Brief Articles

Synthesis and Structure−Activity Relationship of Fluoro Analogues of 8-{2-[4-(4-Methoxyphenyl)piperazin-1yl]ethyl}-8-azaspiro[4.5]decane-7,9-dione as Selective α_{1d}-Adrenergic Receptor Antagonists

Michael J. Konkel,* John M. Wetzel, Marie Cahir,† Douglas A. Craig, Stewart A. Noble,‡ and Charles Gluchowski§

Lundbeck Research USA, Inc., 215 College Road, Paramus, New Jersey 07652

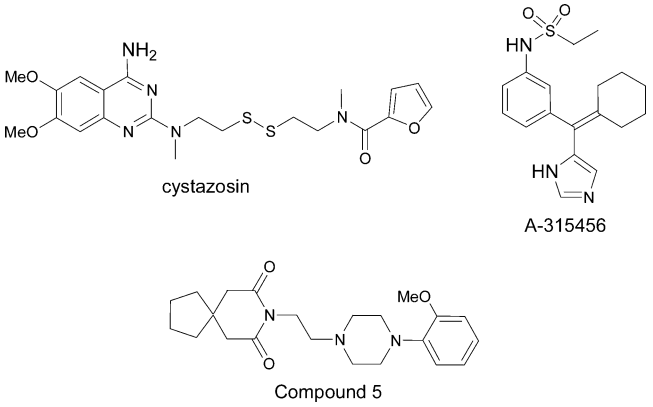
Received October 26, 2004

We have discovered high-affinity antagonists (exemplified by **11** and **12**) that are the most selective for α_{1d}-adrenergic receptors (α_{1d}-AR) reported to date. In cloned receptor assay systems, **12** displays at least 95-fold selectivity for the α_{1d}-AR over all other G-protein-coupled receptors tested, and the subtype selectivity of **11** was confirmed in pharmacologically defined isolated tissue preparations.

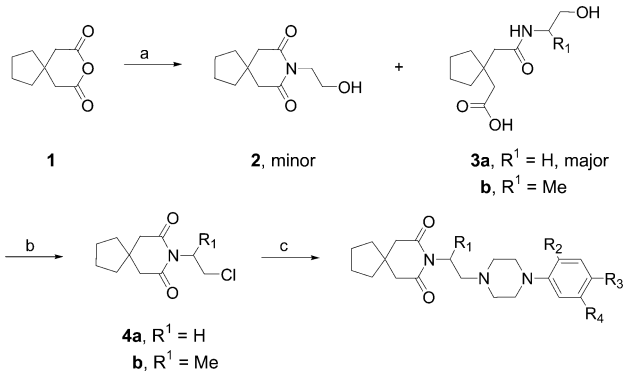
α-Adrenergic receptors (α-ARs) modulate intercellular biochemical processes in response to changes in extracellular concentrations of the neurotransmitter norepinephrine and the circulating hormone epinephrine, leading to widespread physiological actions that make them attractive targets for drug discovery.[1] Antagonists that are highly selective for the α_{1a}-AR are well-known,[1c] and recent reports have described compounds with modest selectivity for the α_{1b}-AR.[2] Saussy et al. have reported that **5** (Chart 1)[3] is selective for the α_{1d}-AR,[4] and this has been confirmed in our assay systems (Table 1). However, **5** ($pK_i = 8.8$ at α_{1d}) also has comparable or higher affinity for several other G-protein-coupled receptors (GPCRs),[4] including the serotonin 5-HT_{1A} receptor and the dopamine D_2 and D_3 receptors (Table 1). Cystazosin[5] has also been reported to be selective for the α_{1D} -AR and devoid of cross-reactivity to 5-HT_{1A} and dopamine receptors. Its subtype selectivity, however, is only about 10-fold. Recently, A-315456 has been reported[6] to be selective for the α_{1D}-AR with low cross reactivity to 5-HT_{1A} and D_2. Also, recently a report by a group from Recordati on analogues of **5** with low cross-reactivity has appeared.[7] The report did not mention whether the Recordati compounds had significant cross-reactivity to dopamine receptors, a known cross-reactivity of **5**.[6]

We describe herein the synthesis and SAR of fluoro analogues of **5** and novel trifluoro analogues that show decreased affinity for 5-HT_{1A}, D_2, and D_3 receptors while maintaining high affinity and subtype selectivity for the α_{1d}-AR.[8,9]

Chart 1



Scheme 1. Synthesis of Compounds **6**−**13**[a]



[a] Reagents and conditions: (a) 2-ethanolamine or 2-aminopropanol; (b) $SOCl_2$, 45% from **1**; (c) substituted *N*-phenylpiperazine, 22−50%.

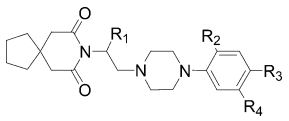
Synthesis

Compounds **6**−**13** were synthesized as outlined in Scheme 1. 3,3-Tetramethyleneglutaric anhydride (**1**) was allowed to react with ethanolamine, giving a mixture of imide **2** and amide **3a**. The crude mixture of imide **2** and amide **3a** was treated with thionyl chloride,

* To whom correspondence should be addressed. Phone: 201-350-0355. Fax: 201-261-0623. E-mail: miko@lundbeck.com.
† Present address: Department of Mental Health, Queen's University Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast, BT9 7BL, N. Ireland.
‡ Present address: Kalypsys, Inc., 11099 North Torrey Pines Road, La Jolla, CA 92037.
§ Present address: Life Science Solutions, 154 Coolspring Ct., Danville, CA 94506.

10.1021/jm0491391 CCC: $30.25
Published on Web 03/30/2005

Table 1. Binding Affinities at Cloned α-Adrenoceptors, 5-HT_{1A}, and Dopamine Receptors



					K_i (nM)[a]					
compd	R1	R2	R3	R4	α_{1d}	α_{1b}	α_{1a}	5-HT_{1A}	D_2	D_3
5	H	OMe	H	H	1.6	191	290	0.46	14	3.1
6	H	F	H	H	0.83	67	630	7.5	140	5.2
7	H	H	F	H	14	255	620	54	2200	91
8	H	F	F	H	5.6	1100	3800	24	NT[b]	NT[b]
9	H	H	F	F	7.9	1400	4100	55	2200	160
10	H	F	H	F	0.95	54	1000	25	120	8.1
11	H	F	F	F	1.9	380	4400	360	700	23
12	(*R*)-Me	F	F	F	1.3	165	14000	300	580	120
13	(*S*)-Me	F	F	F	>124	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]

[a] α_{1d}, α_{1b}, α_{1a}, 5-HT_{1A}, and D_2 are cloned human receptors. D_3 is a cloned rat receptor. K_i determinations are an average of two or more (four to six for key compounds) independent determinations. The margin of error is within 5% of the mean for all data shown. [b] NT: not tested.

resulting in condensation of the amide to the imide and substitution of the hydroxyl group with chloride. The resulting intermediates **4** were treated with the appropriately substituted *N*-arylpiperazines, giving the desired compounds **6**−**13**. The *N*-arylpiperazines were commercially available or synthesized by a previously described procedure.[10] For **12** (and its enantiomer **13**), tetramethyleneglutaric anhydride (**1**) was allowed to react with optically pure (*R*)-2-aminopropanol (or (*S*)-2-aminopropanol), giving imide **3b** that was converted to **4b** by thionyl chloride treatment.

Pharmacology

Radioligand binding experiments were performed on membranes prepared from cells transiently transfected with DNA for the cloned human α-AR (α_{1a}, α_{1b}, and α_{1d}) and 5-HT_{1A}, as described previously.[11] Membranes for dopamine human D_2 and rat D_3 receptors were purchased from New England Nuclear Corporation. The binding affinities (K_i) were determined by displacement of the following radioligands: [^{3}H]prazosin (0.3 nM, α_1-ARs), [^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT, 0.3 nM, 5-HT_{1A}), or [^{3}H]spiperone (1 nM, D_2, D_3). The results are presented in Table 1.

The K_B of **11** at native α_1-ARs was determined by measuring antagonism of phenylephrine-evoked contractions in three pharmacologically defined isolated rat tissue preparations: vas deferens (α_{1A}), spleen (α_{1B}), and thoracic aorta (α_{1D}). In each of the preparations **11** behaved as a competitive antagonist. The K_B determined for each tissue (α_{1A}, 5.4; α_{1B}, 6.7; α_{1D}, 8.8) correlates well with the corresponding K_i derived from binding experiments.

Structure−Activity Relationships

We hypothesized that the selectivity of **5** for the α_{1d}-AR over the α_{1a}- and α_{1b}-ARs could be largely attributed to the imide moiety because many examples were known of 1-substituted 4-(methoxyphenyl)piperazines that were not α_{1d}-selective.[1c] Therefore, we focused our initial studies on modification of the piperazine moiety.

It was found that the methoxyl group of **5** could be replaced with fluorine (**6**), resulting in decreased affinity for the 5-HT_{1A} and D_2 receptors (16- and 13-fold, respectively) but essentially unchanged affinity for the α_{1d} and D_3 receptors (Table 1). The 4-fluoro-substituted **7** displays a 18-fold decrease in α_{1d}-AR affinity and a decrease in the selectivity for α_{1d} versus 5-HT_{1A} compared to the 2-fluoro-substituted **6**. For difluoro substitution, the substitution pattern of the fluorine atoms on the phenyl ring is critical for maximizing the affinity and selectivity for the α_{1d}-AR. For instance, it was found that the affinity for α_{1d} for 2,5-difluoro-substituted **10** is equivalent to the 2-fluoro-substituted **6** while affinity for the 5-HT_{1A} and α_{1a} receptors is decreased. Compared to 2,5-difluoro substitution (**10**), the binding affinity and selectivity for the α_{1d}-AR decreased with 2,4-difluoro substitution (**8**) or 3,4-difluoro substitution (**9**). The trifluorophenyl-substituted **11** exhibits α_{1d}-AR affinity approximately equal to that of **5** while displaying significantly decreased affinity for α_{1a}, 5-HT_{1a}, and D_2 receptors (Table 1). The affinity of **11** for the D_3 receptor was reduced relative to **5** (6-fold) but was still significantly high (K_i = 23 nM).

Placement of a methyl group on the linker (**12**) resulted in decreased binding affinity at the D_3 receptor (K_i = 123 nM) while maintaining high affinity for the α_{1d}-AR (K_i = 1.3 nM) and greater than 100-fold selectivity over other GPCRs including α_{1a}, α_{1b}, α_{2c}, α_{2a}, α_{2b}, D_2, and 5-HT_{1A}. The (*R*)-configuration of the methyl group is important because the (*S*)-isomer was found to have significantly lower binding affinity for the α_{1d}-AR ($K_i \geq$ 124 nM).[12]

In conclusion, we have discovered high-affinity antagonists (exemplified by **11** and **12**) that are the most selective for the α_{1d}-AR reported to date. In cloned receptor assay systems, **12** displays at least 95-fold selectivity for the α_{1d}-AR over all other GPCRs tested, and the subtype selectivity of **11** was confirmed in pharmacologically defined isolated tissue preparations. These compounds display the highest selectivity for the α_{1d}-AR thus far reported and should prove useful for further functional characterization of α_1-ARs in in vivo models. The information gained through such studies will aid in the understanding of the physiological importance of the individual α_1-AR subtypes and potentially lead to the discovery of therapies that benefit from selective modulation of α_1-ARs.

Experimental Section

General Methods. Substituted *N*-phenylpiperazines were synthesized according to the procedure described by Martin.[10] The syntheses of **4** were carried out as described previously by Y. H. Wu.[3] (*R*)-2-Aminopropanol and (*S*)-2-aminopropanol were purchased from Aldrich and both are listed as 97% ee. The actual ee purity for the batch of (*R*)-2-aminopropanol used in the syntheses described herein was 99.9% (GLC) as communicated to us by Aldrich. Enantiomeric purities of **12** and **13** were determined by chiral HPLC, using a Chiralcel OD, 0.46 cm × 25 cm column (Daicel Chemical Industries, LTD), 1 mL/min (5% EtOH/95% hexane with 0.1% TEA). ^{1}H and ^{13}C NMR spectra were obtained at 300 and 75 MHz, respectively, with $CDCl_3$ as solvent and referenced to TMS as an internal standard. Coupling constants (*J*) are reported in Hz.

8-[(1*R*)-2-Chloro-1-methylethyl]-8-azaspiro[4.5]decane-7,9-dione (4b). A mixture of 3,3-tetramethyleneglutaric anhydride (1.12 g, 6.66 mmol) and (*R*)-(−)-2-amino-1-propanol (Aldrich, 1.00 g, 13.3 mmol) in pyridine (15 mL) was heated at reflux for 3 h. The solvent was removed, and the residue was partioned between 1 N HCl (10 mL) and ethyl acetate

(10 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined ethyl acetate fractions were dried over sodium sulfate and then the solvent was removed, leaving a clear oil (1.92 g). A portion of this oil (0.70 g) in benzene (9 mL) and pyridine (0.40 mL) was cooled to 0 °C. Thionyl chloride (0.40 mL) was added dropwise to the mixture, and then the solution was heated at 60 °C for 90 min. The solution was cooled to room temperature, and water (10 mL) was added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The solvent was removed from the combined organic fractions, and the residue was purified by flash chromatography over silica gel, eluting with hexane/ethyl acetate (3:1). The R_f = 0.3 fraction was concentrated, giving the title compound as a pale-yellow oil (294 mg). ^{1}H NMR δ 5.09−5.04 (m, 1H), 4.17 (t, 1H, J = 10.5), 3.66 (dd, 1H, J = 11.1, 5.7), 2.61 (s, 4H), 1.76−1.69 (m, 4H), 1.56−1.51 (m, 4H), 1.40 (d, 3H, J = 6.9). The (*S*)-enantiomer was synthesized in an identical manner.

8-{2-[4-(2-Fluorophenyl)piperazin-1yl]ethyl}-8-azaspiro-[4.5]decane-7,9-dione (6). A mixture of 1-(2-fluorophenyl)-piperazine (100 mg, 0.56 mmol) and 8-(2-chloroethyl)-8-azaspiro-[4.5]decane-7,9-dione (100 mg, 0.44 mmol) was heated with stirring at 160 °C for 5 h. The residue was dissolved in methanol, transferred to a preparative thin layer chromatographic plate (silica gel), and eluted with ethyl acetate/hexane (1:1). A band at R_f = 0.3 was removed and rinsed with chloroform/methanol (4:1). The solvent was removed, giving the title compound as pale-yellow oil (81.7 mg, 0.22 mmol, 50%). ^{1}H NMR δ 7.04 (td, 1H, J = 9.3, 1.5), 7.01 (t, 1H, J = 6.9), 6.97−6.87 (m, 2H), 3.96 (t, 2H, J = 6.6), 3.05 (t, 4H, J = 4.8), 2.67 (t, 4 H, J = 4.7), 2.59 (s, 4H), 2.54 (t, 2H, J = 6.6), 1.73−1.68 (m, 4H), 1.55−1.50 (m, 4H); ^{13}C NMR δ 172.8, 156.3 (d, J = 244.4), 140.8 (d, J = 8.5), 125.0 (d, J = 3.4), 122.8 (d, J = 8.0), 119.5 (d, J = 2.9), 116.7 (d, J = 20.7), 56.1, 53.9 (2C), 51.2 (d, 2C, J = 3.1), 45.5 (2C), 40.2, 38.1 (2C), 37.1, 24.8 (2C); ESI-MS *m/z* 374 (MH^+). The title compound was dissolved in ether and precipitated by addition of 1 N HCl in ether, giving a white solid (mp 212−214 °C).

8-{2-[4-(4-Fluorophenyl)piperazin-1-yl]ethyl}-8-azaspiro[4.5]decane-7,9-dione (7). A mixture of 1-(4-fluorophenyl)piperazine (100 mg, 0.56 mmol) and 8-(2-chloroethyl)-8-azaspiro[4.5]decane-7,9-dione (100 mg, 0.44 mmol) was heated with stirring at 160 °C for 7 h. The residue was dissolved in methanol, transferred to a preparative thin layer chromatographic plate (silica gel), and eluted with ethyl acetate/hexane (1:1). A band at R_f = 0.3 was removed and rinsed with chloroform/methanol (4:1). The solvent was removed, giving the title compound as pale-yellow oil (77.3 mg, 0.21 mmol, 48%). ^{1}H NMR δ 6.95 (dd, 2H, J = 9.3, 8.1), 6.85 (dd, 2H, J = 9.3, 4.8), 3.96 (t, 2H, J = 6.6), 3.05 (t, 4H, J = 5.0), 2.65 (t, 4 H, J = 4.8), 2.59 (s, 4H), 2.54 (t, 2H, J = 6.5), 1.72−1.67 (m, 4H), 1.54−1.49 (m, 4H); ^{13}C NMR δ 172.9, 157.6 (d, J = 237.1), 148.6, 118.2 (d, 2C, J = 7.6), 116.0 (d, 2C, J = 21.9), 56.0, 53.8 (2C), 50.8 (2C), 45.5 (2C), 40.2, 38.1 (2C), 37.1, 24.8 (2C); ESI-MS *m/z* 374 (MH^+). The title compound was dissolved in ether and precipitated by addition of 1 N HCl in ether, giving a white solid (mp 223−224 °C).

8-{2-[4-(3-Fluorophenyl)piperazin-1yl]ethyl}-8-azaspiro-[4.5]decane-7,9-dione (8). A mixture of 1-(4-fluorophenyl)-piperazine (100 mg, 0.56 mmol) and 8-(2-chloroethyl)-8-azaspiro-[4.5]decane-7,9-dione (100 mg, 0.44 mmol) was heated with stirring at 160 °C for 7 h. The residue was dissolved in methanol, transferred to a preparative thin layer chromatographic plate (silica gel), and eluted with ethyl acetate/hexane (1:1). A band at R_f = 0.3 was removed and rinsed with chloroform/methanol (4:1). The solvent was removed, giving the title compound as a pale-yellow oil (63.0 mg, 0.17 mmol, 39%). ^{1}H NMR δ 7.17 (q, 1H, J = 8.1), 6.65 (dd, 1H, J = 8.4, 2.1), 6.57 (dt, 1H, J = 12.3, 2.3), 6.51 (td, 1H, J = 8.1, 2.1), 3.96 (t, 2H, J = 6.5), 3.13 (t, 4H, J = 5.0), 2.63 (t, 4 H, J = 5.0), 2.59 (s, 4H), 2.53 (t, 2H, J = 6.6), 1.74−1.64 (m, 4H), 1.52−1.48 (m, 4H); ^{13}C NMR δ 172.9, 164.4 (d, J = 241.6), 153.6 (d, J = 9.2), 130.6 (d, J = 9.8), 111.6 (d, J = 2.2), 106.2 (d, J = 21.4), 103.1 (d, J = 24.8), 56.0, 53.6 (2C), 49.3 (2C), 45.5 (2C), 40.2, 38.1 (2C), 37.0, 24.8 (2C); ESI-MS *m/z* 374 (MH^+). The title compound was dissolved in ether and precipitated by addition of 1 N HCl in ether, giving a white solid (mp 238−229.5 °C).

8-{2-[4-(3,4-Difluorophenyl)piperazin-1yl]ethyl}-8-azaspiro[4.5]decane-7,9-dione (9). A mixture of 1-(3,4-difluorophenyl)piperazine (100 mg, 0.51 mmol) and 8-(2-chloroethyl)-8-azaspiro[4.5]decane-7,9-dione (100 mg, 0.44 mmol) was heated with stirring at 160 °C for 7 h. The residue was dissolved in methanol, transferred to a preparative thin layer chromatographic plate (silica gel), and eluted with ethyl acetate/hexane (1:1). A band at R_f = 0.3 was removed and rinsed with chloroform/methanol (4:1). The solvent was removed, giving the title compound as a pale-yellow oil (69.8 mg, 0.18 mmol, 41%). ^{1}H NMR δ 7.17 (q, 1H, J = 9.3), 6.65 (ddd, 1H, J = 13.5, 6.9, 3.0), 6.59−6.54 (m, 1H), 3.97 (t, 2H, J = 6.5), 3.07 (t, 4H, J = 4.8), 2.68 (t, 4 H, J = 5.0), 2.60 (s, 4H), 2.58 (t, 2H, J = 6.3), 1.72−1.68 (m, 4H), 1.54−1.50 (m, 4H); ESI-MS *m/z* 392 (MH^+). The title compound was dissolved in ether and precipitated by addition of 1 N HCl in ether, giving white flakes (mp 227−228 °C).

8-{2-[4-(2,5-Difluorophenyl)piperazin-1yl]ethyl}-8-azaspiro[4.5]decane-7,9-dione (10). A mixture of 1-(2,5-difluorophenyl)piperazine (100 mg, 0.51 mmol) and 8-(2-chloroethyl)-8-azaspiro[4.5]decane-7,9-dione (100 mg, 0.44 mmol) was heated with stirring at 160 °C for 5 h. The residue was dissolved in methanol, transferred to a preparative thin layer chromatographic plate (silica gel), and eluted with ethyl acetate/hexane (1:1). A band at R_f = 0.7 was removed and rinsed with chloroform/methanol (4:1). The solvent was removed, giving the title compound as a pale-yellow oil. ^{1}H NMR δ 6.99−6.89 (11-line m, 1H), 6.65−6.52 (m, 2H), 3.95 (t, 2H, J = 6.5), 3.03 (t, 4H, J = 4.7), 2.66 (t, 4 H, J = 4.7), 2.60 (s, 4H), 2.54 (t, 2H, J = 6.6), 1.74−1.69 (m, 4H), 1.55−1.51 (m, 4H); ESI-MS *m/z* 392 (MH^+). The title compound was dissolved in ether and precipitated by addition of 1 N HCl in ether, giving a white solid (64.9 mg, 0.15 mmol, 35%) (mp 237−239 °C).

8-{2-[4-(2,4,5-Trifluorophenyl)piperazin-1yl]ethyl}-8-azaspiro[4.5]decane-7,9-dione (11). A mixture of 1-(2,4,5-trifluorophenyl)piperazine (0.94 g, 4.35 mmol) and 8-(2-chloroethyl)-8-azaspiro[4.5]decane-7,9-dione (1.00 g, 4.35 mmol) was heated with stirring at 160 °C for 7 h. The residue was partitioned between ethyl acetate (40 mL) and saturated aqueous sodium carbonate (40 mL). The aqueous layer was extracted with ethyl acetate (2 × 40 mL), and the combined ethyl acetate fractions dried over sodium sulfate. The solvent was removed, and the residue was purified by flash chromatography over silica gel, eluting with a gradient of hexane to hexane/ethyl acetate (1:1). The solvent was removed from the desired product [R_f = 0.7, hexane/ethyl acetate (1:1)], leaving a pale-tan oil that slowly solidified (0.652 g, 1.60 mmol, 37%, mp 230−234 °C). ^{1}H NMR δ 6.89 (ddd, 1H, J = 11.7, 10.2, 7.5), 6.74 (dt, 1H, J = 12.0, 8.1), 3.95 (t, 2H, J = 6.6), 2.97 (t, 4H, J = 4.7), 2.65 (t, 4 H, J = 4.7), 2.60 (s, 4H), 2.54 (t, 2H, J = 6.5), 1.74−1.70 (m, 4H), 1.55−1.51 (m, 4H); ^{13}C NMR δ 172.7, 151.0 (ddd, J = 243.8, 8.5, 1.7), 146.9 (ddd, J = 241.6, 12.2, 3.2), 144.7 (ddd, J = 242.3, 13.9, 12.4), 137.4 (ddd, J = 9.6, 6.1, 2.9), 107.9 (dd, J = 20.7, 4.1), 106.4 (dd, J = 26.6, 21.5), 55.9, 53.6 (2C), 51.3 (d, 2C, J = 3.0), 45.4 (2C), 40.1, 38.0 (2C), 36.9, 24.7 (2C); ESI-MS *m/z* 410 (MH^+). The title compound was dissolved in ether and precipitated by addition of 1 N HCl in ether, giving a white solid. The solid was recrystallized from hot methanol/chloroform (4:1) (with hexane added to cloudiness), giving white flakes (0.43 g, 0.96 mmol, 22%) (mp 234−236.5 °C).

8-{(1*R*)-2-[4-(2,4,5-Trifluorophenyl)piperazin-1-yl]-1-methylethyl}-8-azaspiro[4.5]decane-7,9-dione (12). A mixture of 1-(2,4,5-trifluorophenyl)piperazine (105 mg, 0.49 mmol) and (*R*)-8-(2-chloro-1-methylethyl)-8-azaspiro[4.5]decane-7,9-dione (105 mg, 0.43 mmol) was heated with stirring at 160 °C for 5 h. The residue was dissolved in methanol, transferred to a preparative thin layer chromatographic plate (silica gel), and eluted with ethyl acetate/hexane (1:1). A band at R_f = 0.8 was removed and rinsed with chloroform/methanol (4:1). The

solvent was removed, giving the title compound as a pale-yellow oil (86.2 mg, 0.20 mmol, 47%, 100% ee). ^{1}H NMR δ 6.89 (ddd, 1H, J = 11.7, 10.2, 7.5), 6.71 (dt, 1H, J = 12.0, 8.1), 5.08−4.96 (m, 1H), 3.14 (dd, 1H, J = 12.6, 10.5), 2.92 (t, 4H, J = 4.7), 2.73−2.66 (m, 2H), 2.58 (s, 4H), 2.51−2.44 (m, 2H), 2.36 (dd, 1H, J = 12.6, 5.4), 1.75−1.68 (m, 4H), 1.57−1.50 (m, 4H), 1.34 (d, 3H, J = 6.9); ESI-MS *m/z* 424 (MH^+). The title compound was dissolved in ether and precipitated by addition of 1 N HCl in ether, giving a white solid (mp 231−235 °C).

8-{(1*S*)-2-[4-(2,4,5-Trifluorophenyl)piperazin-1-yl]-1-methylethyl}-8-azaspiro[4.5]decane-7,9-dione (13). 13 was prepared in a manner analogous to that described above for **11**, giving the title compound as a pale-yellow oil (18.1 mg, 0.043 mmol, 52%, 98% ee). ^{1}H NMR δ 6.89 (ddd, 1H, J = 11.7, 10.2, 7.5), 6.71 (dt, 1H, J = 12.0, 8.1), 5.08−4.96 (m, 1H), 3.14 (dd, 1H, J = 12.6, 10.5), 2.92 (t, 4H, J = 4.7), 2.73−2.66 (m, 2H), 2.58 (s, 4H), 2.51−2.44 (m, 2H), 2.36 (dd, 1H, J = 12.6, 5.4), 1.75−1.68 (m, 4H), 1.57−1.50 (m, 4H), 1.34 (d, 3H, J = 6.9); ESI-MS *m/z* 424 (MH^+). The title compound was dissolved in ether and precipitated by addition of 1 N HCl in ether, giving a white solid (mp 231−235 °C).

Acknowledgment. We are indebted to the following people for their support of this research: Y. Z. Zheng for cell culture and membrane preparation; Thelma Thompson, Dipa Deshpande, and Michelle Iacolina for radioligand displacement assays; Faye Hsieh and Usha Yeramilli for mass spectroscopic analysis; Qingping Han for enantiomeric purity assessments. We are also indebted to the National Institutes of Health for financial support of this project (SBIR Grant 1 R44 NS33418-02).

Supporting Information Available: Results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Byland, D. B.; Eikenberg, D. C.; Hieble, J. P.; Langer, S. Z.; Lefkowitz, R. J.; Minneman, K. P.; Ruffolo, R. R., Jr.; Trendelenburg, U. IV. International Union of Pharmacology Nomenclature of Adrenoceptors. *Pharmacol. Rev.* **1994**, *46*, 121−136. (b) Hieble, J. P.; Bondinell, W. E.; Ruffolo, R. R., Jr. α and *β*-Adrenoceptors: From the Gene to the Clinic. 1. Molecular Biology and Adrenoceptor Subclassification. *J. Med. Chem.* **1995**, *38*, 3415−3444 and references therein. (c) Ruffolo, R. R., Jr.; Bondinell, W. E.; Hieble, J. P. α and *β*-Adrenoceptors: From the Gene to the Clinic. 2. Structure−Activity Relationships and Therapeutic Applications. *J. Med. Chem.* **1995**, *38*, 3681−3716 and references therein.

(2) (a) Giardinà, D.; Crucianelli, M.; Roamnelli, R.; Leonardi, A.; Poggesi, E.; Melchiorre, C. Synthesis and Biological Profile of the Enantiomers of [4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-*cis*-octahydroquinoxalin-1-yl]furan-2-ylmethanone (Cyclazosin), a Potent Competitive α_{1b}-Adrenoceptor Antagonist *J. Med. Chem.* **1996**, *39*, 4602−4607. (b) Patane, M. A.; Scott, A. L.; Broten, T. P.; Chang, R. S. L.; Ransom, R. W.; DiSalvo, J.; Forray, C.; Bock M. G. 4-Amino-2-[4-[1-(benzyloxycarbonyl)-2(*S*)-[[(1,1-dimethylethyl)amino]carbonyl]-piperazinyl]-6,7-dimethoxyquinazoline (L-765,314): A Potent and Selective α_{1b} Adrenergic Receptor Antagonist. *J. Med. Chem*., **1998**, *41*, 1205−1208.

(3) (a) Wu, Y. H. Azaspirodecanediones and Azaspiroundecanediones. U.S. Patent 3,398,151, 1968. (b) Wu, Y. H.; Smith, K. R.; Rayburn, J. W. Psychosedative Agents. *N*-(4-Phenyl-1-piperazinylalkyl)-Substituted Cyclic Imides. *J. Med. Chem.* **1969**, *12*, 876−881.

(4) (a) Goetz, A. S.; King, H. K.; Ward, S. D. C.; True, T. A.; Rimele, T. J.; Saussy, D. L., Jr. BMY 7378 Is a Selective Antagonist of the D Subtype of the α_1-Adrenoceptors. *Eur. J. Pharmacol.* **1995**, *272*, R5−R6. (b) Saussy, D. L., Jr.; Goetz, A. S.; Queen, K. L.; King, H. K.; Lutz, M. W.; Rimele, T. J. Structure Activity Relationships of a Series of Buspirone Analogs at Alpha-1 Adrenoceptors: Further Evidence That Rat Aorta Alpha-1 Adrenoceptors Are of the Alpha-1D-Subtype. *J. Pharmacol. Exp. Ther.* **1996**, *278*, 136−144.

(5) Minarini, A.; Buedriesi, R.; Chiarini, A.; Leonardi, A.; Melchiorre, C. Search for α_1-Adrenoceptor Subtype Selective Antagonists: Design, Synthesis, and Biological Activity of Cystazosin, an α_{1d}-Adrenoceptor Antagonist. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1353−1358.

(6) Buckner, S. A.; Milicic, I.; Daza, A.; Lynch, J. J., III; Kolasa, T.; Nakane, M.; Sullivan, J. P.; Brioni, J. D. A-315456: A Selective α_{1D}-Adrenoceptor Antagonist with Minimal Dopamine D_2 and 5-HT_{1A} Receptor Affinity. *Eur. J. Pharmacol.* **2001**, *433*, 123−127.

(7) Leonardo, A.; Barlocco, D.; Montesano, F.; Cignarella, G.; Motta, G.; Testa, R.; Poggesi, E.; Seeber, M.; De Benedetti, P. G.; Fanelli, F. Synthesis, Screening, and Molecular Modeling of New Potent and Selective Antagonists at the α_{1d}-Adrenergic Receptor. *J. Med. Chem.* **2004**, *47*, 1900−1918.

(8) A part of this work was disclosed at an ACS meeting: Konkel, M. J.; Wetzel, J. M.; Cahir, M.; Craig, D.; Noble, S.; Gluchowski, C. Discovery of Antagonists Selective for the Alpha-1D-Adrenoceptor. Presented at the 216th National Meeting of the American Chemical Society, Boston, MA, August 23−27, 1998; Abstract Medi 129.

(9) Two compounds described in this paper have been cited in reviews: (a) Bremner, J. B.; Griffith, R.; Coban, B. Ligand Design for Alpha(1) Adrenoceptors. *Curr. Med. Chem.* **2001**, *8*, 607−620. (b) Romeo, G.; Materia, L.; Salerno, L.; Russo, F.; Minneman, K. P. Novel Antagonists for α_1-Adrenoceptor Subtypes. *Expert Opin. Ther. Pat.* **2004**, *14*, 619−636.

(10) Martin, G. E.; Elgin, R. J., Jr.; Mathiason, J. R.; Davis, C. B.; Kesslick, J. M.; Baldy, W. J.; Shank, R. P.; DiStefano, D. L.; Fedde, C. L.; Scott, M. K. Activity of Aromatic Substituted Phenylpiperazines Lacking Affinity for Dopamine Sites in a Preclinical Test of Antipsychotic Efficacy. *J. Med. Chem.* **1989**, *32*, 1052−1056.

(11) (a) Forray, C.; Bard, J. A.; Wetzel, J. M.; Chiu, G.; Shapiro, E.; Tang, R.; Lepor, H.; Hartig, P. R.; Weinshank, R. L.; Branchek, T. A.; Gluchowski, C. The α_1-Adrenergic Receptor That Mediates Smooth Muscle Contraction in Human Prostate Has the Pharmacological Properties of the Cloned Human α_{1c} Subtype. *Mol. Pharmacol.* **1994**, *45*, 703−708. (b) Michel, M. C.; Kerker, J.; Branchek, T. A.; Forray, C. Selective Irreversible Binding at α_1- and α_2-Adrenoceptor Subtypes. *Mol. Pharmacol.* **1993**, *44*, 1165−1170.

(12) Since the ee of **13** was 98% and its K_i is 100-fold higher than that for **12**, the observed binding for **13** (K_i = 124 nM) could be accounted for by the 1% of **12** in the sample.

JM0491391