Novel Agonists of $5HT_{2C}$ Receptors. Synthesis and Biological Evaluation of Substituted 2-(Indol-1-yl)-1-methylethylamines and 2-(Indeno[1,2-*b*]pyrrol-1-yl)-1-methylethylamines. Improved Therapeutics for Obsessive Compulsive Disorder†

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The syntheses of a series of substituted 2-(indol-1-yl)-1-methylethylamines and 2-(indeno[1,2-*b*]pyrrol-1-yl)-1-methylethylamines are reported. The binding affinities of the compounds at $5HT_{2C}$ and $5HT_{2A}$ receptors (79% homology in the transmembrane domain) were determined. The ligands displayed selectivity for $5HT_{2C}$ receptors relative to $5HT_{2A}$ receptors. Compounds were functionally characterized both *in vitro* and *in vivo* as $5HT_{2C}$ receptor agonists. **5f**, **5l**, **5n**, **5o**, **5q**, **14c**, **14f**, **14k**, and **14m** exhibited anticompulsive activity in an animal model of obsessive compulsive disorder.

Introduction

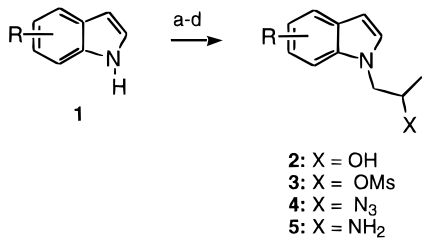
Selective serotonin reuptake inhibitors (SSRIs) increase extracellular levels of serotonin (5HT) and thereby nonselectively cause stimulation of all postsynaptic 5HT receptor subtypes. SSRIs have become standard therapy for neuropsychiatric disorders such as obsessive compulsive disorder (OCD), depression, and panic anxiety. There is accumulating evidence for the involvement of $5HT_{2C}$ receptor-mediated functions in the therapeutic efficacy of SSRIs.[1,2] The increased 5HT synaptic content resulting from the reuptake inhibition also allows 5HT to act on the other 5HT receptor subtypes, possibly explaining some of the side effects associated with SSRI treatment. Selective $5HT_{2C}$ receptor agonists, therefore, may represent a direct means to produce the beneficial therapeutic effects of SSRIs without concomitant side effects.

Our goal was to find $5HT_{2C}$ receptor agonists which (i) display at least 10-fold selectivity versus the $5HT_{2A}$ receptor subtype, for which sequence homology of the transmembrane region is high, (ii) show *in vivo* activity after oral administration in functional models of $5HT_{2C}$ receptor activation, and (iii) demonstrate therapeutic potential in an animal model of obsessive compulsive disorder.

Glennon et al. have shown that *N*,*N*-dimethylisotryptamines, i.e. derivatives of *N*,*N*-dimethyl-2-(indol-1-yl)ethylamines are isosteric with the corresponding *N*,*N*-dimethyltryptamines with respect to serotonin receptor affinity.[3] Such compounds are readily available via N-alkylation. We therefore screened isotryptamines for $5HT_{2C}$ receptor affinity and extended our study to the methylene homologues 1,4-dihydroindeno[1,2-*b*]pyrroles.

In this paper we report on the synthesis and the pharmacology of indoles and 1,4-dihydroindeno[1,2-*b*]-pyrroles in which a 2-aminopropyl side chain is attached to the N atom of the heterocycle. In analogy to phenylalkylamines, the α-methyl group was incorporated in order to suppress metabolic side chain deamination and to increase the lipophilicity of the compounds, allowing better CNS penetration.[4] Within these series of compounds we have identified agonists to the $5HT_{2C}$ receptor binding with high affinity and selectivity versus the $5HT_{2A}$ receptor. Some of these new ligands were evaluated in rats in the schedule-induced polydipsia paradigm, an animal model of obsessive compulsive disorder.[5] As a comparison we have included 5-fluoro-α-tryptamine (**15**) [6] and fluoxetine in our study.

Scheme 1[a]



[a] (a) Propylene oxide, NaH, THF; (b) MsCl, NEt_3, CH_2Cl_2; (c) NaN_3, DMF; (d) PtO_2, H_2, EtOH.

Chemistry

Substituted 2-(indol-1-yl)-1-methylethylamines **5** were prepared according to Scheme 1. Deprotonation of indoles **1** followed by alkylation with propylene oxide led to the secondary alcohols **2**. S_N2 reaction of the corresponding mesylates **3** with sodium azide and reduction of the azides **4** with either hydrogen or $LiAlH_4$ produced the amines **5** with excellent yields. The enantiomerically pure compounds **5k**−**q** were prepared from the (*R*)- or (*S*)-epoxide with inversion of configuration at the stereogenic center. The monosubstituted indoles are commercially available.

The dihalogenated building blocks can be prepared from the corresponding dihalogenated nitrotoluenes as described in the patent literature.[7] For the synthesis of 5-chloro-6-fluoroindole **1k** we have adopted a protocol developed by Wender and White[8] (Scheme 2). 2-Bromo-4-chloro-3-fluorophenylamine (**6**)[9] was acylated with trifluoroacetic anhydride to give **7**. Upon treatment with methyllithium and *tert*-butyllithium, a dilithium

† Dedicated to Prof. Dr. Dieter Seebach on the occasion of his 60th birthday.

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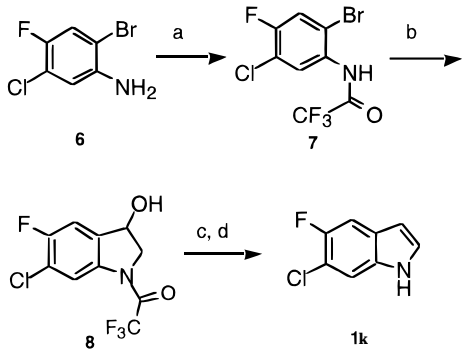
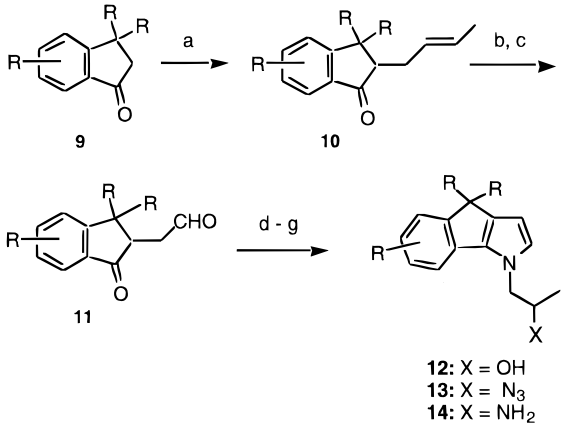
Scheme 2[a]



[a] (a) $(CF_3CO)_2O$, Na_2CO_3, diethyl ether; (b) MeLi, *t*-BuLi, −100 °C, chloroacetaldehyde, THF; (c) *p*-TsA, toluene; (d) NaOH, MeOH.

Scheme 3[a]



[a] (a) 3-Buten-2-ol, *p*-TsA, 2,2-dimethoxypropane; (b) ozone, CH_2Cl_2−MeOH; (c) TFA, CH_2Cl_2; (d) 1-amino-2-propanol, *p*-TsA, toluene; (e) MsCl, NEt_3, CH_2Cl_2; (f) NaN_3, DMF; (g) PtO_2, H_2, EtOH.

reagent was formed which underwent cyclization with chloroacetaldehyde[10] to the hydroxyamide **8**. Dehydration followed by hydrolysis gave **1k** in nine steps and an overall yield of 15%.

The preparation of the substituted 1,4-dihydroindeno-[1,2-*b*]pyrroles is shown in Scheme 3. Alkylation of the indan-1-ones **9** was performed by Claisen rearrangement of an *in situ* formed allyl vinyl ether system. Ozonolysis of **10** and subsequent cleavage of the acetal with TFA led to the 1,4-dicarbonyl compounds **11**, which were then reacted with commercially available 1-amino-2-propanol [(*S*), (*R*), (*RS*)] to yield the 1,4-dihydroindeno-[1,2-*b*]pyrroles **12**. The secondary alcohols were transformed into the amines **14** via the azides **13** as described for the synthesis of the indole derivatives **5**.

Pharmacology

The affinity of the compounds for 5HT$_{2C}$ and 5HT$_{2A}$ human receptors was assessed using displacement of [^{3}H]5HT and [^{3}H]DOB, respectively. To assess functional efficacy at 5HT$_{2C}$ receptors, the ligands were evaluated for stimulation of phosphoinositol turnover in the choroid plexus of the rat. The compounds were also assessed for induction of penile erection in rats which is a symptom of the serotonin syndrome reflecting 5HT$_{2C}$ receptor activation in rodents.[11] Finally, compounds which displayed interesting *in vivo* activity were further tested in the schedule-induced polydipsia model of OCD in rats for potential anticompulsive effects.[5]

Table 1. Substituents, Binding Affinities (pK_i) for 5HT$_{2A}$ and 5HT$_{2C}$ Receptors, Efficacy (pEC$_{50}$ and Intrinsic Activity) in Inducing IP$_3$ Formation *in Vitro*, and Selectivity Ratio 5HT$_{2C}$:5HT$_{2A}$ for **5**, **14**, and **15**

		pK_i		IP$_3$ formation		
compd	R	5HT$_{2A}$	5HT$_{2C}$	pEC$_{50}$	intrinsic activity	ratio
5a(*R*,*S*)	5-OMe	not tested	6.1 ± 0.03	5.0	0.3	
5b(*R*,*S*)	4- OMe	not tested	6.9 ± 0.08	4.9	0.3	
5c(*R*,*S*)	4-Me	7.0 ± 0.01	8.2 ± 0.08	5.6	0.6	16
5d(*R*,*S*)	4-F	6.8 ± 0.06	8.1 ± 0.03	5.9	0.7	20
5e(*R*,*S*)	5-Me	6.1 ± 0.01	7.2 ± 0.03	5.6	0.9	12.5
5f(*R*,*S*)	5-F	6.8 ± 0.02	8.2 ± 0.13	5.8	1	25
5g(*R*,*S*)	5-Cl	6.7 ± 0.04	8.1 ± 0.01	5.7	0.9	25
5h(*R*,*S*)	5-Br	6.8 ± 0.06	8.4 ± 0.07	5.7	0.8	40
5i(*R*,*S*)	6-Me	6.1 ± 0.01	7.8 ± 0.06	5.1	0.9	50
5j(*R*,*S*)	6-F	6.6 ± 0.05	8.4 ± 0.12	6.2	1	63
5k(*R*)	5-F,6-Cl	7.1 ± 0.02	8.0 ± 0.04	5.5	1	8
5l(*S*)	5-F,6-Cl	7.5 ± 0.04	8.9 ± 0.03	6.7	1	25
5m(*R*)	5-F,6-F	7.0 ± 0.03	8.4 ± 0.02	6.9	1	25
5n(*S*)	5-F,6-F	7.0 ± 0.02	9.0 ± 0.04	6.7	1	100
5o(*S*)	5-Cl,6-F	7.4 ± 0.02	8.7 ± 0.04	6.4	1	20
5p(*R*)	4-Cl,5-F	8.0 ± 0.03	8.9 ± 0.02	6.1	0.9	8
5q(*S*)	4-Cl,5-F	7.4 ± 0.03	8.9 ± 0.11	6.5	1	32
14a(*RS*)	5-OMe	5.5 ± 0.06	7.0 ± 0.01	inact		32
14b(*RS*)	6-OMe	6.4 ± 0.02	7.9 ± 0.04	5.7	1	32
14c(*RS*)	7-OMe	6.9 ± 0.06	9.0 ± 0.23	6.4	1	125
14d(*RS*)	8-OMe	6.4 ± 0.03	7.9 ± 0.08	5.2	0.7	32
14e(*R*)	7-OMe	6.9 ± 0.06	8.4 ± 0.04	5.1	0.8	32
14f(*S*)	7-OMe	6.9 ± 0.01	9.0 ± 0.2	6.6	1	125
14g(*S*)	7-F	6.7 ± 0.04	8.5 ± 0.05	6.2	1	63
14h(*S*)	7-Cl	6.7 ± 0.09	8.4 ± 0.02	5.6	0.8	50
14i(*S*)	7-Br	7.0 ± 0.03	8.4 ± 0.09	5.6	1	25
14j(*S*)	7-Me	7.2 ± 0.1	8.1 ± 0.08	6.3	1	8
14k(*S*)	4,4-Me, 7-Me	7.0 ± 0.04	8.5 ± 0.17	6.7	1	32
14l(*S*)	4,4-Me, 7-F	7.5 ±0.01	8.3 ± 0.09	6.7	1	6
14m(*S*)	4,4-Me, 7-OMe	8.0 ± 0.03	9.4 ± 0.1	7.0	1	25
15(*R*,*S*)		7.2 ± 0.02	8.2 ± 0.02	6.8	0.9	10

Table 2. ED$_{50}$ (mg/kg) for Inducing Penile Erection in Rats after sc or po Administration for **5**, **14**, and **15**

5a	>10 sc	**14a**	>10 sc
5b	>10 sc	**14b**	>10 sc
5c	3.2 sc, >30 po	**14c**	0.6 sc, 11 po
5d	>10 sc	**14d**	>10 sc
5e	>10 sc	**14e**	2 sc, >30 po
5f	1 sc, 2.7 po	**14f**	1.2 sc, 10 po
5g	2.3 sc, >30 po	**14g**	1.5 sc, >30 po
5h	4 sc, >30 po	**14h**	2.7 sc, >30 po
5i	3.3 sc, >30 po	**14i**	>10 sc
5j	0.3 sc, >30 po	**14j**	>10 sc
5k	2.1 sc, >30 po	**14k**	0.9 sc, 10 po
5l	0.5 sc, 5.5 po	**14l**	2.7 sc, >30 po
5m	2.7 sc, 30 po	**14m**	0.5 sc, 10 po
5n	0.3 sc, 10 po	**15**	0.8 sc, 9.9 po
5o	1 sc, 15 po		
5p	3.3 sc, inact po		
5q	2.7 sc, >30 po		

Results

The radioligand binding experiments (Table 1) showed higher affinity of the indoles **5** and the indeno[1,2-*b*]-pyrroles **14** for 5HT$_{2C}$ binding sites than for the structurally (79% homology between the transmembrane regions) very similar 5HT$_{2A}$ receptor. Compounds with halogen substituents in position 4, 5, and 6 of the indole ring possess higher affinities for this receptor subtype as compared to derivatives bearing electron-donating substituents such as methoxy and methyl groups. The dihalogenated indoles showed the highest 5HT$_{2C}$ receptor affinities. The (*S*)-enantiomers display higher af-

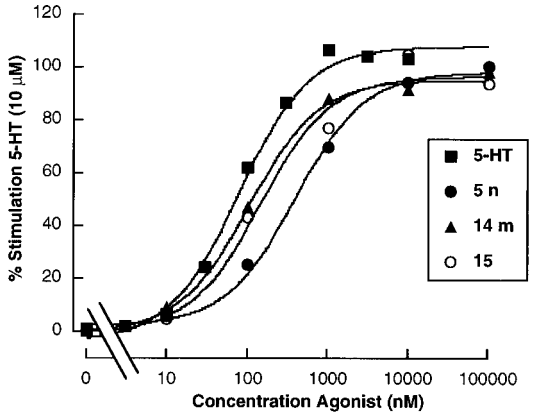
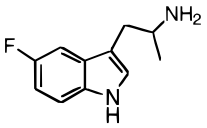


Figure 1. Effects of 5HT, **5n**, **14m**, and **15** on IP_3 formation in the rat choroid plexus. Results are expressed as percentage of the stimulation in IP_3 formation produced by 10 μM 5HT.

finity and selectivity for the $5HT_{2C}$ receptor as compared to their antipodes. Selectivity ratios of 20−100 were found for the (*S*)-configured isomers (e.g. **5l** and **5n**).

In the series of the indeno[1,2-*b*]pyrroles **14**, the optimal position for aromatic substitution turned out to be position 7. In contrast to the indoles, methoxy-substituted indeno[1,2-*b*]pyrroles (e.g. **14f** and **14m**) show increased affinities in comparison to the halogenated compounds and for the (*S*)-configured isomers selectivity ratios of up to 125 were observed.

For the study it was of interest to compare one of the potent and selective ligands with the structural isomer. The fluorinated tryptamine derivative **15** displays similar affinity for the $5HT_{2C}$ receptor as the isomer **5j**, but with reduced selectivity relative to the $5HT_{2A}$ receptor.



15

The effect of the $5HT_{2C}$ receptor ligands in stimulating phosphoinositol formation (cf. IP_3 formation, pEC_{50}, intrinsic activity, Table 1) was studied in rat choroid plexus. Compounds **5a**−**d**, **14a**, and **14d** induced only a submaximal increase whereas the maximum responses of the other derivatives **5e**−**q**, **14b**, **14c**, **14e**−**m**, and **15** were the same as that produced by 5HT (10^{-5} M, intrinsic activity = 1), suggesting that these ligands are full agonists at the $5HT_{2C}$ receptor (cf. **5n**, **14m**, and **15**, Figure 1). *In vivo* results, i.e. induction of penile erections, are presented in Table 2 (although not shown here, the reference compound fluoxetine was found to induce penile erection with ED_{50} = 4.3 mg/kg sc).

SSRIs such as fluoxetine are currently in use for the treatment of OCD. These drugs, however, exhibit a delayed onset of action and less than optimal therapeutic efficacy. Schedule-induced polydipsia in rats has been proposed as a model of OCD.[5] In this model, food-deprived rats which receive intermittently delivered food pellets on a fixed-time schedule typically develop a pattern of excessive drinking, i.e. polydipsia. This paradigm has been pharmacologically validated as a model of OCD. Experimental compounds are tested in this model for their ability to attenuate polydipsic behavior, i.e. for their potential anti-OCD effects. The

Table 3. Activity in Schedule-Induced Polydipsia Model in Rats

compd	min ED	max. suppression (%)	compd	min ED	max. suppression (%)
5f	3 ip	−97	**14c**	10 ip	−79
5l	10 ip	−90	**14f**	1 ip	−97
5n	3 ip	−73	**14k**	10 ip	−76
5o	3 ip	−88	**14m**	1 ip	−75
5q	3 ip	−97	fluoxetine	30 ip	−11
15	1 ip	−96			

selected $5HT_{2C}$ receptor agonists evaluated in the schedule-induced polydipsia model all significantly reduced the excessive drinking with MED values (minimal effective dose; i.e. the lowest dose tested which was found to statistically significantly reduce water intake relative to vehicle treatment) within the dose range 1−30 mg/kg (ip) with doses selected at half-logarithmic units (cf. Table 3). The magnitude of the suppression of polydipsia was compared among all of these compounds for the doses up to 10 mg/kg and was found to be 75% or more. In comparison, fluoxetine was much less potent, first achieving a statistically significant reduction in water intake of only 11% at 30 mg/kg ip (with no appreciable effect at doses up to 10 mg/kg ip).

Conclusions

Compounds were identified which exhibited high-affinity binding to human $5HT_{2C}$ receptors with selectivity versus $5HT_{2A}$ receptors. Such compounds were characterized *in vitro* and *in vivo* as $5HT_{2C}$ agonists. Two of these compounds underwent a broad binding evaluation: **5l** and **14k** exhibited affinity for several other 5HT receptor subtypes (1A, 3, 4, 6, 7) which was at least 2 logarithmic units lower than for $5HT_{2C}$ receptors and had $IC_{50} \geq 1$ μm for 26 other receptors across numerous different neurotransmitter systems (unpublished results). In the isolated rat fundus strip assay, both **5l** and **14k** act as agonists at the $5HT_{2B}$ receptor (pD_2 = 8.0 and 6.1, respectively; unpublished results). At present little is known concerning the physiological function of $5HT_{2B}$ receptors, due in part to the lack of highly selective ligands; interestingly a $5HT_{2C}$ receptor agonist which is structurally different from those described in this report and which exhibited antagonistic activity at the $5HT_{2B}$ receptor was also found to reduce schedule-induced polydipsia (unpublished results). Therefore the $5HT_{2B}$ receptor is unlikely to play a major role in the functional effects described here.

These $5HT_{2C}$ receptor agonists were found to significantly suppress schedule-induced polydipsia in rats, even at doses lacking any appreciable effects on spontaneous behavior. These results suggest that $5HT_{2C}$ receptor agonists may be of therapeutic value in OCD. In this respect, it is interesting to note that although fluoxetine was found to be active in this animal model of OCD, its potency was low when compared to the dose range producing adverse effects. $5HT_{2C}$ receptor agonists may, thus, potentially offer improved therapy of OCD.

Experimental Section

General. Melting points were determined in capillary tubes (Büchi 530 apparatus) and are uncorrected. Column chromatography was carried out by using silica gel (230−400

mesh; Merck) and 0.3−1.0 bar pressure. Spectra were recorded with the following instruments. IR (cm^{-1}): Nicolet-7199-FT-IR. ^{1}H-NMR (δ values in ppm relative to internal TMS, coupling constants J in Hertz): Bruker AC-250 (250 MHz). MS: MS9 updated with a Finnigan MAT data system SS 200. Elementary analyses (C, H, N) for novel compounds were within 0.4% of the theoretical values.

5-Methoxyindole, 4-methoxyindole, 4-methylindole, 5-methylindole, 5-fluoroindole, 5-chloroindole, 5-bromoindole, and 6-methylindole were purchased from Aldrich Chemicals; 4-fluoroindole and 6-fluoroindole, from Sigma; 5-methoxyindan-1-one and 6-methoxyindan-1-one, from Fluka.

Preparation of (*R*)-1-(6-Chloro-5-fluoroindol-1-yl)propan-2-ol (2l) (Standard Procedure A). To a mixture of sodium hydride (0.09 g, 3.7 mmol) in THF (15 mL) was added 6-chloro-5-fluoroindole (**1k**) (0.5 g, 3 mmol) at 0 °C. After 1 h (*R*)-propylene oxide (0.42 mL, 6 mmol) was added, and the mixture was stirred for 48 h at room temperature. The reaction was quenched with water, and the mixture was extracted with diethyl ether and washed with brine. The organic layer was dried, and the solvent was removed. The residue was subjected to chromatography (toluene/ethyl acetate, 19:1, as eluent) to yield **2l** (0.51 g, 74%) as white crystals: mp 104−105 °C; $[\alpha]^{20}_{436} = -60.4°$ (c = 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.26 (d, J = 6 Hz, 3 H), 1.61 (d, J = 5 Hz, 1 H), 3.96 (dd, J = 12.5 Hz, J = 8 Hz, 1 H), 4.12 (dd, J = 12.5 Hz, J = 3.7 Hz, 1 H), 4.20 (m, 1 H), 6.45 (d, J = 3.2 Hz, 1 H), 7.17 (d, J = 3.2 Hz, 1 H), 7.34 (d, J = 9.5 Hz, 1 H), 7.38 (d, J = 7.5 Hz, 1 H); MS (EI) m/z 227 (M^+), 182 (100). Anal. ($C_{11}H_{11}ClFNO$) C, H, N.

Preparation of (*S*)-1-(2-Azidopropyl)-6-chloro-5-fluoroindole (4l) (Standard Procedure B). To a solution of **2l** (0.28 g, 1.2 mmol) in dichloromethane (6 mL) and triethylamine (0.5 mL) was added methanesulfonyl chloride (0.2 mL, 2.5 mmol) at 0 °C. After 1 h ether was added and the mixture was extracted with 1 M sodium carbonate and washed with brine. The organic layer was dried, and the solvent was removed. The residue was taken up in DMF (6 mL), and sodium azide (0.16 g, 2.4 mmol) was added. The reaction mixture was heated for 7 h at 60 °C, poured into water, and extracted with ether. The organic layer was dried, and the solvent was removed. The residue was purified by column chromatography (toluene as eluent) to yield **4l** as yellow oil (0.29 g, 93%): ^{1}H NMR ($CDCl_3$) δ 1.30 (d, J = 6.2 Hz, 3 H), 3.90 (m, 1 H), 4.00 (dd, J = 15, 7 Hz, 1 H), 4.07 (dd, J = 15, 5 Hz, 1 H), 6.48 (d, J = 2.5 Hz, 1 H), 7.14 (d, J = 2.5 Hz, 1 H), 7.34 (d, J = 5 Hz, 1 H), 7.35 (d, J = 10 Hz, 1 H); MS (EI) m/z 252 (M^+), 182 (100).

Preparation of (S)-2-(6-Chloro-5-fluoroindol-1-yl)-1-methylethylamine Fumarate (1:1.6) (5l) (Standard Procedure C). A suspension of 0.02 g of PtO_2 in ethanol (5 mL) was stirred under hydrogen for 0.5 h. After the addition of a solution of **4l** (0.26 g, 1 mmol) in ethanol (5 mL), the mixture was stirred for 2 h, the catalyst was filtered off, and the solvent was removed. The salt was prepared in ether by treatment with fumaric acid to yield 0.25 g (59%) of **5l**: mp 169−171 °C; $[\alpha]^{20}_{436} = 31.6°$ (c = 0.25, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.10 (d, J = 5 Hz, 3 H), 3.51 (m, 1 H), 4.18 (dd, J = 14.5, 7.2 Hz, 1 H), 4.36 (dd, J = 14.5, 6.2 Hz, 1 H), 6.48 (d, J = 2.5 Hz, 1 H), 6.49 (s, 2 H), 7.40 (d, J = 2.5 Hz, 1 H), 7.35 (s, 1 H), 7.42 (d, J = 8 Hz, 1 H); MS (EI) m/z 226 (M^+), 183, 44 (100). Anal. ($C_{11}H_{12}FClN_2 \cdot 1.6C_4H_4O_4$) C, H, N.

Compounds **5a**−**k** and **5m**−**q** were synthesized according to standard procedures A, B, and C.

***(R,S)*-2-(5-Methoxyindol-1-yl)-1-methylethylamine fumarate (1:1) (5a):** 62%; mp 175−176 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.07 (d, J = 6.5 Hz, 3 H), 3.50 (sept, J = 6.5 Hz, 1 H), 3.74 (s, 3 H), 4.16 (dd, J = 15.3, 7.5 Hz, 1 H), 4.36 (dd, J = 15.3, 5.7 Hz, 1 H), 6.37 (d, J = 3 Hz, 1 H), 6.49 (s, 2 H), 6.78 (dd, J = 10, 2.5 Hz, 1 H), 7.05 (d, J = 2.5 Hz, 1 H), 7.33 (d, J = 3 Hz, 1 H), 7.45 (d, J = 10 Hz, 1 H); MS (EI) m/z 204 (M^+), 161, 44 (100). Anal. ($C_{12}H_{16}N_2O \cdot C_4H_4O_4$) C, H, N.

***(R,S)*-2-(4-Methoxyindol-1-yl)-1-methylethylamine fumarate (1:0.5) (5b):** 59%; mp 185−186 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.00 (d, J = 6.5 Hz, 3 H), 3.36 (sept, J = 6.5 Hz, 1 H), 3.86 (s, 1 H), 4.07 (dd, J = 15.3, 7 Hz, 1 H), 4.22 (dd, J = 15.3, 5 Hz, 1 H), 6.43 (d, J = 3 Hz, 1 H), 6.44 (s, 1 H), 6.52 (d, J = 7.5 Hz, 1 H), 7.05 (t, J = 7.5 Hz, 1 H), 7.13 (d, J = 7.5 Hz, 1 H), 7.25 (d, J = 3 Hz, 1 H); MS (EI) m/z 204 (M^+), 161, 44 (100). Anal. ($C_{12}H_{16}N_2O \cdot 0.5C_4H_4O_4$) C, H, N.

***(R,S)*-2-(4-Methylindol-1-yl)-1-methylethylamine fumarate (1:1) (5c):** 92%; mp 163−164 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.08 (d, J = 6.5 Hz, 3 H), 2.46 (s, 3 H), 3.52 (m, 1 H), 4.19 (dd, J = 14.2, 7.5 Hz, 1 H), 4.38 (dd, J = 14.2, 8.2 Hz, 1 H), 6.49 (s, 3 H), 6.83 (d, J = 7 Hz, 1 H), 7.04 (dd, J = 7.5, 7 Hz, 1 H), 7.37 (d, J = 3.2 Hz, 1 H), 7.37 (d, J = 7.5 Hz, 1 H); MS (EI) m/z 188 (M^+), 145, 44 (100). Anal. ($C_{12}H_{16}N_2 \cdot C_4H_4O_4$) C, H, N.

***(R,S)*-2-(4-Fluoroindol-1-yl)-1-methylethylamine fumarate (1:1) (5d):** mp 179−180 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.09 (d, J = 7.5 Hz, 3 H), 3.53 (m, 1 H), 4.24 (dd, J = 15, 7.2 Hz, 1 H), 4.42 (dd, J = 15, 7.5 Hz, 1 H), 6.49 (s, 2 H), 6.54 (d, J = 3 Hz, 1 H), 6.82 (dd, J = 8, 7.7 Hz, 1 H), 7.13 (m, 1 H), 7.43 (d, J = 9 Hz, 1 H), 7.46 (d, J = 3 Hz, 1 H); MS (EI) m/z 192 (M^+), 149, 44 (100). Anal. ($C_{11}H_{13}FN_2 \cdot C_4H_4O_4$) C, H, N.

***(R,S)*-2-(5-Methylindol-1-yl)-1-methylethylamine fumarate (1:1) (5e):** 87%; mp 165−167 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.06 (d, J = 6.5 Hz, 3 H), 2.36 (s, 3 H), 3.50 (m, 1 H), 4.18 (dd, J = 14.2, 7.5 Hz, 1 H), 4.38 (dd, J = 14.2, 5.7 Hz, 1 H), 6.36 (d, J = 3 Hz, 1 H), 6.49 (s, 3 H), 6.97 (d, J = 7 Hz, 1 H), 7.33 (dd, J = 7.5, 7 Hz, 1 H), 7.43 (d, J = 3.2 Hz, 1 H); MS (EI) m/z 188 (M^+), 145, 44 (100). Anal. ($C_{12}H_{16}N_2 \cdot C_4H_4O_4$) C, H, N.

***(R,S)*-2-(5-Fluoroindol-1-yl)-1-methylethylamine fumarate (1:1) (5f):** 95%; mp 169−170 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.08 (d, J = 6.5 Hz, 3 H), 3.52 (m, 1 H), 4.22 (dd, J = 14.5, 7.5 Hz, 1 H), 4.39 (dd, J = 14.5, 6 Hz, 1 H), 6.46 (d, J = 3 Hz, 1 H), 6.49 (s, 2 H), 7.00 (dt, J = 7.5, 2.5 Hz, 1 H), 7.32 (dd, J = 10, 2.5 Hz, 1 H), 7.47 (d, J = 3 Hz, 1 H), 7.58 (dd, J = 9, 4.5 Hz, 1 H); MS (EI) m/z 192 (M^+), 149, 44 (100). Anal. ($C_{11}H_{13}FN_2 \cdot C_4H_4O_4$) C, H, N.

***(R,S)*-2-(5-Chloroindol-1-yl)-1-methylethylamine fumarate (1:2) (5g):** mp 183−185 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.11 (d, J = 6.5 Hz, 3 H), 3.57 (m, 1 H), 4.25 (dd, J = 14.2, 7.5 Hz, 1 H), 4.42 (dd, J = 14.2, 6.2 Hz, 1 H), 6.48 (d, J = 3 Hz, 1 H), 6.54 (s, 2 H), 7.16 (dd, J = 7.5, 2.5 Hz, 1 H), 7.48 (d, J = 3 Hz, 1 H), 7.61 (d, J = 7.5 Hz, 1 H), 7.61 (d, J = 2.5 Hz, 1 H); MS (EI) m/z 208 (M^+), 165, 44 (100). Anal. ($C_{11}H_{13}ClN_2 \cdot 2C_4H_4O_4$) C, H, N.

***(R,S)*-2-(5-Bromoindol-1-yl)-1-methylethylamine fumarate (1:1) (5h):** 93%; mp 196−197 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.05 (d, J = 6.5 Hz, 3 H), 3.49 (m, 1 H), 4.20 (dd, J = 14.5, 7 Hz, 1 H), 4.36 (dd, J = 14.5, 6.2 Hz, 1 H), 6.46 (d, J = 3.2 Hz, 1 H), 6.49 (s, 2 H), 7.26 (dd, J = 8.7, 2 Hz, 1 H), 7.45 (d, J = 3.2 Hz, 1 H), 7.55 (d, J = 8.7 Hz, 1 H), 7.74 (d, J = 2 Hz, 1 H); MS (EI) m/z 252, 254 (M^+), 211, 209, 44 (100). Anal. ($C_{11}H_{13}BrN_2 \cdot C_4H_4O_4$) C, H, N.

***(R,S)*-2-(6-Methylindol-1-yl)-1-methylethylamine fumarate (1:1) (5i):** 60%; mp 152−153 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.09 (d, J = 6.5 Hz, 3 H), 2.41 (s, 3 H), 3.53 (m, 1 H), 4.16 (dd, J = 14.5, 7.5 Hz, 1 H), 4.36 (dd, J = 14.5, 5.7 Hz, 1 H), 6.39 (d, J = 3 Hz, 1 H), 6.50 (s, 2 H), 6.87 (d, J = 8 Hz, 1 H), 7.29 (d, J = 3 Hz, 1 H), 7.35 (s, 1 H), 7.42 (d, J = 8 Hz, 1 H); MS (EI) m/z 188 (M^+), 145, 44 (100). Anal. ($C_{12}H_{16}N_2 \cdot C_4H_4O_4$) C, H, N.

***(R,S)*-2-(6-Fluoroindol-1-yl)-1-methylethylamine fumarate (1:1) (5j):** 78%; mp 158−159 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.10 (d, J = 6.5 Hz, 3 H), 3.51 (m, 1 H), 4.18 (dd, J = 14.5, 7.2 Hz, 1 H), 4.36 (dd, J = 14.5, 6.2 Hz, 1 H), 6.48 (d, J = 2.5 Hz, 1 H), 6.49 (s, 2 H), 6.89 (dt, J = 8.7, 2.2 Hz, 1 H), 7.40 (d, J = 2.5 Hz, 1 H), 7.47 (dd, J = 10.5, 2.2 Hz, 1 H), 7.54 (dd, J = 8.7, 5.5 Hz, 1 H); MS (EI) m/z 192 (M^+), 149, 44 (100). Anal. ($C_{11}H_{13}FN_2 \cdot C_4H_4O_4$) C, H, N.

***(R)*-2-(6-Chloro-5-fluoroindol-1-yl)-1-methylethylamine fumarate (1:1.5) (5k):** 69%; mp 153−154 °C dec; $[\alpha]^{20}_{436} = -28.8°$ (c = 0.25, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.10 (d, J = 5 Hz, 3 H), 3.51 (m, 1 H), 4.18 (dd, J = 14.5, 7.2 Hz, 1 H), 4.36 (dd, J = 14.5, 6.2 Hz, 1 H), 6.48 (d, J = 2.5 Hz, 1 H), 6.49 (s, 2 H), 7.40 (d, J = 2.5 Hz, 1 H), 7.35 (s, 1 H), 7.42 (d, J = 8 Hz, 1 H). Anal. ($C_{11}H_{12}FClN_2 \cdot 1.5C_4H_4O_4$) C, H, N.

(*R*)-2-(5,6-Difluoroindol-1-yl)-1-methylethylamine fumarate (1:1) (5m): 82%; mp 161−162 °C dec; $[\alpha]^{20}_{436} = -34.4°$ (c = 0.25, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.09 (d, J = 6.5 Hz, 3 H), 3.49 (m, 1 H), 4.19 (dd, J = 14.5, 7 Hz, 1 H), 4.33 (dd, J = 14.5, 6.2 Hz, 1 H), 6.48 (d, J = 3.2 Hz, 1 H), 6.49 (s, 2 H), 7.47 (d, J = 3.2 Hz, 1 H), 7.54 (dd, J = 11.2, 7.5 Hz, 1 H), 7.74 (dd, J = 11.7, 7 Hz, 1 H); MS (EI) m/z 210 (M^+), 167, 166, 44 (100). Anal. ($C_{11}H_{12}F_2N_2 \cdot C_4H_4O_4$) C, H, N.

(*S*)-2-(5,6-Difluoroindol-1-yl)-1-methylethylamine fumarate (1:1) (5n): 84%; mp 159−160 °C dec; $[\alpha]^{20}_{436} = +35.2°$ (c = 0.25, MeOH). Anal. ($C_{11}H_{12}F_2N_2 \cdot C_4H_4O_4$) C, H, N.

(*S*)-2-(5-Chloro-6-fluoroindol-1-yl)-1-methylethylamine fumarate (1:1) (5o): mp 158−160 °C dec; $[\alpha]^{20}_{D} = +35.2°$ (c = 0.25, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.09 (d, J = 6.7 Hz, 3 H), 3.50 (m, 1 H), 4.20 (dd, J = 14.5, 7.5 Hz, 1 H), 4.34 (dd, J = 14.5, 6.5 Hz, 1 H), 6.49 (s, 2 H), 6.49 (d, J = 3.2 Hz, 1 H), 7.48 (d, J = 3.2 Hz, 1 H), 7.73 (d, J = 7.5 Hz, 1 H), 7.74 (d, J = 10 Hz, 1 H); MS (EI) m/z 226 (M^+), 183, 44 (100). Anal. ($C_{11}H_{12}FClN_2 \cdot C_4H_4O_4$) C, H, N.

(*R*)-2-(4-Chloro-5-fluoroindol-1-yl)-1-methylethylamine fumarate (1:1) (5p): 84%; mp 186−187 °C dec; $[\alpha]^{20}_{436} = -32.4°$ (c = 0.25, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.08 (d, J = 6.5 Hz, 3 H), 3.48 (m, 1 H), 4.23 (dd, J = 14.5, 7 Hz, 1 H), 4.36 (dd, J = 14.5, 6.5 Hz, 1 H), 6.49 (s, 2 H), 6.54 (d, J = 3.2 Hz, 1 H), 7.19 (t, J = 10 Hz, 1H), 7.60 (d, J = 3.2 Hz, 1 H), 7.42 (d, J = 8 Hz, 1 H); MS (EI) m/z 226 (M^+), 183, 44 (100). Anal. ($C_{11}H_{12}FClN_2 \cdot C_4H_4O_4$) C, H, N.

(*S*)-2-(4-Chloro-5-fluoroindol-1-yl)-1-methylethylamine fumarate (1:1) (5q): 84%; mp 183−184 °C dec; $[\alpha]^{20}_{436} = +32.4°$ (c = 0.25, MeOH). Anal. ($C_{11}H_{12}FClN_2 \cdot C_4H_4O_4$) C, H, N.

***N*-(2-Bromo-5-chloro-4-fluorophenyl)trifluoroacetamide (7).** To a solution of 2-bromo-4-chloro-3-fluorophenylamine (**6**) (111 g, 0.5 mol) in ether (990 mL) at 0 °C were added solid Na_2CO_3 (78 g) and trifluoroacetic anhydride (86 mL, 0.9 mol). After being warmed to room temperature the suspension was stirred for 2.5 h, diluted with ether, and extracted with water. The organic layer was separated and dried (sodium sulfate), and the solvent was removed. The residue was recrystallized from *n*-hexane to yield **7** as yellow crystals (136 g, 86%): mp 86−88 °C; ^{1}H NMR ($CDCl_3$) δ 7.45 (d, J = 7.6 Hz, 1 H), 8.46 (d, J = 7 Hz, 1 H); MS (EI) m/z 319, 321 (M^+), 240 (100). Anal. ($C_8H_3F_4ClBrNO$) C, H, N.

(*R,S*)-1-(Trifluoroacetyl)-6-chloro-5-fluoro-3-hydroxy-2,3-dihydro-1*H*-indole (8). A solution of **7** (24 g, 75 mmol) in THF (750 mL) was cooled to −100 °C. MeLi (75 mmol, 1.6 M in ether) was added, and 10 min later *t*-BuLi (150 mL, 1.7 M in pentane) was also added. After 1 h at −100 °C a solution of chloroacetaldehyde (67.5 mL, 1.7 M in THF) was added. The mixture was stirred at −78 °C for 4 h, and acetic acid (13 mL) was added. After the addition of triethylamine (52 mL), the reaction mixture was allowed to warm to ambient temperature and to stir for 14 h. Ammonium chloride solution (20%, 150 mL) was added, followed by extraction with ether. The organic layer was separated and dried (sodium sulfate), and the solvent was removed. The residue was purified by column chromatography (toluene/ethyl acetate, 19:1) to yield **8** (13g, 61%): mp 97.5−98 °C; ^{1}H NMR ($CDCl_3$) δ 2.36 (d, J = 7 Hz, 1 H), 5.37 (m, 1 H), 7.26 (d, J = 7.7 Hz, 1 H), 8.35 (d, J = 6.25 Hz, 1 H); MS (EI) m/z 283 (M^+), 186, 69 (100). Anal. ($C_{10}H_6F_4ClNO_2$) C, H, N.

6-Chloro-5-fluoroindole (1k). A solution of **8** (5.5 g, 19.5 mmol) and *p*-toluenesulfonic acid monohydrate (0.19 g, 0.9 mmol) in toluene (200 mL) was heated at reflux temperature for 2 h. The solvent was removed, and the residue was dissolved in methanol (800 mL). After the addition of NaOH (1 N, 800 mL), the mixture was refluxed for 2.5 h. Methanol was removed, and the crystals were filtered off and dried: yield 77%; mp 104−105 °C; ^{1}H NMR ($CDCl_3$) δ 6.50 (m, 1 H), 7.24 (m, 1 H), 7.36 (d, J = 9.5 Hz, 1 H), 7.41 (d, J = 6 Hz, 1 H); MS (EI) m/z 169 (M^+), 134, 107 (100).

Preparation of (*R,S*)-2-(2-Buten-1-yl)-3,3,6-trimethyl-1-indanone (10i) (Standard Procedure D). A solution of 3,3,6-trimethylindan-1-one (**9i**)[12−14] (18.9 g, 108 mmol), 3-buten-2-ol (22.4 mL, 0.26 mol), and *p*-toluenesulfonic acid (300 mg) in 2,2-dimethoxypropane (200 mL) was boiled under reflux for 64 h on a Dean−Stark trap filled with molecular sieves (0.4 nm, 2 mm pearl shaped). The solvents were evaporated, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 6:1) to give **10i** (12.7 g, 51%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3 H), 1.45 (s, 3 H), 1.69 (d, J = 2 Hz, 3 H), 2.18 (m, 1 H), 2.39 (s, 3 H), 2.43 (m, 1 H), 2.69 (m, 1 H), 5.58 (m, 2 H), 7.41 (m, 2 H), 7.50 (s, 1 H); MS (EI) m/z 228 (M^+), 213 (M^+ − Me), 173 (100), 159, 115, 55.

Compounds **10a**−**h** and **10j**−**k** were prepared in the same way from 4-methoxyindan-1-one (**9a**),[15] 5-methoxyindan-1-one (**9b**), 6-methoxyindan-1-one (**9c**), 7-methoxyindan-1-one (**9d**),[16] 6-fluoroindan-1-one (**9e**),[17] 6-chloroindan-1-one (**9f**),[16] 6-bromoindan-1-one (**9g**),[17,18] 6-methylindan-1-one (**9h**),[19] 6-fluoro-3,3-dimethylindan-1-one (**9j**),[12−14,17] and 6-methoxy-3,3-dimethylindan-1-one (**9k**),[12−15] respectively.

Preparation of (*R,S*)-2-(2-Oxoethyl)-3,3,6-trimethyl-1-indanone (11i) (Standard Procedure E). An ozone stream (2.5 g of ozone/h) was conducted for 1 h while stirring through a solution of **10i** (12.7 g, 55.6 mmol) in dichloromethane (200 mL) and methanol (40 mL) cooled to −70 °C. Subsequently, the solution was flushed with oxygen for 5 min and with argon for 10 min. After the addition of dimethyl sulfide (6.12 mL, 83.4 mmol), the mixture was stirred at room temperature for 18 h. The reaction mixture was evaporated, the residue was treated with dichloromethane (150 mL) and after the addition of water (25 mL) and trifluoroacetic acid (25 mL), the mixture was stirred at room temperature for 2.5 h. The mixture was subsequently poured into water (150 mL) and neutralized while stirring by addition of hydrogen carbonate. Water (100 mL) was added, the phases were separated, and the aqueous phase was extracted twice with dichloromethane (150 mL each time). The combined organic phases were dried (magnesium sulfate) and concentrated to give **11i** (11.3 g, 94%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.11 (s, 3 H), 1.51 (s, 3 H), 2.41 (s, 3 H), 2.61 (m, 1 H), 3.04 (m, 2 H), 7.40 (d, J = 7 Hz, 1 H), 7.46 (d, J = 7 Hz, 1 H), 7.52 (s, 1 H), 9.99 (s, 1 H); MS (EI) m/z 188 (M^+ − CO), 173 (100), 159, 145, 128, 43.

Preparation of (*R*)-1-(4,4,7-Trimethyl-1,4-dihydroindeno[1,2-*b*]pyrrol-1-yl)propan-2-ol (12k) (Standard Procedure F). A solution of **11i** (2.16 g, 10 mmol) and *p*-toluenesulfonic acid (80 mg) in toluene (90 mL) was heated on a Dean−Stark trap. A solution of (*R*)-1-amino-2-propanol (3.0 g, 40 mmol) in toluene (20 mL) was added dropwise over a period of 5 min. Subsequently, the mixture was boiled for an additional 45 min, during which the solvent was reduced to a volume of 20 mL. The cooled reaction mixture was purified by column chromatography (ethyl acetate/hexane, 1:2) to yield **12k** (1.5 g, 59%) as a brown oil: ^{1}H NMR ($CDCl_3$) δ 1.29 (d, J = 5 Hz, 3 H), 1.41 (s, 6 H), 2.38 (s, 3 H), 3.99 (m, 1 H), 4.18 (m, 2 H), 6.11 (d, J = 2 Hz, 1 H), 6.68 (d, J = 2 Hz, 1 H), 6.90 (d, J = 7 Hz, 1 H), 7.07 (s, 1 H), 7.21 (d, J = 7 Hz, 1 H); MS (EI) m/z 255 (M^+), 240 (100), 194.

Preparation of (*S*)-1-(2-Azidopropyl)-4,4,7-trimethyl-1,4-dihydroindeno[1,2-*b*]pyrrole (13k) (Standard Procedure G). Methanesulfonyl chloride (0.91 mL, 11.7 mmol) was added dropwise while stirring to a solution, cooled to 0 °C, of **12k** (1.5 g, 5.87 mmol) and triethylamine (3.27 mL, 23.5 mmol) in dichloromethane (50 mL), and the mixture was stirred at this temperature for an additional 1.5 h. The reaction mixture was subsequently diluted with dichloromethane (150 mL), washed twice with saturated sodium hydrogen carbonate solution (70 mL each time) and once with brine (70 mL), dried (magnesium sulfate), and evaporated. The residue was dissolved in DMF (50 mL) and treated with sodium azide (0.76 g, 11.7 mmol) and the mixture was heated to 60 °C for 15 h while stirring. After cooling the solution was poured into water (100 mL) and extracted twice with ethyl acetate (100 mL each time). The combined organic phases were washed once with water (100 mL) and once with brine (100 mL), dried (magnesium sulfate) and evaporated. The residue was purified by column chromatography (hexane/ethyl acetate 4:1) to give **13k** (1.13 g, 68%) as a reddish oil: ^{1}H NMR ($CDCl_3$) δ 1.30 (d, J = 5 Hz, 3 H), 1.41 (s, 6 H), 2.39 (s, 3 H), 3.92 (m, 1 H), 4.09 (m, 2 H), 6.12 (d, J = 2 Hz, 1 H), 6.65 (d, J = 2 Hz, 1 H), 6.90

(d, J = 7 Hz, 1 H), 7.03 (s, 1 H), 7.21 (d, J = 7 Hz, 1 H); MS (EI) m/z 280 (M^+), 237 (100) , 194, 181, 56.

Preparation of (*S*)-2-(4,4,7-Trimethyl-1,4-dihydroindeno[1,2-*b*]pyrrol-1-yl)-1-methylethylamine Fumarate (1:1) (14k) (Standard Procedure H). 13k (1.1 g, 3.92 mmol) dissolved in ethanol (50 mL) was hydrogenated over platinum oxide (110 mg) for 4 h at room temperature. The catalyst was subsequently filtered off and rinsed with ethanol, and the solution was evaporated. The colorless residue was dissolved in ether (80 mL), filtered, and treated while stirring with a solution of fumaric acid (455 mg, 3.92 mmol) in methanol (15 mL). The mixture was stirred at room temperature for 24 h, and the crystals were subsequently filtered off to give **14k** (805 mg, 77%) as a white solid: mp 196 °C; $[\alpha]^{20}_D$ = +11.2° (c = 0.25, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.08 (d, J = 5 Hz, 3 H), 1.32 (s, 6 H), 2.32 (s, 3 H), 3.44 (m, 1 H), 4.14 (dd, J = 10, 7 Hz, 1 H), 4.41 (dd, J = 10, 4 Hz, 1 H), 6.06 (d, J = 2 Hz, 1 H), 6.51 (s, 2 H), 6.79 (d, J = 2 Hz, 1 H), 6.84 (d, J = 7 Hz, 1 H), 7.23 (d, J = 7 Hz, 1 H), 7.33 (s, 1 H); MS (EI) m/z 254 (M^+), 211, 196, 44 (100). Anal. ($C_{17}H_{22}N_2$·1$C_4H_4O_4$) C, H, N.

Compounds **14a**−**j** and **14l**,**m** were synthesized according to standard procedures D, E, F, G, and H.

(*R*,*S*)-2-(5-Methoxy-1,4-dihydroindeno[1,2-*b*]pyrrol-1-yl)-1-methylethylamine fumarate (1:0.5) (14a): 83%; mp 194 °C; ^{1}H NMR (DMSO-d_6) δ 1.01 (d, J = 5 Hz, 3 H), 3.30 (s, 3 H), 3.31 (m, 1 H), 3.83 (s, 3 H), 4.08 (dd, J = 10, 7 Hz, 1 H), 4.25 (dd, J = 10, 4 Hz, 1 H), 6.11 (d, J = 2 Hz, 1 H), 6.45 (s, 1 H), 6.76 (d, J = 7 Hz, 1 H), 6.85 (d, J = 2 Hz, 1 H), 7.22 (m, 2 H); MS (EI) m/z 242 (M^+), 199, 44 (100). Anal. ($C_{15}H_{18}N_2O$·0.5$C_4H_4O_4$·0.12MeOH) C, H, N.

(*R*,*S*)-2-(6-Methoxy-1,4-dihydroindeno[1,2-*b*]pyrrol-1-yl)-1-methylethylamine fumarate (1:0.6) (14b): 61%; mp 189 °C; ^{1}H NMR (DMSO-d_6) δ 1.02 (d, J = 5 Hz, 3 H), 3.33 (m, 1 H), 3.39 (s, 3 H), 3.75 (s, 3 H), 4.05 (dd, J = 10, 7 Hz, 1 H), 4.23 (dd, J = 10, 4 Hz, 1 H), 6.08 (d, J = 2 Hz, 1 H), 6.46 (s, 1.2 H), 6.77 (d, J = 2 Hz, 1 H), 6.79 (dd, J = 7, 2 Hz, 1 H), 7.08 (d, J = 2 Hz, 1 H), 7.44 (d, J = 7 Hz, 1 H); MS (EI) m/z 242 (M^+), 199, 44 (100). Anal. ($C_{15}H_{18}N_2O$·0.6$C_4H_4O_4$) C, H, N.

(*R*,*S*)-2-(7-Methoxy-1,4-dihydroindeno[1,2-*b*]pyrrol-1-yl)-1-methylethylamine fumarate (1:0.5) (14c): 79%; mp 203 °C; ^{1}H NMR (DMSO-d_6) δ 1.01 (d, J = 5 Hz, 3 H), 3.33 (m, 1 H), 3.34 (s, 3 H), 3.78 (s, 3 H), 4.07 (dd, J = 10, 7 Hz, 1 H), 4.26 (dd, J = 10, 4 Hz, 1 H), 6.11 (d, J = 2 Hz, 1 H), 6.44 (s, 1 H), 6.63 (dd, J = 7, 2 Hz, 1 H), 6.85 (d, J = 2 Hz, 1 H), 7.08 (d, J = 2 Hz, 1 H), 7.29 (d, J = 7 Hz, 1 H); MS (EI) m/z 242 (M^+), 199, 44 (100). Anal. ($C_{15}H_{18}N_2O$·0.5$C_4H_4O_4$) C, H, N.

(*R*,*S*)-2-(8-Methoxy-1,4-dihydroindeno[1,2-*b*]pyrrol-1-yl)-1-methylethylamine fumarate (1:0.52) (14d): 74%; mp 193 °C; ^{1}H NMR (DMSO-d_6) δ 1.01 (d, J = 5 Hz, 3 H), 3.32 (m, 1 H), 3.41 (s, 3 H), 3.92 (s, 3 H), 4.21 (dd, J = 10, 7 Hz, 1 H), 4.38 (dd, J = 10, 4 Hz, 1 H), 6.12 (d, J = 2 Hz, 1 H), 6.43 (s, 1.04 H), 6.84 (d, J = 2 Hz, 1 H), 6.96 (m, 1 H), 7.05 (m, 2 H); MS (EI) m/z 242 (M^+), 199, 44 (100). Anal. ($C_{15}H_{18}N_2O$·0.52$C_4H_4O_4$) C, H, N.

(*R*)-2-(7-Methoxy-1,4-dihydroindeno[1,2-*b*]pyrrol-1-yl)-1-methylethylamine fumarate (1:0.5) (14e): 68%; mp 207 °C; $[\alpha]^{20}_D$ = −21.6° (c = 0.25, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.02 (d, J = 5 Hz, 3 H), 3.32 (m, 1 H), 3.34 (s, 3 H), 3.78 (s, 3 H), 4.07 (dd, J = 10, 7 Hz, 1 H), 4.26 (dd, J = 10, 4 Hz, 1 H), 6.10 (d, J = 2 Hz, 1 H), 6.45 (s, 1 H), 6.61 (dd, J = 7, 2 Hz, 1 H), 6.86 (d, J = 2 Hz, 1 H), 7.09 (d, J = 2 Hz, 1 H), 7.29 (d, J = 7 Hz, 1 H); MS (EI) m/z 242 (M^+), 199, 44 (100). Anal. ($C_{15}H_{18}N_2O$·0.5$C_4H_4O_4$) C, H, N.

(*S*)-2-(7-Methoxy-1,4-dihydroindeno[1,2-*b*]pyrrol-1-yl)-1-methylethylamine fumarate (1:0.5) (14f): 77%; mp 206 °C; $[\alpha]^{20}_D$ = +23.2° (c = 0.25, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.01 (d, J = 5 Hz, 3 H), 3.32 (m, 1 H), 3.34 (s, 3 H), 3.78 (s, 3 H), 4.07 (dd, J = 10, 7 Hz, 1 H), 4.26 (dd, J = 10, 4 Hz, 1 H), 6.10 (d, J = 2 Hz, 1 H), 6.44 (s, 1 H), 6.62 (dd, J = 7, 2 Hz, 1 H), 6.86 (d, J = 2 Hz, 1 H), 7.09 (d, J = 2 Hz, 1 H), 7.29 (d, J = 7 Hz, 1 H); MS (EI) m/z 242 (M^+), 199, 44 (100). Anal. ($C_{15}H_{18}N_2O$·0.5$C_4H_4O_4$) C, H, N.

(*S*)-2-(7-Fluoro-1,4-dihydroindeno[1,2-*b*]pyrrol-1-yl)-1-methylethylamine fumarate (1:0.5) (14g): 54%; mp 194 °C; $[\alpha]^{20}_D$ = +16.8° (c = 0.25, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.02 (d, J = 5 Hz, 3 H), 3.29 (m, 1 H), 3.40 (s, 3 H), 4.09 (dd, J = 10, 7 Hz, 1 H), 4.23 (dd, J = 10, 4 Hz, 1 H), 6.14 (d, J = 2 Hz, 1 H), 6.45 (s, 1 H), 6.83 (dt, J = 7, 1 Hz, 1 H), 6.91 (d, J = 2 Hz, 1 H), 7.40 (m, 2 H); MS (EI) m/z 230 (M^+), 187, 44 (100). Anal. ($C_{14}H_{15}FN_2$·0.5$C_4H_4O_4$) C, H, F, N.

(*S*)-2-(7-Chloro-1,4-dihydroindeno[1,2-*b*]pyrrol-1-yl)-1-methylethylamine fumarate (1:0.55) (14h): 67%; mp 197 °C; $[\alpha]^{20}_D$ = +16.0° (c = 0.25, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.01 (d, J = 5 Hz, 3 H), 3.30 (m, 1 H), 3.43 (s, 3 H), 4.08 (dd, J = 10, 7 Hz, 1 H), 4.27 (dd, J = 10, 4 Hz, 1 H), 6.15 (d, J = 2 Hz, 1 H), 6.46 (s, 1.1 H), 6.93 (d, J = 2 Hz, 1 H), 7.07 (dd, J = 7, 1 Hz, 1 H), 7.41 (d, J = 7 Hz, 1 H), 7.60 (d, J = 1 Hz, 1 H); MS (EI) m/z 246 (M^+), 203, 44 (100). Anal. ($C_{14}H_{15}ClN_2$·0.55$C_4H_4O_4$) C, H, Cl, N.

(*S*)-2-(7-Bromo-1,4-dihydroindeno[1,2-*b*]pyrrol-1-yl)-1-methylethylamine fumarate (1:0.5) (14i): 50%; mp 197 °C; $[\alpha]^{20}_D$ = +14.8° (c = 0.25, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.01 (d, J = 5 Hz, 3 H), 3.29 (m, 1 H), 3.41 (s, 3 H), 4.09 (dd, J = 10, 7 Hz, 1 H), 4.26 (dd, J = 10, 4 Hz, 1 H), 6.15 (d, J = 2 Hz, 1 H), 6.46 (s, 1 H), 6.93 (d, J = 2 Hz, 1 H), 7.21 (dd, J = 7, 1 Hz, 1 H), 7.35 (d, J = 7 Hz, 1 H), 7.71 (d, J = 1 Hz, 1 H); MS (EI) m/z 290,292 (M^+), 247,249, 44 (100). Anal. ($C_{14}H_{15}BrN_2O$·0.5$C_4H_4O_4$) C, H, Br, N.

(*S*)-2-(7-Methyl-1,4-dihydroindeno[1,2-*b*]pyrrol-1-yl)-1-methylethylamine fumarate (1:0.5) (14j): 65%; mp 194 °C; $[\alpha]^{20}_D$ = +22.8° (c = 0.25, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.03 (d, J = 5 Hz, 3 H), 2.35 (s, 3 H), 3.34 (m, 1 H), 3.36 (s, 3 H), 4.07 (dd, J = 10, 7 Hz, 1 H), 4.28 (dd, J = 10, 4 Hz, 1 H), 6.10 (d, J = 2 Hz, 1 H), 6.46 (s, 1 H), 6.85 (m, 2 H), 7.28 (d, J = 7 Hz, 1 H), 7.38 (s, 1 H); MS (EI) m/z 226 (M^+), 183, 44 (100). Anal. ($C_{15}H_{18}N_2$·0.5$C_4H_4O_4$) C, H, N.

(*S*)-2-(7-Fluoro-4,4-dimethyl-1,4-dihydroindeno[1,2-*b*]-pyrrol-1-yl)-1-methylethylamine fumarate (1:1) (14l): 70%; mp 211 °C; $[\alpha]^{20}_D$ = +8.8° (c = 0.25, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.05 (d, J = 5 Hz, 3 H), 1.35 (s, 6 H), 3.41 (m, 1 H), 4.11 (dd, J = 10, 7 Hz, 1 H), 4.35 (dd, J = 10, 4 Hz, 1 H), 6.09 (d, J = 2 Hz, 1 H), 6.49 (s, 2 H), 6.83 (m, 1 H), 6.87 (d, J = 2 Hz, 1 H), 7.36 (m, 2 H); MS (EI) m/z 258 (M^+), 215, 200, 44 (100). Anal. ($C_{16}H_{19}FN_2$·1$C_4H_4O_4$) C, H, F, N.

(*S*)-2-(7-methoxy-4,4-dimethyl-1,4-dihydro-indeno[1,2-*b*]pyrrol-1-yl)-1-methylethylamine fumarate (1:1) (14m): 60%; mp 181 °C; $[\alpha]^{20}_D$ = +10.0° (c = 0.25, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.05 (d, J = 5 Hz, 3 H), 1.32 (s, 6 H), 3.41 (m, 1 H), 3.77 (s, 3 H), 4.09 (dd, J = 10, 7 Hz, 1 H), 4.33 (dd, J = 10, 4 Hz, 1 H), 6.06 (d, J = 2 Hz, 1 H), 6.47 (s, 2 H), 6.59 (dd, J = 7, 1.5 Hz, 1 H), 6.80 (d, J = 2 Hz, 1 H), 7.03 (d, J = 1.5 Hz, 1 H), 7.24 (d, J = 7 Hz, 1 H); MS (EI) m/z 270 (M^+), 227, 212, 44 (100). Anal. ($C_{17}H_{22}N_2O$·1$C_4H_4O_4$) C, H, N.

Cell Culture and Membrane Preparation. Membranes obtained from NIH 3T3 cell lines expressing either human 5HT$_{2A}$ or human 5HT$_{2C}$ receptors were kindly donated by Dr. Nico Stam (N. V. Organon). For each receptor subtype, a single batch of membranes were grown using fermentation techniques previously described.[20]

Radioligand Binding Assays. Radioligand binding assays were as previously described for the human 5HT$_{2A}$ receptor with minor modifications for the labeling of human 5HT$_{2C}$ receptors. Briefly, on the day of the experiment, membranes were thawed and resuspended in 10 times the original volume of assay buffer. This gives a concentration of approximately 4 × 10^5 cells per assay tube. This assay buffer consisted of Tris-HCl 50 mM, pargyline 10^{-5} M, $MgCl_2$ 5 mM and ascorbic acid 0.1% pH 7.4. All compounds were dissolved in 10% DMSO and diluted in assay buffer. Assays were similar for each receptor and consisted of 100 μL of membrane preparation (depending on the assay), 50 μL of radioligand ([^{3}H]-5HT 1 nM final concentration for labeling human 5HT$_{2C}$ receptor binding sites, and [^{3}H]DOB 1 nM final concentration for labeling human 5HT$_{2A}$ receptors). Nonspecific binding was defined in the presence of 10 μM 5HT in the case of the human 5HT$_{2C}$ receptor and 10 μM methysergide in the case of the human 5HT$_{2A}$ receptor. All incubations were performed at room temperature for 1 h and the reactions stopped by rapid filtration through Whatmann GF/B filters. The filters were washed with 3 × 2 mL of Tris-HCl (50 mM, pH 7.4), and the

radioactivity retained on the filters was measured by scintillation spectroscopy in 2 mL of scintillation fluid. All experiments were performed in triplicate and repeated at least three times.

Saturation analyses were performed for each receptor using at least eight concentrations of each radioligand (concentrations ranging from 0.05 to 10 nM). Dissociation constants (K_d) were calculated using the EBDA/LIGAND program.[21,22]

Displacement curves were constructed for each compound at each receptor using seven concentrations of the displacing agents (one data point per log unit of concentration: 10^{-11}–10^{-5} M). Displacement curves were analyzed using EBDA/LIGAND to calculate pK_i values.

Radioligands. Radioligands were purchased from New England Nuclear. The specific activities of [^{3}H]5HT and [^{3}H]-DOB were 29.7 and 15.0 Ci/mmol.

Tissue Preparation and Incubation for Measurement of IP_3 Production. $5HT_{2C}$ receptor-mediated stimulation of IP_3 production was measured in the choroid plexus of the rat. The choroid plexus was removed, placed in 200 μL of oxygenated Krebs solution, and incubated with 0.35 nmol of myoinositol and 0.35 nmol of [^{3}H]myoinositol for 1 h at 37 °C. During this incubation, the tubes were gassed with 95% oxygen/5% CO_2 every 20 min. A mixture of LiCl and pargyline was then added (final concentration: LiCl = 10 mM, pargyline = 10 μM) and 10 min later the test compounds (final incubation volume = 250 μL). Dose–response curves were constructed from data obtained from three separate measures per data point. The mixture was incubated for a further 0.5 h at 37 °C. The assays were stopped by the addition of 25 μL of a stopping solution ($HClO_4$ 2.64 N + EDTA 40 mM). Assay tubes were frozen on dry ice for 15 min, thawed, and then kept on ice for 1 h. The tubes were then centrifuged for 20 min at 24000*g*. Then, 250 μL of the supernatant was removed and placed in Eppendorf tubes together with 25 μL of 4 M KOH. The samples were mixed well and kept on ice for 15 min. These samples were then recentrifuged for 15 min at 14 000 rpm. We removed 230 μL of supernatant and added 30 μL of phytic acid. The isolation of IP_3 was as described in a previous report.[23]

A concentration response curve was constructed for 5HT, mCPP, and several synthesized compounds. Six concentrations were used per test compound with the highest concentration tested being 0.1 mM. The maximal effect produced by each compound was compared to the stimulation induced by 10 μM 5HT in order to calculate the relative intrinsic activity.

***In Vivo* Functional Test.** In the test used to evaluate $5HT_{2C}$ receptor agonism *in vivo*, elicitation of penile erection was determined in RORO rats (Biological Research Laboratories, CH-4414 Füllinsdorf, Switzerland). All drugs were dissolved or microsuspended in 0.3% v/v Tween-80 in physiological saline. All drug solutions were freshly prepared and injected subcutaneously (sc) in a volume of 5 mL/kg body weight or administered orally in a volume of 10 mL/kg body weight. Control animals were injected with an equivalent volume of vehicle. When drug solutions were prepared from a salt of the compound, the doses refer to the weight of the salt. Eight rats were tested per dose and were individually placed in Plexiglas cages (30 × 25 × 10 cm) to allow counting over a 45 min observation period. When a substance was active in inducing penile erections, half maximal effective doses (ED_{50}) were calculated by probit analysis. In those instances in which not all rats exhibited penile erection, then the approximate doses producing penile erection in half of the rats was used.

Schedule-Induced Polydipsia Task in Rats. Excessive drinking was induced in adult female RORO rats (Biological Research Laboratories, CH-4414 Füllinsdorf, Switzerland) through the use of a fixed-time operant schedule (FT-1 min). The rats were drug experienced and were food deprived overnight prior to each test session. The test apparatus consisted of a sound-attenuated chamber surrounding a Plexiglas test box (30 × 25 × 30 cm) which was equipped with a stainless-steel grid floor and a mechanism to permit the automatic delivery of one 45-mg food pellet (Formula A/I; P. J. Noyes Company, Inc., Lancaster, NH) each min into a food cup located within the apparatus. The test session was 1 h. The experimental compounds were given in 0.3% (w/v) Tween-80 in distilled water in a volume of 2 mL/kg body weight. Treatment was administered 30 min prior to the start of testing. The same group of 10 rats was used to test vehicle and each of the selected doses of a test compound (doses chosen at half-logarithmic units in the dose range 1–30 mg/kg). Test days alternated with training days on which the session proceeded in the same manner as on test days, except no treatment was given and no data were recorded. A bottle containing tap water attached to the test apparatus was always available during test sessions with intake measured to the nearest 1 g. Evaluation was done to compare the effect of each dose to that obtained for the vehicle condition using a two-tailed Wilcoxon test with a p-value of ≤ 0.05 accepted as statistically significant. The lowest dose tested which yielded a statistically significant difference to vehicle treatment (MED, minimum effective dose) was determined.

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