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Synthesis and 5-HT-3 receptor binding activity of 5-[^{125}I]iodo-2,3-dimethoxy-*N*-(1-azabicyclo[2.2.2]oct-3-yl)benzamide and its 5-halogen-2-alkoxyl homologues

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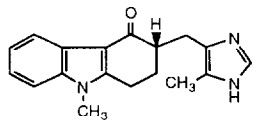
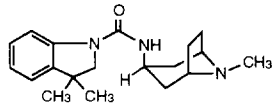
Summary — (*S*)-5-Iodo-2,3-dimethoxy-*N*-(1-azabicyclo[2.2.2]oct-3-yl)benzamide (MIZAC) was prepared from 5-iodo-2,3-dimethoxybenzoyl chloride and (*S*)-3-aminoquinuclidine. [^{125}I]Iodode-stannylation of its corresponding 5-tri-*n*-butyltin derivative gave [^{125}I]-MIZAC at 1800 Ci/mmol. Binding of [^{125}I]-MIZAC in rat entorhinal cortex revealed a K_D of 1.37 ± 0.21 nM. A series of racemic 2-*O*-alkyl derivatives of MIZAC were prepared and 5-HT-3 receptor affinities were determined by inhibition of [^{125}I]-MIZAC binding. Optimal affinity for the receptor was obtained with small, electron-withdrawing substituents in the aromatic 5-position and with bulky substituents in the 3-position. [^{125}I]-MIZAC is a selective radioligand useful for in vitro identification of the 5-HT-3 receptor.

benzamides / 5-HT-3 receptor antagonist / rat brain / iodine-125 / tributyltin

Introduction

Cerebral serotonergic systems are of interest in psychiatric disorders. More than 14 different subtypes of serotonin receptors have been identified to date [1]. Of these, the 5-HT-3 receptor is known to mediate antiemetic action [2], and has received attention in recent years because of its implication in the modulation of behavior in animal models of psychiatric illness [3]. Recent clinical studies suggest a role for 5-HT-3 antagonists in the control of alcohol abuse [4]. We sought to develop a selective, high affinity [^{125}I]iodinated radioligand for use in studying the 5-HT-3 receptor. Several potent analogues of the antiemetic agent ondansetron have been reported. The corresponding 4-imidazolyl analogue, galdansetron (*R*-GR-67330), showed a 50-fold increase in 5-HT-3 receptor affinity [5] and the corresponding 3-aza bioisostere, fabesetron (FK-1052), showed high potency in blocking 2-methyl-5-HT-induced bradycardia [6]. Ramosetron (YM-060) is twice as potent as galdansetron [7], and positional permutation of the indole nitrogen atom of ramosetron has produced agents that are 80 times more potent than ondansetron [8]. Other potent 5-HT-3 receptor antagonists are analogues of tropisetron, eg, itasetron (DAU-6215) [9], its *N*-ethyl homologue BIMU-1 [9], and ricasetron (BRL-46470) [10]. However, none of these agents have proven to be selective for the 5-HT-3 receptor [9, 10], nor have they been radiolabeled with ^{125}I. The only 5-HT-3 receptor antagonist that has been labeled with [^{125}I]iodine is zacopride (AHR-11190) [2, 11, 12].


galdansetron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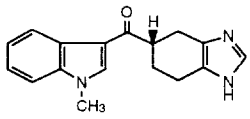
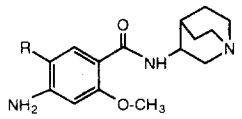

ramosetron


zacopride (R = Cl)
5-iodozacopride (R = I)

Racemic deschloro-5-[^{125}I]iodozacopride has been used for autoradiographic visualization of 5-HT-3 receptors in entorhinal cortex, amygdala and hippocampus of the rat brain [13]. The moderate affinity (K_D 2.6–4.3 nM), substantial nonspecific binding, and

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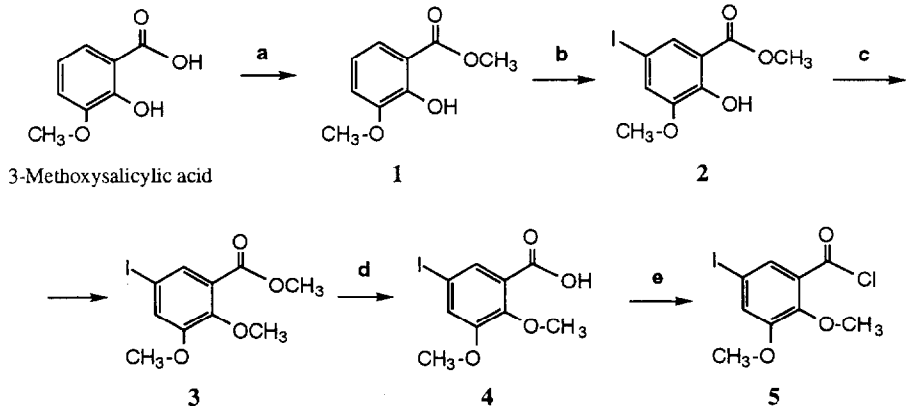
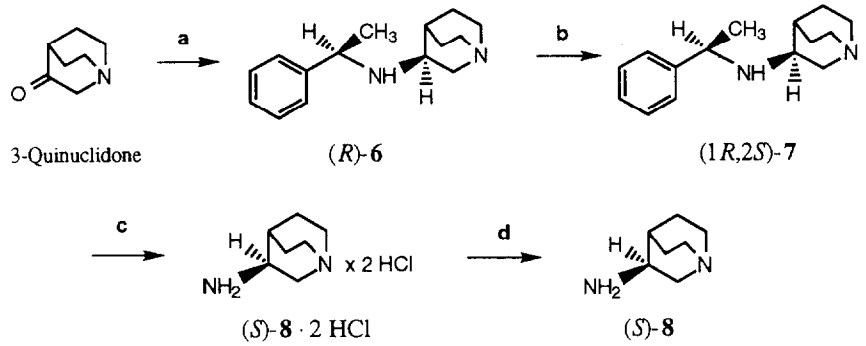
difficulties in the synthesis of 5-[^{125}I]iodozacopride [11, 12] make the study of low density of 5-HT-3 receptors [13, 14] with this ligand difficult. In order to develop a more easily synthesized iodine-substituted benzamide with receptor affinity and selectivity suitable for characterization of the 5-HT-3 receptor, we now report structural modifications of the aromatic substituents of zacopride.

Chemistry

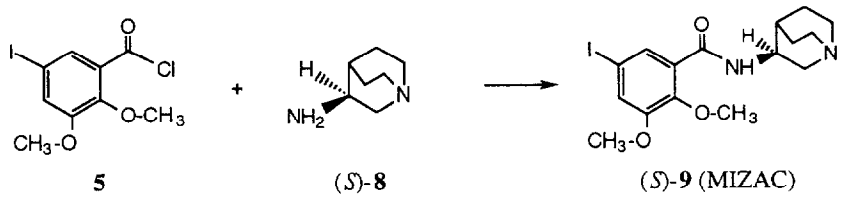
Preparation of (*S*)-2-methoxy-5-iodo-des-4-amino-zacopride (acronym MIZAC), (*S*)-5-iodo-2,3-dimethoxy-*N*-(1-azabicyclo[2.2.2]oct-3-yl)benzamide was accomplished by a modification of the method of Yue et al [15] for the synthesis of 5-iodo-2,3-dimethoxybenzoic acid, followed by amide condensation [16]. The requi-



Scheme 1. Reagents: a) H_2SO_4/MeOH; b) NaI, Chlor – T/DMF; c) Me_2SO_4, K2CO_3/acetone; d) NaOH/EtOH; e) $SOCl_2$/MePh; f) (*S*)–AQN/THF.



Scheme 2. Reagents: a) (*R*)-MeBzNH_2/MePh; b) $NaBH_4$/MeOH; c) H_2, Pd/MeOH; d) 10 N NaOH/EtOH.



Scheme 3. Reagents: compounds **5**, (*S*)-**8**/DMF.

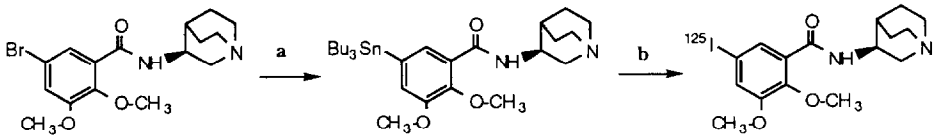
red (*R*)- and (*S*)-3-quinuclidinylamines were prepared as described by Langlois et al [17], and isolated as the free base prior to amide condensations. (The corresponding dihydrochloride salts have since become available from Aldrich, Milwaukee, WI.)

3-Methoxysalicylic acid was esterified by sulfuric acid in methanol to give methyl 3-methoxy-salicylate **1** according to Bishop et al [18]. The ester **1** was iodinated by in situ oxidation of sodium iodide with chloramine-T [15]. Recrystallization of **1** from aqueous methanol removed the toluylsulfonamide which co-extracts in basic solution from the desired methyl 5-iodo-3-methoxysalicylate **2**. The ester **2** was alkylated by either methyl iodide or dimethylsulfate in acetone. The resulting 2,3-dimethoxy ester **3** was hydrolyzed to the corresponding 5-iodo-2,3-dimethoxybenzoic acid **4** [15] by heating with aqueous sodium hydroxide in ethanol. The acid **4** was converted to its acid chloride, **5**, by treatment with thionyl chloride in toluene, catalyzed by 1% dimethylformamide [16]. Compound **5** could be recrystallized from hexane, but was usually used without purification in the amide condensation step.

3-Quinuclidinone hydrochloride was dissolved in 30% sodium hydroxide and the free base was extracted with ether (scheme 2) according to Langlois et al [17]. The amine was heated with (*R*)-(+)-1-methylbenzylamine. Evaporation of the solvent using a water trap gave the Schiff's base (*R*)-**7** as an oil. Reduction of (*R*)-**7** with sodium borohydride in methanol, followed by precipitation of the dihydrochloride with anhydrous hydrochloric acid in 2-propanol and recrystallization twice from a mixture of ethanol and methanol gave the diastereomer (1*R*, 3*S*)-**7**·2 HCl. Removal of the benzyl group by catalytic hydrogenation with palladium hydroxide in aqueous methanol gave the desired diamine dihydrochloride (*S*)-**8**·2 HCl in 30% total yield [17]. The free base was liberated by dissolving (*S*)-**8**·2 HCl in two equivalents of 10 N sodium hydroxide and repeated azeotropic evaporation of anhydrous ethanol while removing the precipitated sodium chloride by filtration. The crystalline free base of (*S*)-3-aminoquinuclidine (*S*)-**8** is stable, but readily forms a carbonate when exposed to the atmosphere.

The acid chloride **5** was condensed with the diamine (*S*)-**8** as the free base in dimethylformamide or acetonitrile in analogy with the synthesis of iodopride [16]. Because of the strongly basic nature of **8**, use of halogenated solvents such as chloroform or methylene chloride caused formation of quaternary addition products which lowered the yields [17]. Consistent yields of 50% recrystallized (*S*)-**9**·HCl were obtained after column chromatography and treatment of the product with anhydrous hydrochloride in 2-propanol. Synthesis of (*R*)-**9** was performed in a similar way using (*R*)-3-aminoquinuclidine, (*R*)-**8** [17].

The tributyltin precursor, (*S*)-5-(tri-*n*-butylstannyl)-2,3-dimethoxy-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-benzamide ((*S*)-**11**) for radiolabeling of (*S*)-**9** was prepared from the corresponding 5-bromo derivative (*S*)-**10** (scheme 4). The latter was obtained from 5-bromo-2,3-dimethoxybenzoic acid [19]. Synthesis of (*R*)-**11** was accomplished in a similar way using (*R*)-**10**. The bromo compounds were preferred over using unlabeled **9** in the synthesis of **11** because of the risk of contamination with carrier iodine in the labeling reaction. We found that isolation of the tributyltin precursor **11** by column chromatography on silica caused traces of iodide to accompany the oily product. However, washing of an etheral solution of **11** with water removed all amounts of iodide. Radioiodination was performed with 5 mCi of radioactive ^{125}I by the method of Clanton et al [20]. Sodium [^{125}I]iodide was added to an ethanolic solution of (*S*)-**11**. Free [^{125}I]iodine was generated in situ by adding 10% hydrogen peroxide to the reaction mixture in 6 N acetic acid (60 min) or by adding chloramine-T to the reaction mixture in 0.2 N hydrochloric acid (1 min). HPLC purification gave (*S*)-[^{125}I]-**9** as a single radioactive product. Comparison of the UV peak of unlabelled (*S*)-**9** gave a specific radioactivity of 1800 Ci/mmol. Reinjection of a sample of the collected fraction showed > 98% radiochemical purity.



(*S*)-**10** (*S*)-**11** (*S*)-[^{125}I]-**9**

Scheme 4. Reagents: a) Bu_6Sn_2, $(Ph_3P)4Pd/Et_3N$; b) $Na^{125}I$, H_2O_2/HCl.

The substituted benzamides **12–28** were prepared from the corresponding substituted salicylic acids using the same method as in the preparation of **9** (schemes 1, 3). Non-crystalline benzamide products were characterized by their NMR spectra and compared with those of the corresponding benzoic acids. The purity and concentration of the stock solutions (10 mM in ethanol) were monitored by reverse phase HPLC at 235 nm. Once the optimal substituent in the aromatic 2-position was established using racemic 3-quinuclidinylbenzamides, the 3-alkoxyl substituted series was investigated using the active (*S*)-enantiomers. Optical rotation at the sodium D-line of the free bases in ethanol provided evidence that no consequential racemization had occurred during the amide condensation.

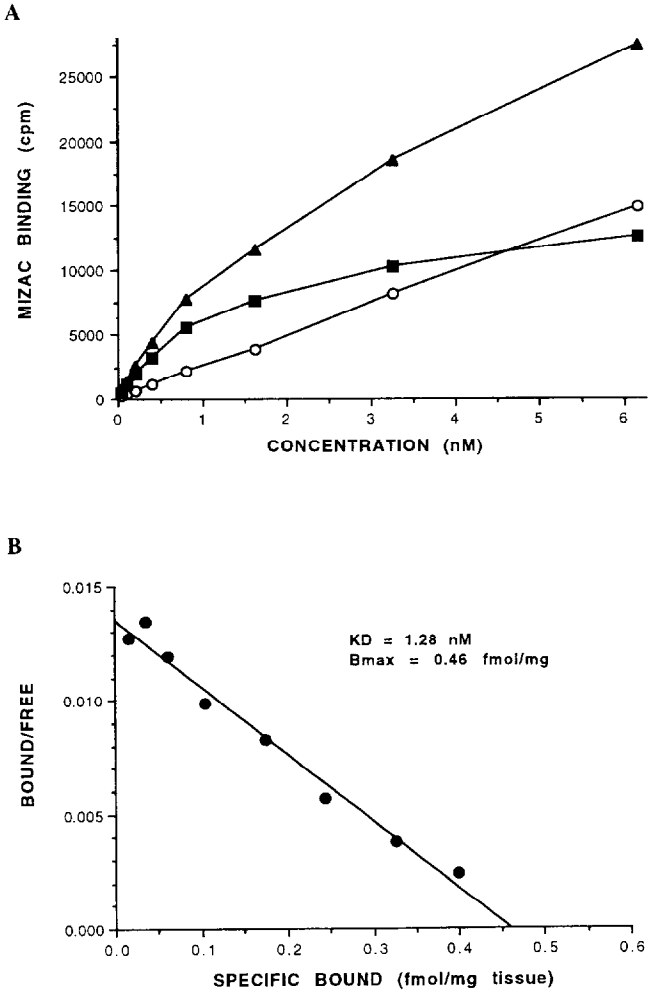


Fig 1. A. Saturation of [125I]-MIZAC binding to whole rat brain. **B.** Scatchard analysis.

Pharmacology

Saturation binding of (*S*)-[^{125}I]-**9** was performed by incubating different ligand concentrations (0.01–100 nM) with homogenates of rat entorhinal cortex, hippocampus, or whole rat brain minus cerebellum using a modified method of Kilpatrick et al [21]. Nonspecific binding to 5-HT-3 receptors was defined by co-incubation with 3 μM bemesetron. Analysis of the binding in whole brain homogenate revealed a single site with an affinity K_D of 1.28 ± 0.16 nM and a receptor density B_{max} of 0.46 ± 0.11 fmol/mg tissue (figs 1A, B). Binding in entorhinal cortex gave an affinity K_D of 1.37 ± 0.21 nM and a receptor density B_{max} of 1.12 ± 0.10 fmol/mg tissue (data not shown). In contrast to the high nonspecific binding (60–75%) observed with racemic galdansetron [22] and 5-iodozacopride [12] at concentrations near their K_D, nonspecific (*S*)-[^{125}I]-**9** binding at 1.3 nM was 12% in the entorhinal cortex and 40% in whole rat brain (fig 2A). Inhibition of 0.4 nM (*S*)-[^{125}I]-**9** binding to rat entorhinal cortex membranes by nine concentrations (0.03 to 300 nM) of the known 5-HT-3 receptor antagonists (*S*)-zacopride [23], LY-278584 [24], iodozacopride [11–13], (*S*)-iodozacopride [25], quipazine [21], bemesetron [21], mianserin [26] and spiperone [27] gave the results shown in table I. The rank order and potencies of these agents in displacing (*S*)-[^{125}I]-**9** binding are consistent with binding to the 5-HT-3 receptor. The inhibition constant of (*S*)-iodozacopride was 1.5 nM; ie, half that of the racemic compound, in agreement with the results of Ponchant et al [12]. When (*S*)-**9** was used to inhibit 0.3 nM (*S*)-[^{125}I]iodozacopride binding from rat hippocampus homogenates, a K_i of 1.23 nM was obtained. Thus, (*S*)-**9** (MIZAC) is approximately twice as potent as racemic 5-iodozacopride (K_i 2.6–4.3 nM) [12, 13]. The dopamine D-2 receptor selectivity of MIZAC binding was evaluated, and gave a K_i of 520 nM (courtesy of NIMH/Novascreen, Hanover MD).

In order to determine the effect of structural modifications on the affinity for the 5-HT-3 receptor, the ability of compounds **9–28** to inhibit (*S*)-[^{125}I]-**9** binding in rat entorhinal cortex was evaluated (table II). The inhibition curves exhibited pseudo-Hill slopes that were not significantly different from unity. A nine-fold difference in affinities between (*R*)-**9** and (*S*)-**9** is similar to the enantioselectivity of the antipodes of zacopride [23]. The first series of compounds (**12–15**) revealed the effect of varying the 5-substituent. The chloro analogues showed the highest affinity and the iodo analogue the lowest. Replacement of the chloro atom with an iodo atom resulted in an eight-fold decrease in affinity for the 5-HT-3 receptor. To further test this relationship, we evaluated the effect of varying the 5-substituent in the 3-methoxy

Table I. Inhibition of [^{125}I]-MIZAC and (*S*)-[^{125}I]iodozacopride binding by 5–HT–3 antagonists.

Compound	*[^{125}I]-MIZAC K_i (nM)*[a]	*(S)-[^{125}I]Iodozacopride K_i (nM)*[b]	*Literature K_i (nM)*	*References*
(*S*)-Zacopride	0.20 ± 0.01	0.22	0.31	[23]
LY-278584	0.87 ± 0.19	1.1	0.69	[24]
5-Iodozacopride	–	2.8	2.6	[11]
(*S*)-5-Iodozacopride	1.3 ± 0.1	1.0	1.2	[25]
Quipazine	3.2 ± 1.4	1.8	1.4	[21]
Bemesetron	29 ± 11	32	55	[21]
Mianserin	54 ± 8	130	34	[26]
Spiperone	> 1000	7640	> 10000	[27]

[a]Average and standard error of two experiments performed in triplicate; [b]inhibition of 0.4 nM (*S*)-[^{125}I]iodozacopride (K_D 1.24 nM) in whole rat brain minus cerebellum [25].

series (**9**, **10**, **22–24**). The results show that, except for having no substituent (**22**), increasing the lipophilicity of the 5-substituent decreased affinity, with the 5-chloro analogue **23** being the most active (fig 2A).

In zacopride, the *p*-amino group seems essential. The des-4-amino analogue (**13**) of zacopride was five-fold less active than zacopride. However, by introducing a 3-methoxy group (**23**) instead of the 4-amino group in the molecule the original activity was restored. Next, we explored the effect of the size of the 2-substituent (**15–21**). The results show that increasing size of the 2-alkoxyl group caused a moderate increase in affinity, peaking with the *O*-isopropyl and *O*-allyl groups. The fact that the bulky isopropyl group (**19**) produced three-fold higher affinity than a methyl group (**15**) suggests that formation of a planar hydrogen bond between the amide hydrogen and oxygen atoms is not required. This is in agreement with the observations made with the zacopride derivatives BMY-33462 [28] and pancopride [29], in which the affinity for the 5-HT-3 receptor increased with increasing bulk of the 2-substituent. However, Clark et al [30] have demonstrated that when the hydrogen bond of this pseudo ring was replaced with covalent carbon bonds in palonosetron (RS-25259), very high affinity was obtained [30, 31]. Finally, the effect of varying the substituent in the 3-position was determined by comparing the activities of **10**, **14**, and **25**. In this series, the 3-ethoxy homologue **25** was five times more active in blocking the 5-HT-3 receptor than the corresponding 3-methoxy compound **10** (fig 2B).

The lipophilicity of a radioligand plays an important role in determining its usefulness in vivo [32]. In order to evaluate these ligands as potential imaging agents, the apparent lipophilicity at pH 7.4, log P_{app}, for selected compounds was measured as the reverse-phase capacity factor (log k_w) and compared to the

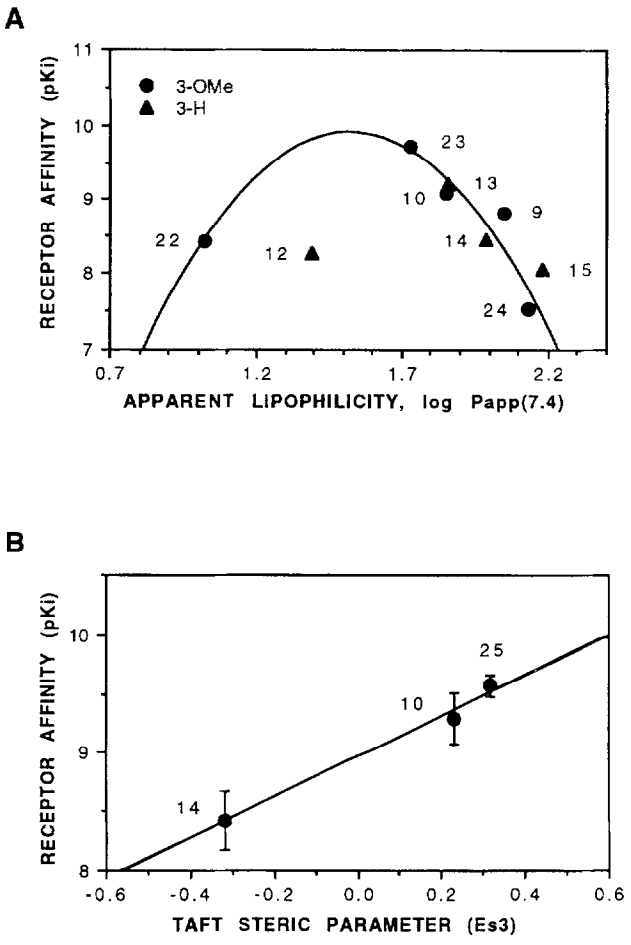
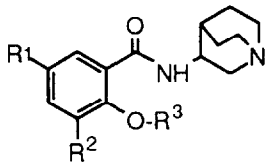


Fig 2. Relationship between the affinity for the 5-HT-3 receptor and (**A**) the apparent lipophilicity and (**B**) the size of the aromatic 3–substituent.

Table II. 5-HT-3 receptor binding affinities and apparent lipophilicity at pH 7.4 of 5-halogen-2,3-dialkoxyl substituted *N*-(1-azabicyclo[2.2.2]oct-3-yl)benzamides.



Compound	R^1	R^2	R^3	K_i (nM)[a]	Log k_w[b]	Log P_{app}[c]
(*S*)-**9**	I	OMe	Me	1.52 ± 0.29	1.910	2.08
(*R*)-**9**	I	OMe	Me	13.1 ± 2.2	–	2.08
(*S*)-**10**	Br	OMe	Me	0.51 ± 0.13	1.861	1.85
12	F	H	Me	5.30 ± 0.20	–	1.39
13	Cl	H	Me	1.19 ± 0.15	–	1.86
14	Br	H	Me	3.8 ± 1.1	1.940	1.99
15	I	H	Me	17.9 ± 2.3	2.081	2.18
16	I	H	Et	7.30 ± 0.37	2.506	2.35
17	I	H	Pr	16.1 ± 2.9	2.794	2.51
18	I	H	All	10.3 ± 1.6	2.637	2.53
19	I	H	*i*-Pr	5.57 ± 0.73	2.641	2.50
20	I	H	2-EtF	17.8 ± 2.1	2.139	2.24
21	I	H	3-PrF	24.3 ± 7.3	2.305	2.37
(*S*)-**22**	H	OMe	Me	3.63 ± 0.50	0.708	1.02
(*S*)-**23**	Cl	OMe	Me	0.19 ± 0.06	1.602	1.73
24	All	OMe	Me	30 ± 15	–	2.13
(*S*)-**25**	Br	OEt	Me	0.27 ± 0.03	2.213	2.14
(*S*)-**26**	Br	OMe	All	0.34 ± 0.10	–	2.20
(*S*)-**27**	I	OMe	Et	1.23 ± 0.35	–	2.22
(*S*)-**28**	I	OMe	All	2.10 ± 0.20	–	2.41

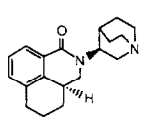
[a]Obtained from the IC_{50} values to displace 0.4 or 0.8 nM (*S*)-[^{125}I]-**9** binding to rat entorhinal cortex; [b]obtained by linear extrapolation of the HPLC capacity factors in methanol – MOPS buffer at pH 7.4; [c]calculated from ClogP and adjusted for amine protonation at pH 7.4, using $pK_a = 8.7 - 0.5\ \Sigma\sigma_{(2,3,5)}$.

calculated values using empirical structural parameters according to Schmidt et al [32]. First, the global (neutral) lipophilicity (log P_{oct}) was obtained from substituent contributions, and then corrected for protonation of the amine. Calculated lipophilicities using the ClogP software [33] gave log P_{oct} values that were less predictive of the experimental apparent lipophilicities (log k_w) than those using the sum of substituent contributions [32].

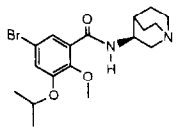
Multiple regression analysis of the 19 compounds in table II showed good correlation with standard QSAR parameters (eq 1). For racemic compounds, half the observed K_i values were used. Based on these results, we conclude that a large substituent is favorable in the aromatic 3-position but unfavorable in the aromatic 5-position.

$$pK_i = 8.25 + 1.00\ Es_{(3)} + 7.12\pi_{(5)} - 5.45\pi_{(5)}^2 - 4.91\ \sigma_{p(5)} \quad (1)$$
$$r = 0.95,\ n = 16,\ s = 0.23,\ F = 23.5$$

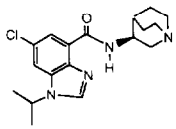
To test the predictive value of eq (1), we calculated that a new compound, (*S*)-**40**, having a large isopropoxyl group in the aromatic 3-position and a moderately large, electron-withdrawing bromo atom in the 5-position, would have a K_i of 0.21 nM. Synthesis of (*S*)-**40** and its inhibition of (*S*)-[^{125}I]-**9** binding gave a K_i of 0.23 nM, thus supporting the validity of the model. This result is also supported by the high 5-HT-3 receptor affinity of the recently reported heterocyclic bioisostere of (*S*)-**40**, RS-16456, (K_i 0.17 nM) [34].



palonosetron



(*S*)-**40**



RS-16456

Conclusions

Evaluation of [^{125}I]-MIZAC showed it to be a selective, high-affinity antagonist of the 5-HT-3 receptor in the rat brain. The 25-fold higher specific activity of an [^{125}I]iodine atom compared to a [^{3}H]methyl group makes [^{125}I]-MIZAC a superior radioligand over (*S*)-[^{3}H]zacopride for in vitro binding studies. By using the corresponding 5-tributylstannyl derivative as precursor, radiolabeled [^{125}I]-MIZAC in high radiochemical yield and specific activity can be easily produced. The convenient methods of preparation and radioiodination of [^{125}I]-MIZAC makes it advantageous for in vitro 5-HT-3 receptor binding studies. Moreover, the QSAR data suggest that potential candidates for SPECT and PET studies might be found in sterically bulky haloalkoxyl 5-chloro homologues of MIZAC, ie, compound (*S*)-**23** [35, 36].

Experimental protocols

Chemistry

(*S*)-Zacopride was prepared from 4-amino-5-chloro-2-methoxybenzoic acid as previously reported [34]. Melting points were determined in open capillary tubes on a Haake/Buchler apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker NB 300 MHz spectrometer in $CDCl_3$ with Me_4Si as internal chemical shift standard. Rotatory powers at the sodium D line were measured in a 1-dm sample tube with a Rudolph Autopol III polarimeter. Combustion analyses were performed by Atlantic Microlabs, Norcross, GA. Analyses indicated by the symbols of the elements were within ± 0.4% of the theoretical values unless otherwise noted.

Methyl 3-methoxysalicylate ***1***
3-Methoxybenzoic acid (16.8 g, 100 mmol) was dissolved in MeOH (200 mL) and 18 M H_2SO_4 (2.0 mL, 38 mmol) was slowly added. The mixture was heated to refluxing temperature for 28 h. The solvent was evaporated and the residue was treated with water (200 mL) and extracted with ether (2 x 200 mL). Washing with water (50 mL), drying (Na_2SO_4), and evaporation of the solvent gave crystalline residue. Recrystallization from MeOH (35 mL) gave 12.7 g (70%) of **1**; mp = 60–62 °C. Lit [18] mp = 61–63 °C.

Methyl 5-iodo-3-methoxysalicylate ***2***
Methyl 3-methoxysalicylate (**1**; 11.0 g, 60 mmol) was dissolved in DMF (150 mL) and NaI (11.0 g, 73 mmol) was added and the mixture was cooled to + 10 °C. Portions of chloramine-T (15.0 g, 66 mmol) were added over 30 min with stirring. The cooling bath was removed and stirring was continued for a further 30 min. A solution of sodium metabisulfite (0.3 g, 1.6 mmol) in water (1000 mL) was added and the mixture was acidified by adding 12 N HCl (6 mL, 72 mmol). Extraction with ether (3 x 300 mL), washing of the combined organic layer with water (50 mL), drying (Na_2SO_4), and evaporation of the solvent gave crystalline **2**. Recrystallization from 95% aqueous methanol (50 mL) gave 8.15 g (44%) of pure **2**; mp = 108–111 °C. Lit [15] mp = 110–112 °C.

Methyl 5-iodo-2,3-dimethoxybenzoate ***3***
Methyl 5-iodo-3-methoxysalicylate [15] (**2**; 7.0 g, 23 mmol) was dissolved in acetone (140 mL) and anhydrous K_2CO_3 (10 g, 70 mmol) was added, followed by dimethyl sulfate (4.4 g, 35 mmol) and heating to refluxing temperature (85 °C) for 8.5 h. Filtration and evaporation of the solvent gave a crystalline residue which was dissolved in ether (200 mL). Washing with water (25 mL), then 0.5 N NaOH (25 mL), drying (Na_2SO_4), and evaporation of the solvent gave 6.18 g (83%) of **3**. Recrystallization from *i*-Pr_2O (35 mL) gave an analytical sample; mp = 55–57 °C. Anal ($C_{10}H_{11}IO_4$): C, H, I.

5-Iodo-2,3-dimethoxybenzoic acid ***4***
Methyl 5-iodo-2,3-dimethoxysalicylate (**3**; 6.0 g, 19 mmol) was dissolved in EtOH (35 mL) and 2 N NaOH (20 mL) was added. The mixture was heated to 95 °C for 1 h. Ice-water (200 mL) was added, followed by ether (200 mL). The organic layer was separated and shaken with water (50 mL). The combined aqueous layer was neutralized with 12 N HCl (4 mL) and the product was extracted with ether (2 x 150 mL). Recrystallization from 60% aqueous EtOH (50 mL) gave 4.35 g (76%) of **4**; mp = 129–130 °C. Lit [15] mp = 128–130 °C.

5-Iodo-2,3-dimethoxybenzoyl chloride ***5***
5-Iodo-2,3-dimethoxybenzoic acid (**4**; 4.3 g, 14 mmol) was dissolved in toluene (65 mL) and thionyl chloride (2.4 mL, 33 mmol) was added, followed by 0.2 mL DMF. The reaction mixture was heated to 65 °C for 1.5 h. Evaporation of the solvent gave 4.7 g (100%) of crystalline **5**. Recrystallization from hexane (15 mL) gave an analytical sample; mp = 69–71 °C.

*(S)-3-Amino-1-azabicyclo[2.2.2]octane (S)-****8***
3-Quinuclidinone hydrochloride (8.1 g, 50 mmol) was dissolved in 5 N NaOH (12 mL) and the free base was extracted with ether (5 x 30 mL). The amine was redissolved in toluene (50 mL) and (*R*)-(+)-1-methylbenzylamine (5.8 g, 50 mmol) was added. The mixture was heated to refluxing temperature (155 °C) with a Dean–Stark water trap for 14 h. Evaporation of the solvent gave the Schiff's base, **6**, as an oil. Reduction of **6** (9.2 g, 40 mmol) with $NaBH_4$ (2.4 g, 60 mmol) in MeOH (600 mL), followed by precipitation of the dihydrochloride with anhydrous 6 N HCl in 2-PrOH (15 mL, 90 mmol) and reducing the volume to 50 mL gave the 1*R*,3'*S* diastereomer (**7**) after recrystallization twice from EtOH/MeOH, 1:1 (160 mL). Removal of the benzyl group of **7** by catalytic hydrogenation with palladium hydroxide in 93% aqueous MeOH (300 mL) gave 3.0 g of the desired diamine dihydrochloride (**8**•2HCl) after recrystallization from 93% EtOH (50 mL); mp = 220 °C. Total yield: 30%. Rotation: $[\alpha]_D^{20}$ – 24 °(*c* 1.0, H_2O), lit [17] $[\alpha]_D^{20}$ – 24.2 ° (*c* 1, H_2O). The free base was liberated by dissolving **8**•2 HCl (3.0 g, 15 mmol) in 3 mL water, adding 10 N NaOH (3.0 mL, 30 mmol) followed by 80 mL of anhydrous EtOH, evaporating of the solvent (3 x 80 mL EtOH), and filtering the precipitated NaCl between each evaporation. The crystalline (*S*)-**8** (1.92 g, 100%) was stable, but formed a carbonate salt when exposed to the atmosphere.

*(R)-3-Amino-1-azabicyclo[2.2.2]octane (R)-****8***
This compound was prepared as described above, using (*S*)-(+)-1-methylbenzylamine [17]. Rotation of (*R*)-**8**•2 HCl: $[\alpha]_D^{20}$ + 23 ° (*c* 1.0, H_2O).

5-Iodo-2,3-dimethoxy-N-(1-azabicyclo[2.2.2]oct-3-yl)benzamide hydrochloride ***9•HCl***
The acid chloride **5** (2.3 g, 7.5 mmol), was condensed with 1.1 g (8.7 mmol) of racemic diamine **8** as the free base in DMF (15 mL). Yield of free base of **9** was 1.5 g (52%) after purification on a SiO_2 chromatography column in EtOAc/EtOH/NH_4OH (50:10:1) and recrystallization from *i*-Pr_2O; mp = 118–

120 °C. ^{1}H-NMR, δ ppm 8.28 (bd, 1, NH), 8.00 (d, 1, J = 2.1 Hz, C-6H), 7.30 (d, 1, J = 2.2 Hz, C-4H), 4.17 (m, 1, C-3'H), 3.91 (s, 3, OCH_3), 3.89 (s, 3, OCH_3), 3.43 (dd, 1, C-2'H), 2.87 (m, 4, C-6' and C-7'H), 2.58 (dd, 1, C-2'H), 2.00 (q, 1, J = 2.0 Hz, C-4'H), 1.5–1.7 (m, 4, C-5' and C-8'H). The hydrochloride salt was prepared by dissolving 175 mg (0.4 mmol) of **9** in acetone (3 mL) and adding 12 N HCl (35 mg, 0.4 mmol). Recrystallization from acetone gave 150 mg of **9**•HCl; mp = 238–240 °C. Anal ($C_{16}H_{21}IN_2O_3$•HCl): C, H, N.

(R)-5-Iodo-2,3-dimethoxy-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide* (R)-***9***
This compound was prepared from 0.86 g (2.9 mmol) of 5-iodo-2,3-dimethoxybenzoic acid [15] (**4**) and 0.50 g (4.0 mmol) of (*R*)-3-amino-1-azabicyclo[2.2.2]octane ((*R*)-**8**) as described for racemic **9** to give 0.69 g of (*R*)-**9** (57%) as an oil. Rotation: $[\alpha]_D^{20}$ + 13 ° (*c* 0.52, MeOH).

(S)-5-Iodo-2,3-dimethoxy-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide hydrochloride* (S)-***9•HCl***
This compound was prepared from 3.07 g (10 mmol) of 5-iodo-2,3-dimethoxybenzoic acid (**4**) and 1.9 g (15 mmol) of (*S*)-3-amino-1-azabicyclo[2.2.2]octane ((*S*)-**8**) as described for racemic **9** to give 2.21 g (53%) of (*R*)-**9** as an oil. Rotation of the free amine $[\alpha]_D^{20}$ – 14 ° (*c* 0.50, MeOH). Recrystallization of 0.1 g of the hydrochloride salt from acetone (5 mL) gave 63 mg of (*S*)-**9**•HCl; mp = 196–198 °C. Anal ($C_{16}H_{21}IN_2O_3$•HCl): C, H, N.

(S)-5-Bromo-2,3-dimethoxy-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide* (S)-***10***
This compound was prepared from 0.80 g (3 mmol) of 5-bromo-2,3-dimethoxybenzoic acid [19] as described for **12**, giving 0.94 g (85%) of (*S*)-**10** as an oil. ^{1}H-NMR, δ ppm 8.28 (b, 1, NH), 7.82 (d, 1, C-6H), 7.15 (d, 1, C-4H), 4.16 (m, 1, C-3'H), 3.91 (s, 3 + 3, $(OCH_3)_2$), 3.42 (dd, 1, C-2'H), 2.87 (m, 4, C-6' and C-7'H), 2.52 (dd, 1, C-2'H), 1.99 (q, 1, J = 2.0 Hz, C-4'H), 1.5–1.7 (m, 4, C-5' and C-8'H). Rotation: $[\alpha]_D^{20}$ – 11 ° (*c* 0.37, EtOH).

(R)-5-Bromo-2,3-dimethoxy-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide* (R)-***10***
This compound was prepared as described for (*S*)-**10** using (*R*)-**8**. Its NMR spectrum was identical to that of (*S*)-**10**. Rotation: $[\alpha]_D^{20}$ + 10 ° (*c* 0.37, EtOH).

(R)-2,3-Dimethoxy-5-(tri-n-*butylstannyl)*-N-*(1-azabicyclo-[2.2.2]oct-3-yl)benzamide* (R)-***11***
(*R*)-5-Bromo-2,3-dimethoxy-*N*-(1-azabicyclo[2.2.2]oct-3-yl)benzamide, (*R*)-**10**, (0.5 g, 2.0 mmol) was treated with bis(tributyltin) (1.16 g, 2.0 mmol) in triethylamine (15 mL) in the presence of tetrakis-(triphenylphosphine)palladium(0) (0.10 g, 0.1 mmol). After refluxing for 18 h the solvent was evaporated and excess reagents removed by passing the residue through a silica gel column in hexane/EtOAc/EtOH/NH_4OH, 14 N (200:200:20:1). Fractions containing (*R*)-**11** were collected, the solvent evaporated, and the residue oil was dissolved in absolute EtOH (2 mg/mL). Rotation: $[\alpha]_D^{20}$ + 13 ° (*c* 0.20, EtOH). ^{1}H-NMR, δ ppm 8.38 (bd, 1, NH), 7.74 (d, 1, C-6H), 7.13 (d, 1, C-4H), 4.30 (m, 1, C-3'H), 3.93 (s, 3, OCH_3), 3.91 (s, 3), 3.56 (dd, 1), 3.03 (m, 4), 2.80 (dd, 1), 2.17 (q, 1), 1.6–1.9 (m, 4), 1.52 (m, 6), 1.33 (q, 6), 1.08 (t, 6), 0.89 (t, 9). Both aromatic signals showed satellite peaks due to 16% natural abundance of ^{117}Sn (7.7%) and ^{119}Sn (8.6%) isotopes, with –1/2 nuclear spin giving a doublet (J_{SnCCH} = 18 Hz) [38].

(S)-2,3-Dimethoxy-5-(tri-n-*butylstannyl)*-N-*(1-azabicyclo-[2.2.2]oct-3-yl)benzamide* (S)-***11***
This compound was prepared from (*S*)-**10** as described for the antipode (*R*)-**11**. Rotation: $[\alpha]_D^{20}$ – 14 ° (*c* 0.10, EtOH). ^{1}H-NMR was identical to that of (*R*)-**11**.

5-Fluoro-2-methoxy-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide hydrate* ***12•H₂O***
5-Fluoro-2-methoxybenzoic acid (1.00 g, 6 mmol) was dissolved in toluene (10 mL) and thionyl chloride (1.0 mL, 13 mmol) was added followed by 0.05 mL of DMF. The reaction mixture was heated to 70 °C. After 1.5 h at the same temperature, the solvent was evaporated and the residue was dissolved in DMF (5.0 mL). Solid free base of 3-aminoquinuclidine (1.0 g, 8 mmol) was added and the mixture was stirred at ambient temperature for 2 h. Water (25 mL) and 2 N NaOH (5 mL) was added and the product was extracted with ether (2 x 25 mL). The combined ether layer was extracted with 1 N HCl (2 x 15 mL) and the combined aqueous layer was made basic with 5 N NaOH (7 mL). The product was extracted with ether (2 x 25 mL). Drying (Na_2SO_4) and evaporation of the solvent gave 0.86 g (51%) of **12**•H_2O after recrystallization from *i*-Pr_2O (20 mL); mp = 89–91 °C. Lit [39], **12**•HCl mp = 246 °C. ^{1}H-NMR, δ ppm 8.23 (b, 1, NH), 7.91 (dd, 1, J = 9.8 and 2.9 Hz, C-6H), 7.12 (m, 1, C-4H), 6.94 (dd, 1, J = 9.1 and 4.1 Hz, C-3H), 4.15 (m, 1, C-3'H), 3.98 (s, 3, OCH_3), 3.43 (dd, 1, C-2'H), 2.86 (m, 4, C-6' and C-7'H), 2.59 (dd, 1, C-2'H), 2.02 (q, 1, C-4'H), 1.5–1.8 (m, 4, C-5' and C-8'H). Anal ($C_{15}H_{19}FN_2O_2$•H_2O): C, H, N.

5-Chloro-2-methoxy-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide* ***13***
This compound was prepared from 5-chloro-2-methoxybenzoic acid (1.9 g, 10 mmol) as described for compound **12** giving 2.10 g (71%) of crystalline **13**. Recrystallization from *i*-Pr_2O (15 mL) gave 1.31 g; mp = 84–86 °C. Lit [39], **13**•HCl mp = 215 °C. ^{1}H-NMR, δ ppm 8.20 (b, 1, NH), 8.17 (d, 1, C-6H), 7.40 (dd, 1, C-4H), 6.94 (d, 1, C-3H), 4.13 (m, 1, C-3'H), 3.99 (s, 3, OCH_3), 3.42 (dd, 1, C-2'H), 2.86 (m, 4, C-6' and C-7'H), 2.59 (dd, 1, C-2'H), 1.99 (q, 1, C-4'H), 1.5–1.7 (m, 4, C-5' and C-8'H). Anal ($C_{15}H_{19}ClN_2O_2$): C, H, N.

5-Bromo-2-methoxy-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide hydrate* ***14•H₂O***
This compound was prepared from 5-bromo-2-methoxybenzoic acid (0.69 g, 3 mmol) as described for compound **12**, giving 0.68 g (67%) of **14**. Recrystallization from *i*-Pr_2O (15 mL) gave 0.37 g of analytical sample; mp = 86–88 °C. Lit [39], **14**•HCl mp = 220 °C. ^{1}H-NMR, δ ppm 8.27 (d, 1, C-6H), 8.20 (b, 1, NH), 7.51 (dd, 1, C-4H), 6.87 (d, 1, C-3H), 4.13 (m, 1, C-3'H), 3.98 (s, 3, OCH_3), 3.42 (dd, 1, C-2'H), 2.86 (m, 4, C-6' and C-7'H), 2.59 (dd, 1, C-2'H), 1.99 (q, 1, C-4'H), 1.5–1.7 (m, 4, C-5' and C-8'H). Anal ($C_{15}H_{19}BrN_2O_2$•H_2O): C, H, N.

5-Iodo-2-methoxy-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide* ***15***
This compound was prepared from 5-iodo-2-methoxybenzoic acid [16] (1.1 g, 4 mmol) as described for compound **12**, giving 0.66 g (43%) of **15** after recrystallization from *i*-Pr_2O (25 mL); mp = 145–147 °C. ^{1}H-NMR, δ ppm 8.45 (d, 1, C-6H), 8.06 (b, 1, NH), 7.71 (dd, 1, C-4H), 6.76 (d, 1, C-3H), 4.12 (m, 1, C-3'H), 3.97 (s, 3, OCH_3), 3.42 (dd, 1, C-2'H), 2.84 (m, 4, C-6' and C-7'H), 2.59 (dd, 1, C-2'H), 1.99 (q, 1, C-4'H), 1.5–1.7 (m, 4, C-5' and C-8'H). Anal ($C_{15}H_{19}IN_2O_2$): C, H, N.

2-Ethoxy-5-iodo-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide* ***16***
This compound was prepared from 2-ethoxy-5-iodobenzoic acid (**29**; 0.7 g, 2.4 mmol) as described for compound **12**,

giving 0.71 g (74%) of **16** after recrystallization from EtOH (14 mL); mp = 159–161 °C. ^{1}H-NMR, δ ppm 8.47 (d, 1, C-6H), 8.26 (b, 1, NH), 7.67 (dd, 1, C-4H), 6.72 (d, 1, C-3H), 4.22 (m, 1, C-3'H), 4.18 (q, 2, OCH_2), 3.49 (dd, 1, C-2'H), 2.88 (m, 4, C-6' and C-7'H), 2.61 (dd, 1, C-2'H), 2.01 (q, 1, C-4'H), 1.6–1.7 (m, 4, C-5' and C-8'H), 1.55 (t, 3, CH_3). Anal ($C_{16}H_{21}IN_2O_2$): C, H, N.

5-Iodo-2-propoxy-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide* ***17***

This compound was prepared from 5-iodo-2-propoxybenzoic acid (**30**; 0.31 g, 1.0 mmol) as described for compound **12**, giving 0.28 g (68%) of **17** after recrystallization from EtOH – *i*-Pr_2O (3 + 3 mL); mp = 131–133 °C. ^{1}H-NMR, δ ppm 8.49 (d, 1, C-6H), 8.19 (bd, 1, NH), 7.70 (dd, 1, C-4H), 6.73 (d, 1, C-3H), 4.19 (m, 1, C-3'H), 4.15 (q, 2, OCH_2), 3.48 (dd, 1, C-2'H), 2.86 (m, 4, C-6' and C-7'H), 2.59 (dd, 1, C-2'H), 2.01 (q, 1, C-4'H), 1.92 (m, 2, CH_2), 1.5–1.8 (m, 4, C-5' and C-8'H), 1.11 (t, 3, CH_3). Anal ($C_{17}H_{23}IN_2O_2$): C, H, N.

5-Iodo-2-(2-propenyloxy)-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide* ***18***

This compound was prepared from 5-iodo-2-(2-propenyloxy)benzoic acid (**31**; 1.0 g, 3.3 mmol) as described for compound **12**, giving 0.81 g (60%) of **18** after recrystallization from EtOH – *i*-Pr_2O (3 + 5 mL); mp = 154–156 °C. ^{1}H-NMR, δ ppm 8.49 (d, 1, C-6H), 8.14 (b, 1, NH), 7.69 (dd, 1, C-4H), 6.74 (d, 1, C-3H), 6.12 (m, 1, C-2"), 5.51 (dd, 1, *J* = 17.3 Hz, $=CH_2$), 5.44 (dd, 1, *J* = 10.3 Hz, $=CH_2$), 4.64 (d, 2, *J* = 6.1 Hz, OCH_2), 4.16 (m, 1, C-3'H), 3.38 (dd, 1, C-2'H), 2.84 (m, 4, C-6' and C-7'H), 2.54 (dd, 1, C-2'H), 1.99 (q, 1, C-4'H), 1.5–1.7 (m, 4, C-5' and C-8'H). Anal ($C_{17}H_{21}IN_2O_2$): C, H, N.

5-Iodo-2-(1-methylethoxy)-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide* ***19***

This compound was prepared from 5-iodo-2-(1-methylethoxy)-benzoic acid (**32**; 0.71 g, 2.3 mmol) as described for compound **12**, giving 0.18 g (19%) of **19** after recrystallization from EtOH – *i*-Pr_2O (6 mL); mp = 118–120 °C. ^{1}H-NMR, δ ppm 8.48 (d, 1, C-6H), 8.28 (bd, 1, NH), 7.68 (dd, 1, C-4H), 6.75 (d, 1, C-3H), 4.75 (dq, 1, OCH_2), 4.12 (m, 1, C-3'H), 3.43 (dd, 1, C-2'H), 2.84 (m, 4, C-6' and C-7'H), 2.54 (dd, 1, C-2'H), 2.00 (q, 1, C-4'H), 1.6–1.7 (m, 4, C-5' and C-8'H), 1.44 (d, 6, $(CH_3)_2$). Anal ($C_{17}H_{23}IN_2O_2$): C, H, N.

2-(2-Fluoroethoxy)-5-iodo-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide* ***20***

This compound was prepared from 5-iodo-2-(2-fluoroethoxy)benzoic acid (**33**; 0.5 g, 1.6 mmol) as described for compound **12**, giving 0.34 g (51%) of **20** after recrystallization from EtOH – *i*-Pr_2O (10 + 5 mL); mp = 153–155 °C. ^{1}H-NMR, δ ppm 8.48 (d, 1, C-6H), 8.03 (bd, 1, NH), 7.70 (dd, 1, C-4H), 6.71 (d, 1, C-3H), 4.84 (dq, 2, *J* = 47.4 Hz, CH_2F), 4.34 (dq, 2, *J* = 27.2 Hz, OCH_2), 4.16 (m, 1, C-3'H), 3.40 (dd, 1, C-2'H), 2.87 (m, 4, C-6' and C-7'H), 2.58 (dd, 1, C-2'H), 2.00 (q, 1, C-4'H), 1.5–1.7 (m, 4, C-5' and C-8'H). Anal ($C_{16}H_{20}FIN_2O_2$): C, H, N.

2-(3-Fluoropropoxy)-5-iodo-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide* ***21***

This compound was prepared from 5-iodo-2-(3-fluoropropoxy)benzoic acid (**34**; 1.0 g, 3.1 mmol) as described for compound **12**, giving 0.84 g (63%) of **21**. Recrystallization from *i*-Pr_2O (5 mL) gave 0.34 g of analytical sample; mp = 134–136 °C. ^{1}H-NMR, δ ppm 8.46 (d, 1, C-6H), 7.93 (bd, 1, NH), 7.69 (dd, 1, C-4H), 6.75 (d, 1, C-3H), 4.65 (dt, 2, *J* = 47.0 Hz, CH_2F), 4.29 (dd, 2, *J* = 27.2 Hz, OCH_2), 4.12 (m, 1, C-3'H), 3.44 (dd, 1, C-2'H), 2.86 (m, 4, C-6' and C-7'H), 2.59 (dd, 1, C-2'H), 2.27 (dt, 2, *J* = 26.8 Hz, CH_2), 1.99 (q, 1, C-4'H), 1.5–1.7 (m, 4, C-5' and C-8'H). Anal ($C_{17}H_{22}FIN_2O_2$): C, H, N.

(S)-2,3-Dimethoxy-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide (S)-**22***

This compound was prepared from 2,3-dimethoxybenzoic acid (1.0 g, 5.5 mmol) and (*S*)-**8** (1.0 g, 7.9 mmol) as described for compound **12**, using MeCN (15 mL) as solvent, giving 1.1 g (69%) of (*S*)-**22**. Crystallization from EtOH – *i*-Pr_2O (2 mL) gave 0.65 g of an analytical sample; mp = 99–101 °C. Rotation: $[\alpha]_D^{20}$ – 9.7 ° (*c* 0.29, EtOH). ^{1}H-NMR, δ ppm 8.37 (bd, 1, NH), 7.70 (dd, 1, *J* = 2.5 and 8.6 Hz, C-6H), 7.17 (t, 1, C-5H), 7.05 (dd, 1, *J* = 2.4 and 8.9 Hz, C-3H), 4.18 (m, 1, C-3'H), 3.92 (s, 3, OCH_3), 3.90 (s, 3, OCH_3), 3.43 (dd, 1, C-2'H), 2.86 (m, 4, C-6' and C-7'H), 2.61 (dd, 1, C-2'H), 2.01 (q, 1, C-4'H), 1.5–1.8 (m, 4, C-5' and C-8'H). Anal ($C_{16}H_{22}N_2O_3$): C, H, N.

(S)-5-Chloro-2,3-dimethoxy-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide (S)-**23***

This compound was prepared from 5-chloro-2,3-dimethoxybenzoic acid [40] (1.0 g, 4.6 mmol) as described for compound **12**, giving 0.58 g (39%) of (*S*)-**23** after recrystallization from *i*-Pr_2O (5 mL); mp = 100–102 °C. Rotation: $[\alpha]_D^{20}$ – 11 ° (*c* 0.32, EtOH). ^{1}H-NMR, δ ppm 8.27 (bd, 1, NH), 7.67 (d, 1, *J* = 2.5 Hz, C-6H), 7.01 (d, 1, *J* = 2.5, C-3H), 4.15 (m, 1, C-3'H), 3.90 (s, 6, $(OCH_3)_2$), 3.43 (dd, 1, C-2'H), 2.85 (m, 4, C-6' and C-7'H), 2.58 (dd, 1, C-2'H), 2.00 (q, 1, C-4'H), 1.5–1.7 (m, 4, C-5' and C-8'H). Anal ($C_{16}H_{21}ClN_2O_3$): C, H, N.

2,3-Dimethoxy-5-(2-propenyl)-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide* ***24***

This compound was prepared from 5-(2-propenyl)-2,3-dimethoxybenzoic acid (**35**; 1.1 g, 5 mmol) as described for compound **12**, giving 0.82 g (50%) of **24** as an oil. Purification by column chromatography on SiO_2 (40 g, 70–270 mesh, 60 Å) gave 0.32 g of analytical sample. ^{1}H-NMR, δ ppm 8.43 (bd, 1, NH), 7.48 (d, 1, *J* = 2.5 Hz, C-6H), 6.89 (d, 1, *J* = 2.5, C-3H), 5.93 (m, 1, CH=), 5.12 (dd, 1, $=CH_2$), 5.08 (dd, 1, $=CH_2$), 4.38 (m, 1, C-3'H), 3.91 (s, 3, OCH_3), 3.89 (s, 3, OCH_3), 3.63 (dd, 1, C-2'H), 3.37 (d, 2, *J* = 6.7 Hz, CH_2), 3.13 (m, 4, C-6' and C-7'H), 2.90 (dd, 1, C-2'H), 2.23 (q, 1, C-4'H), 1.7–2.0 (m, 4, C-5' and C-8'H).

(S)-5-Bromo-3-ethoxy-2-methoxy-N-*(1-azabicyclo[2.2.2]oct-3-yl)benzamide (S)-**25***

This compound was prepared from 5-bromo-3-ethoxy-2-methoxybenzoic acid [40] (0.40 g, 1.5 mmol) as described for compound **12**, giving 0.15 g (26%) of **25** as an oil. Rotation: $[\alpha]_D^{20}$ – 11 ° (*c* 0.38, EtOH). ^{1}H-NMR, δ ppm 8.28 (bd, 1, NH), 7.80 (d, 1, *J* = 2.5 Hz, C-6H), 7.13 (d, 1, *J* = 2.5, C-3H), 4.13 (m, 1, C-3'H), 4.09 (q, 2, OCH_2), 3.83 (s, 3, OCH_3), 3.44 (dd, 1, C-2'H), 2.84 (m, 4, C-6' and C-7'H), 2.57 (dd, 1, C-2'H), 1.99 (q, 1, C-4'H), 1.5–1.7 (m, 4, C-5' and C-8'H), 1.49 (t, 3, CH_3).

(S)-5-Bromo-3-methoxy-2-(2-propenyloxy)-N-*(1-azabicyclo-[2.2.2]oct-3-yl)benzamide (S)-**26***

This compound was prepared from 5-bromo-2-(2-propenyloxy)-3-methoxybenzoic acid (**36**; 0.5 g, 1.7 mmol) as described for compound **12**, giving 0.39 g (57%) of **26** as an oil. Rotation: $[\alpha]_D^{20}$ – 14 ° (*c* 0.40, EtOH). ^{1}H-NMR, δ ppm 8.26 (bd, 1, NH), 7.85 (d, 1, *J* = 2.5 Hz, C-6H), 7.14 (d, 1, *J* = 2.5, C-3H), 6.07 (m, 1, CH=), 5.40 (dd, 1, *J* = 1.4 and 17.3 Hz, $=CH_2$), 5.32 (dd, 1, *J* = 1.4 and 10.3 Hz, $=CH_2$), 4.58 (d, 2, *J* =

6.1 Hz, OCH_2), 4.16 (m, 1, C-3'H), 3.89 (s, 3, OCH_3), 3.38 (dd, 1, C-2'H), 2.83 (m, 4, C-6' and C-7'H), 2.54 (dd, 1, C-2'H), 1.98 (q, 1, C-4'H), 1.5–1.7 (m, 4, C-5' and C-8'H).

*(S)-2-Ethoxy-5-iodo-3-methoxy-*N*-(1-azabicyclo[2.2.2]oct-3-yl)-benzamide (S)-**27***

This compound was prepared from 2-ethoxy-5-iodo-3-methoxybenzoic acid (**37**; 0.64 g, 2 mmol) as described for compound **12**, giving 0.71 g (82%) of (*S*)-**27** as an oil. Rotation: $[\alpha]_D^{20}$ – 12 ° (*c* 0.43, EtOH). ^{1}H-NMR, δ ppm 8.23 (bd, 1, NH), 8.01 (d, 1, *J* = 2.5 Hz, C-6H), 7.29 (d, 1, *J* = 2.5, C-3H), 4.14 (m, 1, C-3'H), 4.11 (q, 2, OCH_2), 3.88 (s, 3, OCH_3), 3.44 (dd, 1, C-2'H), 2.84 (m, 4, C-6' and C-7'H), 2.57 (dd, 1, C-2'H), 1.99 (q, 1, C-4'H), 1.5–1.7 (m, 4, C-5' and C-8'H), 1.41 (t, 3, CH_3).

*(S)-5-Iodo-3-methoxy-2-(2-propenyloxy)-*N*-(1-azabicyclo-[2.2.2]oct-3-yl)benzamide (S)-**28***

This compound was prepared from 1.0 g (3.0 mmol) of 5-iodo-3-methoxy-2-(2-propenyloxy)benzoic acid (**38**) as described for compound **12**, giving 0.67 g (50%) of (*S*)-**28** as an oil. Rotation: $[\alpha]_D^{20}$ – 10 ° (*c* 0.22, EtOH). ^{1}H-NMR, δ ppm 8.23 (bd, 1, NH), 8.03 (d, 1, *J* = 2.5 Hz, C-6H), 7.30 (d, 1, *J* = 2.5, C-3H), 6.07 (m, 1, CH=), 5.40 (dd, 1, *J* = 1.3 and 17.3 Hz, $=CH_2$), 5.32 (dd, 1, *J* = 1.3 and 10.3 Hz, $=CH_2$), 4.58 (d, 2, *J* = 6.1 Hz, OCH_2), 4.16 (m, 1, C-3'H), 3.88 (s, 3, OCH_3), 3.41 (dd, 1, C-2'H), 2.84 (m, 4, C-6' and C-7'H), 2.56 (dd, 1, C-2'H), 1.99 (q, 1, C-4'H), 1.5–1.7 (m, 4, C-5' and C-8'H).

*2-Ethoxy-5-iodobenzoic acid **29***

Methyl 5-iodosalicylate (2.0 g, 7.2 mmol) was dissolved in acetone (50 mL). Anhydrous K_2CO_3 (2.0 g, 14.5 mmol) was added followed by ethyl bromide (2.0 g, 18.3 mmol). The mixture was heated under reflux (85 °C) for 18 h. Insoluble material was removed by filtration and the solvent was removed by evaporation. The residue was dissolved in ether (50 mL) and shaken with 0.5 N NaOH (25 mL) to remove unreacted starting material. Drying (Na_2SO_4) and evaporation gave 1.84 g of methyl 5-iodo-2-ethoxybenzoate as an oil. The oil was dissolved in EtOH (10 mL) and 5 N NaOH (5 mL) was added. The mixture was then heated to 95 °C for 2.5 h. After cooling, water (50 mL) was added followed by shaking with ether (25 mL) to remove unreacted starting materials. The aqueous layer was acidified to pH 3 with 12 N HCl (2.5 mL) and the precipitated product was extracted with ether (2 x 30 mL). Drying (Na_2SO_4) and evaporation gave 1.07 g (51%) of **29** after recrystallization from *i*-Pr_2O (10 mL); mp = 136–138 °C. ^{1}H-NMR, δ ppm 10.5 (b, 1, OH), 8.48 (d, 1, C-6H), 7.81 (dd, 1, C-4H), 6.81 (d, 1, C-3H), 4.33 (dt, 2, OCH_2), 1.59 (t, 3, CH_3). Anal ($C_9H_9IO_3$): C, H, I.

*5-Iodo-2-propoxybenzoic acid **30***

Methyl 5-iodosalicylate (1.0 g, 3.6 mmol) was reacted with propyl bromide (1.0 g, 8.1 mmol) as described for compound **29** to give 1.2 g of methyl 5-iodo-2-propoxybenzoate as an oil. Hydrolysis and extraction as described for compound **29** gave 0.80 g (73%) of **30** after recrystallization from *i*-Pr_2O (7 mL); mp = 80–82 °C. ^{1}H-NMR, δ ppm 10.6 (b, 1, OH), 8.44 (d, 1, C-6H), 7.81 (dd, 1, C-4H), 6.81 (d, 1, C-3H), 4.19 (t, 2, OCH_2), 1.93 (q, 2, CH_2), 1.09 (t, 3, CH_3). Anal ($C_{10}H_{11}IO_3$): C, H, I.

*5-Iodo-2-(2-propenyloxy)benzoic acid **31***

Methyl 5-iodosalicylate (1.0 g, 3.6 mmol) was reacted with allyl bromide (0.6 g, 5.0 mmol) as described for compound **29** to give 1.3 g of methyl 5-iodo-2-(2-propenyloxy)benzoate as an oil. Hydrolysis and extraction as described for compound **29** gave 1.04 g (88%) of **31** after recrystallization from *i*-Pr_2O (12 mL); mp = 92–94 °C. ^{1}H-NMR, δ ppm 10.3 (b, 1, OH), 8.43 (d, 1, C-6H), 7.80 (dd, 1, C-4H), 6.82 (d, 1, C-3H), 5.93 (dt, 1, CH=), 5.53 (d, 1, $=CH_2$), 5.37 (d, 1, $=CH_2$), 4.76 (d, 2, OCH_2). Anal ($C_{10}H_9IO_3$): C, H, I.

*5-Iodo-2-(1-methylethoxy)benzoic acid **32***

Methyl 5-iodosalicylate (2.0 g, 7.2 mmol) was reacted with 2-iodopropane (2.0 g, 11.8 mmol) as described for compound **29** to give 1.76 g of methyl 5-iodo-2-(1-methylethoxy)benzoate as an oil. Hydrolysis and extraction as described for compound **29** gave 0.73 g (33%) of **32** after recrystallization from *i*-Pr_2O (8 mL); mp = 87–89 °C. ^{1}H-NMR, δ ppm 10.5 (b, 1), 8.46 (d, 1), 7.80 (dd, 1), 6.80 (d, 1), 4.84 (dt, 1), 1.47 (d, 6), 10.5 (b, 1, OH), 8.46 (d, 1, C-6H), 7.80 (dd, 1, C-4H), 6.80 (d, 1, C-3H), 4.84 (dt, 2, OCH_2), 1.47 (d, 6, $(CH_3)_2$). Anal ($C_{10}H_{11}IO_3$): C, H, I.

*2-(2-Fluoroethoxy)-5-iodobenzoic acid **33***

Methyl 5-iodosalicylate (1.0 g, 3.6 mmol) was reacted with 1-bromo-2-fluoroethane (1.0 g, 7.9 mmol) as described for compound **29** to give 0.89 g of methyl 5-iodo-2-(2-fluoroethoxy)benzoate as a crystalline residue; mp = 76–78 °C from *i*-Pr_2O (9 mL). Hydrolysis and extraction as described for compound **29** gave 0.69 g (62%) of **33** after recrystallization from *i*-Pr_2O (5 mL); mp = 129–131 °C. ^{1}H-NMR, δ ppm 9.80 (bd, 1, OH), 8.43 (d, 1, C-6H), 7.83 (dd, 1, *J* = 2.6 and 8.9 Hz, C-4H), 6.71 (d, 1, *J* = 8.7 Hz, C-3H), 4.84 (dt, 2, *J* = 46.9 Hz, CH_2F), 4.42 (dt, 2, *J* = 24.8 Hz, OCH_2). Anal ($C_9H_8FIO_3$): C, H, I.

*2-(3-Fluoropropoxy)-5-iodobenzoic acid **34***

Methyl 5-iodosalicylate (1.0 g, 3.6 mmol) was reacted with 1-bromo-3-fluoropropane (0.8 g, 5.7 mmol) as described for compound **29** to give 1.36 g of methyl 5-iodo-2-(3-fluoropropoxy)benzoate as an oil. Hydrolysis and extraction as described for compound **29** gave 1.05 g (90%) of **34** after recrystallization from *i*-Pr_2O (18 mL); mp 90–92 °C. ^{1}H-NMR, δ ppm 10.2 (bd, 1, OH), 8.39 (d, 1, *J* = 2.6 Hz, C-6H), 7.81 (dd, 1, *J* = 2.6 and 8.9 Hz, C-4H), 6.83 (d, 1, *J* = 8.7 Hz, C-3H), 4.68 (dt, 2, *J* = 46.9 Hz, CH_2F), 4.34 (dt, 2, *J* = 24.8 Hz, OCH_2), 2.28 (m, 2, CH_2). Anal ($C_{10}H_{10}FIO_3$): C, H, I.

*2,3-Dimethoxy-5-(2-propenyl)benzoic acid **35***

Methyl 2,3-dimethoxy-5-(2-propenyl)benzoate [17] (2.36 g, 10 mmol) was dissolved in a mixture of EtOH (15 mL) and 2 N NaOH (10 mL). The mixture was heated to refluxing temperature for 1.5 h. Water (100 mL) was added and the solution was washed with ether (50 mL), the aqueous layer acidified with 12 N HCl (2 mL), and the product was extracted with ether (2 x 50 mL). Drying (Na_2SO_4) and evaporation gave 4.9 g (81%) of **35**. Recrystallization from *i*-Pr_2O (10 mL) gave an analytical sample; mp = 87–89 °C. ^{1}H-NMR, δ ppm 7.54 (d, 1, C-6H), 6.98 (d, 1, C-4H), 5.92 (dt, 1, CH=), 5.11 (d, 2, $=CH_2$), 4.05 (s, 3, OCH_3), 3.92 (s, 3, OCH_3), 3.38 (d, 2, *J* = 6.7 Hz, CH_2). Anal ($C_{12}H_{14}O_4$): C, H.

*5-Bromo-3-methoxy-2-(2-propenyloxy)benzoic acid **36***

Methyl 5-bromo-3-methoxysalicylate [40] (2.6 g, 10 mmol) was dissolved in a suspension of K_2CO_3 (2.6 g, 19 mmol) in acetone (100 mL) and allyl bromide (2.0 g, 16 mmol) was added. The mixture was heated to refluxing temperature for 16 h. Filtration, evaporation of the solvent, and extraction with ether (2 x 10 mL) gave 2.57 g of methyl 5-bromo-3-methoxy-2-(2-propenyloxy)benzoate (91%) as an oil. The oil was dissolved in a mixture of EtOH (15 mL) and 2 N NaOH (10 mL) and heated to refluxing temperature for 1.5 h. Water (100 mL) was added and the solution was washed with ether (50 mL), the

aqueous layer acidified with 12 N HCl (2 mL), and the product was extracted with ether (2 x 50 mL). Drying (Na_2SO_4) and evaporation gave 1.90 g (91%) of **36**. Recrystallization from *i*-Pr_2O (10 mL) gave an analytical sample; mp = 119–121 °C. ^{1}H-NMR, δ ppm 10.4 (b, 1, OH), 7.81 (d, 1, *J* = 2.4 Hz, C-6H), 7.23 (d, 1, *J* = 2.4 Hz, C-4H), 6.07 (m, 1, CH=), 5.41 (d, 1, *J* = 17.4 Hz, $=CH_2$), 5.36 (d, 1, *J* = 10.6 Hz, $=CH_2$), 4.74 (d, 2, *J* = 6.4 Hz, OCH_2), 3.92 (s, 3, OCH_3). Anal ($C_{11}H_{11}BrO_4$): C, H, Br.

2-Ethoxy-5-iodo-3-methoxybenzoic acid ***37***
Methyl 5-iodo-3-methoxysalicylate [15] (**2**; 1.2 g, 4 mmol) was treated with diethyl sulfate (1.2 g, 8 mmol) as described for compound **29**, giving 1.0 g of the intermediate methyl 2-ethoxy-5-iodo-3-methoxybenzoate with 2 N NaOH (5 mL) in EtOH (15 mL). Recrystallization from *i*-Pr_2O (20 mL) gave 0.78 g (61%) of **37**; mp = 101–103 °C. ^{1}H-NMR, δ ppm 11.2 (b, 1, OH), 8.04 (d, 1, *J* = 2.4 Hz, C-6H), 7.39 (d, 1, *J* = 2.4 Hz, C-4H), 4.34 (q, 2, *J* = 6.3 Hz, OCH_2), 3.90 (s, 3, OCH_3), 1.46 (s, 3, *J* = 6.3 Hz, CH_3). Anal ($C_{10}H_{11}IO_4$): C, H, I.

5-Iodo-3-methoxy-2-(2-propenyloxy)benzoic acid ***38***
Methyl 5-iodo-3-methoxysalicylate [15] (**2**; 1.5 g, 5 mmol) was treated with allyl bromide (1.2 g, 9 mmol) as described for compound **29**, giving 1.0 g of **38** after hydrolysis of the intermediate methyl 5-iodo-3-methoxy-2-(2-propenyloxy)benzoate with 2 N NaOH (5 mL) in EtOH (15 mL). Recrystallization from *i*-Pr_2O (20 mL) gave an analytical sample; mp = 121–123 °C. ^{1}H-NMR, δ ppm 10.6 (b, OH), 8.03 (d, 1, *J* = 2.4 Hz, C-6H), 7.39 (d, 1, *J* = 2.4, C-3H), 6.06 (m, 1, CH=), 5.41 (dd, 1, *J* = 1.3 and 17.4 Hz, $=CH_2$), 5.36 (dd, 1, *J* = 1.3 and 10.4 Hz, $=CH_2$), 4.75 (d, 2, *J* = 6.3 Hz, OCH_2), 3.91 (s, 3, OCH_3). Anal ($C_{11}H_{11}IO_4$): C, H, I.

5-Bromo-2-methoxy-3-(1-methylethoxy)benzoic acid ***39***
Methyl 3-hydroxysalicylate [41] (4.0 g, 24 mmol) was reacted with 2-iodopropane (4.0 g, 29 mmol) as described for compound **29** to give 2.81 g (56%) of methyl 3-(1-methylethoxy)salicylate as an oil after flash chromatography on silica in hexane/EtOAc (10:1) to remove unreacted starting material. Reaction of the salicylate (2.1 g, 10 mmol) with bromine (1.75 g, 11 mmol) in $CHCl_3$ (20 mL) for 1 h at 20 °C gave 2.89 g (100%) of methyl 5-bromo-3-(1-methylethoxy)salicylate as an oil after extraction with $CHCl_3$ (2 x 50 mL). Treatment of the bromosalicylate (2.89 g, 10 mmol) wth dimethylsulfate (1.46 g, 12 mmol) in a suspension of K_2CO_3 (4.0 g, 29 mmol) in acetone (100 mL) gave 2.91 g (96%) of methyl 5-bromo-2-methoxy-3-(1-methylethoxy)benzoate as an oil after extraction with ether (2 x 50 mL). Hydrolysis of the benzoate (2.42 g, 8 mmol) with 2 N NaOH (5 mL) in EtOH (25 mL) and extraction with ether gave 1.95 g (84%) of **39** after recrystallization from *i*-Pr_2O (10 mL); mp = 70–72 °C. ^{1}H-NMR, δ ppm 11.3 (b, 1, OH), 7.79 (d, 1, C-6H), 7.24 (d, 1, C-4H), 6.80 (d, 1), 4.59 (dq, 1, C-1'H), 4.07 (s, 3, OCH_3), 1.42 (d, 6, C-2'H). Anal ($C_{11}H_{13}BrO_4$): C, H, Br.

(S)-5-Bromo-2-methoxy-3-(1-methylethoxy)-N-*(1-azabicyclo-[2.2.2]oct-3-yl)benzamide (S)-**40***
5-Bromo-2-methoxy-3-(1-methylethoxy)benzoic acid (**39**; 1.0 g, 3.5 mmol) was transformed to its corresponding acid chloride and reacted with an excess of (*S*)-**8**, as described for compound **9**. Workup gave 1.12 g (80%) of (*S*)-**40** as an oil. Rotation: $[\alpha]_D^{20}$ – 8 ° (*c* 0.40, EtOH). ^{1}H-NMR, δ ppm 8.30 (bd, 1, NH), 7.80 (dd, 1, C-6H), 7.14 (d, 1, C-4H), 4.58 (dq, 1, CH), 4.12 (m, 1, C-3'H), 3.92 (s, 3, OCH_3), 3.44 (dd, 1, C-2'H), 2.84 (m, 4), 2.54 (dd, 1, C-2'H), 1.99 (q, 1, C-4'H), 1.6–1.7 (m, 4), 1.44 (d, 6, $(CH_3)_2$).

(R)-5-[^{125}I]Iodo-2,3-dimethoxy-N-*(1-azabicyclo[2.2.2]oct-3-yl)-benzamide (R)-[^{125}I]-**9***
A 1.7 mM ethanolic solution of (*R*)-2,3-dimethoxy-5-(tri-*n*-butylstannyl)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)benzamide ((*R*)-**11**) (10 µL, 17 nmol) was added to 5 mCi of Na^{125}I (2.3 nmol) in 20 µL of 1 N HCl followed by 4 mM chloramine-T in water (10 µL, 40 nmol). After 1 min, 10 µL of 0.2 N sodium metabisulfate was added and the reaction mixture was neutralized by addition of 1.4 N NH_4OH (10 µL, 14 µmol). The product was purified in a reverse-phase HPLC column (Waters Novapak CN) in 30% EtOH – 0.1 M phosphate buffer at pH 6.7 [20]. At 14.2 min (flow rate 1.5 mL/min), a peak corresponding to 40–60% of the chloro derivative (**23**) was seen. Radiochemically pure (*R*)-[^{125}I]-**9** (2.3 mCi in 3.6 mL buffer) with 1800 Ci/mmol specific radioactivity was collected at 18–21 min.

(S)-5-[^{125}I]Iodo-2,3-dimethoxy-N-*(1-azabicyclo[2.2.2]oct-3-yl)-benzamide (S)-[^{125}I]-**9***
To a solution of Na^{125}I (5.0 mCi, NEN-Dupont) in 13 µL of 0.03 mM NaOH (pH 9.5) was added 1.7 mM ethanolic (*S*)-5-(tri-*n*-butylstannyl)-2,3-dimethoxy-*N*-(1-azabicyclo[2.2.2]-octan-3-yl)benzamide ((*S*)-**11**) (10 µL, 17 nmol), prepared by dissolving 68 mg of (*S*)-**11** in 68 mL abs EtOH followed by 6 N HOAc (10 µL, 60 µmol) at 23 °C. A 10% solution of H_2O_2 (10 µL, 30 µmol) was added. After 1 h at 20 °C, the reaction product was purified by HPLC (Waters Novapak, CN) [20]. Collection of the radioactive peak at 18.8–21.6 min gave 3.24 mCi (66%) of pure (*S*)-[^{125}I]-**9** in 3.13 mL buffer. The UV peak at 235 nm showed a peak area corresponding to 2.03 nmol of product giving a specific radioactivity of 1600 Ci/mmol. Reinjection of a 50-µL sample of the collected fraction showed a radiochemical purity of > 98%.

Pharmacology

Male Harlan–Sprague–Dawley rats (200–250 g) were sacrificed, their brains removed and dissected on an ice-cold porcelain dish. The entorhinal cortex was dissected and homogenized (1 g/13 mL) using a Brinkman Polytron (15 s at 12 700 rpm) in a buffer containing 50 mM HEPES pH 7.4, 2.4 mM $MgCl_2$, and 5 mM $CaCl_2$ [21]. The homogenate was centrifuged at 10 000 *g* for 15 min at 4 °C, the membrane pellet resuspended in the same volume of buffer, centrifuged a second time and resuspended in fresh buffer. For saturation studies, the tissue and various concentrations of (*S*)-[^{125}I]-**9** were incubated at 4 °C for 1 h. For competition studies, the tissue and (*S*)-[^{125}I]-**9** (0.4 or 0.8 nM) or (*S*)-[^{125}I]iodozacopride (0.3 nM) [25] were incubated at 4 °C and 20 °C respectively for 1 h with various concentrations of each competing ligand. Bound and free (*S*)-[^{125}I]-**9** were separated by filtration through Whatman GF/B filters presoaked in 0.3% polyethylenimine using a Brandel model M-24R cell harvester. The filters were rinsed three times for 10 s with ice-cold buffer and the filter placed in plastic tubes. Gamma spectrometry was performed with an ICN Isomedic Model 4/600 HE instrument with an efficiency of 80%.

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References

1 Martin GR, Humphrey PPA (1994) *Neuropharmacology* 33, 261–273
2 Smith WL, Alphin RS, Jackson CB, Sancilio LF (1989) *J Pharm Pharmacol* 41, 101–105
3 Costall B, Naylor RJ (1992) *Pharmacol Toxicol* 71, 401–415
4 Swift RM, Davidson D, Whelihan W, Kuznetsov O (1996) *Biol Psychiatry* 40, 514–521
5 Kilpatrick GJ, Butler A, Hagan RM, Jones BJ, Tyers MB (1990) *NS Arch Pharmacol* 342, 22–30
6 Nagakura Y, Kadowaki M, Tokoro K, Tomoi M, Mori J, Kohsaka M (1993) *J Pharmacol Exp Ther* 265, 752–758
7 Ito H, Akuzawa S, Tsutsumi R et al (1995) *Neuropharmacology* 34, 631–637
8 Yamano M, Kamato T, Nishida A et al (1994) *Jpn J Pharmacol* 65, 241–248
9 Turconi M, Nicola M, Gil-Quintero M et al (1990) *J Med Chem* 33, 2101–2108
10 Steward LJ, Ge J, Bentley KR et al (1995) *Br J Pharmacol* 116, 1781–1788
11 Koscielniak T, Ponchant M, Laporte AM et al (1990) *CR Acad Sci Paris, Ser III* 311, 231–237
12 Ponchant M, Koscielniak T, Hamon M, Gozlan H (1991) *J Label Compds Radiopharm* 29, 1147–1155
13 Laporte AM, Koscielniak T, Ponchant M, Verge D, Hamon M, Gozlan H (1992) *Synapse* 10, 271–281
14 Abi-Dargham A, Laurelle M, Wong DT, Robertson DW, Weinberger DR, Kleinman JE (1993) *J Neurochem* 60, 730–737
15 Yue EW, Gerdes M, Mathis CA (1991) *J Org Chem* 56, 5451–5456
16 de Paulis T, Janowsky A, Kessler RM, Clanton JA, Smith HE (1988) *J Med Chem* 31, 2027–2033
17 Langlois M, Meyer C, Soulier JL (1992) *Synth Commun* 22, 1895–1911
18 Bishop JE, Mathis CA, Gerdes JM, Whitney JM, Eaton AM, Mailman RB (1991) *J Med Chem* 34, 1612–1624
19 de Paulis T, Smith HE (1991) *Synth Commun* 21, 1091–1095
20 Clanton JA, de Paulis T, Schmidt DE et al (1991) *J Label Compds Radiopharm* 29, 45–751
21 Kilpatrick GJ, Jones BJ, Tyers MB (1987) *Nature* 330, 746–748
22 Miller K, Weisberg E, Fletcher PW, Teitler M (1992) *Synapse* 11, 58–66
23 Pinkus LM, Sarbin NS, Gordon JC, Munson HR (1990) *Eur J Pharmacol* 179, 231–235
24 Robertson DW, Bloomquist W, Cohen ML, Reid LR, Schenck K, Wong DT (1988) *J Med Chem* 33, 3176–3181
25 Hewlett WA, personal communication
26 Schmidt AW, Peroutka SJ (1990) *Mol Pharmacol* 38, 511–516
27 Hoyer D (1991) In: *5-HT-1A Agonists, 5-HT-3 Antagonists, and Benzodiazopines* (Rodgers RJ, Cooper SJ, eds) John Wiley, Chichester, 31–57
28 Geissler A, Torrente JR, Eison AS et al (1993) *Drug Dev Res* 29, 18–24
29 Fernandez AG, Puig J, Bou J, Gristwood RW, Berga P (1990) *Eur J Pharmacol* 183, 1214
30 Clark R, Miller AB, Berger J et al (1993) *J Med Chem* 36, 2645–2657
31 Wong EHF, Clark R, Leung E et al (1995) *Br J Pharmacol* 114, 851–859
32 Schmidt DE, Votaw JR, Kessler RM, de Paulis T (1994) *J Pharm Sci* 83, 305–315
33 Leo AJ (1993) *Chem Rev* 93, 1281–1306
34 Flippin LA, Carter DS, Berger J et al (1996) *Bioorg Med Chem Lett* 6, 477–480
35 Hewlett WA, de Paulis T, Schmidt DE, Trivedi BL, Mason NS, Ebert MH (1995) *Biol Psychiatry* 37, 668 (abstr)
36 Hewlett WA, de Paulis T, Schmidt DE, Trivedi BL, Ebert MH (1995) *Soc Neurosci Abstr* 21, 776
37 Alphin RS, Smith WL, Munson HR, Borwell RF (1988) *US Pat* 4,717,563
38 Holden NE (1993) In: *CRC Handbook of Chemistry and Physics* (Lide DR, ed) CRC Press, Boca Raton, FL, 7th edn
39 Imbert TF, Dorme NAM, Langlois M (1987) *US Pat* 4,657,911
40 Davies W (1923) *J Chem Soc* 1575–1593
41 King FE, Gilks JH, Partridge MW (1955) *J Chem Soc* 4206–4215