HETEROCYCLES, Vol. 60, No. 4, 2003, pp. 887 - 898
Received, 24th December, 2002, Accepted, 17th February, 2003, Published online, 3rd March, 2003

DOPAMINE/SEROTONIN RECEPTOR LIGANDS VI.[1] DIBENZ[*g,j*]-1-OXA-4-AZACYCLOUNDECENE AND DIBENZ[*d,g*]-2-AZACYCLOUNDECENE: SYNTHESIS OF TWO NEW HETEROCYCLIC RING SYSTEMS AS POTENTIAL LIGANDS FOR DOPAMINE RECEPTOR SUBTYPES

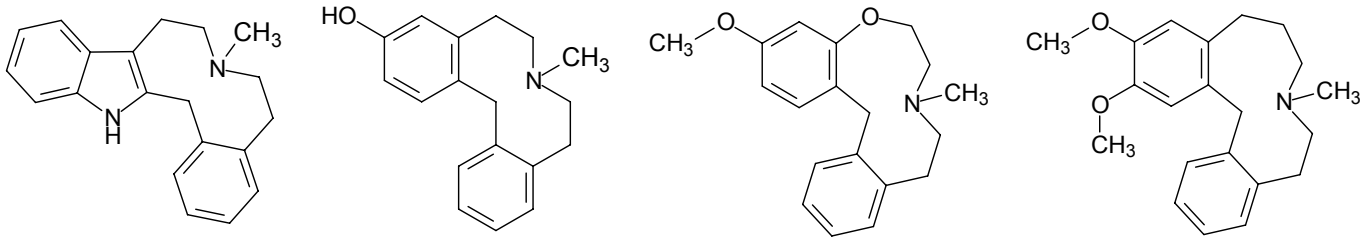
*Thomas W. Wittig, Christoph Enzensperger, and Jochen Lehmann**

Institute of Pharmacy, Friedrich-Schiller-University of Jena,
Philosophenweg 14, 07743 Jena, Germany; email: j.lehmann@uni-jena.de

Abstract- 2-(2-Hydroxyethyl)-*N*-[2-phenoxyethyl]benzamides and 2-(2-hydroxyethyl)-*N*-[2-phenylpropyl]benzamides have been prepared from 2-phenoxyethyl- or 2-phenylpropylamines and isochroman-1-one. Applying Bischler-Napieralski reaction, a tetracyclic isoquinolino[2,1-*d*][1,4]benzoxazepine and a isoquinolino[1,2-*a*][2]benzazepine could be obtained. The titled compounds representing novel 11 membered heterocycles could be prepared by subsequent ring cleavage under Birch conditions after quaternisation with methyl iodide. They are considered to be ligands for dopamine receptors. NMR spectral data indicate different conformations for the two azacycloundecene derivatives.

Heterocyclic compounds containing constrained indolyl- and phenylalkylamin-structures, like the benz[*d*]indolo[2,3-*g*]azecine (**LE 300**),[2] have shown to be potent and selective Dopamine D_1/D_5-receptor subtype antagonists.[1,3] In further studies, the 3-hydroxydibenz[*d*,*g*]azecine (**LE 404**) was found to be an even more potent ligand at the human cloned D_1/D_5- receptor subtypes.[4] Hence we focused our interests on the dibenzo derivatives and synthesized the dibenz[*g,j*]-1-oxa-4-azacycloundecene (**1a**) and the dibenz[*d,g*]-2-azacycloundecene (**1b**) in order to investigate the tolerance of the receptor for the expansion of the 10-membered condensed azecines to 11-membered ring systems and for the different electronical situation in the heterocyclus created by incorporation of an oxygen atom. Meise and coworkers have reported the synthesis

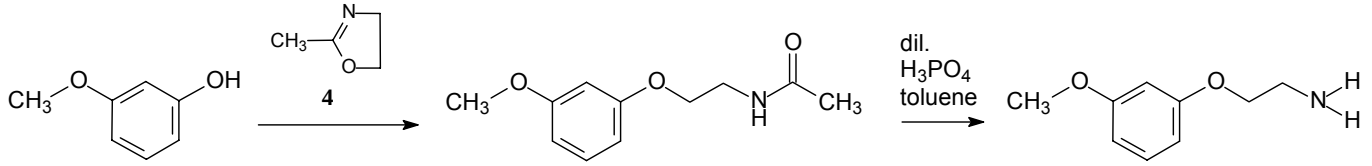
of various homo-isoberberine homologues *via* a Bischler-Napieralski reaction to test them on the inhibition of phosphodiesterases.[5] Based on their synthetic route to isoquinolino[2,1-*d*][4]benzazepines, we prepared the 12,13-dimethoxyhexahydroisoquinolino[1,2-*a*]-[2]benzazepine (**12b**) as described by Meise[5] and the 3-methoxytetrahydro-9*H*-isoquinolino [2,1-*d*][1,4]-benzoxazepine (**12a**), following a modified synthetic approach. Ringexpansion should be conducted by cleaving the central C-N bond of **12a**,**b**.



LE 300 **LE 404** **1a** **1b**

Figure 1: Condensed azecines and new 11-membered analogues with antidopaminergic potential

The benzamides (**7a,b**) were obtained from isochroman-1-one and the appropriate primary amines (**6a,b**) (**Figure 3**). While the 3-phenylpropylamine (**6b**) could be obtained directly by reduc-tion of the corresponding acrylonitrile , the 3-phenoxyethylamine (**6a**) had to be prepared in a two step procedure (**Figure 2**): [6] Nucleophilic ring cleavage of the 2-methyloxazole (**4**) by the phenol (**3**) at 5-position yielded the *N*-[2-phenoxyethyl]acetamide (**5**). Subsequent hydrolysis with diluted phosphoric acid and extraction with toluene gave the primary amine (**6a**), sufficiently pure for further reactions.



3 **5** **6a**

Figure 2: Synthesis of 2-(3-methoxyphenoxy)ethylamine

According to Meise,[5] the yields of the 5-phenylbenz[1,4]oxazepinium- and the 5-phenyl-5*H*-[2]benzazepininium salts (**9a,b**) obtained by Bischler-Napieralski reactions were much higher, when we protected the alcohol group of the benzamides (**7a,b**) as a carbonate function (**8a,b**) and worked in non protic solvents like acetonitrile or nitromethane. The tetracyclic isoquino[2,1-*d*][1,4]benz-oxazepine (**12a**) and isoquinolino[1,2-*a*][2]benzazepine (**12b**) were obtained in high

yields after deprotection and conversion of the resulting alcohol into a chloride moiety (**11a**) by reduction and a second cyclisation step. The synthetic route from the benzamide (**7a,b**) to the tetracyclic compounds (**12a,b**) could be performed advantageously without purification of any of the intermediates. In order to characterize the novel intermediates (**8a**, **9a**, **10a** and **11a**), synthesis of **12a** from **7a** was additionally performed including purification of all of these intermediates.

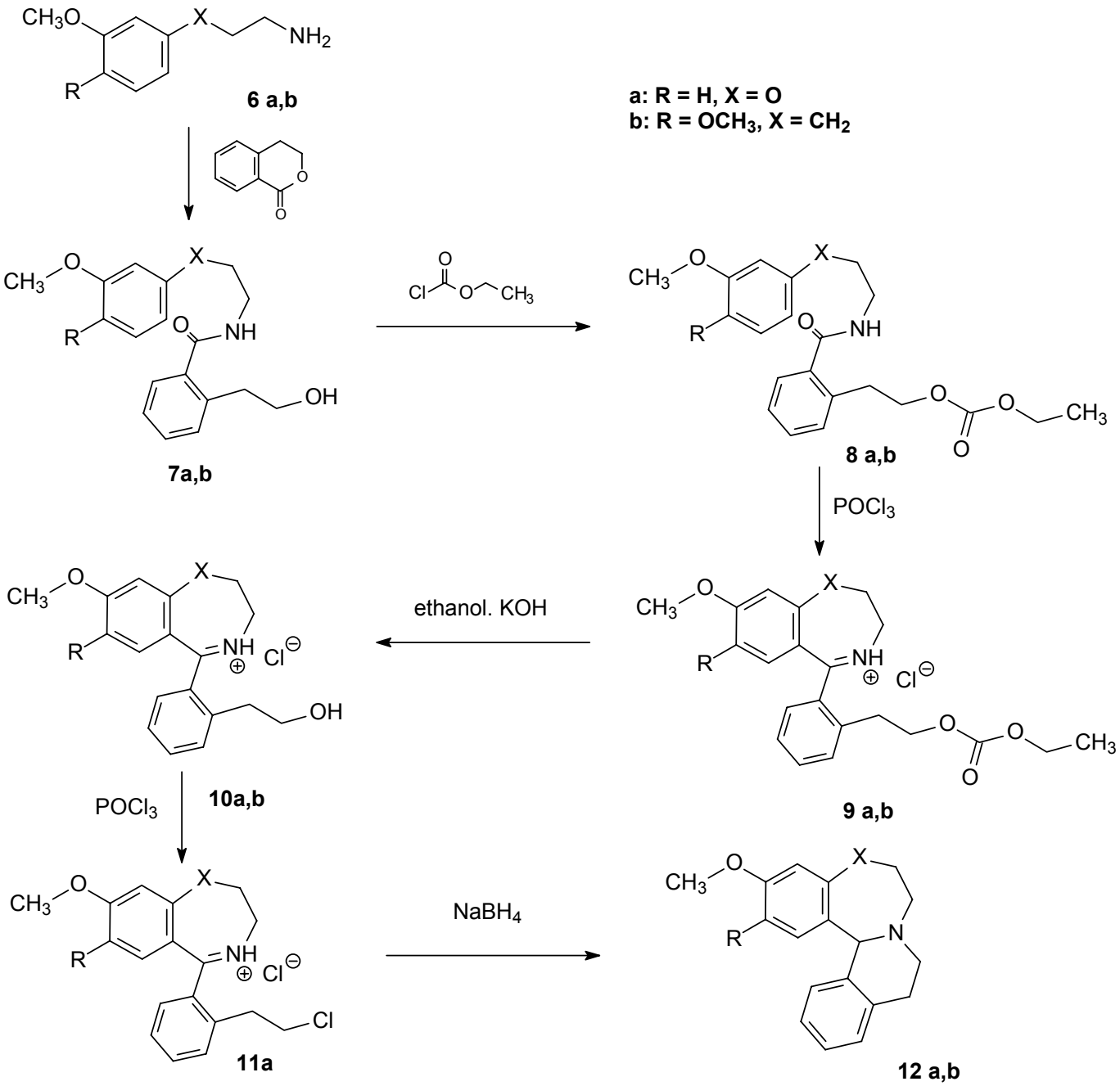


Figure 3: Synthesis of isoquinolino[2,1-*d*][1,4]benzoxazepine and isoquinolino[1,2a][2]benzazepine

Subsequent quaternisation with methyl iodide in toluene gave the isoquinolino[2,1-*d*][1,4]benz-oxazepinium- and isoquinolino[1,2-*a*][2]benzazepinium iodides (**13a,b**) as precursors for the conclusive cleavage to the less constrained tricyclic ring systems (**1a, b**). This was performed under Birch conditions, using metallic sodium in liquid ammonia. The reaction time under birch conditions seems to be crucial for the yield and the chemoselectivity of the cleavage. 6 to 8 minutes were found to be suitable in order to cleave the central C,N-bond, but not to attack the aromatic rings.

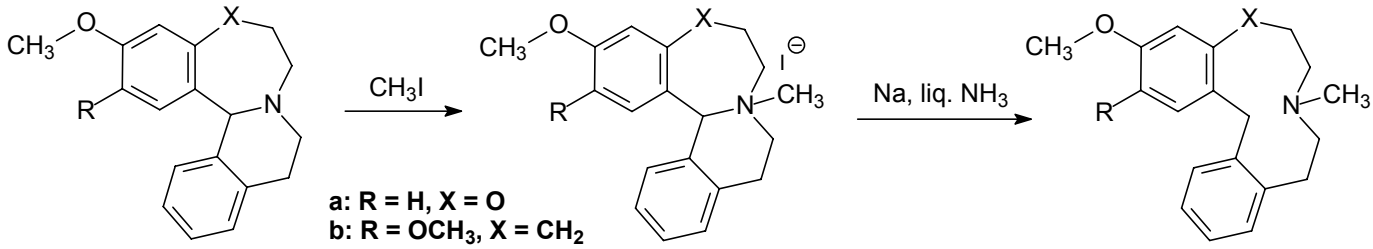
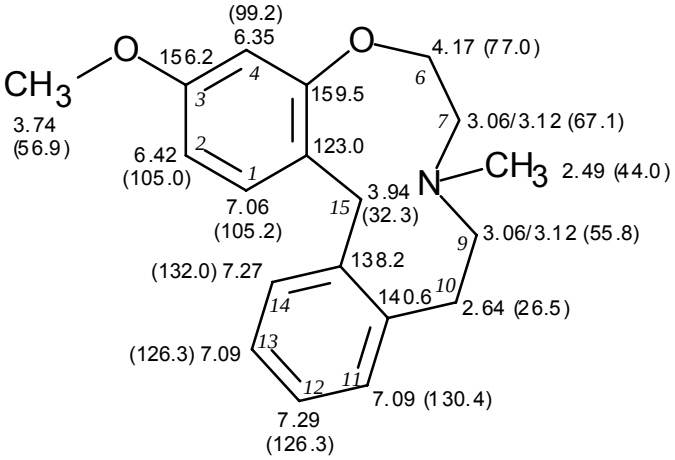


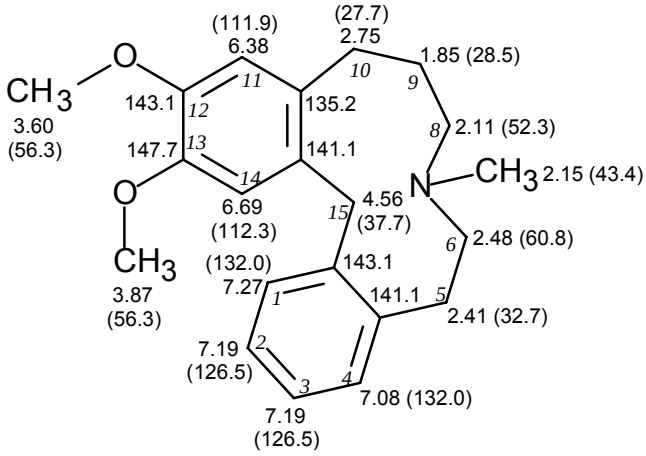
Figure 4: Quaternisation of **12 a,b** and ring cleavage to the titled compounds (**1 a,b**)

STRUCTURAL ASPECTS

Concerning ^{1}H-NMR spectral data of compound (**1b**), the methylene protons next to the nitrogen in the “upper” part of the ring (at C-8) show a remarkable high field shift (δ = 2.11 ppm), compared to the corresponding methylene group (at C-7) of the oxa analogue (2 signals at 3.06 and 3.12 ppm). They even show a lower ppm value than the N-methyl protons (δ = 2.15 ppm). These data indicate different conformations of the two heterocycles. Obviously the methylene group at C-8 in compound (**1b**) is located fairly above the aromatic rings - even more than the exocyclic methyl group - suggesting a cage-like conformation. According to this kind of conformation, both moieties are subjected to a decreased field under the influence of the magnetic field. This is not the case with N-CH_3 and the N-methylenes in compound (**1a**), indicating a more stretched conformation for this heterocycle.



1a



1b

Figure 5: ^{1}H-NMR and ^{13}C-NMR spectral data in ppm for compounds (**1a**) and (**1b**).

EXPERIMENTAL

Melting points are 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 a Bruker DRX-500 (500 MHz) and a Bruker AC 200 spectrometer (200 MHz). Elemental analyses were performed on a Hereus Vario EL apparatus. TLC was performed on silica gel F254 plates (Merck). MS data were determined by GC/MS, using a Hewlett Packard GCD-Plus (G1800C) apparatus (HP-5MS column; J&W Scientific).

N-[2-(3-Methoxyphenoxy)ethyl]acetamide **(5)**

49.6 g (0.4 mol) of 3-methoxyphenol and 34 g (0.4 mol) of 2-methyl-4,5-dihydro-1,3-oxazole were heated at 180°C for 16 h. The resulting mixture was cooled to rt, dissolved in $CHCl_3$ (200 mL) and washed with 2N HCl (3x30 mL), 20% NaOH (3x30 mL) and water (15 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude product was purified by distillation under reduced pressure to give the the pure acetamide (**5**) as a yellow oil. (43.5 g, 52%); bp $_{(0.1\ mbar)}$ 179-184°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.93 (s, 3H, CO-CH_3), 3.56 (q, *J* = 6 Hz, 2H, NH-$\underline{CH_2}$), 3.71 (s, 3H, O-CH_3), 3.94 (t, *J* = 5 Hz, 2H, O-CH_2), 6.04 (br s, 1H, NH), 6.37 – 6.40 (m, 3H, H-arom.), 7.10 (t, *J* = 8 Hz, 1H, H-arom.); Anal. Calcd for $C_{11}H_{15}NO_3$ x 1/8 H_2O: C, 62.4; H, 7.21; N, 6.62. Found: C, 62.6; H, 7.40; N, 6.59.

2-(3-Methoxyphenoxy)ethylamine **(6a)**

41.6 g (0.2 mol) of **5** was added to a mixture of 60 g of orthophosphoric acid (85%) and 20 g of water and refluxed for 16 h. The resulting mixture was cooled in ice, made alkaline (pH 9 - 10) with 20% NaOH and extracted with toluene (3x 30 mL). The combined organic layers were washed with water and brine and dried over $MgSO_4$. The solvent was removed to give the crude product, which was purified by distillation under reduced pressure (105-108°C, 0.1 mbar) and following dropwise addition of 10 mL of HCl-saturated ether solution to give the hydrochloride as a white precipitate, which was recrystallized from methanol. (21.7 g, 65%); mp 135°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 3.01 (t, *J* = 5 Hz, 2H, C$\underline{H_2}$-NH_2), 3.71 (s, 3H, O-CH_3), 3.91 (t, *J* = 5 Hz, 2H, O-CH_2), 6.40 – 6.45 (m, 3H, H-arom.), 7.10 (t, *J* = 8 Hz, H-arom.); Anal. Calcd for $C_9H_{13}NO_2$ x HCl: C, 53.1; H, 6.93; N, 6.88. Found: C, 53.1; H, 6.96; N, 6.72.

3-(3,4-Dimethoxyphenyl)propylamine **(6b)**

21.7 g (111 mmol) of 3-(3,4-dimethoxyphenyl)acrylonitrile were dissolved in 300 mL of EtOH and 25 mL of conc. HCl. The resulting mixture was hydrogenated in a Parr-apparatus with 1.5 g of a palladium-carbon mixture (10% palladium) under stirring at rt and a hydrogen pressure of 5 bar for 72 h. After removal of the catalyst, the solution was concentrated to a 70 mL volume under reduced pressure. The acidic solution was washed twice with ether and made alkaline (pH 9-10) with 20% NaOH. The aqueous phase was extracted with $CHCl_3$ (3x30 mL) and the combined organic layers were washed with water and brine and dried over $MgSO_4$. The solvent was removed to yield the crude product as a yellow oil, which was was purified by distillation under reduced pressure to give a colorless oil. (11.9 g , 53%). bp $_{(1.5\ mbar)}$: 110-113°C, lit.,[7] $_{(0.06\ mbar)}$: 86 - 90 °C; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 1.25 (br s, 2H, NH_2), 1.71 (quint, *J* = 7 Hz, 2H, CH_2-C$\underline{H_2}$-CH_2), 2.55 (t, *J* = 8Hz, 2H, C$\underline{H_2}$-NH_2), 2.65 (t, *J* = 7Hz, 2H, Ph-C$\underline{H_2}$), 3.80 and 3.82 (2x s, 2x 3H, O-CH_3), 6.6-6.8 (m, 3H, H-2, H-5, H-6).

Isochroman-1-one was prepared by oxidation of isochromane with potassium permanganate[8] in a recently modified synthetic approach described by Klinkhammer.[9]

2-(2-Hydroxyethyl)-*N*-[2-(3-methoxyphenoxy)ethyl- and 2-(2-hydroxyethyl)- *N*-[2-(3,4-dimethoxyphenyl)propyl]benzamide **(7a,b)** – general procedure

120 mmol of the primary amine **(6a,b)**, 105 mmol of isochroman-1-one and 1 g of NH_4Cl were heated at 120°C for 8 h. The reaction mixture was cooled to rt, dissolved in $CHCl_3$ (150 mL) and

washed twice with 2N HCl (2 x 30 mL). The solvent was removed under reduced pressure and the residue was heated in 50 mL of a 20% NaOH solution at 70°C on a water bath for 30 min under vigorous stirring. After cooling to rt, the solution was extracted with $CHCl_3$ (3x30 mL). The combined organic layers were washed with water and brine and dried over $MgSO_4$. The solvent was removed to give the crude product, which was recrystallized from ethyl acetate/ether (60:40) to yield a white solid.

2-(2-Hydroxyethyl)-*N*-[2-(3-methoxyphenoxy)ethyl]benzamide **(7a)** (8.3 g, 22%); white crystalls; mp 87°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.89 (t, *J* = 6 Hz, 2H, Ph-CH_2), 3.71 (s, 3H, O-CH_3), 3.75 – 3.85 (m, 4H, N-CH_2-CH_2-O), 4.07 (t, *J* = 6 Hz, 2H, CH_2-OH), 6.4 – 6.5 (m, 3H, H-arom.), 6.83 (br s, 1H, NH), 7.1 – 7.2 (m, 3H, H-arom.), 7.3 – 7.35 (m, 2H, H-arom) ; Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.6; H, 6.66; N, 4.44. Found: C, 68.5; H, 6.78; N, 4.44.
N-[3-(3,4-Dimethoxyphenyl)propyl]-2-(2-hydroxyethyl)benzamide **(7b)** (11.3 g, 29%); beige powder; mp 85°C, lit.,[10] 85 - 86°C; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.8-2.0 (m, 2H, CH_2-CH_2-CH_2), 2.67 (t, *J* = 7.5 Hz, 2H, Ph-CH_2-CH_2-CH_2-), 2.94 (t, *J* = 6Hz, 2H, Ph-CH_2-CH_2-OH), 3.44 (dt, *J* = 7 and 7 Hz, 2H, $PhCH_2CH_2$-CH_2), 3.7 - 3.95 (m with 2 sharp singlets at 3.85 and 3.87, 8H, 2x O-CH_3 and $PhCH_2$-CH_2OH), 4.20 (br s, 1H, OH), 6.50 (br s, 1H, NH), 6.6-6.9 (m, 3H, H-arom.), 7.2-7.5 (m, 4H, H-arom.).

Ethyl 2-[2-({[2-(3-methoxyphenoxy)ethyl]amino}carbonyl)phenyl]- and 2-[2-({[3-(3,4-dimethoxyphenyl)propyl]amino}carbonyl)phenyl]ethylcarbonate **(8a,b)** – general procedure
26 mmol of ethyl chlorocarbonate were dissolved in 25 mL of $CHCl_3$ and added dropwise over half an hour to a solution of 26 mmol of **7a** or **b** dissolved in a mixture of 25 mL of $CHCl_3$ and 40 mL of pyridine. The mixture was stirred for another half an hour at rt and the solvents and the pyridine were removed under reduced pressure. The residue was dissolved in 50 mL of $CHCl_3$, washed with 2N HCl and 20% NaOH (2x 20mL each), and dried over $MgSO_4$. After removal of the solvent the product remained as a dark yellow oil in a sufficient purity as proved by TLC (R_f: 0,73; $CHCl_3$/MeOH 95:5).

Ethyl 2-[2-({[2-(3-methoxyphenoxy)ethyl]amino}carbonyl)phenyl]ethylcarbonate **(8a)**
(9.6 g, 95%); ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.16 (t, *J* = 7 Hz, 3H, CH_2CH_3), 3.08 (t, *J* = 7 Hz, 2H, Ph-CH_2), 3.71 (s, 3H, O-CH_3), 3.77 (dt, *J* = 5 Hz and 5 Hz, 2H, N-CH_2), 4.03 (q, *J* = 7 Hz, 2H, O-CH_2-CH_3), 4.08 (t, *J* = 5 Hz, 2H, PhO-CH_2), 4.30 (t, *J* = 7 Hz, 2H, $COOCH_2$), 6.35 – 6.45

(m, 4H, H-arom.), 7.11 (t, *J* = 7 Hz, 1H, H-arom.), 7.2 – 7.35 (m, 3H, H-arom.); Anal. Calcd for $C_{21}H_{25}NO_6$ x ½ H_2O: C, 63.6; H, 6.81; N, 3.53. Found: C, 63.2; H, 6.50; N, 3.83.

2-[2-({[3-(3,4-Dimethoxyphenyl)propyl]amino}carbonyl)phenyl]ethyl ethylcarbonate **(8b)**

(8.6 g, 83%); mp: 75°C lit.,[10] 75°C; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.21 (t, *J* = 7Hz, 3H, $C\underline{H}_3$-CH_2OCOO), 1.92 (m, 2H, CH_2-$C\underline{H}_2$-CH_2), 2.66 (t, *J* = 7.5Hz, 2H, Ph-$C\underline{H}_2CH_2CH_2$), 3.13 (t, *J* = 6.5Hz, 2H, Ph-$C\underline{H}_2CH_2O$), 3.46 (dt, *J* = 7 and 7Hz, 2H, $PhCH_2CH_2$-$C\underline{H}_2$), 3.84 and 3.86 (2s, 6H, 2x O-CH_3), 4.09 (q, *J* = 7Hz, 2H, CH_3-$C\underline{H}_2OCOO$), 4.38 (t, *J* = 6.5Hz, 2H, CH_3-$C\underline{H}_2OCOO$), 6.0 (br s, 1H, NH), 6.6 - 6.9 (m, 3H, arom.), 7.1-7.4 (m, 4H, arom.).

2-Ethyl-[2-(8-methoxy-2,3-dihydro-1,4-benzoxazepine-5-yl)phenyl]ethylcarbonate hydrochloride **(9a)**

A solution of 7.7 g (20 mmol) of **8a** in 80 mL of acetonitrile and 8 mL (87 mmol) of phosphoric trichloride (each freshly destilled) was refluxed for 6 h. The solvent was removed *in vacuo* and the residue was dissolved in 20 mL of 2N HCl. This mixture was washed with ethyl acetate (2x 20 mL) and the aqueous phase was extracted with $CHCl_3$ (5x 20 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$ and the solvent was removed. The crude product remained as a pale yellow foam, that was recrystallized from EtOH/ether (30:70) to give white crystalls, (3.8 g, 47%); mp 156 – 158°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.22 (t, *J* = 7 Hz, 3H, $COOCH_2$-$C\underline{H}_3$), 2.97 (t, *J* = 7 Hz, 2H, Ph-CH_2), 3.88 (s, 3H, O-CH_3), 4.06 (q, *J* = 7 Hz, 2H, COO-$C\underline{H}_2CH_3$), 4.15 – 4.35 (m, 4H, N-CH_2 and CH_2-OCO), 4.70 – 4.75 (m, 2H, PhO-CH_2), 6.54 (dd, *J* = 2.5 and 5.5 Hz, 1H, H-arom.), 6.65 (d, *J* = 2.5 Hz, 1H, H-arom.), 7.03 (d, *J* = 9.5 Hz, 1H, H-arom.), 7.35 – 7.45 (m, 3H, H-arom.), 7.53 – 7.57 (m, 1H, H-arom.) ; Anal. Calcd for $C_{21}H_{24}NO_5Cl$ x ¼ H_2O: C, 61.4; H, 6.09; N, 3.41. Found: C, 61.4; H, 6.03;N, 3.46.

2-[2-(8-Methoxy-2,3-dihydro-1,4-benzoxazepin-5-yl)phenyl]ethanol hydrochloride **(10a)**

3.2 g (8 mmol) of **9a** were dissolved in 80 mL of a 20% (m/v) ethanolic KOH-solution (EtOH/H_2O 70:30). The solution was stirred at rt for 12 h, concentrated at 40°C on a water bath to half of its volume and adjusted to a pH-value of 3 - 4 with 2N HCl. The mixture was washed with ethyl acetate (2x 20 mL) and the aqueous phase was extracted with $CHCl_3$ (5x 20 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$ and the solvent was removed. The product remained as a white foam-like solid, which showed a sufficient purity. (1.9 g, 69%); mp 188-189°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.65 (t, *J* = 5 Hz, 2H, Ph-CH_2), 3.85 (t, *J* = 5 Hz, 2H, $C\underline{H}_2$-OH), 3.89 (s, 3H, O-CH_3), 4.2 - 4.35 (m, 2H, NH-$C\underline{H}_2$), 4.7 – 4.8 (m, 2H, PhO-CH_2), 6.55 (dd, *J* = 3 and 6 Hz, 1H, H-7'), 6.66 (d, *J* = 3 Hz, 1H, H-9'), 7.02 (d,

J = 9 Hz, 1H, H-6'), 7.28 (d, *J* = 7 Hz, 1H, H-6), 7.35 – 7.4 (m, 2H, H-3 and H-4), 7.57 (dd, *J* = 7 and 7 Hz, 1H, H-5) ; Anal. Calcd for $C_{18}H_{20}NO_3Cl$: C, 60.6; H, 6.31; N, 3.93. Found:C, 60.5; H, 6.28; N, 4.00.

5-[2-(2-Chloroethyl)phenyl]-8-methoxy-2,3-dihydro-1,4-benzoxazepine hydrochlorid **(11a)**

1.7 g (5 mmol) of **10a** in 10 mL (109 mmol) of phosphoric trichloride were heated to 60°C for 15 min. After cooling to rt, 50 mL of petroleum ether (boiling range 40-60°C) was added and the mixture was stirred vigorously. After decanting the petroleum ether, this procedure was repeated another five times with 20 mL of petroleum ether each time. The residue was dissolved in 15 mL of 2N HCl and the aqueous phase was extracted with $CHCl_3$ (5x 10 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$ and the solvent was removed to yield a pale yellow solid in a sufficient purity as proved by TLC (R_f: 0,56; $CHCl_3$/MeOH 95:5). (1.4 g, 80%); mp 138-139°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.95 - 3.2 (m, 2H, Ph-CH_2), 3.70 (mc, 2H, CH_2-Cl), 3.84 (s, 3H, O-CH_3), 4.25 – 4.35 (m, 2H, NH-C$\underline{H_2}$), 4.65 – 4.75 (m, 2H, PhO-CH_2), 6.57 (dd, *J* = 2.5 and 7 Hz, 1H, H-7), 6.67 (d, *J* = 2.5 Hz, 1H, H-8), 7.07 (d, *J* = 9 Hz, 1H, H-6), 7.33 (dd, *J* = 1.5 and 7 Hz, 1H, H-3'), 7.40 (ddd, *J* = 1.5, 7 and 7 Hz, 1H, H-5'), 7.43 (dd, *J* = 1.5 and 7 Hz, H-6'), 7.58 (ddd, *J* = 1.5, 7 and 7 Hz, 1H, H-4'); Anal.Calcd for $C_{18}H_{19}NO_2Cl_2$ x ¾ $CHCl_3$: C, 50.9; H, 4.47; N, 3.17. Found: C, 50.9; H, 4.61; N, 3.21.

12,13-Dimethoxy-5,6,8,9,10,14*b*-hexahydroisoquinolino[1,2-*a*][2]benzazepine **(12b)**

2.8 g (6.7 mmol) of **8b** were dissolved in 65 mL of acetonitrile and 5 mL (54 mmol) of phosphoric trichloride. The mixture was refluxed for 6 h and subsequently stirred overnight. After removal of the solvent, the residue was dissolved in 170 mL of 2N HCl and washed with ethyl acetate (2x35 mL). The aqueous phase was extracted with $CHCl_3$ (5x35 mL), and the combined organic layers were dried over $MgSO_4$ and evaporated. The resulting oil **(9b)** was stirred for 12 h in 65 mL of a 20% (m/v) ethanolic KOH-solution (EtOH/H_2O 70:30), concentrated to half of its volume at 40°C on a water bath and adjusted to a pH-value of 3 - 4 with 2N HCl. The mixture was washed with ethyl acetate (2x 35 mL) and the aqueous phase was extracted with $CHCl_3$ (5x 20 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$ and the solvent was removed to yield an amber oil **(10b)**, which was directly dissolved in 10 mL (109 mmol) of phosphoric trichloride. The mixture was heated to 60°C for 15 min. After cooling to rt, 50 mL of petroleum ether (boiling range 40-60°C) was added and the mixture was stirred vigorously. After decanting the petroleum ether, this procedure was repeated another five times with 20 mL of petroleum ether each time. The remaining yellow oil **(11b)** was dissolved in 85 mL

of MeOH and 1 g (26 mmol) of sodium borohydride was added under stirring and ice cooling over half an hour. The mixture was stirred for another half an hour at rt and concentrated to dryness *in vacuo*. The residue was resuspended in 10 mL of water and extracted with ether (3x15 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$ and the solvent was removed to give an ivory colored oil (1.37 g, 66%); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.65 – 1.95 (m, 2H, CH_2-C<u>H</u>$_2$-CH_2), 2.60-3.35 (m, superposed, 8H, aliphatic H-5, H-6, H-8, H-10), 3.50 (s, 3H, 12-O-CH_3), 3.85 (s, 3H, 13-O-CH_3), 5.12 (s, 1H, Ph-CH-Ph), 5.90 (s, 1H, H-11), 6.69 (s, 1H, H-14), 6.92 (d, *J* = 7.1 Hz, 1H, H-4), 7.05 - 7.2 (m, 3H, H-1, H-2, H-3), Anal. Calcd for $C_{20}H_{23}NO_2$ x H_2O : C, 73.4; H, 7.70; N, 4.28. Found: C, 73.0; H, 7.23; N, 4.19, lit.,[10] (Hydrogen perchlorate): Calcd for $C_{20}H_{23}NO_2$ x $HClO_4$: C, 58.6; H, 5.90; N, 3.42. Found: C, 58.4; H, 5.85; N, 3.33.

<u>3-Methoxy-8-methyl-6,7,10,14b-tetrahydro-9*H*-isoquinolino[2,1-*d*][1,4]benzoxazepiniumiodide</u>
<u>(13a)</u>

1.4 g (4 mmol) of **11a** were dissolved in 30 mL of MeOH and 1 g (26 mmol) of sodium borohydride was added under stirring and ice cooling over half an hour. The mixture was stirred for another half an hour at rt and concentrated to dryness *in vacuo*. The residue was resuspended in 10 mL of water and extracted with ether (3x15 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$ and the solvent was removed to yield a yellow oil **(12a)**, which was subsequently dissolved in 10 mL of dry toluene. A solution of 1.4 g (10 mmol) of methyl iodide in 5 mL of dry toluene was added dropwise and the mixture was refluxed at 90°C. After *ca*. 15 min, a white solid began to precipitate and after refluxing for another 2 h and cooling to rt, the mixture was filtrated and the solid was washed with 50 mL of acetone and dried *in vacuo* without further purification (1.2 g, 70%); mp 230°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.44 – 2.55 (m, 2H, Ph-CH_2), 3.29 (s, 3H, N-CH_3), 3.25 – 3.45 (m, 3H, N-C<u>H</u>HCH_2O and N-CH_2), 3.6 – 3.7 (m, 1H, NCH2-C<u>H</u>HO), 3.77 (s, 3H, O-CH_3), 3.75 – 3.95 (m, 1H, N-CH<u>H</u>CH_2O), 4.34 (mc, 1H, NCH_2CH<u>H</u>O), 6.18 (s, 1H, Ph-CH-Ph), 6.3 – 6.85 (m, 3H, H-arom.), 7.1 – 7.4 (m, 4H, H-arom.) Anal. Calcd for $C_{19}H_{22}NO_2I$: C, 53.9; H, 5.20; N, 3.31. Found: C, 53.7; H, 5.26; N, 3.26.

<u>12,13-Dimethoxy-7-methyl-5,6,8,9,10,14*b*-hexahydroisoquinolino[1,2*a*][2]benzazepineiumiodide</u>
<u>(13b)</u>

0.36 g of **12b** (1.2 mmol) were dissolved in 25 mL of dry toluene. A solution of 1.42 g (10 mmol) of methyl iodide in 5 mL of dry toluene was added dropwise and the mixture was refluxed at

90°C. After stirring and refluxing overnight, a white solid began to precipitate and the mixture was filtrated and the precipitate was recrystallized from MeOH/ethyl acetate (1/1) to form pale yellow cubic crystalls. (1.6 g, 80%); mp 243-245°C; Anal. Calcd for $C_{21}H_{26}NO_2I$: C, 55.85; H, 5.81; N, 3.10. Found: C, 55.84; H, 5.81; N, 3.09.

3-Methoxy-8-methyl-6,7,8,9,10,15-hexahydrodibenzo[*g,j*]-1-oxa-4-azacycloundecene **(1a)** and 12,13-Dimethoxy-7-methyl-6,7,8,9,10,15-hexahydro-5*H*-dibenzo[*d,g*]-2-azacycloundecene **(1b)** - general procedure

A mixture of 0.25 mmol of **13 a** or **b** and 50 mL of liquid ammonia (**13a**) under addition of 0.15 mL of EtOH), were stirred at –40°C and small parts of sodium metal were added portionwise until the mixture carried a deep blue color. After exactly 7 min, the reaction was terminated by adding dropwise a saturated solution of NH_4Cl until the blue color had been completely disappeared. The mixture was stirred at rt under nitrogen, until all ammonia was evaporated. 30 mL of water was added and the emulsion was extracted with ether (3x20 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$ and the solvent was removed to yield the crude product as a pale yellow solid, which was purified by column chromatography (SiO_2^{60}, $CHCl_3$/MeOH = 95:5) and recrystallisation from EtOH.

3-Methoxy-8-methyl-6,7,8,9,10,15-hexahydrodibenzo[*g,j*]-1-oxa-4-azacycloundecene **(1a)**

white powder,(60 mg, 78%); mp 82-83°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.49 (s, 3H, N-CH_3), 2.64 (t, *J* = 8 Hz, Ph-CH_2), 3.06 and 3.12 (2x mc, 4H, 2x NCH_2), 3.74 (s, 3H, O-CH_3), 3.9 – 4.0 (m, 2H, Ph-CH_2-Ph), 4.15 –4.2 (m, 2H, PhO-CH_2), 6.35 (d, *J* = 2.5 Hz, 1H, H-4), 6.42 (dd, *J* = 3 and 5 Hz, 1H, H-2), 7.0 – 7.15 (m, 3H, H-1, H-11 and H-13), 7.29 (d, *J* = 9 Hz, 1H, H-12), 7.38 (d, *J* = 6 Hz, 1H, H-14); ^{13}C-NMR ($CDCl_3$): 26.5 (Ph-CH_2), 32.3 (Ph-CH_2-Ph), 44.0 (N-CH_3), 55.8 (PhCH$_2$-$\underline{C}$H$_2$N), 56.9 (O-CH_3), 67.1 PhOCH$_2$-$\underline{C}$H$_2$N), 77.0 (PhO-CH_2), 99.2 (C-4), 105.0 (C-2), 123.0 (C-15a), 126.3 (C-12 and C-13), 130.4 (C-11 and C-14), 138.2 (C-14a), 140.6 (C-10a), 156.2 (C-3), 159.5 (C-4a); Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.7; H, 7.74; N, 4.71. Found: C,76.3; H, 7.91; N, 4.66; MS: m/z (rel. int.) 297 (M^+, 58), 239 (32), 209 (31), 178 (17), 160 (45), 146 (37), 115 (29), 70 (100), 58 (47).

12,13-Dimethoxy-7-methyl-6,7,8,9,10,15-hexahydro-5*H*-dibenzo[*d,g*]-2-azacycloundecene **(1b)**

white crystalls, (36 mg, 50%); mp 77-78°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.65 – 1.95 (m, 2H, CH_2-C$\underline{H}_2$-CH_2), 2.05 – 2.15 (m, 2H, N-C$\underline{H}_2$$CH_2CH_2$), 2.15 (s, 3H, N-$CH_3$), 2.4 – 2.45 (m, 2H, Ph-C$\underline{H}_2$$CH_2$N), 2.5 – 2.55 (m, 2H, PhCH$_2$-C$\underline{H}_2$N), 2.75 – 2.8 (m, 2H, Ph-C$\underline{H}_2$$CH_2CH_2$N), 3.60 (s, 3H, 12-O-$CH_3$), 3.87 (s, 3H, 13-O-$CH_3$), 4.56 (br s, 2H, Ph-$CH_2$-Ph), 6.38 (s, 1H, H-11), 6.69 (s,

1H, H-14), 7.08 (dd, *J* = 7.2 and 1.6 Hz, 1H, H-4), 7.19 (m, 2H, H-2 and H-3), 7.27 (dd, *J* = 7.2 and 1.6 Hz, 1H, H-1); ^{13}C-NMR ($CDCl_3$): 27.7 (Ph-$\underline{C}H_2CH_2CH_2$), 28.5 (CH_2-$\underline{C}H_2CH_2$), 32.7 (Ph-$\underline{C}H_2CH_2N$), 37.7 (Ph-CH_2-Ph), 43.4 (N-CH_3), 52.3 ($PhCH_2CH_2$-$\underline{C}H_2N$), 56.3 (2x O-CH_3), 60.8 ($PhCH_2$-$\underline{C}H_2N$), 111.9 (C-11), 112.3 (C-14), 126.5 (C-2 and C-3), 132.0 (C-1 and C-4), 133,2 (C-10a), 141.1 (C-14a and C-4a), 143.1 (C-15a), 147.7 (C-12 and C-13); Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.5; H, 8.36; N, 4.30. Found: C, 77.2; H, 8.35; N, 4.28; MS: m/z (rel. int.) 325 (M^+, 28), 239 (15), 178 (15), 160 (19), 146 (13), 115 (13), 70 (53), 58 (100).

REFERENCES

1. M. U. Kassack , B. Höfgen, M. Decker, N. Eckstein, and J. Lehmann, *Naunyn-Schmiedeberg's Arch. Pharmacol.,* 2002, **366**, 543.

2. J. Lehmann, M.Nieger, and T. Witt, *Heterocycles*, 1995, **41**, 119.

3. T. Witt, S. Hock, and J. Lehmann, *J. Med. Chem*, 2000, **43**, 2079.

4. P. Mohr, P.M. Schweikert, T.W. Wittig, M. Decker, S. Elz, and J. Lehmann, *Drugs Fut,* 2002, **27**(Suppl. A), 316.

5. W. Meise, O. Onusseit, and M. Clemens, *Pharmazie*, 1999, **54**, 658.

6. W-Y.Su and G. P. Speranza, *US Patent* (Texaco Chem. Co.), 1994, **No. 5276192**, CA 120:163666.

7. H. Leditschke, G.Vogel, and C. Ther, *German Patent* (Farbwerke Hoechst AG), 1967, **No.1238920**, CA 68:78141.

8. J. H. Markgraf and B.Y. Choi, *Syn Comm.*, 1999, **29**, 2405.

9. W. Klinkhammer, private communication.

10. W. Meise and G. Schlüter, *Liebigs Ann. Chem*., **1987**, 639.