Synthesis and Pharmacological Characterization of 1-Phenyl-, 4-Phenyl-, and 1-Benzyl-1,2,3,4-tetrahydroisoquinolines as Dopamine Receptor Ligands

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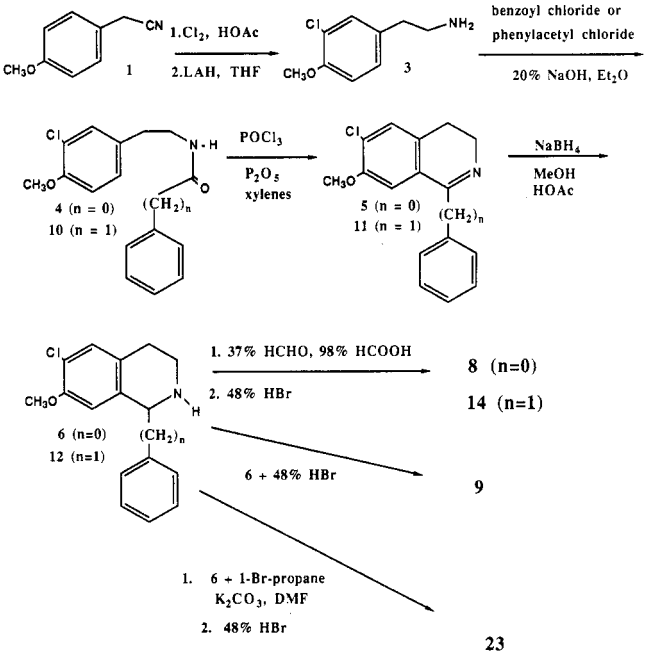
A series of 1-phenyl-, 4-phenyl-, and 1-benzyl-1,2,3,4-tetrahydroisoquinolines have been prepared as ring-contracted analogues of the prototypical D_1 dopamine receptor antagonist SCH23390 [(*R*)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine]. The affinity and selectivity of these isoquinolines for D_1 receptors was determined by three biochemical endpoints in membrane homogenates prepared from rat corpus striatum: the potency to compete for [^{3}H]SCH23390 binding sites; the potency to compete for [^{3}H]spiperone (a D_2 receptor ligand) binding sites; and effects on dopamine-stimulated adenylate cyclase. Competitive binding measurements at D_1 sites showed SCH23390 to possess the highest affinity, followed by 1-phenyl > 1-benzyl > 4-phenyl for the isoquinolines. These results were highly correlated with the ability of the test compounds to antagonize dopamine-stimulated adenylate cyclase (r = 0.98). None of the compounds alone stimulated cAMP formation at concentrations of 10 nM to 100 μM. D_2 competition binding showed the 1-benzyl derivative to possess the highest affinity, followed by 4-phenyl > SCH23390 > 1-phenyl. The tertiary 1-phenyl derivative was more potent than the secondary 1-phenyl analogue in all assays. Interestingly, resolution and single-crystal X-ray analysis of the tertiary *N*-methyl-1-phenyltetrahydroisoquinoline showed the most active enantiomer to possess the *S* absolute configuration, in contrast to the benzazepine (*R*)-SCH23390.

The most accepted classification of dopamine receptors is that of Kebabian and Calne,[1] who divided these receptors on the basis of their biochemical characteristics. The D_1 class was defined as that linked to the stimulation of cAMP synthesis by dopamine, whereas the D_2 class was the one at which dopamine agonists and antipsychotic (neuroleptic) drugs were thought to act to cause their characteristic neurochemical and neurobehavioral effects.[1-6] However, such hypotheses were based on largely indirect evidence and were not reconcilable with many observations. One problem, the inavailability of a selective D_1 antagonist, was resolved with the discovery,[7] radiolabeling,[8] and characterization[9,10] of the potent and selective D_1 antagonist SCH23390 (Chart I). This benzazepine was found to act biochemically to inhibit dopamine-stimulated adenylate cyclase (DSAC)[11,12] and behaviorally to block amphetamine-induced locomotor activity and apomorphine-induced stereotypy.[13,14] Because inhibition of DSAC was not believed to be involved in the neurobehavioral effects mediated by antipsychotic drugs,[3,15,16] it has been hypothesized that there may be some D_1 receptors that are not associated with cAMP synthesis yet are involved in mediating antidopaminergic behavioral effects.[17] More recently, the functional interdependence of D_1 and D_2 receptors in terms of agonist activity has also been described.[17,18]

Investigations into the structural requirements of selective D_1 antagonists have shown that benzazepine derivatives such as SCH23390 are the most potent compounds presently known.[17,19,20] The thioxanthenes, although competitive antagonists at D_1 sites, also show affinity for D_2 sites.[21] A perusal of the current literature revealed the conspicuous absence of tetrahydroisoquinoline derivatives possessing a similar substituent pattern to SCH23390. For this reason, the ring-contracted 1-phenyl, 4-phenyl, and 1-benzyl derivatives of SCH23390 were synthesized and evaluated for their affinities at both D_1 and D_2 receptor sites as well as their abilities to inhibit dopamine-stimulated adenylate cyclase.

Scheme I. Synthesis of 1-Phenyl- and 1-Benzyltetrahydroisoquinolines



Scheme II. Synthesis of 4-Phenyltetrahydroisoquinolines

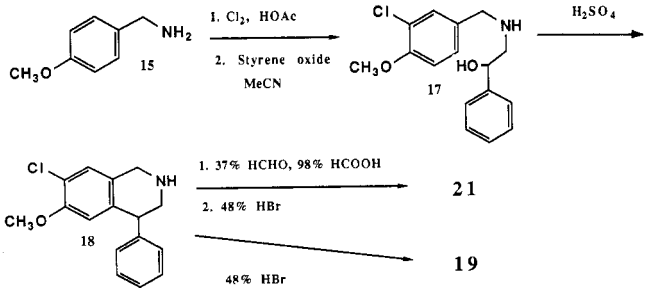


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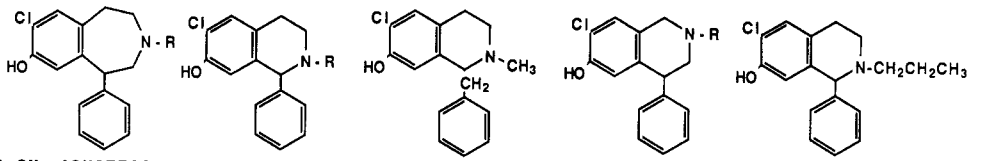
Chart I. Test Compounds



Chemistry

Scheme I outlines the synthesis of racemic **8**, **9**, **14**, and **23** while Scheme II outlines the synthesis of racemic **19** and **21**. Racemic **8** and **14** were synthesized by acylation of **3** followed by Bischler–Napieralski cyclization[22] to afford **5** and **11**. Reduction to the tetrahydroisoquinolines **6** and **12** followed by Eschweiler–Clarke N-methylation[23] afforded **7** and **13**. O-Demethylation of **6**, **7**, and **13** according to the method of Gold and Chang[7] provided the target molecules **9**, **8**, and **14**, respectively.

The synthesis of **21** involved chlorination of **15** followed by reaction with styrene oxide to afford **17**. Acid-catalyzed ring closure to racemic **18** followed by O-demethylation gave compound **19**. Eschweiler–Clarke N-methylation of **18** followed by O-demethylation gave **21**.

Resolution of racemic **8** was accomplished at intermediate **6** by the fractional recrystallization of the diastereomeric *N*-acetyl-D-leucine salts, which has been applied to a class of similarly substituted benzazepines.[7] The (+)-enantiomer of **6** having been obtained allowed for the further resolution of (−)-**6** with *N*-acetyl-L-leucine. Both (−)- and (+)-**6** were then carried through the remainder of the synthesis as previously described to afford (+)- and (−)-**8** as well as (−)- and (+)-**9**, respectively. Compound

Table I. D_1 and D_2 Receptor Affinities and Adenylate Cyclase Inhibitory Potency of Tetrahydroisoquinoline Derivatives

compd	competition for binding site: [^{3}H]-SCH23390[a]	competition for binding site: [^{3}H]-spiperone[b]	D_1 selectivity D_2/D_1	inhibn of DSAC[c]
(±)-**8**	12.5 ± 0.8	915 ± 107	73.2	8.98 ± 1.46
(*S*)-(+)-**8**	6.6 ± 0.7	1850 ± 240	280	6.58 ± 0.83
(*R*)-(−)-**8**	442 ± 27	19200 ± 430	43.4	568 ± 203
(*R*)-(+)-**9**	743 ± 76	26300 ± 1300	35.4	1205 ± 60
(*S*)-(−)-**9**	140 ± 12	3750 ± 270	26.7	109 ± 6
(±)-**14**	53.2 ± 4.0	287 ± 32	5.39	12.5 ± 1.9
(±)-**19**	565 ± 61	3620 ± 600	6.41	1257 ± 272
(±)-**21**	174 ± 17	522 ± 108	3.00	205 ± 14
(*S*)-(+)-**23**	179 ± 5	1900 ± 100	10.6	202 ± 53
SCH23390	0.43 ± 0.04	900[d]	2093	0.47 ± 0.06
SCH24518	2.35 ± 0.29	676 ± 38	288	0.94 ± 0.16
CPZ	50[d]	4.97 ± 0.55	0.10	79[d]

[a] All values expressed as a mean K_i (nM) value ± SEM. Initial concentration of [^{3}H]SCH23390 = 0.25 nM. [b] All values expressed as a mean K_i (nM) value ± SEM. Initial concentration of [^{3}H]-spiperone = 0.02 nM. [c] All values expressed as a mean K_i (nM) value ± SEM. Inhibition determined from the conversion of [^{32}P]ATP to [^{32}P]cAMP. Adenylate cyclase obtained from rat corpus striatum. [d] See ref 25.

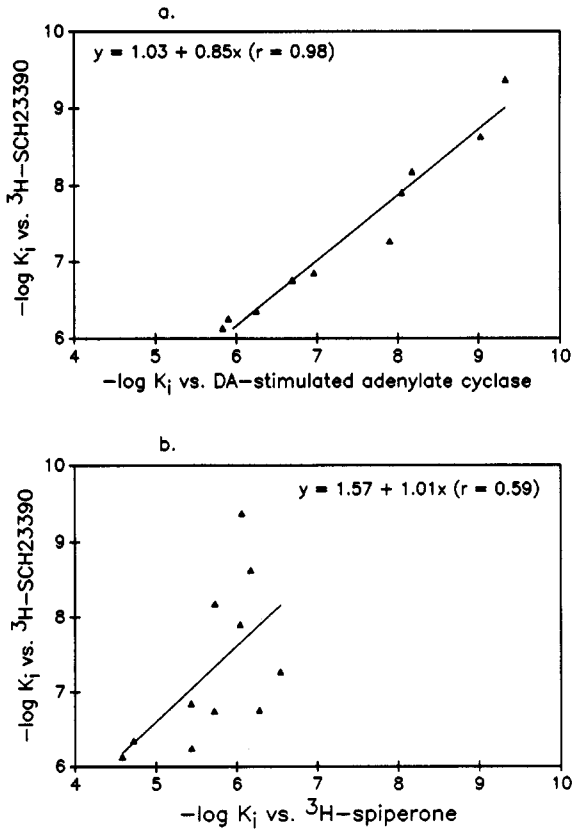


Figure 1.

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(+)-23 was synthesized from (−)-6 via alkylation followed by O-demethylation. Assignment of absolute configuration by single-crystal X-ray analysis showed (−)-6, (+)-7, (+)-8, (−)-9, and (+)-23 to be the *S* enantiomers whereas (+)-6, (−)-7, (−)-8, and (+)-9 were the *R* antipodes.

Results and Discussion

The tetrahydroisoquinolines described in this paper were evaluated in competition binding studies using selective D_1 and D_2 dopamine receptor ligands. The ability to inhibit dopamine-stimulated adenylate cyclase was also determined. Many of the conclusions drawn from this work are supportive of earlier studies performed on a class of similarly substituted benzazepines.[24] Table I shows these data. The 1-phenyl- and 1-benzyltetrahydroisoquinolines were generally more potent than the 4-phenyltetrahydroisoquinolines at D_1 sites. It is evident from these data that (*S*)-(+)-8 was the most potent competitor of [^{3}H]SCH23390 binding. None of the compounds tested had significant D_2 affinity; compound **14** had the highest affinity at D_2 sites with a K_i of approximately 300 nM, followed by the 4-phenyl derivative, **21**. Interestingly, (*S*)-(+)-8 showed even lower affinity for D_2 sites than SCH23390. Figure 1b shows a linear regression analysis of D_1 vs D_2 competition binding. No significant correlation (r = 0.59) exists between competition for D_1 sites and competition for D_2 sites. Figure 1a shows a significant correlation (r = 0.98) between competition for [^{3}H]-SCH23390 sites and ability to inhibit DSAC with (*S*)-(+)-8 possessing the greatest D_1 antagonist potency. It should also be noted that none of the compounds mentioned in this text had D_1 agonist potency in the 10 nM to 100 μM concentration range as evidenced by their lack of ability to stimulate cAMP synthesis. Even the normethyl derivatives **9** and **19** were inactive as agonists at all concentrations tested.

Aside from the obvious structural similarities with the benzazepines (i.e., a one carbon atom difference), tetrahydroisoquinolines as dopaminergic ligands are an interesting class of compounds. Certain naturally occurring, berbine-like tetrahydroisoquinoline alkaloids from the Papaveraceae family have been found to inhibit dopamine-stimulated adenylate cyclase.[27] It has also been proposed that tetrahydroisoquinolines can be formed endogenously in Parkinson's patients treated with large doses of *l*-Dopa concurrent with ethanol ingestion, or via acute ethanol ingestion alone.[28-30] As with benzazepine D_1 ligands, the tetrahydroisoquinolines share the structure–activity relationship of increasing antagonist potency by increasing N-substitution (i.e., 2° vs 3°). The corresponding normethyl derivative of (*S*)-(+)-8, (*S*)-(−)-**9**, was approximately 17 times less potent as a D_1 antagonist; SCH23390 is twice as potent a D_1 antagonist than its normethyl derivative, SCH24518. However, as with the benzazepine series, alkyl substituents > methyl (i.e., the *N*-propyl derivative, **23**) cause D_1 antagonist potency to decrease. It is evident that N-alkylation in the tetrahydroisoquinoline series also plays an important role in selectivity, as well as antagonist potency since (*S*)-(−)-**9** is 10-fold less selective for D_1 sites when compared with (*S*)-(+)-8. Similarly, SCH23390 is 7-fold more selective for D_1 sites than SCH24518.[24] The 7,8-dihydroxy normethyl derivative of SCH23390, SKF38393, is a partial agonist at D_1 sites, whereas the 7,8-dihydroxy-3-methyl derivative, SCH15379, has some antagonist potency, having a K_i of 6.7 nM for inhibition of DSAC.[24] The assumption that a halogen in the aromatic 6-position of the tetrahydroisoquinolines is similar to the 7-halo substituent in the benzazepine series and that this substitution pattern significantly contributes to D_1 antagonism has not been tested here in terms of analogue development, but has been addressed by utilizing computational methods (unpublished results). Nichols and co-workers have shown 4-(chlorohydroxyphenyl)tetrahydroisoquinolines to have micromolar D_1 antagonistic potency;[31] however, the chloro hydroxy substituent pattern with regard to the isoquinoline nucleus does not parallel that of the benzazepines.

Stereochemically, the tetrahydroisoquinolines have been shown in this report to behave oppositely to the benzazepines. It is the *R* enantiomers of the benzazepines that are the highly D_1 selective ligands; the *S* isomer of SCH23390, SCH23388, is competely inactive.[24] However, in the case of the tetrahydroisoquinolines examined here, it is the *S* enantiomers that are more competitive at [^{3}H]SCH23390 sites. This stereochemical trend also holds true in terms of D_1 selectivity (Table I). Thus (*S*)-(+)-8 is approximately 300 times more selective for D_1 sites vs D_2 sites, while (*R*)-8 had considerably less selectivity. In the benzazepine series it is the *R* isomers that possess D_1 selectivity.[24] In fact, it has been shown that the superimposition of (*S*)-(+)-8 upon (*R*)-SCH23390 results in a better RMS fit based on the key pharmacophoric atoms (Cl, N, O, center of phenyl ring) than for (*R*)-(−)-8 (unpublished results). It is hoped that this work will contribute to the emerging topographical description of D_1 dopamine receptors that are associated with [^{3}H]SCH23390 binding and will, in turn, help define better neurochemical and neurobehavioral effects of ligands affecting this site(s).

Experimental Section

All chemicals were used as obtained from the manufacturer. Melting points were recorded on a Mel-Temp melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a JEOL FX-60 60-MHz FT spectrometer (unless otherwise specified) using $CDCl_3$ (Me_4Si) as solvent. Only one NMR analysis per compound was reported, as the spectra of optical antipodes were virtually identical. Thin-layer chromatography was performed by using silica gel 60 coated plates, and column chromatography was performed with silica gel 60 (70–230 mesh). Centrifugal chromatography was carried out on a Harrison Research chromatotron using 2-mm silica plates. Elemental compositions of novel compounds were determined by mass spectrometry on an AEI MS-902 mass spectrometer and/or by elemental analyses that were performed by M-H-W Laboratories, Phoenix, AZ. The latter were correct within ±0.4% of theory. [^{3}H]SCH23390 (79 Ci/mmol) was synthesized by the method of Wyrick and Mailman.[9] [^{3}H]Spiperone was purchased from Amersham Corp. (Arlington Heights, IL). The hemimaleate salt of SCH23390 was provided as a gift by Schering Corp. (Bloomfield, NJ). Radioactivity was quantified by liquid scintillation counting on an LKB Model 1219 Rackbeta counter using Scintiverse E as cocktail. Calculations were performed on an IBM PC AT-compatible computer, using a series of Lotus 1,2,3 templates developed in this laboratory.

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3-Chloro-4-methoxyphenylacetonitrile (2). 4-Methoxyphenylacetonitrile (1) (42.4 g, 0.29 mol) was dissolved in 200 mL of HOAc. A solution of 30.8 g (0.44 mol) of Cl_2 in 300 mL of HOAc was slowly added in portions to the cooled solution of the nitrile (10–15 °C). The reaction mixture was stirred at room temperature for 30 min, and the HOAc was removed under reduced pressure. The reaction was repeated under the same conditions 27.1 g of nitrile, 0.184 mol; Cl_2 15.4 g, 0.218 mol), and the products were combined and distilled at 140–145 °C (0.1–0.2 mmHg) to give a total of 58.5 g (68%) of a brown oil which solidified at room temperature: mp 55–56 °C; ^{1}H NMR ($CDCl_3$) δ 7.32 (d, 1 H, Ar*H*2), 7.22 (q, 1 H, Ar*H*6), 6.90 (d, 1 H, Ar*H*5), 3.92 (s, 3 H, OCH_3), 3.69 (s, 2 H, $PhCH_2$).

3-Chloro-4-methoxyphenethylamine (3). $LiAlH_4$ (8.0 g, 0.21 mol) was suspended in 250 mL of dry THF in a three-neck, 2-L, round-bottom flask equipped with condenser and addition funnel. Compound **2** (31.9 g, 0.176 mol) in 100 mL of THF was added dropwise. The resultant greenish solution was then refluxed for 5 h. Ice water was cautiously added dropwise to inactivate any unreacted hydride. The mixture was filtered and the solid washed several times with Et_2O. The filtrates were dried (Na_2SO_4), filtered, and evaporated in vacuo to afford 33.8 g of a crude brown oil. Distillation (140 °C/0.6 mmHg) resulted in 11.4 g (35%) of a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.20 (d, 1 H, Ar*H*2), 7.04 (q, 1 H, Ar*H*6), 6.83 (d, 1 H, Ar*H*5), 3.88 (s, 3 H, OCH_3), 3.12–2.20 (m, 4 H, $PhCH_2CH_2N$), 1.28 (s, 2 H, NH_2).

***N*-Benzoyl-3-chloro-4-methoxyphenethylamine (4).** To a stirred solution of **3** (2.1 g, 11 mmol) in 75 mL of anhydrous Et_2O under N_2 was added 3.6 mL of 20% NaOH. Freshly distilled benzoyl chloride (1.59 g, 11 mmol) was added dropwise with stirring. A white precipitate formed immediately and the reaction was stirred at room temperature overnight. The colorless crystals were filtered, washed with ether, and dried in vacuo to afford 2.2 g (67%) of a colorless solid: mp 137–140 °C; ^{1}H NMR ($CDCl_3$) δ 7.85–6.78 (m, 8 H, Ar*H*), 3.88 (s, 3 H, OCH_3), 3.66 (t, 2 H, $PhCH_2CH_2N$), 3.04 (t, 2 H, $PhCH_2CH_2N$).

6-Chloro-7-methoxy-1-phenyl-3,4-dihydroisoquinoline (5). To a 250-mL, three-neck, round-bottom flask under N_2 was added **4** (4.1 g, 14 mmol) in 125 mL of dry xylenes. P_2O_5 (4.0 g, 28 mmol) was added in portions followed by the dropwise addition of freshly distilled $POCl_3$ (6.51 g, 42 mmol). The mixture was stirred at reflux under N_2 for 6 h followed by cooling to room temperature, and the xylenes were decanted. The solid residue was triturated with sufficient 10% NaOH to afford a suspension (pH 8–9). The suspension was extracted with CH_2Cl_2 and the organic extracts dried (Na_2SO_4) and evaporated in vacuo to afford 1.7 g (45%) of a reddish oil: ^{1}H NMR ($CDCl_3$) δ 7.46 (s, 5 H, Ar*H*), 7.27 (s, 1 H, Ar*H*5), 6.81 (s, 1 H, Ar*H*8), 4.10–3.50 (t, 2 H, $PhCH_2CH_2N$), 3.70 (s, 3 H, OCH_3), 3.15–2.50 (t, 2 H, $PhCH_2CH_2N$).

6-Chloro-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (6). To a three-neck, round-bottom flask equipped with a magnetic stirrer were added **5** (0.9 g, 3 mmol), 20 mL of MeOH, and 0.38 mL of HOAc under N_2. The solution was cooled to 5 °C, and $NaBH_4$ (0.4 g, 11 mmol) was added in portions. The solution was stirred for 1 h at room temperature, then at 50 °C for 4 h, then at room temperature overnight. Water (15 mL) was added, and the volatiles were evaporated in vacuo. The aqueous phase was extracted with 2 × 25 mL of CH_2Cl_2 and dried (Na_2SO_4), and the volatiles were removed in vacuo to afford 0.565 g of a crude yellow oil. Chromatography using 10 g of silica gel (CH_2Cl_2–MeOH, 95:5) gave 0.285 g (32%) of a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.29 (s, 5 H, Ar*H*), 7.15 (s, 1 H, Ar*H*5), 6.29 (s, 1 H, Ar*H*8), 5.04 (s, 1 H, Ph_2CHN), 3.63 (s, 3 H, OCH_3), 3.40–2.50 (m, 4 H, $PhCH_2CH_2N$), 1.91 (s, 1 H, NH); MS, *m/e* 273.0923 ($C_{16}H_{16}ClNO$ requires 273.0921).

***N*-Methyl-6-chloro-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (7).** Compound **6** (0.9 g, 3.3 mmol), 37% formaldehyde (4.3 mL), and 98% formic acid (6.6 mL) were stirred at reflux under N_2 for 4 h. The volatiles were removed in vacuo, and the remaining residue was adjusted to pH 8.0 with a saturated solution of $NaHCO_3$. The suspension was extracted with CH_2Cl_2, dried (Na_2SO_4), and evaporated in vacuo to afford 0.832 g of a crude yellow gum. Column chromatography using 25 g of silica gel (CH_2Cl_2–MeOH, 97:3) gave 0.611 g (65%) of a yellow solid. An analytical sample converted to the HCl salt and recrystallized from *i*-PrOH melted at 280–282 °C: ^{1}H NMR ($CDCl_3$) δ 7.67 (s, 1 H, Ar*H*5), 7.40–6.80 (m, 5 H, Ar*H*), 6.07 (s, 1 H, Ar*H*8), 4.12 (s, 1 H, Ph_2CHN), 3.80–3.50 (m, 2 H, $PhCH_2CH_2N$), 3.46 (s, 3 H, OCH_3), 3.20–2.35 (m, 2 H, $PhCH_2CH_2N$), 2.14 (s, 3 H, NCH_3); MS, *m/e* (low res) 287 ($C_{17}H_{18}ClNO$ requires 287). Anal. ($C_{17}H_{18}ClNO$) C, H.

***N*-Methyl-6-chloro-7-hydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (8).** Compound **7** (0.600 g, 1.2 mmol) and 48% HBr (12 mL) were heated at 100 °C with stirring for 12 h. The dark green solution was brought to pH 8.0 with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. The resultant 0.459 g of crude solid was chromatographed on a 10-g column of silica gel (CH_2Cl_2–MeOH, 95:5) to give a brownish solid, which was recrystallized from toluene–MeOH to give 0.213 g (65%) of a colorless solid: mp 188–190 °C; ^{1}H NMR ($CDCl_3$) δ 7.76 (s, 1 H, Ar*H*5), 7.50–6.80 (m, 5 H, Ar*H*), 6.11 (s, 1 H, Ar*H*8), 4.95 (br s, 1 H, OH), 4.12 (s, 1 H, Ph_2CHN), 3.20–2.18 (m, 4 H, $PhCH_2CH_2N$), 2.075 (s, 3 H, NCH_3); MS, *m/e* 273.0920 ($C_{16}H_{16}ClNO$ requires 273.0921). Anal. ($C_{16}H_{16}ClNO$) C, H, N.

***(R)*-(+)-6-Chloro-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline ((+)-6).** Racemic **6** (11.6 g, 42 mmol) and *N*-acetyl-D-leucine (7.0 g, 40 mmol) were dissolved under reflux in CH_3CN (216 mL). After the mixture was allowed to sit at room temperature overnight, the white solid was collected and washed with cold CH_3CN followed by Et_2O. The colorless diastereomeric salt mixture was dried in vacuo and the specific rotation determined. This process was repeated until a constant rotation of $[\alpha]^{25}_D$ +22.11° was obtained; mp 160–162 °C. The resultant 6.5 g of salt was stirred in 135 mL each of Et_2O and 0.5 N NaOH to obtain the free base. The Et_2O layer was separated, dried (Na_2SO_4), and evaporated in vacuo to afford 3.6 g of a colorless solid: mp 102–104 °C; $[\alpha]^{25}_D$ +36.70°.

***(S)*-6-Chloro-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline ((−)-6).** The combined mother liquors from the resolution of (+)-**6** were evaporated in vacuo, and the residue was converted to the free base with 250 mL each of Et_2O and 0.5 N NaOH with stirring. The ethereal solution was dried (Na_2SO_4) and evaporated in vacuo to afford 6.2 g of impure free base. Column chromatography on 150 g of silica gel (CH_2Cl_2–MeOH, 96:4) afforded 4.75 g (17 mmol) of a brown solid. This solid was refluxed with *N*-acetyl-L-leucine in 112 mL of CH_3CN for 45 min and allowed to sit at room temperature overnight. The resultant crystals were filtered, washed with cold CH_3CN followed by cold Et_2O, and dried in vacuo to give 5.5 g of a colorless solid. This process was repeated until a constant specific rotation of $[\alpha]^{25}_D$ −22.22° was obtained; mp 184–186 °C. This salt was converted to free base by stirring in 90 mL each of 0.5 N NaOH and Et_2O. The Et_2O layer was dried (Na_2SO_4) and evaporated in vacuo to give 2.4 g of a colorless solid: mp 102–104 °C; $[\alpha]^{25}_D$ −43.30°.

***(R)*-*N*-Methyl-6-chloro-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline ((−)-7).** Compound (+)-**6** (2.6 g, 9.5 mmol) was N-methylated with 98% formic acid (19 mL) and 37% formaldehyde (12.4 mL) as previously described for racemic **7** to give 1.9 g (70%) of a yellow solid: $[\alpha]^{25}_D$ −16.79°.

***(S)*-(+)-*N*-Methyl-6-chloro-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline ((+)-7).** Compound (−)-**6** (1.96 g, 7 mmol) was N-methylated with 98% formic acid (14.3 mL) and 37% formaldehyde (9.3 mL) as previously described for racemic **7** to give 2.1 g (100%) of a yellow oil: $[\alpha]^{25}_D$ +16.48°.

***(R)*-(−)-*N*-Methyl-6-chloro-7-hydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline ((−)-8).** Compound (−)-**7** (1.9 g, 6.6 mmol) was O-demethylated with 48% HBr (66 mL) as previously described for racemic **8** to give 0.764 g (42%) of colorless crystals: mp 172–174 °C; $[\alpha]^{25}_D$ −39.17°.

***(S)*-(+)-*N*-Methyl-6-chloro-7-hydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline ((+)-8).** Compound (+)-**7** (2.04 g, 7.1 mmol) was O-demethylated with 48% HBr (71 mL) as previously described for racemic **8** to give 1.19 g (61%) of a colorless solid: mp 168–172 °C; $[\alpha]^{25}_D$ +36.43°.

***(R)*-(+)-6-Chloro-7-hydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline ((+)-9).** Compound (+)-**6** (0.905 g, 3.3 mmol) was O-demethylated with 48% HBr (33 mL) as previously described for racemic **8** to give 0.099 g (12%) of colorless crystals: mp 162–164 °C; $[\alpha]^{25}_D$ +22.42°; ^{1}H NMR ($CDCl_3$) δ 7.30 (s, 5 H, Ar*H*), 7.13 (s, 1 H, Ar*H*5), 6.40 (s, 1 H, Ar*H*8), 5.02 (s, 1 H, *H*1), 3.28–2.68 (m, 4 H, $PhCH_2CH_2N$), 2.56 (br s, 2 H, O*H* and N*H*).

(S)-(−)-6-Chloro-7-hydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline ((−)-9). Compound (−)-6 (0.328 g, 1.2 mmol) was O-demethylated with 48% HBr (12 mL) as previously described for racemic 8 to give 0.14 g (45%) of colorless crystals: mp 164–166 °C; $[\alpha]^{25}_D$ −21.83°. Anal. ($C_{15}H_{14}ClNO$) C, H, N.

***N*-(Phenylacetyl)-3-chloro-4-methoxyphenethylamine (10).** To a stirred solution of crude 3 (30.2 g, 163 mmol) in Et_2O was added 20% NaOH (53.5 mL) followed by the dropwise, neat addition of phenylacetyl chloride (26.42 g, 171 mmol). After the mixture was allowed to sit at room temperature overnight, the volatiles were removed in vacuo to afford 37.0 g (75%) of a crude brown oil. Flash chromatography on 750 g of silica gel (CH_2Cl_2–MeOH, 95:5) gave 10.4 g of a brown solid: mp 74–75 °C; ^1H NMR ($CDCl_3$) δ 7.80–6.60 (m, 8 H, Ar*H*), 3.95 (s, 3 H, OCH_3), 3.61 (s, 2 H, benzylic *H*), 3.70–3.20 (t, 2 H, PhCH_2CH_2N), 2.90–2.50 (t, 2 H, PhCH_2CH_2N), 1.81 (s, 1 H, N*H*).

1-Benzyl-6-chloro-7-methoxy-3,4-dihydroisoquinoline (11). To a three-neck round-bottom flask equipped with a magnetic stirrer under N_2 was added compound 10 (10.36 g, 34 mmol) in 140 mL of hot, dry xylenes followed by the addition of P_2O_5 (9.66 g, 68 mmol). After the dropwise, neat addition of $POCl_3$ (44.85 g, 293 mmol), the mixture was refluxed for 12 h. The xylenes were decanted, and the resultant brown gum was suspended in and adjusted to pH 9.0 with 10% NaOH. After careful extraction with CH_2Cl_2, drying (Na_2SO_4), and removal of the volatiles in vacuo, 5.95 g of a crude brown gum remained. Flash chromatography on 130 g of silica gel (CH_2Cl_2–Et_2O, 9:1) afforded 1.54 g (16%) of a brown solid: ^1H NMR ($CDCl_3$) δ 7.22 (s, 5 H, Ar*H*), 7.11 (s, 1 H, Ar*H*5), 6.91 (s, 1 H, Ar*H*8), 4.01 (s, 3 H, OCH_3), 3.90–3.40 (t, 2 H, PhCH_2CH_2N), 3.69 (s, 2 H, benzylic *H*), 2.80–2.35 (t, 2 H, PhCH_2CH_2N).

1-Benzyl-6-chloro-7-methoxy-1,2,3,4-tetrahydroisoquinoline (12). To a solution of 11 (1.54 g, 5.4 mmol) in MeOH (41 mL) and HOAc (0.62 mL) was added cautiously $NaBH_4$ (0.68 g, 18 mmol) in small portions. The reaction mixture was refluxed for 10 h and then stirred at room temperature overnight. The volatiles were removed in vacuo, and the solid was adjusted to pH 8.0–9.0 with a saturated solution of $NaHCO_3$. Extraction with CH_2Cl_2, drying of the extracts (Na_2SO_4), and removal of the volatiles in vacuo gave 1.55 g of a crude brown gum. Column chromatography on 40.0 g of silica gel (CH_2Cl_2–MeOH, 96:4) afforded 0.743 g (48%) of a yellow gum: ^1H NMR ($CDCl_3$) δ 7.29 (s, 5 H, Ar*H*), 7.10 (s, 1 H, Ar*H*5), 6.60 (s, 1 H, Ar*H*8), 4.35–3.95 (m, 1 H, *H*1), 3.80 (s, 3 H, OCH_3), 3.35–2.45 (m, 6 H, PhCH_2CH_2N, benzylic *H*), 1.94 (s, 1 H, N*H*).

***N*-Methyl-1-benzyl-6-chloro-7-methoxy-1,2,3,4-tetrahydroisoquinoline (13).** A mixture of 12 (0.743 g, 2.6 mmol), 98% formic acid (5.3 mL), and 37% formaldehyde (3.5 mL) was stirred under reflux for 8 h. The volatiles were removed in vacuo, and the remaining gum was suspended and adjusted to pH 8.0–9.0 with saturated $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2; the extracts were dried (Na_2SO_4), and the volatiles removed in vacuo to afford 0.732 g of crude product. Chromatography on 15.0 g of silica gel (CH_2Cl_2–MeOH, 97:3) gave 0.525 g (67%) of a yellow oil: ^1H NMR ($CDCl_3$) δ 7.28 (s, 5 H, Ar*H*), 7.13 (s, 1 H, Ar*H*5), 6.01 (s, 1 H, Ar*H*8), 4.00–3.10 (dd, 1 H, *H*1), 3.53 (s, 3 H, OCH_3), 3.48–2.68 (m, 6 H, PhCH_2CH_2N, benzylic *H*), 2.61 (s, 3 H, NCH_3).

***N*-Methyl-1-benzyl-6-chloro-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (14).** Compound 13 (0.525 g, 1.7 mmol) and 48% HBr (17.9 mL) were stirred under reflux for 8 h. The mixture was adjusted to pH 8.0–9.0 with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2, and the extracts were dried (Na_2SO_4). The solvent was then evaporated in vacuo to afford 0.471 g of a tan solid. Column chromatography on 10.0 g of silica gel (CH_2Cl_2–MeOH, 95:5) gave 0.380 g (78%) of a colorless solid. An analytical sample recrystallized from toluene–MeOH melted at 174–176 °C: ^1H NMR ($CDCl_3$) δ 7.12 (s, 5 H, Ar*H*), 6.95 (s, 1 H, Ar*H*5), 6.20 (s, 1 H, Ar*H*8), 4.21 (br s, 1 H, O*H*), 3.80–3.35 (dd, 1 H, *H*1), 3.28–2.45 (m, 6 H, PhCH_2CH_2N, benzylic *H*), 2.38 (s, 3 H, NCH_3). Anal. ($C_{17}H_{18}ClNO$) C, H, N.

3-Chloro-4-methoxybenzylamine (16). A solution of Cl_2 (14.2 g, 0.20 mol) in 190 mL of HOAc was added dropwise to a stirred solution of 4-methoxybenzylamine (15) (25.0 g, 182 mmol) in 150 mL of HOAc. The reaction was allowed to stir at room temperature for 1 h, after which time the acetic acid was evaporated in vacuo. The resultant HCl salt was made alkaline with $NaHCO_3$ and then extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and evaporated in vacuo to afford an oil, which was distilled (110 °C/0.3 mmHg) to afford 10.6 g (34%) of a colorless oil: ^1H NMR ($CDCl_3$) δ 7.02 (m, 3 H, Ar*H*3), 3.88 (s, 3 H, CH_3O), 3.80 (s, 2 H, ArCH_2), 3.34 (s, 2 H, NH_2).

***N*-(3-Chloro-4-methoxybenzyl)-2-hydroxyphenethylamine (17).** Compound 16 (10.6 g, 62 mmol) and styrene oxide (7.5 g, 62 mmol) were dissolved in 75 mL of CH_3CN. The mixture was stirred at reflux for 16 h. The solvent was evaporated in vacuo to afford the crude product as an oil, which was chromatographed on a column of silica gel (CH_2Cl_2–MeOH–NH_4OH, 95:5:1) to afford 4.5 g (25%) of 17 as colorless crystals: mp 119–120 °C; ^1H NMR (DMSO-d_6) δ 7.3 (s, 5 H, Ar*H*5), 7.06 (m, 3 H, Ar*H*3), 4.72 (m, 1 H, HOC*H*CH$_2$), 3.86 (s, 3 H, CH_3O), 3.73 (s, 2 H, ArCH_2), 2.86 (d, 2 H, CH_2), 2.14 (s, 1 H, N*H*).

7-Chloro-6-methoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (18). To a stirred solution of H_2SO_4 (35 mL) was added 17 (4.5 g, 15 mmoles) while the temperature was maintained at ≤12 °C. After the addition was complete, the mixture was allowed to stir at room temperature for 2 h. The reaction was poured onto 500 mL of ice followed by the addition of NH_4OH (60 mL) and NaOH (23 g). The suspension was extracted with CH_2Cl_2; the extracts were dried (Na_2SO_4) and evaporated in vacuo to afford 3.9 g (92%) of 18 as a gum: ^1H NMR ($CDCl_3$) δ 7.2 (m, 5 H, Ar*H*5), 7.06 (s, 1 H, Ar*H*5), 6.48 (s, 1 H, Ar*H*8), 4.2 (t, 1 H, C*H*1), 3.72 (s, 3 H, CH_3O), 3.50 (s, 2 H, ArCH_2), 3.32 (d, 2 H, NHCH_2).

7-Chloro-6-hydroxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (19). Compound 18 (3.5 g, 12 mmol) was O-demethylated with 48% HBr (50 mL) as previously described for racemic 8. Recrystallization from benzene–MeOH gave 0.700 g (21%) of a yellow solid: mp 211–214 °C; ^1H NMR ($CDCl_3$) δ 7.18 (m, 5 H, Ar*H*5), 7.06 (s, 1 H, Ar*H*5), 6.52 (s, 1 H, Ar*H*8), 4.20 (t, 1 H, CH_1), 4.00 (s, 2 H, ArCH_2), 3.26 (d, 2 H, NHCH_2). Anal. ($C_{15}H_{14}ClNO$) C, H, N.

***N*-Methyl-7-chloro-6-methoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (20).** Compound 18 (3.0 g, 11 mmol) was N-methylated with 88% formic acid (9.2 mL) and 37% formaldehyde (6.0 mL) as previously described for racemic 7 to give 2.2 g (74%) of a colorless gum: ^1H NMR ($CDCl_3$) δ 7.23 (m, 5 H, Ar*H*5), 6.92 (s, 1 H, Ar*H*5), 6.38 (s, 1 H, Ar*H*8), 420 (t, 1 H, ArC*H*), 3.60 (s, 3 H, CH_3O), 3.50 (s, 2 H, ArCH_2), 2.90 (d, 2 H, NCH_2), 2.39 (s, 3 H, CH_3N).

***N*-Methyl-7-chloro-6-hydroxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (21).** Compound 20 (2.2 g, 7.6 mmol) was O-demethylated with 48% HBr (46 mL) as previously described for racemic 8. Recrystallization from MeOH gave 1.3 g (83%) of a colorless solid: mp 174–175 °C; ^1H NMR ($CDCl_3$) δ 7.26 (s, 5 H, Ar*H*5), 7.03 (d, 1 H, Ar*H*5), 6.44 (s, 1 H, Ar*H*8), 4.22 (t, 1 H, C*H*1), 3.61 (s, 2 H, CH_2), 3.50 (d, 2 H, NCH_2), 2.41 (s, 3 H, CH_3N). Anal. ($C_{16}H_{16}ClNO$) C, H, N.

(S)-(+)-*N*-Propyl-6-chloro-7-hydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (23). To a stirred solution of (−)-6 (0.08 g, 0.29 mmol) in dry DMF (4 mL) was added K_2CO_3 (0.05 g, 0.36 mmol) followed by the dropwise neat addition of 1-bromopropane (0.072 g, 0.59 mmol). The mixture was heated between 50 and 55 °C for 4 h. The resultant brown gum was purified via centrifugal chromatography (hexane–Et_2O, 9:1) to give 0.090 g (0.0285 mmol) (98%) of a brown solid which was O-demethylated as previously described for racemic 8 with 48% HBr (5 mL). Following alkalinization with $NaHCO_3$, extraction with CH_2Cl_2, drying (Na_2SO_4), and removal of the solvent in vacuo, 0.06 g of a crude tan solid was obtained. Centrifugal chromatography (CH_2Cl_2–MeOH, 95:5) afforded 0.048 g (56%) of a tan solid: mp 84–88 °C; $[\alpha]^{25}_D$ +55.31°; ^1H NMR ($CDCl_3$) δ 7.20 (s, 5 H, Ar*H*), 7.00 (s, 1 H, Ar*H*5), 6.20 (s, 1 H, Ar*H*8), 5.15 (br s, 1 H, O*H*), 4.40 (s, 1 H, Ph$_2$C*H*N), 3.10–1.85 (m, 6 H, CH_2CH_3), 1.65–1.10 (sextet, 2 H, CH$_2$CH_2CH$_3$), 0.75–0.51 (t, 3 H, CH_2CH$_2$CH$_3$); MS, *m/e* 301.1230 ($C_{20}H_{22}ClNO$ requires 301.1234).

Radioreceptor Assays. Adult male Sprague–Dawley rats were sacrificed by decapitation and the brains dissected rapidly on ice.[32] The corpus striatum of the animals was removed, frozen imme-

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diately on dry ice, and either used fresh or stored at −80 °C until used in binding studies. Striatal tissue was homogenized in 50 mM HEPES buffer (pH 7.4, 25 °C) at a Brinkman Polytron, PCU-2 setting of 3.0 for 5 s. The tissue suspension was then centrifuged at 32000*g* for 15 min, the supernatant discarded, and this wash step repeated. After the second wash the final pellet was resuspended at a wet weight concentration of 1.25 mg of tissue/mL of buffer for use. Radioligand binding was performed in 12 × 75 mm culture tubes at a total assay volume of 1.0 mL. Each tube contained 100 μL of competitor, 100 μL of radioligand, and 800 μL of tissue homogenate prepared as described above. Competing drugs were dissolved in 0.1% tartaric acid at 1.0 mM concentrations and diluted appropriately with buffer. [^{3}H]-SCH23390[9] and [^{3}H]spiperone,[33] at 0.25 and 0.02 nM concentrations, respectively, were diluted from methanol stock solutions with buffer. All tubes in the spiperone assays also contained a final concentration of 50 nM ketanserin in order to mask 5-HT$_2$ receptor binding. Reactions were initiated by the addition of tissue to tubes already containing radioligand and any competitors. The tubes, which were maintained on ice prior to the addition of tissue, were then vortexed and incubated at 37 °C for 15 min. Binding was terminated by rapid filtration over 1-μm glass fiber filters onto a Skatron cell harvester. IC_{50} values were calculated from a linear regression of a Hill transformation with all n_h values equal to 1 ± 0.1 for these compounds. Therefore, K_i values were calculated on the basis of the Cheng–Prusoff[34] relationship for competitive inhibition.

Adenylate Cyclase Assay. The effects of the test compounds on adenylate cyclase were determined by the method of Schulz and Mailman.[35] The conversion of [^{32}P]ATP to [^{32}P]cyclic AMP (cAMP) in striatal homogenates was quantified by using an automated preparative HPLC procedure, rather than column chromatography,[36] to separate cAMP from other labeled nucleotides. Striatal tissue (obtained as described earlier) was removed and homogenized at 50 mL/g tissue in 5.0 mM HEPES buffer (pH 7.5) containing 2.0 mM EGTA. After nine manual strokes with a Teflon–glass homogenizer, an additional 50 mL/g of 100 mM HEPES–2.0 mM EGTA was added and mixed with one additional stroke. A 20-μL aliquot of this tissue homogenate was added to a prepared reaction mixture, yielding a final volume of 100 μL containing 0.5 mM ATP, [^{32}P]ATP (0.5 μCi), 1.0 mM cAMP, 2.0 mM $MgCl_2$, 0.5 mM IBMX, 0.7 mM HEPES buffer, 2.0 μM GTP, 0–100 μM dopamine, 10 mM phosphocreatine, and 5.0 units of creatine phosphokinase. The reaction was initiated by placing the samples in a water bath at 30 °C and terminated 15 min later by adding 100 μL of 3% SDS. Drugs to be tested (e.g., varying concentrations of a test compound alone or in the presence of 100 μM dopamine) were added in an appropriate vehicle (usually 0.1% tartaric or 0.5 M hydrochloric acid). Subsequent to incubation, proteins and much of the noncyclic nucleotides were precipitated by addition of 300 μL each of 8.0% $ZnSO_4$ and 18% $Ba(OH)_2$ (pH 2.0) to each incubation tube. The samples were centrifuged at 10000*g* for 6 min, and the supernatants were immediately removed and loaded in an autoinjector. The HPLC separations described were carried out with a mobile phase of 100 mM sodium acetate–20% methanol (pH 5.0). A flow rate of 4.0–4.5 mL/min was used for separation. The autoinjector was programmed for a 2-min injection interval, with a rinse between samples. A UV detector equipped for 254 nm detection triggered collection of the cAMP fractions via a fraction collector and a three-way diversion valve. Unlabeled cAMP added to the samples provided the source of UV absorbance.

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Registry No. **1**, 104-47-2; **2**, 7569-58-6; **3**, 7569-87-1; **4**, 115514-67-5; **5**, 115514-68-6; (±)-**6**, 115514-69-7; (+)-**6**, 115589-10-1; (+)-**6**-(D)-*N*-acetylleucine, 115647-99-9; (−)-**6**, 115589-11-2; (−)-**6**-(L)-*N*-acetylleucine, 115648-00-5; (±)-**7**, 115514-70-0; (+)-**7**, 115589-13-4; (−)-**7**, 115589-12-3; (±)-**8**, 115514-71-1; (+)-**8**, 115589-15-6; (−)-**8**, 115589-14-5; (+)-**9**, 115514-85-7; (−)-**9**, 115514-86-8; **10**, 115514-72-2; **11**, 115514-73-3; **12**, 115514-74-4; **13**, 115514-75-5; **14**, 115514-76-6; **15**, 2393-23-9; **16**, 115514-77-7; **17**, 115514-78-8; **18**, 115514-79-9; **19**, 115514-80-2; **20**, 115514-81-3; **21**, 115514-82-4; **23**, 115514-84-6; **23** (O-methylated), 115514-83-5; styrene oxide, 96-09-3.

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Synthesis, Receptor Binding, and Tissue Distribution of (17α,20*E*)- and (17α,20*Z*)-21-[^{125}I]Iodo-19-norpregna-1,3,5(10),20-tetraene-3,17-diol[1]

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The isomeric (17α,20*E*)- and (17α,20*Z*)-(iodovinyl)estradiol derivatives **3** and **6**, and their no-carrier-added (nca) [^{125}I]iodovinyl analogues, were tested for their relative target tissue retention and binding affinity for the estrogen receptor. The (iodovinyl)estradiols **3** and **6** were prepared via destannylation of the (17α,20*E*)- and (17α,20*Z*)-tributylstannyl precursors **2** and **4** with retention of configuration. Selective formation of the *E* or *Z* isomers **2** and **4** during the reaction of 17α-ethynylestradiol **1a** with tri-*n*-butyltin hydride was controlled by the presence or absence of the catalyst, the polarity of the solvent, and the reaction temperature. The nca [^{125}I]iodovinyl analogues [^{125}I]-**3a** and [^{125}I]-**6a** were obtained in good radiochemical yield and high purity by treatment of **2a** and **4a** with [^{125}I]NaI in the presence of H_2O_2 and chloroamine-T, respectively. Of the two isomeric iodovinyl derivatives **3** and **6**, the 20*Z* isomer **6a** exhibited the highest receptor binding affinity and the [^{125}I]-**6a** gave the highest in vivo receptor-mediated target tissue uptake.

Among the various estrogen receptor based radiopharmaceuticals that have been advanced over the past years as possible imaging agents for breast cancer, 17α-iodovinyl derivatives of estradiol and 11β-methoxyestradiol showed the most promising properties. The established synthetic procedures for these 17α-iodovinyl estrogens mainly yield the 20*E* isomers, and, accordingly, only estrogen-receptor binding and in vivo distribution pattern of the latter isomer have been studied.[2-5] However, in the case of the analo-

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