Expedited Articles

5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6*H*-pyrrolo[3,2-*f*]-1,2-benzisoxazol-6-one: A Potent and Centrally-Selective Inhibitor of Acetylcholinesterase with an Improved Margin of Safety

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Received April 10, 1995[®]

A series of *N*-benzylpiperidines (**2a–d**, **10**) with novel isoxazole-containing tricycles has been prepared. This series has shown potent *in vitro* inhibition of the enzyme acetylcholinesterase (AChE), with IC_{50}s = 0.33–3.6 nM. Compound **2a** was the most potent inhibitor with an IC_{50} = 0.33 ± 0.09 nM. Derivatives **2a–d** and **10** displayed weak *in vitro* inhibition of butyrylcholinesterase (BuChE) with IC_{50}s = 600–23 000 nM. The most selective compound was **2a** with a BuChE/AChE ratio in excess of 4 orders of magnitude (>10 000). Pyrrolobenzisoxazole **2a** also displayed a favorable profile *in vivo*. In microdialysis experiments, **2a** produced a 200% increase in extracellular levels of acetylcholine (ACh) at a dose of 0.4 mg/kg in freely moving, conscious rats. Peripheral side effects (salivation ED_{50} = 26 ± 1.5 mg/kg) and acute lethality (LD_{50}[1 h] = 42 mg/kg) were observed at >60-fold higher doses. These data indicate that **2a** is an AChE inhibitor with good central selectivity and a favorable margin of safety. Compound **2a**, designated as CP-118,954, is currently in clinical development for the treatment of cognitive disorders.

The loss of cholinergic neurons is one of the most pronounced and consistent neuropathological findings in the brains of patients with Alzheimer's disease (AD). Cholinergic projections in the basal forebrain and activity of cholinergic markers such as choline acetyltransferase are markedly reduced in AD.[1,2] These findings together with studies which indicate that muscarinic antagonists (*e.g.* scopolamine) can lead to memory impairments in normal subjects[3] have led to the cholinergic hypothesis of AD, which postulates that cognitive decline in patients with AD results from a deficit in cholinergic neurotransmission.[4] Agents which potentiate cholinergic action may thus be useful as palliative therapy in mild to moderate AD or other cognitive disorders such as age-associated memory decline (AAMD).[5]

Clinical studies with different classes of acetylcholinesterase (AChE) inhibitors suggest that these agents may be able to enhance memory in patients with AD.[6,8–11] Recent controlled trials with the aminoacridine tacrine (Figure 1) have demonstrated significant, albeit modest, efficacy in AD.[6] Tacrine, however, also produces a high incidence of elevation of liver enzymes, a dose-limiting side effect that may be related to its chemical structure rather than its pharmacological mechanism.[7] Another type of inhibitor, the carbamate physostigmine (Figure 1), has shown mixed results in clinical studies possibly due to its short half-life and narrow therapeutic index.[8,9] A controlled-release formulation of physostigmine is currently under clinical evaluation.[10] E-2020 (Figure 1), an *N*-benzylpiperidine inhibitor, is also presently being evaluated in the clinic.[11]

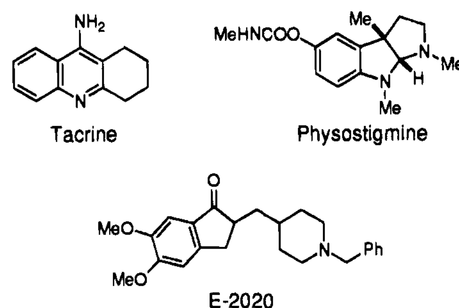

Figure 1. Acetylcholinesterase inhibitors.

We became interested in the *N*-benzylpiperidine class of inhibitors[12] due to their selectivity for acetyl- over butyrylcholinesterase (BuChE), a property not shared by most aminoacridines and carbamates. BuChE is an enzyme found in both the central nervous system and the periphery, and it is abundant in plasma.[13] The physiological role of BuChE has not been clearly defined, but inhibition of this enzyme by nonselective AChE inhibitors may contribute to potentiation of peripheral side effects.[14,21] As a consequence, a selective agent may display enhanced central selectivity, that is, better separation between efficacious doses and onset of side effects. Such selectivity may thus lead to well-tolerated and safer agents in the clinic.

Recently, we reported on novel *N*-benzylpiperidine benzisoxazoles as potent and selective inhibitors of AChE.[15] The *N*-acetyl derivative **1** (Figure 2) displayed potent *in vitro* inhibition (IC_{50} = 2.8 nM) and promising

® Abstract published in *Advance ACS Abstracts*, July 1, 1995.

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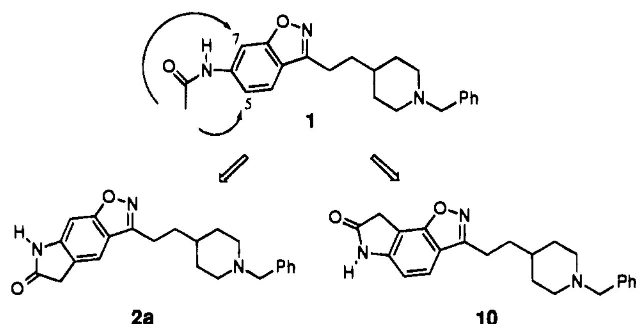
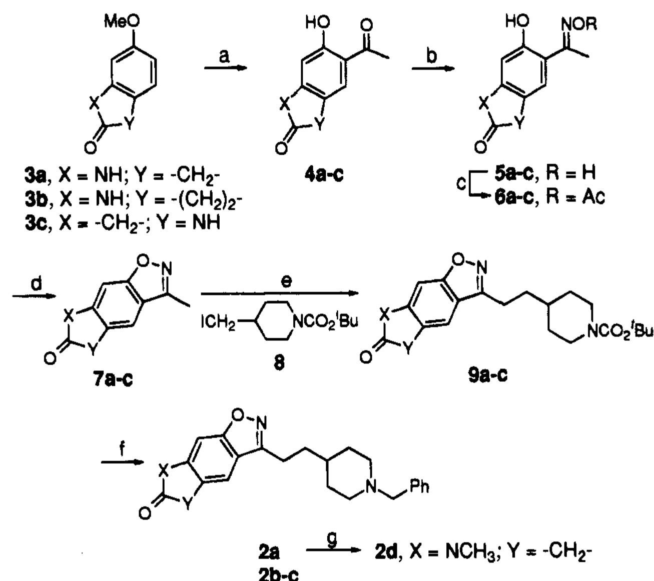


Figure 2. Conformational restriction of the *N*-acetyl side chain in 1 into isomeric frameworks.

Scheme 1



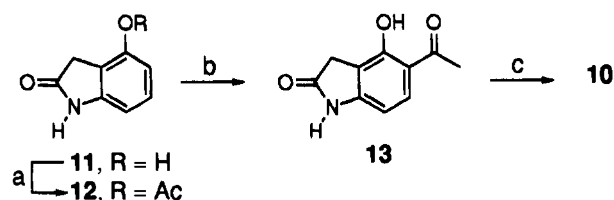
^{a} Reagents: (a) CH_3COCl, $AlCl_3$, CS_2, or 1,2-dichloroethane, reflux, 50–87%; (b) $NH_2OH{\cdot}HCl$, $NaOAc{\cdot}3H_2O$, EtOH, H_2O, reflux, 82–100%; (c) Ac_2O, 80 °C, 54–90%; (d) pyridine, DMF, 130 °C, 12–66%; (e) 4 equiv of LDA, **8**, THF, −78 °C, 51–58%; (f) (i) TFA, CH_2Cl_2, 0 °C; (ii) $PhCH_2Br$, Na_2CO_3, DMF, room temperature, 43–70% overall; (g) NaH, MeI, DMF, room temperature, 36%.

in vivo activity. However, preliminary studies indicated that **1** was metabolically labile, partially undergoing hydrolysis of the acetamido group to produce the corresponding anilino derivative which was 7-fold less potent (IC_{50} = 20 nM). In attempts to enhance the metabolic stability, we proposed the synthesis of *N*-benzylpiperidines with novel isoxazole-containing tricyclic frameworks (Figure 2). The *N*-acetyl functionality would be conformationally restricted in five- (or six-)membered ring heterocycles which were anticipated to be more stable toward metabolic degradation. This article describes the design, synthesis, and biological profile of **2a**, a potent pyrrolobenzisoxazole inhibitor of AChE essentially devoid of BuChE inhibition, and related analogs. In addition, we demonstrate that **2a** is a centrally-selective inhibitor of AChE with an improved margin of safety in comparison to tacrine, the only approved inhibitor for the palliative treatment of AD in the US.

Chemistry

The synthesis of **2a–d** is described in Scheme 1. Friedel–Crafts acylation of **3a–c**[16,17] with acetyl chloride and $AlCl_3$ gave desired *o*-hydroxyacetophenones **4a–c** in 50–90% yield. Treatment with hydroxylamine hydrochloride and sodium acetate in aqueous EtOH afforded oximes **5a–c** which were acylated with acetic anhydride at 80 °C to give the corresponding oxime acetates **6a–c**.[15] Formation of the isoxazole ring[18] was accomplished by heating in DMF in the presence of pyridine to afford tricycles **7a–c**. Selective alkylation of the methyl functionality[15,19] was carried out by deprotonation with 3–4 equiv of LDA in THF at −78 °C followed by addition of iodide **8**[15] to give *N*-BOC carbamates **9a–c**. Removal of the *N*-BOC protecting group was accomplished by treatment with trifluoroacetic acid–CH_2Cl_2 (1:4) at 0 °C for 0.5 h. The intermediate secondary piperidines were not isolated, but treated directly with benzyl bromide and Na_2CO_3 in DMF to afford final *N*-benzylpiperidine tricycles **2a–c**. Deprotonation of **2a** with NaH followed by alkylation with methyl iodide in DMF afforded *N*-methyl analog **2d**. Isomer **10** was prepared from 4-hydroxyoxindole[16] (**11**) as described in Scheme 2. Acetylation under standard conditions (Ac_2O, pyridine) afforded acetate **12** in quantitative yield. Acid-catalyzed Fries rearrangement ($AlCl_3$, 180–190°C) of **12** gave the corresponding *o*-hydroxyacetophenone **13**. Attempts to carry out Friedel–Crafts acylation on 4-methoxyoxindole as described above for **3a,c** only resulted in isolation of the undesired *para*-acetylated isomer. Compound **13** was subjected to the sequence described in Scheme 1 to give oxime **14**, oxime acetate **15**, tricycle **16**, and *N*-BOC carbamate **17** which, after final deprotection and alkylation, afforded N-benzylpiperidine **10**.

Scheme 2



^{a} Reagents: (a) Ac_2O, pyridine, room temperature, quantitative; (b) $AlCl_3$, 180–190 °C, 50%; (c) Scheme 1, steps b–f.

Biological Results and Discussion

In order to enhance the metabolic stability of **1** and further explore structure–activity relationships (SAR), we proposed the synthesis of derivatives in which the *N*-acetyl moiety would be conformationally restricted and incorporated into five- or six-membered ring lactam functionalities. This effort led to the preparation of *N*-benzylpiperidines **2a–d** and **10** containing previously unknown isoxazole tricycles. The *in vitro* inhibition of AChE by these compounds was determined by the method of Ellman *et al.*,[20] and results are presented in Table 1. Compound **2a** was the most potent inhibitor with an IC_{50} = 0.33 nM. Constraining the acetamido functionality in a five-membered ring toward carbon 5 (Figure 2) thus resulted in a favorable conformation in comparison to unrestricted derivative **1**. Expanding the ring by one carbon gave the more flexible six-membered ring derivative **2b** which displayed a 2-fold loss in potency relative to **2a**. Exchanging the position of the lactam nitrogen (**2c**) also resulted in slight loss of inhibitory activity, while N-methylation resulted in an equipotent derivative (**2d**). Finally, constraining the acetamido functionality in a five-membered ring toward carbon 7 (Figure 2) resulted in analog **10** which was 10

Table 1. Comparison of the *in Vitro* Selectivity for AChE[a] *vs* BuChE[b] Displayed by **2a–d**, **10**, and Known AChE Inhibitors

compd	IC_{50} (nM)[c] AChE	BuChE	ratio BuCHE/AChE
1[d]	2.8 ± 2.2	9000 ± 300	3200
2a[e]	0.33 ± 0.09	7200 ± 1200	23000
2b[f]	0.57 ± 0.17	4000 ± 1900	7000
2c[f]	0.95 ± 0.43	3900 ± 1500	4000
2d[g]	0.48 ± 0.05	4500 ± 1200	9300
10[f]	3.6 ± 1.0	2200 ± 600	600
tacrine	170 ± 11	6.0 ± 0.01	0.04
physostigmine	19 ± 5.0	73 ± 6.0	3.8

[a] Source of AChE: human erythrocytes. [b] Source of BuCHE: human serum. [c] IC_{50} values are the mean ± standard deviation of three assays. [d] Fumarate salt. See ref 15. [e] Maleate salt. [f] Free base. [g] Methanesulfonate salt.

times less potent than **2a**, but equipotent with **1**. Obviously, the orientation of the acetamido group is less favorable in isomeric **10**. Even though all compounds are potent inhibitors of AChE, the conformation and orientation of the amide functionality in **2a** seems to be optimum, although not crucial, for inhibitory activity. This SAR is consistent with the model proposed for the binding of this class of inhibitors to AChE (from *Torpedo californica*).[15]

Pyrrolobenzisoxazole **2a** was studied *in vivo* for its ability to elevate ACh after oral administration in rodents. This compound significantly increased extracellular levels of ACh in the striatum of conscious, freely moving rats as determined by microdialysis experiments (Figure 3, panel a). This effect was dose- and time-dependent, with peak elevation of ACh levels taking place at 1–1.5 h after administration of drug. Compound **2a** produced a 200% increase in the area under the curve (AUC) over basal accumulation during the 3 h period after drug administration at a calculated dose of 0.4 mg/kg. In this experiment, **2a** was about 20 times more potent than tacrine which produced a comparable effect at a calculated dose of 9.0 mg/kg (Figure 3, panel b).

Favorable separation between doses that produce desired central effects (elevation of ACh) and those that lead to peripheral side effects (*e.g.* salivation) and lethality is a key feature in the development of successful AChE inhibitors. It has been reported that inhibition of BuChE, under conditions in which AChE is inhibited, results in potentiation of peripheral cholinergic responses *in vitro*.[21] Moreover, Thomsen *et al.*[14] have suggested that selective inhibitors of AChE may be better tolerated than nonselective agents in the treatment of AD. Analogs **2a–d** and **10** displayed weak inhibition of BuChE as shown in Table 1. Pyrrolobenzisoxazole **2a** was essentially devoid of BuChE inhibition with a selectivity ratio in excess of 4 orders of magnitude. Table 2 shows that **2a** exhibited superior selectivity and safety indices over tacrine which, on the other hand, preferentially inhibits BuChE (Table 1). The selectivity index for elevation of extracellular levels of ACh *vs* salivation was 65 for **2a** while tacrine displayed an index of 2.2. In addition, **2a** showed a remarkable margin of safety for an AChE inhibitor. The safety index for elevation of extracellular levels of ACh *vs* lethality was 105 compared to 7.8 for tacrine. These results suggest that the central selectivity and margin of safety of **2a** may be a result of its selective inhibition of AChE *vs* BuChE.

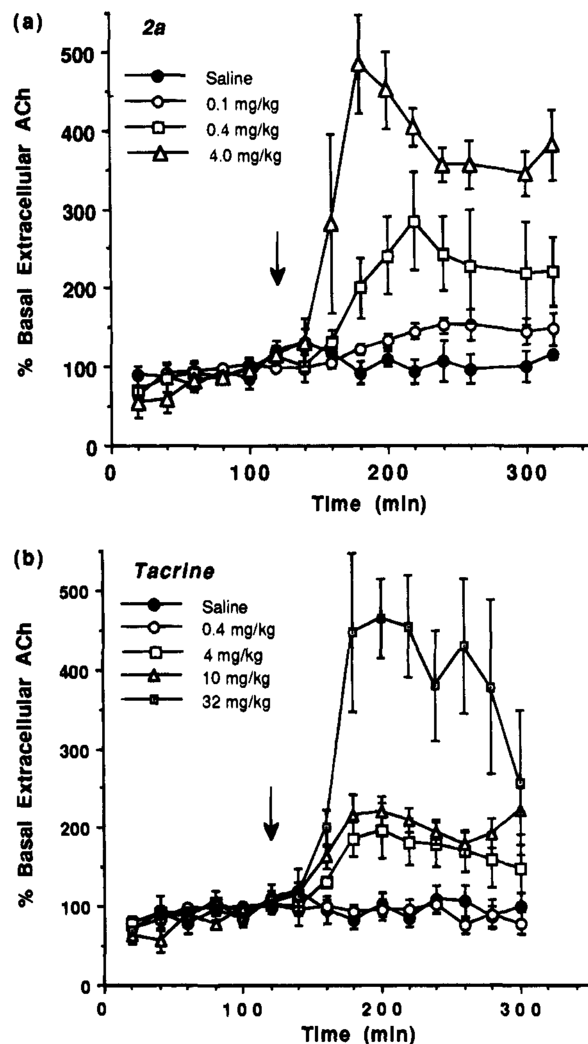


Figure 3. Elevation of extracellular ACh in striatum of conscious, freely moving rats: panel a, **2a**; and panel b, tacrine. Fractions were collected every 20 min for 2 h before drug administration (arrow) and for 3 h following oral administration of drug. Linear regression of the dose–response curves calculated from areas under the curve [ACh (% saline AUC) *vs* dose (mg/kg)] was carried out. On the basis of these calculations, **2a** and tacrine produced a 200% increase in AUC over basal accumulation at doses of 0.4 and 9.0 mg/kg, respectively.

In summary, *N*-benzylpiperidines with novel isoxazole-containing tricycles have been prepared and found to be potent and selective inhibitors of AChE *in vitro*. Pyrrolobenzisoxazole **2a** was the most potent inhibitor of AChE (IC_{50} = 0.33 nM), essentially devoid of BuChE inhibition (IC_{50} = 7200 nM). Compound **2a** also resulted in elevation of ACh *in vivo* as measured by microdialysis experiments in conscious, freely moving rats. In addition, **2a** displayed favorable separation between doses leading to elevation of extracellular ACh and peripheral side effects and lethality, with selectivity and safety indices in excess of 60-fold. The central selectivity and margin of safety for **2a** may be due to its selective inhibition of AChE. Compound **2a**, which has been designated as CP-118,954, is currently in clinical development for the treatment of cognitive disorders.

Experimental Section

Melting points were determined in a Thomas-Hoover or Electrothermal capillary melting point apparatus and are uncorrected. High-field ^{1}H-NMR spectra were recorded on a

Table 2. Cholinergic Effects of **2a** and Tacrine in Rats after Oral Administration:[a] Selectivity and Safety Indices

	2a	tacrine
Central Effects		
extracellular ACh ED_{50} (mg/kg)	0.4 ± 1.2	9.0 ± 1.2
Peripheral Effects		
salivation ED_{50} (mg/kg)	26 ± 1.5	20 ± 1.1
acute lethality LD_{50} (mg/kg)	42 (28–63)	70
Selectivity Index		
salivation/extracellular ACh	65	2.2
Saftey Index		
acute lethality/extracellular ACh	105	7.8

[a] The ED_{50} for extracellular ACh is presented as the dose that produced a 200% increase in the area under the curve (AUC) over basal accumulation during the 3 h period after drug administration. The ED_{50} for salivation was defined as the dose required to produce a level 2 rating on a 0–4 point scale 1 h after treatment. The LD_{50} is defined as the dose that resulted in the death of 50% of the animals 1 h after treatment as determined using a probit analysis. Values are the mean of multiple dose–response experiments (2–3) with a minimum of six animals at each of a minimum of four concentrations of drug. Variability represents sd for ED_{50} values, and 95% confidence intervals are shown in parentheses for LD_{50} measures. No 95% ci for the tacrine LD_{50} is presented because there were only two data points between 100% survival and 100% mortality. Compound **2a** was tested as the maleate salt.

Bruker AM 250, Bruker AM 300, or Varian XL-300 instrument. Low- and high-resolution electron impact mass spectra (EIMS and EIHRMS) were recorded in a Kratos Profile instrument. Low- and high-resolution fast-atom bombardment mass spectra (FABMS and FABHRMS) were recorded in a Kratos Concept instrument. Low-resolution chemical ionization spectra (CIMS) were recorded in a Hewlett-Packard 5989A instrument. Elemental analyses were carried out by Mr. J. W. Greene, Analytical Department, Pfizer Inc, or by Schwarzkopf Microanalytical, Woodside, NY. Flash chromatography was performed on EM Kieselgel 60 (40–60 μm, 230–400 mesh).

All reactions were carried out under a positive pressure of nitrogen, unless otherwise noted. Tetrahydrofuran (THF) was distilled immediately before use from sodium benzophenone ketyl. Anhydrous methylene chloride (CH_2Cl_2), 1,2-dichloroethane, dimethylformamide (DMF), and pyridine were purchased from Aldrich Chemical Co.

5-Acetyl-1,3-dihydro-6-hydroxy-2*H*-indol-2-one (4a). Acetyl chloride (4.09 mL, 0.0575 mol) was added to a slurry of $AlCl_3$ (35.36 g, 0.265 mol) in carbon disulfide (250 mL). After 5 min, 6-methoxyoxindole[16] (**3a**) (7.22 g, 0.0442 mol) was added, and the resulting mixture was heated to reflux for 2.5 h. Excess solvent was decanted, and ice water was added carefully to the residue. The resulting mixture was stirred overnight. The pale yellow solid obtained was collected, washed with water, and dried under high vacuum to give **4a** (7.32 g, 87%). A small sample was purified by recrystallization from EtOAc to give a white solid: mp (EtOAc) 274–275 °C; ^{1}H NMR (DMSO-d_6) δ 13.0 (s, 1H), 10.8 (s, 1H), 7.70 (s, 1H), 6.30 (s, 1H), 3.40 (s, 2H), 2.54 (s, 3H); IR (KBr) 3098, 1721, 1638 cm^{-1}; CIMS *m/e* (rel intensity) 192 ([M + 1]$^+$, 100). Anal. ($C_{10}H_9NO_3$) C, H, N.

6-Acetyl-3,4-dihydro-7-hydroxy-2*H*-quinolin-2-one (4b). Acetyl chloride (2.0 mL, 28.1 mmol) was added to a mixture of 3,4-dihydro-7-methoxy-2*H*-quinolin-2-one[17] (**3b**) (1.99 g, 11.2 mmol) in 1,2-dichloroethane (30 mL). The mixture obtained was cooled to 0 °C, and $AlCl_3$ (6.0 g, 44.98 mmol) was added in portions. The reaction was heated to reflux for 2 h. The mixture was cautiously poured over ice–H_2O, stirred for a minimum of 1 h (to overnight), and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated to give **4b** (1.89 g, 82%) as an off-white solid: mp 263–265 °C; ^{1}H NMR (DMSO-d_6) δ 12.4 (s, 1H), 10.4 (s, 1H), 7.74 (s, 1H), 6.38 (s, 1H), 2.86 (t, 2H, J = 7.4 Hz), 2.56 (s, 3H), 2.46–2.56 (m, 2H); IR (KBr) 3144, 1698, 1644 cm^{-1}; CIMS *m/e* (rel intensity) 206 ([M + 1]$^+$, 100). Anal. ($C_{11}H_{11}NO_3$) C, H, N.

6-Acetyl-1,3-dihydro-5-hydroxy-2*H*-indol-2-one (4c). The procedure described above for the preparation of **4b** was followed with 5-methoxyoxindole[16] (**3c**) (4.4 g, 26.96 mmol), acetyl chloride (4.8 mL, 67.41 mmol), and $AlCl_3$ (14.4 g, 107.8 mmol) in 1,2-dichloroethane (210 mL) for 6 h to give **4c** (2.7 g, 52%) as a pale yellow solid: mp 224–226 °C; ^{1}H NMR (DMSO-d_6) δ 12.0 (s, 1H), 10.4 (s, 1H), 7.12 (s, 1H), 6.89 (s, 1H), 3.54 (s, 2H), 2.61 (s, 3H); IR (KBr) 3208, 1721, 1631 cm^{-1}; EIMS *m/e* (rel intensity) 191 (M$^+$, 100); EIHRMS calcd for $C_{10}H_9NO_3$ 191.0583, found 191.0582.

4-(Acetyloxy)-1,3-dihydro-2*H*-indol-2-one (12). A mixture of 4-hydroxyoxindole[16] (11) (0.80 g, 5.36 mmol) in acetic anhydride (45 mL) and pyridine (15 mL) was stirred at room temperature for 15 min. The mixture was concentrated, and the residue was azeotroped twice from toluene to give **12** (1.01 g, quantitative) as an off-white solid. A small sample was purified by recrystallization from EtOAc to give off-white crystals: mp (EtOAc) 181–182 °C; ^{1}H NMR (DMSO-d_6) δ 10.53 (br s, 1H), 7.21 (t, 1H, J = 8.0 Hz), 6.72 (d, 1H, J = 7.4 Hz), 6.69 (d, 1H, J = 8.5 Hz), 3.32 (s, 2H), 2.27 (s, 3H); IR (KBr) 3186, 1773, 1704, 1636 cm^{-1}; EIMS *m/e* (rel intensity) 191 (M$^+$, 20), 149 (100). Anal. ($C_{10}H_9NO_3$) C, H, N.

5-Acetyl-1,3-dihydro-4-hydroxy-2*H*-indol-2-one (13). An intimate mixture of **12** (0.876 g, 4.58 mmol) and $AlCl_3$ (1.83 g, 13.7 mmol) placed in a tear-shape flask was immersed in an oil bath preheated to 190 °C and heated for 1 h. Ice–water was added cautiously to the cooled reaction mixture which was stirred for 1.5 h. Concentrated HCl was added, and the mixture was extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (1 → 3% MeOH–CH_2Cl_2) gave **13** (0.441 g, 50%) as an off-white solid: mp 255–256 °C dec; ^{1}H NMR (DMSO-d_6) δ 12.6 (s, 1H), 10.8 (s, 1H), 7.85 (d, 1H, J = 8.4 Hz), 6.49 (d, 1H, J = 8.4 Hz), 3.41 (s, 2H), 2.57 (s, 3H); IR (KBr) 3163, 1730, 1656 cm^{-1}; EIMS *m/e* (rel intensity) 191 (M$^+$, 100). Anal. ($C_{10}H_9NO_3 \cdot 0.25H_2O$) C, H, N.

5-Acetyl-1,3-dihydro-6-hydroxy-2*H*-indol-2-one, 5-Oxime (5a). An aqueous solution of hydroxylamine hydrochloride (8.26 g, 0.119 mol) and sodium acetate trihydrate (16.9 g, 0.124 mol) was added to **4a** (9.88 g, 0.0517 mol) in EtOH (600 mL). The resulting mixture was heated to reflux for 20 h. The hot reaction mixture was filtered, and the solid collected was rinsed with EtOH. [Alternate workup: the reaction was concentrated, and the residue was stirred with H_2O. The solid obtained was collected by filtration, and rinsed with H_2O, EtOH and Et_2O.] After drying, **5a** (10.11 g, 95%) was obtained as a pale yellow solid. A small sample was purified by recrystallization from 2-propanol–EtOAc to give a white solid: mp (*i*-PrOH–EtOAc) 301–302 °C; ^{1}H NMR (DMSO-d_6) δ 12.0 (s, 1H), 11.4 (s, 1H), 10.5 (s, 1H), 7.29 (s, 1H), 6.35 (s, 1H), 3.38 (s, 2H), 2.20 (s, 3H); IR (KBr) 3217, 1685, 1634 cm^{-1}; CIMS *m/e* (rel intensity) 207 ([M + 1]$^+$, 100); FABHRMS calcd for $C_{10}H_{10}N_2O_3$ 207.0770 found 207.0768.

A similar procedure was followed for the preparation of oximes **5b,c** and **14** starting from the corresponding *o*-hydroxyacetophenones **4b,c** and **13**.

6-Acetyl-3,4-dihydro-7-hydroxy-2*H*-quinolin-2-one, 6-oxime (5b): 82%, off-white solid; mp 286–288 °C dec; ^{1}H NMR (DMSO-d_6) δ 11.7 (s, 1H), 11.3 (s, 1H), 10.1 (s, 1H), 7.28 (s, 1H), 6.37 (s, 1H), 2.81 (t, 2H, J = 7.5 Hz), 2.43 (t, 2H, J = 7.5 Hz), 2.21 (s, 3H); IR (KBr) 3204, 1659, 1632 cm^{-1}; CIMS *m/e* (rel intensity) 221 ([M + 1]$^+$, 100). Anal. ($C_{11}H_{12}N_2O_3$) C, H, N.

6-Acetyl-1,3-dihydro-5-hydroxy-2*H*-indol-2-one, 6-oxime (5c): 93%, off-white solid; mp 290–293 °C dec; ^{1}H NMR (DMSO-d_6) δ 11.5 (s, 1H), 11.3 (s, 1H), 10.2 (s, 1H), 6.81 (s, 1H), 6.78 (s, 1H), 3.44 (s, 2H), 2.22 (s, 3H); IR (KBr) 2860, 1708, 1674 cm^{-1}; EIMS *m/e* (rel intensity) 206 (M$^+$, 100). Anal. ($C_{10}H_{10}N_2O_3$) C, H, N.

5-Acetyl-1,3-dihydro-4-hydroxy-2*H*-indol-2-one, 5-oxime (14): 100%, off-white solid; mp (EtOAc) 290–291 °C; ^{1}H NMR (DMSO-d_6) δ 12.0 (s, 1H), 11.4 (s, 1H), 10.4 (s, 1H), 7.35 (d, 1H, J = 8.2 Hz), 6.41 (d, 1H, 8.3 Hz), 3.34 (s, 2H), 2.22 (s,

3H); IR (KBr) 3193, 1681, 1626 cm^{-1}; CIMS *m/e* (rel intensity) 207 ([M + 1]$^+$, 100). Anal. ($C_{10}H_{10}N_2O_3$) C, H, N.

5-Acetyl-1,3-dihydro-6-hydroxy-2*H*-indol-2-one, 5-Oxime Acetate (6a). A heterogeneous mixture of **5a** (7.15 g, 34.7 mol) in acetic anhydride (55 mL) was heated at 80°C for 2 h. The cooled reaction mixture was filtered, and the solid collected was rinsed with water. [Alternate workup: the reaction mixture was concentrated, and excess acetic anhydride was removed by concentrating from toluene.] After drying, **6a** (4.67 g, 54%) was obtained as a pale yellow solid. A small sample was purified by recrystallization from acetone to give a white solid: mp (acetone) 208–210 °C; ^{1}H NMR (DMSO-d_6) δ 11.3 (s, 1H), 10.6 (s, 1H), 7.35 (s, 1H), 6.44 (s, 1H), 3.41 (s, 2H), 2.37 (s, 3H), 2.21 (s, 3H); IR (KBr) 3174, 1772, 1707, 1638 cm^{-1}; CIMS *m/e* (rel intensity) 249 ([M + 1]$^+$, 2), 189 (100). Anal. ($C_{12}H_{12}N_2O_4$) C, H, N.

A similar procedure was followed for the preparation of oxime acetates **6b,c** and **15** starting from the corresponding oximes **5b,c**, and **14**.

6-Acetyl-3,4-dihydro-7-hydroxy-2*H*-quinolin-2-one, 6-oxime acetate (6b): 86%, off-white solid; mp (acetone) 221–223 °C dec; ^{1}H NMR (DMSO-d_6) δ 11.0 (s, 1H), 10.2 (s, 1H), 7.36 (s, 1H), 6.44 (s, 1H), 2.82 (t, 2H, *J* = 7.5 Hz), 2.45 (t, 2H, *J* = 7.5 Hz), 2.38 (s, 3H), 2.22 (s, 3H); IR (KBr) 3200, 1765, 1684, 1630 cm^{-1}; FABMS *m/e* (rel intensity) 263 ([M + 1]$^+$, 25), 176 (100). Anal. ($C_{13}H_{14}N_2O_4$) C, H, N.

6-Acetyl-1,3-dihydro-5-hydroxy-2*H*-indol-2-one, 6-oxime acetate (6c): 90%, off-white solid; mp 214–216 °C; ^{1}H NMR (DMSO-d_6) δ 10.4 (s, 1H), 10.2 (s, 1H), 6.86 (s, 1H), 6.81 (s, 1H), 3.48 (s, 2H), 2.37 (s, 3H), 2.22 (s, 3H); IR (KBr) 3082, 1771, 1715, 1625 cm^{-1}; CIMS *m/e* (rel intensity) 249 ([M + 1]$^+$, 35), 191 (100). Anal. ($C_{12}H_{12}N_2O_4$) C, H, N.

5-Acetyl-1,3-dihydro-4-hydroxy-2*H*-indol-2-one, 5-oxime acetate (15): 88%, tan solid; mp 198–200 °C; ^{1}H NMR (DMSO-d_6) δ 11.45 (s, 1H), 10.6 (s, 1H), 7.50 (d, 1H, *J* = 8.2 Hz), 6.49 (d, 1H, *J* = 8.2 Hz), 3.40 (s, 2H), 2.41 (s, 3H), 2.23 (s, 3H); IR (KBr) 3113, 1766, 1716, 1641 cm^{-1}; EIMS *m/e* (rel intensity) 248 (M$^+$, 10), 188 (100). Anal. ($C_{12}H_{12}N_2O_4{\cdot}0.25H_2O$) C, H, N.

5,7-Dihydro-3-methyl-6*H*-pyrrolo[3,2-*f*]-1,2-benzisoxazol-6-one (7a). A mixture of **6a** (4.48 g, 18.0 mmol) and pyridine (14.6 mL, 180 mmol) in dimethylformamide (DMF) (660 mL) was heated at 125–130 °C for 4 h. The cooled reaction mixture was poured over water and extracted with EtOAc (four times). The combined organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. [Alternate workup: the reaction was concentrated *in vacuo* and the residue obtained was subjected to purification.] Purification by silica gel flash chromatography (50% EtOAc/hexanes → 100% EtOAc) gave **7a** (2.20 g, 65%) as an off-white solid. A small sample was further purified by recrystallization from EtOAc to give a white solid: mp (EtOAc) 264–265 °C dec; ^{1}H NMR (DMSO-d_6) δ 10.8 (s, 1H), 7.60 (s, 1H), 6.98 (s, 1H), 3.57 (s, 2H), 2.47 (s, 3H); IR (KBr) 3162, 1703, 1633 cm^{-1}; CIMS *m/e* (rel intensity) 189 ([M + 1]$^+$, 100); FABHRMS calcd for $C_{10}H_8N_2O_2$ 189.0664, found 189.0656.

A similar procedure was followed for the preparation of tricycles **7b,c** and **16** starting from the corresponding oxime acetates **6b,c** and **15**.

5,8-Dihydro-3-methylisoxazolo[4,5-*g*]quinolin-7(6*H*)-one (7b): 66%, pale yellow solid; mp (EtOAc) 309–311 °C dec; ^{1}H NMR (DMSO-d_6) δ 10.4 (s, 1H), 7.62 (s, 1H), 7.02 (s, 1H), 2.99 (t, 2H, *J* = 7.4 Hz), 2.49–2.53 (m, 2H), 2.47 (s, 3H); IR (KBr) 3163, 1686, 1626 cm^{-1}; CIMS *m/e* (rel intensity) 203 ([M + 1]$^+$, 100). Anal. ($C_{11}H_{10}N_2O_2$) C, H, N.

5,7-Dihydro-3-methyl-6*H*-pyrrolo[2,3-*f*]-1,2-benzisoxazol-6-one (7c): 12%, pastel yellow solid; mp 246–248 °C; ^{1}H NMR (DMSO-d_6) δ 10.6 (s, 1H), 7.58 (s, 1H), 7.03 (s, 1H), 3.63 (s, 2H), 2.50 (s, 3H); IR (KBr) 3201, 1709, 1695 cm^{-1}; CIMS *m/e* (rel intensity) 189 ([M + 1]$^+$, 100). Anal. ($C_{10}H_8N_2O_2$) C, H, N.

6,8-Dihydro-3-methyl-7*H*-pyrrolo[2,3-*g*]-1,2-benzisoxazol-7-one (16): 34%, white solid; mp 259–260 °C dec; ^{1}H NMR (DMSO-d_6) δ 10.79 (s, 1H), 7.67 (d, 1H, *J* = 8.5 Hz), 6.92 (d, 1H, *J* = 8.3 Hz), 3.73 (s, 2H), 2.49 (s, 3H); IR (KBr) 3105, 1733, 1649 cm^{-1}; EIMS *m/e* (rel intensity) 188 (M$^+$, 100); EIHRMS calcd for $C_{10}H_8N_2O_2$ 188.05862, found 188.0793.

4-[2-[6,7-Dihydro-6-oxo-5*H*-pyrrolo[3,2-*f*]-1,2-benzisoxazol-3-yl]ethyl]-1-piperidinecarboxylic Acid, 1,1-Dimethylethyl Ester (9a). Freshly prepared 1 M LDA (40.9 mL, 40.9 mmol) was added dropwise to a cold (−78 °C) solution of **7a** (2.33 g, 12.4 mmoL) in THF (50 mL). Immediately after addition was complete, a solution of iodide **8**[15] (4.42 g, 13.6 mmol) in THF (8 mL) was added all at once. The resulting yellow-orange solution was stirred for 4 h at −78 °C. Saturated NH_4Cl was added, and the mixture was extracted with EtOAc (3×). The combined organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (30% EtOAc–CH_2Cl_2) gave recovered starting material (0.210 g, 9%) and **9a** (1.56 g, 76%) as an off-white solid. A small sample of **9a** was further purified by recrystallization from EtOAc to give white crystals: mp (EtOAc) 181–183 °C; ^{1}H NMR ($CDCl_3$) δ 8.48 (s, 1H), 7.44 (s, 1H), 7.03 (s, 1H), 4.08–4.14 (m, 2H), 3.63 (s, 2H), 2.97 (t, 2H, *J* = 7.8 Hz), 2.69 (br t, 2H, *J* = 12.8 Hz), 1.74–1.84 (m, 4H), 1.46–1.55 (m, 1H), 1.46 (s, 9H), 1.18 (ddd, 2H, *J* = 24.4 Hz, *J* = 12.1 Hz, *J* = 4.3 Hz); IR (KBr) 2944, 1715, 1694, 1634 cm^{-1}; CIMS *m/e* (rel intensity) 386 ([M + 1]$^+$, 15), 286 (100). Anal. ($C_{21}H_{27}N_3O_4$) C, H, N.

A similar procedure was followed for the preparation of N-BOC carbamates **9b,c** and **17** starting from the corresponding tricycles **7b,c** and **16**.

4-[2-[5,6,7,8-Tetrahydro-7-oxoisoxazolo[4,5-*g*]quinolin-3-yl]ethyl]-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester (9b): 54%, white solid; mp 210–211 °C; ^{1}H NMR (DMSO-d_6) δ 10.4 (s, 1H), 7.67 (s, 1H), 7.02 (s, 1H), 3.93 (br d, 2H, *J* = 13.4 Hz), 2.89–3.31 (m, 4H), 2.57–2.75 (br m, 2H), 2.49–2.53 (m, 2H), 1.64–1.72 (m, 4H), 1.38 (s, 9H), 1.36–1.50 (m, 1H), 1.01–1.16 (m, 2H); IR (KBr) 3198, 1691, 1630 cm^{-1}; CIMS *m/e* (rel intensity) 400 ([M + 1]$^+$, 15), 300 (100). Anal. ($C_{22}H_{29}N_3O_4{\cdot}0.25H_2O$) C, H, N.

4-[2-[6,7-Dihydro-6-oxo-5*H*-pyrrolo[2,3-*f*]-1,2-benzisoxazol-3-yl]ethyl]-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester (9c): inseparable mixture (3:1) of **9c** and starting material, respectively, as a pale yellow soft solid; ^{1}H NMR ($CDCl_3$) δ 9.84 (s, 1H), 7.45 (s, 1H), 7.05 (s, 1H), 4.05–4.15 (m, 2H), 3.69 (s, 2H), 2.96 (t, 2H, *J* = 7.8 Hz), 2.68 (br t, 2H, *J* = 11.8 Hz), 1.72–1.82 (m, 4H), 1.45 (s, 9H), 1.43–1.53 (m, 1H), 1.15 (ddd, 2H, *J* = 23.6 Hz, *J* = 12.1 Hz, *J* = 4.0 Hz).

4-[2-[7,8-Dihydro-7-oxo-6*H*-pyrrolo[2,3-*g*]-1,2-benzisoxazol-3-yl]ethyl]-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester (17): 51%, pale yellow solid; ^{1}H NMR ($CDCl_3$) δ 8.85 (s, 1H), 7.53 (d, 1H, *J* = 8.1 Hz), 6.95 (d, 1H, *J* = 8.3 Hz), 4.08–4.14 (m, 2H), 3.78 (s, 2H), 2.99 (t, 2H, *J* = 7.8 Hz), 2.68 (br t, 2H, *J* = 12.1 Hz), 1.73–1.84 (m, 4H), 1.46–1.60 (m, 1H), 1.46 (s, 9H), 1.17 (ddd, 2H, *J* = 23.2 Hz, *J* = 12.1 Hz, *J* = 4.3 Hz); EIMS *m/e* (rel intensity) 385 (M$^+$, 30), 57 (100); EIHRMS calcd for $C_{21}H_{27}N_3O_4$ 385.2002, found 385.1999.

5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6*H*-pyrrolo[3,2-*f*]-1,2-benzisoxazol-6-one, Maleate Salt (2a). Trifluoroacetic acid (TFA) (3.3 mL) was added dropwise to a cold (0 °C) solution of **9a** (0.50 g, 1.30 mmol) in CH_2Cl_2 (13 mL). After 30 min, the mixture was concentrated, and excess TFA was removed by concentrating from toluene (two or three times). The crude residue was dissolved in DMF (12.5 mL), and sodium carbonate (Na_2CO_3) (0.689 g, 6.50 mmol) and benzyl bromide (0.186 mL, 1.56 mmol) were added. The resulting mixture was stirred at room temperature for 4 h. The reaction was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in methylene chloride and washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (CH_2Cl_2 → 10% methanol/CH_2Cl_2) gave **2a**, free base (0.343 g, 70%) as a white solid. The maleate salt was prepared by adding a solution of maleic acid (0.061 g, 0.528 mmol) in ethanol (EtOH) (1 mL) to a solution of the free base (0.180 g, 0.48 mmol) in CH_2Cl_2 (10 mL). The solid obtained was collected and purified by recrystallization from 2-propanol to give **2a**, maleate salt (0.173 g, 73%) as an off-white solid: mp (*i*-PrOH) 194–195 °C; ^{1}H NMR (DMSO-d_6) δ 10.82 (s, 1H), 7.65 (s, 1H), 7.48 (s, 5H), 7.00 (s, 1H), 6.03 (s, 2H), 4.24 (br s, 2H), 3.58 (s, 2H), 3.25–3.38 (m,

2H), 2.94 (t, 2H, J = 7.6 Hz), 2.81–2.97 (m, 2H), 1.86–1.96 (m, 2H), 1.62–1.76 (m, 2H), 1.30–1.60 (m, 3H); IR (KBr) 3036, 1713, 1631 cm^{-1}; CIMS m/e (rel intensity) 376 ([M + 1]$^+$, 10), 157 (100). Anal. ($C_{23}H_{25}N_3O_2{\cdot}C_4H_4O_4$) C, H, N.

A similar procedure was followed for the preparation of final compounds **2b,c** and **10**, free bases, starting from the corresponding N-BOC carbamates **9b,c** and **17**.

5,8-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]isoxazolo[4,5-*g*]quinolin-7(6*H*)-one (2b): 43%, white solid; mp (EtOAc–MeOH) 164–166 °C; ^{1}H NMR ($CDCl_3$) δ 9.37 (s, 1H), 7.38 (s, 1H), 7.22–7.36 (m, 5H), 7.01 (s, 1H), 3.55 (s, 2H), 3.09 (t, 2H, J = 7.4 Hz), 2.91–2.97 (m, 4H), 2.70 (t, 2H, J = 7.4 Hz), 2.01 (br t, 2H, J = 10.3 Hz), 1.75–1.80 (m, 4H), 1.39–1.50 (m, 3H); IR (KBr) 3088, 1694, 1631 cm^{-1}; EIMS m/e (rel intensity) 389 (M$^+$, 15), 91 (100); EIHRMS calcd for $C_{24}H_{27}N_3O_2$ 389.2104, found 389.2102. Anal. ($C_{24}H_{27}N_3O_2{\cdot}0.5H_2O$) C, H, N.

5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6*H*-pyrrolo[2,3-*f*]-1,2-benzisoxazol-6-one (2c): 60%, light yellow solid; mp 205–206 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.09 (s, 1H), 7.46 (s, 1H), 7.27–7.33 (m, 5H), 6.99 (s, 1H), 3.68 (s, 2H), 3.50–3.52 (m, 2H), 2.90–2.99 (m, 4H), 1.92–2.05 (m, 2H), 1.70–1.80 (m, 4H), 1.30–1.40 (m, 3H); IR (KBr) 3146, 1701, 1637 cm^{-1}; EIMS m/e (rel intensity) 375 (M$^+$, 5), 91 (100); EIHRMS calcd for $C_{23}H_{25}N_3O_2$ 375.1947, found 375.1953. Anal. ($C_{23}H_{25}N_3O_2$) C, H; N: calcd, 11.19; found, 10.66.

6,8-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-7*H*-pyrrolo[2,3-*g*]-1,2-benzisoxazol-7-one (10): 44%, off-white solid; mp 188–189 °C; ^{1}H NMR ($CDCl_3$) δ 9.59 (s, 1H), 7.51 (d, 1H, J = 8.1 Hz), 7.23–7.33 (m, 5H), 6.94 (d, 1H, J = 8.2 Hz), 3.77 (s, 2H), 3.56 (s, 2H), 2.93–2.99 (m, 4H), 2.02 (br t, 2H, J = 10.7 Hz), 1.75–1.79 (m, 4H), 1.26–1.39 (m, 3H); IR (KBr) 3060, 1714, 1633 cm^{-1}; FABMS m/e (rel intensity) 376 ([M + 1]$^+$, 35), 306 (100). Anal. ($C_{23}H_{25}N_3O_2{\cdot}0.5H_2O$) C, H, N.

5,7-Dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6*H*-pyrrolo[3,2-*f*]-1,2-benzisoxazole-6-one, Methanesulfonate Salt (2d). NaH (60% mineral oil dispersion, 0.121 g, 3.04 mmol) was added to a solution of **2a**, free base (0.950 g, 2.53 mmol) in DMF (30 mL) at room temperature. After evolution of hydrogen gas had subsided, methyl iodide (0.236 mL, 3.79 mmol) was added and the mixture obtained was stirred for 3 h. The reaction was concentrated under high vacuum to half the original volume and diluted with H_2O. The aqueous layer was extracted with CH_2Cl_2, and the separated organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography ($CH_2Cl_2 \rightarrow$ 10% MeOH–CH_2Cl_2) gave **2d**, free base (0.350 g, 36%) as a yellow oil. The methanesulfonate salt was prepared by adding methanesulfonic acid (0.058 mL, 0.90 mol) to a solution of the free base (0.350 g, 0.90 mmol) in CH_2Cl_2 (5 mL). After concentration, the residue was triturated from Et_2O to give **2d**, methanesulfonate salt (0.302 g, 69%) as a yellow solid: mp 164–165 °C dec; ^{1}H NMR (DMSO-d_6) δ 7.69 (s, 1H), 7.49 (s, 5H), 7.32 (s, 1H), 4.28 (s, 2H), 3.64 (s, 2H), 3.35 (br d, 2H, J = 11.6 Hz), 3.18 (s, 3H), 2.85–2.99 (m, 4H), 2.30 (s, 3H), 1.95 (br d, 2H, J = 12.9 Hz), 1.66–1.80 (m, 2H), 1.45–1.60 (m, 1H), 1.35–1.44 (m, 2H); IR (KBr) 1724, 1630 cm^{-1}; EIMS m/e (rel intensity) 389 (M$^+$), 91 (100); EIHRMS calcd for $C_{24}H_{27}N_3O_2$ 389.2104, found 389.2075.

Inhibition of Acetylcholinesterase and Butyrylcholinesterase. The method of Ellman *et al.*[20] was followed. The assay solution consists of a 0.1 M sodium phosphate buffer, pH 8.0, with the addition of 100 μM tetraisopropylpyrophosphoramide (*iso*-OMPA), 100 μM 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), 0.02 unit/mL AChE (Sigma Chemical Co., from human erythrocytes) and 200 μM acetylthiocholine iodide. The final assay volume was 0.25 mL. Test compounds were added to the assay solution prior to enzyme addition, whereupon a 20-min preincubation period with enzyme was followed by addition of substrate. Changes in absorbance at 412 nM were recorded for 5 min. The reaction rates were compared, and the percent inhibition due to the presence of test compounds was calculated.

Inhibition of butyrylcholinesterase was measured as described above for AChE by omitting addition of *iso*-OMPA and substituting 0.02 unit/mL of BuChE (Sigma Chemical Co., from horse serum) and 200 μM butyrylthiocholine for enzyme and substrate, respectively.

***In Vivo* Microdialysis.** Male Sprague–Dawley rats were implanted in the corpus striatum with guide cannulae and dialysis probes (Bioanalytical Systems, West Lafayette, IN) and superfused at a rate of 3 mL/min. The dialysis fluid was a Ringer's buffer (pH 7.2) containing 500 nM physostigmine to reduce degradation of ACh by AChE. Fractions (60 μL) were collected every 20 min for 2 h before drug administration and for 3 h following oral administration of drug. Samples (50 μL) were used directly for HPLC analysis of ACh content as described above. Basal ACh release was defined as the average ACh content in the three fractions just prior to drug administration. ACh content in all fractions was converted to a percentage of these basal control values.

Acknowledgment. The authors wish to thank Mr. P. Bowles for supplying some intermediates. We are also grateful to Dr. J. P. Kiplinger, Mr. R. S. Ware, Mr. M. S. Teague, and Mr. Steve C. Maginess for mass spectra and NMR support and assistance.

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JM950262P