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Brief Article

Dopamine Receptor Ligands. Part 18:[1] Modification of the Structural Skeleton of Indolobenzazecine-Type Dopamine Receptor Antagonists

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On the basis of the $D_{1/5}$-selective dopamine antagonist LE 300 (**1**), an indolo[3,2-*f*]benzazecine derivative, we changed the annulation pattern of the heterocycles. The target compounds represent novel heterocyclic ring systems. The most constrained indolo[4,3a,3-*ef*]benzazecine **2** was inactive, but the indolo[4,3a,3-*fg*]benzazacycloundecene **3** showed antagonistic properties (functional Ca^{2+} assay) with nanomolar affinities (radioligand binding) for all dopamine receptor subtypes, whereas the indolo[2,3-*f*]benzazecine **4** displayed a selectivity profile similar to **3** but with decreased affinities.

Introduction

Dopamine is a major neurotransmitter of the brain involved in the control of movement, emotion, reward, and cognition. Dysfunctions of the dopaminergic system have been associated with several neuropsychiatric disorders including Parkinson's disease, schizophrenia, and drug dependence. The azecine-type dopamine receptor antagonist 7-methyl-6,7,8,9,14,15-hexahydro-5*H*-indolo[3,2-*f*][3]benzazecine (**1**, LE 300)[2−4] represents a novel chemical structure, possessing high affinities and a unique selectivity profile for the D_1-like receptors. Extensive SAR studies have been carried out based on **1** (LE 300) as a lead. The objective of the present study was to rearrange the heterocyclic skeleton of our lead compound **1** in order to assess how different annulation patterns would affect the affinities and selectivities for the dopamine receptors. While retaining the basic structural features of our lead, namely an indole, a benzene ring, and a central *N*-methylated azacycloalkane ring, we mainly wanted to change the annulation of the central alicycle to the indole ring (Chart 1).

Our first targets were analogues of **1**, where the aza-alicycle is fused not to the 2,3- but to the 3,3a,4-positions of the indole. As this annulation pattern might impart some rigidity on the structure, we wanted to synthesize both the indolo-benzazecine **2** and the more flexible indolo-benzazaundecene **3**. Compound **2** resembles the parent compound **1** in containing a 10-membered central alicycle but differs from it in containing a methylene rather than an ethylene chain, connecting the indole ring to the central nitrogen. Conversely, in the ring-expanded structure of compound **3**, the indole ring is connected to the central nitrogen through an ethylene chain. These target compounds, together with their pentacyclic precursors **8** and **12**, are of additional interest due to their structural resemblance to ergolines, especially to the selective D_1 (partial)agonist (−)-4,6,6a,7,8,12b-hexahydro-7-methylindolo[4,3-*ab*]phenanthridine CY 208−243[5,6] (Chart 2). This benzergoline derivative showed 10-fold selectivity for D_5 over D_1 receptor[7] and exhibited in vivo antiparkinsonial activity.[8]

Our second target compound was the indolo-benzazecine **4**, where the 10-membered central alicycle is fused at the 2,3-positions of the indole ring as opposed to the 3,2-fusion pattern of **1** (Chart 1).

Chemistry

To obtain the annulated 10- and 11-membered heterocycles, we had to prepare their ring-closed quinolizine-type precursors. Previously applied methods for the preparation of related quinolizines, namely by reacting the respective aralkylamines with 1-isochromanone[4,9] or with 2(2-chloroethyl)-benzoyl chloride,[10,11] were unsuccessful. So the quinolizine **8** was prepared following a procedure described by Browne for the preparation of analogous benzo-thieno-quinolizine.[12] Reacting 4-aminomethylindole (**5**) with 2-(2-bromoethyl)benzaldehyde (**6**) in dioxane at room temperrature yielded the 3,4-dihydroisoquinolinium salt **7**. This was refluxed in 6N HCl, and the obtained quinolizinium salt was alkalinized to give the quinolizine **8**. Two different procedures yielded the indolobenzazecine **2**. First, the quinolizine **8** was quaternized with methyl iodide and the central C−N bond of the resulting quaternary salt **9** was subsequently cleaved by treatment with sodium in liquid ammonia. Second, the quinolizine **8** was converted with ethylchloroformate/$NaCNBH_3$ to the carbamate derivative **10**, which upon reduction with lithium aluminum hydride also yielded the desired target compound **2**. Spectral data of the products, obtained by both methods, were identical. However, the first route proved to be more advantageous with respect to the yield (Scheme 1).

Applying the procedure, previously described for the synthesis of the quinolizine **2**, failed to produce both the homoquinolizine **12** and quinolizine **15**. 2-(2-Bromoethyl)benzaldehyde (**6**) did not react with the respective amines **11** and **14**

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Chart 1. Rearranging the Indolo[3,2-*f*]benzazecine Skeleton of **1** to Analogue Indolo[4,3a,3-*ef*]benzazecine **2**, Indolo[4,3a,3-*fg*]-benzazaundecene **3** and to Indolo[2,3-*f*]benzazecine **4**

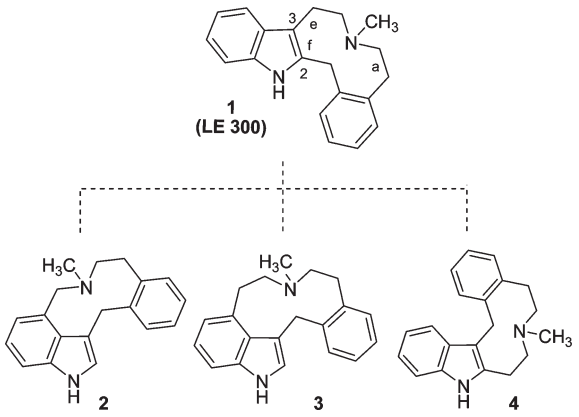
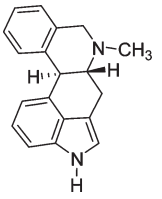


Chart 2. Selective D_1 (Partial) Agonist (−)-4,6,6a,7,8,12b-Hexahydro-7-methylindolo[4,3-*ab*]phenanthridine



at room temperature. Hence, we modified the reaction conditions. 4-(2-Aminoethyl)indole (**11**) or 2-(2-aminoethyl)indole (**14**) were refluxed with 2-(2-bromoethyl)benzaldehyde (**6**) in dioxane in the presence of equimolar amounts of trifluoroacetic acid. This resulted in the direct formation of the salts of the homoquinolizine **12** and quinolizine **15**, respectively. Alkalinization yielded the corresponding bases, which were quaternized with methyl iodide. Finally the obtained quaternary salts **13** and **16** were cleaved using sodium in liquid ammonia to produce the target compounds **3** and **4** (Scheme 2).

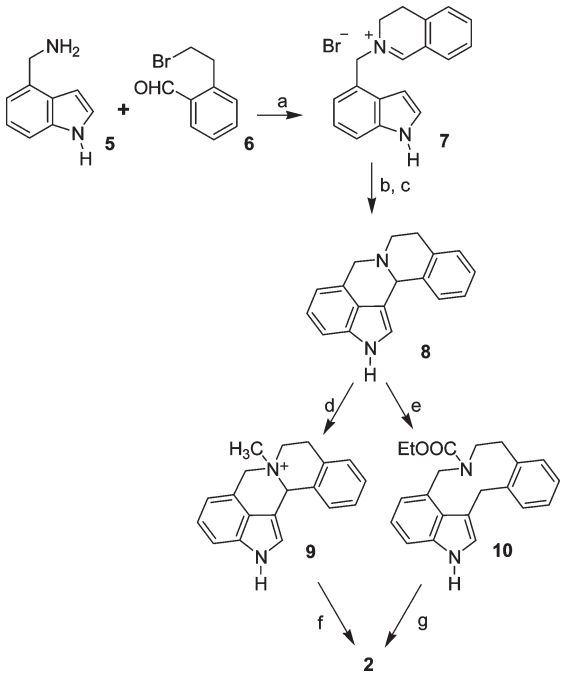
Pharmacology

All the target compounds **2**, **3**, and **4** together with their pentacyclic precursors **8**, **12**, and **15** were screened for their affinities for the human cloned dopamine receptor subtypes D_1, $D_{2\ L}$, D_3, $D_{4.4}$, and D_5. These receptors were stably expressed in HEK293 or CHO cells; [^{3}H]SCH 23390 and [^{3}H]spiperone were used as radioligands at the D_1-like and D_2-like receptors, respectively. K_i values are given in nanomolar units (Table 1). For a detailed protocol, see Supporting Information (SI). Additionally, the compounds were tested in an intracellular Ca^{2+} assay, in order to determine their functionality at the D_1 and D_2 receptors. HEK293 cells stably expressing the respective D-receptor were loaded with a fluorescent dye, and after preincubation with rising concentrations of the test compound, an agonist (SKF 38393 for D_1 and quinpirole for D_2) was injected and the Ca^{2+}-induced fluorescence was measured with a microplate reader. The ability of the test compound to suppress the agonist-induced Ca^{2+} influx is an indication of antagonistic or inverse agonistic properties at the receptor. For a detailed description, see SI.

Results and Discussion

We synthesized three analogues of the lead compound **1**, possessing a modified annulation pattern. All of these

Scheme 1. Total Synthesis of 5-Methyl-4,5,6,7-tetrahydroindolo[4,3a,3-*ef*][3]benzazecine (**2**)[a]



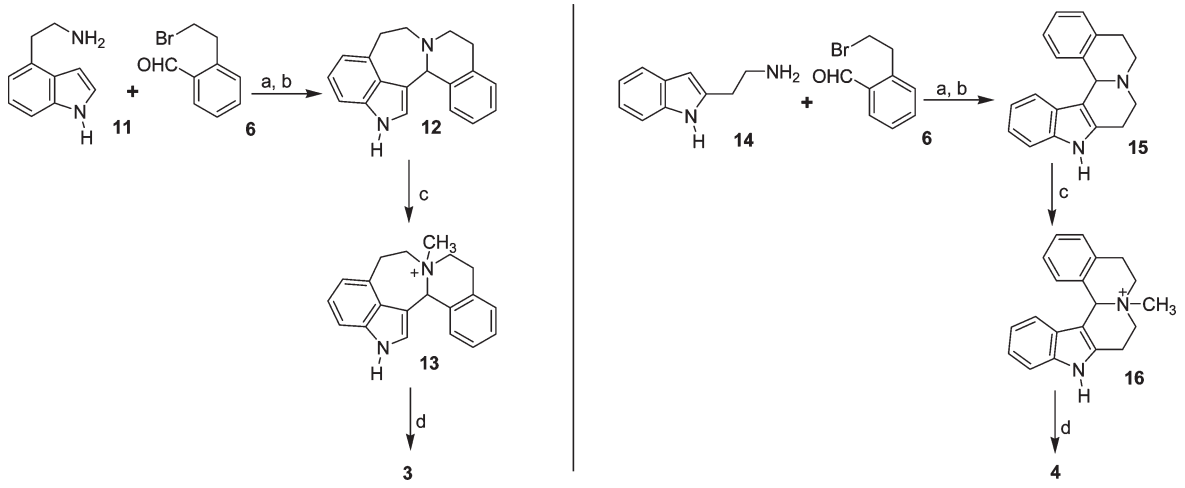
[a] Reagents and conditions: (a) dioxane, rt, 3 h; (b) 6 N HCl, reflux, 4 h; (c) aq NH_4OH; (d) MeI, acetone, rt, 24 h; (e) ClCOOEt, dry THF, −55 °C, 5 h, then $NaCNBH_3$, −55 °C to rt; (f) Na^0, liquid NH_3, −40 °C, 10 min; (g) $LiAlH_4$, dry THF, reflux, 3 h.

compounds, together with their pentacyclic precursors, are derivatives of novel heterocyclic ring systems.

In the radioligand binding experiments, the two homologues, **2** and **3**, where the alicycle is fused at the 3,3a,4 positions of the indole ring, were found to possess surprisingly different affinities: while the indolo[4,3a,3-*ef*]benzazecine **2** showed no significant affinities for all dopamine receptor subtypes (K_i > 10 μM), the ring expanded indolo[4,3a,3-*fg*]-benzazacycloundecene **3** displayed nanomolar affinities, comparable to those of our lead **1**. However, it showed almost equal affinities for the D_1-, D_3-, and D_5-receptor, showing a slightly higher affinity for D_5 compared to D_1. A 10-fold increase in the affinity for D_2 was observed, when compared to our lead **1**, in addition to an improvement in the affinity for the D_4-receptor. The indolo[2,3-*f*]benzazecine **4** showed a nearly similar selectivity pattern like that of compound **3** but with noticeable decrease in the affinities for all D-receptors. Although both compound **2** and our lead **1** contain a benzindolo-azecine moiety, the structure of the former is much more constrained as a consequence of its annulation. In contrast, the ring expanded structure of compound **3** shows higher flexibility, which is accompanied by an extreme increase in affinities. In accordance with our previous studies,[4] only structures showing a certain degree of flexibility display relevant affinities for the dopamine receptors.

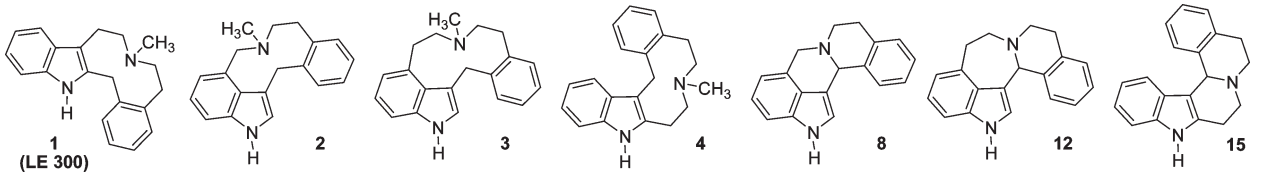
The discrepancy in the activities between both homologues **2** and **3** might be attributed to the different distances between the pharmacophoric groups, which are the central N and both aromatic rings, but also to the different angles between the aromatic rings in both structures. Another possibility may be that analogue **2** is inactive due to the nitrogen's lone e-pair being buried in the center of the ring beneath the *N*-methyl group. Meanwhile, the flexibility of the additional methylene

Scheme 2. Total Synthesis of Benzazacycloundecene **3** and Benzazecine **4**[a]



[a] Reagents and conditions: (a) trifluoroacetic acid, dioxane, reflux, 20 h; (b) 2 N NaOH; (c) MeI, acetone or acetonitrile, rt, 24 h; (d) Na^0, liquid NH_3, −40 °C, 10 min.

Table 1. Affinities (K_i, nM) for Human D_1−D_5 Receptors, Determined by Radioligand Binding Experiments



	K_i (nM)				
compd	HEK D_1	HEK $D_{2\,L}$	HEK D_3	CHO $D_{4.4}$	HEK D_5
1[a]	1.9 ± 0.9	44.5 ± 15.8	25.9	108 ± 39	7.5 ± 0.3
2	> 10000	> 10000	> 10000	> 10000	> 10000
3	4.2 ± 0.5[b]	4.0 ± 0.5[c]	42.9 ± 8.5[c]	39.1 ± 9.6[b]	2.5 ± 0.7[c]
4	28.5 ± 7.2[b]	55.1 ± 15.4[c]	513 ± 217[b]	225 ± 50[c]	10.3 ± 1.5[c]
8	> 10000	> 10000	> 10000	> 10000	> 10000
12	1836 ± 658[b]	4458 ± 1192[c]	> 10000	> 10000	1525 ± 206[c]
15	2101 ± 703[b]	1476 ± 28.5[c]	> 10000	> 10000	> 10000

[a] Values cited from ref 10, CHO cell lines were used for $D_{2\,L}$, D_3, and $D_{4.4}$; HEK cell lines for D_1 and D_5. [b] K_i values are the means of three experiments; performed in triplicate ± SEM. [c] K_i values are the means of two; experiments; performed in triplicate ± SEM.

in analogue **3** might permit low-energy conformations to exist with the N lone e-pair to be directed outward. However, studies have shown that the receptor binding site contains two aromatic subsites around a conserved $Asp^{3.32}$, whose carboxylate group acts as a counterion of the protonated basic N of the ligand.[13] Accordingly, we expect our ligands to interact with the binding sites in an N-protonated form and not with the N lone pair of the free base.

The pentacyclic precursor compounds **8**, **12**, and **15** had generally weak to no affinities. The quinolizine **8** displayed no affinities (K_i > 10 μM) for all dopamine receptors, whereas its homologue **12** showed micromolar ones for the D_1, D_2, and D_5 subtypes. Similarly, the quinolizine **15** showed micromolar affinities for the D_1 and D_2 subtypes. With the exception of the quinolizine **2**, removal of the C−N bond of the quinolizines and the consequent impartment of a moderate flexibility to the central ring results in a dramatic increase in affinities. This is in accordance with some previous observations.[4]

All tested compounds, displaying affinities in the radioligand binding assay, were found to possess antagonistic activities at the D_1 and D_2 receptors in the calcium assay.

We conclude that modifying the annulation pattern of the parent compound **1** does not result in significant changes in the affinities for the different dopamine receptors; equally active (compound **3**) or slightly less active (compound **4**) dopamine antagonists have been obtained. It seems, however, that decreasing the flexibility of the structure together with decreasing the distances between the alicyclic nitrogen and the aromatic moieties both have a negative effect on the affinities and can lead to a complete loss of activity.

Experimental Section

General Methods. Melting points are uncorrected and were measured in open capillary tubes using a Gallenkamp melting point apparatus. ^1H and ^{13}C NMR spectral data were obtained from a Bruker Advance 250 spectrometer (250 MHz) and Advance 400 spectrometer (400 MHz). 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). Purities of the compounds were determined by elemental analysis, performed on a Hereaus Vario EL apparatus. All values for C, H, and N were found to be within ±0.4. All compounds showed > 95% purity.

2,8,9,13b-Tetrahydro-6*H*-isoquino[2,1-*b*]pyrrolo[4,3,2-*de*]-isoquinoline (8). To a stirred solution of 4-aminomethylindole[14] (1.16 g, 8 mmol) in 30 mL dioxane was added dropwise a solution of 2-(2-bromoethyl)benzaldehyde[15] (3.4 g, 16 mmol) in 10 mL dioxane. Stirring was continued for 3 h, whereupon the intermediate isoquinolinium salt separated as a brownish sticky substance. The mixture was then allowed to settle, the supernatant was decanted, the sediment washed twice with dioxane and then twice with diethyl ether, and finally dried under vacuum. The obtained isoquinolinium salt **7** was subsequently, without further purification, dissolved in 30 mL 6 N HCl and the solution was refluxed for 4 h. The formed quinolizinium salt, which separated as white solid, was filtered off, washed several times with cold water, and dried. It was then alkalinized with aqueous ammonia and the formed quinolizine base **8** was extracted with a mixture of dichloromethane/isopropanol (3:1). Finally, the extract was dried over Na_2SO_4 and the solvents removed under reduced pressure to give 0.86 g (41.1%) of a white solid. This was recrystallized from chloroform/ethanol giving cream−white crystals; mp: 185−188 °C. ^{1}H NMR: 250 MHz (DMSO-d_6): δ 2.64−3.01 (m, 4H, 8, 9), 3.93−3.99 (d, J = 15.85, 1H, 6), 4.31−4.37 (d, J = 15.85, 1H, 6), 5.33 (s, 1H, 13b), 6.73−6.76 (m, 2H, Ar-H), 6.98−7.04 (t, 1H, J = 7.4, Ar-H) 7.16−7.27 (m, 4H, Ar-H), 7.41−7.44 (d, J = 7.1, 1H, 5), 10.66 (s, 1H, indole-NH). ^{13}C NMR: 250 MHz (DMSO-d_6): δ 29.43 (9), 46.48 (8), 55.34 (6), 57.8 (13b), 109.48 (3), 113.53 (13c), 113.92 (1), 120.19 (5), 122.51 (11), 124.83 (5b), 126.03 (12), 126.54 (4), 127.24 (13), 128.13 (5a), 129.35 (10), 133.93 (9a), 134.03 (2a), 137.77 (13a). Anal. ($C_{18}H_{16}N_2 \cdot 0.25$EtOH): C, H, N.

General Procedure for the Preparation of Homoquinolizine 12 and Quinolizine 15. A solution of 4-(2-aminoethyl)-[16] or 2-(2-aminoethyl)indole[17] (7.5 mmol), 2-(2-bromoethyl) benzaldehyde (9.4 mmol), and trifluoroacetic acid (7.5 mmol) in dioxane was refluxed under nitrogen for 20 h, whereupon a solid formed. The precipitated salts were filtered off, washed with dioxane and then with diethyl ether, and subsequently dissolved in hot water, filtered, and the filtrate rendered alkaline with 1 N NaOH. Finally, the formed bases were extracted with chloroform and the extracts dried over Na_2SO_4.

2,6,7,9,10,14b-Hexahydroindolo[3′,4′:3,4,5]azepino[2,1-*a*]-isoquinoline (12). Evaporation of the solvent yielded a brown solid that was crystallized from isopropanol/ether and then recrystallized from chloroform to give cream colored crystals; crude yield 89%; mp: 188−190 °C. ^{1}H NMR for the base: 250 MHz ($CDCl_3$): δ 2.75−3.63 (m, 8H, 6, 7, 9, 10), 5.42 (s, 1H, 14b), 6.55 (s, 1H, 1), 6.91−6.94 (d, J = 6.9, 1H, 11), 7.09−7.27 (m, 6H, 3, 4, 5, 12, 13, 14), 8.04 (s, 1H, indole-NH). ^{13}C NMR for HCl salt: 400 MHz (MeOD-d_4): δ 25.60 (10), 28.09 (6), 57.82 (7), 59.39 (9), 66.74 (14b), 109.54 (14c), 110.02 (3), 118.57 (1), 122.64 (4), 125.36 (5b), 126.36 (5), 126.67 (12), 128.16 (14), 128.56 (13), 128.89 (11), 130.58 (5a), 131.19 (14a), 131.94 (10a), 136. (2a). Anal. ($C_{19}H_{18}N_2 \cdot 0.5CHCl_3$): C, H, N.

5,6,8,9,10,14c-Hexahydroindolo[3′,2′:3,4,]pyrido[2,1-*a*]isoquinoline (15). Evaporation of the solvent yielded an orange−brown solid, which was purified by column chromatography (EtOAc−MeOH, 15:1); yield 21%; mp: 197−200 °C (analytical data see SI).

General Procedure for the Preparation of the Quaternary Salts. To a stirred solution of the respective quinolizine or homoquinolizine in acetone (or acetonitrile for compound **15**) was added a 10-fold molar excess of methyl iodide. Stirring was continued for a period ranging from 24 to 48 h, and the formed quaternary salts were isolated (analytical data, see SI).

General Procedure for the Ring-Opening. Ammonia was condensed in a three-necked 100 mL flask, which was equipped with a balloon and a stopper and cooled in a liquid nitrogen bath. After filling $^3/_4$ of the flask's volume, the cooling bath was removed and ammonia was allowed to liquefy. The respective quaternary salts were then added to the stirred liquid ammonia. This was followed by gradual addition of small pieces of sodium metal until the blue color remained for 10 min. A few drops of saturated ammonium chloride solution were added to terminate the reaction, and the mixture was stirred under nitrogen until the liquid ammonia completely evaporated. To the residue was added 10 mL water, and the mixture was then extracted with 30 mL diethyl ether. The organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure to yield the crude products, which (except for compound **2**) were sufficiently pure and did not require further purification.

5-Methyl-4,5,6,7-tetrahydroindolo[4,3a,3-*ef*][3]benzazecine (2). Evaporation of the solvent yielded a cream-colored solid, which was crystallized from chloroform; yield 24%; mp: 257−260 °C. ^{1}H NMR: 250 MHz ($CDCl_3$): δ 1.55 (mc, 2H, 6), 2.12 (s, 3H, N-Me), 2.78 (mc, 2H, 7), 3.15 (mc, 2H, 4), 4.58 (s, br, 2H, 12), 6.73−6.76 (d, J = 7.1, 1H, Ar-H), 6.97−7.26 (m, 7H, Ar-H), 8.00 (s, 1H, indole-NH). HRMS 276.1621 (calcd for $C_{19}H_{20}N_2$: 276.1626). Anal. ($C_{19}H_{20}N_2$): C, H, N.

6-Methyl-5,6,7,8,13,15-hexahydro-4*H*-indolo[4,3a,3-*fg*][3]benzazacycloundecene (3). Evaporation of the solvent yielded a yellowish solid; yield 62%; mp: 157−159 °C. ^{1}H NMR: 250 MHz ($CDCl_3$): δ 2.49 (s, 3H, N-Me), 2.88 (mc, 4H, 4, 8), 3.07 (mc, 4H, 5, 7), 4.42 (s, 2H, 13), 6.79−6.82 (d, J = 7.1, 1H, Ar-H), 7.02−7.27 (m, 7H, Ar-H), 8.39 (s, 1H, indole-NH). ^{13}C NMR: ($CDCl_3$): δ 28.96 (4), 29.03 (8), 44,64 (N-Me), 56.72 (7), 57.66 (5), 109.63 (1), 115.15 (13), 121.24 (3), 124.68 (2), 124.68 (10), 125.61 (3b), 126.04 (14), 126.14 (12), 129.33 (11), 130.34 (9), 133.39 (3a), 137.58 (8a), 140.11 (14a) 140.89 (12a). Anal. ($C_{20}H_{22}N_2 \cdot 0.67H_2O$): C, H, N.

7-Methyl-6,7,8,9,10,15-hexahydroindolo[2,3-*f*][3]benzazecine (4). Evaporation of the solvent yielded a beige solid; yield 65%; mp: 139−141 °C (analytical data see SI).

Ethyl 4,5,6,7-Tetrahydroindolo[4,3a,3-*ef*][3]benzazecine-5-carboxylate (10). A stirred solution of the quinolizine **8** (0.56 g, 2.2 mmol) in 200 mL of dry THF was cooled in methanol/dry ice at −55 °C. While keeping the reaction mixture under nitrogen, ethyl chloroformate (1.26 g, 11.6 mmol) was added and stirring was continued for 5 h. Then a solution of sodium cyanoborohydride (0.46 g; 7.3 mmol) in 10 mL dry THF was added at −55 °C and the reaction mixture was stirred overnight while allowing it to reach room temperature. It was subsequently treated with 120 mL of 2 N NaOH, the THF layer was separated, washed with brine, and finally the organic layer was evaporated under reduced pressure (analytical data, see SI).

Reduction of the Carbamate. A solution of compound **10** (200 mg, 0.6 mmol) in 10 mL of THF was slowly added to an ice-cooled, stirred suspension of lithium aluminum hydride (100 mg, 2.6 mmol) in 15 mL of dry THF while keeping the reaction under nitrogen. After the addition was completed, the reaction mixture was heated under reflux for 3 h. It was then cooled in an ice bath, and the excess of unreacted lithium aluminum hydride was quenched by careful addition of saturated potassium sodium tartarate solution until no H_2 evolved. The resulting suspension was then filtered off and the filtrate evaporated under reduced pressure to yield compound **2**, which was crystallized from chloroform yielding white crystals; yield 40%; mp: 257−260 °C. ^{1}H NMR: 250 MHz ($CDCl_3$): δ 1.56 (mc, 2H, 7), 2.13 (s, 3H, N-Me), 2.79 (mc, 2H, 6), (mc, 2H, 4), (s, br, 2H, 12), 6.73−6.76 (d, J = 7, 1H, Ar-H), 7.00−7.26 (m, 7H, Ar-H), 8.00 (s, 1H, NH).

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Supporting Information Available: Detailed synthetic procedures as well as physical and spectral data for some target and intermediary compounds; table of elemental analysis for key compounds; a detailed protocol for the pharmacological assays.

This material is available free of charge via the Internet at http://pubs.acs.org.

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