Preparation and Anticonvulsant Activity of a Series of Functionalized α-Aromatic and α-Heteroaromatic Amino Acids

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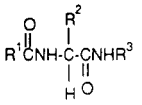
We recently reported the potent anticonvulsant activity of (*R,S*)-α-acetamido-*N*-benzyl-α-phenylacetamide (**2b**). Selectively substituted derivatives of this compound have now been prepared (23 examples) and evaluated in the maximal electroshock seizure (MES) and horizontal screen (tox) tests in mice. In several key cases, replacement of the α-phenyl substituent in **2b** by a relatively small, electron-rich, heteroaromatic moiety led to a substantial improvement in the anticonvulsant potency of the drug candidate. The most active compounds were (*R,S*)-α-acetamido-*N*-benzyl-2-furanacetamide (**2g**) and (*R,S*)-α-acetamido-*N*-benzyl-2-pyrroleacetamide (**2i**). After ip administration, the MES ED_{50} values for **2g** (10.3 mg/kg) and **2i** (16.1 mg/kg) compared well with phenytoin (9.50 mg/kg). Evaluation of the two individual enantiomers of **2g** demonstrated that the anticonvulsant activity resided in the *R* stereoisomer. The low ED_{50} value (3.3 mg/kg) for (*R*)-**2g** contributed to the large protective index (TD_{50}/ED_{50}) observed for this drug candidate, which approached that of phenytoin.

Recently we have reported the excellent anticonvulsant activities of functionalized amino acid derivatives **1**.[1-5]



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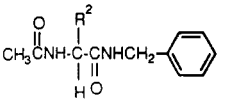


2 a $R^2 = CH_3$
b $R^2 = Ph$

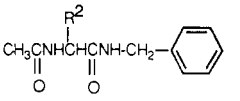
The pharmacological data suggested that these compounds comprised a new and important class of anticonvulsant agents.[6] The structure–activity profile for **1** indicated that stringent steric and electronic requirements existed for optimal anticonvulsant activity. Excellent protection against maximal electroshock seizures (MES) in mice was observed for functionalized amino acid racemates containing an *N*-benzylamide moiety, an acetylated amino group, and either a methyl (**2a**) or a phenyl (**2b**) substituent on the α-carbon. The median effective doses (ED_{50}) for **2a** and **2b** in mice (ip) were 76.5 and 20.3 mg/kg, respectively.[3] These values compared favorably with the corresponding ED_{50} value obtained for the proven antiepileptic phenobarbital (21.8 mg/kg).[7] Significantly, evaluation of the individual enantiomers of **2a** and **2b** showed that the anticonvulsant activity resided primarily in the *R* stereoisomers.[1,4,5] In both cases, the *R* isomer was over 10 times more effective in the MES test than the corresponding *S* enantiomer. This difference in activity represented the greatest eudismic ratio[8] reported to date for MES-selective anticonvulsants.

The pronounced activity observed for **2b** prompted our investigation of the anticonvulsant properties of a select series of functionalized amino acids in which the α-substituent is either an aromatic or a heteroaromatic group. In this paper, the synthesis, physical properties, and anticonvulsant activities of these compounds are described. Evidence is presented that placement of a relatively small, electron-rich, heteroaromatic moiety at the α-site leads to a substantial enhancement in the anticonvulsant activity of the drug candidate and that the high eudismic ratio observed for **2a** and **2b** is preserved for the most active member of this series of compounds.

Selection of Compounds

(*R,S*)-α-Acetamido-*N*-benzyl-α-phenylacetamide[3] (**2b**) served as the parent compound in this study (Table I). In the first series of functionalized amino acid derivatives

Table I. Selected Physical and Pharmacological Data in Mice for *R,S*-α-Aromatic and α-Heteroaromatic Substituted Functionalized Amino Acid Derivatives **2**[a]



2

no.	R^2	mp[b]	MES[c] ED_{50}	tox[d] TD_{50}
2b[e]	C_6H_5	202–203	32.1 (27.5–40.2)	>40
2c	4-C_6H_4OH	232–235	>300	*f*
2d	4-$C_6H_4OCH_3$	196–198	>300	*f*
2e	2-OH-5-$CH_3C_6H_3$	183–185	>300	*f*
2f	2-$C_{10}H_7$	210–211	>300	>300
2g	2-furanyl	178–179	10.3 (9.1–11.6)	~40
2h	5-CH_3-2-furanyl	148–150	19.2 (16.4–23.8)	75.4
2i	2-pyrrolyl	174–175	16.1 (13.2–19.9)	>30, <100
2j	5-CH_3-2-pyrrolyl	167–168	36.5 (30.6–57.1)	*f*
2k	1-CH_3-2-pyrrolyl	179–181	~300	*f*
2l	2-thienyl	167–169	44.8 (38.9–51.4)	>30, <100
2m	3-thienyl	198–199	87.8 (69.9–150)	>100
2n	benzo[*b*]furan-2-yl	195–196	>100, <300	>100, <300
2o	indol-3-yl	213–214	>300	<300
2p	benzo[*b*]thien-2-yl	226–227	>100, <300	>100, <300
phenytoin[g]			9.5 (8.1–10.4)	65.5 (52.5–72.1)
phenobarbital[g]			21.8 (15.0–22.5)	69.0 (62.8–72.9)
valproate[g]			272 (247–338)	426 (369–450)

[a] The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in mg/kg. Numbers in parentheses are 95% confidence intervals. [b] Melting points (°C) are uncorrected. [c] MES = maximal electroshock seizure test. [d] Tox = neurologic toxicity determined from horizontal screen. [e] Reference 3. [f] Not determined. [g] Reference 7.

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† University of Houston.
‡ Lilly Research Laboratories.

(1) Kohn, H.; Conley, J. D. *Chem. Br.* **1988**, *24*, 231.
(2) Cortes, S.; Liao, Z.-K.; Watson, D.; Kohn, H. *J. Med. Chem.* **1985**, *28*, 601.
(3) Conley, J. D.; Kohn, H. *J. Med. Chem.* **1987**, *30*, 567.
(4) Kohn, H.; Conley, J. D.; Leander, J. D. *Brain Res.* **1988**, *457*, 371.
(5) Conley, J. D.; Kohn, H., unpublished results.

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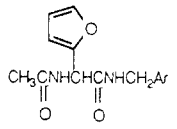
Table II. Selected Physical and Pharmacological Data in Mice for Fluoro-Substituted (*R,S*)-α-Acetamido-*N*-substituted-benzyl-2-furanacetamides **3**



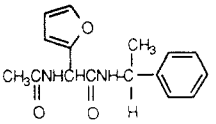
3

no.	Ar	mp[b]	MES[c] ED_{50}	tox[d] TD_{50}
2g	C_6H_5	178–179	10.3 (9.1–11.6)	~40
3a	2-FC_6H_4	193–195	40.0	*e*
3b	3-FC_6H_4	163–165	13.3 (11.5–15.3)	136 (115–162)
3c	4-FC_6H_4	188–190	12.7 (10.4–15.1)	144 (123–171)
3d	2,5-$F_2C_6H_3$	177–178	23.8 (20.2–28.4)	*e*
3e	2,6-$F_2C_6H_3$	237–239	>25, <100	*e*

[a] The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in mg/kg. Numbers in parentheses are 95% confidence intervals. [b] Melting points (°C) and uncorrected. [c] MES = maximal electroshock seizure test. [d] Tox = neurologic toxicity determined from horizontal screen. [e] Not determined.

selected for synthesis, the α-substituent was systematically varied. Both aromatic (**2c–f**) and heteroaromatic (**2g–p**) moieties were incorporated into the amino acid backbone. In all cases, the functionalized amino acid racemates were prepared and tested.

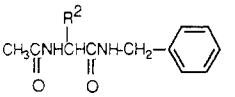
The pharmacological properties observed for **2g** warranted further investigation of this compound. Accordingly, two different types of structural modifications of the N-terminal benzyl moiety were made. First, a series of racemic fluorine-substituted benzylamides **3a–e** were synthesized (Table II). Impetus for this study was provided by an earlier observation that a modest improvement of the overall activity of **2a** in mice (ip) was obtained upon incorporation of a fluorine atom at the meta position of the aromatic ring.[3] The second structural modification examined for **2g** involved the replacement of the *N*-benzylamide group by the corresponding *N*-α-methylbenzylamides. Use of (*R*)-α-methylbenzylamine and (*S*)-α-methylbenzylamine in the synthesis permitted the preparation and pharmacological evaluation of each of the four individual diastereomers of **4**.



4

The final group of drug candidates synthesized were the individual *R*-(−) and *S*-(+) stereoisomers of **2g** (Table III). The marked selectivity previously noted[1,4,5] for the individual enantiomers of **2a** and **2b** prompted this investigation.

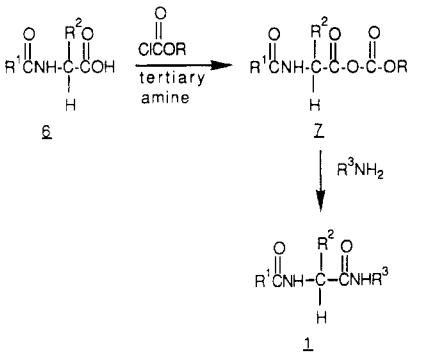
Table III. Selected Physical and Pharmacological Data in Mice for Functionalized Amino Acid Stereoisomers



no.	R^2	mp[b]	MES[c] ED_{50}	tox[d] TD_{50}
(*R,S*)-**2g**	2-furanyl	178–179	10.3 (9.1–11.6)	~40
(*R*)-**2g**	2-furanyl	196–197	3.3 (2.8–3.9)	23.8
(*S*)-**2g**	2-furanyl	196–197	>25	>200
(*R,S*)-**2a**[e]	CH_3	139–141	76.5 (66.6–89.0)	454 (417–501)
(*R*)-**2a**[e]	CH_3	139–141	54.8 (50.3–59.7)	214 (148–262)
(*S*)-**2a**[e]	CH_3	139–142	548 (463–741)	841 (691–954)
(*R,S*)-**2b**[f]	C_6H_5	202–203	32.1 (27.5–40.2)	>40
(*R*)-**2b**[f]	C_6H_5	219–221	26.4 (21.1–32.0)	>80
(*S*)-**2b**[f]	C_6H_5	221–222	>300	>100, <300

[a] The compounds were administered intraperitoneally. ED_{50} and TD_{50} values are in mg/kg. Numbers in parentheses are 95% confidence intervals. [b] Melting points (°C) are uncorrected. [c] MES = maximal electroshock seizure test. [d] Tox = neurologic toxicity determined from horizontal screen. [e] Values determined at the Epilepsy Branch, NINCD, NIH; see ref 4. The median toxic dose (TD_{50}) was determined by using the rotorod test (see: Durham, N. W.; Miya, T. S. *J. Am. Pharm. Assoc.* **1957**, *46*, 208). [f] Reference 4.

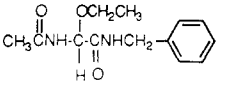
Scheme I. Preparation of Compound **1** via the Mixed Carbonic Anhydride Method



6 **7** **1**

Chemistry

The strategies employed in the synthesis of the functionalized amino acid derivatives were patterned after procedures previously employed. The preparation of compounds **2c–e,g–i,k,l,n–p** have been reported.[9] Introduction of the aromatic or heteroaromatic group at carbon 2 in compounds **2c–e,g–l,n–p** was accomplished by an amidoalkylation reaction using 2-acetamido-*N*-benzyl-2-ethoxyacetamide (**5**), BF_3, and the appropriate aromatic substrate. The reactions proceeded in moderate yields (28–67%) with excellent regioselectivity.



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The remaining compounds in this study were prepared by the mixed carbonic anhydride method (Scheme I).[10] In

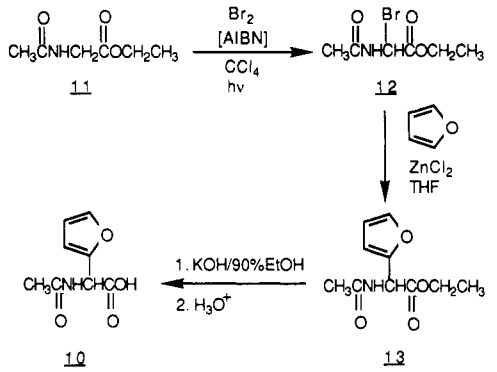
(6) For the pharmacological properties of the related α,α-dialkyl-α-phthalimidoacetamides and α,α-dialkyl-α-benzamidoacetamides, see: Upham, S. D.; Dermer, O. C. *J. Org. Chem.* **1957**, *22*, 799.

(7) Porter, R. J.; Cereghino, J. J.; Gladding, G. D.; Hessie, B. J.; Kupferberg, H. J.; Scoville, B.; White, B. G. *Cleveland Clin. Q.* **1984**, *51*, 293.

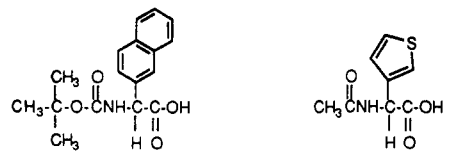
(8) Eudismic ratio = ratio of activities of the two enantiomers. See: Lehmann, P. A. *Trends Pharmacol. Sci.* **1982**, *3*, 103.

(9) LeGall, P.; Sawhney, K. N.; Conley, J. D.; Kohn, H. *Int. J. Pept. Protein Res.* **1988**, *32*, 279.

Scheme II. Improved Procedure for the Preparation of (*R,S*)-α-Acetamido-2-furanacetic Acid (**10**)



this procedure, the N-acylated amino acid **6** was treated with an alkyl chloroformate in the presence of a tertiary amine to generate the mixed N-acyl amino acid carbonic ester anhydride **7**. This intermediate was not isolated but reacted in situ with the appropriate amine (R^3NH_2) to produce the N-acyl amino acid N-substituted amide **1**. The starting N-acylated amino acid selected for the synthesis of **2f** was *N*-*t*-Boc-(*R,S*)-2-naphthylglycine[11] (**8**).



Subsequent removal (CF_3CO_2H) of the N-protecting group after the mixed carbonic anhydride coupling step, followed by acetylation with acetyl chloride and triethylamine, yielded **2f**. In the synthesis of (*R,S*)-**2g**, (*R*)-**2g**, (*S*)-**2g**, **2m**, **3**, and **4** the appropriate N-acetyl amino acid was directly employed, thereby simplifying the experimental procedure. Synthesis of (*R,S*)-α-acetamido-3-thiopheneacetic acid (**9**) was readily accomplished beginning with (*R,S*)-α-amino-3-thiopheneacetic acid and acetic anhydride. An improved procedure (Scheme II) was developed for the synthesis of (*R,S*)-α-acetamido-2-furanacetic acid (**10**). This functionalized amino acid served as the starting material for compounds **2g**, **3**, and **4**. The method adopted took advantage of the recent report on the employment of protected α-bromo amino acid derivatives as electrophilic glycine templates in amino acid synthesis.[12] Accordingly, ethyl acetamido-2-bromoacetate[13] (**12**) was prepared from ethyl acetamidoacetate (**11**) and then treated with furan and $ZnCl_2$ to give **13**. Hydrolysis of the ethyl ester yielded **10**, the necessary precursor for the mixed carbonic anhydride coupling procedure (Scheme I). The overall yield for **10** in this three-step sequence was 65%.

Several different alkyl chloroformates and tertiary amines were examined for the mixed carbonic anhydride reaction beginning with **10**. Higher conversion rates were generally obtained with isobutyl chloroformate and 4-methylmorpholine.[10] The yields for the final coupling step

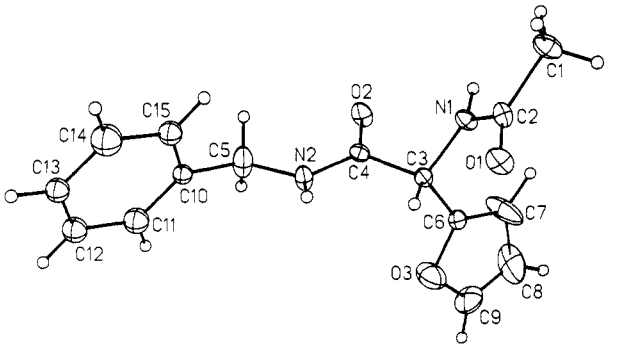
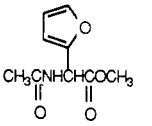


Figure 1. ORTEP view of compound (*R*)-**2g** with atom labeling scheme. The thermal ellipsoids are 20% equiprobability envelopes, with hydrogens as spheres of arbitrary diameter. Only one orientation of the disordered phenyl ring is shown.

for the preparation of the fluorine-substituted aryl amides **3** (Table II) ranged from 50 to 88%. A comparable synthetic protocol was adopted for methylbenzyl amides **4**. The configuration at C-2 in each of the four individual diastereomers of **4** was not determined.

Synthesis of the two enantiomeric forms of **2g**, (*R*)-**2g**, and (*S*)-**2g** (Table III) was achieved by resolution of racemic **10** via fractional recrystallization of the diastereomeric salts formed with (*R*)- and (*S*)-α-methylbenzylamine, respectively, and then coupling the individual stereoisomers with benzylamine. Use of isobutyl chloroformate and 4-methylmorpholine in the mixed carbonic anhydride coupling procedure did not lead to significant amounts of racemization of **2g**. An X-ray crystallographic structural determination of (*R*)-**2g** was conducted to provide basic information concerning the solid-state structure of this compound, and the ORTEP view is presented in Figure 1. Thermal disorder limited the amount of data obtainable in this determination, but some useful observations concerning the structure of the molecular backbone of (*R*)-**2g** in the solid state can still be made. Significant double bond character in the C–N peptide linkages were indicated by unusually short N1–C2 (1.338 (9) Å) and N2–C4 (1.323 (8) Å) bond lengths and unusually long C1–C2 (1.509 (9) Å) and C3–C4 (1.534 (8) Å) bond lengths [for $C(sp^2)$–$C(sp^3)$]. Comparable observations have been previously noted in related compounds.[14] The torsion angles about N1–C2 and N2–C4 are essentially 0°, as would be expected in this highly conjugated system, and the sum of the angles about both nitrogens is 359°, indicating virtual planarity and substantial delocalization of the lone electron pairs.

The absolute configurations of the enantiomers of **10** were determined by converting an enriched sample of (*R*)-**10** to the corresponding methyl ester (*R*)-**14** with diazomethane. The optical rotation observed for this adduct [$[\alpha]^{26}_D = -95°$ (c = 1, MeOH)] was comparable to a sample obtained after treatment of racemic **14**[9] with papain



in aqueous DMF. This enzymatic system has been re-

(10) For an excellent discussion and review of this method, see: Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1967**, *89*, 5012.

(11) Kukolja, S.; Draheim, S. E.; Pfeil, J. L.; Cooper, R. D. G.; Graves, B. J.; Holmes, R. E.; Neel, D. A.; Huffman, G. W.; Webber, J. A.; Kinneck, M. D.; Vasileff, R. T.; Foster, B. J. *J. Med. Chem.* **1985**, *28*, 1886.

(12) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547.

(13) Kuber, R.; Steglich, W. *Liebigs Ann. Chem.* **1983**, 599.

(14) (a) Ishida, T.; Tanabe, N.; Inoue, M. *Acta Crystallogr.* **1983**, *C39*, 110. (b) Kojima, T.; Tanaka, I.; Ashida, T. *Ibid.* **1982**, *B38*, 221. (c) Hansen, L. K.; Hagen, E. A.; Loennechen, T.; Aasen, A. J. *Acta Chem. Scand.* **1982**, *B36*, 327. (d) Aubry, A.; Vitoux, B.; Boussard, G.; Marraud, M. *Int. J. Pept. Protein Res.* **1981**, *18*, 195 and references therein.

ported to selectively hydrolyze racemic N-protected furylglycine methyl esters to the free (S)-acids and unreacted (R)-esters in high enantiomeric excess.[15]

Several attempts were conducted to directly employ chiral (R)-13 or (R)-14 (obtained by papain-mediated hydrolysis of the corresponding racemic esters) for the preparation of (R)-2g. Unfortunately, treatment of either ester with benzylamine in the absence or presence of NaCN gave racemic 2g.[16]

Pharmacological Evaluation

The N-acetyl amino acid N-substituted amides 2–4 were tested for anticonvulsant activity by using the procedures described by Krall et al.[17] All compounds were administered intraperitoneally (ip) in mice. Tables I–III list the median effective dose (ED_{50}) values required to prevent seizures in the MES test by racemic 2, racemic 3, and the individual enantiomers of 2g, respectively. Included in these tables are the median toxic dose (TD_{50}) values determined for select compounds by using the horizontal screen test.[18]

Table I lists the pharmacological data for those compounds in which only the α-carbon moiety has been modified. Evaluation of this subset of results revealed several important observations. First, addition of electron-releasing hydroxy (i.e., 2c and 2e) or methoxy (i.e., 2d) groups to the α-substituted phenyl group in 2b or expansion of the aromatic ring from the phenyl group in 2b to the naphthyl residue in 2f led to a precipitous drop in anticonvulsant potency. Second, replacement of the α-phenyl ring in 2b with an electron-rich, five-membered heteroaromatic ring resulted in a substantial improvement in the potency of the compound in the MES test. Notable protection against seizures were observed for the racemates of 2g–j and 2l. The ED_{50} values for these compounds compared favorably with the reported data for phenytoin.[7] Third, placement of a methyl substituent on the five-membered heteroaromatic ring was accompanied by a decrease in the potency of the drug candidate versus the unsubstituted compounds (i.e., 2h versus 2g; 2j, 2k versus 2i). Fourth, replacement of the α-heteroaromatic substituent by the corresponding benzoheteroaromatic group led to a reduction in biological activity (i.e., 2n–p). This observation paralleled the results obtained for 2b versus 2f.

The second and third series of compounds tested for anticonvulsant activity were adducts in which the terminal N-benzylamide moiety in 2g was altered. Table II lists the comparative data obtained for five fluorine-substituted derivatives. All the compounds exhibited pronounced activity in the MES test. The meta (3b) and para (3c) fluoro adducts displayed activities comparable to that of 2g, while a small reduction in activity versus 2g was noted for ortho derivative 3a, and the two difluoro analogues 3d and 3e. These data contrasted with the pharmacological results secured from the α-methylbenzylamides 4a–d. Increasing the size of the benzylamide moiety by incorporation of an α-methyl group resulted in a significant decrease in the anticonvulsant potency of the drug candidate regardless of the stereochemical relationship between the two asymmetric centers. The MES ED_{50} values for these compounds were all greater than 100 mg/kg. A similar trend was previously noted in the 2-acetamido-N-benzylpropionamide (2a) series.[3]

Table III lists the pharmacological data for the two individual isomers of 2g along with the racemic mixture, as well as the corresponding data for 2a and 2b.[4] In all three series of compounds a pronounced improvement in anticonvulsant potency was noted for the R enantiomer versus either the S isomer or the racemate. Moreover, in each case little activity in the MES test was observed for the S enantiomer. The ED_{50} value of (R)-2g was 3.3 mg/kg, which was considerably lower than that reported for phenytoin[7] (ED_{50} = 9.5 mg/kg). The enhanced potency of (R)-2g contributed to the observed high protective index (TD_{50}/ED_{50} = 7.2) for this compound, which compared favorably with the value observed for phenytoin (TD_{50}/ED_{50} = 6.9).

Conclusions

The pharmacological data obtained in this investigation significantly extended the structure–activity profile previously reported for functionalized amino acid derivatives.[2,3] The observed data supported our hypothesis that stringent steric and electronic requirements exist for maximal anticonvulsant activity in this novel class of compounds.[3] The outstanding potencies noted for 2g and 2i in the MES test suggested that the placement of relatively small, electron-rich groups at the α-position in 1 was beneficial for anticonvulsant activity. Furthermore, our finding that the primary activity of 2g resided in the R enantiomer provided additional evidence for the marked stereospecificity exhibited in this new class of anticonvulsants. Additional studies are in progress investigating the generality of this class of compounds as well as their mode of action.

Experimental Section

Chemistry. General Methods. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on Perkin-Elmer 1330 and 283 spectrometers and calibrated against the 1601 cm^{-1} band of polystyrene. Absorption values are expressed in wavenumbers (cm^{-1}). Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were taken on Nicolet NT-300 and General Electric QE-300 NMR instruments. Chemical shifts (δ) are in parts per million (ppm) relative to Me_4Si and coupling constants (J values) are in hertz. Low-resolution mass spectra (MS) were recorded at an ionizing voltage of 70 eV with a Varian MAT CH-5 spectrometer at the Lilly Research Laboratories. Microanalyses were provided by the Physical Chemistry Department of the Lilly Research Laboratories. Thin- and thick-layer chromatography were run on precoated silica gel GHLF microscope slides (2.5 × 10 cm; Analtech No. 21521) or silica gel GHLF (20 × 20 cm; Analtech 11187).

Preparation of (R,S)-2-Acetamido-N-benzyl-2-(5-methylpyrrolyl)acetamide (2j). 2-Acetamido-N-benzyl-2-ethoxyacetamide[9] (5, 2.00 g, 8 mmol) was suspended in anhydrous Et_2O (175 mL), and then $BF_3{\cdot}Et_2O$ (1.38 g, 9.7 mmol) was added and the resulting solution was stirred (15 min). 2-Methylpyrrole[19] (0.85 g, 10 mmol) was then added and the reaction mixture was stirred under N_2 (6 days), during which time the color of the reaction mixture turned reddish brown and a dark-brown deposit formed at the bottom of the flask. The clear solution was decanted and treated with an aqueous saturated $NaHCO_3$ solution containing ice (100 mL) for 30 min. The aqueous reaction mixture was extracted with EtOAc (3 × 30 mL). The combined extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. The brown oily residue was purified by flash column chromatography using 2% MeOH/$CHCl_3$ as the eluent to yield 0.20 g (9%) of the

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desired product. Compound **2j** was recrystallized from ethyl acetate/hexane to give a light yellow amorphous solid: R_f 0.44 (95:5, $CHCl_3$/MeOH); mp 167–168 °C; IR (KBr) 3250, 1630, 1520, 1420, 1360, 1300, 1260, 1230, 1160, 1110, 1020 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.87 (s, 3 H), 2.13 (s, 3 H), 4.27 (br s, 2 H), 5.33 (d, J = 7.4 Hz, 1 H), 5.60 (s, 1 H), 5.77 (s, 1 H), 7.19–7.30 (m, 5 H), 8.22 (d, J = 7.4 Hz, 1 H), 8.45 (t, J = 5.5 Hz, 1 H), 10.38 (s, 1 H); ^{13}C NMR (DMSO-d_6) 12.74, 22.49, 42.11, 51.21, 105.09, 106.07, 126.16, 126.64, 126.85, 127.09 (2 C), 128.17 (2 C), 139.33, 168.88, 169.79 ppm. Anal. ($C_{16}H_{19}N_3O_2$) C, H, N.

Preparation of (*R*,*S*)-2-Acetamido-*N*-benzyl-2-(2-naphthyl)acetamide (2f). *N*-*t*-Boc-(*R*,*S*)-2-naphthylglycine *N*-Benzylamide. *N*-*t*-Boc-(*R*,*S*)-2-naphthylglycine[11] (8, 7.53 g, 25 mmol) was combined with CH_3CN (100 mL) and the mixture was placed into an ice/salt water bath (−5 °C). Et_3N (2.53 g, 3.50 mL, 25 mmol) was added dropwise, followed by ethyl chloroformate (2.71 g, 2.40 mL, 25 mmol). All additions were done slowly so that the temperature of the mixture did not rise above 0 °C. The mixture was then stirred at −5 °C (20 min). Benzylamine (2.95 g, 3.0 mL, 27.5 mmol) in CH_3CN (10 mL) was added dropwise and the mixture was stirred at −5 °C (1 h) and then room temperature (18 h). The brown mixture was concentrated in vacuo and the residue was combined with hot THF and cooled in the freezer (3 h), resulting in the formation of a white precipitate. The mixture was filtered and the precipitate was collected, dried in vacuo, and identified as Et_3NHCl. The filtrate was concentrated in vacuo and the resulting solid was recrystallized from chloroform/hexane: yield 4.18 g (43%); mp 127–129 °C; IR (KBr) 3240, 1635, 1520, 1505, 1460, 1370, 720, 705 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.31 (s, 9 H), 4.32 (s, 2 H), 5.42 (s, 1 H), 7.14–7.79 (m, 12 H), the N-H protons were not detected; ^{13}C NMR (DMSO-d_6) 28.2 (3C), 43.3, 58.3, 80.0, 124.6, 126.1, 126.2, 126.3, 127.1, 127.2 (2 C), 127.5, 127.9, 128.3 (2 C), 128.6, 133.0, 133.2, 135.9, 137.7, 155.3, 170.3 ppm. Anal. ($C_{24}H_{26}N_2O_3$) C, H, N.

(*R*,*S*)-2-Naphthylglycine *N*-Benzylamide Methanesulfonate. The Boc-protected amino acid *N*-benzylamide (3.91 g, 10 mmol) was dissolved in trifluoroacetic acid (25 mL) and was stirred at room temperature (30 min), during which time gas evolved. The solution was concentrated in vacuo and the residue was redissolved in MeOH (50 mL). Methanesulfonic acid (0.96 g, 0.65 mL, 10 mmol) was added dropwise and stirred (5 min). After concentrating the solution in vacuo, the residue was repeatedly dissolved in MeOH and the solvent was removed (3 × 50 mL). The residue was then dried under vacuum (18 h), leaving a yellow oil. Trituration with CH_2Cl_2 gave a white solid: yield 2.48 g (83%); mp 180–182 °C; IR (KBr) 3245, 1655, 1460, 1385, 730, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.35 (s, 3 H), 4.33 (d, J = 5.5 Hz, 2 H), 5.18 (s, 1 H), 7.15–8.09 (m, 12 H), 8.78 (s, 1 H), 9.06 (t, J = 5.5 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 39.5, 42.3, 55.7, 124.8, 126.6, 126.7, 127.0, 127.5, 127.8, 128.0 (2 C), 128.3, 131.4, 132.4, 132.8, 138.3, 167.1 ppm. The resonances for the remaining aromatic carbons were not detected. Anal. ($C_{20}H_{22}N_2O_4S$) C, H, N.

(*R*,*S*)-2-Acetamido-*N*-benzyl-2-(2-naphthyl)acetamide (2f). (*R*,*S*)-2-Naphthylglycine *N*-benzylamide methanesulfonate (1.59 g, 4.1 mmol) was suspended in CH_3CN (25 mL) and was then cooled in an ice bath. Et_3N (0.83 g, 1.20 mL, 8.2 mmol) was added dropwise, followed by acetyl chloride (0.32 g, 0.30 mL, 4.1 mmol). The ice bath was removed and stirring was continued at room temperature (18 h). The solution was concentrated in vacuo and the residue was recrystallized from 1:1 95% EtOH/H_2O: yield 1.31 g (95%); mp 210–211 °C; IR (KBr) 3230, 1710, 1625, 1535, 1465, 760, 710 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.94 (s, 3 H), 4.30 (d, J = 5.2 Hz, 2 H), 5.86 (d, J = 7.9 Hz, 1 H), 7.15–7.91 (m, 12 H), 8.63 (d, J = 7.9 Hz, 1 H), 8.33 (t, J = 5.2 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 22.5, 42.2, 56.6, 125.5, 126.0, 126.1, 126.3, 126.8, 127.1 (2 C), 127.5, 127.7, 127.9, 128.2 (2 C), 132.4, 132.8, 136.5, 139.1, 169.2, 170.0 ppm. Anal. ($C_{21}H_{20}N_2O_2$) C, H, N.

Preparation of (*R*,*S*)-α-Acetamido-*N*-benzyl-3-thiopheneacetamide (2m). (*R*,*S*)-α-Acetamido-3-thiopheneacetic Acid (9). (*R*,*S*)-α-Amino-3-thiopheneacetic acid (3.92 g, 25 mmol) was combined with H_2O (55 mL) and was cooled in an ice water bath. Solid NaOH (1.00 g, 25 mmol) was added in one portion and the reaction mixture was stirred until homogeneous. Ac_2O (5.10 g, 4.70 mL, 50 mmol) was added dropwise, followed by aqueous NaOH (5 M, 15 mL). The solution was stirred at a temperature below 25 °C (15 min). Acidification of the reaction solution with concentrated HCl (pH 1, 15 mL) led to the formation of a precipitate. The mixture was filtered and the collected white solid was recrystallized from 1:1 95% EtOH/H_2O, producing light yellow crystals: yield 3.55 g (75%); mp 190–192 °C; ^1H NMR (DMSO-d_6) δ 1.90 (s, 3 H), 5.42 (d, J = 7.6 Hz, 1 H), 7.13 (d, J = 5.0 Hz, 1 H), 7.50–7.55 (m, 2 H), 8.69 (d, J = 7.6 Hz, 1 H), 12.89 (s, 1 H); ^{13}C NMR (DMSO-d_6) 22.3, 52.2, 123.3, 126.5, 127.2, 137.3, 169.3, 171.8 ppm. Anal. ($C_8H_9NO_3S$) C, H, N.

(*R*,*S*)-α-Acetamido-*N*-benzyl-3-thiopheneacetamide (2m). With the procedure previously described for the preparation of *N*-*t*-Boc-(*R*,*S*)-2-naphthylglycine *N*-benzylamide, compound **9** (2.99 g, 15 mmol) was treated with Et_3N (1.51 g, 2.10 mL, 15 mmol) and ethyl chloroformate (1.63 g, 1.43 mL, 15 mmol) and benzylamine (1.77 g, 16.5 mmol). The filtrate upon workup was concentrated in vacuo and the resulting yellow solid was recrystallized from 1:1 95% EtOH/H_2O: yield 1.91 g (44%); mp 198–199 °C; IR (KBr) 3460, 1675, 1570, 1400, 720, 695 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.91 (s, 3 H), 4.29 (d, J = 5.2 Hz, 2 H), 5.61 (d, J = 7.9 Hz, 1 H), 7.14–7.50 (m, 8 H), 8.55 (d, J = 7.9 Hz, 1 H), 8.74 (t, J = 5.2 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 22.3, 42.0, 52.5, 122.4, 126.1, 126.7, 127.0 (3 C), 128.2 (2 C), 139.0, 139.2, 169.0, 169.8 ppm. Anal. ($C_{15}H_{16}N_2O_2S$) C, H, N.

Synthesis of (*R*,*S*)-Ethyl α-Acetamido-2-furanacetate (13). An ethereal solution of $ZnCl_2$ (1 N, 28.00 mL, 0.028 mol) was added to a stirred solution of **12**[13] (4.40 g, 0.019 mol) and furan (11.23 g, 0.165 mol) in dry THF (100 mL), and allowed to stir at room temperature (5 h). The mixture was then treated with H_2O (50 mL), the organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were combined and dried (Na_2SO_4), and the volatile materials were removed by distillation in vacuo to give approximately 4.00 g (97%) of light-brown semisolid material. TLC analysis showed a major spot at R_f 0.30 (1% MeOH/$CHCl_3$). The desired compound was purified by flash column chromatography on silica gel using 1% MeOH/$CHCl_3$ as the eluent to give 3.60 g (87%) of a beige solid: mp 68–70 °C (lit.[9] mp 69–70 °C).

Preparation of (*R*,*S*)-α-Acetamido-2-furanacetic Acid (10). Compound **13** (4.00 g, 19 mmol) was dissolved in 90:10 EtOH/H_2O (150 mL) and then KOH (2.00 g, 35 mmol) was added and the resulting solution was stirred at room temperature (48 h). The reaction was concentrated in vacuo and the residue was diluted with H_2O and then washed with Et_2O (3 × 50 mL). The aqueous layer was then made acidic with 8.5% H_3PO_4 and extracted with EtOAc (3 × 150 mL). The organic layers were combined, dried (Na_2SO_4), and evaporated to dryness in vacuo to give **10**: yield 2.65 g (76%), mp 172–174 °C (lit.[9] mp 171–172 °C); R_f 0.37 (8:1:1 2-propanol/NH_4OH/H_2O).

Synthesis of (*R*,*S*)-α-Acetamido-*N*-benzyl-substituted-2-furanacetamides (2–4). General Procedure. 4-Methylmorpholine (1 equiv) was added to a solution of **10** (1 equiv) in dry THF (75 mL/10 mmol) at −10 to −15 °C under N_2. After stirring (2 min), isobutyl chloroformate (1 equiv) was added, leading to the precipitation of a white solid. The reaction was allowed to proceed for two additional minutes and then a solution of the substituted benzylamine (1 equiv) in THF (10 mL/10 mmol) was added over 5 min at −10 to −15 °C. The reaction mixture was allowed to stir at room temperature for 5 min and then the 4-methylmorpholine hydrochloride salt was filtered. The organic layer was concentrated in vacuo, the residue was triturated with EtOAc, and the remaining white solid was filtered. Concentration of the EtOAc layer led to additional amounts of the white solid. The desired product was purified by recrystallization or flash chromatography of the combined solid material.

Using this procedure the following compounds were prepared.

(*R*,*S*)-α-Acetamido-*N*-benzyl-2-furanacetamide (2g). Using benzylamine (0.27 g, 2.56 mmol) and racemic **10** (0.47 g, 2.56 mmol) gave 0.46 g (65%) of **2g**. The product was recrystallized from EtOAc to give a white solid: mp 177–178 °C (lit.[9] mp 178–179 °C); R_f 0.30 (2% MeOH/$CHCl_3$); ^1H NMR (DMSO-d_6) δ 1.90 (s, 3 H), 4.31 (d, J = 6.0 Hz, 2 H), 5.58 (d, J = 8.1 Hz, 1 H), 6.27–6.33 (m, 1 H), 6.40–6.44 (m, 1 H), 7.20–7.36 (m, 5 H), 7.60–7.64 (m, 1 H), 8.57 (d, J = 8.1 Hz, 1 H), 8.73 (t, J = 6.0 Hz, 1 H).

(*R*,*S*)-α-Acetamido-*N*-(2-fluorobenzyl)-2-furanacetamide (3a). Using 2-fluorobenzylamine (1.13 g, 9.0 mmol) and racemic

acid **10** (1.50 g, 8.2 mmol) gave 1.20 g (50%) of **3a**: mp 193–195 °C (recrystallized from EtOAc); R_f 0.36 (4% MeOH/$CHCl_3$); IR (KBr) 3270, 1630, 1520, 1440, 1360, 1220, 1180, 1140, 1100, 1000, 740 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.89 (s, 3 H), 4.33 (d, J = 5.5 Hz, 2 H), 5.58 (d, J = 8.0 Hz, 1 H), 6.28 (s, 1 H), 6.29 (s, 1 H), 7.13–7.35 (m, 4 H), 7.62 (s, 1 H), 8.61 (d, J = 8.0 Hz, 1 H), 8.76 (t, J = 5.5 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 22.35, 36.12 (d, J_{CF} = 6.6 Hz), 50.88, 107.64, 110.43, 115.04 (d, J_{CF} = 21.4 Hz), 124.29 (d, J_{CF} = 4.2 Hz), 125.64 (d, J_{CF} = 15.0 Hz), 128.94 (d, J_{CF} = 9.0 Hz), 129.27 (d, J_{CF} = 5.5 Hz), 142.66, 151.07, 159.99 (d, J_{CF} = 244.4 Hz), 168.17, 169.24 ppm. Anal. ($C_{15}H_{15}N_2O_3F$) C, H, N.

(*R*,*S*)-α-Acetamido-*N*-(3-fluorobenzyl)-2-furanacetamide (3b). Making use of 3-fluorobenzylamine (1.13 g, 9.0 mmol) and racemic **10** (1.50 g, 8.2 mmol) gave 1.90 g (80%) of **3b**: mp 163–165 °C (recrystallized from EtOAc); R_f 0.30 (4% MeOH/$CHCl_3$); IR (KBr) 3230, 1630, 1540, 1440, 1360, 1220, 1140, 1000, 730 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.89 (s, 3 H), 4.31 (d, J = 5.5 Hz, 2 H), 5.55 (d, J = 7.8 Hz, 1 H), 6.31 (s, 1 H), 6.42 (s, 1 H), 6.98–7.37 (m, 4 H), 7.62 (s, 1 H), 8.61 (d, J = 7.8 Hz, 1 H), 8.70 (t, J = 5.5 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 22.35, 41.71, 51.01, 107.73, 110.59, 113.50 (d, J_{CF} = 21.6 Hz), 113.60 (d, J_{CF} = 22.3 Hz), 122.95, 130.18 (d, J_{CF} = 8.6 Hz), 142.21 (d, J_{CF} = 7.5 Hz), 142.66, 151.03, 162.28 (d, J_{CF} = 243.3 Hz), 168.23, 169.31 ppm. Anal. ($C_{15}H_{15}N_2O_3F$) C, H, N.

(*R*,*S*)-α-Acetamido-*N*-(4-fluorobenzyl)-2-furanacetamide (3c). Using racemic acid **10** (1.50 g, 8.2 mmol) and 4-fluorobenzylamine (1.13 g, 9.0 mmol) gave 2.10 g (88%) of **3c**: mp 188–190 °C (recrystallized from EtOAc); R_f 0.30 (4% MeOH/$CHCl_3$); IR (KBr) 3230, 1620, 1500, 1360, 1320, 1260, 1210, 1140, 1000, 820, 780, 730 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.88 (s, 3 H), 4.27 (d, J = 5.5 Hz, 2 H), 5.55 (d, J = 8.0 Hz, 1 H), 6.27 (s, 1 H), 6.41 (s, 1 H), 7.09–7.15 (m, 2 H), 7.21–7.27 (m, 2 H), 7.61 (s, 1 H), 8.58 (d, J = 8.0 Hz, 1 H), 8.75 (t, J = 5.5 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 22.28, 41.51, 50.87, 107.52, 110.46, 114.90 (d, J_{CF} = 21.1 Hz), 129.48 (d, J_{CF} = 8.3 Hz), 135.23 (d, J_{CF} = 3.2 Hz), 142.53, 151.08, 161.12 (d, J_{CF} = 242.2 Hz), 167.95, 169.13 ppm. Anal. ($C_{15}H_{15}N_2O_3F$) C, H, N.

(*R*,*S*)-α-Acetamido-*N*-(2,5-difluorobenzyl)-2-furanacetamide (3d). Using 2,5-difluorobenzylamine (1.30 g, 9.0 mmol) and racemic acid **10** (1.50 g, 8.2 mmol) gave 1.60 g (64%) of **3d**: mp 177–178 °C (recrystallized from EtOAc); R_f 0.38 (4% MeOH/$CHCl_3$); IR (KBr) 3230, 1620, 1520, 1480, 1360, 1260, 1230, 1180, 1140, 1000, 860, 810, 730, 710 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.89 (s, 3 H), 4.31 (d, J = 5.5 Hz, 2 H), 5.55 (d, J = 7.7 Hz, 1 H), 6.32 (s, 1 H), 6.43 (s, 1 H), 7.22–7.25 (m, 3 H), 7.62 (s, 1 H), 8.62 (d, J = 7.7 Hz, 1 H), 8.78 (t, J = 5.5 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 22.30, 35.98 (d, J_{CF} = 5.8 Hz), 51.02, 107.81, 110.58, 115.06 (dd, J_{CF} = 19.5, 25.6 Hz), 115.16 (dd, J_{CF} = 15.6, 24.7 Hz), 116.52 (dd, J_{CF} = 10.1, 23.9 Hz), 127.98 (dd, J_{CF} = 9.2, 17.7 Hz), 142.69, 150.78, 155.89 (d, J_{CF} = 239.0 Hz), 158.18 (d, J_{CF} = 238.8 Hz), 168.38, 169.35 ppm. Anal. ($C_{15}H_{14}N_2O_3F_2$) C, H, N.

(*R*,*S*)-α-Acetamido-*N*-(2,6-difluorobenzyl)-2-furanacetamide (3e). Making use of 2,6-difluorobenzylamine (1.30 g, 9.0 mmol) and racemic acid **10** (1.50 g, 8.2 mmol) gave 1.90 g (73%) of **3e**: mp 237–239 °C (recrystallized from EtOH); IR (KBr) 3230, 1620, 1530, 1460, 1360, 1320, 1260, 1220, 1160, 1140, 1030, 1000, 820, 780, 750, 740, 710 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.86 (s, 3 H), 4.33 (d, J = 4.5 Hz, 2 H), 5.53 (d, J = 8.3 Hz, 1 H), 6.17 (s, 1 H), 6.38 (s, 1 H), 7.05–7.10 (m, 2 H), 7.36–7.41 (m, 1 H), 7.60 (s, 1 H), 8.52 (d, J = 8.3 Hz, 1 H), 8.66 (t, J = 4.5 Hz, 1 H); ^{13}C NMR (DMSO-d_6) 22.33, 30.74 (t, J_{CF} = 4.4 Hz), 50.48, 107.24, 110.40, 111.61 (dd, J_{CF} = 8.0, 25.1 Hz), 113.67 (t, J_{CF} = 19.5 Hz), 129.98 (t, J_{CF} = 10.5 Hz), 142.50, 151.23, 160.93 (d, J_{CF} = 248.1 Hz), 161.10 (d, J_{CF} = 248.1 Hz), 167.59, 169.00 ppm. Anal. ($C_{15}H_{14}N_2O_3F_2$) C, H, N.

(*S*)-α-Acetamido-*N*-((*R*)-α-methylbenzyl)-2-furanacetamide and (*R*)-α-Acetamido-*N*-((*R*)-α-methylbenzyl)-2-furanacetamide (4a and 4b). Using (*R*)-α-methylbenzylamine (1.10 g, 9.0 mmol) and racemic **10** (1.50 g, 8.2 mmol) gave a crude mixture (2.00 g) which was purified by flash column chromatography on SiO_2 gel using 2% MeOH/$CHCl_3$ as the eluent to give **4a** and **4b**.

Compound **4a**: yield 0.70 g (30%); mp 224–226 °C (recrystallized from EtOAc); $[\alpha]^{26}_D$ = +127.4° (c = 1, MeOH); R_f 0.32 (2% MeOH/$CHCl_3$); IR (KBr) 3250, 1620, 1520, 1440, 1360, 1300, 1270, 1220, 1140, 1000, 800, 740, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.31 (d, J = 6.9 Hz, 3 H), 1.86 (s, 3 H), 4.85–4.98 (m, 1 H), 5.61 (d, J = 8.2 Hz, 1 H), 6.27 (s, 1 H), 6.42 (s, 1 H), 7.22–7.32 (m, 5 H), 7.62 (s, 1 H), 8.51 (d, J = 8.2 Hz, 1 H), 8.70 (d, J = 7.9 Hz, 1 H), addition of (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of **4a** gave only one signal for the acetyl methyl protons; ^{13}C NMR (DMSO-d_6) 22.27 (2 C), 48.17, 50.73, 107.22, 110.47, 126.01 (2 C), 126.67, 128.21 (2 C), 142.52, 144.08, 151.42, 166.96, 168.97 ppm. Anal. ($C_{16}H_{18}N_2O_3$) C, H, N.

Compound **4b**: yield 0.72 g (32%); mp 216–218 °C (recrystallized from EtOAc); $[\alpha]^{26}_D$ = +0.3 ± 0.1° (c = 1, MeOH); R_f 0.27 (2% MeOH/$CHCl_3$); IR (KBr) 3250, 1620, 1520, 1440, 1360, 1270, 1230, 1140, 1000, 740, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.36 (d, J = 6.9 Hz, 3 H), 1.90 (s, 3 H), 4.85–5.00 (m, 1 H), 5.64 (d, J = 8.2 Hz, 1 H), 6.16 (s, 1 H), 6.38 (s, 1 H), 7.20–7.29 (m, 5 H), 7.59 (s, 1 H), 8.53 (d, J = 8.2 Hz, 1 H), 8.72 (d, J = 7.8 Hz, 1 H), addition of (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of **4b** gave only one signal for the acetyl methyl protons; ^{13}C NMR (DMSO-d_6) 22.32, 22.50, 48.03, 50.64, 107.20, 110.41, 125.75 (2 C), 126.59, 128.14 (2 C), 142.48, 144.19, 151.38, 166.92, 169.02 ppm. Anal. ($C_{16}H_{18}N_2O_3$) C, H, N.

(*R*)-α-Acetamido-*N*-((*S*)-α-methylbenzyl)-2-furanacetamide and (*S*)-α-Acetamido-*N*-((*S*)-α-methylbenzyl)-2-furanacetamide (4c and 4d). Making use of (*S*)-α-methylbenzylamine (1.00 g, 8.2 mmol) and racemic **10** (1.50 g, 8.2 mmol) gave a diastereomeric mixture of **4c** and **4d** (2.00 g). The two isomers were separated by flash column chromatography on SiO_2 gel using 2% MeOH/$CHCl_3$ as the eluent.

Compound **4c**: yield 0.36 g (15%); mp 224–226 °C (recrystallized from EtOAc); $[\alpha]^{26}_D$ = −138 ± 2° (c = 1, MeOH); R_f 0.32 (2% MeOH/$CHCl_3$); IR (KBr) 3250, 1620, 1530, 1360, 1270, 1220, 1140, 1000, 740, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.31 (d, J = 6.8 Hz, 3 H), 1.85 (s, 3 H), 4.85–4.98 (m, 1 H), 5.60 (d, J = 8.2 Hz, 1 H), 6.28 (s, 1 H), 6.42 (s, 1 H), 7.22–7.32 (m, 5 H), 7.62 (s, 1 H), 8.51 (d, J = 8.2 Hz, 1 H), 8.70 (d, J = 7.8 Hz, 1 H), addition of (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of **4c** gave only one signal for the acetamide methyl protons; ^{13}C NMR (DMSO-d_6) 22.30 (2 C), 48.18, 50.74, 107.26, 110.51, 126.03 (2 C), 126.71, 128.25 (2 C), 142.57, 144.12, 151.44, 166.98, 169.00 ppm. Anal. ($C_{16}H_{18}N_2O_3$) C, H, N.

Compound **4d**: yield 0.45 g (19%); mp 216–218 °C (recrystallized from EtOAc); $[\alpha]^{26}_D$ = −2° (c = 1, MeOH); R_f 0.27 (2% MeOH/$CHCl_3$); IR (KBr) 3250, 1630, 1520, 1440, 1360, 1270, 1220, 1200, 1140, 1000, 740, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.35 (d, J = 6.7 Hz, 3 H), 1.89 (s, 3 H), 4.85–4.99 (m, 1 H), 5.63 (d, J = 8.2 Hz, 1 H), 6.15 (s, 1 H), 6.38 (s, 1 H), 7.19–7.29 (m, 5 H), 7.58 (s, 1 H), 8.52 (d, J = 8.2 Hz, 1 H), 8.71 (d, J = 7.6 Hz, 1 H), addition of (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of **4d** gave only one signal for the acetamide methyl protons; ^{13}C NMR (DMSO-d_6) 22.32, 22.53, 48.03, 50.63, 107.22, 110.42, 125.75 (2 C), 126.61, 128.16 (2 C), 142.50, 144.21, 151.38, 166.92, 169.04 ppm. Anal. ($C_{16}H_{18}N_2O_3$) C, H, N.

(*R*)-(−)-α-Acetamido-*N*-benzyl-2-furanacetamide ((*R*)-2g). Starting with (*R*)-**10** (2.45 g, 13.38 mmol) and benzylamine (1.43 g, 13.38 mmol), 2.54 g (70%) of pure (*R*)-**2g** was obtained. The product was further recrystallized from EtOAc to give 2.30 g of (*R*)-**2g**: mp 196–197 °C; $[\alpha]^{26}_D$ = −78.3° (c = 1, MeOH), addition of (*R*)-(−)-mandelic acid to a $CDCl_3$ solution of (*R*)-**2g** gave only one signal for the acetamide methyl protons; mass spectrum, m/e (relative intensity) 272 (M^+, 2), 184 (2), 165 (2), 140 (8), 139 (88), 138 (34), 97 (46), 96 (100), 91 (63). Anal. ($C_{15}H_{16}N_2O_3$) C, H, N.

(*S*)-(+)-α-Acetamido-*N*-benzyl-2-furanacetamide ((*S*)-2g). Using (*S*)-**10** (2.83 g, 15.46 mmol) and benzylamine (1.65 g, 15.46 mmol) gave 3.80 g of the *S* enriched **2g**. ^1H NMR ($CDCl_3$) analysis with (*R*)-(−)-mandelic acid showed that it was greater than 80% enriched in the *S*-(-) enantiomer **2g**. The pure *S* enantiomer (1.60 g) was obtained by recrystallization from absolute EtOH: mp 196–197 °C; $[\alpha]^{26}_D$ = +79.0° (c = 1, MeOH); mass spectrum m/e (relative intensity) 273 (M^+ + 1,3), 229 (2), 214 (2), 184 (1), 165 (7), 157 (4), 140 (33), 139 (100), 138 (95), 97 (98), 96 (100), 91 (98). Anal. ($C_{15}H_{16}N_2O_3$) C, H, N.

Resolution of (*R*,*S*)-α-Acetamido-2-furanacetic Acid (10) Using (*R*)-(+)-α-Methylbenzylamine and (*S*)-(−)-α-Methylbenzylamine. (*R*)-α-Methylbenzylamine (13.22 g, 0.11 mol) was added to an absolute EtOH solution (550 mL) of racemic **10** (20.00 g, 0.11 mol). The resulting solution was cooled in the freezer overnight. The white precipitate (12.00 g) which separated

upon cooling was filtered, and the mother liquor was evaporated to give a salt which was later used for obtaining (*S*)-**10**. The initial precipitate was recrystallized (3×) from absolute EtOH to yield 4.20 g of the pure diastereomeric salt (*R*)-(α-methylbenzyl)ammonium (*R*)-α-acetamido-2-furanacetate: mp 173–175 °C; $[\alpha]^{26}_D$ = −108° (*c* = 1, MeOH). Anal. ($C_{16}H_{20}N_2O_4$) C, H, N.

The diastereomeric salt was treated with 5% aqueous NH_4OH, extracted with Et_2O (3 × 50 mL), and then acidified with an 8.5% aqueous solution of H_3PO_4 and then extracted with EtOAc (3 × 100 mL) to yield 2.45 g (25%) of (*R*)-**10**: mp 169–171 °C; $[\alpha]^{26}_D$ = −184.2° (*c* = 1, MeOH). Anal. ($C_8H_9NO_4$) C, H, N.

The salt obtained after evaporation of the main mother liquor was hydrolyzed with 5% aqueous NH_4OH to give 10.10 g of the enriched (*S*)-**10** [$[\alpha]^{26}_D$ = +47.7° (*c* = 1, MeOH)]. (*S*)-α-Methylbenzylamine (6.70 g, 0.055 mol) was added to a solution of enriched (*S*)-**10** (10.10 g, 0.055 mol) in absolute EtOH (275 mL). The white precipitate of the diastereomeric salt (8.10 g) that separated upon cooling of the solution in the freezer (1 h) was filtered. The salt was recrystallized from absolute EtOH (3×) to yield 3.00 g of (*S*)-(α-methylbenzyl)ammonium (*S*)-α-acetamido-2-furanacetate: mp 172–174 °C; $[\alpha]^{26}_D$ = +106° (*c* = 1, MeOH). Anal. ($C_{16}H_{20}N_2O_4$) C, H, N.

The salt from the third recrystallization was treated with 5% aqueous NH_4OH, extracted with Et_2O (3 × 50 mL), then acidified with an 8.5% aqueous solution of H_3PO_4, and then extracted with EtOAc (3 × 100 mL) to give 1.63 g (32%) of (*S*)-**10**: mp 169–171 °C; $[\alpha]^{26}_D$ = +182° (*c* = 1, MeOH).

Enzymatic Resolution of (*R,S*)-(±) Methyl α-Acetamido-2-furanacetate (14). Racemic **14**[9] (0.50 g, 2.54 mmol) was dissolved in DMF (4 mL) and the solution was diluted with H_2O (20 mL). Phosphate buffer (0.2 mL, 0.1 M) and β-mercaptoethanol (0.2 mL) were then added, and the pH of the solution was adjusted to 7.0 by addition of an aqueous 1 N HCl solution. Upon addition of papain (Sigma, Catalog Number P3375, activity 2.8, 50 mg) the pH of the solution dropped below 7.0. The pH of the solution was maintained at 7.0 by addition of aqueous 0.1 N NaOH solution with the aid of a pH stat instrument. The hydrolysis reaction was slow, and therefore, a second lot of papain (50 mg) was added to the reaction mixture. After 9.9 mL of alkali (78% of the theoretical amount) had been added (5 h), the pH of the solution was raised to 8.0 by addition of aqueous 0.1 N NaOH. The reaction mixture was extracted with EtOAc (3 × 30 mL), and the combined extracts were dried (Na_2SO_4). The solvent was removed in vacuo, giving an oily residue containing desired ester (*R*)-**14**, DMF, and β-mercaptoethanol. The DMF was removed by distillation under reduced pressure (40–45 °C, 0.8 Torr) and the residue was purified by flash chromatography on SiO_2 using 1% MeOH/$CHCl_3$ as the eluent. The compound obtained was triturated with H_2O and filtered to give 0.05 g of (*R*)-**14**: $[\alpha]^{26}_D$ = −115° (*c* = 1, MeOH). Extraction of the acidified aqueous layer with EtOAc gave an inseparable gel which did not permit isolation of (*S*)-**10**.

Enzymatic Resolution of (*R,S*)-(±) Ethyl α-Acetamido-2-furanacetate (13). Racemic **13** (0.50 g, 2.37 mmol) was dissolved in DMF (4 mL), H_2O (20 mL), and phosphate buffer (0.1 mL, 0.1 M). β-Mercaptoethanol (0.1 mL) was added to the above solution and the pH of the solution was adjusted to 7.0 by addition of aqueous 1 N HCl. Papain (Sigma, Catalog Number P3375, activity 2.8, 0.10 g) was added and the pH of the reaction was maintained between 6.90 and 7.35 by the manual addition of aqueous 0.1 N NaOH. After approximately 2.5 mL of the alkali solution had been added, the rate of pH change versus time slowed down. Additional papain (2 × 0.10 g) and β-mercaptoethanol (0.2 mL) were added. After a total of 10.3 mL of alkali had been added (87% of the theoretical amount) (7.5 h), the pH of the solution was raised to 8.0 and the alkaline solution was extracted with EtOAc (3 × 30 mL). The combined extracts were dried (Na_2SO_4) and the solvent was removed. The residue that was obtained contained DMF and β-mercaptoethanol. The volatile materials were removed by distillation under reduced pressure (40–45 °C, 0.2–0.8 Torr), and the residue was purified by flash chromatography on silica gel using 1% MeOH/$CHCl_3$ as the eluent to yield 0.20 g (80%) of (*R*)-**13**: mp 65–67 °C; $[\alpha]^{26}_D$ = −69.6° (*c* = 1, EtOH).

Synthesis of *R*-(−) Enriched Methyl α-Acetamido-2-furanacetate (14). A solution of *R*-(−) enriched **10** (0.10 g, 0.55 mmol, $[\alpha]^{26}_D$ = −176.5° (*c* = 1, MeOH)) in a minimum amount of MeOH (5 mL) was mixed with an ethereal solution of diazomethane at 0 °C. The reaction was allowed to stand (1 h) at this temperature and then the excess diazomethane was removed by flushing the reaction solution with N_2. The solvent was removed by distillation in vacuo to give a quantitative yield of *R* enriched **14**: R_f 0.43 (3% MeOH/$CHCl_3$); $[\alpha]^{26}_D$ = −95° (*c* = 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3 H), 3.77 (s, 3 H), 5.77 (d, *J* = 7.9 Hz, 1 H), 6.36 (s, 2 H), 6.67 (br s, 1 H), 7.36 (s, 1 H); ^{13}C NMR ($CDCl_3$) 22.82, 50.14, 52.95, 108.65, 110.66, 142.74, 148.50, 169.37, 169.51 ppm.

X-ray Crystal Structure of (*R*)-(−)-α-Acetamido-*N*-benzyl-2-furanacetamide ((*R*)-2g). Colorless, orthorhombic, thin needles were grown by slow cooling of a sample dissolved in absolute EtOH. Data collection was performed with a Nicolet R3m/v automatic diffractometer using MoKα radiation. The unit-cell parameters are *a* = 4.788 (1) Å, *b* = 13.364 (6) Å, *c* = 22.580 (9) Å, and V = 1445 Å^3 in space group $P2_12_12_1$. The structure was solved using Nicolet's SHELXTL PLUS direct methods program, yielding coordinates for most of the non-hydrogen atoms in the asymmetric unit, which consisted of the complete molecule. The remaining non-hydrogen atoms were located in subsequent Fourier syntheses. The usual sequence of isotropic and anisotropic refinements were followed, after which all hydrogens were entered in ideal calculated positions. Only H_1 and H_2 on the nitrogens were allowed to refine independently, the rest being constrained to riding motion. Excessive "thermal motion" was noted in the phenyl ring, and it was decided to refine a disordered model at this site. There were no heavy atoms in the compound, and thus it was not possible to determine the correct absolute configuration. Therefore, the chirality was adjusted so as to make the C_3 absolute configuration *R*, which is consistent with (*R*)-**14**. For compound (*R*)-**2g** after all shift/esd ratios were less than 0.5, convergence was reached at *R* = 0.058 (R_w = 0.034).

Pharmacology. Initial anticonvulsant evaluation of these compounds was conducted with at least three dose levels (30, 100, and 300 mg/kg) administered intraperitoneally. All tests were performed with male CF-1 mice from Charles River Breeding Laboratories (Portage, MI). Test solutions of all compounds were dissolved in 30% polyethylene glycol 400. Four mice at each dose level were tested at 0.5, 1, and 4 h after administration to determine if there was protection against MES seizures.

MES seizures were elicited by electrical current (ac 60 cps, 50 mA, 0.2 s) applied via corneal electrodes. A drop of 0.9% saline was instilled on the eye prior to application of the electrodes to insure electrical contact. Abolition of the hind limb tonic extension component of the seizure was defined as protection in the MES test.

After optimal time period for activity and the approximate dose range were determined, a dose–response curve was generated with at least three or four doses and 10–12 mice per dose. The MES ED_{50} is the estimated dose from the dose–response data to protect 50% of the mice in the MES test. Neurological impairment was measured in mice by using the horizontal screen (tox) test.[18] Previously trained mice were dosed with the compound and then placed individually on top of a square (13 × 13 cm) wire screen (no. 4 mesh) which was mounted on a vertical rod. The rod was then rotated 180°, and the number of mice that returned to the top of the screen within 1 min was determined. To determine ED_{50}s, a dose–response curve was determined at the time of peak anticonvulsant activity with at least three to four doses and 12 mice per dose. The TD_{50} is the estimated dose from the dose response data to impair 50% of the mice.

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Registry No. **2c**, 124421-21-2; **2d**, 124421-22-3; **2e**, 124421-23-4; **2f**, 124421-24-5; **2g**, 124421-25-6; (*R*)-**2g**, 124509-55-3; (*S*)-**2g**, 124509-56-4; **2h**, 124421-26-7; **2i**, 124421-27-8; **2j**, 124421-28-9; **2k**, 124441-50-5; **2l**, 124421-29-0; **2m**, 124421-30-3; **2n**, 124421-31-4;

2o, 124421-32-5; **2p**, 124421-33-6; **3a**, 124421-34-7; **3b**, 124421-35-8; **3c**, 124421-36-9; **3d**, 124421-37-0; **3e**, 124421-38-1; **4a**, 124421-44-9; **4b**, 124421-45-0; **4c**, 124421-46-1; **4d**, 124421-47-2; **5**, 117422-80-7; **8**, 33741-79-6; **9**, 117422-79-4; **10**, 117422-81-8; (*R*)-**10**, 124509-57-5; (*S*)-**10**, 124509-58-6; **12**, 124421-42-7; **13**, 124421-43-8; (*R*)-**13**, 124509-63-3; **14**, 124421-48-3; (*R*)-**14**, 124509-62-2; (±)-(BOC)-NHCH(2-$C_{10}H_7$)CONHCH$_2$Ph, 124421-39-2; (±)-$H_2NCH(2\text{-}C_{10}H_7)CONHCH_2Ph\cdot MeSO_3H$, 124421-41-6; 2-$FC_6H_4CH_2NH_2$, 89-99-6; 3-$FC_6H_4CH_2NH_2$, 100-82-3; 4-$FC_6H_4CH_2NH_2$, 140-75-0; 2,5-$F_2C_6H_3CH_2NH_2$, 85118-06-5; 2,6-$F_2C_6H_3CH_2NH_2$, 69385-30-4; (*R*)-PhCHMeNH$_2$, 3886-69-9; (*S*)-PhCHMeNH$_2$, 2627-86-3; 2-methylpyrrole, 636-41-9; (±)-α-amino-32-thiopheneacetic acid, 38150-49-1; furan, 110-00-9; (*R*)-(α-methylbenzyl)ammonium (*R*)-α-acetamido-2-furanacetate, 124509-59-7; (*S*)-(α-methylbenzyl)ammonium (*S*)-α-acetamido-2-furanacetate, 124509-60-0; (*R*)-(α-methylbenzyl)ammonium (*S*)-α-acetamido-2-furanacetate, 124509-61-1.

Supplementary Material Available: Tables listing data collection and processing parameters (Table IV), atomic coordinates and equivalent isotropic displacement parameters (Table V), bond lengths (Table VI), bond angles (Table VII), and hydrogen-bonding parameters (Table VIII) (4 pages); observed and calculated structure factors (Table IX) for compound (*R*)-**2g** (3 pages). Ordering information is given on any current masthead page.

Synthesis and Anticonvulsant Activity of 2-Benzylglutarimides

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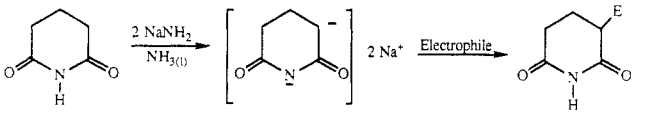
A series of 2-benzylglutarimides (**4**) and their *N*-methyl analogues (**5**) were prepared according to the Topliss scheme for the selection of benzyl substituents to maximize anticonvulsant activity. A total of 22 such compounds were subjected to initial (phase I) screening in mice against seizures induced by maximal electroschock (MES) and pentylenetetrazol (scMet) and in the rotorod assay for neurotoxicity. From this series of test compounds, 10 were advanced to quantitative (phase II) testing. Of these, 2-(4-chlorobenzyl)glutarimide (**4b**) emerged as the most promising anticonvulsant drug candidate by demonstrating both good anti-scMet and anti-MES activity combined with low neurotoxicity after intraperitoneal administration in mice. In drug differentiation tests, **4b** was also effective in nontoxic doses against seizures induced by bicuculline, picrotoxin, and strychnine. When compared with the clinically useful drugs phenytoin, carbamazepine, phenobarbital, valproate, and ethosuximide, **4b** exhibited an overall pharmacological profile most closely resembling that of valproate.

The past decade has witnessed a resurgence of interest in the development of new anticonvulsant drugs. Recent estimates indicate that 1% of the population is affected by some form of epilepsy and that 20–40% of epileptic patients fail to experience significant seizure control with the drugs currently available.[2] Furthermore, the anticonvulsant drugs presently used in clinical practice suffer from a broad range of adverse side effects.[2,3] No single drug is effective against the various forms and degrees of convulsive disorders and the necessity for repeat and combination therapy[3b] not only increases the danger of toxic effects but also contributes to the dissatisfaction of the patient. Consequently, there is a need for new antiepileptic substances having greater specificity and fewer toxic side effects.

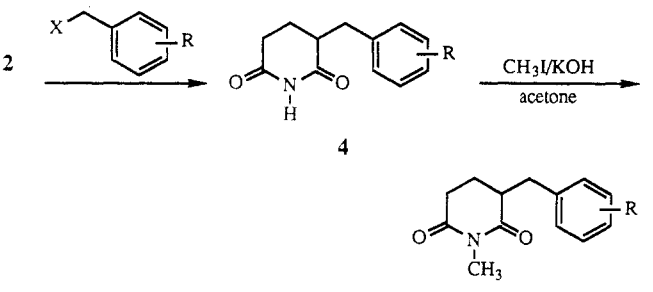
Even though the search for antiepileptic drugs has recently been extended to novel structural types,[4] the classical group of cyclic imides, because of their demonstrated anticonvulsant potency, continue to receive considerable attention.[5] Within the last 20 years, however, there are surprisingly few reports concerning the observation and evaluation of anticonvulsant properties for substituted glutarimides.[5e,6-8]

Scheme I



1 2 3

Scheme II



4 5

Our earlier discovery that the dianion (**2**) prepared from glutarimide (**1**) and sodium amide in liquid ammonia reacted with electrophiles such as alkyl halides, aldehydes, ketones, and esters exclusively at the carbanion site provided a convenient, one-step route to 2-substituted glu-

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