(free base, $CDCl_3$): δ 1.1 (t, 6, $CH_2CH_3$), 1.9 (br s, 6, cyclopentyl), 2.4-2.9 (complex m, 8, $-CH_2-$), 4.2 (t, 3, $-OCH_2-$), 7.4-7.8 (m, 4, ArH). Anal. ($C_{19}H_{26}N_2O_2$·HCl·0.5$H_2O$): C, H, N.

**Radioligand Binding Assays.** Measurement of binding to muscarinic receptor subtypes was performed with minor modifications of the methods of Watson et al.[24,25] Male Sprague-Dawley rats were anesthetized with $CO_2$ and sacrificed by decapitation. Tissues were dissected and placed in the appropriate assay buffers. The $M_1$ binding assay used [$^3$H]pirenzepine (PZ, 87 Ci/mmol, New England Nuclear) as the ligand, rat cortex as the source of tissue, and 50 mM HEPES-KOH as the assay buffer, while the $M_2$ binding assay used [$^3$H]-(-)-quinuclidinyl benzilate (QNB, 32 Ci/mmol, New England Nuclear) as the ligand, rat heart as the source of tissue, and 50 mM Tris-HCl as the assay buffer. Tissues were homogenized with a Polytron at setting 6 for 15 s at a concentration of 10 mg/mL ([$^3$H]PZ) or minced and then homogenized at setting 8 for 15 s at a concentration of 8 mg/mL ([$^3$H]QNB). The homogenates were centrifuged at 48000*g* for 10 min at 4 °C, resuspended, and washed twice. Assay tubes contained 500 μL of tissue, 100 μL of ligand, and sufficient buffer for a final volume of 1 mL for [$^3$H]PZ binding and 2 mL for [$^3$H]QNB binding. Final ligand concentrations were 0.5 nM for [$^3$H]PZ binding and 0.1 nM for [$^3$H]QNB binding. Nonspecific binding for both assays was defined by 1 μM atropine. Displacement experiments at 13 concentrations of nonlabeled drug were performed in triplicate. Incubations were conducted for 1 h at room temperature for [$^3$H]PZ binding, and at 37 °C for [$^3$H]QNB binding. Incubations were terminated by filtration through Whatman GF/B filters that were presoaked with 0.1% polyethylenimine for at least 1 h, followed by three 4-mL washes with ice-cold assay buffer. Following addition of scintillation cocktail, samples were allowed to equilibrate for at least 8 h. The amount of bound radioactivity was determined by liquid scintillation spectrometry using a Beckman LS 5000TA liquid scintillation counter with an efficiency for tritium of ca. 60%. Inhibition constants ($K_i$ values) for the binding of test compounds to recognition sites were calculated with the EBDA/LIGAND program.[26] Data are the mean of at least three separate experiments performed in triplicate.

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**Registry No.** **1**, 77-22-5; **4**, 52648-77-8; **5**, 135569-16-3; **5**·HCl, 98636-73-8; **6**, 135569-18-5; **6**·HCl, 135569-17-4; **7a**, 135569-19-6; **7b**, 135569-34-5; **8a**, 135569-20-9; **8b**, 135569-35-6; **9a**, 135569-21-0; **9b**, 135569-36-7; **10**, 135569-23-2; **10**·HCl, 135569-22-1; **11**, 135569-24-3; **12**, 91640-63-0; **13**, 135569-25-4; **14**, 135569-27-6; **14**·HCl, 135569-26-5; **15**, 135569-28-7; **16**, 135569-29-8; **17**, 135569-31-2; **17**·HCl, 135569-30-1; **18**, 135569-33-4; **18**·HCl, 135569-32-3; $HOCH_2CH_2NEt_2$, 100-37-8; $ClCH_2CH_2NEt_2$, 100-35-6; $Br(CH_2)_4Br$, 110-52-1; potassium 1-(4-nitrophenyl)cyclopentanecarboxylate, 89490-69-7.

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# Synthesis and Muscarinic Cholinergic Receptor Affinities of 3-Quinuclidinyl α-(Alkoxyalkyl)-α-aryl-α-hydroxyacetates

Victor I. Cohen,* Raymond E. Gibson,† Linda H. Fan, Rosanna De La Cruz, Miriam S. Gitler, Erin Hariman, and Richard C. Reba

*Section of Radiopharmaceutical Chemistry, George Washington University Medical Center, Washington, D.C. 20037.*
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Seven analogues of 3-quinuclidinyl benzilate (QNB) in which one phenyl ring was replaced by an alkoxyalkyl moiety were synthesized and their affinities for the muscarinic cholinergic receptor determined. An oxygen in the β-position of the moiety was not well-tolerated. By contrast, an oxygen in the γ-position did not change the affinity for the muscarinic receptor. However, when a bromine was placed on the remaining phenyl ring, the affinity was significantly reduced in striking contrast to results obtained on halogenation of QNB.

We have developed radiohalogenated (*R,R*)- and (*R,S*)-1-azabicyclo[2.2.2]oct-3-yl α-hydroxy-α-(4-iodophenyl)-α-phenylacetate (4IQNB) as agents for imaging muscarinic acetylcholine receptors (m-AChR) in the central nervous system.[1,2] When labeled with $^{125}$I, these radiotracers provide highly selective receptor localization.[3,4] The (*R,R*)-[$^{123}$I]-4IQNB has been used to obtain images of the distribution of the m-AChR in healthy individuals[5,6] and patients with dementias.[7,8] Pharmacokinetic studies[9] in rat indicate that the concentration of radiohalogenated 4IQNB which localizes in the brain is, in part, a function of the concentration of m-AChR. A positive correlation has also been shown between the concentration of m-AChR in various structures in the brain and the concentration of radioiodinated 4IQNB in these structures at single times

* To whom correspondence should be addressed.
† Present address: Radiopharmacology, Merck Sharp and Dohme Research Laboratories, West Point, PA 19486.

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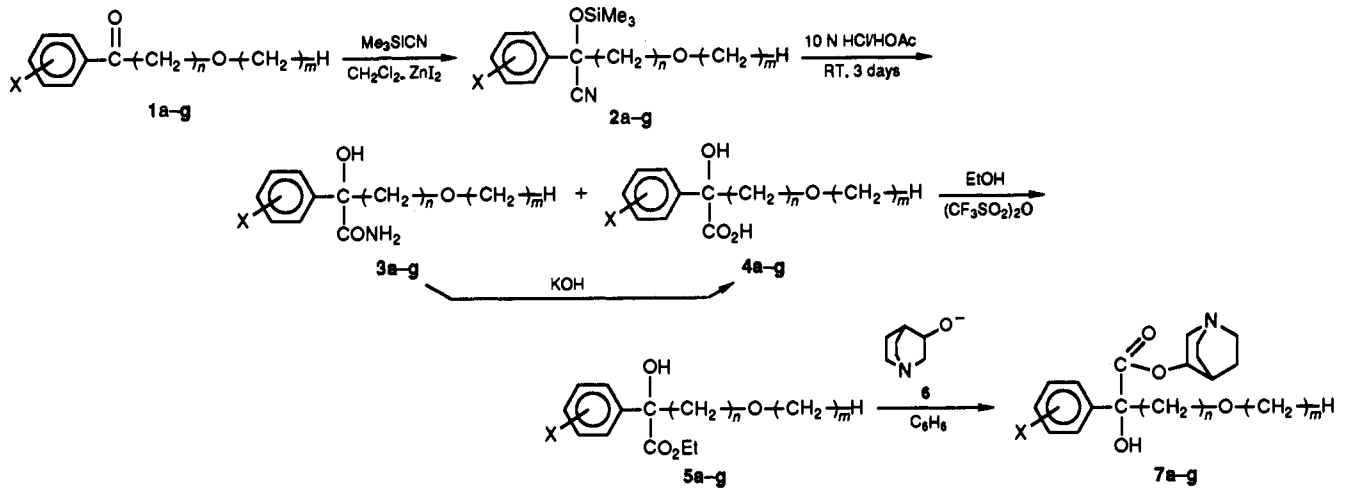
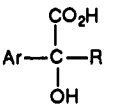
**Scheme I**




following intravenous injection of the radiotracer (at 1 h[4,10] and 3 h[11] in rats and at 21 h[7] in man). These results support the conclusion that (*R*,*R*)-[$^{123}$I]-4IQNB provides information on the in vivo concentration of m-AChR.[12]

Despite these positive features, 4IQNB may not be the ideal muscarinic receptor radiotracer. The pharmacokinetics of distribution to the brain in man is surprisingly slow, with peak accumulations occurring >15 h postinjection.[6] One possible explanation for this slow rate of accumulation is that 4IQNB is a lipophilic ligand which initially distributes systematically and slowly redistributes to the brain, the organ with the highest concentration of m-AChR. Additionally, we have shown that [$^3$H]QNB provides a 10-fold higher concentration in rat brain than that obtained with (*R*,*R*)-[$^{125}$I]-4IQNB, which was not related to differences in blood–brain-barrier permeability.[3] The difference between the extent of localization of the two radioligands may also be attributed to the lower lipophilicity of QNB compared to that of its iodinated analogue: lower lipophilicity would reduce radioligand binding to plasma proteins which would lead to a greater free-plasma concentration available for binding to receptor. If lipophilicity is the cause of the slow rate of accumulation of (*R*,*R*)-[$^{123}$I]-4IQNB in man and the reduced concentration in brain of the radioiodinated tracer compared to

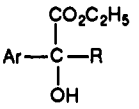
**Table I.** Data on (*RS*)-α-(Alkoxyalkyl)-α-hydroxy-α-arylacetic Acids



| no. | R | Ar | % yield | $R_f$[a] | anal. |
|---|---|---|---|---|---|
| **4a** | $CH_3OCH_2$ | Ph | 32 | 0.26 | C,H |
| **4b** | $CH_3CH_2OCH_2$ | Ph | 76 | 0.34 | C,H |
| **4c** | $CH_3CH_2CH_2OCH_2$ | Ph | 33 | 0.31 | C,H |
| **4d** | $CH_3OCH_2CH_2$ | Ph | 39 | 0.33 | C,H |
| **4e** | $CH_3CH_2OCH_2CH_2$ | Ph | 40 | 0.34 | C,H |
| **4f** | $CH_3OCH_2CH_2$ | 3-$BrC_6H_4$ | 36 | 0.31 | C,H,Br |
| **4g** | $CH_3OCH_2CH_2$ | 4-$BrC_6H_4$ | 18 | 0.30 | C,H,Br |

[a] Toluene/HOAc (9:1).

**Table II.** Data on (*RS*)-Ethyl α-(Alkoxyalkyl)-α-hydroxy-α-arylacetates



| no. | R | Ar | % yield | $R_f$[a] | anal. |
|---|---|---|---|---|---|
| **5a** | $CH_3OCH_2$ | Ph | 88 | 0.26 | C,H |
| **5b** | $CH_3CH_2OCH_2$ | Ph | 87 | 0.29 | C,H |
| **5c** | $CH_3CH_2CH_2OCH_2$ | Ph | 95 | 0.48 | C,H |
| **5d** | $CH_3OCH_2CH_2$ | Ph | 70 | 0.30 | C,H |
| **5e** | $CH_3CH_2OCH_2CH_2$ | Ph | 83 | 0.32 | C,H |
| **5f** | $CH_3OCH_2CH_2$ | 3-$BrC_6H_4$ | 86 | 0.30 | C,H,Br |
| **5g** | $CH_3OCH_2CH_2$ | 4-$BrC_6H_4$ | 75 | 0.37 | C,H,Br |

[a] Toluene/HOAc (9:1).

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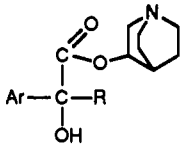
**Table III.** Data on (*RS*)-1-Azabicyclo[2.2.2]oct-3-yl (*RS*)-α-Hydroxy-α-(alkoxyalkyl)-α-arylacetates



| no. | R | Ar | % yield | mp (°C) | $R_f$[a] | anal. |
|---|---|---|---|---|---|---|
| **7a** | $CH_3OCH_2$ | Ph | 39 | 142–152[b] | 0.40[b] | C, H, N |
| **7b** | $CH_3CH_2OCH_2$ | Ph | 37 | 131[b] | 0.45[b] | C, H, N |
| **7c** | $CH_3CH_2CH_2OCH_2$ | Ph | 57 | 60 | 0.48 | C, H, N |
| **7d** | $CH_3OCH_2CH_2$ | Ph | 31 | | 0.57 | C, H, N |
| **7e** | $CH_3CH_2OCH_2CH_2$ | Ph | 24 | | 0.61 | C, H, N |
| **7f** | $CH_3OCH_2CH_2$ | 3-$BrC_6H_4$ | 30 | | 0.60 | C, H, Br, N |
| **7g** | $CH_3OCH_2CH_2$ | 4-$BrC_6H_4$ | 33 | | 0.60 | C, H, Br, N |

[a] $MeOH/NH_4OH$ (98:2). [b] Oxalate.

**Table IV.** Results of Affinity Constants for Alkoxyalkyl Analogues of QNB for the Muscarinic Receptor from Rat Corpus Stratium

| no. | X | *n* | *m* | $K_A$,[a] $M^{-1}$ | % CV[b] | % RBI[c] |
|---|---|---|---|---|---|---|
| **7a** | H | 1 | 1 | $1.47 \times 10^8$ | 6.1 | 4.0 |
| **7b** | H | 1 | 2 | $3.26 \times 10^8$ | 9.6 | 8.0 |
| **7c** | H | 1 | 3 | $2.66 \times 10^8$ | 10.8 | 6.1 |
| **7d** | H | 2 | 1 | $4.27 \times 10^9$ | 10.5 | 87.3 |
| **7e** | H | 2 | 2 | $8.64 \times 10^8$ | 7.0 | 17.3 |
| **7f** | 3-Br | 2 | 1 | $1.29 \times 10^8$ | 5.2 | 2.7 |
| **7g** | 4-Br | 2 | 1 | $1.73 \times 10^8$ | 6.5 | 3.4 |
| | QNB | | | $4.50 \times 10^8$ | | 100 |

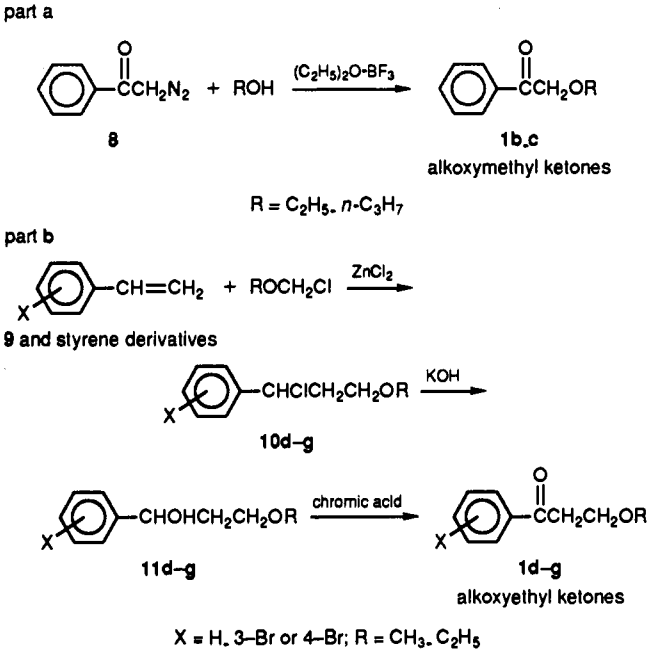
[a] Affinity constant from LIGAND program with CV's of ≤20%. A difference in receptor affinity of 4-fold is significant ($p < 0.05$). [b] Coefficient of variation between each analogue determinations. [c] Relative binding index = $[K_A/K_A(QNB)] \times 100$.

[$^3$H]QNB, a radioiodinated tracer for the m-AChR with reduced lipophilicity should result in an increased rate of delivery of radiotracer to the brain and a higher percent localization of the injected dose. These improvements would thus lower the dosage needed to provide equivalent images to those obtained with (*R,R*)-[$^{123}$I]-4IQNB. In order to reduce the lipophilicity, we have synthesized analogues of QNB in which one of the phenyl rings is replaced by an alkoxyalkyl moiety and determined their affinities for the m-AChR from rat corpus striatum. Brominated derivatives of the highest affinity compound were then prepared because of the relative ease of synthesis, and the physicochemical properties and affinity of the brominated analogue should be similar to that of an iodinated product.[13]

## Chemistry

Compound **7a** (Table III) was synthesized according to Scheme I. The sequential hydrolysis scheme was necessary to reduce side products which were difficult to separate. Amide **3a** was isolated from acid **4a** and treated with 30% aqueous potassium hydroxide to increase the yield of **4a**. The desired alkoxymethyl ketones (Scheme II, part a) were synthesized by treating diazoacetophenone with the corresponding alcohol. The alkoxyethyl ketones (Scheme II, part b) were prepared by treating the chloromethyl methyl or ethyl ethers and styrene derivatives with zinc chloride in carbon tetrachloride. The chlorides were converted to alcohols with aqueous KOH, and the alcohols converted to ketones by a Jones oxidation. Subsequent reaction of alkoxymethyl- and alkoxyethylphenyl ketones with trimethylsilyl cyanide via the reaction shown in Scheme I, followed by hydrolysis, esterification with ethanol, and then transesterification with 3-quinuclidinol

**Scheme II**




(6), yielded the 3-quinuclidinyl α-(alkoxymethyl)- and α-(2-alkoxyethyl)-α-hydroxy-α-phenylacetates (**7**). We also prepared two halogenated analogues (**7f** and **7g**) starting with 3- and 4-bromostyrene (Scheme II, part b).

The retention times on reverse-phase HPLC of these analogues compared to that of QNB were determined as an indication of their relative lipophilicities.

## Results and Discussion

One of the phenyl rings of QNB can be replaced by n-butyl, c-hexyl, c-pentyl, or methyl (QNA: 3-quinuclidinyl α-phenyl-α-hydroxy-α-methylacetate) groups with no significant change in the affinity for the muscarinic receptor from brain.[14,15] However, substitution of the phenyl ring

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Table V. Relative Lipophilicity for Alkoxyalkyl Analogues of QNB[a]

| no. | retention time, min | no. | retention time, min |
|---|---|---|---|
| **7a** | 3.7 | **7f** | 14.2 |
| **7b** | 9.9 | **7g** | 14.9 |
| **7c** | 13.3 | QNB | 13.2 |
| **7d** | 9.1 | 4-BrQNB | 25.2 |
| **7e** | 17.6 | 4-IQNB | 29.3 |

[a] Compounds were chromatographed on a water 8MB $C_{18}$ 10 Radial Pak column eluted at 1 mL/min with methanol/water/acetonitrile (50:40:10) containing 1 g/L of sodium 1-octanesulfonate and 1.2 mL/L of formic acid. The compounds were detected by absorption at 280 nm.

by the methoxymethyl moiety (**7a**) leads to a highly significant 25-fold loss in affinity (Table IV). Increasing the lipophilicity by increasing the number of methylenes [ethoxymethyl (**7b**), and propoxymethyl (**7c**)] did not overcome the adverse interaction, i.e., the affinities of **7a–c** are the same. A loss of affinity caused by a polar $\beta$-atom has been reported by Rzeszotarski et al. for a series of QNA analogues substituted with tertiary amines.[15] However, we have recently reported the synthesis and evaluation of analogues of QNB in which one phenyl ring is replaced by 2- and 3-furyl moieties.[16] These constrained analogues with oxygen in the $\beta$-position exhibited the same affinity for the m-AChR as QNB. When the oxygen is in the $\gamma$-position (**7d**), the affinity for the muscarinic receptor is not different than that of QNB. An increase by one methylene [ethoxyethyl (**7e**)] results in a loss of 4-fold compared to the activity of **7d**.

Since the affinity of **7d** is similar to that of QNB and the lipophilicity is less (Table V), we prepared two derivatives of **7d** which contain bromine on the phenyl ring. The resultant derivatives of **7d**, compounds **7f** and **7g**, exhibit HPLC retention times similar to that of QNB and significantly less than those of the 4-halogenated derivatives of QNB (Table V), thus satisfying one of our goals. However, halogenation in the meta (**7f**) or para positions (**7g**) resulted in a profound loss of affinity (Table IV). Halogenation of QNB in the 3- or 4-position did not result in different affinities for the m-AChR from rat corpus striatum.[13] These results suggest that the nature of the second substituent on the carbinol alters the interaction of the remaining phenyl ring with the accessory binding sites on the m-AChR resulting in reduced bulk tolerance for the halogen. These results also indicate that alkoxyalkyl analogues of 4IQNB will not have affinities sufficient for evaluation as potential muscarinic receptor radiotracers.

## Experimental Section

The melting points were obtained on a Fisher-John apparatus. The IR spectra of the compounds, neat or in a KBr pellet, were obtained on a Perkin-Elmer 1710 infrared Fourier transform spectrometer. $^1$H NMR spectra were recorded on a Bruker AC-300 instrument and are expressed as parts per million ($\delta$) from internal tetramethylsilane. HPLC was performed on an Altex Model 110A. The elemental analyses were performed by Galbraith Laboratories, Inc. (P. O. Box 4187, Knoxville, TN). The results obtained are within ±0.4% of the theoretical values. 2-Methoxyacetophenone, trimethylsilyl cyanide, styrene, 3- and 4-bromostyrenes, chloromethyl methyl ether, chloroethyl methyl ether, and 3-quinuclidinol were obtained from Aldrich.

**2-Ethoxyacetophenone (1b) and 2-Propoxyacetophenone (1c).** The diazoacetophenone (**8**)[17] was converted to the 2-ethoxy or 2-propoxyacetophenone with ethanol or propanol in the presence of boron trifluoride etherate.[18]

**General Procedure for the Preparation of 3-Alkoxy-1-arylpropyl Chlorides (10d–g).** They were prepared by treating styrene **9** or its derivatives and chloromethyl methyl ether or chloromethyl ethyl ether with anhydrous zinc chloride in carbon tetrachloride by method reported by Mamedov and Khydrov.[19]

**General Procedure for the Preparation of 2-Alkoxyethyl Aryl Ketones (1d–g).** The 3-alkoxy-1-arylpropyl chlorides (**10d–g**) were converted to the (2-alkoxyethyl)arylmethanol compounds (**11d–g**), with 20% aqueous potassium hydroxide.[20] The alcohol was converted to the respective ketone **1d–g** by a Jones oxidation.[21]

**Typical Procedure for the Preparation of (*RS*)-α-(Alkoxyalkyl)-α-hydroxy-α-arylacetic Acids (Table I). α-(Methoxymethyl)-α-hydroxy-α-phenylacetic Acid (4a).** 2-Methoxyacetophenone (25 g, 0.166 mol) in methylene chloride (500 mL) was allowed to react with trimethylsilyl cyanide (25g, 0.25 mol) in the presence of zinc iodide (1 g) at room temperature with stirring for 1 day. The mixture was washed with saturated sodium bicarbonate and water. The solvent was removed under reduced pressure. The crude (trimethylsilyl)cyanohydrin (**2a**) was added to a mixture of glacial acetic acid (100 mL) and hydrochloric acid (100 mL) and was stirred at room temperature for 3 days. The mixture was evaporated under reduced pressure. The residue was suspended in 20% sodium bicarbonate and extracted with ethyl acetate. The aqueous layer was acidified with 6 M hydrochloric acid and extracted with ethyl acetate. The extract was dried with magnesium sulfate and the solvent was removed under reduced pressure to yield 5 g of acid derivative **4a**. The first ethyl acetate extraction (**3a**) was evaporated to dryness and the residue was refluxed with 100 mL of 30% potassium hydroxide for 6 h with stirring. After workup 5.5 g of acid **4a** was obtained. The overall yield was 10.5 g (32%). TLC [silica gel, toluene/HOAc (9:1)]: $R_f$ 0.26. IR (neat): 3453, 1688 cm$^{-1}$. Anal. ($C_{10}H_{12}O_4$) C, H.

**Typical Procedure for the Preparation of Ethyl (*RS*)-α-(Alkoxyalkyl)-α-hydroxy-α-arylacetates (Table II). Ethyl α-Hydroxy-α-(methoxymethyl)-α-phenylacetate (5a).** To a solution of α-(methoxymethyl)-α-hydroxy-α-phenylacetic acid (**4a**; 15 g, 0.076 mol) in ethanol (250 mL) was added 5 mL of trifluoromethanesulfonic anhydride. The mixture was heated at reflux for 8 h. The solvent was evaporated under reduced pressure. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. Removal of the solvent afforded 15 g (88%) of ethyl ester; TLC [silica gel, toluene/HOAc(9:1)]: $R_f$ 0.26; IR (neat): 3500, 2930, 1729 cm$^{-1}$. Anal. ($C_{12}H_{16}O_4$) C, H.

**Typical Procedure for the Preparation of (*RS*)-1-Azabicyclo[2.2.2]oct-3-yl (*RS*)-α-Hydroxy-α-(alkoxyalkyl)-α-arylacetates (Table III). (*RS*)-1-Azabicyclo[2.2.2]oct-3-yl**

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**(*RS*)-α-Hydroxy-α-(methoxymethyl)-α-phenylacetate (7a).** A solution of 5.12 g (0.04 mol) of (*RS*)-3-quinuclidinol (6) in 200 mL of anhydrous benzene was heated at reflux for 1 h (Dean-Stark trap used to remove traces of water), and then 0.4 g of sodium was added and the mixture was refluxed with stirring for 1 h. After removal of the remaining sodium, 6 g (0.027 mol) of **5a** was added and the reaction mixture was heated again at reflux for 24 h. After the solvent was removed, the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, and dried over magnesium sulfate. After removal of the solvent, an oil remained. The oxalate salt was recrystallized from ethanol/petroleum ether to yield 4.2 g (39%). Mp: 142–152 °C. TLC [oxalate; silica gel, MeOH/$NH_4OH$ (98:2)]: $R_f$ 0.4. IR (oxalate, KBr): 3424, 2940, 1737 $cm^{-1}$. Anal. ($C_{19}H_{25}NO_8$) C, H, N.

**Tissue Preparation.** The muscarinic acetylcholine receptor was prepared as previously described.[22] Brains were removed from freshly decapitated male Sprague–Dawley rats (200–250 g) and immediately placed on ice. The corpus striatum (CS) was dissected, immediately frozen, and stored at −80 °C until used. Receptors prepared from tissue stored up to 1 year exhibit the same binding properties as that of freshly prepared samples. Samples of 0.15–0.2 fg of CS were homogenized in 20 mL of ice-cold 0.9% saline containing 10 mM Tris buffer (pH 7.4) and 10% sucrose (buffer I), using a Polytron PC-U (medium speed, two bursts of 15 s each). The membranes containing receptors were used without further purification. The 10% sucrose aids in maintaining a uniform suspension of the homogenate while sampling. The concentration of m-AChR was ca. 1 nM. Upon diluting in the assay system, the final concentration of receptor was approximately 20 pM.

**Determination of Apparent Equilibrium Association Constants.** The apparent equilibrium association constants ($K_A$) for the muscarinic ligands presented in Table I were determined by competitive ligand binding assay using [$^3$H]QNB as the radiotracer.[13] The compounds were dissolved in 100% EtOH and added to 4 mL of Tris-buffered (10 mM, pH 7.4) 0.9% saline containing $2.5 \times 10^{-10}$ M [$^3$H]QNB at a final concentration of 0.5% EtOH. Concentrations of EtOH <2% do not affect the binding parameters of QNB to the m-AChR. Competition curves were generated by using 12 concentrations of unlabeled compound from $10^{-12}$ to $10^{-6}$ M for (±)-QNB and compounds that exhibited affinities within 5-fold of QNB, and from $10^{-10}$ to $10^{-5}$ M for compounds with affinities that differed from that of QNB by greater than 5-fold. Aliquots of 0.1 mL of tissue preparation were added, and the mixture was vortexed and incubated at room temperature for 2 h. The incubation mixture was rapidly filtered on a GF/C filter paper, washed with 10 mL of ice-cold saline, air-dried, placed in Ecoscint A (National Diagnostics) scintillation cocktail, and counted for 5 min each. Data were analyzed by using the LIGAND program of Munson and Rodbard.[23] $K_A$ values were obtained by using pooled data of at least five determinations in duplicate on separate days.

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**Supplementary Material Available:** Tables listing IR data of compounds **4a–g** and IR and NMR data of compounds **5a–g** and **7a–g** (3 pages). Ordering information is given on any current masthead page.

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# 2-Phenyl-3*H*-imidazo[4,5-*b*]pyridine-3-acetamides as Non-Benzodiazepine Anticonvulsants and Anxiolytics†

Bruce E. Tomczuk,*,‡ C. R. Taylor, Jr.,‡ L. Meredith Moses,‡ Deborah B. Sutherland,‡ Young S. Lo,‡ David N. Johnson,§ William B. Kinnier,∥ and Brian F. Kilpatrick∥

*Department of Chemical Research, Department of Pharmacology, and Department of Molecular Biology, A. H. Robins Company, P.O. Box 26609, Richmond, Virginia 23261-6609.* *Received January 15, 1991*

A series of 2-phenyl-3*H*-imidazo[4,5-*b*]pyridine-3-acetamides were designed and synthesized as non-benzodiazepine anxiolytics based on a molecular disconnection of a typical 1,4-benzodiazepine (BZD). A number of these compounds showed submicromolar potency in a [$^3$H]benzodiazepine binding assay in vitro and good potency in protecting rodents against pentylenetetrazole-induced seizures. Compound **84** appears to be a selective anticonvulsant (pentylenetetrazole) agent when tested against a profile of chemically and electrically induced seizures in mice. In addition, compound **148** appears to be a selective anxiolytic/hypnotic agent on the basis of biochemical and pharmacological characterization. It appears to be a full BZD agonist as assessed by GABA shift ratio and to be effective in punishment and nonpunishment animal models of anxiety. In addition, it shows a lower side-effect profile than diazepam as assessed by rotorod neurotoxicity and potentiation of ethanol-induced sleep time in mice. The chemistry and structure-activity relationships of this series is discussed.

The benzodiazepines (BZDs) are currently the agents of choice in the clinical treatment of anxiety, but undesirable side effects such as ataxia, sedation, psychological dependence, and a synergistic effect with central nervous system depressants has prompted a search for a non-benzodiazepine anxiolytic which would be free of these effects. Several compounds have shown potential for activity during the last decade including CL-218,872 (I),[1] zopiclone (II),[2] zolpidem (III),[3] CGS-9896 (IV),[4] and bu-

* Present address: Eastman Kodak Co., Life Sciences Research Laboratories, Rochester, NY 14650-2158.

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‡ Department of Chemical Research.
§ Department of Pharmacology.
∥ Department of Molecular Biology.

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