Synthesis of alkylene linked bis-THA and alkylene linked benzyl-THA as highly potent and selective inhibitors and molecular probes of acetylcholinesterase

Yuan-Ping Pang,*[,a] Feng Hong,[a] Polly Quiram,[b] Tanya Jelacic[b] and Stephen Brimijoin[b]

[a] *Neurochemistry Research, Mayo Foundation for Medical Education and Research, 4500 San Pablo Road, Jacksonville, FL 32224, USA*
[b] *Department of Pharmacology, Mayo Foundation for Medical Education and Research, 200 First Street Southwest, Rochester, MN 55905, USA*

An efficient and economical synthesis of a series of rationally designed novel 9,9′-(alkane-1,-ω-diyldiimino)-1,2,3,4-tetrahydroacridines (ω = 7–10) and a second series of new analogues, 9-(ω-phenylalkylamino)-1,2,3,4-tetrahydroacridines (ω = 4–10), is reported. Compounds in the first series are found to be up to 10 000-fold more selective and 1000-fold more potent in reversibly inhibiting rat acetylcholinesterase (AChE) than the monomer, 9-amino-1,2,3,4-tetrahydroacridine (THA). Some members in the latter series (ω = 7–8) are slightly more potent than THA in inhibiting AChE but still more selective. These compounds can serve as (i) important chemical tools to evaluate the role of AChE inhibition by THA, a clinical drug, in treating Alzheimer's disease, (ii) effective, safer and low-cost insecticides and parasiticides, (iii) potential blockers of the K^+ channel and the *N*-methyl-D-aspartate receptor channel, and perhaps (iv) improved therapeutics for Alzheimer's disease.

Introduction

Alzheimer's disease, a devastating neurodegenerative disorder which is characterized by dramatic personality changes and global cognitive decline, currently affects approximately 4 million Americans, taking more than 100 000 lives each year.[1] This disease is pathologically characterized by the degeneration of the basal forebrain cholinergic system and the deposition of amyloid plaques in the brain.[2,3] One possible approach to treating this disease is to restore the level of neurotransmitter acetylcholine, which is found to be lowered in brains of the Alzheimer's patients, by inhibiting acetylcholinesterase (AChE) with reversible inhibitors. One such AChE inhibitor 9-amino-1,2,3,4-tetrahydroacridine (THA, also known as tacrine or COGNEX, Fig. 1) is currently approved by the United States Food and Drug Administration for the palliative treatment of mild and moderate Alzheimer's disease.[4] However, THA also has many other actions in the central nervous system besides inhibiting AChE. It is thus uncertain if the role of AChE inhibition by THA is significant in treating Alzheimer's disease. Furthermore, the use of THA is currently limited by its serious hepatotoxicity.

It is therefore desirable to develop more potent and selective inhibitors of AChE as chemical tools to evaluate the therapeutic role of AChE inhibition in treating Alzheimer's disease. Such inhibitors might also turn out to be improved therapeutic agents, if the role of AChE inhibition is indeed significant. With these aims, we designed two classes of novel THA analogues (**1** and **2**, Fig. 1) according to THA's multiple binding sites in AChE identified by the docking study and our new strategy for prototype optimization.[5] This strategy emphasizes that one can modify a prototype by using extensive computer-modelling of ligand docking with target proteins to identify low affinity binding sites, that would be missed by X-ray crystallography, for the prototype. The potency and selectivity of the prototype can be improved by connecting the two molecules with an alkylene chain spaced to permit simultaneous binding at the X-ray- and docking-determined binding sites. Through the docking study, we revealed that THA can not only bind to the catalytic site of AChE, but also to a site near residues Trp[279], Tyr[70] and Phe[290] of the Torpedo enzyme,[6,7] although X-ray crystallography revealed that THA binds only to the catalytic site.[8]

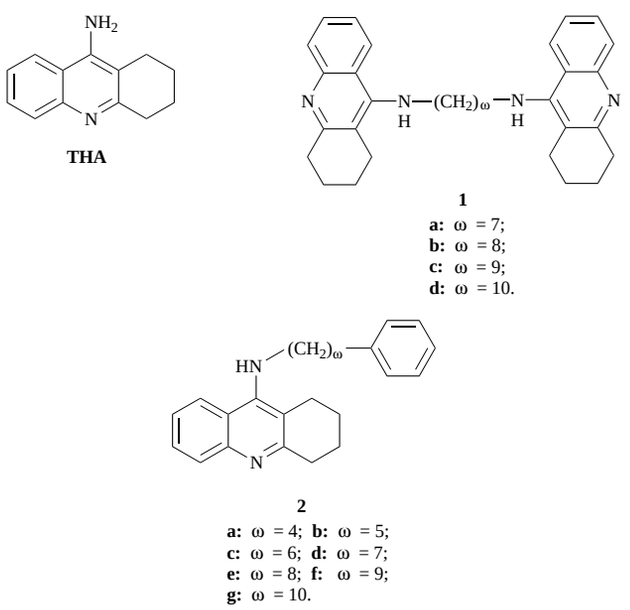


Fig. 1 Structures of THA and analogues **1** and **2**

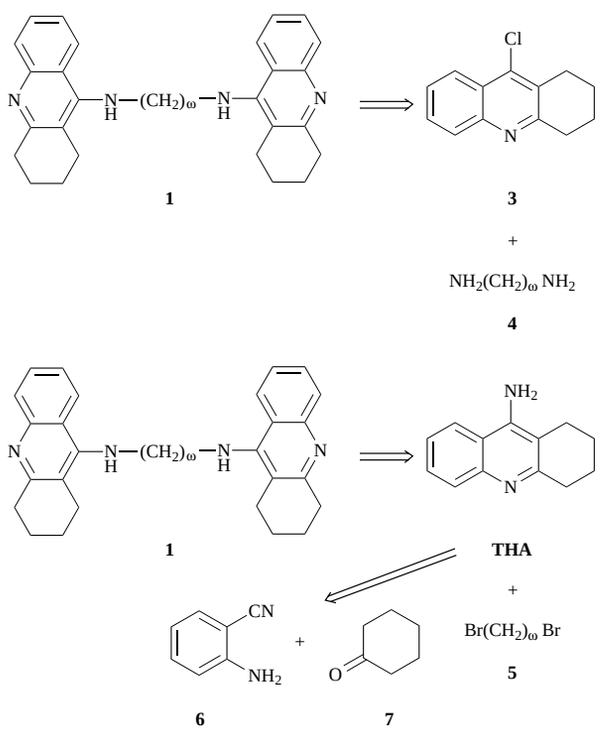
Additional reasons to synthesize such compounds were the following. AChE inhibition is lethal to most insects and parasites. Compounds **1** and **2** might, therefore, be used as effective, safer, and low-cost insecticides and parasiticides to replace the current organophosphate- and carbamate-pesticides which have problems of insecticide resistance and human poisoning. Resistance to insecticides mainly results from three mechanisms: (i) insecticide penetration is reduced, (ii) the insecticide is more efficiently metabolized by esterases, mixed function oxidases, or glutathione transferases, and (iii) mutations of the

residues in AChE's active site.[9] Compounds **1** and **2** are esterase-insensitive, and were crafted according to their predicted interactions with the conserved residues of AChE. Furthermore, they are reversible, AChE-selective, and substantially more potent than several of the organophosphates and carbamates in current use (*vide infra*), the risk of acute or chronic insecticide poisoning to humans may be reduced. In addition, their synthesis requires only one simple reaction (*vide infra*). Compounds **1** and **2** are also potentially useful as blockers of the K^+ channel and the *N*-methyl-D-aspartate (NMDA) receptor channel, because there is impressive structural similarity between compound **1** and recognized antagonists of these same channels.[10–12]

Newly synthesized compounds in the first series were found up to 10 000-fold more selective and 1000-fold more potent in reversibly inhibiting acetylcholinesterase (AChE) than the monomer THA. On the other hand, some members (ω = 7–8) in the second series were slightly more potent than THA in inhibiting AChE, while still more selective than the parent compound.[5] In this article, we report an efficient and economical synthesis of these compounds, which should provide others with opportunities to further study their potential biological applications.

Synthesis

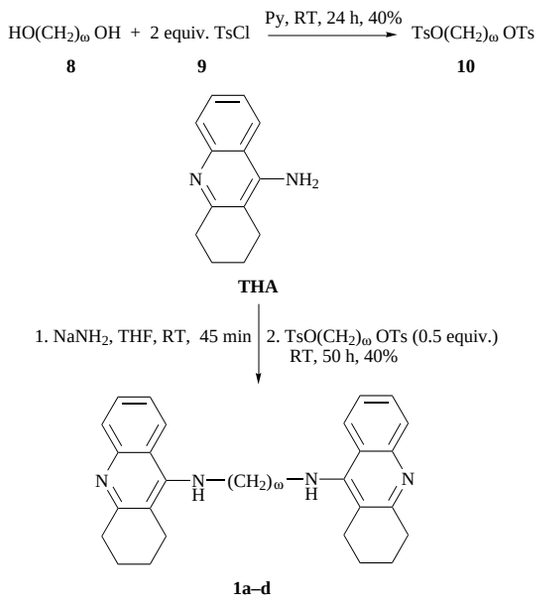
Two general, straightforward routes to synthesize compounds **1** and **2** were devised (see Scheme 1). Although there were literature examples for the synthesis in strategy A,[11,13] we decided against this strategy simply because synthon **3** was both unavailable commercially and relatively expensive to make. Instead, we focused on strategy B in which we could use commercially available THA as an intermediate: thus, reaction of 2 equiv. of THA anions (*vide infra*) with dibromoalkane would yield compound **1**. An additional advantage of strategy B was that the intermediate THA could be efficiently and economically synthesized by the literature procedures.[14] The total synthesis of compounds **1** and **2** by strategy B was not only efficient but also economical, which was very important for the development of these compounds as the above-mentioned therapeutic agents.



Scheme 1 Retrosynthetic analysis of compound 1. Top: Strategy A; Bottom: Strategy B.

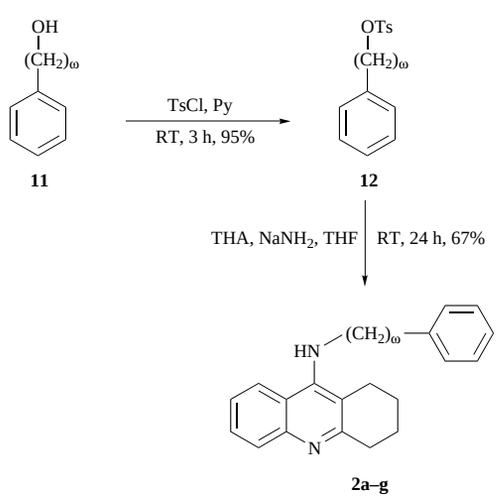
At the outset of this work, we conducted the one-step synthesis of compound **1** as outlined in strategy B. Reaction of dibromoheptane with THA anion, which was generated by treating the commercially available THA in its base form with sodium amide purchased from Aldrich, indeed gave the desired compound **1a**. However, the yield of the reaction was rather low. Furthermore, the reaction time was too long to identify conveniently the optimal compounds in the two classes of the designed compounds, partly because bromine was not an efficient leaving group for the S_N2 nucleophilic substitution. We accordingly revised our synthesis to a two-step synthesis for compounds **1** and **2** in which a better leaving group, tosylate, was used in place of bromine as described below. After identification of the optimal compounds, the one-step synthesis could be used to produce the desired compounds in large quantity if the time factor was not important to production.

Class I analogues **1a–d** were readily prepared according to Scheme 2. The commercially available alkane-1,ω-diols (ω = 7–10) were first converted into ditosylates[15–22] in *ca.* 40% yield by treating the alcohol with 2 equiv. of tosyl chloride in pyridine. The ditosylate was then treated at room temperature with 2 equiv. of THA anions prepared as above to give the desired compound.



Scheme 2 Synthesis of compound **1**

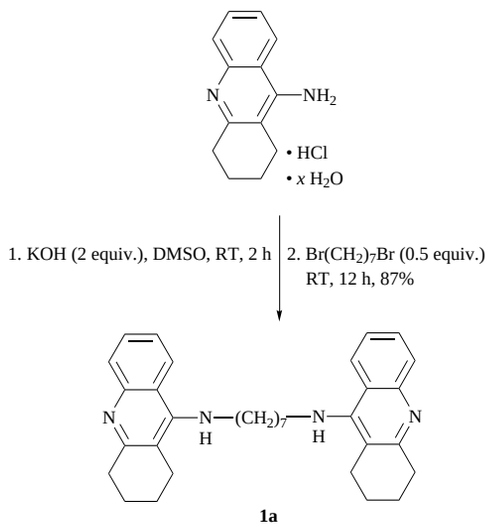
Class II analogues **2a–g** were easily prepared according to Scheme 3.The commercially available ω-phenyl-1-alkyl alcohols



Scheme 3 Synthesis of compound **2**

(ω = 4–10) were first converted into tosylates[23,24] in *ca.* 95% yield by treating with tosyl chloride in pyridine. The tosylate was then treated at room temperature with 1 equiv. of the THA anion prepared as above to yield the desired analogue.

After the most potent and selective AChE inhibitor **1a** had been identified,[5] we then turned our effort to optimize its synthesis. Among various reaction conditions we tried, we found the procedure in Scheme 4 most efficient and economical in producing compound **1a** on a gram scale.



Scheme 4 Synthesis of compound **1a**

Biological evaluation

Newly synthesized compounds in their salt form were tested *in vitro* for selectivity and potency as cholinesterase inhibitors. The measured IC_{50} values for inhibitions of AChE and a related enzyme, butyrylcholinesterase (BChE), are listed in Table 1.[5]

Clearly, as compared with THA, compound **1** is up to 10 000 times more selective and 1000 times more potent in inhibiting rat brain AChE, while compounds **2d**,**e** are slightly more potent than THA in inhibiting AChE, though still more selective for this enzyme. In addition, lipophilicity of compounds **1** and **2** was found increased over THA. This is evidenced by the fact that these compounds in their salt form were not completely dissolved in aqueous ethanol until the percentage of EtOH was raised to 40%, while THA in its salt form was readily dissolved in ethanol-free aqueous media. The results of these biological evaluations suggest that the newly synthesized compounds may be useful for one or more of the above-mentioned applications, because of (i) their greatly improved potency and selectivity in AChE inhibition; (ii) their increased hydrophobicity and (iii) their efficient and economical synthesis.

Experimental

THF was distilled from sodium benzophenone ketyl prior to use. Solvents used for chromatography were purchased in 5-gal drums. Silica gel 60 (Merck, 230–400 mesh ASTM for flash chromatography) was used for column chromatography. TLC was performed on Merck silica gel 60F-254 (0.25 mm, precoated on glass). Other reagents were used as supplied by the Aldrich Chemical Co. and Lancaster Synthesis Inc. NMR spectra were taken on a Bruker AC-300 (300 MHz for ^{1}H and 75.46 MHz for ^{13}C) instrument. Chemical shifts are reported in δ unit with reference to Me_4Si (δ = 0.00 ppm) for ^{1}H or $CDCl_3$ (δ = 77.00 ppm) for ^{13}C as internal standards. *J* Values are recorded in Hz. Mass spectra were obtained on a SINNIGAN MAT-90 instrument. High resolution mass data were collected by employing EI at 70 eV with PFK reference or by using ESI with a reference material of PEG 400. Melting points were determined in open capillary tubes on a Gallenkamp capillary melting point apparatus and are uncorrected.

Table 1 IC_{50}'s of THA and analogues **1** and **2** for inhibitions of AChE and BChE. IC_{50} values were computed by a non-linear least squares regression program which also provided an estimate of statistical precision (standard error of the mean)

	IC_{50} (nM)		
	rat brain AChE	rat serum BChE	Selectivity for AChE[b]
THA	590 ± 37	44 ± 2.0	0.1
1a	0.40 ± 0.025	390 ± 66	980
1b	0.66 ± 0.20	340 ± 13	520
1c	0.77 ± 0.11	190 ± 30	250
1d	3.1 ± 0.75	440 ± 100	140
2a	1 400 ± 140	NA[a]	NA
2b	1 500 ± 190	520 ± 50	0.4
2c	610 ± 23	810 ± 120	1.4
2d	390 ± 12	1 000 ± 35	2.6
2e	210 ± 19	2 400 ± 210	11.4
2f	20 000 ± 950	9 300 ± 1 800	0.5
2g	27 000 ± 4 000	9 400 ± 550	0.4

[a] NA: not available. [b] selectivity for AChE: IC_{50} for BChE divided by IC_{50} for AChE.

Heptane-1,7-diyl ditoluene-4-sulfonate 10a[15,16]

Pyridine (7 ml) was added to toluene-*p*-sulfonyl chloride (4326 mg, 22.7 mmol) at room temperature under N_2. The colour of the solution changed immediately to yellow after addition. A solution of heptane-1,7-diol (1.00 g, 7.6 mmol) in pyridine (7 ml) was then added dropwise to the reaction solution at 0 °C. The resulting solution was stirred at 0 °C for 30 min, and then slowly warmed to room temperature; it was then stirred at room temperature for 24 h. White precipitates were generated and the solution turned brownish. The tosylate was extracted with $CHCl_3$ and the extract washed with saturated aqueous NH_4Cl. Work-up followed by flash chromatography of the product on silica gel eluting with 30% EtOAc in hexane yielded the tosylate as white crystals (1332 mg, 40%): mp 76.6–77.5 °C; ν_{max}(KBr)/cm^{-1} 3449, 2953, 2859, 1597, 1474, 1354, 1188, 1098, 955, 839, 665 and 556; δ_H($CDCl_3$, 300 MHz) 7.79 (d, *J* 9.0, 4 H), 7.35 (d, *J* 9.0, 4 H), 3.99 (t, *J* 6.0, 4 H), 2.45 (s, 6 H), 1.68–1.54 (m, 4 H) and 1.36–1.18 (m, 6 H); δ_C($CDCl_3$, 75.46 MHz) 144.60, 132.80, 129.66, 127.59, 70.32, 28.37, 27.95, 24.88 and 21.39; *m/z* (EI) 440 (M^+), 172, 155, 97, 91 and 55 [Found (HRMS): *m/z* 440.1317. Calc. for $C_{21}H_{28}S_2O_6$: 440.1327].

Octane-1,8-diyl ditoluene-4-sulfonate 10b[15,17,18]

A similar procedure to that described in the preceding reaction afforded the product as white crystals: mp 71.2–72.9 °C; ν_{max}(KBr)/cm^{-1} 3449, 2928, 2855, 1597, 1476, 1356, 1188, 1098, 951, 839, 816, 667 and 577; δ_H($CDCl_3$, 300 MHz) 7.79 (d, *J* 9.0, 4 H), 7.35 (d, *J* 9.0, 4 H), 4.00 (t, *J* 6.0, 4 H), 2.45 (s, 6 H), 1.68–1.58 (m, 4 H) and 1.38–1.16 (m, 8 H); δ_C($CDCl_3$, 75.46 MHz) 144.65, 133.05, 129.76, 127.78, 70.50, 28.64, 28.57, 25.10 and 21.56; *m/z* (EI) 454 (M^+), 283, 173, 155, 111, 91 and 60 [Found (HRMS): *m/z* 454.1477. Calc. for $C_{22}H_{30}S_2O_6$: 454.1484].

Nonane-1,9-diyl ditoluene-4-sulfonate 10c[15,22]

A similar procedure to that described for the preparation of compound **10a** afforded the product as white crystals: mp 52.7–53.6 °C; ν_{max}(KBr)/cm^{-1} 3447, 2959, 2932, 2866, 1595, 1468, 1356, 1190, 1096, 995, 959, 818, 764, 662 and 575; δ_H($CDCl_3$, 300 MHz) 7.79 (d, *J* 9.0, 4 H), 7.35 (d, *J* 9.0, 4 H), 4.01 (t, *J* 6.0, 4 H), 2.45 (s, 6 H), 1.78–1.58 (m, 4 H) and 1.36–1.18 (m, 10 H); δ_C($CDCl_3$, 75.46 MHz) 144.58, 132.93, 129.69, 127.67, 70.53, 28.90, 28.56, 25.08 and 21.45; *m/z* (EI) 468 (M^+), 173, 155, 125, 91 and 69 [Found (HRMS): *m/z* 468.1628. Calc. for $C_{23}H_{32}S_2O_6$: 468.1640].

Decane-1,10-diyl ditoluene-4-sulfonate 10d[15,19–21]

A similar procedure to that described for the preparation of compound **10a** afforded the product as white crystals: mp 107.6–108.1 °C; ν_{max}(KBr)/cm^{-1} 3447, 2992, 2934, 2853, 1597, 1474, 1356, 1179, 1098, 968, 843, 665 and 556; δ_H($CDCl_3$, 300 MHz) 7.79 (d, *J* 9.0, 4 H), 7.35 (d, *J* 9.0, 4 H), 4.01 (t, *J* 6.0, 4 H), 2.45 (s, 6 H), 1.68–1.58 (m, 4 H) and 1.35–1.16 (m, 12 H); δ_C($CDCl_3$, 75.46 MHz) 144.60, 133.10, 129.74, 127.78, 70.61, 29.10, 28.74, 25.21 and 21.56; *m/z* (EI) 482 (M^+), 155, 139, 97, 91 and 83 [Found (HRMS): *m/z* 482.1786. Calc. for $C_{24}H_{34}S_2O_6$: 482.1797].

9,9′-(Heptane-1,7-diyldiimino)di-1,2,3,4-tetrahydroacridine 1a

A solution of THA (1015 mg, 5.1 mmol) in THF (4 ml) was added to a suspension of $NaNH_2$ (240 mg, 6.2 mmol) in THF (4 ml) under N_2. The orange–red mixture was vigorously stirred at room temperature for 45 min after which a solution of compound **10a** (749 mg, 1.7 mmol) in THF (8 ml) was then added to it. Stirring was continued at room temperature for 50 h after which the product was extracted with EtOAc and the solution washed with saturated aqueous Na_2CO_3. Work-up followed by flash chromatography on NH_3-saturated silica gel eluting with 5% methanol in $CHCl_3$ afforded the product as a yellow oil (318 mg, 38%); ν_{max}($CDCl_3$)/cm^{-1} 3347, 3061, 2932, 2859, 2180, 1615, 1580, 1562, 1499, 1420, 1358, 1296, 1273, 1167, 1130, 941, 909, 762, 731, 679 and 640; δ_H($CDCl_3$, 300 MHz) 7.94 (d, *J* 9.0, 2 H), 7.90 (d, *J* 9.0, 2 H), 7.55 (t, *J* 8.0, 2 H), 7.34 (t, *J* 5.0, 2 H), 3.91 (s, 2 H), 3.54–3.38 (m, 4 H), 3.11–2.99 (m, 4 H), 2.78–2.66 (m, 4 H), 1.99–1.85 (m, 8 H), 1.71–1.57 (m, 4 H) and 1.46–1.31 (m, 6 H); δ_C($CDCl_3$, 75.46 MHz) 158.35, 150.49, 147.40, 128.65, 128.04, 123.38, 122.65, 120.11, 115.79, 49.25, 33.96, 31.52, 28.95, 26.67, 24.65, 22.90 and 22.65; *m/z* (ESI) 493 $[M + H]^+$ and 247 $[M + 2 H]^{2+}$ {Found (HRMS): *m/z* 493.3319. $[M + H]^+$ for $C_{33}H_{40}N_4$: 493.3331}. Optimized procedure: a solution of THA·HCl·*x*H_2O (1199 mg) in DMSO (20 ml) was added to powdered KOH (758 mg, 11.5 mmol) under argon. The mixture was vigorously stirred at room temperature for 2 h after which 1,7-dibromoheptane (556 mg, 2.15 mmol) was added to the reaction mixture. After the resulting mixture had been stirred at room temperature for 12 h, it was poured into water (100 ml) and extracted with EtOAc (3 × 80 ml). A similar chromatography procedure to that described earlier afforded the desired product (1057 mg, 87%).

9,9′-(Octane-1,8-diyldiimino)di-1,2,3,4-tetrahydroacridine 1b

A similar procedure to that described in the preceding preparation afforded the product as a yellow oil; ν_{max}($CDCl_3$)/cm^{-1} 3347, 3063, 2932, 2857, 2182, 1615, 1582, 1564, 1503, 1420, 1360, 1298, 1273, 1130, 939, 909, 762, 731 and 640; δ_H($CDCl_3$, 300 MHz) 7.95 (d, *J* 9.0, 2 H), 7.90 (d, *J* 9.0, 2 H), 7.55 (t, *J* 8.0, 2 H), 7.34 (t, *J* 5.0, 2 H), 3.92 (s, 2 H), 3.47 (t, *J* 8.0, 4 H), 3.11–2.99 (m, 4 H), 2.78–2.66 (m, 4 H), 2.00–1.83 (m, 8 H), 1.71–1.54 (m, 4 H) and 1.45–1.21 (m, 8 H); δ_C($CDCl_3$, 75.46 MHz) 158.38, 150.55, 147.45, 128.70, 128.06, 123.40, 122.70, 120.14, 115.79, 49.34, 34.00, 31.60, 29.12, 26.69, 24.68, 22.95 and 22.70; *m/z* (ESI) 507 $[M + H]^+$ and 254 $[M + 2 H]^{2+}$ {Found (HRMS): *m/z* 507.3475. Calc. $[M + H]^+$ for $C_{34}H_{42}N_4$: 507.3487}.

9,9′-(Nonane-1,9-diyldiimino)di-1,2,3,4-tetrahydroacridine 1c

A similar procedure to that described for the preparation of compound **1a** afforded the product as a yellow oil; ν_{max}($CDCl_3$)/cm^{-1} 3356, 3063, 2930, 2857, 2182, 1615, 1582, 1564, 1505, 1418, 1360, 1298, 1273, 1130, 909, 762, 731, 681 and 640; δ_H($CDCl_3$, 300 MHz) 7.95 (d, *J* 9.0, 2 H), 7.90 (d, *J* 9.0, 2 H), 7.55 (t, *J* 8.0, 2 H), 7.34 (t, *J* 5.0, 2 H), 3.93 (s, 2 H), 3.47 (t, *J* 6.0, 4 H), 3.11–2.99 (m, 4 H), 2.78–2.66 (m, 4 H), 1.99–1.85 (m, 8 H), 1.73–1.55 (m, 4 H) and 1.44–1.21 (m, 10 H); δ_C($CDCl_3$, 75.46 MHz) 158.32, 150.54, 147.42, 128.64, 128.01, 123.35, 122.68, 120.11, 115.71, 49.31, 33.95, 31.60, 29.23, 29.08, 26.72, 24.64, 22.92 and 22.66; *m/z* (ESI) 521 $[M + H]^+$ and 261 $[M + 2 H]^{2+}$ {Found (HRMS): *m/z* 521.3629. Calc. $[M + H]^+$ for $C_{35}H_{44}N_4$: 521.3644}.

9,9′-(Decane-1,10-diyldiimino)di-1,2,3,4-tetrahydroacridine 1d

A similar procedure to that described for the preparation of compound **1a** afforded the product as a yellow oil; ν_{max}($CDCl_3$)/cm^{-1} 3345, 3063, 2928, 2855, 2182, 1615, 1582, 1564, 1503, 1420, 1360, 1296, 1169, 1130, 941, 909, 762, 731 and 679; δ_H($CDCl_3$, 300 MHz) 7.96 (d, *J* 9.0, 2 H), 7.90 (d, *J* 9.0, 2 H), 7.55 (t, *J* 8.0, 2 H), 7.34 (t, *J* 5.0, 2 H), 3.93 (s, 2 H), 3.47 (t, *J* 8.0, 4 H), 3.11–2.99 (m, 4 H), 2.78–2.66 (m, 4 H), 1.99–1.85 (m, 8 H), 1.72–1.55 (m, 4 H) and 1.44–1.22 (m, 12 H); δ_C($CDCl_3$, 75.46 MHz) 158.34, 150.60, 147.44, 128.65, 128.06, 123.38, 122.73, 120.12, 115.71, 49.38, 33.97, 31.65, 29.28, 29.18, 26.78, 24.67, 22.95 and 22.70; *m/z* (ESI) 535 $[M + H]^+$ and 268 $[M + 2 H]^{2+}$ {Found (HRMS): *m/z* 535.3803. Calc. $[M + H]^+$ for $C_{36}H_{46}N_4$: 535.3800}.

4-Phenylbutyl toluene-4-sulfonate 12a[23]

Pyridine (10 ml) was added to toluene-*p*-sulfonyl chloride (1487 mg, 7.8 mmol) at room temperature under N_2. The colour of the solution changed immediately to yellow after addition. 4-Phenylbutan-1-ol (781 mg, 5.2 mmol) was added dropwise to the solution after which it was stirred at room temperature for 3 h. White precipitates were generated and the colour of the solution turned brownish. The tosylate was extracted with EtOAc and the solution was washed with saturated aqueous NH_4Cl. Work-up followed by flash chromatography on silica gel eluting with 10% EtOAc in hexane yielded the tosylate as a colourless oil (1.5 g, 95%); ν_{max}($CDCl_3$)/cm^{-1} 3061, 3028, 2945, 2861, 1923, 1807, 1659, 1599, 1495, 1454, 1360, 1308, 1292, 1177, 1098, 1018, 936 and 816; δ_H($CDCl_3$, 300 MHz) 7.78 (d, *J* 9.0, 2 H), 7.33 (d, *J* 6.0, 2 H), 7.28–7.24 (m, 2 H), 7.20–7.15 (m, 1 H), 7.10 (d, *J* 6.0, 2 H), 4.03 (t, *J* 6.0, 2 H), 2.56 (t, *J* 6.0, 2 H), 2.44 (s, 3 H) and 1.74–1.57 (m, 4 H); δ_C($CDCl_3$, 75.46 MHz) 144.51, 141.31, 132.81, 129.63, 128.09, 127.56, 125.64, 70.22, 34.78, 28.03, 26.81 and 21.34; *m/z* (EI) 304 (M^+), 178, 132, 117, 104 and 91 [Found (HRMS): *m/z* 304.1126. Calc. for $C_{17}H_{20}SO_3$: 304.1133].

5-Phenylpentyl toluene-4-sulfonate 12b[24]

A similar procedure to that described for the preparation of compound **12a** afforded the product as a colourless oil; ν_{max}($CDCl_3$)/cm^{-1} 3063, 3027, 2938, 2859, 1923, 1807, 1599, 1495, 1454, 1358, 1175, 1098, 1030, 947, 910, 814, 748, 700 and 664; δ_H($CDCl_3$, 300 MHz) 7.78 (d, *J* 9.0, 2 H), 7.33 (d, *J* 9.0, 2 H), 7.29–7.24 (m, 2 H), 7.20–7.17 (m, 1 H), 7.12 (d, *J* 6.0, 2 H), 4.01 (t, *J* 6.0, 2 H), 2.56 (t, *J* 8.0, 2 H), 2.44 (s, 3 H), 1.71–1.62 (m, 2 H), 1.59–1.51 (m, 2 H) and 1.39–1.31 (m, 2 H); δ_C($CDCl_3$, 75.46 MHz) 144.35, 141.78, 132.76, 129.51, 127.95, 127.90, 127.43, 126.98, 125.36, 70.17, 35.23, 30.31, 28.25, 24.57 and 21.17; *m/z* (EI) 318 (M^+), 146, 117, 104 and 91 [Found (HRMS): *m/z* 318.1275. Calc. for $C_{18}H_{22}SO_3$: 318.1290].

6-Phenylhexyl toluene-4-sulfonate 12c

A similar procedure to that described for the preparation of compound **12a** afforded the product as a colourless oil; ν_{max}($CDCl_3$)/cm^{-1} 3061, 3027, 2932, 2857, 2361, 2342, 1599, 1495, 1454, 1360, 1177, 1098, 959, 918, 816, 748, 700 and 665; δ_H($CDCl_3$, 300 MHz) 7.78 (d, *J* 9.0, 2 H), 7.34 (d, *J* 9.0, 2 H), 7.29–7.25 (m, 2 H), 7.19–7.13 (m, 3 H), 4.01 (t, *J* 6.0, 2 H), 2.56 (t, *J* 8.0, 2 H), 2.44 (s, 3 H), 1.65–1.54 (m, 4 H) and 1.36–1.23 (m, 4 H); δ_C($CDCl_3$, 75.46 MHz) 144.40, 142.15, 132.86, 129.55, 128.03, 127.95, 127.51, 125.35, 70.34, 35.42, 30.87, 28.39, 28.20, 24.88 and 21.26; *m/z* (EI) 332 (M^+), 160, 117, 104 and 91 [Found (HRMS): *m/z* 332.1425. Calc. for $C_{19}H_{24}SO_3$: 332.1446].

7-Phenylheptyl toluene-4-sulfonate 12d

A similar procedure to that described for the preparation of

compound **12a** afforded the product as a colourless oil; $\nu_{max}(CDCl_3)/cm^{-1}$ 3061, 3027, 2930, 2857, 1599, 1495, 1454, 1360, 1177, 1098, 1020, 961, 930, 816, 748, 700, 664, 575 and 556; $\delta_H(CDCl_3$, 300 MHz) 7.78 (d, *J* 9.0, 2 H), 7.33 (d, *J* 6.0, 2 H), 7.29–7.25 (m, 2 H), 7.19–7.14 (m, 3 H), 4.01 (t, *J* 6.0, 2 H), 2.57 (t, *J* 8.0, 2 H), 2.44 (s, 3 H), 1.65–1.52 (m, 4 H) and 1.39–1.21 (m, 6 H); $\delta_C(CDCl_3$, 75.46 MHz) 144.47, 142.43, 132.99, 129.62, 128.15, 128.03, 127.62, 125.41, 70.45, 35.64, 31.09, 28.77, 28.54, 25.04 and 21.37; *m/z* (EI) 346 (M^+), 174, 117, 104 and 91 [Found (HRMS): *m/z* 346.1595. Calc. for $C_{20}H_{26}SO_3$: 346.1603].

8-Phenyloctyl toluene-4-sulfonate 12e

A similar procedure to that described for the preparation of compound **12a** afforded the product as a colourless oil; $\nu_{max}(CDCl_3)/cm^{-1}$ 3061, 3027, 2926, 2855, 1923, 1807, 1655, 1599, 1495, 1454, 1358, 1306, 1292, 1177, 1098, 1030, 941, 814, 748, 700 and 664; $\delta_H(CDCl_3$, 300 MHz) 7.79 (d, *J* 9.0, 2 H), 7.33 (d, *J* 6.0, 2 H), 7.27–7.25 (m, 2 H), 7.19–7.15 (m, 3 H), 4.01 (t, *J* 6.0, 2 H), 2.58 (t, *J* 8.0, 2 H), 2.44 (s, 3 H), 1.64–1.55 (m, 4 H) and 1.35–1.20 (m, 8 H); $\delta_C(CDCl_3$, 75.46 MHz) 144.47, 142.55, 133.01, 129.64, 128.18, 128.04, 127.66, 125.41, 70.50, 35.73, 31.23, 29.04, 28.91, 28.60, 25.10 and 21.41; *m/z* (EI) 360 (M^+), 188, 117, 104 and 91 [Found (HRMS): *m/z* 360.1753. Calc. for $C_{21}H_{28}SO_3$: 360.1759].

9-Phenylnonyl toluene-4-sulfonate 12f

A similar procedure to that described for the preparation of compound **12a** afforded the product as a colourless oil; $\nu_{max}(CDCl_3)/cm^{-1}$ 3063, 3027, 2928, 2855, 1599, 1495, 1454, 1360, 1177, 953, 916, 816, 748, 700, 664, 577 and 556; $\delta_H(CDCl_3$, 300 MHz) 7.79 (d, *J* 9.0, 2 H), 7.34 (d, *J* 9.0, 2 H), 7.30–7.25 (m, 2 H), 7.19–7.16 (m, 3 H), 4.01 (t, *J* 6.0, 2 H), 2.59 (t, *J* 8.0, 2 H), 2.44 (s, 3 H), 1.65–1.57 (m, 4 H) and 1.35–1.17 (m, 10 H); $\delta_C(CDCl_3$, 75.46 MHz) 144.49, 142.68, 133.08, 129.68, 128.23, 128.09, 127.71, 125.44, 70.56, 35.81, 31.34, 29.15, 29.09, 28.75, 28.64, 25.16 and 21.47; *m/z* (EI) 374 (M^+), 202, 117, 104 and 91 [Found (HRMS): *m/z* 374.1899. Calc. for $C_{22}H_{30}SO_3$: 374.1916].

10-Phenyldecyl toluene-4-sulfonate 12g

A similar procedure to that described for the preparation of compound **12a** afforded the product as a colourless oil; $\nu_{max}(CDCl_3)/cm^{-1}$ 3061, 3027, 2926, 2855, 1921, 1805, 1653, 1599, 1495, 1454, 1360, 1306, 1292, 1177, 1098, 1020, 959, 928 and 816; $\delta_H(CDCl_3$, 300 MHz) 7.79 (d, *J* 9.0, 2 H), 3.34 (d, *J* 9.0, 2 H), 7.30–7.25 (m, 2 H), 7.18–7.16 (m, 3 H), 4.01 (t, *J* 6.0, 2 H), 2.59 (t, *J* 8.0, 2 H), 2.44 (s, 3 H), 1.65–1.57 (m, 4 H) and 1.28–1.21 (m, 12 H); $\delta_C(CDCl_3$, 75.46 MHz) 144.53, 142.79, 133.20, 129.71, 128.31, 128.14, 127.79, 125.47, 70.62, 35.89, 31.41, 29.33, 29.26, 29.20, 28.81, 28.73, 25.24 and 21.53; *m/z* (EI) 388 (M^+), 216, 117, 104 and 91 [Found (HRMS): *m/z* 388.2060. Calc. for $C_{23}H_{32}SO_3$: 388.2072].

(4-Phenylbutyl)(1,2,3,4-tetrahydroacridin-9-yl)amine 2a

A solution of THA (458 mg, 2.3 mmol) in THF (5 ml) was added to a suspension of $NaNH_2$ (180 mg, 4.6 mmol) in THF (2 ml) under N_2. The mixture was vigorously stirred at room temperature for 45 min after which a solution of compound **12a** (700 mg, 2.3 mmol) in THF (14 ml) was added to it. The resulting orange–red mixture was stirred at room temperature for 24 h and then extracted with EtOAc. The extract was washed with saturated aqueous Na_2CO_3 and work-up followed by flash chromatography on NH_3-saturated silica gel eluting with 30% EtOAc in hexane afforded the product as a yellow oil (509 mg, 67%); $\nu_{max}(CDCl_3)/cm^{-1}$ 3351, 3061, 3025, 2934, 2859, 1655, 1615, 1582, 1562, 1497, 1452, 1420, 1362, 1333, 1142, 943, 856, 762 and 700; $\delta_H(CDCl_3$, 300 MHz) 7.91 (t, *J* 9.0, 2 H), 7.55–7.52 (m, 1 H), 7.36–7.26 (m, 3 H), 7.21–7.14 (m, 3 H), 3.89 (s, 1 H), 3.49 (t, *J* 8.0, 2 H), 3.11–2.99 (m, 2 H), 2.70–2.56 (m, 4 H), 1.96–1.87 (m, 4 H) and 1.77–1.67 (m, 4 H); $\delta_C(CDCl_3$, 75.46 MHz) 158.34, 150.48, 147.42, 141.73, 128.68, 128.20, 128.06, 125.74, 123.43, 122.65, 120.17, 115.90, 49.13, 35.39, 33.97, 31.10, 28.53, 24.63, 22.90 and 22.66; *m/z* (ESI) 331 $[M + H]^+$ {Found (HRMS): *m/z* 331.2164. Calc. $[M + H]^+$ for $C_{23}H_{26}N_2$: 331.2174}.

(5-Phenylpentyl)(1,2,3,4-tetrahydroacridin-9-yl)amine 2b

A similar procedure to that described for the preparation of the preceding compound afforded the product as a yellow oil; $\nu_{max}(CDCl_3)/cm^{-1}$ 3347, 3061, 3025, 2932, 2857, 1615, 1603, 1562, 1497, 1452, 1420, 1358, 1298, 1125, 939, 909, 762 and 700; $\delta_H(CDCl_3$, 300 MHz) 7.91 (t, *J* 9.0, 2 H), 7.59–7.50 (m, 1 H), 7.36–7.25 (m, 3 H), 7.20–7.14 (m, 3 H), 3.90 (s, 1 H), 3.54–3.42 (m, 2 H), 3.10–2.98 (m, 2 H), 2.69–2.59 (m, 4 H), 1.93–1.90 (m, 4 H), 1.71–1.61 (m, 4 H) and 1.47–1.39 (m, 2 H); $\delta_C(CDCl_3$, 75.46 (MHz) 158.17, 150.32, 147.34, 141.92, 128.57, 128.06, 128.01, 127.87, 125.46, 123.23, 122.59, 120.00, 115.60, 49.06, 35.45, 33.89, 31.30, 30.78, 26.16, 24.48, 22.79 and 22.54; *m/z* (ESI) 345 $[M + H]^+$ {Found (HRMS): *m/z* 345.2326. Calc. $[M + H]^+$ for $C_{24}H_{28}N_2$: 345.2330}.

(6-Phenylhexyl)(1,2,3,4-tetrahydroacridin-9-yl)amine 2c

A similar procedure to that described for the preparation of compound **12a** afforded the product as a yellow oil; $\nu_{max}(CDCl_3)/cm^{-1}$ 3345, 3061, 3025, 2930, 2857, 1615, 1582, 1562, 1497, 1454, 1420, 1360, 1298, 1125, 941, 909, 762 and 698; $\delta_H(CDCl_3$, 300 MHz) 7.92 (dd, *J* 9.0, 15.0, 2 H), 7.60–7.50 (m, 1 H), 7.36–7.25 (m, 3 H), 7.20–7.15 (m, 3 H), 3.92 (s, 1 H), 3.49–3.45 (m, 2 H), 3.11–3.01 (m, 2 H), 2.77–2.65 (m, 2 H), 2.60 (t, *J* 8.0, 2 H), 1.96–1.90 (m, 4 H), 1.67–1.58 (m, 4 H) and 1.48–1.35 (m, 4 H); $\delta_C(CDCl_3$, 75.46 MHz) 158.33, 150.51, 147.47, 142.35, 128.71, 128.20, 128.11, 128.04, 125.52, 123.38, 122.69, 120.14, 115.74, 49.32, 35.66, 34.01, 31.55, 31.16, 28.81, 26.67, 24.66, 22.94 and 22.69; *m/z* (ESI) 359 $[M + H]^+$ {Found (HRMS): *m/z* 359.2485. Calc. $[M + H]^+$ for $C_{25}H_{30}N_2$: 359.2487}.

(7-Phenylheptyl)(1,2,3,4-tetrahydroacridin-9-yl)amine 2d

A similar procedure to that described for the preparation of compound **2a** afforded the product as a yellow oil; $\nu_{max}(CDCl_3)/cm^{-1}$ 3347, 3061, 3025, 2930, 2855, 1615, 1603, 1562, 1497, 1454, 1420, 1360, 1123, 1028, 943, 762 and 698; $\delta_H(CDCl_3$, 300 MHz) 7.92 (dd, *J* 9.0, 15.0, 2 H), 7.54 (t, *J* 8.0, 1 H), 7.36–7.19 (m, 3 H), 7.17–715 (m, 3 H), 3.92 (s, 1 H), 3.49–3.46 (m, 2 H), 3.11–2.99 (m, 2 H), 2.78–2.66 (m, 2 H), 2.59 (t, *J* 8.0, 2 H), 1.94–1.90 (m, 4 H), 1.67–1.58 (m, 4 H) and 1.41–1.33 (m, 6 H); $\delta_C(CDCl_3$, 75.46 MHz) 158.33, 150.54, 147.50, 142.51, 128.73, 128.21, 128.09, 125.47, 123.35, 122.71, 120.14, 115.71, 49.35, 35.75, 34.03, 31.62, 31.21, 29.09, 28.98, 26.72, 24.65, 22.95 and 22.70; *m/z* (ESI) 373 $[M + H]^+$ {Found (HRMS): *m/z* 373.2643. Calc. $[M + H]^+$ for $C_{26}H_{32}N_2$: 373.2644}.

(8-Phenyloctyl)(1,2,3,4-tetrahydroacridin-9-yl)amine 2e

A similar procedure to that described for the preparation of compound **12a** afforded the product as a yellow oil; $\nu_{max}(CDCl_3)/cm^{-1}$ 3354, 3061, 3025, 2928, 2855, 1615, 1582, 1562, 1497, 1454, 1420, 1358, 1296, 1273, 1121, 1028, 943, 909, 760 and 698; $\delta_H(CDCl_3$, 300 MHz) 7.92 (dd, *J* 9.0, 15, 2 H), 7.60–7.50 (m, 1 H), 7.36–7.24 (m, 3 H), 7.19–7.15 (m, 3 H), 3.92 (s, 1 H), 3.49–3.42 (m, 2 H), 3.06–3.04 (m, 2 H), 2.78–2.66 (m, 2 H), 2.59 (t, *J* 9.0, 2 H), 1.94–1.87 (m, 4 H), 1.67–1.58 (m, 4 H) and 1.40–1.31 (m, 8 H); $\delta_C(CDCl_3$, 75.46 MHz) 158.46, 150.68, 147.56, 142.73, 128.79, 128.32, 128.17, 125.53, 123.47, 122.80, 120.23, 115.83, 49.50, 35.89, 34.10, 31.74, 31.38, 29.32, 29.23, 29.12, 26.87, 24.75, 23.04 and 22.79; *m/z* (ESI) 387 $[M + H]^+$ {Found (HRMS): *m/z* 387.2789. Calc. $[M + H]^+$ for $C_{27}H_{34}N_2$: 387.2800}.

(9-Phenylnonyl)(1,2,3,4-tetrahydroacridin-9-yl)amine 2f

A similar procedure to that described for the preparation of compound **2a** afforded the product as a yellow oil; $\nu_{max}(CDCl_3)/$

cm^{-1} 3354, 3061, 3027, 2928, 2855, 2180, 1615, 1582, 1564, 1497, 1454, 1418, 1360, 1298, 1121, 941, 909, 760 and 698; $\delta_H(CDCl_3$, 300 MHz) 7.93 (dd, *J* 9.0, 18.0, 2 H), 7.60–7.49 (m, 1 H), 7.36–7.25 (m, 3 H), 7.19–7.16 (m, 3 H), 3.92 (s, 1 H), 3.49–3.45 (m, 2 H), 3.06–3.04 (m, 2 H), 2.76–2.65 (m, 2 H), 2.59 (t, *J* 8.0, 2 H), 1.94–1.90 (m, 4 H), 1.67–1.58 (m, 4 H) and 1.40–1.29 (m, 10 H); $\delta_C(CDCl_3$, 75.46 MHz) 158.18, 150.46, 147.38, 142.54, 128.59, 128.12, 127.95, 125.31, 123.23, 122.65, 120.03, 115.55, 49.25, 35.72, 33.91, 31.52, 31.24, 29.19, 29.14, 29.01, 26.67, 24.54, 22.84 and 22.59; *m/z* (ESI) 401 $[M + H]^+$ {Found (HRMS): *m/z* 401.2960. Calc. $[M + H]^+$ for $C_{28}H_{36}N_2$: 401.2956}.

(10-Phenyldecyl)(1,2,3,4-tetrahydroacridine-9-yl)amine 2g

A similar procedure to that described for the preparation of compound **2a** afforded the product as a yellow oil; $\nu_{max}(CDCl_3)$/cm^{-1} 3370, 3061, 3025, 2926, 2855, 1657, 1582, 1562, 1497, 1454, 1420, 1362, 1123, 762 and 698; $\delta_H(CDCl_3$, 300 MHz) 7.93 (dd, *J* 9.0, 18.0, 2 H), 7.60–7.50 (m, 1 H), 7.37–7.25 (m, 3 H), 7.19–7.14 (m, 3 H), 3.93 (s, 1 H), 3.54–3.42 (m, 2 H), 3.11–2.99 (m, 2 H), 2.76–2.66 (m, 2 H), 2.59 (t, *J* 8.0, 2 H), 1.94–1.90 (m, 4 H), 1.67–1.58 (m, 4 H) and 1.40–1.27 (m, 12 H); $\delta_C(CDCl_3$, 75.46 MHz) 158.42, 150.65, 147.55, 142.79, 128.77, 128.29, 128.12, 125.47, 123.43, 122.78, 120.20, 115.79, 49.48, 35.89, 34.08, 31.71, 31.41, 29.41, 29.37, 29.28, 29.23, 26.86, 24.73, 23.01 and 22.76; *m/z* (ESI) 415 $[M + H]^+$ {Found (HRMS): *m/z* 415.3119. Calc. $[M + H]^+$ for $C_{29}H_{38}N_2$: 415.3113}.

Acknowledgements

Support by the Mayo Foundation, the NSF/PSC (Y.-P. P.) and the NIH (W. S. B.) is gratefully acknowledged. We thank M. Stacy of the Mayo Foundation for the support of computing resources and L. M. Benson of the Mayo Foundation for the mass spectral analysis.

References

1 R. Tanzi, S. Gaston, A. Bush, D. Romano, W. Pettingell, J. Peppercorn, M. Paradis, S. Gurubhagavatula, B. Jenkins and W. Wasco, *Genetica*, 1993, **91**, 255.
2 D. J. Selkoe, *Neuron*, 1991, **6**, 487.
3 Z. S. Khachaturian, *Arch. Neurol.*, 1985, **42**, 1097.
4 K. L. Davis and P. Powchik, *Lancet*, 1995, **345**, 625.
5 Y.-P. Pang, P. Quiram, T. Jelacic, F. Hong and S. Brimijoin, *J. Biol. Chem.*, 1996, **271**, 23646.
6 Y.-P. Pang and A. P. Kozikowski, *J. Comput.-Aided Mol. Design.*, 1994, **8**, 669.
7 Y.-P. Pang and P. A. Kollman, *Perspectives of Drug Discovery and Design*, 1995, **3**, 106.
8 M. Harel, I. Schalk, L. Ehretsabatier, F. Bouet, M. Goeldner, C. Hirth, P. H. Axelsen, I. Silman and J. L. Sussman, *Proc. Natl. Acad. Sci. USA*, 1993, **90**, 9031.
9 A. Mutero, M. Pralavorio, J. M. Bride and D. Fournier, *Proc. Natl. Acad. Sci. USA*, 1994, **91**, 5922.
10 J. Patocka, J. Bajgar, J. Bielavsky and J. Fusek, *Collect. Czech., Chem. Commun.*, 1976, **41**, 816.
11 D. Galanakis, C. A. Davis, B. Del Rey Herrero, C. R. Ganellin, P. M. Dunn and D. H. Jenkinson, *J. Med. Chem.*, 1995, **38**, 595.
12 M. E. Nelson and E. X. Albuquerque, *Mol. Pharmacol.*, 1994, **46**, 151.
13 T. K. Chen, R. Fico and E. S. Canellakis, *J. Med. Chem.*, 1978, **21**, 868.
14 G. M. Shutske, G. M. Bores, K. C. Bradshaw, F. P. Huger, K. J. Kapples, R. D. Larsen, D. K. Rush and J. D. Tomer, *Bioorg. Med. Chem. Lett.*, 1992, **8**, 865.
15 J. C. Hogan and R. D. Gandour, *J. Org. Chem.*, 1992, **57**, 55.
16 A. H. Sommers and J. D. Barnes, *J. Am. Chem. Soc.*, 1957, **79**, 3491.
17 D. H. Busch, D. J. Olszanski, J. C. Stevens, W. P. Schammel, M. Kojima, N. Herron, L. L. Zimmer, K. A. Holter and J. Mocak, *J. Am. Chem. Soc.*, 1981, **103**, 1472.
18 A. J. Streitwieser, *J. Am. Chem. Soc.*, 1955, **7**, 195.
19 G. Wittig and J. E. Grolig, *Chem. Ber.*, 1961, **94**, 2148.
20 E. J. P. Fear, J. Thrower and J. Veitch, *J. Chem. Soc.*, 1958, 1322.
21 R. Gerdil, *Helv. Chem. Acta*, 1973, **56**, 1859.
22 G. B. Butler and R. J. Angelo, *J. Am. Chem. Soc.*, 1956, **78**, 4797.
23 K. V. Subbarao, N. P. Damodaran and S. Dev, *Tetrahedron*, 1987, **43**, 2543.
24 M. Julia and J.-C. Chottard, *Bull. Soc. Chem. Fr.*, 1968, 3691.

Paper 6/01642A
Received 8*th March* 1996
Accepted 2*nd September* 1996