Synthesis of 4,4-bis(2-methylphenyl)-3-butenyl (and butyl) analogs of 4-phenyl-1,4- and 6-phenyl-1,6-dihydropyridine-3-carboxylic acids and their evaluation as neuronal GABA-uptake inhibitors

Nadeem Iqbal, Zhong-Yong Wei, Glen B. Baker, and Edward E. Knaus

Abstract: Treatment of 3-[2-(4,4-dimethyl-4,5-dihydrooxazolin-2-yl)]-4-phenyl-1,4-dihydropyridine (**13**) with NaH–DMSO, and then reaction with 1,1-bis(2-methylphenyl)-4-bromobutane (**12***c*) afforded 1-[4,4-bis(2-methylphenyl)butyl]-3-[2-(4,4-dimethyl-4,5-dihydrooxazolin-2-yl)]-4-phenyl-1,4-dihydropyridine (**14**). Reaction of methyl nicotinate with 2.1 equivalents **12***c* or 1,1-bis(2-methylphenyl)-4-bromo-1-butene (**11***b*) afforded 4,4-bis(2-methylphenyl)butyl 1-[4,4-bis(2-methylphenyl)butyl]pyridinium-3-carboxylate bromide (**17**) or 4,4-bis(2-methylphenyl)-3-butenyl 1-[4,4-bis(2-methylphenyl)-3-butenyl]pyridinium-3-carboxylate bromide (**18**), respectively. The nonregioselective reaction of the pyridinium salts (**17/18**) with PhMgCl in THF at −23°C using a catalytic amount of CuI afforded a mixture of isomeric 4-phenyl-1,4-dihydropyridyl (**21** or **22**) and 6-phenyl-1,6-dihydropyridyl (**27** or **28**) products in a ratio of approximately 1:1. All attempts to hydrolyze the 4,4-bis(2-methylphenyl)butyl or 3-butenyl ester moiety of **21/22** or **27/28** to a carboxyl group resulted in decomposition products. In contrast, the corresponding 3-(2-cyanoethyl) esters (**23**, **24**, **29**, **30**) were readily converted to the corresponding carboxyl analogs (**25**, **26**, **31**, **32**) via a β-elimination reaction of acrylonitrile using the non-nucleophilic base DBU. The 4-phenyl-1,4-dihydropyridyl (**14**, **25**, **26**) and 6-phenyl-1,6-dihydropyridyl (**27/28** or **31/32**) compounds inhibited the in vitro uptake of [^{3}H]GABA into striatal prisms in the 21–44% range at a 10^{-4} M test compound concentration, relative to the reference drug nipecotic acid (87% inhibition). Structure–activity correlations showed the dihydropyridyl C-3 substituent was a determinant of [^{3}H]GABA uptake where the potency order was CO_2H > 2-(4,4-dimethyl-4,5-dihydrooxazolin-2-yl) > $CO_2(CH_2)_3CH$-(*o*-tolyl)$_2$ and $CO_2(CH_2)_2CH{=}C$-(*o*-tolyl)$_2$. Compounds possessing C-3 and (or) N-1 $CO_2(CH_2)_3CH$-(*o*-tolyl)$_2$ substituents were generally more potent than analogs having $CO_2(CH_2)_2CH{=}C$-(*o*-tolyl)$_2$ substituents. In general, 1,6-dihydropyridyl compounds were more potent than the corresponding 1,4-dihydropyridyl isomers.

Key words: 1,4- and 1,6-dihydropyridines, GABA-uptake inhibitors.

Résumé : Le traitement de la 3-[2-(4,4-diméthyl-4,5-dihydrooxazolin-2-yl)]-4-phényl-1,4-dihydropyridine (**13**) par du NaH–DMSO, suivi d'une réaction avec du 1,1-bis(2-méthylphényl)-4-bromobutane (**12***c*) conduit à la 1-[4,4-bis(2-méthylphényl)butyl]-3-[2-(4,4-diméthyl-4,5-dihydrooxazolin-2-yl)]-4-phényl-1,4-dihydropyridine (**14**). La réaction du nicotinate de méthyle avec 2,1 équivalents de **12***c* ou du 1,1-bis(2-méthylphényl)-4-bromobut-1-ène (**11***b*) fournit le bromure du 1-[4,4-bis(2-méthylphényl)butyl]pyridinium-3-carboxylate de 4,4-bis(2)-méthylphényl)butyle (**17**) ou le bromure du 1-[4-4-bis(2-méthylphényl)but-3-énYl]pyridinium-3-carboxylate de 4,4-bis(2-méthylphényl)but-3-ényle, respectivement. La réaction non régiosélective des sels de pyridinium (**17/18**) avec le PhMgCl dans le THF, à 23°C, en présence d'une quantité catalytique de CuI conduit à un mélange de produits isomères 4-phényl-1,4-dihydropyridylés (**21** ou **22**) et 6-phényl-1,6-dihydropyridylés (**27** ou **28**) dans un rapport approximativement 1 : 1. Tous les essais d'hydrolyser les portions 4,4-bis(2-méthylphényl)butyles ou but-3-énYles des esters **21/22** ou **27/28** en groupe carboxylique n'ont conduit qu'à des produits de décomposition. Par opposition, l'utilisation de la base non nucléophilique DBU permet de transformer facilement les esters 3-(2-cyanoéthylés) (**23**, **24**, **29**, **30**) en analogues carboxylés correspondants (**25**, **26**, **31**, **32**) par une réaction d'élimination-β d'acrylonitrile. Lors d'essais à des concentrations de 10^{-4} M des composés 4-phényl-1,4-dihydropyridylés (**14**, **25**, **26**) et 6-phényl-1,6-dihydropyridylés (**27/28** ou

Received September 3, 1996.

This paper is dedicated to Professor William A. Ayer on the occasion of his 65th birthday.

N. Iqbal, Z.-Y. Wei,[1] G.B. Baker, and E.E. Knaus.[2] Faculty of Pharmacy and Pharmaceutical Sciences, and Department of Psychiatry, Neurochemical Research Unit, University of Alberta, Edmonton, AB T6G 2N8, Canada.

[1] Current address: Astra Pain Research Unit, Bld 3000, 275 Bis Armand-Frappier, Laval, QC H7V 4A7.
[2] Author to whom correspondence may be addressed. Telephone: (403) 492-5993. Fax: (403) 492-1217. E-mail: eknaus@pharmacy.ualberta.ca

31/32), ceux-ci inhibent l'assimilation in vitro du [^{3}H]-«GABA» dans des prismes striataux par des facteurs de 21–44% alors que le médicament de référence, l'acide nopécotique, provoque une inhibition de 87%. Des corrélations structure–activité ont permis de démontrer que le substituant en C-3 du dihydropyridyle est déterminant dans l'assimilation du [^{3}H]-«GABA» et que l'importance de l'activité de ces substituants varie dans l'ordre CO_2H > 2-(4,4-diméthyl-4,5-dihydrooxazon-2-yl) > $CO_2(CH_2)_3CH$-(*o*-tolyl)$_2$ et $CO_2(CH_2)_2CH{=}C$-(*o*-tolyl)$_2$. Les composés comportant des substituants $CO_2(CH_2)_3CH$-(*o*-tolyl)$_2$ en C-3 ou en N-1 sont généralement plus actifs que les analogues possédant des substituants $CO_2(CH_2)_2CH{=}C$-(*o*-tolyl)$_2$. En général, les composés 1,6-dihydropyridylés sont plus actifs que les isomères correspondants 1,4-dihydropyridylés.

Mots clés : 1,4- et 1,6-dihydropyridines, inhibiteurs de l'assimilation de «GABA».

[Traduit par la rédaction]

Introduction

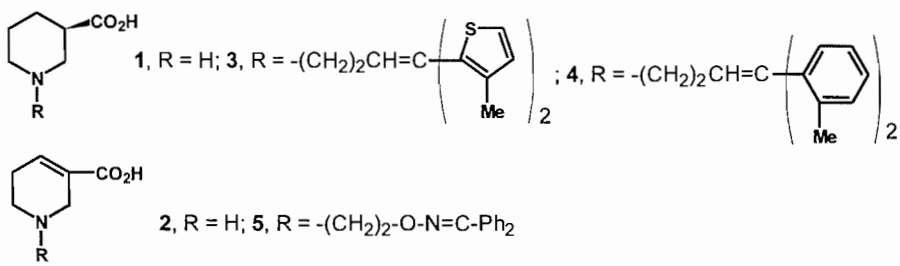
γ-Aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system (CNS) (1), has been estimated to be present in 60–70% of all synapses within the CNS (2). GABA-mediated neurotransmission is terminated by its rapid uptake via specific, high-affinity transporters located in the presynaptic terminal and (or) surrounding glial cells (3). A reduction in GABA neurotransmission has been implicated in the etiology of a variety of neurological disorders including epilepsy, anxiety, and pain (1). One mechanistic approach to elevate GABA neurotransmission in the CNS involves the inhibition of GABA uptake into neurons and glia. Conventional GABA-uptake inhibitors such as the cyclic amino acids nipecotic acid (**1**) and guvacine (**2**), which can be viewed as conformationally restricted analogs, display in vitro activity as GABA-uptake inhibitors. However, **1** and **2** do not readily cross the blood–brain barrier (BBB), presumably due to their hydrophilic nature (4–6), which precludes their therapeutic usefulness. To overcome this problem, lipophilic side chains were attached to the nitrogen atom of nipecotic acid (**1**) and guvacine (**2**). Thus, tiagabine (**3**), the 4,4-bis(2-methylphenyl)-3-butenyl compound (**4**), and NNC-711 (**5**) were found to be potent GABA-uptake inhibitors that possessed in vivo efficacy as anticonvulsant agents (1, 7, 8). Compounds **3** and **4** having a substituent in an "*ortho*" position in one or both aromatic/heteroaromatic groups exhibited the most potent in vitro GABA-uptake inhibition (7). It was anticipated that coupling a lipophilic 4,4-bis(2-methylphenyl)-3-butenyl or 4,4-bis(2-methylphenyl)butyl moiety to the N-1 position of a 3-carboxy-4-phenyl-1,4-dihydropyridyl moiety would provide agents that inhibit GABA uptake into neurons. This postulate was based on the fact that (*i*) 1-alkyl-1,4-dihydronicotinate esters and related nicotinic acid derivatives exhibit potent anticonvulsant activity in the maximal electroshock screen (9, 10), and (*ii*) that a substituent at the C-4 position of nipecotic acid (**1**) possessing a 1-(4-CF_3-C_6H_4)$_2$-$CHOCH_2CH_2$- substituent is tolerated with respect to GABA-uptake inhibition (11). We now report the synthesis of 4,4-bis(2-methylphenyl)-3-butenyl- and 4,4-bis(2-methylphenyl)butyl analogs of 4-phenyl-1,4- and 6-phenyl-1,6-dihydropyridine-3-carboxylates and their evaluation as neuronal GABA-uptake inhibitors.

Chemistry

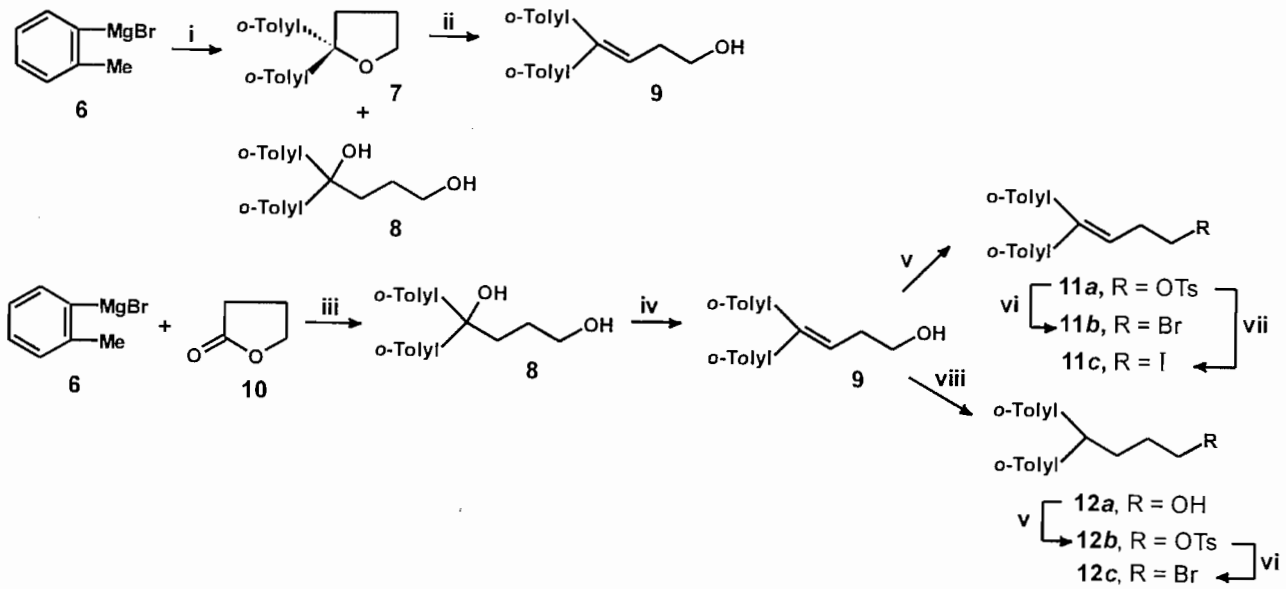
Our intitial attempt to prepare 1,1-bis(2-methylphenyl)-4-bromo-1-butene (**11***b*) by reaction of *ortho*-tolylmagnesium bromide with ethyl 4-bromobutyrate afforded a mixture of 2,2-bis(2-methylphenyl)tetrahydrofuran (**7**, 14%) and 1,1-bis(2-methylphenyl)-1,4-butanediol (**8**, 10%), which are likely produced by the respective cyclization and hydrolysis of the intermediate product (*ortho*-tolyl)$_2$-$C(OH)(CH_2)_3Br$ as illustrated in Scheme 1. Since the 1,4-butanediol product **8** was readily converted to 1,1-bis(2-methylphenyl)-1-buten-4-ol (**9**, 94%) using HCl, an alternate preparation of 1,1-bis(2-methylphenyl)-1,4-butanediol (**8**) was investigated. Accordingly, reaction of *ortho*-tolylmagnesium bromide with γ-butyrolactone (**10**) afforded **8** (90%), which was readily converted to 1,1-bis(2-methylphenyl)-1-buten-4-ol (**9**, 90%) by acid-catalyzed dehydration using HCl. Elaboration of **9** to the tosylate analog (**11***a*) and subsequent reaction with either LiBr or NaI in acetone afforded the respective 1,1-bis(2-methylphenyl)-4-bromo-1-butene (**11***b*, 88%) or iodide (**11***c*, 85%). Hydrogenation of 1,1-bis(2-methylphenyl)-1-buten-4-ol (**9**) using 10% Pd/C and H_2 gas at 60 psi (1 psi = 6.9 kPa) gave 1,1-bis(2-methylphenyl)-4-hydroxybutane (**12***a*, 94%), which was elaborated to the tosylate analog (**12***b*, 83%) and then to 1,1-bis(2-methylphenyl)-4-bromobutane (**12***c*, 83%).

The reaction of 3-[2-(4,4-dimethyl-4,5-dihydrooxazolin-2-yl)]-4-phenyl-1,4-dihydropyridine (**13**) (12) with NaH in DMSO, followed by reaction with 1,1-bis(2-methylphenyl)-4-bromobutane (**12***c*), afforded the *N*-alkylated product **14** (19%) as illustrated in Scheme 2.

Reaction of methyl nicotinate with 2.1 equivalents of 1,1-

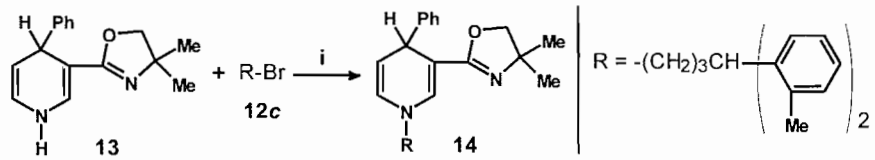


Scheme 1.



Reagents: i, $EtO_2C(CH_2)_3Br$, THF, 0°C → 25°C, 4 h and then aqueous NH_4Cl hydrolysis; ii, 6 N HCl, EtOH, THF, reflux, 4 h; iii, THF, 25°C, 2 h and then aqueous NH_4Cl hydrolysis; iv, 4 N HCl, EtOH, reflux, 6 h; v, 4-Me-C_6H_4-SO_2Cl, pyridine, CH_2Cl_2, 25°C, 12 h and then aqueous NH_4Cl hydrolysis; vi, LiBr, acetone, reflux, 12 h; vii, NaI, acetone, reflux, 12 h; viii, 10% Pd/C, EtOH, H_2 gas, 60 psi, 4 h, 25°C.

Scheme 2.



Reagents: i, NaH/DMSO, 25°C, 12 h.

bis(2-methylphenyl)-4-bromobutane (**12***c*) afforded the pyridinium salt (**17**, 74%) (see Scheme 3). When 1.1 equivalents of **12***c* were employed, **12***c* was all consumed but a considerable amount of methyl nicotinate remained. Similar results were observed in the synthesis of **18** (67%) using a similar reaction with 1,1-bis(2-methylphenyl)-4-bromo-1-butene (**11***b*). A plausible explanation for the replacement of the methyl R^1 substituent by a 4,4-bis(2-methylphenyl)butyl (**17**) or a 4,4-bis(2-methylphenyl)-3-butenyl (**18**) substituent is shown in Scheme 4. This replacement of the Me R^1 substituent proceeds to completion since the volatile by-product MeBr (bp 4°C) would escape from the reaction mixture (reflux in MeCN for 48 h). No product resulting from replacement of the cyanoethyl moiety of **16** was isolated for similar reactions of **16** with either **11***b* or **12***c*.

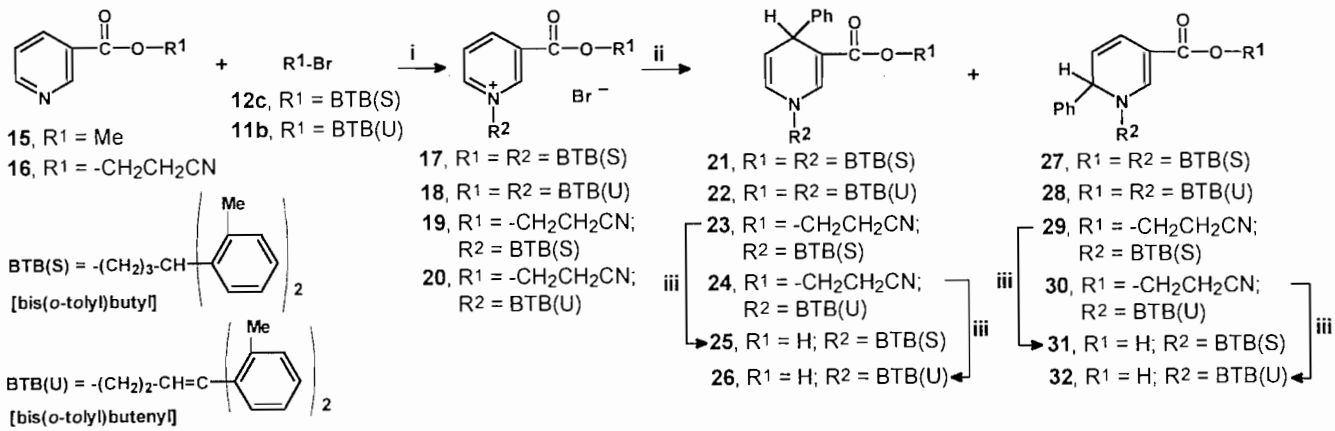
The nonregioselective reaction of the pyridinium salts (**17**–**20**) with PhMgCl in THF at −23°C using a catalytic amount of CuI afforded a mixture of isomeric 4-phenyl-1,4-dihydropyridyl and 6-phenyl-1,6-dihydropyridyl products in a ratio of approximately 1:1 (**17** → **21** (22%) + **27** (18%); **18** → **22** (24%) + **28** (19%); **19** → **23** (22%) + **29** (20%); **20** → **24** (20%) + **30** (21%)). No product resulting from reaction of the Grignard reagent with the methyl ester moiety was detected. Comins et al. (13) observed that the CuI-catalyzed reaction of methyl nicotinate with phenyl chloroformate in THF – methyl sulfide (3 equiv.) at −20°C resulted in regioselective attack at C-4 (1,4-dihydropyridine : 1,6-dihydropyridine = 95:5).

All attempts to hydrolyze the 4,4-bis(2-methylphenyl)butyl (**21**, **27**), or 4,4-bis(2-methylphenyl)-3-butenyl (**22**, **28**), ester moiety to the corresponding acid using ethanolic NaOH or LiOH were unsuccessful since only decomposition products were produced. In contrast, the cyanoethyl esters were readily converted to the carboxyl analog using the non-nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), which proceeds via a β-elimination reaction of acrylonitrile (14) (**23** → **25** (70%); **24** → **26** (56%); **29** → **31** (62%); **30** → **32** (50%)). 2-Cyanoethyl nicotinate (**16**), required for the preparation of the pyridinium salts (**19**, **20**), was prepared by the condensation of nicotinoyl chloride with 2-cyanoethanol in the presence of Et_3N (85%).

Biological evaluation as GABA-uptake inhibitors

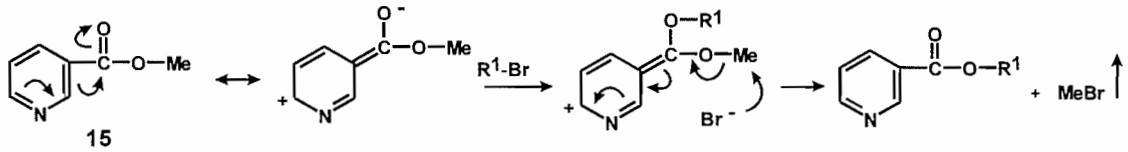
The 1,4-dihydropyridyl (DHP) (**21**–**26**) and 1,6-dihydropyridyl (**27**–**32**) ring systems possess conformational and steric features that are distinctly different from those present in nipecotic acid (**1**), which exists in a chair conformation. Hoffman

Scheme 3.



Reagents: i, dry MeCN, reflux, 48 h; ii, dry THF, CuI, PhMgCl, −23°C, 30 min; iii, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), MeOH, 25°C, 14 h.

Scheme 4.

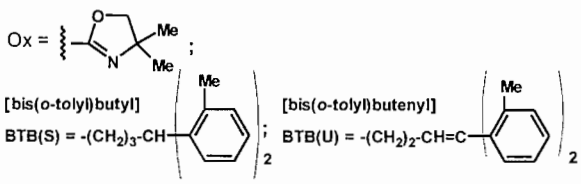


and Cimeraglia (15) reported, based on ab initio STO-3G calculations for 4-phenyl-3,5-dicarboxy-1,4-dihydropyridine, that the boat conformation of the 1,4-dihydropyridine ring is favored over a planar ring arrangement, that ring distortion was greater at C-4 than at N-1, and that the C-4 phenyl substituent on the 1,4-DHP ring having a pseudoaxial orientation relative to the plane of the olefinic bonds was unequivocally favored (16). Related theoretical calculations indicated that 1,4-dihydronicotinamide (17) and 1,4-DHP calcium channel antagonists (18) also exist in a boat conformation. The 1,6-DHP ring system is less puckered that the boat-shaped 1,4-DHP ring system, or the chair-shaped piperidine ring system. While the diene (C=C-C=C) moiety of the 1,6-DHP ring system is quasi-planar, there is distortion at the C-6 and N-1 positions. These differences, together with the steric effects due to the ester, N-1, and the 1,4-DHP C-4 and 1,6-DHP C-6, substituents (**21–32**) are expected to alter the overall volume of the molecule, the in vivo biodistribution of the drug between hydrophobic and hydrophilic tissues, and their affinity for a brain GABA transporter(s) (19).

All of the compounds evaluated in the in vitro [^{3}H]GABA-uptake inhibition striatal tissue assay, except for **21** and **22**, which were inactive, inhibited uptake in the 21–44% range, relative to the reference drug nipecotic acid (87% inhibition), at a test compound concentration of 10^{-4} M (see Table 1). All compounds (**14**, **21/22**, **25/28**, and **31/32**) were inactive inhibitors at a test compound concentration of 10^{-5} M relative to nipecotic acid (48% inhibition). Although the differences in percent inhibition of [^{3}H]GABA uptake were sometimes small, some structure–activity correlations are evident. In the 1,4-DHP series of compounds the C-3 R^1 substituent was a determinant of activity where the relative potency order was CO_2H (**25**) > 4,4-dimethyl-4,5-dihydrooxazolin-2-yl) (**14**) > $CO_2BTB(S)$ (**21**, inactive), and CO_2H (**26**) > $CO_2BTB(U)$ (**22**, inactive). These results indicate the 2-(4,4-dimethyl-4,5-dihydrooxazolin-2-yl) ring system (**14**) is a bioisostere of a carboxyl group (**25**) with respect to [^{3}H]GABA-uptake inhibition. A similar activity profile was observed in the 1,6-DHP series of compounds where CO_2H (**31**) ≥ $CO_2BTB(S)$ (**27**) and CO_2H (**32**) > $CO_2BTB(U)$ (**28**). A comparison of compounds having C-3 and (or) N-1 $CO_2BTB(S)$ and $CO_2BTB(U)$ substituents indicated that the relative activity order was generally $CO_2BTB(S)$ > $CO_2BTB(U)$ (**26** > **25** and **27** > **28**), although **31** and **32** were equipotent. In general, the relative potency order was 1,6-DHP > 1,4-DHP (**27** > **21** (inactive), **28** > **22** (inactive), **32** > **26** and **31** ≈ **25**). Although this class of 1,4- and 1,6-DHP compounds are less effective in vitro inhibitors of [^{3}H]GABA uptake than the hydrophilic cyclic amino acid nipecotic acid, which does not readily cross the blood–brain barrier, their enhanced lipohilicity, and potentially more favorable brain uptake, could result in a greater inhibition of neuronal GABA uptake in vivo, and hence therapeutic efficacy.

The stability of the 1,4- (**14**, **21/22**, **25/26**) and 1,6- (**27/28**, **31/32**) dihydropyridine analogs during the in vitro [^{3}H]GABA-uptake inhibition assay in striatal tissue was not determined. These 1,4- and 1,6-dihydropyridine analogs could undergo partial oxidation to an inactive pyridinium species (20, 21), whereas the 1,4-dihydropyridine analogs could undergo hydration to yield the corresponding 6-hydroxy-1,4,5,6-tetrahydropyridine analog (20, 22), which may also conceivably act as a GABA-uptake inhibitor. The 4- or 6-

Table 1. In vitro inhibition of [^{3}H]GABA uptake in striatal tissue by 1,4- (**14**, **21/22**, **25/26**) and 1,6- (**27/28**, **31/32**) dihydropyridine analogs.



Compound	R^1	R^2	% Inhibition, 10^{-4} M[a]
14	-Ox	BTB(S)	34.6 ± 6.7 (4)
21	-CO_2BTB(S)	BTB(S)	Inactive (4)
22	-CO_2BTB(U)	BTB(U)	Inactive (4)
25	-CO_2H	BTB(S)	44.1 ± 3.3 (5)
26	-CO_2H	BTB(U)	27.2 ± 7.0 (5)
27	-CO_2BTB(S)	BTB(S)	31.4 ± 1.8 (4)
28	-CO_2BTB(U)	BTB(U)	21.1 ± 10.6 (4)
31	-CO_2H	BTB(S)	38.8 ± 7.8 (5)
32	-CO_2H	BTB(U)	40.4 ± 3.0 (5)
Nipecotic acid[b]			87.1 ± 1.6 (11)

[a]The result is presented as the mean ± S.E.M. with the number of experiments shown in parentheses.

[b]At a concentration of 10^{-5} M, nipecotic acid inhibited [^{3}H]GABA uptake by 48.5 ± 6.1% (n = 5).

phenyl substituent is expected to alter the redox potential of these dihydropyridine compounds. The longer N substituents (BTB(S), BTB(U)) are expected to decrease the oxidation rate, which is potentially attributed to steric crowding and a lower degree of solvation for lipophilic derivatives (21). On the basis of previous in vitro and in vivo studies for 3-[2-[[(1-methyl-1,4-dihydropyrid-3-yl)carbonyl]oxy]-ethyl] 5-methyl 1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-3,5-pyridinedicarboxylate (23), it is not expected that oxidative and (or) hydration transformations had a significant effect under the incubation conditions employed in the in vitro [^{3}H]GABA-uptake inhibition assay.

Experimental

Melting points were determined using a Buchi capilliary apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) were determined on a Bruker AM-300 spectrometer. The assignment of exchangeable protons (O*H*, N*H*) was confirmed by the addition of D_2O. ^{13}C NMR spectra were acquired using the *J* modulated spin echo technique where methyl and methine carbon resonances appear as positive peaks, and methylene and quaternary carbon resonances appear as negative peaks. High-resolution electron impact (EI) mass spectra were determined using an AEI-MS-50 mass spectrometer. Infrared (IR) spectra were acquired using a Nicolet 550 Series II Magna FT-IR spectrometer. Silica gel column chromatography was carried out using Merck 7734 silica gel (60–200 mesh). 3-[2-(4,4-Dimethyl-4,5-dihydrooxazolin-2-yl)]-4-phenyl-1,4-dihydropyridine (**13**) was prepared using a literature procedure (12). γ-Butyrolactone was purchased from the Aldrich Co. [^{3}H]GABA (specific activity 36.8 Ci/mmol) was purchased from New England Nuclear.

2,2-Bis(2-methylphenyl)tetrahydrofuran (7) and 1,1-bis(2-methylphenyl)-1,4-butanediol (8, Method A)

A solution of *o*-tolylmagnesium chloride in THF (0.1 mol, 100 mL of 1 M) was added dropwise to a solution of ethyl 4-bromobutyrate (9.75 g, 50 mmol) in THF (150 mL) at 0°C with stirring. The reaction was allowed to proceed at 25°C for 4 h, the reaction mixture was cooled to 0°C, and a saturated aqueous solution of NH_4Cl (100 mL) was added. The aqueous fraction was extracted with EtOAc (3 × 100 mL), the combined organic solutions were washed with brine (100 mL), and the organic solution was dried ($MgSO_4$). Removal of the solvent in vacuo gave a residue that was purified by silica gel flash chromatography. Elution with EtOAc–hexane (1:49, v/v) afforded **7** (1.76 g, 14%). Continued elution with EtOAc–hexane (2:3, v/v) gave **8** (1.35 g, 10%).

Fraction 1 (7): mp 120–121°C (recrystallized from hexane); ^{1}H NMR ($CDCl_3$) δ: 1.97 (s, 6H, tolyl *Me*'s), 2.04 (m, 2H, tetrahydrofuranyl H-4), 2.60 (t, *J* = 7.2 Hz, 2H, tetrahydrofuranyl H-3), 4.04 (t, *J* = 7.2 Hz, 2H, tetrahydrofuranyl H-5), 7.03 (dd,

J = 6.8, J = 1.7 Hz, 2H, tolyl H-3), 7.17 (m, 4H, tolyl H-4, H-5), 7.63 (dd, J = 7.2, J = 1.8 Hz, 2H, tolyl H-6); ^{13}C NMR ($CDCl_3$) δ: 21.5, 25.7, 36.3, 67.4, 88.7, 124.9, 126.7, 127.0, 132.1, 136.2, 143.1. Anal. calcd. for $C_{18}H_{20}O$: C 85.67, H 7.99; found: C 85.30, H 7.90.

*Fraction 2 (**8**)*: mp 161–163°C (recrystallized from EtOAc); ^{1}H NMR (CD_3COCD_3) δ: 1.47 (m, 2H, CH_2CH_2OH), 1.86 (s, 6H, tolyl *Me*'s), 2.44 (m, 2H, C(OH)CH_2), 2.86 and 2.89 (two s, 1H each, O*H*'s), 3.52 (m, 2H, CH_2OH), 6.98 (d, J = 7.2 Hz, 2H, tolyl H-3), 7.14 (m, 4H, tolyl H-4, H-5), 7.73 (dd, J = 7.6, J = 1.0 Hz, 2H, tolyl H-6); ^{13}C NMR (CD_3COCD_3) δ: 21.6, 28.2, 37.9, 62.9, 78.0, 125.6, 127.4, 128.0, 132.6, 136.9, 145.7. Anal. calcd. for $C_{18}H_{22}O_2$: C 79.96, H 8.20; found: C 79.73, H 8.28.

1,1-Bis(2-methylphenyl)-1-buten-4-ol (9, Method A)
A solution of **7** (1.25 g, 5 mmol) in THF (5 mL), EtOH (5 mL), and 6 N HCl (5 mL) was refluxed for 4 h; the reaction mixture was cooled to 25°C, and extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with brine (40 mL) and dried ($MgSO_4$). Removal of the solvent in vacuo gave a residue that was purified by silica gel flash chromatography using EtOAc–hexane (1:4, v/v) as eluant to yield **9** as an oil (1.18 g, 94%); ^{1}H NMR ($CDCl_3$) δ: 2.07 (m, 1H, O*H*), 2.14 and 2.31 (two s, 3H each, tolyl *Me*'s), 2.35 (m, 2H, CH_2CH_2OH), 3.70 (t, J = 6.7 Hz, 2H, CH_2OH), 5.83 (t, J = 7.2 Hz, 1H, C═C*H*), 7.10–7.25 (m, 8H, tolyl H-3, H-4, H-5, H-6).

1,1-Bis(2-methylphenyl)-1,4-butanediol (8, Method B)
A solution of **6** in THF (110 mL of a 1 M solution, 0.11 mol) was added to a solution of γ-butyrolactone (4.3 g, 50 mmol) in THF (150 mL) at 0°C with stirring, and the reaction was allowed to proceed at 25°C for 2 h. The reaction mixture was cooled to 0°C, saturated aqueous NH_4Cl (100 mL) was added, and the aqueous fraction was extracted with EtOAc (3 × 100 mL). The combined organic fractions were washed with brine (50 mL), the organic solution was dried ($MgSO_4$), and the solvent was removed in vacuo. Purification of the residue obtained by silica gel flash column chromatography using EtOAc–hexane (2:3, v/v) as eluant afforded **8** (12.15 g, 90%), which was identical (mp, ^{1}H NMR) to **8** prepared according to Method A. Product **8**, required for all subsequent reactions, was prepared according to Method B.

1,1-Bis(2-methylphenyl)-1-buten-4-ol (9, Method B)
A solution of **8** (8.1 g, 30 mmol, from Method B) in EtOH (30 mL) and 4 N HCl (30 mL) was heated at reflux for 6 h; the reaction mixture was cooled to 25°C, and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (60 mL), the organic fraction was dried ($MgSO_4$), and the solvent was removed in vacuo. Purification of the residue by silica gel flash column chromatography using EtOAc–hexane (1:4, v/v) as eluant yielded **9** as an oil (6.8 g, 90%), which was identical to **9** prepared according to Method A).

1,1-Bis(2-methylphenyl)-4-(4-methylbenzenesulfonyloxy)-1-butene (11*a*)
p-Toluensulfonyl chloride (9.5 g, 50 mmol) was added to a solution of **9** (6.3 g, 25 mmol) in pyridine (4.75 g, 60 mmol) and CH_2Cl_2 (100 mL) at 0°C with stirring, and the reaction was allowed to proceed at 25°C for 12 h. Saturated aqueous NH_4Cl (100 mL) was added, the mixture was extracted with EtOAc (3 × 100 mL), the combined organic extracts were washed with brine (2 × 50 mL), and the organic fraction was dried ($MgSO_4$). Removal of the solvent in vacuo gave a residue that was purified by silica gel column chromatography using EtOAc–hexane (1:9, v/v) as eluant to give **11*a*** (9.2 g, 92%); ^{1}H NMR ($CDCl_3$) δ: 2.03 (s, 3H, tosyl *Me*), 2.10 and 2.28 (two s, 3H each, tolyl *Me*'s), 2.39 (m, 2H, butenyl H-3), 4.12 (t, J = 6.7 Hz, 2H, CH_2OTs), 5.76 (t, J = 7.2 Hz, 1H, C═C*H*), 7.05–7.20 (m, 12H, phenyl hydrogens). Product **11*a*** was used immediately in subsequent reactions for the preparation of **11*b*** and **11*c***.

1,1-Bis(2-methylphenyl)-4-bromo-1-butene (11*b*)
A mixture of **11*a*** (4.1 g, 10 mmol) and LiBr (3.48 g, 40 mmol) in acetone (80 mL) was refluxed for 12 h; the reaction mixture was cooled to 25°C, and then poured onto saturated aqueous NH_4Cl (50 mL). Extraction with EtOAc (3 × 50 mL), washing the combined EtOAc extracts with brine (50 mL), drying the EtOAc fraction ($MgSO_4$), and removal of the solvent in vacuo gave a residue. Purification by silica gel column chromatography using EtOAc–hexane (1:99, v/v) as eluant yielded **11*b*** (2.77 g, 88%); ^{1}H NMR ($CDCl_3$) δ: 2.19 and 2.40 (two s, 3H each, tolyl *Me*'s), 2.70 (m, 2H, butenyl H-3), 3.49 (t, J = 6.7 Hz, 2H, CH_2Br), 5.87 (t, J = 7.1 Hz, 1H, C═C*H*), 7.15–7.30 (m, 8H, phenyl hydrogens); ^{13}C NMR ($CDCl_3$) δ: 19.9, 21.1, 32.5, 32.7, 125.3, 125.5, 126.8, 127.2, 129.8, 130.3, 130.8, 135.4, 136.1, 139.5, 141.8, 143.0. Product **11*b*** was used immediately in subsequent reactions.

1,1-Bis(2-methylphenyl)-4-iodo-1-butene (11*c*)
A mixture of **11*a*** (4.1 g, 10 mmol) and NaI (3.0 g, 20 mmol) in acetone (80 mL) was refluxed for 12 h, the reaction was completed, and the product purified according to the procedure described for the preparation of **11*b*** above, to yield **11*c*** (3.08 g, 85%); ^{1}H NMR ($CDCl_3$) δ: 2.12 and 2.32 (two s, 3H each, tolyl *Me*'s), 2.65 (m, 2H, butenyl H-3), 3.20 (t, J = 6.9 Hz, 2H, CH_2I), 5.75 (t, J = 7.1 Hz, 1H, C═C*H*), 7.10–7.25 (m, 8H, phenyl hydrogens).

1,1-Bis(2-methylphenyl)-4-hydroxybutane (12*a*)
10% Palladium-on-charcoal (800 mg) was added to a solution of **9** (8.0 g, 31.7 mmol) in ethanol (40 mL) and the mixture was agitated at 25°C for 4 h under hydrogen gas at 60 psi. The reaction mixture was filtered, the solvent was removed in vacuo, and the residue was purified by silica gel column chromatography using EtOAc–hexane (1:4, v/v) as eluant to yield **12*a*** as an oil (7.6 g, 95%); IR (film): 3360 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.60–1.70 (m, 2H, $CH_2CH_2CH_2$), 2.0–2.08 (m, 2H, $CH_2CH_2CH_2OH$), 2.31 (s, 6H, tolyl *Me*'s), 3.67 (t, J = 7.0 Hz, 2H, OCH_2), 4.29 (t, J = 7.0 Hz, 1H, $CHCH_2$), 7.08–7.20 (m, 8H, phenyl hydrogens). Product **12*a*** was used immediately in the subsequent reaction.

1,1-Bis(2-methylphenyl)-4-(4-methylbenzensulfonyloxy)-butane (12*b*)
p-Toluenesulfonyl chloride (9.5 g, 50 mmol) was added to a solution of **12*a*** (6.35 g, 25 mmol) in pyridine (4.75 g, 60 mmol) and CH_2Cl_2 (100 mL) at 0°C with stirring. The reaction

was allowed to proceed at 25°C for 12 h and the reaction mixture was poured onto a solution of saturated aqueous NH_4Cl (100 mL). Extraction with EtOAc (3 × 100 mL), washing the combined extracts with brine (50 mL), drying the organic fraction ($MgSO_4$), and removal of the solvent in vacuo gave a residue. Purification by silica gel column chromatography using EtOAc–hexane as eluant (1:9, v/v) gave **12***b* (9.0 g, 83%) as a solid; mp 103°C (recrystallized from EtOAc–hexane); ^{1}H NMR ($CDCl_3$) δ: 1.66–1.76 (m, 2H, CH_2CH_2OH), 1.92–2.0 (m, 2H, $CHCH_2CH_2$), 2.26 (s, 6H, tolyl *Me*'s), 2.46 (s, 3H, *p*-tosyl *Me*), 4.05 (t, *J* = 7.0 Hz, 2H, OCH_2), 4.21 (t, *J* = 7.0 Hz, 1H, $CHCH_2$), 7.06–7.16 (m, 8H, *o*-tolyl ring hydrogens), 7.34 and 7.79 (two d, *J* = 8.0 Hz, 2H each, tosyl ring hydrogens). Product **12***b* was used immediately in the subsequent reaction.

1,1-Bis(2-methylphenyl)-4-bromobutane (12*c*)

A mixture of **12***b* (4.08 g, 10 mmol) and LiBr (3.41 g, 40 mmol) in acetone (80 mL) was refluxed for 12h. The reaction mixture was cooled to 25°C, and the mixture was poured onto an aqueous solution of saturated NH_4Cl (50 mL). Extraction with EtOAc (3 × 50 mL), drying the EtOAc extract ($MgSO_4$), and removal of the solvent in vacuo gave a residue. Purification by silica gel column chromatography using EtOAc–hexane (1:99, v/v) as eluant afforded **12***c* as an oil (2.8 g, 83%); ^{1}H NMR ($CDCl_3$) δ: 1.90–2.01 (m, 2H, CH_2CH_2Br), 2.08–2.16 (m, 2H, $CHCH_2$), 2.30 (s, 6H, *o*-tolyl *Me*'s), 3.44 (t, *J* = 7.0 Hz, 2H, CH_2Br), 4.29 (t, *J* = 7.0 Hz, 1H, $CHCH_2$), 7.10–7.22 (m, 8H, phenyl hydrogens).

1-[4,4-Bis(2-methylphenyl)butyl]-3-[2-(4,4-dimethyl-4,5-dihydrooxazolin-2-yl)]-4-phenyl-1,4-dihydropyridine (14)

Sodium hydride (100 mg, 3.26 mmol, 80% suspension in mineral oil) was washed with dry hexane and dried under a nitrogen atmosphere prior to addition of DMSO (5 mL). A solution of **13** (1.37 g, 2.8 mmol) in DMSO (30 mL) was added dropwise at 25°C during 30 min under a nitrogen atmosphere with stirring. The reaction mixture was maintained at 50°C for 30 min, and then at 25°C for 1.5 h at which time no further evolution of hydrogen gas was observed. A solution of **12***c* (0.88 g, 2.8 mmol) in DMSO (2 mL) was added during a 10 min period, and the reaction was allowed to proceed at 25°C for 12 h. Excess DMSO was partially removed in vacuo, the reaction mixture was poured onto ice-water (5 mL), extracted with ether (3 × 100 mL), the ether extract was dried (Na_2SO_4), and the solvent was removed in vacuo to give a residue. Purification by silica gel column chromatography using EtOAc–hexane (1:1, v/v) as eluant gave **14** as an oil (0.5 g, 19%); IR (film): 1589, 1491, 1458 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 and 1.26 (two s, 3H each, oxazolinyl *Me*'s), 1.60–1.80 (m, 2H, $CHCH_2CH_2$), 1.90–2.10 (m, 2H, $CHCH_2$), 2.30 and 2.32 (two s, 3H each, tolyl *Me*'s), 3.24 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.82 (m, 2H, OCH_2), 4.27 (t, *J* = 7.0 Hz, 1H, $CHCH_2$), 4.68 (d, $J_{4,5}$ = 5.0 Hz, 1H, H-4), 4.88 (dd, $J_{5,6}$ = 8.0, $J_{4,5}$ = 5.0 Hz, 1H, H-5), 5.92 (d, $J_{5,6}$ = 8.0 Hz, 1H, H-6), 6.98 (s, 1H, H-2), 7.10–7.40 (m, 13H, phenyl hydrogens). Anal. calcd. for $C_{34}H_{38}N_2O\cdot 1H_2O$: C 80.27, H 7.92, N 5.50; found: C 79.92, H 8.10, N 5.13.

4,4-Bis(2-methylphenyl)butyl 1-[4,4-bis(2-methylphenyl)-butyl]pyridinium-3-carboxylate bromide (17)

A mixture of methyl nicotinate (137 mg, 1.0 mmol) and **12***c* (350 mg, 1.1 mmol) in dry MeCN (20 mL) was refluxed for 24 h. TLC analysis indicated that **12***c* was all consumed, but a considerable amount of methyl nicotinate was still present. Additional **12***c* (317 mg, 1 mmol) was added and the reaction was continued at reflux for 24 h at which time TLC showed the reaction was nearly complete. After cooling to 25°C, the solid product was filtered, washed with ether, and dried (Na_2SO_4) to afford **17** (0.5 g, 74%); mp 80°C; IR (KBr): 1737, 1638 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 1.72–2.10 (m, 8H, -CH_2CH_2CH-), 2.21 and 2.23 (two s, 6H each, tolyl *Me*'s), 4.20–4.30 (m, 2H, CH_2CH), 4.41 (t, *J* = 7.0 Hz, 2H, OCH_2), 4.66–4.78 (m, 2H, NCH_2), 7.04–7.24 (m, 16H, phenyl hydrogens), 8.26 (dd, $J_{4,5}$ = 8.0 Hz, $J_{5,6}$ = 6.0 Hz, 1H, H-5), 8.96 (d, $J_{4,5}$ = 8.0 Hz, 1H, H-4), 9.30 (d, $J_{5,6}$ = 6.0 Hz, 1H, H-6), 9.58 (s, 1H, H-2). The pyridinium salts **18** (from reaction of **15** with 2.1 equivalents of **11***b*), **19** (from reaction of **16** with 1.1 equivalents of **12***c*) and **20** (from reaction of **16** with 1.1 equivalents of **11***b*) were prepared using a similar procedure.

4,4-Bis(2-methylphenyl)-3-butenyl 1-[4,4-bis(2-methylphenyl)-3-butenyl]pyridinium-3-carboxylate bromide (18)

Yield: 67%; mp 75°C; IR (KBr): 1738, 1639, 1490 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 1.86, 2.0, 2.06, and 2.22 (four s, 3H each, tolyl *Me*'s), 2.42–2.58 and 2.60–2.78 (two m, 2H each, OCH_2CH_2, NCH_2CH_2), 4.48 (t, *J* = 7.0 Hz, 2H, OCH_2), 4.82–4.90 (m, 2H, NCH_2), 5.92–5.94 (m, 1H, CH=C), 6.54 (t, *J* = 7.0 Hz, 1H, CH=C), 6.92–7.30 (m, 16H, phenyl hydrogens), 8.30 (dd, $J_{4,5}$ = 8.0, $J_{5,6}$ = 6.0 Hz, 1H, H-5), 8.98 (d, $J_{4,5}$ = 8.0 Hz, 1H, H-4), 9.29 (d, $J_{5,6}$ = 6.0 Hz, 1H, H-6), 9.56 (s, 1H, H-2).

2-Cyanoethyl 1-[4,4-bis(2-methylphenyl)butyl]pyridinium-3-carboxylate bromide (19)

Yield: 72%; mp 180–183°C; IR (KBr): 2253 (CN), 1737, 1638 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 1.90–2.04 (m, 4H, $CH_2CH_2CH_2CH$), 2.24 (s, 6H, tolyl *Me*'s), 3.11 (t, *J* = 6.0 Hz, 2H, CH_2CN), 4.25 (t, *J* = 7.0 Hz, 1H, CH_2CH), 4.60 (t, *J* = 6.0 Hz, 2H, OCH_2), 4.72–4.82 (m, 2H, NCH_2), 7.06–7.20 (m, 8H, phenyl hydrogens), 8.32 (dd, $J_{4,5}$ = 8.0, $J_{5,6}$ = 6.0 Hz, 1H, H-5), 8.98 (d, $J_{4,5}$ = 8.0 Hz, 1H, H-4), 9.34 (d, $J_{5,6}$ = 6.0 Hz, 1H, H-6), 9.66 (s, 1H, H-2).

2-Cyanoethyl 1-[4,4-bis(2-methylphenyl)-3-butenyl]pyridinium-3-carboxylate bromide (20)

Yield: 60%; mp 75–79°C; IR (KBr): 2250 (CN), 1740 (CO_2); ^{1}H NMR (DMSO-d_6) δ: 1.90 and 2.04 (two s, 3H each, tolyl *Me*'s), 2.64–2.76 (m, 2H, CH_2CH_2CH), 3.10 (t, *J* = 6.0 Hz, 2H, CH_2CN), 4.60 (t, *J* = 6.0 Hz, 2H, OCH_2), 4.88 (t, *J* = 7.0 Hz, 2H, NCH_2), 5.86 (t, *J* = 7.0 Hz, 1H, CH_2=CH), 6.92–7.20 (m, 8H, phenyl hydrogens), 8.32 (dd, $J_{4,5}$ = 8.0, $J_{5,6}$ = 6.0 Hz, 1H, H-5), 9.0 (d, $J_{4,5}$ = 8.0 Hz, 1H, H-4), 9.32 (d, $J_{5,6}$ = 6.0 Hz, 1H, H-6), 9.61 (s, 1H, H-2).

2-Cyanoethyl nicotinate (16)

A solution of 2-cyanoethanol (0.71 g, 10 mmol) in dry CH_2Cl_2 (5 mL) was added, during 10 min with stirring, to a solution of nicotinoyl chloride (1.78 g, 10 mmol) in dry CH_2Cl_2 (20 mL) at 0°C under a nitrogen atmosphere. The reaction was allowed to proceed at 0°C for 30 min and then at 25°C for 14 h. Water (20 mL) was added, the mixture was extracted with EtOAc (3 × 50 mL), the EtOAc extracts were washed with brine (2 × 50

mL), and the EtOAc solution was dried (Na_2SO_4). Removal of the solvent in vacuo gave a residue that was purified by silica gel column chromatography using EtOAc–hexane (1:4, v/v) as eluant to yield **16** (1.5 g, 85%) as an oil; IR (film): 2253 (CN), 1728 (CO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.88 (t, J = 6.0 Hz, 2H, CH_2CN), 4.58 (t, J = 6.0 Hz, 2H, OCH_2), 7.44 (dd, $J_{4,5}$ = 8.0, $J_{5,6}$ = 6.0 Hz, 1H, H-5), 8.32 (dt, $J_{4,5}$ = 8.0, $J_{4,6}$ = $J_{2,4}$ = 2.0 Hz, 1H, H-4), 8.85 (dd, $J_{5,6}$ = 6.0, $J_{4,6}$ = 2.0 Hz, 1H, H-6), 9.26 (d, $J_{2,4}$ = 2.0 Hz, 1H, H-2).

4,4-Bis(2-methylphenyl)butyl 1-[4,4-bis(2-methylphenyl)-butyl]-4-phenyl-1,4-dihydropyridine-3-carboxylate (21) and 4,4-bis(2-methylphenyl)butyl 1-[4,4-bis(2-methylphenyl)butyl]-6-phenyl-1,6-dihydropyridine-3-carboxylate (27). General method for the synthesis of 1,2- and 1,6-dihydropyridines

A solution of the pyridinium salt **17** (0.675 g, 1 mmol) in dry THF (20 mL) and CuI (35 mg) was stirred under a nitrogen atmosphere until a homogeneous solution was obtained. This solution was cooled to −23°C (Dry Ice – CCl_4 bath), PhMgCl (0.6 mL of a 2 M solution in THF, 1.2 mmol) was added dropwise with stirring, and the reaction mixture was maintained at −23°C for 30 min prior to warming to 25°C. Quenching the reaction with saturated aqueous NH_4Cl (5 mL), extraction with EtOAc (3 × 30 mL), washing the combined EtOAc extracts with brine (2 × 30 mL), drying the EtOAc solution ($MgSO_4$), and removal of the solvent in vacuo afforded a residue. Purification of the residue by silica gel column chromatography using EtOAc–hexane (3:7, v/v) as eluant gave **21** as an amorphous solid. Continued elution afforded **27** as an oil. Attempts to recrystallize **21** and **27** resulted in partial decomposition. Compounds **22** (amorphous solid) and **28** (oil), **23** (oil) and **29** (oil), **24** (oil) and **30** (oil) were also prepared using this general procedure (same molar quantities of reactants).

*Product **21***: (150 mg, 22%); mp 48°C; IR (KBr): 1687, 1589 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.52–1.64, 1.66–1.72, 1.80–1.90, and 1.96–2.06 (four m, 2H each, $OCH_2CH_2CH_2CH$, $NCH_2CH_2CH_2CH$), 2.25, 2.26, 2.30, and 2.32 (four s, 3H each, tolyl *Me*'s), 3.26 (t, J = 7.0 Hz, 2H, NCH_2), 3.93–4.09 (m, 2H, OCH_2), 4.18 and 4.27 (two t, J = 7.0 Hz, 1H each, CH_2CH), 4.52 (d, $J_{4,5}$ = 4.5 Hz, 1H, H-4), 4.90 (dd, $J_{5,6}$ = 8.0, $J_{4,5}$ = 4.5 Hz, 1H, H-5), 5.85 (d, $J_{5,6}$ = 8.0 Hz, 1H, H-6), 7.05–7.15 (m, 22H, H-2, phenyl hydrogens). Exact Mass calcd. for $C_{48}H_{51}NO_2$: 673.3919; found: 673.3904.

*Product **27***: (120 mg, 18%); IR (film): 1687, 1589 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 1.42–1.64 and 1.96–2.0 (two m, 4H each, $OCH_2CH_2CH_2CH$, $NCH_2CH_2CH_2CH$), 2.18 and 2.20 (two s, 3H each, tolyl *Me*'s), 2.22 (s, 6H, tolyl *Me*'s), 3.3–3.4 (m, 2H, NCH_2), 4.04 (t, J = 7.0 Hz, 2H, OCH_2), 4.18 and 4.25 (two t, J = 7.0 Hz, 1H each, CH_2CH), 5.08 (dd, $J_{4,5}$ = 9.5, $J_{5,6}$ = 5.0 Hz, 1H, H-5), 5.18 (d, $J_{5,6}$ = 5.0 Hz, 1H, H-6), 6.24 (d, $J_{4,5}$ = 9.5 Hz, 1H, H-4), 7.07–7.40 (m, 21H, phenyl hydrogens), 7.48 (s, 1H, H-2). Exact Mass calcd. for $C_{48}H_{51}NO_2$: 673.3919; found: 673.3907.

4,4-Bis(2-methylphenyl)-3-butenyl 1-[4,4-bis(2-methylphenyl)-3-butenyl]-4-phenyl-1,4-dihydropyridine-3-carboxylate (22)

Yield: 165 mg, 24%; mp 35°C; IR (KBr): 1687, 1589 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.09, 2.10, 2.21, and 2.24 (four s, 3H each, tolyl *Me*'s), 2.22–2.40 (m, 4H, $CH_2CH{=}C$), 3.31 (t, J = 7.0 Hz, 2H, NCH_2), 4.04 (t, J = 7.0 Hz, 2H, OCH_2), 4.50 (d, $J_{4,5}$ = 4.5 Hz, 1H, H-4), 4.86 (dd, $J_{5,6}$ = 8.0, $J_{4,5}$ = 4.5 Hz, 1H, H-5), 5.64 (t, J = 7.0 Hz, 1H, $CH_2CH{=}C$), 5.72–5.80 (m, 2H, $CH_2CH{=}C$, H-6), 7.02–7.30 (m, 22H, H-2, phenyl hydrogens). Exact Mass calcd. for $C_{48}H_{47}NO_2$: 669.3607; found: 669.3606.

4,4-Bis(2-methylphenyl)-3-butenyl 1-[4,4-bis(2-methylphenyl)-3-butenyl]-6-phenyl-1,6-dihydropyridine-3-carboxylate (28)

Yield: 125 mg, 19%; IR (film): 1687, 1638, 1573 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.10, 2.16, 2.24, and 2.30 (four s, 3H each, tolyl *Me*'s), 2.40–2.50 (m, 4H, $CH_2CH{=}C$), 3.02–3.20 (m, 2H, NCH_2), 4.20–4.30 (m, 2H, OCH_2), 4.95 (dd, $J_{4,5}$ = 9.5, $J_{5,6}$ = 5.0 Hz, 1H, H-5), 5.01 (d, $J_{5,6}$ = 5.0 H, 1H, H-6), 5.70 and 5.88 (two t, J = 7.0 Hz, 1H each, $CH_2CH{=}C$), 6.43 (d, $J_{4,5}$ = 9.5 Hz, 1H, H-4), 7.08–7.37 (m, 21H, phenyl hydrogens), 7.39 (s 1H, H-2). Exact Mass calcd. for $C_{48}H_{47}NO_2$: 669.3607; found: 669.3580.

*2-Cyanoethyl 1-[4,4-bis(2-methylphenyl)butyl]-4-phenyl-1,4-dihydropyridine-3-carboxylate (**23**)*

Yield: 110 mg, 22%; IR (film): 2395 (CN), 1687, 1589 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 1.50–1.62 (m, 2H, $CH_2CH_2CH_2$), 1.80–1.98 (m, 2H, $NCH_2CH_2CH_2CH$), 2.24 and 2.26 (two s, 3H each, tolyl *Me*'s), 2.70–2.80 (m, 2H, CH_2CN), 3.30–3.46 (m, 2H, NCH_2), 4.09–4.14 (m, 2H, OCH_2), 4.24 (t, J = 7.0 Hz, 1H, CH_2CH), 4.38 (d, $J_{4,5}$ = 4.5 Hz, 1H, H-4), 4.88 (dd, $J_{5,6}$ = 8.0, $J_{4,5}$ = 4.5 Hz, 1H, H-5), 6.12 (d, $J_{5,6}$ = 8.0 Hz, 1H, H-6), 7.04–7.28 (m, 13H, phenyl hydrogens), 7.38 (s, 1H, H-2). Product **23** was used immediately for the preparation of **25**.

*2-Cyanoethyl 1-[4,4-bis(2-methylphenyl)butyl]-6-phenyl-1,6-dihydropyridine-3-carboxylate (**29**)*

Yield: 100 mg, 20%; IR (film): 2385 (CN), 1679, 1638 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 1.42–1.60 (m, 2H, CH_2CH_2CH), 1.70–1.80 (m, 2H, CH_2CH_2CH), 2.18 and 2.20 (two s, 3H each, tolyl *Me*'s), 2.86 (t, J = 6.0 Hz, 2H, CH_2CN), 3.30–3.40 (m, 2H, NCH_2), 4.26 (t, J = 7.0 Hz, 3H total, OCH_2, CH_2CH), 5.09 (dd, $J_{4,5}$ = 9.5, $J_{5,6}$ = 5.0 Hz, 1H, H-5), 5.20 (d, $J_{5,6}$ = 5.0 Hz, 1H, H-6), 6.26 (d, $J_{5,6}$ = 9.5 Hz, 1H, H-4), 7.07–7.40 (m, 13H, phenyl hydrogens), 7.54 (s, 1H, H-2). Product **29** was used immediately for the synthesis of **31**.

*2-Cyanoethyl 1-[4,4-bis(2-methylphenyl)-3-butenyl]-4-phenyl-1,4-dihydropyridine-3-carboxylate (**24**)*

Yield: 100 mg, 20%; IR (film): 2196 (CN), 1671, 1638 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.02 and 2.06 (two s, 3H each, tolyl *Me*'s), 2.18–2.28 (m, 2H, $CH_2CH{=}$), 2.68–2.76 (m, 2H, CH_2CN), 3.43 (t, J = 7.0 Hz, 2H, NCH_2), 4.08 (t, J = 6.0 Hz, 2H, OCH_2), 4.33 (d, $J_{4,5}$ = 4.5 Hz, 1H, H-4), 4.74 (dd, $J_{5,6}$ = 8.0, $J_{4,5}$ = 4.5 Hz, 1H, H-5), 5.77 (t, J = 7.0 Hz, 1H, $CH_2CH{=}$), 5.96 (d, $J_{5,6}$ = 8.0 Hz, 1H, H-6), 7.0–7.24 (m, 13H, phenyl hydrogens), 7.29 (s, 1H, H-2). Product **24** was used immediately for the synthesis of **26**.

*2-Cyanoethyl 1-[4,4-bis(2-methylphenyl)-3-butenyl]-6-phenyl-1,6-dihydropyridine-3-carboxylate (**30**)*

Yield: 105 mg, 21%; IR (film): 2368 (CN), 1687, 1581 cm^{-1};

^{1}H NMR ($CDCl_3$) δ: 2.10 and 2.24 (two s, 3H each, tolyl *Me*'s), 2.30–2.40 (m, 2H, CH_2CH), 2.74 (t, J = 6.0 Hz, 2H, CH_2CN), 3.02–3.20 (m, 2H, NCH_2), 4.26–4.40 (m, 2H, OCH_2), 4.96 (dd, $J_{4,5}$ = 9.5, $J_{5,6}$ = 5.0 Hz, 1H, H-5), 5.02 (d, $J_{5,6}$ = 5.0 Hz, 1H, H-6), 5.69 (t, J = 7.0 Hz, 1H, CH_2CH=), 6.69 (d, $J_{4,5}$ = 9.5 Hz, 1H, H-4), 7.04–7.36 (m, 13H, phenyl hydrogens), 7.43 (s, 1H, H-2). Product **30** was used immediately for the synthesis of **32**.

1-[4,4-Bis(2-methylphenyl)butyl]-4-phenyl-1,4-dihydropyridine-3-carboxylic acid (25). General procedure

A solution of **23** (100 mg, 0.2 mmol) and DBU (91 mg, 0.6 mmol) in MeOH (10 mL) was stirred at 25°C for 14 h, and the solvent was removed in vacuo to give an oil residue. Addition of 0.5 N HCl to the oil (pH 1–2) precipitated **25** as a solid, which was filtered and recrystallized from Et_2O–hexane (62 mg, 70%); mp 101–102°C; IR (KBr): 2551–2942 (CO_2H), 1638, 1564 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 1.46–1.62 (m, 2H, CH_2CH_2CH), 1.82–1.98 (m, 2H, CH_2CH_2CH), 2.23 and 2.26 (two s, 3H each, tolyl *Me*'s), 3.30–3.42 (m, 2H, NCH_2), 4.24 (t, J = 7.0 Hz, 1H, CH_2CH), 4.34 (d, $J_{4,5}$ = 4.5 Hz, 1H, H-4), 4.80 (dd, $J_{5,6}$ = 8.0, $J_{4,5}$ = 4.5 Hz, 1H, H-5), 6.06 (d, $J_{5,6}$ = 8.0 Hz, 1H, H-6), 7.04–7.24 (m, 13H, phenyl hydrogens), 7.30 (s, 1H, H-2), 11.14 (s, 1H, CO_2H). Anal. calcd. for $C_{30}H_{31}NO_2 \cdot 3/4H_2O$: C 79.88, H 7.26, N 3.10; found: C 79.80, H 7.41, N 3.00. A similar procedure was used for the reactions **29** → **31**, **24** → **26**, and **30** → **32** using the same molar quantities of reactants.

1-[4,4-Bis(2-methylphenyl)butyl]-6-phenyl-1,6-dihydropyridine-3-carboxylic acid (31)

Yield: 55 mg, 62%; mp 85°C; IR (KBr): 3543–2951 (CO_2H), 1630, 1573 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 1.42–1.56 (m, 2H, CH_2CH_2CH), 1.74–1.88 (m, 2H, CH_2CH_2CH), 2.18 and 2.20 (two s, 3H each, tolyl *Me*'s), 3.32–3.50 (m, 2H, NCH_2), 4.16 (t, J = 7.0 Hz, 1H, CH_2CH), 5.04 (dd, $J_{4,5}$ = 9.5, $J_{5,6}$ = 5.0 Hz, 1H, H-5), 5.15 (d, $J_{5,6}$ = 5.0 Hz, 1H, H-6), 6.24 (d, $J_{4,5}$ = 9.5 Hz, 1H, H-4), 7.07–7.34 (m, 13H, phenyl hydrogens), 7.44 (s, 1H, H-2), 11.0 (s, 1H, CO_2H). Anal. calcd. for $C_{30}H_{31}NO_2$: C 82.35, H 7.14, N 3.20; found: C 81.97, H 7.23, N 3.17.

1-[4,4-Bis(2-methylphenyl)-3-butenyl]-4-phenyl-1,4-dihydropyridine-3-carboxylic acid (26)

Yield: 50 mg, 56%; mp 130–131°C; IR (KBr): 3518–2992 (CO_2H), 1671, 1646, 1589 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ: 2.04 and 2.16 (two s, 3H each, tolyl *Me*'s), 2.17–2.28 (m, 2H, CH_2CH=), 3.43 (t, J = 7.0 Hz, 2H, NCH_2), 4.32 (d, $J_{4,5}$ = 4.5 Hz, 1H, H-4), 474 (d, $J_{5,6}$ = 8.0, $J_{4,5}$ = 4.5 Hz, 1H, H-5), 5.77 (t, J = 7.0 Hz, 1H, CH_2CH=), 5.96 (d, $J_{5,6}$ = 8.0 Hz, 1H, H-6), 7.04–7.22 (m, 13H, phenyl hydrogens), 7.28 (s, 1H, H-2), 11.1 (s, 1H, CO_{2H}). Anal. calcd. for $C_{30}H_{29}NO_2$: C 82.73, H 6.71, N 3.22; found: C 82.48, H 6.83, N 3.32.

1-[4,4-Bis(2-methylphenyl)-3-butenyl]-6-phenyl-1,6-dihydropyridine-3-carboxylic acid (32)

Yield: (45 mg, 50%); mp 80–82°C; IR (KBr): 3567–2959 (CO_2H), 1630, 1564 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 2.01 and 2.17 (two s, 3H each, tolyl *Me*'s), 2.20–2.30 (m, 2H, CH_2CH=), 3.34–3.50 (m, 2H, NCH_2), 4.90–5.0 (m, 2H, H-5, H-6), 5.72 (t, J = 7.0 Hz, 1H, CH_2CH=), 6.20 (d, $J_{4,5}$ = 9.5 Hz, 1H, H-4), 7.0–7.34 (m, 13H, phenyl hydrogens), 7.45 (s, 1H, H-2), 11.0 (s, 1H, CO_2H). Anal. calcd. for $C_{30}H_{29}NO_2$: C 82.73, H 6.71, N 3.22; found: C 82.50, H 6.79, N 3.41.

[^{3}H]GABA-uptake inhibition assay

Male Sprague–Dawley rats were sacrificed by decapitation and the brains were immediately removed and cooled in ice-cold incubation medium. The brains were then transferred to Petri dishs on ice, and the striata were dissected out and chopped into prisms (0.1 mm × 0.1 mm × approximately 2 mm) using a McIlwain tissue chopper. These prisms were suspended in incubation medium that was used for the [^{3}H]GABA-uptake experiments, essentially using the procedure of Iversen and Neal (24). Aminooxyacetic acid (100 mM) was added to the incubation medium to inhibit GABA-transaminase. [^{3}H]GABA (specific activity 36.8 Ci/mmol, which was mixed with unlabeled GABA to give a final concentration of 1.0 mM) was added to the flasks, after a 15 min preincubation of the the prisms at 37°C, in the presence or absence (control) of the test compound. Incubation was continued at 37°C for 5 min, and the contents of the flasks were transferred to a Millipore filter apparatus containing 12 wells with paper filters, and connected to a vacuum line. The samples were rapidly washed twice with incubation medium at 37°C, and the filters added to scintillation vials containing Ready-Safe® scintillation fluid. The amount of radioactivity in the test sample was measured using a liquid scintillation counter, and the % inhibition of [^{3}H]GABA uptake by the test compound (relative to the control) was calculated.

Acknowledgments

We are grateful to the Medical Research Council of Canada (Grant No. MT-8892) for financial support of this research.

References

1. P.D. Suzdak. Drugs Future, **18**, 1129 (1993), and refs. cited therein.
2. S. Fahn. *In* GABA in nervous system function. *Edited by* T. Chase and D. Tower. Raven Press, New York. 1976. pp. 169–183.
3. B.J. Kanner and S. Schuldiner. Mechanism of transport and storage of neurotransmitters. Critical review of biochemistry. Vol. 22. CRC Press, Boca Raton, Fla. 1987. pp. 1–38.
4. D. Lodge, G.A. Johnston, D.R. Curtis, and S.J. Brand. Brain Res. **136**, 513 (1977).
5. H.H. Frey, C. Popp, and W. Loscher. Neuropharmacology, **18**, 581 (1979).
6. M.J. Croucher, B.S. Meldrum, and P. Krogsgaard. Eur. J. Pharmacol. **89**, 217 (1983).
7. K.E. Andersen, C. Braestrup, F.C. Gronwald, A.S. Jorgensen, E.B. Nielsen, U. Sonnewald, P.O. Sorensen, P.D. Suzdak, and L.J. Knutsen. J. Med. Chem. **36**, 1716 (1993).
8. P.D. Suzdak, K. Frederiksen, K.E. Andersen, P.O. Sorensen, L.J. Knutsen, and E.B. Nielsen. Eur. J. Pharmacol. **223**, 189 (1992).
9. E. Pop, M.E. Brewster, and N. Bodor. Drugs Future, **16**, 221 (1991).
10. M. Brewster. Abstract No. 133, 201st ACS National Meeting, Medicinal Chemistry Division, Atlanta, Ga., April 14–19, 1991.
11. M.R. Pavia, S.J. Lobbestael, D. Nugiel, D.R. Mayhugh, V.E. Gregor, C.P. Taylor, R.D. Schwarz, L. Brahce, and M.G. Vartanian. J. Med. Chem. **35**, 4238 (1992).
12. S.K. Dubey and E.E. Knaus. Heterocycles, **22**, 1091 (1984).

13. D.L. Comins, E.D. Stroud, and J.J. Herrick. Heterocycles, **22**, 151 (1984).
14. S.-H. Yiu and E.E. Knaus. Org. Prep. Proced. Int. **28**, 91 (1996).
15. H.J. Hoffmann and R. Cimeraglia. FEBS Lett. **241**, 38 (1988).
16. H.J. Hoffmann and R. Cimiraglia. J. Mol. Struct. (Theochem), **205**, 1 (1990).
17. Y.-D. Wu and K.N. Houk. J. Org. Chem. **58**, 2043 (1993).
18. P.P. Mager, R.A. Coburn, A.J. Solo, D.J. Triggle, and H. Roth. Drug Des. Discovery, **8**, 273 (1992).
19. T.G. Murali Dhar, L.A. Borden, S. Tyagarajan, K.E. Smith, T.A. Branchek, R.L. Weinshank, and C. Gluchowski. J. Med. Chem. **37**, 2334 (1994).
20. E. Pop, M.E. Brewster, and N. Bodor. Drugs Future, **16**, 221 (1991).
21. M.E. Brewster, A. Simay, K. Czako, D. Winwood, H. Farag, and N. Bodor. J. Org. Chem. **54**, 3721 (1989).
22. E. Pop, Z.Z. Liu, J. Vlasak, W.R. Anderson, M.E. Brewster, and N. Bodor. Pharm. Sci. **1**, 265 (1995), and refs. cited therein.
23. S.-H. Yiu and E.E. Knaus. J. Med. Chem. **39**, 4576 (1996).
24. L.L. Iversen and M.J. Neal. J. Neurochem. **15**, 1141 (1968).