Dopamine/Serotonin Receptor Ligands. 16.[1] Expanding Dibenz[*d,g*]azecines to 11- and 12-Membered Homologues. Interaction with Dopamine D_1−D_5 Receptors

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Received April 3, 2007

Oxygenated 7-methyl-5,6,7,8,9,14-hexahydrodibenz[*d,g*]azecines are potent dopamine receptor antagonists, preferentially at D_1/D_5. We synthesized the hydroxylated, methoxylated, and chlorinated 11-membered and 12-membered homologues of these 10-membered heterocycles. Their affinities for the human cloned D_1−D_5 receptors (radioligand binding) and functionalities (calcium assay) were measured. Enlarging the dibenzazecines to the corresponding dibenzazacycloundecenes and dibenzazacyclododecenes generally maintains the high antagonistic affinity for D_1/D_5 but also leads to a compound with a clozapine-like binding profile due to additional affinity for D_4.

Introduction

Dopamine-receptor-mediated neurotransmission plays a key role in psychiatric, motor, and endocrinologic disorders, and antagonists at the dopamine receptors are widely used as antipsychotics. Because of a lack of highly subtype selective D_1 and D_5 receptor ligands, knowledge of physiological impacts of agonism or antagonism at these receptors is very limited. Discoveries such as the functional interaction between the D_1 and the NMDA receptors[2] and the direct coupling of the D_5 receptor with the $GABA_a$-R γ-subunit[3] further increase the interest in selective D_1 and D_5 ligands as pharmacological tools or as potential therapeutic agents. Antagonists at the D_1 receptor family such as ecopipam have been suggested for the treatment of obsessive compulsive disorder (OCD), obesity, metabolic disorders, eating disorders such as hyperphagia, and diabetes.[4,5] These compounds have also been suggested to be useful in treating alcohol[6] or cocaine[7−9] addiction. Many scientists are convinced nowadays that so-called "dirty drugs" or multiacting receptor targeted antipsychotics (MARTA) do have advantages over selective compounds especially for the treatment of psychosis.[10,11]

With regard to the azecine-type dopamine receptor ligands, we have performed SAR studies that included variation of the aromatic parts (benzene replaced by indole, thiophene. and 1-methyl-1*H*-pyrrole), contraction of the central heterocycle from 10 to 9,[12] or insertion of an oxygen atom.[13] Expansion of the central N-heterocycle has been successfully conducted for the benzindoloazecine ring system (**1** → **4**)[14] but not for any dibenzazecine derivatives such as **2** and **3** (Chart 1).

In the present study we performed the homologization of the hydroxylated and methoxylated hexahydrodibenz[*d,g*]azecines **2** and **3**, and the resulting 11- and 12-membered heterocycles were investigated with respect to their affinities and selectivity profiles for the D_1−D_5 receptors. Retaining the aromatic substitution pattern unchanged should allow us to exclusively identify the influence of the ring expansion on affinity and selectivity. We prepared the 12-membered target compounds **9**,**10** and both of the possible regioisomers **5**,**6** and **7**,**8** of the nonsymmetric 11-membered ring (Chart 2).

We also wanted to synthesize and screen an open-ring, more flexible derivative of ecopipam (**11** (SCH 39166), Chart 3).

Chart 1. Lead Structures **1** (LE 300) and 3-Hydroxy- and Methoxydibenz[*d,g*]azecines **2** and **3** and 11-Membered Homologue **4** with Improved Affinity over **1**

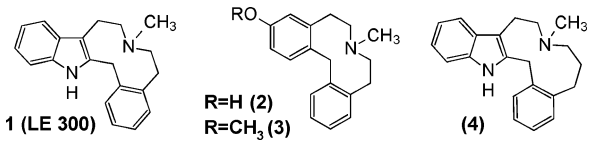


Chart 2. Homologization of Dibenzazecines **2** and **3** to Corresponding Dibenzazacycloundecenes (**5**−**8**) and Dibenzazacyclododecenes (**9** and **10**).

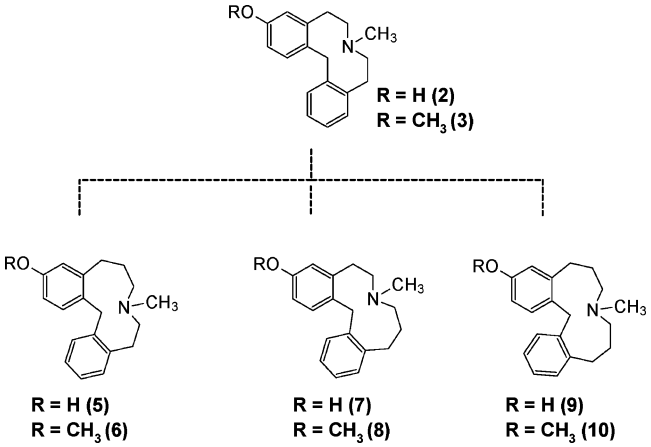
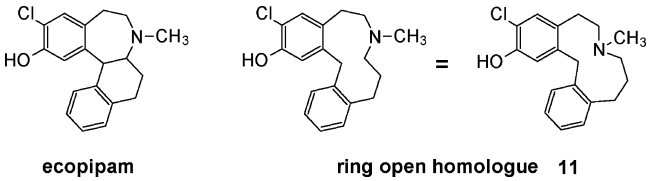


Chart 3. Open-Ring Derivative of Ecopipam



Ecopipam represents a rigidified benzazepine-type D_1/D_5 antagonist that may be useful for treating obesity and has reached a phase 3 clinical study.[5] Furthermore, studies with humans have been performed to investigate its effects on reducing alcohol or cocaine dependency.[7−9]

Finally we aimed for the nor-compound **25**, which is not only important with regard to SAR but also obligatory for developing an optional ^{11}C-methylated positron emission tomography (PET)

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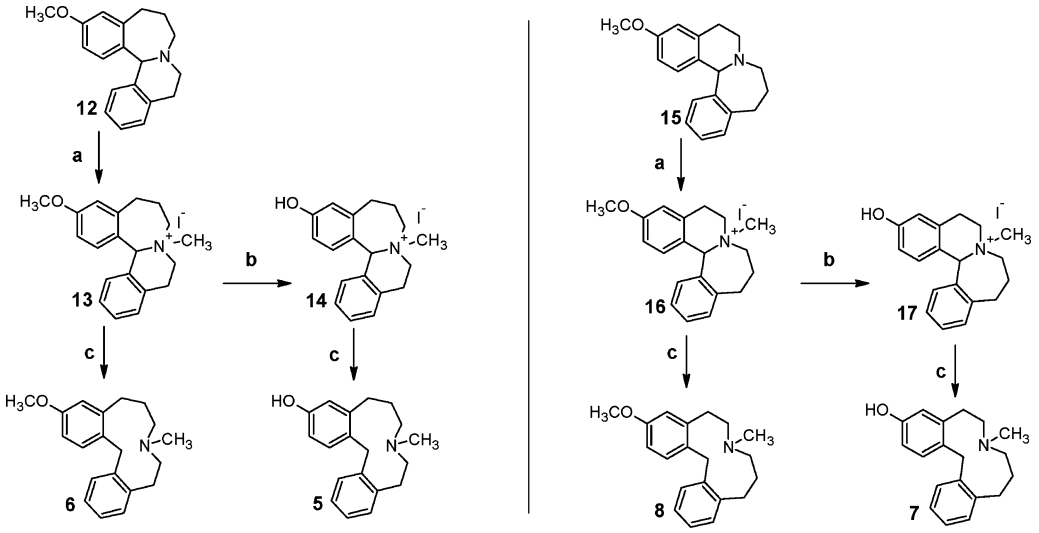
10.1021/jm070388+ CCC: $37.00
Published on Web 08/04/2007

Scheme 1. Synthesis of the Azacycloundecenes **5**−**8**[a]



[a] (a) Methyl iodide, acetonitrile; (b) HBr, glacial acetic acid; (c) Na/NH_3^{liq}.

ligand. And we elaborated a new route for the preparation of *N*-desalkyl derivatives in this class of compounds by applying ethyl chloridocarbonate (see Scheme 1).[15]

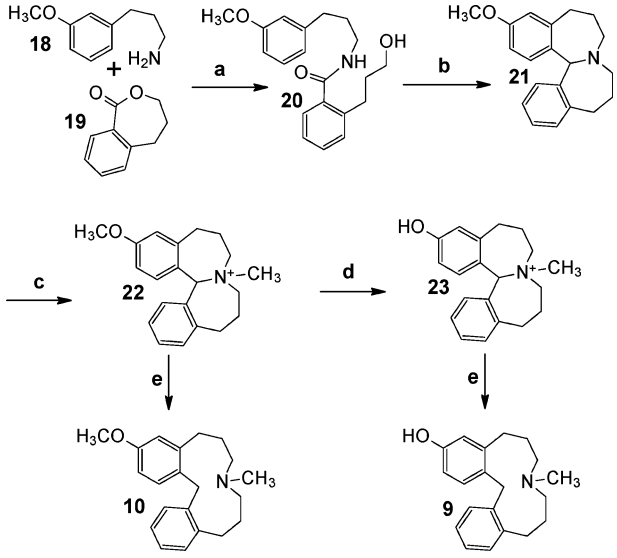
Chemistry

In order to obtain the 11-membered dibenzazacycloundecens **5**−**8**, we first synthesized the appropriate tetracyclic precursor molecules **12** and **15** following a route that has been described.[16,17] We used 3-methoxyphenylpropylamine and isochromanone to prepare **12**[16] and 3-methoxyphenethylamine and the benzoxepinone derivative **19** to get **15**.[17] **19** was synthesized from tetralone by applying a five-step route described by Krollpfeiffer and Müller.[18] The homoquinolizine derivatives **12** and **15** were converted to their quaternary salts **13** and **16** with methyl iodide in acetonitrile. Cleavage of the methoxy ether was accomplished with hydrobromic acid in glacial acetic acid. Birch conditions were used for the ring-opening procedure (Scheme 1).

The corresponding 12-membered congener was prepared analogously starting from the two three-carbon synthons **18** and **19** (Scheme 2). The resulting hydroxypropylbenzamide derivative **20** was successfully converted to the benzazepinobenzazepine **21** by applying a Bischler−Napieralski cyclization and $NaBH_4$ reduction sequence that has been performed as well for the synthesis of **15**.[17] Methylation and ether cleavage of the resulting quaternary salt **22** produced the respective phenolic compound **23**. Ring cleavage of **22** and **23** gave the azacycloundecene derivatives **9** and **10**.

Chlorinated target compounds including the 11-membered "opened" ecopipam (Chart 3) could not be synthesized as described in Scheme 1 because the chlorine atom was completely removed under Birch conditions. So we looked for other ring cleavage procedures. Furthermore, we were interested in having a nonmethylated derivative such as compound **25** for pharmacological screening. Treatment with ethyl chloridocarbonate/$NaCNBH_3$[19] proved to be a milder method for cleaving the central C−N bond compared to sodium in liquid ammonia, and **12** was transferred easily to the urethane derivative **24**. Simultaneous cleavage of the ether moiety and hydrolysis of the urethane **24** were accomplished with BBr_3 as formerly described by Tanaka et al.[15] to yield in the phenolic nor-compound **25**. As outlined in Scheme 3, this route also represents a further approach to N-methylated azacycloundecenes by $LiAlH_4$ reduction of the urethane, allowing us to prepare compound **6** from **13** as well as from **24**. Furthermore, Scheme 3 shows that nor-compounds can be synthesized either from quinolizine-like derivatives (e.g., **12**) or from "opened" azecine-like compounds by demethylation (e.g., **6**).

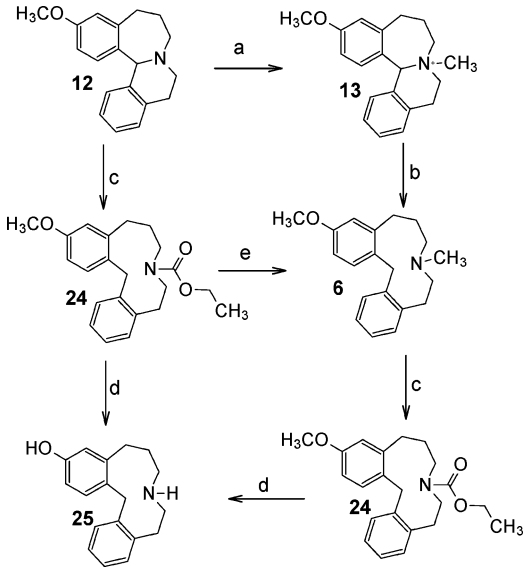
Scheme 2. Synthesis of the Azacyclododecenes **9** and **10**[a]



[a] (a) Toluene, reflux; (b) (1) $POCl_3$/acetonitrile, reflux; (2) $NaBH_4$/MeOH; (c) methyl iodide, acetonitrile; (d) HBr, glacial acetic acid; (e) Na/NH_3^{liq}.

For the synthesis of the "opened" ecopipam, 2-(4-methoxyphenyl)ethylamine was chlorinated to **26**[20] and reacted with the benzoxepinone **19** to yield the benzamide **27** (Scheme 4). Applying the usual treatment with $POCl_3/NaBH_4$ unfortunately resulted in the benzazepine derivative **28**, probably via a cyclic chloroiminium salt. So we protected the hydroxy group[16] and performed a first cyclization of **29** toward the substituted benzene with $POCl_3$ yielding a dihydroisoquinoline derivative, which was deprotected by KOH. The hydroxy group of this intermediate was chlorinated with $POCl_3$, and a subsequent reduction of the dihydroisoquinolinium derivative with $NaBH_4$ gave way to the second ring closure, yielding the homoquinolizine derivative **30** ("one-pot" procedure; intermediates are not shown in Scheme 4). Reaction with methyl iodide produced the quaternary salt **31**, which yielded the deschloro compound **32** after Birch reduction. The phenolic quaternary salt **33** was

Scheme 3. Different Approaches for Ring Cleavage and Synthesis of nor-Compounds[a]



[a] (a) Methyl iodide, acetonitrile; (b) Na/NH_3^{liq}; (c) ethyl chloridocarbonate THF, $NaCNBH_3$, −78 °C to room temp; (d) BBr_3 $CHCl_3$; (e) THF, $LiAlH_4$.

obtained from **31** by treatment with HBr/HOAc. Ring cleavage under Birch conditions gave, as expected, the dechlorinated phenolic azacycloundecene derivative **34**.

To avoid dechlorination, other conditions for cleaving the C−N bond in compound **30** were selectively investigated, including C,N-hydrogenolysis with PtO_2/H_2 or treatment with ethyl chloridocarbonate/$NaCNBH_3$, but unfortunately none of them turned out to be successful. In contrast to compound **12** (Scheme 3), unreacted starting material was recovered after all of these experiments. This may indicate that the aromatic substituents significantly influence the ability of the quinolozines and homoquinolizines to undergo ring cleavage. Accordingly, we had to reintroduce the chlorine after ring cleavage. We treated **34** with $SOCl_2$ in glacial acetic acid at low temperatures and detected four different compounds by GC/MS: unreacted starting material, very low amounts of two monochlorinated compounds, and one compound bearing two chlorine atoms. Recrystallization, column chromatography, and preparative TLC failed to separate and isolate the two monochlorinated compounds. Only starting material **34** and the dichlorinated target compound **35** could be isolated.

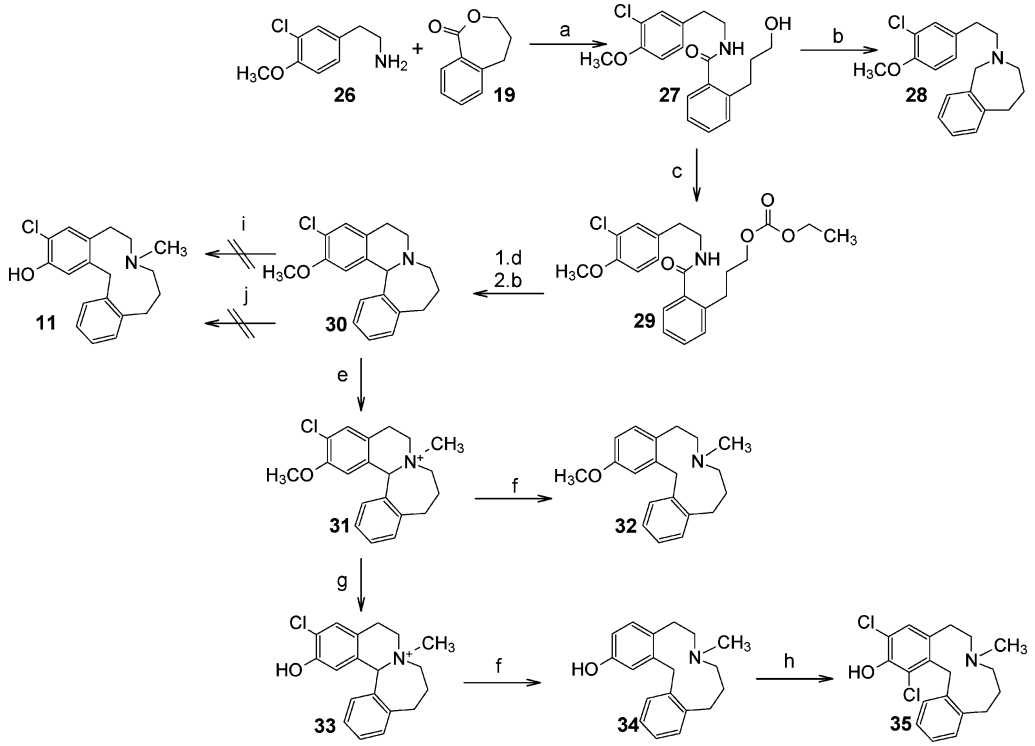
Pharmacology

Compounds were screened for their affinities for the human cloned receptor subtypes D_1, D_{2L}, D_3, $D_{4.4}$, and D_5 in radioligand displacement experiments. K_i values are given in nanomolar units (Table 1). For a detailed description, see the Supporting Information. Additionally, the compounds were tested in an intracellular Ca^{2+} assay with regard to their functionality for the D_1, D_{2L}, and D_5 receptors. HEK293 cells stably expressing the respective D receptor were loaded with a fluorescent dye (Oregon green), and after preincubation with rising concentrations of a test compound, an agonist (SKF 38393) was injected and fluorescence was measured with a NOVOSTAR microplate reader. Suppressing the agonist-induced Ca^{2+} influx with the test compound indicates antagonistic or inverse agonistic properties at the receptor. For a detailed description see the Supporting Information.

Results and Discussion

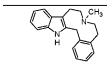
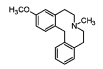
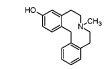
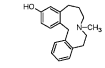
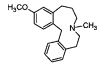
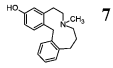
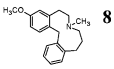
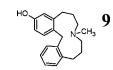
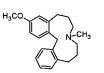
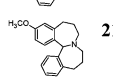
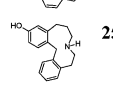
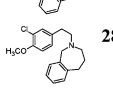
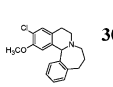
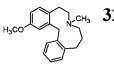
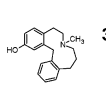
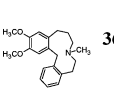
We synthesized 10 dibenzazacycloundecenes or dibenzazacyclododecenes. The benzazepino[1,2-*a*][2]benzazepine **21** and the dibenzo[*e*,*h*]azacyclododecenes **9** and **10** are derivatives of

Scheme 4. Efforts to Synthesize the Open-Ring Derivative of Ecopipam **11**[a]



[a] (a) Toluene, reflux; (b) ethyl chloridocarbonate, toluene/pyridine; (c) $POCl_3$/acetonitrile, reflux; (d) (1) KOH EtOH/H_2O; (2) $POCl_3$; (e) methyl iodide, acetonitrile; (f) Na/NH_3^{liq}; (g) HBr, glacial acetic acid; (h) $SOCl_2$, glacial acetic acid; (i) (1) ethyl chloridocarbonate THF, $NaCNBH_3$, −78 °C to room temp; (2) THF, $LiAlH_4$; (j) PtO_2/H_2.

Table 1. Affinities (K_i values) for Dopamine Receptor Subtypes Measured by Radioligand Binding Studies

Compounds		K_i [nM] (Radioligand binding studies)				
		D_1	D_{2L}	D_3	$D_{4.4}$	D_5
	**1**	1.9 ± 0.5[a]	44.7 ± 15.8[a]	40.35[a]	74.9 ± 50[a]	7.5 ± 0.3[a]
	**2**	28.5 ± 9.7[a]	13.0 ± 9.0[a]	75.7 ± 7.3[a]	43.4[a]	54 ± 20
	**3**	0.39 ± 0.22[a]	17.5 ± 1.5[a]	47.5 ± 24[a]	11.3 ± 1[a]	1.5 ± 0.5
	**5**	13.9 ±2	518 ± 269	6122 ± 269	2258 ± 2253	17 ± 6
	**6**	29.4 ± 6.3	25 ± 0.8	3136 ± 625	1103 ± 521	55 ± 16
	**7**	3.2 ± 1.7	74 ± 71	100.0 ± 29	60.15 ± 29	9.8 ± 5.4
	**8**	18.5 ± 5	87 ± 9	507 ± 355	271 ± 73	4.6 ± 1.4
	**9**	83 ± 45	382 ± 7	3964 ± 1193	422 ± 228	95 ± 59
	**10**	23.5 ± 12	172 ± 5	1349 ± 281	2869 ± 199	53 ± 29
	**21**	> 10000	> 10000	> 10000	> 10000	> 10000
	**25**	291 ± 135	857 ± 98	6896 ± 549	4256 ± 562	314 ± 284
	**28**	> 10000	> 10000	> 10000	> 10000	> 10000
	**30**	> 10000	> 10000	> 10000	> 10000	> 10000
	**32**	137± 45	1396 ± 875	23903 ± 7268	2763 ± 455	75 ± 70
	**34**	70 ± 21	63 ± 40	776 ± 153	3751 ± 2227	69 ± 19
	**36**	579 ± 39	1028 ± 461	14830 ± 670	5048± 2807	510 ± 102
Clozapine[b]		266	184	269	24	255

[a] Values from ref 12. [b] Values from the PDSP database.[21]

novel heterocyclic ring systems. We have recently published the synthesis of the dibenzazacycloundecene derivative **36**.[13] Furthermore, the 11- and 12-membered heterocycles can be considered ring-enlarged homologues of the previously described highly potent dibenzazecine-type dopamine receptor antagonists.[12,20] Using radioligand displacement experiments, we screened these target compounds and some of the intermediates for their affinity for all human cloned dopamine receptors. As radioligands, we used [^{3}H]SCH 23390 for the D_1 receptor family and [^{3}H]spiperone for the D_2 family. The functionality of the compounds was determined using a fluorescent calcium assay (see Supporting Information). All of the active compounds in Table 1 proved to be antagonists or inverse agonists, preferentially for the D_1/D_5 family. The K_i values of the novel monooxygenated N-methylated target compounds range from 3.2 to 137 for D_1, from 4.6 to 95 for D_5, from 11 to 1396 for D_{2L}, from 100 to >10000 for D_3, and from 15 to 3751 nM for $D_{4.4}$.

The more constrained tetracyclic homoquinolizine derivatives **12**, **15**, **21**, and **30** did not display any significant affinity for any of the dopamine receptor subtypes, whereas for all of the 11- and 12-membered "open" target compounds, which include phenylethyl- and phenylpropylamine moieties in a very moderately constrained way, reasonable to high affinities were found. Interestingly, the affinities of the two possible types of the 11-membered derivatives for the dopamine receptors are significantly different. The position of the nitrogen in relation to the substituted benzene ring is crucial. Compounds with the nitrogen closer to the substituted benzene ring (**7**, **8**) are more active than the other regioisomers, where the distance between the nitrogen and the substituted benzene is greater (**5**, **6**). This finding is completely in line with our previous investigation of the respective 11-membered benzindoloazacycloundecene derivatives.[14]

The hydroxylated dibenzazacycloundecenes **5**, **7**, and **34** exhibit higher affinities for the D_1 receptor than do their methoxylated analogues **6**, **8**, and **32**. Affinities of **7** and **34** are twice as high as those of **8** and **32**, and the phenolic **5** is nearly 6 times more potent than the methoxy derivative **6**. Basically, these results resemble the affinity profiles we have found for the 10-membered counterparts, but there the OH compound **2** is even 70 times more active than the MeO compound **3**.[20] Interestingly, the affinity of the *N*-methyl derivative **6** for all receptor subtypes decreases dramatically when the *N*-methyl is replaced by NH (**25**). The functional assay showed that **25** maintained the antagonistic activity and did not switch into an agonist, as do some benzazepine-type ligands with a free NH (e.g., SKF 38393). With regard to the compounds' affinity for dopamine receptors, that of the 11-membered compound with two MeO substituents **36** is low and that of the benzazepine **28** is nonexistent. Expanding the size of the central N-heterocycle from 11 to 12 proved to be less favorable. The affinities of **9** and **10** for D_1 and D_5 are comparatively low, and in contrast to the affinities of all of the 11-membered compounds (see Table 1) and the previously investigated 10-membered compounds, the affinities of the methoxy derivative (**10**) are higher than those of phenolic **9** (Table 1).

The chlorination of **34**, yielding **35**, did not improve the affinity for the D_1 and D_5 receptor but revealed a new subtype selectivity profile. Surprisingly, the affinities for D_{2L} and $D_{4.4}$ (11 and 15 nM) are higher than for D_1 and D_5 (124 and 89 nM). We found **35** to be the first "dibenzazecine-type" dopamine receptor antagonist without selectivity toward the D_1 receptor family. The additional high affinity for the $D_{4.4}$ receptor subtype characterizes **35** as a compound with a binding profile that resembles the profile of the well-established atypical antipsychotic clozapine (Table).

The radioligand binding data of the ring-enlarged compounds were used among other data to investigate the molecular mechanism of the interaction of antagonistic compounds with the dopamine D_1 receptor. For this purpose, the novel xMaP-4D-QSAR technique was applied. A companion paper on this is in preparation (Josef Scheiber, Christoph Enzensperger, Jochen Lehmann, and Knut Baumann).

Experimental Section

Most of the protocols for the preparation of the target compounds and intermediates together with their physical and spectral data (NMR, GC/MS) are given in the Supporting Information.

Ring Opening. General Procedure. A 100 mL three-neck flask equipped with a balloon as an overflow tank was cooled in a liquid nitrogen bath. Ammonia was condensed into this flask until the flask was $^3/_4$ filled. The cooling bath was removed, and the ammonia was allowed to liquefy. The quaternary salts (e.g., **13**, **14**, **16**, **17**, **22**, **23**, **31**, **33**) were added. Rice-grain-sized pieces of sodium were added to the stirred mixture until the developing blue color remained for 10−15 min. The mixture was quenched by adding 1−2 drops of saturated aqueous NH_4Cl. The ammonia was evaporated under nitrogen, and 5 mL of water and then 15 mL of diethyl ether were added to the residue. The mixture was stirred until two phases formed. The aqueous phase was extracted with diethyl ether (3 × 15 mL). For the phenolic compounds the pH was adjusted to 8. The ethereal phase was dried over $MgSO_4$ and evaporated to yield the open-ring compounds, usually with sufficient purity. If necessary, the product was purified as described in the Supporting Information.

Synthesis of the Quaternary Salts (e.g., 13, 14, 16, 17, 22, 23, 31, 33). General Procedure. A 10-fold molar excess of methyl iodide was added to a stirred solution of the respective homoquinolozine in acetonitrile. Under nitrogen, the mixture was stirred for 48h at ∼40 °C. The precipitated solids were isolated by filtration and dried in vacuo (yield, ∼90%).

Synthesis of Homoquinolizines. General Procedure Exemplified for Compound 30. According to ref 16, a solution of 4.4 g (10,4 mmol) of the protected benzamide **29** in 150 mL of a 2:1 mixture of acetonitrile and $POCl_3$ was refluxed for 4 days under nitrogen. The solvents were removed in vacuo, the residue was portioned between 170 mL of 2 N HCl and 30 mL of ethyl acetate, and the aqueous layer was washed with 20 mL of ethyl acetate. The dihydroisoquinolinium salt was extracted as an ion pair from the acidic aqueous layer with chloroform (5 × 40 mL). The combined chloroform layers were evaporated, and the residue (2.44 g) was stirred into 70 mL of a 20% KOH solution in aqueous ethanol (70% EtOH, 30% H_2O) at room temperature for 12 h. The solvents were concentrated in vacuo to about 10 mL, maintaining the temperature below 40 °C. An amount of 160 mL of 2 N HCl was added to this residue and extracted with chloroform (5 × 30 mL). After the mixture was dried (Na_2SO_4) and evaporated, the remaining oil was dissolved in 17 mL of $POCl_3$ and stirred for 15 min at 60 °C. The mixture was cooled to room temperature, and an amount of 100 mL of petroleum ether (40−60) was added under vigorous stirring. The oil was allowed to deposit, and the upper layer, containing $POCl_3$ and petroleum ether, was decanted and discarded. This procedure was repeated until no more $POCl_3$ was detected by smell. An amount of 3 g of $NaBH_4$ was added under cooling to the residue, dissolved in 85 mL of methanol. After the reaction subsided, the solution was refluxed for 1 h, evaporated to dryness, and redissolved with 150 mL of water. Extraction with diethyl ether (5 × 40 mL), drying (Na_2SO_4), and evaporating yielded 1.3 g of the crude **30** as a free base. The HCl salt was obtained by dissolving the base in 10 mL of diethyl ether and adding ethereal HCl. The precipitated HCl salt was recrystallized from isopropanol. The total yield of **30** (based on **29**) was 1.2 g (39%).

Ether Cleavage of Methoxylated Quaternary Salts (13, 16, 22, 31). General Procedure. The quaternary salt of the respective methoxy compound was dissolved in a mixture of 20 mL of glacial acetic acid and 20 mL of aqueous HBr (48%) and refluxed under nitrogen for 5 h. The solvents were removed in vacuo, and the residue was crystallized from methanol/diethyl ether.

Preparation of 2-(2-Hydroxyalkyl)-*N*-(2-phenylalkyl)benzamides (20, 27). General Procedure. A solution of 40 mmol of the respective phenylalkylamine and 40 mmol of the lactone in 40 mL of toluene was refluxed for 24 h. The mixture was washed with 2 N HCl (5 × 30 mL), and the organic layer was evaporated to dryness. An amount of 50 mL of 20% NaOH was added to the residue and stirred vigorously at 70 °C. A total of 100 mL of chloroform was added to the residue, after which the organic layer was separated, dried (Na_2SO_4), and evaporated to dryness. Some diethyl ether was added to the resulting oil; storage in the refrigerator induced crystallization. The crystals were removed by filtration, washed with small amounts of diethyl ether, and dried.

Chlorination of Azacycloundecene (34 → 35). A solution of 0.56 g (2 mmol) of **34** in 4 mL of glacial acetic acid was stirred and cooled carefully to prevent glacial acetic acid from solidifying. A solution of 200 μL (2.5 mmol) of sulfuryl chloride in 200 μL of glacial acetic acid was added slowly and dropwise. The mixture was allowed to return to room temperature overnight. An amount of 10 mL of diethyl ether was added, and the precipitated hydrochloride salts were dissolved in methanol. GC/MS of the free bases showed four peaks: starting material, two monochlorinated compounds, and a double-chlorinated compound. The double-chlorinated compound could be separated by column chromatography, but no monochlorinated compound could be separated by column chromatography, preparative TLC, or recrystallization.

Ring Cleavage (12 → 24) or Demethylation (6 → 24) with Ethyl Chloridocarbonate and $NaCNBH_3$. General Procedure. A solution of 3.5 mmol of the respective quinolizine derivative/or *N*-methylazacycloundecene in 75 mL of dry THF was cooled under nitrogen to −75 °C in a methanol/dry ice bath. With a syringe, an amount of 20 mmol (1.9 mL) of ethyl chloridocarbonate was added through a septum in several small portions. The mixture was stirred for 4 h, and the temperature was allowed to come up to −40 °C. The mixture was cooled again to −75 °C, and a total of 12.3 mmol (770 mg) of $NaCNBH_3$ in 6 mL of dry THF was added dropwise during a period of 10 min. The reaction mixture was stirred in an ice bath overnight and allowed to return to room temperature overnight again. A total of 175 mL of 2 N NaOH was added to the resulting emulsion and stirred for 10 min. The THF layer was separated and evaporated in vacuo, and the aqueous layer was extracted with dichloromethane (2 × 50 mL) and added to the evaporated THF layer. The combined organic phases were dried over Na_2SO_4 and evaporated. The oily residue contained the crude carbamate, which was used for either $LiAlH_4$ reduction or hydrolysis with BBr_3. The yield for the ring opening was approximately quantitative, and the yield for the demethylation was about 80%.

Simultaneous Ether Cleavage and Carbamate Hydrolysis with BBr_3. General Procedure Exemplified for Compound 25. According to ref 15, a solution of 1 mmol of the respective methoxylated carbamate in 10 mL of dry toluene and then 5 mmol (473 μL) of boron tribromide were added under nitrogen by injecting it through a septum. The mixture was refluxed for 2.5 h, allowed to return to room temperature, and quenched with 30 mL of ice−water. The aqueous layer was washed two times with toluene (unreacted carbamate could then be recovered from the toluene). The pH value of the water layer was adjusted to 8−9 with ammonia, and the aqueous layer was extracted with chloroform (5 × 30 mL). The pooled extracts were dried (Na_2SO_4) and evaporated. The oily residue was dissolved in 5 mL of diethyl ether, and the hydrochloride salt was formed by adding ethereal HCl. Recrystallization was performed from diethyl ether and isopropanol.

$LiAlH_4$ Reduction of the Phenolic Carbamate 24 to 6. A suspension of 20 mmol (150 mg) $LiAlH_4$ in 20 mL of dry THF was stirred and cooled to 0 °C. Under nitrogen, a solution of 1.47 mmol (520 mg) of **24** in 8 mL of THF was added in small portions by injecting it through a septum. The mixture was refluxed for 4 h and stirred overnight. The excess $LiAlH_4$ was decomposed by the dropwise addition of 5 mL of 50% aqueous THF. The solids were removed by filtration, and THF was evaporated from the liquid. The aqueous residue was portioned between 20 mL of diethyl ether and 20 mL of 2 N HCl. The phases were separated, and the aqueous layer was washed with diethyl ether (2 × 20 mL). The water phase was adjusted to pH 8−9 and again extracted with dichloromethane (3 × 50 mL) to yield a white foam of **6** after drying (Na_2SO_4) and evaporation. The yield was 316 mg, 73%.

Pharmacology. Experimental details of the radioligand binding studies and the calcium assay are described in the Supporting Information.

Acknowledgment. Appreciation is expressed to Josef Scheiber for fruitful discussions.

Supporting Information Available: Synthetic procedures and analytical data for intermediates and target compounds; details of the screening methods and cell cultivation (Ca assay and radioligand displacement experiments). This material is available free of charge via the Internet at http://pubs.acs.org.

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JM070388+