

# Syntheses and Biological Properties of Chiral Fluoroalkyl Quinuclidinyl Benzilates

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Previously, (*R*)-quinuclidinyl (*R*)-4-iodobenzilate ((*R,R*)-IQNB), a muscarinic receptor antagonist, has been labeled with <sup>123</sup>I and <sup>125</sup>I for use in *in vitro* and *in vivo* studies in animals and humans. We have prepared fluoroalkyl analogs of QNB, which are amenable to labeling with <sup>18</sup>F, for potential imaging applications with positron emission tomography. The enantiomers of (fluoroalkyl)benzyl acids were prepared via an enantioselective Grignard addition reaction. Subsequent coupling of the enantiomeric (fluoroalkyl)benzyl acid with a selected enantiomer of quinuclidinol provides fluorinated analogs of QNB with known stereochemistry at each of the stereogenic centers. These compounds exhibit different affinities for the muscarinic receptor tissue subtypes *in vitro*. (*R,R*)-4-(Fluoromethyl)-QNB, (*R,R*)-IQNB, and (*R,R*)-4-(fluoroethyl)-QNB exhibit selectivity for the M1 subtype, and (*R,S*)-4-(fluoromethyl)-QNB exhibits selectivity for the M2 subtype.

## Introduction

Muscarinic acetylcholine receptors are G protein coupled receptors which exhibit multiple subtypes. Four tissue subtypes (M1, M2, M3, and M4) have been identified on the basis of differential affinity to a number of pharmaceuticals. In addition, five discrete receptor proteins (m1, m2, m3, m4, and m5) have been cloned from a variety of species. The m1, m3, and m5 receptors are linked to phosphoinositol turnover. The m2 and m4 are coupled to adenylate cyclase.<sup>1</sup> Comparison of the results from pharmacological quantitation of M1–M4 subtypes in the brain and antibody quantitation of m1–m4 indicates a very good correlation.<sup>2</sup>

Muscarinic receptor subtypes are observed in a number of organs and are implicated in various diseases.<sup>3</sup> Our particular interests are in the development of highly specific ligands that can be utilized for biomedical imaging of the M2/m2 subtype for the study of Alzheimer's disease<sup>4</sup> and the M3/m3 subtype for investigation in Sjögren's syndrome.<sup>5</sup> Analysis of postmortem brain of Alzheimer's patients shows **conservation** of M1 subtype concentration but a significant **reduction** in the concentration of M2 subtype in cortical regions. The M2 receptor is believed to be a presynaptic autoreceptor.<sup>6</sup>

A number of groups have labeled high-affinity muscarinic ligands for use in positron emission tomography (PET) and single-photon emission-computed tomography (SPECT) to attempt to study pharmacology in the brain. Imaging studies have also been conducted in the heart to quantitate M2 subtype.<sup>7,8</sup> These tracer methodologies may allow confirmation of the postmortem observations in Alzheimer's disease and the evaluation of therapy.

A number of halogenated derivatives of quinuclidinyl benzilate (QNB) have been prepared, but there is no trend in subtype specificity as a function of the halogen or the positional isomer.<sup>9</sup> (*R*)-Quinuclidinyl (*R*)-4-iodobenzilate ((*R,R*)-IQNB, **25**), labeled with <sup>125</sup>I or <sup>123</sup>I, is a high-affinity muscarinic antagonist which has been utilized for *in vitro* assays as well as *in vivo* SPECT imaging.<sup>10–13</sup> Other alkyl analogs of QNB<sup>14</sup> have been tested *in vitro*, and all isomers of an iodopropenyl analog (IQNP) have been prepared and studied.<sup>15</sup> Iodine-labeled isomers of dexetimide have been prepared and studied in muscarinic systems.<sup>16–18</sup>

PET investigators have studied <sup>11</sup>C analogs of acridine,<sup>19</sup> benztropine,<sup>20</sup> dexetimide,<sup>21</sup> QNB,<sup>22</sup> *N*-methylscopolamine,<sup>23</sup> and tropanyl benzilate.<sup>24</sup> Isomeric <sup>18</sup>F analogs of dexetimide have been prepared.<sup>25</sup> All of these PET ligands are reported to have poor subtype selectivity.

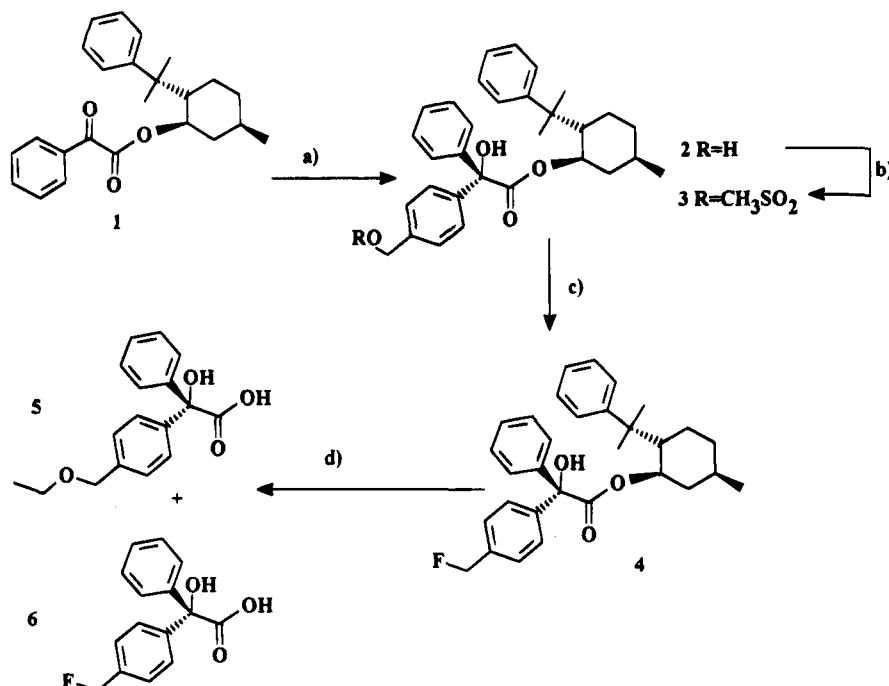
Since our focus is the development of radiolabeled compounds for utilization in PET, we set out to discover an M2 selective ligand which could be labeled with fluorine-18 and applied to the determination of muscarinic receptor concentration *in vivo*. We chose to study new fluorine-containing analogs of quinuclidinyl benzilate. Substituted analogs of QNB offer the interesting feature of two chiral centers. The absolute configuration at the two chiral centers affects the kinetic and thermodynamic properties of receptor binding. The *R* configuration at the quinuclidinyl center provides higher anticholinergic activity than does the *S* configuration as is demonstrated by the higher anticholinergic activity of (*R*)-QNB compared to its *S* enantiomer.<sup>26</sup>

The absolute configuration at the benzilic acid center of (*R,R*)-IQNB had been assigned on the basis of earlier literature that reported higher muscarinic activity for esters of (*R*)-2-cyclohexyl-2-hydroxybenzeneacetates.<sup>27</sup> Inversion of configuration at the benzilic carbon of IQNB is reported to cause a significant difference in the kinetics of ligand binding.<sup>28</sup>

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Scheme 1<sup>a</sup>

<sup>a</sup> (a) BrMgPhCH<sub>2</sub>OtBDMS/THF, then HF/CH<sub>3</sub>CN; (b) CH<sub>3</sub>SO<sub>2</sub>Cl; (c) Me<sub>4</sub>NHF<sub>2</sub>; (d) KOH/ethanol.

This report describes the synthesis of fluoroalkyl analogs of QNB and supporting experiments to verify configurational assignments. We have conducted stereoselective syntheses of (*R*)- or (*S*)-(fluoroalkyl)benzoic acids according to our published method,<sup>29</sup> which is based on the previous work of Whitesell.<sup>30</sup> These acids were subsequently coupled to (*R*)- or (*S*)-quinuclidinol to provide a number of fluoroalkyl analogs of QNB. We utilized the same stereoselective reaction for the synthesis of (*R,R*)-IQNB and verified the absolute configuration by a combination of HPLC methods. In this work we report the single-crystal X-ray analysis of (*R,R*)-IQNB.<sup>31</sup> In addition the *in vitro* binding affinities to muscarinic receptor subtypes are reported.

## Results and Discussion

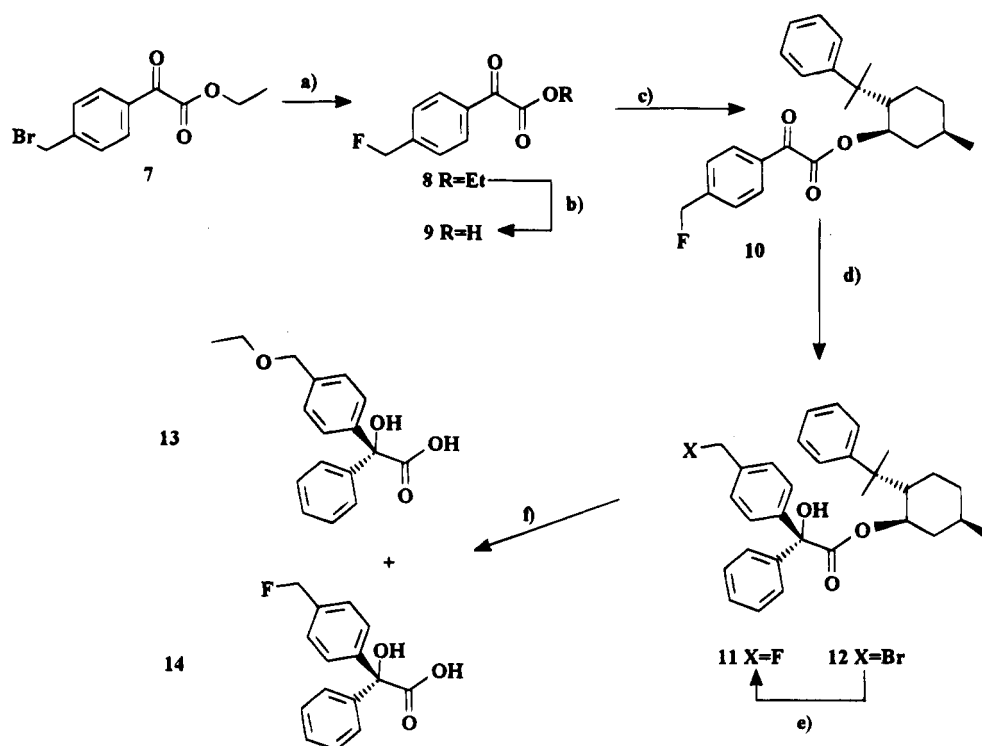
**Chemical Synthesis.** Whitesell had previously reported the use of 8-phenylmenthyl esters to allow the enantioselective addition of a Grignard to an  $\alpha$ -keto ester.<sup>30</sup> The enantioselectivity of the addition to the benzoyl formates is quite high when conducted at dry ice/acetone bath temperature. Analysis of the diastereomers by reverse phase HPLC shows only about 3% of the minor diastereomer. The chiral auxiliary allows synthesis of both enantiomers by selection of the sequence of adding the functionality. Addition of a substituted aromatic Grignard to the unsubstituted benzoyl formate ester results in the generation of the *S* stereogenic center. Addition of phenylmagnesium bromide to a substituted benzyl formate results in the *R* stereogenic center. We previously exploited this reaction to prepare (*R*)-4-iodobenzilic acid and both (*R*)- and (*S*)-4-(fluoroethyl)benzilic acids.<sup>29</sup>

In addition, we synthesized (*R,R*)-IQNB and showed by HPLC analysis that it was the same diastereomer as the authentic product obtained from Nordion International. We have verified the absolute configuration

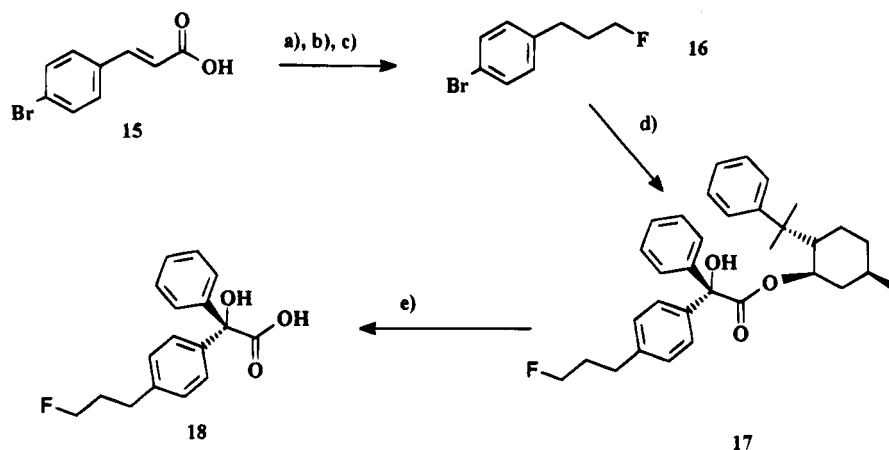
of the authentic product by X-ray diffraction analysis (see supplementary material).

For this study we prepared both enantiomers of 4-(fluoromethyl)benzilic acid. (*S*)-4-(Fluoromethyl)benzilic acid (**6**) is prepared by first making (*S*)-4-(hydroxymethyl)benzilate (**2**) followed by conversion to 4-(fluoromethyl)benzilate via a mesylate and subsequent hydrolysis of the chiral auxiliary (Scheme 1). (*R*)-4-(Fluoromethyl)benzilic acid (**14**) is prepared by first making [4-(fluoromethyl)benzoyl]formic acid (**9**) (Scheme 2). The acid was esterified with the chiral auxiliary to provide **10**; subsequent addition of phenylmagnesium bromide yields **11**, and hydrolysis of the chiral auxiliary provides (*R*)-4-(fluoromethyl)benzilic acid (**14**) (Scheme 2). The syntheses of these molecules presented two unique challenges. First, phenylmagnesium bromide addition to 8-phenylmenthyl [4-(fluoromethyl)benzoyl]formate (**10**) resulted in some exchange of the benzoic fluoride with bromide (Scheme 2). On the basis of TLC analysis, the two products were in nearly equal amounts. The bromo product **12** was identified on the basis of CIMS, which showed the expected molecular ion cluster, and the <sup>1</sup>H-NMR benzoic singlet at  $\delta$  4.4. The mixture of bromo (**12**) and fluoro (**11**) products was treated with Me<sub>4</sub>NHF<sub>2</sub> to convert the bromo into the fluoro product. Second, in the basic ester hydrolysis, some of the benzoic fluoride was displaced by ethanol to yield the corresponding ethyl ethers **5** or **13** (Schemes 1 and 2). These side products were identified on the basis of the <sup>1</sup>H-NMR of the crude product. Also, after coupling of the mixture with quinuclidinol, the ethoxy-QNB was identified by GCMS. The QNB esters undergo a cleavage in the EI which leaves, as the base peak, the diarylcarbinol fragment. These ethers could be separated from the desired fluoro products by crystallization.

(*S*)-4-(3-Fluoropropyl)benzilic acid (**18**) was prepared by addition of [4-(3-fluoropropyl)phenyl]magnesium bromide to benzoylformate **1**. 4-(3-Fluoropropyl)phenyl

Scheme 2<sup>a</sup>

<sup>a</sup> (a)  $\text{Me}_4\text{NHF}_2$ ; (b)  $\text{NaOH}$ ; (c)  $\text{Cl}_2\text{CHOCH}_3$ , then 8-phenylmenthol; (d)  $\text{PhMgBr}$ ; (e)  $\text{Me}_4\text{NHF}_2$ ; (f)  $\text{KOH/ethanol}$ .

Scheme 3<sup>a</sup>

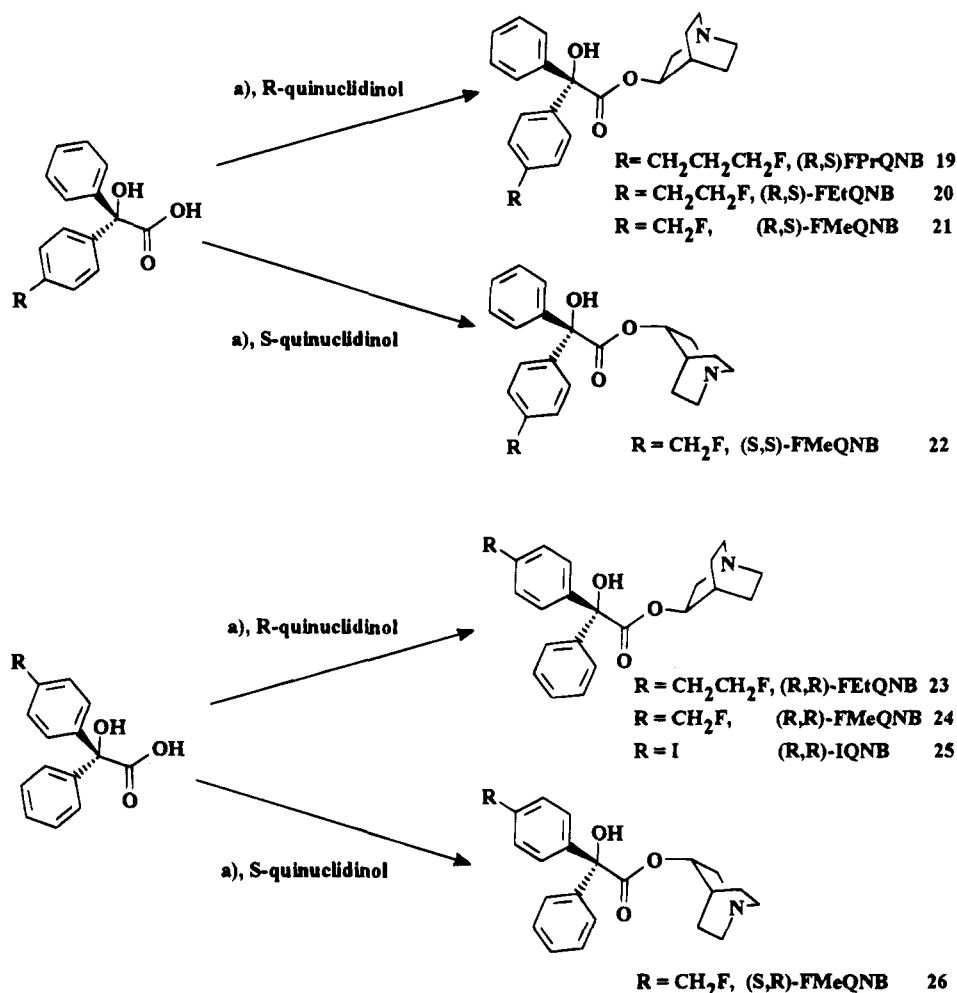
<sup>a</sup> (a)  $\text{LiAlH}_4$ ; (b)  $(\text{CF}_3\text{SO}_2)_2\text{O}$ ; (c)  $\text{Me}_4\text{NHF}_2$ ; (d)  $\text{Mg}$ , **1**; (e)  $\text{KOH/ethanol}$ .

bromide was prepared in two steps from 3-(4-bromophenyl)-1-propanol. 4-Bromocinnamic acid (**15**) is reduced to the alcohol with  $\text{LiAlH}_4$  (Scheme 3).<sup>32</sup> Formation of the triflate and subsequent displacement by reaction with  $\text{Me}_4\text{NHF}_2$  gave the fluoropropyl compound **16**.

Coupling of the chiral benzilic acids to the pure enantiomers of quinuclidinol was accomplished by treating the acid with carbonyl diimidazole in DMF followed by addition of the desired enantiomer of quinuclidinol (Scheme 4).<sup>33</sup> The purity of the isolated products was evaluated by GCMS and reverse phase HPLC (see the experimental and supplementary material). The (fluoroethyl)-QNB analogs were found to contain an approximately 5% impurity based on UV area. This component was identified as the 4-vinyl analog (resulting from HF elimination during the hydrolysis of the 8-phenylmenthyl ester) on the basis of the GCMS

spectrum (base peak  $m/z$  209) and the characteristic styrene signals in the  $^1\text{H-NMR}$ . The integration of HPLC chromatograms may be misleading as to the amount of impurity due to the difference in the chromophore for these two compounds. By  $^1\text{H-NMR}$  integration the minor impurity represents 2–3%. These compounds were tested for muscarinic affinity at this purity level.

**Diastereomeric Purity.** The diastereomeric purity of the final products could only be determined by normal phase HPLC in the case of (fluoropropyl)-QNB **19** (see the experimental and supplementary material). No satisfactory resolution of the diastereomers of the other (fluoroalkyl)-QNB analogs could be achieved. We did find, however, a satisfactory resolution by reverse phase HPLC of the diastereomers of the 8-phenylmenthyl esters of hydroxymethyl and fluoroalkyl analogs (see the experimental and supplementary material). The poor-

Scheme 4<sup>a</sup><sup>a</sup> (a) CDL/DMF.

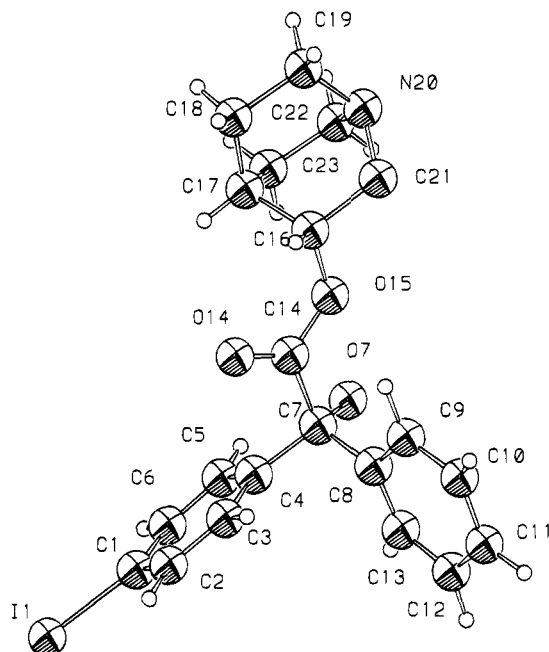
est resolution is obtained with the (fluoromethyl)-benzilate esters, but even so, the presence of 5% of the minor diastereomer should be detectable. In all cases, the major stereoisomer comprises  $\geq 95\%$  of the mixture. None of the chemical steps in conversion of these intermediates will result in epimerization of the benzilic center. This statement is supported by the resulting diastereomeric purity of (fluoropropyl)-QNB 19 and IQNB (25).<sup>29</sup> We are confident that the diastereomeric purity of the final (fluoroalkyl)-QNB analogs will be  $\geq 95\%$ .

**X-ray Crystal Structure.** We have previously synthesized (*R,R*)-IQNB (25) using the same route described here and have shown using HPLC that our product is the same diastereomer as authentic (*R,R*)-IQNB.<sup>29</sup> The absolute configuration of the authentic (*R,R*)-IQNB was confirmed by X-ray crystallography. It is important to note that in the previously published synthesis of IQNB the absolute stereochemistry was established only at the quinuclidinyl center.<sup>28,34</sup> The configuration at the benzilic center was assigned on the basis of the muscarinic affinity.<sup>28</sup>

The refinement depicted by the ZORTEP<sup>35</sup> drawing in the Figure 1 had final parameters  $R = 0.093$ ,  $R_w = 0.098$ , and  $S = 2.97(5)$ . The opposite configuration had  $R = 0.115$ ,  $R_w = 0.122$ , and  $S = 3.66(6)$ . The  $R$ -factors are not very low, probably because of the small size and lower than usual quality of the crystals, but suffice to

define the configuration. Bond lengths of refined atoms have ESDs in the range 0.02–0.03 Å. Details of the crystal structure and tables of coordinates and dimensions are provided as supplementary material. Our assignment of absolute configuration at the benzilic acid center of all of our compounds is supported by this crystal structure.

**In Vitro Affinity.** The *in vitro* binding of these QNB analogs was evaluated by NovaScreen in a five-point binding curve for the three tissue subtypes M1, M2, and M3. LIGAND was used to calculate the affinity constants and the standard error (Table 1). With the exception of (*R*)-QNB and (*R,R*)-IQNB, affinities at M3 are greater than 30 nM. The *R* configuration at the benzilic center imparts higher affinity at M1 sites. None of the three compounds containing an (*S*)-quinuclidinyl center (22, 26, nor (*S,S*)-IQNB) display selectivity for any subtype. The three *R,R* diastereomers, (*R,R*)-4-(2-fluoroethyl)-QNB (23), (*R,R*)-4-(fluoromethyl)-QNB (24), and (*R,R*)-IQNB (25), exhibit 9-, 7.6-, and 12-fold selectivity, respectively, for the M1 subtype over M2. The *R,S* diastereomers show sub-nanomolar affinity but no M1/M2 selectivity with the exception of (*R,S*)-4-(fluoromethyl)-QNB (21), which exhibits a 6.8-fold selectivity for the M2 subtype over M1. Interestingly, high M1 selectivity is displayed by (*R,R*)-(fluoromethyl)-QNB 24, while the highest M2 selectivity is displayed by its (*R,S*)-(fluoromethyl)-QNB diastereomer 21. The



**Figure 1.** ZORTEP projection of the crystal structure of (*R,R*)-IQNB.

**Table 1.** *In Vitro* Affinities Determined in a Five-Point Binding Curve (NovaScreen) in the Three Major Muscarinic Tissue Subtypes<sup>a</sup>

| compound                          | <i>K<sub>i</sub></i> , nM (SE, %) |           |            |
|-----------------------------------|-----------------------------------|-----------|------------|
|                                   | M1                                | m2        | M3         |
| ( <i>R</i> )-QNB                  | 0.22 (323)                        | 0.18 (12) | 4.63 (112) |
| <b>19</b> , ( <i>R,S</i> )-FPrQNB | 0.20 (99)                         | 0.38 (42) | 59.4 (9)   |
| <b>20</b> , ( <i>R,S</i> )-FETQNB | 0.26 (52)                         | 0.31 (24) | 84.7 (4)   |
| <b>21</b> , ( <i>R,S</i> )-FMeQNB | 0.89 (32)                         | 0.13 (35) | 168 (10)   |
| <b>22</b> , ( <i>S,S</i> )-FMeQNB | 5.5 (28)                          | 3.3 (14)  | 38.6 (57)  |
| ( <i>S,S</i> )-IQNB               | 4.6 (8)                           | 9.0 (4)   | 40.5 (8)   |
| <b>23</b> , ( <i>R,R</i> )-FETQNB | 0.84 (8)                          | 7.6 (17)  | >10 000    |
| <b>24</b> , ( <i>R,R</i> )-FMeQNB | 0.11 (5)                          | 0.84 (15) | 92.2 (32)  |
| <b>25</b> , ( <i>R,R</i> )-IQNB   | 0.34 (24)                         | 4.2 (21)  | 8.1 (29)   |
| <b>26</b> , ( <i>S,R</i> )-FMeQNB | 17.9 (20)                         | 11.6 (42) | >10 000    |

<sup>a</sup> The first configuration refers to the quinuclidinyl center. Numbers in parentheses are standard errors as determined by LIGAND.

presence of the *S* configuration at the benzilic center serves to increase the affinity at M2. We have conducted a number of competitive inhibition studies *in vivo* to study subtype selectivity. These results are the subject of another manuscript.<sup>36</sup>

## Conclusion

We have prepared a number of fluoroalkyl analogs of QNB of differing stereochemistry at the two stereogenic centers. Analysis of the muscarinic subtype selectivity *in vitro* shows the effect of the chiral configuration on the affinity. None of the (fluoroalkyl)-QNB analogs display affinity at M3 higher than 38 nM. The *R* configuration of the quinuclidinyl center imparts higher affinity. Analogs with the *R* configuration at the benzilic center display higher affinity at M1 and have selectivity over M2. M1 selectivity is displayed by (*R,R*)-(fluoroethyl)-QNB **23**, (*R,R*)-(fluoromethyl)-QNB **24**, and (*R,R*)-IQNB (**25**). These analogs with the *S* configuration at the benzilic center display high affinity at both M1 and M2 and, with the exception of (*R,S*)-(fluoromethyl)-QNB **21**, exhibit no subtype selectivity. (*R,S*)-(Fluoromethyl)-QNB **21**, the most M2 selective com-

pound of those tested, shows a 6.8-fold higher affinity at M2 compared to M1.

## Experimental Section

(*R,R*)-IQNB (**25**), (*R*)-4-(2-fluoroethyl)benzilic acid, (*S*)-4-(2-fluoroethyl)benzilic acid, and 8-phenylmenthyl benzoylformate were prepared as previously described.<sup>29</sup> Crystalline authentic (*R,R*)-IQNB was received as a generous gift from Nordion International and used for X-ray crystal structure determination. Ethyl [4-(bromomethyl)benzoyl]formate (**7**) was prepared according to literature methods.<sup>37</sup> (*R*)- and (*S*)-quinuclidinol were resolved using the method of Ringdahl.<sup>38</sup>

<sup>1</sup>H-, <sup>13</sup>C-, and <sup>19</sup>F-NMR spectra were obtained at the appropriate frequency on a Varian VXR-200 spectrometer. All samples were in CDCl<sub>3</sub> unless otherwise noted, and chemical shifts for <sup>1</sup>H and <sup>13</sup>C are reported in units of  $\delta$  with tetramethylsilane as internal standard. <sup>19</sup>F chemical shifts are reported relative to CFCl<sub>3</sub>. GCMS data were obtained on a HP 5970A mass selective detector coupled to an HP 5880A gas chromatograph and employed a 12.5 m HP1 column. Column oven programming is expressed in the experimental in the following format 150/2/15/250. This means the program began at 150 °C isothermal for 2 min followed by ramping at 15 °C/min to a final temperature of 250 °C.

HPLC condition A was used for the determination of a diastereomeric purity of the 8-phenylmenthyl esters of benzilic acids. Condition A utilized a Beckman C-18 column (4.6  $\times$  250 mm) eluting with 65% acetonitrile and 35% water at 2 mL/min unless otherwise indicated. UV detection was conducted at 230 nm with a 24 nm bandwidth. The diastereomeric resolution was satisfactory for all pairs except the fluoromethyl diastereomers where a 5% impurity may be difficult to detect. HPLC condition B was used, along with GCMS, for chemical purity of the final QNB analogs. Condition B employed an AXXIOM C-18 column (4.6  $\times$  250 mm) eluting with 65% acetonitrile and 35% buffer (5 mM Et<sub>3</sub>N, 5 mM NaH<sub>2</sub>PO<sub>4</sub>, pH 7) at 1.5 mL/min.

EI, CI, and high-resolution EI mass spectra (HREIMS) were provided by the Laboratory of Analytical Chemistry of the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK), Bethesda, MD. Microanalyses were performed by Galbraith Laboratories Inc., Knoxville, TN, or Atlantic Micro-Labs, Norcross, GA.

**(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (S)- $\alpha$ -Hydroxy- $\alpha$ -[4-(hydroxymethyl)phenyl]benzeneacetate (8-Phenylmenthyl (S)-(hydroxymethyl)-benzilate, **2**.** The Grignard prepared from *tert*-butyl-dimethylsilyl-protected *p*-bromobenzyl alcohol (966 mg, 3.22 mmol) and Mg (85 mg) was added dropwise over 7 min into a cooled (−78 °C) solution of 8-phenylmenthyl benzoylformate (**1**) (1 g, 2.747 mmol) in 5 mL of THF. The reaction mixture was allowed to warm to room temperature and stir overnight. The reaction mixture was poured into 25 mL of 10% NH<sub>4</sub>Cl and extracted with two portions of CHCl<sub>3</sub> (25 mL). The combined organic layers were dried and the volatiles evaporated. The residue was taken up in CH<sub>3</sub>CN (30 mL) and treated with 3 mL of aqueous concentrated HF for 1 h. Water (60 mL) was added and the solution neutralized with Na<sub>2</sub>OH and extracted with two portions of CHCl<sub>3</sub> (100 mL). The combined organics were dried and the volatiles evaporated. The residue was subjected to flash chromatography (30 mm column, 25% EtOAc in hexane) to give the product **2** (884 mg, 68%). <sup>1</sup>H-NMR:  $\delta$  7.48 (d, *J* = 7 Hz, 2H), 7.45–7.21 (m, 7H), 7.1 (s, 5H), 4.9 (dt, *J* = 11, 4 Hz, 1H), 4.7 (d, *J* = 5 Hz, 2H), 2.9 (s, 1H), 2.1–1.82 (m, 3H), 1.7–1.2 (m, 4H), 1.1 (s, 3H), 1.00 (s, 3H), 0.86 (d, *J* = 7 Hz, 3H), 1.2–0.9 (m, 2H). HPLC A: *t<sub>R</sub>* = 13.26 min, 96.5%. EIMS: 472 (3), 259 (5), 213 (100). HREIMS: calcd for C<sub>31</sub>H<sub>36</sub>O<sub>4</sub>, 472.2592; obsvd, 472.2592.

**(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (S)- $\alpha$ -Hydroxy- $\alpha$ -[4-(fluoromethyl)phenyl]benzeneacetate (8-Phenylmenthyl (S)-(fluoromethyl)benzilate, **4**.** A solution of benzyl alcohol **2** (698 mg, 1.48 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was cooled in ice and treated with Et<sub>3</sub>N (329  $\mu$ L, 2.37 mmol) and methanesulfonyl chloride (183  $\mu$ L, 271 mg, 2.37 mmol). The reaction was followed by TLC, and at 1 h

the mixture was washed with water. The aqueous was back-extracted with  $\text{CH}_2\text{Cl}_2$ , the combined organic layers were dried, and the volatiles were evaporated. The residue was subjected to flash chromatography (30 mm column, 30% EtOAc/hexane) to give the mesylate product **3** (768 mg, 94%).  $^1\text{H-NMR}$ :  $\delta$  7.5 (ABq, 4H), 7.29–7.20 (m, 5H), 7.11 (s, 5H), 5.2 (s, 2H), 4.8 (dt,  $J = 11, 4$  Hz, 1H), 2.9 (s, 3H), 2.8 (s, 1H), 2.2–1.85 (m, 2H), 1.7–1.3 (m, 3H), 1.2–0.7 (2H), 1.1 (s, 3H), 1.0 (s, 3H), 0.8 (d,  $J = 7$  Hz, 3H). CIMS: 568 ( $\text{M}^+(\text{NH}_4)$ ). EIMS: 455, 397, 319.

A solution of the mesylate **3** (665 mg, 1.21 mmol) in 20 mL of  $\text{CH}_3\text{CN}$  was treated with  $\text{Me}_4\text{NHF}_2$  (450 mg, 3.9 mol) and heated at reflux for 4 h. The reaction mixture was diluted with water (50 mL) and extracted with  $\text{CHCl}_3$  ( $2 \times 30$  mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent was evaporated. The residue represented 562 mg, 98% yield.  $^1\text{H-NMR}$ :  $\delta$  7.54–7.50 (d,  $J = 8$  Hz, 2H), 7.49–7.15 (m, 7H), 7.11 (s, 5H), 5.42 (d,  $J = 47$  Hz, 2H), 4.87 (dt,  $J = 11, 4$  Hz, 1H), 2.8 (brs, 1H), 2.19–1.94 (m, 2H), 1.7–1.59 (m, 2H), 1.59–1.35 (m, 1H), 1.09 (s, 3H), 1.02 (s, 3H), 0.86 (d,  $J = 7$  Hz, 3H), 1.27–0.82 (m, 2H). HPLC A:  $t_R = 40.530$  min,  $\geq 95\%$ . CIMS: 492 ( $\text{M}^+(\text{NH}_4)$ ). HREIMS: calcd for  $\text{C}_{31}\text{H}_{35}\text{FO}_3$ , 474.2570; obsd, 474.2561.

**General Procedure for Benzilic Ester Hydrolysis.** The 8-phenylmenthyl ester was dissolved in ethanol:water (5:1, v/v), and KOH (45% aqueous, 5 equiv) was added. The resulting mixture was heated in a 65 °C oil bath for 2–3 h. The reaction solution was concentrated under vacuum and the residue diluted with 25 mL of 1 N NaOH and extracted with  $\text{CHCl}_3$ . The aqueous phase was acidified with concentrated HCl and extracted with 1:1 EtOAc: $\text{CHCl}_3$ . The organic phase was dried and evaporated; the resulting residue was crystallized to give the acid.

**(S)- $\alpha$ -Hydroxy- $\alpha$ -[4-(fluoromethyl)phenyl]benzeneacetic Acid ((S)-(Fluoromethyl)benzilic acid, **6**).** Following the general procedure for benzilic ester hydrolysis, 8-phenylmenthyl ester **4** (547 mg, 1.154 mmol) was converted into the acid. The crude product was contaminated with a small amount of ethyl ether **5** as indicated by these selected signals in the  $^1\text{H-NMR}$  at  $\delta$  4.52 (s), 3.60 (q), 1.26 (t). The crude material was crystallized from benzene/hexane to yield the *S* acid **6** (163 mg, 54%). Mp: 101–103 °C dec.  $^1\text{H-NMR}$ :  $\delta$  7.6–7.2 (m, 9H), 5.38 (d,  $J = 48$  Hz, 2H). CIMS: 278 ( $\text{M}^+(\text{NH}_4)$ ), 30, 260 (5), 232 (100). Anal. ( $\text{C}_{15}\text{H}_{13}\text{FO}_3$ ) C, H, F.

**Ethyl 4-(Fluoromethyl)benzoylformate (**8**).**  $\text{Me}_4\text{NHF}_2$  (2.5 g, 22.2 mmol) was added to a solution of ethyl 4-(bromomethyl)benzoylformate (**7**) (2 g, 7.4 mmol) in 40 mL of  $\text{CH}_3\text{CN}$ . The mixture was heated at reflux for 95 min. The solution was cooled, and the solids were removed by filtration. The  $\text{CH}_3\text{CN}$  was evaporated and the residue taken up in 25 mL of water and extracted with 25 mL of  $\text{CH}_2\text{Cl}_2$ . The  $\text{CH}_2\text{Cl}_2$  layer was back-extracted with water and dried. Evaporation of the solvent and Kugelrohr distillation of the residue gave the product (1.093 g, 70%).  $^1\text{H-NMR}$ :  $\delta$  8.05 (d,  $J = 8$  Hz, 2H), 7.5 (d,  $J = 8$  Hz, 2H), 5.4 (d,  $J = 47$  Hz, 2H), 4.4 (q,  $J = 7$  Hz, 2H), 1.4 (t,  $J = 7$  Hz, 3H). GCMS: 100/2/15/250, time 5.620 min, 182 (1.2), 137 (100), 109 (38), 107 (5), 83 (21). Anal. ( $\text{C}_{11}\text{H}_{11}\text{FO}_3$ )H; C: calcd, 62.85; found, 61.82. F: calcd, 9.04; found, 8.32.

**4-(Fluoromethyl)benzoylformic Acid (**9**).** The ester **8** (1.08 g, 5 mmol) was treated with 3 mL of 2 N NaOH. The mixture was stirred for 1 h. During this time a homogeneous solution formed. The solution was acidified with concentrated HCl and extracted with  $\text{CHCl}_3$ . The organic layers were dried and evaporated. The residual solid was crystallized from benzene/hexane to yield the product (679 mg, 75%). Mp: 73–75 °C.  $^1\text{H-NMR}$ :  $\delta$  9.3–9.1 (brs, 1H), 8.35 (d,  $J = 8$  Hz, 2H), 7.50 (d,  $J = 8$  Hz, 2H), 5.5 (d,  $J = 47$  Hz, 2H). Anal. ( $\text{C}_9\text{H}_7\text{FO}_3$ ) C, H, F.

**(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl [4-(Fluoromethyl)benzoyl]formate (8-Phenylmenthyl(fluoromethyl)benzoyl]formate, **10**).** The solid acid **9** (2.16 g, 11.86 mmol) was treated with  $\alpha,\alpha$ -dichloromethyl methyl ether (1.09 mL, 11.86 mmol) at 50 °C for 2 h. The solution was removed from the heating bath and diluted with 30 mL of  $\text{CH}_2\text{Cl}_2$ . Meanwhile, 8-phenylmenthol (2.397 g, 10.33

mmol) was dissolved in 30 mL of  $\text{CH}_2\text{Cl}_2$  and cooled in ice.  $\text{Et}_3\text{N}$  (2.5 mL) was added. Then the solution of the acid chloride was added dropwise over 20 min. The reaction solution was allowed to warm to room temperature and stir overnight. The solution was partitioned with 40 mL of water. The organic layer was dried and evaporated. The residue was subjected to flash chromatography (40 mm column, 10% EtOAc, hexane) to yield the product (3.5 g, 85%). Recrystallization from ethanol yielded the product **10** (1.46 g, 35%), and a second crop was obtained (750 mg, 18%). Mp: 57–60 °C.  $^1\text{H-NMR}$ :  $\delta$  7.98 (d,  $J = 8$  Hz, 2H), 7.47 (d,  $J = 8$  Hz, 2H), 7.22 (d,  $J = 8$  Hz, 2H), 7.19–6.94 (m, 3H), 5.47 (d,  $J = 47$  Hz, 2H), 5.02 (dt,  $J = 13, 4$  Hz, 1H), 2.14–2.01 (m, 2H), 1.66–1.58 (m, 2H), 1.35 (s, 3H), 1.30 (s, 3H), 1.35–0.78 (m, 4H), 0.92 (d,  $J = 6$  Hz, 3H). CIMS: 414 ( $\text{M}^+(\text{NH}_4)$ ). EIMS: 396 (<1), 214 (20), 119 (100), 105 (95). HREIMS: calcd for  $\text{C}_{25}\text{H}_{29}\text{FO}_3$ , 396.2100; obsd, 396.2101. GCMS: 100/2/15/250, 15.274 min, 277 (1), 214 (10), 119 (100). Anal. ( $\text{C}_{25}\text{H}_{29}\text{FO}_3$ ) C, H, F.

**(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (*R*)- $\alpha$ -Hydroxy- $\alpha$ -[4-(fluoromethyl)phenyl]benzeneacetate (8-Phenylmenthyl (*R*)-4-(fluoromethyl)benzilate, **11**).** A solution of 8-phenylmenthyl[(fluoromethyl)benzoyl]formate (**10**) (750 mg, 1.9 mmol) in 10 mL THF was cooled in a dry ice/acetone bath. Phenylmagnesium bromide (1.5 mL of 2.5M) was added dropwise over 5–10 min. The reaction mixture was maintained at dry ice/acetone temperature for 2 h and then allowed to warm to room temperature and stir overnight. The reaction was quenched with 30 mL of 10%  $\text{NH}_4\text{Cl}$  and the mixture extracted twice with  $\text{CHCl}_3$ . The combined organic layers were dried, the organic solvent was evaporated, and the residue was subjected to flash chromatography (30 mm column, 1:1  $\text{CH}_2\text{Cl}_2$ :hexane). A mixture of bromomethyl (**12**) and fluoromethyl (**11**) products were obtained (749 mg). The two components could only be partially separated by flash chromatography. The identity of **12** is supported by  $\text{CI-NH}_3$  which shows a bromine cluster of 552, 554 ( $\text{M}^+(\text{NH}_4)$ ) and  $^1\text{H-NMR}$  which displays a benzilic singlet at  $\delta$  4.4.

This mixture was dissolved in 15 mL of  $\text{CH}_3\text{CN}$ , treated with  $\text{Me}_4\text{NHF}_2$  (348 mg), and heated at reflux for 2 h. The solution was poured into water and extracted with  $\text{CHCl}_3$  ( $2 \times 25$  mL). The combined organic layers were dried and the solvents evaporated to yield the fluoromethyl product **11** (740 mg, 82%).  $^1\text{H-NMR}$ :  $\delta$  7.4–7.2 (m, 9H), 7.0 (s, 5H), 5.3 (d,  $J = 48$  Hz, 2H), 4.88 (dt,  $J = 11, 4$  Hz, 1H), 2.72 (s, 1H). 2.2–1.90 (m, 2H), 1.8–1.3 (m, 3H), 0.8–1.2 (m, 2H), 1.1 (s, 3H), 1.0 (s, 3H), 0.86 (d,  $J = 7$  Hz, 3H). HPLC A:  $t_R = 41.97$  min,  $\geq 95\%$ . EIMS: 474 (<1), 368 (4), 199 (33), 119 (100).

**(*R*)- $\alpha$ -Hydroxy- $\alpha$ -[4-(fluoromethyl)phenyl]benzeneacetic Acid ((*R*)-4-(fluoromethyl)benzilic acid, **14**).** Following the general procedure for benzilic ester hydrolysis, 8-phenylmenthyl (*R*)-4-(fluoromethyl)benzilic acid (**11**) (658 mg, 1.38 mmol) was converted into the *R* acid **14**. The crude product was contaminated with a small amount of ethyl ether **15** as indicated by the selected signals in the  $^1\text{H-NMR}$   $\delta$  4.5 (s), 3.53 (q), 1.20 (t). The crude product was successfully crystallized from a solution of 2 mL of hexane and 1 mL of benzene and recrystallized from the same mixture (153 mg, 42%). Mp: 85–93 °C dec.  $^1\text{H-NMR}$  (acetone):  $\delta$  7.6–7.2 (m, 9H), 5.4 (d,  $J = 48$  Hz, 2H). CIMS: 278 (80), 232 (100). Anal. ( $\text{C}_{15}\text{H}_{13}\text{FO}_3$ ) C, H, F.

**(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (*S*)- $\alpha$ -Hydroxy- $\alpha$ -[4-(3-fluoropropyl)phenyl]benzeneacetate (8-Phenylmenthyl (*S*)-4-(3-fluoropropyl)benzilate, **17**).** 3-(4-Bromophenyl)-1-propanol was prepared from 4-bromocinnamic acid according to the literature procedure.<sup>32</sup> In our hands the product was contaminated with up to 10% 3-phenyl-1-propanol. The alcohol was converted in two steps to the fluoride. Triflic anhydride (2 equiv) was dissolved in  $\text{CH}_2\text{Cl}_2$  (175 mL) and cooled in an ice bath. A solution of the alcohol (57 mmol) and pyridine (2 equiv) in  $\text{CH}_2\text{Cl}_2$  (100 mL) was added dropwise over 1 h. After stirring for an additional 30 min, the solution was washed with water, dried, and evaporated. The residue was taken up in  $\text{CH}_3\text{CN}$  (140 mL) and treated with 3 equiv of  $\text{Me}_4\text{NHF}_2$ . The solution was stirred at room temperature for 1 h and the  $\text{CH}_3\text{CN}$  removed

under vacuum. The residue was diluted with water and extracted with hexane. The hexane was dried and evaporated. The residue was eluted through a 3 in.  $\times$  40 mm silica gel column with hexane. The major fraction was collected to yield 9 g of alkyl fluoride **16** contaminated with the debrominated 3-phenyl-1-fluoropropane. This material was used without additional purification.

A solution of 3-(4-bromophenyl)-1-fluoropropane (**16**) (1 g, 4.6 mmol) in 5 mL of THF was added to Mg (131 mg, 5.45 mmol). A few crystals of  $I_2$  were added, and the mixture was heated to reflux. After 1 h, the solution was diluted with 5 mL of THF and added via syringe over 5 min to a solution of 8-phenylmenthyl benzoylformate (**1**) (1.2 g, 3.5 mmol) in 10 mL of THF which had been cooled in a dry ice/acetone bath. The reaction mixture was allowed to come to room temperature and stir overnight. The solution was poured into 100 mL of 10%  $NH_4Cl$  and extracted with  $2 \times 100$  mL of  $CHCl_3$ . The organic layers were dried and concentrated to an oil. The residual material was subjected to flash chromatography (40 mm, 10% EtOAc, hexane). The product **17** (720 mg, 41%) was obtained as an oil.  $^1H$ -NMR:  $\delta$  7.45–7.25 (m, 9H), 7.10 (brs, 5H), 4.88 (dt,  $J = 11$ , 4 Hz, 1H), 4.46 (tt,  $J = 47$ , 6 Hz, 2H), 2.95 (s, 1H), 2.85–2.70 (m, 2H), 2.18–1.90 (m, 4H), 1.7–1.2 (m, 4H), 1.10 (s, 3H), 0.95 (s, 3H), 0.85 (d,  $J = 7$  Hz, 3H), 0.83–1.1 (m, 2H).  $^{19}F$ -NMR:  $\delta$  -217.7 (tt,  $J = 53$ , 21 Hz). HPLC A: 95% ACN, 5% water, 1 mL/min,  $t_R = 5.9$  min, >98%. EIMS: 502 (1), 243 (100). HREIMS: calcd for  $C_{33}H_{39}FO_3$ , 502.2883; obsvd, 502.2903.

**(S)- $\alpha$ -Hydroxy- $\alpha$ -[4-(3-fluoropropyl)phenyl]benzeneacetic Acid ((S)-4-(3-Fluoropropyl)benzilic acid, **18**)**. Following the general procedure for benzilic ester hydrolysis, 8-phenylmenthyl ester **17** (919 mg, 1.83 mmol) was converted into the acid **18**. In this case, following the time of heating, the reaction mixture was first partitioned with ethyl acetate and 1 N HCl. The organic phase was concentrated under vacuum. The residue was chromatographed through 4 in. of silica gel in a 40 mm column by first eluting with 10% EtOAc in hexane to elute the 8-phenylmenthol and subsequently with 1:1 EtOAc:hexane containing 0.5% HOAc to provide the product which partially solidified upon standing (401 mg, 76%).  $^1H$ -NMR:  $\delta$  7.49–7.12 (m, 9H), 4.46 (dt,  $J = 47$ , 6 Hz, 2H), 2.75 (t,  $J = 7$  Hz, 2H), 2.0 (dm, 2H).  $^{19}F$ -NMR:  $\delta$  -219.96 (tt,  $J = 47$ , 25 Hz). CIMS: 306 ( $M^+(NH_4)$ ). Anal. ( $C_{17}H_{17}FO_3$ ) C, H, F.

**General Procedure for Coupling the Resolved Benzilic Acid with Resolved Quinuclidinol**. The benzilic acid was dissolved in DMF and carbonyldiimidazole was added. The resulting solution was stirred at room temperature for 1 h. The appropriate enantiomer of quinuclidinol was added and the reaction solution stirred overnight. The reaction mixture was diluted with 0.1 N NaOH and extracted with two or three portions of  $CHCl_3$ . The combined organics were dried and evaporated. The DMF was removed under high vacuum. The residue was subjected to flash chromatography (silica gel, 90%  $CHCl_3$ , 9% methanol, 1%  $NH_4OH$ ).

**(R)-Azabicyclo[2.2.2]oct-3-yl (S)- $\alpha$ -Hydroxy- $\alpha$ -[4-(3-fluoropropyl)phenyl]benzeneacetate ((R,S)-FPrQNB, **19**)**. Following the general procedure, (S)-4-(3-fluoropropyl)benzilic acid (**18**) (150 mg, 0.52 mmol) in 2 mL of DMF was treated with carbonyldiimidazole (84 mg, 0.52 mmol) and (R)-quinuclidinol (66 mg, 0.52 mmol). The product was obtained as a foamy solid (102 mg, 50%).  $^1H$ -NMR:  $\delta$  7.45–7.25 (m, 7H), 7.2–7.1 (m, 2H), 5.9 (brs, 1H), 4.85–4.95 (m, 1H), 4.4 (dt,  $J = 48$ , 5 Hz, 2H), 3.2–3.0 (m, 1H), 2.8–2.3 (m, 7H), 2.1–1.8 (m, 3H), 1.7–1.4 (m, 2H), 1.4–1.1 (m, 2H).  $^{19}F$ -NMR:  $\delta$  -219.9 (tt,  $J = 47$ , 25 Hz). GCMS: 150/2/15/250, 13.59 min, 397 ( $M^+$ , 3.5), 398 (1.1), 243 (100), 165 (13), 105 (35), 77 (15). HPLC B:  $t_R = 14.97$  min, >98%. HPLC: column Perkin-Elmer SI (4.6  $\times$  75 mm), 98.5%  $CH_2Cl_2$ , 1.44% ethanol, 0.2% ethylamine, 0.4% water, flow 2 mL/min, UV detection at 250 nm,  $t_R = 16.131$  min, 98.2%. EIMS: 397 (15), 243 (100). HREIMS: calcd for  $C_{24}H_{28}FNO_3$ , 397.2053; obsvd, 397.2039.

**(R)-Azabicyclo[2.2.2]oct-3-yl (S)- $\alpha$ -Hydroxy- $\alpha$ -[4-(2-fluoroethyl)phenyl]benzeneacetate ((R,R)-FEtQNB, **20**)**. Following the general procedure, (S)-4-(2-fluoroethyl)benzilic acid (207 mg, 0.755 mmol) in 3 mL of DMF was treated with

carbonyldiimidazole (138 mg, 0.831 mmol) and (R)-quinuclidinol (105 mg, 0.831 mmol). The product was obtained as a foamy solid contaminated with imidazole. This residue was taken up in 10 mL of  $CHCl_3$  and washed with 10 mL of 0.1 N NaOH. The organic layer was dried, and the volatiles were evaporated to give the product (151 mg, 52%). A small amount (2–3%) of the HF elimination byproduct was observed in the  $^1H$ -NMR 6.70 (dd,  $J = 17$ , 11 Hz), 5.75 (dd,  $J = 17$ , 1 Hz), 5.25 (dd,  $J = 11$ , 1 Hz).  $^1H$ -NMR:  $\delta$  7.45–7.28 (m, 7), 7.28–7.26 (m, 2H), 4.95–4.85 (m, 1H), 4.65 (dt,  $J = 47$ , 7 Hz, 2H), 3.2–3.1 (m, 1H), 2.97 (dt,  $J = 23$ , 6 Hz, 2H), 2.6–2.4 (m, 5H), 2.0–1.9 (m, 1H), 1.6–1.2 (m, 4H).  $^{19}F$ -NMR:  $\delta$  -215.9 (dt,  $J = 47$ , 23 Hz). GCMS: 150/2/15/250, 11.923 min, 383 (8), 384 (2), 229 (100), 126 (34). HPLC B:  $t_R = 11.5$  min, 94.5%. EIMS: 383 (20), 229 (100). HREIMS: calcd for  $C_{23}H_{26}FNO_3$ , 383.1896; obsvd, 383.1879.

**(R)-Azabicyclo[2.2.2]oct-3-yl (S)- $\alpha$ -Hydroxy- $\alpha$ -[4-(fluoromethyl)phenyl]benzeneacetate ((R,S)-FMeQNB, **21**)**. Following the general procedure, (S)-4-(fluoromethyl)benzilic acid (**6**) (106 mg, 0.407 mmol) in 2 mL of DMF was treated with carbonyldiimidazole (71 mg, 0.437 mmol) and (S)-quinuclidinol (57 mg, 0.448 mmol). The product was obtained as a foam (58 mg, 37%).  $^1H$ -NMR:  $\delta$  7.5–7.2 (m, 9H), 5.6 (d,  $J = 48$  Hz, 2H), 5.0–4.9 (m, 1H), 3.2–3.0 (m, 1H), 2.8–2.4 (m, 5H), 1.9–2.00 (m, 1H), 1.7–1.4 (m, 2H), 1.4–1.1 (m, 2H).  $^{19}F$ -NMR:  $\delta$  -208.3 (t,  $J = 48$  Hz). GCMS: 150/2/15/250, 10.804 min, 369 (16), 215 (100), 126 (56). HPLC B:  $t_R = 10.9$  min, >99%. EIMS: 369 (2), 215 (40), 137 (60), 119 (70), 105 (100), 77 (75). HREIMS: calcd for  $C_{22}H_{24}FNO_3$ , 369.1740; obsvd, 369.1727.

**(S)-Azabicyclo[2.2.2]oct-3-yl (S)- $\alpha$ -Hydroxy- $\alpha$ -[4-(fluoromethyl)phenyl]benzeneacetate ((S,S)-FMeQNB, **22**)**. Following the general procedure, (S)-4-(fluoromethyl)benzilic acid (**6**) (109 mg, 0.419 mmol) in 2 mL of DMF was treated with carbonyldiimidazole (71 mg, 0.437 mmol) and (S)-quinuclidinol (57 mg, 0.450 mmol). This product could be crystallized; however, an unknown impurity required removal. An analytical sample was obtained following preparative HPLC (Beckman ODS, 9.4  $\times$  250, 30% ACN, 70% water, 0.1 % TFA). Product was obtained (25 mg).  $^1H$ -NMR:  $\delta$  7.51–7.28 (m, 9H), 5.38 (d,  $J = 48$  Hz, 2H), 4.99–4.93 (m, 1H), 3.20–3.12 (m, 1H), 2.74–2.50 (m, 4H), 2.0–1.98 (m, 1H), 1.75–1.22 (m, 4H).  $^{19}F$ -NMR:  $\delta$  -208.5 (t,  $J = 47$  Hz). GCMS: 150/2/15/250, 10.803 min, 369 (16), 370 (4), 215 (100), 126 (53). HPLC B:  $t_R = 10.6$  min, >98%. HREIMS: calcd for  $C_{22}H_{24}FNO_3$ , 369.1740; obsvd, 369.1748.

**(R)-Azabicyclo[2.2.2]oct-3-yl (R)- $\alpha$ -Hydroxy- $\alpha$ -[4-(2-fluoroethyl)phenyl]benzeneacetate ((R,R)-FEtQNB, **23**)**. Following the general procedure, (R)-4-(2-fluoroethyl)benzilic acid (176 mg, 0.642 mmol) in 3 mL of DMF was treated with carbonyldiimidazole (109 mg, 0.674 mmol) and (R)-quinuclidinol (85 mg, 0.674 mmol). The product (160 mg) was obtained after flash chromatography as a foamy solid contaminated with imidazole. This product was taken up in 15 mL of  $CHCl_3$  and washed with 10 mL of 0.1 N NaOH. The organic layer was dried and the volatile evaporated to give the product (140 mg, 57%). The product was contaminated with a small amount (about 2%) of the HF elimination product on the basis of the minor signals in the  $^1H$ -NMR 6.71 (dd,  $J = 18$ , 11 Hz), 5.76 (dd,  $J = 18$ , 1 Hz), 5.26 (dd,  $J = 11$ , 1 Hz).  $^1H$ -NMR:  $\delta$  7.5–7.1 (m, 9H), 4.85–4.95 (m, 1H), 4.6 (dt,  $J = 47$ , 6 Hz, 2H), 3.0–3.2 (m, 1H), 3.0 (dt,  $J = 24$ , 7 Hz, 2H), 2.4–2.6 (m, 5H), 1.97–1.92 (m, 1), 1.2–1.6 (m, 4H).  $^{19}F$ -NMR:  $\delta$  -215.4 (tt,  $J = 47$ , 24 Hz). GCMS: 150/2/15/250, 11.921 min, 383 (7), 348 (2), 229 (100), 126 (34). HPLC B:  $t_R = 11.4$  min, 96.1%. EIMS: 383 (15), 229 (100). HREIMS: calcd for  $C_{23}H_{26}FNO_3$ , 383.1896; obsvd, 383.1882.

**(R)-Azabicyclo[2.2.2]oct-3-yl (R)- $\alpha$ -Hydroxy- $\alpha$ -[4-(fluoromethyl)phenyl]benzeneacetate ((R,R)-FMeQNB, **24**)**. Following the general procedure, (R)-4-(fluoromethyl)benzilic acid (**14**) (100 mg, 0.384 mmol) in 2 mL of DMF was treated with carbonyldiimidazole (71 mg, 0.437 mmol) and (R)-quinuclidinol (59 mg, 0.393 mmol). Flash chromatography was not required because crystallization could be accomplished from  $CH_3CN$  to give 61 mg (43%) of product. Mp: 181–184  $^{\circ}C$ .  $^1H$ -NMR:  $\delta$  7.5–7.2 (m, 9H), 5.6 (d,  $J = 48$  Hz, 2H), 4.9–

5.0 (m, 1H), 3.2–3.0 (m, 1H), 2.8–2.4 (m, 5H), 1.9–2.00 (m, 1H), 1.7–1.4 (m, 2H), 1.4–1.1 (m, 2H). HPLC B:  $t_R$  = 10.8 min, >98%. GCMS: 150/2/15/250, 10.826 min, 369 (19), 370 (4.3), 215 (100), 126 (51). HREIMS: calcd for  $C_{22}H_{24}FNO_3$ , 369.1740; obsvd, 369.1752.

**(S)-Azabicyclo[2.2.2]oct-3-yl (R)- $\alpha$ -Hydroxy- $\alpha$ -(4-(fluoromethyl)phenyl)benzeneacetate ((S,R)-FMeQNB, 26).** Following the general procedure, (R)-4-(fluoromethyl)benzoic acid (14) (100 mg, 0.384 mmol) in 2 mL of DMF was treated with carbonyldiimidazole (71 mg, 0.437 mmol) and (S)-quinuclidinol (50 mg, 0.393 mmol). The analytical sample was obtained after preparative HPLC (Beckman ODS, 9.4  $\times$  250, 30% ACN, 70% water, 0.1 % TFA). Product was obtained (17 mg).  $^1H$ -NMR:  $\delta$  7.5–7.2 (m, 9H), 5.38 (d,  $J$  = 54 Hz, 2H), 5.0–4.9 (m, 1H), 3.3–3.1 (ddd,  $J$  = 13, 8, 2 Hz, 1H), 2.70–2.5 (m, 5H), 2.0–1.95 (m, 1H), 1.7–1.2 (m, 4H). GCMS: 150/2/15/250, 10.779 min, 369 (15), 370 (4), 215 (100), 126 (58). HPLC B:  $t_R$  = 10.8 min, >98%. HREIMS: calcd for  $C_{22}H_{24}FNO_3$ , 369.1740; obsvd, 369.1749.

**In Vitro Binding Studies.** These assays were conducted by NovaScreen.<sup>39</sup> The assays were conducted as follows: M1—competitive inhibition of [ $^3H$ ]pirenzepine binding in bovine striatal membranes using atropine ( $10^{-5}$  M) as the positive control;<sup>40</sup> M2—competitive inhibition of [ $^3H$ ]AF-DX 384 in rat heart membrane with methoctramine as the positive control ( $10^{-6}$  M);<sup>41</sup> M3—competitive inhibition of [ $^3H$ ]-N-methylscopolamine in guinea pig ileum with 4-DAMP (4-(diphenylacetoxyl)-N-methylpiperidine methiodide) as the positive control with atropine as displacer.<sup>42</sup> The raw data from NovaScreen was analyzed using LIGAND to give the  $K_i$  and the standard errors.

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**Supplementary Material Available:** Single-crystal X-ray analysis of (R,R)-IQNB, GCMS data for compounds 19–24 and 26, HPLC chromatograms for compounds 4, 11, 19–24, and 26, table of  $^{13}C$ -NMR data, and  $^1H$ -NMR of 20 and 23 (16 pages). Ordering information is given on any current masthead page.

## References

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