOAc); mp 153−154 °C; $[\alpha]^{26.2}_D$ −28.1° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.38 (d, *J* = 7.2 Hz, 3H), 1.94 (s, 3H), 4.32 (d, *J* = 5.7 Hz, 2H), 4.46−4.57 (m, 1H), 5.02 (s, 2H), 6.38−6.46 (br d, 1H), 6.78−6.85 (br m, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.98−7.04 (m, 1H), 7.10−7.20 (m, 4H), 7.30−7.37 (m, 1H). MS (M + H^+) (ESI^+) 345.2 [M + H^+] (calcd for $C_{19}H_{21}FN_2O_3H^+$ 345.2). Anal. ($C_{19}H_{21}FN_2O_3$): C, H, F, N.

Preparation of (*R*)-*N*-4′-((3″-Fluoro)benzyloxy)benzyl 2-Acetamido-3-methylbutanamide ((*R*)-7). Trifluoroacetic acid (2 mL) was added to a CH_2Cl_2 (10 mL) solution of solution (*R*)-**33** (1.00 g, 2.3 mmol) at 0 °C, and the solution was stirred at room temperature (16 h). The reaction solution was concentrated in vacuo, dried (30 min), and CH_2Cl_2 (20 mL), and a saturated aqueous Na_2CO_3 solution (20 mL) were added. The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 20 mL). The organic layers were combined and concentrated under vacuum.

The residue was dissolved in CH_2Cl_2 (20 mL) and Et_3N (0.49 mL, 3.5 mmol) and AcCl (200 μL, 2.8 mmol) were successively added at 0 °C. The mixture was stirred at room temperature (3 h), aqueous 10% citric acid (60 mL) was added, and the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (2 × 30 mL). All the organic layers were combined, washed with aqueous saturated $NaHCO_3$ (30 mL), and H_2O (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was recrystallized with EtOAc to obtain (*R*)-**7** (585 mg, 68%) as a white solid: R_f = 0.26 (EtOAc); mp 199−200 °C; $[\alpha]^{25.2}_D$ +25.6° (*c* 0.5, MeOH). ^1H NMR (400 MHz, DMSO-d_6) δ 0.81 (d, *J* = 3.0 Hz, 3H), 0.83 (d, *J* = 3.0 Hz, 3H), 1.87 (s, 3H), 1.90−1.99 (m, 1H), 4.12−4.43 (dd, *J* = 6.4, 8.8 Hz, 1H), 4.19 (d, *J* = 5.8 Hz, 2H), 5.11 (s, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 7.11−7.19 (m, 3H), 7.24−7.28 (m, 2H), 7.39−7.46 (m, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 8.38 (t, *J* = 5.8 Hz, 1H). HRMS (M + Na^+) (ESI^+) 395.1747 [M + Na^+] (calcd for $C_{21}H_{25}FN_2O_3Na^+$ 395.1747). Anal. ($C_{21}H_{25}FN_2O_3$): C, H, F, N.

Preparation of (*R*)-*N*-4′-((3″-Fluoro)benzyloxy)benzyl 2-Acetamido-3,3-dimethylbutanamide ((*R*)-8). Employing a procedure similar to (*R*)-**7** and using (*R*)-*N*-4′-((3″-fluoro)benzyloxy)benzyl 2-amino-3,3-dimethylbutanamide (1.20 g, 3.3 mmol), CH_2Cl_2 (40 mL), Et_3N (0.93 mL, 6.6 mmol), and AcCl (0.34 mL, 4.8 mmol) gave after workup and purification by flash column chromatography on silica gel with EtOAc/hexanes (8/2 to 10/0) as the eluant (*R*)-**8** as a white solid (1.03 g, 81%): R_f = 0.56 (EtOAc); mp 64−66 °C; $[\alpha]^{27.0}_D$ −15.6° (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 9H), 1.89 (s, 3H), 4.42 (1/2 ABq, *J* = 5.2, 14.4 Hz, 1H), 4.34−4.40 (m, CH, 1H), 5.02 (s, 2H), 6.41 (br d, *J* = 8.8 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.85−6.96 (br m, 1H), 7.00 (t, *J* = 8.4 Hz, 1H), 7.11−7.18 (m, 4H), 7.30−7.36 (m, 1H). HRMS (M + Na^+)

(ESI$^+$) 409.1903 [M + Na$^+$] (calcd for $C_{22}H_{27}FN_2O_3Na^+$ 409.1903). Anal. ($C_{22}H_{27}FN_2O_3$): C, H, F, N.

Preparation of *N*-4′-((3″-Fluoro)benzyloxy)benzyl 2-Acetamido-2-(pyridin-2-yl)acetamide ((*R*,*S*)-9). To a solution of **38** (1.81 g, 4.77 mmol, 1 equiv) in MeOH (95 mL) was added ammonium formate (1.21 g, 19.08 mmol, 4 equiv) as a solid, and then the reaction mixture was stirred at room temperature (5 min). Zn dust (Sigma-Aldrich < 10 μm, 1.20 g, 19.08 mmol, 4 equiv) was added and the reaction heated at reflux (6 h) and then maintained at room temperature (16 h). The reaction mixture was filtered through celite. The filtrate was concentrated, and the residue was dissolved in CH_2Cl_2 (100 mL). The CH_2Cl_2 layer was washed with a brine (2 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude **39** was used without further purification for the next step: R_f = 0.00 (EtOAc).

Compound **39** (4.77 mmol, 1 equiv) was dissolved in CH_2Cl_2 (100 mL) and then triethylamine (0.8 mL, 5.72 mmol, 1.2 equiv) and AcCl (0.4 mL, 5.72 mmol, 1.2 equiv) were carefully added at 0 °C, and the resulting solution was stirred at room temperature (2 h). An aqueous saturated $NaHCO_3$ solution (100 mL) was added, and the organic layer was extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by chromatography on silica gel with EtOAc/hexanes (7/3 to 10/0) as the eluent. The residue was recrystallized (EtOAc) to obtain (*R*,*S*)-**9** as a white solid (935 mg, 48%): R_f = 0.47 (EtOAc); mp 154−155 °C. ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3H), 4.29−4.41 (m, 2H), 5.03 (s, 2H), 5.56 (d, *J* = 6.0 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 2H), 6.98−7.43 (m, 10H), 7.70 (dt, *J* = 1.6, 7.8 Hz, 1H), 8.50−8.52 (m, 1H). Anal. ($C_{23}H_{22}FN_3O_3$): C, H, F, N.

Preparation of (*R*)-*N*-4′-((3″-Fluoro)benzyloxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-10). A saturated HCl solution in dioxane (1 mmol/2 mL, 21.75 mL) was added to (*R*)-*N*-4′-((3″-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)-amino-3-methoxypropionamide (4.70 g, 10.9 mmol) at 0 °C, and the solution was stirred at room temperature (4 h). The reaction solution was concentrated in vacuo and dried (30 min).

Employing a procedure similar to (*R*)-**7**, and using the residue, CH_2Cl_2 (40 mL), Et_3N (4.47 mL, 32.6 mmol), and AcCl (1.16 mL, 16.30 mmol) gave after workup and recrystallization (EtOAc) (*R*)-**10** (2.60 g, 65%) as a white solid: R_f = 0.29 (7/3 hexanes/EtOAc); mp 152 °C; $[\alpha]^{24.5}_D$ −18.9° (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3H), 3.37 (s, 3H), 3.43 (dd, *J* = 7.2, 9.0 Hz, 1H), 3.79 (dd, *J* = 3.9, 9.0 Hz, 1H), 4.40 (d, *J* = 5.7 Hz, 2H), 4.49−4.55 (m, 1H), 5.05 (s, 2H), 6.43 (br d, *J* = 7.2 Hz, 1H), 6.64−6.83 (br m, 1H), 6.89−7.05 (m, 3H), 7.10−7.22 (m, 4H), 7.31−7.38 (m, 1H). HRMS (M+H$^+$) (ESI$^+$) 375.1720 [M+H$^+$] (calcd for $C_{20}H_{23}FN_2O_4H^+$ 375.1720). Anal. ($C_{20}H_{23}FN_2O_4$): C, H, F, N.

Preparation of (*S*)-*N*-4′-((3″-Fluoro)benzyloxy)benzyl 2-Acetamido-3-methoxypropionamide ((*S*)-10). A saturated HCl solution in dioxane (1 mmol/2 mL, 20.8 mL) was added to (*S*)-*N*-4′-((3″-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)-amino-3-methoxypropionamide (4.50 g, 10.4 mmol) at 0 °C, and the solution was stirred at room temperature (4 h). The reaction solution was concentrated in vacuo and dried (30 min).

Employing a procedure similar to (*R*)-**7**, and using the residue, CH_2Cl_2 (40 mL), Et_3N (4.3 mL, 31.2 mmol), and AcCl (1.1 mL, 15.6 mmol) gave after recrystallization (EtOAc) (*S*)-**10** (3.10 g, 80%) as a white solid: R_f = 0.29 (7/3 hexanes/EtOAc); mp 149−150 °C; $[\alpha]^{24.5}_D$ +18.8° (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H), 3.36 (s, 3H), 3.43 (dd, *J* = 7.5, 9.1 Hz, 1H), 3.79 (dd, *J* = 4.2, 9.1 Hz, 1H), 4.40 (d, *J* = 5.7 Hz, 2H), 4.50−4.55 (m, 1H), 5.05 (s, 2H), 6.47 (br d, *J* = 6.0 Hz, 1H), 6.70−6.79 (br m, 1H), 6.90−7.05 (m, 3H), 7.10−7.22 (m, 4H), 7.31−7.38 (m, 1H). HRMS (M + H$^+$) (ESI$^+$) 375.1720 [M + H$^+$] (calcd for $C_{20}H_{23}FN_2O_4H^+$ 375.1720). Anal. ($C_{20}H_{23}FN_2O_4$): C, H, F, N.

Preparation of (*R*)-*N*-(3″-Fluorobiphenyl-4-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-11). To a flame-dried Schlenck tube, under Ar, containing a dioxane (22.5 mL) solution of (*R*)-**69**[18] (1.50 g, 4.0 mmol), palladiumtetrakis(triphenylphosphine) (464 mg, 0.402), and 3-fluorophenylboronic acid (**70**) (670 mg, 4.80 mmol) was added an aqueous solution (9 mL) of Cs_2CO_3 (2.60 g, 8.0 mmol). The mixture was stirred at reflux (16 h). Then MeOH and silica gel were added, and the volatiles were concentrated in vacuo. The residue was purified by flash chromatography on silica gel with EtOAc/MeOH (10/0 to 9/1) as the eluant to obtain (*R*)-**11** (0.95 g, 60%) as a yellowish solid. To remove traces of palladium impurities, the solid was treated with 6.00 g of resin scavenger (SPM32, PhosPhonics) in CH_2Cl_2. The mixture was stirred at room temperature (2 h), filtered, and the filtrate evaporated under vacuum to obtain 800 mg (58%) of (*R*)-**11** as a white solid: R_f = 0.22 (EtOAc); mp 170−172 °C; $[\alpha]^{25.3}_D$ = −8.1° (c 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3H), 3.39 (s, 3H), 3.47 (d, *J* = 7.5, 9.3 Hz, 1H), 3.81 (d, *J* = 3.9, 9.3 Hz, 1H), 4.45−4.55 (m, 2H), 4.56−4.63 (m, 1H), 6.53 (br d, *J* = 6.6 Hz, 1H), 6.93−7.07 (m, 2H), 7.23−7.51 (m, 5H), 7.53 (d, *J* = 8.1 Hz, 2H). HRMS (M + Cs$^+$) (ESI$^+$) 477.0591 [M + Cs$^+$] (calcd for $C_{19}H_{21}FN_2O_3Cs^+$ 477.0587). Anal. ($C_{19}H_{21}FN_2O_3$): C, H, F, N.

Preparation of (*R*)-*N*-4′-((3″-Fluoro)phenoxy)benzyl 2-*N*-Acetamido-3-methoxypropionamide ((*R*)-12). A saturated HCl solution in dioxane (1 mmol/2 mL, 16.7 mL) was added to an Et_2O (8 mL) solution of (*R*)-*N*-4′-((3″-fluoro)phenoxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (3.50 g, 8.4 mmol) at 0 °C, and the solution was stirred at room temperature (16 h). The reaction solution was concentrated in vacuo and dried (30 min).

Employing a procedure similar to (*R*)-**7**, and using the residue, CH_2Cl_2 (40 mL), Et_3N (3.52 mL, 25.1 mmol), and AcCl (0.91 mL, 12.5 mmol) gave after workup and purification by flash column chromatography on silica gel with EtOAc as the eluant (*R*)-**12** as a white solid (1.30 g, 43%): R_f = 0.45 (EtOAc); mp 125−126 °C; $[\alpha]^{25.3}_D$ −14.8° (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04 (s, 3H), 3.39 (s, 3H), 3.45 (dd, *J* = 7.5, 9.3 Hz, 1H), 3.81 (dd, *J* = 4.2, 9.3 Hz, 1H), 4.45 (d, *J* = 6.0 Hz, 2H), 4.53−4.59 (m, 1H), 6.48 (br d, *J* = 6.0 Hz, 1H), 6.68 (dt, *J* = 2.4, 10.2 Hz, 1H), 6.74−6.89 (m, 3H), 6.99 (d, *J* = 9.0 Hz, 2H), 7.21−7.34 (m, 3H). HRMS (M+H$^+$) (ESI$^+$) 361.1564 [M+H$^+$] (calcd for $C_{19}H_{21}FN_2O_4H^+$ 361.1563). Anal. ($C_{19}H_{21}FN_2O_4$): C, H, F, N.

Preparation of (*R*)-*N*-4′-((3″-Fluoro)phenethyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-13). Pd/C (18 mg) was added to an EtOH solution of (*R*)-**14** (180 mg, 0.49 mmol), and the mixture was stirred at room temperature under H_2 (1 atm) (36 h). The reaction mixture was filtered through a pad of celite, and the pad was washed successively with EtOH and CH_2Cl_2. The filtrate was concentrated under vacuum to obtain (*R*)-**13** (170 mg, 94%) as a white solid: R_f = 0.29 (EtOAc); mp 134−136 °C; $[\alpha]^{24.4}_D$ = −12.3° (*c* 0.48, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 3H), 2.90 (s, 4H), 3.38 (s, 3H), 3.43 (dd, *J* = 7.6, 9.2 Hz, 1H), 3.81 (dd, *J* = 4.0, 9.2 Hz, 1H), 4.40−4.47 (m, 2H), 4.50−4.55 (m, 1H), 6.41−6.47 (br m, 1H), 6.68−6.75 (br m, 1H), 6.84−6.94 (m, 3H), 7.11−7.25 (m, 5H). HRMS (M+H$^+$) (ESI$^+$) 373.1927 [M+H$^+$] (calcd for $C_{21}H_{25}FN_2O_3H^+$ 373.1927). Anal. ($C_{21}H_{25}FN_2O_3 \cdot 0.32H_2O$): C, H, N.

Preparation of (2-*R*,*E*)-*N*-4′-((3″-Fluoro)styryl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-14). To a flame-dried Schlenck tube, under Ar, containing a dioxane (22.5 mL) solution of (*R*)-**69**[18] (1.50 g, 4.0 mmol), palladiumtetrakis(triphenylphosphine) (464 mg, 0.402 mmol), and *trans*-2-((3-fluoro)phenyl)vinylboronic acid (**71**) (800 mg, 4.82 mmol) was added an aqueous solution (9 mL) of Cs_2CO_3 (2.60 g, 8.0 mmol). The mixture was stirred at reflux (16 h). Then, MeOH and silica gel were added. The volatiles were concentrated in vacuo, and the residue was purified by flash chromatography on silica gel with EtOAc/MeOH (10/0 to 9/1) as the eluant to obtain (*R*)-**14** (0.90 g, 60%) as a yellowish solid. To remove traces of palladium impurities, the solid was treated with 6.00 g of resin scavenger (SPM32, PhosPhonics) in CH_2Cl_2. The mixture was stirred at room temperature (2 h), and filtered, and the filtrate was evaporated under vacuum to obtain 560 mg (37%) of (*R*)-**14** as a

white solid: R_f = 0.53 (EtOAc); mp 206−208 °C; $[\alpha]^{27}_D$ = −20.6° (c 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 2.04 (s, 3H), 3.40 (s, 3H), 3.40−3.48 (m, 1H), 3.83 (d, J = 3.9, 8.7 Hz, 1H), 4.47−4.56 (m, 3H), 6.41−6.49 (br d, 1H), 6.75−7.02 (br t, 1H), 6.92−7.01 (m), 7.07 (d, J = 2.7 Hz), 7.18−7.35 (m), 7.47 (d, J = 8.4 Hz) (10H). LRMS (M + Na^+) (ESI^+) 393.1 [M + Na^+] (calcd for $C_{21}H_{23}FN_2O_3Na^+$ 393.1). Anal. ($C_{21}H_{23}FN_2O_3$): C, H, F, N.

Preparation of (*R*)-*N*-4′-(((3″-Fluoro)phenyl)ethynyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-15). To an anhydrous THF (70 mL) solution of (*R*)-**69**[18] (2.60 g, 7.0 mmol) were sequentially added triethylamine (0.95 mL, 14.0 mmol), 3-(fluoro)-phenylacetylene (**72**) (1.20 mL, 10.37 mmol), dichlorobis(triphenylphosphine)palladium(II) (491 mg, 0.70 mmol), and CuI (200 mg, 0.1.05 mmol) under Ar. The mixture was stirred at room temperature (16 h), and then MeOH and silica gel were added. The volatiles were concentrated in vacuo, and the residue was purified by flash chromatography on silica gel with EtOAc/MeOH (9/1) as the eluant to obtain (*R*)-**15** (2.40 g, 93%) as a yellowish solid. To remove traces of palladium impurities, the solid was treated with 21.00 g of resin scavenger (SPM32, PhosPhonics) in CH_2Cl_2. The mixture was stirred at room temperature (2 h), and filtered, and the filtrate was evaporated under vacuum. The solid was recrystallized with EtOAc to obtain 1.20 g (46%) of (*R*)-**15** as a white solid: R_f = 0.26 (EtOAc); mp 200−202 °C; $[\alpha]^{24}_D$ = −2.6° (c 0.5, $CHCl_3$). ^1H NMR (DMSO-d_6) δ 1.88 (s, 3H), 3.27 (s, 3H), 3.48−3.57 (m, 2H), 4.33 (d, J = 6.1 Hz, 2H), 4.45−4.53 (m, 1H), 7.25−7.32 (m, 3H), 7.38−7.53 (m, 5H), 8.13 (d, J = 6.3 Hz, 1H), 8.56 (br t, J = 6.1 Hz, 1H). HRMS (M + H^+) (ESI^+) 369.1614 [M + H^+] (calcd for $C_{21}H_{21}FN_2O_3H^+$ 369.1614). Anal. ($C_{21}H_{21}FN_2O_3$): C, H, F, N.

Preparation of (*R*)-*N*-4′-(((3″-Fluoro)phenoxy)methyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-16). A saturated HCl solution in dioxane (1 mmol/2 mL, 10.2 mL) was added to (*R*)-*N*-4′-(((3″-fluoro)phenoxy)methyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (2.20 g, 5.1 mmol) at 0 °C, and the solution was stirred at room temperature (2 h). The reaction solution was concentrated in vacuo and dried (30 min) to provide (*R*)-2-amino-*N*-4′-(((3″-fluoro)phenoxy)-methyl)benzyl-3-methoxypropionamide hydrochloride as a white solid (1.80 g, quant.).

Employing a procedure similar to (*R*)-**7**, and using triethylamine (1.5 mL, 5.2 mmol), acetyl chloride (380 μL, 10.7 mmol), CH_2Cl_2 (20 mL), and (*R*)-*N*-4′-(((3″-fluoro)phenoxy)methyl)-benzyl 2-amino-3-methoxypropionamide hydrochloride (1.30 g, 3.5 mmol), gave after workup and recrystallization (EtOAc) (*R*)-**16** (900 mg, 68%) as a white solid: R_f = 0.18 (EtOAc); mp 140−142 °C; $[\alpha]^{26.9}_D$ −21.0° (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 2.04 (s, 3H), 3.41 (s, 3H), 3.43 (dd, J = 7.5, 9.2 Hz, 1H), 3.82 (dd, J = 3.9, 9.2 Hz, 1H), 4.47−4.59 (m, 3H), 5.03 (s, 2H), 6.38−6.43 (br d, 1H), 6.64−6.78 (m, 4H), 7.14−7.30 (m, 3H), 7.40 (d, J = 8.4 Hz, 2H). LRMS (M + Na^+) (ESI^+) 397.1 [M + Na^+] (calcd for $C_{20}H_{23}FN_2O_4H^+$ 397.1). Anal. ($C_{20}H_{23}FN_2O_4$): C, H, F, N.

Preparation of (*R*)-*N*-4′-((3″-Fluoro)benzylamino)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-17). Compound **67**·HCl (293 mg, 1.1 mmol) was added to a THF (10 mL) solution of the (*R*)-**68** (161 mg, 1.0 mmol), and the mixture was stirred at room temperature (5 min) and then NMM (121 μL, 1.1 mmol) was added. The mixture was stirred at room temperature (5 min) and DMTMM (332 mg, 1.2 mmol) was added, and the mixture was stirred at room temperature (16 h). The white precipitate was filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (5/5) to EtOAc/acetone (5/5) as the eluant to obtain (*R*)-**17** as a yellow solid (140 mg, 35%): R_f = 0.37 (EtOAc); mp 78−81 °C; $[\alpha]^{26.9}_D$ −15.0° (c 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 2.03 (s, 3H), 3.36 (s, 3H), 3.40 (dd, J = 7.2, 9.0 Hz, 1H), 3.82 (dd, J = 4.2, 9.0 Hz, 1H), 4.12−4.19 (br m, 1H), 4.31−4.37 (m, 4H), 4.46−4.52 (m, 1H), 6.38−6.45 (br m, 1H), 6.57 (d, J = 9.0 Hz, 3H), 6.91−6.89 (m, 1H), 7.05−7.15 (m, 4H), 7.27−7.34 (m, 1H). HRMS (M + H^+) (ESI^+) 374.1880 [M + H^+] (calcd for $C_{20}H_{24}FN_3O_3H^+$ 374.1879).

Preparation of (*R*)-*N*-4′-(((3″-Fluoro)benzyloxy)methyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-18). A saturated HCl solution in dioxane (1 mmol/2 mL, 1.2 mL) was added to (*R*)-*N*-4′-(((3″-fluoro)benzyloxy)methyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)-amino-3-methoxypropionamide (1.10 g, 5.8 mmol) at 0 °C, and the solution was stirred at room temperature (16 h). The reaction solution was concentrated in vacuo and dried (30 min).

Employing a procedure similar to (*R*)-**7**, and using the residue, CH_2Cl_2 (20 mL), Et_3N (1.40 mL, 9.8 mmol), and AcCl (356 μL, 4.9 mmol), gave after workup and recrystallization (EtOAc) (*R*)-**18** (450 mg, 47%) as a white solid: R_f = 0.26 (EtOAc); mp 140−142 °C; $[\alpha]^{25.2}_D$ −21.0° (c 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 2.04 (s, 3H), 3.39 (s, 3H), 3.43 (dd, J = 7.8, 9.0 Hz, 1H), 3.82 (dd, J = 3.9, 9.0 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 4.48−4.56 (m, 1H), 4.54 (s, 2H), 4.55 (s, 2H), 6.42 (br d, J = 6.6 Hz, 1H), 6.71−6.79 (br t, 1H), 6.96−7.15 (m, 3H), 7.24−7.35 (m, 5H). Anal. ($C_{21}H_{25}FN_2O_4$): C, H, F, N.

Preparation of (*R*)-*N*-4′-((3″-Fluoro)phenethoxy)benzyl 2-*N*-Acetamido-3-methoxypropionamide ((*R*)-19). A saturated HCl solution in dioxane (1 mmol/2 mL, 10.0 mL) was added to an Et_2O (5 mL) solution of (*R*)-*N*-4′-((3″-fluoro)phenethoxy)-benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropion-amide (2.20 g, 5.0 mmol) at 0 °C, and the solution was stirred at room temperature (16 h). The reaction solution was concentrated in vacuo and dried (30 min).

Employing a procedure similar to (*R*)-**7**, and using the residue, CH_2Cl_2 (30 mL), Et_3N (2.1 mL, 15.0 mmol), and AcCl (0.54 mL, 7.5 mmol), gave after workup and recrystallization (EtOAc) (*R*)-**19** as a white solid (1.30 g, 66%): R_f = 0.28 (EtOAc); mp 147−148 °C; $[\alpha]^{25.2}_D$ −16.6° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 3H), 3.08 (t, J = 7.1 Hz, 2H), 3.36 (s, 3H), 3.39−3.44 (m, 1H), 3.79 (dd, J = 4.8, 9.6 Hz, 1H), 4.15 (t, J = 7.1 Hz, 2H), 4.33−4.44 (m, 2H), 4.49−4.54 (m, 1H), 6.44 (br d, J = 6.4 Hz, 1H), 6.65−6.73 (br t, 1H), 6.84 (d, J = 8.0 Hz, 2H), 6.90−7.06 (m, 3H), 7.16 (d, J = 8.0 Hz, 2H), 7.23−7.29 (m, 1H). HRMS (M + Na^+) (ESI^+) 411.1696 [M + H^+] (calcd for $C_{21}H_{25}FN_2O_4Na^+$ 411.1697). Anal. ($C_{21}H_{25}FN_2O_4$): C, H, F, N.

Preparation of (*R*)-*N*-4′-(Benzyloxy)benzyl 2-*N*-Acetamido-3-methoxypropionamide ((*R*)-20). A saturated HCl solution in dioxane (1 mmol/2 mL, 24.1 mL) was added to an Et_2O (10 mL) solution of (*R*)-*N*-4′-(benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbo-nyl)amino-3-methoxypropionamide (5.00 g, 12.1 mmol) at 0 °C, and the solution was stirred at room temperature (16 h). The reaction solution was concentrated in vacuo and dried (30 min).

Employing a procedure similar to (*R*)-**7**, and using the residue, CH_2Cl_2 (60 mL), Et_3N (5.1 mL, 36.3 mmol), and AcCl (1.4 mL, 18.8 mmol), gave after workup and recrystallization (EtOAc) (*R*)-**20** as a white solid (2.60 g, 60%): R_f = 0.28 (EtOAc); mp 149 °C; $[\alpha]^{25.1}_D$ −26.8° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 3H), 3.36 (s, 3H), 3.39−3.44 (br m, 1H), 3.79−4.02 (dd, J = 4.2, 9.4 Hz, 1H), 4.36−4.44 (m, 2H), 4.48−4.55 (m, 1H), 5.05 (s, 2H), 6.42 (br d, J = 6.0 Hz, 1H), 6.64−6.71 (br m, 1H), 6.93 (d, J = 7.8 Hz, 2H), 7.18 (d, J = 7.8 Hz, 2H), 7.29−7.44 (m, 5H). HRMS (M + Na^+) (ESI^+) 379.1634 [M + Na^+] (calcd for $C_{20}H_{24}N_2O_4Na^+$ 379.1634). Anal. ($C_{20}H_{24}N_2O_4$): C, H, N.

Preparation of (*R*)-*N*-4′-((2″-Fluoro)benzyloxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-21). A saturated HCl solution in dioxane (1 mmol/2 mL, 11.57 mL) was added to (*R*)-*N*-4′-((2″-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-meth-oxypropionamide (2.50 g, 5.8 mmol) at 0 °C, and the solution was stirred at room temperature (16 h). The reaction solution was concentrated in vacuo and dried (30 min).

Employing a procedure similar to (*R*)-**7**, and using the residue (1.70 g, 5.1 mmol), CH_2Cl_2 (20 mL), Et_3N (2.10 mL, 15.3 mmol), and AcCl (550 μL, 7.6 mmol), gave after workup and recrystallization (EtOAc) (*R*)-**21** (1.25 g, 65%) as a white solid: R_f = 0.28 (EtOAc); mp 173−174 °C; $[\alpha]^{24.6}_D$ −20.7° (c 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 3H), 3.37 (s, 3H), 3.42 (dd, J = 7.6, 9.0 Hz, 1H), 3.79 (dd, J = 4.0, 9.0 Hz, 1H), 4.34−4.44

(m, 2H), 4.49−4.54 (m, 1H), 5.12 (s, 2H), 6.43 (br d, J = 6.4 Hz, 1H), 6.66−6.72 (br t, 1H), 6.94 (d, J = 8.0 Hz, 2H), 7.06−7.21 (m, 4H), 7.28−7.34 (m, 1H), 7.49 (td, J = 1.6, 7.6 Hz, 1H). HRMS (M + H^+) (ESI^+) 375.1720 [M + H^+] (calcd for $C_{20}H_{23}FN_2O_4H^+$ 375.1720). Anal. ($C_{20}H_{23}FN_2O_4$): C, H, F, N.

Preparation of (*R*)-*N*-4′-((4″-Fluoro)benzyloxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-22). A saturated HCl solution in dioxane (1 mmol/2 mL, 11.57 mL) was added to (*R*)-*N*-4′-((4″-fluoro)benzyloxy)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (2.50 g, 5.8 mmol) at 0 °C, and the solution was stirred at room temperature (16 h). The reaction solution was concentrated in vacuo and dried (30 min).

Employing a procedure similar to (*R*)-**7**, and using the residue (1.85 g, 5.6 mmol), CH_2Cl_2 (30 mL), Et_3N (2.36 mL, 16.8 mmol), and AcCl (608 μL, 8.4 mmol), gave after workup and recrystallization (EtOAc) (*R*)-**22** (1.28 g, 61%) as a white solid: R_f = 0.22 (EtOAc); mp 166−167 °C; $[\alpha]^{25.2}_D$ −19.4° (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 3H), 3.37 (s, 3H), 3.42 (dd, J = 7.6, 9.4 Hz, 1H), 3.79 (dd, J = 4.0, 9.4 Hz, 1H), 4.40 (d, J = 5.2 Hz, 2H), 4.49−4.54 (m, 1H), 5.01 (s, 2H), 6.40 (br d, J = 5.6 Hz, 1H), 6.62−6.69 (br t, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.07 (t, J = 8.8 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.37−7.41 (m, 2H). HRMS (M+H^+) (ESI^+) 375.1720 [M+H^+] (calcd for $C_{20}H_{23}FN_2O_4H^+$ 375.1720). Anal. ($C_{20}H_{23}FN_2O_4$): C, H, F, N.

Preparation of *N*-4′-((3″-Fluoro)benzyloxy)benzyl Acetamide (23). Employing a procedure similar to (*R*)-**7**, and using 4-((3′-fluoro)benzyloxy)benzylamine (**32**) (1.00 g, 4.3 mmol), CH_2Cl_2 (40 mL), Et_3N (728 μL, 5.2 mmol), and AcCl (376 μL, 5.2 mmol), gave after workup and trituration (Et_2O) **23** (810 mg, 69%) as a white solid: R_f = 0.39 (EtOAc); mp 131−132 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 1.84 (s, 3H), 4.16 (d, J = 5.6 Hz, 2H), 5.11 (s, 2H), 6.95 (d, J = 8.8 Hz, 2H), 7.11−7.18 (m, 3H), 7.24−7.29 (m, 2H), 7.40−7.45 (m, 1H), 8.21−8.24 (br t, 1H). HRMS (M + Na^+) (ESI^+) 296.1063 [M + Na^+] (calcd for $C_{16}H_{16}FNO_2Na^+$ 296.1062). Anal. ($C_{16}H_{16}FNO_2$): C, H, F, N.

Preparation of 2-(4′-((3″-Fluoro)benzyloxy)benzyl)amino-3-methoxypropionamide (74). A solution of **79** (1.50 g, 4.32 mmol) in NH_3 (7 N in MeOH, 150 mL) was stirred at room temperature in a sealed tube (7 d). The solution was concentrated in vacuo, and the residue was recrystallized (EtOAc) to obtain **74** as a white solid (350 mg, 24%): R_f = 0.25 (EtOAc); mp 84−85 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.31−3.36 (m, 4H), 3.60 (d, J = 5.7 Hz, 2H), 3.71 (1/2 AB_q, J = 12.9 Hz, 1H), 3.78 (1/2 AB_q, J = 12.9 Hz, 1H), 5.06 (s, 2H), 5.40−5.44 (br s, 1H), 7.10 (d, J = 9.0 Hz, 2H), 6.96−7.05 (br dt, 1H), 7.13−7.25 (m, 4H), 7.31−7.38 (m, 1H). M_r (+ESI) 355.16 [M+Na]$^+$ (calcd for $C_{18}H_{21}FN_2O_3Na^+$ [M+355.14]$^+$). Anal. ($C_{18}H_{21}FN_2O_3$): C, H, F, N.

Preparation of 2-(4′-((3″-Fluoro)benzyloxy)benzyl)amino-2-(furan-2-yl)acetamide Oxalate (75). A solution of **87** (880 mg, 0.05 mmol) in NH_3 (7 N in MeOH, 88 mL) was stirred at 4 °C (16 h). The solution was concentrated in vacuo, and the residue was dissolved in THF (2.3 mL) to obtain a 1 N solution. To this solution, oxalic acid (2 N in THF, 4.6 mL) was added. After standing at room temperature (16 h) the precipitate was collected, dried, and recrystallized with *i*-PrOH. The white solid was recrystallized (absolute EtOH) to obtain **75** as a white solid (520 mg, 51%): R_f = 0.15 (EtOAc); mp 194−195 °C. ^1H NMR (DMSO-d_6) δ 3.75 (s, 2H), 4.54 (s, 1H), 5.14 (s, 2H), 6.44−6.45 (m, 1H), 6.48−6.50 (m, 1H), 7.51 (d, J = 9.0 Hz, 2H), 7.03−7.19 (m, 1H), 7.26−7.31 (m, 3H), 7.41−7.51 (m, 2H), 7.71−7.73 (m, 2H). M_r (+ESI) 355.13 [M + H]$^+$ (calcd for $C_{22}H_{21}FN_2O_7H^+$ 355.15 [M + H]$^+$). Anal. ($C_{22}H_{21}FN_2O_7$): C, H, F, N.

Pharmacology. Compounds were screened under the auspices of the National Institutes of Health's Anticonvulsant Screening Program. Experiments were performed in male rodents [albino Carworth Farms no. 1 mice (intraperitoneal route, ip), albino Sprague−Dawley rats (oral route, po)]. Housing, handling, and feeding were in accordance with recommendations contained in the "Guide for the Care and Use of Laboratory Animals". Anticonvulsant activity was established using the MES test,[29] 6 Hz,[42] hippocampal kindled seizure,[45] and the scMet test,[44] according to previously reported methods.[16]

Formalin Test.[50a] The formalin test involved injection of 0.5% formalin into the mouse hind paw. Injection led to a biphasic behavioral response characterized by licking of the affected paw. The number of licks was measured as a proxy for perceived pain. The first phase is termed the "acute" phase, and the second phase is termed the "inflammatory" phase. Each trial involved 16 animals, 8 controls given an ip injection of vehicle and 8 given the test compound at a specified dose. The amount of time that each animal spends licking was monitored at 2 min intervals, and monitoring continued for 45 min. Plots of time licking versus time provided a biphasic response and permitted the area under the curve (AUC) to be determined for each animal for the acute and inflammatory phases. The AUC for each compound-treated animal was compared to the average result from the control group, yielding an average percent of control (reported with the SEM and p value).

Partial Sciatic Ligation Model.[47] Rats were anesthetized with sodium pentobarbital and the depth of anesthesia monitored by their response to a tail pinch and observation of the depth of respiration. After surgical exposure of the sciatic nerve, the nerve was slightly elevated, and approximately one-third to one-half of the nerve was tied off. Typically, the surgical procedure was done on the right side, while a sham surgery was performed on the left hind leg where the sciatic nerve was only exposed. After recovery (7 d), the animals were tested for the development of mechanical allodynia. The animals are placed in a bottomless plexiglass box placed on a wire mesh ($^1/_4$″) platform. After a 30−60 min acclimation period, a baseline mechanical sensitivity was determined by applying a series of calibrated Von Frey fibres perpendicularly to the plantar surface of each hind paw and holding it in place for 6 s with enough force to slightly bend the fiber. After a positive response (withdrawal of the foot) was observed, a weaker fiber was applied until a 50% threshold for withdrawal could be determined. The allodynic threshold was then redetermined after ip administration of the test compound. Testing was conducted at the time-to-peak effect of the compound in the MES test.

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Supporting Information Available: Synthetic procedures for the intermediates leading to the preparation of **5**,**9**, (*R*)-**6**−**8**, (*R*)-**10**−**22**, (*S*)-**6**, (*S*)-**10**, **74**, and **75**, elemental analyses, ^1H and ^{13}C NMR spectra of compounds **5**, (*R*)-**6**−**8**, **9**, (*R*)-**10**−**22**, (*S*)-**6**, (*S*)-**10**, **74**, and **75** evaluated in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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