Dopamine/Serotonin Receptor Ligands. 12[1]: SAR Studies on Hexahydro-dibenz[*d,g*]azecines Lead to 4-Chloro-7-methyl-5,6,7,8,9,14-hexahydrodibenz[*d,g*]azecin-3-ol, the First Picomolar D_5-Selective Dopamine-Receptor Antagonist

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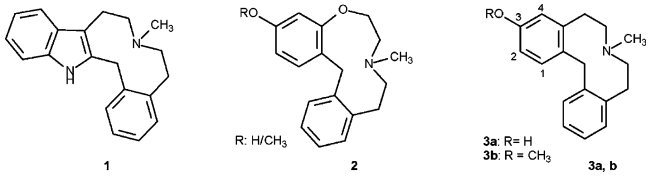
Hydroxylated, methoxylated, and/or chlorinated 7-methyl-5,6,7,8,9,14-hexahydrodibenz[*d,g*]azecines were generally synthesized out of substituted 2-phenylethylamines and isochromanones by Bischler−Napieralski cyclization of the resulting benzamides to dibenzoquinolizines and the quaternization and cleavage of the central C−N bond under Birch conditions. Chlorination of 2-phenylethylamines was useful for the site direction of cyclization, but chlorine atoms were removed under Birch conditions so that chlorination had to be repeated to get the respective chlorinated dibenz[*d,g*]azecines. The target compounds were tested for their affinity at the different human-cloned dopamine-receptor subtypes (D_1 family, D_2 family). Generally, hydroxylation and chlorination of the dibenz-azecines increased affinities significantly. 1-Chloro-2-hydroxy-hexahydro-dibenz[*d,g*]azecine was a subnanomolar antagonist at both subtype families. 4-Chloro-3-hydroxy-7-methyl-5,6,7,8,9,14-hexahydro-dibenz[*d,g*]azecine was identified as the most potent and selective dopamine D_5 receptor ligand described to date with $K_i(D_1) = 0.83$, $K_i(D_{2L}) = 4.0$, $K_i(D_3) = 24.6$, $K_i(D_4) = 5.2$ nM, and $K_i(D_5) = 57$ pM (radioligand binding experiments), respectively.

Introduction

Dopamine-receptor-mediated neurotransmission plays a key role in psychiatric, motoric, and endocrinological disorders, especially because of the application of antagonists as antipsychotics. Because of a lack of highly selective D_1- and D_5-receptor ligands, knowledge about the physiological impact of activation or antagonism of these single receptors, especially the D_5 receptor, is strictly limited or nonexistent.[2] The D_5 receptor is of special interest, because it is, in contrast to the D_1 receptor, directly coupled to the $GABA_A$ receptor, enabling inhibitory functional interactions.[3] It might also be of therapeutic relevance concerning cocaine addiction because of the fact that it was shown in D_5 knockout mice that the D_5 receptor seems to be involved in the locomotor-stimulant effects of cocaine, whereas there is only little involvement in the discriminative-stimulus effects of cocaine.[4] Our lead structure LE300 (7-methyl-6,7,8,9,14,15-hexahydro-5*H*-indolo[3,2-*f*][3]-benzazecine (**1**); Chart 1, Table 1) represents a potent D_1-family-selective ligand, which was shown to antagonize the discriminative-stimulus effects of cocaine and to attenuate locomotor activity without showing cocaine-like effects.[5,6] We have intensively performed SAR studies within this novel class of dopamine receptor ligands, including variations in ring size,[1,7] the insertion of an additional oxygen atom into the alicyclus (**2**),[8] and changing one of the aromatic moieties (indole replaced by benzene, thiophene, and 1-methyl-1*H*-pyrrole, respectively) and its location with respect to each other at the central alicyclic ring.[1]

Hexahydro-dibenzo[*d,g*]azecines (**3**) turned out to be highly potent at the D_1-subtype family, especially the 3-hydroxy- and 3-methoxy-compounds.[1] In the present study, different positions of the hydroxy/methoxy groups should be evaluated with respect to their affinities and selectivity profiles. Apart from changing the position of the hydroxy/methoxy group at one of the benzene rings, the introduction of a second hydroxy/methoxy group at the second benzene ring should also be performed to improve affinities and/or selectivities thereby gaining additional information about the structural properties of future dopamine receptor antagonists to be designed. The dibenz[*g,j*]-1-oxa-4-azacycloundecenes (**2**) in which one benzene is substituted by one +M and −I substituent (actually two such substituents when taking into account the phenol ether group of the 11-membered ring) showed for the first time some selectivity toward D_5 within the D_1-subtype family.[8] Therefore, the introduction of a chlorine atom as an additional +M and −I substituent into the substituted benzene ring of dibenz[*d,g*]azecines (**3**) seemed to be promising. Also the nonsubtype-selective D_1/D_5 antagonist SCH 23390 ((5*R*)-8-chloro-3-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-ol) bears a chlorine substituent and a hydroxy group at the condensed benzene ring.[9] Conclusively, the optimal position of chlorine in the hydroxylated/methoxylated hexahydro-dibenz[*d,g*]azecine template should be evaluated.

Chart 1. Lead Structures LE300 (**1**), Dibenz[*g,j*][1,4]oxazacycloundecenes (**2**), and 3-Hydroxy/Methoxy-dibenz[*d,g*]azecines (**3**)



1 2 3a, b

Chemistry

3-Hydroxy-7-methyl-5,6,7,8,9,14-hexahydrodibenz[*d,g*]azecine[1] (**3a**) served as the starting material for the introduction of additional chlorine atoms into the hydroxy-substituted benzene ring by a reaction of **3a** with sulfonyl dichloride in glacial acetic acid yielding the 4-chloro- and the 2,4-dichloro-substituted compounds (**3c** and **3d**).[10] No compound with chlorination exclusively in position 2 could be detected. This means that

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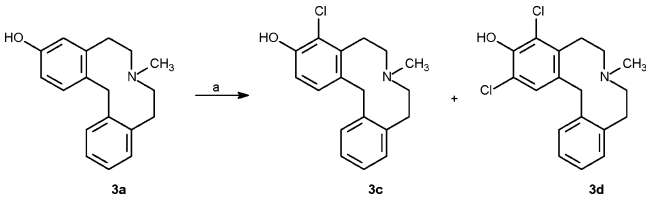
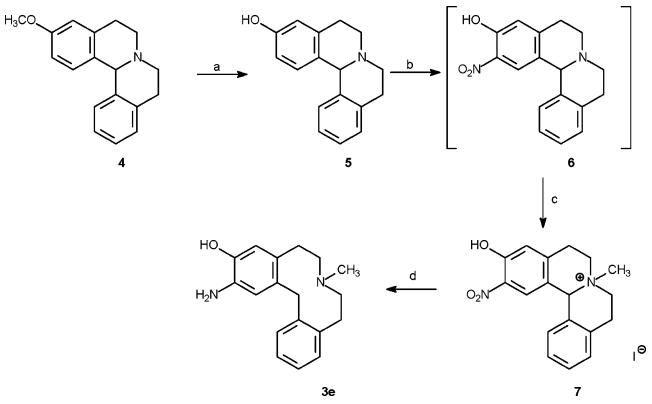
Scheme 1. Synthesis of 4-Chloro- (**3c**) and 2,4-Dichloro-3-hydroxy-dibenz[*d,g*]azecine (**3d**)[a]



[a] a: SO_2Cl_2, glacial acetic acid.

Scheme 2. Synthesis of 2-Amino-3-hydroxy-7-methyl-5,6,7,8,9,14-hexahydrodibenz[*d,g*]azecine (**3e**)[a]



[a] a: 47% HBr; b: concentrated HNO_3, glacial acetic acid; c: CH_3I; and d: Na°, liq. NH_3.

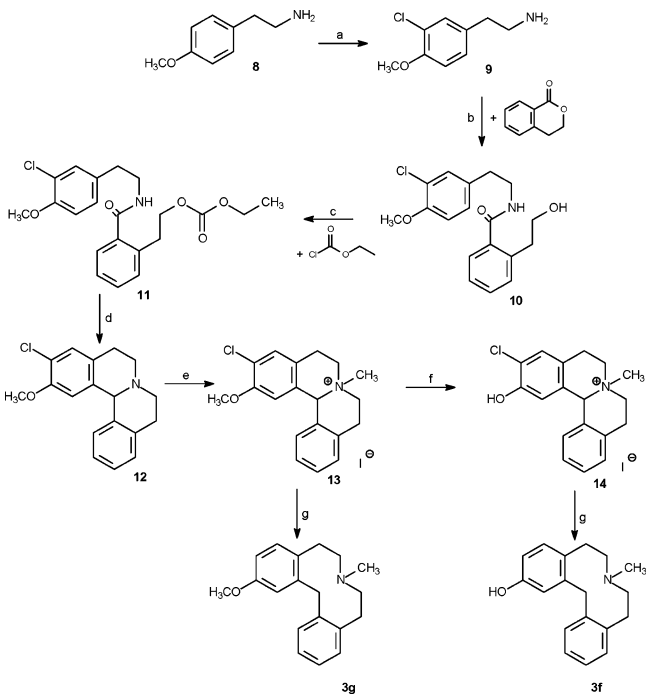
substitution in this position only takes place after the chlorination of position 4 (Scheme 1).

We also introduced an amino-group into position 2, yielding compound **3e**, which opens the possibility to further modifications. The 3-methoxy-dibenz[*a,h*]quinolizine (**4**) was prepared from isochromanone and 2-(3-methoxyphenyl)ethylamine by the Bischler−Napieralski reaction followed by reduction with sodium borohydride.[11] The ether bond was cleaved with hydrogen bromide followed by nitration.[1,11,12] Resulting crude product **6** was methylated, and the central C−N bond cleaved under Birch conditions. Under these conditions, the nitro group was also reduced to yield **3e** (Scheme 2).

The synthesis of 3-chloro-2-hydroxy- and 3-chloro-2-methoxy-dibenz[*d,g*]azecines turned out to be difficult because of the need to activate the right positions by appropriate substituents to successfully perform the Bischler−Napieralski cyclization and to regulate the sensitivity of the chloro substituents toward the reductive media. 2-(4-Methoxyphenyl)ethylamine (**8**) was chlorinated and reacted with isochromanone to a benzamide (Scheme 3).[1,10] The free hydroxy group was protected with ethyl chloridocarbonate to prevent lactamization under Bischler−Napieralski conditions.[8] The reaction of protected compound **11** with phosphoryl chloride produced a dihydroisoquinoline, which was deprotected by KOH, and subsequent ring closure yielded respective quinolizine (**12**) after the reduction by sodium borohydride.[1,8] The ether bond could be cleaved after N-methylation to yield phenol **14**, but under ring-opening conditions the chlorine atoms were removed. Therefore, the initial chlorination step could theoretically be skipped to synthesize the 2-hydroxy/2-methoxy compounds (**3f** and **g**), although it was found to facilitate ring-closure in the Bischler−Napieralski reaction (Scheme 3).

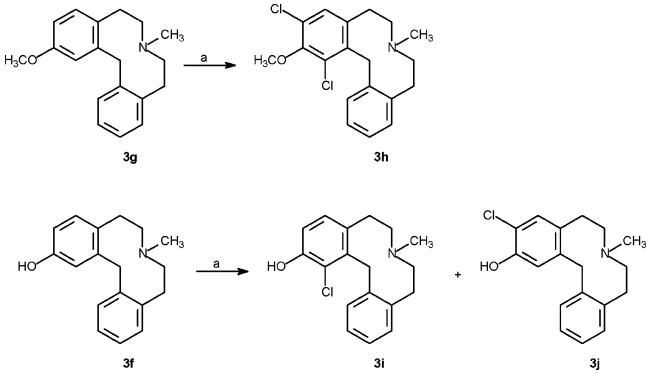
To avoid dechlorination, different C−N cleaving conditions were applied, including PtO_2/H_2, Pd/H_2, thiophenol/NaOH, and NaH/DMSO, but none of them was successful.

Scheme 3. Synthesis of 2-Hydroxy- (**3f**) and 2-Methoxy-7-methyl-5,6,7,8,9,14-hexahydrodibenz[*d,g*]azecine (**3g**)[a]



[a] a: SO_2Cl_2, glacial acetic acid; b: 5 h, 120 °C; c: pyridine, 1h, at room temperature; d: (1) $POCl_3$, (2) KOH, (3) $POCl_3$, and (4) $NaBH_4$; e: CH_3I; f: 47% HBr; and g: Na°, liq. NH_3.

Scheme 4. Synthesis of 1,3-Dichloro-2-methoxy- (**3h**), 1-Chloro-2-hydroxy- (**3i**), and 3-Chloro-2-hydroxy-7-methyl-5,6,7,8,9,14-hexahydrodibenz[*d,g*]azecine (**3j**)[a]

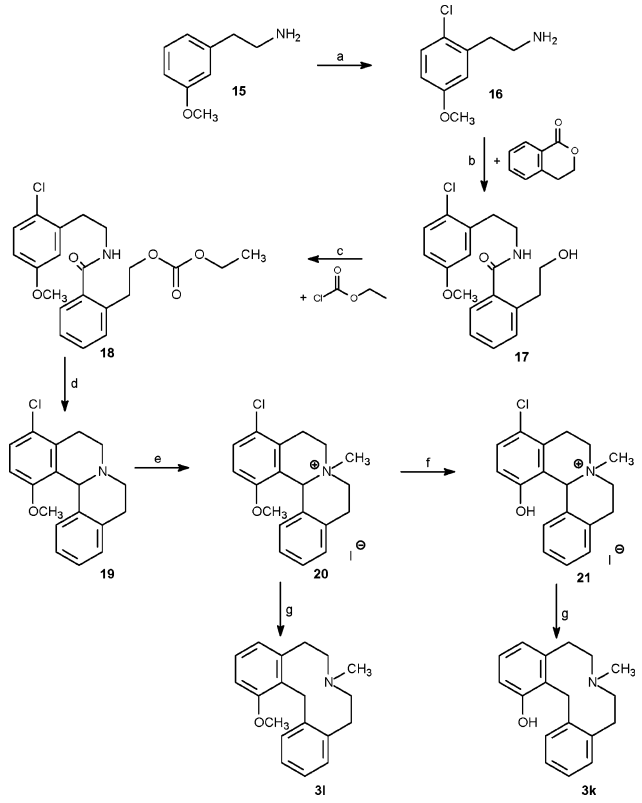


[a] a: SO_2Cl_2, glacial acetic acid.

The chlorination of 2-methoxy-dibenz[*d,g*]azecine (**3g**) yielded the 1,3-dichloro compound **3h**, whereas careful chlorination of 2-hydroxydibenz[*d,g*]azecine (**3f**) yielded the 1-chloro (**3i**) and 3-chloro compounds (**3j**), although in poor yields (**3i**: 8%, **3j**: 3.4%; Scheme 4).[10]

For the synthesis of 1-hydroxy- and 1-methoxy-dibenz[*d,g*]-azecines (**3k** and **l**), 2-(3-methoxyphenyl)ethylamine (**15**) was chlorinated in the first step (Scheme 5).[10] In contrast to the chlorination of 1-(3-methoxyphenyl)methylamine, which yields the ortho product,[10] we only found chlorination in the position para to the methoxy group. The reaction with isochromanone, protection of the hydroxy-group (to prevent lactamization), cyclization, reduction, methylation, and C−N cleavage yields 1-methoxy-dibenz[*d,g*]azecine (**3l**). Ether cleavage prior to C−N cleavage yields the corresponding 1-hydroxy compound (**3k**) (Scheme 5). Again, the chlorine atom was removed under Birch conditions. Nevertheless, the chlorine atom is essential for site

Scheme 5. Synthesis of 1-Hydroxy- (**3k**) and 1-Methoxy-7-methyl-5,6,7,8,9,14-hexahydrodibenz[*d*,*g*]azecine (**3l**)[a]



[a] a: SO_2Cl_2, glacial acetic acid; b: 5 h, 120 °C; c: pyridine, 1h, at room temperature; d: (1) $POCl_3$, (2) KOH, (3) $POCl_3$, and (4) $NaBH_4$; e: CH_3I; f: 47% HBr; and g: Na°, liq. NH_3.

direction because in an unsubstituted compound, the para position of the ring-opened compound is more activated than the ortho position, and cyclization would probably occur at this position yielding 3-methoxy-dibenz[*d*,*g*]azecine (**3b**) (Chart 2).

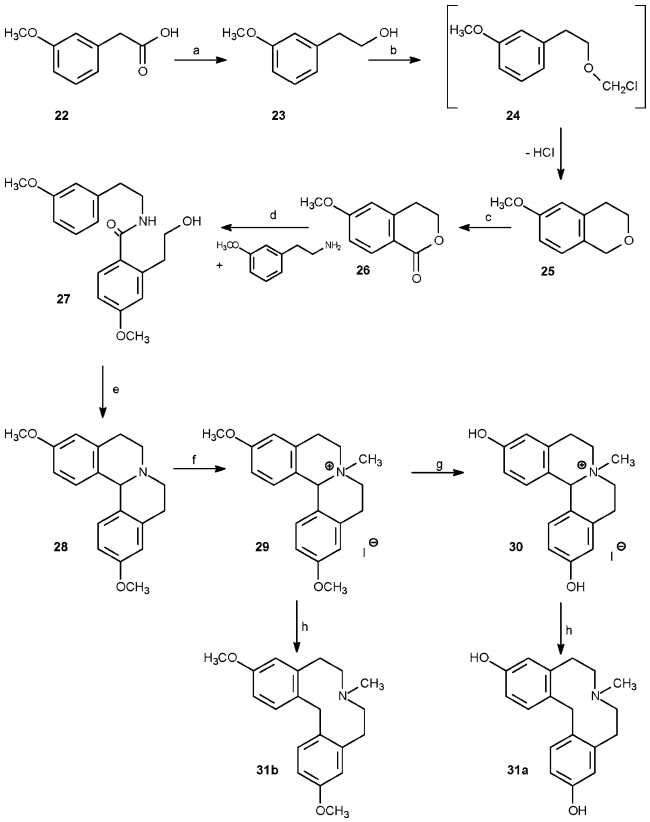
To estimate the influence of an additional hydroxy and methoxy group at the second benzene ring, 3,11-dihydroxy-dibenz[*d*,*g*]azecine (**31a**) and 3,11-dimethoxy-dibenz[*d*,*g*]azecine (**31b**) were prepared. The synthesis of the compounds was performed analogous to that for the dibenz[*d*,*g*]azecines described before (Schemes 3 and 5), starting from 6-methoxyisochromanone (**26**) and 2-(3-methoxyphenyl)ethylamine. Compound **26** was prepared from (3-methoxyphenyl)acetic acid (**22**) by reduction with $LiAlH_4$,[13] followed by a reaction of resulting alcohol **23** with formaldehyde/HCl(g)[14] and finally, the oxidation of resulting 6-methoxyisochroman (**25**) with potassium permanganate in the presence of a phase transfer catalyst.[15, 16]

Biology/SAR

Compounds **3c**−**l** and **31a** and **b** were screened for their binding affinities to human-cloned dopamine-receptor subtypes by in vitro radioligand-binding studies following the protocol previously described.[1, 7]

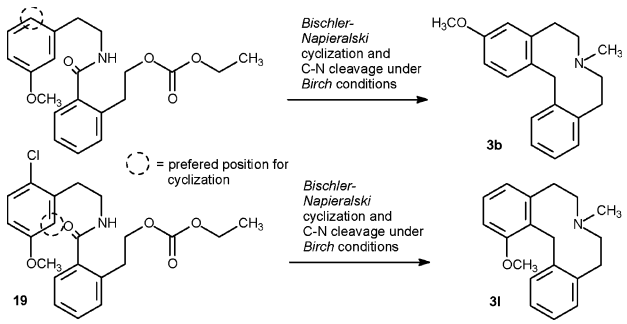
D_1, D_{2L}, D_3, and D_5 receptors were stably expressed in HEK 293 or CHO cells. [^{3}H]SCH 23390 and [^{3}H]spiperone were used as radioligands for experiments at the D_1- and D_2-receptor family, respectively. Incubations at 27 °C were terminated after 90 min by rapid filtration with a Perkin-Elmer Mach III harvester. Two to three independent experiments each were carried out in triplicate. K_i values (in nM) were calculated from IC_{50} values applying the equation of Cheng and Prusoff[17] (Table 1).

Scheme 6. Synthesis of 3,11-Dihydroxy- (**31a**) and 3,11-Dimethoxy-7-methyl-5,6,7,8,9,14-hexahydrodibenz[*d*,*g*]azecine (**31b**)[a]



[a] a: $LiAlH_4$; b: (1) $(CH_2O)_n$ and (2) HCl_g; c: $KMnO_4$; d: 2h, 140 °C; e: (1) $POCl_3$ and (2) $NaBH_4$; f: CH_3I; g: 47% HBr; and h: Na°, liq. NH_3.

Chart 2. Site Direction of the Chloro Substitution during Bischler−Napieralski Cyclization to Avoid Cyclization in the para Position (to yield **3b**) Instead of the ortho Position (to yield **3l**)



In addition, the compounds were tested in an intracellular Ca^{2+} assay developed in our group, which has been described in detail in recent literature.[1,18] HEK293 cells, stably expressing the respective hD receptor, were loaded with a fluorescent dye (Oregon Green), and after preincubation with rising concentrations of the test compound, an agonist (SKF 38393) was injected, and the fluorescence was measured with a NOVOSTAR microplate reader. In this assay, the ability of the test compound to suppress agonist-induced Ca^{2+} influx with rising concentrations is an indication of antagonistic or inverse agonistic behavior at the hD receptor subtype. From the inhibition curve, a K_i value can be defined, which is similar to that obtained by radioligand-binding studies (Table 1).[18]

Like dibenz[*d*,*g*]azecines **3a** and **3b**, all of the novel dibenz-[*d*,*g*]azecines **3c**−**l** synthesized showed antagonistic properties in the calcium assay (data not shown).[1,18]

Table 1. K_I Values of Dibenz[*d*,*g*]azecines **3a**−**l** and **31a** and **b** at Dopamine-Receptor Subtypes Measured by Radioligand-Binding Studies (Affinities) and an Intracellular Calcium Assay (Inhibitory Activities)[7,18]

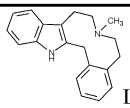
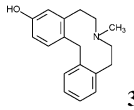
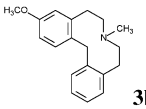
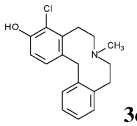
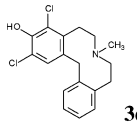
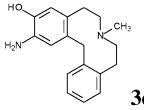
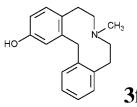
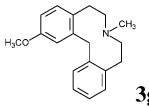
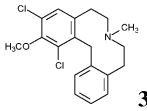
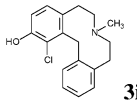
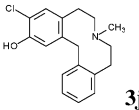
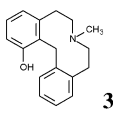
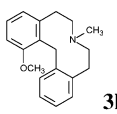
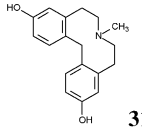
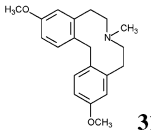
Compound	K_i [nM] (Radioligand binding studies / calcium assay)			
	D_1	D_{2L}	D_3	D_5
 LE300 (**1**)	1.9 ± 0.5[a] / 60.4 ± 20.4[a]	44.7 ± 15.8[a] / 19.0 ± 11.7[a]	n. d. / n. d.	7.5 ± 0.3[a] / 12.7 ± 9.0[a]
 **3a**	0.39 ± 0.22[b] / 1.35 ± 0.25[b]	17.5 ± 1.5[b] / 33.5 ± 17.0[b]	47.5 ± 24 / n. d.	1.5 ± 0.5[b] / 1.69 ± 1.9[b]
 **3b**	28.5 ± 9.7[b] / 24.1 ± 3.9[b]	13.0 ± 9.0[b] / 0.55 ± 0.23[b]	75.7 ± 7.3 / n. d.	n. d. / 7.2 ± 3.8[b]
 **3c**[c]	0.83 ± 0.15 / 0.46 ± 0.36	4.0 ± 1.9 / 6.1 ± 4.8	24.6 ± 6.4 / n. d.	0.057 ± 0.06 / 0.053 ± 0.02
 **3d**	3.2 ± 0.6 / 3.8 ± 1.4	88 ± 21 / 37.5 ± 12	n. d. / n. d.	n. d. / 1.2 ± 0.7
 **3e**	9.3 ± 3.3 / 20.9 ± 9.5	37.3± 10.8 / 26.1 ± 1.0	n. d. / n. d.	226.5 ± 75.5 / 39.5 ± 11.2
 **3f**	8.9 ± 0.8 / 76.5 ± 16.5	36.9 ± 27.8 / 2.6 ± 0.6	296 ± 60 / n. d.	42.3 ± 22.4 / 37.5 ± 22.5
 **3g**	82 ± 30 / 567 ± 70	62 ± 5 / 21.1 ± 2.5	150.5 ± 57.5 / n. d.	n. d. / 1050 ± 309
 **3h**	25.3 ± 55 / 34 ± 27	210 ± 133 / 2.5 ± 0.8	415 ± 138 / n. d.	n. d. / 59 ± 47
 **3i**	0.46 ± 0.22 / 6.8 ± 4.9	0.99 ± 0.02 / 0.13 ± 0.06	1.88 ± 0.33 / n. d.	0.98 ± 0.83 / 1.6 ± 0.7
 **3j**	3.1 ± 1.7 / 10.8 ± 9.2	2.0 ± 0.5 / 4.8 ± 2.5	27.7 ± 12.2 / n. d.	4.9 ± 2.4 / 3.1 ± 0.7
 **3k**	8.7 ± 2.0 / 64.1 ± 19.5	84 ± 3 / 7.9 ± 0.3	215 ± 94 / n. d.	n. d. / 10.4 ± 4.0
 **3l**	7.6 ± 1.5 / 37.6 ± 1.2	164 ± 12 / 39.9 ± 38	1833 ± 292 / n. d.	n. d. / 54.6 ± 33.5

Table 1. (Continued)

Compound	K_i [nM] (Radioligand binding studies / calcium assay)			
	D_1	D_{2L}	D_3	D_5
 **31a**	2.0 ± 1.2 / 3.3 ± 0.1	58.7 ± 11.7 / 19.0 ± 10.5	342 ± 99 / n. d.	1.68 ± 0.6 / 0.54 ± 0.36
 **31b**	9.4 ± 1.0 / 26.9 ± 11.4	6.5 ± 0.2 / 0.62 ± 0.34	101.5 ± 4.5 / n. d.	12.6 ± 9.8 / 11.5 ± 7.5

[a] See ref 18. [b] See ref 1. [c] K_i (D_4) = 18.7 ± 20.0 nM (radioligand-binding studies).

Comparing 3,11-dihydroxy- (**31a**) and 3,11-dimethoxy-dibenz-[*d*,*g*]azecine (**31b**) with their monosubstituted analogues **3a** and **3b**, respectively, we found that the selectivities for hydroxy compounds **3a** and **31a** stay the same, but with a 5-fold lower affinity at both subtype families for the dihydroxy compound. For the 3,11-dimethoxy-dibenz[*d*,*g*]azecine (**31b**), the affinities are slightly higher than the ones for **3b** in the binding studies. In the calcium assay, the affinities do not differ at all. Subsequently, we have focused on the substitution pattern of only one benzene ring.

Concerning the influence of the position of the hydroxy and methoxy groups, the 3-hydroxy/methoxy compounds (**3a** and **b**) are the most active ones. There is a slight decrease for the 2-substituted compounds (**3f** and **g**) and almost no change in affinity from position 2 to position 1 (**3k** and **l**), which has almost the same binding profile as the unsubstituted dibenz-[*d*,*g*]azecine.[1] Therefore in position 1, these substituents do not seem to interact with the receptor. Generally, there is only a minor influence of the position of the hydroxy/methoxy group on compound activity. Methoxylated compounds (**3b** and **g**) have a roughly 10-fold lower affinity at the D_1 receptor than the respective hydroxy compounds (**3a** and **f**).[1]

2-Amino-3-hydroxy-7-methyl-5,6,7,8,9,14-hexahydrodibenz-[*d*,*g*]azecine (**3e**) is also a nanomolar ligand at both subtype families but does not show any significant improvement either in affinity or selectivity compared to the other substitution patterns described in this work. This corresponds to the finding that 2,3-dihydroxy-7-methyl-5,6,7,8,9,14-hexahydrodibenz[*d*,*g*]-azecine, although structurally very similar to the endogenous ligand dopamine, is far less active than 3-hydroxy compound **3a**.[1]

The most interesting compounds, both in terms of selectivity and affinity, are the chlorinated hydroxy-7-methyl-5,6,7,8,9,14-hexahydrodibenz[*d*,*g*]azecines (**3c**, **d**, and **h**−**j**). Concerning 2-hydroxy-dibenz[*d*,*g*]azecine **3f**, its 3-chloro-substituted derivative **3j** loses its selectivity to the D_1 family but increases in affinity at all of the dopamine-receptor subtypes tested, being a nanomolar antagonist at all subtypes. The 1-chloro compound **3i** (LE-PM 452) is also not selective but represents a sub-nanomolar ligand at the D_1 and D_2 families. Being such a potent ligand at all subtypes is remarkable, especially because this compound also shows high nanomolar affinity to the D_3 receptor. Compound **3i** is by far the most potent D_3 antagonist in the range of our compounds because of the chlorination in position 1. Interestingly, the binding profile of 2-methoxylated-dibenz[*d*,*g*]azecine (**3g**) is not significantly different from that of 1,3-dichloro-2-methoxy-dibenz[*d*,*g*]azecine (**3h**). These compounds represent one of the rare cases in which the radioligand results and those from the calcium assay differ: in the calcium assay both compounds are D_2 selective (**3g** is more pronounced), whereas **3h** shows a 10-fold D_1 selectivity in the radioligand-binding studies (correlating to a less pronounced selectivity toward D_2 in the binding studies). These findings cannot be easily explained, but might be due to the fact that the radioligand studies measure affinities in equilibrium, whereas an equilibrium might not be reached before measurements are taken in the calcium assay.[1,18] Therefore, kinetic effects might become relevant.

Similar to 1,3-dichloro-2-methoxy-dibenz[*d*,*g*]azecine (**3h**), 2,4-dichloro-3-hydroxy-dibenz[*d*,*g*]azecine (**3d**) also shows slightly lower affinities than those of unchlorinated compounds **3a** and **3b**, respectively. Compound **3h** shows 10-fold D_1 selectivity in contrast to **3b**. But 4-chloro-3-hydroxy-dibenz-[*d*,*g*]azecine (**3c**) (LE-PM 436) is a subnanomolar ligand toward the D_1 receptor (>30-fold selectivity $D_1 > D_2$) with an even higher affinity toward D_5, showing a $K_i(D_5)$ of 57 pM and therefore representing the most potent D_5 antagonist to our knowledge. Its 10−15-fold fold selectivity $D_5 > D_1$ is almost in the range of the 3-methoxylated dibenz[*g*,*j*]-1-oxa-4-aza-cycloundecene (**2**) previously described, but in contrast to **2**, the D_5 selectivity goes together with an outstanding picomolar affinity.[8]

Conclusions

All of the dibenz[*d*,*g*]azecines **3c**−**l** synthesized were found to be nanomolar ligands at the dopamine receptors with more or less pronounced selectivity toward the D_1 family. The lowest affinity at D_1 shows 2-methoxy compound **3g** ($K_i(D_1)$ = 82 nM). The substitution pattern strongly influences the affinities and selectivities. Compound **3i** is a subnanomolar ligand at all of the dopamine receptors tested (D_1, D_{2L}, D_3, D_5) but lacks in selectivity. Compound **3c** shows subnanomolar affinities only at the D_1 familiy and an almost 15-fold selectivity toward the D_5 subtype within the D_1 family, being the most potent ligand at the dopamine D_5 receptor described to date with $K_i(D_5)$ = 57 pM.

Experimental Section

General. Melting points were uncorrected and were measured in open capillary tubes using a Gallenkamp melting-point apparatus. ^{1}H NMR and ^{13}C NMR spectral data were obtained from Bruker Avance 250 and Avance 400 spectrometers (250 MHz, 400 MHz, respectively). Elemental analyses were performed on a Vario EL III apparatus (Firma elementar Analysensysteme GmbH, Germany).

TLC was performed on silica gel 60 F_{254} plates (Merck). For some separations (see respective procedures) a chromatotron, model 8924 by Harrison Research (Palo Alto, CA), was applied using 2 mm silica gel 60 PF_{254}. MS data were determined by GC/MS, using a Hewlett-Packard GCD-Plus (G1800C) apparatus (HP-5MS column; J&W Scientific). IR data were obtained from a Magna-IR FT-IR spectrometer, system 550 by Nicolet (WI).

Detailed/specified descriptions for the preparation of target compounds/respective intermediates and their physical/spectral data (NMR, MS, IR) are reported in the Supporting Information.

General Procedure 1: Synthesis of Dibenzo[*d,g*]azecines (3). A solution of the given amounts of dibenzo[*a,h*]quinazolinium iodide (**13**, **14**, **20**, **21**, **29**, and **30**) in 50 mL of liquid ammonia was stirred at −40 °C under a nitrogen atmosphere. Small parts of sodium metal (∼4 mm^3) were added portionwise until the mixture showed a deep-blue color. After 15 min, the reaction was terminated by adding dropwise a saturated aqueous solution of NH_4Cl until the blue color completely disappeared. The mixture was stirred at room temperature under nitrogen until the ammonia had completely evaporated. Then, 50 mL of 2N HCl was added, and the emulsion was extracted with ether (3 × 20 mL). The combined organic layers were discarded, the pH adjusted to 7, and the aqueous phase extracted with methylene chloride (3 × 15 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield the crude product, which was purified as described in the Supporting Information for the individual compounds.

General Procedure 2: Synthesis of Dibenzo[*a,h*]quinazolinium Iodides (13, 20, and 29). The given amounts of dibenzo[*a,h*]quinolizine (**12**, **19**, and **28**) were dissolved in 30 mL of dried acetone and then excess methyl iodide was added, and the mixture was stirred under nitrogen at 65 °C for 18 h. After cooling, the white solid was filtered off, washed with acetone, and dried in vacuo.

General Procedure 3: Synthesis of Dibenzo[*a,h*]quinolizines from *O*-Protected Benzamides (12 and 19). A solution of 10 mmol of the respective benzamides (**11** and **18**) in 80 mL of acetonitrile and 8 mL (87 mmol) of phosphoric trichloride (each freshly distilled) was heated at 95 °C for 18 h. After cooling, the solvent was removed under reduced pressure, and the dark residue was dissolved in 50 mL of 2N HCl. This mixture was washed with chloroform (5 × 20 mL), and after drying over $MgSO_4$, the solvent of the combined organic layers was removed in vacuo. To the residual oil, 60 mL of a 20% KOH solution in aqueous ethanol (70% EtOH, 30% H_2O) was added and the mixture stirred for 16 h at r.t.

After removal of the solvent in vacuo, the solution was acidified with concentrated HCl and extracted with chloroform (6 × 20 mL), and after drying over $MgSO_4$, the solvent of the combined organic layers was removed under reduced pressure. The residue was dissolved in 15 mL of phosphoric trichloride and heated for 15 min under stirring at 60 °C. After cooling, 50 mL of petrol ether (60/40) was added, and the mixture was intensively extracted three times so that a dark oil could separate. Finally, the dark residue was dissolved in 50 mL of methanol, to which 3 g (78 mmol) of sodium borohydride was added under stirring and cooling over ice for 30 min. The mixture was stirred for another 30 min at r.t. and concentrated to dryness in vacuo. The residue was resuspended in 50 mL of water and extracted with diethyl ether (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield the crude product, which was purified as described in the Supporting Information.

General Procedure 4: Protection of the Hydroxy Groups of 2-(2-Hydroxyethyl)-*N*-(2-phenylethyl)benzamides (11 and 18). To a solution of 2.4 mmol of the respective 2-(2-hydroxyethyl)-*N*-(2-phenylethyl)benzamides (**10** and **17**) in 45 mL of pyridine/chloroform (2/1) were added under stirring 2 g (18.9 mmol) of ethyl chloroformiate (ethyl chloridocarbonate) in 15 mL of chloroform over 30 min. The stirring was continued for 1 h at room temperature, after which the solvent was removed in vacuo and the residue dissolved in 60 mL of methylene chloride. The solution was washed twice with 2N HCl, once each with 2N NaOH and water. After drying over $MgSO_4$, the solvent was removed in vacuo, and the residual oil triturated with a few milliliters of diethyl ether. After cooling, a white solid (**18**: beige solid) formed and was filtered off, washed with ether, and dried in vacuo.

General Procedure 5: Ether Cleavage of Methoxy-dibenzo-[*a,h*]quinazolinium Iodides (14, 21, and 30). A solution of 1.2 mmol of the respective methoxy-dibenzo[*a,h*]quinazolinium iodides (**13**, **20**, and **29**) in 40 mL of 47% hydrogen bromide was refluxed under stirring for 5 h. After cooling, the solvent was removed in vacuo, the residue dissolved in 50 mL of methanol, a small amount of charcoal was added, and the mixture was heated under reflux for 1 h. The hot suspension was filtered and the solvent removed under reduced pressure. Purification of the crude product is described in the Supporting Information.

General Procedure 6: Preparation of 2-(2-Hydroxyethyl)-*N*-(2-phenylethyl)benzamides (10, 17, and 27). A mixture of 27 mmol of the respective 2-phenylethylamine (e.g., **9** and **16**) and 27 mmol of the respective isochromanone was stirred at 120 °C for 5h. After cooling, the resulting oil was dissolved in 50 mL of chloroform and this solution extracted with 2N HCl (2 × 30 mL). The organic layer was dried over $MgSO_4$ and the solvent removed in vacuo. The residual oil was heated with 50 mL of 20% aqueous NaOH at 70 °C for 30 min. After cooling, the solution was extracted with chloroform (3 × 40 mL), the organic layers dried over $MgSO_4$, the solvent evaporated, and the crude product purified as described in the Supporting Information.

General Procedure 7: Chlorination of 2-Phenylethylamines (2-(3-Chloro-4-methoxyphenyl)ethylamine (9) Hydrochloride and 2-(2-Chloro-5-methoxyphenyl)ethylamine (16) Hydrochloride). To a solution of 10 g (66.1 mmol) of 2-(4-methoxyphenyl)-ethylamine (**8**) or 2-(3-methoxyphenyl)ethylamine (**15**) in 130 mL of glacial acetic acid, 13.4 g (99.2 mmol) of sulfonyl chloride was added under stirring and cooling over ice so that the temperature did not exceed 25 °C. A solid formed but dissolved again later. After 3 h, 200 mL of diethyl ether was added, and the stirring was continued for 1h. The precipitate formed was filtered off and was recrystallized from MeOH/diethyl ether.

Pharmacology. Experimental details of both the radioligand-binding studies[7] and the calcium assay[1,18] have been described in detail in recent publications.

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Supporting Information Available: Synthetic procedures and spectral characterization for compounds **3**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org

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