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Asymmetric Synthesis of 1-Substituted Tetrahydro-3-benzazepines as NMDA Receptor Antagonists

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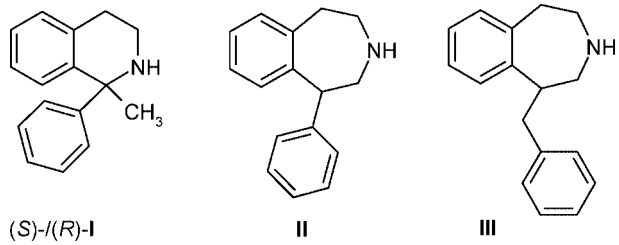
A novel asymmetric synthesis of 1-substituted tetrahydro-3-benzazepines (*R*)-**15** and (*S*)-**15** has been performed. Starting with *o*-phenylenediacetic acid (**1**) and (*R*)-phenylglycinol as chiral auxiliary the tricyclic oxazololactam (3*R*)-**10** was synthesized as key intermediate. Deprotonation of (3*R*)-**10** with LDA led to an enolate, which was trapped with different arylalkyl and alkyl halides to yield 6-substituted oxazololactams (6*R*)-**12** with high diastereoselectivity. The best diastereomeric ratio (about 95:5) was achieved with benzyl bromide and 2-methylbenzyl bromide. The diastereomers were separated using preparative HPLC to obtain diastereomerically pure (6*R*)-**12**. Two successive reduction procedures ($LiAlH_4/AlCl_3$, then NH_4HCO_2, Pd/C) led to enantiomerically pure 1-substituted tetrahydro-3-benzazepines (*R*)-**15**. Starting the synthesis with (*R*)- and (*S*)-phenylglycinol provided both enantiomers (*R*)-**15** and (*S*)-**15**, which were investigated for their affinity to the PCP binding site of the NMDA receptor. The NMDA receptor affinities of the enantiomeric pairs are very similar. With a K_i value of 1.66 μM the 2-methylbenzyl-substituted derivative (*R*)-**15c** displays the highest NMDA receptor affinity in this series.

1. Introduction

The NMDA receptor represents an excitatory ionotropic glutamate receptor, which plays a crucial role in several neurological processes like learning and memory.[1,2] However, overstimulation of the NMDA receptor with the endogenic ligand (*S*)-glutamate leads to a massive influx of Ca^{2+}-ions through the ion channel into the neuron. The increase of the intracellular Ca^{2+}-concentration causes acute damage of neurons, which is observed after stroke or brain injury. The NMDA receptor is also involved in the development of chronic neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, epilepsy and amyotrophic lateral sclerosis. Therefore, the NMDA receptor represents an interesting target for the therapy of these neurological disorders.[3,4]

In the focus of our interest are ligands, which interact with the PCP binding site located inside of the ion channel. Ligands interacting with the PCP binding site act as uncompetitive NMDA receptor antagonists because they block the channel and therefore stop the Ca^{2+} influx.

1-Substituted tetrahydroisoquinolines have been described as highly active antagonists of the NMDA receptor. The interaction with the PCP binding site depends strongly on the stereochemistry. For example (*S*)-**I** displays high NMDA receptor affinity (K_i = 35.4 nM) whereas its enantiomer (*R*)-**I** is less active (K_i = 3756 nM).[5] Recently, we found that the homologous tetrahydro-3-benzazepines **II** (K_i = 8.74 μM) and **III** (K_i = 1.05 μM) also interact with the PCP binding site of the NMDA receptor.[6] (see Figure 1) However, only racemates have been considered in this study.



(*S*)-/(*R*)-**I** **II** **III**

Figure 1. Lead compounds with NMDA receptor affinity.

In this communication we describe the first general asymmetric synthesis of 1-substituted tetrahydro-3-benzazepines **VI** (see Figure 2). The concept of using bicyclic lactam **IV** derived from phenylglycinol should be applied. Diastereoselective alkylation of **IV** should yield the substituted lactam **V**, which after reduction and hydrogenolysis should give the desired 1-substituted tetrahydro-3-benzazepines **VI** in enantiomerically pure form. In order to investigate the relationship between the stereochemistry and the NMDA receptor affinity both enantiomers were to be prepared.

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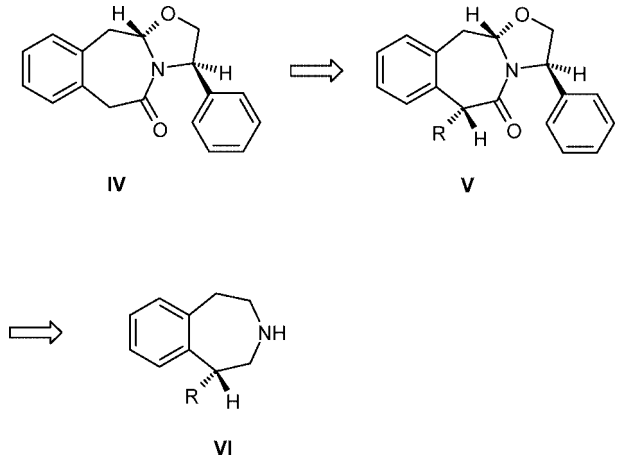
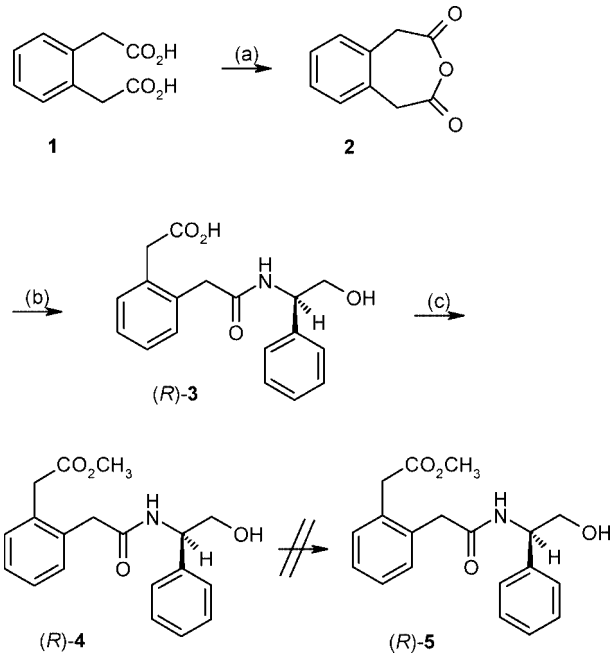


Figure 2. Concept of the asymmetric synthesis of 1-substituted tetrahydro-3-benzazepines.

The asymmetric synthesis of enantiomerically pure piperidine derivatives using chiral bicyclic lactams derived from (*R*)- or (*S*)-phenylglycinol as chiral auxiliary has been described in literature.[7–10] The concept of using phenylglycinol as chiral auxiliary was also applied to the synthesis of enantiomerically pure substituted piperazines[11] and tetrahydroisoquinolines.[12,13]



Scheme 1. Reagents and conditions: (a) $SOCl_2$, toluene, reflux. (b) (*R*)-phenylglycinol, NEt_3, CH_2Cl_2, room temp. (c) Me_3SiCl, CH_3OH, 0 °C.

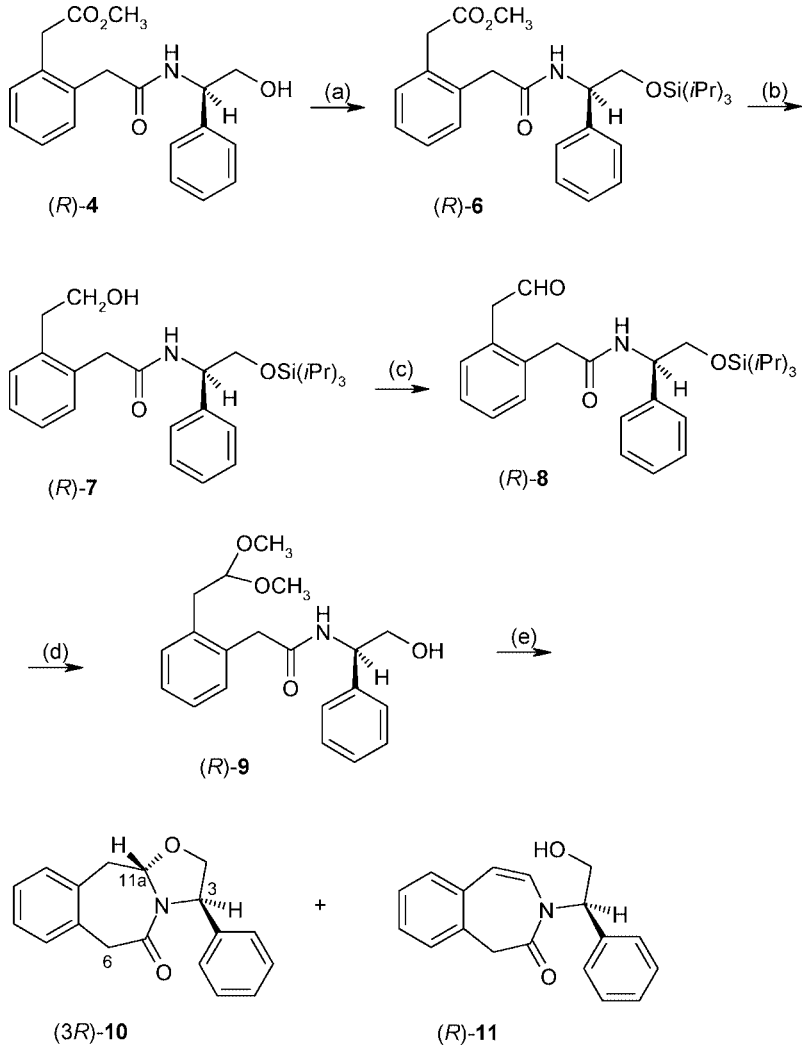
2. Chemistry

According to our plan (see Figure 2) the oxazolo[3]-benzazepinone **10** represents the key intermediate of the synthesis. The synthesis of **10** (Scheme 1 and Scheme 2) started from the commercially available *o*-phenylenediacetic acid **1** which was transformed with $SOCl_2$ into anhydride **2**. The chiral information was introduced by reaction of the anhydride **2** with (*R*)-phenylglycinol to afford the amido acid (*R*)-**3**. In order to obtain the oxazolo[3]benzazepinone (3*R*)-**10** it was necessary to reduce the carboxylic acid of (*R*)-**3** to the oxidation level of an aldehyde. First, the direct reduction of the methyl ester (*R*)-**4** was investigated using diisobutylaluminium hydride as selective reducing agent.[14,15] However, all attempts failed to obtain the aldehyde (*R*)-**5** since overreduction to the corresponding alcohol took place (Scheme 1).

Therefore it was planned to reduce the ester (*R*)-**4** to the corresponding alcohol and subsequently oxidize the primary alcohol to an aldehyde. For this purpose protection of the alcohol group of the phenylglycinol moiety was necessary, which was performed with triisopropylsilyl chloride and imidazole to afford the silyl ether (*R*)-**6**.[16] Reduction of the ester (*R*)-**6** with $LiBH_4$ provided quantitatively the primary alcohol (*R*)-**7**. Selective oxidization of the alcohol (*R*)-**7** with Dess–Martin periodinan[17,18] led to the aldehyde (*R*)-**8** in 83% yield. Deprotection of the silyl ether and acetalization of the aldehyde (*R*)-**8** proceeded upon treatment with CH_3OH and HCl to give the amido acetal (*R*)-**9**. Finally, the amido acetal (*R*)-**9** was cyclized with catalytic amounts of HCl in $CHCl_3$. The desired oxazolo[3]benzazepinone (3*R*)-**10** was isolated by flash chromatography in 54% yield. Furthermore a small amount (7%) of the side product (*R*)-**11** was isolated. The highest yield of the product (3*R*)-**10** (54%) was obtained by performing the cyclization of (*R*)-**9** at 0 °C. Raising of reaction temperature led to increasing amounts of the side product (*R*)-**11**.

The oxazolo[3]benzazepinone (3*R*)-**10** was formed as a single diastereomer. Careful thin layer chromatography and HPLC analysis of the crude product mixture did not indicate the presence of the second diastereomer. These observations point out that the cyclization of (*R*)-**9** to (3*R*)-**10** is a highly diastereoselective reaction. The relative configuration of (3*R*)-**10** was determined by nuclear Overhauser effect (NOE). Irradiation with the resonance frequency of the proton in position 11a (δ = 5.1 ppm) resulted in increasing of the signals of the phenyl protons. An increase of the signal at 5.4 ppm (3-H) was not observed. Therefore, the proton in position 11a and the phenyl residue in position 3 are *cis* configured. Thus, the novel chiral center C-11a is (*S*)-configured.

Next the diastereoselective alkylation in position 6 of the oxazolo[3]benzazepinone (3*R*)-**10** was investigated. The amide (3*R*)-**10** was deprotonated with LDA to provide an enolate, which was trapped with various arylalkyl and alkyl halides. After careful optimization of the reaction conditions the alkylation was performed successfully and reproducibly. In order to obtain the enantiomeric 3-benzazepines the oxazolo[3]benzazepine (3*S*)-**10** was synthesized analogously using (*S*)-phenylglycinol as chiral auxiliary. The corresponding deprotonation and alkylation is also shown in Scheme 3.



Scheme 2. Reagents and conditions: (a) triisopropylsilyl chloride, imidazole, DMF, room temp. (b) $LiBH_4$, THF, room temp. (c) Dess–Martin periodinane, CH_2Cl_2, room temp. (d) HCl, 1% in CH_3OH, room temp. (e) $CHCl_3$, HCl, room temp.

The ratio of the diastereomeric alkylation products **12**/**13** was determined by HPLC analysis. All products with arylalkyl substituents **12a**–**d** were obtained with high diastereoselectivity. Only 4.9 to 7.8% of the minor diastereomer **13a**–**d** was detected. The alkylation of (3*R*)-**10** and (3*S*)-**10** with CH_3I provided the diastereomeric products **12e** and **13e** in the ratio of about 80:20, respectively (see Table 1 and Figure 3).

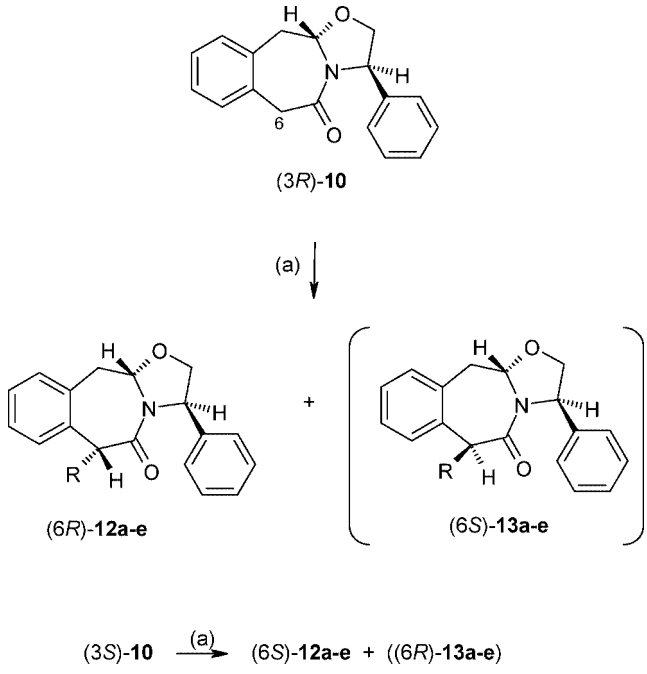
In order to identify the minor diastereomer HPLC analysis was combined with MS and DAD detection. At last the mixture of diastereomers (6*R*)-**12**/(6*S*)-**13** and (6*S*)-**12**/(6*R*)-**13** was separated by preparative RP18-HPLC respectively, to obtain diastereomerically pure products. The recorded ^1H NMR spectra of the purified products unequivocally prove the structures of the minor diastereomers **13a**–**e**.

The relative configuration of the new stereogenic center was determined by X-ray crystal structure analysis of the benzylated derivative (6*R*)-**12a**. The X-ray crystal structure analysis revealed (*R*)-configuration in position 6 and confirmed the (*S*)-configuration of C-11a[19] (Figure 4 right).

On the left side in Figure 4 a model of the enolate of (3*R*)-**10** is depicted. The model shows axial orientation of the phenyl moiety of the oxazolidine substructure favoring *Re*-face attack at the enolate double bond by the corresponding alkyl halides.

According to comparable diastereoselectivity, chromatographic and spectroscopic properties, (*R*)-configuration was assigned to the novel chiral center in position 6 of the major diastereomers **12b**–**e** and (*S*)-configuration to the minor diastereomers **13b**–**e**.

In order to get to the enantiomerically pure 1-substituted tetrahydro-3-benzazepines **15** the diastereomerically pure tricyclic compounds **12** were reduced in two steps. First reaction with $LiAlH_4/AlCl_3$[10,20] led to reduction of the amide and reductive opening of the oxazolidine ring to afford the *N*-benzyl derivatives **14a**–**e** with excellent yields. Careful HPLC and LC/MS-analysis of **14** showed that the reduction proceeded without any epimerization in position 1. Finally hydrogenolysis of the diastereomerically pure derivatives **14a**–**e** with ammonium formate and Pd/C[21] re-



(3*S*)-**10** $\xrightarrow{(a)}$ (6*S*)-**12a-e** + ((6*R*)-**13a-e**)

Scheme 3. Reagents and conditions: (a) LDA, RX, THF, 0 °C. **a**: RX = $C_6H_5CH_2Br$; **b**: RX = $C_6H_5CH_2CH_2I$; **c**: RX = 2-$CH_3C_6H_4CH_2Br$; **d**: RX = 4-$H_3COC_6H_4CH_2Br$; **e**: RX = CH_3I.

Table 1. Ratio of the diastereomeric alkylation products **12/13** formed by alkylation of (3*R*)-**10** and (3*S*)-**10** (HPLC analysis).

R	(*R*) series		(*S*) series	
CH_2-	(6*R*)-**12a**	95.1 %	(6*S*)-**12a**	93.4 %
	(6*S*)-**13a**	4.9 %	(6*R*)-**13a**	6.6 %
CH_2-	(6*R*)-**12b**	92.7 %	(6*S*)-**12b**	92.2 %
	(6*S*)-**13b**	7.3 %	(6*R*)-**13b**	7.8 %
CH_2-, CH_3	(6*R*)-**12c**	93.3 %	(6*S*)-**12c**	95.0 %
	(6*S*)-**13c**	6.7 %	(6*R*)-**13c**	5.0 %
CH_2-, H_3CO	(6*R*)-**12d**	92.8 %	(6*S*)-**12d**	94.2 %
	(6*S*)-**13d**	7.2 %	(6*R*)-**13d**	5.8 %
H_3C—	(6*R*)-**12e**	80.3 %	(6*S*)-**12e**	78.9 %
	(6*S*)-**13e**	19.7 %	(6*R*)-**13e**	21.1 %

sulted in the desired enantiomerically pure 1-substituted tetrahydro-3-benzazepines **15a**–**e** (Scheme 4).

3. Receptor Binding Studies

The affinity of the 1,3-disubstituted 3-benzazepines (1*R*)- and (1*S*)-**14a**–**e** and the 1-substituted 3-benzazepines (*R*)- and (*S*)-**15a**–**e** to the PCP binding site of the NMDA receptor as well as to the σ_1 and σ_2 receptor was determined in competition experiments with radioligands. The affinity towards σ receptors was included into this study, because some potent NMDA antagonists also interact with σ receptors and vice versa. In the assay systems the radioligands [^{3}H]-(+)-MK-801 (NMDA), [^{3}H]-(+)-pentazocine (σ_1) and [^{3}H]-ditolylguanidine (σ_2) were employed. The receptor affinities are summarized in Table 2. When the screening with high test compound concentrations indicated low affinity only the inhibition of the radioligand binding (in%) at a test compound concentration of 10 μM is listed. Only one experiment was performed for medium affinity compounds, whereas three experiments were carried out for high affinity compounds. In these cases the standard error of the mean was calculated and is given in Table 2.

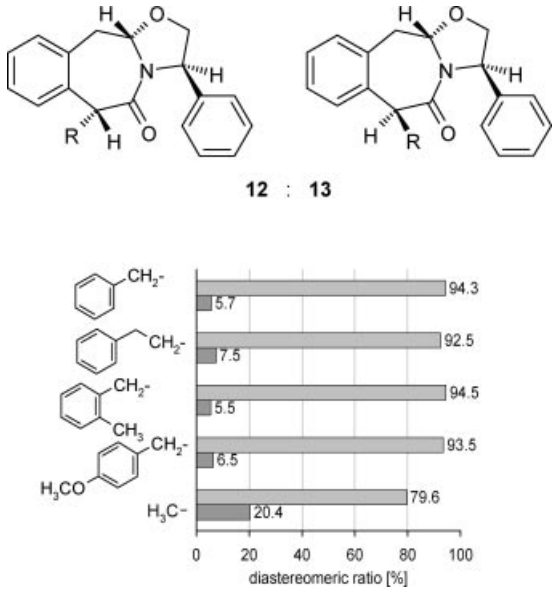


Figure 3. Mean values of the product ratios **12/13** in the (*R*)- and (*S*)-series depending on different substituents.

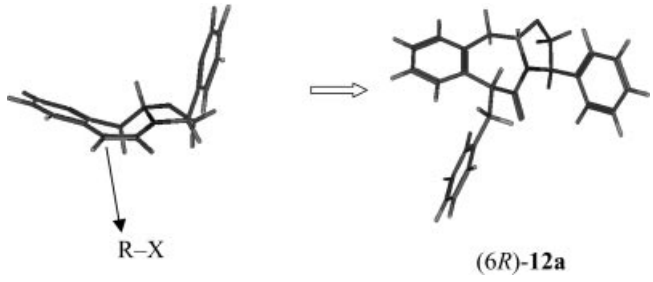
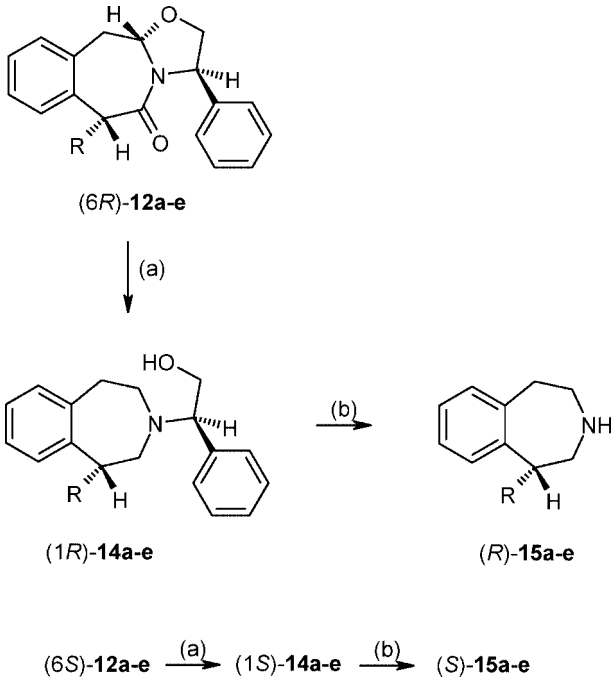


Figure 4. Model of the enolate of (3*R*)-**10** (left) and X-ray crystal structure of the benzylated oxazolobenzazepine (6*R*)-**12a** (right).

The 1,3-disubstituted 3-benzazepines **14a**–**e** reveal very low affinities toward the PCP-binding site of the NMDA receptor. However the arylalkyl-substituted tetrahydro-3-benzazepines **15a**–**d** are binding in the low micromolar range. The enantioselective NMDA receptor interaction of **15a**–**d** is shown graphically in Figure 5. Since both enantiomers of the methyl-substituted 3-benzazepines (*R*)-and (*S*)-



Scheme 4. Reagents and conditions: (a) $LiAlH_4$, $AlCl_3$, THF, 0 °C, (b) NH_4HCOO, Pd/C, CH_3OH, reflux. **a**: R = $PhCH_2$; **b**: R = $PhCH_2CH_2$; **c**: R = 2-$CH_3C_6H_4CH_2$; **d**: R = 4-$H_3COC_6H_4CH_2$; **e**: R = CH_3.

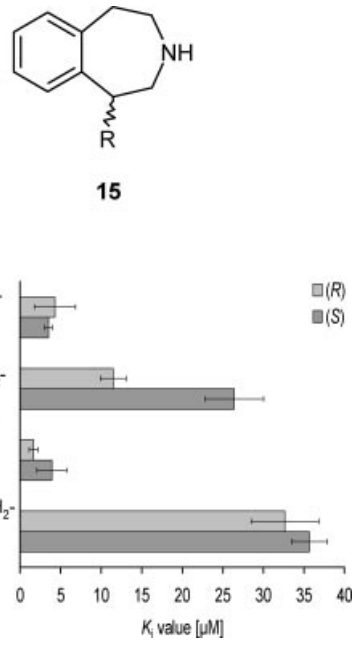


Figure 5. NMDA receptor affinities of enantiomerically pure 1-substituted 3-benzazepines **15a**–**15d**.

15e led to very low inhibition of the radioligand binding at a test concentration of 10 µM the K_i values were not determined.

Within this series of ligands the 3-benzazepines with a benzyl (**15a**) and a 2-methylbenzyl (**15c**) residue possess the highest NMDA receptor affinities, the K_i values are in the range between 1.7 to 4.3 µM. Extension of the aryl–nitrogen distance of the substituent **15b** and introduction of an electron donating methoxy group **15d** lead to reduced NMDA

Table 2. Affinities of the 3-benzazepines towards NMDA, σ_1 and σ_2 receptors.

Compd.	R	NMDA K_i [µM] ± SEM[a]	σ_1 K_i [µM] ± SEM[a]	σ_2 K_i [µM] ± SEM[a]
(1*R*)-**14a**	benzyl	23	3.8	9.7
(1*S*)-**14a**	benzyl	(0%)	(5%)	13.0
(*R*)-**15a**	benzyl	4.3 ± 2.5	3.4	4.04
(*S*)-**15a**	benzyl	3.5 ± 0.4	26	5.8
(1*R*)-**14b**	phenethyl	(0%)	2.7	3.6
(1*S*)-**14b**	phenethyl	(0%)	(10%)	35
(*R*)-**15b**	phenethyl	11 ± 2	5.3	1.1
(*S*)-**15b**	phenethyl	26 ± 4	0%	4.2
(1*R*)-**14c**	2-methylbenzyl	(0%)	(0%)	(10%)
(1*S*)-**14c**	2-methylbenzyl	(0%)	5.0	29
(*R*)-**15c**	2-methylbenzyl	1.7 ± 0.5	14	5.2
(*S*)-**15c**	2-methylbenzyl	3.8 ± 1.5	5.7	2.8
(1*R*)-**14d**	4-methoxybenzyl	(0%)	13	15
(1*S*)-**14d**	4-methoxybenzyl	(0%)	(0%)	2.5
(*R*)-**15d**	4-methoxybenzyl	33 ± 4	2.3	7.9
(*S*)-**15d**	4-methoxybenzyl	36 ± 2	8.3	7.0
(1*R*)-**14e**	methyl	(0%)	0.69 ± 0.4	5.9
(1*S*)-**14e**	methyl	22	2.1	(0%)
(*R*)-**15e**	methyl	(0%)	10	10
(*S*)-**15e**	methyl	(5%)	9.0	20
(+)-MK-801		2.89 ± 1.14 nM	–	–
Dexoxadrol		38.9 ± 9.9 nM	–	–
(+)-Pentazocine		–	2.2 ± 1.2 nM	–
Haloperidol		–	1.9 ± 0.4 nM	–
Ditolylguanidine		–	–	20.2 ± 2.3 nM

[a] Values in % give the inhibition of the radioligand binding at a test compound concentration of 10 µM.

receptor affinity. Surprisingly, significant differences between the NMDA receptor affinities of the enantiomeric pairs are not observed. According to Figure 5 the (*R*)-enantiomers (except **15a**) seem to have slightly higher affinities than their (*S*)-enantiomers. However, with the exception of the low affinity phenethyl derivative **15b** the preference of the NMDA receptor for the (*R*)-enantiomers is not significant.

The methylated 3-benzazepines **14e** and **15e** display very low NMDA receptor affinity. Obviously small substituents in position 1 of the 3-benzazepine ring system are unfavorable for high NMDA receptor affinity.

The σ receptor affinities of the 3-benzazepines **14a**–**d** and **15a**–**d** with arylalkyl substituents are very similar. These results indicate that the nature of the C-1 substituent, an additional substituent in position 3 and the C-1 configuration do not significantly influence the σ_1 and σ_2 receptor affinity.

However, the σ receptor affinities of the methylated 3-benzazepines **14e** and **15e** are very interesting. The (*R*)-configured 3-benzazepine (1*R*)-**14e** (K_i = 0.69 μM) represents the most active σ_1 ligand in this series. The σ_1 affinity of (1*R*)-**14e** is about eightfold higher than its σ_2 receptor affinity. The enantiomer (1*S*)-**14e** reveals also σ_1 receptor selectivity. The similar σ_1 receptor affinities of the enantiomers (1*R*)-**14e** and (1*S*)-**14e** leads to the conclusion that the configuration in position 1 has only little influence on the σ_1 receptor interaction.

The enantiomeric 1-methyl-3-benzazepines (*R*)- and (*S*)-**15e** reveal very similar σ_1 and σ_2 receptor affinity. Furthermore a significant difference in receptor interaction between the (*R*)- and (*S*)-configured 3-benzazepines was not determined.

4. Conclusion

Herein, we have presented the first general asymmetric synthesis of enantiomerically pure 1-substituted tetrahydro-3-benzazepines **14** and **15**. Exemplarily, five different substituents have been introduced in position 1 and the corresponding 3-benzazepines have been pharmacologically evaluated in receptor binding studies. 3-Benzazepines with a benzyl (**15a**) and a 2-methylbenzyl (**15c**) substituent show the highest NMDA receptor affinity (K_i = 1.7–4.3 μM). However, an enantioselective receptor interaction was not observed. This is probably due to the low affinity of the ligands. In order to improve the NMDA receptor affinity and the enantioselective receptor interaction further variations of the 3-benzazepine ring system will be performed following the method described in this communication.

5. Experimental Section

5.1. General: Unless otherwise noted, moisture-sensitive reactions were conducted under dry nitrogen. Petroleum ether used refers to the fraction boiling at 40–60 °C. Thin layer chromatography: Silica gel 60 F_{254} plates (Merck). Flash chromatography (fc):[22] Silica gel 60, 40–63 μm (Merck), parentheses include: Diameter of the column [cm], eluent, fraction size [mL], R_f. Melting points: Melting Point Apparatus SMP3 (Stuart Scientific). Elemental analyses: VarioEL (Elementar). MS: GCQ Finnigan MAT (thermo-Finnigan), EI = electron impact. IR: ATR-FT-IR-480 Plus Fourier Transform Spektrometer (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Mercury-400BB spectrometer (Varian), δ in ppm related to tetramethylsilane; the assignments of ^{1}H and ^{13}C NMR signals were supported by 2D NMR techniques. HPLC: Hitachi LaChrom L-7150 (Merck). Optical rotation: Polarimeter 341 (Perkin–Elmer), λ = 589 nm, unit, *c* (g/100 mL), solvent, 1 dm, 20 °C.

5.2. General Procedures

5.2.1. General Procedure A: Synthesis of the 6-Substituted Oxazolo-benzazepinones 12a–e, 13a–e: A solution of oxazolo-benzazepinone **10** in THF was cooled to 0 °C under nitrogen atmosphere. A solution of LDA (2 M in THF) was added and the mixture was stirred for 1 h at 0 °C. Then, the respective alkyl- or arylalkyl halide was added and the mixture was stirred for another 2–2.5 h at 0 °C. The mixture was quenched with a saturated NH_4Cl solution and extracted three times with Et_2O. The organic layer was washed with a saturated NH_4Cl solution and with H_2O. The combined aqueous layers were reextracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo.

5.2.2. General Procedure B. Reduction of the 6-Substituted Oxazolo-benzazepinones 14a–e: Under N_2 $AlCl_3$ was dissolved in THF at 0 °C. After 5 min a $LiAlH_4$ solution (1 M in THF) was added. The mixture was stirred for 20 min at room temp. Then the mixture was cooled to 0 °C and a solution of the respective 6-substituted oxazolo-benzazepinone **12** in THF was added. After 1–2 h the reaction was quenched with H_2O. After addition of Et_2O (10 mL) the mixture was washed three times with H_2O. The combined aqueous layers were reextracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo.

5.2.3. General Procedure C. Synthesis of the 1-Substituted 3-Benzazepines 15a–e: The respective 1-substituted 3-benzazepine **14** was dissolved in MeOH. Then dry ammonium formate and Pd/C were added and the mixture was heated under reflux for 2–4.5 h. The catalyst was removed by filtration and the solution was concentrated in vacuo.

5.3. 1,5-Dihydro-3-benzoxepine-2,4-dione (2): To a solution of *o*-phenylenediacetic acid (**1**, 4.85 g, 25.0 mmol) in toluene (50 mL) thionyl chloride (1.8 mL, 25.0 mmol) was added dropwise. The mixture was heated under reflux for 24 h and then concentrated in vacuo. The product was directly used without further purification. The yield of **2** (88%) was determined by integration of characteristic NMR signals. $C_{10}H_8O_3$ (176.2). IR: $\tilde{\nu}$ = 1745. ^{1}H NMR ($CDCl_3$): δ = 4.05 (s, 4 H, CH_2COOR), 7.20–7.30 (m, 4 H, arom.) ppm.

5.4. (*R*)-2-{[*N*-(2-Hydroxy-1-phenylethyl)carbamoylmethyl]phenyl}-acetic Acid [(*R*)-3]: To a solution of anhydride **2** (264 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) triethylamine (0.21 mL, 1.5 mmol) and a solution of (*R*)-phenylglycinol (206 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) were added. The mixture was stirred for 3 h at room temp. Then the mixture was extracted four times with 0.15 M NaOH. The combined aqueous layers were acidified with 1 M HCl (pH 3) and extracted three times with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to one third of the original volume. Overnight colorless crystals were formed, which were isolated by filtration. Colorless solid, m.p. 150.7–151.8 °C, yield 0.37 g (79%). $[\alpha]_{589}^{20}$ = –61.3 (*c* = 0.925, MeOH). $C_{18}H_{19}NO_4$ (313.4). MS (EI): *m*/*z* = 295 [M – H_2O], 282 [M – CH_2OH], 106

[C_7H_8N]. IR: $\tilde{\nu}$ = 3447 (O–H), 3315 (N–H), 3021 (C–H), 1706 (CO_2H), 1649 (CONH), 1535 (N–H). ^{1}H NMR ([D$_6$]DMSO): δ = 3.32–3.70 (m, 6 H, CH_2COOH, CH_2CON, CH_2OH), 4.78–4.83 (m, 1 H, NHC*H*Ph), 7.13–7.28 (m, 9 H, arom.), 8.48 (d, J = 8.2 Hz, 1 H, N*H*) ppm. ^{13}C NMR ([D$_6$]DMSO): δ [ppm] = 55.8 (1 C, NH*C*HPh), 65.4 (1 C, *C*H$_2$OH), 127.1, 127.4, 127.4, 127.5, 128.7, 130.6, 131.0, 134.9, 136.2, 141.9 (12 C, arom.), 170.4 (1 C, *C*ONH), 173.4 (1 C, *C*OOH). The signals for the Ar*C*H$_2$ carbon atoms are superimposed by the DMSO signal at δ = 40 ppm.

5.5. (*S*)-2-{[*N*-(2-Hydroxy-1-phenylethyl)carbamoylmethyl]phenyl}-acetic Acid [(*S*)-3]: The synthesis of (*S*)-**3** was performed as described for (*R*)-**3** using anhydride **2** (3.9 g, 22.1 mmol) in CH_2Cl_2 (115 mL), triethylamine (3.1 mL, 22.1 mmol) and (*S*)-phenylglycinol (3.0 g, 22.1 mmol) in CH_2Cl_2 (30 mL). Colorless solid, m.p. 151.9 °C, yield 3.73 g (54%). $[\alpha]_{589}^{20}$ = +60.5 (c = 1.035, MeOH).

5.6. Methyl (*R*)-2-{2-[*N*-(2-Hydroxy-1-phenylethyl)carbamoylmethyl]phenyl}acetate [(*R*)-4]: Amido acid (*R*)-**3** (1.02 g, 3.25 mmol) was dissolved in MeOH (80 mL), the solution was cooled to 0 °C and trimethylsilyl chloride (1.23 mL, 9.75 mmol) was added. The reaction mixture was stirred for 19 h at room temp. Then the mixture was concentrated in vacuo. The residue was dissolved in Et_2O and concentrated again in vacuo. The residue was purified by fc (Ø 4 cm, petroleum ether/ethyl acetate = 2:5, 30 mL, R_f = 0.25). Colorless solid, m.p. 117.4–118.1 °C, yield 886 mg (83%). $[\alpha]_{589}^{20}$ = –4.35 (c = 2.2, CH_2Cl_2). $C_{19}H_{21}NO_4$ (327.4). Calcd C 69.71, H 6.47, N 4.28, found C 69.65, H 6.47, N 4.25. MS (EI): m/z = 296 [M – OCH_3], 106 [C_7H_8N]. IR: $\tilde{\nu}$ = 3512 (O–H), 3287 (N–H), 2950 (C–H), 1718 (CO_2CH_3), 1648 (CONH), 1539 (N–H). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.32 (s, 1 H, O*H*), 3.67–3.82 (m, 9 H, CH_2COOCH_3, CH_2CON, CH_2OH), 5.04–5.08 (m, 1 H, NHC*H*Ph), 6.55 (d, J = 6.3 Hz, 1 H, N*H*), 7.15–7.33 (m, 9 H, arom.). ^{13}C NMR ($CDCl_3$): δ [ppm] = 38.9 (1 C, Ar*C*H$_2$), 41.2 (1 C, Ar*C*H$_2$), 52.7 (1 C, *C*H$_3$), 56.2 (1 C, NH*C*HPh), 66.5 (1 C, *C*H$_2$OH), 126.8, 127.9, 128.2, 128.5, 128.9, 131.0, 131.5, 133.1, 134.2, 139.2 (12 C, arom.), 171.4 (1 C, *C*ONH), 173.1 (1 C, *C*O-OCH_3).

5.7. Methyl (*S*)-2-{2-[*N*-(2-Hydroxy-1-phenylethyl)carbamoylmethyl]phenyl}acetate [(*S*)-4]: The synthesis of (*S*)-**4** was performed as described for (*R*)-**4** using amido acid (*S*)-**3** (2.1 g, 6.70 mmol) in MeOH (100 mL), trimethylsilyl chloride (2.5 mL, 20.1 mmol). Colorless solid, m.p. 118.2 °C, yield 1.28 g (58%). $[\alpha]_{589}^{20}$ = +3.86 (c = 2.5, CH_2Cl_2).

5.8. Methyl (*R*)-2-⟨2-{*N*-[1-Phenyl-2-(triisopropylsilyloxy)ethyl]-carbamoylmethyl}phenyl⟩acetate [(*R*)-6]: Amido ester (*R*)-**4** (1.27 g, 3.88 mmol) and imidazole (660.4 mg, 9.7 mmol) were dissolved in DMF (4 mL). triisopropylsilyl chloride (1.00 mL, 4.66 mmol) was added dropwise and the mixture was stirred for 16 h at room temp. The mixture was quenched with H_2O. The aqueous layer was extracted with Et_2O, the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by fc (Ø 4 cm, petroleum ether/ethyl acetate = 5:2, 30 mL, R_f = 0.25). Colorless oil, yield 1.72 g (91%). $[\alpha]_{589}^{20}$ = +21.7 (c = 0.5, CH_2Cl_2). $C_{28}H_{41}NO_4Si$ (483.7). Calcd. C 69.52, H 8.54, N 2.90, found C 69.16, H 8.50, N 2.91. MS (EI): m/z = 484 [M], 106 [C_7H_8N]. IR: $\tilde{\nu}$ = 3316 (N–H), 2941, 2864 (C–H), 1734 (CO_2CH_3), 1647 (CONH), 1522 (N–H). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.81–0.91 [m, 21 H, Si{CH(CH_3)$_2$}$_3$], 3.65 (s, 3 H, OCH_3), 3.66 (s, 2 H, CH_2), 3.69 (s, 2 H, CH_2), 3.76 (dd, J = 9.8/3.9 Hz, 1 H, CH_2OSi), 3.87 (dd, J = 9.4/3.9 Hz, 1 H, CH_2OSi), 5.01 (dt, J = 7.8/3.9 Hz, 1 H, NHC*H*Ph), 6.47 (d, J = 7.8 Hz, 1 H, N*H*), 7.15–7.30 (m, 9 H, arom.). ^{13}C NMR ($CDCl_3$): δ [ppm] = 11.9 (6C, SiCHCH_3), 18.0 (3 C, Si*C*HCH$_3$), 38.8 (1 C, Ar*C*H$_2$), 41.7 (1 C, Ar*C*H$_2$), 52.4 (1 C, CO_2CH_3), 54.9 (1 C, NH*C*HPh), 66.9 (1 C, *C*H$_2$OSi), 126.9, 127.4, 128.2, 128.4, 128.5, 131.1, 131.4, 133.5, 134.3, 140.4 (12 C, arom.), 170.2 (1 C, *C*ONH), 172.0 (1 C, *C*OOCH$_3$).

5.9. Methyl (*S*)-2-⟨2-{*N*-[1-Phenyl-2-(triisopropylsilyloxy)ethyl]-carbamoylmethyl}phenyl⟩-acetate [(*S*)-6]: The synthesis of (*S*)-**6** was performed as described for (*R*)-**6** using amido ester (*S*)-**4** (1.1 g, 3.4 mmol), imidazole (0.58 g, 8.48 mmol) and triisopropylsilyl chloride (0.88 mL, 4.1 mmol). Colorless oil, yield 1.40 g (85%). $[\alpha]_{589}^{20}$ = –20.2 (c = 0.5, CH_2Cl_2).

5.10. (*R*)-2-[2-(2-Hydroxyethyl)phenyl]-*N*-[1-phenyl-2-(triisopropylsilyloxy)ethyl]acetamide [(*R*)-7]: To a solution of (*R*)-**6** (2.69 g, 5.57 mmol) in THF (40 mL) a $LiBH_4$ solution (2 M in THF; 11.1 mL, 22.3 mmol) was added. The mixture was stirred for 18 h at room temp. The mixture was quenched with a saturated solution of NH_4Cl. The mixture was extracted with Et_2O, the organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by fc (Ø 5 cm, petroleum ether/ethyl acetate = 2:5, 30 mL, R_f = 0.47) to get a colorless oil, yield 2.37 g (93%). $[\alpha]_{589}^{20}$ = +18.3 (c = 1.34, CH_2Cl_2). $C_{27}H_{41}NO_3Si$ (455.7). Calcd. C 71.16, H 9.07, N 3.07, found C 70.76, H 9.29, N 3.08. MS (EI): m/z = 456 [M], 412 [M – C_2H_4O], 106 [C_7H_8N]. IR: $\tilde{\nu}$ = 3402 (O–H), 3284 (N–H), 2940, 2863 (C–H), 1646 (CONH), 1507 (N–H). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.81–0.92 [m, 21 H, Si{CH(CH_3)$_2$}$_3$], 2.12 (s, 1 H, O*H*), 2.87 (t, J = 6.6 Hz, 2 H, CH_2CH$_2$OH), 3.70 (s, 2 H, CH_2CONH), 3.76 (dd, J = 10.2/3.9 Hz, 1 H, CH_2OSi), 3.80 (t, J = 6.6 Hz, 2 H, CH$_2$CH_2OH), 3.88 (dd, J = 10.2/3.9 Hz, 1 H, CH_2OSi), 5.00 (dt, J = 7.0/3.9 Hz, 1 H, NHC*H*Ph), 6.53 (d, J = 7.0 Hz, 1 H, N*H*), 7.14–7.28 (m, 9 H, arom.). ^{13}C NMR ($CDCl_3$): δ [ppm] = 11.9 (6C, SiCH*C*H$_3$), 18.0 (3 C, Si*C*HCH$_3$), 36.2 (1 C, Ar*C*H$_2$), 41.5 (1 C, Ar*C*H$_2$), 54.9 (1 C, NH*C*HPh), 63.3 (1 C,*C*H$_2$OH), 66.8 (1 C, *C*H$_2$OSi), 126.9, 127.5, 127.5, 128.3, 128.5, 130.9, 131.0, 133.8, 138.0, 140.3 (12 C, arom.), 170.9 (1 C, *C*ONH).

5.11. (*S*)-2-[2-(2-Hydroxyethyl)phenyl]-*N*-[1-phenyl-2-(triisopropylsilyloxy)ethyl]acetamide [(*S*)-7]: The synthesis of (*S*)-**7** was performed as described for (*R*)-**7** using (*S*)-**6** (1.03 g, 2.13 mmol) in THF (50 mL), $LiBH_4$ solution (2 M in THF, 4.26 mL, 8.52 mmol). Colorless oil, yield 759 mg (78%). $[\alpha]_{589}^{20}$ = –18.6 (c = 1.01, CH_2Cl_2).

5.12. (*R*)-2-[2-(Formylmethyl)phenyl]-*N*-[1-phenyl-2-(triisopropylsilyloxy)ethyl]acetamide [(*R*)-8]: Dess–Martin periodinane (893 mg, 2.12 mmol) was dissolved in CH_2Cl_2 (20 mL). Then a solution of alcohol (*R*)-**7** (800 mg, 1.76 mmol) in CH_2Cl_2 (25 mL) was added dropwise. The mixture was stirred for 1 h at room temp. Then Et_2O (20 mL) and 1 M NaOH (10 mL) were added and the mixture was stirred for 15 min. The organic layer was washed with 1 M NaOH (20 mL) and H_2O (15 mL). The aqueous layer was extracted three times with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by fc (Ø 4 cm, petroleum ether/ethyl acetate = 2:5, 20 mL, R_f = 0.73). Colorless oil, yield 657 mg (83%). $[\alpha]_{589}^{20}$ = +9.44 (c = 4.48, CH_2Cl_2). $C_{27}H_{39}NO_3Si$ (453.7). MS (EI): m/z = 454 [M], 410 [M – C_2H_4O], 106 [C_7H_8N]. IR: $\tilde{\nu}$ = 2941, 2863 (C–H), 1724 (CHO), 1645 (CONH), 1533 (N–H). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.75–0.88 [m, 21 H, Si{CH(CH_3)$_2$}$_3$], 3.53 (s, 2 H, CH_2CONH), 3.68 (d, J = 1.6 Hz, 2 H, CH_2CHO), 3.69 (dd, J = 9.8/3.9 Hz, 1 H, CH_2OSi), 3.82 (dd, J = 9.8/3.9 Hz, 1 H, CH_2OSi), 4.91 (dt, J = 7.8/3.9 Hz, 1 H, NHC*H*Ph), 6.30 (d, J = 7.8 Hz, 1 H, N*H*), 7.09–7.24 (m, 9 H, arom.), 9.62 (t, J = 1.5 Hz, 1 H, CH$_2$C*H*O).

5.13. (*S*)-2-[2-(Formylmethyl)phenyl]-*N*-[1-phenyl-2-(triisopropylsilyloxy)ethyl]acetamide [(*S*)-8]: The synthesis of (*S*)-**8** was performed as described for (*R*)-**8** using alcohol (*S*)-**7** (647 mg, 1.42 mmol) and Dess–Martin periodinane (691 mg, 1.63 mmol) in

CH_2Cl_2 (40 mL). Colorless oil, yield 550.3 mg (85%). $[\alpha]_{589}^{20}$ = –8.43 (c = 2.53, CH_2Cl_2).

5.14. (*R*)-2-[2-(2,2-Dimethoxyethyl)phenyl]-*N*-(2-hydroxy-1-phenylethyl)acetamide [(*R*)-9]: Amido aldehyde (*R*)-**8** (552 mg, 1.22 mmol) was dissolved in a 1% methanolic HCl (40 mL). The mixture was stirred for 5 h at room temp. Then a saturated solution of $NaHCO_3$ was added. The aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with a saturated solution of $NaHCO_3$ and with H_2O. The combined aqueous layers were reectracted with Et_2O. The Et_2O solution was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by fc (Ø 2 cm, petroleum ether/ethyl acetate = 1:6, 10 mL, R_f = 0.24). Pale yellow oil, which solidified in the refrigerator to give a pale yellow solid, m.p. 84.1–85.6 °C, yield 368 mg (88%). $[\alpha]_{589}^{20}$ = +5.90 (c = 0.67, CH_2Cl_2). $C_{20}H_{25}NO_4$ (343.4) Calcd. C 69.95, H 7.43, N 4.08, found C 69.86, H 7.55, N 3.89. MS (EI): m/z = 312 [M – OCH_3], 106 [C_7H_8N]. IR: $\tilde{\nu}$ = 3584 (O–H), 3285 (N–H), 3062, 2943 (C–H), 1644 (CONH), 1539 (N–H), 1071 (C–O–C). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.67 (s, 1 H, O*H*), 2.94 [dd, J = 5.5/14.1 Hz, 1 H, CH_2CH(OCH$_3$)$_2$], 2.99 [dd, J = 5.5/14.1 Hz, 1 H, CH_2CH-(OCH$_3$)$_2$], 3.28 (s, 3 H, OCH_3), 3.29 (s, 3 H, OCH_3), 3.72–3.80 (m, 4 H, CH_2CONH, CHCH_2OH), 4.55 [t, J = 5.6 Hz, 1 H, CH$_2$C*H*(OCH$_3$)$_2$], 5.07–5.08 (m, 1 H, NHC*H*Ph), 6.17 (d, J = 7.2 Hz, 1 H, N*H*), 7.12–7.32 (m, 9 H, arom.).

5.15. (*S*)-2-[2-(2,2-Dimethoxyethyl)phenyl]-*N*-(2-hydroxy-1-phenylethyl)acetamide [(*S*)-9]: The synthesis of (*S*)-**9** was performed as described for (*R*)-**9** using amido aldehyde (*S*)-**8** (471 mg, 1.04 mmol) 1% methanolic HCl (40 mL). Pale yellow solid, m.p. 88.0 °C, yield 252.3 g (70%). $[\alpha]_{589}^{20}$ = –6.93 (c = 1.00, CH_2Cl_2).

5.16. (3*R*,11a*S*)-3-Phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(3*R*)-10] and (*R*)-3-(2-Hydroxy-1-phenylethyl)-1,3-dihydro-3-benzazepin-2-one [(*R*)-11]: To a solution of amido acetal (*R*)-**9** (101 mg, 0.29 mmol) in $CHCl_3$ (50 mL) 2–3 drops of conc. HCl were added. The mixture was stirred for 3 h at 0 °C and then concentrated in vacuo. The residue was purified by fc [Ø 2 cm, petroleum ether/ethyl acetate = 5:2, 10 mL, R_f [(3*R*)-**10**] = 0.22, R_f [(*R*)-**11**] = 0.51]. Two products were isolated:

(3*R*)-10: Colorless solid, m.p. 151.8–152.5 °C, yield 44.4 mg (54%). $[\alpha]_{589}^{20}$ = +31.9 (c = 0.54, CH_2Cl_2). $C_{18}H_{17}NO_2$ (279.3) Calcd. C 77.40, H 6.13, N 5.01, found C 77.20, H 6.03, N 5.07. MS (EI): m/z = 279 [M], 120 [PhCHCH$_2$O]. IR: $\tilde{\nu}$ = 2926 (C–H), 1640 (C=O). ^{1}H NMR ($CDCl_3$): δ [ppm] = 3.33–3.41 (m, 2 H, CH_2CHON), 3.74 (dd, J = 8.8/7.2 Hz, 1 H, OCH_2CH), 3.85 (d, J = 16.5 Hz, 1 H, CH_2C=O), 3.96 (d, J = 16.4 Hz, 1 H, CH_2C=O), 4.46 (t, J = 8.4 Hz, 1 H, OCH_2CH), 5.06 (dd, J = 7.1/5.1 Hz, 1 H, CH$_2$C*H*NO), 5.40 (t, J = 7.6 Hz, 1 H, OCH$_2$C*H*), 7.17–7.31 (m, 9 H, arom.). ^{13}C NMR ($CDCl_3$): δ [ppm] = 37.1 (1 C, *C*H$_2$CHON), 43.3 (1 C, *C*H$_2$C=O), 60.2 (1 C, *C*HCH$_2$O), 71.8 (1 C, CH*C*H$_2$O), 89.2 (1 C, CH$_2$*C*HON), 126.3, 127.8, 128.1, 129.0, 129.5, 129.6, 133.8, 134.2, 140.1 (12 C, arom.), 167.0 (1 C, *C*ONR$_2$).

(*R*)-11: Colorless solid, yield 4.5 mg (5.4%). $[\alpha]_{589}^{20}$ = –62.1 (c = 1.01, CH_2Cl_2). $C_{18}H_{17}NO_2$ (279.3). MS (EI): m/z = 261 [M – H_2O]. IR: $\tilde{\nu}$ = 3316 (OH), 3030, 2957 (C–H), 1660 (C=O). ^{1}H NMR ($CDCl_3$): δ [ppm] = 3.44 (d, J = 12.1 Hz, 1 H, ArCH_2C=O), 3.65 (d, J = 12.5 Hz, 1 H, ArCH_2C=O), 3.83 (dd, J = 11.5/8.4 Hz, 1 H, PhCHCH_2OH), 3.88 (dd, J = 11.7/6.7 Hz, 1 H, PhCHCH_2OH), 6.00 (t, J = 8.2/6.7 Hz, 1 H, PhC*H*CH$_2$OH), 6.08 (d, J = 9.4 Hz, 1 H, C*H*=CH), 6.39 (d, J = 9.4 Hz, 1 H, CH=C*H*), 7.17–7.31 (m, 9 H, arom.).

5.17. (3*S*,11a*R*)-3-Phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(3*S*)-10]: The synthesis of (3*S*)-**10** was performed as described for (3*R*)-**10** using amido acetal (*S*)-**9** (1.29 g, 3.76 mmol) in $CHCl_3$ (800 mL) and 12 drops of conc. HCl. Colorless solid, m.p. 152.2 °C, yield 527.4 mg (50%). $[\alpha]_{589}^{20}$ = –31.2 (c = 0.51, CH_2Cl_2). The side product (*S*)-**11** was not isolated.

5.18. (3*R*,6*R*,11a*S*)-6-Benzyl-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(6*R*)-12a] and (3*R*,6*S*,11a*S*)-6-Benzyl-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(6*S*)-13a]: According to the General Procedure **A** oxazolo-benzazepinone (3*R*)-**10** (200 mg, 0.716 mmol) in THF (50 mL) was treated with LDA solution (394 µL, 0.788 mmol) and benzyl bromide (85.0 µL, 0.716 mmol). The residue was purified by fc [Ø 3 cm, cyclohexane/ethyl acetate = 8:2, 10 mL, R_f [(6*R*)-**12a**] = 0.33, R_f [(6*S*)-**13a**] = 0.31] to obtain a mixture of diastereomers, yield 249.0 mg (94%), diastereomeric ratio (HPLC): 95.1:4.9 [(6*R*)-**12a**:(6*S*)-**13a**]. The diastereomers were separated by another fc {Ø 3 cm, cyclohexane/ethyl acetate = 30:2, 5 mL, tlc: cyclohexane/ethyl acetate = 5:2, R_f [(6*R*)-**12a**] = 0.43, R_f [(6*S*)-**13a**] = 0.38}.

(6*R*)-12a: Colorless solid, m.p. 128.0–128.9 °C, yield 148.7 mg (56%), *de* 99.85% (HPLC). $[\alpha]_{589}^{20}$ = –114.9 (c = 0.432, CH_2Cl_2). $C_{25}H_{23}NO_2$ (369.5) Calcd. C 81.27, H 6.27, N 3.79, found C 81.16, H 6.25, N 3.66. MS (EI): m/z = 369 [M], 278 [M-Benzyl], 120 [PHCHCH$_2$O], 91[C_7H_7]. IR: $\tilde{\nu}$ = 3025, 2939, 2871 (C–H), 1651 (C=O). ^{1}H NMR ($CDCl_3$): δ [ppm] = 3.11 (dd, J = 14.1/7.0 Hz, 1 H, CH_2CHC=O), 3.21 (dd, J = 15.3/5.1 Hz, 1 H, CH_2CHNO), 3.43 (dd, J = 15.6/3.9 Hz, 1 H, CH_2CHNO), 3.60 (dd, J = 8.6/7.8 Hz, 1 H, OCH_2CH), 3.59 (dd, J = 13.4/7.0 Hz, 1 H, CH_2CHC=O), 4.04 (t, J = 7.0 Hz, 1 H, CH$_2$C*H*C=O), 4.29 (t, J = 8.2 Hz, 1 H, OCH_2CH), 5.14 (t, J = 4.3 Hz, 1 H, CH$_2$C*H*NO), 5.22 (t, J = 8.3 Hz, 1 H, OCH$_2$C*H*), 6.95–7.23 (m, 14 H, arom.). ^{13}C NMR ($CDCl_3$): δ [ppm] = 36.5 (1 C, *C*H$_2$CHC=O), 37.3 (1 C, *C*H$_2$CHON), 51.9 (1 C, CH$_2$*C*HC=O), 60.6 (1 C, *C*HCH$_2$O), 71.6 (1 C, CH*C*H$_2$O), 88.7 (1 C, CH$_2$*C*HON), 126.3, 126.4, 127.7, 128.0, 128.5, 128.5, 128.9, 129.4, 130.4, 133.1, 140.0, 140.1 (18 C, arom.), 169.0 (1 C, *C*ONR$_2$).

(6*S*)-13a: Colorless solid, yield: 6.4 mg (2.4%). ^{1}H NMR ($CDCl_3$): δ [ppm] = 3.18 (dd, J = 14.6/7.6 Hz, 1 H, CH_2CHC=O), 3.25 (dd, J = 14.7/3.3 Hz, 1 H, CH_2CHNO), 3.49 (dd, J = 14.6/10.7 Hz, 1 H, CH_2CHNO), 3.61 (dd, J = 14.6/7.2 Hz, 1 H, CH_2CHC=O), 3.75 (dd, J = 8.8/5.7 Hz, 1 H, OCH_2CH), 4.29 (t, J = 7.4 Hz, 1 H, CH$_2$C*H*C=O), 4.38 (dd, J = 8.7/7.9 Hz, 1 H, OCH_2CH), 5.14 (dd, J = 10.7/3.3 Hz, 1 H, CH$_2$C*H*NO), 5.31 (dd, J = 7.8/5.7 Hz, 1 H, OCH$_2$C*H*), 7.01–7.21 (m, 14 H, arom.).

5.19. (3*S*,6*S*,11a*R*)-6-Benzyl-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(6*S*)-12a] and (3*S*,6*R*,11a*R*)-6-Benzyl-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(6*R*)-13a]: The synthesis of (6*S*)-**12a** was performed as described for (6*R*)-**12a** according to the General Procedure **A** using oxazolo-benzazepinone (3*S*)-**10** (200 mg, 0.716 mmol) in $THF_{abs.}$ (50 mL), LDA solution (394 µL, 0.788 mmol) and benzyl bromide (85.0 µL, 0.716 mmol). (6*S*)-**12a**: colorless solid, yield 148 mg (56%), *de* 100% (HPLC) after fc purification. $[\alpha]_{589}^{20}$ = +113.5 (c = 0.14, CH_2Cl_2). (6*R*)-**13a**: Colorless solid, yield 5.3 mg (2.0%).

5.20. (3*R*,6*R*,11a*S*)-6-Phenethyl-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(6*R*)-12b] and (3*R*,6*S*,11a*S*)-6-Phenethyl-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo-[2,3-*b*][3]benzazepin-5(6*H*)-one [(6*S*)-13b]: According to the General Procedure **A** oxazolo-benzazepinone (3*R*)-**10** (136.2 mg, 0.488 mmol) in THF (35 mL) was treated with LDA solution (317 µL, 0.634 mmol) and 2-phenylethyl iodide (84.9 µL 0.585 mmol). The residue was purified by fc [Ø 3 cm, cyclohexane/ethyl acetate = 15:2, 10 mL, R_f [(6*R*)-**12b**] = 0.48, R_f [(6*S*)-**13b**] = 0.44 in cyclohex-

ane/ethyl acetate = 5:2]. to obtain a mixture of diastereomers 95.6 mg (51%), diastereomeric ratio (HPLC): 92.7:7.3 (6*R*)-**12b**/(6*S*)-**13b**. The diastereomers were separated by preparative HPLC [Phenomenex Gemini C18 5 µM, 250 × 21.2 mm, MeOH/H_2O = 75:25, flow 13 mL/min, λ = 254 nm, 30 mg, t_R [(6*R*)-**12b**] = 41.0 min, t_R [(6*S*)-**13b**] = 46.3 min].

(6*R*)-12b: Colorless solid, m.p. 142.7–143.5 °C, yield 79.6 mg (43%), *de* 100% (HPLC). $[\alpha]_{589}^{20}$ = –98.8 (*c* = 0.52, CH_2Cl_2). $C_{26}H_{25}NO_2$ (383.5). Calcd. C 81.43, H 6.57, N 3.65, found 80.91, H 6.71, N 3.39. MS (EI): *m*/*z* = 383 [M], 279 [M – CH_2CHPhenyl], 91 [C_7H_7]. IR: $\tilde{\nu}$ = 3025, 2918, 2865 (C–H), 1658 (C=O). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.08–2.16 (m, 1 H, CH_2CH_2CH), 2.52–2.69 (m, 3 H, CH_2CH_2CH), 3.28 (dd, *J* = 15.5/4.1 Hz, 1 H, CH_2CHNO), 3.40 (dd, *J* = 15.6/4.4 Hz, 1 H, CH_2CHNO), 3.63 (t, *J* = 8.2 Hz, 1 H, OCH_2CH), 3.72 (t, *J* = 6.8 Hz, 1 H, $CH_2CHC{=}O$), 4.25 (t, *J* = 8.5 Hz, 1 H, OCH_2CH), 5.13–5.18 (m, 2 H, CH_2CHNO, OCH_2CH), 7.06–7.28 (m, 14 H, arom.). ^{13}C NMR ($CDCl_3$): δ [ppm] = 30.8 (1 C, CH_2CH_2Ph), 33.9 (1 C, CH_2CH_2Ph), 36.9 (1 C, CH_2CHON), 47.6 (1 C, $CH_2CHC{=}O$), 60.4 (1 C, $CHCH_2O$), 71.6 (1 C, $CHCH_2O$), 88.4 (1 C, CH_2CHON), 126.2, 126.4, 126.5, 127.6, 127.7, 128.1, 128.6, 128.8, 129.0, 130.5, 133.3, 138.3, 140.5, 141.8 (18 C, arom.), 169.1 (1 C, $CONR_2$).

(6*S*)-13b: Colorless solid, yield 7.4 mg (3.9%). $C_{26}H_{25}NO_2$ (383.5). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.20–2.25 (m, 1 H, CH_2CH_2CH), 2.58–2.72 (m, 3 H, CH_2CH_2CH), 3.28 (dd, *J* = 14.7/3.4 Hz, 1 H, CH_2CHNO), 3.45 (dd, *J* = 14.7/10.4 Hz, 1 H, CH_2CHNO), 3.82 (dd, *J* = 8.6/5.8 Hz, 1 H, OCH_2CH), 3.93 (t, *J* = 7.3 Hz, 1 H, $CH_2CHC{=}O$), 4.46 (t, *J* = 8.2 Hz, 1 H, OCH_2CH), 5.19 (dd, *J* = 10.6/3.2 Hz, 1 H, CH_2CHNO), 5.40 (dd, *J* = 7.5/5.9 Hz, 1 H, OCH_2CH), 7.11–7.31 (m, 14 H, arom.).

5.21. (3*S*,6*S*,11a*R*)-6-Phenethyl-3-phenyl-2,3,11,11a-tetrahydro[1,3]-oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(*S*)-12b] and (3*S*,6*R*,11a*R*)-6-Phenethyl-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(*R*)-13b]: The synthesis of (6*S*)-**12b** was performed as described for (6*R*)-**12b**. (3*S*)-**10** (230 mg, 0.823 mmol) in THF (57 mL) was treated with LDA solution (535 µL, 1.07 mmol) and 2-phenylethy iodide (143 µL, 0.99 mmol). (6*S*)-**12b**: Colorless solid, m.p. 141.9–142.7 °C, yield 126 mg (40%), *de* 100% (HPLC). $[\alpha]_{589}^{20}$ = +102.7 (*c* = 0.81, CH_2Cl_2). (6*R*)-**13b**: Colorless solid, yield 13.5 mg (4.3%).

5.22. (3*R*,6*R*,11a*S*)-6-(2-Methylbenzyl)-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(6*R*)-12c] and (3*R*,6*S*,11a*S*)-6-(2-Methylbenzyl)-3-phenyl-2,3,11,11a-tetrahydro-[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(6*S*)-13c]: According to the General Procedure **A** oxazolo-benzazepinone (3*R*)-**10** (100 mg, 0.358 mmol) in THF (25 mL) was treated with LDA solution (215 µL, 0.430 mmol) and 2-methylbenzyl bromide (52.6 µL 0.394 mmol). The residue was purified by fc [Ø 2 cm, cyclohexane/ethyl acetate = 15:2, 5 mL, R_f [(6*R*)-**12c**] = 0.37, R_f [(6*S*)-**13c**] = 0.32 in cyclohexane/ethyl acetate = 5:2]. to obtain a mixture of diastereomers: 114.2 mg (83%), diastereomeric ratio (HPLC): 93.3:6.7 [(6*R*)-**12c**:(6*S*)-**13c**]. The diastereomers were separated by preparative HPLC [Phenomenex Gemini C18 5 µm, 250 × 21.2 mm, MeOH/H_2O = 75:25, flow 14 mL/min, λ = 254 nm, 23 mg, t_R[(6*R*)-**12c**] = 38.2 min, t_R[(6*S*)-**13c**] = 40.2 min].

(6*R*)-12c: Colorless solid, m.p. 69.2–71.4 °C, yield 77.0 mg (56%), *de* 99.3% (HPLC). $[\alpha]_{589}^{20}$ = –74.7 (*c* = 0.56, CH_2Cl_2). $C_{26}H_{25}NO_2$ (383.5). HPLC purity: a) Phenomenex Gemini C18, 80% Methanol/20% H_2O, flow 0.8 mL/min, λ = 254 nm, t_R = 19.0 min, purity 98.5%; b) RP Select B LiChrospher, 60% CH_3CN/40% H_2O, flow 0.6 mL/min, λ = 254 nm, t_R = 9.9 min, purity 97.8%. MS (EI): *m*/*z* = 383 [M], 278 [M – CH_2CH_3Phenyl], 77 [C_6H_5]. IR: $\tilde{\nu}$ = 3026, 2869 (C–H), 1653 (C=O). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.20 (s, 3 H, ArCH_3), 3.17 (dd, *J* = 14.1/8.7 Hz, 1 H, $CH_2CHC{=}O$), 3.41 (dd, *J* = 14.9/6.7 Hz, 1 H, CH_2CHNO), 3.49 (dd, *J* = 14.9/3.2 Hz, 1 H, CH_2CHNO), 3.61 (dd, *J* = 14.1/5.5 Hz, 1 H, $CH_2CHC{=}O$), 3.70 (t, *J* = 8.6 Hz, 1 H, OCH_2CH), 4.05 (dd, *J* = 8.6/5.5 Hz, 1 H, $CH_2CHC{=}O$), 4.42 (t, *J* = 8.6 Hz, 1 H, OCH_2CH), 5.19 (dd, *J* = 6.3/3.6 Hz, 1 H, CH_2CHNO), 5.35 (t, *J* = 8.2 Hz, 1 H, OCH_2CH), 6.76–7.30 (m, 13 H, arom.). ^{13}C NMR ($CDCl_3$): δ [ppm] = 19.5 (1 C, ArCH_3); 35.1 (1 C, $CH_2CHC{=}O$), 37.6 (1 C, CH_2CHON), 52.2 (1 C, $CH_2CHC{=}O$), 61.0 (1 C, $CHCH_2O$), 71.8 (1 C, $CHCH_2O$), 89.3 (1 C, CH_2CHON), 125.8, 126.4, 126.5, 127.8, 128.9, 129.8, 130.3, 130.3, 133.0, 136.8, 137.4, 137.8, 140.0 (18 C, arom.), 169.4 (1 C, $CONR_2$).

(6*S*)-13c: Colorless solid, yield: 6.1 mg (4.4%). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.17 (s, 3 H, ArCH_3), 3.19 (dd, *J* = 15.0/8.2 Hz, 1 H, $CH_2CHC{=}O$), 3.29 (dd, *J* = 14.9/3.1 Hz, 1 H, CH_2CHNO), 3.45–3.53 (m, 2 H, CH_2CHNO, $CH_2CHC{=}O$), 3.79 (dd, *J* = 8.8/5.4 Hz, 1 H, OCH_2CH), 4.22 (dd, *J* = 7.9/6.6 Hz, 1 H, $CH_2CHC{=}O$), 4.39 (dd, *J* = 8.7/7.8 Hz, 1 H, OCH_2CH), 5.29–5.33 (m, 2 H, CH_2CHNO, OCH_2CH), 6.85–7.23 (m, 13 H, arom.).

5.23. (3*S*,6*S*,11a*R*)-6-(2-Methylbenzyl)-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(6S-12c)] and (3*S*,6*R*,11a*R*)-6-(2-Methylbenzyl)-3-phenyl-2,3,11,11a-tetrahydro-[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(6S-13c)]: The synthesis of (6*S*)-**12c** was performed as described for (6*R*)-**12c** using (3*S*)-**10** (176 mg, 0.629 mmol) in THF (45 mL), LDA solution (377 µL, 0.754 mmol) and 2-methylbenzyl bromide (92.3 µL, 0.691 mmol). (6*S*)-**12c**: Colorless solid, yield 89.6 mg (37%), *de* 98.7% (HPLC). $[\alpha]_{589}^{20}$ = +73.2 (*c* = 0.87, CH_2Cl_2). HPLC purity: a) Phenomenex Gemini C18, 80% MeOH/20% H_2O, flow 0.8 mL/min, λ = 254 nm, t_R = 14.9 min, purity 94.8%; b) Phenomenex Gemini C18, 80% MeOH/20% H_2O, flow 0.8 mL/min, λ = 220 nm, t_R = 14.8 min, purity 95.5%. mp: 69.5–71.2 °C. (6*R*)-**13c**: Colorless solid, yield 3.1 mg (1.3%).

5.24. (3*R*,6*R*,11a*S*)-6-(4-Methoxybenzyl)-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(6*R*)-12d] and (3*R*,6*S*,11a*S*)-6-(4-Methoxybenzyl)-3-phenyl-2,3,11,11a-tetrahydro-[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(6*S*)-13d]: According to the General Procedure **A** oxazolo-benzazepinone (3*R*)-**10** (173 mg, 0.618 mmol) in THF (45 mL) was treated with LDA solution (371 µL, 0.741 mmol) and 4-methoxybenzyl bromide (97.9 µL 0.680 mmol). The residue was purified by fc (Ø 3 cm, cyclohexane/ethyl acetate = 15:2, 10 mL), R_f [(6*R*)-**12d**] = 0.27, R_f [(6*S*)-**13d**] = 0.22 in cyclohexane/ethyl acetate = 5:2 to obtain a mixture of diastereomers, yield 193.0 mg (78%), diastereomeric ratio (HPLC): 92.8:7.2 [(6*R*)-**12d**:(6*S*)-**13d**]. The diastereomers were separated by preparative HPLC [Phenomenex Gemini C18 5 µm, 250 × 21.2 mm, MeOH/H_2O = 75:25, flow 14 mL/min, λ = 254 nm, 50 mg, t_R[(6*R*)-**12d**] = 26.3 min, t_R[(6*S*)-**13d**] = 28.3 min].

(6*R*)-12d: Colorless solid, m.p. 65.2–66.1 °C, yield 98.9 mg (40%), *de* 98.6% (HPLC). $[\alpha]_{589}^{20}$ = –106.9 (*c* = 0.98, CH_2Cl_2). $C_{26}H_{25}NO_3$ (399.5). HPLC purity: a) Phenomenex Gemini C18 5 µm, 75% MeOH/25% H_2O, flow 0.8 mL/min, λ = 254 nm, t_R = 21.5 min, purity 97.6%; b) RP Select B LiChrospher, 80% CH_3CN/20% H_2O, flow 0.8 mL/min, λ = 254 nm, t_R = 5.7 min, purity 96.7%. MS (EI): *m*/*z* = 399 [M], 121 [$CH_2C_6H_4OCH_3$]. IR: $\tilde{\nu}$ = 2931, 2834 (C–H), 1651 (C=O), 1245 (O–CH_3). ^{1}H NMR ($CDCl_3$): δ [ppm] = 3.11 (dd, *J* = 13.6/7.3 Hz, 1 H, $CH_2CHC{=}O$), 3.26 (dd, *J* = 15.1/5.3 Hz, 1 H, CH_2CHNO), 3.48 (dd, *J* = 15.3/3.5 Hz, 1 H, CH_2CHNO), 3.58 (dd, *J* = 13.7/7.0 Hz, 1 H, $CH_2CHC{=}O$), 3.67 (t, *J* = 8.5 Hz, 1 H, OCH_2CH), 3.75 (s, 3 H, OCH_3), 4.04 (t, *J* = 7.1 Hz, 1 H, $CH_2CHC{=}O$), 4.35 (t, *J* = 8.4 Hz, 1 H, OCH_2CH),

5.18 (t, J = 4.5 Hz, 1 H, CH_2CHNO), 5.28 (t, J = 8.0 Hz, 1 H, OCH_2CH), 6.96–7.29 (m, 13 H, arom.). ^{13}C NMR ($CDCl_3$): δ [ppm] = 35.9 (1 C, $CH_2CHC{=}O$), 37.4 (1 C, CH_2CHON), 52.3 (1 C, $CH_2CHC{=}O$), 55.4 (1 C, OCH_3), 60.6 (1 C, $CHCH_2O$), 71.6 (1 C, $CHCH_2O$), 88.8 (1 C, CH_2CHON), 126.3, 127.7, 128.0, 128.9, 130.3, 130.4, 132.1, 133.1, 137.9, 140.1 (18 C, arom.), 169.1 (1 C, $CONR_2$).

(6*S*)-13d: Colorless solid, yield 4.2 mg (1.7%). ^1H NMR ($CDCl_3$): δ [ppm] = 3.11 (dd, J = 14.3/7.3 Hz, 1 H, $CH_2CHC{=}O$), 3.25 (dd, J = 14.9/3.2 Hz, 1 H, CH_2CHNO), 3.43–3.54 (m, 2 H, CH_2CHNO, $CH_2CHC{=}O$), 3.77 (dd, J = 9.0/5.5 Hz, 1 H, OCH_2CH), 3.68 (s, 3 H, OCH_3), 4.22 (t, J = 7.3 Hz, 1 H, $CH_2CHC{=}O$), 4.37 (t, J = 8.4 Hz, 1 H, OCH_2CH), 5.19 (dd, J = 10.6/3.1 Hz, 1 H, CH_2CHNO), 5.30 (t, J = 6.5 Hz, 1 H, OCH_2CH), 6.59–7.24 (m, 13 H, arom.).

5.254. (3*S*,6*S*,11a*R*)-6-(4-Methoxybenzyl)-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(6*S*)-12d] and (3*S*,6*R*,11a*R*)-6-(4-Methoxybenzyl)-3-phenyl-2,3,11,11a-tetrahydro-[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(6*R*)-13d]: The synthesis of (6*S*)-**12d** was performed as described for (6*R*)-**12d** using (3*S*)-**10** (173 mg, 0.62 mmol) in THF (45 mL), LDA solution (372 µL, 0.744 mmol) and 4-methoxybenzyl bromide (98.3 µL, 0.682 mmol). (6*S*)-**12d**: Colorless solid, m.p. 64.8–65.9 °C, yield 91.2 mg (37%), *de* 100% (HPLC). $[\alpha]_{589}^{20}$ = +105.3 (c = 0.85, CH_2Cl_2). $C_{26}H_{25}NO_2$ (399.5). HPLC-purity: a) Phenomenex Gemini C18 5 µm, 80% MeOH/20% H_2O flow 0.8 mL/min, λ = 254 nm, t_R = 13.0 min, purity 99.8%; b) RP Select B LiChrospher, 60% CH_3CN/40% H_2O, flow 0.8 mL/min, λ = 254 nm, t_R = 14.6 min, purity 99.8%. (6*R*)-**13d**: Colorless solid, yield 6.6 mg (2.7%).

5.26. (3*R*,6*R*,11a*S*)-6-Methyl-3-phenyl-2,3,11,11a-tetrahydro-[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(6*R*)-12e] and (3*R*,6*S*,11a*S*)-6-Methyl-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo-[2,3-*b*][3]benzazepin-5(6*H*)-one [(6*S*)-13e]: According to the General Procedure **A** oxazolo-benzazepinone (3*R*)-**10** (194 mg, 0.700 mmol) in THF (20 mL) was treated with LDA solution (417 µL, 0.835 mmol) and methyl iodide (47.6 µL 0.765 mmol). The residue was purified by fc [Ø 3 cm, cyclohexane/ethyl acetate = 8:2, 5 mL, R_f [(6*R*)-**12e**] = 0.33, R_f [(6*S*)-**13e**] = 0.26 in cyclohexane/ethyl acetate = 5:2] to obtain a mixture of diastereomers, yield 168.1 mg (82%), diastereomeric ratio (HPLC): 80.3:19.7 [(6*R*)-**12e**:(6*S*)-**13e**]. The diastereomers were separated by preparative HPLC [Phenomenex Gemini C18 5 µM, 250×21.2 mm, MeOH/H_2O = 75/25, flow 12 mL/min, λ = 254 nm, 23 mg, t_R[(6*R*)-**12e**] = 13.4 min, t_R[(6*S*)-**13e**] = 17.2 min].

(6*R*)-12e: Colorless solid, m.p. 166.3 °C, yield 113.6 mg (55%), *de* 100% (HPLC). $[\alpha]_{589}^{20}$ = –184.8 (c = 0.63, CH_2Cl_2). $C_{19}H_{19}NO_2$ (293.4) Calcd. C 77.79, H 6.53, N 4.77, found C 77.63, H 6.73, N 4.54. MS (EI): m/z = 293 [M], 120 [$PhCHCH_2O$], 91 [C_7H_7], 77 [C_6H_5]. IR: $\tilde{\nu}$ = 3030, 2872 (C–H), 1653 (C=O). ^1H NMR ($CDCl_3$): δ [ppm] = 1.57 (d, J = 7.1 Hz, 3 H, CH_3CH), 3.37 (dd, J = 15.4/3.9 Hz, 1 H, CH_2CHNO), 3.59 (dd, J = 15.4/4.2 Hz, 1 H, CH_2CHNO), 3.72 (dd, J = 8.9/7.5 Hz, 1 H, OCH_2CH), 4.02 (q, J = 7.0 Hz, 1 H, CH_3CH), 4.31 (dd, J = 8.8/8.2 Hz, 1 H, OCH_2CH), 5.20 (t, J = 7.8 Hz, 1 H, OCH_2CH), 5.31 (t, J = 4.0 Hz, 1 H, CH_2CHNO), 7.24–7.34 (m, 9 H, arom.).

(6*S*)-13e: Colorless solid, yield 27.8 mg (13.5%). ^1H NMR ($CDCl_3$): δ [ppm] = 1.64 (d, J = 7.1 Hz, 3 H, CH_3CH), 3.27 (dd, J = 13.9/3.2 Hz, 1 H, CH_2CHNO), 3.54 (dd, J = 13.8/11.2 Hz, 1 H, CH_2CHNO), 3.74 (dd, J = 8.8/7.2 Hz, 1 H, OCH_2CH), 4.13 (q, J = 7.0 Hz, 1 H, CH_3CH), 4.48 (t, J = 8.5 Hz, 1 H, OCH_2CH), 4.93 (dd, J = 11.2/3.1 Hz, 1 H, CH_2CHNO), 5.43 (t, J = 7.7 Hz, 1 H, OCH_2CH), 7.08–7.33 (m, 9 H, arom.).

5.27. (3*S*,6*S*,11a*R*)-6-Methyl-3-phenyl-2,3,11,11a-tetrahydro[1,3]-oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one [(6*S*)-12e] and (3*S*,6*R*,11a*R*)-6-Methyl-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[2,3-*b*][3]benz-azepin-5(6*H*)-one [(6*R*)-13e]: The synthesis of (6*S*)-**12e** was performed as described for (6*R*)-**12e** using (3*S*)-**10** (214 mg, 0.766 mmol) in THF (45 mL), LDA solution (460 µL, 0.920 mmol) and methyl iodide (52.5 µL, 0.843 mmol). (6*S*)-**12e**: Colorless solid, m.p. 167.2–168.8 °C, yield 83.4 mg (37%), *de* 100% (HPLC). $[\alpha]_{589}^{20}$ = +187.7 (c = 0.33, CH_2Cl_2). HPLC-purity: a) Phenomenex Gemini C18 5 µm, 75% MeOH/25% H_2O flow 0.6 mL/min, λ = 254 nm, t_R = 10.8 min, purity 99.4%; b) RP Select B LiChrospher, 80% CH_3CN/20% H_2O, flow 0.6 mL/min, λ = 254 nm, t_R = 7.1 min, purity 99.8%. (6*R*)-**13e**: Colorless solid, yield 20.6 mg (9.2%).

5.28. (2*R*)-2-[(1*R*)-1-Benzyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-3-yl]-2-phenylethan-1-ol [(1*R*)-14a]: According to the General Procedure **B** $AlCl_3$ (49.3 mg, 0.37 mmol) in THF (3 mL) and $LiAlH_4$ solution (1.12 mL, 1.12 mmol) were treated with (6*R*)-**12a** (148 mg, 0.40 mmol) in THF (3 mL). The residue was purified by fc (Ø 2 cm, cyclohexane/ethyl acetate = 8:2, 5 mL, R_f = 0.23). Colorless solid, m.p. 99.7–100.2 °C, yield 115 mg (80%). $[\alpha]_{589}^{20}$ = –41.6 (c = 1.45, CH_2Cl_2). $C_{25}H_{27}NO$ (357.5). Calcd. C 83.99, H 7.61, N 3.92, found C 83.25, H 7.58, N 3.80. HPLC purity: a) RP 18 Superspher®100, 80% MeOH/20% H_2O +0.1% Et_2NH, flow 0.8 mL/min, λ = 254 nm, t_R = 26.0 min, purity 98.2%, b) RP 8e LiChrospher®100, 60% CH_3CN/40% H_2O + 0.1% Et_2NH, flow 0.8 mL/min, λ = 254 nm, t_R = 29.0 min, purity 96.8%. MS (EI): m/z = 326 [M – CH_2OH], 91 [C_7H_7]. IR: $\tilde{\nu}$ = 3448 (O–H), 3025, 2923, 2848 (C–H). ^1H NMR ([D_6]DMSO): δ [ppm] = 2.12–2.17 (m, 1 H, CH_2CH_2N), 2.38–2.41 (m, 1 H, $CHCH_2N$), 2.59–2.61 (m, 1 H, $CHCH_2N$), 2.78 (dd, J = 14.9/7.0 Hz, 1 H, $PhCH_2CH$), 2.85–2.94 (m, 2 H, CH_2CH_2N, CH_2CH_2N), 3.06–3.15 (m, 3 H, CH_2CH_2N, $PhCH_2CH$, $PhCH_2CH$), 3.55–3.64 (m, 2 H, $CHCH_2OH$, $CHCH_2OH$), 3.77–3.81 (m, 1 H, $CHCH_2OH$), 4.37–4.40 (m, 1 H, OH), 6.90–7.25 (m, 14 H, arom.). ^{13}C NMR ([D_6]DMSO): δ [ppm] = 37.2 (1 C, $PhCH_2CH$), 37.9 (1 C, CH_2CH_2N), 49.5 (1 C, $PhCH_2CH$), 52.5 (1 C, CH_2CH_2N), 56.9 (1 C, $CHCH_2N$), 61.9 (1 C, $CHCH_2OH$), 72.1 (1 C, $CHCH_2OH$), 126.4, 126.5, 126.6, 127.5, 128.4, 128.7, 129.0, 129.2, 129.8, 130.2, 139.0, 141.5, 141.7, 144.8 (18 C, arom.).

5.29. (2*S*)-2-[(1*S*)-1-Benzyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-3-yl]-2-phenylethan-1-ol [(1*S*)-14a]: The synthesis of (1*S*)-**14a** was performed as described for (1*R*)-**14a** according to the General Procedure **B** using $AlCl_3$ (38.9 mg, 0.292 mmol) in THF (3 mL), $LiAlH_4$ solution (881 µL, 0.881 mmol) and (6*S*)-**12a** (117 mg, 0.317 mmol) in THF (4 mL). Colorless solid, m.p. 100.1–100.7 °C, yield 97.7 mg (86%). $[\alpha]_{589}^{20}$ = +44.2 (c = 0.49, CH_2Cl_2). $C_{25}H_{27}NO$ (357.5). HPLC-purity: a) RP 18 Superspher®100, 80% MeOH/20% H_2O + 0.1% Et_2NH, flow 0.8 mL/min, λ = 220 nm, t_R = 19.2 min, purity 98.2%; b) RP 8e LiChrospher®100, 60% CH_3CN/40% H_2O + 0.1% Et_2NH, flow 0.8 mL/min, λ = 220 nm, t_R = 22.5 min, purity 96.4%.

5.30. (2*R*)-2-[(1*R*)-1-Phenethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-3-yl]-2-phenylethan-1-ol [(1*R*)-14b]: According to the General Procedure **B** $AlCl_3$ (28.7 mg, 0.215 mmol) in $THF_{abs.}$ (3 mL) and $LiAlH_4$ solution (0.65 mL, 0.65 mmol) were treated with (6*R*)-**12b** (89.6 mg, 0.23 mmol) in THF (3 mL). The residue was purified by fc (Ø 1 cm, cyclohexane/ethyl acetate = 8:2, 5 mL, R_f = 0.30). Colorless oil, yield 78.9 mg (91%). $[\alpha]_{589}^{20}$ = –20.0 (c = 1.19, CH_2Cl_2). $C_{26}H_{29}NO$ (371.5). HPLC purity: a) Phenomenex Gemini C18 5 µm, 60% CH_3CN/40% H_2O + 0.1% Et_2NH, flow 0.8 mL/min, λ = 220 nm, t_R = 68.3 min, purity 96.1%; b) RP 18 Superspher®100,

80% MeOH/20% H_2O + 0.1% Et_2NH, flow 0.8 mL/min, λ = 254 nm, t_R = 37.0 min, purity 99.6%. MS (EI): *m/z* = 372 [M], 91 [C_7H_7]. IR: $\tilde{\nu}$ = 3426 (O–H), 3059, 3024, 2932 (C–H). ^{1}H NMR ([D$_6$]DMSO): δ [ppm] = 1.82–1.91 (m, 1 H, CH_2CH$_2$CH), 2.00–2.10 (m, 1 H, CH_2CH$_2$CH), 2.15–2.21 (m, 1 H, CHCH_2N), 2.31–2.38 (m, 1 H, ArCH_2CH$_2$N), 2.45–2.55 (m, 3 H, ArCH_2CH_2N), 2.68–2.76 (m, 2 H, CH$_2$CH_2CH, CH$_2$CH$_2$C*H*), 2.82–2.91 (m, 1 H, CHCH_2N), 2.98–3.03 (m, 1 H, CH$_2$CH_2CH), 3.71–3.77 (m, 2 H, C*H*CH$_2$OH, CHCH_2OH), 3.88–3.95 (m, 1 H, CHCH_2OH), 4.40–4.43 (m, 1 H, O*H*) 6.96–7.30 (m, 14 H, arom.). ^{13}C NMR ([D$_6$]-DMSO): δ [ppm] = 33.6 (1 C, *C*H$_2$CH$_2$CH), 34.1 (1 C, *C*H$_2$CH$_2$N), 37.3 (1 C, CH$_2$*C*H$_2$CH), 47.9 (1 C, CH$_2$CH$_2$*C*H), 53.0 (1 C, CH$_2$*C*H$_2$N), 56.9 (1 C, CH*C*H$_2$N), 61.6 (1 C, *C*H$_2$CHOH), 72.0 (1 C, CH$_2$*C*HOH) 126.3, 126.5, 126.6, 127.5, 128.4, 128.9, 129.1, 129.3, 130.4, 139.6, 141.3, 143.0, 145.3 (18 C, arom.).

5.31. (2*S*)-2-[(1*S*)-1-Phenethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-3-yl]-2-phenylethan-1-ol [(1*S*)-14b]: The synthesis of (1*S*)-**14b** was performed as described for (1*R*)-**14b** using $AlCl_3$ (38.8 mg, 0.291 mmol), $LiAlH_4$ solution (879 µL, 0.879 mmol) and (6*S*)-**12b** (121 mg, 0.316 mmol) in THF (4 mL). Colorless oil, yield 107 mg (91%). $[\alpha]_{589}^{20}$ = +20.2 (*c* = 1.05, CH_2Cl_2). HPLC purity: a) Phenomenex Gemini C18 5 µm, 80% MeOH/20% H_2O + 0.1% Et_2NH, flow 1.2 mL/min, λ = 254 nm, t_R = 26.2 min, purity 99.6%; b) RP Select B LiChrospher, 60% CH_3CN/40% H_2O + 0.1% Et_2NH, flow 1.2 mL/min, λ = 254 nm, t_R = 33.4 min, purity 97.9%.

5.32. (2*R*)-2-[(1*R*)-1-(2-Methylbenzyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-3-yl]-2-phenylethan-1-ol [(1*R*)-14c]: According to the General Procedure **B** $AlCl_3$ (44.4 mg, 0.33 mmol) in THF (3 mL) and $LiAlH_4$ solution (1.00 mL, 1.00 mmol) were treated with (6*R*)-**12c** (139 mg, 0.36 mmol) in THF (4 mL). The residue was purified by fc (Ø 2 cm, cyclohexane/ethyl acetate = 8:2, 5 mL, R_f = 0.31). Colorless solid, m.p. 116.6–117.8 °C, yield 115 mg (85%). $[\alpha]_{589}^{20}$ = –49.3 (*c* = 0.68, CH_2Cl_2). $C_{26}H_{29}NO$ (371.5). HPLC purity: a) Phenomenex Gemini C18 5 µm, 80% MeOH/20% H_2O + 0.1% Et_2NH, flow 1.0 mL/min, λ = 254 nm, t_R = 19.4 min, purity 97.3%; b) RP Select B LiChrospher, 80% CH_3CN/20% H_2O + 0.1% Et_2NH, flow 1.0 mL/min, λ = 220 nm, t_R = 7.4 min, purity 96.3%. MS (EI): *m/z* = 340 [M – CH_2OH]. IR: $\tilde{\nu}$ = 3482 (O–H), 3019, 2931, 2832, (C–H). ^{1}H NMR ([D$_6$]DMSO): δ [ppm] = 2.10–2.17 (m, 1 H, CH$_2$CH_2N), 2.14 (s, 3 H, CH_3), 2.35–2.38 (m, 1 H, CHCH_2N), 2.67–2.73 (m, 1 H, CHCH_2N), 2.75–2.91 (m, 1 H, PhCH_2CH), 2.84–2.88 (m, 1 H, PhCH_2CH), 2.92–2.97 (m, 2 H, CH_2CH$_2$N, CH$_2$CH_2N), 3.10–3.18 (m, 2 H, CH_2CH$_2$N, PhCH$_2$C*H*), 3.61–3.70 (m, 2 H, CHCH_2OH, C*H*CH$_2$OH), 3.82–3.87 (m, 1 H, CHCH_2OH), 4.42–4.44 (m, 1 H, O*H*), 6.79–7.26 (m, 13 H, arom.). ^{13}C NMR ([D$_6$]DMSO): δ [ppm] = 19.7 (1 C, CH_3), 35.0 (1 C, Ph*C*H$_2$CH), 37.4 (1 C, *C*H$_2$CH$_2$N), 48.6 (1 C, PhCH$_2$*C*H), 52.5 (1 C, CH$_2$*C*H$_2$N), 57.1 (1 C, CH*C*H$_2$N), 61.8 (1 C, CH*C*H$_2$OH), 72.2 (1 C, *C*HCH$_2$OH), 126.2, 126.5, 126.6, 127.5, 128.4, 129.3, 130.3, 130.5, 136.5, 139.0, 139.6, 141.5, 144.8 (18 C, arom.).

5.33. (2*S*)-2-[(1*S*)-1-(2-Methylbenzyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-3-yl]-2-phenylethan-1-ol [(1*S*)-14c]: The synthesis of (1*S*)-**14c** was performed as described for (1*R*)-**14c** using $AlCl_3$ (28.0 mg, 0.210 mmol) in $THF_{abs.}$ (3 mL), $LiAlH_4$ solution (635 µL, 0.635 mmol) and (6*S*)-**12c** (87.6 mg, 0.228 mmol) in THF (4 mL). Colorless solid, m.p. 116.6–117.5 °C, yield 72.3 mg (85%). $[\alpha]_{589}^{20}$ = +47.9 (*c* = 1.38, CH_2Cl_2). $C_{26}H_{29}NO$ (371.5). HPLC purity: a) Phenomenex Gemini C18 5 µm, 80% MeOH/20% H_2O flow 1.0 mL/min, λ = 220 nm, t_R = 33.9 min, purity 97.9%; b) RP Select B LiChrospher, 60% CH_3CN/40% H_2O + 0.1% Et_2NH, flow 1.0 mL/min, λ = 220 nm, t_R = 29.7 min, purity 96.4%.

5.34. (2*R*)-2-[(1*R*)-1-(4-Methoxybenzyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-3-yl]-2-phenylethan-1-ol [(1*R*)-14d]: According to the General Procedure **B** $AlCl_3$ (30.7 mg, 0.230 mmol) in $THF_{abs.}$ (3 mL) and $LiAlH_4$ solution (0.70 mL, 0.70 mmol) were treated with (6*R*)-**12d** (99.9 mg, 0.250 mmol) in THF (4 mL). The residue was purified by fc (Ø 2 cm, cyclohexane/ethyl acetate = 8:2, 5 mL, R_f = 0.28). Colorless oil, yield 86.0 mg (89%). $[\alpha]_{589}^{20}$ = –60.9 (*c* = 1.46, CH_2Cl_2). $C_{26}H_{29}NO_2$ (387.5). HPLC purity: a) Phenomenex Gemini C18 5 µm, 80% MeOH/20% H_2O + 0.1% Et_2NH, flow 1.0 mL/min, λ = 254 nm, t_R = 15.0 min, purity 96.6%; b) RP Select B LiChrospher, 60% CH_3CN/40% H_2O + 0.1% Et_2NH, flow 0.8 mL/min, λ = 220 nm, t_R = 17.3 min, purity 98.3%. MS (EI): *m/z* = 357 [M – OCH_3], 121 [$CH_2C_6H_4OCH_3$]. IR: $\tilde{\nu}$ = 3419 (O–H), 2932, 2831 (C–H), 1243 (O–CH_3). ^{1}H NMR ([D$_6$]DMSO): δ [ppm] = 2.09–2.18 (m, 1 H, CH$_2$CH_2N), 2.38–2.41 (m, 1 H, CHCH_2N), 2.56–2.65 (m, 1 H, CHCH_2N), 2.75–2.87 (m, 3 H, CH$_2$CH_2N, CH_2CH$_2$N), 2.98–3.12 (m, 3 H, PhCH$_2$C*H*, PhCH_2CH), 3.55–3.64 (m, 2 H, CHCH_2OH, C*H*CH$_2$OH), 3.70 (s, 3 H, OCH_3), 3.78–3.83 (m, 1 H, CHCH_2OH), 4.38–4.41 (m, 1 H, O*H*), 6.77–7.24 (m, 13 H, arom.). ^{13}C NMR ([D$_6$]DMSO): δ [ppm] = 37.0 (1 C, Ph*C*H$_2$CH), 37.2 (1 C, *C*H$_2$CH$_2$N), 49.8 (1 C, PhCH$_2$*C*H), 52.4 (1 C, CH$_2$*C*H$_2$N), 55.6 (1 C, OCH_3), 56.9 (1 C, CH*C*H$_2$N), 61.9 (1 C, CH*C*H$_2$OH), 72.1 (1 C, *C*HCH$_2$OH), 126.5, 127.4, 128.4, 129.2, 130.2, 130.7, 133.5, 139.0, 141.5, 144.9, 160.0 (18 C, arom.).

5.35. (2*S*)-2-[(1*S*)-1-(4-Methoxybenzyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-3-yl]-2-phenylethan-1-ol [(1*S*)-14d]: The synthesis of (1*S*)-**14d** was performed as described for (1*R*)-**14d** using $AlCl_3$ (27.6 mg, 0.207 mmol) in THF (3 mL), $LiAlH_4$ solution (626 µL, 0.626 mmol) and (6*S*)-**12d** (90.0 mg, 0.225 mmol) in THF (4 mL). Colorless oil, yield 76.0 mg (87%). $[\alpha]_{589}^{20}$ = +63.2 (*c* = 1.32, CH_2Cl_2). HPLC purity: a) Phenomenex Gemini C18 5 µm, 80% MeOH/20% H_2O + 0.1% Et_2NH, flow 1.0 mL/min, λ = 254 nm, t_R = 11.1 min, purity 95.7%, b) RP Select B LiChrospher, 60% CH_3CN/40% H_2O + 0.1% Et_2NH, flow 1.0 mL/min, λ = 220 nm, t_R = 11.8 min, purity 96.4%.

5.36. (2*R*)-2-[(1*R*)-1-Methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-3-yl]-2-phenylethan-1-ol [(1*R*)-14e]: According to the General Procedure **B** $AlCl_3$ (47.5 mg, 0.36 mmol) in THF (3 mL) and $LiAlH_4$ solution (1.08 mL, 1.08 mmol) were treated with (6*R*)-**12e** (113.6 mg, 0.39 mmol) in THF (3 mL). The residue was purified by fc (Ø 2 cm, cyclohexane/ethyl acetate = 8:2, 5 mL, R_f = 0.20). Colorless oil, yield 98.7 mg (91%). $[\alpha]_{589}^{20}$ = –10.5 (*c* = 1.29, CH_2Cl_2). $C_{19}H_{23}NO$ (281.4). HPLC purity: a) RP 18 LiChrospher®100, 80% MeOH/20% H_2O + 0.1% Et_2NH, flow 0.6 mL/min, λ = 254 nm, t_R = 14.8 min, purity 97.0%; b) RP 8e LiChrospher®100, 60% CH_3CN/40% H_2O + 0.1% Et_2NH, flow 0.6 mL/min, λ = 254 nm, t_R = 15.5 min, purity 99.1%. MS (EI): *m/z* = 250 [M – CH_2OH], 91 [C_7H_7], 77 [C_6H_5]. IR: $\tilde{\nu}$ = 3409 (O–H), 2958, 2928 (C–H). ^{1}H NMR ([D$_6$]DMSO): δ [ppm] = 2.13 (d, *J* = 7.2 Hz, 3 H, CH_3), 2.29–2.33 (m, 1 H, CHCH_2N), 2.50–2.60 (m, 2 H, CH$_2$CH_2N), 2.65–2.68 (m, 1 H, CHCH_2N), 2.83–2.85 (m, 2 H, CH_2CH$_2$N), 2.98–3.05 (m, 1 H, CH_3C*H*), 3.67–3.73 (m, 2 H, C*H*CH$_2$OH, CHCH_2OH), 3.83–3.90 (m, 1 H, CHCH_2OH), 4.38–4.41 (m, 1 H, OH), 7.00–7.27 (m, 9 H, arom.). ^{13}C NMR ([D$_6$]DMSO): δ [ppm] = 18.9 (1 C, *C*H$_3$), 37.0 (1 C, *C*H$_2$CH$_2$N), 53.1 (1 C, CH$_2$*C*H$_2$N), 59.0 (1 C, CH*C*H$_2$N), 61.8 (1 C, CH*C*H$_2$OH), 71.3 (1 C, *C*HCH$_2$OH), 126.4, 126.7, 127.4, 128.4, 129.2, 129.8, 139.7, 141.7, 146.1 (12 C, arom.), the CH_3–*C*H signal is superimposed by the DMSO signal.

5.37. (2*S*)-2-[(1*S*)-1-Methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-3-yl]-2-phenylethan-1-ol [(1*S*)-14e]: The synthesis of (1*S*)-**14e** was per-

formed as described for (1*R*)-**14e** using $AlCl_3$ (35.0 mg, 0.262 mmol) in THF (3 mL), $LiAlH_4$ solution (793 µL, 0.793 mmol) and (6*S*)-**12e** (83.7 mg, 0.285 mmol) in THF (4 mL). Colorless oil, yield 58.0 mg (72%). $[\alpha]_{589}^{20}$ = +15.6 (*c* = 2.86, CH_2Cl_2). HPLC purity: a) Phenomenex Gemini C18 5 µm, 80% MeOH/20% H_2O + 0.1% Et_2NH, flow 0.6 mL/min, λ = 254 nm, t_R = 20.2 min, purity 95.8%, b) RP Select B LiChrospher, 80% CH_3CN/20% H_2O + 0.1% Et_2NH, flow 1.0 mL/min, λ = 254 nm, t_R = 5.3 min, purity 97.0%.

5.38. (*R*)-1-Benzyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(*R*)-15a]: According to the General Procedure **C** a solution of (1*R*)-**14a** (72.4 mg, 0.203 mmol) in MeOH (20 mL) was treated with ammonium formate (128 mg, 2.0 mmol) and Pd/C (7.2 mg). The residue was purified by fc (Ø 1 cm, CH_2Cl_2/acetone = 1:8, 5 mL, R_f = 0.10). Pale yellow oil, yield 35.7 mg (74%). $[\alpha]_{589}^{20}$ = –35.0 (*c* = 0.67, CH_2Cl_2). $C_{17}H_{19}N$ (237.4). HPLC purity: a) RP 18 Superspher® 100, 80% MeOH/20% H_2O + 0.1% Et_2NH, flow 0.6 mL/min, λ = 254 nm, t_R = 20.7 min, purity 95.2%; b) RP 8e LiChrospher®100, 60% CH_3CN/40% H_2O + 0.1% Et_2NH, flow 0.6 mL/min, λ = 254 nm, t_R = 15.6 min. purity 96.6%. MS (EI): *m*/*z* = 237 [M], 222 [M – NH], 146 [M – benzyl], 91 [C_7H_7]. IR: $\tilde{\nu}$ = 3343 (N–H), 3060, 3023, 2925, 2816 [υ(C–H)], 1491, 1452 [δ(C–H)]. ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.06 (m, 1 H, N*H*), 2.75–2.93 (m, 4 H, CH_2NHCH_2), 2.99–3.15 (m, 5 H, ArCH_2, ArC*H*, PhCH_2), 6.91–7.20 (m, 9 H, arom.).

5.39. (*S*)-1-Benzyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(*S*)-15a]: The synthesis of (*S*)-**15a** was performed as described for (*R*)-**15a**. (1*S*)-**14a** (83 mg, 0.232 mmol) in CH_3OH (15 mL) was treated with ammonium formate (146.4 mg, 2.32 mmol) and Pd/C (8.3 mg). Pale yellow oil, yield 49.3 mg (90%). $[\alpha]_{589}^{20}$ = +34.7 (*c* = 0.27, CH_2Cl_2). HPLC purity: a) RP 18 Superspher®100, 60% CH_3CN/40% H_2O + 0.1% Et_2NH, flow 0.6 mL/min, λ = 254 nm, t_R = 28.5 min, purity 96.2%; b) Phenomenex Gemini C18, 80% MeOH/20% H_2O + 0.1% Et_2NH, flow 0.6 mL/min, λ = 254 nm, t_R = 12.9 min, purity 96.4%.

5.40. (*R*)-1-Phenethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin [(*R*)-15b]: According to the General Procedure **C** (1*R*)-**14b** (54.1 mg, 0.146 mmol) in MeOH (15 mL) was treated with ammonium formate (91.8 mg, 1.46 mmol) and Pd/C (5.4 mg). The residue was purified by fc (Ø 2 cm, CH_2Cl_2/methanol = 8:1, 5 mL, R_f = 0.40). The combined fractions were dried (K_2CO_3) and concentrated in vacuo. Pale yellow oil, yield 21.4 mg (58%). $[\alpha]_{589}^{20}$ = +17.0 (*c* = 0.38, CH_2Cl_2). $C_{18}H_{21}N$ (251.4). HPLC purity: a) Phenomenex Gemini C18, 80% Methanol/20% H_2O + 0.1% Et_2NH, flow 0.8 mL/min, λ = 254 nm, t_R = 11.9 min, purity 97.8%; b) RP Select B LiChrospher, 60% CH_3CN/40% H_2O + 0.1% Et_2NH, flow 1.0 mL/min, λ = 254 nm, t_R = 24.1 min, purity 98.3%. MS (EI): *m*/*z* = 251 [M], 236 [M – NH], 147 [$PhCH_2CH_2CHCH_2NH$], 91 [C_7H_7]. IR: $\tilde{\nu}$ = 3343 (N–H), 3022, 2924, 2852 (C–H), 1491, 1452 (C–H). ^{1}H NMR (Pyridin-D_5): δ [ppm] = 0.95–0.99 (m, 2 H, CH_2CH_2CH), 1.31–1.38 (m, 1 H, CH_2CH_2CH), 1.44–1.54 (m, 3 H, CH_2CH_2NH, CH_2CH_2NH, CH_2CH_2CH), 1.57–1.62 (m, 1 H, $CHCH_2NH$), 1.72–1.76 (m, 1 H, $CHCH_2NH$), 1.89–1.98 (m, 3 H, CH_2CH_2NH, CH_2CH_2NH, $CHCH_2NH$), 5.93–6.15 (m, 9 H, arom.). ^{13}C NMR (Pyridin-D_5): δ [ppm] = 32.1 (1 C, CH_2CH_2CH), 33.2 (1 C, CH_2CH_2CH), 38.9 (1 C, CH_2CH_2NH), 48.0 (1 C, $CHCH_2$), 48.3 (1 C, CH_2CH_2NH), 51.6 (1 C, $CHCH_2$), 124.9, 125.2, 125.3, 127.6, 127.7, 129.7, 140.6, 142.0, 144.2 (12 C, arom.).

5.41. (*S*)-1-Phenethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(*S*)-15b]: The synthesis of (*S*)-**15b** was performed as described for (*R*)-**15b** using (1*S*)-**14b** (100 mg, 0.269 mmol) in methanol (15 mL), ammonium formate (170 mg, 2.69 mmol) and Pd/C (10.0 mg). Pale yellow oil, yield 44.3 mg (66%). $[\alpha]_{589}^{20}$ = –16.1 (*c* = 2.00, CH_2Cl_2). $C_{18}H_{21}N$ (251.4). HPLC purity: a) Phenomenex Gemini C18, 80% Methanol/20% H_2O + 0.1% Et_2NH, flow 0.8 mL/min, λ = 220 nm, t_R = 15.7 min, purity 98.2%; b) RP Select B LiChrospher, 60% CH_3CN/40% H_2O + 0.1% Et_2NH, flow 1.0 mL/min, λ = 220 nm, t_R = 26.1 min, purity 97.1%.

5.42. (*R*)-1-(2-Methylbenzyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(*R*)-15c]: According to the General Procedure **C** (1*R*)-**14c** (99.5 mg, 0.268 mmol) in MeOH (20 mL) was treated with ammonium formate (169 mg, 2.68 mmol) and Pd/C (10.0 mg). The residue was purified by fc (Ø 2 cm, CH_2Cl_2/methanol = 8:1, 5 mL, R_f = 0.29). The combined fractions were dried (K_2CO_3) and concentrated in vacuo. Pale yellow oil, yield 36.4 mg (54%). $[\alpha]_{589}^{20}$ = –48.1 (*c* = 1.66, CH_2Cl_2). $C_{18}H_{21}N$ (251.4). HPLC purity: a) Phenomenex Gemini C18 5 µm, 80% MeOH/20% H_2O + 0.1% Et_2NH, flow 0.8 mL/min, λ = 254 nm, t_R = 9.6 min, purity 99.2%; b) RP Select B LiChrospher, 80% CH_3CN/20% H_2O + 0.1% Et_2NH, flow 1.0 mL/min, λ = 254 nm, t_R = 9.4 min, purity 98.3%. MS (EI): *m*/*z* = 252 [M], 236 [M – NH], 146 [M – $CH_2C_6H_4CH_3$]. IR: $\tilde{\nu}$ = 3344 (N–H), 3013, 2927, 2815 (C–H), 1490, 1448 (C–H). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.25 (s, 3 H, CH_3), 2.81–2.93 (m, 2 H, ArCH_2, CH_2NH), 3.00–3.14 (m, 5 H, ArCH_2, CH_2NH, C*H*), 3.17–3.27 (m, 2 H, ArCH_2, CH_2NH), 6.89–7.26 (m, 8 H, arom.). ^{13}C NMR ($CDCl_3$): δ [ppm] = 19.7 (3 C, CH_3), 34.9 (1 C, Ar*C*H_2), 40.0 (1 C, Ar*C*H_2), 49.0 (1 C, *C*H_2NH), 49.9 (1 C, *C*H), 52.0 (1 C, *C*H_2NH), 125.9, 129.4, 130.2, 130.5, 136.5, 139.3, 141.2, 144.3 (12 C, arom.).

5.43. (*S*)-1-(2-Methylbenzyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(*S*)-15c]: The synthesis of (*S*)-**15c** was performed as described for (*R*)-**15c** using (1*S*)-**14c** (65.5 mg, 0.176 mmol) in MeOH (15 mL), ammonium formate (111.2 mg, 1.76 mmol) and Pd/C (6.5 mg). Pale yellow oil, yield 24.0 mg (54%). $[\alpha]_{589}^{20}$ = +48.4 (*c* = 0.21, CH_2Cl_2). $C_{18}H_{21}N$ (251.4). HPLC purity: a) Phenomenex Gemini C18, 80% MeOH/20% H_2O + 0.1% Et_2NH, flow 0.8 mL/min, λ = 254 nm, t_R = 11.2 min, purity 97.2%; b) RP Select B LiChrospher, 80% CH_3CN/20% H_2O + 0.1% Et_2NH, flow 1.0 mL/min, λ = 254 nm, t_R = 8.5 min, purity 96.5%.

5.44. (*R*)-1-(4-Methoxybenzyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(*R*)-15d]: According to the General Procedure **C** (1*R*)-**14d** (76.5 mg, 0.197 mmol) in MeOH (18 mL) was treated with ammonium formate (125 mg, 1.97 mmol) and Pd/C (7.7 mg). The residue was purified by fc (Ø 2 cm, CH_2Cl_2/methanol = 8:1, 5 mL, R_f = 0.25). The combined fractions were dried (K_2CO_3) and concentrated in vacuo. Pale yellow oil, yield 27.4 mg (52%). $[\alpha]_{589}^{20}$ = –60.9 (*c* = 1.01, CH_2Cl_2). $C_{18}H_{21}NO$ (267.4). HPLC purity: a) Phenomenex Gemini C18 5 µm, 80% MeOH/20% H_2O + 0.1% Et_2NH, flow 0.8 mL/min, λ = 254 nm, t_R = 7.9 min, purity 96.6%, b) RP Select B LiChrospher, 60% CH_3CN/40% H_2O + 0.1% Et_2NH, flow 1.0 mL/min, λ = 254 nm, t_R = 12.8 min, purity 98.3%. MS (EI): *m*/*z* = 267 [M], 146 [M – $CH_2C_6H_4OCH_3$], 121 [$CH_2C_6H_4OCH_3$]. IR: $\tilde{\nu}$ = 3344 (N–H), 3013, 2927, 2815 (C–H), 1490, 1448 (C–H). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.83–2.91 (m, 2 H, CH_2NH, ArCH_2), 2.93–2.97 (m, 2 H, CH_2NH), 3.02–3.04 (m, 2 H, ArCH_2), 3.07–3.21 (m, 3 H, C*H*, CH_2NH, ArCH_2), 3.77 (s, 3 H, OCH_3), 6.71–7.26 (m, 8 H, arom.). ^{13}C NMR ($CDCl_3$): δ [ppm] = 36.9 (1 C, Ar*C*H_2), 39.5 (1 C, Ar*C*H_2), 48.7 (1 C, *C*H_2NH), 50.5 (1 C, *C*H), 51.4 (1 C, *C*H_2NH), 55.5 (1 C, O*C*H_3), 126.5, 129.1, 130.3, 130.4, 132.9, 141.0, 144.2, 158.1 (12 C, arom.).

5.45. (*S*)-1-(4-Methoxybenzyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(*S*)-15d]: The synthesis of (*S*)-**15d** was performed as described for (*R*)-**15d** using (1*S*)-**14d** (67.4 mg, 0.174 mmol) in MeOH (15 mL), ammonium formate (109.7 mg, 1.74 mmol) and Pd/C (6.7 mg). Pale yellow oil, yield 19.5 mg (42%). $[\alpha]_{589}^{20}$ = +63.8 (*c* = 0.87, CH_2Cl_2).

HPLC purity: a) Phenomenex Gemini C18, 80% MeOH/20% H_2O + 0.1% Et_2NH, flow 0.8 mL/min, λ = 254 nm, t_R = 11.1 min, purity 98.9%, b) RP Select B LiChrospher, 60% CH_3CN/40% H_2O + 0.1% Et_2NH, flow 1.0 mL/min, λ = 220 nm, t_R = 16.9 min, purity 99.2%.

5.46. (*R*)-1-Methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(*R*)-15e]: According to the General Procedure **C** (1*R*)-**14e** (86.9 mg, 0.309 mmol) in MeOH (20 mL) was treated with ammonium formate (195 mg, 3.09 mmol) and Pd/C (8.7 mg). The residue was purified by fc (Ø 1 cm, CH_2Cl_2/methanol = 8:1, 5 mL, R_f = 0.10). The combined fractions were dried (K_2CO_3) and concentrated in vacuo. Pale yellow oil, yield 22.7 mg (46%). $[\alpha]_{589}^{20}$ = +3.54 (c = 0.87, CH_2Cl_2). $C_{11}H_{15}N$ (161.3). HPLC purity: a) Phenomenex Gemini C18 5 μm, 80% MeOH/20% H_2O + 0.1% Et_2NH, flow 0.6 mL/min, λ = 254 nm, t_R = 8.3 min, purity 97.8%, b) RP Select B LiChrospher, 80% CH_3CN/20% H_2O + 0.1% Et_2NH, flow 1.2 mL/min, λ = 254 nm, t_R = 12.0 min, purity 97.4%. MS (EI): m/z = 161 [M], 146 [M – NH], 119 [M – CH_3CHCH_2]. IR: $\tilde{\nu}$ = 3358 (N–H), 3016, 2924 (C–H), 1489, 1450 (C–H). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.41 (d, J = 7.4 Hz, 3 H, CH_3), 2.80–2.83 (m, 1 H, CHCH_2NH), 2.97–3.02 (m, 2 H, CH_2CH_2NH, ArCH_2), 3.18–3.21 (m, 3 H, CH_2CH_2NH, ArCH_2, CHCH_2NH), 3.30–3.34 (m, 1 H, CH), 7.10–7.26 (m, 4 H, arom.). ^{13}C NMR ($CDCl_3$): δ [ppm] = 18.1 (1 C, CH_3), 36.3 (1 C, ArCH_2), 38.6 (1 C, ArCH), 46.7 (1 C, CH_2NH), 53.2 (1 C, CH_2NH), 126.9, 127.2, 130.0, 140.1, 144.2 (6 C, arom.).

5.47. (*S*)-1-Methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(*S*)-15e]: The synthesis of (*S*)-**15e** was performed as described for (*R*)-**15e** using (1*S*)-**14e** (54.4 mg, 0.193 mmol) in MeOH (15 mL), ammonium formate (122 mg, 1.93 mmol) and Pd/C (5.4 mg). Pale yellow oil, yield 9.5 mg (31%). $[\alpha]_{589}^{20}$ = –2.85 (c = 0.43, CH_2Cl_2). HPLC purity: a) Phenomenex Gemini C18, 80% MeOH/20% H_2O + 0.1% Et_2NH, flow 0.6 mL/min, λ = 254 nm, t_R = 9.2 min, purity 98.5%, b) RP Select B LiChrospher, 80% CH_3CN/20% H_2O + 0.1% Et_2NH, flow 1.2 mL/min, λ = 254 nm, t_R = 12.0 min, purity 97.9%.

6. Receptor Binding Studies

6.1. Materials and General Procedures: Homogenizer: Elvehjem Potter (B. Braun Biotech International). Centrifuge: High-speed cooling centrifuge model Sorvall RC-5C plus (Thermo Finnigan). Filter: Printed Filtermat Typ B (Perkin–Elmer), presoaked in 0.5% aqueous polyethylenimine for 2 h at room temp. before use. The filtration was carried out with a MicroBeta FilterMate-96 Harvester (Perkin–Elmer). The scintillation analysis was performed using Meltilex (Typ A) solid scintillator (Perkin–Elmer). The solid scintillator was melted on the filtermat at a temperature of 95 °C for 5 min. After solidification of the scintillator at room temp., the scintillation was measured using a MicroBeta Trilux scintillation analyzer (Perkin–Elmer). The counting efficiency was 40%. All experiments were carried out in triplicates using standard 96-well-multiplates (Diagonal). The IC_{50} values were determined in competition experiments with six concentrations of the test compounds and were calculated with the program GraphPad Prism® 3.0 (GraphPad Software) by non-linear regression analysis. The K_i values were calculated according to Cheng and Prusoff[23] and are given as mean value + SEM from three independent experiments.

6.2. Determination of the Affinity to the Phencyclidine Binding Site of the NMDA Receptor:

6.2.1. Preparation of the Receptor Material: Fresh pig brain cortex was homogenized with the potter (500–800 rpm, 10 up-and-down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200 *g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 23500 *g* for 20 min at 4 °C. The pellet was resuspended in buffer (5 mM Tris-acetate with 1 mM EDTA, pH 7.5) and centrifuged again at 31000× g (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in buffer, the protein concentration was determined according to the method of Bradford[24] using bovine serum albumin as standard, and subsequently the preparation was frozen (–83 °C) in 1.5 mL portions containing about 0.8 mg protein/mL.

6.2.2. Performance of the Assay: The test was performed with the radioligand [^{3}H]-(+)-MK-801 (22.0 Ci/mmol; Perkin–Elmer). The thawed membrane preparation (about 100 μg of the protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H]-(+)-MK-801, and TRIS/EDTA-buffer (5 mM/1 mM, pH 7.5) in a total volume of 200 μL for 180 min at room temp. The incubation was terminated by rapid filtration through the presoaked filtermats using the cell harvester. After washing each well five times with 300 μL of water, the filtermats were dried at 95 °C. Subsequently, the solid scintillator was placed on the filtermat and melted at 95 °C. After 5 min, the solid scintillator was allowed to solidify at room temperature. The bound radioactivity trapped on the filters was counted in the scintillation analyzer. The non-specific binding was determined with 10 μM (+)-MK-801. The K_d value of the radioligand [^{3}H]-(+)-MK-801 is 2.26 nM.

6.3. Determination of the σ_1 Receptor Affinity (modified according to ref.[25])

6.3.1. Preparation of the Receptor Material: Five guinea pig brains were homogenized with the potter (500–800 rpm, 10 up-and-down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200× g for 10 min at 4 °C. The supernatant was separated and centrifuged at 23500× g for 20 min at 4 °C. The pellet was resuspended in buffer (50 mM TRIS, pH 7.4) and incubated at room temp. for 30 min. After the incubation, the suspension was centrifuged again at 23500 *g* for 20 min at 4 °C. The final pellet was resuspended in buffer, the protein concentration was determined according to the method of Bradford[24] using bovine serum albumin as standard, and subsequently the preparation was frozen (–80 °C) in 1.5 mL portions containing about 1.5 mg protein/mL.

6.3.2. Performance of the σ_1 Assay: The test was performed with the radioligand [^{3}H]-(+)-pentazocine (42.5 Ci/mmol; Perkin–Elmer). The thawed membrane preparation (about 75 μg of the protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H]-(+)-pentazocine, and buffer (50 mM TRIS, pH 7.4) in a total volume of 200 μL for 180 min at 37 °C. The incubation was terminated by rapid filtration through the presoaked filtermats using the cell harvester. After washing each well five times with 300 μL of water, the filtermats were dried at 95 °C. Subsequently, the solid scintillator was placed on the filtermat and melted at 95 °C. After 5 min, the solid scintillator was allowed to solidify at room temp. The bound radioactivity trapped on the filters was counted in the scintillation analyzer. The non-specific binding was determined with 10 μM (+)-pentazocine. The K_d value of the radioligand [^{3}H]-(+)-pentazocine is 2.9 nM.[26]

6.4. Determination of the σ_2 Receptor Affinity (modified according to ref.[25])

6.4.1 Preparation of the Receptor Material: 2 rat livers were cut into small pieces and homogenized with the potter (500–800 rpm, 10 up-and-down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200× g for 10 min at 4 °C. The supernatant was separated and centrifuged at 31000 *g* for 20 min at 4 °C. The pellet was resuspended in buffer (50 mM TRIS, pH 8.0) and incubated at room temp. for 30 min. After the incubation, the sus-

pension was centrifuged again at 31000 *g* for 20 min at 4 °C. The final pellet was resuspended in buffer, the protein concentration was determined according to the method of Bradford[24] using bovine serum albumin as standard, and subsequently the preparation was frozen (–80 °C) in 1.5 mL portions containing about 2 mg protein/mL.

6.4.2. Performance of the σ_2 Assay: The test was performed with the radioligand [^{3}H]-ditolylguanidine (50 Ci/mmol; ARC). The thawed membrane preparation (about 100 μg of the protein) was incubated with various concentrations of test compounds, 3 nM [^{3}H]-ditolylguanidine, 500 nM (+)-pentazocine and buffer (50 mM TRIS, pH 8.0) in a total volume of 200 μL for 180 min at 25 °C. The incubation was terminated by rapid filtration through the presoaked filtermats using the cell harvester. After washing each well five times with 300 μL of water, the filtermats were dried at 95 °C. Subsequently, the solid scintillator was placed on the filtermat and melted at 95 °C. After 5 min, the solid scintillator was allowed to solidify at room temp. The bound radioactivity trapped on the filters was counted in the scintillation analyzer. The non-specific binding was determined with 10 μM ditolylguanidine. The K_d value of the radioligand [^{3}H]-ditolylguanidine is 17.9 nM.[27]

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