Articles

Synthesis of Novel GABA Uptake Inhibitors. 4.[1] Bioisosteric Transformation and Successive Optimization of Known GABA Uptake Inhibitors Leading to a Series of Potent Anticonvulsant Drug Candidates

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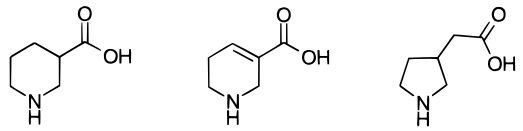
By bioisosteric transformations and successive optimization of known GABA uptake inhibitors, several series of novel GABA uptake inhibitors have been prepared by different synthetic approaches. These compounds are derivatives of nipecotic acid and guvacine, substituted at the nitrogen of these amino acids by various lipophilic moieties such as diarylaminoalkoxyalkyl or diarylalkoxyalkyl. The in vitro values for inhibition of [^{3}H]GABA uptake in rat synaptosomes was determined for each compound, and it was found that the most potent compound from this series, (*R*)-1-(2-(3,3-diphenyl-1-propyloxy)ethyl)-3-piperidinecarboxylic acid hydrochloride (**29**), is so far the most potent parent compound inhibiting GABA uptake into synaptosomes. Structure−activity results confirm our earlier observations, that an electronegative center in the chain connecting the amino acid and diaryl moiety is very critical in order to obtain high in vitro potency. 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). Some of the compounds tested show a high in vivo potency comparable with that of the recently launched anticonvulsant product **6** ((*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 human. These approaches include direct agonism of the GABA receptors,[11,12] inhibition of enzymatic breakdown of GABA,[13,14] or 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 humans.[16] However, in principle, GABA uptake inhibitors should exert a more therapeutically useful influence than GABA agonists. 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 either by 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] It was found that the type of GABA uptake inhibitors described in this paper is binding to the GAT-1 subtype.



1 2 3

Figure 1. Three cyclic amino acids which 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**)[18,19] (Figure 1) which can be considered as conformationally restricted GABA analogues[20] display in vitro activity as inhibitors of [^{3}H]GABA uptake. However, compounds **1**−**3** do not readily cross the blood-brain barrier.[18,21,22] In the 1980s, novel series of lipophilic GABA uptake inhibitors that possess potent activity in vitro and in vivo were described.[23−26] These compounds

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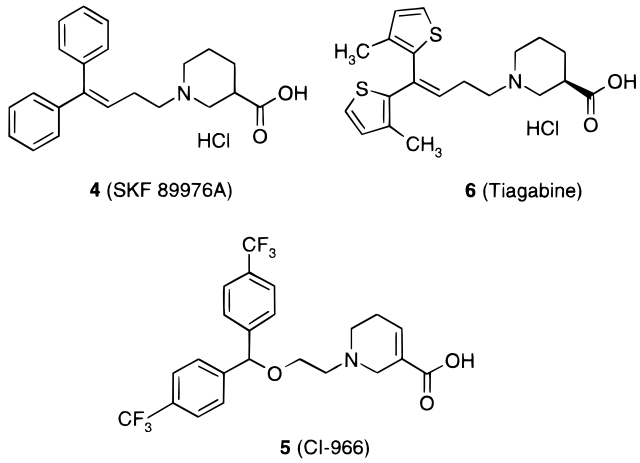


Figure 2. Lipophilic reference GABA uptake inhibitors.

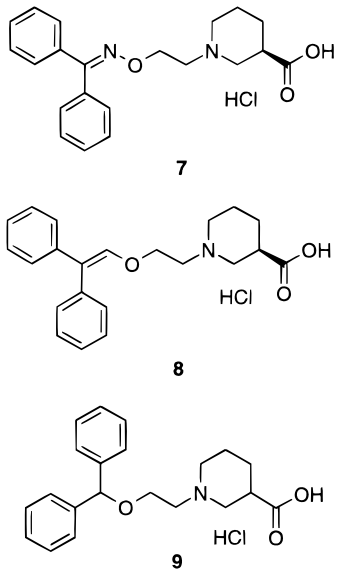


Figure 3. Potent GABA uptake inhibitors with an electronegative moiety introduced in the chain.

differ from compounds **1**−**3** in that they readily cross the blood-brain barrier probably due to the attachment of a lipophilic anchor to the nitrogen 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[23,27,28] in some animal models predictive of anticonvulsant activity.[29] The compounds also displayed reduced CNS depressant effects compared with some commonly used anticonvulsant drugs, such as diazepam.[30] These observations have also stimulated others to investigate this field,[31−36] leading to the discovery of a highly lipophilic GABA uptake inhibitor with CNS activity, **5** (CI-966). This compound was discovered at Parke-Davis/Warner-Lambert and has been investigated in a phase I clinical trial.[37] From our laboratory we have previously reported on the structure−activity studies leading to the choice of **6** (tiagabine, NO-328, or NNC 05-0328) as an anticonvulsant drug candidate.[24−26,38−40] Extensive pharmacological[41,42] and clinical investigations have been completed on **6** with proven anticonvulsant efficacy in humans.[43,44] This novel antiepileptic agent has now been launched for add-on therapy in the treatment of epilepsy.

During the development of this new drug we have continuously searched for GABA uptake inhibitors with improved properties as second-generation compounds. This resulted in a series of novel and highly potent GABA uptake inhibitors, of which **7** and **8** are examples[1] (Figure 3). In this type of compound we applied the electronegative principle in the chain and thereby improved in vitro GABA uptake inhibition considerably compared to compounds such as **4**−**6**. In our continued search for GABA uptake inhibitors with improved biological properties, we have investigated other structural features around these reference compounds. In one of these investigations we have modified compounds **4** and **9**[33,35,38] (analogue of **5**, Figure 3) by successive isosteric replacement, optimization of chain length, and electrostatic optimization into a series of new GABA uptake inhibitors. The synthesis[45] and biological activity of this series of GABA uptake inhibitors **10**−**35** (Table 1) will now be reported.

Chemistry

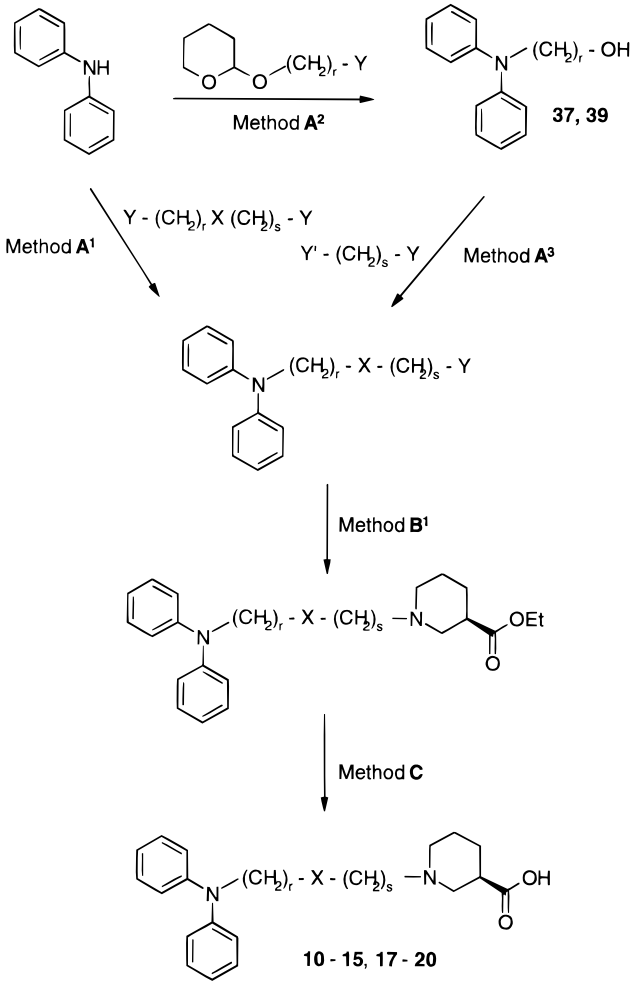
The overall general strategy used for the preparation of the new compounds presented in Table 1 was via *N*-alkylation of the parent cyclic amino acids **1** or **2**,[46] with the appropriate halogenide (Schemes 1−3, method B[1]) or mesylate or tosylate (Scheme 4, method B[2]). The parent cyclic amino acids were protected as their ester derivatives for this reaction. The separate enantiomers of **1** could be prepared by the published procedure involving resolution with either L-(+)- or with D-(−)-tartaric acid giving (*R*)- or (*S*)-ethyl nipecotate, respectively.[47,48]

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 featured in Table 1, isolated generally as their crystalline hydrochloride salts. Preparation of the various halides or mesylates of the diaryl chains used are further illustrated in Schemes 1−4.

Starting from diphenylamine several different methods were used to produce the desired chains in one or several steps (Scheme 1). *N*-Alkylation of diphenylamine with a bis-halogenide furnished the desired halogenide directly (method A[1]). For this *N*-alkylation NaH was used in a high-boiling solvent like dibutyl ether. This method was applicable for straight alkyl chains or the diethyl ether chain, as bis-chloroethyl ether is readily available. Alternatively, when oxygen was desired in the chain a two-step sequence was employed (methods A[2] and A[3]) in which the chain was built in successive alkylation steps (Scheme 1). *N*-Alkylation of diphenylamine with the appropriate haloalkyl tetrahydro-2-pyranyl ether[49−51] using NaH in a high-boiling solvent like diethylene glycol diethyl ether followed by removal of the THP group by hydrolysis in dilute acid furnished 2-(diphenylamino)ethanol[52] and 3-(diphenylamino)-1-propanol[53] (method A[2]). These alcohols were elongated by *O*-alkylation with a dihaloalkane in a high boiling solvent like dibutyl ether in the presence of NaH to give the desired diphenylaminoalkoxyalkyl halides (method A[3]). The halides were then converted into **10**−**15** and **17**−**20** by the general methods B[1] and C described above.

In general, aryl-substituted diphenylamines were not employed in the structure−activity studies concerning

Scheme 1. Synthesis of (*R*)-1-(Diphenylaminoalkyl)-3-piperidinecarboxylic acids **10**−**15** and (*R*)-1-(Diphenylaminoalkoxyalkyl)-3-piperidinecarboxylic Acids **17**−**20**[a]



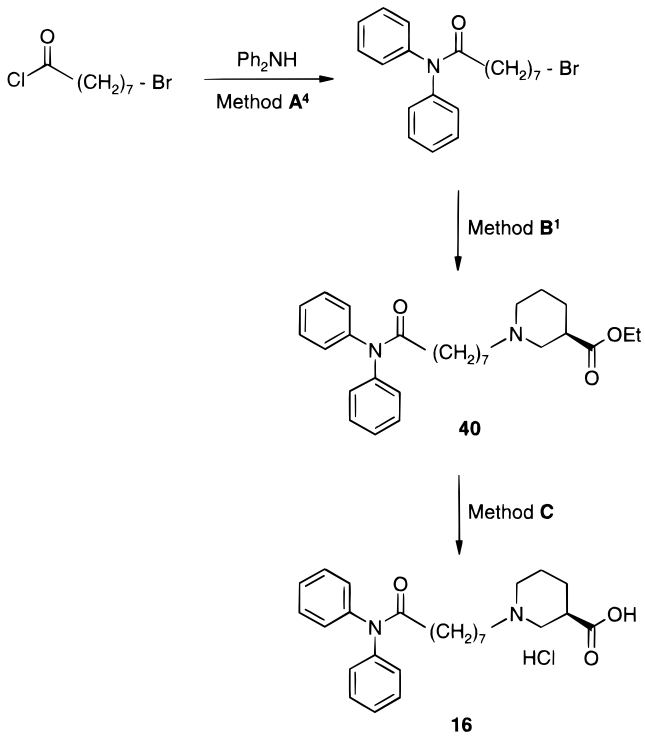
[a] Y, Y′ = Cl or Br; **10**−**15**: X = CH_2; *r* = 2−5; *s* = 0; **17**−**20**: X = O, OCH_2CH_2O; *r* = 2−3; *s* = 2−4. Methods A^1, A^2, and A^3: NaH, dibutyl ether, reflux. Method B^1: K_2CO_3, dibutyl ether or acetone, (*R*)-3-piperidinecarboxylic acid ethyl ester, reflux. Method C: (1) NaOH, EtOH, room temperature; (2) HCl.

substitution pattern on the aryl moieties. The reason being that this type of substituted starting amine is not very accessible, illustrated by tedious methods for their preparation and the low number of publications describing only a poor diversity of such derivatives of diphenylamine. Therefore, this type of structure−activity investigation was made on the diarylallyl or diarylalkyl derivatives described below, as aryl-substituted starting materials for this type of compound are much more accessible.

In the preparation of the more rigid amide analogue **16** of the above diphenylamine derivatives, the sodium salt of diphenylamine was acylated with 8-bromooctanoyl chloride in dibutyl ether (Scheme 2, method A^4). This furnished the desired 8-bromo-*N*,*N*-diphenyloctanamide which was converted into **16** by the general methods B^1 and C described above.

In Scheme 3, several methods for the preparation of diarylpropenyloxyalkyl and diarylpropoxyalkyl derivatives of **1** and **2** are illustrated. The preferred and general method utilized the appropriate diarylallyl bromide as starting material (method A^5). The allyl

Scheme 2. Synthesis of (*R*)-1-(8-(Diphenylamino)-8-oxo-1-octyl)-3-piperidinecarboxylic Acid **16**[a]



[a] Method A^4: NaH, dibutyl ether, reflux. Method B^1: K_2CO_3, acetone, (*R*)-3-piperidinecarboxylic acid ethyl ester, reflux. Method C: (1) NaOH, EtOH, room temperature; (2) HCl.

bromides used were prepared by known methods[54−57] from the appropriate propiophenone and an arylmagnesium reagent followed by dehydration in dilute acid and then bromination by NBS/peroxide. To elongate the chain in the allyl bromides, O-alkylation of a diol was employed (method A^5). 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 afforded a suspension of the corresponding lithiate salt to which the appropriate allyl bromide was added. The reaction mixture was then allowed to react for several days and worked up to give the diarylpropenyloxy alcohols. Further reaction of these alcohols via their mesylates or tosylates by the general methods B^2 and C described above produced the acids **21**−**26** with an unsaturated chain.

Preparation of compounds with a saturated chain can be accomplished in three different ways. The most convenient and direct route to produce chain-saturated derivatives is by catalytic hydrogenation of the corresponding acids holding an unsaturated chain (method D^2). Hydrogenation of the acid hydrochlorides **22** and **23** in the presence of 10% Pd/C in methanol afforded the corresponding saturated acid hydrochlorides **31** and **32**. However, it was observed that the ether linkage of the starting allyl ether was partly cleaved during hydrogenation.[58] This cleavage resulted in a byproduct with comparable polarity as in the product which made workup more tedious. To circumvent this problem, an alternative method was used in which hydrogenation was performed at an earlier step in the synthesis (method D^1). Hydrogenation of the hydroxyalkyl allyl ethers in the presence of 10% Pd/C in dioxane afforded the corresponding hydroxyalkyl alkyl ethers. Further

reaction of these saturated ethers by the general methods B[2] and C described above produced the acids **30** and **33**. This method is also critical for the preparation of derivatives of **2**, as the double bond in 1,2,5,6-tetrahydro-3-pyridinecarboxylic acid is easily hydrogenated. Therefore, the reductive step in the preparation of **33** must be performed before this amino acid is introduced in the synthesis.

The third method used for the preparation of diarylpropoxyalkyl derivatives employs 3,3-diphenyl-1-propanol as starting material (method A[6]). *O*-Alkylation of this alcohol with 2-bromoethyl tetrahydro-2-pyranyl ether in the presence of NaH in dibutyl ether followed by hydrolysis in dilute acid furnished the 2-(3,3-diphenyl-1-propyloxy)ethanol in a moderate yield. Further reaction of this alcohol by the general methods B[2] and C described above gave the acid **29**. However, this method was not generally employed, as the appropriate propanols are less available than the allyl bromides.

The diphenylalkenyl derivatives **27** and **28** were prepared via the diphenylalkenyl bromides (Scheme 4). Addition of 2 equiv of phenyllithium at low temperature to ethyl 6-bromohexanoate or ethyl 8-bromooctanoate followed by dehydration in dilute acid furnished the desired diphenylalkenyl bromides (method A[7]). The use of these bromides in the general methods B[1] and C described above produced the acids **27** and **28**. The double bonds in these acids could then be hydrogenated at normal pressure using 10% Pd/C in aqueous solution (method D[3]) to give the corresponding diphenylalkyl derivatives, exemplified by **34**.

To investigate whether a basic moiety was allowed in the chain, compound **35** was prepared (Scheme 5). 1-Bromo-3,3-diphenylpropane was treated with a 33% ethanolic methylamine solution at room temperature to give *N*-(3,3-diphenyl-1-propyl)-*N*-methylamine.[59] This secondary amine was then alkylated with (*R*)-1-(2-bromoethyl)-3-piperidinecarboxylic acid ethyl ester[60] in acetone in the presence of K_2CO_3 to give the ethyl ester derivative of **35** (method B[3]). Hydrolysis of the ester by the general method C afforded the desired acid derivative **35**.

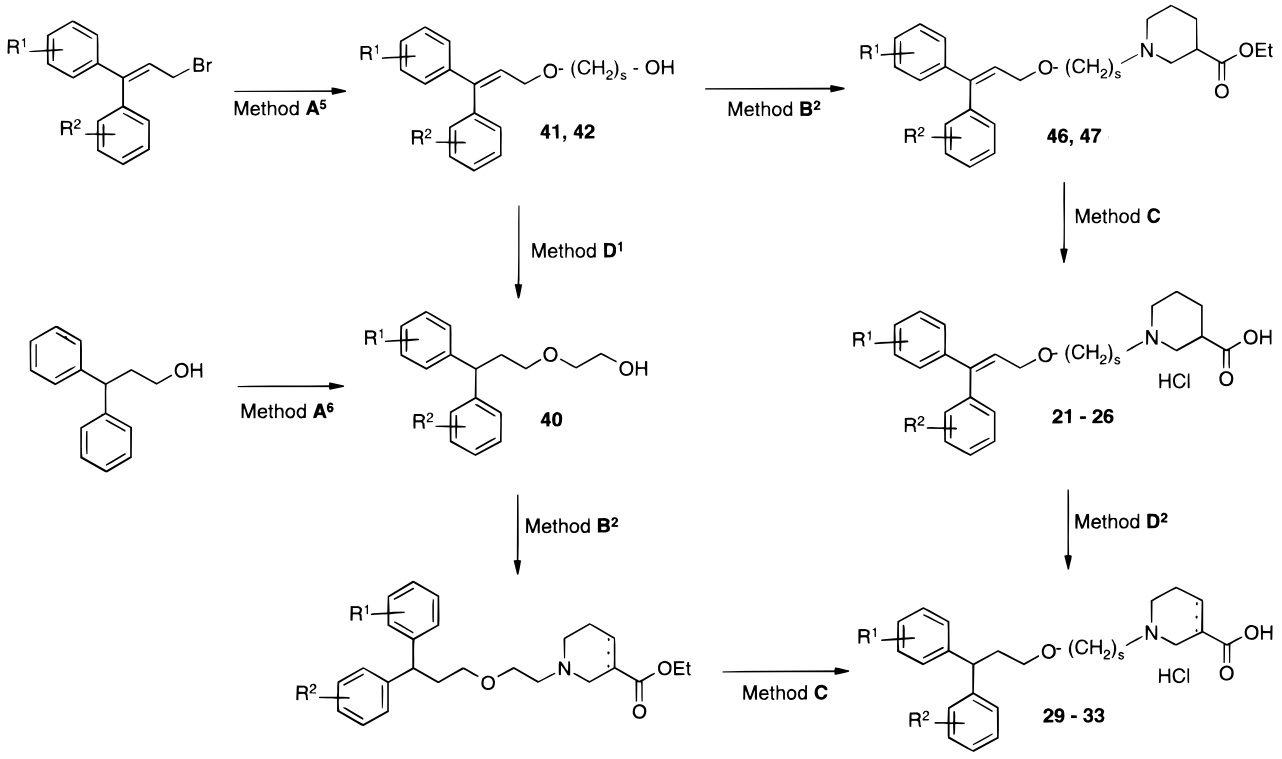
Biological Results and Discussion

With the aim to identify GABA uptake inhibitors with improved pharmacological properties, a large range of new GABA uptake inhibitors have been prepared.[45] Some representative examples of these compounds are included in Table 1. Their IC_{50} values for in vitro inhibition of [^{3}H]GABA uptake determined essentially by Fjalland's method[61] are included (mean of two determinations is given).

In the compounds **10**−**35**, steric and electronic properties of the aryl moieties as well as the chain linking the aryl and amino acid parts of the molecules have been varied in order to probe the requirements for inhibiting GABA transport at the site[62−65] involved in the uptake of GABA from the synaptic cleft into neuronal and glial cell bodies.

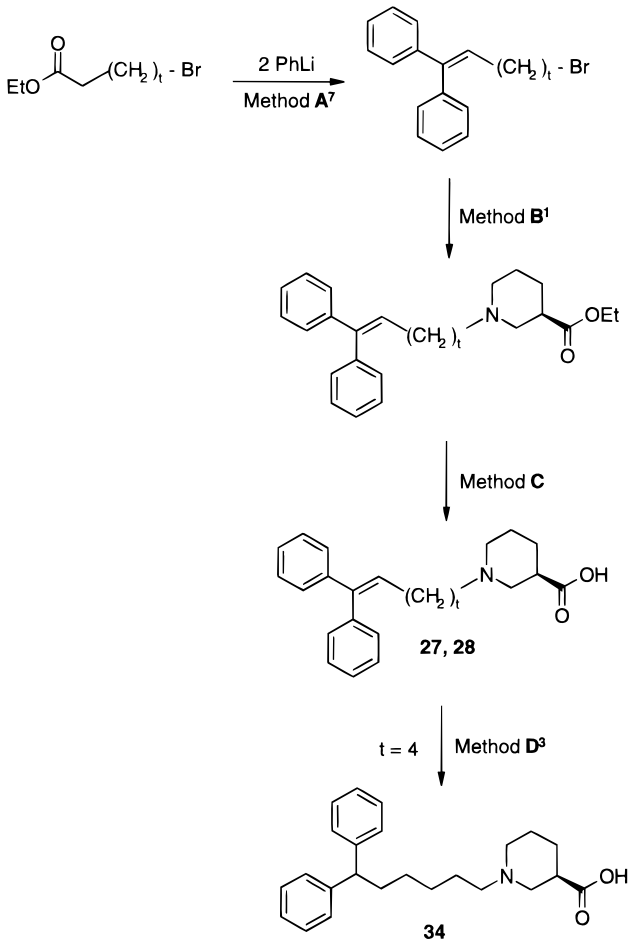
In the first series of diphenylamine derivatives represented by compounds **10**−**15** (Table 1), the central chain moieties (>C═CH− or >CH−O−) between the

Scheme 3. Synthesis of (1,1-Diaryl-1-propen-3-yl)oxyalkyl Amino Acids **21**−**26** and (3,3-Diaryl-1-propyl)oxyalkyl Amino Acids **29**−**33**[a]



[a] $s = 2-3$; R^1 and R^2, see Table 1. Method A[5]: *n*-BuLi, ethylene glycol or 1,3-propanediol, room temperature. Method A[6]: (1) NaH, dibutyl ether, reflux; (2) 2-bromoethyl tetrahydropyranyl ether, reflux; (3) H_2SO_4, *i*-PrOH, 60 °C. Method B[2]: (1) *n*-BuLi, THF or toluene, 10 °C; (2) *p*-tosyl chloride, room temperature; (3) K_2CO_3, (*R*)-3-piperidinecarboxylic acid ethyl ester or 1,2,5,6-tetrahydro-3-pyridinecarboxylic acid ethyl ester, reflux. Method C: (1) NaOH, EtOH, room temperature; (2) HCl. Method D[1]: H_2, 10% Pd/C, 1 atm, dioxane. Method D[2]: H_2, 10% Pd/C, 1 atm, MeOH.

Scheme 4. Synthesis of (*R*)-1-(Diphenylalkenyl)-3-piperidinecarboxylic Acids **27** and **28** and (*R*)-1-(6,6-Diphenyl-5-hexen-1-yl)-3-piperidinecarboxylic Acid **34**[a]

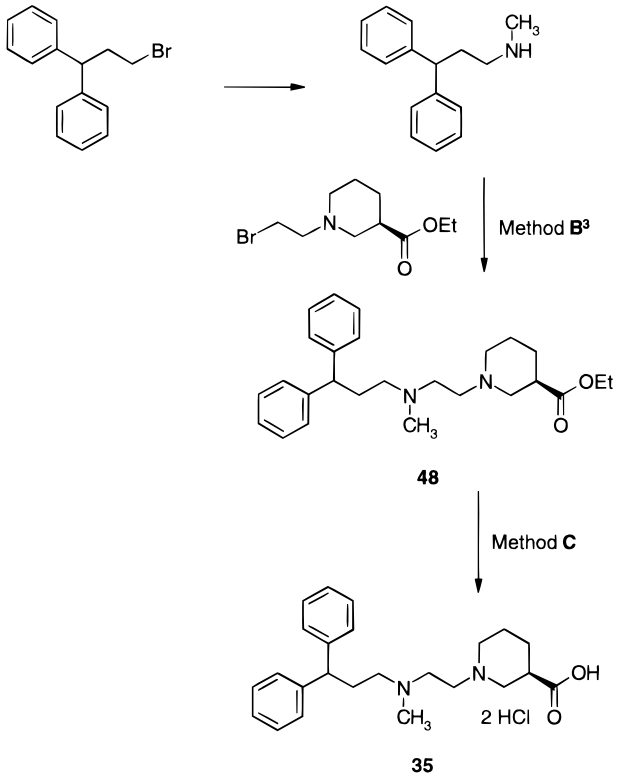


[a] $t = 4$ (**27**, **34**) or 6 (**28**). Method A[7]: (1) 2 PhLi, Et_2O, -60 °C; (2) H_2SO_4, *i*-PrOH, reflux. Method B[1]: K_2CO_3, (*R*)-3-piperidinecarboxylic acid ethyl ester, reflux. Method C: (1) NaOH, EtOH, room temperature; (2) HCl. Method D[3]: H_2, 10% Pd/C, 1 atm, H_2O.

aryl groups in **4** or **9**, respectively, have been replaced by the isosteric >N−CH_2− moiety. It is obvious from the data presented in Table 1 that direct replacement is not allowed as potency is completely lost when comparing the activity of compound **10** with that **4** and **9**. However, successive elongation of the chain in compound **10** leads to improved potency as shown in examples **11**−**14**. With an optimum of seven carbon atoms, as in example **14**, potency has been totally recovered again compared to the reference compounds. Further extension of the chain leads to a decrease in potency as shown by example **15**. Introduction of the conformationally more restricted amide moiety, as in example **16**, leads to a complete loss in affinity for the GABA uptake site.

With the optimized length of the chain we now applied the electronegative principle which we have described earlier.[1] In the second series of diphenylamine derivatives represented by compounds **17**−**20** (Table 1), an oxygen has been introduced in the chain. In this series the placement of the oxygen is very critical as can be seen by comparison of examples **18** and **19**. Further, to obtain potency optimization in this series, it is beneficial to shorten the chain length as illustrated by example **17**.

Scheme 5. Synthesis of (*R*)-1-(2-(*N*-(3,3-Diphenyl-1-propyl)-*N*-methylamino)ethyl)-3-piperidinecarboxylic Acid **35**[a]

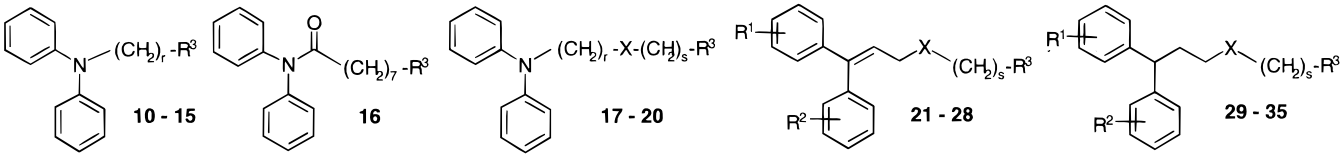


[a] Method B[3]: K_2CO_3, acetone, room temperature. Method C: (1) NaOH, EtOH, room temperature; (2) HCl.

Having applied the electronegative principle and having optimized the chain length in the diphenylamine series as discussed above, which resulted in the most potent compound **17** for the above-mentioned series, a reversed isosteric transformation was made from the >N−CH_2− moiety in this compound to a >C=CH− group represented in the corresponding allyl ether derivative **21**. Comparing the potency of this compound with that of the reference compounds **4** and **9**, this reverse change does not affect the potency significantly, as compound **21** is only moderately weaker than compound **17**. In the third series of allyl ether derivatives **21**−**26** prepared around **21**, the substitution pattern has been varied. As we have shown earlier,[1,38] an *o*-methyl substitution on both phenyl groups, as in example **23**, is beneficial for potency. As these methyl substituents only allow the out-of-plane conformations of the aryl groups in this compound, they may introduce the preferred conformations of the aryl groups in the binding site. One *o*-methyl substituent, as in example **22**, seems not to create enough strain in the diaryl moiety of this compound to improve potency compared to the parent compound **21**. As can be seen from the examples **25** and **26**, substitution in the para position affects binding negatively, although it does not abolish potency totally.

In the series of hydrogenated ether derivatives **29**−**33** a very different SAR is observed compared to the allyl ethers discussed above. Examples **29** and **30** from

Table 1. Chemical and Biological Data of the Novel GABA Uptake Inhibitors **10**−**35**



no.	*r*	*s*	R^1	R^2	X	R^{3a}	method for synthesis	mp (°C)	formula	microanalyses[b]	inhibition of GABA uptake IC_{50}(nM)[c]
4							[d]				330
6							[e]				67
7							[e]				137
8							[e]				104
9							[d]				1407
10	3					(*R*)-N	A^1B^1C	138−140[f]	$C_{21}H_{26}N_2O_2$,HCl	C,H,N,Cl	>9000
11	4					(*R*)-N	A^1B^1C	196−198[f]	$C_{22}H_{28}N_2O_2$,HCl	C,H,N,Cl	2608
12	5					(*R*)-N	A^1B^1C	175−178[f]	$C_{23}H_{30}N_2O_2$,HCl,2H_2O	C,H,N,Cl	1381
13	6					(*R*)-N	A^1B^1C	143−146[g]	$C_{24}H_{32}N_2O_2$,HCl	C,H,N,Cl	659
14	7					(*R*)-N	A^1B^1C	115−120[f]	$C_{25}H_{34}N_2O_2$,HCl	C,H,N,Cl	232
15	8					(*R*)-N	A^1B^1C	80−86[f]	$C_{26}H_{36}N_2O_2$,HCl	C,H,N,Cl	1293
16						(*R*)-N	A^4B^1C	amorphous	$C_{26}H_{34}N_2O_3$,HCl,H_2O	C,H,N	>9000
17	2	2			−O−	(*R*)-N	A^1B^1C	145−148[f]	$C_{22}H_{28}N_2O_3$,HCl,2H_2O	C,H,N,Cl	90
18	2	4			−O−	(*R*)-N	$A^2A^3B^1C$	oil	$C_{24}H_{32}N_2O_3$,HCl	C,H,N,Cl	300
19	3	3			−O−	(*R*)-N	$A^2A^3B^2C$	138−140[f]	$C_{24}H_{32}N_2O_3$,HCl	C,H,N,Cl	>3000
20	2	2			$-OCH_2CH_2O-$	(*R*)-N	A^1B^1C	oil	$C_{24}H_{32}N_2O_4$,HCl,H_2O	C,H,N,Cl	>9000
21		2	H	H	−O−	(*R*)-N	A^5B^2C	160−165[f]	$C_{23}H_{27}NO_3$,HCl,2H_2O	C,H,N,Cl	258
22		2	2-CH_3	H	−O−	(*R*)-N	A^5B^2C	145−150[h]	$C_{24}H_{29}NO_3$,HCl	C,H,N,Cl	236
23		2	2-CH_3	2-CH_3	−O−	(*R*)-N	A^5B^2C	188−190[i]	$C_{25}H_{31}NO_3$,HCl	C,H,N	114
24		3	2-CH_3	2-CH_3	−O−	(*R*)-N	A^5B^2C	156−158[i]	$C_{26}H_{33}NO_3$,HCl	C,H,N	75
25		2	4-Cl	4-Cl	−O−	(*R*)-N	A^5B^2C	203−204[f]	$C_{23}H_{25}Cl_2NO_3$,HCl,H_2O	C,H,N,Cl	955
26		2	4-F	4-F	−O−	(*R*)-N	A^5B^2C	184−186[f]	$C_{23}H_{25}F_2NO_3$,HCl	C,H,N	1462
27		2	H	H	$-CH_2-$	(*R*)-N	A^7B^1C	164−168[h]	$C_{24}H_{29}NO_2$,HCl	C,H,N,Cl	2256
28		4	H	H	$-CH_2-$	(*R*)-N	A^7B^1C	90−95[j]	$C_{26}H_{33}NO_2$,HCl,2H_2O	C,H,N,Cl	1359
29		2	H	H	−O−	(*R*)-N	A^6B^2C	178−179[f]	$C_{23}H_{29}NO_3$,HCl,2H_2O	C,H,N,Cl	55
30		2	H	H	−O−	GUV	$A^5D^1B^2C$	155−156[h]	$C_{23}H_{27}NO_3$,HCl	C,H,N,Cl	48
31		2	2-CH_3	H	−O−	(*R*)-N	$A^5B^2CD^2$	137−140[h]	$C_{24}H_{29}NO_3$,HCl,2H_2O	C,H,N,Cl	86
32		2	2-CH_3	2-CH_3	−O−	(*R*)-N	$A^5B^2CD^2$	193−196[h]	$C_{25}H_{33}NO_3$,HCl	C,H,N	358
33		2	4-F	4-F	−O−	(*R*)-N	$A^5D^1B^2C$	154−156[j]	$C_{23}H_{27}F_2NO_3$,HCl	C,H,N	675
34		2	H	H	$-CH_2-$	(*R*)-N	$A^7B^1CD^3$	148−150[f]	$C_{24}H_{31}NO_2$,HCl,4H_2O	C,H,N,Cl	1585
35		2	H	H	>NCH_3	(*R*)-N	B^3C	232−234[k]	$C_{24}H_{32}N_2O_2$,2HCl	C,H,N,Cl	5699

[a] N represents nipecotic acid (see **1**); GUV represents guvacine (see **2**); both 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), mean of two determinations. [d] Ref 38. [e] Ref 1. Compounds were crystallized from [f]acetone; [g]CH_2Cl_2; [h]EtOAc/acetone; [i]MeOH/$PhCH_3$; [j]EtOAc; [k]2-PrOH.

this series are so far the most potent parent compounds inhibiting GABA uptake into synaptosomes. Opposite to the observations made above, the effects of *o*-methyl substituents on the phenyl groups are very different in this series. One *o*-methyl substituent, as in example **31**, lowers the potency to some extent, but *o*-methyl substituents on both phenyl groups, as in example **32**, lower the potency considerably in this series. The explanation for this missing ortho effect may be the change in the strain between the aryl groups going from a strained sp^2 system in the allyl ethers to a less strained sp^3 system in the hydrogenated analogues. In the former series, the methyl substituents are needed in order to bring the aryl groups in a preferred out-of-plane conformation, whereas in the latter series, the aryl groups are easily oriented in the preferred conformations due to the sp^3 system. Again, para substitution is not beneficial in this series either as exemplified by compound **33**.

To further investigate the importance on potency of the oxygen in the chain, oxygen has been replaced by a methylene group, as in examples **27**, **28**, and **34**. Inspection of the data in Table 1 show that this replacement lowers the potency 10 times in the allyl ether series (**27** compared to **21**) and 50 times in the hydrogenated series (**34** compared to **29**) indicating that the oxygen may be an important pharmacophoric element which participates in binding to the GABA uptake site. On the other hand, oxygen in the chain instead of a methylene group will create a much higher degree of rotational freedom, which may increase the probability for the molecule to populate more preferred conformations for binding to the GABA uptake site. Another exchange of oxygen is shown in example **35** where the oxygen atom of **29** was replaced by >NMe. The low affinity of **35** shows that this replacement is not beneficial; however, the major loss of activity may be due to the steric bulk introduced by the methyl group. Attempts to prepare the nonmethylated compound have so far been unsuccessful.

In Table 2 the in vivo anticonvulsant effect in mice (expressed as ED_{50} values in mg/kg) for representative compounds which inhibited [^{3}H]GABA uptake is illustrated. The anticonvulsant effect is measured as 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.[26] In Table 2 we have also listed the ED_{50} values found in the rotarod performance test and calculated the protective index as the ratio between ED_{50} values found in

Table 2. Anticonvulsant Properties of Selected Compounds

no.	DMCM ED_{50} (mg/kg)[a]	rotarod ED_{50} (mg/kg)[b]	protective index[c]
4	3.1		
6	1.2	5.5	4.6
7	3.2		
8	1.5	5.4	3.6
9	6.0		
12	36		
13	36		
14	12		
17	10	16	1.6
18	34		
21	3.8	23	6.1
22	5.4	21	3.9
23	3.4	14	4.1
24	5.0	24	4.8
25	>60		
28	75	>90	>1.2
29	1.7	9.0	5.3
30	1.6	6.8	4.3
31	4.4	19	4.3
32	6.8	30	4.4
33	21	54	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 and inhibition of DMCM-induced convulsions in mice.

the rotarod performance test and inhibition of DMCM-induced convulsions in mice. As can be seen from Table 2 the compounds with highest affinity for the GABA uptake site, generally, also show a high in vivo potency. Further, the two most potent compounds (**24** and **29**) show an in vivo potency and protective index comparable to that of reference compounds such as **6** and **8**.

Conclusion

In our initial communication[38] we concluded on some of the reasoning behind the selection of **6** as an anticonvulsant drug candidate. However, during development of this compound, a demand for a second generation compound with a longer duration of action and broader therapeutic window became clear. Therefore we initiated the search for novel series of compounds which could be selected and optimized with respect to these features. With the compounds described in this publication, we have now identified several series of GABA uptake inhibitors with high in vitro potency and in vivo efficacy which are comparable with those found for compound **6**. These new anticonvulsant compounds could therefore potentially serve as second-generation drug candidates. A broad range of compounds from these novel series[45] as well as those described earlier[1] have now been put through extended investigations for a longer duration of action and metabolism studies as well as for a broader therapeutic ratio. However, these investigations have not revealed any suitable compounds for further development so far. The effort to refine the pharmacological profile of this type of compound has therefore been continued and resulted in the identification of new classes of compounds which will be reported at a later date.

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 were 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 which can be prepared by methods known per se.[49−57] Column chromatography was carried out using the technique described by Still et al.,[66] on Merck silica gel 60 (Art. 9385) using thick-walled glass columns and TLCs on Merck silica gel 60, 5 × 20 cm plates (Art. 5714).

Synaptosomal [^{3}H]GABA Uptake. Uptake of [^{3}H]GABA into synaptosomal preparations was assayed by a filtration assay.[61] 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; 50 μL of this synaptosomal suspension (0.1 mg of 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 50 μL of [^{3}H]GABA (final concentration 0.9 nM) and unlabeled GABA (final concentration 0.9 nM) were 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 DMCM in Mice.[26] 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 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.[26] The animals were pretrained in the rotarod apparatus (Ugo-Basile, Italy) for 2 min before testing (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}B^1: (*R*)-1-(6-(Diphenylamino)-1-hexyl)-3-piperidinecarboxylic Acid Ethyl Ester (36). A mixture of NaH (0.7 g, 0.023 mol, 80% oil dispersion) and diphenylamine (3.4 g, 0.020 mol) in dry dibutyl ether (30 mL) was heated at reflux for 1 h under N_2. The reaction mixture was cooled and 1,6-dibromohexane (3.1 mL) was added. The mixture was heated at reflux for 3 h and then cooled to 40 °C. Ethyl (*R*)-3-piperidinecarboxylate (3.5 g, 0.022 mol) and K_2CO_3 (3.1 g, 0.022 mol) were added and the mixture was heated at reflux for 16 h under N_2. EtOAc (50 mL) was added, the mixture was filtered, and the solvent was evaporated. The residue was purified by chromatography on silica gel (200 g, *n*-heptane/THF = 4:1) to give 3.4 g (42%) of **36** as an oil: TLC R_f 0.26 (SiO_2; *n*-heptane/THF = 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, 3H, CH_2CH_3), 1.2−2.1 (m, 14H, $NCH_2CH_2CH_2CH$ and $CH_2(CH_2)_4CH_2$), 2.29 (t, 2H, $NCH_2(CH_2)_5$), 2.54 (m, 1H, $CHCO_2$-Et), 2.74 (d, 1H, NCH_2CH), 2.97 (d, 1H, NCH_2CH), 3.67 (t, 2H,

Ph_2NCH_2), 4.12 (q, 2H, CH_2CH_3), 6.94 (t, 2H, *p*-Ar*H*), 6.98 (d, 4H, *o*-Ar*H*), 7.26 (t, 4H, *m*-Ar*H*).

Method A[2]: 2-(Diphenylamino)ethanol (37).[52] A mixture of NaH (2.0 g, 0.050 mol, 60% oil dispersion), diphenylamine (7.6 g, 0.045 mol), and dry diethylene glycol dimethyl ether (30 mL) was stirred for 3 h at 135 °C under N_2. The reaction mixture was cooled and placed on an ice-bath. 2-Bromoethyl tetrahydropyran-2-yl ether (10.5 g, 0.050 mol) in dry dibutyl ether (15 mL) was added and the mixture was stirred for 3 h at 120 °C. The mixture was cooled, poured into water (300 mL), and extracted with EtOAc (2 × 200 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated. The residue was dissolved in 2-propanol (150 mL) and 4 N H_2SO_4 (30 mL) was added. The mixture was stirred at 60 °C for 30 min and 4 N NaOH was added until pH 7. The neutralized mixture was poured into H_2O (1 L) and extracted with EtOAc (2 × 250 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by chromatography on silica gel (200 g, *n*-heptane/THF = 4:1) to give 5.4 g (56%) of **37** as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.84 (t, 1H, O*H*), 3.83 (q, 2H, CH_2O), 3.93 (t, 2H, NCH_2), 6.99 (t, 2H, *p*-Ar*H*), 7.07 (d, 4H, *o*-Ar*H*), 7.30 (t, 4H, *m*-Ar*H*).

3-(Diphenylamino)-1-propanol (38).[53] Prepared in 46% yield from 3-bromo-1-propyl tetrahydro-2-pyranyl ether by a method similar to that described above: ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.55 (s, 1H, O*H*), 1.85 (quint, 2H, $CH_2CH_2CH_2$), 3.66 (t, 2H, CH_2OH), 3.80 (t, 2H, NCH_2), 6.8−7.4 (m, 10H, Ar*H*).

Method A[3]B[1]: (*R*)-1-(4-(2-(Diphenylamino)ethoxy)-1-butyl)-3-piperidinecarboxylic Acid Ethyl Ester **(39)**. NaH (0.4 g, 10.0 mmol, 60% oil dispersion) was suspended in dry dibutyl ether (25 mL) under N_2 and **37** (2.1 g, 10.0 mmol) was added. The mixture was stirred for 1 h at room temperature and then heated at 130 °C for 1 h. LiH (0.1 g) was added and the mixture was heated at reflux for 1 h. The mixture was cooled to 80 °C and 1-bromo-4-chlorobutane (2.0 g, 12 mmol) was added. The reaction mixture was heated at reflux for 12 h and then another portion of 1-bromo-4-chlorobutane (4.0 g, 23 mmol) was added. Heating was continued for another 24 h. Dibutyl ether (25 mL) was added to the cooled reaction mixture and then, carefully, H_2O (25 mL) was added. The organic phase was separated and dried (K_2CO_3) and the solvent evaporated. The residue was purified by chromatography on silica gel (100 g, *n*-heptane/THF = 4:1) to give 2.0 g of 1-chloro-4-(2-(diphenylamino)ethoxy)butane. A suspension of the above chloride (2.0 g, 6.6 mmol), ethyl (*R*)-3-piperidinecarboxylate (1.1 g, 7.0 mmol), K_2CO_3 (1.0 g, 7.2 mmol), and dry dibutyl ether (25 mL) was heated at 150 °C for 4 h. The mixture was cooled and filtered and the solvent evaporated. The residue was purified by chromatography on silica gel (150 g, *n*-heptane/THF = 4:1) to give 1.5 g (34%) of **39** as an oil: TLC R_f 0.23 (SiO_2; *n*-heptane/THF = 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, 3H, CH_2CH_3), 1.4−2.1 (m, 10H, N $CH_2CH_2CH_2$CH and N $CH_2CH_2CH_2CH_2$O), 2.34 (t, 2H, $NCH_2CH_2CH_2CH_2$O), 2.56 (m, 1H, $CHCO_2$Et), 2.75 (d, 1H, NCH_2CH), 2.98 (d, 1H, NCH_2-CH), 3.44 (t, 2H, $NCH_2CH_2CH_2CH_2$O), 3.65 (t, 2H, N CH_2CH_2O), 3.95 (t, 2H, NCH_2CH_2O), 4.15 (q, 2H, CH_2CH_3), 6.96 (t, 2H, *p*-Ar*H*), 7.06 (d, 4H, *o*-Ar*H*), 7.29 (t, 4H, *m*-Ar*H*).

Method A[4]B[1]: (*R*)-1-(8-(Diphenylamino)-8-oxo-1-octyl)-3-piperidinecarboxylic Acid Ethyl Ester (40). A mixture of NaH (0.40 g, 0.010 mol, 60% oil dispersion), diphenylamine (1.7 g, 0.010 mol), and dry dibutyl ether (25 mL) was stirred for 3 h at reflux under N_2. The reaction mixture was allowed to cool to 60 °C and 8-bromooctanoyl chloride (2.4 g, 10 mmol) was added. Then the mixture was heated at reflux for 3 h. To the cooled mixture were added ice-cold 2 N HCl (50 mL) and EtOAc (50 mL). The phases were separated, the organic phase was dried (Na_2SO_4), and the solvent was evaporated. The residue was dissolved in acetone (25 mL) and ethyl (*R*)-piperidinecarboxylate (2.0 g, 12.7 mmol) and K_2CO_3 (1.8 g, 13 mmol) were added. The mixture was heated at reflux for 8 h and then stirred at room temperature for 2 days. The reaction mixture was filtered and the solvent evaporated to give an oily residue which was purified by chromatography on silica gel (150 g, *n*-heptane/EtOAc = 3:7) to give 1.3 g of **40** (29%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, 3H, CH_2CH_3), 1.2−2.1 (m, 16H, $NCH_2CH_2CH_2$CH and $CH_2(CH_2)_5CH_2$), 2.25 (t, 2H, CH_2C=O), 2.27 (t, 2H, N $CH_2(CH_2)$6), 2.55 (m, 1H, $CHCO_2$-Et), 2.76 (d, 1H, NCH_2CH), 2.98 (d, 1H, NCH_2CH), 4.12 (q, 2H, CH_2CH_3), 7.2−7.4 (m, 10H, Ar*H*).

Method A[5]: 2-((1-(2-Methylphenyl)-1-phenyl-1-propen-3-yl)oxy)ethanol (41). A solution of *n*-BuLi in hexanes (13.0 mL, 2.5 M) was added dropwise under N_2 to ethylene glycol (30 mL) at 10 °C. When addition was complete the mixture was stirred 0.5 h at room temperature. 3-Bromo-1-(2-methylphenyl)-1-phenyl-1-propene (9.3 g, 32 mmol) was added and the reaction mixture was stirred at room temperature for 100 h. The mixture was poured in H_2O (200 mL) and extracted with EtOAc (3 × 75 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated. Chromatography of the residue on silica gel (200 g, *n*-heptane/THF = 4:1) provided 3.9 g (45%) of **41**: TLC R_f 0.20 (SiO2; *n*-heptane/THF = 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz shows mixture (1:9) of the two *E*/*Z* isomers) δ major isomer 2.06 (s, 3H, CH_3), 3.47 (t, 2H, CH_2CH_2OH), 3.69 (t, 2H, CH_2OH), 3.93 (br m, 2H, =$CHCH_2$), 6.36 (t, 1H, =C*H*), 7.1−7.3 (m, 9H, Ar*H*); δ minor isomer 2.02 (s, 3H, CH_3), 3.56 (t, 2H, CH_2CH_2OH), 3.74 (t, 2H, CH_2OH), 4.27 (d, 2H, =$CHCH_2$), 5.86 (t, 1H, =C*H*), 7.1−7.3 (m, 9H, Ar*H*).

3-((1,1-Bis(2-methylphenyl)-1-propen-3-yl)oxy)-1-propanol (42). A solution of *n*-BuLi in hexanes (15.2 mL, 2.5 M) was added dropwise under N_2 to 1,3-propanediol (31 mL) on an ice bath. When addition was complete the mixture was stirred 0.5 h at room temperature. 3-Bromo-1,1-bis(2-methylphenyl)-1-propene (11.5 g, 38 mmol) was added and the reaction mixture was stirred at room temperature for 48 h and at 75 °C for 36 h. H_2O (100 mL) was added and the mixture was extracted with EtOAc (100 mL). The phases were separated and the organic phase was washed with H_2O (2 × 50 mL) and dried ($MgSO_4$) and the solvent evaporated. Chromatography of the residue on silica gel (300 g) using a gradient of *n*-heptane in EtOAc as eluent provided 3.5 g (31%) of **42**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80 (quint, 2H, $CH_2CH_2CH_2$), 2.07 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.36 (t, 1H, O*H*), 3.57 (t, 2H, OCH_2CH_2), 3.76 (q, 2H, CH_2OH), 3.97 (d, 2H, =$CHCH_2O$), 5.93 (t, 1H, =C*H*), 7.1−7.2 (m, 8H, Ar*H*).

Method A[6]: 2-(3,3-Diphenyl-1-propyloxy)ethanol (43). A mixture of NaH (0.80 g, 0.020 mol, 60% oil dispersion) and 3,3-diphenyl-1-propanol (4.25 g, 0.020 mol) in dry dibutyl ether (30 mL) was stirred at room temperature for 30 min and then heated at reflux for 2.5 h under N_2. The reaction mixture was cooled to 60 °C, 2-bromoethyl tetrahydro-2-pyranyl ether (4.2 g, 0.020 mol) was added, and the mixture was heated at reflux for 16 h under N_2. The reaction mixture was cooled and washed with H_2O and the organic solvent evaporated. Chromatography of the residue on silica gel (150 g, *n*-heptane/THF = 4:1) provided 2.6 g of an oil, which was dissolved in 2-propanol (25 mL). 4 N H_2SO_4 (10 mL) was added and the mixture was stirred at 60 °C for 1 h. CH_2Cl_2 (250 mL) was introduced and the separated organic phase was washed with H_2O (2 × 100 mL) and 5% aqueous $NaHCO_3$ (100 mL). The organic phase was dried (Na_2SO_4) and the solvent evaporated. This afforded 2.5 g (49%) of **43** as an oil. The ^{1}H NMR spectra was identical with that obtained from the material prepared by method D[1].

Method A[7]: 8-Bromo-1,1-diphenyl-1-octene (44). A solution of ethyl 8-bromooctanoate (2.5 g, 10 mmol) in dry Et_2O (5 mL) was added at −35 °C to a mixture of phenyllithium (12 mL, 24 mmol, 2 M in *c*-hexane/Et_2O) and dry Et_2O (15 mL) kept under N_2. When addition was complete the mixture was stirred at −35 °C for 1 h and then at −60 °C for 5 h. 4 N H_2SO_4 (10 mL) was added at −60 °C and the reaction mixture was allowed to warm to 10 °C. The phases were separated and from the organic phase the solvent was evaporated. The oily residue was dissolved in a mixture of 2-propanol (50 mL) and 4 N H_2SO_4 (20 mL) and heated at reflux for 1 h. The mixture was allowed to cool and the volatiles were removed to give a residue which was diluted with water and then extracted with Et_2O (2 × 50 mL). The combined organic extracts were dried

(Na_2SO_4) and the solvent was evaporated to give 3.1 g of **44** (90%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.2−1.9 (m, 8H, =CHCH$_2$CH_2CH_2CH_2CH_2CH$_2$Br), 2.11 (q, 2H, =CHCH_2), 3.35 (t, 2H, CH_2Br), 6.07 (t, 1H, =C*H*), 7.15−7.6 (m, 10 H, Ar*H*).

Method B[1]: (*R*)-1-(8,8-Diphenyl-7-octen-1-yl)-3-piperidinecarboxylic Acid Ethyl Ester (45). A suspension of **44** (3.1 g, 9.0 mmol), ethyl (*R*)-piperidinecarboxylate (2.0 g, 12.7 mmol), K_2CO_3 (1.9 g, 13.5 mmol), and KI (0.2 g) in acetone (30 mL) was stirred at room temperature for 4 days. The mixture was filtered and the solvent evaporated. The oily residue was purified by chromatography on silica gel (200 g, *n*-heptane/EtOAc = 7:3) to give 1.6 g (42%) of **45** as an oil: TLC R_f 0.20 (SiO_2; *n*-heptane/EtOAc = 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, 3H, CH$_2$CH_3), 1.3−2.1 (m, 14H, NCH_2-CH_2CH_2CH and =CHCH$_2$CH_2CH_2CH_2CH_2CH$_2$), 2.10 (q, 2H, =CHCH_2), 2.28 (t, 2H, NCH_2CH$_2$CH$_2$CH$_2$CH$_2$), 2.55 (m, 1H, C*H*CO$_2$Et), 2.76 (d, 1H, NCH_2CH), 2.99 (d, 1H, NCH_2CH), 4.11 (q, 2H, CH_2CH$_3$), 6.06 (t, 1H, =C*H*), 7.15−7.4 (m, 10H, Ar*H*).

Method B[2]: (*R*)-1-(2-((1-(2-Methylphenyl)-1-phenyl-1-propen-3-yl)oxy)ethyl)-3-piperidinecarboxylic Acid Ethyl Ester (46). A solution of **41** (3.4 g, 12.5 mmol) in dry THF (30 mL) kept under N_2 was cooled to 10 °C. A solution of *n*-BuLi in hexanes (5.5 mL, 2.5 M) was added dropwise and the reaction mixture was stirred for 0.5 h at room temperature. *p*-Toluenesulfonyl chloride (2.6 g, 13.8 mmol) was added and the mixture was stirred at room temperature for 1.5 h. Ethyl (*R*)-3-piperidinecarboxylate (2.9 g, 18.8 mmol) and K_2CO_3 (2.6 g, 18.8 mmol) were added and the mixture was heated at reflux for 18 h. The cooled reaction mixture was poured into ice−water (200 mL) and extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with a 10% sodium citrate buffer solution (2 × 100 mL, pH 6). The organic phase was extracted with a 5% citric acid solution (4 × 75 mL) and the combined acidic aqueous extracts were washed with toluene (50 mL). To the acidic aqueous solution was added 4 N NaOH until pH 9 and this solution was immediately extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated to give 2.3 g (45%) of **46** as an oil: TLC R_f 0.23 (SiO_2; *n*-heptane/THF = 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz shows a mixture (1:9) of the two *E*/*Z* isomers) δ major isomer 1.25 (t, 3H, CH$_2$CH_3), 1.35−1.75 (m, 3H, N CH_2CH_2CH_2CH), 1.95−2.05 (m, 5H, NCH_2CH_2CH_2CH and ArCH_3), 2.57 (m, 3H, C*H*CO$_2$Et and OCH$_2$CH_2N), 2.80 (d, 1H, NCH_2CH), 3.03 (d, 1H, NCH_2CH), 3.50 (t, 2H, OCH_2CH$_2$N), 3.90 (brs, 2H, =CH CH_2), 4.12 (q, 2H, CH_2CH$_3$), 6.35 (t, 1H, =C*H*CH$_2$), 7.1−7.3 (m, 9H, Ar*H*); δ minor isomer 1.25 (t, 3H, CH$_2$CH_3), 1.35−1.75 (m, 3H, NCH_2CH_2CH_2CH), 1.95−2.05 (m, 5H, N CH_2CH_2-CH_2CH and ArCH_3), 2.57 (m, 3H, C*H*CO$_2$Et and O CH$_2$CH_2N), 2.80 (d, 1H, NCH_2CH), 3.03 (d, 1H, NCH_2CH), 3.58 (t, 2H, OCH_2CH$_2$N), 4.12 (q, 2H, CH_2CH$_3$), 4.26 (d, 2H, =CHCH_2), 5.85 (t, 1H, =C*H*CH$_2$), 7.1−7.3 (m, 9H, Ar*H*).

(*R*)-1-(3-((1,1-Bis(2-methylphenyl)-1-propen-3-yl)oxy)-1-propyl)-3-piperidinecarboxylic Acid Ethyl Ester (47). A solution of **42** (3.45 g, 11.6 mmol) in dry toluene (150 mL) was cooled on an ice bath and a solution of *n*-BuLi in hexanes (5.1 mL, 2.5 M) was added dropwise. The reaction mixture was stirred for 15 min at room temperature, *p*-toluenesulfonyl chloride (2.44 g, 12.8 mmol) was added, and the mixture was stirred at room temperature for 3 h. Ethyl (*R*)-3-piperidinecarboxylate (4.5 g, 23.3 mmol) and K_2CO_3 (3.2 g, 23.3 mmol) were added and the mixture was stirred at room temperature for 0.5 h and then at 75 °C for 12 h. KI (1.0 g) and acetone (40 mL) were added and the mixture was heated at reflux for 15 h. The reaction mixture was diluted with acetone (50 mL) and cooled and the solvent evaporated. Chromatography of the residue on silica gel (280 g) using a gradient of *n*-heptane in EtOAc as eluent afforded 2.6 g (52%) of **47** as an oil: TLC R_f 0.52 (SiO_2; MeOH/EtOAc = 1:9); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.17 (t, 3H, CH$_2$CH_3), 1.35−1.75 (m, 6H, NCH_2CH_2CH_2-CH and O CH$_2$CH_2CH$_2$N), 1.95 (m, 1H, NCH_2CH_2CH_2CH), 2.02 (s, 3H, ArCH_3), 2.13 (m, 1H, NCH_2CH_2CH_2CH), 2.22 (s, 3H, ArCH_3), 2.27 (m, 2H, OCH$_2$CH$_2$CH_2N), 2.42 (m, 1H, C*H*CO$_2$Et), 2.55 (d, 1H, NCH_2CH), 2.71 (d, 1H, NCH_2CH), 3.35 (m, 2H, OCH_2CH$_2$CH$_2$N), 3.85 (d, 2H, =CHCH_2), 4.03 (q, 2H, CH_2CH$_3$), 5.85 (t, 1H, =C*H*CH$_2$), 7.0−7.2 (m, 8H, Ar*H*).

Method B[3]: (*R*)-1-(2-(*N*-(3,3-Diphenyl-1-propyl)-*N*-methylamino)ethyl)-3-piperidinecarboxylic Acid Ethyl Ester (48). A suspension of (3,3-diphenyl-1-propyl)(methyl)amine[59] (1.1 g, 4.7 mmol), K_2CO_3 (1.9 g, 14 mmol), and (*R*)-1-(2-bromoethyl)-3-piperidinecarboxylic acid ethyl ester[60] (1.6, 4.7 mmol) in acetone (25 mL) was stirred at room temperature for 3 weeks. The reaction mixture was filtered and the solvent was evaporated. The oily residue was purified by chromatography on silica gel (200 g, *n*-heptane/THF = 1:1) to give 0.7 g (36%) of **48** as an oil: R_f 0.07 (SiO_2; *n*-heptane/THF = 1:1); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.15 (t, 3H, CH$_2$CH_3), 1.37 (m, 1H, NCH$_2$CH_2CH_2CH), 1.58 (m, 1H, NCH$_2$CH_2CH_2CH), 1.75 (m, 1H, NCH$_2$CH_2CH_2CH), 1.95 (t, 1H, NCH$_2$CH_2CH_2CH), 2.08−2.35 (m, 13H, NCH_2CH$_2$CH$_2$CH and CHCH_2CH_2N(CH_3)-CH_2CH_2), 2.42 (m, 1H, C*H*CO$_2$Et), 2.57 (d, 1H, NCH_2CH), 2.78 (d, 1H, NCH_2CH), 3.99 (t, 1H, Ph$_2$C*H*), 4.03 (q, 2H, CH_2CH$_3$), 7.1−7.3 (m, 10H, Ar*H*).

Method C: Hydrolysis of 3-Piperidine- and 1,2,5,6-Tetrahydro-3-pyridinecarboxylic Acid Ester Derivatives 10−30, 33, and 35. 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 on 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-(3,3-Diphenyl-1-propyloxy)ethanol (43). 2-((1,1-Diphenyl-1-propen-3-yl)oxy)ethanol (4.0 g, 15.7 mmol) was dissolved in dry dioxane (80 mL) and stirred under an atmosphere of hydrogen for 3 h at room temperature in the presence of 10% Pd/C catalyst (50% aqueous paste) and then filtered. The solvent was evaporated to give 4.0 g (100%) of **43**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.23 (brs, 1H, O*H*), 2.34 (q, 2H, CH$_2$CH_2CH$_2$), 3.39 (t, 2H, CHCH$_2$C*H*2O), 3.42 (t, 2H, CH_2-CH$_2$OH), 3.65 (t, 2H, CH_2OH), 4.10 (t, 1H, C*H*), 7.15−7.25 (m, 10H, Ar*H*).

Method D[2]: (*R*)-1-(2-(3,3-Bis(2-methylphenyl)-1-propyloxy)ethyl)-3-piperidinecarboxylic Acid Hydrochloride (32). A solution of **23** (1.1 g, 2.6 mmol) in MeOH (25 mL) was stirred under an atmosphere of hydrogen for 1 h at room temperature in the presence of 10% Pd/C catalyst (35% aqueous paste) and then filtered. The filtrate was evaporated to dryness leaving a residue which was treated with a mixture of EtOAc and acetone to give a solid which was recrystallized from a mixture of MeOH and toluene to give 0.75 g (67%) of **32** as a solid (Table 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.43 (brs, 1H, NCH$_2$CH_2CH_2CH), 1.83 (m, 2H, NCH$_2$CH_2CH_2CH), 2.00 (brs, 1H, NCH$_2$CH_2CH_2CH), 2.15 (q, 2H, Ph$_2$CHCH_2), 2.24 (s, 6H, 2 x CH_3), 2.95 (m, 3H, C*H*CO$_2$Et and NCH_2CH$_2$CH$_2$), 3.25 (brs, 2H, NCH$_2$CH_2O), 3.40 (t, 2H, CHCH$_2$CH_2O), 3.45 (brs, 1H, NCH_2CH), 3.62 (brs, 1H, NCH_2CH), 3.75 (brs, 2H, NCH_2CH$_2$O), 4.38 (t, 1H, Ph$_2$C*H*), 7.05−7.15 (m, 8H, Ar*H*), 10.75 (brs, 1H, N*H*), 12.85 (brs, 1H, COO*H*).

Method D[3]: (*R*)-1-(6,6-Diphenyl-1-hexyl)-3-piperidinecarboxylic Acid Hydrochloride (34). A solution of **27** (0.6 g, 1.5 mmol) in H_2O (25 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 reevaporated with acetone and then crystallized from a mixture of Et_2O and acetone. This afforded 0.5 g (83%) of **34** (Table 1): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.15−1.35 (m, 4H, CHCH$_2$(CH_2)$_3$), 1.48 (brs, 1H, NCH$_2$CH_2CH_2CH), 1.65 (m, 2H, CHCH$_2$(CH_2)$_3$), 1.80 (m, 2H, NCH$_2$CH_2CH_2CH), 1.95 (brs, 1H, NCH$_2$CH_2CH_2CH), 2.03 (q, 2H, Ph$_2$CHCH_2), 2.75 (m, 1H, C*H*CO$_2$Et), 2.9 (m, 4H, CH_2NCH_2CH$_2$CH$_2$CH), 3.30 (brs, 1H, NCH_2CH), 3.40 (brs, 1H, NCH_2CH), 3.90 (t, 1H, Ph$_2$C*H*), 7.1−7.3 (m, 10H, Ar*H*).

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