Notes

Synthesis and *in Vitro* Characterization of *N*-[5-(4,5-Dihydro-1*H*-imidazol-2-yl)-2-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]methanesulfonamide and Its Enantiomers: A Novel Selective α_{1A} Receptor Agonist[1]

Michael D. Meyer,* Robert J. Altenbach, Arthur A. Hancock, Steven A. Buckner, Sheila M. Knepper, and James F. Kerwin, Jr.

Pharmaceutical Discovery D-47C, Abbott Laboratories, Abbott Park, Illinois 60064-3500

Received May 15, 1996[⊗]

The existence of multiple subtypes of the α_1 adrenergic receptor has been demonstrated both pharmacologically and by molecular biological cloning techniques. The development of subtype selective antagonists has been the focus of much research within the pharmaceutical industry, and clinical evidence now exists that α-1A selective antagonists will have utility in the treatment of benign prostatic hyperplasia. However, highly subtype selective agonists are not known. Herein we report the synthesis and pharmacological characterization of *N*-[5-(4,5-dihydro-1*H*-imidazol-2-yl)-2-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]methanesulfonamide and its enantiomers, a highly potent full agonist with excellent selectivity for the α_{1A} receptor subtype.

Introduction

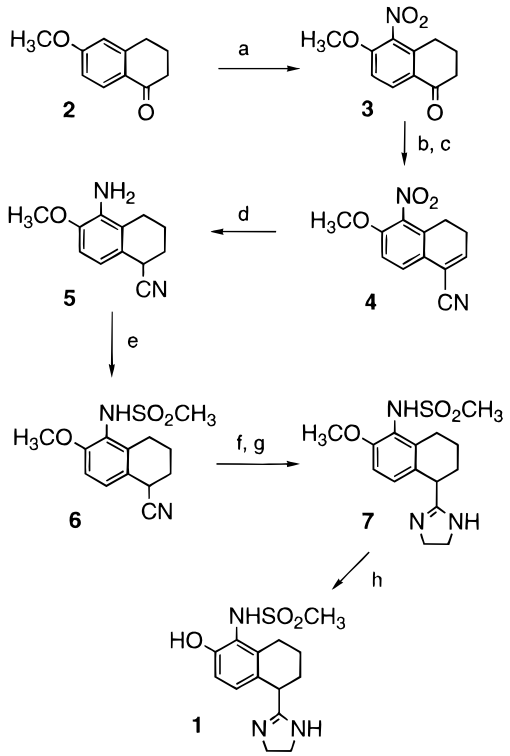
Only recently has the existence of multiple subtypes of the α_1 adrenergic receptor been observed both pharmacologically[2,3] and by molecular biological cloning techniques.[4,5,9] The therapeutic implications of α_1 subtype selective agents are significant, most notably in the treatment of benign prostatic hyperplasia (BPH). The paucity of subtype selective agents and, in particular, subtype selective agonists has hindered the delineation of the roles that α_1 receptors play in both normal physiology and disease states.

During the course of an investigation into the discovery and development of α-2 agonist compounds, certain substituted tetralin imidazolines exhibited high potency in an *in vitro* screen for α-1 functional activity, yet exhibited very poor binding affinity in a rat liver derived α-1 binding assay. Once the existence of multiple subtypes of the α-1 receptor was established, re-evaluation of these "outliers" revealed a series of compounds exhibiting subtype selectivity for the α_{1A} binding site, with **1** being the most potent and selective from this class. Herein, we report the synthesis and pharmacological characterization of **1** and its respective enantiomers, a highly subtype selective and potent full agonist at the α_{1A} adrenoceptor subtype.

Chemistry

Compound **1** was prepared as shown in Scheme 1. 6-Methoxytetralone was nitrated to yield a mixture of 5- and 7-mono nitro products, which could be separated by fractional crystallization. The 5-nitro isomer **3** was treated with diethyl cyanophosphonate and LiCN(cat.) to yield an intermediate cyanohydrin diethyl phosphate ester, which upon treatment with pTsOH in refluxing toluene yielded the unsaturated nitrile **4**. Concomitant reduction of the nitro group and double bond yielded the saturated nitrile **5**, which was treated with methanesulfonyl chloride to yield the sulfonamide **6**. The nitrile was then converted to an intermediate imino ether by treatment with anhydrous HCl in methanol/methylene chloride, which upon treatment with ethylenediamine yielded the imidazoline **7**. Cleavage of the methyl ether with BBr_3 in methylene chloride yielded the racemate **1**.

Scheme 1[a]



[a] (a) HNO_3, AcOH; (b) diethyl cyanophosphonate, LiCN; (c) pTsOH; (d) H_2, Pd; (e) CH_3SO_2Cl, Et_3N; (f) HCl, MeOH; (g) ethylenediamine; (h) BBr_3, CH_2Cl_2.

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1996.

S0022-2623(96)00354-8 CCC: $12.00

Table 1. Receptor Binding Affinities[a]

compound	pK_i α_{1A}	α_{1a}	α_{1b}	α_{1d}	sel (A:b)	sel (A:d)
1	8.05 ± 0.20 (7)	7.52 ± 0.09 (7)	5.68 ± 0.46 (7)	5.87 ± 0.20 (6)	234	153
10	8.65 ± 0.64 (3)	7.76 ± 0.18 (4)	5.55 ± 0.28 (4)	5.99 ± 0.38 (4)	1260	457
11	6.02 ± 0.39 (9)	5.84 ± 0.33 (10)	4.76 ± 0.36 (9)	5.53 ± 0.49 (8)	18	3
norepinephrine	6.55 ± 0.03 (190)	6.35 ± 0.04 (202)	6.58 ± 0.03 (194)	7.65 ± 0.05 (186)	0.9	0.08
phenylephrine	6.01 ± 0.30 (6)	6.03 ± 0.68 (6)	5.90 ± 0.25 (5)	6.79 ± 0.21 (5)	1.3	0.17
oxymetazoline	8.19 ± 0.22 (5)	7.88 ± 0.39 (5)	6.69 ± 0.16 (5)	6.48 ± 0.43 (5)	32	55
5-methylurapidil	8.82 ± 0.15 (10)	9.20 ± 0.10 (12)	7.43 ± 0.08 (12)	7.86 ± 0.08 (14)	25	9.1

[a] Data are presented as pK_i values followed by 95% confidence limits and number of determinations in parentheses. Rat submaxillary glands were used as a source of α_{1A} receptors; α_{1a} binding was performed using bovine clonal α_{1a} receptors as described by Schwinn et al.;[9] α_{1b} binding was performed using hamster clonal α_{1b} receptors as described by Cotecchia et al.;[4] and α_{1d} binding was performed using rat clonal α_{1d} receptors as described by Schwinn et al.[9]

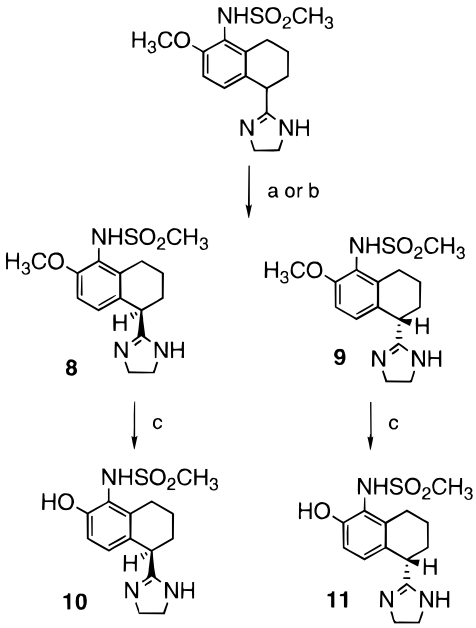
Resolution of **1** was performed as shown in Scheme 2. Fractional crystallization of the diastereomeric dibenzoyltartaric acid salts of the racemic methyl ether precursor **7**, followed by recrystallization until a constant rotation was obtained, yielded the resolved enantiomers **8** and **9**. Cleavage with BBr_3 yielded the (*R*) and (*S*) enantiomers **10** and **11**, respectively.

Results and Discussion

Radioligand binding affinities for the compounds described in this study were determined in either tissue-based receptor populations (rat submaxillary gland for α_{1A} binding site) or clonal cell lines derived from bovine for α_{1a}, hamster for α_{1b}, or rat for α_{1d}. The nomenclature conventions proposed by Bylund et al.,[6] Ford et al.,[7] and Hieble et al.,[8] in which pharmacologically defined receptors are capitalized and cloned receptors are designated with small letters, has been adopted. Also, as proposed by Bylund, Ford, and Hielbe, the α_{1c} nomenclature[9] has been replaced by α_{1a} and the α_{1d} nomenclature has been assigned to the binding site previously referred to as α_{1a} or $\alpha_{1a/d}$. Functional *in vitro* agonist activity was determined in the rat vas deferens and canine prostate for α_{1A} activity, rat spleen for α_{1B}, and the rat aorta for α_{1D}.[10,11] Results are compared to the standard α_1 agonists norepinephrine, phenylephrine, and oxymetazoline (Tables 1 and 2). Radioligand binding data for the prototypical α_{1a} selective antagonist 5-methylurapidil is included for comparison. Both the radioligand binding and functional assays support the characterization of **1** and its active (*R*) enantiomer **10** as highly selective and potent α_{1A} agonists. Radioligand binding affinity and *in vitro* functional activity were stereoselective, with the less active (*S*) enantiomer showing nearly 3 orders of magnitude weaker affinity to the α_{1A} binding site and greater than 3 orders of magnitude weaker activity in the *in vitro* dog prostate model. The relative potency of **1** vs the natural neurotransmitter NE is quite remarkable as well, showing >200-fold and 100-fold more potency in the rat vas deferens and isolated canine prostate models, respectively.

The enhanced potency and excellent selectivity for the α_{1A} subtype of the α-1 adrenergic receptor should make **1** and it active enantiomer **10** valuable pharmacological tools in further elucidating the role of adrenergic receptor subtypes in normal function and disease states.

Scheme 2[a]



[a] (a) (−)-Dibenzoyltartaric acid; (b) (+)-dibenzoyltartaric acid; (c) BBr_3, CH_2Cl_2.

Experimental Section

General. Melting points were determined with a Thomas Hoover melting point apparatus and are uncorrected. All spectral and analytical data were obtained through the Abbott analytical department. Elemental analyses were obtained from Robertson Microlit Laboratories, Inc., Madison, NJ. Analytical thin-layer chromatography was performed using 5 cm × 10 cm plates coated with a 0.25 mm thickness of silica gel containing F-254 indicator (E. Merck). Flash chromatography was performed with silica gel 60 (E. Merck 9285, 230−400 mesh).

3,4-Dihydro-6-methoxy-5-nitro-1(2*H*)-naphthalenone (3). 6-Methoxy-1-tetralone (176 g, 1.0 mol) was dissolved in acetic anhydride (900 mL) and was cooled in an ice bath. A solution of 90% HNO_3 (70 mL) in acetic acid (60 mL) was added dropwise over 1.75 h, keeping the reaction temperature at or below 5 °C. After 2 h of stirring at 0 °C, the resulting solid was collected by filtration and was washed with Et_2O (2×, 500 mL). The solid (197 g, a 1:1 mixture of the 5- and 7-nitromethoxytetralones) was recrystallized from 1.5 L of benzene. The resulting crystals (enriched in the 7-nitro isomer) were removed by filtration, and the filtrate was concentrated to dryness (97 g) and recrystallized from MeOH (3 L). The

Table 2. *In Vitro* Agonist Potencies (pEC_{50})[a]

compound	α_{1A} rat vas deferens	α_{1A} canine prostate	α_{1B} rat spleen	α_{1D} rat aorta
1	8.24 ± 0.15	7.66 ± 0.22	6.50 ± 0.23	5.59 ± 0.23
	(8)	(6)	(8)	(4)
	108%	91%	73%	100%
10	8.28 ± 0.13	8.25 ± 0.13	6.73 ± 0.44	5.99 ± 0.21
	(4)	(2)	(4)	(4)
	78%	63%	94%	103%
11	4.51 ± 0.57	4.61 ± 0.45	<4	<4
	(4)	(2)	(4)	(4)
	45%	24%	not quantifiable	not quantifiable
norepinephrine	5.93 ± 0.24	5.66 ± 0.49	4.99 ± 0.12	7.92 ± 0.46
	(4)	(4)	(8)	(3)
	105%	117%	215%	113%
phenylephrine	5.78 ± 0.23	5.53 ± 0.18	4.96 ± 0.27	6.81 ± 0.53
	(9)	(9)	(9)	(4)
	100%	100%	100%	100%
oxymetazoline	6.54 ± 0.67	6.46 ± 0.38	6.47 ± 1.24	5.08 ± 0.27
	(4)	(8)	(4)	(4)
	80%	71%	35%	83%

[a] Data are presented as pEC_{50} values followed by 95% confidence limits, number of determinations (in parentheses), and E_{max} as a percent response of the control agonist phenylephrine.

crystals (77 g) were collected by filtration and recrystallized again from MeOH (2.6 L) to yield 58 g (26%) of the title compound: mp 162−163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.11−2.20 (m, 2H), 2.64 (dd, J = 7, 6 Hz, 2H), 2.87 (t, J = 6 Hz, 2H), 3.97 (s, 3H), 7.01 (d, J = 9 Hz, 1H), 8.18 (d, J = 9 Hz, 1H); MS (DCI/NH_3) m/z 222 $(M + H)^+$, 239 $(M + NH_4)^+$. Anal. ($C_{11}H_{11}NO_4$) C, H, N.

3,4-Dihydro-6-methoxy-5-nitro-1-naphthalenecarbonitrile (4). To a suspension of **3** (58.0 g, 0.26 mol) in dry THF (600 mL) at 0 °C under N_2 was added 0.5 M LiCN in DMF (105 mL, 0.052 mol) followed by diethyl cyanophosphonate (80 mL, 0.52 mol). After 2.5 h of stirring at 0 °C, the reaction mixture was concentrated *in vacuo*. The resulting oil was partitioned between 2:1 Et_2O:EtOAc (750 mL) and H_2O (500 mL). The layers were separated, and the aqueous layer was extracted with 2:1 Et_2O:EtOAc (300 mL). The combined organics were washed with H_2O (500 mL) and brine (250 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was taken up in toluene (200 mL) and was added to a suspension of anhydrous *p*-toluenesulfonic acid (15 g) in toluene (600 mL). The reaction mixture was heated to 80 °C for 15 min, cooled, and partitioned between EtOAc (1 L) and cold 2.5 M NaOH (400 mL). The layers were separated, and the aqueous was extracted with EtOAc (500 mL). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and recrystallized from 250 mL of hot EtOAc. The crystals (40 g) were isolated, and the mother liquors were concentrated and chromatographed (1:1 hex:CH_2Cl_2, then CH_2Cl_2) to provide an additional 16 g of product [total yield, 56 g (93%)]: mp 163−165 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48−2.56 (m, 2H), 2.78 (t, J = 8 Hz, 2H), 3.92 (s, 3H), 6.85 (t, J = 5 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.53 (d, J = 9 Hz, 1H); MS (DCI/NH_3) m/z 248 $(M + NH_4)^+$. Anal. ($C_{12}H_{10}N_2O_3$) C, H, N.

5-Amino-1,2,3,4-tetrahydro-6-methoxy-1-naphthalenecarbonitrile (5). A solution of **4** (28 g, 0.12 mol) in 900 mL of EtOAc and 10% Pd/C (2.3 g) was stirred rapidly under an atmosphere of H_2 for 48 h at ambient temperature. The reaction was filtered and concentrated, and the product was recrystallized from EtOAc to yield 15 g of the title compound. Chromatography of the mother liquors (4:1 CH_2Cl_2:hexanes) provided an additional 6 g of **5** [total yield, 21 g (85%)]: mp 138−139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83−1.96 (m, 1H), 2.04−2.15 (m, 3H), 2.42−2.61 (m, 2H), 3.79 (bs, 2H), 3.85 (s, 3H), 3.89−3.96 (m, 1H), 6.72 (d, J = 9 Hz, 1H), 6.78 (d, J = 9 Hz, 1H); MS (DCI/NH_3) m/z 203 $(M + H)^+$. Anal. ($C_{12}H_{14}N_2O$) C, H, N.

***N*-(5-Cyano-5,6,7,8-tetrahydro-2-methoxy-1-naphthalenyl)methanesulfonamide (6).** To an solution of **5** (42 g, 0.21 mol) and pyridine (50 mL, 0.62 mol) in CH_2Cl_2 (750 mL) was added methanesulfonyl chloride (18 mL, 0.23 mol) over 5 min. Stirring was continued for 48 h. The reaction mixture, which was heterogeneous due to the precipitation of the product, was treated with 600 mL of 1 M HCl and 100 mL of EtOH. The organic layer was separated from the aqueous layer which contained solid product. The aqueous layer was extracted with 5:1 CH_2Cl_2:EtOH (3 × 600 mL). Solid product present in the combined organic layers was collected by filtration, and the filtrate was dried ($MgSO_4$), filtered, and concentrated. The combined products were treated with 800 mL of EtOH and heated to reflux for 30 min. The mixture was allowed to cool to room temperature, and the solid was collected by filtration, washed with EtOH, and dried under vacuum to yield 55 g (94%): mp 206−207 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73−1.87 (m, 1H), 1.89−2.04 (m, 1H), 2.04−2.20 (m, 2H), 2.98 (s, 3H), 3.05 (q, J = 7 Hz, 2H), 3.90 (s, 3H), 3.96 (t, J = 6 Hz, 1H), 5.94 (s, 1H), 6.87 (d, J = 9 Hz, 1H), 7.36 (d, J = 9 Hz, 1H); MS (DCI/NH_3) m/z 298 $(M + NH_4)^+$. Anal. ($C_{13}H_{16}N_2O_3S$) C, H, N.

***N*-[5-(4,5-Dihydro-1*H*-imidazol-2-yl)-5,6,7,8-tetrahydro-2-methoxy-1-naphthalenyl]methanesulfonamide (7).** The nitrile **6** (54.6 g, 0.19 mol) was dissolved in 1:1 MeOH:CH_2Cl_2 (3 L) and cooled to 0 °C. HCl gas was bubbled into the solution until saturated. After being stirred at ambient temperature for 18 h, the reaction mixture was concentrated to a solid and was dried under vacuum to remove the excess HCl. The solid was suspended in EtOH (1 L), and ethylenediamine (200 mL) was added. After 24 h of stirring at room temperature, the reaction mixture was concentrated to dryness and the product was recrystallized from MeOH. The solid (the free base of the imidazoline) was collected by filtration. The filtrate was concentrated and chromatographed (2% MeOH in CH_2Cl_2 saturated with NH_3). A total of 54.1 g (86%) of product was obtained: mp 203−205 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.57−1.72 (m, 1H), 1.87−2.08 (m, 3H), 2.85−3.07 (m, 2H), 2.99 (s, 1H), 3.48−3.68 (m, 4H), 3.79 (t, J = 7 Hz, 1H), 3.86 (s, 3H), 6.89 (d, J = 9 Hz, 1H), 7.07 (d, J = 9 Hz, 1H).

***(R)*-*N*-[5-(4,5-Dihydro-1*H*-imidazol-2-yl)-5,6,7,8-tetrahydro-2-methoxy-1-naphthalenyl]methanesulfonamide Hydrochloride (8).** The racemate **7** (44 g, 0.14 mol) and dibenzoyl-L-tartaric acid (49.4 g, 0.14 mol) were taken up in 500 mL of hot MeOH, and crystals were allowed to form at room temperature overnight. The crystals (85 g) were collected by filtration, washed with MeOH (300 mL), redissolved in 2 L of hot MeOH, and allowed to recrystallize overnight. A small sample was converted to its HCl salt (see general procedure below), and optical rotation was determined. Recrystallization was continued until no further change in rotation was observed. Two recrystallizations were generally sufficient. After two recrystallizations and conversion to its HCl salt, 13.2 g was obtained: mp 237−238 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.74−1.89 (m, 2H), 1.91−2.03 (m, 1H), 2.11−2.23 (m, 1H), 3.00 (t, J = 6 Hz, 2H), 3.04 (s, 3H), 3.89 (s, 3H), 3.91−3.99 (m, 4H), 4.14 (t, J = 7 Hz, 1H), 7.00 (d, J = 9 Hz, 1H), 7.12 (d, J = 9 Hz, 1H); MS (DCI/NH_3) m/z 324 $(M + H)^+$; $[\alpha]_D$ = +10.5° (c = 1.3, CH_3OH). Anal. ($C_{15}H_{22}ClN_3O_3S$) C, H, N.

General Procedure for Conversion of Dibenzoyltar-

tarate Salt to HCl Salt. The dibenzoyltartaric acid salt of the imidazoline (13.7 g, 19.6 mmol) was added portionwise to a stirred solution of 1 M HCl in Et_2O (30 mL) and MeOH (30 mL). The solution was filtered and rinsed through a cotton plug to remove particulate matter which accumulated during the previous recrystallizations. Et_2O (400 mL) was then added dropwise over 20 min to the stirred solution. After 30 min of standing, the HCl salt which had precipitated was collected by filtration and was washed repeatedly with Et_2O; 7.0 g (99%) was obtained.

(*S*)-*N*-[5-(4,5-Dihydro-1*H*-imidazol-2-yl)-5,6,7,8-tetrahydro-2-methoxy-1-naphthalenyl]methanesulfonamide Hydrochloride (9). Following a procedure identical to the one used for the (*R*) enantiomer, **7** (24 g, 74 mmol) was resolved using dibenzoyl-D-tartaric acid (26.1 g, 74 mmol) and was converted to the HCl salt. After two recrystallizations, 7.2 g of the title compound was obtained: mp 237−238 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.74−1.89 (m, 2H), 1.91−2.03 (m, 1H), 2.11−2.23 (m, 1H), 3.00 (t, J = 6 Hz, 2H), 3.04 (s, 3H), 3.89 (s, 3H), 3.91−3.99 (m, 4H), 4.14 (t, J = 7 Hz, 1H), 7.00 (d, J = 9 Hz, 1H), 7.12 (d, J = 9 Hz, 1H); MS (DCI/NH_3) m/z 324 (M + H)$^+$; $[\alpha]_D$ = −10.5° (c = 1.4, MeOH). Anal. ($C_{15}H_{22}ClN_3O_3S$) C, H, N.

(*R*)-*N*-[5-(4,5-Dihydro-1*H*-imidazol-2-yl)-5,6,7,8-tetrahydro-2-hydroxy-1-naphthalenyl]methanesulfonamide Hydrobromide (10). The methyl ether **8** (6.9 g, 19 mmol) was suspended in dry CH_2Cl_2 (500 mL) under N_2 and was cooled to −78 °C. BBr_3 (12.7 mL, 130 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C and was stirred at 0 °C for 3 h. The reaction mixture was cooled to −78 °C and quenched by the slow addition of MeOH (100 mL). The reaction mixture was allowed to warm to room temperature, diluted with MeOH, and concentrated to dryness. The residue was taken up in MeOH and concentrated several times in order to remove residual HBr. The product was recrystallized from EtOH to yield 4.9 g (65%) of the title compound: mp 244−246 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.73−1.86 (m, 2H), 1.90−2.02 (m, 1H), 2.09−2.21 (m, 1H), 2.98 (t, J = 6 Hz, 2H), 3.09 (s, 3H), 3.89−3.98 (m, 4H), 4.09 (t, J = 6 Hz, 1H), 6.82 (d, J = 9 Hz, 1H), 6.95 (dd, J = 9, 1 Hz, 1H); MS (DCI/NH_3) m/z 310 (M + H)$^+$; $[\alpha]_D$ = +24.1° (c = 1.16, MeOH). Anal. ($C_{14}H_{20}BrN_3O_3S$) C, H, N.

(*S*)-*N*-[5-(4,5-Dihydro-1*H*-imidazol-2-yl)-5,6,7,8-tetrahydro-2-hydroxy-1-naphthalenyl]methanesulfonamide Hydrobromide (11). Following a procedure identical to the one used for the (*R*) enantiomer, **9** (7.2 g, 0.020 mol) provided 6.6 g (85%) of the title compound: mp 244−245 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.73−1.86 (m, 2H), 1.90−2.02 (m, 1H), 2.09−2.21 (m, 1H), 2.98 (t, J = 6 Hz, 2H), 3.09 (s, 3H), 3.89−3.98 (m, 4H), 4.09 (t, J = 6 Hz, 1H), 6.82 (d, J = 9 Hz, 1H), 6.95 (dd, J = 9, 1 Hz, 1H); MS (DCI/NH_3) m/z 310 (M + H)$^+$; $[\alpha]_D$ = −24.1° (c = 1.4, MeOH). Anal. ($C_{14}H_{20}BrN_3O_3S$) C, H, N.

***N*-[5-(4,5-Dihydro-1*H*-imidazol-2-yl)-5,6,7,8-tetrahydro-2-hydroxy-1-naphthalenyl]methanesulfonamide Hydrobromide (1).** Following a procedure identical to the one used for the (*R*) enantiomer, **7** (1.53 g, 0.0047 mol) provided 1.60 g (85%) of the title compound: mp 261−262 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.73−1.86 (m, 2H), 1.90−2.02 (m, 1H), 2.09−2.21 (m, 1H), 2.98 (t, J = 6 Hz, 2H), 3.09 (s, 3H), 3.89−3.98 (m, 4H), 4.09 (t, J = 6 Hz, 1H), 6.82 (d, J = 9 Hz, 1H), 6.95 (dd, J = 9, 1 Hz, 1H); MS (DCI/NH_3) m/z 310 (M + H)$^+$. Anal. ($C_{14}H_{20}BrN_3O_3S$) C, H, N.

References

(1) Knepper, S. M.; Bucker, S. A.; Brune, M. E.; DeBernardis, J. F.; Meyer, M. D.; Hancock, A. A. A-61603, A Potent Alpha-1-Adrenergic Receptor Agonist, Selective For The Alpha-1a Receptor Subtype. *J. Pharmacol. Exp. Ther.* **1995**, *274*, 97−103.

(2) Han, C.; Abel, P. W.; Minneman, K. P. Heterogeneity of α1-adrenergic receptors revealed by chloroethylclonidine. *Mol. Pharmacol.* **1987**, *32*, 505−510.

(3) Gross, G.; Hanft, G.; Rugevics, C. 5-Methyl-urapidil discriminates between subtypes of the α1-adrenoceptor. *Eur. J. Pharmacol.* **1988**, *151*, 333−335

(4) Cotecchia, S.; Schwinn, D. A.; Randall, R. R.; Lefkowitz, R. J.; Caron, M. G.; Koblika, B. K. Molecular cloning and expression of the cDNA for the hamster α1-adrenergic receptor. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 7159−7163.

(5) Perez, D. M.; Piascik, M. T.; Graham, R. M. Solution-phase library screening for the identification of rare clones: Isolation of an α-1D-adrenergic receptor cDNA. *Mol. Pharmacol.* **1991**, *40*, 876−883.

(6) Bylund, D. B.; Eikenberg, D. C.; Hieble, J. P.; Langer, S. Z.; Lefkowitz, R. J.; Minneman, K. P.; Molinoff, P. B.; Ruffolo, R. R.; Trendelenburg, U. International Union of Pharmacology Nomenclature of Adrenoceptors. *Pharmacol. Rev.* **1994**, *46*, 121−136.

(7) Ford, A. P. D.; Williams, T. J.; Blue, D. R.; Clarke, D. E. α-1 Adrenoceptor classification: Sharpening Occam's Razor. *Trends Pharmacol. Sci.* **1994**, *15*, 167−170.

(8) Hieble, J. P.; Bylund, D. B.; Clarke, D. E.; Eikenburg, D. C.; Langer, S. Z.; Lefkowitz, R. J.; Minneman, K. P.; Ruffolo, R. R., Jr. International Union of Pharmacology. X. Recommendation for Nomenclature of Alpha 1-adrenoceptors: Consensus Update. *Pharmacol. Rev.* **1995**, *47*, 267−270.

(9) Schwinn, D. A.; Lomasney, J. W.; Lorenz, W.; Szklut, P. J.; Fremeau, R. T., Jr.; Yang-Feng, T. L.; Caron, M. G.; Lefkowitz, R. J.; Cotecchia, S. Molecular cloning and expression of the cDNA for a novel α1-adrenergic receptor subtype. *J. Biol. Chem.* **1990**, *265*, 8183−8189.

(10) Aboud, R.; Shaffii, M.; Docherty, J. R. Investigation of the subtypes of α-1 adrenoceptors mediating contractions of rat aorta, vas deferens and spleen. *Br. J. Pharmacol.* **1993**, *109*, 80−87.

(11) Buckner, S. A.; Oheim, K.; Morse, P.; Knepper, S.; Hancock, A. A. Alpha-1-Adrenoceptor Induced Contractility in Rat Aorta is Mediated by the $Alpha_{1D}$ Subtype. *Eur. J. Pharmacol.* **1996**, *297*, 241−248.

JM960354U