Synthesis and Anticonvulsant Activity of a New Class of 2-[(Arylalkyl)amino]alkanamide Derivatives

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Although most epilepsies are adequately treated by conventional antiepileptic therapy, there remains an unfulfilled need for safer and more effective anticonvulsant agents. Starting from milacemide, a weak anticonvulsant, and trying to elucidate its mechanism of action, we discovered a structurally novel class of potent and preclinically safe anticonvulsants. Here we report the structure−activity relationship (SAR) study within this series of compounds. Different parts of the structural lead 2-[[4-(3-chlorobenzoxy)benzyl]amino]acetamide (**6**) were thus varied (Figure 1), and many potent anticonvulsants were found. As an outcome of this study, **57** ((*S*)-2-[[4-(3-fluorobenzoxy)benzyl]amino]propanamide methanesulfonate, PNU-151774E) emerged as a promising candidate for further development for its potent anticonvulsant activity and outstanding therapeutic indexes (TIs) in different animal tests.

Introduction

Epilepsy collectively describes a wide variety of disorders more properly referred to as the human epilepsies. Despite their different nature and causes, they are all characterized by the common feature of recurrent seizure attacks. Seizures are due to the abrupt, paroxysmal discharge of a large population of neurons firing synchronously and are divided into two major categories depending on whether the initial discharge arises within a system of neurons localized in a discrete area of the cerebral gray matter (partial or focal seizures) or diffusely in both hemispheres (generalized seizures). Generalized seizures may be convulsive (tonic myoclonic, tonic clonic, depending on the characteristics of the muscle contraction) or nonconvulsive, as in the case of the so-called pure *petit mal* where the paroxysmal discharge can be accompanied only by suspension of consciousness without motor phenomena. It is estimated that in developed countries 0.5−1% of the population suffers from epilepsy, the highest incidence being found in children and the elderly.[1]

Epilepsy is not an orphan disease. Actually epilepsy has been the first neurological condition for which an effective treatment, bromide salts, became available as early as 1857. A significant number of effective antiepileptic drugs (AEDs) are now on the market. Classical AEDs comprise phenobarbital (PB), available since 1911; phenytoin (PHT), marketed in 1939; carbamazepine (CBZ), used for epilepsy in Europe from the mid-1960s; and valproic acid (VPA), available in several European countries as of the late 1960s.[2] The total market of anticonvulsants in 1992 was 1065 million USD; projections for the year 2000 are of about 2 billion USD.

With the available AEDs on the market, about 70% of people with epilepsy achieve satisfactory seizure control. Better responses are obtained in certain types of seizures (typical absence), whereas poor responses are frequently seen in patients with mixed seizure types, atonic seizures, and Lennox−Gastaut syndrome. Still about 30% (600 000 people in the United States) do not respond to the available AEDs administered either in monotherapy or in combination. The need for newer anticonvulsants is not restricted to those unresponsive patients: particularly, dose-related adverse effects, teratogenicity, idiosyncratic reactions, and drug−drug interactions are important limiting factors preventing the achievement of the full therapeutic potential for all major AEDs.

In the past decade, there has been an increase in the availability of AEDs for clinical evaluation.[3] As a result, since 1989, six new AEDs have been licensed in Europe (vigabatrin, lamotrigine, gabapentin, oxcarbazepine, felbamate, and piracetam), three in the United States (felbamate, gabapentin, and lamotrigine), and one in Japan (zonisamide). Although none of the new drugs have been yet shown to have greater efficacy than currently used products in monotherapy, they are perceived as being better tolerated.[4]

Milacemide (**1**, 2-(*n*-pentylamino)acetamide; Chart 1) had been reported to be an antagonist of iv-bicuculline (iv-BIC)-induced seizures with a novel mechanism of action, being less effective or inactive in inhibiting other chemically or physically induced seizures in animal models of epilepsy.[5] Due to marginal effects seen in

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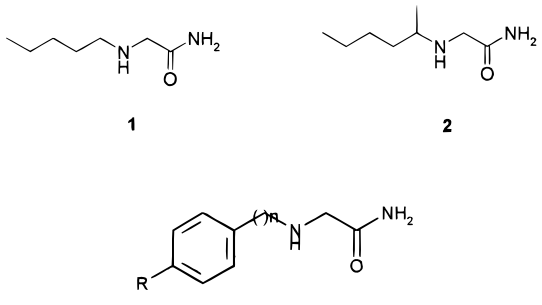
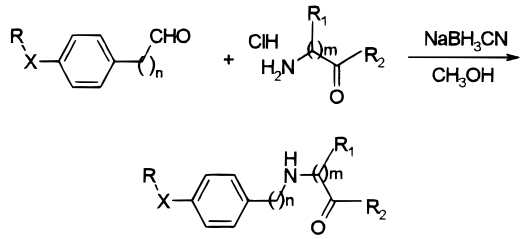
Chart 1



1 **2**

3: R = H; n = 2
4: R = H; n = 1
5: R = 3-Chlorobenzyloxy; n = 2
6: R = 3-Chlorobenzyloxy; n = 1

Scheme 1



7, 9-12, 15-16, 19-37, 40-75

clinical trials, development of the compound was no longer pursued.

Our aims were to verify the mechanism(s) of action of milacemide and to identify compounds more potent and with a wider range of anticonvulsant spectrum than milacemide. Following the suggestion that anticonvulsant activity of milacemide could be related to its MAO-B-mediated degradation,[6,7] we first designed a set of molecules involving retention of the acetamide portion but replacement of the pentylamino moiety with residues present in the structures of substrates and inhibitors of the MAO (Chart 1).[8] None of the tested molecules were shown to be substrates for MAOs, but some of them were found to be inhibitors of both forms of MAO, mainly the B form. No relationship between the anticonvulsant activity and inhibition of MAO could be established. Furthermore α-methylmilacemide **(2**; Chart 1**)**, which is not oxidized by either MAO-A or MAO-B, was equipotent to milacemide in the iv-BIC test.[9] Nevertheless the significant increase in anticonvulsant activity observed with the first derivatives of milacemide led us to explore the 2-substituted amino amide class and allowed us access to a new series of potent anticonvulsant compounds.

Chemistry

The synthesis of most of the compounds (**7, 9**−**12, 15**−**16, 19**−**37, 40**−**75**) (Tables 1 and 2) was accomplished by reductive alkylation of the appropriate α-amino amide derivative with the corresponding aldehyde using a previously described protocol (Scheme 1).[10] The reductive amination of a variety of aldehydes (particularly substituted benzaldehydes) with different α-amino acid derivatives is of broad scope and occurs with moderate to good yields using sodium cyanoborohydride in methanol as a reducing agent. Scheme 2 reports the syntheses of compounds **8, 13, 14, 17, 18, 38**, and **39**. Standard methods were used to alkylate the precursors of compounds **13, 14**, and **18**, while the reductive amination protocol was followed for the synthesis of compounds **38** and **39**.

Physical properties of the compounds are reported in Tables 1−3 and in the Experimental Section. Preparations of compounds **35**, **44**, **48**, **50**, and **70** and their precursors have been already described.[10] Previously unreported aldehydes were synthesized by methods in analogy to those reported in the literature.[11]

Biology

Compounds were tested and selected for more extensive pharmacological evaluation on the basis of a widely accepted screening funnel for new anticonvulsants.[12] Considering that the anticonvulsant activity of **1** was originally described using the iv-BIC test in mice,[6] this test was selected for preliminary screening. Observation of gross behavioral toxicity signs such as loss of righting reflex, impaired gait, impaired breathing, and hypotonia was also considered as criteria for selecting compounds to be submitted for further anticonvulsant evaluation using the maximal electroshock test (MES) and for a quantitative determination of toxicity using motor impairment as measured by the rotorod test (RT) (see Tables 4 and 5). A restricted number of products were evaluated in other chemically induced seizures (Table 6). These tests are considered to predict the clinical efficacy of new compounds against the most common types of seizures in epileptic patients.

Results and Discussion

A first group of molecules (**3**−**6**; Chart 1) was designed to evaluate the role played by the *N*-pentyl chain of milacemide in determining its, albeit weak, anticonvulsant activity (Table 4).[8] The *N*-(phenylethyl)glycinamide (**3**) emerged as a more effective agent, while the *N*-benzyl derivative (**4**) was endowed with weaker activity. When a 4-(3-chlorobenzoxy) group was placed into **3** and **4**, a reversal in anticonvulsant potency was observed. Compound **6**, being the most active in the BIC and confirming its efficacy in the MES test (Table 4), was then chosen as a lead for developing a new class of anticonvulsants. Several structural parts of **6** might be envisaged as critical determinants for activity (Figure 1). As a first issue we decided to evaluate the importance of the amide function versus activity (A, Figure 1). A set of compounds **(6**−**12)** was therefore synthesized (Table 1) and tested (Table 4). Anticonvulsant activity was found to reside in the amides: in particular, beside the unsubstituted **(6)**, the monomethylamide **(7)** was also effective, and since this feature was always confirmed throughout the whole series, primary and secondary amides were considered interchangeable for further structure−activity relationship (SAR) studies. Similarly, the presence of a 3-chloro substituent on the remote aromatic ring was shown to be optional for activity throughout the whole series, as exemplified by comparison of **6** with **9**. The tertiary amide **(8)** was also active but showed clear signs of gross behavioral toxicity at lower doses. The amino acid derivative **(10)** and the ethyl **(11)** and benzyl **(12)** esters displayed only weak activity in the iv-BIC test.

Scheme 2

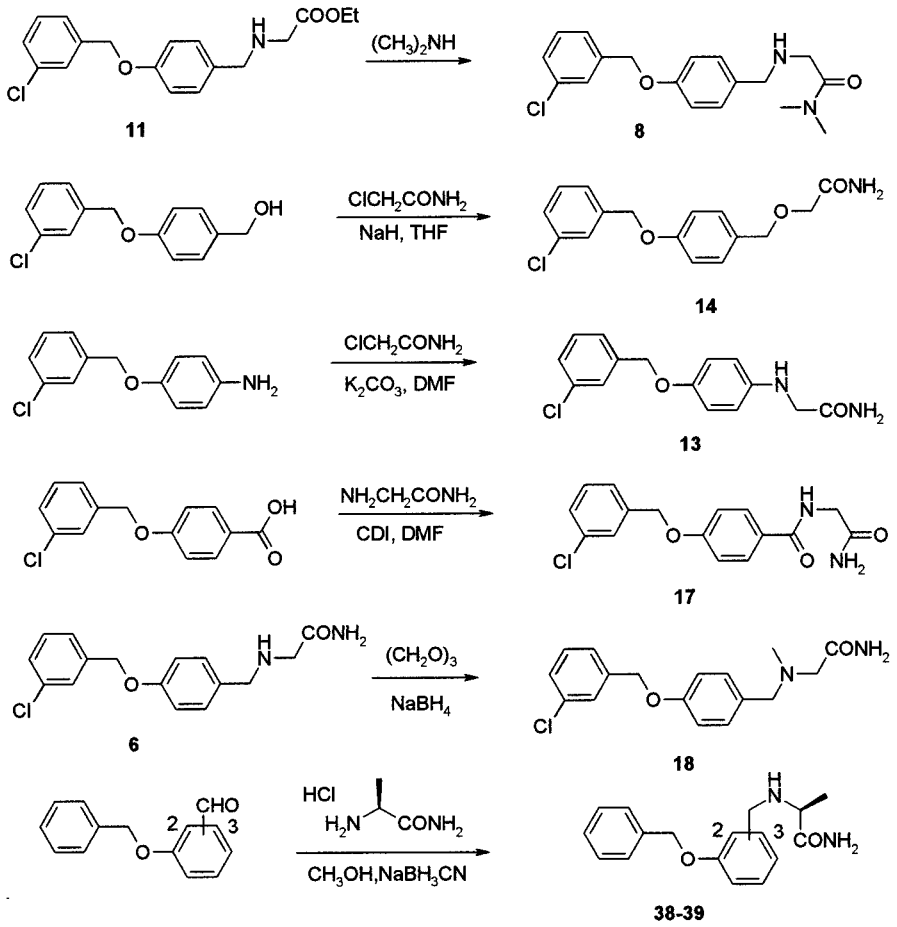


Table 1. Structural and Physical Data for Compounds **7**, **9**−**12**, **15**, **16**, and **19**−**37** (Scheme 1)

entry	R	X	*m*	*n*	R_1	R_2	conf	mp (°C)	$[\alpha]_D$[a]
7	3-Cl-C_6H_4-	-CH_2O-	1	1	H	$NHCH_3$		224−225	
9	C_6H_5-	-CH_2O-	1	1	H	NH_2		250 dec	
10	3-Cl-C_6H_4-	-CH_2O-	1	1	H	OH		150 dec	
11	3-Cl-C_6H_4-	-CH_2O-	1	1	H	OEt		118−121.5	
12	3-Cl-C_6H_4-	-CH_2O-	1	1	H	OBn		161.5−164	
15	3-Cl-C_6H_4-	-CH_2O-	2	2	H	NH_2		192−195	
16	3-Cl-C_6H_4-	-CH_2O-	3	1	H	NH_2		219−222	
19	C_6H_5-	-CH_2O-	1	1	CH_3	NH_2	*S*	229−232	+13.3
20	C_6H_5-	-CH_2O-	1	1	CH_3	NH_2	*R*	228−231	−13.0
21	C_6H_5-	-CH_2O-	1	1	CH_3	$NHCH_3$	*S*	188−191	−4.9[b]
22	C_6H_5-	-CH_2O-	1	1	CH_3	$NHCH_3$	*R*	134−137	−13.0
23	C_6H_5-	-CH_2O-	1	1	CH_2OH	$NHCH_3$	*S*	102−104	+13.7
24	C_6H_5-	-CH_2O-	1	1	CH_2OH	NH_2	*S*	128−130	+16.5
25	C_6H_5-	-CH_2O-	1	1	CH_2OH	$NHCH_3$	*R*	100−103	−12.9
26	C_6H_5-	-CH_2O-	1	1	CH_2Ph	$NHCH_3$	*S*	224−227	+40.3
27	C_6H_5-	-CH_2O-	1	1	CH_2Ph	$NHCH_3$	*R*	223−227	−39.9
28	C_6H_5-	-CH_2O-	1	1	$CH_2CH_2SCH_3$	$NHCH_3$	*S*	150−152	+27.0
29	C_6H_5-	-CH_2O-	1	1	$CH_2CH_2SCH_3$	$NHCH_3$	*R*	150−153	−27.5
30	C_6H_5-	-CH_2O-	1	1	$CH(CH_3)_2$	$NHCH_3$	*S*	160−163	+21.3
31	C_6H_5-	-CH_2O-	1	1	$CH(CH_3)_2$	$NHCH_3$	*R*	161−164	−21.2
32	C_6H_5-	-CH_2O-	1	1	$CH_2CH(CH_3)_2$	$NHCH_3$	*S*	141−144	+17.7
33	C_6H_5-	-CH_2O-	1	1	$CH_2CH(CH_3)_2$	$NHCH_3$	*R*	141−144	−16.9
34	C_6H_5-	-CH_2O-	1	1	$CH_2(OH)CH_3$	$NHCH_3$	2*R*,3*S*	187.5−191	−11.4
35	C_6H_5-	-CH_2O-	1	1	$CH_2(OH)CH_3$	$NHCH_3$	2*S*,3*R*	ref 10	ref 10
36	C_6H_5-	-CH_2O-	1	1	CH_2CH_3	NH_2	*S*	197−199	+19.1
37	C_6H_5-	-CH_2O-	1	1	CH_2CH_3	NH_2	*R*	198−200	+18.4

[a] See Experimental Section. [b] $c = 0.5$, HCl−EtOH, 1:1.

The importance of the relative position of the amino and amido groups with respect to the central aromatic ring and the type of spacer used (B and C, Figure 1) were also explored, but no active compounds were identified (compounds **13**−**17**). A preserved amino function was also found to be mandatory for robust activity since its replacement with oxygen **(16)** or its transformation into an amidic nitrogen **(17)** gave far less-active compounds. When the amino group was tertiarized by introducing a methyl group (**18**), some

Table 2. Structural and Physical Data for Compounds **40**−**75** (Scheme 1)

entry	R	X	*m*	*n*	R_1	R_2	conf	mp (°C)	$[\alpha]_D$[a]
40	C_6H_5-	bond	1	1	CH_3	NH_2	*S*	>250	+20.3
41	C_6H_5-	-O-	1	1	CH_3	NH_2	*S*	211−213	+15.1
42	C_6H_5-	$-CH_2-$	1	1	CH_3	NH_2	*S*	180−183	+12.0
43	C_6H_5-	$-CH_2CH_2-$	1	1	CH_3	NH_2	*S*	229−231	+14.0
44	C_6H_5-	$-CH_2S-$	1	1	CH_3	NH_2	*S*	ref 10	ref 10
45	C_6H_5-	$-CH_2NH-$	1	1	CH_3	NH_2	*S*	173 dec	+8.4
46	C_6H_5-	$-OCH_2-$	1	1	CH_3	NH_2	*S*	214−217	+12.6
47	C_6H_5-	$-(CH_2)_2O-$	1	1	CH_3	NH_2	*S*	179−181	+11.1
48	C_6H_5-	$-CH_2N(CH_3)$	1	1	CH_3	NH_2	*S*	ref 10	ref 10
49	C_6H_5-	$-NHCH_2-$	1	1	CH_3	NH_2	*S*	134−137	+1.8[b]
50	C_6H_5-	$-(CH_2)_3O-$	1	1	CH_3	NH_2	*S*	ref 10	ref 10
51	C_6H_5-	-CONH-	1	1	CH_3	NH_2	*S*	200 dec	+17.3
52	C_6H_5-	-CH=CH-	1	1	CH_3	NH_2	*S*	>250	+25.4
53	2-Cl-C_6H_4-	$-CH_2O-$	1	1	CH_3	NH_2	*S*	134−136	+12.4
54	2-Cl-C_6H_4-	$-CH_2O-$	1	1	CH_3	NH_2	*R*	132−134	−12.1
55	4-F-C_6H_4-	$-CH_2O-$	1	1	CH_3	NH_2	*S*	214−216.5	+13.2
56	2-F-C_6H_4-	$-CH_2O-$	1	1	CH_3	NH_2	*S*	238−239	+12.2
57	3-F-C_6H_4-	$-CH_2O-$	1	1	CH_3	NH_2	*S*	210 dec	+12.9
58	3-MeO-	$-CH_2O-$	1	1	CH_2OH	$NHCH_3$	*S*	85−87	+11.9
59	3-NO_2-C_6H_4-	$-CH_2O-$	1	1	CH_2OH	$NHCH_3$	*S*	171−173	+12.3
60	3-CN-C_6H_4-	$-CH_2O-$	1	1	CH_2OH	$NHCH_3$	*S*	132−134	+12.6
61	4-Cl-C_6H_4-	$-CH_2O-$	1	1	CH_2OH	$NHCH_3$	*S*	139−141	+12.7
62	3-CH_3-C_6H_4-	$-CH_2O-$	1	1	CH_2OH	$NHCH_3$	*S*	183−185	+13.2
63	3-CF_3-C_6H_4-	$-CH_2O-$	1	1	CH_2OH	$NHCH_3$	*S*	115−117	+11.5
64	2-CF_3-C_6H_4-	$-CH_2O-$	1	1	CH_2OH	$NHCH_3$	*S*	120.5−124	+11.1
65	2-F-C_6H_4-	$-CH_2O-$	1	1	CH_2OH	$NHCH_3$	*S*	129−131	+11.4
66	3-F-C_6H_4-	$-CH_2O-$	1	1	CH_2OH	$NHCH_3$	*S*	135−138	+11.4
67	2-pyridyl-	$-CH_2O-$	1	1	CH_3	NH_2	*S*	154−157	+19.4
68	3-pyridyl-	$-CH_2O-$	1	1	CH_3	NH_2	*S*	165−168	+21.4
69	4-pyridyl-	$-CH_2O-$	1	1	CH_3	NH_2	*S*	182−185	+21.5
70	2-thienyl-	$-CH_2O-$	1	1	CH_3	NH_2	*S*	ref 10	ref 10
71	3-thienyl-	$-CH_2O-$	1	1	CH_3	NH_2	*S*	192−195	+12.8
72	2-furyl-	$-CH_2O-$	1	1	CH_3	NH_2	*S*	206−208	+18.6
73	3-furyl-	$-CH_2O-$	1	1	CH_3	NH_2	*S*	195−196	+18.6
74	cyclopropyl-	$-CH_2O-$	1	1	CH_3	NH_2	*S*	114−116	+20.7
75	cyclohexyl-	$-CH_2O-$	1	1	CH_3	NH_2	*S*	224−226	+12.7

[a] See Experimental Section. [b] $c = 0.5$, EtOH.

Table 3. Physical Data for Compounds **13**, **14**, **17**, **18**, **38**, and **39** (Scheme 2)

entry	salt	subst	conf	mp (°C)	$[\alpha]_D$[a]
8				123−125	
13	HCl			204−207	
14	HCl			123−124.5	
17				197−198	
18	HCl			111.5−113.5	
38	CH_3SO_3H	3-	*S*	179−181	+12.6
39	CH_3SO_3H	2-	*S*	135−137	+17.7

[a] See Experimental Section.

activity was still retained but signs of motor impairment were observed at doses lower than those for the secondary amine derivative **(6)**.

At this stage we felt that variation in the "amino acidic" part of the molecule (B, Figure 1) could give us the most relevant information. Replacement with different α-amino amide derivatives for the glycinamide part of **6** enabled us with several potent anticonvulsants (**19**−**36**, Table 1). The alanine **(19**−**22)** and serine **(23**−**25)** derivatives were both potent and boasted high therapeutic indexes (TIs) when compared with classical and new-generation anticonvulsants. The result of this part of the SAR indicated that a wide range of stereoelectronic features was tolerated as far as α-substitution on the amino amide center was regarded. Noteworthly, there was no stereoselectivity in the anticonvulsive effect since several couples of (*R*)- and (*S*)-amino amide residues were tested and found to be roughly equally active. In general, however, *R*-enantiomers showed signs of gross behavioral toxicity at doses lower than those of the *S*-enantiomers. Only when the bulkier phenylalanine residue was introduced (**26** vs **27**) did the *R*-enantiomer **(27)** display some activity, the *S*-enantiomer **(26)** being inactive.

Thus, the first part of our SAR analysis on the benzylamino amide moiety of **6** provided the alanine and the serine derivatives **19** and **23** as further lead compounds. These compounds were then used to assess the influence of changes in the benzoxybenzyl part of the structure. Further changes were devised, aimed at defining the effect of the relative position of the benzyloxy and the amino amide functions (Figure 1, D), the role of a different spacer (E) between the aromatic rings, and the substitution pattern of the remote aromatic ring or its replacement with a heteroaromatic moiety (F). Modification of the relative position of the methylamino and benzyloxy moieties (Figure 1, D) from para to meta and ortho resulted in a clear decrease in anticonvulsant activity (**19** vs **38** and **39**). The effect on activity by placing different spacers between the aromatic rings (E, Figure 1) was modulated by the length of the bridge as well by the presence of heteroatoms in the spacer. The biphenyl derivative **(40)** was much less active. Notably, the (*E*)-styryl derivative **(52)** proved inefficacious as did the benzamido derivative **(51)**. Several variations in the interaromatic chain yielded active compounds **(41**−**50)**. The most active compounds beside the benzyloxy derivative **(19)** were the benzylamino **(45)** and 3-phenylpropoxy **(50)** derivatives.

Table 4. Pharmacological Data in Mice for Compounds **1**−**39**

	anticonvulsant potency ED_{50} (mg/kg)		neurological impairment TD_{50} (mg/kg)
entry	iv-BIC	MES	rotorod
1	701 (270−1817)		
2	640 (312−1313)		
3	286 (209−392)		
4	490 (105−2273)		
5	192 (148−249)		
6	107 (40.1−284)	28.5 (20.8−39.0)	
7	30.5 (14.7−63.3)	48.6 (35.5−66.6)	
8	54.2 (35.5−82.8)[a]		
9	68.6 (49.6−94.7)	11.5 (8.31−15.5)	473 (404−556)
10	4/20@400 mg/kg		
11	3/20@400 mg/kg		
12	6/20@400 mg/kg		
13	5/20@400 mg/kg		
14	7/20@400 mg/kg		
15	8/20@400 mg/kg		
16	8/20@400 mg/kg		
17	5/20@400 mg/kg		
18	114 (44.6−294)	70 (49.2−294)	
19	23.8 (16.2−35.1)	17.1 (10.2−28.7)	328 (254−424)
20	16.9 (12.5−22.8)[a]		
21	40.5 (27.1−60.4)	7.0 (3.5−9.5)	353 (304−411)
22	8.4 (6.8−10.3)	7.0 (6.1−8.1)	224 (166−303)
23	16.3 (12.5−21.2)[a]	22.8 (17.8−30.2)[a]	
24	133 (100−177)		
25	15.0 (11.6−19.4)	9.9 (8.2−11.9)	167 (132−211)
26	2/20@400 mg/kg		
27	61.2 (41.4−90.7)		
28	0/20@400 mg/kg		
29	239 (174−318)		
30	112 (95.2−132)		
31	55.4 (27.2−113)		
32	192 (148−249)		
33	5/20@100 mg/kg		
34	21.0 (13.4−32.8)[a]		
35	34.2 (20.3−57.4)[a]		
36	55.0 (40.3−74.9)	7.2 (3.0−10.8)	277 (215−358)
37	119 (91.3−154)		
38	79.7 (46.7−136)		
39	210 (166−267)		

[a] Compound at 200 mg/kg induced impaired gait, loss of the righting reflex, and impaired breathing.

Table 5. Pharmacological Data in Mice for Compounds **40**−**75**

	anticonvulsant potency ED_{50} (mg/kg)		neurological impairment TD_{50} (mg/kg)
entry	iv-BIC	MES	rotorod
40	231 (169−312)		
41	64.0 (44.5−91.7)	41.5 (26.2−57.1)	
42	15.7 (11.5−21.4)	22.5 (17.5−28.0)	752 (404−1401)
43	40.3 (29.7−54.9)	17.8 (13.5−23.6)	630 (519−765)
44	24.8 (18.9−32.7)	8.6 (5.9−12.5)	633 (538−745)
45	9.3 (7.3−12.0)	11.5 (9.0−14.7)	217 (195−238)
46	40.3 (30.3−53.6)	10.6 (7.42−15.1)	597 (524−681)
47	24.9 (12.5−49.3)	12.2 (8.9−17.6)	1121 (909−1384)
48	39.6 (30.9−50.8)[a]	6.5 (4.0−8.8)[a]	
49	119 (91.2−155)		
50	19.0 (11.6−31.0)	6.7 (5.2−8.8)	584 (410−831)
51	1/10@400 mg/kg		
52	5/20@400 mg/kg		
53	17.4 (12.3−24.7)	50.8 (35.9−71.7)	525 (410−673)
54	18.4 (12.8−26.4)[a]		
55	132 (99.3−175)	16.3 (7.2−37.1)	
56	25.8 (19.8−39.5)	7.0 (5.3−9.1)	549 (406−741)
57	26.9 (22.3−32.5)	8.0 (7.0−9.1)	626 (557−703)
58	109 (63.8−185)		
59	7/20@400 mg/kg		
60	24.0 (10.1−91.9)[b]	15.2 (8.5−27.3)[b]	
61	216 (120−387)		
62	41.3 (31.7−53.8)	30.6 (10.7−87.5)	1247 (835−1836)
63	19.5 (15.6−24.4)	13.1 (8.8−19.5)	750 (646−1067)
64	85.6 (71.2−103)		
65	12.4 (10.1−15.4)	19.8 (14.1−27.8)	371 (291−474)
66	25.1 (6.0−39.5)	13.0 (8.8−18.8)	915 (725−1378)
67	172 (145−204)		
68	0/20@400 mg/kg		
69	2/10@400 mg/kg		
70	61.6 (46.7−81.2)		
71	114 (73−185)		
72	116 (73−185)		
73	152 (122−190)		
74	124 (103−149)		
75	131 (91.5−187)		

[a] Compound at 200 mg/kg induced impaired gait, loss of the righting reflex, and impaired breathing. [b] Compound at 400 mg/kg induced slight hypotonia.

Further structure−activity work was planned in order to explore the effect of the substitution pattern (**53**−**66**, Tables 2 and 5) and of replacement of the aromatic moiety with a heteroaromatic moiety or a cycloalkyl ring (**67**−**75**). By introducing different substituents in various positions of the remote aromatic ring, it was shown that 2- and 3-halo-substituted compounds were the most active compounds. Replacement of the aromatic ring with a heteroaromatic or cycloalkyl moiety did not bring about any advantage in terms of potency.

As a final outcome of the SAR study of this class of molecules, four compounds (**45**, **50**, **57**, and **66**) were chosen as further leads to be studied in more detail. These compounds were evaluated in a battery of anticonvulsant tests for assessing the broadness of their anticonvulsant efficacy (Table 6). Comparison with established and new-generation anticonvulsants fueled the interest in this class of compounds for the very broad spectrum of anticonvulsant activity as well as for the outstanding TIs displayed.

After preliminary absorption−disposition−metabolism−excretion (ADME) studies and toxicology, **57** emerged as the most promising compound for further preclinical studies. Studies are ongoing to elucidate the mechanism of action of this class of compounds: preliminarly, **57** has been shown to be a potent voltage- and frequency-dependent neuronal sodium channel blocker[13] and glutamate release inhibitor.[14] Repeated treatment with **57** in mice increased the MES ED_{50} by only 17.6%, and the acute and repeated treatment MES ED_{50}'s in these conditions overlap. These data suggest lack of tolerance.[15]

Some of the compounds of the series were also endowed with MAO-B reversible inhibitory activity (e.g., **57**).[16] While this feature can be regarded as a plus due to the recent association between MAO-B inhibition and neuroprotection,[17] no direct relationship between enzyme inhibition and anticonvulsant activity could be drawn within this series. The value of **57** as a potential new agent against resistant epilepsies is underscored by its outstanding activity in a rat kindling model at doses well below those causing toxicity.[15] **57** was also found to be active in preventing neuronal cell loss and protecting from status epilepticus (SE) evoked by systemic administration of an excitotoxin kainic acid, a rigid analogue of glutamate.[15]

Conclusions

Starting from a weak anticonvulsant such as milacemide (**1**) and trying to define its mechanism of action, we found a novel class of potent, orally active, safe

Table 6. Pharmacological Data for Selected Compounds versus Reference Standards (Mice, po)[a]

compd	MES	BIC	PTX	3-MPA	STRY	rotorod
45	11.5 (9.0−14.7) [18.9]	9.3 (7.3−12.0) [23.3]	37.5 (28.8−48.8) [5.8]	16.3 (10.8−24.4) [13.3]	50.3 (30.1−66.0) [4.3]	217 (195−238)
50	6.7 (5.2−8.8) [87.1]	19.0 (11.6−31.0) [30.7]	35.4 (24.9−50.1) [16.5]	16.2 (6.2−42.0) [36.0]	75.4 (55.2−103) [7.7]	584 (410−831)
57	8.0 (7.0−9.1) [78.2]	26.9 (22.3−32.5) [23.3]	60.6 (39.6−92.6) [10.3]	21.5 (16.8−27.5) [29.1]	104.1 (67.5−160.7) [6.0]	626 (557−703)
66	13.0 (8.8−18.8) [70.4]	25.1 (6.0−39.5) [36.4]	120 (78−204) [7.6]	35.6 (27.8−45.5) [25.7]	>250 [<3.6]	915 (725−1378)
phenytoin	3.8 (2.3−6.1) [17.0]	42.1 (29.0−61.1) [5.8]	>100 [<2.4]	11.3 (4.6−27.9) [21.5]	>200 [<1.2]	243 (142−415)
carbamazepine	9.8 (8.2−11.7) [10.8]	6.7 (5.5−8.0) [15.8]	40.6 (32.6−50.6) [2.6]	20.1 (15.5−25.7) [5.3]	43.8 (24.1−79.3) [2.4]	106 (93−121)
valproate	189 (169−212) [6.2]	414 (360−478) [2.8]	350 (276−443) [3.4]	167 (126−222) [7.0]	538 (478−607) [2.2]	1178 (1020−1360)
lamotrigine	2.2 (1.3−3.8) [38.2]	10.2 (6.4−16.0) [8.2]	>40 [<2.1]	>40 [<2.1]	>40 [<2.1]	84 (75−95)
diazepam	1.2 (0.57−2.5) [5.7]	0.29 (0.21−0.42) [23.4]	0.52 (0.41−0.66) [13.1]	0.62 (0.42−0.92) [11.0]	0.58 (0.45−0.74) [11.7]	6.8 (5.0−9.3)

[a] Therapeutic index calculated by ED_{50}(test)/TD_{50}(rotorod), in brackets. MES, maximal electroshock test; BIC, bicuculline test; PTX, picrotoxin test; 3-MPA, 3-mercaptopropionic acid test; STRY, strychnine test.

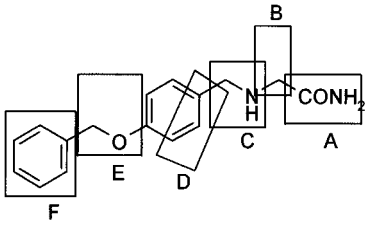


Figure 1. Regions of compound **6** targeted for chemical modifications.

anticonvulsants. Extensive SAR analysis allowed us to choose from this class (*S*)-2-[[4-(3-fluorobenzoxy)benzyl]-amino]propanamide methanesulfonate (**57**), a promising candidate to further development. The detailed mechanism of action of this class of compounds is under active investigation. Preliminary results point toward a potent sodium channel-blocking activity.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries, with a Buchi 535 melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba 1106 instrument, and C, H, and N results were within ±0.4% of theoretical values (15 out of 64 compounds were within ±0.43−1.11% in the C result). ^{1}H NMR spectra were recorded on either a Varian VXR-200 or Bruker WP-80 SY spectrometer, using the solvent as internal standard; chemical shifts are expressed in ppm (δ). Electron impact (EI) mass spectra (MS) were obtained on Varian MAT CH7 instrument. Optical activity was measured with a Jasco DIP 140 polarimeter, operating at 25 °C, and at λ = 589 nm, using a 10-cm cuvette; a concentration of 1.1% in 98% acetic acid was used unless otherwise indicated (see Tables 1−3). Organic solutions, where applicable, were dried over anhydrous Na_2SO_4 and evaporated using a Heidolph VV 2000 rotary evaporator at 15−20 mmHg. Flash column chromatographic separations were carried out on 40/60 μm silica gel (Carlo Erba). Thin-layer chromatography was performed on Whatman silica gel 60 plates coated with 250-μm layer, with fluorescent indicator. Components were visualized by UV light (λ = 254 nm), by iodine vapor, or by spraying with 2,4-dinitrophenylhydrazine reagent. Amino acids were visualized using a ninhydrin spray reagent. Dichloromethane was distilled from P_2O_5 and stored over 4-Å molecular sieves. All experiments dealing with moisture-sensitive compounds were conducted under dry nitrogen. Starting materials, unless otherwise specified, were commercially available (Aldrich, Fluka), of the best grade, and used without further purification.

Method A (Scheme 1): General Procedure for Reductive Alkylation of α-Amino Acid Derivatives. To a suspension of starting α-amino acid amide or ester hydrochloride (11 mmol) and powdered 3-Å molecular sieves (2.5 g) in dry methanol (70 mL) kept under nitrogen was added $NaBH_3$-CN (8 mmol), and the mixture was stirred at room temperature for 15 min. Then the appropriate aldehyde (10 mmol) was added in a single portion. (CAUTION: sodium cyanide is produced). The reaction mixture was allowed to reach 30−35 °C and then stirred at room temperature for 3 h. After filtration, the solvent was evaporated to give a residue which was flash-chromatographed using CH_2Cl_2−CH_3OH−30% NH_4-OH (99:1:0.1 to 95:5:0.5 depending on the type of α-amino acid derivative and aldehyde used) to give the N-alkylated compound. The final products were tested as either the free base or its hydrochloride or methanesulfonate salt. Following the procedure above the following compounds were prepared (for mp and $[\alpha]^{25}_D$, see Tables 1−3).

2-[[4-(3-Chlorobenzoxy)benzyl]amino]-*N*-methylacetamide, hydrochloride (7): 42%; ^{1}H NMR (200 MHz, DMSO-d_6) 2.62 (d, J = 4.6 Hz, 3H, CONHCH_3), 3.56 (s, 2H, NHCH_2CO), 4.06 (s, 2H, ArCH_2NH), 5.14 (s, 2H, ArCH_2O), 7.05 (m, 2H, H3, H5), 7.3−7.6 (m, 6H, H2, H6, H2′, H4′, H5′, H6′), 8.37 (q, J = 4.6 Hz, 1H, CO*NH*CH$_3$), 9.3 (br s, 2H, NH_2^+); MS m/z 318 ($M^{\bullet+}$), 260, 246, 231, 125 (100). Anal. ($C_{17}H_{19}ClN_2O_2$·HCl) C, H, Cl, N.

2-[(4-Benzoxybenzyl)amino]acetamide, hydrochloride (9): 38%; ^{1}H NMR (80 MHz, DMSO-d_6) 3.53 (s, 2H, NHCH_2-CO), 4.05 (s, 2H, ArCH_2NH), 5.1 (s, 2H, ArCH_2O), 7.03 (m, 2H, H3, H5), 7.2−7.6 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′), 7.8, 7.4 (2 br s, 2H, $CONH_2$), 9.3 (br s, 2H, NH_2^+); MS m/z 270 ($M^{\bullet+}$), 226, 212, 197, 91 (100). Anal. ($C_{16}H_{18}N_2O_2$·HCl) C, H, N, Cl.

2-[[4-(3-Chlorobenzoxy)benzyl]amino]acetic acid, hydrochloride (10): 75%; ^{1}H NMR (80 MHz, DMSO-d_6) 3.73 (s, 2H, NHCH_2COOH), 4.04 (s, 2H, ArCH_2NH), 5.04 (s, 2H, ArCH_2O), 7.04 (m, 2H, H3, H5), 7.2−7.6 (m, 7H, H2, H6, H2′, H4′, H5′, H6′), 9.4 (br s, 2H, NH_2^+); MS m/z 305 ($M^{\bullet+}$), 260, 246, 231, 125 (100). Anal. ($C_{16}H_{16}ClNO_3$·HCl) C, H, Cl, N.

Ethyl 2-[[4-(3-Chlorobenzoxy)benzyl]amino]acetate, hydrochloride (11): 34%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.15 (t, J = 7.0 Hz, 3H, COOCH$_2$CH_3), 3.95 (s, 2H, NHCH_2-COO), 4.01 (q, J = 7.0 Hz, 2H, COOCH_2CH$_3$), 4.12 (s, 2H, ArCH_2NH), 5.12 (s, 2H, ArCH_2O), 7.04 (m, 2H, H3, H5), 7.3−7.6 (m, 6H, H2, H6, H2′, H4′, H5′, H6′), 9.7 (br s, 2H, NH_2^+); MS m/z 333 ($M^{\bullet+}$), 246, 231, 125 (100). Anal. ($C_{18}H_{20}ClNO_3$·HCl) C, H, Cl, N.

Benzyl 2-[[4-(3-Chlorobenzoxy)benzyl]amino]acetate, hydrochloride (12): 18%; ^{1}H NMR (200 MHz, DMSO-d_6) 3.97 (s, 2H, NHCH_2COO), 4.09 (s, 2H, ArCH_2NH), 5.15, 5.21 (2 s, 4H, ArCH_2O, COOCH_2Ph), 7.05 (m, 2H, H3, H5), 7.3−

7.6 (m, 6H, H2, H6, H2′, H4′, H5′, H6′), 9.5 (br s, 2H, NH_2^+); MS *m/z* 395 ($M^{\bullet+}$), 304, 231, 125 (100), 91. Anal. ($C_{23}H_{22}ClNO_3 \cdot HCl$) H, N; C: calcd, 63.90; found, 63.07. Cl: calcd, 16.40; found, 17.14.

3-[[[4-(3-Chlorobenzoxy)phenyl]ethyl]amino]propanamide, hydrochloride (15): 22%; ^{1}H NMR (80 MHz, DMSO-d_6) 2.3−3.4 (m, 8H, ArCH_2CH_2NHCH_2CH_2), 5.07 (s, 2H, ArCH_2O), 6.7−7.8 (m, 10H, CONH2$^+$ aromatics), 9.1 (br s, 2H, NH_2^+); MS *m/z* 332 ($M^{\bullet+}$), 232, 125, 101 (100). Anal. ($C_{18}H_{21}ClN_2O_2 \cdot HCl$) C, H, Cl, N.

3-[[[4-(3-Chlorobenzoxy)phenyl]propyl]amino]-acetamide, hydrochloride (16): 60%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.87 (m, 2H, Ar$CH_2CH_2CH_2$NH), 2.4−3.0 (m, 4H, Ar$CH_2CH_2CH_2$NH), 3.63 (s, 2H, CH_2CO), 5.08 (s, 2H, ArCH_2O), 6.93 (m, 2H, H3, H5), 7.12 (m, 2H, H2, H6), 7.3−7.5 (m, 4H, H2′, H4′, H5′, H6′), 7.54, 7.9 (2 s, 2H, $CONH_2$), 9.0 (br s, 2H, NH_2^+); MS *m/z* 332 ($M^{\bullet+}$), 288, 231, 125 (100). Anal. ($C_{18}H_{21}ClN_2O_2 \cdot HCl$) C, H, Cl, N.

(*S*)-(+)-2-[(4-Benzoxybenzyl)amino]propanamide, hydrochloride (19): 65%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.39 (d, J = 7.0 Hz, 3H, CH_3CH), 2.30 (s, 3H, CH_3SO_3-), 3.69 (q, J = 7.0 Hz, 1H, CH_3CH), 4.0 (s, 2H, ArCH_2NH), 5.12 (s, 2H, ArCH_2O), 7.05 (m, 2H, H3, H5), 7.2−7.5 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′), 7.62, 7.89 (2 s, 2H, $CONH_2$), 9.0 (br s, 2H, NH_2^+); MS *m/z* 284 ($M^{\bullet+}$), 240, 212, 197, 91 (100). Anal. ($C_{17}H_{20}N_2O_2 \cdot HCl$) C, H, Cl, N.

(*R*)-(−)-2-[(4-Benzoxybenzyl)amino]propanamide, hydrochloride (20): 61%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.39 (d, J = 6.9 Hz, 3H, CH_3CH), 2.30 (s, 3H, CH_3SO_3-), 3.70 (m, 1H, CH_3CH), 4.0 (s, 2H, ArCH_2NH), 5.11 (s, 2H, ArCH_2O), 7.05 (m, 2H, H3, H5), 7.2−7.5 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′), 7.62, 7.89 (2 s, 2H, $CONH_2$), 9.0 (br s, 2H, NH_2^+); MS *m/z* 284 ($M^{\bullet+}$), 240, 212, 197, 91 (100). Anal. ($C_{17}H_{20}N_2O_2 \cdot HCl$) C, H, Cl, N.

(*S*)-(−)-2-[(4-Benzoxybenzyl)amino]-*N*-methylpropanamide, hydrochloride (21): 52%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.37 (d, J = 7.0 Hz, 3H, CH_3CH), 2.30 (s, 3H, CH_3SO_3-), 2.65 (d, J = 4.5 Hz, 3H, CONHCH_3), 3.70 (m, 1H, CH_3CH), 3.98 (m, 2H, ArCH_2NH), 5.12 (s, 2H, ArCH_2O), 7.05 (m, 2H, H3, H5), 7.2−7.5 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′), 8.40 (q, J = 4.5 Hz, 1H, CONHCH$_3$), 9.0 (2 br s, 2H, NH_2^+); MS *m/z* 298 ($M^{\bullet+}$), 240, 212, 197, 91 (100). Anal. ($C_{18}H_{22}N_2O_2 \cdot HCl$) C, H, Cl, N.

(*R*)-(−)-2-[(4-Benzoxybenzyl)amino]-*N*-methylpropanamide, methanesulfonate (22): 31%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.36 (d, J = 6.9 Hz, 3H, CH_3CH), 2.30 (s, 3H, CH_3SO_3-), 2.65 (d, J = 4.6 Hz, 3H, CONHCH_3), 3.69 (q, J = 6.9 Hz, 1H, CH_3CH), 3.97 (s, 2H, ArCH_2NH), 5.12 (s, 2H, ArCH_2O), 7.05 (m, 2H, H3, H5), 7.2−7.5 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′), 8.38 (q, J = 4.6 Hz, 1H, CONHCH$_3$), 9.0 (2 br s, 2H, NH_2^+); MS *m/z* 298 ($M^{\bullet+}$), 240, 212, 197, 91 (100). Anal. ($C_{18}H_{22}N_2O_2 \cdot CH_3SO_3H$) C, H, N, S.

(*S*)-(+)-2-[(4-Benzoxybenzyl)amino]-3-hydroxy-*N*-methylpropanamide (23): 59%; ^{1}H NMR (200 MHz, DMSO-d_6) 2.3 (s, 3H, CH_3SO_3-), 2.64 (d, J = 4.6 Hz, 3H, CONHCH_3), 3.5−3.8 (m, 3H, $CHCH_2$OH), 4.02 (s, 2H, ArCH_2NH), 5.11 (s, 2H, ArCH_2O), 5.48 (t, J = 5.0 Hz, 1H, CH_2OH), 7.03 (m, 2H, H3, H5), 7.2−7.5 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′), 8.34 (q, J = 4.6 Hz, 1H, CONHCH$_3$), 9.0 (br s, 2H, NH_2^+); MS *m/z* 314 ($M^{\bullet+}$), 256, 212, 197, 91 (100). Anal. ($C_{18}H_{22}N_2O_3$) C, H, N.

(*S*)-(+)-2-[(4-Benzoxybenzyl)amino]propanamide (24): 57%; ^{1}H NMR (200 MHz, DMSO-d_6) 2.28 (s, 3H, CH_3SO_3-), 3.61 (m, 1H, CHCH$_2$OH), 3.77 (m, 2H, CHCH_2OH), 4.05 (m, 2H, ArCH_2NH), 5.11 (s, 2H, ArCH_2O), 5.5 (br s, 1H, CH_2OH), 7.04 (m, 2H, H3, H5), 7.2−7.5 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′), 7.65, 7.84 (2 s, 2H, $CONH_2$), 9.0 (br s, 2H, NH_2^+); MS *m/z* 300 ($M^{\bullet+}$), 256, 212, 197, 91 (100). Anal. ($C_{17}H_{20}N_2O_3$) C, H, N.

(*R*)-(−)-2-[(4-Benzoxybenzyl)amino]-3-hydroxy-*N*-methylpropanamide (25): 44%; ^{1}H NMR (200 MHz, $CDCl_3$) 1.79 (d, J = 4.9 Hz, 3H, CONHCH_3), 3.2 (t, J = 5.4 Hz, 1H, CHCH$_2$OH), 3.6−3.9 (m, 4H, ArCH_2NH, CHCH_2OH), 5.05 (s, 2H, ArCH_2O), 6.98 (m, 2H, H3, H5), 7.1−7.5 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′); MS *m/z* 314 ($M^{\bullet+}$), 256, 212, 197, 91 (100). Anal. ($C_{18}H_{22}N_2O_3$) C, H, N.

(*S*)-(+)-2-[(4-Benzoxybenzyl)amino]-3-phenyl-*N*-methylpropanamide, hydrochloride (26): 77%; ^{1}H NMR (200 MHz, DMSO-d_6) 2.48 (d, J = 4.8 Hz, 3H, CONHCH_3), 3.00 (dd, J = 9.7, 13.2 Hz, 1H, ArCH_AH_BCHCO), 3.29 (dd, J = 4.6, 13.2 Hz, 1H, ArCH_AH_BCHCO), 3.8−4.1 (m, 3H, ArCH_2NH, CHCO), 5.12 (s, 2H, ArCH_2O), 6.9−7.5 (m, 14H, aromatics), 8.38 (q, J = 4.8 Hz, 1H, CONHCH$_3$), 9.4, 10.0 (2 br s, 2H, NH_2^+); MS *m/z* 374 ($M^{\bullet+}$), 316, 283, 212, 197, 91 (100). Anal. ($C_{24}H_{26}N_2O_2 \cdot HCl$) H, Cl, N, S; C: calcd, 70.15; found, 69.43.

(*R*)-(−)-2-[(4-Benzoxybenzyl)amino]-3-phenyl-*N*-methylpropanamide, hydrochloride (27): 84%; ^{1}H NMR (200 MHz, DMSO-d_6) 2.48 (d, J = 4.8 Hz, 3H, CONHCH_3), 2.98 (dd, J = 9.5, 13.5 Hz, 1H, ArCH_AH_BCHCO), 3.23 (dd, J = 4.1, 13.5 Hz, 1H, ArCH_AH_BCHCO), 3.7−4.0 (m, 3H, ArCH_2NH, CHCO), 5.12 (s, 2H, ArCH_2O), 6.9−7.5 (m, 14H, aromatics), 8.28 (q, J = 4.8 Hz, 1H, CONHCH$_3$), 9.4, 9.7 (2 br s, 2H, NH_2^+); MS *m/z* 374 ($M^{\bullet+}$), 316, 283, 212, 197, 91 (100). Anal. ($C_{24}H_{26}N_2O_2 \cdot HCl$) H, Cl, N; C: calcd, 70.15; found, 69.34.

(*S*)-(+)-2-[(4-Benzoxybenzyl)amino]-4-(methylthio)butanamide, hydrochloride (28): 69%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.8−2.3 (m, 2H, CH_2CH$_2$S), 2.02 (s, 3H, SCH_3), 2.3−2.5 (m, 2H, CH$_2CH_2$S), 2.65 (d, J = 4.6 Hz, 3H, CONHCH_3), 3.74 (m, 1H, NHCHCO), 3.95 (s, 2H, ArCH_2NH), 5.12 (s, 2H, ArCH_2O), 7.02 (m, 2H, H3, H5), 7.2−7.5 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′), 8.63 (q, J = 4.6 Hz, 1H, CONHCH$_3$), 9.2, 9.7 (2 br s, 2H, NH_2^+); MS *m/z* 358 ($M^{\bullet+}$), 300, 212, 197, 91 (100). Anal. ($C_{20}H_{26}N_2O_2S \cdot HCl$) C, H, Cl, N, S.

(*R*)-(−)-2-[(4-Benzoxybenzyl)amino]-4-(methylthio)butanamide, hydrochloride (29): 62%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.8−2.3 (m, 2H, CH_2CH$_2$S), 2.02 (s, 3H, SCH_3), 2.3−2.5 (m, 2H, CH$_2CH_2$S), 2.65 (d, J = 4.6 Hz, 3H, CONHCH_3), 3.72 (m, 1H, NHCHCO), 3.94 (m, 2H, ArCH_2NH), 5.11 (s, 2H, ArCH_2O), 7.02 (m, 2H, H3, H5), 7.2−7.5 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′), 8.63 (q, J = 4.6 Hz, 1H, CONHCH$_3$), 9.2, 9.7 (2 br s, 2H, NH_2^+); MS *m/z* 358 ($M^{\bullet+}$), 300, 212, 197, 91 (100). Anal. ($C_{20}H_{26}N_2O_2S \cdot HCl$) C, H, Cl, N, S.

(*R*)-(−)-2-[(4-Benzoxybenzyl)amino]-3-methyl-*N*-methylbutanamide, hydrochloride (30): 64%; ^{1}H NMR (200 MHz, DMSO-d_6) 0.88, 0.93 (2 d, J = 6.8 Hz, 6H, $(CH_3)_2$CH), 2.2 (m, 1H, $(CH_3)_2CH$), 2.61 (d, J = 4.5 Hz, 3H, CONHCH_3), 3.45 (m, 1H, NHCHCO), 3.8−4.1 (m, 2H, ArCH_2NH), 5.11 (s, 2H, ArCH_2O), 7.01 (m, 2H, H3, H5), 7.2−7.5 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′), 8.51 (q, J = 4.5 Hz, 1H, CONHCH$_3$), 9.0, 9.5 (2 br s, 2H, NH_2^+); MS *m/z* 326 ($M^{\bullet+}$), 268, 212, 197, 91 (100). Anal. ($C_{20}H_{26}N_2O_2 \cdot HCl$) H, Cl, N; C: calcd, 66.19; found, 65.70.

(*R*)-(−)-2-[(4-Benzoxybenzyl)amino]-3-methyl-*N*-methylbutanamide, hydrochloride (31): 62%; ^{1}H NMR (80 MHz, DMSO-d_6) 0.88, 0.93 (2 d, J = 6.8 Hz, 6H, $(CH_3)_2$CH), 1.9−2.4 (m, 1H, $(CH_3)_2CH$), 2.61 (d, J = 4.5 Hz, 3H, CONHCH_3), 3.45 (m, 1H, NHCHCO), 3.96.1 (s, 2H, ArCH_2NH), 5.11 (s, 2H, ArCH_2O), 7.01 (m, 2H, H3, H5), 7.2−7.6 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′), 8.43 (q, J = 4.5 Hz, 1H, CONHCH$_3$), 9.2 (br s, 2H, NH_2^+); MS *m/z* 326 ($M^{\bullet+}$), 268, 212, 197, 91 (100). Anal. ($C_{20}H_{26}N_2O_2 \cdot HCl$) C, H, Cl, N.

(*S*)-(+)-2-[(4-Benzoxybenzyl)amino]-4-methyl-*N*-methylpentanamide, hydrochloride (32): 63%; ^{1}H NMR (200 MHz, DMSO-d_6) 0.82, 0.86 (2 d, J = 6.3 Hz, 6H, $(CH_3)_2$CH), 1.3−1.8 (m, 3H, $(CH_3)_2CHCH_2$), 2.64 (d, J = 4.6 Hz, 3H, CONHCH_3), 3.66 (m, 1H, NHCHCO), 3.75−4.1 (m, 2H, ArCH_2-NH), 5.11 (s, 2H, ArCH_2O), 7.02 (m, 2H, H3, H5), 7.2−7.5 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′), 8.72 (q, J = 4.6 Hz, 1H, CONHCH$_3$), 9.2, 9.6 (2 br s, 2H, NH_2^+); MS *m/z* 340 ($M^{\bullet+}$), 282, 212, 197, 91 (100). Anal. ($C_{21}H_{28}N_2O_2 \cdot HCl$) H, Cl, N; C: calcd, 66.92; found, 65.16.

(*R*)-(−)-2-[(4-Benzoxybenzyl)amino]-4-methyl-*N*-methylpentanamide, hydrochloride (33): 58%; ^{1}H NMR (200 MHz, DMSO-d_6) 0.82, 0.86 (2 d, J = 6.3 Hz, 6H, $(CH_3)_2$CH), 1.3−1.8 (m, 3H, $(CH_3)_2CHCH_2$), 2.64 (d, J = 4.6 Hz, 3H, CONHCH_3), 3.66 (m, 1H, NHCHCO), 3.75−4.1 (m, 2H, ArCH_2-NH), 5.11 (s, 2H, ArCH_2O), 7.02 (m, 2H, H3, H5), 7.2−7.5 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′), 8.74 (q, J = 4.6 Hz, 1H,

CO*NH*CH_3), 9.2, 9.6 (2 br s, 2H, NH_2^+); MS *m/z* 340 ($M^{\bullet+}$), 282, 212, 197, 91 (100). Anal. ($C_{21}H_{28}N_2O_2$·HCl) H, Cl, N; C: calcd, 66.92; found, 65.23.

(2*R*,3*S*)-(−)-2-[(4-Benzoxybenzyl)amino]-3-hydroxy-*N*-methylbutanamide, hydrochloride (34): 65%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.05 (d, *J* = 6.4 Hz, 3H, *C*H_3CHOH), 2.61 (d, *J* = 4.5 Hz, 3H, CONH*C*H_3), 3.34 (d, *J* = 7.7 Hz, 1H, NH*CH*CONH), 3.8−4.1 (m, 3H, Ar*C*H_2NH, CH_3*CH*OH), 5.1 (s, 2H, Ar*C*H_2O), 5.7 (br s, 1H, *OH*), 7.02 (m, 2H, H3, H5), 7.2−7.5 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′), 8.57 (q, *J* = 4.5 Hz, 1H, CO*NH*CH_3), 9.2 (br s, 2H, NH_2^+); MS *m/z* 328 ($M^{\bullet+}$), 270, 212, 197, 91 (100). Anal. ($C_{19}H_{24}N_2O_3$·HCl) C, H, Cl, N.

(*S*)-(+)-2-[(4-Benzoxybenzyl)amino]butanamide, methanesulfonate (36): 49%; ^{1}H NMR (200 MHz, DMSO-d_6) 0.88 (t, *J* = 7.5 Hz, 3H, CH_2*C*H_3), 1.6−2.0 (m, 2H, *C*H_2CH_3), 2.3 (s, 3H, CH_3SO_3-), 3.58 (dd, *J* = 5.2, 7.1 Hz, 1H, *CH*CH_2CH_3), 3.98 (s, 2H, Ar*C*H_2NH), 5.12 (s, 2H, Ar*C*H_2O), 7.05 (m, 2H, H3, H5), 7.2−7.5 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′), 7.69, 7.93 (2 s, 2H, $CONH_2$), 8.9 (br s, 2H, NH_2^+); MS *m/z* 298 ($M^{\bullet+}$), 254, 212, 197, 91 (100). Anal. ($C_{18}H_{22}N_2O_2$·CH_3SO_3H) C, H, N, S.

(*R*)-(−)-2-[(4-Benzoxybenzyl)amino]butanamide, methanesulfonate (37): 46%; ^{1}H NMR (200 MHz, DMSO-d_6) 0.86 (t, *J* = 7.5 Hz, 3H, *C*H_3CH_2), 1.7 (m, 2H, CH_3*C*H_2), 2.3 (s, 3H, CH_3SO_3-), 3.3 (m, 1H, *CH*CH_2CH_3), 3.76, 3.87 (2 d, *J* = 13.1 Hz, 2H, Ar*C*H_2NH), 5.11 (s, 2H, Ar*C*H_2O), 7.01 (m, 2H, H3, H5), 7.2−7.5 (m, 7H, H2, H6, H2′, H3′, H4′, H5′, H6′), 7.45, 7.71 (2 s, 2H, $CONH_2$); MS *m/z* 298 ($M^{\bullet+}$), 254, 212, 197, 91 (100). Anal. ($C_{18}H_{22}N_2O_2$·CH_3SO_3H) C, H, N, S.

(*S*)-(+)-2-[(3-Benzoxybenzyl)amino]propionamide, methanesulfonate (38): 52%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.41 (d, *J* = 7.0 Hz, 3H, *C*H_3CH), 2.3 (s, 3H, CH_3SO_3-), 3.73 (q, *J* = 7.0 Hz, 1H, CH_3*CH*), 4.06 (s, 2H, Ar*C*H_2NH), 5.11 (s, 2H, Ar*C*H_2O), 7.05 (m, 2H, H6, H4), 7.18 (t, *J* = 1.9 Hz, 1H, H2), 7.2−7.5 (m, 6H, H2′, H3′, H4′, H5′, H6′, H5), 7.62, 789 (2 s, 2H, $CONH_2$), 9.1 (br s, 2H, NH_2^+); MS *m/z* 284 ($M^{\bullet+}$), 240, 212, 197, 91 (100). Anal. ($C_{17}H_{20}N_2O_2$·CH_3SO_3H) C, H, N, S.

(*S*)-(+)-2-[(2-Benzoxybenzyl)amino]propanamide, methanesulfonate (39): 25%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.39 (d, *J* = 7.0 Hz, 3H, *C*H_3CH), 2.3 (s, 3H, CH_3SO_3-), 3.75 (q, *J* = 7.0 Hz, 1H, CH_3*CH*), 4.12 (s, 2H, Ar*C*H_2NH), 5.18 (s, 2H, Ar*C*H_2O), 7.0 (m, 1H, H5), 7.14 (d, *J* = 7.9 Hz, 1H, H3), 7.2−7.6 (m, 7H, H2′, H3′, H4′, H5′, H6′, H4, H6), 7.61, 7.88 (2 s, 2H, $CONH_2$), 8.9 (br s, 2H, NH_2^+); MS *m/z* 284 ($M^{\bullet+}$), 240, 212, 197, 91 (100). Anal. ($C_{17}H_{20}N_2O_2$·CH_3SO_3H) C, H, N, S.

(*S*)-(+)-2-[(4-Phenylbenzyl)amino]propanamide, methanesulfonate (40): 48%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.43 (d, *J* = 7.0 Hz, 3H, *C*H_3CH), 2.3 (s, 3H, CH_3SO_3-), 3.77 (q, *J* = 7.0 Hz, 1H, CH_3*CH*), 4.13 (s, 2H, Ar*C*H_2NH), 7.3−7.8 (m, 9H, aromatics), 7.65, 792 (2 s, 2H, $CONH_2$), 9.1 (br s, 2H, NH_2^+); MS *m/z* 254 ($M^{\bullet+}$), 210, 182, 167 (100). Anal. ($C_{16}H_{18}N_2O$·CH_3SO_3H) C, H, N, S.

(*S*)-(+)-2-[(4-Phenoxybenzyl)amino]propanamide, methanesulfonate (41): 44%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.4 (d, *J* = 7.0 Hz, 3H, *C*H_3CH), 2.3 (s, 3H, CH_3SO_3-), 3.76 (q, *J* = 7.0 Hz, 1H, CH_3*CH*), 4.03, 4.10 (2 d, *J* = 13.2 Hz, 2H, Ar*C*H_2-NH), 6.9−7.6 (m, 9H, aromatics), 7.5, 7.87 (2 s, 2H, $CONH_2$), 9.0 (br s, 2H, NH_2^+); MS *m/z* 270 ($M^{\bullet+}$), 226, 198, 183 (100), 77. Anal. ($C_{16}H_{18}N_2O_2$·CH_3SO_3H) C, H, N, S.

(*S*)-(+)-2-[(4-Benzylbenzyl)amino]propanamide, methanesulfonate (42): 37%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.40 (d, *J* = 7.0 Hz, 3H, *C*H_3CH), 2.3 (s, 3H, CH_3SO_3-), 3.72 (q, *J* = 7.0 Hz, 1H, CH_3*CH*), 3.96 (s, 2H, Ar*C*H_2Ar), 4.03 (s, 2H, Ar*C*H_2-NH), 7.1−7.5 (m, 9H, aromatics), 7.64, 7.90 (2 s, 2H, $CONH_2$), 9.0 (br s, 2H, NH_2^+); MS *m/z* 268 ($M^{\bullet+}$), 224, 196, 181 (100), 91. Anal. ($C_{17}H_{20}N_2O$·CH_3SO_3H) C, H, N, S.

(*S*)-(+)-2-[[4-(2-Phenylethyl)benzyl]amino]propanamide, methanesulfonate (43): 42%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.37 (d, *J* = 7.0 Hz, 3H, *C*H_3CH), 2.3 (s, 3H, CH_3SO_3-), 2.88 (s, 4H, $ArCH_2CH_2Ar$), 3.61 (q, *J* = 7.0 Hz, 1H, CH_3*CH*), 3.97 (s, 2H, Ar*C*H_2NH), 7.1−7.4 (m, 9H, aromatics), 7.55, 7.82 (2 s, 2H, $CONH_2$), 8.5 (br s, 2H, NH_2^+); MS *m/z* 238, 210, 195, 91 (100). Anal. ($C_{18}H_{22}N_2O$·CH_3SO_3H) C, H, N, S.

(*S*)-(+)-2-[[4-(Benzylamino)benzyl]amino]propanamide, dihydrochloride (45): 24%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.39 (d, *J* = 7.0 Hz, 3H, *C*H_3CH), 3.67 (m, 1H, CH_3*CH*), 3.88 (m, 2H, Ar*C*H_2NHCH), 4.32 (s, 2H, Ar*C*H_2-NHAr), 6.77 (m, 2H, H3, H5), 7.1−7.5 (m, 7H, H2′, H3′, H4′, H5′, H6′, H2, H6), 7.59, 7.98 (2 s, 2H, $CONH_2$), 8.9, 9.4 (2 br s, 2H, NH_2^+); MS *m/z* (M•+), 211, 196, 91 (100). Anal. ($C_{17}H_{21}N_3O$·2HCl) H, Cl, N; C: calcd, 57.30; found, 56.56.

(*S*)-(+)-2-[[4-(Phenoxymethyl)benzyl]amino]propanamide, methanesulfonate (46): 42%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.41 (d, *J* = 7.0 Hz, 3H, *C*H_3CH), 2.30 (s, 3H, CH_3SO_3-), 3.75 (q, *J* = 7.0 Hz, 1H, CH_3*CH*), 4.09 (s, 2H, Ar*C*H_2-NH), 5.12 (s, 2H, Ar*C*H_2O), 6.8−7.6 (m, 9H, aromatics), 7.65, 7.92 (2 s, 2H, $CONH_2$), 9.1 (br s, 2H, NH_2^+); MS *m/z* 284 ($M^{\bullet+}$), 240, 212, 197, 104 (100). Anal. ($C_{17}H_{20}N_2O_2$·CH_3SO_3H). C, H, N, S.

(*S*)-(+)-2-[[4-(2-Phenylethoxy)benzyl]amino]propanamide, methanesulfonate (47): 50%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.39 (d, *J* = 7.0 Hz, 3H, *C*H_3CH), 2.30 (s, 3H, CH_3SO_3-), 3.03 (t, *J* = 7.0 Hz, 2H, OCH_2*C*H_2), 3.68 (q, *J* = 7.0 Hz, 1H, CH_3*CH*), 4.00 (s, 2H, Ar*C*H_2NH), 4.20 (t, *J* = 7.0 Hz, 2H, O*C*H_2CH_2), 6.99 (m, 2H, H3, H5), 7.1−7.5 (m, 7H, H2′, H3′, H4′, H5′, H6′, H2, H6), 7.63, 7.88 (2 s, 2H, $CONH_2$), 8.9 (br s, 2H, NH_2^+); MS *m/z* 298 ($M^{\bullet+}$), 254, 226, 211, 105 (100). Anal. ($C_{18}H_{22}N_2O_2$·CH_3SO_3H) C, H, N.

(*S*)-(+)-2-[[4-[(Phenylamino)methyl]benzyl]amino]-propanamide, dihydrochloride (49): 45%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.43 (d, *J* = 7.0 Hz, 3H, *C*H_3CH), 3.73 (m, 1H, CH_3*CH*), 4.03 (m, 2H, Ar*C*H_2NHCH), 4.42 (s, 2H, ArNH*C*H_2Ar), 6.9−7.4 (m, 5H, H2′, H3′, H4′, H5′, H6′), 7.48 (s, 4H, H2, H3, H5, H6), 7.62, 8.04 (2 s, 2H, $CONH_2$), 9.2, 9.8 (2 br s, 2H, $ArCH_2NH_2^+CH$); MS *m/z* 283 ($M^{\bullet+}$), 239, 211, 196 (100), 104. Anal. ($C_{17}H_{21}N_3O$·2HCl) C, H, N.

(*S*)-(+)-2-[[4-(Benzoylamino)benzyl]amino]propanamide, methanesulfonate (51): 53%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.42 (d, *J* = 7.0 Hz, 3H, *C*H_3CH), 2.3 (s, 3H, CH_3SO_3-), 3.72 (q, *J* = 7.0 Hz, 1H, CH_3*CH*), 4.04 (s, 2H, Ar*C*H_2-NH), 7.3−8.0 (m, 11H, aromatics, $CONH_2$), 9.1 (br s, 2H, NH_2^+), 10.38 (s, 1H, CO*NH*Ar); MS *m/z* 297 ($M^{\bullet+}$), 253, 225, 210, 105 (100). Anal. ($C_{17}H_{19}N_3O_2$·CH_3SO_3H) H, N, S; C: calcd, 54.95; found, 54.41.

(*S*)-(+)-2-[[4-(*E*)-Styrylbenzyl)amino]propanamide, methanesulfonate (52): 26%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.42 (d, *J* = 7.0 Hz, 3H, *C*H_3CH), 2.3 (s, 3H, CH_3SO_3-), 3.73 (q, *J* = 7.0 Hz, 1H, CH_3*CH*), 4.09 (s, 2H, Ar*C*H_2NH), 7.1−7.8 (m, 11H, aromatics, ArC*H*═C*H*Ar), 7.9, 7.62 (2 s, 2H, $CONH_2$), 9.05 (br s, 2H, NH_2^+); MS *m/z* 280 ($M^{\bullet+}$), 236, 208, 193 (100). Anal. ($C_{18}H_{20}N_2O$·CH_3SO_3H) C, H, N, S.

(*S*)-(+)-2-[[4-(2-Chlorobenzoxy)benzyl]amino]propanamide, methanesulfonate (53): 30%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.40 (d, *J* = 7.0 Hz, 3H, *C*H_3CH), 2.30 (s, 3H, CH_3SO_3-), 3.71 (q, *J* = 7.0 Hz, 1H, CH_3*CH*), 4.0 (s, 2H, Ar*C*H_2-NH), 5.17 (s, 2H, Ar*C*H_2O), 7.08 (m, 2H, H3, H5), 7.3−7.7 (m, 6H, H2, H6, H3′, H4′, H5′, H6′), 7.64, 7.91 (2 s, 2H, $CONH_2$), 9.0 (br s, 2H, NH_2^+); MS *m/z* 318 ($M^{\bullet+}$), 274, 246, 231, 125 (100). Anal. ($C_{17}H_{19}ClN_2O_2$·CH_3SO_3H) C, H, Cl, N, S.

(*R*)-(−)-2-[[4-(2-Chlorobenzoxy)benzyl]amino]propanamide, methanesulfonate (54): 31%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.39 (d, *J* = 7.0 Hz, 3H, *C*H_3CH), 2.30 (s, 3H, CH_3SO_3-), 3.70 (q, *J* = 7.0 Hz, 1H, CH_3*CH*), 4.01 (s, 2H, Ar*C*H_2-NH), 5.17 (s, 2H, Ar*C*H_2O), 7.08 (m, 2H, H3, H5), 7.3−7.7 (m, 6H, H2, H6, H3′, H4′, H5′, H6′), 7.63, 7.89 (2 s, 2H, $CONH_2$), 9.0 (br s, 2H, NH_2^+); MS *m/z* 318 ($M^{\bullet+}$), 274, 246, 231, 125 (100). Anal. ($C_{17}H_{19}ClN_2O_2$·CH_3SO_3H) C, H, Cl, N, S.

(*S*)-(+)-2-[[4-(4-Fluorobenzoxy)benzyl]amino]propanamide, methanesulfonate (55): 42%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.40 (d, *J* = 7.0 Hz, 3H, *C*H_3CH), 2.30 (s, 3H, CH_3SO_3-), 3.70 (q, *J* = 7.0 Hz, 1H, CH_3*CH*), 4.01 (s, 2H, Ar*C*H_2-NH), 5.10 (s, 2H, Ar*C*H_2O), 7.0−7.6 (m, 8H, aromatics), 7.62, 7.88 (2 s, 2H, $CONH_2$), 9.0 (br s, 2H, NH_2^+); MS *m/z* 302 ($M^{\bullet+}$), 258, 230, 215, 109 (100). Anal. ($C_{17}H_{19}FN_2O_2$·CH_3SO_3H) C, H, F, N, S.

(*S*)-(+)-2-[[4-(2-Fluorobenzoxy)benzyl]amino]propanamide, methanesulfonate (56): 60%; ^{1}H NMR (200 MHz,

DMSO-d_6) 1.39 (d, J = 6.9 Hz, 3H, CH_3CH), 2.30 (s, 3H, CH_3SO_3-), 3.71 (q, J = 6.9 Hz, 1H, CHCH$_3$), 4.01 (m, 2H, ArCH_2NH), 5.15 (s, 2H, ArCH_2O), 7.08 (m, 2H, H3, H5), 7.1−7.6 (m, 6H, H3′, H4′, H5′, H6′, H2, H6), 7.63,7.89 (2 s, 2H, CONH$_2$), 9.0 (br s, 2H, NH_2^+); MS *m*/*z* 302 ($M^{\bullet+}$), 258, 230, 215, 109 (100). Anal. ($C_{17}H_{19}FN_2O_2 \cdot CH_3SO_3H$) C, H, F, N, S.

(*S*)-(+)-2-[[4-(3-Fluorobenzoxy)benzyl]amino]propanamide, methanesulfonate (57): 45%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.39 (d, J = 6.8 Hz, 3H, CH_3CH), 2.29 (s, 3H, CH_3SO_3-), 3.70 (q, J = 6.8 Hz, 1H, CHCH$_3$), 4.01 (s, 2H, ArCH_2NH), 5.15 (s, 2H, ArCH_2O), 7.06 (m, 2H, H3, H5), 7.1−7.4 (m, 4H, H2′, H4′, H5′, H6′), 7.39 (m, 2H, H2, H6), 7.60, 7.86 (2 s, 2H, CONH$_2$), 8.96 (br s, 2H, NH_2^+); MS *m*/*z* 302 ($M^{\bullet+}$), 258, 230, 215, 109 (100). Anal. ($C_{17}H_{19}FN_2O_2 \cdot CH_3SO_3H$) C, H, F, N, S.

(*S*)-(+)-2-[[4-(3-Methoxybenzoxy)benzyl]amino]-3-hydroxy-*N*-methylpropanamide (58): 21%; ^{1}H NMR (200 MHz, DMSO-d_6) 2.4 (br s, 1H, ArCH$_2$*NH*), 2.59 (d, J = 4.8 Hz, 3H, CONHCH_3), 2.97 (t, J = 5.4 Hz, 1H, CHCH$_2$OH), 3.3−3.7 (m, 4H, ArCH_2NH, CHCH_2OH), 3.74 (s, 3H, OCH_3), 4.72 (t, J = 5.7, 1H, CH$_2$*OH*), 5.04 (s, 2H, ArCH_2O), 6.8−7.4 (8H, aromatics), 7.76 (q, J = 4.8 Hz, 1H, CO*NH*CH$_3$); MS *m*/*z* 286 ($M^{\bullet+}$), 242, 227, 121 (100). Anal. ($C_{19}H_{24}N_2O_4$) H, N; C: calcd, 66.23; found, 65.43.

(*S*)-(+)-2-[[4-(3-Nitrobenzoxy)benzyl]amino]-3-hydroxy-*N*-methylpropanamide (59): 20%; ^{1}H NMR (200 MHz, DMSO-d_6) 2.58 (d, J = 4.8 Hz, 3H, CONHCH_3), 2.98 (t, J = 5.5 Hz, 1H, CHCH$_2$OH), 3.3−3.7 (m, 4H, ArCH_2NH, CHCH_2-OH), 4.73 (t, J = 5.7 Hz, 1H, CHCH$_2$*OH*), 5.24 (s, 2H, ArCH_2O), 6.96 (m, 2H, H3, H5), 7.26 (m, 2H, H2, H6), 7.68 (t, J = 7.9 Hz, 1H, H5′), 7.77 (q, J = 4.8 Hz, 1H, CO*NH*CH$_3$), 7.89 (dd, J = 7.9, 1.9 Hz, 1H, H6′), 8.17 (dd, J = 7.9, 1.9 Hz, 1H, H4′), 8.29 (t, J = 1.9 Hz, 1H, H2′); MS *m*/*z* 359 ($M^{\bullet+}$), 301, 257, 242, 136 (100). Anal. ($C_{18}H_{21}N_3O_5$) H, N; C: calcd, 60.15; found, 59.49.

(*S*)-(+)-2-[[4-(3-Cyanobenzoxy)benzyl]amino]-3-hydroxy-*N*-methylpropanamide (60): 45%; ^{1}H NMR (200 MHz, DMSO-d_6) 2.3 (br s, 1H, CH$_2$*NH*), 2.58 (d, J = 4.8 Hz, 3H, CONHCH_3), 2.97 (t, J = 5.6 Hz, 1H, CHCH$_2$OH), 3.3−3.7 (m, 4H, ArCH_2NH, CHCH_2OH), 4.73 (t, J = 5.7 Hz, 1H, CHCH$_2$*OH*), 5.14 (s, 2H, ArCH_2O), 6.94 (m, 2H, H3, H5), 7.25 (m, 2H, H2, H6), 7.59 (t, J = 7.7 Hz, 1H, H5′), 7.7−8.0 (m, 4H, H2′, H4′, H6′, CO*NH*CH$_3$); MS *m*/*z* 339 ($M^{\bullet+}$), 281, 237, 222, 116 (100). Anal. ($C_{19}H_{21}N_3O_3$) H, N; C: calcd, 67.24; found, 66.13.

(*S*)-(+)-2-[[4-(4-Chlorobenzoxy)benzyl]amino]-3-hydroxy-*N*-methylpropanamide (61): 71%; ^{1}H NMR (200 MHz, DMSO-d_6) 2.3 (br s, 3H, ArCH$_2$*NH*), 2.59 (d, J = 4.8 Hz, 3H, CONHCH_3), 2.97 (t, J = 5.6 Hz, 1H, CHCH$_2$OH), 3.3−3.7 (m, 4H, ArCH_2NH, CHCH_2OH), 4.73 (t, J = 5.7, 1H, CH$_2$*OH*), 5.07 (s, 2H, ArCH_2O), 6.92 (m, 2H, H3, H5), 7.24 (m, 2H, H2, H6), 7.44 (s, 4H, H2′, H3′, H5′, H6′), 7.78 (q, J = 4.8 Hz, 1H, CO*NH*CH$_3$); MS *m*/*z* 348 ($M^{\bullet+}$), 290, 246, 231, 125 (100). Anal. ($C_{18}H_{21}ClN_2O_3$) C, H, Cl, N.

(*S*)-(+)-2-[[4-(3-Methylbenzoxy)benzyl]amino]-3-hydroxy-*N*-methylpropanamide, methanesulfonate (62): 63%; ^{1}H NMR (80 MHz, DMSO-d_6) 2.3 (s, 6H, CH_3SO_3-, CH_3-Ar), 2.65 (d, J = 4.6 Hz, 3H, CONHCH_3), 3.5−3.9 (m, 3H, $CHCH_2$OH), 4.05 (s, 2H, ArCH_2NH), 5.1 (s, 2H, ArCH_2O), 6.9−7.5 (m, 9H, aromatics), 8.33 (q, J = 4.6 Hz, 1H, CO*NH*CH$_3$), 9.0 (br s, 2H, NH_2^+); MS *m*/*z* 328 ($M^{\bullet+}$), 270, 226, 211, 105 (100). Anal. ($C_{19}H_{24}N_2O_3 \cdot CH_3SO_3H$) C, H, N, S.

(*S*)-(+)-2-[[4-[3-(Trifluoromethyl)benzoxy]benzyl]-amino]-3-hydroxy-*N*-methylpropanamide, methanesulfonate (63): 13%; ^{1}H NMR (200 MHz, DMSO-d_6) 2.3 (s, 3H, CH_3SO_3-), 2.64 (d, J = 4.6 Hz, 3H, CONHCH_3), 3.5−3.8 (m, 3H, $CHCH_2$OH), 4.03 (s, 2H, ArCH_2NH), 5.23 (s, 2H, ArCH_2O), 5.48 (t, J = 4.8 Hz, 1H, CH$_2$*OH*), 7.07 (m, 2H, H3, H5), 7.39 (m, 2H, H2, H6), 7.5−7.9 (m, 4H, H2′, H4′, H5′, H6′), 8.34 (q, J = 4.8 Hz, 1H, CO*NH*CH$_3$), 9.0 (br s, 2H, NH_2^+); MS *m*/*z* 382 ($M^{\bullet+}$), 324, 280, 265, 159 (100). Anal. ($C_{19}H_{21}F_3N_2O_3 \cdot CH_3SO_3H$) C, H, F, N, S.

(*S*)-(+)-2-[[4-[2-(Trifluoromethyl)benzoxy]benzyl]amino]-3-hydroxy-*N*-methylpropanamide, methanesulfonate (64): 45%; ^{1}H NMR (200 MHz, DMSO-d_6) 2.3 (s, 3H, CH_3SO_3-), 2.64 (d, J = 4.6 Hz, 3H, CONHCH_3), 3.5−3.8 (m, 3H, $CHCH_2$OH), 4.04 (s, 2H, ArCH_2NH), 5.23 (s, 2H, ArCH_2O), 5.48 (t, J = 4.9 Hz, 1H, CH$_2$*OH*), 7.04 (m, 2H, H3, H5), 7.4 (m, 2H, H2, H6), 7.5−7.9 (m, 4H, H3′, H4′, H5′, H6′), 8.34 (q, J = 4.6 Hz, 1H, CO*NH*CH$_3$), 9.0 (br s, 2H, NH_2^+); MS *m*/*z* 382 ($M^{\bullet+}$), 324, 280, 265, 159 (100). Anal. ($C_{19}H_{21}F_3N_2O_3 \cdot CH_3SO_3H \cdot 0.37H_2O$) C, H, F, N, S, H_2O.

(*S*)-(+)-2-[[4-(2-Fluorobenzoxy)benzyl]amino]-3-hydroxy-*N*-methylpropanamide, methanesulfonate (65): 56%; ^{1}H NMR (200 MHz, DMSO-d_6) 2.3 (s, 3H, CH_3SO_3-), 2.64 (d, J = 4.6 Hz, 3H, CONHCH_3), 3.5−3.8 (m, 3H, $CHCH_2$OH), 4.05 (s, 2H, ArCH_2NH), 5.14 (s, 2H, ArCH_2O), 5.5 (br s, 1H, CH$_2$*OH*), 7.0−7.6 (m, 9H, aromatics), 8.34 (q, J = 4.6 Hz, 1H, CO*NH*CH$_3$), 9.1 (br s, 2H, NH_2^+); MS *m*/*z* 332 ($M^{\bullet+}$), 274, 230, 215, 109 (100). Anal. ($C_{18}H_{21}FN_2O_3 \cdot CH_3SO_3H$) C, H, F, N, S.

(*S*)-(+)-2-[[4-(3-Fluorobenzoxy)benzyl]amino]-3-hydroxy-*N*-methylpropanamide, methanesulfonate (66): 61%; ^{1}H NMR (200 MHz, DMSO): 2.3 (s, 3H, CH_3SO_3H), 2.64 (d, J = 4.6 Hz, 3H, CONHCH_3), 3.5−3.8 (m, 3H, $CHCH_2$OH), 4.03 (s, 2H, ArCH_2NH), 5.15 (s, 2H, ArCH_2O), 5.45 (t, J = 5.0 Hz, 1H, CH$_2$*OH*), 7.0−7.5 (m, 9H, aromatics), 8.33 (q, J = 4.6 Hz, 1H, CO*NH*CH$_3$), 8.9 (br s, 2H, NH_2^+); MS *m*/*z* 332 ($M^{\bullet+}$), 274, 230, 215, 109 (100). Anal. ($C_{18}H_{21}FN_2O_3 \cdot CH_3SO_3H$) C, H, F, N, S.

(*S*)-(+)-2-[[4-(2-Pyridylmethoxy)benzyl]amino]propanamide (67): 65%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.1 (d, J = 6.7 Hz, 3H, CH_3CH), 2.97 (q, J = 6.7 Hz, 1H, CH$_3$*CH*), 3.44, 3.58 (2 d, J = 13.3 Hz, 2H, ArCH_2NH), 5.14 (s, 2H, CH$_2$O), 6.94 (m, 3H, CONH$_A$, H3, H5), 7.22 (m, 2H, H2, H6), 7.3 (m, 2H, CONH$_B$, H5′), 7.48 (d, J = 7.8 Hz, 1H, H3′), 7.81 (ddd, J = 7.8, 7.8, 1.9 Hz, 1H, H4′), 8.56 (dd, J = 4.8, 1.9 Hz, 1H, H5′); MS *m*/*z* 285 ($M^{\bullet+}$), 241, 213, 198 (100), 92. Anal. ($C_{16}H_{19}N_3O_2$) H, N; C: calcd, 67.35; found, 65.94.

(*S*)-(+)-2-[[4-(3-Pyridylmethoxy)benzyl]amino]propanamide (68): 12%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.1 (d, J = 6.9 Hz, 3H, CH_3CH), 2.3 (br s, 1H, ArCH$_2$*NH*), 2.98 (q, J = 6.9 Hz, 1H, CH$_3$*CH*), 3.45, 3.59 (2 d, J = 13.2 Hz, 2H, ArCH_2-NH), 5.12 (s, 2H, CH$_2$O), 6.9, 7.3 (2 br s, 2H, CONH$_2$), 6.95 (m, 2H, H3, H5), 7.23 (m, 2H, H2, H6), 7.41 (ddd, J = 7.9, 4.9, 0.9 Hz, 1H, H5′), 7.85 (ddd, J = 7.9, 1.9, 1.9 Hz, 1H, H4′), 8.53 (dd, J = 4.9, 1.9 Hz, 1H, H6′), 8.65 (dd, J = 1.9, 0.9 Hz, 1H, H2′); MS *m*/*z* 285 ($M^{\bullet+}$), 241, 213, 198 (100), 92. Anal. ($C_{16}H_{19}N_3O_2$) C, H, N.

(*S*)-(+)-2-[[4-(4-Pyridylmethoxy)benzyl]amino]propanamide (69): 46%; ^{1}H NMR (200 MHz, $CDCl_3$) 1.32 (d, J = 7.0 Hz, 3H, CH_3CH), 3.22 (q, J = 7.0 Hz, 1H, CH$_3$*CH*), 3.65, 3.73 (2 d, J = 13.0 Hz, 2H, ArCH_2NH), 5.07 (s, 2H, CH$_2$O), 5.4, 7.0 (2 br s, 2H, CONH$_2$), 6.89 (m, 2H, H3, H5), 7.20 (m, 2H, H2, H6), 7.32 (m, 2H, H3′, H5′), 8.58 (m, 2H, H2′, H6′); MS *m*/*z* 285 ($M^{\bullet+}$), 241, 213, 198 (100), 92. Anal. ($C_{16}H_{19}N_3O_2$) C, H, N.

(*S*)-(+)-2-[[4-(3-Thienyloxy)benzyl]amino]propanamide, methanesulfonate (71): 52%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.40 (d, J = 7.0 Hz, 3H, CH_3CH), 2.3 (s, 3H, CH_3SO_3-), 3.72 (q, J = 7.0 Hz, 1H, CH$_3$*CH*), 4.0 (s, 2H, ArCH_2-NH), 5.11 (s, 2H, ArCH_2O), 7.05 (m, 2H, H3, H5), 7.16 (dd, J = 1.6, 4.8 Hz, 1H, H4′), 7.38 (m, 2H, H2, H6), 7.55 (m, 2H, H2′, H5′), 7.62, 7.89 (2 s, 2H, CONH$_2$), 9.0 (br s, 2H, NH_2^+); MS *m*/*z* 290 ($M^{\bullet+}$), 246, 218, 203, 97 (100). Anal. ($C_{15}H_{18}N_2O_2S \cdot CH_3SO_3H$) C, H, N, S.

(*S*)-(+)-2-[[4-(2-Furfuryloxy)benzyl]amino]propanamide, methanesulfonate (72): 52%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.39 (d, J = 7.0 Hz, 3H, CH_3CH), 2.30 (s, 3H, CH_3SO_3-), 3.69 (q, J = 7.0 Hz, 1H, CH$_3$*CH*), 4.0 (s, 2H, ArCH_2-NH), 5.07 (s, 2H, ArCH_2O), 6.46 (dd, J = 1.9, 3.3 Hz, 1H, H4′), 6.59 (dd, J = 3.3, 0.8 Hz, 1H, H3′), 7.07 (m, 2H, H3, H5), 7.39 (m, 2H, H2, H6), 7.6, 7.87 (2 s, 2H, CONH$_2$), 7.68 (dd, J = 1.9, 0.8 Hz, 1H, H5′), 8.9 (br s, 2H, NH_2^+); MS *m*/*z* 274 ($M^{\bullet+}$), 230, 202, 187, 81 (100). Anal. ($C_{15}H_{18}N_2O_3 \cdot CH_3SO_3H$) C, H, N, S.

(*S*)-(+)-2-[[4-(3-Furfuryloxy)benzyl]amino]propanamide, methanesulfonate (73): 36%; ^{1}H NMR (200 MHz, DMSO-d_6) 1.39 (d, J = 7.0 Hz, 3H, CH_3CH), 2.30 (s, 3H, CH_3SO_3-), 3.69 (q, J = 7.0 Hz, 1H, CH$_3$*CH*), 4.0 (s, 2H, ArCH_2-

NH), 4.98 (s, 2H, ArCH_2O), 6.55 (d, J = 2.1 Hz, 1H, H4′), 7.04 (m, 2H, H3, H5), 7.38 (m, 2H, H2, H6), 7.6, 7.87 (2 s, 2H, $CONH_2$), 7.66, 7.78 (2 m, 2H, H2′, H5′), 8.9 (br s, 2H, NH_2^+); MS *m*/*z* 274 ($M^{\bullet+}$), 230, 202, 187, 81 (100). Anal. ($C_{15}H_{18}N_2O_3 \cdot CH_3SO_3H$) C, H, N, S.

(*S*)-(+)-2-[[4-(Cyclopropylmethoxy)benzyl]amino]-propanamide (74): 37%; ^{1}H NMR (200 MHz, $CDCl_3$) 0.2−1.4 (m, 5H, cyclopropyl), 1.31 (d, J = 6.9 Hz, 3H, CH_3CH), 3.21 (q, J = 6.9 Hz, 1H, CH_3CH), 3.63, 3.7 (2 d, J = 12.9 Hz, 2H, ArCH_2NH), 3.77 (d, J = 7.0 Hz, CH_2O), 5.5, 7.1 (2 br s, 2H, $CONH_2$), 6.84 (m, 2H, H3, H5), 7.17 (m, 2H, H2, H6); MS *m*/*z* 248 ($M^{\bullet+}$), 204, 176, 161, 107 (100). Anal. ($C_{14}H_{20}N_2O_2$) H, N; C: calcd, 67.78; found, 67.26.

(*S*)-(+)-2-[[4-(Cyclohexylmethoxy)benzyl]amino]propanamide, methanesulfonate (75): 33%; ^{1}H NMR (200 MHz, DMSO-d_6) 0.9−1.9 (m, 11H, cyclohexyl), 1.39 (d, J = 6.9 Hz, 3H, CH_3CH), 2.3 (s, 3H, CH_3SO_3-), 3.68 (q, J = 6.9 Hz, 1H, CH_3CH), 3.78 (d, J = 6.1 Hz, 2H, OCH_2), 4.0 (s, 2H, ArCH_2-NH), 6.96 (m, 2H, H3, H5), 7.36 (m, 2H, H2, H6), 7.6, 7.87 (2 s, 2H, $CONH_2$), 8.95 (br s, 2H, NH_2^+); MS *m*/*z* 290 ($M^{\bullet+}$), 246, 218, 203, 107 (100). Anal. ($C_{17}H_{26}N_2O_2 \cdot CH_3SO_3H$) C, H, N, S.

Method B (Scheme 2): Alkylations with 2-Chloroacetamide. A portion of 17.5 g (0.065 mol) of 4-(2-chlorobenzoxy)aniline hydrochloride was mixed with 13.6 g (0.162 mol) of sodium bicarbonate (0.162 mol) and 6.06 g (0.065 mol) of 2-chloroacetamide in anhydrous ethanol (300 mL). The mixture was refluxed for 40 h, filtered, and evaporated. The crude residue was taken up with water, extracted with ethyl acetate (4 × 40 mL), washed with brine, evaporated, and treated with the stoichiometric amount of 2 N HCl; the crude hydrochloride was recrystallized from anhydrous ethanol (9.1 g, 41%) to give **2-[[4-(3-chlorobenzoxy)phenyl]amino]acetamide, hydrochloride (13):** ^{1}H NMR (80 MHz, DMSO-d_6) 3.87 (s, 2H, NHCH_2CO), 5.1 (s, 2H, ArCH_2O), 7.0 (m, 2H, H3, H5), 7.26 (m, 2H, H2, H6), 7.2−7.9 (m, 6H, $CONH_2$, H2′, H4′, H5′, H6′); MS *m*/*z* 290 ($M^{\bullet+}$), 246, 165 (100). Anal. ($C_{15}H_{15}ClN_2O_2 \cdot HCl$) C, H, Cl, N.

To a solution of 4-(3-chlorobenzoxy)benzyl alcohol (15 g, 0.0603 mol) in anhydrous THF (120 mL) was added 0.9 g (0.00243 mol) of tetrabutylammonium iodide at room temperature. To the stirred mixture was added 2.41 g (0.0603 mol) of 60% sodium hydride portionwise. After stirring for 1 h at room temperature, 7.5 g (0.080 mol) of 2-chloraacetamide in anhydrous THF (20 mL) was added. The mixture was heated at 50 °C for 18 h and then treated with an excess of 0.1 N HCl (50 mL), the THF was evaporated, and the aqueous suspension was extracted with ethyl acetate (3 × 40 mL), washed with brine, and evaporated. The crude residue was chromatographed on silica gel (CH_2Cl_2−CH_3OH−30% NH_4OH, 170:30:2) to afford 13.9 g (67%) of **2-[4-(3-chlorobenzoxy)benzoxy]acetamide, hydrochloride (14)**: ^{1}H NMR (200 MHz, $CDCl_3$) 3.96 (s, 2H, OCH_2CONH_2), 4.51 (s, 2H, ArCH_2OCH_2-$CONH_2$), 5.04 (s, 2H, ArCH_2OAr), 5.6, 6.5 (2 br s, 2H, $CONH_2$), 6.94 (m, 2H, H3, H5), 7.2−7.5 (m, 6H, H2, H6, H2′, H4′, H5′, H6′); MS *m*/*z* 305 ($M^{\bullet+}$), 247, 125 (100). Anal. **(**$C_{17}H_{19}ClN_2O_2$) C, H, Cl, N.

2-[[4-(3-Chlorobenzoxy)benzyl]amino]-*N*,*N*-dimethylacetamide, Hydrochloride (8). Ethyl ester **11** (3 g, 8.99 mmol) was dissolved in diethylamine (70 mL), and the mixture was heated at 60 °C for 7 h. After standing overnight at room temperature, the solution was evaporated and the residue chromatographed on silica gel ($CHCl_3$−CH_3OH−30% NH_4H, 98:2:0.2) to give 0.7 g (22%) of a colorless fluid which was transformed into its hydrochloride salt: ^{1}H NMR (200 MHz, DMSO-d_6) 2.86, 2.89 (2 s, 6H, $N(CH_3)_2$), 3.9−4.1 (m, 4H, CH_2-NHCH_2CO), 5.15 (s, 2H, ArCH_2O), 7.04 (m, 2H, H3, H5), 7.3−7.6 (m, 6H, H2, H6, H2′, H4′, H5′, H6′), 9.3 (br s, 2H, NH_2^+); MS *m*/*z* 332 ($M^{\bullet+}$), 260, 246, 231, 125 (100%). Anal. ($C_{18}H_{21}$-$ClN_2O_2 \cdot HCl$) H, Cl, N; C: calcd, 57.74; found, 57.07.

2-[4-(3-Chlorobenzoxy)benzamido]acetamide (17). A solution of 4-(3-chlorobenzoxy)benzoic acid (13.5 g, 0.05 mol) was dissolved in anhydrous DMF (250 mL). To this solution was added 10.83 g (0.0668 mol) of carbonyldiimidazole (CDI) portionwise. Stirring was maintained for 1 h; then glycinamide (5.68 g, 0.0766 mol) and triethylamine (7.22 mL, 5.24 g, 0.052 mol) were added. The mixture was kept at room temperature for 24 h and then taken up with water; a bright solid precipitated and was filtered and recrystallized from 90% ethanol to afford 4.15 g (26%) of **17**: ^{1}H NMR (200 MHz, DMSO-d_6) 3.77 (d, J = 5.9 Hz, 2H, CONHCH_2), 5.18 (s, 2H, ArCH_2O), 7.0, 7.33 (2 s, 2H, $CONH_2$), 7.07 (m, 2H, H3, H5), 7.3−7.6 (m, 4H, H2′, H4′, H5′, H6′), 7.84 (m, 2H, H2, H6), 8.52 (t, J = 5.9 Hz, 1H, CONHCH$_2$); MS *m*/*z* 318 ($M^{\bullet+}$), 244, 125 (100). Anal. ($C_{16}H_{15}ClN_2O_3$) C, H, Cl, N.

2-[[4-(3-Chlorobenzoxy)benzyl]methylamino]acetamide, Hydrochloride (18). The amino amide **6** (2 g, 6.56 mmol) was dissolved in methanol (30 mL) in a flask fitted with an outlet device connected to a ferrous sulfate solution. To the stirred mixture was added 0.33 g (5.24 mmol) of sodium cyanoborohydride in a single portion. Stirring was continued for 15 min at room temperature; then 1 mL (13 mmol) of 40% aqueous formaldehyde was dropped while maintaining the temperature below 30 °C. After 1 h the mixture was evaporated, taken up with dichloromethane, and flash-chromatographed on silica gel using dichloromethane−methanol (99:1) as eluent. The tertiary amine **18** was obtained as a white solid (42%): ^{1}H NMR (200 MHz, $CDCl_3$) 2.28 (s, 3H, NCH_3), 3.01 (s, 2H, NCH_2CO), 3.51 (s, 2H, ArCH_2N), 5.02 (s, 2H, ArCH_2O), 5.8, 7.0 (2 br s, 2H, $CONH_2$), 6.91 (m, 2H, H3, H5), 7.1−7.5 (m, 6H, H2, H6, H2′,H4′, H5′, H6′); MS *m*/*z* 318 ($M^{\bullet+}$), 260, 246, 231, 125 (100). Anal. ($C_{17}H_{19}ClN_2O_2$) C, H, N, Cl.

Biological Testing. Maximal Electroshock Test (MES): Male Crl:CD-1(ICR)BR mice (Charles River, Italy) weighing between 19 and 21 g and male Crl:(WI)BR rats (Charles River, Italy) weighing between 190 and 210 g at time of testing were used. Animals were housed in groups of 10 and kept in a temperature (21 ± 1 °C-controlled) and relative humidity (60%)-controlled room on a 12-h light/dark cycle (lights on between 06:00 and 18:00 h). The procedure described by White et al.[18] was used. Briefly, an electrical stimulus sufficient to produce a hindlimb tonic extensor response in at least 97% of control animals was delivered using an Ugo Basile electroconvulsive generator (model ECT UNIT 7801). The stimulus was delivered intra-aurally through clip electrodes in both rats (0.2 s of a 160-mA shock, with a pulse train of 60 Hz having a pulse duration of 0.4 ms[19]) and mice (0.7 s of a 28-mA shock, with a pulse train of 80 Hz having a pulse duration of 0.4 ms[20]). The acute effects of compounds administered 60 min orally (po) or 30 min intraperitoneally (ip) before MES induction were examined. The volume of administration was 5 mL/kg. Complete suppression of the hindlimb tonic extensor component of seizures was taken as evidence of anticonvulsant activity. The ED_{50} of each compound (95% confidence interval) was calculated using Probit analysis.[21] Group sizes of 10−20 animals/dose were used.

Chemically Induced Seizures: For tonic extensor seizures, male Crl:CD-1(ICR)BR mice (Charles River, Italy) weighing between 22 and 24 g were used under the same experimental conditions as reported above. The doses of chemical convulsants used were those able to induce tonic extensor convulsions in at least 97% of vehicle-treated mice. These doses were bicuculline (BIC), 0.6 mg/kg intraventricularly (icv);[22] picrotoxin (PTX), 6 mg/kg subcutaneously (sc)[23] (with modifications, i.e., the hindlimb tonic extension was used as end point); 3-mercaptopropionic acid (3-MPA), 60 mg/kg (sc)[22] (with modifications, i.e., the hindlimb tonic extension was used as end point); strychnine (STRY), 0.55 mg/kg (iv)[24] (with modifications, i.e., the hindlimb tonic extension was used as end point). The compounds were orally administered to mice 60 min before either iv administration of BIC and STRY or subcutaneous injection of PTX and 3-MPA. Mice were treated with a dose of 85 mg/kg (sc) PTZ according to the method described by Löscher and Schmidt.[24] This dose of PTZ induces seizures in at least 97% of mice treated. Compounds were administered ip to mice 30 min before a sc administration of PTZ. Mice were individually housed and observed for the

presence of loss of righting reflexes lasting at least 3 s for the 30 min following treatment with the chemical convulsant. The volume of administration was 5 mL/kg. The ED_{50} of each compound (95% confidence interval) was calculated using Probit analysis.[21] Group sizes of 10−20 animals/dose were normally used.

Rotorod Test: Male Crl:CD-1(ICR)BR mice (Charles River, Italy) weighing between 22 and 24 g were used. Animals were housed in the same environmental conditions as reported above. The compounds were administered po to trained mice 60 min before being placed on an Ugo Basile rotorod (special model). This rotorod had a 3-cm diameter rod which rotated at 10 rpm. The number of animals falling over a 2-min test period was monitored.[25] The toxic dose causing 50% of treated animals to fall from the rotorod (TD_{50}) of each compound was calculated. This dose was combined with the effective dose of each anticonvulsant in each test necessary to protect 50% of the animals treated (ED_{50}) in order to calculate therapeutic indexes (TI) of each compound relative to the specific anticonvulsant test. The acute effects of compounds administered (po) 60 min before the test were examined. The volume of administration was 5 mL/kg. The ED_{50} of each compound (95% confidence interval) was calculated using Probit analysis.[21] Group sizes of 10−20 animals/dose were normally used.

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Registry Numbers: 4-(3-chlorobenzoxy)benzaldehyde (59067-43-5), 4-(2-chlorobenzoxy)benzaldehyde (70627-21-3), 4-(3-fluorobenzoxy)benzaldehyde (66472-57-2), 4-(2-fluorobenzoxy)benzaldehyde (70627-20-8), 4-(4-chlorobenzoxy)benzaldehyde (59067-46-8), 4-[3-(trifluoromethyl)benzoxy)benzaldehyde (70627-18-8), 4-(2-furfuryloxy)benzaldehyde (149806-87-1), 4-(phenylcarbamoyl)benzaldehyde (65854-93-5), 4-benzylbenzaldehyde (67468-65-9), 3-benzoxybenzaldehyde (1700-37-4), 2-benzoxybenzaldehyde (5896-17-3), 4-[(phenylamino)benzyl]-benzaldehyde (BRN 3265597), 4-(3-chlorobenzoxy)-aniline, hydrochloride (130461-76-8), 4-(3-chlorobenzoxy)-benzyl alcohol (134561-23-2), 4-(3-chlorobenzoxy)benzoic acid (84403-70-3), L-alaninamide, hydrochloride (33208-99-0), L-serinamide, hydrochloride (65414-74-6), D-serinamide, hydrochloride (122702-20-9), L-serinamide, *N*-methyl, hydrochloride (90762-13-3), D-serinamide, *N*-methyl, hydrochloride (90762-14-4), L-leucinamide, *N*-methyl, hydrochloride (99145-71-8), D-leucinamide, *N*-methyl, hydrochloride (108131-54-0), L-valinamide, *N*-methyl, hydrochloride (87105-26-8), D-valinamide, *N*-methyl, hydrochloride (132204-10-5), L-threoninamide, *N*-methyl, hydrochloride (79009-37-3), L-methionine, *N*-methyl, hydrochloride (94847-37-7), (*S*)-2-aminobutanamide, hydrochloride (53726-14-0), (*R*)-2-aminobutanamide (73240-11-0), L-phenylalaninamide, *N*-methyl, hydrochloride (35373-92-3), D-phenylalaninamide, *N*-methyl, hydrochloride (144836-90-8).

Supporting Information Available: Synthesis, spectroscopic data, and physicochemical data for previously unreported aldehyde precursors (3 pages). Ordering information is given on any current masthead page.

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