Dopamine/Serotonin Receptor Ligands. 10:[1] SAR Studies on Azecine-type Dopamine Receptor Ligands by Functional Screening at Human Cloned D_1, D_{2L}, and D_5 Receptors with a Microplate Reader Based Calcium Assay Lead to a Novel Potent D_1/D_5 Selective Antagonist

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On the basis of the benz[*d*]indolo[2,3-*g*]azecine derivative **1** (LE300), structure−activity relations were investigated in order to identify the pharmacophore in this new class of ligands. Various structural modifications were performed and the inhibitory activities at human cloned D_1, D_{2L}, and D_5 receptors were measured by using a simple fluorescence microplate reader based calcium assay. Subsequently, the affinities of active compounds were estimated by radioligand binding experiments. Deleting one of the aromatic rings as well as replacing it by a phenyl moiety abolishes the inhibitory activities almost completely. Contraction of the 10-membered central ring decreases them significantly. The replacement of indole by thiophene or *N*-methylpyrrole reduces the inhibitory activity, whereas replacing the indole by benzene increases it. Finally, the hydroxylated dibenz[*d*,*g*]azecine derivative **11d** (LE404) was found to be more active than the lead **1** in the functional calcium assay as well as in radioligand displacement experiments.

Introduction

The dopaminergic system plays an important role in regulating neuronal motor control, cognition, event prediction, emotion, and vascular function. Neuropsychiatric diseases such as schizophrenia, Parkinson's disease, or addiction are strongly related to a disregulation of the dopaminergic signal transduction.[2,3] Thus, dopamine receptors are attractive as therapeutic targets. There are five dopamine receptor subtypes that may be divided into two subfamilies: the G_s-coupled D_1-like receptors (D_1, D_5) and the G_i-coupled D_2-like receptors (D_2, D_3, D_4).[4] Although agonists and antagonists with a certain subtype selectivity are available, there is still a need for truly subtype selective ligands, e.g. as tools for pharmacological binding studies. On the other hand, therapy of schizophrenia with antipsychotic drugs can implicate severe side effects, such as extrapyramidal motor effects. Higher subtype selectivity or new binding profiles and combinations of different dopamine receptor subtypes, respectively, may lead to more effective neuroleptic drugs with fewer therapy-limiting side effects.

The idea behind the synthesis of the new heterocyclic system of **1** (Figure 1) was to incorporate the substructures of tryptamine and β-phenylethylamine into a moderately constrained 10-membered azecine ring.[5] **1** represents a chemically novel type of dopamine receptor antagonist showing subnanomolar affinity for the rat striatal D_1 receptor and nanomolar affinity for human dopamine and serotonin receptors.[5−7]

The heterocyclic system of the lead **1** consists of the indole, the benzene, the central azecine ring, and a methyl group as N-substituent. The objective of our present study was to estimate the pharmacological relevance of these moieties. Therefore, we synthesized different N-alkylated derivatives **1a,b,c** of **1**, ring-contracted azonine analogues **2**, derivatives lacking the indole (**3**) and the benzene part (**4**), respectively, and a series of compounds where the condensed benzene is replaced by phenyl in different positions (**5**). Furthermore, the compounds **6** and **7** (azonine analogues of **4** and **5**) and some azecines, derived from **1** by replacing the benzene ring with pyrrole (**8**) and the indole nucleus with pyrrole (**9**) (differently annelated than the indole in **1** due to synthetic availability), thiophene (**10**), and benzene (**11**), respectively, were synthesized (Figure 1). For investigating SAR, the inhibitory activities of all compounds were measured by using a recently established microplate reader based functional calcium assay.[8] Subsequently, the affinities of the active derivatives were determined by radioligand binding experiments.

Chemistry

The benzindoloazecines **1a**−**c** were prepared starting from tryptamine and isochromanone by a lactamization, cyclization, reduction (→**12**), quaternization (→ **13a**−**c**), ring-extension sequence as previously described for **1** ($R = CH_3$) (Figure 2).[5] A crucial step is the Birch cleavage of **13a**−**c**. Extensive reduction attacking the aromatic systems and a nonselective C,N-cleavage, yielding **12** again, were shown to be the main side reactions. The synthesis of nine-membered analogues is shown in Figure 3.

Two methoxylated derivatives **3a** ($R' = OCH_3$, $R'' = H$) and **3b** ($R' = R'' = OCH_3$) of the "deindolized" **1** have been prepared as described previously.[9] Compound **4a**, which has been introduced as a potential diuretic,[10,11] can be considered as **1** without the benzene ring and was synthesized by us according to Figure 4. Since N-alkylation and not the favored N-acylation is the decisive initial step in the formation of lactams from lactones,[12] the alkylation of tryptamine with ethyl 5-bromopentanoate yielded **16** in higher yields than δ-valerolactone did.

The nine-membered analogue **6** is known[10] but was obtained by us differently starting from compounds **18** or **19**, respectively (Figure 5).

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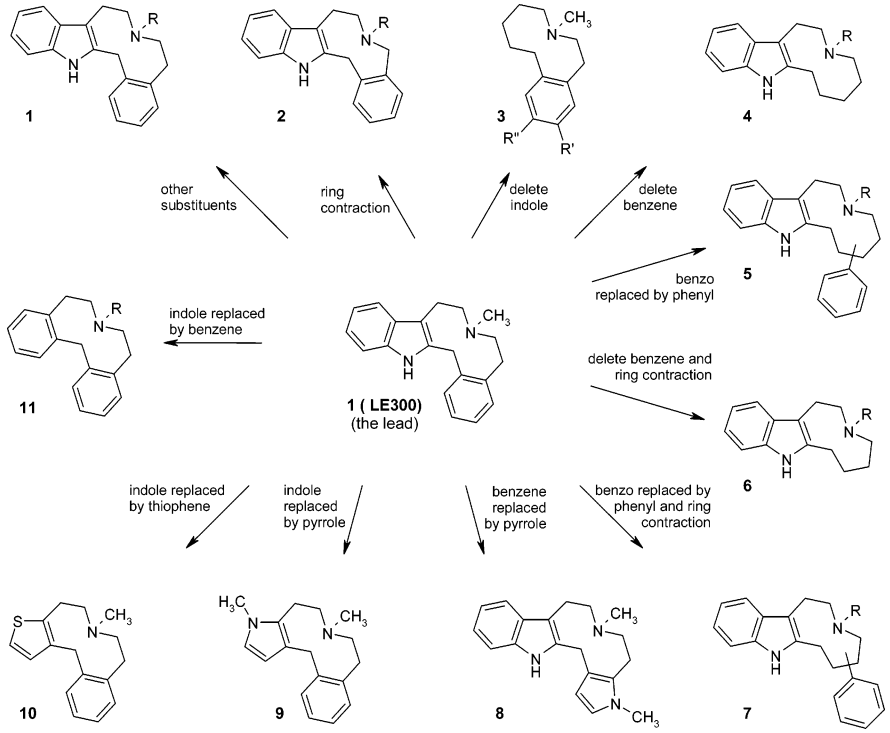

Figure 1. Structural variations of the lead compound **1**. R = CH_3 and other alkyl; R′, R″ = H, OCH_3.

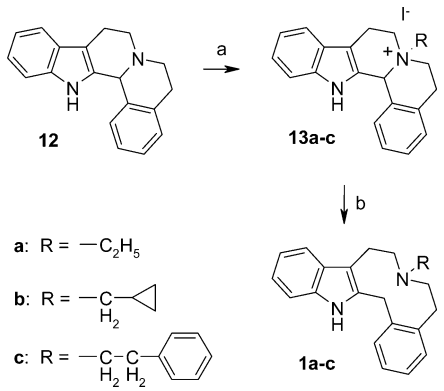

Figure 2. Variation of *N*-alkyl in **1**. Reagents: (a) R−I or R−Br; (b) Na^0/liq NH_3.

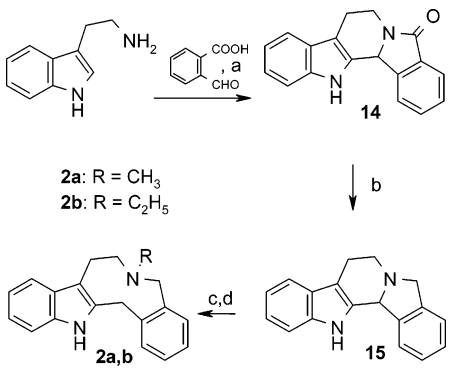

Figure 3. Synthesis of Benzindoloazonines. Reagents: (a) 2 N H_2SO_4, EtOH, H_2O, reflux; (b) $LiAlH_4$; (c) R−I; (d) Na^0/liq NH_3.

The phenylated *δ*-valerolactone **21** and the corresponding phenylated *δ*-bromopentanoates **22** and **27**, obtained from the lactones **21** and **26** by treatment with HBr gas in ethanolic solution, were shown to be useful starting materials in the syntheses of phenylated indoloazecines **5a,b**. **21** was obtained by reduction of 4-benzoylbutyric acid according to the procedure of Julia and Rouault.[13] Treatment of **21** with tryptamine gave

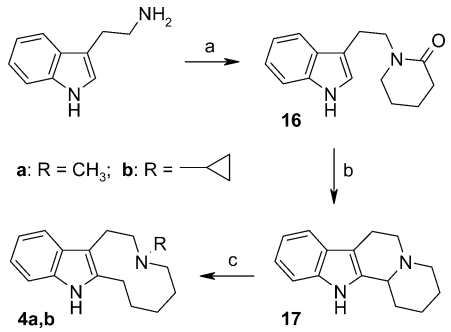

Figure 4. Synthesis of indoloazecines. Reagents: (a) ethyl 5-bromopentanoate; (b) $LiAlH_4$; (c) (1) R−X, (2) Na^0/liq NH_3.

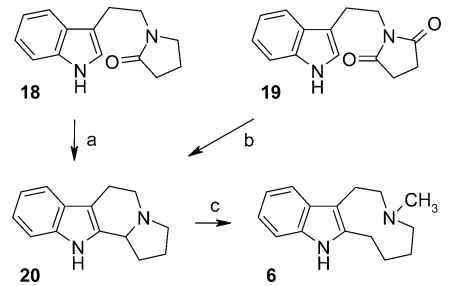

Figure 5. Synthesis of indoloazonines. Reagents: (a) (1) $POCl_3$, reflux, (2) H_2O, NaOH, (iminium salt), (3) $NaBH_4$; (b) (1) Et_3OBF_4, (2) $NaBH_4$, (3) $LiAlH_4$; (c) (1) MeI, acetone, (2) Na^0/liq NH_3.

the hydroxyamide **24** under mild conditions and via **22** the lactam **23** under more drastic conditions. **24** was shown to be more reactive than the other hydroxyamides we have investigated. Therefore, **25** could be obtained from both **23** and **24**. Quaternization and reductive cleavage finally afforded the target compound **5a** (Figure 6).

Synthesis of the 7-phenylazecino[5,4-*b*]indole derivative **5b** was conducted analogously to the unphenylated compounds **4a,b**. Since the reduction of 2-phenylglutaric anhydride[14] gave mixtures of α-phenyl- and *γ*-phenyl-*δ*-valerolactone, which could not be separated sufficiently by distillation, the lactone

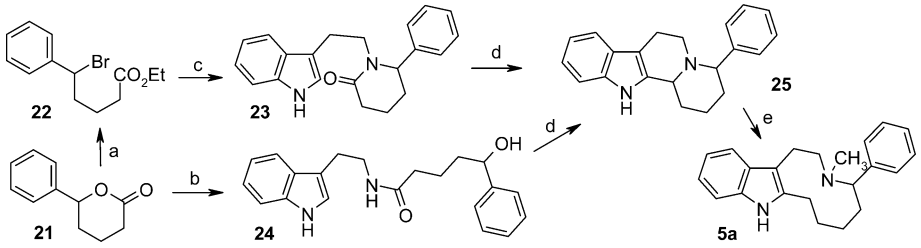

Figure 6. Synthesis of phenylated indoloazecines. Reagents: (a) HBr, EtOH; (b) tryptamine, EtOH, reflux; (c) tryptamine, K_2CO_3, KI, *n*-BuOH, reflux; (d) (1) $POCl_3$, reflux, (2) H_2O, NaOH, (iminium salt), (3) $NaBH_4$; (e) (1) MeI, acetone, (2) Na^0/liq NH_3.

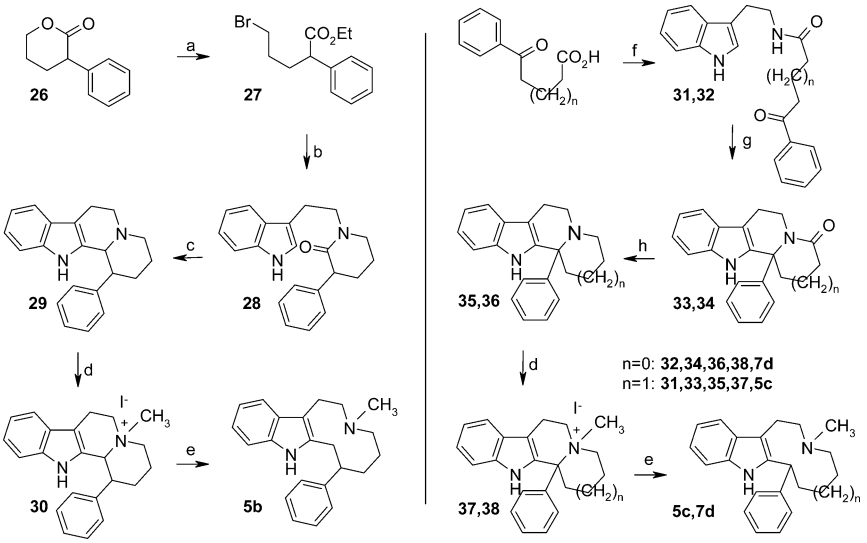

Figure 7. Synthesis of phenyllated indoloazecines. Reagents: (a) HBr, EtOH; (b) tryptamine, K_2CO_3, KI, *n*-BuOH, reflux; (c) (1) $POCl_3$, reflux, (2) H_2O, NaOH, (iminium salt), (3) $NaBH_4$; (d) MeI, diethyl ether; (e) Na^0/liq NH_3; (f) tryptamine, $(CH_3)_3N$, $CHCl_3$; (g) methanolic HCl (2%); (h) THF, $LiAlH_4$, reflux.

26 was prepared by alkylation of diethyl phenylmalonate with 3-chloropropyl acetate, hydrolysis, decarboxylation, and cyclization.[15] **26** was transferred into the bromo ester **27**, which reacted with tryptamine to give the lactam **28** or the corresponding hydroxyamide, respectively, according to the reaction conditions. Again, **27** proved to be more suitable to proceed to the target compound **5b** (Figure 7) than **26**. Compound **29**, as well as all the other phenylated quinolizines, showed two sets of signals in the ^{1}H NMR spectra due to formation of diastereomeres. The 8-phenylazecino[5,4-*b*]indole **5c**[16,17] and the 7-phenylazonino[5,4-*b*]indole **7d**[16,18] were prepared as reported in the literature and outlined in Figure 7.

Figure 8 demonstrates the synthesis of the novel 4-phenyl- (**7a**), 5-phenyl- (**7c**), and 6-phenylazonino[5,4-*b*]indoles (**7b**) via **41**, **49**, **44**. α- (**43**) and γ-phenylbutyrolactone (**39**) proved to be much more reactive with regard to the lactamization with tryptamine than β-phenylbutyrolactone (**46**) and its homologous α- and δ-phenyl-δ-valerolactones, respectively. Transformation into the bromo esters was not necessary. Several attempts to prepare the lactam out of lactone **46** and tryptamine only gave the corresponding hydroxyamide, which produced many byproducts in the transformation into the indolizine, but tryptamine and the bromo ester **47** reacted to **48** successfully.

Due to the lower reactivity of benzene compared to indole, the Bischler−Napieralsky-type cyclizations of *N*-phenylethyl lactams[19] comparable to, for example, *N*-indolylethyl lactams **16**, **18**, **23**, **28**, or of *N*-(phenylethyl)hydroxyamides related to **24** did not work. So we synthesized **52**[20] and the novel **51** from 2-arylethyl chlorides and suitable nitriles under more drastic conditions using tin tetrachloride and proceeded as outlined in Figure 9. Interestingly, the symmetric dibenzoquinolizine **58** showed an eight-proton singlet signal for the protons 5, 6, 8, 9 (δ = 2.8 ppm) due to identical chemical shifts and high conformational mobility. Methoxylated analogues are more reactive, and cyclization could be performed via hydroxyamides **60a,b** (Figure 10). The phenolic target compounds were obtained by ether cleavage with 47% HBr using **11b** for preparation of **11c** and the quaternary salt of **61a** for **11d**.

Pharmacology

Screening of compounds for agonistic and antagonistic activity at G-protein-coupled dopamine receptors was performed using a calcium assay developed by us recently.[8] This functional assay is based on the measurement of intracellular Ca^{2+} using fluorescent dye Oregon Green and a fluorescence microplate reader. The assay is fast, simple, and avoids the use of radioactivity. This functional calcium assay was conducted with recombinant HEK293 cell lines stably expressing hD_1, hD_{2L}, and hD_5 dopamine receptors, respectively, by performing dose−response curves of standard agonists and standard antagonists. EC_{50} values of standard agonists and K_i values of standard antagonists obtained by the calcium assay were in concordance with literature-based data. This made the calcium assay appear well suitable for the purpose of screening compounds at dopaminergic receptors.

The target compounds and many of the intermediates synthesized in this study were screened for agonistic and antagonistic activity. None of these showed agonistic activity at the three dopamine receptors investigated. The inhibitory activity was preliminarily measured by preincubation of recombinant cells with test compound in a 10 μM concentration. After injection of standard agonist the decrease of the agonist-induced

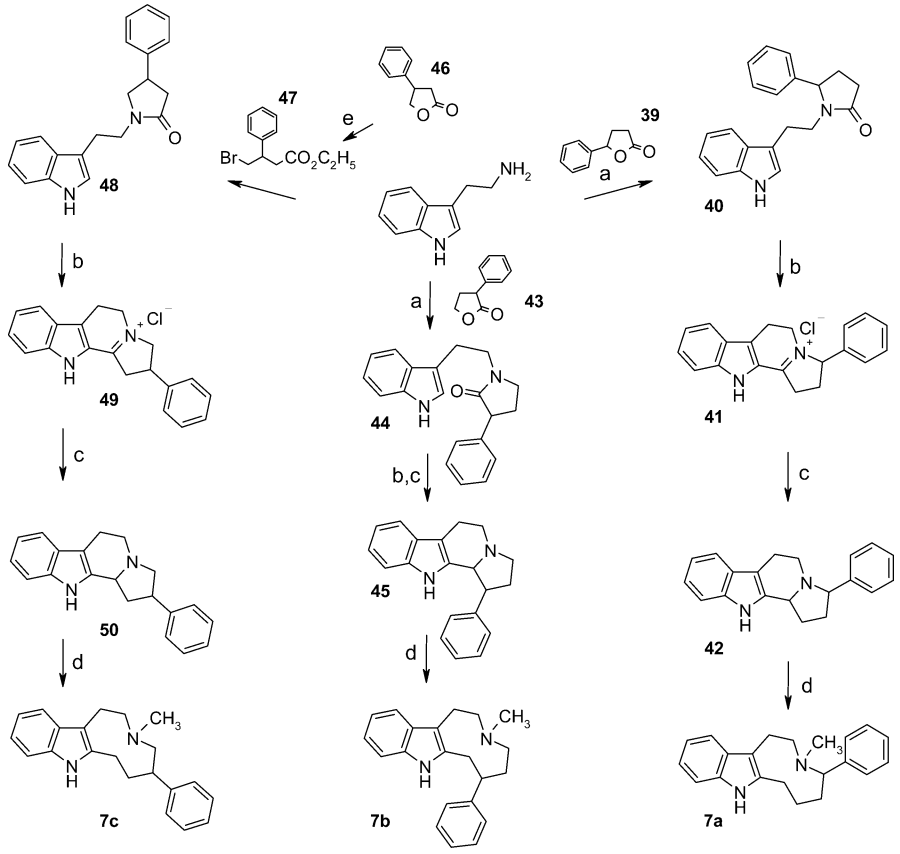

Figure 8. Synthesis of phenylated indoloazonines. Reagents: (a) 200 °C; (b) (1) $POCl_3$, reflux, (2) H_2O, NaOH; (c) $NaBH_4$; (d) (1) MeI, acetone, (2) Na^0/liq NH_3; (e) HBr, EtOH.

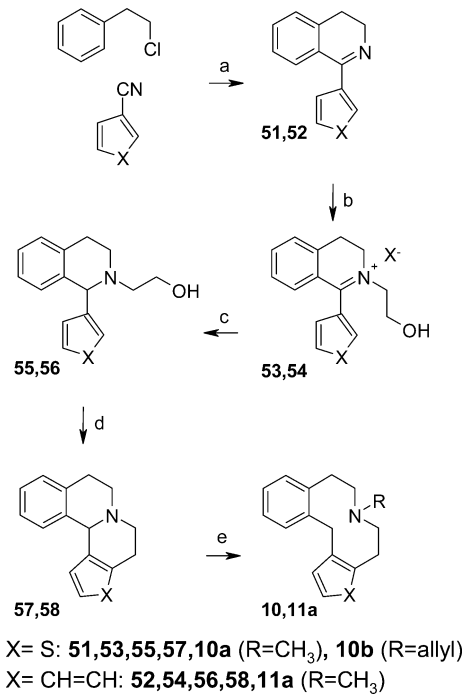

Figure 9. Synthesis of dibenzo- and benzothienoazecines. Reagents: (a) $SnCl_4$; (b) $Br(I)CH_2CH_2OH$; (c) H_2/PtO_2/EtOH (for **56**); $NaBH_4$ (for **55**); (d) polyphosphoric acid, 160 °C; (e) (1) R−I (quaternary salts), (2) Na^0/liq NH_3.

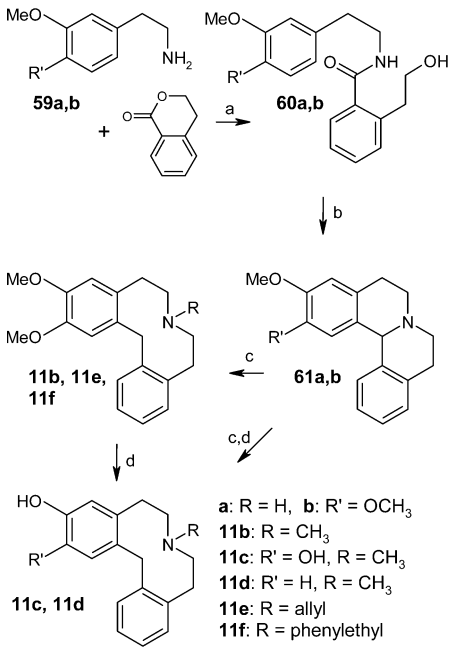

Figure 10. Synthesis of hydroxylated and methoxylated dibenzazecines. Reagents: (a) toluene, reflux; (b) (1) $POCl_3$, (2) $NaBH_4$/MeOH; (c) (1) R−X, (2) Na^0/liq NH_3; (d) HBr.

fluorescence signal was determined (standard agonist concentration for hD_1, SKF38393, 100 nM; hD_{2L}, quinpirole, 30 nM; and hD_5, SKF38393, 10 nM). Compounds **1b**, **1c**, **2b**, **3b**, **4a**, **4b**, **5a**−**5c**, **6**, **7a**, **7c**, **7d**, **8**, **10b**, **11b**, **11e**, **11f**, **15**, **17**, **21**−**32**, **35**, **42**, **43**, **45**−**47**, and **50** showed less than 50% signal reduction (K_i > 10 μM). Two of these compounds were found to have moderate affinity for hD_{2L}: **5a** ($K_i \sim 0.5$ μM) and **7a** ($K_i \sim 0.1$ μM). Eight compounds showed a signal reduction of more than 50% and were further characterized by determination of IC_{50} and K_i values, respectively. K_i values are given in Table 1.

Table 1. Inhibitory Activities at Human Cloned Dopamine Receptors—Ca^{2+} Assay Data

	K_i (nM) ± SEM[a]		
compd	hD_1	hD_{2L}	hD_5
LE300	60.4 ± 20.4	19.0 ± 11.7	12.7 ± 6.35
1a	170 ± 63	82.6 ± 24.5	22.3 ± 11.1
7b	742 ± 253	943 ± 194	112 ± 50.5
9	~1000	264 ± 46	337 ± 138
10a	207 ± 74.5	92.0 ± 29.3	33.7 ± 14.3
11a	40.4 ± 4.84	8.47 ± 4.32	3.09 ± 3.19
11c	20.7 ± 5.65	65.7 ± 28.3	2.32 ± 1.90
11d	6.93 ± 5.31	33.5 ± 17.0	1.69 ± 1.94

[a] At least three independent experiments were carried out in triplicate each.

Table 2. Affinities for Human Cloned Dopamine Receptors—Radioligand Binding Data

	K_i (nM) ± SEM[a]			
compd	hD_1	hD_{2L}	hD_4	hD_5
LE300[6]	1.9 ± 0.5	44.7 ± 15.8	109 ± 39	7.5 ± 0.3
1a	16.4 ± 12.0	253 ± 38	378.5 ± 8	14.7 ± 2.5
1b	767 ± 24	>5000	>5000	893 ± 32
9	61 ± 8.0	712 ± 46	1647 ± 95	361 ± 38
10a	10.7 ± 5.2	198 ± 16	299 ± 41	79.1 ± 5.3
11a[b]	4.5 ± 2.1	56.5 ± 9.0	134 ± 15	11.2 ± 1.8
11b	509 ± 51	>5000	2514 ± 101	2610 ± 120
11c	341 ± 41	>5000	165 ± 12	1078 ± 42
11d[c]	0.39 ± 0.22	17.5 ± 2.1	11.3 ± 1.0	1.5 ± 0.2

[a] At least two independent experiments were carried out in triplicate each. [b] D_3: 52.5 ± 6.4. [c] hD_3: 47.5 ± 24.0.

The binding properties of compounds identified as potent antagonists in the calcium assay were further characterized by radioligand binding studies.[23,8] These experiments included the determination of binding affinities at the hD_4 receptor. **11d** and the unsubstituted **11a** were also tested at the D_3 receptor; therefore, the complete dopamine receptor binding profiles of these highly potent compounds have been determined (Table 2).

Discussion

The microplate reader based calcium assay is a very useful method for simply and quickly selecting the active ones out of a considerable number of compounds and characterizing them as antagonists that can then proceed to radioligand binding experiments for further evaluations. Comparing radioligand and calcium data, it can be seen that there are differences in the K_i values obtained. Since the calcium-assay monitors a fast calcium-signal, these results represent nonequilibrium data, whereas radioligand binding studies were performed under equilibrium conditions. As a general rule, it could be shown that values taken from radioligand binding studies reveal higher D_1 selectivities than the nonequilibrium calcium data.[6]

Concerning SAR, it first should be pointed out which of the structural modifications lead to a significant decrease or loss of inhibitory activity and binding affinities, respectively: Larger substituents at the aliphatic nitrogen atom in **1** lower the inhibitory affinities significantly and the affinities measured by radioligand binding studies dramatically (compare compounds **1**, **1a**, **1b**, Tables 1 and 2). Generally, methyl seems to be the optimum in terms of activity. A second benzene or another aromatic ring system is obviously essential for dopaminergic activity. Both 9- and 10-membered ring systems lacking the benzene ring lose the inhibitory activities almost completely (compounds **4** and **6**). This finding is in accordance with previous results, which showed that 3-benzazecines and 3-benzazonines do not show dopaminergic activity.[9]

The annelated benzene in **1** cannot be replaced with phenyl to maintain pharmacological activity. All of the compounds containing a phenyl group at the aliphatic ring system (both in 9- and 10-membered rings) lose their activity, irrespective of its location in position 4, 5, 6, or 7 in the azonine ring (compounds **7a**−**d**) and 4, 7, or 8 in the azecine ring system (compounds **5a**−**c**), respectively. Only a phenyl group in position 6 of the azonine (**7b**) produces some activity. These binding profiles are quite surprising, since the increase of flexibility of the pharmacophoric benzene ring was supposed to increase affinity.

In contrast to all of the other structural variations, the substitution of the indole **1** moiety against other aromatic ring systems yielded antagonists with considerable inhibitory activity. Inhibitory activities for hD_1, hD_2, and hD_5 and affinities for hD_1, hD_2, hD_4, and hD_5 are given in Tables 1 and 2. 1-Methyl-1*H*-pyrrole or thiophene instead of indole generally decreases the affinities compared to the lead **1** more (**9**) or less (**10a**). A second annelated benzene replacing the indole (**11a**) increases the inhibitory activities moderately compared to **1** (Table 1). The decreased affinities go together with a slightly improved selectivity toward the D_1 receptor subtype family (Table 2). Conclusively, we tried to optimize the new D1/D5-selective lead structure **11a** by introducing a "dopamine-like" hydroxylation in positions 2 and 3, which unfortunately did not improve affinities. Interestingly, the dihydroxylated compound **11c** showed much higher inhibitory activities in the calcium assay compared to the affinities resulting from the radioligand binding experiments. The most potent compound in the whole series was the monohydroxylated 3-hydroxy-7-methyl-5,6,7,8,9,14-hexahydrodibenz[*d*,*g*]azecine **11d** (LE404), which displayed low nanomolar affinities for all dopamine receptor subtypes and subnanomolar affinity toward the D_1 receptor in the radioligand binding experiment.

Conclusion

Performing intensive investigations on structure−activity relationships within the new class of azecine-type dopamine receptor ligands led to the following conclusions: two aromatic rings annelated to the central 10-membered azecine are indispensable for high affinities at the dopamine receptors. The indole or the benzene moiety in the lead compound **1** cannot be replaced by phenyl but by other annelated aromatics, such as 1-methyl-1*H*-pyrrole, thiophene, and benzene instead of indole, respectively. Especially, the dibenzazecines show slightly improved selectivity profiles toward the D_1 receptor subtype family with the same or even higher affinities. A hydroxy substituent in position 2 leads to a novel highly potent ligand reaching subnanomolar affinity at the D_1 receptor.

Experimental Section

Chemistry. Melting points are uncorrected and were measured in open capillary tubes, using a Gallenkamp melting point apparatus. ^1H NMR spectral data were obtained from a Bruker Advance 250 spectrometer (250 MHz). Elemental analyses were performed on a Hereaus Vario EL apparatus. TLC was performed on silica gel F254 plates (Merck). MS data were determined by GC/MS, using a Hewlett-Packard GCD-Plus (G1800C) apparatus (HP-5MS column; J&W Scientific). Silica gel column chromatography utilized mainly silica gel 60 63−200 μm (Baker). Experimental procedures and spectroscopic data for compounds **13b,c**, **1b,c**, **2a,b**, **4b**, **18**, **19**, **6**, **21**−**25**, **5a,b**, **27**−**29**, **39**, **40**, **42**−**45**, **47**, **48**, **50**, **7a**−**c**, **10b**, **54**, **56**, **58**, **60b**, **11b,c,e,f**, **60a,b**, and **61a** and elemental analyses are given in the Supporting Information.

General Procedure for the Synthesis of Quaternary Indolizinium and Quinolizinium Salts (GP1). Typically, 24 mmol of alkyl halide was added to a solution of 8 mmol of the corresponding quinolizine or indolizine in 100 mL of dry acetone and the mixture was stirred for 20 h at room temperature. The precipitated solid was separated, washed with ether, and used for the subsequent Birch cleavage without further purification.

General Procedure for the Synthesis of Azonines and Azecines (GP2). The given amount of quaternary quinolinium or indolizinium salt, respectively, was dissolved in 50 mL of liquid ammonia and stirred at −40 to −50 °C (methanol/dry ice). Absolute ethanol (1.5 mL) was added, and subsequently, small pieces of sodium were added until the mixture turned blue, and the color remained for 1 h. Then ammonium chloride was added till the blue color disappeared. Overnight the solution was allowed to reach room temperature while the ammonia evaporated. After addition of 60 mL of water, the aqueous phase was extracted three times with 75 mL of diethyl ether. The ether fractions were washed with 2.5% aqueous sodium hydroxide solution and dried, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography over aluminum oxide (neutral, activity III) with diethyl ether/petrolether (bp 40−60 °C) 1:2 as eluent.

General Procedure for the Cyclization of Lactams and Reduction to Indolizines and Quinolizines (GP3). The given amount of lactam was dissolved in the given amount of $POCl_3$. The mixture was heated under reflux for the reported time. After cooling, excess phosphorus oxychloride was destroyed by carefully adding dropwise a 10% sodium hydroxide solution. For complete hydrolysis, the suspension was stirred for 12 h at room temperature. The solid formed was separated, dried, and dissolved in 150 mL of methanol. To this solution the given amount of solid sodium borohydride was slowly added under ice-cooling over a period of 15 min. The resulting suspension was stirred for 1 h at room temperature and the solvent removed under reduced pressure. The residue was dissolved in 100 mL of water and extracted three times with 60 mL of diethyl ether. The ether was dried and evaporated under reduced pressure. The crude product was purified as described.

7-Ethyl-5,6,8,9,14,14b-hexahydrobenz[*a*]indolo[3,2-*h*]quinolizinium iodide (13a) was synthesized according to GP1 using 2.2 g (8 mmol) of **12**[5] and ethyl iodide to yield 2.8 g (85%) of a colorless, amorphic solid: mp 217 °C; IR (KBr) 3270, 2850, 1445, 1130, 742 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.91 (s, 1H, NH), 7.59 (d, J = 7 Hz, 1H, H-1), 7.51 (d, J = 7 Hz, 1H, H-10), 7.39 (d, J = 7 Hz, 1H, H-13), 7.46−7.38 (m, 3H, H-2, H-4), 7.14 (td, J = 7/1 Hz, 1H, H-12), 7.03 (td, J = 7/1 Hz, 1H, H-11), 6.22 (s, 1H, H-14b), 4.08−3.89 (m, 4H, H-6, H-8), 3.60 (q, 2H, H-1′), 3.28−3.04 (m, 4H, H-5, H-9), 1.41 (t, J = 7 Hz, 3H, CH_3). Anal. ($C_{21}H_{23}N_2I$) C, H, N.

7-Cyclopropylmethyl-5,6,8,9,14,14b-hexahydrobenz[*a*]indolo[3,2-*h*]quinolizinium bromide (13b): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{23}H_{25}N_2Br$) C, H, N. See Supporting Information.

7-Phenylethyl-5,6,8,9,14,14b-hexahydrobenz[*a*]indolo[3,2-*h*]-quinolizinium bromide (13c): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{27}H_{27}N_2Br$) C, H, N. See Supporting Information.

7-Ethyl-6,7,8,9,14,15-hexahydro-5*H*-benz[*d*]indolo[2,3-*g*]azecine (1a) was synthesized according to GP2 using 1.5 g (3.5 mmol) of **13a** to yield 0.5 g (53%) of a colorless solid: IR (KBr) 3411, 2925, 1488, 739 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.73 (s, 1H, NH), 7.48 (dt, J = 6/2 Hz, 1H, H-1), 7.34 (dt, J = 8/1 Hz, 1H, H-10), 7.24 (dd, J = 7/1 Hz, 1H, H-13), 7.13−7.08 (m, 3H, H-1), 6.96 (ddd, J = 7/7/1 Hz, H-12), 6.88 (ddd, J = 8/7/1 Hz, 1H, H-11), 4.13 (s, 2H, H-15), 2.82 (dd, J = 7/3 Hz, 2H, H-6), 2.79 (dd, J = 6/2 Hz, 2H, H-8), 2.70 (dd, J = 6/2 Hz, 2H, H-9), 2.66 (dd, J = 7/3 Hz, 2H, H-5), 2.20 (q, J = 7 Hz, 2H, H-1′), 0.59 (t, J = 7 Hz, 3H, CH_3). Anal. ($C_{21}H_{24}N_2$) C, H, N.

7-Cyclopropylmethyl-6,7,8,9,14,15-hexahydro-5*H*-benz[*d*]indolo[2,3-*g*]azecine (1b): NMR (DMSO-d_6) was conducted. Anal. ($C_{23}H_{26}N_2$) C, H, N. See Supporting Information.

7-Phenylethyl-6,7,8,9,14,15-hexahydro-5*H*-benz[*d*]indolo[2,3-*g*]azecine (1c): NMR (DMSO-d_6) was conducted. Anal. ($C_{27}H_{28}N_2$) C, H, N.

7,8,13,13b-Tetrahydro-5*H*-benz[1,2]indolizino[8,7-*b*]indol-5-one (14). H_2SO_4 (20 mL, 2 N) was added to a solution of tryptamine (3.2 g, 20 mmol) and *o*-formylbenzoic acid (3 g, 20 mmol) dissolved in a mixture of 100 mL of ethanol and 100 mL of water and refluxed under nitrogen for 72 h. After cooling to room temperature, 30−40% of the product precipitated. The precipitate was collected by filtration and the filtrate evaporated to 50%. Again, product precipitated and was isolated. Recrystallization from ethanol yielded 3.78 g (69%) of **14** as a beige powder: mp 212−214 °C; IR (KBr) 3260, 1665, 730 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.37 (s, 1H, NH), 8.30 (ddd, J = 7/1.5/0.8 Hz, 1H, H-4), 7.75 (ddd, J = 7/1.5/0.8 Hz, 1H, H-1), 7.71 (dt, J = 7/1.4 Hz, 1H, H-3), 7.54 (dt, J = 7/1.4 Hz, 1H, H-2), 7.41 (ddd, J = 7.5/1.3/0.7 Hz, 2H, H-9, H-12), 7.10 (td, J = 7/1.5 Hz, 1H, H-11), 6.98 (td, J = 7/ 1.5 Hz, 1H, H-10), 6.05 (s, 1H, H-13b), 4.60 (dd, J = 14/5 Hz, 1H, H-7), 3.33 (dd, J = 14/5 Hz, 1H, H-7), 2.91−2.58 (m, 2H, H-8). Anal. ($C_{18}H_{14}N_2O$) C, H, N.

7,8,13,13b-Tetrahydro-5*H*-benz[1,2]indolizino[8,7-*b*]indole (15). $LiAlH_4$ (0.75 g, 10 mmol) was slowly added at 5−10 °C within 30 min to 1.16 g of **14** (4.2 mmol) dissolved in 50 mL of dry THF. The mixture was refluxed for 18 h, cooled to room temperature, and hydrolyzed at 5−10 °C by dropwise addition of 10% aqueous NaOH solution. The solution was extracted repeatedly with diethyl ether. The combined organic layers were dried with $MgSO_4$ and evaporated in vacuo. The remaining solid was recrystallized from ethanol to yield 0.56 g (51%) of slightly yellow crystals: mp 225 °C (dec); IR 2905, 2820, 1440, 731 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.78 (s, 1H, NH), 7.83 (d, J = 7 Hz, 1H, H-1), 7.38 (d, J = 7 Hz, 1H, H-4), 7.35−7.20 (m, 4H, H-2, H-3, H-9, H-12), 7.02 (td, J = 7/1 Hz, 1H, H-11), 6.93 (td, J = 7/1 Hz, 1H, H-10), 5.50 (s, 1H, H-13b), 4.15 (d, J = 14 Hz, 1H, H-5), 4.07 (d, J = 14 Hz, 1H, H-5), 3.77−2.92 (m, 4H, H-7, H-8). Anal. ($C_{18}H_{16}N_2$) C, H, N.

6-Methyl-5,6,7,8,13,14-hexahydroindolo[3,2-*e*]benzazonine (2a): ^1H NMR (DMSO-d_6) was conducted.

6-Ethyl-5,6,7,8,13,14-hexahydroindolo[3,2-*e*]benzazonine (2b): ^1H NMR (DMSO-d_6) was conducted.

***N*-[2-(1*H*-Indol-3-yl)ethyl]piperidin-2-one (16).** Tryptamine (16 g, 0.1 mol), 21 g (0.1 mol) of ethyl bromopentanoate, and 16 g of potassium carbonate were dissolved in 200 mL of *n*-butanol and refluxed for 16 h. After cooling and filtration, the solid was washed with 100 mL of *n*-butanol. The organic phase was removed under reduced pressure and the residual brown oil recrystallized from toluene 8.48 g (35%) to yield a beige solid: mp 156−158 °C; IR (KBr) 3260, 1608, 755, 745 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.85 (s, 1H, NH), 7.5 (d, J = 8 Hz, 1H, H-4), 7.32 (d, J = 8 Hz, 1H, H-7), 7.1 (s, 1H, H-2), 7.08−6.9 (m, 2H, H-5, H-6), 3.45 (t, J = 5 Hz, 2H, H-1′), 3.1−3.0 (m, 2H, H-6), 2.85 (t, J = 4 Hz, 2H, H-2′), 2.25−2.1 (m, 2H, H-3), 1.65−1.45 (m, 4H, H-4, H-5). Anal. ($C_{15}H_{18}N_2O$) C, H, N.

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (17) was synthesized according to GP3 using 5.0 g (0.02 mol) of **16**, dissolved in 100 mL of toluene and 20 mL of phosphorus oxychloride, to yield 2.33 g (51.6%) of a yellow solid: mp 150−152 °C; IR (KBr) 3400, 1445, 735 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.9 (s, 1H, NH), 7.53−7.49 (m, 1H, H-8), 7.26−7.22 (m, 1H, H-11), 7.19−7.11 (m, 2H, H-9, H-10), 3.23−3.17 (m, 1H, H-12b), 3.14−3.0 (m, 3H, H-7b, H-4b, H-6b), 2.77−2.61 (m, 2H, H-6a, H-7a), 2.44−2.36 (m, 1H, H-4a), 2.1−1.94 (m, 1H, H-1b), 1.9−1.82 (m, 1H, H-2b), 1.81−1.7 (m, 2H, H-3), 1.65−1.55 (m, 1H, H-1a), 1.5−1.4 (m, 1H, H-2a). Anal. C, H, N.

3-Methyl-1,2,3,4,5,6,7,8-octahydro-9*H*-azecino[5,4-*b*]indole (4a). Step 1. *N*-Methyl-5,8,9,13b-tetrahydro-6*H*-isoquino[1,2-*a*]isoquinolinium Iodide. To a solution of 1.0 g (4 mmol) of **17** in 20 mL of toluene was added 10 mL (155 mmol) of methyl iodide. The mixture was stirred at room temperature for 3 h. The colorless crystals were separated by means of filtration and dried in vacuo to yield 1.5 g (93%): mp 221−224 °C; IR (KBr) 3300, 1450, 750 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.15 (s, 1H, NH), 7.5 (d, J = 7 Hz,

1H, H-8), 7.35 (d, J = 7 Hz, 1H, H-11), 7.25−7.0 (m, 3H, H-9, H-10), 4.9−4.8 (m, 1H, H-12b), 4.1−3.8 (m, 1H, H-6b), 3.7−3.3 (m, 3H, H-4, H-6a), 3.25 (s, 3H, CH_3), 3.15−3.0 (m, 2H, H-7), 2.4−1.3 (m, 6H, H-1, H-2, H-3). Anal. ($C_{16}H_{21}N_2I$) C, H, N. **Step 2. 4a** was synthesized according to GP2 using 1.0 g (4 mmol) of the quatenary quinolizinium salt (see step 1) to yield 0.43 g (44.5%) of colorless crystals: mp 99−101 °C (lit.[10] mp 98−99 °C); IR (KBr) 3410, 2920, 2760, 1460, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (s, 1H, NH), 7.55−7.45 (m, 1H, H-13), 7.3−7.25 (m, 1H, H-10), 7.15−7.0 (m, 2H, H-11, H-12), 2.95−2.85 (m, 4H, H-2, H-4), 2.75−2.65 (m, 2H, H-1), 2.4 (t, J = 5.4 Hz, 2H, H-8), 2.05 (s, 3H, CH_3), 1.9−1.8 (m, 2H, H-5), 1.6−1.3 (m, 4H, H-6, H-7). Anal. ($C_{16}H_{22}N_2$) C, H, N.

3-Cyclopropylmethyl-1,2,3,4,5,6,7,8-octahydro-9*H*-azecino-[5,4-*b*]indole (4b): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{19}H_{26}N_2 \cdot 0.6C_4H_{10}O$) C, H, N.

***N*-[2-(1*H*-Indol-3-yl)ethyl]pyrrolidin-2-one (18):** ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{14}H_{16}N_2O$) C, H, N.

***N*-[2-(1*H*-Indol-3-yl)ethyl]pyrrolidine-2,5-dione (19):** ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{14}H_{14}N_2O_2$) C, H, N.

2,3,5,6,11,11b-Hexahydro-1*H*-indolizino[8,7-*b*]indole (20) (method a) was synthesized according to GP3 using 5.0 g (0.02 mol) of **18**, dissolved in 100 mL of toluene and 20 mL of phosphorus oxychloride, to yield 1.73 g (67.9%) of a beige solid: mp 173−174 °C; IR (KBr) 2920, 1440, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.85 (s, 1H, NH), 7.57−7.54 (m, 1H, H-7), 7.28−7.15 (m, 3H, H-8, H-9, H-10), 4.28−4.21 (m, 1H, H-11b), 3.4−3.33 (dd, J = 2.6/5.0 Hz, 1H, H-5b), 3.2−3.1 (m, 1H, H-5a), 3.06−2.91 (m, 3H, H-3, H-6a), 2.76−2.68 (ddd, J = 2.2/2.4/3.2 Hz, 1H, H-6a), 2.31−2.18 (m, 1H, H-2b), 1.98−1.82 (m, 3H, H1, H-2a). Anal. ($C_{14}H_{16}N_2$) C, H, N.

Method b. 19 (1 g, 4 mmol) was dissolved in 200 mL of dichlormethane, and 4.5 g (24 mmol) of Et_3OBF_4 was added under argon atmosphere. The solution was stirred free from light for 48 h at room temperature. The precipitated yellow solid was filtered off and dissolved in 20 mL of dry tetrahydrofuran. To this solution was added 0.25 g of sodium borohydride slowly under ice-cooling. The resulting suspension was stirred for 3.5 h at room temperature and the solvent removed under reduced pressure. The residue was dissolved in 100 mL of water and extracted three times with 50 mL of ethyl acetate. The combined organic phases were removed under reduced pressure and the residual solid was recrystallized from chloroform/petroleum ether. After that the colorless solid was dissolved again in 20 mL of dry tetrahydrofuran. Under ice-cooling this solution was added dropwise to a suspension of 0.3 g of lithium aluminum hydride in 10 mL of tetrahydrofuran. The suspension was refluxed for 10 h. Subsequently, the hydride was destroyed by dropwise adding of 2 mL of acetone and 50 mL of sodium hydroxide (5%). The precipitated solid was separated and washed with 100 mL of tetrahydrofuran. The organic layer was removed under reduced pressure and the residual yellow oil was recrystallized from toluene/*n*-hexane (1:3) to yield 0.24 g (53%). Analytical data are as described for method a above.

3-Methyl-1,2,3,4,5,6,7,8-octahydroazonino[5,4-*b*]indole (6): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{15}H_{20}N_2$) C, H, N.

6-Phenyltetrahydro-2*H*-pyran-2-one (21): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{11}H_{12}O_2$) C, H, N.

Ethyl 5-bromo-5-phenylpentanoate (22): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{13}H_{17}O_2Br$) C, H, N.

1-[2-(1*H*-Indol-3-yl)ethyl]-6-phenylpiperidin-2-one (23): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{21}H_{22}N_2O$) C, H, N.

5-Hydroxy-*N*-[2-(1*H*-indol-3-yl)ethyl]-5-phenylpentanamide (24): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{21}H_{24}N_2O_2$) C, H, N.

4-Phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (25): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{21}H_{22}N_2 \cdot {}^1/_2H_2O$) C, H, N.

3-Methyl-4-phenyl-2,3,4,5,6,7,8,9-octahydro-1*H*-azecino[5,4-*b*]indole (5a). ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{22}H_{26}N_2$) C, H, N.

3-Phenyltetrahydro-2*H*-pyran-2-one (26). This compound was prepared as reported in the literature.[15]

Ethyl 5-bromo-2-phenylpentanoate (27): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{13}H_{17Br}O_2$) C, H, N.

1-[2-(1*H*-Indol-3-yl)ethyl]-3-phenyl-2-piperidinone (28): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{21}H_{22}N_2O$) C, H, N.

1-Phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (29): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{21}H_{22}N_2 \cdot {}^1/_4H_2O$) C, H, N.

3-Methyl-7-phenyl-2,3,4,5,6,7,8,9-octahydro-1*H*-azecino[5,4-*b*]indole (5b): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{22}H_{26}N_2$) C, H, N.

The following compounds were prepared as reported in the literature:[16] *N*-[2-(1*H*-indol-3-yl)ethyl]-4-oxo-4-phenylbutanamide (**31**); *N*-[2-(1*H*-indol-3-yl)ethyl]-5-oxo-5-phenylpentanamide (**32**); 12b-phenyl-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one (**33**); 11b-phenyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (34); 12b-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-*a*]quinolizine (**35**); 11b-phenyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole (**36**); 5-methyl-12b-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizinium iodide (**37**); 4-methyl-11b-phenyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indolium iodide (**38**); 3-methyl-8-phenyl-2,3,4,5,6,7,8,9-octahydro-1*H*-azecino[5,4-*b*]indole (**5c**); and 3-methyl-7-phenyl-1,2,3,4,5,6,7,8-octahydro-azonino[5,4-*b*]indole (**7d**).

γ-Phenylbutyrolactone (39): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{10}H_{10}O_2 \cdot {}^1/_4H_2O$) C, H, N.

1-[2-(1*H*-Indol-3-yl)ethyl]-5-phenylpyrrolidin-2-one (40): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{20}H_{20}N_2O \cdot {}^1/_4H_2O$) C, H, N.

3-Phenyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole (42): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{20}H_{20}N_2 \cdot {}^1/_4H_2O$) C, H, N.

α-Phenylbutyrolactone (43): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{10}H_{10}O_2 \cdot {}^1/_2H_2O$) C, H, N.

1-[2-(1*H*-Indol-3-yl)ethyl]-3-phenyl-2-pyrrolidinone (44): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{20}H_{20}N_2O \cdot {}^1/_4H_2O$) C, H, N.

1-Phenyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole (45): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{20}H_{20}N_2$) C, H, N.

β-Phenylbutyrolactone (46). α-Bromoacetophenone (39.8 g, 0.2 mol) and 31.24 g (0.2 mol) of the potassium salt of methylmalonate were dissolved in 200 mL of DMSO and stirred for 1 h at room temperature. Ammonium acetate (15.4 g, 0.2 mol) was added and the solution was stirred for further 14 h. After addition of 100 mL of DMSO, 7.6 g (0.2 mol) of sodium borohydride was slowly added and the mixture stirred for 2 h at 40 °C. Subsequently, 7.6 g (0.2 mol) of acetic acid was added and the reaction stirred for 2 h further at 40 °C. Water (10 mL) was added and the mixture refluxed for 18 h. Afterward, the solution was poured into 500 mL of ice water and extracted with diethyl ether using an extractor. Removing of the organic phase under reduced pressure yielded a brown oil, which was purified by distillation, to yield 22 g (68%) of a yellow solid: mp 39−41 °C; IR (KBr) 2900, 1765, 755, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.3 (s, 5H, arom H)), 4.7 (dd, J = 7.8/8.7 Hz, 1H, H-5b), 4.3 (dd, J = 7.8/8.7 Hz, 1H, H-5a), 3.8 (m, 1H, H-4), 2.75 (m, 2H, H-3). Anal. ($C_{10}H_{10}O_2$) C, H, N.

Ethyl 4-bromo-3-phenylpentanoate (47): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{12}H_{15}BrO_2$) C, H, N.

1-[2-(1*H*-Indol-3-yl)ethyl]-4-phenyl-2-pyrrolidinone (48): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{20}H_{20}N_2O$) C, H, N.

2-Phenyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole (50): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{20}H_{20}N_2 \cdot {}^1/_2H_2O$) C, H, N.

3-Methyl-4-phenyl-1,2,3,4,5,6,7,8-octahydroazonino[5,4-*b*]indole (7a): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{21}H_{24}N_2$) C, H, N.

3-Methyl-5-phenyl-1,2,3,4,5,6,7,8-octahydroazonino[5,4-*b*]indole (7c): ^1H NMR (DMSO-d_6) was conducted. Anal. ($C_{21}H_{24}N_2$) C, H, N.

3-Methyl-6-phenyl-1,2,3,4,5,6,7,8-octahydroazonino[5,4-*b*]indole (7b). ^{1}H NMR (DMSO-d_6) was conducted. Anal. ($C_{20}H_{20}N_2 \cdot {}^1/_2H_2O$) C, H, N.

3,4-Dihydro-1-(3-thienyl)isoquinoline (51). Into 11 g (0.1 mmol) of stirred, freshly distilled 3-thiophencarbonitrile was added 40 g (185 mmol) of stannous(IV) chloride at room temperature. Hereby a complex formed that was heated to 95 °C and melted. Then 14.0 g (0.1 mol) of 2-phenylethyl chloride was added. The mixture was stirred at 110−120 °C for 4 h. Then it was mixed into 20% sodium hydroxide solution and stirred until an oily phase accumulated. This oil was separated and distilled with an aircooler. Overnight the oil became resin-like to yield 10.0 g (46.9%): bp 160 °C (0.1 mbar); IR (KBr) 3500−2700, 1700−1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.7 (d, 1H, arom), 8.3 (d, 1H, arom), 8.0−6.8 (m, 5H, arom), 5.2 (s, 1H, H-1), 3.9−3.5 (m, 2H, CH_2), 3.3−2.6 (m, 2H, CH_2). Anal. ($C_{13}H_{11}NS$) C, H, N.

***N*-Hydroxyethyl-3,4-dihydro-1-(3-thienyl)isoquinolinium Iodide (53).** 2-Iodoethanol (10 g, 58 mmol) was added to a solution of 10 g (46.9 mmol) of **51** in 100 mL of toluene. The mixture was stirred for 42 h under argon at 90 °C. The solvent was removed under reduced pressure and 100 mL of acetone was added. Yellow crystals formed rapidly, which were filtered off and dried in a vacuum to yield 7.0 g (37%): mp 165 °C; IR (KBr): 3400−3200, 3100, 1630−1570, 1610, 1570, 1510 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.3−8.2 (m, 1H, arom), 7.9−7.7 (m, 2H, arom), 7.6−7.3 (m, 3H, arom), 7.2−7.1 (m, 1H, arom), 5.4 (s, 1H, OH), 4.3−4.2 (t, 2H, H-3), 4.2−4.1 (t, 2H, H-9), 3.9−3.8 (t, 2H, H-10), 3.4−3.25 (t, 2H, H-4). Anal. ($C_{15}H_{16}INOS$) C, H, N.

2-(1-Thien-3-yl-3,4-dihydroisoquinolin-2(1*H*)-yl)ethanol (55). To a solution of 3.5 g (9 mmol) of **53** in 150 mL of methanol was added 9 g (238 mmol) of sodium borohydride in small amounts over 2 h. The mixture was boiled under reflux for 0.5 h. After cooling, the solvent was removed under reduced pressure. Water was added and twice extracted with 200 mL of ethyl acetate. The solvent was removed in vacuo. In the cold, crystals formed after 2 days to yield 2 g (84.9%): mp 49 °C; IR (KBr) 3800−3000, 2950, 2920, 2360, 1670−1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.4−7.35 (m, 1H, arom), 7.15−6.85 (m, 6H, arom), 5.05 (s, 1H, H-1), 4.4 (s, 1H, OH), 3.6−3.4 and 2.9−2.5 (m, 8H, aliph). Anal. ($C_{15}H_{17}NOS$) C, H, N.

4,7,8,12b-Tetrahydro-5*H*-thieno[3′,2′:3,4]pyrido[2,1-*a*]isoquinoline (57). A slurry of 1.8 g (4.7 mmol) of **55** in 40 g of polyphosphoric acid was heated and stirred at 160 °C for 6 h. The reaction was carried out under argon. The warm mixture was put onto ice and stirred until the ice had melted. It was extracted with 40 mL of diethyl ether and the ether was discarded. The mixture was neutralized with sodium hydroxide and twice extracted with 40 mL of ether. The solution was filtered through silica gel. Upon removing the ether, small yellow crystals were obtained, which were dissolved in 20 mL of ethanol and recrystallized in the cold. Afterward, the crystals were dried in vacuo to yield 1 g (55,9%) of yellow crystals: mp 101 °C; IR (KBr) 3060, 3020, 3010−2600, 1800−1700, 1660−1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.5−6.8 (m, 6H, arom), 5.15 (s, 1H, H-12b), 3.5−2.5 (m, 8H, aliph). Anal. ($C_{15}H_{15}NS$) C, H, N.

6-Methyl-4,5,6,7,8,13-hexahydrothieno[2,3-*f*][3]benzazecine (10a). Step 1. 6-Methyl-4,7,8,12b-tetrahydro-5*H*-thieno[3′,2′:3,4]-pyrido[2,1-*a*]isoquinolin-6-ium iodide was synthesized according to GP1 using 1 g (4.1 mmol) of **57** dissolved in 50 mL of acetone and 1 mL (16 mmol) of methyl iodide to yield 0.35 g (22.3%) of colorless crystals: mp 265 °C; IR (KBr) 3100−2800, 1700, 1495 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.6−7.2 (m, 5H, arom), 6.8 (d, 1H, H-12), 5.95 (s, 1H, H-12), 4.1−3.0 (m, 8H, aliph). Anal. ($C_{16}H_{18}NSI$) C, H, N. **Step 2. 10a** was synthesized according to GP2 using 0.35 g (0.9 mmol) of the quaternary salt (see step 1 above) as starting material. The oily product was purified by means of column chromatography using diethyl ether as eluent. The resinous product was recrystallized from methanol. In the cold, crystals formed, which were filtered off and dried in vacuo to yield 0.08 g (34.4%): mp 40 °C; IR (KBr) 3060−2600, 1800−1650, 1600, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.25−6.9 (m, 6H, arom), 4.19 (s, 2H, H-13), 2.85−2.6 (m, 8H, aliph), 2.25 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 140.3, 139.8, 138.2, 137.6 (4C, quat), 130.3, 129.8, 128.8, 126.3, 126.2, 121.3 (6C, arom), 60.0 (C-6), 61.0 (C-8), 45.6 (CH_3), 35.0 (C-5), 34.0 (C-9), 29.0 (C-13). Anal. ($C_{16}H_{19}NS$) C, H, N.

6-Allyl-4,5,6,7,8,13-hexahydrothieno[2,3-*f*][3]benzazecine (10b): ^{1}H NMR (DMSO-d_6) was conducted. Anal. ($C_{18}H_{21}NS$) C, H, N.

1-Phenyl-3,4-dihydroisoquinoline (52). This compound was prepared as reported in the literature.[20]

***N*-Hydroxyethyl-1-phenyl-3,4-dihydroisoquinolinium bromide (54):** ^{1}H NMR (DMSO-d_6) was conducted. Anal. ($C_{17}H_{18}$-BrNO) C, H, N.

2-(2-Hydroxyethyl)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (56): ^{1}H NMR (DMSO-d_6) was conducted. Anal. ($C_{17}H_{19}NO$) C, H, N.

5,8,9,13b-Tetrahydro-6*H*-isoquino[1,2-*a*]isoquinoline (58): ^{1}H NMR (DMSO-d_6) was conducted. Anal. ($C_{17}H_{17}N$) C, H, N.

7-Methyl-5,6,7,8,9,14-hexahydrodibenz[*d,g*]azecine (11a). Step 1. 7-Methyl-5,8,9,13b-tetrahydro-6*H*-isoquino[1,2-*a*]isoquinolinium iodide was synthesized according to GP1 using 1.6 g (6.8 mmol) of **58** in 40 mL of acetone and 1.8 mL (28 mmol) of methyl iodide to yield 1.85 g (72%) of colorless crystals: mp 258 °C; IR (KBr) 3460, 2881, 1497, 1440, 929, 775 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.5−7.3 (m, 6H, arom), 7.2−7.1 (d, 2H, arom), 5.95 (s, 1H, H-13b), 3.82 (t, 4H, H-6, H-8), 3.35 (s, 3H, CH_3), 3.3−3.15 (m, 2H, H-5, H-9). Anal. ($C_{18}H_{20}NI$) C, H, N. **Step 2. 11a** was synthesized according to GP2 using 0.75 g (2 mmol) of the quaternary salt (see step 1) as starting material. The product was purified by column chromatography using diethyl ether as eluent. The crude product was recrystallized from ethanol. The crystals were separated by filtration and dried in vacuo to yield 0.35 g (69.7%): mp 62 °C; IR (KBr) 2942, 2790, 1493, 1445, 1054, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29−7.25 (m, J = 9.1 Hz, 2H, H-1, H-13), 7.14−7.09 (m, J = 9.1 Hz, 4H, H-2, H-3, H-11, H-12), 7.07−7.02 (m, J = 9.1 Hz, 2H, H-4, H-10), 4.4 (s, 2H, H-14), 2.7−2.5 (m, 8H, aliph), 2.2 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 141.3, 141.1 (4C, quat.), 130.9, 130.6, 126.4, 126.3 (8C, arom), 60.8 (C-6, C-8), 46.8 (CH_3), 38.6 (C-14), 34.8 (C-5, C-9); MS *m*/*z* (% rel int) = 251 $[M]^{+\bullet}$ (30.6), 236 (16.7), 222 (3.6), 205 (12.9), 193 (82.5), 179 (100.0), 165 (20.8), 146 (95.6), 133 (7.7), 115 (33.8), 103 (8.3), 91 (15.5), 77 (9.1), 71 (24.9), 58 (31.5). Anal. ($C_{18}H_{21}N$) C, H, N.

2-(2-Hydroxyethyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]benzamide (60b): ^{1}H NMR (DMSO-d_6) was conducted. Anal. ($C_{18}H_{21}NO_3$) C, H, N.

2,3-Dimethoxy-5,6,8,9-tetrahydro-13b*H*-dibenzo[*a,h*]quinolizine (61b): ^{1}H NMR (DMSO-d_6) was conducted. Anal. ($C_{19}H_{21}$-NO_2) C, H, N.

2,3-Dimethoxy-7-methyl-5,6,7,8,9,14-hexahydrodibenzo[*d,g*]-azecine (11b): ^{1}H NMR (DMSO-d_6) was conducted. Anal. ($C_{20}H_{25}NO_2$) C, H, N.

7-Allyl-2,3-dimethoxy-5,6,7,8,9,14-hexahydrodibenz[*d,g*]azecine (11e): ^{1}H NMR (DMSO-d_6) was conducted. Anal. ($C_{22}H_{27}NO_2$) C, H, N.

2,3-Dimethoxy-7-phenylethyl-5,6,7,8,9,14-hexahydrodibenz-[*d,g*]azecine (11f): ^{1}H NMR (DMSO-d_6) was conducted. Anal. ($C_{27}H_{31}NO_2$) C, H, N.

7-Methyl-2,3-dihydroxy-5,6,7,8,9,14-hexahydrodibenzo[*d,g*]-azecine hydrobromide (11c): ^{1}H NMR (DMSO-d_6) was conducted. Anal. ($C_{18}H_{22}NO_2Br$) C, H, N.

2-(2-Hydroxyethyl)-*N*-[2-(3-methoxyphenyl)ethyl]benzamide (60a): ^{1}H NMR (DMSO-d_6) was conducted. Anal. ($C_{18}H_{21}NO_3$) C, H, N.

3-Methoxy-5,6,8,9-tetrahydro-13b*H*-dibenzo[*a,h*]quinolizine (61a). ^{1}H NMR (DMSO-d_6) was conducted. Anal. ($C_{18}H_{19}NO$) C, H, N.

3-Hydroxy-7-methyl-5,6,7,8,9,14-hexahydrodibenz[*d,g*]azecine (11d). Step 1. 3-Methoxy-7-methyl-5,6,8,9-tetrahydro-13b*H*-dibenzo[*a,h*]quinolizinium iodide was synthesized according to GP1 using 5.38 g (20.3 mmol) of **61a** in 50 mL of acetone and 5 mL (80 mmol) of methyl iodide. The mixture was stirred for 18 h

at room temperature and yielded 2.5 g (44%) of colorless crystals: mp 231 °C; IR (KBr) 3100−2750, 1610−1550, 1500−1480 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.4−6.8 (m, 7H, arom), 5.82 (s, 1H, H-13b), 3.75 (s, 3H, OCH_3), 3.35 (s, 3H, NCH_3), 3.65−3.38, 3.38−3.1 (m, 8H, H-5, H-6, H-8, H-9). Anal. ($C_{19}H_{22}INO$) C, H, N. **Step 2. 3-Hydroxy-7-methyl-5,6,8,9-tetrahydro-13b*H*-dibenzo[*a*,*h*]quinolizinium Bromide.** A solution of 0.5 g (1.2 mmol) of the quaternary salt (see step 1) in 50 mL of 47% hydrobromic acid was kept boiling for 4 h under argon. The solution was removed under reduced pressure. The remaining solid was suspended in acetone, filtered off, and dried in vacuo to yield 45 g (93%): mp 260 °C; IR (KBr) 3300−2700, 1640−1550 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.55 (s, 1H, OH), 7.5−6.7 (m, 7H, arom), 5.8 (s, 1H, H-13b), 3.8 (m, 4H, H-6, H-8), 3.76 (s, 3H, NCH_3), 3.2 (m, 4H, H-5, H-9). Anal. ($C_{18}H_{20}BrNO$) C, H, N. **Step 3. 11d** was synthesized according to GP2 using 0.5 g (1.3 mmol) of the quaternary hydroxylated salt (see step 2). The crude product was recrystallized from methanol to yield 0.27 g (79%) of colorless crystals: mp 72 °C; IR (KBr) 3500−2200, 1670−1570, 1540−1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35−7.0 (m, 5H, arom), 6.62−6.5 (dd, J = 7.0/2.3 Hz, 1H, H-2) (d, J = 2.3 Hz, 1H, H-4), 5.1 (s, 1H, OH), 4.2 (s, 2H, H-14), 2.8−2.7 (m, 8H, H-5, H-6, H-8, H-9), 2.3 (s, 3H, NCH_3); ^{13}C NMR ($CDCl_3$) δ 154.8, 141.7, 140.6, 140.2 (4C, quat.), 131.6, 131.5, 130.6, 130.5, 126.4 (5C, arom), 117.3, 113.7 (C-2, C-4), 58.8 (C-6, C-8), 46.2 ($N-CH_3$), 36.7 (C-14), 32.4, 32.5 (C-5, C-9); MS *m*/*z* (% rel int) = 267 $[M]^{+\cdot}$ (45.3), 252 (12.8), 221 (12.4), 209 (85.9), 195 (86.9), 178 (25.1), 162 (100.0), 146 (75.1), 133 (23.7), 115 (51.9), 103 (19.1), 91 (34.4), 77 (31.7), 58 (99.7). Anal. ($C_{18}H_{21}NO$) C, H, N.

3,6-Dimethyl-3,4,5,6,7,9,13,14-octahydro[3,2-*g*]azecine (8) and **3,6-dimethyl-4,5,6,7,8,13-hexahydro-3*H*-benzo[*d*]pyrrolo[3,2-*g*]-azecine (9)** were prepared as reported previously.[24]

Pharmacology. Functional Assay Measuring Intracellular Ca^{2+} Concentrations by a Fluorescence Microplate Reader. Ca^{2+} fluorescence measurements were performed using a FLUOstar microplate reader (BMG LabTechnologies, Offenburg, Germany) equipped with dual injectors. Screening for agonistic activity was performed using a NOVOstar microplate reader (BMG LabTechnologies) with a pipettor system. HEK293 cells recombinatly expressing dopamine hD_1, hD_{2L}, or hD_5 receptors, respectively, were harvested with 0.05% trypsin/0.02% EDTA (Sigma Chemical) and rinsed with culture medium containing 10% fetal bovine serum (Sigma Chemical). Pelleted cells were then resuspended in fresh medium and allowed to recover under 5% CO_2 at 37 °C for 1 h while being vortexed every 15 min. After two washes with Krebs-HEPES buffer (118 mM NaCl, 4.7 mM KCl, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 4.2 mM $NaHCO_3$, 11.7 mM D-glucose, 1.3 mM $CaCl_2$, 10 mM HEPES, pH 7.4), cells were loaded with 3 μM Oregon Green 488 BAPTA-1/AM (Molecular Probes, Eugene, OR) for 1 h at 25 °C in the same buffer containing 1% Pluronic F-127 (Sigma Chemical). Then, cells were rinsed three times with Krebs-HEPES buffer containing 0.5% bovine serum albumin (BSA) (Sigma Chemical), diluted, and evenly plated into 96-well plates (OptiPlate HTRF-96, Packard, Meriden, CT; Cellstar, Tissue Culture Plate, 96W, Greiner Bio-One, Frickenhausen, Germany). Microplates were kept at 37 °C. Agonistic activity was tested by injecting buffer alone, standard agonist, or test compounds, respectively, dissolved in buffer sequentially into separate wells. Fluorescence intensity was measured at 538 nm (bandwidth 25 nm) for 30 s at 0.4-s intervals. Excitation wavelength was 485 nm (bandwidth 20 nm). Screening of compounds for antagonistic activity or dose−response curves in the presence of an antagonist were performed by preincubating the cells with the compounds at 37 °C for 30 min prior to injection of standard agonist. Final concentration of test compounds for screening of agonistic or antagonistic activity was 10 μM, respectively. SKF 38393 was used as standard agonist for hD_1 (final concentraion: 100 nM) and hD_5 receptors (final concentration 10 nM), and quinpirole was used for hD_{2L} receptors (final concentration 30 nM).

IC_{50} values were obtained by determination of the maximum fluorescence intensity of each data set and nonlinear regression with a sigmoidal dose−response equation using a four-parameter logistic equation on Prism 3.0 (GraphPad Software, San Diego, CA). K_i values were then calculated to account for different agonist concentrations and EC_{50} values by applying a modified Cheng−Prusoff equation[25]

$$K_i = \frac{IC_{50}}{1 + \frac{L}{EC_{50}}}$$

where L is the concentration (M) of standard agonist, e.g., SKF 38393 or quinpirole, and EC_{50} is the 50% effective concentration (M) of the standard agonists SKF 38393 or quinpirole, respectively.

The determination of binding affinities by radioligand binding studies has been intensively described by us recently.[6,23] All binding assays were performed with whole-cell-suspensions. cDNA for hD_1 and hD_5 cloned in pGEM3 (Promega, Madison, WI) was obtained from Dr. David Grandy (Portland, OR). cDNA for hD_{2L} was obtained from Dr. Shine (Darlinghurst, Australia). The stably transfected CHO-$hD_{4.4}$ cell line was obtained from Dr. H. H. M. Van Tol (Toronto, Canada). All donations are gratefully acknowledged.

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Supporting Information Available: Routine experimental procedures, routine spectroscopic data, and elemental analysis results. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Wittig T. W.; Decker M.; Lehmann, J. Dopamine/Serotonin Receptor Ligands. 9: Oxygen-Containing Midsized Heterocyclic Ring-Systems and Nonrigidized Analogues. A Step toward Dopamine D_5 Receptor Selectivity. *J. Med. Chem.* **2004**, *47*, 4155−4158.

(2) Missale, C.; Nash, S. R.; Robinson, S. W.; Jaber, M.; Caron, M. G. Dopamine Receptors: From Structure to Function. *Physiol. Rev.* **1998**, *78*, 189−225.

(3) Sidhu, A.; Niznik, H. B. Coupling of Dopamine Receptor Subtypes to Multiple and Diverse G Proteins. *Int. J. Dev. Neurosci.* **2000**, *18*, 669−677.

(4) Seeman, P.; Van Tol, H. H. Dopamine Receptor Pharmacology. *Trends Pharmacol. Sci.* **1994**, *15*, 264−270.

(5) Witt, T.; Hock, F.; Lehmann, J. 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. *J. Med. Chem.* **2000**, *43*, 2079−2081.

(6) Kassack, M. U.; Höfgen, B.; Decker, M.; Eckstein N., Lehmann, J. Pharmacological Characterization of the Benz[*d*]indolo[2,3-*g*]azecine LE 300, a Novel Type of Nanomolar Dopamine Receptor Antagonist. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2002**, *366*, 543−550.

(7) Decker, M.; Schleifer, K.-J.; Nieger, M.; Lehmann, J. Dopamine/Serotonin Receptor Ligands. Part VIII: The Dopamine Receptor Antagonist LE300−Modelled and X-ray Structure Plus Further Pharmacological Characterization, including Serotonin Receptor Binding, Biogenic Amine Transporter Testing and In Vivo Testings. *Eur. J. Med. Chem.* **2004**, *39*, 481−489.

(8) Kassack, M. U.; Höfgen, B.; Lehmann, J.; Eckstein, N.; Quillan, J. M. Functional Screening of G Protein-coupled Receptors by Measuring Intracellular Calcium with a Fluorescence Microplate Reader. *J. Biomol. Screen.* **2002**, *7*, 233−246.

(9) El-Subbagh, H.; Wittig, T.; Decker, M.; Elz, S.; Nieger, M.; Lehmann, J. Dopamine/Serotonin Receptor Ligands. Part IV: Synthesis and Pharmacology of Novel 3-Benzazecines and 3-Benzazonines as Potential 5-HT_{2A} and Dopamine Receptor Ligands. *Arch. Pharm. Pharm. Med. Chem.* **2002**, *335*, 443−448.

(10) Herbst, D.; Rees, R.; Hughes, G. A.; Smith, H. The Preparation and Biological Activities of Some Azonino- and Azecinoindoles and Benzazecines. *J. Med. Chem.* **1966**, *9*, 864−868.

(11) Dolby, L. J.; Gribble, G. W. Conversion of Tetrahydro-β-carbolines into 2-Acylindoles. *J. Org. Chem.* **1967**, *35*, 1391−1398.

(12) Decker, M.; Nguyen, T. T. H.; Lehmann J. Investigations into the Mechanism of Lactamization of Lactones Yielding in a Novel Route to Biologically Active Tryptamine Derivatives. *Tetrahedron* **2004**, *60*, 4567−4578.

(13) Julia, M.; Rouault, A. Synthesis of Cyclobutanecarboxylic Acids. *Bull. Soc. Chim. Fr.* **1959**, 1833−1840.
(14) Wolf, R. M.; Francotte, E.; Lohmann, D. Quantitative Correlation between Calculated Molecular Properties and Retention of a Series of Structurally Related Racemates on Cellulose Triacetate. *J. Chem. Soc. Perkin Trans. 2* **1988**, *6*, 893−901.
(15) Shepherd, R. G. Preparation of α-Aryl-γ-butyrolactones. WO 9412487 A119940609, 1994.
(16) Houlihan, W. J.; Manning, R. E. Antidepressant Azecino- and Azonino[5,4-*b*]indoles. U.S. Patent 3,478,051, 1969.
(17) Shiroyan, F. R.; Terzyan, A. G.; Gevorkyan, Y. A.; Tatevosyan, G. T. Indole Derivatives. XXV. Substituted 1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizines Containing Angular Ethyl and Phenyl Groups. *Arm. Khim. Zh.* **1968**, *21*, 1025−1033.
(18) Wawzonek, S.; Nordstrom, J. D. Hexahydro-11H-pyrrolo[2,1-*a*]-β-carbolines and Tetrahydro-13H-isoindolo[1,2-*a*]-β-carbolines. *J. Med. Chem.* **1965**, *8*, 265−267.
(19) Mika, H. J.; Meise, W. Cyclisierung von N-(2-Phenyl)-2-(2-hydroxyethyl)benzamiden. *Arch. Pharm. (Weinheim, Ger.)* **1985**, *318*, 168−174.
(20) Vlaeminck, E.; De Cock, D.; Tourweand and G. Van Binst, G. Synthesis and Conformation of 5,6,8,9-Tetrahydro-13b-dibenzo[*a*,*h*]-quinolizine and 5,6,8,9,14,14b-Hexahydrobenzo[*a*]-indolo[3,2-*h*]-quinolizine. *Heterocycles* **1981**, 1213−1218.
(21) Meise, W.; Müller, H. L. Neue Synthese von Dibenzo[*a*,*h*]chinolizinen. *Synthesis* **1976**, *11*, 719−721.
(22) Van Binst, G.; Baert, R. B. Benzo- and indoloquinolizine derivatives. III. Synthesis and Structural Assignments of 4b,5,6,7,8,8a,10,11-Octahydro-15b*H*-tribenzo[*a*,*c*,*h*]quinolizine (4b,5,6,7,8,8a,10,11-Octahydro-15b*H*-isoquino[2,1-*f*]phenanthridine) *J. Heterocycl. Chem.* **1975**, *12* (6), 1165−1174.
(23) Decker, M.; Lehmann J. Dopamine/Serotonin Receptor Ligands. Part VII: Novel 3-Substituted 5-Phenyl-1,2,3,4,5,6-hexahydro-azepino-[4,5-*b*]-indoles as Ligands for the Dopamine Receptors. *Arch. Pharm. Pharm. Med. Chem.* **2003**, *336*, 466−476.
(24) Rostom S. A. F, Farghaly A. M., Soliman F. S. G. S., El-Semary M. M., Elz S, Lehmann J. Derivatives of the Novel Heterocycles indolo-[3,2-*d*]pyrrolo[3,2-*g*]azecine and Benzo[*d*]pyrrolo[3,2-*g*]azecine—Synthesis and 5-HT_{2A} Antagonist Activity Compared to the Analogous Benz[*d*]indolo[2,3-*g*]azecine LE 300. *Arch. Pharm. Pharm. Med. Chem.* **2001**, *334*, 227−230.
(25) Cheng, Y.; Prusoff, W. Relationship between the Inhibition Constant (K_i) and the Concentration of Inhibitor Which Causes 50 Per Cent Inhibition (IC_{50}) of an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.

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