7-Methyl-6,7,8,9,14,15-hexahydro-5*H*-benz[*d*]indolo[2,3-*g*]azecine: A New Heterocyclic System and a New Lead Compound for Dopamine Receptor Antagonists

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Partially hydrogenated derivatives of the new heterocyclic ring systems benz[*d*]indolo[2,3-*g*]-azecine and bisindolo[3,2-*d*][2,3-*g*]azecine were synthesized starting from lactones and amines via the described synthetic methods. In binding assays with rat striatal receptors, 7-methyl-6,7,8,9,14,15-hexahydro-5*H*-benz[*d*]indolo[2,3-*g*]azecine (**LE 300**) proved to be of high affinity for the D_1 binding site (K_i = 0.08 nmol for displacement of [^{3}H]SCH23390), being superior in this assay to standards such as butaclamol and SCH23390. This compound was characterized as a dopamine antagonist by conditioned avoidance response test with mice. Thus, **LE 300** represents the lead of a new class of dopamine antagonists for future investigations.

Introduction

According to Anderson and Nielsen, D_1-selective dopamine antagonists appear to be the most promising of the new approaches to neuroleptics.[1] Other authors express preference for D_3,[2] D_4,[3] or combined affinities for more than one dopamine and serotonine receptor subtype. Looking for new structures which may meet these different demands, it is obvious that modification of the chemical structure of the endogenous ligands serotonin and dopamine may be useful. Rigidification of the arylalkylamine chain of these neurotransmitters usually decreases affinity, but it is also possible that it may enhance selectivity for receptor subtypes. The objective of our efforts is to obtain moderately constrained compounds with the tryptamine and *β*-phenylethylamine structure incorporated into a 10-membered azecine ring. In this study we report on the synthesis and the dopaminergic receptor affinities of 6,7,8,9,14,15-hexahydro-5*H*-benz[*d*]indolo[2,3-*g*]azecine and 5,6,7,8,9,14,15,16-octahydrobisindolo[3,2-*d*][2,3-*g*]azecine derivatives.

Chemistry

The *cis*-configurated (NOE and X-ray) quinolizine **3** was prepared as reported earlier from the lactone **1** following a lactamization−cyclization−reduction sequence.[4] Ring extension by cleaving the central C−N bond of **3** was not possible via *N*-oxides or by catalytic hydrogenolysis, but rather by treatment of the corresponding quaternary quinolizinium salt with sodium or lithium in liquid ammonia (Scheme 1). **LE 300** could not be obtained from **1** and *β*-phenylethylamine because $POCl_3$-induced cyclization of the corresponding lactam (the demethoxylated analogue of **2**) failed due to the reduced reactivity of the nonactivated benzene ring. We were successful after reversal of roles, using tryptamine as the amine and isochromanone as the source for the *β*-phenylethyl moiety. **11** was prepared starting from **1** and tryptamine[4] via **9** and **10**. The notable shifts in the ^{1}H NMR of the N−CH_3 signals from the usually expected $\delta \approx 2.2$ to δ 1.98 (**5**), δ 1.99 (**LE 300**), and δ 2.00 (**11**) indicate that the NCH_3 moiety is located partially above the aromatic planes and not as an extended conformation in solution.

Pharmacology

The affinities for a number of different receptors isolated from tissues of rats or pigs were investigated in order to estimate the pharmacological quality of the new compounds. The compounds were tested in a standard receptor screening program for new drugs. Table 1 gives the results of these preliminary assays together with some K_i values for the adreno α_1 site.

Although both the azecines (**5**, **LE 300**, and **11**) and also the quinolizines (**3**, **6,** and **9)** are conformationally restricted *β*-arylethylamines, all the quinolizine derivatives do not show any affinity for the dopamine, serotonin, or other binding sites listed in Table 1, except their high affinity for the α_1-adreno receptor with K_i values ranging from 17 to 79 nmol (see footnote of Table 1).

The removal of the central C−N bond is a stroke of conformational liberation and dramatically increases the affinity of the resulting azecines for the dopaminergic and serotonergic receptors. The striking result in Table 2 is the high affinity of **LE 300** for the D_1 receptor relative to D_2, 5-HT_2, and α_1 receptors with selectivity ratios 75:1, 250:1, and 137:1, respectively. With respect to competitive displacement of SCH23390, a K_i value of 0.08 nmol was determined. The ratio of affinities may be useful for the development of atypical antipsychotic agents.[5] To our surprise, the more "dopamine-like" dimethoxylated **5** displays a much lower affinity. In climbing avoidance tests after intracerebroventricular application (exclusion of biotransformation) with mice, **LE 300** proved to be a dopamine antagonist. According to our experiments and the literature available to date,

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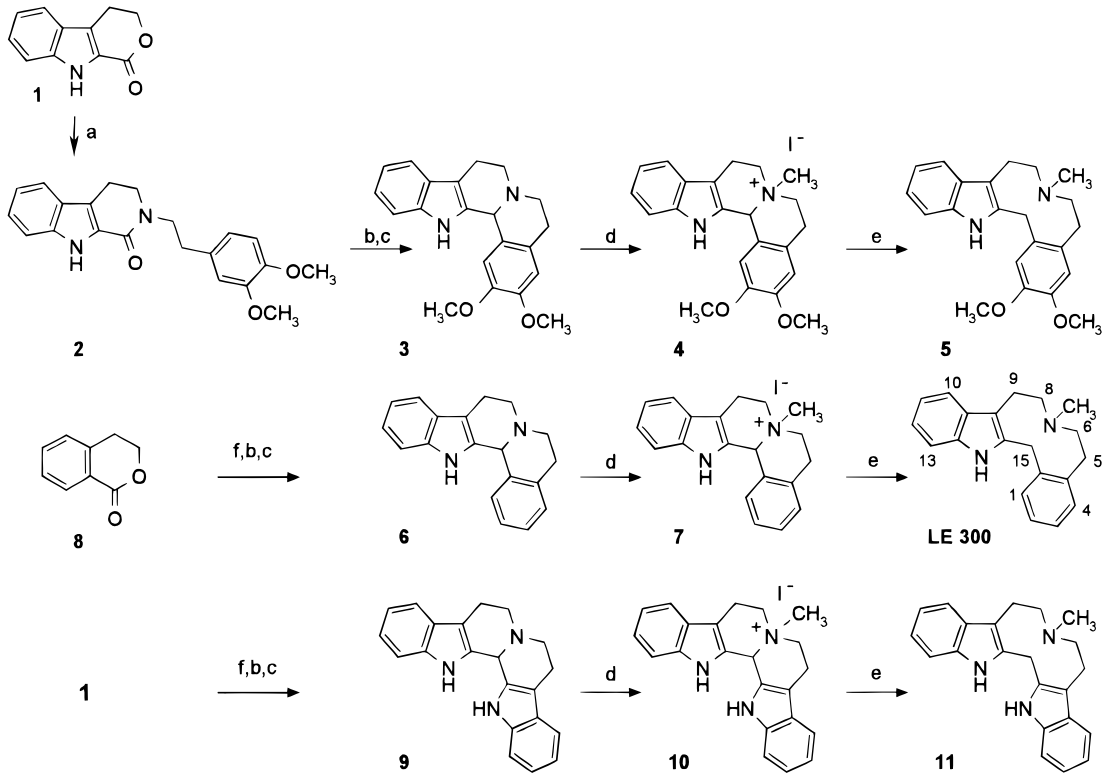
Scheme 1[a]



[a] (a) 3,4-Dimethoxyphenylethylamine; (b) $POCl_3$; (c) $NaBH_4$; (d) CH_3-I; (e) $Na/NH_3(l)$; (f) tryptamine.

Table 1. Decrease (%) of Receptor-Bound Radioactivity by 10^{-5} or 10^{-6} M Solutions of **3**, **5**, **6**, **9**−**11**, and **LE 300**

radioligand (receptor)	**6**	**3**	**9**	**10**	**5**	**11**	**LE 300**	concn
prazosin (α_1)	−82[a]	−94[b]	−88[c]	−64	nd[d]	nd	−97[e]	10^{-6}
pirenzepin (ACh-M_1)	−22	−11	−18	−15	−22	−14	−9	10^{-6}
SCH23390 (dopamine D_1)	nd	nd	nd	nd	−82	−95	−99	10^{-6}
spiperone (dopamine D_2)	−19	−11	−51	−22	−77	−95	−97	10^{-5}
MK-801 (NMDA)	−33	−14	−52	−20	−44	−56	−18	10^{-5}
AMPA (quisqualat)	3	−1	−1	11	−8	0	−3	10^{-5}
8-OH-DPAT (5-HT_{1A})	−12	−21	−25	−3	−22	−25	−72	10^{-6}
paroxetin (5-HT carrier)	−32	−8	−45	−33	−2	−13	−8	10^{-6}
ketanserin (5-HT_2)	−41	−32	−52	−32	−67	−80	−97	10^{-6}
muscimol (GABA-A)	−17	−26	5	−4	−23	−4	−9	10^{-5}
[^{125}I]sarafatoxin (Endo)	−1	0	1	0	1	0	0	10^{-5}
cytisin (ACh-Nic)	0	−4	1	3	−10	−7	−3	10^{-5}
glibenclamide (K^+)	12	11	7	6	1	0	10	10^{-5}
CPDPX (adenosine-A_1)	13	26	17	11	3	−6	5	10^{-6}
NBTI (adenosine carrier)	−29	−17	1	7	−9	−11	−14	10^{-5}
PDBU (phorbol)	−6	−9	−15	−17	−1	−5	0	10^{-5}
bradykinin	−2	9	2	−4	−19	−21	−2	10^{-5}
angiotensin II	0	6	0	−3	9	9	6	10^{-5}

[a] K_i: 79 nmol. [b] K_i: 17 nmol. [c] K_i: 76 nmol. [d] nd: not determined. [e] K_i: 11 nmol.

LE 300 belongs to the most potent D_1 antagonists at the rat striatal receptor.

Experimental Section

Melting points were measured in open capillary tubes on a Gallenkamp melting point apparatus and are uncorrected. Spectral data were obtained on the following instruments: IR, Perkin-Elmer 1420; ^{1}H NMR, Varian XL300 (300 MHz) and Bruker AC 200 (200 MHz); ^{13}C NMR, Varian XL300 (75.43 MHz) and Bruker AC 200 (50.32 MHz); chemical shifts were assigned with the help of HH- and CH-COSY and *J* values are in Hz; mass spectroscopy, MS-30 and MS-50 of A.E.I., Manchester, England. The ionization energy was 70 eV and the source temperature was 180 °C. Elemental analyses were performed on a Hereus apparatus. Found values were all within ±0.4% of the theoretical values except when indicated.

Table 2. K_i Values (nmol) for D_1, D_2, and 5-HT_2 Rat Striatal Receptors (n = 3−7)

compound	D_1 ([^{3}H]SCH23390)	D_2 ([^{3}H]spiperone)	5-HT_2 ([^{3}H]RP62203)
LE 300	0.08	6.0	20.0
5	91	730	960
11	9.6	79	180
(+)-butaclamol	1.8	3.6	nd[a]
mianserin	nd	nd	5.1

[a] nd: not determined.

The preparation of receptors and binding measurements were done with minor changes according to standard procedures described elsewhere.[6]

7-Methyl-5,6,8,9,14,14b-hexahydrobenz[*a*]indolo[3,2-*h*]-quinolizinium Iodide (7). 2.2 g of **6**[4] (8 mmol) in 60 mL of dry acetone and 2 mL of methyl iodide (32 mmol) were stirred for 18 h at 35 °C. The solid was filtered and dried in vaccuo: yield 2.7 g (81%), white powder, mp 267 °C; IR (KBr) 3280, 2860, 1490 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.22 (s, 3H, CH_3), 3.10−3.25 (m, 4H, CH_2's at C_5 and C_9), 3.78−4.02 (m, 4H, CH_2's at C_6 and C_8), 6.25 (s, 1H, CH at C_{14b}), 7.04 (td, J = 7.5/1, 1H, CH at C_{11}), 7.15 (td, J = 7.5/1, 1H, CH at C_{12}), 7.38−7.48 (m, 4H, CH's at C_{2-4}, and C_{13}), 7.54 (d, J = 7.5, 1H, CH at C_{10}), 7.56 (d, J = 7.5, 1H, CH at C_1), 10.90 (s, 1H, NH). Anal. ($C_{20}H_{21}N_2^+I^-$) C,H,N.

2,3-Dimethoxy-7-methyl-5,6,8,9,14,14b-hexahydrobenz[*a*]-indolo[3,2-*h*]quinolizinium Iodide (4). 2.68 g of **3**[4] (8 mmol) in 60 mL of dry acetone and 2 mL of methyl iodide (32 mmol) were stirred for 6 h at 35 °C and worked up as described above: yield 3.08 g (80.9%), white powder, mp 264 °C; IR 3280 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.24 (s, 3H, CH_3), 3.05−3.15 (m, 4H, CH_2's at C_5 and C_9), 3.78 (s, 3H, OCH_3 at C_2), 3.86 (s, 3H,

OCH_3 at C_3), 3.70−4.02 (m, 4H, CH_2's at C_6 and C_8), 6.00 (s, 1H, CH at C_{14b}), 6.993 (s, 1H, CH at C_4), 7.06 (td, J = 7.5/1, 1H, CH at C_{11}), 7.08 (s, 1H, CH at C_1), 7.14 (td, J = 7.5/1, 1H, CH at C_{12}), 7.52 (d, J = 7.5, 1H, CH at C_{10}), 10.90 (s, 1H, NH). Anal. ($C_{22}H_{25}N_2O_2^+I^-$) C,H,N.

7-Methyl-5,6,8,9,14,14b-hexahydro-15*H*-bisindolo[2,3-*a*]-[3,2-*h*]quinolizinium Iodide (10). 1.2 g of **9**[4] (4 mmol) in 25 mL of dry acetone and 1 mL of methyl iodide (16 mmol) were stirred for 18 h at 35 °C. The solid was separated and dried in vaccuo: yield 1.55 g (85%), white powder, mp 275−76 °C; IR (KBr) 3250, 755, 740 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.32 (s, 3H, CH_3), 3.15 (s,br, 4H, CH_2's at C_5 and C_9), 4.00 (s,br, 4H, CH_2's at C_6 and C_8), 6.30 (s, 1H, CH at C_{14b}), 7.08 (td, J = 7.5/1, 2H, CH's at C_3 and C_{11}), 7.20 (td, J = 7.5/1, 2H, CH's C_2 and C_{12}), 7.50 (d, J = 7.5, 2H, CH's at C_1 and C_{13}), 7.56 (d, J = 7.5, 2H, CH's at C_4 and C_{10}), 11.10 (s, 2H, NH). Anal. ($C_{22}H_{22}N_3^+I^-\cdot$0.33acetone) H,N; C: calcd, 58.03; found, 58.77.

7-Methyl-6,7,8,9,14,15-hexahydro-5*H*-benz[*d*]indolo-[2,3-*g*]azecine (LE 300). A solution of 0.9 g of **7** (2.1 mmol) in 5 mL of absolute ethanol was added to 125 mL of liquid ammonia. The addition of 0.5 g of sodium lead to the formation of a dark blue reaction mixture. When the dark blue color began to vanish, small portions of sodium were added within a period of 20 min. After this time NH_4Cl was added when necessary to destroy the dark blue complex. The ammonia was allowed to evaporate. When this process finished, nitrogen was led through to drive away the remaining ethanol and to establish a saturated atmosphere. The residue was diluted with water (50 mL) and extracted with ether (3 × 100 mL). The combined organic extracts were washed with 2.5% aqueous NaOH (30 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography using aluminum oxide, activated with 6% of water and diethyl ether/petroleum ether, 5:1: yield 0.22 g (36%), white solid, mp 56−58 °C; IR (KBr) 3400, 1480, 1455, 735 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.99 (s, 3H, CH_3), 2.65 (dd, J = 7/3, 2H, CH_2 at C_5), 2.66 (dd, J = 6/2, 2H, CH_2 at C_9), 2.79 (dd, J = 6/2, 2H, CH_2 at C_8), 2.87 (dd, J = 7/3, 2H, CH_2 at C_6), 4.15 (s, 2H, CH_2 at C_{15}), 6.87 (ddd, J = 8/7/1, 1H, CH at C_{11}), 6.97 (ddd, J = 7/7/1, 1H, CH at C_{12}), 7.09−7.14 (m, 3H, CH's at C_2, C_3 and C_4), 7.25 (dd, J = 7/1, 1H, CH at C_{13}), 7.34 (dd, J = 8/1, 1H, CH at C_{10}), 7.53 (dd, J = 6/2, 1H, CH at C_1), 10.77 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 23.92 (C_9), 30.49 (C_{15}), 33.38 (C_5), 46.53 (CH_3), 58.16 (C_8), 59.30 (C_6), 108.94 (C_{9a}), 110.22 (C_{13}), 117.02 (C_{10}), 117.68 (C_{11}), 119.73 (C_{12}), 125.45 (C_3), 125.89 (C_2), 128.01 (C_{9b}), 129.55 (C_4), 129.96 (C_1), 135.07 (C_{13a} and C_{14a}), 138.27 (C_{4a}), 139.60 (C_{15a}); MS 290 (100%), 245 (50%), 218 (48%), 146 (46%); HRMS 290.1783 (calcd for $C_{20}H_{22}N_2$: 290.1787). Anal. ($C_{20}H_{22}N_2\cdot$0.5Et_2O) C,H,N.

2,3-Dimethoxy-7-methyl-6,7,8,9,14,15-hexahydro-5*H*-benz[*d*]indolo[2,3-*g*]azecine (5). The compound was prepared as described for **LE 300**, but the reaction time was 30 min and the mobile phase for column chromatography was diethyl ether: yield 0.12 (17%), white solid, mp 78 °C; IR 3380, 1510, 1455, 740 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.98 (s, 3H, CH_3), 2.67 (m, 4H, CH_2's at C_5 and C_9) 2.85 (m, 4H, CH_2's at C_6 and C_8), 3.68, 3.78 (2 s, 6H, 2 OCH_3), 4.03 (s, 2H, CH_2 at C_{15}), 6.68 (s, 1H, CH at C_4), 6.88 (td, J = 6/1, 1H, CH at C_{11}), 6.98 (td, J = 61, 1H, CH at C_{12}), 7.15 (s, 1H, CH at C_1), 7.28 (dd, J = 6/1, 1H, CH at C_{13}), 10.78 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 24.22 (C_9), 30.07 (C_{15}), 33.12 (C_5), 47.53 (CH_3), 55.53 (OCH_3 an C_{16}), 55.74 (OCH_3 an C 15), 58.60 (C_8), 59.82 (C_6), 108.85 (C_{9a}), 110.45 (C_{13}), 113.30 (C_4), 114.11 (C_1), 117.38 (C_{10}), 117.94 (C_{11}), 120.00 (C_{12}), 128.19 (C_{9b}), 131.85 (C_{15a}), 135.50 (C_{14a}), 135.57 (C_{13a}), 138.27 (C_{4a}), 146.89 (C_3), 147.12 (C_2); MS 351 (23%), 350 (89%), 185 (30%), 143 (43%), 75 (35%), 58 (100%); HRMS 350.1998 (calcd for $C_{22}H_{26}N_2O_2$: 350.1994). Anal. ($C_{22}H_{26}N_2O_2$) C,H,N.

7-Methyl-5,6,7,8,9,14,15,16-octahydrobisindolo[3,2-*d*]-[2,3-*g*]azecine (11). The compound was prepared from 2 mmol of **10** as described for **LE 300**, but sodium was replaced by lithium, the reaction time was 1 h and the mobile phase for column chromatography was diethyl ether: yield 0.12 g (18%), beige solid, mp 128−130 °C; IR 3400, 740 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.00 (s, 3H, CH_3), 2.50−2.75 (m, 8H, CH_2's at C_5, C_6, C_7 and C_8), 4.25 (s, 2H, CH_2 at C_{15}), 6.92 (t, J = 6, 2H, CH's at C_3 and C_{11}), 7.02 (t, J = 6, 2H, CH's at C_2 and C_{12}), 7.28 (d, J = 6, 2H, CH's at C_1 and C_{13}), 7.39 (d, J = 6, 2H, CH's at C_4 and C_{10}), 10.78 (s, 2H, 2 NH); ^{13}C NMR (DMSO-d_6) δ 22.85 (C_5, C_9), 25.36 (C_{15}), 33.12 (C_5), 44.57 (CH_3), 57.28 (C_6, C_8), 109.73 (C_{4b}, C_{9a}), 110.40 (C_1, C_{13}), 117.20 (C_4, C_{10}), 114.11 (C_1), 118.01 (C_3, C_{11}), 120.10 (C_2, C_{12}), 128.30 (C_{4a},C_{9b}), 133.57 (C_{14a}, C_{15a}), 134.99 (C_{13a}, C_{16a}); MS 330 (28%), 329 (80%), 271 (52%), 143 (100%), 58 (67%); HRMS 329.1892 (calcd for $C_{22}H_{23}N_3$: 329.1892). Anal. ($C_{22}H_{23}N_3$) C,H,N.

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