Novel Dual Inhibitors of AChE and MAO Derived from Hydroxy Aminoindan and Phenethylamine as Potential Treatment for Alzheimer's Disease

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Carbamate derivatives of *N*-propargylaminoindans (Series I) and *N*-propargylphenethylamines (Series II) were synthesized via multistep procedures from the corresponding hydroxy precursors. The respective rasagiline- and selegiline-related series were designed to combine inhibitory activities of both acetylcholine esterase (AChE) and monoamine oxidase (MAO) by virtue of their carbamoyl and propargylamine pharmacophores. Each compound was tested for these activities in vitro in order to find molecules with similar potencies against each enzyme. Compounds with such dual AChE and MAO inhibitory activities are expected to have potential for the treatment of Alzheimer's disease. The observed SAR also offers insight into the requirements of the active sites on these enzymes. A carbamate moiety was found to be essential for AChE inhibition, which was absent in the corresponding hydroxy precursors. The propargyl group caused 2−70-fold decrease in AChE inhibitory activity (depending on the position of the carbamoyl group) of Series I, but had little or no effect in Series II. Thus, the 6- and 7-carbamyloxyphenyls in Series I were either equipotent to, or slightly (2- to 5-fold) less active as AChE inhibitors than, the corresponding compounds in Series II, while the 4-carbamyloxyphenyls were more potent. The presence of the carbamate moiety in 6- and 7-carbamyloxyphenyls of Series I, considerably decreased MAO-A and -B inhibitory activity, compared to that of the parent hydroxy analogues, while the opposite was true for Series II. Thus, the 6- and 7-carbamyloxyphenyls in Series I were 2−3 orders of magnitude weaker MAO inhibitors while the 4- carbamyloxyphenyls were equipotent with the corresponding compounds in Series II. In both series, *N*-methylation of the propargylamine enhanced the MAO (A and B equally) inhibitory activities and decreased the AChE inhibitory activity. Two candidates belonging to the indan and tetralin ring systems (**24c**, **27b**) and one phenethylamine (**53d)** were identified as possible leads for further development based on the following criteria: (a) comparable AChE and MAO-B inhibitory activities, (b) good to moderate AChE inhibitory activity, and (c) lack of strong MAO-A selectivity. However, it is likely that these compounds will be metabolized to the corresponding phenols, with inhibitory activities against AChE and/or MAO-A or -B, different from those of the parent carbamates. Thus, the apparent enzyme inhibition will be a result of the combined inhibition of all of these individual metabolites. The results of our ongoing in vivo screening programs will be published elsewhere.

Introduction

Alzheimer's disease (AD) is characterized by a progressive impairment in memory and intellectual ability, accompanied by behavioral disturbances and a decreasing ability to perform basic activities of daily living. The degree of memory impairment correlates well with the loss of cholinergic transmission in the temporal lobe and other cortical brain regions innervated by neurons arising in the nucleus basalis of Meynert.[1] In addition, depressive symptoms occur in subjects with AD,[2] and these may be associated with decreases in serotoninergic and noradrenergic transmission in the limbic system.[3] Although the cause of progressive neuronal degeneration in AD is not known, evidence for the presence of oxidative stress, mediated by increased levels of iron, breakdown of peroxynitrite, and nitration of tyrosine residues in cell membrane proteins has been reported.[4] Monoamine oxidase B (MAO-B) activity also increases in association with gliosis, which can result in higher levels of H_2O_2 and oxidative free radicals.[5]

Currently, the only approved therapy for AD is based on a reduction of the cognitive deficits by enhancing

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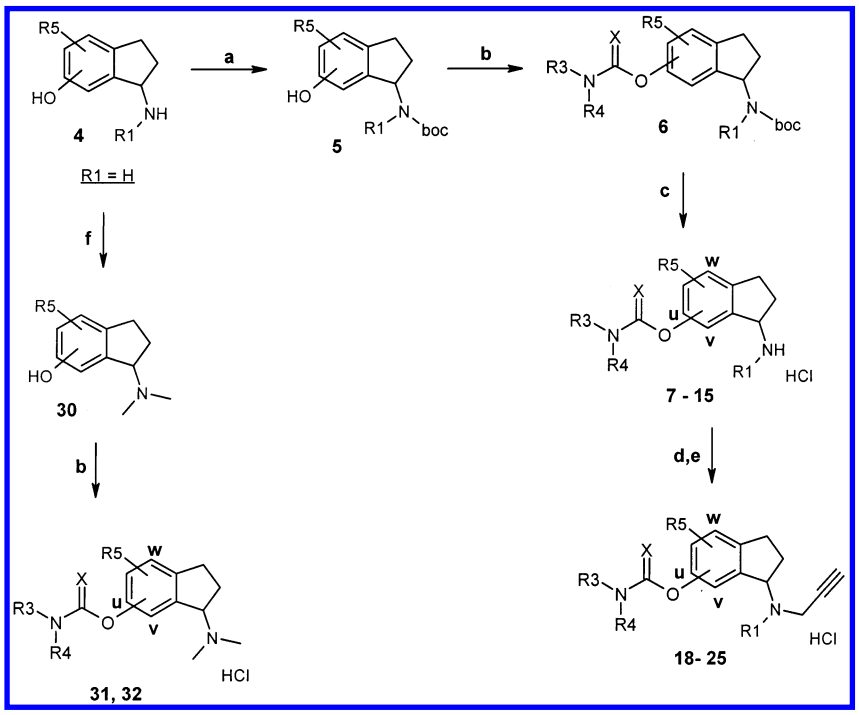
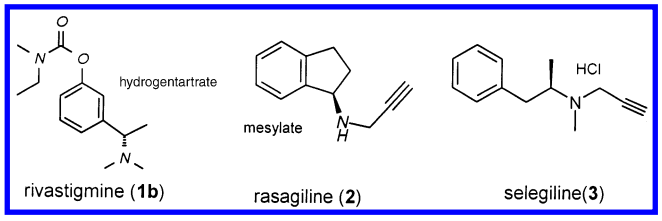
Scheme 1[a]



[a] (a) $(Boc)_2O$, Et_3N, THF, rt; (b) R_3R_4NCXCl (X = O, S), CH_3CN, NaH, rt or R_4NCO, Et_3N, CH_2Cl_2,rt; (c) HCl/dioxane, rt; (d) propargyl bromide, K_2CO_3, CH_3CN or DMA, rt; (e) HCl/Et_2O, rt; (f) $NaCNBH_3/(CH_2O)_n$.

cholinergic transmission through inhibition of acetylcholinesterase (AChE). These anti-AChE agents include tacrine, galanthamine, donepezil, and rivastigmine (**1b**), which have been shown to induce a modest improvement in memory and cognitive function,[6] but do not appear to prevent or slow the progressive neurodegeneration. On the other hand, selegiline, a selective MAO-B inhibitor, has been reported to retard the further deterioration of cognitive functions to more advanced milestones in AD.[7] The propargylamine pharmacophore of rasagiline (**2**), selegiline (**3**), and related compounds also appears to have neuropotective activity independent of MAO inhibition.[8−10] Because of the complexity of AD, it is unlikely that a single pharmacological action will provide a comprehensive and satisfactory therapeutic solution for such patients. Such therapy is more likely to be achieved by the use of compounds that incorporate several pharmacological traits into a single molecular entity and will work in a synergistic manner. Attempts to combine anti-AChE



and anti-MAO activities in one molecular entity have previously been reported.[11−15] Imino 1,2,3,4-tetrahydrocyclopent[*b*]indole carbamates, hybrids of physostigmine, an AChE inhibitor, and the MAO inhibitors selegiline and tranylcypromine, were generated by incorporating a carbamate and either a propargylamine or a cyclopropylamine moiety into a single molecular scaffold.[12] The *N*-alkylimine precursors of these compounds were reversible MAO inhibitors in vitro. Some of the imino 1,2,3,4-tetrahydrocyclopent[*b*]indole carbamates were potent dual inhibitors of AChE and MAO in vitro, but exhibited low activity after oral administration, possibly because of poor brain penetration or low bioavailability.[12,13] *N*-Pyrimidine 4-acetylaniline derivatives possessing AChE and reversible MAO-A inhibitory activity in vitro have also been reported.[14] Several 7-aryloxycoumarin derivatives with known MAO inhibitory activity were shown to act as noncompetitive AChE inhibitors.[15]

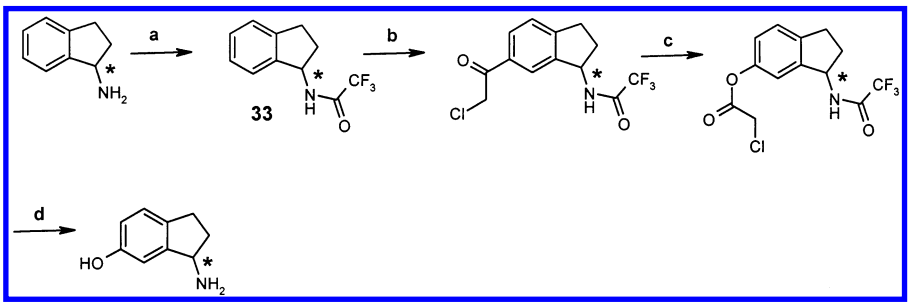
The present study describes the preparation and preliminary in vitro screening of two series of dual MAO and AChE inhibitors that are based on introduction of a carbamate moiety, to confer AChE inhibitory activity on either rasagiline (Series I) or selegiline (Series II), both of which are MAO-B inhibitors with neuroprotective activity in vitro and in vivo.[8,16−19] We anticipated that in addition to reduction in oxidative stress,[20] drugs that possess MAO-A inhibitory activity might also have a direct effect on cognition and act as antidepressant agents.

Our goal is identification of propargylamino carbamates that are equipotent as MAO and AChE inhibitors and therefore may be used for the treatment of AD and other neurodegenerative diseases. By combining SAR and modeling data, we will also gain insight into the requirements of the active sites on these two enzymes.

Chemistry

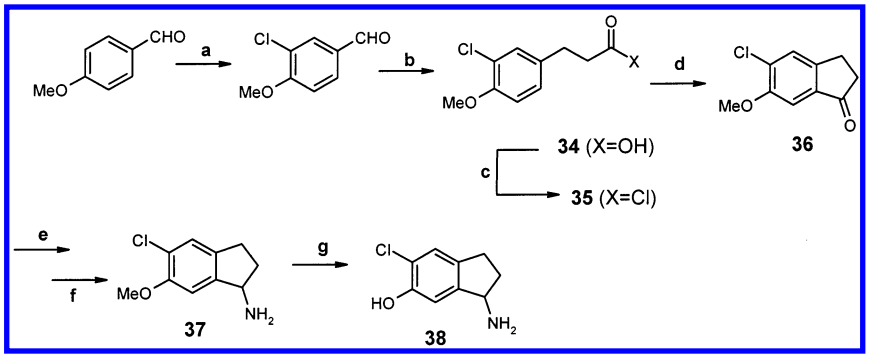
Series I. In general, compounds of Series I were synthesized via a four-step procedure from hydroxy aminoindans **4** (Scheme 1) or analogous hydroxy aminotetralins, as follows. Hydroxy amines were *N*-Boc protected (Boc_2O, Et_3N, THF) and carbamoylated by carbamoyl/thiocarbamoyl chlorides or by alkyl isocyan-

Scheme 2[a]



[a] (a) $(CF_3CO)_2O$, KOH, toluene, H_2O, rt; (b) $ClCH_2COCl$, $AlCl_3$,1,2-DCE, rt; (c) mCPBA,CH_2Cl_2,TFA,rt; (d) K_2CO_3, MeOH, H_2O, 70 °C.

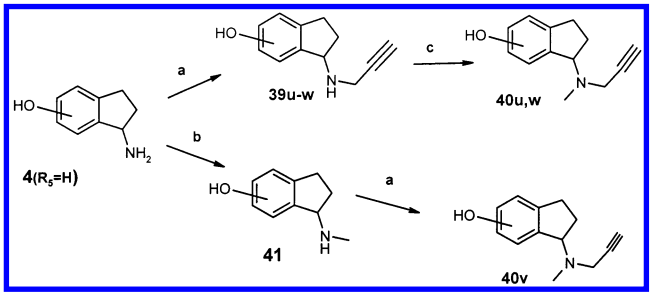
Scheme 3[a]



[a] (a) SO_2Cl_2, AcOH, rt; (b) 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid), Et_3N, HCO_2H; (c) $SOCl_2$, reflux; (d) $AlCl_3$, CH_2Cl_2, 0 °C, then rt; (e) NH_2OH, NaOAc, H_2O, EtOH, reflux; (f) MoO_3, MeOH, DMF, rt; (g) HBr, AcOH, H_2O, reflux.

ates to give the dialkyl and monoalkyl carbamates (**6**), respectively. The carbamates were selectively Boc-deprotected (HCl, dioxane) and propargylated (propargyl bromide, K_2CO_3, CH_3CN). The target compounds were finally isolated as salts. This synthetic strategy was chosen rather than the more economical approach of preparing first hydroxy propargylaminoindans (**39**) as common intermediates for the various carbamates, because we also wanted to test the biological activities of the non-propargyl carbamates. The order of propargylation and carbamoylation was reversed in the 1-methyl-2-propynyl analogues **26**, and 6-hydroxy-1-aminoindan was first propargylated by 3-mesyloxy-1-butyne.[21] Compounds **31a** and **32a** were obtained by carbamoylation of the corresponding hydroxy-*N*,*N*-dimethyl-1-aminoindan **30**. The *N*-methyl propargyl carbamates **19c**, **22b**, **22c**, and **29b** were prepared by N-monomethylation of the corresponding nor compounds. Racemic starting hydroxy amines **4** were prepared according to known procedures.[22−27] Optically pure 6-hydroxy-1-aminoindan was prepared either by optical resolution of the racemic mixture[28] or via a regioselective Friedel−Crafts chloroacetylation of the *N*-trifluoroacetyl derivative (**33**) of optically pure 1-aminoindan (prepared from indene via *N*-benzyl-1-aminoindan[29]), followed by a Baeyer−Villiger oxidation and finally hydrolysis (Scheme 2). This method was first reported[30] for the preparation of 6-hydroxyindole and was successfully applied to the synthesis of our aminoindan derivatives. The chloro analogues **24** were synthesized from 5-chloro-6-hydroxy-1-aminoindan **38**, which was prepared from *p*-methoxybenzaldehyde (Scheme 3) as follows: reaction with sulfuryl chloride gave the 3-chloro derivative,[31] which was reacted[32] with Meldrum's acid[33] (HCO_2H, Et_3N) to give 3-(3-chloro-4-methoxyphenyl)-propionic acid **34**, which after being converted to the acid chloride was cyclized to the indanone **36**. The latter was converted to the amine **37**[34] via the oxime and finally demethylated. Hydroxy aminotetralins were prepared according to previously reported procedures.[35] Compounds **39u−w** (potential metabolites of the target carbamates) were prepared (Scheme 4) by reacting hydroxy aminoindans **4(R5=H)** with propargyl bromide in *N*,*N*-dimethylacetamide (DMA) or acetonitrile with potassium carbonate as base. The *N*-Me derivatives **40** were prepared either by *N*-methylation of **39** ($NaCNBH_3$/$(CH_2O)_n$) or by propargylation of *N*-Me hydroxy aminoindans **41**. NMR data of these compounds are shown in Table 1.

Scheme 4. Preparation of **39u−w** and **40u−w**[a]



[a] (a) Propargyl bromide; (b) HCO_2Et, then LAH; (c) $NaCNBH_3$, $(CH_2O)_n$.

Intermediates and target compounds are depicted in Table 2. Full spectral (^{1}H NMR, IR, MS) and elemental data are included in the Supporting Information. ^{1}H NMR data for a few representative compounds are shown in Table 1. The *N*-Boc-protected intermediates **5** (obtained in nearly quantitative yields) and their carbamates **6** were shown to be pure by TLC and were not further characterized.

Table 1. ^{1}H NMR of Hydroxy *N*-Propargylaminoindans **39** and Selected Compounds of Series I and II

compd	δ in ppm, D_2O
39u	7.28 (d), 7.01 (d), 6.94 (dd), 4.88 (dd, 1H), 3.96 (m, 2H), 3.03 (m, 1H), 3.02 (s, 1H), 2.90 (m, 1H), 2.80 (s, 3H), 2.56 (m, 1H), 2.27 (m, 1H)
39w	7.30 (t), 7.16 (d), 6.98 (d), 4.99 (dd, 1H), 4.02 (m, 2H), 3.06 (m, 1H), 3.06 (s, 1H), 2.95 (m, 1H), 2.60 (m, 1H), 2.32 (m, 1H)
39v	7.35 (t), 6.98 (d), 6.83 (dd), 5.07 (dd, 1H), 4.01 (m, 2H), 3.16 (m, 1H), 3.01 (m, 1H), 3.0 (s, 1H), 2.57 (m, 1H), 2.30 (m, 1H)
18b[a]	7.47 (d, 1H, J = 8.3 Hz), 7.31 (d, 1H, J = 2.2 Hz), 7.20 (dd, 1H, J = 8.3, 2.2 Hz), 5.0 (dd, 1H, J = 7.7, 3.2 Hz), 4.34 (s, 1H, $CH_{tartaric}$), 4.0 (m, 2H, CH_2C≡CH), 3.56 (q, 1H, J = 7.1, NCH_2CH$_3$), 3.40 (q, 1H, J = 7.1, NCH_2CH$_3$), 3.18 (m, 1H, CH_2), 3.15 (s, 1.5H, NCH_3), 3.02 (s, 1.5H, NCH_3), 3.02 (m, 1H, CH_2), 3.07 (t, 1H, J = 2.5, C≡CH), 2.64 (m, 1H, CH_2), 2.36 (m, 1H, CH_2), 1.28 (t, 1.5H, J = 7.1 Hz, CH_3), 1.21 (t, 1.5H, J = 7.1 Hz, CH_3)
22a	7.56 (t, 1H, J = 8.1 Hz), 7.39 (d, 1H, J = 8.1 Hz), 7.12 (d, 1H, J = 8.1 Hz), 5.30 (br d, 1H, J = 8.2 Hz), 4.12 (m, 2H, CH_2C≡CH), 3.28 (m, 1H, CH_2), 3.20 (s, 1.5H, CONCH_3), 3.02 (s, 1.5H, CONCH_3), 3.08 (m, 1H, CH_2), 3.23 (t, 1H J = 2.5, C≡CH), 2.78 (s, 3H, NCH_3), 2.55 (m, 2H, CH_2)
23a	7.51 (d, 1H, J = 7.7 Hz), 7.47 (t, 1H, J = 7.7 Hz), 7.23 (d, 1H, J = 7.7 Hz), 5.07 (dd, 1H, J = 7.7, 3.2 Hz), 4.05 (m, 2H, CH_2C≡CH), 3.29 (s, 1.5H, NCH_3), 3.08 (s, 1H, CH_2), 3.07 (t, 1H, J = 2.6 Hz), 3.03 (s, 1.5H, NCH_3), 2.95 (m, 1H, CH_2), 3.23 (t, 1H J = 2.5, C≡CH), 2.65 (m, 1H, CH_2), 2.35 (m, 2H, CH_2)
53a	7.50 (dd, 1H, J = 8.7, 7.7 Hz), 7.29 (d, 1H, J = 7.7 Hz), 7.14 (m, 2H), 4.15 (d, 2H, HC≡CH_2), 4.02 (m, 1H, ArCH$_2$C(Me)H), 3.25 (dd, 1H, J = 13.5, 5.5, ArCH_2), 3.18 (m, 1H, C≡CH), 3.18 (s, 3H, CONCH$_3$), 3.02 (s, 3H, CONCH$_3$), 2.99 (s, 3H, NCH$_3$), 2.97 (m, 1H, ArCH_2)
(*R*)-**52i**	7.50 (t, 1H, J = 7.7 Hz), 7.28 (d, 1H, J = 7.7 Hz), 7.12 (m, 2H), 4.02 (m, 2H, HC≡CCH_2), 3.82 (m, 1H, ArCH$_2$C(Me)H), 3.55 (t, 1H, J = 7.7 Hz, CH$_3$CH$_2$CH$_2$$CH_2$N), 3.39 (t, 1H, J = 7.7 Hz, CH$_3$CH$_2$CH$_2$$CH_2$N), 3.18 (m, 1H, Ar$CH_2$), 3.03 (t, 1H, J = 2.5 Hz, C≡CH), 2.98 (m, 1H, ArCH_2), 1.67 (m, 2H, CH$_3$CH$_2$$CH_2CH_2$N), 1.42 (m, 2H, CH$_3$$CH_2CH_2CH_2$N), 0.99 (t, 1.5H, J = 7.0 Hz), 0.97 (t, 1.5H, J = 7.0 Hz)

[a] Isolated as hemitartrate.

The dialkyl (but not mono) carbamates exhibit a typical pattern, resulting from the presence in solution of two equilibrating rotameric species. The rotational energy barrier of the C−N bond in some representative compounds (Table 3) lie in the range of 14.6−16.6 kcal/mol[36] and are in good agreement with literature data for a series of dialkyl 3-(dimethylaminoethyl)phenyl carbamates.[37] The energy barrier ($\Delta G^{\ddagger}$) for each compound was calculated from the following approximation: $\Delta G^{\ddagger} = 19.14 \times T_{coal}(9.97 + \log T_{coal}/\delta\nu) \times 2.39 \times 10^{-4}$ kcal/mol; where: T_{coal} is the coalescence temperature in K, and $\delta\nu$ is the chemical shift difference, in hertz, between the signals of the same alkyl substituent at the syn and anti positions.

Series II. Racemic compounds were synthesized via a four-step procedure from the corresponding 3-(2-aminoethyl)phenols **42** (Scheme 5), and optical isomers were prepared either from **57** or **58** (Scheme 6). Thus, in analogy with Series I, hydroxy amines **42** were *N*-Boc-protected (Boc_2O, Et_3N, THF) and carbamoylated by carbamoyl chlorides or alkyl isocyanates. The carbamates were selectively Boc-deprotected (HCl, dioxane) and propargylated (propargyl bromide, K_2CO_3, ACN). The target compounds were finally isolated as salts. The order of propargylation and carbamoylation was reversed for **53** (compound **42**, R1 = Me, R6 = Me, was first propargylated to **55q** which was then carbamylated), thus avoiding the need for Boc protection and deprotection (Scheme 5). Also, the 1-methyl-2-propynyl analogues **54** were prepared by first propargylating 2-aminoethyl-3-phenol **42** with 3-mesyloxy-1- butyne,[21] followed by Boc protection and carbamylation. Racemic starting hydroxy amines were prepared by known procedures.[22,24,38−40]

Optical isomers of **58** were prepared from enantiomerically pure **57** which was obtained from its racemic mixture (**56**) by resolution with tartaric acid (Scheme 6). (*S*)-**57** was isolated with L-tartaric acid,[41,42] and the (*R*) isomer was prepared either by using D-tartaric acid, or by isolation from the mother liquors of the (*S*) isomer. The *N*-Me group was then introduced by reductive alkylation (HCO_2Et,[26], LAH [27]). This approach, with initial resolution of 3-(2-aminopropyl)phenol, was found to be superior to the reported asymmetric synthesis of **58**.[43,44]

Compounds **55n**−**q** (potential metabolites of the target carbamates) were prepared by reacting aminoethyl phenols **42** with propargyl bromide in DMA with potassium carbonate as base.

Intermediates and target compounds are depicted in Table 4. Full spectral (^{1}H NMR, IR, MS) and elemental data are included in the Supporting Information. ^{1}H NMR data for a few representative compounds are depicted in Table 1. The *N*-Boc-protected intermediates **43** (obtained in nearly quantitative yields) and the corresponding carbamates **44** were shown to be pure by TLC and were not further characterized.

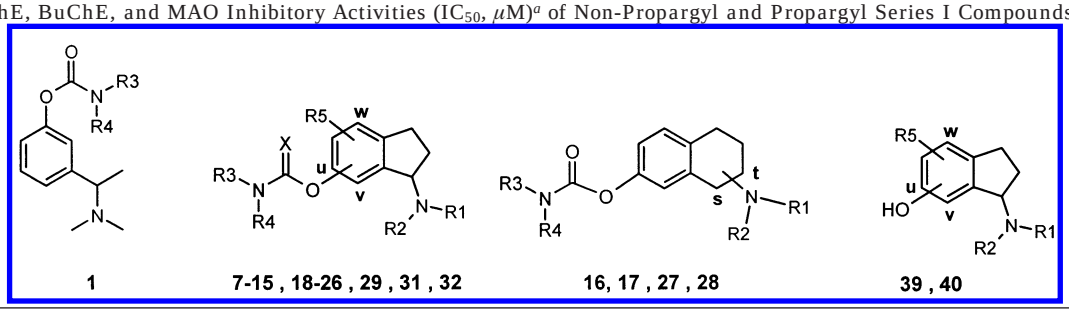
In analogy to Series I, the dialkyl carbamates exhibit a typical pattern, resulting from the presence in solution of two equilibrating rotameric species with rotational energy barriers in the range of 15.5−16.2 kcal/mol[36] (**50a**−**c**).

Results and Discussion

Compounds were tested for their in vitro inhibitory activity on purified AChE (from human erythrocytes) and MAO-A and -B (from rat brain homogenates). Selected compounds were also tested for in vitro BuChE (from horse serum) inhibitory activity. Data are summarized for series I and II in Tables 2 and 4, respectively.

Series I. AChE. Several structural elements were found to influence AChE inhibitory (AChEI) activity. One of the most important is the nature of the carbamoyl nitrogen substituents. Analysis of the results of subgroups of Me,R disubstituted carbamates in the 6-substituted series reveals that the aryl,Me carbamates **18f** and **18m** are the most, and the Et,Me **18b** the least, potent (Ar > Me > Bu ≃ Pr > Et). A similar order of potency of Me > Pr > Et was also found for the 4- and 7-substituted carbamates. An analogous relationship between chemical structure and AChEI activity in a series of mono- and dialkyl 3-(1-dimethylamino ethyl)-phenyl carbamates has previously been reported by

Table 2. AChE, BuChE, and MAO Inhibitory Activities (IC_{50}, μM)[a] of Non-Propargyl and Propargyl Series I Compounds



compd	mp (solvent)[b]	R1	R2[c]	R3	R4	R5	X	O-pos	N-pos	AChE	BuChE	AChE/BuChE	MAO-A	MAO-B
1a		–	–	Me	Me					0.03				
1b		–	–	Me	Et					0.92 (0.74−1.2)	0.83 (0.81−0.86)	1.1		
7a	156−8 (A)	H	H	Me	Me	H	O	u		0.76 (0.45−1.8)	0.63 (0.34−1.03)	1.2	80 (30−230)	>1000
7b	150−2 (A)	H	H	Me	Et	H	O	u		19.0 (8.99−49.4)	1.9 (0.76−4.2)	10.0	12.9 (9.4−17.7)	>1000
(*R*)-7b	197−8 (A)	H	H	Me	Et	H	O	u		6.14 (3.18−17.9)	1.96 (1.63−2.45)		5.6 (4.3−7.3)	>1000
7c	165−7 (A)	H	H	Me	n-Pr	H	O	u		7.3 (5.5−10.2)			32	>1000
7d	111−12 (B)	H	H	Me	*n*-hexyl	H	O	u		0.53 (0.49−0.58)				
7e	207−8 (A)	H	H	Me	cyclohexyl	H	O	u		3.96 (2.85−6.01)				
7f	225−7 (D)	H	H	Me	*p*-MeOPh	H	O	u		0.30 (0.28−0.32)	9.91 (7.65−13.2)	0.03		
7g	191−2 (C)	H	H	H	Et	H	O	u		17.7 (7.33−61.5)				
7h	171−3 (C)	H	H	H	n-Pr	H	O	u		1.48 (1.27−1.80)				
8a	178−80 (A)	H	Me	Me	Me	H	O	u		1.07 (0.99−1.20)	0.95 (0.85−1.96)	1	50 (32−82)	>1000
8b	172−4 (A)	H	Me	Me	Et	H	O	u		38.6 (28.1−58.3)			22 (9−55)	>1000
9a	172−4 (A)	H	Et	Me	Me	H	O	u		24.5 (14.8−44.9)			500 (290−920)	>1000
10a	190−2 (A)	H	n-Pr	Me	Et	H	O	u		3.6 (2.5−5.8)				
11a	156−60 (A)	H	H	Me	Me	H	O	v		0.46 (0.44−0.49)				
11b	185−7 (A)	H	H	Me	Et	H	O	v		10.5 (6.02−21.4)				>1000
11c	153−5 (A)	H	H	Me	n-Pr	H	O	v					1000	>1000
12a	169−71 (B)	H	Me	Me	Me	H	O	v		0.51 (0.50−0.53)				
13a	198−200 (A)	H	H	Me	Me	H	O	w		0.009 (0.008−0.012)	0.014 (0.009−0.024)	0.64	9.8 (7.6−12.5)	>1000
13b	183−5 (A)	H	H	Me	Et	H	O	w		0.026 (0.025−0.027)	0.054 (0.038−0.064)	0.48	7.9 (5.6−11.1)	>1000
16a	196−8 (A)	H	H	Me	Me	H	O	u	s	1.48 (1.27−1.86)				
16b	166−8 (A)	H	H	Me	Et	H	O	u	s	6.22 (3.87−11.9)	5.41 (3.19−4.99)	1.15	1000	
17a	d	H	H	Me	Me	H	O	u	t	3.24 (2.35−4.98)				
17b	d	H	H	Me	Et	H	O	u	t	79.6 (33.4−148)				
18a	180−2 (F)	H	Pg	Me	Me	H	O	u		2.9 (1.64−7.91)	2.07 (1.78−2.48)	1.40	750 (560−1000)	530 (200−1400)
(*R*)-**18a**	139−41 (A)	H	Pg	Me	Me	H	O	u		1.8 (1.57−2.08)				
(*S*)-**18a**	138−40 (A)	H	Pg	Me	Me	H	O	u		2.25 (1.67−3.57)				
18b	194−6 (F)	H	Pg	Me	Et	H	O	u		47.0 (11.9−128)	1.5 (0.8−3.2)	31.3	250 (190−310)	>1000
(*R*)-**18b**	159−60 (A)	H	Pg	Me	Et	H	O	u		31.8 (11.5−133)	1.98 (1.54−2.83)	16.1	300 (220−410)	>1000
(*S*)-**18b**	160−2 (A)	H	Pg	Me	Et	H	O	u		34.9 (13.6−128)	2.2 (1.6−3.6)	15.9	550 (460−1400)	>1000
18c	183−5 (F)	H	Pg	Me	n-Pr	H	O	u		14.6 (6.4−45.9)	14.8 (6.3−52.4)	1	240 (170−340)	410 (360−470)
(*R*)-**18c**	126−8 (A)	H	Pg	Me	n-Pr	H	O	u		10.8 (5.24−30.8)	14.9 (6.8−31.2)	0.72		

Table 2 (Continued)

compd	mp (solvent)[b]	R1	R2[c]	R3	R4	R5	X	O-pos	N-pos	AChE	BuChE	AChE/BuChE	MAO-A	MAO-B
(*S*)-**18c**	135−7 (A)	H	Pg	Me	n-Pr	H	O	u		8.5 (2.0−15.2)	12.4 (4.8−73.9)	0.7		
18d	106−8 (F)	H	Pg	Me	*n*-hexyl	H	O	u		15.7 (7.81−39.2)	7.50 (5.02−12.2)	2.1	>1000	>1000
18e	174−5 (A)	H	Pg	Me	cyclohexyl	H	O	u		41.2 (13.6−198)	5.56 (2.77−15.4)	7.4	170 (94−340)	10 (9−20)
18f	172−4 (A)	H	Pg	Me	*p*-MeOPh	H	O	u		0.86 (0.76−1.05)	6.4 (4.9−11.2)	0.13	700 (540−850)	500 (260−1100)
18g	175−7 (F)	H	Pg	H	Et	H	O	u		13.7 (4.50−28.6)				
18h	165−7 (F)	H	Pg	H	n-Pr	H	O	u		2.38 (1.85−3.26)			69 (47−101)	25 (14−43)
(*S*)-**18h**	124−6 (E)	H	Pg	Me	n-Pr	H	O	u					>1000	>1000
18i	168−70 (A)	H	Pg	Me	n-Bu	H	O	u		11.3 (5.96−26.7)	53.7 (29.6−110)	0.2		
(*R*)-**18i**	86−8 (A)	H	Pg	Me	n-Bu	H	O	u		11.6 (7.5−19.5)			220 (150−320)	150 (30−230)
(*S*)-**18i**	88−9 (A)	H	Pg	Me	n-Bu	H	O	u		9.3 (4.6−25.8)				
18j	148−50 (A)	H	Pg	Et	n-Bu	H	O	u		72.4 (31.2−202)	3.03 (1.19−6.10)	23.9		
18k	178−80 (A)	H	Pg	Et	cyclohexyl	H	O	u		17.9 (6.9−40.6)				
18l	188−90 (A)	H	Pg	Me	Bn	H	O	u		1.78 (1.28−3.30)	1.26 (0.99−1.91)	1.4	40 (21−77)	120 (60−240)
18m	182−4 (A)	H	Pg	Me	Ph	H	O	u		0.55 (0.54−0.56)	16.6 (8.68−38.6)	0.03	80 (55−108)	100 (70−140)
19a	199−201 (F)	Me	Pg	Me	Me	H	O	u		12.9 (5.5−45.9)			36 (29−44)	47 (6−350)
19b	196−8 (A)	Me	Pg	Me	Et	H	O	u		>1300				
(*R*)-**19b**	78−80 (A)	Me	Pg	Me	Et	H	O	u		1200	0.55 (0.21−1.26)	2182	4 (2−8)	12 (5−28)
19c	119−21 (A)	Me	Pg	Me	n-Pr	H	O	u		≫1000			5.6 (3.7−8.5)	9.2 (4.4−19)
20a	212−3 (F)	Et	Pg	Me	Me	H	O	u		17.9 (8.6−46.9)			>1000	>1000
21a	219−20 (F)	H	Pg	Me	Me	H	O	v		2.5 (1.7−6.4)	2.8 (2.1−4.1)	0.9	>1000	>1000
21b	208−9 (F)	H	Pg	Me	Et	H	O	v		525 (224−1012)	0.31 (0.25−0.40)	1693	>1000	>1000
21c	185−6 (F)	H	Pg	Me	n-Pr	H	O	v		45.8 (33.2−96.7)				
22a	169−71 (F)	Me	Pg	Me	Me	H	O	v		7.0 (3.6−18.5)			330 (260−420)	730 (590−900)
22b	148−50 (H)	Me	Pg	Me	Et	H	O	v		439 (252−806)	20 (10.7−43.7)	22.0	65 (49−86)	100 (40−280)
22c	65−7 (A)	Me	Pg	Me	n-Pr	H	O	v		≫1000			71 (57−89)	63 (40−100)
23a	196−8 (A)	H	Pg	Me	Me	H	O	w		0.053 (0.045−0.057)			0.26 (0.22−0.29)	86 (80−92)
23b	183−5 (A)	H	Pg	Me	Et	H	O	w		2.15 (1.89−2.50)	0.019 (0.016−0.021)	113	0.83 (0.72−0.97)	150 (90−260)
24b	161−3 (A)	H	Pg	Me	Et	5-Cl	O	u		25.5 (11.3−56.8)				
24c	164−6 (A)	H	Pg	Me	n-Pr	5-Cl	O	u		43.9 (42.5−45.9)			375 (315−465)	32 (18−59)
25a	152−4 (A)	H	Pg	Me	Me	H	S	u		>500			130 (75−240)	98 (77−123)
25b	193−5 (A)	H	Pg	Me	Et	H	S	u		>500				
26a	195−7 (F)	H	1-MePg	Me	Me	H	O	u		1.80 (1.52−2.21)	2.34 (1.44−5.39)	0.77	>1000	>1000
27a	207−9 (A)	H	Pg	Me	Me	H	O	u	s	3.94 (3.18−5.07)			560 (460−680)	>1000
27b	201−3 (A)	H	Pg	Me	Et	H	O	u	s	52.4 (29.3−103)			85 (57−125)	120 (70−2100
28a	206−8 (G)	H	Pg	Me	Me	H	O	u	t	4.1 (2.2−10.1)	0.77 (0.71−0.86)	5.5	2 (1.8−2.4)	1000
28b	208−9 (F)	H	Pg	Me	Et	H	O	u	t	204 (26.2−5898)	0.29 (0.28−0.30)	703	2 (1.8−2.75)	120 (75−200)
29b	72−4 (A)	Me	Pg	Me	Et	H	O	w		14.9 (12.0−19.1)	0.79 (0.70−0.92)	18.9	0.027 (0.022−0.035)	4 (3.0−5.3)
31a	164−6 (A)	Me	Me	Me	Me	H	O	u		2.15 (1.66−3.14)			1000	>1000
32a	134−5 (A)	Me	Me	Me	Me	H	O	w		0.013 (0.012−0.014)			10 (5.6−19.6)	>1000

Table 2 (Continued)

compd	mp (solvent)[b]	R1	R2[c]	R3	R4	R5	X	O-pos	N-pos	AChE	BuChE	AChE/BuChE	MAO-A	MAO-B
39u	172−4 (F)	H	Pg	−	−	H	−	u					0.67 (0.47−0.93)	0.6 (0.4−0.8)
(*R*)-**39u**	174−6 (A)	H	Pg	−	−	H	−	u					0.3 (0.28−0.34)	0.23)0.1−0.5)
(*S*)-**39u**	175−7 (D)	H	Pg	−	−	H	−	u					440 (370−520)	300 (120−570)
39v	166−8 (A)	H	Pg	−	−	H	−	v					1.3 (1.0−1.8)	2.1 (1.6−2.9)
39w	196−8 (A)	H	Pg	−	−	H	−	w					0.9 (0.5−1.6)	0.9 (0.7−1.3)
40u	210−11 (F)	Me	Pg	−	−	H	−	u					0.015 (0.014−0.016)	0.03 (0.02−0.06)
(*R*)-**40u**	71−2 (A)	Me	Pg	−	−	H	−	u					0.007 (0.005−0.010)	0.02 (0.019−0.021)
(*S*)-**40u**	82−4 (A)	Me	Pg	−	−	H	−	u					12 (6−23)	23 (22−24)
40v	83−5 (A)	Me	Pg	−	−	H	−	v					0.07 (0.05−0.010)	0.05 (0.04−0.07)
40w	160−2 (A)	Me	Pg	−	−	H	−	w					0.008 (0.005−0.012)	0.07 (0.06−0.09)

[a] Numbers in parentheses represent 95% confidence interval. Blank box where IC_{50} was not determined. [b] A, Et_2O; B, dioxane; C, MeOH/EtOAc; D, ^{i}PrOH; E, dioxane/Et_2O; F, ^{i}PrOH/Et_2O; G, MeOH/Et_2O; H, MeOH; I, EtOAc, Et_2O; J, EtOAc. [c] Pg = propargyl, 1-MePg = 1-methylprop-2-ynyl. [d] Not determined.

Table 3. C−N Rotational Energy Barrier Data (^{1}H NMR) of Selected Series I Propargyl Carbamates[a]

compd	coal. peak (*)	$\delta\nu$ (Hz), RT	$T_{coal.}$ (°C)	solvent	$\Delta G^{\ddagger}$, kcal/mol
18a	CH_3(*)	71.4	67−68	buffer	16.56
	CH_3(*)	72.0	69	D_2O	16.66
18b	CH_3(*)	67.9	56	buffer	16.04
	CH_2(*)CH_3	75.5	56	buffer	15.97
	CH_2(*)CH_3	76.0	60	D_2O	16.16
18c	CH_3(*)	68.4	65	buffer	16.49
	CH_3(*)	68.4	65	D_2O	16.49
	CH_2(*)CH_2CH_3	79.6	65	buffer	16.39
	CH_2(*)CH_2CH_3	79.4	65	D_2O	16.39
18e	CH_3(*)	63.2	50	D_2O	15.78
18m	CH_3(*)	71.7	30	D_2O/buffer	14.69
18k	CH_2(*)CH_3	55.9	43	D_2O	15.50

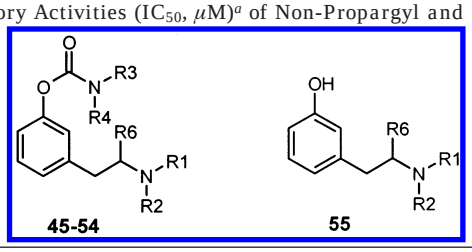
[a] Measurements were performed on Varian 500 Inova. Coalescence temperature is ±1°C.

Weinstock et al.[37,45] The authors showed a close correlation between the amount of energy needed to overcome the restriction of rotation about the amide bond ($\Delta G^{\ddagger}$) and the affinity of the inhibitor for the enzyme. However, additional examples in Series I, such as the Et,cyclohexyl analogue **18k**, which has a $\Delta G^{\ddagger}$ value lower than that of **18b** (Table 3), but about three times the potency of the latter (IC_{50} 17.9 vs 47 μM), suggests that there may be other explanations for the reduction in potency induced by the ethyl substituent. Furthermore, the most potent compound of the propargylated 6-carbamates of Series I, the Me,Ph derivative **18m**, exhibits the lowest $\Delta G^{\ddagger}$ value of all the compounds for which T_c was determined. The high potency of the aryl carbamates **18f** and **18m** may be explained by the $\pi-\pi$ interaction with phenylalanines 288 and 290 located at the bottom of the gorge, adjacent to the active site.[46] The anomalous "ethyl" effect was also observed by Lieske and co-workers[47] who found the diethyl carbamoyl derivative to be the least active in a series of 5-(1,3,3-trimethylindolinyl) carbamates, ~7400 less potent (k_i) than the dimethylcarbamoyl analogue. The two monosubstituted carbamates tested for AChE inhibitory activity (**18g** and **18h**) are more potent than the corresponding methyl disubstituted analogues. Here, too, the propyl is more potent than the ethyl carbamate, as previously reported for other carbamates by Weinstock et al.[45]

The steric influence of the size of the alkyl substituent on inhibitory potency against BuChE is quite different. In this enzyme, the two phenylalanines at the active site of AChE have been replaced by leucine and valine. These amino acid substitutions enlarge the size of the active site on BuChE relative to that of AChE, resulting in a different order of potency among the alkyl substituents: Me = Et > Bu > Pr = Ar for the inhibition of this enzyme by Series I compounds. The different inhibitory potencies of these compounds against AChE and BuChE may also result from variations in other amino acids, such as tryptophan, at the entrance to the gorge of AChE, which is replaced by alanine in BuChE.[46] Thus, the Et,Me carbamates were found to show the highest selectivity for BuChE inhibition and the Me,Ph were the most selective for AChE. Since AChE is lost in the brains of subjects with AD as the cholinergic neurons degenerate,[48] but BuChE, which is found in glial cells remains unchanged, or is even increased,[49] drugs that also block BuChE could increase acetylcholine levels more effectively than AChE-selective inhibitors and help to maintain ACh levels for interaction with its receptors.

Substituting sulfur for oxygen (thiocarbamates) results in a decrease of AChEI activity (**25a** vs **18a**). We also studied the effect of *N*-indanylamine substitution on AChEI activity. The *N*-propargyl-6-carbamoyl aminoindans (**18a**,**b**,**c**) are 2−5 times less potent in AChEI than the parent primary amines (**7a**,**b**,**c**). For the 4- and 7-substituted carbamoyl aminoindans, N-propargylation results in 5−7-fold loss of potency for the Me,Me carbamates (**21a** and **23a**) and 50−83-fold loss of potency for the Et,Me carbamates (**21b** and **23b**) in comparison to the parent primary amines (**11a**, **13a** and **11b**,**13b**, respectively). The effect of other N-alkylations on AChEI activity is less clear-cut. In the 6- and 7-carbamoyl series, *N*-methyl substitution at the prop-

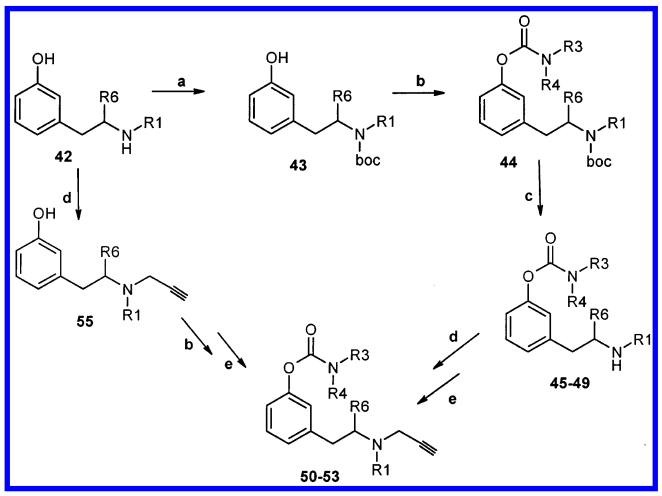
Table 4. AChE, BuChE, and MAO Inhibitory Activities (IC_{50}, μM)[a] of Non-Propargyl and Propargyl Series II Compounds



compd	mp (solvent)[b]	R1	R2[c]	R3	R4	R6	AChE	BuChE	AChE/BuChE	MAO-A	MAO−B
45a	125−7 (A)	H	H	Me	Me	H	0.23 (0.18−0.44)			95 (60−150)	>1000
45b	103−5 (A)	H	H	Me	Et	H	35.5 (22.2−56.8)			180 (100−310)	>1000
45c	83−5 (A)	H	H	Me	n-Pr	H	7.8 (4.7−15.6)			240 (110−520)	>1000
46a	126−8 (A)	H	Me	Me	Me	H	0.28 (0.12−0.41)			22 (9−52)	>1000
46b	*d*	H	Me	Me	Et	H	20.7 (12.7−36.8)			20 (11−38)	>1000
48a	127−9 (F)	Me	Me	Me	Me	H	0.16 (0.12−0.32)			51 (43−61)	>1000
50a	138−9 (F)	H	Pg	Me	Me	H	0.22 (0.18−0.32)	0.21 (0.16−0.41)	1.05	2.7 (1.3−5.6)	24 (11−52)
50b	113−15 (F)	H	Pg	Me	Et	H	30.2 (9.46−68.1)	0.54 (0.22−1.54)	55.9	2.6 (1.7−3.9)	7.8 (5.8−10.5)
50c	108−10 (F)	H	Pg	Me	n-Pr	H	15.4 (6.0−41.2)	1.9 (1.6−2.4)	8.1	1.8 (1.5−2.2)	0.29 (0.19−0.44)
51a	150−2 (F)	Me	Pg	Me	Me	H	0.85 (0.79−0.93)			0.3 (0.1−0.9)	2.8 (1.5−5.2)
51b	152−4 (F)	Me	Pg	Me	Et	H	16.6 (7.3−50.4)			0.8 (0.5−1.4)	0.8 (0.4−1.3)
52a	166−70 (A)	H	Pg	Me	Me	Me	0.54 (0.32−0.98)	1.09 (1.00−1.20)	0.50	6.9 (6.3−7.7)	5.7 (4.8−6.9)
52b	119−121 (A)	H	Pg	Me	Et	Me	33.9 (12.6−74.0)	0.93 (0.90−0.95)	36.5	2.1 (1.8−2.5)	12.8 (9.5−17.2)
52c	170−2 (A)	H	Pg	Me	n-Pr	Me	19.1 (13.6−27.3)	2.07 (1.19−8.56)	9.2	14.6 (12.1−17.6)	0.17 (0.08−0.38)
52e	100−2 (A)	H	Pg	Me	cyclohexyl	Me	3.6 (2.2−6.9)			18 (14−24)	0.23 (0.18−0.30)
52i	87−9 (A)	H	Pg	Me	n-Bu	Me	12.2 (5.4−38.2)	2.75 (1.89−4.67)	4.4	15 (13−17)	0.4 (0.2−0.8)
53a	158−160 (F)	Me	Pg	Me	Me	Me	1.64 (1.32−2.23)	0.75 (0.73−0.77)	2.2	0.12 (0.09−0.16)	0.8 (0.3−1.2)
53b	144−6 (F)	Me	Pg	Me	Et	Me	234 (91.8−732)	1.5 (1.38−1.65)	153	0.12 (0.09−0.16)	0.1 (0.07−0.59)
53c	d	Me	Pg	Me	n-Pr	Me	33.1 (9.8−157)	22.8 (13.7−27.8)	1.45		
53d	95−7 (A)	Me	Pg	Me	n-hexyl	Me	3.06 (2.36−4.22)	0.72 (0.64−0.89)	4.25	20 (8−43)	1.5 (0.8−2.9)
(*R*)-**53d**	92−4 (I)	Me	Pg	Me	n-hexyl	Me	2.0 (1.7−2.5)				
(*S*)-**53d**	95−6 (J)	Me	Pg	Me	n-hexyl	Me	3.4 (2.2−6.4)				
53e	105−7 (A)	Me	Pg	Me	cyclohexyl	Me	8.67 (3.69−33.1)	0.67 (0.45−1.08)	12.9	1.7 (0.8−3.7)	0.24 (0.11−0.57)
(*R*)-**53e**	118−9 (I)	Me	Pg	Me	cyclohexyl	Me	7.9 (5.6−11.9)			0.9 (0.8−1.0)	0.22 (0.19−0.26)
(*S*)-**53e**	119−20 (I)	Me	Pg	Me	cyclohexyl	Me	6.3 (2.8−27.5)			1.1 (0.8−1.5)	0.28 (0.23−0.34)
54a	151−3 (F)	H	1-MePg	Me	Me	H	0.17 (0.16−0.18)	0.24 (0.23−0.26)	0.7	440 (230−820)	> 1000
54b	135−7 (F)	H	1-MePg	Me	Et	H	13.9 (7.99−27.5)	0.24 (0.20−0.36)	57.9		
55n	140−2 (F)	H	Pg	−	−	H				67 (14−340)	107 (22−530)
55o	111−2 (F)	Me	Pg	−	−	H				1.3 (0.5−3.7)	6.4 (3.6−11.3)
55p	111−3 (A)	H	Pg	−	−	Me				830 (600−1100)	230 (150−360)
55q	88−90 (A)	Me	Pg	−	−	Me				8.9 (4.7−16.8)	4.8 (2.8−8.3)

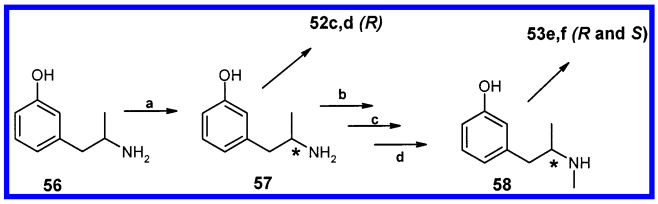
[a] Numbers in parentheses represent 95% confidence interval. Blank box where IC_{50} was not determined. [b] A, Et_2O; B, dioxane; C, MeOH/EtOAc; D, ^{i}PrOH; E, dioxane/Et_2O; F, ^{i}PrOH/Et_2O; G, MeOH/Et_2O; H, MeOH; I, EtOAc, Et_2O; J, EtOAc. [c] Pg = propargyl, 1-MePg = 1-methylprop-2-ynyl. [d] Not determined.

Scheme 5[a]



[a] (a) $(Boc)_2O$, Et_3N, THF, rt; (b) R_3R_4NCOCl, CH_3CN,NaH, rt; (c) HCl, dioxane, rt; (d) propargyl bromide, K_2CO_3, CH_3CN or DMA, rt; (e) HCl/Et_2O, rt.

Scheme 6[a]



[a] (a) (1) L-Tartaric acid, MeOH, reflux. (2) 25 % NH_4OH, rt; (b) HCO_2Et, reflux; (c) LAH, THF, 5 °C, then rt; (d) HCl, Et_2O, rt.

argylamine nitrogen virtually eliminates the AChEI activity (IC_{50} > 1000 μM) of the Et,Me and Me,Pr analogues (**19b**, **19c**, **22c**). The effect is considerably smaller in the 4-series, where **29b** is only ~7-fold less potent than **23b**. Similarly, among the Me,Me carbamates, the *N*-methyl propargylamines (**19a**, **22a**) have activities slightly lower (3−4-fold) than those of the corresponding secondary propargylamines (**18a**, **21a**).

By contrast, N-methylation increases both BuChEI activity and selectivity of the 6-carbamates, while having the opposite effect on the 4- and 7-analogues.

The chirality of the indanylamine does not affect AChEI, in analogy with the lack of enantioselectivity reported for a series of hexahydrochromeno[4,3-*b*]pyrrole carbamates.[50]

The Me,Me carbamates of the 1-aminotetralin (**27a**) and 2-aminotetralin (**28a**) analogues, as well as the Et,Me derivative of 1-aminotetralin (**27b**), are comparable to the corresponding 1-aminoindan derivatives (**18a**,**b**) in AChEI activity. However, the 2-aminotetralin Et,Me carbamate **28b** is about 4 times less active than **18b**.

Aminoindans **31a** and **32a** may be considered as conformationally constrained analogues of **1a**, the dimethyl analogue of rivastigmine. The comparable AChEI activities of **32a** and **1a** suggest that the bioactive conformation of (the flexible) **1a** is similar to that of **32a**. While in both aminoindans the carbamate moiety is oriented "meta" to the "aminobenzyl" group, the two structures differ significantly. Thus, assuming that the amine orients the carbamate in the active site, there seems to be some steric interference with the ring methylenes of **31a** that prevents it from aligning itself to the active site.[51] Compound **13a** (the primary amine analogue of **32a**) is the most active non-propargyl carbamate of both series, with an IC_{50} of 9 nM.

Such an analysis may also explain the observed influence of the position of the ring substitution of the carbamate moiety on AChE inhibitory activity of the propargylamines, with potency decreasing as a function of its position from 4 > 6 > 7. In fact, the 4-carbamate **23a** is the most potent AChE inhibitor of all the propargyl carbamates of both series, with an IC_{50} of 53 nM. A similar SAR was reported by Bolognesi et al. for a series of carbamate regioisomers.[50] The influence of the position of the carbamate on AChEI activity in Series I seems to be due to the overall shape of the molecule and the effect this has on its fit in the active pocket (Figure 1). The lower potencies of the *N*-methyl propargylamines may also relate to this steric interference in the active site and reflect subtle differences in the binding orientation of the Me,Me carbamates in comparison to that of the Et,Me analogues.

MAO. We also addressed the SAR implications of our results for MAO inhibition and A/B selectivity. Introduction of a hydroxy group in any position on the parent propargylaminoindan nucleus results in a decrease of 1−2 orders of magnitude in MAO-B inhibitory activity, thereby causing a loss of A/B selectivity. The addition of the carbamate moiety (which is essential for AChE inhibition) in the case of the 6- and 7-hydroxy propargylaminoindans **39u** and **39v**, respectively, results in a further 100−1000-fold decrease of MAO-A and -B inhibitory potency in **18a**,**b**,**c** and **21a**,**b**. By contrast, carbamylation of 4-hydroxy-*N*-propargyl-1-aminoindan **39w** results in only a 70-fold decrease in MAO-B and a 4-fold *increase* in MAO A inhibitory potency, making **23a** and **23b** MAO-A selective inhibitors (virtually the only substituted propargylaminoindans (PAI's) with appreciable A/B selectivity, Tables 2 and 5).

The nature of the *N*-carbamoyl substituents had some effect on MAOI potency and selectivity. In the 6-substituted series (compounds **18**), which was more extensively studied, the more bulky substituents tend to increase inhibitory potency for both MAO-A and -B (cf for example **18e**,**l**,**m**).

As shown for AChE, the position of the carbamate has a profound effect on MAO inhibitory activity. The order of potency is the same as for AChEI, and decreases as a function of position from 4 > 6 > 7. Thus, in this series, only the 4-substituted carbamates have significant (<1 μM) MAOI potency in vitro. This structure−activity relationship may be useful in gaining some insight into the putative active site of MAO (vide infra).

We also modified the orientation of the two pharmacophores by preparing aminotetralins. The dimethylcarbamoyl derivative of 1-propargylaminotetralin (**27a**) shares low MAO-A and -B inhibitory potency with the analogous indan derivative **18a**, while the Et,Me analogue **27b** is comparatively more active than **18b**. However, the 2-aminotetralin derivatives **28a** and **28b** have remarkably high MAO-A inhibitory activity as compared to **18a** and **18b**. In fact, they approach the 4-carbamoyl propargylaminoindans (compounds **23**) in MAOI potency. Compounds **28** and **23** may be considered rigid conformers of the phenethylamines **52** (Table

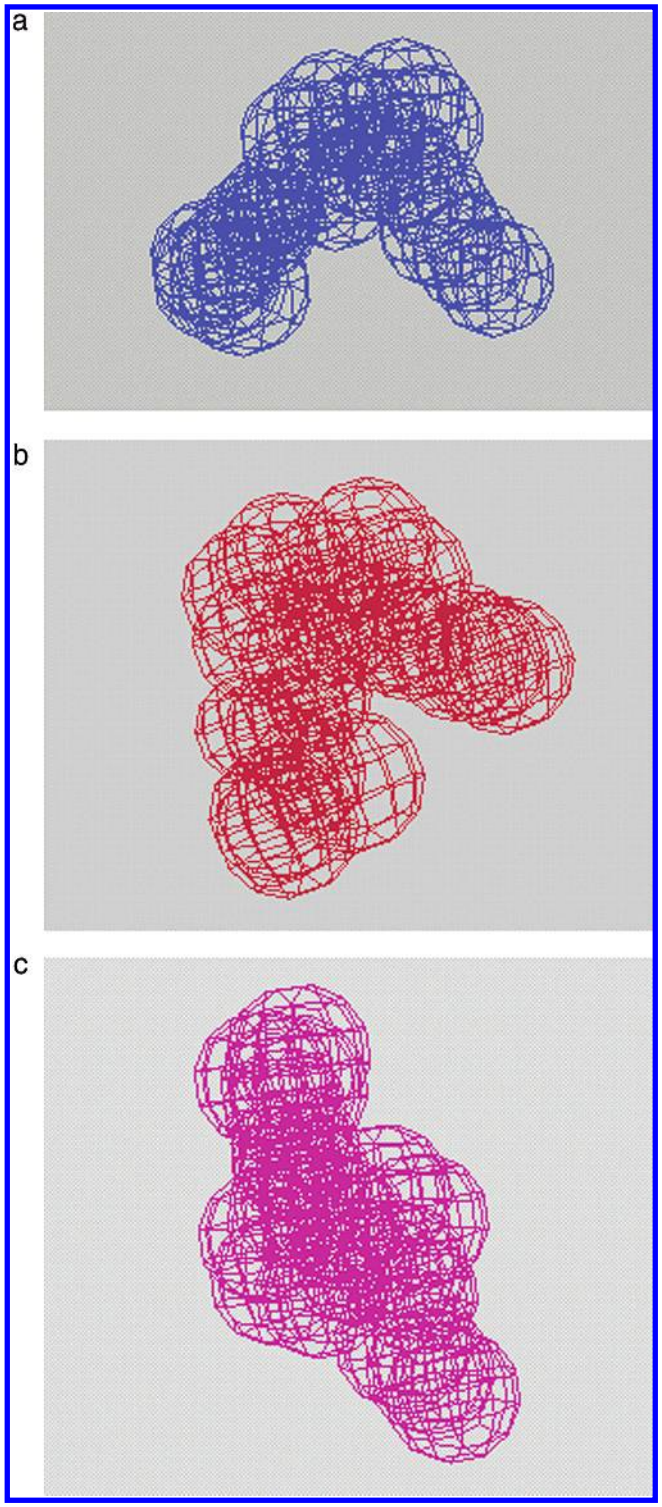


Figure 1. Overall shape of minimum energy conformations of representative propargyl carbamates (Series I). (a) Blue, **18b**; (b) red, **21b**; (c) magenta, **23b**.

4) and are superimposable using *Catalyst* molecular modeling software (Molecular Simulations Inc., San Diego, CA). Compounds **27** have a higher *displacement RMS* value and thus are less superimposable than the others (Figure 2). However, compounds **28** behave in analogy with other compounds in Series I with relatively low potency for MAO-B inhibition, thus having more A-selectivity in comparison to the nonselective 2-propargylaminotetralin (with IC_{50}'s for A and B inhibition of of 0.05 and 0.04 μM, respectively[52]).

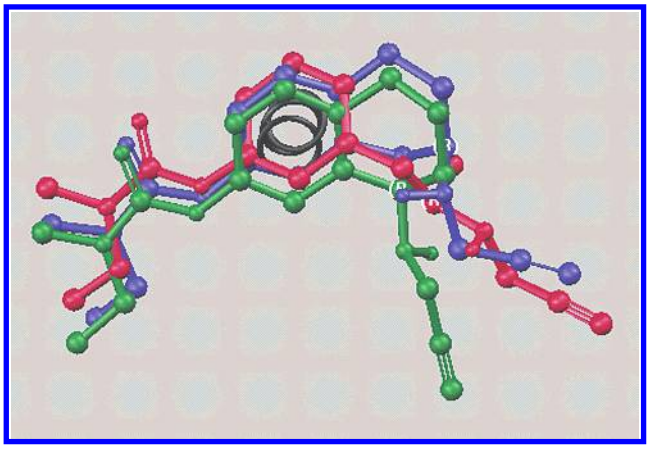


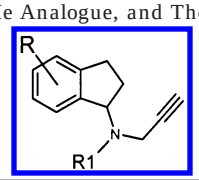
Figure 2. Superposition of 1- and 2-aminotetralin derivatives on **52b**. Red, **52b**; blue, **28b**; green, **27b**.

N-Methyl substitution at the propargylamine of propargylamino hydroxy and carbamate derivatives results in an increase in MAOI (both A and B) activity of all positional isomers (4-, 6-, and 7-), so that they are also not A/B selective (Table 5). In contrast, N-methylation of R-PAI itself (rasagiline)[53] resulted in a slight *decrease* in MAO-B inhibitory activity. Thus, MPAI is a potent MAOI with some A selectivity in comparison to rasagiline, which is a potent B-selective MAOI. The potency of *S*-PAI as an inhibitor of *both* A and B was significantly increased by N-methylation. The effect of the *N*-Me group on MAOI activity may be the net outcome resulting from several parameters, such as hydrophobicity, steric volume, hydrogen bonding, all of which may have a significant bearing on binding to the enzyme:[54]

- The propargylamine nitrogen may act either as an hydrogen bonding (HB) donor or acceptor, and both these features are incorporated in the putative pharmacophore modeled (vide infra). However, the consistently higher potency of all the *N*-Me analogues may imply that the HB *donating effect* of the nitrogen is not crucial for binding, since in this case it can only act as an HB *acceptor*.
- The steric constraint imposed by the Me group may stabilize a specific conformation which binds better to the enzyme.
- There may be favorable hydrophobic interactions between the Me group and a specific lipophilic feature in the binding pocket.

The A/B selectivities of PAI and its *N*-Me derivative (both racemic and *R*) have been investigated by several groups. Kalir, Sabbagh, and Youdim[55] found that racemic PAI (AGN-1135) is more B-selective than its *N*-methyl analogue (AGN-1133). Riederer et al.[56] explained the different selectivities of AGN-1135 and 1133 toward the two MAO isoforms (1135: B-selective, 1133: nonselective) by the steric hindrance conferred by the methyl group in the active site on MAO-B. However, the lack of selectivity actually results from the increased potency of the *N*-Me compound toward MAO-A (the reduced B activity is secondary). In fact, rasagiline ((*R*)-AGN-1135) may be the only PAI with an *N*-Me derivative, which is less potent as a MAO-B inhibitor. We have now shown with great consistency, that *N*-Me derivatives of all ring substituted PAI's are *more* potent

Table 5. MAO Inhibitory Activity of Rasagiline, Its *N*-Me Analogue, and Their Hydroxy and Carbamyloxy Congeners



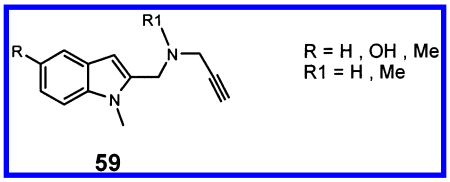
				IC_{50} (μM)[a]			NH/NMe[b]	
R	compd/ stereochem	subst posit	R1	A	B	A/B	A	B
	rasagiline		H	0.41 (0.28−0.54)	0.0044 (0.0035−0.053)	93	136	0.44
H	*R*-MPAI		Me	0.003	0.01	0.3		
	S-PAI		H	22	17	1.3	314	340
	S-MPAI		Me	0.07	0.05	1.4		
	39u	6	H	0.67 (0.47−0.93)	0.6 (0.4−0.8)	1.1	45	20
	40u	6	Me	0.015 (0.014−0.016)	0.03 (0.02−0.06)	0.5		
	(*R*)-**39u**	6	H	0.3 (0.28−0.34)	0.23)0.1−0.5)	1.3	43	11.5
	(*R*)-**40u**	6	Me	0.007 (0.005−0.010)	0.02 (0.019−0.021)	0.35		
OH	(*S*)-**39u**	6	H	440 (370−520)	300 (120−570)	1.47	37	13
	(*S*)-**40u**	6	Me	12 (6−23)	23 (22−24)	0.52		
	39v	7	H	1.3 (1.0−1.8)	2.1 (1.6−2.9)	0.62	19	42
	40v	7	Me	0.07 (0.05−0.010)	0.05 (0.04−0.07)	1.4		
	39w	4	H	0.9 (0.5−1.6)	0.9 (0.7−1.3)	1.0	113	13
	40w	4	Me	0.008 (0.005−0.012)	0.07 (0.06−0.09)	0.11		
	(*R*)-**18b**	6	H	300 (220−410)	>1000	0.3	75	83
	(*R*)-**19b**	6	Me	4 (2−8)	12 (5−28)	0.33		
	18c	6	H	240 (170−340)	410 (360−470)	0.59	43	45
-OCON(Me)R_4[c]	**19c**	6	Me	5.6 (3.7−8.5)	9.2 (4.4−19)	0.61		
	21b	7	H	>1000	>1000	∼1	>15	>10
	22b	7	Me	65 (49−86)	100 (40−280)	0.65		
	23b	4	H	0.83 (0.72−0.97)	150 (90−260)	0.005	31	38
	29b	4	Me	0.027 (0.022−0.035)	4 (3.0−5.3)	0.007		

[a] Numbers in parentheses represent 95% confidence interval. [b] Ratio between IC_{50}'s of unsubstituted and *N*-Me substituted propargylamines. [c] **b**, R_4= Et; **c**, R_4= n-Pr.

inhibitors of both MAO-A and -B than the parent secondary PAI's.

These observations are more consistent with those of Polymeropoulos,[57] who explained the greater MAO-B inhibitory potency of (*R*)-*N*-Me PAI relative to (*R*)-PAI (he does not address the question of selectivity), by the higher lipophilicity of the tertiary amine allowing better binding to the lipophilic pocket of MAO-B and offering more effective orientation to the flavin complex

However, the uncertainty of extrapolating such data is apparent from results recently reported by Moron et al.[58] for MAO inhibition of a series of substituted propargylaminoindoles (**59**). In these, the effect of



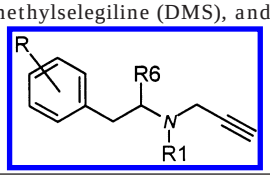
N-methylation is strongly dependent on the indole substituent, ranging from an enhancement of 3 orders of magnitude to a decrease in potency by a factor of 10 with concomitant differences between MAO-A and -B.[59]

In the one case where MAOI was determined for each member of a chiral pair (**18b**), there was no real difference between the enantiomers in potency or selectivity. This is further indication of the very special properties of rasagiline, in which there is a difference of four-orders-of-magnitude between the enantiomers in MAO-B inhibitory potency.

Replacement of the propargyl group with 1-methyl-2-propynyl results in a further decrease in MAO inhibitory activity (**26a** vs **18a**), in analogy to other propargylamines.[21] For instance, the pargyline derivative is several orders of magnitude less potent than the parent (from 9×10^{-7} to $>10^{-3}$).[60]

Compound **24c**, with an additional ring substituent (5-chloro), has an interesting profile, with less AChE

Table 6. MAO Inhibitory Activity of Selegiline, Desmethylselegiline (DMS), and Their Hydroxy and Carbamyloxy Congeners



				IC_{50} (μM)[a]		A/B	NH/NMe[b]	
R	compd	R1	R6	A	B		A	B
H	DMS	H	Me	195 (100−340)	0.32 (0.27−0.36)	610	162	46
	selegiline	Me	Me	1.2 (1.1−1.3)	0.007 (0.004−0.014)	171		
	55n	H	H	67 (14−340)	107 (22−530)	0.63	51	17
OH	**55o**	Me	H	1.3 (0.5−3.7)	6.4 (3.6−11.3)	0.20		
	55p	H	Me	830 (600−1100)	230 (150−360)	3.6	>93	>48
	55q	Me	Me	8.9 (4.7−16.8)	4.8 (2.8−8.3)	1.85		
	50a	H	H	2.7 (1.3−5.6)	24 (11−52)	0.11	9	8.6
	51a	Me	H	0.3 (0.1−0.9)	2.8 (1.5−5.2)	0.11		
	50b	H	H	2.6 (1.7−3.9)	7.8 (5.8−10.5)	0.33	3.3	9.8
OCON(Me)R_4[c]	**51b**	Me	H	0.8 (0.5−1.4)	0.8 (0.4−1.3)	1		
	52a	H	Me	6.9 (6.3−7.7)	5.7 (4.8−6.9)	1.21	58	7
	53a	Me	Me	0.12 (0.09−0.16)	0.8 (0.3−1.2)	0.15		
	52b	H	Me	2.1 (1.8−2.5)	12.8 (9.5−17.2)	0.16	17.5	128
	53b	Me	Me	0.12 (0.09−0.16)	0.1 (0.07−0.59)	1.2		

[a] Numbers in parentheses represent 95% confidence interval. [b] Ratio between IC_{50}'s of unsubstituted and N-Me substituted propargylamines. [c] **a**, R_4 = Me; **b**, R_4 = Et.

and MAO-A inhibitory potency than **18c**, but 8-fold more MAO-B inhibitory potency. As a result, this is the only MAO-B-selective compound in Series I with similar IC_{50} values for MAO-B and AChE inhibition.

Series II. AChE. As in Series I, AChEI activity is highly dependent on the nature of the carbamoyl substituents, exhibiting the same order of reactivity, namely Me ∼ Bu, hexyl > Pr > Et. The low potency of the Et substituent is most pronounced in the R1=R6=Me case (**53b** vs **51b**, **52b**, **54b**). This anomalous behavior of the Et,Me carbamates has already been discussed for Series I.

In both Series I and II, the change in the size of the alkyl substituents on the carbamoyl nitrogen has a much less pronounced effect on BuChE inhibition than on that of AChE. Thus, the Et,Me carbamates have similar or greater potency as BuChE inhibitors than the other carbamates, and tend to be the most selective against BuChE (**50b**, **52b**, **53b**, and **54b**). In Series II, we have prepared derivatives with methyl substitution at (i) phenethyl C2 (R6 = Me), (ii) the 2-propynylamine nitrogen (R1 = Me), and (iii) C1 of 2-propynyl, and combinations thereof. The AChEI potency of the 2-Me phenethyl derivatives is little affected by the presence of the Me group (cf **52a**,**b**,**c** vs **50a**,**b**,**c**). In contrast, the AChE potency decreases in most of the *N*-Me analogues (cf **53b** vs **50b**). The 1-methyl-2-propynyl derivatives **54a**,**b** are equipotent to the propargyl analogues **50a**,**b**, supporting the nonsignificance of steric requirements in this area.

Amine N-substitution (propargyl and/or additional methyl) has a tendency to lower AChEI potency, most markedly in **52b** and **53b**, but this effect is not fully consistent.

MAO. Introduction of a hydroxy group into the parent compounds of Series II (Table 6) has a more subtle effect on activity than in Series I. The MAO-B inhibitory potencies of the *N*-methyl derivatives (**55o** and **55q**) are 500 times lower than that of selegiline (**2**), although they are about the same for MAO-A inhibition. As a result, there is little or no A/B selectivity in these compounds. The nor analogues (**55n** and **55p**) too are considerably less potent against MAO-B than is *N*-desmethylselegiline (DMS).

As in Series I, the *N*-Me propargyl compounds are more potent than the secondary amines (**51** and **53** vs **50** and **52**, respectively). Likewise, selegiline has been reported to be 60 times more potent an inhibitor of MAO-B than its desmethyl analogue[61] (Table 6). However, in contrast to Series I, the presence of the carbamate moiety confers a greater MAO inhibitory activity than that of the parent hydroxy analogues, sometimes very significantly (**50a**,**b** vs **55n**, or **52a**,**b** vs **55p**). No clear trend for the effect of carbamate *N*-alkyl substituents on MAO inhibitory activity could be discerned.

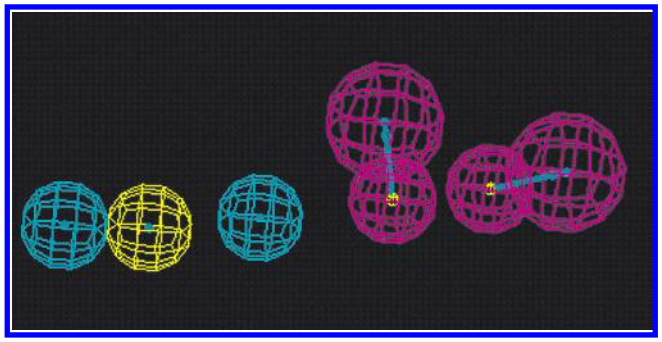


Figure 3. Putative MAO pharmacophore. Light blue, hydrophobes; yellow, carbamate centroid; magenta, HB donor or acceptor.

The absolute configuration of the 2-methylphenethyl has no effect on MAO-inhibitory activity, as shown by the almost equal potency of the two optical isomers of **53e**. Thus, in both series the bulky ring substitution decreases the importance of chirality and of A/B selectivity in comparison to rasagiline or selegiline. In common with all other examples (vide supra), the 1-methyl-2-propynylamine derivatives have a very low MAOI activity,[60] e.g., **54a** vs **50a**. It is noteworthy that both selegiline and rasagiline are unique in their series in MAO-B inhibitory potency and selectivity, relative to analogues in each series, despite the structural differences between them.

Implications for a Putative MAO Active Site. The in vitro results described above have important implications for understanding the steric requirements of the active sites of the various enzymes.[54]

In an attempt to correlate MAOI activity to structure in general, and the carbamate position in particular, we modeled five representative compounds (**18b**, **21b**, **23b**, **28b**, **52b**, Figure 3) using *Catalyst* molecular modeling software. As the absolute configuration of the propargylamine-bearing carbon does not significantly affect MAOI activity in these compounds, only one optical isomer (*S*) of each compound was modeled. A putative pharmacophore, based on the three active analogues (**28b**, **23b**, **52b**), was identified, comprising the following elements (Figure 3): (1) a carbamate group, featured by its geometrical center (carbamate centroid) and by a hydrophobic element (Et,Me substituents), (2) an aromatic hydrophobe, (3) an HB donor/acceptor (propargylamine nitrogen), and (4) an HB donor (acetylenic CH). If we assume that the carbamate moiety interacts with a feature of the active site and thus determines the orientation of the propargylamine, the three active analogues correlate well. However, for **18b** and **21b** (Figure 4) the propargylamine moiety (essential for MAOI potency) is markedly misoriented and presumably cannot interact with the FAD at the active site.[62] In fact, the 6-carbamoyl-*N*-propargylaminoindans (**18**) are even less potent MAO-A inhibitors than their parent 6-carbamoylaminoindans (**7**).

The higher potency of the *N*-Me derivatives for both MAO-A and -B suggests that methyl substitution exerts a counter-balancing effect.

Kinetics of AChE Inhibition. The bimolecular rate constants for carbamoylation of AChE (k_i) by four of the compounds were determined and compared to that of rivastigmine **1b** (Table 7)**.** The results of the kinetics experiment suggest that the cyclic compounds (e.g., **24c**, **27b**, and **(*R*)-18b**) have a slower rate of inhibition of AChE than the open-chain amines (rivastigmine **1b** and **53d**). The presence of a propargyl group and the identity of the carbamoyl substituents exert a smaller effect. The slow onset of enzyme activity by the ring-closed compounds is expected to enhance their therapeutic utility by reducing the intensity of adverse effects due to the slower build-up of excess cholinergic activity.

In Vitro/in Vivo Correlation and Metabolism. Preliminary in vivo studies suggest that the propargyl carbamates of both series will undergo analogous metabolism including stepwise loss of either or both the carbamoyl and propargyl moieties (**X**, **Y**, **Z**, Scheme 7, as well as other metabolites). Thus, the in vivo pharmacological profile will be determined not only by the enzyme inhibitory potency of the parent compounds but also by that of their metabolites. Thus, in Series I, most of the in vivo MAOI will be due to metabolites **X** while the principal AChE inhibitors (metabolites **Y** or the parent) will depend on the carbamate substitution position. For instance, the metabolites for compound **18b** include compound **39u** (**X**) which is at least 4 orders of magnitude more potent in MAOI (A and B), and compound **7b** (**Y**) which is 5 times more potent in AChEI.

By contrast, in Series II, the parent compound is more active than, or at least equipotent to, either metabolite **X** or **Y** for both enzymes. Metabolites **Z** have negligible inhibitory activity in both series. In any case, the ultimate MAOI/AChEI ratio in vivo will be determined by the pharmacokinetics of the various metabolites and their bioavailability.

Conclusions

We have described the preparation and in vitro activity of aminoindan (Series I) and phenethylamine (Series II) derivatives incorporating two pharmacophores: a carbamate and a propargyl group.

In Series I, MAO and AChE inhibitory potency of the carbamates decreases as a function of position 4 > 6 > 7. Series II can be viewed as being somewhat isosteric to either 4- or 6-substituted Series I, with pharmacological activity also intermediate between the two. In general, 6- and 7-carbamoyloxy PAI's (Series I) are either equipotent to, or slightly (2−5-fold) less active (as AChE inhibitors) than, the corresponding phenethylamine derivatives (PPE's, Series II), while the 4-analogues are more potent. The same trend is observed for MAO inhibition, but in this case the 6- and 7-carbamoyl PAI's are *2−3 orders of magnitude* less potent inhibitors of this enzyme, while the 4-analogues are equipotent to the PPE's (MAO-A).

In Series I, the 6- and 7-hydroxy compounds are more potent MAO inhibitors than the corresponding carbamates while the 4-hydroxy (A only) and Series II hydroxy compounds are less potent than their corresponding carbamates. However, in all examples the hydroxy derivatives are less potent than the unsubstituted parent compounds (rasagiline and selegiline). In both series, and for all regioisomers, AChEI activity depends primarily on the carbamoyl nitrogen substituents, with Et,Me being the least potent.

The *N*-propargyl group decreases AChEI activity (as compared to the non-propargyl analogues) in Series I,

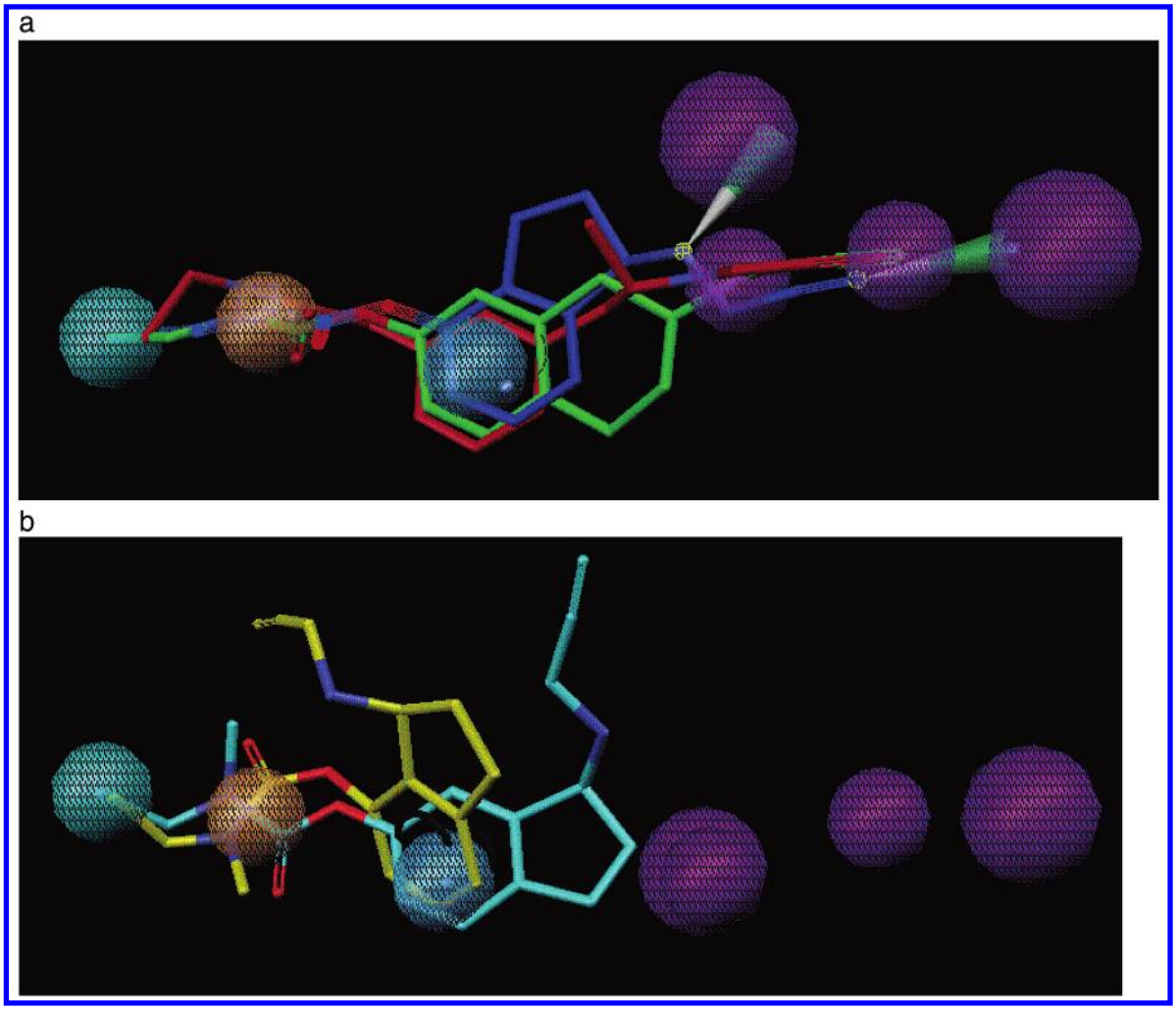


Figure 4. Correlation between active and nonactive compounds and the putative MAO pharmacophore. (a) Actives: red, **52b**; green, **28b**; blue, **23b**. (b) Nonactives: yellow, **21b**; cyan, **18b**.

Table 7. Bimolecular Rate Constants for Carbamylation by Selected Compounds

	pseudo-first-order rate constant k_{obs} (min^{-1}) ± SEM						
compd	2.5 μM	5 μM	10 μM	20 μM	40 μM	50 μM	k_i[a]
1b	19 ± 3	–	33 ± 3	44 ± 3	–	–	1432 ± 191
53d	14 ± 1	15 ± 1	23 ± 2	30 ± 2	55 ± 1	63 ± 1	1035 ± 60
		50 μM	100 μM	200 μM	300 μM	400 μM	
24c	–	17 ± 1	22 ± 1	–	34 ± 1	38 ± 2	59 ± 5
27b	–	21 ± 1	30 ± 1	39 ± 1	48 ± 2	68 ± 1	101 ± 12
(*R*)-**18b**	–	16 ± 1	21 ± 1	32 ± 1	42 ± 2	52 ± 1	102 ± 5

[a] Bimolecular rate constant (M^{-1} min^{-1}) ± SEM.

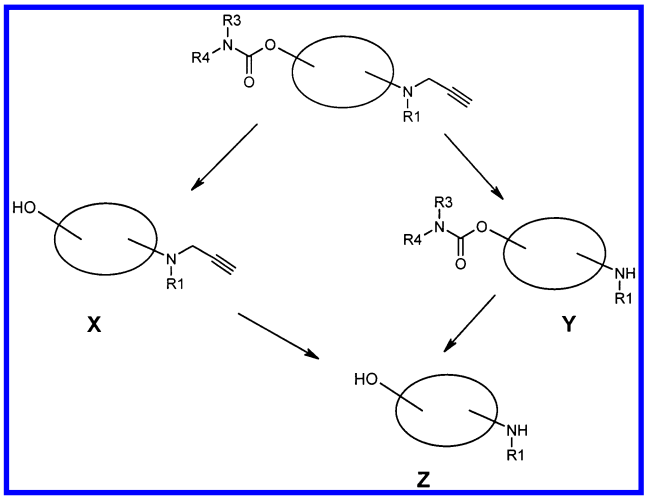
while having little or no effect in Series II. *N*-methylation at the propargylamine nitrogen has a dual effect in both series: it increases MAOI (A and B) and decreases AChEI activities.

Three candidates (**24c**, **27b**, **53d**) were identified as possible leads for further development, based on the following criteria: (a) comparable AChE and MAO-B inhibitory activities, (b) good to moderate AChE inhibitory activity, and (c) lack of strong A selectivity. However, it is likely that these compounds will be metabolized to derivatives with inhibitory activities against AChE and/or MAO-A or -B, which are different from those of the parent compounds. Thus, the final enzyme inhibition will be a result of the combined action of all of these individual metabolites. The results of our ongoing in vivo screening program will be published elsewhere.

Experimental Section

Chemistry. General. All commercial chemicals and solvents were reagent grade and were used without further purification unless otherwise specified. Melting points were determined on a Buchi B-540 apparatus and are uncorrected. Elemental analyses were carried out at the Hebrew University of Jerusalem, and the results are within ±0.4% of the theoretical values. Merck silica gel 60 F254 plated were used for analytical TLC (visualized with UV light and iodine vapors); flash column chromatography was performed on Merck silica gel 60 (230−400 mesh). ^{1}H NMR spectra were recorded in DMSO-d_6, $CDCl_3$, or D_2O by means of a Varian Gemini-300

Scheme 7. Putative Metabolic Pathways for Series I and II



spectrometer. Chemical shifts were expressed in δ (ppm) relative to TMS (in DMSO-d_6 or $CDCl_3$) as internal standard, or to HOD (4.80 ppm, in D_2O), and coupling constants (J) are in hertz. Mass spectra were recorded on a Finnigan 4021 spectrometer. Reaction conditions were not optimized.

Dialkylcarbamoyl chlorides were prepared by reacting dialkylamines with either phosgene in toluene[63] or carbon dioxide and thionyl chloride.[64] Dialkyl thiocarbamoyl chlorides were prepared from thiophosgene.[65]

Full experimental details are given for representative examples of the various synthetic steps. Full spectral and analytical data may be found in the Supporting Information.

A note on nomenclature: To avoid confusion (due to the different ranking of hydroxy and carbamoyl functionalities) and maintain uniformity through the entire text, we have decided to use the more straightforward (albeit not always formal) numbering system for the compounds of Series I**.** Thus, both hydroxy compounds and their carbamates are designated 4-, 6-, and 7- substituted derivatives of 1-aminoindan (e.g., 4-, 6-, and 7-hydroxy-1-aminoindan instead of 1-amino-indan-4-ol, 3-amino-indan-5-ol, and 3-amino-indan-4-ol, respectively).

Series I. 1. Boc-Protection: 6-Hydroxy-*N*-Boc 1-aminoindan (5, R1=H). A solution of 6-hydroxy 1-aminoindan (**4**,**R1=H**) (16 g, 107 mmol), di-*tert*-butyl dicarbonate (23.8 g, 109.2 mmol), and Et_3N (16.74 mL, 120 mmol) in THF (375 mL) was stirred at room temperature for 20 h. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in CH_2Cl_2 (200 mL), washed with water (200 mL), dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc 2:1) to give 23 g of a solid (86%), mp: 104−5 °C.

2. Carbamylation: 6-(*N*-Me,*N*-Et carbamyloxy)-*N*-Boc 1-aminoindan (6, R1=H). To a stirred and ice-cooled solution of **5**, **R1=H** (7.5 g, 30 mmol) in acetonitrile (75 mL) was added *N*-Me,*N*-Et carbamoyl chloride (4.4 g, 36 mmol), followed by a dropwise addition of NaH (60% in oil, 1.56 g, 39 mmol). The reaction mixture was stirred for 2 h at room temperature under argon. After evaporation of the solvent in vacuo, water (100 mL) was added and extracted with ether (3 × 100 mL). The organic phase was washed with dilute NaOH (pH 10−11), dried, and evaporated to dryness in vacuo. Purification by column chromatography (hexane:EtOAc 2:1) afforded 7.8 g (77%) of a solid, mp: 97−8 °C.

6-(*N*-Alkyl carbamyloxy)-*N*-Boc 1-aminoindan (6, R1=H, R3=H). The alkyl isocyanate (1 mmol) and a few drops of Et_3N were added to a solution of **5**,**R1=H** (250 mg, 1 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 20 h and evaporated to dryness and the residual solid triturated with *n*-hexane. The crude free base was converted to the HCl salt by 6.7 M HCl/dioxane, and the crude salt was crystallized from MeOH/EtOAc.

3. Boc-Deprotection: 6-(*N*-Me,*N*-Et carbamyloxy)-1-aminoindan·HCl (7b·HCl). Compound **6**, **R1=H** (7.8 g, 23.3 mmol) was dissolved in dioxane (80 mL), and a 20% HCl/dioxane (80 mL) was added. After 2 h stirring at room temperature, the solvent was evaporated in vacuo and the residue was treated with dry ether (200 mL). The mixture was stirred at room temperature for 4 h and filtered, to give 6.15 g (22.7 mmol, 97%).

4. Propargylation: 6-(*N*-Me,*N*-Et carbamyloxy)-*N*-propargyl-1-aminoindan·HCl (18b·HCl). To a stirred mixture of **7b**·HCl (5.2 g, 19.2 mmol) and potassium carbonate (5.31 g, 38.4 mmol) in acetonitrile (250 mL) was added a solution of propargyl bromide (2.06 g, 17.28 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature under nitrogen for 25 h and filtered. The filtrate was evaporated to dryness in vacuo, and the residue was purified by column chromatography (EtOAc) to give 3.6 g (13.2 mmol, 69%) of the free base as a yellow oil. The free base was dissolved in dry ether (150 mL), and HCl/ether (15 mL) was added. The mixture was stirred at room temperature for 1 h and filtered, and the solid was recrystallized from ^{i}PrOH/ether to give 3.5 g (11.3 mmol, 59%) of the title compound as a white solid.

6-(*N*,*N*-Dimethylcarbamyloxy)-*N*-propargyl-1-aminoindan Mesylate (18a Mesylate). To a stirred mixture of **7a**·HCl (1.88 g, 7.33 mmol), K_2CO_3 (2.03 g, 14.66 mmol), and acetonitrile (70 mL) was added a solution of propargyl bromide (0.79 g, 6.6 mmol) in CH_3CN (5 mL) dropwise over 5 min, under nitrogen. The mixture was stirred under N_2 for 24 h and filtered, and the solvent was removed at reduced pressure. The residue was taken up into water (150 mL) and toluene (150 mL). This mixture was stirred while adjusting the pH of the aqueous layer to 3.75 by the addition of 20% aq HCl. The aqueous layer was separated and extracted with toluene (2 × 100 mL) and brought carefully to pH 7.5 by the addition of 10% aq NaOH solution. It was then extracted with toluene (5 × 70 mL). The combined toluene layers were dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure to give 1.06 g (62%) of a yellow oil. To a stirred solution of the free base (1.65 g, 6.4 mmol) in anhyd ether (60 mL) was added dropwise a solution of methanesulfonic acid (0.7 g, 7.29 mmol) in ether (10 mL). The resulting suspension was stirred at 25° C for 30 min and then allowed to settle for an additional 30 min. The ether was then decanted off, and the residue was dried in vacuo. It was then recrystallized from ^{i}PrOH/ether to give 2.05 g of a white solid (90.3%).

7-(*N*-Me,*N*-Et carbamyloxy)-*N*-methyl,*N*-propargyl-1-aminoindan·HCl (22b·HCl). A mixture of **21b** (330 mg, 1.21 mmol), paraformaldehyde (165 mg), and $NaCNBH_3$ (95 mg, 1.51 mmol) in absol MeOH (25 mL) was refluxed under nitrogen for 4 h. The reaction mixture was evaporated to dryness under reduced pressure, and the viscous oily residue was purified by chromatography (hexane:EtOAc 70:30) to give 270 mg (78%) of the free base as a light viscous oil. The latter was converted to the HCl salt by ethereal HCl. The crude salt was then dissolved in dry MeOH (30 mL), to give, after evaporation of the solvent, 245 mg (81%) of a white solid, mp 147−50 °C.

Preparation of 5-Chloro-6-hydroxy-1-aminoindan (38, Scheme 3): (1) 3-Chloro-4-methoxybenzaldehyde. Sulfuryl chloride (270 g, 2 mol) was added to a solution of 4-methoxybenzaldehyde (136 g, 1 mol) in acetic acid (300 mL) at 20−30 °C for 2 h while the reaction mixture was well stirred and cooled. It was then allowed to stand at room temperature for 1 day. The yellow solution was poured onto a mixture (1.2 kg) of water and ice. The solid was collected by filtration, washed three times with ice-cold water and once with *n*-hexane, dried under vacuum over $CaCl_2$, then over NaOH, to give 170.6 g (100%), mp 40−46 °C. It was used in the next step without any purification. A small sample was crystallized from *n*-hexane, mp 54−56 °C (54−56 °C[31a], 62 °C[31b]).

(2) 3-(3-Chloro-4-methoxyphenyl)propionic Acid (34). A mixture of crude 3-chloro-4-methoxybenzaldehyde (170.6 g, 1 mol), Meldrum's acid[33] (144.1 g, 1 mol), triethylammonium formate (250 mL, prepared from triethylamine (168 mL, 1.2

mol) and formic acid (113 mL, 3 mol)), and DMF (200 mL) was stirred at room temperature for 6 h and set aside at room temperature for 18 h. The reaction mixture was then heated to 100 °C within 2 h, stirred at 95−100 °C for 2 h, cooled to 40 °C and poured onto a mixture of ice−water (1200 g) and concd HCl (120 mL). The solid was collected by filtration, washed twice with cold water, dissolved in acetone (300 mL) at room temperature, and treated with charcoal (10 g). Ice (450 g) was added to the filtrate (450 mL), and the mixture was allowed to stand at 5 °C for 3 days. The crystals were collected by filtration, washed with 50% EtOH, and dried in a desiccator. The mother liquor was evaporated to dryness, and the oily residue was triturated with cold 50% EtOH. The solid was then collected by filtration, washed, and dried. The combined solids (107 g) were dissolved in EtOH (450 mL) at room temperature and treated with charcoal (5 g). Ice cold water (450 mL) was added to the ethanolic filtrate, and the mixture was cooled and filtered. The solid was washed with 50% EtOH and dried (88 g, 41%, based on 4-methoxybenzaldehyde), mp 113−116 °C.

(3) 3-(3-Chloro-4-methoxyphenyl)propionyl Chloride (35). A mixture of thionyl chloride (87 mL) and **34** (129 g, 0.6 mol) was stirred at room temperature for 0.5 h and heated to 100 °C within 1 h. This temperature was maintained for an additional 1 h. The excess of $SOCl_2$ was distilled off under reduced pressure. Toluene was added and then distilled off, to give 139.8 g (0.6 mol, 100%) of a crude product which was used in the next step without further purification.

(4) 5-Chloro-6-methoxy-1-indanone (36). Crude **35** (35 g, 27.5 mL) was added to a stirred suspension of $AlCl_3$ (22 g) in CH_2Cl_2 (1350 mL) at 0−5 °C, and the suspension was stirred at this temperature for 1 h. A second aliquot of crude **35** (27.5 mL) and $AlCl_3$ (22 g) was added with additional stirring at 0−5 °C for 1 h. The reaction mixture was allowed to warm to room temperature, stirred for an additional 1 h, and poured onto a mixture of ice, water (1.5 kg), and concd HCl (72 mL). CH_2Cl_2 (600 mL) was added to the mixture under efficient stirring. The phases were separated, and the organic layer was dried and treated with charcoal. The filtrate was concentrated to half of volume, stored at −15 °C, filtered, washed with cold CH_2Cl_2 and MeOH, and dried (102.7 g, 87%), mp 165−166 °C.

(5) 5-Chloro-6-methoxy-1-indanone Oxime. A mixture of **36** (98.3 g, 0.5 mol), hydroxylamine hydorchloride (69.5 g, 1 mol), sodium acetate (82 g, 1 mol), ethanol (450 mL), and water (250 mL) was refluxed for 1 h. The reaction mixture was allowed to cool to room temperature, cooled to 5 °C, and filtered. The solid was washed with water and cold EtOH and dried (102.6 g, 97%), mp 208−210 °C.

(6) 5-Chloro-6-methoxy-1-aminoindan·HCl (37·HCl). A solution of $NaBH_4$ (37.8 g, 1 mol) in DMF (300 mL) was added to a stirred mixture of MoO_3 (54.0 g, 0.25 mol) and 5-chloro-6-methoxy-1-indanone oxime (52.9 g, 0.25 mol) in MeOH (1000 mL) at room temperature under N_2 for 2 h. Water (200 mL) was added to the reaction mixture over a period of 10 min. MeOH was distilled off under reduced pressure, and concd HCl (150 mL) and crushed ice (70 g) were added to the residue. The solid was removed by filtration, and ice (50 g) and 10 N KOH (200 mL) were added to the filtrate. The suspension was filtered and the cake washed with water and CH_2Cl_2. The filtrate was extracted with CH_2Cl_2 (3 × 600 mL), and concd HCl (21 mL) was added to the combined organic layers under stirring. The mixture was well shaken and stored at 5 °C for 3 days. The crystals were then collected by filtration, washed three times with CH_2Cl_2, and dried (29.1 g). A second crop of 8.9 g was obtained from the mother liquors (total yield 65%), mp 257−260 °C (dec).

(7) 5-Chloro-6-hydroxy-1-aminoindan (38). A mixture of **37**·HCl (35.1 g, 0.15 mol), 45% aq HBr (300 mL), and 33% HBr/AcOH (150 mL) was refluxed for 1 h and evaporated to dryness under reduced pressure, and the residue was dissolved in water (350 mL). The dark solution was treated with charcoal (1.5 g) at room temperature for 0.5 h, the charcoal was filtered off, and 10 N KOH was added to the clear solution (pH 8.5). The resulting solid was collected by filtration, washed with water, dried (17.6 g, 64%), and crystallized from MeOH (15.2 g, 55%), mp 207−209 °C (dec).

Preparation of Optical Isomers of 6-Hydroxy-1-aminoindan (*R/S* 4,R1=H,R5=H, Scheme 2): (1) *N*-Trifluoroacetyl-(*R/S*)-1-aminoindan (33). To an ice- cooled solution of trifluoroacetic anhydride (194.6 g, 0.926 mol) in toluene (680 mL) was added dropwise a solution of 98% optically pure (chiral HPLC)[66] (*R/S*)-1-aminoindan (113.32 g 0.85 mol) in toluene (50 mL) and stirred under ice-cooling for 3.5 h. A solution of KOH (67.25 g, 1.2 mol) in water (1000 mL) was then added, and the reaction mixture stirred for further 2 h at room temperature. The solid was collected by filtration, washed with water (680 mL), and dried to give 152 g (78%) of a white solid, mp: 153−154 °C. The solution was evaporated, and the crystals were collected by filtration, washed with water, and dried. This second crop (25 g) was crystallized from a mixture of hexane and ethyl acetate to give 18 g (9%) of a white solid, mp:153−154°C. The total yield was 170 g (87%).

6-Chloroacetyl-*N*-trifluoroacetyl-(*R/S*)-1-aminoindan. To a suspension of $AlCl_3$ (89.2 g, 0.67 mol) in 1,2-dichloroethane (600 mL) was added chloroacetyl chloride (55.7 mL, 78.9 g, 0.7 mol) dropwise at 0−5 °C under nitrogen for 20 min and left to warm to room temperature. To this mixture was added **33** (34.4 g, 0.15 mol) over a period of 3 h at room temperature. The resulting mixture was then stirred for an additional 30 min and poured onto a mixture of ice-cold water (1.5 L) and 1,2-dichloroethane (1 L). The mixture was stirred for 5 min, and the layers were separated. The aqueous layer was extracted with 1,2-dichloroethane (2 × 750 mL). The combined organic layers were washed with water (2 × 900 mL) and 5% aqueous $NaHCO_3$ (3 × 900 mL). The organic layer was dried and the solvent evaporated to give a solid, which was crystallized from ethanol to give 31.2 g (68%) of a white solid mp: 166−167°C.

(3) 6-Chloroacetoxyl-*N*-trifluoroacetyl-(*R/S*)-1-aminoindan. 6-Choroacetyl-*N*-trifluoroacetyl-(*R/S*)-1-aminoindan (30.57 g, 0.1 mol) was dissolved in anhydrous dichloromethane (210 mL) and 3-chloroperoxybenzoic acid (70%, 44.87 g, 0.26 mol) was added in one portion. The suspension was cooled to 0°C, and trifluoroacetic acid (11.4 g, 0.1 mol) was added dropwise over 5−10 min. The reaction flask was protected from light, and the mixture was stirred for 3−5 days at room temperature, poured onto water (300 mL), and neutralized with ammonium hydroxide solution. The layers were separated, and the aqueous layer was extracted with dichloromethane (200 mL). The combined organic layers were dried, and the solvent was evaporated to give a solid, which was crystallized from ethanol to give 15 g (48%) of a white solid mp: 169−170 °C.

(4) 6-Hydroxy-(*R/S*)-1-aminoindan ((*R/S*)-4,R1=H,-R5=H). A suspension of 6-chloroacetoxy-*N*-trifluoroacetyl-(R/S)-1-aminoindan (25.4 g, 0.11 mol) and K_2CO_3 (38.0 g, 0.275 mol) in a mixture of methanol (275 mL) and water (175 mL) was stirred at 70 °C for 1.5 h. Methanol was removed in vacuo, and the aqueous phase was neutralized with 10% HCl. The mixture was filtered and the solid was washed with water. The mother liquor was concentrated to a small volume, and the resulting suspension was neutralized and filtered. The brown solid was crystallized twice from methanol to give 7.0 g (43%) of a white solid, mp 200−203 °C.

Preparation of 6-Hydroxy-1-(1-methylpropargyl)aminoindan·HCl (4,R1=1-methylpropargyl,R5=H). (1) 3-Mesyloxy-1-butyne.[21] To a solution of 10 g (0.147 mol) of (±) 3-butyn-2-ol and 29.8 mL (0.215 mol) of triethylamine in 250 mL of methylene chloride cooled at −50 °C was added 14.4 mL (0.185 mol) of mesyl chloride within 1.5 h under stirring. The solution was allowed to warm to room temperature and stirred for 1 h. The solution was washed twice with water and then evaporated to dryness to give the crude product (21.3 g), which was used for the next step without purification.

^{1}H NMR (δ, DMSO-d_6): 1.52, 1.58 (3H, s, CH_3), 3.2 (3H, s, CH_3), 3.8 (1H, s, C*H*), 5.35 (1H, m, C*H*) ppm.

(2) 6-Hydroxy-1-(1-methylpropargyl)aminoindan·HCl (4,R1=1-methylpropargyl,R5=H). To a solution of 17.4 g

of 6-hydroxy-1-aminoindan in 500 mL DMF, 16.2 mL triethylamine and 17.1 g 3-mesyloxy-1-butyne was added; the solution was allowed to stand at room temperature for 82 h, poured into 1000 mL water and extracted with 3 × 200 mL ethyl acetate. The organic phase was washed with 3 × 100 mL water, dried on $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by column chromatography (ethyl acetate); the free base ($R_f = 0.765$) was dissolved in ether and treated with gaseous HCl to give the HCl salt (5.25 g, mp: 206−209 °C). Anal. Calcd. for $C_{13}H_{15}NO$ HCl (237.72): C, 65.67; H, 6.78; N, 5.89. Found: C ,63.51; H , 6.71; N , 5.66.

^{1}H NMR (δ, DMSO-d_6): 1.55 (3H, tr, CH_3); 2.1−3.2 (4H, m, 2CH_2); 3.50, 4.0 (1H, s, C*H*); 4.15, 4.4 (1H, m, C*H*); 4.8 (1H, m, C*H*); 6.85−7.15 (3H, m, *Ar*); 9.6 (1H, s, O*H*); 9.5−10.0 (1H, m, N*H*) ppm.

Preparation of Hydroxy Propargylaminoindans 39. A mixture of hydroxy 1-aminoindan **4**,**R1**=**H**,**R5**=**H** (35 mmol), propargyl bromide (35 mmol), and potassium carbonate (35 mmol) in DMA (100 mL) was stirred at room temperature for 24 h. The reaction mixture was filtered, diluted with water (200 mL), and extracted with toluene (4 × 100 mL). The organic extracts were combined, dried, and evaporated to dryness under reduced pressure. The residue was then subjected to flash column chromatography (hexane: EtOAc 1:1).

Preparation of Hydroxy *N*-Me,*N*-Propargylaminoindans 40. (1) A mixture of **39u** (5.0 g, 26.7 mmol), paraformaldehyde (3.6 g, 30 mmol), and $NaCNBH_3$ (1.96 g, 31.2 mmol) in absol MeOH (90 mL) was refluxed under argon for 4 h. The crude product (**40u**) obtained after evaporation of the solvent was purified by flash chromatography (hexane: EtOAc 70:30) and converted to its HCl salt (Etheral HCl), 4.2 g (17.6 mmol, 66%). Analogously, **40w** was prepared from **39w**.

(2) N-Methylation of 7-hydroxy-1-aminoindan **4**,**R1**=**H**,**R5**=**H**: Refluxing the latter (3.7 g, 24.8 mmol) in ethyl formate (200 mL) for 18 h afforded, after removal of ethyl formate and flash chromatography, 4.1 g (93%) of *N*-formyl-7-hydroxy-1-aminoindan. A solution of the latter in dry THF (70 mL) was added to an ice-cooled and stirred suspension of LAH in dry THF (100 mL). The reaction mixture was stirred for 9 h at room temperature, ice-cooled and treated with water (100 mL). The pH was adjusted to ca. 8−9, water (200 mL) was added, and the mixture was extracted with ether (6 × 250 mL). The combined ethereal extracts were dried and evaporated to dryness to give 3.2 g (94%) of 7-hydroxy-*N*-methyl-1-aminoindan. Reaction with propargyl bromide (as described for **39**) afforded **40v** in 53%.

Series II. 1. Boc Protection: 3-Hydroxy-*N*-Boc,*N*-methylphenethylamine (43,R1=Me,R6=H). To a solution of 3-hydroxy-*N*-methylphenethylamine (**42**,**R1**=**Me**,**R6**=**H**) (8.33 g, 55.17 mmol) in dioxane (80 mL) and water (80 mL) were added $NaHCO_3$ (13.65 g) and di-*tert*-butyl dicarbonate (13.65 g, 62.54 mmol). The reaction mixture was stirred at room temperature for 4 h and evaporated to dryness in vacuo. The residue was taken up in a water:dioxane mixture (400 mL, 1:1), and the layers were separated. The aqueous layer was re-extracted with ether (2 × 75 mL), and the combined ether layer was dried (Na_2SO_4) and evaporated to dryness in vacuo. The oily residue was purified by column chromatography (hexane:EtOAc 2:1) to give 10.2 g (74%) of the title compound as a viscous yellow oil.

2. Carbamylation: 3-(*N*-Me,*N*-nPr carbamyloxy) *N*-Boc,*N*-methylphenethylamine (44,R1=Me,R6=H). To an ice-cooled solution of **43**,**R1**=**Me**,**R6**=**H**) (5.0 g, 19.9 mmol) in dry acetonitrile (65 mL) was added, under nitrogen, *N*-methyl,*N*-*n*-propyl carbamoyl chloride (4.66 g, 34.43 mmol), followed by the portionwise addition of NaH (60% disp. in oil, 1.03 g, 25.87 mmol). The reaction mixture was stirred at room temperature under nitrogen for 6 h and evaporated to dryness in vacuo. Water (200 mL) was added, the pH was adjusted to ∼9, and the aqueous layer was extracted with ether (4 × 100 mL). The combined ether layer was washed with NaOH solution (pH 9.5) and water (150 mL), dried (Na_2SO_4), and evaporated to dryness in vacuo to give an oil which was purified by column chromatography (hexane:EtOAc 2:1), affording 6.0 g (86%) of the title compound as a yellow oil.

The monoalkyl carbamates **45g** and **45h** were prepared by the procedure described above for monoalkyl carbamates of Series I.

3. Boc-Deprotection: 3-(*N*-Me,*N*-nPr carbamyloxy) *N*-Methylphenethylamine·HCl (46c·HCl) 44,R1=Me,R6=H (6.0 g, 17.14 mmol) was dissolved in dioxane (60 mL), and 20% HCl/ether (60 mL) was added. The mixture was stirred at room temperature for 4 h and evaporated to dryness in vacuo, and the residual oil was treated with ether (2 × 150 mL), to give, after stirring and ice-cooling, 4.6 g (93.5%) of the title compound as a white solid.

4. Propargylation: 3-(*N*-Me,*N*-Et carbamyloxy) *N*-Propargylphenylpropylamine·HCl (52b·HCl). A solution of propargyl bromide (1.1 g, 9.1 mmol) in acetonitrile (8.5 mL) was added dropwise to a stirred mixture of **47b**·HCl (2.4 g, 8.8 mmol) and potassium carbonate (2.8 g) in acetonitrile (25 mL), and the mixture was stirred at room temperature for 7 h. The reaction mixture was filtered, and the filtrate was removed under reduced pressure. The residue was purified by column chromatography (hexane:EtOAc 2:1) to give 1.76 g of the title compound as the free base (73%). The free base was dissolved in dry ether (50 mL), and HCl/ether was added (to pH 1). The mixture was stirred for 4 h at room temperature and filtered, and the solid was washed with cold ether, to give, after drying at 60° C in vacuo, 1.5 g (4.82 mmol, 55%).

Preparation of Optical Isomers of 3-(*N*-Methyl,*N*-cyclohexylcarbamyloxy)-*N*-methyl-*N*-propargylphenylpropylamine Mesylate ((*S*)-53e Mesylate). (1) (*S*)-3-(2-Aminopropyl)phenol ((*S*)-57): Racemic **56** (11.78 g, 77.92 mmol) and L-tartaric acid (11.70 g, 77.95 mmol) were heated to reflux in methanol (520 mL). The yellow solution was then concentrated to a volume of 200 mL, and the heat was removed. The white suspension formed upon cooling to room temperature was set aside for 24 h and filtered (18.9 g), the solid thus obtained was heated to reflux in methanol (480 mL), and the mixture was concentrated to a volume of 200 mL. On cooling, a white solid precipitated, which was collected by filtration after 3 h and dried (10.16 g), mp 174−176 °C, lit.[23] 184−185 °C, $[\alpha]_D$ +18.08°($c = 2$, H_2O) lit.[23] +29.5° ($c = 2$, H_2O). The tartrate salt was converted into its free base by dissolving it in 22% ammonium hydroxide solution (1 L) and extracting with CH_2Cl_2 (50 × 70 mL). After drying and evaporation of solvent, 4.35 g of (S)-**57** was obtained as an off-white solid, $[\alpha]_D$ +12° ($c = 1.3$, methanol) lit.[41] +14.9° ($c = 1.3$, methanol).

(*R*)-**57** was similarly obtained from **56** and D-tartaric acid: $[\alpha]_D$ −13.9° ($c = 1.3$, methanol) lit.[41] −14.9° ($c = 1.3$, methanol).

(2) (*S*)-3-Hydroxy-*N*-methyl,*N*-propargylphenylpropylamine ((*S*)-55q). To a solution of (*S*)-**58** (4.4 g, 21.8 mmol), obtained from (*S*)-**57** via N-formylation[40] followed by reduction,[41] in dimethylacetamide (200 mL) stirred at 25 °C under a nitrogen atmosphere, was added K_2CO_3 (6.04 g, 43.64 mmol), and the mixture was stirred for 10 min. Then a solution of propargyl bromide (2.34 g, 19.64 mmol) in dimethylacetamide (10 mL) was added over 2 min, and the mixture was stirred at 25 °C for 24 h. Water (250 mL) was added, and the mixture was stirred until all the solid material dissolved. The aqueous layer was extracted with toluene (10 × 75 mL). The layers were separated, and the combined toluene layer was washed with saturated brine (2 × 150 mL) and dried (Na_2SO_4). Removal of solvent at reduced pressure gave an orange oil, which was purified by flash column chromatography using ethyl acetate as the eluent. This gave 3.60 g (90.2%) of the title compound as an orange oil.

Using this procedure, (*R*)-**55q** was obtained in 80%.

(3) (*S*)-3-(*N*-Methyl,*N*-cyclohexylcarbamyloxy)-*N*-methyl,*N*-propargylphenylpropylamine Mesylate ((*S*)-53e Mesylate). To a solution of compound (*S*)-**55q** (1.80 g, 8.87 mmol) in dry acetonitrile (100 mL) cooled in an ice bath was added under nitrogen *N*-methyl-*N*-cyclohexylcarbamyl chloride (2.70 g, 15.39 mmol) followed by the portionwise addition of NaH (60% oil dispersion, 0.467 g, 11.69 mmol). The mixture was then stirred at room temperature under nitrogen for 18

h. Solvent was removed at reduced pressure, and water (100 mL) and ether (150 mL) were added. The mixture was stirred until all the material dissolved. The layers were separated, and the aqueous layer was reextracted with ether (4 × 70 mL). The combined ether layers were washed with KOH solution (pH 9.5), then water, and dried (Na_2SO_4). Removal of solvent at reduced pressure gave 3.87 g of an orange oil which was purified by flash column chromatography using ethyl acetate as the eluent. This gave 2.57 g (84.5%) of the title compound (free base) as a yellow oil. The free base was dissolved in dry EtOAc (9 mL), and a solution of 95% ethanesulfonic acid (0.79 g, 6.81 mmol) in EtOAc (1.5 mL) was added. The solution was cooled to 5 °C and stirred at this temperature. After 15 min, a white solid precipitated, and the suspension was stirred at 5 °C for 3 h. The solid was collected by filtration using a minimum amount of ice-cold ethyl acetate. This gave 2.3 g (75%) of a white solid having a melting point of 118−120 °C.

Pharmacology. AChE Inhibition. Human acetylcholinesterase (AChE; EC 3.1.1.7) purified from red blood cells and equine butyrylcholinesterase (BuChE; EC 3.1.1.8) purified from serum (Sigma Chemical Co., St Louis, MO) were used for determination of cholinesterase inhibitory activity of the compounds. Assays were performed as described by Ellman et al.[67] using 200 μM acetylcholine as substrate for AChE and 200 μM butyrylthiocholine as substrate for BuChE. Compounds were preincubated with the enzyme for 60 min at 37 °C in 0.1 M phosphate buffer, pH 7.4, before addition of substrate. Assays were performed in triplicate and four-point dose−response curves were obtained for each compound. The percent inhibition of enzyme activity in the absence of compounds was used to calculate IC_{50}'s and their fiducial limits by means of the statistical program Origin version 7 from a plot of log(10) of concentration against % enzyme inhibition. The bimolecular rate constant (k_i) for carbamylation of human erythrocyte enzyme for four of the compounds and for rivastigmine were determined under the same conditions as those described above. The pseudo-first-order rate constants (k_{obs}) for progressive AChE inhibition at 4−5 concentrations of each inhibitor were established as described by Bar-On et al.[51] by means of the statistical program Origin version 7. From these we calculated the apparent bimolecular rate constant k_i for each compound.

MAO Inhibition. Inhibition by the compounds of MAO-A and MAO-B was determined by a method adapted from Tipton and Youdim.[68] Rat brain was homogenized in sucrose (0.3 M) and served as the source of enzymes. The compound under test was diluted from 10^{-2}M to 10^{-9}M in 0.05 M phosphate buffer (pH 7.4) containing 0.15 μM selegiline for determination of MAO-A, or in 0.05 M phosphate buffer containing 0.15 μM clorgyline for determination of MAO-B. Fifty microliters of a suitable dilution of the enzyme preparation was added to test tubes containing 100 μL of phosphate buffer (control test tubes); test tubes containing 100 μL of phosphate buffer and 10 μL of 0.01 M tranylcypromine (blank); test tubes containing 100 μL of various dilutions of the compounds. Incubation was carried out for 60 min at 37 °C. Substrates (^{14}C-5-hydroxytryptamine creatinine disulfate (100 μM) for determination of MAO-A) or (^{14}C-phenylethylamine (10 μM) for determination of MAO-B) were then added and the incubation continued for a further 30 and 20 min, respectively. The reaction was stopped with 250 μL of 2 M citric acid. Radioactive metabolites were extracted into toluene/ethyl acetate (1:1 v/v), a solution of 2,5-diphenyloxazole was added to a final concentration of 0.4%, and the metabolite content was estimated by liquid scintillation counting. Activity in the presence of the drug was expressed as a percentage of that of the control. Assays were performed in duplicates, and variation between the duplicates did not exceed 6%. Dose−response curves consisted of 6−7 points. Sigmoid curves and IC_{50} calculations were carried out using "Prism" software.

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Supporting Information Available: Spectral (^{1}H NMR, IR, MS) and analytical (C,H,N) data. This material is available free of charge via the Internet at http://pubs.acs.org.

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