The Synthesis of Novel GABA Uptake Inhibitors. 1. Elucidation of the Structure–Activity Studies Leading to the Choice of (*R*)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic Acid (Tiagabine) as an Anticonvulsant Drug Candidate

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A series of different synthetic approaches to novel GABA uptake inhibitors are described, leading to examples which are derivatives of nipecotic acid and guvacine, substituted at nitrogen by 4,4-diaryl-3-butenyl or 2-(diphenylmethoxy)ethyl moieties. The in vitro value for inhibition of [^{3}H]-GABA uptake in rat synaptosomes was determined for each compound. It was found that the most potent examples are those having a substituent in an "ortho" position in one or both aromatic/heteroaromatic groups. The majority of the compounds described are structurally related to tiagabine, (*R*)-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid hydrochloride (NNC 05-0328) and some of the reasoning behind the selection of this compound as a drug candidate is summarized.

Introduction

γ-Aminobutyric acid (GABA) is recognized as the principal inhibitory neurotransmitter in the mammalian central nervous system (CNS).[1,2] It has been estimated that approximately 40% of synapses in the CNS are GABA'ergic.[3] Attenuation of GABA'ergic neurotransmission has been postulated as being involved in the pathophysiology of several CNS disorders in humans, for example anxiety, pain, and epilepsy.[4–6] As a result, much interest has recently been focused on the various potential pharmacological approaches to the enhancement of GABA'ergic function in humans,[7] for example, by the direct agonism of GABA receptors,[8,9] the inhibition of enzymatic breakdown of GABA,[10,11] or by the inhibition of the uptake of GABA into neuronal and glial cell bodies.[12,13]

It is well documented that GABA agonists are responsible for a number of unacceptable side effects in humans.[14] 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. We therefore opted for the GABA uptake inhibition approach in investigating a potential new treatment for epilepsy.

Since it was understood that some reference GABA uptake inhibitors showed potent anticonvulsant effects in rodents[15–17] and that a firm connection between the inhibitory influence of GABA and epilepsy in larger mammals had been established by direct brain administration of GABA in primates,[18] we commenced a planned synthesis program to provide novel CNS-targeted inhibitors of GABA uptake.

It was discovered some years ago that a number of cyclic amino acids such as nipecotic acid 1, guvacine 2, and homo-β-proline 3[19,20] (which can be considered as conformationally-restricted GABA analogs[21]) display in vitro activity as inhibitors of [^{3}H]-GABA uptake. This finding stimulated interest in the notion that the above compounds could be used as the basis for the design of new centrally-acting drugs. However, detailed investigation of compounds 1–3 has supported the conclusion that these cyclic amino acids do not readily cross the blood brain barrier.[19,22,23] The obvious modification of preparing the more lipophilic prodrug esters[8] of 1 and 2 provided compounds which were protective in various seizure models;[19,24] despite this, their cholinergic effects[25] had a negative influence on their in vivo utility.

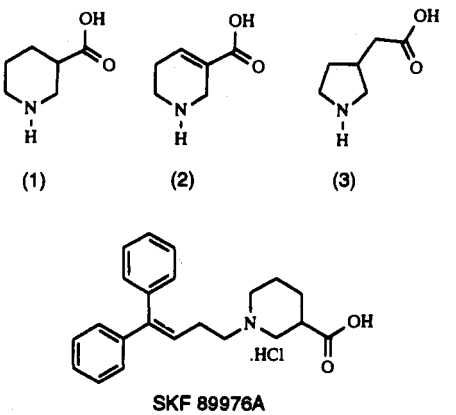

Figure 1.

In the early 1980s some lipophilic derivatives of the amino acids 1–3 were prepared which apparently do cross the blood brain barrier following peripheral administration.[26] These compounds, an example of which is SKF 89976A, containing a lipophilic moiety attached to the nitrogen atom of the cyclic amino acids 1–3, exhibited promising seizure protection[15,16] in some animal models predictive of anticonvulsant activity.[27] The compounds also displayed reduced CNS depressant effects compared with some commonly used anticonvulsant drugs, such as diazepam.[28] These observations have also stimulated others to investigate this field,[29,30] leading to the discovery of a highly lipophilic GABA uptake inhibitor with CNS activity, CI-966. This compound is a diaryl ether derivative[31,32] (Figure 2) and resulted from a research program at Parke-Davis/Warner-Lambert. CI-966 has been investigated in a phase I clinical trial.[33]

We wish to report the synthesis[34] and biological activity of a series of novel and selective GABA uptake inhibitors

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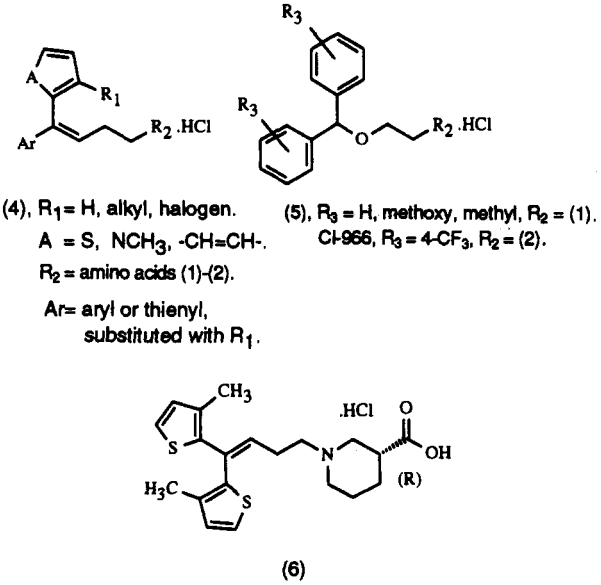


Figure 2.

(represented by the general formulas 4 and 5) which exhibit an improved potency and pharmacological profile as compared to earlier examples.

One compound from the above series, (*R*)-1-[4,4-bis-(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid (6) (NNC 05-0328, tiagabine), has progressed to phase II human clinical trials. The pharmacology[35,36] in laboratory animals and the biochemistry[37,38] of tiagabine has been presented elsewhere, providing evidence of the compound's potency and selective mode of action. In addition to the demonstrated anticonvulsant effect (with minimal observed tolerance[39]) of tiagabine, we have also been able to show that in relevant animal models, the compound possesses some analgesic[40] and anxiolytic[41] activity. Furthermore, in animal models of cognitive impairment, it has been demonstrated that following subchronic treatment, tolerance develops to memory impairing side effects produced by very high doses of tiagabine, whereas no tolerance developed to its anticonvulsant effect.[42] The results of the human clinical trials of tiagabine have now been reported in preliminary form.[43]

Chemistry

The overall strategy used for the preparation of the new butenyl GABA uptake inhibitors of general formula 4 was via N-alkylation of the parent cyclic amino acids 1 and 2, with 4-halo- or 4-tosyl-1,1-diaryl/heteroaryl-1-butenes, as shown in Scheme I. 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-(+)-(giving (*R*)-ethyl nipecotate) or with D-(−)-tartaric acid.[44,45] For diaryl ether derivatives of general formula 5, ether formation was carried out with a diaryl methanol and a preformed 1-(2-hydroxyethyl)amino acid ester.

The N-alkylated amino acid ester derivatives were saponified under basic conditions, also illustrated in Scheme I, to provide the free acids featured in Table I, isolated generally as their crystalline hydrochloride salts.

The four different synthetic routes used in the preparation of the requisite 4-halo- or 4-tosyl-1,1-diaryl/heteroaryl-1-butenes are outlined in methods A–D, Scheme I. Scheme II covers methods E (giving diaryl ethers) and F (providing amide structures).

Method A. The basis of this method is the well-established acid-catalyzed opening of a cyclopropyl ring.[46] A diaryl/heteroaryl ketone, for example 7, is converted into a cyclopropylcarbinol derivative by reaction with cyclopropylmagnesium bromide. This product can be transformed to a 4-bromo-1,1-diaryl/heteroaryl-1-butene such as 8, with hydrobromic acid in acetic acid. An alternative cyclopropyl ring opening procedure utilizing halotrimethylsilanes,[47] in particular bromotrimethylsilane, has also been applied successfully to the preparation of this class of compounds (see method D).

Method B. This approach to diarylbutenyl derivatives is suitable for the preparation of symmetrical examples. The nucleophilic attack of an organolithium species, for example 2-lithio-3-methylthiophene 9 (derived from 2-bromo-3-methylthiophene),[48] on a 4-halobutyrate ester at low temperature provided 4-bromo-1,1-bis(3-methyl-2-thienyl)-1-butene 8 after dehydration of the intermediate 4-bromo-1,1-dithienyl-1-butanol. This bromide is reacted further as described above. Control of reaction conditions is important here because the formation of a 2,2-dithienylfuran derivative can be detected at higher temperatures.

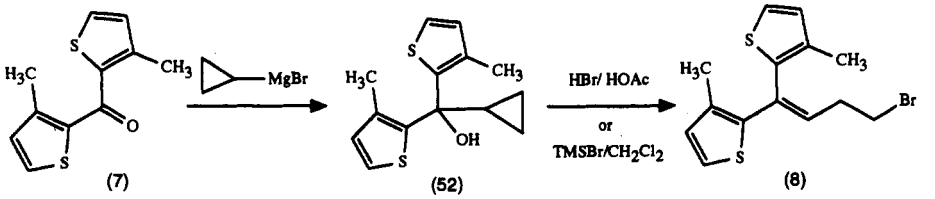
Method C. There are few syntheses of 2,2-diaryl- and heteroaryltetrahydrofurans described.[49–52] However, we have found that the reaction of, for example, 4-chloro-1-(2-thienyl)-2-butanone with a Grignard reagent provided the 2,2-disubstituted tetrahydrofuran 10 in good yield.[53] The tetrahydrofuran ring could subsequently be opened, with concomitant dehydration, in the presence of aqueous hydrochloric acid to provide an unsymmetrical butenol 11. Conversion of this alcohol into 4-(3-methyl-2-thienyl)-4-(2-thienyl)-3-butenyl 4-methylbenzenesulfonate (12)[54] proceeded well using *p*-toluenesulfonyl chloride in pyridine/chloroform at 45 °C. However, at reflux, the predominant product was the corresponding 4-chloro-1-butene derivative 13. It was found that either 12 or 13 could be used to alkylate the guvacine or nipecotic acid esters.

Method D. This method shares a common cyclopropylcarbinol intermediate 14 with method A, but this is instead prepared from a cyclopropylphenylmethanone such as 15 using either a Grignard reagent or organolithium reagent, for example 2-lithio-1-methylpyrrole 16. In this example, treatment of the cyclopropylcarbinol 14 with bromotrimethylsilane[47] provided 4-bromo-1-(1-methyl-2-pyrrolyl)-1-phenyl-1-butene (17) which could be employed to alkylate, for example, guvacine ethyl ester 18[55] in the conventional way. The resultant ester 19 was isolated as a hydrochloride salt by treating the free base in warm toluene with a stoichiometric quantity of methanol followed by chlorotrimethylsilane.[56] This procedure has been found to be generally useful for the isolation of hydrochloride salts under anhydrous conditions.

Method E. Diaryl ether-containing GABA uptake inhibitors were not generally known in the literature when the novel examples 20, 21 and 22 were prepared. The synthetic strategy we adopted at the outset of this work is therefore rather different from the published methods[31,57] and has the advantage that the synthon 23 is common to all the preparations despite changes in the diaryl methyl ether moiety. This 1-(2-hydroxyethyl)-nipecotic acid ester could be isolated in satisfactory yield by distillation and was allowed to react with a diarylmethanol derivative under dehydrative conditions[58] to give the ether 24, which was saponified to 20.

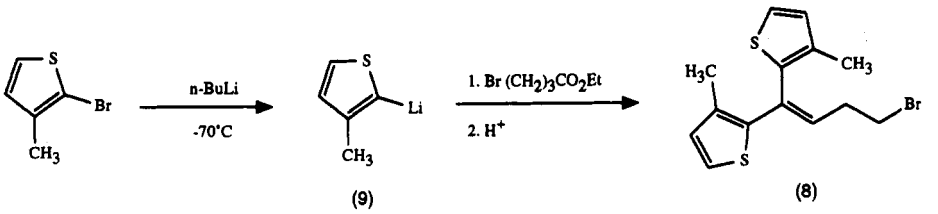
Scheme I. Synthetic Routes to Butenyl GABA Uptake Inhibitors

Method A:



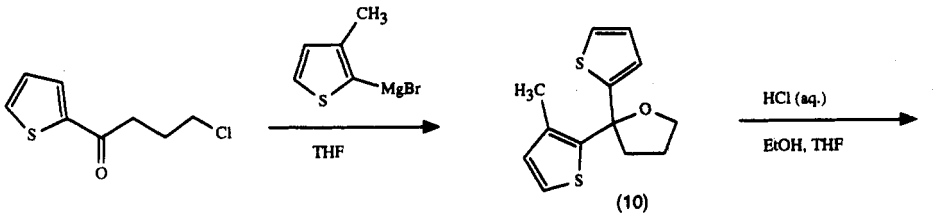
(7) (52) (8)

Method B:

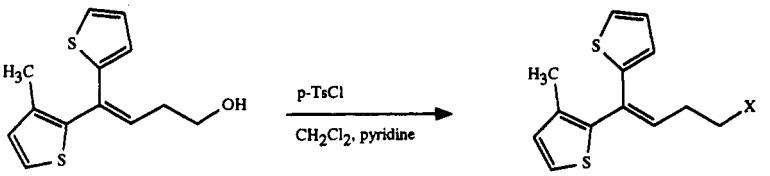


(9) (8)

Method C:

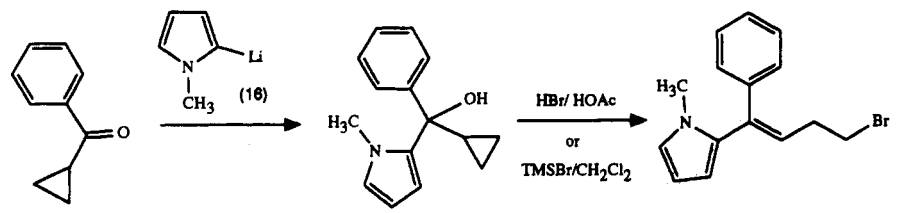


(10)



(11) (12) X = -OTs. (13) X = -Cl.

Method D:



(15) (14) (17)

Final stages (with Tiagabine as illustration):

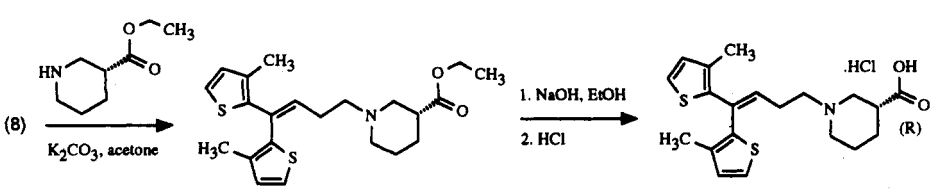


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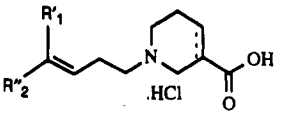
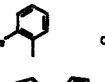
Table I. [^{3}H]GABA Uptake: 4,4-Diaryl/heteroarylbutenyl Derivatives



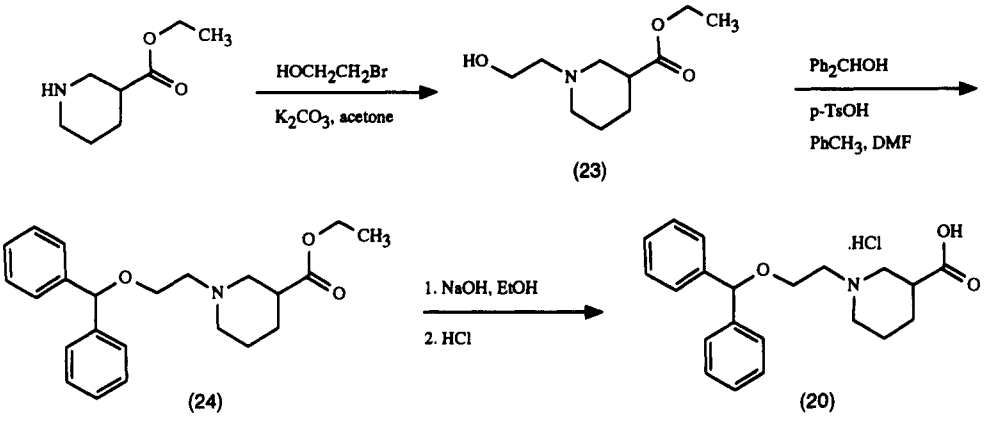
compd no.	R'$_1$	R''$_2$	R$_2$	method	mp (°C)	empirical formula	analysis	IC$_{50}$ (nM) (mean ± SE)
6			(*R*)-N	A	183.5–185.5[a]	$C_{20}H_{25}NO_2S_2$·HCl·0.75C_3H_6O	C,H,N,Cl,S	67 ± 5
28			(*S*)-N	A	183.5–185.5[a]	$C_{20}H_{25}NO_2S_2$·HCl·0.75C_3H_6O	C,H,N,Cl,S	218 ± 13
29			N	A	203–205[b]	$C_{20}H_{25}NO_2S_2$·HCl	C,H,N,Cl,S	87 ● 4
30			G	A	208–209[a]	$C_{20}H_{23}NO_2S_2$·HCl·0.5C_3H_6O·0.5H_2O	C,H,N,Cl,S	138 ● 6
31			(*R*)-N	A	65–67[d]	$C_{22}H_{27}NO_2S$·0.5H_2O	C,H,N,S	78 ± 3
32			(*S*)-N	A	196–197[a]	$C_{22}H_{27}NO_2S$·HCl	C,H,N,Cl;S	383 ± 53
33			G	A	216–217[b]	$C_{22}H_{25}NO_2S$·HCl	C,H,N,Cl,S	130 ● 12
34			(*R*)-N	D	208–10[a]	$C_{24}H_{29}NO_2$·HCl	C,H,N	82 ± 13
35			(*R*)-N	A	217–219[a]	$C_{22}H_{23}NO_2$·HCl·0.25H_2O	C,H,N,Cl	1920 ± 25
36			G	A	amorphous	$C_{20}H_{21}NO_2S$·HCl	C,H,Cl,N,S	265 ± 24
37			G	A	252–254[a]	$C_{21}H_{21}Cl_2NO_2S$·HCl	C,H,N,S	320 ± 29
38			G	A	amorphous	$C_{21}H_{21}Cl_2NO_2S$·HCl	C,H,N,Cl,S	1864 ± 295
39			N	A	181–182[a]	$C_{18}H_{21}NO_2S_2$·HCl	C,H,N	256 ± 61
40			(*R*)-N	A	209–210[b]	$C_{19}H_{23}NO_2S_2$·HCl	C,H,N,Cl,S	61 ± 9
41			(*S*)-N	C	170–173[c,f,g]	$C_{19}H_{23}NO_2S_2$·HCl·0.15$PhCH_3$	C,H,N,Cl,S	690 ± 75
42			G	A	224–226[e]	$C_{19}H_{21}NO_2S_2$·HCl	C,H,N,Cl	112 ± 10
43			N	C	189–191[c,d]	$C_{21}H_{24}NO_2S$·HCl	C,H,N,S	290 ± 27
44			(*R*)-N	D	207–210[d]	$C_{22}H_{26}ClNO_2S$·HCl·0.5H_2O	C,H,N	113 ± 9
45			G	D	260–264[d]	$C_{22}H_{24}ClNO_2S$·HCl·0.5H_2O	C,H,N,Cl,N	300 ● 6
46			(*R*)-N	D	189–191[b,c]	$C_{22}H_{29}NO_2S$·HCl·0.25H_2O	C,H,N,Cl	247 ● 15
47			(*R*)-N	A	200–201[b]	$C_{22}H_{29}NO_2S$·HCl	C,H,N	264 ● 37
48			G	A	218–220[f,h]	$C_{21}H_{20}ClNO_2S$·HCl	C,H,N,S	848 ± 79
49			G	D	193–195[e]	$C_{21}H_{24}N_2O_2S$·HCl	C,H,N,Cl	130 ± 17
SKF 89976A			N					330 ± 36
SKF 100330A			G					341 ± 51

footnotes to Table I

[a–h] Crystallization solvents: *a*, acetone; *b*, 2-propanol; *c*, Et_2O; *d*, CH_2Cl_2; *e*, H_2O; *f*, toluene; *g*, EtOH; *h*, methanol. N represents nipecotic acid (see 1), G represents guvacine (see 2); both are alkylated on nitrogen; R_2 refers to 4.

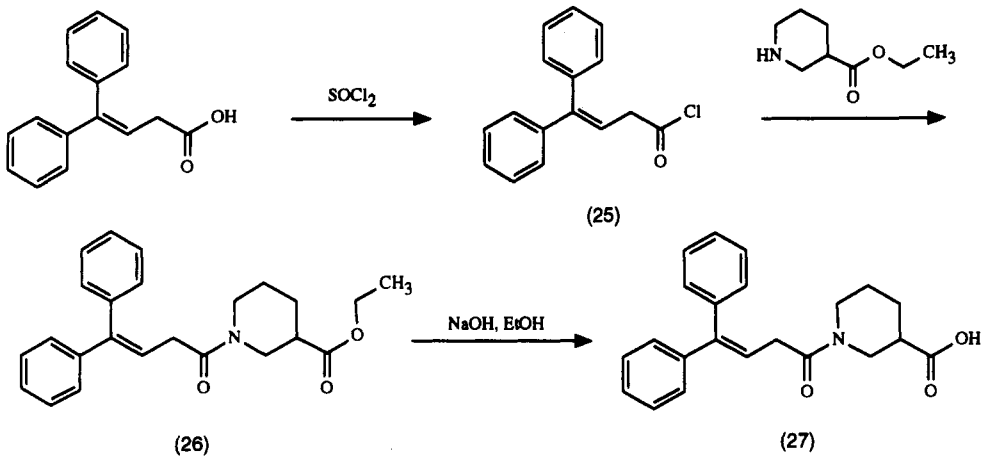
Scheme II. Synthetic Routes to Other GABA Uptake Inhibitors

Method E



(23) (24) (20)

Method F



(25) (26) (27)

Method F. Acylation of ethyl nipecotate with the acid chloride **25** of 4,4-diphenyl-3-butenoic acid provided an amide ester **26** which was saponified to provide example **27**.

Biological Results and Discussion

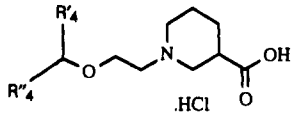
With a view to identifying novel GABA uptake inhibitors with improved potency and selectivity, a large range of 4,4-disubstituted 3-butenyl GABA uptake inhibitors containing both aryl and heteroaryl groups have been prepared.[59,60] Some representative examples of these structures are included in Table I. Their IC_{50} values for in vitro inhibition of [^{3}H]GABA uptake, determined essentially by Fjalland's method[61] are included. A mean of three to seven determinations is given, with standard errors (SE) included.

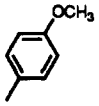
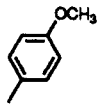
In these examples, some of the steric and electronic properties of the aryl and heteroaryl moieties have been varied in order to prove the requirements for inhibiting GABA transport at the site[62–65] involved in the uptake of GABA from the synaptic cleft into neuronal and glial cell bodies. When compared to some reference centrally acting GABA uptake inhibitors, such as SKF 89976A and SKF 100330A (Table I), compounds comprising of simple thiophene/phenyl isosteric replacements, giving the examples **36** and **39**, showed no significant improvement in potency over the parent compounds.

The two phenyl groups, as in SKF 89976A, were incorporated into a tricyclic system reminiscent of known psychotropic molecules to give the novel derivative **35**. This compound was only weakly active as a GABA uptake inhibitor. Our conclusion from this conformationally restricted analogue was to target compounds incorporating alkyl substituents which would have a limiting effect on the possible coplanarity of the two aryl moieties as a result of steric repulsion.

Inspection of Table I reveals that many of the novel examples containing substituted thiophenes exhibit increased potency in vitro as inhibitors of GABA uptake. In particular, the examples with a substituent located in an "ortho" position on one or both of the heteroaromatic/aromatic moieties, such as **6**, **29**, **30**, **31**, and **40**, showed much increased potency compared to **36** and **39**, with either one or two *o*-methyl groups apparently being the preferred substitution pattern. This same tendency is observed with the introduction of two *o*-methyl groups in SKF 89976A, providing the novel bis(2-methylphenyl) example **34** and resulting in a 4-fold increase in in vitro potency.

Table II. [^{3}H]GABA Uptake: Diaryl Ether Derivatives



compd no.	R'4	R''4	R_2	method	mp (°C)	empirical formula	analysis	IC_{50} (nM) (mean ± SE)
20			N	E	176–178[a]	$C_{21}H_{25}NO_3$·HCl	C,H,N,Cl	1370 ± 35
21			N	E	167–169[a]	$C_{23}H_{29}NO_5$·HCl	C,H,N	>3000
22			N	E	195–197[b]	$C_{23}H_{29}NO_3$·HCl	C,H,N	388 ± 85

[a,b] Crystallization solvents: *a*, 2-propanol; *b*, Et_2O.

Table III. In Vivo Anticonvulsant Effects

compd	[^{3}H]GABA uptake: IC_{50} (nM) (from Table I)	inhibition of DMCM-induced seizures in mice: ED_{50} (mg/kg) after ip administration
40	60	2.5
6	67	1.2
31	78	1.2
34	82	1.3
29	87	2.6
42	112	2.1
44	113	3.0
33	130	1.9
49	130	1.8
30	138	1.8
SKF 89976A	330	3.1
SKF 100330A	341	3.6
diazepam		2.5

Another replacement of a phenyl group by a heterocycle which we found could be tolerated in this series is that in the 1-methyl-2-pyrrolyl derivative **49**. This example retained a high degree of in vitro potency compared to SKF 100330A. Generally, a conclusion from Table I is that either one or two ortho substituents will improve the activity of compounds which are otherwise not outstanding inhibitors of [^{3}H]GABA uptake.

The requirement for a basic center (the amino acid nitrogen) in these GABA uptake inhibitors is illustrated by the activity of the amide **27** which had an IC_{50} of 49 000 nM for in vitro inhibition of [^{3}H]GABA uptake.

Where both the *R*- and *S*-enantiomers of target nipecotic acid **1** derivatives were prepared, the *R*-enantiomer possesses a clear potency advantage, such as in the cases of **6**, **31**, and **40** compared to **28**, **32**, and **41**. Another observed trend amongst the amino acid moieties in these examples is that N-substituted derivatives of guvacine **2** tend to be either weaker or equipotent in terms of their in vitro activity than their (*R*)-nipecotic counterparts; this phenomenon is seen most clearly when comparing **33** with **31** or **42** with **40**.

Table II illustrates the diaryl ether derivatives which were also prepared as centrally acting GABA uptake inhibitors. The three examples **20**, **21**, and **22** were significantly weaker in terms of in vitro inhibition of [^{3}H]-GABA uptake than similarly substituted examples in Table I; note for example the bis(2-methylphenyl)methyl ether **22** compared to **34**. The ortho effect as discussed above is also apparent in these compounds.

In Table III the in vivo anticonvulsant effect in mice of the 10 most potent compounds in inhibition of [^{3}H]GABA uptake is illustrated, expressed as ED_{50} values in milligrams per kilogram. The convulsion model used is based on observing the 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 receptor agonist. The experimental procedure has been described previously.[36] The potent in vivo anticonvulsant effect of **6** is apparent from Table III.

Conclusion

Given the background elucidated above, the reasons for selecting tiagabine (**6**) as a candidate for clinical development can be summarized as follows. It is a symmetrical bis(3-methyl-2-thienyl) derivative which makes it more straightforward in preparation than other potent but unsymmetrical examples such as **31** and **40**. The drug has a suitable lipophilicity (log P = 1.59 using the octanol/pH 7.4 buffer method) for availability in the central nervous system.[66] This value is significantly lower than for other clinically investigated examples. Tiagabine is a single enantiomer; a highly potent and selective in vitro inhibitor of [^{3}H]GABA uptake[37] with a highly promising in vivo profile as an anticonvulsant agent[35,36] and therefore represents a prototype for future drug development in this field.

Experimental Section

Physical Methods. Melting points were determined in open capillary tubes on a Büchi 535 melting point apparatus and are uncorrected. The structures of tested compounds are consistent with spectroscopic data and satisfactory elemental analyses (for C, H, N with a Perkin-Elmer Model 240 elemental analyzer; S and Cl were determined by the Schöniger combustion method) were obtained within ±0.4% of theoretical values where given. ^{1}H NMR spectra were recorded on a Bruker WM400 spectrometer with TMS as 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. Column chromatography was carried out using the technique described by W. C. Still et al.[67] on Merck silica gel 60 (Art 9385) using thick-walled glass columns. HPLC was carried out on a Waters Model 510 chromatograph interfaced via a system module to a Waters 490 multiwavelength detector to a reversed-phase C_{18} column (250 × 4 mm, 5 μm, 100 Å; eluent flow rate 1 mL/min at 35 °C). Retention times are given in minutes.

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.

Fifty microlitres 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 were 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 Tables I and II.

Chemistry. Each of the methods A–F are 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 I.

1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic Acid Hydrochloride (29) (Method A). Bis(3-methyl-2-thienyl)methanol (51). Magnesium turnings (8.65 g, 0.34 mol) in anhydrous Et_2O (20 mL) were treated with 2-bromo-3-methylthiophene (prepared as described by Kellogg et al.)[48] (63.0 g, 0.36 mol) in anhydrous Et_2O (100 mL) under a nitrogen atmosphere. After the initial exothermic reaction had subsided the reaction mixture was stirred for 1 h and a solution of 3-methylthiophene-2-carboxaldehyde (42.7 g, 0.34 mol) in anhydrous Et_2O (100 mL) was added dropwise. The resultant mixture was stirred for 1 h and then cooled to 5 °C. Water (100 mL) and saturated aqueous NH_4Cl (50 mL) were carefully added. The aqueous phase was acidified with 4 N aqueous HCl. Water (100 mL) and Et_2O (100 mL) were added, and the phases were separated. The organic phase was washed with 10% aqueous Na_2CO_3 (50 mL), dried (Na_2SO_4), and evaporated in vacuo to give **51** (72.4 g, 95%) as an oil: R_f = 0.40 (SiO_2, 70:30 *n*-heptane/THF); ^{1}H NMR ($CDCl_3$) δ 1.88 (br s, 1 H), 2.06 (s, 6 H), 6.15 (br s, 1 H), 6.64 (d, 2 H), 7.00 (d, 2 H).

Bis(3-methyl-2-thienyl)methanone (7). To a solution of **51** (72.4 g, 0.32 mol) in CH_2Cl_2 (500 mL) was introduced activated MnO_2 (155.0 g, 1.78 mol) at room temperature. The mixture was stirred for 16 h at room temperature and filtered. The filtrate was evaporated, and the resultant residue was fractionated in vacuo (122–134 °C (0.2 mmHg)) to give **8** as an oil (50.6 g, 76%): ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 6 H), 6.90 (d, 2 H), 7.40 (d, 2 H).

4-Bromo-1,1-bis(3-methyl-2-thienyl)-1-butene (8). Magnesium turnings (10.7 g, 0.44 mol) in anhydrous THF (40 mL) were treated with cyclopropyl bromide (53.4 g, 0.44 mol) in anhydrous THF (60 mL) under a nitrogen atmosphere. After the initial exotherm had subsided, the reaction mixture was heated at reflux for 0.5 h and anhydrous THF (50 mL) was introduced. The mixture was allowed to cool to room temperature, and a solution of **7** (50.6 g, 0.25 mol) in anhydrous THF (50 mL) was added dropwise. The resultant mixture was heated at reflux for 1.5 h and allowed to cool to ambient temperature, and H_2O (200 mL) was carefully introduced. The pH of the aqueous phase was adjusted to 3 with 4 N aqueous HCl, and the phases were separated. The aqueous phase was extracted with THF (50 mL), and the combined organic phases were dried (Na_2SO_4). The solvent was evaporated in vacuo to give cyclopropylbis(3-methyl-2-thienyl)methanol (**52**) (63.2 g, 98%) as an oil. This carbinol was dissolved directly in acetic acid (300 mL), and 48% aqueous HBr (250 mL) was added dropwise at 10 °C. The solution was stirred for 1.5 h, and water (1000 mL) was added. This mixture was extracted with Et_2O (500 mL), and the phases were separated. The organic phase was washed with 10% aqueous K_2CO_3 until the washings were measured at pH 11, dried (Na_2SO_4), and evaporated in vacuo to a residue. Flash chromatography on silica gel (90:10 *n*-heptane/THF) provided **8** (36.5 g, 46%) as an oil: R_f = 0.53 (SiO_2, 70:30 *n*-heptane/THF); ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3 H), 2.07 (s, 3 H), 2.71 (q, 2 H), 3.44 (t, 2 H), 6.08 (t, 1 H), 6.80 (d, 1 H), 6.87 (d, 1 H), 7.09 (d, 1 H), 7.25 (d, 1 H).

Ethyl 1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylate (53). The bromide **8** (6.55 g, 0.02 mol) was dissolved in acetone (50 mL), and ethyl 3-piperidine carboxylate (3.14 g, 0.02 mol), KI (0.30 g, 0.002 mol), and K_2CO_3 (3.0 g, 0.02 mol) were added to give a slurry which was stirred at ambient temperature for 44 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to an oil. Flash chromatography on silica gel (90:10 *n*-heptane/THF) provided **53** (6.3 g, 78%) as a gum; R_f = 0.34 (SiO_2, 70:30 *n*-heptane/THF); ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3 H), 2.03 (s, 3 H), 2.04 (s, 3 H), 2.33 (q, 2 H), 2.48 (t, 2 H), 4.12 (q, 2 H), 6.05 (t, 1 H), 6.77 (d, 1 H), 6.85 (d, 1 H), 7.21 (d, 1 H).

1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic Acid Hydrochloride (29). To a solution of **53** (6.3 g, 0.016 mol) in EtOH (30 mL) was added at room temperature 12 M aqueous NaOH (2.5 mL). The mixture was stirred for 4 h at room temperature and cooled to ca. 5 °C. The pH was adjusted to ca. 1 with 4 N aqueous HCl, CH_2Cl_2 (600 mL) was added, and the phases were separated. The organic phase was washed with water (5 mL) and dried (Na_2SO_4). The solvent was removed in vacuo, and the solid residue was recrystallized from 2-propanol (150 mL) to provide **29** (4.4 g, 69%) as a white solid: mp 203–205 °C; ^{1}H NMR (DMSO-d_6/D_2O) δ 2.02 (s, 3 H), 2.04 (s, 3 H), 6.05 (t, 1 H), 6.90 (d, 1 H), 7.02 (d, 1 H), 7.28 (d, 1 H), 7.46 (d, 1 H). Anal. ($C_{20}H_{25}NO_2S_2$·HCl) C, H, N, Cl, S.

(*R*)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic Acid (6) (Method B). 4-Bromo-1,1-bis(3-methyl-2-thienyl)-1-butene (8). A mixture of *n*-butyllithium (44 mL, 0.11 mol, 2.5 M) and anhydrous Et_2O (60 mL) was placed on an ice bath. A solution of 2-bromo-3-methylthiophene[48] (17.7 g, 0.10 mol) in anhydrous Et_2O (25 mL) was added within 30 min while the temperature was kept at 5–10 °C. Stirring was continued at 10 °C for another 15 min before the mixture was cooled to −70 °C. A solution of ethyl 4-bromobutyrate (7.8 g, 0.040 mol) in anhydrous Et_2O (25 mL) was added at such a rate to the 2-lithio-3-methylthiophene **9** that the temperature was kept below −65 °C. When the addition was complete the mixture was stirred at −70 °C for 2.5 h. Cold water (30 mL) and cold aqueous 1 N HCl (15 mL) were introduced successively while the temperature was kept below 0 °C. The reaction mixture was stirred for 15 min to allow the temperature to rise above 0 °C, and the phases were separated. The aqueous phase was extracted with Et_2O (50 mL), and the combined organic phases were washed with cold water (25 mL) and brine (25 mL). After the solution was dried over anhydrous Na_2SO_4, the solvent was evaporated in vacuo to an oil (18.7 g) which was dissolved in 2-propanol (100 mL). A 20% aqueous H_2SO_4 solution (10 mL) was added, and the mixture was stirred at room temperature for 3 h. The solvents were evaporated in vacuo to give a residue which was partitioned between CH_2Cl_2 (200 mL) and a saturated $NaHCO_3$ solution (50 mL). The phases were separated, and the aqueous phase (with pH 8–9) was extracted further with CH_2Cl_2 (50 mL). The combined organic phases were washed with water (50 mL), brine (50 mL), and dried (Na_2SO_4). The solvent was evaporated in vacuo to give an oil which was purified on a silica gel column (1:10 THF/*n*-heptane) to provide **8** (10.1 g, 77% from ethyl 4-bromobutyrate) as a yellow oil, R_f = 0.53 (SiO_2, 70:30 *n*-heptane/THF), which was found to be identical to that obtained by method A.

Ethyl (*R*)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylate (54). A mixture of **8** (3.3 g, 10 mmol) and ethyl (*R*)-3-piperidinecarboxylate[44,45] (1.6 g, 10 mmol) were reacted as described for compound **53** to afford the desired ester **54** (2.0 g, 50%) as an gum: R_f = 0.34 (SiO_2; 30:70 THF/*n*-heptane); $[\alpha]_D^{25}$ = −25.5° (*c* = 1.00, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3 H), 2.03 (s, 3 H), 2.04 (s, 3 H), 2.33 (q, 2 H), 2.48 (t, 2 H), 4.12 (q, 2 H), 4.12 (q, 2 H), 6.05 (t, 1 H), 6.77 (d, 1 H), 6.85 (d, 1 H), 7.21 (d, 1 H). Anal. ($C_{22}H_{29}NO_2S_2$) C, H, N.

(*R*)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic Acid Hydrochloride (6). The above ester **54** (5.9 g, 15 mmol) was hydrolyzed as described for compound **29**. The resultant solid residue was recrystallized from acetone and dried in vacuo to provide **6** (5.6 g, 79%) as a white solid: mp 183.5–185.5 °C; $[\alpha]_D^{25}$ = −10.0° (*c* = 1.0, H_2O); ^{1}H NMR (DMSO-d_6) δ 1.97 (s, 3 H), 2.02 (s, 3 H), 5.98 (t, 1 H), 6.85 (d, 1 H), 6.96 (d, 1 H), 7.34 (d, 1 H), 7.52 (d, 1 H). Anal. ($C_{20}H_{25}NO_2S_2$·0.75C_3H_6O) C, H, N, Cl, S.

(*S*)-1-[4-(3-Methyl-2-thienyl)-4-(2-thienyl)-3-butenyl]-3-

piperidinecarboxylic Acid Hydrochloride (41) (Method C). 2-(3-Methyl-2-thienyl)-2-(2-thienyl)tetrahydrofuran (10). Magnesium turnings (4.7 g, 0.19 mol) in anhydrous THF (75 mL) were treated with 2-bromo-3-methylthiophene in anhydrous THF (125 mL) under a nitrogen atmosphere. After the initial exotherm had subsided, the reaction mixture was heated at reflux for 1 h before being allowed to cool to ambient temperature. A solution of 4-chloro-1-(2-thienyl)butanone (27.8 g, 0.148 mol) in THF (75 mL) was added dropwise. The reaction mixture was heated at reflux for 0.5 h and allowed to cool. Concentrated aqueous NH_4Cl (175 mL) was carefully introduced before extraction with EtOAc (3 × 200 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to an oil. Flash chromatography on silica gel (40:1 *n*-heptane/EtOAc) provided **10** (25.6 g, 69%) as an oil: R_f = 0.57 (SiO_2, 2:1 cyclohexane/EtOAc); ^1H NMR ($CDCl_3$) δ 2.10 (s, 3 H), 2.0–2.18 (m, 2 H), 2.56–2.70 (m, 2 H), 4.02–4.11 (m, 2 H), 6.82 (d, 1 H), 6.87 (t, 1 H), 6.91 (t, 1 H), 7.09 (d, 1 H), 7.23 (d, 1 H). Anal. ($C_{13}H_{14}OS_2$) C, H.

4-(3-Methyl-2-thienyl)-4-(2-thienyl)-3-butenol (11). The disubstituted tetrahydrofuran **10** (3.1 g, 12.4 mmol) was dissolved in a mixture of THF (20 mL) and EtOH (20 mL), and 2 N aqueous HCl (10 mL) was introduced. The reaction mixture was heated at 80 °C for 1.75 h and evaporated in vacuo to an oil which was purified by flash chromatography on silica gel (9:1 → 5:1 cyclohexane/EtOAc), providing **11** (2.56 g, 83%) as an oil (a ca. 85:15 mixture of *E*- and *Z*-isomers): R_f = 0.14 (SiO_2, 70:30 *n*-heptane/EtOAc); ^1H NMR ($CDCl_3$) δ 2.06 (s, 3 H), 2.32 (q, 2 H), 3.66–3.73 (br m, 2 H), 6.36 (t, 1 H), 6.67–7.27 (m, 5 H) (major isomer); 2.01 (s, 3 H), 2.70 (q, 3 H), 3.76–3.83 (br m, 2 H), 5.89 (t, 1 H), 6.80–7.33 (m, 5 H) (minor isomer). Anal. ($C_{13}H_{14}OS_2 \cdot 0.1H_2O$) C, H, S.

4-(3-Methyl-2-thienyl)-4-(2-thienyl)-3-butenyl 4-Methylbenzenesulfonate (12). The butenol **11** (4.28 g, 17 mmol) was dissolved in EtOH-free $CHCl_3$ (80 mL), and pyridine (4.0 mL) was added. *p*-Toluenesulfonyl chloride (6.60 g, 34.6 mmol) in EtOH-free $CHCl_3$ (160 mL) was added dropwise. The solution was stirred at ambient temperature for 72 h and cooled to −35 °C, and further *p*-toluenesulfonyl chloride (6.60 g, 34.6 mmol) in EtOH-free $CHCl_3$ (150 mL) was added dropwise followed by pyridine (4.0 mL). Stirring was continued for 48 h. Pyridine (3.0 mL) and *p*-toluenesulfonyl chloride (3.30 g, 17.3 mmol) were introduced at −35 °C, and the reaction mixture was heated at 45 °C for 48 h. The reaction mixture was evaporated to a residue, to which water (100 mL) and EtOAc (100 mL) were added. The EtOAc layer was separated, washed with water (3 × 100 mL), dried ($MgSO_4$), and evaporated in vacuo to an oil which was purified by flash chromatography on silica gel (20:1 → 10:1 heptane/THF), providing the desired tosylate **12** as an oil (4.38 g, 64%) (a ca. 90:10 mixture of geometric isomers): R_f = 0.17 (SiO_2, 70:30 *n*-heptane/EtOAc); ^1H NMR ($CDCl_3$) δ 2.00 (s, 3 H), 2.38 (q, 2 H), 2.44 (s, 3 H), 4.06 (t, 2 H), 6.16 (t, 1 H), 6.65–7.84 (m, 5 H) (major isomer only quoted).

Ethyl (*S*)-1-[4-(3-Methyl-2-thienyl)-4-(2-thienyl)-3-butenyl]-3-piperidinecarboxylate (55). Ethyl (*S*)-3-piperidinecarboxylate[44,45] (10.0 g, 63.6 mmol) and **12** (4.35 g, 10.7 mmol) were reacted as described for compound **53**. The residue on evaporation of the filtrate was dissolved in EtOAc (200 mL), and a pH 5 aqueous tartaric acid solution (200 mL) was added (in order to remove unreacted ethyl (*S*)-3-piperidinecarboxylate). The EtOAc phase was separated and dried to give a gum (3.6 g) which was purified by flash chromatography on silica gel (90:10 cyclohexane/EtOAc) to provide **55** (3.3 g, 79%) as a gum: R_f = 0.42 (SiO_2, 1:1 cyclohexane/EtOAc); ^1H NMR ($CDCl_3$) δ 1.24 (t, 3 H), 2.07 (s, 3 H), 4.12 (q, 2 H), 6.31 (t, 1 H), 6.66 (d, 1 H), 6.91 (m, 2 H), 7.12 (d, 1 H), 7.26 (dd, 2 H) (major isomer only quoted). Anal. ($C_{21}H_{27}NO_2S_2$) C, H, N.

(*S*)-1-[4-(3-Methyl-2-thienyl)-4-(2-thienyl)-3-butenyl]-3-piperidinecarboxylic Acid Hydrochloride (41). The ester **55** (3.10 g, 7.96 mmol) was hydrolyzed as described for compound **29**, giving a residue which was dissolved in toluene (300 mL). Chlorotrimethylsilane (1.01 mL) and CH_3OH (0.35 mL) were added to dry toluene (50 mL), this mixture was added to the above toluene solution of **41**, and the solid HCl salt which precipitated was collected by filtration. This solid was dissolved in EtOH (10 mL), and this solution was added dropwise to a mixture of Et_2O (250 mL) and toluene (250 mL), providing a white crystalline solid which was collected and dried to give **41** (2.28 g, 72%): mp 170–173 °C; ^1H NMR (DMSO-d_6) δ 2.03 (s, 3 H), 6.35 (t, 1 H), 6.83 (d, 1 H), 7.00 (t, 1 H), 7.04 (d, 1 H), 7.45 (d, 2 H), 7.58 (d, 1 H). Anal. ($C_{19}H_{23}NO_2S_2 \cdot HCl$) C, H, N, Cl, S.

1-[4-(1-Methyl-2-pyrrolyl)-4-phenyl-3-butenyl]-1,2,5,6-tetrahydro-3-pyridinecarboxylic Acid Hydrochloride (49) (Method D). Cyclopropyl(1-methyl-2-pyrrolyl)phenylmethanol (14). To a well-stirred solution of 2.5 M *n*-butyllithium in hexanes (205 mL, 0.51 mol) was added dropwise freshly distilled TMEDA (59.6 g, 0.51 mol) at room temperature under a nitrogen atmosphere. Freshly distilled 1-methylpyrrole (55.5 g, 0.68 mol) was carefully introduced at room temperature to provide (1-methyl-2-pyrrolyl)lithium **16**. The mixture was stirred for 15 min, and cyclopropylphenylmethanone **15** (51.5 g, 0.34 mol) was added dropwise. The reaction mixture was stirred for 0.5 h at room temperature; water (200 mL) was added. The phases were separated, and the aqueous phase was extracted with cyclohexane (50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give **14** as an yellow oil in quantitative yield: R_f = 0.17 (SiO_2, 50:50 CH_2Cl_2/*n*-heptane); ^1H NMR ($CDCl_3$) δ 1.86 (s, 1 H), 3.18 (s, 3 H), 6.10 (t, 1 H), 6.57 (d, 2 H), 7.14–7.34 (m, 5 H).

4-Bromo-1-(1-methyl-2-pyrrolyl)-1-phenyl-1-butene (17). A solution of bromotrimethylsilane (25.5 mL, 0.20 mol) in anhydrous EtOH-free CH_2Cl_2 (700 mL) was added dropwise at 10 °C to a solution of **14** (45.0 g, 0.20 mol) in anhydrous CH_2Cl_2 (900 mL) under a nitrogen atmosphere.[47] The reaction mixture was stirred for 0.5 h at 10 °C, allowed to reach ambient temperature, and washed with 5% aqueous $NaHCO_3$ (2 × 150 mL). The organic phase was filtered through a pad of silica gel (Lichroprep 40-63$_\mu$, 150 mL). The filtrate was dried (Na_2SO_4) and evaporated in vacuo to give **17** (53.4 g, 93%) as an oil (an *E*/*Z* mixture): R_f = 0.36 (SiO_2, 50:50 CH_2Cl_2/*n*-heptane); ^1H NMR ($CDCl_3$) δ 2.78 (q, 2 H), 3.18 (s, 3 H), 3.43 (t, 2 H), 6.14 (dd, 1 H), 6.20–6.26 (m, 2 H), 6.58 (dd, 1 H), 7.20–7.40 (m, 5 H) (major geometric isomer); 3.25 (s, 3 H), 5.87 (t, 1 H), 6.10 (s, 1 H), 6.58 (s, 1 H) (minor isomer).

Ethyl 1-[4-(1-Methyl-2-pyrrolyl)-4-phenyl-3-butenyl]-1,2,5,6-tetrahydro-3-pyridinecarboxylate Hydrochloride (19). The bromide **17** (42.5 g, 0.14 mol) was reacted with ethyl 1,2,5,6-tetrahydro-3-pyridinecarboxylate (**18**)[55] (21.9 g, 0.14 mol) as described for compound **53**. The residue on evaporation of the filtrate was dissolved in EtOAc (600 mL). The resulting solution was evaporated to 500 mL in order to remove residual acetone, and water (100 mL) was introduced. The pH of the aqueous phase was adjusted to 4.0 with aqueous tartaric acid (34% wt/vol), and the phases were separated. Water (50 mL) was added to the organic phase, and pH in the aqueous phase was adjusted to 8.0 with 2 N aqueous NaOH. The organic phase was washed with brine and dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was dissolved in toluene (175 mL), and this solution was heated to 45 °C. CH_3OH (6.5 mL, 0.16 mol) and chlorotrimethylsilane (20.2 mL, 0.16 mol) were added sequentially, and the reaction mixture was stirred at ambient temperature for 18 h and then at 0 °C for 2 h, during which time the hydrochloride salt precipitated.[56] This precipitate was collected by filtration, washed with cold toluene (50 mL), and dried to give **19** (44.8 g, 69%). A portion (10 g, 0.025 mol) was recrystallized from water (50 mL) to give a crystalline solid (9.0 g, 62%): mp 135–7 °C; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3 H), 2.66 (m, 2 H), 3.16 (s, 3 H), 4.18 (q, 2 H), 6.10 (m, 2 H), 6.29 (t, 1 H), 6.83 (br s, 1 H), 7.06 (br s, 1 H), 7.16–7.36 (m, 5 H).

1-[4-(1-Methyl-2-pyrrolyl)-4-phenyl-3-butenyl]-1,2,5,6-tetrahydro-3-pyridinecarboxylic Acid Hydrochloride (49). The ester **19** (23.5 g, 0.06 mol) was hydrolyzed as described for compound **29**. After the reaction mixture was stirred for 4 h at room temperature the residual EtOH was removed by distillation in vacuo and CH_2Cl_2 (400 mL) was added. Concentrated aqueous HCl (24.6 mL) was introduced at 10 °C followed by a small amount of ice to dissolve precipitated NaCl. The phases were quickly separated, and the organic phase was separated and kept at 5 °C for 1 h. The solid product which precipitated was collected by filtration, dried in vacuo, and recrystallized from acetone (250 mL) to give the analytically pure **49** as a white solid (13.8 g, 63%): mp 180.5–182.5 °C; ^1H NMR (DMSO-d_6) δ 3.15 (s, 3 H), 6.10 (m, 2 H), 6.29 (t, 1 H), 6.82 (br s, 1 H), 7.00 (br s, 1 H), 7.15–7.45 (m, 5 H). Anal. ($C_{21}H_{24}N_2O_2 \cdot HCl$) C, H, N, Cl.

1-[2-(Diphenylmethoxy)ethyl]-3-piperidinecarboxylic Acid Hydrochloride (20) (Method E). Ethyl 1-(2-Hydroxyethyl)-3-piperidinecarboxylate (23). A mixture of K_2CO_3 (365 g, 2.64 mol), KI (44 g, 0.26 mol), ethyl 3-piperidinecarboxylate (207 g, 1.32 mol), 2-bromoethanol (175 g, 1.40 mol), and acetone (600 mL) was stirred at room temperature for 18 h. The reaction mixture was filtered, and from the filtrate the solvent was evaporated in vacuo to give a residue which was fractionated to provide 174 g (65%) of **23** (bp 110–115 °C (1.0 mmHg)); ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3 H), 1.6 (m, 2 H), 1.75 (m, 1 H), 1.9 (m, 1 H), 2.2 (m, 1 H), 2.4 (m, 1 H), 2.55 (m, 3 H), 2.75 (m, 1 H), 2.9 (m, 1 H), 3.10 (br s, 1 H), 3.63 (m, 2 H), 4.16 (q, 2 H).

Ethyl 1-[2-(Diphenylmethoxy)ethyl]-3-piperidinecarboxylate (24). From a mixture of DMF (30 mL), toluene (100 mL), benzhydrol (3.7 g, 20 mmol), **23** (4.0 g, 20 mmol), and *p*-toluenesulfonic acid monohydrate (8.0 g, 42 mmol) was removed water azeotropically over 1.25 h by means of a Dean–Stark trap. The reaction mixture was cooled and poured into a mixture of ice water (150 mL) and 25% aqueous NH_3 (100 mL). The phases were separated, and the aqueous phase was extracted with toluene (50 mL). The combined organic phases were washed with brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo to give an oily residue which was purified by flash chromatography on silica gel (1:4 THF/*n*-heptane) to afford (2.8 g, 38%) of **24** as an oil. A small portion was subjected to Kugelrohr distillation to provide an analytically pure sample (250 °C (0.5 mmHg)); ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3 H), 2.68 (t, 2 H), 3.59 (t, 2 H), 4.12 (q, 2 H), 5.37 (s, 1 H), 7.2–7.4 (m, 10 H). Anal. ($C_{23}H_{29}NO_3$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-3-piperidinecarboxylic Acid Hydrochloride (20). The ester **24** (0.92 g, 2.5 mmol) was hydrolyzed as described for compound **29**. The oily residue on evaporation was dissolved in dry diethyl ether (150 mL) and left to crystallize. The solid formed was collected by filtration, recrystallized from 2-propanol, and dried in vacuo to give **20** (0.41 g, 43%) as a white solid: mp 176–178 °C; ^{1}H NMR (DMSO-d_6) δ 1.4–2.0 (m, 4 H), 2.8–3.8 (m, 9 H), 5.56 (s, 1 H), 7.2–7.4 (m, 10 H). Anal. ($C_{21}H_{25}NO_3$·HCl) C, H, N, Cl.

1-[4,4-Diphenyl-1-oxo-3-butenyl]-3-piperidinecarboxylic Acid (27) (Method F). Ethyl 1-[4,4-Diphenyl-1-oxo-3-butenyl]-3-piperidinecarboxylate (26). A mixture of 4,4-diphenyl-3-butenoic acid[68] (4.8 g, 0.020 mol) and thionyl chloride (30 mL) was stirred at room temperature for 75 min. Excess thionyl chloride was removed in vacuo to give an oily residue which was dissolved in toluene (30 mL). A solution of ethyl 3-piperidinecarboxylate (7.3 g, 0.046 mol) in toluene (20 mL) was added, and the resulting suspension was stirred at room temperature for 2 h. The reaction mixture was treated successively with 4 N aqueous HCl (50 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (50 mL). The organic phase was separated and dried ($MgSO_4$), and the solvent was evaporated in vacuo to give a residue which was purified by chromatography on silica gel (3:7 THF/*n*-heptane). An oil (4.6 g) was obtained which could be crystallized from a mixture of diethyl ether and petroleum ether (1:20). The solid which formed was collected by filtration and recrystallized from cyclohexane to give **26** (3.2 g, 41%) as a solid (a ca. 1:1 mixture of amide rotamers): mp 83–85 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3 H), 1.26 (t, 3 H), 3.20 (m, 2 H), 3.25 (d, 2 H), 4.10 (q, 2 H), 4.15 (q, 2 H), 6.27 (t, 1 H), 6.30 (t, 1 H); 7.2–7.4 (m, 10 + 10 H).

1-[4,4-Diphenyl-1-oxo-3-butenyl]-3-piperidinecarboxylic Acid (27). To a stirred solution of **26** (1.0 g, 2.7 mmol) in a mixture of EtOH (5 mL) and acetone (10 mL) was added 12 N NaOH (0.25 mL). The mixture was stirred at room temperature for 4 h before acidification with a 2 N aqueous HCl. CH_2Cl_2 (20 mL) was introduced with vigorous stirring, and the phases were separated. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was suspended in Et_2O (50 mL) and filtered. From the filtrate the solvent was evaporated in vacuo to give a residue which was treated with a mixture of THF and petroleum ether and allowed to crystallize. This afforded **27** (0.3 g, 32%) as a solid (a ca. 1:1 mixture of amide rotamers): mp 113–115 °C; ^{1}H NMR ($CDCl_3$) δ 3.20 (d, 2 H), 3.25 (d, 2 H), 6.23 (t, 1 H), 7.2–7.4 (m, 10 + 10 H). Anal. ($C_{22}H_{23}NO_3$·0.5H_2O) C, H, N.

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