Synthesis of Novel γ-Aminobutyric Acid (GABA) Uptake Inhibitors. 5.[1] Preparation and Structure−Activity Studies of Tricyclic Analogues of Known GABA Uptake Inhibitors

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On the basis of the SAR of a series of known γ-aminobutyric acid (GABA) uptake inhibitors, including **4** (SKF 89976), new tricyclic analogues have been prepared. These novel compounds are derivatives of nipecotic acid, guvacine, and homo-β-proline, substituted at the nitrogen of these amino acids by various lipophilic moieties such as (10,11-dihydro-5H-dibenz[*b*,*f*]azepin-5-yl)alkoxyalkyl or (10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ylidene)alkoxyalkyl. The in vitro values for inhibition of [^{3}H]-GABA uptake in rat synaptosomes was determined for each compound in this new series, and it was found that several of the novel compounds showed a high potency comparable with that of the reference compounds **4**, **5** (tiagabine), and **6** (CI-966). Several of the novel compounds were also evaluated for their ability in vivo to inhibit clonic seizures induced by a 15 mg/kg (ip) dose of methyl 6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate (DMCM). One compound, (*R*)-1-(2-(2-(10,11-dihydro-5H-dibenz[*b*,*f*]azepin-5-yl)-ethoxy)ethyl)-3-piperidinecarboxylic acid (**23**), was selected for further biological investigations and showed a protective index comparable to or slightly better than that of the recently launched anticonvulsant product **5** ((*R*)-1-(4,4-bis(3-methyl-2-thienyl)-3-butenyl)-3-piperidinecarboxylic acid).

Introduction

γ-Aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the mammalian central nervous system (CNS).[2−6] GABA has been estimated to be present in 60−70% of all synapses in the CNS.[7] A decrease in GABA′ergic neurotransmission appears to be involved in the etiology of several neurological disorders, including anxiety, pain, and epilepsy.[4,5,8−10] Thus, numerous investigations have focused on finding novel approaches to modulate GABA′ergic function in man. These approaches include direct agonism of the GABA receptors,[11,12] inhibition of enzymatic breakdown of GABA,[13,14] and inhibition of the uptake of GABA into neuronal and glial cell bodies.[5,15] It is well documented that GABA agonists are responsible for a number of unacceptable side effects in man.[16] However, in principle, GABA uptake inhibitors should exert a more therapeutically useful influence than GABA agonists on the GABA neurotransmission. This is because a major enhancement of GABA′ergic neurotransmission would only take place under conditions where GABA is already being released physiologically. GABA can be removed from the synapse by either a high-affinity sodium-dependent GABA uptake carrier into neuronal or glial cells or by diffusion from the synapse. The GABA uptake system has traditionally been classified as either neuronal or glial on the basis of pharmacological selectivity of cyclic amino acid GABA uptake inhibitors.[5] However, several investigators have recently cloned and sequenced subtypes of the GABA uptake carrier, and the selectivity of novel and hitherto known GABA uptake inhibitors on these subtypes has been investigated.[17,18] It was found that the type of GABA uptake inhibitors described in this paper is highly selective for the GAT-1 subtype.

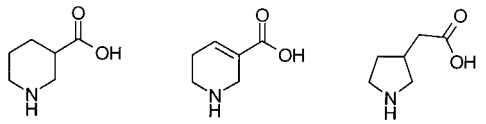

Figure 1. Three cyclic amino acids that act as GABA uptake inhibitors: nipecotic acid **1**, guvacine **2**, and homo-β-proline **3**.

Nipecotic acid **1**, guvacine **2**, and homo-β-proline **3**[19,20] (Figure 1), which can be considered as conformationally constrained GABA analogues,[21] display in vitro activity as inhibitors of [^{3}H]-GABA uptake. However, compounds **1**−**3** do not readily cross the blood brain barrier.[19,22,23] Recently, novel series of lipophilic GABA uptake inhibitors that possess potent activity in vitro and in vivo were described.[24−27] These compounds differ from compounds **1**−**3** in that they readily cross the blood brain barrier because of the attachment of a lipophilic anchor to the nitrogen atom in compounds **1**−**3**.

In the early 1980s such lipophilic derivatives of amino acids **1**−**3** were described for the first time. These compounds, an example of which is **4** (SKF 89976A, Figure 2), exhibited promising seizure protection[24,28,29] in several animal models predictive for anticonvulsant activity.[30] The compounds also displayed reduced CNS

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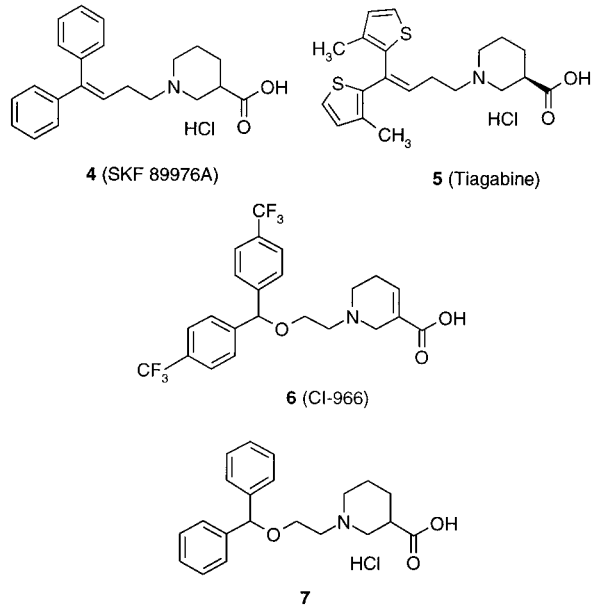


Figure 2. Lipophilic reference GABA uptake inhibitors.

depressant effects compared with some commonly used anticonvulsant drugs, such as diazepam.[31] These observations have also stimulated others to investigate this field,[32−40] leading to the discovery of a highly lipophilic GABA uptake inhibitor with CNS activity, **6** (CI-966). This compound was discovered at Parke-Davis/Warner-Lambert and has been investigated in a phase I clinical trial.[41] From our laboratory we have previously reported on the structure−activity studies, which have led to the identification of **5** (tiagabine, NO-328, NNC 05−0328) as an anticonvulsant drug candidate.[25−27,42,43] Extensive pharmacological[44,45] and clinical investigations have been completed on **5** with proven anticonvulsant efficacy in man.[46,47] This novel antiepileptic agent has now been launched for add-on therapy in the treatment of epilepsy.

With this new drug as a benchmark we have continuously searched for novel GABA uptake inhibitors with improved properties as second-generation compounds. This resulted in the synthesis of a series of novel and highly potent GABA uptake inhibitors of which **8**−**11** are examples[1,48−51] (Figure 3). In these compounds we applied the electronegative principle in the chain and thereby improved GABA uptake inhibition considerably compared to compounds such as **4**−**6**. In our continued search for novel GABA uptake inhibitors with improved biological properties, we have investigated other structural features around these reference compounds. We have transformed the diaryl moieties of the reference compounds, listed in Figures 2 and 3, into various tricyclic ring systems to give a series of new GABA uptake inhibitors. The synthesis[52] and biological activity of this series of GABA uptake inhibitors **16**−**38** (Table 1) will now be reported.

Only a few examples of similar tricyclic derivatives of the amino acids **1**−**3** have been reported previously, all without significant affinity for the GABA uptake site. These examples (**12**,[42] **13**,[53] **14**,[34] and **15**[32]) are listed in Figure 4. Recently, several tricyclic antidepressants have been evaluated for their affinity for three GABA transporter subtypes.[54] Among these tricyclic antidepressants, Amitriptyline and Desipramine showed

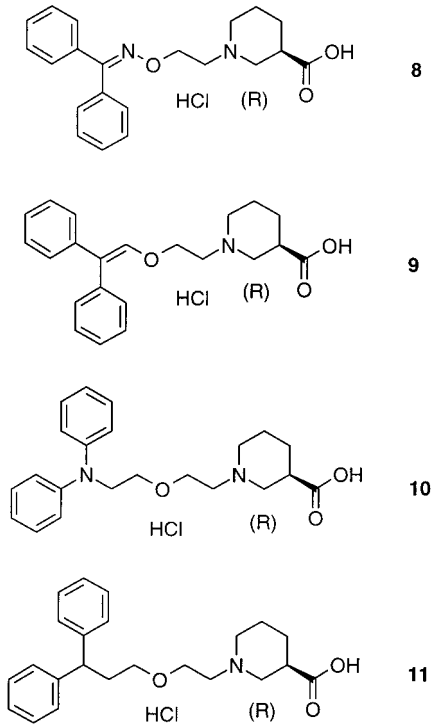


Figure 3. Potent GABA uptake inhibitors with an electronegative moiety introduced in the chain.

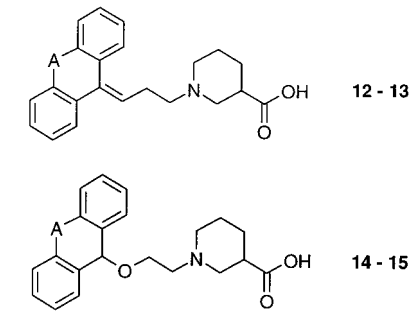


Figure 4. Known tricyclic derivatives of nipecotic acid **1** that does not possess any significant affinity for the GABA uptake site: A = bond (**12**, **14**), $-CH_2CH_2-$ (**13**), $-CH=CH-$ (**15**).

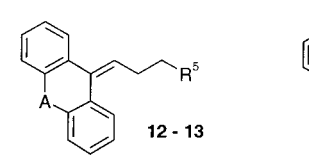
modest activity on the various subtypes of the GABA uptake site.

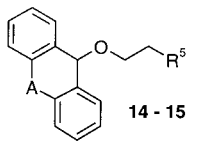
Chemistry

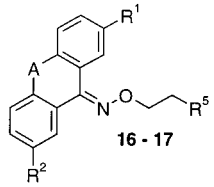
The overall general strategy used for synthesis of the new compounds presented in Table 1 was via N-alkylation of the parent cyclic amino acid **1**, **2**,[55] or **3**,[20] with the appropriate halogenide (Schemes 2 and 3, method B[1]) or mesylate/tosylate (Schemes 3 and 4, methods B[2] and B[3]). An exception to this general strategy is the synthesis of the tricyclic oxime ethers **16** and **17** (Scheme 1) in which the amino acid is introduced by O-alkylation of the corresponding 10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-one oximes[56] with (*R*)-1-(2-bromoethyl)-3-piperidinecarboxylic acid ethyl ester[50] (method A[1]).

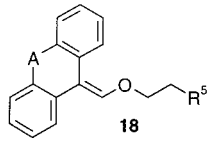
In the O- and N-alkylation reactions the cyclic amino acids were protected as their ester derivatives. The separate enantiomers of **1** could be prepared by the published procedure involving resolution with either L-(+)- or D-(−)-tartaric acid, giving (*R*)- or (*S*)-ethyl nipecotate, respectively.[57,58]

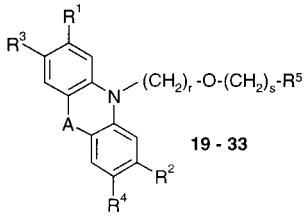
Table 1. Chemical and Biological Data

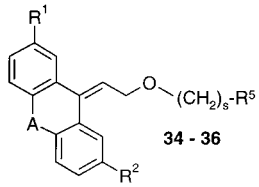


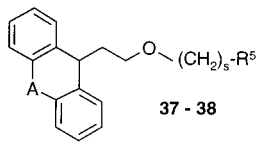












no.	r	s	A	R^1	R^2	R^3	R^4	R^5 [a]	method for synthesis	mp (°C)	formula	micro-analyses[b]	GABA uptake IC_{50} (nM)[c]
4													330
7									*d*,*e*				1370
8									*f*				82
9									*f*				87
10									*g*				90
11									*g*				55
12			bond					(*R*)-N	*d*				2018
13			CH_2CH_2					N	*h*				13600
14			bond					N	*e*				NA[e]
15			CH=CH					N	*i*				2500[i]
16			CH_2CH_2	H	H			(*R*)-N	A^1C	229230[j]	$C_{23}H_{26}N_2O_3$,HCl	C,H,N,Cl	1161
17			CH_2CH_2	Cl	Cl			(*R*)-N	A^1C	143144[j]	$C_{23}H_{24}Cl_2N_2O_3$,HCl	C,H,N	5509
18			CH_2CH_2					(*R*)-N	A^2B^1C	157160[l]	$C_{24}H_{27}NO_3$,HCl,0.25H_2O	C,H,N	2177
19	2	2	bond	H	H	H	H	(*R*)-N	A^3B^1C	175177[j]	$C_{22}H_{26}N_2O_3$,HCl,0.25H_2O	C,H,N,Cl	>40000
20	2	2	O	H	H	H	H	(*R*)-N	A^5B^2C	161164[j]	$C_{22}H_{27}N_2O_4$,HCl	C,H,N	14600
21	2	2	S	H	H	H	H	(*R*)-N	A^5B^2C	188189[k]	$C_{22}H_{27}N_2O_4$,HCl	C,H,N	308
22	2	2	S	CF_3	H	H	H	(*S*)-N	A^5B^2C	amorph	$C_{23}H_{26}F_3N_2O_3S$,HCl	C,H,N	105
23	2	2	CH_2CH_2	H	H	H	H	(*R*)-N	A^3B^1C	185186[j]	$C_{24}H_{30}N_2O_3$,HCl	C,H,N	184
24	2	2	CH_2CH_2	H	H	H	H	GUV	A^3B^1C	amorph	$C_{24}H_{28}N_2O_3$,HCl,H_2O	C,H,N	644
25	2	2	CH_2CH_2	H	H	H	H	HOM	A^3B^1C	amorph	$C_{24}H_{30}N_2O_3$,HCl	C,H,N	51
26	2	2	CH=CH	H	H	H	H	(*R*)-N	A^4B^2C	169[j]	$C_{24}H_{28}N_2O_3$,HCl	C,H,N,Cl	647
27	2	2	CH_2CH_2	Cl	H	H	H	(*R*)-N	A^4B^2C	amorph	$C_{24}H_{29}ClN_2O_3$,HCl	C,H,N	74
28	2	2	CH_2CH_2	Cl	Cl	H	H	(*R*)-N	A^5B^2C	213214[j]	$C_{24}H_{29}Cl_2N_2O_3$,HCl	C,H,N	68
29	2	2	CH_2CH_2	F	H	H	H	(*R*)-N	A^4B^2C	amorph	$C_{24}H_{29}FN_2O_3$,HCl,C_3H_6O	C,H,N,Cl	265
30	2	2	CH_2CH_2	H	H	F	F	(*R*)-N	A^5B^2C	153155[j]	$C_{24}H_{28}F_2N_2O_3$,HCl,0.25H_2O	C,H,N	248
31	2	2	CH_2CH_2	H	H	Br	Br	(*R*)-N	A^5B^2C	163164[l]	$C_{24}H_{28}Br_2N_2O_3$,HCl	C,H,N	1031
32	3	2	CH_2CH_2	H	H	H	H	(*R*)-N	$A^6A^7B^3C$	130132[l]	$C_{25}H_{32}N_2O_3$,HCl	C,H,N	696
33	2	2	$CH_2CH_2CH_2$	H	H	H	H	(*R*)-N	A^5B^2C	204206[m]	$C_{25}H_{33}N_2O_3$,HCl	C,H,N,Cl	851
34		2	CH_2CH_2	H	H			(*R*)-N	A^8B^2C	157159[j]	$C_{25}H_{29}NO_3$,HCl	C,H,N	770
35		2	CH_2CH_2	Cl	H			(*R*)-N	A^8B^3C	amorph	$C_{25}H_{28}ClNO_3$,HCl,H_2O	C,H,N	2495
36		3	CH_2CH_2	H	H			(*R*)-N	A^8B^2C	7880[j]	$C_{26}H_{31}NO_3$,HCl,0.75H_2O	C,H,N,Cl	460
37		2	CH_2CH_2					(*R*)-N	$A^8B^2CD^2$	160161[j]	$C_{25}H_{31}NO_3$,HCl,0.5H_2O	C,H,N	561
38		2	CH_2CH_2					GUV	$A^8D^1B^2C$	154155[j]	$C_{25}H_{29}NO_3$,HCl	C,H,N,Cl	1202

[a] N represents nipecotic acid (see **1**); GUV represents guvacine (see **2**); HOM represents homo-β-proline (see **3**). All three are alkylated on nitrogen. [b] All compounds were analyzed for C, H, and N and are within ±0.4% of the theoretical values. [c] Inhibition of GABA uptake in synaptosomes: IC_{50} (nM) is the mean of two determinations. [d] Reference 42. [e] Reference 34. NA = no activity. [f] Reference 48. [g] Reference 1. [h] Reference 53. [i] Reference 32. [j] Compounds were crystallized from acetone. [k] Compounds were crystallized from CH_2Cl_2. [l] Compounds were crystallized from EtOAc/acetone. [m] Compounds were crystallized from 2-propanol.

The N-alkylated amino acid ester derivatives were saponified under basic conditions (Schemes 1−4, method C) to provide the free N-alkylated amino acids, shown in Table 1, generally isolated as their crystalline hydrochloride salts.

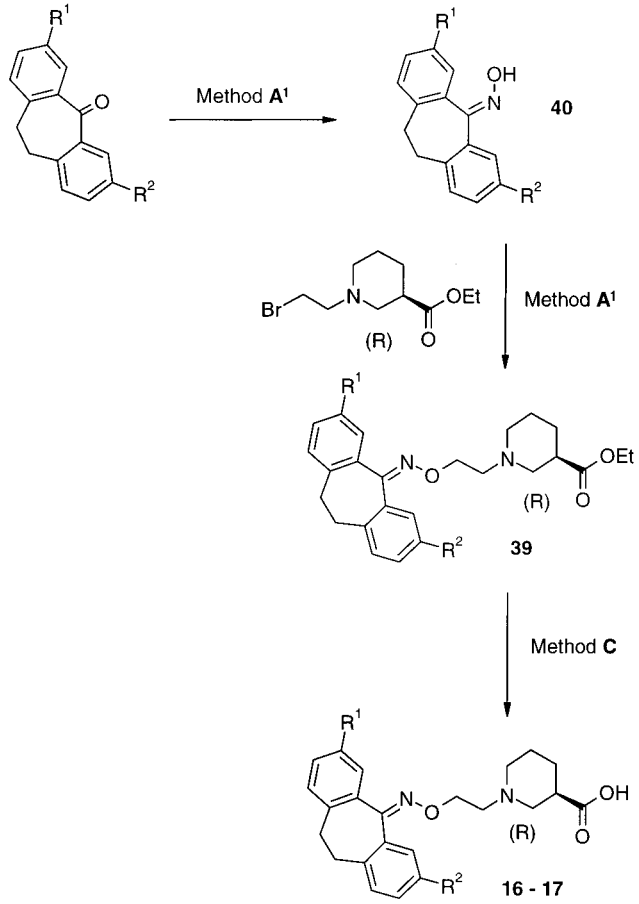
Preparation of the various halides, mesylates, or tosylates of the tricyclic derivatives used are further illustrated in Schemes 2−4.

The vinyl ether derivative **18** (Scheme 2) was prepared from 10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene-5-carboxaldehyde[59] under phase-transfer conditions. The enolate of this aldehyde was O-alkylated with 1,2-dibromoethane in a mixture of CH_2Cl_2 and 12 N NaOH, using 10% tetrabutylammonium bromide as the phase-transfer catalyst to give the bromo derivative **41** (method A^2). Further reaction of **41** by general methods B^1 and C provided the vinyl ether **18** (Table 1).

Starting from the appropriate azatricycle (i.e., 9H-carbazole, 10H-phenoxazine, 10H-phenothiazine, 5H-dibenz[*b*,*f*]azepine, 10,11-dihydro-5H-dibenz[*b*,*f*]azepine,[60−63] or 5,6,7,12-tetrahydrodibenz[*b*,*g*]azocine[64]), several different methods were used to assemble the desired intermediates for the final alkylation reactions in one or several steps (Scheme 3).

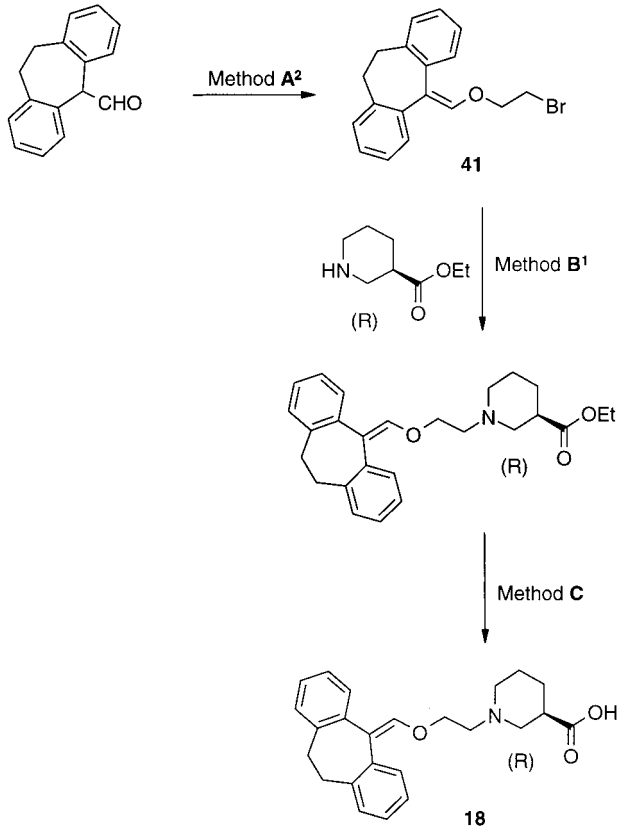
N-Alkylation of carbazole or 10,11-dihydro-5H-dibenz[*b*,*f*]azepine with 2,2′-dichlorodiethyl ether furnished the desired halogenides directly (method A^3). For this N-alkylation NaH was used in a high boiling solvent like

Scheme 1. Synthesis of (*R*)-1-(2-((10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ylidene)aminooxy)ethyl)-3-piperidinecarboxylic Acids **16** and **17**[a]



[a] R^1 and R^2; see Table 1. Method A^1: (1) NH_2OH,HCl, pyridine, reflux; (2) K_2CO_3, acetone, room temperature. Method C: (1) NaOH, EtOH, room temperature; (2) HCl.

Scheme 2. Synthesis of (*R*)-1-(2-((10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ylidene)methoxy)ethyl)-3-piperidinecarboxylic Acid **18**[a]

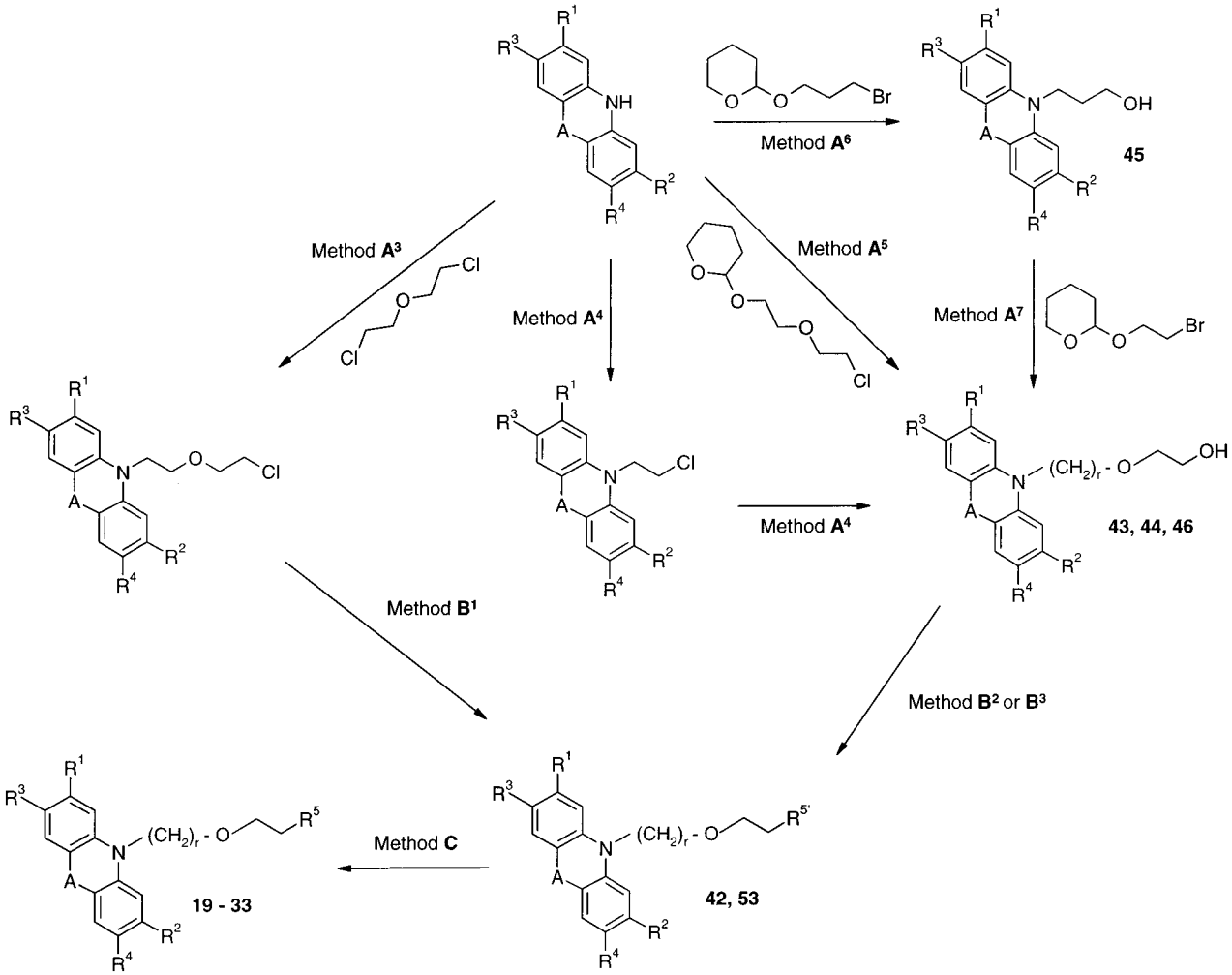


[a] Method A^2: TBAB, CH_2Cl_2, 1,2-dibromoethane, 12 M NaOH, room temperature. Method B^1: K_2CO_3, acetone, (*R*)-3-piperidinecarboxylic acid ethyl ester, reflux. Method C: (1) NaOH, EtOH, room temperature; (2) HCl.

dibutyl ether. A modification of this method is illustrated in method A^5 (Scheme 3) in which 2-(2-((tetrahydro-2-pyranyl)oxy)ethoxy)ethyl chloride[65] was used instead of 2,2′-dichlorodiethyl ether. This N-alkylation step under reaction conditions similar to those for method A^3 yielded the pyranyl ethers, which after hydrolysis in dilute mineral acid afforded the corresponding alcohols (i.e., **44**). Alternatively, two-step reaction sequences were used in which the alkoxyalkyl chain was built in successive alkylation steps as outlined in Scheme 3 (methods A^4, A^6, and A^7). N-Acylation of the appropriate azatricycle with chloroacetyl chloride gave the corresponding chloroacetamide derivatives (method A^4), which in a one-pot reaction were reduced with B_2H_6 in THF to give the *N*-(2-chloroethyl)azatricycles. The chlorides were transferred by reaction with the potassium salt of ethylene glycol in ethylene glycol at 150 °C to the *N*-(2-(2-hydroxyethoxy)ethyl)azatricycles (i.e., **43**). These alcohols were converted to the N-alkylated amino acid derivatives **26**−**27** and **29** (Table 1) via their mesylates by general methods B^2 and C described above. A second two-step reaction method applied to the alkoxyalkyl chains is outlined in Scheme 3 as methods A^6 and A^7. In this procedure, 10,11-dihydro-5H-dibenz[*b*,*f*]azepine was N-alkylated with 3-bromo-1-propyl tetrahydro-2-pyranyl ether,[65−67] using NaH in a high-boiling solvent like dibutyl ether. The resulting tetrahydropyranyl ether was hydrolyzed in dilute mineral acid, yielding the corresponding 3-(10,11-dihydro-5H-dibenz[*b*,*f*]azepin-5-yl)-1-propanol **45** (method A^6). This alcohol was O-alkylated with 2-bromoethyl tetrahydro-2-pyranyl ether[65−67] using NaH in a high-boiling solvent like dibutyl ether. The resulting tetrahydropyranyl ether was hydrolyzed in dilute mineral acid to give the desired 2-(3-(10,11-dihydro-5H-dibenz[*b*,*f*]-azepin-5-yl)-1-propoxy)ethanol **46** (method A^7). Further reaction of **46** via the mesylate by general methods B^3 and C described above gave the amino acid derivative **32** (Table 1).

In Scheme 4, the methods used in the preparation of (2-(10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ylidene)-ethoxy)alkyl and (2-(10,11-dihydro-5H-dibenzo[*a*,*d*]-cyclohepten-5-yl)ethoxy)alkyl derivatives of **1** and **2** are illustrated. The key intermediate in these methods was the appropriately substituted 5-(2-bromoethylidene)-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene. Two procedures for the preparation of these bromides were investigated, and the most convenient method found is a modification of a previously reported procedure.[68] In this procedure, the appropriately substituted 10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-one[69,70] was reacted with vinylmagnesium bromide to give the corresponding substituted 5-ethenyl-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ols (i.e., **48**). The reduced ketones, i.e., 10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ols, were observed as byproducts in this Grignard

Scheme 3. Synthesis of 9-Carbazolyl-, 5-Phenoxazinyl-, 5-Phenothiazinyl-, and 5-Dibenz[*b*,*f*]azepinylalkyloxyalkylamino Acids **19**−**33**[a]

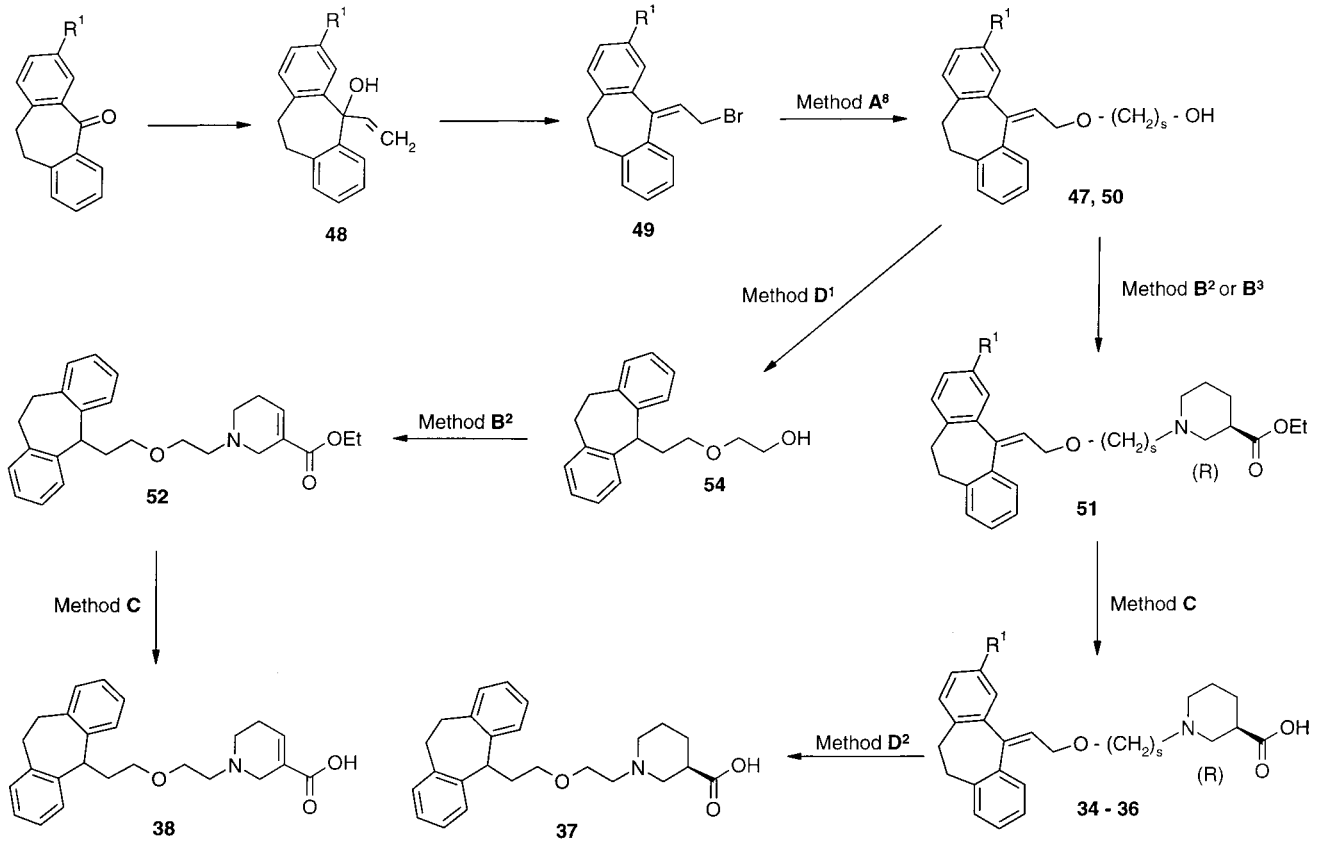


[a] $r = 2-3$; $s = 2$; A, R^1, R^2, R^3, R^4 and R^5, see Table 1. $R^{5'}$ represents the ethyl ester derivatives of amino acids **1**, **2**, or **3**. Method A[3]: NaH, dibutyl ether, reflux. Method A[4]: (1) chloroacetyl chloride, toluene, reflux; (2) $NaBH_4$, THF, $BF_3{\cdot}Et_2O$, 5−10 °C; (3) potassium *t*-butoxide, ethylene glycol, THF, 150 °C. Methods A[5], A[6], and A[7]: NaH, dibutyl ether, reflux. Method B[1]: ethyl ester of **1**, **2**, or **3**, 150 °C. Method B[2]: (1) *n*-butyllithium, THF, 10 °C; (2) *p*-toluenesulfonyl chloride or methanesulfonyl chloride, room temperature; (3) K_2CO_3, ethyl ester of **1** or **2**, room temperature. Method B[3]: (1) triethylamine, toluene, methanesulfonyl chloride; (2) K_2CO_3, (*R*)-3-piperidinecarboxylic acid ethyl ester, reflux. Method C: (1) NaOH, EtOH, room temperature; (2) HCl.

reaction[71] but in a much lower yield than if ethylmagnesium bromide were used instead of vinylmagnesium bromide. Reaction of the 5-ethenyl-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ols with trimethylsilyl bromide in CH_2Cl_2 at room temperature for a few minutes furnished the 5-(2-bromoethylidene)-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptenes (i.e., **49**) in quantitative yield. An alternative procedure was investigated in which ethylmagnesium bromide was used instead of vinylmagnesium bromide to give the intermediate 5-ethyl-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ols, which were dehydrated in dilute mineral acid to the 5-ethylidene-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptenes. Attempts to brominate these olefins with NBS/peroxide in the allylic position were not successful because an almost 1:1 mixture of the allylic and vinylic bromides was obtained, which in our hands could not be separated. This result and the above-mentioned higher reducing capability of ethylmagnesium bromide[72] compared to vinylmagnesium bromide led us to use only the path outlined in Scheme 4. The 5-(2-bromoethylidene)-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptenes (i.e., **49**) were converted to the 2-(10,11-dihydro-5H-dibenzo-[*a*,*d*]cyclohepten-5-ylidene)ethoxy alcohols (i.e., **47**, **50**) by the Lindy procedure (method A[8]). A solution of *n*-butyllithium in hexanes was carefully added at 10 °C to either ethylene glycol or 1,3-propanediol through which a steady stream of dry nitrogen was passed. This resulted in a suspension of the corresponding lithiate salt to which the appropriate 5-(2-bromoethylidene)-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene was added. The reaction mixture was then allowed to react for several days to give the alcohols **47** and **50**. These alcohols were converted via their mesylates by general methods B[2] (*n*-butyllithium)/B[3] (triethylamine) and C described above to produce the chain unsaturated acids **34**−**36**.

Two different routes accomplished preparation of compounds **37** and **38** in which the chain is saturated. The most convenient and direct route to produce chain saturated derivatives is catalytic hydrogenation of the corresponding chain unsaturated acids (method D[2]). Hydrogenation of the chain unsaturated acid hydrochloride **34** in the presence of 10% Pd/C in methanol

Scheme 4. Synthesis of (2-(10,11-Dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ylidene)ethoxy)alkylamino Acids **34**−**37** and (2-(10,11-Dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-yl)ethoxy)alkylamino Acids **37** and **38**[a]



[a] $s = 2-3$; R^1, see Table 1. Method A^8: (1) vinylmagnesium bromide, THF, 50−60 °C; (2) trimethylsilyl bromide, CH_2Cl_2, room temperature; (3) *n*-butyllithium, ethylene glycol, cyclohexane, room temperature. Method B^2: (1) *n*-butyllithium, THF, 10 °C; (2) methanesulfonyl chloride, room temperature; (3) K_2CO_3, ethyl ester of **1** or **2**, room temperature. Method B^3: (1) triethylamine, toluene, methanesulfonyl chloride; (2) K_2CO_3, (*R*)-3-piperidinecarboxylic acid ethyl ester, reflux. Method C: (1) NaOH, EtOH, room temperature; (2) HCl. Method D^1: H_2, 10% Pd/C, 10 atm, dioxane. Method D^2: H_2, 10% Pd/C, 1 atm, MeOH.

afforded the chain saturated acid hydrochloride **37**. However, it was observed that the ether linkage of the starting allyl ether was partly cleaved during hydrogenation.[74] This cleavage resulted in a byproduct with polarity comparable to that of the product, which made workup more tedious. To circumvent this problem, an alternative method was used for the synthesis of compound **38** in which hydrogenation was performed at an earlier step in the synthesis (method D^1). Hydrogenation of the (2-(10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ylidene)ethoxy)ethanol **47** in the presence of 10% Pd/C in dioxane afforded the corresponding (2-(10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-yl)ethoxy)-ethanol **54**. Although cleavage of the ether linkage was also observed in this reaction, purification at this stage proved to be easier than at a later step in the synthesis. The alcohol **54** was converted to compound **38** by general methods B^2 and C described above. This method (method D^1) is mandatory for the synthesis of derivatives of amino acid **2** because the double bond in 1,2,5,6-tetrahydro-3-pyridinecarboxylic acid is easily hydrogenated.

Biological Results and Discussion

In our search for novel GABA uptake inhibitors with high potency and selectivity, a large range of new tricyclic GABA uptake inhibitors have been prepared.[52] Some representative examples of these structures are included in Table 1. Their IC_{50} values for in vitro inhibition of [^{3}H]-GABA uptake determined essentially by Fjalland's method[74] are included (mean of two determinations is given).

In these examples, steric and electronic properties of the tricyclic moieties, as well as the chain linking the tricycle and amino acid part of the molecules together, have been varied in order to probe the requirements for inhibiting GABA transport at the site[75−78] involved in the uptake of GABA from the synaptic cleft into neuronal and glial cell bodies.

As can be seen from the in vitro data in Table 1, exchange of the diaryl moieties in compounds like **4** and **7**−**11** into a tricyclic moiety generally leads to loss in GABA uptake inhibition. However, two of the exchanges presented in Table 1 do not seem to be that critical. Transformation of **7** into **15** only gives a 2-fold loss in GABA uptake inhibition, and transformation of **10** into **23** gives a compound with comparable potency. From the series of compounds representing the transformation of **10** into **19, 20, 21, 23, 26**, and **33**, it can be seen that the type of bridge (column A, Table 1) linking the two aryl groups together is very crucial for retaining inhibition of GABA uptake. An optimal bridge seems to be obtained in either the phenothiazine **21** or the 10,11-dihydro-5H-dibenz[*b*,*f*]azepine **23**. In these two ring systems the fold angles between the two planes of the benzo rings[79,80] may be optimal in order to fulfill the out-of-plane geometry of the two aryl groups as previ-

ously described for other potent GABA uptake inhibitors.[1,42,48] It is evident from the data in Table 1 that the most successful exchanges are those performed on the diphenylamino derivative **10**. All the transformations performed from the other parent compounds **4, 7**−**9**, and **11**, which all contain a carbon atom between the aryl groups and which connect the tricycle to the chain, lead to a major decrease in GABA uptake inhibition. The explanation for this observation may be that the much higher flexibility of the sp^3 nitrogen in the azatricycles allows the molecule to adapt much better a preferred overall conformation for binding to the GABA uptake site in these compounds.

The influence of substituents on the tricyclic moieties has been investigated only to some extent because substituted derivatives of the tricycles used in this work in general are not readily available. However, in the 10,11-dihydro-5H-dibenz[*b*,*f*]azepine series several substituted analogues of compound **23** have been prepared. As can be seen from the data in Table 1, a 3-chloro substituent improves affinity for the GABA uptake site compared to compound **23**. However, an additional chloro substituent in the symmetrical 7-position, compound **28**, does not significantly improve potency further. Interestingly, a small fluoro substituent in the 3-position, compound **29**, lowers the affinity compared to example **23**. Substituents in the 2- and 8-positions are certainly not beneficial for potency as can be seen from the activities of compounds **30** and **31**, although fluoro substituents such as those in **30** do not lower inhibition of GABA uptake significantly when compared to those in **23**. In the two remaining series, the oxime derivatives (**16** and **17**) and the allyl ether derivatives (**34**−**36**), in which substituents have been introduced, i.e., compounds **17** and **35**, 3-chloro or 3,7-dichloro substituents, which improved potency in the 10,11-dihydro-5H-dibenz[*b*,*f*]azepine series (**23**−**31**), are certainly not beneficial for obtaining higher potency for the two series of compounds.

In the 10,11-dihydro-5H-dibenz[*b*,*f*]azepine series we have also prepared analogues of example **23** in which nipecotic acid has been replaced by guvacine or homo-*β*-proline represented by the compounds **24** or **25**, respectively. In the more flexible homo-*β*-proline derivative **25**, potency has been improved 3-fold when compared to the activity of compound **23** and has become the most potent example in this series of compounds. In the more rigid guvacine analogue **24**, affinity for the GABA uptake site has been lowered by 4-fold compared to the activity of compound **23**. This observation is not in agreement with what we have generally seen in our previous work,[1,42,48] in which nipecotic acid and guvacine derivatives have shown the same order of inhibition toward the GABA uptake site. This lack of equipotency is also found in the nipecotic acid derivative **37** and guvacine derivative **38**.

In Table 2 the in vivo anticonvulsant effect in mice is shown for representative compounds and expressed as ED_{50} values in milligram per kilogram. The convulsion model used is based on observed inhibition of clonic seizures induced by a 15 mg/kg intraperitoneal (ip) dose of the chemoconvulsant methyl 6,7-dimethoxy-4-ethyl-*β*-carboline-3-carboxylate (DMCM), an inverse benzodiazepine agonist. The experimental procedure has been described previously.[27] In Table 2 we have also listed the ED_{50} values found in the rotarod performance test in mice and calculated the protective index as the ratio of ED_{50} values for inhibition of motility on the rotarod to those for inhibition of DMCM induced convulsions. Generally, as can be seen from Table 2, the tricyclic derivatives from this work show a very low in vivo potency compared to reference compounds **4**, **5**, and **7**−**11**. In addition, the protective indexes, where determined, were also found to be lower than that determined for **5**. However, an exception is given by compound **23**, which shows a lower in vivo potency but a protective index that is comparable with or even better than that determined for **5**.

Table 2. Anticonvulsant Properties of Selected Compounds

no.	DMCM ED_{50}[a] (mg/kg)	rotarod ED_{50}[b] (mg/kg)	protective index[c]
4	3.1		
5	1.2	5.5	4.6
7	6.0		
8	3.2		
9	1.5	5.4	3.6
10	10	16	1.6
11	1.7	9.0	5.3
13	>60	>60	
16	30	>100	>3.3
17	35	40	1.1
21	30	54	1.8
22	38	>60	1.6
23	15	85	5.7
24	7.3	21	2.9
25	31	100	3.2
26	30	>30	>1.0
27	15	>30	>2.0
28	45	>100	>2.2
32	50	>60	>1.2
33	60	>90	>1.5
34	30	>100	>3.3
35	50	>60	>1.2
36	60	>150	>2.5
37	23	>60	>2.6

[a] Inhibition of DMCM-induced seizures in mice: ED_{50} (mg/kg) after ip administration. [b] Rotarod in mice: ED_{50} (mg/kg) after ip administration. [c] Ratio for ED_{50} values for inhibition of rotarod to inhibition of DMCM-induced convulsions in mice.

Conclusion

Previously[42] we have given a summary on the selection of **5** as an anticonvulsant drug candidate. During development of this compound a demand for a second-generation compound with a longer duration of action and broader therapeutic window became evident. Therefore, the search for novel series of compounds that could be investigated and optimized with respect to these features was initiated and has resulted in potent GABA uptake inhibitors, which have been reported previously.[1,48] In this publication we have described the identification of a series of novel GABA uptake inhibitors from which compound **23** was selected for further biological investigations. Although this compound displays an in vivo potency lower than that found for **5**, the protective index is comparable to or slightly better than that determined for **5**. Together with other compounds reported previously,[1,48] compound **23** was therefore considered as a potential second-generation compound. To identify even better compounds, the search for novel potent GABA uptake inhibitors with a longer duration of action and broader therapeutic window was

continued, and the results of this search will be reported in subsequent papers.

Experimental Section

General. Melting points were determined in open capillary tubes on a Büchi 535 melting point apparatus and are uncorrected. The structures of all compounds are consistent with spectroscopic data, and satisfactory elemental analyses were obtained within ±0.4% of theoretical values where given. Elemental C, H, and N were determined with a Perkin-Elmer model 240 elemental analyzer; Cl was determined by the Schöniger combustion method. ^{1}H NMR spectra were recorded on a Bruker WM400 spectrometer with TMS as internal standard, with illustrative chemical shifts quoted in ppm (δ) in the solvents indicated. Compounds used as starting materials are either known compounds or compounds that can be prepared by methods known per se. The tetrahydropyranyl ethers used were prepared according to reported methods.[65−67] The 5-(2-bromoethylidene)-10,11-dihydro-5H-dibenzo[*a*,*d*]-cycloheptenes used were prepared by modified reported methods.[68] The following starting materials were prepared as previously reported: substituted 10,11-dihydro-5H-dibenz[*b*,*f*]-azepines,[60−63] 5,6,7,12-tetrahydrodibenz[*b*,*g*]azocine,[64] substituted 10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ones,[68,69] 10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-one oximes,[56] and 10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-carboxaldehyde.[59] Column chromatography was carried out using the technique described by W. C. Still et al.,[81] on Merck silica gel 60 (Art 9385) using thick-walled glass columns and TLCs on Merck silica gel 60, 5 cm × 20 cm plates (Art 5714).

Synaptosomal [^{3}H]-GABA Uptake. Uptake of [^{3}H]-GABA into synaptosomal preparations was assayed by a filtration assay.[74] Rat forebrain was rapidly excised and homogenized in 20 mL of ice-cold 0.32 M sucrose with a hand-driven Teflon/glass Potter−Elvehjem homogenizer. The homogenate was centrifuged for 10 min at 600 *g* at 4 °C. The pellet was resuspended in 50 volumes of ice-cold buffer (120 mM NaCl, 0.18 mM KCl, 2.30 mM $CaCl_2$, 4.0 mM $MgSO_4$, 12.66 mM Na_2HPO_4, 2.97 mM NaH_2PO_4, and 10.0 mM glucose, pH 7.4) at 4 °C. An amount of 50 μL of this synaptosomal suspension (0.1 mg protein), diluted into 300 μL of phosphate buffer and 100 μL of test substance solutions in water, was preincubated for 8 min at 30 °C. Then a total of 50 μL of [^{3}H]-GABA (final concentration of 0.9 nM) and unlabeled GABA (final concentration of 0.9 nM) was added before continuing incubation for another 8 min. Synaptosomes were then recovered by rapid filtration through Whatman GF/F glass fiber filters under vacuum. Filters were washed twice, each time with 10 mL of ice-cold isotonic saline, and the tritium trapped on the filters was assessed by conventional scintillation counting in 4 mL of Filter-Count (Packard). Non-carrier-mediated uptake was determined in the presence of nipecotic acid (500 μM) and was subtracted from total binding to give carrier-mediated [^{3}H]-GABA uptake. The IC_{50} value obtained for each example is shown in Table 1.

Antagonism of Seizures Induced by Methyl 6,7-Dimethoxy-4-ethyl-β-carboline-3-carboxylate (DMCM) in Mice.[27] Female NMRI mice were used. The test drug was injected ip 30 min prior to the seizure test. In this test the animals were injected ip with 15 mg/kg of DMCM and were observed for the next 30 min for the presence of clonic seizures and death (N = 5−10/dose). The ED_{50} value obtained for each example is shown in Table 2.

Rotarod Test in Mice.[27] The animals were pretrained in the rotarod apparatus (Ugo-Basile, Italy) for 2 min before being tested (speed: 6 rpm). The rod diameter was 3 cm. In the test procedure, the animals were placed on the rotating rod. If the animal fell from the rod, the animal was immediately picked up by the tail and again placed on the rod. Testing was stopped when a total of 10 failures were obtained or 2 min had elapsed.

Chemistry. Each of the methods A−D is illustrated by the preparation of the following derivatives. Although the methods are illustrated for specific compounds, the methods have been found to be general for the examples in Table 1.

Method A[1]: (*R*)-1-(2-((3,7-Dichloro-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-yl-idene)aminooxy)ethyl)-3-piperidinecarboxylic Acid Ethyl Ester (39). A mixture of 3,7-dichloro-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-one[69] (2.2 g, 7.9 mmol) and NH_2OH, HCl (4.0 g, 58 mmol) in pyridine (30 mL) was heated at reflux temperature for 48 h. The reaction mixture was allowed to cool, and the solvent was evaporated. The residue was dissolved in EtOAc (100 mL) and washed with water (25 mL) and a 10% aqueous citric acid solution (50 mL). After the mixture was dried (Na_2SO_4) the solvent was evaporated to give a quantitative yield of 3,7-dichloro-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-one oxime (**40**) as a solid; mp 178−180 °C. A mixture of **40** (2.3 g, 8 mmol), (*R*)-1-(2-bromoethyl)-3-piperidinecarboxylic acid ethyl ester hydrobromide[50] (4.1 g, 12 mmol), K_2CO_3 (2.9 g, 21 mmol), and acetone (30 mL) was stirred at room temperature for 5 days. The mixture was filtered and the solvent evaporated. The residue was purified by column chromatography on silica gel (150 g, heptane/EtOAc = 7:3) to give 2.5 g (66%) of **39** as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (t, J = 7 Hz, 3H, CH_2CH_3), 1.35−2.25 (m, 6H, $NCH_2CH_2CH_2CH$), 2.55−2.65 (m, 1H, $CHCO_2Et$), 2.75 (t, J = 5 Hz, 2H, OCH_2CH_2N), 2.77−2.83 (m, 1H, NCH_2CH), 3.00−3.10 (m, 5H, NCH_2CH + $PhCH_2CH_2$-Ph), 4.12 (q, J = 7 Hz, 2H, CH_2CH_3), 4.35 (t, J = 5 Hz, 2H, OCH_2CH_2N), 7.03 (d, J = 9 Hz, 1H, Ar*H*), 7.16 (d, J = 9 Hz, 1H, Ar*H*), 7.24 (dd, J = 9 and 2 Hz, 2H, Ar*H*), 7.42 (d, J = 2 Hz, 1H, Ar*H*), 7.57 (d, J = 2 Hz, 1H, Ar*H*).

Method A[2]: 2-((10,11-Dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ylidene)methoxy)ethyl Bromide (41). To a solution of 10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-carboxaldehyde[59] (11.3 g, 51 mmol) and tetrabutylammonium bromide (1.64 g, 5.1 mmol) in CH_2Cl_2 (100 mL) was added 1,2-dibromoethane (62 mL) and 12 M NaOH (100 mL). The reaction mixture was stirred vigorously overnight, and CH_2Cl_2 (100 mL) was added. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (100 mL). The combined organic phases were washed with 0.2 M HCl (100 mL) and brine (25 mL) and dried ($MgSO_4$). The solvent was evaporated to give 14.1 g of **41** as an oil. TLC, R_f: 0.48 (SiO_2; EtOAc/*n*-heptane = 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.12 (s, 4H, $PhCH_2CH_2Ph$), 3.50 (t, J = 7 Hz, 2H, CH_2Br), 4.16 (t, J = 7 Hz, 2H, CH_2O), 6.41 (s, 1H, =C*H*), 7.05−7.25 (m, 8H, Ar*H*).

Method A[3]B[1]: (*R*)-1-(2-(2-(10,11-Dihydro-5H-dibenz-[*b*,*f*]azepin-5-yl)ethoxy)ethyl)-3-piperidinecarboxylic Acid Ethyl Ester (42). A mixture of NaH (0.40 g, 10 mmol, 60% oil dispersion) and 10,11-dihydro-5H-dibenz[*b*,*f*]azepine (1.95 g, 10 mmol) in dry dibutyl ether (30 mL) was heated at reflux for 3.5 h under N_2. The reaction mixture was cooled to 100 °C and 2,2′-dichlorodiethyl ether (4.7 mL) was added, and the mixture was heated at reflux for 16 h. The reaction mixture was cooled, and H_2O (50 mL) was added. The mixture was extracted with toluene (100 mL), and the organic extract was dried (Na_2SO_4). The solvent was evaporated to give 2.8 g of an oily residue containing 2-chloro-1-(2-(10,11-dihydro-5H-dibenz[*b*,*f*]azepin-5-yl)ethoxy)ethane. Ethyl (*R*)-3-piperidinecarboxylate (3.0 g, 19 mmol) was added to the residue, and the mixture was heated at 150 °C for 1.5 h. The reaction mixture was allowed to cool to 80 °C, and toluene (100 mL) was added. The mixture was then allowed to cool to room temperature, and a solution of K_2CO_3 (1.4 g) in H_2O (100 mL) was added. The phases were separated, and the organic phase was washed successively with H_2O, an aqueous NaOAc solution (pH 5), and an aqueous citric acid solution (pH 5). The organic phase was then extracted with a 5% aqueous citric acid solution (50 mL). The acidic (pH 1) aqueous extract was washed with toluene (2 × 50 mL), and then 4 N NaOH was added until pH 6−7. The aqueous mixture was extracted with toluene, and the organic extract was treated with charcoal and dried (Na_2SO_4). The solvent was evaporated to give 2.1 g (50%) of **42** as an oil. TLC, R_f: 0.20 (SiO_2; *n*-heptane/THF = 7:3). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (t, J = 7 Hz, 3H, CH_2CH_3), 1.35−2.18 (m, 6H, $NCH_2CH_2CH_2CH$), 2.47−2.58 (m, 3H, $CHCO_2Et$ and OCH_2CH_2N), 2.77 (d, J = 6 Hz, 1H, NCH_2CH),

2.98 (d, J = 6 Hz, 1H, NCH_2CH), 3.18 (s, 4H, PhCH_2CH_2Ph), 3.49 (t, J = 6 Hz, 2H, CH_2O), 3.57 (t, J = 6 Hz, 2H, CH_2O), 3.99 (t, J = 6 Hz, 2H, NCH_2CH$_2$O), 4.12 (q, J = 7 Hz, 2H, CH_2CH$_3$), 6.88−7.13 (m, 8H, ArH).

Method A[4]: 2-(2-(3-Chloro-10,11-dihydro-5H-dibenz-[*b,f*]azepin-5-yl)ethoxy)ethanol (43). A mixture of 3-chloro-10,11-dihydro-5H-dibenz[*b,f*]azepine[61] (6.4 g, 28 mmol) and chloroacetyl chloride (3.5 g, 31 mmol) in toluene (75 mL) was heated at reflux under N_2 for 12 h. The mixture was filtered and concentrated. The residue was re-evaporated with EtOH and then CH_2Cl_2. To the residue was added Et_2O (20 mL), and the mixture was left for crystallization. The solid was isolated by filtration and dried to give 4.0 g (53%) of 3-chloro-5-chloroacetyl-10,11-dihydro-5H-dibenz[*b,f*]azepine as a solid; mp 125−128 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.78−2.88 (m, 2H, PhCH_2CH_2Ph), 3.30−3.50 (m, 2H, PhCH_2CH_2Ph), 3.93−4.15 (m, 2H, COCH_2Cl), 7.05−7.40 (m, 7H, ArH).

$NaBH_4$ (0.34 g, 8.9 mmol) was added under N_2 to a solution of the above amide (2.0 g, 7.4 mmol) in dry THF (20 mL). The mixture was cooled in an ice bath to 5−10 °C, and BF_3·Et_2O (1.6 g, 11.1 mmol) was added dropwise and slowly. When addition was completed, the mixture was stirred at 10 °C for 1 h and then 2 h at room temperature. Carefully, MeOH (2 mL) was added followed by H_2O (4 mL). The resulting solution was concentrated, and the residue dissolved in Et_2O (100 mL). The organic solution was washed with H_2O (2 × 50 mL), dried ($MgSO_4$), and filtered. The solvent was evaporated, and the residue was re-evaporated with EtOH and then CH_2Cl_2. This afforded 1.75 g (80%) of 3-chloro-5-(2-chloroethyl)-10,11-dihydro-5H-dibenz[*b,f*]azepine as an oil. TLC, R_f: 0.60 (SiO_2; heptane/EtOAc = 3:2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.11−3.21 (m, 4H, PhCH_2CH_2Ph), 3.60 (t, J = 6 Hz, 2H, CH_2Cl), 4.08 (t, J = 6 Hz, 2H, NCH_2), 6.85−7.18 (m, 7H, ArH).

Potassium *t*-butoxide (1.3 g, 11.6 mmol) was carefully added to ethylene glycol (7.2 g, 116 mmol) under N_2. When addition was completed, the mixture was stirred at 50 °C for 1 h. The above chloride (1.7 g, 5.8 mmol) dissolved in THF (5 mL) was added and the reaction mixture was heated at 150 °C for 24 h. Additional potassium *t*-butoxide (0.7 g, 5.8 mmol) was carefully added, and heating was continued for another 24 h. To the cooled reaction mixture was added ice−water (100 mL), and the mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography on silica gel (80 g, heptane/EtOAc = 3:2) to give 1.0 g (56%) of **43** as an oil. TLC, R_f: 0.31 (SiO_2; heptane/EtOAc = 3:2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.81 (brs, 1H, OH), 3.08−3.18 (m, 4H, PhCH_2CH_2Ph), 3.43 (t, J = 5 Hz, 2H, CH_2OH), 3.58−3.67 (m, 4H, 2 × CH_2O), 3.95 (t, J = 5 Hz, 2H, NCH_2), 6.84−7.17 (m, 7H, ArH).

Method A[5]: 2-(2-(10H-Phenothiazin-10-yl)ethoxy)ethanol (44). Phenothiazine (3.8 g, 19 mmol) was added to a suspension of NaH (0.92 g, 23 mmol, 60% oil dispersion) in dry dibutyl ether (25 mL) under N_2. The mixture was heated at 135 °C for 1 h and then allowed to cool to approximately 100 °C. 2-Chloro-(2-((tetrahydro-2-pyranyl)oxy)ethoxy)ethane (8 g, 38 mmol) was added in one portion, and the mixture was heated overnight at 110 °C. The reaction mixture was poured in H_2O (250 mL) and extracted with CH_2Cl_2 (3 × 50 mL) and Et_2O (50 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was evaporated, leaving an oil that was purified by column chromatography on silica gel using CH_2Cl_2 as eluent. This afforded 3.9 g of 10-(2-(2-((tetrahydro-2-pyranyl)oxy)ethoxy)ethyl)-10H-phenothiazine. TLC, R_f: 0.72 (SiO_2; CH_2Cl_2/MeOH = 19:1). A mixture of this pyranyl derivative (3.8 g, 10 mmol), 2-propanol (50 mL), and 4 M H_2SO_4 (8 mL) was heated at 60 °C for 3 h and then left overnight at room temperature. The reaction mixture was poured into a mixture of H_2O (500 mL) and 4 N NaOH (17 mL). The mixture was extracted with Et_2O (150 mL), and the organic extract was washed with brine and dried (Na_2SO_4). The solvent was evaporated to give 1.5 g of **44**. TLC, R_f: 0.52 (SiO_2; CH_2Cl_2/MeOH = 19:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.22 (brs, 1H, OH), 3.54 (t, J = 5 Hz, 2H, CH_2CH$_2$OH), 3.65 (t, J = 5 Hz, 2H, CH_2OH), 3.82 (t, J = 6 Hz, 2H, NCH$_2$CH_2O), 4.10 (t, J = 6 Hz, 2H, NCH_2), 6.85−7.15 (m, 8H, ArH).

Method A[6]: 3-(10,11-Dihydro-5H-dibenz[*b,f*]azepin-5-yl)-1-propanol (45). To a solution of 10,11-dihydro-5H-dibenz-[*b,f*]azepine (8.1 g, 0.040 mol) in dry dibutyl ether (60 mL) kept under N_2, NaH (1.6 g, 0.040 mol, 60% oil dispersion) was carefully added. The reaction mixture was heated at reflux for 4 h and then allowed to cool to 80 °C. 3-Bromo-1-propyl tetrahydro-2-pyranyl ether (10.7 g, 0.048 mol) was added, and the mixture was heated at reflux for 16 h. To the cooled reaction mixture was added H_2O (20 mL), and the phases were separated. From the organic phase the solvent was evaporated, and the residue was dissolved in a mixture of MeOH (150 mL) and 4 N HCl (50 mL). The mixture was heated at reflux for 15 min and then stirred for 1 h at room temperature. H_2O (250 mL) was added, and the mixture was extracted with EtOAc (2 × 200 mL). The combined organic extracts were dried (Na_2SO_4) and filtered, and the solvent was evaporated. This afforded a residue, which was purified by chromatography on silica gel (200 g, *n*-heptane/EtOAc = 3:2) to give 5.5 g of **45** as an oil. TLC, R_f: 0.30 (SiO_2; *n*-heptane/EtOAc = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.42 (brs, 1H, OH), 1.83 (quint, J = 6 Hz, 2H, CH$_2$CH_2CH$_2$), 3.16 (s, 4H, PhCH_2CH_2Ph), 3.67 (t, J = 6 Hz, 2H, CH_2OH), 3.86 (t, J = 6 Hz, 2H, NCH_2), 6.92 (t, J = 7 Hz, 2H, ArH), 7.10−7.15 (m, 6H, ArH).

Method A[7]: 2-((3-(10,11-Dihydro-5H-dibenz[*b,f*]azepin-5-yl)-1-propyl)oxy)ethanol (46). A mixture of NaH (0.40 g, 0.010 mol, 60% oil dispersion), **45** (2.5 g, 0.010 mol), and dry dibutyl ether (25 mL) was stirred for 16 h at reflux under N_2. The reaction mixture was allowed to cool, and 2-bromoethyl tetrahydro-2-pyranyl ether (2.5 g, 12 mmol) was added and then heated at reflux for 16 h. To the cooled mixture was added H_2O (10 mL), and the phases were separated. From the organic phase the solvent was evaporated to give a residue, which was purified by chromatography on silica gel (200 g, *n*-heptane/EtOAc = 7:3). This afforded 1.5 g of the tetrahydro-2-pyranyl intermediate. TLC, R_f: 0.55 (SiO_2; *n*-heptane/EtOAc = 1:1). This intermediate was dissolved in a mixture of MeOH (30 mL) and 4 N HCl (15 mL), and the mixture was heated at reflux for 15 min. The reaction mixture was allowed to cool, and MeOH was evaporated. H_2O was added, and the mixture was extracted with EtOAc. The organic extract was washed with 5% aqueous $NaHCO_3$ and dried (Na_2SO_4), and the solvent was evaporated. This afforded 0.6 g (20%) of **46** as an oil. TLC, R_f: 0.33 (SiO_2; *n*-heptane/EtOAc = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.62 (brs, 1H, OH), 1.85 (quint, J = 6 Hz, 2H, CH$_2$CH_2CH$_2$), 3.16 (s, 4H, PhCH_2CH_2Ph), 3.48 (t, J = 5 Hz, 2H, OCH_2CH$_2$OH), 3.51 (t, J = 6 Hz, 2H, CH$_2$CH$_2$CH_2O), 3.66 (t, J = 5 Hz, 2H, CH_2OH), 3.84 (t, J = 6 Hz, 2H, NCH_2), 6.92 (t, J = 7 Hz, 2H, ArH), 7.05−7.15 (m, 6H, ArH).

Method A[8]: 2-(2-(10,11-Dihydro-5H-dibenzo[*a,d*]cyclohepten-5-ylidene)ethoxy)ethanol (47). A solution of 10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5-one (9.4 g, 45 mmol) in dry THF (100 mL) was placed under N_2. A solution of vinylmagnesium bromide in THF (100 mL, 0.5 M) was added at such a rate to keep the reaction temperature at 30−35 °C. When addition was completed, the mixture was heated at 50−60 °C for 1.5 h. The reaction mixture was cooled in an ice bath, and a solution of NH_4Cl (10 g) in H_2O (50 mL) was carefully added. Et_2O (100 mL) was added, and the phases were separated. The aqueous phase was extracted with Et_2O (100 mL), and the combined organic phases were dried (Na_2SO_4). The solvent was evaporated to give a residue, which was re-evaporated twice with CH_2Cl_2 to give 11.8 g of 5-ethenyl-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5-ol (**48**). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.27 (s, 1H, OH), 2.84−2.92 (m, 2H, PhCH_2-CH_2Ph), 3.38−3.50 (m, 2H, PhCH_2CH_2Ph), 4.92 (d, J = 18 Hz, 1H, CH=CH_2 trans), 5.23 (d, J = 10 Hz, 1H, CH=CH_2 cis), 6.35 (dd, J = 10 and 18 Hz, 1H, CH=), 7.08−7.25 (m, 6H, ArH), 7.90 (dd, J = 2 and 9 Hz, 2H, ArH).

The alcohol **48** (9.2 g) was dissolved in CH_2Cl_2 (100 mL), and the mixture was placed in an ice bath. A solution of trimethylsilyl bromide (6.6 g, 43 mmol) in CH_2Cl_2 (50 mL) was

added dropwise within 30 min. When addition was completed, the mixture was stirred at room temperature for 45 min. Ice−water (50 mL) and saturated $NaHCO_3$ (200 mL) was added. The phases were separated, and the organic phase was dried (Na_2SO_4). The solvent was evaporated to give a residue, which was re-evaporated with cyclohexane. This afforded 10.5 of 5-(2-bromoethylidene)-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene (**49**). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.75−3.40 (m, 4H, PhCH_2CH_2Ph), 4.05 (t, J = 8 Hz, 2H, CH_2Br), 6.15 (t, J = 8 Hz, 1H, =C*H*), 7.05−7.35 (m, 8H, Ar*H*).

A solution of *n*-butyllithium in hexanes (12 mL, 2.5 M) was carefully added dropwise at 10 °C to ethylene glycol (25 mL) under N_2. When addition was completed, the mixture was stirred at room temperature for 30 min. A solution of **49** (7.1 g) in cyclohexane (20 mL) was added in one portion, and vigorous stirring and a strong N_2 flow removed the hexanes. Then the reaction mixture was stirred at room temperature for 68 h. H_2O (30 mL) was added, and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated. The oily residue was purified by column chromatography on silica gel (150 g, THF/*n*-heptane = 3:7) to give 2.4 g of **47** as an oil. TLC, R_f: 0.18 (SiO_2; THF/*n*-heptane = 3:7). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.97 (t, J = 5 Hz, 1H, O*H*), 2.65−3.55 (m, 6H, PhCH_2CH_2Ph + OCH_2CH_2OH), 3.70 (dt, J = 5 and 5 Hz, 2H, CH_2OH), 4.08 (d, 2H, =CHCH_2O), 6.03 (t, J = 7 Hz, 1H, =C*H*), 7.05−7.35 (m, 8H, Ar*H*).

3-(2-(10,11-Dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ylidene)ethoxy)propanol (50). A solution of *n*-butyllithium in hexanes (16.8 mL, 2.5 M) was carefully added dropwise at 10 °C to propylene glycol (25 mL) under N_2. When addition was completed, the mixture was stirred at room temperature for 15 min. A solution of **49** (10.1 g) in cyclohexane (30 mL) was added in one portion, and the reaction mixture was stirred at room temperature for 42 h. H_2O (40 mL) was added, and the mixture was extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with H_2O (15 mL) and dried (Na_2SO_4), and the solvent was evaporated. The oily residue was purified by column chromatography on silica gel (200 g, THF/*n*-heptane = 3:7) to afford 4.2 g of **50** as an oil. TLC, R_f: 0.18 (SiO_2; THF/*n*-heptane = 3:7). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.80 (quint, J = 6 Hz, 2H, $CH_2CH_2CH_2$), 2.33 (brs, 1H, O*H*), 2.65−3.65 (m, 6H, PhCH_2CH_2Ph + OCH_2CH_2OH), 3.72−3.78 (m, 2H, CH_2OH), 3.90−4.20 (m, 2H, =CHCH_2O), 6.01 (t, J = 7 Hz, 1H, =C*H*), 7.05−7.35 (m, 8H, Ar*H*).

Method B[2]: (*R*)-1-(3-(2-(10,11-Dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ylidene)ethoxy)-1-propyl)-3-piperidinecarboxylic Acid Ethyl Ester (51). A solution of **50** (4.2 g, 14.3 mmol) in dry THF (30 mL) was placed under N_2 in an ice bath. A solution of *n*-butyllithium in hexanes (5.7 mL, 2.5 M) was added dropwise within 15 min, and the mixture was stirred for another 15 min. *p*-Toluenesulfonyl chloride (2.7 g, 14.0 mmol) was added in one portion, and the mixture was stirred at room temperature for 30 min. The solvent was evaporated, keeping a low bath temperature. The oily residue was dissolved in acetone (25 mL), and ethyl (*R*)-3-piperidinecarboxylate (3.3 g, 21.0 mmol) and K_2CO_3 (3.5 g, 25.0 mmol) were added. The mixture was stirred at room temperature for 120 h. The mixture was filtered, and the solvent was evaporated. The oily residue was purified by column chromatography on silica gel (100 g, EtOAc/*n*-heptane = 2:3) to give 3.0 g of **51** as an oil. TLC, R_f: 0.19 (SiO_2; EtOAc/*n*-heptane = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24 (t, J = 7 Hz, 3H, CH_2CH_3), 1.37−2.15 (m, 8H, NCH_2CH_2CH_2CH and NCH_2CH_2CH_2O), 2.39 (t, J = 7 Hz, 2H, NCH_2CH_2CH_2O), 2.48−2.53 (m, 1H, C*H*CO_2Et), 2.73 (d, J = 5 Hz, 1H, NCH_2CH), 2.81 (brs, 2H, PhCH_2CH_2Ph), 3.32 (brs, 2H, PhCH_2CH_2Ph), 3.41 (brs, 2H, OCH_2CH_2), 3.95 (brs, 2H, OCH_2CH=), 4.10 (q, J = 7 Hz, 2H, C$H_2$$CH_3$), 6.02 (t, J = 7 Hz, 1H, =C*H*), 7.05−7.35 (m, 8H, Ar*H*).

1-(2-(2-(10,11-Dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-yl)ethoxy)ethyl)-1,2,5,6-tetrahydro-3-pyridinecarboxylic Acid Ethyl Ester (52). A solution of **54** (2.2 g, 7.4 mmol) in dry THF (20 mL) was placed under N_2 in an ice bath. A solution of *n*-butyllithium in hexanes (3.0 mL, 2.5 M) was added dropwise within 15 min, and the mixture was stirred for another 15 min. Methanesulfonyl chloride (0.85 g, 7.4 mmol) was added in one portion, and the mixture was stirred in an ice bath for 45 min. The solvent was evaporated, and the residue was dissolved in acetone (25 mL). Ethyl 1,2,5,6-tetrahydro-3-pyridinecarboxylate hydrochloride (1.5 g, 7.8 mmol) and K_2CO_3 (2.5 g, 18 mmol) were added, and the mixture was stirred at reflux for 16 h. The mixture was filtered, and the solvent was evaporated. The oily residue was purified by column chromatography on silica gel (150 g, EtOAc/*n*-heptane = 1:1) to give 1.3 g of **52** as an oil. TLC, R_f: 0.14 (SiO_2; EtOAc/*n*-heptane = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.27 (t, J = 7 Hz, 3H, CH_2CH_3), 2.30−2.40 (m, 4H, NCH_2CH_2-CH = and CHCH_2CH_2O), 2.62 (t, J = 6 Hz, 2H, NCH_2-CH_2CH=), 2.74 (t, J = 6 Hz, 2H, OCH_2CH_2N), 2.95−3.07 (m, 2H, PhCH_2CH_2Ph), 3.28 (s, 2H, NCH_2C=), 3.30−3.40 (m, 4H, PhCH_2CH_2Ph and CHCH_2CH_2O), 3.55 (t, J = 6 Hz, 2H, OCH_2-CH_2N), 4.18 (q, J = 7 Hz, 2H, C$H_2$$CH_3$), 4.22 (t, J = 6 Hz, C*H*CH_2), 7.00 (s, 1H, =CH), 7.05−7.20 (m, 8H, Ar*H*).

Method B[3]: (*R*)-1-(2-(2-(10H-Phenothiazin-10-yl)ethoxy)-ethyl)-3-piperidine-carboxylic Acid Ethyl Ester (53). A well-stirred mixture of **44** (1.5 g, 5.2 mmol), TEA (1.8 mL), and toluene (20 mL) placed under N_2 was cooled in an ice bath. A solution of methanesulfonyl chloride (1.5 g, 10.4 mmol) in toluene (5 mL) was added within 15 min. Stirring was continued for 45 min in an ice bath and then for 30 min at room temperature. H_2O (15 mL) was added, and the mixture was stirred at room temperature for 15 min. The phases were separated, and the aqueous phase was extracted with toluene (20 mL). The combined organic extracts were washed with 5% $NaHCO_3$ and with brine and dried (Na_2SO_4). The solvent was evaporated to give an oil, which was dissolved in toluene (30 mL). To this solution was added K_2CO_3 (2.5 g, 18.3 mmol) and ethyl (*R*)-3-piperidinecarboxylate tartrate (3.2 g, 10.4 mmol), and the suspension was heated at reflux for 3 days. The cooled reaction mixture was filtered and the solid washed with a small portion of toluene. The filtrate was concentrated to give a residue, which was dissolved in a mixture of EtOAc (30 mL) and H_2O (30 mL). A 34% aqueous solution of tartaric acid was added until pH 4. The phases were separated, and the aqueous phase was extracted with EtOAc (15 mL). To the combined organic phases, H_2O (10 mL) and a 34% aqueous solution of tartaric acid (3.5 mL) were added. The phases were separated, and the organic phase was extracted with a mixture of H_2O (10 mL) and a 34% aqueous solution of tartaric acid (2 mL). The acidic aqueous phases were combined and washed with EtOAc (15 mL). All the organic phases were discarded and to the acidic aqueous phase were added EtOAc (50 mL) and H_2O (50 mL). A solution of 4 N NaOH was added until pH 8.5, and the phases were separated. The aqueous phase was extracted with EtOAc (15 mL), and the combined EtOAc phases were washed with brine and dried (Na_2SO_4). The solvent was evaporated to give 0.8 g of **53** as an oil. TLC, R_f: 0.20 (SiO_2; CH_2Cl_2/MeOH/CH_3COOH = 20:2:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24 (t, J = 7 Hz, 3H, CH_2CH_3), 1.35−2.22 (m, 6H, NCH_2CH_2CH_2CH), 2.52−2.62 (m, 3H, C*H*CO_2Et + OCH_2CH_2-NCH_2), 2.81 (d, J = 6 Hz, 1H, NCH_2CH), 3.02 (d, J = 6 Hz, 1H, NCH_2CH), 3.61 (t, J = 6 Hz, 2H, OC$H_2$$CH_2$NCH), 3.81 (t, J = 6 Hz, 2H, Ph_2NCH_2CH_2O), 4.08 (t, J = 6 Hz, 2H, Ph_2NCH_2-CH_2O), 4.12 (q, J = 7 Hz, 2H, C$H_2$$CH_3$), 6.90−7.15 (m, 8H, Ar*H*).

Method C: Hydrolysis of 3-Piperidinecarboxylic, 3-Pyrrolidineacetic, and 1,2,5,6-Tetrahydro-3-pyridinecarboxylic Acid Ester Derivatives. General Method. The ester under consideration (1.0 mmol) was dissolved in ethanol (3 mL), and 3 mmol of 4 or 12 N NaOH was added. The reaction mixture was stirred at room temperature until TLC indicated complete reaction (3−6 h). A concentrated aqueous HCl solution was added with cooling in an ice bath until pH 1. Then CH_2Cl_2 (100 mL) was added, and the resulting emulsion was dried (Na_2SO_4). The solvent was evaporated to give a residue, which was crystallized from acetone. Recrystallization afforded the pure acid hydrochlorides for which the data are shown in Table 1.

Method D[1]: 2-(2-(10,11-Dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-yl)ethoxy)ethanol (54). A solution of **47** (2.4 g, 8.2 mmol) in dioxane (25 mL) was hydrogenated at 10 atm for 16 h at room temperature in the presence of 10 % Pd/C catalyst (50 % aqueous paste). The mixture was filtered, and the filtrate was concentrated to give an oily residue that was re-evaporated with CCl_4. This afforded 2.2 g of **54** as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.90 (brs, 1H, O*H*), 2.35 (q, J = 6 Hz, 2H, CHCH_2CH$_2$), 2.95−3.05 (m, 2H, PhCH_2CH_2Ph), 3.30−3.40 (m, 2H, PhCH_2CH_2Ph), 3.38 (t, J = 6 Hz, 2H, CHCH$_2$-CH_2O), 3.44 (t, J = 5 Hz, 2H, OCH_2CH$_2$OH), 3.70 (t, J = 5 Hz, 2H, CH_2OH), 4.20 (t, J = 6 Hz, 1H, C*H*), 7.08−7.18 (m, 8H, Ar*H*).

Method D[2]: (*R*)-1-(2-(2-(10,11-Dihydro-5H-dibenzo[*a*,*d*]-cyclohepten-5-yl)ethoxy)ethyl)-3-piperidinecarboxylic Acid Hydrochloride (37). A solution of **34** (0.2 g, 0.5 mmol) in MeOH (10 mL) was stirred under an atmosphere of hydrogen for 16 h at room temperature in the presence of 10 % Pd/C catalyst (50 % aqueous paste). The mixture was filtered, and the solvent was evaporated to give an oily residue, which was re-evaporated with acetone and then crystallized from acetone (10 mL). This afforded 0.13 g (65%) of **37**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.45 (brs, 1H, NCH$_2$CH_2CH_2-CH), 1.78−1.97 (m, 2H, NCH$_2$CH_2CH_2CH), 1.98−2.12 (brs, 1H, NCH$_2$CH_2CH_2CH), 2.22−2.31 (m, 2H, Ph$_2$CHCH_2), 2.85−3.35 (m, 11H, C*H*CO$_2$Et, NCH_2CH$_2$CH$_2$, 2 × CH_2O and PhCH_2CH_2-Ph), 3.45 (brs, 1H, NCH_2CH), 3.60 (brs,1H, NCH_2CH), 3.73 (brs, 2H, NCH_2CH$_2$O), 4.24 (brs, 1H, Ph$_2$C*H*), 7.10−7.20 (m, 8H, Ar*H*), 10.92 (brs, 1H, N*H*), 12.85 (brs, 1H, COO*H*).

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