A Novel Non-phenolic Dibenzazecine Derivative with Nanomolar Affinities for Dopamine Receptors

by **Dina Robaa**[a]), **Shams ElDin AbulAzm**[b]), **Jochen Lehmann**[a])[c]), and **Christoph Enzensperger***[a])

[a]) Institut für Pharmazie, Lehrstuhl für Pharmazeutische/Medizinische Chemie, Friedrich Schiller Universität Jena, Philosophenweg 14, D-07743 Jena (e-mail: ch.enzensperger@uni-jena.de)

[b]) Department of Medicinal Chemistry, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt

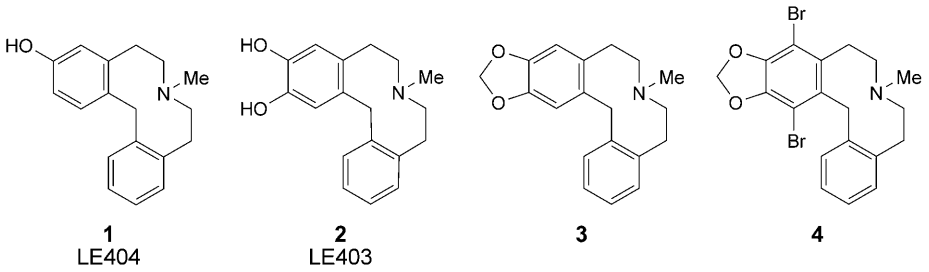
[c]) College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

Dibenzazecines are a novel class of dopamine receptor antagonists, characterized by their high affinities as well as their tendency for D_1 selectivity. Hitherto, the most active dibenzazecines were phenolic in nature; a 3-OH substituent was found to result in the highest affinities. However, the phenolic nature of these compounds mostly renders them unsuitable for *in vivo* application, due to the poor pharmacokinetic profile, imparted by the phenolic group. A novel dibenzazecine derivative was prepared, with methylenedioxy moiety, connecting C(2) amd C(3), instead of the 3-OH group. The newly synthesized derivative **3** showed high affinities similar to the lead LE404, displaying nanomolar affinities for all dopamine receptor subtypes. Its dibrominated derivative **4**, though exhibiting almost a fivefold decrease in affinities, still displayed nanomolar ones for all dopamine receptors, except for D_4. In a functional Ca^{2+} assay, both compounds **3** and **4** were found to possess antagonistic properties towards the dopamine receptors.

Introduction. – Dopamine is a regulator of numerous physiological functions in the central nervous system (CNS) and the periphery. Dysfunctions of the dopaminergic system have been implicated in the pathogenesis of several neurological disorders, including schizophrenia, *Parkinson*'s disease, depression, attention-deficit hyperactivity disorder (ADHD), as well as drug and alcohol addiction [1][2].

Dibenz[*d*,*g*]azecines are a novel class of dopamine receptor antagonists, which are distinguished by their new chemical structure, as well as their high affinities for dopamine receptors, predominantly for the D_1 family [3][4]. SAR Studies on this new class of compounds revealed that derivatives that encompass a dibenz[*d*,*g*]azecine moiety as the backbone structure and bear a OH substituent at C(3) (*e.g.*, compound **1**; LE404; *Fig.*), display the highest affinities, specifically for human D_1 and D_5 receptors [3–5]. Changing the position of the OH group or replacing it by a MeO group both led to decreased affinities [4]. Surprisingly, a 2,3-dihydroxy substitution pattern (compound **2**; LE403; *Fig.*), which exhibits the highest structural resemblance to dopamine, the natural ligand, showed *ca.* 100–1000-fold lower affinities than the monohydroxylated LE404 **1** [3].

However, the high affinities of these dopamine antagonists are coupled with drawbacks. Phenols and especially dihydroxylated compounds tend to be chemically unstable. Due to their phenolic nature, these compounds are predisposed to poor



1 LE404 **2** LE403 **3** **4**

Figure. *The 3-hydroxybenzazecine derivative LE404* (**1**)*, the less active 2,3-dihydroxy analog LE403* (**2**)*, and the target methylenedioxy analogs* **3** *and* **4**

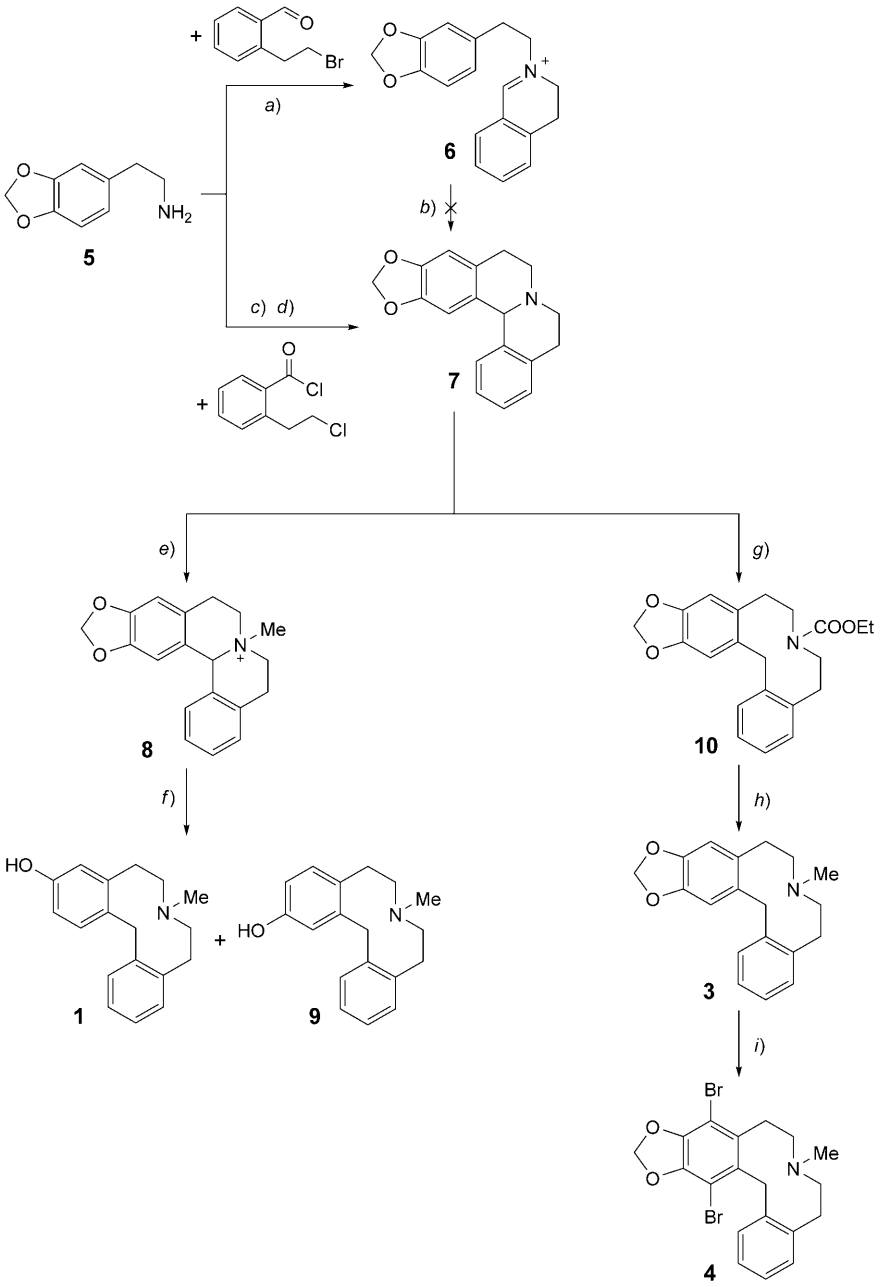
pharmacokinetics (low bioavailability), which would restrict their utility for *in vivo* experiments and render them unsuitable for clinical development. Accordingly, our preliminary *in vivo* evaluations have shown that compound **1** (LE404) has a low oral bioavailability when administered to rats [6]. Studies on other classes of phenolic dopamine antagonists, in particular SCH23390 and SCH39166, have led to similar results [7][8]. Both compounds showed very low bioavailability besides a short duration of action. The latter fact has been attributed to the fast biotransformation of these phenolic compounds, occurring mainly by glucuronidation at the phenolic function [7][8]. Analogs lacking this phenolic group have indeed been found to exhibit better pharmacokinetics and longer duration of action, which is more advantageous for *in vivo* application [9].

Aim of the present study was to prepare a dibenz[*d*,*g*]azecine in which C(2) and C(3) are connected through a methylenedioxy, $-OCH_2O-$, moiety. This was appealing for the following reasons.

- Our previous studies have shown that the nature, number, and position of the substituents at the benzene ring significantly affect the binding affinities. It was hence interesting to investigate the influence of this spatially rather confined group on the affinities. A $-OCH_2O-$ moiety shares similar electronic properties with the 2,3-dihydroxy and 2,3-dimethoxy substituents, but is spatially distinct from all previously examined substitution patterns.
- Compared with the previously synthesized phenolic dibenzazecines, the target compound **3** is presumably chemically more stable and conceivably of better pharmacokinetics.

Results. – *Chemistry.* As outlined in the *Scheme*, the target dibenzazecine **3** was obtained *via* its pentacyclic precursor quinolizine **7**. Our previously established procedure, according to which the amine was reacted with 2-(2-bromoethyl)benzaldehyde in the presence of CF_3COOH (TFA) [10], only yielded the intermediary isoquinolinium salt **6** and not the expected quinolizine **7**. Attempts to cyclize the obtained isoquinolinium salt by *Pictet–Spengler* cyclization with 6N HCl were unsuccessful. The quinolizine **7** was thus prepared through the reaction of the precursor amine **5** with 2-(chloroethyl)benzoyl chloride, and the obtained intermediate was directly cyclized under *Bischler–Napieralski* conditions and subsequently reduced.

Scheme



a) TFA, dioxane, reflux, 12 h. *b*) 6N HCl, reflux, 10 h. *c*) Et_3N, CH_2Cl_2, r.t., 90 min. *d*) $POCl_3$/MeCN 1:2, reflux, 36 h; $NaBH_4$, MeOH, reflux, 2 h. *e*) MeI, acetone. *f*) Na, liq. NH_3, $-40°$, 10 min. *g*) ClCOOEt, dry THF, $-65°$, 4 h, then $NaCNBH_3$, $-65°$ to r.t.; *h*) $LiAlH_4$, dry THF, reflux, 2 h. *i*) Br_2, $AlCl_3$, CH_2Cl_2, r.t., 10 h.

Conversion of the quinolizine **7** to the target dibenzazecine **3** was similarly knotty. Conventionally at that step, the quinolizine derivative **7** was quaternized with MeI and the obtained quaternary salt was cleaved under *Birch* conditions to the corresponding azecine. In this case, reduction of the quaternary salt **8** with Na in liquid NH_3 gave a 1:1 mixture of two different compounds having the same molecular weight. These substances were identified by means of GC/MS as the phenolic azecines **1** (LE404) and **9**, which was confirmed by spiking the GC/MS with reference samples of **1** and **9**, both available in our laboratory from previous work. The phenomenon of the cleavage of the $-OCH_2O-$ moiety under various reductive conditions has been already described [11][12]. For instance, reduction under *Birch* conditions (Na and liquid NH_3) was found to result in the cleavage of methylenedioxy derivatives, yielding the respective *p*-phenolic compounds [11]. It has been suggested that the nature of the substituent positioned opposite to the $-OCH_2O-$ moiety directs the site of cleavage, which leads to the formation of either the *m*- or *p*-phenolic compound. In our case, however, cleavage of the $-OCH_2O-$ group occurred at two different positions and not at only one position, as observed with reported methylenedioxy derivatives [11]. This, of course, may be attributed to the fact that both substituents across the $-OCH_2O-$ group exert equal effects.

To accomplish ring opening and avoid degradation of the methylenedioxy function, the quinolizine **7** was first converted to the carbamate **10** according to [13], which was subsequently reduced with $LiAlH_4$ to give the target compound **3**. This azecine was further dibrominated to examine the impact of the additional Br-atoms on the affinities. Unfortunately, the monobrominated derivatives could not be obtained, even when equimolar amounts of Br_2 were used.

Pharmacology. The target compounds **3** and **4**, as well as the precursor quinolizine **7** were screened for their affinities for the human cloned dopamine receptor subtypes D_1, D_{2L}, D_3, $D_{4.4}$, and D_5. These receptors were stably expressed in HEK293 or CHO cells; [^{3}H]SCH23390 and [^{3}H]spiperone were used as radioligands at the D_1- and D_2-like receptors, respectively. K_i Values are given in nanomolar units (*Table*). In addition, the compounds were tested in an intracellular Ca^{2+} assay, to determine their functionality at the D_1 and D_2 receptors. For this purpose, 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. Both the radioligand-binding assay and the Ca^{2+} assay have been described in detail in [10].

Discussion. – The newly synthesized dibenzazecine derivative **3** proved to be a highly active dopamine antagonist (functional Ca^{2+} assay), showing comparatively high affinities at the different dopamine receptors as the lead compound **1** (LE404), all lying in the nanomolar range. The D_1-selectivity profile, encountered with most members of this class of dopamine antagonists, was, however, lost. Compound **3** displayed equal affinities for the D_1 and D_2 subtypes, and showed the highest selectivity for the D_5 receptor ($D_1/D_5 \approx 7$). With respect to the affinities, compound **3** is superior to

Table. *Affinities* (K_i [nM]) *for Human* D_1–D_5 *Receptors, Determined by Radioligand-Binding Experiments*

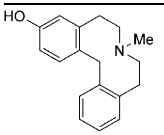
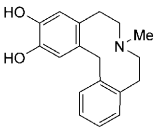
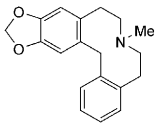
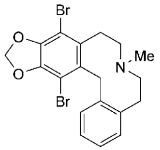
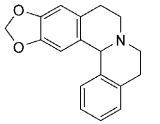
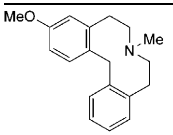
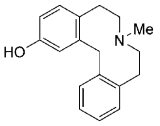
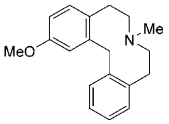
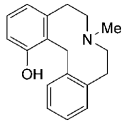
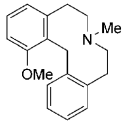
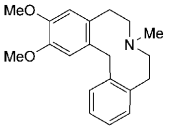
Compounds		K_i [nM]				
		HEK D_1	HEK D_{2L}	HEK D_3	CHO $D_{4.4}$	HEK D_5
	**1** (LE404)	0.39 ± 0.22[a])	17.5 ± 1.5[a])	47.5 ± 24[b])	11.3 ± 1.0[a])	1.5 ± 0.5[a])
	**2** (LE403)	341 ± 41[a])	> 5000[a])	n.d.	165 ± 12[a])	1078 ± 42[a])
	**3**	3.6 ± 1[c])	5.5 ± 1.2[c])	20.6 ± 5.5[c])	46.0 ± 9.9[c])	0.5 ± 0.01[c])
	**4**	35.0 ± 14.5[c])	30.0 ± 19.6[c])	38.9 ± 1.1[c])	2760 ± 552[c])	4.7 ± 1.9[c])
	**7**	> 10000	> 10000	> 10000	> 10000	> 10000

Table (cont.)

Compounds		K_i [nM]				
		HEK D_1	HEK D_{2L}	HEK D_3	CHO $D_{4.4}$	HEK D_5
	**11**	28.5 ± 9.7[b])	13.0 ± 9.00[b])	75.7 ± 7.30[b])	43.4 ± 13.3[d])	54.0 ± 20[d])
	**12**	8.9 ± 0.8[b])	36.9 ± 27.8[b])	296 ± 60.0[b])	913 ± 79.0	8.92 ± 0.82
	**13**	82.0 ± 30[b])	62.0 ± 5.00[b])	151 ± 57.5[b])	5987 ± 675	14.4 ± 8.5
	**14**	8.70 ± 2.00[b])	84.1 ± 2.75[b])	215 ± 94[b])	202 ± 73.5	8.6 ± 3.9
	**15**	7.6 ± 1.5 [b])	164 ± 12 [b])	1833 ± 292 [b])	390 ± 160	10.5 ± 2.8
	**16**	509 ± 51	> 5000	n.d.	2514 ± 101	2610 ± 120

[a]) Values from [3]. [b]) Values from [4]. [c]) K_i Values are the means of two experiments; performed in triplicate ± SEM. [d]) Values from [14].

previously synthesized 1- and 2-monohydroxy derivatives, **14** and **12**, respectively, and the 1-, 2- and 3-monomethoxy derivatives, **15**, **13**, and **11**, respectively, and similarly active to the 3-hydroxy compound **1**. Compared with the 2,3-dihydroxy and the 2,3-dimethoxy derivative, **2** and **16**, respectively, **3** showed a tremendous improvement in affinities; almost 100-fold increase in the affinity for D_1 and 1000-fold for D_2 and D_5 was observed. The dibromo derivative **4** displayed the highest affinity for the D_5 receptor; for the D_1, D_2, and D_3, it showed similar but somewhat lower affinities, while the D_4 affinities were strongly decreased.

Previous SAR studies have already indicated that a OH group at C(3) of the dibenzazecine ring is crucial for high affinities. It presumably interacts through H-bond formation with a serine residue (Ser 5.46 or Ser 5.50) in the receptor-binding pocket, as already observed with other dopamine antagonists at the D_2 receptor [15]. Derivatives with a MeO substituent especially at C(2) or C(3) showed significantly decreased affinities. This could be attributed to the fact that a MeO group, which rotates freely, is spatially too bulky for the receptor binding site. A 2,3-dimethoxy substitution pattern requires much more space due the free internal rotation of both MeO groups, hence, resulting in a pronounced decrease in affinities. Conversely, a $-OCH_2O-$ moiety, which requires less space due to its restricted rotation, showed similarly high affinities as the highly active 3-OH derivative **1**. From our observations, it can be concluded that the phenolic compounds rather act as H-acceptor than as H-donor.

Taken together, a $-OCH_2O-$ moiety connecting C(2) and C(3) of the dibenzazecine ring is not only favored in terms of chemical stability and pharmacokinetics but also in regards to the binding affinities to dopamine receptors.

Experimental Part

General. TLC: silica gel *F254* plates (*Merck*). M.p.: in open cap. tubes, with a *Gallenkamp* melting point apparatus; uncorrected. ^{1}H- and ^{13}C-NMR spectra: *Bruker Advance 250* spectrometer (250 MHz) and *Advance 400* spectrometer (400 MHz); δ in ppm, J in Hz. MS: by GC/MS, using a *Hewlett Packard GCD-Plus* (*G1800C*) apparatus (*HP-5MS* column; *J&W Scientific*); *m/z* (rel. %). 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-[2-(1,3-Benzodioxol-5-yl)ethyl]-3,4-dihydroisoquinolinium Trifluoroacetate (**6**). A soln. of *2-(1,3-benzodioxol-5-yl)ethylamine* (**5**; 1.65 g, 10 mmol), 2-(2-bromoethyl)benzaldehyde [16] (3.2 g, 15 mmol), and CF_3COOH (TFA; 1.7 g, 15 mmol) in dioxane (40 ml) was heated under reflux for 12 h. The isoquinolinium salt, and not the expected quinolizinium salt, separated as a yellow solid. This was filtered off, washed with dioxane, then Et_2O, and dried to give **6** (1.2 g, 36%). M.p. 214–216°. ^{1}H-NMR (250 MHz, CD_3OD): 3.19 (*t*, $J=7$, CH_2(4)); 3.28 (*t*, $J=8$, CH_2CH_2N); 4.13 (*t*, $J=8$, CH_2CH_2N); 4.27 (*t*, $J=7$, CH_2(3)); 5.93 (*s*, OCH_2O); 6.74 – 6.81 (m_c, 2 arom. H); 6.89 (*s*, 1 arom. H); 7.48–7.56 (*m*, 2 arom. H); 7.73–7.83 (*m*, 2 arom. H); 8.91 (*s*, N^+=CH).

*5,8,9,14b-Tetrahydro-6*H*-[1,3]dioxolo[4,5-*g*]isoquinolino[1,2-*a*]isoquinoline* (**7**). To an ice-cooled soln. of **5** (2.97 g, 18 mmol) in CH_2Cl_2 (30 ml) was added Et_3N (5.45 g, 54 mmol), followed by a soln. of 2-(chloroethyl)benzoyl chloride (4.02 g, 19.8 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred at r.t. for 90 min, subsequently washed with 10% HCl (2×30 ml), followed by brine (30 ml). The org. layer was dried (Na_2SO_4) and evaporated under reduced pressure to yield a brown oil. This crude amide was dissolved in a mixture of $POCl_3$/MeCN (15 ml/30 ml), and the mixture was heated under reflux for 36 h. The solvents were then removed under reduced pressure, and the remaining $POCl_3$ was removed by washing with petroleum ether (40–60°), followed by Et_2O. The residue was dissolved in MeOH (150 ml) without prior purification, then $NaBH_4$ (4 g) was carefully added to the ice-cooled soln. The mixture was

heated under reflux for 2 h, the solvent was subsequently removed under reduced pressure, and the residue was treated with H_2O (100 ml), and the mixture was extracted with Et_2O (2 × 100 ml). The collected org. layers were dried (Na_2SO_4) and evaporated under reduced pressure. The obtained oil was purified by column chromatography (CC; AcOEt/MeOH 9:1) to yield **7** (0.52 g, 10%). Yellowish white oil, which solidified on standing. M.p. 122–123°. ^{1}H-NMR (250 MHz, $CDCl_3$): 2.74–2.94, 3.04–3.26 (2*m*, CH_2(5,6,8,9)); 5.00 (*s*, H–C(14b)); 5.89, 5.91 (2*s*, CH_2(12)); 6.61 (*s*, H–C(10)); 6.69 (*s*, H–C(14)); 7.11–7.26 (*m*, H–C(1–4)). GC/MS: 278 (100), 250 (25), 191 (8), 178 (14), 165 (16), 148 (11), 130 (11), 115 (24), 103 (19), 89 (23), 77 (39), 63 (30). Anal. calc. for $C_{18}H_{17}NO_2 \cdot 0.1$ AcOEt: C 76.79, H 6.23, N 4.86; found: C 76.73, H 6.19, N 4.94.

*Ethyl 5,8,9,15-Tetrahydrobenzo[*d*][1,3]benzodioxolo[5,6-*g*]azecine-7(6*H*)-carboxylate* (**10**). A stirred soln. of **7** (0.78 g, 2.7 mmol) in dry THF (50 ml) was cooled in MeOH/dry ice at −65°. While keeping the mixture under N_2, ClCOOEt (1.63 g, 15 mmol) was added, and stirring was continued for 4 h. Then, a soln. of $NaCNBH_3$ (0.59 g; 9.4 mmol) in dry THF (10 ml) was slowly added at −65°, and the mixture was stirred overnight, while allowing it to reach r.t. The mixture was subsequently treated with 2N NaOH (120 ml), the THF layer was separated, washed with brine, and finally the org. layer was evaporated under reduced pressure to give a yellow waxy solid. The obtained product was purified by CC (AcOEt/hexane, 1:2) to yield **10** (0.65 g, 69%). White solid. M.p. 110°. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.77, 0.97 (2*t*, *J* = 11, *Me*CH_2); 2.35, 2.48 (2*t*, *J* = 9, CH_2(5)); 2.86–2.94 (*m*, CH_2(9)); 3.40–3.57 (*m*, CH_2(6,8)); 3.74, 3.86 (2*q*, *J* = 11, MeCH_2); 3.98 (*s*, CH_2(15)); 5.89 (*s*, CH_2(12)); 6.57, 6.61, 6.64, 6.74 (4*s*, H–C(10,14)); 7.03–7.26 (*m*, H–C(1–4)). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.35, 14.33 (*Me*CH_2); 32.63, 33.09 (C(5)); 33.82, 34.17 (C(9)); 37.94, 38.44 (C(15)); 51.74, 51.86 (C(6)); 52.85, 53.69 (C(8)); 60.80, 60.90 (Me*C*H_2); 100.78 (C(12)); 126.23, 126.47, 126.68, 126.75 (C(2,3)); 129.97, 130.92 (C(1)); 131.06, 132.08 (C(4)); 132.39, 132.77 (C(9a)); 133.46, 133.67 (C(14a)); 139.53, 139.60 (C(4a)); 140.00, 140.34 (C(15a)); 146.07, 146.26, 146.56 (C(10a,13a)); 156.38 (C=O). GC/MS: 353 (28), 280 (9), 248 (31), 237 (16), 220 (72), 207 (12), 191 (17), 178 (70), 165 (100), 152 (47), 139 (19), 128 (30), 115 (64), 104 (70), 91 (41), 77 (55), 65 (41). Anal. calc. for $C_{21}H_{23}NO_4$: C 71.37, H 6.56, N 3.96; found: C 71.17, H 6.58, N 3.87.

*5,6,7,8,9,15-Hexahydro-7-methylbenzo[*d*][1,3]benzodioxolo[5,6-*g*]azecine* (**3**). A soln. of **10** (0.8 g, 2.3 mmol) in dry THF (20 ml) was slowly added to an ice-cooled, stirred suspension of $LiAlH_4$ (0.25 mg, 9 mmol) in dry THF (75 ml), while keeping the reaction under N_2. After the addition was completed, the mixture was heated under reflux for 2 h. It was then cooled in an ice-bath, and the reaction was quenched by careful addition of sat. potassium sodium tartrate soln., until no further H_2 evolved. The resulting suspension was then filtered off, and the filtrate was evaporated under reduced pressure to give **3** (0.65 g, 97%). White waxy solid. The obtained product was purified by CC (AcOEt/MeOH 9:1). M.p. 70–71°. ^{1}H-NMR (250 MHz, $CDCl_3$): 2.26 (*s*, NMe); 2.64–2.71 (m_c, CH_2(5,6,8,9)); 4.35 (*s*, CH_2(15)); 5.88 (*s*, CH_2(12)); 6.56 (*s*, H–C(10)); 6.75 (*s*, H–C(14)); 7.04–7.33 (*m*, H–C(1–4)). ^{13}C-NMR (62.5 MHz, $CDCl_3$): 34.46, 34.48 (C(5,9)); 38.06 (C(15)); 46.92 (NMe); 60.70, 60.74 (C(6,8)); 100.66 (C(12)); 109.99 (C(10,14)); 126.10, 126.29 (C(2,3)); 130.52, 130.89 (C(1,4)); 133.63, 133.88 (C(9a,14a)); 141.02, 141.09 (C(4a,15a)); 145.78, 145.84 (C(10a,13a)). GC/MS: 295 (12), 237 (30), 223 (38), 207 (10), 190 (32), 178 (60), 165 (100), 152 (39), 139 (16), 128 (21), 115 (55), 103 (33), 89 (43), 71 (60), 63 (41). Anal. calc. for $C_{19}H_{21}NO_2 \cdot 0.1$ AcOEt: C 76.60, H 7.22, N 4.60; found: C 76.78, H 7.28, N 4.57.

*10,14-Dibromo-5,6,7,8,9,15-hexahydro-7-methylbenzo[*d*][1,3]benzodioxolo[5,6-*g*]azecine* (**4**). To a suspension of **3** (0.15 g, 0.5 mmol) and anh. $AlCl_3$ (0.03 g, 0.23 mmol) in CH_2Cl_2 (4 ml) was slowly added a soln. of Br_2 (0.4 g, 2.5 mmol) in CH_2Cl_2 (2 ml). After 10 h of stirring at r.t., the mixture was poured into a sat. soln. of $Na_2S_2O_5$ (50 ml) and extracted with CH_2Cl_2 (2 × 15 ml). The extract was washed with sat. $NaHCO_3$ soln. (2 × 50 ml) and H_2O (2 × 50 ml). The org. layer was dried (Na_2SO_4) and evaporated under reduced pressure, leaving a brownish solid, which was crystallized from MeOH to give **4** (0.15 g, 67.6%). Yellow crystals. M.p. 135–136°. ^{1}H-NMR (250 MHz, $CDCl_3$): 2.35 (*s*, NMe); 2.65–2.78 (*m*, CH_2(5,6,8,9)); 4.86 (*s*, CH_2(15)); 6.09 (*s*, CH_2(12)); 7.03–7.26 (*m*, H–C(1–4)). ^{13}C-NMR (62.5 MHz, $CDCl_3$): 32.71 (C(5)); 34.88 (C(9)); 37.95 (C(15)); 46.54 (NMe); 58.89 (C(6)); 60.79 (C(8)); 101.26 (C(12)); 104.23, 104.43 (C(10,14)); 126.24 (C(2)); 126.43 (C(3)); 130.15 (C(4)); 130.79 (C(1)); 135.17 (C(9a)); 135.59 (C(14a)); 139.31 (C(4a)); 141.35 (C(15a)); 144.20, 144.27 (C(10a,13a)). Anal. calc. for $C_{19}H_{19}Br_2NO_2$: C 50.36, H 4.23, Br 35.26, N 3.09; found: C 50.20, H 4.29, Br 35.08, N 2.96.

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