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Syntheses of Benzoquinolizidine and Benzoindolizidine Derivatives as Anti-amnesic Agents

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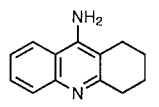
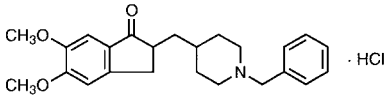
Abstract—Tacrine, one of the drugs available for Alzheimer's disease based on the cholinergic approach, suffers from considerable toxicity. Many analogues of tacrine have been prepared which retain the pharmacologically rich aminopyridine or aminoquinoline motifs. The current research was undertaken to produce an acetylcholinesterase inhibitor by employing 11-aminobenzoquinolizidines (**4**) and 10-aminobenzoindolizidines (**5**) as templates. Thus, we aimed to achieve three goals relative to tacrine: eliminate the pyridine and quinoline moieties and render the molecule less flat. Overall, the compounds we prepared were poorer inhibitors of acetylcholinesterase compared to tacrine. The single exception was compound **6f** which exhibited an effect comparable to that of tacrine, but only at a dose of the order of 10^{-3} M. However, despite the poor acetylcholinesterase inhibition by **6b**, this compound proved to be an effective anti-amnesic agent at 45 mg/kg dose.

Introduction

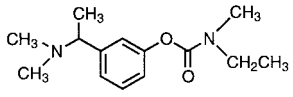
The cholinergic approach to Alzheimer's disease received an encouraging signal due to the recent approval of tacrine hydrochloride (Cognex®) as the first drug for the treatment of this disease; it was launched in 1993. Tacrine (**1**) is a complex pharmacological agent[1] which also inhibits the enzyme acetylcholinesterase (AcChE), thus maintaining synaptic residence of acetylcholine (AcCh).[2] Two other AcChE inhibitors have been marketed recently: donezepil (Aricept®, **2**)[3] and rivastigmine (Exelon, **3**).[4] The deficiency of tacrine as a drug is related to liver toxicity and peripheral cholinomimetic actions.[5] Tacrine belongs to the well known structural class of aminopyridines[6] which represent an interesting group of potassium channel blockers, but are toxic. It also incorporates the template of 4-aminoquinoline, well known for diverse pharmacological activity.[7] Furthermore, tacrine possesses a relatively flat aromatic structure which may be prone to intercalation.



Tacrine (**1**)



Aricept (**2**)



Exelon (**3**)

Many analogues of tacrine have been prepared.[8] Most of these are structurally closely related to the parent compound and retain the aminopyridine or aminoquinoline moiety.

Our approach to the problem of maintaining the AcChE inhibitory activity while diminishing the toxicity is based on the incorporation of the 11-amino benzoquinolizidine (**4**) and 10-aminobenzoindolizidine (**5**) moieties as the templates for AcChE inhibitors. In **4** and **5** we have eliminated the pyridine and quinoline

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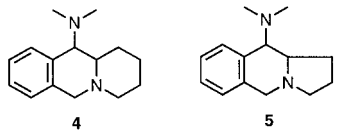


4 5

moieties while maintaining the two amino functionalities and rendering the molecule less flat. We now report the preparation of these two classes of compounds.

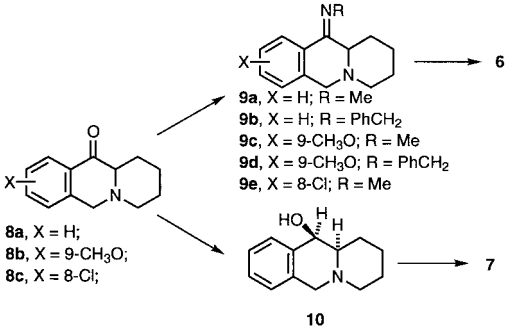
Chemistry

Both structures **6** and its oxygen analogue **7** were derived from different substituted benzoquinolizinones **8**. Structure **6** could be obtained from **8** via an imine

6a, X = H; R = H
6b, X = H; R = Me
6c, X = H; R = $PhCH_2$
6d, X = 9-CH_3O; R = Me
6e, X = 9-CH_3O; R = $PhCH_2$
6f, X = 8-Cl; R = Me

7

intermediate **9**, and structure **7** could be obtained from **8** via alcohol **10**.



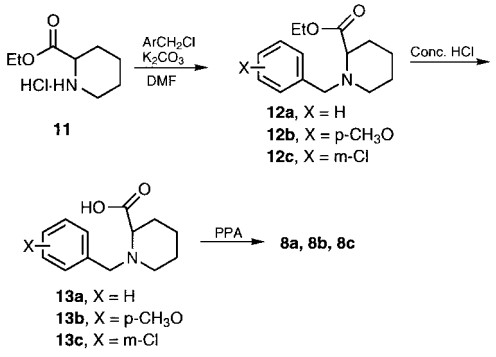
9a, X = H; R = Me
9b, X = H; R = $PhCH_2$
9c, X = 9-CH_3O; R = Me
9d, X = 9-CH_3O; R = $PhCH_2$
9e, X = 8-Cl; R = Me

8a, X = H;
8b, X = 9-CH_3O;
8c, X = 8-Cl;

6 7

10

The starting ketone **8a** was prepared according to the literature.[9] *N*-Benzylation of ethyl pipecolinate hydrochloride (**11**) was followed by HCl-catalyzed hydrolysis of the resulting ester **12a** to give acid **13a** which was cyclized with polyphosphoric acid to give 1,3,4,11a-tetrahydro-2*H*-benzo[*b*]quinolizin-11(6*H*)-one (**8a**). Ketones **8b** and **8c** are prepared similarly via ester **12b** and **12c**, and acids **13b** and **13c**.

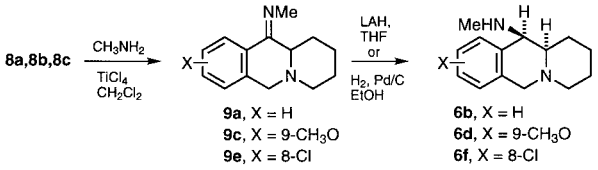


11

12a, X = H
12b, X = p-CH_3O
12c, X = m-Cl

13a, X = H
13b, X = p-CH_3O
13c, X = m-Cl

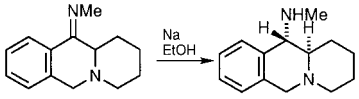
The amination of ketone **8a** with methylamine was carried out in methylene chloride via the imine intermediate **9a**; reduction by $LiAlH_4$ (LAH) or catalytic hydrogenation gave the desired reduced product as a single *cis*† isomer **6b** ($J = 2.4$ Hz, C<u>H</u>–N). (The stereoselectivity in this reduction is consistent with that reported for the reduction of **8a** to alcohol **10**).[9]



9a, X = H
9c, X = 9-CH_3O
9e, X = 8-Cl

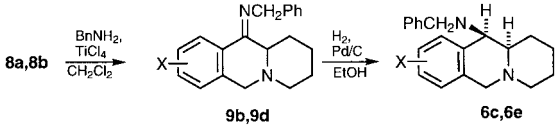
6b, X = H
6d, X = 9-CH_3O
6f, X = 8-Cl

The *trans* isomer **14** ($J = 8.6$ Hz for C<u>H</u>–N) was obtained as the major product in the reduction of imine **9a** with sodium metal in ethanol. The product ratio of *trans* to *cis* is 3:2. As reported previously for the reduction of oximes,[10] reaction with sodium in ethanol allows thermodynamic control to give the more stable product **14** as the major isomer.



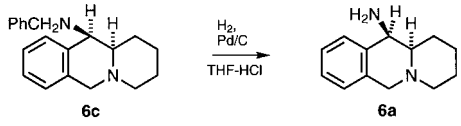
9a 14

The benzyl amine derivatives **6c** and **6e** were prepared via the benzyl imine **9b** and **9d** followed by hydrogenation under neutral conditions.



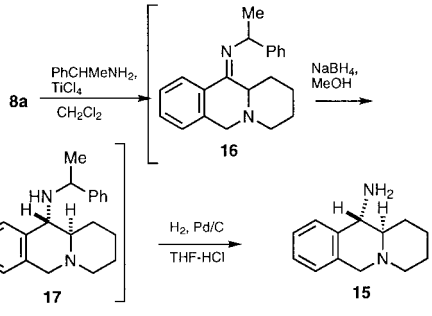
9b,9d 6c,6e

When **6c** was subjected to further hydrogenation in presence of hydrochloric acid, the benzyl group was cleaved cleanly to give primary amine **6a**.



6c 6a

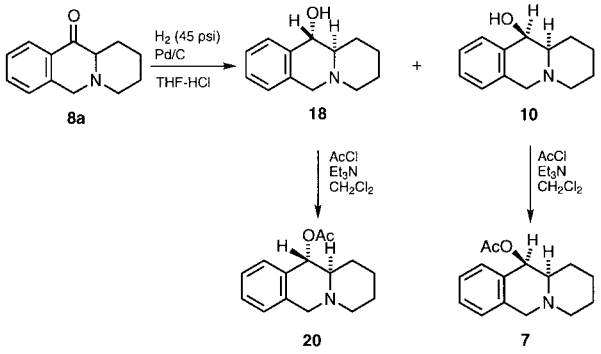
Attempts to make its *trans*-isomer **15** by sodium/ethanol reduction of **9b** failed; starting material was recovered. However, **15** was obtained from the α-phenethyl imine intermediate **16**.[11] Compound **16** was reduced to secondary amine **17** which was hydrogenated to give the *trans* primary amine **15** ($J = 8.6$ Hz for C<u>H</u>–N).



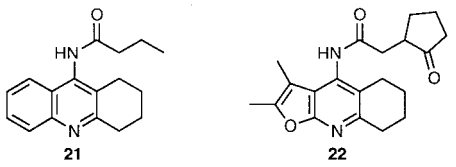
16 17 15

† We define stereochemistry by the relationship of the bridgehead hydrogen and the benzylic hydrogen on the adjacent carbon. In their ^{1}H NMR spectra, the *cis* isomers show small *J* values. In the original paper[9] describing alcohol **10**, the stereochemistry was defined by the relationship of the bridgehead hydrogen and the hydroxyl group.

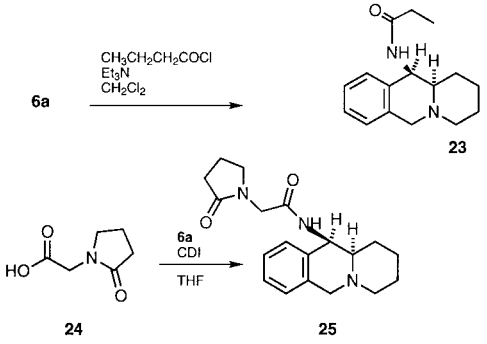
Ketone **8a** was hydrogenated to alcohols **18** and **10**, which were converted to the corresponding acetates **20** and **7**.



Chaki and co-workers found that the 4-acylaminopyridine derivative **21** shows better choline uptake activity when compared to tacrine.[12] Structure–activity relationship studies led to compound **22** with even better activity.[13]

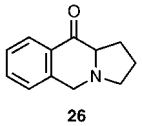


Based on the similarity suggested above between tacrine and **6a**, we synthesized the butyramide **23** by the acylation of **6a** with butyryl chloride and triethylamine. In addition compound **25** was prepared by the condensation of 2-oxo-1-pyrrolidineacetic acid (**24**) and **6a** in the presence of CDI.

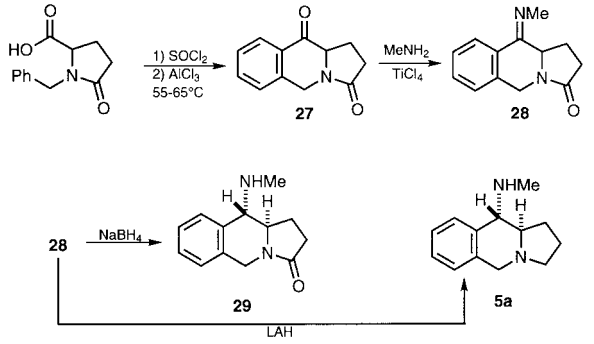


Because of the interesting activity of compound **6b**, the preparation of the analogous indolizidine **5a** was undertaken.

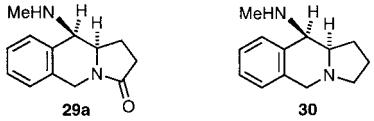
Efforts to cyclize *N*-benzylpyrrolidine-2-carboxylic acid, analogous to that of *N*-benzylpipecolic acid, failed to produce ketone **26**. Therefore an indirect route to the desired indolizidine derivatives **5** was developed.



Benzindolizidine-3, 10-dione **27**[14] was converted to the 3-*N*-methylimine **28**, which was then reduced with lithium aluminum hydride to give **5a**, ($J = 10.01$ Hz, C<u>H</u>–N) contaminated with ~10% of the *cis*-isomer **30**. Reduction of **28** with sodium borohydride produced aminolactam **29** ($J = 9.46$ Hz, C<u>H</u>–NHCH$_3$), again containing ~10% of the *cis*-isomer.



Attempts to prepare pure *cis*-isomer **30** by catalytic hydrogenation of the methylimine of ketone **26** were frustrated by lack of a good route to **26**.[14] The *cis* isomer of **29**, namely **29a**, was obtained in low yield by catalytic hydrogenation of imine **28**.



Biological Studies

Overall, these benzoquinolizidine and benzoindolizidine derivatives were poor inhibitors of acetylcholinesterase, as compared to that observed with tacrine (Table 1). The single exception was **6f**, which exhibited an effect comparable to that of tacrine, but only at a dose in the order of 10^{-3}M. In general, cholinesterase inhibition was similar to that determined for acetylcholinesterase. However, in some cases a stimulatory effect was observed at lower concentrations (for example see compounds **6a** and **6b**). Inhibition of acetylcholinesterase by these benzoquinolizidine and benzoindolizidine derivatives appeared to be competitive in nature as kinetic studies with **6b**, **5a** and tacrine revealed an equivalent K_i of 0.03 mM acetylthiocholine iodide substrate (Fig. 1). However, the inhibitory concentration of tacrine (5 μM) was 100-times lower than that observed for either **6b** or **5a** (500 μM) (data not shown for tacrine).

Evaluation of the in vivo anti-amnesic action of these derivatives confirmed the lack of a tacrine-like anti-acetylcholinesterase action as the majority of compounds tested failed to reverse scopolamine-induced amnesia of the passive avoidance response (Table 2). However, despite the lack of acetylcholinesterase inhibition by **6b**, this compound proved to be an effective anti-amnesic agent at concentrations of 45 mg/kg. Thus, this benzoquinolizidine and benzoindolizidine series would appear to include agents with an anti-amnesic action that is independent of an anti-cholinesterase effect. This suggestion is supported further by the lack of in vivo effect with **6f** despite this compound being an order of magnitude more potent acetylcholinesterase

inhibitor than **6b**. In general, all agents were devoid of any overt behavioural toxicity, the single exception being **6a** which induced amnesia when administered alone.

Structure–Activity Relationship

The structure–activity relationship defining compound **6b** as the antiamnesic lead may be summarized as follows: (1) the 6-6-6 ring system is preferred to 6-6-5; (2) *cis* stereochemistry is preferred to *trans*; (3) the 11-amino group is best as a secondary amine with a small substitutent such as methyl; (4) unsubstituted aromatic ring is preferred.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian spectrometer at 300 MHz for proton and 75.4 MHz for carbon in $CDCl_3$ solution. The predicted carbon spectra were obtained from the ACD Labs CNMR program. Peak positions are indicated in ppm downfield from internal TMS in δ units. Mass spectra were obtained on a MAT CH-5-DF (FAB), and Finnigan 8230 B (EI) mass spectrometers. IR spectra were recorded on a Perkin–Elmer 1420 Ratio Recording IR spectrophotometer.

Flash column chromatography was done on silica gel (E. M. Merck silica gel 60, 230–400 mesh) in the stated solvents. Melting points were obtained on a Thomas–Hoover apparatus and are uncorrected. Product purities were routinely checked by TLC. THF was tested for peroxides (aqueous KI) prior to use and used without further purification or drying. All reactions were performed under a nitrogen atmosphere in oven- or flame-dried glassware unless otherwise noted. The multiplicities of the ^{13}C signals were determined by DEPT experiments; s = C; d = CH; t = CH_2; q = CH_3. Methylamine was obtained from either lecture bottle (Aldrich) or aqueous solution (40%, Fluka) by distillation. Ethyl pipecolinate was purchased from Aldrich.

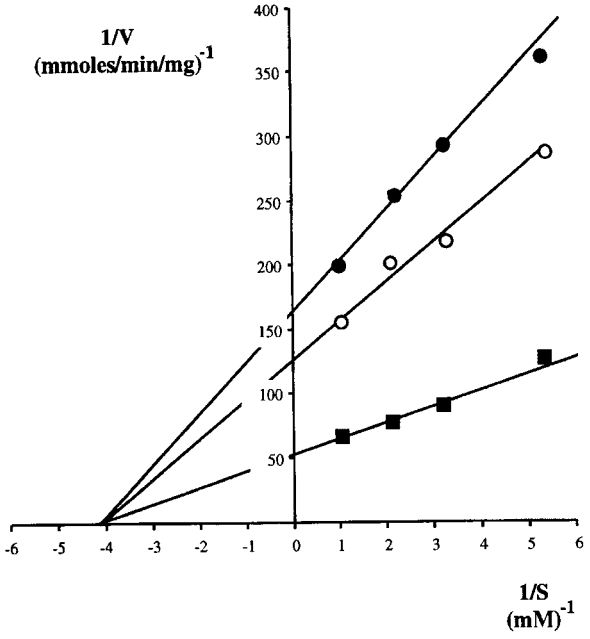


Figure 1. Influence of benzoquinolizidine and benzoindolizidine derivatives on rat brain acetylcholinesterase activity. The data are illustrated as Lineweaver–Burke plots for control (closed squares) and **6b** (0.5 mM; closed circles) and **5a** (0.5 mM; open circles).

Table 1. Inhibition of rat cholinesterase and acetylcholinesterase activity by benzoquinolizidine and benzoindolizidine derivatives and tacrine

	Acetylcholinesterase activity[a]			Cholinesterase activity[a]		
Test Compounds	10^{-3} M	10^{-5} M	10^{-7} M	10^{-3} M	10^{-5} M	10^{-7} M
6a	105.3	105.3	115.0	12.5	112.5	134.0
6c	105.3	100.0	121.1	8.3	120.8	127.5
14	42.1	100.0	105.3	50.0	100.0	101.3
6b	21.1	110.5	115.8	16.7	125.0	139.0
18	105.3	126.3	121.1	82.9	86.70	87.4
10	90.9	100.0	108.7	25.7	60.0	62.3
20	30.4	86.9	95.7	22.9	60.0	75.7
7	17.4	78.3	91.3	14.3	65.7	77.4
6d	42.2	91.6	102.5	40.4	94.9	88.9
6e	18.6	89.3	78.4	14.1	85.7	78.2
6f	2.3	69.6	94.2	2.7	73.3	102.9
23	28.4	74.8	78.8	24.2	91.9	93.8
25	41.7	91.3	104.7	45.2	103.7	107.8
Tacrine	5.4	7.4	42.8	17.8	14.9	42.9

[a] Activity was determined as mmol/min/mg protein and is presented as percent of the control value.

Table 2. Reversal of scopolamine-induced amnesia of a passive avoidance response by benzoquinolizidine and benzoindolizidine derivatives[a]

	6a (l0 mg/kg)	**6a** (30 mg/kg)	**6c** (10 mg/kg)	**6b** (10 mg/kg)	**6b** (30 mg/kg)	**6b** (45 mg/kg)	**6d** (10 mg/kg)	**6f** (30 mg/kg)
Vehicle (0.9% saline)	600 ± 0 (6)	427 ± 121 (6)	357 ± 94 (6)	357 ± 94 (6)	368 ± 84 (6)	484 ± 67 (6)	508 ± 100 (3)	409 ± 44 (9)
Scopolamine (0.8 mg/kg)	44 ± 10 (6)	44 ± 20 (5)	18 ± 5 (6)	21 ± 5 (6)	167 ± 86 (6)	37 ± 6 (6)	41 ± 10 (6)	33 ± 6 (9)
Test compound + scopolamine (0.8 mg/kg)	148 ± 101 (5)	132 ± 103 (6)	48 ± 14 (14)	104 ± 48 (12)	258 ± 156 (5)	322 ± 112 (8)*	54 ± 20 (6)	142 ± 62 (9)
Test compound alone	292 ± 92 (6)†	188 ± 102 (6)	410 ± 115 (6)	459 ± 53 (12)	529 ± 78 (6)	340 ± 146 (5)	592 ± 9 (6)	323 ± 65 (9)

[a] Results are expressed as the mean ± SEM (*n*) of recall latency to enter the dark compartment of the passive avoidance apparatus. Significant reversal by the test analogues of the Scopolamine-induced recall deficit is indicated by an asterisk ($P \leq 0.05$). Recall deficits induced by the test compounds are indicated by † ($P \leq 0.05$).

Ethyl *N*-(4-methoxyphenylmethyl)-pipecolinate (12b). *p*-Methoxybenzyl chloride (55 mmol, 8.61 g) was added to a mixture of K_2CO_3 (56 mmol, 7.74 g) and ethyl pipecolinate hydrochloride (50 mmol, 9.68 g) in DMF (55 mL). The mixture was stirred for 3 days at 62°C, and was filtered. Ice-cold HCl solution (1.5 N, 50 mL) was added to the filtrate and it was extracted with ether (3×100 mL). The aqueous phase was basified with NaOH solution (40%) and extracted with ether (5×100 mL). The combined extracts were washed with brine, dried with Na_2SO_4 and $MgSO_4$ and concentrated in vacuo to give **12b** as a yellow oil (7.12 g): ^{1}H NMR (300 MHz) δ 7.23 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.70 (s, Me), 3.73 (d, J = 13.1 Hz, 1H), 3.34 (d, J = 13.6 Hz, 1H), 3.08 (dd, J = 8.2, 4.3 Hz, 1H), 2.93 (m, 1H), 2.10 (m, 2H), 1.80 (m, 2H), 1.56 (m, 3H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 174.00, 158.68, 130.43, 130.01, 113.46, 64.55, 60.30, 59.87, 55.20, 50.15, 29.64, 25.24, 22.67, 14.33; MS (EI) 277 (2, M), 204 (90), 121 (100); HRMS (EI) *m*/*e* calcd for $C_{16}H_{23}NO_3$ 277.1678, found 277.1682.

Ethyl *N*-(3-chlorophenylmethyl)pipecolinate (12c). A mixture of 3-chlorobenzyl chloride (11 mmol, 1.4 mL), ethyl pipecolinate hydrochloride (10 mmol, 1.94 g) and K_2CO_3 (12 mmol, 1.69 g) in DMF (10 mL) was stirred at 60 °C for 3 days. It was then diluted with ether (50 mL) and filtered. The filtrate was concentrated in vacuo to give **12c** as a yellow oil (2.79 g): ^{1}H NMR (300 MHz) δ 7.21–7.35 (m, 4 H), 4.20 (q, J = 7.1 Hz, 2 H), 3.77 (d, J = 13.6 Hz, 1H), 3.37 (d, J = 13.6 Hz, 1 H), 3.14 (dd, J = 7.5 Hz, 4.6 Hz, 1H), 2.92 (dt, J = 11.9, 5.4 Hz, 1H), 2.15 (m, 1H), 1.34–1.90 (m, 6H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 173.74 (s), 140.73 (s), 134.06 (s), 129.35 (d), 128.99 (d), 127.14 (d), 64.33 (d), 60.34 (t), 59.98 (t), 50.11 (t), 29.52 (t), 25.25 (t), 22.39 (t), 14.30 (q); MS (FAB) 282 (98, M + H), 208 (100); HRMS (FAB) *m*/*e* calcd for ($C_{15}H_{20}ClNO_2$ + H) 282.1261, found 282.1248.

***N*-(4-Methoxyphenylmethyl)pipecolinic acid hydrochloride (13b).** A mixture of **12b** (7.12 g) and concd HCl (100 mL) was refluxed for 8 h. Solvent was removed in vacuo and 2-propanol was added to the residue. Upon cooling, a pale yellow solid was obtained as **13b** (2.08 g): mp 199–201 °C (2-propanol); ^{1}H NMR (300 MHz, D_2O) δ 7.42 (d, J = 8.1 Hz, 2 H), 7.05 (d, J = 8.1 Hz, 2 H), 4.45 (d, J = 13.1 Hz, 1 H), 4.09 (d, J = 13.1 Hz, 1 H), 3.84 (s, Me); MS (EI) 249 (2, M), 204 (38), 121 (100); Anal. calcd for $C_{14}H_{19}NO_3 \cdot HCl \cdot 0.2H_2O$: C, 58.11; H, 7.11; N 4.84; Cl, 12.25; found C, 58.02; H, 7.21; N, 4.64; Cl, 12.57. The mother liquor was concentrated to give a foam (5.59 g) which was identical to **13b** by ^{1}H NMR.

***N*-(3-Chlorophenylmethyl)pipecolinic acid hydrochloride (13c).** Using the same procedure as above, ethyl *N*-(3-chlorophenylmethyl)-pipecolinate (**12c**, 2.79 g) was converted to **13c** (2.78 g): 221–223 °C (MeOH:2-propanol); ^{1}H NMR (300 MHz, D_2O) δ 7.40–7.55 (m, 4 H), 4.54 (d, J = 12.9 Hz, 1 H), 4.13 (d, J = 13.2 Hz, 1 H), 3.88 (dd, J = 11.9 Hz, 3.5 Hz, 1 H), 3.48 (br d, J = 12.9 Hz, 1 H), 3.02 (td, J = 12.6, 3.0 Hz, 1 H), 2.31 (m, 1 H), 1.50–1.90 (m, 5 H); ^{13}C NMR (75.4 MHz, D_2O) δ 172.08, 134.25, 131.24, 130.67, 130.31, 130.25, 129.87, 65.37, 59.12, 51.66, 27.80, 21.95, 20.77; MS (FAB) 253 (2, M^+), 208 (100), 125 (59); Anal. calcd for $C_{13}H_{16}ClNO_2 \cdot HCl$: C, 53.81; H, 5.90; N 4.83; Cl, 24.43; found C, 53.52; H, 6.14; N, 4.85; Cl, 24.15.

1,3,4,11a-Tetrahydro-2*H*-benzo[*b*]quinolizin-11(6*H*)-one (8a). The following is a modification of the procedure reported.[9] Acid **13a** (5.10 g, 20.0 mmol) was placed in a 500-mL round-bottomed flask. Polyphosphoric acid (200 g) was added. The mixture was heated in an oil bath gradually to 140 °C with stirring. It was stirred at 140 °C until the bubbling stopped, then cooled to rt and poured into ice. The mixture was neutralized with aqueous NaOH (40%) and extracted with ether (5×80 mL). The combined extracts were washed with brine (2×50 mL), dried (Na_2SO_4) and concentrated in vacuo to give a red solid (3.08 g, 77%): 71–72 °C (benzene, lit[9] 68–69 °C); ^{1}H NMR (300 MHz) δ 8.02 (dd, J = 7.8, 1.3 Hz, 1H), 7.50 (td, J = 7.3, 1.4 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 3.88 (d, J = 15.2 Hz, H-6), 3.68 (d, J = 14.9 Hz, H-6), 3.09 (br d, J = 11.2 Hz, 1H), 2.77 (br d, J = 10.5 Hz, 1H), 2.44 (m, 1H), 2.35 (td, J = 11.3, 3.5 Hz, 1H), 1.90 (br d, J = 12.5 Hz, 1 H), 1.32–1.76 (m, 4 H); ^{13}C NMR (75.4 MHz) δ 195.87, 141.73, 133.53, 130.12, 127.34, 127.00, 126.17, 69.21, 57.14, 56.13, 26.66, 25.02, 23.81.

1,3,4,11a-Tetrahydro-9-methoxy-2*H*-benzo[*b*]quinolizin-11(6*H*)-one (8b). By using above procedure, *N*-(4-methoxyphenylmethyl) pipecolinic acid hydrochloride (**13b**, 2.98 g) was converted to ketone **8b** (950 mg, 41%): mp 117–119 °C (ether); ^{1}H NMR (300 MHz) δ 7.48 (d, J = 2.7 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.08 (dd, J = 8.4, 2.7 Hz, 1H), 3.84 (s, Me), 3.84 (d, J = 14.8 Hz, 1H), 3.61 (d, J = 14.8 Hz, 1H), 3.08 (br d, J = 11.1 Hz, 1H), 2.74 (br d, J = 10.1 Hz, 1H), 2.42 (m 1 H), 2.34 (td, J = 11.3, 3.6 Hz, 1H), 1.90 (m, 1H), 1.15–1.80 (m, 4H); ^{13}C NMR (75.4 MHz) δ 195.89, 158.84, 134.60, 131.02, 127.51, 121.88, 108.96, 69.01, 56.61, 56.13, 55.52, 26.74, 25.03, 23.87; MS (El) 231 (64, M), 203 (53), 202 (53), 174 (10), 161 (83), 148 (27), 121 (100), 120 (31); Anal. calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06; found C, 72.47; H, 7.47; N, 5.91.

1,3,4,11a-Tetrahydro-8-chloro-2*H*-benzo[*b*]quinolizin-11 (6H)-one (8c). By using above procedure, *N*-(3-chlorophenylmethyl) pipecolinic acid hydrochloride (**13c**, 901 mg) was converted to ketone **8c** (451 mg, 64%) which was crystallized from methanol to give a solid: mp 106–108 °C; ^{1}H NMR (300 MHz) δ 7.94 (d, J = 8.4 Hz, 1H), 7.32 (dd, J = 8.4, 2.0 Hz, 1 H), 7.22 (m, 1H), 3.82 (d, J = 15.3 Hz, 1H), 3.64 (d, J = 15.3 Hz, 1H), 3.06 (br d, J = 11.4 Hz, 1H), 2.76 (br d, J = 10.5 Hz, 1H), 2.36 (m, 2H), 1.88 (m, 1H), 1.30–1.70 (m, 4H); ^{13}C NMR (75.4 MHz) δ 194.85 (s), 143.70 (s), 139.77 (s), 128.68 (d), 128.65 (s), 127.82 (d), 126.15 (d), 68.97 (d), 56.69 (t), 56.01 (t), 26.58 (t), 24.97 (t), 23.70 (t); MS (El) 235 (51, M), 206 (63), 165 (100); Anal. calcd for $C_{13}H_{14}ClNO$: C, 66.24; H, 5.99; Cl, 15.04; N, 5.94; found C, 66.18; H, 6.02; Cl, 15.19; N, 5.85.

Methylimine 9a. A solution of ketone **8a** (1.10 g, 5.47 mmol) in CH_2Cl_2 (20 mL) was added to methylamine (5 mL) followed by the addition of $TiCl_4$ (2.74 mmol, 2.74 mL of 1.0 M solution in toluene). The

mixture was stirred at rt for 10 h. It was filtered through Celite and rinsed with CH_2Cl_2. The filtrate was concentrated in vacuo to give a mixture of red solid and oil (1.29 g, 100%) which was directly used for the next step without purification.

***cis*-*N*-Methyl-1,3,4,6,11,11a-hexahydro-11-amino-2*H*-benzo[*b*]quinolizidine (6b).** Imine **9a** (3.05 mmol, based on starting ketone **8a** was dissolved in THF (20 mL). LAH (380 mg) was added gradually to the mixture. The suspension was heated at reflux for 0.5 h and then stirred at rt for 10 h and quenched by the successive addition of H_2O (380 mL), NaOH (aqueous, 15%, 380 μL) and H_2O (1.1 mL). The mixture was filtered and rinsed with ether. The filtrate was concentrated to give **6b** as a red oil (513 mg, 79% based on starting ketone **8a**), identical by ^{1}H NMR to the compound obtained below by catalytic hydrogenation.

Catalytic hydrogenation of imine **6a** (2.39 mmol, based on the starting ketone **8a**) in absolute ethanol (10 mL) with Pd on carbon (10%, 210 mg) for 12 h at a pressure of 46 psi gave **6b** as an oil (421 mg, 82% based on starting ketone **8a**): ^{1}H NMR (300 MHz) δ 7.05–7.22 (m, 4 H), 4.00 (d, J = 16.0 Hz, H-6), 3.34 (d, J = 16.0 Hz, H-6), 3.24 (d, J = 2.4 Hz, 1H), 3.07 (br d, J = 11.3 Hz, 1H), 2.39 (dt, J = 11.2, 2.8 Hz, 1H), 2.36 (s, CH_3), 2.10 (m, 2H), 1.94 (m, 1H, NH), 1.83 (m, 1H), 1.70 (m, 3H), 1.33 (m, 1H); ^{13}C NMR (75.4 MHz) δ 136.26, 134.10, 128.88, 126.83, 126.23, 125.13, 61.80, 60.43, 58.32, 56.67, 34.36, 28.20, 25.57, 24.37; HCl salt mp: > 230 °C (MeOH:2-PrOH:ether); MS (FAB), *m*/*e* 217 (100, M + H), 186 (36); HRMS (FAB) *m*/*e* calcd for $C_{14}H_{20}N_2$ + H) 217.1705, found 217.1704; Anal. calcd for $C_{14}H_{20}N_2$·2HCl: C, 58.14; H, 7.67; Cl, 24.51; N, 9.68. Found: C, 58.21; H, 7.86; Cl, 24.35; N, 9.58.

In the same way **6d** was prepared from ketone **8b** via imine **9b** and was obtained as an oil: ^{1}H NMR (300 MHz) δ 6.97 (d, J = 8.4 Hz, 1H), 6.77 (dd, J = 8.4 2.7 Hz, 1H), 6.67 (d, J = 2.6 Hz, 1H), 3.93 (d, J = 15.4 Hz, 1H), 3.79 (s, OCH3), 3.26 (d, J = 15.3 Hz, 1H), 3.18 (d, J = 2.4 Hz, 1H), 3.05 (br d, J = 11.3 Hz, 1H), 2.38 (s, NCH3), 1.25–2.36 (m, 8 H); ^{13}C NMR δ 157.07, 137.61, 127.15, 126.18, 113.59, 112.89, 61.83, 60.75, 57.79, 56.68, 55.19, 34.57, 28.13, 25.56, 24.37; MS (FAB) 247 (100, M + H), 216 (88), 163 (66); HCl salt mp: > 230 °C (MeOH:2-PrOH:ether); Anal. calcd for $C_{15}H_{22}N_2O$·2HCl·0.2H_2O: C, 55.80; H, 7.62; Cl, 21.96; N, 8.68; found C, 56.15; H, 7.59; Cl, 21.64; N, 8.56.

6f. The imine **9e** (1.06 g) was dissolved in THF (10 mL), Pt/C sulfided (Aldrich) (410 mg) was added and the mixture was hydrogenated (50 psi) for 18 h at rt. It was filtered and concentrated. The residue was chromatographed on silica gel eluting with CH_2Cl_2:MeOH:NH_4OH (150:8:1) to give **6f** as a red oil (287 mg, 27%): ^{1}H NMR (300 MHz) δ 7.07 (m, 3H), 3.93 (d, J = 16.2 Hz, 1H), 3.28 (d, J = 16.5 Hz, 1H), 3.22 (d, J = 2.4 Hz, 1H), 3.04 (br d, J = 10.8 Hz, 1H), 2.32 (s, CH_3), 1.20–2.10 (m, 8H); ^{13}C NMR δ 135.93 (s), 134.54 (s), 132.35 (s), 130.13 (d), 126.03 (d), 125.29 (d), 61.51 (d), 59.64 (d), 57.79 (t), 56.43 (t), 34.01 (q), 27.93 (t), 25.39 (t), 24.17 (t); MS (FAB) 251 (78, M + H), 154 (100), 136 (77); HRMS (FAB) *m*/*e* calcd for ($C_{14}H_{19}ClN^2$ + H) 251.1315, found 251.1319; The amine was converted to the hydrochloride and crystallized from MeOH:2-PrOH:ether to give a gray solid: mp > 230 °C; Anal. calcd for $C_{14}H_{19}ClN_2$·2HCl·0.2C_3-H_8O: C, 52.24; H, 6.79; Cl, 31.68; N, 8.34; found C, 52.04; H, 6.51; Cl, 31.36; N, 8.25.

***trans*-*N*-Methyl-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizin-11-amine (14).** The imine **9a** (1.29 g, 5.47 mmol based on ketone **8a**) was dissolved in absolute ethanol (20 mL). Sodium (2.23 g) was added in small pieces to maintain the reaction at reflux. After all the sodium was added, more ethanol (10 mL) was added to complete the reaction. The mixture was then cooled to 0 °C and water (10 mL) was slowly added. Ethanol was removed on a rotary evaporator. The residue was extracted with ether (4×40 mL), and the combined extracts were washed with brine (2×20 mL), dried (Na_2SO_4) and concentrated in vacuo to give a red oil (780 mg, 66%). ^{1}H NMR showed that the product contained about 30% starting material. It was reduced again by the addition of sodium (1.43 g) to the solution of the oil in ethanol (20 mL). The reaction mixture was quenched by the addition of water (10 mL). Aqueous HCl solution (3 N, 50 mL) was added and the mixture was extracted with ether (50 mL). The aqueous layer was basified by the addition of solid NaOH, and was extracted with ether (3×50 mL). The combined extracts were dried and concentrated in vacuo to give a red oil (659 mg, 56%, *trans:cis* = 3:2 by NMR). The oil was separated on radial chromatography eluting with CH_2Cl_2:MeOH:NH_4OH (150:8:1) to give two fractions (339 mg, *trans:cis* = 3:2; 30 mg, *trans:cis* = 9:1). The NMR below was run on the latter fraction.

14. ^{1}H NMR (300 MHz) δ 7.39 (d, J = 7.6 Hz, 1H), 7.22 (t, J = 7.3 Hz, 1H), 7.14 (td, J = 7.4, 1.0 Hz, 1H), 7.03 (d, J = 7.3 Hz, 1H), 3.72 (d, J = 14.9 Hz, 1H), 3.64 (d, J = 8.4 Hz, 1H), 3.39 (d, J = 15.1 Hz, 1H), 3.05 (br d, J = 11.3 Hz, 1H), 2.30 (s, CH_3), 1.25–2.30 (m, 9H); ^{13}C NMR (75.4 MHz) δ 136.08, 135.48, 126.94, 126.61, 126.64, 125.84, 62.55, 61.86, 58.01, 56.32, 31.81, 31.05, 25.25, 24.23; MS (FAB), *m*/*e* 217 (100, M + H), 186 (29); HRMS (FAB) *m*/*e* calcd for ($C_{14}H_{20}N_2O$ + H) 217.1705, found 217.1708.

***cis*-*N*-Benzyl-1,3,4,6,11,11a-hexahydro-11-amino-2*H*-benzo-[*b*]quinolizidine (6c).** Benzylamine (1.2 mL, 10.76 mmol) was added to a solution of ketone **8a** (721 mg, 3.59 mmol) in CH_2Cl_2 (20 mL) followed by the addition of $TiCl_4$ (1.8 mmol, 1.8 mL of 1.0 M solution in toluene). The mixture was stirred at rt for 20 h. It was filtered through Celite and the solid rinsed with CH_2Cl_2. The filtrate was concentrated in vacuo to give **9b** as a yellow solid which was directly used for the next step without purification.

The benzylimine **9b** (189 mg) was dissolved in absolute ethanol (5 mL) and palladium on carbon (10%, 74 mg) was added. The mixture was hydrogenated in a Parr for 5 h at a pressure of 46 psi and then filtered through Celite. The filtrate was concentrated to give **6c** as a yellow oil (93 mg, 50%): ^{1}H NMR (300 MHz) δ 7.01–7.40 (m, 9 H), 4.00 (d, J = 15.9 Hz, 1H), 3.86 (d, J = 13.8 Hz, 1H), 3.69 (d, J = 13.5 Hz, 1H), 3.336 (d, J = 15.9 Hz,

1H), 3.335 (d, $J=1.8$ Hz, 1H), 3.08 (br d, $J=11.4$ Hz, 1H), 1.25–2.42 (m, 8H); ^{13}C NMR (75.4 MHz) δ 141.17, 137.05, 134.17, 128.57, 128.24, 128.12, 126.66, 126.55, 126.31, 125.22, 62.15, 58.42, 57.36, 56.76, 50.92, 28.15, 25.65, 24.44; MS (FAB), *m/e* 293 (100, M + H), 209 (6), 198 (36), 186 (61), 91 (30); HRMS (FAB) *m/e* calcd for ($C_2H_2N_2$ + H) 293.2018, found 293.2009. HCl salt was prepared from ethereal HCl solution and crystallized from MeOH:2-PrOH:ether: mp 185–188 °C; Anal. calcd for $C_{20}H_{24}N_2$·HCl: C, 73.04; H, 7.66; Cl, 10.78; N, 8.52. Found: C, 72.73; H, 7.72; Cl, 11.11; N, 8.14.

6e. Compound **6e** was obtained as a brown oil (313 mg, 50%) from corresponding imine **9d** (614 mg): ^{1}H NMR (300 MHz) δ 7.20–7.40 (m, 5H), 6.97 (d, $J=8.7$ Hz, 1H), 6.76 (dd, $J=8.4$, 2.7 Hz, 1H), 6.52 (d, $J=2.7$ Hz, 1H), 3.97 (d, $J=15.6$ Hz, 1H), 3.88 (d, $J=13.5$ Hz, 1H), 3.76 (s, CH_3O), 3.74 (d, $J=13.5$ Hz, 1H), 3.32 (d, $J=1.8$ Hz, 1H), 3.28 (d, $J=15.6$ Hz, 1H), 3.09 (br d, $J=11.1$ Hz, 1H), 1.30–2.40 (m, 8 H); ^{13}C NMR (75.4 MHz) δ 157.27, 141.13, 138.07, 128.33, 128.21, 127.26, 126.65, 113.16, 62.23, 57.83, 57.46, 56.79, 55.25, 51.18, 28.12, 25.60, 24.41, two aromatic signals are not discernible due to overlap (one quaternary, one CH); MS (FAB), *m/e* 323 (100, M + H), 239 (4), 216 (39), 108 (3), 91 (10). HCl salt was prepared from ethereal HCl solution and crystallized from MeOH:2-PrOH: mp 213–215 °C; Anal. calcd for $C_{21}H_{26}N_2O$·2HCl: C, 63.80; H, 7.14; Cl, 17.93; N, 7.09. Found: C, 63.83; H, 6.92; Cl, 17.47; N, 7.02.

***cis*-1,3,4,6,11,11a-Hexahydro-11-amino-2*H*-benzo[*b*]quinolizidine (6a).** Pd on carbon (10%, 154 mg) was added to a solution of *N*-benzylamine **6c** (93 mg) in THF (10 mL) and aqueous HCl (0.5 N, 1 mL). The mixture was hydrogenated in a Parr. Work up, as above, gave **6a** as a colorless oil (29 mg): ^{1}H NMR (300 MHz) δ 7.00–7.25 (m, 4H), 3.93 (d, $J=15.7$ Hz, 1H), 3.58 (d, $J=2.6$ Hz, 1H), 3.33 (d, $J=15.7$ Hz, 1H), 3.01 (br d, $J=11.3$ Hz, 1H), 2.32 (dt, $J=10.8$, 3.0 Hz, 1H), 2.12 (td, $J=11.6$, 3.6 Hz, 1H), 1.25–1.93 (m, 8H); ^{13}C NMR (75.4 MHz) δ 139.86, 133.60, 128.66, 126.73, 126.46, 125.85, 61.64, 58.60, 56.57, 53.11, 28.40, 25.70, 24.37; MS (FAB), *m/e* 203 (100, M + H), 186 (33), 84 (10); HRMS (FAB) *m/e* calcd for ($C_{13}H_{18}N_2$ + H) 203.1548, found 203.1560; the hydrochloride was prepared with ethereal HCl and was crystallized from MeOH:2-PrOH:ether: mp > 230 °C; Anal. calcd for $C_{13}H_{18}N_2$· 2HCl·0.6H_2O·0.2 isopropanol: C, 54.84; H, 7.65; Cl, 23.81; N, 9.41. Found: C, 54.86; H, 7.69; Cl, 23.80; N, 9.32.

***trans*-1,3,4,6,11,11a-Hexahydro-11-amino-2*H*-benzo[*b*]quinolizidine (15).** (±)-α-Methylbenzylamine (0.99 mL, 7.70 mmol) was added to a solution of ketone **8a** (516 mg, 2.57 mmol) in CH_2Cl_2 (20 mL) followed by the addition of $TiCl_4$ (1.28 mmol, 1.28 mL of 1.0 M solution in toluene). The mixture was stirred at rt for 20 h. Hexanes (20 mL) was added and the suspension was filtered through Celite. The filtrate was concentrated in vacuo to give a red oil (719 mg) which was directly used for the next step without purification.

Part of above oil (464 mg) was dissolved in MeOH (1 mL) and added to a $NaBH_4$ suspension in MeOH (4 mL) at 0 °C. After 30 min., it was warmed to rt and stirred overnight. The reaction was quenched by the addition of water and MeOH was removed in vacuo. The residue was extracted with ether, dried (Na_2SO_4) and concentrated in vacuo to give an oil. The oil was dissolved in EtOH (5 mL) and HCl (3 N, 2 mL) and hydrogenated for 12 h with a Parr apparatus (50 psi) catalyzed by Pd/C (201 mg). It was worked up and the crude product was purified by chromatography (silica gel column eluting with CH_2Cl_2:MeOH:NH_4OH) to give **15** as a red oil (47 mg): ^{1}H NMR (300 MHz) δ 7.51 (d, $J=7.7$ Hz, 1H), 7.22 (d, $J=7.4$ Hz, 1H), 7.15 (d, $J=7.3$ Hz, 1H), 7.01 (d, $J=7.5$ Hz, 1H), 3.78 (d, $J=15.1$ Hz, 1H), 3.67 (d, $J=8.6$ Hz, 1H), 3.43 (d, $J=15.1$ Hz, 1H), 3.05 (br d, $J=11.2$ Hz, 1H), 2.30 (m, 1H), 2.16 (dt, $J=11.4$, 3.9 Hz, 1H), 1.24–1.96 (m, 8H); ^{13}C NMR (75.4 MHz) δd 138.54, 134.00, 126.84, 126.72, 126.41, 125.61, 67.60, 58.29, 56.20, 55.55, 30.89, 25.38, 24.11; MS (FAB), *m/e* 203 (100, M + H), 186 (45); HRMS (FAB) *m/e* calcd for ($C_{13}H_{18}N_2$ + H) 203.1548, found 203.1531.

***trans*-1,3,4,6,11,11a-Hexahydro-2*H*-benzo[*b*]quinolizin-11-ol (18) and *cis*-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizin-11-ol (10).** A mixture of ketone **8a** (0.97 g, 4.83 mmol) and Pd/C (10%, 1.50 g) in THF (50 mL) and HCl (0.5 N, 5 mL) was hydrogenated in a Parr apparatus (45 psi) for 15 h. The mixture was basified with NaOH (2 N) and extracted with ether. The extract was dried (Na_2SO_4) and concentrated in vacuo to give a solid (790 mg). The solid was recrystallized from benzene to give **18** (410 mg) as a colorless solid, mp 158–160 °C (lit.[9] 162 °C). The mother liquor was evaporated and the residue was crystallized from ethanol to give **10** (132 mg) as a colorless solid, mp 152–154 °C.

18. ^{1}H NMR (300 MHz) δ 7.52 (d, $J=7.3$ Hz, 1H), 7.22 (m, 2 H), 7.03 (d, $J=7.3$ Hz, 1H), 4.47 (d, $J=8.4$ Hz, 1H), 3.81 (d, $J=15.3$ Hz, 1H), 3.44 (d, $J=15.3$ Hz, 1H), 3.04 (br d, $J=11.3$ Hz, 1H), 2.33 (m, 1H), 2.18 (td, $J=11.5$, 3.9 Hz, 1H), 2.07 (m, 1H), 1.30–1.90 (m, 6H).

10. ^{1}H NMR (300 MHz) δ 7.35 (m, 1H), 7.22 (m, 2H), 6.94 (m, 1H), 4.12 (s, 1H), 3.56 (s, OH), 3.39 (d, $J=15.7$ Hz, 1H), 3.16 (d, $J=15.6$ Hz, 1H), 2.93 (br d, $J=10.9$ Hz, 1H), 2.24 (dt, $J=11.2$, 2.7 Hz, 1 H), 1.20–2.10 (m, 7 H); ^{13}C NMR (75.4 MHz) δ 137.11, 134.04, 129.41, 127.54, 126.52, 126.08, 69.67, 62.39, 58.02, 56.14, 27.36, 25.23, 24.07; MS (FAB), *m/e* 204 (100, M + H), 186 (40), 84 (50); Anal. calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.94; H, 8.49; N, 6.74.

***trans*-1,3,4,6,11,11a-Hexahydro-11-acetyl-2*H*-benzo[*b*]quinolizidine (20).** A solution of AcCl (238 mL, 3.34 mmol) in CH_2Cl_2 (2 mL) was added to a solution of alcohol **18** (563 mg, 2.78 mmol) and Et_3N (465 mL, 3.34 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred at rt for 2 h and then diluted with CH_2Cl_2 (50 mL). The solution was washed with Na_2CO_3 (satd, 10 mL) and H_2O (10 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on silica gel column eluting with $CHCl_3$:MeOH:NH_4OH (99:0.8:0.2) followed by crystallization (EtOAc:

hexanes) to give **20** as a yellow solid: mp 116–117 °C; ^{1}H NMR (300 MHz) δ 7.03–7.22 (m, 4H), 5.97 (d, J = 8.6 Hz, H-11), 3.82 (d, J = 15.3 Hz, H-6), 3.49 (d, J = 15.1, H-6), 3.06 (br d, J = 11.2 Hz, 1H), 2.20–2.35 (m, 2H), 2.17 (s, CH_3), 1.64–1.96 (m, 3H), 1.25–1.47 (m, 3H); ^{13}C NMR (75.4 MHz) δ 171.16, 135.06, 132.43, 129.56, 128.35, 126.73, 125.80, 70.00, 61.21, 58.09, 56.48, 27.40, 25.36, 24.07, 21.24; MS (EI), *m*/*e* 246 (87, M + H), 186 (100); Anal. calcd for $C_{15}H_{19}NO_2 \cdot 0.1H_2O$: C, 72.91; H, 7.83; N, 5.67. Found: C, 72.87; H, 7.73; N, 5.60.

***cis*-1,3,4,6,11,11a-Hexahydro-11-acetoxy-2*H*-benzo[*b*]quinolizidine (7).** A solution of AcCl (82 mg, 1.05 mmol) in CH_2Cl_2 (1 mL) was added to a solution of alcohol **10** (193 mg, 0.95 mmol) and Et_3N (146 mL, 1.05 mmol) in CH_2Cl_2 (5 mL) at rt. The mixture was stirred at rt for 3 h and then diluted with CH_2Cl_2 (50 mL). The solution was washed with Na_2CO_3 (satd, 10 mL) and H_2O (10 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on silica gel column eluting with $CHCl_3$:MeOH:NH_4OH (99:0.8:0.2) followed by crystallization (EtOAc:hexanes) to give **7** as a yellow solid (59 mg, 26%): mp 92–94 °C; ^{1}H NMR (300 MHz) δ 7.16–7.34 (m, 3H), 7.07 (d, J = 7.4 Hz, 1H), 5.98 (d, J = 2.8 Hz, H-11), 4.00 (d, J = 15.6 Hz, H-6), 3.35 (d, J = 15.6, H-6), 3.19 (br d, J = 11.5 Hz, 1H), 2.45 (dt, J = 10.8, 3.1 Hz, 1H), 2.11 (s, CH_3), 1.85 (m, 1 H), 1.50–1.75 (m, 5 H), 1.35 (m, 1 H); ^{13}C NMR (75.4 MHz) δ 171.16, 135.06, 132.43, 129.56, 128.35, 126.73, 125.80, 70.00, 61.21, 58.09, 56.48, 27.40, 25.36, 24.07, 21.24; MS (EI), *m*/*e* 244 (6, M−H), 202 (54), 185 (100), 156 (23), 143 (13), 129 (15), 120 (60); HRMS (EI) *m*/*e* calcd for ($C_{15}H_{19}NO_2$−H) 244.1338, found 244.1330; Anal. calcd for $C_{15}H_{19}NO_2 \cdot H_2O$: C, 72.91; H, 7.83; N, 5.67. Found: C, 72.81; H, 7.56; N, 5.56.

***N*-Butyryl 6a (23).** Butyryl chloride (2.82 mmol, 295 mL) in CH_2Cl_2 (5 mL) was added dropwise to a solution of **6a** (2.56 mmol, 518 mg) and triethylamine (2.82 mmol, 393 mL) in CH_2Cl_2 (40 mL). The mixture was stirred overnight at rt. Saturated Na_2CO_3 solution (10 mL) was added and the aqueous layer was extracted with additional CH_2Cl_2 (2×30 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel eluting with CH_2Cl_2:MeOH:NH_4OH (150:8:1) to give **23** as a brown solid (299 mg, 43%): mp 141–143 °C; ^{1}H NMR (300 MHz) δ 7.34 (dd, J = 6.6, 2.4 Hz, 1H), 7.14–7.23 (m, 2H), 7.02 (dd, J = 6.6, 2.1 Hz, 1H), 6.10 (d, J = 9.6 Hz, 1H), 5.06 (dd, J = 9.9, 2.7 Hz, 1H), 3.92 (d, J = 15.6 Hz, 1H), 3.37 (d, J = 15.6 Hz, 1H), 3.09 (br d, J = 11.4 Hz, 1H), 2.44 (dt, J = 10.8, 3.0 Hz, 1H), 2.40 (m, 3H), 1.25–1.80 (m, 8H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75.4 MHz) δ 171.98, 135.98, 133.78, 129.19, 127.36, 126.75, 125.67, 60.78, 58.46, 56.37, 49.48, 38.85, 27.89, 25.57, 23.86, 19.21, 13.75; MS (FAB), *m*/*e* (100, M + H); Anal. calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 74.85; H, 8.67; N, 10.01.

***N*-[α-*N*-(2-oxopyrrolidinyl)acetyl 6a (25).** A solution of methyl 2-oxo-1-pyrrolidineacetate (10 mmol, 1.57 g, Aldrich) in THF (20 mL) and NaOH (1 N, 10 mL) was stirred at rt for 24 h. The mixture was acidified by the addition of HCl (1 N) and extracted with $CHCl_3$ (3×20 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give acid **24** as a colorless solid: mp 140–142 °C; ^{1}H NMR (300 MHz) δ 8.92 (br s, OH), 4.09 (s, 2 H), 3.53 (t, J = 7.1 Hz, 2H), 2.48 (t, J = 8.1 Hz, 2H), 2.10 (quin, J = 7.5 Hz, 2H); ^{13}C NMR (75.4 MHz) δ 176.72, 171.59, 48.13, 44.19, 30.35, 17.90; MS (FAB), *m*/*e* 144 (100, M + H), 98 (19); Anal. calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79. Found: C, 49.99; H, 6.21; N, 9.78.

A mixture of **24** (2.52 mmol, 360 mg) and carbonyldiimidazole (2.52 mmol, 408 mg) in THF (20 mL) was stirred at rt for 2 h. Compound **6a** in THF (5 mL) was added in 5 min. The mixture was stirred at rt for 40 h. It was acidified by the addition of HCl (0.5 N, 20 mL) and washed with ether (2×30 mL). The aqueous layer was basified by the addition of solid NaOH, and extracted with ether (3×50 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a brown solid. The solid was washed with ethyl acetate to give **25** as an off-white solid (387 mg, 47%): mp 174–176 °C (EtOAc); ^{1}H NMR (300 MHz) δ 7.32 (br d, J = 7.4 Hz, 1H), 7.13–7.23 (m, 2H), 7.02 (br d, J = 6.9 Hz, 1H), 6.46 (d, J = 9.6 Hz, NH), 4.97 (dd, J = 9.6, 2.4 Hz, 1H), 3.83–4.00 (m, 3H), 3.36–3.54 (m, 2H), 3.36 (d, J = 15.6 Hz, 1H), 3.08 (br d, J = 11.1 Hz, 1H), 1.26–2.49 (m, 12H); ^{13}C NMR (75.4 MHz) δ 175.56, 166.91, 135.52, 133.94, 128.97, 127.55, 126.69, 125.79, 60.34, 58.35, 56.15, 50.05, 48.01, 46.72, 30.33, 27.87, 25.55, 23.80, 17.97; MS (FAB), *m*/*e* 328 (100, M + H), 185 (38); Anal. calcd for $C_{19}H_{25}N_3O_2$: C, 69.70; H, 7.70; N, 12.83. Found: C, 69.46; H, 7.73; N, 12.69.

***trans*-10-*N*-Methylaminobenzindolizidine (5a).** Methylamine (lecture bottle, Fluka) was condensed at −78 °C into a flask containing the ketone 271 (8.8 mmol, 1.756 g) and CH_2Cl_2 (30 mL) was added. $TiCl_4$ (4.4 mmol, 4.4 mL of 1 M solution in toluene) was gradually added at −78 °C and the mixture was stirred at −78 °C for 30 min, then at rt for 22 h under N_2. Petroleum ether (bp 35–60 °C) (80 mL) was added and then the mixture was filtered through Celite. The filtrate was concentrated in vacuo to give **28** as a red viscous oil (1.63 g). ^{1}H NMR ($CDCl_3$): δ 1.90 (m, 1H), 2.42 (m, 1H), 2.56 (m, 1H), 2.79 (m, 1H), 3.45 (s, 3H), 4.04 (d, 1H), 4.87 (m, 1H), 5.14 (d, 1H), 7.15–7.44 (m, 3H), 8.00 (d, 1H).

Crude imine **28** (880 mg, 4.1 mmol) in 12 mL of THF was added dropwise to a suspension of $LiAlH_4$ (623 mg, 4.1 mmol) in 12 mL of THF at rt under N_2. After gently refluxing for 15.5 h, the mixture was cooled to rt, quenched by successive addition of water (0.88 mL), 15% NaOH (0.88 mL), and water (2.6 mL). This mixture was filtered through Celite and concentrated. The residue was dissolved in $CHCl_3$, dried over Na_2SO_4, filtered and concentrated to give 600 mg of a dark red viscous residue. It was dissolved in $CHCl_3$ and flash chromatographed on silica in CH_2Cl_2:MeOH:NH_4OH (95:4:1) to give 547 mg of a dark red viscous residue, **5a**: ^{1}H NMR ($CDCl_3$) δ 1.69 (m, 1H), 1.87 (m, 2H), 2.28 (m, 1H), 2.41 (s, 3H), 2.47 (m, 1H), 2.58 (m, 1H), 3.17 (m, 1H),

3.62 (d, $J=14.0$ Hz, 1H), 3.79 (d, $J=10.01$ Hz, 1H), 4.03 (d, $J=14.03$ Hz, 1H), 7.09 (d, $J=7.63$ Hz, 1H), 7.17 (t, $J=7.76$, 15.13 Hz, 1H), 7.25 (t, $J=7.23$, 14.47 Hz, 1H), 7.52 (d, $J=7.63$ Hz, 1H), NH is not discernible and probably appears between δ 1 and δ 4; ^{13}C NMR ($CDCl_3$) δ 21.57, 30.04, 32.33, 54.71, 55.85, 62.70, 64.92, 126.20 (2C), 126.37, 126.63, 135.83, 137.24; IR (neat film) 3285 (broad), 3060, 3020, 2950, 2870, 2795, 1735–1565 (broad) 1475, 1450, 1155, 1035, 920, 905, 780, 720 cm^{-1}; MS (FAB) *m/e* 203 (M+H, 74.8%), 201 (74.1), 172 (M−$NHCH_3$, 100), 170 (85), 133 (53.1), 132 (27), 118 (17.7). HRMS (FAB): $C_{13}H_{18}N_2$, calcd 202.1469 Found 203.1555 M+H).

***trans*-10-*N*-Methylaminobenzindolizidin-3-one (29).** Crude imine **28** (800 mg, 3.7 mmol) was dissolved in 13 mL of absolute ethanol and cooled to 0 °C. The cold solution was treated with portions of $NaBH_4$ (560 mg, 14.8 mmol) with stirring at 0 °C for 30 min, then at rt for 18 h. Quenching with water (20 mL) followed by extraction with CH_2Cl_2 (4×20 mL), drying and concentration gave 677 mg of residue, which was chromatographed as described for **5a** above to give 456 mg of a yellow oil. After extraction into acid and basification, recovery and rechromatography yielded 424 mg (53%) of a yellow oil that crystallized on standing; mp 88–90 °C. ^{1}H NMR ($CDCl_3$) δ 2.05 (m, 1H), 2.48 (s, 3H), 2.40–2.48 (m, 3H), 3.65 (d, $J=9.46$ Hz, 1H), 3.70 (m, 1H), 4.24 (d, $J=17.45$ Hz, 1H), 4.92 (d, $J=17.45$ Hz, 1H), 7.16 (d, $J=6.85$ Hz, 1H), 7.25 (m, 2H), 7.53 (d, $J=7.22$ Hz, 1H). (The presence of *cis* isomer (10%) was indicated by a doublet of the benzylic hydrogen at δ 3.45 ($J=2.63$ Hz). IR (neat film): 3430, 3345, 1670, 1655, 1575, 1283, 1093, 1080, 975, 749 cm^{-1}; MS (FAB): *m/z* 217 (M+H, 100), 186 (41), 154 (15), 133 (27), 118 (14); HRMS (FAB) calcd for $C_{13}H_{17}N_2O$ (M+H): 217.1341; obs. 217.1359. Anal. calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.11; H, 7.33; N, 12.88.

***cis*-10-*N*-Methylaminobenzindolizidin-3-one (29a).** A mixture of imine **28** (159 mg) and Pd/C (10%, 110 mg) in EtOH (10 mL) was hydrogenated (50 psi) overnight, and then filtered. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel eluting with (CH_2Cl_2:MeOH:NH_4OH (150:8:1) to give **29a** as an oil (11 mg, 8%): ^{1}H NMR (300 MHz) δ 7.25 (m, 4H), 4.92 (d, $J=18.0$ Hz, 1H), 4.31 (d, $J=17.7$ Hz, 1H), 3.95 (m, 1H), 3.43 (d, $J=2.7$ Hz, 1H), 2.38 (s, NCH_3); MS (FAB), *m/e* 217 (100, M+H), 154 (55), 136 (45).

Determination of cholinesterase and acetylcholinesterase activities. Wistar rat brain (postnatal day 80) was homogenized in 10% (w/v) of icecold 50 mM Tris-buffered saline (0.9% w/v) containing ethylenediaminetetraacetic acid (1 mM), bovine serum albumin (1% w/v) and Triton X 100 (0.5% w/v). Homogenates were centrifuged at 10,000 g for 10 min at 4 °C. Supernatants were decanted and stored in aliquots at −70 °C until required. Protein content was determined by the method of Lowry et al.[15]

Enzyme activity was assayed according to the spectrophotometric method of Ellman et al.[16] with the modifications described by Whittaker.[17] Briefly, the assay was carried out at room temperature using 0.1 M phosphate buffer, pH 8.0, containing 0.075 M acetylthiocholine iodide, 0.01 M 5,5-dithio-bis-2-nitrobenzoic acid (DTNB) and, in the case of acetylcholinesterase determinations, 0.03 M ethopropazine. The DTNB was prepared in 0.1 M phosphate buffer, pH 7.0, which contained 0.018 M sodium bicarbonate to ensure stability. The ethopropazine was prepared in ethanol, the concentration of which never exceeded 0.3%. The reaction was started by the addition of 15 μL of enzyme preparation to a final assay volume of 1.585 mL, mixed thoroughly and progress was monitored continuously for 5 min at 412 nM in a Philips PU 8625 UV/VIS spectrophotometer. All solutions were freshly prepared and protected from light. The acetylthiocholine, DTNB, and ethopropazine were obtained from Sigma Chemical Co. Ltd. (UK). All other reagents were of the highest grade available from routine suppliers.

For K_m and V_{max} determinations, the concentration of acetylthiocholine iodide ranged from 8.52 to 93 mM. The analogues to be tested were added to a final concentration of 0.5 mM. In the majority of cases these were soluble in aqueous solutions; however, where compounds were insoluble, either dimethylsulfoxide (DMSO) or citric acid was employed as a vehicle and this was included always in the control.

Passive avoidance training. Postnatal day 80 male Wistar rats (300–350 g) were obtained from the Biomedical Facility, University College Dublin. These were housed singly in a 12 h light/dark cycle with food and water available ad libitum. Animals employed for neurobehavioural studies were maintained and handled in the test environment for 5 days prior to the commencement of studies. Animals were handled daily for a minimum of 3 min and, on days 3, 4 and 5, their weights monitored and spontaneous behavior was assessed in an open field apparatus for 5 min. On day of training and immediately preceding time of recall, spontaneous behavior was reassessed. All studies were carried out in a soundproofed, darkened room and all experimental procedures were approved by the Review Committee of the Biomedical Facility of University College, Dublin and were carried out by individuals who held the appropriate licence issued by the Ministry of Health.

Animals were trained in a one-trial, step-through, light–dark passive avoidance paradigm as described previously.[18] The apparatus consisted of a box measuring 300 mm wide ×260 mm deep×270 mm high. The front and top were transparent, allowing observation of behavior inside the apparatus. The box was divided into two compartments, separated by a central shutter that contained a small opening 50 mm wide and 75 mm high. The smaller of the compartments measured 90 mm in width and contained a low power (6v) illumination source—the lighted compartment. The larger compartment measured 210 mm in width and was not illuminated. The floor of the dark compartment consisted of a grid of stainless steel bars which could deliver a

remotely-controlled, scrambled footshock (0.75 mA every 0.5 ms) of 5 s duration. Training entailed the animal being placed within the light compartment, and recording the latency to enter the dark compartment with all four paws; at that time the animal received the remote footshock. Animals were tested for recall of this inhibitory stimulus prior to sacrifice by placing them into the light compartment and noting their latency to enter the dark compartment. A criterion period of 600 s was used. On the day of training animals were administered the test compound or saline control via the intraperitoneal route 30 min prior to training. Animals rendered amnesic received scopolamine (0.8 mg/kg ip) 20 min prior to training.

Recall latency was assessed at 24 h post training. The results are expressed as the mean ± SEM and significance determined using the Mann–Whitney U-test for nonparametric data.

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