Synthesis and Receptor Affinities of New 3-Quinuclidinyl α-Heteroaryl-α-aryl-α-hydroxyacetates

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Abstract □ Five analogues of 3-quinuclidinyl benzilate were prepared in which one phenyl ring was substituted by a heterocycle; a bromine was included on either the remaining phenyl or the heterocycle to provide information relating to the affinity of potential radiohalogenated derivatives. Their affinities for the muscarinic cholinergic receptor were determined. Replacing a phenyl ring with either the 2- or 3-furyl moiety or the 2- or 3-thienyl moiety did not significantly alter the affinity to the muscarinic receptor compared with 3-quinuclidinyl 4-bromobenzilate.

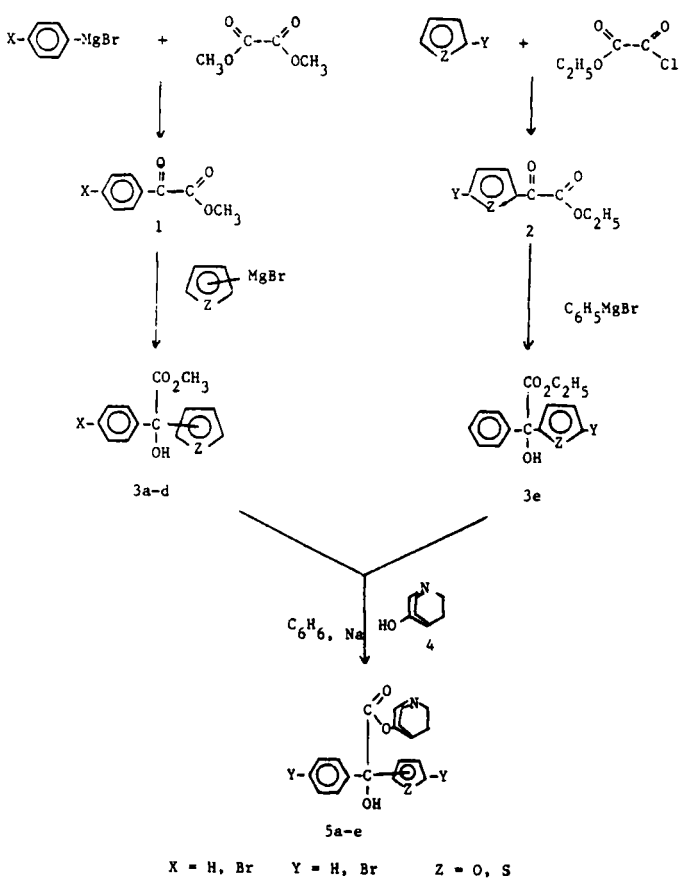
We developed radiohalogenated (*R,R*)- and (*R,S*)-3-quinuclidinyl-4-iodobenzilate (4-IQNB) as agents for imaging muscarinic acetylcholine receptors (m-AChR) in the central nervous system (CNS).[1] When radiolabeled with iodine-125, these radiotracers provide highly selective receptor localization in experimental animals,[2,3] and (*R,R*)-[^{123}I]4-IQNB has been used to obtain images of the distribution of the m-AChR in humans.[4,5] The pharmacokinetics of receptor localization for the (*R,R*)-diastereomer in the CNS of humans is slow, with peak accumulations occurring >16 h after intravenous injection. This finding suggests that the lipophilic radiotracer initially distributes systematically; this distribution is followed by recirculation and slow redistribution into the brain. Reducing the lipophilicity of such a radiotracer should allow more rapid delivery to the brain.

In addition, we have shown that [^{3}H]3-quinuclidinyl benzilate ([^{3}H]QNB) provides a 4- to 10-fold higher localization in rat brain compared with (*R,R*)-[^{125}I]4-IQNB. The lipophilicity of [^{3}H]QNB is 10-fold lower than that of (*R,R*)-4-IQNB, and this nonspecific binding will be less, thereby providing greater availability of the radiotracer for binding to the CNS receptor. Therefore, an increase in the percentage of the injected dose of a radiohalogenated radiotracer delivered to the brain should also result from reduced lipophilicity.[2] This increased delivery to the brain will result in a lower radioactive dose necessary to provide images equivalent to those obtained with the current doses of radiotracers.

The radiosynthesis of a candidate receptor-binding radiotracer is usually a time-consuming process, which may yield a radioligand that does not have the desired physicochemical and biochemical properties. Therefore, the first step in evaluating compounds as candidates for radiosynthesis is to prepare unlabeled analogues, which permit the determination of affinity constants and lipophilicities and provide analytical standards for characterization of the radiohalogenated product.[6] To this end, we previously evaluated analogues of QNB in which one phenyl ring was replaced by an alkoxyalkyl moiety,[7] but we were unable to define a structure that tolerates the less lipophilic alkoxyalkyl substituent when bromine was substituted on the remaining phenyl ring. We have therefore synthesized analogues of 4-IQNB that are designed to exhibit lower lipophilicities by replacing one of the phenyl rings of QNB with heterocyclic moieties. Because a halogen is necessary on either the remaining phenyl ring or the heterocycle, we determined the affinities of brominated analogues to m-AChR.

Results

Chemistry—The required methyl 4-bromophenylglyoxalate (1) was synthesized from the reaction between 4-bromophenylmagnesium bromide with an excess of dimethyl oxalate at −70 °C. The reaction between ethyl oxalyl chloride with 2-bromothiophene provides ethyl 2-(5-bromothienyl)glyoxalate (2). Compounds 1 and 2 react with an equivalent amount of Grignard reagent to provide methyl or ethyl α-aryl-α-heteroarylglycolates (**3a–e**). Transesterification of the methyl or ethyl esters (**3a–e**) with (*R,S*)-3-quinuclidinol (4) in the presence of sodium metal provides the final products (**5a–e**, Scheme I). Racemic quinuclidinol was used in these syntheses, because the reference compound, QNB, is also a racemate. The (*S*)-isomer does not contribute significantly to



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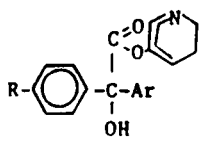
the affinity of these compounds, so the relative binding index generated in the binding studies represents a comparison of the (*R*)-3-quinuclidinyl esters. The heteroaryl analogues are also diastereomers, the carbinol carbon of the α-hydroxy acetate being chiral. Studies on the active diastereomers of 4-IQNB, (*R,R*)-4-IQNB and (*R,S*)-4-IQNB, indicate that the equilibrium affinity constants of these two diastereomers are not significantly different.[3] We therefore did not resolve the (*R,R*)- and (*R,S*)-diastereomers.

Discussion

The relative affinities for the m-AChR from rat corpus striatum of five analogues of QNB, in which one phenyl ring is substituted by a heteroaryl moiety (Scheme I, **5a–e**), are presented in Table I. In each compound, a bromine was included on the remaining phenyl ring or, in one case, on the heteroaryl ring, to provide information relating to the affinity of the potential radiohalogenated derivatives. For reference, we also include data on QNB, 3-quinuclidinyl α-(4-bromophenyl)-α-hydroxyphenylacetate(4-BrQNB), and 4-IQNB. Replacing one phenyl ring with either the 2-furyl (**5a**), 3-furyl (**5b**), 2-thienyl (**5c**), or 3-thienyl (**5d**) moiety did not significantly alter the affinity for the m-AChR as compared with QNB or the 4-halogenated derivatives of QNB. The thienyl analogue with bromine incorporated in the heteroaryl ring (**5e**) also exhibited the same affinity for the m-AChR. This insensitivity to changes in one phenyl ring is in accordance with previous studies in which substituting a halogen on one phenyl ring of QNB or replacing one phenyl ring by cyclohexyl, cyclopentyl, or *n*-butyl did not significantly alter the affinity of the analogues for the m-AChR.[8]

We determined the retention times of these compounds on reversed-phase HPLC as an indication of relative lipophilicity (Table II). Although none of the new analogues (**5a–e**) exhibited lipophilicities as low as QNB, they were all significantly less lipophilic than 4-IQNB, a compound that has been successfully used to image receptor distribution in humans.[4,5] Because the 2- and 3-furyl analogues exhibited the lowest lipophilicities of the new compounds, they are reasonable candidates for radiosynthesis. In addition, as potential receptor-binding radiotracers for the in vivo imaging of m-AChR, these analogues should have better properties (pharmacokinetics and dosimetry) than 4-IQNB.

Table I—K_A Values of Binding of Heterocyclic Analogues of QNB to the m-AChR from Rat Corpus Striatum



Compound	$K_A \times 10^9$ M^{-1} [a]	CV, %[b]	RBI, %[c]
5a (R = Br, Ar = 2-furyl)	1.67	4.97	34
5b (R = Br, Ar = 3-furyl)	3.31	8.95	77
5c (R = Br, Ar = 2-thienyl)	5.54	4.14	120
5d (R = Br, Ar = 3-thienyl)	5.14	5.56	130
5e [R = H, Ar = 2-(5-bromothienyl)]	5.07	3.71	112
QNB	4.47	5.71	100
4-BrQNB[d]	2.51	—[e]	69
4-IQNB[d]	2.37	—	65

[a] Data from LIGAND program. [b] Coefficient of variation between analogue determinations. [c] Relative binding index = [K_A/k_A (QNB)] × 100. [d] Data from ref 8. [e] —, Not reported.

Table II—Relative Lipophilicities of Heterocyclic Analogues of QNB[a]

Compound	Retention Time, min
5a	15.2
5b	17.4
5c	20.8
5d	22.2
5e	22.0
QNB	12.8
4-BrQNB	25.1
4-IQNB	29.3

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

Experimental Section

Chemistry—The melting points (mp) were obtained on a Fisher-John apparatus. The IR spectra of the compounds, neat or in KBr pellet, were obtained on a Perkin-Elmer 1710 infrared Fourier transform spectrometer. The ^1H NMR spectra were recorded on a Bruker AC-300 instrument, and chemical shifts are expressed as parts per million (δ) from the internal reference tetramethylsilane. HPLC was performed on an Altex model 110A. Elemental analyses were performed by Galbraith Laboratories, Inc. (Knoxville, TN). The results obtained are within ±0.4% of the theoretical values. Dimethyl oxalate, 1,4-dibromobenzene, ethyl oxalyl chloride, quinuclidinol, 2- and 3-bromothiophene, and 3-bromofuran were obtained from Aldrich.

Methyl 4-Bromophenylglyoxalate (1)—4-Bromophenylmagnesium bromide was made in the usual way from 70 g (0.3 mol) of 1,4-dibromobenzene and 7 g (0.29 mol) of magnesium in 500 mL of ether. The Grignard solution was then added in a dropwise manner (under nitrogen) to a stirred solution of 72 g (0.61 mol) of dimethyl oxalate in 500 mL of ether cooled to −70 °C. After the mixture was stirred for an additional hour, the cooling bath was removed. When the temperature reached 0 °C, 500 mL of dilute sulfuric acid was added. The ether layer was separated, washed with dilute sodium bicarbonate and water, and dried. After evaporation of the solvent, the residue was purified by column chromatography (silica, toluene) to yield 40 g (55%) of the product: mp 48 °C; TLC [silica gel, toluene:HOAc (9:1)]: retardation factor (R_f) 0.86; IR (neat): 1740, 1692 cm^{-1}. Anal. ($C_9H_7BrO_3$) C, H, Br.

Ethyl 2-(5-Bromothienyl)glyoxalate (2)—A mixture of 16.3 g (0.1 mol) of 2-bromothiophene, 13.7 g (0.1 mol) of ethyl oxalyl chloride and 100 mL of tetrachloroethane was poured into a 500-mL, three-necked flask fitted with a stirrer and a thermometer. The mixture was cooled to −5 °C and stirred vigorously, and 14.7 g (0.11 mol) of aluminum chloride was added, portionwise, during a period of 1 h. The material was stirred for 3 h at room temperature and treated with ice and HCl. The organic layer was separated and shaken successively with five portions of water, dilute sodium bicarbonate solution, and water. The solution was dried over magnesium sulfate, the solvent was removed, and the residue was recrystallized from hexane to yield 7.8 g (30%) of product: mp 67 °C; TLC [silica gel, toluene:HOAc (9:1)]: R_f 0.72; IR (KBr): 2936, 1732, 1663 cm^{-1}. Anal. ($C_8H_7BrO_3S$) C, H, Br, S.

Methyl α-(4-Bromophenyl)-α-(2-furyl)-α-hydroxyacetate (3a)—A solution of 2-furylmagnesium bromide was prepared in the usual way from 1.47 g (0.01 mol) of 2-bromofuran and 0.24 g (0.01 mol) of magnesium in 20 mL of ether. The Grignard solution was transferred to a dropping funnel and slowly added to a solution of 2.18 g (0.009 mol) of **1** in 20 mL of ether. The reaction mixture was stirred at room temperature for 2 h and then hydrolyzed with ammonium chloride solution. Then, the reaction mixture was worked up in the usual way. The residue was purified by column chromatography (silica, toluene) to yield the product (1.36 g, 44%) as a pale yellow oil: TLC [silica gel, toluene:HOAc (9:1)]: R_f 0.58; IR (neat): 3434, 2958, 1734, 1232 cm^{-1}. Anal. ($C_{13}H_{11}BrO_4$) C, H, Br.

Methyl α-(4-Bromophenyl)-α-(3-furyl)-α-hydroxyacetate (3b)—3-Furyllithium was prepared from 7.3 g (0.05 mol) of 3-bromofuran in 50 mL of ether and 4.48 g (0.07 mol) of *n*-butyllithium in 70 mL of ether at −70 °C and was subsequently added at −70 °C (under nitrogen) to a well-stirred solution of magnesium bromide [12.9 g

(0.05 mol) in 150 mL of ether]. A clear solution of 3-furylmagnesium bromide, which after 30 min was cooled to −70 °C, was added in a dropwise manner, under nitrogen, to a solution of 4.86 g (0.02 mol) of 1 in 100 mL of ether, and the mixture was cooled to −70 °C. The cooling bath was removed, and after the mixture was stirred for 1 h at room temperature, ammonium chloride solution was added. The ether layer was separated and dried over sodium sulfate. After filtration and evaporation of the solvent, 6 g of product was obtained. The residue was charged on a silica gel column and eluted with toluene. Appropriate pure fractions were combined and evaporated to yield the desired compound (4.1 g, 66%) as a pale yellow oil: TLC [silica gel, toluene:HOAc (9:1)]: R_f 0.54; IR (neat): 3436, 2957, 1737, 1266 cm^{-1}. Anal. ($C_{13}H_{11}BrO_4$) C, H, Br.

Methyl α-(4-Bromophenyl)-α-(2-thienyl)-α-hydroxyacetate (3c)—A solution of 2-thienylmagnesium bromide was prepared from 1.63 g (0.01 mol) of 2-bromothiophene and 0.24 g (0.01 mol) of magnesium, and this reagent was added to 2.18 g (0.009 mol) of 1 according to the method of preparation of 3a to yield 1.8 g (61%) of product as a brown oil: TLC [silica gel, toluene:HOAc (9:1)]: R_f 0.72; IR (neat): 3485, 2978, 1728, 1229 cm^{-1}. Anal. ($C_{13}H_{11}BrO_3S$) C, H, Br, S.

Methyl α-(4-Bromophenyl)-α-(3-thienyl)-α-hydroxyacetate (3d)—3-Thienyllithium was prepared from 4.89 g (0.03 mol) of 3-bromothiophene and 2.68 g (0.042 mol) of *n*-butyllithium in ether at −70 °C and added to a solution of magnesium bromide. The resulting 3-thienylmagnesium bromide was added to 7.29 g (0.03 mol) of 1 according to the procedure described for the preparation of 3b to yield 4.8 g (49%) of product as a brown oil: TLC [silica gel, toluene: HOAc (9:1)]: R_f 0.68; IR (neat): 3483, 2981, 1729, 1231 cm^{-1}. Anal. ($C_{13}H_{11}BrO_3S$) C, H, Br, S.

Ethyl α-Phenyl-α-[2-(5-bromothienyl)]-α-hydroxyacetate (3e)—A solution of phenylmagnesium bromide (9 g, 0.05 mol) in ether (30 mL) was added in a dropwise manner to 13.15 g (0.05 mol) of 2 dissolved in 25 mL of ether. The latter was placed in a three-necked, 200-mL flask fitted with a stirrer and reflux condenser and stirred during the addition of phenylmagnesium bromide. After complete addition of phenylmagnesium bromide, the mixture was stirred for 1 h at room temperature, refluxed for 1 h, cooled, treated with dilute sulfuric acid, and extracted several times with ether. After removal of the solvent, the product obtained weighed 15.2 g (88%). The impure compound was charged on a silica gel column and eluted with toluene. Appropriate pure fractions were combined and evaporated to yield the desired compound (10.5 g, 61%) as a pale yellow oil: TLC [silica gel, toluene:HOAc (9:1)]: R_f 0.7; IR (neat): 3482, 2994, 1732, 1254 cm^{-1}. Anal. ($C_{14}H_{13}BrO_3S$) C, H, Br, S.

1-Azabicyclo[2.2.2]oct-3-yl α-(4-Bromophenyl)-α-(2-furyl)-α-hydroxyacetate (5a)—A solution of 1.27 g (0.01 mol) of (*R,S*)-3-quinuclidinol in 100 mL of anhydrous benzene was refluxed for 1 h (a Dean–Stark trap was used to remove traces of water); then, 0.4 g of sodium was added, and the mixture was refluxed with stirring for 1 h. After removal of the remaining sodium, 1.24 g (0.004 mol) of 3a was added, and the reaction mixture was refluxed again for 24 h. After the solvent was removed, the residue was suspended in 100 mL of water and extracted with ethyl acetate. The organic layer was washed repeatedly with water and then dried over magnesium sulfate. The filtrate was spin evaporated, and the residue was charged on a silica gel column and eluted with acetone to yield 0.42 g (26%) of product: mp 135 °C; TLC [silica gel, NH_4OH:MeOH (2:98)]: R_f 0.61; IR (KBr): 3379, 2931, 1740, 1244 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.48 (m, 5H), 6.34 (m, 1H), 6.21 (m, 1H), 4.94 (m, 1H), 3.13 (m, 1H), 2.70 (m, 5H), 2.08 (m, 1H), 1.49 (m, 4H). Anal. ($C_{19}H_{20}BrNO_4$) C, H, Br, N.

1-Azabicyclo[2.2.2]oct-3-yl α-(4-Bromophenyl)-α-(3-furyl)-α-hydroxyacetate (5b)—3-Quinuclidinol (1.27 g, 0.01 mol) was dissolved in 200 mL of anhydrous benzene and refluxed for 1 h (a Dean–Stark head was used to remove any traces of moisture). A 0.1-g piece of sodium metal was added, and the mixture was refluxed for 1 h. The remaining unreacted sodium was removed, and 3.1 g (0.01 mol) of 3b was added. The reaction mixture was refluxed overnight and then evaporated to dryness. The residue was dissolved in ethyl acetate and washed repeatedly with water. After drying over sodium sulfate, the solution was spin evaporated. The residual oil was chromatographed on a silica gel column in acetone to yield the purified compound (0.6 g, 14.5%): mp 164–168 °C; TLC [silica gel, NH_4OH:MeOH (2:98)]: R_f 0.6; IR (KBr): 3425, 2955, 1738, 1228 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.43 (m, 6H), 6.40 (m, 1H), 4.91 (m, 1H), 3.18 (m, 1H), 2.70 (m, 5H), 2.04 (m, 1H), 1.41 (m, 4H). Anal. ($C_{19}H_{20}BrNO_4$) C, H, Br, N.

1-Azabicyclo[2.2.2]oct-3-yl α-(4-Bromophenyl)-α-(2-thienyl)-α-hydroxyacetate (5c)—This compound was prepared from 3c (3.27 g, 0.01 mol) and 4 (1.27 g, 0.01 mol) in the same manner as 5a. The oxalate salt was recrystallized from ethanol to yield 2.2 g (42%) of 5c: mp 99–104 °C; TLC [oxalate, silica gel, NH_4OH:MeOH (2:98)]: R_f 0.63; IR (oxalate, KBr): 3452, 2980, 1742, 1245 cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 7.54 (m, 3H), 7.44 (m, 2H), 7.09 (dd, J = 3.6, 1.0 Hz, 1H), 7.01 (dd, J = 5.1, 3.6 Hz, 1H), 5.10 (m, 1H), 3.59 (m, 1H), 3.02 (m, 5H), 2.17 (m, 1H), 1.74 (m, 2H), 1.56 (m, 2H). Anal. ($C_{21}H_{22}BrNO_7S$) C, H, Br, N, S.

1-Azabicyclo[2.2.2]oct-3-yl α-(4-Bromophenyl)-α-(3-thienyl)-α-hydroxyacetate (5d)—This compound was prepared from 3d (3.27 g, 0.01 mol) and 4 (1.27 g, 0.01 mol) in the same manner as 5b, and a brown oil was obtained. The oxalate salt was recrystallized from ethanol:petroleum ether to yield 1.7 g (33%) of product: mp 99–102 °C; TLC [oxalate, silica gel, MeOH:NH_4OH (98:2)]: R_f 0.64; IR (oxalate, KBr): 3449, 2975, 1741, 1243 cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 7.67 (m, 1H), 7.55 (m, 3H), 7.33 (d, J = 8.0 Hz, 2H), 6.86 (m, 1H), 5.08 (m, 1H), 3.60 (m, 1H), 3.06 (m, 5H), 2.15 (m, 1H), 1.79 (m, 2H), 1.50 (m, 2H). Anal. ($C_{21}H_{22}BrNO_7S$) C, H, Br, N, S.

1-Azabicyclo[2.2.2]oct-3-yl α-Phenyl-α-[2-(5-bromothienyl)]-α-hydroxyacetate (5e)—This compound was prepared from 3e (13.64 g, 0.04 mol) and 4 (5.10 g, 0.04 mol) in the same manner as 5a. The residue was recrystallized from ethanol:water (8:2) to yield 5.61 g (34%) of product: mp 156–165 °C; TLC [silica gel, MeOH:NH_4OH (98:2)]: R_f 0.6; IR (KBr): 3439, 2965, 1738, 1241 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.50 (m, 2H), 7.35 (m, 3H), 6.97 (d, J = 3.9 Hz, 1H), 6.90 (d, J = 3.9 Hz, 1H), 4.97 (m, 1H), 3.22 (m, 1H), 2.71 (m, 5H), 1.98 (m, 1H), 1.62 (m, 4H). Anal. ($C_{19}H_{20}BrNO_3S$) C, H, Br, N. S.

Tissue Preparation—The m-AChR was prepared as previously described.[9] Brains were removed from freshly decapitated male Sprague-Dawley rats (200–250 g) and immediately placed on ice. The corpus striatum 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 those of freshly prepared receptors. Samples of 0.15–0.2 g of CS were homogenized in 20 mL of ice-cold 0.9% saline containing 10 mM tris(hydroxymethyl)aminomethane buffer (pH 7.4) and 10% sucrose (buffer I), with a Brinkman Polytron PC-U (medium speed, two 15-s bursts). The receptors were used without further purification. The 10% sucrose buffer aids in maintaining a uniform suspension of the homogenate while sampling. The concentration of m-AChR was ~1 nM. When the assay system was diluted, the final concentration of receptor was ~20 pM.

Determination of Apparent Equilibrium Association Constants—The apparent equilibrium association constants (K_A) for the muscarinic ligands (Table I) were determined by competitive ligand-binding assay with [^{3}H]QNB as the radiotracer.[10] The compounds were dissolved in 100% EtOH and added to 4 mL of tris(hydroxymethyl)aminomethane-buffered (10 mM, pH 7.4) 0.9% saline containing 2.5 × 10^{-10} M [^{3}H]QNB at a final concentration of 0.5% EtOH. When concentrations of EtOH are <2%, the parameters of QNB binding to the m-AChR are not affected. Competition curves were generated with 12 concentrations of unlabeled compounds: 10^{-12}–10^{-6} M for (+)-QNB and compounds with affinities of up to fivefold that of QNB and 10^{-10}–10^{-5} M for compounds with affinities that differed from that of QNB by greater than fivefold. Aliquots (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 with the LIGAND program of Munson and Rodbard.[11] The K_A values were obtained from pooled data of at least five determinations in duplicate on separate days.

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