Novel Tacrine Analogues for Potential Use against Alzheimer's Disease: Potent and Selective Acetylcholinesterase Inhibitors and 5-HT Uptake Inhibitors

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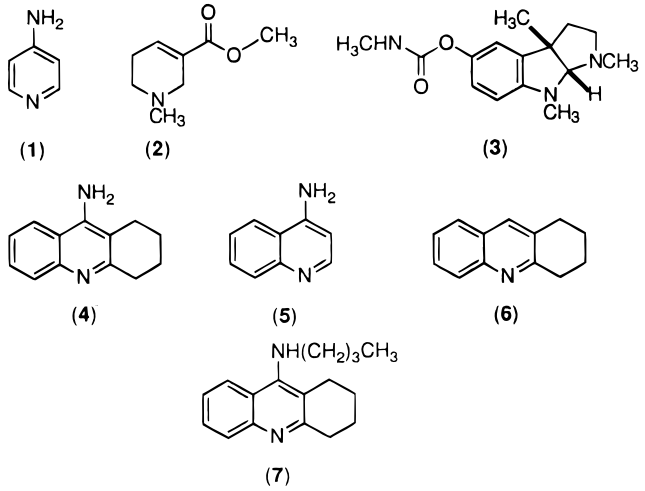
Several novel analogues of tacrine have been synthesized and tested for their ability to inhibit acetylcholinesterase, butyrylcholinesterase, and neuronal uptake of 5-HT (serotonin) and noradrenaline. Changes in the size of the carbocyclic ring of tacrine produced modest potency against cholinesterase enzymes. Addition of a fourth ring resulted in compounds with marked selectivity for acetylcholinesterase (AChE) over butyrylcholinesterase (BChE): *e.g.* 6-amino-4,5-benzo-5*H*-cyclopenta[1,2-*b*]-quinoline (**14a**) had an IC_{50} of 0.35 μM against AChE and 3.1 μM against BChE. Some tetracyclic compounds are 100−400 times more active than tacrine as inhibitors of neuronal uptake of serotonin, in particular 13-amino-6,7-dihydro-5*H*-benzo-[3,4]cyclohepta[1,2-*b*]quinoline (**18**), which had an IC_{50} of 20 nM. These compounds would be expected to facilitate both cholinergic and monoaminergic transmission. They should be worth investigating in models of memory impairment.

Introduction

Dementia is the most common psychiatric disorder of old age, and Alzheimer's disease[1] is its most common cause. Alzheimer's disease involves the degeneration of cholinergic neurones in the cerebral cortex and hippocampus, areas of the brain particularly associated with memory, higher intellectual functioning, and consciousness.[2] The biochemical deficits also extend into other neurochemical systems, affecting the levels of monoamine transmitters for example,[3] but the most profound and consistent loss is that of cholinergic transmission. Consequently, much research concerns enhancing the cholinergic system in some way,[4] ranging from the use of acetylcholine-releasing agents such as 4-aminopyridine[5] (**1**); the acetylcholine precursor, choline[6]; cholinergic agonists, *e.g.* arecoline (**2**); and anticholinesterase drugs, *e.g.* physostigmine (**3**). However, one drug in particular has become the subject of intense pharmacological scrutiny for its efficacy in alleviating the symptoms of Alzheimer's disease, namely 9-amino-1,2,3,4-tetrahydroacridine, commonly referred to as tacrine[7] (**4**).

Tacrine (**4**)[8] was found to be a potent acetylcholinesterase inhibitor[9,10] in 1953 and, subsequently, an even stronger inhibitor of the butyrylcholinesterase family of enzymes.[11] More recently, tacrine has been shown to possess a much broader pharmacological profile than cholinesterase inhibition: blockage of potassium channels,[12] inhibition of the neuronal monoamine uptake processes,[13] and inhibition of monamine oxidase[14] have all been reported. Since tacrine has been used to alleviate the symptoms of Alzheimer's disease with greater apparent success than other anticholinesterase drugs tried earlier, tacrine's heightened efficacy could be related to these other pharmacological actions.[15]

The aim of this study was to produce novel tacrine analogues for pharmacological evaluation against cholinesterase activity and monoamine uptake processes and to elucidate criteria for designing more active molecules for future testing. A more active and more selective inhibitor of acetylcholinesterase activity than tacrine that also had more potent ability to block neuronal reuptake of 5-hydroxytryptamine (5-HT, serotonin) and noradrenaline would be of interest as a potential treatment to alleviate the symptoms of Alzheimer's disease. Inhibition of acetylcholinesterase would potentiate the remaining cholinergic transmission in affected brain regions, while block of monoamine uptake would potentiate transmission in pathways involving 5-HT and noradrenaline, which are also known to be affected in Alzheimer's disease.[3]



From previously published work on tacrine analogues, there is little information about structure−activity relationships for inhibition of monoamine uptake processes, but there has been some work on inhibition of cholinesterase activity. Our starting point, then, was the study by Kaul,[14a] who had compared the anticholinesterase activities of 4-aminopyridine (**1**), 4-aminoquinoline (**5**), tetrahydroacridine (**6**), and 9-(*N*-*n*-butylamino)-1,2,3,4-tetrahydroacridine (**7**). His results showed that 4-aminopyridine (**1**) and 4-aminoquinoline

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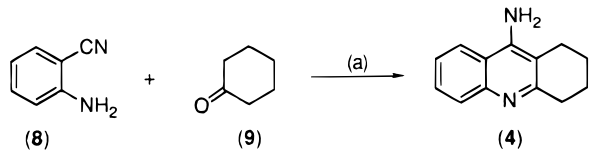
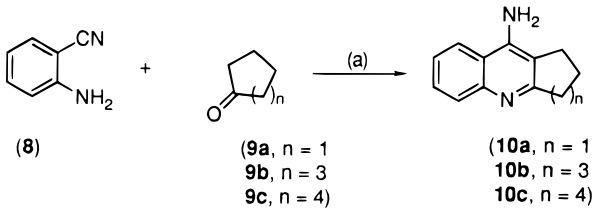
Scheme 1[a]



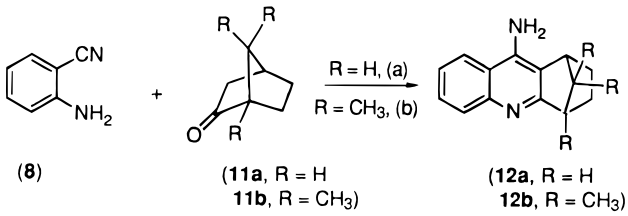
[a] (a) $BF_3 \cdot Et_2O$.

Scheme 2[a]



[a] (a) $BF_3 \cdot Et_2O$.

Scheme 3[a]



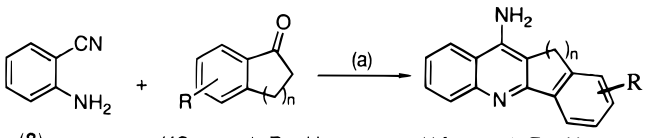
[a] (a) $BF_3 \cdot Et_2O$; (b) molecular seives 5 Å, $BF_3 \cdot Et_2O$.

(**5**) had only a very weak anticholinesterase activity although their basicities were almost equal to that of tacrine. The *N*-butyl derivative (**7**) was not particularly active, with the butyl chain hindering the interaction of the compound with the enzyme, but tetrahydroacridine (**6**), a much weaker base, was found to be almost as active as tacrine itself. These results indicate that the cyclohexyl ring is important for anticholinesterase activity. Subsequent examination of the X-ray crystal structure of tacrine with acetylcholinesterase[16] revealed that the 4-aminoquinoline portion of the tacrine molecule seemed to be responsible for the binding of the drug to the enzyme, while the cyclohexyl ring acted mostly as a block to the substrate at the active site. Hence, the series of compounds devised for synthesis during this study was designed to investigate the effects on anticholinesterase activity of changing the cyclohexyl ring, *i.e.* by altering the ring size, bridging the ring, fusing a benzene ring to the equivalent of the cyclohexyl ring, and introducing heteroatoms and various substituents. These investigations were considered necessary because previous research had provided only sparse and fragmentary information on compounds with structural changes specific to only the cyclohexyl ring, and because conventional substitutions of the aromatic ring and at the amino nitrogen had proven relatively fruitless. In addition, these structural changes were investigated for their effects on inhibition of neuronal uptake of 5-HT and noradrenaline.

Chemistry

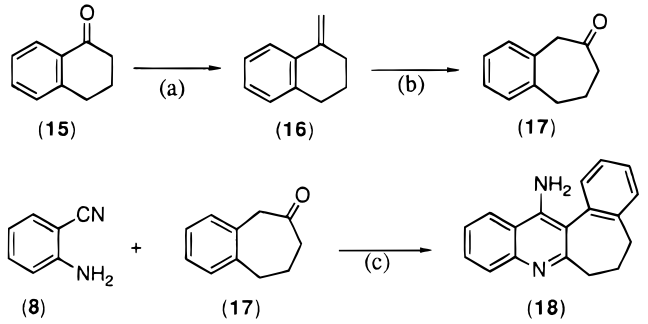
The Lewis acid mediated cyclodehydration reaction between anthranilonitrile (**8**) and cyclohexanone (**9**) which gave tacrine (**4**)[17] (Scheme 1) was adapted to produce the following ranges of compounds by substituting cyclohexanone (**9**) with the appropriate cyclic

Scheme 4[a]



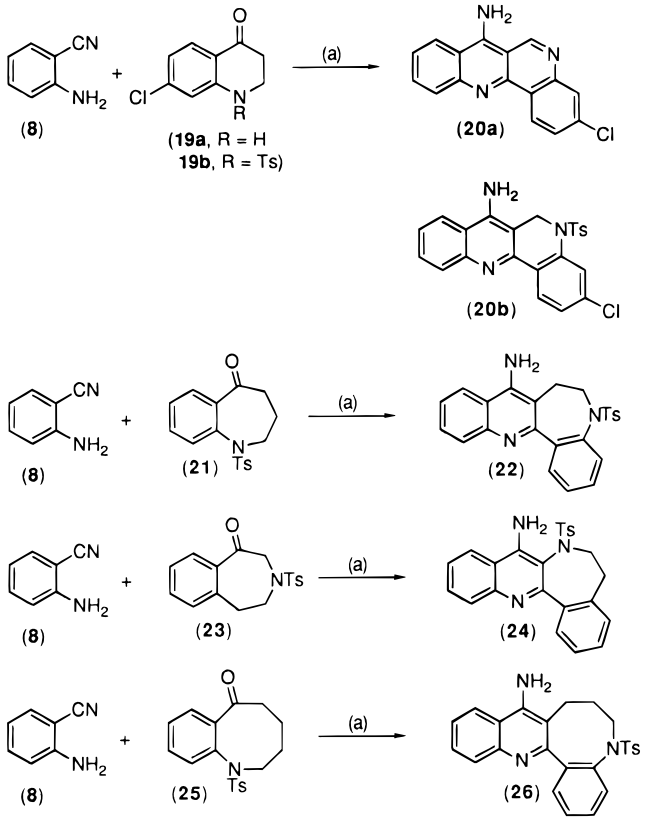
[a] (a) $BF_3 \cdot Et_2O$.

Scheme 5[a]



[a] (a) PhP_3CH_2I, THF; (b) $AgNO_3$, I_2, MeOH, H_2O; (c) $BF_3 \cdot Et_2O$.

Scheme 6[a]

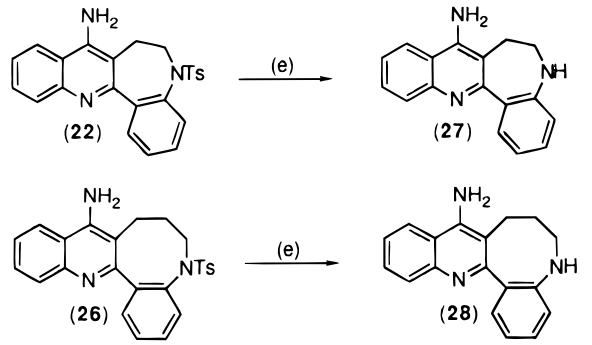


[a] (a) $BF_3 \cdot Et_2O$.

ketones (Schemes 2−6). After experimentation with various Lewis acids, the reagent of choice became boron trifluoride diethyl etherate.

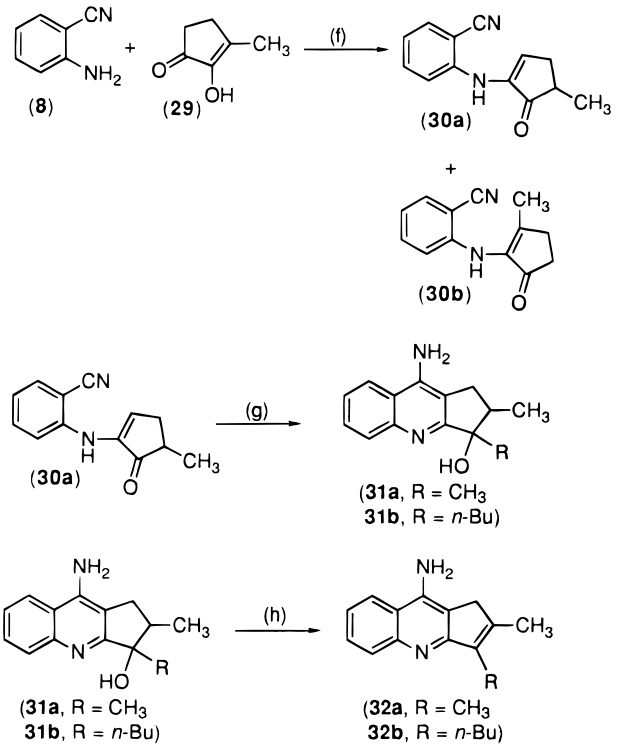
6-Benzosuberone (**17**) was synthesized by the ring expansion of 1,2,3,4-tetrahydro-1-methylenenaphthalene (**16**) in a method using silver nitrate and iodine in aqueous methanol devised by Proctor *et al.*[18] 1,2,3,4-Tetrahydro-1-methylenenaphthalene (**16**) was itself syn-

Scheme 7[a]



[a] (e) Sodium naphthalenide, DME.

Scheme 8[a]



[a] (f) TsOH, toluene; (g) RLi, THF; R = Me, *n*-Bu; (h) H_2SO_4 (aq).

thesized by the Wittig methylenation of 1-tetralone[19] (**15**) (Scheme 5).

Compounds **22** and **26** were detosylated[20] to their corresponding secondary amines (Scheme 7).

Using a different chemical route (Scheme 8), the ketone 2-hydroxy-3-methylcyclopent-2-enone (cyclotene)[21] (**29**) was successfully condensed with anthranilonitrile (**8**) to produce the enamine intermediate *N*-(4-methyl-5-oxocyclopenten-1-yl)-1-aminobenzonitrile (**30a**) which was separated from its minor isomer (**30b**) by column chromatography. Reaction of **30a** with 2 equiv of an organolithium reagent (methyllithium, *n*-butyllithium) produced a nucleophilic attack on the carbonyl group with a comcomitant cyclization to produce 9-amino-2,3-dihydro-2-methyl-1*H*-cyclopenta[1,2-*b*]quinolines (**31a** and **31b**) of undetermined stereochemistry. Subsequent dehydration of these tertiary alcohols **31a** and **31b** produced the corresponding alkenes **32a** and **32b**.

Results and Discussion

Four different pharmacological actions of the novel tacrine analogues were determined: acetyl- and butyrylcholinesterase inhibition and inhibition of neuronal uptake of 5-HT (serotonin) and noradrenaline. The results are summarized in Tables 1 and 2.

Table 1. Anticholinesterase Activity of Tacrine Analogues

	IC_{50} (μM ± SEM, n = 5)	
compd	AChE	BChE
4	0.078 ± 0.001	0.025 ± 0.002
10a	0.056 ± 0.004	0.052 ± 0.008
10b	0.039 ± 0.008	0.014 ± 0.002
10c	9.1 ± 0.6	2.3 ± 0.08
12a	0.24 ± 0.03	0.041 ± 0.005
12b	110.0 ± 5.3	88.0 ± 10
14a	0.35 ± 0.06	3.1 ± 0.4
14b	37.4 ± 2.9	3.3 ± 0.06
14c	47.5 ± 2.3	no block[a]
14d	144.1 ± 7.3	10.3 ± 0.7
14e	166.1 ± 74.3	36.0 ± 9.0
14f	68.8 ± 4.2	>100 μM
18	38.2 ± 8.1	26.4 ± 0.44
20a	no block[a]	no block[a]
27	69.4 ± 3.6	18.9 ± 2.6
28	391.1 ± 51.3	6.7 ± 0.64
31a	134.0 ± 0.4	12.2 ± 0.6
31b	91.0 ± 26.0	81.0 ± 3.8
32a	3.5 ± 0.4	5.9 ± 0.5
32b	25.0 ± 1.3	42.0 ± 2.8

[a] No significant block when tested at 100 μM.

Table 2. Inhibition of 5-Hydroxytryptamine and Noradrenaline Uptake by Tacrine Analogues

	IC_{50} (μM)[a]	
compd	5-HT uptake	noradrenaline uptake
4	7.6 ± 0.6	7.9 ± 0.7
10a	21.0 ± 1.9	0.6 ± 0.2
10b	3.6 ± 0.7	6.9 ± 0.8
10c	1.1 ± 0.3	0.8 ± 0.2
12a	0.2 ± 0.05	6.1 ± 0.4
12b	13.0 ± 2.9	nd
14a	2.2 ± 1.1	2.3 ± 1.0
14b	4.6 ± 0.6	12.1 ± 1.6
14c	5.8 ± 0.7	1.4 ± 0.1
14d	14.3 ± 1.8	41.04 ± 2.4
14e	4.7 ± 0.5	1.8 ± 0.3
14f	0.7 ± 0.3	3.6 ± 0.4
18	0.02 ± 0.001	nd
20a	>95 μM	0.2 ± 0.02
27	4.2 ± 0.7	3.0 ± 0.8
28	6.9 ± 0.8	2.5 ± 0.2
31a	4.4 ± 0.4	nd
31b	7.1 ± 1.0	12.0 ± 1.4
32a	5.1 ± 0.6	nd
32b	13.0 ± 0.8	nd
fluoxetine	0.13 ± 0.03	nd
desipramine	nd	1.7 ± 0.3

[a] ±95% confidence limits; nd = not determined.

Tacrine (**4**) is about three times more active at inhibiting butyrylcholinesterase than acetylcholinesterase (Table 1). Changing the size of the carbocyclic ring revealed that increasing from a cyclopentyl (compound **10a**) to a cycloheptyl (compound **10b**) ring increased the potency against butyrylcholinesterase activity significantly (almost 4-fold), although there was a smaller increase in potency against acetylcholinesterase activity (2-fold). However, the cyclooctyl derivative (compound **10c**) showed a 100-fold reduction in anticholinesterase activity, possibly due to the increase in bulk and flexibility of the carbocyclic ring.

Insertion of a methylene bridge across the cyclohexyl ring of tacrine (compound **12a**) produced a loss in anticholinesterase activity that was markedly enhanced

with increasing substituent bulk upon the bridge by three methyl groups (compound **12b**).

Fusing a benzene ring to the alicyclic ring to give compounds **14a**−**f** resulted in compounds with very much reduced activity in the cholinesterase assays compared to tacrine (**4**). However, the compound **14a** derived from indanone was highly selective for acetylcholinesterase, rather than butyrylcholinesterase, in contrast to tacrine (Table 1). Other tetracyclic compounds (**18**, **20a**, **27**, **28**) and their tosylated forms (**20b, 22, 24, 26**) had much weaker cholinesterase blocking activity than that of tacrine (data not shown). Compound **28** was about 50 times more effective against butyrylcholinesterase than against acetylcholinesterase.

Compounds **31a** and **31b** had much less activity against both cholinesterases in comparison with the unsubstituted 9-amino-2,3-dihydro-1*H*-cyclopenta[*b*]-quinoline (**10a**). The corresponding dehydrated products, compounds (**32a**, **32b**), were more active than **31a** and **31b** but still weaker than **10c**.

With respect to monoamine uptake, tacrine (**4**) has a relatively weak inhibitor of both 5-HT and noradrenaline uptake (Table 2). Decreasing the size of the carbocyclic ring (**10a**) resulted in a 3-fold loss of potency, compared with tacrine, against 5-HT uptake, but a 10 times increase in potency against noradrenaline uptake. Increasing the ring size from that of tacrine caused about a 10-fold increase in potency against the two uptake processes (compounds **10b** and **10c**).

Changing the bulk around the cycohexyl ring of tacrine by inserting a methylene bridge resulted in a more potent and more selective inhibitor of 5-HT uptake than tacrine (see compounf **12a**, Table 2). Addition of methyl substituents to the methylene bridge resulted in a marked loss of activity (in compound **12b**).

Fusing a benzene ring to the carbocyclic ring gave compounds **14a**−**f** that were generally more active than tacrine as uptake inhibitors (Table 2). **14f**, with a 3-methoxy substituent on a seven-membered carbocyclic ring, was 10 times more potent than tacrine on 5-HT uptake and twice as active as tacrine on noradrenaline uptake. When a benzene ring was fused at the 3,4-position rather than the 6,7-position of the cycloheptyl ring (compound **18**), the activity against 5-HT uptake was dramatically enhanced: 400 times more active than tacrine (**4**) and 200 times more active than compound **14e**. For reference, the IC_{50} of the standard compound fluoxetine for 5-HT uptake was similar to that of compound **12a** and 6 times greater than that of compound **18** (Table 2).

Compounds containing nitrogen within the carbocyclic ring (compounds **20a**, **27**, **28**) tended to have reduced activity against 5-HT uptake, compared with tacrine (**4**) (Table 2). However, compound **20a**, a fully aromatic dibenzonaphthyridine, demonstrated a potent and selective block of noradrenaline uptake. The tosylated compounds (**20b, 22, 24, 26**) were inactive.

To summarize, systematic ranges of compounds have been designed, synthesized, and subjected to pharmacological evaluation. Several criteria have been established for the further design of tacrine analogues for potential use against Alzheimer's disease: *i.e.* avoidance of (a) bridging across the cyclohexyl ring, (b) insertion of a nitrogen heteroatom into the carbocyclic ring, (c) carbocyclic ring greater than seven-membered, and (d) fusion of a benzene ring. However, the biological results indicate that certain structures, derived from **12a, 14a**, and **18**, could be useful templates for further work in this area. Compared with tacrine (**4**), 6-amino-4,5-benzo-5*H*-cyclopenta[1,2-*b*]quinoline (**14a**) is 30 times more selective for acetylcholinesterase over butyrylcholinesterase, and it is also a 3-fold more potent inhibitor of 5-HT and noradrenaline uptake than is tacrine. 8-Amino-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]quinoline (**14e**), its methoxy analogue (**14f**), and particularly its structural isomer 13-amino-6,7-dihydro-5*H*-benzo-[3,4]cyclohepta[1,2-*b*]quinoline (**18**) all gave potent aminergic uptake inhibition. Given that Alzheimer's disease involves a loss of cholinergic and aminergic transmission, the availability of compounds with potent effects on acetylcholinesterase and monoamine uptake processes could be an exciting prospect, and they deserve to be tested in models of memory impairment.

Experimental Section

Melting points were obtained on a Gallenkamp melting point apparatus in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a Perkin-Elmer R32 spectrometer operating at 90 MHz, on a Bruker WM250 spectrometer operating at 250.13 MHz, and on a Bruker AMX400 spectrometer operating at 400.13 MHz, with the WM250 and the AMX400 in Fourier Transform mode. *J* values are given in hertz. Infrared spectra were recorded on a Unicam Mattson 1000 series FTIR spectrometer as thin films, as Nujol mulls, or in solution cells. Flash column chromatography was carried out using CAMLAB Art. Nr 81538 MN Kieselgel 60 (0.040−0.063 mm) and Merck 7735 silica gel type 60 (0.125−0.250 mm). Samples were applied in solution or adsorbed onto silica. Mass spectra were obtained on a AEIMST double-focusing mass spectrometer, modified with a solid state console using a GEC 905 computer based data system. Carbon, hydrogen, and nitrogen analyses were determined on a Carlo Erba 1106 analyzer using a technique based on the classical Pregl Dumas method. Halogens were determined by combusting the sample in an oxygen flask containing hydrogen peroxide and potassium hydroxide and titrating an alcoholic solution of the products with mercuric nitrate using diphenylcarbazone as indicator (Mercurimetric method). Sulfur was determined by combusting the sample in an oxygen flask containing hydrogen peroxide and water and titrating an alcoholic solution of the products with barium perchlorate using the mixed indicator THORON and methylene blue. Toluene was dried over sodium; THF was predried with anhydrous sodium sulfate and distilled over calcium hydride or sodium benzophenone ketyl. All solutions were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate and filtered. Thin layer chromatography was carried out on plastic sheets pre-coated with 0.25 mm silica gel containing fluorescent indicator UV_{254}, or with 0.2 mm aluminum oxide also with fluorescent indicator UV_{254}, both supplied by CAMLAB. Elemental analyses are indicated only by the symbol of the elements; analytical results were within 0.4% of the theoretical values unless otherwise noted.

General Method for the Cyclodehydration Reaction. Anthranilonitrile (**8**), ketone (1.1 equiv) and sodium-dried toluene (120 mL) were placed in a three-necked round-bottomed flask fitted with an overhead stirrer. Boron trifluoride diethyl etherate (1.1 equiv) was added slowly *via* syringe, and the reaction mixture was heated at reflux for 24 h. On cooling, the toluene was decanted and, to liberate the product, the remaining solids were treated with sodium hydroxide (2 M, 120 mL) and heated at reflux for 24 h. After cooling, the organic components were extracted with chloroform, the organic layers were combined and dried, and the solvent was evaporated *in vacuo* to give the desired product. Maleate salts were prepared by refluxing a solution of the free base with 1 equiv of maleic acid.

9-Amino-1,2,3,4-tetrahydroacridine (4). Recrystallized: mp 178−180 °C (aqueous EtOH) [lit.[22] mp 178−179 °C]; M^+, 198.1144; ^{1}H NMR ($CDCl_3$) δ 1.86−1.95 (4H, m, 2CH_2), 2.57 (2H, t, J = 6.2, CH_2), 3.01 (2H, t, J = 5.5, CH_2), 4.68 (2H, br s, exchanges with D_2O, NH_2), 7.33 (1H, td, J = 8.2, 1.2, aryl-H), 7.54 (1H, td, J = 6.8, 1.3, aryl-H), 7.67 (1H, dd, J = 8.4, 0.8, aryl-H), 7.88 (1H, d, J = 8.4, aryl-H). Maleate salt: mp 50−55 °C. Anal. ($C_{13}H_{14}N_2$) C, H, N.

9-Amino-2,3-dihydro-1*H*-cyclopenta[1,2-*b*]quinoline (10a). Anthranilonitrile (**8**) (5.0 g, 42.3 mmol), cyclopentanone (**9a**) (4.1 g, 46.7 mmol), boron trifluoride diethyl etherate (1 M, 10 mL, 81.8 mmol) gave the title compound (**10a**) (3.2 g, 41% crude). Recrystallized: mp 180−182 °C (aqueous EtOH); ^{1}H NMR ($CDCl_3$) δ 2.19 (2H, quintet, J = 7.6, CH_2), 2.88 (2H, t, J = 7.5, CH_2), 3.10 (2H, t, J =7.8, CH_2), 4.65 (2H br s, exchanges with D_2O, NH_2), 7.33 (1H, t, J = 8.05, aryl-H), 7.57 (1H, t, J = 8.11, aryl-H), 7.71 (1H, d, J = 8.3, aryl-H), 7.89 (1H, d, J = 8.4, aryl-H). Anal. ($C_{12}H_{12}N_2$) C, H, N. Maleate salt mp: 100−105 °C; ^{1}H NMR (CD_3OD) δ 2.34 (2H, quintet, J = 7.8, CH_2), 2.97 (2H, t, J = 7.1, CH_2), 3.23 (2H, t, J = 7.8, CH_2), 6.23 (2H, s, maleate), 7.61 (1H, td, J = 6.9, 1.3, aryl-H), 7.35 (1H, d, J = 8.5, aryl-H), 7.86 (1H, td, J = 6.9, 1.2, aryl-H), 8.23 (1H, dd, J = 8.5, 0.7, aryl-H). Anal. ($C_{12}H_{12}N_2$) C, H, N.

11-Amino-2,3,4,5-tetrahydro-1*H*-cyclohepta[1,2-*b*]quinoline (10b). Anthranilonitrile (**8**) (10.0 g, 84.7 mmol), cycloheptanone (**9b**) (11.4 g, 101.8 mmol) and boron trifluoride diethyl etherate (1 M, 12.5 mL, 102.3 mmol) gave the title compound (**10b**) (10.9 g, 61% crude). Recrystallized: mp 167−171 °C (EtOH) (lit.[23] mp 178 °C); ^{1}H NMR ($CDCl_3$) δ 1.64−1.92 (6H, m, 3CH_2), 2.74 (2H, m, CH_2), 3.13 (2H, m, CH_2), 4.68 (2H, br s, exchanges with D_2O, NH_2), 7.39 (1H, td, J = 7.00, 1.22, aryl-H), 7.56 (1H, td, J = 6.89, 1.31, aryl-H), 7.68 (1H, dd, J = 8.31, 0.74, aryl-H), 7.91 (1H, d, J = 8.41, 0.61, aryl-H). Anal. ($C_{14}H_{16}N_2$) C, H, N. Maleate salt: mp 161−163 °C; ^{1}H NMR (CD_3OD) δ 1.65−1.96 (6H, m, 3CH_2), 2.91 (2H, m, CH_2), 3.13 (2H, m, CH_2), 6.25 (2H, s, maleate), 7.61(1H, td, J = 6.8, 1.4, aryl-H), 7.75 (1H, d, J =8.4, 0.5, aryl-H), 7.85 (1H, td, J = 6.7, 1.2, aryl-H), 8.28 (1H, dd, J = 8.5, 0.5, aryl-H). Anal. ($C_{14}H_{16}N_2{\cdot}C_4H_4O_4$) C, H, N.

12-Amino-1,2,3,4,5,6-hexahydrocycloocta[1,2-*b*]quinoline (10c). Anthranilonitrile (**8**) (5.0 g, 42.3 mmol), cyclooctanone (**9c**) (6.1 mL, 46.7 mmol), and boron trifluoride diethyl etherate (1 M, 5.6 mL, 46.7 mmol) gave the title compound (**10c**) (7.4 g, 78% crude). Recrystallized: mp 198−200 °C (EtOH) (lit.[24] mp 198−200 °C); ^{1}H NMR ($CDCl_3$) δ 1.20−1.55 (4H, m, 2CH_2), 1.60−1.95 (4H, m, 2CH_2), 2.87 (2H, m, CH_2), 3.10 (2H, m, CH_2), 4.70 (2H, br s, exchanges with D_2O, NH_2), 7.39 (1H, td, J = 6.8, 1.3, aryl-H), 7.57 (1H, td, J = 8.3, 1.4, aryl-H), 7.70 (1H, dd, J = 8.3, 0.7, aryl-H), 7.95 (1H, dd, J = 8.4, 0.6, aryl-H). Anal. ($C_{15}H_{18}N_2$) C, H, N. Maleate salt: mp 168−170 °C; ^{1}H NMR (CD_3OD) δ 1.35−1.56 (4H, m, 2CH_2), 1.57−1.95 (4H, m, 2CH_2), 2.9−3.0 (2H, m, CH_2), 3.05−3.15 (2H, m, 2CH_2), 6.24 (2H, s, maleate), 7.62 (1H, t, J = 8.1, aryl-H), 7.76 (1H, d, J = 7.8, aryl-H), 7.83 (1H, t, J = 6.7, aryl-H), 8.31 (1H, d, J = 8.4, aryl-H). Anal. ($C_{15}H_{18}N_2{\cdot}C_4H_4O_4$) C, H, N.

9-Amino-1,4-methano-1,2,3,4-tetrahydroacridine (12a). Anthranilonitrile (**8**) (5.0 g, 42.3 mmol), norcamphor (**11a**) (5.0 g, 45.5 mmol) and boron trifluoride diethyl etherate (1 M, 5.1 mL, 41.7 mmol) gave the title compound (**12a**, 2.5 g, 29% crude). Recrystallized: mp 186−187 °C (EtOH) (lit[25] mp 186−188 °C) M^+, 210.1158; ^{1}H NMR ($CDCl_3$) δ 1.31−1.36 (1H, m, CH_2), 1.42−1.46 (1H, m, CH_2), 1.66 (1H, dt, J = 9.04, 1.52, CH_2), 1.87−1.90 (1H, m, CH_2), 1.96−2.08 (2H, m, CH_2), 3.49 (2H, d, J = 11.44, CH_2), 4.54 (2H, br s, exchanges with D_2O, NH_2), 7.39 (1H, t, J = 7.00, aryl-H), 7.57 (1H, t, J = 6.96, aryl-H), 7.71 (1H, d, J = 8.32, aryl-H), 7.96 (1H, d, J = 8.44, aryl-H).

9-Amino-1,4-methano-1,2,3,4-tetrahydro-4,11,11-trimethylacridine (12b). Anthranilonitrile (**8**) (5.0 g, 42.3 mmol) and (*R*)-(+)-camphor (**11b**) (7.0 g, 46.7 mmol) were placed in toluene (70 mL). Molecular sieves 5 Å (50 g) were added and the reaction was heated at reflux for 1 h. On cooling, the mixture was filtered, boron trifluoride diethyl etherate (1 M, 7.7 mL, 63.0 mmol) was added, and the reaction mixture was heated at reflux for 24 h. The toluene was decanted, and the remaining solids were heated at reflux with sodium hydroxide (2 M, 100 mL) for 24 h. On cooling, the organic components were extracted with chloroform, the extracts were combined and dried, and the solvent was evaporated *in vacuo* to give a golden oil. On trituration with petroleum ether (60−80 °C) this gave a white precipitate which was removed by filtration to give the title compound (**12b**) (0.4 g, 3.8%): mp 150−154 °C; M^+, 252.1631; ^{1}H NMR ($CDCl_3$) δ 0.63 (3H, s, CH_3), 0.83−1.43 (8H, m, 2CH_3, 2H), 1.90 (1H, td, J = 9.66, 2.99), 2.07−2.17 (1H, m), 2.91 (1H, d, J = 3.81), 4.43 (2H, br s, exchanges with D_2O, NH_2), 7.39 (1H, td, J = 6.88, 1.27, aryl-H), 7.56 (1H, td, J = 6.91, 1.46, aryl-H), 7.71 (1H, dd, J = 8.23, 1.32, aryl-H), 8.02 (1H, dd, J = 8.39, 1.13, aryl-H). Anal. ($C_{17}H_{20}N_2$) C, H, N.

6-Amino-4,5-benzo-5*H*-cyclopenta[1,2-*b*]quinoline (14a). Anthranilonitrile (**8**) (4.6 g, 38.9 mmol), indan-1-one (**13a**) (5.6 g, 42.4 mmol), and boron trifluoride diethyl etherate (1 M, 5.3 mL, 43.3 mmol) gave the title compound (**14a**) (0.25 g, 2.6% crude). Recrystallized: mp 239−240 °C dec (EtOH); M^+ 232.1006; ^{1}H NMR (CD_3OD) δ 3.78 (2H, s, CH_2), 7.20−7.69 (5H, m, aryl-H), 7.94 (1H, d, J = 8.5, aryl-H), 8.03 (1H, d, J = 8.4, aryl-H), 8.10−8.25 (1H, m, aryl-H). Anal. ($C_{17}H_{20}N_2$) C, H, N. Maleate salt: mp 212−214 °C; ^{1}H NMR (DMSO-d_6) δ 3.91 (2H, s, CH_2), 2.60−4.70 (2H, br s, exchanges with D_2O, NH_2), 6.06 (2H, s, maleate), 7.50−8.00 (6H, m, aryl-H), 8.18 (1H, d, J = 7.2, aryl-H), 8.43 (1H, d, J = 8.4, aryl-H), 8.71 (2H, br s, exchanges with D_2O, maleate). Anal. ($C_{17}H_{20}N_2{\cdot}C_4H_4O_4$) C, H, N.

11-Amino-1,2-dihydrobenz[*c*]acridine (14b). Anthranilonitrile (**8**) (2.0 g, 16.9 mmol), 1-tetralone (3,4-dihydro-2*H*-naphthalen-1-one) (**13b**) (2.7 g, 18.5 mmol), and boron trifluoride diethyl etherate (1 M, 2.3 mL, 18.8 mmol) were treated according to the general procedure to give the title compound (**14b**) (3.75 g, 90% crude). Recrystallized: mp 138−140 °C (EtOH); M^+, 246.1159; ^{1}H NMR ($CDCl_3$) δ 2.6−3.1 (4H, m, 2CH_2), 4.55 (2H, br s, exchanges with D_2O, NH_2), 7.10−7.80 (6H, m, aryl-H), 8.00−8.20 (1H, m, aryl-H), 8.5−8.7 (1H, m, aryl-H). Anal. ($C_{17}H_{14}N_2$) C, H, N. Maleate salt: mp 207−209 °C; δ_H(250 MHz, CD_3OD) 2.7−3.2 (4H, m, CH_2), 6.22 (2H, s, maleate), 7.3−7.7 (4H, m, aryl-H), 7.87 (1H, t, J = 7.3, aryl-H), 7.95−8.2 (2H, m, aryl-H), 8.35 (1H, d, J = 7.6, aryl-H). Anal. ($C_{17}H_{14}N_2{\cdot}C_4H_4O_4$) C, H, N.

11-Amino-1,2-dihydro-3-methoxybenz[*c*]acridine (14c). Anthranilonitrile (**8**) (5.0 g, 42.3 mmol), 5-methoxy-1-tetralone (**13c**) (8.1 g, 46.0 mmol), and boron trifluoride diethyl etherate (1 M, 5.7 mL, 46.6 mmol) gave the title compound (**14c**) (5.5 g, 47% crude). Recrystallized: mp 126−129 °C ($CHCl_3$). M^+, 276.1265; ^{1}H NMR ($CDCl_3$) δ 2.5−3.2 (4H, m, 2CH_2), 3.9 (3H, s, CH_3), 4.6 (2H, br s, exchanges with D_2O, NH_2), 6.8−7.0 (1H, d, J = 9, aryl-H), 7.2−7.8 (2H, m, aryl-H), 8.0−8.35 (1H, m, aryl-H). Anal. ($C_{18}H_{16}N_2O$), C, H, N. Maleate salt: mp 210−216 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.70−3.05 (4H, m, CH_2), 3.89 (3H, s, CH_2), 6.03 (2H, s, maleate), 7.29 (1H, d, J = 8.1, aryl-H), 7.52 (1H, t, J = 8.0, aryl-H), 7.64 (1H, t, J = 7.3, aryl-H), 7.81 (1H, d, J = 7.8, aryl-H), 7.90 (1H, t, J = 7.4, aryl-H), 7.13 (1H, d, J = 8.3, aryl-H), 8.45 (1H, d, J = 8.3, aryl-H), 8.57 (2H, br s, maleate). Anal. ($C_{18}H_{16}N_2O{\cdot}C_4H_4O_4$) C, H, N.

11-Amino-1,2-dihydro-4-chlorobenz[*c*]acridine (14d). Anthranilonitrile (**8**) (5.0 g, 42.3 mmol), 6-chloro-1-tetralone (**13d**) (8.8 g, 48.7 mmol), and boron trifluoride diethyl etherate (1 M, 6.4 mL, 52.4 mmol) gave the title compound (**14d**), 3.3 g, 28% (crude). Recrystallized: mp 205−208 °C (EtOH); M^+, 280.0769; ^{1}H NMR ($CDCl_3$) δ 2.7−3.1 (4H, m, 2CH_2), 4.6 (2H, br s, exchanges with D_2O, NH_2), 7.1−8.2 (6H, m, aryl-H), 8.5 (1H, d, J = 8.1, aryl-H). Anal. ($C_{17}H_{15}N_2Cl$) C,H,N,Cl. Maleate salt: mp 220−221 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.30−3.06 (4H, m, 2CH_2), 3.34 (2H, br s, NH_2), 6.05 (2H, s, maleate), 7.55−7.70 (3H, m, aryl-H), 7.88 (1H, t, J = 7.9, aryl-H), 8.07 (1H, d, J = 8.5, aryl-H), 8.19 (1H, d, J = 8.1, aryl-H), 8.43 (1H, d, J = 8.3, aryl-H), 8.51 (2H, br s, maleate). Anal. ($C_{17}H_{15}N_2Cl{\cdot}C_4H_4O_4$) C, H, N, Cl.

8-Amino-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]-quinoline (14e). Anthranilonitrile (**8**) (2.0 g, 16.9 mmol), 5-benzosuberone (6,7,8,9-tetrahydrobenzocyclohepten-5-one) (**13e**) (3.0 g, 18.7 mmol), and boron trifluoride diethyl etherate (1 M, 2.6 mL, 18.7 mmol) gave the title compound (**14e**) (3.5

g, 80% crude). Recrystallized: mp 190−192 °C (EtOH); found M^+, 260.1304; ^{1}H NMR (DMSO-d_6) δ 1.9−2.8 (6H, m, 3CH_3), 6.55 (2H, br s, exchanges with D_2O, NH_2), 7.1−7.95 (7H, m, aryl-*H*), 8.2−8.35 (1H, m, aryl-*H*). Anal. ($C_{18}H_{16}N_2$) C, H, N. Maleate salt: mp 186−188 °C; ^{1}H NMR (CD_3OD) δ 2.25 (2H, br s, CH_2), 2.63 (2H, br s, CH_2), 5.07 (2H, br s, CH_2), 6.19 (2H, s, maleate), 7.35−8.05 (7H, m, aryl-*H*), 8.35 (1H, d, J = 8.4, aryl-*H*). Anal. ($C_{18}H_{16}N_2 \cdot C_4H_4O_4$) C, H, N.

8-Amino-6,7-dihydro-3-methoxy-5*H*-benzo[6,7]cyclohepta[1,2-*b*]quinoline (14f). Anthranilonitrile (**8**) (5.0 g, 42.3 mmol), 2-methoxy-5-benzosuberone (**13f**) (8.7 g, 45.8 mmol) and boron trifluoride diethyl etherate (1 M, 6.2 mL, 50.7 mmol) were treated according to the general procedure to give the title compound (**14f**) (9.1 g, 75% crude). Recrystallized: mp 206−210 °C (EtOH); M^+, 290.1419; ^{1}H NMR (DMSO-d_6) δ 1.8−2.8 (6H, m, 3CH_2), 3.85 (3H, s, CH_3), 6.5 (2H, br s, exchanges with D_2O, NH_2), 6.75−8.4 (7H, m, aryl-*H*). Anal. ($C_{19}H_{18}N_2O$) C, H, N. Maleate salt: mp 216−218 °C; ^{1}H NMR (CD_3OD) δ 2.20−2.75 (6H, m, 3CH_3), 3.89 (3H, s, CH_3), 6.21 (2H, s, maleate), 6.95−7.10 (2H, m, aryl-*H*), 7.60−7.72 (2H, m, aryl-*H*), 7.85−7.95 (2H, m, aryl-*H*), 8.35 (1H, d, J = 8.7, aryl-*H*). Anal. ($C_{19}H_{18}N_2O \cdot C_4H_4O_4$) C, H, N.

1,2,3,4-Tetrahydro-1-methylenenaphthalene (16).[19] 1-Tetralone (**15**) (3.3 mL, 24.8 mmol) was reacted with the phosphonium salt $PPh_3CH_2^+$ I^- (184) (10 g, 24.8 mmol) according to the published procedure to give a purple oil (14.0 g). This was purified by Kugelröhr distillation (0.2 mmHg, 65 °C) to give the title compound (**16**) as a clear oil (1.9 g, 54%): ^{1}H NMR ($CDCl_3$) δ 1.9 (m, 2H, CH_2), 2.5 (t, 2H, CH_2), 2.8 (t, 2H, CH_2), 4.95 (s, 1H, C*H*), 5.45 (s, 1H, C*H*), 7.0−7.6 (m, 4H, aryl-*H*).

2,3,4,5-Tetrahydrobenzocyclohepten-2(1*H*)-one (17).[18] Silver nitrate (17.9 g, 92 mmol) was stirred vigorously in methanol (50 mL) and water (50 mL) until it had dissolved. A solution of 1,2,3,4-tetrahydro-1-methylenenaphthalene (**16**) (6.6 g, 45.8 mmol) in THF (100 mL) was added, followed immediately by iodine (12.7 g, 50 mmol), and reacted according to the published procedure[18] to give the title compound (**17**) as a clear oil (3.9 g, 53% crude): ^{1}H NMR ($CDCl_3$) δ 2.0 (2H, m, CH_2), 2.55 (2H, t, CH_2), 3.0 (2H, m, CH_2), 3.8 (2H, s, CH_2), 7.2 (4H, s, aryl-*H*). IR (thin film) 1705 cm^{-1} C=O stretch.

13-Amino-6,7-dihydro-5*H*-benzo[3,4]cyclohepta[1,2-*b*]quinoline (18). Anthranilonitrile (**8**) (1.0 g, 8.5 mmol), 6-benzosuberone (6,7,8,9-tetrahydrobenzocyclohepten-6(5*H*)-one) (**17**) (1.5 g, 9.4 mmol) and boron trifluoride diethyl etherate (1 M complex, 1.2 mL, 9.8 mmol) were treated according to the general procedure to give the title compound (**18**), 0.7 g, 30% (crude). Recrystallized: mp 177−179 °C (EtOH); M^+, 260.1315; ^{1}H NMR ($CDCl_3$) δ 2.08−2.68 (5H, m), 2.82−2.90 (1H, m), 4.96 (2H, br s, exchanges with D_2O, NH_2), 7.34−7.66 (6H, m, aryl-*H*), 7.79 (1H, d, J = 8.35, aryl-*H*), 7.00 (1H, d, J = 8.43, aryl-*H*). Anal. ($C_{18}H_{16}N_2$) C, H, N.

7-Amino-3-chlorodibenzo[*b,h*][1,6]naphthyridine (20a). Anthranilonitrile (**8**) (0.3 g, 2.5 mmol), 4-keto-7-chloro-1,2,3,4-tetrahydroquinoline[26] (**19a**) (0.5 g, 2.8 mmol), and boron trifluoride diethyl etherate (1 M, 0.34 mL, 2.8 mmol) were treated according to the general procedure to give the title compound (**20a**) (0.15 g, 21% yield crude). Recrystallized: mp >220 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 7.49 (1H, ddd, J = 8.24, 1.24, aryl-*H*), 7.66 (1H, dd, J = 8.7, 2.2, aryl-*H*), 7.82 (1H, ddd, J = 8.4, 1.3, aryl-*H*), 7.98 (2H, m, aryl-*H*), 8.43 (2H, br s, exchanges with D_2O, NH_2), 8.51 (1H, dd, J = 8.5, 0.8, aryl-*H*), 9.04 (1H, d, J = 8.7, aryl-*H*), 9.76 (1H, s, aryl-*H*). Anal. ($C_{16}H_{10}N_3Cl$) C, H, N, Cl.

7-Amino-3-chloro-5,6-dihydro-5-*N*-tosyldibenz[*b,h*][1,6]naphthyridine (20b). Anthranilonitrile (**8**) (0.6 g, 5.4 mmol), 4-keto-7-chloro-1,2,3,4-tetrahydro-*N*-tosylquinoline[26] (**19a**) (2.0 g, 5.9 mmol), and boron trifluoride diethyl etherate (1 M, 0.7 mL, 5.7 mmol) were treated according to the general procedure to give the title compound (**20b**) (3.4 g, 60% crude). Recrystallized: mp 246−248 °C (EtOH); M^+, 435.0805; ^{1}H NMR (DMSO-d_6) δ 1.70 (3H, s, CH_3), 4.94 (2H, s, CH_2), 6.68 (2H, d, J = 8.26, Ts-H, aryl-*H*), 6.87 (2H, br s, exchanges with D_2O, NH_2), 7.06 (2H, d, J = 8.19, Ts-H, aryl-*H*), 7.47−7.68 (5H, m, aryl-*H*), 8.11 (1H, d, J = 8.35, aryl-*H*), 8.21 (1H, d, J = 8.43, aryl-*H*). Anal. ($C_{23}H_{18}N_3O_2SCl$) C, H, N, S, Cl.

8-Amino-6,7-dihydro-5-*N*-tosylquinolino[3,2-*d*][5*H*]-1-benzazepine (22). Anthranilonitrile (**8**) (2.0 g, 16.9 mmol), 1,2,3,4-tetrahydro-1-*N*-tosyl-benzazepin-5-one (**21**)[27] (5.9 g, 18.9 mmol), and boron trifluoride diethyl etherate (1 M, 2.3 mL, 18.8 mmol) were treated according to the general procedure to give the title compound (**22**) (5.4 g, 76% crude). Recrystallized: mp >250 °C (EtOH/MeOH); M^+, 415.1347; ^{1}H NMR (DMSO-d_6) δ 1.76 (3H, s, Ts-CH_3), 2.30 (1H, br s, CH_2), 3.10 (1H, br s, CH_2), 3.91 (1H, br s, CH_2), 4.20 (1H, br s, CH_2), 6.45 (2H, br s, exchanges with D_2O, NH_2), 6.51 (2H, d, J = 7.9, Ts-aryl-*H*), 6.92 (2H, dt, J = 8.3, 2.0, Ts-aryl-*H*), 7.36 (1H, ddd, J = 6.7, 1.3, aryl-*H*), 7.39−7.41 (1H, m, aryl-*H*), 7.51−7.58 (3H, m, aryl-*H*), 7.69 (1H, dd, J = 8.4, 0.7, aryl-*H*), 7.72−7.74 (1H, m, aryl-*H*), 8.06 (1H, dd, J = 8.3, 0.8, aryl-*H*). Anal. ($C_{24}H_{21}N_3O_2S$) C, H, N, S.

8-Amino-6,7-dihydro-7-*N*-tosylquinolino[3,2-*d*][5*H*]-3-benzazepine (24). Anthranilonitrile (**8**) (0.7 g, 6.3 mmol), 1,2,3,4-tetrahydro-3-*N*-tosylbenzazepin-5-one[29] (**23**) (2.0 g, 6.4 mmol), and boron trifluoride diethyl etherate (1 M, 0.8 mL, 6.5 mmol) gave the title compound (**24**) (1.6 g, 63% crude). Chromatography of a sample on neutral alumina with chloroform (100%), chloroform/methanol (1:1), and then ethanol (100%) as eluents yielded the pure title compound: mp 227−229 °C; M^+, 415.1329; ^{1}H NMR ($CDCl_3$) δ 2.32 (3H, s, Ts-CH_3), 2.58 (1H, dd, J = 14.24, 4.48, CH_2), 2.71 (1H, td, J = 13.78, 6.28, CH_2), 4.14−4.18 (1H, m, CH_2), 4.47 (1H, td, J = 13.68, 5.32, CH_2), 5.61 (2H, br s, exchanges with D_2O, NH_2), 6.83 (2H, d, J = 8.24 aryl-*H*), 6.98 (3H, dt, J = 8.36, 1.8, aryl-*H*), 7.04 (1H, td, J = 7.52, 1.2, aryl-*H*), 7.13 (1H, td, J = 7.42, 1.52, aryl-*H*), 7.17 (1H, dd, J = 7.51, 1.4, aryl-*H*), 7.49 (1H, ddd, J = 7.62, 1.36, aryl-*H*), 7.69 (1H, ddd, J = 7.7, 1.32, aryl-*H*), 7.84 (1H, dd, J = 8.42, 0.8, aryl-*H*), 8.01 (1H, dd, J = 8.44, 0.72, aryl-*H*). Anal. ($C_{24}H_{21}N_3O_2S$) C, H, N, S.

9-Amino-5,6,7,8-tetrahydro-5-*N*-tosylquinolino[3,2-*e*]-1-benzazocine (26). Anthranilonitrile (**8**) (0.5 g, 4.5 mmol), 2,3,4,5-tetrahydro-*N*-tosyl-1*H*-benzazocin-6-one[30] (**25**) (2.0 g, 4.6 mmol), and boron trifluoride diethyl etherate (1 M, 0.56 mL, 4.6 mmol) gave the title compound (**26**), 0.7 g, 35% (crude). Recrystallized: mp >250 °C (EtOAc/EtOH); M^+ 429.1507; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 1.52−1.75 (2H, m, CH_2), 1.93 (3H, s, Ts-CH_3), 2.06 (1H, ddd, J = 14.2, 10.2, 1.4, CH_2), 2.59 (1H, dd, J = 7.5, CH_2), 3.06−3.17 (1H, m, CH_2), 4.32 (1H, dd, J = 15.0, 4.8, CH_2), 6.48 (1H, d, J = 7.9, aryl-*H*), 6.91 (2H, dt, J = 8.5, 2.0, Ts-H, aryl-*H*), 7.10−7.13 (1H, m, aryl-*H*), 7.26−7.37 (3H, m, aryl-*H*), 7.45 (1H, ddd, J = 6.8, 1.3, aryl-*H*), 7.49−7.52 (1H, m, aryl-*H*), 7.67−7.73 (1H, m, aryl-*H*). Anal. ($C_{25}H_{12}N_3O_2S$) C, H, N, S.

Detosylation Method with Sodium Naphthalenide.[20] Sodium naphthalenide was prepared by the addition, under nitrogen, of clean pieces of sodium metal to a stirred solution of naphthalene (1 equiv) in anhydrous, degassed dimethoxyethane (DME) to which was added the tosylated compound in dry DME was added, according to the published procedure.[20]

8-Amino-6,7-dihydro-5*H*-quinolino[3,2-*d*]-1-benzazepine (27). Sodium (0.7 g, 32.3 mmol), naphthalene (4.1 g, 32.0 mmol), and degassed DME (120 mL) were treated according to the above procedure, giving a solution of sodium naphthalenide to which was added the tosylated compound, 8-amino-6,7-dihydro-5-*N*-tosyl-5*H*-quinolino[3,2-*d*]-1-benzazepine (**22**) (6.1 g, 14.7 mmol) in dry DME. After reaction the title compound (**27**) was isolated (1.9 g, 51.2% crude); ^{1}H NMR (CD_3OD) δ 2.87 (2H, t, J = 6.09, CH_2), 3.64 (2H, t, J = 6.27, CH_2), 6.95 (1H, d, J = 7.86, aryl-*H*), 7.12 (1H, t, J = 7.54, aryl-*H*), 7.26−7.44 (2H, m, aryl-*H*), 7.59 (1H, t, J = 7.01, aryl-*H*), 7.74 (1H, d, J = 7.63, aryl-*H*), 7.90 (1H, d, J = 8.15, aryl-*H*), 8.07 (1H, d, J = 8.42, aryl-*H*); M^+ 261.1259. Hydrated hydrochloride salt formed for analysis, mp 308−313 °C; ^{1}H NMR (CD_3OD/D_2O) δ 2.98 (2H, t, J = 6.56Hz, CH_2), 4.00 (2H, t, J = 7.23, CH_2), 7.72−8.00 (7H, m, aryl-*H*), 8.34 (1H, d, J = 8.51, aryl-*H*). Anal. ($C_{17}H_{15}N_3 \cdot 2HCl \cdot 2H_2O$) C, H, N, Cl.

9-Amino-5,6,7,8-tetrahydroquinolino[3,2-*e*]-1-benzazocine (28). Sodium (0.2 g, 8.7 mmol) and naphthalene (1.1 g, 8.2 mmol) in DME (60 mL) were treated according to the above procedure, giving a sodium naphthalenide solution to which

was added the tosylated compound, 9-amino-5,6,7,8-tetrahydro-5-*N*-tosylquinolino[3,2-*e*]-1-benzazocine (**26**) (0.7 g, 1.6 mmol) in dry DME. After reaction the title compound (**28**) was isolated (0.1 g, 24% crude): mp 237−240 °C; M^+ 275.1416; ^{1}H NMR (CD_3OD) δ 1.63−1.72 (1H, m, CH_2), 1.83−1.94 (1H, m, CH_2), 2.85−3.17 (4H, m, 2CH_2), 6.59−6.65 (2H, m, aryl-*H*), 7.07 (1H, t, 1J = 7.77, aryl-*H*), 7.16 (1H, d, J = 8.07, aryl-*H*), 7.40 (1H, t, J = 7.17, aryl-*H*), 7.57 (1H, t, J = 7.68, aryl-*H*), 7.85 (1H, d, J = 8.49, aryl-*H*), 8.04 (1H, d, J = 8.40, aryl-*H*).

***N*-(4-Methyl-5-oxocyclopenten-1-yl)-2-aminobenzonitrile (30a) and *N*-(2-Methyl-5-oxocyclopenten-1-yl)-2-aminobenzonitrile (30b).** Anthranilonitrile (**8**) (5.0 g, 42.3 mmol), 2-hydroxy-3-methyl-2-cyclopenten-1-one (cyclotene) (**29**) (5.2 g, 46.6 mmol), and *p*-toluenesulfonic acid (1.0 g, 5.8 mmol) in toluene (150 mL) were refluxed with a Dean−Stark water separator for 40 min. On cooling, the solvent was evaporated *in vacuo* to give a dark red oil which solidified on standing. Chromatography on silica gel with ethyl acetate−petroleum ether (60−80 °C) (1:4 then 1:3) gave two products. **(a) *N*-(4-Methyl-5-oxocyclopenten-1-yl)-2-aminobenzonitrile (30a) (7.2 g, 80%).** Recrystallized: mp 79−81 °C [diethyl ether−petroleum ether (60−80 °C) (3:1)]; M^+, 212.0952; ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, d, J = 7.48, CH_3), 2.23 (1H, ddd, J = 18.15, 2.11, 1.00, CH_2), 2.49 (1H, quintet of d, J = 7.43, 2.08, CH_2), 2.95 (1H, ddd, J = 18.15, 3.31, CH_2), 6.78−6.81 (2H, m, 1H exchanges with D_2O, N*H*, to give t, 1H, J = 3.22, CH_2), 6.93 (1H, td, J = 7.56, 0.98, aryl-*H*), 7.32 (1H, d, J = 9.09, aryl-*H*), 7.50 (2H, t, J = 9.73, aryl-*H*); IR (Nujol mull) 3361 (NH stretch), 2213 (CN stretch), 1753 cm^{-1} (C=O stretch). Anal. ($C_{13}H_{12}N_2O$) C, H, N.

(b) *N*-(2-Methyl-5-oxocyclopenten-1-yl)-2-aminobenzonitrile (30b) (0.7 g, 7%). Recrystallized: mp 96−98 °C [diethyl ether−petroleum ether (60−80 °C) (3:1)]; M^+, 212.0921; ^{1}H NMR ($CDCl_3$) δ 1.98 (3H, s, CH_3), 2.50−2.67 (4H, m, 2CH_2), 5.91 (1H, br s, exchanges with D_2O, N*H*), 6.52 (1H, d, J = 8.31, aryl-*H*), 6.83 (1H, td, J = 7.51, 0.97, aryl-*H*), 7.36 (1H, td, J = 7.89, 1.63, aryl-*H*), 7.46 (1H, dt, J = 7.80, 0.35, aryl-*H*); IR (Nujol mull) 3350 (NH stretch), 2220 (CN stretch), 1750 cm^{-1} (C=O stretch). Anal. ($C_{13}H_{12}N_2O$) C, H, N.

9-Amino-2,3-dihydro-2,3-dimethyl-3-hydroxy-1*H*-cyclopenta[1,2-*b*]quinoline (31a). *N*-(4-Methyl-5-oxocyclopenten-1-yl)-2-aminobenzonitrile (**30a**) (4.0 g, 18.9 mmol) in anhydrous THF (75 mL) under nitrogen was cooled to −78 °C while stirring. Methyllithium (1.5 M solution in diethyl ether, complexed with LiBr, 31.5 mL, 47.2 mmol) was added dropwise *via* syringe and the reaction left to stir and warm up to room temperature over 24 h. Water (30 mL) was added to quench the reaction. The organic layer was separated and dried and the solvent evaporated *in vacuo* to give the title compound (**31a**) (4.2 g, 99% crude). Recrystallized: mp 229−230 °C dec (MeOH/Et_2O); M^+, 228.1265; ^{1}H NMR (CD_3OD) δ 1.19 (3H, d, J = 6.95, CH_3), 1.16 (3H, s, CH_3), 2.25 (1H, q, J = 7.07, CH_2), 2.51 (1H, q, J =7.99, CH_2), 2.93 (1H, q, J = 7.59, CH_2), 7.37 (1H, td, J = 6.81, 1.26, aryl-*H*), 7.56 (1H, td, J = 6.83, 1.43, aryl-*H*), 7.90 (1H, dd, J = 8.50, 0.66, aryl-*H*), 8.03 (1H, dd, J = 8.46, 1.02, aryl-*H*). Anal. ($C_{14}H_{16}N_2O$) C, H, N.

9-Amino-3-*n*-butyl-2,3-dihydro-3-hydroxy-2-methyl-1*H*-cyclopenta[1,2-*b*]quinoline (31b). *N*-(4-Methyl-5-oxocyclopenten-1-yl)-2-aminobenzonitrile (**30a**) (1.0 g, 4.7 mmol) in anhydrous THF under nitrogen was cooled to −78 °C, *n*-butyllithium (1.6 M solution in hexanes, 7.4 mL, 11.8 mmol) was added dropwise *via* syringe, and the reaction was left to stir and warm up to room temperature over 24 h. Water (20 mL) was then added to quench the reaction. The organic layer was separated and dried and the solvent evaporated *in vacuo* to give the title compound (**31b**) (0.67 g, 52% crude). Recrystallized: mp 172−173 °C (MeOH/Et_2O); M^+, 270.1733; ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, J = 6.76, CH_3), 1.13−1.36 (7H, m, CH_2CH_2CH_3), 1.85−2.08 (2H, m, CH_2), 2.43−2.89 (2H, m, CH_2), 2.96 (1H, q, J = 9.81), 7.36 (1H, td, J = 6.79, 1.26, aryl-*H*), 7.55 (1H, td, J = 6.82, 1.41, aryl-*H*), 7.90 (1H, dd, J = 8.51, 0.66, aryl-*H*), 8.03 (1H, dd, J = 8.42, 0.91, aryl-*H*). Anal. ($C_{17}H_{22}N_2O$) C, H, N.

9-Amino-2,3-dimethyl-1*H*-cyclopent-2-enyl[1,2-*b*]quinoline (32a). Sulfuric acid (30%, 150 mL) and 9-amino-2,3-dihydro-2,3-dimethyl-3-hydroxy-1*H*-cyclopenta[*b*]quinoline (**31a**) (4.3 g, 18.6 mmol) was heated at reflux for 24 h. On cooling, the solution was basified with sodium hydroxide (2 M), and the organic components were extracted with chloroform. The organic extracts were combined and dried, and the solvent was evaporated *in vacuo* to give the title compound (**32a**) (3.9 g, 99% yield, crude). Recrystallized: mp >320 °C (MeOH); M^+, 210.1161; ^{1}H NMR (CD_3OD) δ 2.02 (3H, s, CH_3), 2.05 (3H, s, CH_3), 3.05* (1.5H, br s, CH_2), 7.32 (1H, td, J = 6.87, 1.23, aryl-*H*), 7.52 (1H, td, J = 6.87, 1.39, aryl-*H*), 7.89 (1H, d, J = 8.49, aryl-*H*), 7.99 (1H, d, J = 8.33, aryl-*H*). Anal. ($C_{14}H_{14}N_2$) C, H, N.

*This signal disappeared after several days exchanging with D_2O.

9-Amino-3-*n*-butyl-2-methyl-1*H*-cyclopenten-2-yl[1,2-*b*]-quinoline (32b). Sulfuric acid (98%, 30 mL) was added to 9-amino-3-*n*-butyl-2,3-dihydro-3-hydroxy-2-methyl-1*H*-cyclopenta[*b*]quinoline (**31b**) (1.3 g, 4.9 mmol), and the mixture was heated at reflux for 24 h. On cooling, the solution was basified with sodium hydroxide (2 M) and extracted with chloroform. The organic extracts were combined and dried, and the solvent was evaporated *in vacuo* to give the title compound (**32b**) (0.89 g, 72%, crude): M^+ 252.1628; ^{1}H NMR (CD_3OD) δ 0.97 (3H, t, J = 7.15, CH_3), 1.40−1.59 (4H, m, 2CH_2), 2.27 (3H, s, CH_3), 2.70 (2H, t, J = 7.23, CH_2), 3.34 (1H, s, CH_2), 3.47 (1H, s, CH_2), 7.60 (1H, t, J = 7.28, aryl-*H*), 7.84 (1H, t, J = 8.26, aryl-*H*), 8.03 (1H, d, J = 8.84, aryl-*H*), 8.27 (1H, d, J = 8.40, aryl-*H*). Anal. ($C_{17}H_{20}N$) C, H, N.

Pharmacology. Anticholinesterase Activity. This was based on measuring the hydrolysis of acetylthiocholine and the subsequent reaction of thiocholine with 4,4-dithiopyridine to form 4-thiopyridine.[31,32] Acetylcholinesterase was obtained from homogenates of rat brain[32] and butyrylcholinesterase was obtained from human plasma.

Monoamine Uptake Inhibition. Synaptosomes were prepared from homogenates of rat brain. Inhibition of uptake of [^{3}H]5-HT and [^{3}H]noradrenaline was measured at 37 °C as described previously.[33,34] Nonspecific uptake was determined in the presence of 10 μM fluoxetine (for 5-HT) or 1 μM desipramine (for noradrenaline).

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